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Chemotherapy of malignant lymphoma

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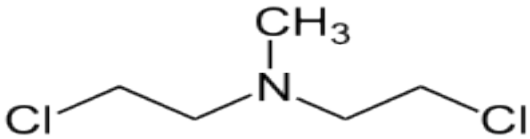
Chemotherapy of malignant lymphoma

- History of and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

Mechlorethamin

The first cytostatic drug in lymphoma

Name	**Mechlorethamin**	**Strukturformel:**
Other names	**N,N-Bis(2-chlorethyl)-N-methylamin** **Chlormethin** **Stickstofflost** **N-Lost** **HN2**	

Mechlorethamin (Stickstoff-Lost) is an alkylating agent, and is mainly used in the chemotherapy of Hodgkin lymphoma (trade name *Mustargen*®, USA, CH)

Mustargen and the history of alkylating agents

- Mustargen as antitumor agent evolved from observed effects of mustard gas in ww1
- Depression of the hematopoietic system was observed in survivors
- Nitrogen mustard is an alkylating agent
- First non-hormonal chemical demonstrating clear clinical antitumor activity
- Studies published in 1946 demonstrated regression especially of lymphomas
- Nitrogen mustard (mechlorethamine, mustargen) and other less toxic and more clinically effective derivatives were developed

Colvin OM. History of the alkylating agents; 19(3):363-371.
Cancer Principley & Practice of Oncology, de Vita V, et al (eds), 2001

MOPP

Combination chemotherapy

(M)ustargen (also known as mechlorethamine, mustine, or nitrogen mustard)
(O)ncovin (also known as Vincristine or VCR)
(P)rocarbazine (also known as Matulane or Natulan)
(P)rednisone (also known as Deltasone or Orasone)

Drug	Dose	Mode	Days
(M)ustargen	6 mg/m²	iv bolus	1 + 8
(O)ncovin	1.4 mg/m² (max 2)	iv bolus	1 + 8
(P)rocarbazine	100 mg/m²	po qd	1 - 14
(P)rednisone	40 mg/m²	po qd	1 - 14

MOPP

Major Side effects

Alopecia (hair loss)

Skin sensitivity

Nausea, vomiting

Chills, constipation

Sterility (dose and age dependent)

Second cancer

https://en.wikipedia.org/wiki/MOPP

COPP

Combination chemotherapy

Drug	Dose	Mode	Days
(C)yclophosphamide	600 mg/m²	iv infusion	1 + 8
(O)ncovin	1.4 mg/m² (max. 2 mg)	iv bolus	1 + 8
(P)rocarbazine	100 mg/m²	PO qd	1 - 10
(P)rednisone	40 mg/m²	PO qd	1 - 14

Major side effects of COPP

Myelosuppression

Hair loss

Nausea and vomiting

Infection

Fatigue

Bleeding

Peripheral neuropathy

Gonadal toxicity

Infertility

ABVD

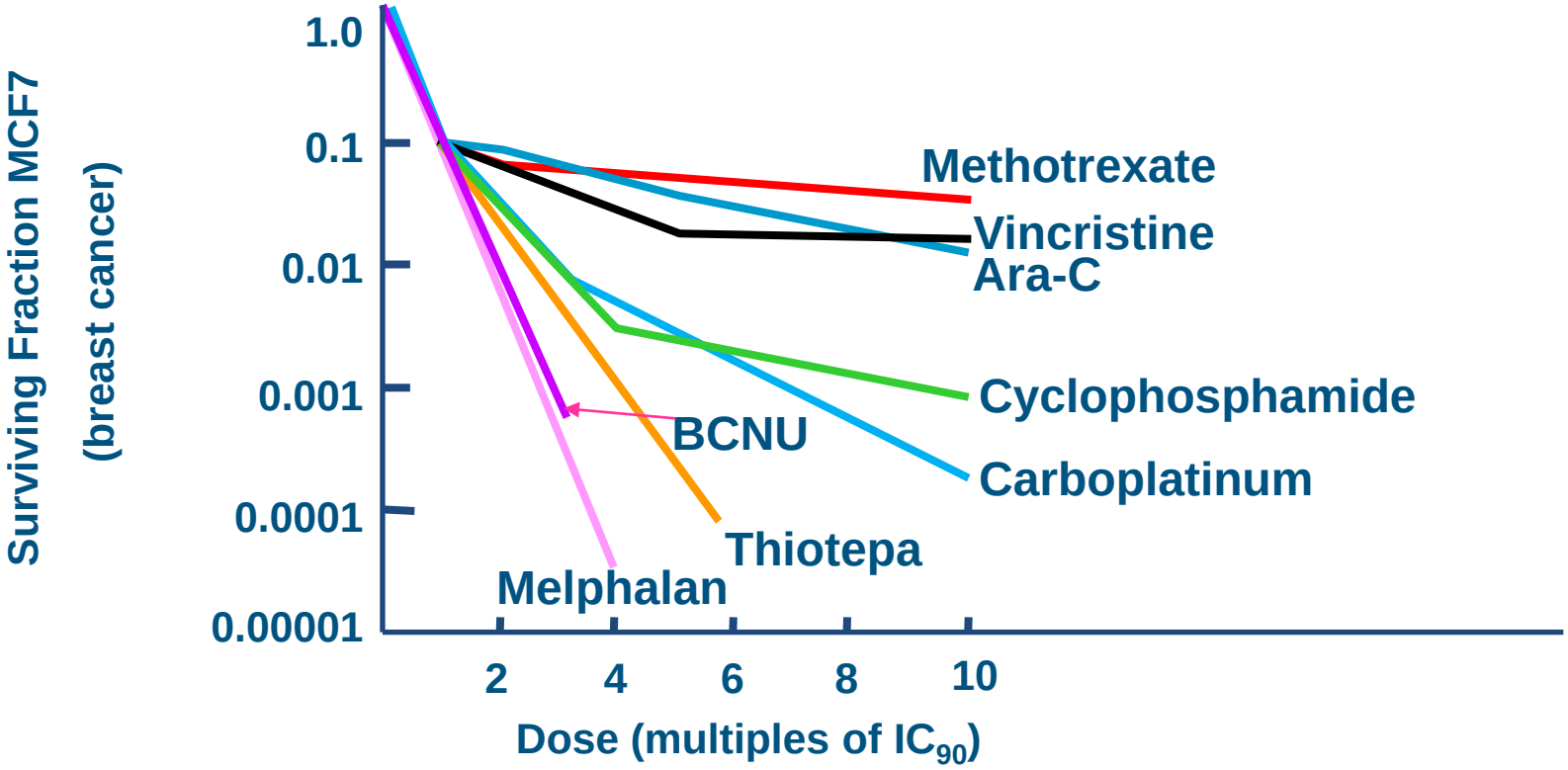
Combination chemotherapy

(A)driamycin (also known as doxorubicin/(H)ydroxydaunorubicin, designated as H in CHOP)
(B)leomycin
(V)inblastine
(D)acarbazine (similar to (P)rocarbazine, designated as P in MOPP and in COPP)

Drug	Dose	Mode	Days
(A)driamycin	25 mg/m²	iv bolus	1 + 15
(B)leomycin	10 IU/m²	iv bolus	1 + 15
(V)inblastine	6 mg/m²	iv bolus	1 + 15
(D)acarbazine	375 mg/m²	iv infusion	1 + 15

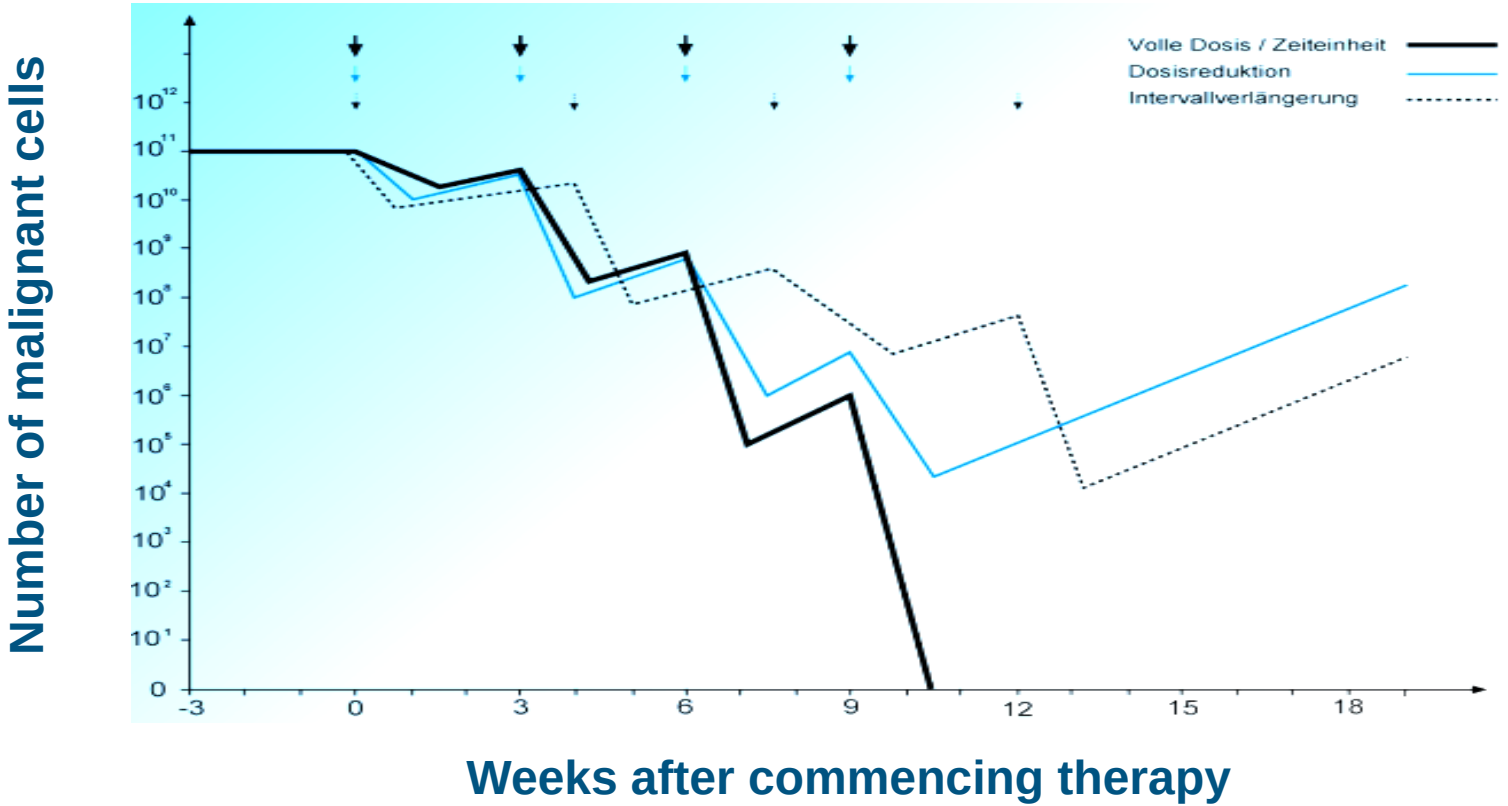
Correlation of dose and efficacy

Cytostatic drugs *in vitro*



Correlation of dose density and response

Chemosensitive malignancies



C. Jackisch

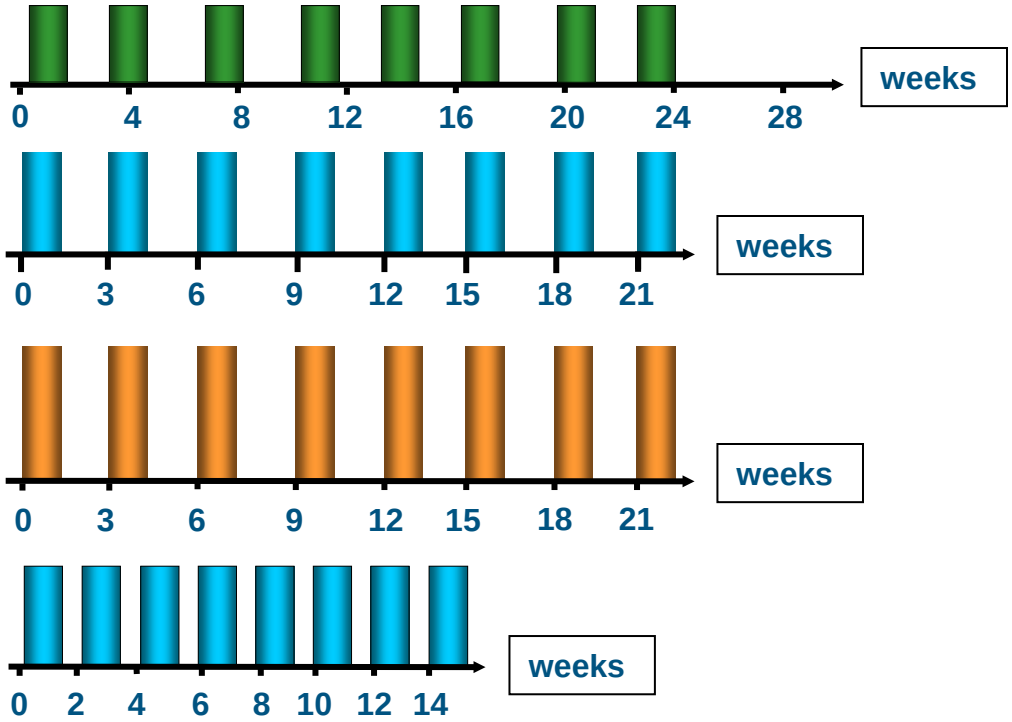
Dose-intensification strategies
for first-line Lymphoma treatment

Conventional chemo

BEACOPP baseline

BEACOPP escalated

CHOP-14, BEACOPP-14



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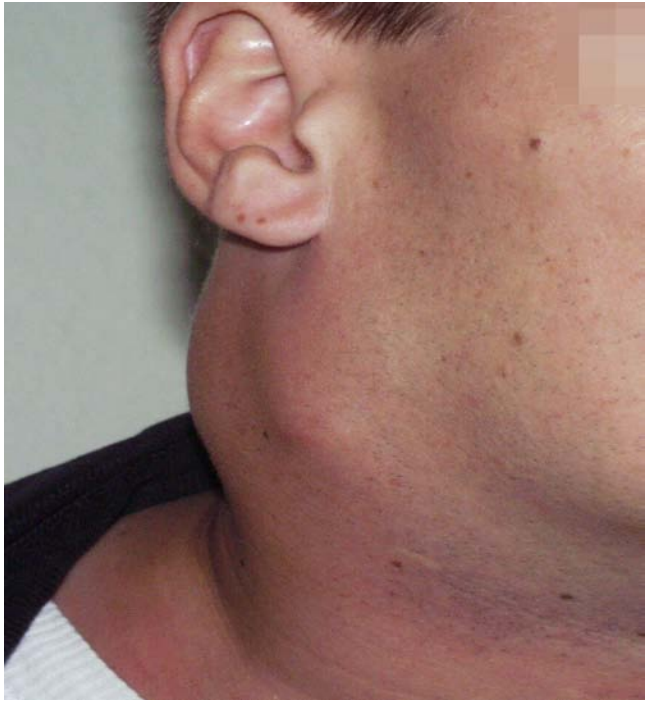
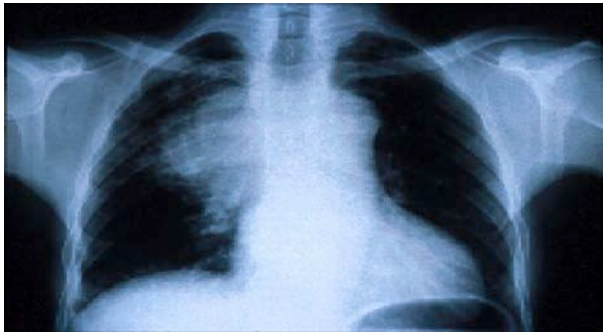
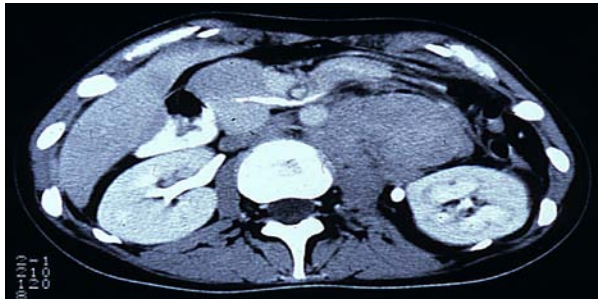
Hodgkin Lymphoma
Clinical Presentation







WHO Classification for HL (2001)

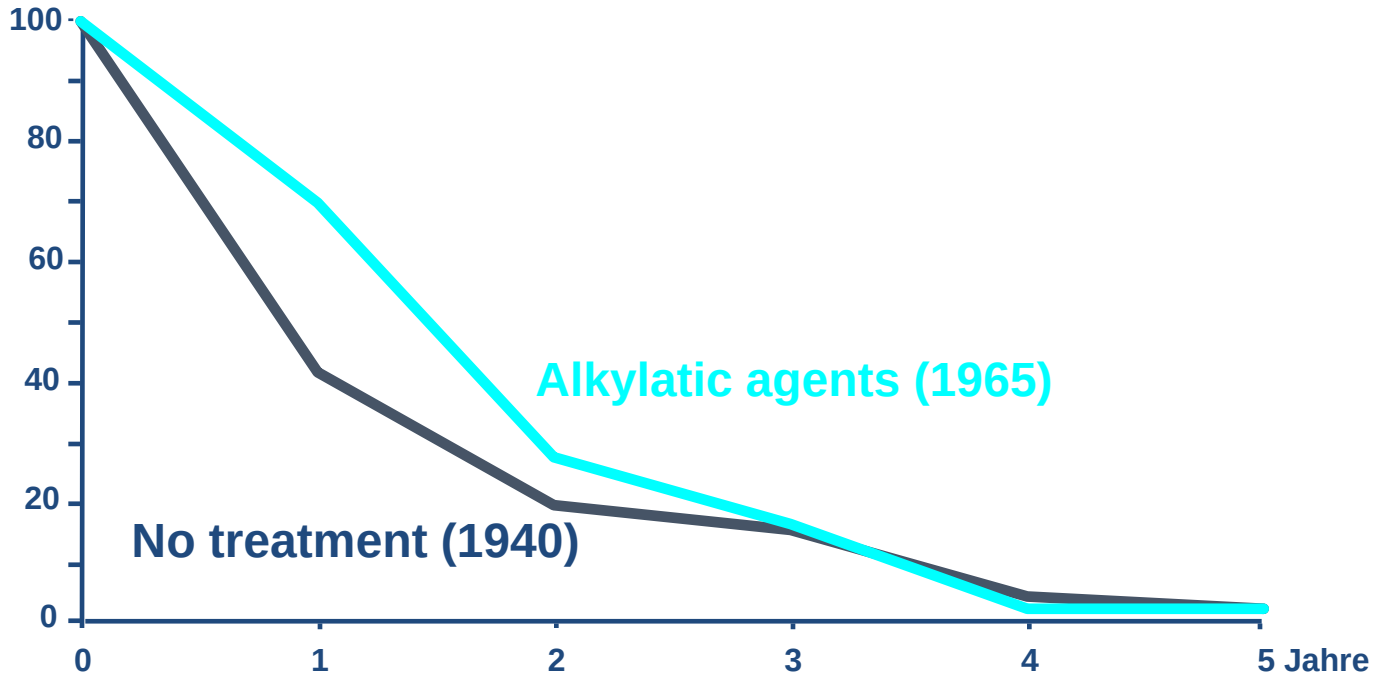
Classical HL (cHL)

- **Lymphocyte-rich classical HL (5%)**
- **Nodular Sclerosis (60-80%)**
- **Mixed Cellularity (25-30%)**
- **Lymphocyte Depletion (1%)**

Nodular Lymphocyte predominant HL (5%)

Hodgkin Lymphoma

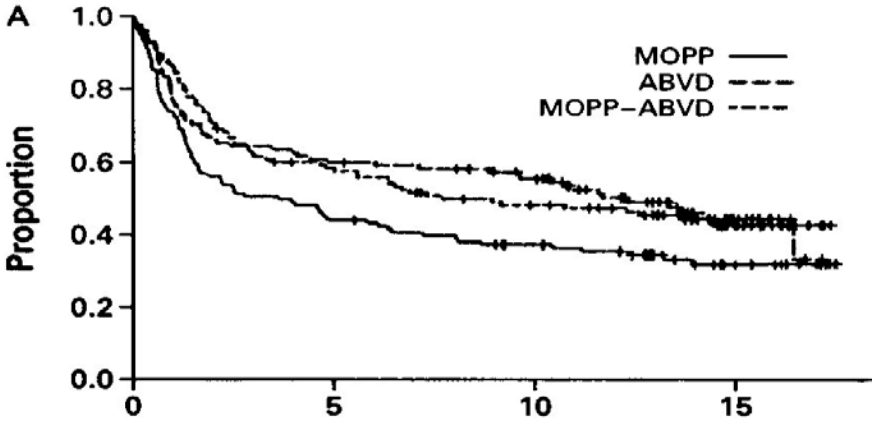
Historical prognosis in advanced stages



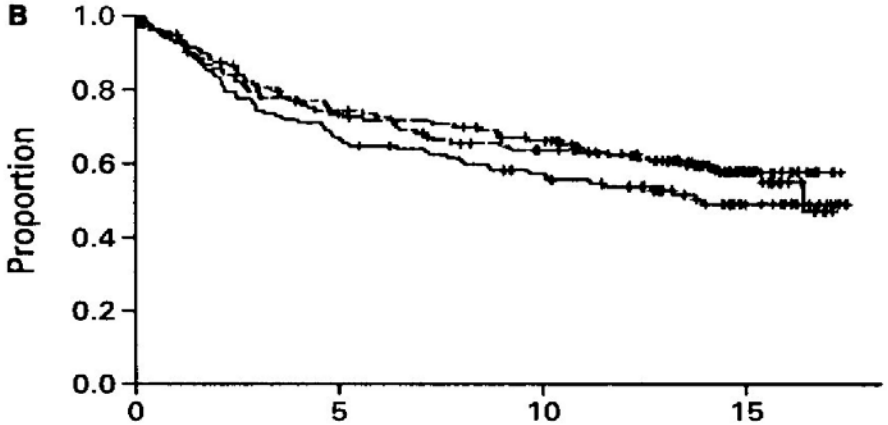
HL treated with MOPP and ABVD

Patients in advanced stages

FFTF



OS

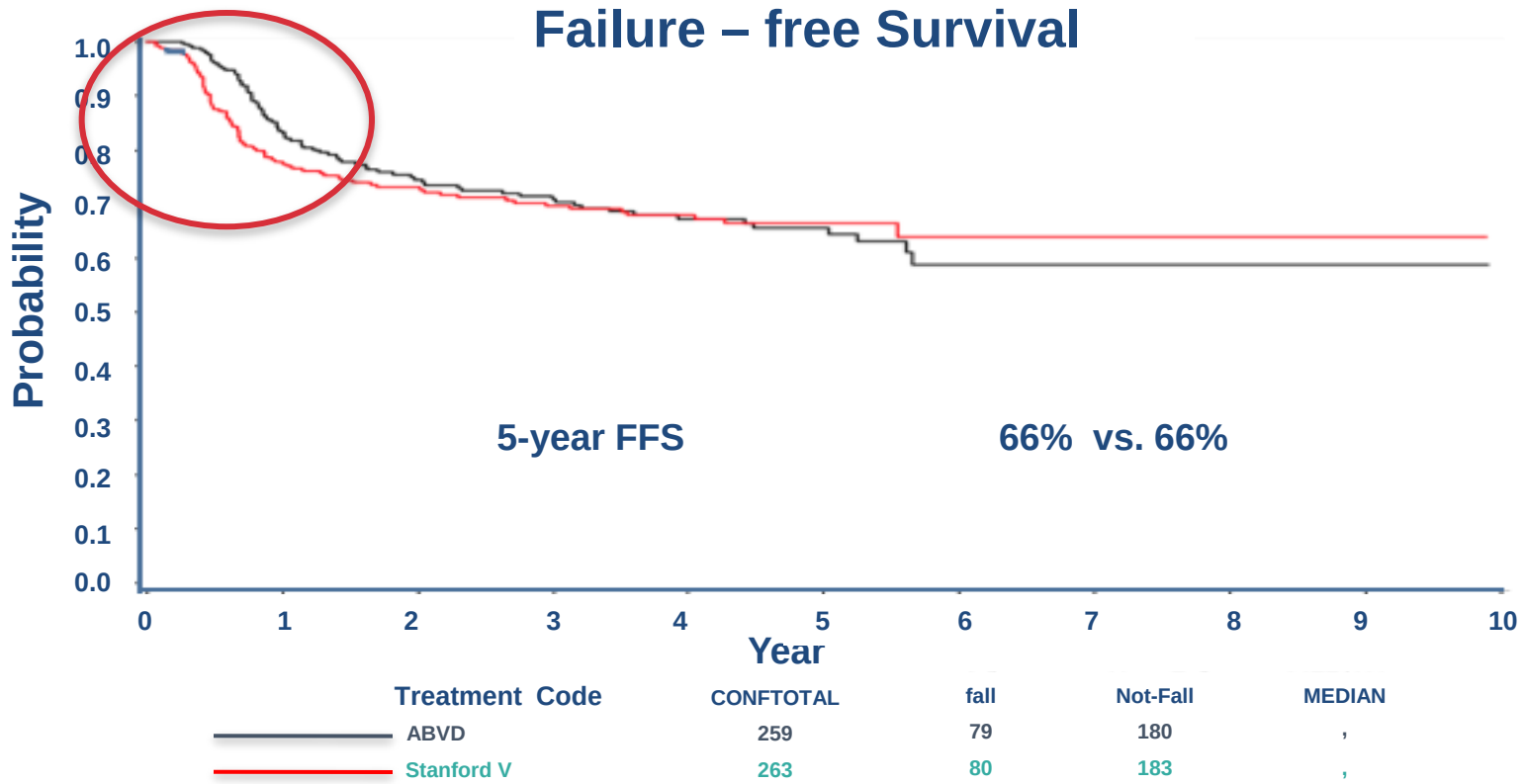


Years after study entry

Canellos G et al NEJM 2002

US Intergroup Trial E2496

ABVD vs Stanford



Gordon et al; JCO 2013

What about ABVD needs improving?

- Bleomycin lung toxicity with ABVD
- Efficacy of ABVD is decreased in certain subgroups
  - In patients with stage III/IV disease, the 5-year FFS is about 65%
  - In patients >60 years, the 5-year FFS is poor
  - In patients with IPS 3-7, the 5-year FFS is about 65%
- Long-term tumour control of 70% not good enough

Improve efficacy!

BEACOPP

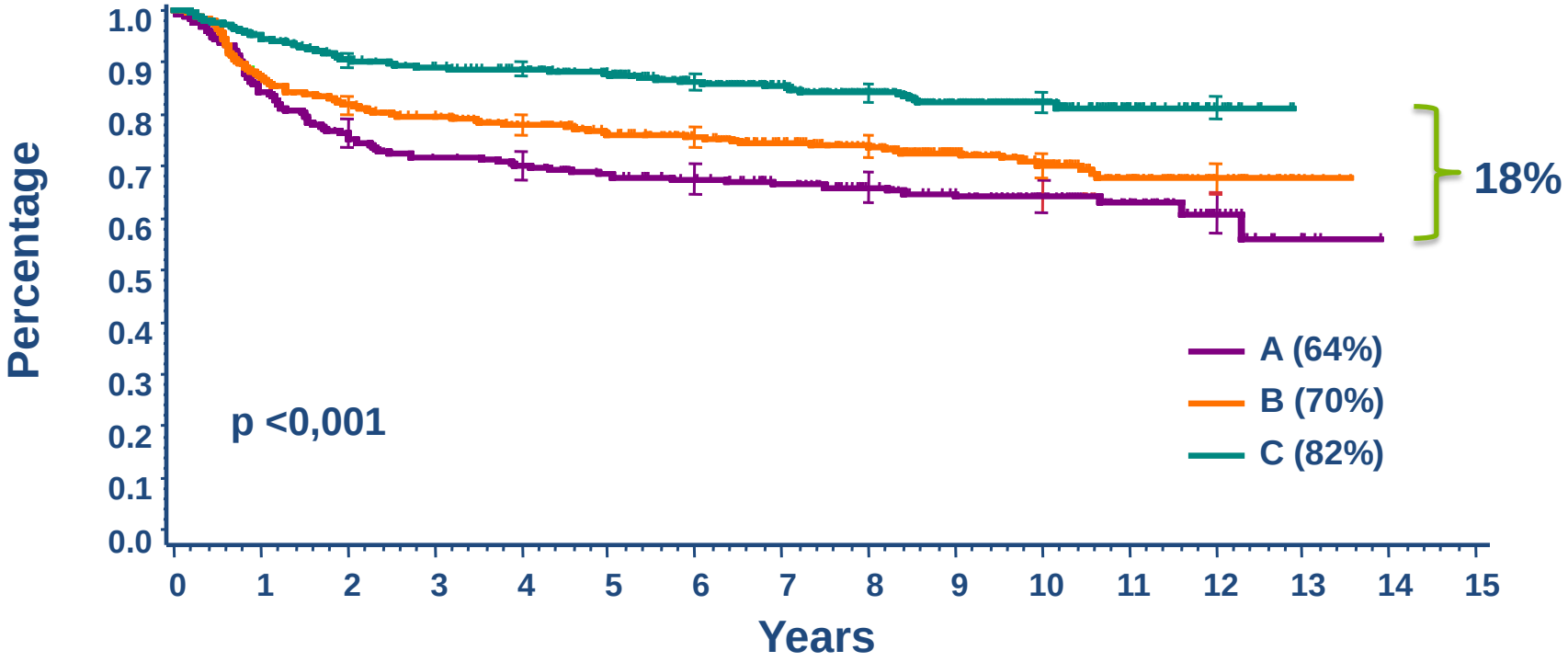
Baseline (base) and escalated (esc)

Drug	base[2]	esc[2]	Route	Schedule
Bleomycin	10	10	iv	8
Etoposide	100	200	iv	1-3
Adriamycin	25	35	iv	1
Cyclophosphamide	650	1250	iv	1
Vincristine	1.4[1]	1.4[1]	iv	8
Procarbazine	100	100	po	1-7
Prednison		40	40	po 1-14
G-CSF	-	+	sc	8-14

[1]max. 2,0mg
[2]mg/m^2

GHSG HD9 trial

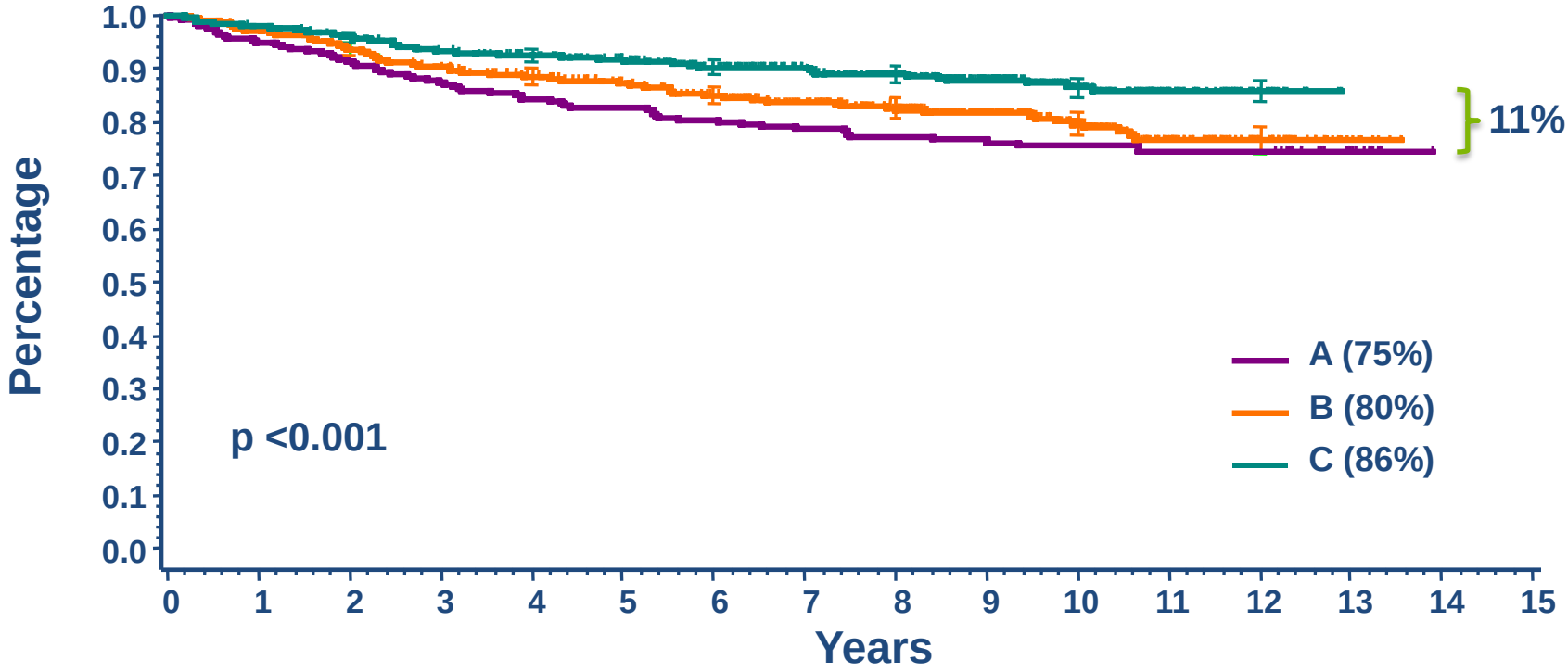
FFTF by treatment arm



Engert A et al, JCO 2009

GHSG HD9 trial

OS by treatment arm



Engert et al; JCO 2009

GHSG HD9 Trial

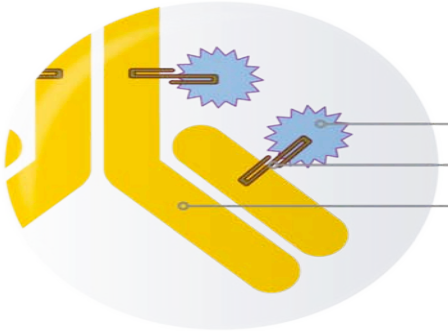
Causes of death at 10 years (% of all pts)

	C/ABVD n=261	BEAbase n=469	BEAesc n=466
HL	11.5	8.1	2.8
Acute tox. (first-line)	1.9	1.5	1.7
Acute tox. (salvage)	1.9	1.5	0.6
Second malignancy	3.1	3.6	3.2
Cardio-respiratory	1.2	0.9	0.9
Pulmonary	0.4	0.4	0.2
Other/unknown	3.8	3.0	2.1
All deaths	25	20	14

Engert et al; JCO 2009

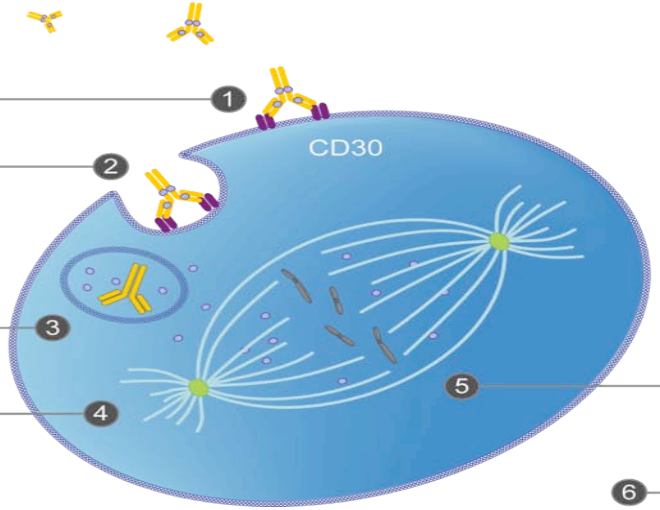
Brentuximab Vedotin

Mechanism of action



Brentuximab vedotin (SGN-35) ADC

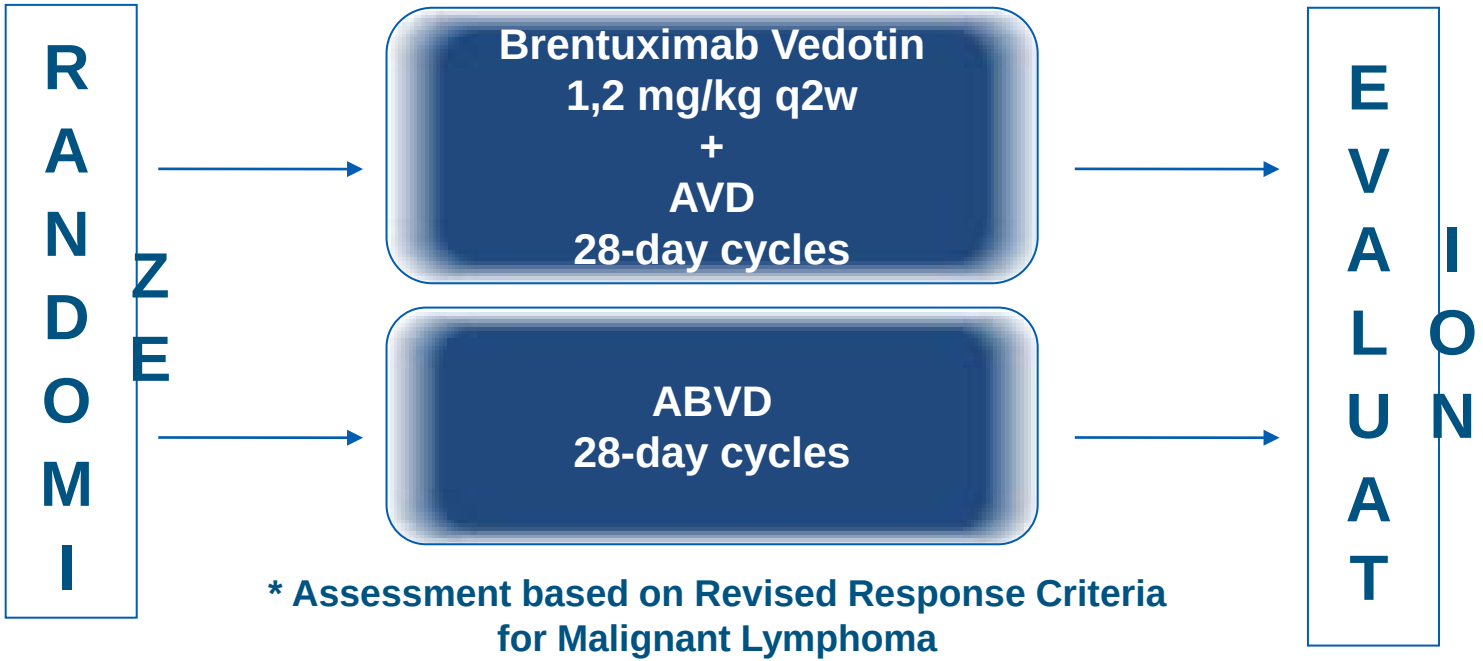
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody



1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts Microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

ECHELON-1: Phase III Trial

BV + AVD vs. ABVD in frontline advanced cHL



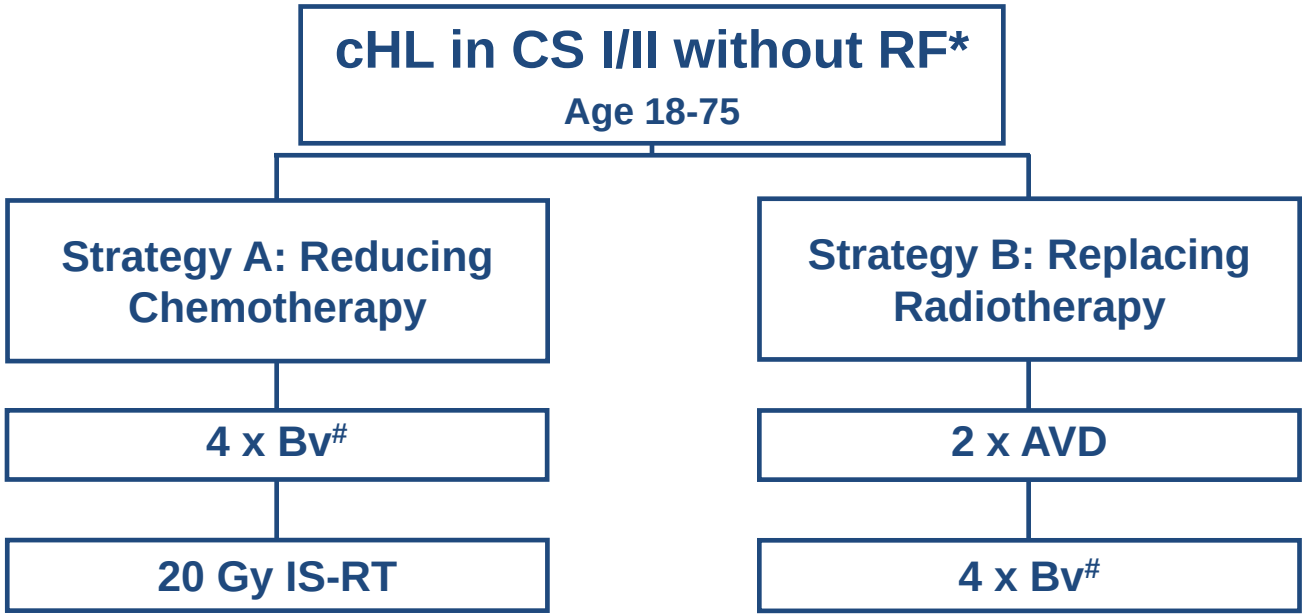
Younes et al, ASCO 2013; Chicago, US (Abstract #TPS8612)

Remodeling BEACOPPesc

Targeted BEACOPP Phase II Trial

Drug	Day	BEACOPP	BrECAPP	BrECADD
Bleomycin	8	10		
Etoposide	**1-3**	**200**	**200**	**150**
Adriamycin	**1**	**35**	**35**	**40**
Cyclophosphamide	**2**	**1250**	**1250**	**1250**
Vincristine	8	1.4		
Brentuximab vedotin	1		**1.8**	**1.8**
Procarbazine	1-7	100	100	
Prednisone	1-14	40	40	
Dacarbazine	**2-3**			**250**
Dexamethasone	**1-4**			**40**
Efficacy index (Hasenclever)			**26.9**	**25.8**

GHSG Phase II trial
in early-stage favorable HL

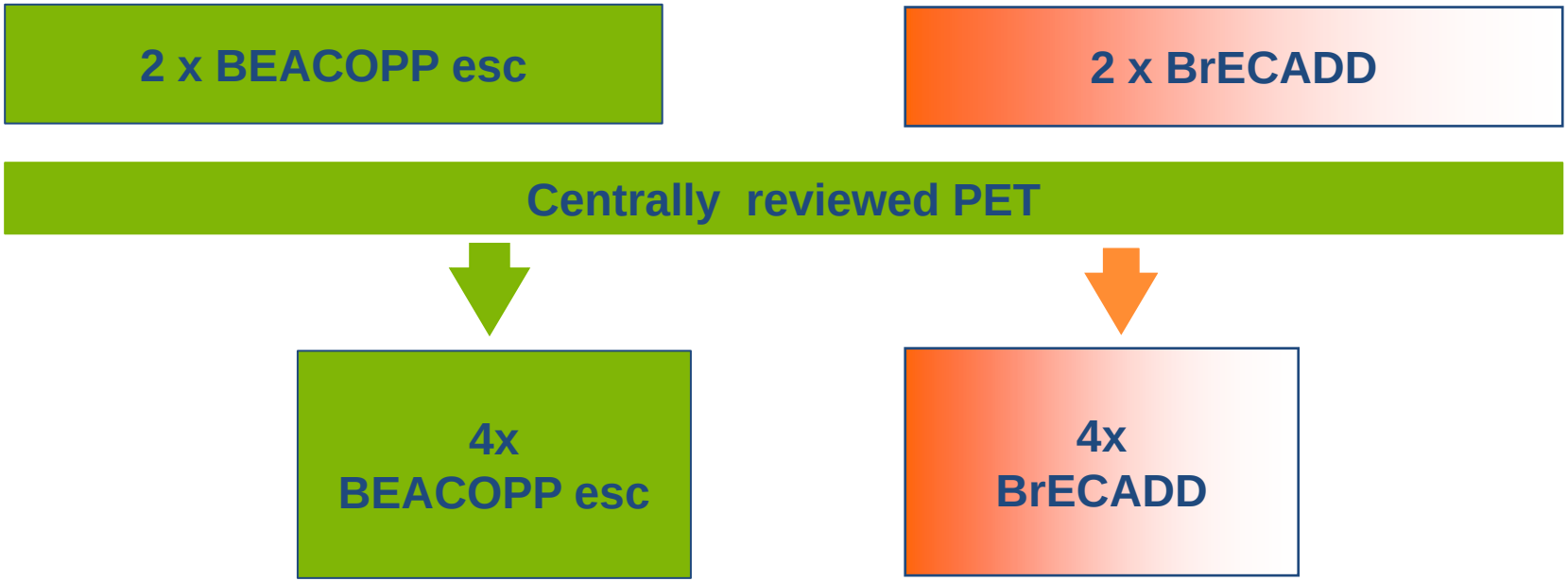


*a) large mediastinal mass b) extranodal disease c) elevated ESR d) ≥3 nodal areas

to be discussed: 1.8 mg/kg every 3 weeks or 1.2 mg/kg every 2 weeks

HD21: GHSG Perspective

BV in advanced stage HL



End of therapy and residual nodes > 2.5 cm:

PET positiv: **Rx**

PET negative: **Follow up**

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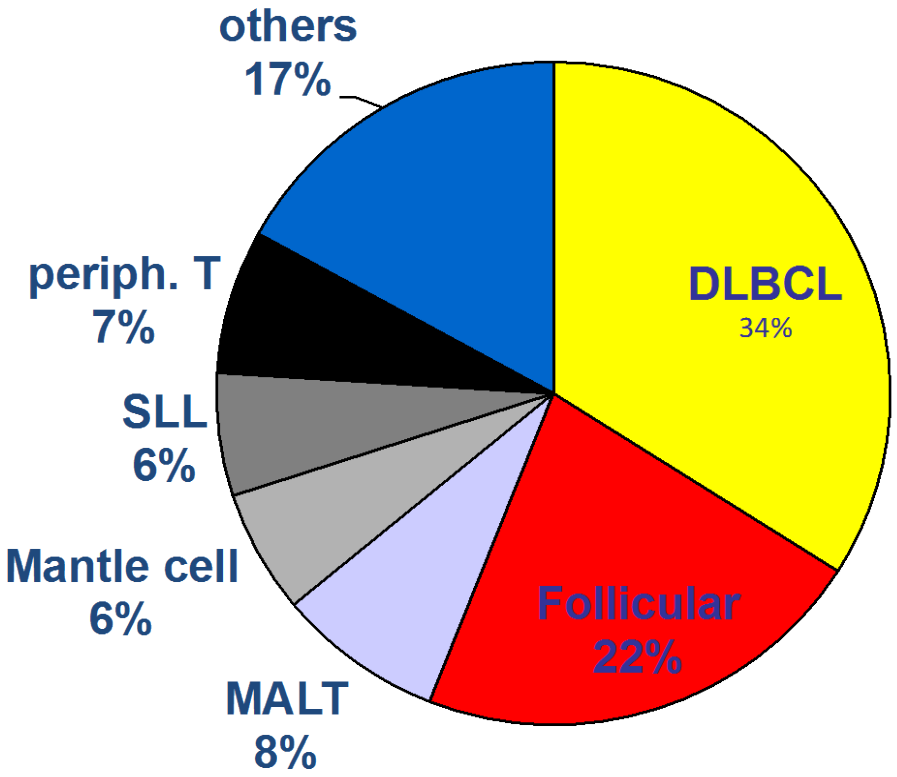
Non Hodgkin lymphoma

Subtypes



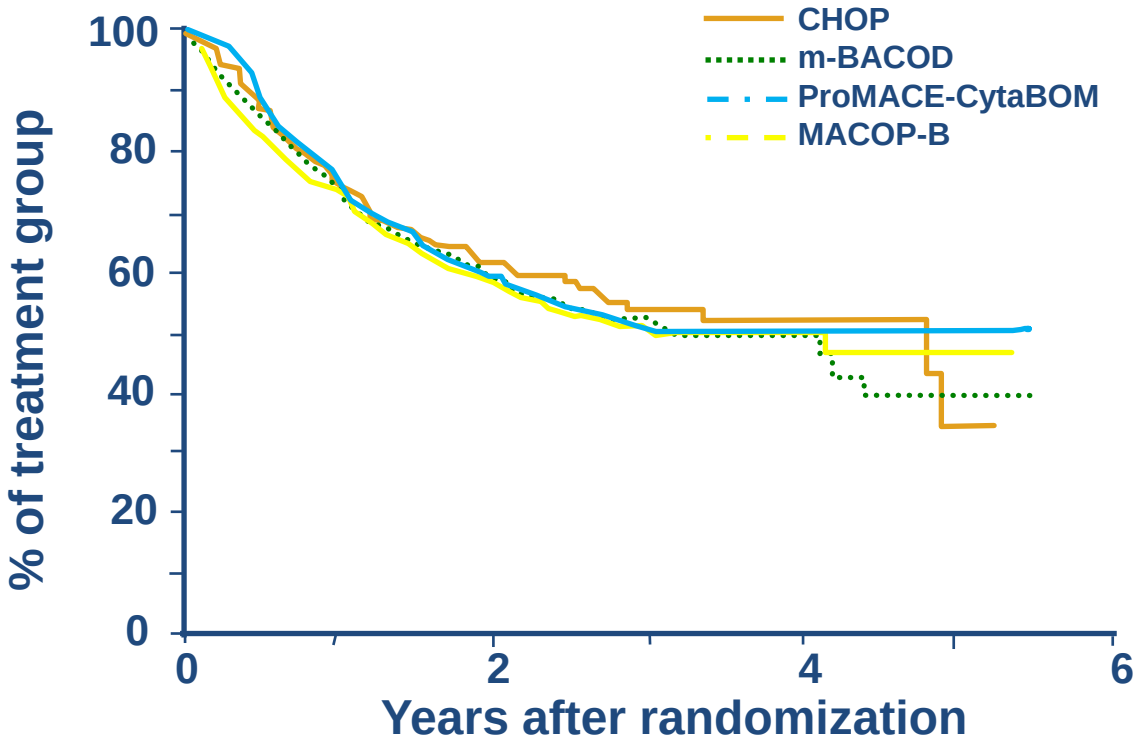
CHOP-21

Combination chemotherapy

(C)yclophosphamid
(H)ydroxydaunorubicin (Doxorubicin)
(O)ncovin®) (Vincristin)
(P)redniso(lo)n

Drug	Dose	Mode	Days
(C)yclophosphamid	750 mg/m^2	iv	1
(H)ydroxydaunorubicin (Doxorubicin)	50 mg/m^2	iv	1
(O)Ncovin® (Vincristin)	1,4 mg/m^2	iv	1
(P)redniso(lo)n	100 mg/m^2	po	1 - 5

SWOG: CHOP *vs* 3 intensive regimens in advanced NHL



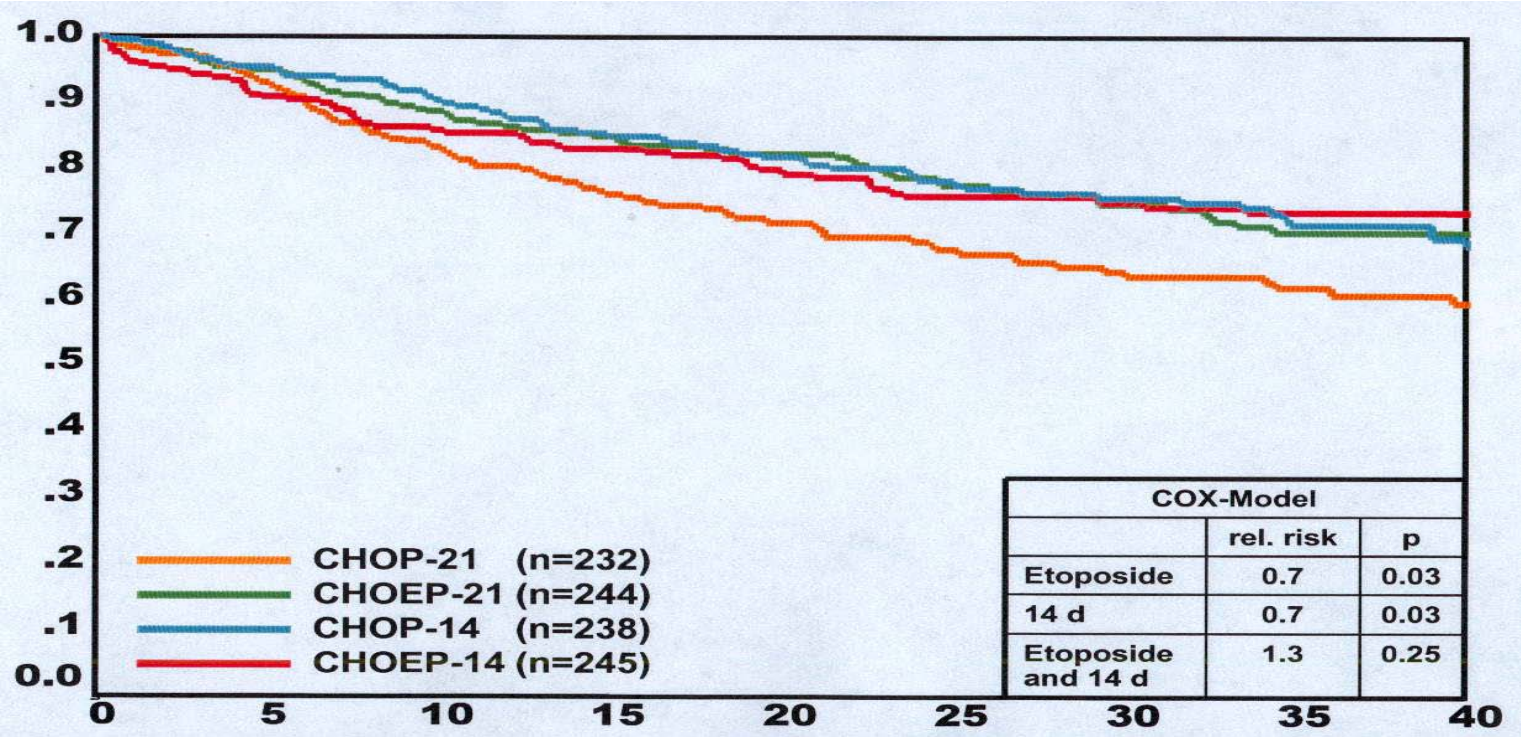
Patients at risk	3-year estimate (%)
225	54
223	52
233	50
218	50

p = 0.90

Fischer *et al.* *NEJM* 1993; 328: 1002–6

NHL-B

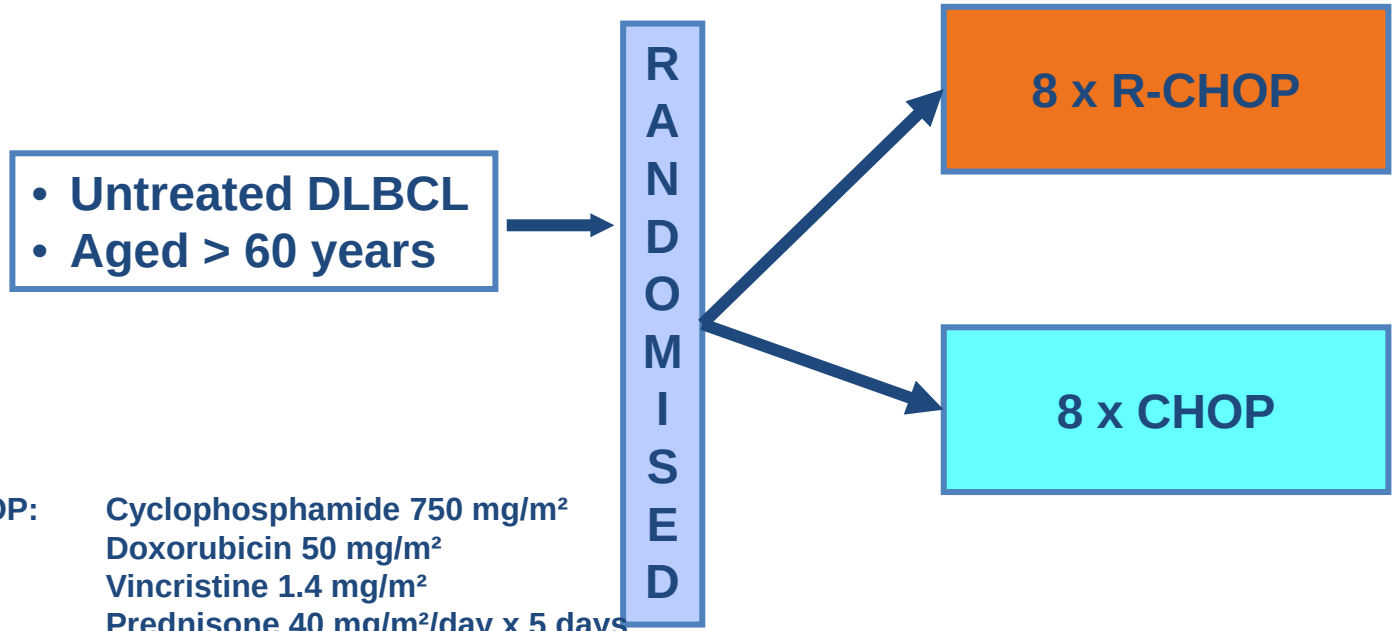
OS of all patients (*n* = 956)



COX-Model		
	rel. risk	p
Etoposide	0.7	0.03
14 d	0.7	0.03
Etoposide and 14 d	1.3	0.25

Pfreundschuh *et al* 2000: unpublished data

GELA LNH-98.5:
Trial design



CHOP: Cyclophosphamide 750 mg/m²
Doxorubicin 50 mg/m²
Vincristine 1.4 mg/m²
Prednisone 40 mg/m²/day x 5 days

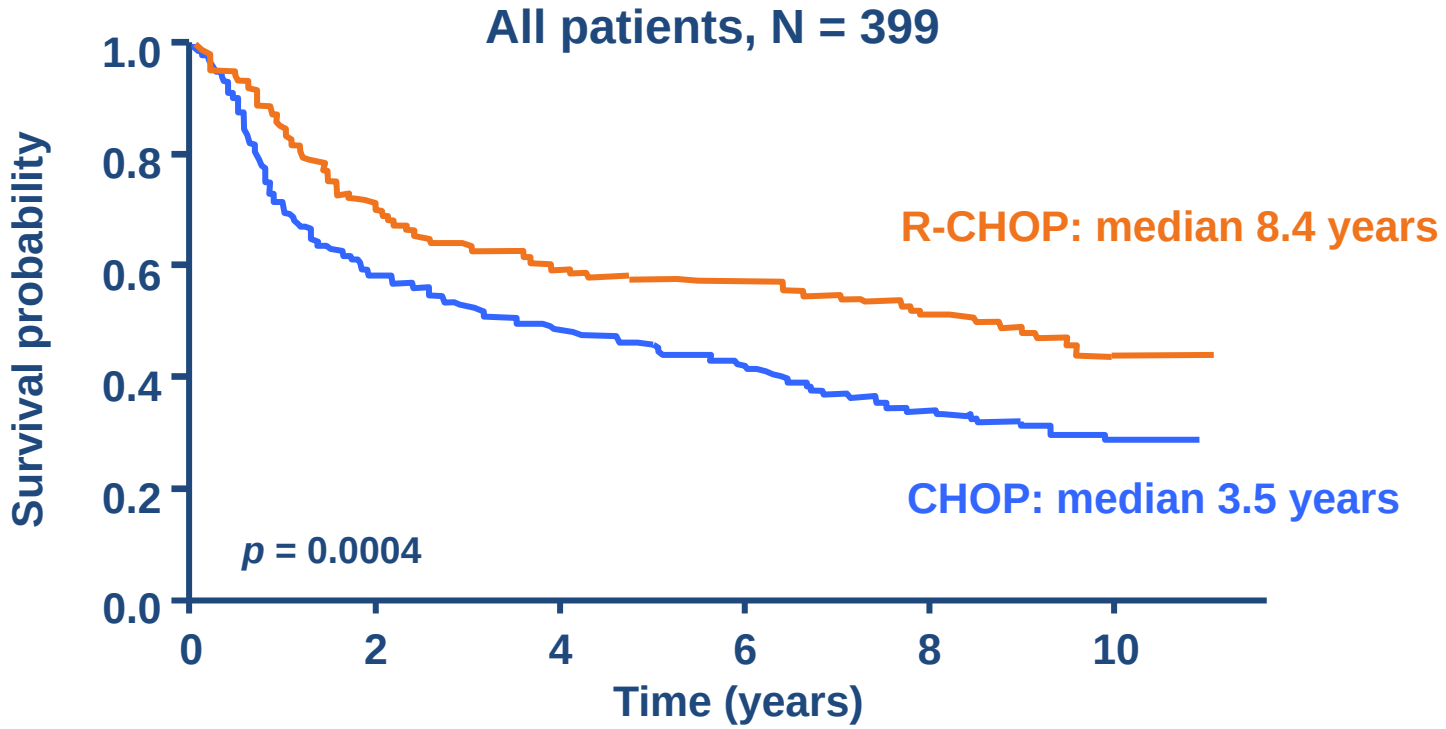
R-CHOP: Rituximab 375 mg/m² Day 1 of each cycle

Cycles every 21 days

Coiffier B, *et al. Blood* 2010; 116:2040–2045.

GELA LNH-98.5 10-year follow-up

Overall survival

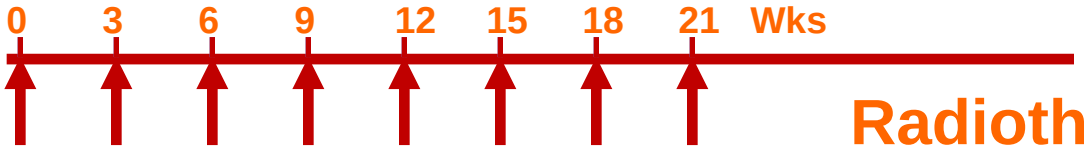


Coiffier B, *et al. Blood* 2010; 116:2040–2045.

Standard Regimen for DLBCL Patients

R-CHOP

R-CHOP 21



Radiotherapy?

Results with R-CHOP in DLBCL

- **5-year survival according to aaIPI & age***
  - **aaIPI score = 0: >85%**
  - **Young, aaIPI score = 1: >80%**
  - **Young, aaIPI score >1: 60%**
  - **Elderly, aaIPI score >0: 50%**
  - **Very old: 30%**
- **For 30-40% of patients, R-CHOP is not satisfactory**

*Poor performance status (ECOG 2-4); Elevated LDH; Stage III or IV

How to further improve DLBCL

- **Refractory**
  - Use new drugs
  - Subgroup of patients with high risk
- **Relapse**
  - Higher dose chemotherapy
  - Prevent relapse
- **At time of relapse**
  - Better salvage regimens

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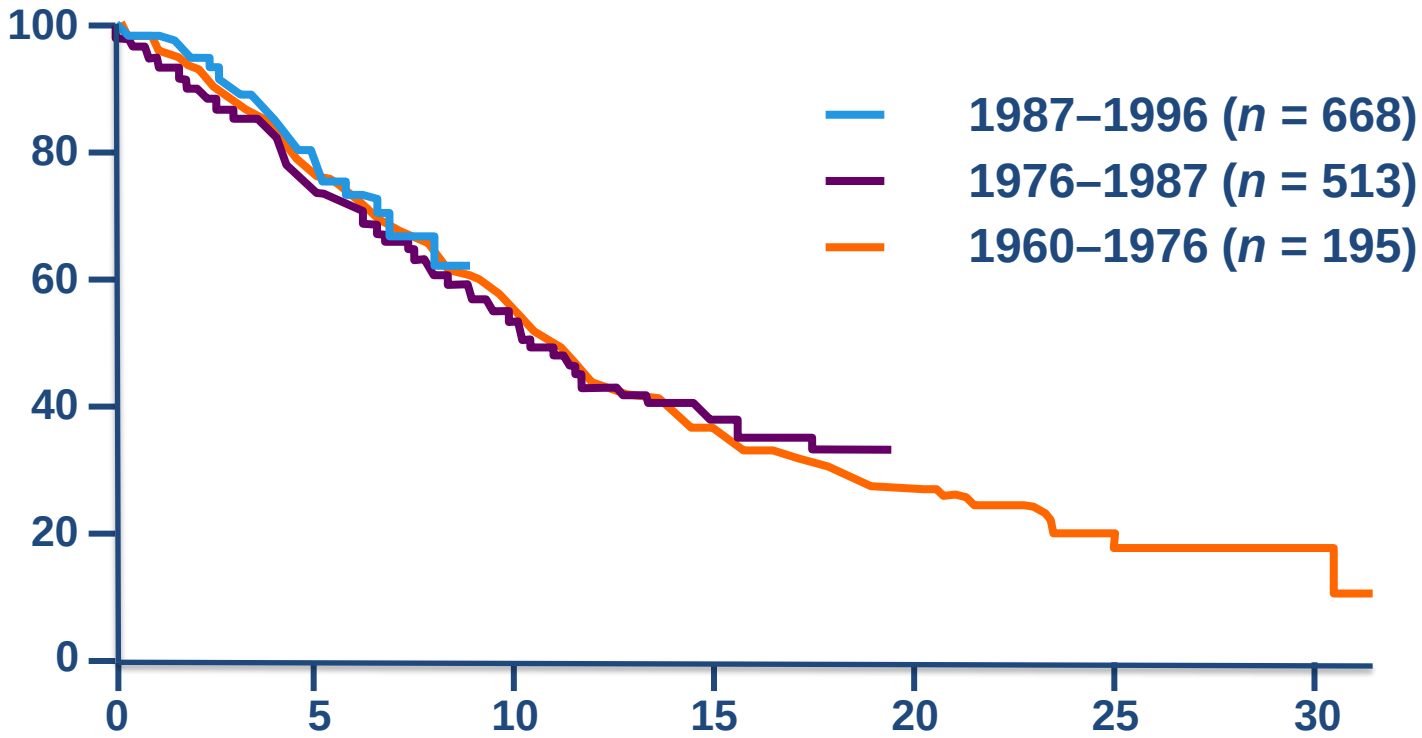
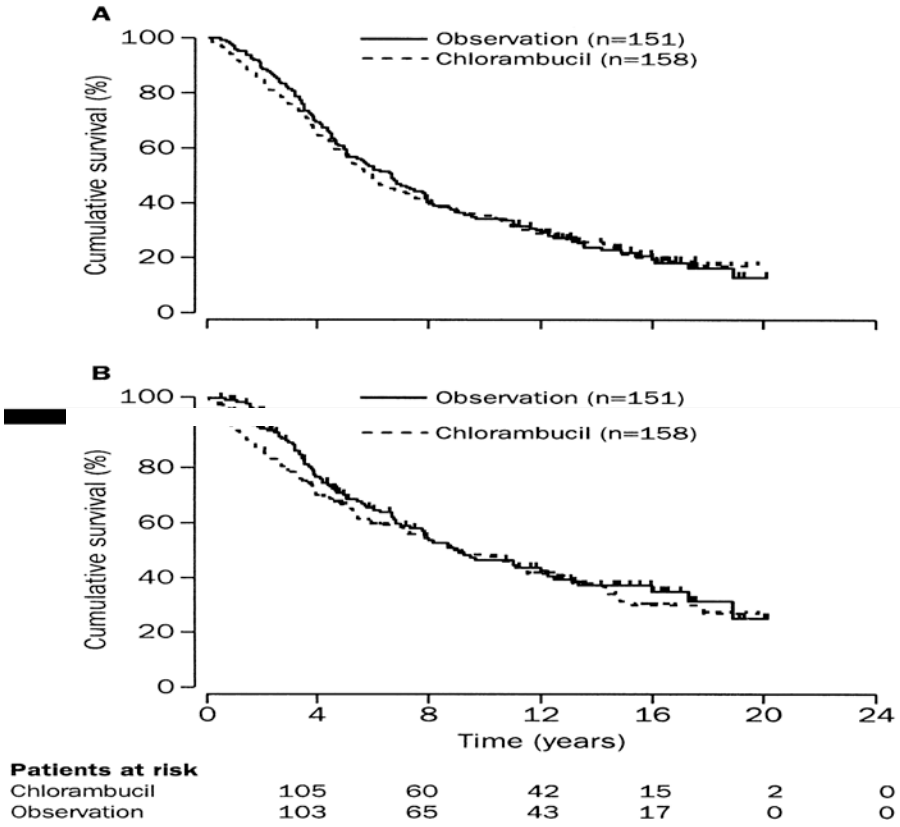
Indolent NHL – Overall Survival



Horning. *Semin Oncol*. 1993; 20(suppl 5): 75–88

FL: Watch & wait or early treatment?



Overall survival

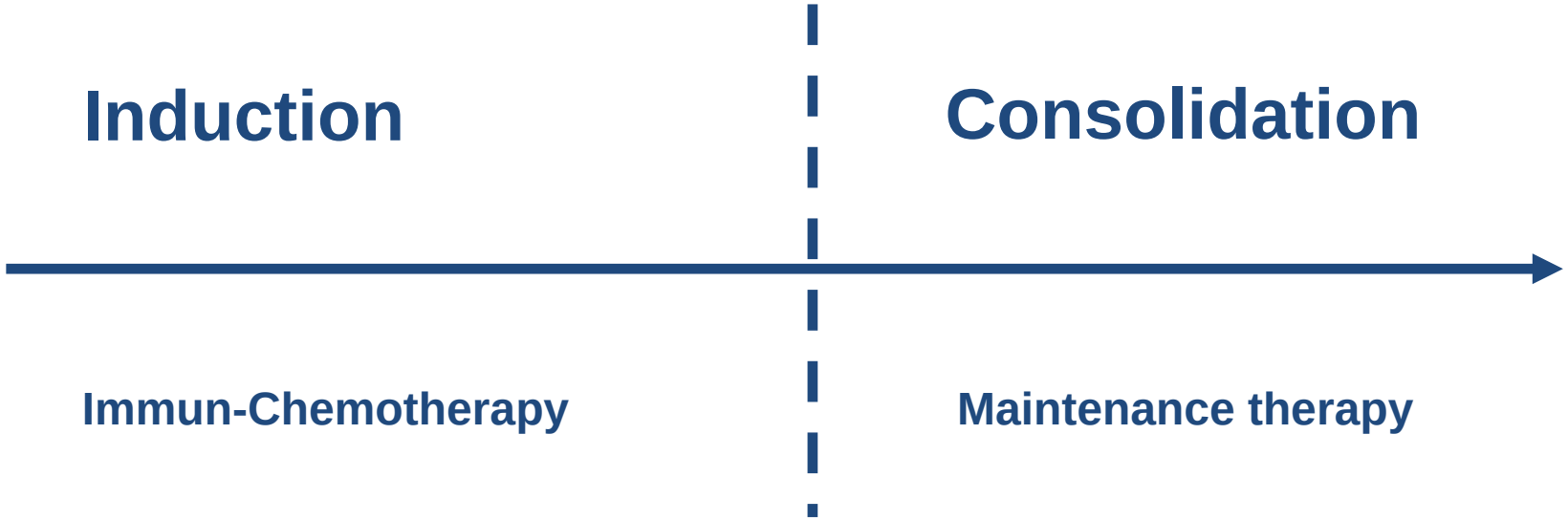
Disease-associated survival

Ardeshna KM et al. Lancet 262: 516, 2003

FL: Clinical Symptoms trigger Treatment

- **B-symptoms**
- **Hematopoietic failure**
  (Hb<11g/dl, granulocytes <1.500/µl, platelets <100.000 /µl)
- **Large tumor burden**
  (3 areas >5 cm or 1 area >7.5 cm)
- **Rapid progression**
  (increase of tumor mass >50% within 6 months)
- **Complications due to disease**
  (pain, infarction of spleen, hyperviscosity syndrome, etc.)
- **No role for FLIPI, LDH, B2M, age, stage, or bone marrow involvement**

Treatment Strategies in indolent Lymphoma



Standard of Care in Pts with indolent Lymphoma

- Still a role for watch & wait in asymptomatic pts
- Wait for indication of treatment
- Combined R-chemo standard; R-CHOP most often used
- No clear superiority of R-CHOP over R-CVP
- BR with longer PFS and lower toxicity
- R-chemo plus R-maintenance current best option in follicular particularly in relapsed disease
- No relevant role for high-dose chemo and ASCT
- Perspectives: Bortezomib, Lenalidomide, Obinutuzumab (GA101), Ofatumumab, Temsirolimus, Ibrutinib, Idelalisib, ABT-199

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Chemotherapy of malignant lymphoma

- Development of multi-agent chemo led to cure in lymphoma patients
- Most frequently used today are CHOP, ABVD and BEACOPP
- Typical side effects include alopecia, aplasia, infection, neuropathy, fatigue and infertility
- Major long-term effects are 2nd neoplasia and organ failure
- Prognosis of pts much worse at relapse (DLBCL, HL)
- New less toxic drugs have become available and might improve the long-term prognosis


Save The Date * Gürzenich, Cologne
October
22–25
2016
ISHL 10
www.hodgkinsymposium.org
GHSG
www.ghsg.org

Aggressive NHL:
Prognostic factors - aaIPI

- Poor performance status (ECOG 2-4)
- Elevated lactate dehydrogenase (LDH)
- Stage III or IV disease

- **Risk groups:**
  - 0 : low risk
  - 1 : low-intermediate
  - 2 : high-intermediate
  - 3 : high risk

The International Non-Hodgkin's Lymphoma Prognostic Factors Project
N Engl J Med 1993; 329:987–994.

WWW.ESTRO.ORG/SCHOOL

Treatment of advanced stage Hodgkin lymphoma

Andreas Engert, MD

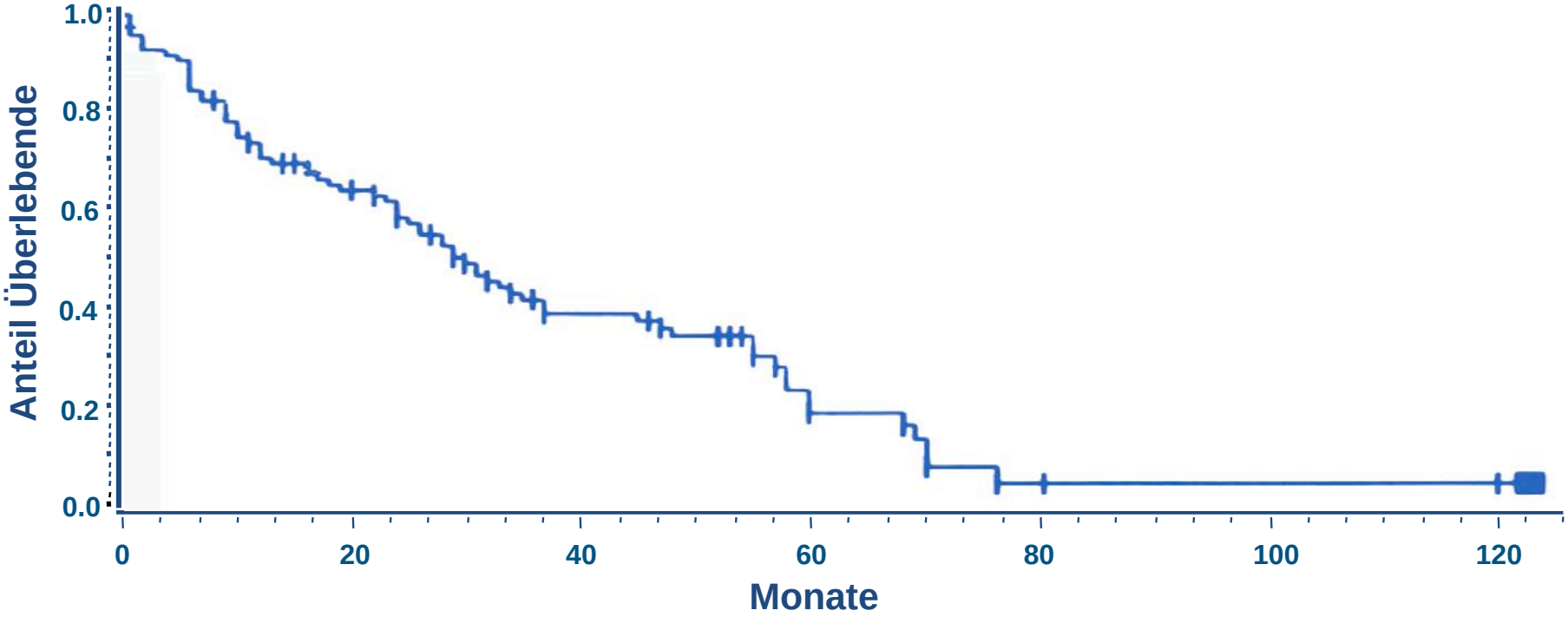
Chairman, German Hodgkin Study Group
University Hospital of Cologne

Treatment of advanced stage HL

- Background
- Conventional Chemo
- PET-driven trials
- Summary

Hodgkin Lymphom – Historische Prognose

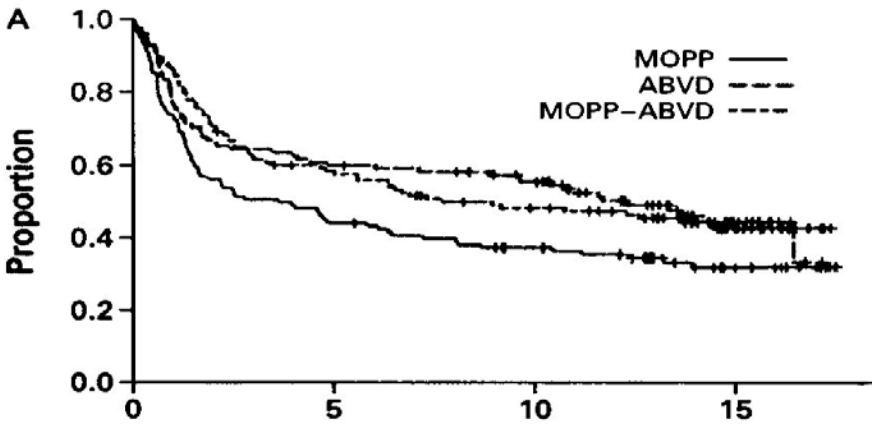
Überleben von Hodgkin-Patienten in Köln 1960 bis 1967
Alle Stadien, n=109



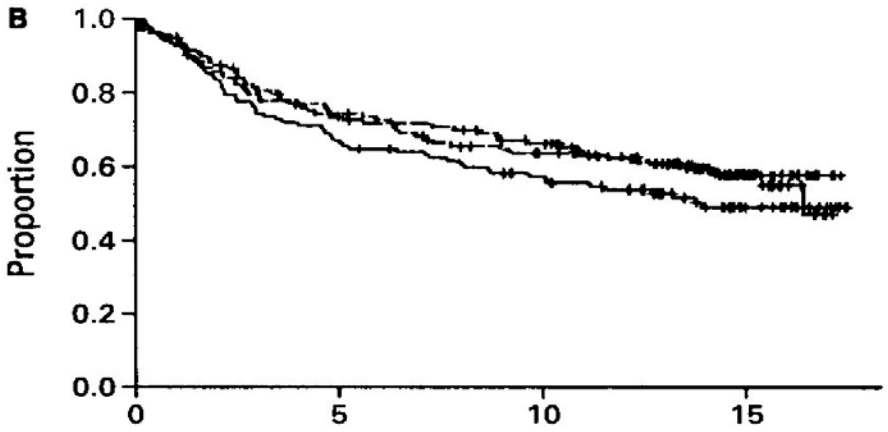
Long-term Results of HL

Patients in advanced Stages

FFTF



OS

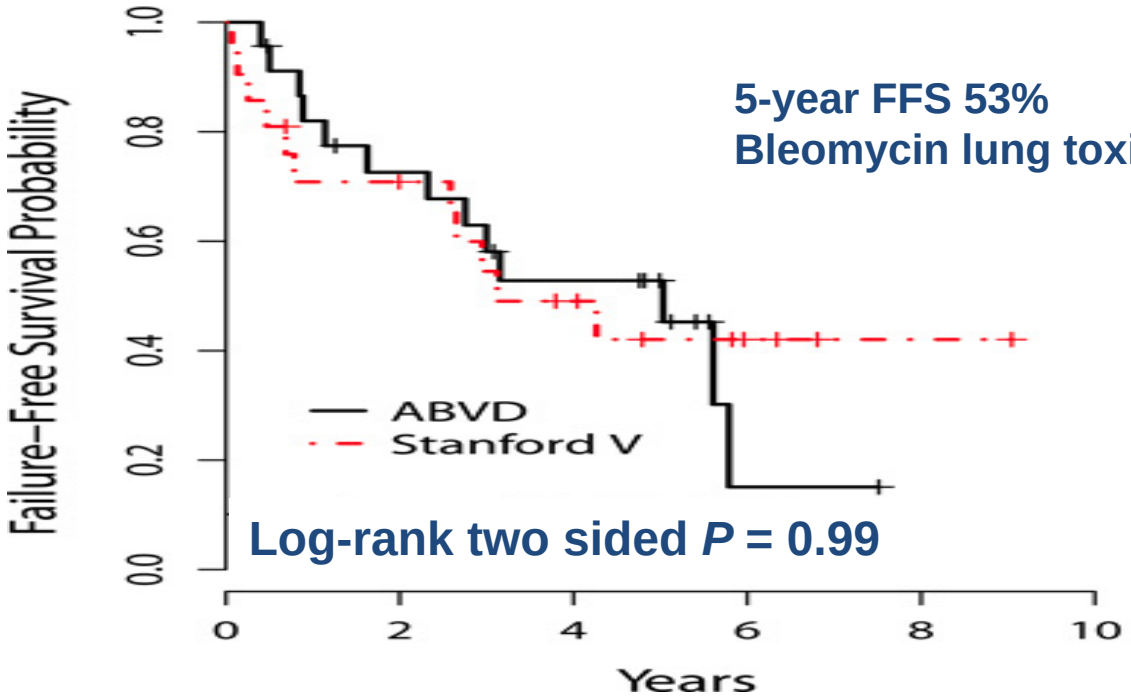


Years after study entry

Canellos et al NEJM 2002

Efficacy and Tolerability of ABVD

HL patients >60y (E2496; n=45)



5-year FFS 53%
Bleomycin lung toxicity in 24% (18% died)

Evens AM, Br J Haematol; 2013;161(1):76-86

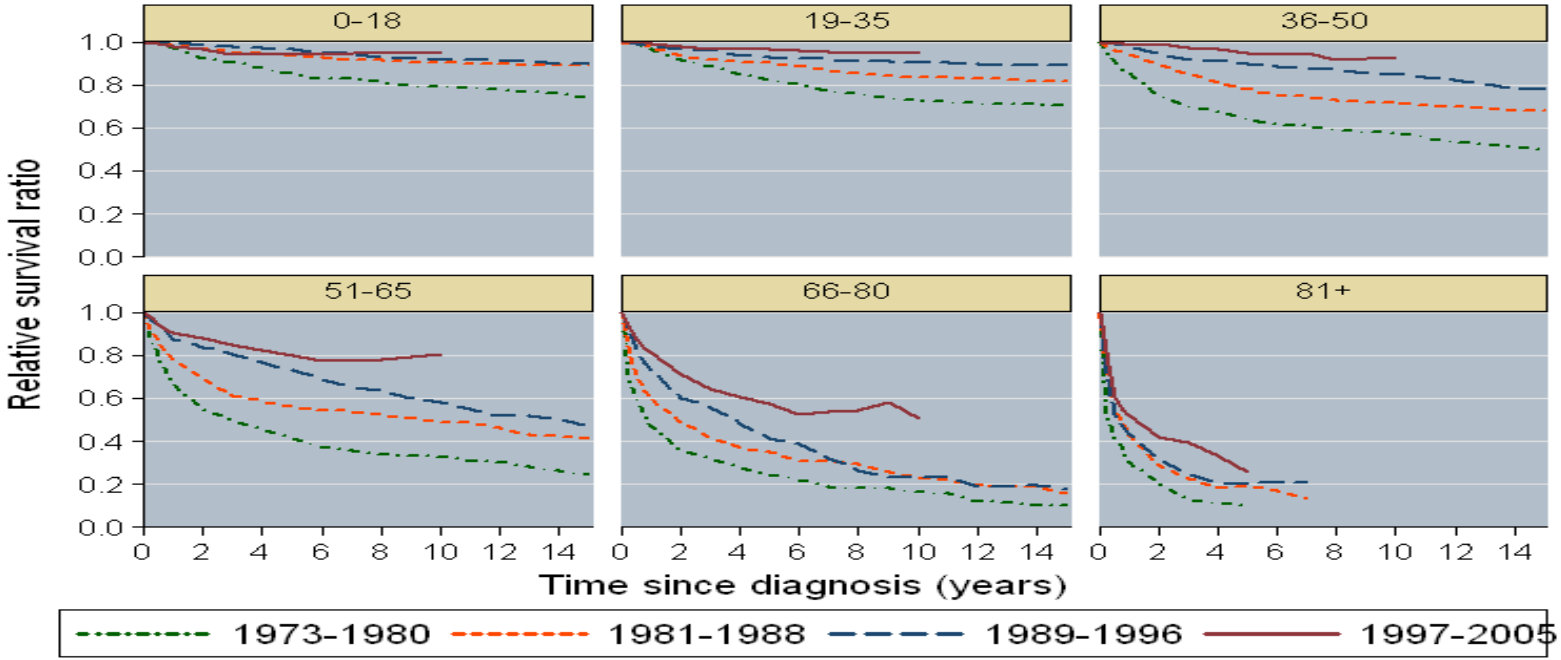
Hodgkin Lymphoma

Late side effects after treatment

- **2nd NPL**
  - **AML**
  - **NHL**
  - **Solid tumours**
- **Organ damage**
  - **Lung**
  - **Heart**
  - **Thyroid**
- **Others**
  - **Fertility**
  - **Fatigue**
  - **Psycho-social**

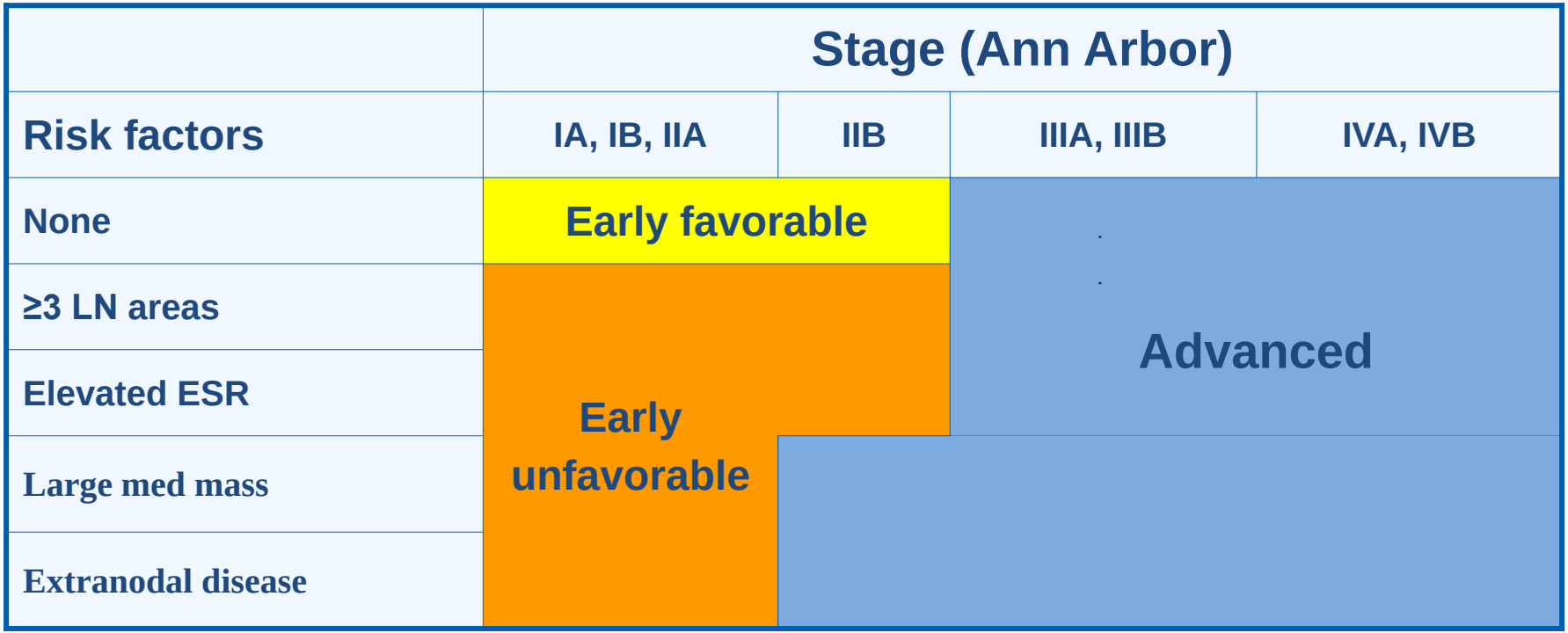
Hodgkin Lymphoma

Cumulative relative survival of HL pts in Sweden



Courtesy of Magnus Björkholm 2010

GHSG Risk Allocation for HL Patients



GHSG 2000

Treatment of advanced stage HL

- Background
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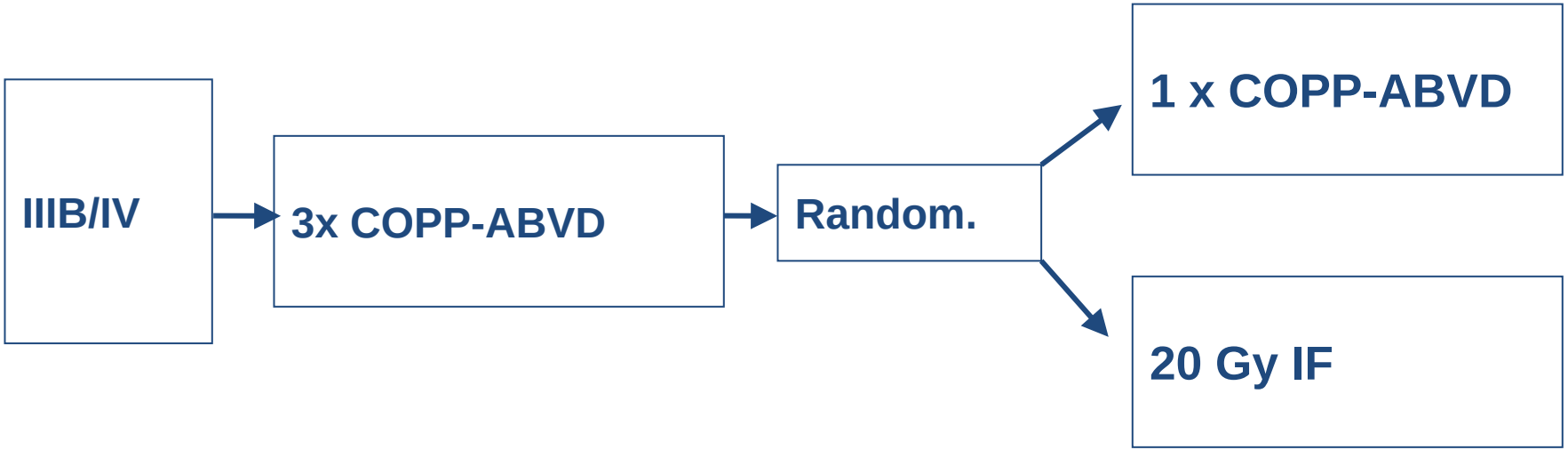
GHSG HD-3 Study

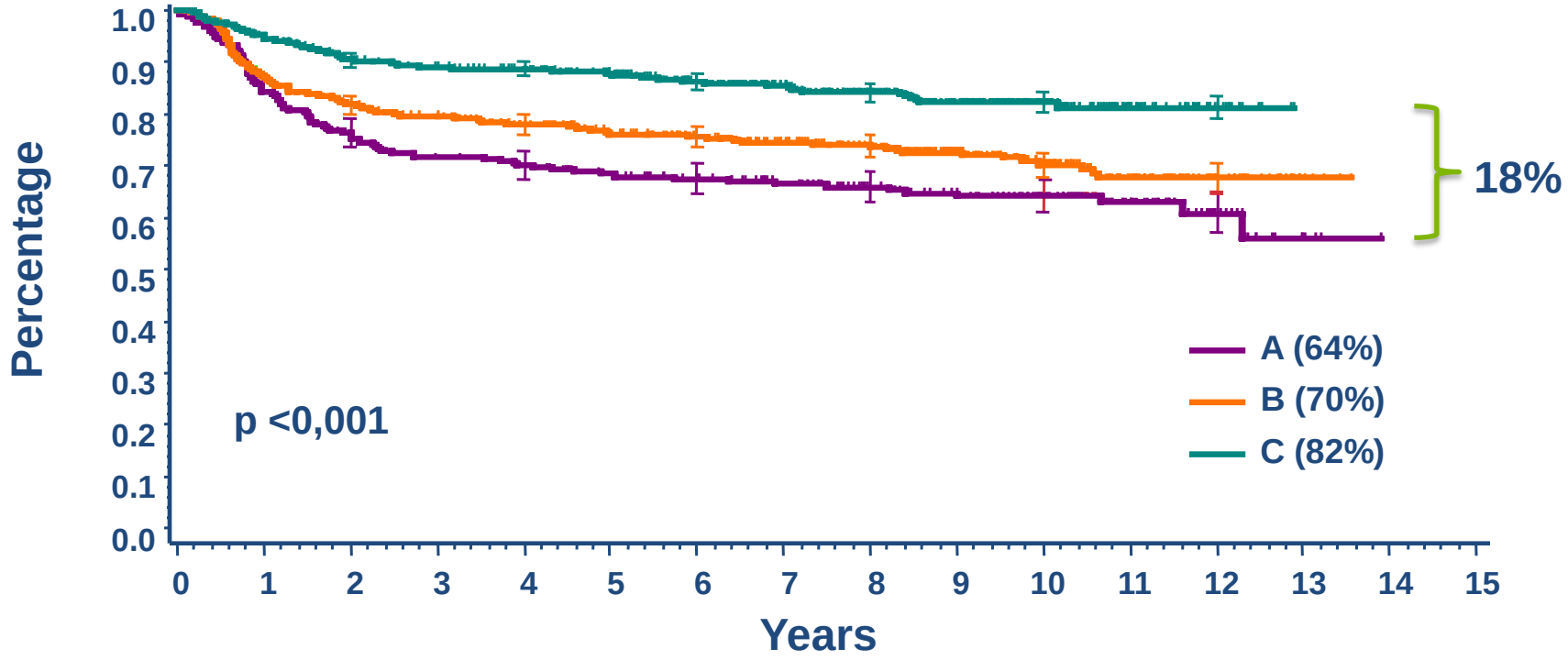
Design



Recruited 199 pts (1982-88)

GHSG HD9 trial

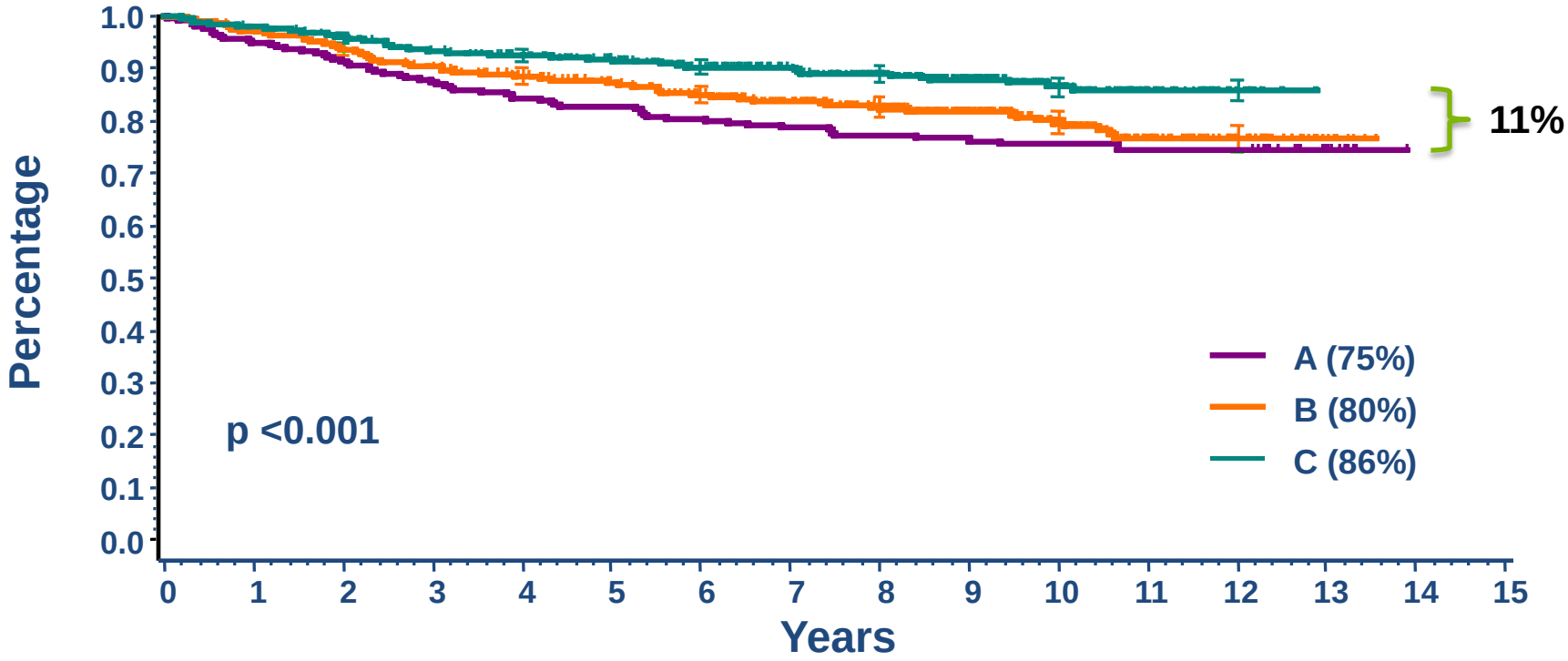
FFTF by treatment arm



Engert A et al, JCO 2009

GHSG HD9 trial

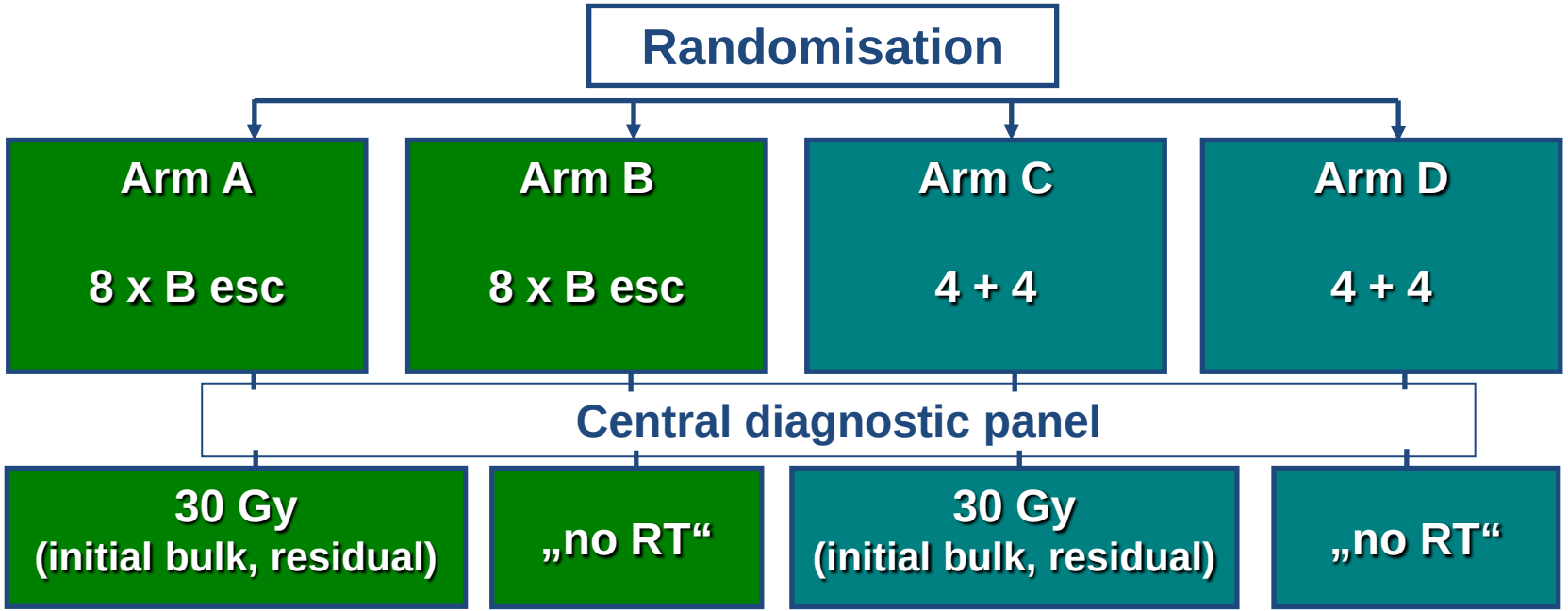
OS by treatment arm



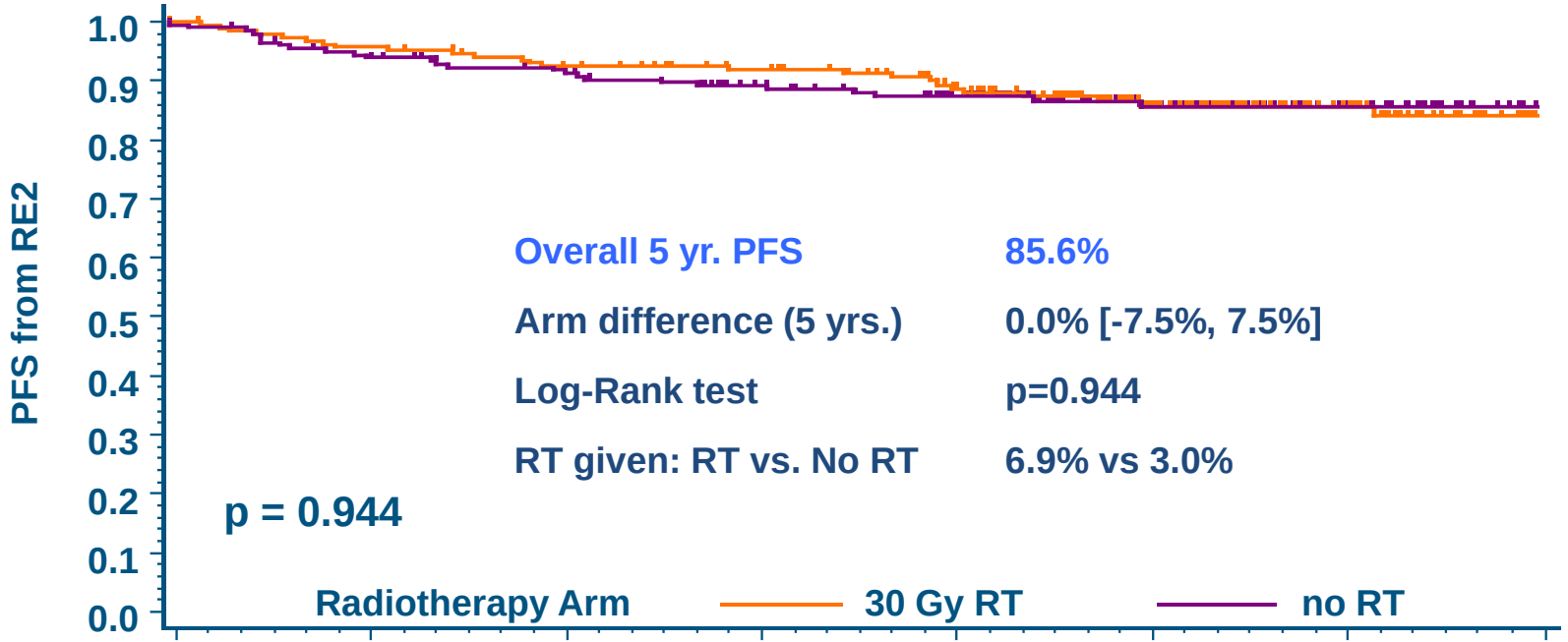
Engert et al; JCO 2009

HD12 trial design for advanced stages

De-escalation of RT possible?

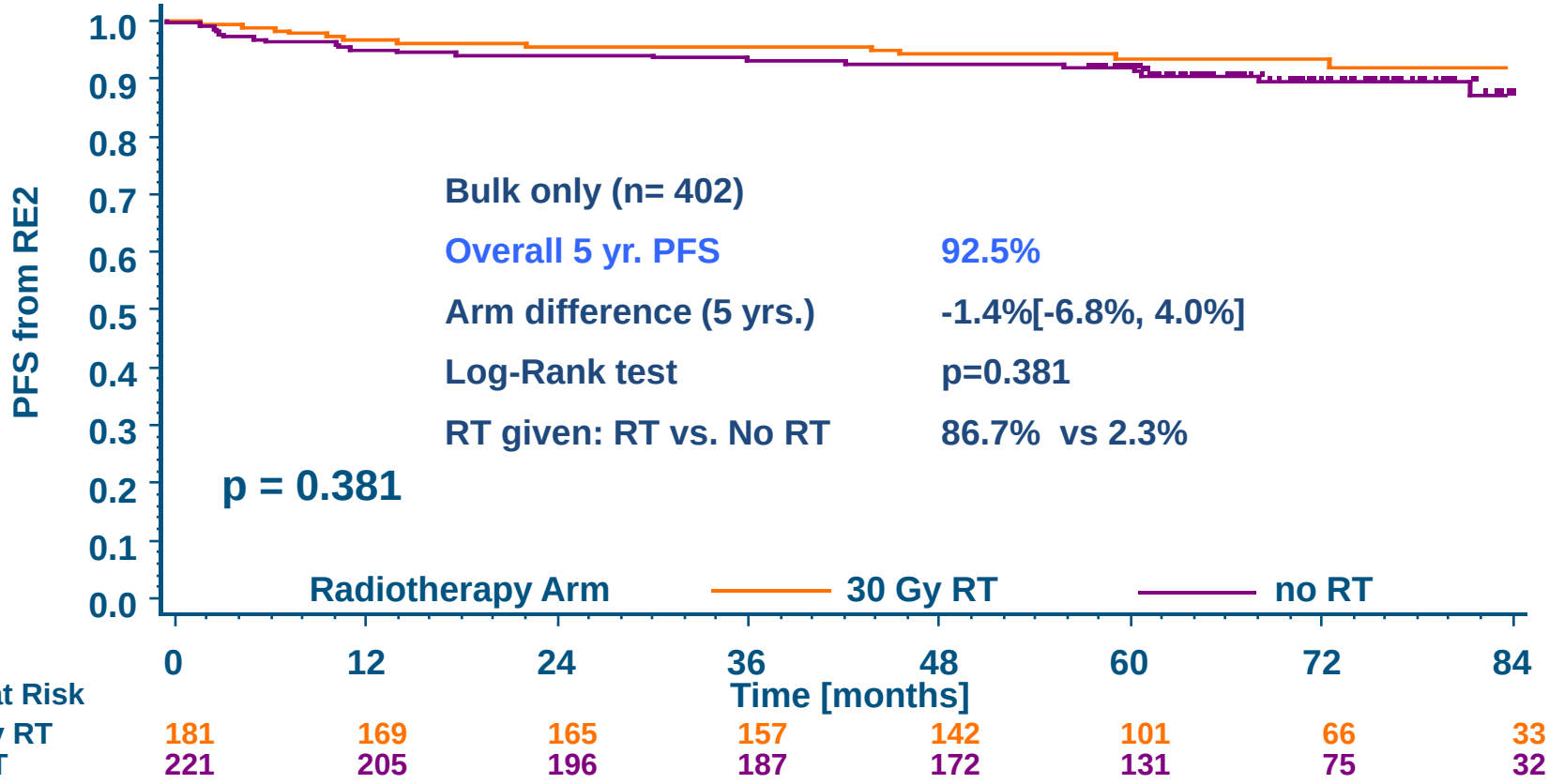


HD12 pts with no bulk and no rest (PFS n=388)

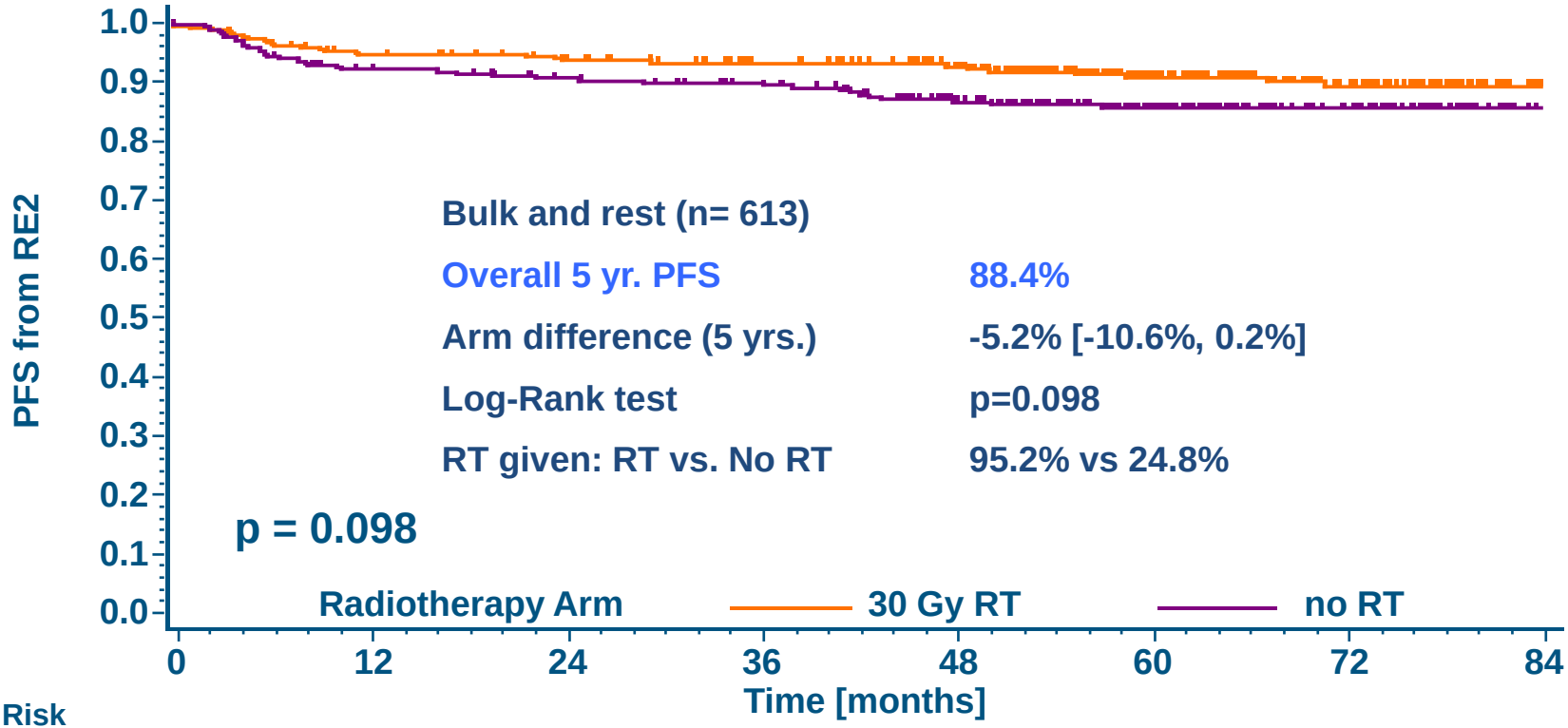


Pts. at Risk								
30 Gy RT	188	177	168	158	139	94	55	20
no RT	200	184	173	155	138	94	53	24

HD12 patients with bulk only (PFS; n=402)



HD12 pts with bulk and rest (PFS n=613)



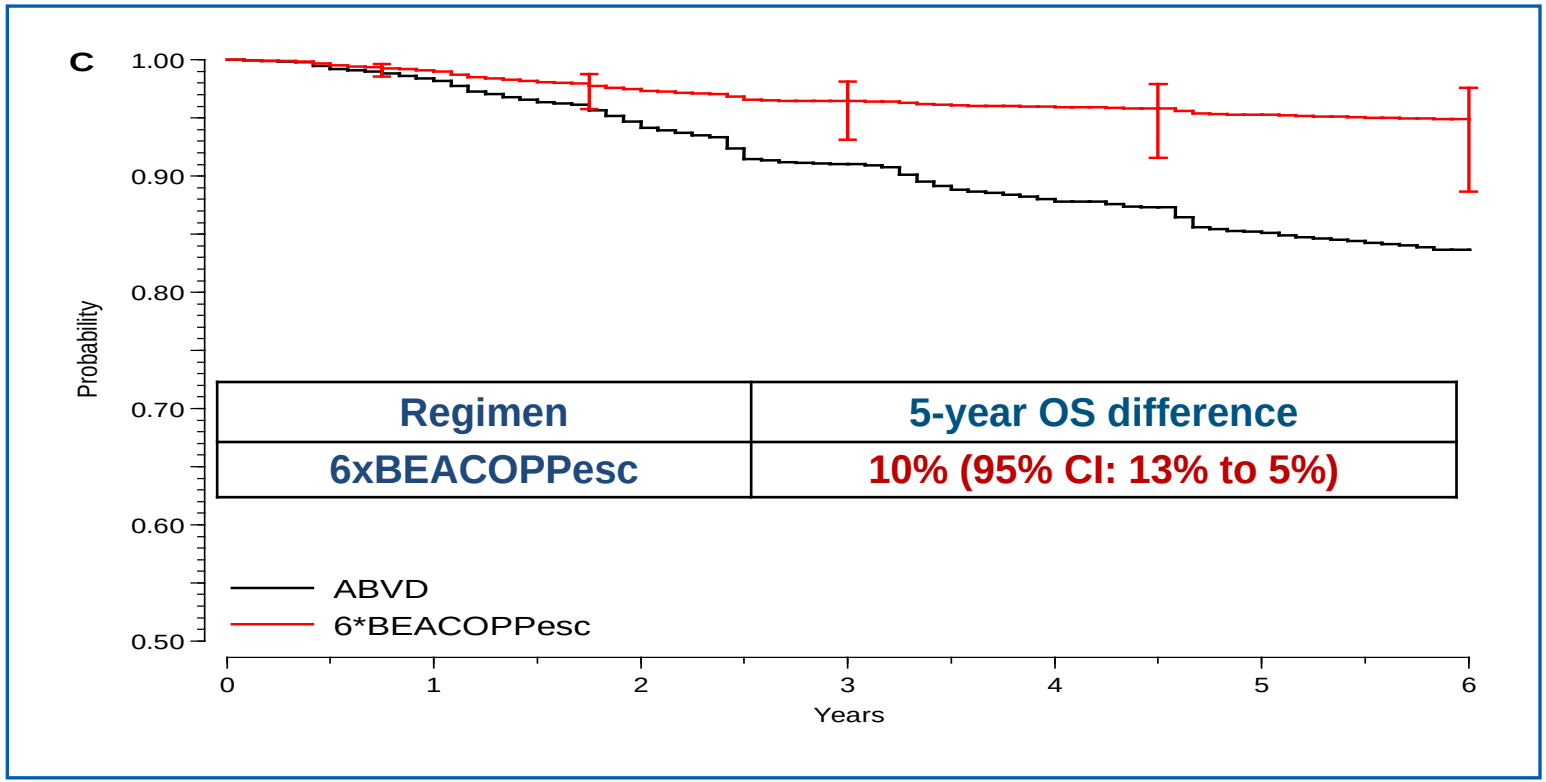
Pts. at Risk								
30 Gy RT	331	305	294	274	250	175	105	42
no RT	282	250	239	230	198	142	85	38

Direct comparison of
ABVD and BEACOPP variants

Treatment	5-y PFS	Diff. (%)	5-y OS	Diff. (%)	Reference
ABVD	68	13	84	8	Federico, JCO 2009
4 + 2	81		92		
ABVD	73	12	84	5	Viviani, NEJM 2011
4 + 4	85		89		
ABVD	69	15	87	4	Carde, ASCO 2012
4 + 4	84		90		
ABVD	75	18	92	7	Mounier, ISHL9 2013
4 + 4	93		99		

Reconstructed individual OS

ABVD versus 6xBEACOPPesc



Regimen	5-year OS difference
6xBEACOPPesc	10% (95% CI: 13% to 5%)

Skoetz et al, Lancet Oncol. 2013

TRM of BEACOPP escalated*

Multivariate model

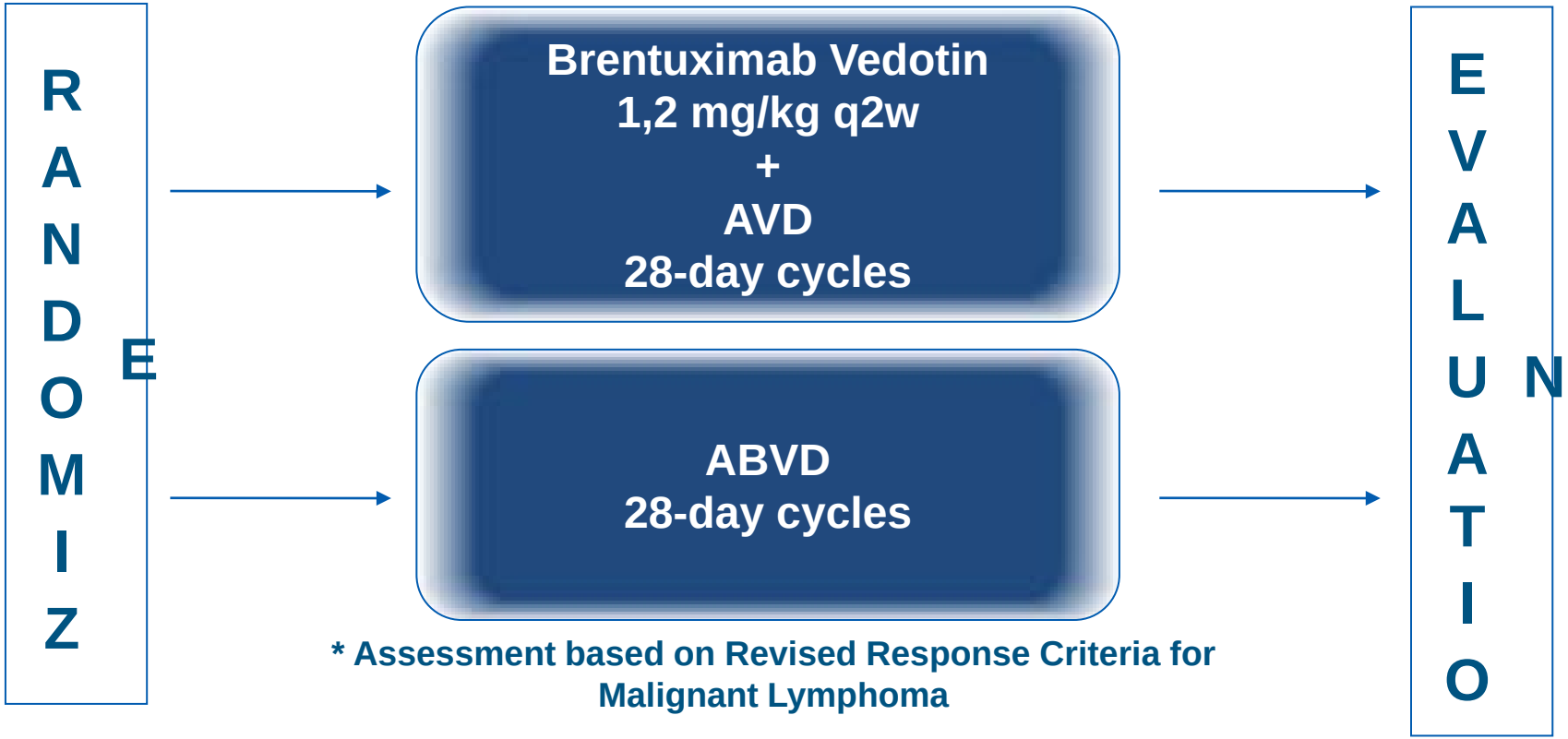
Age≥40	Age≥50	ECOG 2 or Karn.<80	Patients	TRM rate
-	-	-	2156	0.7
+	-	-	590	1.7
-	-	+	108	0.9
+	+	-	445	5.6
+	-	+	40	13.3
+	+	+	45	15.0

*Pts treated in HD9, 12, 15 (64/3565; 1.9%)

Wongso et al, JCO 2013

ECHELON-1: Phase III Trial

BV + AVD vs. ABVD in frontline advanced cHL



* Assessment based on Revised Response Criteria for Malignant Lymphoma

Younes et al, ASCO 2013; Chicago, US (Abstract #TPS8612)

BV: Increased Pulmonary Toxicity

Phase I Combination of BV and ABVD

Preferred term	ABVD with Brentuximab vedotin N=25	AVD with Brentuximab vedotin N=26
Any event	11 (44)	0
Pulmonary toxicity	9 (36)	0
Interstitial lung disease	1 (4)	0
Pneumonitis	1 (4)	0

Ansell S et al. presented at ASH 2012, San Diego, USA

Treatment of advanced stage HL

- Background
- Conventional Chemo
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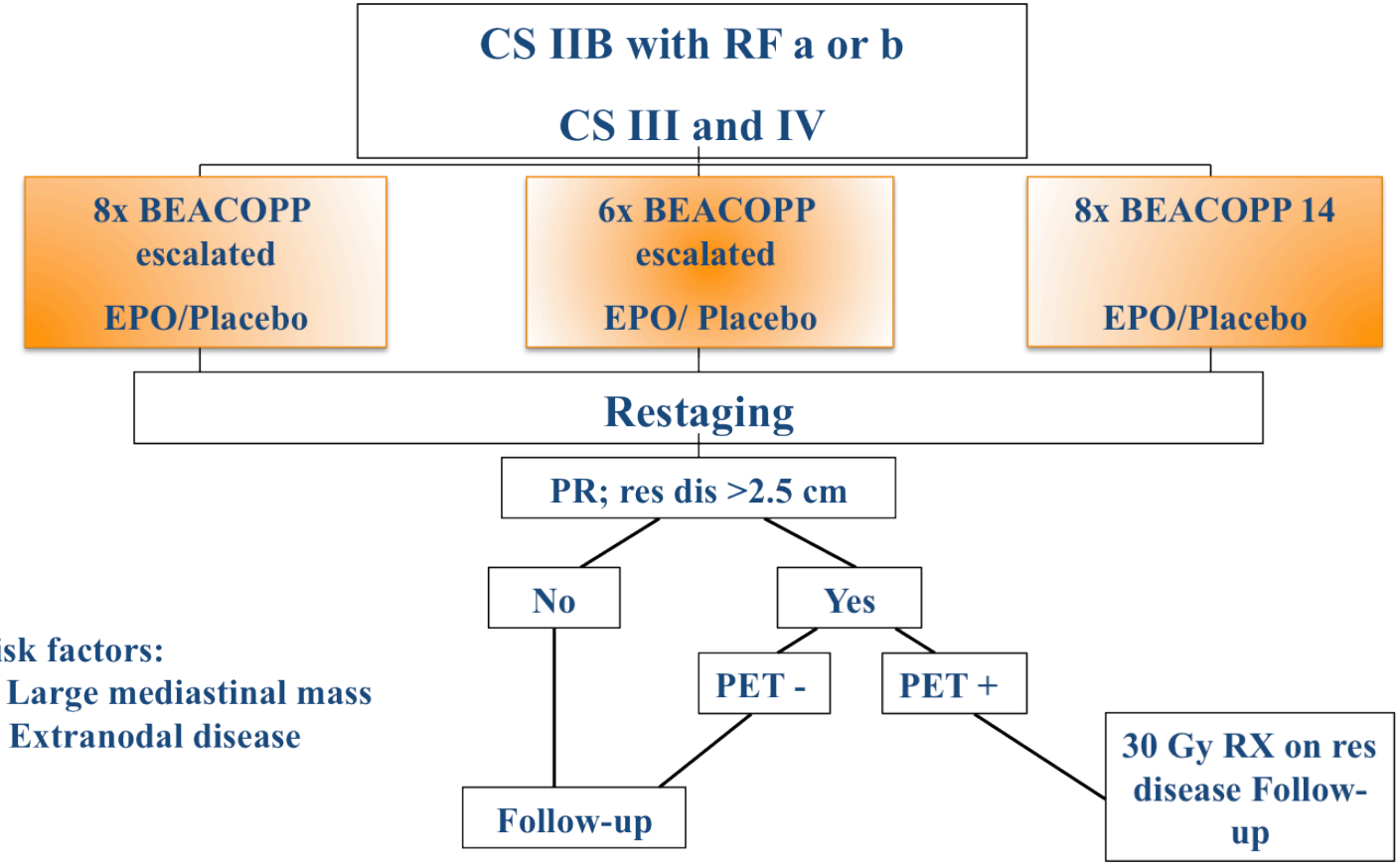
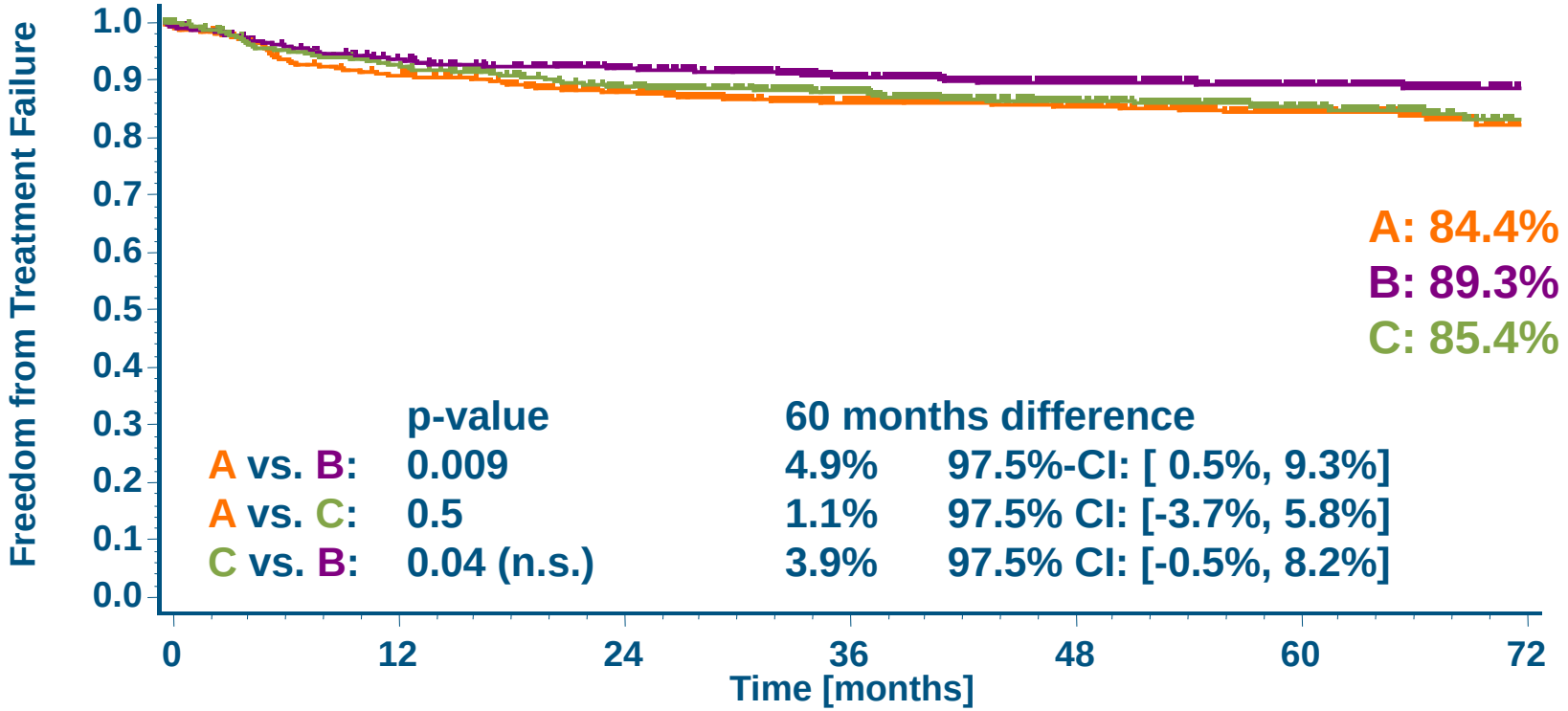
GHSG HD15 trial
for advanced stages



Risk factors:
a) Large mediastinal mass
b) Extranodal disease

HD15 in advanced HL

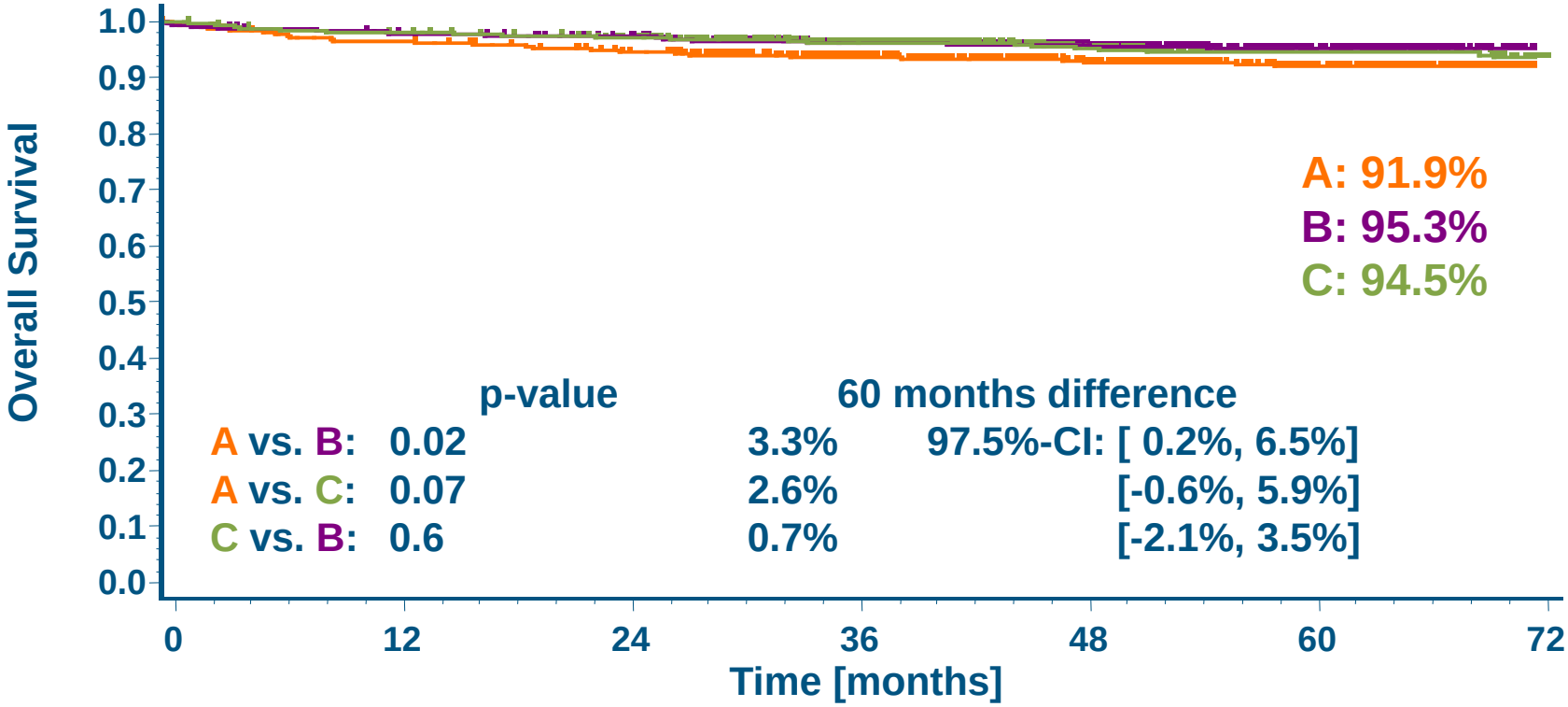
Freedom from Treatment Failure (FFTF)



Engert A et al, Lancet 2012

HD15 in advanced HL

Overall Survival (OS @ 5yrs)



Engert A et al, Lancet 2012

HD15 in advanced HL

Mortality (% of pts)

	$8xB_{esc}$	$6xB_{esc}$
HL	1.8	1.5
TRM 1st line	2.1	0.8
2nd NPL	1.8	0.7
Others	1.3	1.2
Overall	7.5	4.6

HD15-PET trial

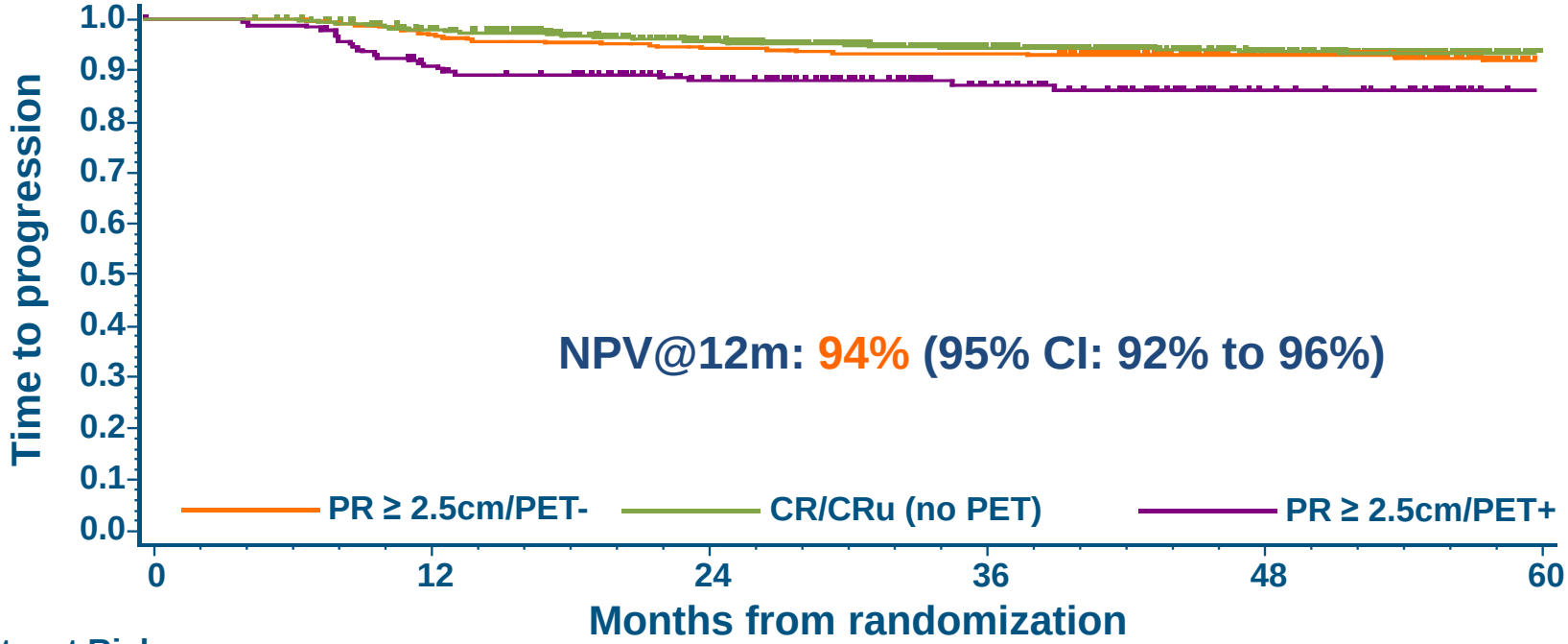
Activity of residual masses ≥ 2.5cm by PET (n=728)*

PET-negative:	**540 (74%)**
PET-positive:	**188 (26%)**

***Patients qualified for the PET question**
PET evaluated by PET panel

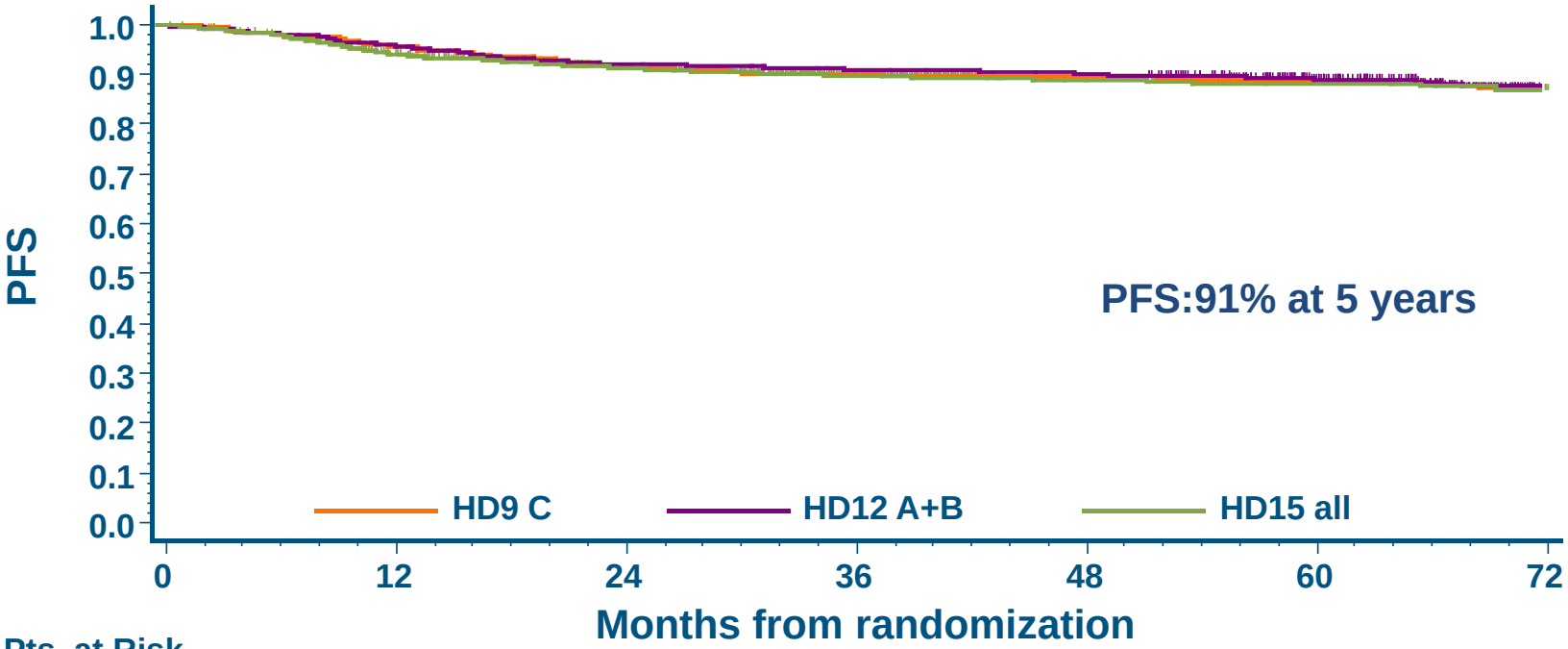
HD15-PET trial

Impact of response and PET status (TTP)



Pts. at Risk						
PET-	540	517	449	338	224	118
PET+	188	166	139	97	58	35
CR/CRu	854	811	690	482	303	155

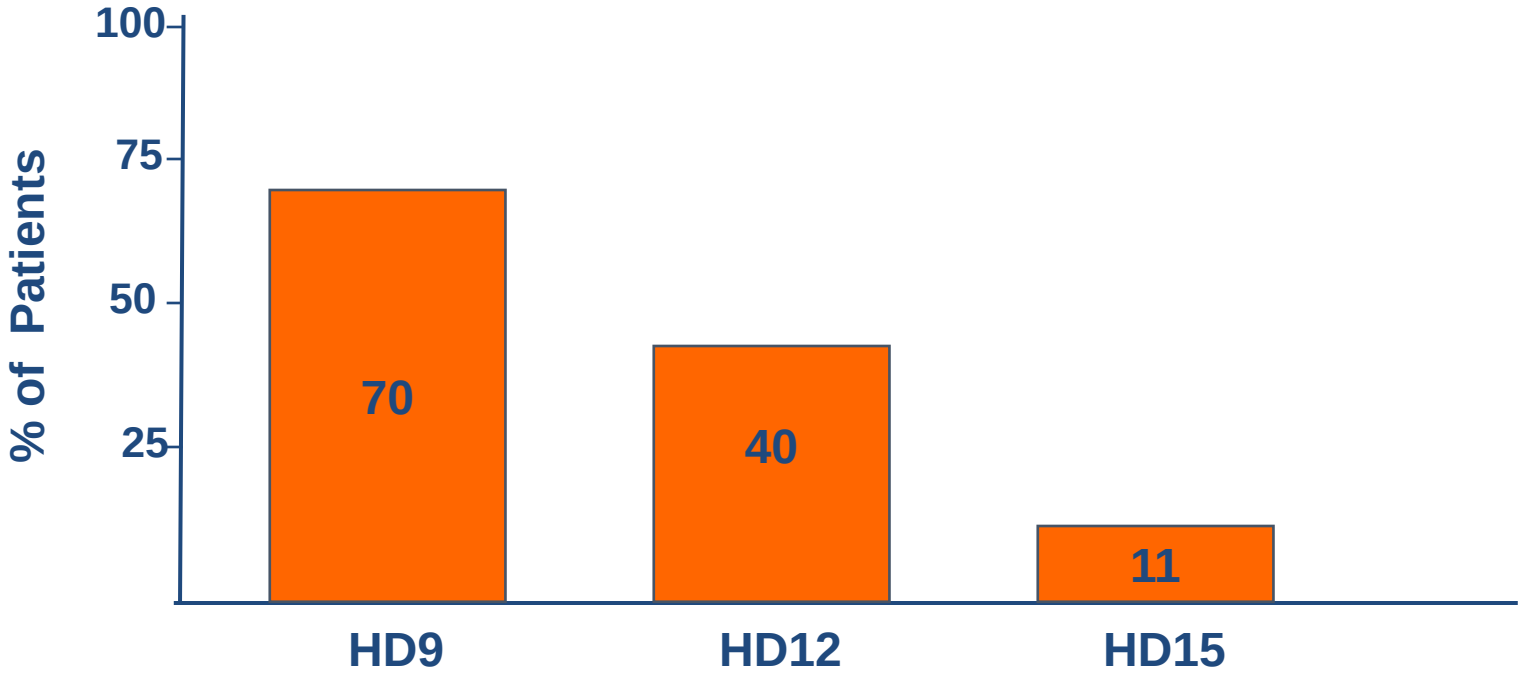
Tumour control
in GHSG trials HD9, HD12, HD15



Pts. at Risk							
HD9 C	431	409	385	374	358	334	298
HD12 A+B	715	669	619	592	543	447	282
HD15 all	2012	1848	1560	1122	702	359	122

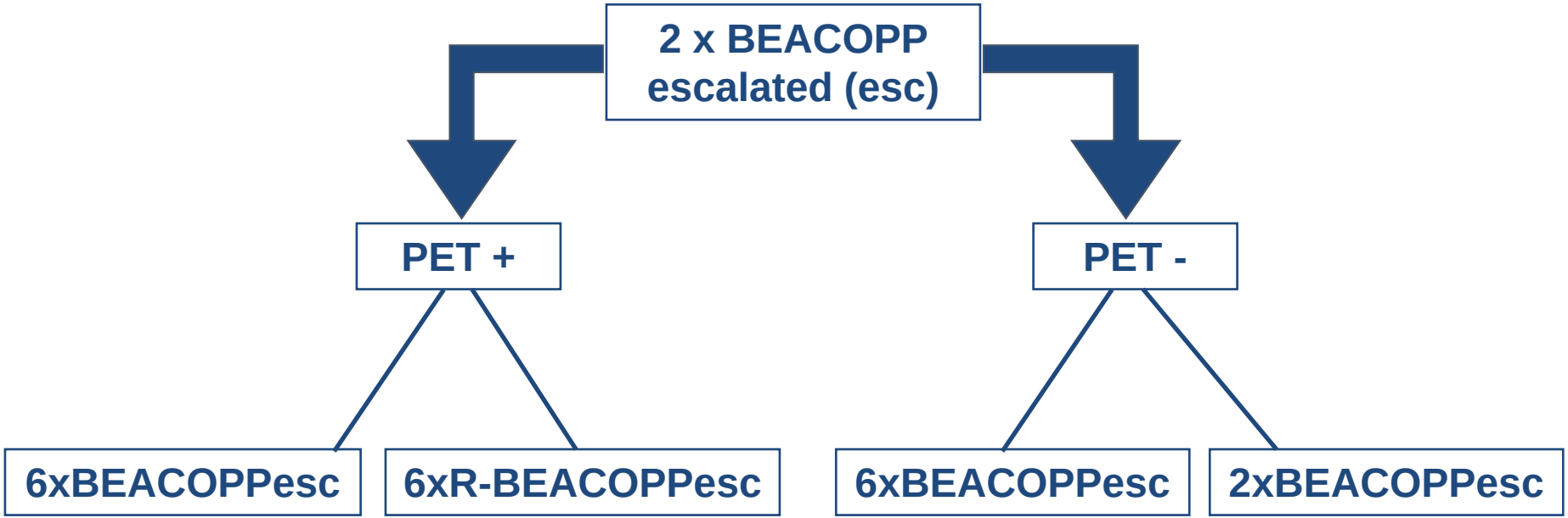
Additional RT after chemo

GHSG studies HD9, HD12 and HD15 (% of all pts)



GHSG HD18 trial

for advanced stages

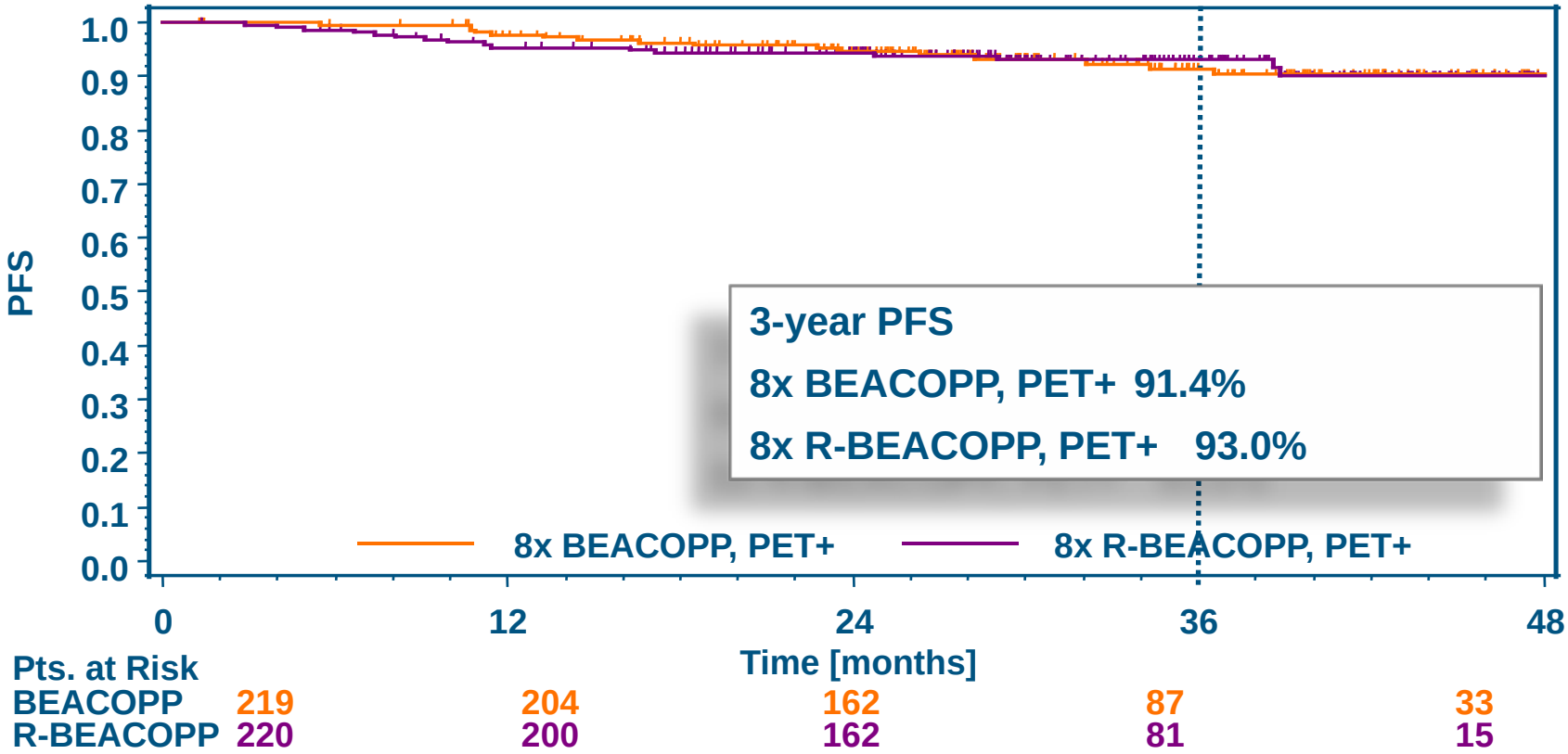


After chemo: PET; RX to PET+ res nodes >2.5 cm

PET-: Follow up

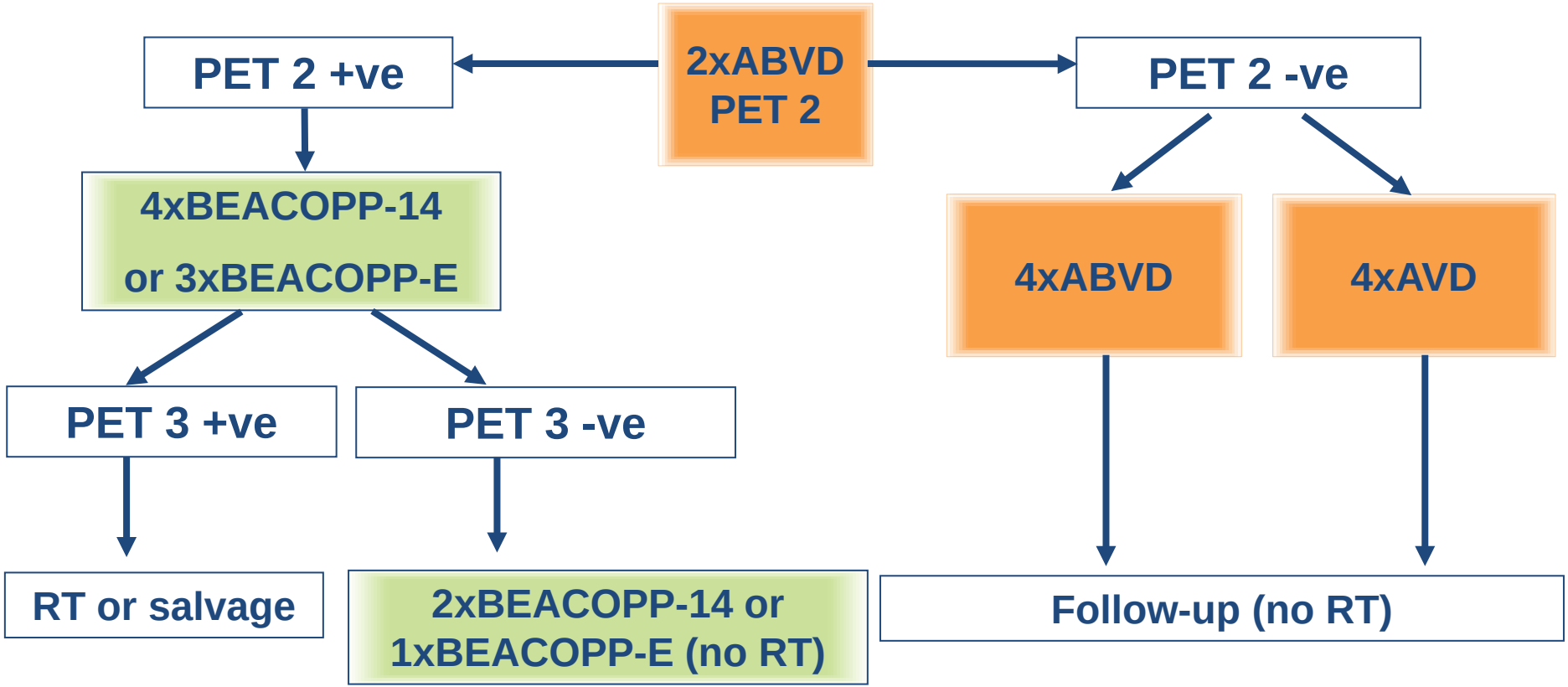
GHSG HD18 trial

for advanced stages: PFS Arm A



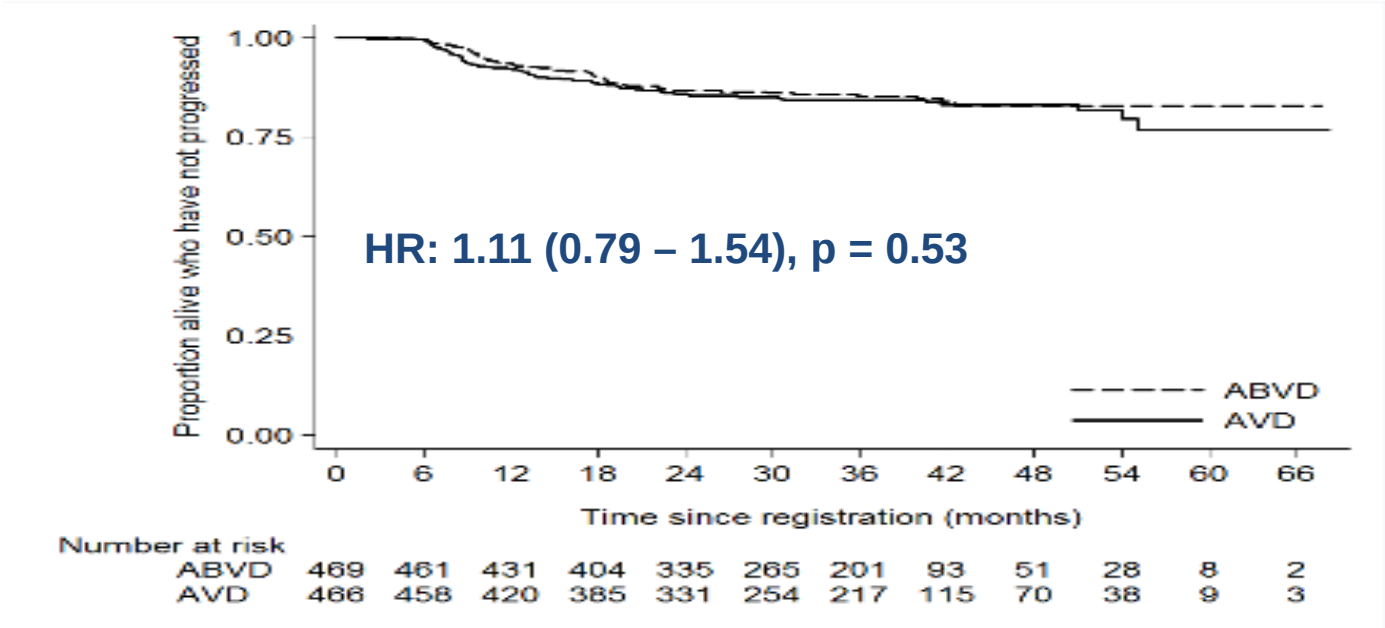
UK RATHL Trial

Advanced stage HL; IPS 0-7



RATHL: Impact of Bleomycin

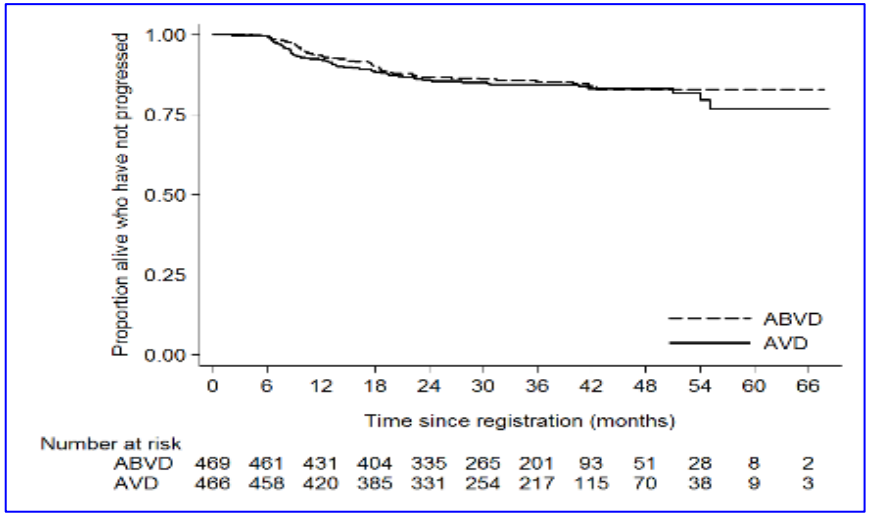
PFS for PET-negative patients (ITT)



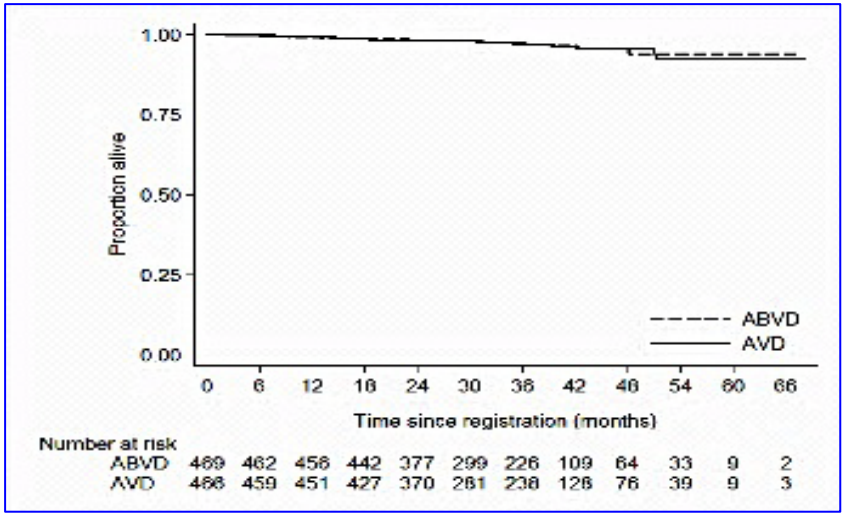
Johnson et al; Lugano 2015

UK RATHL Trial

PFS for PET-negative patients (ITT)



3 year PFS (%)
ABVD 85.4 - AVD 84.4

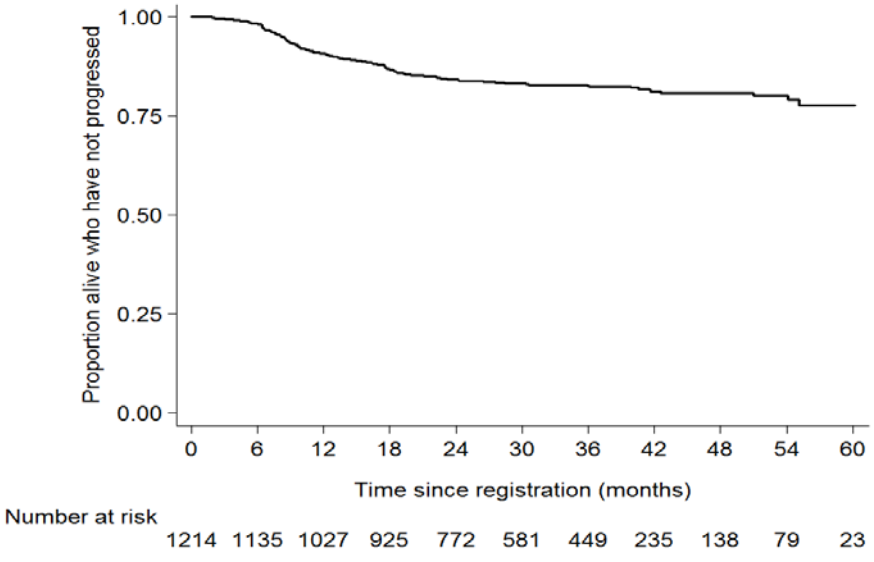


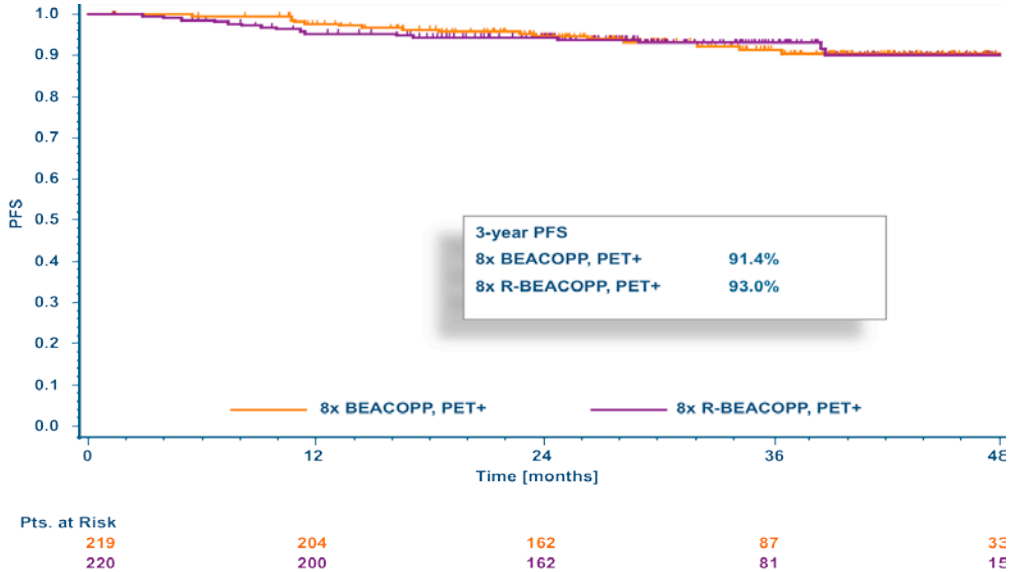
3 year OS (%)
ABVD 97.1 - AVD 97.4

Johnson et al; Lugano 2015

Comparing RATHL and HD18

PFS at 3 years





RATHL (all)

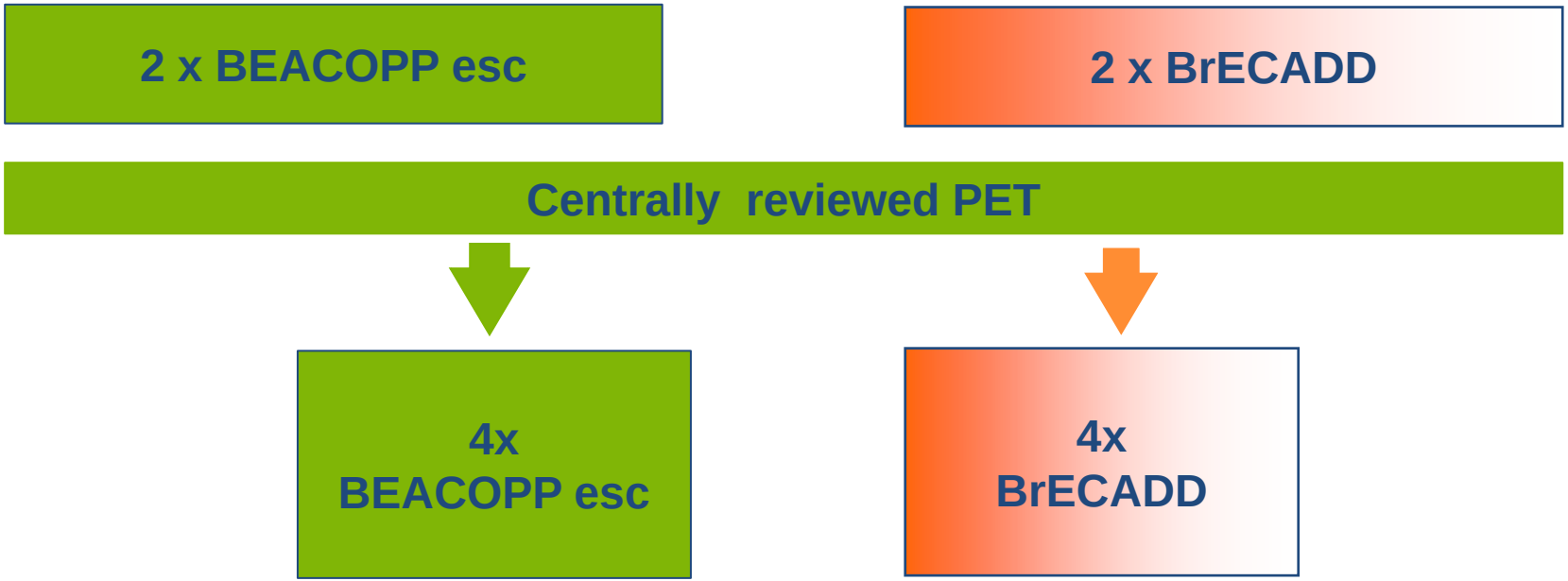
3 year PFS: 82.6% (80.2 – 84.8)

HD18 (PET+ only):

3 year PFS 91.4% – 93.0%

HD21: GHSG Perspective

BV in advanced stage HL



End of therapy and residual nodes > 2.5 cm:

PET positiv: **Rx**

PET negative: **Follow up**

Treatment of advanced stage HL

- Background
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Advanced stage HL

Summary

- HL became curable with the introduction of multi-agent chemo
- ABVD associated with 65-70% PFS and 75-80% OS @5yrs
- B.esc gave 15-20% better PFS and 10-15% better OS than ABVD
- Treatment-related mortality and 2nd npl of BEACOPP similar to ABVD; more hematotox and infertility
- 6xB.esc: tumour control 89%, OS 95%; PET-guided RT (HD15)
- B.esc not to be used in pts >40 yrs and poor performance
- Ongoing trials evaluate PET-guided strategies and combining BV with ABVD (enhance efficacy) BEACOPP (reduce toxicity)


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GHSG
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Relapsed and refractory Hodgkin Lymphoma

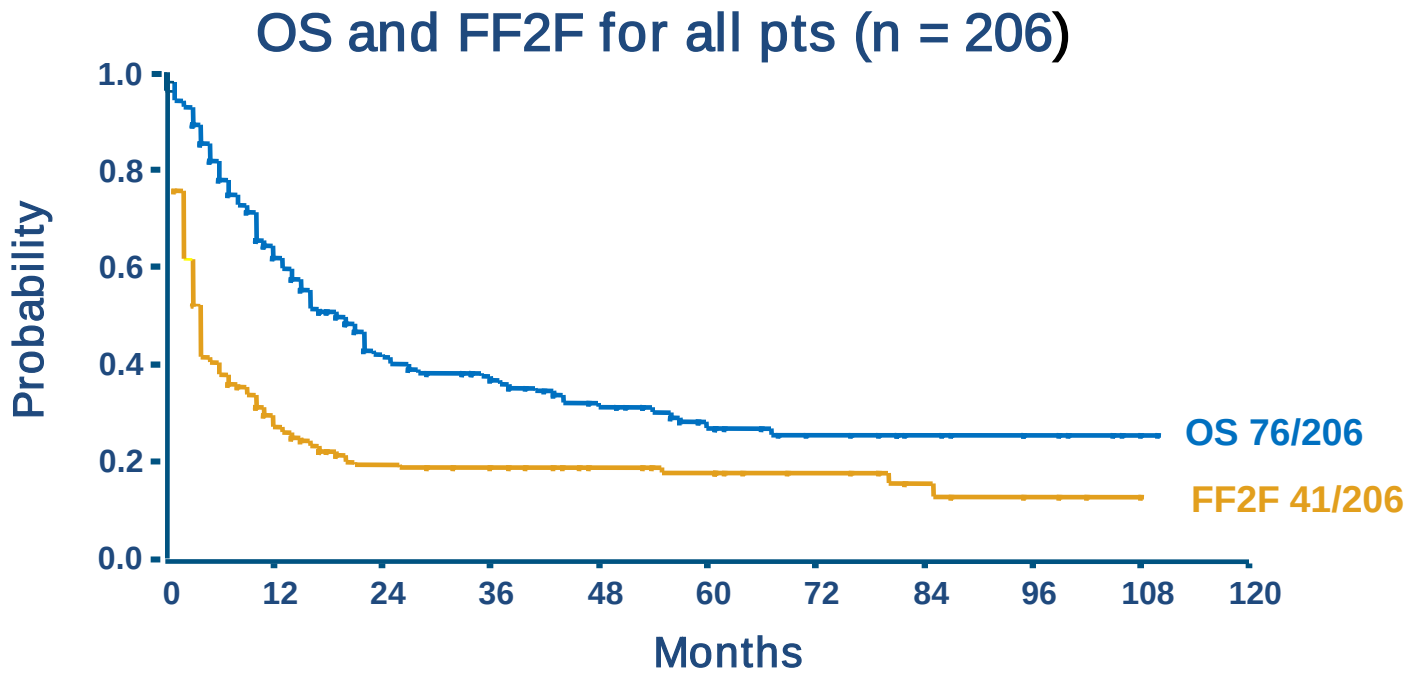
Andreas Engert, MD

Chairman, German Hodgkin Study Group
University Hospital of Cologne

Relapsed and refractory HL

- Background
- Previous approaches
- Brentuximab Vedotin
- Immunecheckpoint Inhibitors
- Summary

Primary Progressive HL
1988-1998 (GHSG)

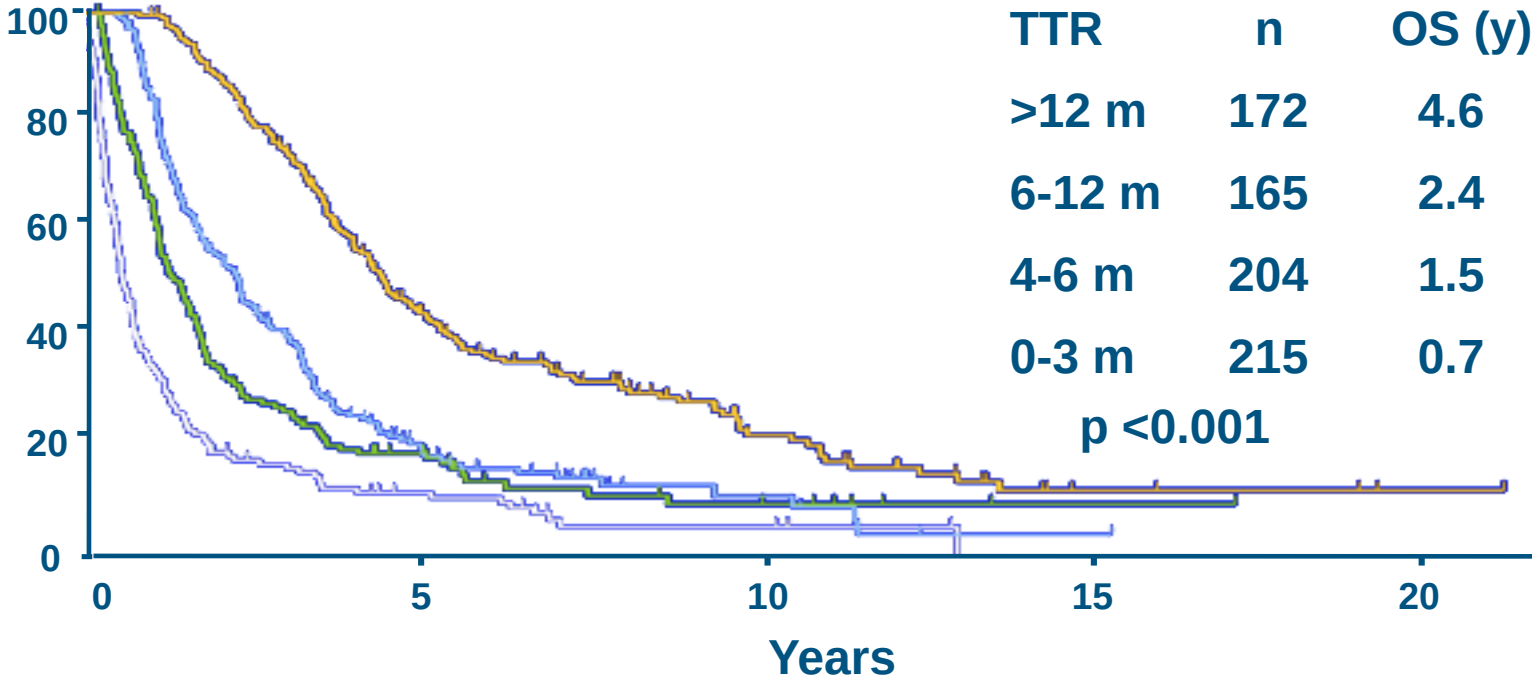


HD – hodgkins disease; OS – overall survival

Josting A, et al. Blood. 2000;96(4):1280-1286

Relapse After Auto-TX

OS by time to relapse after TX (n=756)



TTR	n	OS (y)
>12 m	172	4.6
6-12 m	165	2.4
4-6 m	204	1.5
0-3 m	215	0.7

p <0.001

Arai et al. Leukemia & Lymphoma 2013

Relapsed and refractory HL

- Background
- Previous approaches
- Brentuximab Vedotin
- Immunecheckpoint Inhibitors
- Summary

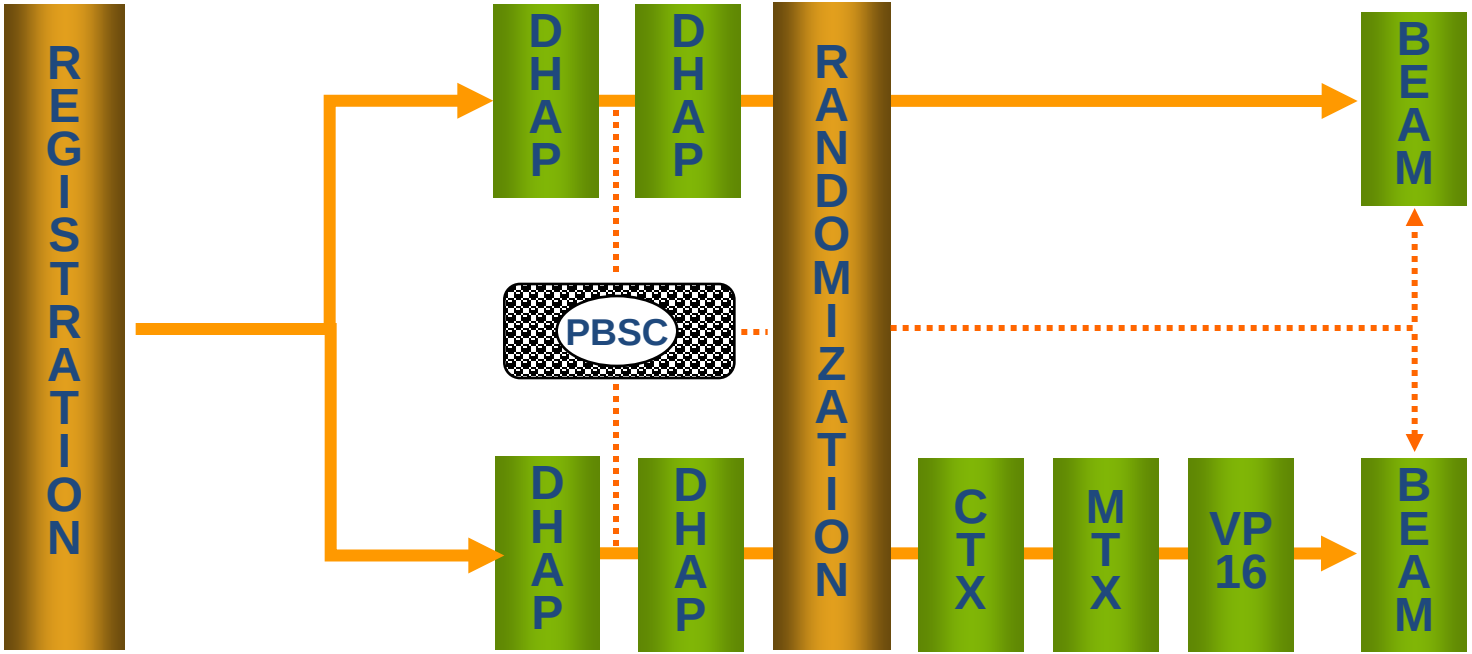
Relapsed Hodgkin Lymphoma

Selected conventional salvage regimen

Regimen	n	RR	TRM	Author
DHAP	102	88	0	Josting A Oncol 2002
IGEV	91	81	0	Santoro A Oncol 2007
ICE	65	88	2	Moschkowitz Blood 2001
ASHAP	57	70	0	Rodriguez Blood 1999
GVD	91	70	0	Bartlett A Oncol 2007

HDR2: European Intergroup Trial

Relapsed Hodgkin Lymphoma*

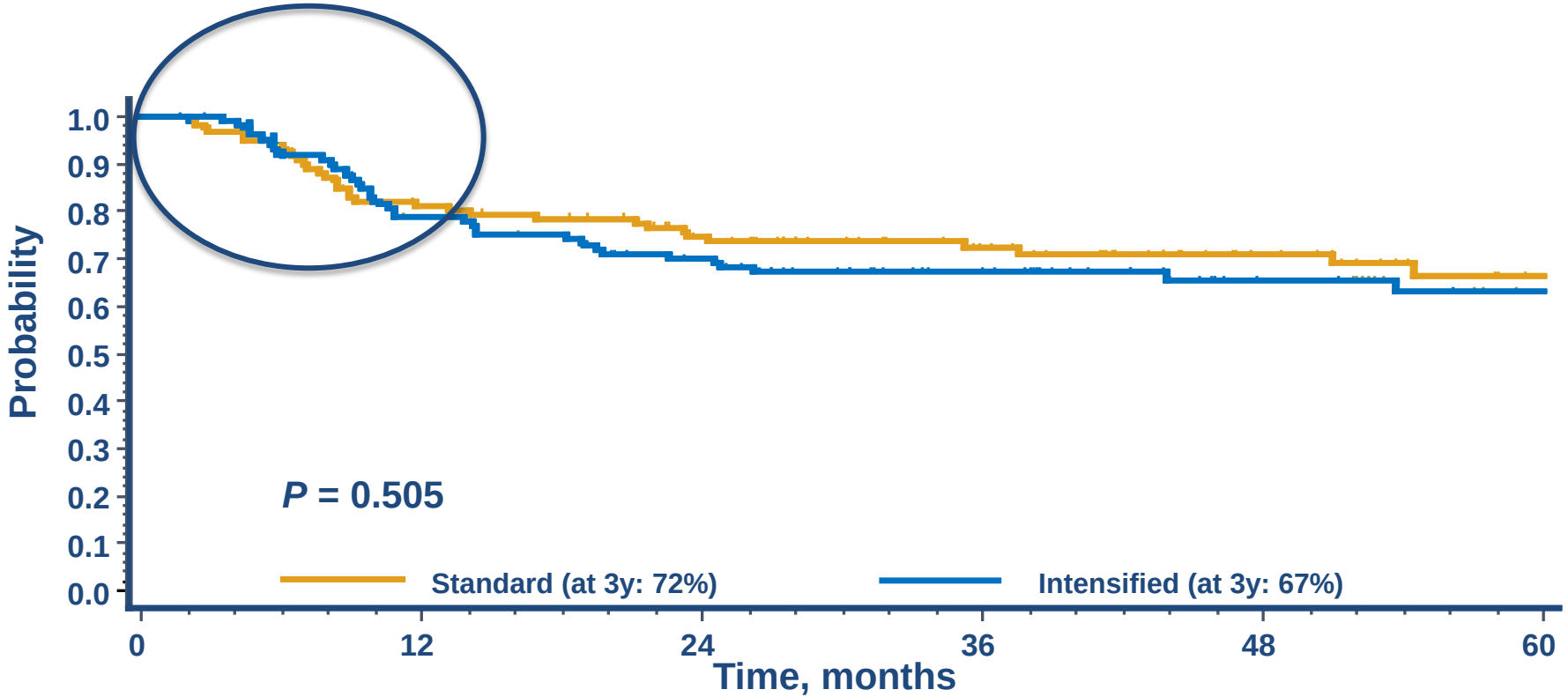


*GHSG, EORTC, EBMT, GELTAMO

Josting A et al, J Clin Oncol. 2010;28(34):5074-5080

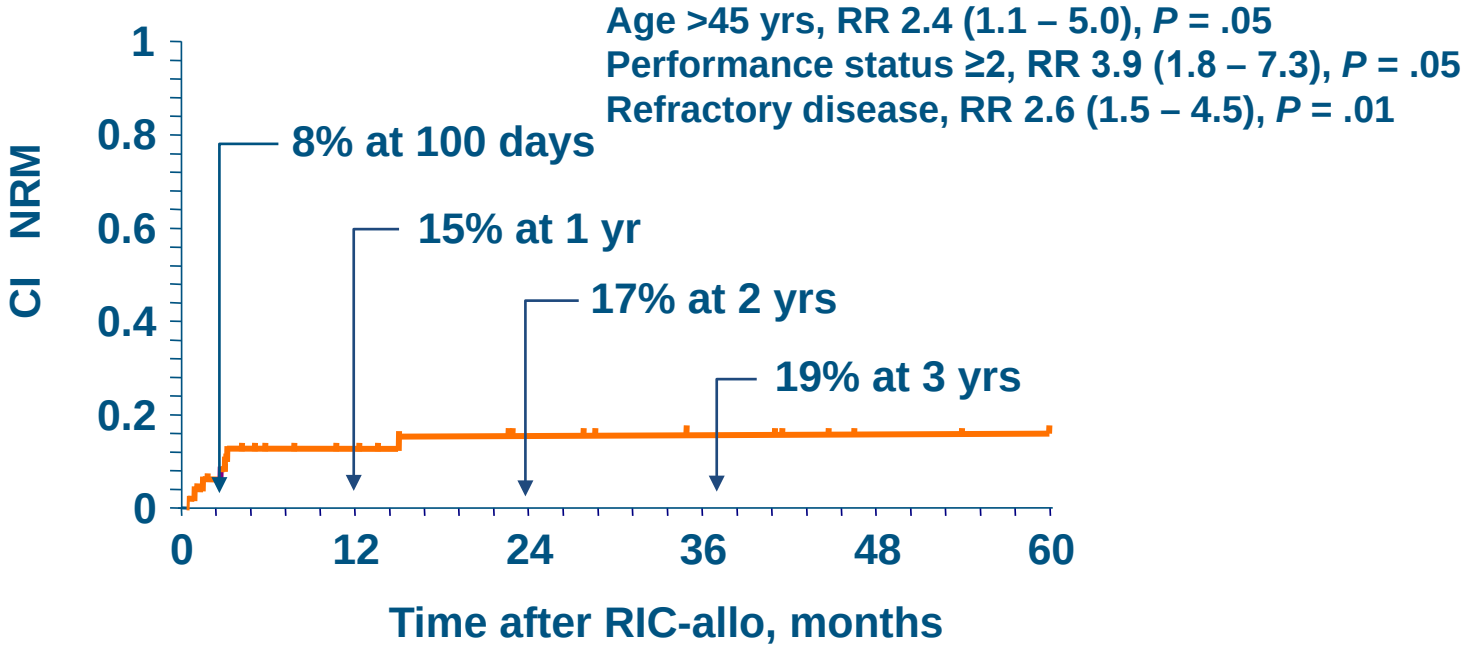
HDR2 Study for Relapsed HL

PFS by Treatment Arm (Final Analysis)



Josting et al, JCO 2010

RIC-Allo Trial in Relapsed
or Refractory HL (Non-relapse Mortality)

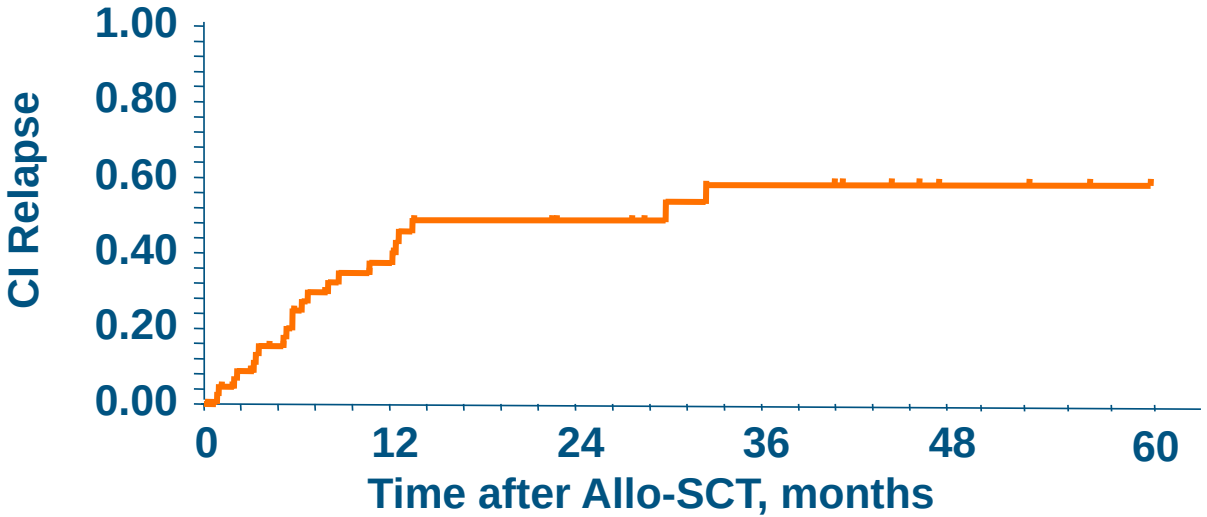


RIC-allo - reduced-intensity conditioning allogenic stem cell transplantation; HL – Hodgkin lymphoma; NRM – non-relapse mortality

Sureda A, et al. Blood. 2009;114: A 658

RIC-Allo Trial in Relapsed
or Refractory HL (Relapse Rate)

≥3 lines of tx, RR 1.7 (1.2 – 2.5), *P* = .03
Refractory disease, RR 2.1 (1.5 – 2.9), *P* = .01



37 % at 1yr
49 % at 2yrs
59 % at 3 yrs

Median time to relapse: 6m (3-35)

RIC-allo - reduced-intensity conditioning allogenic stem cell transplantation; HL – Hodgkin lymphoma; tx – therapy; allo-SCT- allogeneic stem cell transplantation

Sureda A, et al. Blood. 2009;114: A 658

New Antibodies and Molecules
in Hodgkin Lymphoma

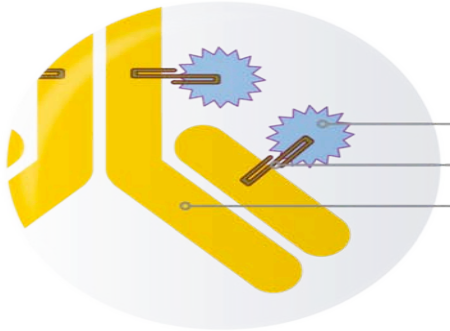
- Brentuximab Vedotin (anti-CD30 ADC)
- AFM13 (CD16/CD30 bispecific)
- Lenalidomide (IMID)
- Everolimus, (mTor-inhibitor)
- Rituximab, Ofatumumab (anti-CD20)
- Panobinostat, Mocitinostat (H-DAC inhibitors)
- TKI´s, JAK2i, PARPi
- PD-1 inhibitors

Relapsed and refractory HL

- Background
- Previous approaches
- Brentuximab Vedotin
- Immunecheckpoint Inhibitors
- Summary

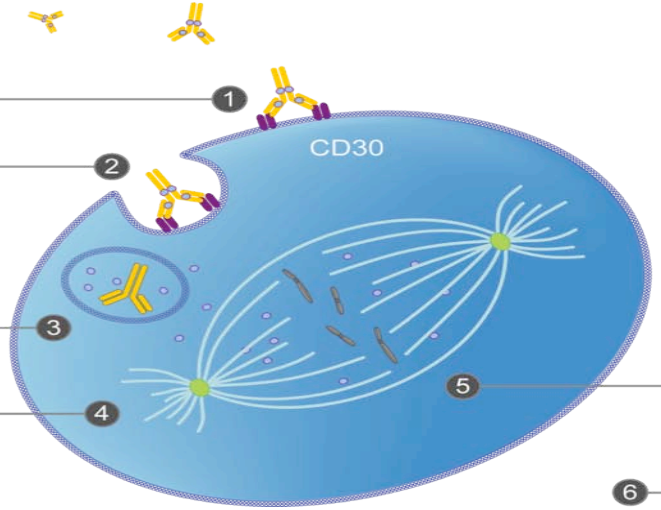
Brentuximab Vedotin (SGN-35)

Mechanism of action



Brentuximab vedotin (SGN-35) ADC

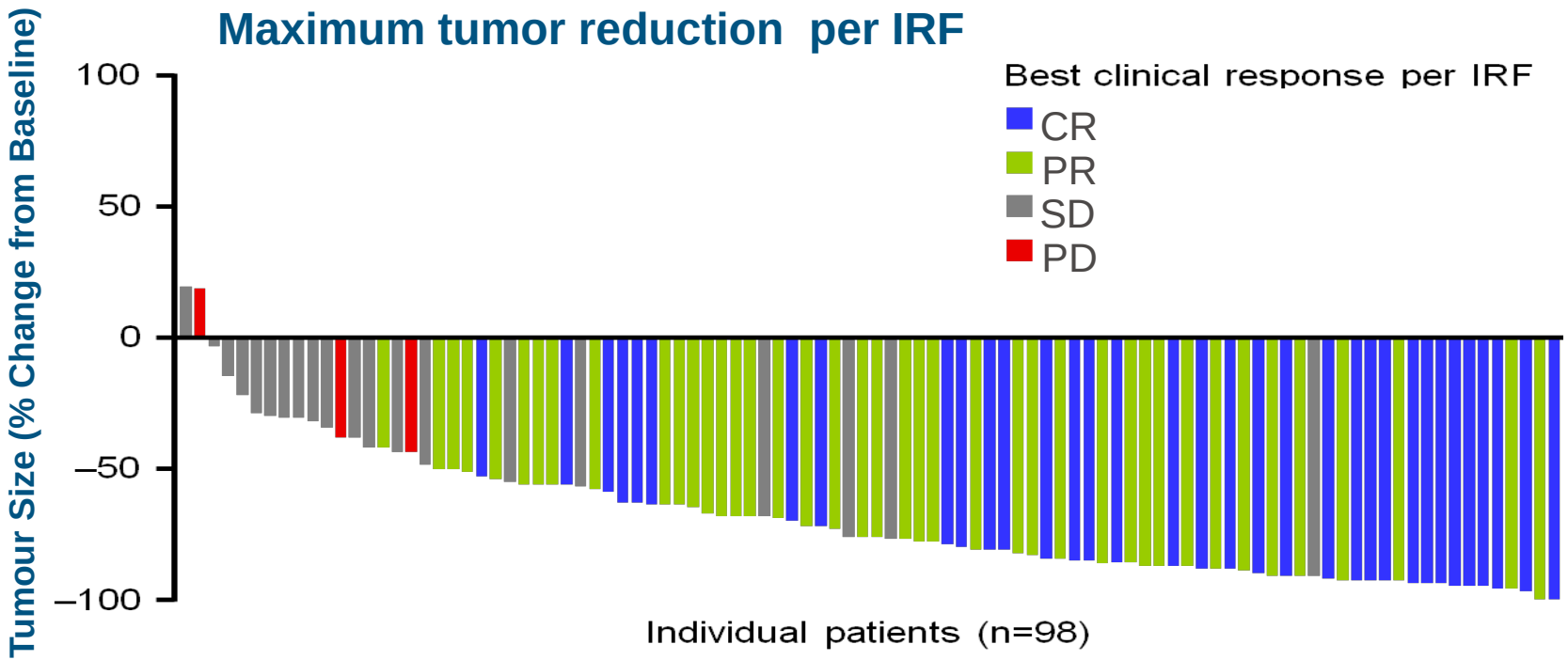
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody



1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts Microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

Phase II Pivotal Study of BV

Patients with R/R HL post ASCT

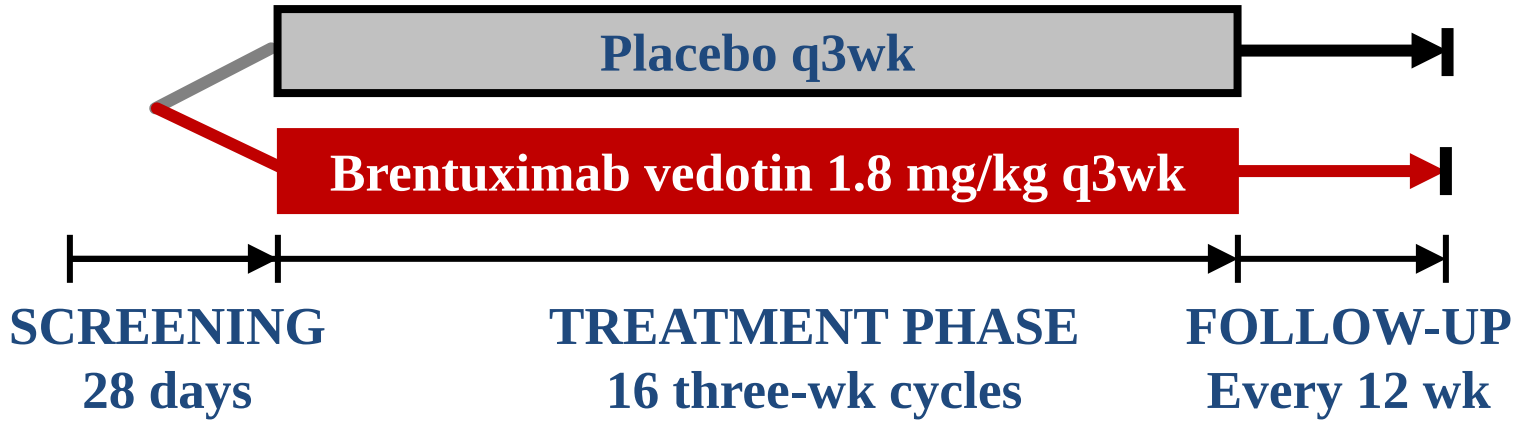


Younes A et al, J Clin Oncol 2012;30: 2183-2189.

Random. Phase III (AETHERA)

BV in HL pts

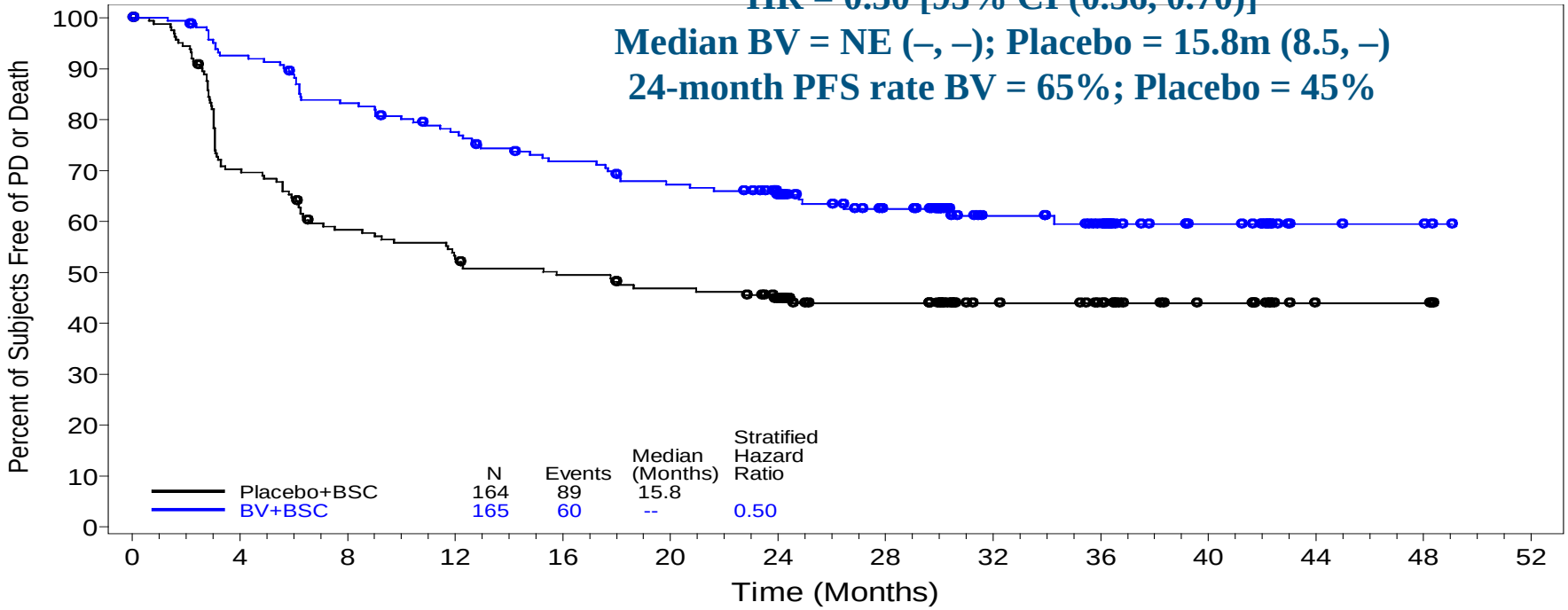
N = 322 HL post ASCT
high risk (no CR, r/r <12 mo, ex-nodal)



Assessments: 3, 6, 9, 12, 18, 24 mo, then every 6 mo
Follow-up: every 12 wk until death

AETHERA

PFS per Investigator



N at Risk (Events)

Pla+BSC	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	71 (85)	61 (88)	45 (89)	28 (89)	23 (89)	13 (89)	3 (89)	3 (89)	0 (89)
BV+BSC	165 (0)	149 (12)	133 (27)	122 (36)	111 (45)	103 (52)	90 (55)	62 (58)	40 (59)	33 (60)	16 (60)	4 (60)	3 (60)	0 (60)

Relapsed and refractory HL

- Background
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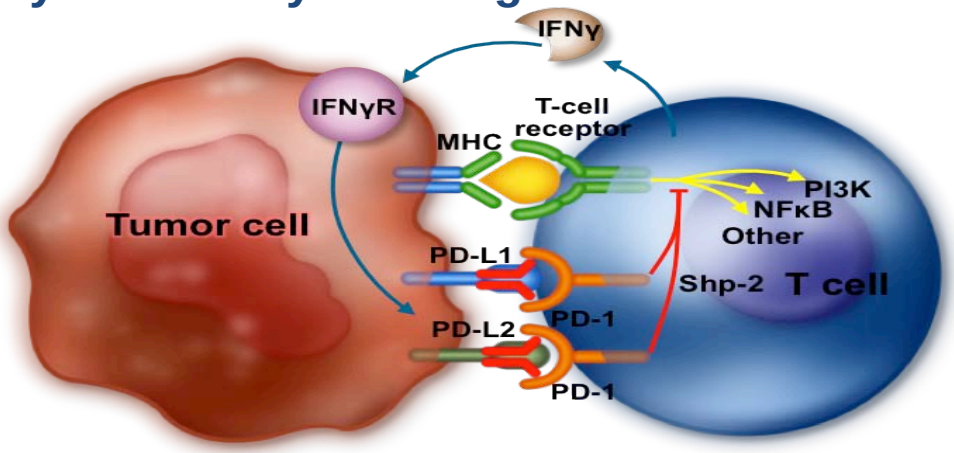
- Summary

PD-1 Blockade

- PD-1 engagement by its ligands results in transient down-regulation of T-cell function (T-cell exhaustion).
- Nivolumab (BMS) and Pembrolizumab (MSD) fully human/humanized anti-PD-1 antibody selectively blocking the PD-1 and PD-L1/PD-L2 interaction.

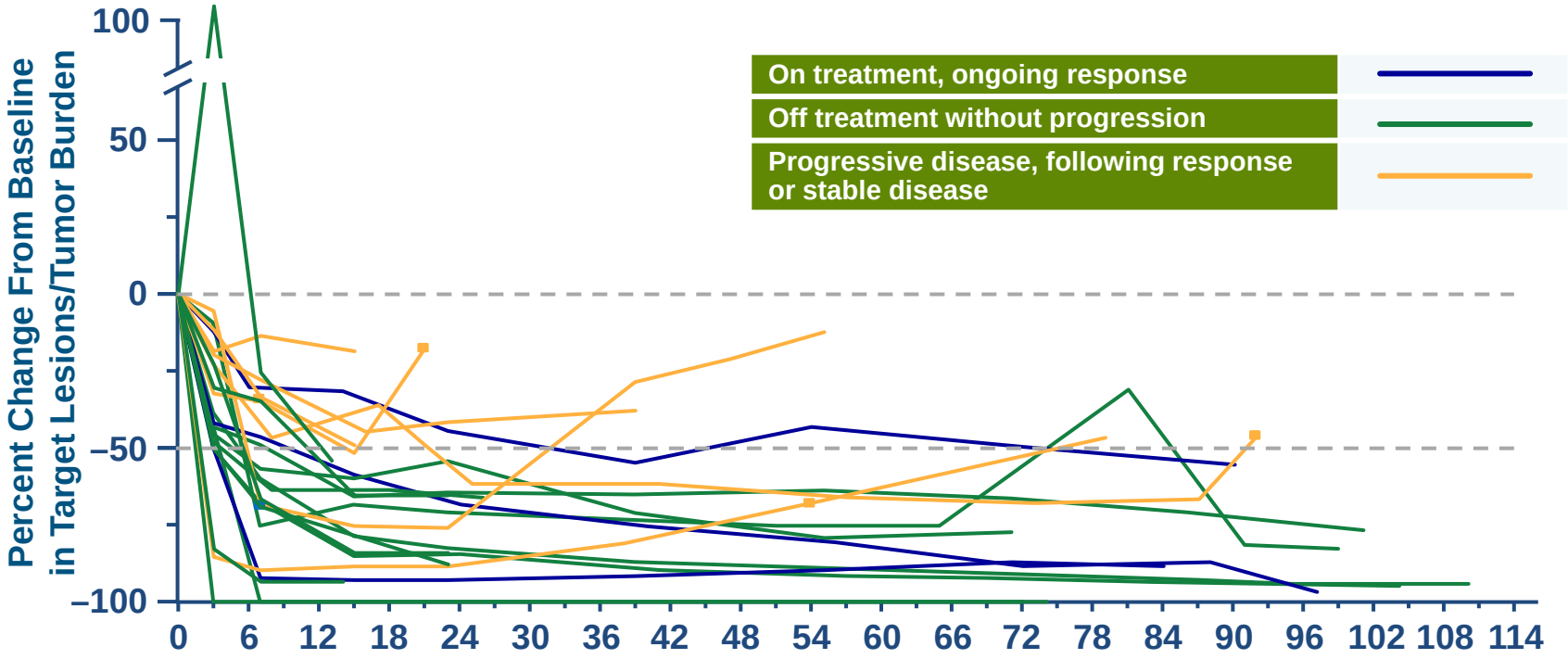


- PD-1 blockade through monoclonal antibody therapy has single-agent activity in a range of solid tumors

Brahmer et al, NEJM 2012;366:2455. Topalian et al, NEJM 2012;366:2443-54

Nivolumab in r&r HL

Durability of reponse

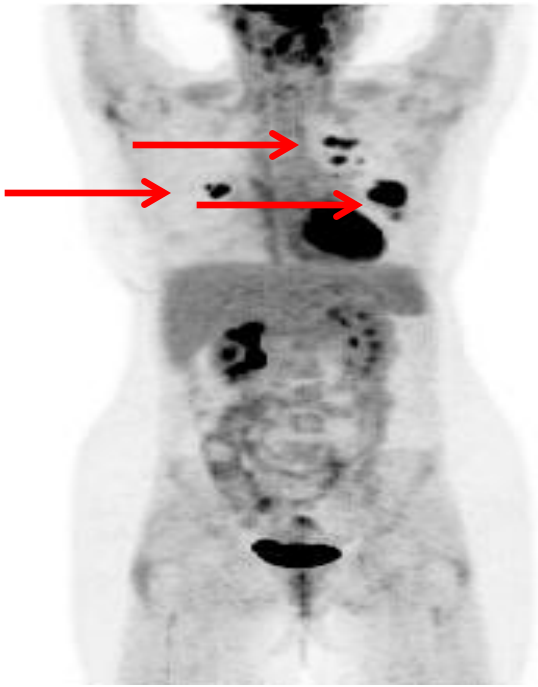


- First occurrence of new lesion

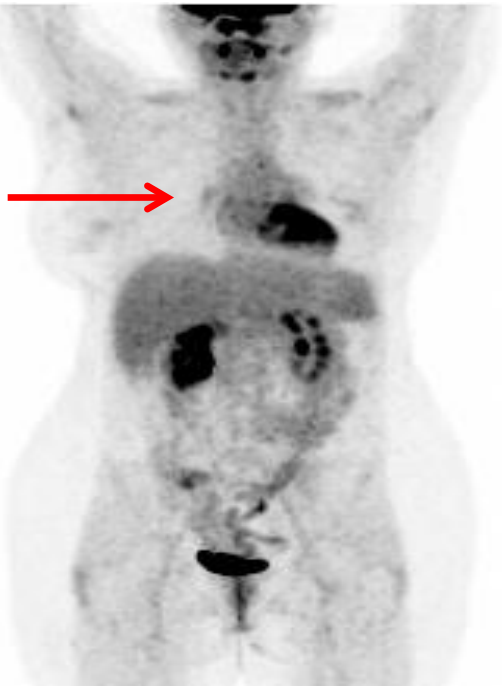
Ansell et al, ASH 2015

Patient M.M.; 39y

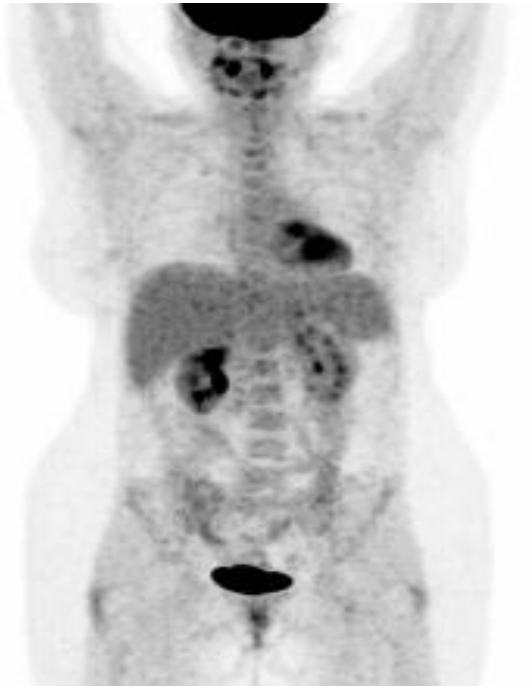
1st diagnosis 2011 (5 prior treatments)



October 2014



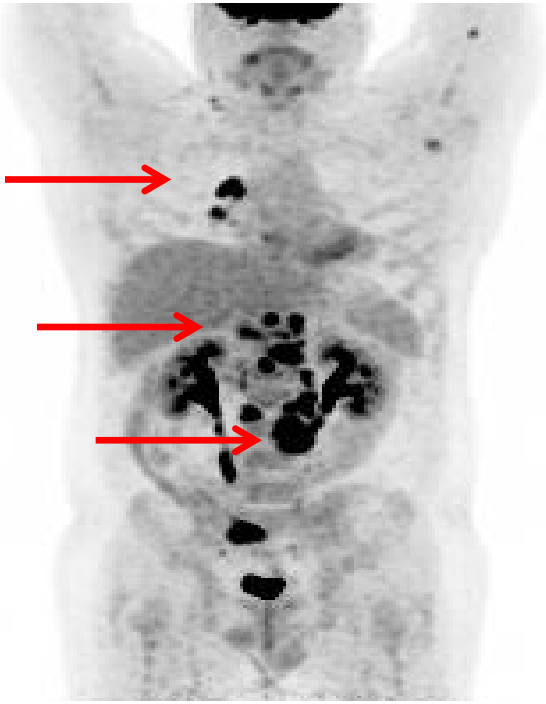
February 2015



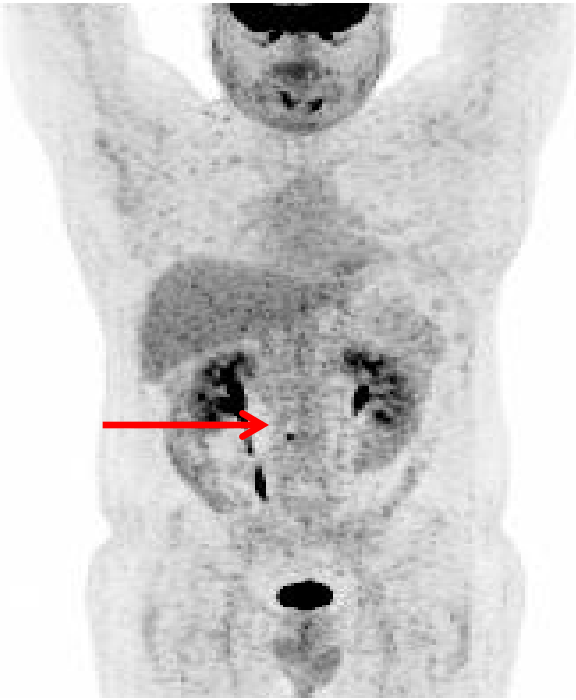
May 2015

Patient D.P.; 48y

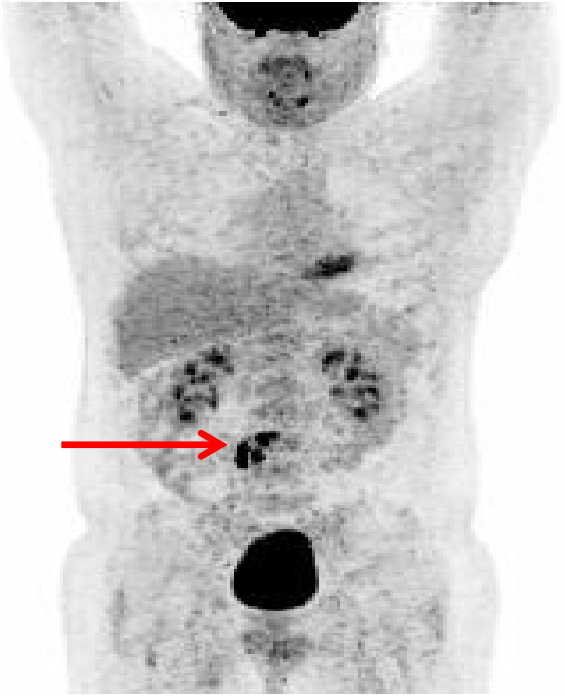
1st diagnosis 2009 (6 prior therapies)



Sept 2014



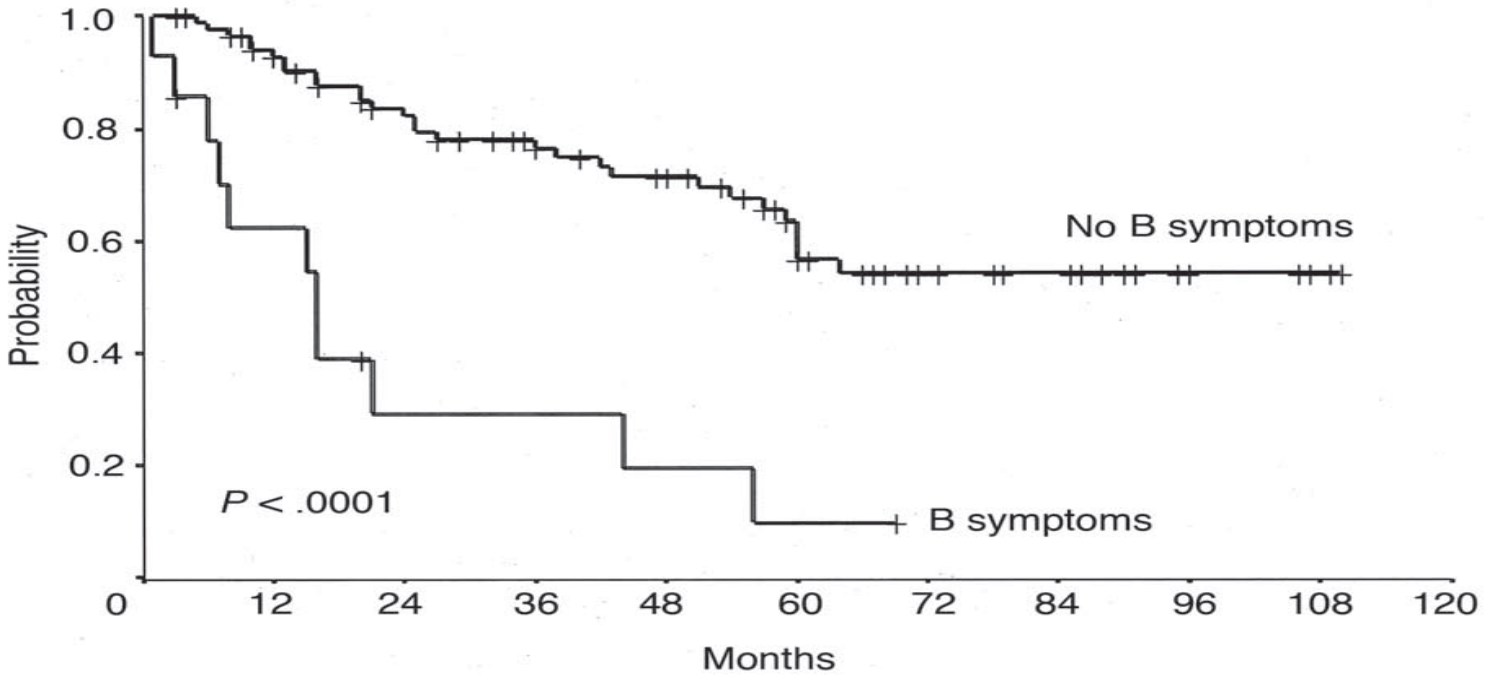
January 2015



June 2015

RT in Relapsed/Refractory HL

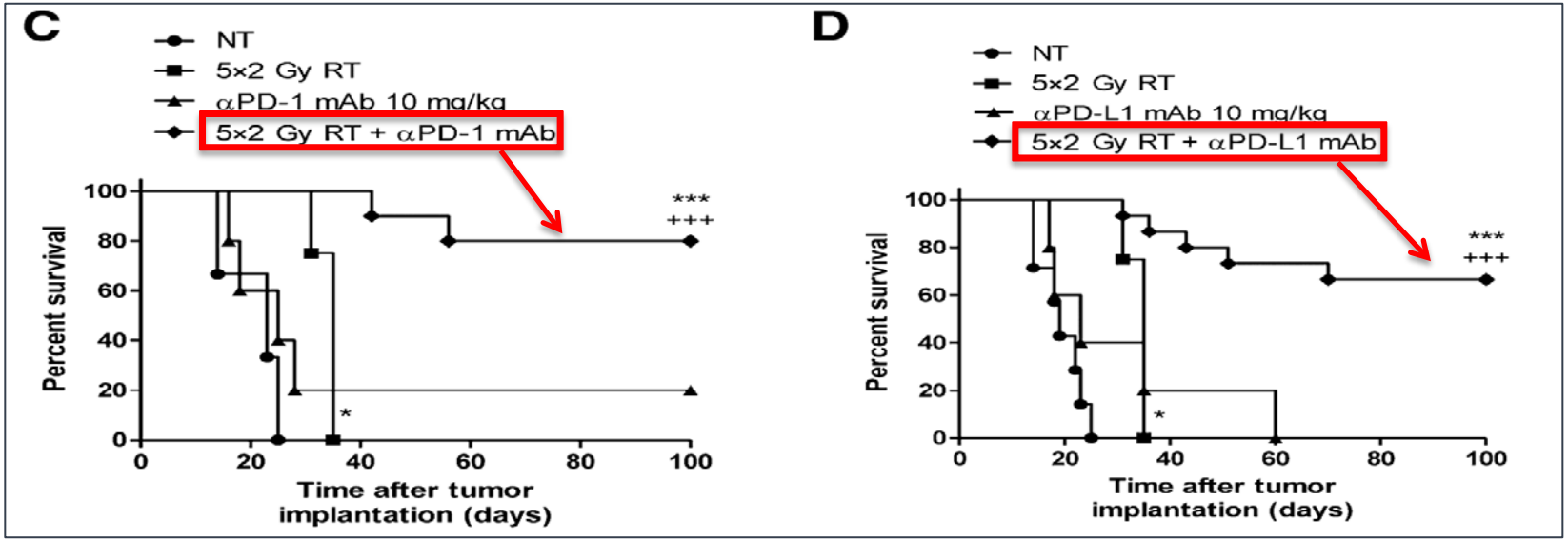
B-Symptoms at Progression or Relapse



Josting A et al. JCO 2005

Anti-PD1 moabs and RT

Synergism in preclinical models

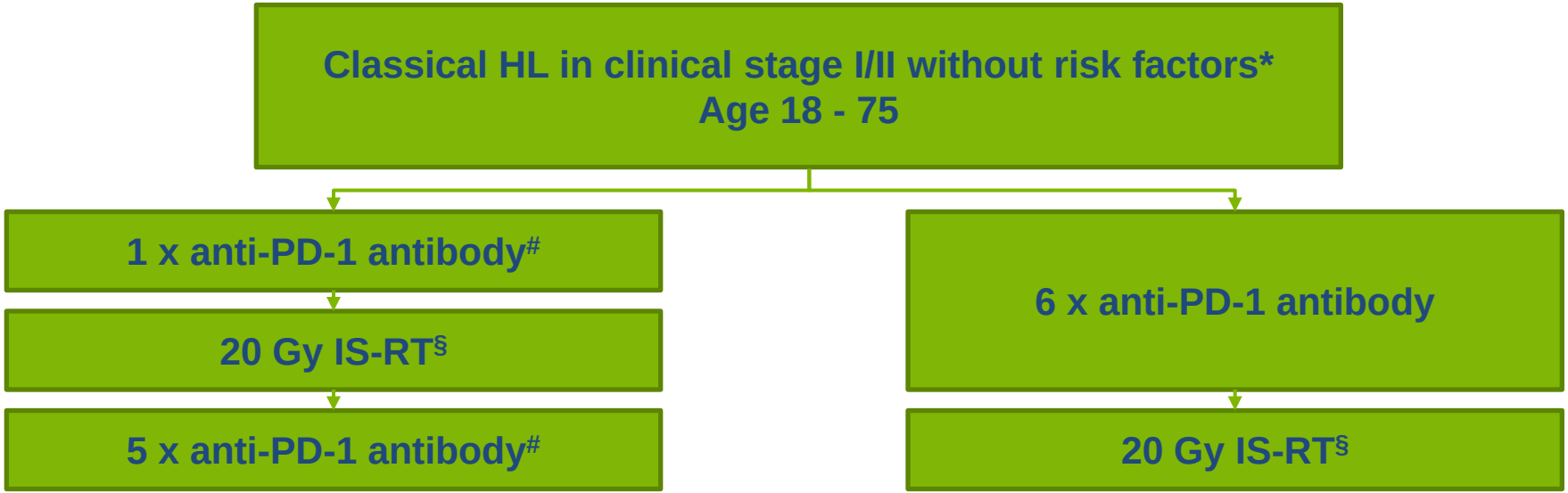


CT26 colorektal cancer-bearing mice received 10Gy RT in 5 daily fractions of 2Gy alone or in combination with either aPD-1 (C) or aPD-L1 (D)

Dovedi et al. 2014

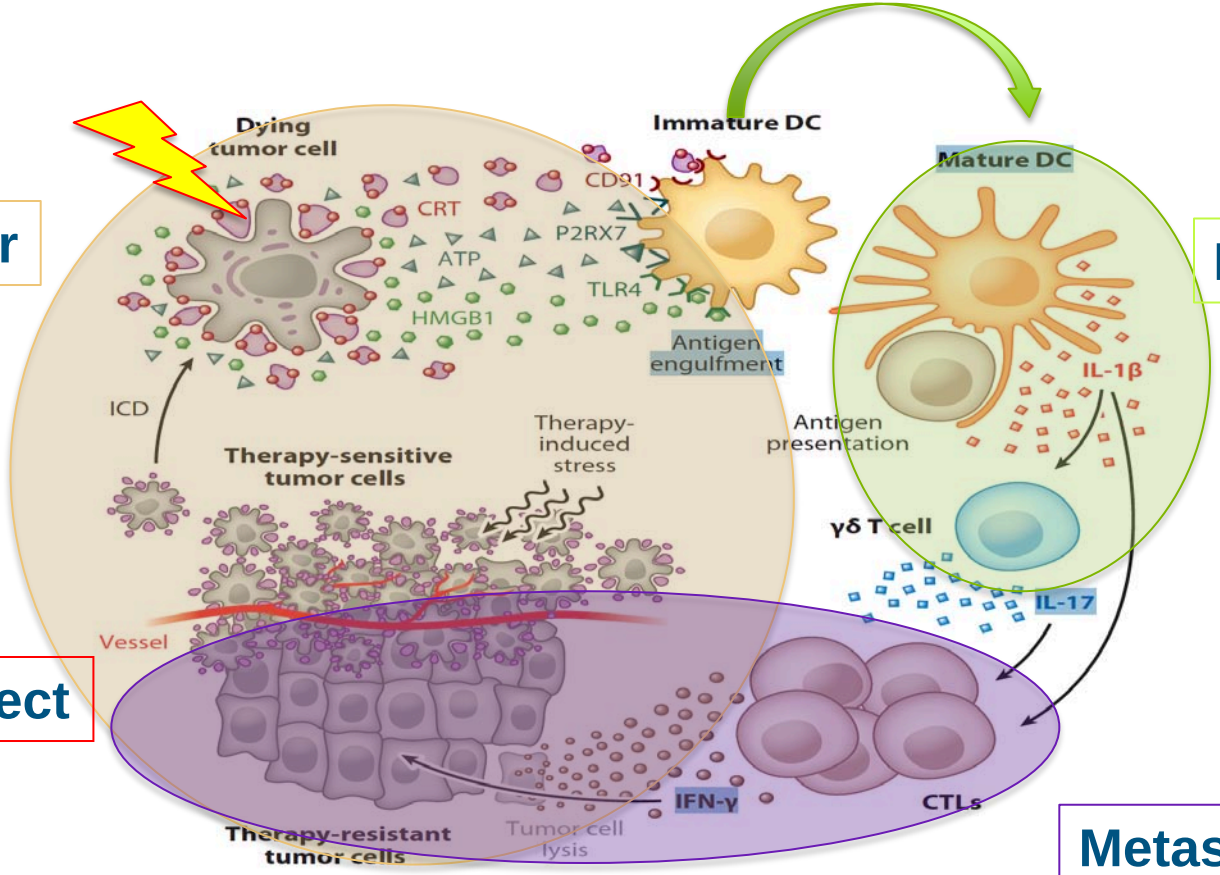
Phase II trial

RT and anti-PD1 in early favorable cHL



* Risk factors: Large med mass, extranodal lesion, elevated ESR, ≥ 3 nodal areas
# x mg/kg every 2 weeks
§ IS-RT starts on day 5 after the first infusion on the anti-PD-1 antibody

Immunogenic cell death (ICD)

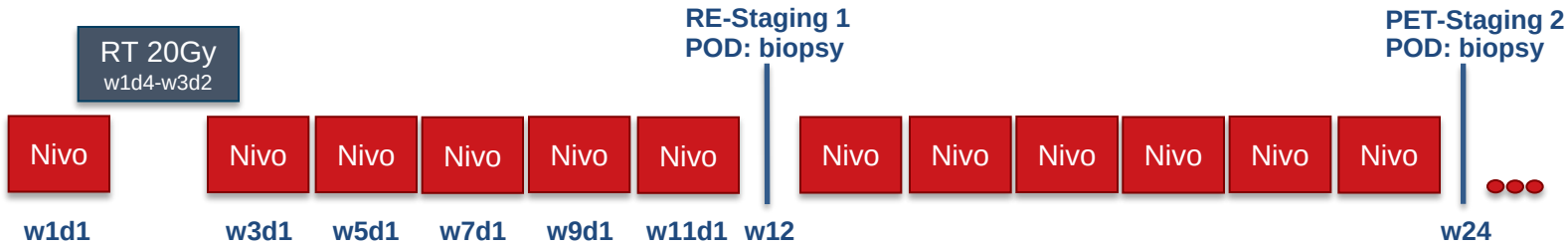


Kroemer et al. 2013

Abscopal Phase II Study
Flowchart

relapsed/refractory cHL

anti-PD1 pretreated



Simon‘s two stage *Optimal* design (α=0.05):

- **H0: ARR <5% → will be rejected with 95% power if real ARR is ≥30%**

Relapsed and refractory HL

- Background
- Previous approaches
- Brentuximab Vedotin
- Immunecheckpoint Inhibitors
- Summary

Relapsed and refractory Lymphoma
Summary

- Prognosis of r&r HL still to be improved
- DHAP or other reinduction followed by BEAM and ASCT standard in relapsed lymphoma; intensification not helpful (HDR2)
- BV effective and well tolerated; currently being evaluated in combination with other drugs
- Anti-PD1´s represent a new class of drugs showing very promising activity in r/r lymphoma
- GHSG to conduct trials with anti-PD1´s in cHL (early favorable, unfavorable, abscopal)
- Can new drugs replace radio- or chemotherapy in lymphoma?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Current approaches and emerging therapies in the treatment of malignant lymphoma

Andreas Engert, MD

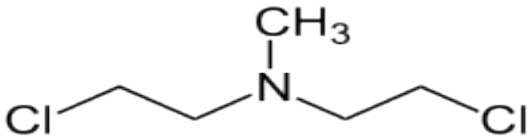
Chairman, German Hodgkin Study Group
University Hospital of Cologne

Chemotherapy of malignant lymphoma

- History of and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

Mechlorethamin

The first cytostatic drug in lymphoma

Name	**Mechlorethamin**	**Strukturformel:**
Other names	**N,N-Bis(2-chlorethyl)-N-methylamin** **Chlormethin** **Stickstofflost** **N-Lost** **HN2**	

Mechlorethamin (Stickstoff-Lost) is an alkylating agent, and is mainly used in the chemotherapy of Hodgkin lymphoma (trade name *Mustargen*®, USA, CH)

Mustargen and the history of alkylating agents

- Mustargen as antitumor agent evolved from observed effects of mustard gas in ww1
- Depression of the hematopoietic system was observed in survivors
- Nitrogen mustard is an alkylating agent
- First non-hormonal chemical demonstrating clear clinical antitumor activity
- Studies published in 1946 demonstrated regression especially of lymphomas
- Nitrogen mustard (mechlorethamine, mustargen) and other less toxic and more clinically effective derivatives were developed

Colvin OM. History of the alkylating agents; 19(3):363-371.
Cancer Principley & Practice of Oncology, de Vita V, et al (eds), 2001

MOPP

Combination chemotherapy

(M)ustargen (also known as mechlorethamine, mustine, or nitrogen mustard)
(O)ncovin (also known as Vincristine or VCR)
(P)rocarbazine (also known as Matulane or Natulan)
(P)rednisone (also known as Deltasone or Orasone)

Drug	Dose	Mode	Days
(M)ustargen	6 mg/m²	iv bolus	1 + 8
(O)ncovin	1.4 mg/m² (max 2)	iv bolus	1 + 8
(P)rocarbazine	100 mg/m²	po qd	1 - 14
(P)rednisone	40 mg/m²	po qd	1 - 14

MOPP

Major Side effects

Alopecia (hair loss)

Skin sensitivity

Nausea, vomiting

Chills, constipation

Sterility (dose and age dependent)

Second cancer

https://en.wikipedia.org/wiki/MOPP

COPP

Combination chemotherapy

Drug	Dose	Mode	Days
(C)yclophosphamide	600 mg/m²	iv infusion	1 + 8
(O)ncovin	1.4 mg/m² (max. 2 mg)	iv bolus	1 + 8
(P)rocarbazine	100 mg/m²	PO qd	1 - 10
(P)rednisone	40 mg/m²	PO qd	1 - 14

Major side effects of COPP

Myelosuppression

Hair loss

Nausea and vomiting

Infection

Fatigue

Bleeding

Peripheral neuropathy

Gonadal toxicity

Infertility

ABVD

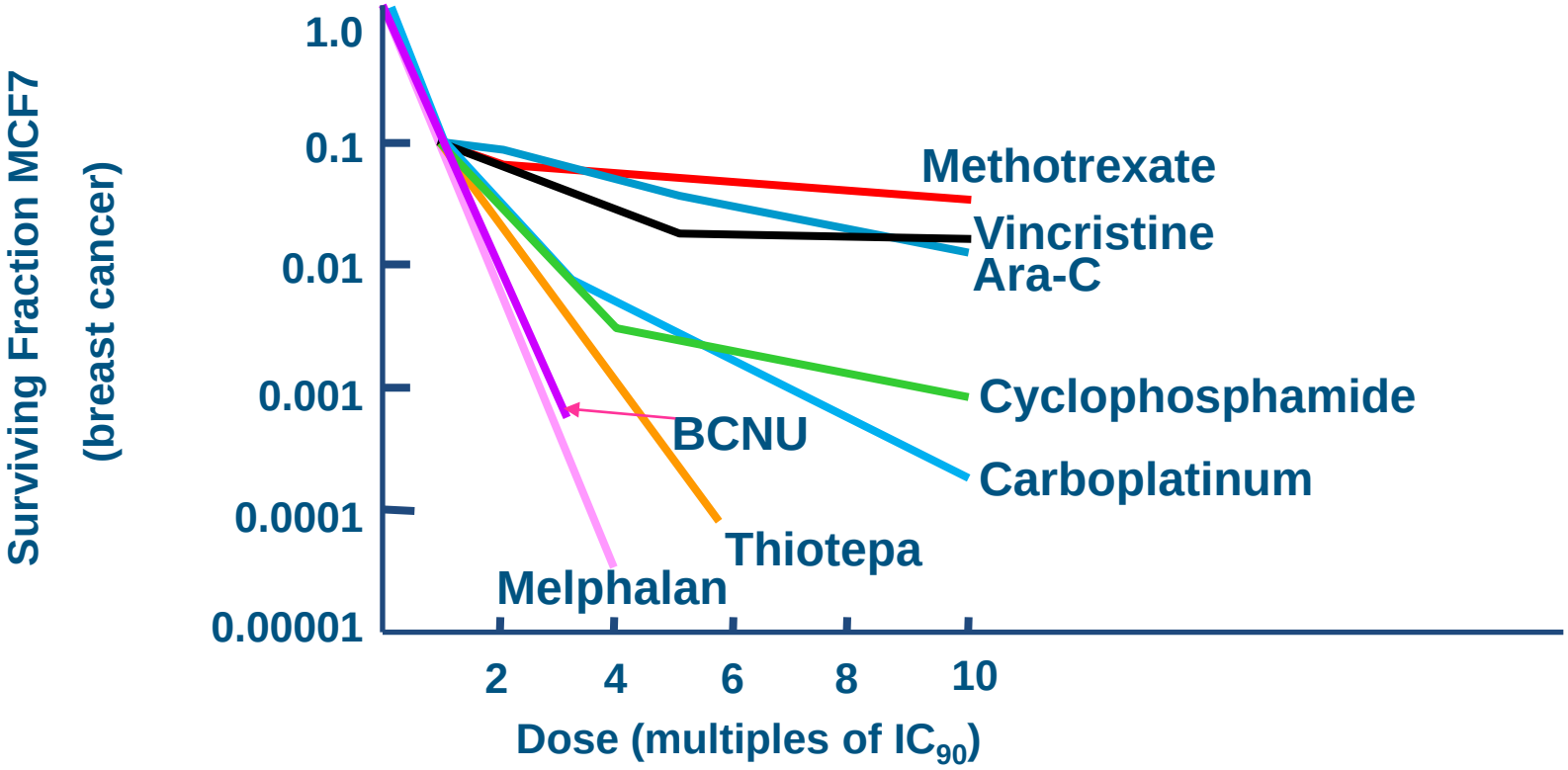
Combination chemotherapy

(A)driamycin (also known as doxorubicin/(H)ydroxydaunorubicin, designated as H in CHOP)
(B)leomycin
(V)inblastine
(D)acarbazine (similar to (P)rocarbazine, designated as P in MOPP and in COPP)

Drug	Dose	Mode	Days
(A)driamycin	25 mg/m²	iv bolus	1 + 15
(B)leomycin	10 IU/m²	iv bolus	1 + 15
(V)inblastine	6 mg/m²	iv bolus	1 + 15
(D)acarbazine	375 mg/m²	iv infusion	1 + 15

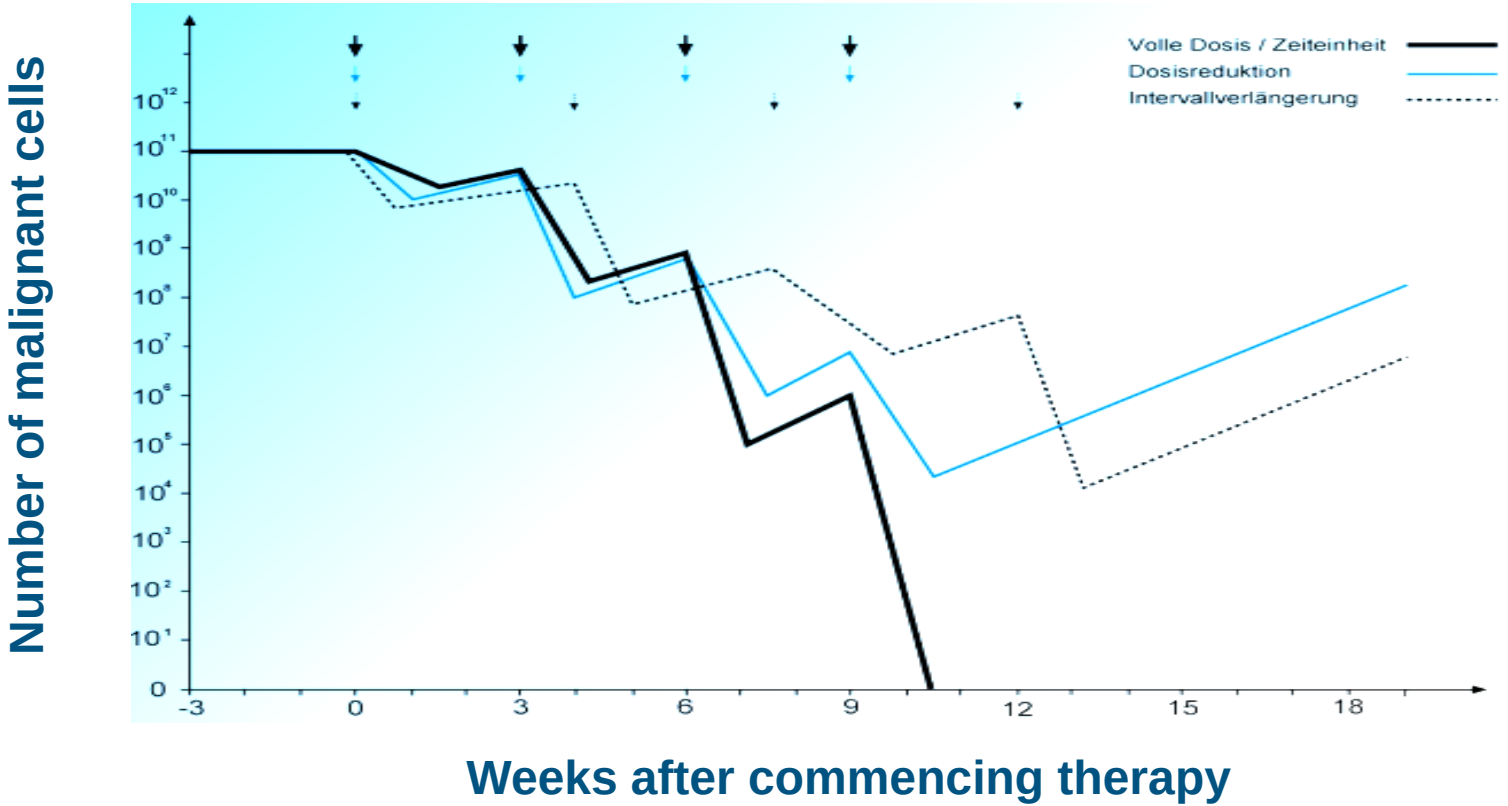
Correlation of dose and efficacy

Cytostatic drugs *in vitro*



Correlation of dose density and response

Chemosensitive malignancies



C. Jackisch

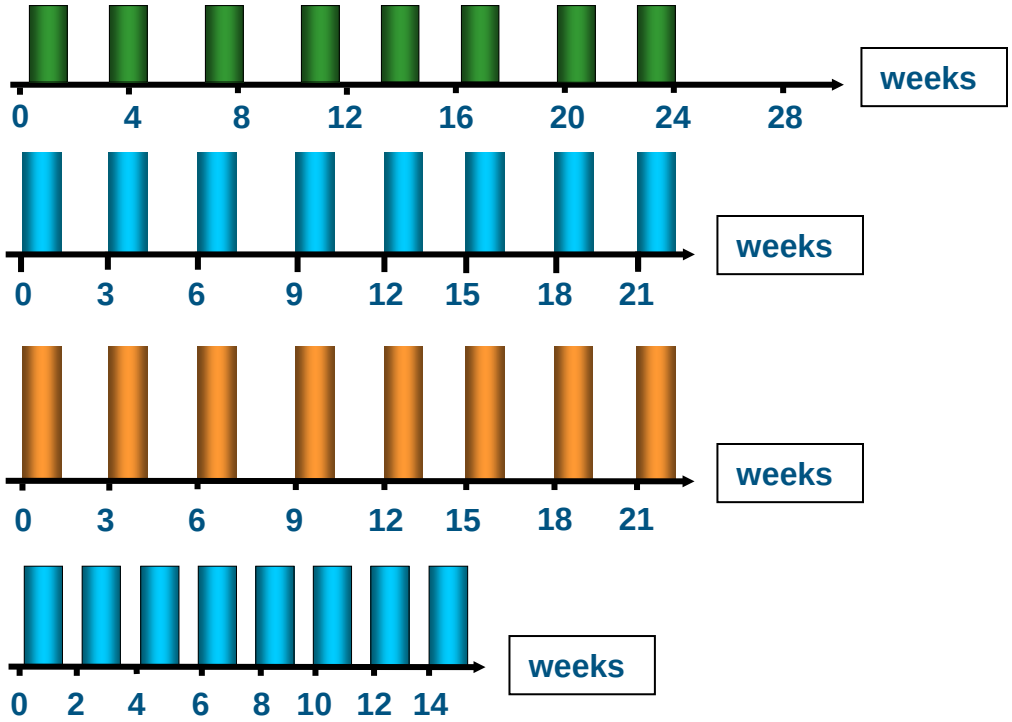
Dose-intensification strategies
for first-line Lymphoma treatment

Conventional chemo

BEACOPP baseline

BEACOPP escalated

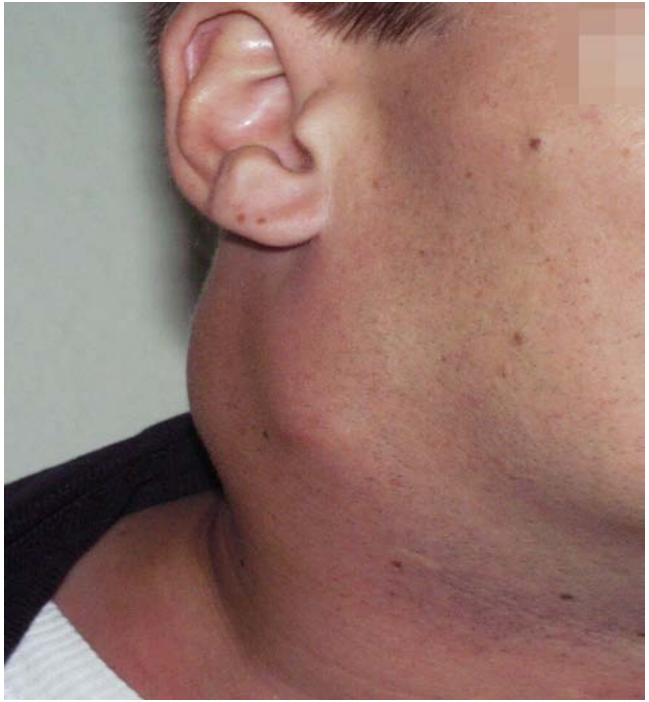
CHOP-14, BEACOPP-14

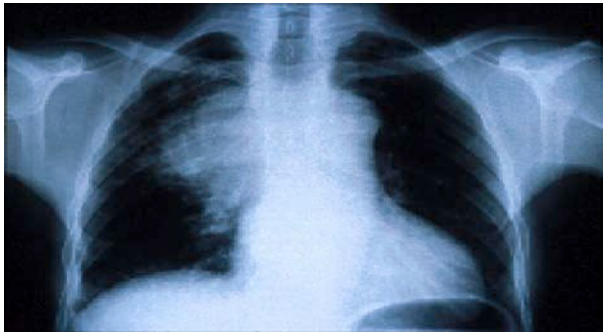


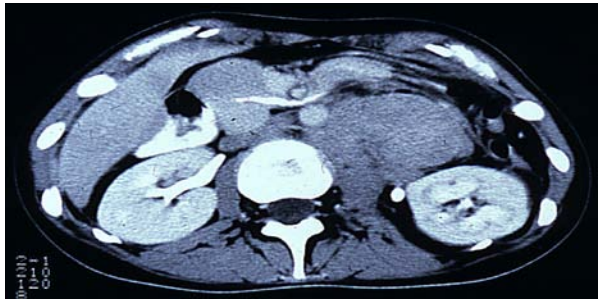
Chemotherapy of malignant lymphoma

- History and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

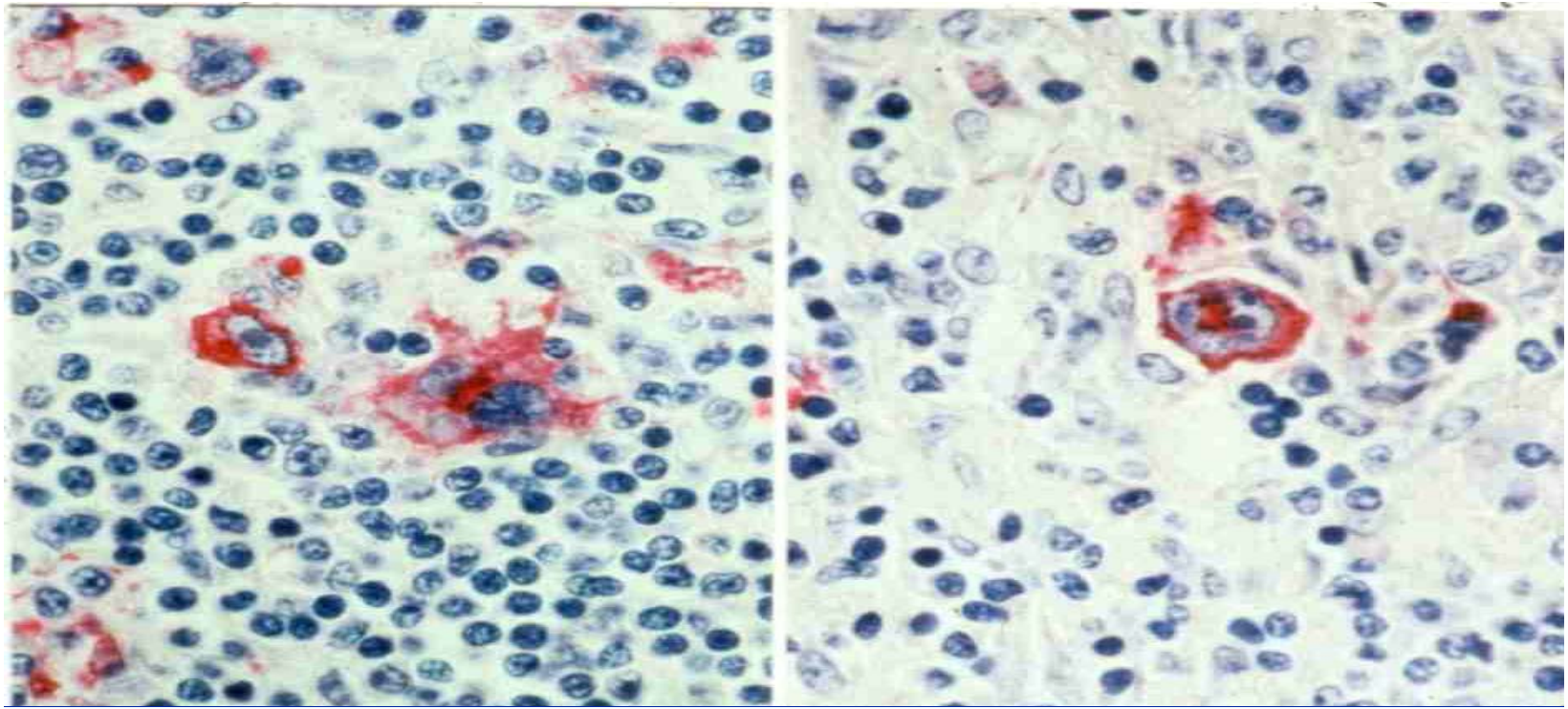
Hodgkin Lymphoma
Clinical Presentation







Hodgkin Lymphoma
Immunohistology



WHO Classification for HL (2001)

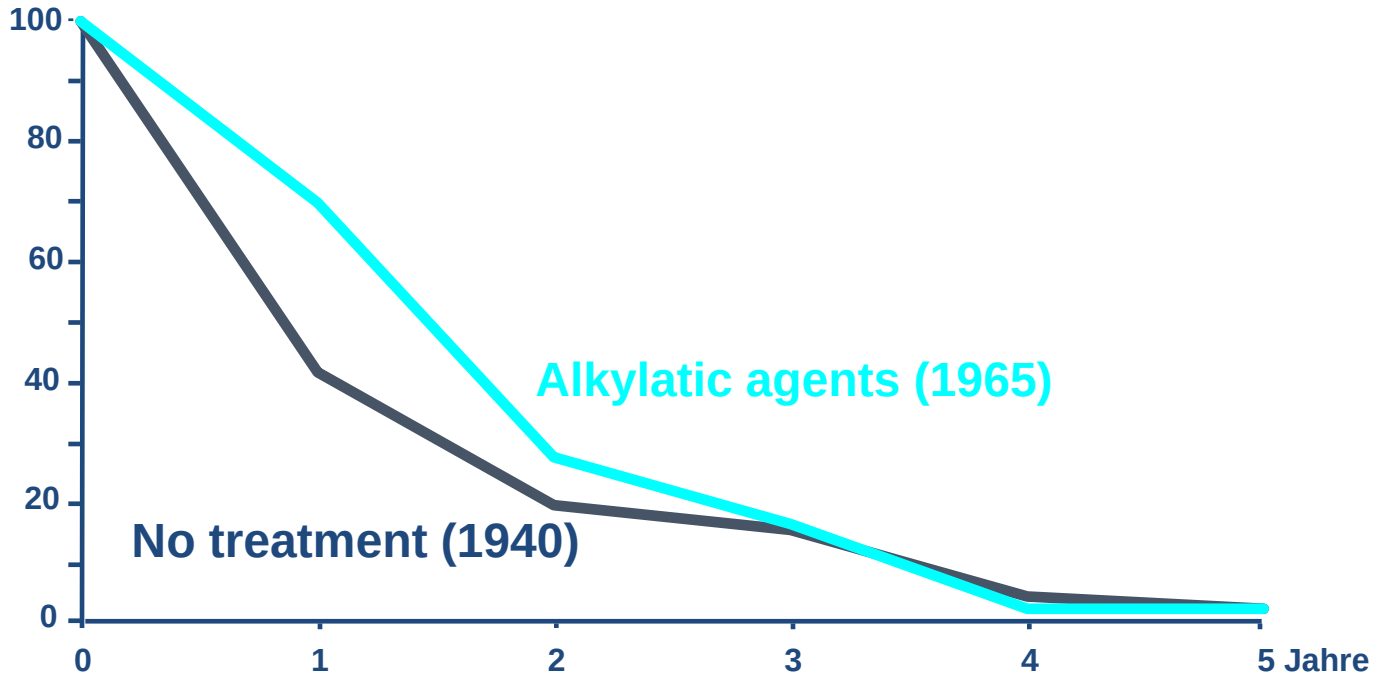
Classical HL (cHL)

- **Lymphocyte-rich classical HL (5%)**
- **Nodular Sclerosis (60-80%)**
- **Mixed Cellularity (25-30%)**
- **Lymphocyte Depletion (1%)**

Nodular Lymphocyte predominant HL (5%)

Hodgkin Lymphoma

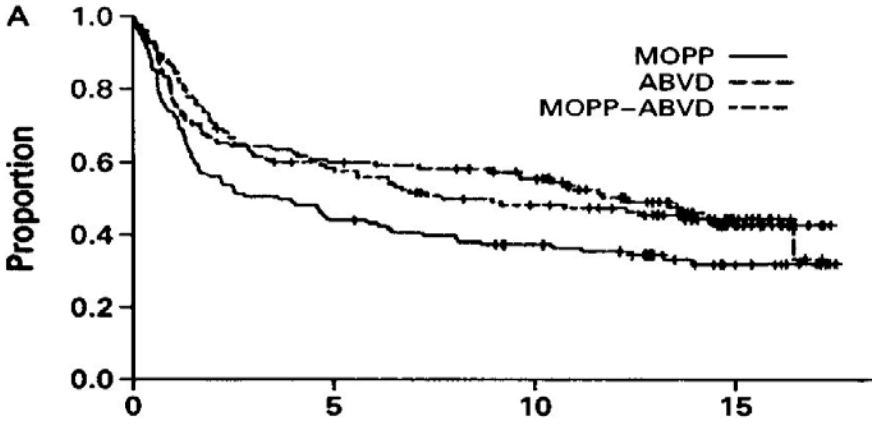
Historical prognosis in advanced stages



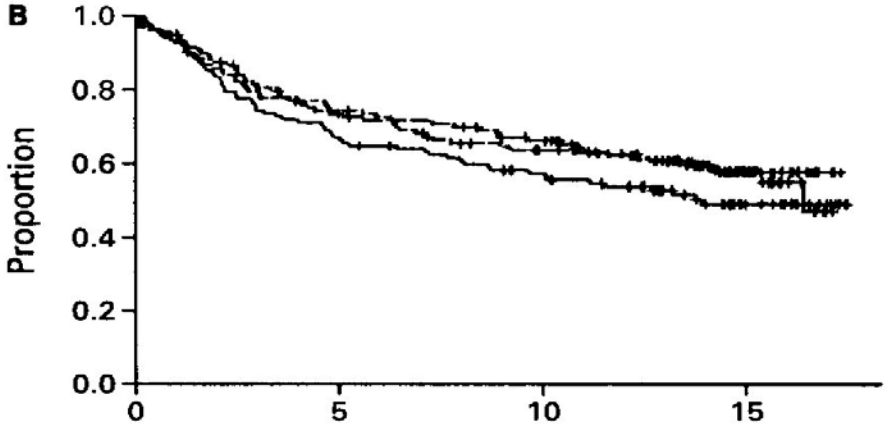
HL treated with MOPP and ABVD

Patients in advanced stages

FFTF



OS

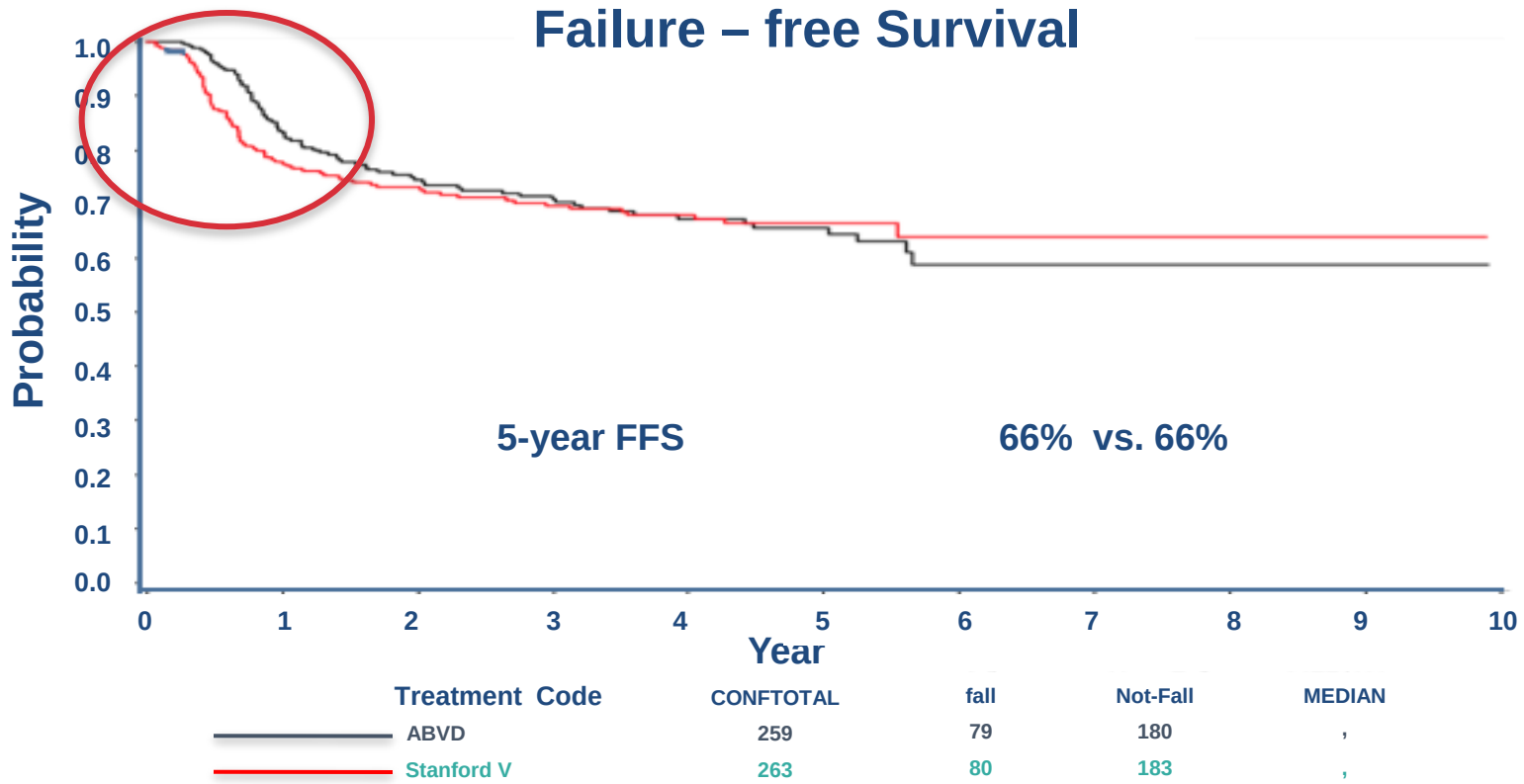


Years after study entry

Canellos G et al NEJM 2002

US Intergroup Trial E2496

ABVD vs Stanford



Gordon et al; JCO 2013

What about ABVD needs improving?

- Bleomycin lung toxicity with ABVD
- Efficacy of ABVD is decreased in certain subgroups
  - In patients with stage III/IV disease, the 5-year FFS is about 65%
  - In patients >60 years, the 5-year FFS is poor
  - In patients with IPS 3-7, the 5-year FFS is about 65%
- Long-term tumour control of 70% not good enough

Improve efficacy!

BEACOPP

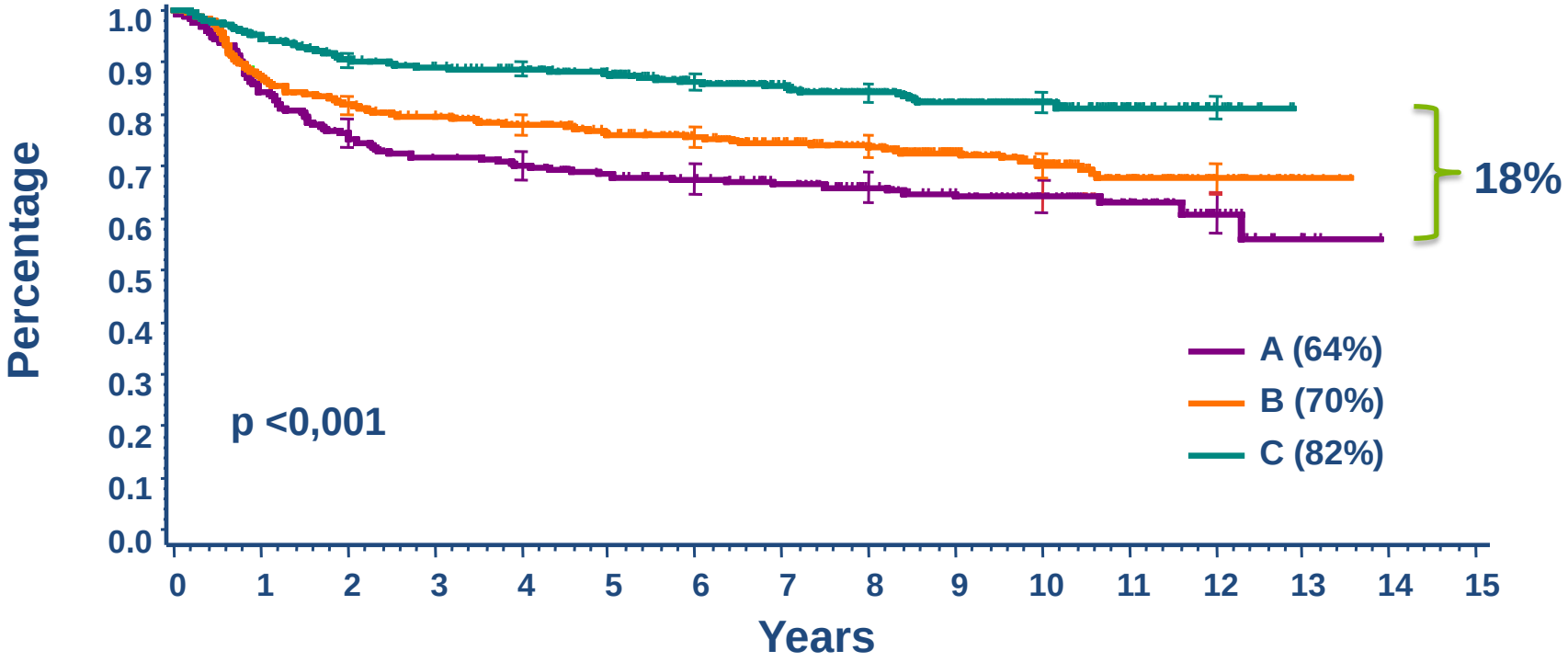
Baseline (base) and escalated (esc)

Drug	base[2]	esc[2]	Route	Schedule
Bleomycin	10	10	iv	8
Etoposide	100	200	iv	1-3
Adriamycin	25	35	iv	1
Cyclophosphamide	650	1250	iv	1
Vincristine	1.4[1]	1.4[1]	iv	8
Procarbazine	100	100	po	1-7
Prednison		40	40	po 1-14
G-CSF	-	+	sc	8-14

[1]max. 2,0mg
[2]mg/m^2

GHSG HD9 trial

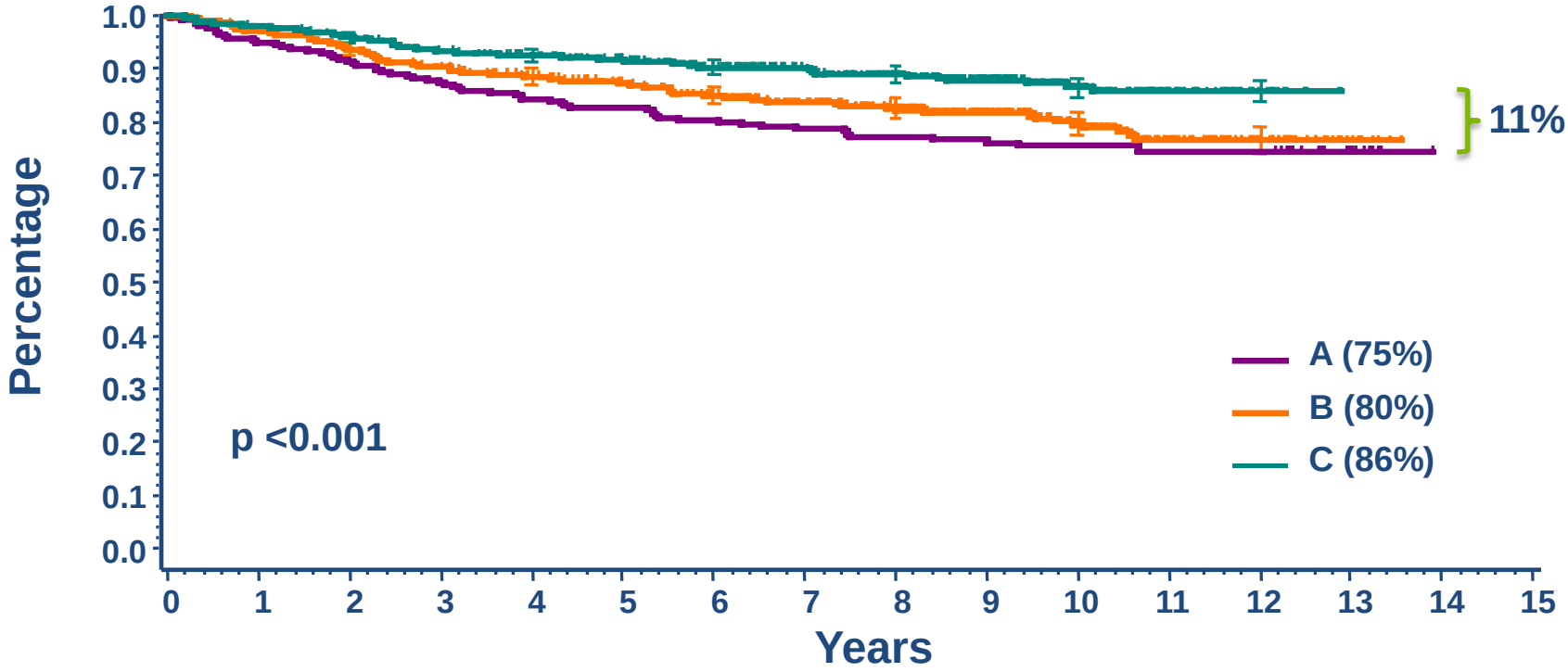
FFTF by treatment arm



Engert A et al, JCO 2009

GHSG HD9 trial

OS by treatment arm



Engert et al; JCO 2009

GHSG HD9 Trial

Causes of death at 10 years (% of all pts)

	C/ABVD n=261	BEAbase n=469	BEAesc n=466
HL	11.5	8.1	2.8
Acute tox. (first-line)	1.9	1.5	1.7
Acute tox. (salvage)	1.9	1.5	0.6
Second malignancy	3.1	3.6	3.2
Cardio-respiratory	1.2	0.9	0.9
Pulmonary	0.4	0.4	0.2
Other/unknown	3.8	3.0	2.1
All deaths	25	20	14

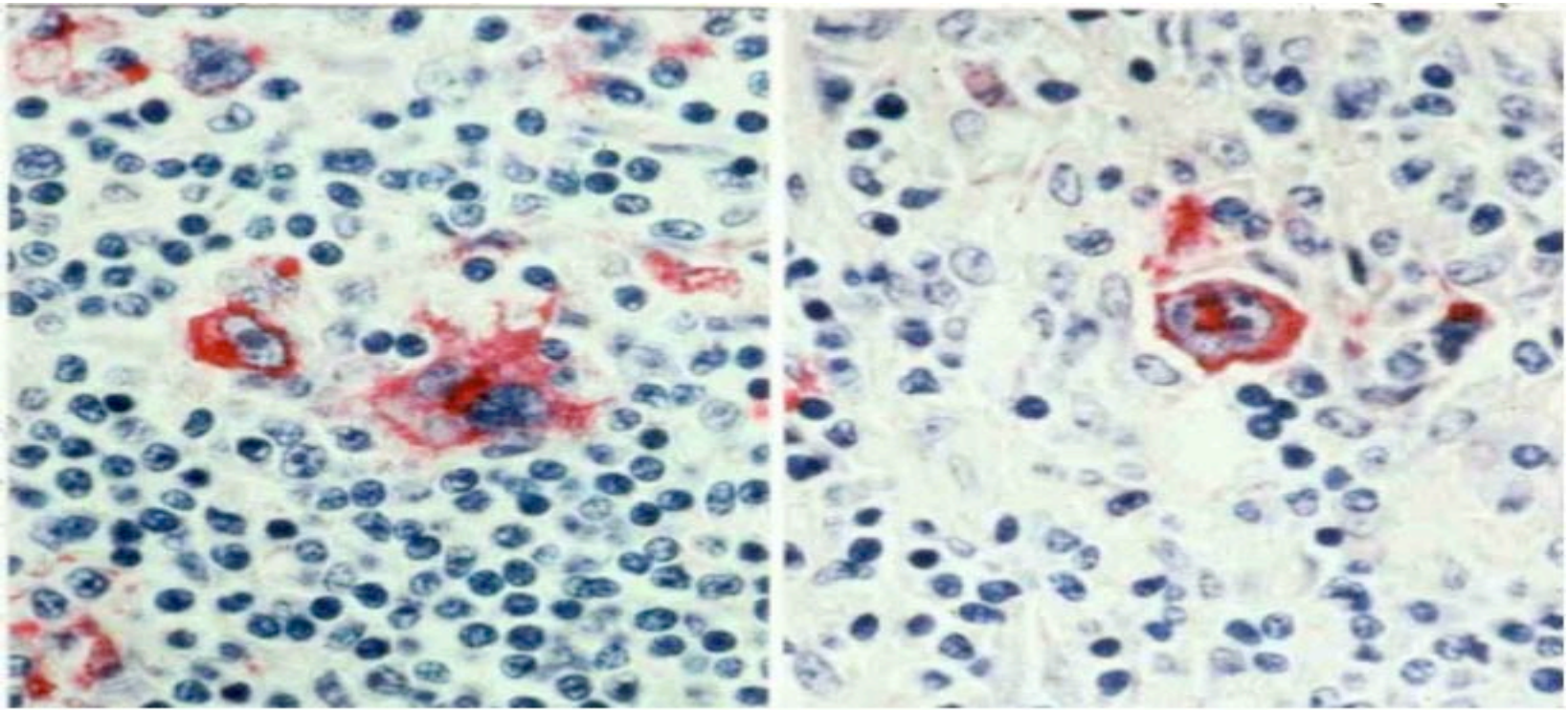
Engert et al; JCO 2009

How can we improve BEACOPP$_{escalated}$?

Early mortality	**linked to dose-intensity and Kairos principle, not to a specific drug**
sAML/MDS	**cyclophosphamide, etoposide, procarbazine**
Infertility	**cyclophosphamide, procarbazine**
Organ toxicity	**bleomycin: lung, vincristine: PNP, steroids: infections**

Immunohistology of cHL

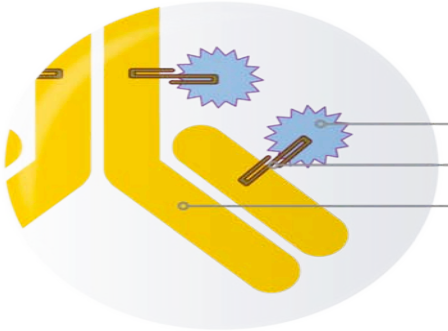
CD30 staining



Courtesy of H. Stein

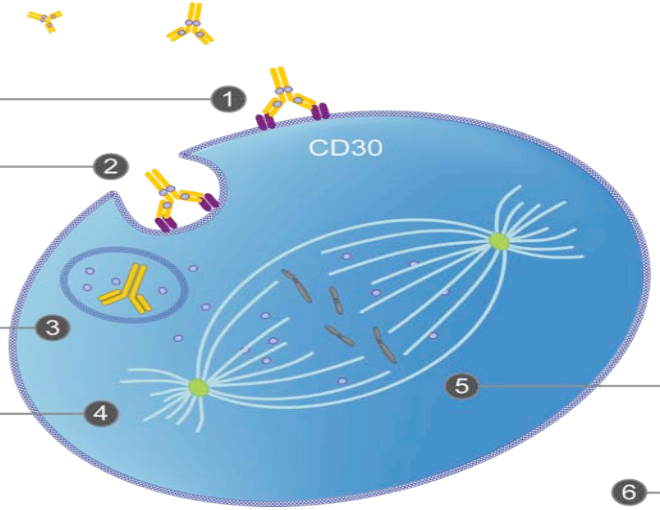
Brentuximab Vedotin

Mechanism of action



Brentuximab vedotin (SGN-35) ADC

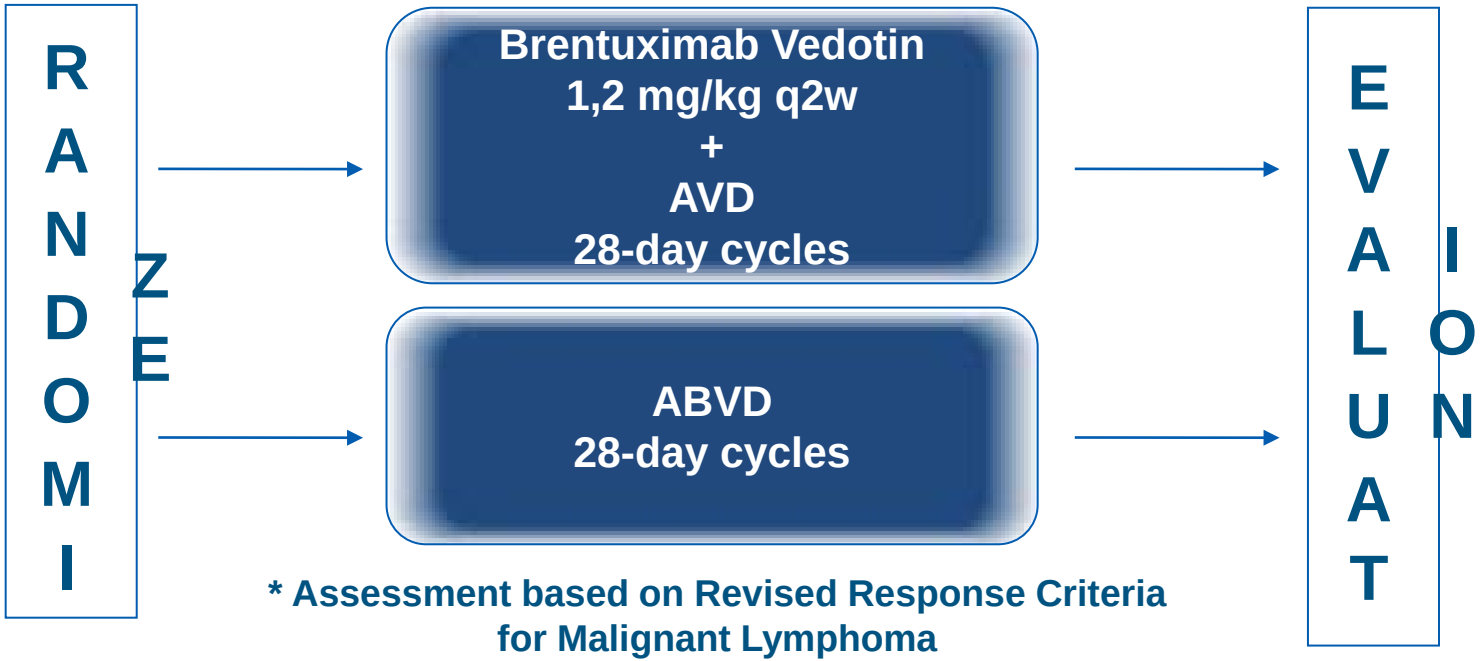
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody



1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts Microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

ECHELON-1: Phase III Trial

BV + AVD vs. ABVD in frontline advanced cHL



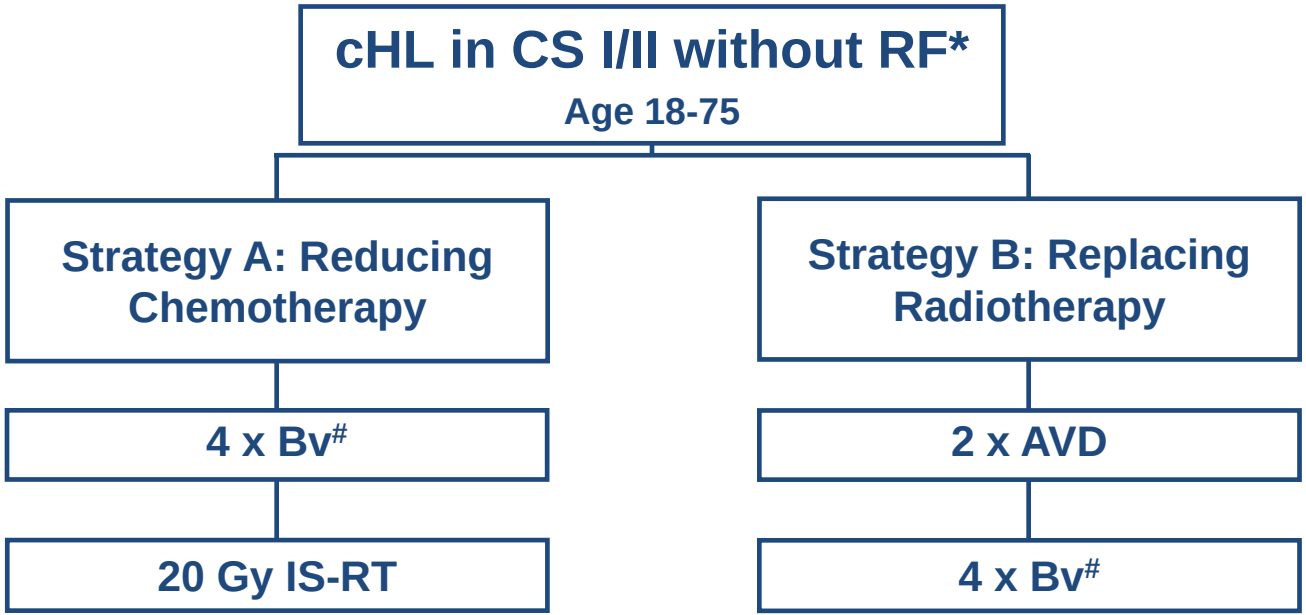
Younes et al, ASCO 2013; Chicago, US (Abstract #TPS8612)

Remodeling BEACOPPesc

Targeted BEACOPP Phase II Trial

Drug	Day	BEACOPP	BrECAPP	BrECADD
Bleomycin	8	10		
Etoposide	**1-3**	**200**	**200**	**150**
Adriamycin	**1**	**35**	**35**	**40**
Cyclophosphamide	**2**	**1250**	**1250**	**1250**
Vincristine	8	1.4		
Brentuximab vedotin	1		**1.8**	**1.8**
Procarbazine	1-7	100	100	
Prednisone	1-14	40	40	
Dacarbazine	**2-3**			**250**
Dexamethasone	**1-4**			**40**
Efficacy index (Hasenclever)			**26.9**	**25.8**

GHSG Phase II trial
in early-stage favorable HL

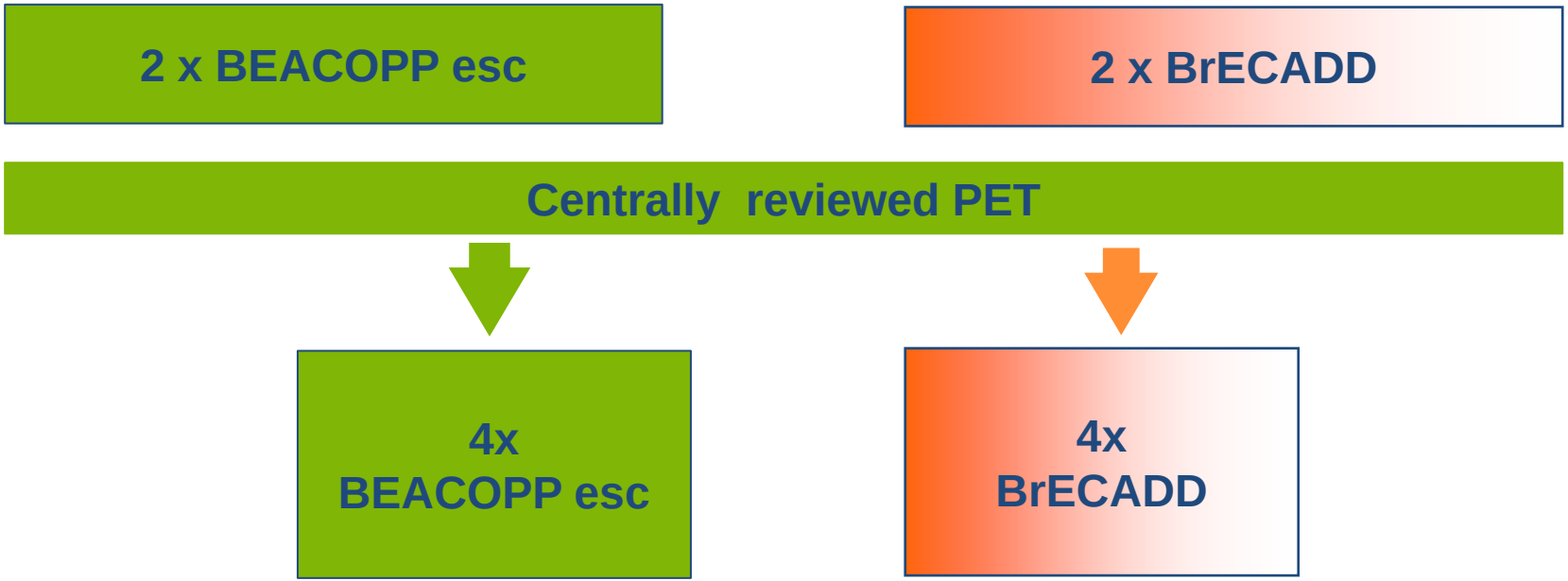


*a) large mediastinal mass b) extranodal disease c) elevated ESR d) ≥3 nodal areas

to be discussed: 1.8 mg/kg every 3 weeks or 1.2 mg/kg every 2 weeks

HD21: GHSG Perspective

BV in advanced stage HL



End of therapy and residual nodes > 2.5 cm:

PET positiv: **Rx**

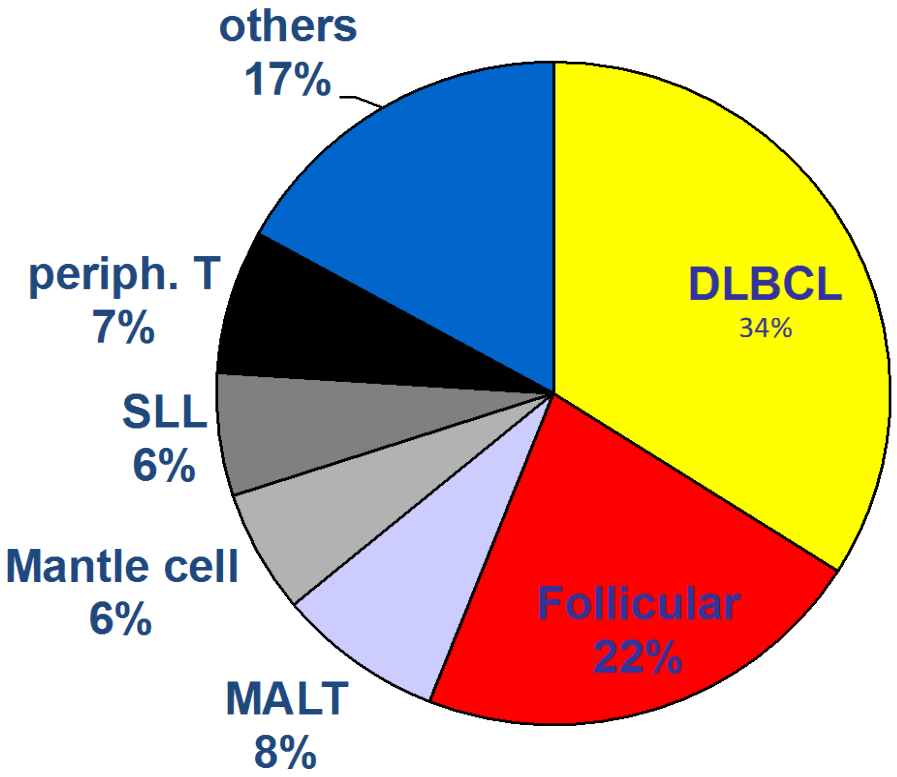
PET negative: **Follow up**

Chemotherapy of malignant lymphoma

- History and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

Non Hodgkin lymphoma

Subtypes



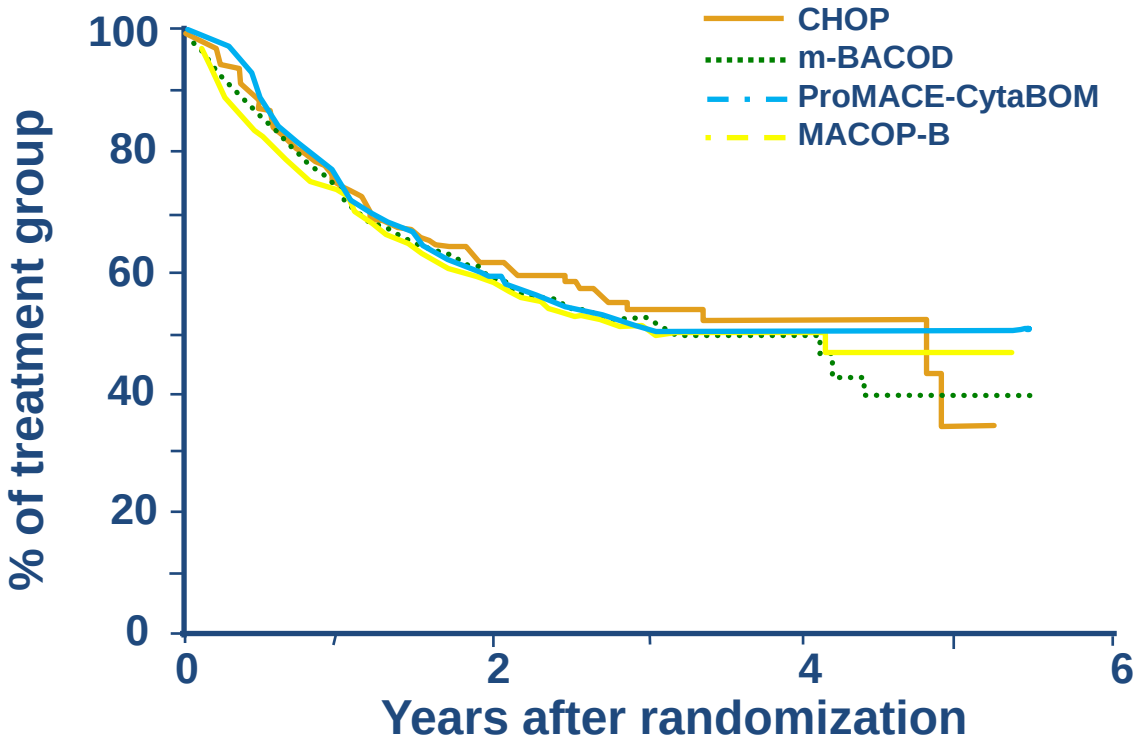
CHOP-21

Combination chemotherapy

(C)yclophosphamid
(H)ydroxydaunorubicin (Doxorubicin)
(O)ncovin®) (Vincristin)
(P)redniso(lo)n

Drug	Dose	Mode	Days
(C)yclophosphamid	750 mg/m^2	iv	1
(H)ydroxydaunorubicin (Doxorubicin)	50 mg/m^2	iv	1
(O)Ncovin® (Vincristin)	1,4 mg/m^2	iv	1
(P)redniso(lo)n	100 mg/m^2	po	1 - 5

SWOG: CHOP *vs* 3 intensive regimens in advanced NHL



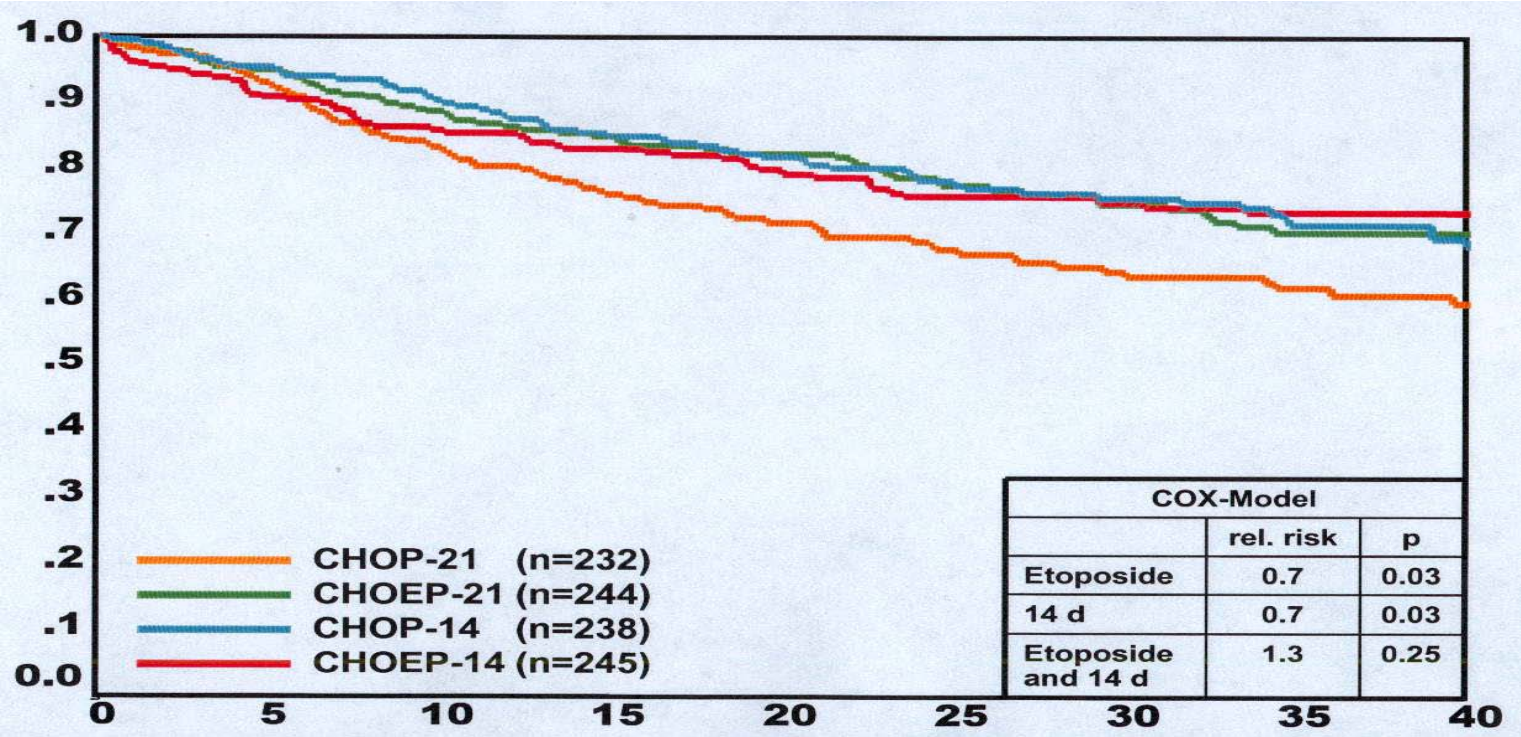
Patients at risk	3-year estimate (%)
225	54
223	52
233	50
218	50

p = 0.90

Fischer *et al.* *NEJM* 1993; 328: 1002–6

NHL-B

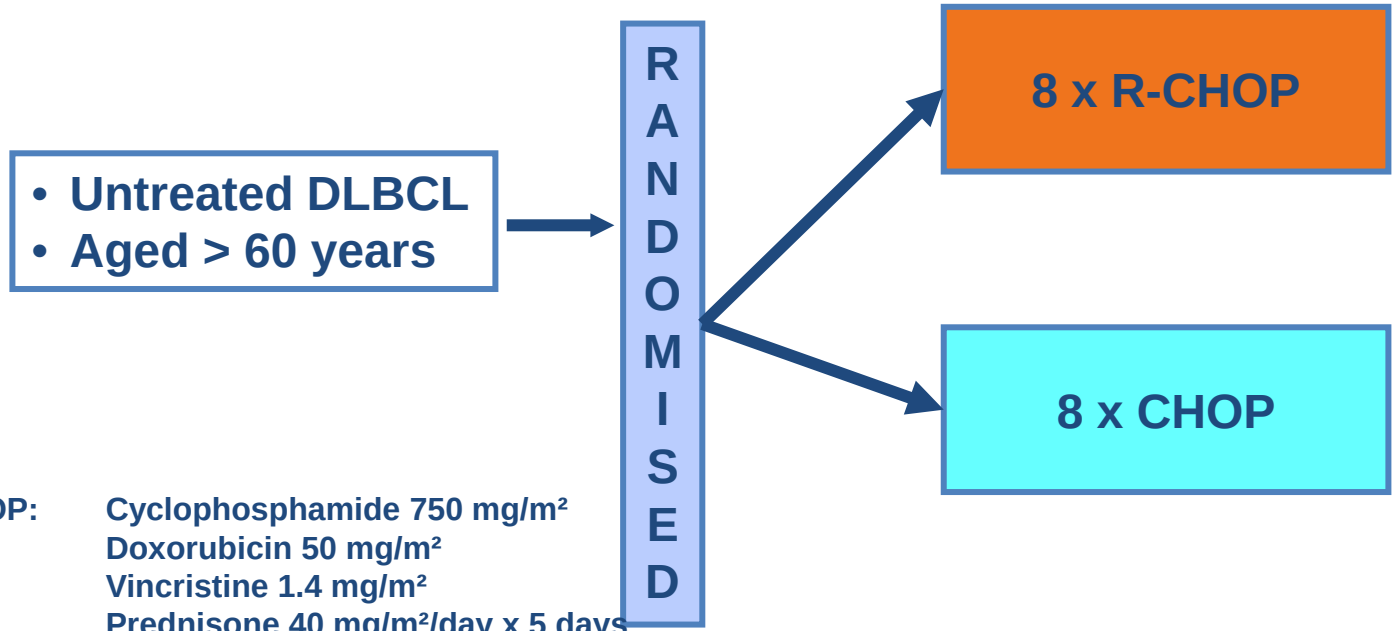
OS of all patients (*n* = 956)



COX-Model		
	rel. risk	p
Etoposide	0.7	0.03
14 d	0.7	0.03
Etoposide and 14 d	1.3	0.25

Pfreundschuh *et al* 2000: unpublished data

GELA LNH-98.5:
Trial design



CHOP: Cyclophosphamide 750 mg/m²
Doxorubicin 50 mg/m²
Vincristine 1.4 mg/m²
Prednisone 40 mg/m²/day x 5 days

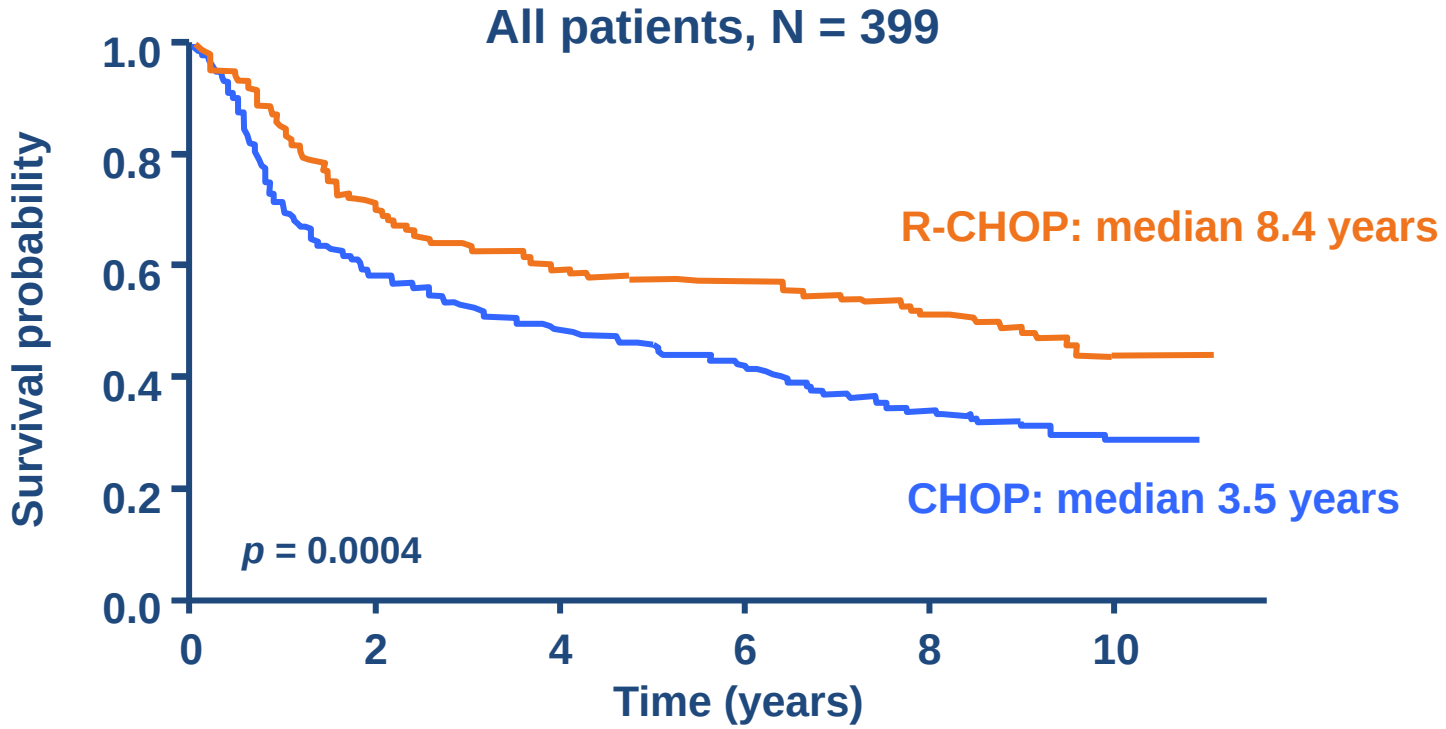
R-CHOP: Rituximab 375 mg/m² Day 1 of each cycle

Cycles every 21 days

Coiffier B, *et al. Blood* 2010; 116:2040–2045.

GELA LNH-98.5 10-year follow-up

Overall survival

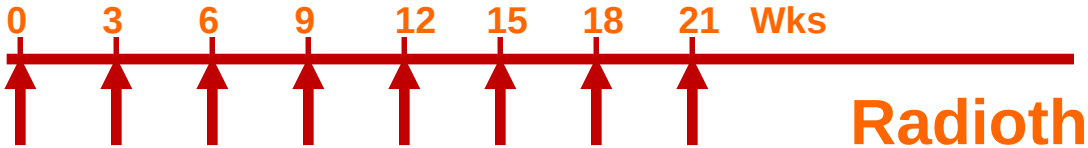


Coiffier B, *et al. Blood* 2010; 116:2040–2045.

Standard Regimen for DLBCL Patients

R-CHOP

R-CHOP 21



Radiotherapy?

Aggressive NHL:
Prognostic factors - aaIPI

- Poor performance status (ECOG 2-4)
- Elevated lactate dehydrogenase (LDH)
- Stage III or IV disease

- **Risk groups:**
  - 0 : low risk
  - 1 : low-intermediate
  - 2 : high-intermediate
  - 3 : high risk

The International Non-Hodgkin's Lymphoma Prognostic Factors Project
N Engl J Med 1993; 329:987–994.

Results with R-CHOP in DLBCL

- 5-year survival according to aaIPI & age
  - aaIPI score = 0: >85%
  - Young, aaIPI score = 1: >80%
  - Young, aaIPI score >1: 60%
  - Elderly, aaIPI score >0: 50%
  - Very old: 30%
- For 30-40% of patients, R-CHOP is not satisfactory

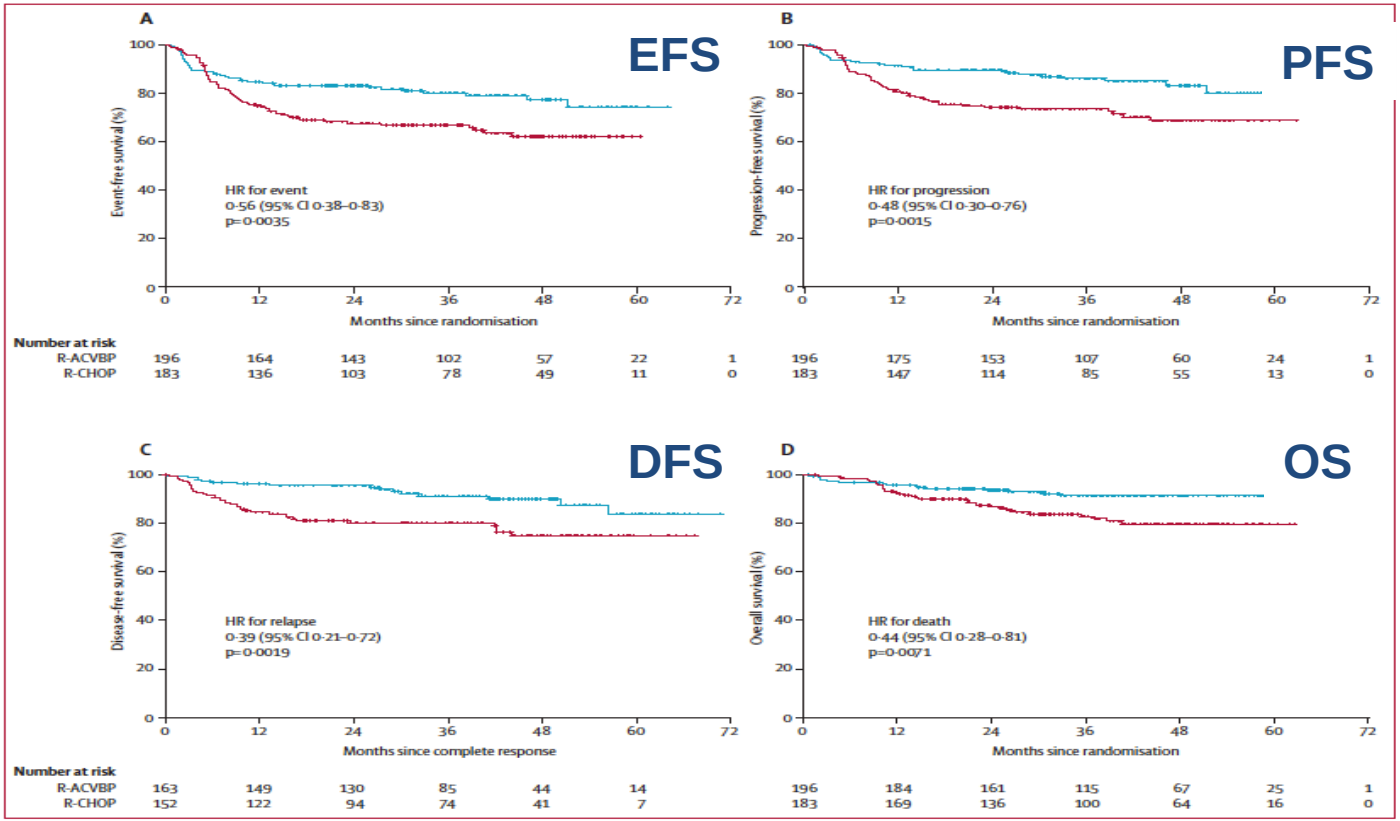
How to further improve DLBCL

- **Refractory**
  - Use new drugs
  - Subgroup of patients with high risk
- **Relapse**
  - Higher dose chemotherapy
  - Prevent relapse
- **At time of relapse**
  - Better salvage regimens

DLBCL: Higher dose regimen

LNH03-2B study

R-ACVBP
R-CHOP



C Rechert et al. Lancet 2011;378:1858

DLBCL: Salvage therapy

- No good regimen
  - R-DHAP, R-ICE, R-ESHAP, R-GDP
  - All identical, few CR, particularly for early relapses
- Necessity to design a New Regimen
  - With all/some new drugs
  - Plus rituximab or another antibody
  - Plus chemotherapy
- Before autologous transplant

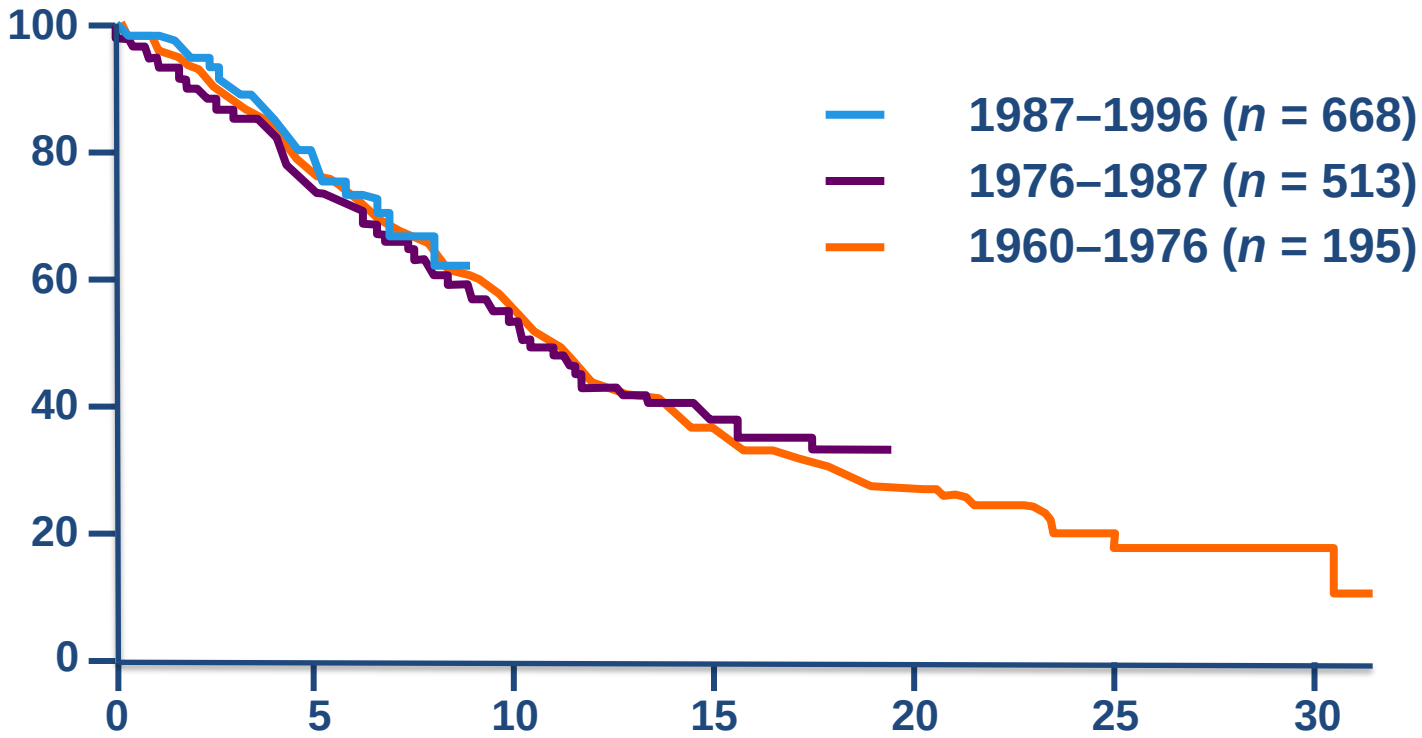
DLBCL: Conclusions

- **Medical need: new combinations for poor risk patients**
  - **If possible to identify them**
- **Particularly for refractory/early relapse**
- **New drugs combination at time of relapse**
- **Look at cure**

Chemotherapy of malignant lymphoma

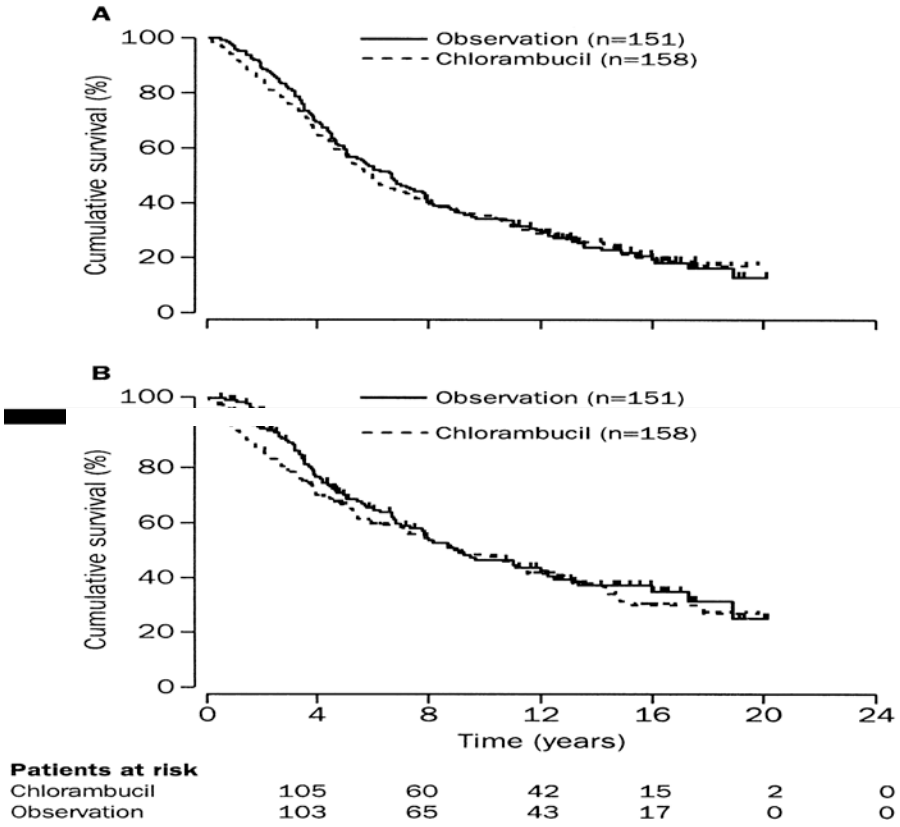
- History and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

Indolent NHL – Overall Survival



Horning. *Semin Oncol*. 1993; 20(suppl 5): 75–88

FL: Watch & wait or early treatment?



Overall survival

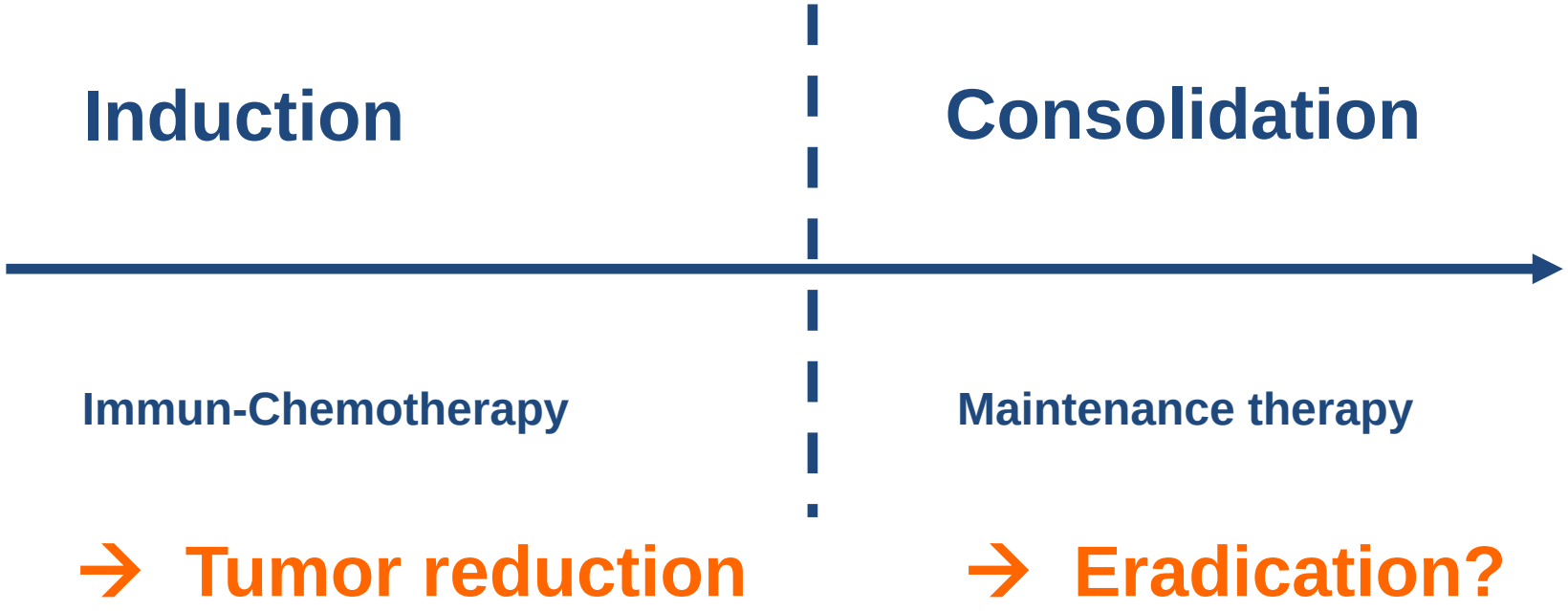
Disease-associated survival

Ardeshna KM et al. Lancet 262: 516, 2003

FL: Reasons to initiate treatment

- **B-symptoms**
- **Hematopoietic failure**
  (Hb<11g/dl, granulocytes <1.500/µl, platelets <100.000 /µl)
- **Large tumor burden**
  (3 areas >5 cm or 1 area >7.5 cm)
- **Rapid progression**
  (increase of tumor mass >50% within 6 months)
- **Complications due to disease**
  (pain, infarction of spleen, hyperviscosity syndrome, etc.)
- **No role for FLIPI, LDH, B2M, age, stage, or bone marrow involvement**

Treatment strategies in indolent lymphomas



Standard of care in pts with indolent lymphomas

- Still a role for watch & wait in asymptomatic pts
- Wait for indication of treatment
- Combined R-chemo standard; R-CHOP most often used
- No clear superiority of R-CHOP over R-CVP
- BR with longer PFS and lower toxicity
- R-chemo plus R-maintenance current best option in follicular particularly in relapsed disease
- No relevant role for high-dose chemo and ASCT
- Perspectives: Bortezomib, Lenalidomide, Obinutuzumab (GA101), Ofatumumab, Temsirolimus, Ibrutinib, Idelalisib, ABT-199

Chemotherapy of malignant lymphoma

- History and principles of chemotherapy
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma
- Summary

Chemotherapy of malignant lymphoma

- Development of multi-agent chemo led to cure in lymphoma patients
- Most frequently used today are CHOP, ABVD and BEACOPP
- Typical side effects include alopecia, aplasia, infection, neuropathy, fatigue and infertility
- Major long-term effects are 2nd neoplasia and organ failure
- Prognosis of pts much worse at relapse (DLBCL, HL)
- New less toxic drugs have become available and might improve the long-term prognosis

WWW.ESTRO.ORG/SCHOOL

Combined Modality Treatment of Hodgkin Lymphoma

Andreas Engert, MD

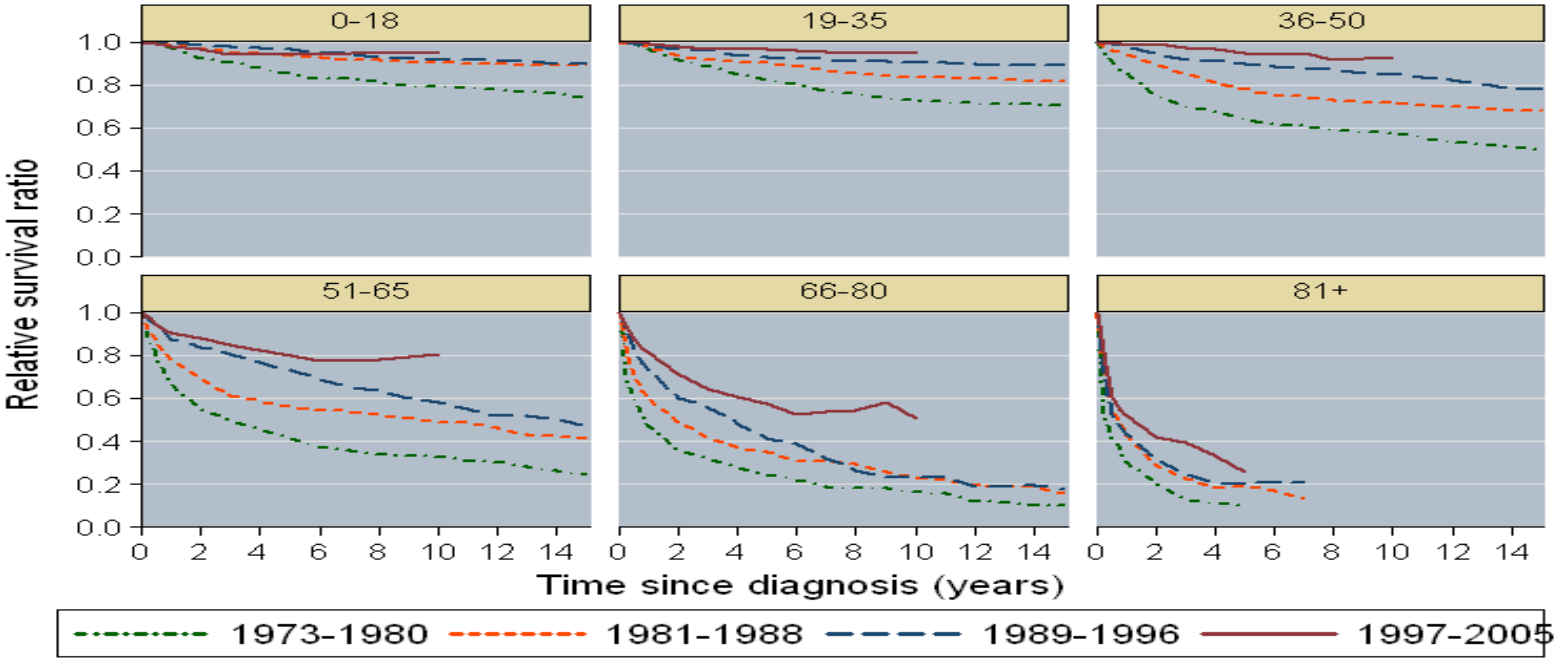
Chairman, German Hodgkin Study Group
University Hospital of Cologne

Combined Modality Treatment of HL

- **Background**
- **Hodgkin Lymphoma – early stages**
- **PET-driven trials**
- **Chemo-Immunotherapy**
- **Summary**

Hodgkin Lymphoma

Cumulative relative survival of HL pts in Sweden



Courtesy of Magnus Björkholm 2010

Hodgkin Lymphoma

Late side effects after treatment

- **2nd NPL**
  - **AML**
  - **NHL**
  - **Solid tumours**
- **Organ damage**
  - **Lung**
  - **Heart**
  - **Thyroid**
- **Others**
  - **Fertility**
  - **Fatigue**
  - **Psycho-social**

GHSG Clinical Trials

Patients recruited since 1978

1978 - 88	HD 1 - 3	506
1988 - 94	HD 4 - 6	2035
1994 - 98	HD 7 - 9	2865
1998 - 02	HD10-12	3948
2003 - 09	HD13-15	5171
2010 - 16	HD16-18	4279
Total		18804

Combined Modality Treatment of HL

- Background
- Hodgkin Lymphoma – early stages
- PET-driven trials
- Chemo-Immunotherapy
- Summary

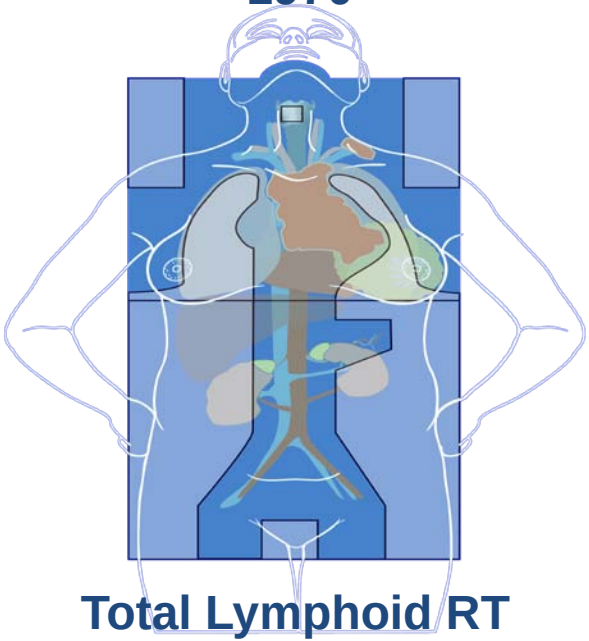
GHSG Risk Allocation for HL Patients

<table>
<tr><th></th><th colspan="4">Stage (Ann Arbor)</th></tr>
<tr><th>Risk factors</th><th>IA, IB, IIA</th><th>IIB</th><th>IIIA, IIIB</th><th>IVA, IVB</th></tr>
<tr><td>None</td><td colspan="2">Early favorable</td><td colspan="2" rowspan="2">Advanced</td></tr>
<tr><td>≥3 LN areas</td><td colspan="2" rowspan="4">Early unfavorable</td></tr>
<tr><td>Elevated ESR</td><td colspan="2" rowspan="3">Advanced</td></tr>
<tr><td>Large med mass</td></tr>
<tr><td>Extranodal disease</td></tr>
</table>

GHSG 2000

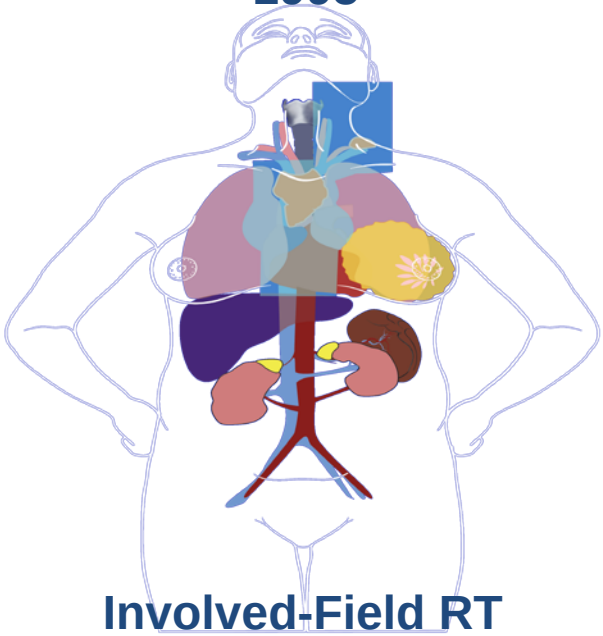
Hodgkin Lymphoma
Evolution of Radiotherapy

1970



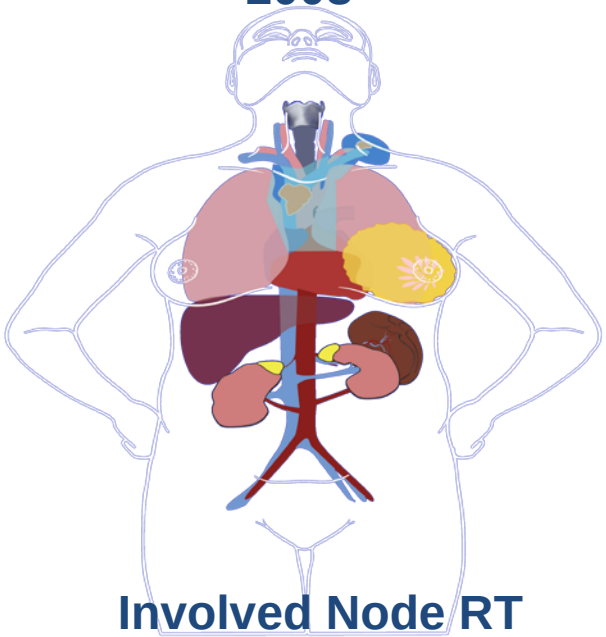
Total Lymphoid RT
44 Gy

1995



Involved-Field RT
36 Gy

2008

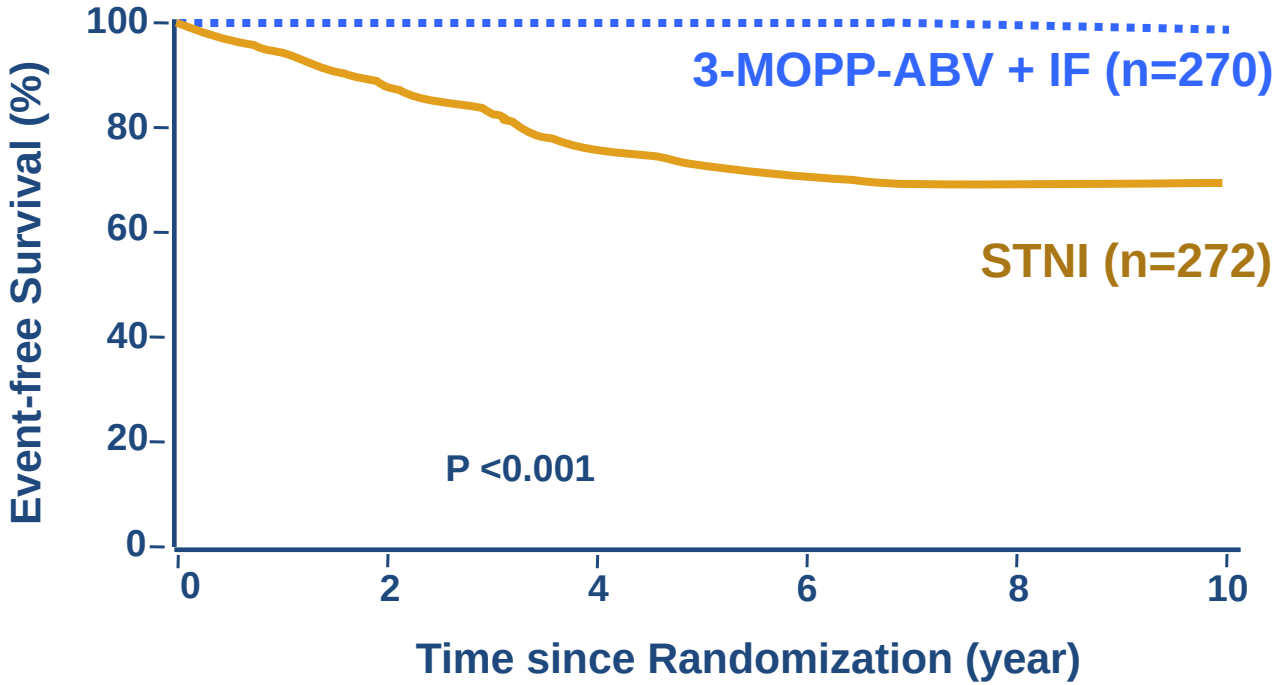


Involved Node RT
20-30 Gy

Adapted from Yahalom, Lugano 2008

EORTC H8F Clinical Trial

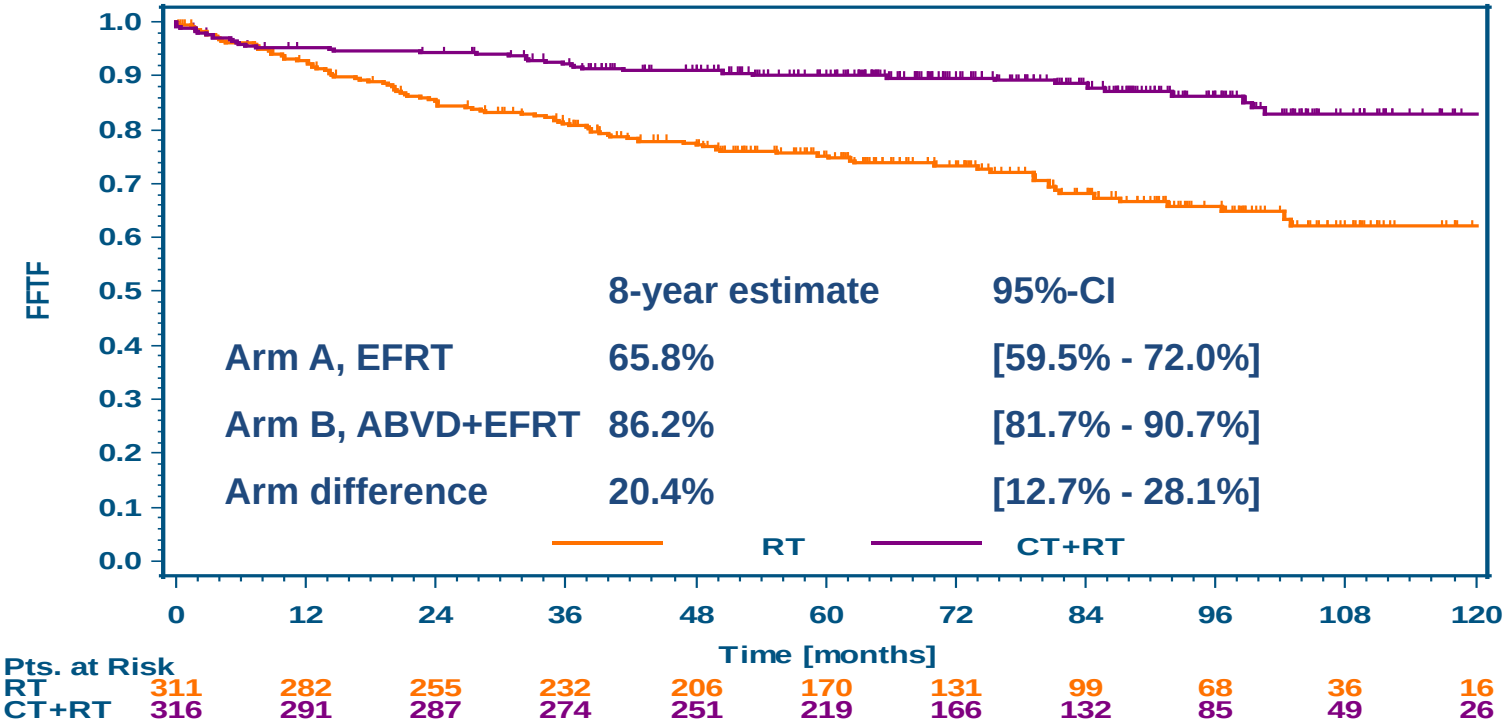
FFTF for pts with early favorable



Ferme et al; NEJM 2007

GHSG HD7 Clinical Trial

For early favorable HL (FFTF)



Engert et al; JCO 2007

HD7: Long-term Outcome

PFS

15-year estimate [95%-CI]
Arm A: 52.2% [44.9% to 59.5%]
Arm B: 72.8% [65.6% to 80.0%]
diff: 20.6% [10.4% to 30.9%]
HR = 0.45 [0.332 to 0.612]
Median observation time 120 months

OS

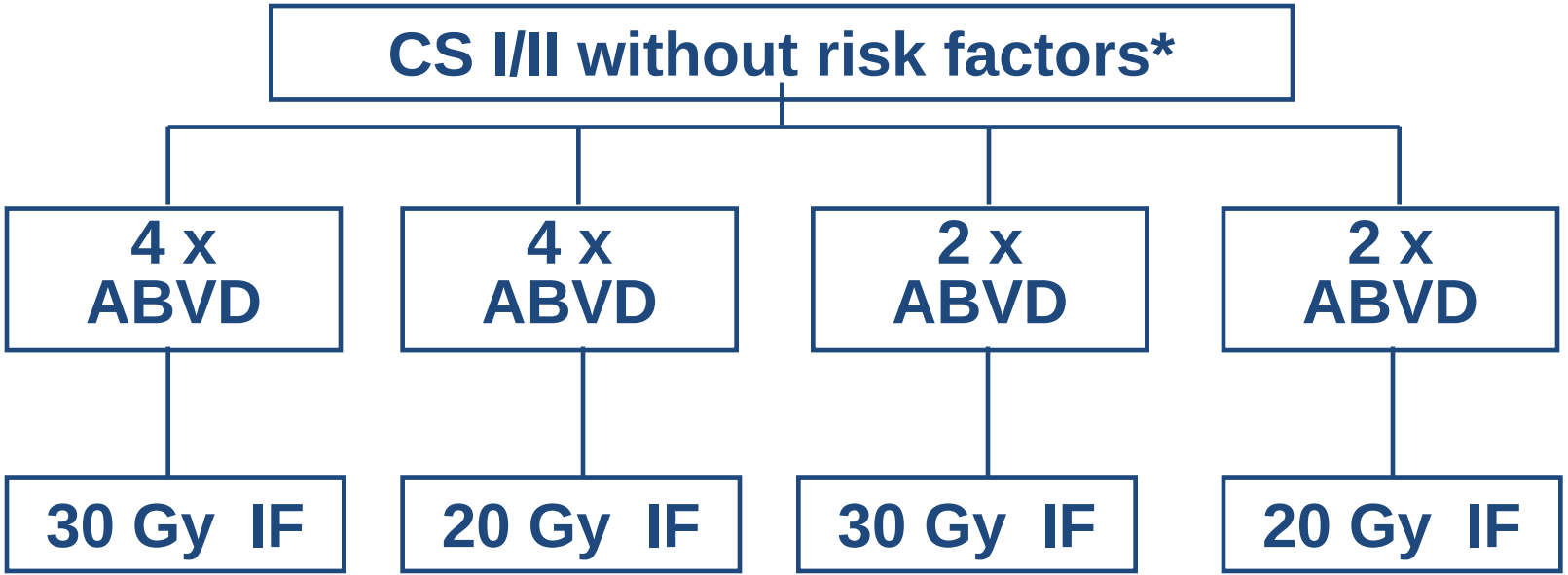
15-year estimate [95%-CI]
Arm A: 71.1% [71.2% to 83.0%]
Arm B: 79.7% [73.9% to 85.6%]
diff: 2.7% [-5.7% to 11.0%]
HR = 0.813 [0.560 to 1.179]
Median observation time 136 months

→ Significantly superior 15-year PFS with CMT compared to EF-RT only
→ No significant difference in 15-year overall survival (OS) observed

Bröckelmann et al; EHA 2016

GHSG HD10 Clinical Trial

Early favorable HL

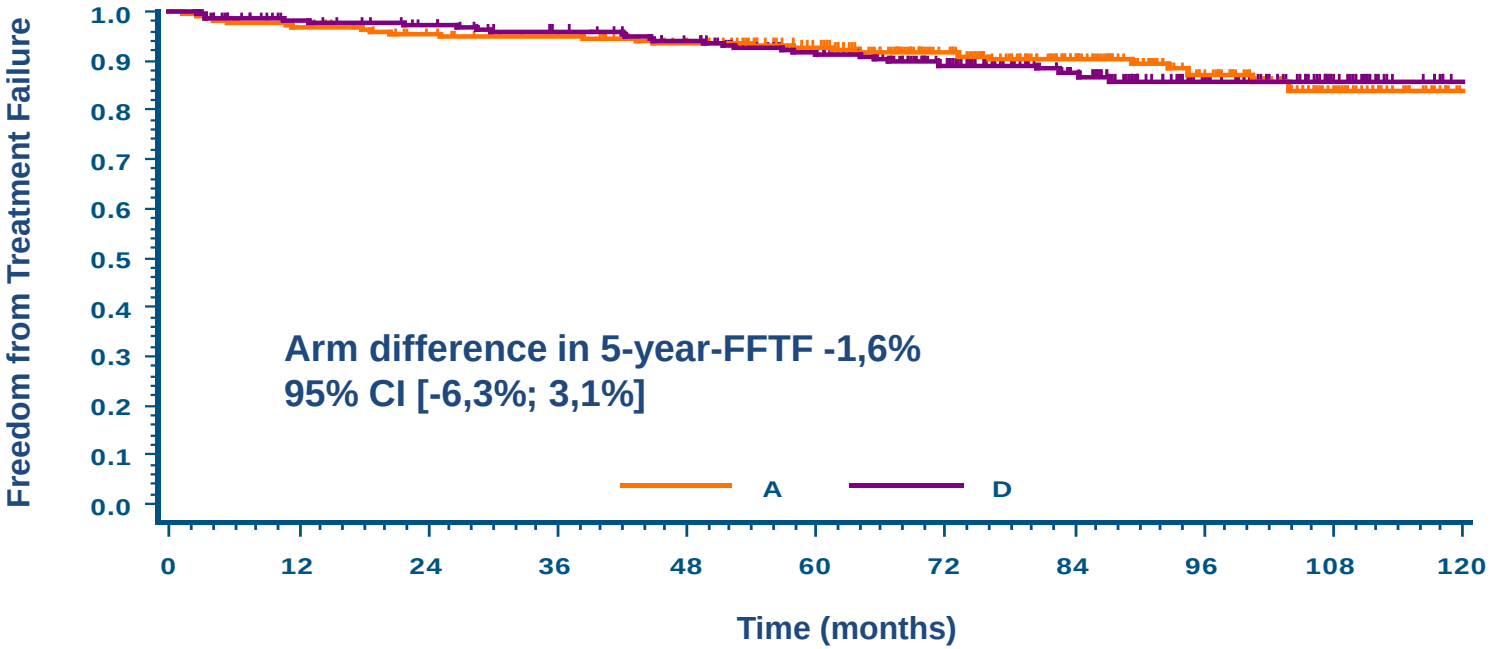


*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved

GHSG 2010

GHSG HD10 Clinical Trial

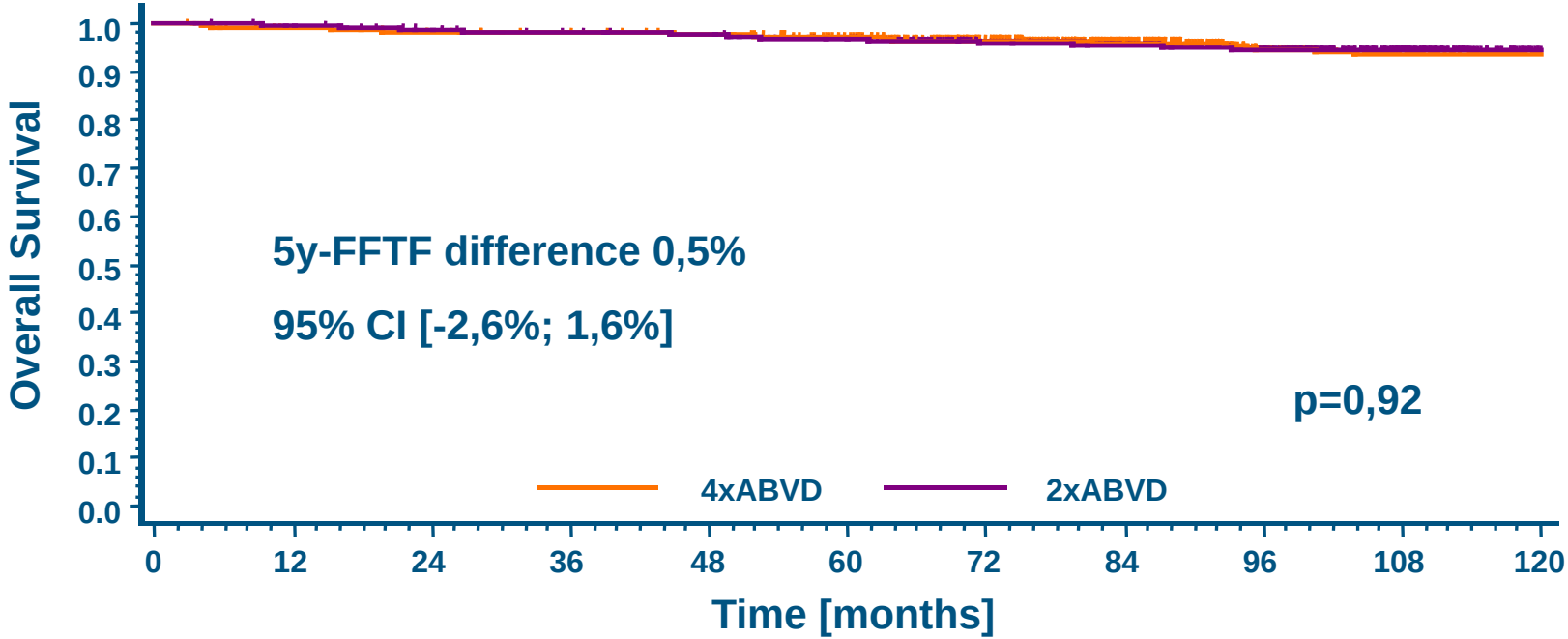
Weakest vs strongest arm (FFTF)



Engert A et al; NEJM 2010

GHSG HD10 Clinical Trial

Overall Survival



Engert et al; NEJM 2010

HD10: Long-term outcome

	10 year estimate [95%-CI]	Hazard Ratio [95%-CI]
4ABVD+30Gy	87.4% [82.9% to 91.9%]	
2ABVD+20Gy	87.2% [82.9% to 91.5%]	1.0 [0.6 to 1.5]
Difference	-0.2% [-6.4% to 6.0%]	

Median observation time 98 months

	10 year estimate [95%-CI]	Hazard Ratio [95%-CI]
4ABVD+30Gy	93.6% [90.5% to 96.7%]	
2ABVD+20Gy	94.1% [91.1% to 97.1%]	0.9 [0.5 to 1.6]
Difference	0.5% [-3.8% to 4.9%]	

Median observation time 113 months

→ No difference in 10-year PFS and OS between most and least intensive arms of therapy (i.e. 4 vs. 2xABVD and 20 vs. 30Gy IF-RT)

Bröckelmann et al; EHA 2016

HD10: Second Neoplasia

	10-year estimate [95%-CI]
4ABVD+30Gy	8.4% [4.6% to 12.3%]
4ABVD+20Gy	6.3% [2.8% to 9.8%]
2ABVD+30Gy	7.5% [3.7% to 11.3%]
2ABVD+20Gy	8.9% [4.8% to 13.0%]

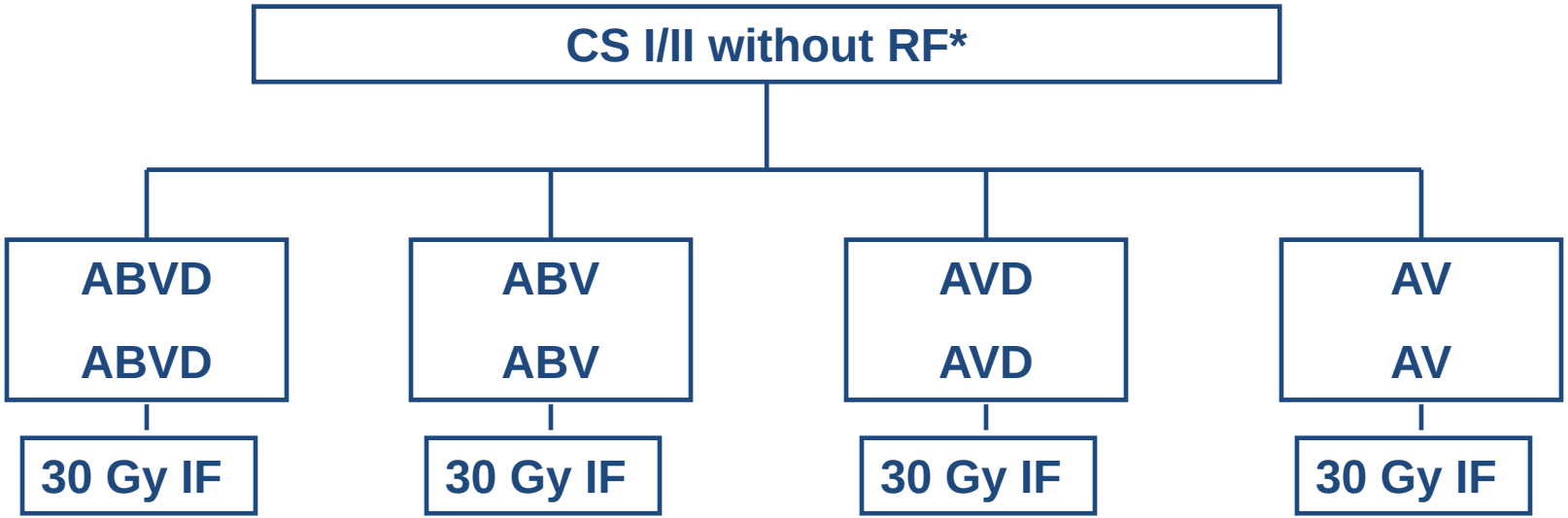
Median observation time 98 months

→ **No difference in SIR for any SN: A= 2.1, B= 1.5, C= 1.6, D= 2.1**
compared to the age- and sex-specific incidence in the German general population

Bröckelmann et al; EHA 2016

GHSG HD13 Clinical Trial

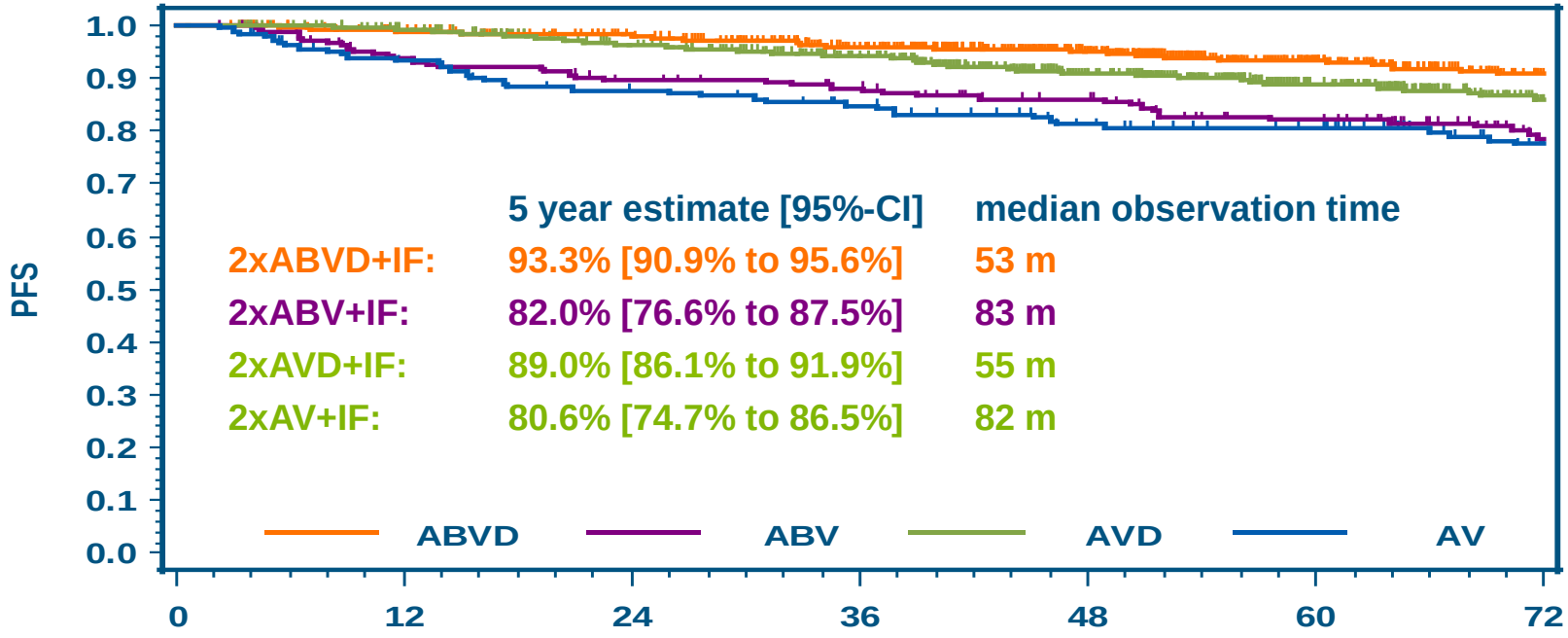
Early favorable HL



*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved

HD13: Progression-free survival

All patients (ITT)

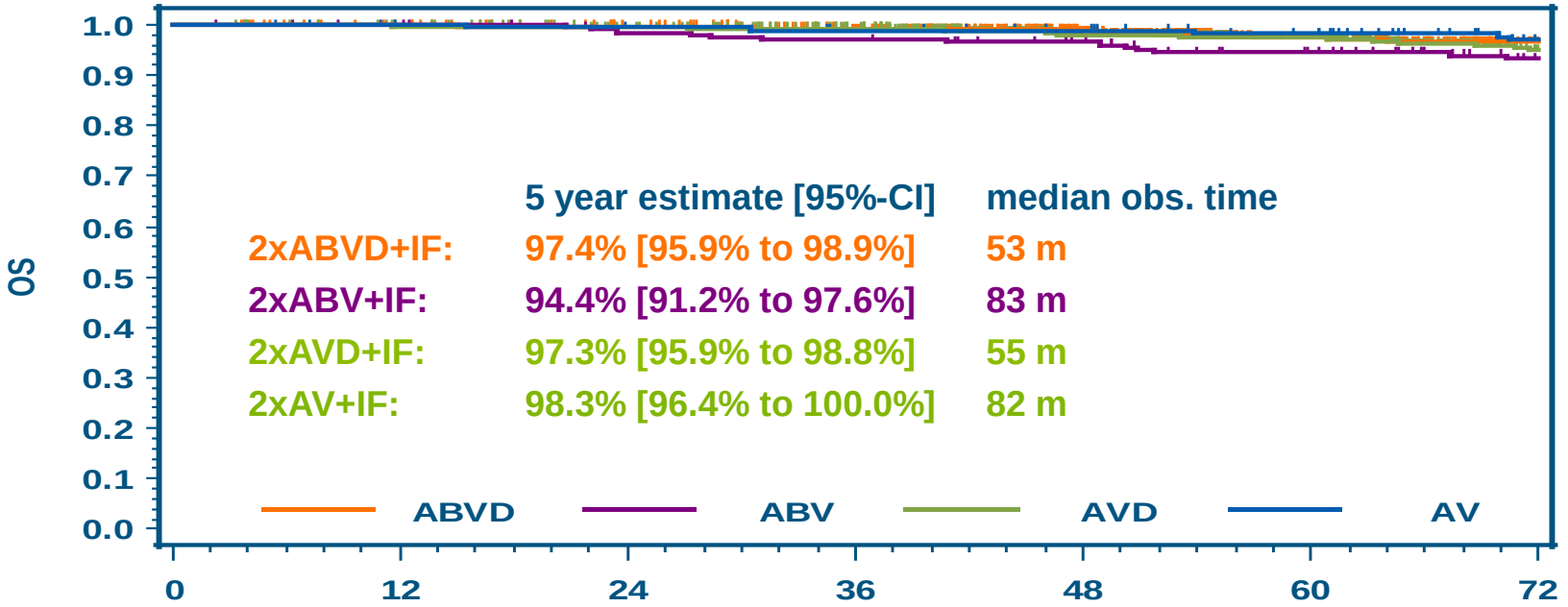


Pts. at Risk							
ABVD	623	593	556	490	362	228	130
ABV	209	189	178	170	156	139	109
AVD	620	592	540	477	344	230	126
AV	186	166	153	144	128	118	93

Behringer et al, Lancet 2014

HD13: Overall survival

All patients (ITT)

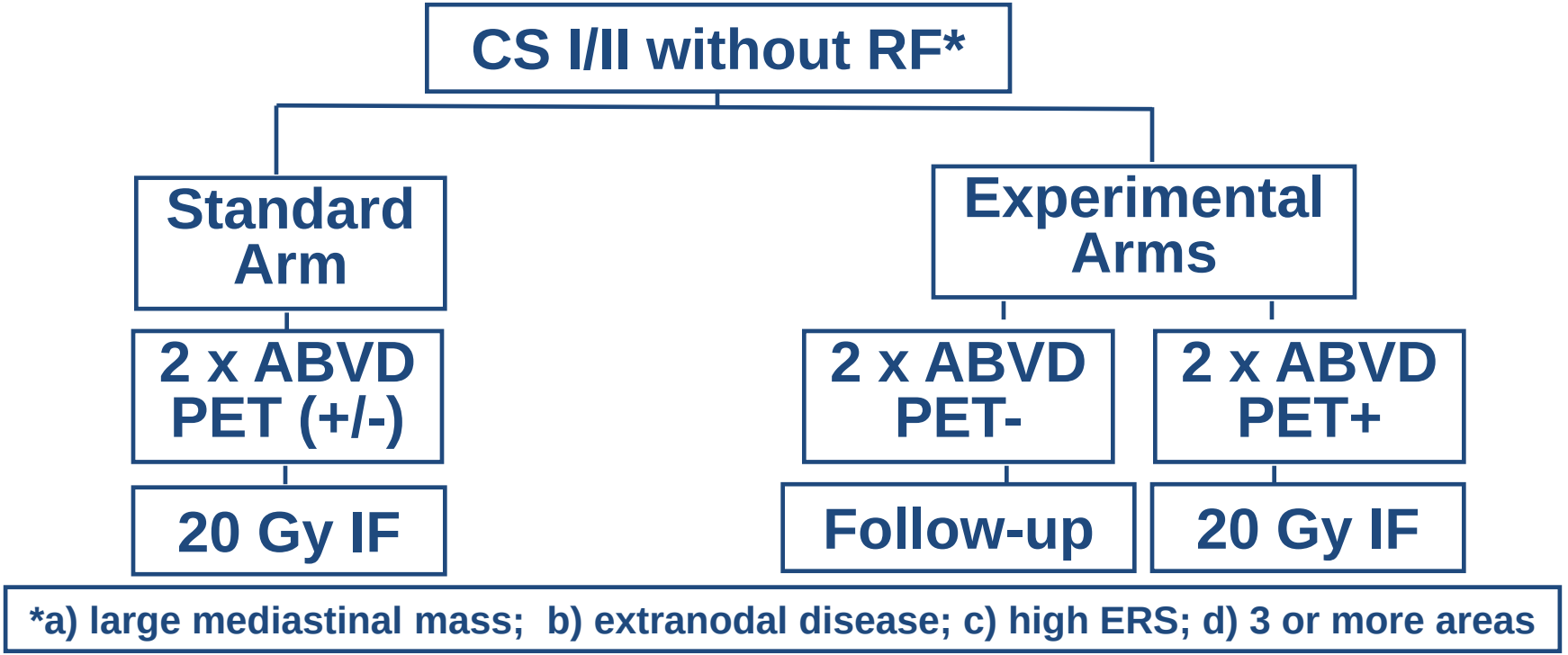


Pts. at Risk							
ABVD	623	609	590	551	431	298	183
ABV	209	206	198	195	187	173	154
AVD	620	608	587	550	424	306	191
AV	186	182	180	177	173	164	142

Behringer et al, Lancet 2014

HD16 GHSG trial

for early favorable HL



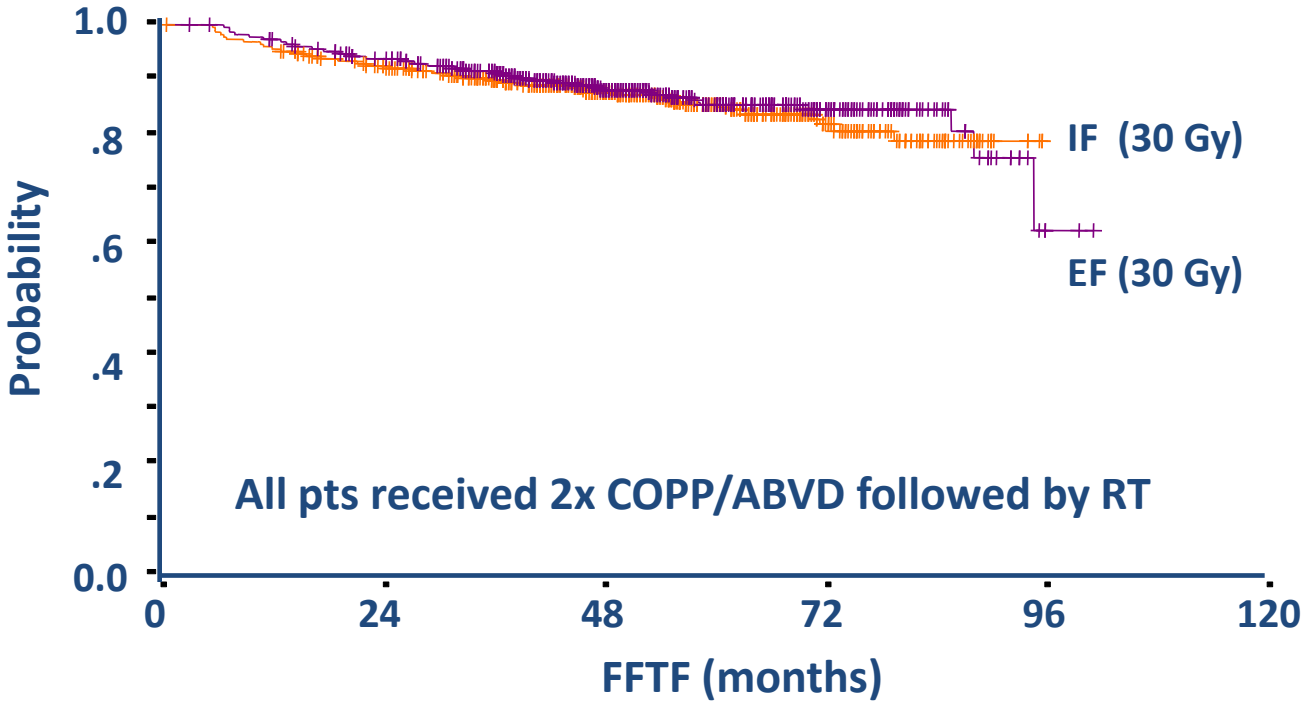
GHSG Risk Allocation for HL Patients

<table>
<tr><th></th><th colspan="4">Stage (Ann Arbor)</th></tr>
<tr><th>Risk factors</th><th>IA, IB, IIA</th><th>IIB</th><th>IIIA, IIIB</th><th>IVA, IVB</th></tr>
<tr><td>None</td><td colspan="2">Early favorable</td><td colspan="2" rowspan="2">Advanced</td></tr>
<tr><td>≥3 LN areas</td><td colspan="2" rowspan="4">Early unfavorable</td></tr>
<tr><td>Elevated ESR</td><td colspan="2" rowspan="3">Advanced</td></tr>
<tr><td>Large med mass</td></tr>
<tr><td>Extranodal disease</td></tr>
</table>

GHSG 2000

HD8 Clinical Trial

Early unfavorable HL (FFTF)



FFTF @ 5years:

EF-RT: 85.0%

IF-RT: 85.9%

p = 0.543

Engert et al JCO 2003

HD8: Long-term Outcome

PFS

15 year estimate [95%-CI]

EF: 72.7% [68.2% to 77.2%]

IF: 73.8% [69.2% to 78.3%]

diff: 1.1% [-5.3% to 7.5%]

Hazard Ratio 0.98 [0.76 to 1.25]

Median observation time 153 months

OS

15 year estimate [95%-CI]

EF: 80.5% [76.7% to 84.3%]

IF: 82.4% [78.7% to 86.0%]

diff: 1.8% [-3.4% to 7.1%]

Hazard Ratio 0.88 [0.66 to 1.16]

Median observation time 174 months

→ No difference in 15-year PFS and OS between consolidative EF and IF-RT after 2x COPP/ABVD in early-stage unfavorable HL.

Bröckelmann et al; EHA 2016

HD8: Second Neoplasia

15-year estimate [95%-CI]

EF: 17.1% [13.2% to 21.1%]

IF: 14.2% [10.4% to 18.1%]

diff: -2.9% [-8.4% to 2.6%]

Median observation time 153 months

→ **Trend towards increased SIR with EF: 3.6 (2.9-4.0) vs. 2.6 (2.0-3.3)**
compared to the age- and sex-specific incidence in the German general population

Bröckelmann et al; EHA 2016

HD11: Long-term Outcome

PFS ABVD

	10 year estimate [95%-CI]	Hazard Ratio [95%-CI]
ABVD+30Gy	83.9% [79.4% to 88.3%]	
ABVD+20Gy	75.6% [70.3% to 80.9%]	1.5 [1.0 to 2.1]
Difference	-8.3% [-15.2% to -1.3%]	

Median observation time 105 months

PFS BEACOPP$_{base}$

	10 year estimate [95%-CI]	Hazard Ratio [95%-CI]
BEAbase+30Gy	84.0% [79.6% to 88.4%]	
BEAbase+20Gy	83.7% [79.2% to 88.3%]	1.0 [0.7 to 1.5]
Difference	-0.3% [-6.6% to 6.0%]	

Median observation time 108 months

- Inferior 10-year PFS with 20Gy IF-RT instead of 30Gy after 4x ABVD
- No difference after 4x BEACOPP$_{base}$
- No difference regarding 10-year OS

OS

	10 year estimate [95%-CI]	Hazard Ratio [95%-CI]
ABVD+30Gy	90.9% [87.5% to 94.2%]	
ABVD+20Gy	89.5% [86.1% to 93.0%]	1.2 [0.7 to 1.9]
BEAbase+30Gy	90.5% [87.2% to 93.9%]	1.0 [0.6 to 1.7]
BEAbase+20Gy	91.4% [88.2% to 94.7%]	1.0 [0.6 to 1.7]

Median observation time 117 months

Bröckelmann et al; EHA 2016

HD11: Second Neoplasias

10-year estimate [95%-CI]	
ABVD+30Gy	5.8% [2.7% to 9.0%]
ABVD+20Gy	6.5% [3.7% to 9.3%]
Bbas+30Gy	6.7% [3.7% to 9.7%]
Bbas+20Gy	5.4% [2.5% to 8.3%]

Median observation time 106 months

→ **No difference in the SIR: A= 1.4, B= 2.4, C= 2.2, D= 1.7**

compared to the age- and sex-specific incidence in the German general population

Bröckelmann et al; EHA 2016

Combined Modality Treatment of HL

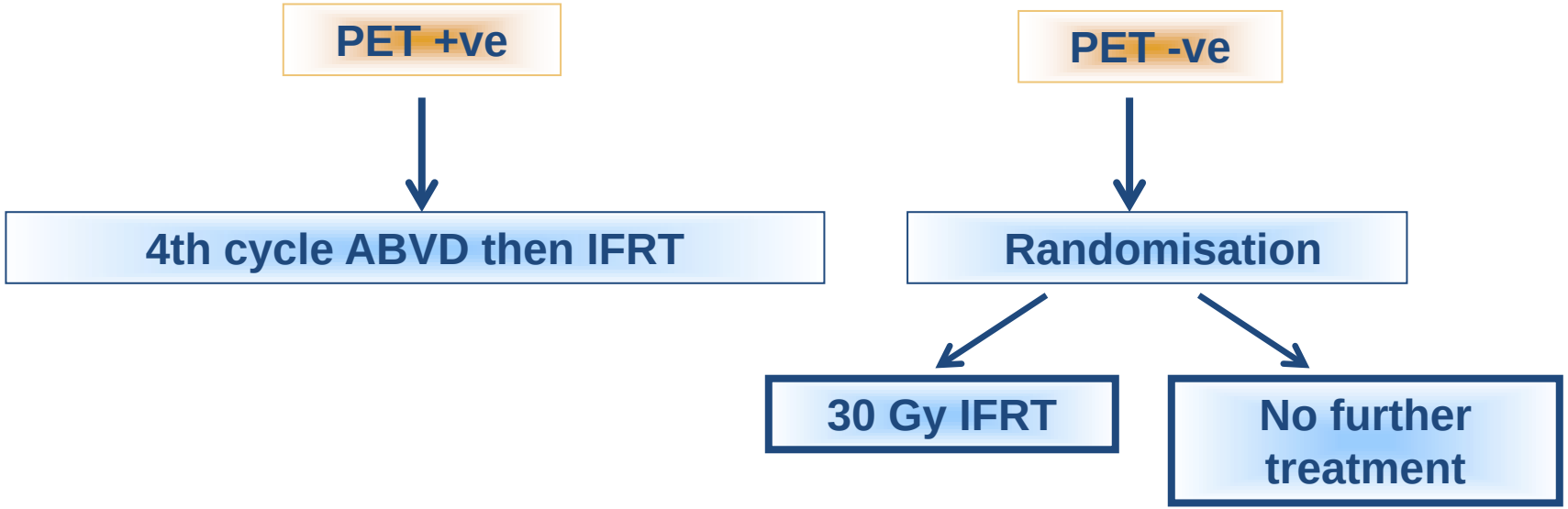
- Background
- Hodgkin Lymphoma – early stages
- PET-driven trials
- Chemo-Immunotherapy
- Summary

UK NCRI RAPID trial

In early stage HL

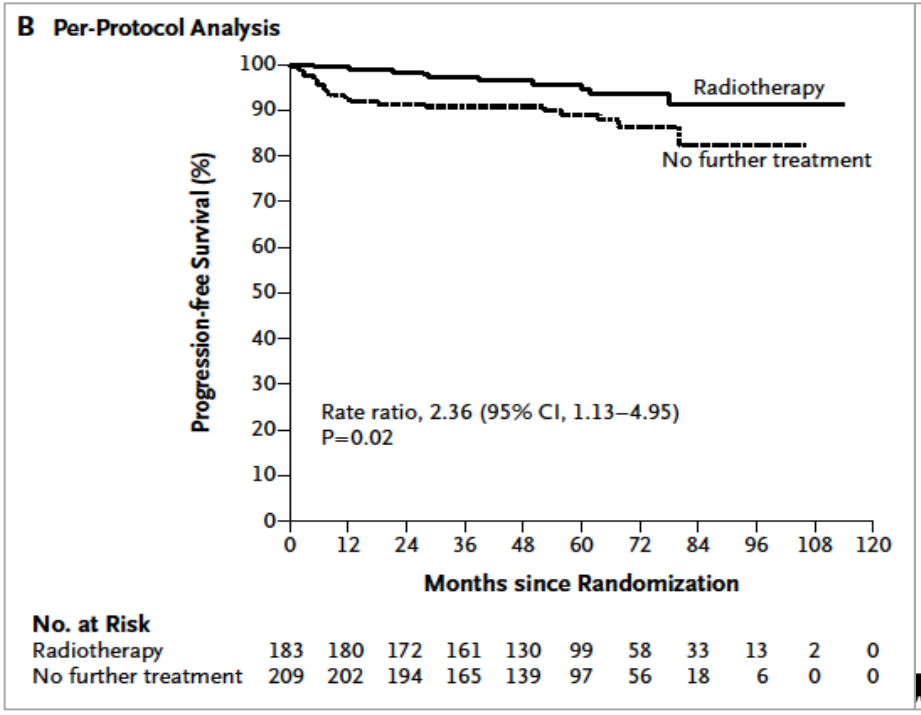
Initial treatment: 3xABVD

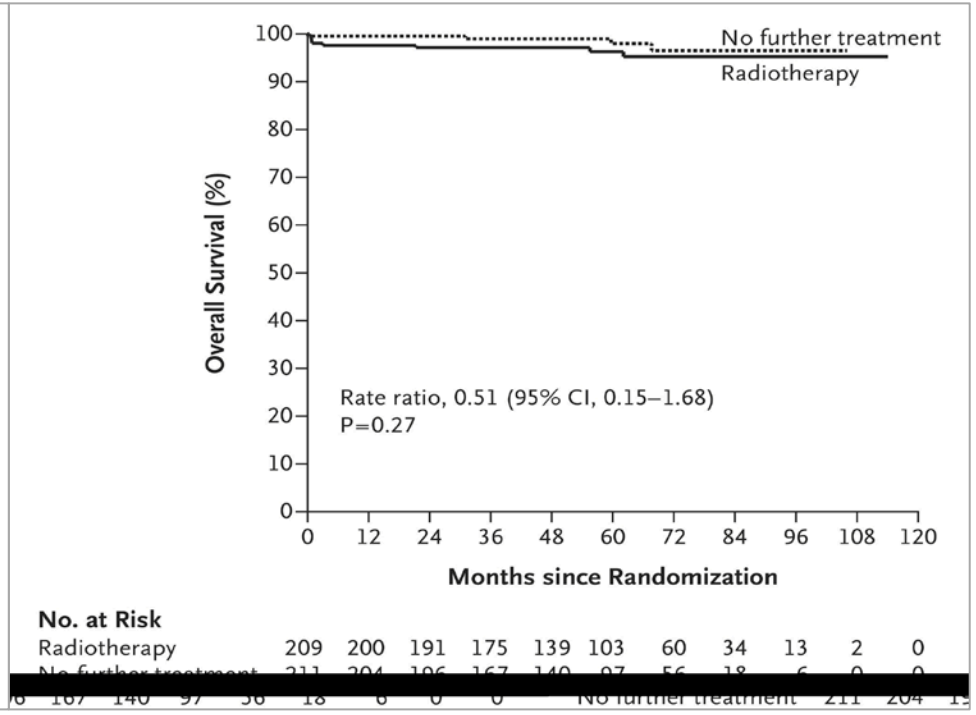
Re-assessment: if response, PET scan performed



UK NCRI RAPID trial

Early stage HL



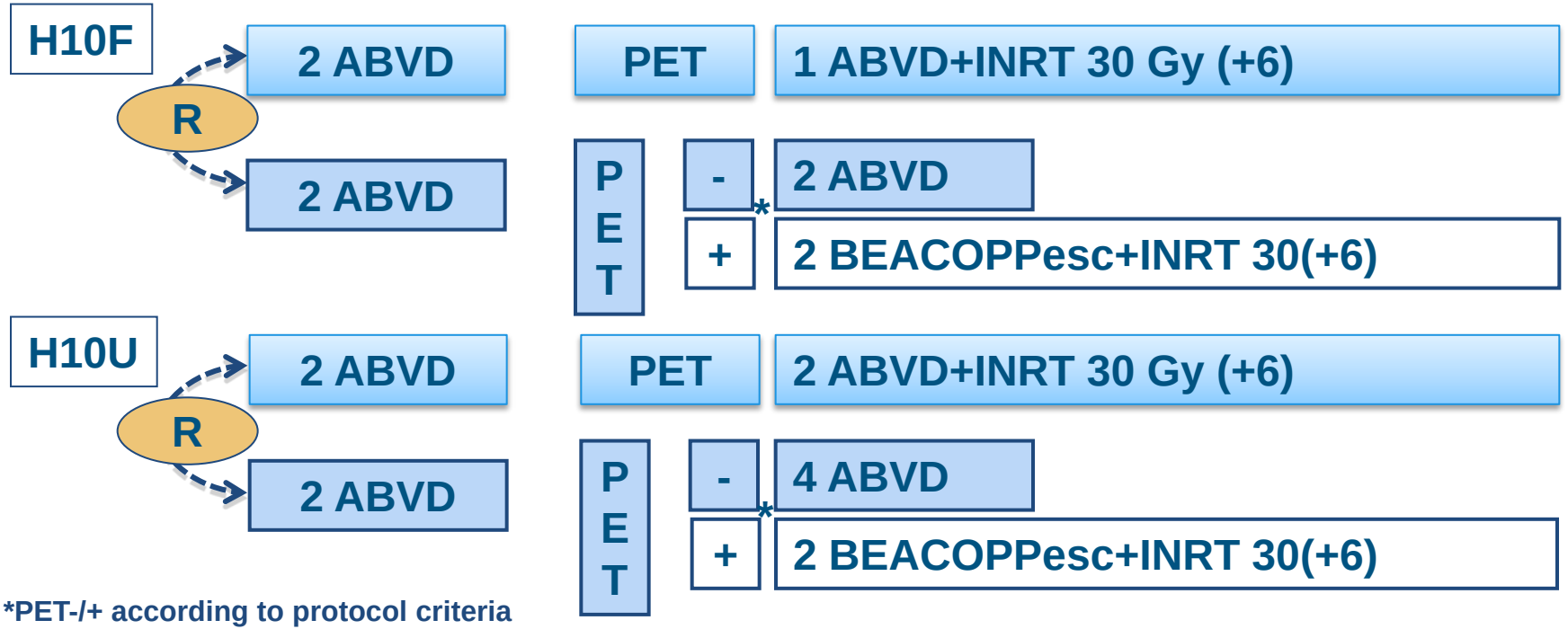


Radford J et al; NEJM (2015) 372;17:1598-1605

EORTC/GELA/IIL H10 Study

For early favorable and unfavorable

H10 (#20051): study design



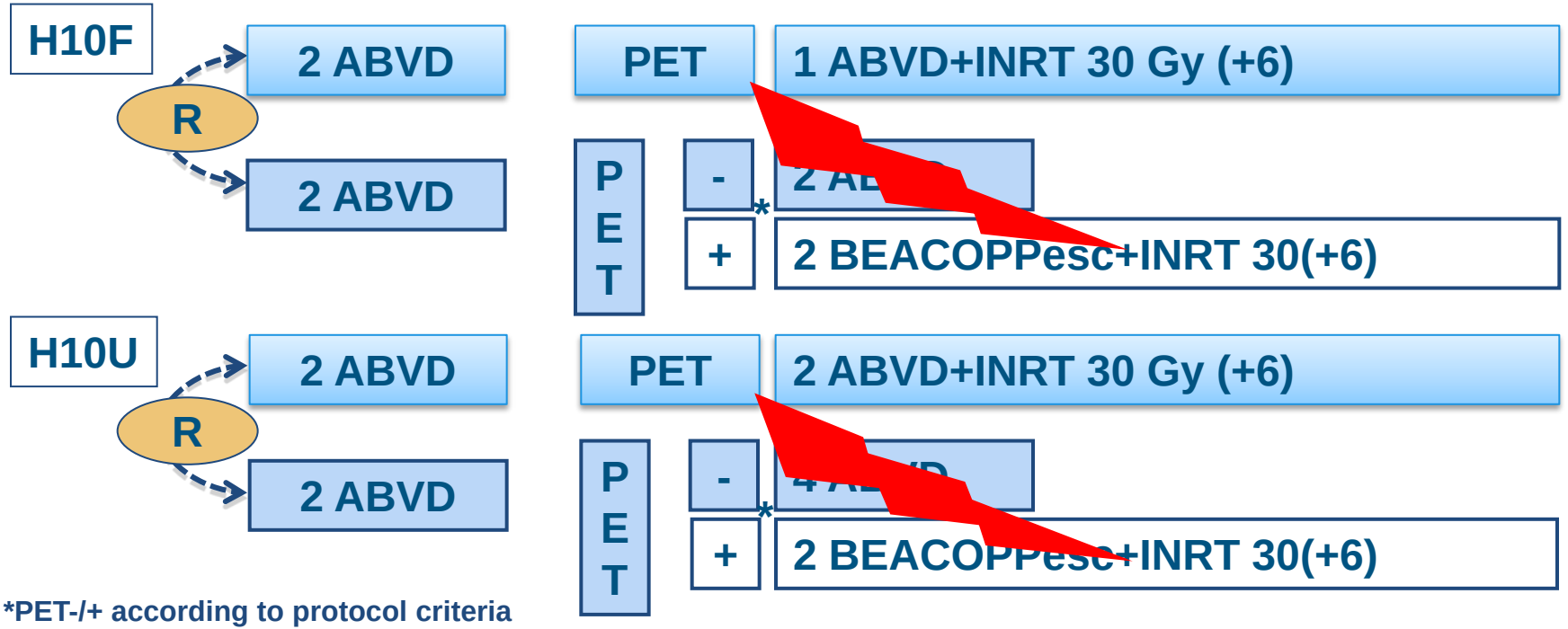
*PET-/+ according to protocol criteria

Hodgkin - CS I/II – untreated - 15-70 yrs – supradiaphragmatic - no NLPHL

EORTC/GELA/IIL H10 Study

For early favorable and unfavorable

H10 (#20051): study design



*PET-/+ according to protocol criteria

Hodgkin - CS I/II – untreated - 15-70 yrs – supradiaphragmatic - no NLPHL

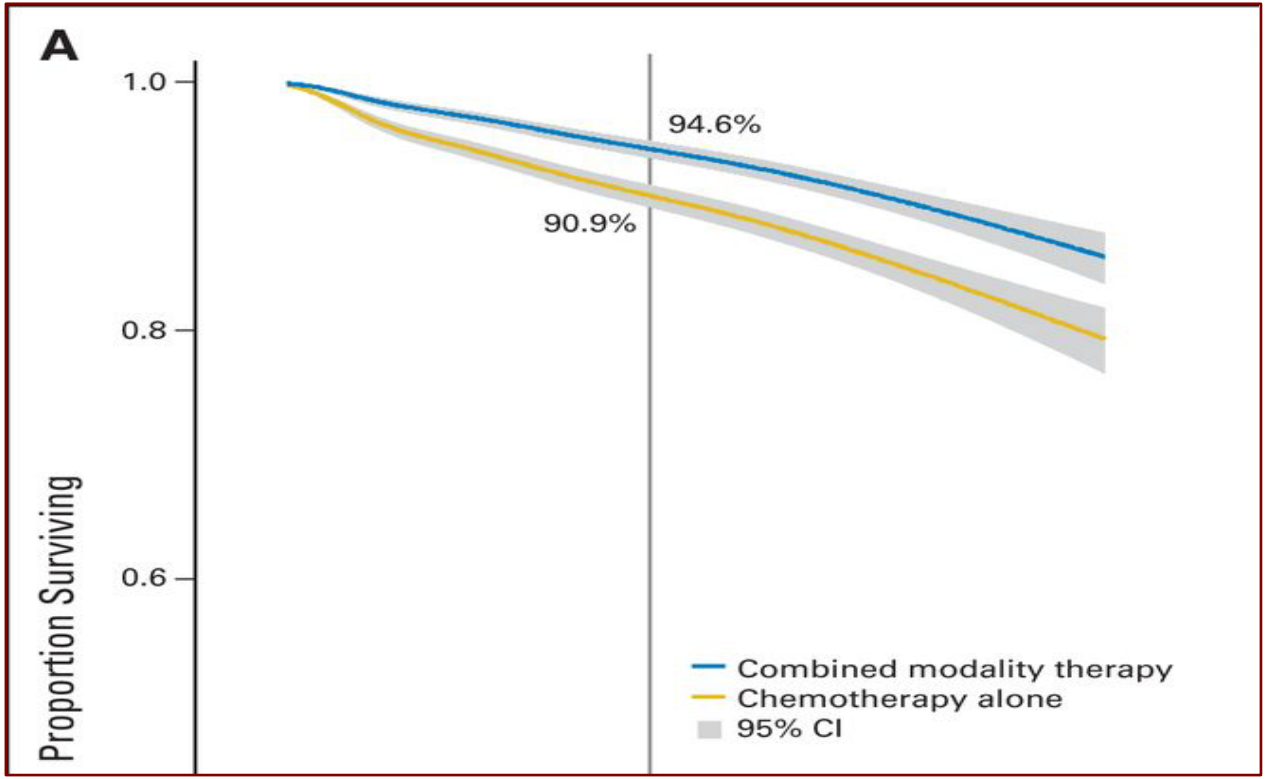
UK RAPID; EORTC/LYSA H10

RT or no RT in PET-negative early stage

- Central PET review necessary
- More events in PET- patients with chemo only
- Similar findings but opposite conclusions (8 vs 20 and 8 vs 25 events) between RAPID[1] and H10[2]
- Rapid failed to demonstrate non-inferiority (HR 1.57; p=0.27) with PFS differences of up to 8.8% (ITT) and 11.0% (per protocol)
- No difference between PET+ and PET- patients –questionable role of PET in this setting!
- Deleting RT in PET- early stage HL still experimental

[1]Radford et al; NEJM 2015
[2]Raemakers et al; JCO 2015

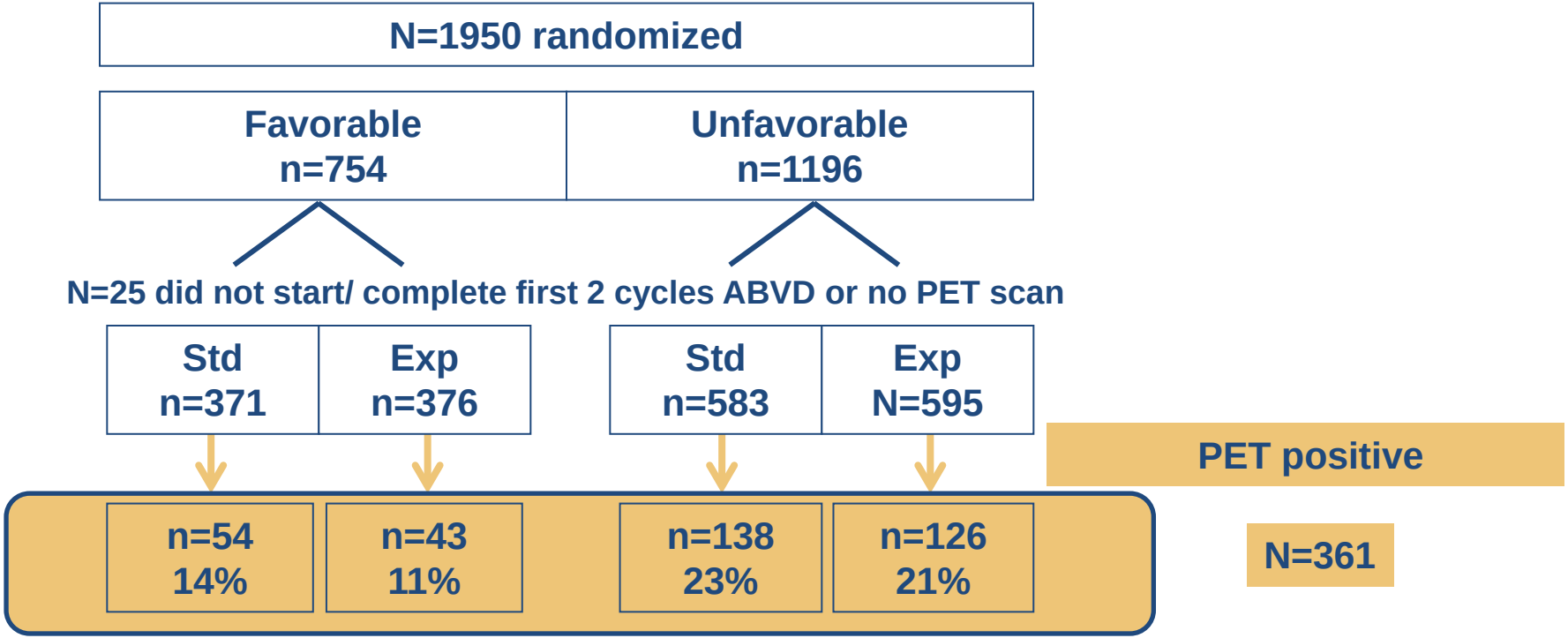
CMT or chemo alone in early cHL



Olszewski et al; JCO 2015;33:625-633

EORTC/GELA/IIL H10 Study

Accrual 2006 - 2011

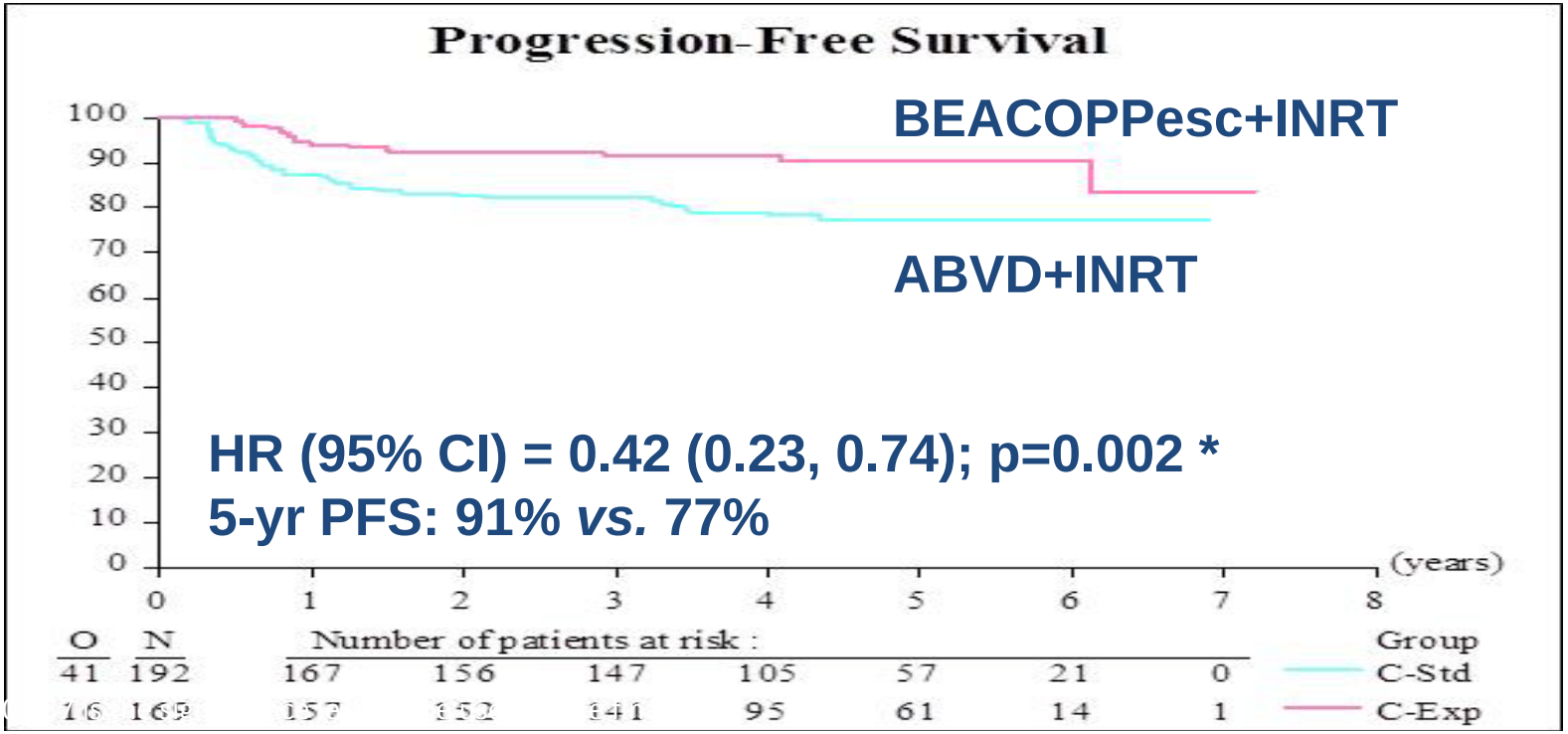


Median FU 4.5 yrs

Raemaekers et al; ICML 2015

PET+ after 2xABVD: B.esc *vs.* ABVD

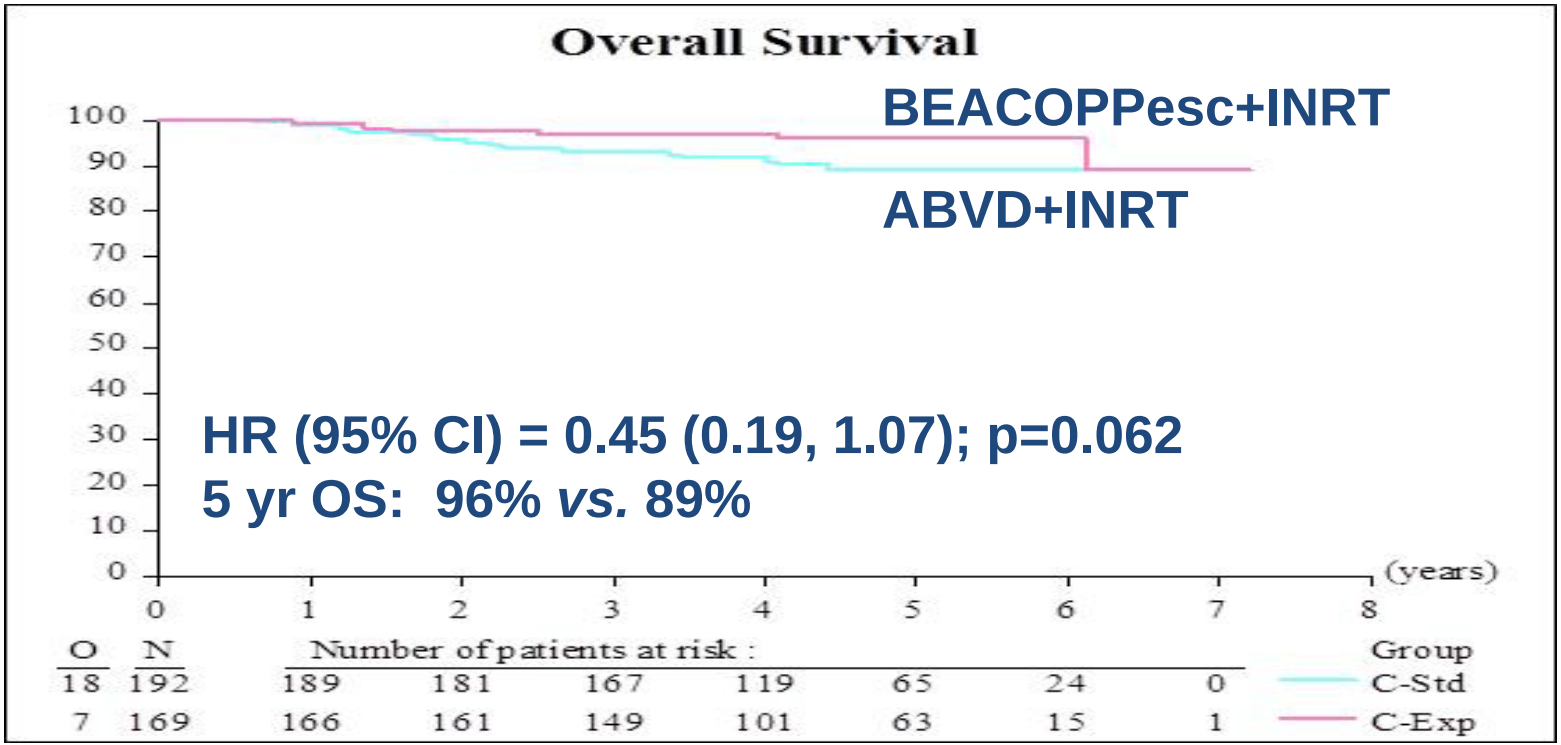
Progression-free survival (PFS)



Raemaekers et al; ICML 2015

PET+ group: BEACOPPesc *vs.* ABVD

Overall Survival (OS)



Raemaekers et al; ICML 2015

Combined Modality Treatment of HL

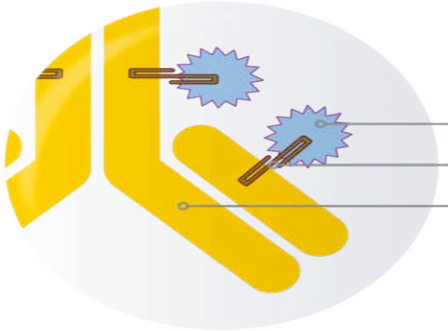
- Background
- Hodgkin Lymphoma – early stages
- PET-driven trials
- Chemo-Immunotherapy
- Summary

New Antibodies and Molecules
in Malignant Lymphoma

- Brentuximab Vedotin (anti-CD30 ADC)
- AFM13 (CD16/CD30 bispecific)
- Lenalidomide (IMID)
- Everolimus, (mTor-inhibitor)
- Rituximab, Ofatumumab (anti-CD20)
- Panobinostat, Mocitinostat (H-DAC inhibitors)
- TKI´s, JAK2i, PARPi
- PD-1 inhibitors

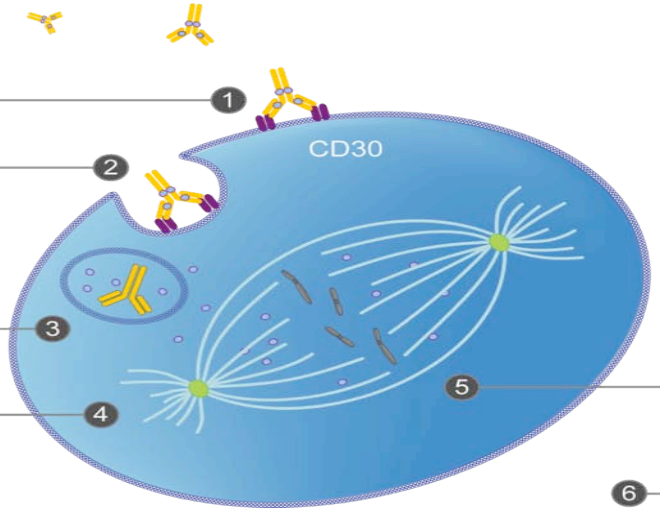
Brentuximab Vedotin (SGN-35)

Mechanism of action



Brentuximab vedotin (SGN-35) ADC

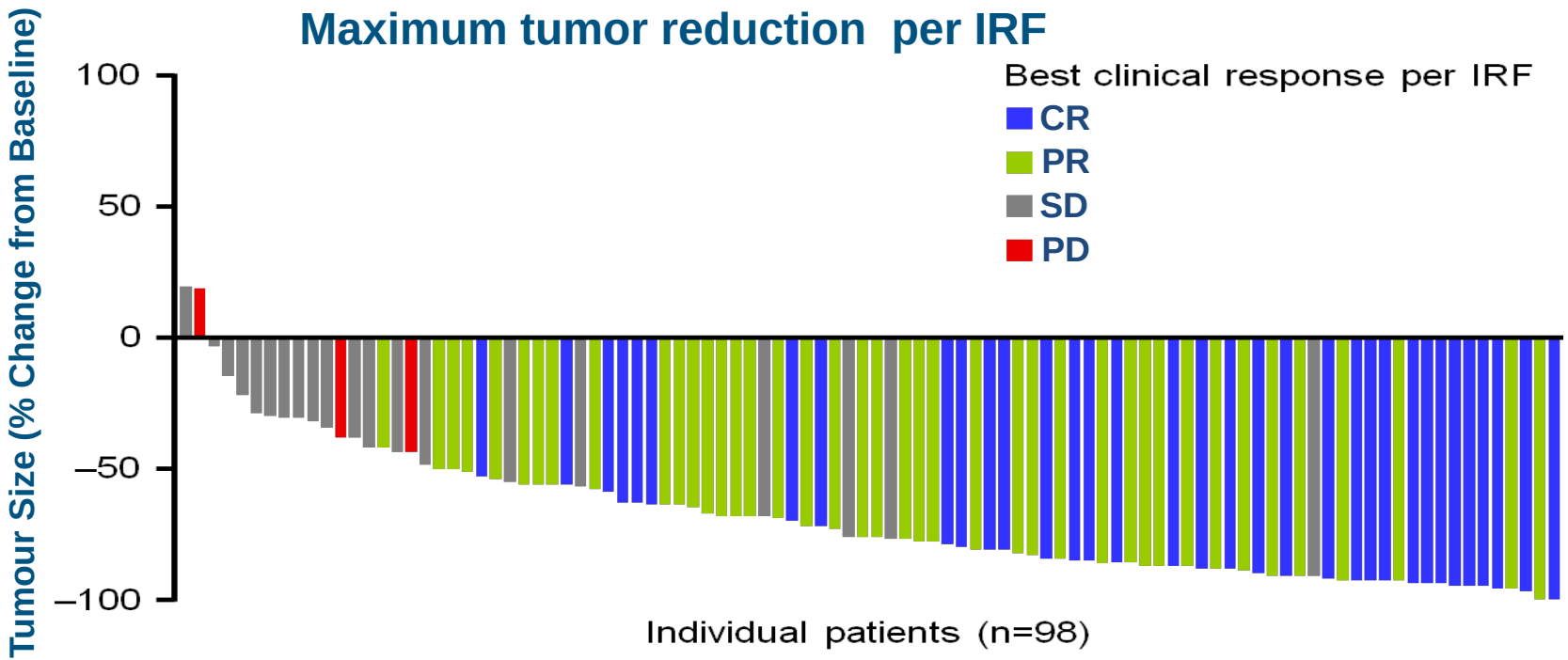
- monomethyl auristatin E (MMAE), potent antitubulin agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody



1. ADC binds to CD30
2. ADC-CD30 complex traffics to lysosome
3. MMAE is released
4. MMAE disrupts Microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

Phase II Pivotal Study of BV

Patients with R/R HL post ASCT



Younes A et al; J Clin Oncol 2012;30: 2183-2189.

Phase II Pivotal Study of BV

Safety (AEs in ≥20% of pts)

Adverse event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Peripheral sensory neuropathy	47	9	0
Fatigue	46	2	0
Nausea	42	0	0
Upper respiratory tract infection	37	0	0
Diarrhoea	36	1	0
Pyrexia	29	2	0
Neutropenia	22	14	6
Vomiting	22	0	0
Cough	21	0	0

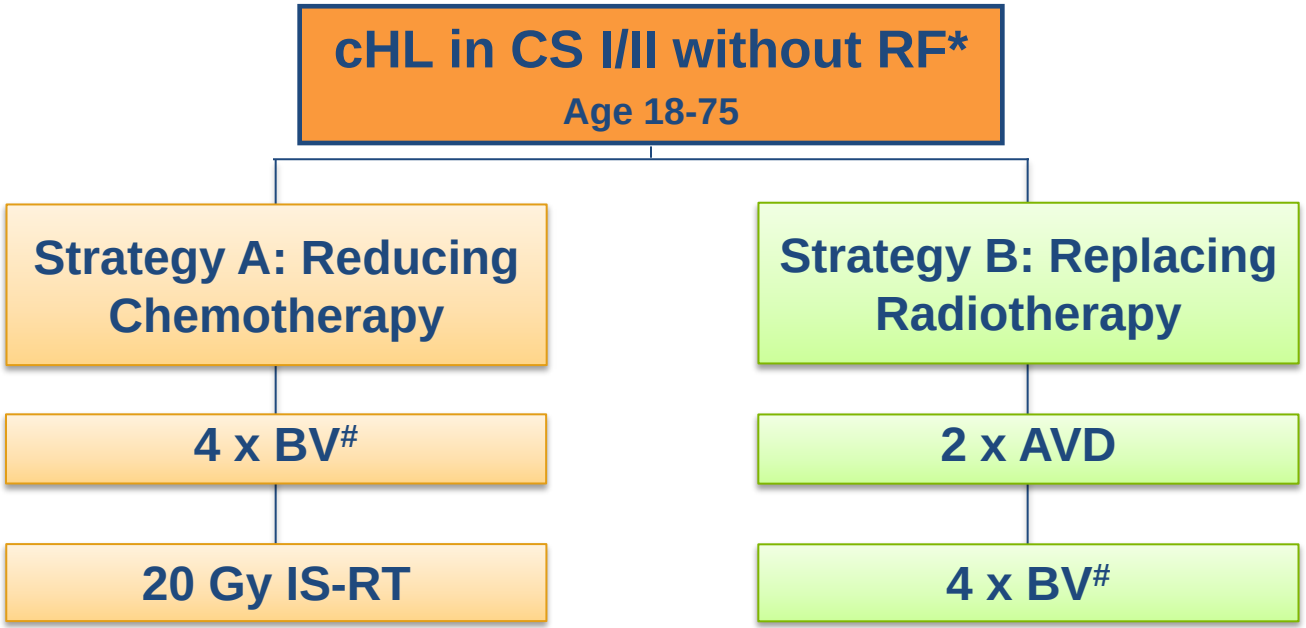
Other grade 3/4 events in ≥5% of patients:

- Thrombocytopenia: 8%
- Anaemia: 6%

BV – Brentuximab Vedotin; AEs – adverse events; pts – patients

Adapted from Chen R et al; Blood, Nov 2012;120: 3689 (ASH abstract)

GHSG Phase II trial
in early-stage favorable HL

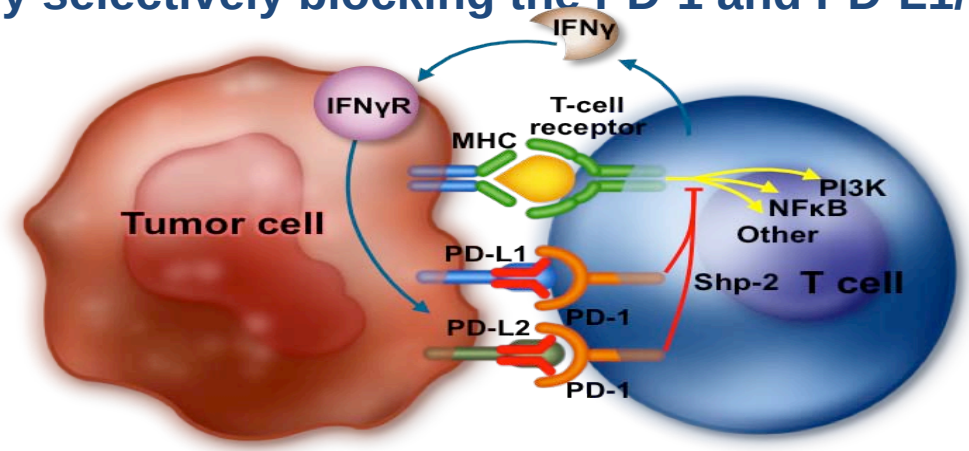


*a) large mediastinal mass b) extranodal disease c) elevated ESR d) ≥3 nodal areas

1.8 mg/kg every 3 weeks

PD-1 Blockade

- PD-1 engagement by its ligands results in transient down-regulation of T-cell function (T-cell exhaustion).
- Nivolumab (BMS) and Pembrolizumab (MSD) fully human/humanized anti-PD-1 antibody selectively blocking the PD-1 and PD-L1/PD-L2 interaction.

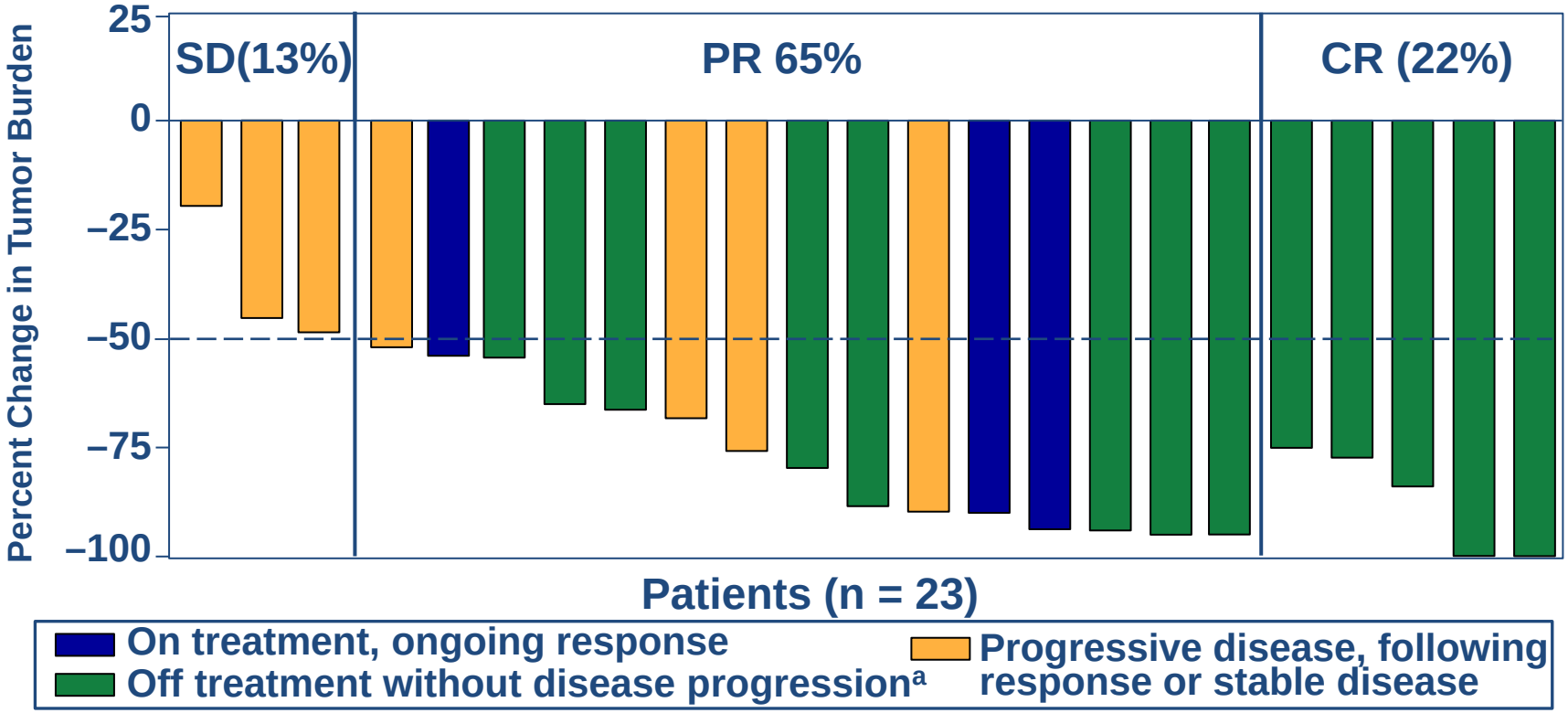


- PD-1 blockade through monoclonal antibody therapy has single-agent activity in a range of solid tumors

Brahmer et al; NEJM 2012;366:2455. Topalian et al; NEJM 2012;366:2443-54

Nivolumab in r&r HL

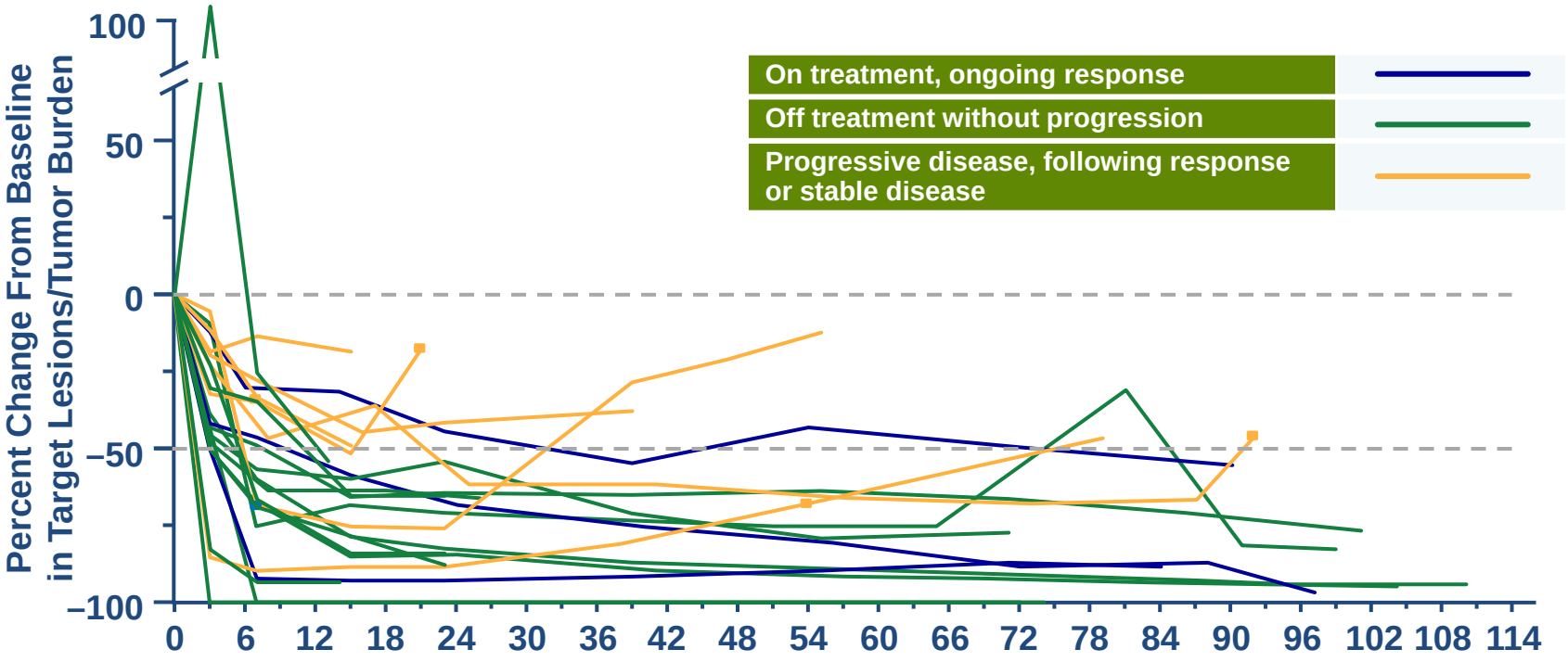
Best response



Ansell et al; ASH 2015

Nivolumab in r&r HL

Durability of response

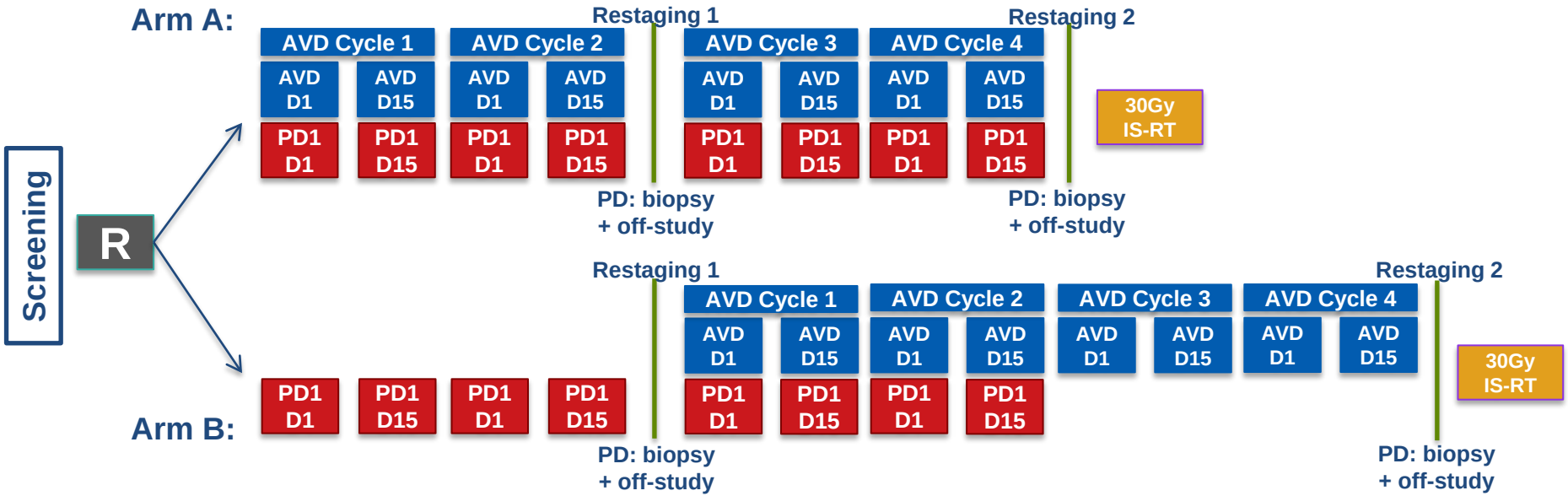


- First occurrence of new lesion

Ansell et al; ASH 2015

HD20 Pilot

Randomized trial in early unfavorable HL



AVD: Adriamycin, Vinblastin, Dacarbazine; PD1: anti-PD1-antibody

Combined Modality Treatment of HL

- Background
- Hodgkin Lymphoma – early stages
- PET-driven trials
- Chemo-Immunotherapy
- Summary

Combined Modality Treatment of Lymphoma

- Despite the impressive cure rate in HL, elderly and r&r pts still constitute an area of unmet medical need
- In early favorable, 2xABVD+20Gy IFRT; more chemo not better
- In early unfavorable, 2+2+IFRT or 4xABVD+IFRT; 6x chemo not better (H8U)
- CMT standard of care in early stage HL (OS better!)
- Rapid and H10 gave conflicting results; PET+ pts in H10 benefit from dose escalation with Besc.
- Need to develop less toxic regimen; BV and anti-PD1 might at least in part replace chemo- and radiotherapy in HL

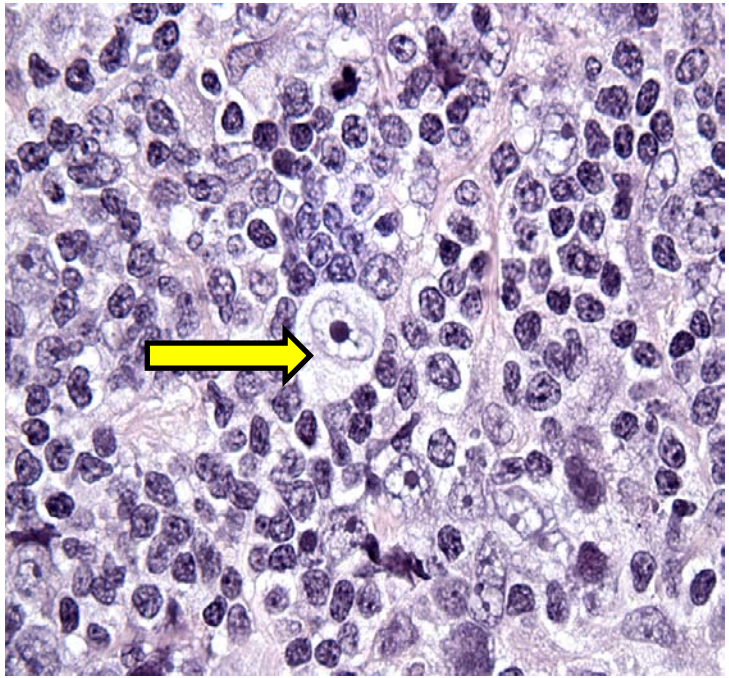
PD-1 Blockade in HL

Background

Pathology of cHL: rare malignant Reed-Sternberg cells within an extensive inflammatory/immune cell infiltrate.

Genetic analyses: frequent 9p24.1 amplification with upregulation of PD-1 ligands and JAK2.

Hypothesis: cHL may have a genetically driven dependence on PD-1.



Juszczynski et al; PNAS 2007, 104: 13134
Green et al; Blood 2010, 116: 3268; Chen et al; Clin Cancer Res 2013, 19:3462

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Case extranodal NHL woman born 1981

Medical history:

2000 Breast enlargement

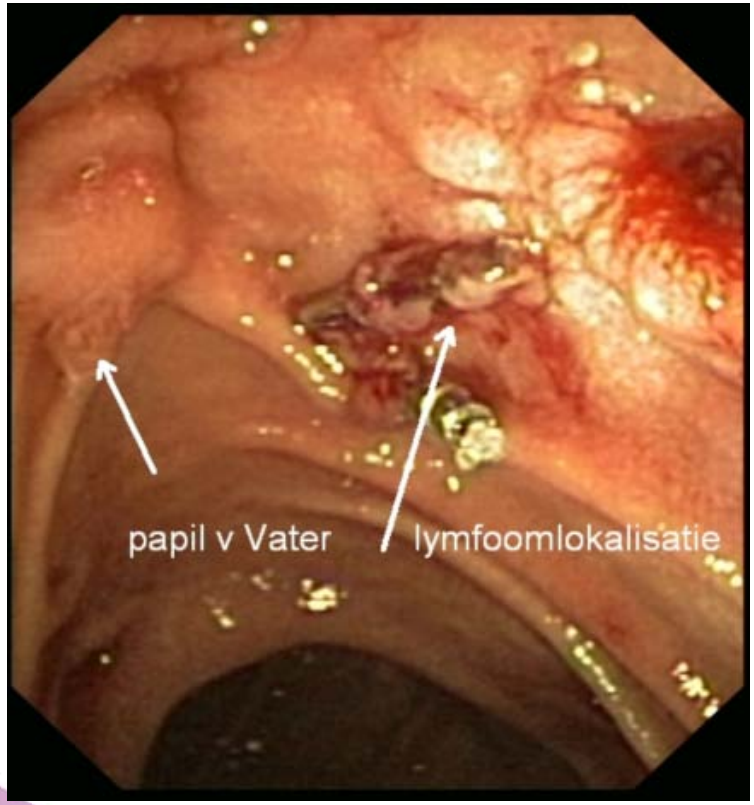
2012 Analysis of abdominal complaints (loss of appetite, sometimes pain upper abdomen, weight loss about 10 kg)

Physical examination: no abnormalities

Lab: no abnormalities

Gastroscopy: in duodenum at level of Vater's papilla irregular mucosa area with diameter of a couple of cm

Case extranodal NHL woman born 1981



PA: low grade NHL, best qualified as follicular lymphoma

PET-CT scan: no abnormalities

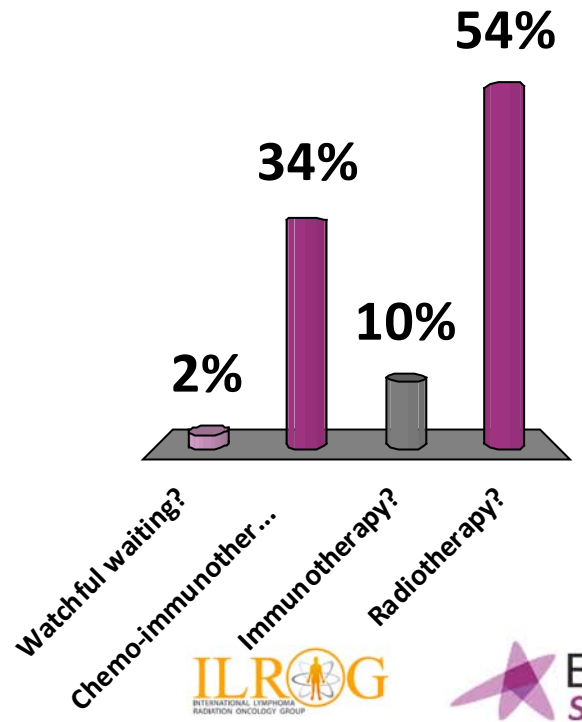
CT-abdomen: no abnormalities

BM: negative

C: 31-year old woman with stage IE low grade NHL (follicular) in duodenum

What would you do?

A. Watchful waiting?
B. Chemo-immunotherapy?
C. Immunotherapy?
D. Radiotherapy?

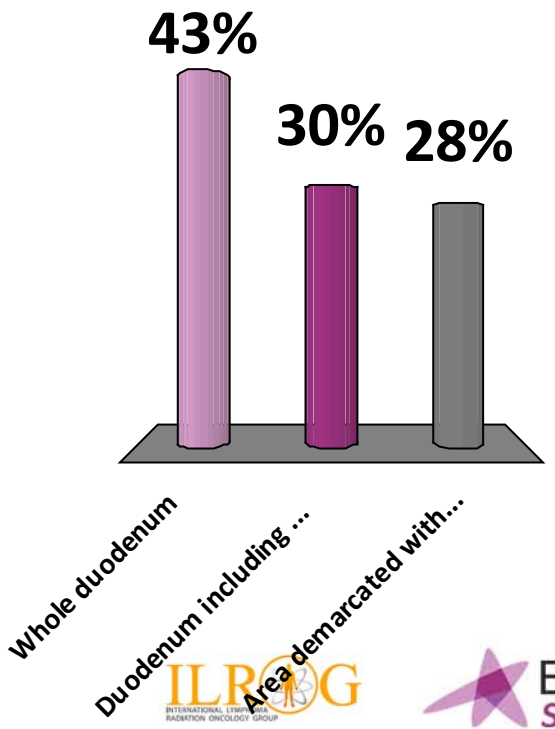


ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

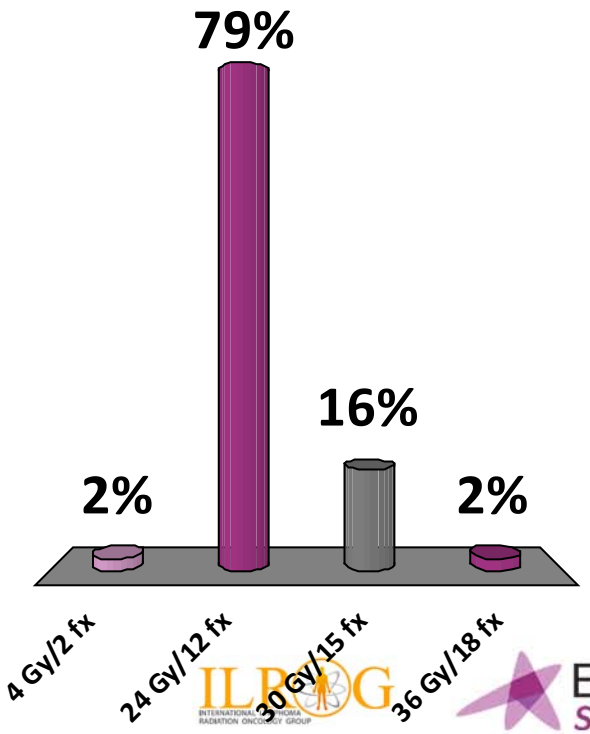
Target volume radiotherapy?

A. Whole duodenum
B. Duodenum including regional nodes
C. Area demarcated with clips with 2 cm margin

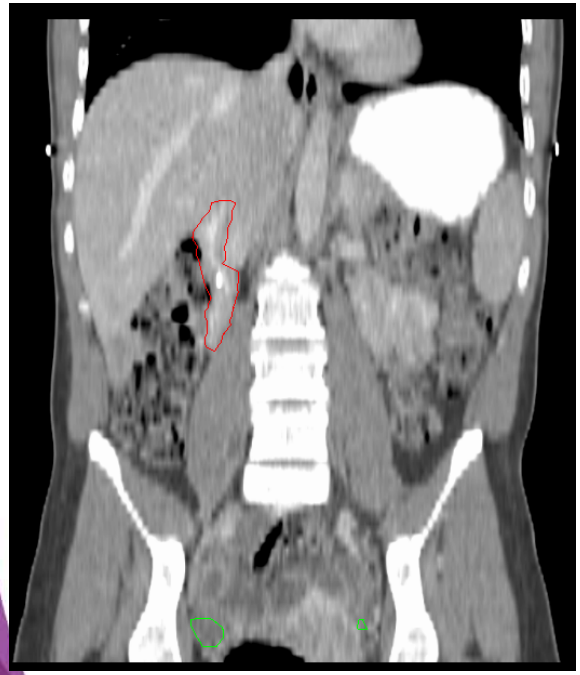


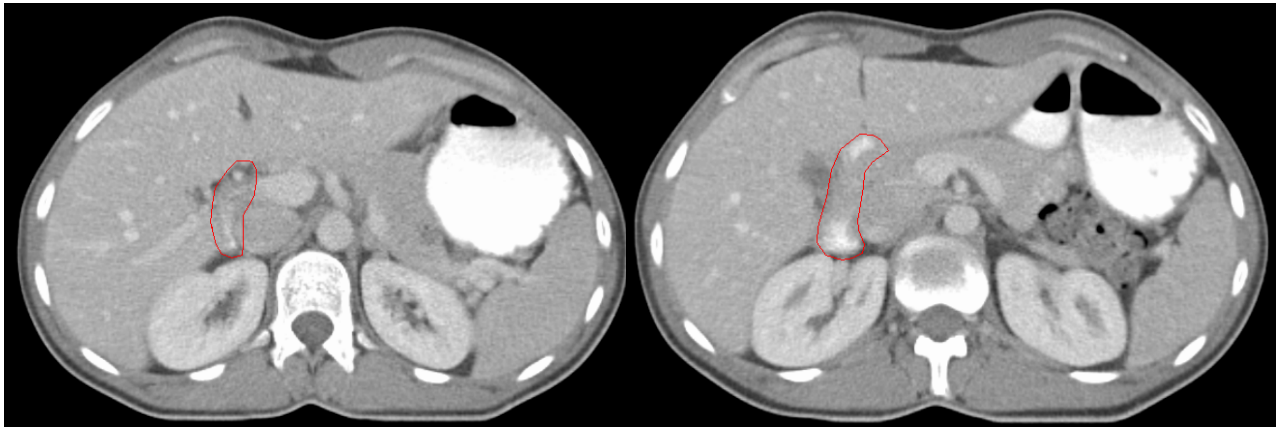
In case of RT what dose would you give?

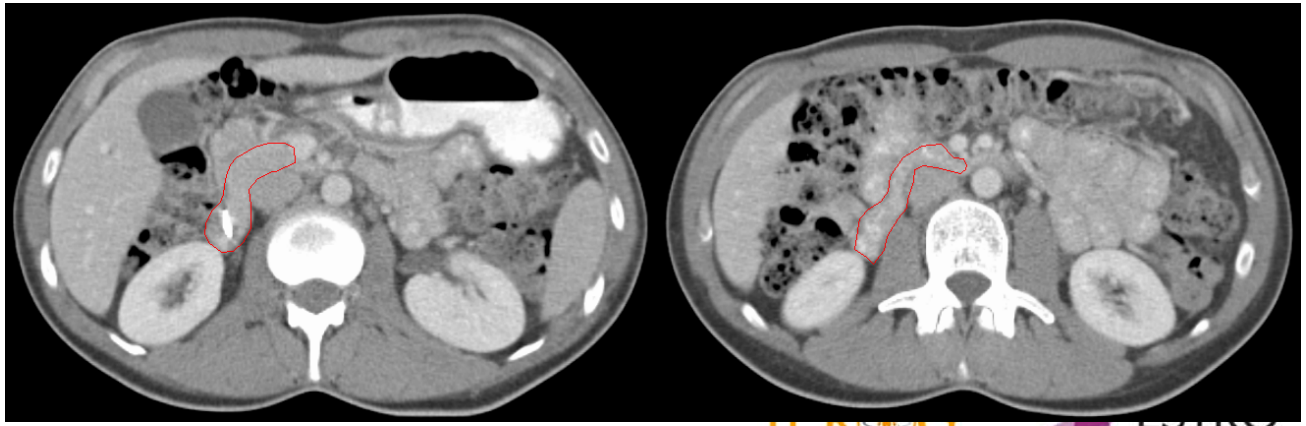
A. 4 Gy/2 fx
B. 24 Gy/12 fx
C. 30 Gy/15 fx
D. 36 Gy/18 fx



Case extranodal NHL woman born 1981

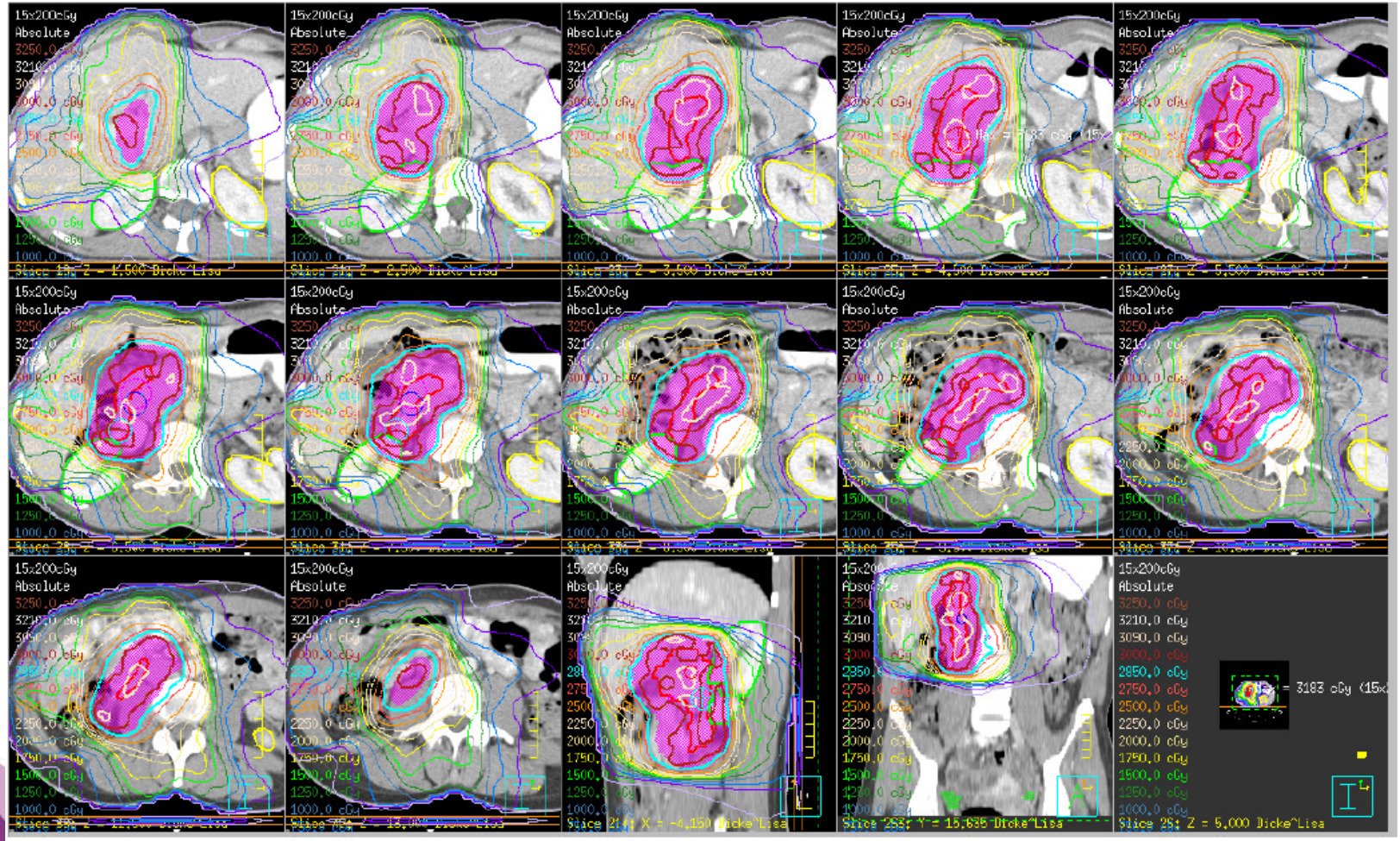






CTV in red

Case extranodal NHL woman born 1981



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Aggressive nodal NHL, the role of RT: **volume, dose and technique**

Berthe Aleman

Radiation oncologist

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Aggressive nodal NHL, the role of radiotherapy: volume, dose and technique

Curative radiotherapy

- Early stage
- Advanced stage
- Relapsed/refractory disease

Palliative radiotherapy

Aggressive nodal NHL – early stage
Target volume

- Past: involved field radiotherapy +/- boost on bulk or residual disease
- Present: involved site radiotherapy (ISRT) +/- boost on bulk or residual disease

Aggressive nodal NHL – early stage
Target volume

CTV:

- Pre-chemotherapy or pre-surgery volume Gross Tumor Volume (GTV)
- Changes in normal anatomy after initial treatment response should be taken into account
- Potential Boost CTV: post-chemotherapy GTV (based op PET-CT-scan)

Illidge et al, IJROBP 2015

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Aggressive nodal NHL – advanced stage

Target volume

CTV

- Pre-chemotherapy Pre-chemotherapy bulky Gross Tumor Volume (GTV)
- Post-chemotherapy residual mass containing PET positive areas on post-chemotherapy scan
- Potential Boost CTV: post-chemotherapy GTV (on PET-CT-scan)

Illidge et al, IJROBP 2015

Aggressive nodal NHL – refractory disease

Target volume

GTV:

- Site(s) of refractory disease

CTV:

- Usually only site(s) of refractory disease with margin for microscopical disease

Illidge et al, IJROBP 2015

RT Dose

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Phase III Trial on RT Dose

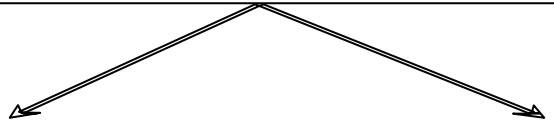
640 Sites of Aggressive NHL

82% DLBCL

33% stage III-IV

73% as post-chemo consolidative RT

10% received Rituximab



30 Gy in 15 fractions

40-45 Gy in 20-23 fractions

Lowry et al. Rad Onc 2011

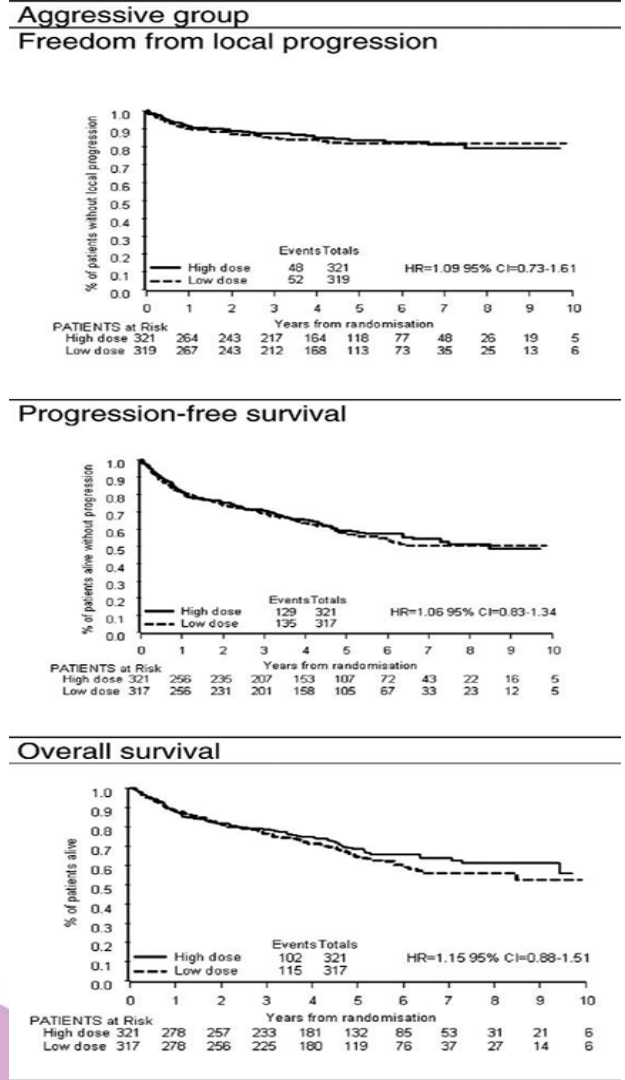
30 Gy vs 40-45 Gy

- Median f/u 5.6 years

	30 Gy (n=319)	40-45 Gy (n=321)	P-value
5y FFLP	82%	85%	0.66
5y OS	64%	68%	0.29

FFLP: Freedom from local progression; OS: Overall Survival

Lowry et al. Rad Onc 2011



Caveats:

- Included pts treated with RT receiving salvage/palliative RT
- No chemo data
- Systemic treatment mostly without rituximab
- Lack of functional imaging of response to chemo

Lowry et al. Rad Onc 2011

CR to Chemo

Study	# Pts in CR	Chemo	Med fu	Response assessment	RT Dose (Gy)	LC
Zinzani, 1999	38	MACOP-B	39 mo	Gallium	30-36	100%
Kahn, 2006	16	CHOP x 4-6	40 mo	PET	Med: 30.6	100%
Halasz, 2010	39	R-CHOP	46.5 mo	PET	Med: 36	100%
Phan, 2010	142	R-CHOP in 70%	36 mo	PET	If no residual CT dz: 30 If > 5 cm or dz: 36-39.6	100%
Dorth, 2012	79	R-CHOP in 65%	56 mo	Gallium (14%) or PET (73%)	Med: 25	92%
Shi, 2013	14	R-CHOP	32.9	PET (85%)	Med: 30.6	92%

Courtesy: Andrea Ng

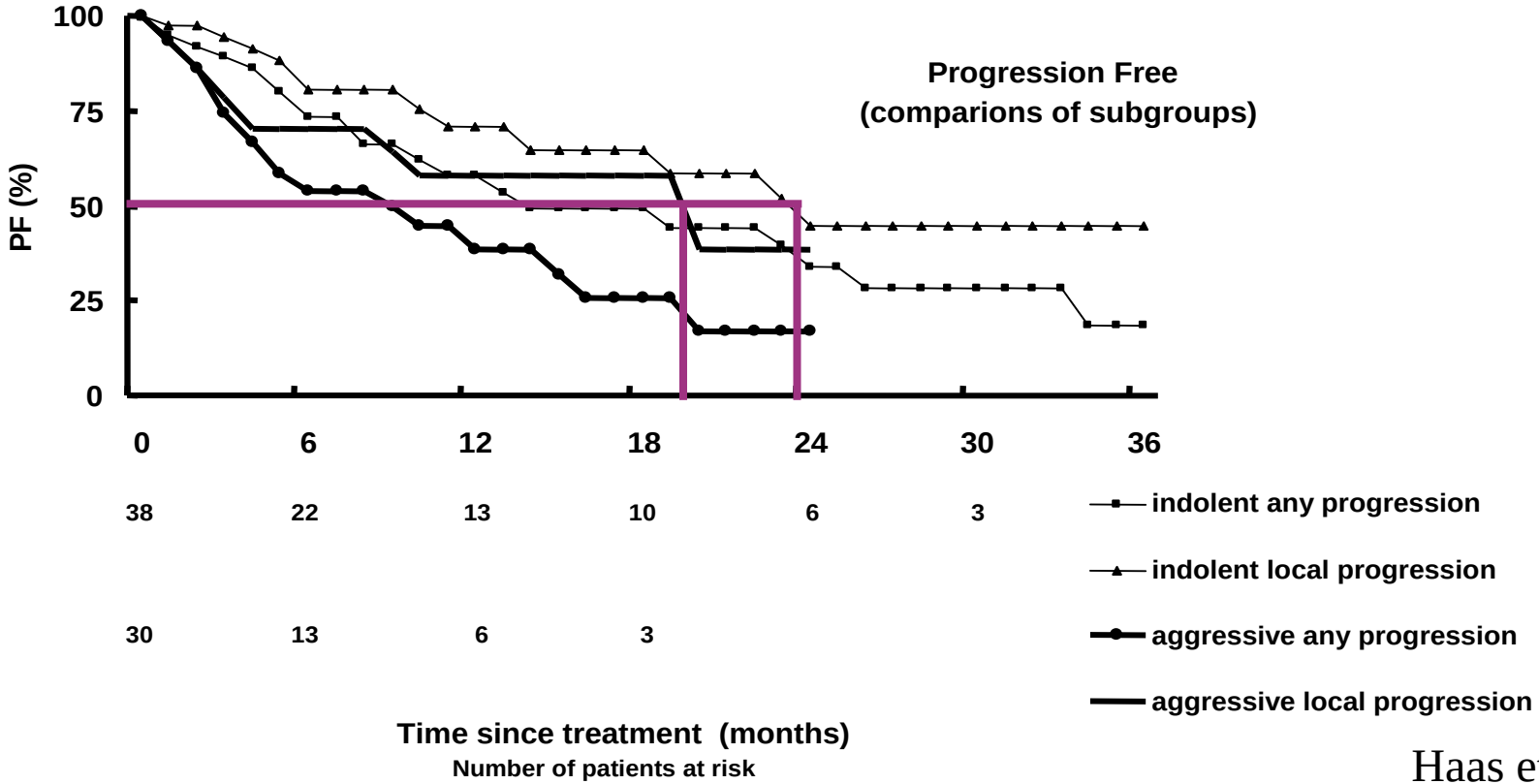
See also: Ng et al JCO 2016

Palliative radiotherapy

- RT of nodal areas in case chemotherapy is not feasible/indicated
  - 2x2 Gy – response rate ±80% (CR ±35%)

Haas et al, EJC 2005

LD-IF-RT in other B-cell malignancies; results according to histological subtype



Haas et al, EJC 2005

Palliative radiotherapy

- RT of nodal areas in case chemotherapy is not indicated
  - 2x2 Gy – response rate ±80% (CR ±35%)
  - Schedule equivalent to 10-12x3 Gy

Summary RT Dose to aggressive Nodal NHL

Setting	RT Dose
CR to Chemo	30 Gy (1.8- 2 Gy/Fx)
PR to Chemo	30-40 Gy (1.8-2 Gy/Fx)
Post-ASCT	30-40 Gy (1.8-2 Gy/Fx)
Primary refractory (CR to salvage CT)	30-40 Gy (1.8-2 Gy/Fx)
Primary refractory (unresponsive to CT)	45-55 Gy (1.8-2 Gy/Fx)
Palliative	4 Gy (2-4 Gy/Fx) 30-36 Gy (3 Gy/Fx)

RT technical isssues

RT technique

- Same as in Hodgkin lymphoma and indolent NHL

Constraints

- Since many patients are > 60 years second malignancy risk is usually not an issue
- OAR usually lungs, heart, kidneys, bowels

Illidge et al, IJROBP 2015

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Aggressive nodal NHL- early stage
Principles of ISRT for Nodal Sites

- CT or PET/CT information of pre-chemotherapy disease (ideally in treatment position)
- Planning requirements: CT-based simulation
- Goal to target site of originally involved lymph node(s)
  - Field encompasses the original volume prior to surgery or chemotherapy
  - Spares uninvolved organs once lymph node has regressed
  - Imaging modalities such as PET and MRI can enhance

Courtesy: Terezakis

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Re-Examining the Role of Radiation Therapy for Diffuse Large B-Cell Lymphoma in the Modern Era

Andrea K. Ng, *Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
Bouthaina Shbib Dabaja, *The University of Texas MD Anderson Cancer Center, Houston, TX*
Richard T. Hoppe, *Stanford University School of Medicine, Stanford, CA*
Timothy Illidge, *University of Manchester, Manchester Academic Health Sciences Centre, The Christie National Health Service Foundation Trust, Manchester, United Kingdom*
Joachim Yahalom, *Memorial Sloan Kettering Cancer Center, New York, NY*

JCO, 2016; 1443-1447

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Questions?

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Extranodal lymphomas: Characteristics, the role of radiotherapy, volumes doses and techniques:

Primary breast lymphoma

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Breast lymphoma

General

- Clinical presentation: usually unilateral painless breast mass
- Average age at diagnosis: 55 to 60 years

Pathology

- B-cell lymphoma
  - Mostly DLBCL
  - Also: indolent lymphomas such as marginal zone lymphoma and follicular lymphoma
- T-cell lymphoma
  - Breast Implant–Associated Anaplastic Large-Cell Lymphoma

Literature

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Patients and methods:

- A retrospective international study in 204 patients
- Treatment period: 1980 to 2003
- Median age: 64 years
- Unilateral disease (stage IE or IIE): 95% of patients

Ryan et al, Ann Oncol 2008

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Treatment	No of pts	%
Surgery only	11	5
RT only	14	7
CT only	31	15
S + RT	15	7
S + CT	32	16
RT + CT	59	29
S + RT + CT	42	21
Any surgery	100	49
Any RT	130	64
Any CT	164	80

- 87% of CT- regimens contained anthracycline
- Intrathecal CT as CNS prophylaxis: 8 patients

Ryan et al, Ann Oncol 2008

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Treatment	No of pts	%
Surgery only	11	5
RT only	14	7
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S + RT	15	7
S + CT	32	16
RT + CT	59	29
S + RT + CT	42	21
Any surgery	100	49
Any RT	130	64
Any CT	164	80

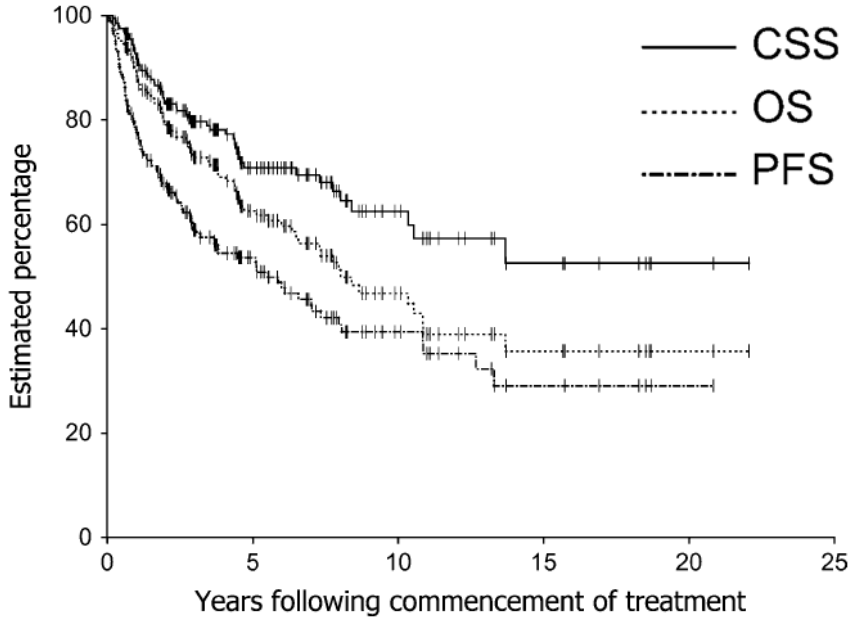
Initially involved breast only: 50%
Initially involved breast + regional lymph nodes: 35%

Median RT dose: 40 Gy
Range RT dose: 4-60 Gy

Ryan et al, Ann Oncol 2008

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group;

cause specific survival, overall survival and progression free survival



Median CSS: not reached

Median OS: 8.0 years

Median PFS: 5.5 years

Ryan et al, Ann Oncol 2008

Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Results:

- MFA: favourable IPI score, anthracycline-containing chemotherapy, and radiotherapy (RT) were significantly associated with longer OS (each $P \leq 0.03$).
- There was no benefit from mastectomy, as opposed to biopsy or lumpectomy only.
- At a median follow-up time of 5.5 years, 37% of patients had progressed—16% in the same or contralateral breast, 5% in the central nervous system, and 14% in other extranodal sites.

Ryan et al, Ann Oncol 2008

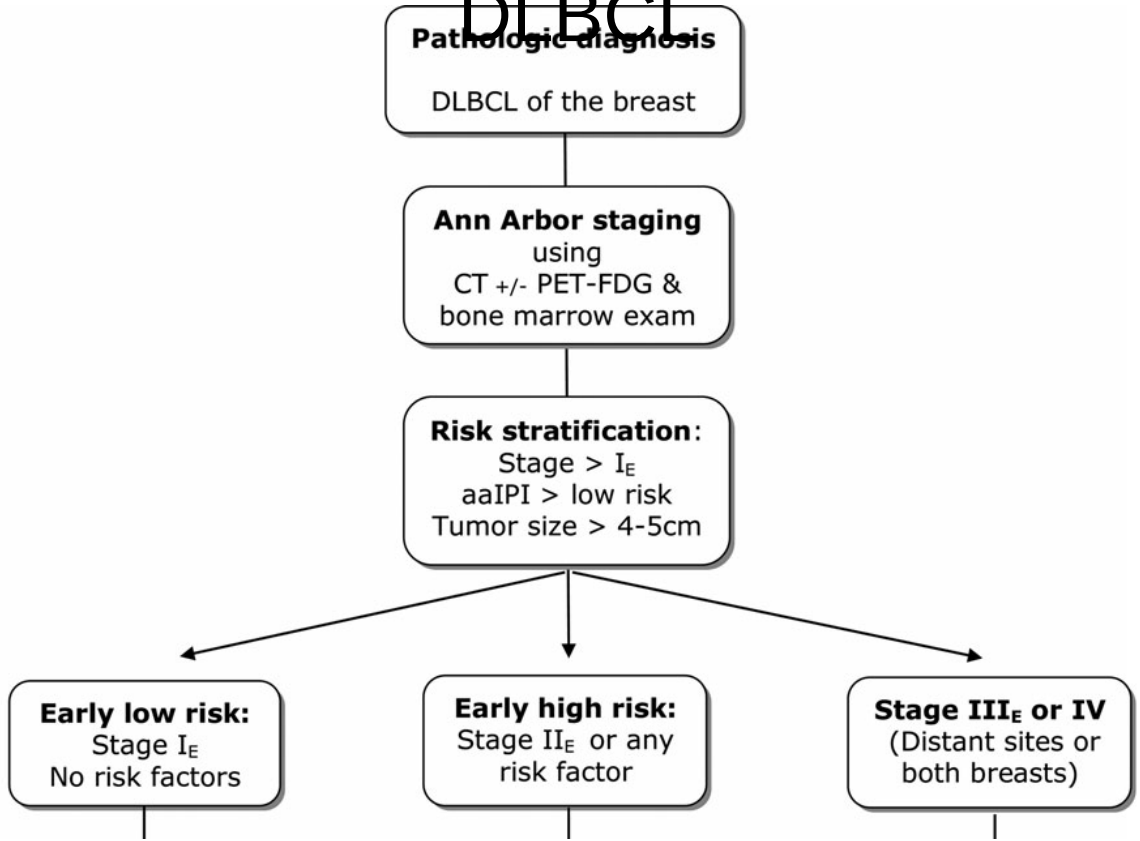
Primary diffuse large B-cell lymphoma of the breast: a study by the International Extranodal Lymphoma Study Group

Conclusions:

- Limited surgery+anthracycline-containing CT +IFRT: best outcome in the pre-rituximab era
- Prospective study needed

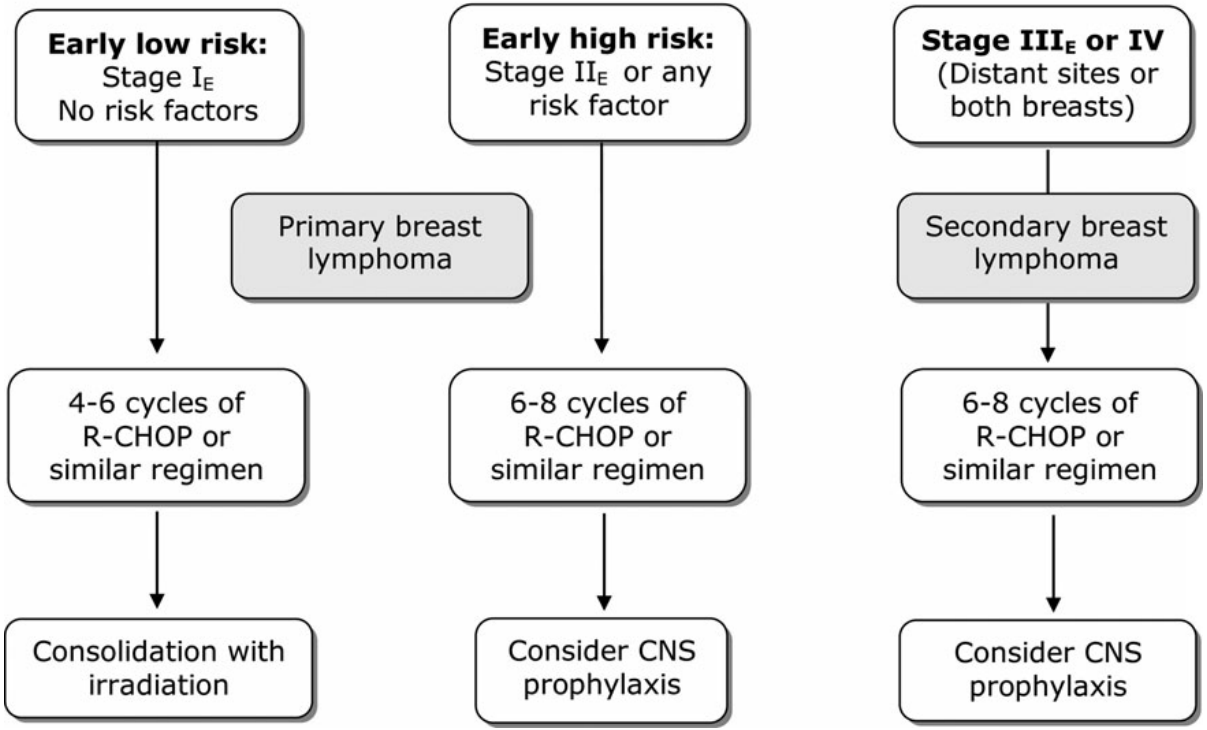
Ryan et al, Ann Oncol 2008

Suggested algorithm for newly diagnosed PB-DLBCL



Aviv et al, Ann Oncol 2013

Suggested algorithm for newly diagnosed PB-DLBCL



No recommendation on RT dose/fields

Aviv et al, Ann Oncol 2013

Follicular and marginal zone primary breast lymphoma (PBL): results from International Extranodal Lymphoma Study Group

Patients and methods:

- International retrospective study
- 60 cases of PBL (36 follicular and 24 marginal-zone lymphoma)
- Stage IE or IIE: 57 patients and IVE: 3 patients (bilateral breast)
- Treatment period: 1980 to 2003

Martinelli et al, Ann Oncol 2009

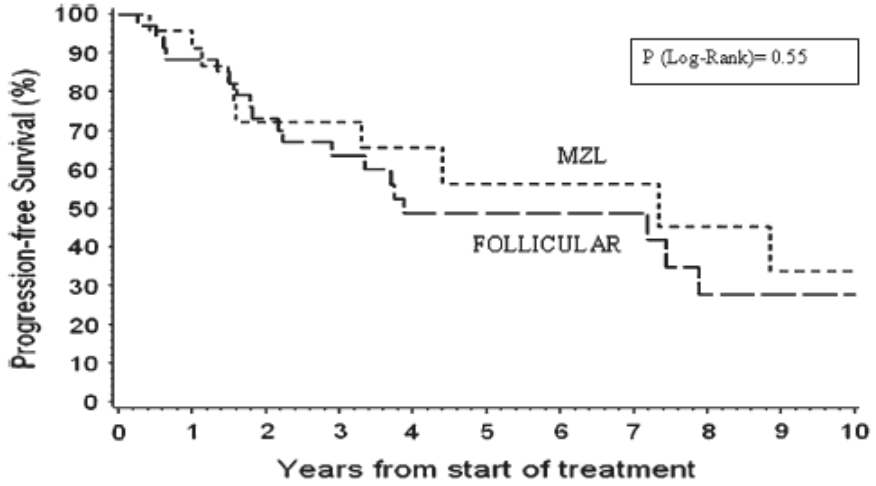
Follicular and marginal zone primary breast lymphoma (PBL): results from International Extranodal Lymphoma Study Group

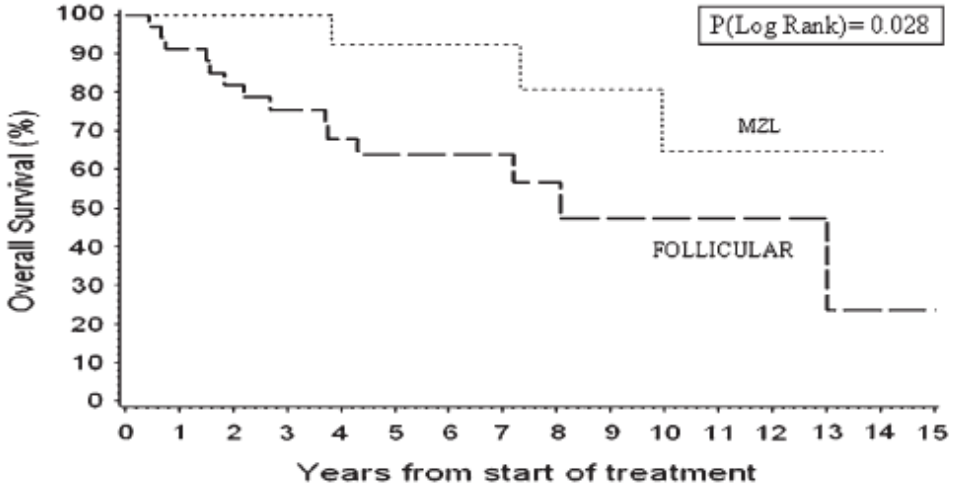
Results:

- First-line treatment:
  - Surgery +/- other: 67%
  - CT +/- other: 42%
  - RT +/- other: 52%
- RT to breast fields in 36 patients (dose range 25–50 Gy, median 38 Gy) and nodal fields (axilla and supraclavicular) in 18 patients (dose range 30–46 Gy, median 36 Gy).

Martinelli et al, Ann Oncol 2009

15-year PFS and OS in follicular and marginal zone primary breast lymphoma

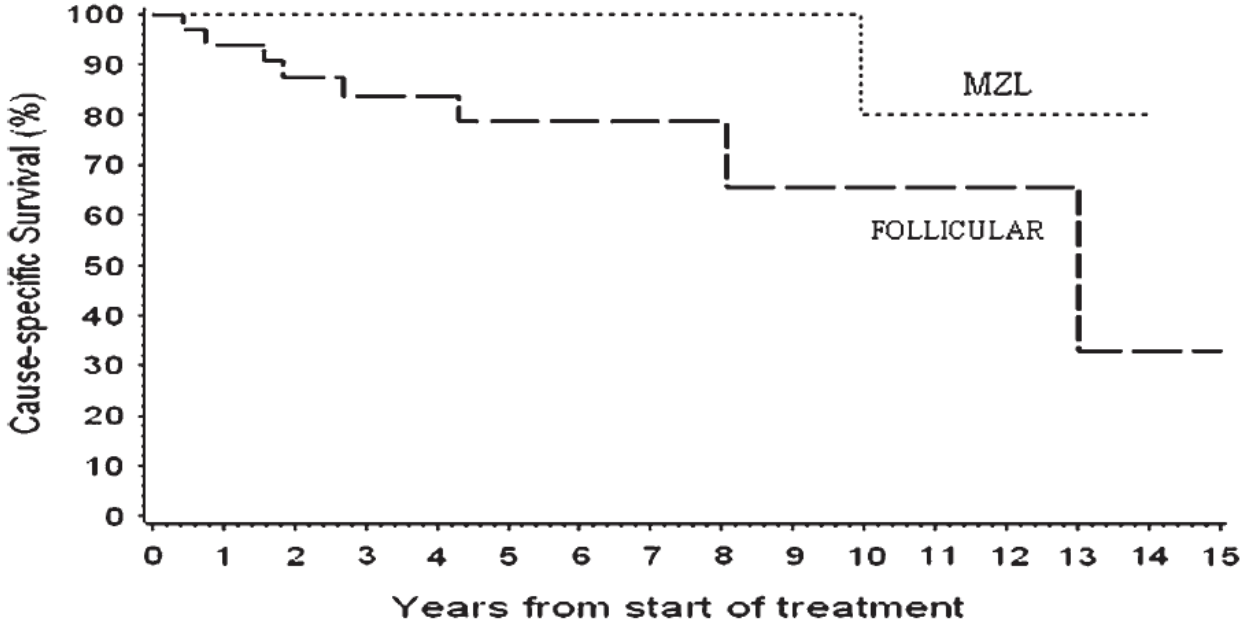




Overall response rate: 98% (93% complete response)
Relapses were mostly in distant sites (18 of 23 cases)
No patients relapsed within RT fields.

Martinelli et al, Ann Oncol 2009

15-year cause specific survival in follicular and marginal zone primary breast lymphoma



Martinelli et al, Ann Oncol 2009

Follicular and marginal zone primary breast lymphoma (PBL): results from International Extranodal Lymphoma Study Group

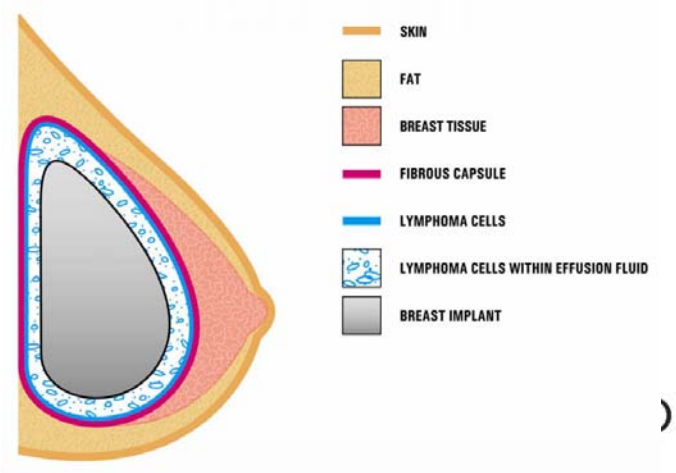
Conclusions:

- Outcome MZL PBL comparable to other primary extranodal MZL (=indolent)
- Patients with follicular PBL had inferior PFS and OS when compared with limited-stage nodal follicular non-Hodgkin's lymphomas.

Martinelli et al, Ann Oncol 2009

Breast Implant–Associated Anaplastic Large-Cell Lymphoma

- T-cell lymphoma arising around breast implant
- 1st case reported in 1997
- Estimated annual incidence 0.1- 0.3 per 100,000 women with implants



Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma

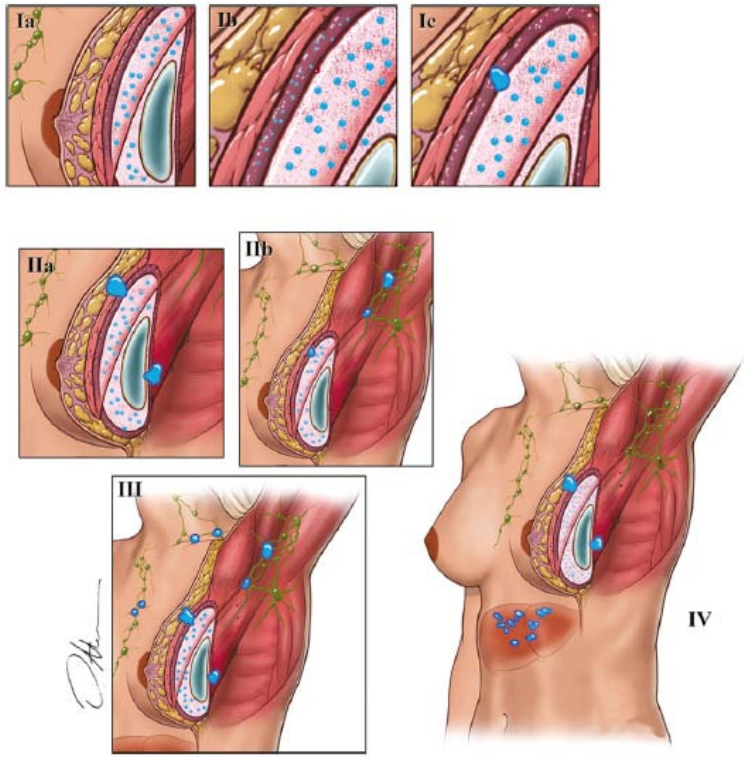


Table 1. Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma

TNM or Stage Designation	Description
T: tumor extent	
T1	Confined to effusion or a layer on luminal side of capsule
T2	Early capsule infiltration
T3	Cell aggregates or sheets infiltrating the capsule
T4	Lymphoma infiltrates beyond the capsule
N: lymph node	
N0	No lymph node involvement
N1	One regional lymph node (+)
N2	Multiple regional lymph nodes (+)
M: metastasis	
M0	No distant spread
M1	Spread to other organs/distant sites
Stage	
IA	T1N0M0
IB	T2N0M0
IC	T3N0M0
IIA	T4N0M0
IIB	T1-3N1M0
III	T4N1-2M0
IV	TanyNanyM1

Breast Implant–Associated Anaplastic Large-Cell Lymphoma

(retrospective analysis 87 patients)

Purpose

- To evaluate the efficacy of different therapies used in patients with BI-ALCL to determine an optimal treatment approach.

Patients and Methods

- A clinical follow-up of 87 patients with BI-ALCL, including 50 previously reported in the literature and 37 unreported.

Clemens et al., JCO 2016

Breast Implant–Associated Anaplastic Large-Cell Lymphoma

(retrospective analysis 87 patients)

Results

- Median follow-up time: 45 months (range, 3 to 217 months).
- Median OS time after diagnosis of BI-ALCL:13 years
- OS rate: 93% and 89% at 3 and 5 years, respectively
- Significantly EFS and OS in patients with:
  - lymphoma confined by the fibrous capsule surrounding the implant (vs lymphoma that had spread beyond the capsule)
  - a complete surgical excision that consisted of total capsulectomy with breast implant removal compared (vs partial capsulectomy, systemic chemotherapy, or radiation therapy)

Clemens et al., JCO 2016

Breast Implant–Associated Anaplastic Large-Cell Lymphoma

(retrospective analysis 87 patients)

Conclusion

- Surgical management with complete surgical excision is essential to achieve optimal EFS in patients with BI-ALCL

Clemens et al., JCO 2016

Radiotherapy

Breast lymphoma

Volume

- CTV for primary or consolidation RT: whole breast
- Uninvolved lymph nodes need not be included in CTV
- Partial breast irradiation is considered by some experts under special circumstances

Yahalom et al. ILROG guideline, IJROBP 2015

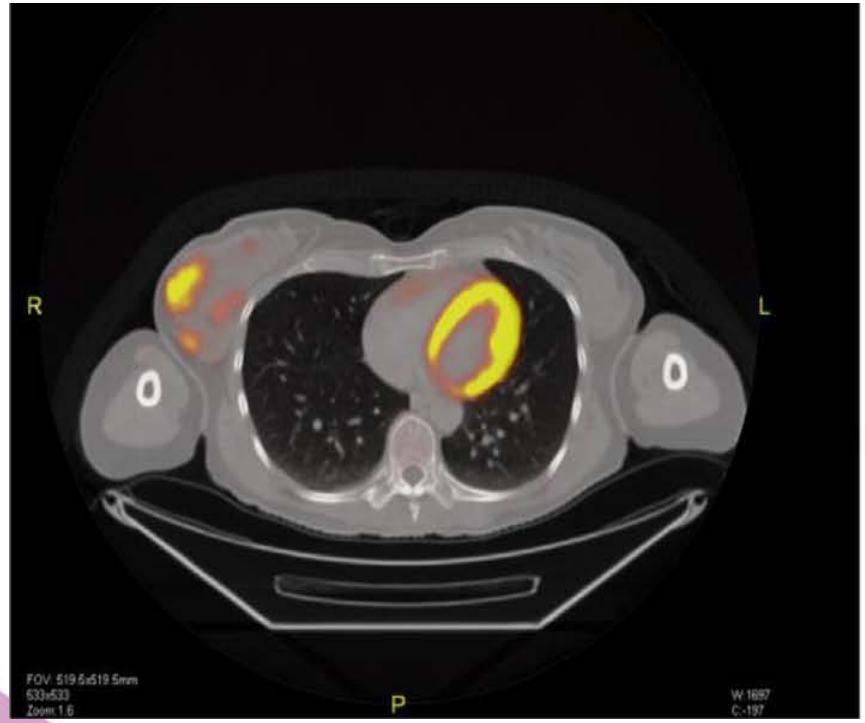
Breast lymphoma

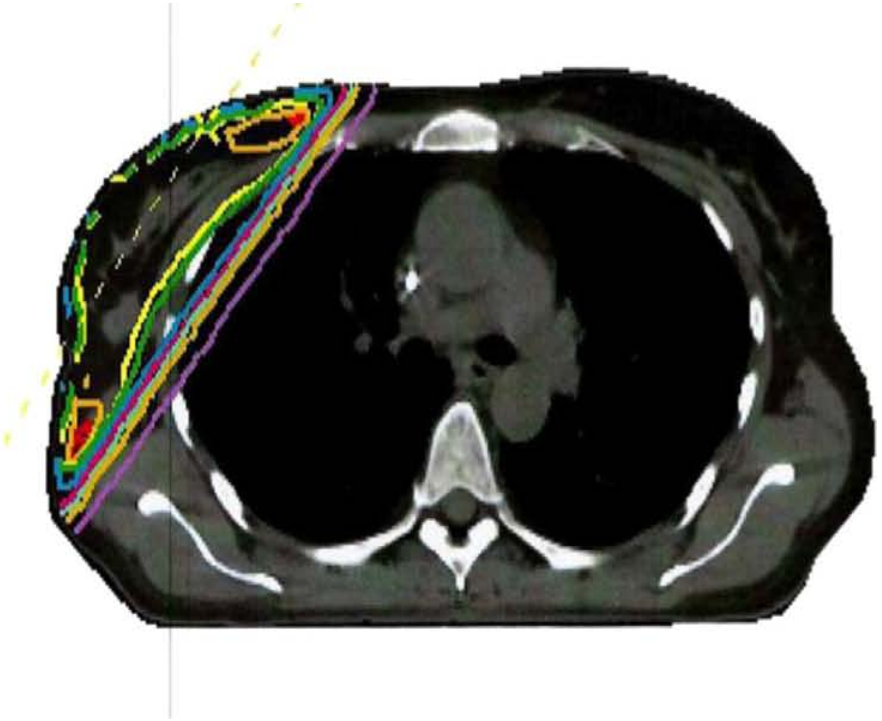
Technique

- Breast immobilization with the arm up, or prone technique for large pendulous breast.
- 3D conformal or IMRT depending on local preference

Yahalom et al. ILROG guideline, IJROBP 2015

49-year old woman with DLBCL right breast in CR after chemo





Yahalom et al. ILROG guideline, IJROBP 2015

Breast lymphoma

Radiation dose (curative setting):

- Indolent lymphoma: 30 Gy/15 fx
- DLBCL:
  - CR after chemo: 30 Gy/15 fx
  - PR after chemo: 40 Gy/20 fx

Questions?

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Long term toxicity

Late effects after Hodgkin lymphoma: incidence and clinical implications

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Content

- Background
- Second malignancies
  - Risks of important SMN (breast, GI and lung cancer)
  - 40 year risk of second malignancies after HL
- Cardiovascular disease
- Clinical implications

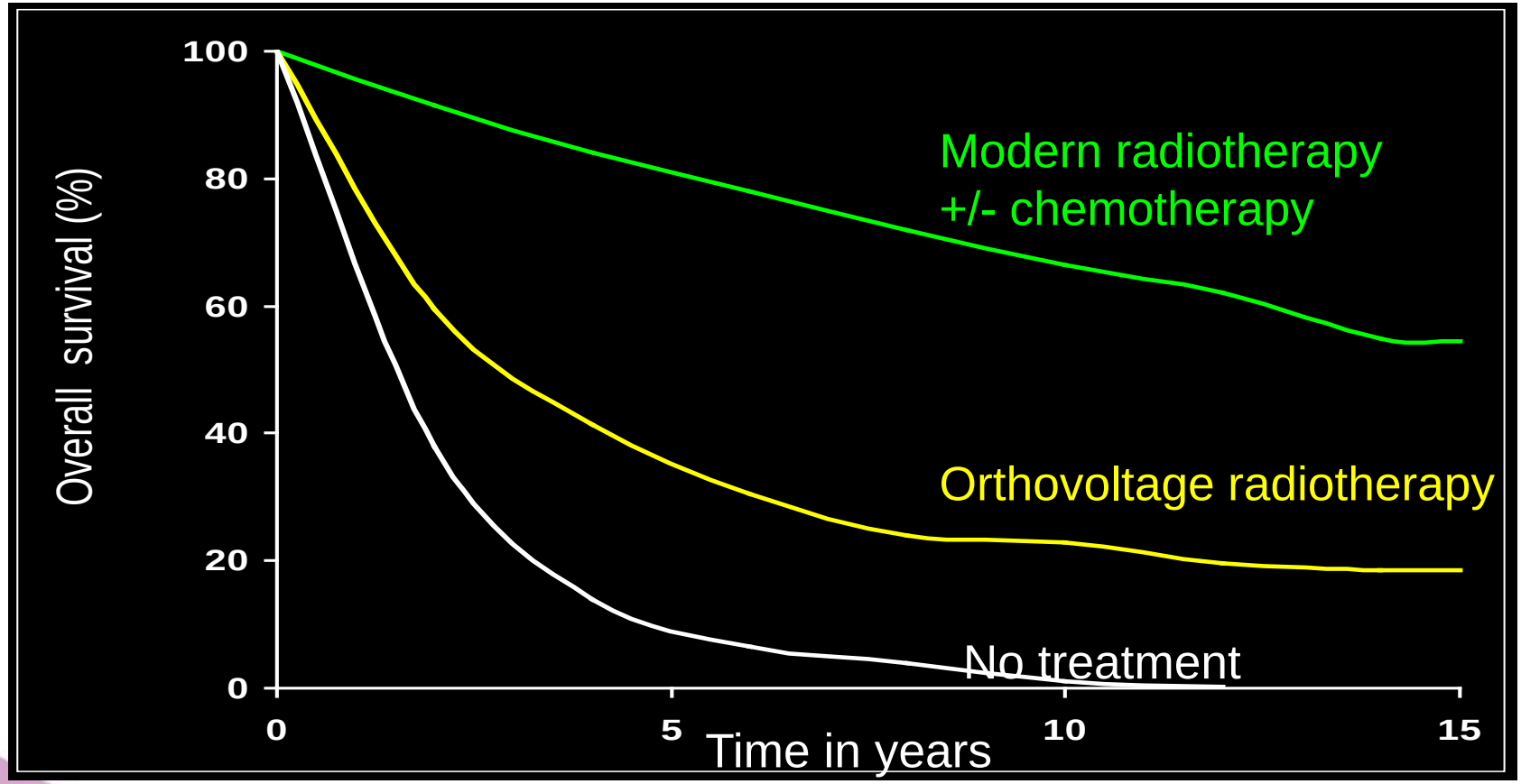
Hodgkin's disease

Nowadays Hodgkin lymphoma

Thomas Hodgkin, 1798-1866

- 0.4% of all new cancers
- 400 new cases per year in NL (16 million inhabitants)
- 67% of all cases below age 45
- Second most common malignancy in young adults
- The prototype of a curable malignancy

Survival after Hodgkin lymphoma

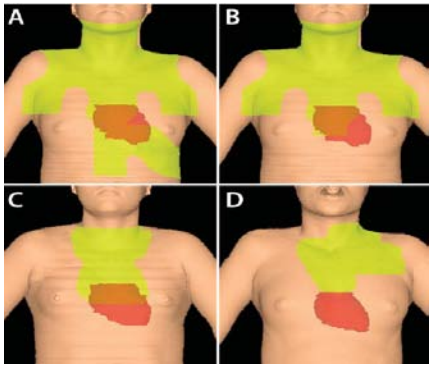


Kaplan 1978

HL treatment changes since 1965

	Chemotherapy Trend: ↓ dose alkylating		**Radiotherapy** Trend: ↓ RT target volumes, ↓ RT dose
<1980	MOPP(like) & single agents	<1980	Classical fields
1980-1995	MOPP/ABVD; MOPP ABV	1980-1995	Classical fields; IFRT
>1995	ABVD; MOPP-ABV; EBVP; BEACOPP	>1995	IFRT
>2012	Brentuximab-vedotin containing regimens	>2006	INRT; ISRT

MOPP: Mechlorethamine, vincristine, procarbazine, prednison
ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine
ABV: Doxorubicin, bleomycin, vinblastine
BEACOPP: Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednison



Hodgson, ASH educational 2011

HL treatment changes since 1965

Chemotherapy Trend: ↓ dose alkylating		Radiotherapy Trend: ↓ RT target volumes, ↓ RT dose	
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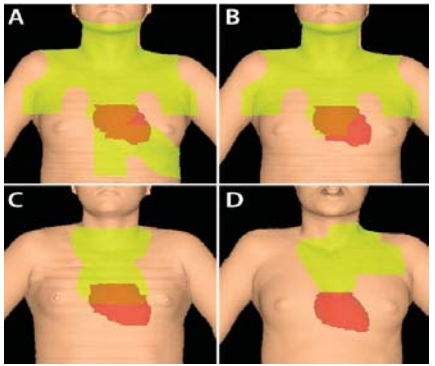
MOPP: Mechlorethamine, vincristine, procarbazine, prednison
ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine
ABV: Doxorubicin, bleomycin, vinblastine
BEACOPP: Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednison



Hodgson, ASH educational 2011

Successes of HL treatment

⬇

Long-term survival

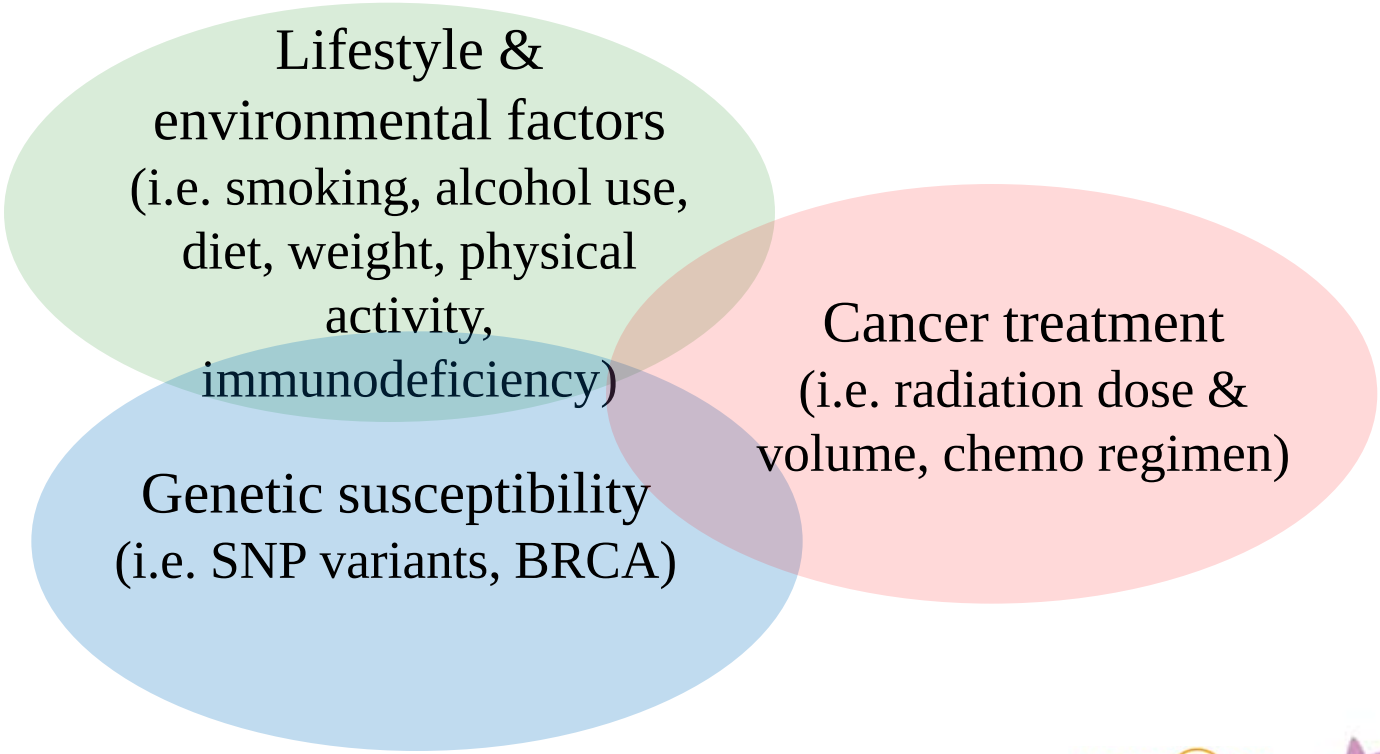
⬇

Possibility to observe late adverse effects of treatment

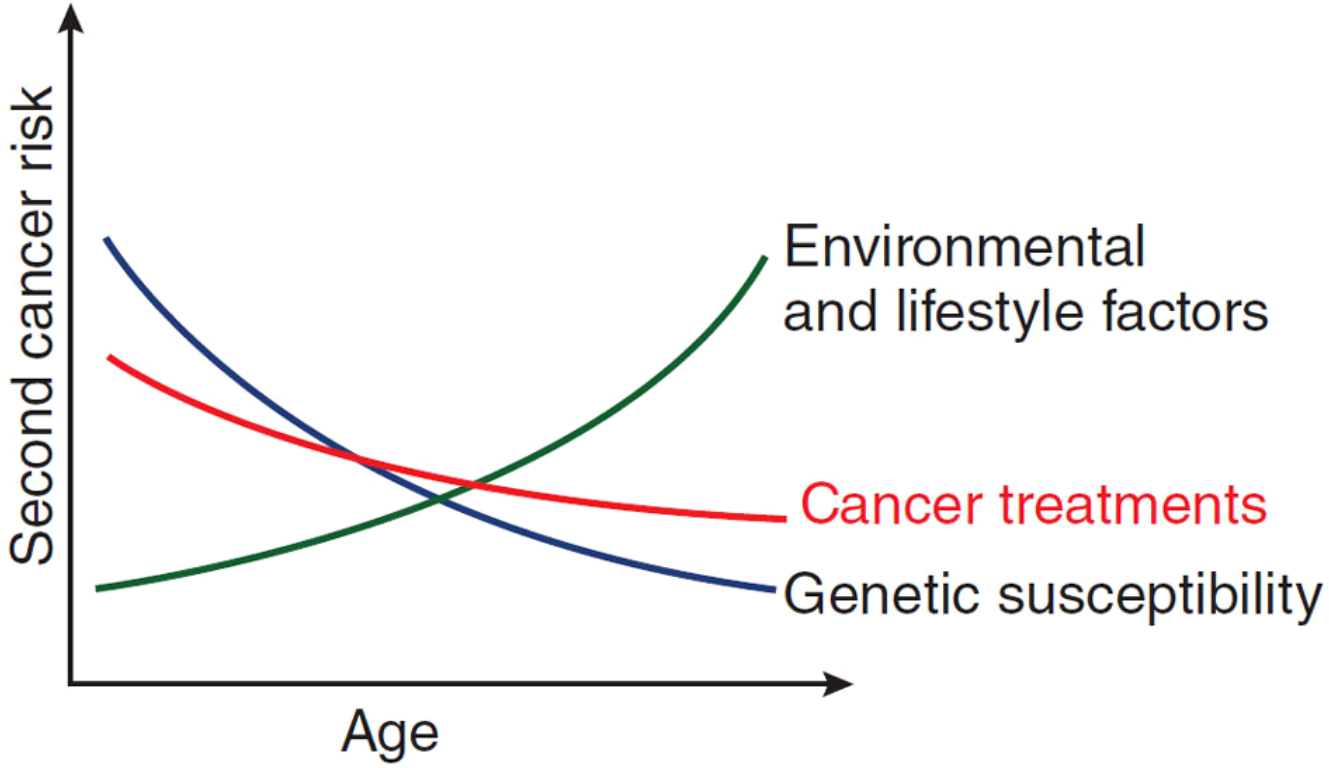
Late effects of treatment for Hodgkin lymphoma

Second malignancies
Cardiovascular disease
Cerebrovascular disease
Diabetes mellitus
Gonadotoxicity
Pulmonary toxicity
Gastrointestinal toxicity
Thyroid dysfunction
Infections
Fatigue

Causes of second cancers



Causes of second cancers in relation to age



Morton & Chanock. Nat Med 2011

Risk measures in late effect research

- Standardized Incidence Ratio (SIR) =

  Observed / Expected numbers of events =

  Relative risk compared to general population

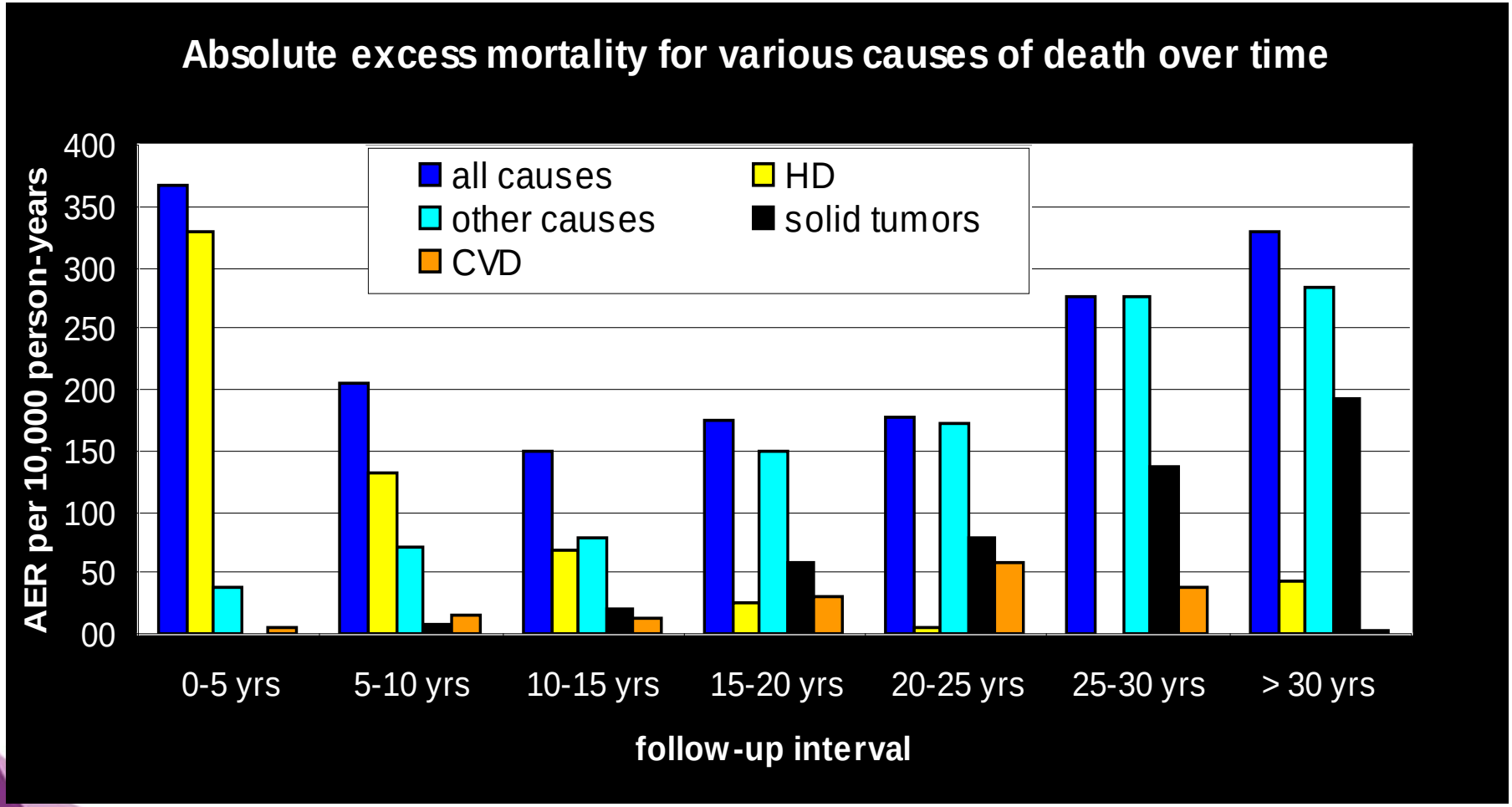
  - High SIR for rare event → low absolute risk

- Absolute excess risk (AER) =

  Excess number of events beyond expected number / 10,000 persons/ year

- Cumulative incidence = % developing event, accounting for death as a competing risk

- Hazard ratio = RR for treatment A vs treatment B



Aleman et al., JCO 2003; 21:3431

Risks of Second Malignancy following HL combined results from 3 large studies* (n=9618)

Site or Type	Obs	SIR	AER
All SMN	747	3.8	62.2
Solid tumors	519	2.8	37.9
Lung	155	4.3	13.4
GI tract	115	2.4	7.0
Stomach	29	2.8	2.1
Female breast	76	2.7	13.2
Thyroid	14	9.2	1.4
Leukemia	116	22.3	12.5
ANLL	63	94.8	14.9

SIR: Standardized Incidence Ratio; AER: Absolute Excess Risk per 10,000 persons/year
*Based on Hancock 1996; Van Leeuwen 2000; Swerdlow 2000

Survival outcome after a second malignancy

n=1319 ; treatment period: 1969 and 1997; median fup 12 years.

Second malignancy	No. of pts	5-yr survival estimate (%)	95% CI	Median survival, yrs
All sites	181	38.1	(29.7-46.5)	3.2
Acute leukemia	23	4.9	(0.0-14.2)	0.4
NHL	24	49.6	(28.0, 71.2)	2.4
All solid tumors	131	42.1	(31.6, 52.5)	4.3
Breast	39	76.1	(57.4-94.8)	Not yet reached
Lung	22	0.0	—	1.0
Gastrointestinal	24	12.4	(0-28.1)	1.9

Ng et al., Blood 2002

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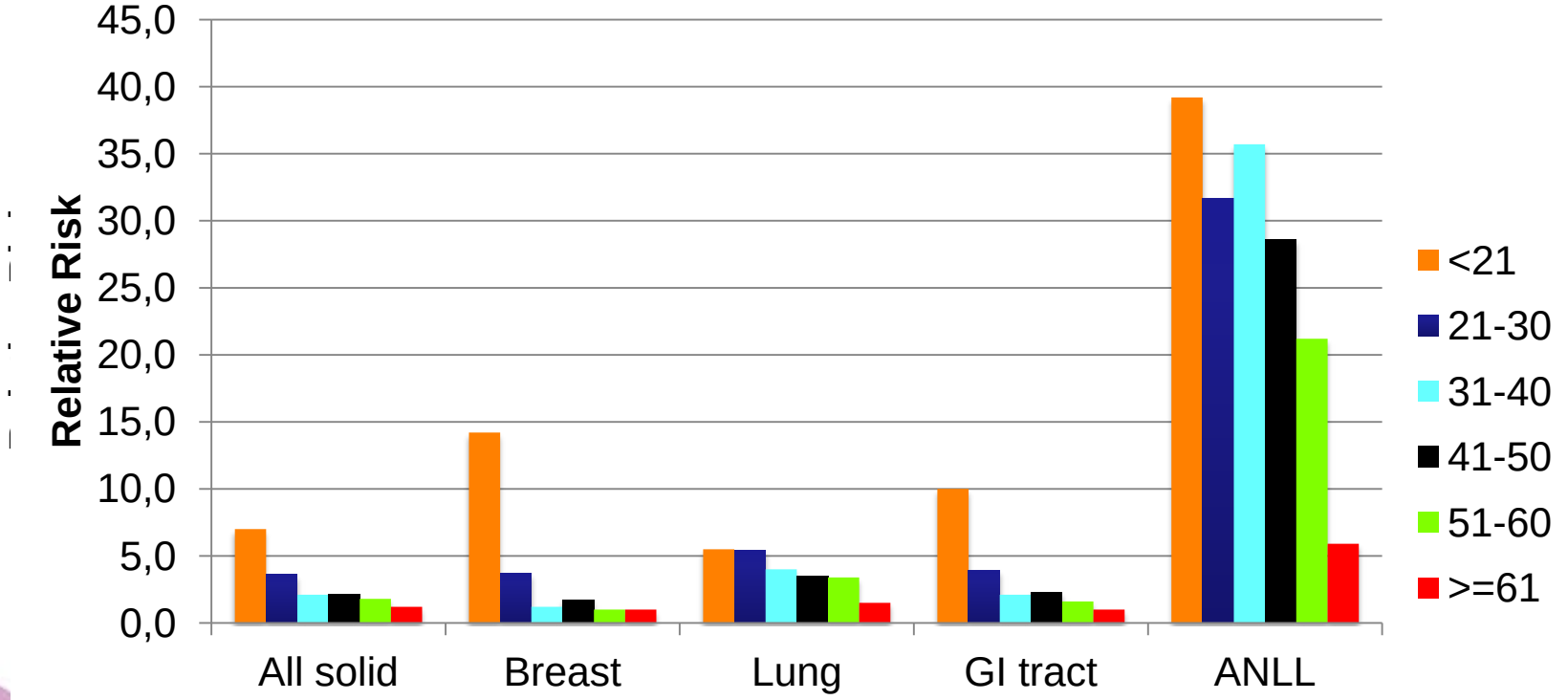
Gastrointestinal	24	12.4	(0-28.1)	1.9

Ng et al., Blood 2002

Relative risks of SMN by age at HL diagnosis

International cohort study: 32,591 HL patients

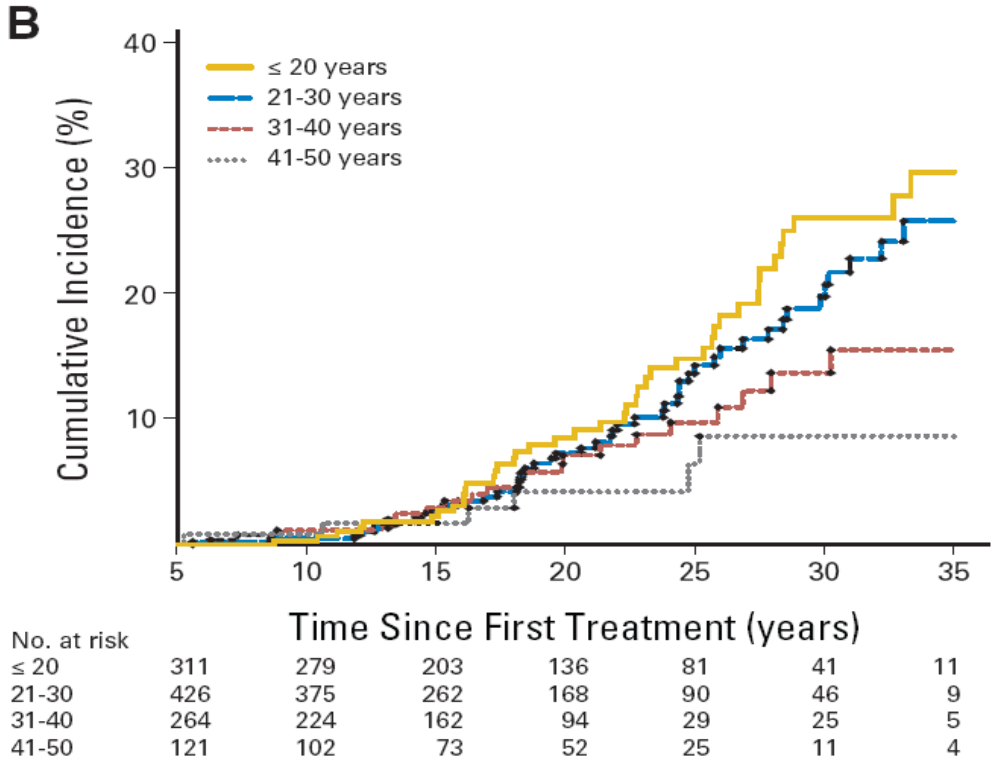
1,111 25-years survivors, population-based



Adapted from Dores JCO 2002; 20:3484

Cumulative incidence of breast cancer by age at HL

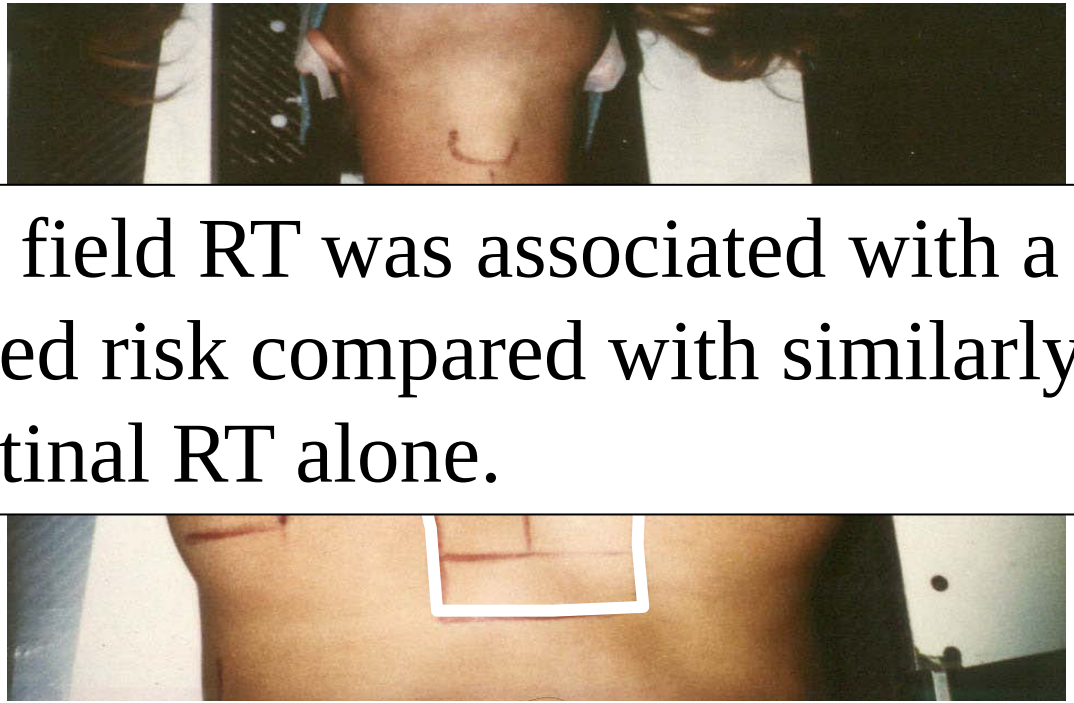
(1,122 female 5-year survivors treated for HL <51 years between 1965 and 1995)



No. at risk							
≤ 20	311	279	203	136	81	41	11
21-30	426	375	262	168	90	46	9
31-40	264	224	162	94	29	25	5
41-50	121	102	73	52	25	11	4

De Bruin et al. JCO 2009; 27(26): 4239-4246

From mantle field to IFRT



Mantle field RT was associated with a 2.7-fold increased risk compared with similarly dosed mediastinal RT alone.

De Bruin et al, JCO 2009

Breast cancer following HL

a Dutch case-control study

Radiation dose in Gy (median)	**Cases**	**Controls**	**OR†**	**95%CI**
<4 (3.6)	9	47	1.0*	Ref
4-24 (15.5)	10	39	1.11	0.32-3.85
24-38.5 (30.2)	14	44	4.20	0.99-17.8
≥38.5 (40.7)	15	45	5.16	1.27-21.0

van Leeuwen JNCI 2003: 95;971

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a Dutch case-control study

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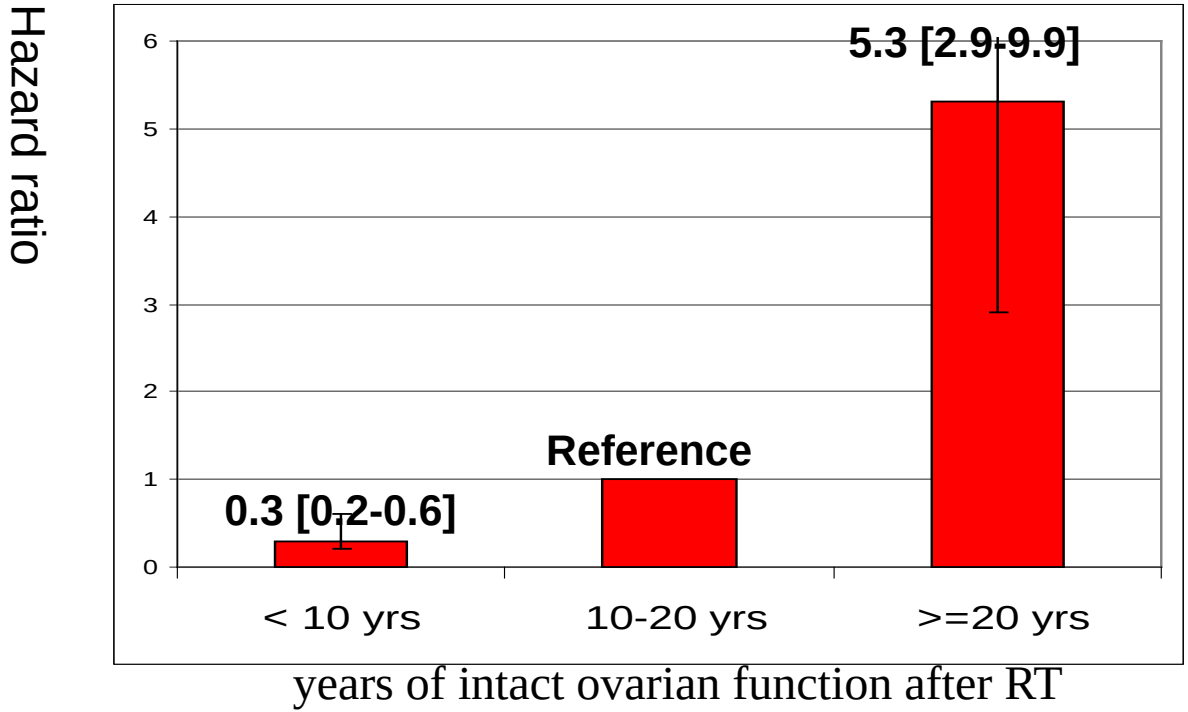
≥38.5 (40.7)	15	45	5.16	1.27-21.0
Overall treatment	**Cases**	**Controls**	**OR†**	**95%CI**
RT only	30	68	1.0	Ref
RT+CT	18	104	0.45	0.22-0.91

* P trend <0.001; † adjusted for RT dose ovary and CT

- Highest risks in youngest patients
- Induction period: 10-15 years

van Leeuwen JNCI 2003: 95;971

Risk of breast cancer after RT for HL, by duration of ovarian function after RT

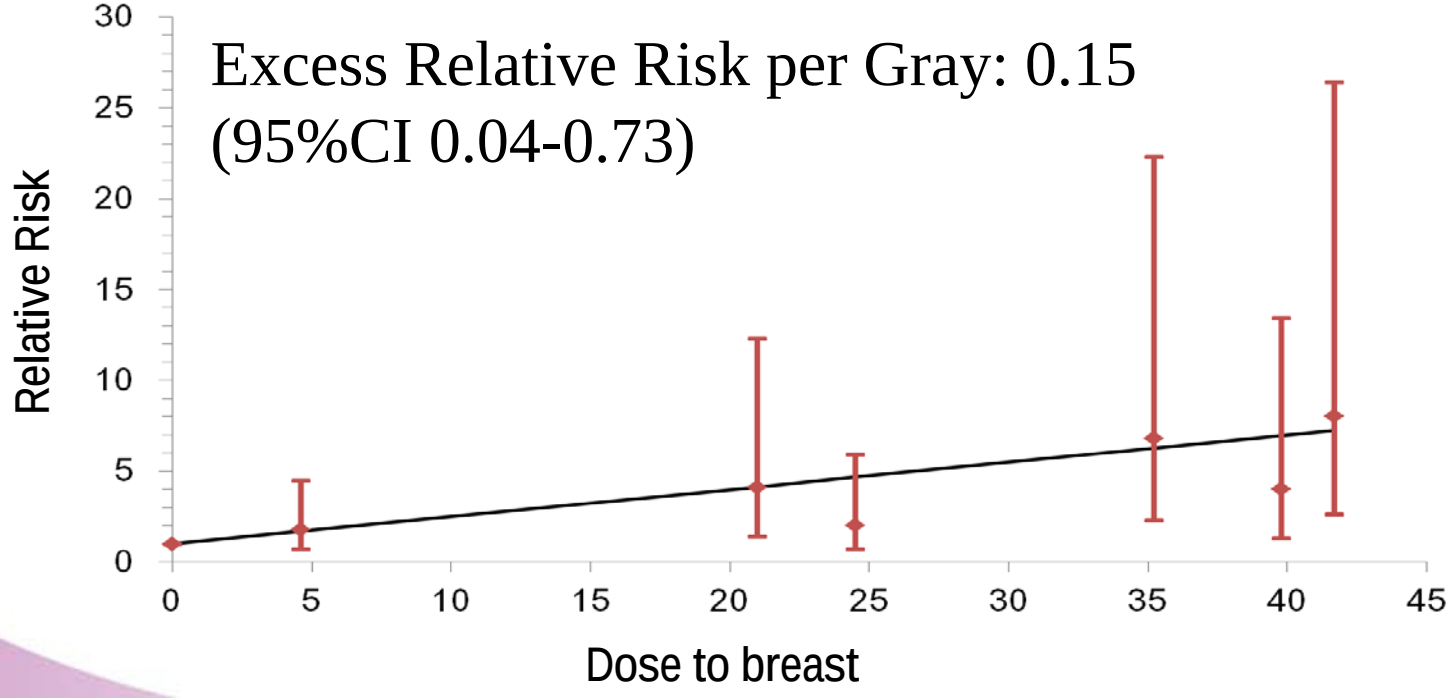


→ Ovarian hormones crucial in radiation-induced breast carcinogenesis

De Bruin et al, JCO 2009

Radiation dose and breast cancer risk in HL survivors (Travis et al. JAMA 2003; 290:465)

International case-control study, 105 breast cancer cases and 266 matched controls; Radiation dose to breast tumor location was estimated.



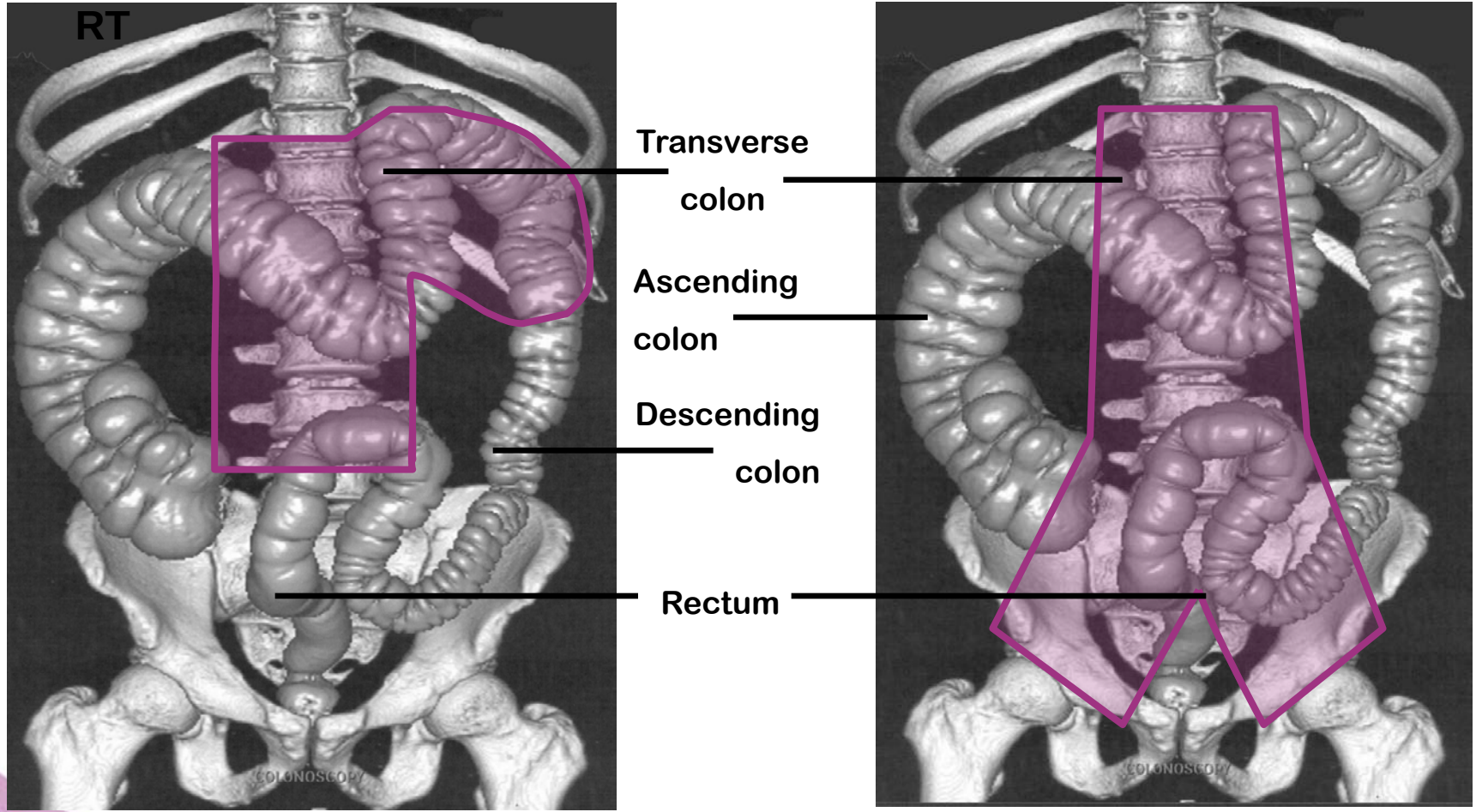
Literature on CRC risk after HL or childhood cancer and in A-bomb survivors

- Colorectum: important site of excess cancer in HL survivors
- ↑ colon cancer risk after exposure to low RT doses, whereas ↑ rectal cancer risk after higher doses
- Excess CRC risk appears 10 years after exposure

Birdwell et al., 1997; Hodgson et al., 2007; Van den Belt-Dusebout et al, 2009; Henderson et al 2012 (CCS); Nottage et al 2012 (CCS);Life Span Studies; Eggermond work in progress

Para-aortic ± spleen RT

Inverted Y RT



Schaapveld, Eggermond et al submitted

SIR & AER of CRC

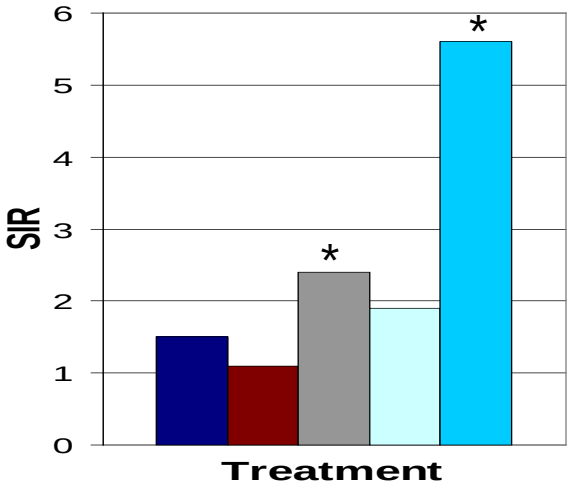
in 2,820 5-year Dutch HL survivors, diagnosed<51 years, treated1965-1995; median fup 21.5 years

Tumor site	O	SIR (95%CI)	AER (95%CI)
Colorectal cancer	49	2.7*	6.3*
Colon	30	2.7*	3.9*
Ascending colon	10	2.3*	1.1
Transverse colon	11	7.5*	2.0
Descending colon	7	1.3	0.4
Colon, NOS	2	5.5	0.3
Rectum	19	2.7*	2.4

SIR = Standardized Incidence Ratio (observed/expected) * p <0.05
AER = Absolute Excess Risk **per 10.000 patients/yr**
NOS = Not otherwise specified

Schaapveld, Eggermond et al submitted

Risk of CRC by HL treatment



CT only

Supra RT only

Supra RT + CT

Infra ± supra RT, no CT

Infra ± supra RT + CT

Treatment	Obs	Exp	SIR
CT only	3	2.0	1.5
Supra RT only	3	2.7	1.1
Supra RT + CT	13	5.3	2.4*
Infra ± supra RT, no CT	8	4.2	1.9
Infra ± supra RT + CT	22	4.0	5.6*

* p <0.05

Supra = supradiaphragmatic, infra = infradiaphragmatic

Schaapveld, Eggermond et al submitted

Clinical implications

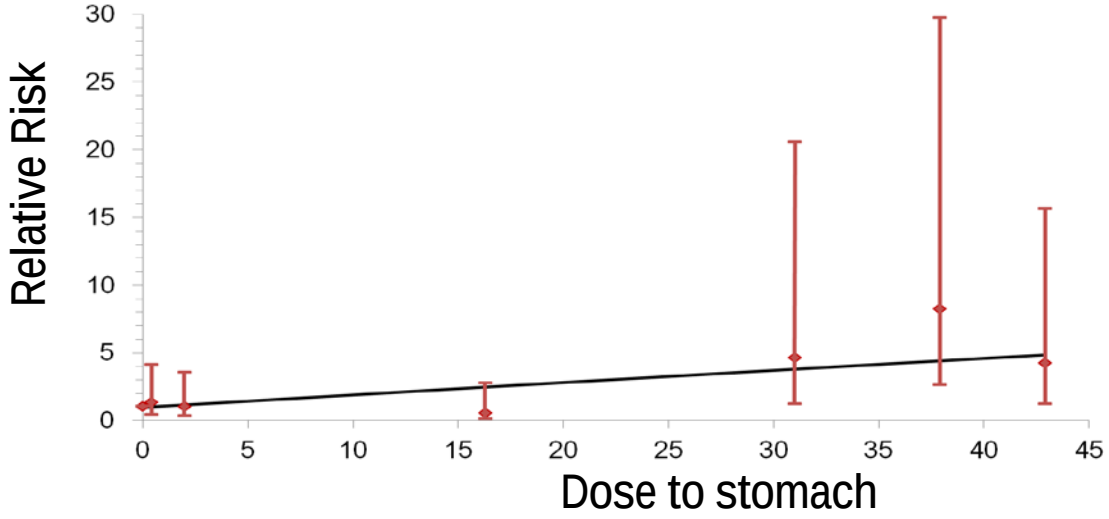
- 47-year old HL survivor (treated < 25 yr) same CRC risk as 55-60 year old person from general population (0.5%)
- Need for screening guidelines for HL survivors
- COG guideline: colonoscopy after ≥ 30 Gy abdominal RT

  10 yrs after RT or at age 35
- Starting age? Also after procarbazine CT?
- Implications for the use of procarbazine in new treatment regimens?

Schaapveld, Eggermond et al submitted

Radiation dose and stomach cancer risk in Hodgkin lymphoma survivors

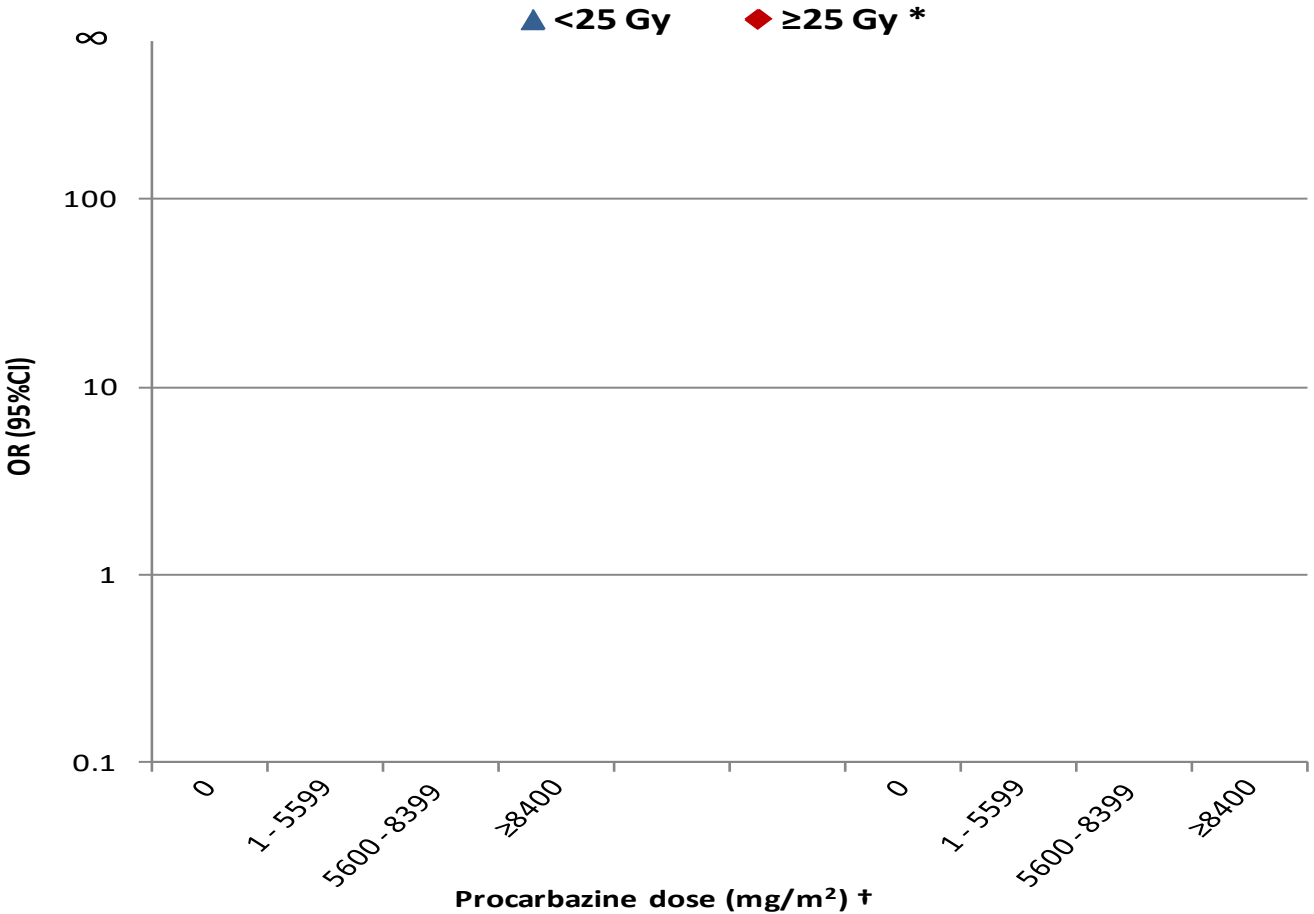
International nested case-control study, 89 stomach cancer cases and 190 matched controls; Radiation dosimetry to estimate dose to area of stomach tumor Morton et al. JCO 2013



RRs adjusted for alkylating agent CT dose

Excess Relative Risk per Gray 0.09 (95%CI 0.04-0.21)

Risk of stomach cancer after HL in relation to radiation dose to the stomach and procarbazine dose.



4.2 g/m^2 procarbazine≈3x MOPP or 6 MOPP-ABV(D)

Morton et al, JCO 2013

Lung cancer after HL
Joint effects of smoking and treatment

- Risks from smoking multiply risks from treatment
- Smoking is the major cause of lung cancer (only 7 out of 222 cases were never smokers)

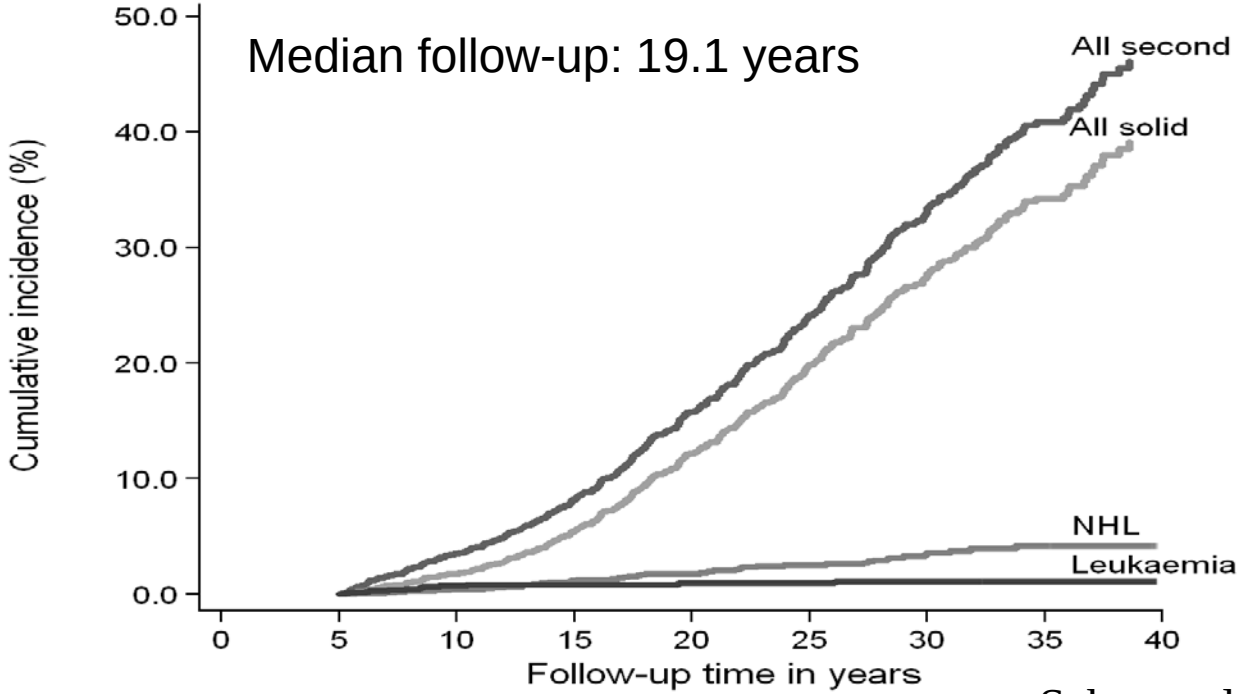
	RR non/light smokers	RR smokers
No RT (< 5 Gy), no CT	1.0 (ref)	6.0 (1.9-20.4)
RT (≥ 5 Gy), no CT	7.2 (2.9-21.2)	20.2 (6.8-68)
No RT (< 5 Gy), CT	4.3 (1.8-11.7)	16.8 (6.2-53)
RT (≥ 5 Gy), CT	7.2 (2.8-21.6)	49.1 (15.1-187)

Travis et al. JNCI 2002; 94:182

Has second malignancy risk changed over time?

Cumulative incidence of second malignancies, in the presence of competing risks

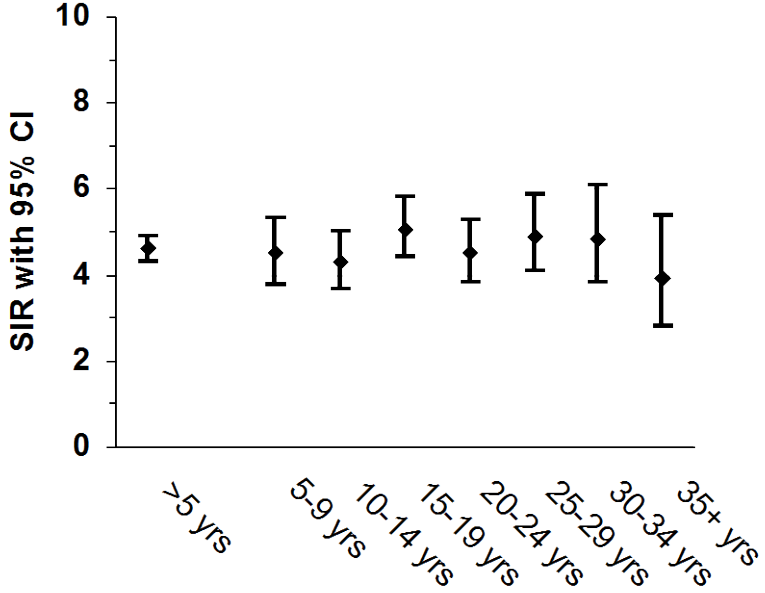
Dutch 5 year HL survivors treated 1965-2000 at age 15-51 years (n=3,905)

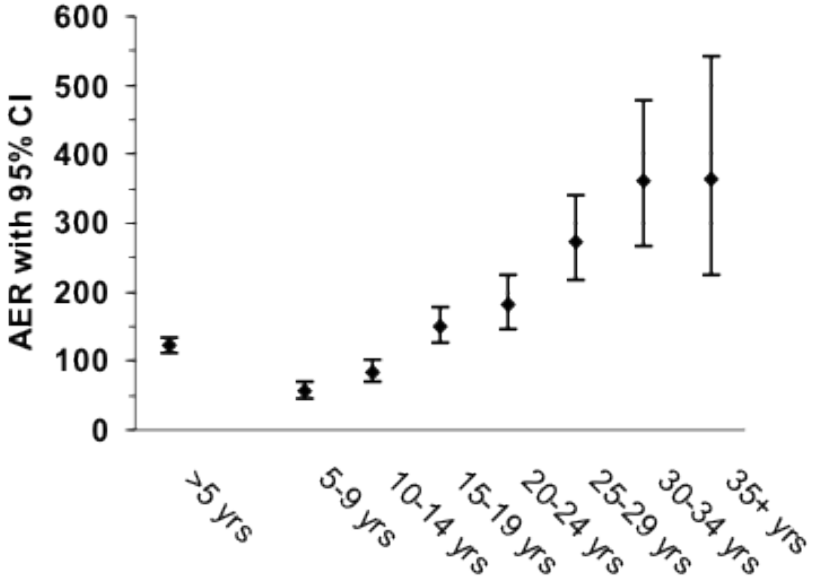


Schaapveld et al , submitted

Solid tumor risk by follow up interval

Dutch 5 year HL survivors treated 1965-2000 at age 15-51 years (n=3,905)

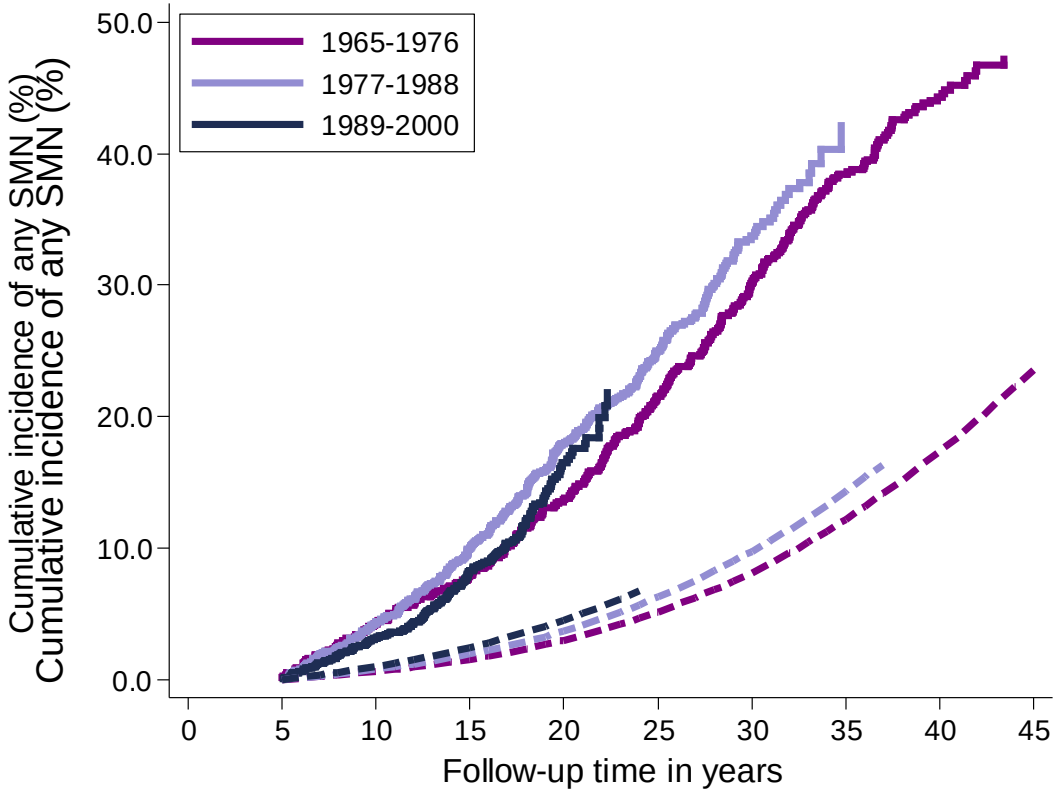




AER per 10,000 patients/yrs

Schaapveld et al , NEJM 2015

Cumulative incidence any SMN by period

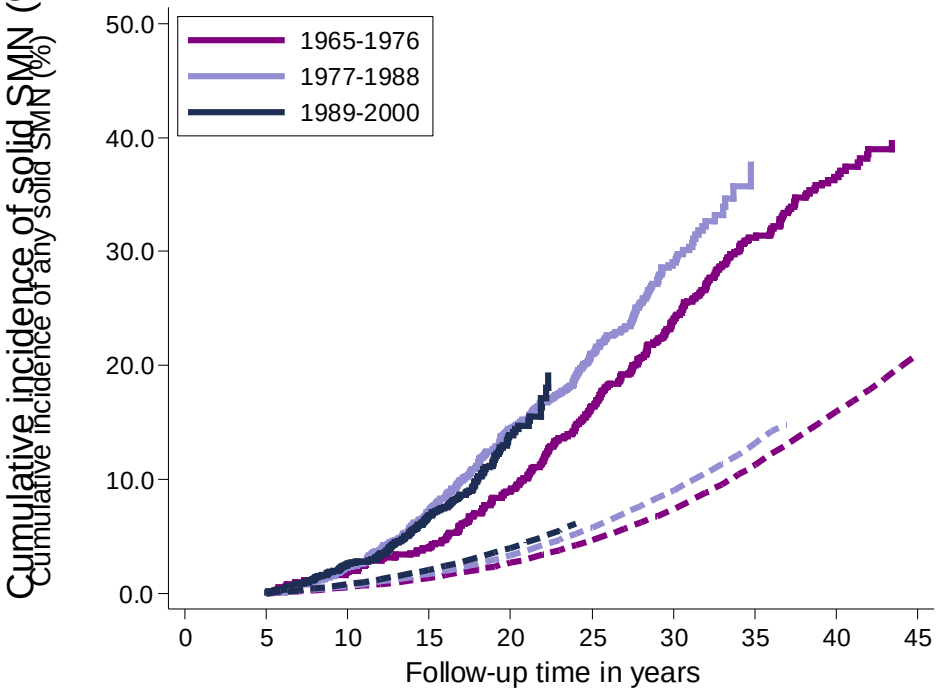


sHR: 0.79 (95%CI 0.65-0.95)
1990-2000 versus 1965-1979
adjusted for age & gender
follow-up<20years
$P_{\text{-trend:}}$0.015

Cumulative incidence
40 yrs after HL: 48.5%

Schaapveld et al , NEJM 2015

Cumulative incidence of solid tumors by treatment period

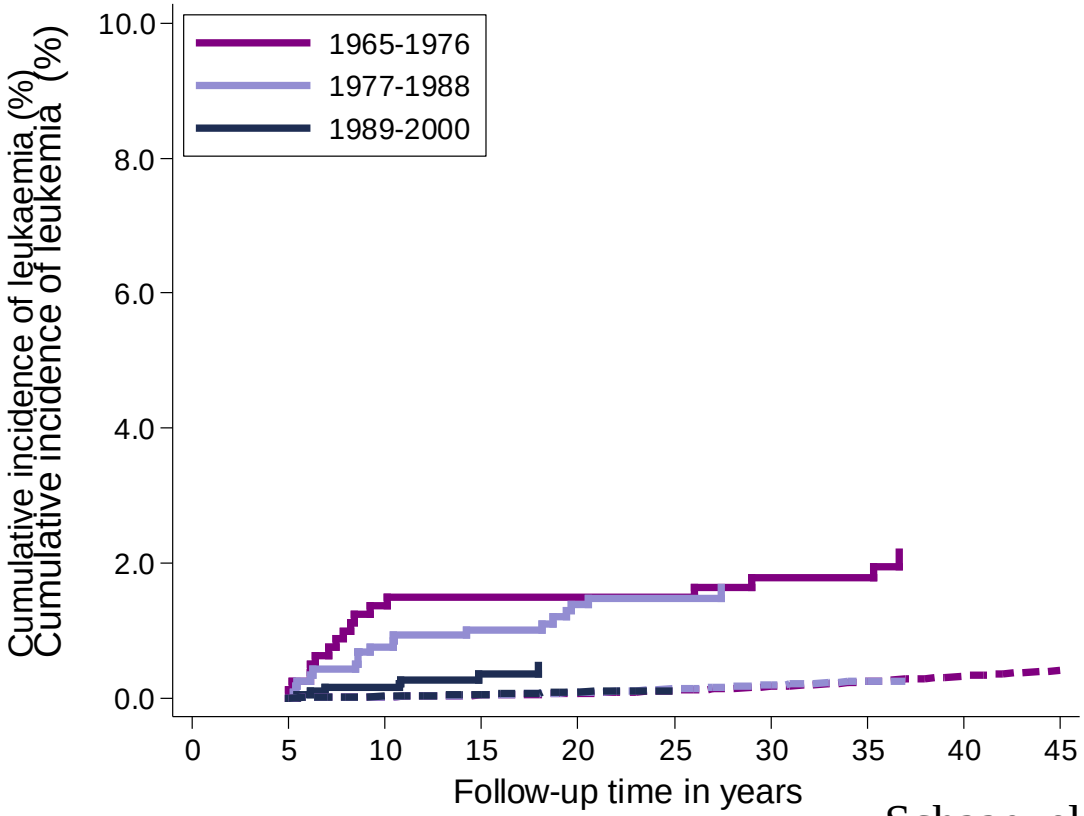


sHR 0.94 (95%CI 0.77-1.15)

1990-2000 versus 1965-1979
adjusted for age & gender
follow-up<20years

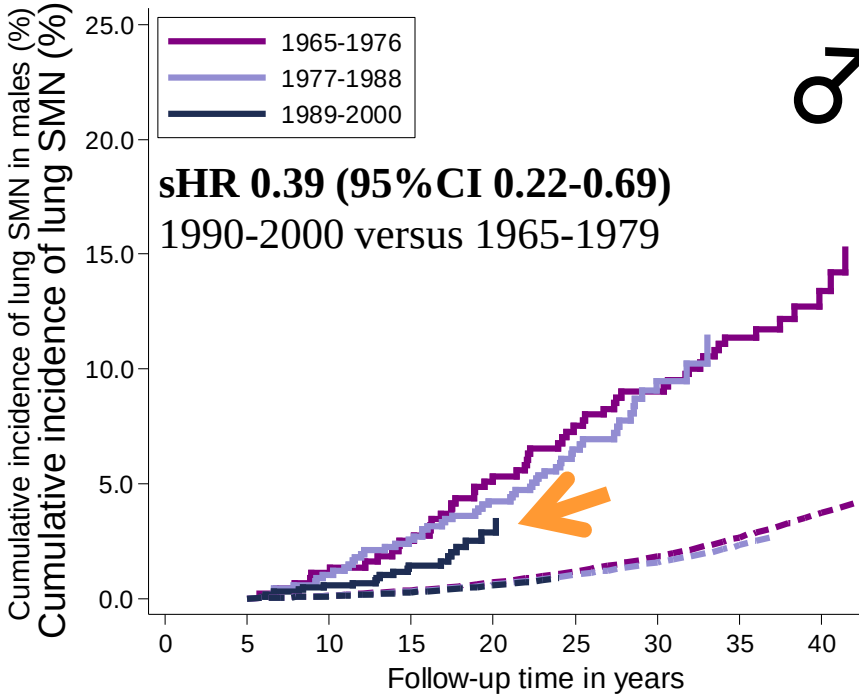
Schaapveld et al , NEJM 2015

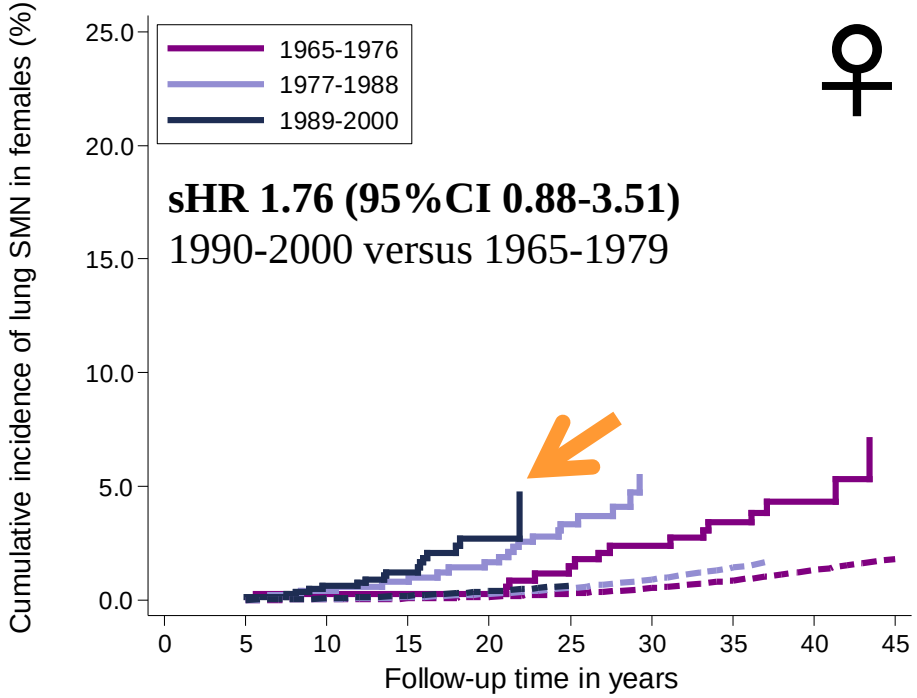
Cumulative incidence of leukemia (excluding MDS)



Schaapveld et al , NEJM 2015

Trend in cumulative incidence* of lung cancer by period of treatment and sex in 5 year HL survivors (n=3,905) and the general population





*estimated in the presence of death as a competing risk
Subdistribution HR are adjusted for age and follow-up<20 years

Schaapveld et al , NEJM 2015

Conclusions

- Risk of hematological SMNs has decreased over time
- Risk solid SMNs does not appear to decrease in patients treated before 2000, potentially due to changes in chemotherapy regimens and more breast cancer screening.
- Awareness of increased SMN risk remains crucial for HL survivors.

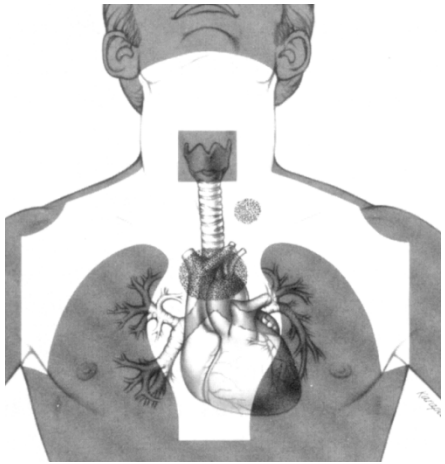
Schaapveld et al , submitted

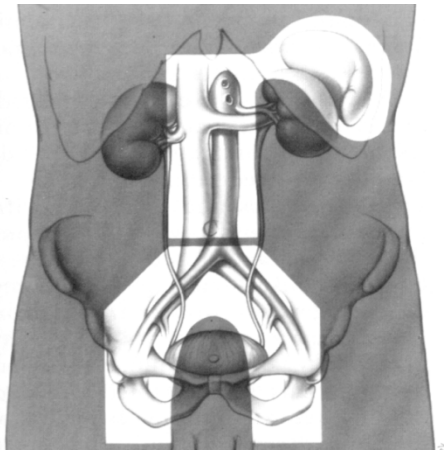
Summary SMN

- Risks of RT associated SMN:
  - Volume related
  - Linear ↑ with dose for most SMN (except thyroid cancer)
- Emerging data on CT related solid ca risks
- Many data on late effects based on outdated treatments
- Imaging and RT techniques have improved → more effective and less toxic treatments

Causes cardiovascular damage

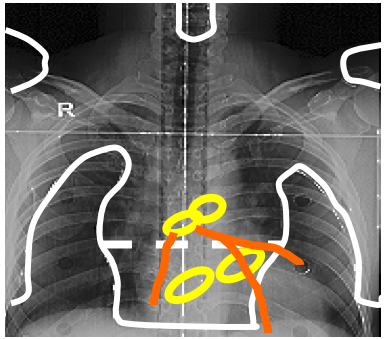
- Chemotherapy (anthracyclines)
- Radiotherapy





RT-associated heart diseases

- Coronary heart disease
- Myocardial dysfunction
- Valvular abnormalities
- Pericardial abnormalities
- Electrical conduction disorders

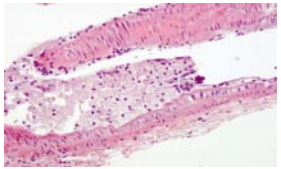


Cardiovascular toxicity

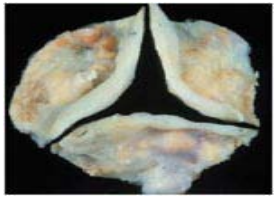
Differences in mechanisms

Radiation

Damage to vasculature (vulnerable plaques*)



Damage to valves



Damage to myocytes

*Russell, Stewart, Hoving
Sawyer et al. Circulation 2002
Lim et al. J Biol Chem. 2004

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

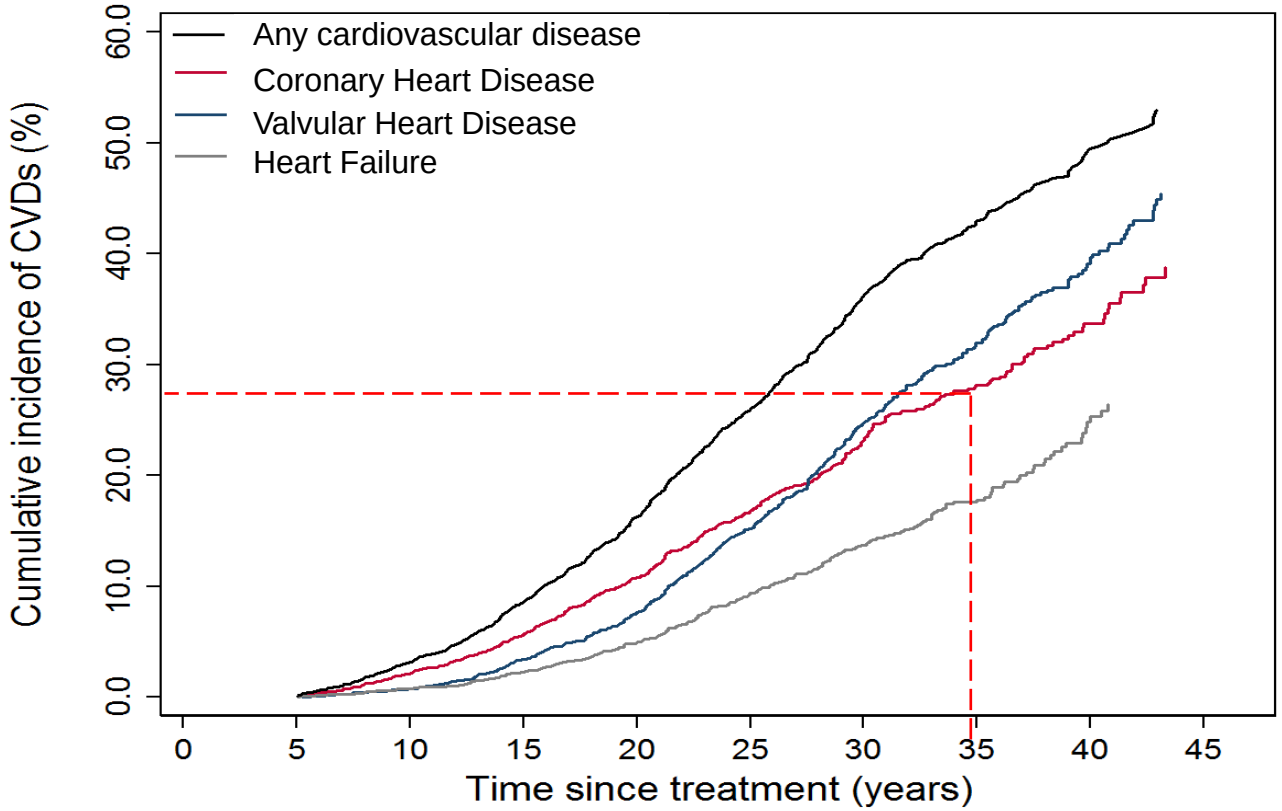
ESTRO School

Literature cardiovascular disease after HL

- Mediastinal radiotherapy increases *mortality* of CVD, esp. coronary artery disease
  (Boivin, Cancer 1992; 69:1241; Hancock, JAMA 1993; 270:1949; Swerdlow JNCI 2007; 99:206; Aleman JCO 2003; 21:3431)
- Fewer studies examined CVD *morbidity*
  (Hull JAMA 2003; 290:2831; Aleman, Blood 2007; 109:1878; Glanzmann, Rad Oncol 1998; 46:51)
- Increased mortality for > 25yrs
- Also increased risk for valvular disease *(Aleman, Blood 2007; Hull, JAMA 2003)*

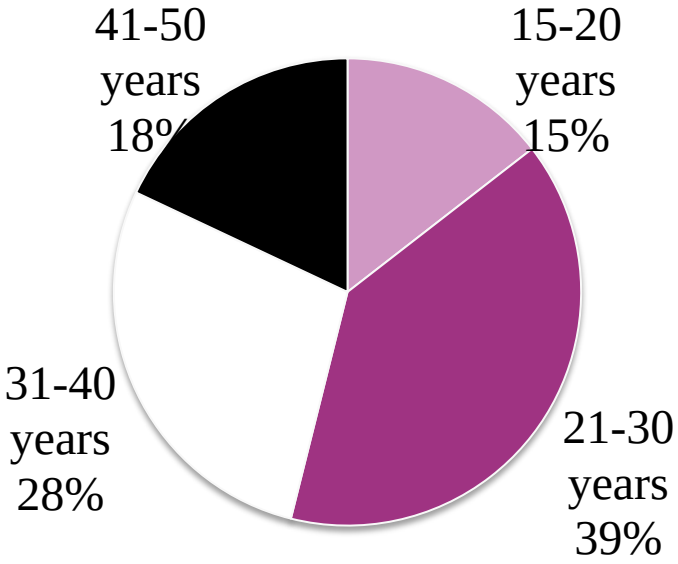
Morbidity of cardiovascular disease

(all events in 2524 5-year survivors of HL treated before age 51 between 1965-1995)

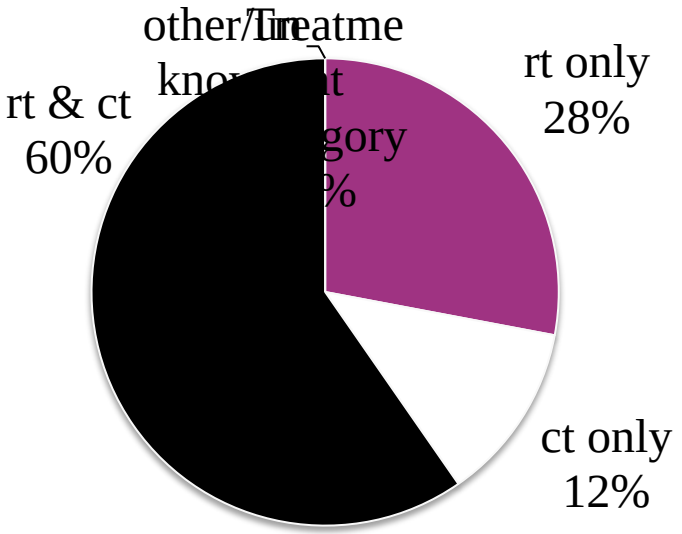


Van Nimwegen et al., JAMA int med 2015

HL age distribution



HL treatment



41% anthracycline-containing chemotherapy

Over time ↓ use mantle field and abdominal RT

Schaapveld, work in progress

Nested case-control studies

Endpoints:

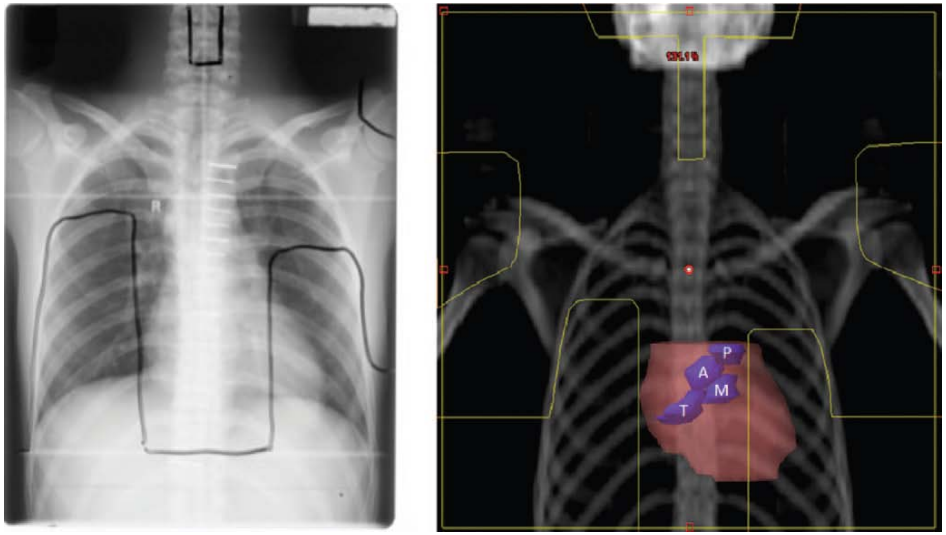
- Valvular heart disease
- Ischemic heart disease
- Heart failure

First events!

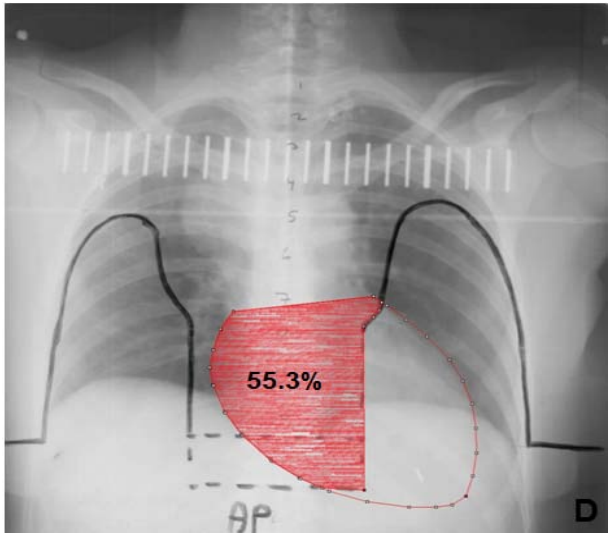
Nested case-control studies

Dosimetry:

CT-based



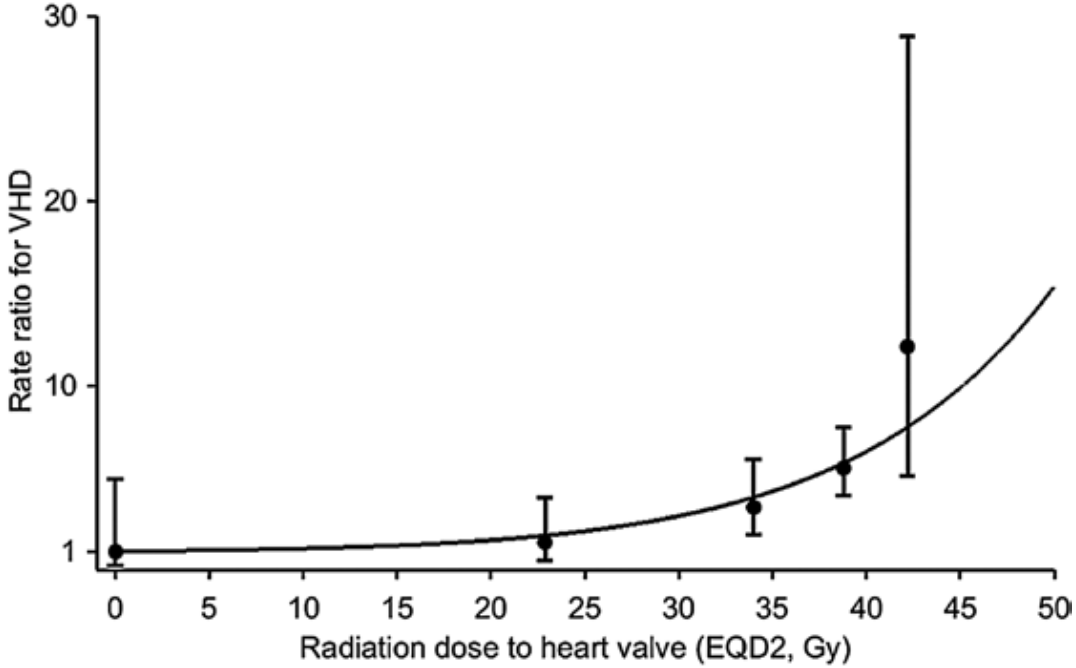
Simplified 2D method



Cutter, Schaapveld et al. JNCI 2015

Valvular heart disease after HL

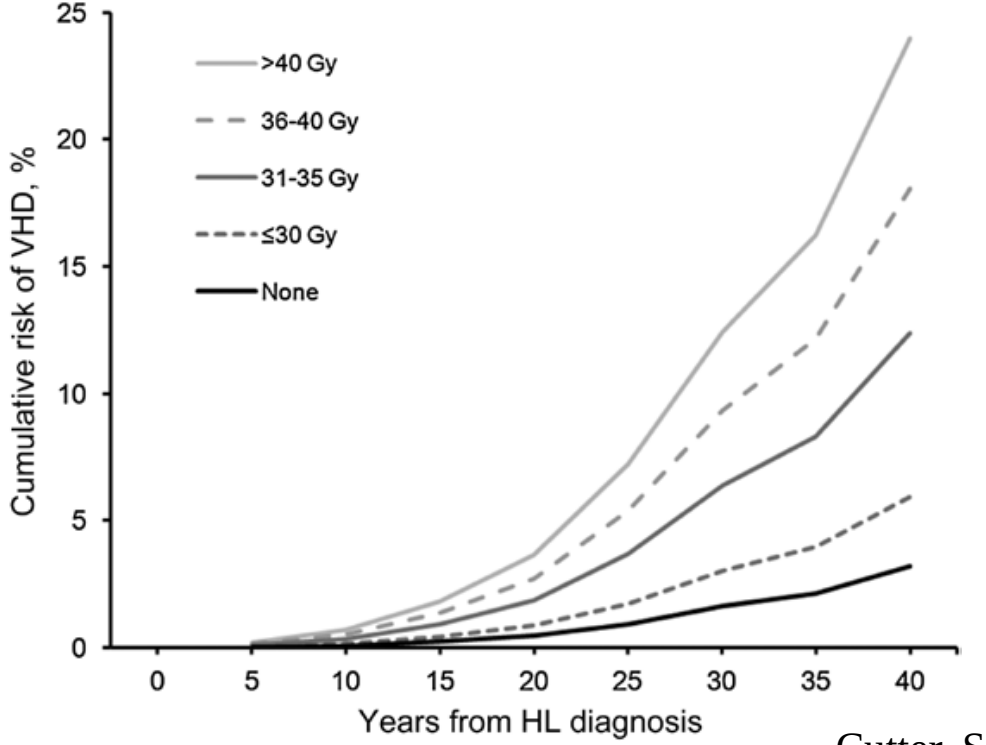
89 cases and 200 controls nested in cohort of 1852 Dutch five-year survivors of HL treated between 1965 and 1995



Cutter, Schaapveld et al. JNCI 2015

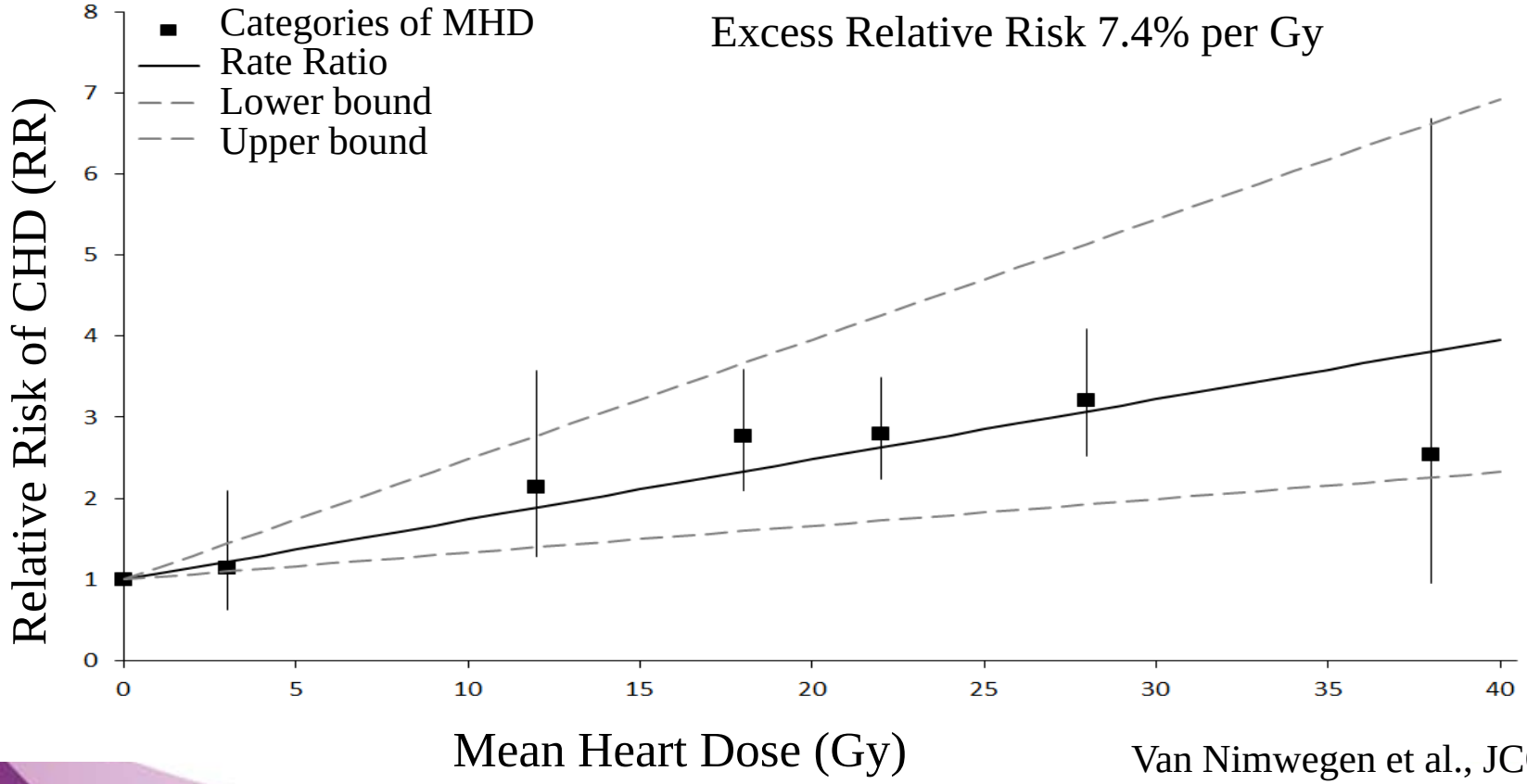
Valvular heart disease after HL

89 cases and 200 controls nested in cohort of 1,852 Dutch five-year survivors of HL treated between 1965 and 1995



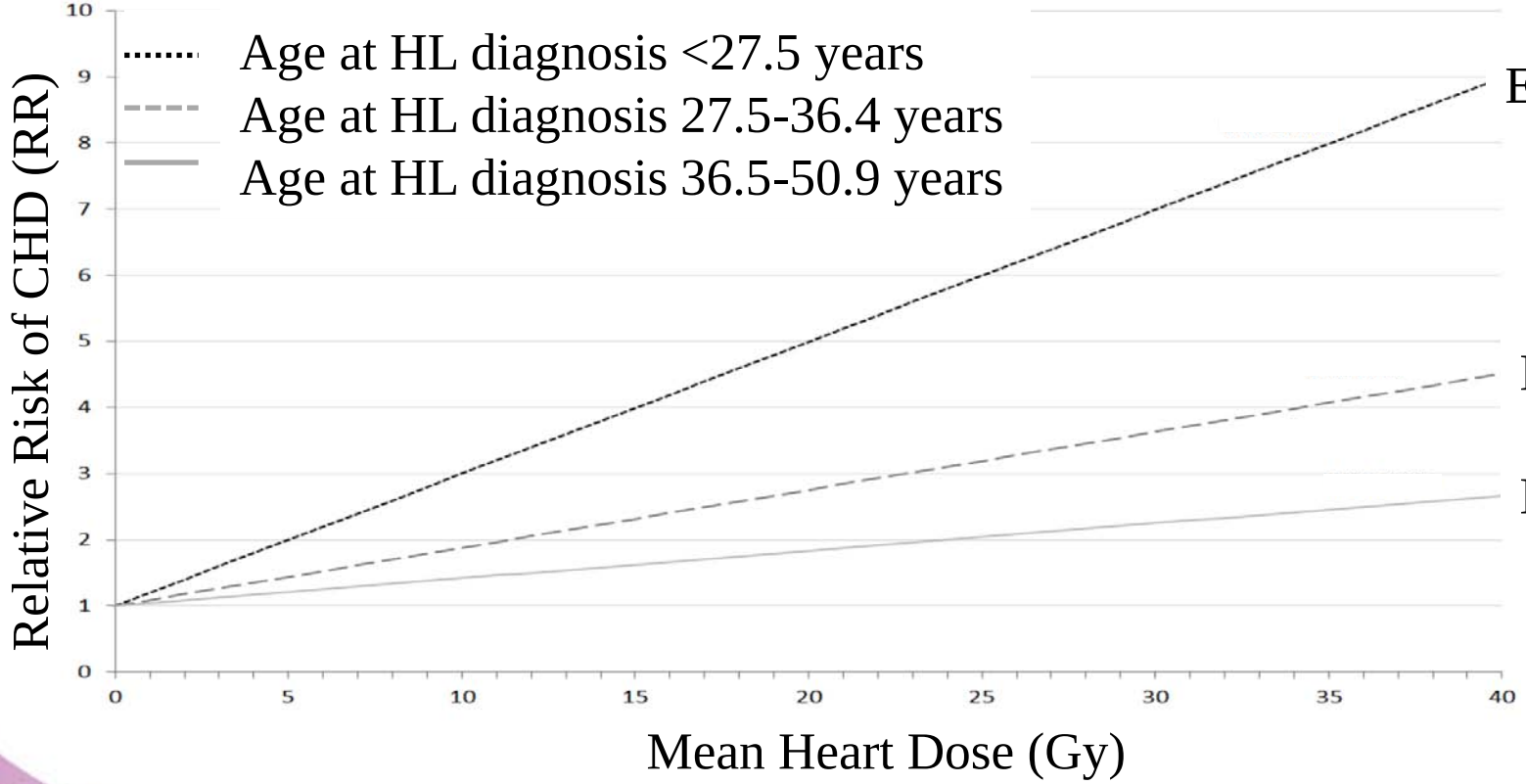
Cutter, Schaapveld et al. JNCI 2015

Coronary heart disease after HL; 325 cases and 1,204 controls nested in a cohort of 2,617 Dutch 5-year HL survivors treated between 1965 and 1995



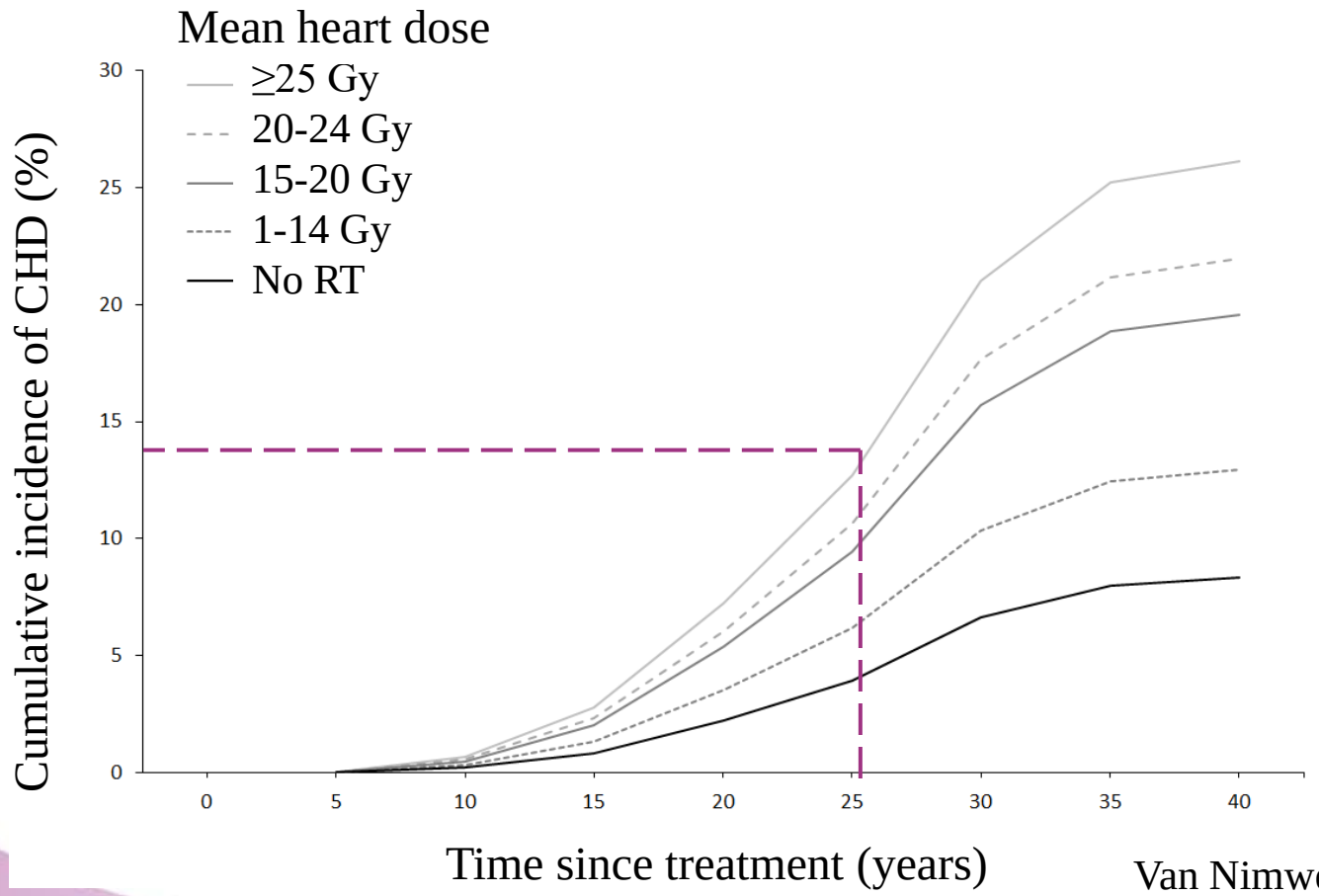
Van Nimwegen et al., JCO

Dose-response by tertiles of age at HL treatment



Van Nimwegen et al., JCO

Dose-associated cumulative incidence



Van Nimwegen et al., JCO

Established CVD Risk factors

Risk factor	RR¥	95%CI	p
Diabetes mellitus	2.0	1.4-2.8	<0.001
Hypercholesterolemia	2.1	1.6-2.7	<0.001
Hypertension	1.5	1.2-2.0	0.001
Obesity (BMI≥30) at cut-off	1.6	1.2-2.2	<0.001
≥1 risk factors	2.5	1.8-3.4	<0.001
Recent smoker at cut-off (<5 yrs)	1.6	1.1-2.2	0.007

¥ adjusted for mediastinal radiotherapy

Van Nimwegen et al., JCO

Established CVD Risk factors

Risk factor		p_{trend}
Physical acti		
Not active (<		
Moderately a		
Very active (		0.136

*p<0.05

¥ adjusted for n

¤ analyzed in s naire (84 cases and 158

Van Nimwegen et al., JCO

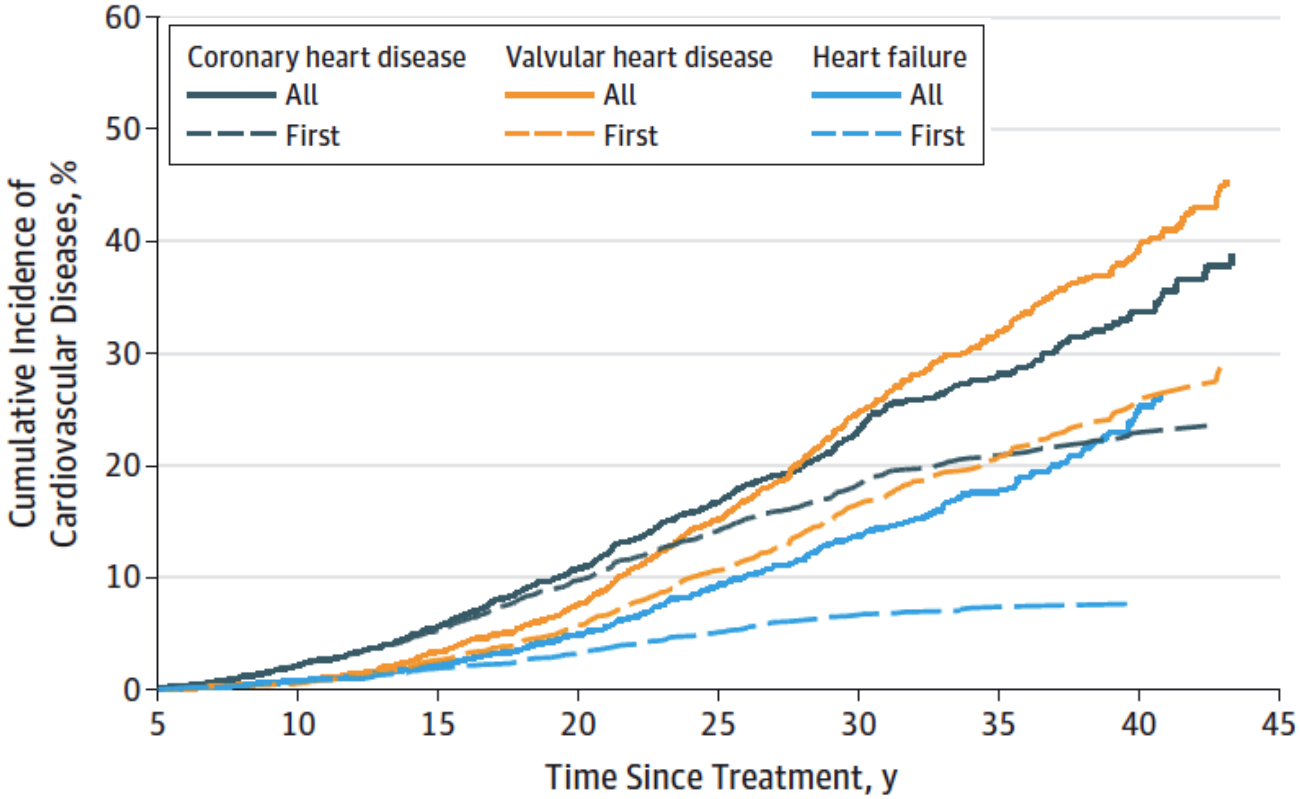
Conclusions ischemic heart disease after HL

- Linear dose response relationship with overall risk increase of 7.4%/Gy
  - 2.5-fold increased risk at MHD of 20 Gy
  - Higher ERR for patients treated <27.5 years
- Established risk factors & recent smoking ↑ CHD risk
- High levels of physicial activity ↓ CHD risk
- Results enable risk prediction

Van Nimwegen et al., JCO

Cumulative incidence of all and first cardiovascular disease

(in 2524 5-year survivors of HL treated before age 51 between 1965-1995)



Van Nimwegen et al., JAMA int med 2015

Heart failure after HL (1st event)

Results case controle study were shown, but slides were removed because the data have not been published yet

van Nimwegen et al, submitted

Conclusions CVD after HL (literature and Dutch HL cohort)

- After mediastinal RT increased riks of coronary events, valvular disease, CHF
- After 40 yrs: risk of any CVD after mediastinal RT = 50% vs 26% (no mediastinal RT)
- Risk remains increased ≥ 40 yrs
- Younger age at RT → higher risk
- Additive effects of RT and anthracyclines on CHF risk

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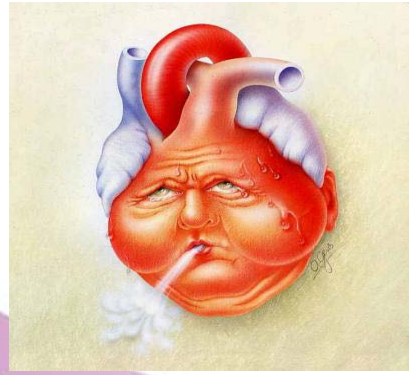
Anthracyclines

- Anthracyclines damage myocytes
- Cardiotoxicity may present as ECG changes and arrhythmias, or as cardiomyopathy possibly leading to heart failure
- Dose-effect relationship

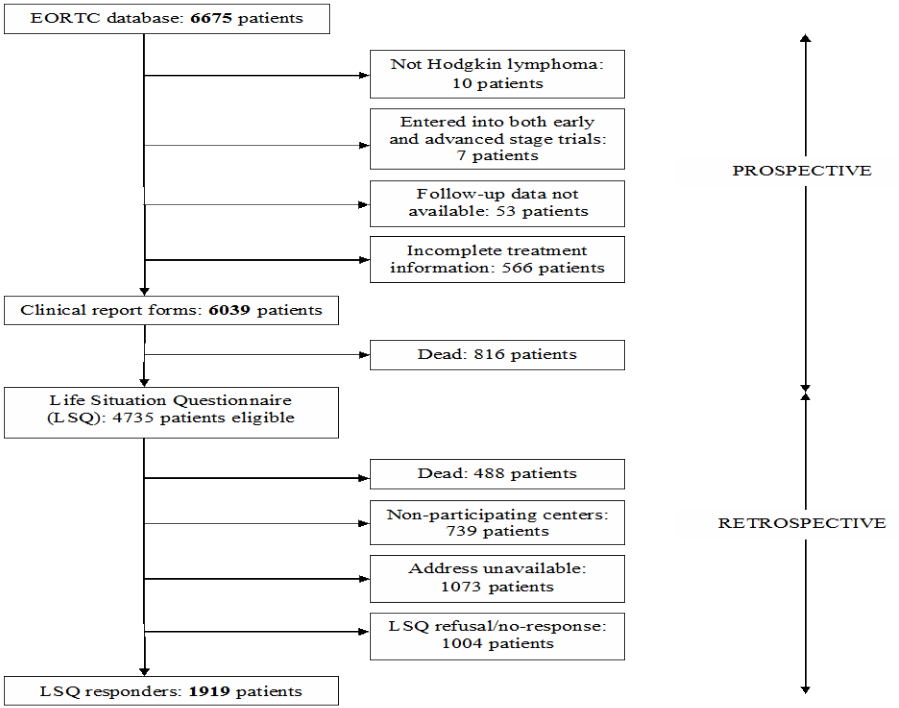


Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

- Incidence of CVD was reported during follow-up and updated through a patient-reported questionnaire, mailed in 2009–2010

Maraldo et al, Lancet Hemat 2015

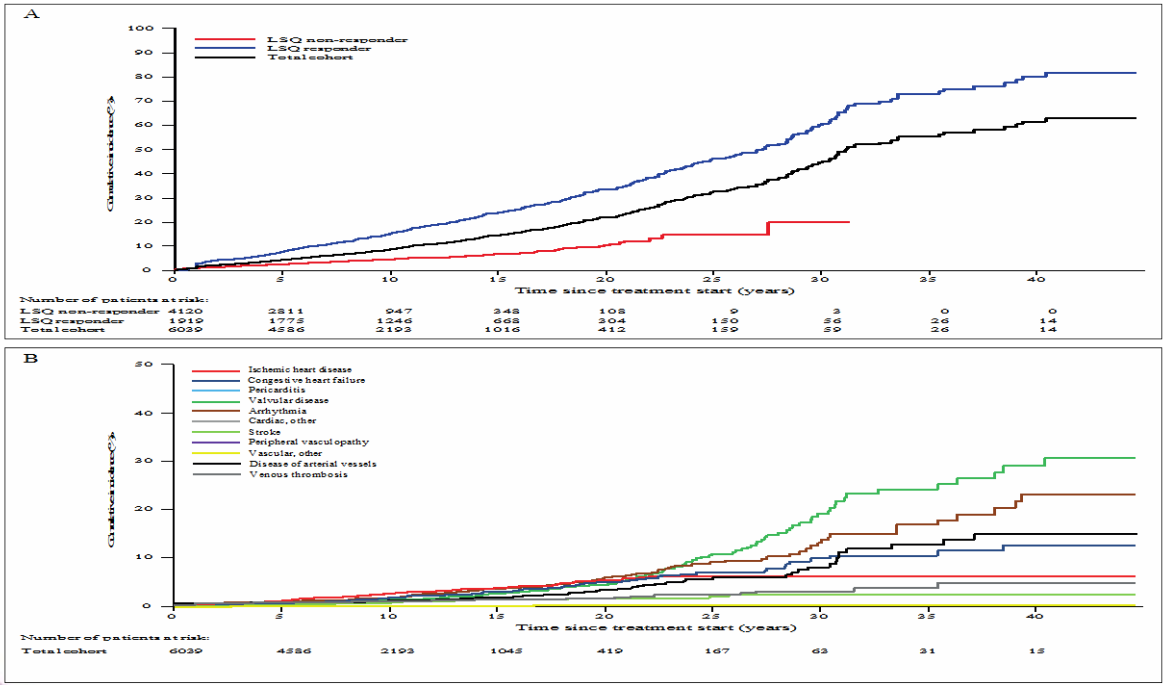
CVD after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials



Maraldo et al, Lancet Hemat 2015

Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

Cumulative incidence curves of first cardiovascular disease by LSQ-responder status and for the whole cohort (n=6,039)



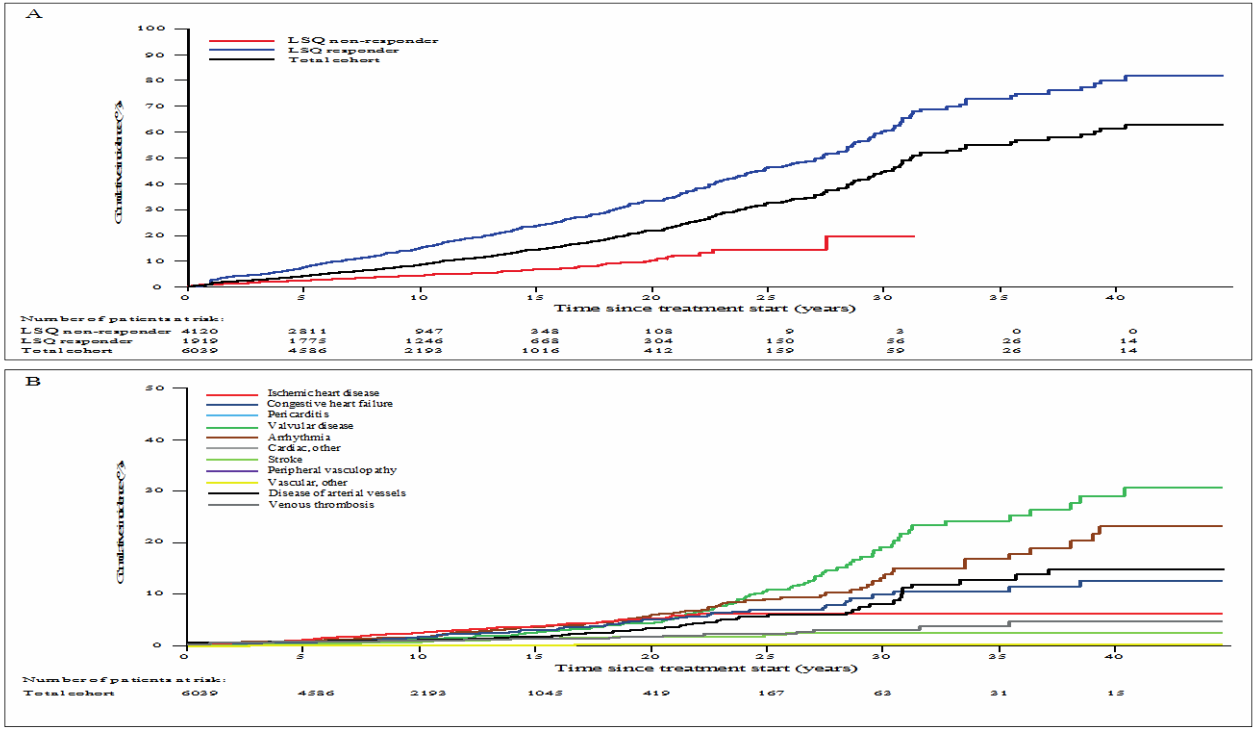
LSQ responder

Total cohort

LSQ non responder

Maraldo et al, Lancet Hemat in 2015

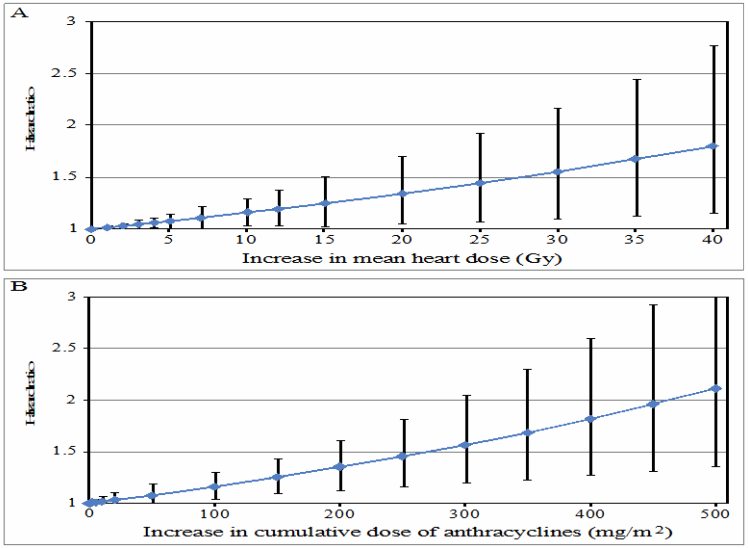
Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

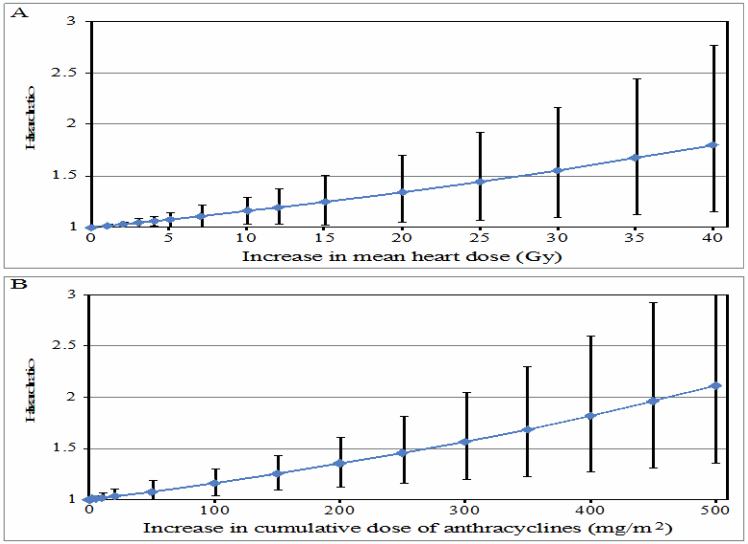


Maraldo et al, Lancet Hemat 2015

Cardiovascular disease after therapy for HL:
A detailed analysis of 9 collaborative EORTC-LYSA trials

The mean heart radiation dose and the cumulative dose of anthracyclines were significant predictors of CVD, with an increase in hazard rate of 1·5% (95% CI: 0·6–2·4%) per 1 Gy increase in mean heart dose and 7·7% (95% CI: 2·1–13·7%) per 50 mg/m2 increase in cumulative anthracycline dose.





Maraldo et al, Lancet Hemat 2015

Optimize treatment ?

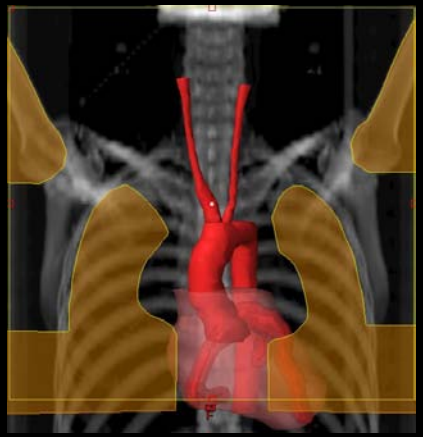
Disease control

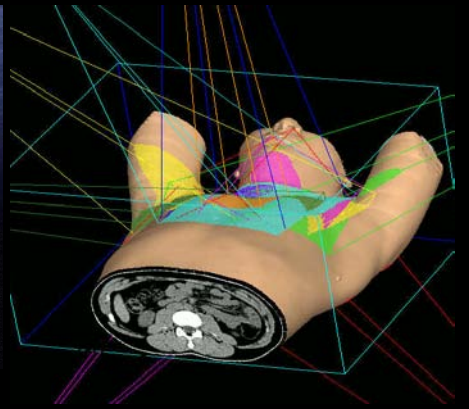
Chance early and late side effects

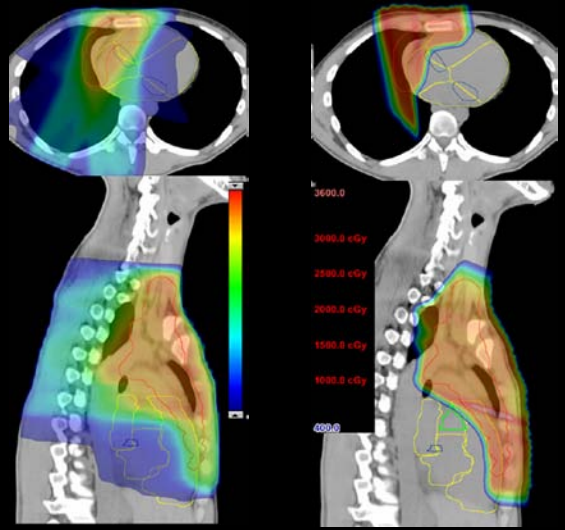
Treatment optimization:

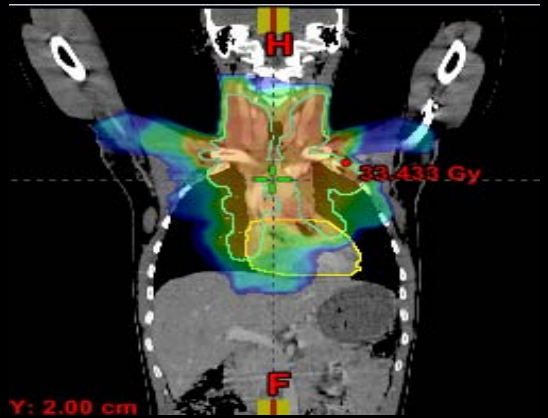
Extensively discussed during course:

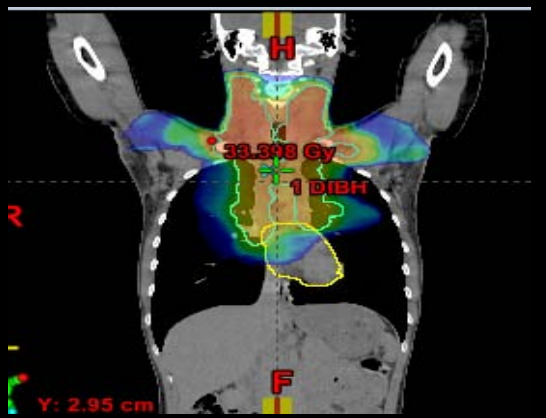
- Balancing systemic and local treatment
- Optimal RT technique (including optimal preparation of RT, careful choice target volume, optimal planning, introduction of DIBH, protons etc)





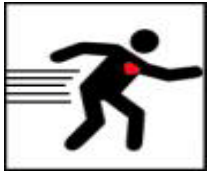

3600.0
3000.0 cGy
2500.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
400.0


H
33.433 Gy
F
Y: 2.00 cm


H
33.398 Gy
1 DIBH
R
F
Y: 2.95 cm

Limit risk of (treatment -related) side effects Patient

- Adjust lifestyle - no smoking
- Visit doctor in case of complaints



BETER-project:

A nationwide survivorship care program for adult (non-)Hodgkin lymphoma survivors

Future

- Development of risk prediction models including all available information on late effects
- Improve documentation of applied treatment (including dose to OAR)

Acknowledgements

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Henk van den Berg, Heleen v.d. Pal, Leontien Kremer
VUMC
Josée Zijlstra
Netherlands Cancer Registry
University of Oxford
David Cutter, Sarah Darby

Hodgkin lymphoma survivors

Funding by the Dutch Cancer Society
NKI 2004-3068, 2010-4720

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Extranodal lymphomas: Characteristics, the role of radiotherapy, volumes doses and techniques:

Testicular lymphoma

Berthe Aleman

Radiation oncologist

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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Testicular lymphoma

General

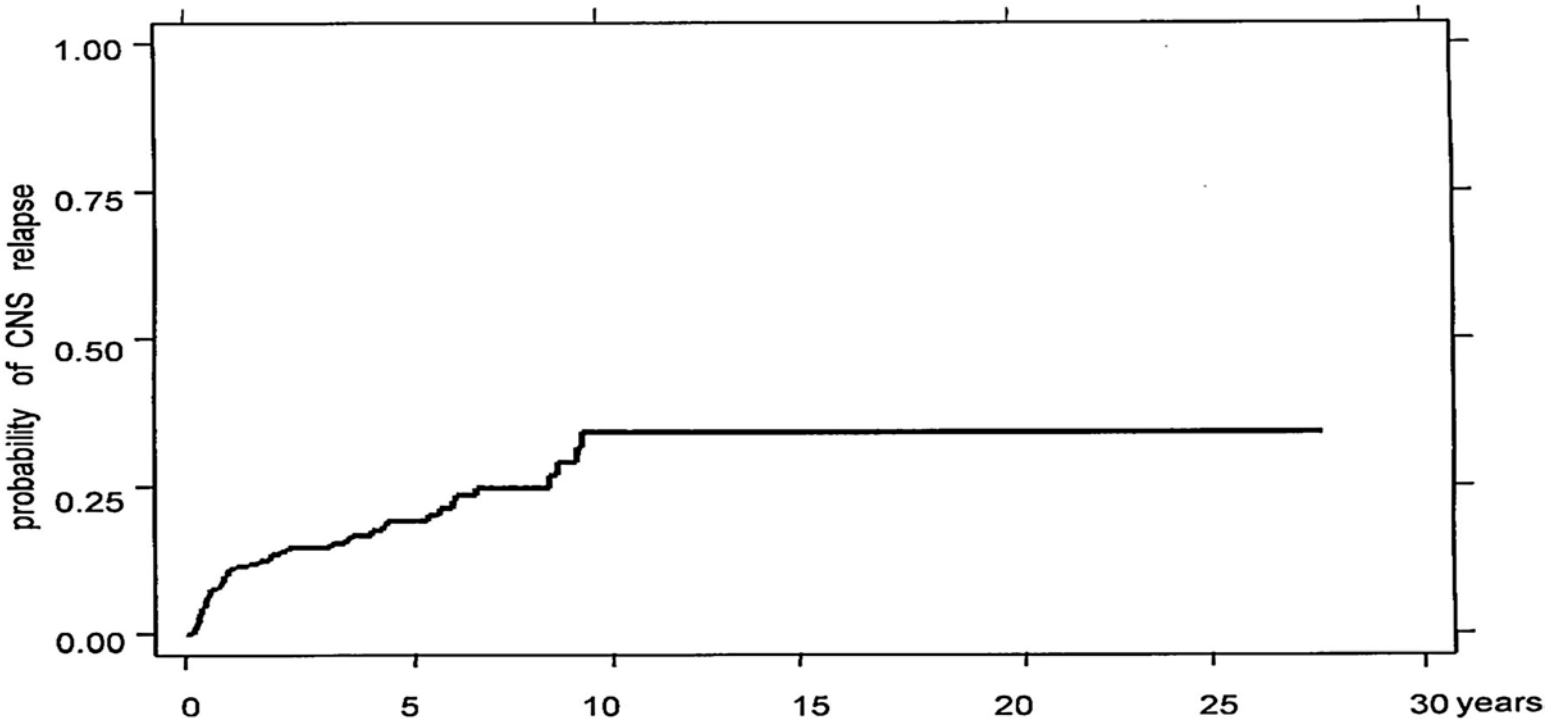
- Primary testicular lymphoma (PTL) is an uncommon and aggressive form of extranodal non-Hodgkin lymphoma (NHL)
- Annual incidence at 0.09 to 0.26 per 100 000 population
- 0,5% of testicular malignancies and 1-2% of all NHL cases
- Median age at diagnosis: 66 - 68 years

Testicular lymphoma

General (continued)

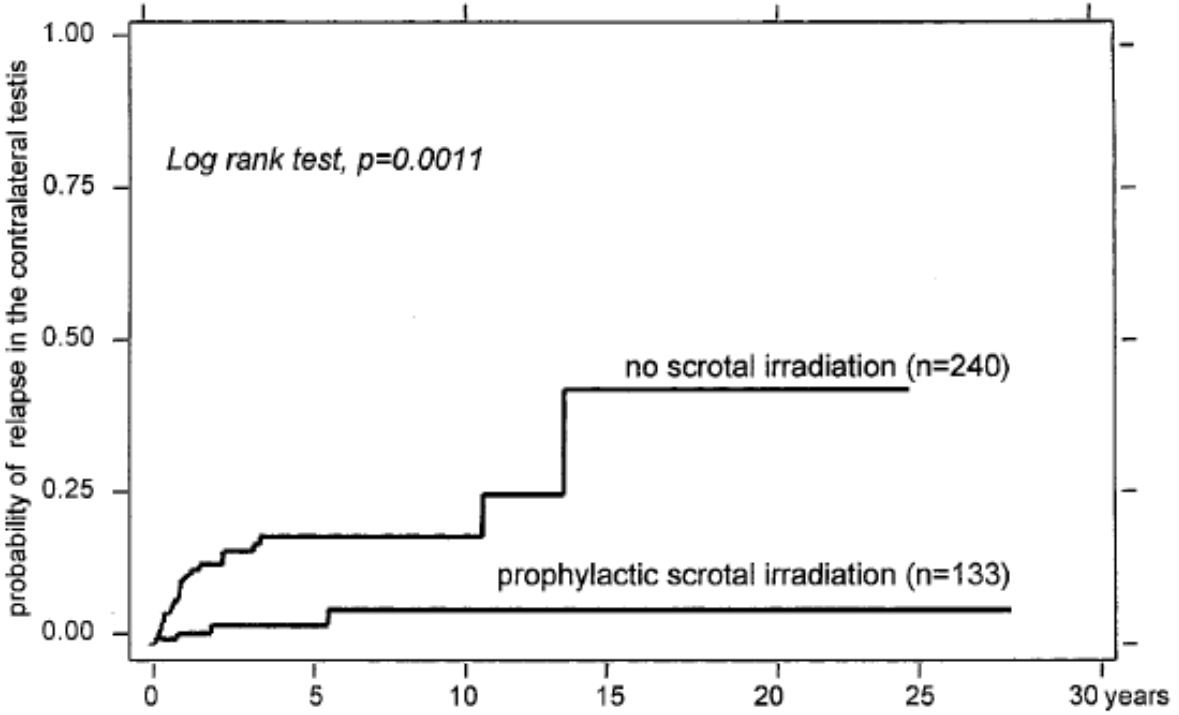
- PTL is both the most common testicular malignancy in men age >60 years and the most common bilateral testicular neoplasm.
- The common histology is DLBCL
- Sanctuary sites: CNS and contralateral testicle

Time to CNS recurrence; IELSG retrospective study (n=381; 1968-1998)



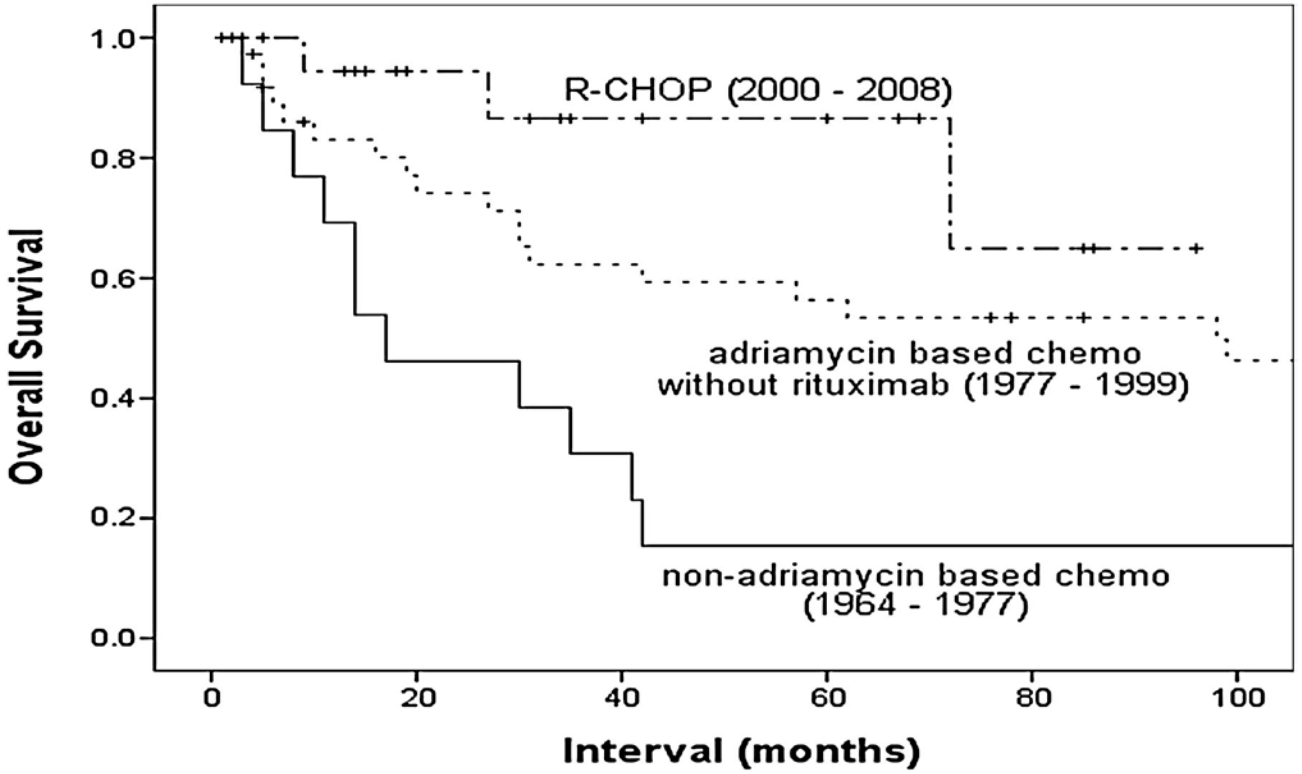
Zucca et al, J Clin Oncol 2003:20-27

Continuous risk of recurrence in the contralateral testis by prophylactic scrotal radiotherapy; IELSG retrospective study (n=381; 1968-1998)



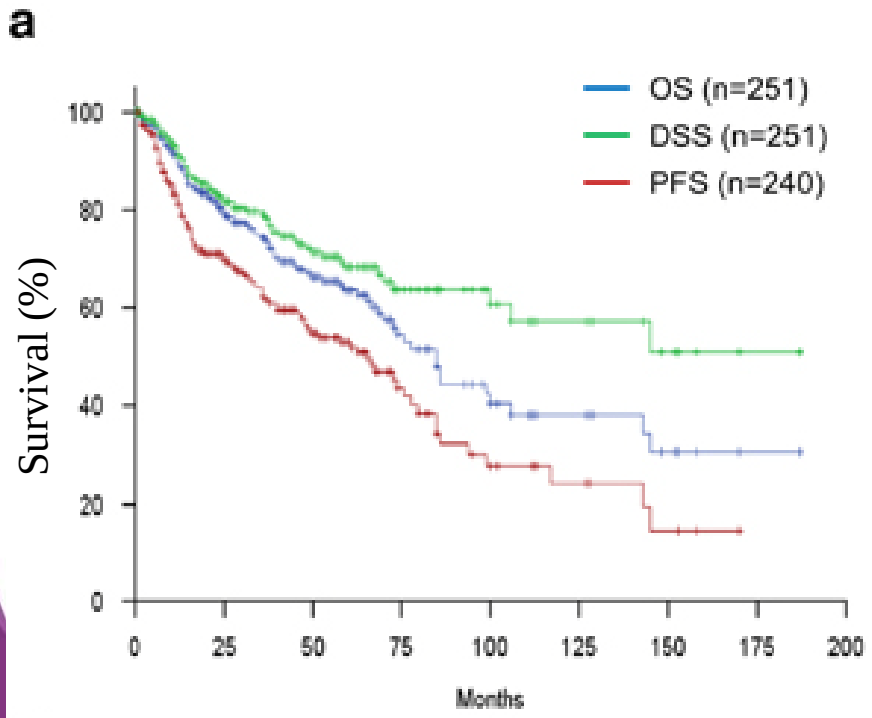
Zucca et al, J Clin Oncol 2003:20-27

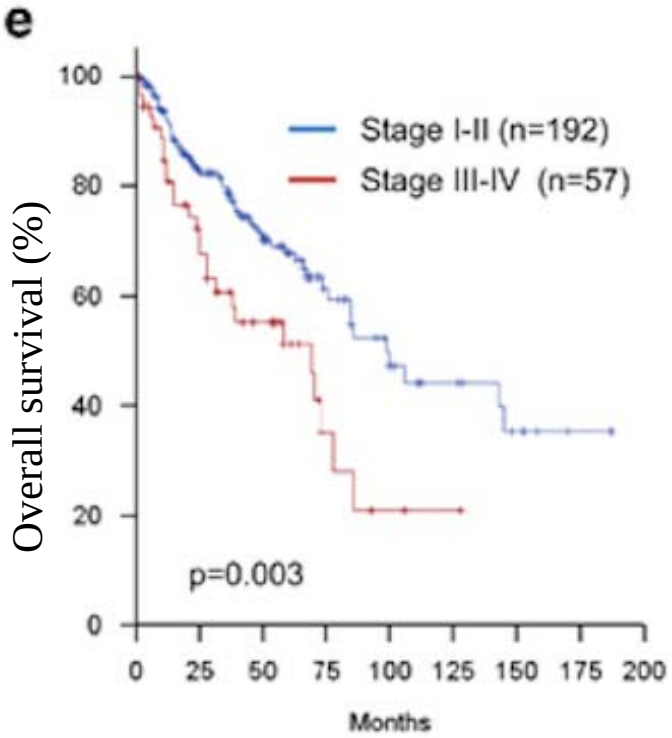
OS of patients with PTL treated at MDACC, by chemotherapy strategy



Mazloom et al. Leuk Lymphoma 2010: 1217-1224

Primary testicular diffuse large B-cell lymphoma displays distinct clinical and biological features for treatment failure in rituximab era: a report from the International PTL Consortium (n=280; 1993-2014)





Deng et al, Leukemia 2016: 361-372

Primary testicular diffuse large B-cell lymphoma displays distinct clinical and biological features for treatment failure in rituximab era:
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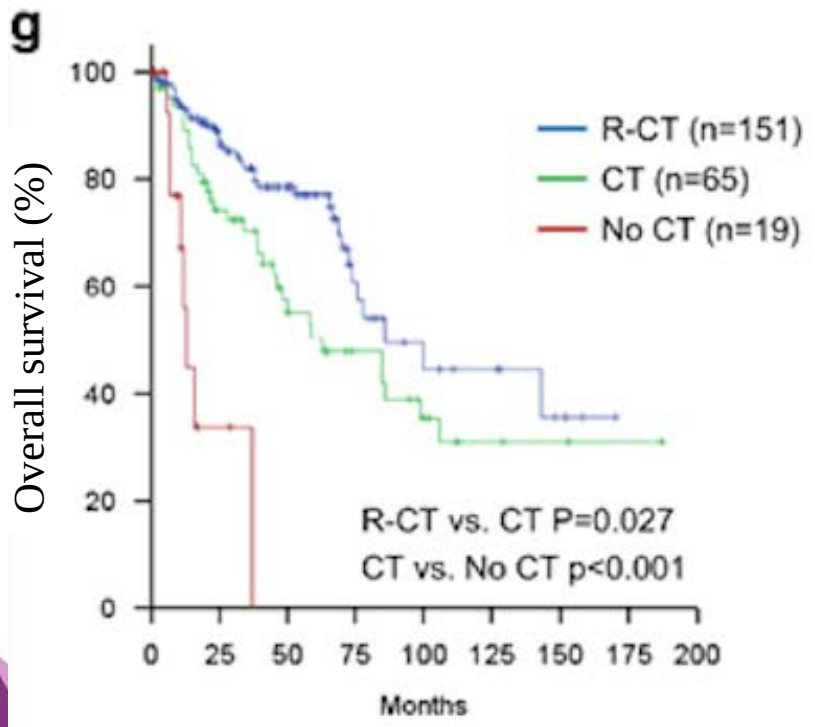
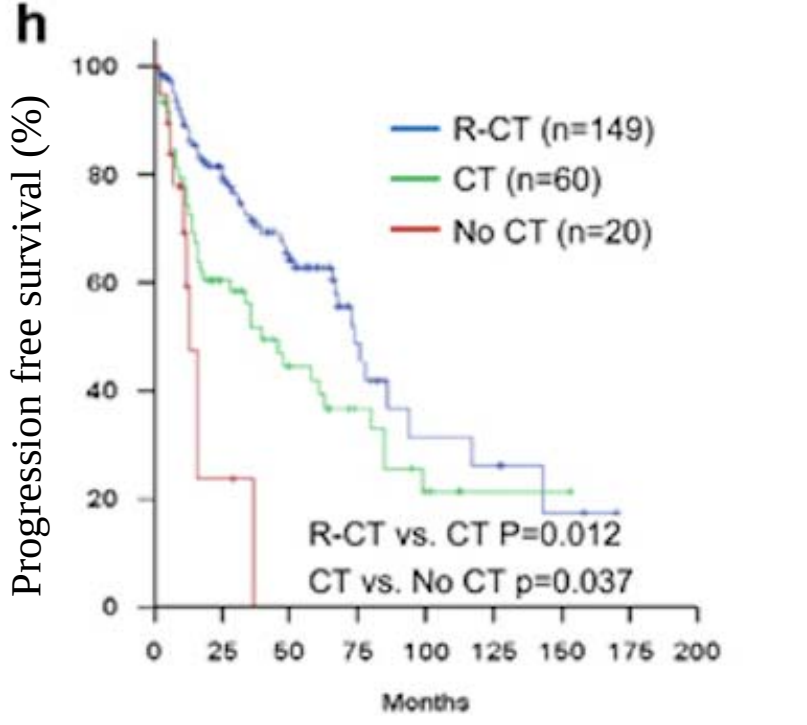
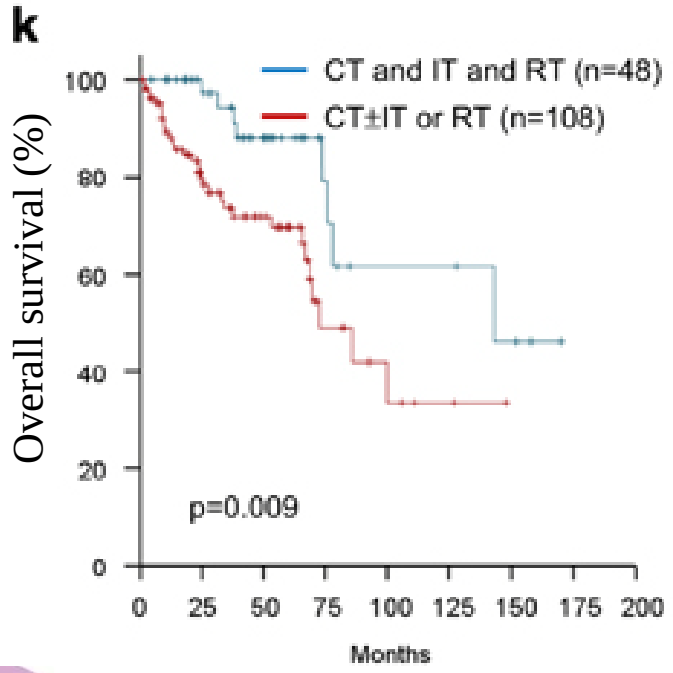




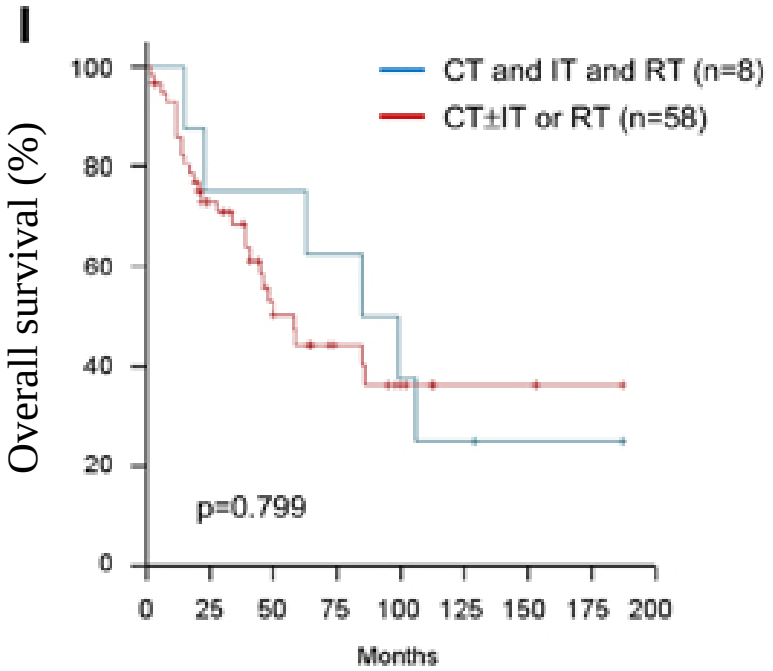
Deng et al, Leukemia 2016: 361-372

Primary testicular diffuse large B-cell lymphoma displays distinct clinical and biological features for treatment failure in rituximab era: a report from the International PTL Consortium (n=280; 1993-2014)

Treatment with rituximab



Treatment without rituximab



Deng et al, Leukemia 2016: 361-372

Prognostic factors for PFS in PTL

Adverse prognostic factors for PFS in studies of PTL
Age >70 y
Advanced stage
B symptoms
ECOG performance status >1
>1 extranodal site
Involvement of extranodal sites other than testis
Tumor diameter >10 cm
Raised serum LDH
Raised serum β_2-microglobulin
Hypoalbuminemia
Involvement of the left testis

Cheah et al. Blood 2014;123:486-493

Testicular lymphoma

Treatment

- R-CHOP or more aggressive regimens
- Intrathecal or intravenous methotrexate
- RT is given to the involved testis (if not resected) and to the remaining testis and scrotum
- RT may be given to involved abdominopelvic nodes in stage IIE disease.

Yahalom et al. ILROG guideline, IJROBP 2015

Testicular lymphoma
Prophylactic RT contralateral testicle

Volume

- An anterior electron field with energy calculated according the thickness of the scrotum/testis is set; bolus may be required.

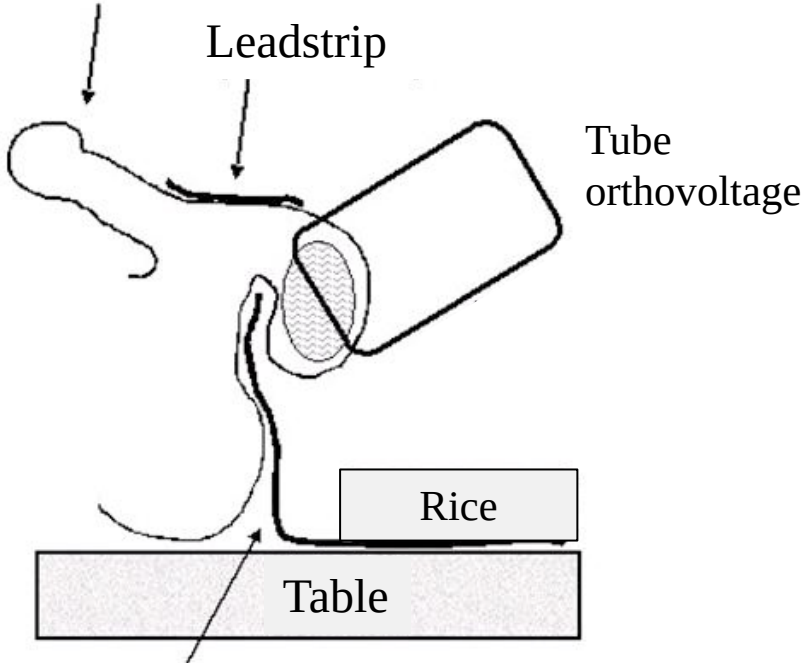
Yahalom et al. ILROG guideline, IJROBP 2015

Setup radiotherapy testicle

With the patient supine in a frog-leg position, the penis is lifted and taped to the abdominal wall, and the scrotum is supported and immobilized with bolus under and around the scrotum.

Yahalom et al. ILROG guideline, IJROBP 2015

Penis taped to the abdominal wall



Leadstrip on perineum and anus

Testicular lymphoma

Dose

- Dose to testis: 25 to 30 Gy in 1.5 to 2 Gy per fraction

Yahalom et al. ILROG guideline, IJROBP 2015

Testicular lymphoma

Questions:

- Is 25-30 Gy safe?
- Could we use a lower dose ? 18 Gy? 20 Gy?
- Could surgery be an alternative?

- What to do during follow up?
  - Lab? Testosterone?

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Deep inspiration breath hold in thoracic tumours: imaging and treatment

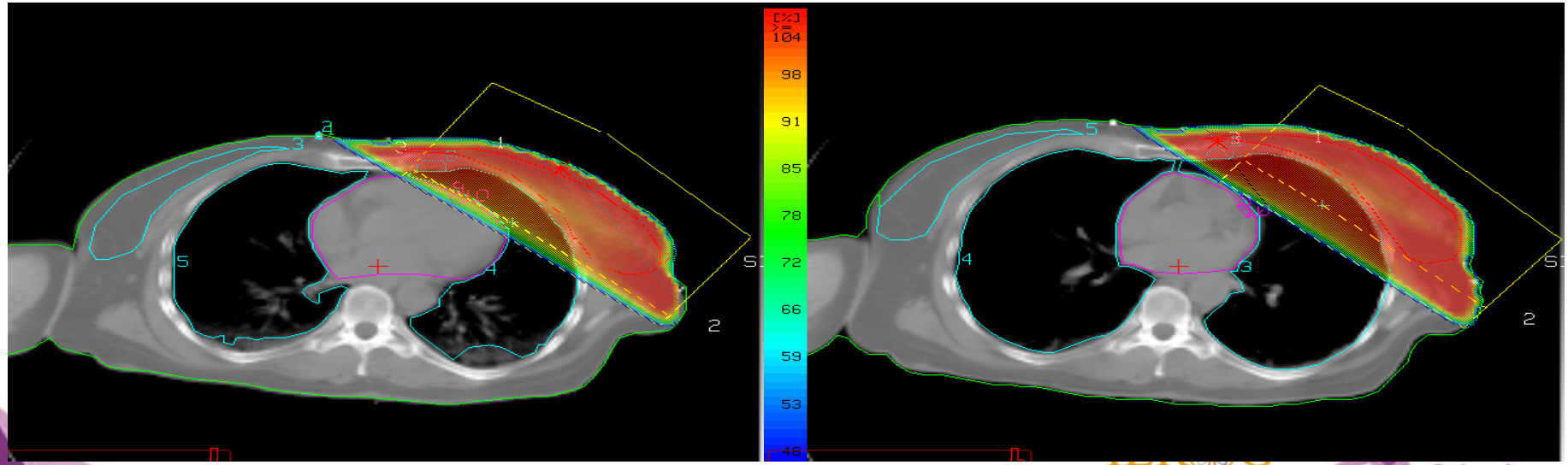
Marianne C Aznar

Dept. Of Oncology, Copenhagen University Hospital, Rigshospitalet

With the help of the Dept. of Clinical Physiology, Nuclear Medicine and PET

At Rigshospitalet

- Deep inspiration treatment since 2003 in left-sided breast cancer patients
- > 1000 patients



LYMPHOMA: A SPECIAL CASE

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INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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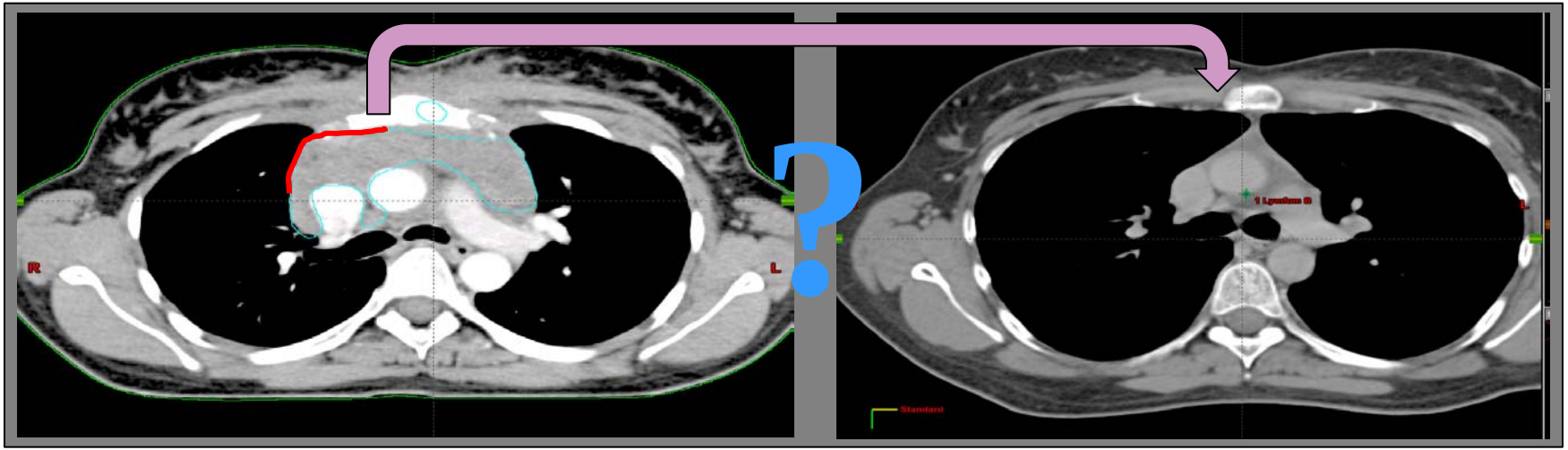
Fusing prechemo and planning images

Pre-chemo PET/CT

free breathing

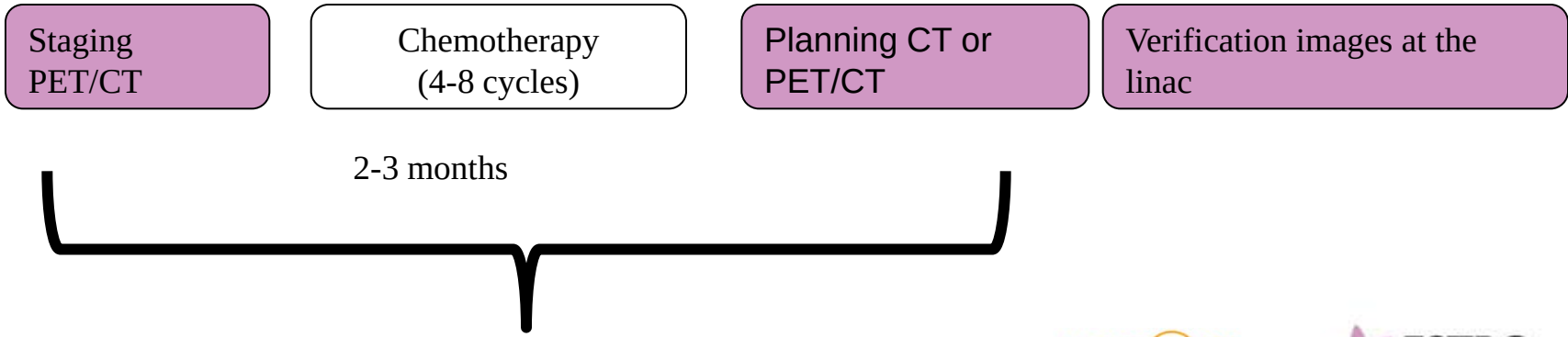
Planning CT

at deep inspiration



DIBH through the whole imaging chain

- All images in DIBH



Rigshospitalet (The Finsen Center)

- 3500 patients /year

- 2 dedicated CT scanners
- 1 dedicated MR scanner
- Joint facilities with Nuclear Medicine department
  - 4 PET/CT, one dedicated to RT planning
  - 1 PET/MR
  - Radiographers rotating between departments
  - 1 radiologist hired by both departments

- 11 linacs

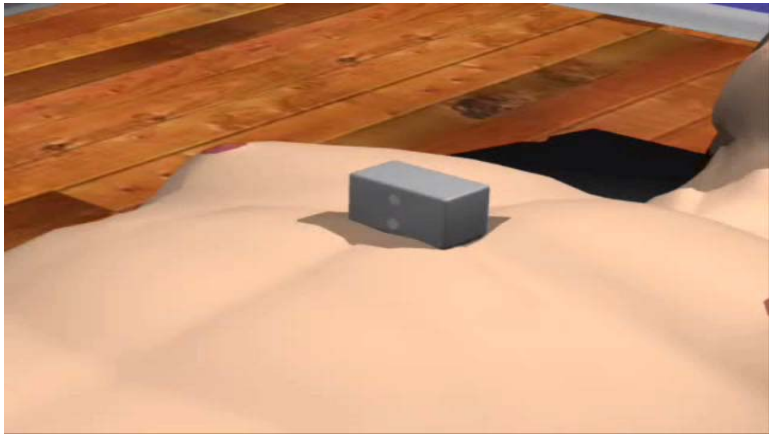
How to handle registration uncertainties ?

- Ensure a treatment-like position already at staging
  - Flat table top
  - Arms up
  - Chest board

- Provide DIBH PET/CT at staging

- All these take time, logistic effort, and a good collaboration with the PET department!

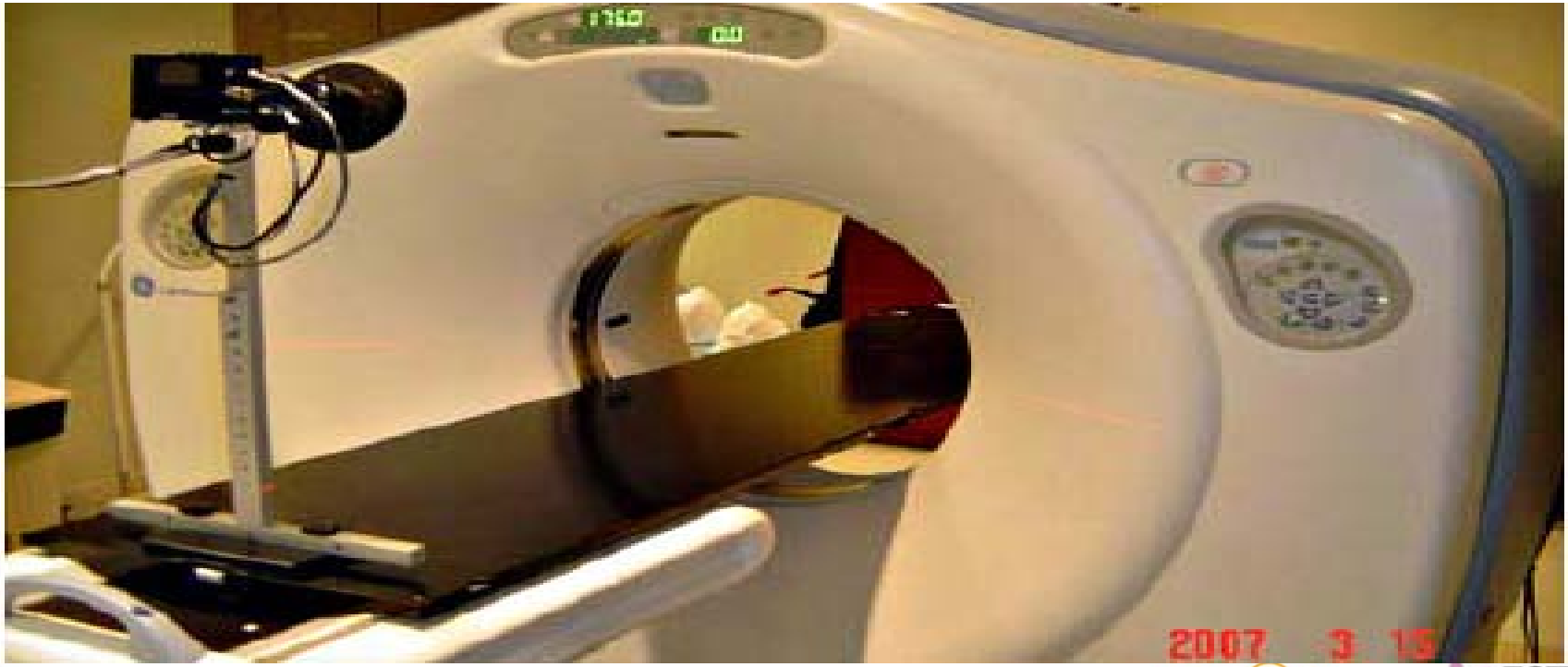
Respiration monitoring



<u>Varian RPM system:</u>
Deep inspiration breath hold
Gating
4D CT

On all linacs and scanners

CT + PET/CT



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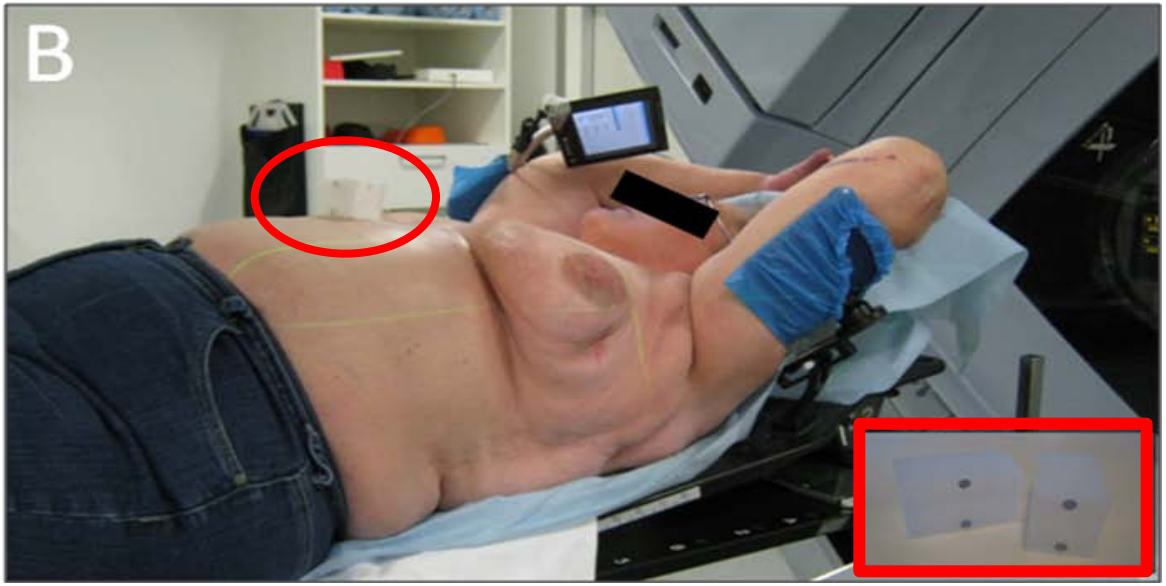
Equipment

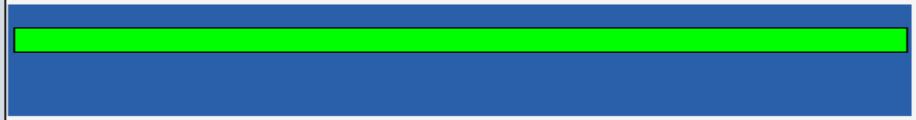
Courtesy of Sidsel Damkjær, Copenhagen



At Rigshospitalet: RPM system from Varian + third part screens/goggles

Alternatives: ABC system from Elekta, VisionRT, C-RAD sentinel...

Free breathing



Deep inspiration
breath hold

Take home message (1)

- Keep patient instruction and information as simple as possible
- Coach before scanning (30 min) or directly at the scanner (5-10 min): equivalent results !!
- Extra time necessary at the scanner (install equipement, etc… plus extra acquisition) : 15-30 min
- Good communication with PET extremely valuable !

PET/CT acquisition in practice

•Pre chemo scan: *400 MBq* FDG on Siemens Biograph 40 PET/CT

• Free breathing scan followed by one FOV scan in breath hold

•3 breath holds of 20 seconds each

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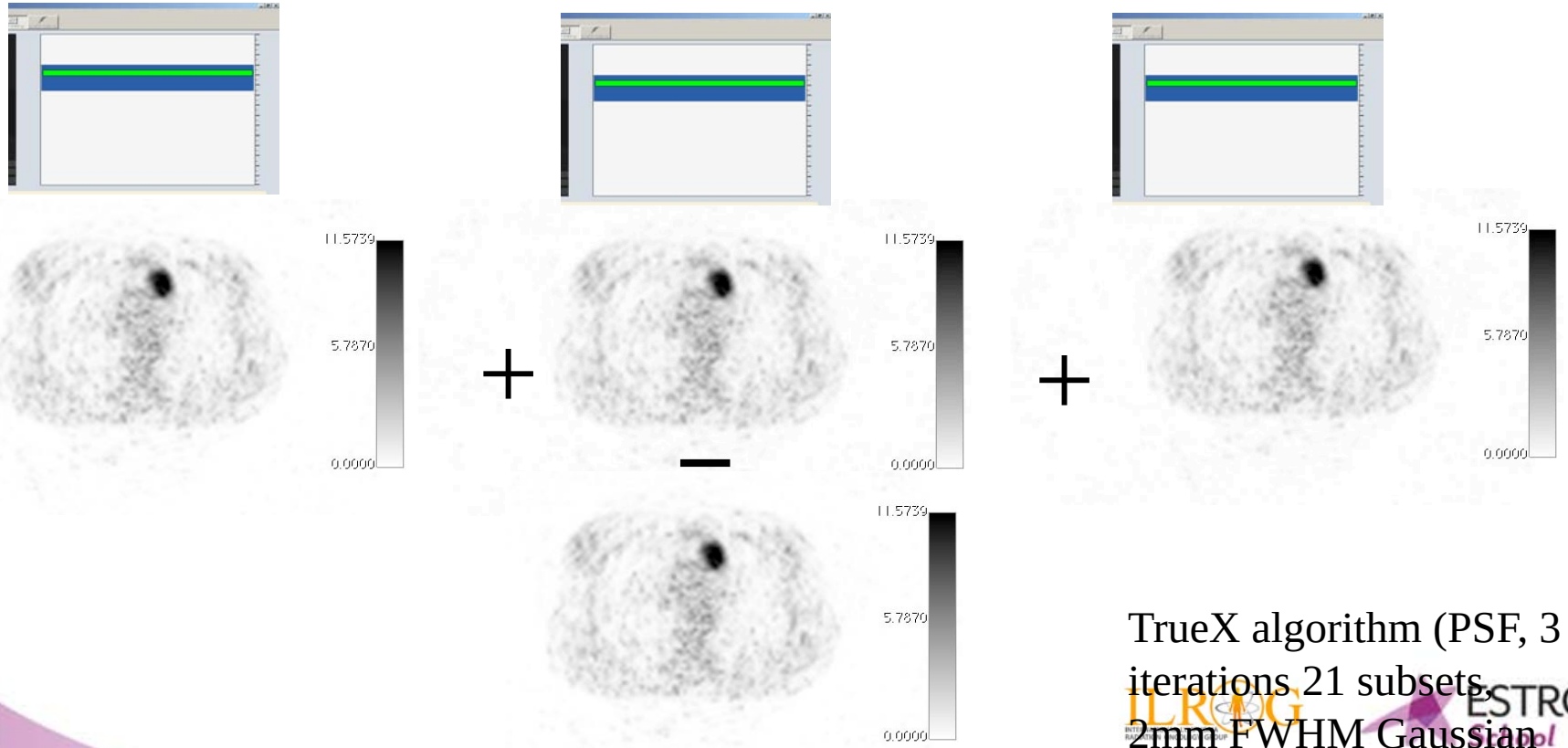
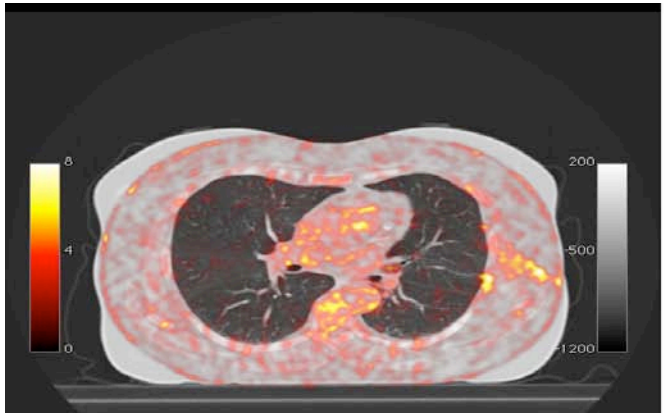
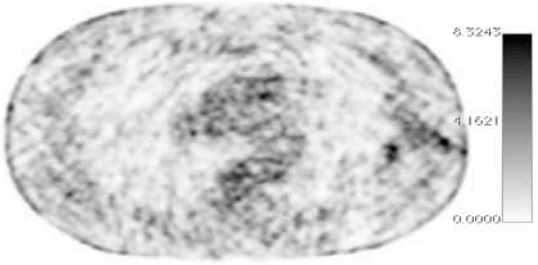
Methods: Image reconstruction

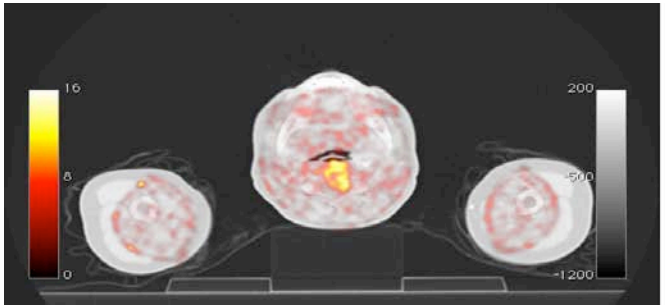


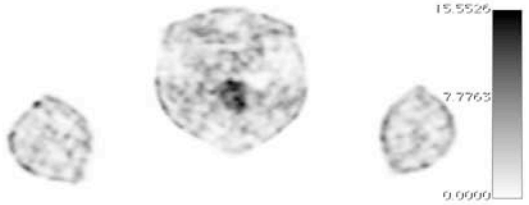
TrueX algorithm (PSF, 3 iterations 21 subsets, 2mm FWHM Gaussian filtering

Some problems at start-up !!









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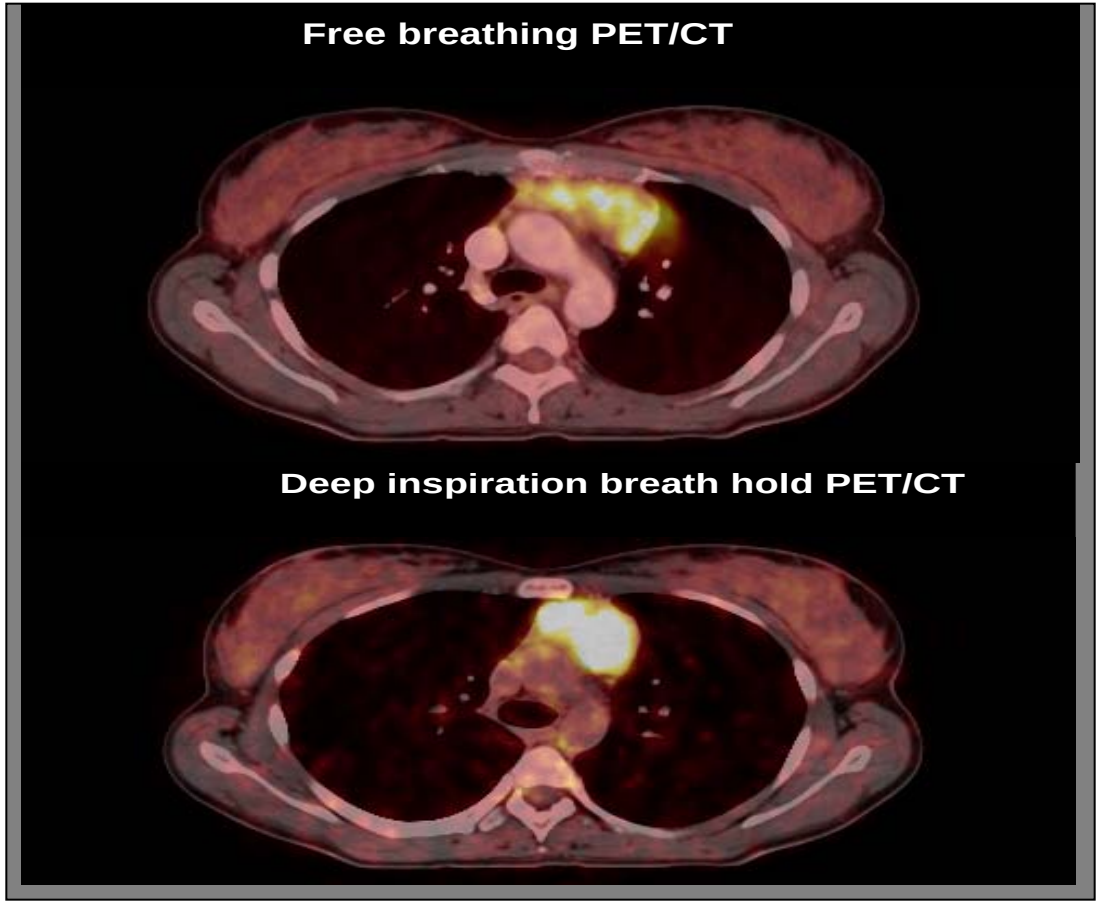
Results: reduced respiration artifacts



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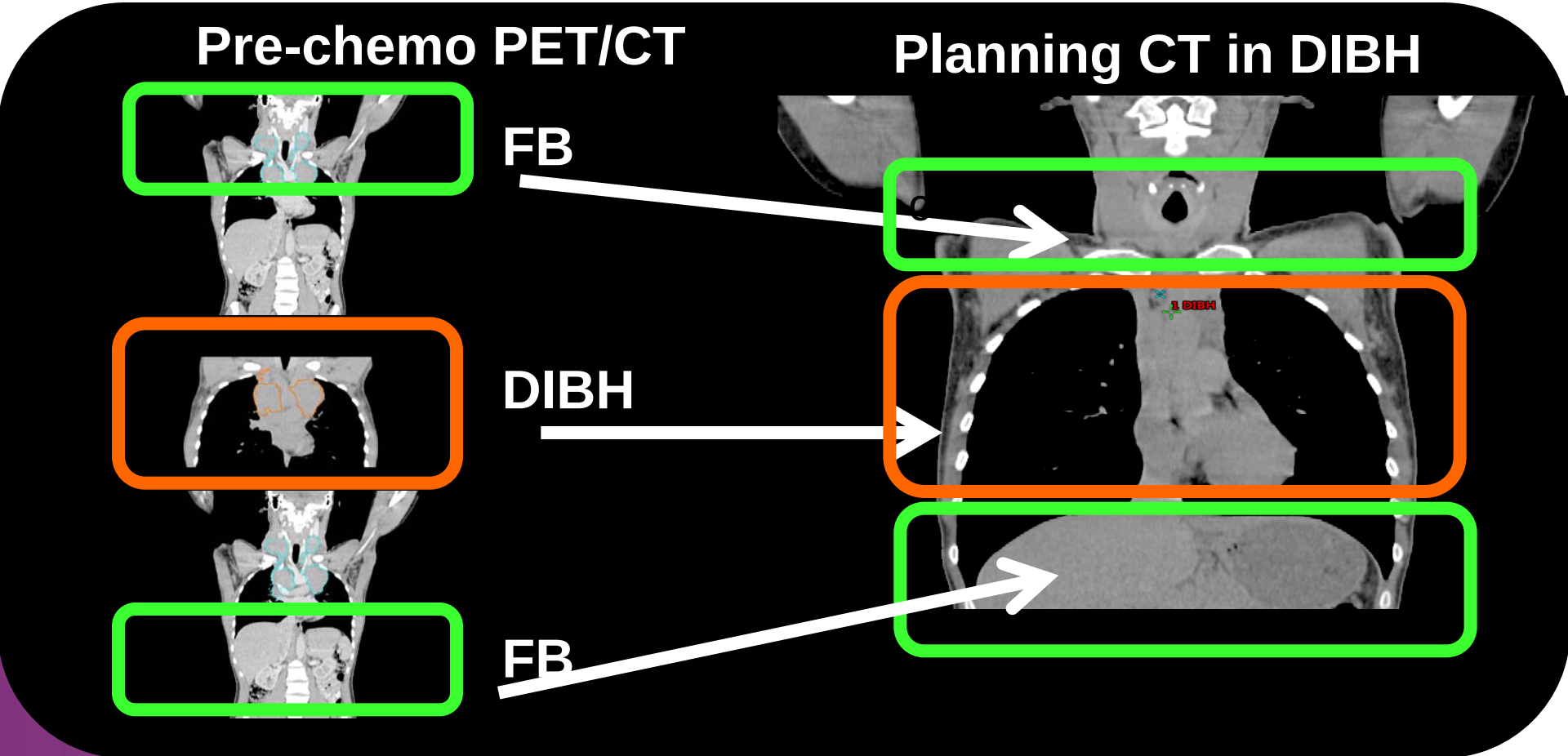
Registration for contouring



Mediastinal lymphoma

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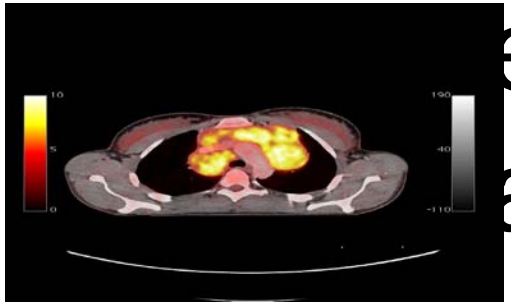

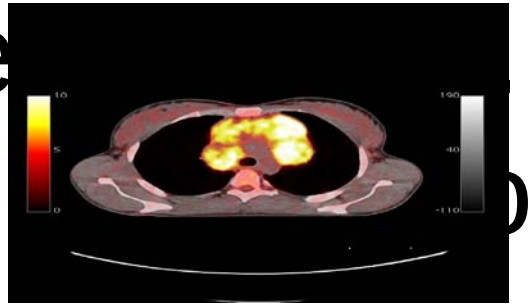

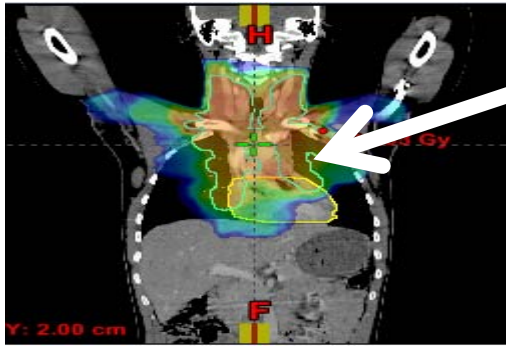

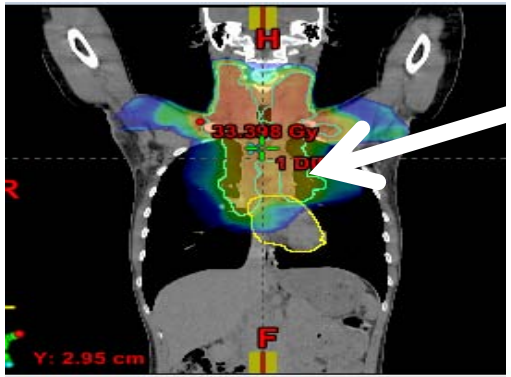

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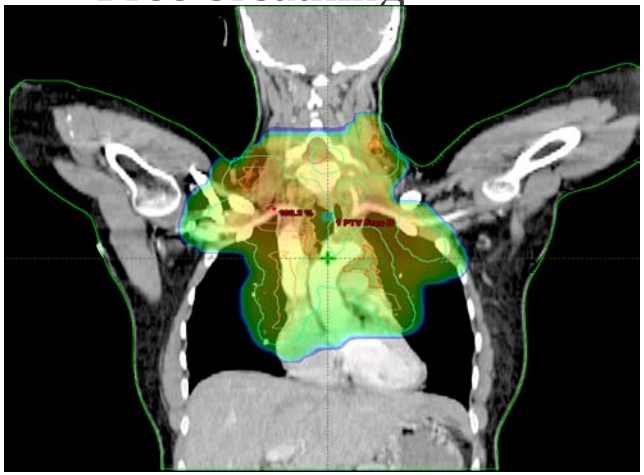
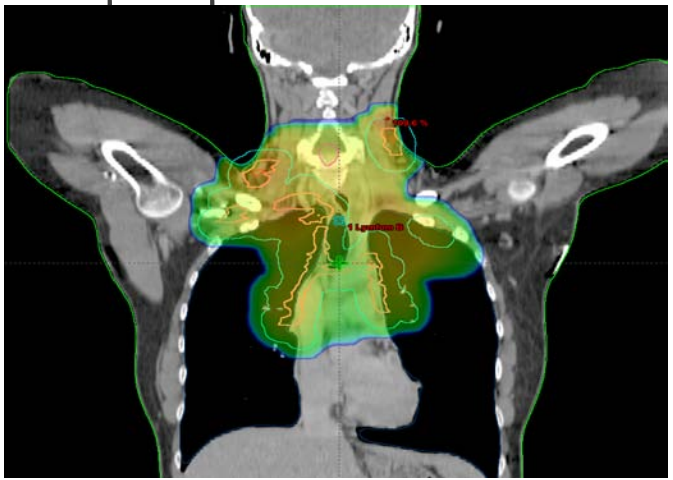
Breath hold decreases the exposure of healthy tissues

- Free breathing

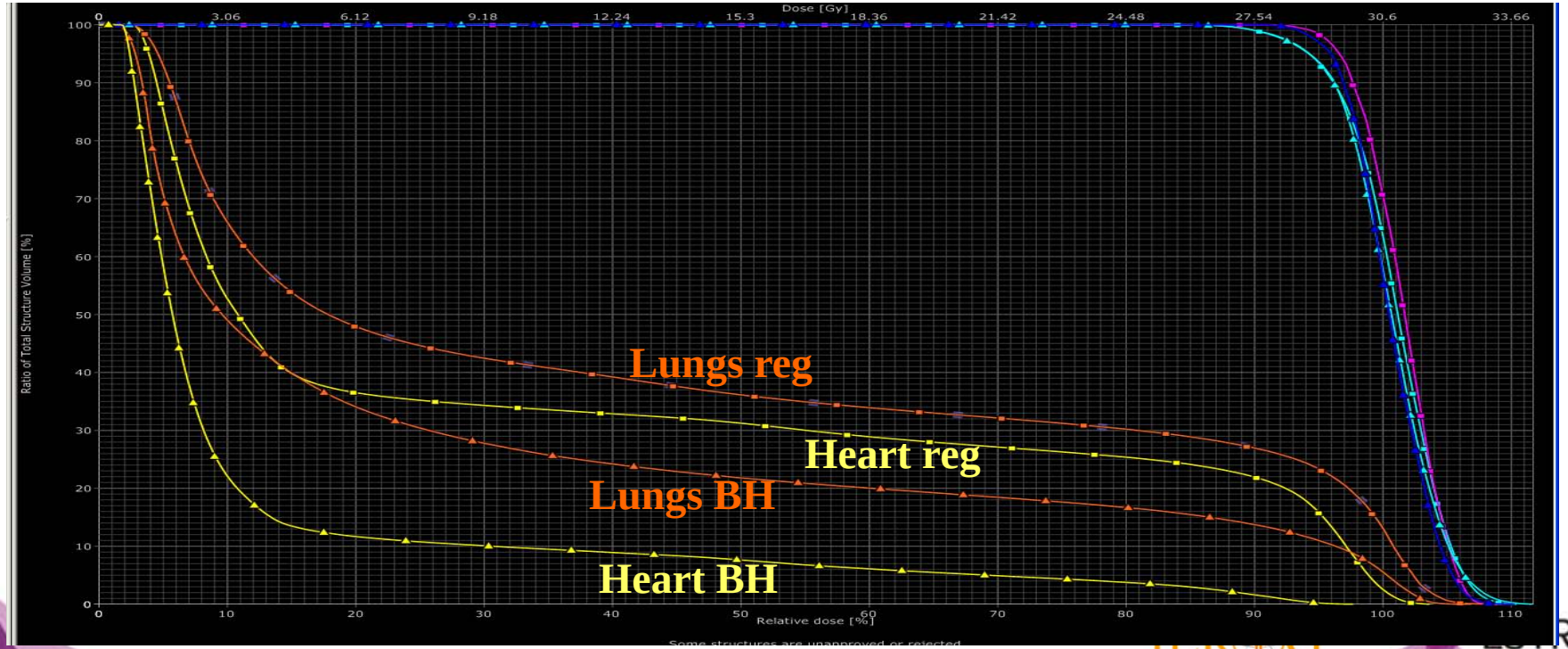


- Deep inspiration breath-hold

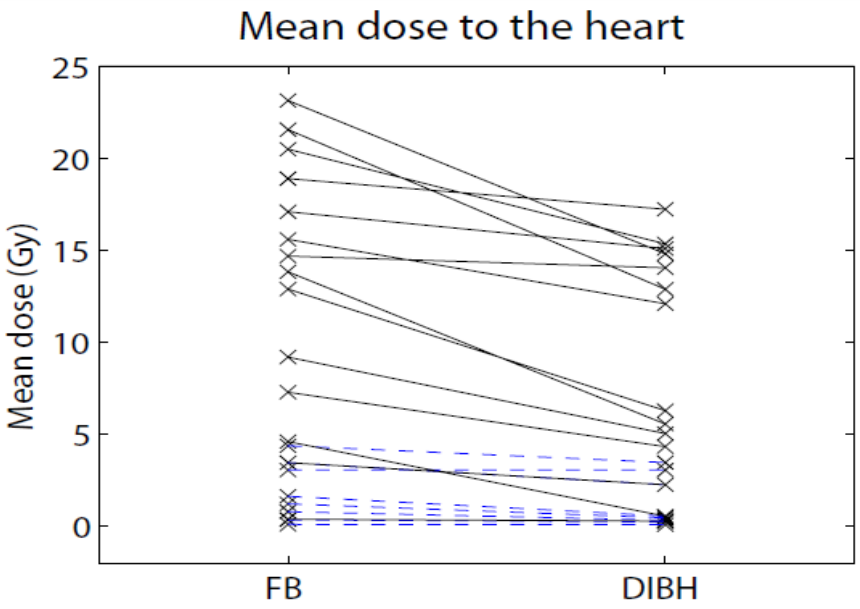


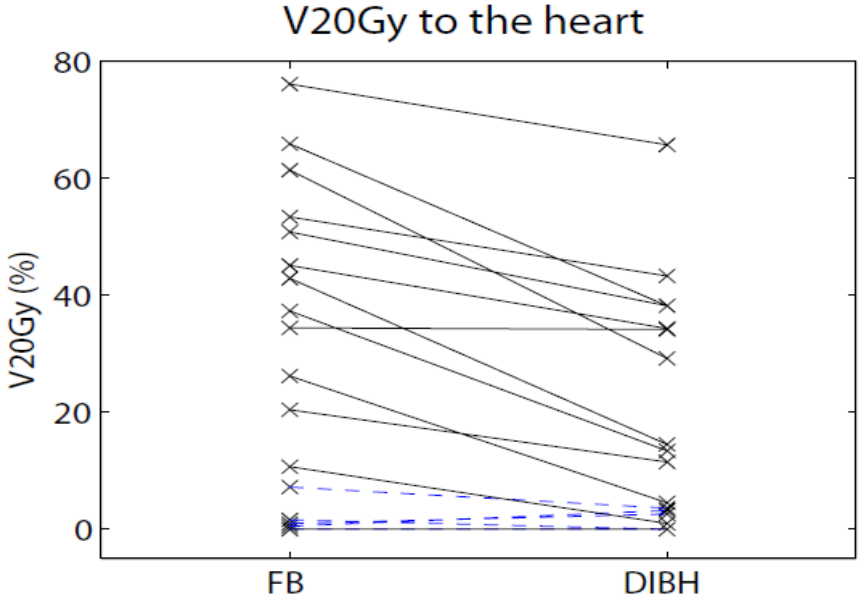
Notice lung volume and heart position

Mean dose to lungs: 8.5Gy vs 12.8 Gy



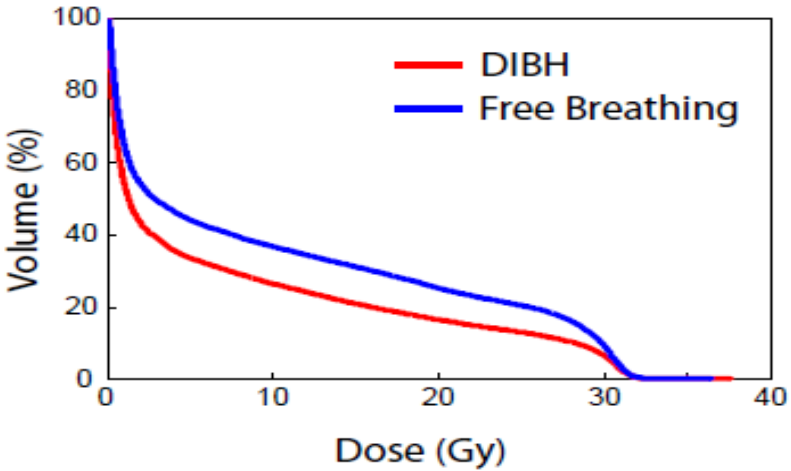
Benefit: inter-patient variation



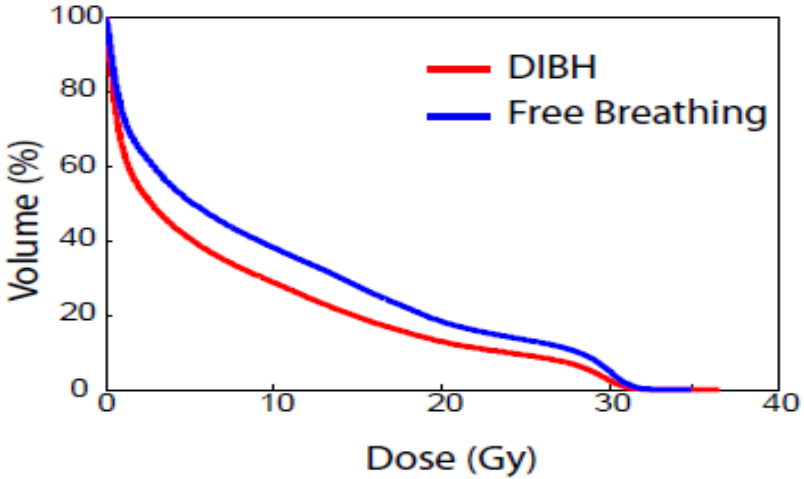


Benefit: over the whole group

Lung

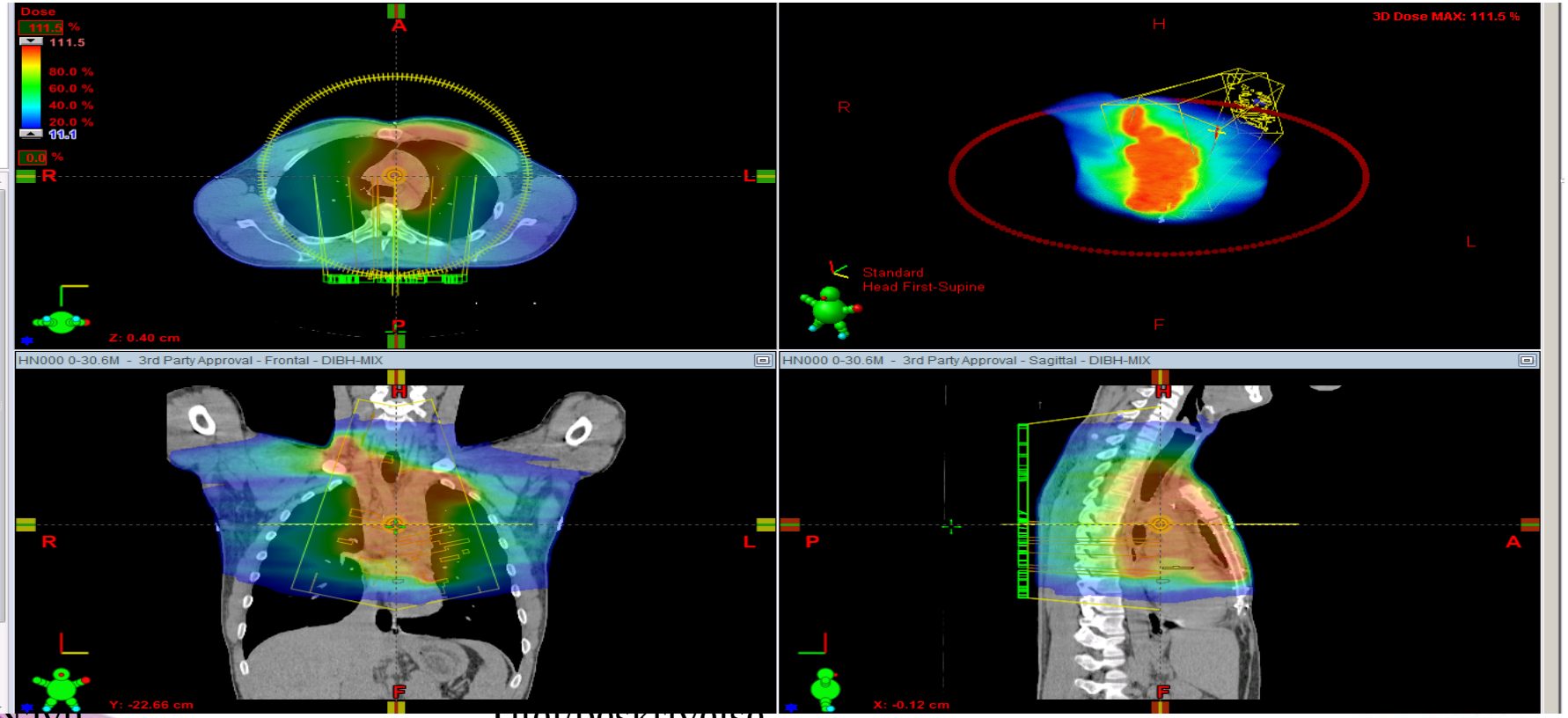


Heart



RPM integrated with linac
Beam switches on and off automatically

DIBH + VMAT/IMRT



Combining DIBH and VMAT

At Rigshospitalet:

For IGRT: 2 very short DIBHs (one per image)
For each 3D field: one DIBH
For each arc: 1 to 2 DIBHs

Total: worst case scenario 8-10 breath holds of 10 to 20 sec (patient catches her breath between fields)

Treatment time slot of 10-15 min

Take home message (2): treatment planning

- Having the staging PET/CT in DIBH increased our physicians' confidence
- The dosimetric benefit was clear enough to make DIBH our standard treatment for HL
- However, we still acquire a free breathing planning CT on top of the DIBH planning CT
- Tendency to combine DIBH with VMAT

IGRT

POSITION VERIFICATION IN DIBH

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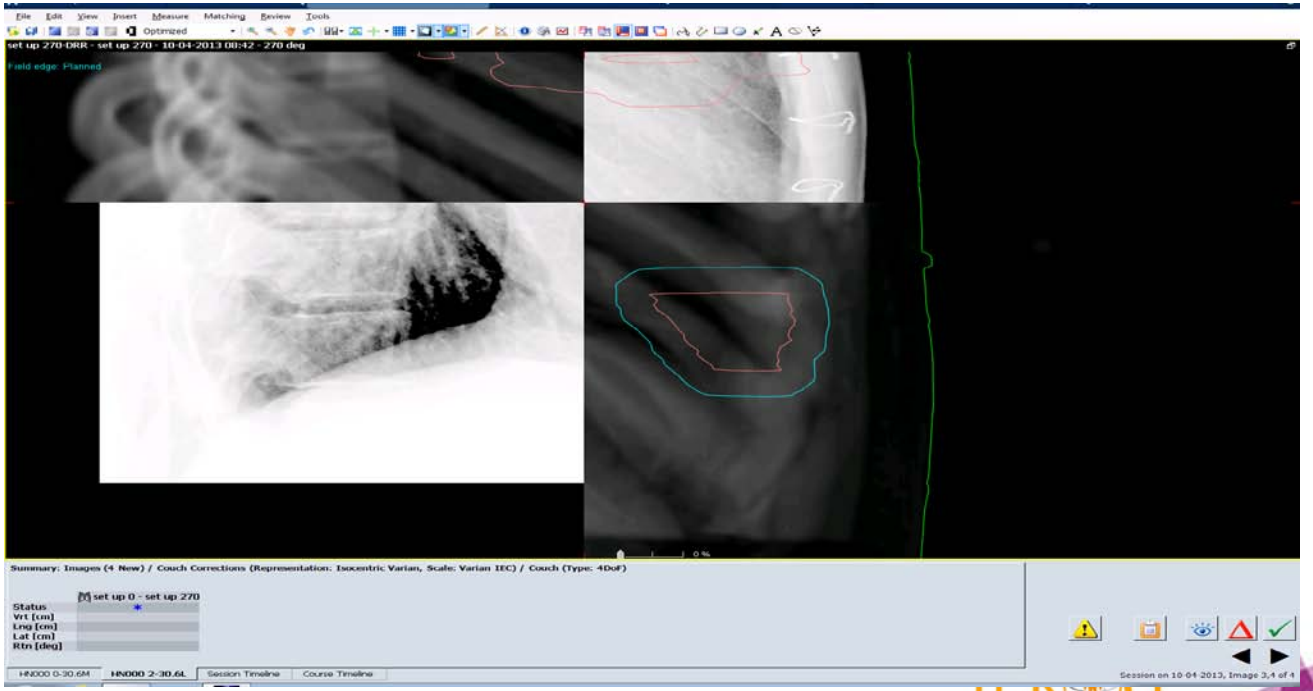
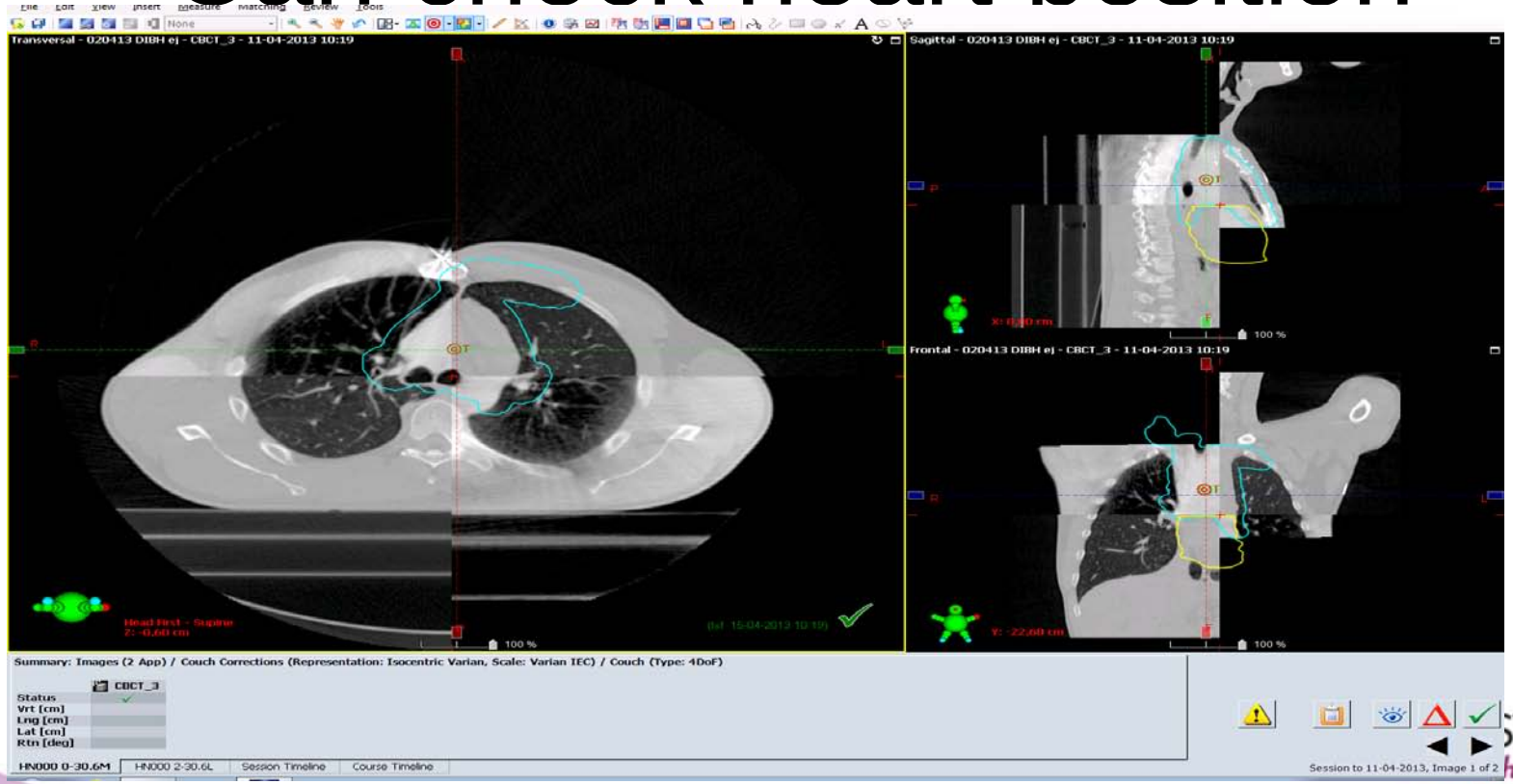
Daily 2D images: fuse on spine, check sternum



Can check heart position



Some challenges with CBCT in DIBH

- Requires 2-3 additional breath holds
  - But remember: young/fit patients
- Manually operated
- Some resistance to introduce it as a daily modality !

Some possible compromises…

- Daily 2D DIBH images
- Daily 2D DIBH images + weekly DIBH CBCT (with/without a physicist present)
- Daily DIBH CBCT with a longer treatment slot

A note about margins…

- In free breathing: 1cm, 1.5 cm sup-inf
- In DIBH: 1 cm all around ?
- A study of interfraction variation demonstrated that margins could NOT be reduced with DIBH
  - Back to 1cm, 1.5 cm sup-inf

Take home message (3): treatment delivery

- Patient compliance is excellent
- DIBH CBCT is possible, but there is a learning curve

Conclusion

- DIBH implementation in lymphoma very succesful
- Protocol in lung cancer patients ongoing

- Clear dosimetric benefit, even when using VMAT/IMRT

- Ressource investment: the ”sore points” are
  - PET scanning time
  - IGRT
  - And even then, they remain very manageable !

NEXT FRONTIERS?

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DIBH and proton therapy?

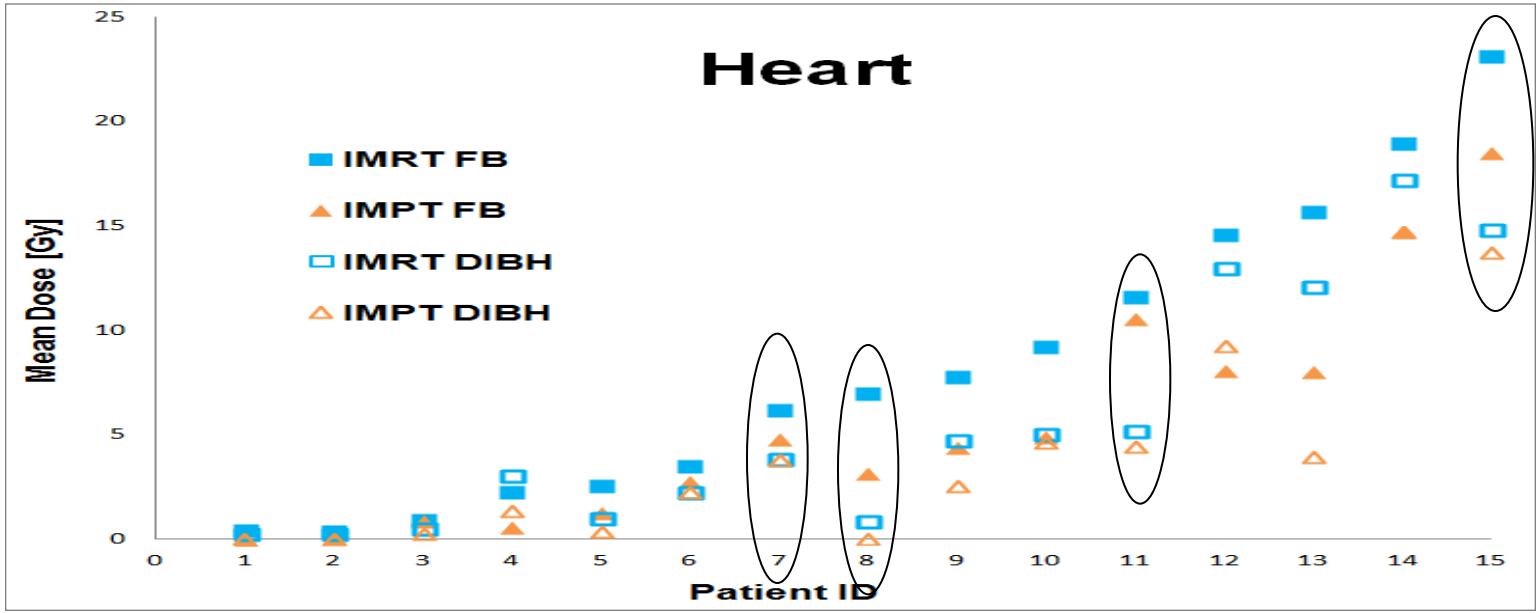
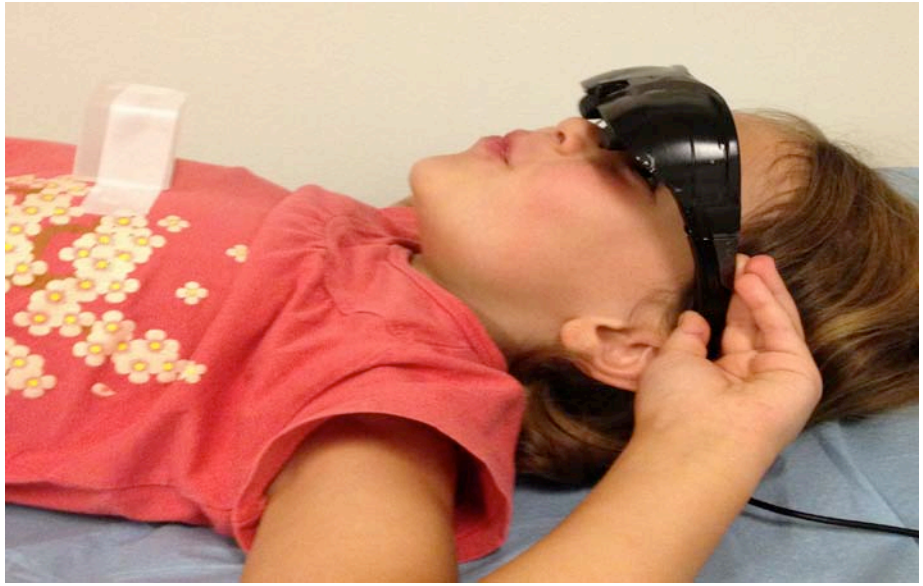


Figure 2. Mean dose to the heart for each modality for each patient (sorted by dose from IMRT FB). The difference in dose from each modality varied between patients.

TEDDI

- Pediatric phase II
- Multi national (DK, SE, FI)
- PI: Maja Maraldo MD PhD



- Compliance (reproducibility), dosimetric benefit, patient experience

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Acknowledgments

Department of radiation therapy, especially:

- Peter M Pedersen
- Maja Maraldo
- Lena Specht
- Ivan Vogelius
- Mirjana Josipovic
- Sidsel Damkjær
- Deborah Schut

Department of Clinical Physiology Nuclear Medicine and PET, especially:

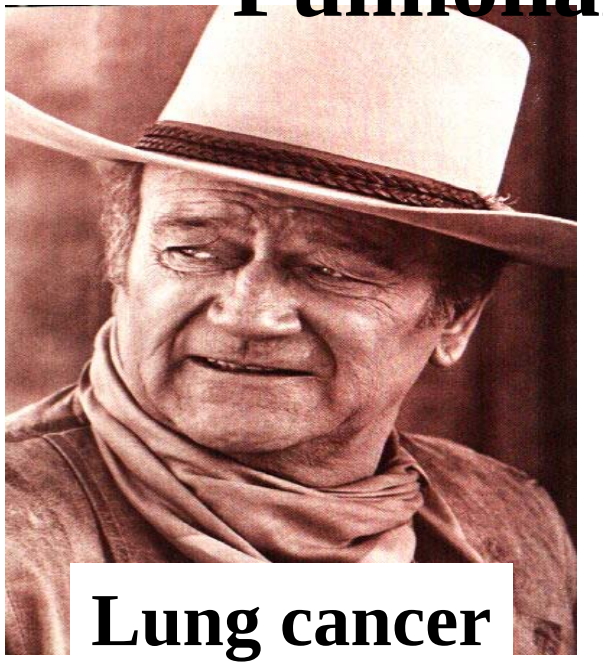
- Anne Kiil Berthelsen
- Flemming Andersen
- Annika Loft
- Thomas Levin Klausen
- Marianne Federspiel

Keep breathing ☺

Quiet free breathing

Extra slides

Compliance ?
Pulmonary function ?



Lung cancer

Breast cancer

Courtesy of Matthias Guckenberger

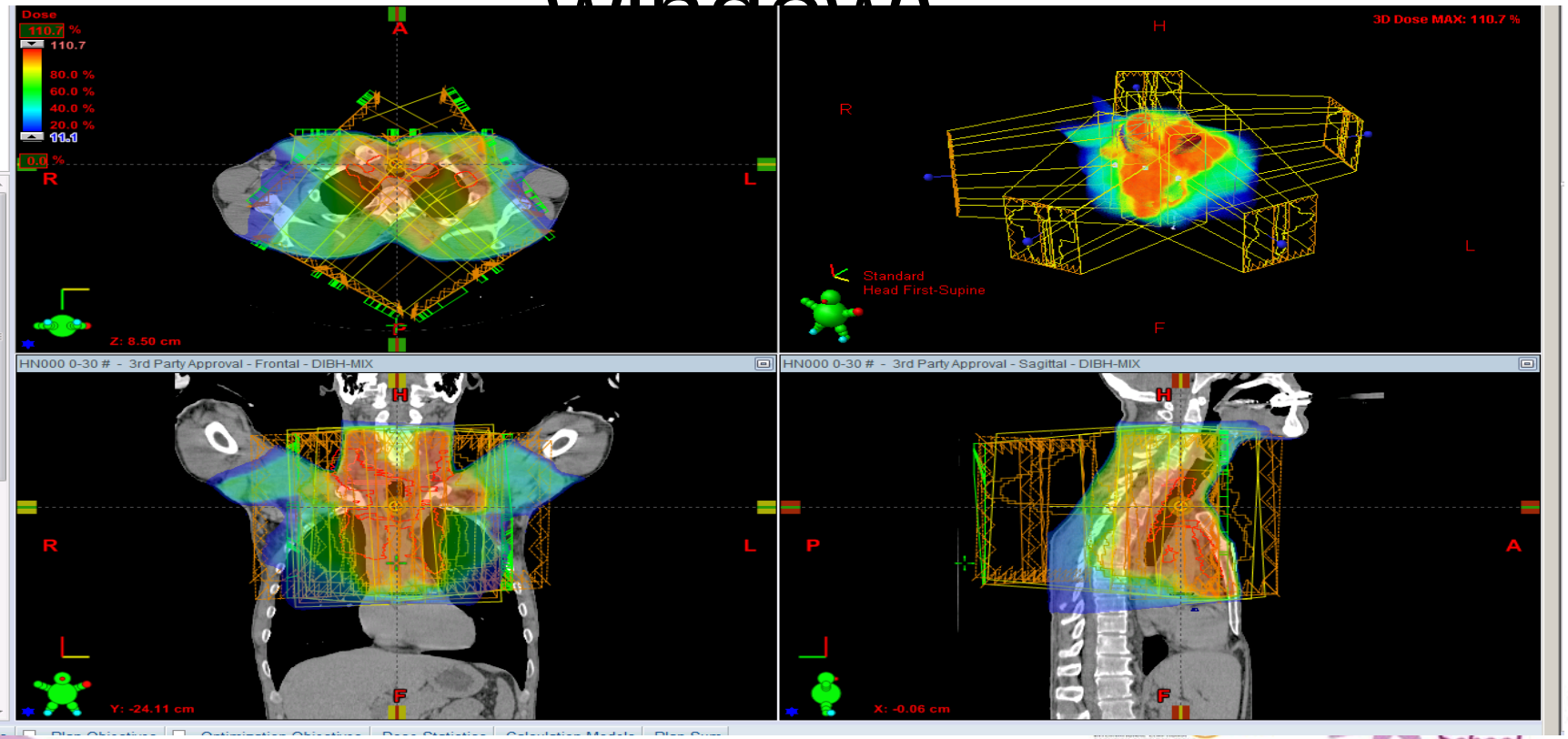
Our experience with DIBH for breast cancer

- Standard solution for most patients
- We stopped acquiring a free breathing CT
- Coaching: directly during CT simulation (10 min extra)
- Treatment within a standard treatment slot (10 min, 15 min on first fraction)
- Combine with IMRT/VMAT in about 10% patients

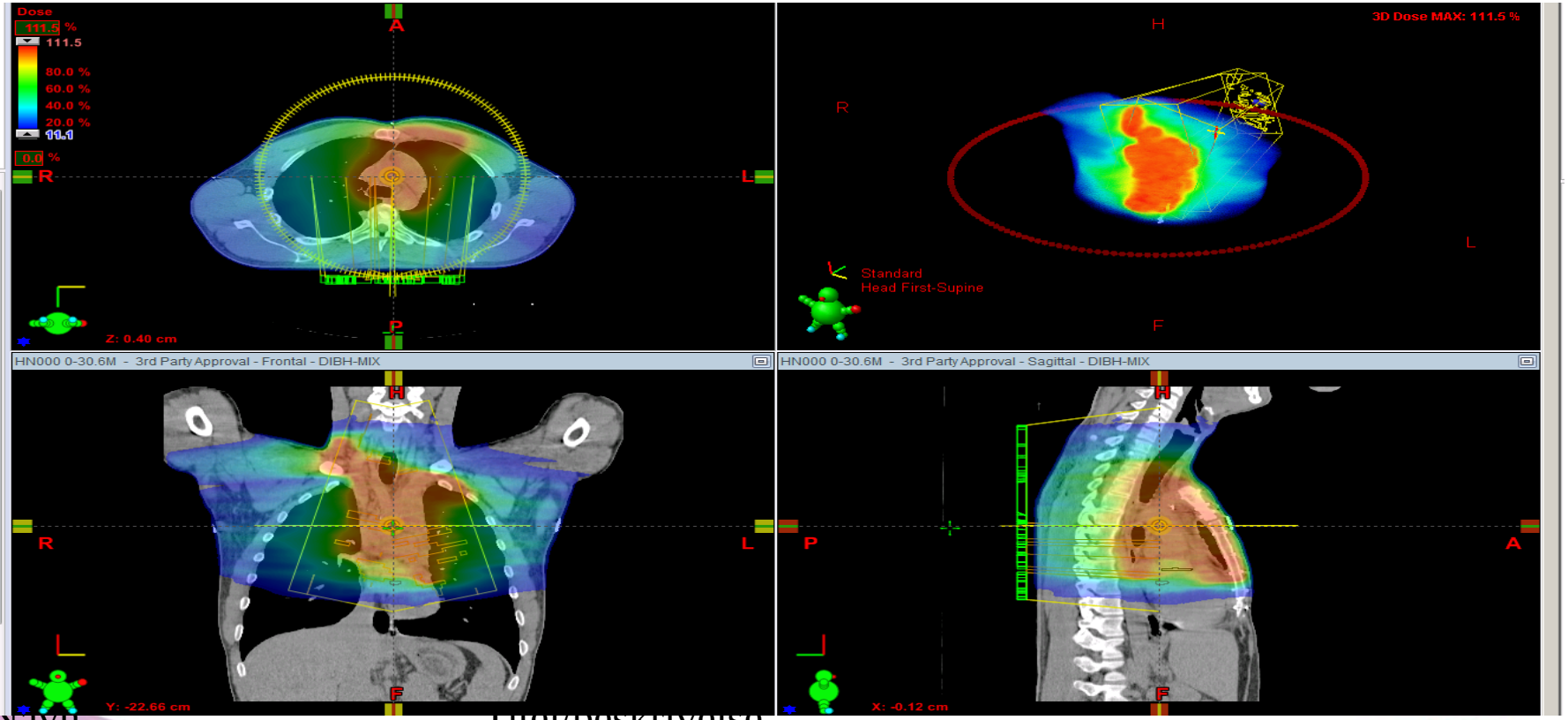
Treatment

DIBH + IMRT/RA

Fixed beam IMRT (sliding window)

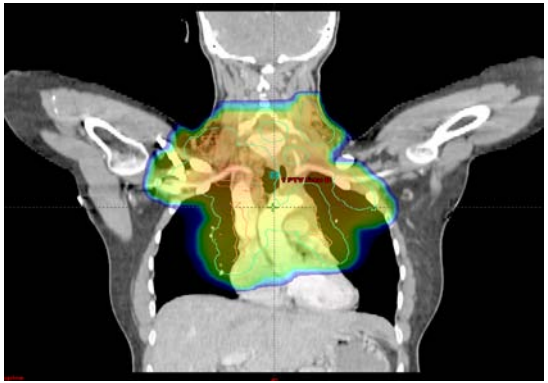


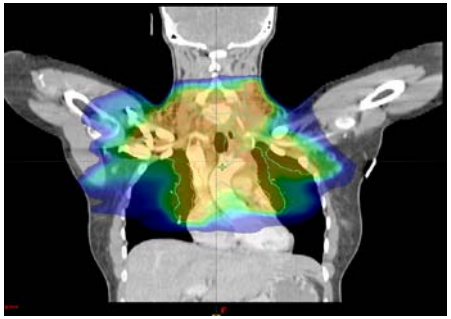
DIBH + RA


Dose
111.5 %
111.5
80.0 %
60.0 %
40.0 %
20.0 %
11.1
0.0 %
A
R
L
P
Z: 0.40 cm
H
R
3D Dose MAX: 111.5 %
L
Standard
Head First-Supine
F
HN000 0-30.6M - 3rd Party Approval - Frontal - DIBH-MIX
H
R
L
F
Y: -22.66 cm
HN000 0-30.6M - 3rd Party Approval - Sagittal - DIBH-MIX
H
P
A
F
X: -0.12 cm

What to choose: IMRT? DIBH or both?

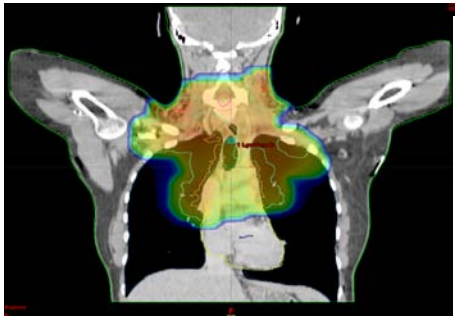
- Free breathing (AP-PA)





•Intensity-modulated radiation therapy

<u>NB: dose bath</u>



- Deep inspiration breath-hold (AP-PA)

<u>NB: lung and heart position</u>

Petersen et al Acta Oncologica; Aznar et al IJROBP 2015

Results: Dose

	Free Breathing		Deep Inspiration Breath Hold	
	3D	IMRT	3D	IMRT
Mean dose (Gy)				
Heart	**13.8** (1.2-24.0)	**10.6** (0.9-16.3)	**9.7** (0.5-21.7)	**7.5** (0.5-13.7)
Lungs	**13.0** (3.2-19.1)	**12.3** (4.0-17.5)	**9.8** (2.4-13.4)	**9.9** (3.3-12.7)
Breasts*	**4.6** (0.4-9.2)	**6.3** (0.7-8.9)	**4.7** (0.4-10.4)	**5.9** (1.0-9.2)

(*: 8 patients for breast cancer and mean dose). Median values and range are presented.

Results: Excess absolute risk (%)

	Free Breathing		Deep Inspitation Breath Hold	
	3D	IMRT	3D	IMRT
Cardiovascular disease	**1.8** (0.5-6.1)	**1.6** (0.5-2.6)	**1.3** (0.5-4.8)	**1.0** (0.5-2.0)
Lung cancer	**8.8** (4.8-14.8)	**8.8** (5.3-13.5)	**8.2** (4.1-11.3)	**8.1** (4.4-10.7)
Breast Cancer*	**13.0** (6.9-15.0)	**13.3** (7.7-17.1)	**11.8** (6.7-15.9)	**13.5** (7.3-15.3)

(*: 8 patients for breast cancer and mean dose). Median values and range are presented.

Results: Life years lost (y)

	Free breathing		Deep Inspiration Breath Hold	
	3D	IMRT	3D	IMRT
Life years lost	**1.2** (0.3-2.0)	**1.1** (0.3-1.9)	**1.0** (0.2-1.5)	**0.9** (0.3-1.5)

- $p < 0.05$ for free breathing vs breath hold, but not for 3D versus IMRT within the same breathing technique
- 3D- DIBH is superior to free breathing IMRT

IGRT

POSITION VERIFICATION IN DIBH

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Summary and future work

- breath-hold PET now standard in mediastinal lymphoma

  - Different optimal techniques for men and women?
  - Different optimal technique depending on the patient's age?
  - Do we really need the PET/CT in DIBH?
  - Would it enable us to reduce margins? (PET/CT…. CBCT….)

Beyond breast and lymphoma

DIBH FOR LUNG CANCER?

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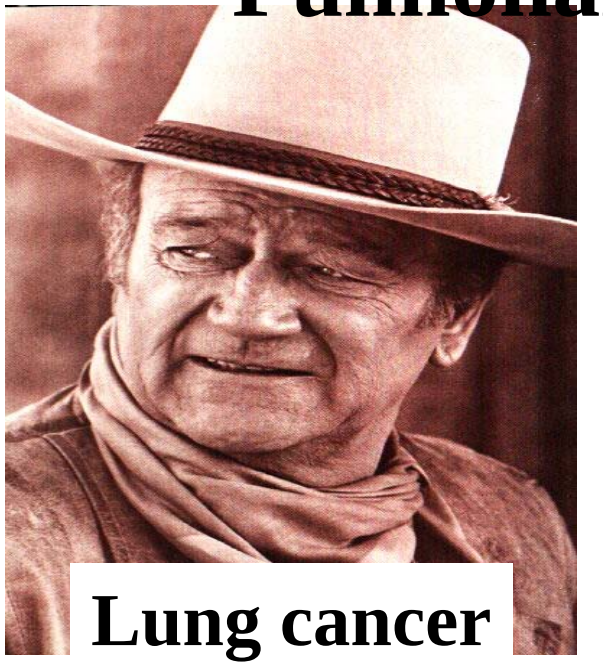
Compliance ?
Pulmonary function ?



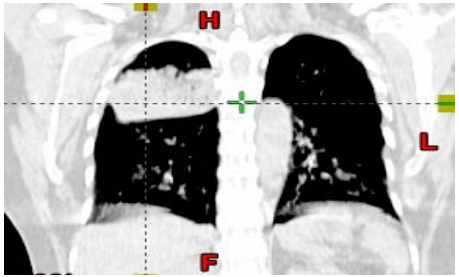
Lung cancer

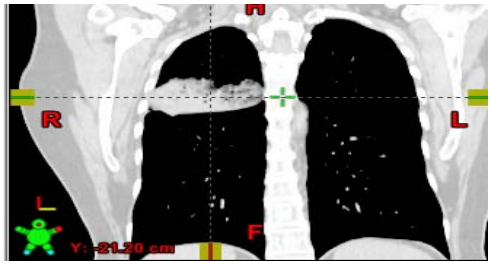
Breast cancer

Courtesy of Matthias Guckenberger

Hypotheses:

- **Deep** inspiration breath hold reduces toxicity
  - not just motion elimination (i.e. margin reduction), but also increase in lung volume

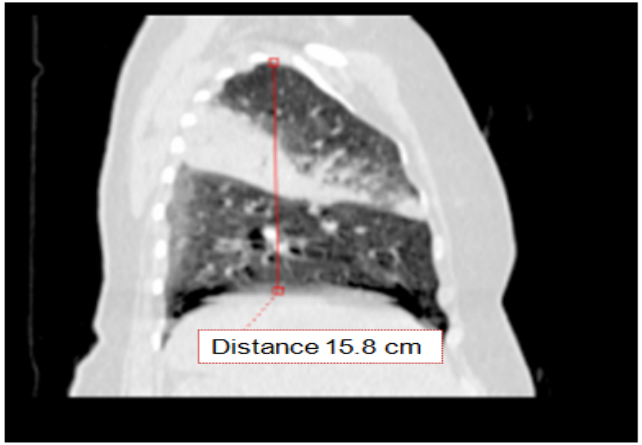




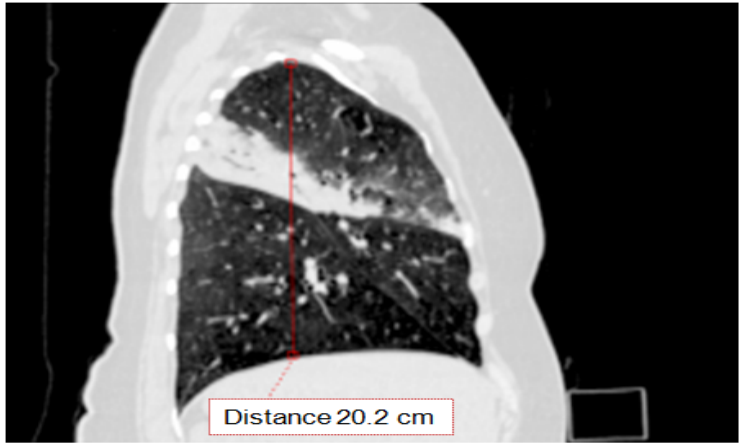
- We believe that over 50% of NSCLC

Potential of DIBH in lung cancer

Midventilation phase of the **free breathing** 4DCT



CT in visually guided voluntary **deep inspiration breath-hold**



- Increased lung volume (on average: 60%)

Potential of DIBH in lung cancer

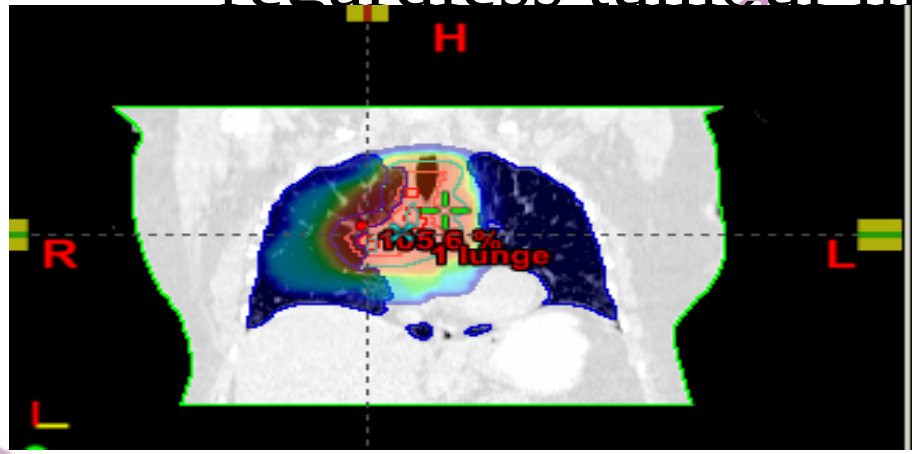
Patients with small target volume – too high toxicity

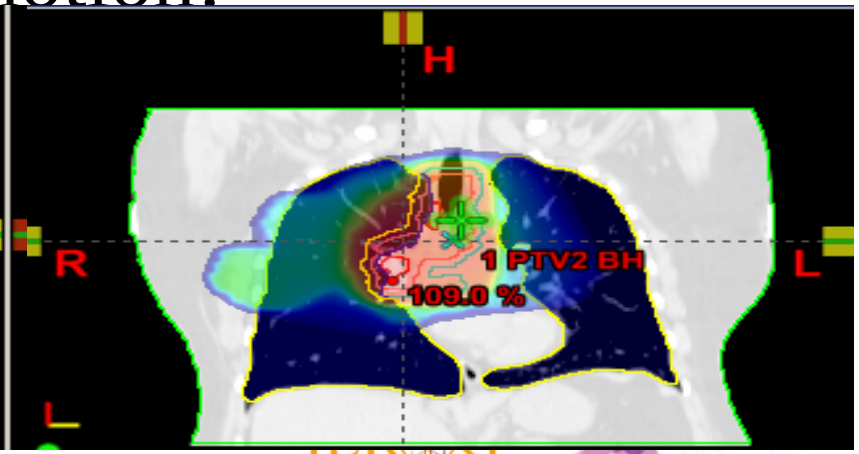
1st lung cancer pt treated in DIBH

- regardless tumour motion!

Free breathing

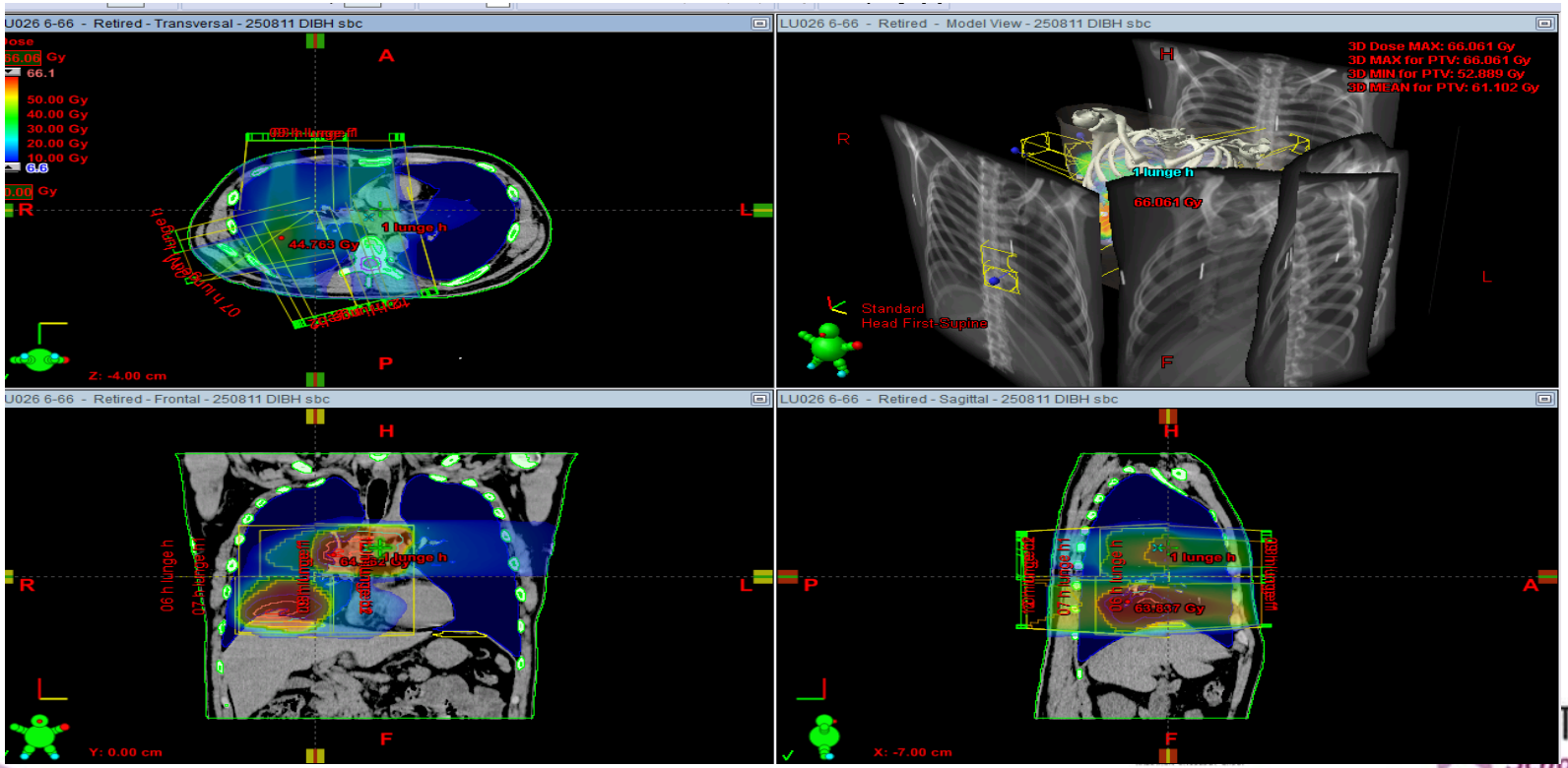
DIBH

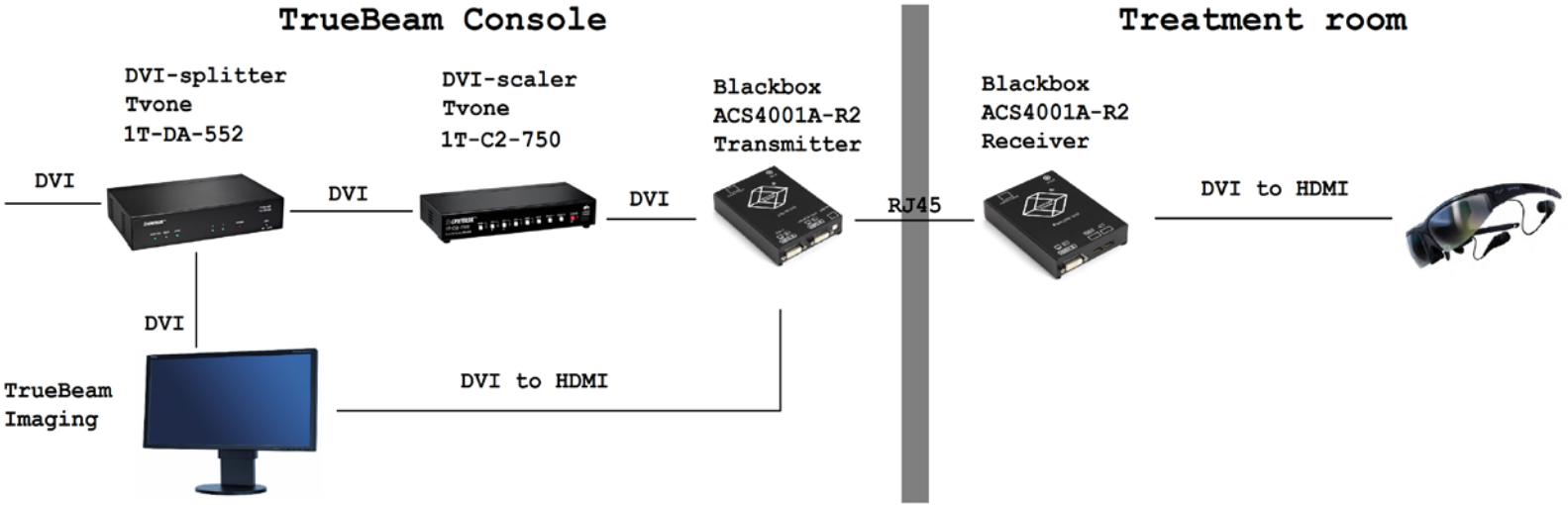




School

Patient #2: where it can go wrong…




TrueBeam Console
Treatment room
DVI-splitter
Tvone
1T-DA-552
DVI-scaler
Tvone
1T-C2-750
Blackbox
ACS4001A-R2
Transmitter
Blackbox
ACS4001A-R2
Receiver
DVI
DVI
DVI
RJ45
DVI to HDMI
DVI
TrueBeam
Imaging
DVI to HDMI

Titles in Arial

- Text in Georgia or Times New Roman

Copy/paste your original slides into this powerpoint file and make sure you use the option ‘use destination theme’.

Theme colors (ESTRO school) and fonts (Arial/Georgia/Times New Roman) are set as default.

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Imaging for radiotherapy of lymphomas

Anne Kiil Berthelsen,
Department of Oncology
Section of Radiotherapy
Department of Clinical Physiology, Nuclear Medicin & PET
Rigshospitalet
Denmark

Staging and response criteria

- 1999 National Cancer Institute Working Group
- 2007 International Working Group
- 2011 Lugano imaging

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Staging PET/CT

- Flat tabletop
- 2mm slice thickness
- IV-contrast
- Oral contrast
- Arms up if possible
- Both staging and CT for radiation planning
- If suspicion of mediastinal involvment
- Breath hold DIBH

The Copenhagen Model

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Staging with CT

- Up to 6 of the largest nodes/nodal masses that are measurable in two diameters, longest and shortest, in different regions, include mediastinal and retroperitoneal disease if involved.
- Node LD longer than 1.5 cm
- Extranodal LD longer than 1.0 cm

PET/CT interpretation

- Indikation
- Injected dose
- PET interpretation
- CT interpretation
- Table of lymphoma measurements
- Final PET/CT conclusion

Indikation: Status efter afsluttet kemoterapi for anaplastisk, storcellet ALK negativt lymfom.

18-08-2015 gives i.v. 315 MBq F-18 FDG
mhp. Wb PET/CT FDG. PET 4

Beskrivelse:
PET-scanning:
Sammenholdt med PET/CT-scanning 24.06.15 ses tiltagende metabolisk aktivitet i tidligere beskrevne lymfeknuder periklavikulært og subpektoralt på ve. side samt i ve. aksil. Ligeledes indtryk af tiltagende FDG-optagelse i lymfeknuderne i hø. lyskeregion. Tilkommet moderat øget FDG-optagelse i lymfeknuder langs arcus aortae. Lymfeknuder med den højeste metaboliske aktivitet findes subpektoralt på ve. side og i ve. aksil, hvor aktivitetsniveauet overstiger baggrundsaktiviteten i leverparenkymet. Derudover kan der ikke påvises patologisk øget FDG-optagelse nogetsteds.

CT-scanning af hals, thorax og abdomen efter peroral, men uden i.v. kontrast på baggrund af kendt allergi:
Viser, sammenholdt med CT 24.06.15, tiltagende størrelse af nogle lymfeknuder periklavikulært på ve. side samt i ve. aksil, ligesom der er indtryk af tilkomne, men små, lymfeknuder i mediastinum superius sin. En del af de tidligere sete lymfeknuder i skemaet er dog aftaget i størrelse. Fortsat ikke forandringer i lungeparenkym eller intraabdominale organer. Ossøst uændrede forhold. Tumor 6 målte ved forrige undersøgelse 2,6 x 2,4 cm.

Tumor 1 IMA 102 Ve. halsrod 1,8 x 1,1 cm
Tumor 2 IMA 138 Ve. aksil 3,0 x 1,8 cm
Tumor 3 IMA 155 Distalt i ve. aksil 1,0 x 0,9 cm
Tumor 4 IMA 373 Iliaca externa kar dxt. 1,4 x 0,7 cm
Tumor 5 IMA 390 Hø. ingvinalregion 1,0 x 0,9 cm
Tumor 6 IMA 138 Ve. aksil 3,2, x 3,3 cm.

Konklusion:
Sammenholdt med PET/CT-scanning 24.06.15 samlet set indtryk af progression med tiltagende metabolisk aktivitet i lymfeknuder både over og under diaphragma, hvoraf nogle ses med tiltagende størrelse og andre aftagende.

Louise Alslev/Elisabeth Albrecht-Beste/vrø
20-08-2015

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IV-Contrast

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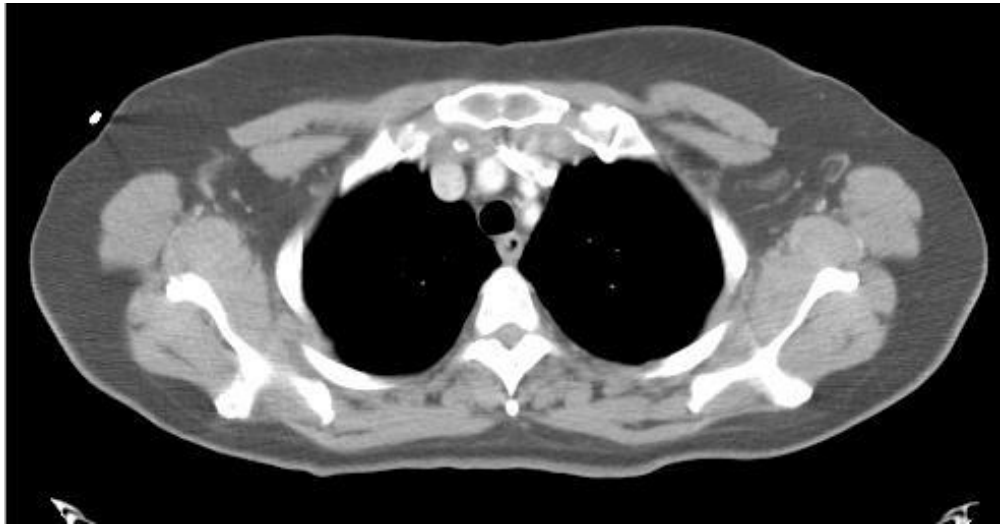
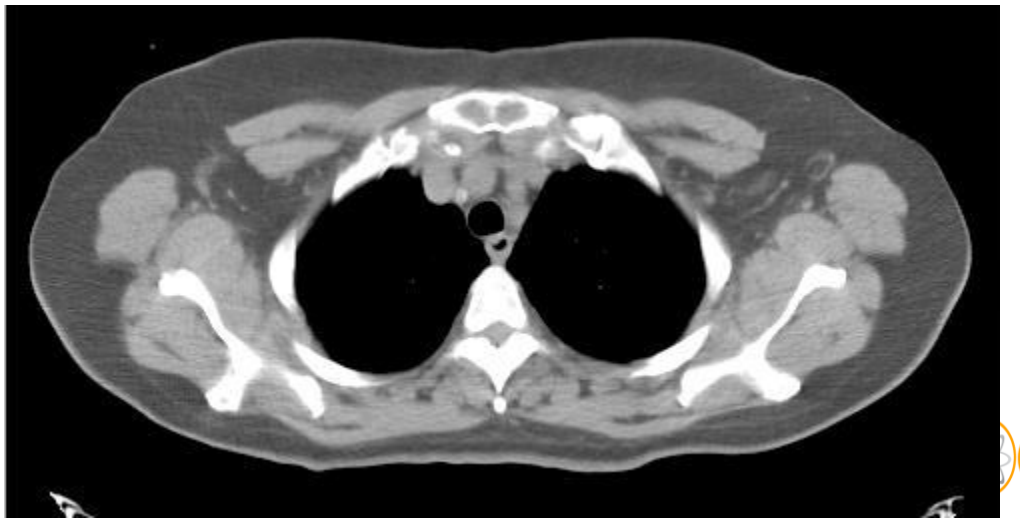
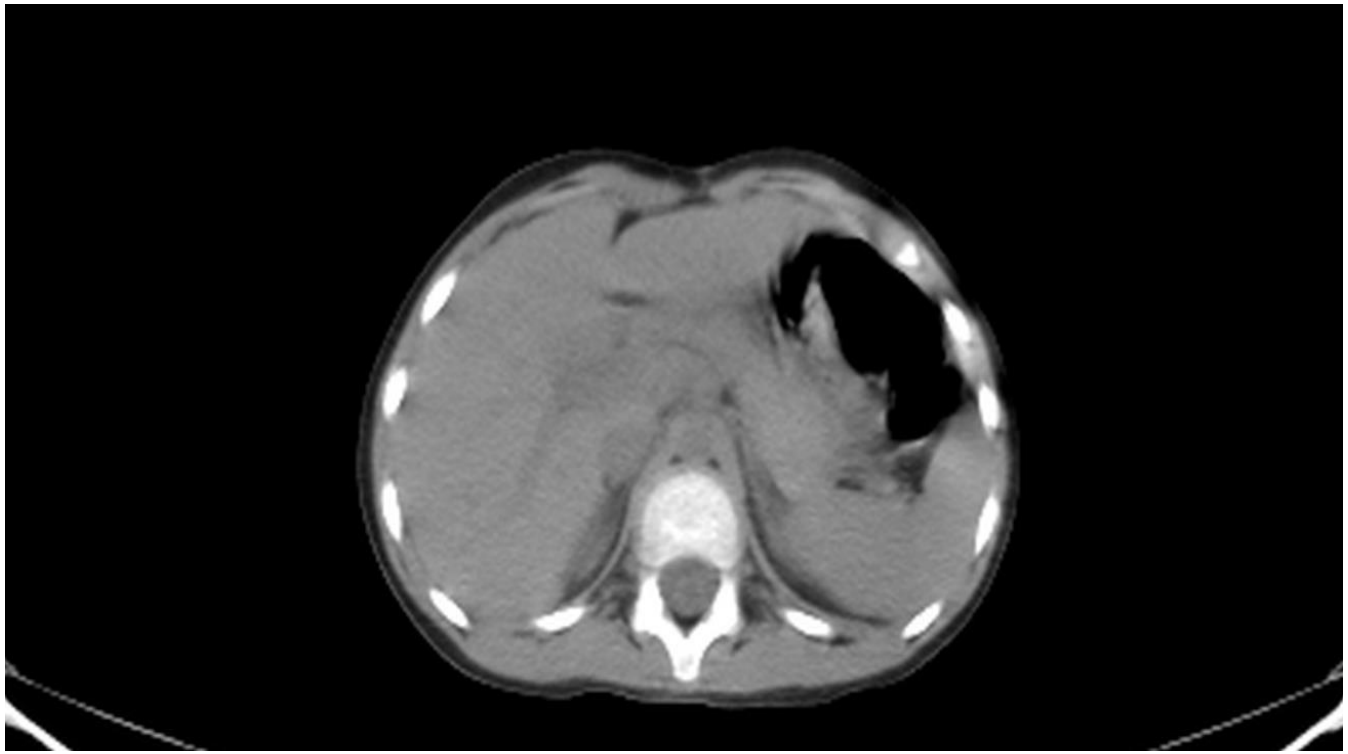
with and without IV contrast





CT scan without IV contrast



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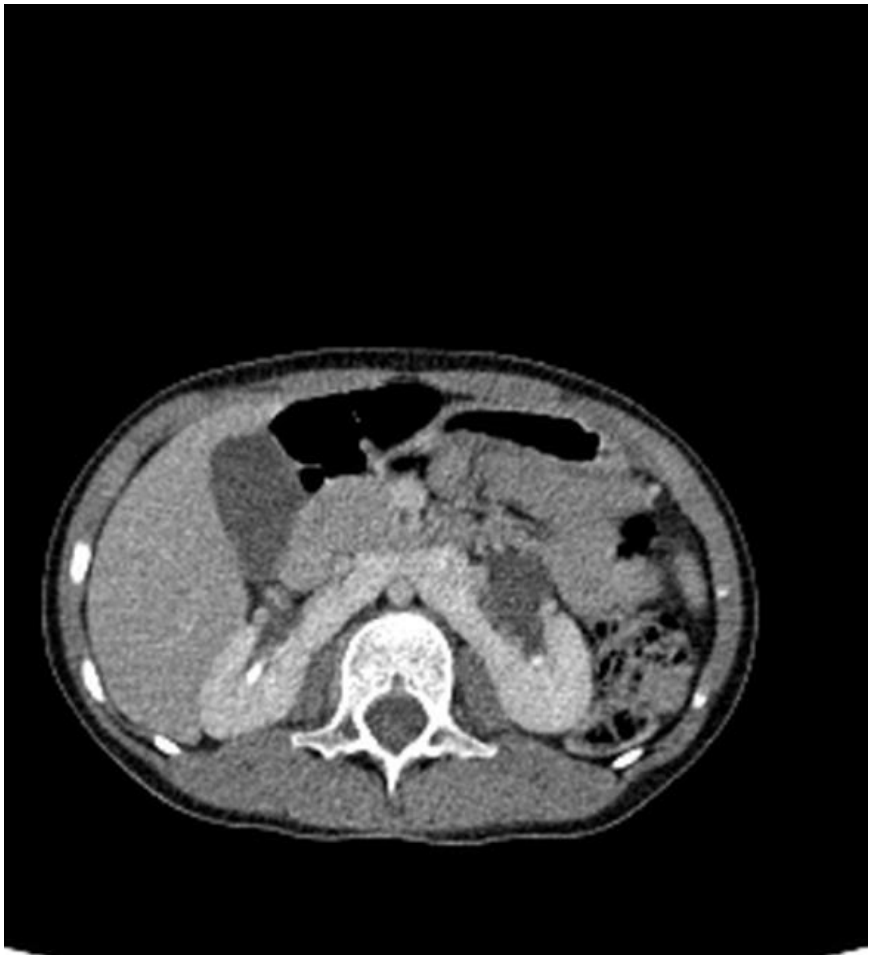
CT scan with IV contrast



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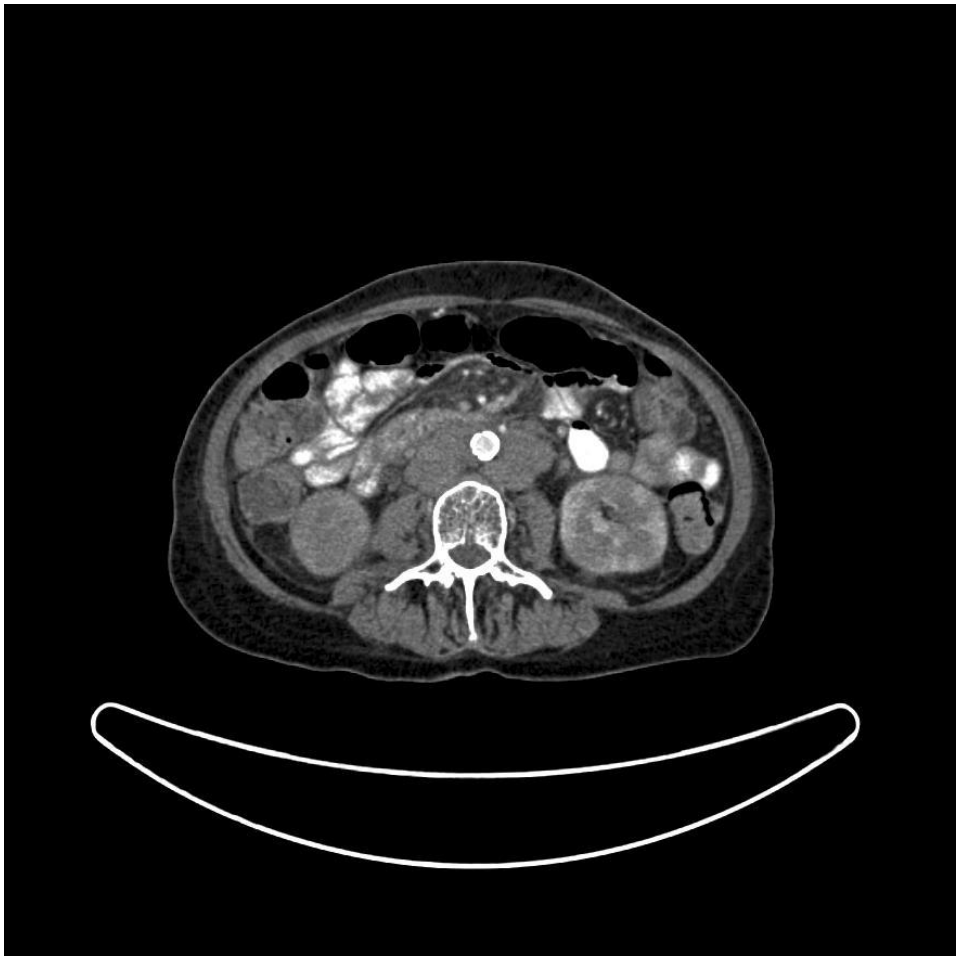
Oral contrast



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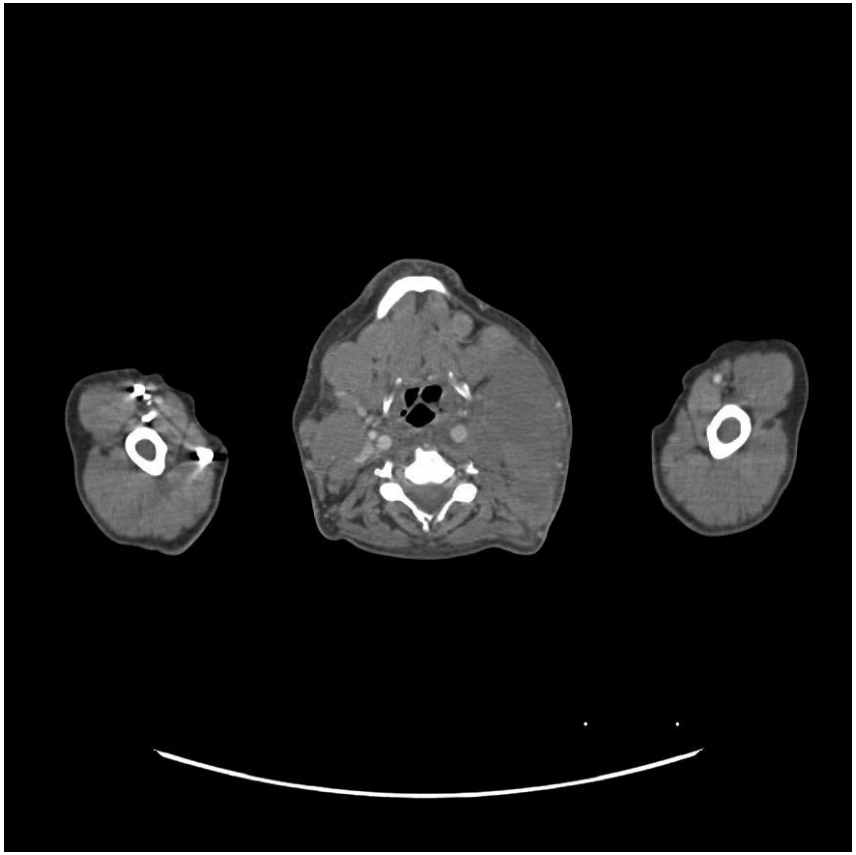
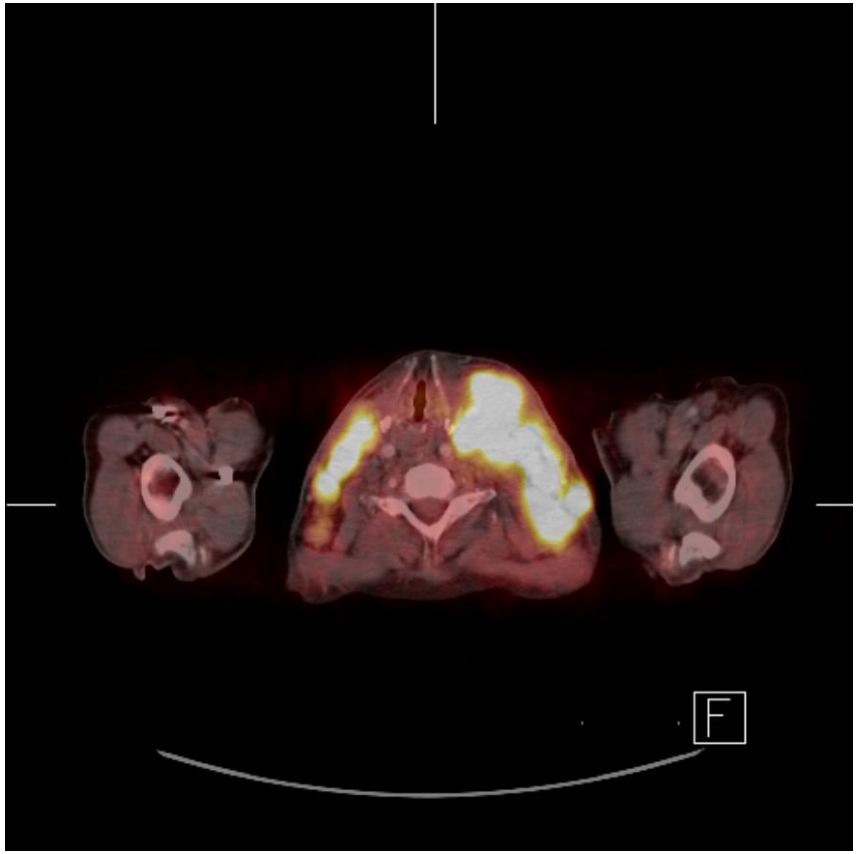
Lymph node > 1.5 cm





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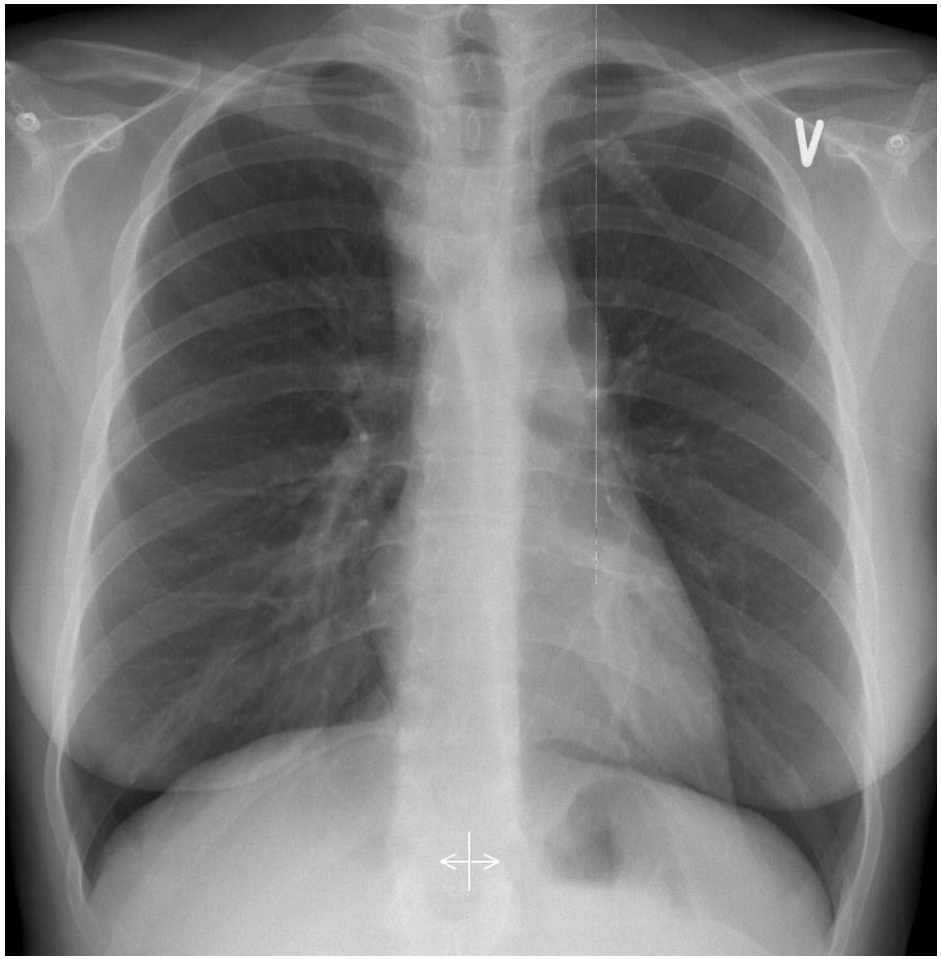
Chest X-ray is not required



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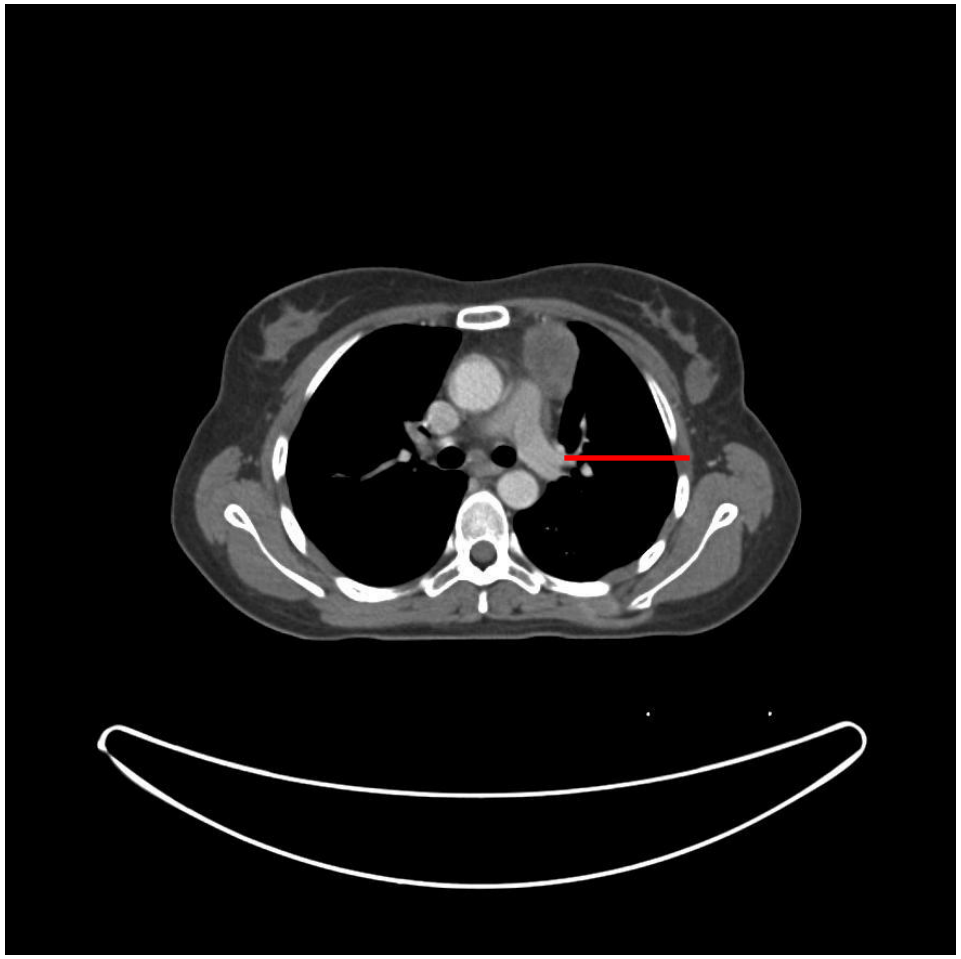
10 % have a normal chest x-ray



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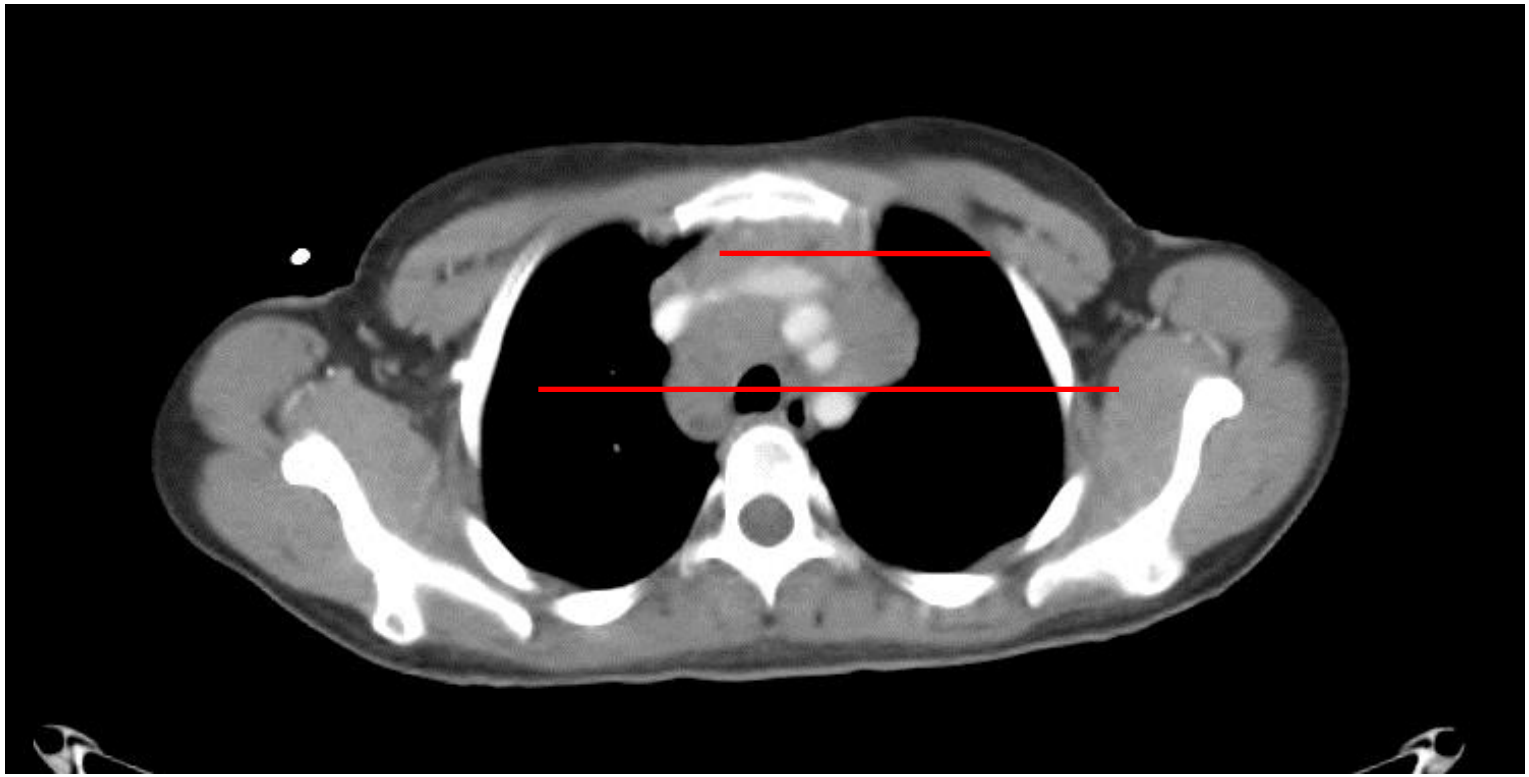
Enlarged mediastinum



10 cm or greater than 1/3 of the trans-thoracic diameter at any level of thoracic vertebrae

CT identifies more hilar nodes

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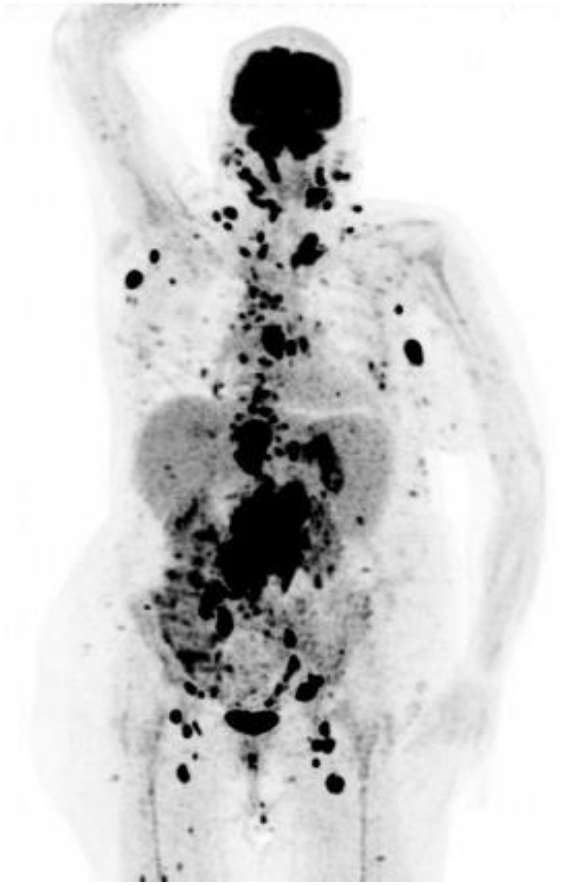
Lymphomas can be found anywhere



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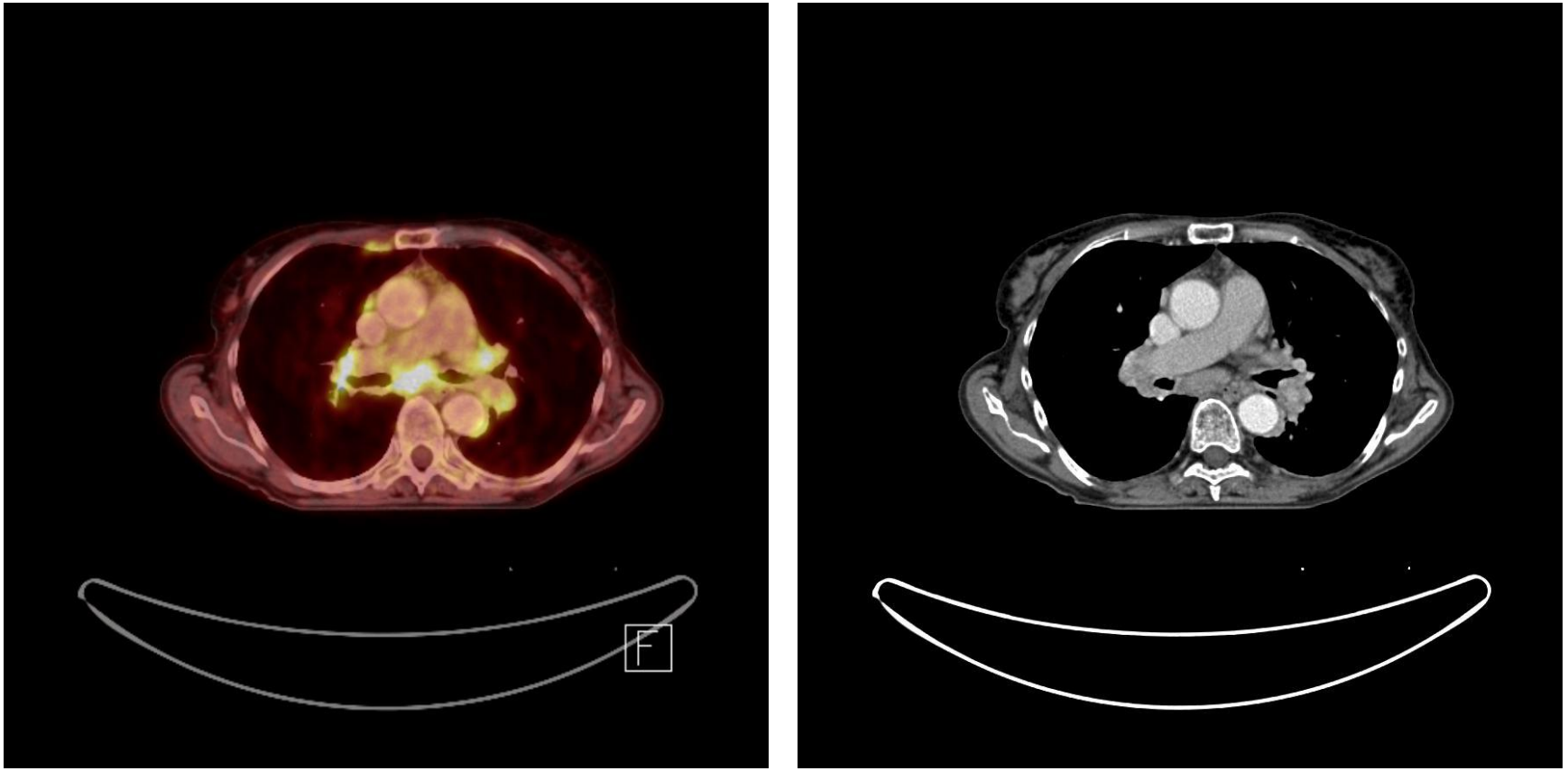
Lungs, involvement of lymph nodes



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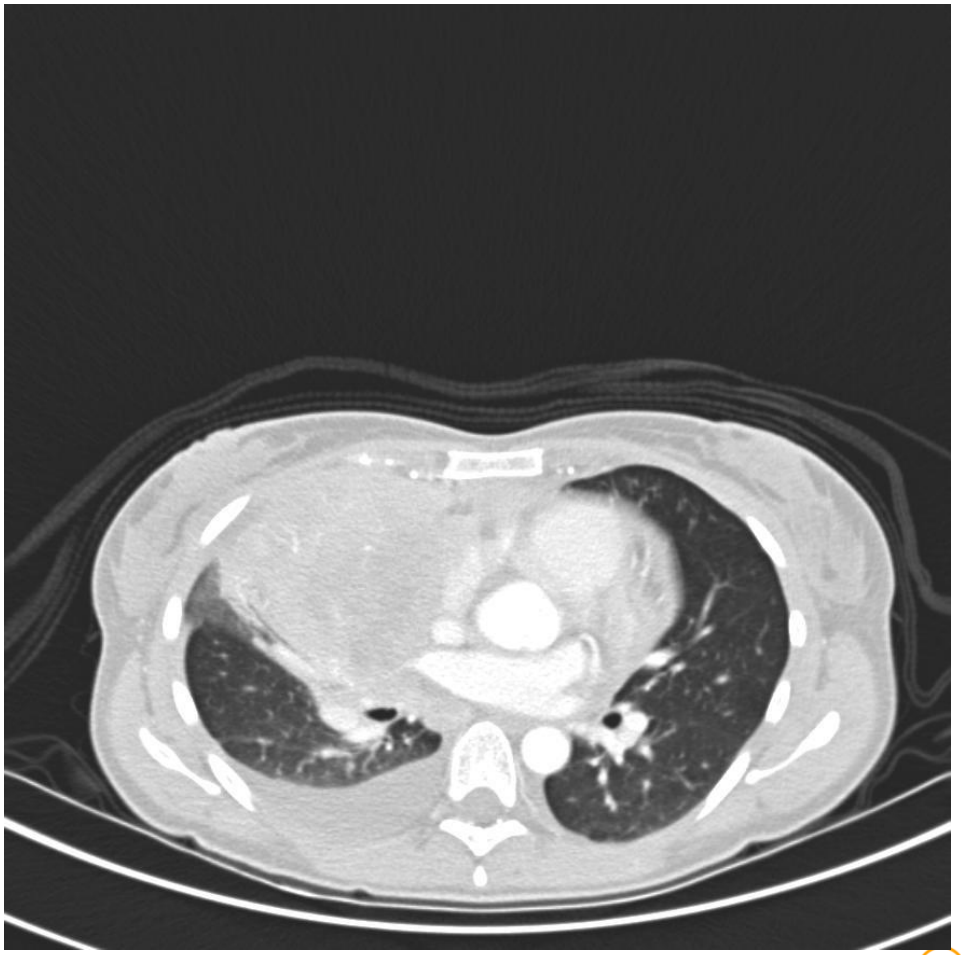
Lungs



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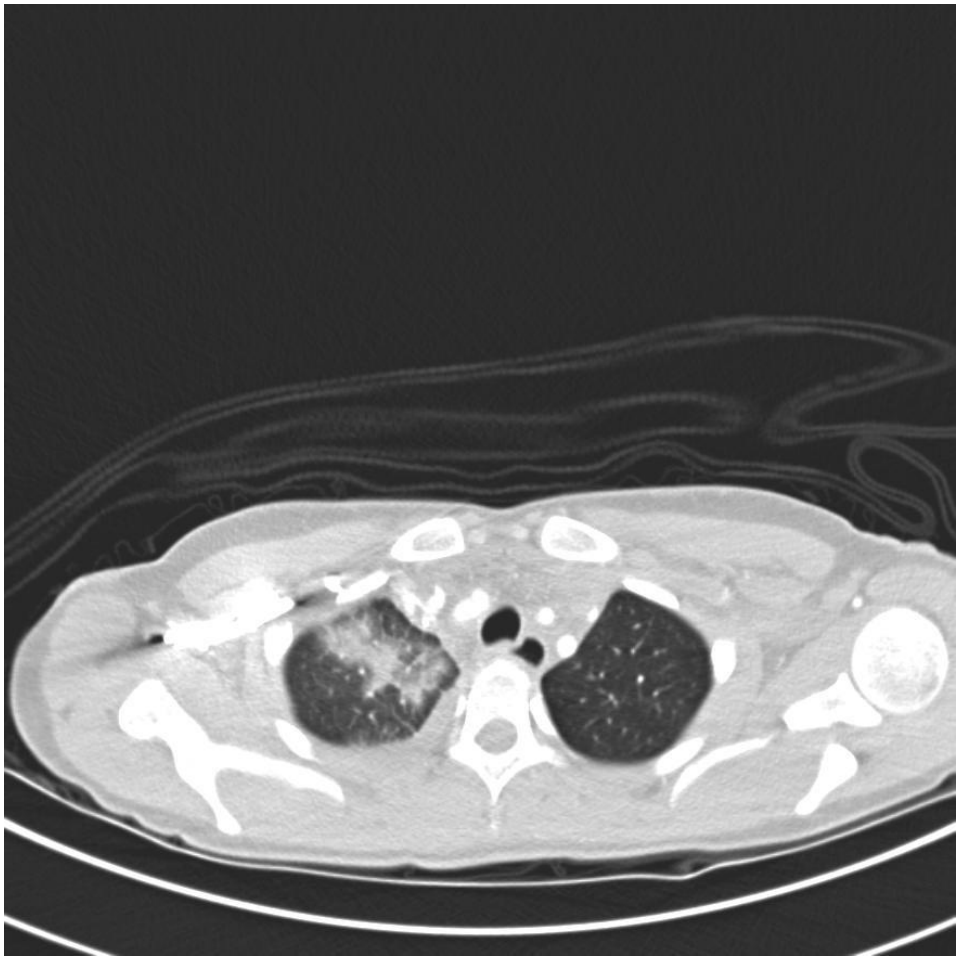
More diffuse infiltration, snow balls



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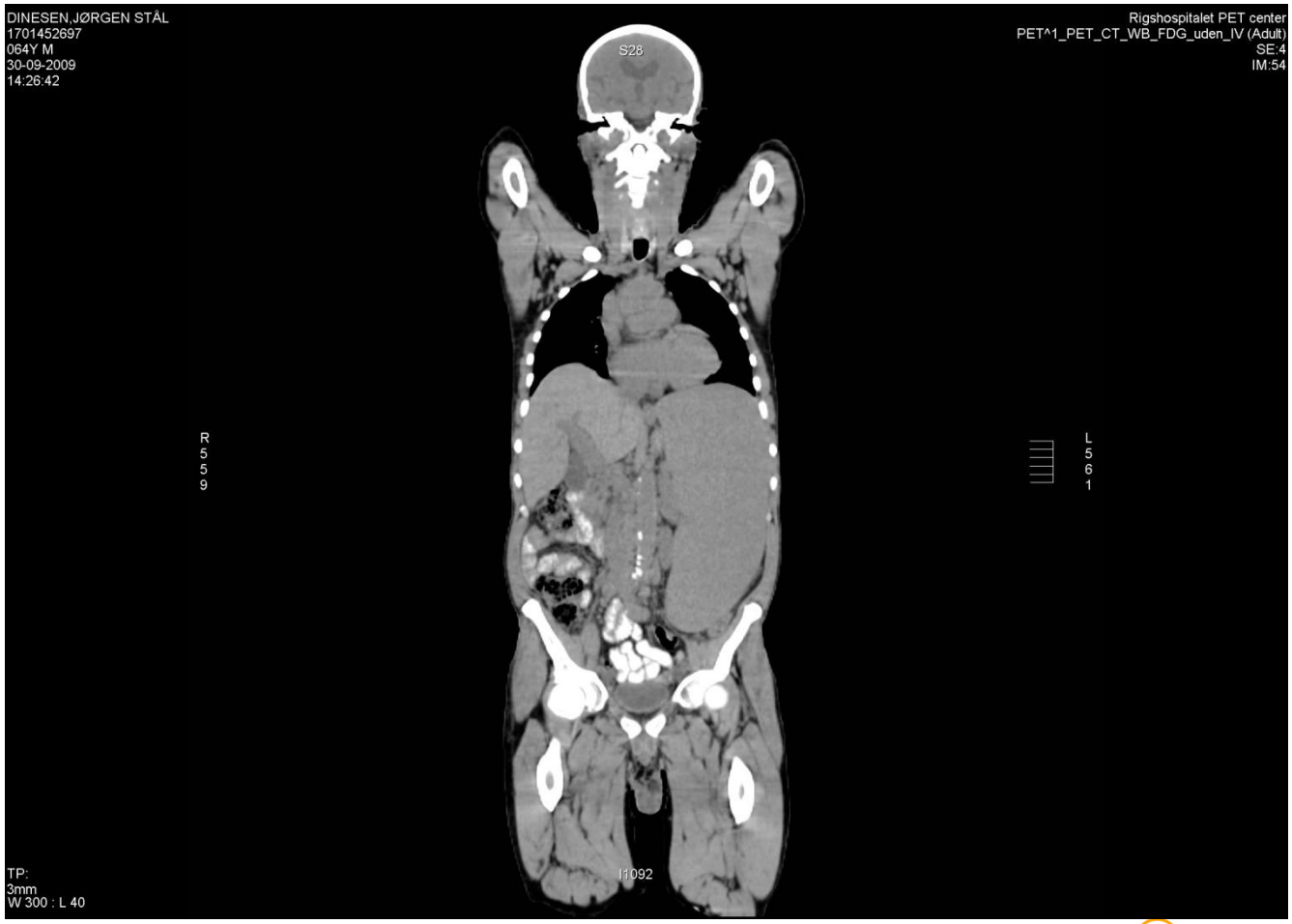
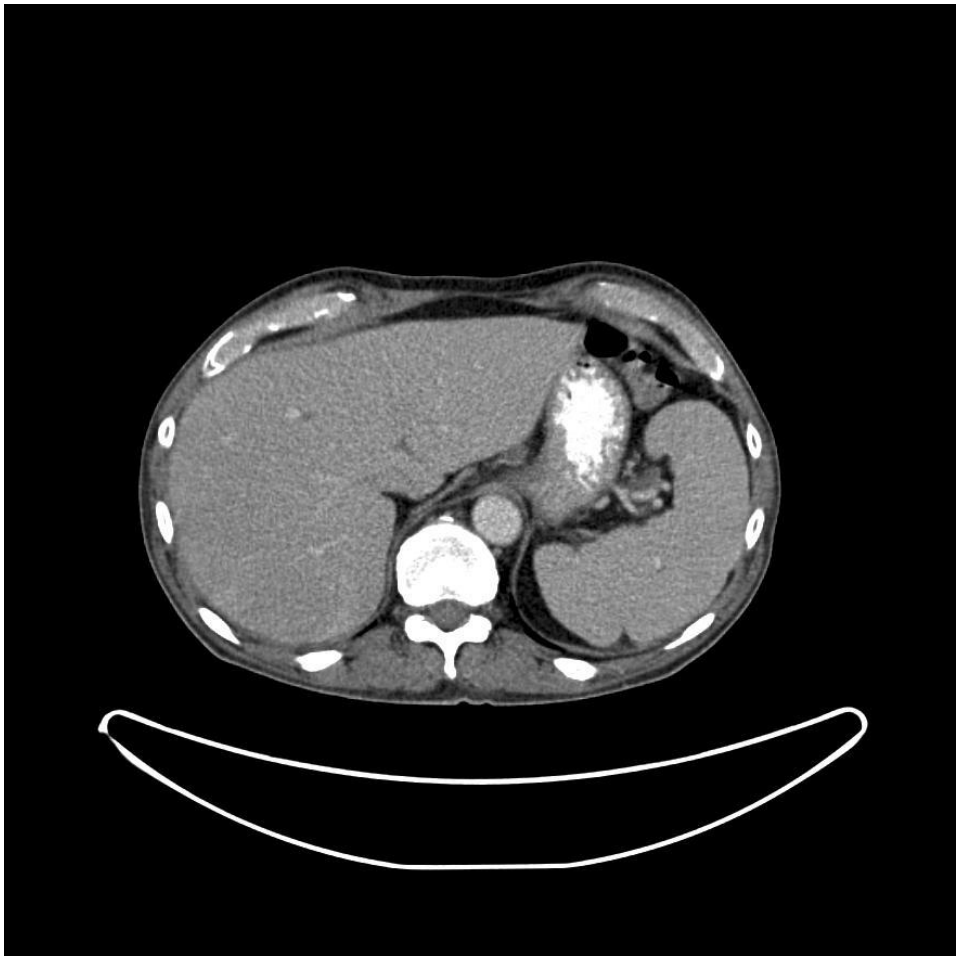
Spleen involvement

- Normal size and still contain lymphoma or enlarged and not involved.
- 10 -12 cm in vertical length. 13 cm.
- Best determined by PET/CT
- Diffuse infiltration
- Focal nodular lesion
- Large solitary mass

Spleen – large solitary mass



Spleen diffuse infiltration



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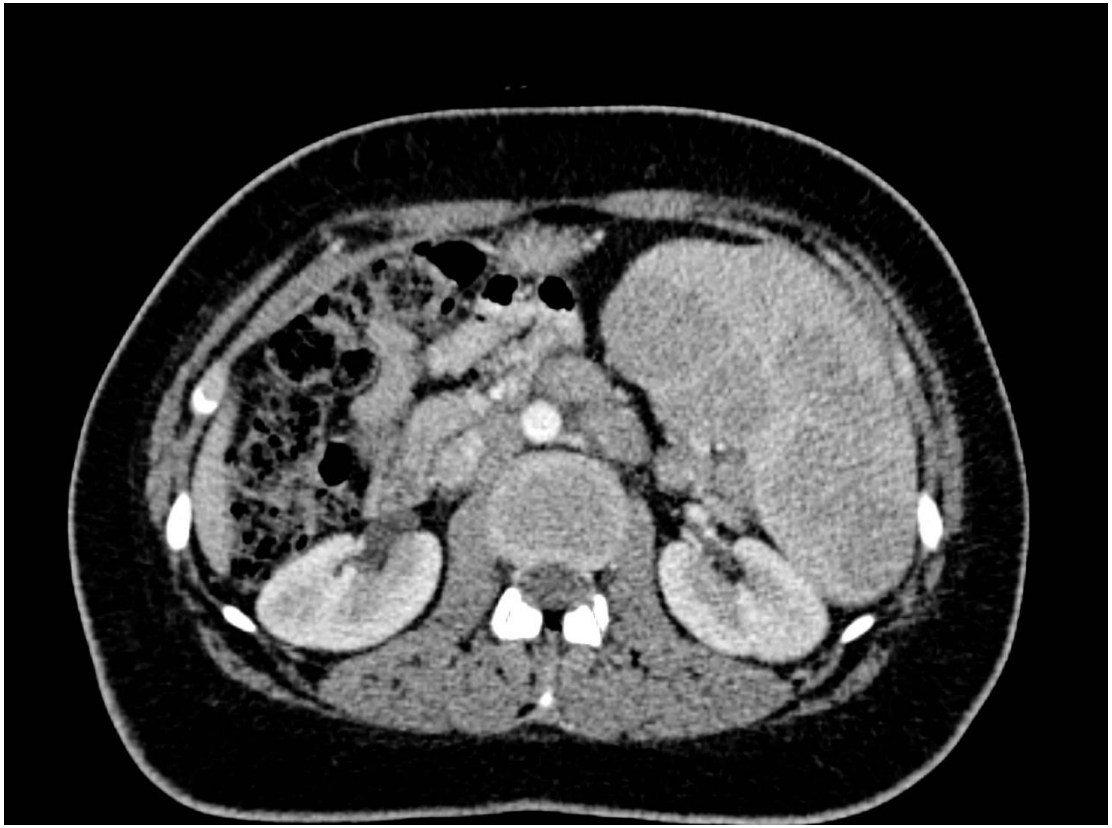
Spleen Focal nodula lesion



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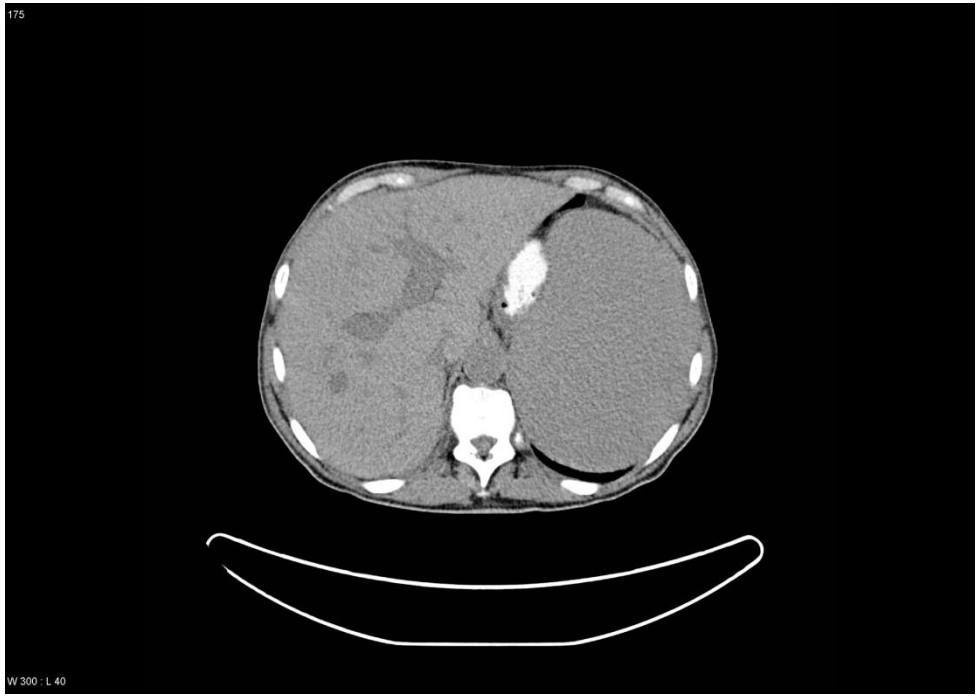
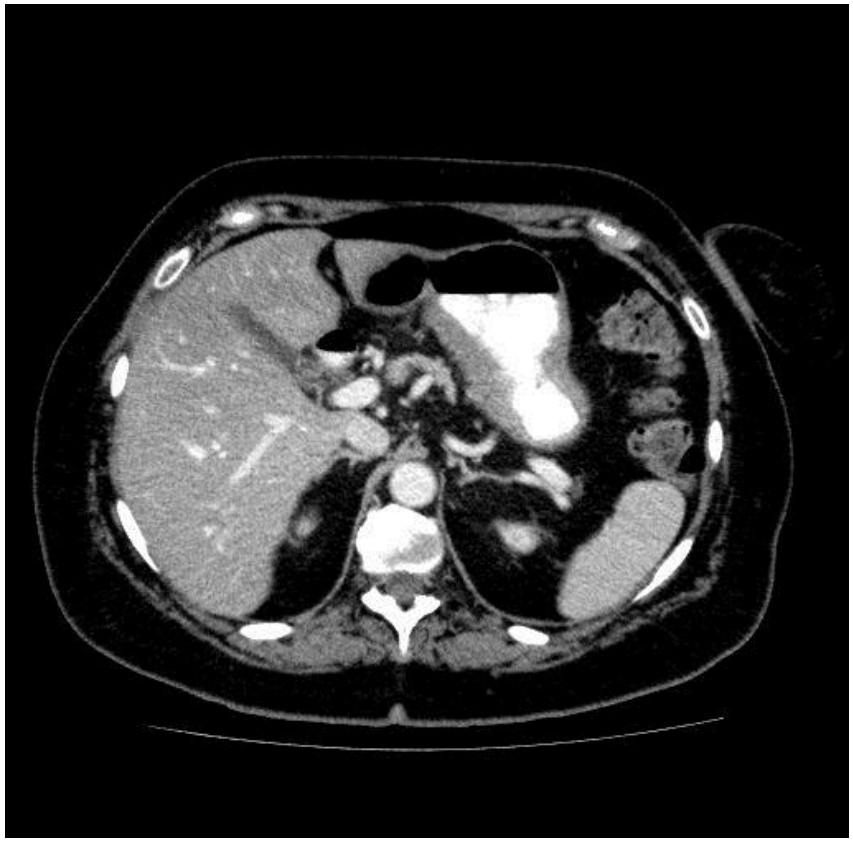
Liver involvement also best detected with PET/CT



Lymphoma in the stomach



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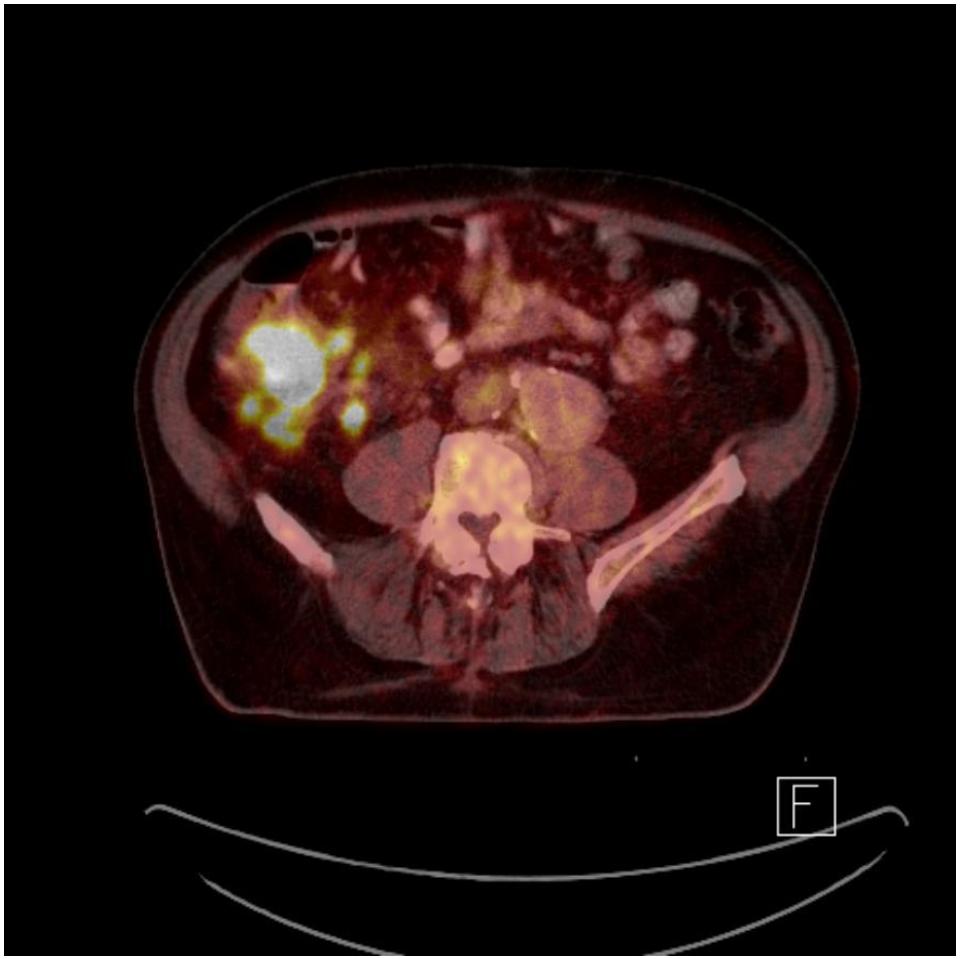
Colon



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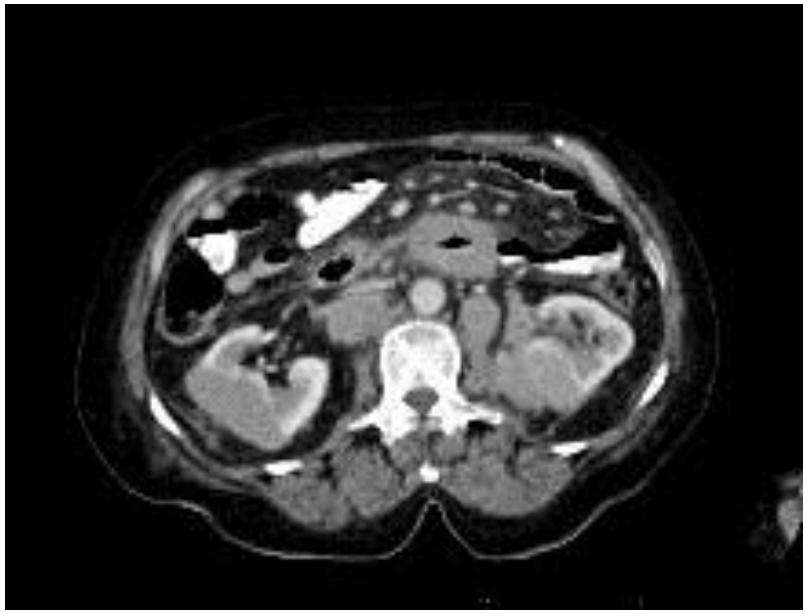
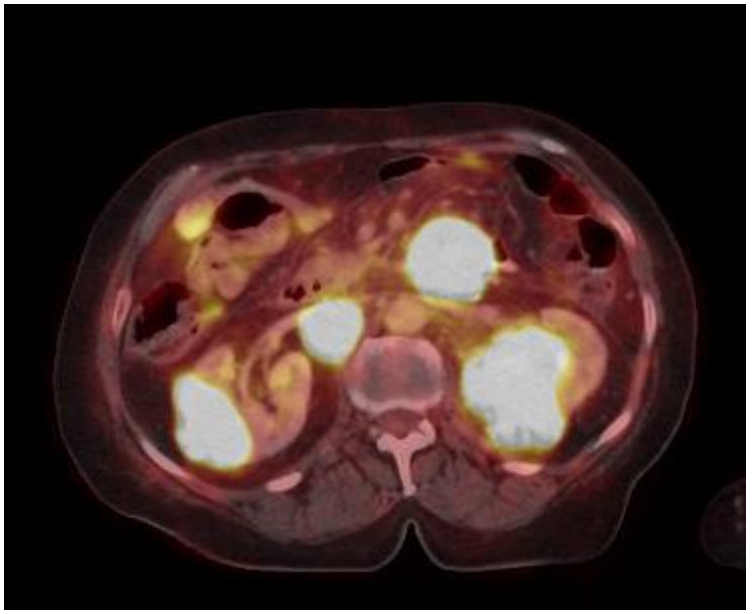
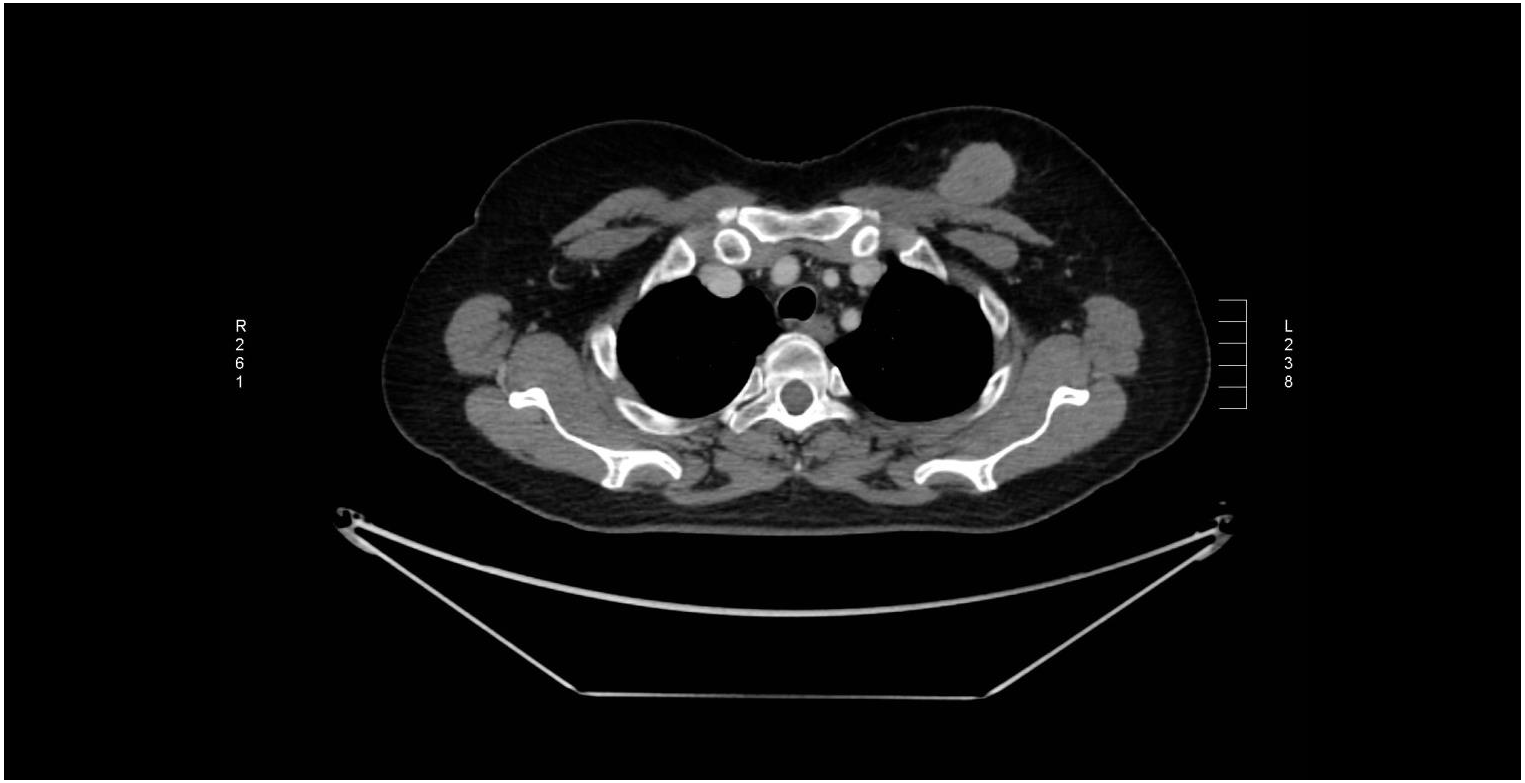
Kidneys





Mamma



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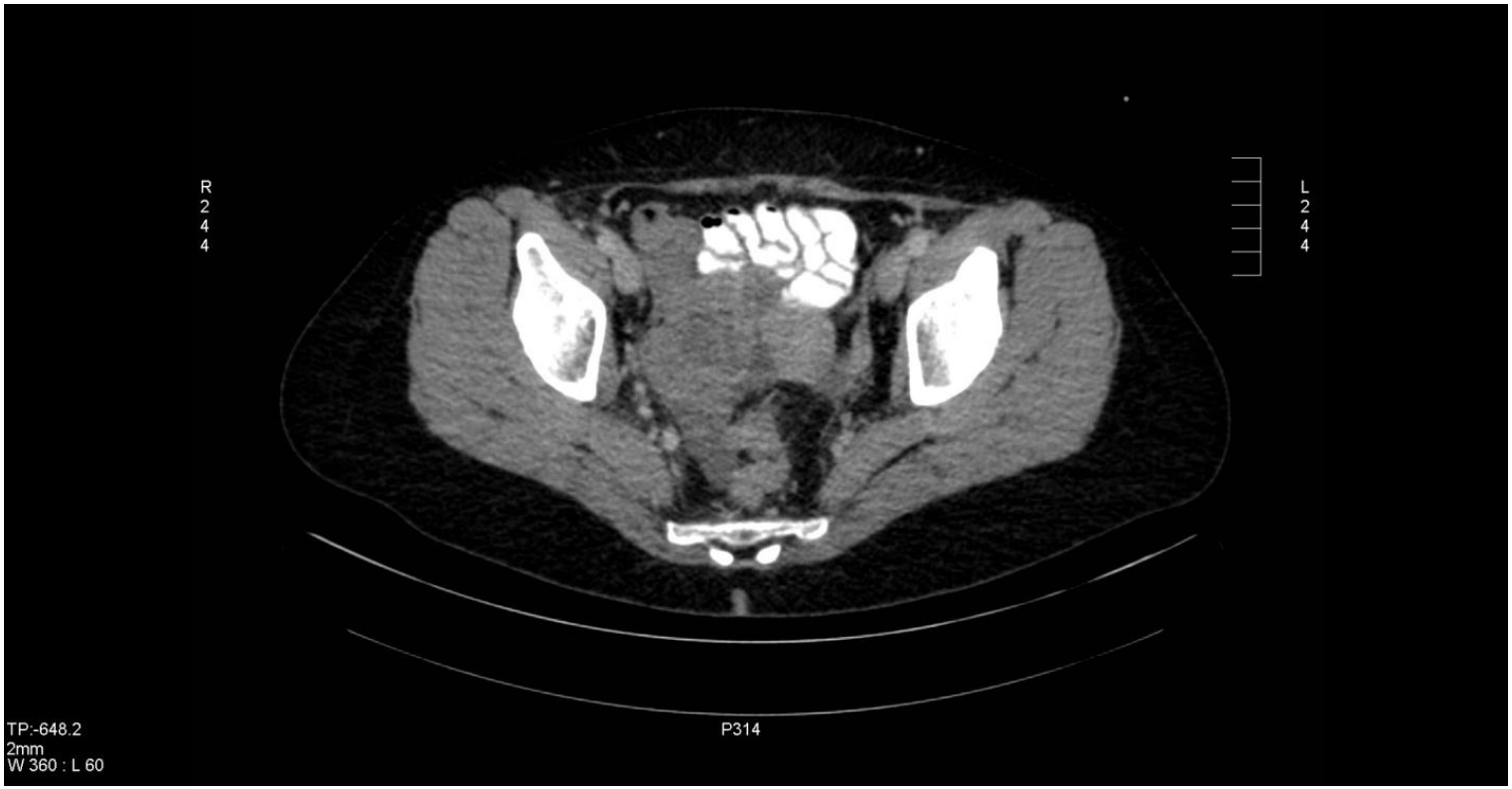
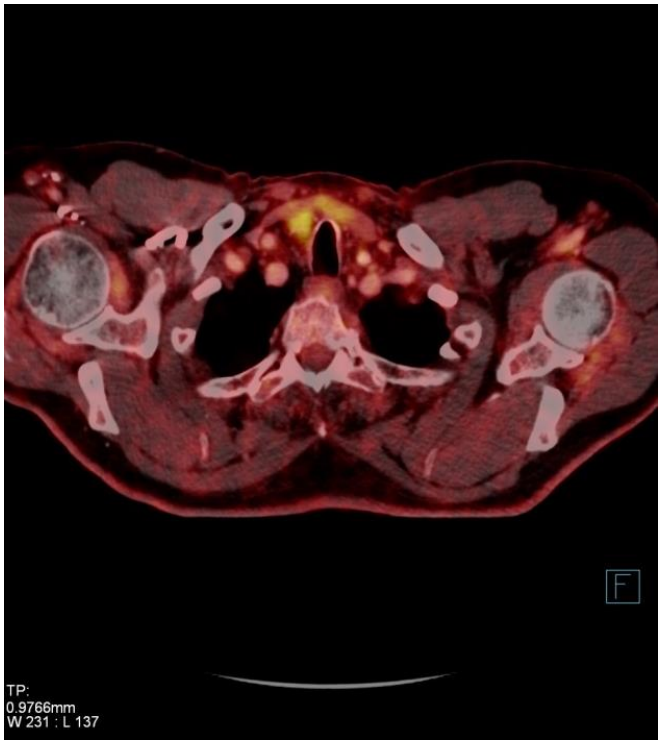
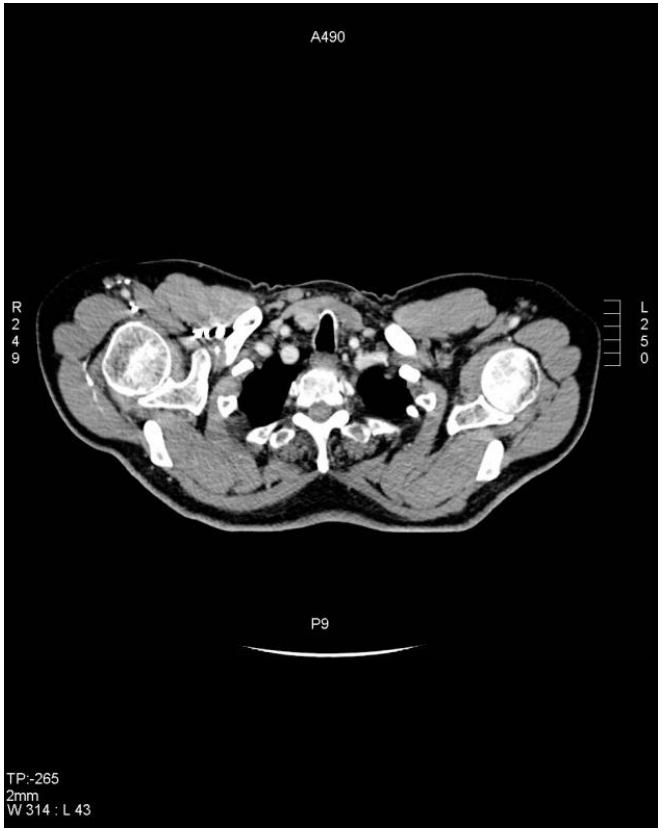
Ovaries



Thyroid gland





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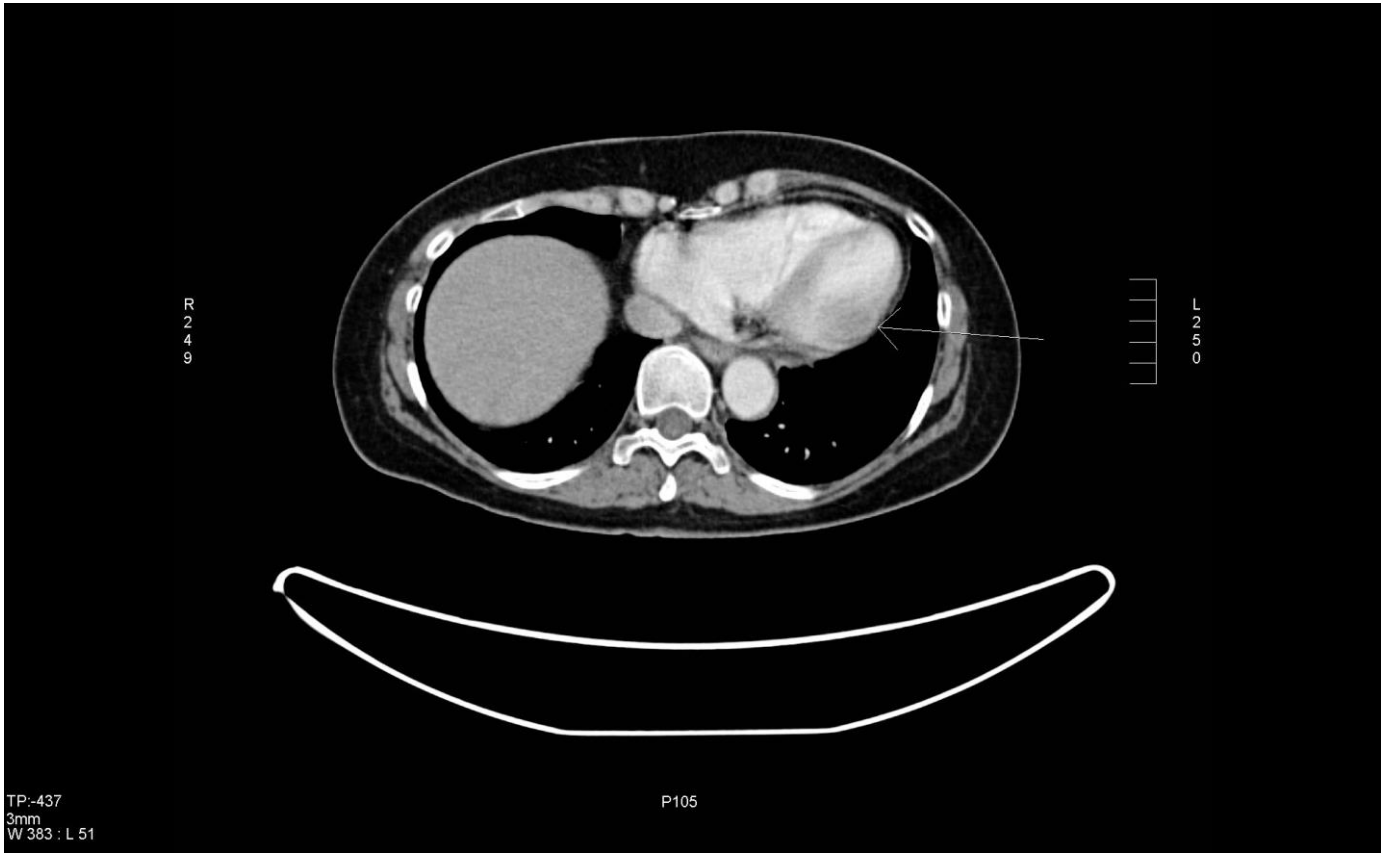
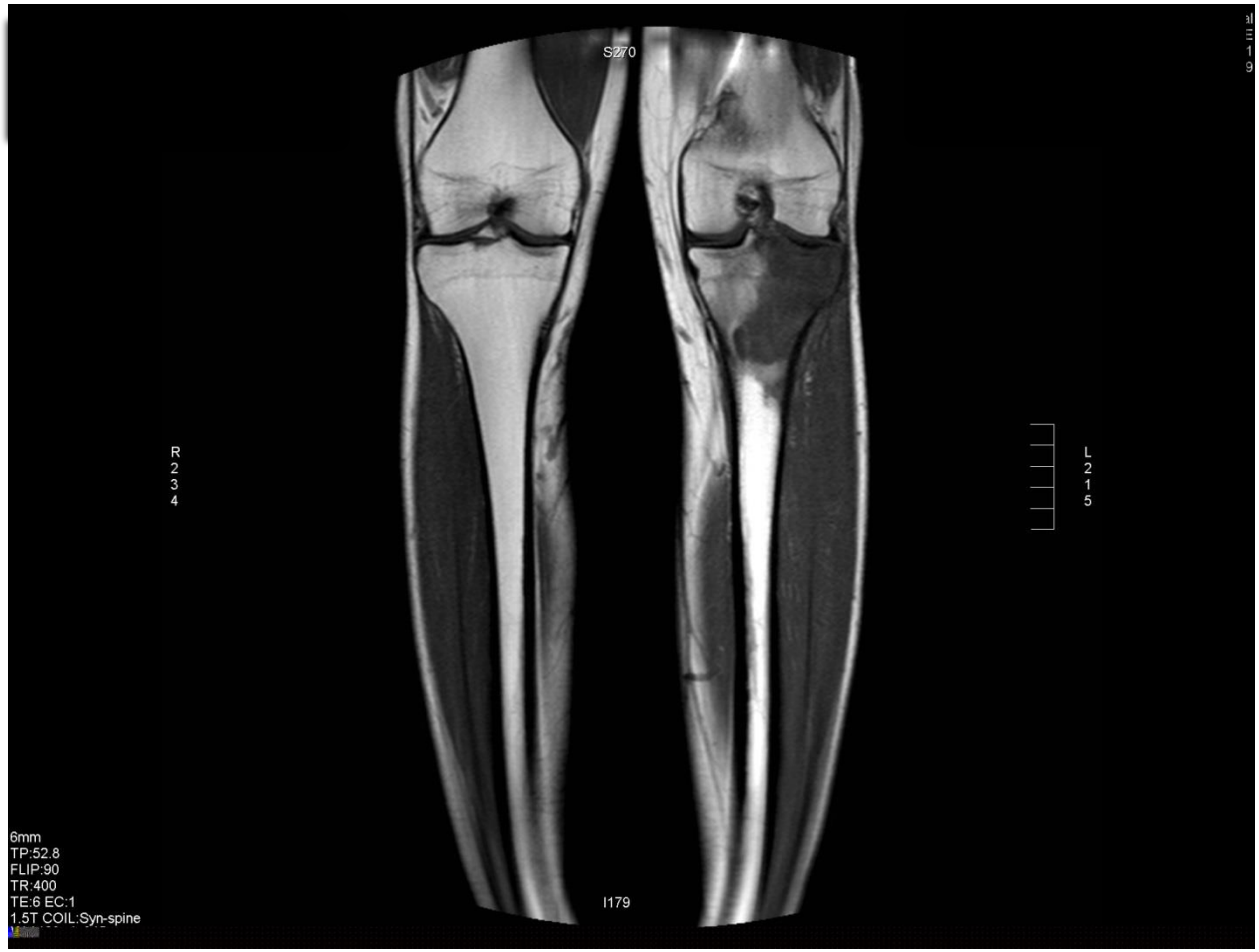
The Heart



The bone


S270
R
2
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2
1
5
6mm
TP:52.8
FLIP:90
TR:400
TE:6 EC:1
1.5T COIL:Syn-spine
I179

Conclusion

- Good images are nescessary for staging as well as treatment planning
- CT and PET/CT are complementary to the clinical examination for treatment planning
- Lymphoma treatment is difficult and collaboration between experts is mandatory

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Contouring Workshop

Anne Kiil Berthelsen
Berthe Aleman
Lena Specht

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Guidelines for radiotherapy of lymphomas, implemented by NCCN and most cooperative groups

Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)

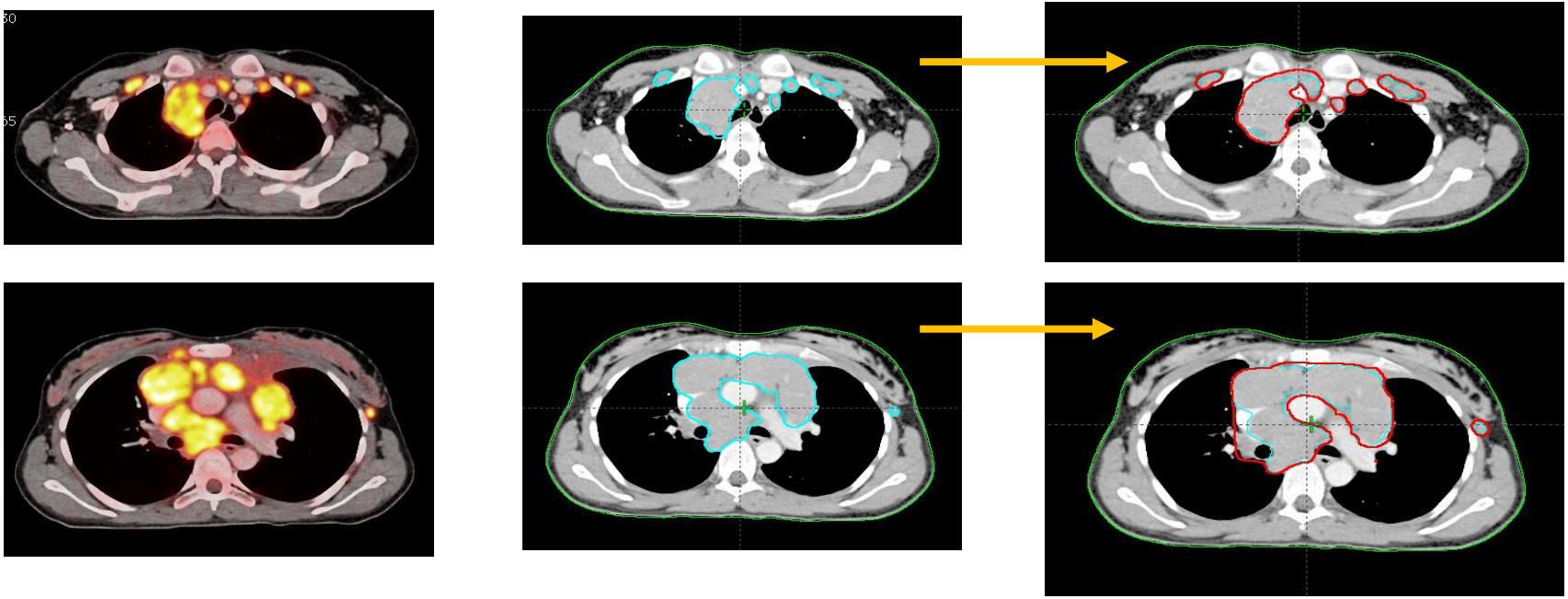
Lena Specht, MD, PhD,* Joachim Yahalom, MD,† Tim Illidge, MD, PhD,‡ Anne Kiil Berthelsen, MD,§ Louis S. Constine, MD,|| Hans Theodor Eich, MD, PhD,¶ Theodore Girinsky, MD,# Richard T. Hoppe, MD,** Peter Mauch, MD,†† N. George Mikhaeel, MD,‡‡ and Andrea Ng, MD, MPH††, on behalf of ILROG

IJROBP 2014; 89: 854-62

Pre-chemo PET/CT scan

PET+ volume

Gross tumour volume GTV



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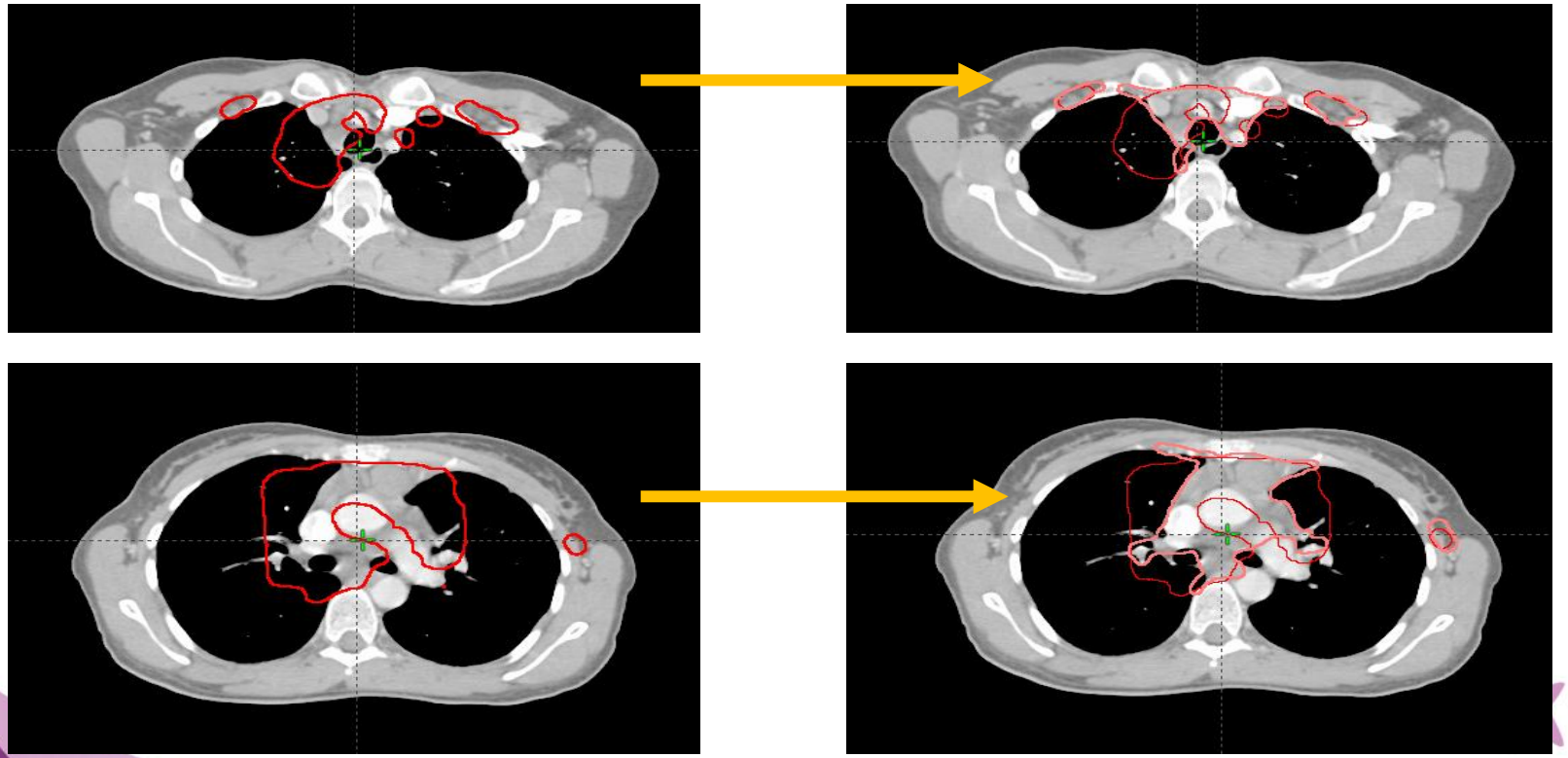
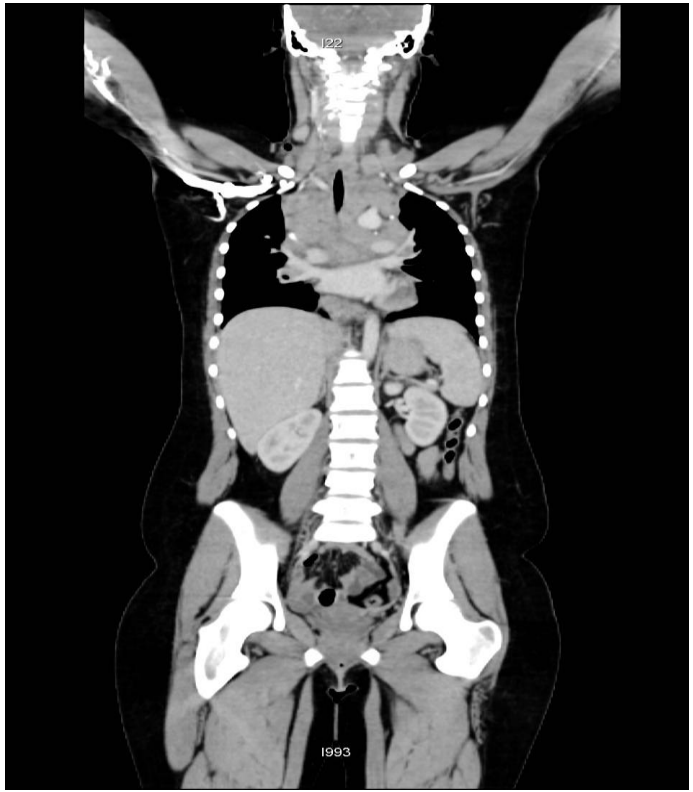
Post-chemo planning CT scan

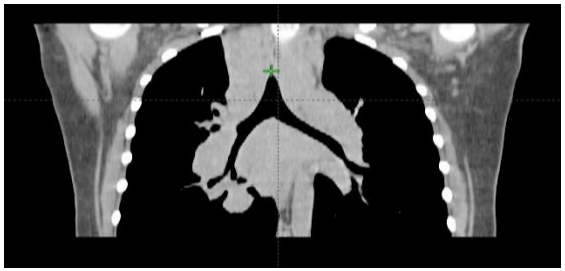
Pre-chemo gross tumour volume

Post-chemo clinical target volume



Breathing adaptation, technique





Pre-chemo whole-body PET/CT scan in free breathing in treatment position on flat table top

+ deep inspiration PET/CT of the chest

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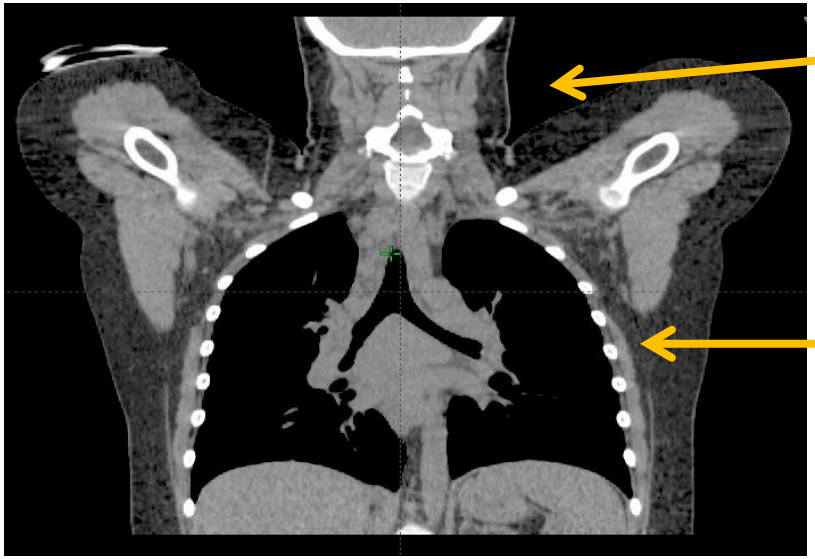
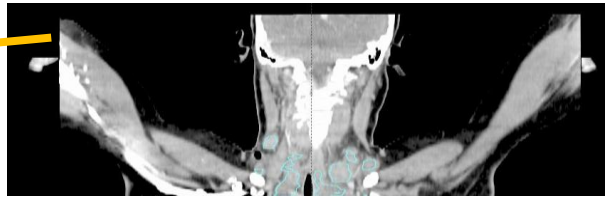
Breathing adaptation, technique

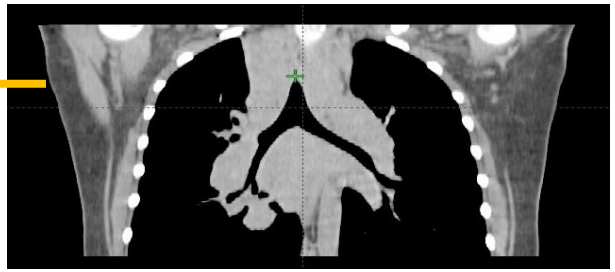
Post-chemo planning CT in DIBH



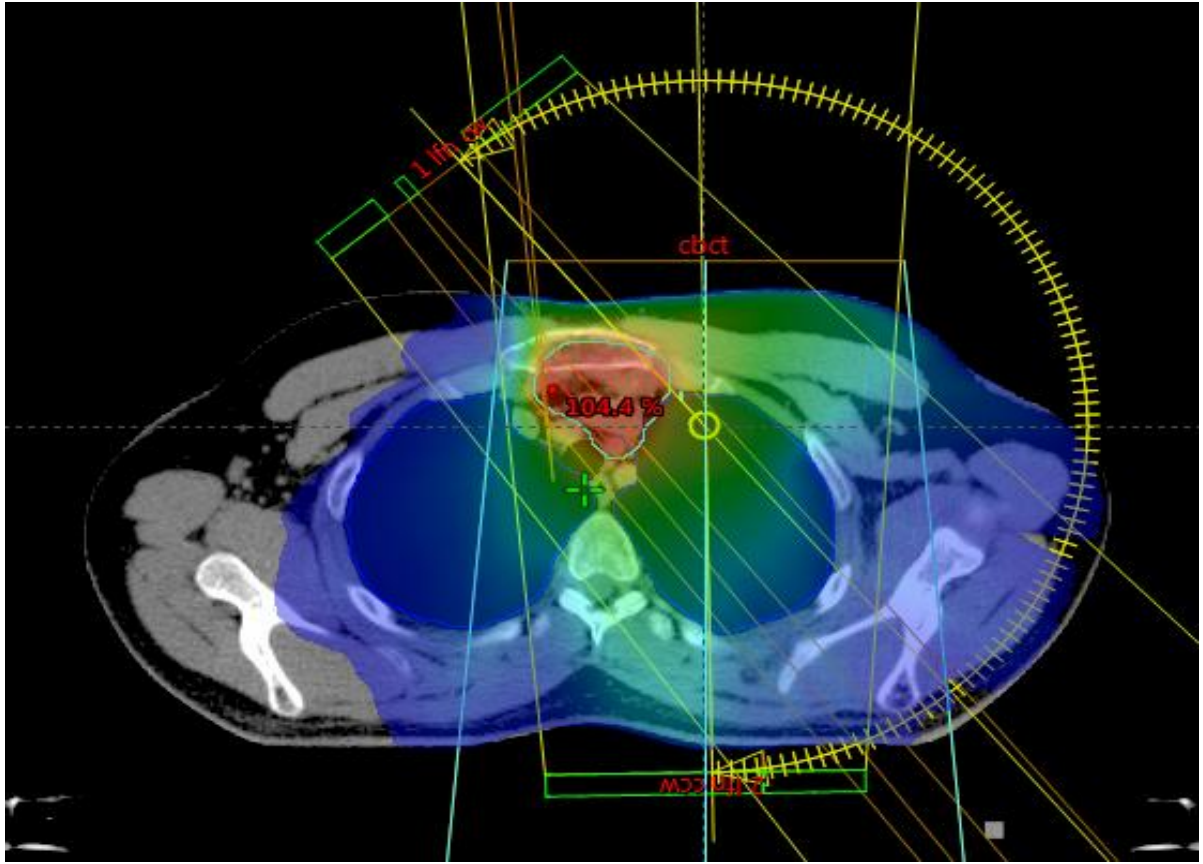
Pre-chemo PET/CT scan

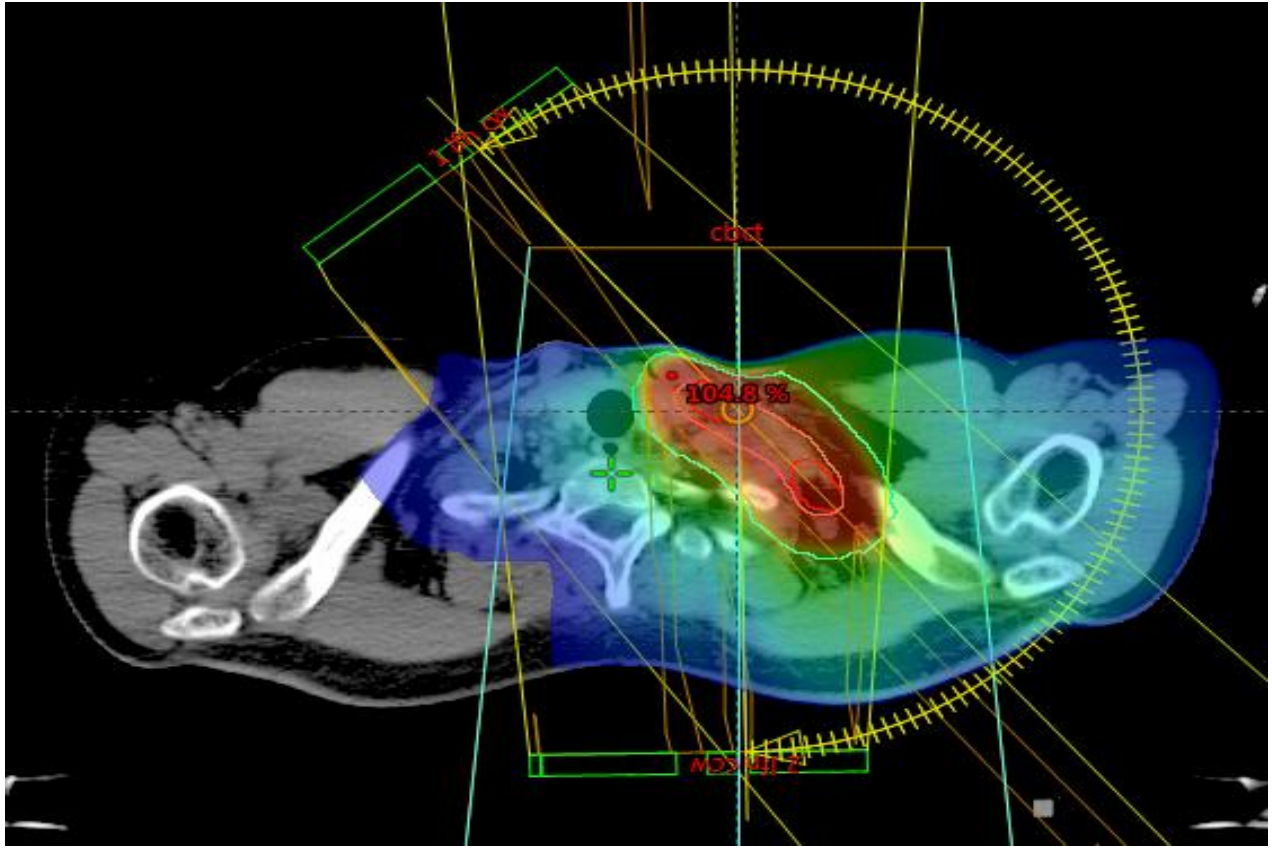


FB



DIBH


cbct
104.4 %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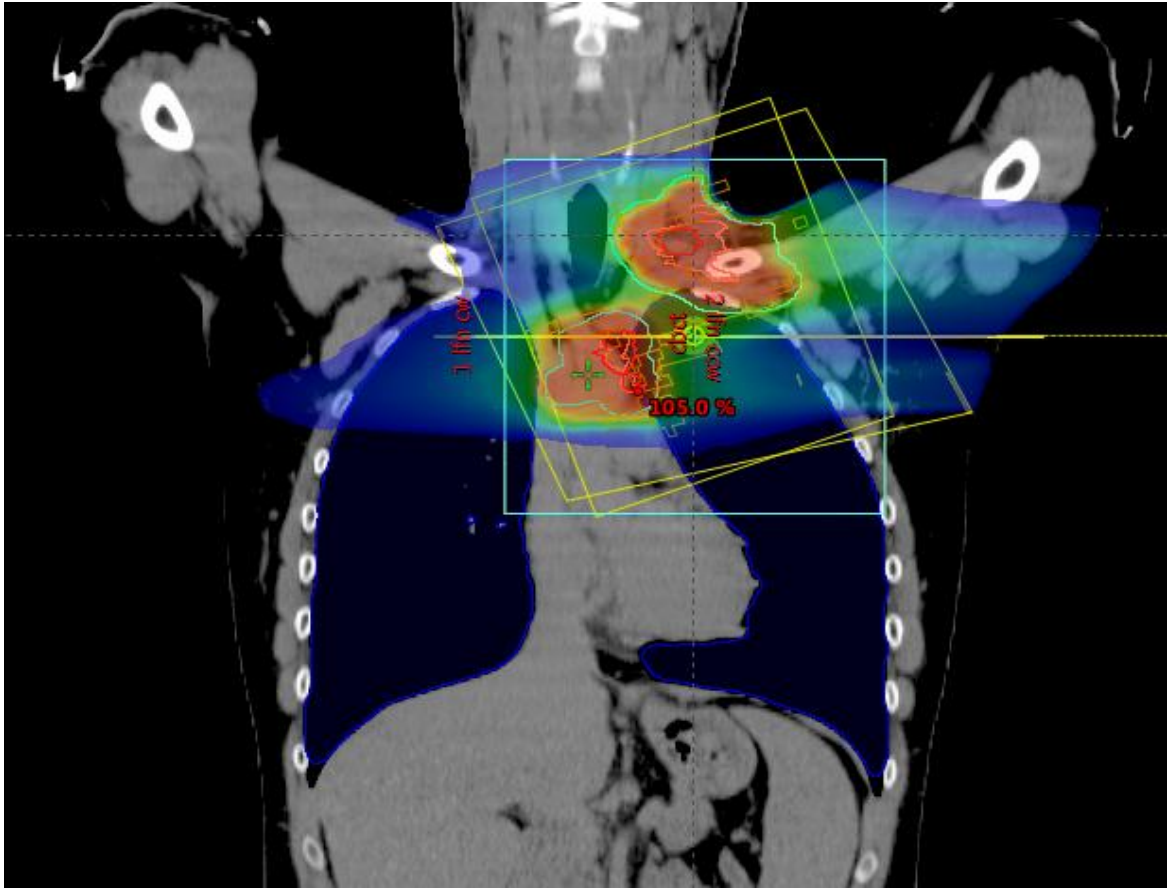
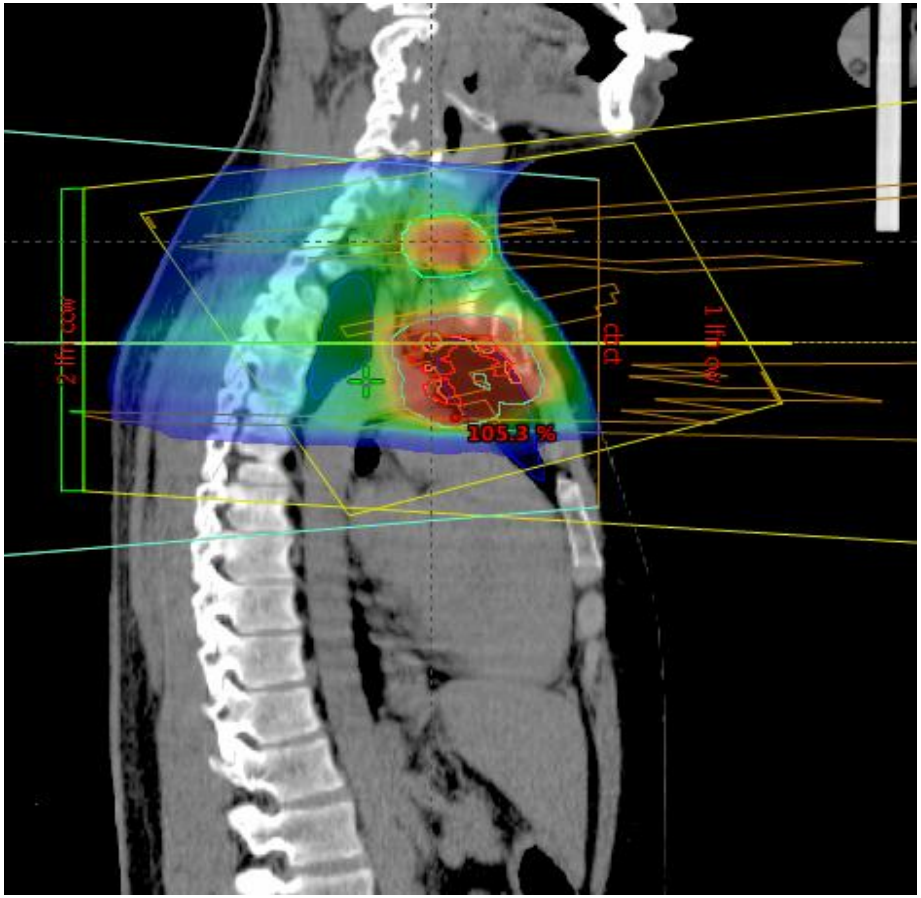
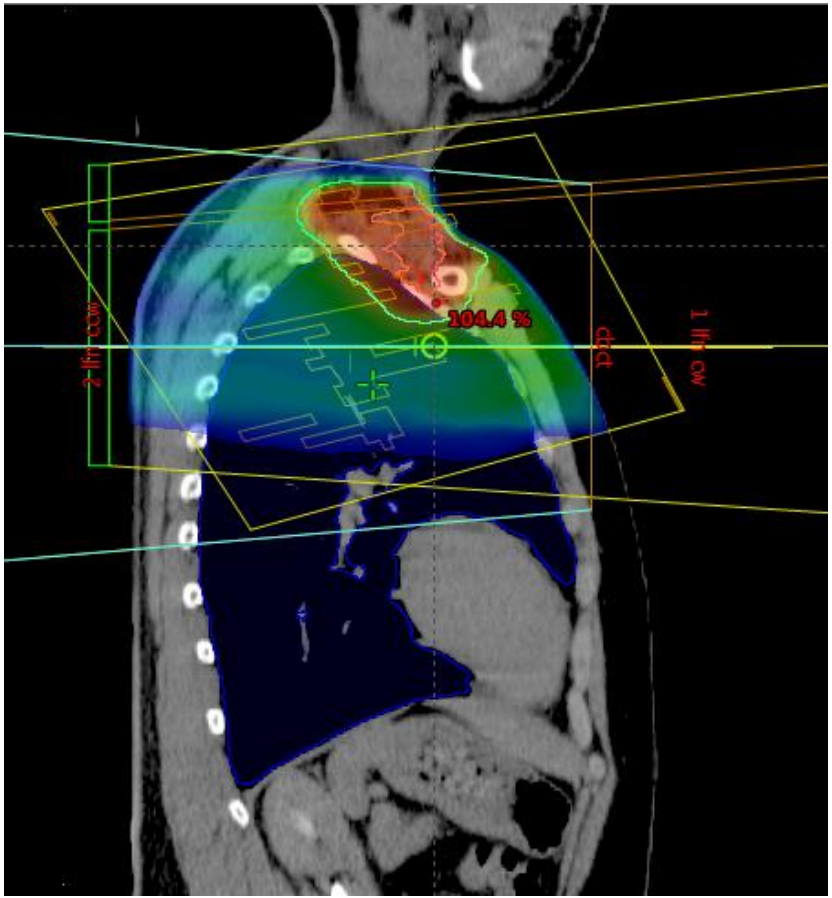
104.8 %


105.0 %


105.3 %


104.4 %
2 Ifrt cow
ctct
1 Ifrt cw

Guidelines

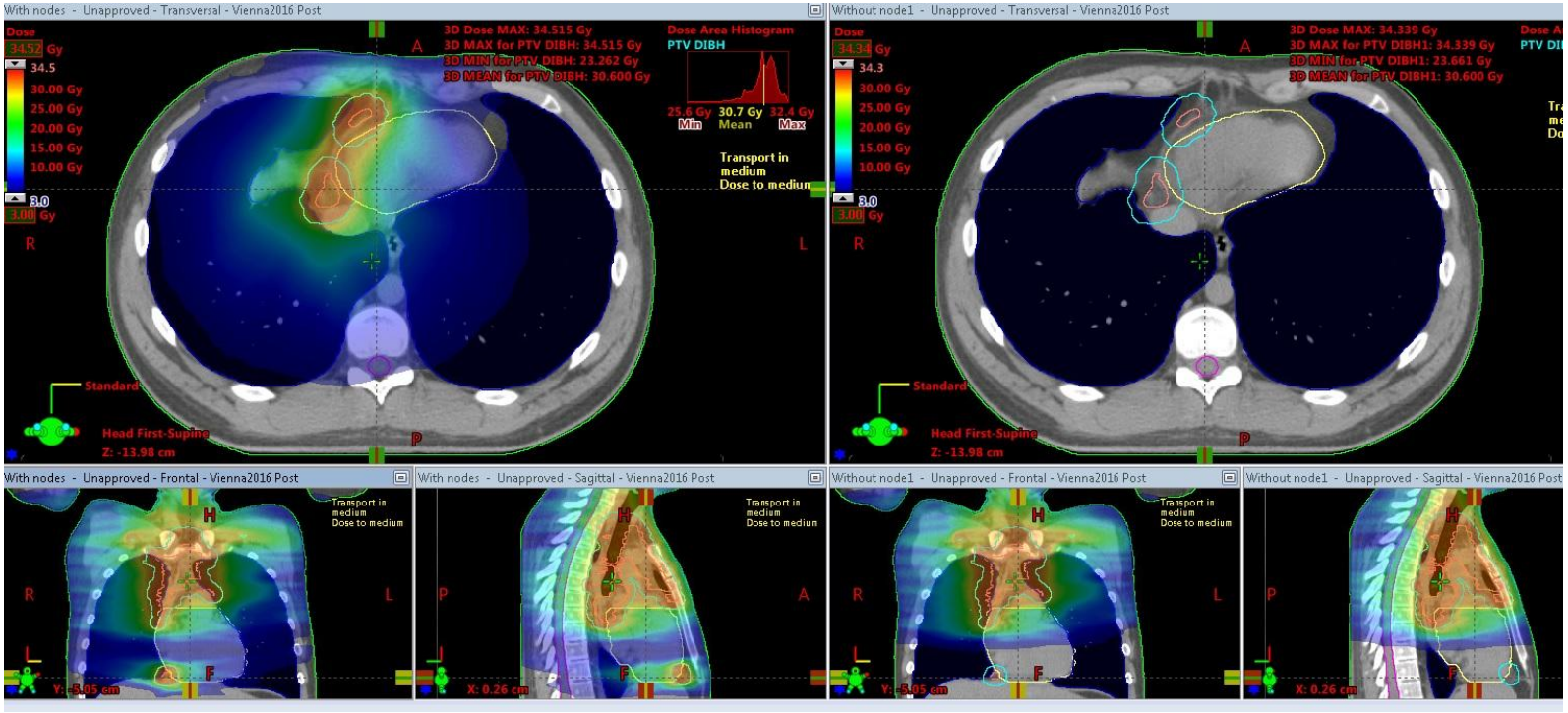
Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

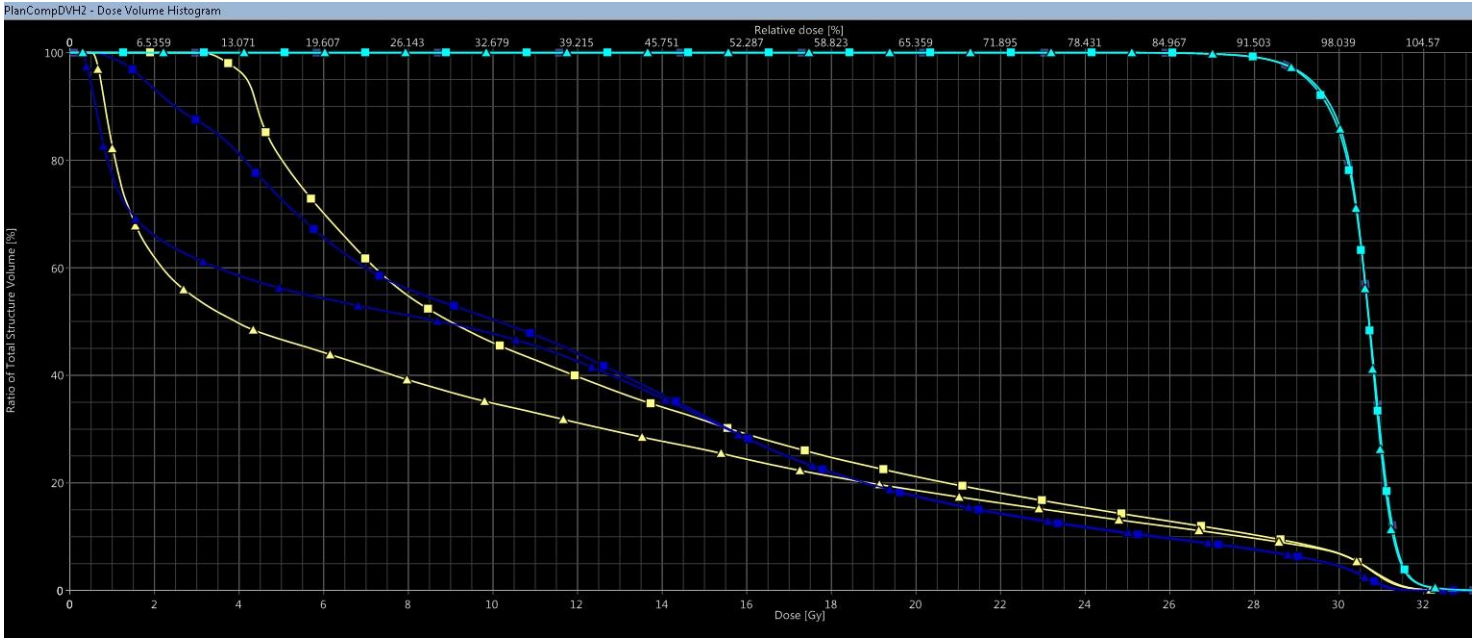
Joachim Yahalom, MD,* Tim Illidge, MD, PhD,† Lena Specht, MD, PhD,‡ Richard T. Hoppe, MD,§ Ye-Xiong Li, MD,|| Richard Tsang, MD,¶ and Andrew Wirth, MD#, on behalf of the International Lymphoma Radiation Oncology Group

IJROBP 2015; 92: 11-31

Discussion after contouring

Should we or should we not include the small nodes in the inferior part of the mediastinum, considering the dose to the heart and the lungs?





	Plan with inferior nodes (squares)	Plan without inferior nodes (triangles)
Mean heart dose	12.6 Gy	9.2 Gy
Mean lung dose	11.8 Gy	10.4 Gy

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WWW.ESTRO.ORG/SCHOOL

Systemic approaches to early and advanced marginal zone lymphoma

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September 2016

The faces of MZL

Third most common NHL (5-17% of total)

	Extra nodal MZL	Splenic MZL	Nodal MZL
% on MZL	70%	20%	10%
Median age	60	65	50-60
Pathogenesis	Hp, C.jejuni, C. psittaci, B burgdoferi	Unknown, HCV	Unknown, HCV
	t(11;18)	3q and gain 12q	Nil typical
Typical clinical presentation	I_E disease	Abnormal blood count, splenomegaly	Adenopathy

Splenic Marginal Zone Lymphoma

- Prominent splenomegaly: variable involvement of lymph nodes, bone marrow, peripheral blood, Splenic hilar lymph nodes and bone marrow are often involved
- lymphoma cells may be found in the peripheral blood as villous lymphocytes <1%
- Association with hepatitis C infection has been reported, although the prevalence ranges from 36% to less than 10%
- Abdominal discomfort due to splenomegaly
- Modest cytopenias that are primarily due to splenic sequestration (less marrow infiltration).
- Typically diagnose on BM, may need splenectomy
- Intergruppo Italian Linformi 309 patients, 5-year cause-specific survival 76%.

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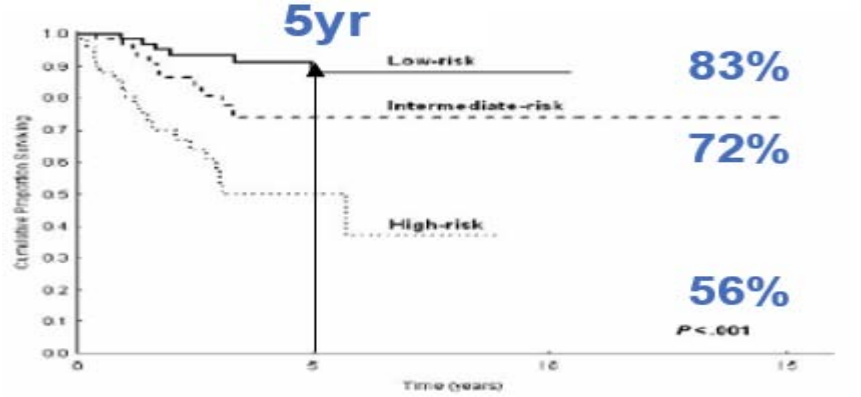
SMZL : LDH Hb=12 Albumin

SMZL score : 0 factor / 1 F / ≥ 2 F = IIL score

	OS p
Hemoglobin 12g/dl	0.05
LDH	0.008
Albumin	<0.001

Arcaini L. et al. 2006



CSS of 233 patients with splenic MZL

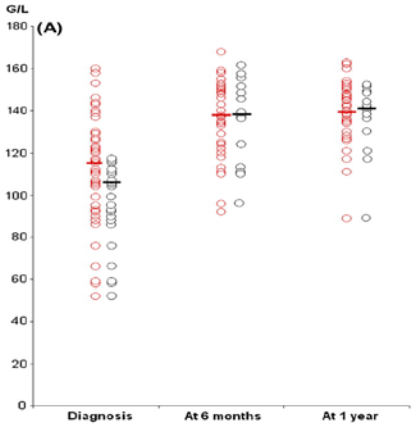
Many asymptomatic at diagnosis…watch and wait

If associated with HCV, then treat. May induce remission

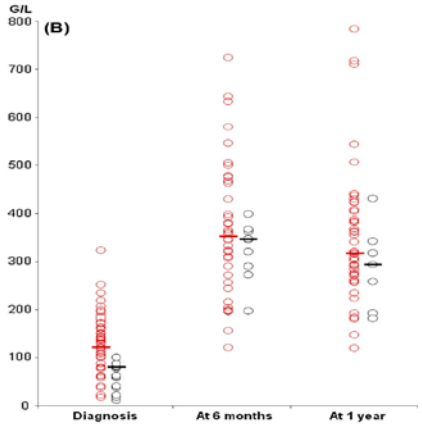
More common HCV neg. Initiate therapy when nodal disease bulky, patient symptomatic or cytopenias

…..Splenectomy

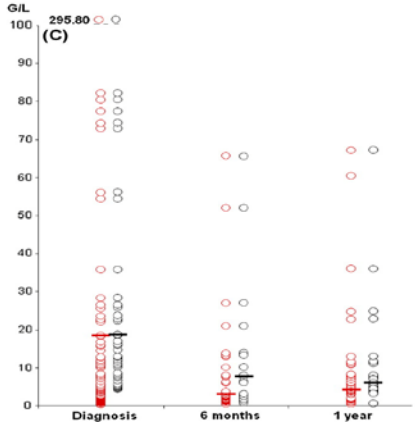
Haemoglobin



Platelets



Lymphocytes



- Clearly improves haematological parameters
- Symptomatic improvement
- Associated morbidity

Lenglet et al 2014

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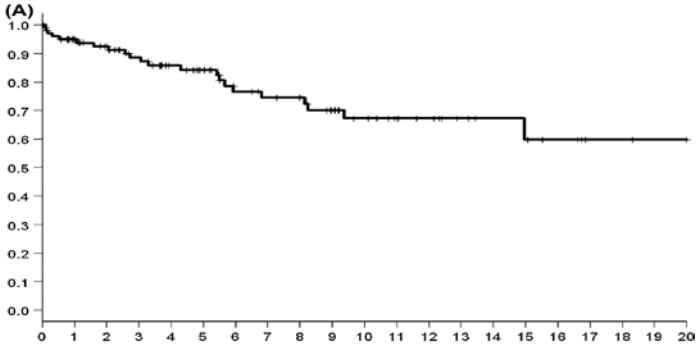
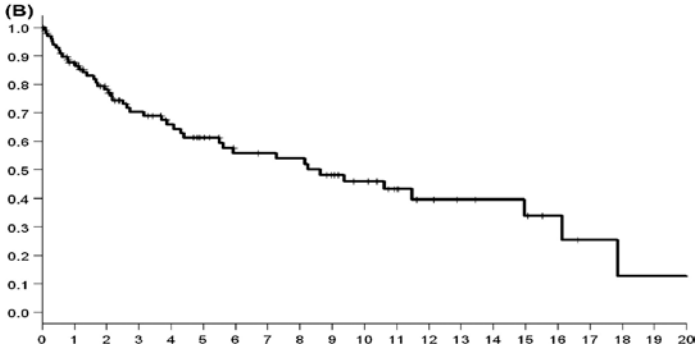
OS



PFS



	PFS	OS
5 year	61%	84%
10 year	46%	67%

Lenglet et al 2014

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Rituximab

Response	No. of Patients (%)			Total (n = 43)
	Rituximab (n = 26)†	Chemoimmunotherapy (n = 6)‡	Chemotherapy (n = 11)	
CR	8 (31)	1 (17)	2 (18)	11 (26)
Cru	3 (12)	1 (17)	0	4 (9)
PR	12 (46)	3 (50)	4 (36)	19 (44)
CR, CRu, and PR	23 (88)	5 (83)	6 (55)	34 (79)

Tsimberidou et al. 2006

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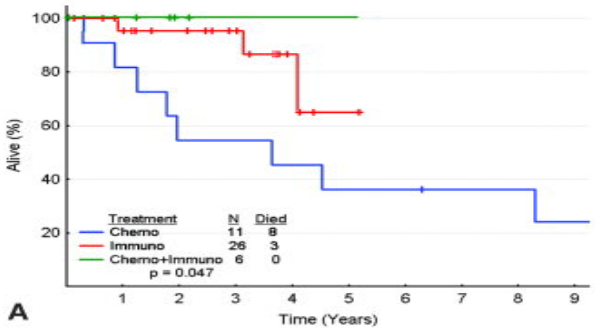
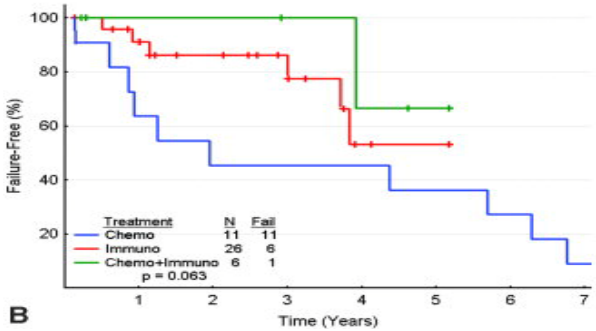
Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone

OS



FFS



Cancer
Volume 107, Issue 1, pages 125-135, 12 MAY 2006 DOI: 10.1002/cncr.21931
http://onlinelibrary.wiley.com/doi/10.1002/cncr.21931/full#fig3

Authors	Schedule	n	Status of disease	Response Rate	CR /CRu	PR	PFS (At n years)	OS (At n years)
Rituximab alone								
Tsimberidou et al. 2004	R once/W x 4 or 8	26	1rst line	88%	43%	46%	86% (3y)	95% (3y)
Kalpadakis et al. 2007	R once/W x 6	16	1rst line	100%	79%	11%	92% (2.1y)	100% (3y)
Bennett et al. 2005	R once/W x 4	14	1rst line	78%	57%	21%	60% (6y)	80% (6y)
Kalpadakis et al. 2013	R once/W x 6	85	1rst line	95%	71%	24%	92% (5y)	73% (5y)
Rituximab and Chemotherapy								
Tsimberidou et al. 2004	R-FMD or RFC	6	1rst line	83%	34%	50%	100% (3)	100% (3)
Arcaini et al. 2004	R-CVP	3	1rst line	100%	-	-	100% (1.3)	100% (1.3)
Cervetti et al. 2004	2-Cda	50	1rst line or relapsed	63%	62%	-	83% (2)	NA

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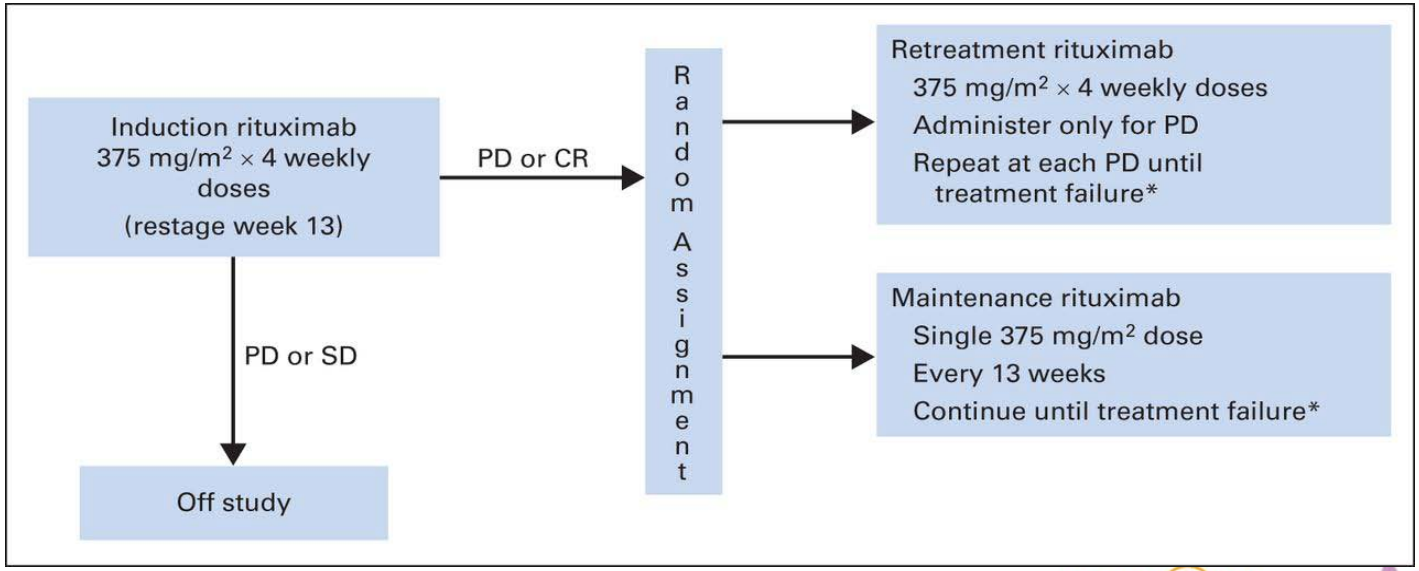
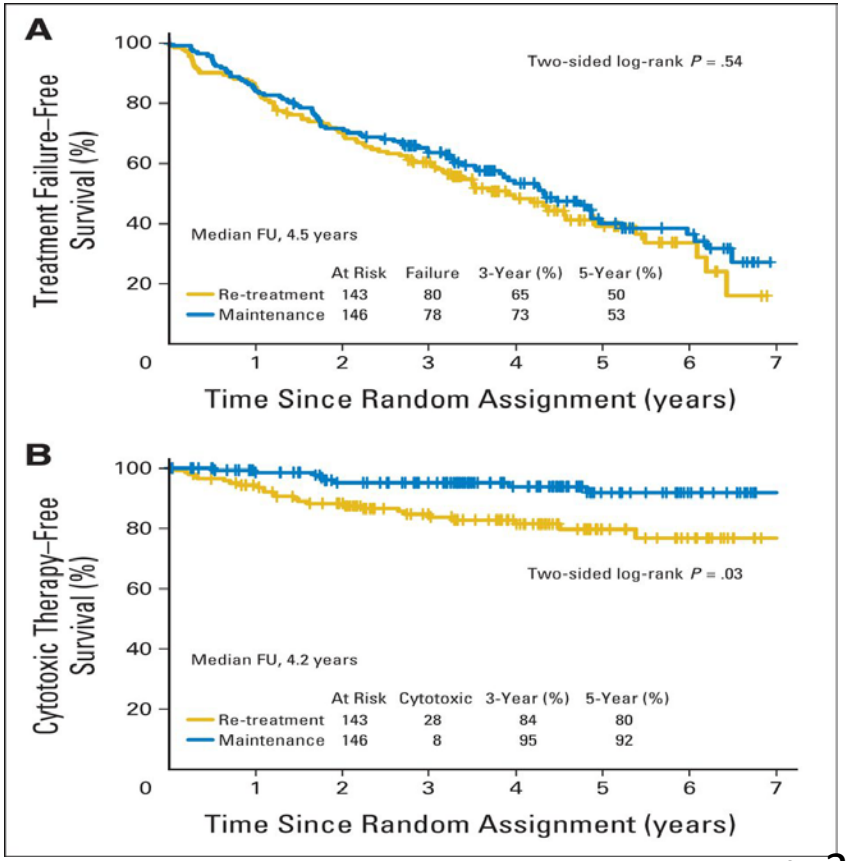
RESORT trial

Rituximab Extended Schedule or Re-Treatment Trial

N=289. Previously untreated low burden



Brad S. Kahl et al. JCO **2014;32:3096-3102**



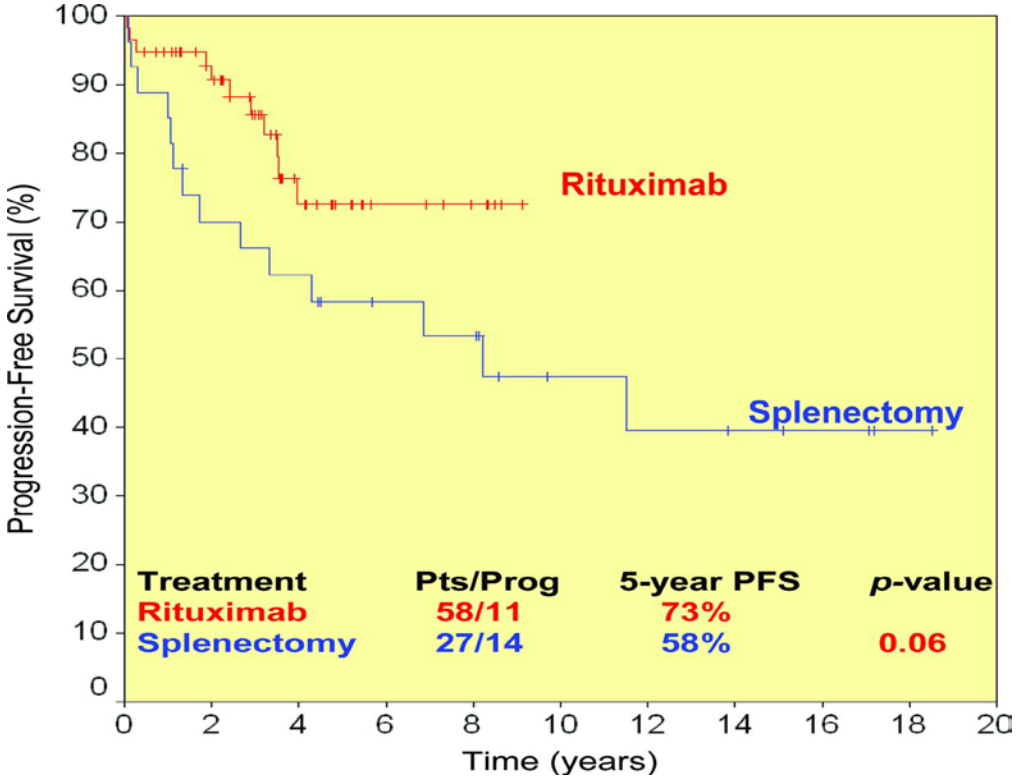
Time to treatment failure

Time to first cytotoxic therapy

n=298

Brad S. Kahl et al. JCO 2014;32:3096-3102

Progression-free survival (PFS) probability in rituximab-treated (red line) and splenectomized patients (blue line) after 5 years.



Christina Kalpadakis et al. The Oncologist 2013;18:190-197

So…first line rituximab…

Maintenance rituximab can be considered, but not standard of care

Splenectomy for poor responders and relapse

Patient specific discussion

Nodal MZL

- <2% NHL median age 60
- Upto 30% have Hep C + serology (variable)
- Generalised asymptomatic LN;
- BM in 30-60%..exclude dissemination of ENMZL
- Few therapeutic trials – same principles as other ‘indolent’ lymphomas..watch and wait
- 60-80% alive at 5 years

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BR vs. R-CHOP as First Line Treatment in Patients with Indolent and Mantle Cell Lymphomas (MCL): Updated Results from the StiL NHL1 Study

Eligible patients:

- CD20-postiive FL, WM, MZL, SLL, MCL (elderly)
- No previous treatment
- Stage III or IV

(n = 549)

RANDOMISE

Bendamustine-Rituximab (BR)

Bendamustine 90 mg/m² days 1-2
Rituximab 375 mg/m² day 1

CHOP-Rituximab (R-CHOP)

Cyclophosphamide 750 mg/m² day 1
Doxorubicin 50 mg/m² day 1
Vincristine 1.4 mg/m² day 1
Prednisone 100 mg/days days 1-5
Rituximab 375 mg/m² day 1

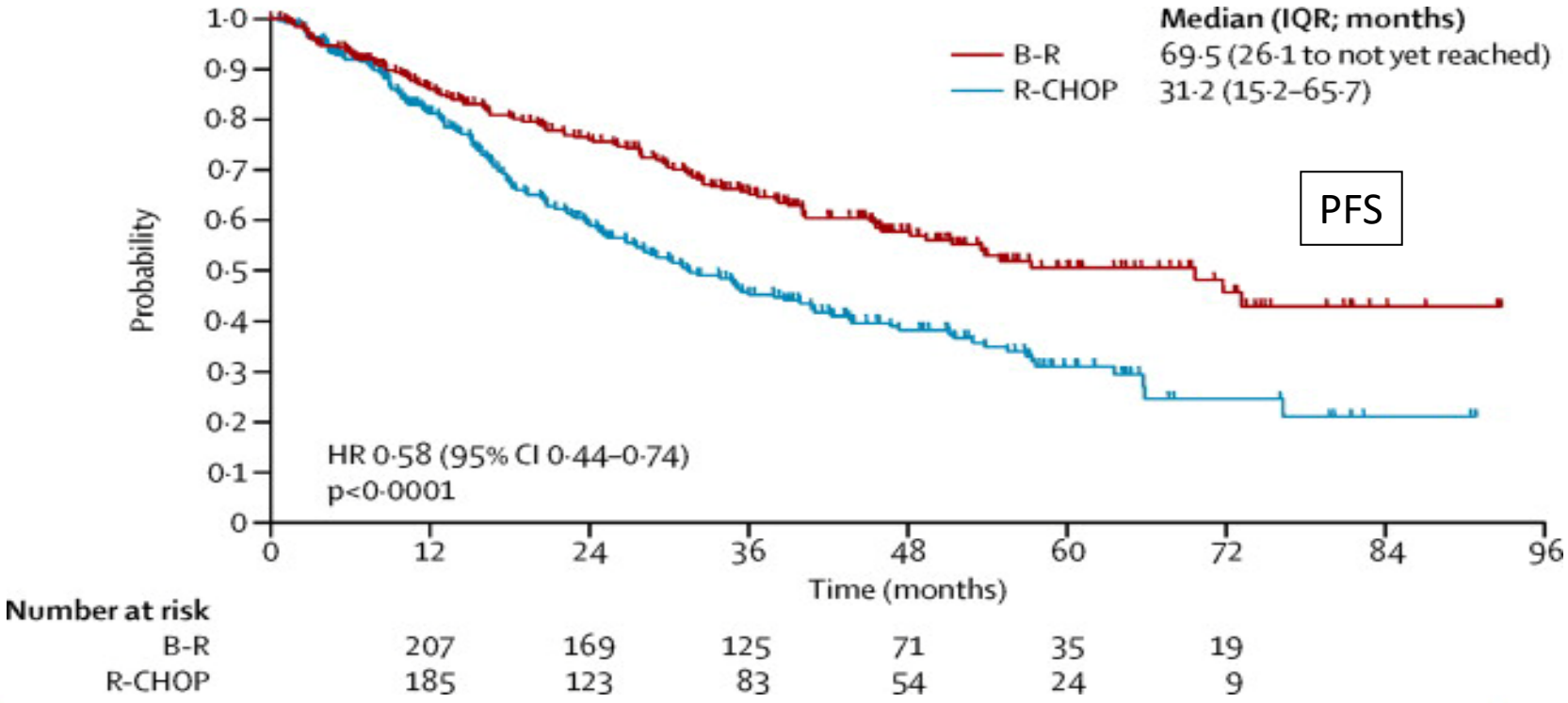
Primary objective

- **To prove the non-inferiority of BR vs. R-CHOP defined as a decrease of < 10% in progression-free survival (PFS) after 3 years**

Secondary objectives

- **Time to next treatment (TTNT), event-free survival (EFS), overall survival (OS)**
- **Acute and late toxicities, infectious complications**
- **Stem cell mobilization capacity in younger patients**

StiL Study



No difference in OS

Rummel et al Lancet April 2013

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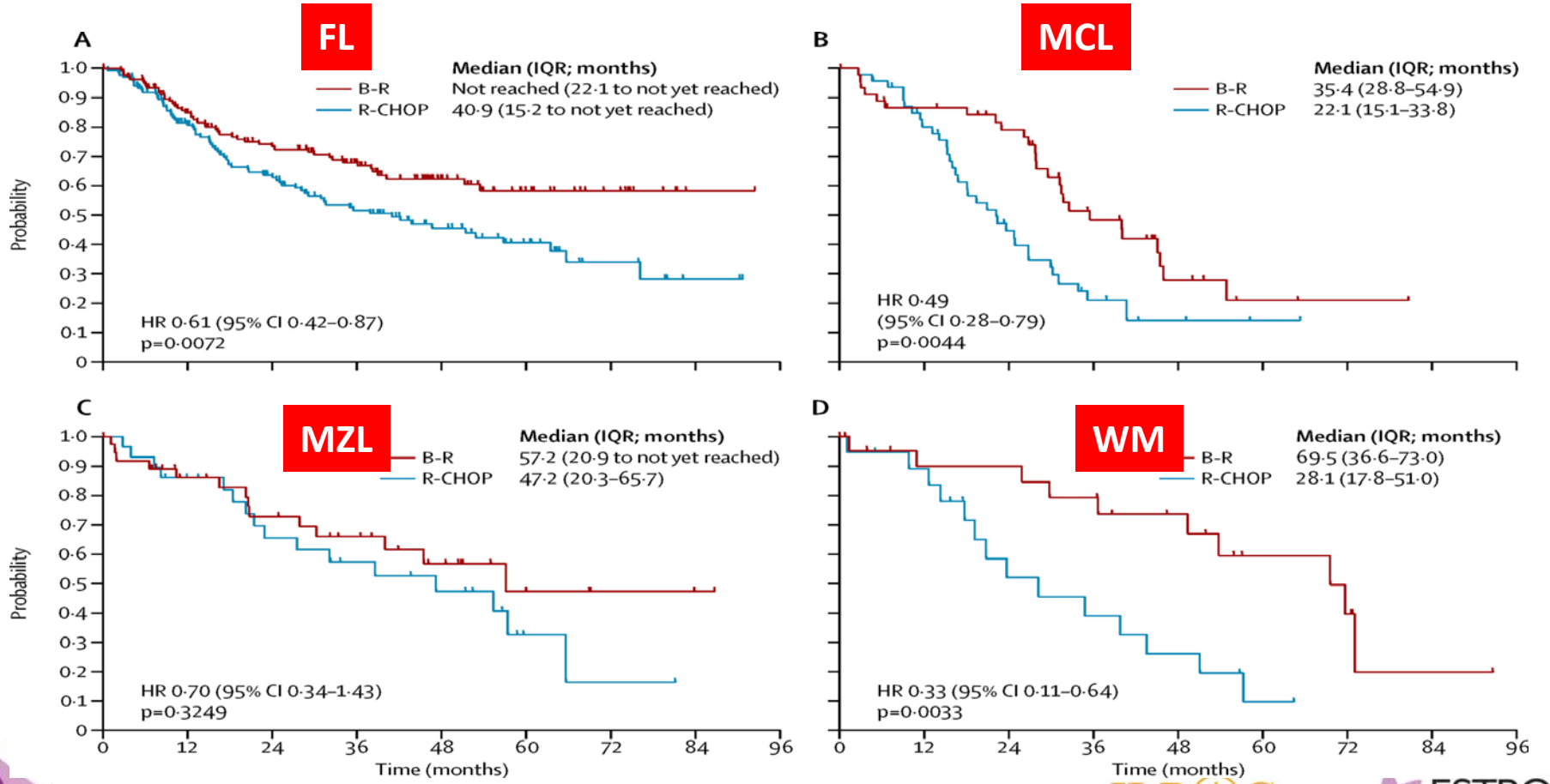
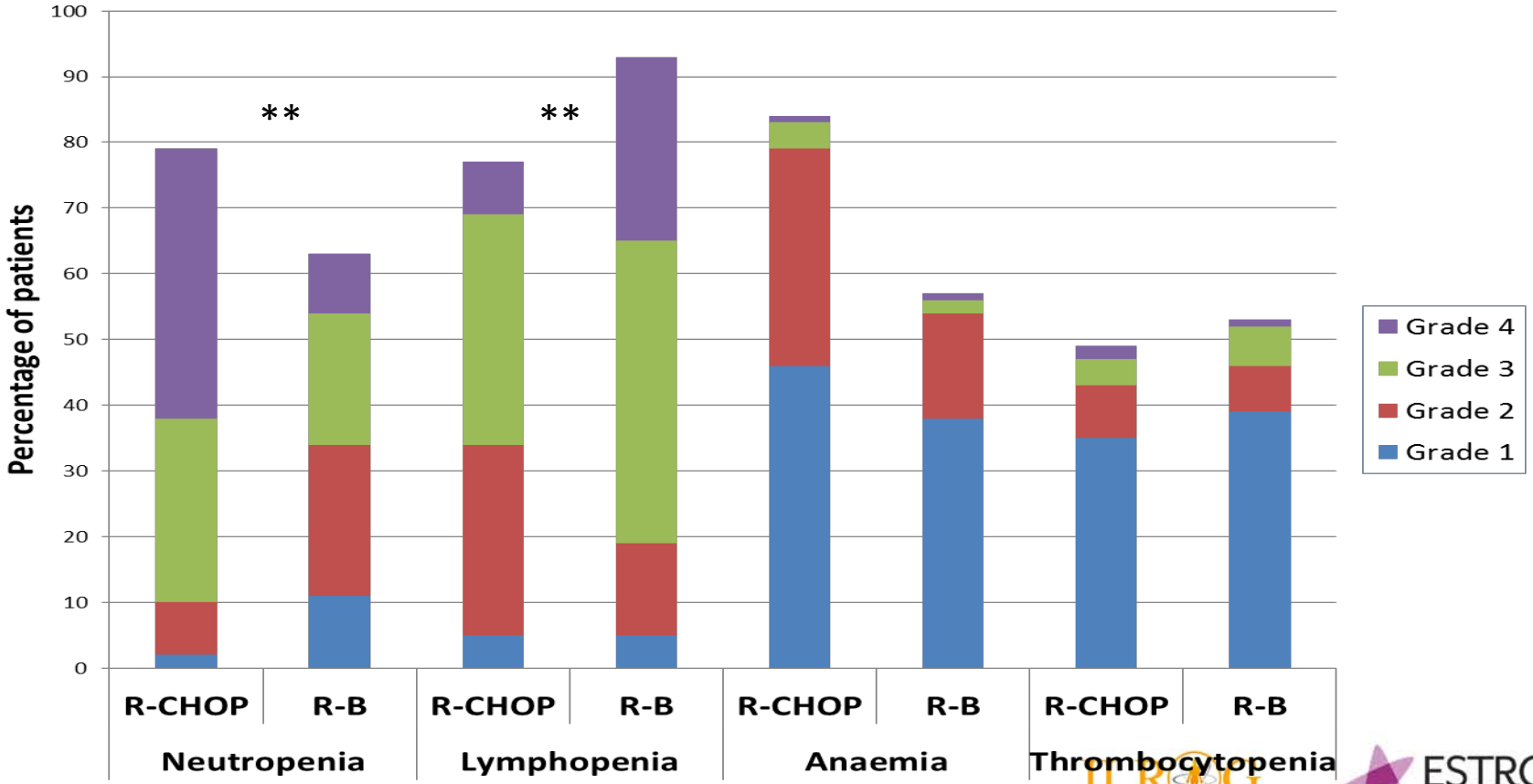


Progression Free Survival

Rummel et al. Lancet 2013

Haemtological toxicity



** P<0.0001 for grade 3/4

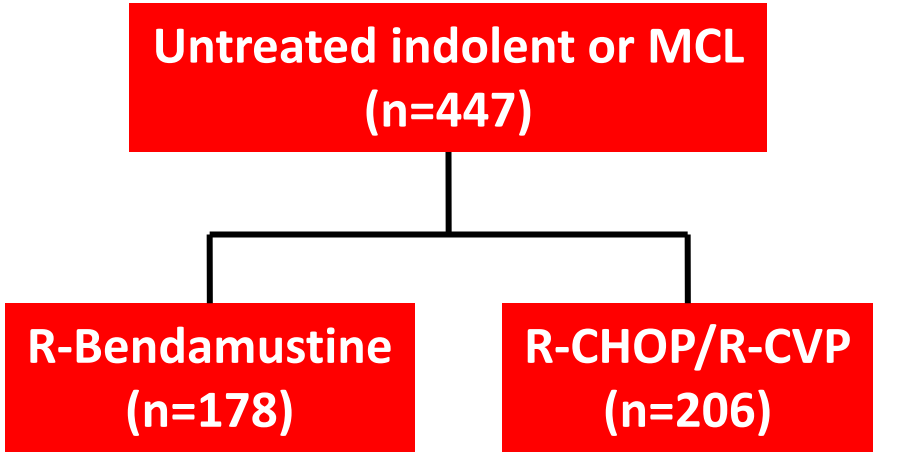
Rummel et al Lancet April 2013

Non-haematological toxicity

	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

Rummel et al Lancet April 2013

The BRIGHT STUDY

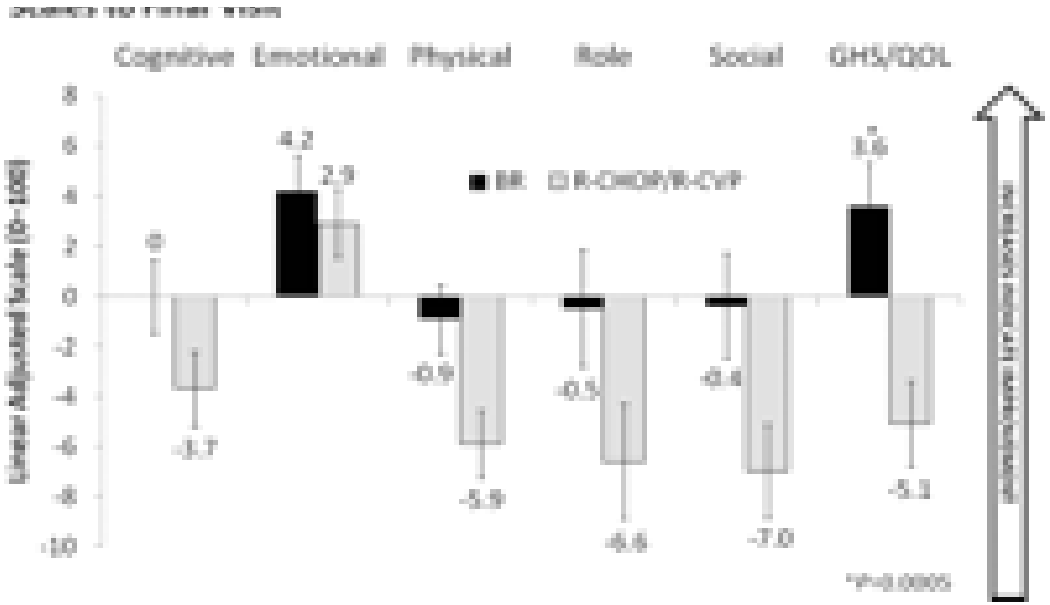


Powered for non-inferiority in CR rate

CR rate	R-B	R-CHOP/ R-CVP	Ratio	*P* (s
Evaluable, IRC	31%	25%	1.25 (0.93–1.73)	0.0225
Randomized, IRC NHL	27%	23%	1.16 (0.81–1.65)	0.1289
Randomized IRC MCL	51%	24%	1.95 (1.01–3.77)	0.0180

Flinn et al ASH 2012

Quality of life….



BR significantly improved GHS/QOL, compared with R-CHOP/R-CVP

BR provided improved patient QOL scores for most aspects of functioning and symptoms, as measured by the QLQ-C30

Burke et al ASH 2012

Extranodal MZL

- Can arise in virtually every tissue
- Chronic antigen stimulation
- Impressive results with H. pylori eradication in gastric…reasonable impressive outcomes in occular adnexal and HCV management
- Systemic therapies traditionally reserved for local treatment failure or advanced stage

Involved organ	Targeted pathogen	Antibiotic regimen	Type of study	Patients (n)	Overall lymphoma remission rate
Stomach	H. pylori	Mostly proton pump inhibitor plus clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10–14 days	>30 studies either retrospective or prospective	>1,400	~75%
Ocular adnexa	C. psittaci	Doxycycline, 100 mg twice a day × 21 days	2 prospective, 4 retrospective, 1 case report	120	48%
Skin	B. burgdorferi	Ceftriaxone, 2 g/day ×14 days (in most cases)	Case reports	5	40%
Various (also including nodal and splenic MZL)	HCV	IFN plus ribavirin	7 retrospective series and several case reports	>110	~75%

Zucca et al Clin Cancer Res 2014

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Chemotherapy: IELSG 19

Response	Chl	R-Chl	R
ORR	110 (85%)	124 (95%)	104 (79%)
CR*	**80 (62%)**	**104 (80%)**	**73 (55%)**
PR	30 (23%)	20 (15%)	31 (23%)
SD	11 (8%)	1 (<1%)	15 (11%)
PD	7 (5%)	4 (3%)	9 (7%)
NA	2 (1.5%)	2 (1.5%)	4 (3%)

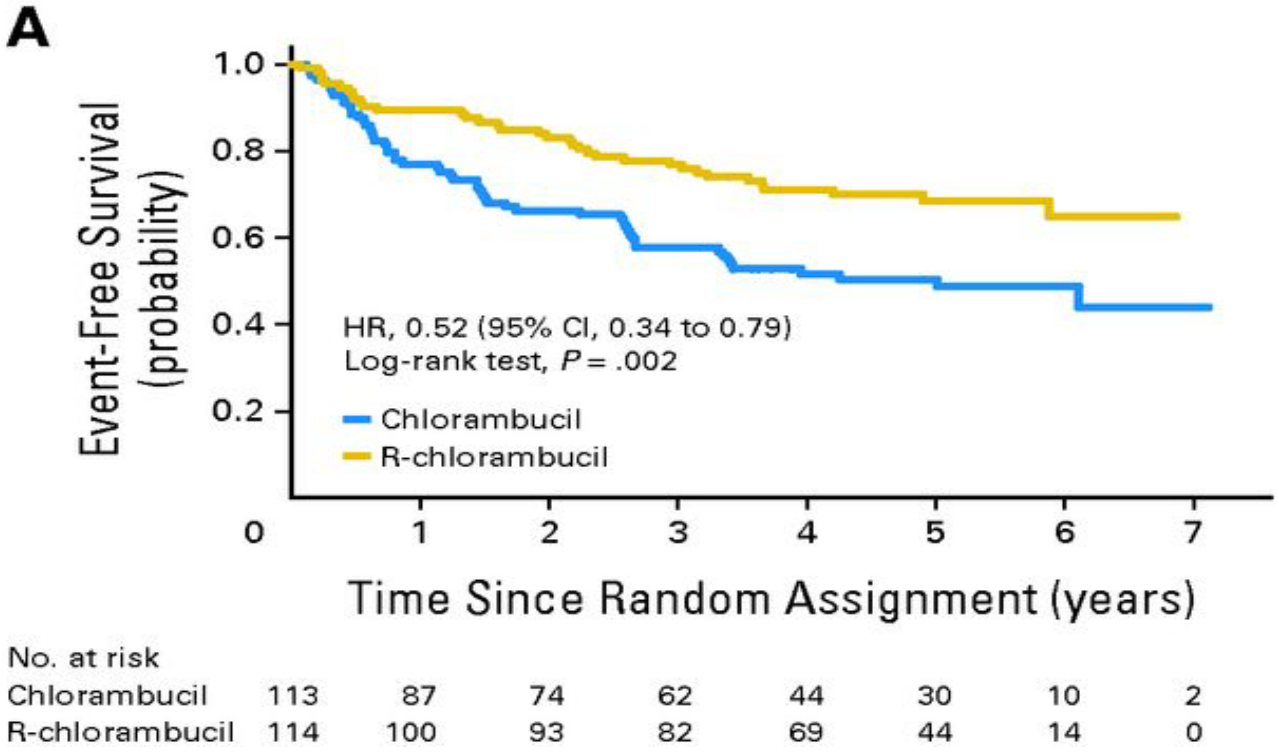
* R-Chl *vs.* Chl, P=0.001 R-Chl *vs.* R, P<0.001; Chl *vs.* R, P= 0.372

Emanuele Zucca et al. JCO 2013;31:565-572

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

Event-free survival

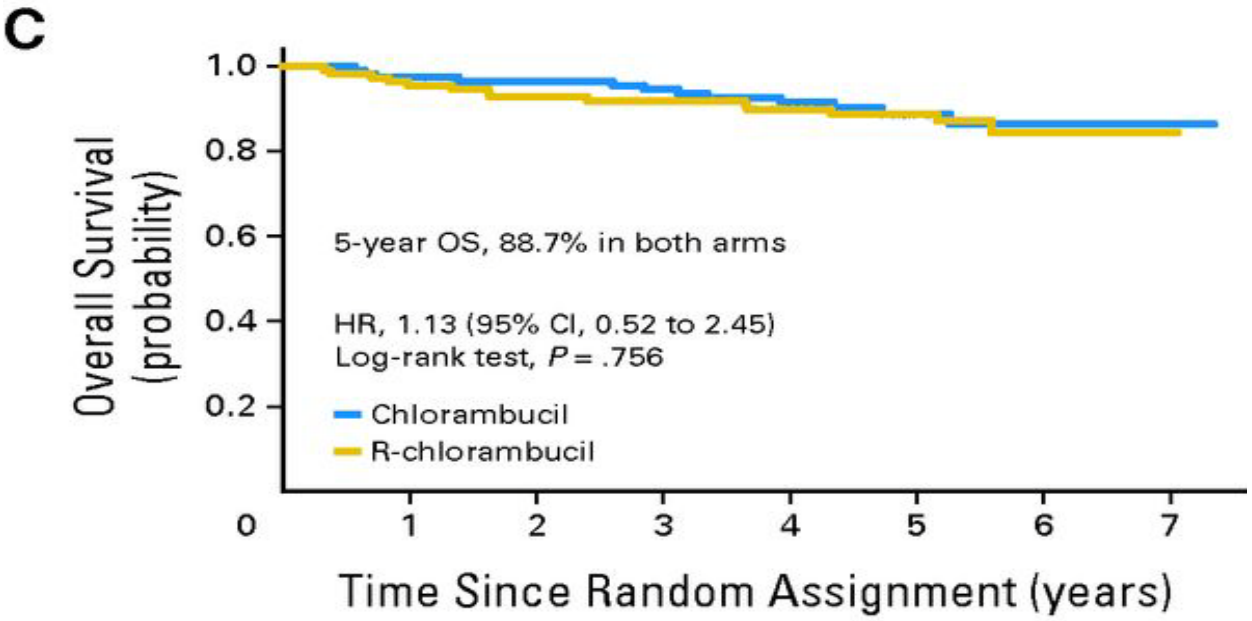


Emanuele Zucca et al. JCO 2013;31:565-572

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

Overall survival.



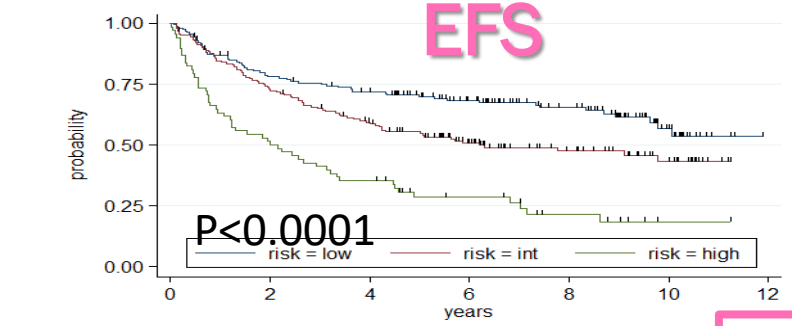
Emanuele Zucca et al. JCO 2013;31:565-572

MALT lymphoma : LDH, Age, Stage

MALT score : 0 factor / 1 F / ≥ 2

0 factor, n=167
1 factor, n= 164
2-3 factors, n=68

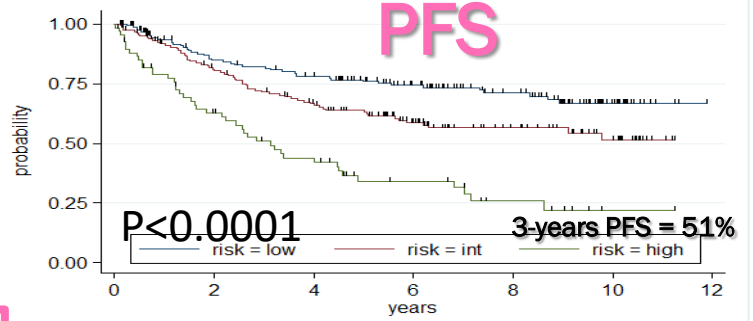
EFS



Number at risk

risk = low	167	126	112	84	57	20	
risk = int	164	119	92	59	34	16	
risk = high	68	35	24	14	7	1	

PFS

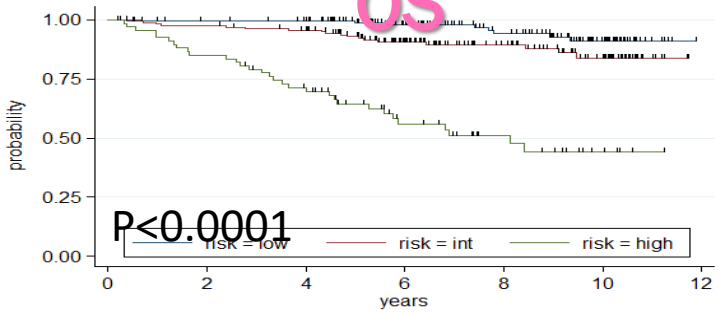


Number at risk

risk = low	167	126	112	84	57	20	0
risk = int	164	120	93	60	35	17	0
risk = high	68	38	25	14	7	1	0

LDH >N
AGE >70
STAGE>2

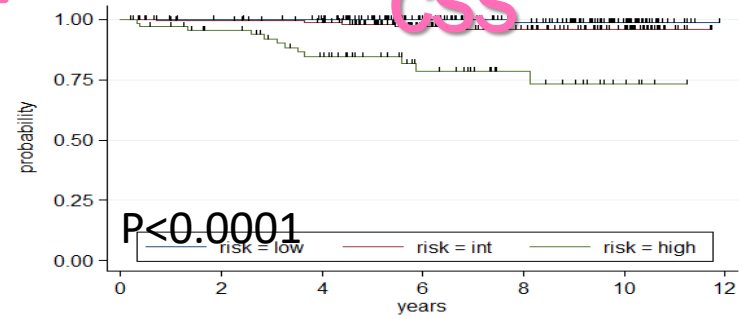
OS



Number at risk

risk = low	167	159	154	113	78	31	0
risk = int	164	159	150	96	61	31	0
risk = high	68	57	45	25	15	6	0

CSS

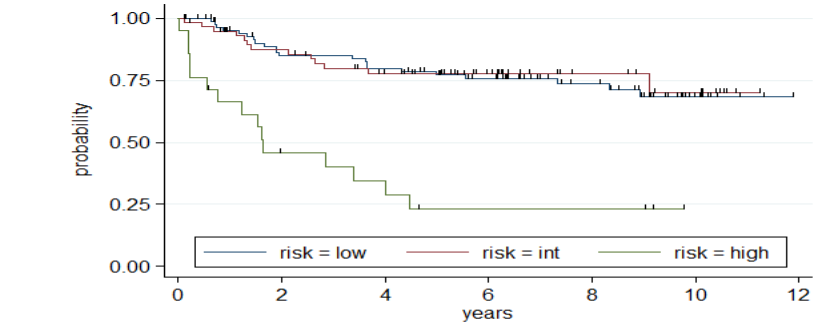


Number at risk

risk = low	167	159	154	113	78	31	0
risk = int	164	159	150	96	61	31	0
risk = high	68	57	45	25	15	6	0

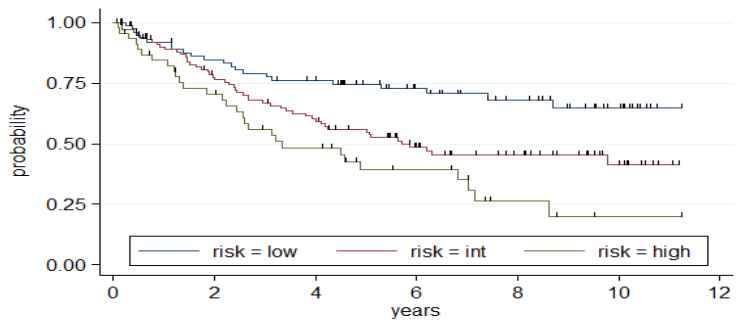
PFS by MALT prognostic score

gastric MALT



Number at risk							
risk = low	89	67	62	50	33	9	0
risk = int	60	47	37	26	12	8	0
risk = high	21	8	6	3	3	0	0

Non-gastric MALT



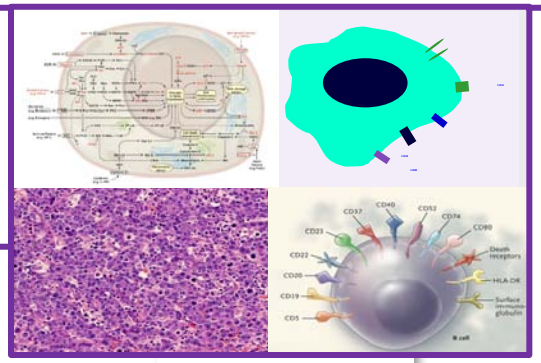
Number at risk							
risk = low	78	59	50	34	24	11	0
risk = int	104	73	56	34	23	9	0
risk = high	47	30	19	11	4	1	0

Microenvironment

- **Lenalidomide**
- **T-cell exhaustion**

Actionable mutations

- **EZH2** — E7438
- **CD79a/b** — AEB071



Pathways

- **Proteosome inhibitors** — Bortezomib
- **PI3k inhibitor** — idelalisib, copanlisib, duvelisib
- **Survivin inhibitors** — YM155
- **Syk inhibitor** — Fostamatinib
- **mTOR inhibitors** — Everolimus, Temsirolimus
- **Bcl-2 family inhibitors** — ABT-199
- **Btk inhibitor** — Ibrutinib + others
- **Hsp 90 inhibitors** — KW 2478

Surface markers

- **Anti CD20 moAb** — Ofatumumab, GA-101
- **Anti CD40 moAb** — Dacetuzumab
- **Anti CD22** — Epratuzumab, Inotuzumab Ozogamicin, polatuzumab
- **HDAC inhibitors** — Vorinostat, Panobinostat
- **PKC inhibitors** — Enzastaurin
- **Aurora kinase inhibitors**
- **Nedd8-activating enzyme inhibitor** — MLN4924

Microenvironment

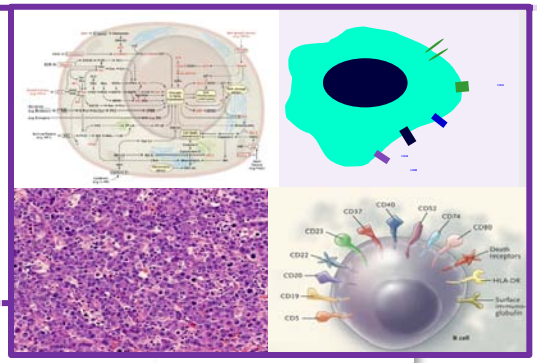
Lenalidomide

T-cell exhaustion

Actionable mutations

EZH2
E7438

CD79a/b
AEB071



Surface markers

Anti CD20 moAb
Ofatumumab
GA-101

Anti CD40 moAb
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Anti CD22
Epratuzumab
Inotuzumab Ozogamicin
polatuzumab

Pathways

Proteosome inhibitors
Bortezomib

Bcl-2 family inhibitors
ABT-263

Survivin inhibitors
YM155

Syk inhibitor
Fostamatinib

mTOR inhibitors
Everolimus
Temsirolimus

PI3k inhibitor
GS1101
BAY80

Btk inhibitor
Ibrutinib + others

Hsp 90 inhibitors
KW 2478

HDAC inhibitors
Vorinostat
Panobinostat

PKC inhibitors
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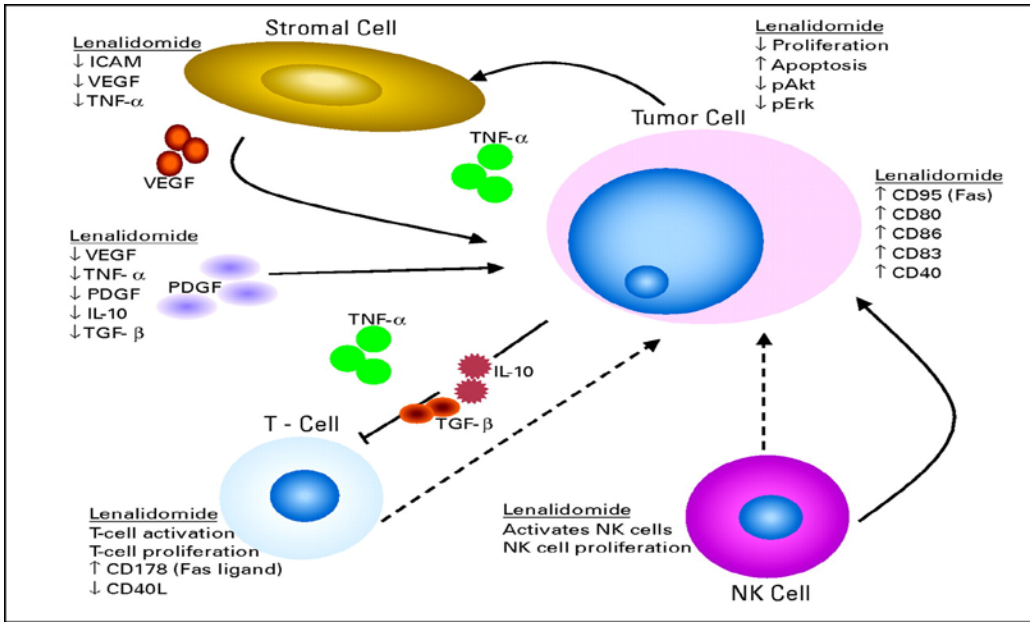
Aurora kinase inhibitors

Nedd8-activating enzyme inhibitor
MLN4924

Lenalidomide

- Immunomodulatory properties
- Modulation of both cellular and cytokine tumour cell microenvironment
- Activates T cell and NK response to tumour cell
- Down regulates pro-survival cytokines
- Approval in myeloma



Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

The R^2 regimen (Fowler at al. Lancet Oncol 2014)

- Preclinical data suggests that lenalidomide may augment immune effector function and enhance rituximab mediated ADCC
- Previously untreated advanced stage ‘indolent lymphoma’

Lenalidomide	20mg po	Day 1-21 q28
Rituximab	375mg iv	Day 1
6 cycles. Responders continued to 12 cycles		

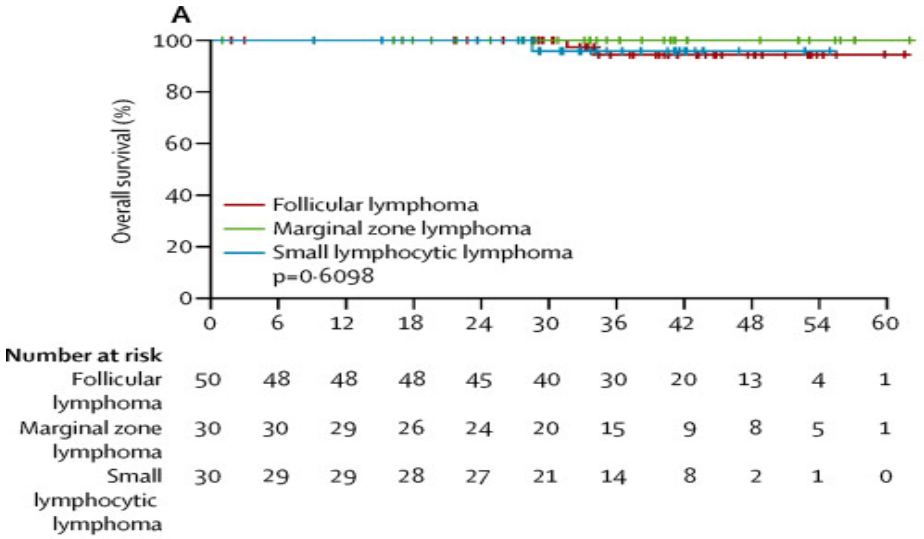
- n=110 (103 pts. evaluable) 57% GELF criteria for high tumour burden

Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

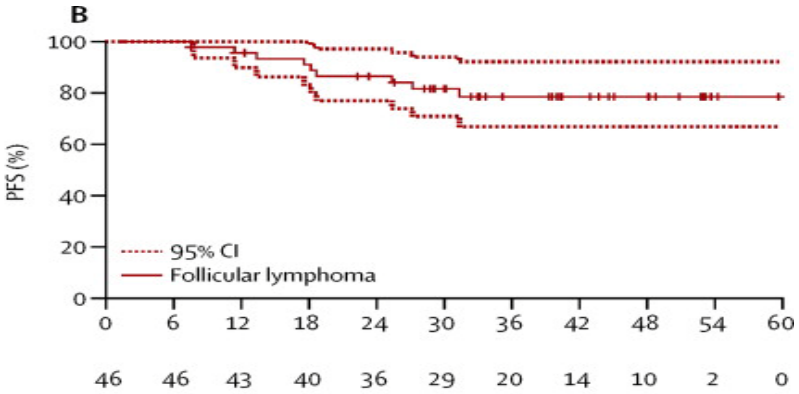
%	ORR	CR/CR(u)	PR	SD	PD
Follicular (n=46)	98	87	11	2	0
Small lymphocytic (n=30)	80	27	53	13	7
Marginal zone (n=27)	89	67	22	11	0
All (n=103)	**90**	**64**	**26**	**8**	**2**

Fowler et al Lancet Oncol 15 (12), 2014, 1311-1318

Overall survival



Progression-free survival: Follicular lymphoma



Fowler et al Lancet Oncol 15 (12), 2014, 1311-1318

Toxicity of R^2

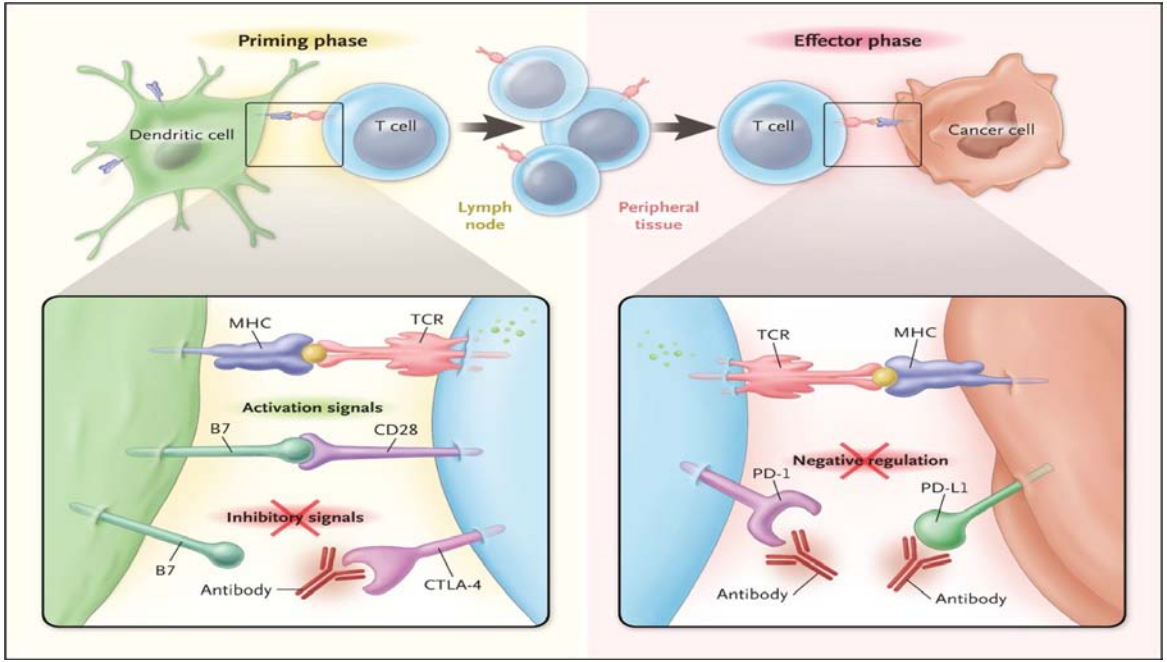
	Grade >3
Neutropenia	40%
Thrombocytopenia	4%
Rash	7%
Muscle pain	6%
fatigue	3%
VTE	3%

Fowler et al Lancet Oncol 15 (12), 2014, 1311-1318

Long term???

Exhausted T-cells

- Blocking immune checkpoints may promote endogenous antitumour activity
- PD1: Inhibitory receptor on activated T-cells, B-cells, NK and myeloid cells. Inhibition of T-cell activation when engaged by ligands (PDL1/2)
- PD1 expressed on T-cells when exposed to tumour, and associated with exhaustion. Blocking can restore function



Ribas A. N Engl J Med 2012;366:2517-2519.

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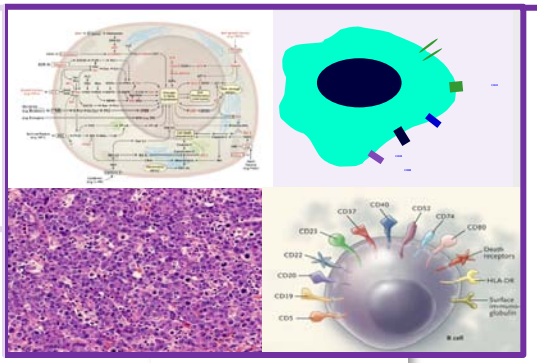

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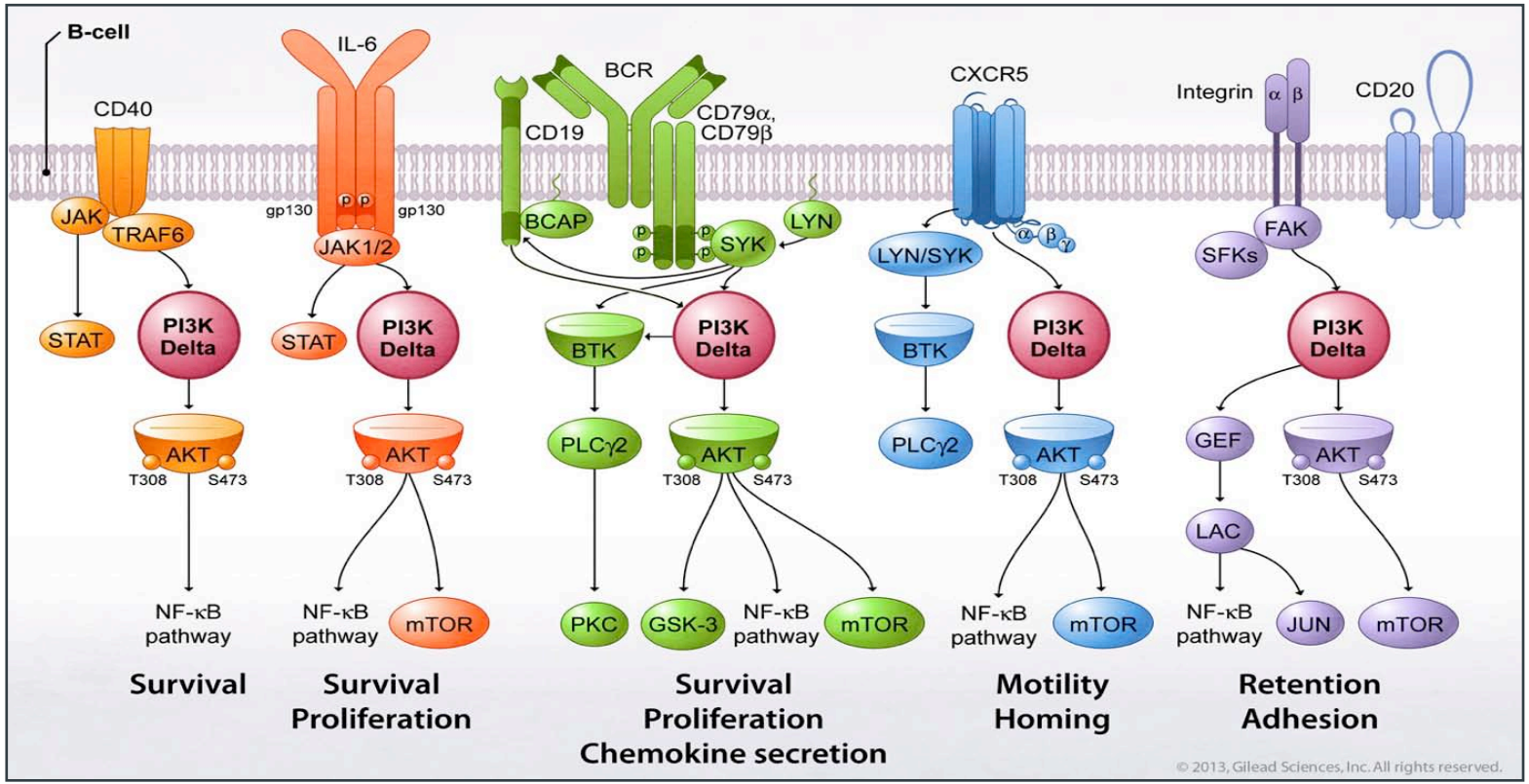
- **Nedd8-activating enzyme inhibitor**: MLN4924

PI3Kδ Inhibition Impacts Multiple Critical Pathways in iNHL



Idelalisib is highly selective for PI3Kδ isoform

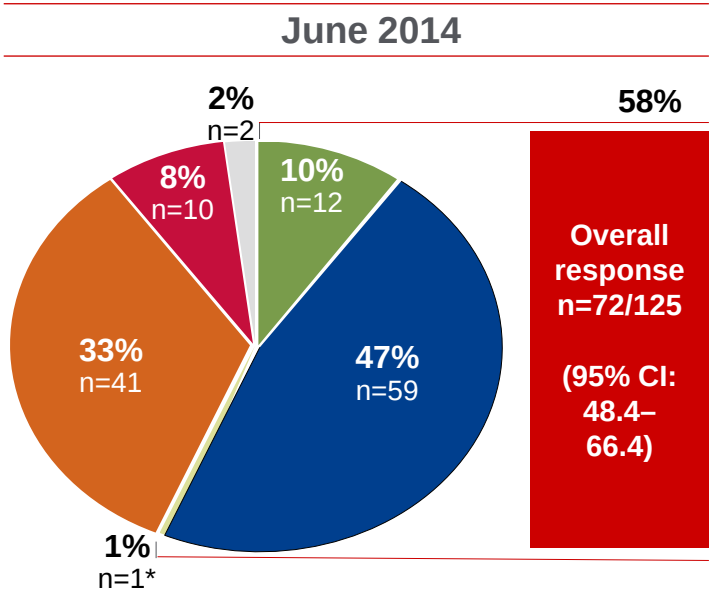
Class I PI3K isoform[1]

Expression	Ubiquitous	Ubiquitous	Leukocytes	Leukocytes
EC_{50} nM	>20,000	1900	3000	8

- Promising activity in relapsed / refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) in a Phase I study[2]

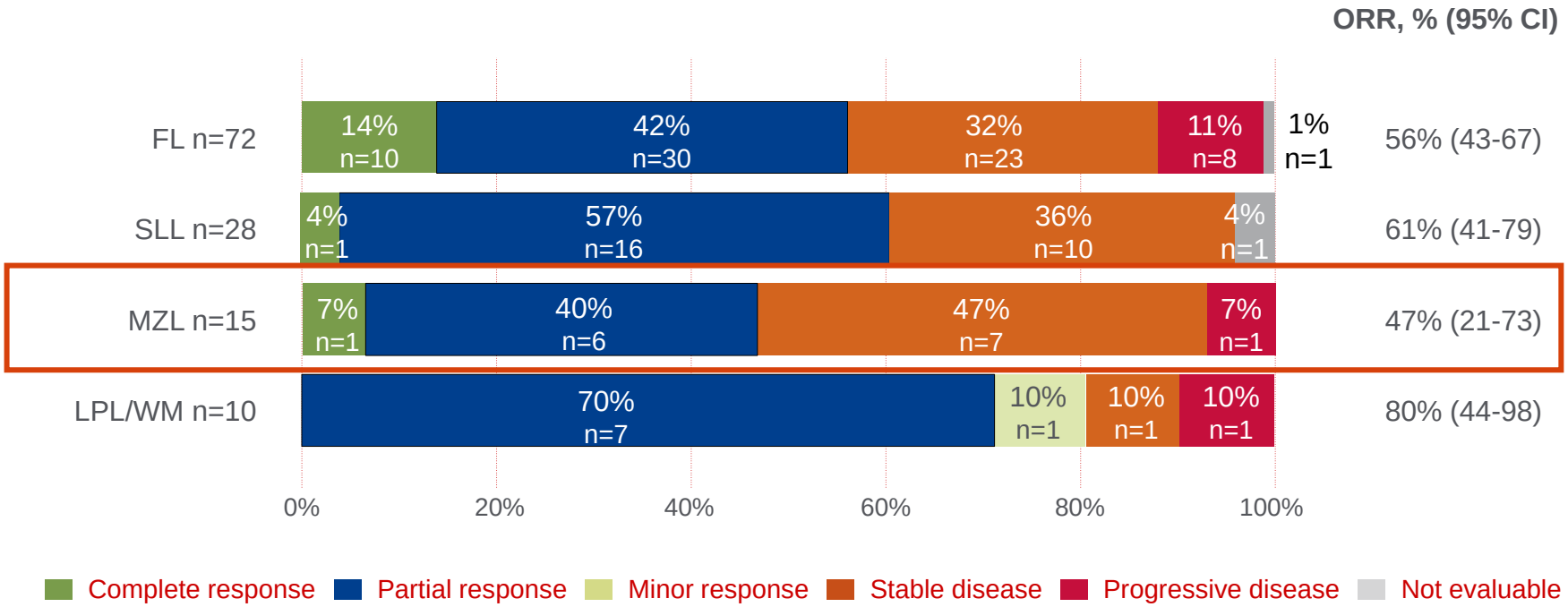
1. *Lannutti BJ, et al. Blood 2011;117:591-4;*
2. *Flinn IW, et al. Blood 2014;123:3406-13*;

Overall response rate: 09 study



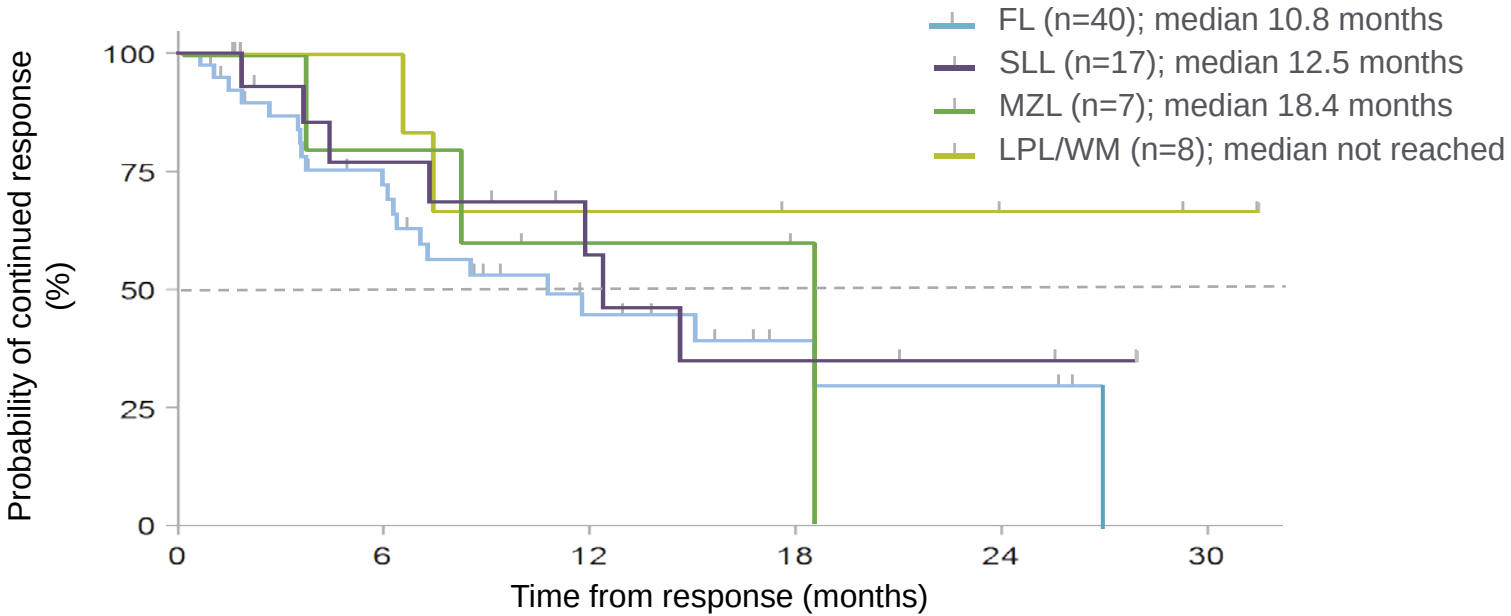
*LPL/WM patient

Overall response rate by disease subgroups*



*2014 data

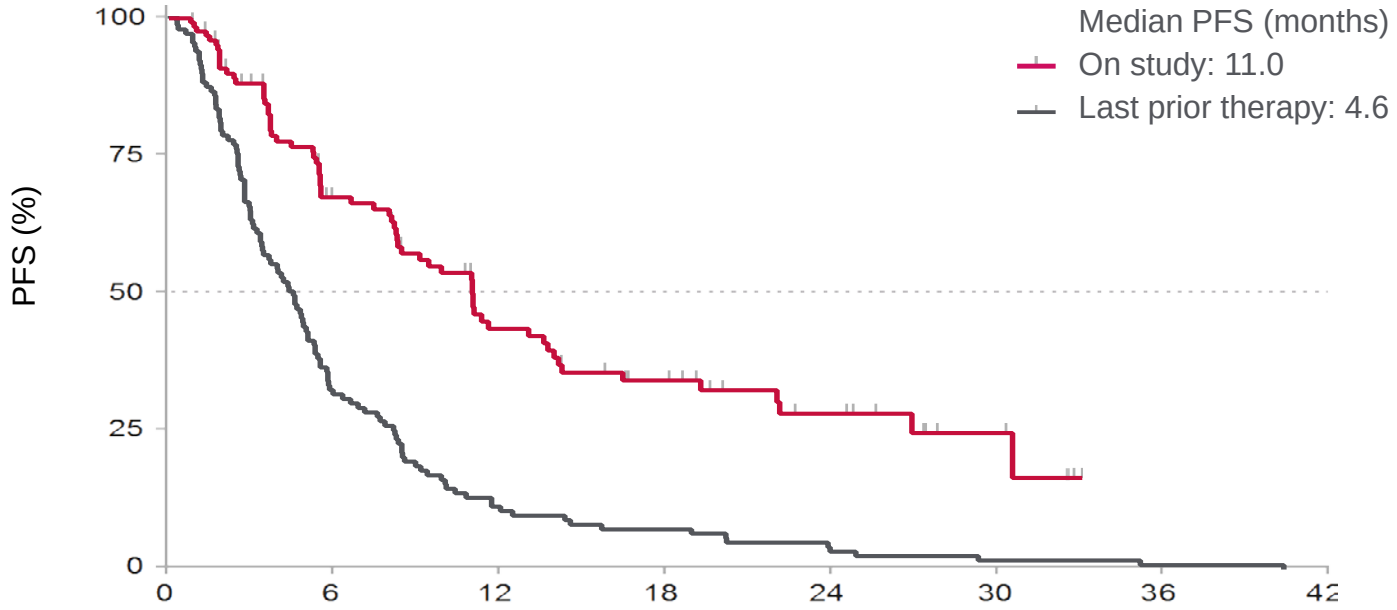
Duration of response by disease group



Patients at risk, n

40	24	10	4	3	
17	9	5	3	2	
7	4	2	1		
8	6	4	3	2	1

PFS: On study vs. last prior therapy

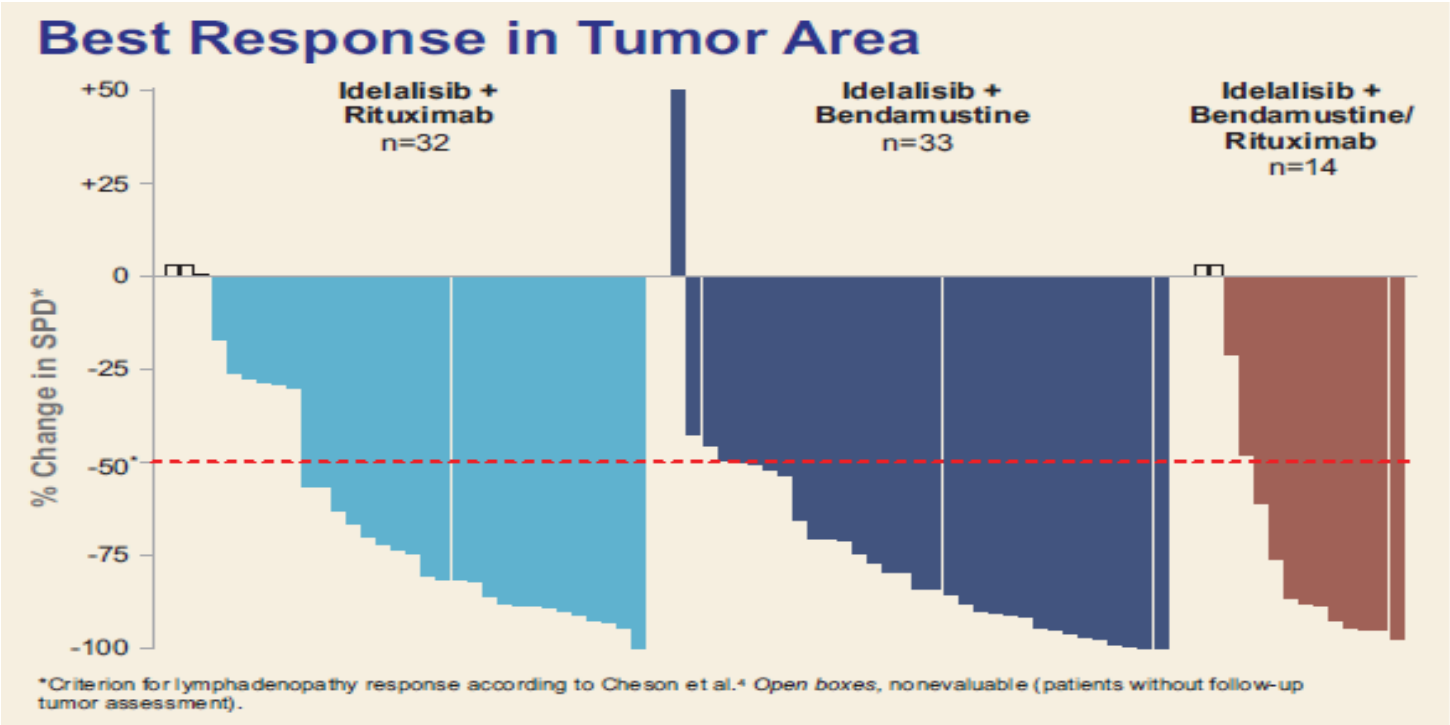


Patients at risk, n

125	60	33	22	12	4	
125	40	14	9	5	2	1

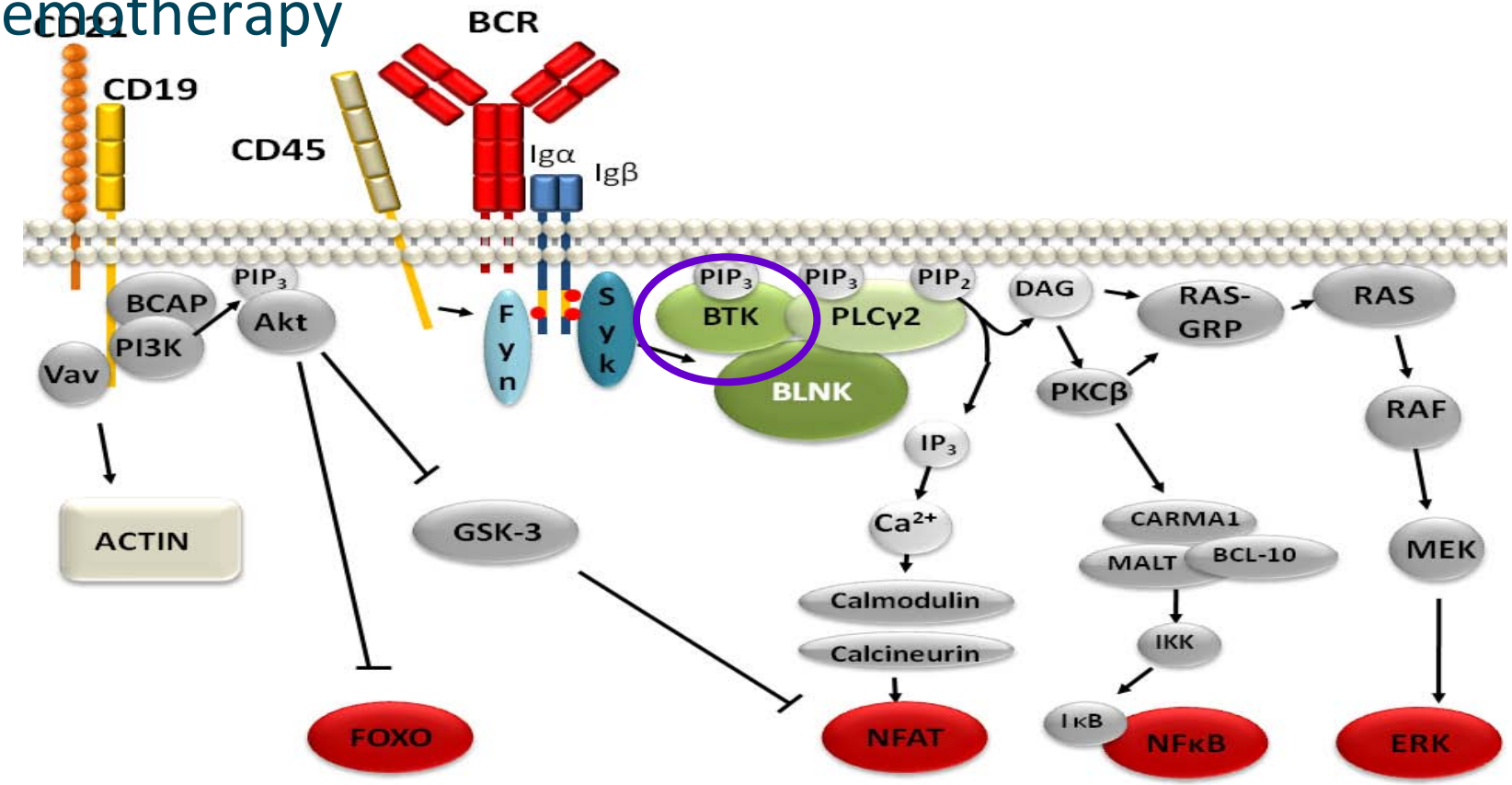
Adverse events occurring in >12% of patients

AE, n (%)	Any grade	Grade ≥3
Diarrhoea/colitis	63 (50)	24 (19)
Cough	40 (32)	0
Nausea	39 (31)	2 (2)
Fatigue	38 (30)	2 (2)
Pyrexia	38 (30)	4 (3)
Dyspnoea	23 (18)	6 (5)
Decreased appetite	23 (18)	1 (1)
Abdominal pain	21 (17)	3 (2)
Upper respiratory infection	21 (17)	0
Vomiting	20 (16)	3 (2)
Decreased weight	19 (15)	0
Night sweats	18 (14)	0
Pneumonia	18 (14)	15 (12)
Rash	17 (14)	2 (2)
Asthenia	16 (13)	4 (3)
Headache	16 (13)	1 (1)

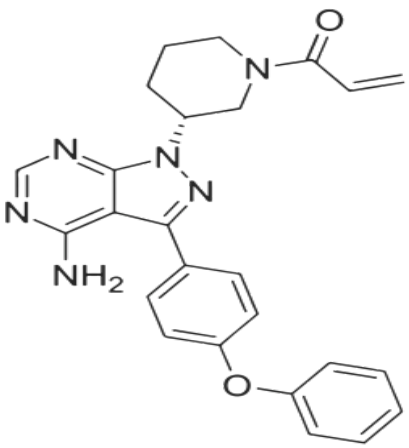


de Vos et al ASH 2014

B-cell receptor signalling. ..Inhibit and spare the chemotherapy



Ibrutinib: Mechanism of action



Chemical structure of ibrutinib [4]

Interactions between the tumour microenvironment and malignant B cells play an important role in B-cell homing, adhesion and migration through activation of intracellular pathways in the B cells.[1,2]

BTK's pivotal role in signalling through B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion.[3]

Covalent binding in ATP pocket of BTKL….believed to disrupt key malignant processes and:[3,4]

- Induce apoptosis; Inhibit adhesion (may lead to lymphocytosis)

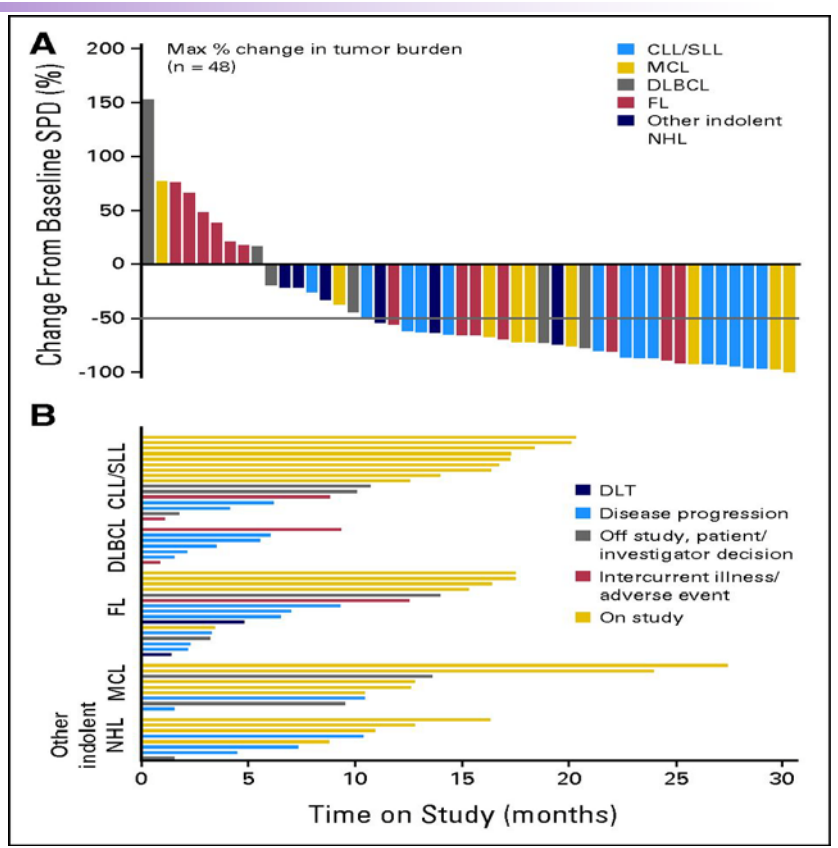
1. de Gorter DJJ, et al. Immunity 2007;26:93-104. **2.** Burger JA, et al. Bloo
2. d 2009;114:3367-3375. **3.** Buggy J et al. Int Rev Immunol 2012; 31:119-132. **4.** Chavez J, et al. Core Evid 2013; 8:37-45.

Ibrutinib in B-cell lymphoma

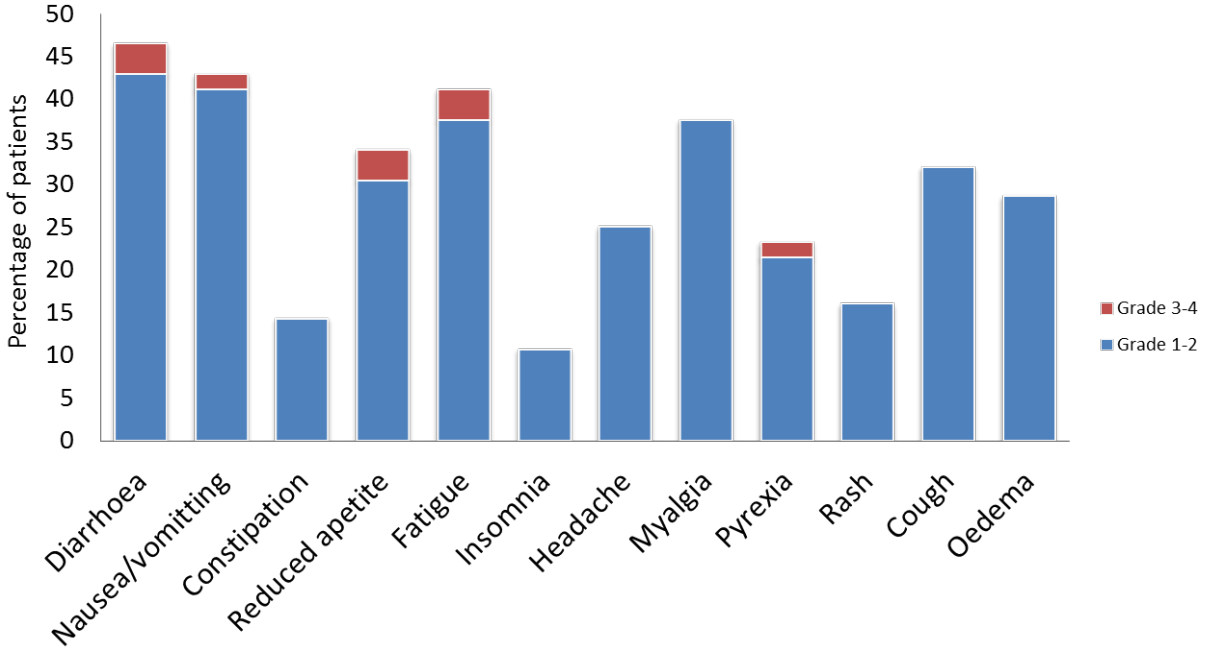
	Responders (n/N)
Mantle cell	7/9
CLL/SLL	11/16
FL	6/16
DLBCL	2/7
WM	3/4
ORR	**60%**

N=56. Median 3 (1-10) prior therapies

Advani R H et al. JCO 2013;31:88-94



Toxicity



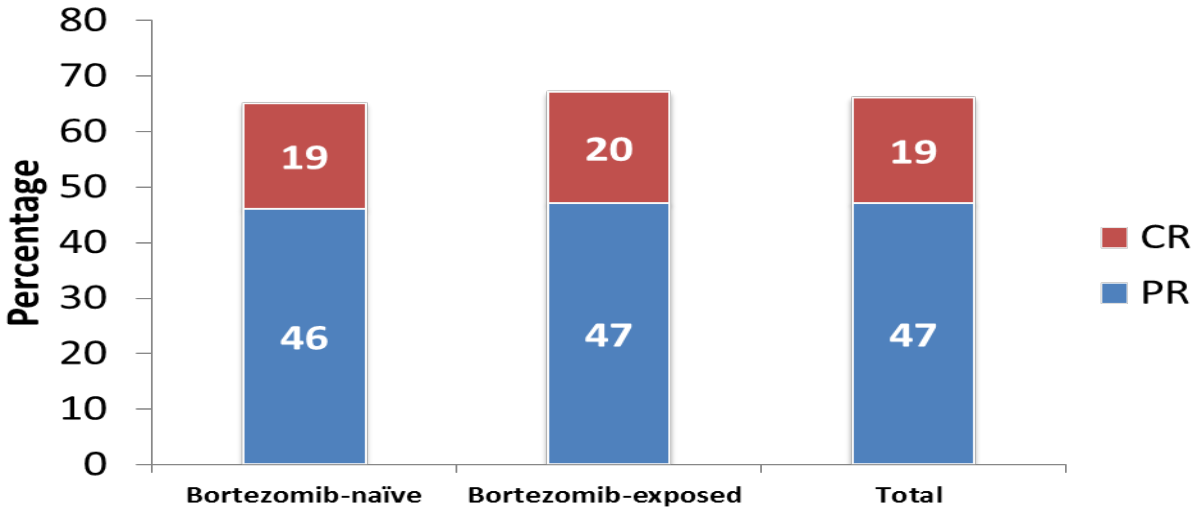
Grade ≥3 haematological toxicity:
Neutropenia 13%, thrombocytopenia 7%;
anaemia 7%
No decrease in Igs

Advani R H et al. JCO 2013;31:88-94

Ibrutininb in Mantle cell

115 pts with MCL (bortezomib-naïve n=65; bortezomib-exposed n=50); median age 68; median 3 (1-6) prior therapies;
44% refractory

17.5 months estimated median response duration
13.9 months estimated median progression-free survival

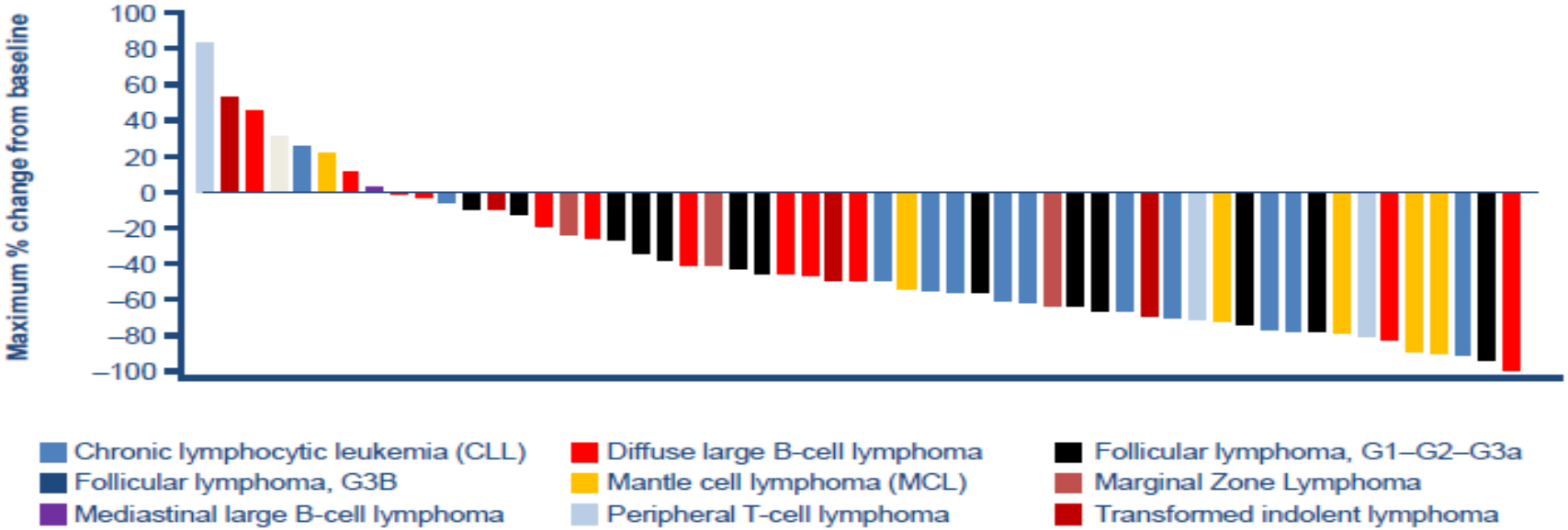


Wang M et al. N Engl J Med 2013; 369: 507-516.

Other inhibitors of PI3K

Class I PI3K Isoform	α	β	γ	δ
Expression	**Ubiquitous**	**Ubiquitous**	**Leukocytes**	**Leukocytes**
	Insulin signaling Mutated in solid tumours	Platelet activation Neutrophil function Insulin signaling	Mast cell activation Innate immunity Immune tracking	B and T cell activation Fc receptor signaling

Copanlisib



AEs ≥3. Neutropenia 24% ; hypertension 37%; hyperglycaemia 22%

Dreyling et al ASH 2014

BCL-2 Inhibition

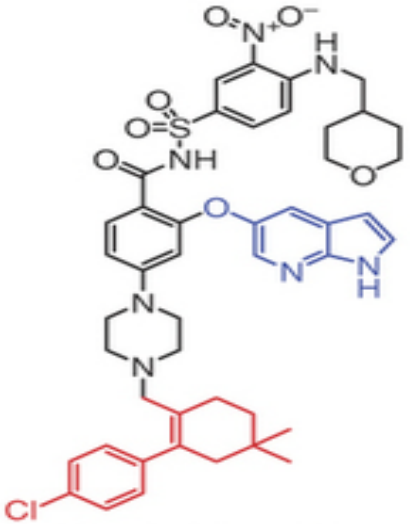
Bcl-2 highly expressed in FL

GDC-0199 oral active Bcl-2 inhibitor
Phase I dose escalation
200-900 mg cohorts
N=44 with NHL
FL =11 (26%)

Nausea (34%), diarrhoea (25%), fatigue (21%)

Tumour lysis in 1 patient each with DLBCL and MCL

3/11 responses in FL



GDC-0199

Obinutuzumab: Putative mechanism(s) of action

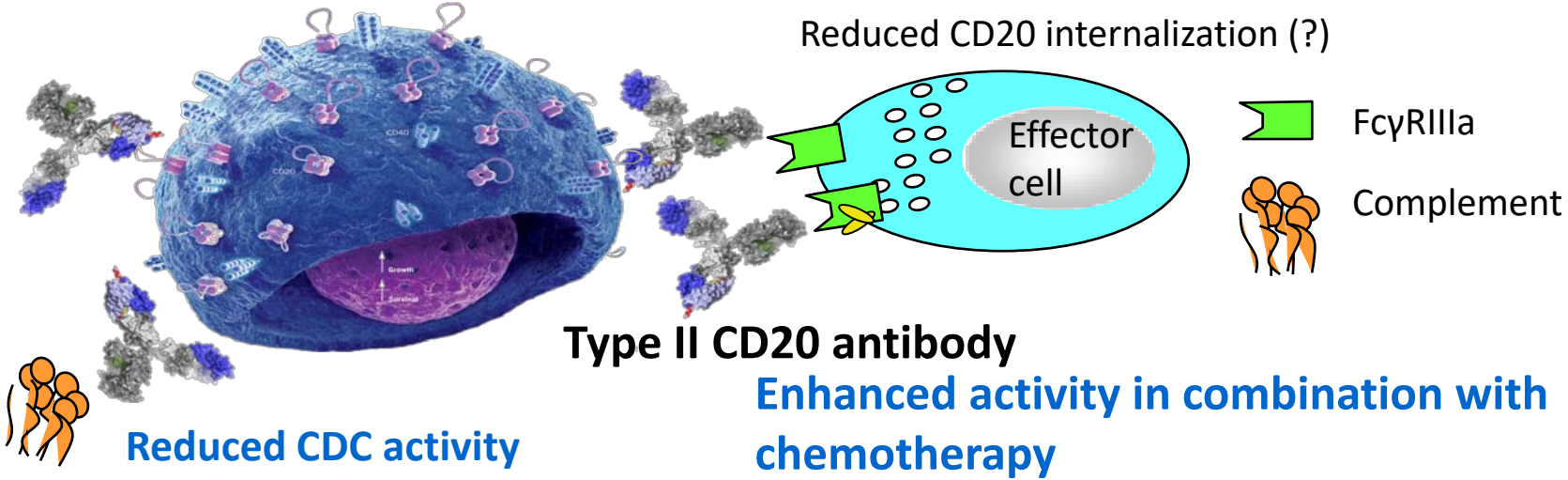
Increased direct cell death

Type II antibody & elbow-hinge modification

Increased ADCC

Higher affinity to the 'ADCC receptor' FcγRIIIa (GlycoMab TM technology) &

Reduced CD20 internalization (?)

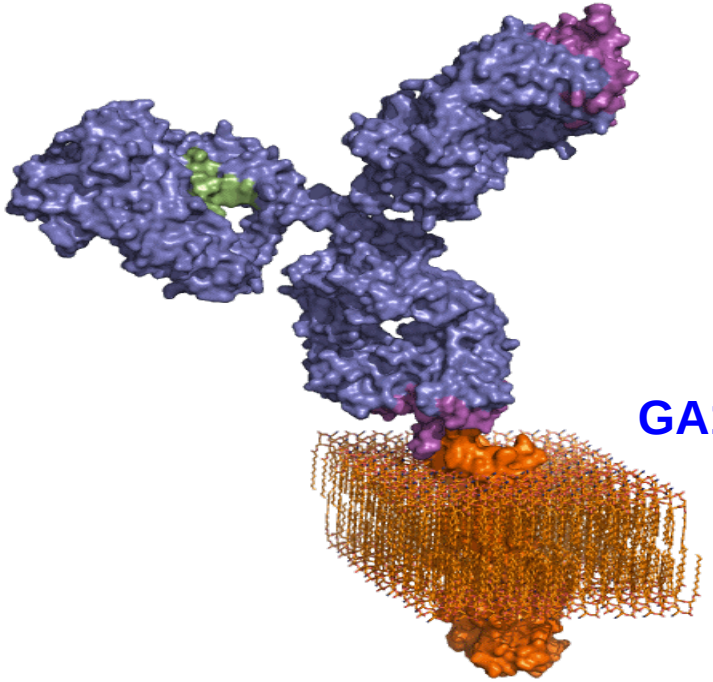


Reduced CDC activity

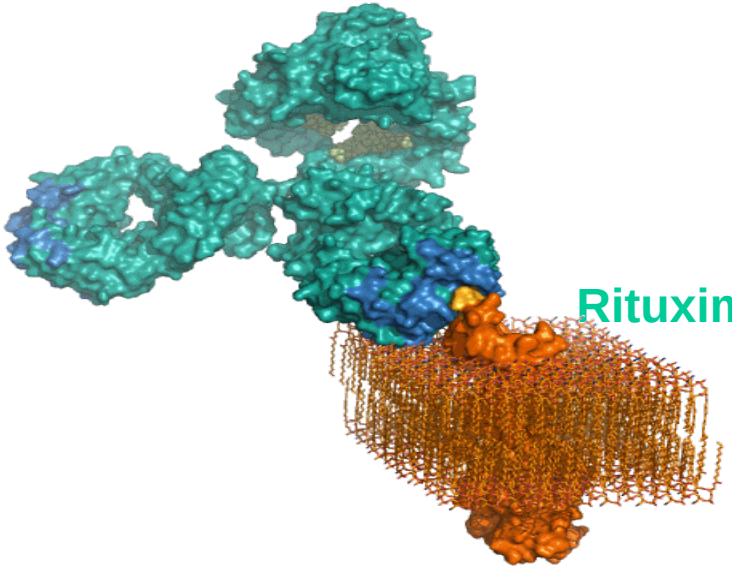
Type II antibody

Enhanced activity in combination with chemotherapy

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity



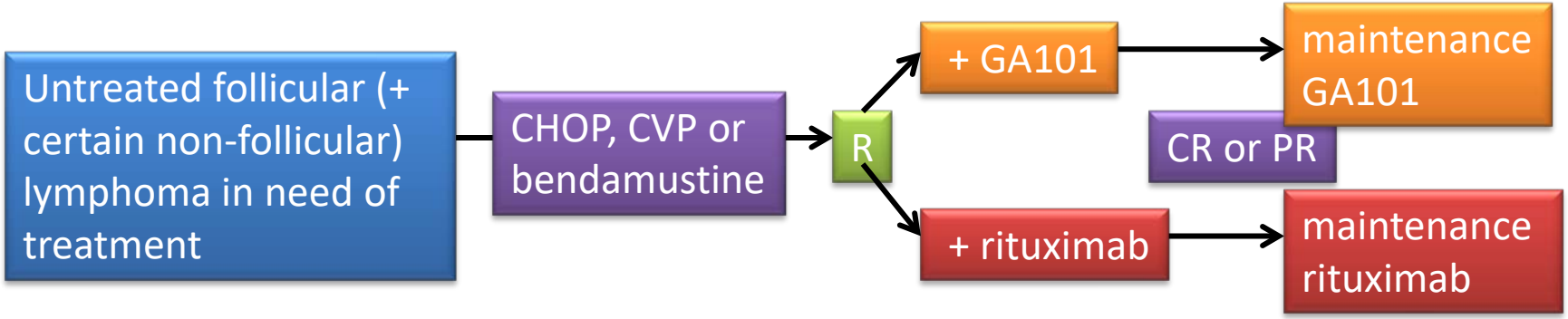
GA101



Rituximab

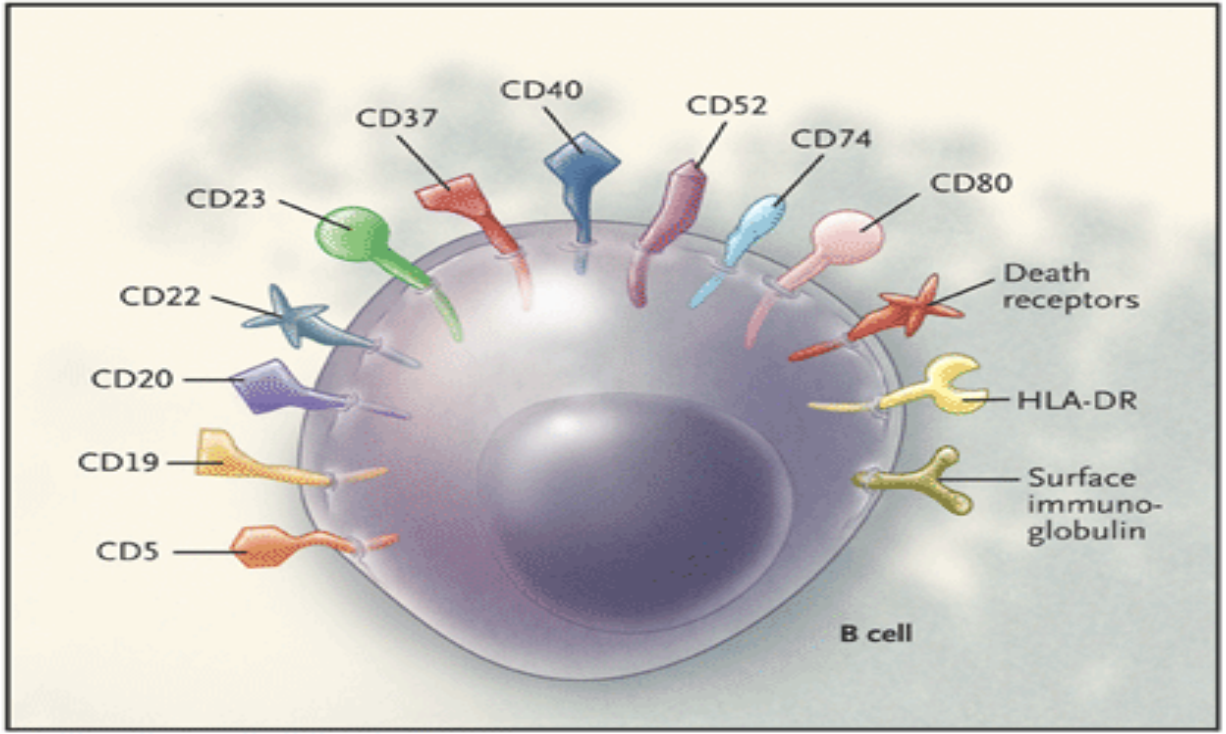
M. Schwaiger, W. Schäfer

GALLIUM



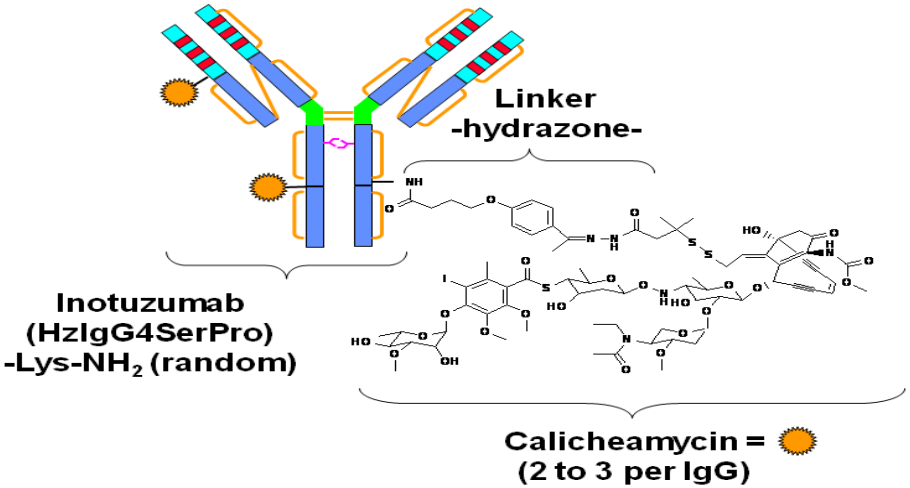
Target 1200 FL, 200 non-follicular

What about the other targets?

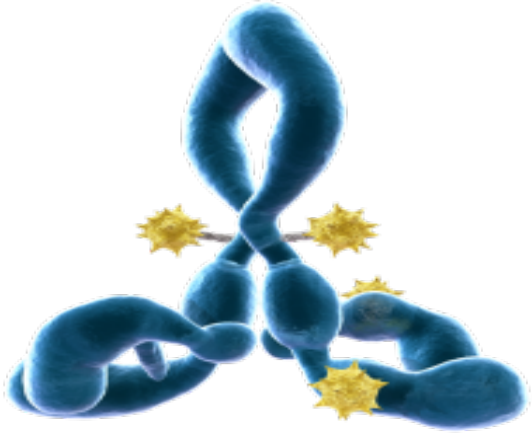


Targeted chemotherapy in clinical development

Antibody-drug conjugates



Target CD22



Polatuzumab
Vedotin

Target CD79b

In summary…

- Huge progress in our understanding of MZL
- Lack of good data
- A wealth of new therapies
- International collaboration to test and define treatment strategies

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Systemic management of Advanced Stage DLBCL

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University of Southampton

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September 2016

UNIVERSITY OF Southampton

CANCER RESEARCH UK

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

Conflicts of Interest

Celgene: Research funding; Advisory Board; Honorarium

Roche: Advisory Boards; Honorarium; Research support

Gilead: Advisory Boards; Honorarium; Research support

Takeda: Advisory Boards; Honorarium; Research support, Travel to scientific conferences

CTI: Advisory Boards; Honorarium; Travel to scientific conferences

Mundipharma: Advisory Boards; Honorarium; Travel to scientific conferences

GSK: Research support

Bayer: Research support

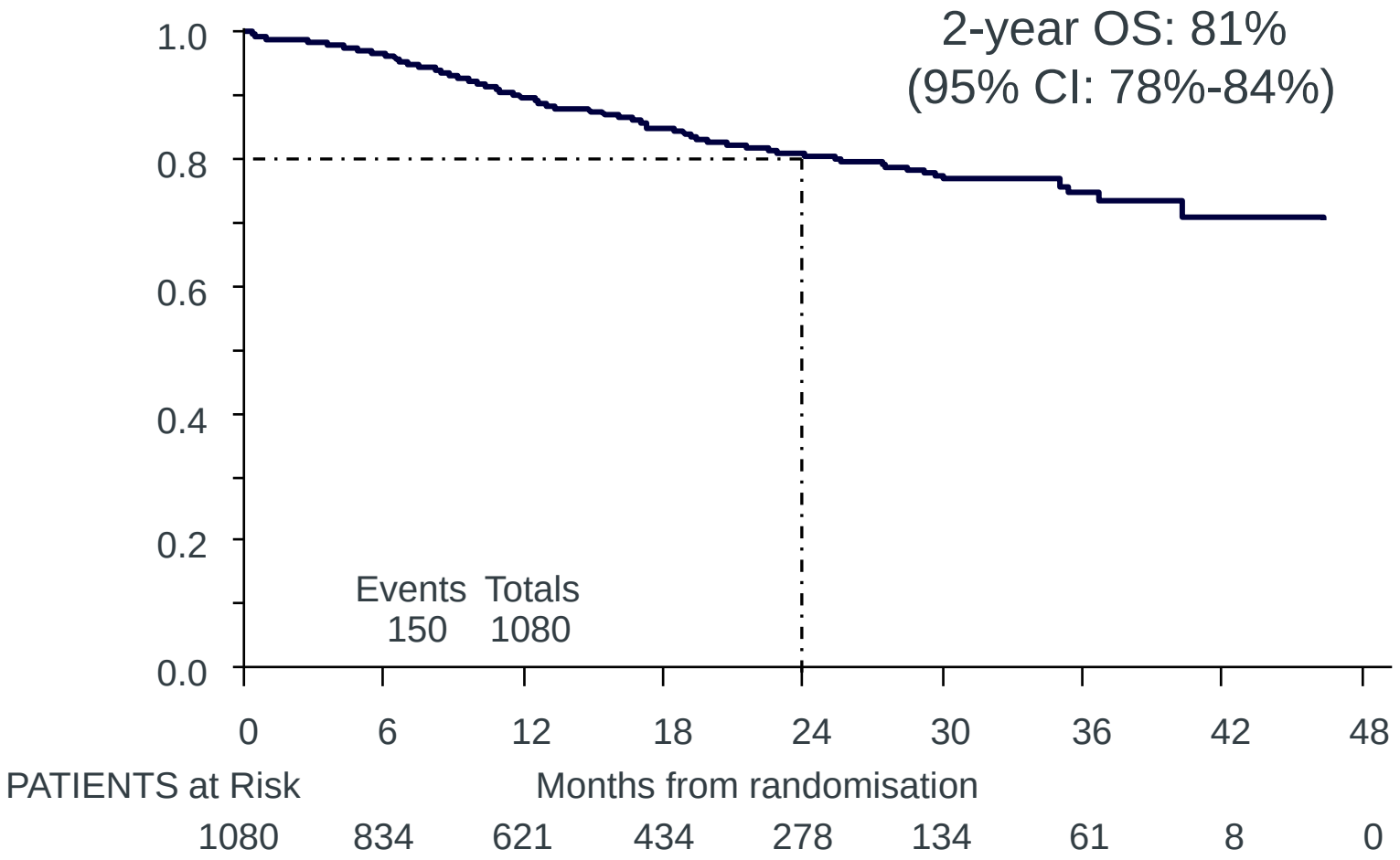
Janssen: Honorarium; Research support

Karyopharma: Advisory Board; Research support

Pfizer: Research support; Honorarium

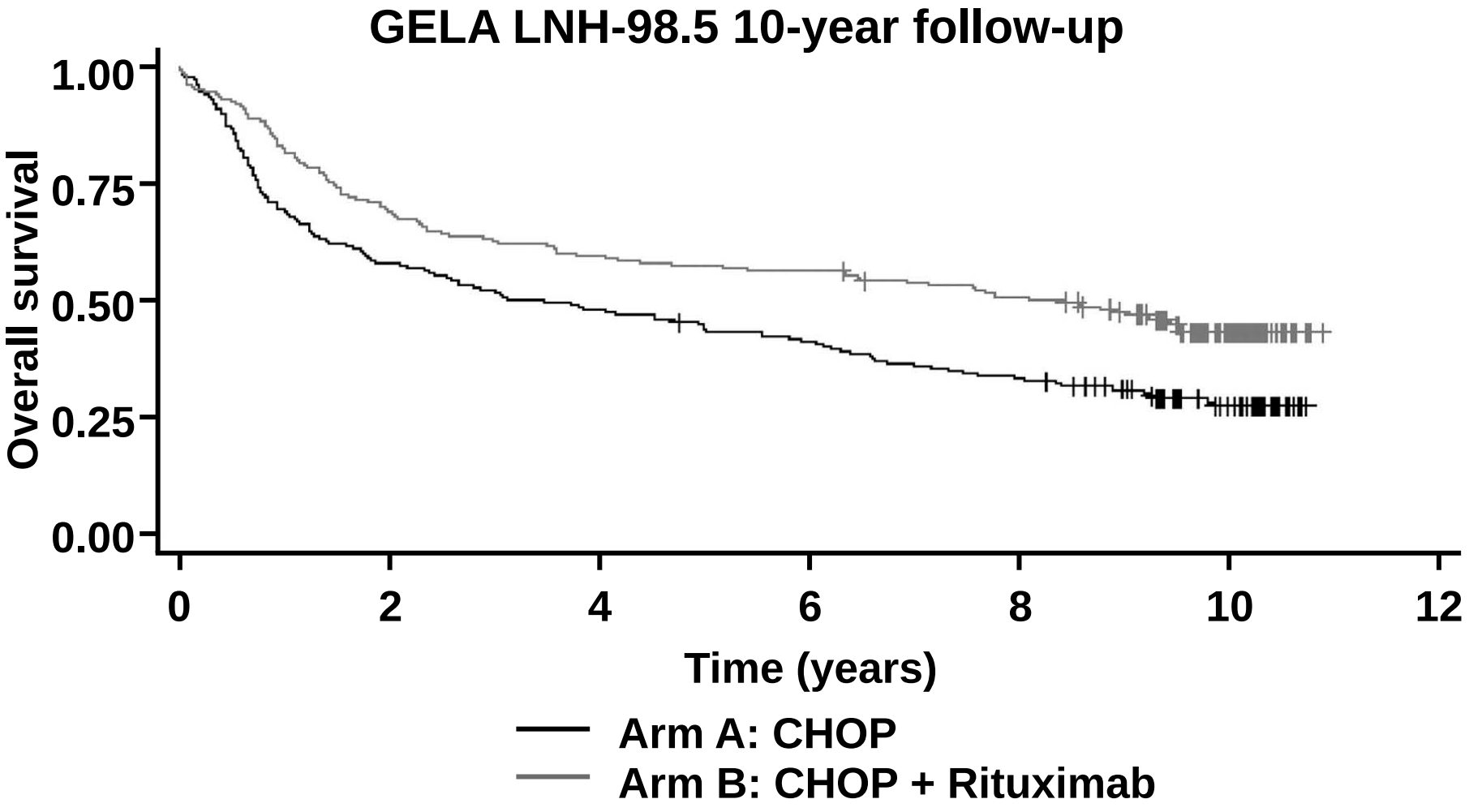
DLBCL is a curable disease

Overall survival: UK R-CHOP 14 vs 21



Cunningham, J Clin Oncol (2009) 27:15s,

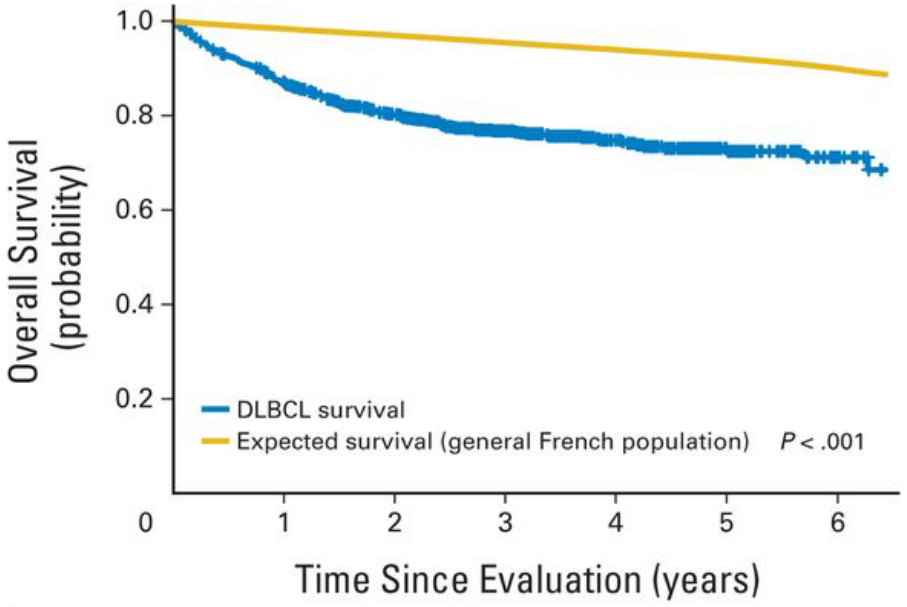
The benefit of rituximab is maintained over time



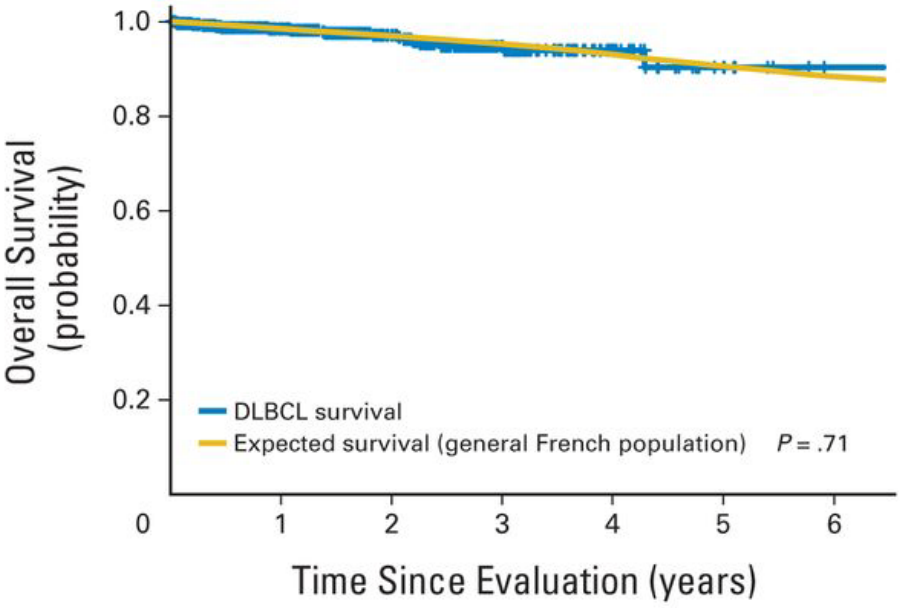
Coiffier B et al. Blood 2010;116:2040-2045

Events occur early…

Overall survival from diagnosis

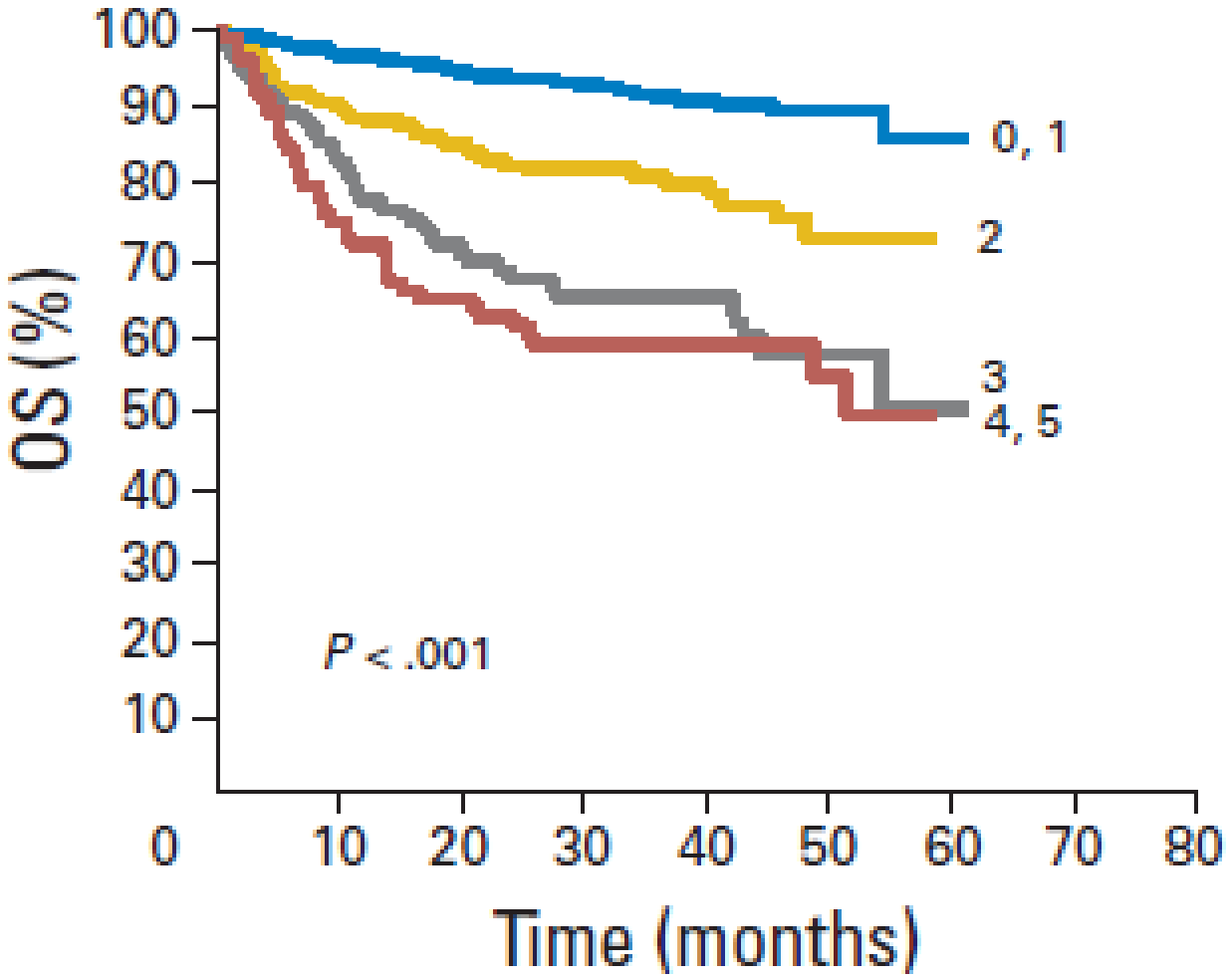


Overall survival from 2 years event free



Maurer M J et al. JCO 2014;32:1066-1073

…but how can we improve the outcomes for those with less favourable prognosis?



IPI

Age greater than 60 years
Stage III or IV disease
Elevated serum LDH
ECOG ≥ 2
More than 1 extranodal site

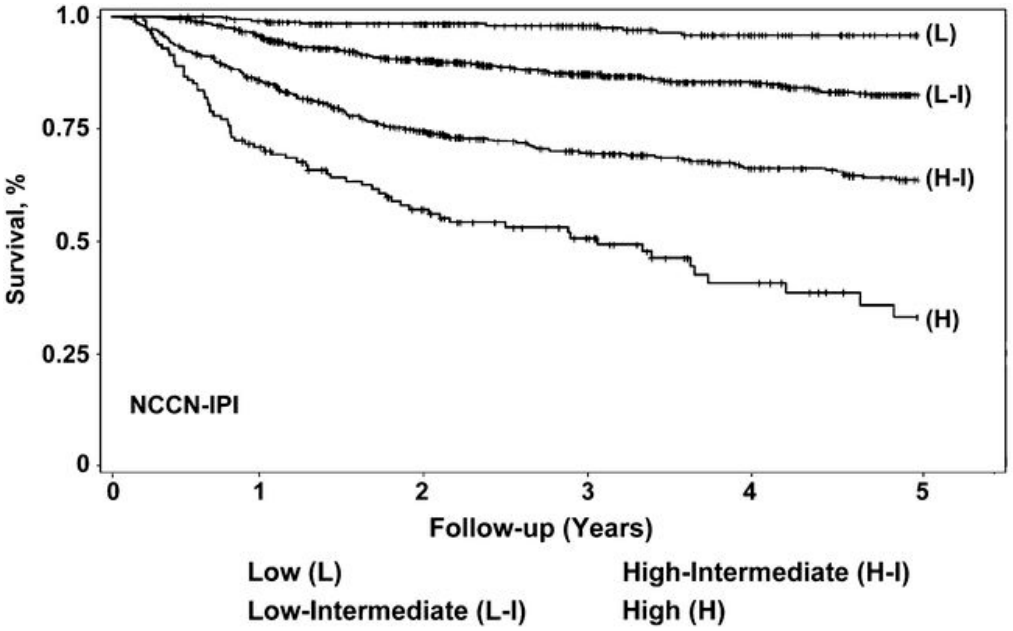
Age adjusted IPI

Stage
LDH
Performance status

Ziepert at al. J Clin Oncol 28:2373-2380.

The NCCN-IPI…more discriminative than IPI

NCCN-IPI	Score
Age, y	
>40 to ≤60	1
>60 to ≤75	2
>75	3
LDH, normalized	
>1 to ≤3	1
>3	2
Ann Arbor stage III-IV	1
Extranodal disease*	1
Performance status ≥2	1



low (0-1), low-intermediate (2-3), high-intermediate (4-5), and high (6-8)

Zhou Z et al. Blood 2014;123:837-842

ESMO Guidelines

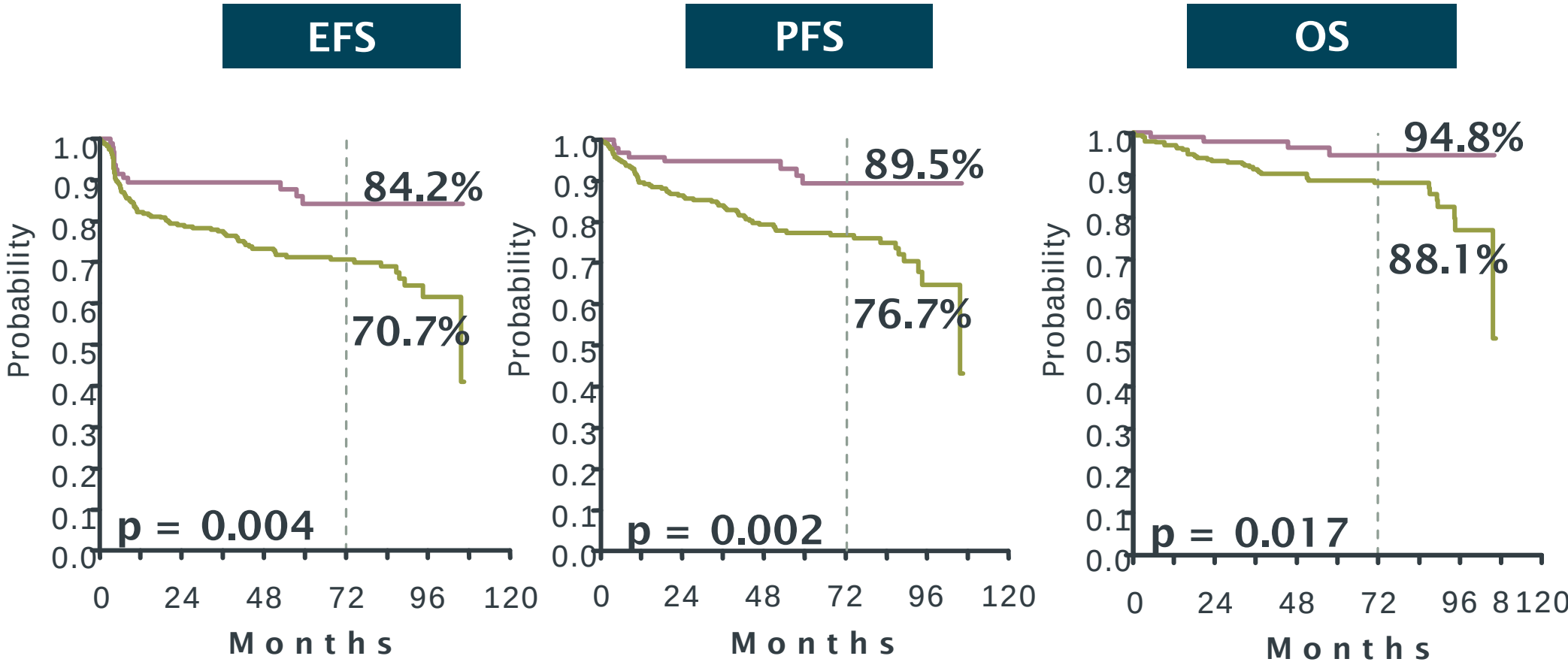
Young (age <61)

aaIPI=0 no bulk	aaIPI=1/aaIPI=0 +bulk
R-CHOP 21 x6	R-ACVBP + consolid.
	R-CHOP 21 x6 + IFRT (to bulk)

Some groups are doing very well.....

Prognostic Groups in the MInT Trial: Favourable vs. Unfavourable

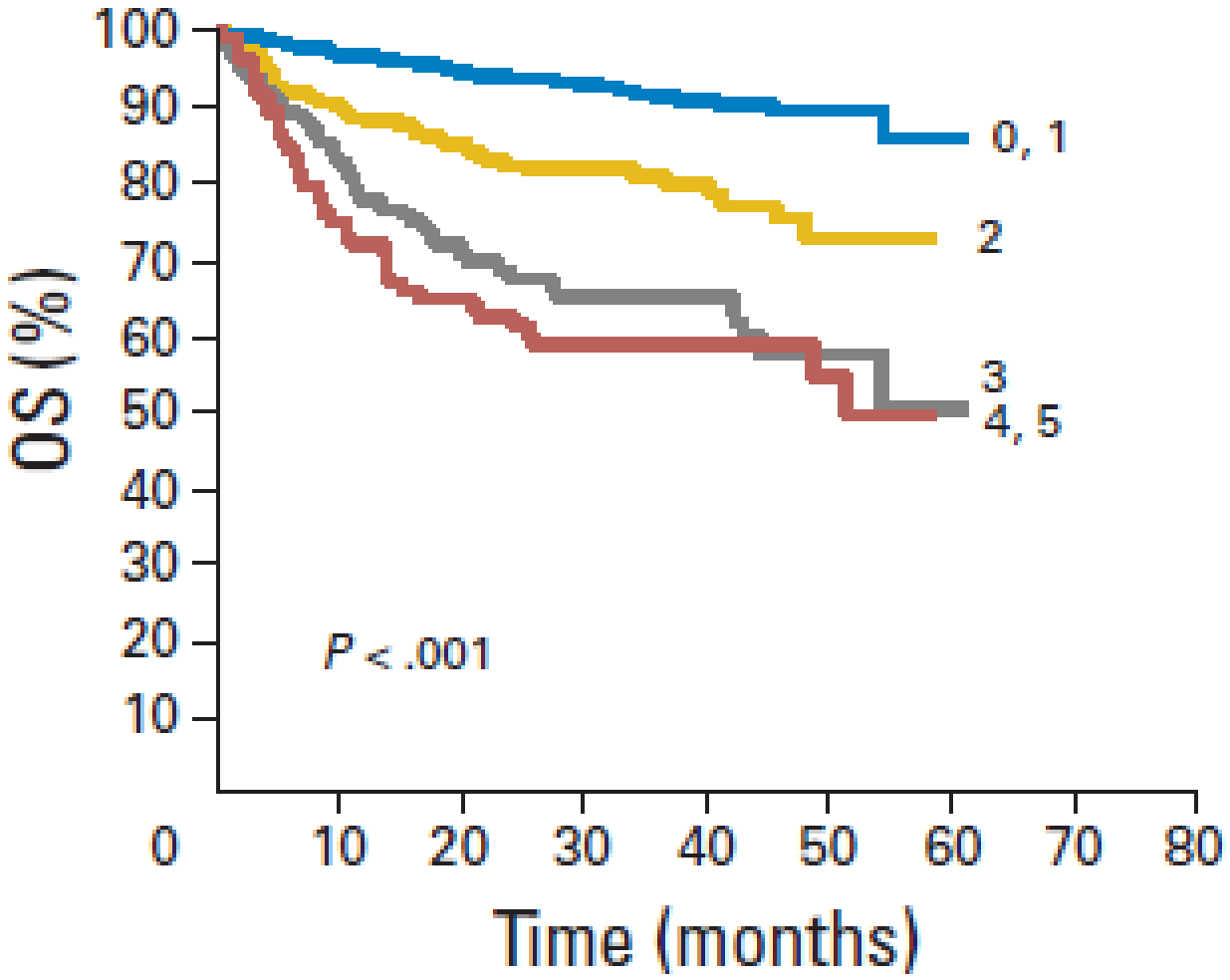
Pfreundschuh et al. ASH 2010



Favourable: IPI=0 / ∅ bulk

Unfavourable: IPI=1 and / or bulk

…but how can we improve the outcomes for those with less favourable prognosis?



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Age greater than 60 years
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ESMO Guidelines

Young (age <61)

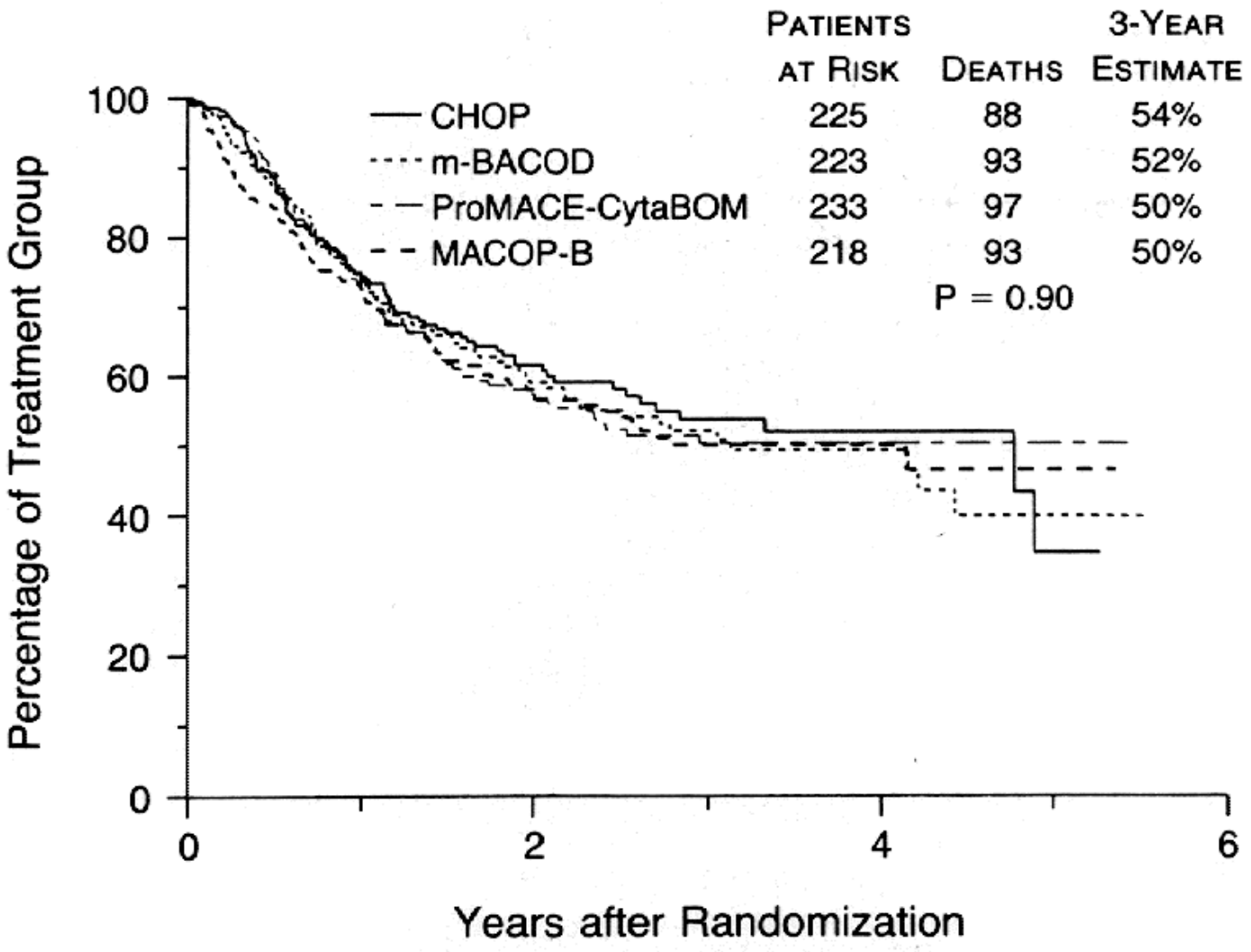
aaIPI=0 no bulk	aaIPI=1/aaIPI=0 +bulk	aaIPI≥2
R-CHOP 21 x6	R-ACVBP + consolid.	R-CHOP 21 x8
	R-CHOP 21 x6 + IFRT (to bulk)	R-CHOP 14 x6 +Rx2
		R-CHEOP14 x6
		R-ACVBP + HDT
		R-CHOP14 +HDT
		Clinical trial

No clear standard in this group

Is there much yet to be achieved with conventional chemotherapy

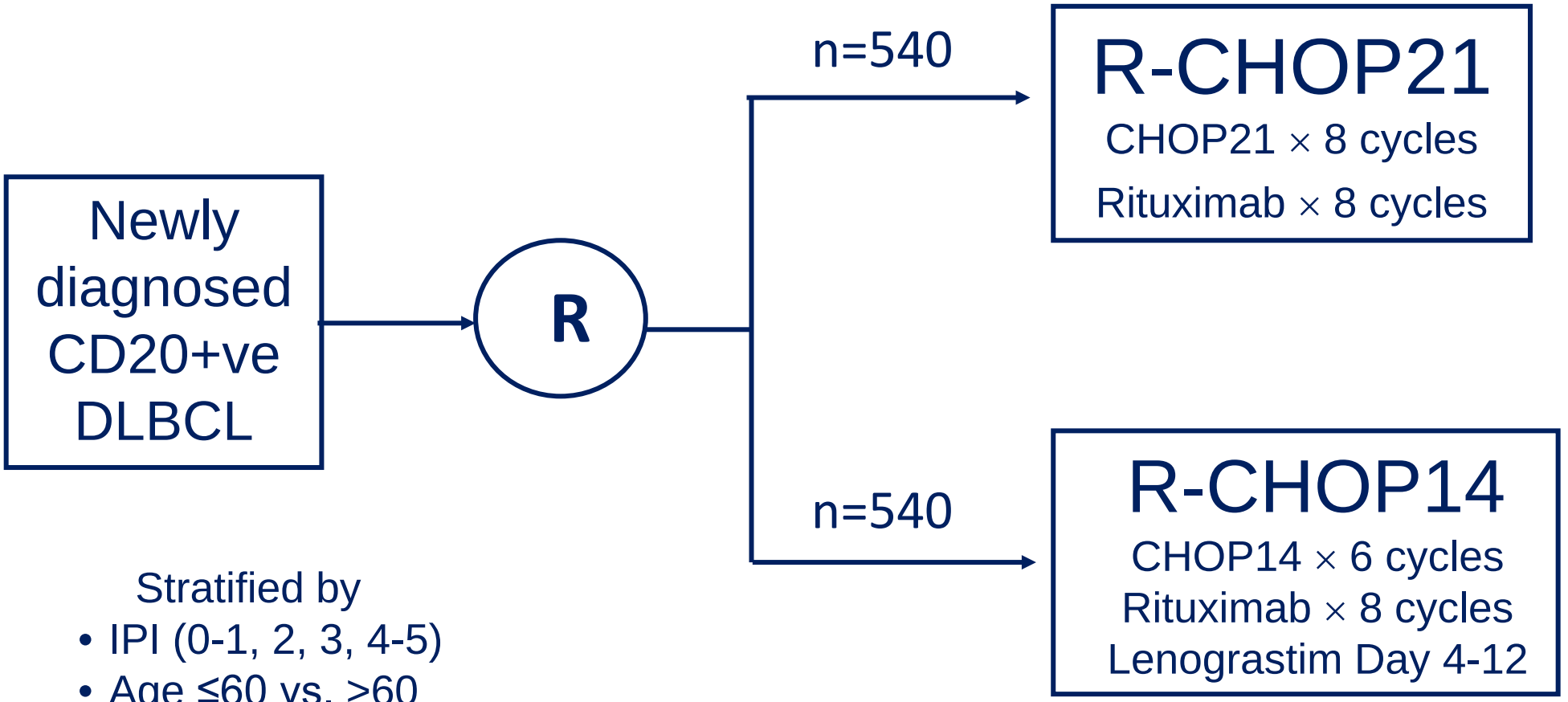
Probably not…..

Intensified regimens…might they hold the answer?



Fisher RI, et al . N Engl J Med1993; 328:1002– 006.

Dose Density: UK R-CHOP14 vs. 21



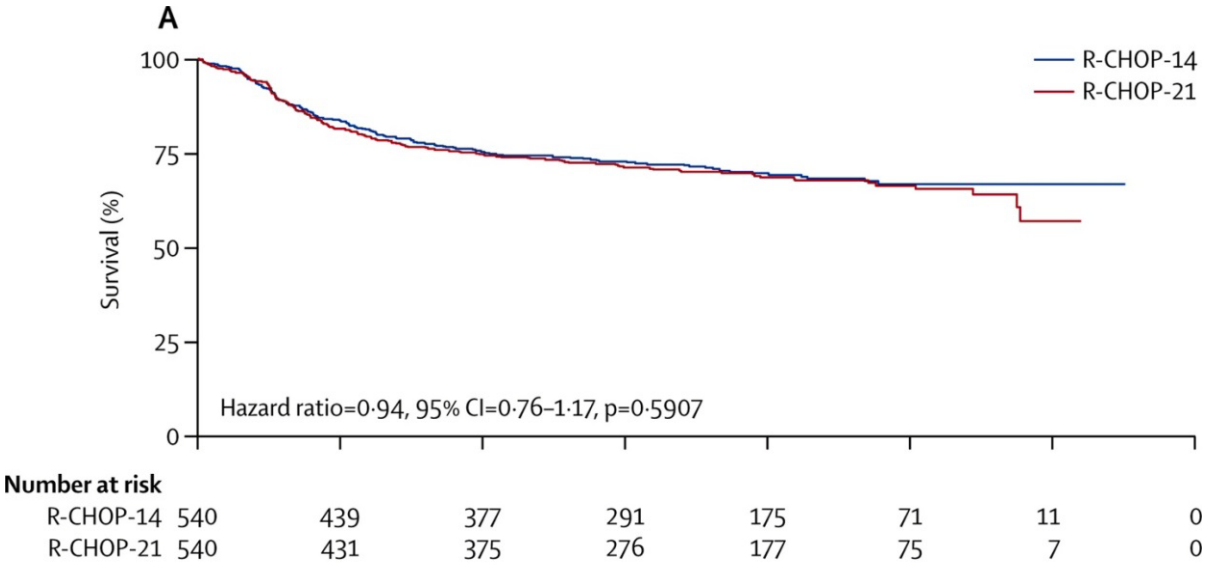
Stratified by
- IPI (0-1, 2, 3, 4-5)
- Age ≤60 vs. >60
- Treatment centre

1080 patients; 119 sites
Recruitment March 2005 - Nov 2008

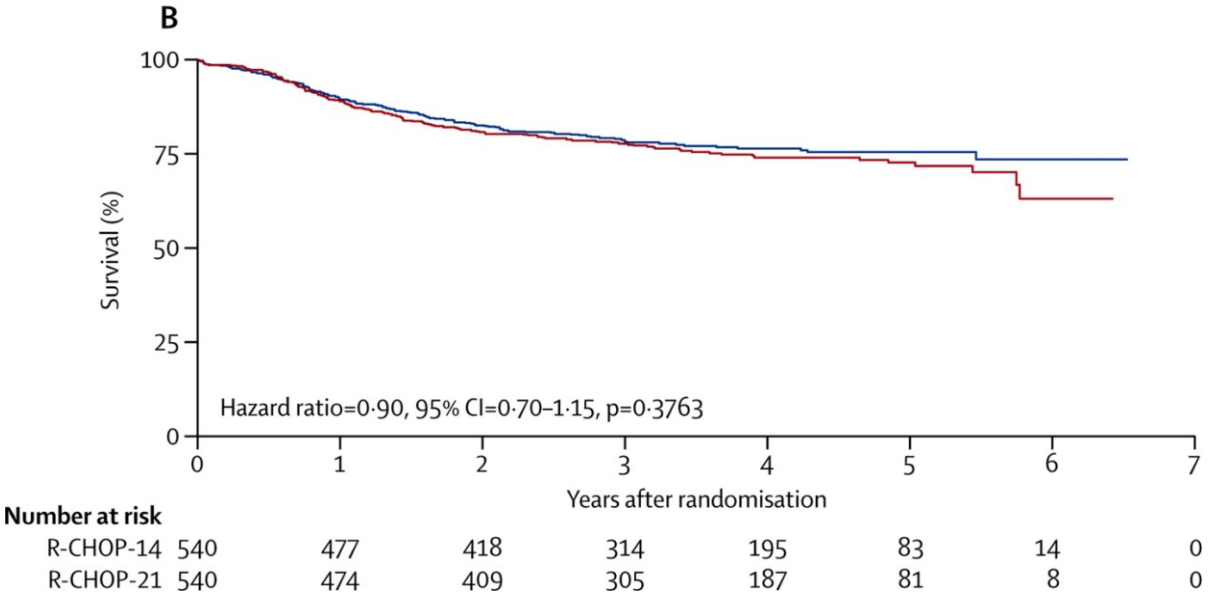
Cunningham, D, *et al. Lance*t 2013; 381:1817–1826.

R-CHOP14 vs 21: no difference in outcome

Progression -free survival

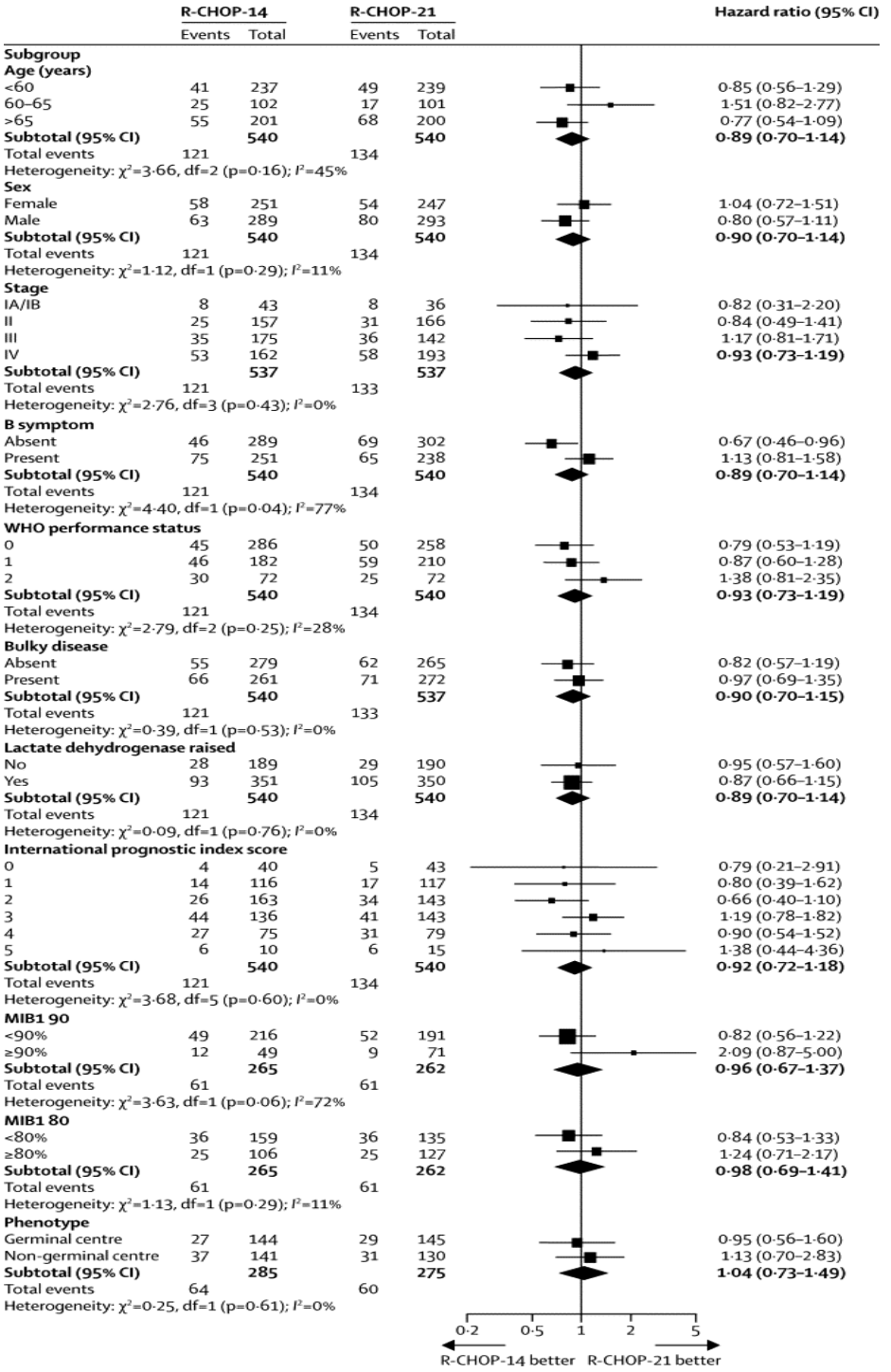


Overall survival



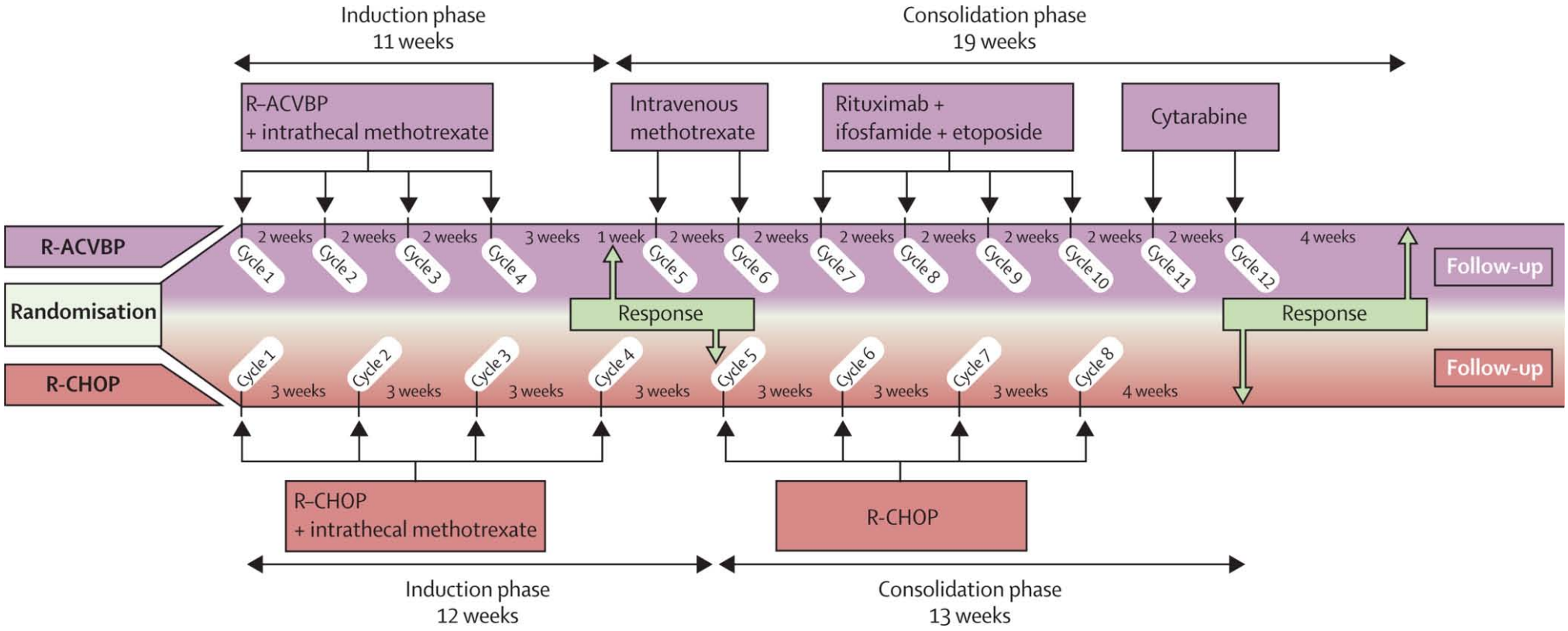
Cunningham, D, *et al. Lance*t 2013; 381:1817–1826.

R-CHOP14 vs 21: no subgroup could be identified



Cunningham, D, *et al. Lance*t 2013; 381:1817–1826.

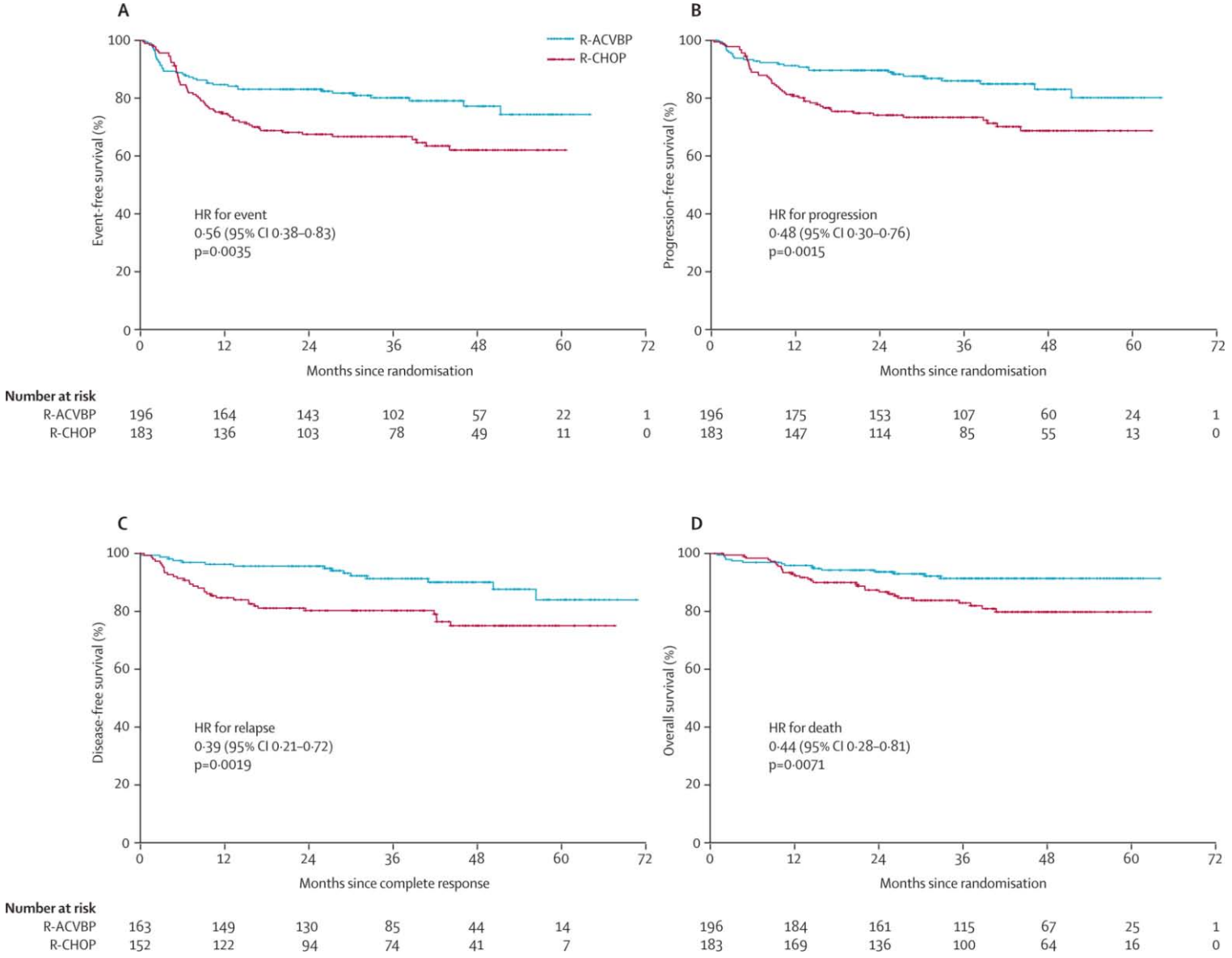
Other ways of improving dose intensity: GELA LNH03-2B



Young (age 18-59) aa IPI 1
n=380
Median age 47
55% stage III/IV, 44% bulk

Recher C, *et al Lancet* 2011: 378:1858-18676.

Improved outcome in R-ACVBP arm



Recher C, *et al Lancet* 2011: 378:1858-18676.

- Improvement in EFS, PFS and OS
- Outcome of R-CHOP x 8 arm inferior to those observed in MInT with R-CHOP x 6
- Excess utilisation of healthcare resource
- Excess of toxicity

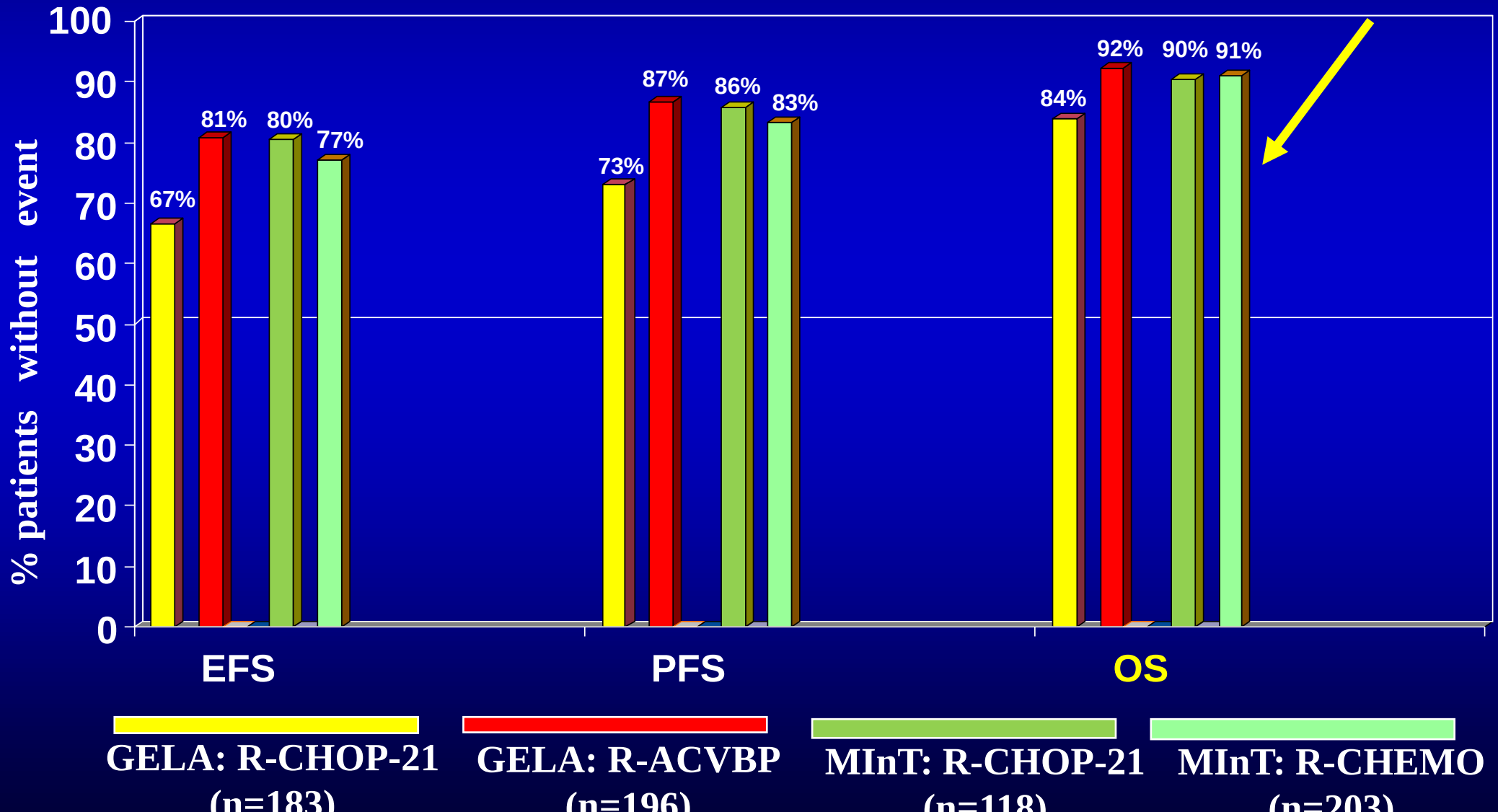
	R-ACVBP	R-CHOP
Toxicity (grade ≥3)		
Neutropenia	78%	64%
Anemia	35%	5%
Thrombocytopenia	30%	3%
Febrile neutropenia	38%	9%
Toxic deaths (n)	3	2

Recher C, *et al Lancet* 2011: 378:1858-1867.

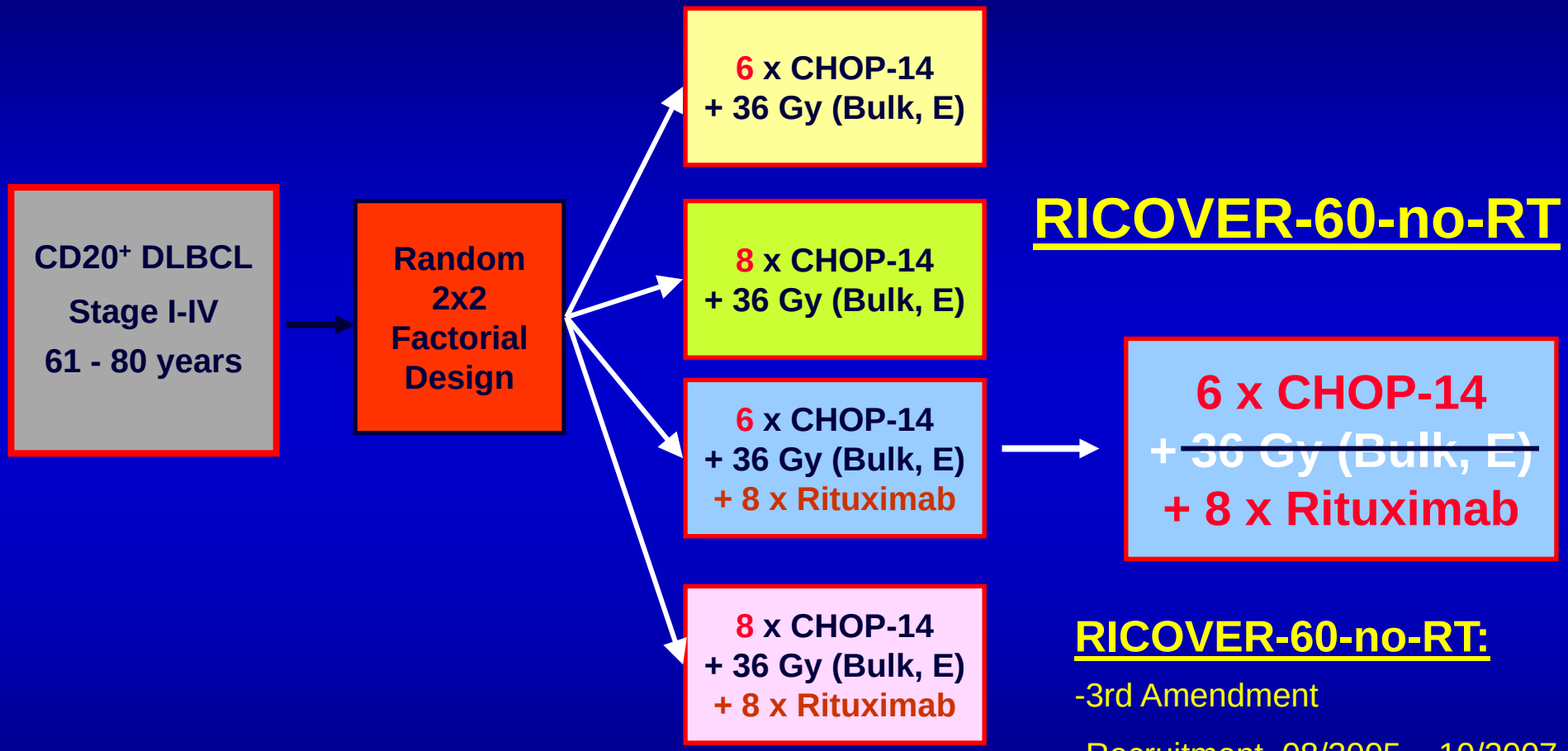
LNH 03-2B vs. MInT$_{aaIPI=1}$

Courtesy of Prof. Pfreundschuh

3-Year Results



Radiotherapy to bulky disease – RICOVER-60



RICOVER-60-no-RT:

-3rd Amendment

-Recruitment 08/2005 – 10/2007

-Number of Patients 166

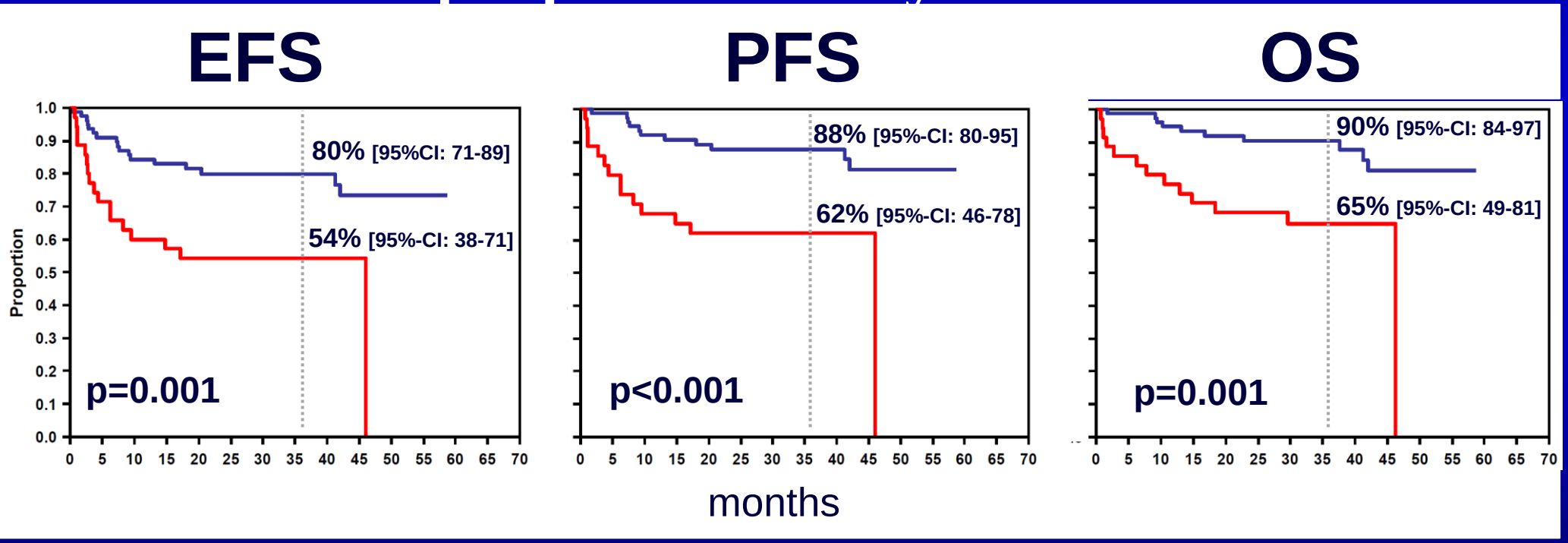
-Median Observation 39 Months

Pfreundschuh, Lancet Oncol, 2008

Held, JCO 2014

RICOVER-60-no-RT *Outcome (bulky disease)*

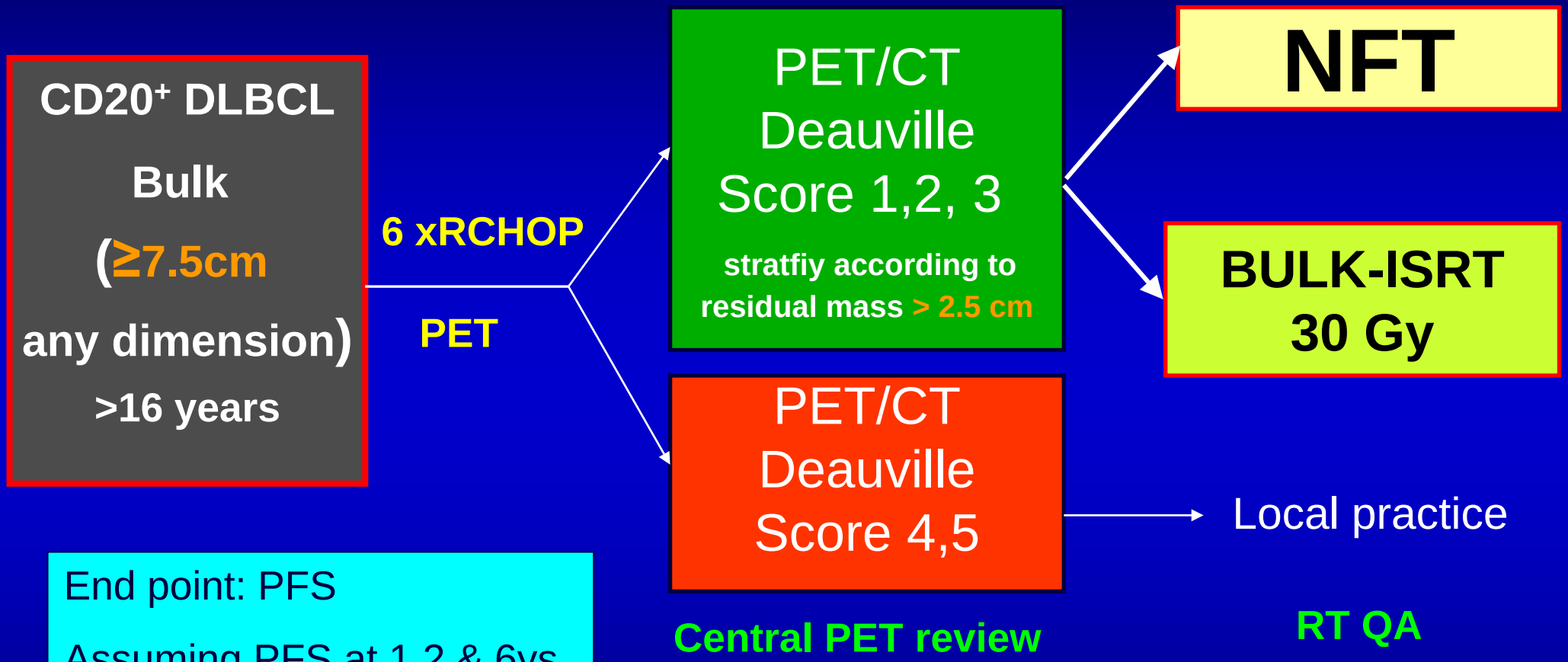
per protocol Analysis



Held, JCO 2014

DSHNHL

Outline of trial design in DLBCL



End point: PFS

Assuming PFS at 1,2 & 6ys of 80%, 75% and 73% in the NFT arm and 88%, 85% and 83% in RT arm (HR=0.565):

Sample size: 480 (5ys)

R-CODOX-M + R-IVAC:UK Study

(McMillan et al ICML 2015)

Rationale for use of R-CODOX –M and R-IVAC in poor risk DLBCL (IPI 3-5):

- Modified Magrath Burkitt Regimen
- Dose intensity is delivered from day 1
- Intense CNS directed therapy is achieved

- 2 doses of Rituximab given with each R-CODOX and 1 with each R-IVAC (TOTAL 8 doses)
- Pegylated G-CSF (NEULASTA) was given on D13 (cycle 1 & 3) and D7 (cycles 2 & 4).

Baseline characteristics

		N(%)
Median age (range)		50 (19 – 65)
Gender		
	Male	67 (61.5)
	Female	42 (38.5)
WHO Performance Status		
	0	20 (18.2)
	1	29 (26.4)
	2	42 (38.5)
	3	18 (16.5)
Stage		
	III	14 (12.8)
	IV	95 (87.2)

	N(%)
B Symptoms present	77 (70.6)
Bulky Disease present	61 (56.0)
Proven CNS Disease	11 (10.1)
IPI Score	
3	70 (64.2)
4	38 (34.9)
5	1 (0.9)
Age Adjusted IPI Score	
AA IPI 1	1 (0.9)
AA IPI 2	52 (47.7)
AA IPI 3	56 (51.4)

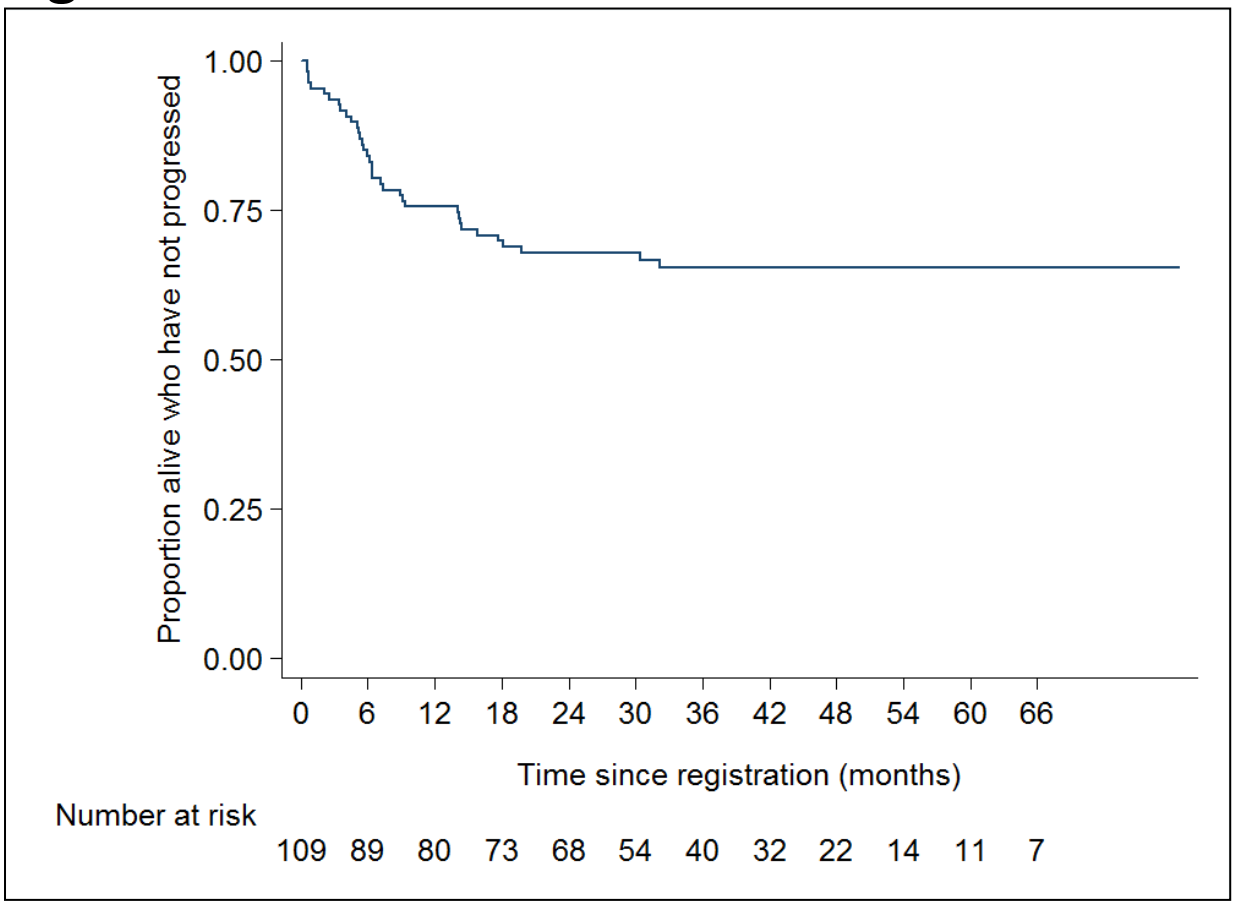
Toxicity

- All patients experienced at least one grade 3+ adverse event (AE)
- Five treatment related deaths were recorded:
  - all 5 were PS 3
  - ages: 53,55, 56, 56 and 60

Adverse Event in At least 10%	Worst Grade
	Grade 3-4 N(%)
Neutropenia	**104 (95.4)**
Thrombocytopenia	**101 (92.7)**
Infection	**69 (63.3)**
Mucositis	**38 (34.9)**
Anaemia	**32 (29.4)**
Fever	**19 (17.4)**
Febrile Neutropenia	**18 (16.5)**
Pain	**17 (15.6)**
Leukopenia	**13 (11.9)**
Diarrhoea	**12 (11.0)**
Nausea	**12 (11.0)**
Anorexia	**11 (10.1)**
Any grade 3/4 AE	**108 (99.1)**

Progression Free Survival

With a median follow-up of 37.7 months, thirty-seven patients have progressed or died.



Age adjusted IPI groups

2 year PFS estimate:

75.0% (60.9 - 84.6) for aaIPI 2

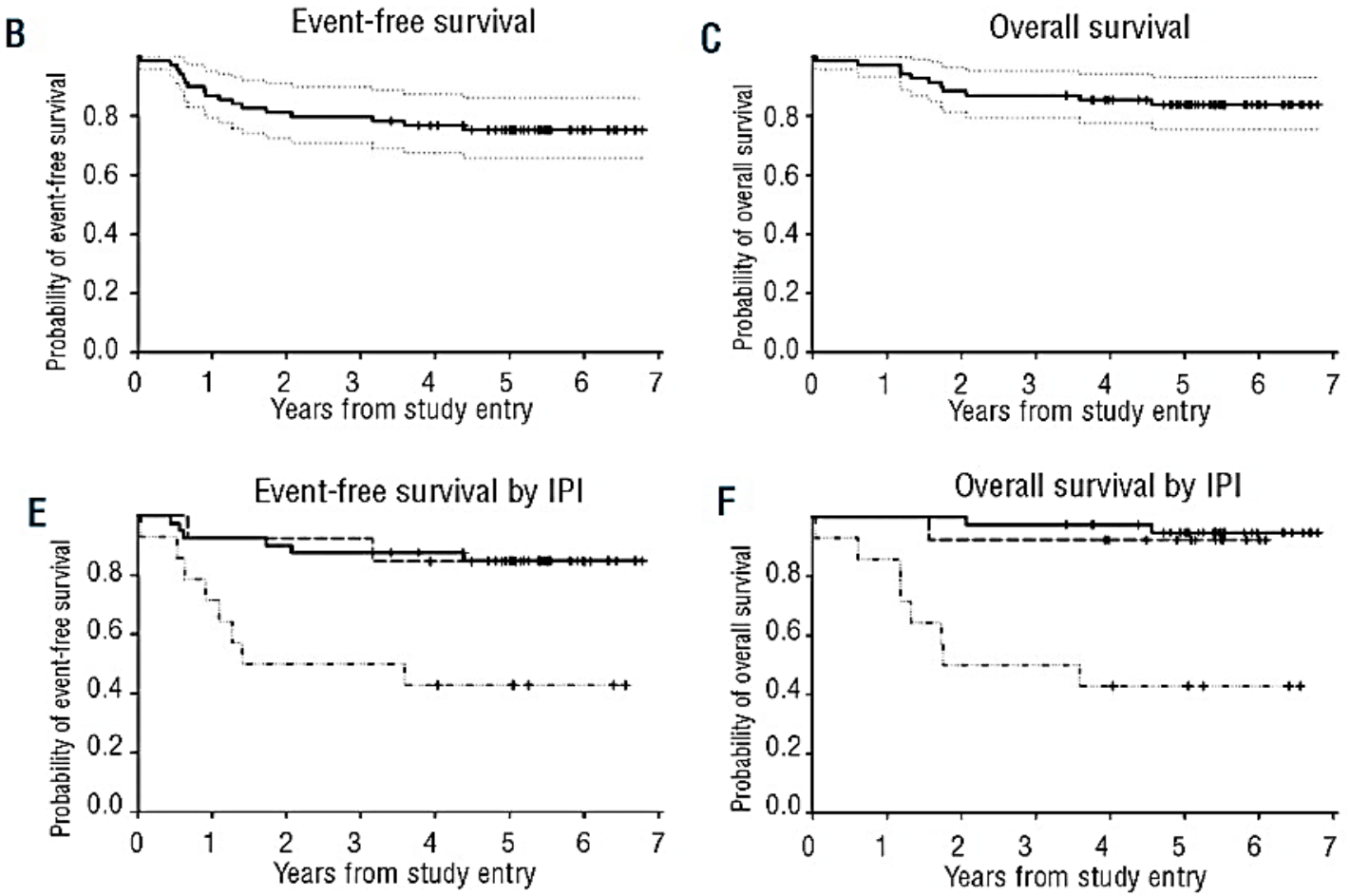
60.7% (46.1 - 72.3) for aaIIPI 3

PFS estimate at 2 years: 68.0% (95% CI: 58.2 – 75.9)

PFS estimate at 36.5 months: 65.3% (55.2 – 73.7)

Ongoing approaches to intensification…

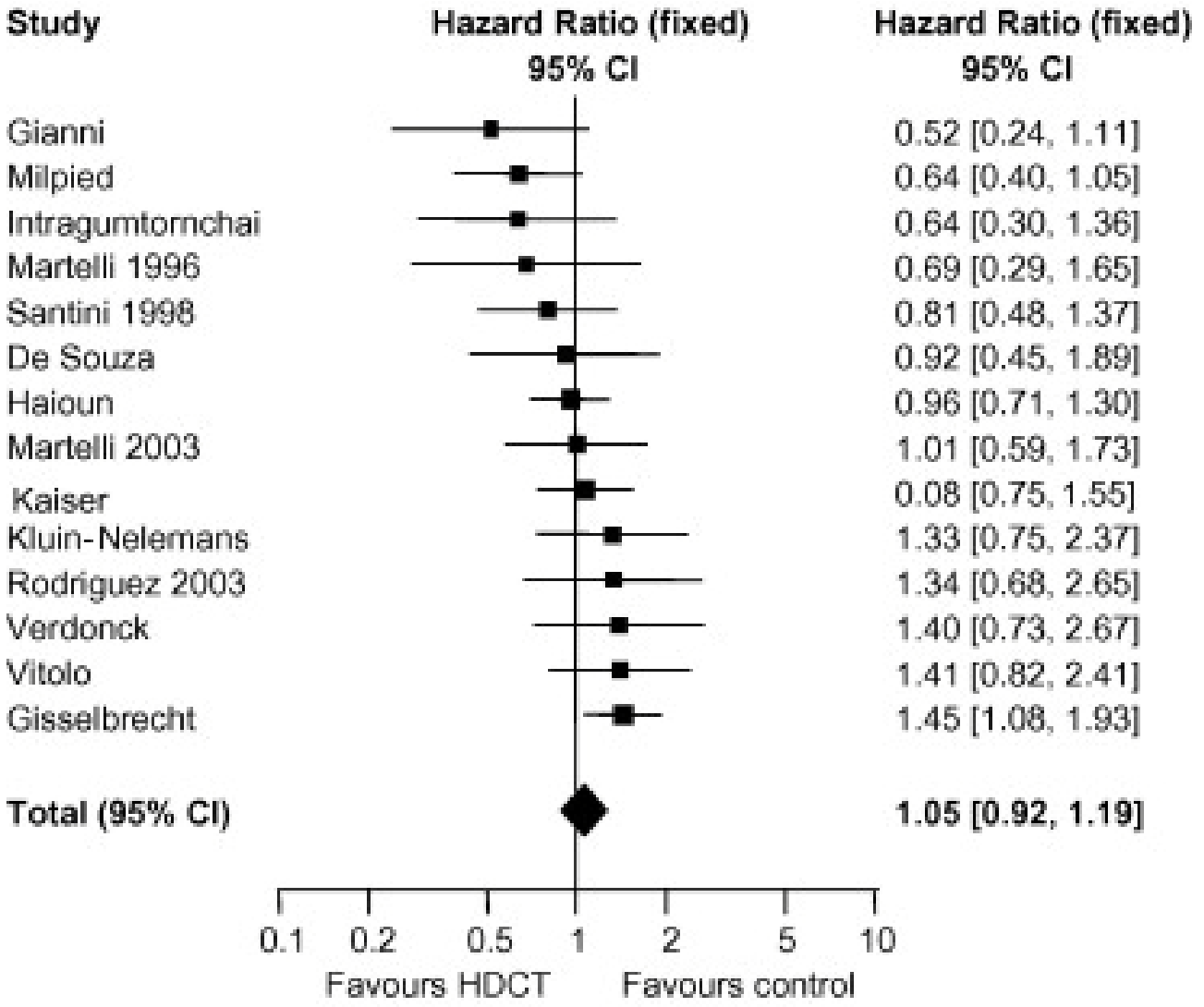
DA-EPOCH-R



- CALGB R-CHOP vs DA-EPOCH-R

Wilson W H et al. Haematologica 2012;97:758-765

Increasing dose intensity…High dose therapy

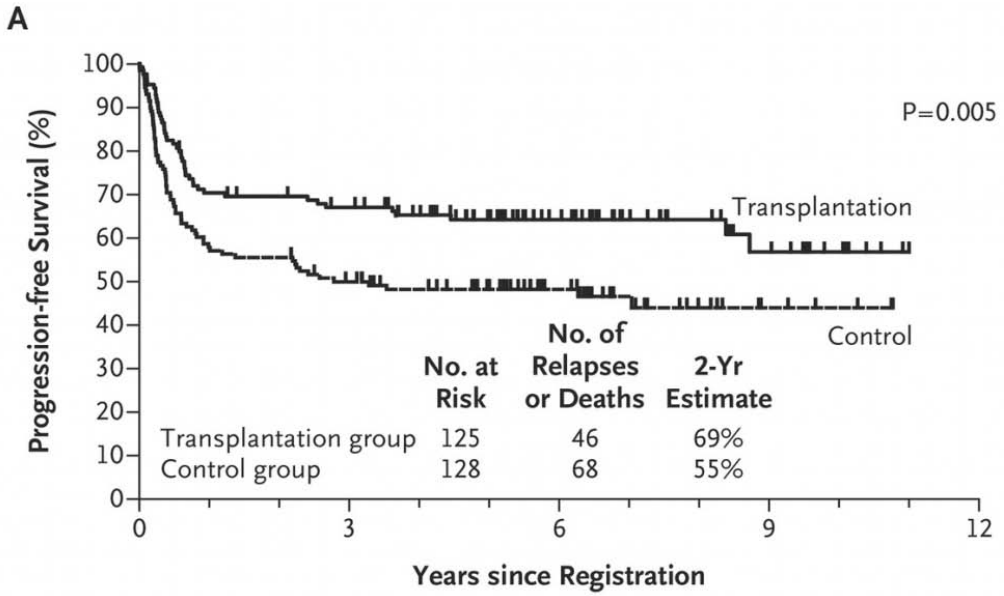


Greb A, *et al. Cancer Treat Rev* 2007; 33: 338–346

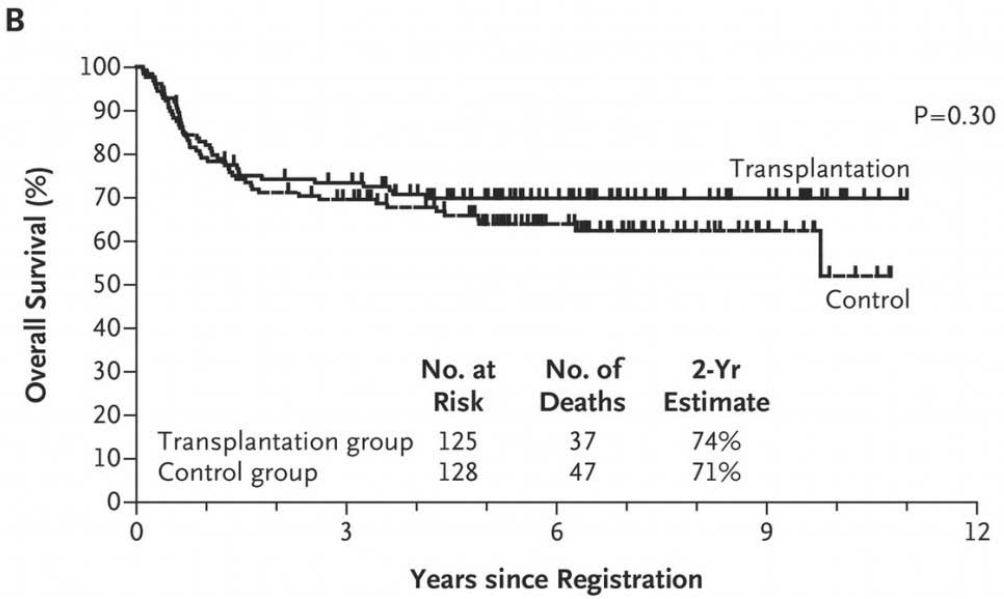
…may improve PFS for poorer prognosis patients

All patients high or high-intermediate IPI

PFS



OS



Stiff PJ et al. N Engl J Med 2013;369:1681-1690

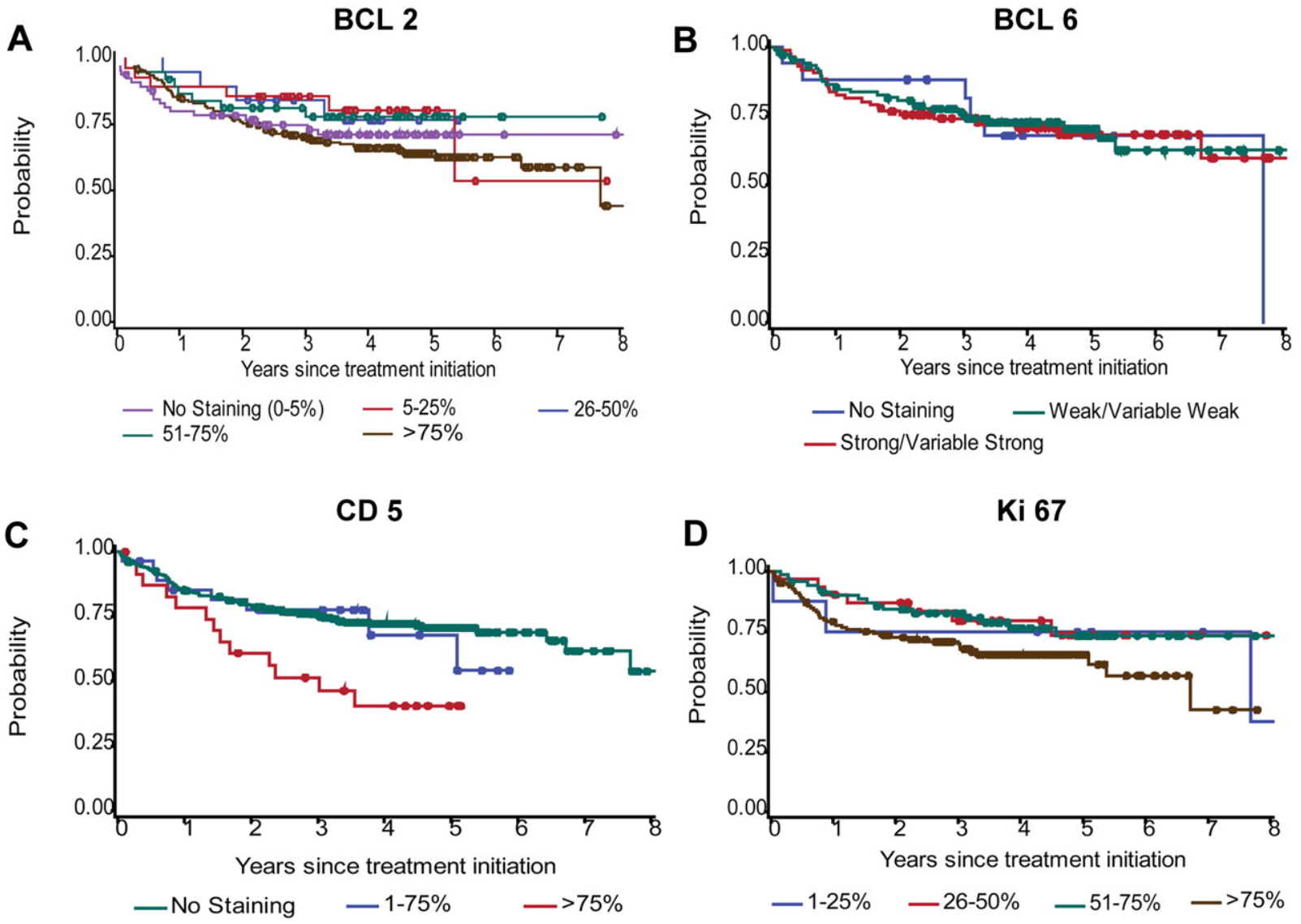
No mention so far of capitalising our insights from biology……

- If we can get the biomarkers right then will be able to identify patients that may benefit from intensification or specific targeted therapies.

Cell cycle regulation
p53
p16
p27
Cyclin D2
Ki67
c-myc
Apoptosis related
Bcl-2
B-cell differentiation
Bcl-6
CD10
CD5
FoxP1
CD21
Adhesion molecules
ICAM-1
Microenvironment
VEGF
CD40
HIF-1α

Adapted from Lossos and Morganstein JCO 2006;24:995

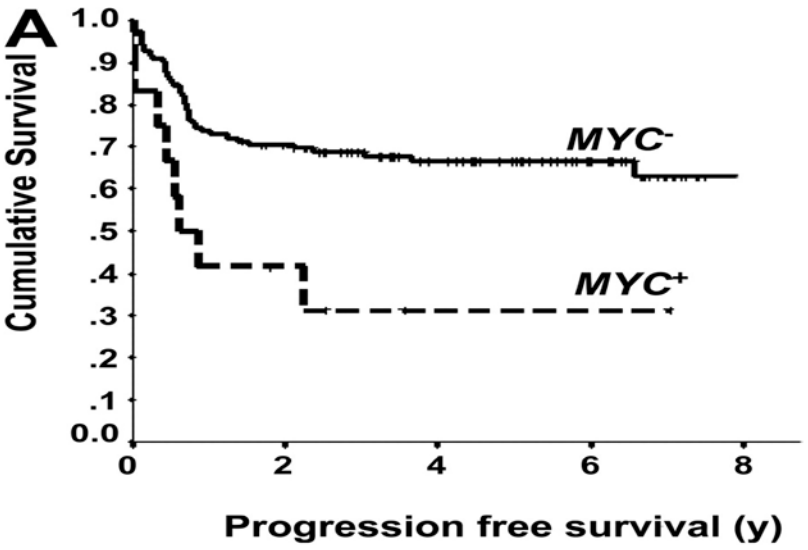
Overall survival of R-CHOP-treated patients in Lunenburg analysis

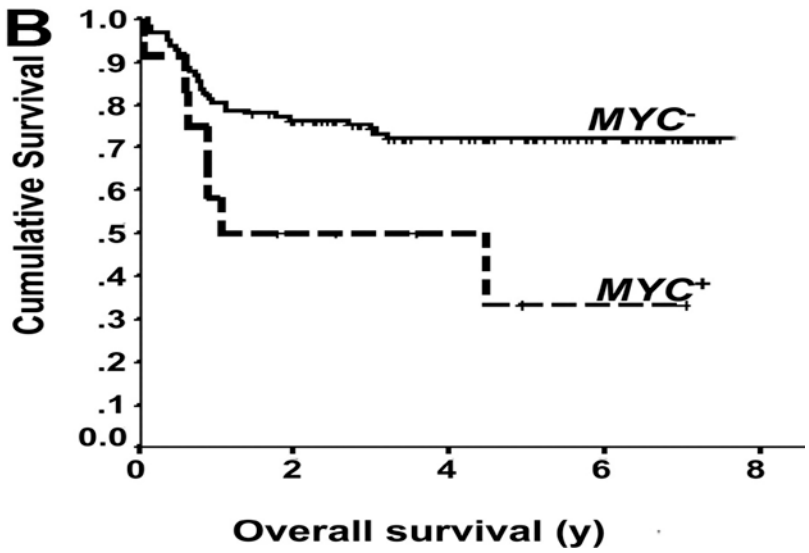


Salles G et al. Blood 2011;117:7070-7078

MYC translocations

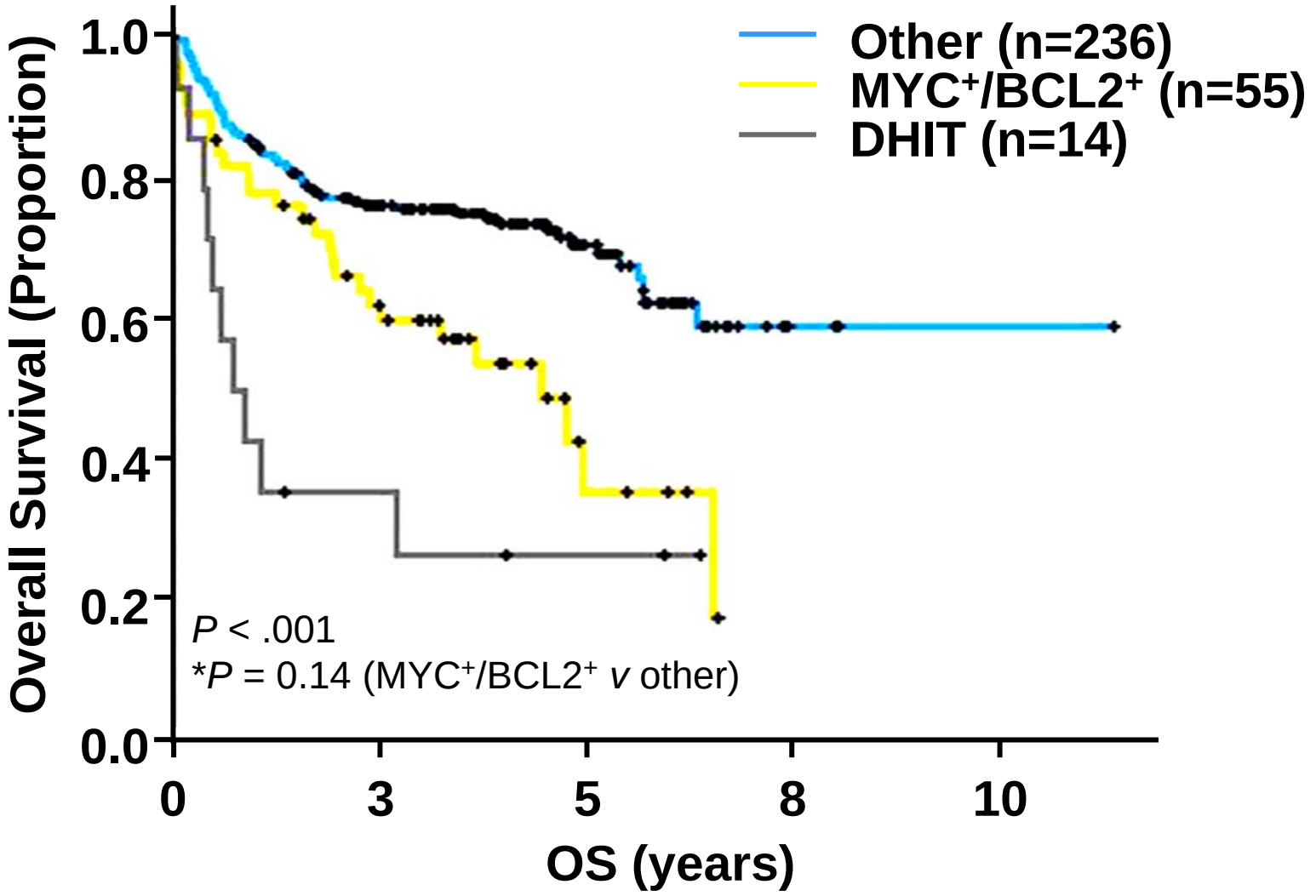
- Present in 5-10%
- Typically t(8:14)(q24;q32) but non-Ig locus
- 5 year PFS 31% vs 66% (P=0.006)
- Higher risk of CNS recurrence
- No particular baseline clinical feature
- Complex karyotype
- *MYC* FISH for all patients?
- **Median presentation in 7th decade…limits options for therapy**
- Impact of non-*IGH* partners





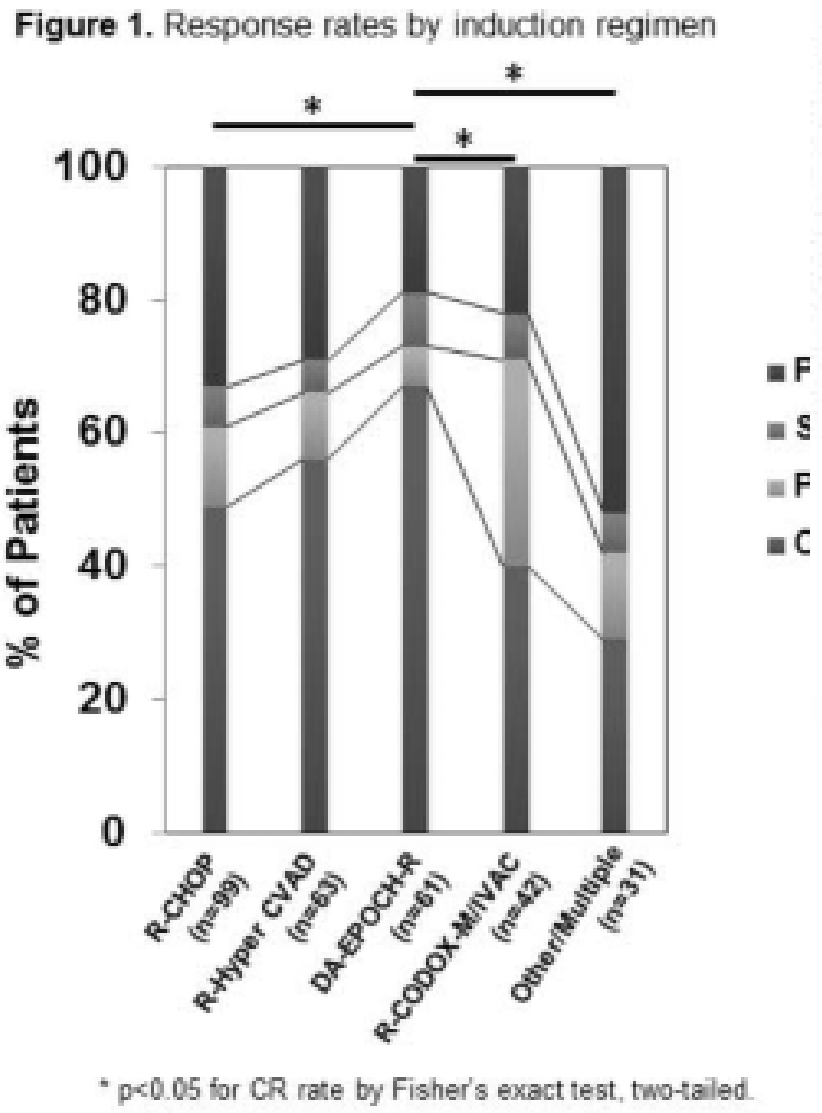
Savage K J et al. Blood 2009;114:3533-3537

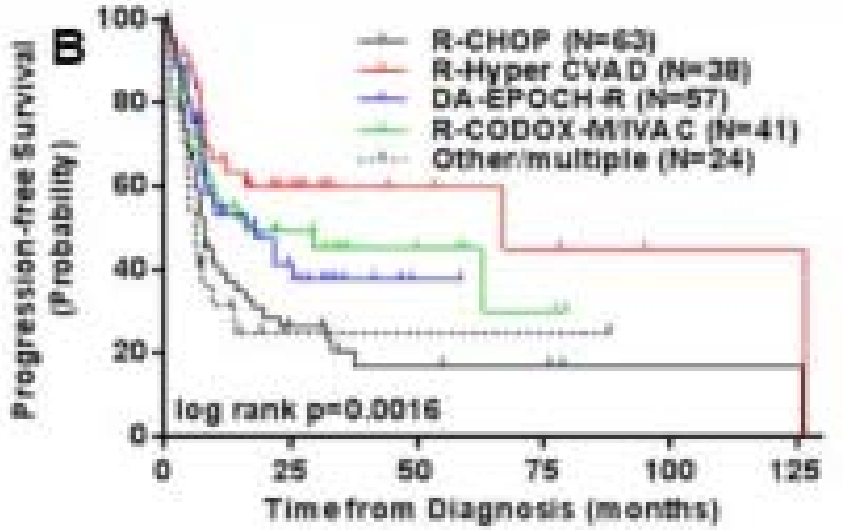
MYC/BCL2 and dual translocation



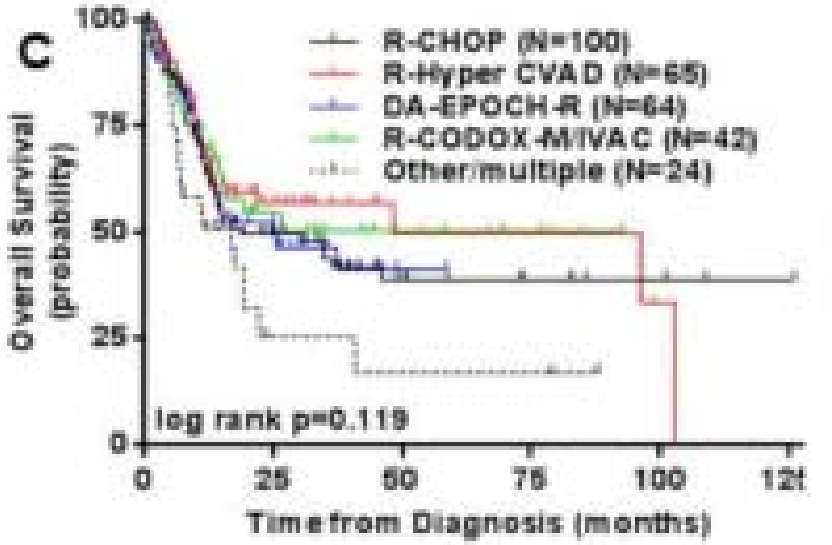
Johnson N A et al. JCO 2012;30:3452-3459

A role for intensified therapies?





PFS

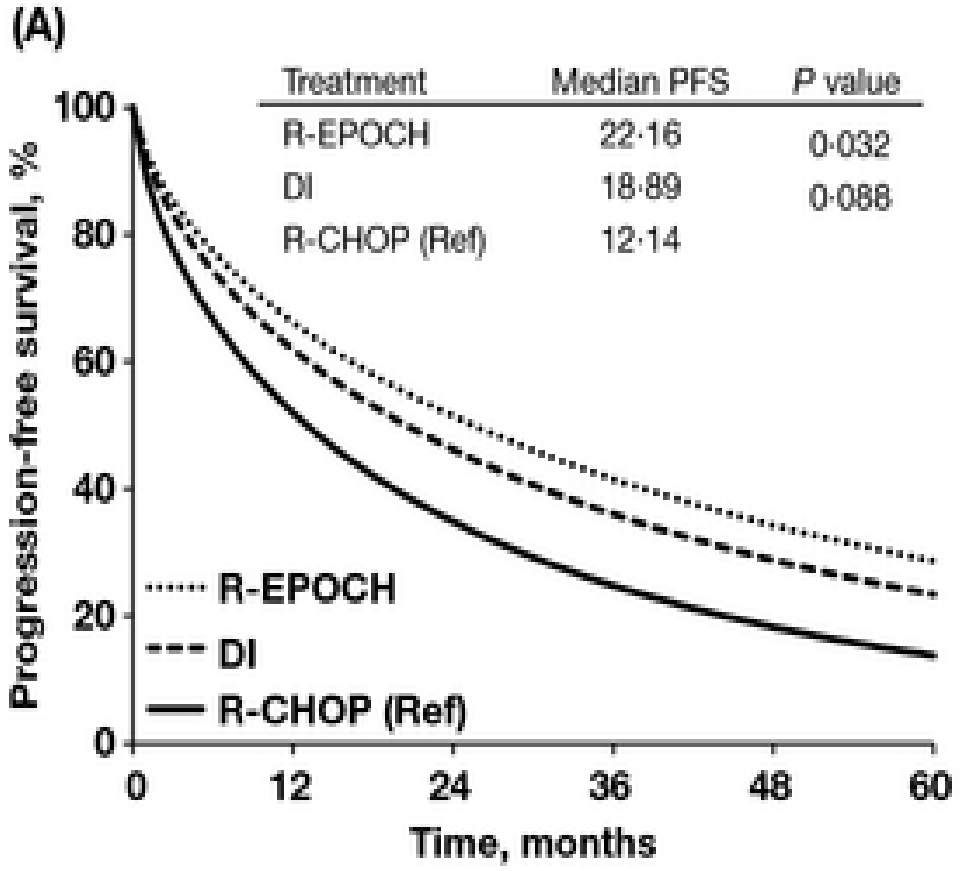


OS

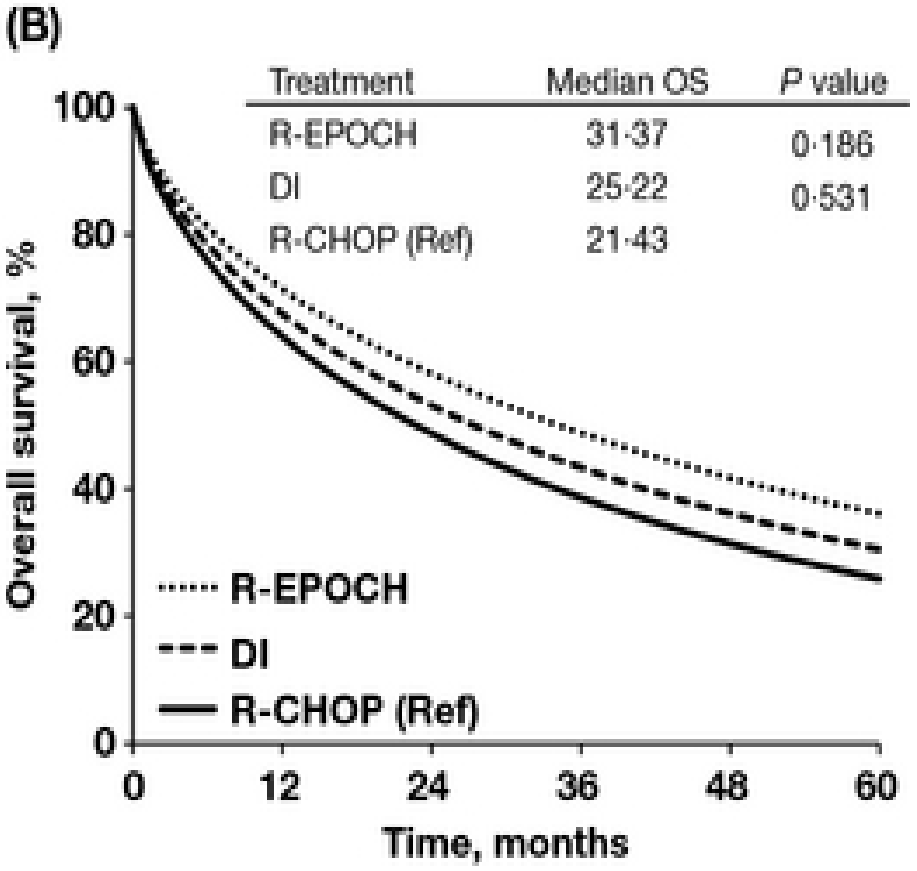
Petrich at al Blood 2014

Meta-analysis (Howlett et al. BJH 2015)

394 patients



PFS



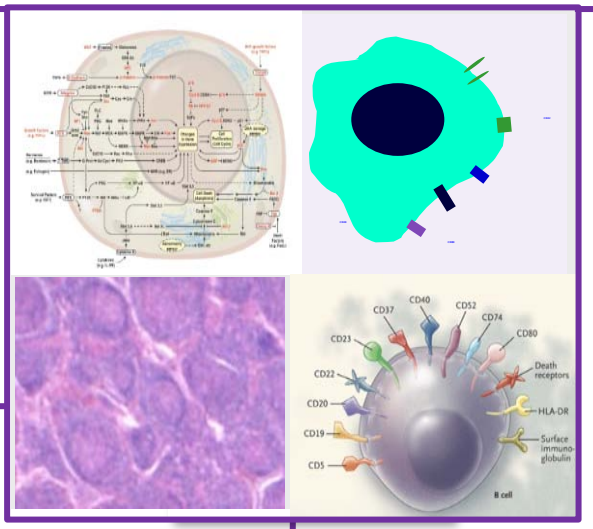
OS

Microenvironment

- Lenalidomide
- T-cell exhaustion

Actionable mutations

- EZH2 — E7438
- CD79a/b — AEB071



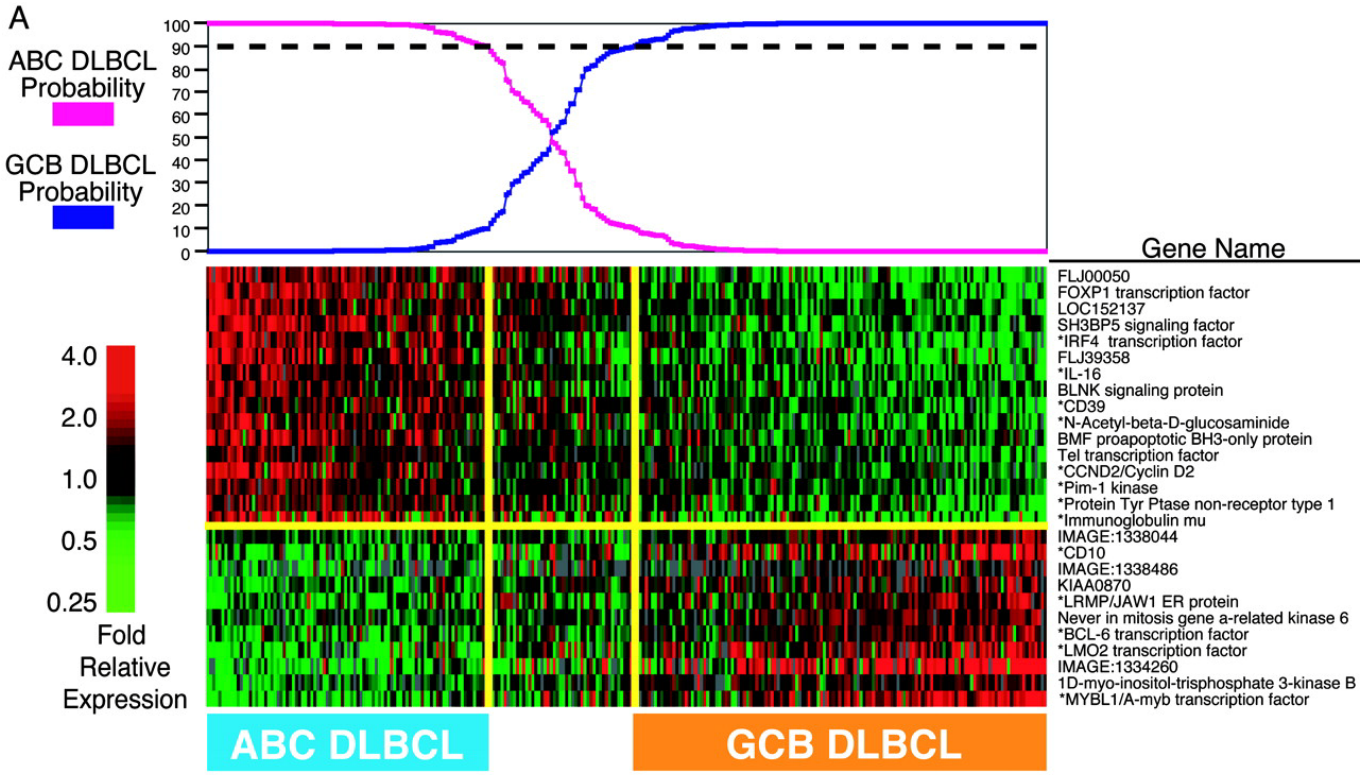
Surface markers

- **Anti CD20 moAb** — Ofatumumab, GA-101
- **Anti CD40 moAb** — Dacetuzumab
- **Anti CD22** — Epratuzumab, Inotuzumab Ozogamicin, polatuzumab

Pathways

- **Proteosome inhibitors** — Bortezomib
- **Bcl-2 family inhibitors** — ABT-263
- **Survivin inhibitors** — YM155
- **Syk inhibitors** — Fostamatinib, entosplentib
- **mTOR inhibitors** — Everolimus, Temsirolimus
- **PI3K inhibitors** — Idelalisib, Copanlisib, Duvelisib, TGR-1202
- **Btk inhibitors** — Ibrutinib, ONO/GS-4059, ACP-196
- **Hsp 90 inhibitors** — KW 2478
- **HDAC inhibitors** — Vorinostat, Panobinostat
- **PKC inhibitors** — Enzastaurin
- **Aurora kinase inhibitors**
- **Nedd8-activating enzyme inhibitors** — MLN4924

Complex models of biological heterogeneity



B

Model Prediction

DLBCL Subgroup by Hierarchical Clustering

	ABC	GCB	Other
ABC	37	1	4
GCB	1	58	8

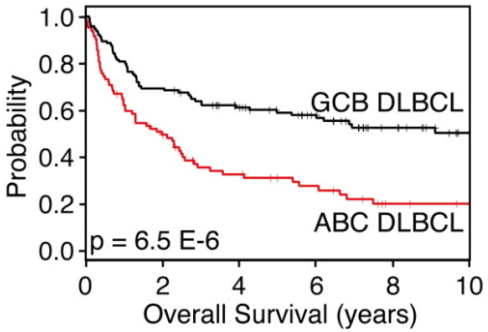
Training Set

	ABC	GCB	Other
ABC	38	1	2
GCB	2	57	8
Type 3	14	18	25

Validation Set

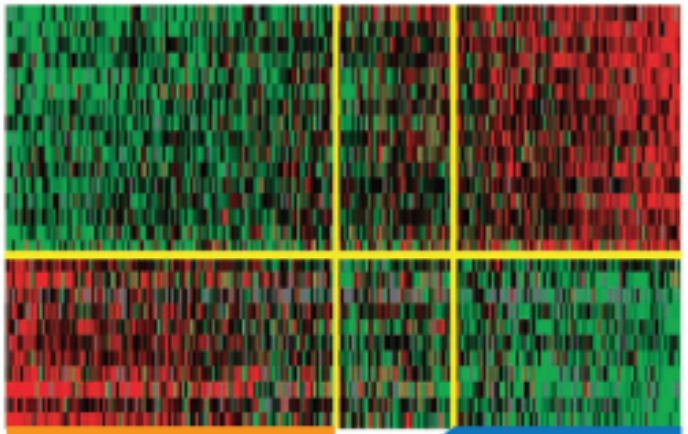
	ABC	GCB	Other
ABC	75	2	6
GCB	3	115	16
Type 3	14	18	25

All Samples



Wright, George et al. (2003) Proc. Natl. Acad. Sci. USA 100, 9991-9996

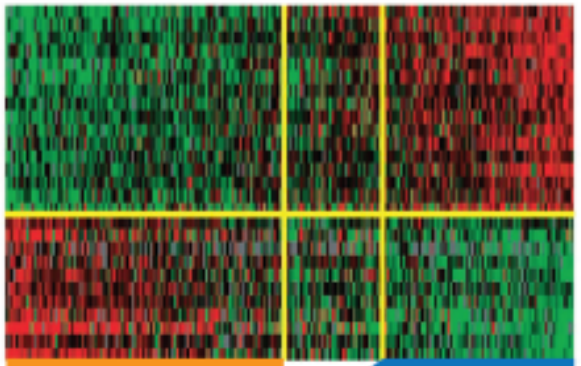
Translocations and Copy Number Changes



	GCB	ABC
BCL6 translocation	11%	22%
MYC translocation	14%	9%
BCL2 translocation	45%	0%
PTEN deletion	11%	0%
REL amplification	26%	5%
BCL2 amplification	1%	11%
CDKN2A/B deletion	4%	30%
PRDM1 deletion	0%	26%
SPIB amplification	3%	26%

Lenz et al Proc Natl Acad Sci USA 2008

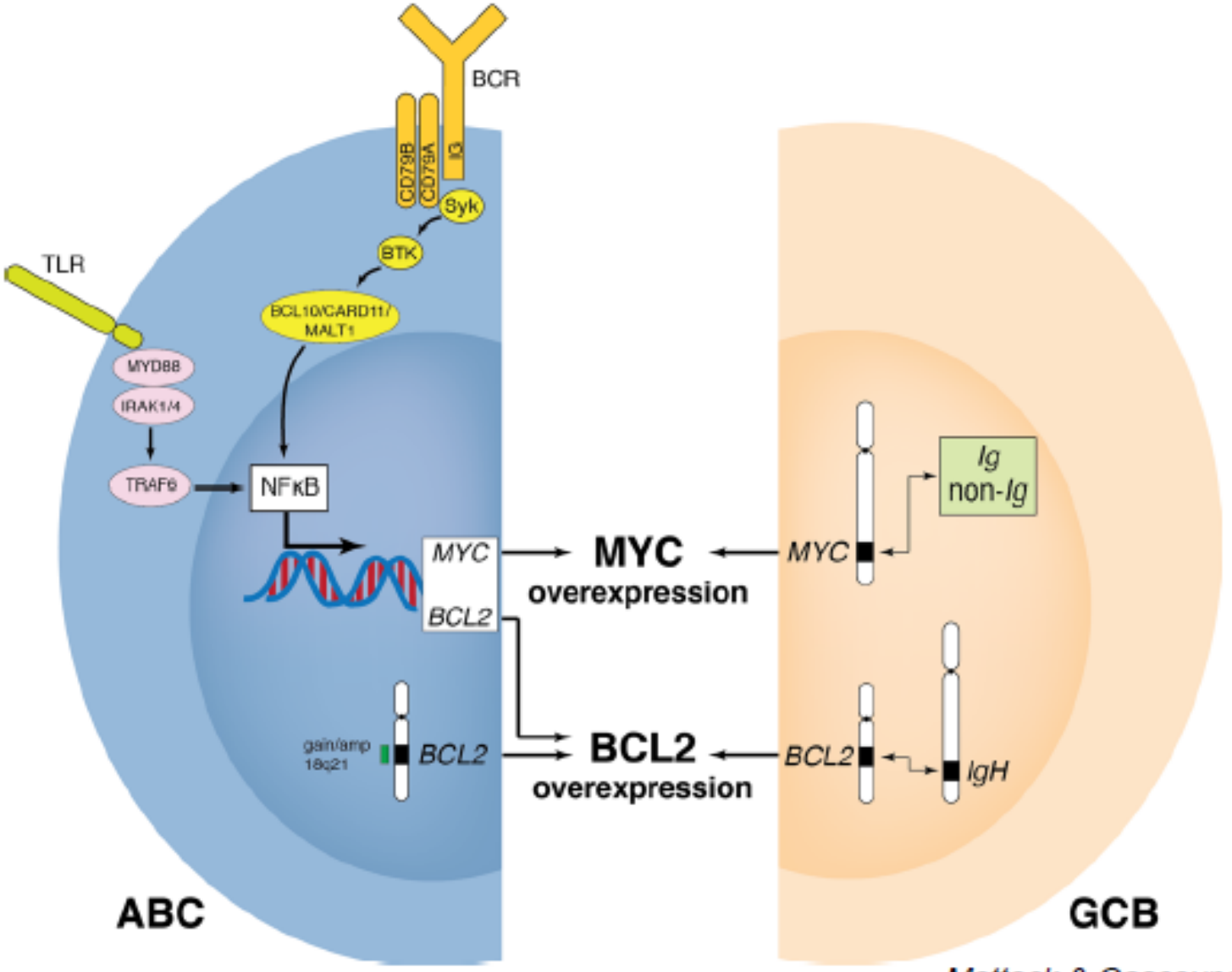
Recurrent Gene Mutations



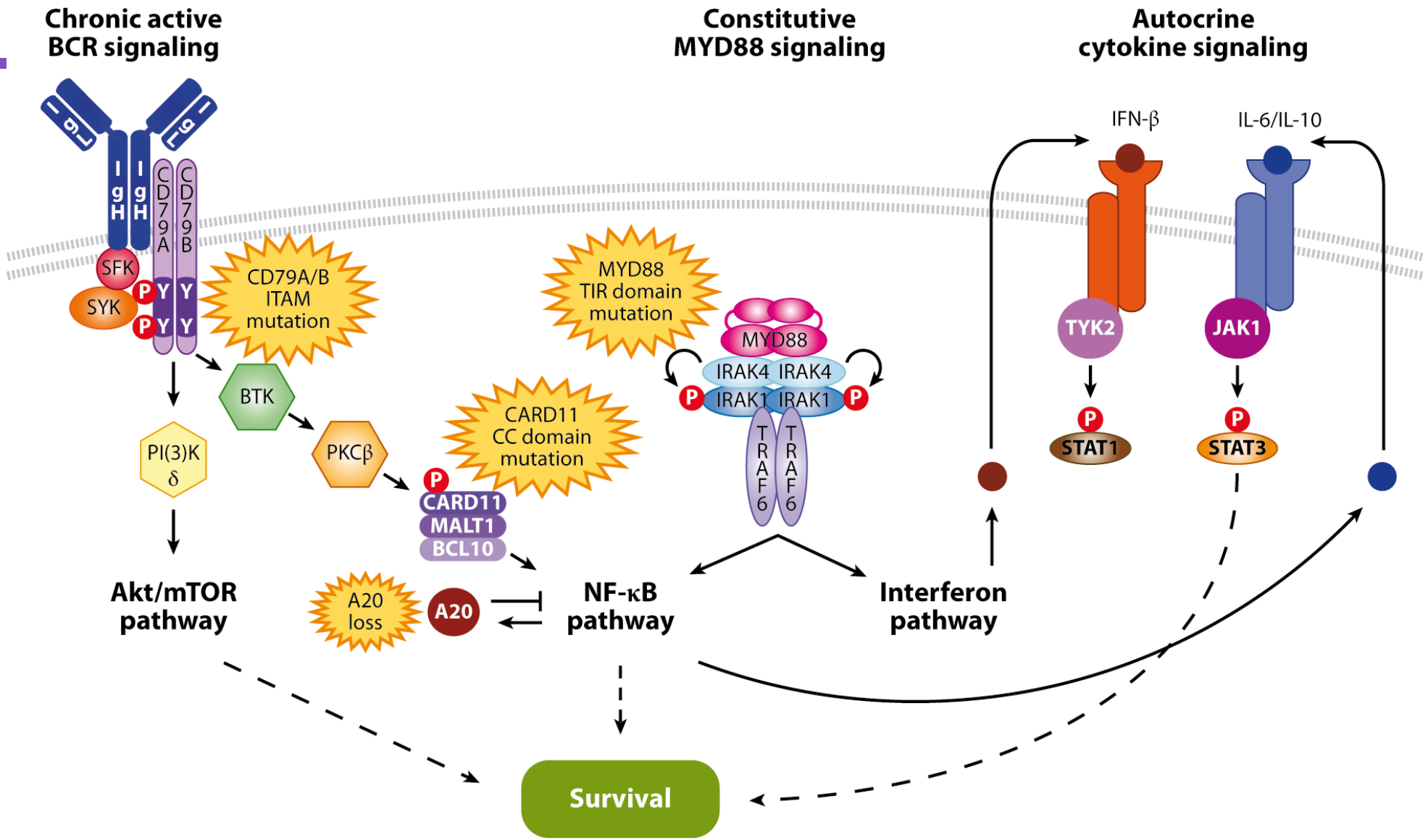
	GCB	ABC
CREBBP	32%	9%
FOXO1	11%	8%
MLL2	27%	21%
TP53	26%	18%
EZH2	22%	0%
GNA13	29%	0%
MEF2B	22%	0%
SGK1	24%	0%
TNFRSF14	13%	0%
CARD11	4%	10%
CD79B	2%	21%
MYD88	2%	29%
PRDM1	0%	27%

Morin et al Nat Genet 2010
Davis et al Nature 2010
Ngo et al Nature 2011
Morin et al Nature 2011
Pasqualucci et al Nat Genet 2011

Mechanisms that deregulate MYC & BCL2 in DLBCL

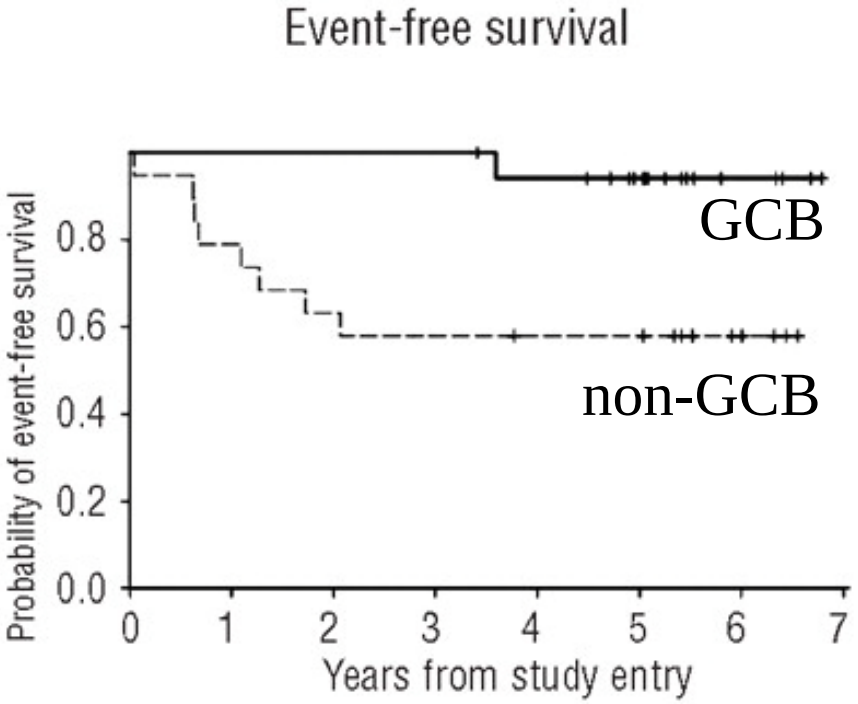


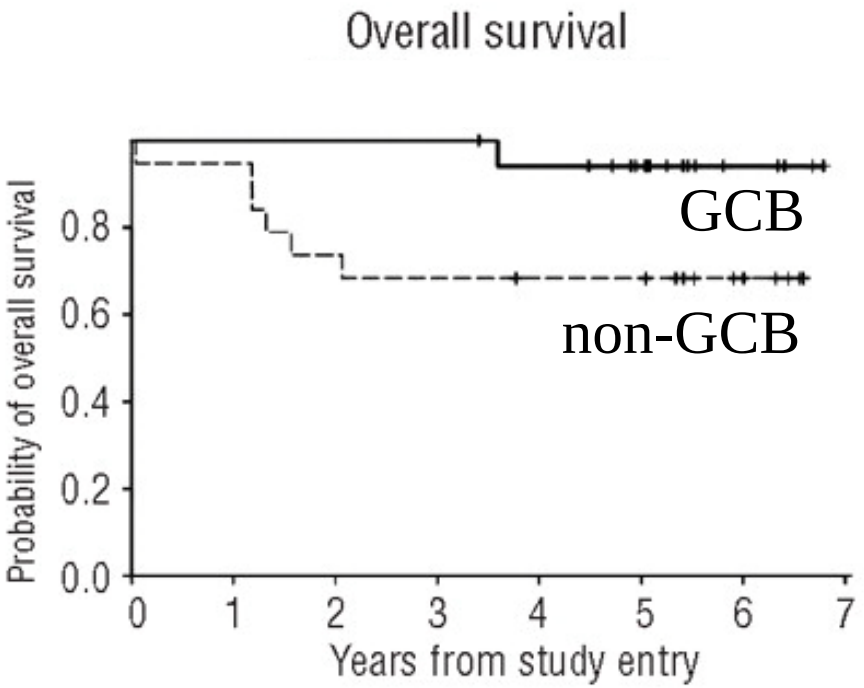
Mottock & Gascoyne, CCR 2014



Schaffer A L, et al. 2012. Ann. Rev. Immunol 30:565-610

Differential outcomes with DA-EPOCH-R



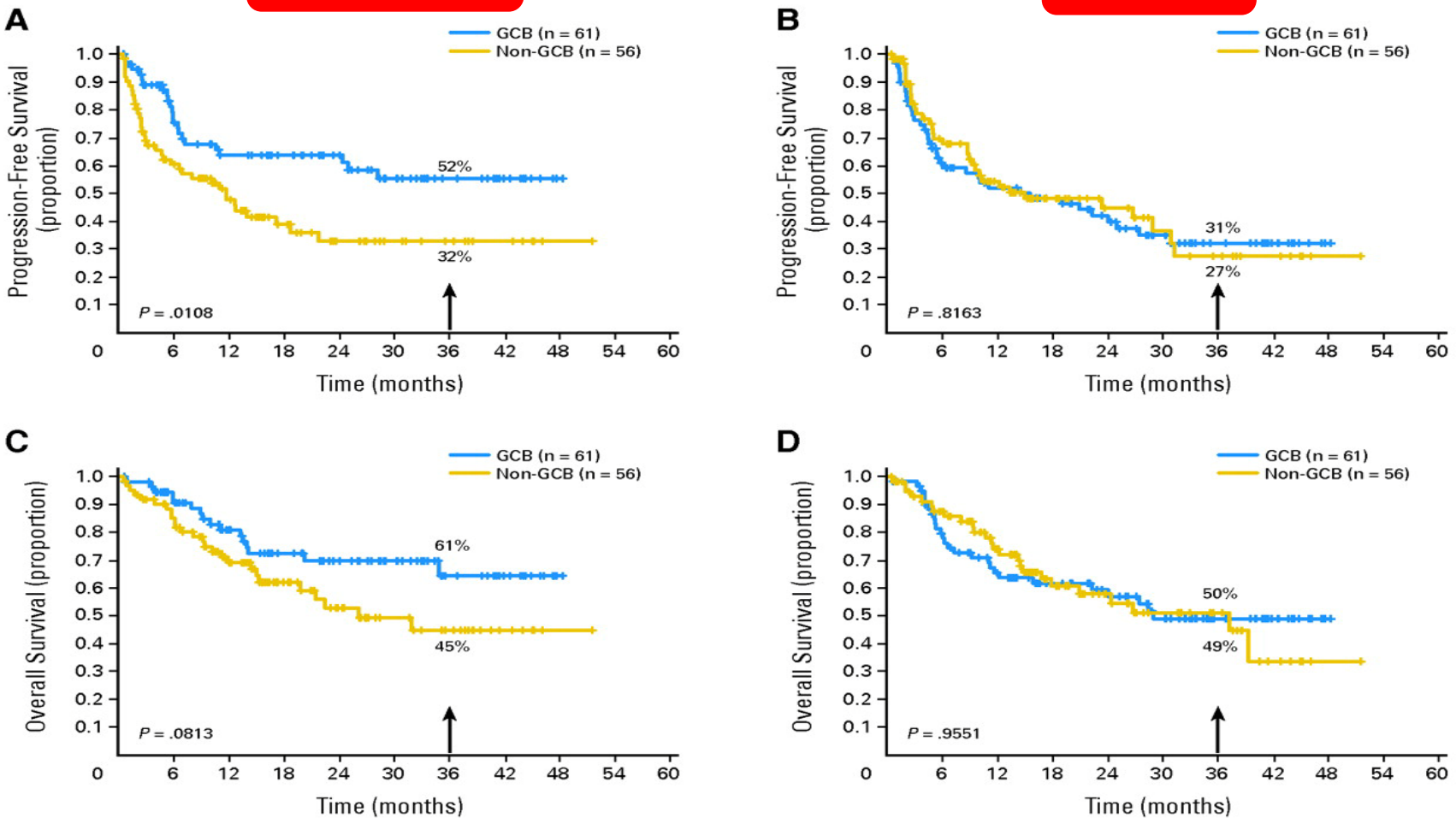


Wilson W H et al. Haematologica 2012;97:758-765

Differential outcome in the relapsed setting

R-DHAP

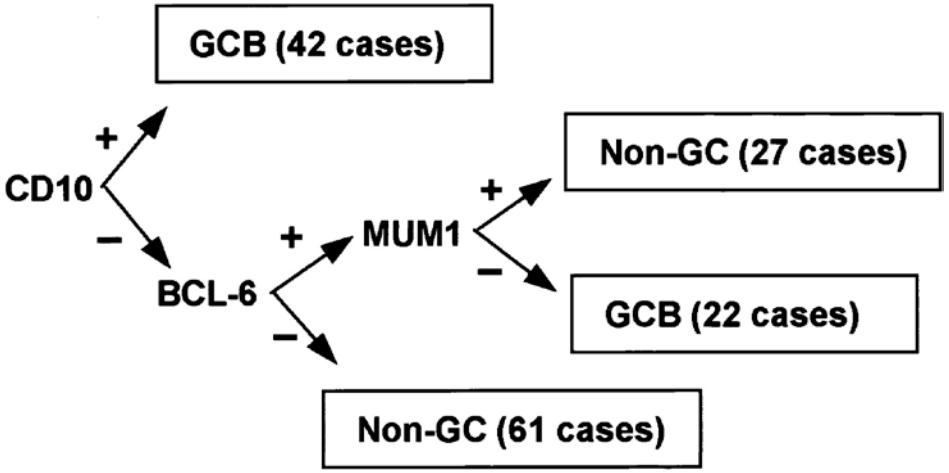
R-ICE

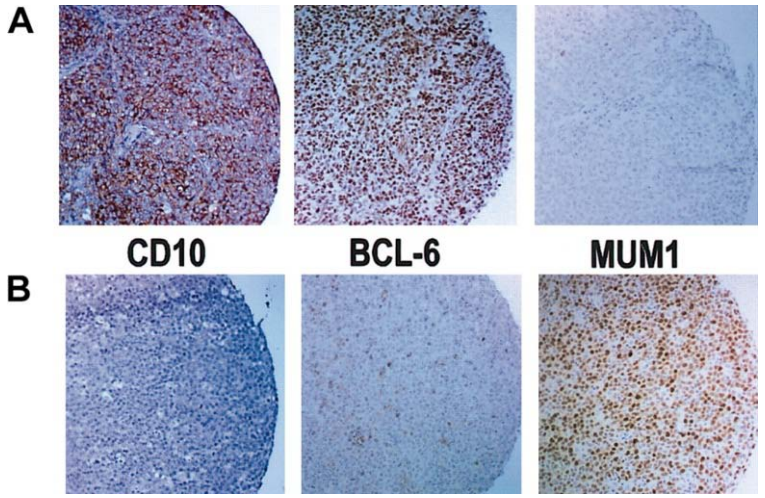


N=232; 50% split GCB and non GCB

Thieblemont C *et al. J Clin Oncol* 2011;29:4079-4087

But how to distinguish phenotype?

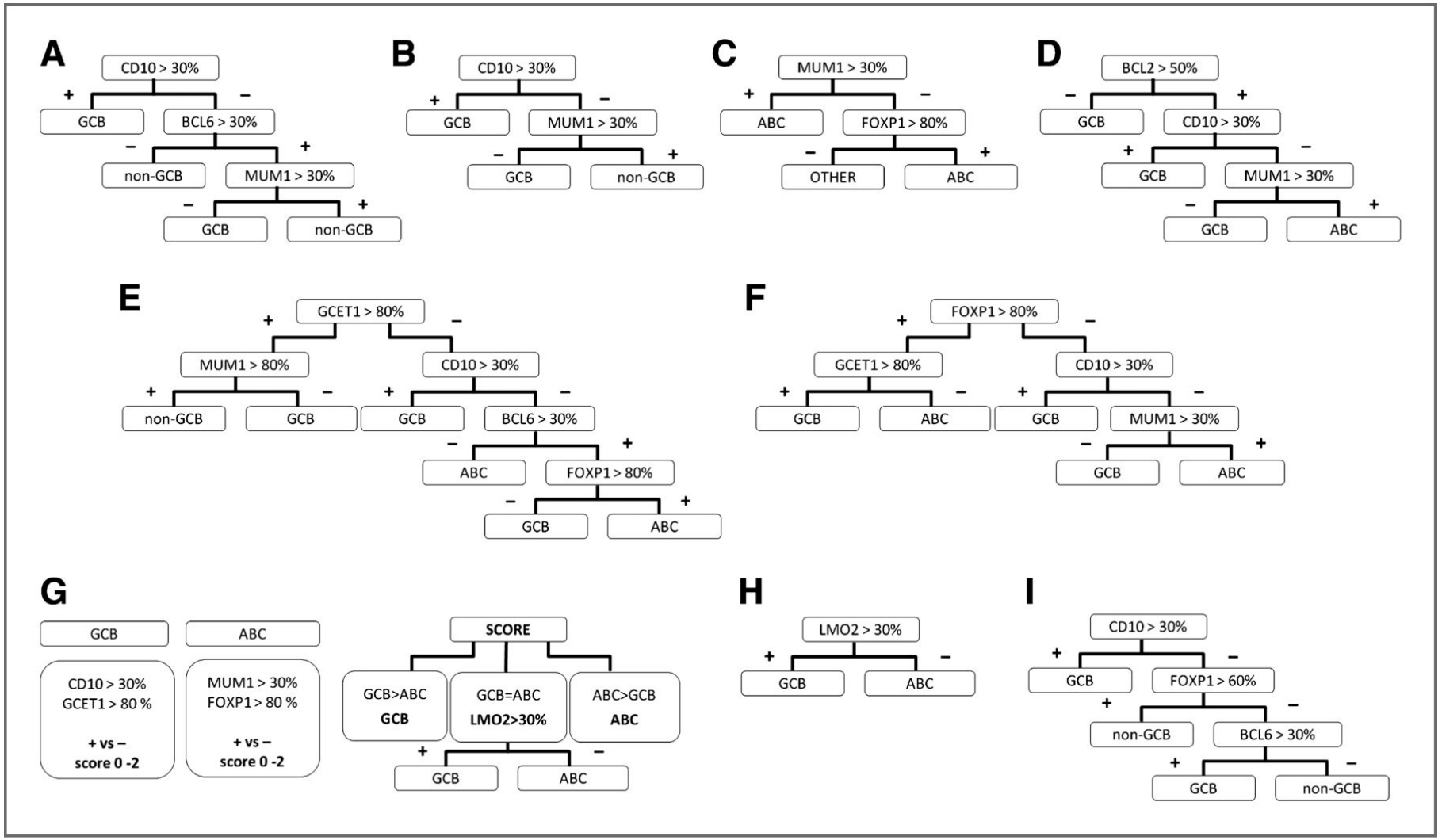




- Getting it right is important when looking prospectively at therapy, not prognosis
- The immunophenotype is not that good:
  - CD10+ (about 1/3), Mum-1-: Almost all GCB
  - CD10- (2/3) hard to distinguish ABC from GCB on immuno's
  - Bcl-6 is a difficult stain
  - Discordance with mRNA (~20%)
- Conflicting IHC datasets
- Lunenberg project demonstrates poor correlation between centres (technical and interpretative)

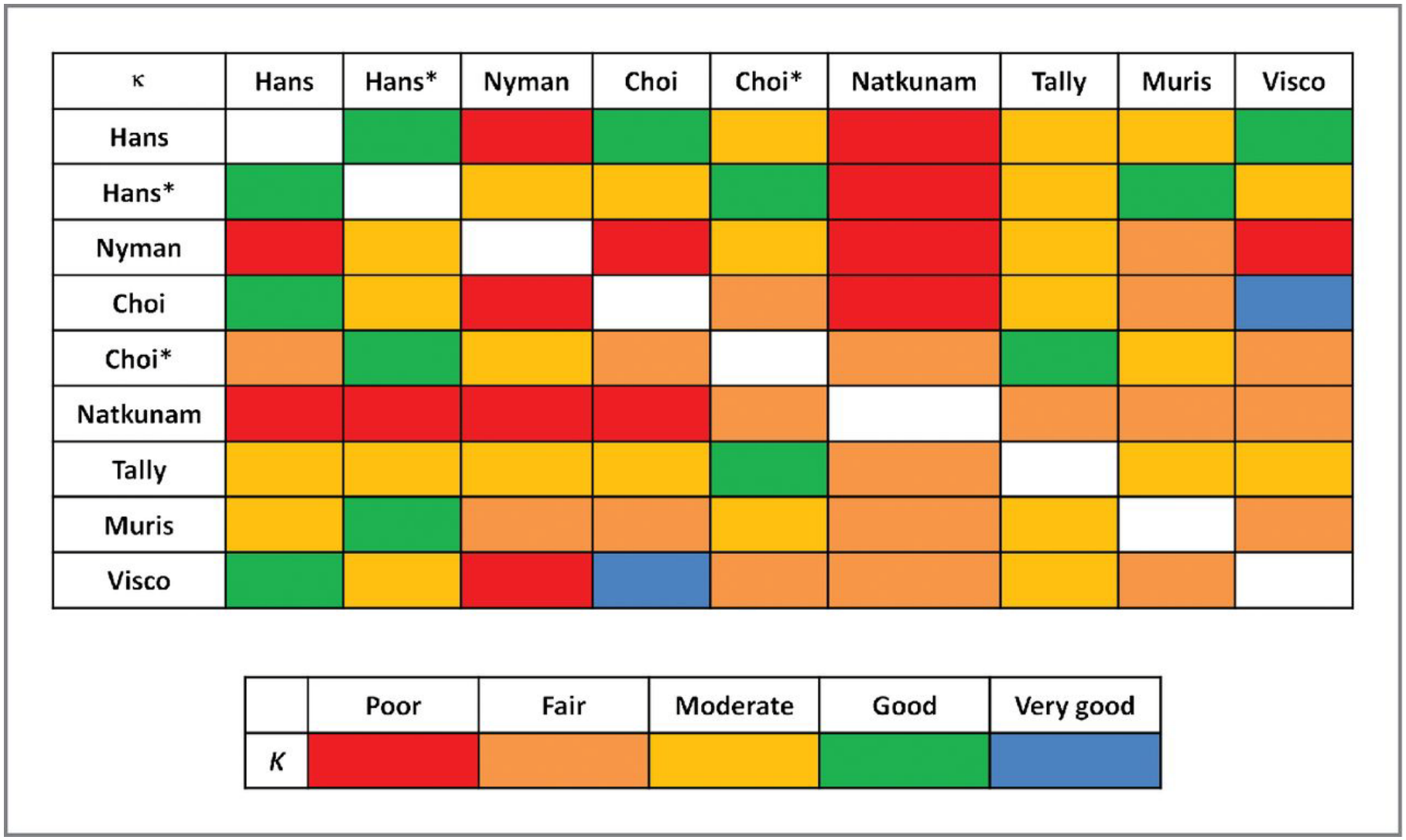
Hans, C. P. et al. Blood 2004;103:275-282

Lots of different IHC Algorithms…



Rita Coutinho et al. Clin Cancer Res 2013;19:6686-6695

But correlation is poor….



Rita Coutinho et al. Clin Cancer Res 2013;19:6686-6695

Pairwise agreement according to κ statistics. *, Modified.

Transcriptome analysis: DLBCL automatic classifier

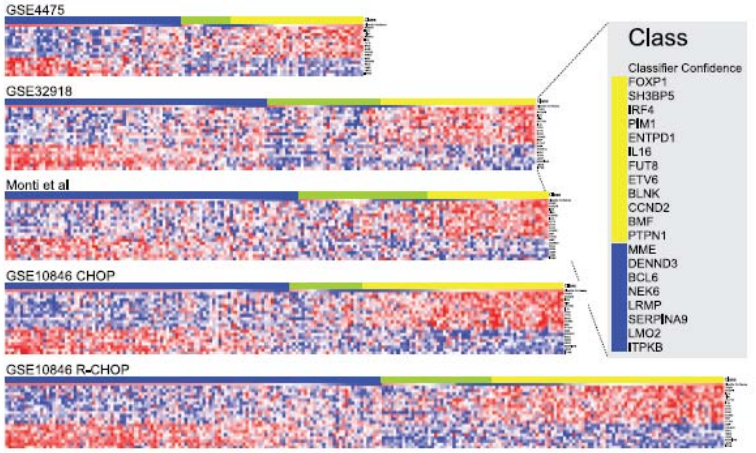
GEP can now be reliably be performed using FFPE tissue – Illumina DASL array, allow for use of partially degraded RNA (spans short sequence).

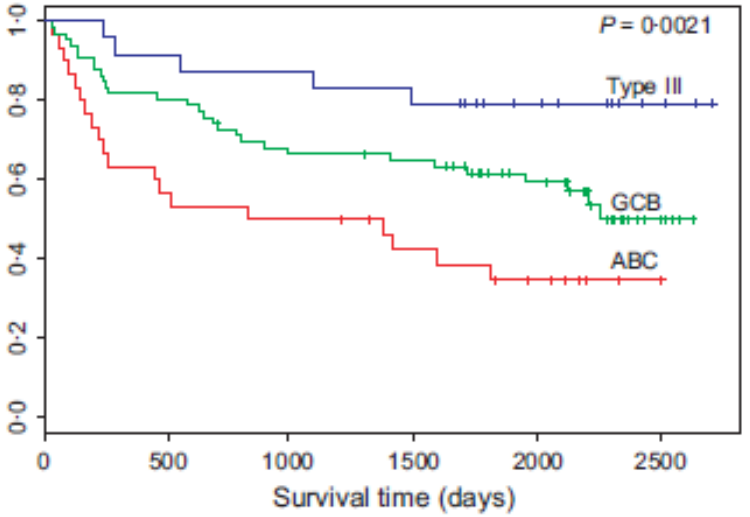
Derived from multiple sample sets

Algorithm allowing classification sample by sample, week on week

Cross platform validation; correlates with predicted mutation profile

Outcomes in validated in population based analysis

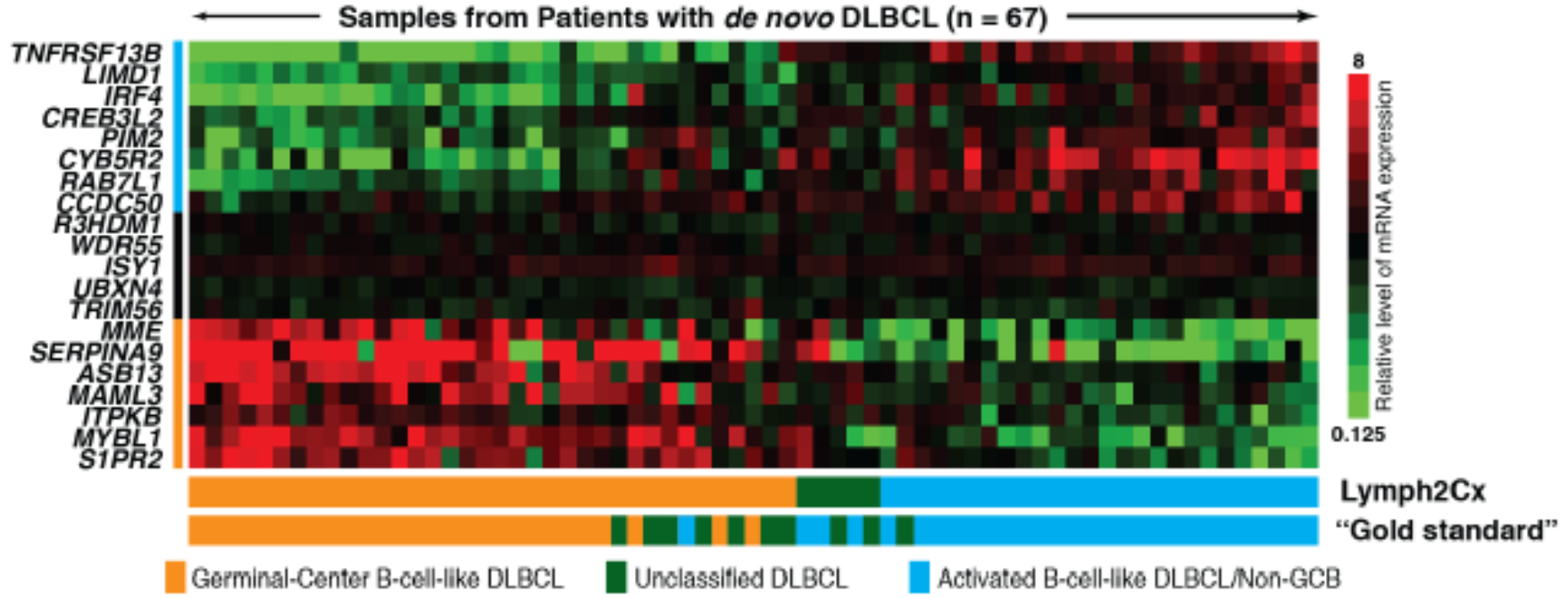




Barrans SL, *et al. Brit J Haematol* 2012 159 (4) 441-453
Care M, et al. PLoS ONE 8(2) : e55895

Reliable tools in formalin-fixed paraffin-embedded tissue

- **NanoString Technology**

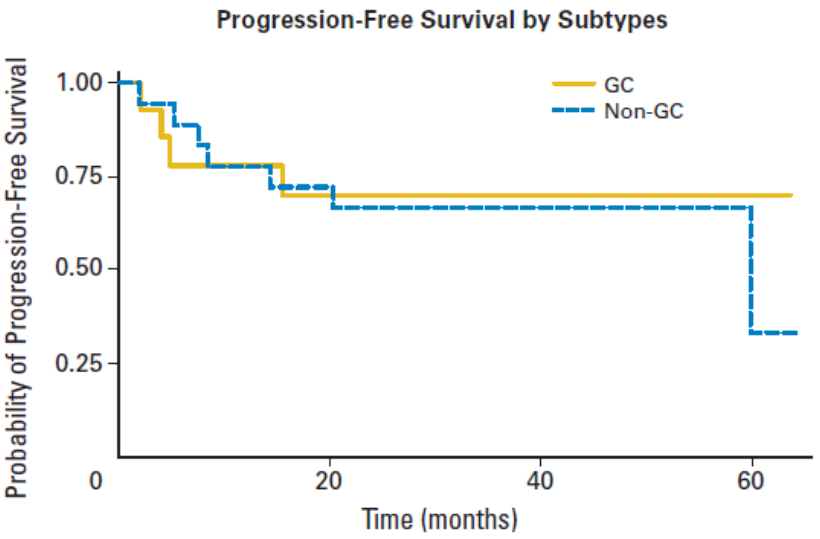


2% misclassification of ABC/GCB compared with GEP on fresh frozen tissue

Scott et al, Blood 2014

Is it possible to reverse the adverse outcomes of ABC DLBCL?

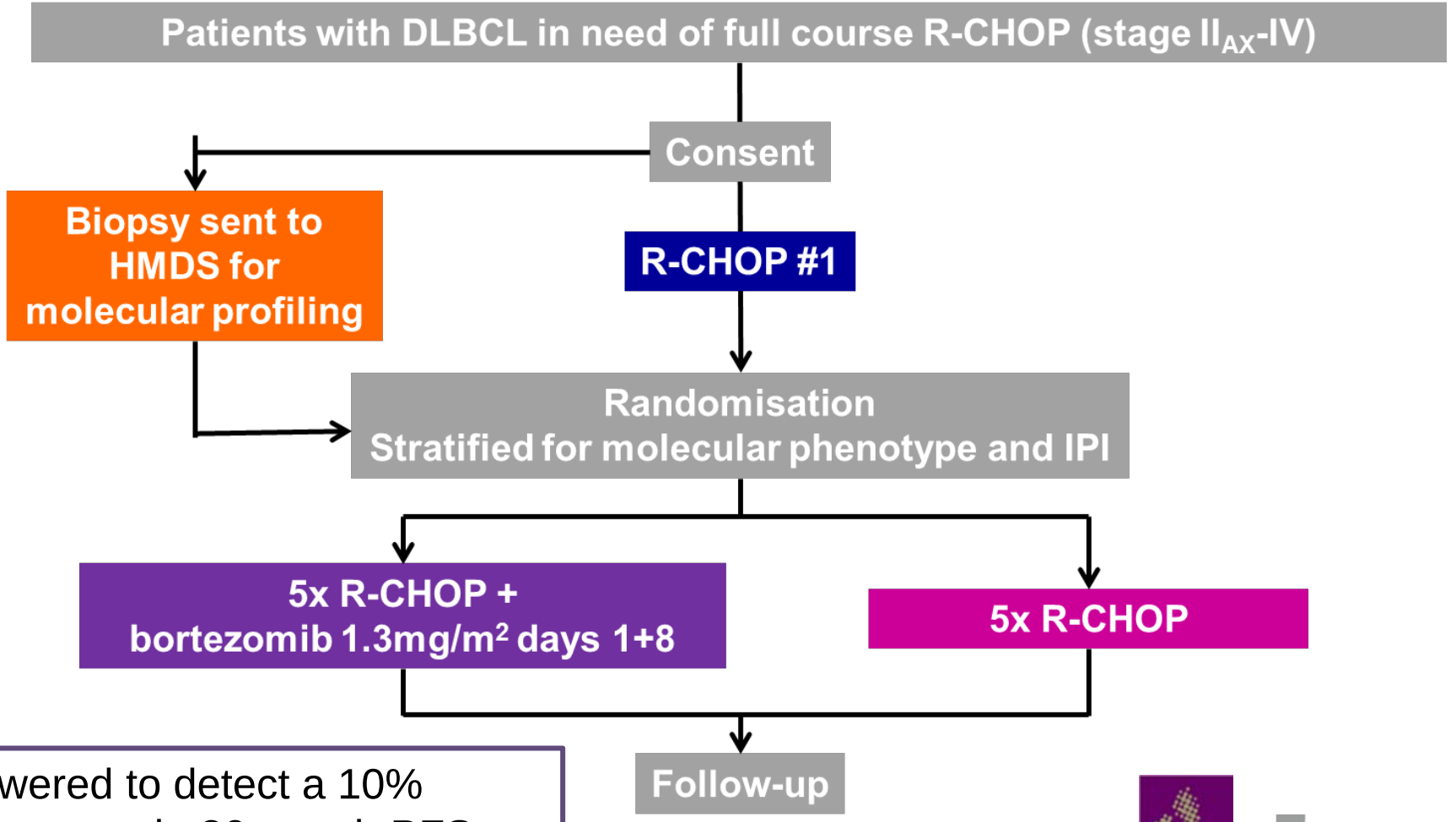
- The nuclear factor-kB (NF-kB) pathway is constitutively activated in ABC DLBCL[1]
- The proteasome inhibitor bortezomib is a potent inhibitor of NF-κB[2]; may therefore have specific utility in non-GCB DLBCL and overcoming the negative prognosis associated with non-GCB phenotype[3,4]



Ruan J et al. J Clin Oncol. 2011;29(6):690-697

[1]Davis RE et al. J Exp Med. 2001;194(12):1861-1874.
[2]Bu R et al. Leuk Lymphoma. 2014; 55(2):415-424.
[3]Ruan J et al. J Clin Oncol. 2011;29(6):690-697.
[4]Dunleavy et al. Blood. 2009; 113(24):6069-6076.

Study design



Powered to detect a 10% improvement in 30 month PFS (α=0.05; power 0.9). n=688 ABC and GCB randomised. ABC 260

Amendment 2nd May 2014
Bortezomib 1.6 mg/m² day 1+8 sub cut

NCRI National Cancer Research Institute

SAKK

REMoDL-B

Disposition by cell of origin

REMoDL-B

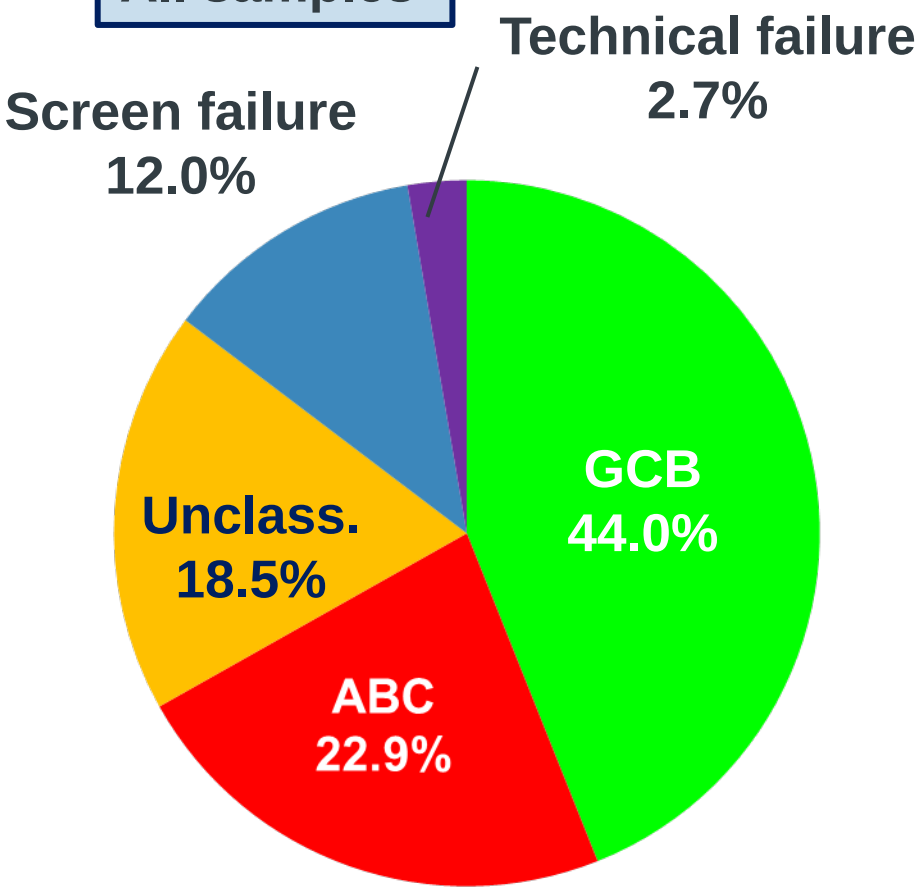
1132 patients registered. 1085 patients eligible and randomised

(incorrect histology; did not meet eligibility criteria; no block; 2 early deaths before profile)

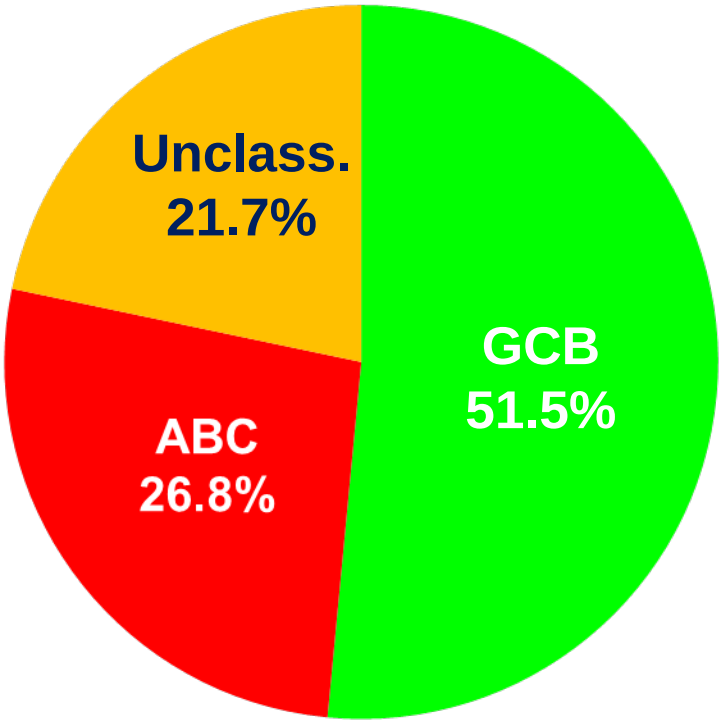
Median turn around = 10 days

Similar success rate with both surgical and core biopsies

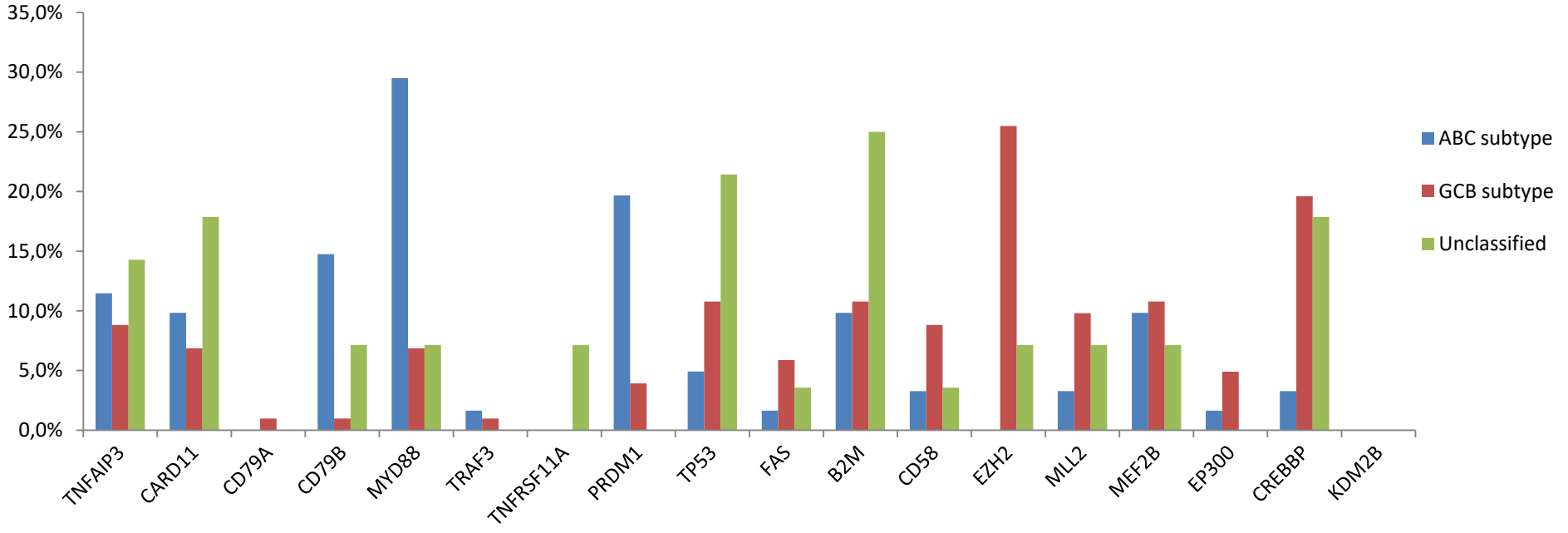
All samples



Samples with successful profile



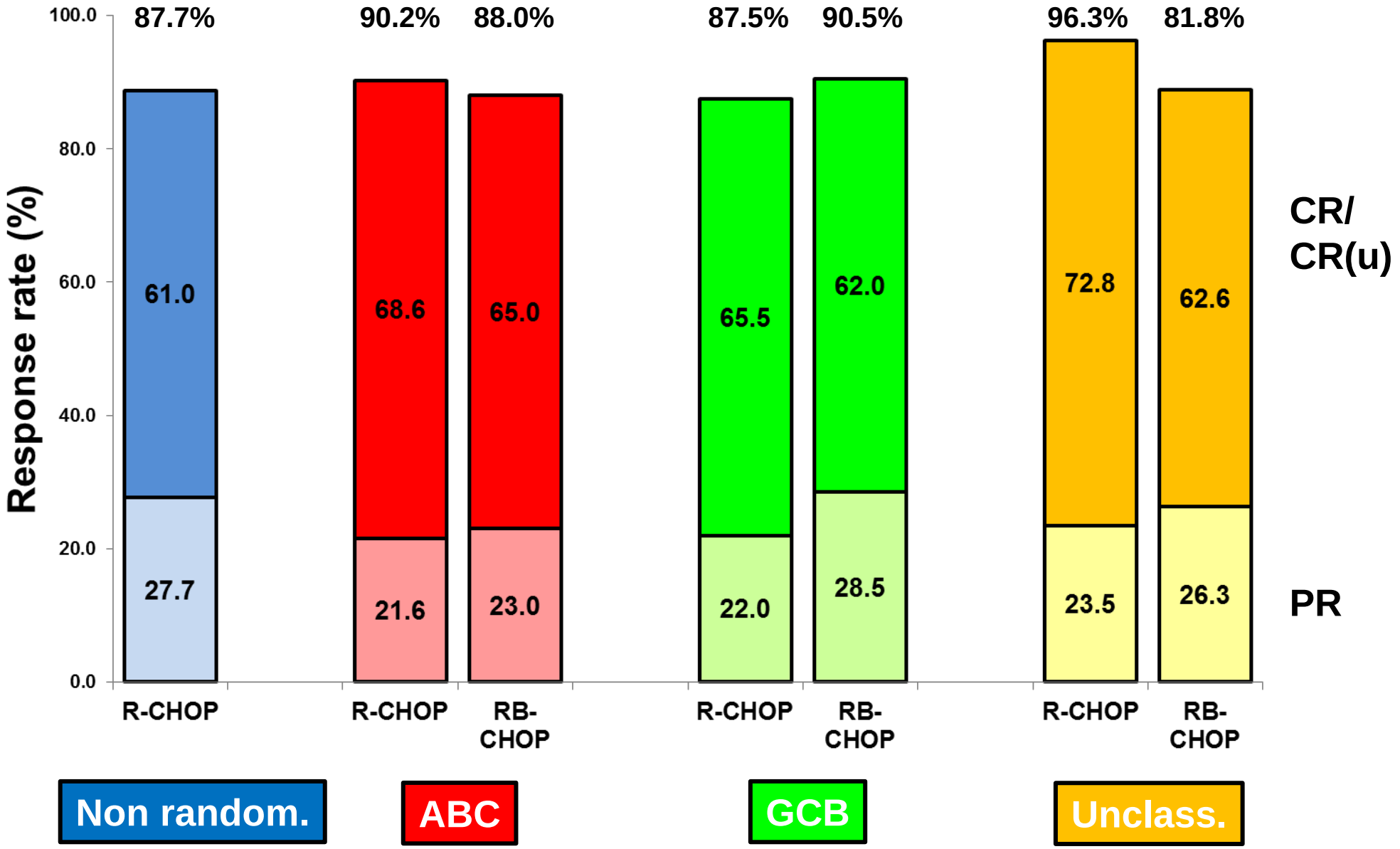
Gene mutations vs subtype (n=191)



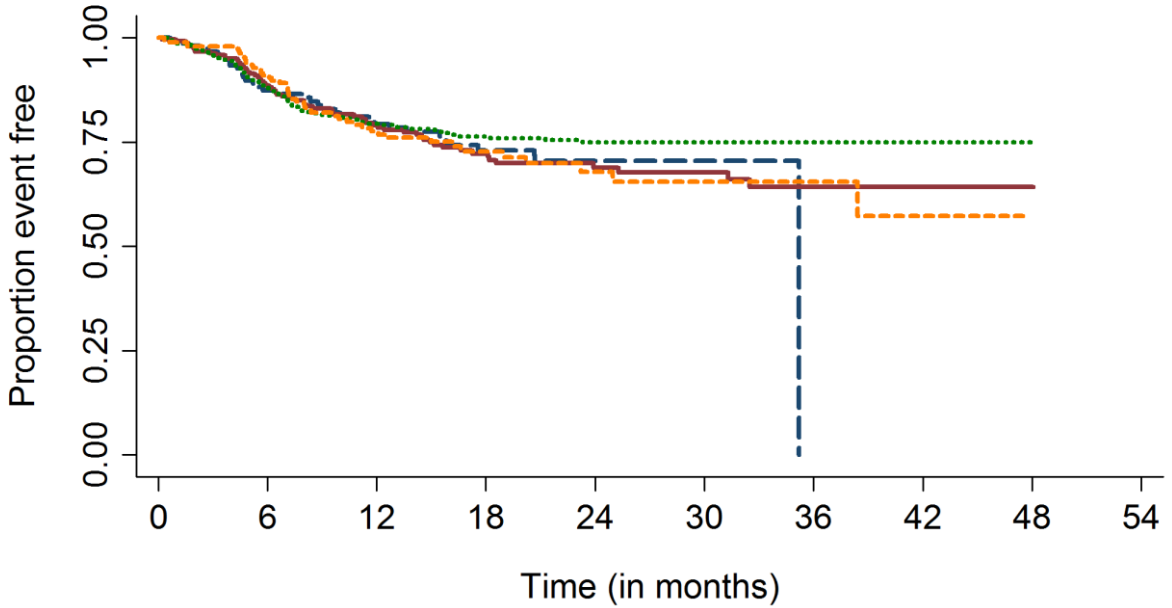
- 73% have a mutation detectable in 1 or more genes (range 0-5)
- MYD88 was most commonly mutated (in 30% of ABC and 7% of GCB).
- EZH2 mutations were restricted to the GCB category (26%)
- MYD88, CD79a/b and PRDM1 were more commonly associated with ABC.
- Where MYD88 was seen in GCB cases, coexisting mutations imply an origin from transformed follicular lymphoma.
- B2M mutations were commonly identified across all subtypes, but specifically enriched in Type III (unclassified) cases (25%)

Barrans et al. ASH 2015

Response rate (%): Molecular profile and arm

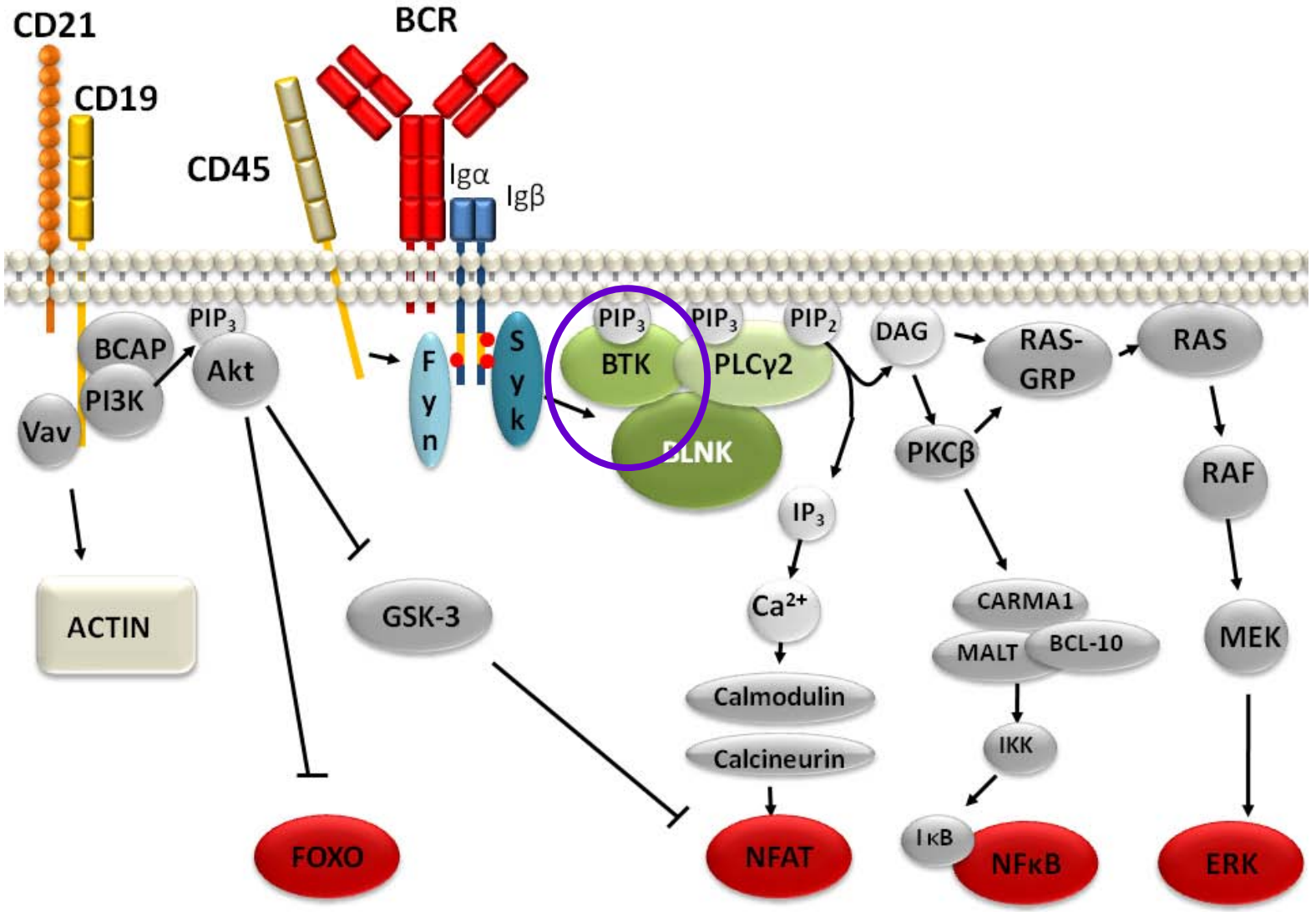


Progression-free survival by molecular profile

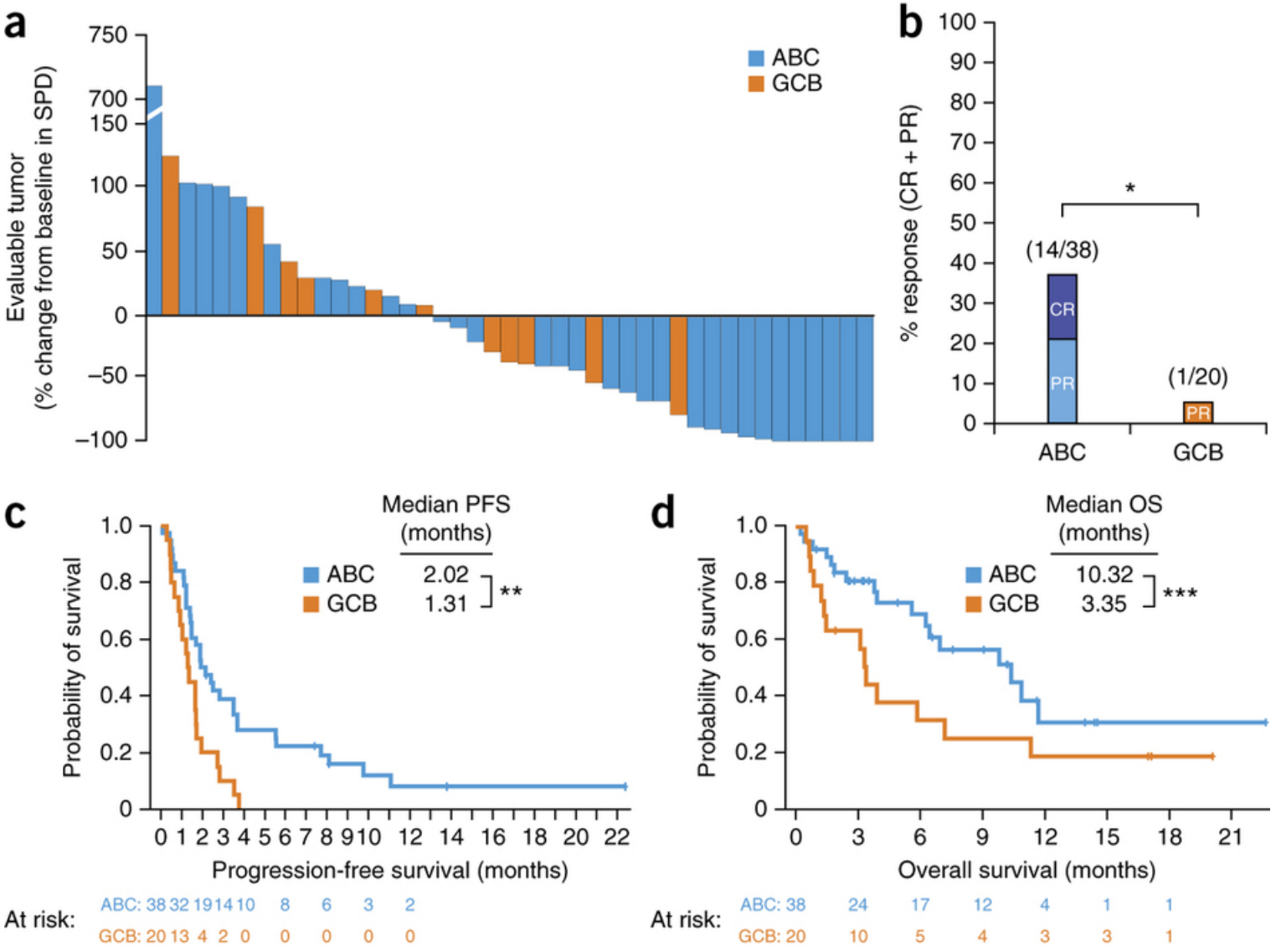


Characteristic	FAIL (n=159)	ABC (n=248)	GCB (n=477)	Unc. (n=201)	Total (n=1085)
PFS at 12 months – % (95% CI)	79.3 (71.2, 85.4)	79.0 (73.0, 83.9)	79.5 (75.3, 83.1)	77.6 (70.2, 83.4)	79.0 (76.2, 81.5)
PFS at 24 months – % (95% CI)	70.5 (61.0, 78.1)	68.9 (61.5, 75.1)	75.0 (70.2, 79.1)	67.8 (58.1, 75.8)	71.7 (68.4, 74.8)
No. of events observed	36	65	98	46	245
Proportion of patients with an event	23.1%	26.6%	20.6%	23.2%	22.8%
Median follow up, in months (95% CI)	16.9 (14.3, 24.7)	17.2 (15.8, 21.6)	16.5 (15.7, 17.7)	14.3 (12.9, 15.8)	16.3 (15.7, 17.0)

B-cell receptor signalling



Ibrutinib: May target specific sub-types with novel agents



Wilson et al 2015

Ibrutininb in combination with R-CHOP

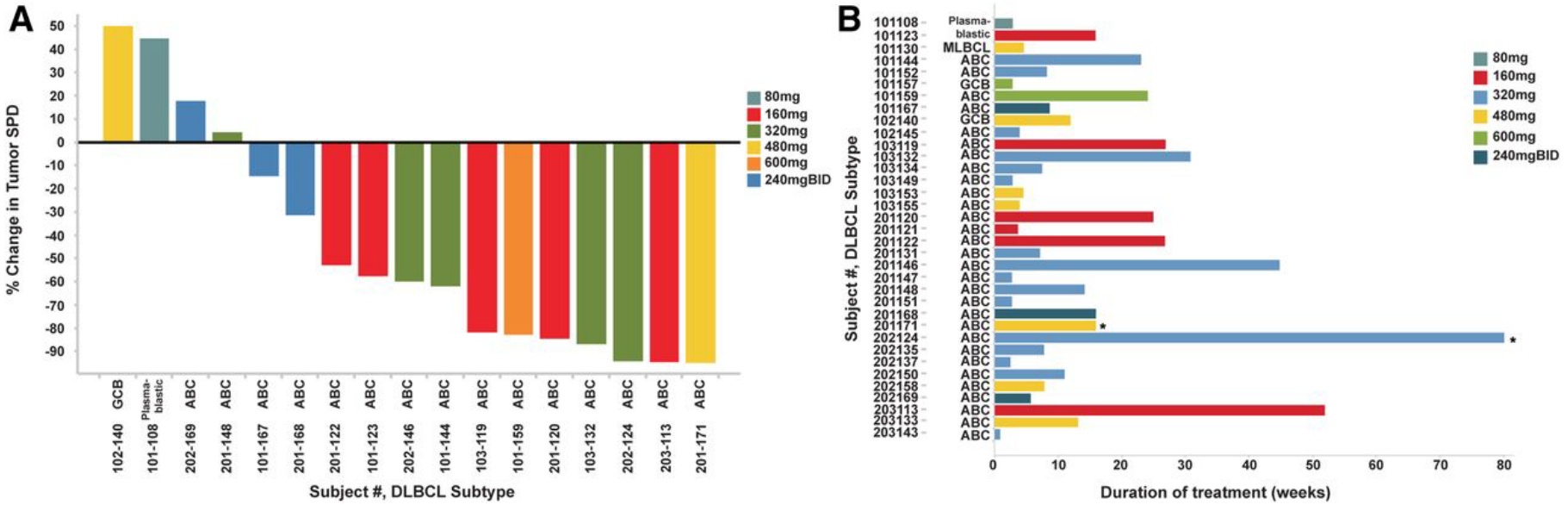
	280 mg (n=7)	420 mg (n=4)	560 mg (n=21)	Combined (n=32)	All (n=33)
Overall response	6 (86%)	4 (100%)	20 (95%)	30 (94%)	30 (91%)
Complete response	5 (71%)	3 (75%)	15 (71%)	23 (72%)	23 (70%)
Partial response	1 (14%)	1 (25%)	5 (24%)	7 (22%)	7 (21%)
Stable disease	0	0	0	0	0
Progressive disease	0	0	0	0	0
Not evaluable	1 (14%)	0	1 (5%)	2 (6%)	3 (9%)

No difference according to cell of origin

Younes et al. Lancet Oncology 2014

A second generation of BTKi: Enhanced kinase selectivity

Efficacy of ONO/GS-4059 in patients with DLBCL. (A) Waterfall plot for all DLBCL patients by dose cohort (n = 17), showing response evaluated by CT imaging.



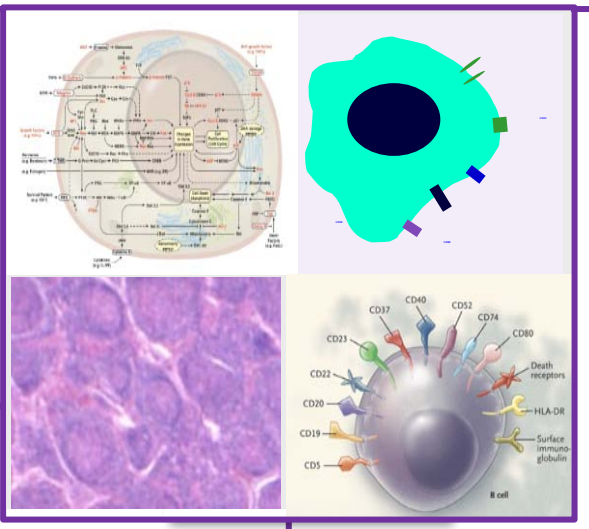
Harriet S. Walter et al. Blood 2016;127:411-419

Microenvironment

- Lenalidomide
- T-cell exhaustion

Actionable mutations

- **EZH2** — E7438
- **CD79a/b** — AEB071



Pathways

- **Proteosome inhibitors** — Bortezomib
- **Bcl-2 family inhibitors** — ABT-263
- **Survivin inhibitors** — YM155
- **Syk inhibitors** — Fostamatinib, entosplentib
- **mTOR inhibitors** — Everolimus, Temsirolimus
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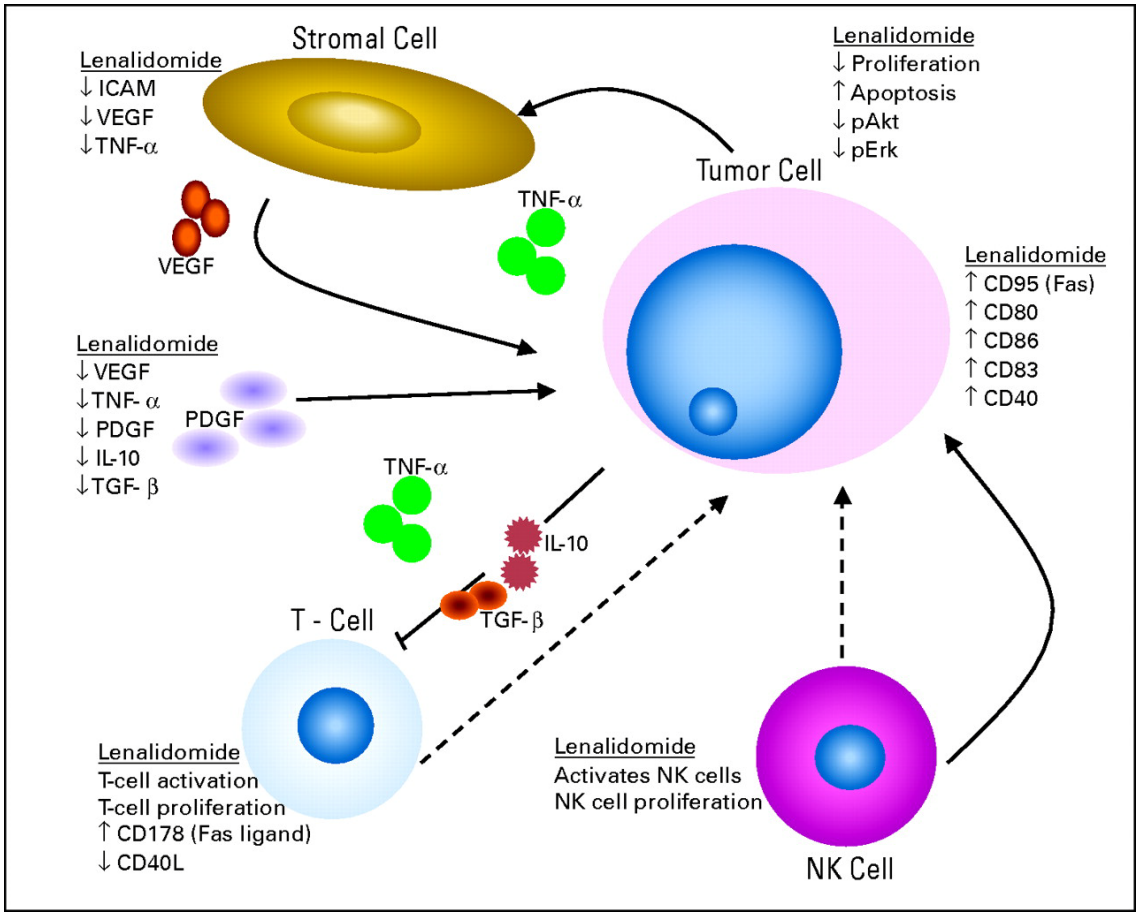
- **Hsp 90 inhibitors** — KW 2478

Surface markers

- **Anti CD20 moAb** — Ofatumumab, GA-101
- **Anti CD40 moAb** — Dacetuzumab
- **Anti CD22** — Epratuzumab, Inotuzumab Ozogamicin, polatuzumab
- **HDAC inhibitors** — Vorinostat, Panobinostat
- **PKC inhibitors** — Enzastaurin
- **Aurora kinase inhibitors**
- **Nedd8-activating enzyme inhibitors** — MLN4924

Lenalidomide

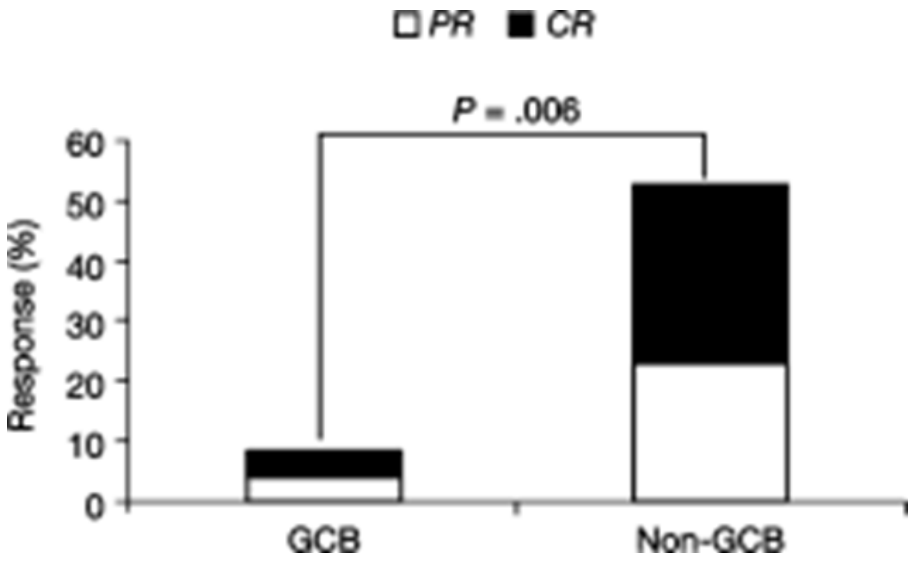
- Immunomodulatory properties
- Modulation of both cellular and cytokine tumour cell microenvironment
- Activates T cell and NK response to tumour cell
- Down regulates pro-survival cytokines
- Approval in myeloma



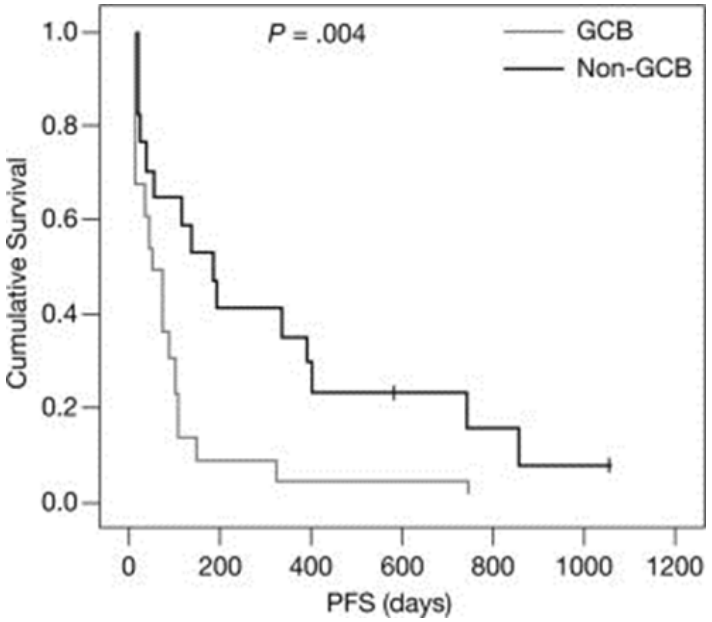
Chanan-Khan, A. A. et al. J Clin Oncol; 26:1544-1552 2008

Differential response according to cell of origin in DLBCL (n=40). Retrospective review.

Response rates



Progression-free survival

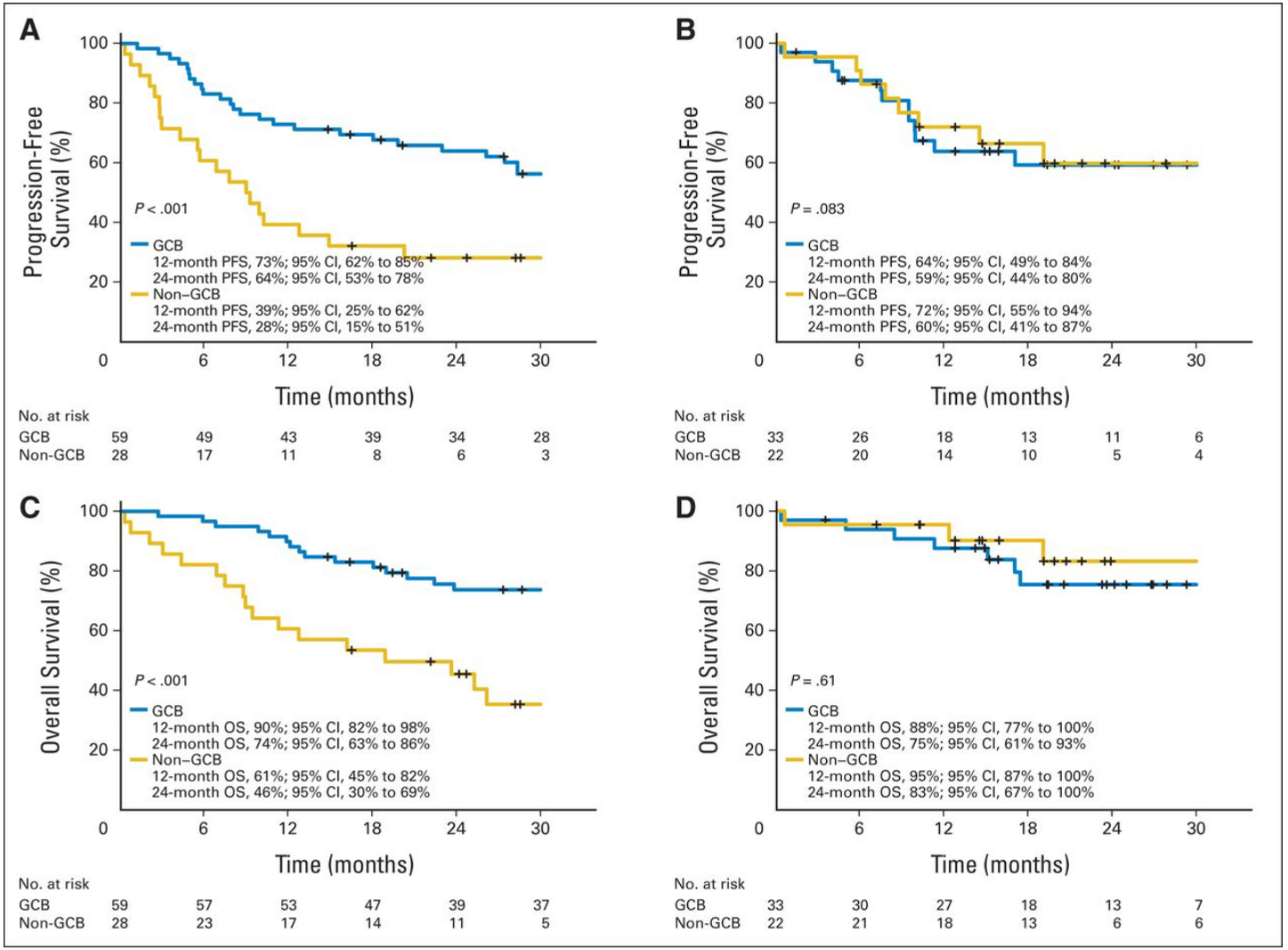


Hernandez-Ilizaliturri et al. Cancer 2011

Can over come the adverse outcome of ABC phenotype….

R-CHOP

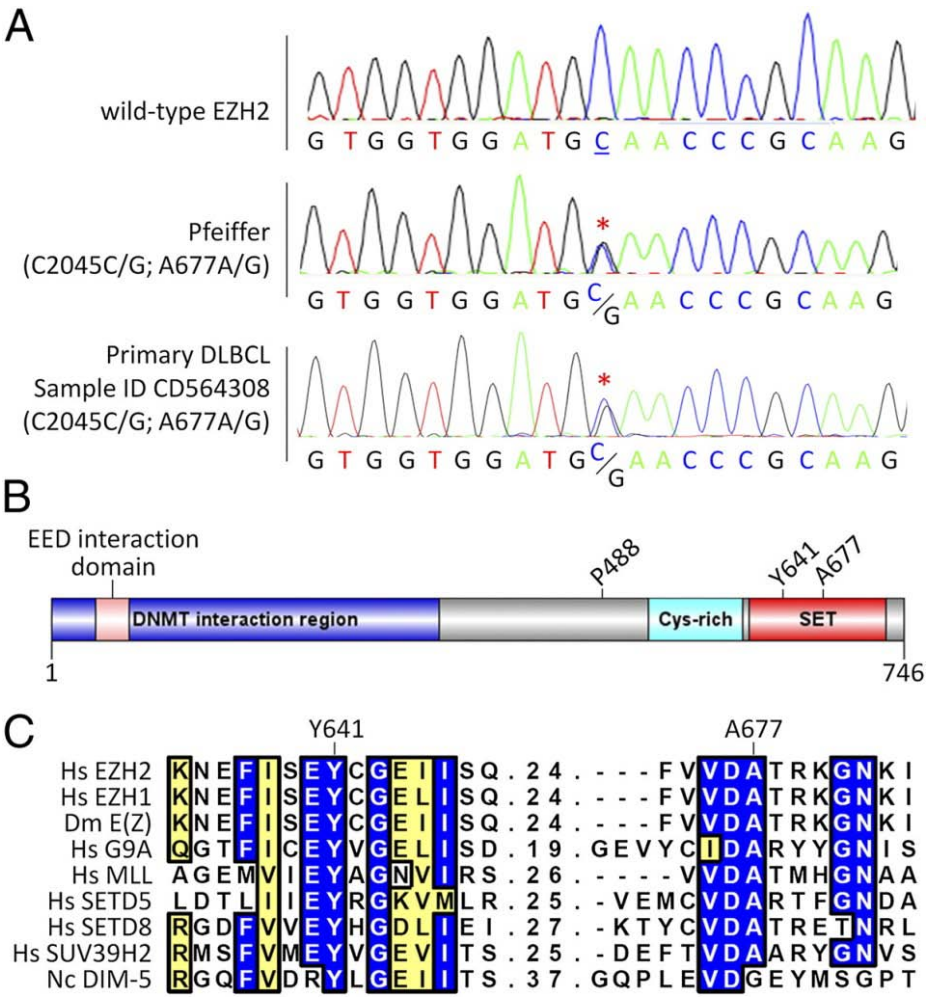
R2-CHOP



Grzegorz S. Nowakowski et al. JCO 2015;33:251-257

What about the GCB Phenotype?

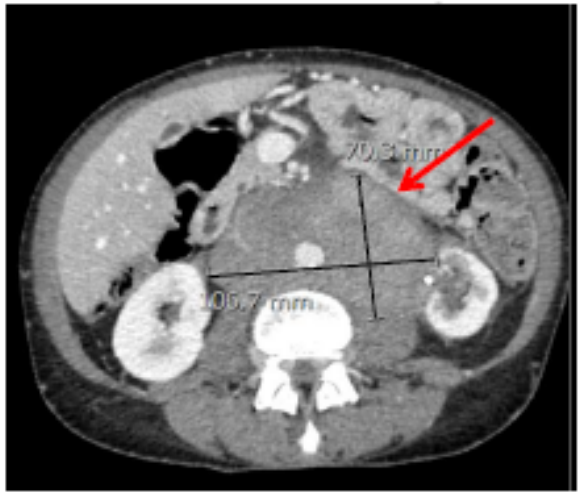
- Enhancer of Zeste 2 (EZH2) is the enzyme component of the Polycomb Repressive Complex 2 (PRC2) that methylates histone H3 on lysine 27 (H3K27)
- Somatic activating mutations in EZH2 have been identified in follicular and GCB-DLBCL *[Morin, 2010; Morin, 2011; Pasqualucci, 2011];*
- The frequency of the most prevalent mutation, Y641, 22% in DLBCL.
- Inhibitors in early phase investigation



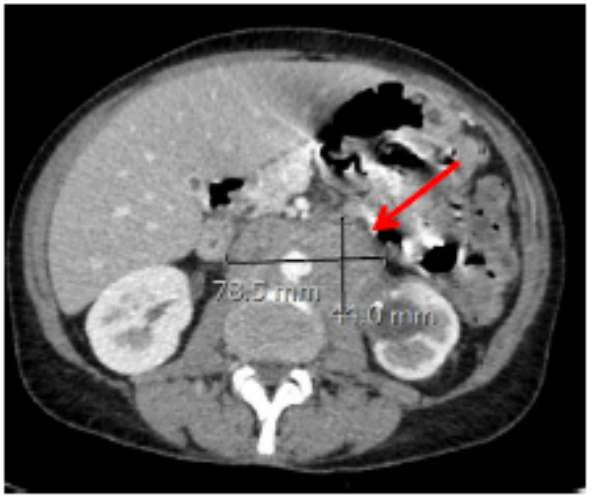
McCabe M T et al. *Proc Nat Acad Sci USA* 2012;109:2989-2994

Activity in EZH2 mutated DLBCL (Ribrag et al ASH 2015)

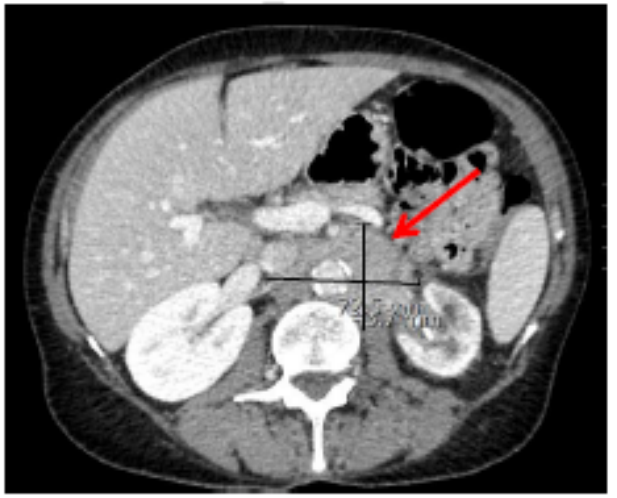
53 year old female (EZH2^{Y646H}) treated at RP2D (800 mg BID)



Baseline SPD: 8282mm²

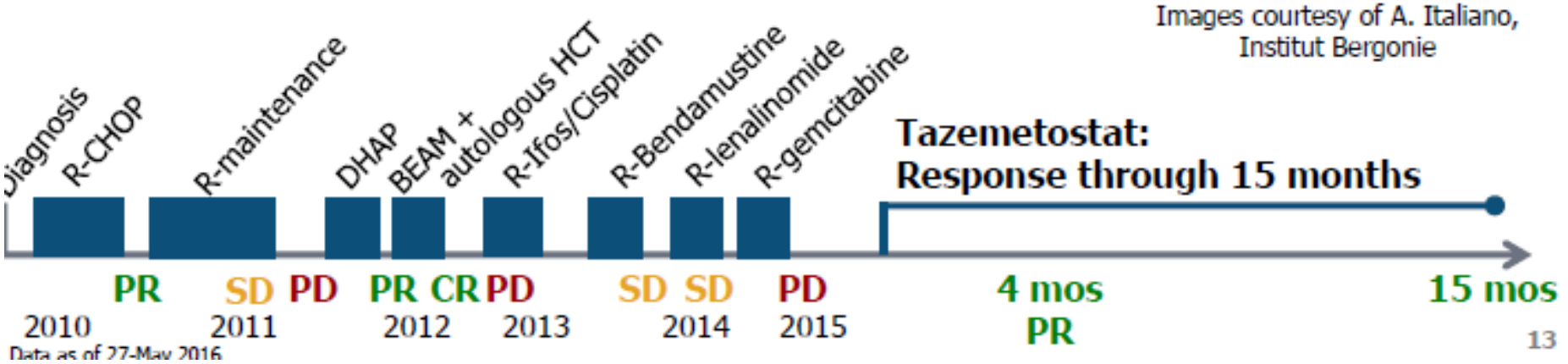


Wk 16 SPD: 3864 mm² (PR)

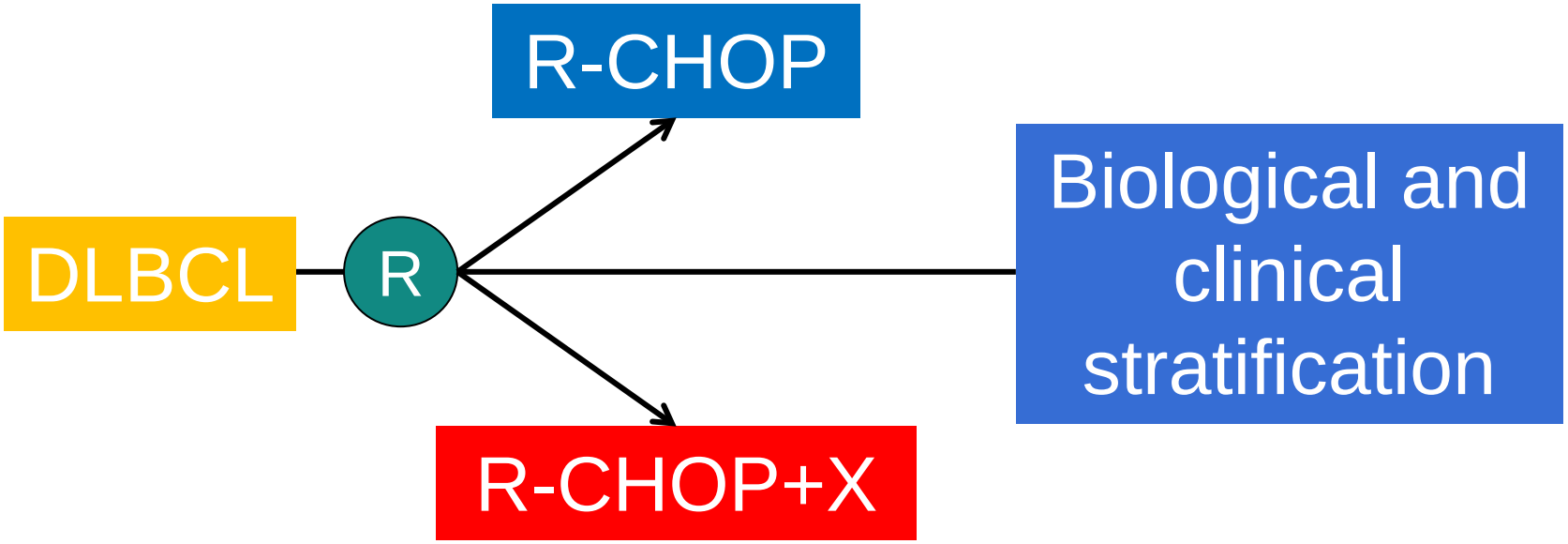


Wk 40 SPD: 3506 mm² (PR)

Images courtesy of A. Italiano, Institut Bergonie



The paradigm for study design….



Ongoing X=
Lenalidomide
Ibrutinib
Bortezomib
Brentuximab
everolimus
More to come…

Can we practically deliver this design in phase III with so many agents?

Microenvironment

- Lenalidomide
- T-cell exhaustion

Actionable mutations

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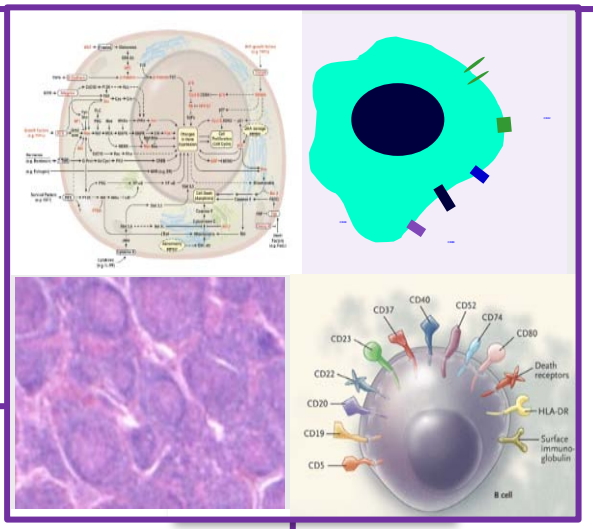
- CD79a/b — AEB071



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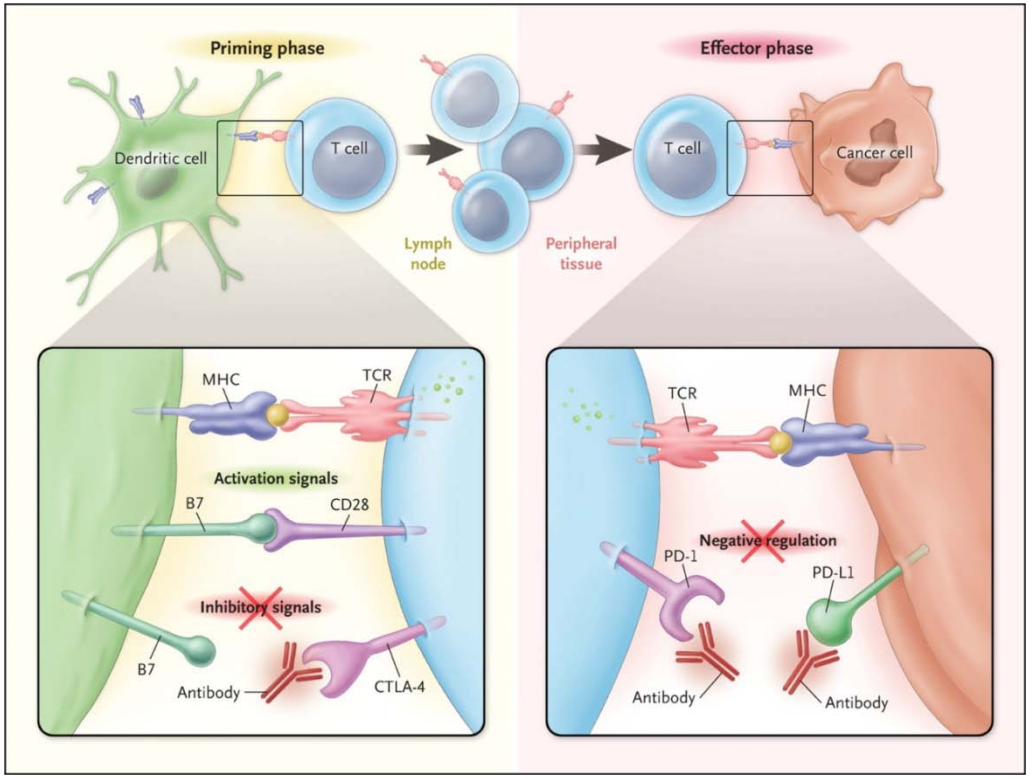
Exhausted T-Cells and Checkpoint blockade therapy

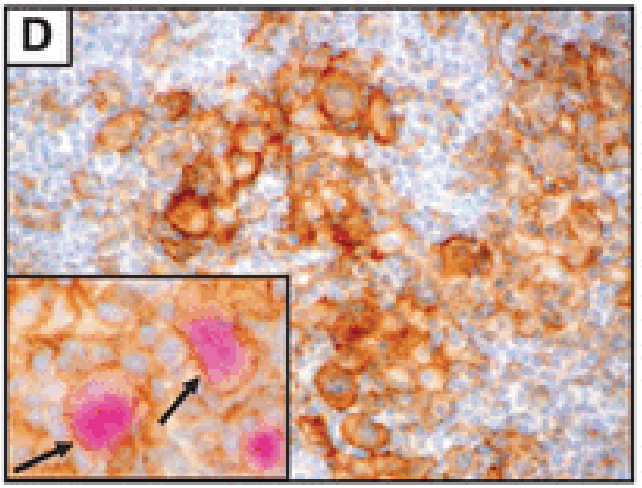
- Important interplay between malignant cells and microenvironment.
- …eventually ineffective. Immune escape or immune checkpoints
- Blocking immune checkpoints may promote endogenous antitumour activity
- PD1: Inhibitory receptor on activated T-cells, B-cells, NK and myeloid cells. Inhibition of T-cell activation when engaged by ligands (PDL1/2)
- PD1 expressed on T-cells when exposed to tumour, and associated with exhaustion. Blocking can restore function



Ribas A. N Engl J Med 2012;366:2517-2519.

PD1/PD-L1 in DLBCL

- Investigation of nivolumab (anti PD-1), pembrolizumab (anti PD-1), avelumab (PD-1), durvalumab (anti PD-L1) and atezoluimumab (PD-L1), in DLBCL
- PD-L1 expressed on about 30% of patients with DLBCL (more frequent in PMBL)
- High is EBV +ve DLBCL and TCRLCL (Chen et al. Clin Canc Res 2013)
- Nivoulumab ORR DLBCL 36% (n=11) median duration of response 22 weeks (Lesokhin et al. ASH 2014)
- Is PD-L1 expression a biomarker of activity



(Chen et al. Clin Canc Res 2013)

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Lenalidomide

T-cell exhaustion

Actionable mutations

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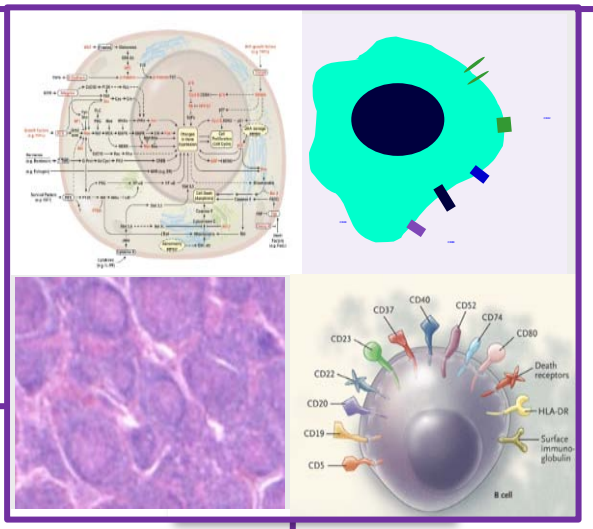
E7438

CD79a/b
AEB071



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HDAC inhibitors
Vorinostat
Panobinostat

PKC inhibitors
Enzastaurin

Aurora kinase inhibitors

Nedd8-activating enzyme inhibitors
MLN4924

Obinutuzumab: Putative mechanism(s) of action

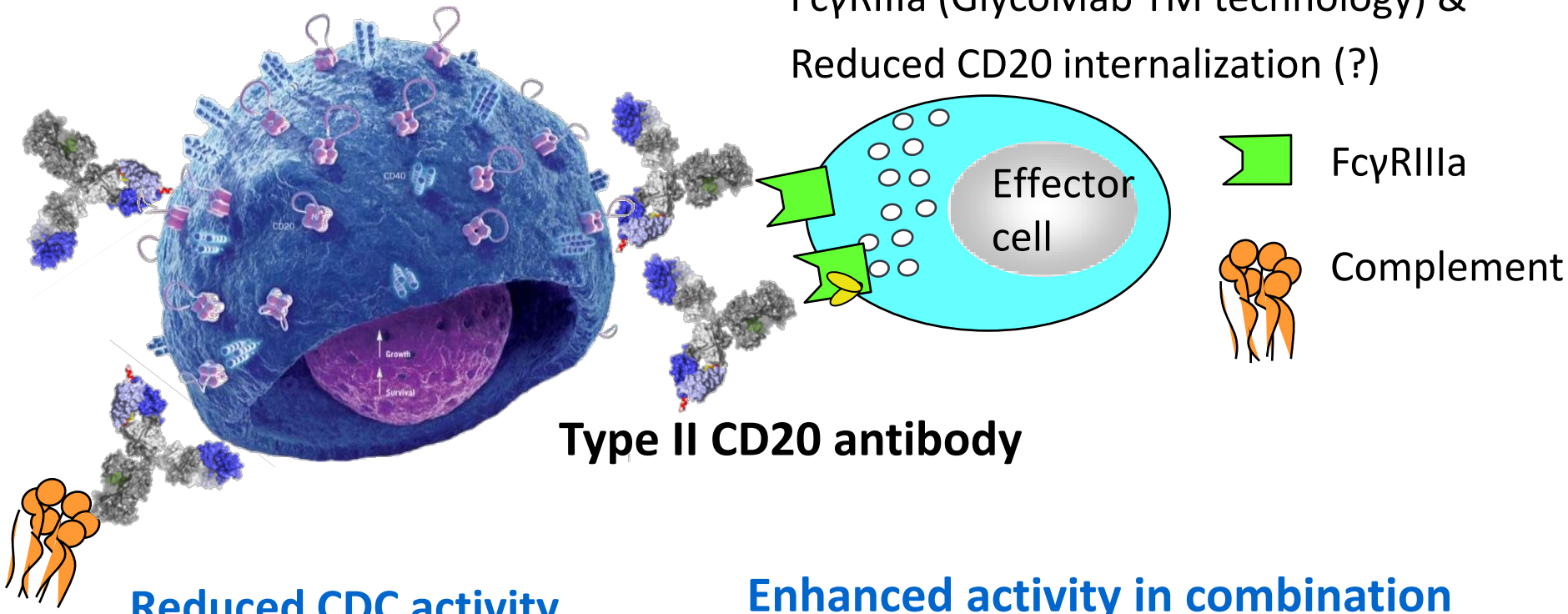
Increased direct cell death

Type II antibody & elbow-hinge modification

Increased ADCC

Higher affinity to the 'ADCC receptor' FcγRIIIa (GlycoMab TM technology) &

Reduced CD20 internalization (?)



Type II CD20 antibody

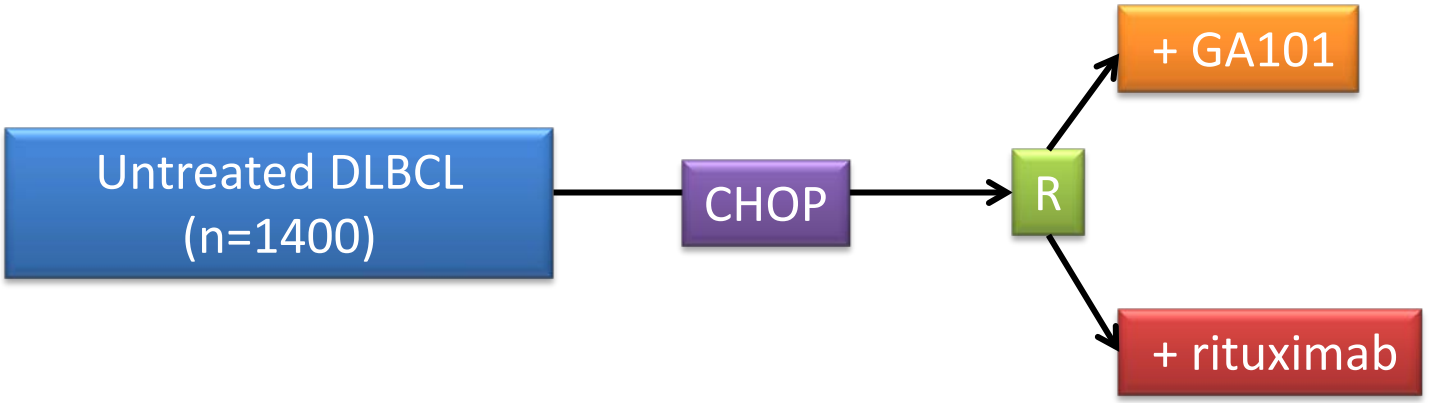
Reduced CDC activity

Type II antibody

Enhanced activity in combination with chemotherapy

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity

Goya Study



ENDPOINTS

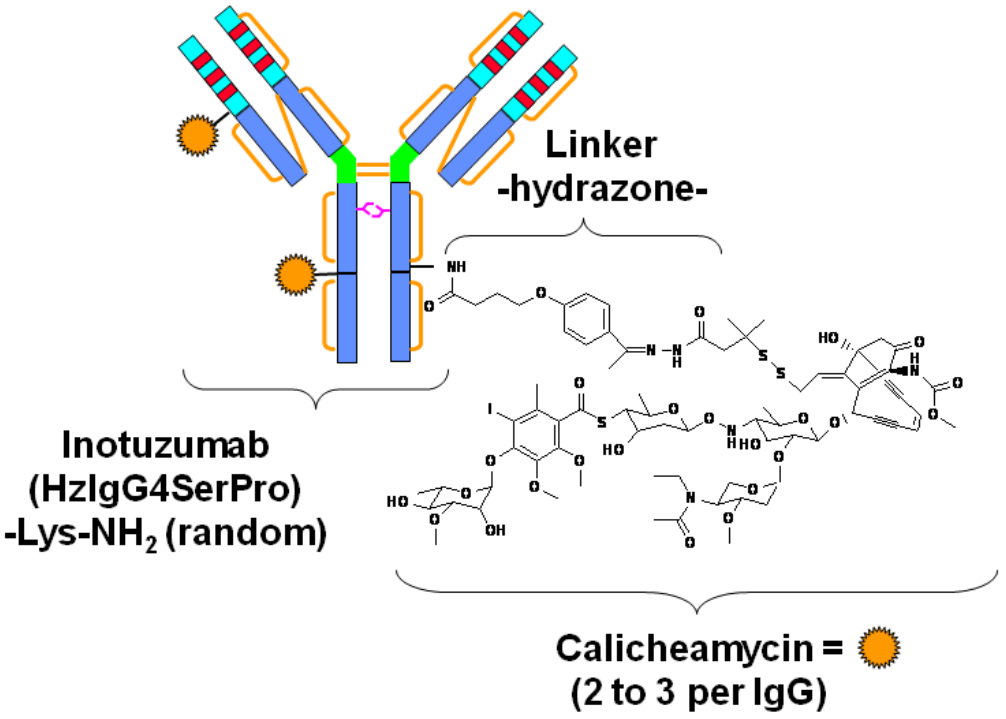
1º: PFS in FL population

2º:

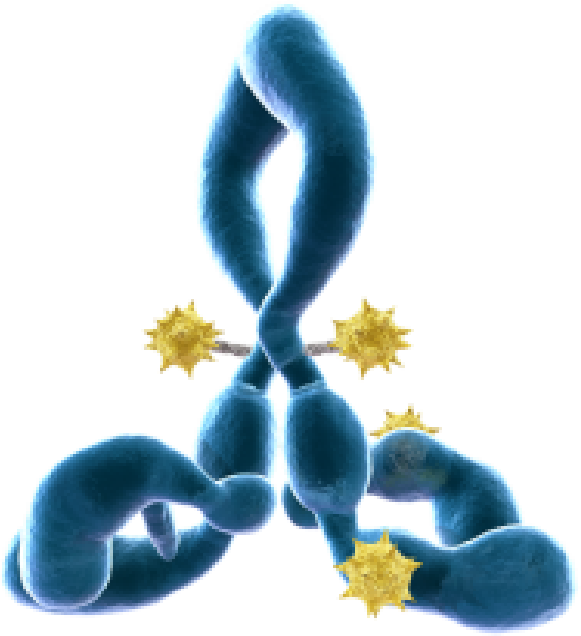
- PFS in whole population
- PFS by Independent Review Committee (IRC)
- ORR/CR rate at end of induction (with and without PET) Investigator and IRC
- overall survival, EFS, disease-free survival (DFS), duration of response, and time to next anti-lymphoma treatment between the two arms
- Safety
- patient-reported outcomes (PROs) in both arms

Targeted chemotherapy in clinical development

Antibody-drug conjugates



Target CD22



Polatuzumab
Vedotin

Target CD79b

Conclusions

- Targeted therapies may potentially change the landscape of therapy for DLBCL..not yet
- Much still needs to be proved and phase III studies (no matter how difficult) are needed..and how to sequence
- We need to continue to better understand and exploit the biology.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The Royal Melbourne Hospital

PeterMac

RADIOTHERAPY IN MODERN LYMPHOMA MANAGEMENT

7-8 APRIL 2017
PETER MACCALLUM CANCER CENTRE
AT THE VICTORIAN COMPREHENSIVE CANCER CENTRE BUILDING
MELBOURNE, AUSTRALIA

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Thank you

Farewell

Safe trip home

Hope to see you at other lymphoma events in the future

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General principles of treatment: Radiotherapy

Lena Specht MD DMSc
Professor of Oncology, University of Copenhagen, Denmark
Chief Oncologist, Depts. of Oncology and Haematology, Rigshospitalet, Copenhagen
Vice-chairman, International Lymphoma Radiation Oncology Group

Facts about radiotherapy in lymphomas

- Most lymphoma types are highly radiosensitive
- Radiotherapy was the first modality to cure lymphomas
- Radiotherapy has serious long-term sequelae
- Modern highly conformal limited and fairly low dose radiotherapy has markedly decreased these risks

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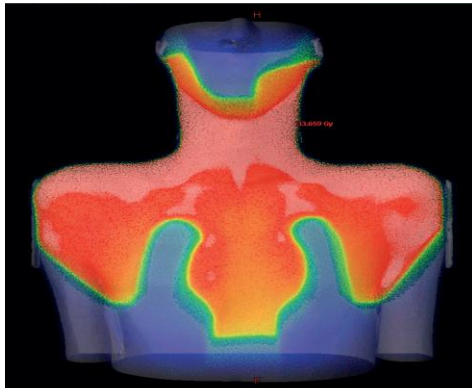
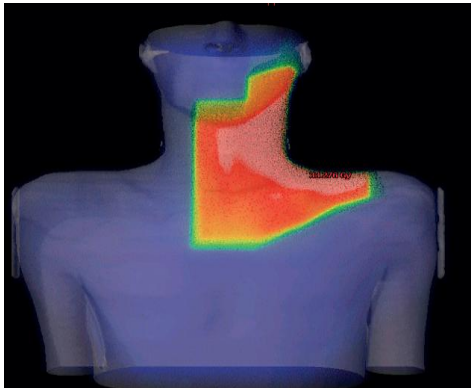
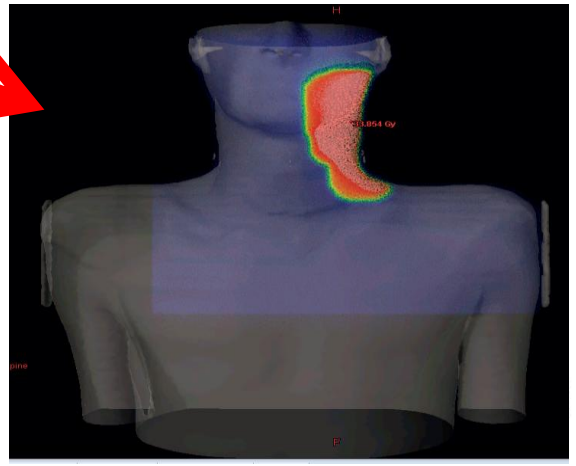
Mantle field (EFRT) or involved field (IFRT)





Based on:
- 2 D planning
- Regions
- Bony landmarks defining fields
- ”Fixed” margins

Involved site (ISRT) or involved node (INRT)



Based on:
- 3 D planning
- Actual lymphoma involvement
- Contouring of volumes (GTV, CTV, PTV)
- Margins (GTV CTV) based on clinical judgement and (CTV PTV) based on internal and setup uncertainties

Target volume for radiation therapy depends on lymphoma type and stage

- Aggressive lymphomas
  - Effective chemotherapy deals with microscopic disease (true for B-cell lymphomas, less so for T-cell lymphomas)
  - Target in early stage disease is only the tissue volume which initially contained macroscopic lymphoma
  - Target in advanced disease is only residual disease, or intially bulky or extranodal disease
- Indolent lymphomas
  - Incurable with chemotherapy only
  - In early stage disease RT is the primary treatment. Target is the macroscopic lymphoma and adjacent nodes in that site with a generous margin
  - In advanced disease RT is palliative. Target is localized symptomatic disease

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Extranodal lymphomas

Aggressive lymphomas

- Same principles as for nodal lymphomas
- In many organs (e.g., stomach, salivary glands, thyroid gland, CNS) lymphoma is multifocal. Hence, the whole organ is treated even if apparently only partially involved
- Even with modern imaging it may be difficult to accurately define the exact extent of disease in many extranodal sites. Hence, the whole organ is treated even if apparently only partially involved

Indolent lymphomas

- Same principles as for nodal lymphomas
- Whole organ is usually treated even if apparently only partially involved (for the same reasons as for aggressive lymphomas)
- Uninvolved nodes are not routinely included in the CTV. First echelon nodes of uncertain status close to the primary organ may be included

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Modern radiotherapy guidelines developed by

- Previous wide field and involved field replaced by limited volumes based solely on detectable involvement at presentation
- ICRU concepts of GTV, CTV, ITV, and PTV are used
- New concept, Involved Site RadioTherapy (ISRT), defines CTV on this basis
- Previous doses were higher that necessary, replaced by lower doses in most lymphoma types

Gross tumor volume (GTV) (ICRU 83)

- Gross demonstrable extent and location of the tumor (lymphoma)
- Original (before any treatment) lymphoma: pre-chemo GTV
  - Seen on CT: pre-chemo GTV(CT)
  - Seen on FDG-PET: pre-chemo GTV(PET)
- Residual (after systemic treatment) lymphoma: post-chemo GTV
  - Seen on CT: post-chemo GTV(CT)
  - Seen on FDG-PET: postchemo GTV(PET)

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Clinical target volume (CTV) (ICRU 83)

- Volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy
- Encompasses the original (before any treatment) lymphoma (pre-chemo GTV), modified to account for anatomic changes if treated with chemotherapy up front
- Normal structures (e.g., lungs, kidneys, muscles) that were clearly uninvolved should be excluded
- Residual lymphoma (post-chemo GTV) is always part of the CTV

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Internal target volume (ITV) (ICRU 83)

- Defined in ICRU 62, optional in ICRU 83
- CTV + margin for uncertainties in size, shape, and position of the CTV
- Mostly relevant when the target is moving (chest and upper abdomen)
- Margins may be obtained from 4-D CT, fluoroscopy or from expert clinician
- Margins should be added quadratically: $\sigma' = \sqrt{(\sigma^2_m + \sigma^2_s)}$

Equation for right-angled triangle

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Planning target volume (PTV) (ICRU 83)

- Accounts for set-up uncertainties in patient position and beam alignment during planning and through all treatment sessions
- Function of immobilization device, body site, and patient cooperation
- Geometrical concept introduced to ensure that CTV and/or ITV are properly covered
- Applied by clinician or treatment planner

ISRT scenarios

- Optimal pre-chemo imaging of all the initially involved lymphomas is available and image fusion with the planning CT-scan is possible:
  - INRT
- Pre-chemo imaging (CT, PET, or MR) of all the initially involved lymphomas is available, but image fusion with the planning CT-scan is not possible:
  - Contour with pre-chemo images as a visual aid, allowing for uncertainties of the contouring and differences in positioning
- Pre-chemo imaging not available:
  - Gather as much information as possible from the pre-chemo physical examination, location of scar tissue, patient's and family's recollections, making generous allowance for the many uncertainties in the process

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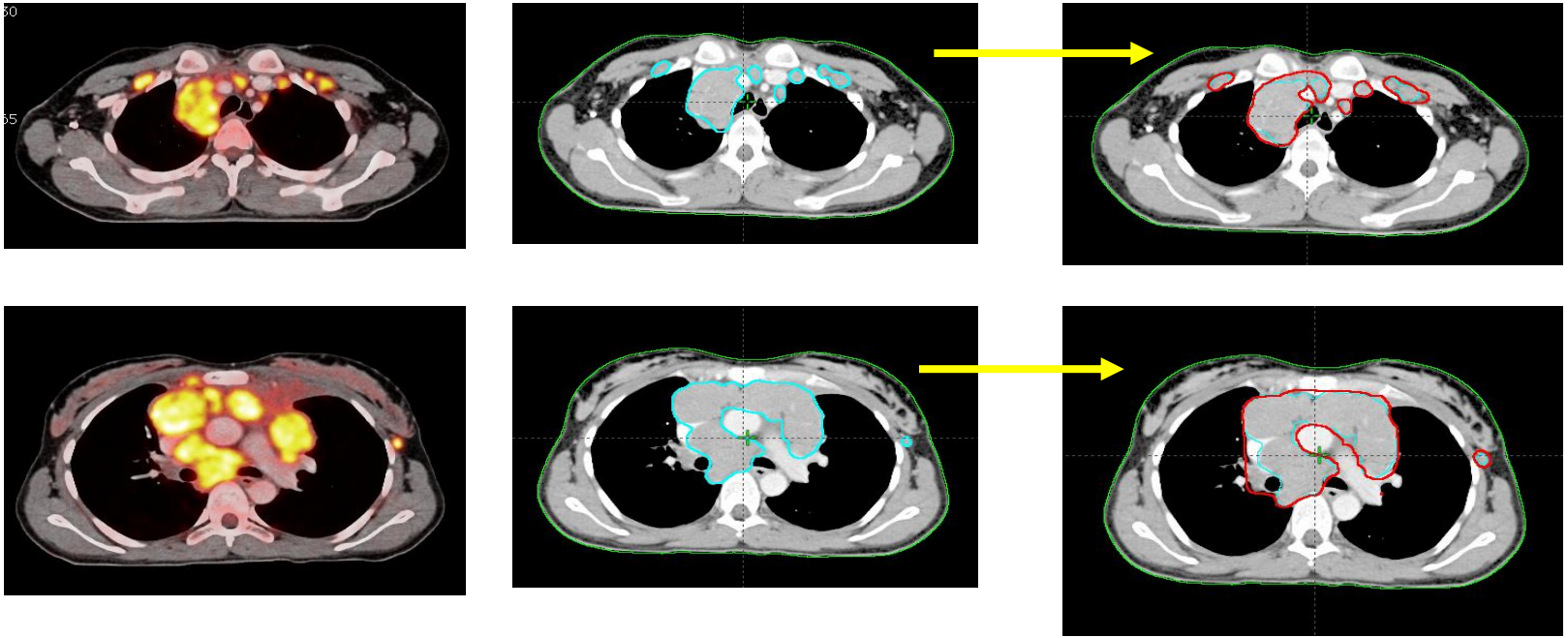
Pre-chemo PET/CT scan

PET+ volume

Gross tumour volume GTV
(pre-chemo)



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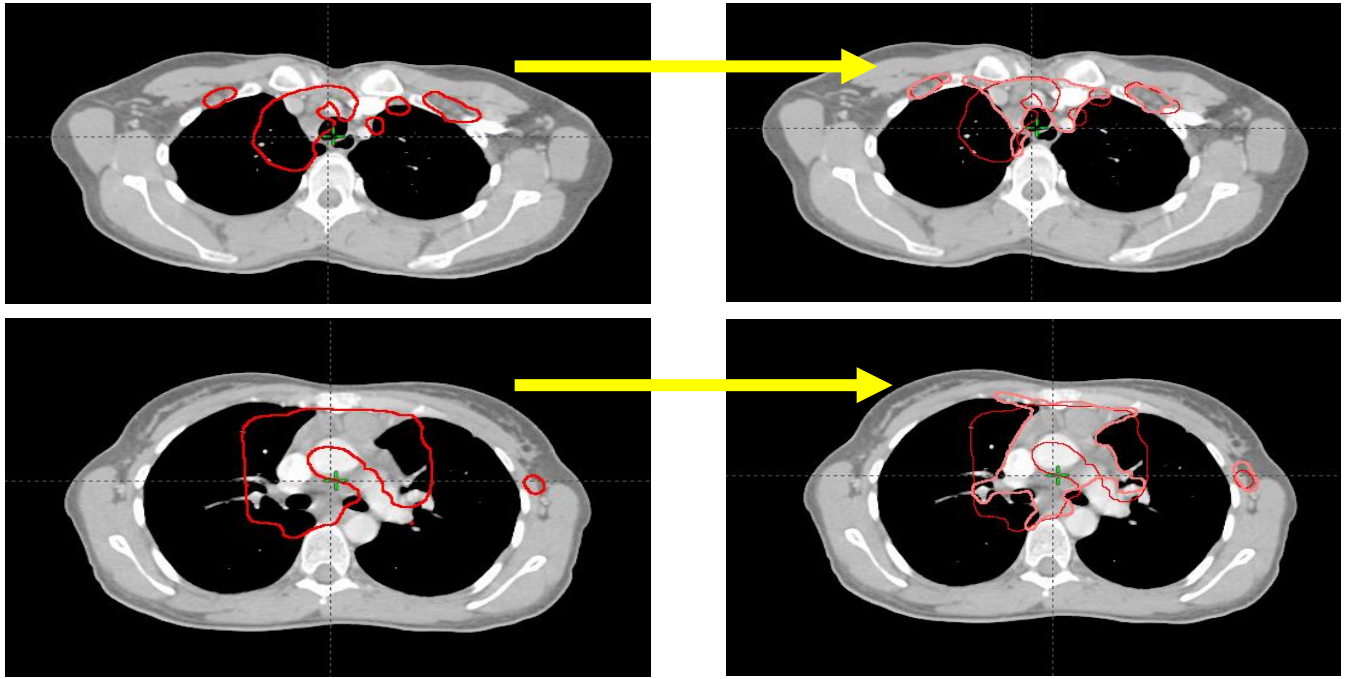
Post-chemo planning CT scan

Pre-chemo gross tumour volume

Post-chemo clinical target volume



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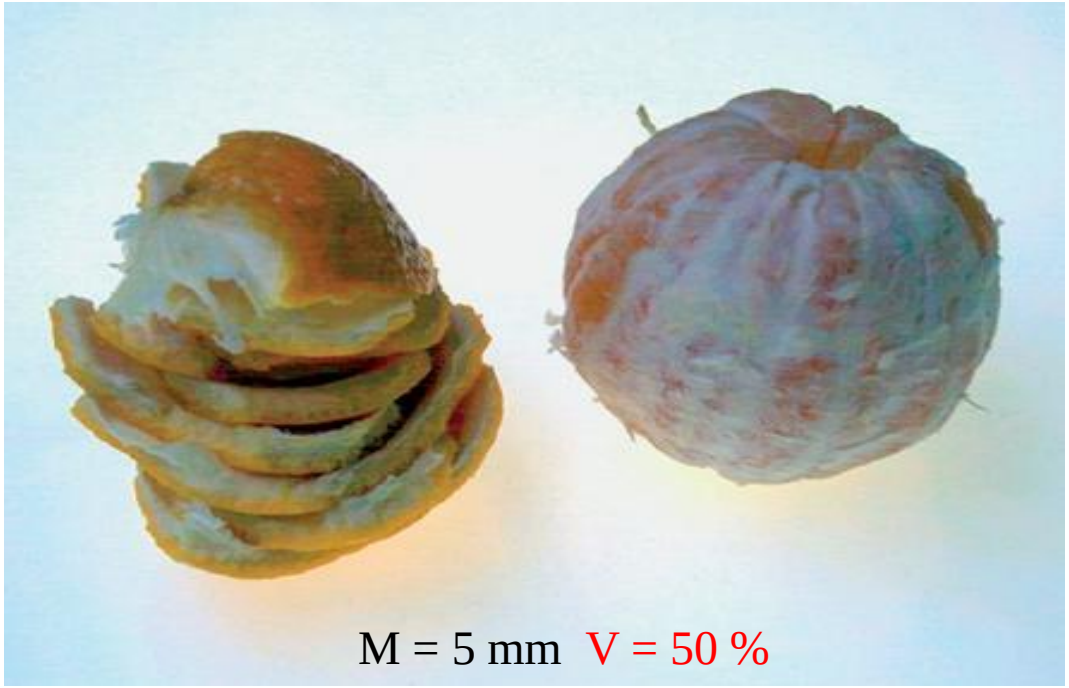
Margins and corresponding tissue volumes



Verellen D et al.
Nat Rev Cancer
2007; 7: 949-60

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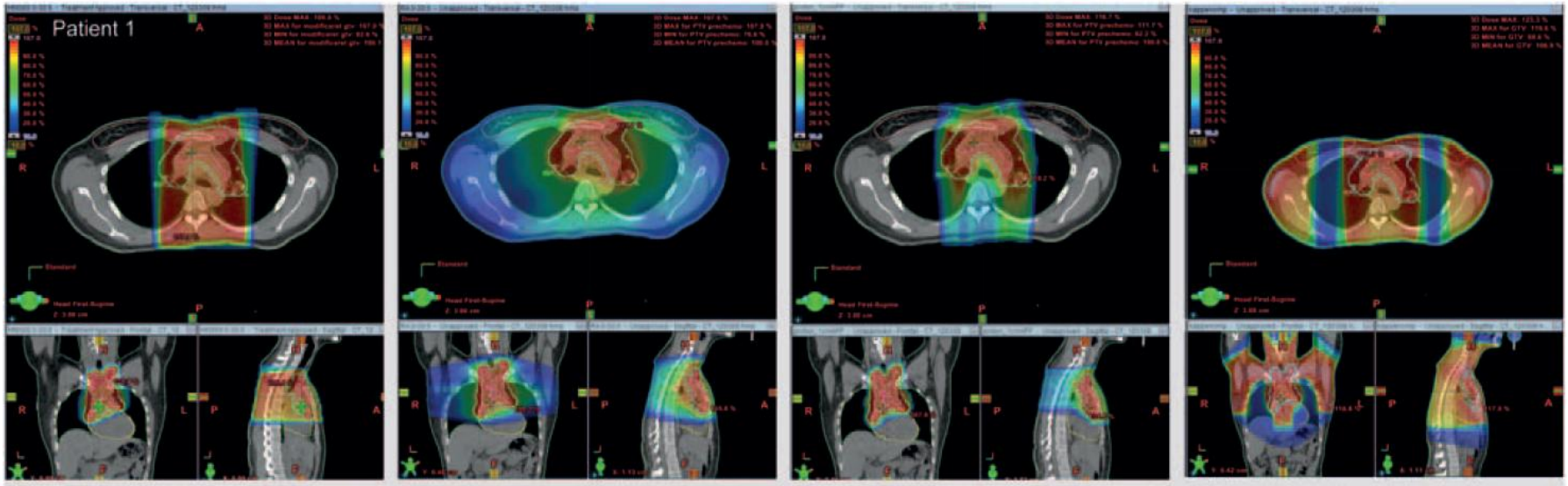
Different modern techniques vs. extended fields of the past

AP-PA IMRT IMPT Mantle field



Maraldo M et al. Ann Oncol 2013; 24: 2113-8

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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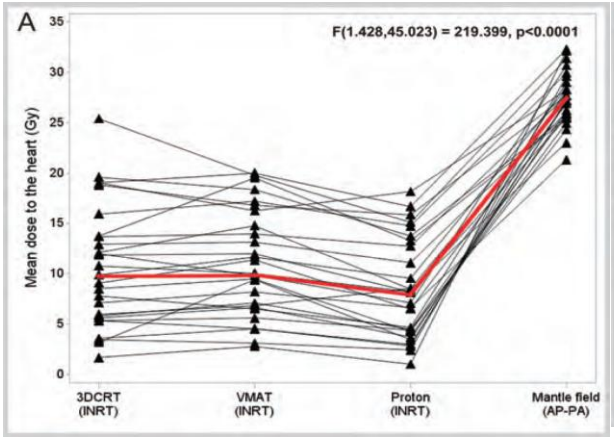
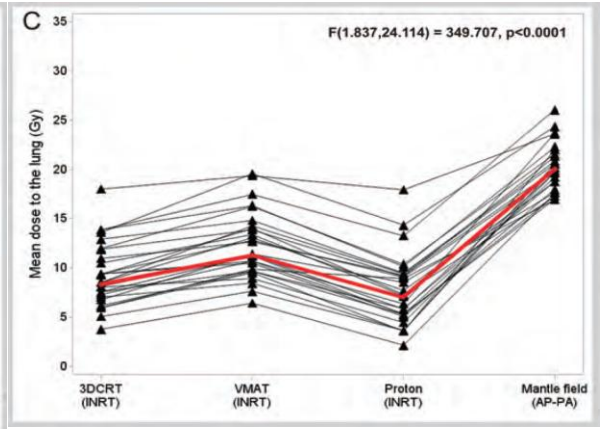
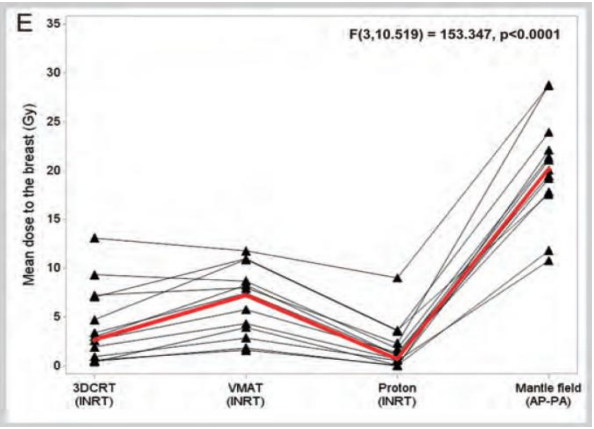
Mean doses to heart, lungs, and breasts in 27 early stage HL patients with mediastinal involvement with different techniques

3D conformal, IMRT (volumetric arc), proton therapy, and conventional mantle field







Maraldo M et al. Ann Oncol 2013; 24: 2113-8

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Lifetime excess risks in 27 early stage HL patients with mediastinal involvement with different techniques

3D conformal, IMRT (volumetric arc), proton therapy, and conventional mantle field

	3D CRT		VMAT		PT		MF	
	Median	Range	Median	Range	Median	Range	Median	Range
Risk estimates (%)								
Cardiac mortality (CMort)	1.0	(0.2–2.7)	1.1	(0.3–2.1)	0.9	(0.1–1.9)	2.9	(2.2–3.4)
Cardiac morbidity (CMorb)	1.3	(0.5–7.1)	1.3	(0.6–4.0)	1.1	(0.5–3.3)	8.6	(4.6–14.3)
Myocardial infarction (MI)	5.5	(0.7–30.1)	5.9	(1.1–23.8)	4.7	(0.4–20.4)	19.8	(6.9–37.7)
Valvular disease (VD)	0	(0–0.2)	0	(0)	0	(0)	0.4	(0–3.7)
Radiation-induced lung cancer (LC)	4.4	(2.4–9.7)	6.0	(3.1–11.4)	3.3	(1.4–9.7)	10.5	(6.3–15.1)
Radiation-induced breast cancer (BC)	3.7	(0.2–11.8)	8.0	(0.6–13.4)	1.4	(0–8.1)	23.0	(7.5–34.5)
Life years lost (LYL)								
Total LYL	0.9	(0.2–1.6)	1.1	(0.2–2.3)	0.7	(0.1–1.6)	2.1	(0.6–3.6)

Maraldo M et al. Ann Oncol 2013; 24: 2113-8

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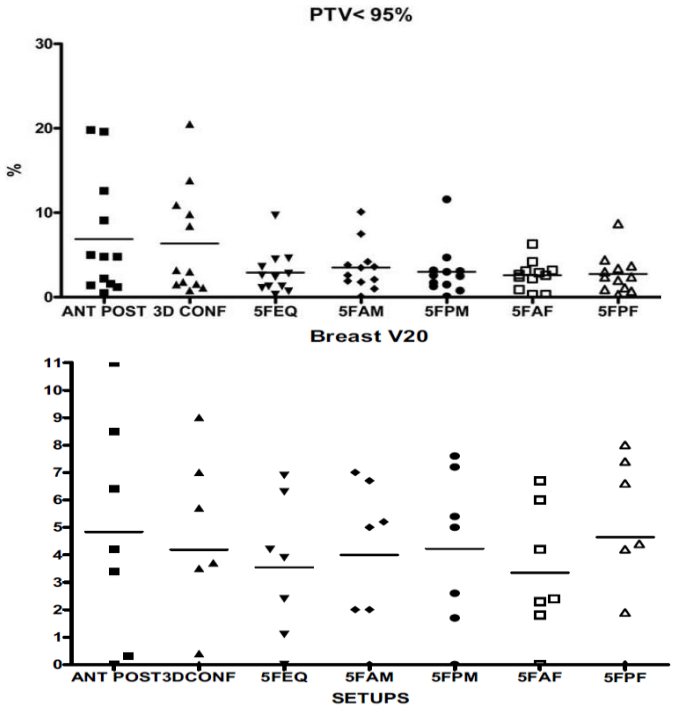
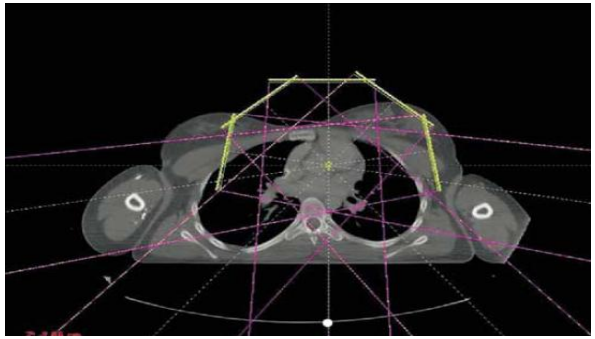
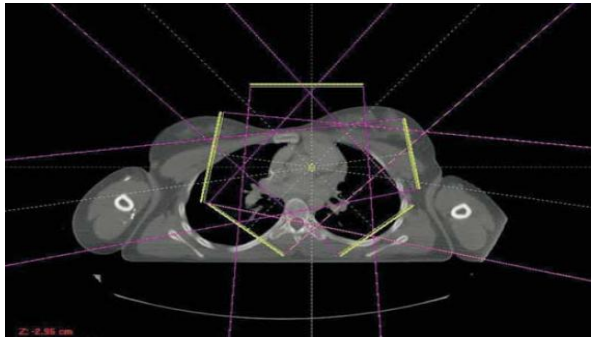
Optimizing IMRT with ”intelligent” beam orientation





Focus on anterior mass (FAM)



Avoid the breasts (FAF)

Girinsky et al. IJROBP 2006; 64: 218-26

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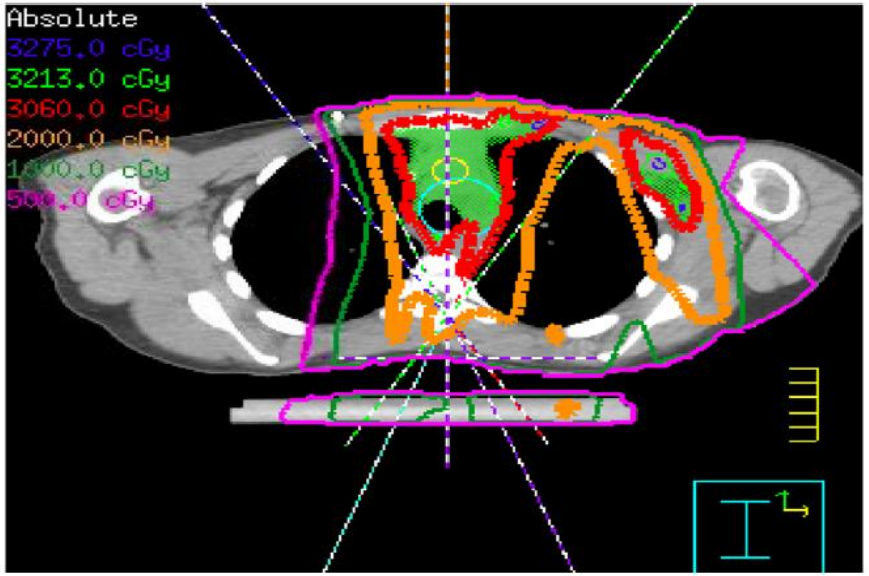
Optimizing IMRT with ”intelligent” beam orientation

”Butterfly technique”



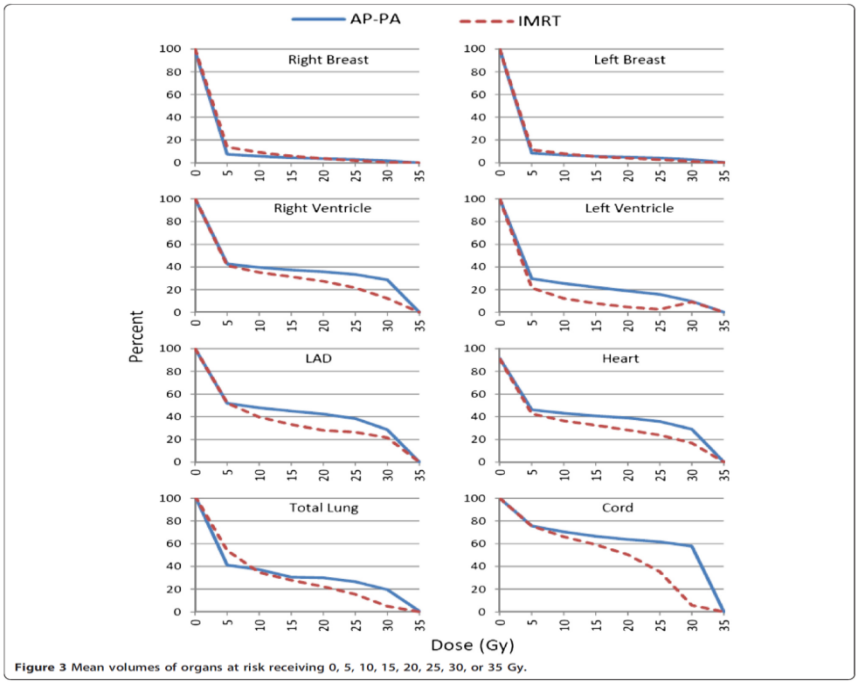


Figure 3 Mean volumes of organs at risk receiving 0, 5, 10, 15, 20, 25, 30, or 35 Gy.

Voong et al. Radiat Oncol 2014; 9: 94

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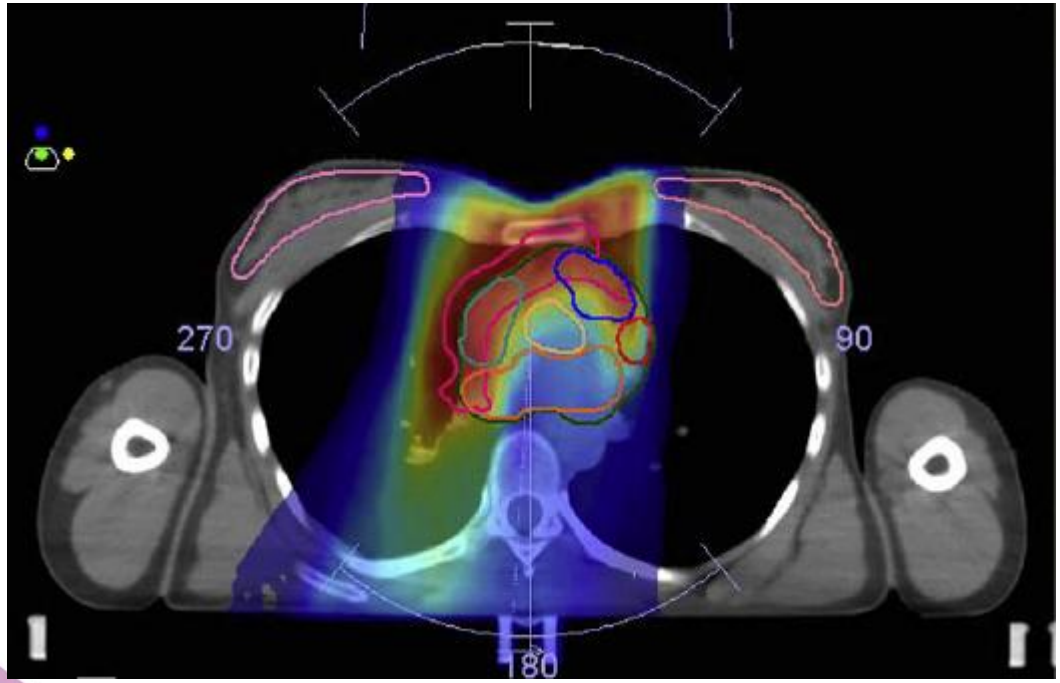
Optimizing IMRT with ”intelligent” beam orientation

2 coplanar arcs + 1 non-coplanar



Site	Mean AER and SD		*P* value
	3D-CRT	VMAT	
Cardiac diseases	0.74 ± 1.50	0.37 ± 0.45	.038
Aortic valve	2.15 ± 2.27	0.26 ± 0.63	<.0001
Pulmonic valve	3.13 ± 3.24	1.36 ± 1.88	<.0001
Mitral valve	0.29 ± 1.10	0.003 ± 0.007	.12
Tricuspid valve	0.73 ± 2.11	0.07 ± 0.36	.045
All valves	1.57 ± 2.55	0.42 ± 1.14	<.0001

Target	Mean OED and SD		*P* value
	3D-CRT	VMAT	
Lung			
All	2.16 ± 0.84	2.28 ± 0.73	.025
No neck	1.59 ± 0.73	1.91 ± 0.62	.001
Unilateral neck	2.31 ± 0.85	2.46 ± 0.81	.03
Bilateral neck	2.33 ± 0.76	2.22 ± 0.57	.23
Breast			
All	0.22 ± 0.15	0.22 ± 0.16	.72
No neck	0.17 ± 0.13	0.20 ± 0.13	.34
Unilateral neck	0.26 ± 0.18	0.25 ± 0.19	.88
Bilateral neck	0.20 ± 0.12	0.16 ± 0.09	.02
Thyroid			
All	3.29 ± 1.77	3.34 ± 1.75	.35
No neck	0.30 ± 0.16	0.41 ± 0.36	.29
Unilateral neck	3.65 ± 0.83	3.73 ± 0.81	.48
Bilateral neck	4.83 ± 0.62	4.83 ± 0.68	.94

Filippi et al. IRJOBP 2015; 92: 161-8

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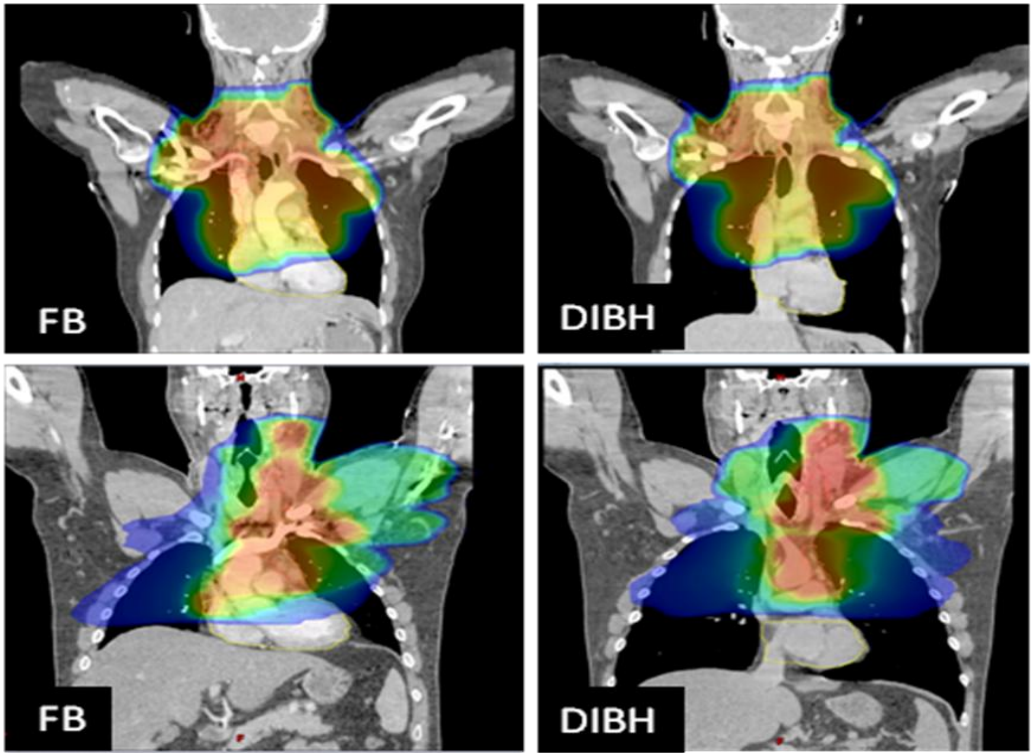
Breathing adapted RT



Petersen PM et al. Acta Oncol 2015; 54: 60-6

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Table II. Dose characteristics with free breathing (FB) and deep inspiration breath-hold (DIBH).

	FB (median, range)		DIBH (median, range)		Difference (median, range)		p-Value*
Target							
PTV volume (cm^3)	1198	(132, 1877)	945	(131, 1949)	62	(−361, 634)	0.07
CTV volume (cm^3)	213	(21, 511)	198	(14, 561)	3	(−126, 209)	0.60
PTV $V_{95\%}$ (%)	94	(61, 98)	93	(78–97)	1	(−18, 7.4)	0.12
Lung							
Lung volume (cm^3)	2924	(1908, 5228)	4936	(3391, 8776)	−2300	(−5272, −1093)	<0.01
Mean lung dose (Gy)	8.5	(0.95, 18.9)	7.2	(1.0, 12.5)	2.0	(−0.08, 6.4)	<0.01
Lung V_{20Gy} (%)	14	(0, 46)	11	(0, 32)	5.3	(−1, 17)	<0.01
Heart							
Mean heart dose (Gy)	6.0	(0.12, 23)	3.9	(0.10, 17)	1.4	(0, 8.6)	<0.01
Heart V_{20Gy} (%)	15	(0.00, 76)	4.1	(0.00, 66)	6.3	(−2.7, 32)	<0.01
Heart V_{30Gy} (%)	2.0	(0.00, 35)	0.00	(0.00, 27)	0.8	(−7, 16)	0.01
Mean aortic valves dose (Gy)	26	(0.23, 31)	16	(0.20, 31)	1.9	(−1.8, 14)	<0.01
Mean mitral valve dose (Gy)	7.1	(0.12, 30)	1.9	(0.10, 29)	0.58	(−1.3, 16)	<0.01
Mean tricuspid valves dose (Gy)	2.6	(0.11, 30)	1.7	(0.10, 30)	0.43	(−4.6, 20)	0.01
Mean pulmonic valves dose (Gy)	26	(0.26, 32)	15	(0.23, 32)	1.4	(−1.9, 21)	<0.01
Mean LAD dose (Gy)	8.9	(0.10, 29)	5.0	(0.09, 27)	0.80	(−1.8, 14)	<0.01
Mean LMA dose (Gy)	25	(0.25, 32)	18	(0.20, 32)	3.0	(−11, 21)	<0.01
Mean LC dose (Gy)	11	(0.18, 31)	7.7	(0.15, 31)	0.40	(−4.0, 25)	0.02
Mean RCA dose (Gy)	27	(0.16, 31)	17	(0.01, 32)	0.29	(−17, 24)	0.06
Breast							
Mean dose right breast (Gy)	5.0	(0.11, 15)	6.4	(0.074, 13)	0.00	(−4.8, 2.2)	0.47
Mean dose left breast (Gy)	3.7	(0.11, 15)	3.2	(0.090, 13)	0.01	(−3.6, 6.8)	0.22

Petersen PM et al. Acta Oncol 2015; 54: 60-6

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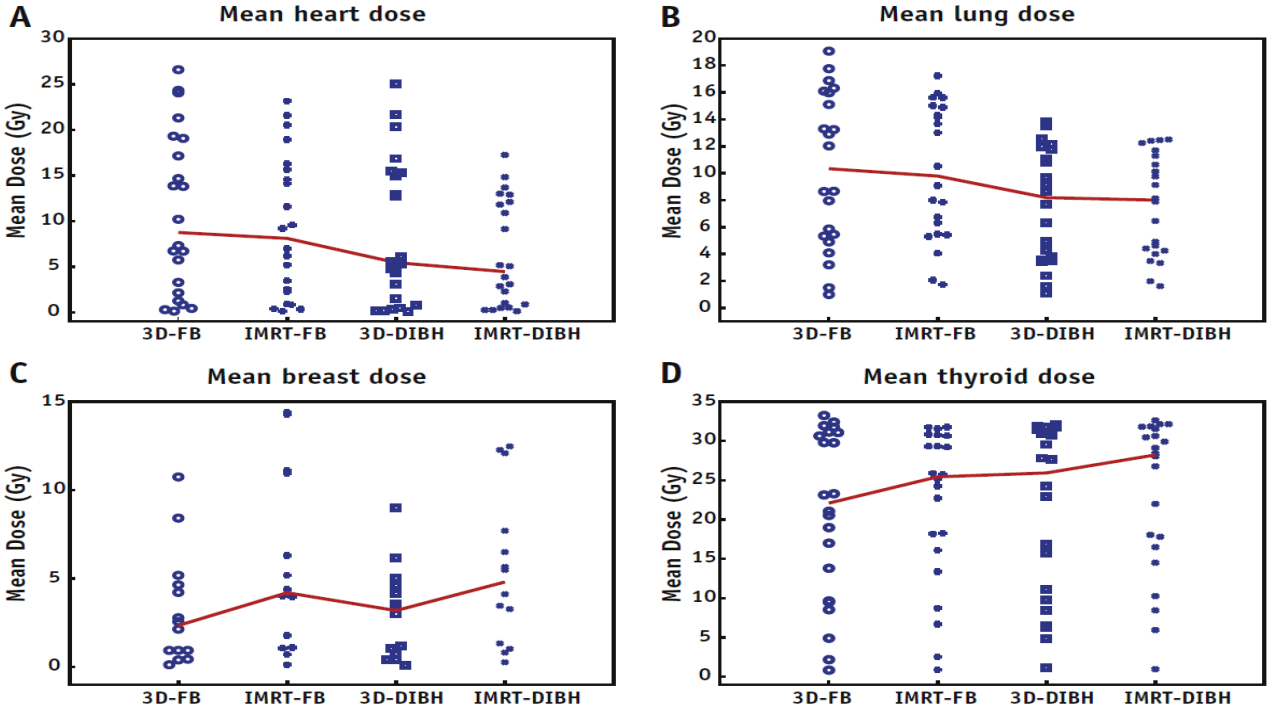
Breathing adaptation and highly conformal treatment (IMRT), what can we achieve?



Aznar et al. IJROBP 2015; 92: 169-74

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Which technique is preferable?

- Depends on the location of the target
- Dose plans for different alternatives should be compared
- Considerations of normal tissue toxicity varies between patients depending on:
  - Age
  - Gender
  - Comorbidities
  - Risk factors for other diseases
- Even low doses to normal tissues, previously considered safe, result in significant risks of morbidity and mortality in long-term survivors
- Doses to all normal structures should be kept as low as possible, but some structures are more critical than others

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Constraints, are they useful for lymphomas?

Organ at risk	Limiting dose/volume
Brain stem	If whole organ irradiated, $D_{max} < 54$ Gy to any part of the volume If partial volume irradiated, $D_{1-10\ cm^3} \leq 59$ Gy
Breast	Minimise volume inside PTV, particularly in young women ≤30 years. Mean dose ≤ 2 Gy
Cochlea	Mean dose ≤ 45 Gy
Coronary artery	Minimise volume inside treatment field and keep doses as low as possible without compromising on PTV coverage
Heart	Mean dose < 26 Gy; $D_{100} < 30$ Gy $V_{30} < 46\%$; $V_{33} < 60\%$, $V_{38} < 33\%$, $V_{42} < 20\%$
Kidney	Single kidney irradiated: V_{15} of 65–70%, Both kidneys irradiated: V_{15} of 20–25% for each kidney; mean dose < 18 Gy. Partial kidney irradiation (all constraints are for combined kidneys): mean dose < 18 Gy $V_{28} < 20\%$, $V_{23} < 30\%$, $V_{20} < 32\%$, $V_{12} < 55\%$. If mean dose to one kidney >18 Gy, V_6 for remaining kidney <30%
Lens	Maximum dose of 6 Gy to any part of the volume unless compromising PTV coverage
Liver	Mean dose < 32 Gy; V_{40} of 30–35%; D_{100} of 25 Gy, D_{66} of 28 Gy, D_{33} of 38 Gy
Lung (whole)	$V_{20} \leq 30\%$, Mean lung dose (MLD) ≤ 20 Gy
Oesophagus	Mean dose < 34 Gy, $V_{35} < 50\%$
Optic chiasm	$D_{max} < 55$ Gy to any part of the volume
Optic nerve	$D_{max} < 55$ Gy to any part of the volume
Ovary	D_{max} <10 Gy to any part of the volume outside PTV. If inside PTV discuss individual case with clinician
Parotid	Bilateral irradiation: mean dose < 25 Gy. Unilateral irradiation: mean dose < 20 Gy to the contralateral parotid
Small bowel	For individual loops $V_{15} < 120\ cm^3$ For whole peritoneal cavity $V_{45} < 195\ cm^3$
Spinal cord	$D_{max} \leq 50$ Gy to any part of the volume
Stomach	$D_{100} < 45$ Gy
Testis	Maximum dose of 2 Gy to any part of the volume
Thyroid	$D_{100} < 45$ Gy

Hoskin PJ et al, Clin Oncol 2013; 25: 49-58

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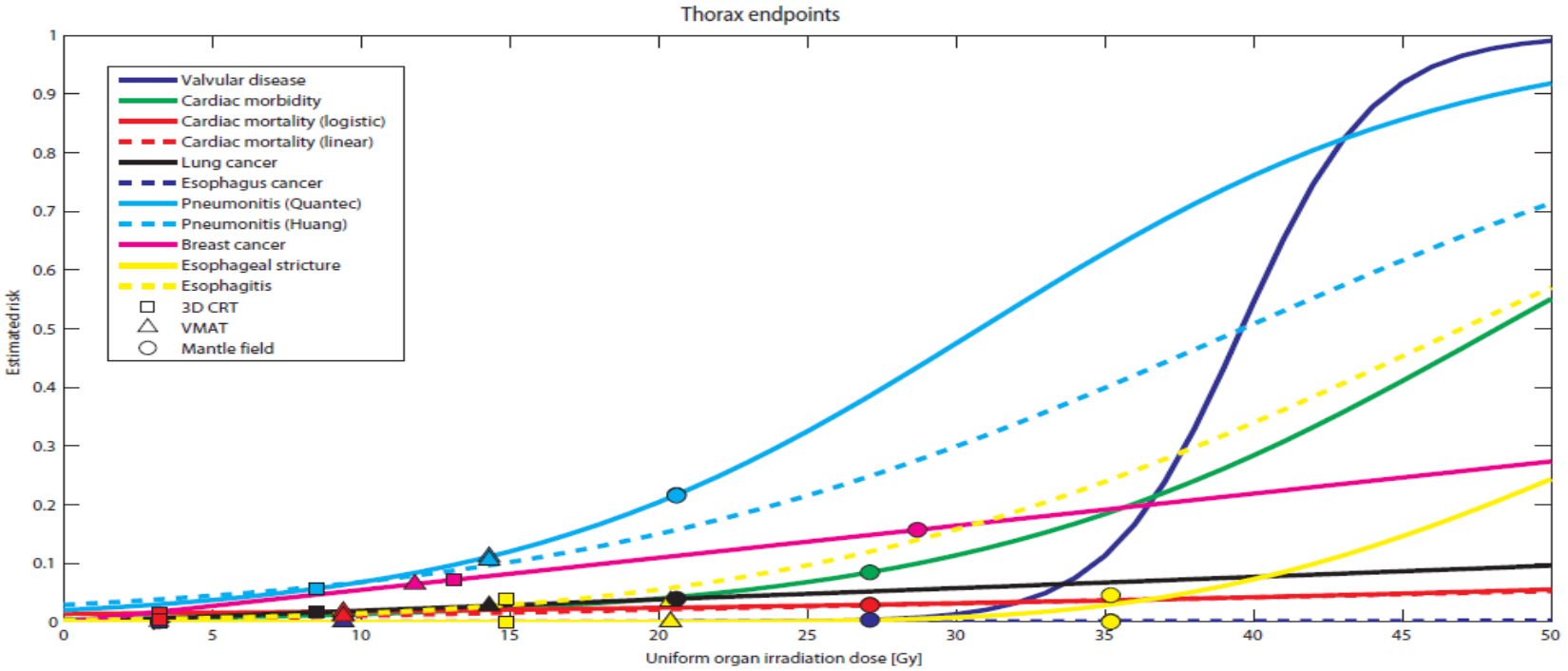
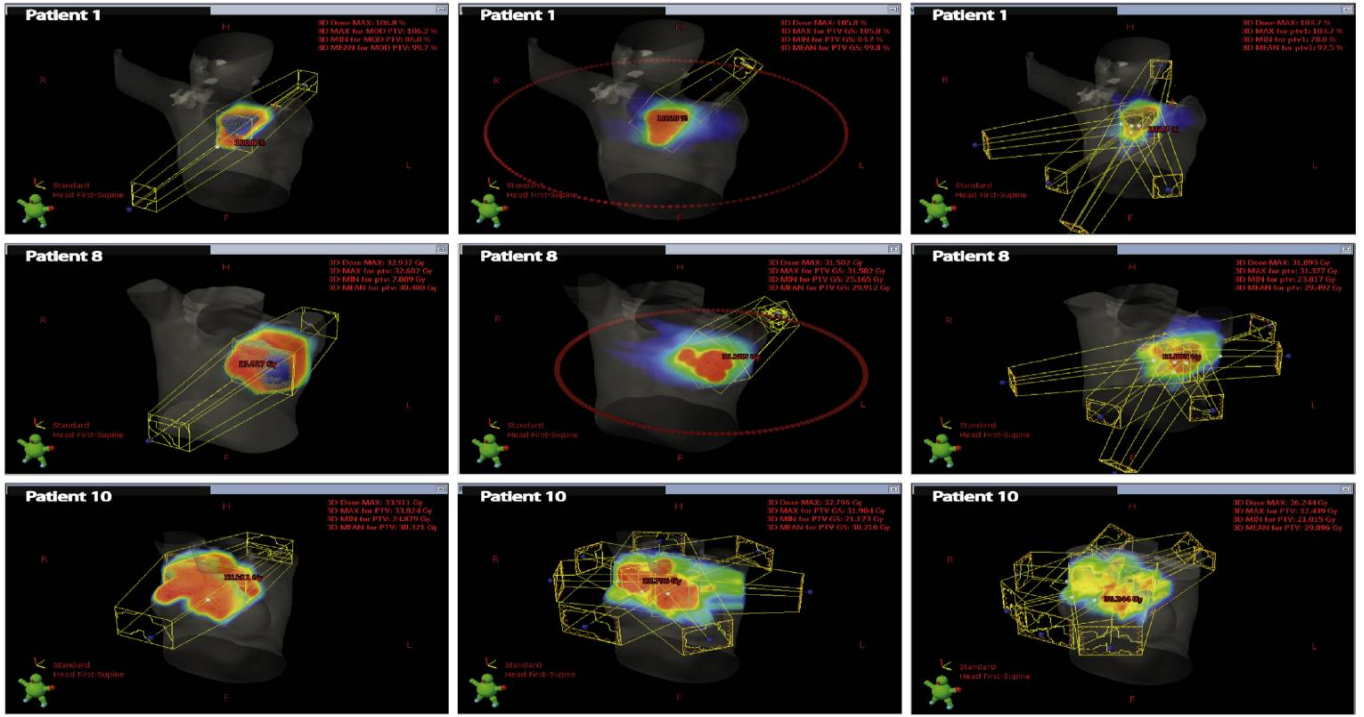
Ideally, normal tissue complication probability models for all relevant risk organs should be combined for each treatment plan



Brodin NP et al, IJROBP 2014;88:433-45

Same patient, different solutions



Maraldo M et al. IJROBP 2015; 92: 144-52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Extranodal lymphomas: Head and neck

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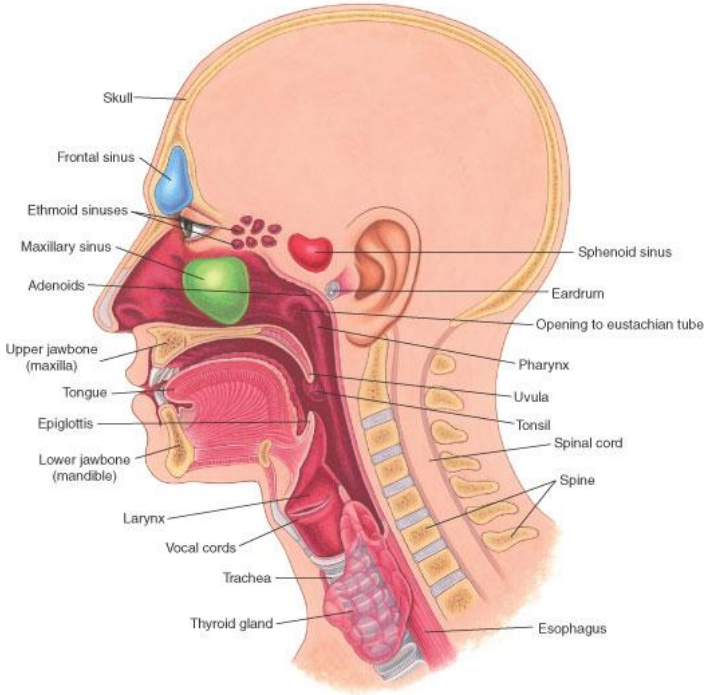
Extranodal (not necessarily extralymphatic) sites in the upper aerodigestive tract



- Nasal cavity and paranasal sinuses: NK/T-cell lymphomas (Eastern Asia and South America) and DLBCL (Western countries)

- Pharynx (most often in Waldeyer's ring: lymphatic tissue formed by palatine tonsils, adenoids in posterior nasopharynx, lingual tonsil, and intervening lymphoid tissues): DLBCL

- Oral cavity, larynx and hyphopharynx: rare, include indolent lymphomas, mantle cell lymphomas and DLBCL

- Parotid and other salivary glands: MALT lymphomas

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Head & neck lymphomas, general principles

- Pre-treatment work-up:
  - Detailed ENT examination incl. fiberoptic examination, evt. under general anaesthesia
  - Imaging with PET and CT, MRI for skull base, cranial cavity, cranial nerve, sinuses, and infratemporal fossa

Head & neck lymphomas, general principles

- ISRT to sites of initial definite or suspected involvement
- Prophylactic RT of uninvolved lymph node regions is not routine
- Optimal immobilization, e.g. a 5-point thermoplastic mask
- RT techniques as for solid tumors in the head & neck area often appropriate

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Head & neck lymphomas, indolent

- Localized indolent disease: RT primary curative modality, 24-30 Gy
- Lymphoma is often multifocal, and the involved organ is often treated in its entirety
- First echelon nodes of uncertain status close to the primary organ may be included
- Advanced indolent disease: RT may provide effective palliation, 4 Gy effective in most patients

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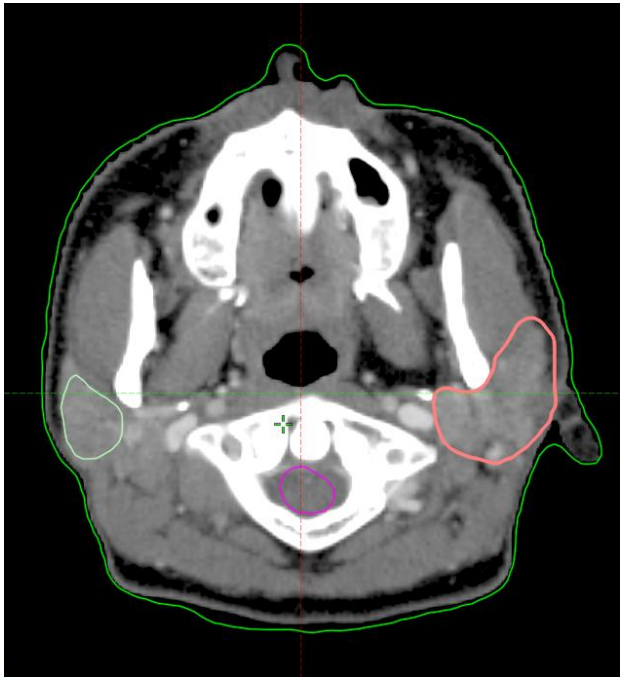
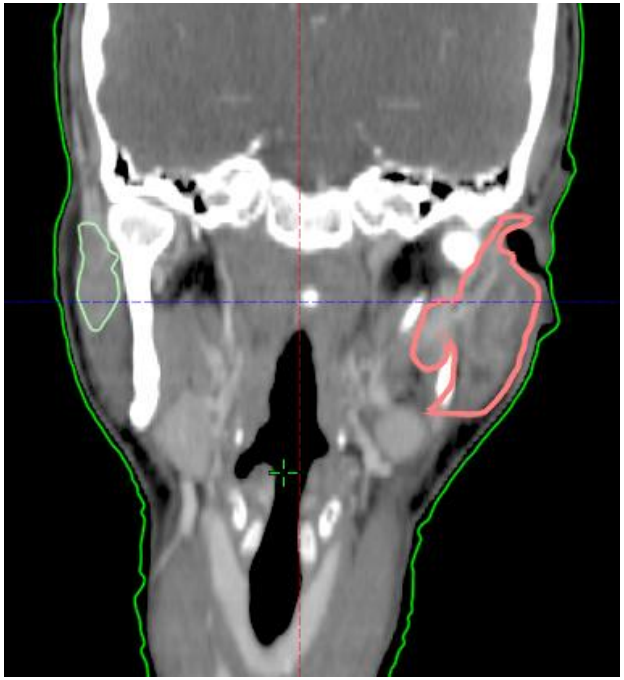
MALT lymphoma in left parotid gland

Post-op images





- 40 year female with swelling in left angular and preauricular area, waxing and waning for two years
- Previous FNA inconclusive
- Excisional biopsy: MALT lymphoma
- No post-op abnormality on PET/CT-scan.

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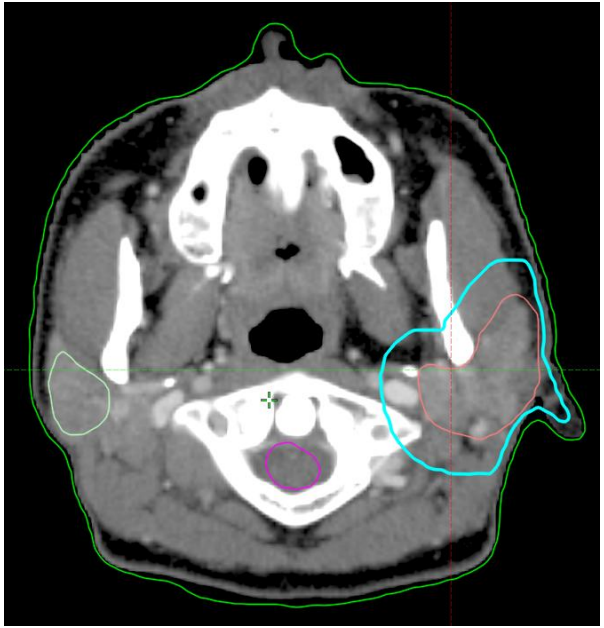
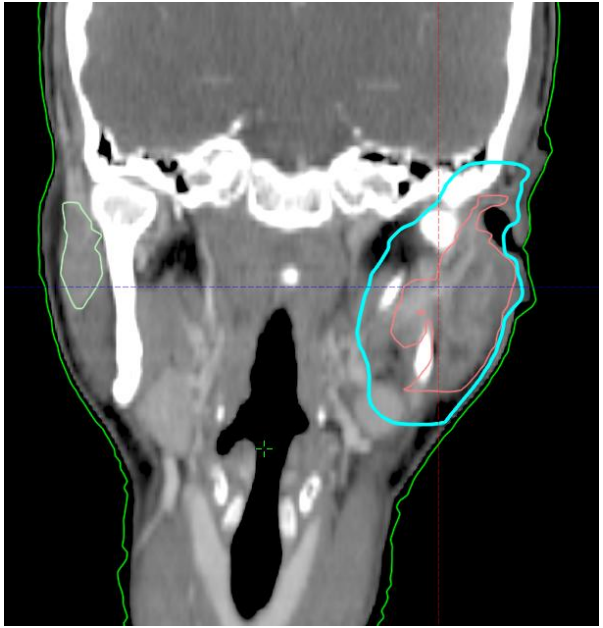
PTV





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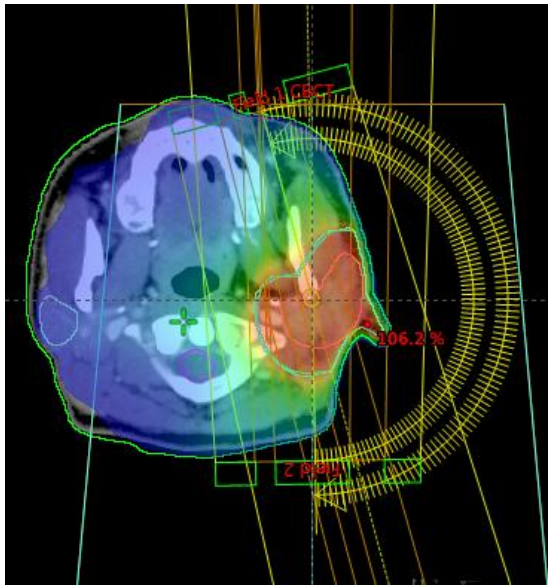
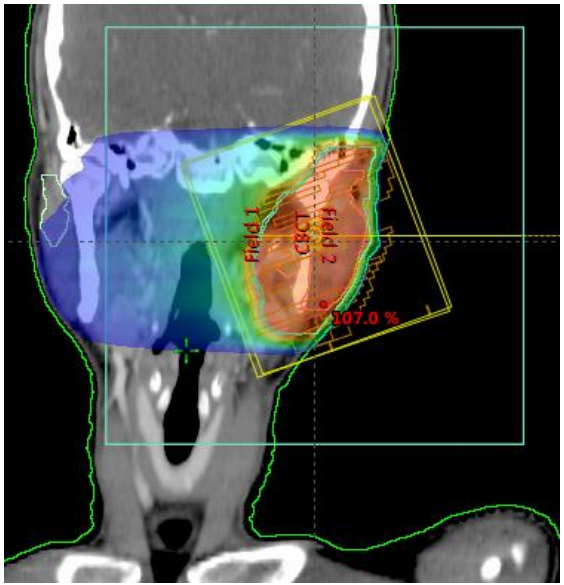
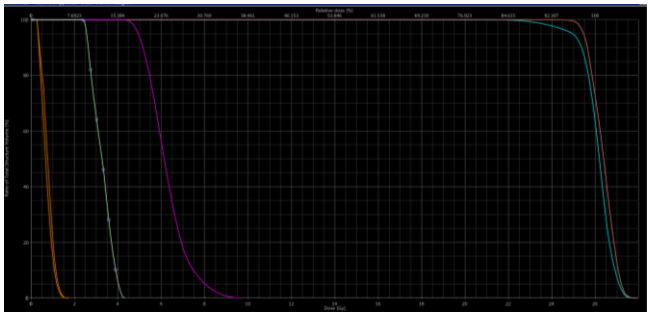
Treatment plan (RapidArc)







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Head & neck lymphomas, aggressive

- Localized aggressive disease: Systemic therapy is the primary treatment. RT is used as consolidary treatment, dose 30-36 Gy after CR, 40-45 Gy if gross residual disease
- Radiation volumes may be limited to part of an organ after excellent response to systemic treatment, which controls microscopic disease
- Advanced aggressive disease: RT to initial bulk according to RICOVER and UNFOLDER studies, extranodal disease unclear (Waldeyer's ring was not considered extranodal in RICOVER)

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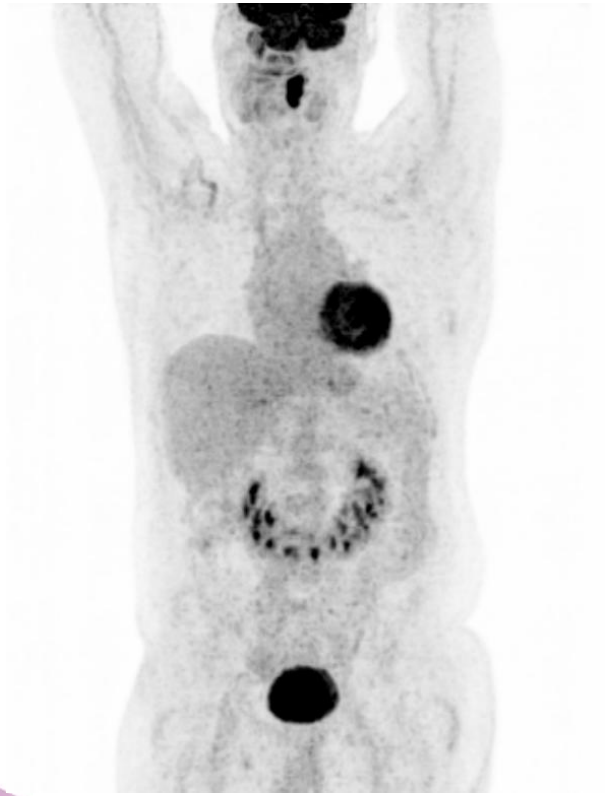
DLBCL in tonsil



- 74 year old male with DLBCL of the left tonsilla
- Whole body PET/CT (September 4, 2014) showed no signs of lymphoma elsewhere, the patient had no B-symptoms, LDH was normal
- He was in stage IA, and was treated with 3 cycles of R-CHOP followed by ISRT to 30 Gy
- Since then in continuous CR

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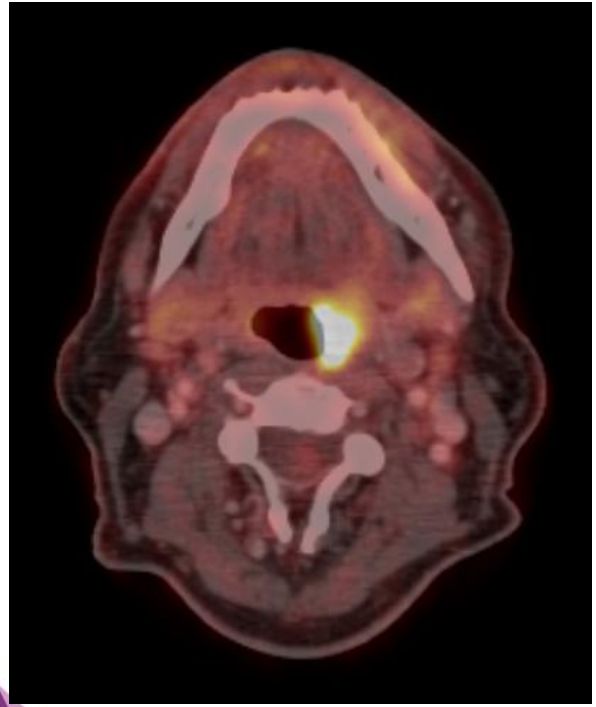
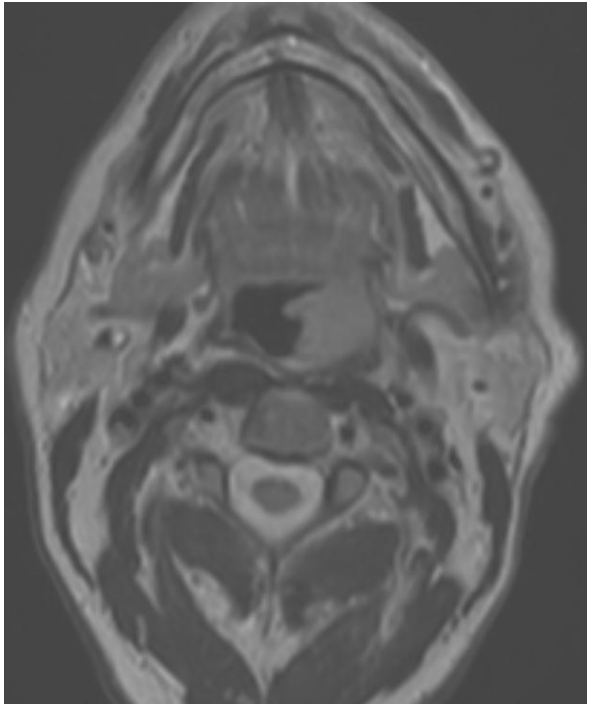
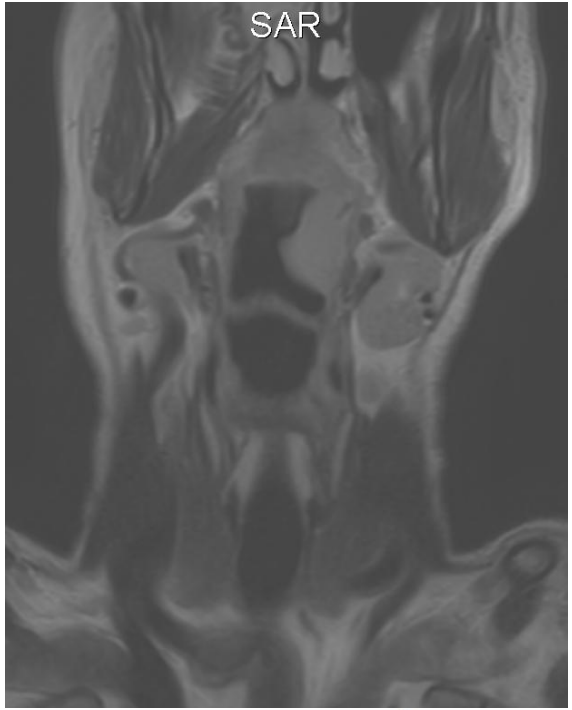
Pre-chemo images







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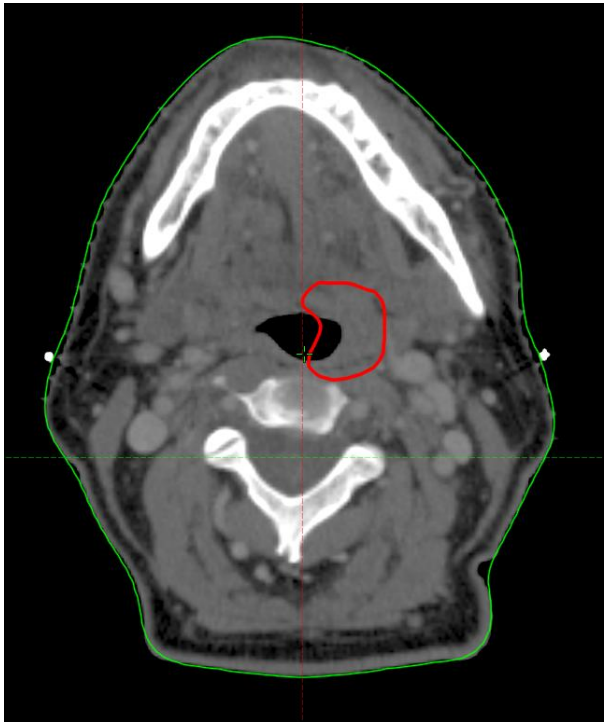
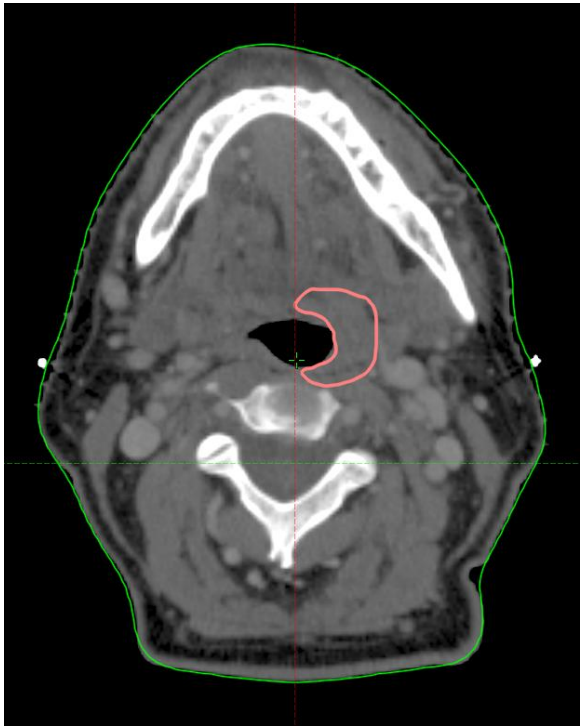
Post-chemo planning CT

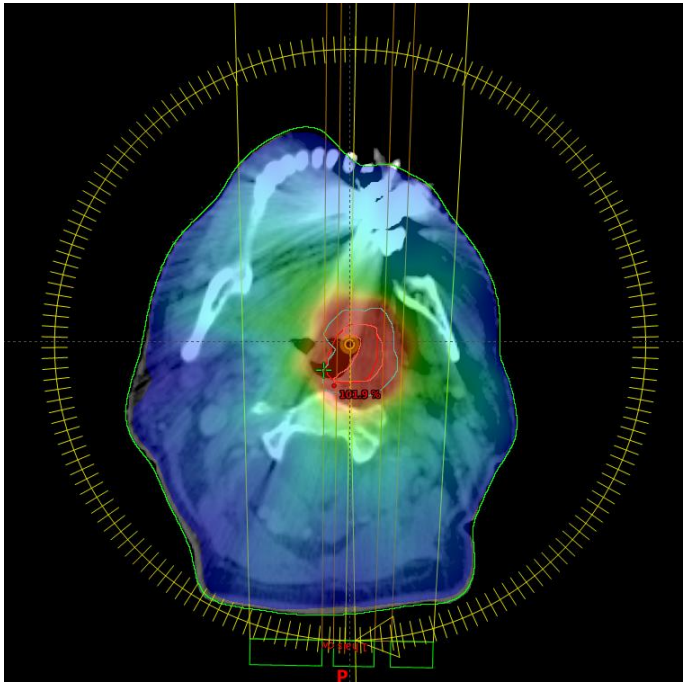
Pre-chemo
GTV

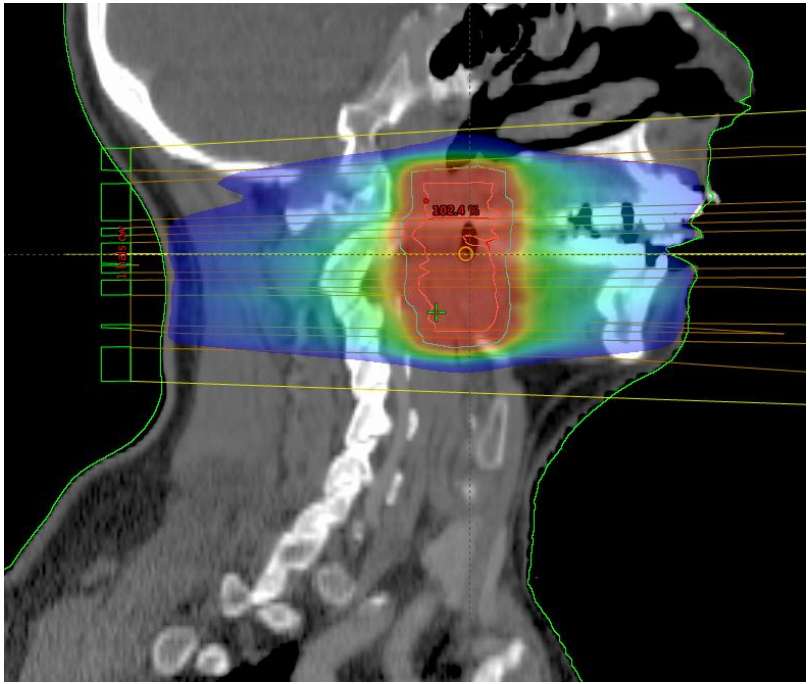




Post-chemo
CTV

Treatment plan (RapidArc)





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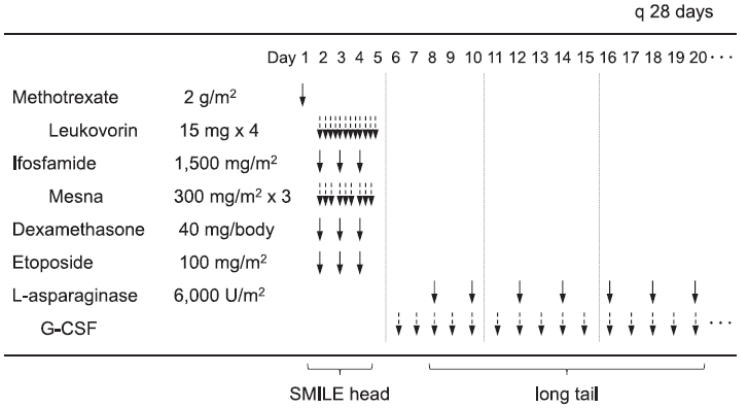
NK/T-cell lymphomas, nasal type

- Associated with Epstein-Barr virus
- More common in Asians and native Americans in Central and South America
- Usually involves nasal cavity and/or paranasal sinuses, Waldeyer's ring may also be involved
- Outside the upper aerodigestive tract it presents in advanced stages and unfavourable prognosis

NK/T-cell lymphomas, nasal type

- Frequently express multidrug resistant P-glycoprotein
- Responds poorly to anthracycline-based chemotherapy (e.g., CHOP-like regimens)
- L-asparaginase is effective: SMILE regimen



NK/T-cell lymphomas, nasal type

- Early stage disease: SMILE (or other effective regimen) x 2
- Radiotherapy is an essential component of treatment and must:
  - Come in early
  - Doses ≥ 50 Gy

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NK/T-cell lymphoma, nasal type

Courtesy of Dr. Shunan Qi, Memorial Sloan Kettering Cancer Center, New York, and Chinese Academy of Medical Sciences, Beijing

- **Challenges for GTV contouring**
  - Lesions often associated with mucosa surface
  - Lesions are accompanied with inflammation/necrosis
  - Lesions sit in an area with rich lymphoid tissues
- **Rationales guiding CTV contouring**
  - Experience with chemotherapy is limited (SMILE, non-MDR drugs)
  - RT is the most effective treatment
  - Close association between local control and survival
  - Uncertainty of disease boundaries
  - Local invasiveness of the disease nature

Extended ISRT!

- Irradiate the whole involved cavity and adjacent structures!

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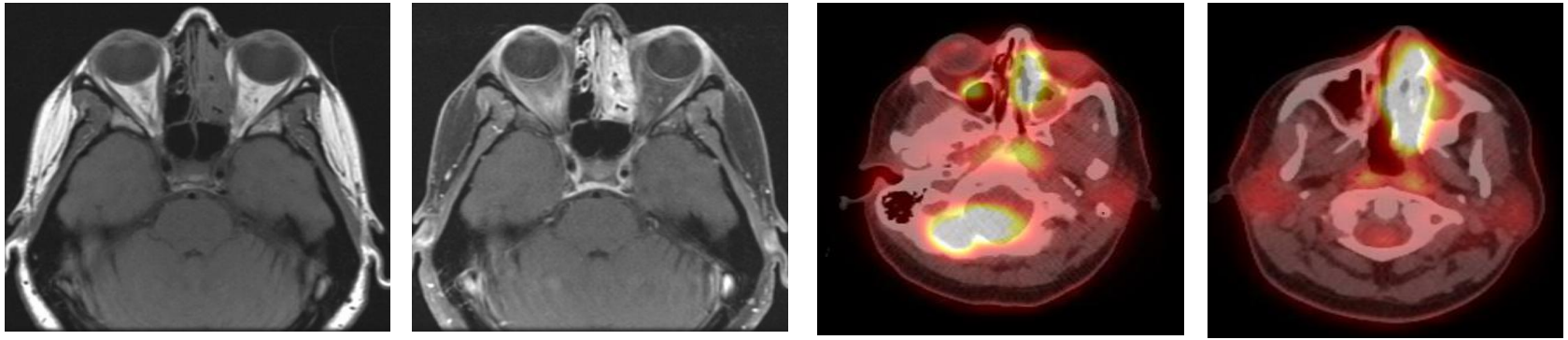
Extranodal NK/T cell lymphoma, nasal type, CS IEA, involving left nasal cavity, IPI: 0

- The treatment plan was 2 cycles of SMILE followed by extended involved site radiation therapy (extended ISRT) to 45 Gy
- The patient received 2 cycles of SMILE, and responded immediately with CR on the post-chemotherapy planning PET/CT scan



Pre-chemo images

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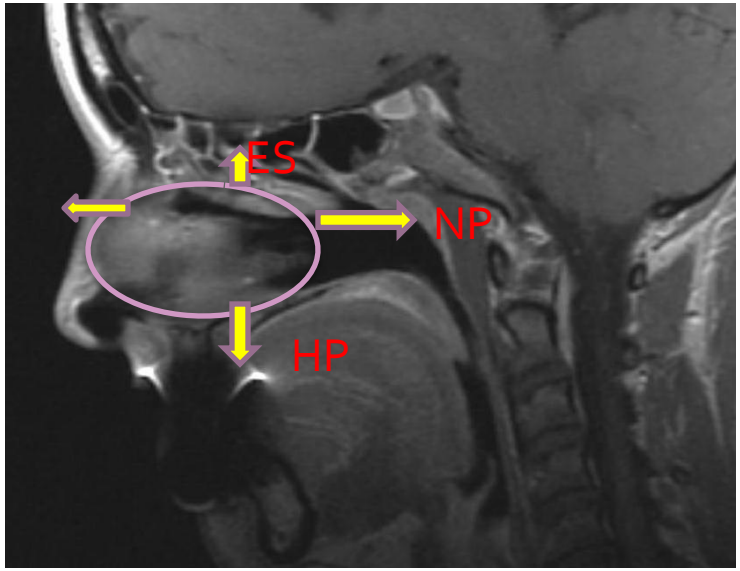
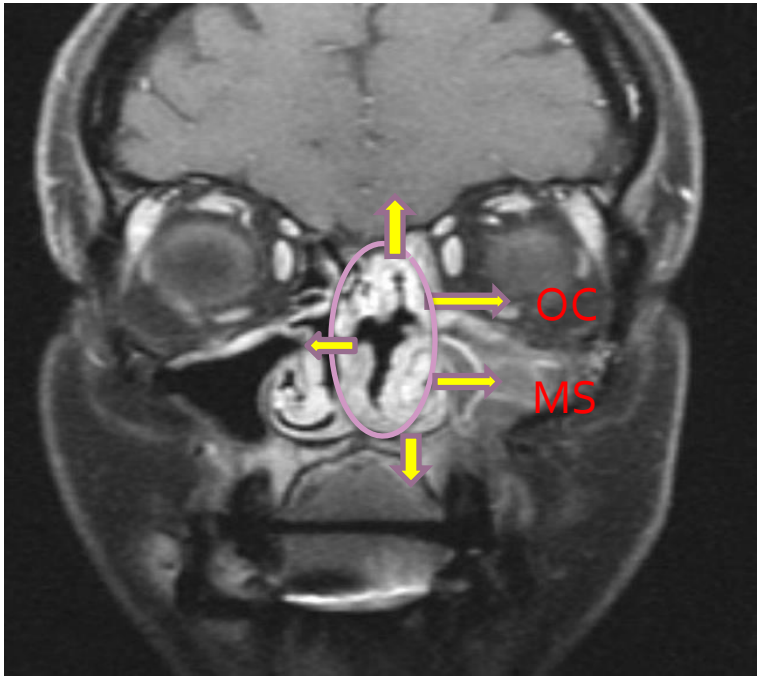
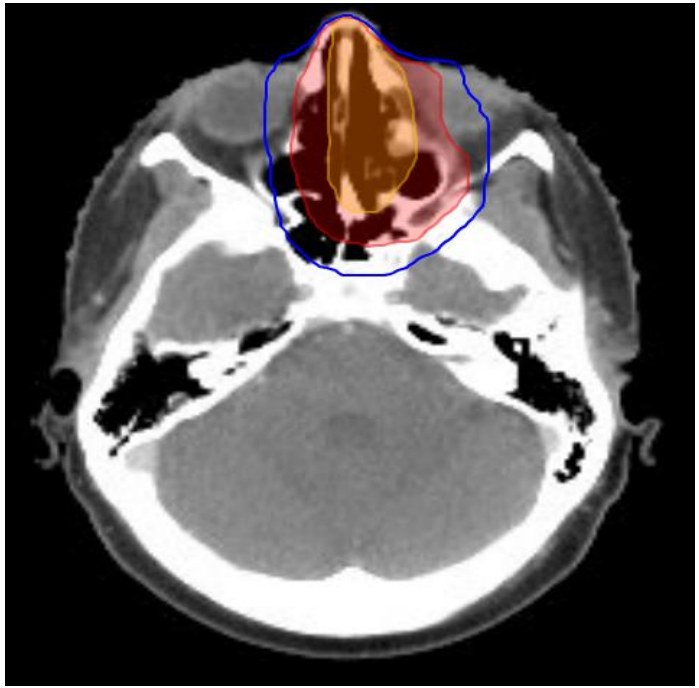
Nasal cavity and adjacent structures





CTV



Pre-chemo GTV	CTV	note
left nasal cavity, medial left orbital wall, left ethmoid and medial wall of left maxillary sinuses	bilateral nasal cavity+ left maxillary sinus + bilateral ethmoid sinuses + part of sphenoid sinus	Beginning of maxillary sinus slice to remind the coverage of whole ipsilateral maxillary sinus

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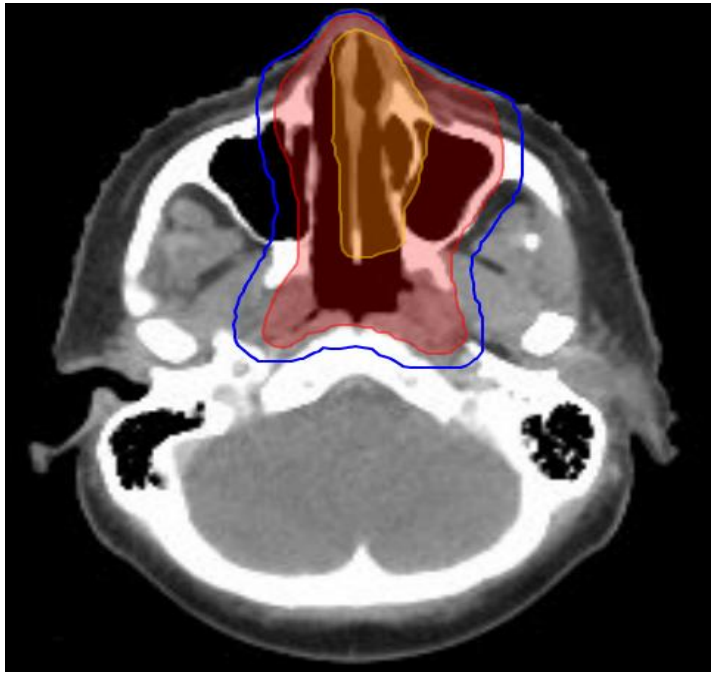
CTV



Pre-chemo GTV	CTV	note
Left nasal cavity, medial wall of left maxillary sinuses	bilateral nasal cavity+ left maxillary sinus + nasopharynx	Typical nasal cavity slice with maximum lesion presentation (CTV covering bilateral nasal cavity, nasopharynx, ipsilateral maxillary sinus)

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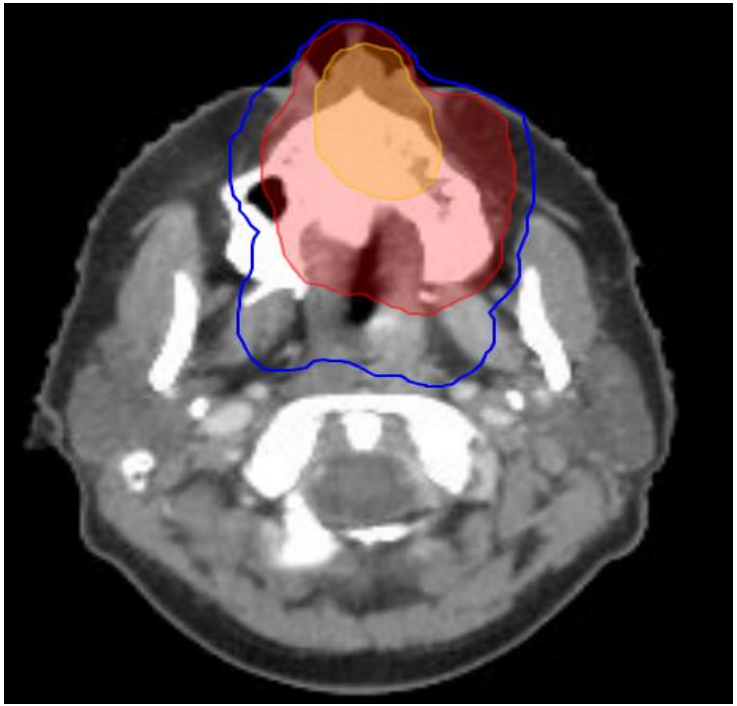
CTV



Pre-chemo GTV	CTV	note
Bottom of left nasal cavity (hard palate)	Bilateral nostril + Left part of hard palate (gum)	Bottom slice of GTV to stress the inclusion of hard palate and gum

Key points

- Multimodality evaluation before treatment
- Non-MDR chemotherapy regimen with L-asparaginase
- Early RT
- Extended ISRT

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Treatment of advanced stage Follicular non Hodgkin Lymphoma including Radioimmunotherapy

Tim Illidge
BSc PhD DRCOG FRCP FRCR FRCPath

Institute of Cancer Sciences
Manchester Academic Health Sciences Centre
Manchester University
The Christie Hospital
Manchester , UK

Decision making in Follicular Lymphoma

- Follicular lymphoma diverse disease, biologically and clinically.
  - Indolent and asymptomatic disease with low tumor burdens
  - More aggressive and symptomatic disease with high tumor burden.
- Decision-making to treat in the frontline therapy based on
  - Histology
  - Disease burden
  - Patient symptoms
  - Patient characteristics, morbidities and choice

Goals of therapy versus toxicity / tolerability in Follicular Lymphoma

- FL generally considered incurable - most patients will require additional therapy in their lifetime.
- First line treatment options trade off between remission duration versus toxicity. Eg R-CHOP induces more durable remissions relative to R-CVP but carries more short-term toxicity and more risk for late cardiotoxicity
- In absence of proven OS advantage for one choice versus another, no one ‘‘right’’ approach.
- Treatment decision is patient-specific, incorporating goals of treatment with the patient’s unique situation
  - Age, comorbidities, tumour burden, patient preferences.

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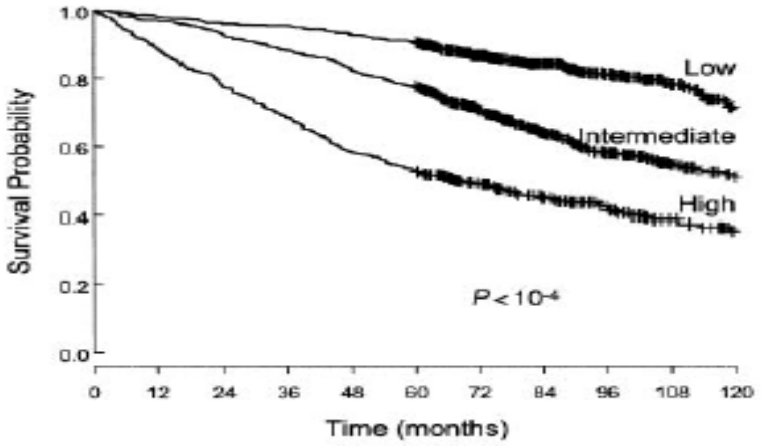
Follicular Lymphoma International Prognostic Index (FLIPI and F2) –

- Nodal regions > 4
- Elevated LDH
- Age > 60
- Stage III/IV
- Haemoglobulin < 12 g/dl
- Serum B2 microglobulin (F2)



Risk Group	# Factors	% Pt	5-yr OS	10-yr OS
Low	0–1	36%	90.6%	70.7%
Intermediate	2	37%	77.8%	50.9%
High	3–5	27%	52.5%	35.5%

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Decision making in Initial treatment of Follicular Lymphoma

Newly diagnosed FL

Symptomatic

Asymptomatic

High Tumour burden	Low Tumour burden	High tumour burden	Low tumour burden
R-Chemo (Consider age and comorbidities for chemo backbone)	Rituximab or R-Chemo	R-Chemo Consider GELF or other criteria for Initiation of treatment	Watch and wait vs Rituximab

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Established definitions of when treatment required

Patients with at least one of the following requiring initiation of treatment:

- Bulky disease (nodal or extranodal mass > 7cm)
- B symptoms
- Elevated serum LDH (> ULN) or β2-microglobulin (> 3mg/L)
- Involvement of ≥ 3 nodal sites (each > 3 cm)
- Symptomatic splenic enlargement, compressive syndrome, pleural/peritoneal effusion

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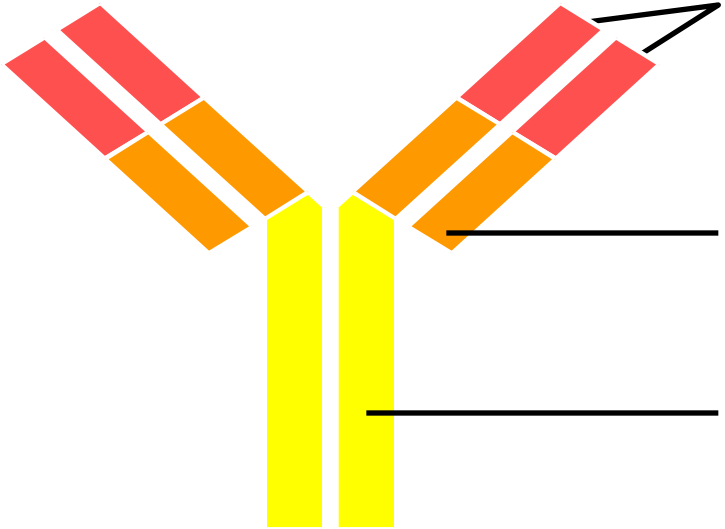
Treatments approaches for those requiring treatment (high tumour burden)

General approach : rituximab and ……

- alkylating agents +/- anthracycline
- Bendamustine / Purine analogues
- alternative non chemotherapy options
- Radioimmunotherapy
- Lenalidomide and rituximab
- New generation anti-CD20 antibodies (Ofatumumab, GA101 [Obinutuzumab]).

Rituximab: An engineered murine/human chimeric monoclonal antibody – granted US FDA approval for treatment of cancer 1997



Murine-variable regions bind specifically to CD20 on B cells

Human κ constant regions

Human IgG_1 Fc domain works in synergy with human effector mechanisms

Rituximab-Chemotherapy in Untreated Advanced Follicular NHL

Study	Treatment, n	Median FU, months	ORR, %	CR, %	Median TTP/ TTF/ EFS, mo	OS, %
Marcus et al. 2008	CVP, 159	53	57	10	15	77
	R-CVP, 162		81	41	34	83
					P<.0001	*P*=.0290
Hiddemann et al. 2005	CHOP-IFN, 205	18	90	17	29	90
	R-CHOP-IFN, 223		96	20	NR	95
					P<.001	*P*=.016
Herold et al. 2007	MCP-IFN, 96	47	75	25	26	74
	R-MCP-IFN, 105		92	50	NR	87
					P<.0001	*P*=.0096
Salles et al. 2008	CHVP-IFN, 183	42	73	63	46	84
	R-CHVP-IFN, 175		84	79	67	91
					P<.0001	*P*=.029

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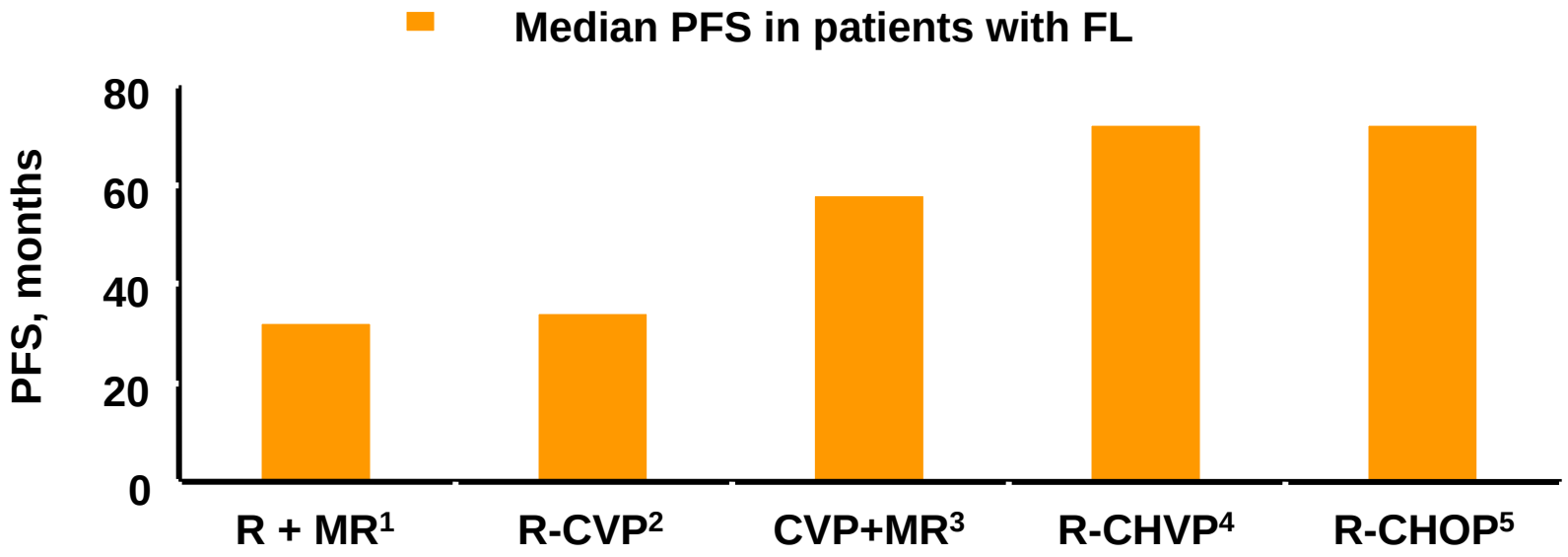
Progression-Free Survival Depends on First-Line Treatment



1. Hainsworth JD, et al. *J Clin Oncol.* 2005;23(6):1088-1095. 2. Marcus R, et al. *J Clin Oncol.* 2008;26(28):4579-4586. 3. Hochster H, et al. *J Clin Oncol.* 2009;27(10):1607-1614. 4. Salles G, et al. *Blood.* 2008;112(13):4824-4831. 5. Buske C, et al. *Blood.* 2008;112: Abstract 2599.

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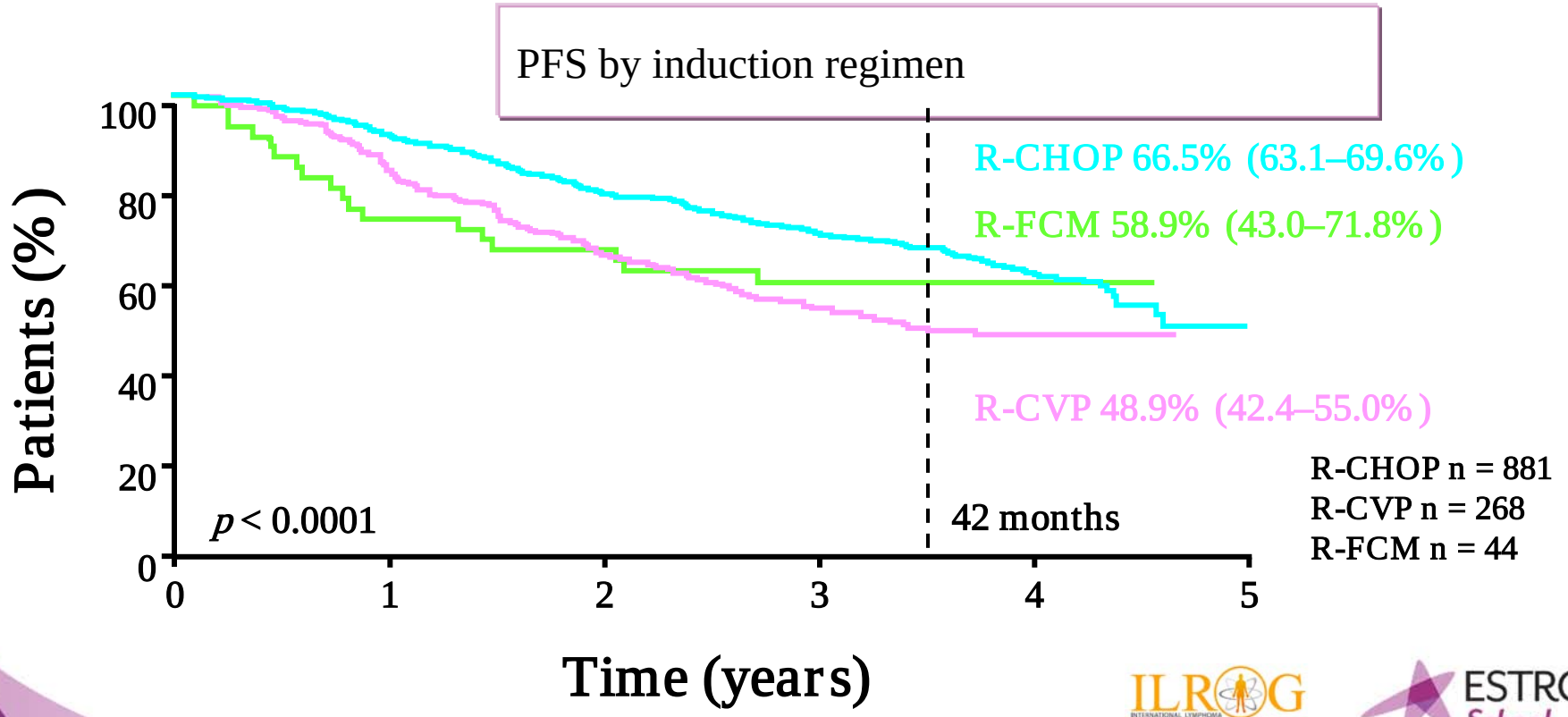
R-CVP versus R-CHOP versus R-FM as first-line therapy for advanced-stage follicular lymphoma: Final results of FOLL05 trial from the Fondazione Italiana Linfomi (FIL). Federico et al J Clin Oncol 2013

- Randomized trial comparing R-CVP with R-CHOP and R-FM.
- 534 patients were enrolled; 30 excluded. Median age 56 years (range 30-75), 63% stage IV disease, 37% had 3-5 FLIPI and 27% 3-5 FLIPI2 scores.
- ORR (CR+ PR) for whole group was 91% (p=0.247). After median follow-up of 34 months, 208 events for TTF were recorded;

R-CVP versus R-CHOP versus R-FM as first-line therapy for advanced-stage follicular lymphoma: Final results of FOLL05 trial from the Fondazione Italiana Linfomi (FIL).Federico et al J Clin Oncol 2013



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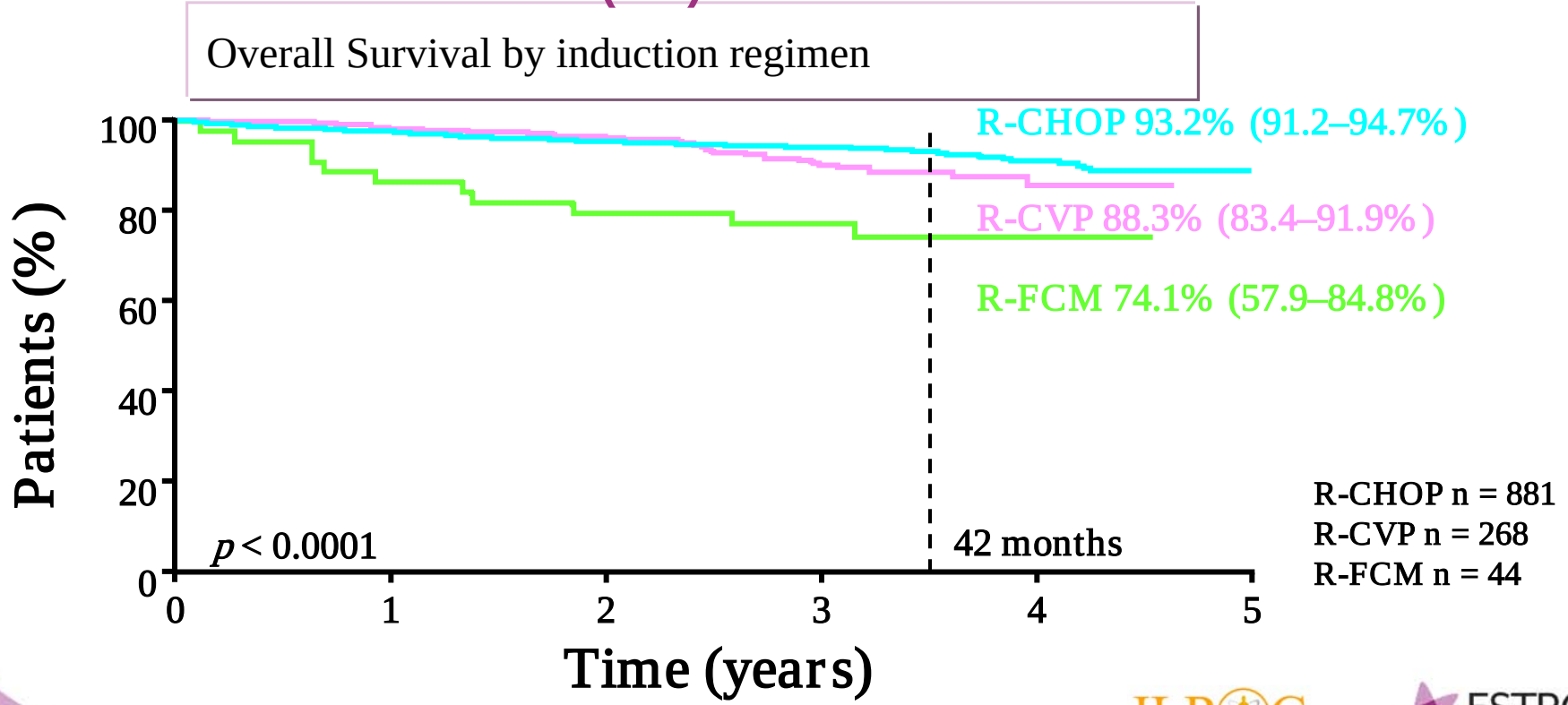

Second malignancies seen in 23 patients (2%, 3% and 8% in R-CVP, R-CHOP and R-FM, respectively).

StiL R-Benda vs R-CHOP

Rummel MJ et al : Lancet Feb 20, 2013

	B-R n = 261	CHOP-R n = 253
Median age, years (range)	64 (34–83)	63 (31–82)
B-symptoms	100 (38)	74 (29)
Ann Arbor stage III/IV, n (%)	252 (96)	244 (97)
Lactate dehydrogenase > ULN, n (%)	100 (38)	84 (33)
Histology n (%)		
Follicular	139 (53)	140 (55)
Mantle cell	46 (18)	48 (19)
Lymphoplasmacytic	22 (8)	19 (8)
SLL	10 (4)	11 (4)
High-risk FLIPI, n (%)	63 (46)	64 (48)

- No observed differences between the two study arms

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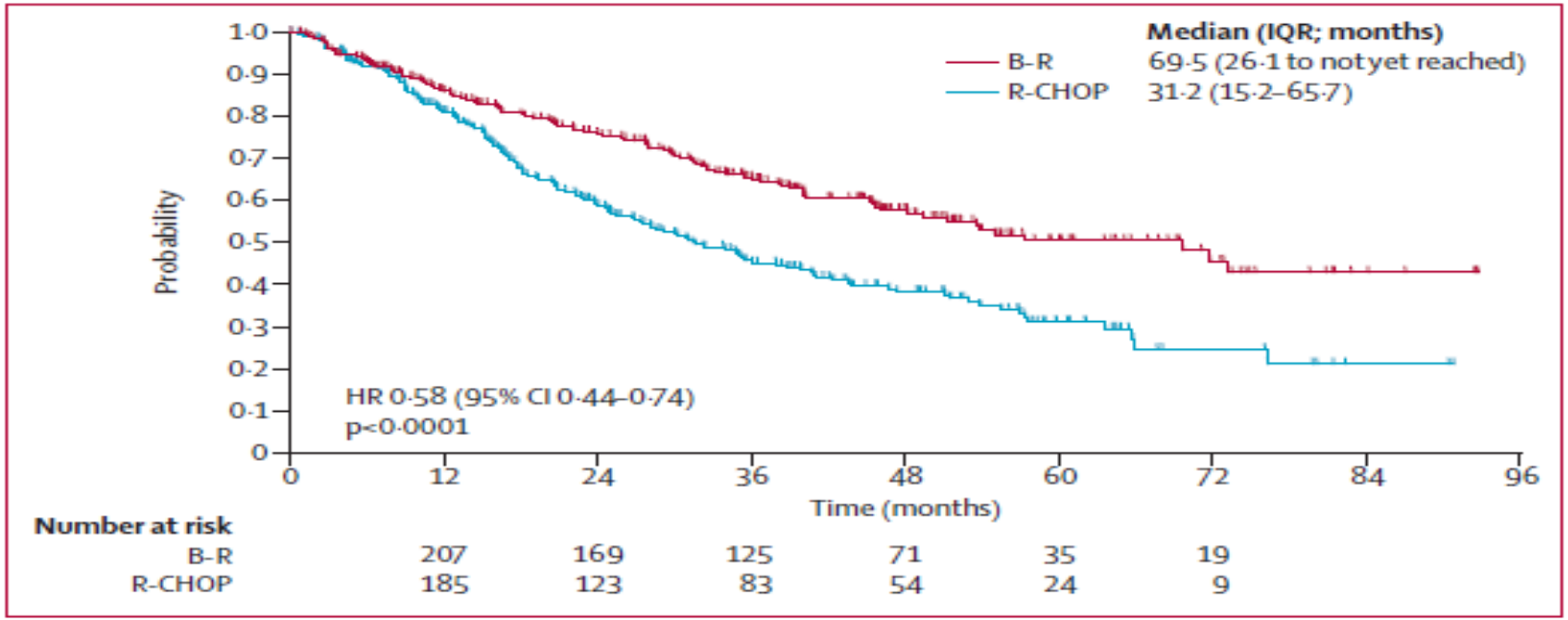
StiL R-Benda vs R-CHOP

Rummel MJ et al : Lancet Feb 20, 2013



•B-R more favorable acute tolerability profile. Severe neutropenia was markedly decreased with B-R (29% vs. 69% with RCHOP), less parasthesias, stomatitis and infections

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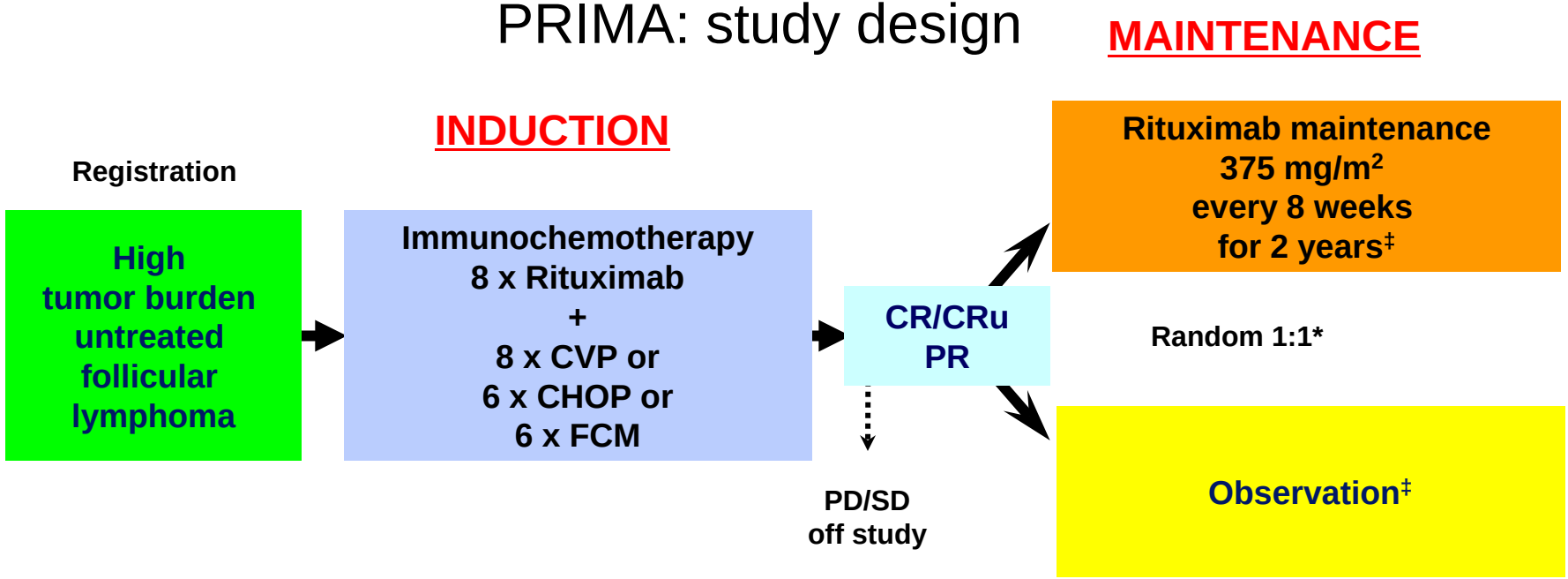
Maintenance Rituximab after Induction immunochemotherapy
PRIMA: study design

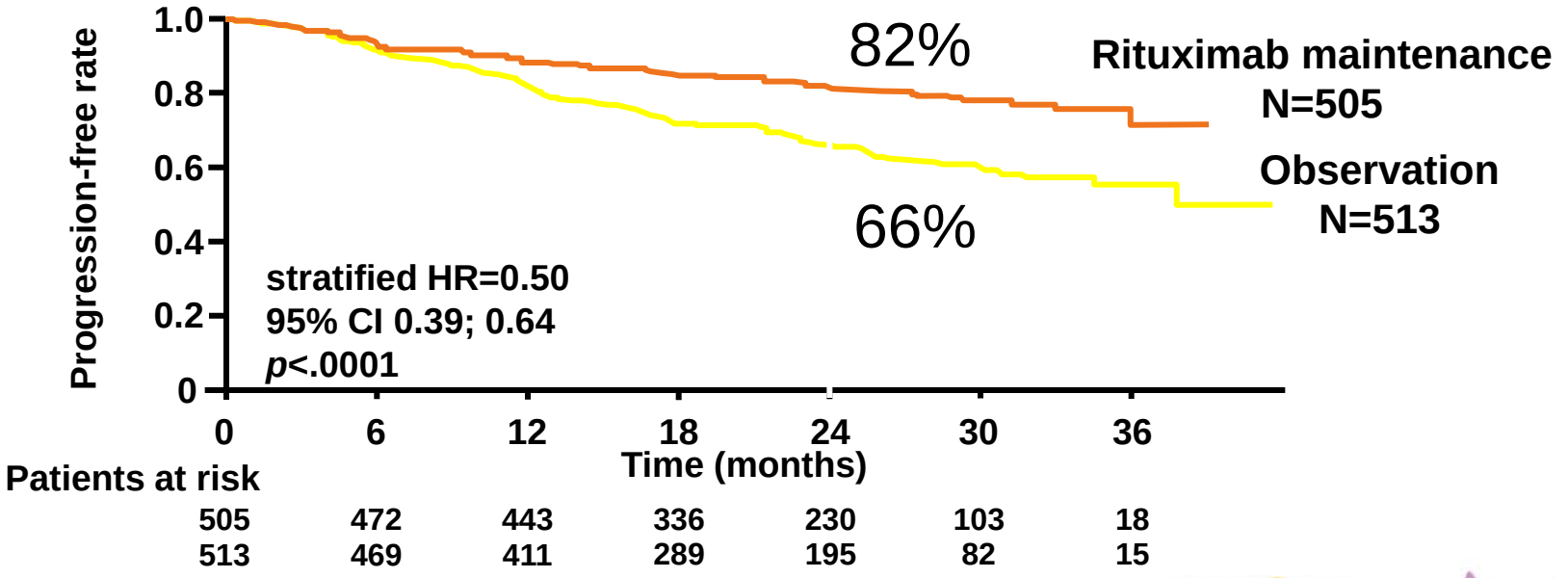


* Stratified by response after induction, regimen of chemo, and geographic region

‡ Frequency of clinical, biological and CT-scan assessments identical in both arms

Five additional years of follow-up

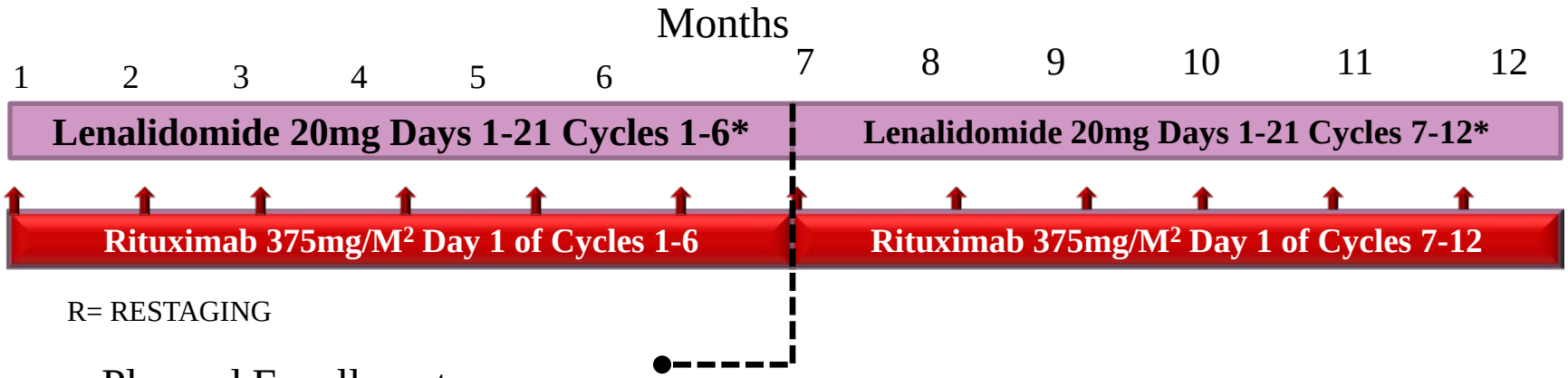
Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to **rituximab** plus chemotherapy (PRIMA): a phase 3, randomised controlled trial.
Salles G et al Lancet. 2011 Jan 1;377(9759):42-51



Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial

Fowler et al Lancet Oncol. 2014 Nov;15(12):15.

Can cytotoxic chemotherapy be avoided ?



- Planned Enrollment
  - N= 50 Follicular lymphoma (grade I/II)
  - N=30 Small lymphocytic lymphoma
  - N=30 Marginal zone lymphoma

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Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial

Fowler et al Lancet Oncol. 2014 Nov;15(12):15.

Response Rates of R^2

				All Patients	
	SLL (N=30)	**Marginal (N=27)***	**Follicular (N=46)***	Eval (N=103)	ITT (N=110)
ORR, n (%)	24 (80)	24(89)	45(98)	93(90)	93(85)
CR/Cru	8(27)	18(67)	40(87)	66(64)	66(60)
PR	16(53)	6(22)	5(11)	27(26)	27(25)
SD, n (%)	4(13)	3(11)	1(2)	8(8)	8(7)
PD, n (%)	2(7)	0	0	2(2)	2(2)

*7 pts not evaluable for response:

- 5 due to adverse event in cycle 1
- 1 due to non-compliance
- 1 due to withdrawal of consent

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Fowler N, et al ASH 2012.

Can cytotoxic chemotherapy be avoided ?

The "RELEVANCE" Trial (Rituximab and Lenalidomide Versus Any Chemotherapy)

- Phase 3 randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Chemotherapy Followed by Rituximab in Untreated Follicular Lymphoma.
- Comparator R-CHOP, R-CVP, R-Bendamustine.
- 7 to 8 weeks later responding patients will continue with 375 mg/m2 rituximab every 8 weeks for 12 cycles.

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Conclusions therapy in advanced stage FL

- Decision-making to treat in the frontline therapy based on; disease burden, patient symptoms, patient characteristics, morbidities and patient choice
- Right choice of initial therapy is the one that gives the best chance of durable remission and lowest toxicity profile for that patient.
- R-Chemo standard of care, randomised studies versus Lenalidomide and Rituximab awaited
- Maintenance Rituximab in responders to induction R-Chemo chemotherapy plus rituximab

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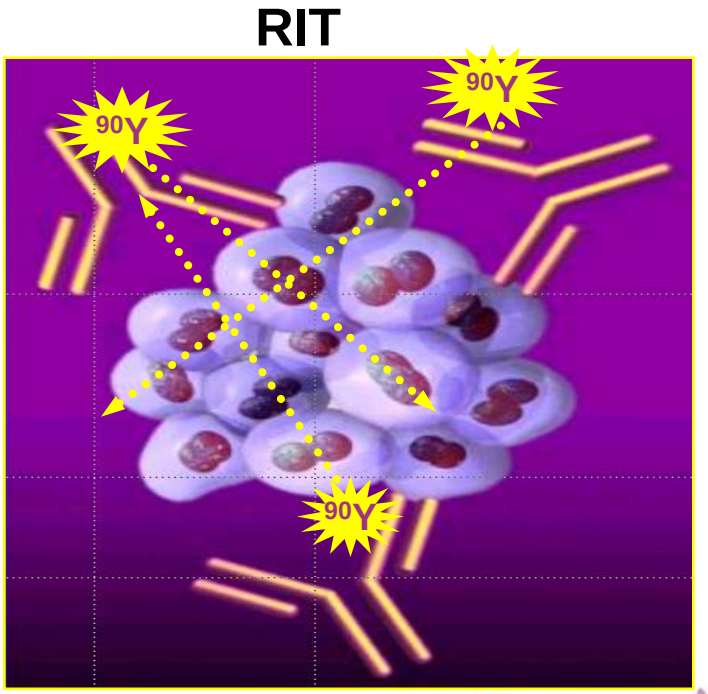
Radioimmunotherapy – a unique tool targeting radiosensitivity

- Lymphoma cells are inherently sensitive to radiation
- Radiotherapy effective in chemotherapy-refractory patients
- Continuous delivery of low-dose radiation and antibody effector mechanisms
- Radiation also destroys tumour cells distant from targeted tumour cell



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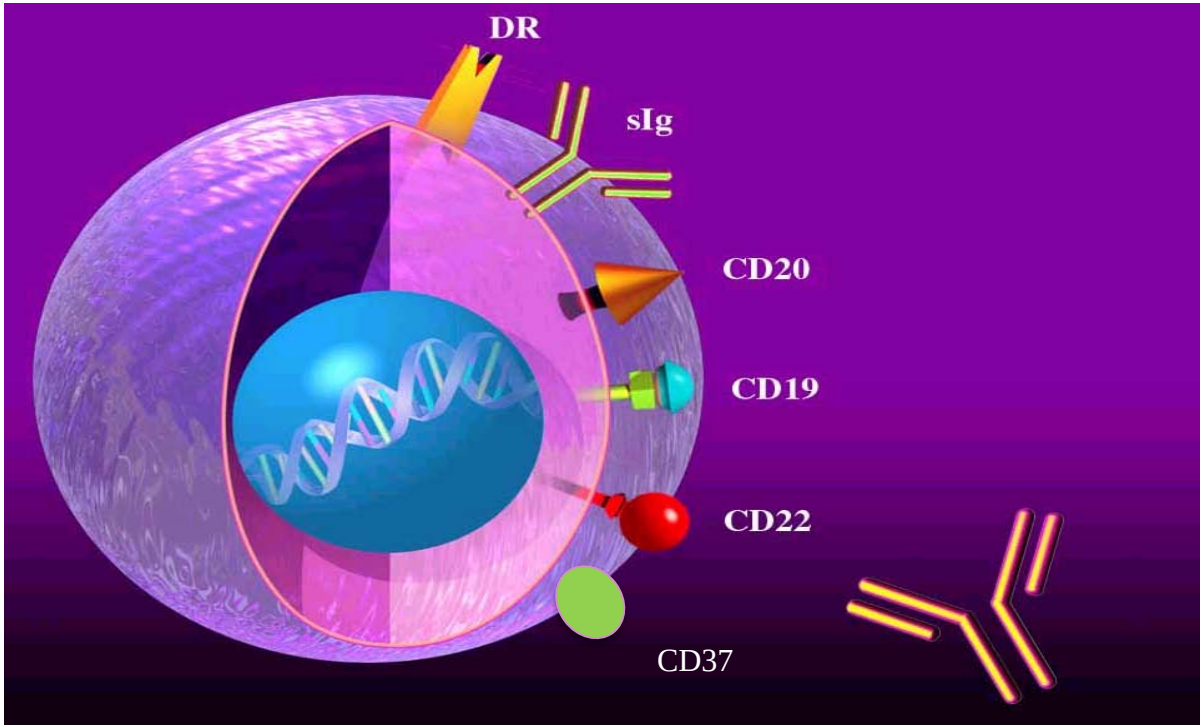
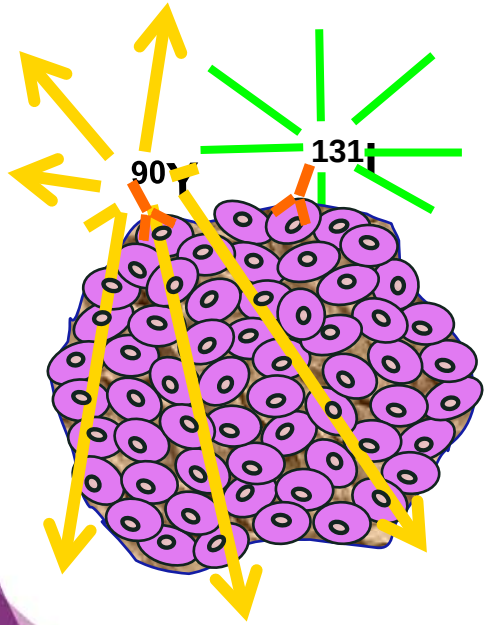
B-cell lymphomas express several antigens that can be targeted



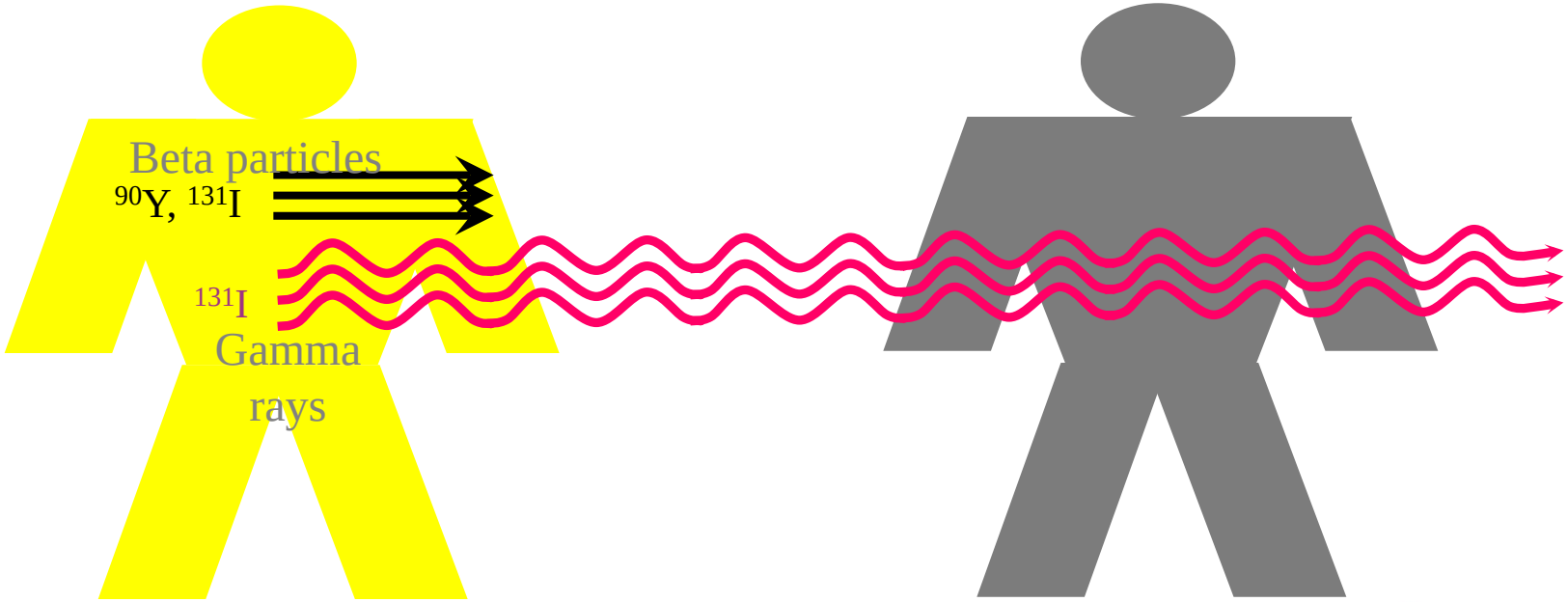
Adapted from Press, OW. *Semin Oncol* 1999; 26: 5(Suppl 14) 58–65

Choice of radioisotope



Properties	^{90}Yttrium	^{131}Iodine
Half-life	64 hours	192 hours
Energy emitter	Beta (2.3 MeV)	Gamma (0.36 MeV) Beta (0.6 MeV)
Path length	χ_{90} 5 mm	χ_{90} 0.8 mm
Urinary excretion	Minimal 7% in 7 days	Extensive/variable 46 - 90% in 2 days
Dosing	Based on weight and platelet count	Clearance based dosing using whole body dosimetry
Administration	Outpatient	Inpatient or restrictions to protect family/public

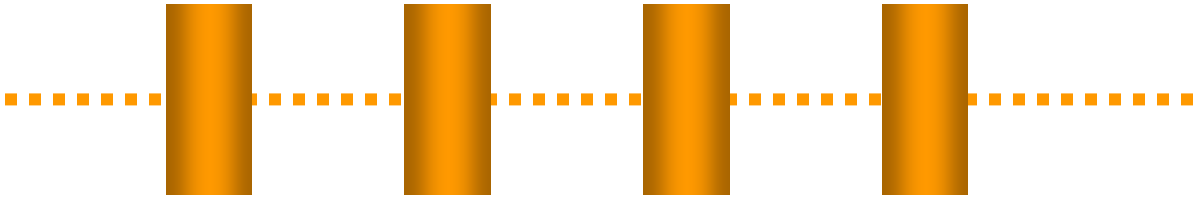
Penetration of Particulate and Electromagnetic Radiation



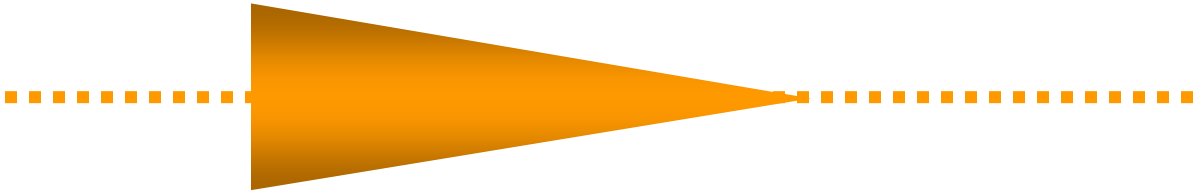
Radiation delivery profile of conventional radiotherapy versus targeted radiotherapy

Radioimmunotherapy delivers radiation at a lower rate, and continuous delivery may provide less opportunity for DNA repair

Fractionated external beam radiotherapy



Targeted radiotherapy



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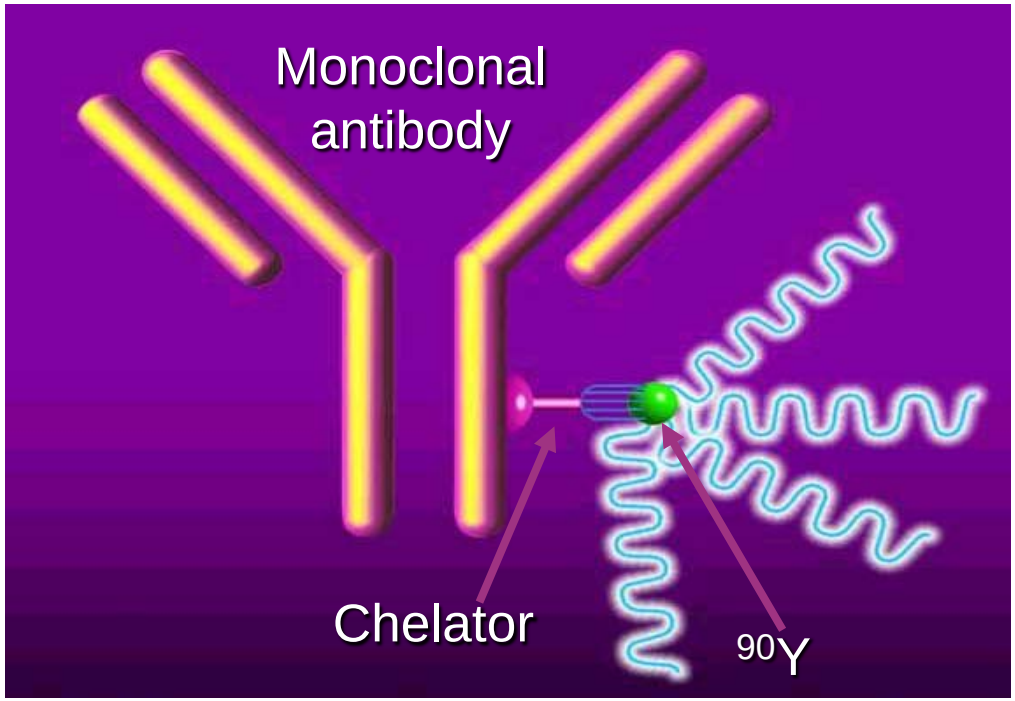
Yttrium-90 Ibritumomab tiuxetan (Zevalin™)



- Ibritumomab
  - Murine monoclonal antibody parent of Rituximab
- Tiuxetan

  Conjugated to antibody, forming strong urea-type bond

  Stable retention of ^{90}Y
- 90Y – Beta emitter

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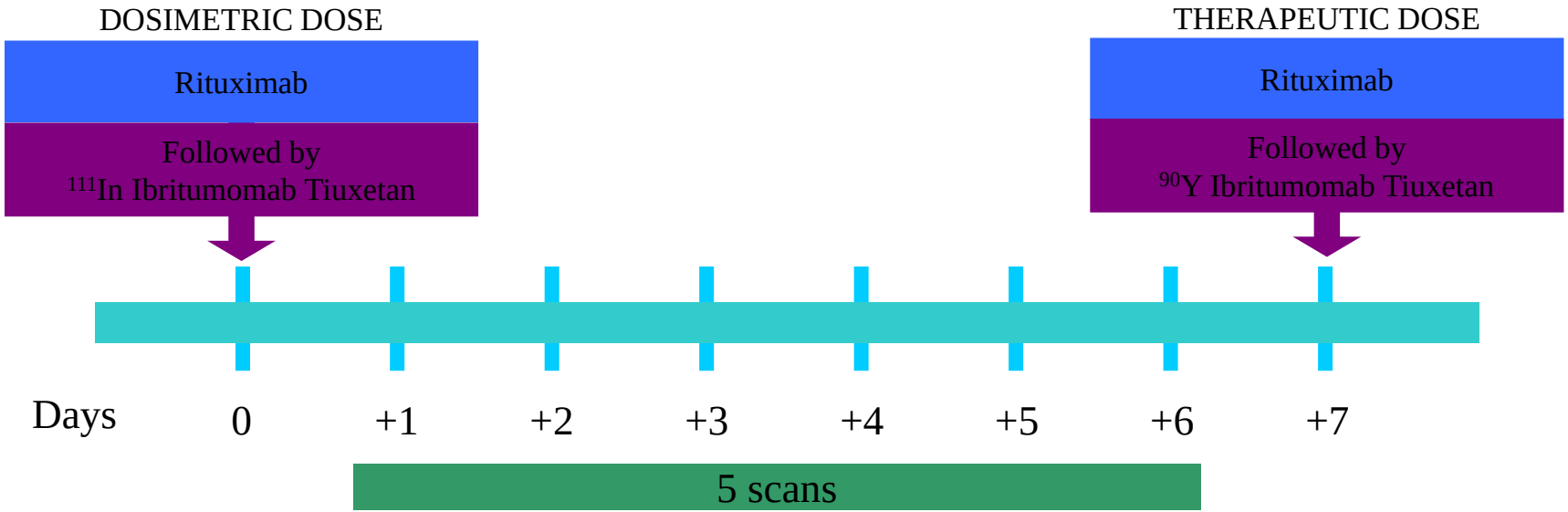
^{90}Y Ibritumomab Tiuxetan treatment is completed in 7 days



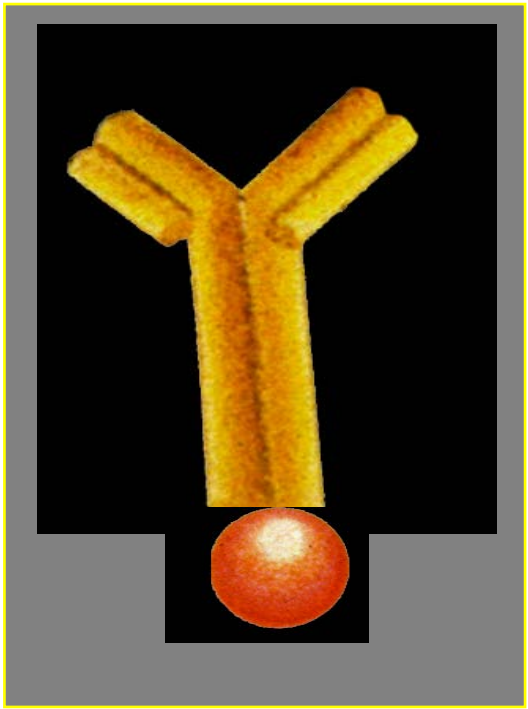
Dosimetric dose: Rituximab 250 mg/m^2; ^{111}In Ibritumomab Tiuxetan 5mCi ^{111}In, 1.6 mg Ibritumomab Tiuxetan

Therapeutic dose: Rituximab 250 mg/m^2; ^{90}Y Ibritumomab Tiuxetan 0.4mCi ^{90}Y for patients with platelet count >150,000 cells/mm^3 or 0.4 mCi/kg for a platelet count 100,000–149,000 cells/mm^3

Wiseman GA, *et al*. *Eur J Nucl Med* 2000; 27: 766–77

^{131}I Tositumomab (Anti-B1): Mechanism Of Action

- **Tositumomab**
  - Murine IgG2a anti-CD20 mAb
  - Triggers apoptosis, via unique epitope
- **Iodine-131 radioisotope**
  - Beta emission
    - Short pathlength “crossfire” effect (~1 mm)
  - Gamma emission
    - Allows individual dosimetry
    - Essential component of treatment



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Treatment Regimen for ^{131}I Tositumomab (Licensed in USA – no longer available)

Thyroprotection: Day -1 continuing through 14 days post-therapeutic dose

Day 0

Dosimetric dose
(450 mg tositumomab,
5 mCi ^{131}I tositumomab
[35 mg])

- Unlabeled predose infused over 1 hour
- Dosimetric dose used to determine individual pharmacokinetics

→

Whole body counts x 3

→

Day 7–14

Therapeutic dose
(450 mg tositumomab,
mCi dose of
^{131}I tositumomab [35 mg] to deliver desired cGy TBD)

- Unlabeled predose infused over 1 hour
- Administered mCi activity determined by gamma counts

ILROG International Lymphoma Radiation Oncology Group

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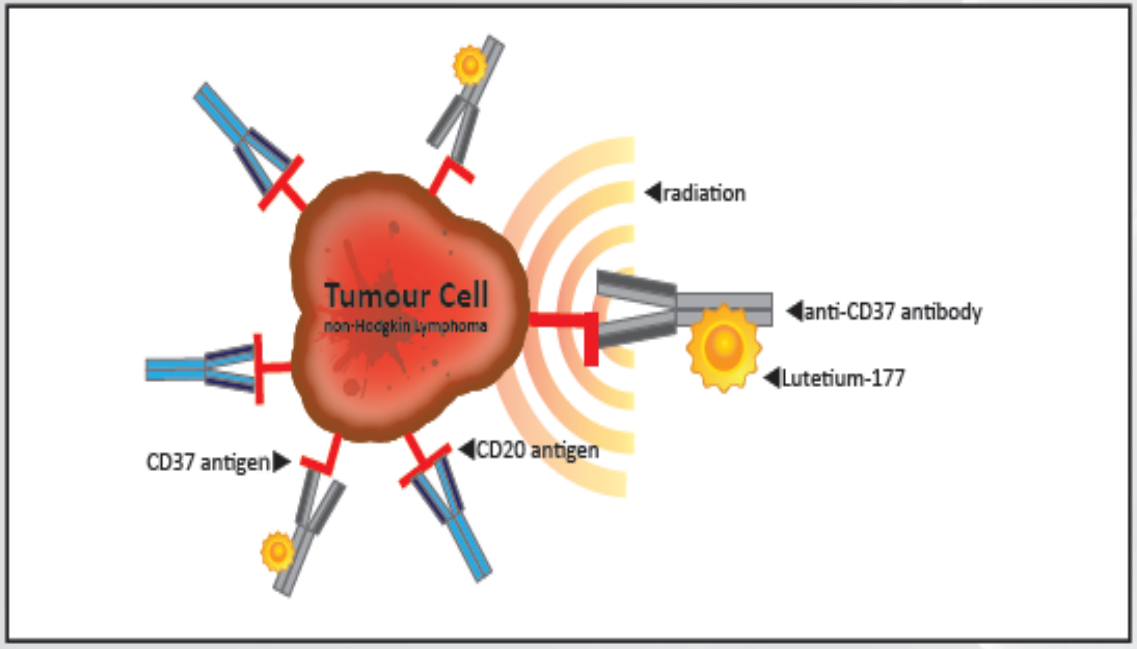
Results of a phase 1 study of ^{177}Lu-DOTA-HH1 anti body radionuclide (Betalutin) conjugate for patients with relapsed CD37+ non-Hodgkin lymphomas – Lugano 2015



177Lu-DOTA-HH1 (Betalutin)

- Murine mAb HH1
- Chelate to chemical linker DOTA
- Beta emitting lutetium-177 (t1/2= 6.7 days)

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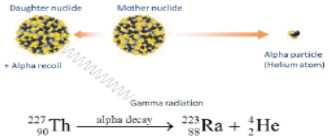
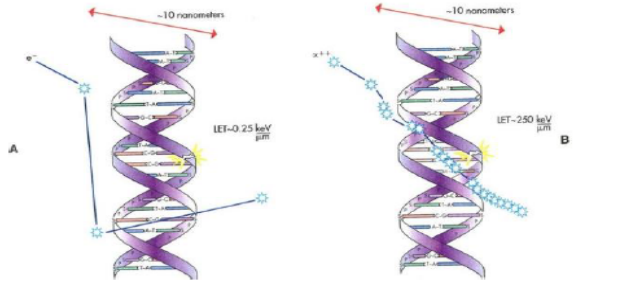
Alpha: Mechanism of Action



- The alpha-particle: a high energy, heavy charged particle
  - High Linear Energy Transfer (LET) = energy deposited per unit path length
  - High Relative Biological Effectiveness (RBE) = ratio of the effectiveness of one type of ionising radiation relative to another given the same amount of absorbed energy
- Alpha-particles deposit all their energy over a very short distance (2-10 cell diameters)
  - High propensity for Double Strand Breaks (DSB) due to direct DNA damage
  - No special shielding requirements when administering the dose

Low LET radiation vs. High LET radiation



LET: Beta (~0.2 keV/µm) Alpha (>100 keV/µm)

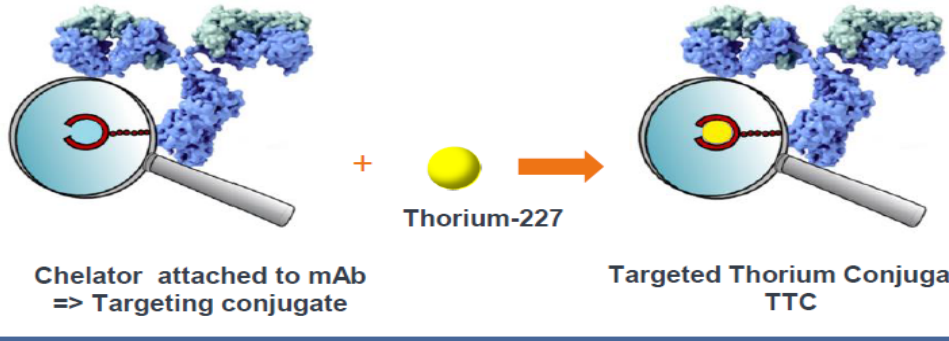
β-RIT for B-Cell Non-Hodgkins Lymphoma

- **Epratuzumab**: humanised mAb to CD22
- Clinical studies performed in NHL patients using naked mAb, beta emitters ^{131}I and ^{90}Y
  - 90Y-epratuzumab; 53% ORR (N=17) in DLBCL (3 median prior treatments), 5 of 6 at MTD (6 mCi/m^2)

Thorium-227 anti-CD22

What Makes Thorium-227 Unique?

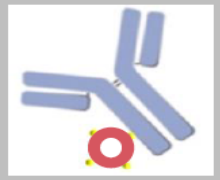
- Half-life (18.7 days) ideal for manufacture and commercial distribution
- Optimal physical half-life for tumor delivery by mAbs
- Radium-223 daughter has a 'clean' well understood clearance route
- Th(IV) forms highly stable complexes with specific chelators at ambient temp.



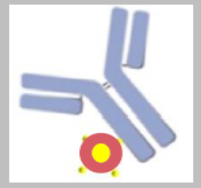
Rapid and stable chelation

Three principal forms of mAb being injected:

mAb
20%



mAb conjugate
80%



Th-labelled mAb conjugate
<0.1%

Three key components:

- Thorium-227
- Chelator
- Targeting molecule antibody

Defining features of RIT in relapsed Follicular Lymphoma

- High response rates
- Durable remissions
  - in chemo-refractory disease
  - in rituximab-refractory disease

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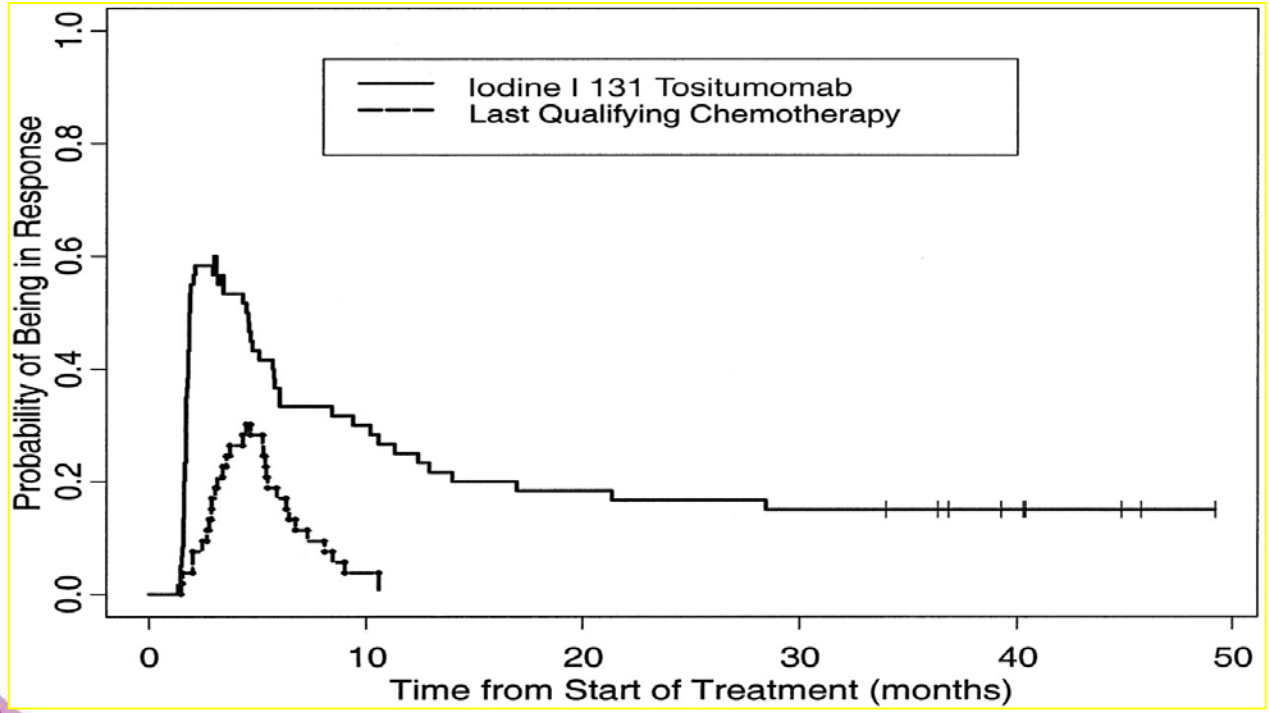
Pivotal Study of ^{131}I Tositumomab

Kaminski MS, et al. *J Clin Oncol*. 2001;19:3918–3928

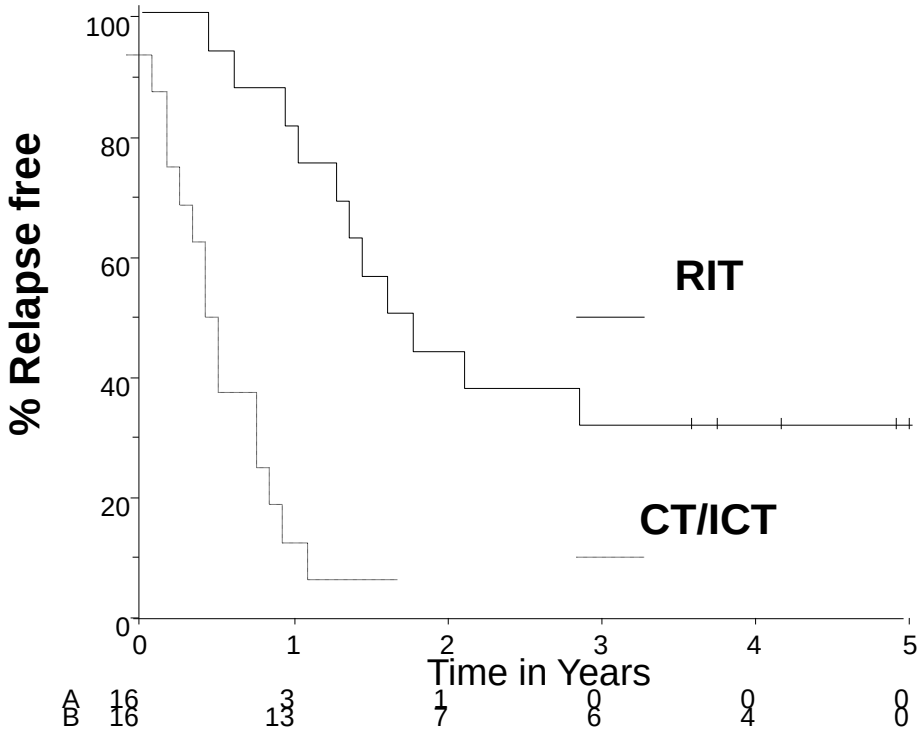


- **9 of 12 CR patients remain in CR 7 years**
- **7 patients in CR 4.9 to 7.2 years after RIT**

Kaminski MS, et al. *J Clin Oncol*. 2001;19:3918–3928.

Progression Free Survival of 131I Rituximab vs Last qualifying chemotherapy.

Illidge et al Blood 2009



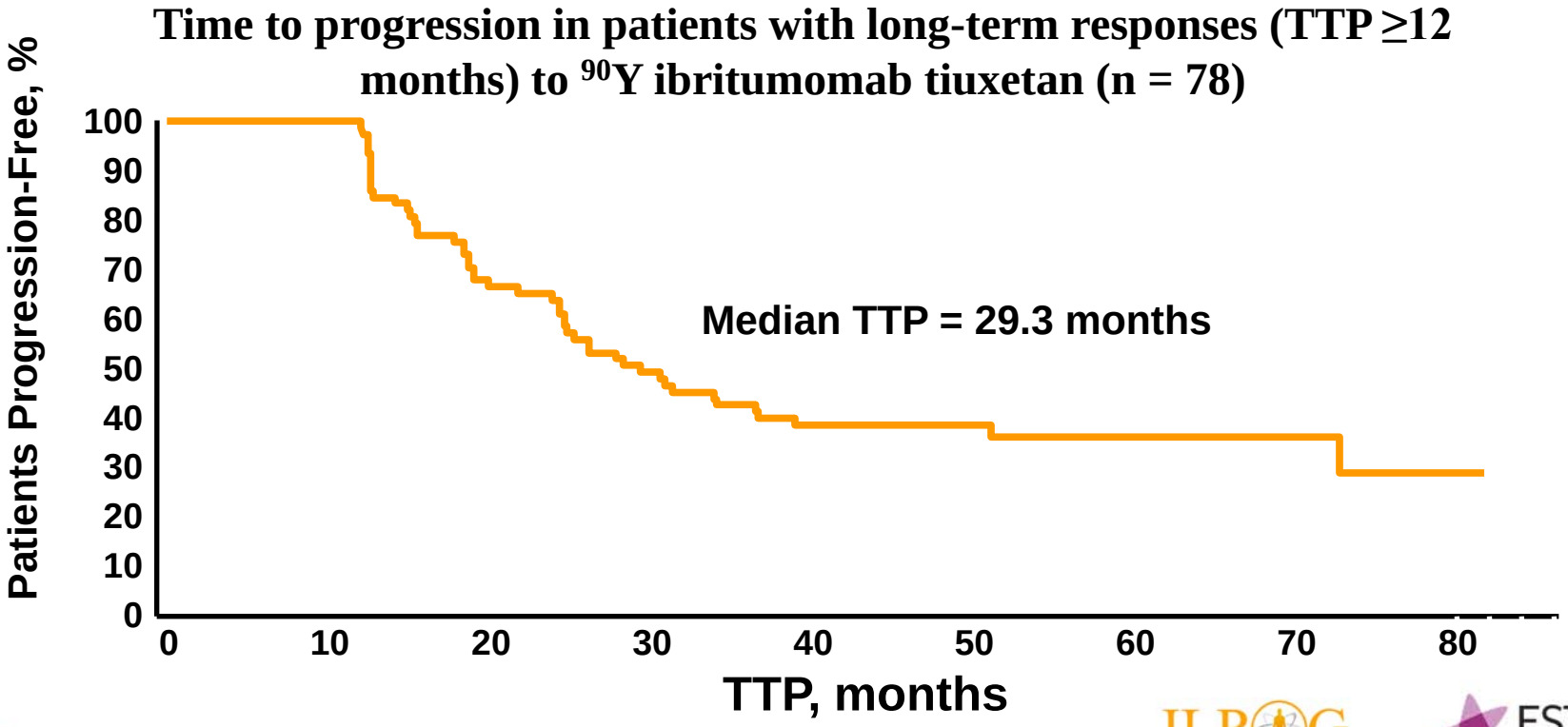
Duration of Response in ^{90}Y Ibritumomab Tiuxetan Trials

	Phase I-II *n* = 51	Phase II *n* = 30	Phase III *n* = 73
Overall Response, %	73	83	80
Median DR, months	11.7	11.5	13.9
CR/CRu, %	29*	47	34
Median DR, months	28*	23	23
Ongoing CR/CRu, %	19	14	32
Median DR, months	62.1	41.2	42.2
Range	60+ to 66+	40+ to 42+	33+ to 48+

***Patients with CR only.**

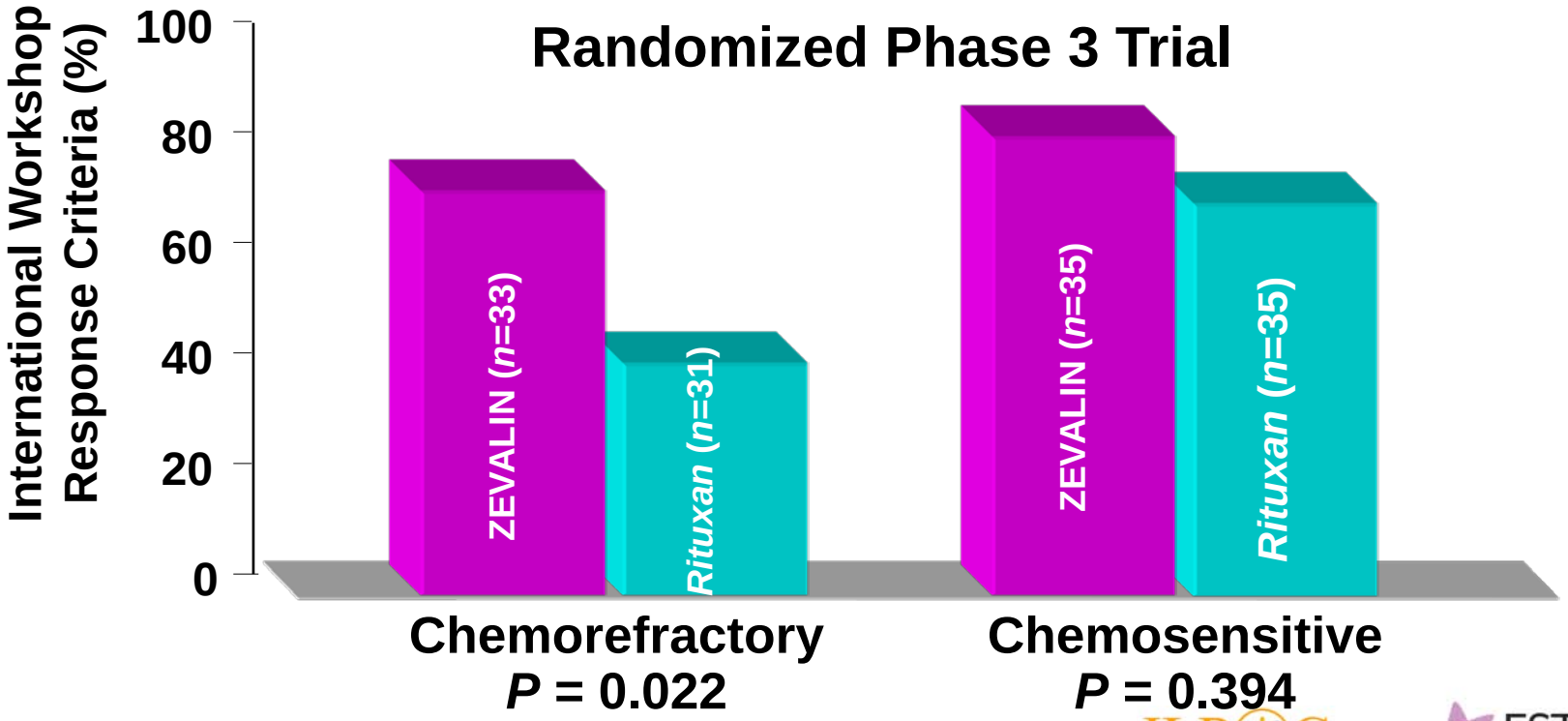
Gordon et al. Blood 2004.

Durability of Clinical Responses with ^{90}Y Ibritumomab Tiuxetan



Wiseman GA, et al. *Cancer Biother Radiopharm*. 2005;20(2):185-188.

^{90}Y Ibritumomab tiuxetan : Active in Chemorefractory NHL



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Multivariate analysis of prognostic factors correlated with response to Zevalin for NHL

- Analysis of 4 clinical registrational studies
- Patients with extensive prior therapy (1-9 regimens), bulky disease, splenomegaly
- Disease bulk (< 5 cm) correlated with overall response rate (89 patients ORR 90% ($p<0.001$)
- Other unfavourable characteristics (high LDH, extranodal disease, splenomegaly, extensive prior therapy, elevated peripheral B cell count) that might have been expected to confer a reduced probability of response failed to do so

Czuczman et al Proc ASCO 2002

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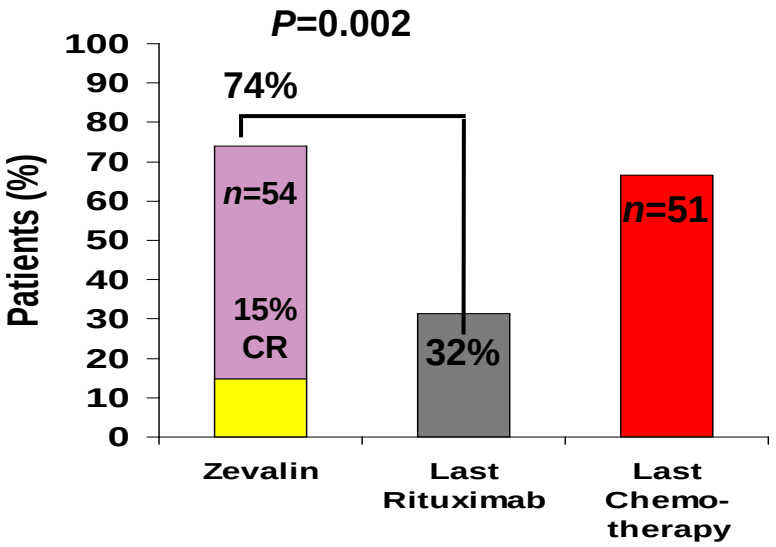
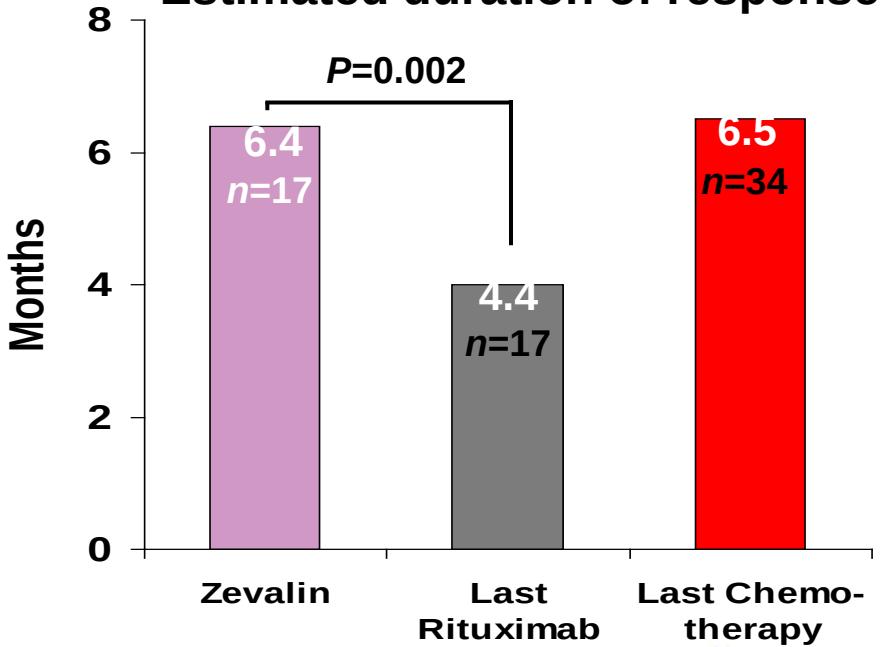
Rituximab-Refractory Trial: Patient Response to Zevalin

Overall response rate



Estimated duration of response

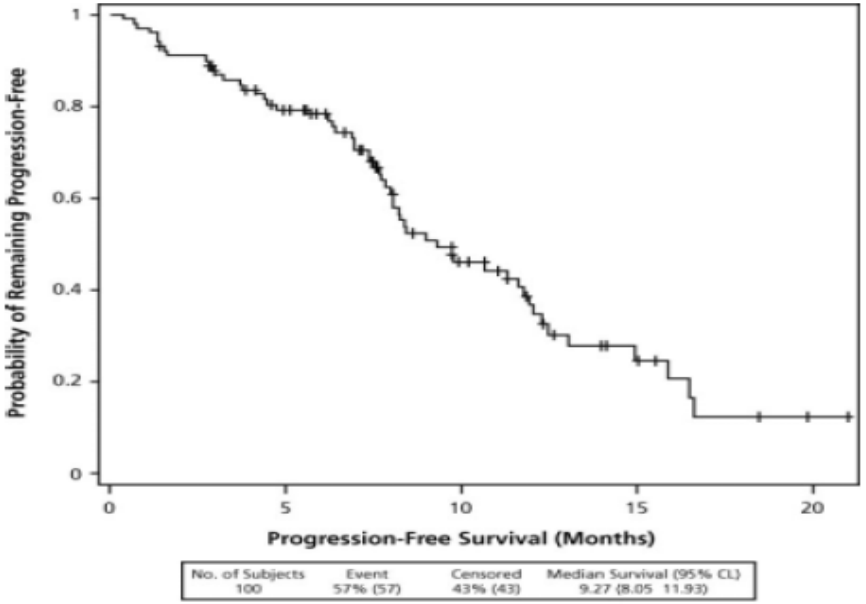


Median TTP in responders 9.1 months (range: 3.5 to 25.9+ months)

Bendamustine in Rituximab refractory FL

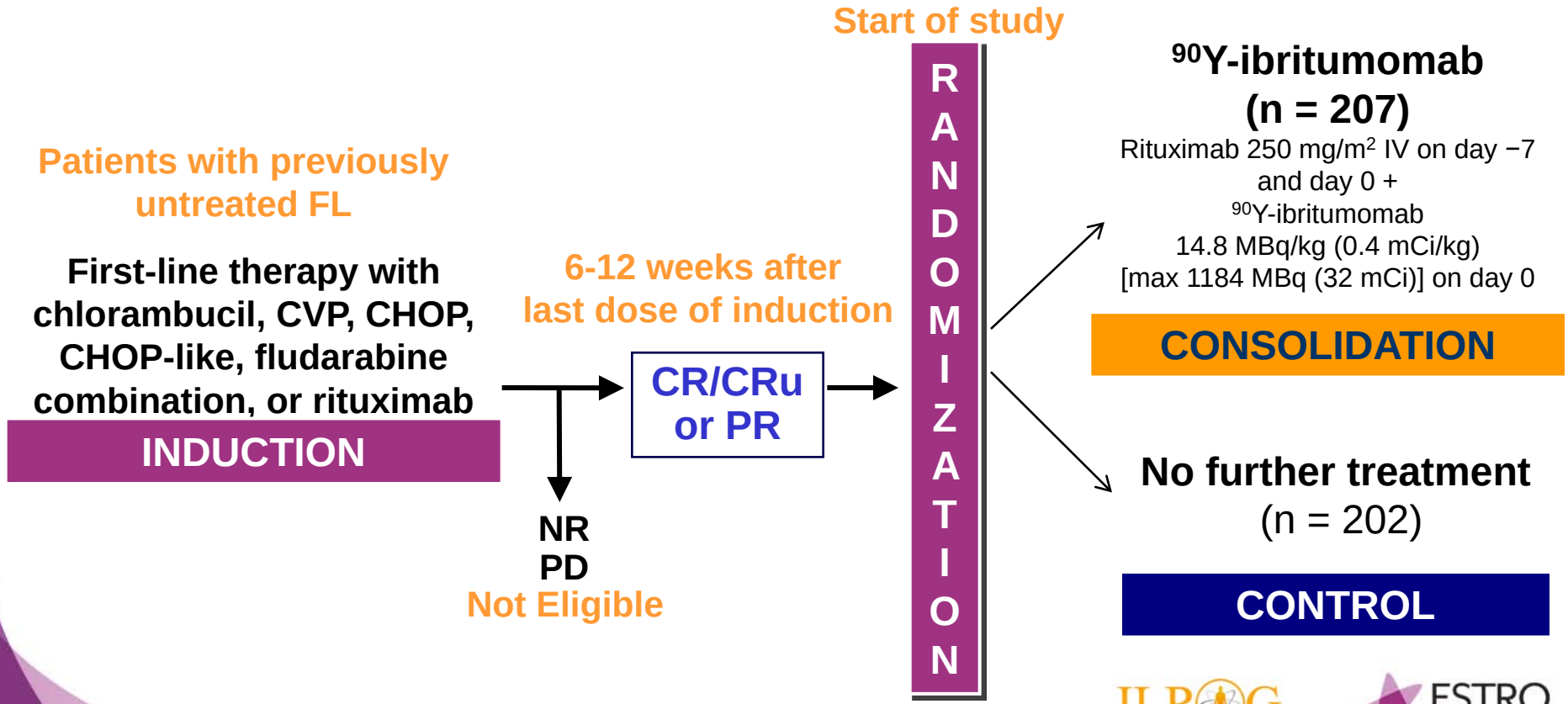
100 patients rituximab refractory
Bendamustine: 120 mg/m^2

ORR: 75%
CR: 14%
Median PFS: 9 months



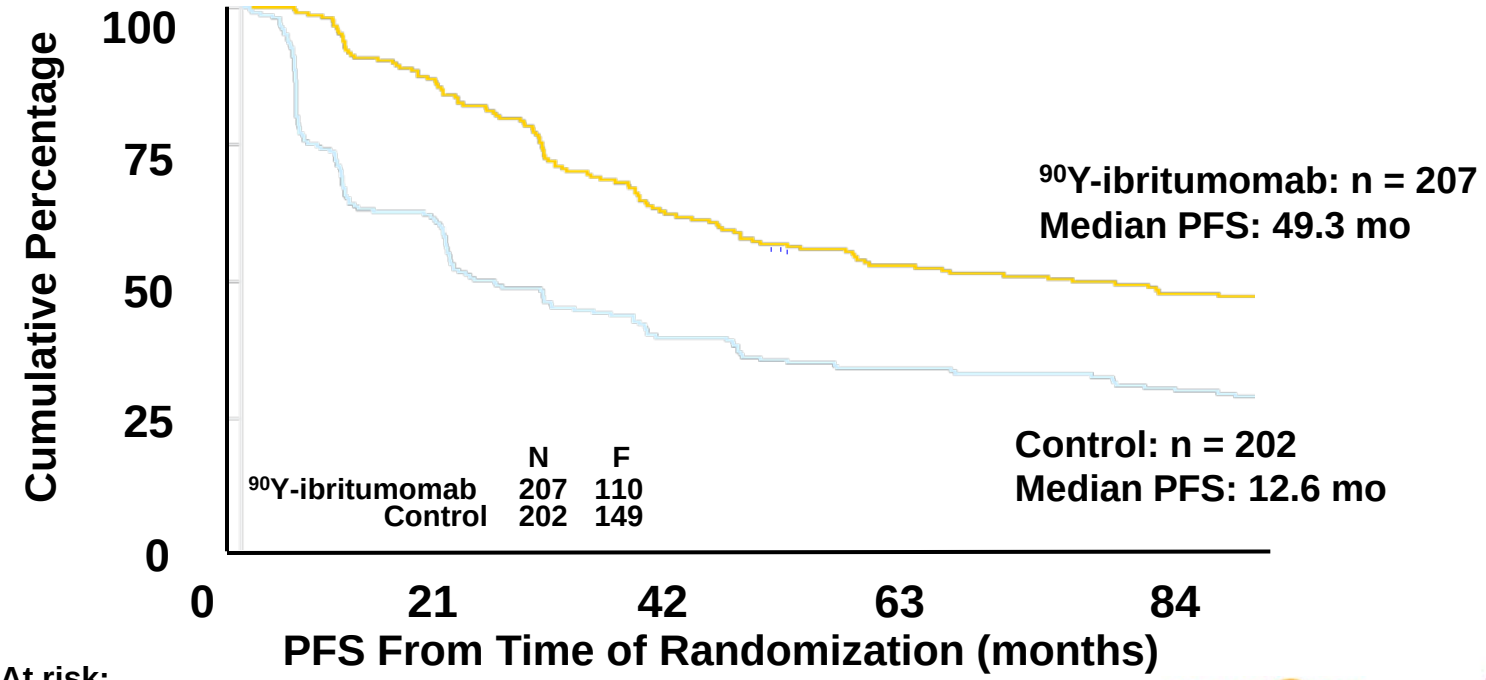
Kahl BS, et al. *Cancer.* 2010;116(1):106-114.

Radioimmunotherapy consolidation FIT Study



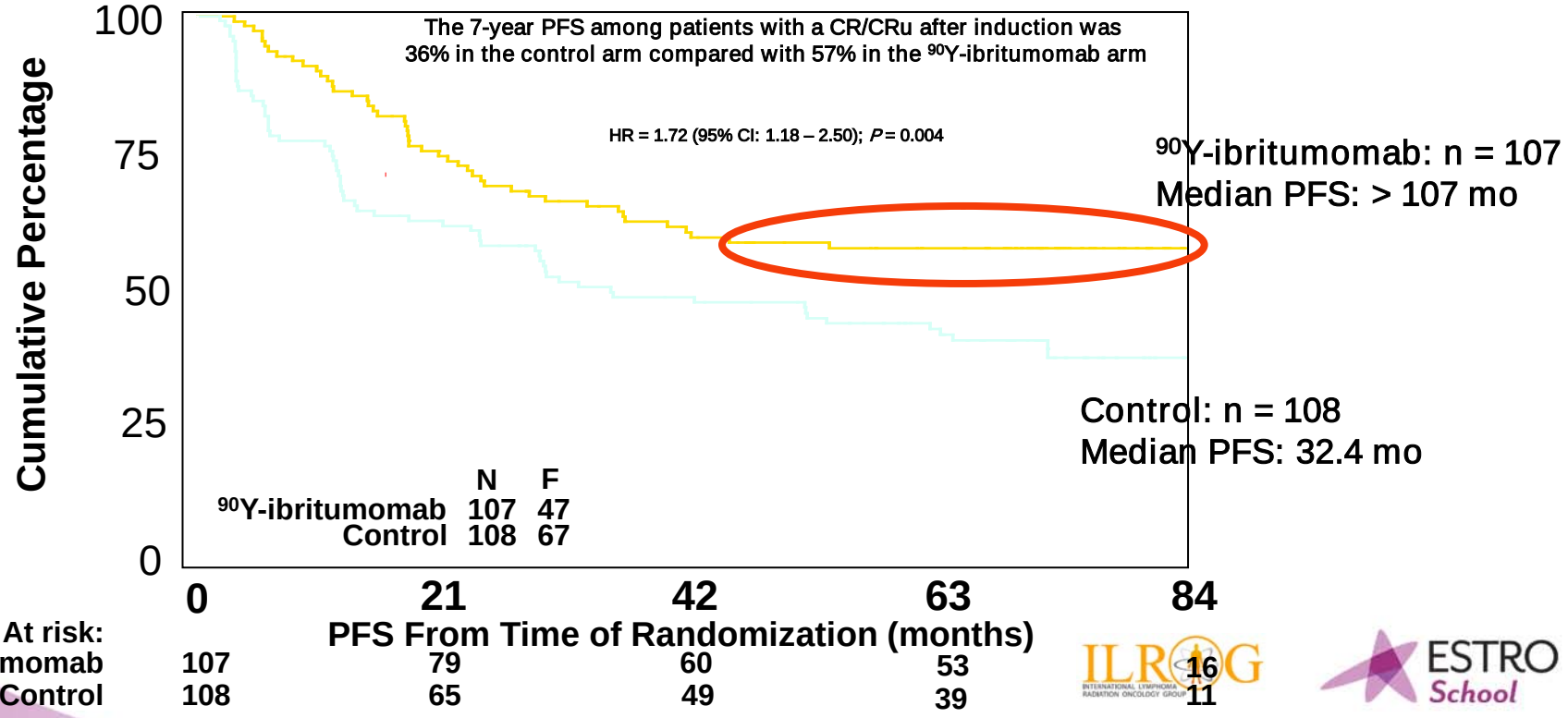
Morschhauser et al. *J Clin Oncol*. 2008;26:5156-5164

Overall PFS For Treatment Groups



90Y ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: updated results after a median follow-up of 7.3 years from the International, Randomized, Phase III First-Line Indolent trial.

Morschhauser F, et al J Clin Oncol. 2013 ;31(16):1977-83.

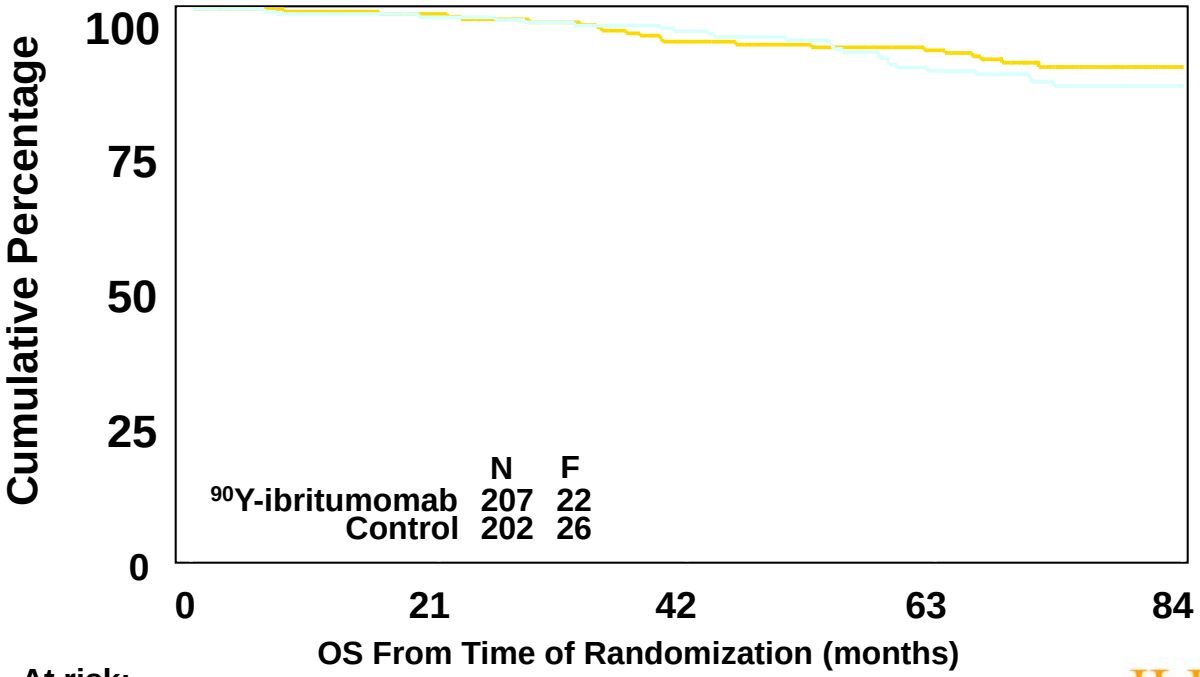


Overall Survival for Treatment Groups

7-year OS 86% in control arm compared with 89% in the ^{90}Y-ibritumomab arm
HR = 1.50 (95% CI: 0.84 – 2.68); *P* = 0.478

^{90}Y-ibritumomab: n = 207
Median OS: > 110 mo

Control: n = 202
Median OS: > 113 mo



At risk:					
^{90}Y-ibritumomab	207	200	178	166	47
Control	202	192	175	152	45

FIT TRIAL
Conclusions after 7 years Follow-up

- ^{90}Y-Ibritumomab consolidation confers a durable PFS benefit for patients with advanced FL
  - 3-year PFS advantage for patients in the ITT population
  - At least a 6-year PFS advantage for patients with a CR/CRu after induction > 5-year advantage in time to next treatment

- No unexpected toxicities emerging

  Annualized rate of secondary MDS/AML was 0.55% in the Zevalin arm

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Does ^{90}Y Ibritumomab Consolidation after first line R-Chemo Induction in Follicular Lymphoma improve outcome?

- FIT study (R-chemo subgroup; n=59)
  - CR rate after Zevalin : 93% (controls: 71%)
  - PFS at 84 months: 64% Zevalin vs 23% controls (median follow-up: 71.6 months)

- ECOG 1496 6-8 x chemo - CR/PR/SD randomised 16 cycles of Rituximab – similar results for PFS

- Randomised (^{90}Y Ibritumomab) vs in Rituximab maintenance (ROZETTA study) no significant difference in PFS

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Responses rates of Zevalin monotherapy versus R-chemo in first line therapy of Follicular NHL

	ORR (%)	CR (%)	Reference
R-CHOP	96	20	Hiddemann et al., 2005
R-CVP	81	41	Marcus et al., 2005
R-MCP	92	50	Herold et al., 2005
Zevalin	84	53	Scholz et al., 2012
Zevalin	96	70	Illidge et al 2014
Bexxar	95	75	Kaminski et al., 2010

Conclusions – Role of RIT in Follicular lymphoma

- RIT simple and effective treatment; most active drug in NHL, unique mechanism of action
  - Effective (high response rate, durable remission) and underused single treatment in relapsed and rituximab refractory disease
  - Patients in ^{90}Y-ibritumomab arm had a greater than 5-year advantage in time to next treatment in FIT trial as consolidation
  - Phase II data as single agents Zevalin RIT in untreated follicular lymphoma show high response rates and durable remission
  - Novel Radioimmunconjugates are being developed but pathways to registration and routine clinical use are challenging.

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The role of radiotherapy in Early stage stage HL

Tim Illidge MD PhD

Head of Division of Cancer Sciences

University of Manchester,

Manchester Academic Health Science Centre,

The Christie NHS Foundation Trust, UK

Overview of talk

1. **Review clinical data on management of early stage HL**

– *Should combined modality treatment still be the standard approach ?*

2. **Recent progress in using FDG PET to guide therapy and delivery of RT in HL**

- *Are we ready to make treatments decisions based on FDG-PET to potentially omit RT ?*

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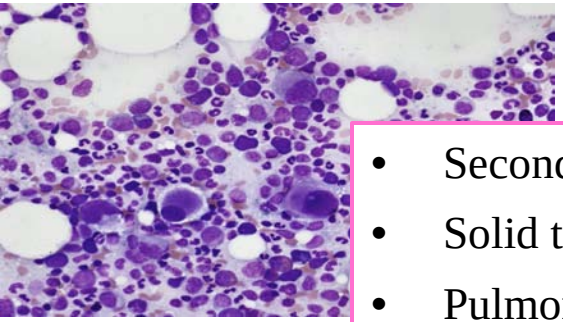
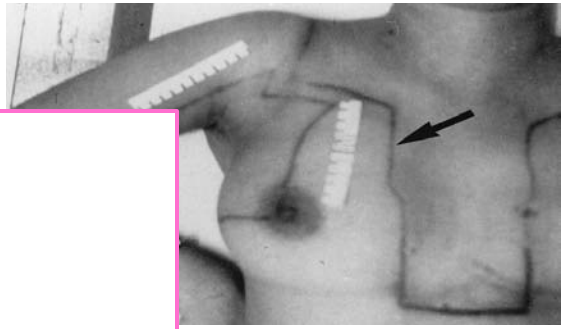
Overall results of therapy for early disease

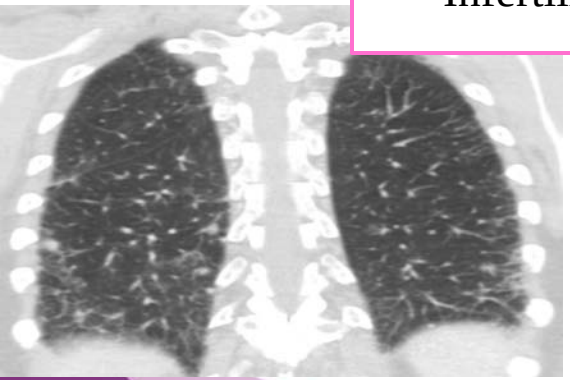
- Up to 90% cures with first line therapy
- About 95% alive at 5 years
- Primary focus of research is to
  - maintain (? improve) this result
  - minimise toxicity

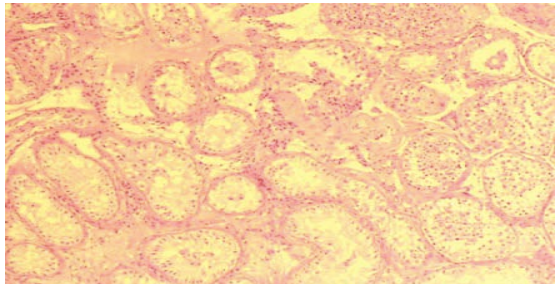
Late effects to avoid as cures increase

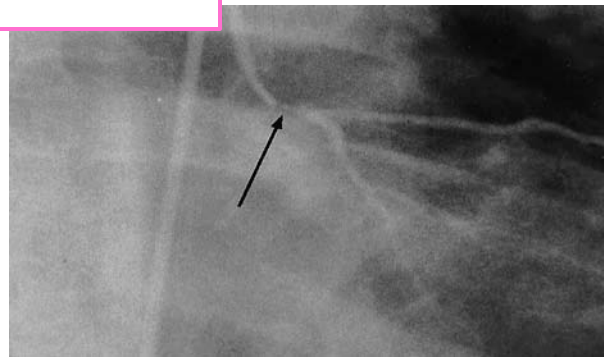




- Secondary MDS/AML from alkylating agents
- Solid tumours from extended field radiation
- Pulmonary fibrosis from bleomycin
- Ischaemic heart disease from mediastinal irradiation and doxorubicin
- Infertility from alkylating agents







Clinical risk-adapted and PET response-adapted approaches

Clinical Risk adapted:

To what degree can we reduce treatment based on clinical prognostic data?

Clinical response adapted:

Is functional imaging response on FDG-PET a better indicator of prognosis?

(and will modifying therapy according to PET CT improve Overall Survival)

Objectives in Early stage Hodgkin Lymphoma

Current standard of care : Baseline risk stratification

	EORTC	GHSG	NCIC/ECOG	NCCN 2010
Risk factors	a) Large mediastinal mass (> 1/3) b) Age ≥50 years c) ESR ≥50 without B-symptoms or ≥30 with B-symptoms d) ≥4 nodal areas	a) Large mediastinal mass b) Extranodal disease c) ESR ≥50 without B-symptoms or ≥30 with B-symptoms d) ≥3 nodal areas	a) Histology other than LP/NS b) Age ≥40 years c) ESR ≥50 d) ≥ 4 nodal areas	a) Large mediastinal mass (> 1/3) or > 10 cm b) ESR ≥50 or any B-ysmptoms c) ≥3 nodal areas d) > 1 extranodal lesion
Favorable	CS I-II (supradiaphragmatic) without risk factors	CS I-II without risk factors	CS I-II without risk factors	CS I-II without risk factors
Unfavorable	CS I-II (supradiaphragmatic) with ≥1 risk factors	CS I or CS IIA with ≥1 risk factors CS IIB with c) or d) but without a) and b)	CS I-II with ≥ 1 risk factors	CS I-II with ≥ 1 risk factors (differentiating between bulky disease and other risk factors for treatment guidelines)

Results from the trials
Early stage disease

- Chemotherapy improves the cure rate over radiation alone (EORTC-H7)
- Sub-optimal chemotherapy (EBVP) needs RT for best results (EORTC-H9)
- Reducing size of the radiation field is safe
- Reducing the radiation dose is possible for good prognosis disease, or after adequate chemotherapy
- Omitting radiotherapy altogether may be possible for some patients: can we predict who they are?

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German HD 10 study: reducing therapy in early favourable disease

1370 pts 1998-2003

Early Favourable disease:

I_A/II_A

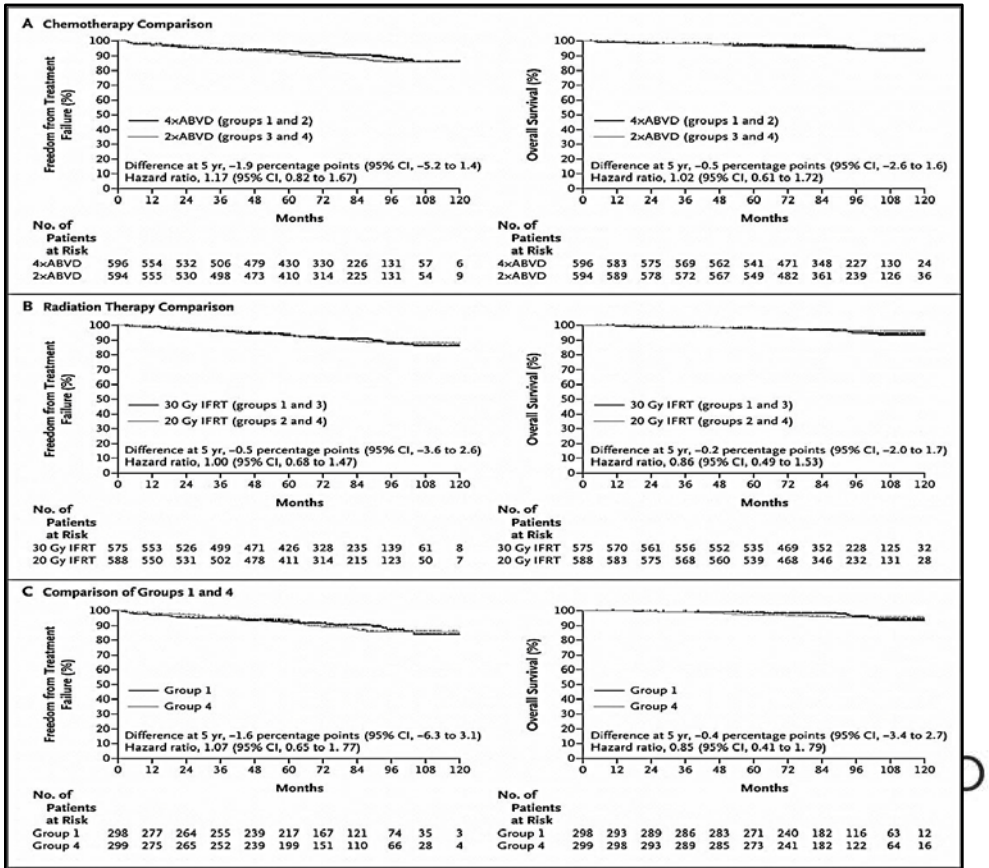
ABVD

2 cycles 4 cycles

Involved field RT

20 Gy 30 Gy

Results equivalent for all 4 arms: 5yr FFTF 92% OS 97%



Engert A et al. N Engl J Med 2010;363:640-652.

German HD 11 Study:

Lower threshold of therapy for early unfavourable disease

1395 pts 1998-2003

Early Unfavourable disease

Chemotherapy

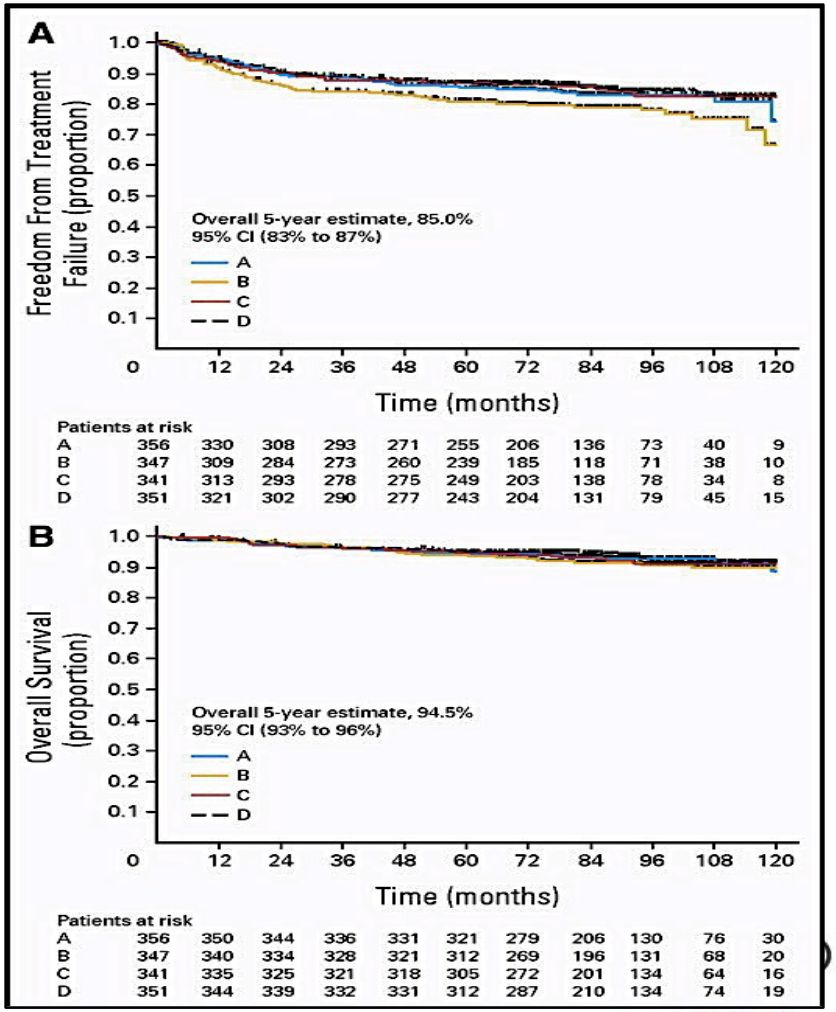
4 ABVD 4 BEACOPP

Involved field RT

20 Gy 30 Gy

ABVD + 20Gy inferior on FFTF

Eich H T et al. J Clin Oncol 2010;28:4199-4206



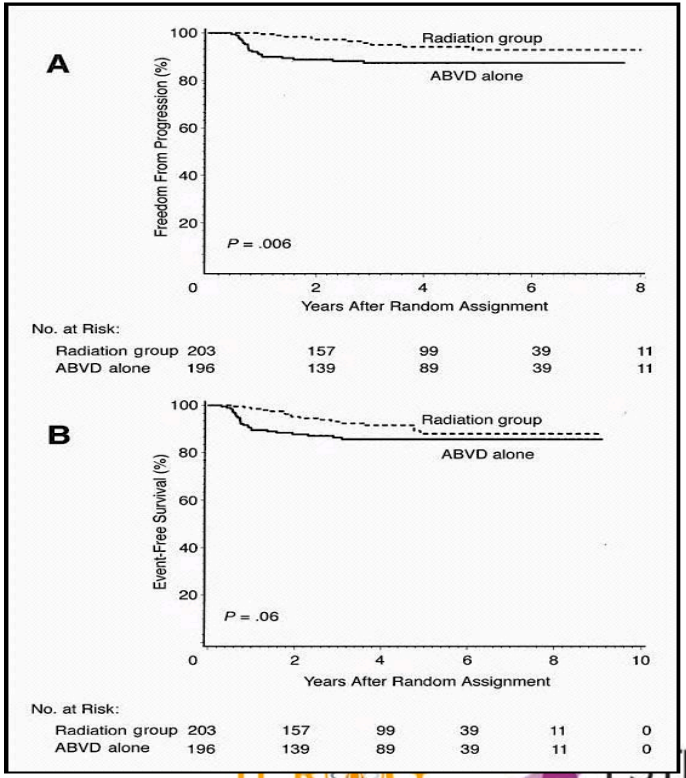
NCIC/ECOG HD6 study: Omitting radiation completely might be detrimental for disease control…

399 patients with early stage disease

Favourable:
STNI vs ABVD 4-6 cycles

Unfavourable:
2 ABVD + STNI vs ABVD 4-6 cycles

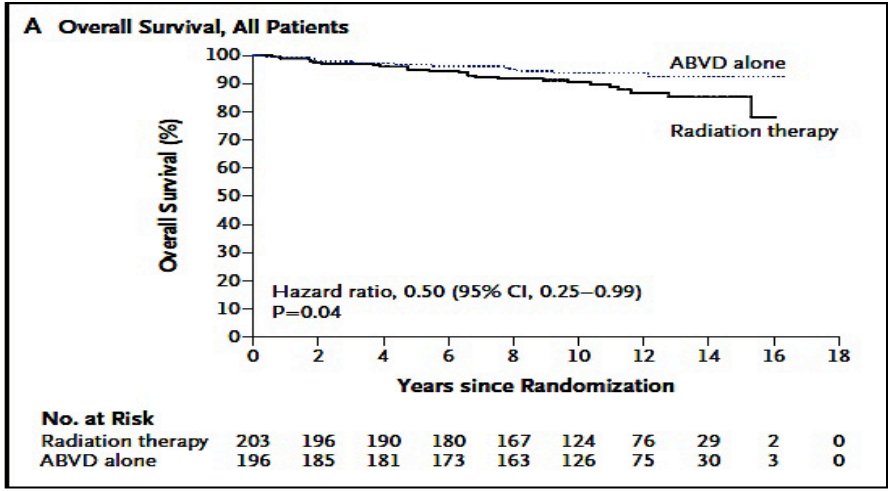
Inferior EFS, FFP with ABVD alone

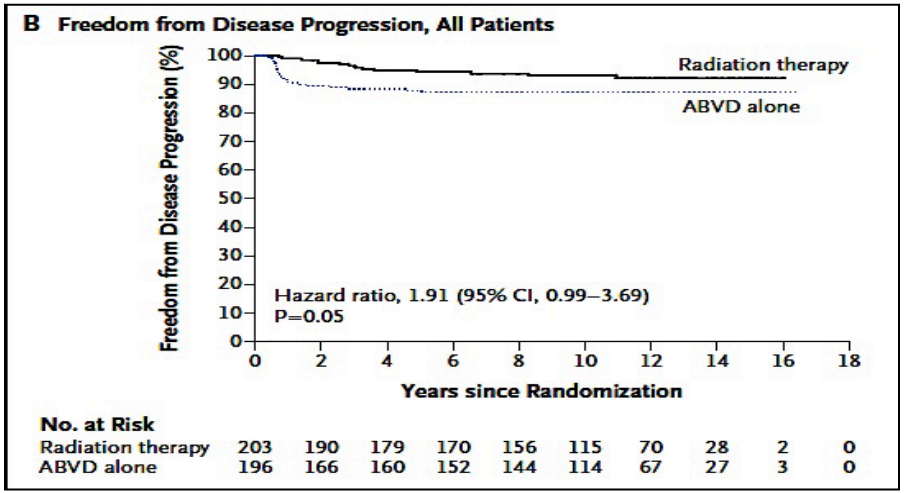


Meyer, R. M. et al. J Clin Oncol; 23:4634-4642 2005

Omitting RT safer in the long run ?

Meyer et al., N Engl J Med 2012; 366:399-408





Median 11.3 yrs follow-up.

OS at 12 yrs 94 vs 87% EFS 85 vs 80%

Deaths: RT arm: 4 HL (9 2nd cancer, 2 cardiac, 3 infection, 5 other)

ABVD arm: 5 HL (4 2nd cancer, 2 cardiac)

NCIC CTG ECOG HD.6 Trial
Unfavorable Cohort-Causes of Death

Cause of Death	ABVD alone (137)	ABVD+STNI (139)
Hodgkin Lymphoma	5	4
Cardiac	2	2
Second CA	4	9
Infection	0	3
Other	0	*5
TOTAL	11	23

*Alzheimer disease, drowning, suicide, resp failure, unknown

From Meyer R *et al. NEJM* 2012;366:399-408

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NCIC CTG ECOG HD.6 Trial
Small numbers and unusual events

- Unusual deaths correct from statistical point of view - misleading not attributable to radiotherapy.
- No death of "other" causes in chemotherapy alone group or in STNI favourable group. Imbalance misleading in favour of chemotherapy alone group.
- Without these unusual events - negative study without a survival difference but with a significantly better tumor control for the RT group
- Imbalance due to an undersized and incompletely recruited study with a small number of events.

What do we learn from NCIC/ECOG HD6 ?

- Improving long term OS depends on :
  - Effective initial therapy. RT leads to better disease control
  - Developing treatment approaches with less late toxicity (second cancers, lung injury, cardiac toxicity, infertility) is important to improving long term survival
- Small studies with just a few unusual events can influence conclusions much less likely to happen in large studies

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What don't we learn from HD6 ?

- How does full course (4-6) ABVD compare with 2 x ABVD and modern small RT field : PFS and OS, patient tolerability and quality of life

- What are the acute and late consequences of replacing 2 x ABVD and modern small RT field versus more cycles of chemotherapy ?

No RCT to address questions

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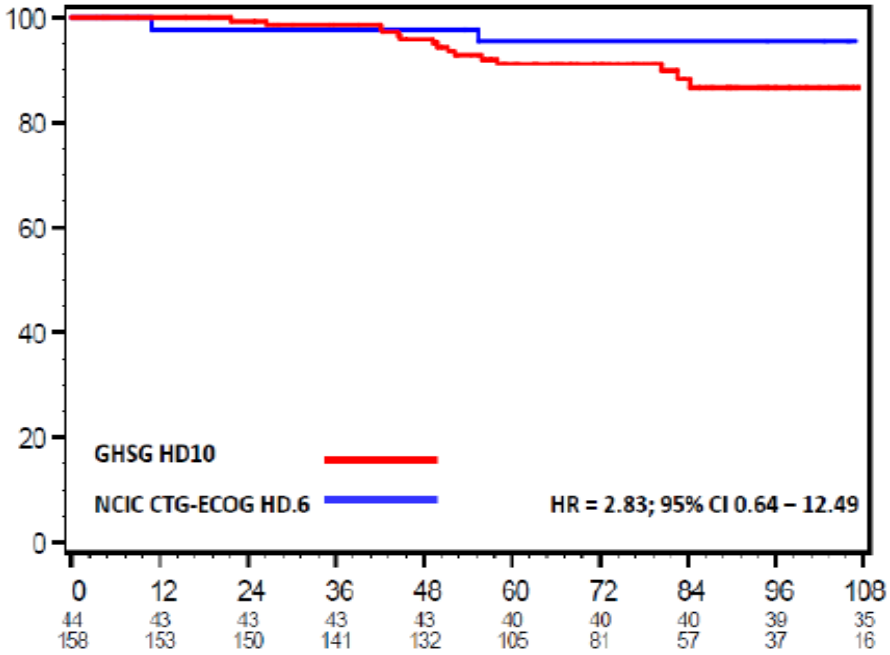
GHSG HD10, HD11 (CMT) Comparison with NCIC CTG HD.6 (ABVD alone)

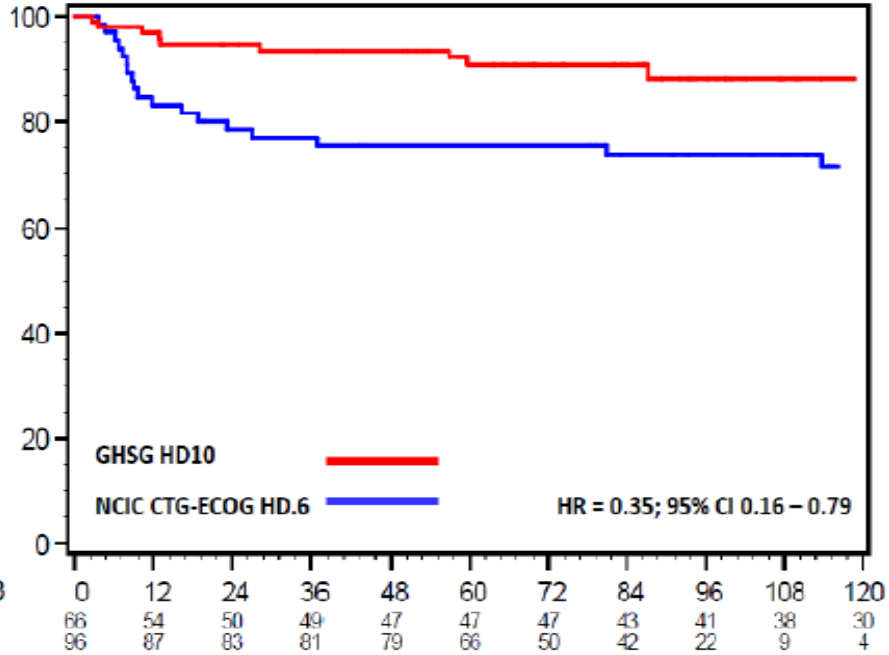
Endpoint	GHSG HD10/11	NCIC CTG HD.6	HR	95% CI
8-yr PFS	89%	86%	0.71	0.42-1.18
8- yr OS	95%	95%	1.09	0.49-2.40
8-yr TTP	93%	87%	0.44	0.24-0.78
# ABVD	2-4 (2.5)	4-6 (~5)		

from Hay AE *et al., ASH Abstract 2012;548*

Combined Modality vs ABVD alone

Status after 2xABVD (HD10 eligible pts; PFS)





CR/CRu

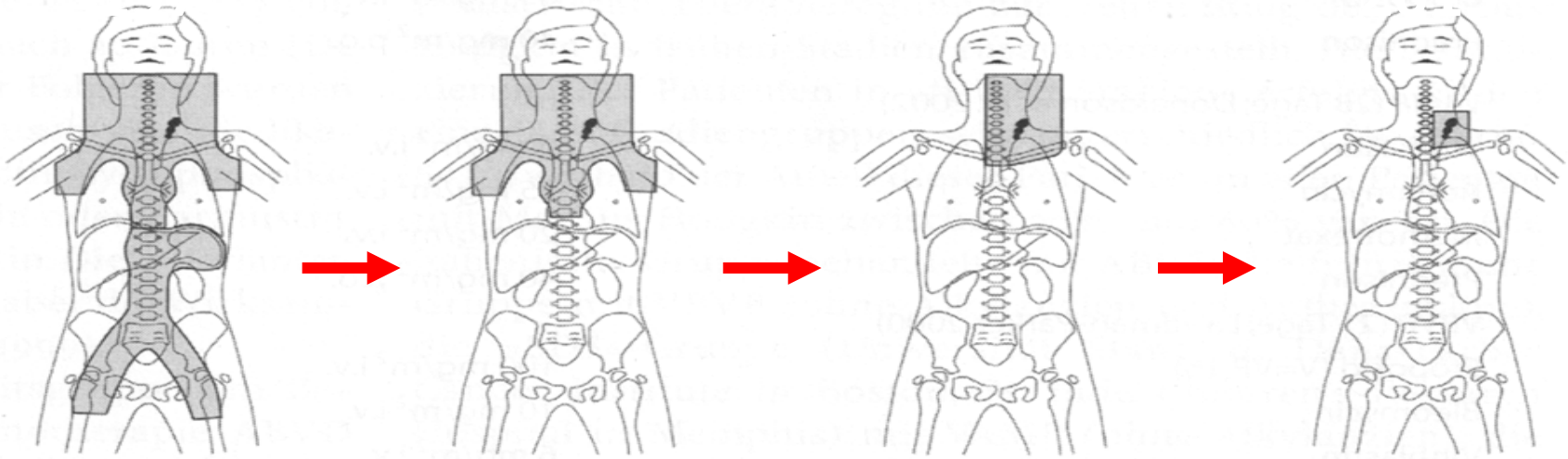
No CR/CRu

Hay A et al, ASH 2012

Key questions in using Combined Modality Treatment in early stage HL

- Is the initial gain in local control with RT offset by the long term risks of RT ?
- Do modern RT approaches with substantial reduction in field size and RT doses maintain excellent initial control and reduce late toxicities leading to improved long term survival over chemotherapy alone ?

Transformation of RT Volumes / Doses in HL
ISRT – Specht L et al IJROBP 2014



Total nodal **Regional nodal** **Involved field** **Involved site**

Dose: 30-44 Gy → **20-30 Gy**

Two thirds of women with early-stage HD do not require radiation of the axillae
Substantial reduction in breast, lung cancer risk, cardiac morbidity

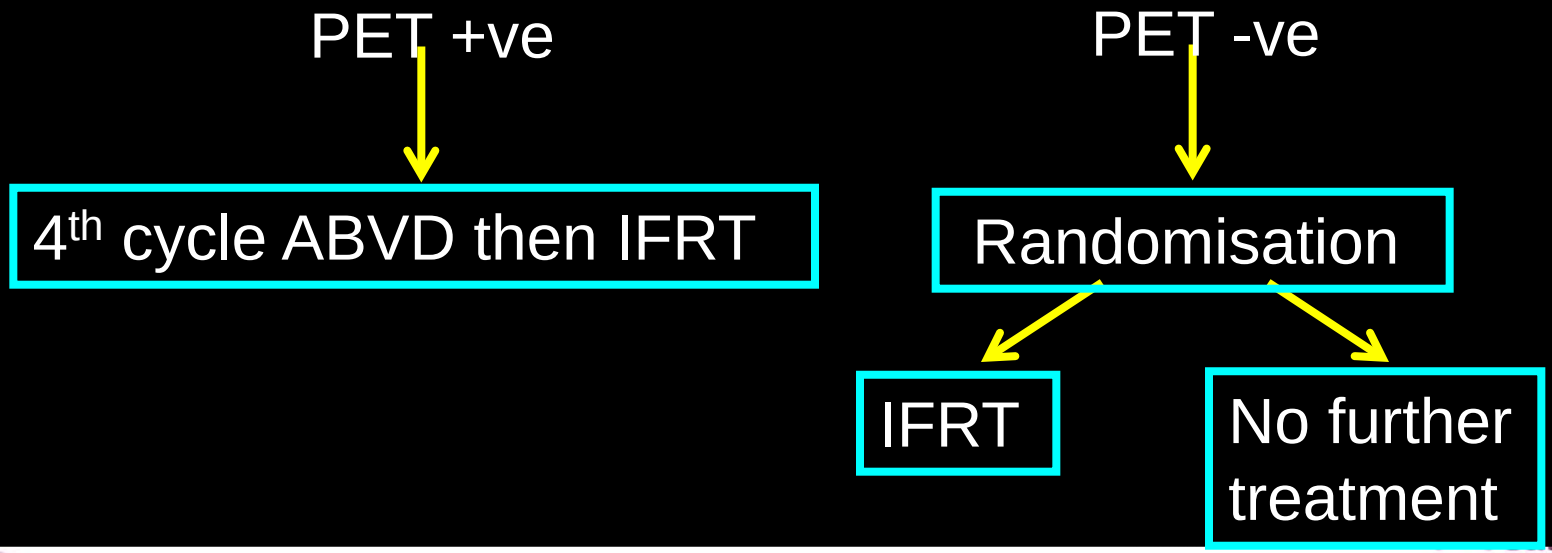
The Challenge of ^{18}FDG PET CT in HL : Converting large SUV numbers into Binary (Positive / Negative) and making sense of it

- Can we use FDG-PET to select patients who can be cured with less chemotherapy and no RT ?
- Primary objective UK NCRI RAPID and EORTC H10 trials
  - Is chemotherapy alone as effective - but less toxic to combined modality treatment in patients with CS I/II HL in terms of PFS in patients who are FDG-PET scan negative* after 3 cycles (UK NCRI) or two cycles (EORTC H10) of ABVD? *(non-inferiority)*

UK NCRI RAPID - trial design

Initial treatment: **ABVD x 3**

Re-assessment: **if NR/PD, patient goes off study**
FDG-PET scan performed



UK NCRI RAPID in early HL study Demographics

- 602 patients newly diagnosed HL (2003-2010)
- 321 male, 281 female median age - 34 years
- Stage IA, 139 (33%), stage IIA, 281 (67%)
- 67.8% favourable by GHSG criteria

UK NCRI RAPID study

PET scores after 3 cycles ABVD

- After 3 cycles ABVD - 571 pts had FDG PET CT scan :
- Deauville 5 point score :
  - Score 1 : 301 (52.7%) **74.7% PET NEGATIVE**
  - Score 2 : 125 (22.0%)
  - Score 3 : 90 (15.7%) **25.3% PET POSTIVE**
  - Score 4 : 32 (5.6%)
  - Score 5 : 23 (4.0%)
- 420 of 426 PET –ve pts randomised to IFRT (209) or NFT (211)
- 6 not randomised; pt choice 3, clinician choice 2, error 1

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UK NCRI RAPID Trial

	PET3		CT/RT	3-yr PFS (%)	3-yr OS (%)
ABVDx3	**Negative (74.7%)**	→ R →	No Further Rx (N=211)	90.8	99.5
			IFRT (N=209)	94.5	97.0
	Positive (25.3%)		ABVDx1 + IFRT (N=145)	85.9	93.9

3 year PFS 94.5% (91.3%-97.7) versus 90.8% (86.8-94.7%) HR 1.51 in favour of IFRT p=0.23

Radford J *et al., NEJM 2015*

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UK NCRI RAPID Trial

Per protocol analysis of randomised patients

- 28 patients excluded from the 420 randomised

- **26 in the IFRT arm did not receive RT**
  - 19 patient or clinician choice
  - 5 died in IFRT arm (before IFRT)
  - 1 had pneumonia
  - 2 withdrew consent
- 2 in the NFT arm received RT

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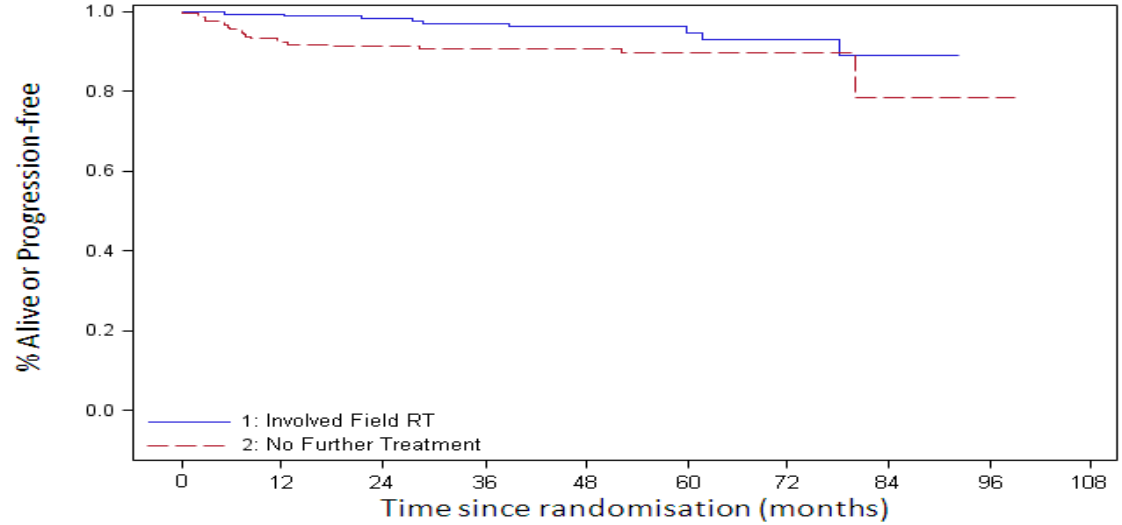
UK RAPID Deaths in IFRT arm that did not receive IFRT : Older patients tolerate ABVD badly

Demographics	Cause of death
Female 73 years, Stage I	died 9 weeks pneumonitis
Male 70 years Stage I	died 4 weeks pneumonitis
Male 62 years stage I	died 7 weeks, intracerebral haemorrhage and respiratory failure
Male 71 years, stage I	died 3 weeks, cause not yet determined
Male 61 years, stage II	died 4 months, AITL

–Böll B, et al ABVD in Older Patients with Early Stage Hodgkin Lymphoma Treated within the German Hodgkin Study Group HD10 and HD11 Trials J Clin Oncol. 2013 Mar 18. [Epub ahead of print]

UK NCRI RAPID Trial

PFS in the randomised PET –ve population (per protocol analysis, n=392)



Number at risk:

IFRT	183	179	162	129	98	65	38	17	0	0
NFT	209	188	163	132	100	60	18	4	2	0

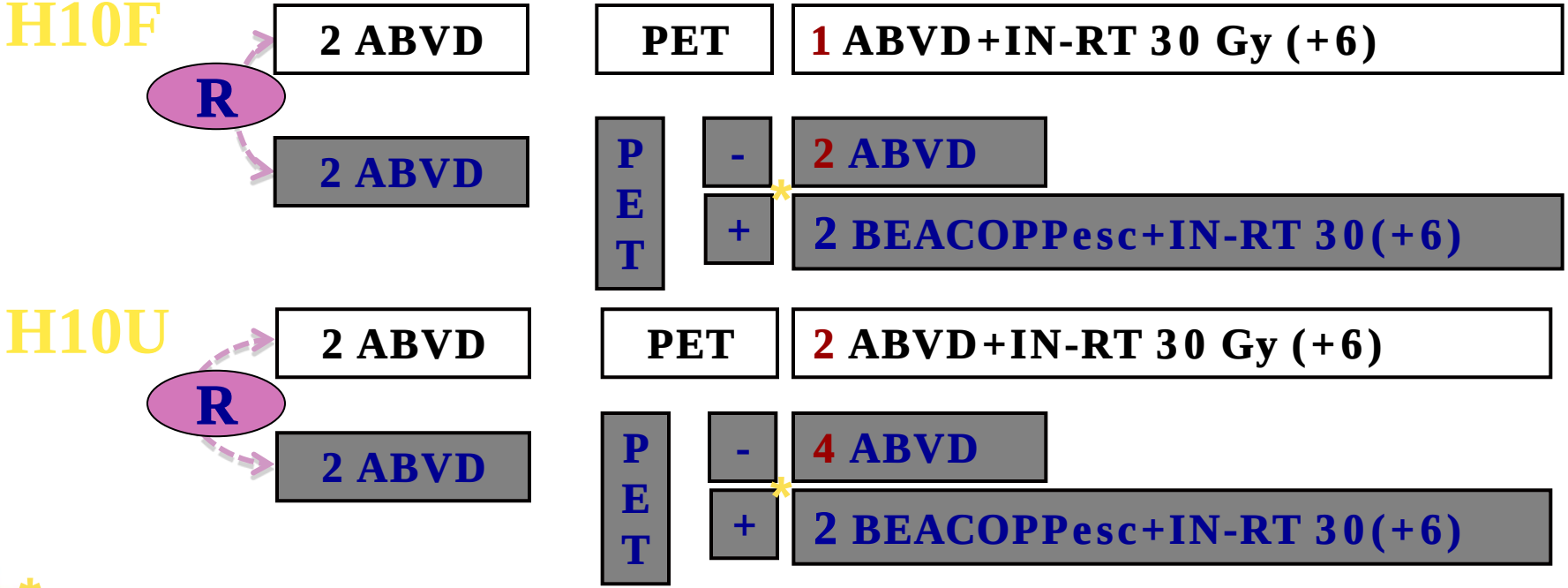
Per protocol analysis in 392 PET – ve patients

3 year PFS 97.0% IFRT vs 90.7% NFT (p=0.03) in favour of RT

Summary of UK NCRI RAPID study

- Analysis presented at 48.6 months and following 36 events
- Conservative definition : 74.7% of patients PET –ve after ABVD x 3
- Per protocol analysis in 392 PET – ve patients 3 year PFS 97.0% IFRT vs 90.7% NFT (p=0.03) in favour of RT

EORTC/ LYSA/ FIL H10 (#20051): study design



Hodgkin - CS I/II – supradiaphragmatic - untreated - 15-70 yrs - no NLPHL

EORTC/LYSA/FIL H10 Trial

H10F	Chemo	PET2	CT/RT	# Events	1-yr PFS
Standard	ABVDx2 ⟹	+/- ⟹	INRT	1/188	100%
Experimental	ABVDx2 ⟹	negative ⟹	ABVDx2	9/193	94.9%
		positive	BEACOPPesc x2 + INRT		

H10U	Chemo	PET2	CT/RT	# Events	1-yr PFS
Standard	ABVDx2 ⟹	+/- ⟹	ABVDx2 + INRT	7/251	97.3%
Experimental	ABVDx2 ⟹	negative ⟹	ABVDx4	16/268	94.7%
		positive	BEACOPPesc x2 + INRT		

Adapted from Ansell S M et al. ASH Abstract 2022

Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial.

Raemaekers JM, et al; J Clin Oncol. 2014 Apr 20;32(12):1188-94

- Analysis included 1,137 patients.
  - Favorable subgroup - 85.8% negative early PET scan
  - Unfavourable subgroup - 74.8% negative early PET scan

- IDMC concluded unlikely to show non-inferiority in the final results for the experimental arm and advised stopping random assignment for early PET-negative patients.

- CONCLUSION: CMT resulted in fewer early progressions in clinical stage I/II HL, although early outcome was excellent in both arms. The final analysis will reveal whether this finding is maintained over time.

Conclusions for FDG PET in Early HL

- Using FDG PET may be possible to identify a group of patients with an excellent "early" outcome from chemotherapy alone
- EORTC H10 trial – failed to achieve this goal
  - Favorable subgroup: 14.2% positive early PET scan
- UK NCRI RAPID results were achieved in the setting of
  - Very conservative definition of PET negative 25.3 % PET positive
  - Quality controlled PET image acquisition / Central review of PET images at the Core Lab
  - What is the QA like in your routine clinical practice ?
- Longer follow-up is required to establish the impact of a PET negative approach on 10 and 20 year survival and cause of death

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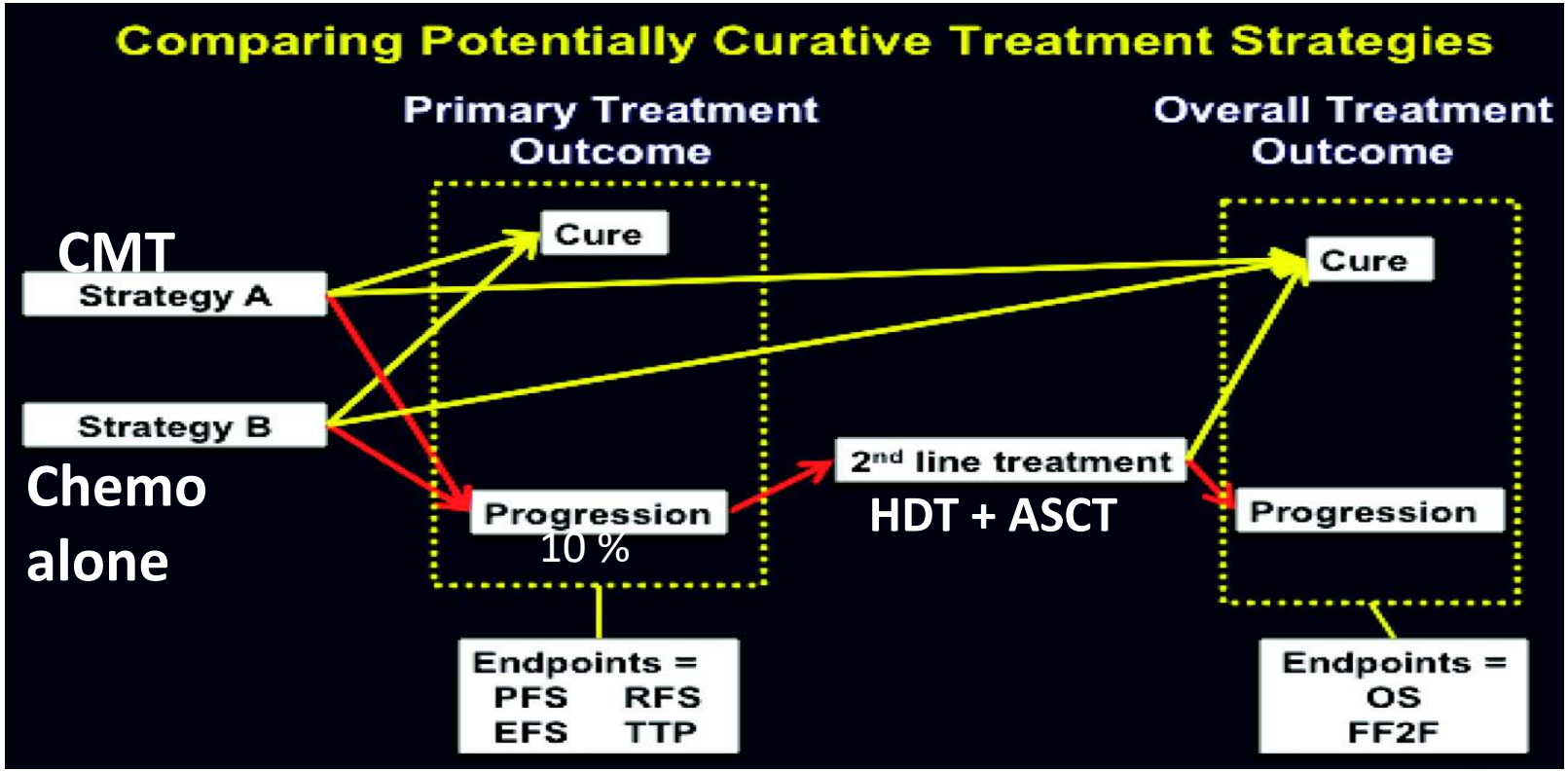
How to compare the effectiveness of two potentially curative treatment strategies.



Connors J M The Oncologist 2012;17:1011-1013

Which Patients with Stage I-II Hodgkin Lymphoma for Contemporary Combined Modality Therapy in PET era ?

- As a treatment option for patients with favorable disease, especially when risk late toxicity of RT considered lower than risk of relapse (Age, site of disease, sex)
- Older patients –risks associated with ABVD
- Definitely for patients with a positive interim PET scan (~25%)
- Definitely for patients with large mediastinal adenopathy - female patients ?

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Conclusions

- Large numbers of well conduction RCT supporting CMT in early stage HL
- Lack of randomised trials comparing chemotherapy alone vs contemporary CMT.
- Recent FDG-PET data inform patient specific discussions about risk of relapse (increased with chemo alone) versus late toxicity (increased with CMT)
- Response adapted treatment using FDG PET - Ongoing challenges to implement in routine clinical practice and QA measures are required to meet Deauville criteria

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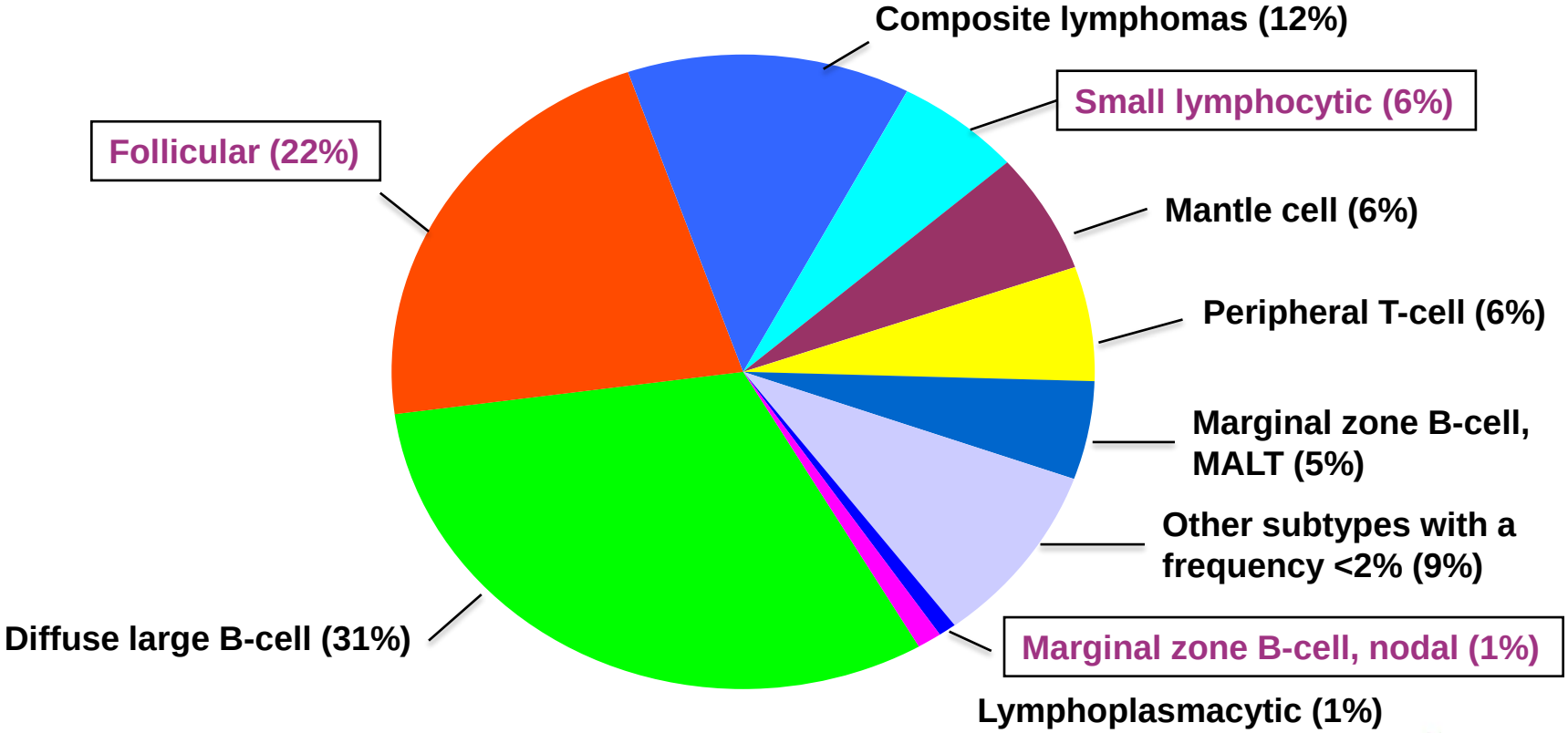
Indolent nodal non Hodgkin Lymphoma
The role of radiotherapy in early stage

Tim Illidge
BSc PhD DRCOG FRCP FRCR FRCPath

Institute of Cancer Sciences
Manchester Academic Health Sciences Centre
Manchester University
The Christie Hospital
Manchester , UK

Frequency of NHL Subtypes in Adults



Armitage et al. *J Clin Oncol*. 1998;16:2780–2795.

Indolent lymphomas

- Approximately 40–50 % of all NHL (follicular lymphoma 25%; SLL 6%, Marginal zone 10%)
- Most advanced stage cannot be cured by conventional therapy, minority of patients present with localised disease. Thorough staging with bone marrow biopsy and FDG-PET essential
- Therapy guidelines
  - Stage I/II:radiotherapy
  - Stage III/IV: chemotherapy, when needed

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Indolent Lymphomas
Treatment of stage I and II

- Standard: Involved Field Radiotherapy (IFRT)
- The shape of the survival curve suggests a possible plateau in the potential for a cure
- Most relapses occur outside the radiation field

Results of radiotherapy in stage I/II:

	5 years	10 years	15 years	20 years
Survival	82%	64%	44%	35%
Relapse-free	55%	44%	40%	37%

Ref.: MacManus,MP et al.; JCO 14: 1282-90 (1996)

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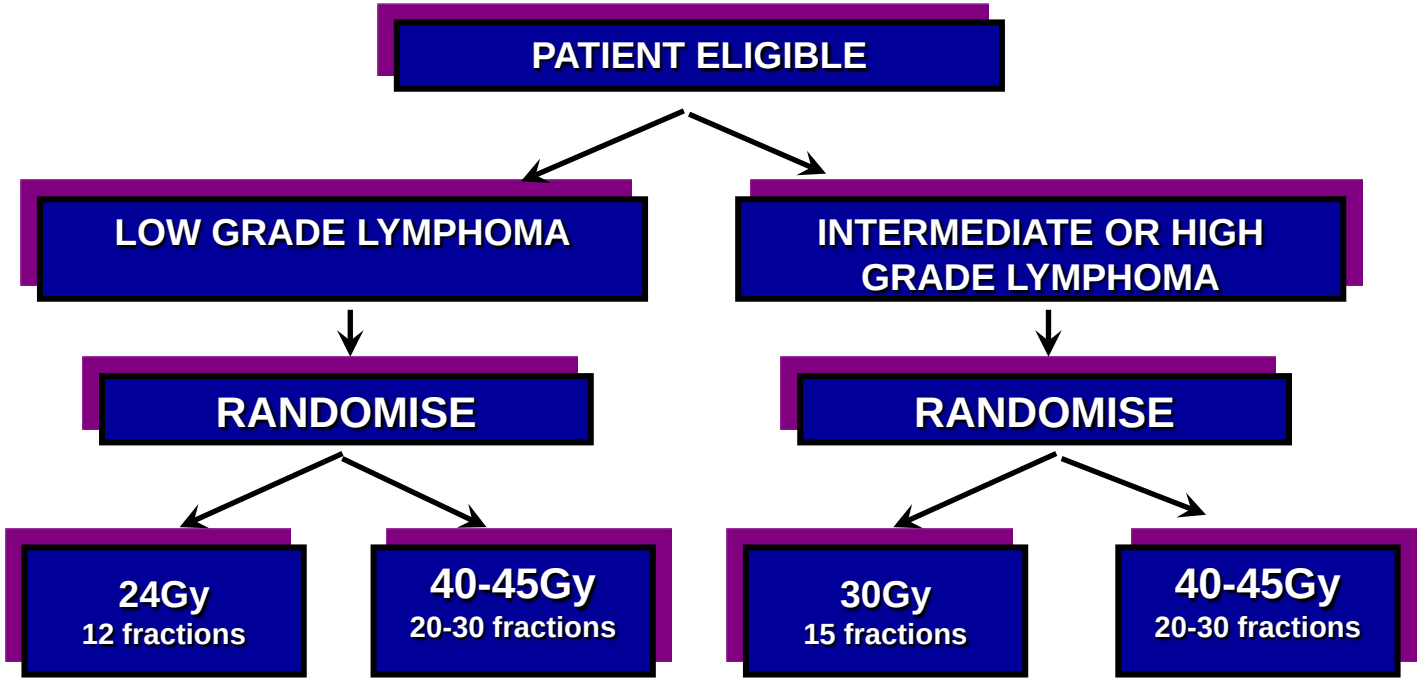
Hypothesis: Is more dose better?

Reduced dose radiotherapy for NHL : A randomised phase III trial

Lowry L, Smith P, Qian W, Falk S, Benstead K, Illidge T, Linch D, Robinson M, Jack A, Hoskin P.

Radiother Oncol. 2011 Jun 9.



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Indications for Radiotherapy

%	LG		IHG	
	24Gy	40-45Gy	30Gy	40-45Gy
Radical	77	79	48	51
Palliative	19	14	7	5
Consolidation	3	7	45	45

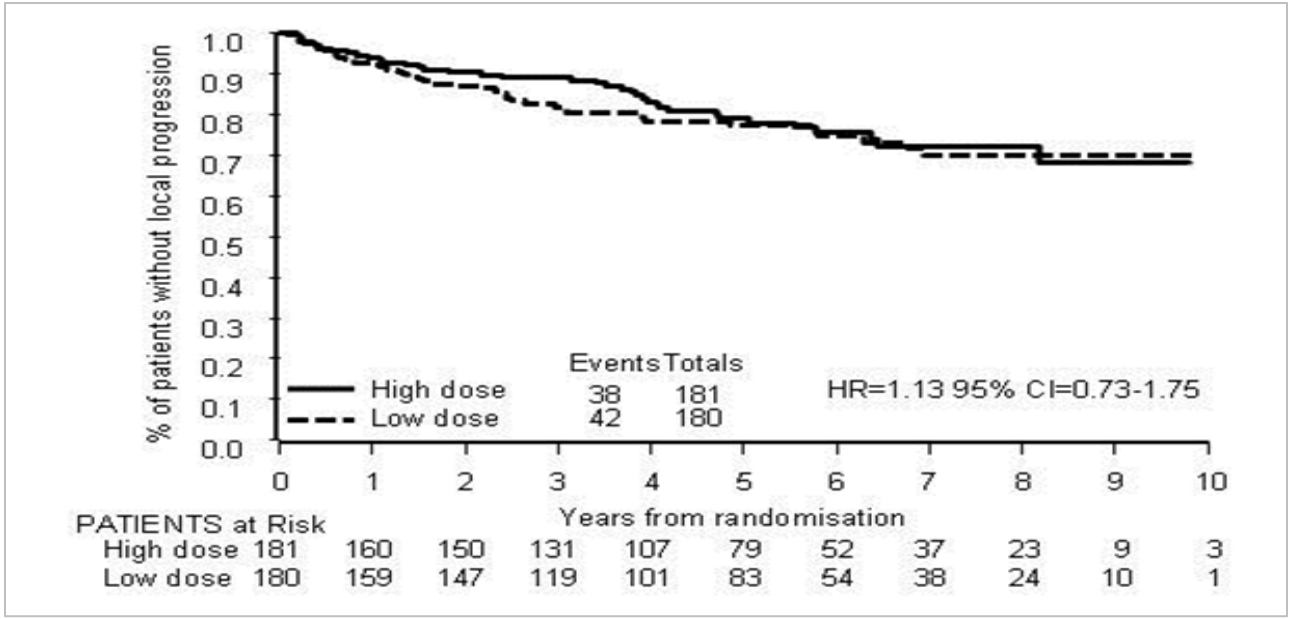
Acute RT Toxicity

%	LG		IHG	
	24Gy	40-45Gy	30Gy	40-45Gy
Erythema	33	49	25	38
Dry desquamation	12	19	12	15
Moist desquamation	1	8	3	5
Mucositis	25	26	17	22
Nausea / Vomiting	10	12	5	6
Diarrhoea	7	12	6	7

Local Control at 1 month

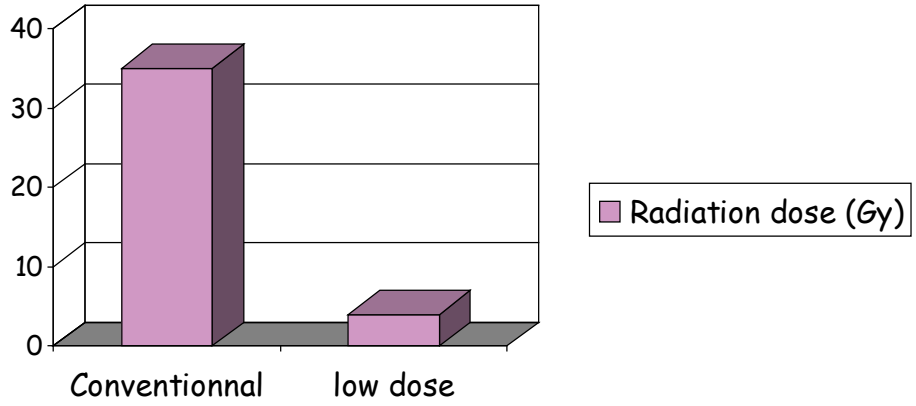
	LG		IHG	
%	24Gy	40-45Gy	30Gy	40-45Gy
Complete Regression	82	80	84	85
Partial Regression (>50%)	11	14	9	8
Stable Disease	6	5	5	5
Progression	2	1	2	3

RT dose 24 Gy vs 40 Gy in indolent NHL



[1] Lisa Lowry, Paul Smith, Wendi Qian, Stephen Falk, Kim Benstead, Tim Illidge, David Linch, Martin Robinson, Andrew Jack, Peter Hoskin *'Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial'* Radiotherapy and Oncology 100 (2011) 86–92

Radiation sensitivity of indolent lymphomas



Clinical study on 109 patients (2003) -
(2 X 2 Gy) in indolent Lymphoma
- Local response rate 92 %
- Complete response 61 %
- Very rapid responses, No side effects

(Haas et al. JCO. 2003)

'immune signature' genes, activated by RT including

macrophages (e.g., CD68, TLR4),

TH1 immune response (e.g., IL18, CXCL9, 10, 11),

clearance of apoptotic cells

(Knoops L et al Blood 2007)

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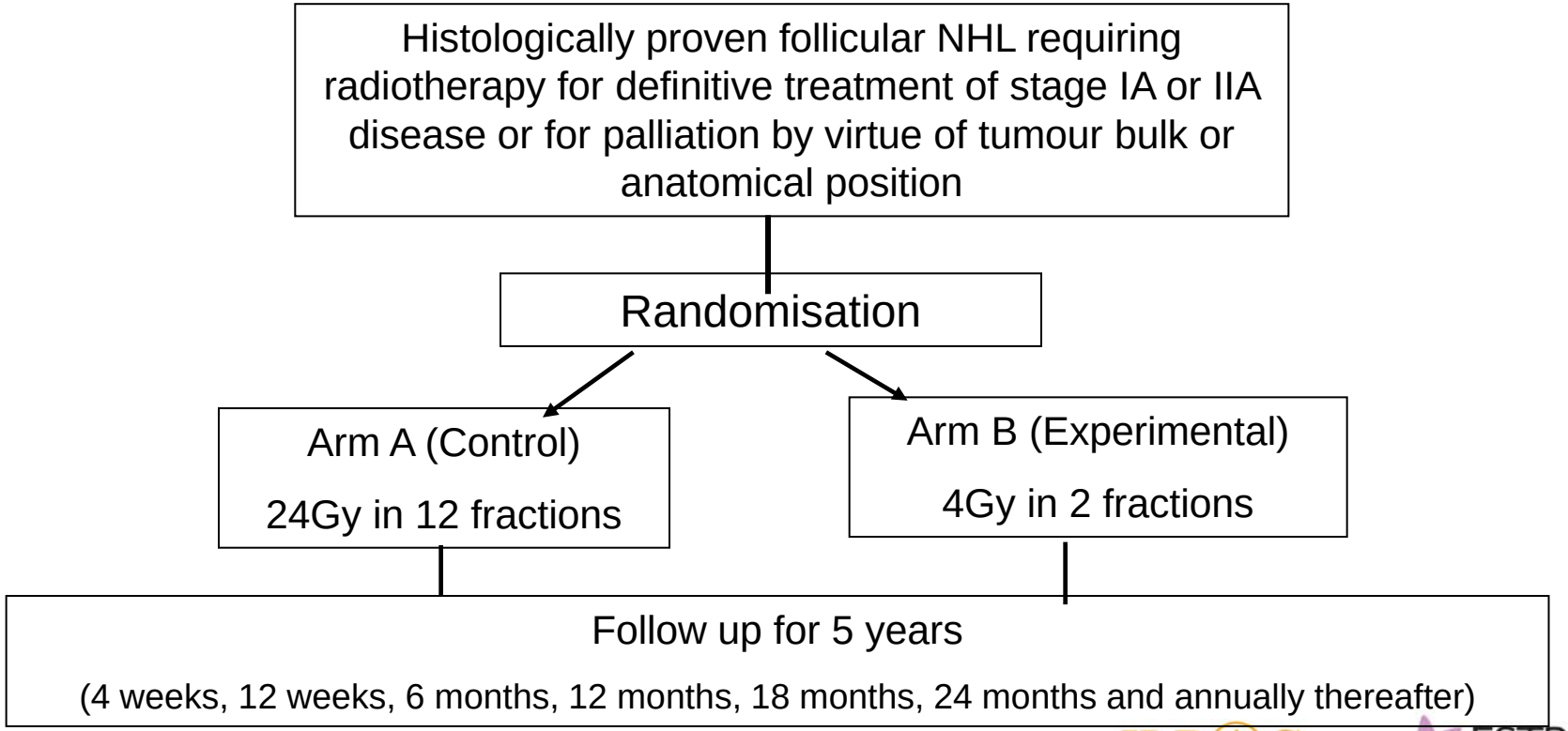
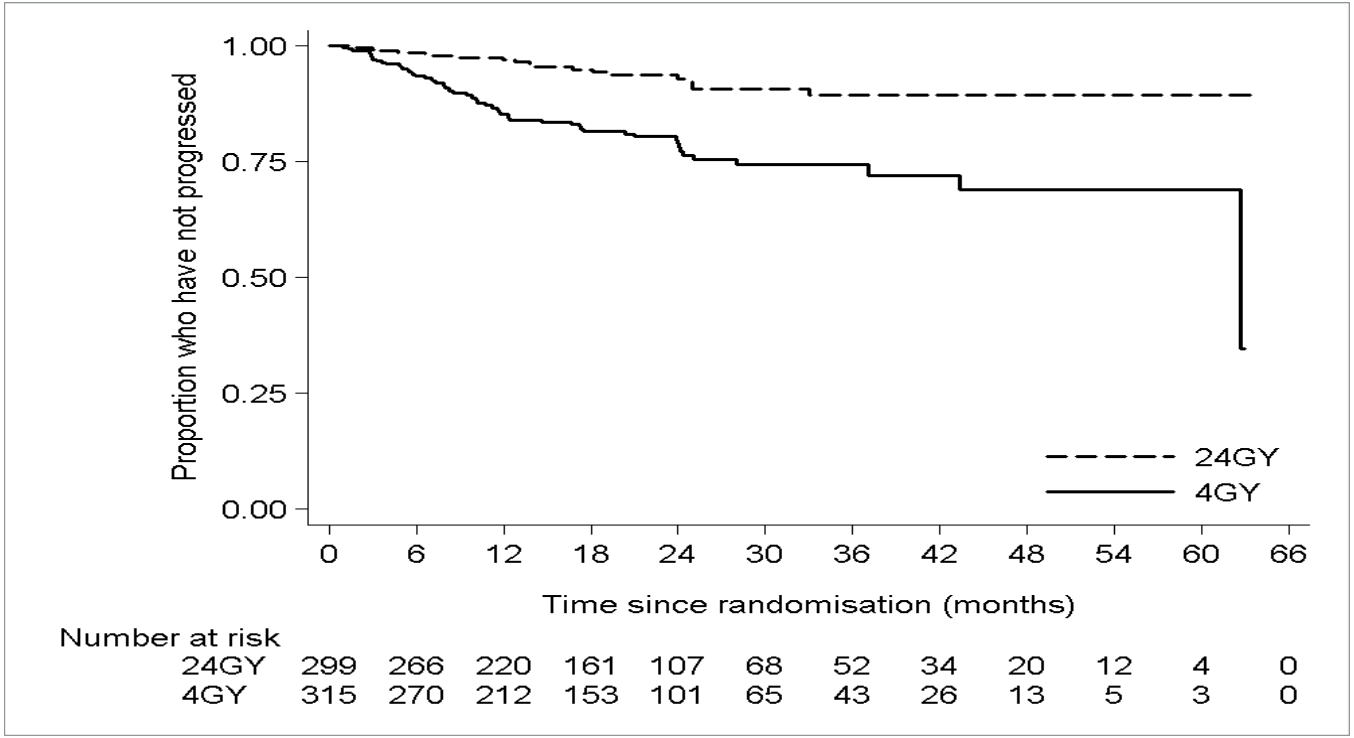
FoRT: Study design : A randomised trial of low dose radiotherapy for follicular lymphoma



NCRI FORT Trial 24 Gy vs 4 Gy : Local PFS



2 Year local progression free rate: 93.7% (24Gy) and 80.4% (4Gy) Hazard Ratio: 3.49 (95% CI: 2.06 - 5.90), p<0.001,

UK NCRI FORT trial Summary and conclusion

- 4Gy in 2 fractions inferior to 24Gy in 12 fractions in achieving a durable local progression free interval in follicular and marginal zone NHL.
- 24Gy in 12 fractions should remain the standard schedule for indolent lymphoma.
- 4Gy in 2 fractions is effective (ORR 74.1%; CR rate: 44.3%, PR rate: 29.8%) and may be considered for palliative treatment or retreatment.

Is radiotherapy curative for stage I and II low-grade follicular lymphoma?

Results of a long-term follow-up study of patients treated at Stanford University.

Mac Manus MP, Hoppe RT J Clin Oncol 1996 Apr;14(4):1282-90.

- 177 patients with stage I (n = 73 [41%]) and II (n = 104 [59%]) follicular lymphoma Stanford University 1961 and 1994.
- RT either to one side of the diaphragm (IFRT or EFRT or to both sides (total lymphoid irradiation [TLI] or subtotal lymphoid irradiation [STLI]. Doses 35 to 50 Gy.
- Median follow-up 7.7 years, longest 31 years. Median survival time 13.8 years.

Is radiotherapy curative for stage I and II low-grade follicular lymphoma?

Results of a long-term follow-up study of patients treated at Stanford University.

Mac Manus MP, Hoppe RT J Clin Oncol 1996 Apr;14(4):1282-90.

- At 5, 10, 15, and 20 years, 55%, 44%, 40%, and 37% of patients, respectively, were relapse-free. Only five of 47 patients who reached 10 years without relapse subsequently developed recurrence.
- Survival and freedom from relapse (FFR) significantly worse for older patients.
- Patients who have remained free of disease for 10 years are unlikely to relapse

Radiotherapy alone for stage I-III low grade follicular lymphoma: long-term outcome and comparison of extended field and total nodal irradiation.

Guckenberger M Radiat Oncol 2012 Jun 24;7**:103.**

- To analyze long-term results of radiotherapy alone for stage I-III low grade follicular lymphoma and to compare outcome after extended field irradiation (EFI) and total nodal irradiation (TNI).

- Between 1982 and 2007, 107 patients were treated with RT alone for low grade follicular lymphoma at Ann Arbor stage I (n = 50), stage II (n = 36) and stage III (n = 21);

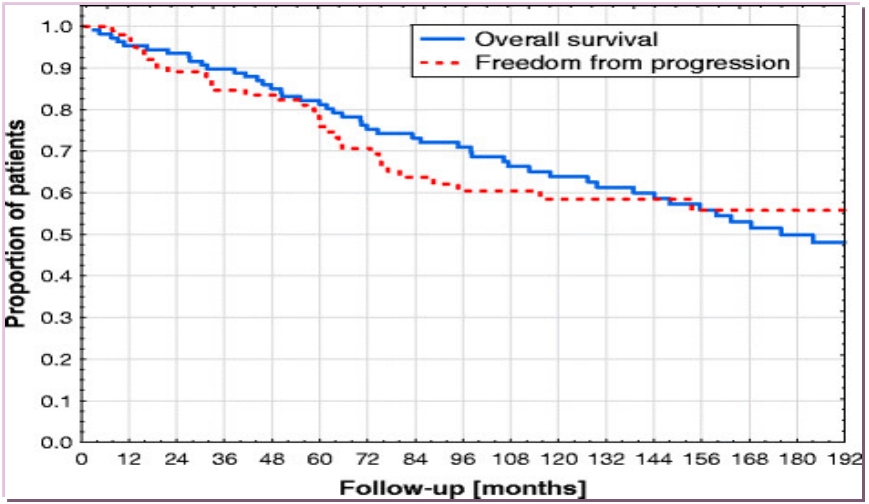
- 48 and 59 patients were treated with EFI and TNI, respectively.

- The median total dose in the first treatment series of the diaphragmatic side with larger lymphoma burden was 38 Gy (25 Gy - 50 Gy) and after an interval of median 30 days, a total dose of 28 Gy (12.6 Gy - 45 Gy) was given in the second treatment series completing TNI.

Radiotherapy alone for stage I-III low grade follicular lymphoma: long-term outcome and comparison of extended field and total nodal irradiation.

Guckenberger M Radiat Oncol 2012 Jun 24;7:103.

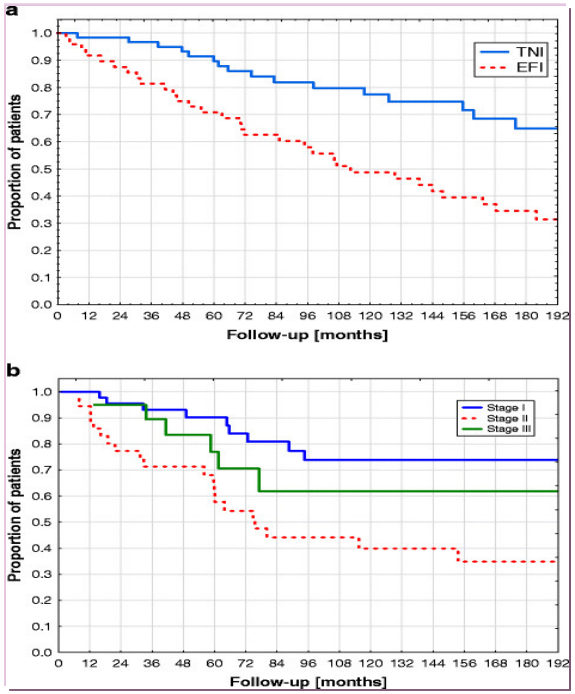
- After a median follow-up of 14 years for living patients, 10-years and 15-years overall survival (OS) were 64% and 50%, respectively.
- Survival was not significantly different between stages I, II and III
- Acute toxicity was significantly increased after TNI compared to EFI with a trend to increased late toxicity as well.



Radiotherapy alone for stage I-III low grade follicular lymphoma: long-term outcome and comparison of extended field and total nodal irradiation.

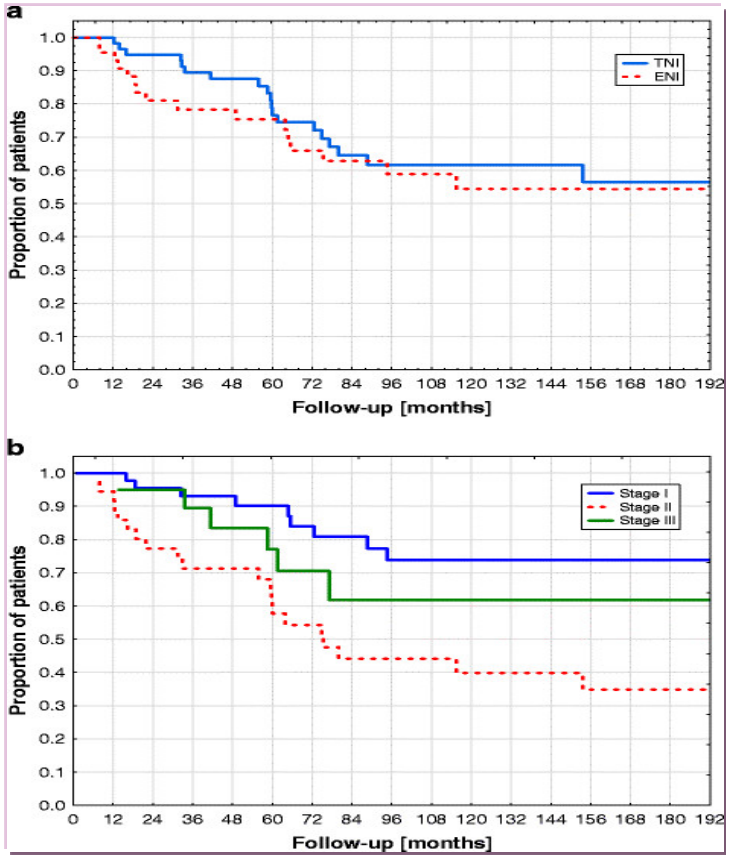
Guckenberger M Radiat Oncol 2012 Jun 24;7:103.

- TNI and EFI resulted in 15-years OS of 65% and 34% but patients treated with TNI were younger, had better performance status and higher stage of disease compared to patients treated with EFI.
- Kaplan Meier Curves showing (a) **overall survival** in relationship to TNI versus EFI (no significant difference)
- And (b) stage of disease (no significant differences)



Radiotherapy alone for stage I-III low grade follicular lymphoma: long-term outcome and comparison of extended field and total nodal irradiation.

Guckenberger M Radiat Oncol 2012 Jun 24;7:103.



(a) Kaplan Meier Curves showing **freedom from disease progression** in relationship to TNI versus EFI (no significant difference)

(b) Stage of disease (significant difference between stage I and stage II)

Radiotherapy alone for stage I and II follicular lymphoma resulted in long-term OS with high rates of disease control; no benefit of TNI over EFI was observed.

Is radiotherapy curative for stage I and II low-grade follicular lymphoma?
Should RT alone remain standard of care ?

- US lymphocare 206 of 471 patients stage 1 follicular lymphoma “rigorously staged” - Treatments given
  - R-chemo (28%)
  - RT (27%)
  - Observation (17%)
  - Systemic + RT (13%),
  - rituximab monotherapy (12%), and other (3%).
- Median follow-up of 57 months, 44 (21%) progression events. PFS significantly improved with either R-chemo or systemic and RT. No differences in OS. (Friedberg J et al JCO 2012)

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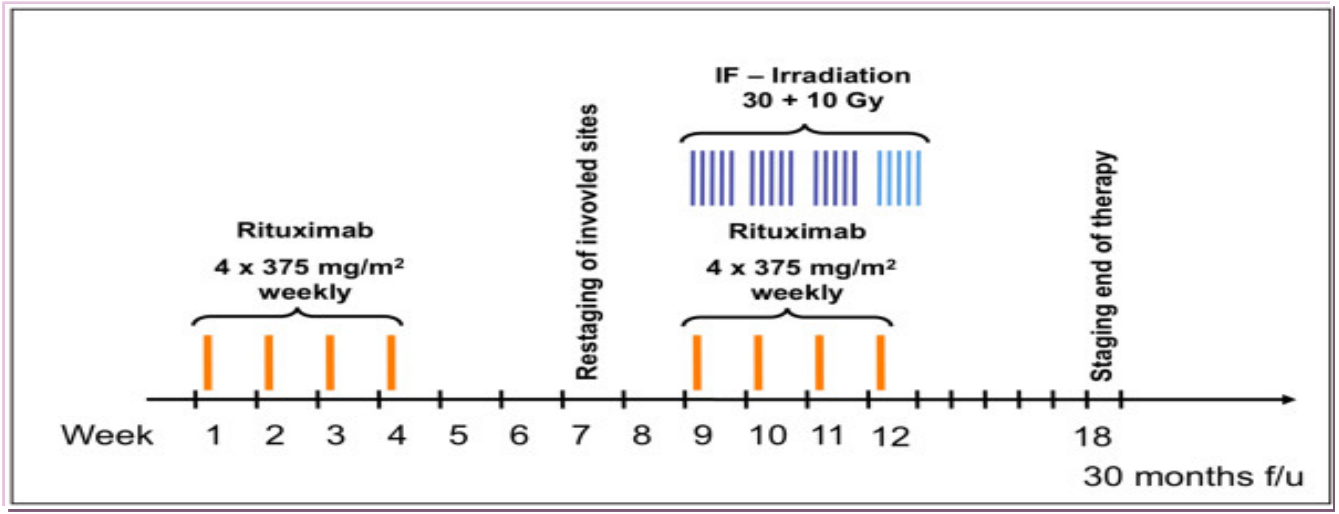
Treatment of limited stage follicular lymphoma with Rituximab immunotherapy and involved field radiotherapy in a prospective multicenter Phase II trial-MIR trial.

Witzens-Harig M, et al BMC cancer. 2011; 11: 87



Treatment of limited stage follicular lymphoma with Rituximab immunotherapy and involved field radiotherapy in a prospective multicenter Phase II trial-MIR trial.

Witzens-Harig M, et al BMC cancer. 2011; 11: 87

- Trial aims at testing the combination's efficacy and safety n= 85 patients.
- Primary endpoint of the study is progression free survival.
- Secondary endpoints are :
    - Response rate to Rituximab,
    - Complete remission rate at week 18,
    - Relapse rate,
    - Relapse pattern,
    - Relapse free survival,
    - Overall survival,
    - Toxicity
    - Quality of life.

Conclusions

- “Rigorous staging” is required to determine appropriate patients to consider IFRT, including BM biopsy and FDG-PET scan
- RT remains treat of choice of stage I/II indolent lymphomas and results in long term progression free survival and possible “cure” for patients still in remission past 10 years
- For early stage disease 24 Gy in 12 fractions remains the standard of care for most patients and provides better local control and 4 Gy in 2 fractions

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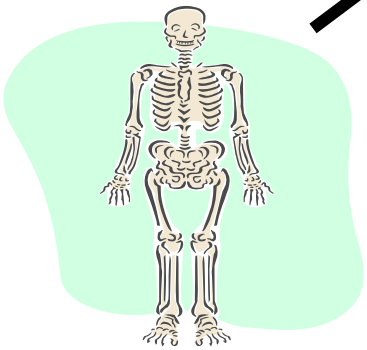
Immunotherapy and new immunological approaches

Tim Illidge
Professor of Targeted Therapy and Oncology
BSc PhD DRCOG FRCP FRCR FRCPath
Division of Cancer Sciences
Manchester Academic Health Sciences Centre
University
The Christie Hospital
Manchester , UK

Outline of talk

- Principles of immunotherapy
- Radiotherapy interacting with host immune system
- RT immunomodulatory combination approaches
- Immune check-point inhibitors

The normal immune system



Innate immunity

Macrophage / DC

Skin

Bowel

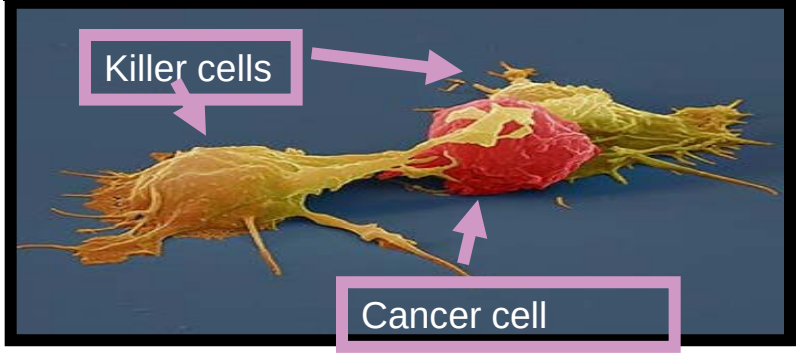
Cells

Adaptive immunity

T cell ,

antibody

Antibodies



Cancer Immunotherapy

- Ultimate goal : to make use of host immune system to eliminate malignant cancer cells
- Passive immunotherapy eg monoclonal antibodies, using host immune effector cells for Antibody Dependent Cellular Cytotoxicity (ADCC), Donor lymphocyte infusions (DLI)
- Active immunotherapy eg vaccination, generating a host immune response

Rituximab – Anti-CD20 mAb and NHL

- Revolutionised the treatment of NHL, improving outcome for patients with B cell malignancies

- Addition of Rituximab to CHOP chemotherapy in DLBCL (aggressive lymphoma) survival increased for the first time in 25 years (Coiffier et al NEJM 2002)

- Rituximab - chemotherapy in FL (indolent lymphoma) dramatically increased relapse free survival and Overall survival (Marcus et al Blood 2005). Now given as maintenance every 2-3 months for 2 years after induction therapy (Salles et Lancet 2011)

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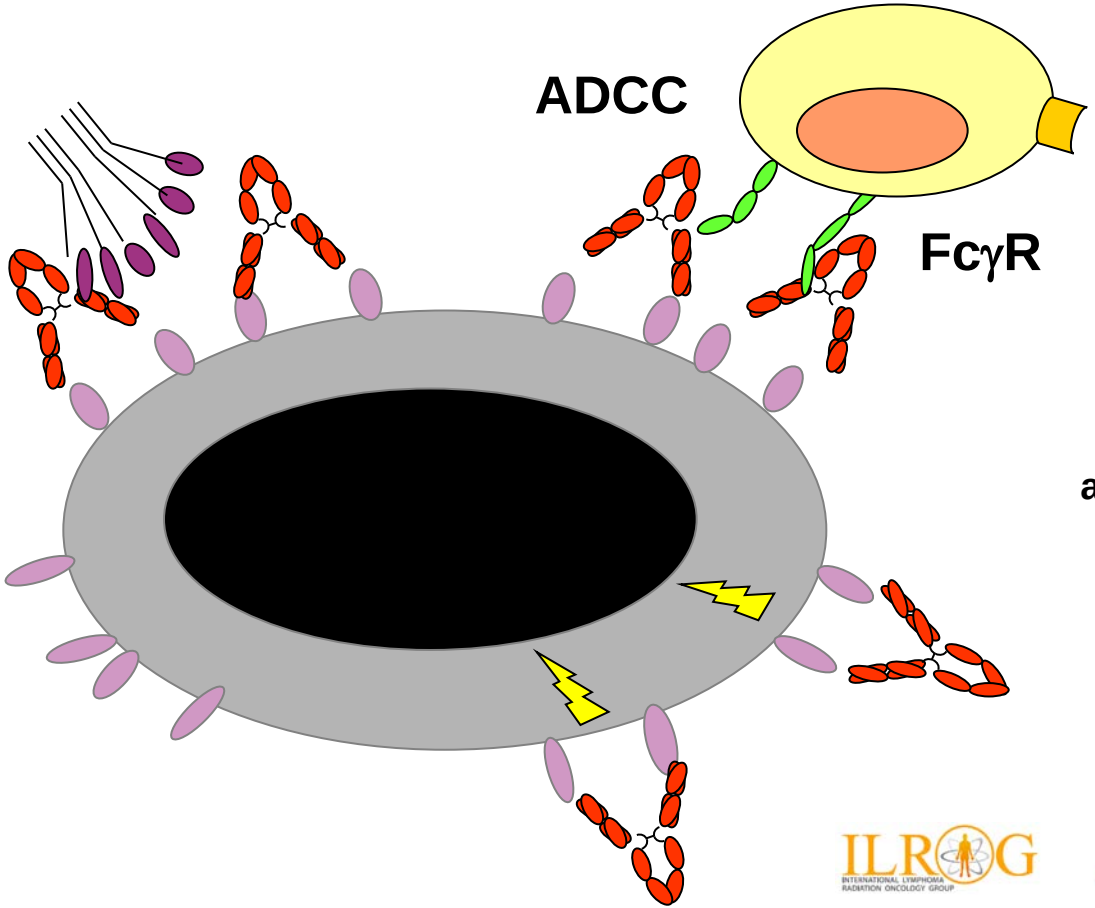
Potential Effects of antibodies upon Tumour cells

Complement Fixation



Promote active death Signalling DCD

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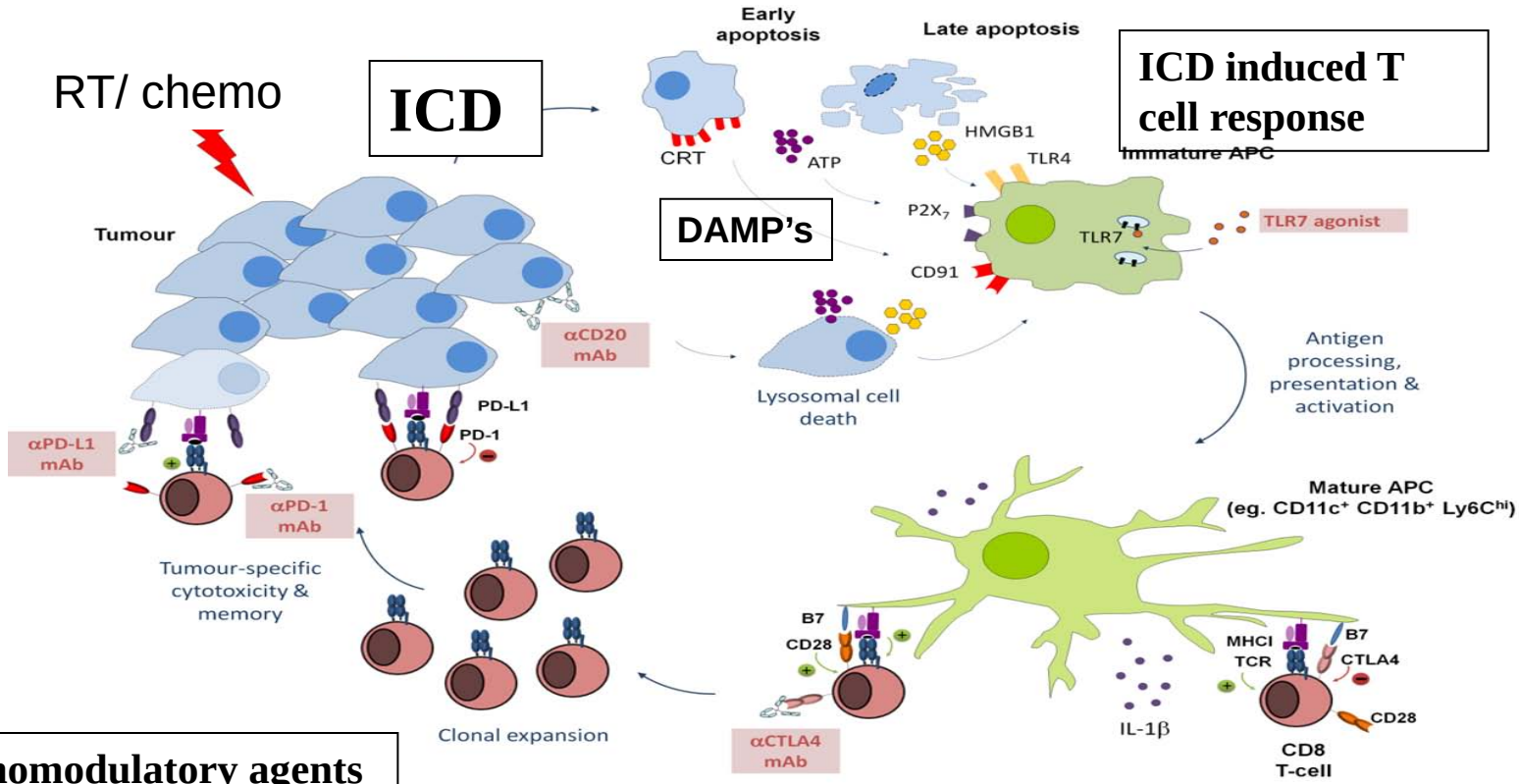
Outline of talk

- Principles of immunotherapy
- **Radiotherapy interacting with host immune system**
- RT immunomodulatory combination approaches
- Immune check-point inhibitors

Potential Effects of Tumour Radiotherapy on the Immune System



Immunomodulatory agents to enhance T cell response

Is there a relationship between immune activation and tumour response after RT ?

- **What is the nature and sequence of RT induced immune activation in the tumour microenvironment ?**

- What is the nature of the immunosuppression in the tumour microenvironment and can it be overcome ?

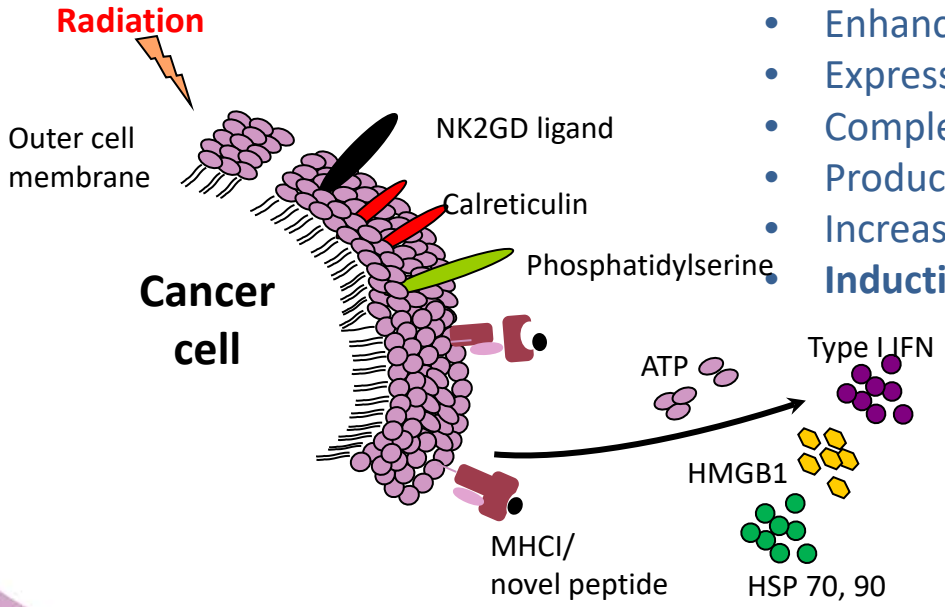
  - Enhancing the anti-tumour immune response with RT in combination with immunomodulatory agents

  - Outlining the key immune effector cells in the TME required to prime an

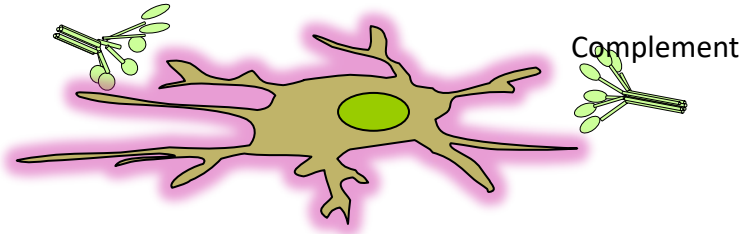
Radiation Therapy : a potentially important modifier of the immune response to tumour

Impact of radiation therapy on the generation of tumour-specific immunity:

- Enhanced antigen release
- Expression of NK2GD ligands
- Complement deposition
- Production of type I IFN
- Increased MHC and neo-antigen expression
- **Induction of immunogenic cell death**



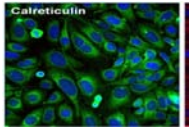
Find me, eat me signals



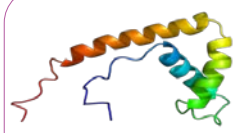
Dendritic cell activation

Three key damage-associated molecular patterns (DAMP) associated with Immunogenic Cell Death (ICD) - Effect of RT dose and fractionation ?

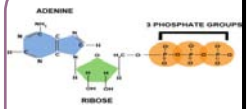
Apoptotic sub-routines considered to be immunogenic based on the coordination release of DAMP's which promote immune activation



Ecto-Calreticulin
ER resident protein, chaperone for miss-folded proteins preventing export
Ectopic surface expression associated with DC uptake



HMGB1 (High mobility group box 1 protein)
Chromatin binding nuclear protein
Binds RAGE (receptor for advanced glycosylation end-product) and Toll-like receptor (TLR) family members (eg. TLR4). **Promotes antigen presentation by DC**



ATP
Attracts monocytes to site of apoptosis "find me" signal
Activates NLRP3 inflammasome in DC and IL-1β secretion
Secretion linked to autophagy in pre-mortem "destined-to-die" cells

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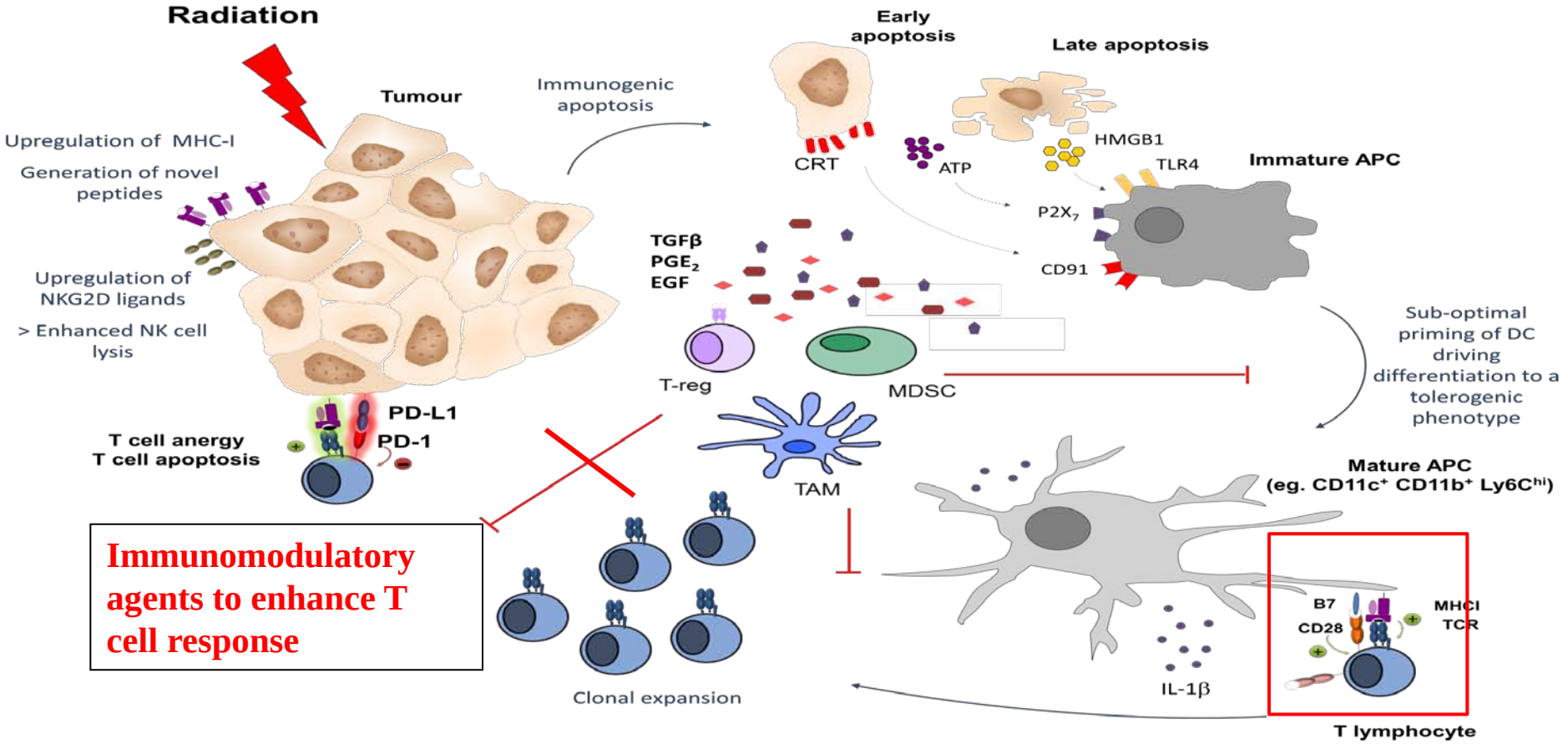
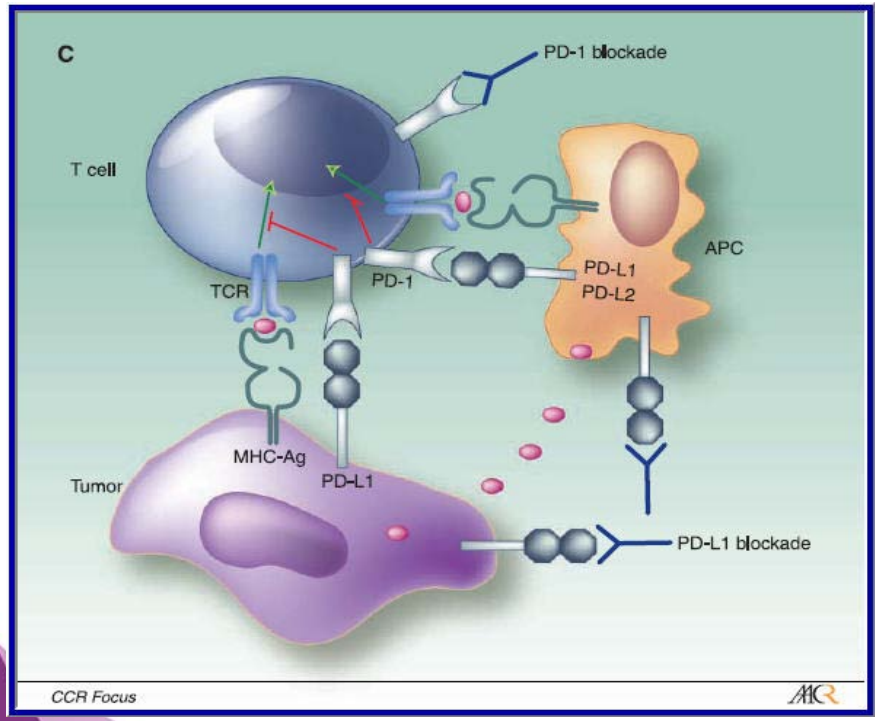
Is there a relationship between immune activation and tumour response after RT ?

- What is the nature and sequence of RT induced immune activation in the tumour microenvironment ?
- **What is the nature of the immunosuppression in the tumour microenvironment and can it be overcome ?**
  - Enhancing the anti-tumour immune response with RT in combination with immunomodulatory agents

Enhancing the immune response of Radiotherapy using immunomodulatory agents



Exploiting Immune Checkpoints Inhibitors : key to progress in developing therapeutics



- Survival of cancer cells depends on their ability to evade the anti-tumor immune response initiated by the host. A key mechanism of immune evasion - direct inhibition of cytotoxic T-cells

- T-cell activation is two-step process:

1. Antigen recognition
2. Generation of an antigen-independent co-regulatory signal that determines whether the T cell will be switched on or off in response to the antigen.

This second step is overseen by the immune checkpoint pathways, which are either stimulatory or inhibitory

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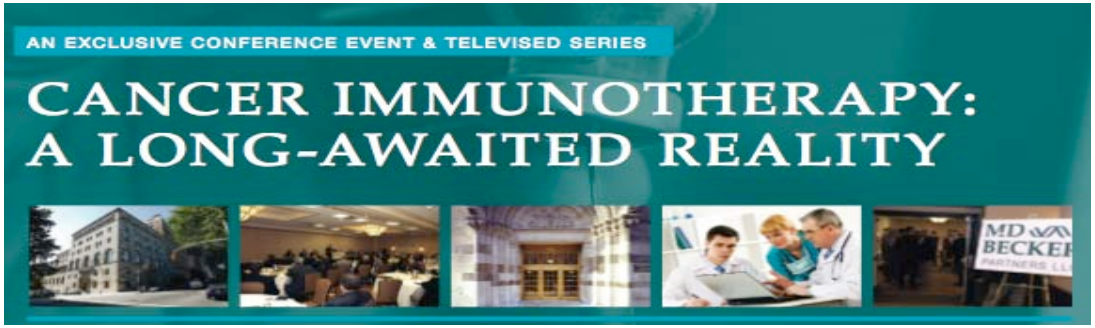
Tumour immunotherapy finally arrives



Science
AAAS

Immunotherapy earns its spot in the ranks of cancer therapy

Feb. 2012
J. Exp. Med. Vol. 209 No. 2 201-209

Drew Pardoll and Charles Drake

Breakthrough of the Year 2013

Cancer immunotherapy comes of age

Ira Mellman[1], George Coukos[2] & Glenn Dranoff[3]

480 | NATURE | VOL 480 | 22/29 DECEMBER 2011

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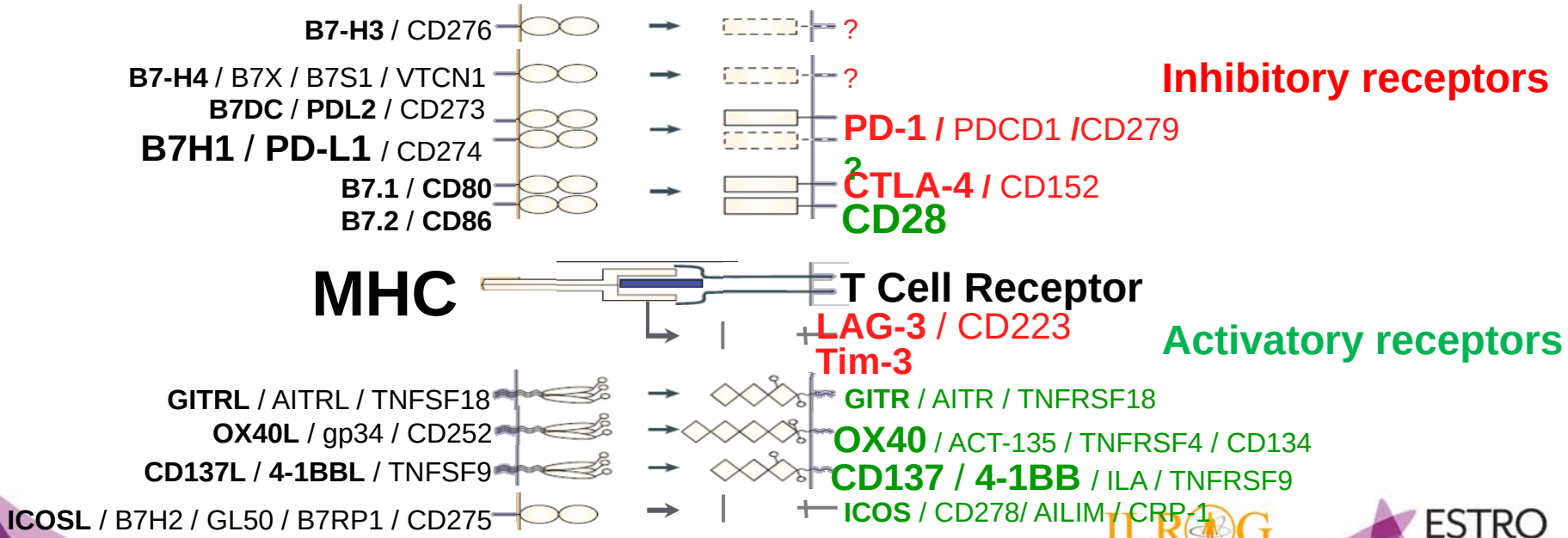
Understanding T- cell Immune Check-Points in the Tumour Microenvironment and Reversing Immunosuppression

Antigen Presenting Cell

T Cell



Inhibitory receptors

Activatory receptors

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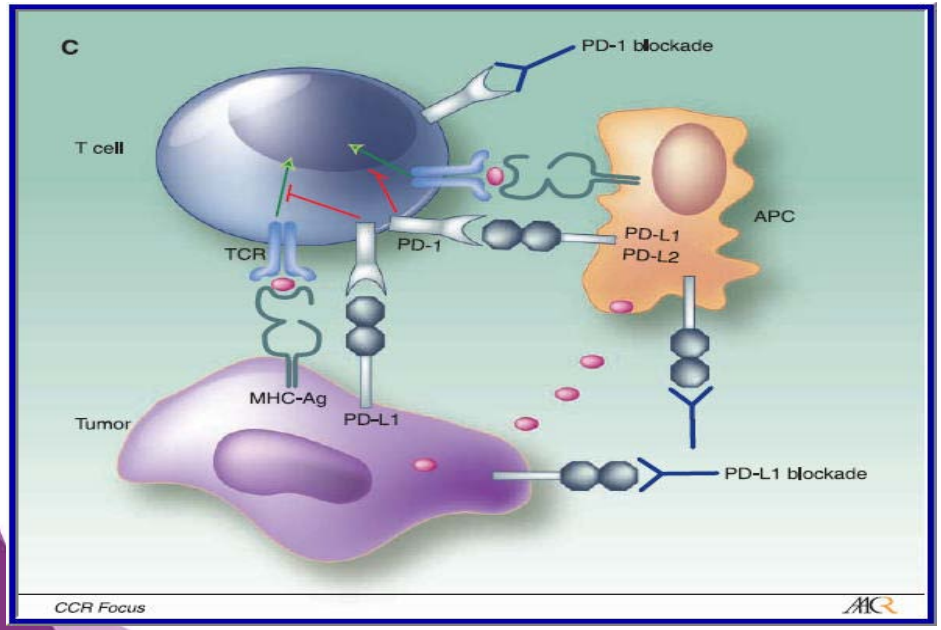
Rationale for Targeting PD1/PD-L1 Pathway in Cancer

- PD1 expressed by Tregs, activated T cells (CD4 and CD8), activated B cells, NK cells
- PD-L1 is expressed by APCs and several cancers



- Upon interaction with ligands, PD-L1 and PD-L2, initiates an inhibitory signaling network that switches off activated T cells
- Results in T cell exhaustion / anergy - poor effector function
- Anti-PD1/PDL1 mAb led to durable clinical responses in NSCLC, RCC, Melanoma, HL

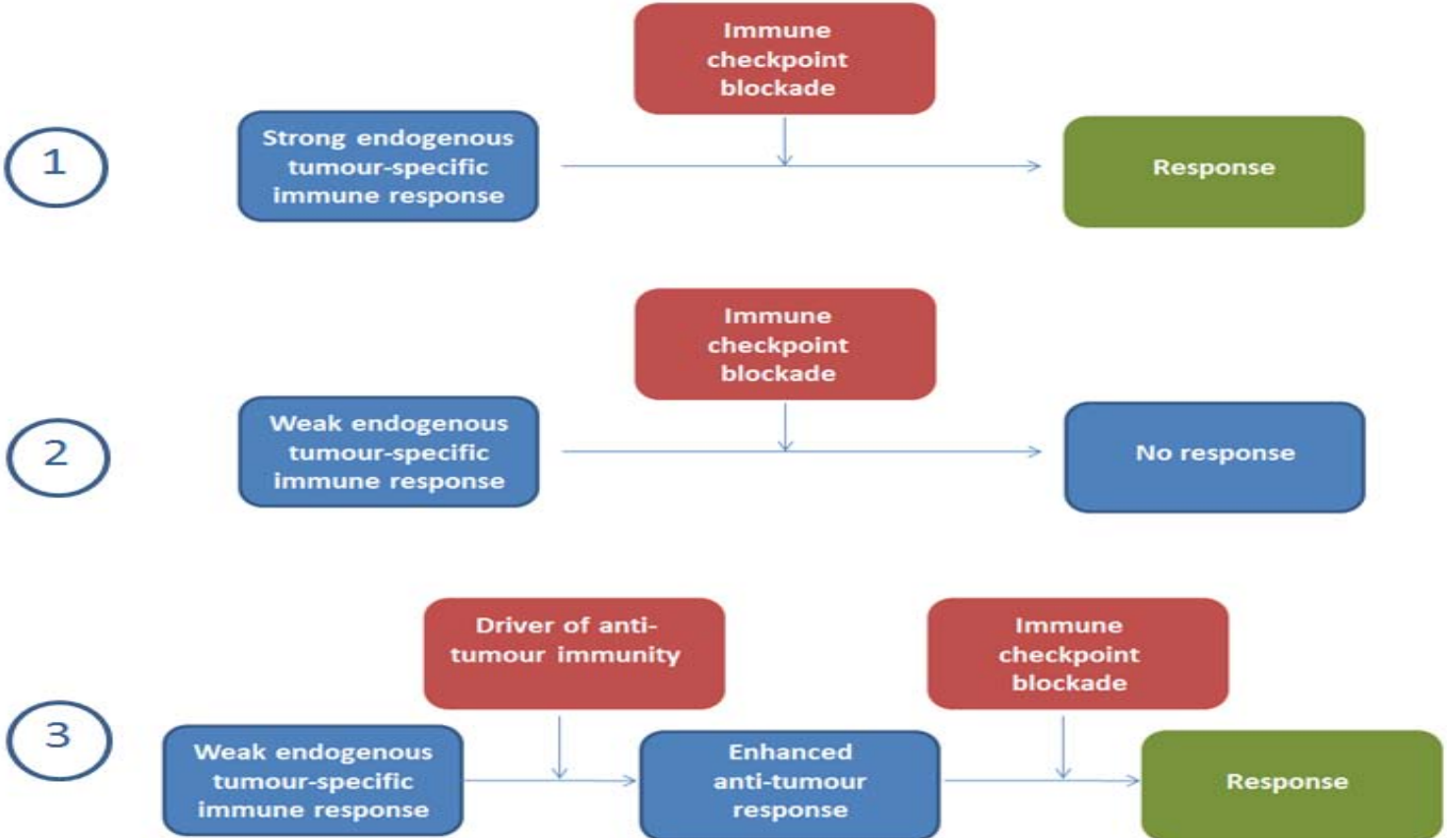
PD1 – programmed death 1; PDL – programmed death ligand;
NK – natural killer; APCs - antigen presenting cells

Shekhar S & Yang X. Cellular & Molecular Immunology 2012;9:380–5.

Outline of talk

- Principles of immunotherapy
- Radiotherapy interacting with host immune system
- **RT immunomodulatory combination approaches**
- Immune check-point inhibitors

Rationale for RT and immunotherapy combination approaches



Optimal results will require combinations – RT an ideal partner

Is there a relationship between immune activation and tumour response after RT ?

- What is the nature and sequence of RT induced immune activation in the tumour microenvironment ?

- What is the nature of the immunosuppression in the tumour microenvironment and can it be overcome ?
  - **Enhancing the anti-tumour immune response with RT in combination with immunomodulatory agents**

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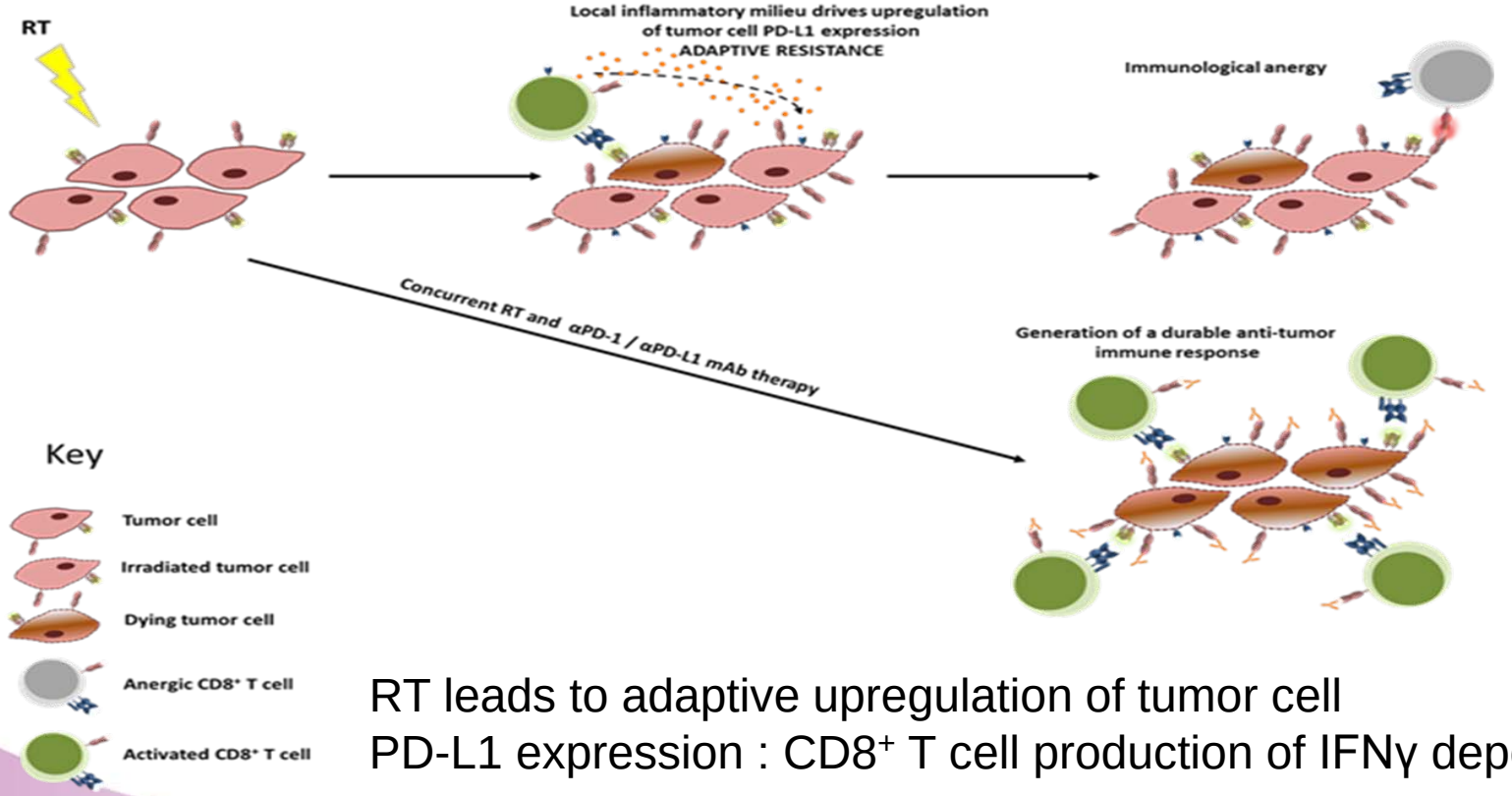
Acquired Resistance to Fractionated Radiotherapy Can Be Overcome by Concurrent PD-L1 Blockade

Simon J. Dovedi[1], Amy L. Adlard[2], Grazyna Lipowska-Bhalla[1], Conor McKenna[1], Sherrie Jones[1], Eleanor J. Cheadle[1], Ian J. Stratford[2], Edmund Poon[3], Michelle Morrow[3], Ross Stewart[3], Hazel Jones[3], Robert W. Wilkinson[3], Jamie Honeychurch[1], and Tim M. Illidge[1]

Cancer Research



RT leads to adaptive upregulation of tumor cell PD-L1 expression : $CD8^+$ T cell production of IFNγ dependent

Acquired Resistance to Fractionated Radiotherapy Can Be Overcome by Concurrent PD-L1 Blockade

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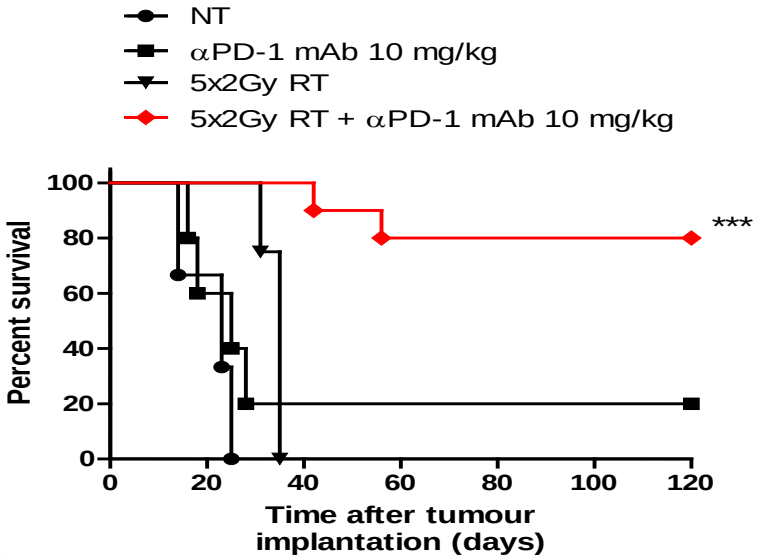

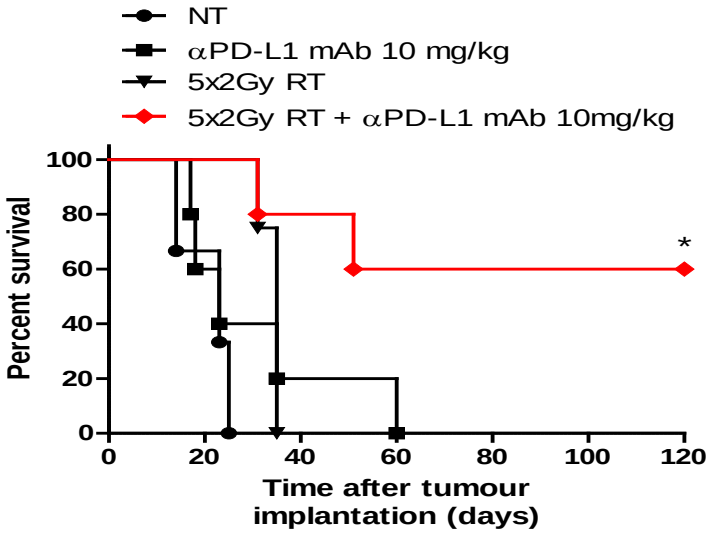

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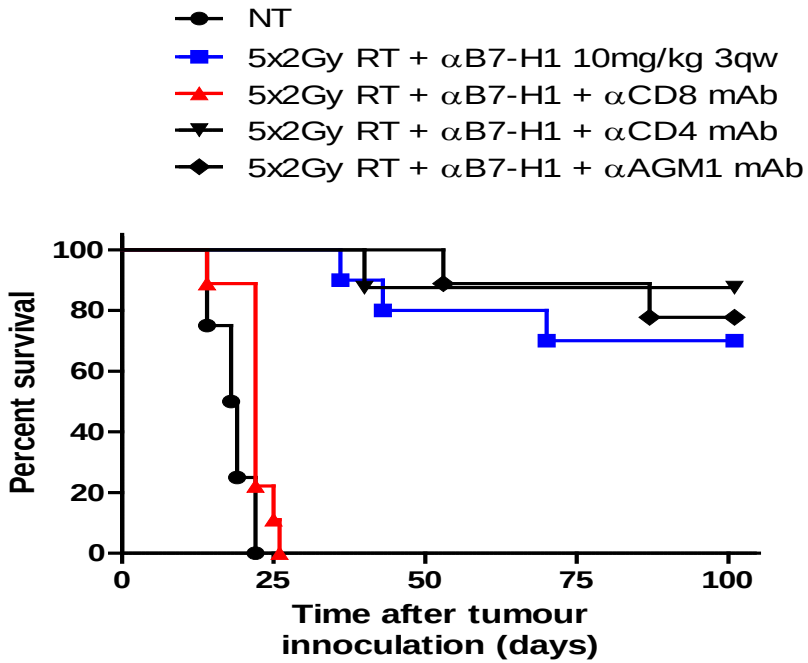
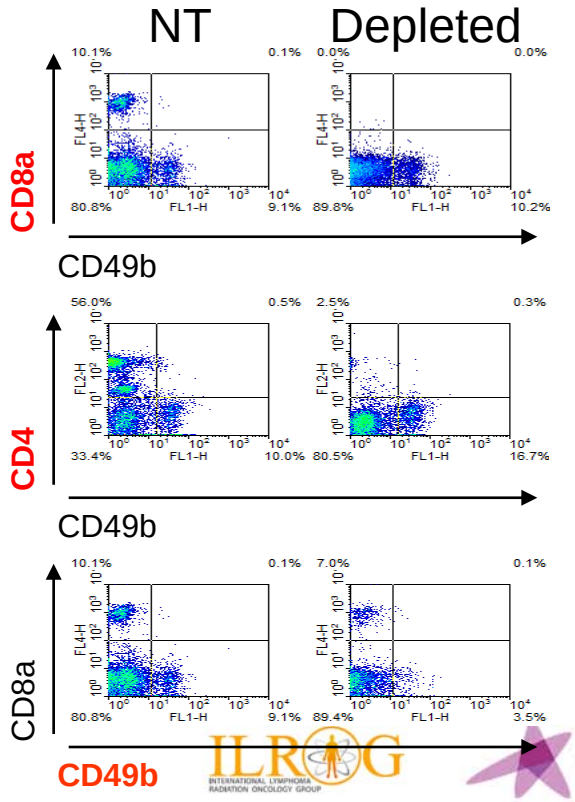
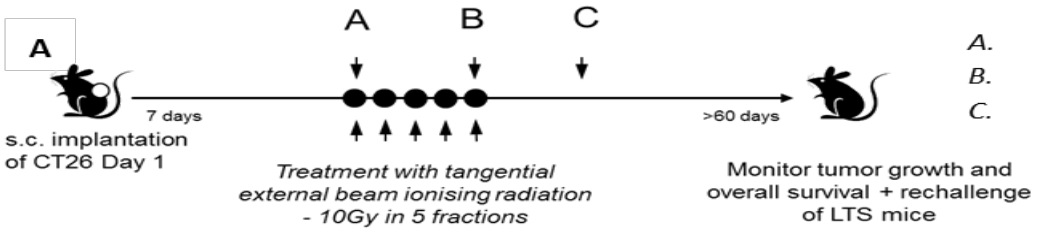


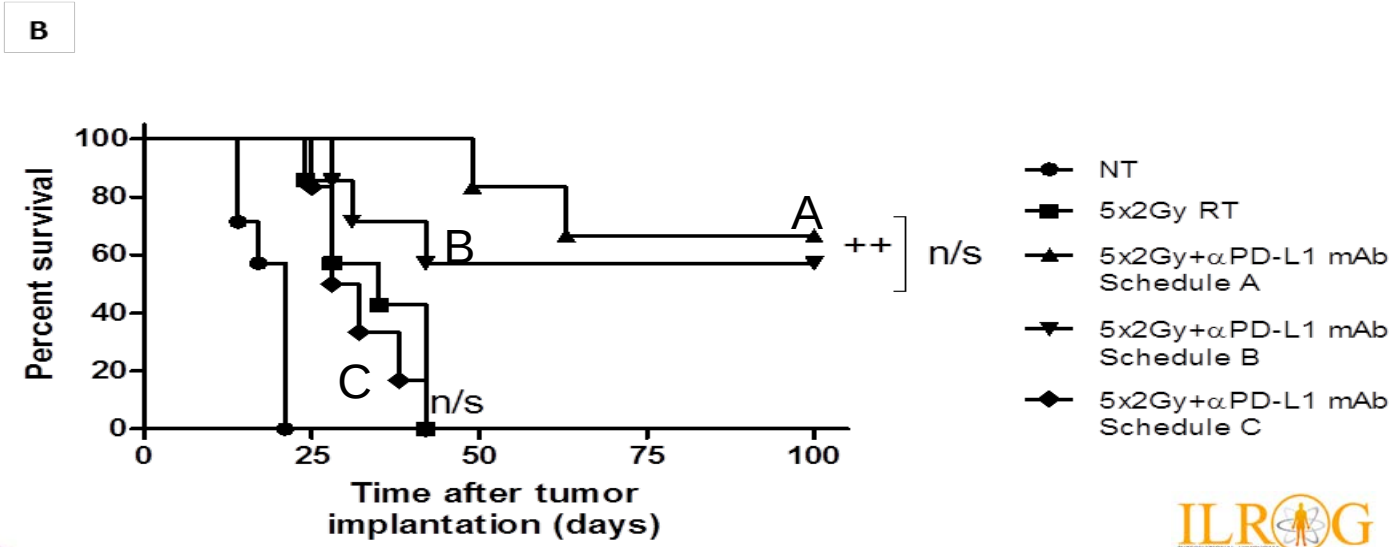


Efficacy of RT and anti-PD-L1 combination is CD8⁺ T cell dependent

Scheduling of RT and anti-PD-L1 combination determines outcome



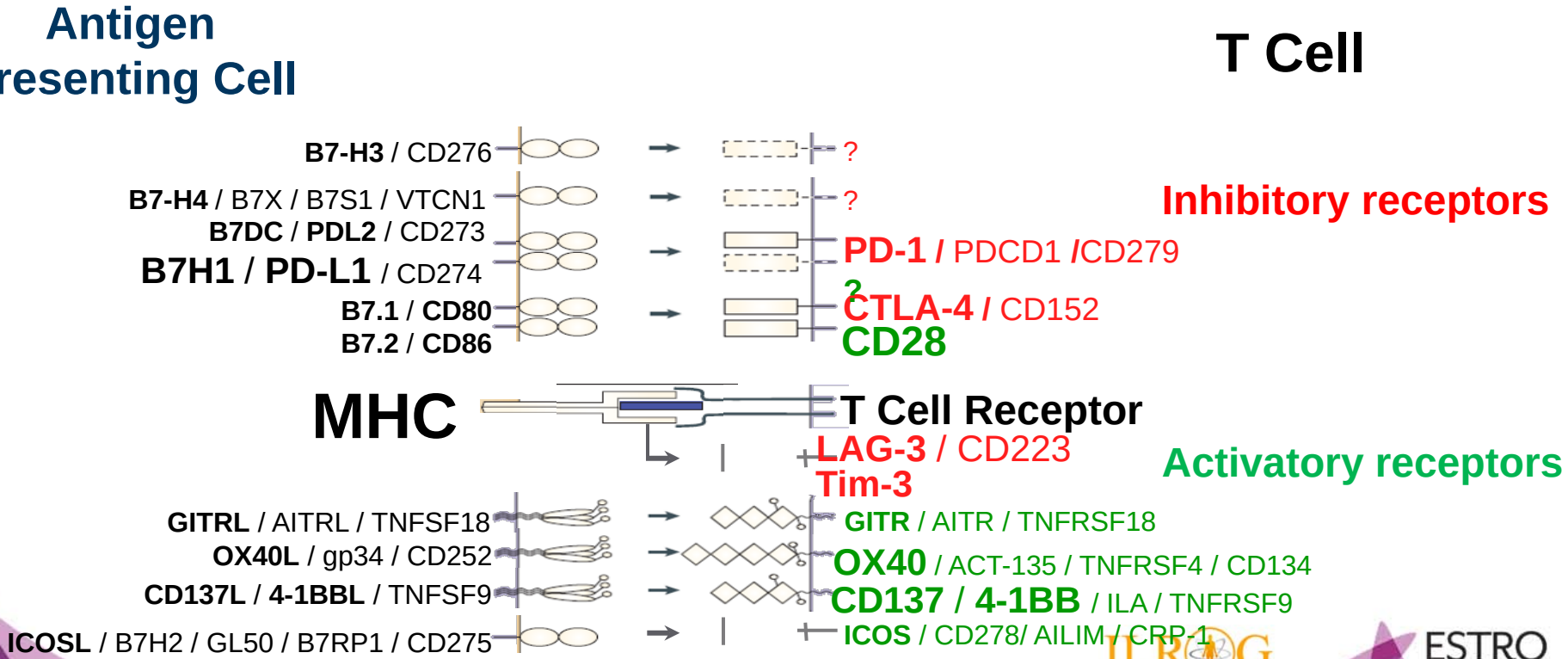
A. αPD-L1 mAb starting on day 1 of RT
B. αPD-L1 mAb starting on day 5 of RT
C. αPD-L1 mAb starting 7 days after the last dose of RT



Outline of talk

- Principles of immunotherapy
- Radiotherapy interacting with host immune system
- RT immunomodulatory combination approaches
- **Immune check-point inhibitors**

Understanding T- cell Immune Check-Points in the Tumor Microenvironment and Reversing Immunosuppression



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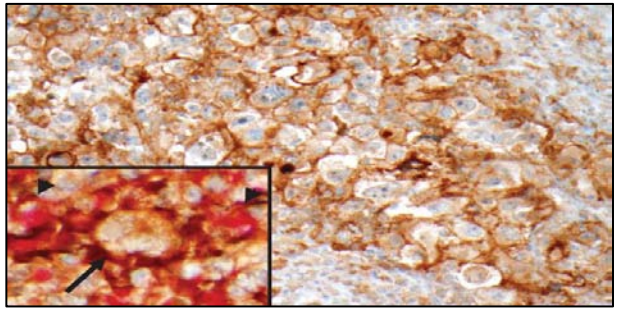
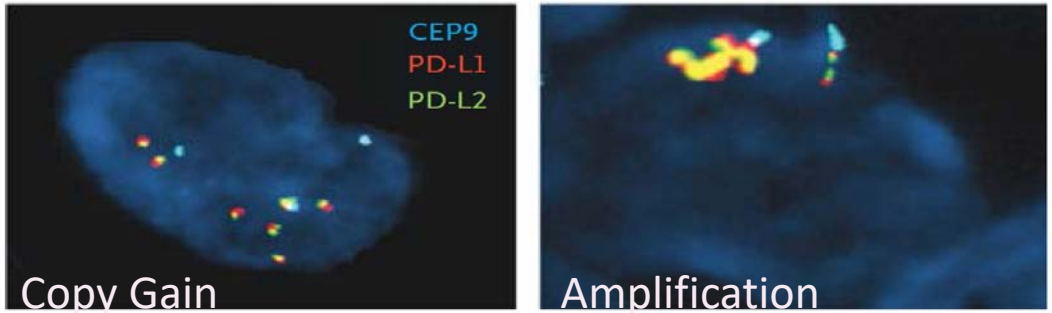
Anti-PD1 in Hodgkin Lymphoma

- Classical Hodgkin lymphoma (cHL) is characterized by expression of PD-L1 and PD-L2 on malignant Reed–Sternberg cells and on inflammatory cells in the tumor microenvironment
- PD-L1 expression in cHL frequently occurs in the setting of genetic amplification of the 9p24.1 locus
- Prognosis for patients with relapsed cHL is poor



PD-L1 expression in cHL

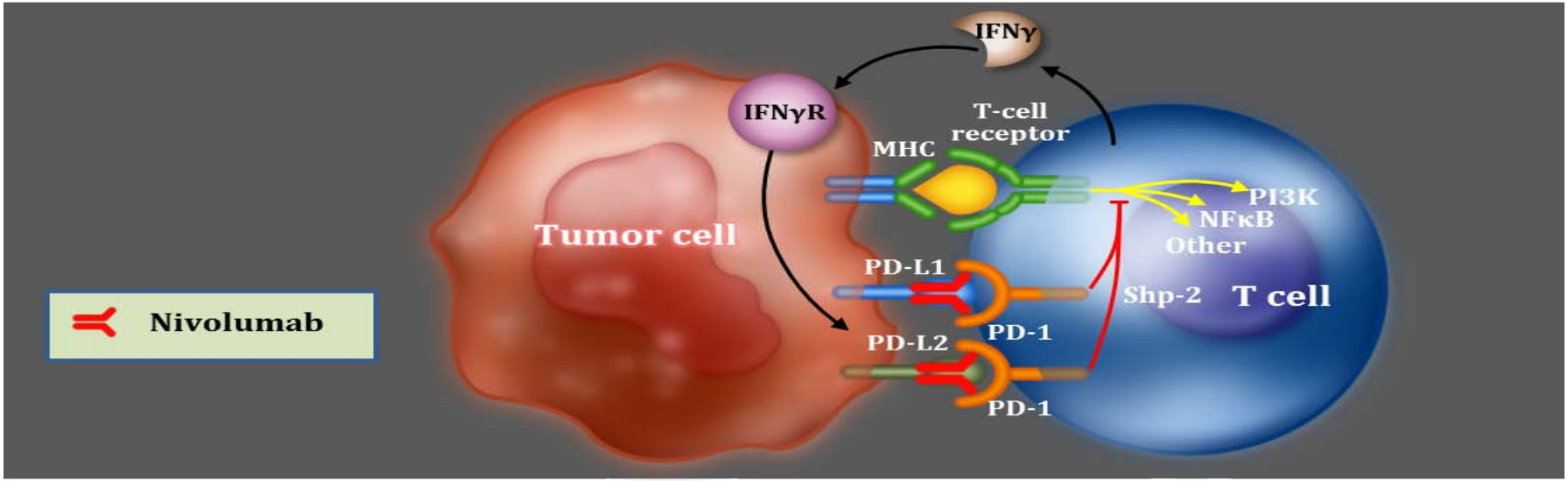


PD-L1/L2 copy gains and amplification visible by FISH

Chen BJ, et al. *Clin Cancer Res.* 2013;19:3462–3473.
Ansell SM, et al. *N Engl J Med*. 2015;372:311–319.

Anti-PD1 - Nivolumab Mechanism of Action

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody targeting the programmed death-1 (PD-1) immune checkpoint pathway



IFN, interferon; MHC, major histocompatibility complex; PI3K, phosphoinositide 3-kinase.

Initial Responses and response duration

Ansel et al N Engl J Med 2015; 372:311-319

	cHL (n = 23)
	76 Weeks
Overall response, n (%)	20 (87)
Partial response rate, n (%)	15 (65)
Complete response rate , n (%)	5 (22)
24-week progression-free survival, %	87%
Duration of response, median (range)	NR (18–82+)

Select Treatment-Related Adverse Events

Adverse Event	cHL (n = 23)	
	Any Grade, n (%)	Resolved, %
Gastrointestinal	4 (17)	
Diarrhea	3 (13)	100
Colitis	1 (4)	100
Hepatic	2 (9)	
ALT increased	1 (4)	100
AST increased	1 (4)	100
Blood alkaline phosphatase increased	1 (4)	0
Pulmonary	1 (4)	
Pneumonitis	1 (4)	100
Skin	5 (22)	
Rash	4 (17)	100
Pruritus	3 (13)	100
Pruritic rash	1 (4)	100
Skin hypopigmentation	1 (4)	0
Endocrine disorders		
Hyperthyroidism	4 (17)	75
Hypersensitivity/infusion reaction	2 (9)	
Bronchospasm	1 (4)	100
Infusion-related reaction	1 (4)	100

- **All AEs were Grade 1/2 except colitis and pneumonitis which were Grade 3**
- **There were no Grade 4 or Grade 5 AEs and no treatment-related deaths**

Select Treatment-Related Adverse Events

Adverse Event	cHL (n = 23)	
	Any Grade, n (%)	Resolved, %
Gastrointestinal	4 (17)	
Diarrhea	3 (13)	100
Colitis	1 (4)	100
Hepatic	2 (9)	
ALT increased	1 (4)	100
AST increased	1 (4)	100
Blood alkaline phosphatase increased	1 (4)	0
Pulmonary	1 (4)	
Pneumonitis	1 (4)	100
Skin	5 (22)	
Rash	4 (17)	100
Pruritus	3 (13)	100
Pruritic rash	1 (4)	100
Skin hypopigmentation	1 (4)	0
Endocrine disorders		
Hyperthyroidism	4 (17)	75
Hypersensitivity/infusion reaction	2 (9)	
Bronchospasm	1 (4)	100
Infusion-related reaction	1 (4)	100

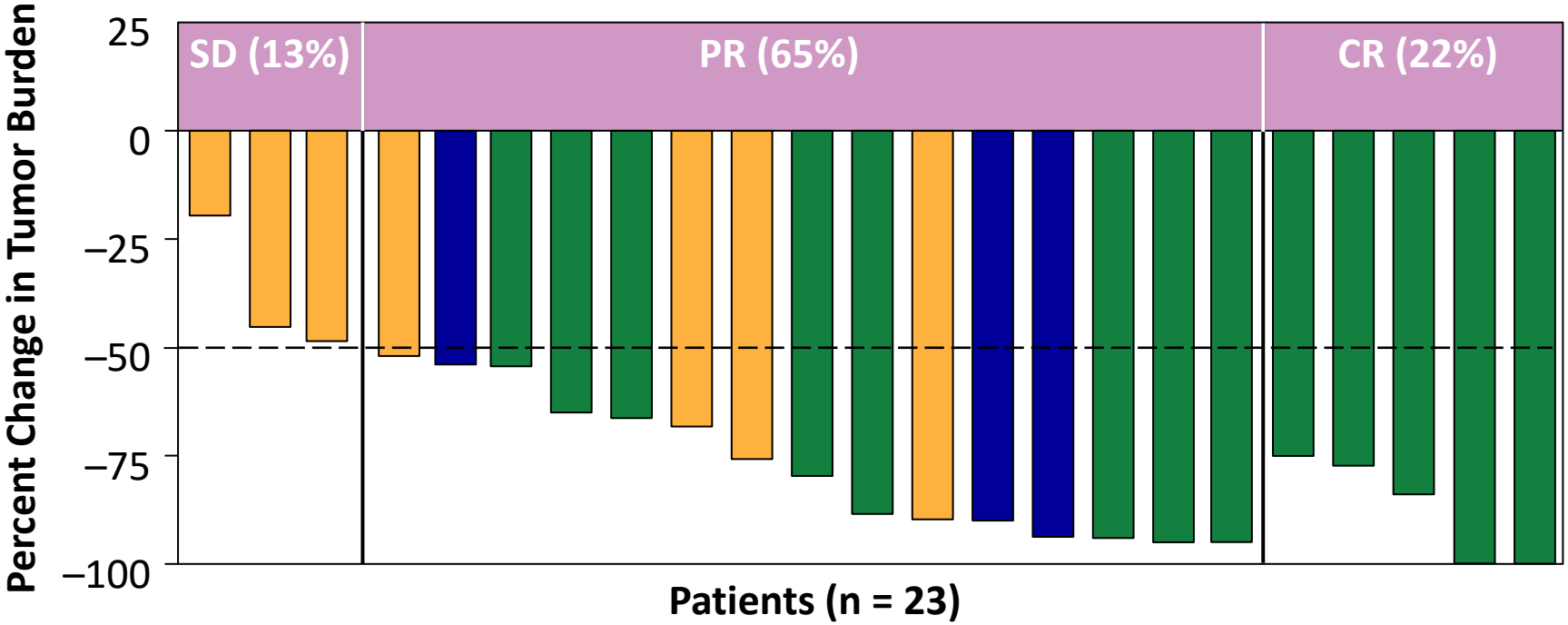
- All AEs were Grade 1/2 except colitis and pneumonitis which were Grade 3
- There were no Grade 4 or Grade 5 AEs and no treatment-related deaths

Treatment-Related Serious Adverse Events

Adverse Event, n (%)	cHL (n = 23)	
	Any Grade	Grade 3–4
Any event	3 (13)	2 (9)
Lymph node pain	1 (4)	0 (0)
Pancreatitis	1 (4)	1 (4)
Myelodysplastic syndrome	1 (4)	1 (4)

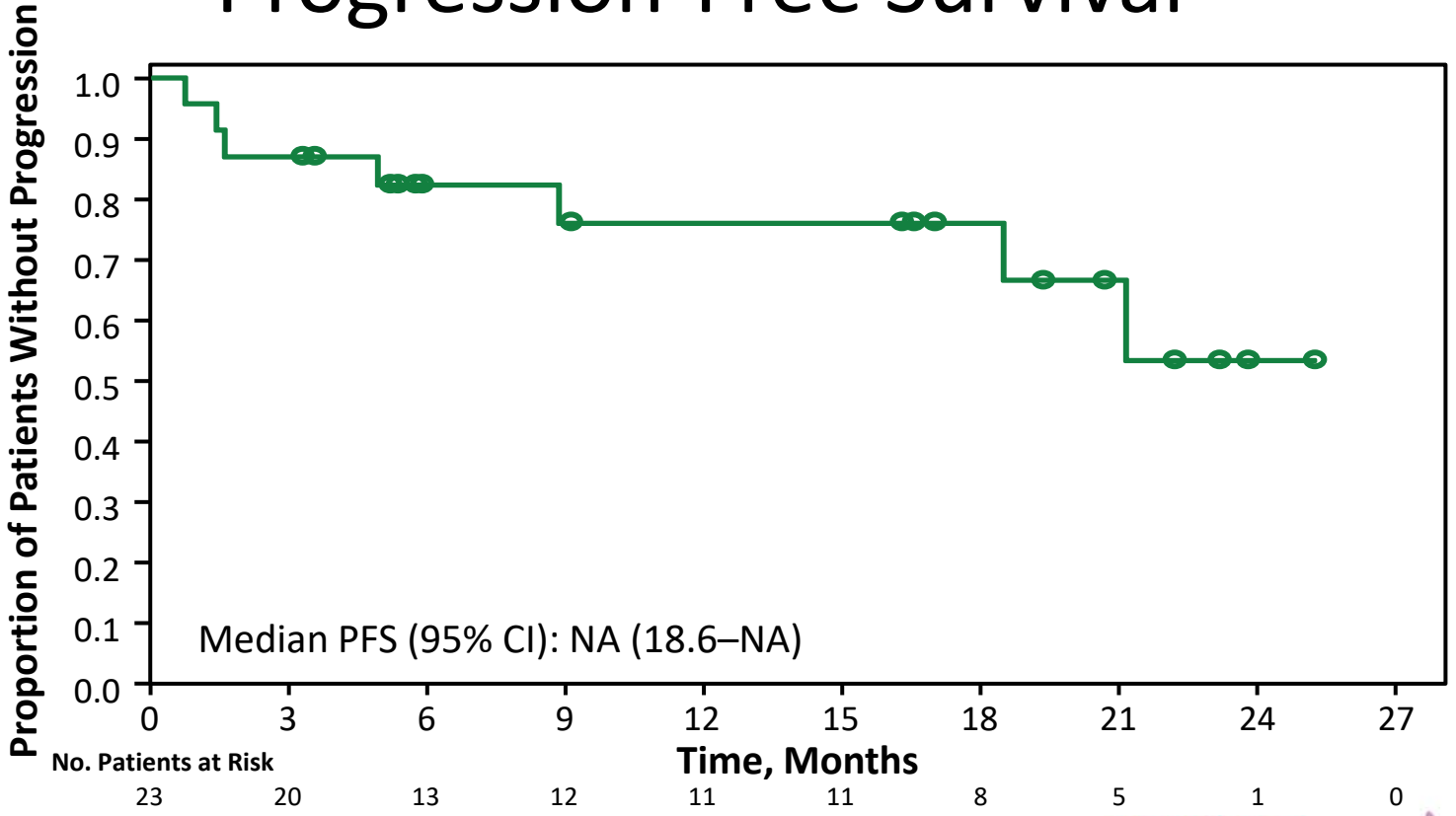
- **3 patients discontinued due to adverse events**
  - **2 discontinuations were study drug related (pancreatitis, myelodysplastic syndrome)**

Best Response



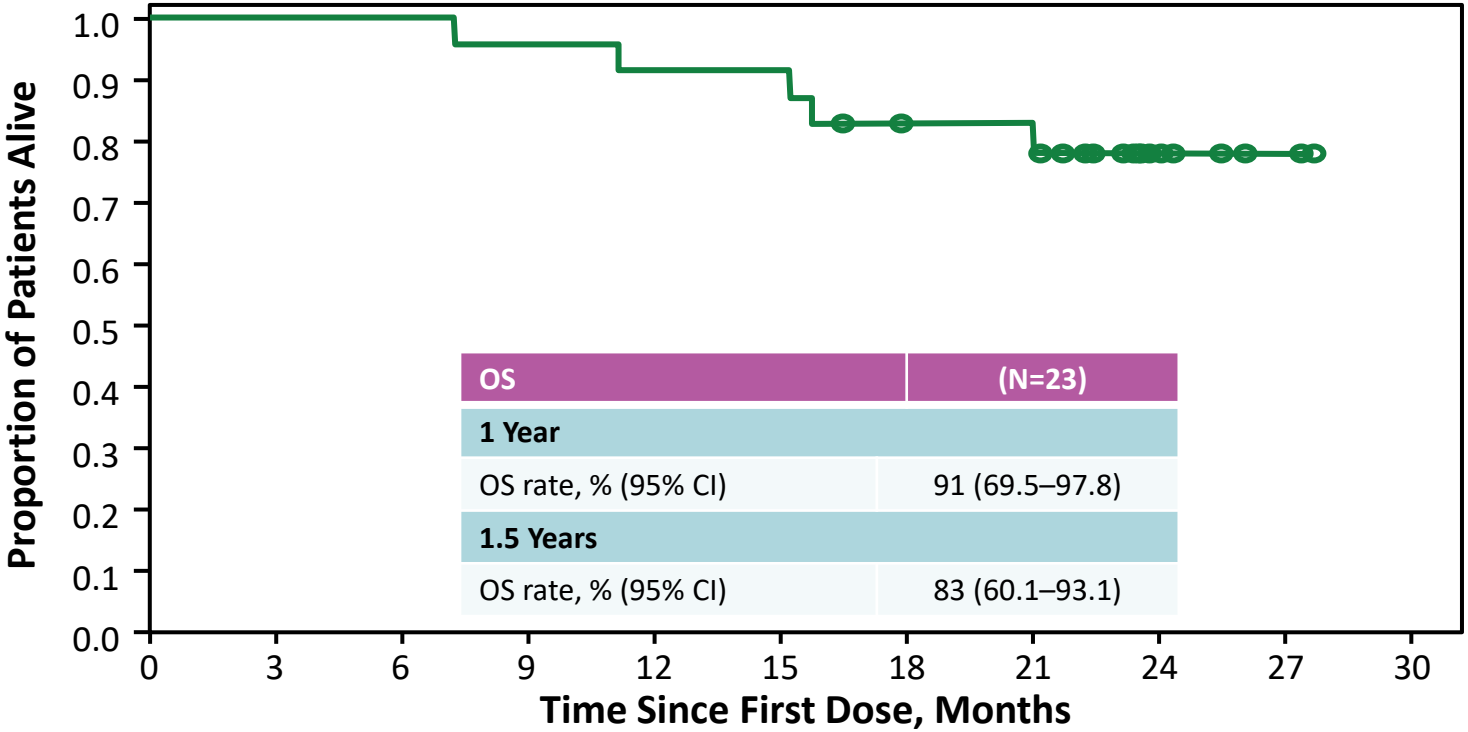
[a]Maximum clinical benefit, transplant, or toxicity

Progression-Free Survival



- **Median follow-up: 101 wks**
- **Median PFS not reached**

Overall Survival



OS	(N=23)
1 Year	
OS rate, % (95% CI)	91 (69.5–97.8)
1.5 Years	
OS rate, % (95% CI)	83 (60.1–93.1)

No. Patients at Risk

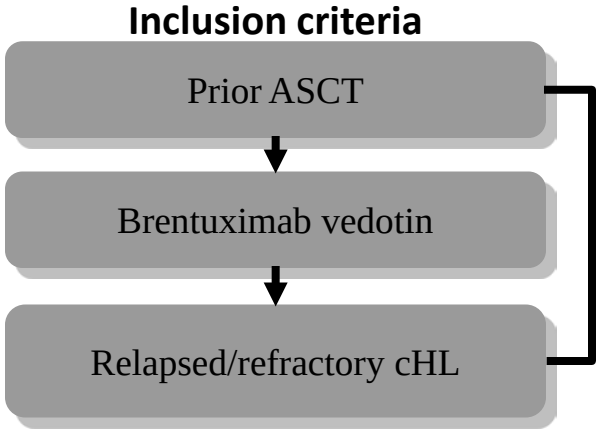
23	23	23	22	21	21	18	17	7	2	0

Summary

- With longer follow-up, nivolumab in cHL resulted in :
  - Durable CRs and PRs
  - Consistent and manageable adverse event profile
- Long-term therapy (up to 2 yr) appears feasible
- Durable responses and encouraging PFS and OS
- These data support the further investigation of nivolumab in patients with cHL in a larger, ongoing phase 2 study, CHECKMATE 205

CheckMate 205: Study Design, Cohort B
Engert et al 2015

- Registrational phase 2 study conducted in Europe and North America



Single-arm
Nivolumab 3 mg/kg
(every 2 weeks)
Treatment until disease progression or unacceptable toxicity

Minimum follow-up:
6 months

Primary endpoint
- ORR assessed by IRRC[a]

Secondary and other endpoints
- IRRC-assessed DOR for complete and partial remission
- Investigator-assessed ORR and DOR
- IRRC-assessed PFS
- OS
- Safety
- QoL
- Biomarkers

- Patients could elect to discontinue nivolumab and proceed to allogeneic hematopoietic stem cell transplantation

[a]Per the 2007 International Working Group (IWG) criteria. IRRC = independent radiologic review committee

Treatment Status

Disposition, n (%)	Patients (N = 80)
Patients treated	**80 (100)**
Patients still on treatment	**51 (64)**
Patients off treatment	**29 (36)**
Reason off treatment	
Disease progression	13 (16)
Study drug toxicity	4 (5)
Patient proceeded to allogeneic HSCT	6 (8)
Other: patient request, lost to follow-up, not reported, or investigator decision	6 (8)

- All patients who stopped nivolumab to receive HSCT were alive at data cut-off

Response Rates

	IRRC (N = 80)	Investigator (N = 80)
Objective response rate, n (%)	**53 (66)**	**58 (73)**
95% CI	55–76	61–82
Best overall response, n (%)		
Complete remission	7 (9)	22 (28)
Partial remission	46 (58)	36 (45)
Stable disease	18 (23)	18 (23)
Progressive disease	6 (8)	3 (4)
Unable to determine	3 (4)	1 (1)

Patients with no prior response to most recent brentuximab vedotin treatment	IRRC (N = 43)	Investigator (N = 43)
Objective response rate, n (%)	**31 (72)**	**35 (81)**

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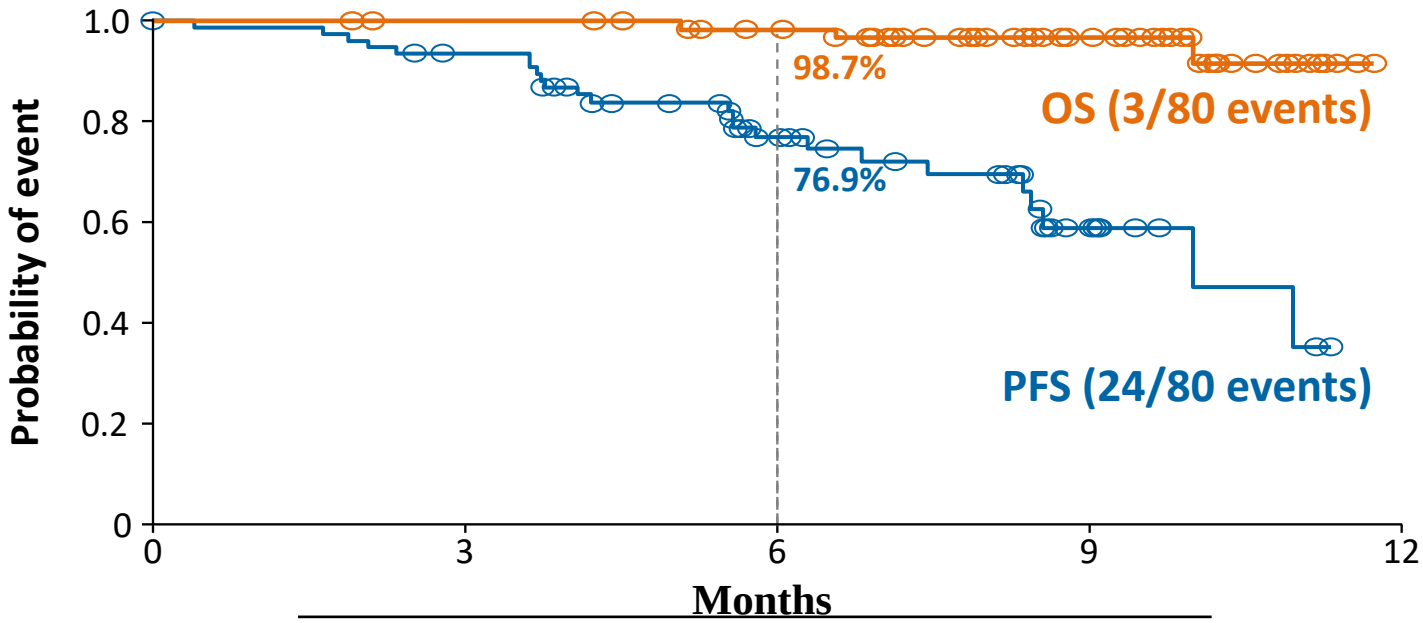
Progression-Free and Overall Survival



Median follow-up (range)	**8.9 months** (1.9–11.7)
Median PFS (95% CI)	**10.0 months** (8.41–NA)
PFS rate at 6 months (95% CI)	**76.9%** (65%–85%)
Median OS	**Not reached**
OS rate at 6 months (95% CI)	**98.7%** (91%–100%)

PFS per IRRC assessment

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Adverse Events

Total patients with an event (%)	Any grade	Grade 3–4
Any AE	79 (99)	32 (40)
Treatment-related AE	72 (90)	20 (25)
Treatment-related AE leading to discontinuation:	3 (4)	2 (3)
Autoimmune hepatitis	1	1
Increased ALT and AST	1	1
Multi-organ failure*	1	0
Treatment-related serious AE	5 (6)	0
Treatment-related death	0	0

- Serious AEs (SAEs) included pyrexia, tumour progression, arrhythmia, infusion reaction, septic meningitis, and pneumonia (≤4% each)
- *One patient experienced a grade 5 SAE of multi-organ failure due to Epstein Barr virus–positive T-cell lymphoma

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Summary

- In this registrational study in heavily pretreated patients with cHL who had failed ASCT and brentuximab vedotin, nivolumab demonstrated:
  - High ORR (IRRC-assessed ORR of 66%); investigator-assessed ORR of 73%
  - Durable responses, including durable partial responses, 62% ongoing responses
  - Median time to response of 2.1 months
  - Acceptable safety profile, consistent with previous reports
- On May 17, 2016, the U. S. Food and Drug Administration granted accelerated approval to nivolumab for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin (Adcetris).

Phase 1b KEYNOTE-013 KEYTRUDA® (Pembrolizumab), Anti-PD-1 Therapy, in Relapsed/Refractory Classical Hodgkin Lymphoma

- Pembrolizumab 10 mg/kg every two weeks relapsed/refractory classical HL progressed after brentuximab vedotin after failure of ASCT, or transplant-ineligible (n=29).
- Median time to response was 12 weeks
- Adverse events (≥2 patients) included hypothyroidism (n=3), pneumonitis (n=3), constipation (n=2), diarrhea (n=2), nausea (n=2), hypercholesterolemia (n=2), hypertriglyceridemia (n=2) and hematuria (n=2)
- Sixteen patients (55%) experienced at least one treatment-related adverse event of any grade
  - Grade 3 AEs in 3 patients: axillary pain, hypoxia, joint swelling, and pneumonitis; no Grade 4 AEs reported

PD1 – programmed death 1; ASCT – autologous stem cell transplantation; AEs – adverse events

Moskowitz C et al. ASH 2014. Oral 290

Phase 1b KEYNOTE-013 KEYTRUDA® (Pembrolizumab) Anti-PD-1 Therapy, in Relapsed/Refractory Classical HL

Antitumor Activity by International Harmonization Project Response Criteria*

	Transplant Ineligible or Refused n=9 (%)	**Transplant Failure n=20 (%)**	**Total n=29 (%)**
Overall Response Rate	**4 (44)**	**15 (75)**	**19 (66)**
Complete Remission	**2 (22)**	**4 (20)**	**6 (21)**
Partial Remission	2 (22)	11 (55)	13 (45)
Stable Disease	3 (33)	3 (15)	6 (21)
Clinical Benefit Rate	**7 (78)**	**18 (90)**	**25 (86)**
Progressive Disease	2 (22)	2 (10)	4 (14)

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Moskowitz C et al. ASH 2014. Oral 290

PD-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment

Philippe Armand, et al Blood 2015 126:584

- ORR among the 31 patients was 65% (90% CI, 48-79).
- Five patients achieved CR (16%), 15 partial remission (48%), and 7 (23%) stable disease as their best response.
- With a median follow-up of 9.7 (1.3-17.5) months, median DOR not been reached (0+ to 13.4+ months).
- As of the data cut-off, 14 patients (45%) remained on treatment; 2 (6%) patients discontinued for toxicity, 12 (39%) for progression, and 3 (10%) for other reasons.
- Of the 20 responses, 14 are ongoing.

PD-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment

Philippe Armand, et al Blood 2015 126:584

- Eleven patients had evaluable pre-treatment tumor tissue (archival or obtained for study). Among them, 10 (91%) were PD-L1+ by **immunohistochemistry (IHC).**
- Among 6 available tumor samples obtained at week 13, 4 (57%) were PD-L1+. Additionally, 10/10 patients assessed for PD-L2 expression by IHC showed high levels of PD-L2 staining.
- Based on **flow cytometry** analyses, a significant increase was observed at the 13-week time point in the absolute number of circulating total lymphocytes, T cells (CD4 and CD8 subsets), as well as NK cells.
- **NanoString RNA profiling** of pre- and post-treatment blood samples showed that several prespecified gene expression signatures were significantly upregulated with treatment, including the **10-gene IFN-γ-induced signature**, the 18-gene expanded immune signature, and the 13-gene TCR signature.

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PD-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment

Philippe Armand, et al Blood 2015 126:584

- **Conclusions:** PD-1 blockade with pembrolizumab was associated with a favorable safety profile and a high response rate in a very heavily pretreated cohort of patients with cHL.

- Responses appear durable with ongoing follow-up.

- Biomarker analyses confirm the frequent presence of PD-L1 and PD-L2 in tumors and further suggest that pembrolizumab results in an expansion of circulating T- and NK-cell populations, as well as in activation of IFN-γ.

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Conclusions

- Anti-PD1 mAb are likely to play an important role in management of relapsed and refractory HL
- Role of anti-PD1 in other lymphoma much less well defined and requires further study most likely in combinations with RT other immune checkpoint inhibitors and targeted therapies
- Timing dose and scheduling of RT with immunoregulatory agents requires further investigation
- Many new immune checkpoint inhibitors being investigated (Tim-3, Lag-3)
- Biomarkers of response and toxicity required

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Summary : radiotherapy - immunothrapy

- RT can induce immunogenic tumour cell death (ICD)

  - Understanding more about effect of RT dose and fractionation on DAMP release and ICD will be important in making progress

- RT a potentially important component to improve systemic anti-tumour immunity

  - Overcoming extrinsic tumor micro-environmental immunosuppressive factors critical to exploiting systemic anti-tumour immune responses to RT

- The efficacy of RT can be greatly enhanced in combination with immunoregulatory agents and holds great promise to improve outcome for a range of cancers

  - Well designed clinical trials required with high quality translational science including immunological biomarkers of response

Acknowledgements

- Steve Ansel
- Phillipe Arnaud
- Andreas Engert

Questions

- Thanks for listening

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KING'S HEALTH PARTNERS

Pioneering better health for all

KING'S College LONDON

University of London

Guy's and St Thomas' NHS

NHS Foundation Trust

Imaging in the Management of Lymphoma

Prof George Mikhaeel

Professor of Radiation Oncology
King's College London
Consultant Clinical Oncologist
Guy's & St Thomas' Hospital
London, UK

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Outline

- Staging
- Response assessment

Lugano Classification
2014

- RT planning

Imaging in Modern RT for Lymphoma

Old RT	Modern RT
Large volume + high dose	Smaller **volume** + lower **dose**
Conventional Sim	**CT** Sim
2D planning: Anatomical borders related to bony landmarks	**3D** outlining
Simple calculation	**Computerised** calculation – 3D dosimetry
No correction for tissue inhomogeneity	Correction for tissue **inhomogeneity**
AP / PA	Possibility of **complex** field arrangement if appropriate
No OAR doses	**OAR** doses and constraints
Blocks	**MLC**s
Sometimes: only 1 field treated daily or patients turned round between fields	**All** fields treated daily Pt in same position ± **immobilisation**
Crude verification of delivery (beam film)	Verification with **Image-guidance** (IGRT)

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Recent advances in RT based on imaging

- Diagnostic imaging:
  - Improvement in CT
  - PET/CT

Improved diagnostic accuracy & pt selection

- RT planning:
  - CT-based planning: 3D target definition, Thin-slice CT, 4D CT
  - Multimodality image fusion: PET & MRI

Improved T targeting & Normal tissue sparing

- RT Delivery:
  - Treatment verification with IGRT
    - Set-up modification
    - Planning modification (Adaptive RT)
  - DIBH

Improved accuracy of delivery

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The Lugano Classification - 2014

- 2007: IWG-IHP criteria
- 2009: Deauville workshop
- 2011: 11-ICML-Lugano: workshop
- 2012: Imaging workshop, London
- 2013: 12-ICML-Lugano: workshop
  Menton PET meeting
  International consultation
- 2014: 2 JCO consensus publications

(clinical practice & phase III studies)

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The Lugano Classification - 2014

JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

JCO 2014 32:3048-3058

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

Sally F. Barrington, N. George Mikhaeel, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Müeller, Lawrence H. Schwartz, Emanuele Zucca, Richard I. Fisher, Judith Trotman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O'Doherty, Roland Hustinx, Alberto Biggi, and Bruce D. Cheson

JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

JCO 2014 2: 3059-3067

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

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What is new?

(compared to 2007)

Staging:

- PET/CT for routine staging of FDG-avid Lymphomas
- BMBx not required for HL and most DLBCL
- Simplification of Ann Arbor

Response assessment:

- PET/CT is standard of care for remission assessment
- Standard tool for reporting response is 5-PS (Deauville criteria)
- Deauville Criteria can be used to assign metabolic response categories (CMR, PMR, NMR, PMD)
- Revised CT size criteria

Surveillance:

- Routine scanning discouraged.

PET/CT as standard imaging for staging

- PET-CT should be used for routine staging of FDG-avid lymphomas
  - Most lymphomas take up FDG
  - More accurate > CT especially **EN sites**
  - PET results in more **upstaging** > down staging
  - Management change: largest effect in FL (upstaging of early disease)

- PET is important for **RT volumes <IFRT**

- can be used to direct biopsy
  (especially if suspected transformation)

- A baseline PET-CT scan is also desirable for subsequent response assessment

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Which lymphomas are FDG avid?

Histology and numbers of patients included in studies	Percentage FDG-avid
Hodgkin lymphoma (n = 489)	97 - 100
Diffuse Large B cell lymphoma (n = 446)	97 - 100
Follicular lymphoma (n = 622)	91 - 100
Mantle cell lymphoma (n = 83)	100
Burkitt lymphoma (n = 24)	100
Lymphoblastic lymphoma (n = 6)	100
Marginal zone lymphoma, nodal (n = 14)	100
MALT marginal zone lymphoma (n = 227)	54 - 81
Marginal zone lymphoma, splenic (n = 13)	53 - 67
Marginal zone lymphoma, unspecified (n = 12)	67
Small lymphocytic lymphoma (n = 49)	47 - 83
Peripheral T-cell lymphoma (n = 93)	86 - 98
Anaplastic large T-cell lymphoma (n = 37)	94 -100 (but only 27% of cutaneous sites)
Natural killer/T-cell lymphoma (n = 80)	83 - 100
Angioimmunoblastic T-cell lymphoma (n = 31)	78 - 100
Enteropathy type T-cell lymphoma (n = 20)	67 - 100
Mycosis fungoides (n = 24)	83 -100
Sezary Syndrome (n = 8)	100 (but only 62% of cutaneous sites)
Primary cutaneous anaplastic large T-cell lymphoma (n =14)	40-60
Lymphomatoid papulosis (n = 2)	50
Subcutaneous panniculitis-like T-cell lymphoma (n = 7)	71
Cutaneous B-cell lymphoma (n = 2)	0

EN MZL + SLL

some cut T

Modified from Weiler-Sagie et al

Bone Marrow Assessment

- HL: PET/CT only (BMBx no longer required)

High sensitivity and specificity
Large studies showed: v small % of false -ve but no change in therapy

- DLBCL: PET/CT enough in most cases

High sensitivity and specificity
But: small % of **false –ve** (small volume 10-20%)
possibility of missing **LG** component
Histologically +ve BM may be more **prognostically** important
So BMBx indicated only if result may change management

- FL / LG-NHL: BMBx is mandatory

High false negative rate

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review

Annals of Oncology 00: 1–7, 2013
doi:10.1093/annonc/mdt533

Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary?

H. J. A. Adams[1], T. C. Kwee[1*], B. de Keizer[1], R. Fijnheer[2], J. M. H. de Klerk[3], A. S. Littooij[1] & R. A. J. Nievelstein[1]

[1]Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht; [2]Departments of Hematology; [3]Nuclear Medicine, Meander Medical Center, Amersfoort, The Netherlands

Table 5. Results of seven of nine included studies that allowed calculation of sensitivity and specificity

Study (year)	Sensitivity (%)		Specificity (%)	
	Value	95% CI	Value	95% CI
Cortés-Romera et al. (2013) [17]	100	75.3–100	100	92.6–100
Agrawal et al. (2013) [18]	87.5	47.3–99.7	100	85.2–100
Muzahir et al. (2012) [19]	100	90.5–100	100	95.8–100
El-Galaly et al. (2012) [20]	94.9	87.4–98.6	100	99.0–100
Mittal et al. (2011) [22]	100	47.8–100	86.7	59.5–98.3
Cheng et al. (2011) [23]	100	39.8–100	100	87.2–100
Moulin-Romsee et al. (2010) [24]	100	81.5–100	100	94.5–100
Pooled estimate	96.9	93.0–99.0	99.7	98.9–100

N = 955 patients ; weighted summary proportion of patients PET/CT negative and BMB positive 1.1% (95% CI 0.6 – 2.0 %)

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Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-013-2623-4

REVIEW ARTICLE

FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis

Hugo J. A. Adams · Thomas C. Kwee · Bart de Keizer · Rob Fijnheer · John M. H. de Klerk · Rutger A. J. Nievelstein

Reference	Sensitivity (%)		Specificity (%)	
	Value	95 % CI	Value	95 % CI
Khan et al. [23]	94.3	80.8 – 99.3	100	96.2 – 100
Cortes-Romera et al. [24]	95.8	78.9 – 99.9	100	93.9 – 100
Berthet et al. [25]	93.9	79.8 – 99.3	99.0	94.6 – 100
Hong et al. [26]	70.8	48.9 – 87.4	100	94.5 – 100
Pelosi et al. [27]	84.0	63.9 – 95.5	100	96.2 – 100
Ribrag et al. [29]	88.9	51.8 – 99.7	100	89.7 – 100
Pooled estimate	88.7	82.5 – 93.3	99.8	98.8 – 100

N = 654 patients ; weighted summary proportion of patients PET/CT negative and BMB positive 3.1% (95% CI 1.8 – 5.0 %)

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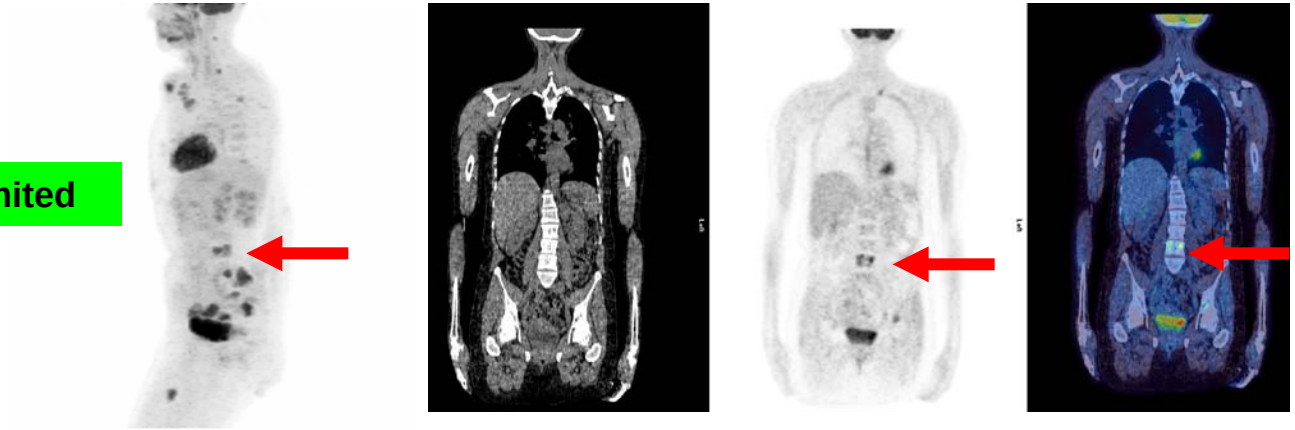
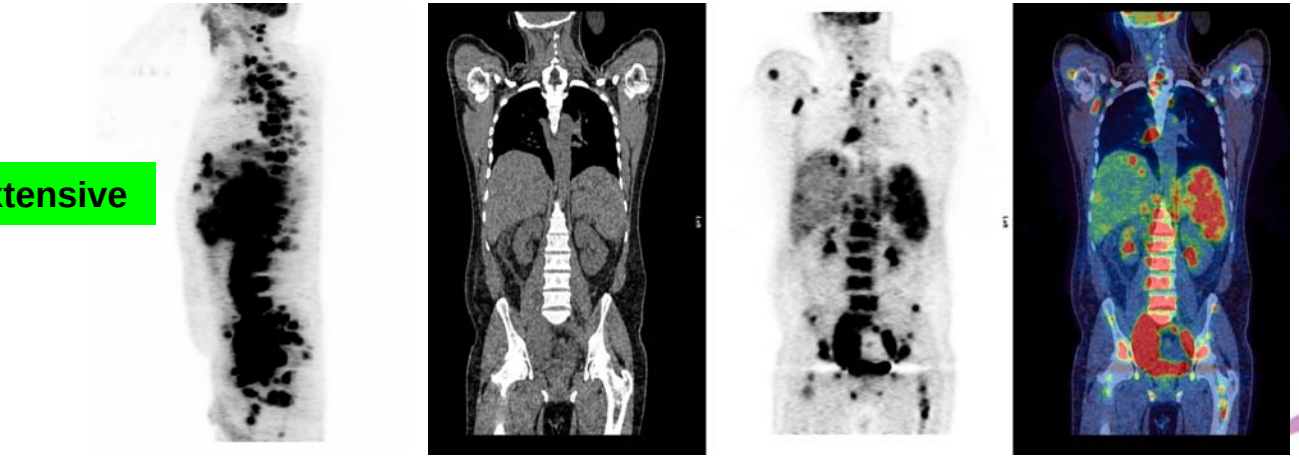
BM Involvement

Limited



Extensive



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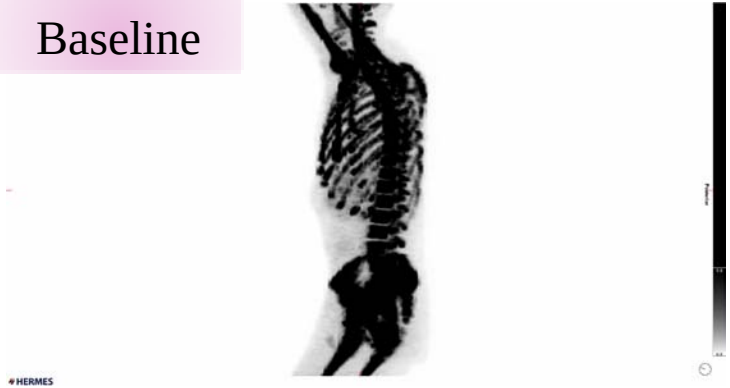
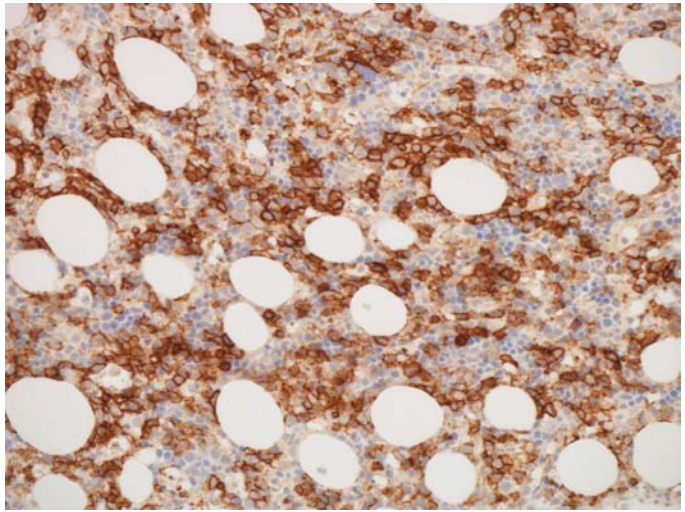
Interpretation of DIFFUSE marrow uptake

Diffuse uptake may not necessarily indicate BMI

- indicates hyperplasia in HL
- occurs with chemotherapy & GCSF
- can indicate BMI or hyperplasia in DLBCL

Baseline





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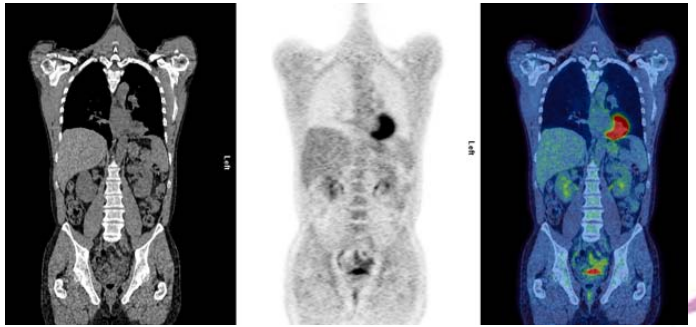

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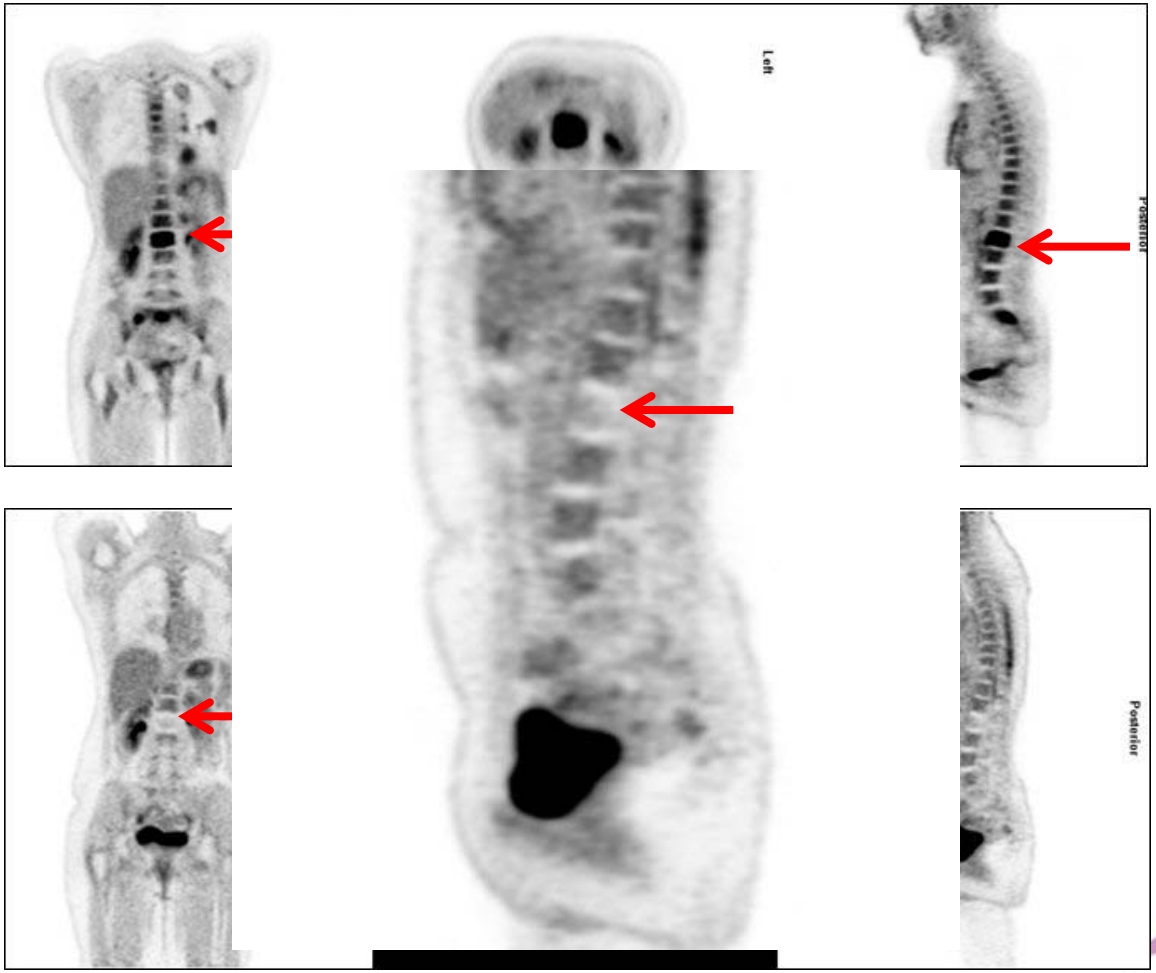
Baseline

Response



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Splenic Involvement

SIZE:

- Wide range of size (race, body size and height)

- Normal size spleen may contain lymphoma and enlarged spleen may be due to other causes

- No agreement on:
  - Single, multiple or volumetric measurement
  - Cut-off

Recommendations for splenic evaluation:

- PET/CT: Best method (diffuse, focal)

- CT: cut-off for splenomegaly is 13cm vertical length

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Simplified Ann Arbor

A / B designation only for HL

Table 2. Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

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Prognostic value of Initial Bulk

- Bulk is –ve prognostic factor

- Bulk in the era of Prognostic scores
  - Prognostic factor (still one of the best ways to reflect disease burden).
  - Choice of Therapy: bulk is part of many treatment algorithms
  - Radiotherapy is frequently based on bulk

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Stage & Bulk in prognostic indices

Disease	Subgroup		Prognostic Index	Includes stage?	Includes bulk?
Hodgkin	Early stage	**GHSG** **EORTC**	Early & Intermediate Favourable &Unfavourable	**Yes** **Yes**	**Yes** **Yes**
	Advanced st	**Hasenclever (IPS)**	Score 0-7	**Yes**	No
DLBCL	All	**IPI**	Score 0-5 (4gps)	**Yes**	No
	<60 ys	**aaIPI**	Score 0-4 (4gps)	**Yes**	No
	Early stage	**Stage adjusted IPI**	Score 0-5		**Yes**
	Rituximab	**R-IPI**	As IPI, but 3 groups	**Yes**	No
	All	**NCCN-IPI**	As IPI but Score 0-8	**Yes**	No
Follicular	all	**FLIPI**	Score 0-5 (3gps)	**Yes**	No
		FLIPI-2	Score 0-5 (3gps)	No	**Yes**
Mantle	all	**MIPI**	Score 0-11	No	No

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Recommendations for Bulk

- No agreed definition:
  - HL: 10 cm or 1/3 thoracic diam at any level?
  - DLBCL: 6 – 10 cm? 7.5cm?
  - FL: 6 cm?

- Maximum tumour dimension (MTD) on CT should be recorded at staging*

  * *Term X need no longer be used*

- Methods of Volumetric Measurement of total tumour volume should be explored

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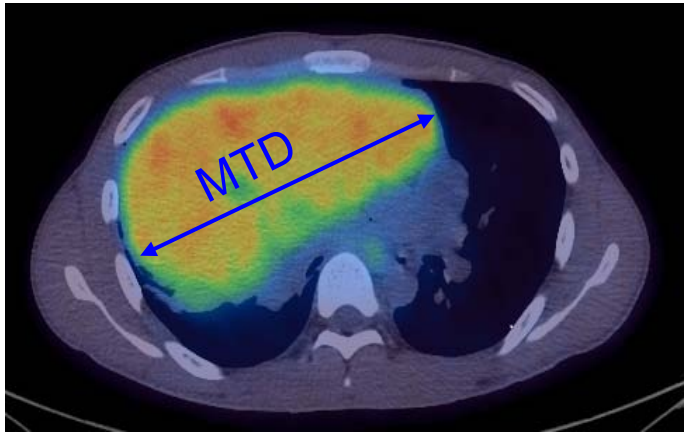
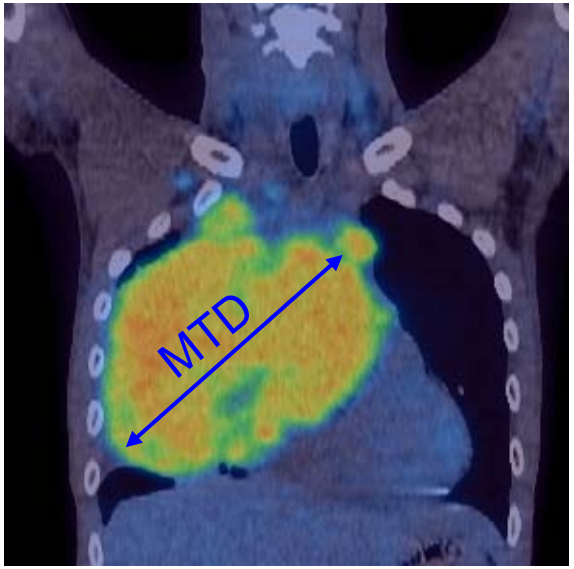
Maximum Tumour Dimension (MTD)

longest dimension in transverse & longitudinal planes

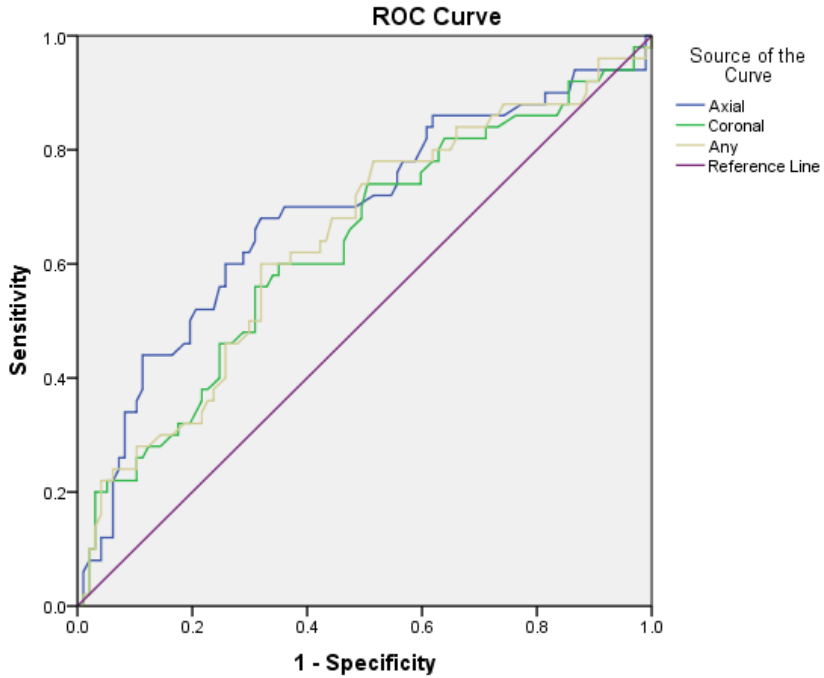




Max Tumour Dimension (147 DLBCL pts)

MTD (cm)	Transverse	longitudinal
Mean	7.5	9.0
Median	6.6	8.4
Range	1.0 – 20.7	1.0 – 28.1

MTD best cut-off to predict PFS



	Optimal Cut off (cm)	Sensitivity	Specificity
Axial	7.55	.68	.68
Coronal	9.3	.60	.65
Any direction	10.35	.60	.68

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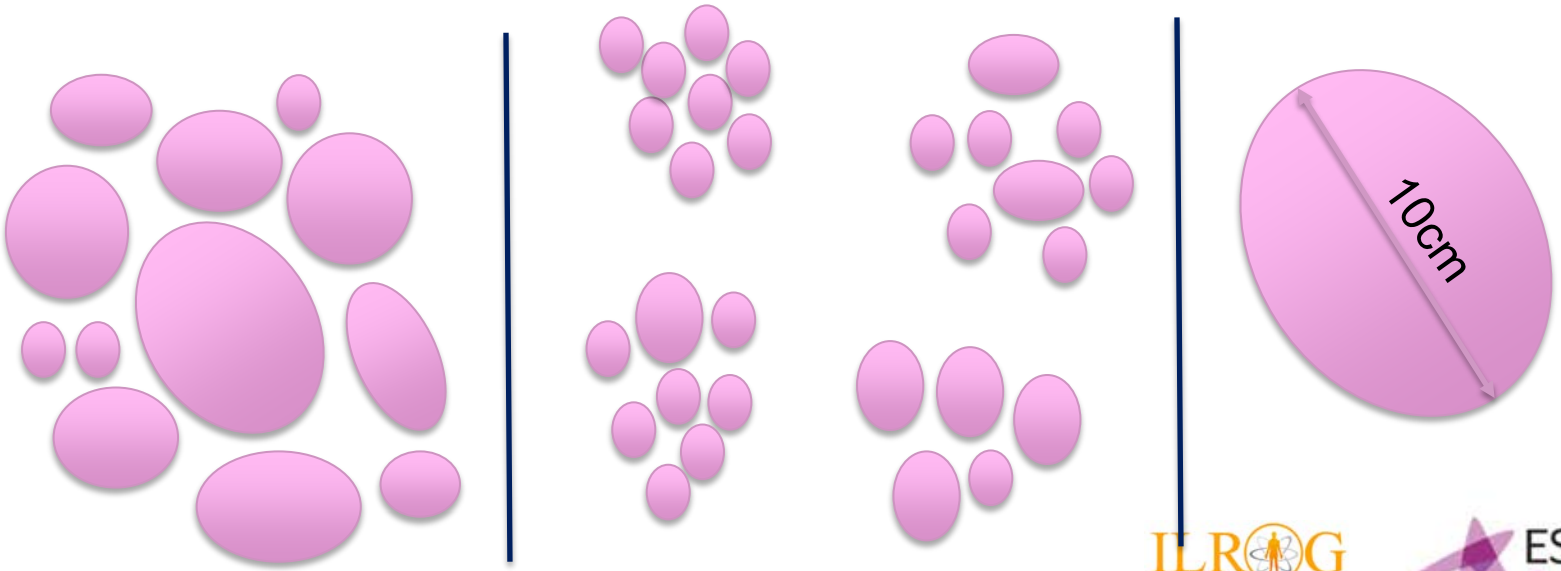
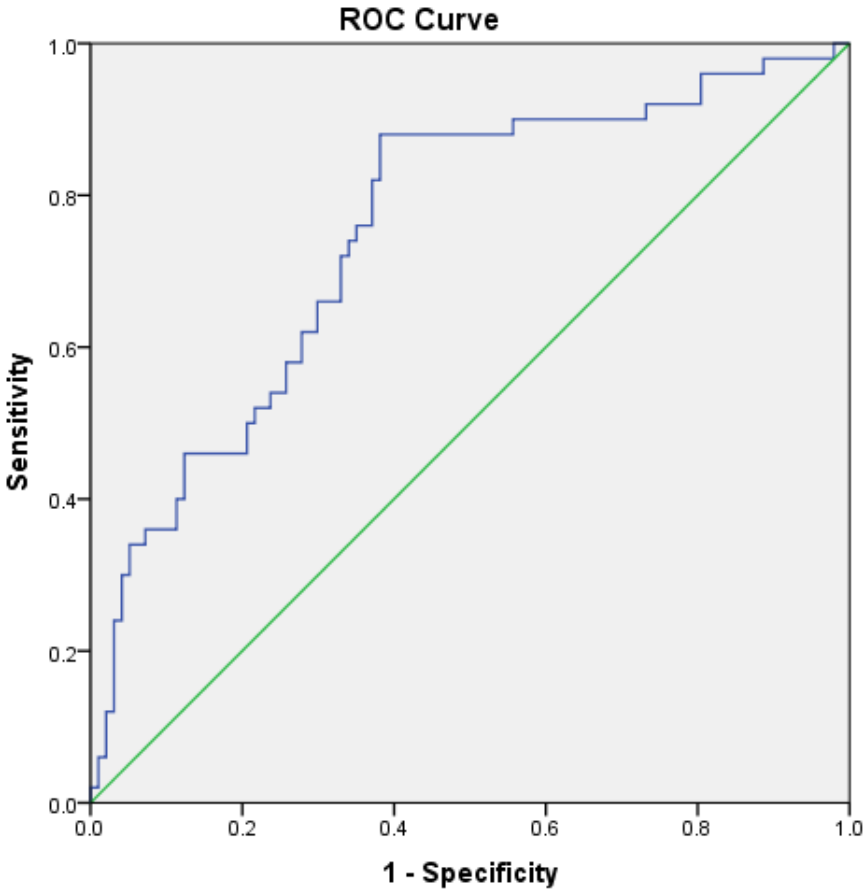
Metabolic tumour volume

- Total volume of metabolically active tumour tissue, defined by FDG uptake above a specific threshold.
- More accurate representation of tumour burden

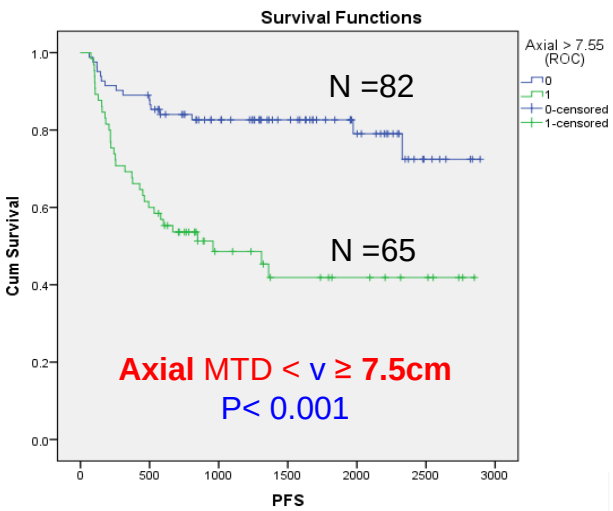


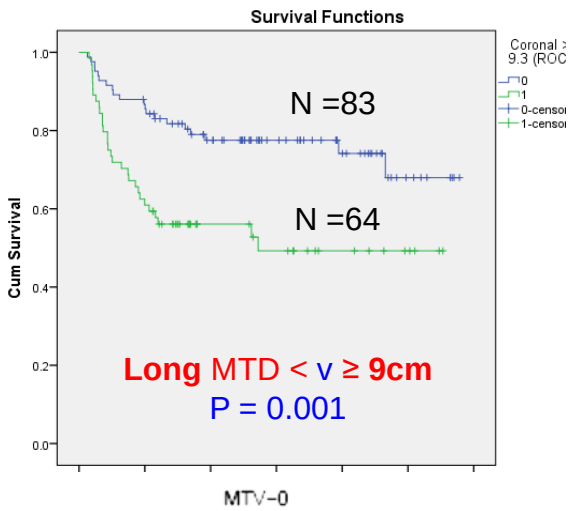
MTV Cut-off

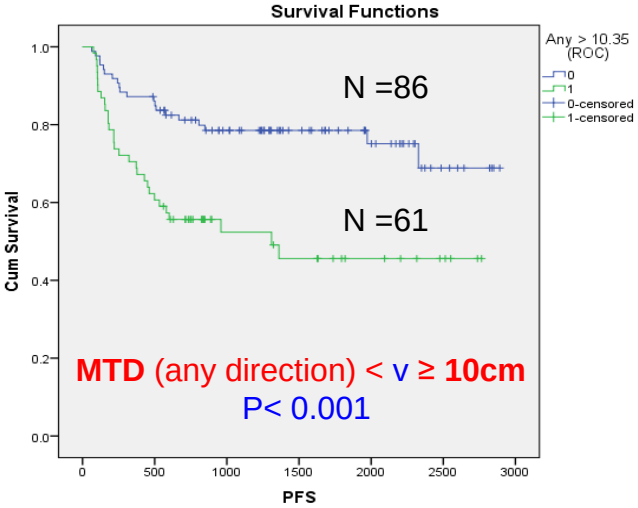


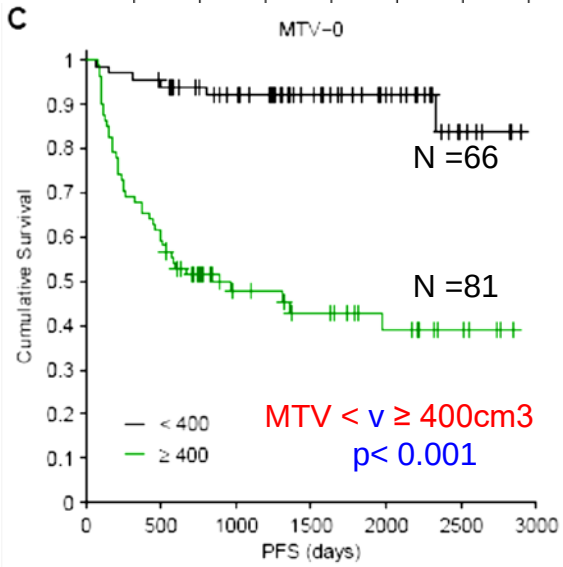
Best cut-off =

396.12 (400) cm3









Mikhaeel ASTRO 2015

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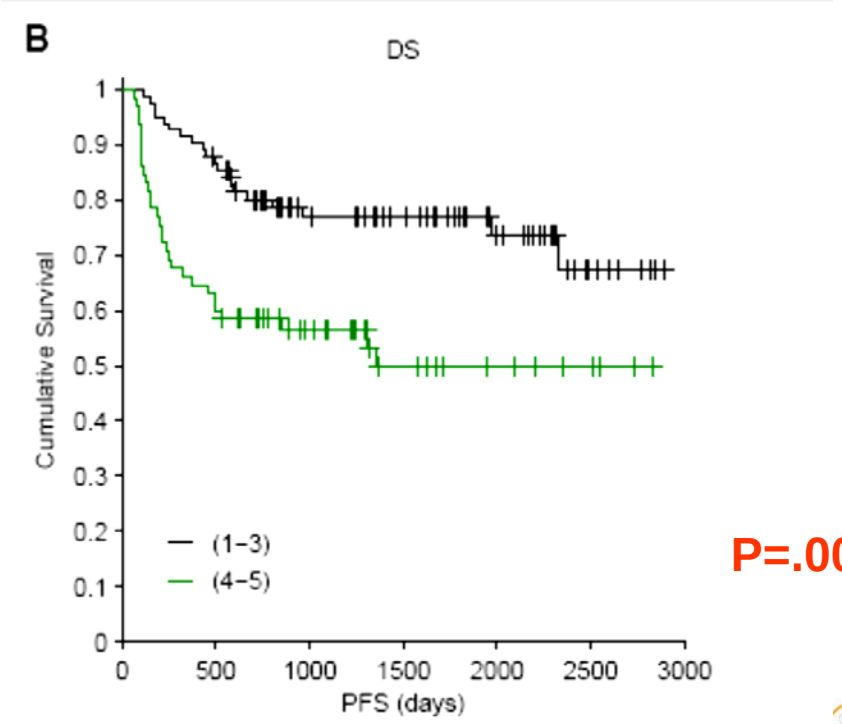
Combining baseline MTV with early response

PET after 2 cycles
RCHOP



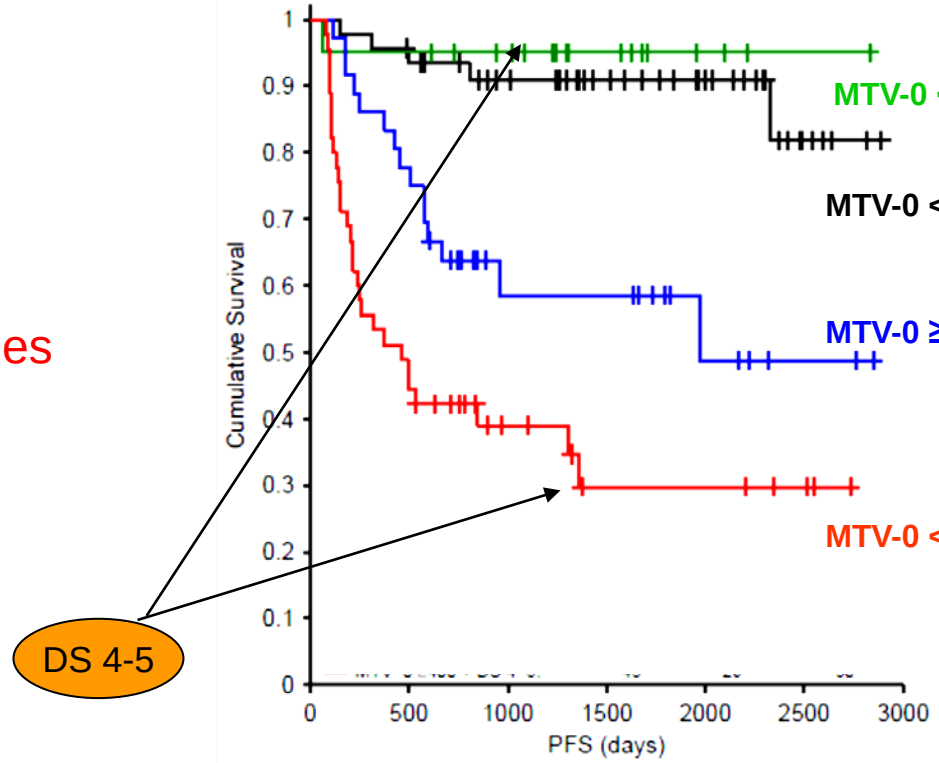
P=.001

DLBCL:

Baseline MTV

+

DS after 2 cycles



	At risk	events	5y-PFS
MTV-0 <400 + DS 4-5	20	1	95%
MTV-0 <400 + DS 1-3	46	5	90.9%
MTV-0 ≥400 + DS 1-3	36	15	58.5%
MTV-0 <400 + DS 4-5	45	29	29.7%

Mikhaeel Eur J Nucl Med 2016

Response assessment

What is new?
(compared to 2007)

Staging:
- PET/CT for routine staging of FDG-avid Lymphomas
- BMBx not required for HL and most DLBCL
- Simplification of Ann Arbor

Response assessment:
- PET/CT is standard of care for remission assessment
- Standard tool for reporting response is 5-PS (Deauville criteria)
- Deauville Criteria can be used to assign metabolic response categories (CMR, PMR, NMR, PMD)
- Revised CT size criteria

Surveillance:
- Routine scanning discouraged.

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Change from IHP to Deauville

- IHP (Juweid):
  - Lesions ≥2cm: CMR is <mediastinum (MBP)
  - Lesions <2cm: CMR is <background
- Deauville:
  - 5 degrees of response
  - MBP and liver thresholds
  - No lesion-size dependence
- Main reasons to change:
  - Change in technology
  - Accumulating data on data on 5PS:
    - Several studies reported improved PPV while maintaining NPP
    - High inter-observer agreement
    - At least 8 studies using DS

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Escalation
De-escalation

Negative scan

Score 1 no uptake

Score 2 uptake ≤ mediastinum

Score 3 uptake > mediastinum but ≤ liver

Positive scan

Score 4 uptake > liver at any site

Score 5 uptake > liver and new sites of disease

:

new areas of uptake unlikely to be related to lymphoma

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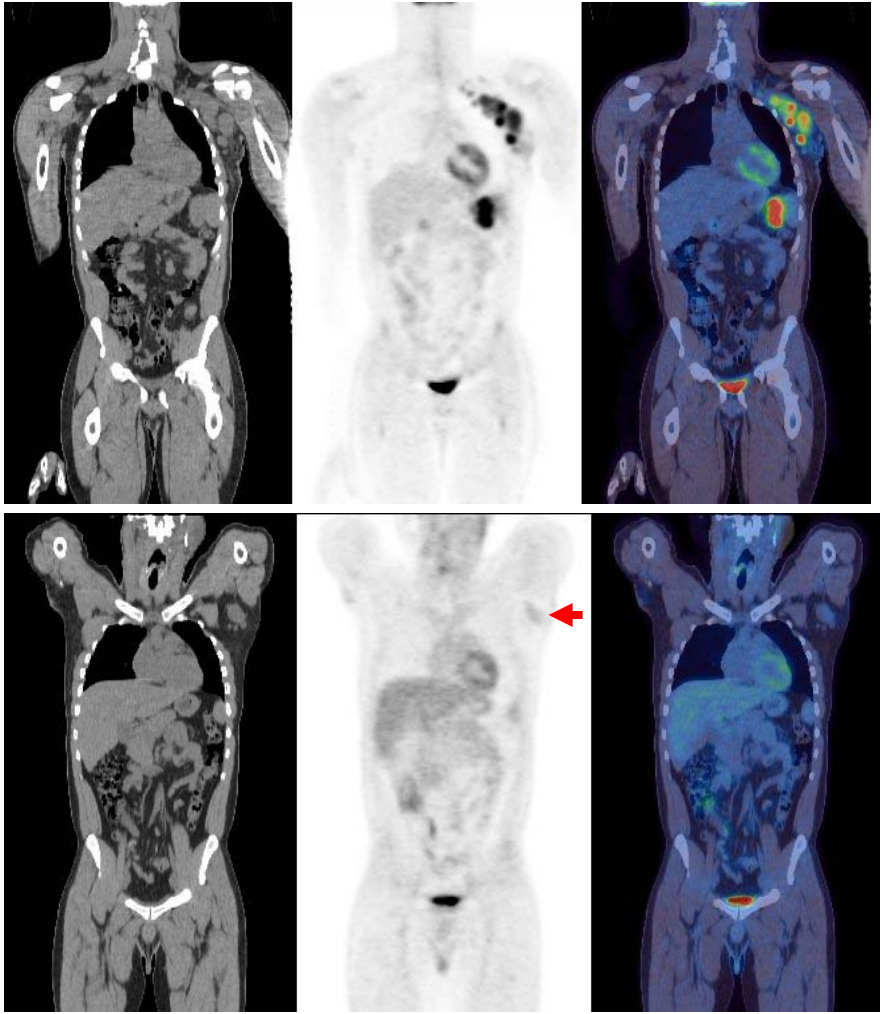
Score 3

Pre

Post



uptake > mediastinum

but < liver

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Score 3

- Main difference with IHP
- Score 3 Definition: uptake > mediast. but ≤ liver
- Is it CMR or PMR? (disease, timing, treatment)

- iPET v ePET:
  - **iPET:** good response (& subsequent Rx planned)
  - **ePET:** CMR?

- Clinical Practice v Trials:
  - Clinical practice: consider prognosis & available options (e.g. RT)
  - Trials: depending on question; escalation v de-escalation

Score 4 & 5

- Definition:
  - Score 4: **moderately** increased uptake > liver
  - Score 5: **markedly** increased uptake
    OR new lesion(s) likely to be lymphoma

- Difference between “moderate” and “marked”:
  - Moderate: ≥ 130% liver uptake (measured over a large area)
  - Marked: 2 -3 times uptake of liver

- How:
  - Visually
  - SUV aid when close (SUVmax v SUVmean)

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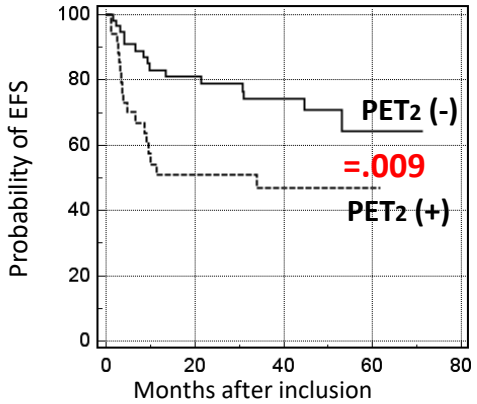
Visual vs. quantitative analysis
DLBCL 2 cycles

n = 92 PET 2

Visual analysis

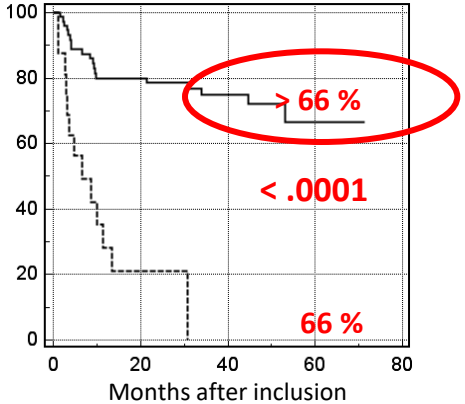


NPV=74%, PPV=50%

n = 80 PET 2

Quantitative analysis

(% reduction SUVmax)



NPV=73.6%, PPV=84.6%

Lin et al al. JNM 2007;48:1626-32

c/o M Meignan, Creteil , France

Challenges with quantitation

Standardised methods :

- PET acquisition
- QC - calibration and monitoring of cameras

Less reliable if low baseline SUV or high residual uptake

SUV cannot always be measured

(17% in Casanovas et al. Blood 2011;118:37-43)

Variation in optimal cut-offs by different groups

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Recommendation:
Quantitation for Response

- Data suggest that Quantitative methods e.g. delta SUV could be used to improve on visual analysis for response assessment in DLBCL but requires further validation in clinical trials [PS: PETAL study ASH 2014]

- Standardisation of PET methods is mandatory for use of quantitative approaches and desirable for routine clinical practice

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Revised criteria for response assessment

	PET-CT BASED RESPONSE	CT-BASED RESPONSE
	Complete Metabolic Response (CMR)	Complete Radiologic Response (CR)
	Partial Metabolic Response (PMR)	Partial Remission (PR)
	No Metabolic Response (NMR)	Stable disease (SD)
	Progressive Metabolic Dis (PMD)	Progressive disease (PD)

	PET-CT BASED RESPONSE	CT-BASED RESPONSE
	Complete Metabolic Response (CMR) **of the following**	**Complete Radiologic Response (CR)** **of the following**
Lymph nodes and Extranodal sites	**Score 1, 2, or 3* ± a residual mass**	**Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi.** **No EN sites.**
Non-measured lesion/s	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC -ve
	Partial Metabolic Response (PMR) **ANY of the following**	**Partial Remission (PR)** **ALL of the following**
Lymph nodes and extranodal sites	**Score 4,5** with reduced uptake compared with baseline and residual mass(es) of any size.** *At* these findings suggest responding disease. *At* these findings indicate residual disease	**≥ 50% decrease in SPD of up to 6 target measureable nodes and EN sites**
Non-measured lesions	Not applicable	Absent/normal, or regressed but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in spleen length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline	Not applicable

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	No Metabolic Response (NMR)	Stable disease (SD)
Lymph nodes & EN sites	**Score 4 or 5 + no significant change in uptake from baseline**.	**< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes & EN sites;**
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
	Progressive Metabolic Dis (PMD) **ANY of the following**	**Progressive disease (PD)** **ANY of the following**
Lymph nodes & EN sites	**Score 4,5 + an increase in uptake from baseline** **&/or** **New FDG-avid foci consistent with lymphoma**	**PPD Progression:** **An individual node must be abnormal with:** **• LDi > 1.5 cm &** **• Increase by ≥ 50% from PPD nadir AND** **An increase in LDi or SDi from nadir** **0.5 cm for lesions ≤ 2 cm** **1.0 cm for lesions > 2 cm** **Spleen must increase by ≥ 50% of previous increase**
Non-measured lesions	None	**New** or clear **progression** of pre-existing non-measured lesions
New lesions	**New** FDG-avid foci consistent with lymphoma rather than another aetiology eg infection/inflammation If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	**Regrowth** of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis if less than 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG avid foci.	New or recurrent involvement

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PET-CT BASED RESPONSE
Complete Metabolic Response (CMR)
Score 1, 2, or (3)* ± a residual mass
Partial Metabolic Response (PMR)
Score 4,5** with reduced uptake compared with baseline
No Metabolic Response (NMR)
Score 4,5 + no significant change in uptake from baseline.
Progressive Metabolic Dis (PMD)
Score 4,5 + an increase in uptake from baseline &/or New FDG-avid foci consistent with lymphoma

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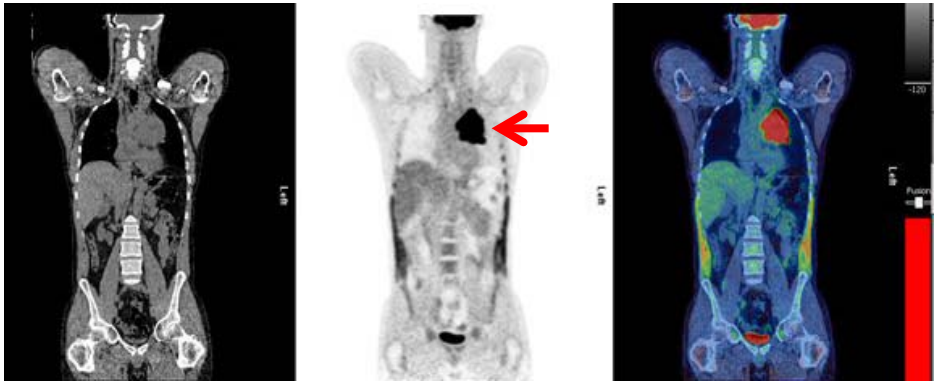
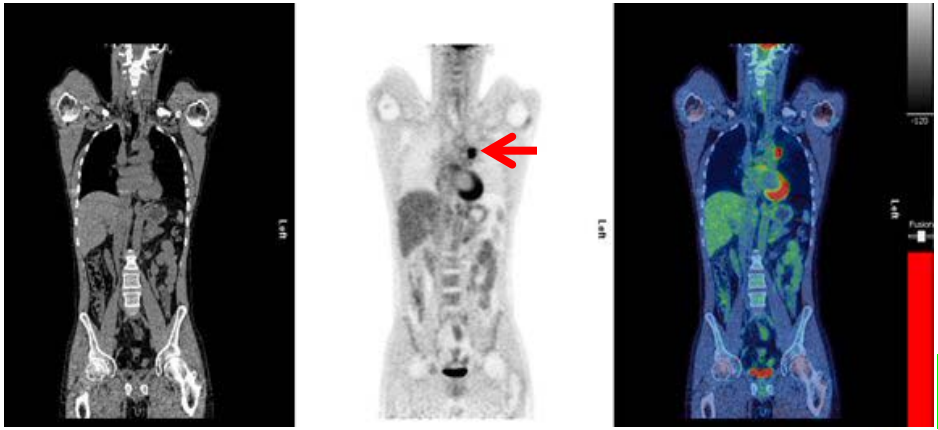
Baseline



Response



Score 5

PMR

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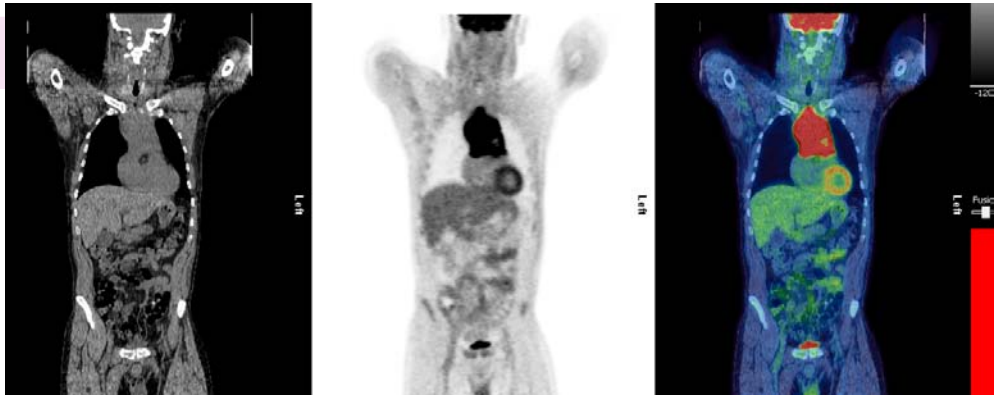
Baseline



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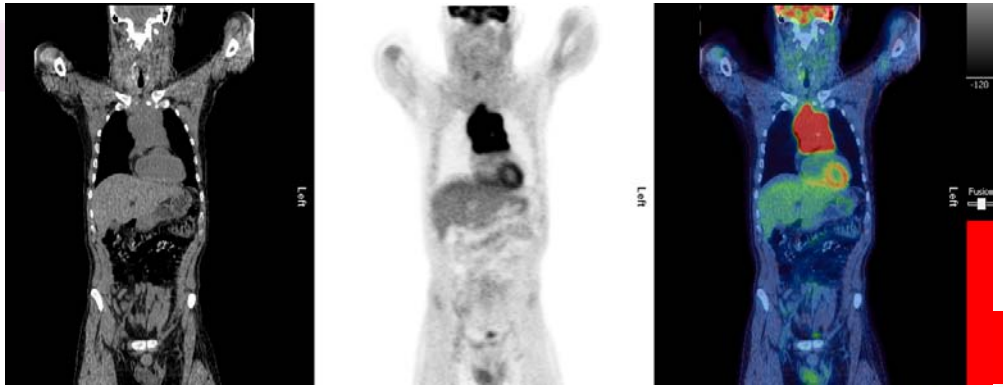

Score 5

NMR

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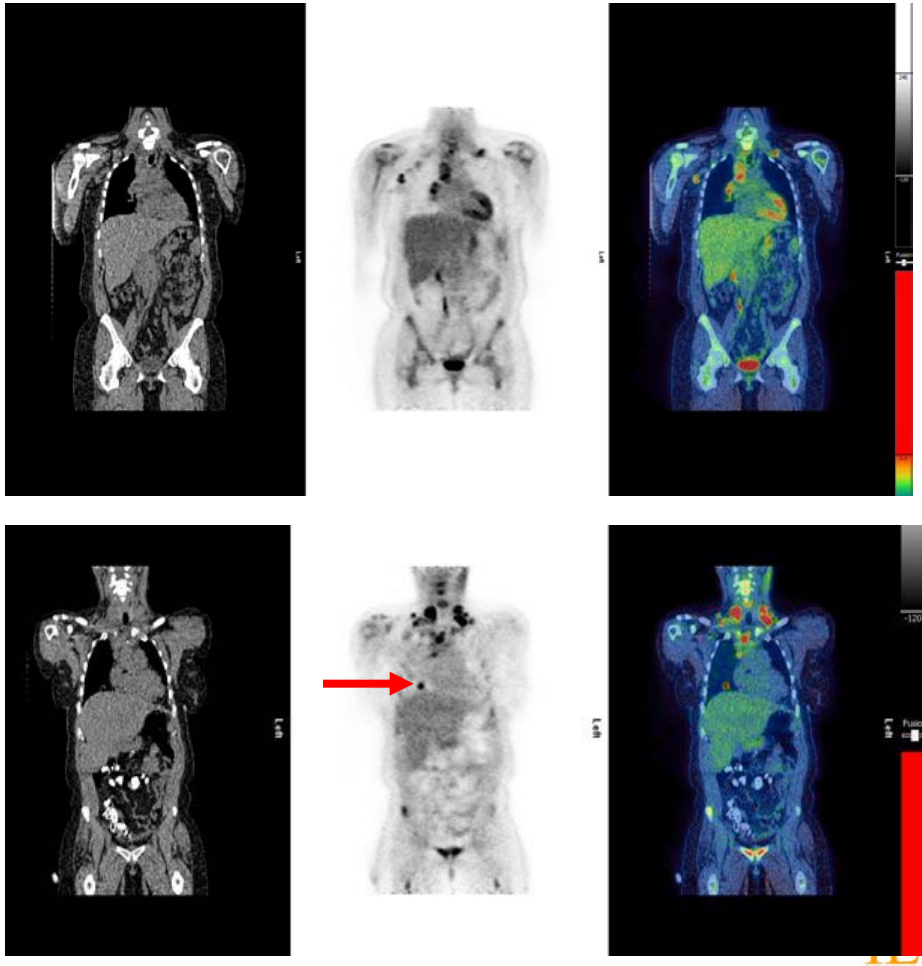

Score 5

PMD

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Recommendation:
Residual metabolic activity

- Biopsy of residual metabolically active tissue is recommended if salvage treatment is considered

Or

- an interval scan where clinical likelihood of disease is low to decide on treatment (or not)

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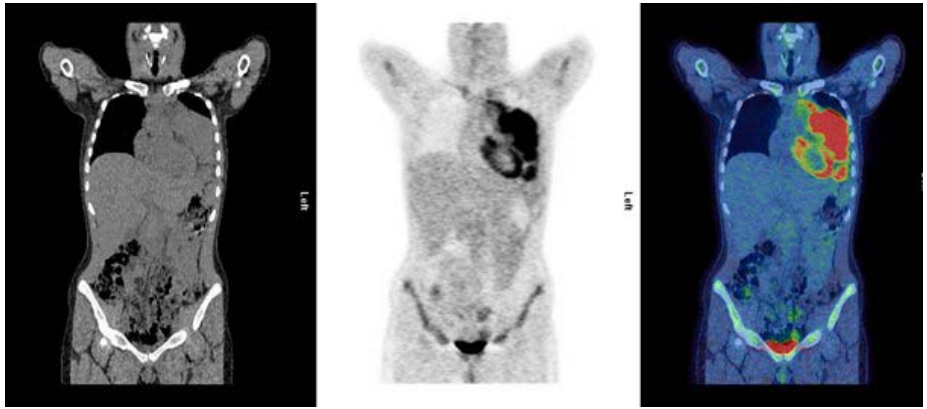
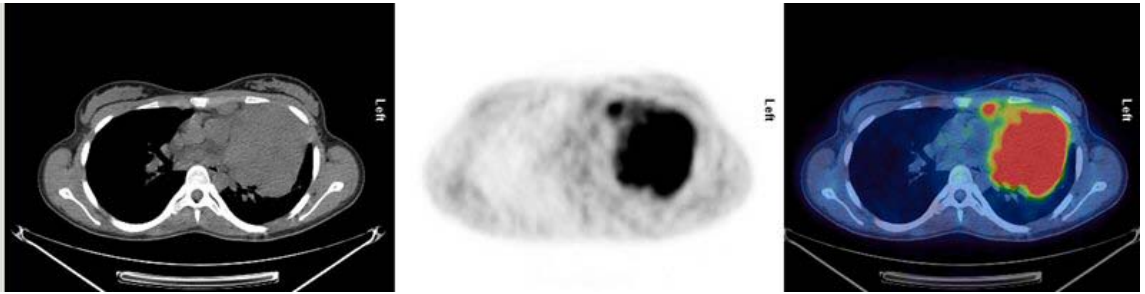
HL

Staging





Mediastinal disease; left internal mammary

& paracardiac nodes

Stage II

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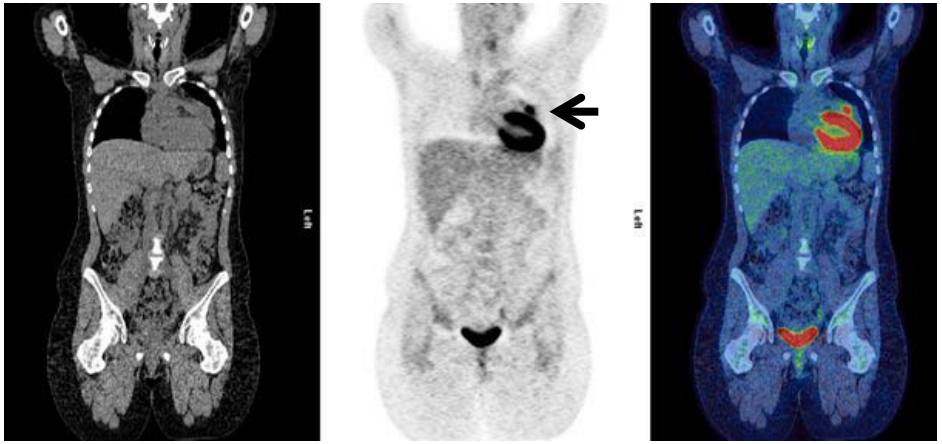
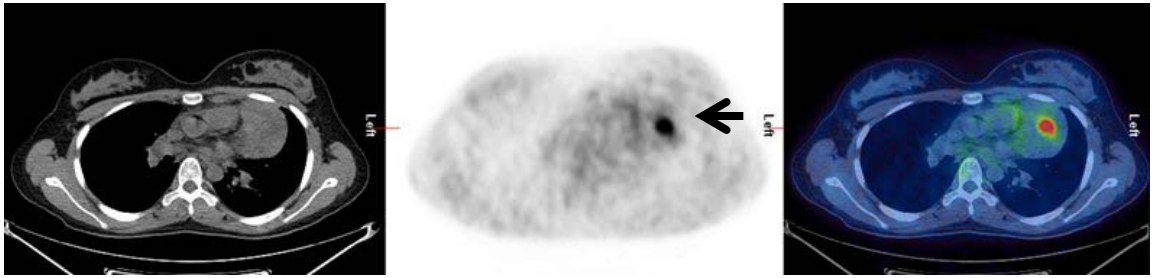
6 ABVD

PMR





Residual uptake mediastinum > Liver SUV 7.2 (more than 3 x liver) Score 5

King's College London & Guy's and St Thomas' PET Centre

ILROG International Lymphoma Radiation Oncology Group

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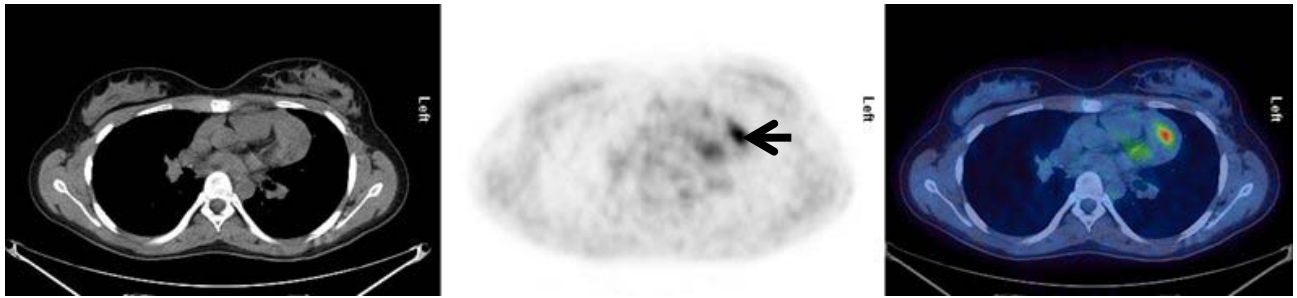
3 months post chemo + IFRT

PMR

Residual uptake mediastinum > Liver

SUV 4.4 ; Score 4

Interval scan 3 months



Residual uptake mediastinum > Liver

SUV 5.4 ; Score 4

King's College London & Guy's and St Thomas' PET Centre

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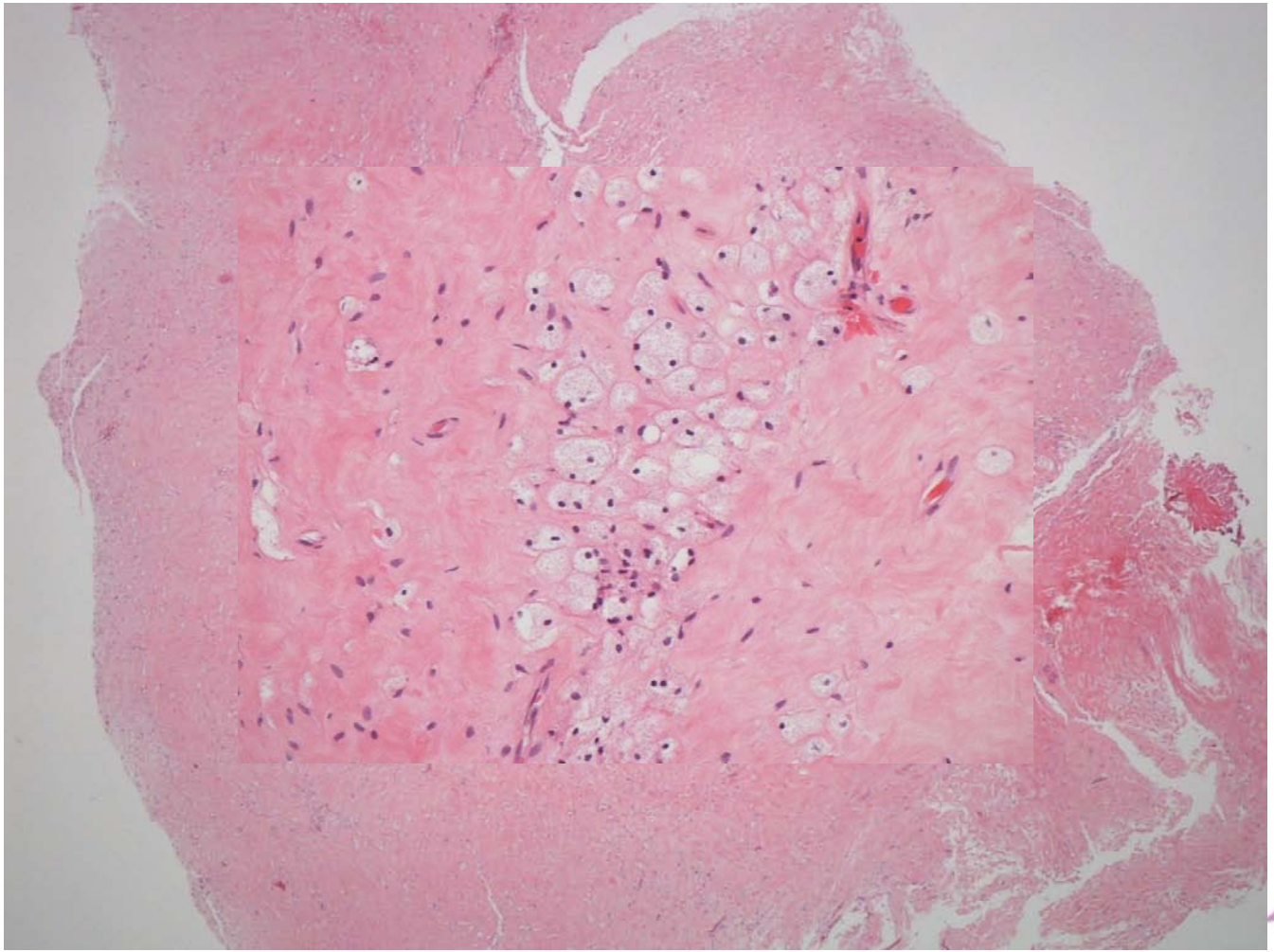

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Recent advances in RT based on imaging

- Diagnostic imaging: *Improved diagnostic accuracy & pt selection*
  - Improvement in CT
  - PET/CT

- RT planning: *Improved Targeting & Normal tissue sparing*
  - CT-based planning: 3D target definition, Thin-slice CT, 4D CT
  - Multimodality image fusion: PET & MRI

- RT Delivery: *Improved accuracy of delivery*
  - Treatment verification with IGRT
    - Set-up modification
    - Planning modification (Adaptive RT)
  - DIBH

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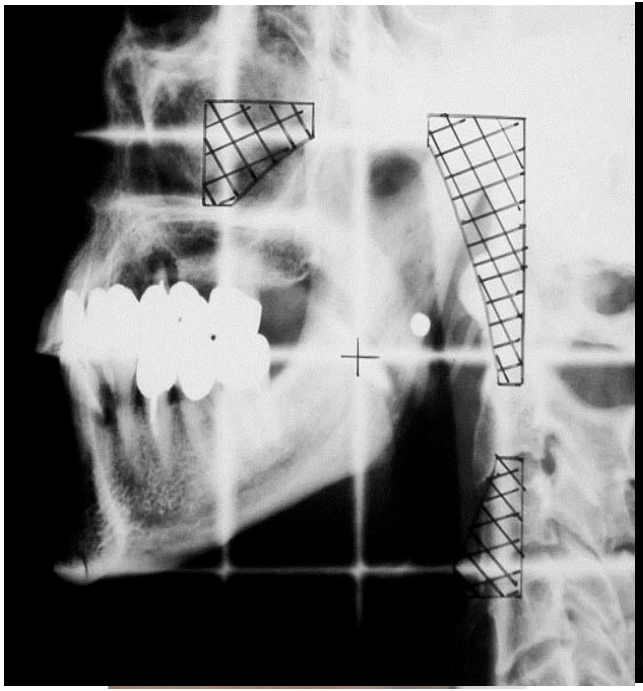
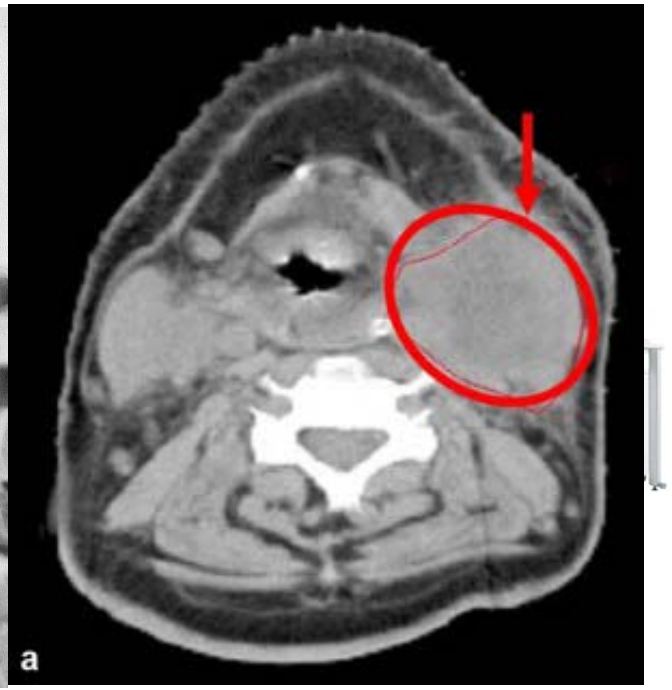
CT-based planning



Conventional Simulation



CT Simulation

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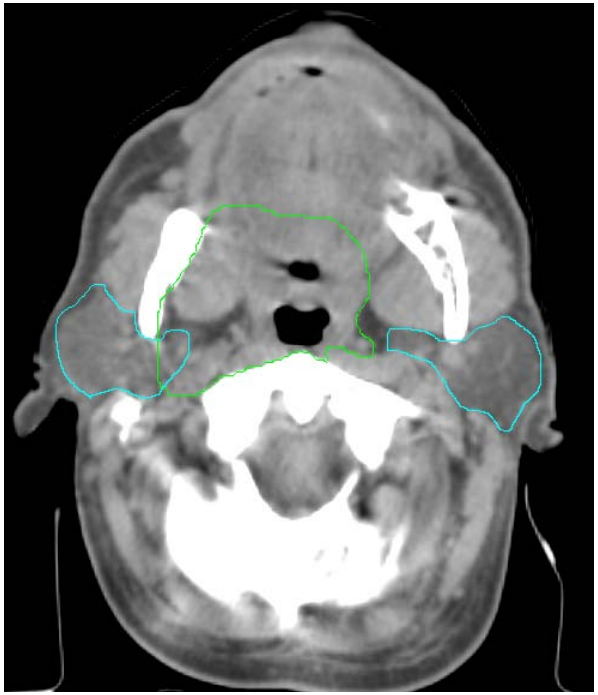
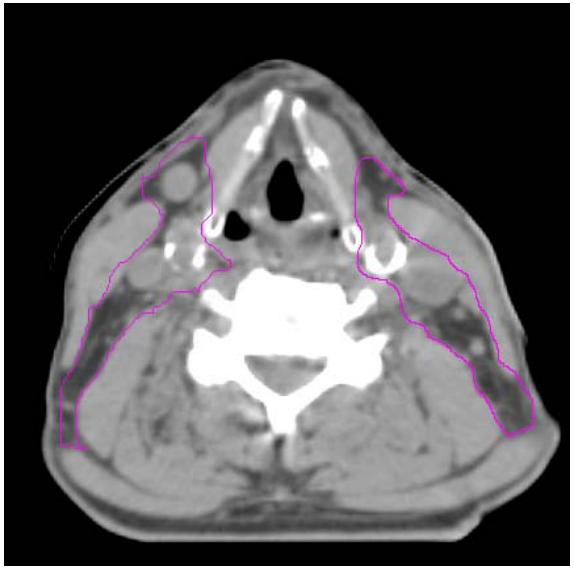
3D CT based planning



1.25 mm slices



Outlining of tumour

+ normal organs

FDG-PET for target definition

- It makes sense to use the most accurate method

- RT has changed to smaller volumes (INRT or ISRT)
- 3D-conforml / IMRT dose is more conformal to target than AP/PA

- *Accurate definition of nodal involvement is essential*
- PET is essential for volumes less than IFRT & modern techniques

- ILROG guidelines

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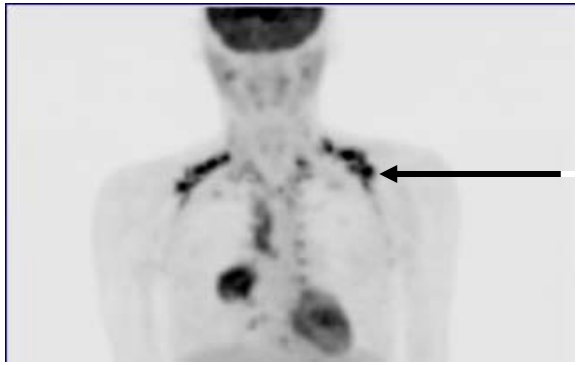
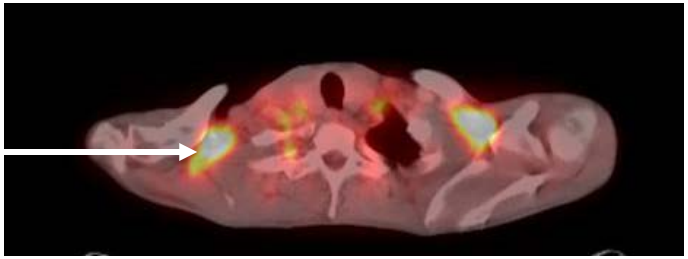
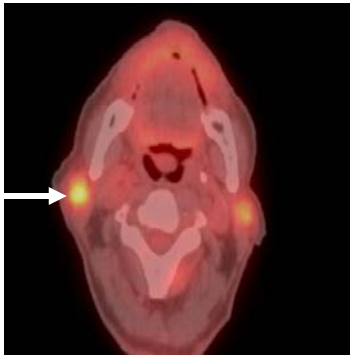
FDG-PET pitfalls

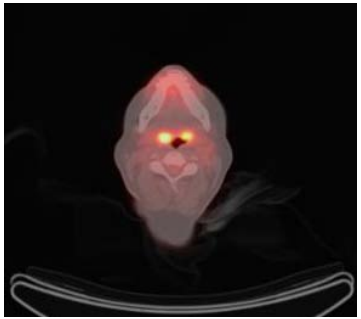




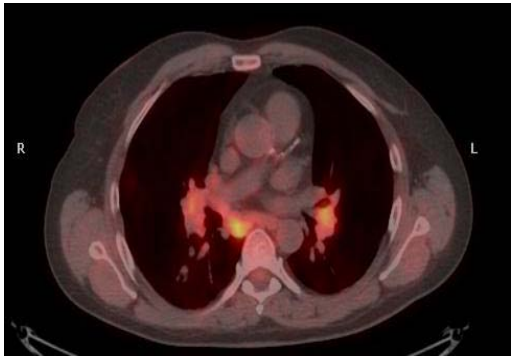
Brown fat



Pleomorphic adenoma



Physiologic uptake



Sarcoidosis

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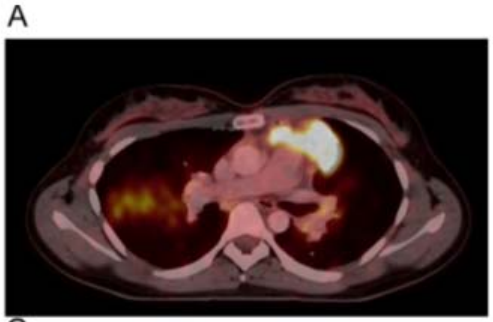
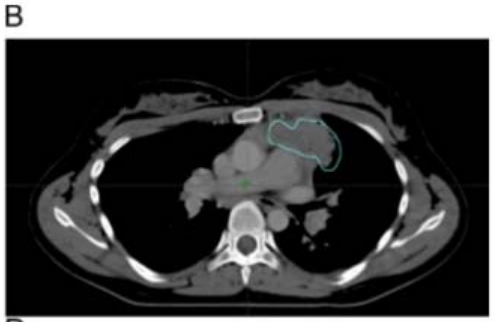
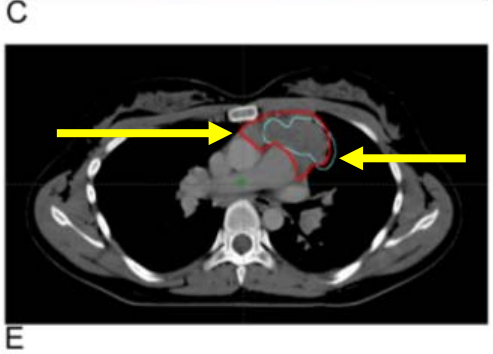
Pre-chemo PET

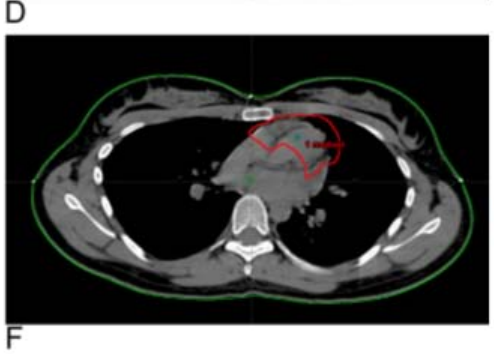




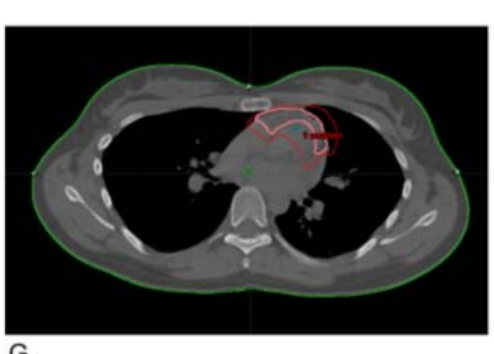
Pre-chemo PET-GTV



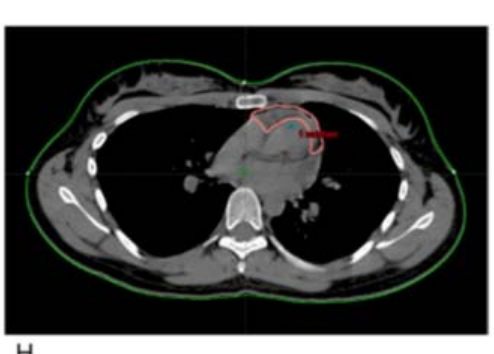
Pre-chemo CT-GTV



Pre-chemo GTV superimposed on post-chemo CT



Pre-chemo CTV excluding normal structures



Illidge. IJROBP 2014 89: 49

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IMPACT OF PET ON TARGET DEFINITION

Effect of PET on TV definition

Table Studies examining the influence of information obtained from PET/CT scanning on lymphoma radiation therapy planning

Study (reference)	No. and lymphoma subtype	Type of study	Techniques of RT and PET/CT data interpretation	Findings	% change
Lee et al, 2004 (61)	15 thoracic lymphoma (10 HL, 5 NHL)	Single center	AP-PA parallel opposed VAM	Median GTV (CT) = 29.4 cm^2 Median GTV (PET) = 7.9 cm^2	na
Hutchings et al, 2007 (62)	30 early-stage HL	Single center	IFRT VAM	Target volumes unchanged in 21, larger in 7 (median 17%), and smaller in 2 (8% and 30%)	30%
Girinsky et al, 2007	30 early-stage supradiaphramatic HL	Single center	INRT SUV	Larger volumes with PET. PET showed avid nodes not shown on CT in 36% of cases. 25% of CT anatomic volume was PET avid	36%
Terezakis et al, 2011 (63)	29 lymphoma and hematologic malignancies (21 NHL, 5 HL, and 3 plasma cell neoplasms)	Single center	IFRT SUV	Target volume changed in 23 of 32 treatment sites with PET data. PTV increased in 15 sites (median 11%) and decreased in 8 sites (median 20%)	72%
Pommier et al, 2011 (64)	124 early-stage HL	Multicenter	IFRT VAM	With pre-RT PET information, RT was cancelled in 4.8% of cases, and treatment modifications occurred in 12.9% of cases	18%
					18 - 72%

Yeoh & Mikhaeel. IJROBP 2012

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Hodgkin Lymphoma

135 patients, H10 study, INRT

International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Role of FDG-PET in the Implementation of Involved-Node Radiation Therapy for Hodgkin Lymphoma Patients

Théodore Girinsky, MD,* Anne Aupérin, MD, PhD,† Vincent Ribrag, MD,‡ Manel Elleuch, MD,§ Christophe Fermé, MD,‡ Guillaume Bonniaud, PhD,|| Claude Ruelle,¶ Jean-Louis Alberini, MD,# Aljosa Celebic,† and Véronique Edeline, MD#

Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1047–1052, 2014

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How often does PET detect more nodes?

Table 1 Comparison between the number of lymph nodes and lymph-node areas per patient detected by CT scan and PET-CT before chemotherapy

Parameter	All CT scans	CT scan without IV contrast	CT scan with IV contrast	χ^2 test *P* value
No. of patients	135	88	47	
No. of patients with at least one additional LN detected by PET-CT %	95	68	27	.016
(95% CI)	70.4% (61.9 - 77.9)	77.3% (67.1 - 85.5)	57.5% (42.2 - 71.7)	
No. of patients with at least one additional LN area detected by PET-CT %	55	43	12	.009
(95% CI)	40.7% (32.4 - 49.5)	48.9% (38.0 - 59.7)	21.8% (13.9 - 40.3)	

Abbreviations: CI = confidence interval; CT = computed tomography; IV = intravenous; PET = positron emission tomography; LN = lymph node.

Impact of PET on target volume

Table 2 Impact of FDG-PET on the pre-chemotherapy GTV (cm^3) measured by CT scan and PET-CT before chemotherapy (134 patients)

Measure	Volume determination with CT scan	Volume determination with PET-CT	% increase*	Paired *t*-test *P* value
Mean (±SD)	501.1 (±331.7)	526.9 (±334.4)	8.8% (±24.0)	<.0001
Median (range)	452 (39 - 1972)	485 (44 - 2095)	1.9% (-36 to +184)	

Abbreviations: CT = computed tomography; PET = positron emission tomography; GTV = gross tumor volume.

* In 87 of 134 patients (64.9%) there was an increase in the GTV idem than table 3 for presentation using PET. In 28 of 134 patients (20.9%) there was a decrease because the pre-chemotherapy gross tumor volume was smaller using PET.

Table 3 Impact of FDG-PET on post-chemotherapy CTV (cm^3) measured by conventional CT scan and PET-CT (115 patients)

	post-chemotherapy CTV (115 patients)			
Measure	CT scan	PET-CT	% increase**	Paired *t*-test *P* Value
Mean (±SD)	327.2 (±155.2)	350.7 (±171.1)	7.1% (±13.5)	<.0001
Median (range)	317(33 - 873)	328 (33 - 968)	2.2% (-19 - +92)	

Abbreviations: CT = computed tomography; CTV = clinical tumor volume; PET = positron emission tomography.

** In 69 of 115 patients (60%) there was an increase in CTV using PET. In 7 of 115 patients (6.1%) there was a decrease in CTV using PET.

NHL (74%)

118 patients, single institution, ISRT (?)

International Journal of Radiation Oncology biology • physics

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Clinical Investigation: Lymphoma

A Prospective Study of ^{18}FDG-PET With CT Coregistration for Radiation Treatment Planning of Lymphomas and Other Hematologic Malignancies

Stephanie A. Terezakis, MD,*,§ Heiko Schöder, MD,† Alexander Kowalski, MS,* Patrick McCann, BA,* Remy Lim, MD,† Alla Turlakov, MD,† Mithat Gonen, PhD,‡ Chris Barker, MD,* Anuj Goenka, MD,* Shona Lovie, MPH,* and Joachim Yahalom, MD*

Int J Radiation Oncol Biol Phys, Vol. 89, No. 2, pp. 376–383, 2014

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Terezakis 2014 - methods

GTV outlined independently:

- on CT & PET
- by RO & NMP

GTV delineation:

- FDG-avid lesions defined by 40% of SUVmax
- GTV edge defined by CT abnormality
- Other areas visible on CT but <40%
- Questionable LNs in *proximity* to GTV

Results - Comparison of volumes

For RO:

- PET resulted in similar increase (38) and decrease (41)
- But magnitude of decrease was bigger

For NMP:

- decrease (52) was > increase (27)
- NMP volumes were generally smaller (particularly PET-TV)

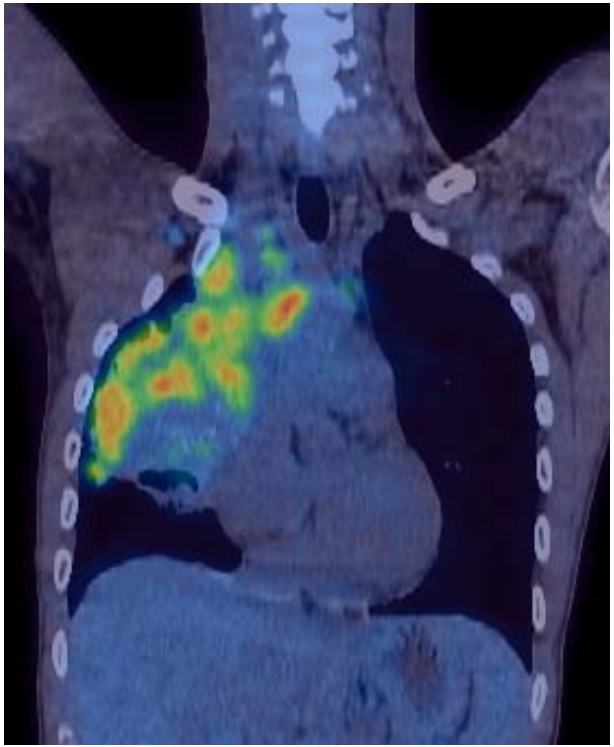
PET Resolution & Detection limit

- Function of intensity of uptake and size
- Modern cameras and addition of CT improved resolution
- But: PET is not a “microscopic imaging”
- Evidence from benefit of RT in PET-ve patients e.g.
  - H10
  - RAPID
  - …. and how –ve or CMR is defined is important
- Microscopic disease presence is probably a function of residual soft tissue (on CT)

Clinical examples

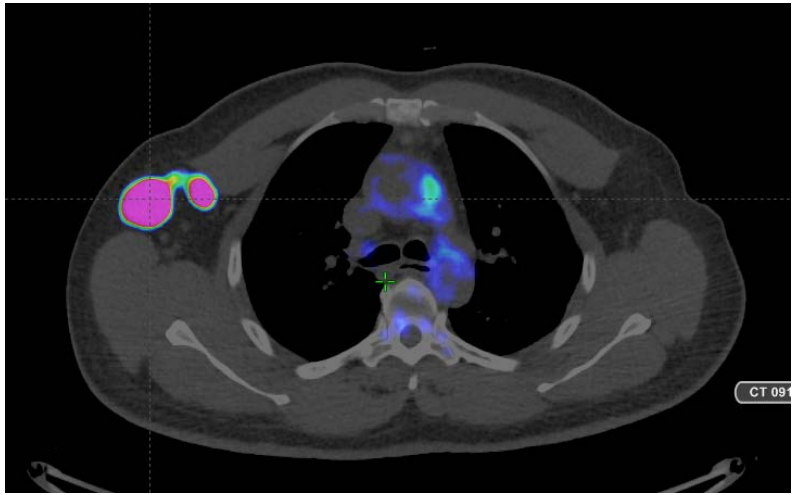
non-FDG-avid areas in a mass

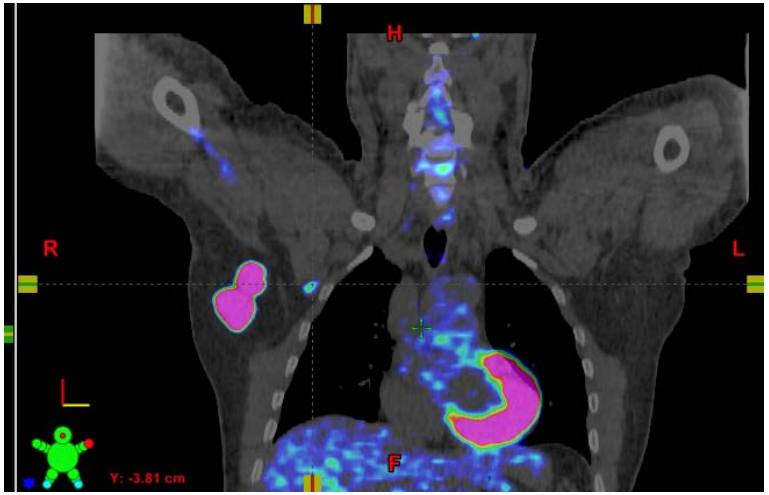
DLBCL



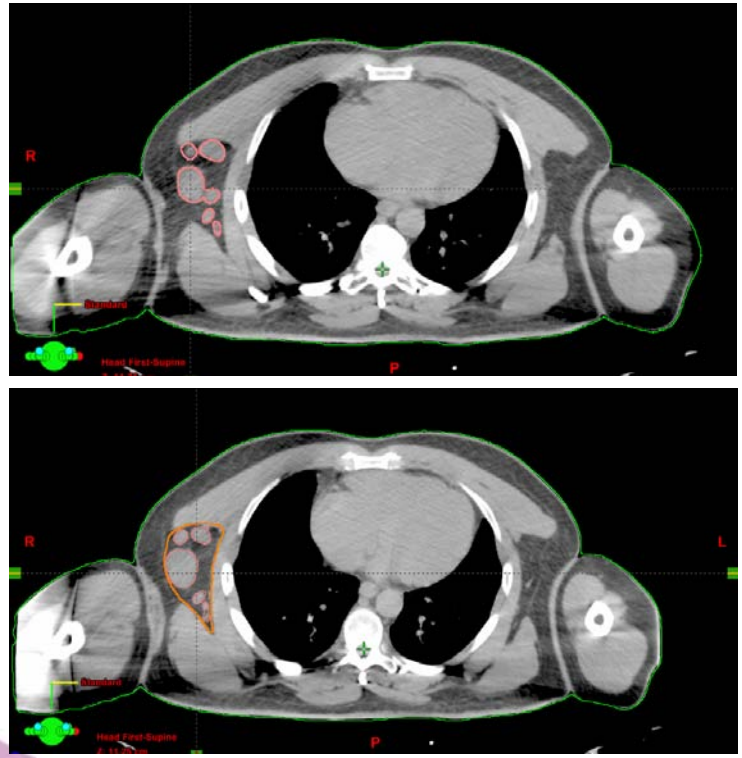
non-FDG-avid LNs

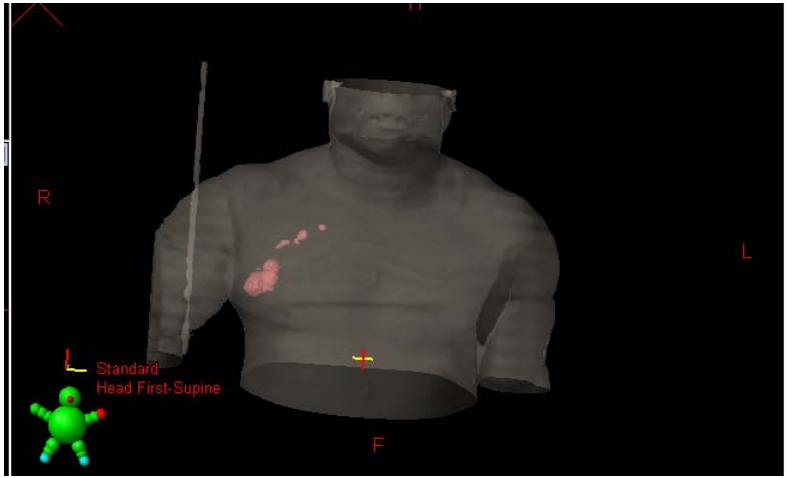
Stage 1 NLP R axilla



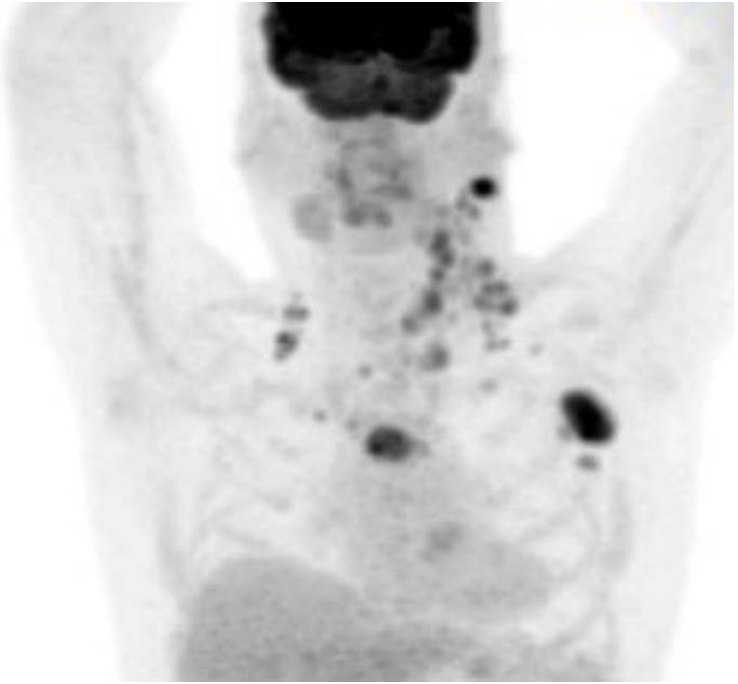


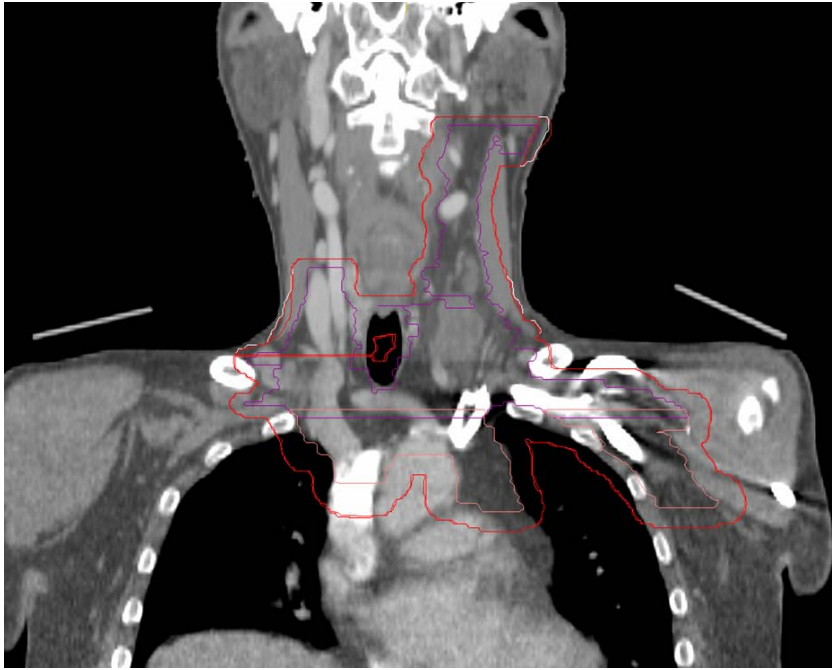
non-FDG-avid LN – No chemo





Skip areas – Stage 2 cHL





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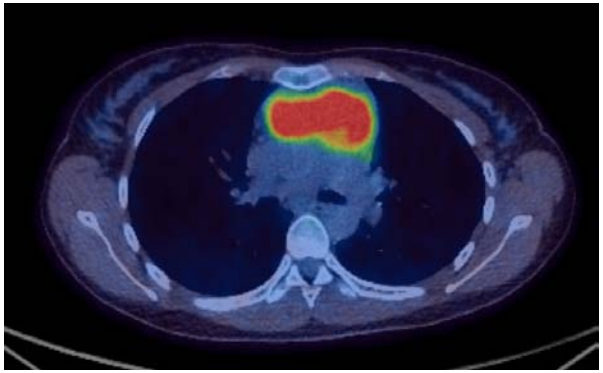
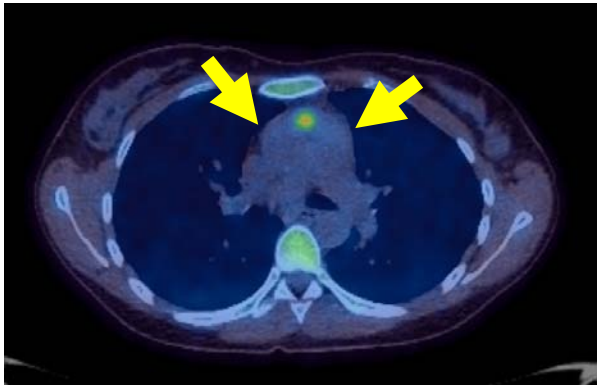
PMR after chemo – residual mass + a focus of residual activity

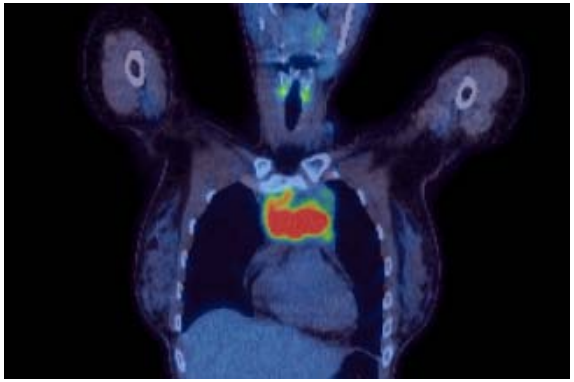
cHL > ABVDx6

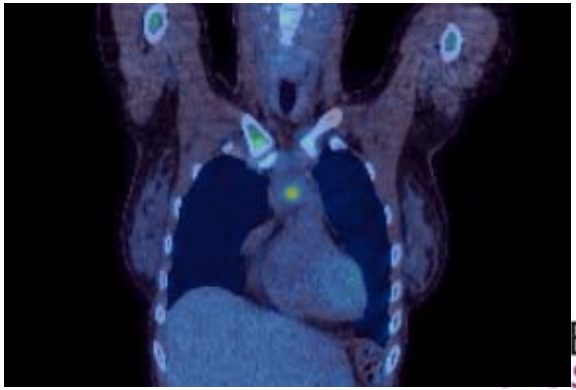
Pre

Post









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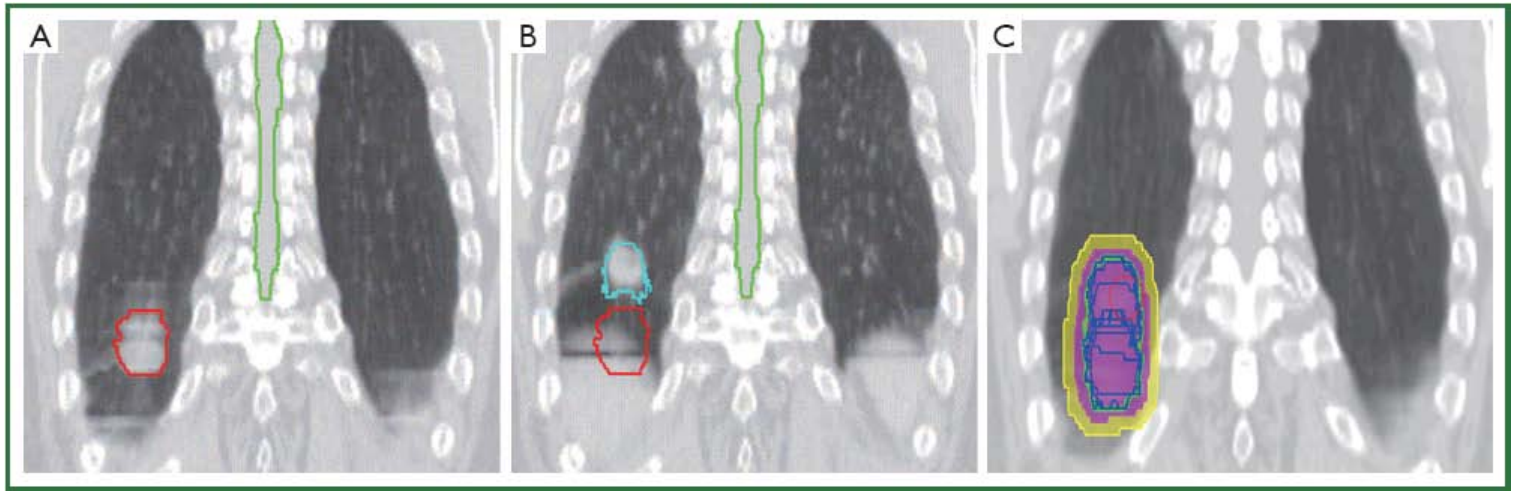
4D-CT

- Useful for sites with significant organ motion:
  - Thorax
  - Upper abdomen: stomach, spleen



Recent advances in RT based on imaging

- Diagnostic imaging: *Improved diagnostic accuracy & pt selection*
  - Improvement in CT
  - PET/CT
- RT planning: *Improved Targeting & Normal tissue sparing*
  - CT-based planning: 3D target definition, Thin-slice CT, 4D CT
  - Multimodality image fusion: PET & MRI
- RT Delivery: *Improved accuracy of delivery*
  - Treatment verification with IGRT
    - Set-up modification
    - Planning modification (Adaptive RT)
  - DIBH

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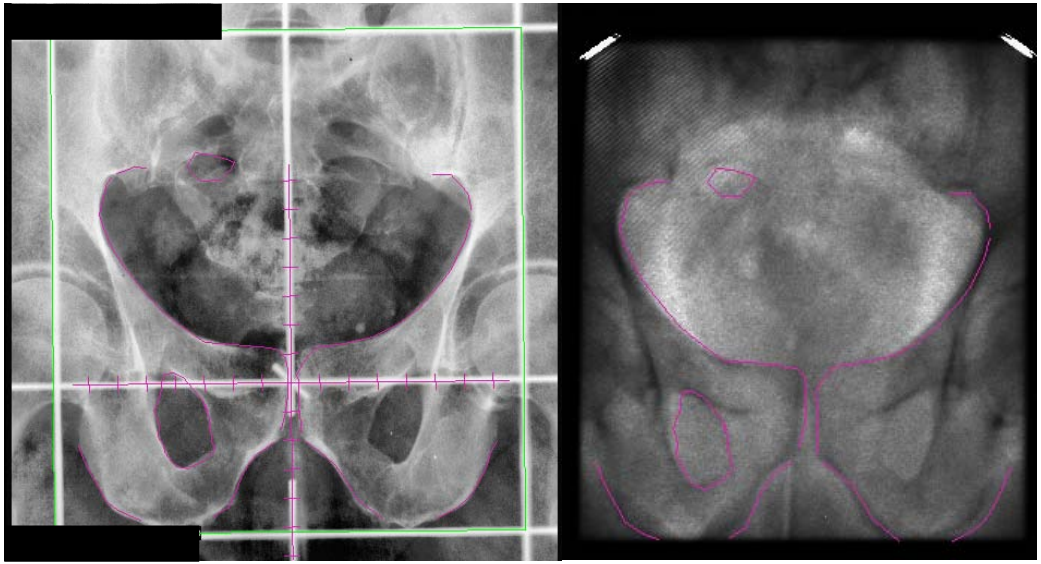
Treatment verification

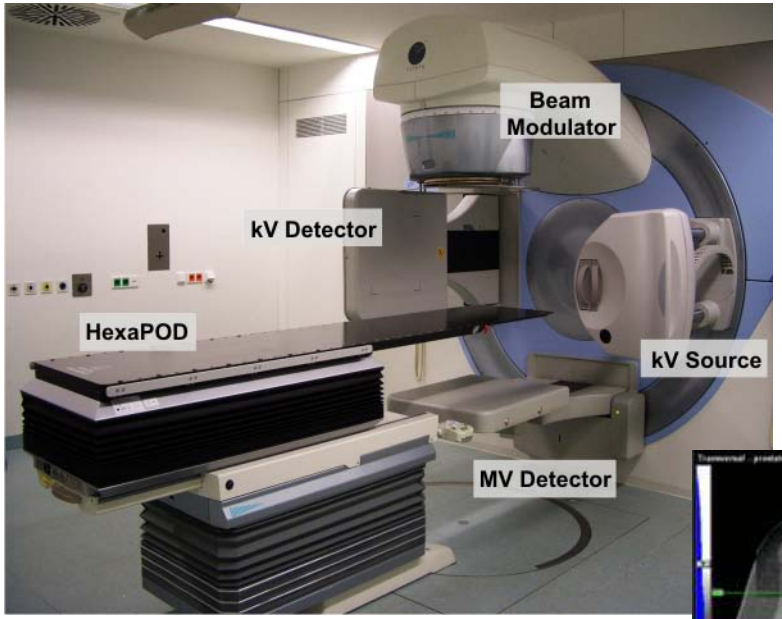
The past



Simulator image **MV image**

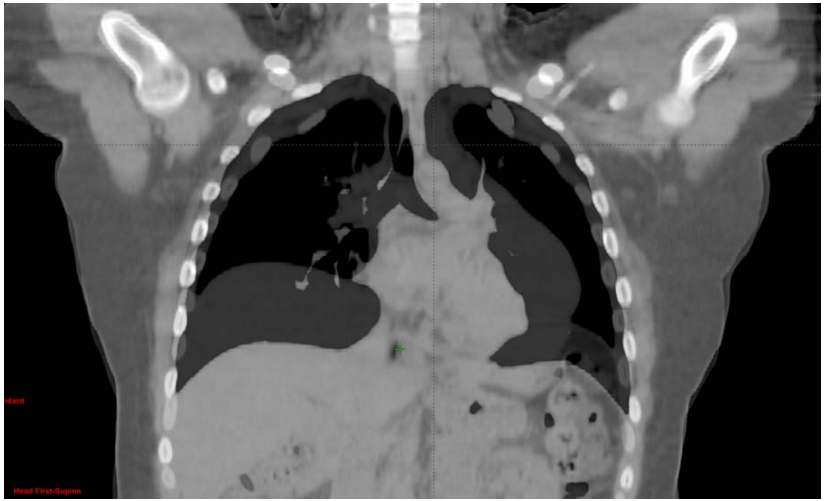
Treatment verification

The present



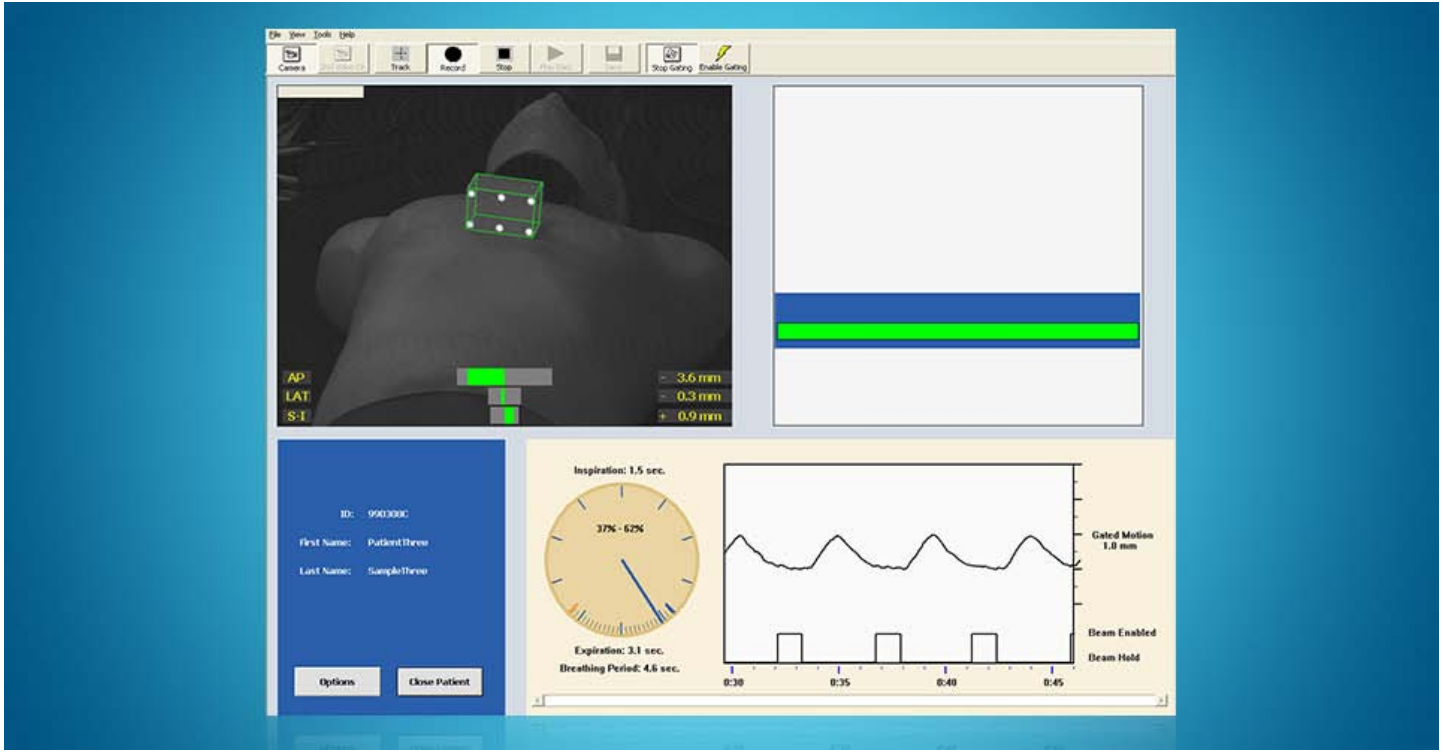
1) **set-up modification**
2) **Planning modification (Adaptive Radiotherapy)**

Deep Inspiration Breath Hold



- Expands lungs
- Moves heart downwards and clockwise
- Elongates mediastinum
- Moves ant. mediastinum away from oesophagus & Sp cord
- ?moves breasts out

Real-time Position Management (RPM)



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Nodular Lymphocyte Predominant HL
Role of Radiotherapy

Prof George Mikhaeel

Professor of Radiation Oncology
King's College London
Consultant Clinical Oncologist
Guy's & St Thomas' Hospital
London, UK

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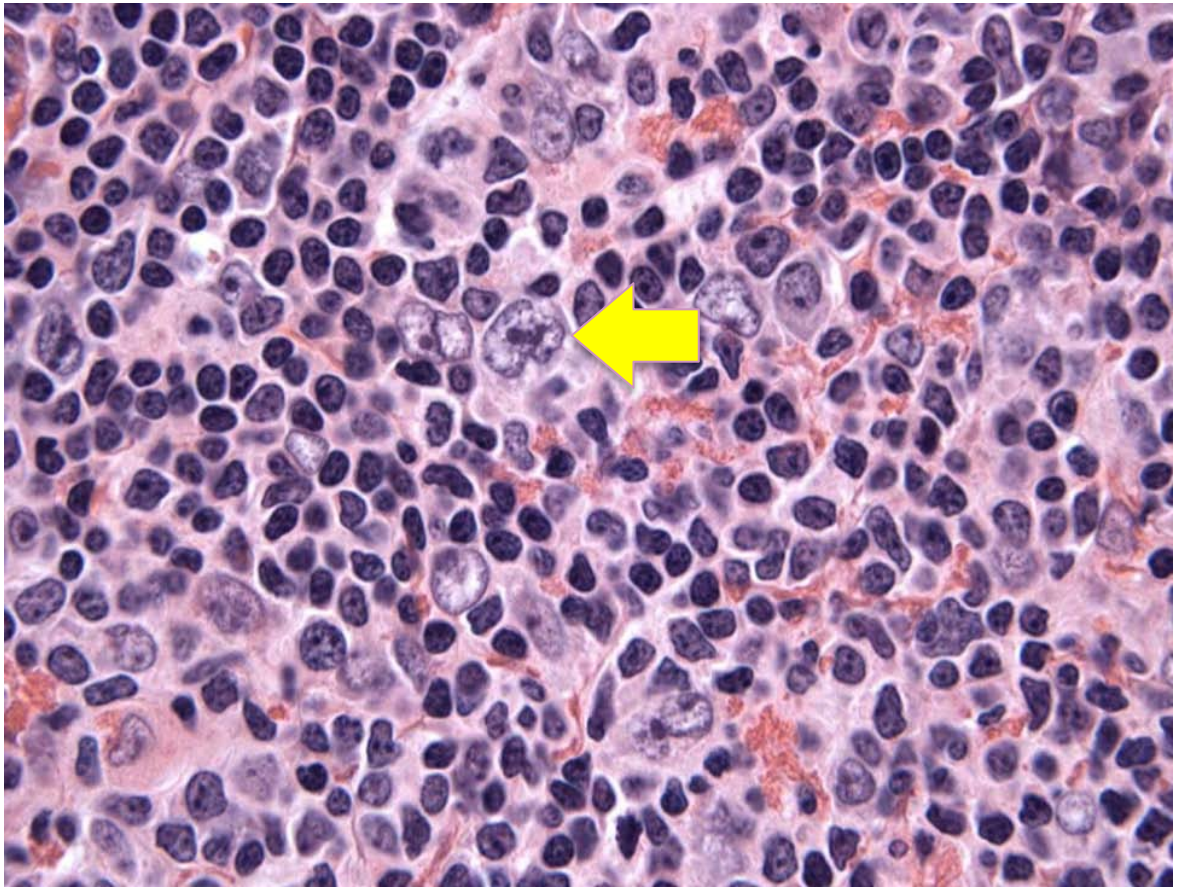
Incidence

- 5% of all HL
- 1.5 / 1m population/ y
- Recently recognized category:
  - 1944: Jackson & Parker: granuloma variant of HL
  - 1994: REAL classification (CD20+ LP, L&H/ popcorn cells)
  - 2001: WHO (separated from cHL as NLP)
- No prospective studies:
  - Re-analysis of previous studies
  - Institutional / registry based retrospective studies

Characteristics

- Histology:
  - LP cells: b-cell markers (CD20, CD79a, CD45) but not CD15, CD30
  - Initially thought: similar to FL, but now thought to be closest to DLBCL (particularly T-cell-rich)
  - NFkB activation
  - DD: progressive transformation of germinal centre.

Popcorn cell



Characteristics (2)

- Clinically:
  - Long history of lymphadenopathy
  - Male predominance (75%)
  - Familial risk described
  - Mediastinal sparing
  - EN sites rare

Characteristics (3)

- Prognosis:
  - Early stage: highly curable
  - Advanced stage: multiply relapsing
  - Transformation to HG-NHL particularly TCR-DLBCL
  - Importance of Bx of every relapse + long FU
  - Death due to NLP is uncommon

VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Transformation to Aggressive Lymphoma in Nodular Lymphocyte-Predominant Hodgkin's Lymphoma

Mubarak Al-Mansour, Joseph M. Connors, Randy D. Gascoyne, Brian Skinnider, and Kerry J. Savage

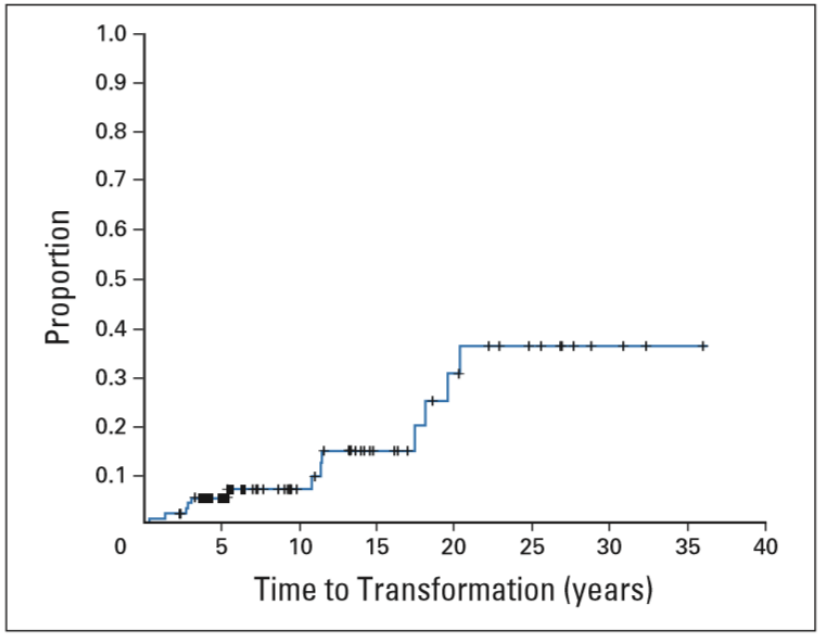


Fig 1. Time to transformation in patients with nodular lymphocyte-predominant Hodgkin's lymphoma.

- 95 pts, mFU 6.5ys
- Transf = 14%
- 10 y actuarial risk 7%
- 20 y actuarial risk 30%
- Risk fs:
  - advanced stage
  - spleen / abdominal presentation

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CME Article

Large B-cell transformation in nodular lymphocyte-predominant Hodgkin lymphoma: 40-year experience from a single institution

Saad Sirop Kenderian,[1] Thomas M. Habermann,[1] William R. Macon,[2] Kay M. Ristow,[1] Stephen M. Ansell,[1] Joseph P. Colgan,[1] Patrick B. Johnston,[1] David J. Inwards,[1] Svetomir N. Markovic,[1] Ivana N. Micallef,[1] Carrie A. Thompson,[1] Luis F. Porrata,[1] James A. Martenson,[3] Thomas E. Witzig,[1] and Grzegorz S. Nowakowski[1]

[1]Division of Hematology, Department of Internal Medicine, [2]Department of Laboratory Medicine and Pathology, and [3]Department of Radiation Oncology, Mayo Clinic, Rochester, MN

BLOOD, 21 APRIL 2016 • VOLUME 127, NUMBER 16

- 222 pts
- mFU 16 ys
- Transf = 7.6%
- RF:
  - Spleen
  - Chemo

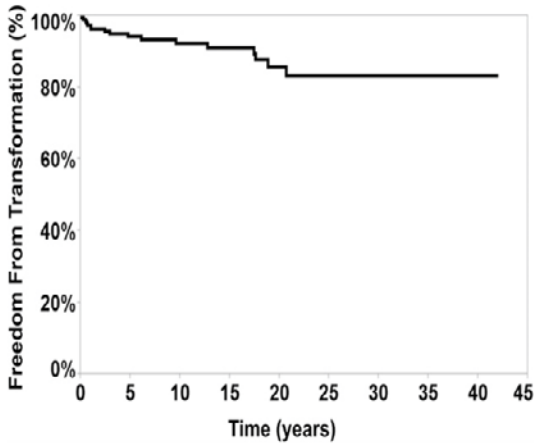

Figure 2. Freedom from transformation into DLBCL in 222 patients with NLPHL.

Key Points

- The risk of transformation of NLPHL to DLBCL is 0.74 per 100 patient-years of follow-up.
- Risk factors for transformation include prior exposure to chemotherapy and splenic involvement at time of diagnosis.

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Prognostic score

Prognostic scoring model for NLPHL patients
a. Features and assigned score

Feature		Scoring points
Histopathologic subtype	Typical pattern (A and/or B)	0
	Morphologic variant (C, D, E, and/or F)	1
Albumin	≥4 g/dL	0
	<4 g/dL	1
Gender	Female	0
	Male	2

b. Risk groups and corresponding outcomes

Risk group	Overall score	5-y PFS, %	5-y OS, %
Low risk	0-1	95.2	98.7
Intermediate risk	2	87.5	96.2
High risk	3-4	68.7	88.3

Adapted from Table 3 in Hartmann et al that begins on page 4246.

Hartmann Blood 2013

NLP versus cHL

International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Characteristics and Outcomes of Patients With Nodular Lymphocyte-Predominant Hodgkin Lymphoma Versus Those With Classical Hodgkin Lymphoma: A Population-Based Analysis

Naamit K. Gerber, MD,* Coral L. Atoria, MPH,† Elena B. Elkin, PhD,† and Joachim Yahalom, MD*

*Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York; and †Department of Epidemiology and Biostatistics, Health Outcomes Research Group, New York, New York

Received Dec 15, 2014, and in revised form Jan 27, 2015. Accepted for publication Feb 5, 2015.

1,162 NLP 29,000 cHL mFU 7ys

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NLP ——

cHL - - - -

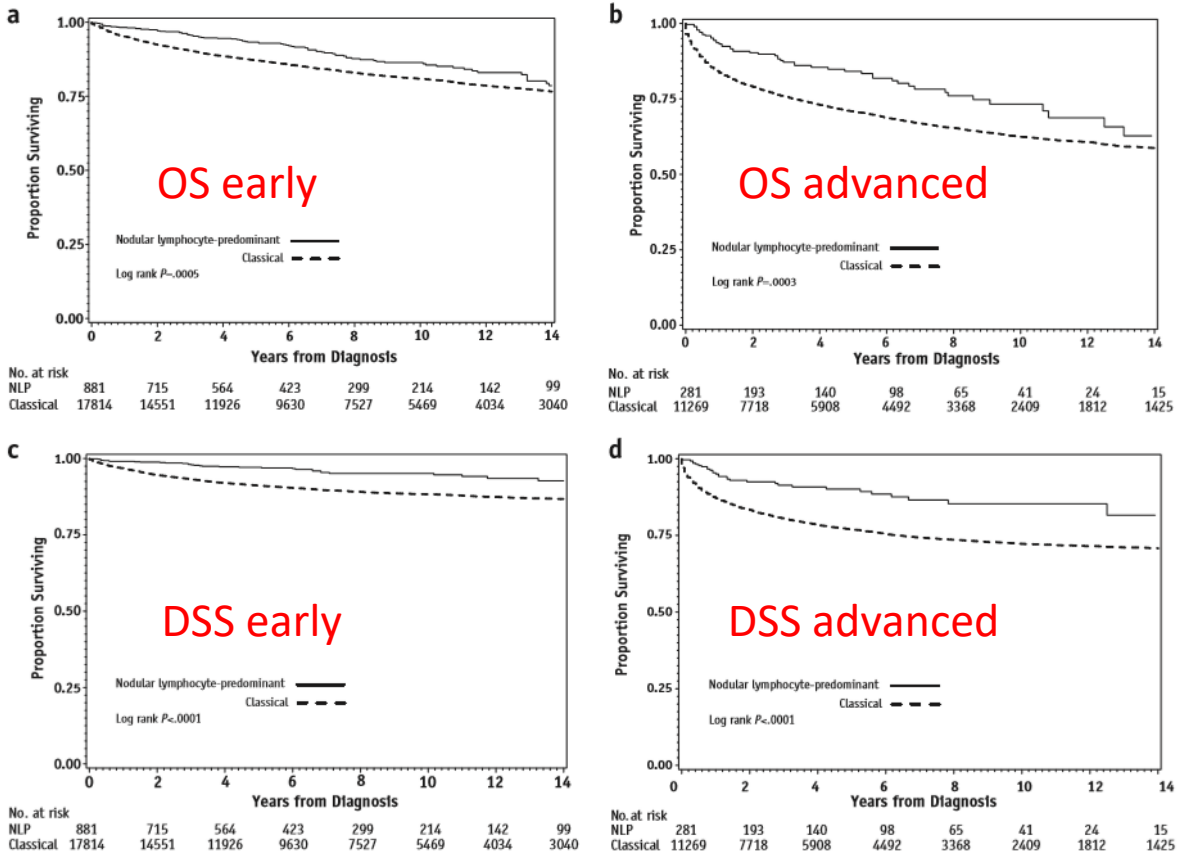

Fig. 1. (a) Overall survival for early stage patients by subtype. (b) Overall survival for advanced stage patients by subtype. (c) Disease-specific survival for early stage patients by subtype. (d) Disease-specific survival for advanced stage patients by subtype. NLP = nodular lymphocyte-predominant Hodgkin lymphoma.

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Diagnostic work up

- As cHL

- NLP is FDG avid:
  - PET is useful for staging and response assessment.
  - Essential for early stage managed by RT alone (more accurate staging)
  - Useful for RT planning

Management

- Generally:
  - Early stage: RT
  - Advanced stage: systemic treatment
- Important considerations in Treatment:
  - Early:
    - RT: outcome, volume & dose
    - Role of excision alone
    - Role of CMT
  - Advanced:
    - Which chemo
    - Role of Rituximab

Outcome of RT in early stage

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Long-Term Course of Patients With Stage IA Nodular Lymphocyte-Predominant Hodgkin Lymphoma: A Report From the German Hodgkin Study Group

Dennis A. Eichenauer, Annette Plütschow, Michael Fuchs, Bastian von Tresckow, Boris Böll, Karolin Behringer, Volker Diehl, Hans Theodor Eich, Peter Borchmann, and Andreas Engert

All authors: University Hospital Cologne, Cologne; and Hans Theodor Eich, University Hospital Münster, Münster, Germany.

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/15/3399-1/$20.00

DOI: 10.1200/JCO.2014.60.4363

ABSTRACT

Purpose
The optimal treatment of stage IA nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is not well defined. Thus, we performed an analysis using the database of the German Hodgkin Study Group.

Patients and Methods
The long-term outcome of 256 patients with stage IA NLPHL was evaluated. Patients had received combined-modality treatment (CMT; n = 72), extended-field radiotherapy (EF-RT; n = 49), involved-field radiotherapy (IF-RT; n = 108), or four weekly standard doses of rituximab (n = 27) within German Hodgkin Study Group clinical trial protocols between 1988 and 2009.

Results
The median age at NLPHL diagnosis was 39 years (range, 16 to 75 years). Most patients were male (76%). The whole patient group had a median follow-up of 91 months (CMT: 95 months; EF-RT: 110 months; IF-RT: 87 months; rituximab: 49 months). At 8 years, progression-free survival and overall survival rates were 88.5% and 98.6% for CMT, 84.3% and 95.7% for EF-RT, and 91.9% and 99.0% for IF-RT, respectively. Patients treated with rituximab had 4-year progression-free and overall survival rates of 81.0% and 100%, respectively. A second malignancy during the course of follow-up was diagnosed in 17 (6.6%) of 256 patients. A total of 12 deaths occurred. However, only one patient died from NLPHL.

Conclusion
Tumor control in this analysis was equivalent with CMT, EF-RT, and IF-RT. Therefore, IF-RT, which is associated with the lowest risk for the development of toxic effects, should be considered as standard of care for patients with stage IA NLPHL. Rituximab alone is associated with an increased risk of relapse in this patient population.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

Variable	No. of Patients
Total	256
Treatment modality	
EF-RT	49
IF-RT	108
CMT	72
Rituximab	27

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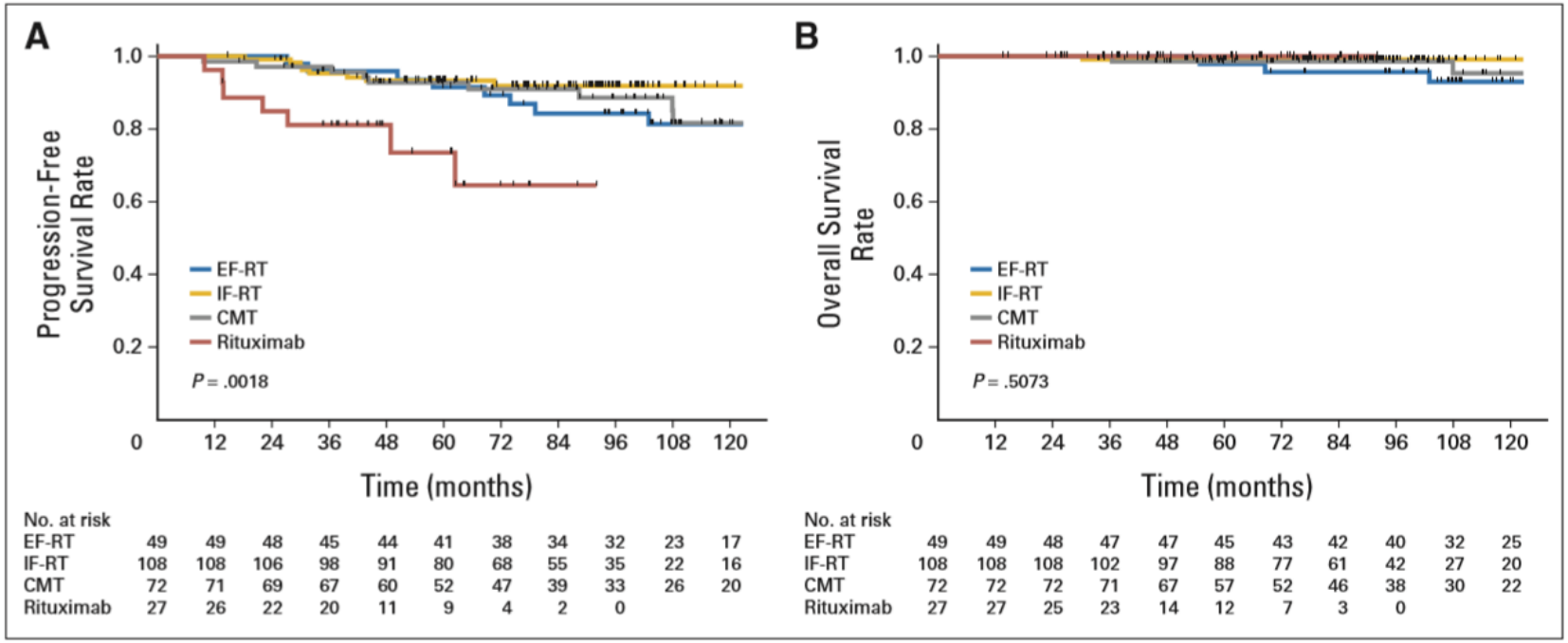

Fig 1. (A) Progression-free survival and (B) overall survival among patients with stage IA nodular lymphocyte-predominant Hodgkin lymphoma treated with combined-modality treatment (CMT), extended-field radiotherapy (EF-RT), involved-field radiotherapy (IF-RT), or rituximab.

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Table 3. Four-Year PFS of Patients Treated for Stage IA NLPHL

Variable	No. of Patients	No. of Events (%)	4-Year PFS Rate (%; 95% CI)	Log-Rank *P*	Cox Univariate Hazard Ratio (95% CI)
Total	256	45 (18)	92.3 (89.0 to 95.6)		—
Treatment modality				.0018	
EF-RT	49	15 (31)	95.8 (90.2 to 100.0)		1.56 (0.68 to 3.58)
IF-RT	108	11 (10)	93.2 (88.4 to 98.1)		—
CMT	72	12 (17)	92.9 (86.8 to 98.9)		1.00 (0.43 to 2.35)
Rituximab	27	7 (26)	81.0 (66.0 to 96.0)		4.99 (1.88 to 13.21)

Abbreviations: CMT, combined-modality treatment; EF-RT, extended-field radiotherapy; IF-RT, involved-field radiotherapy; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PFS, progression-free survival.

Table 2. Eight-Year PFS of Patients Treated for Stage IA NLPHL

Variable	No. of Patients	No. of Events (%)	8-Year PFS Rate (%; 95% CI)	Log-Rank *P*	Cox Univariate Hazard Ratio (95% CI)
Total	229	38 (17)	88.9 (84.5 to 93.4)		—
Treatment modality				.4305	
EF-RT	49	15 (31)	84.3 (73.6 to 95.0)		—
IF-RT	108	11 (10)	91.9 (86.5 to 97.3)		0.64 (0.28 to 1.47)
CMT	72	12 (17)	88.5 (80.3 to 96.8)		0.64 (0.30 to 1.39)

Abbreviations: CMT, combined-modality treatment; EF-RT, extended-field radiotherapy; IF-RT, involved-field radiotherapy; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PFS, progression-free survival.

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Table 4. Characteristics of Second Malignancies After Treatment for Stage IA NLPHL

Secondary Malignancy	Chronic Myeloid Leukemia (n = 1)	Non-Hodgkin Lymphoma (N = 7)	Solid Tumor (N = 9)	Total (n = 17)
Time to secondary malignancy, years				
Median	16.6	6.2	5.7	6.2
Range	16.6-16.6	1.0-15.8	2.0-16.4	1.0-16.6
Secondary solid tumors according to localization, No.				
Missing			0	
Colorectal cancer			2	
Lung cancer			2	
Breast cancer			1	
Stomach cancer			1	
Bladder cancer			1	
Salivary gland cancer			1	
Unknown localization			1	
Secondary non-Hodgkin lymphoma according to histology, No.				
Missing		0		
Diffuse large B-cell lymphoma		3		
T-cell–rich B-cell lymphoma		2		
Follicular lymphoma		1		
Marginal zone lymphoma		1		

Abbreviation: NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma.

Only 1 Death from NLP

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CMT / Chemo for early stage

- No RCT
- RT outcome is excellent. Difficult to improve on.
- Limited data on role of CMT in early stage dis
  - *Canadian* data on short course ABVD suggests benefit
  - but other studies (*MDACC, GHSG, Harvard*) show no benefit
  - RT alone remains standard
- Chemo alone strategy in children: limited data
- Rituximab alone: limited data (GHSG 28 pts, Stanford 13 pts):
  - 100% response, but 25% relapse. Not recommended.

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Treating limited-stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome

Kerry J. Savage,[1] Brian Skinnider,[2] Mubarak Al-Mansour,[1] Laurie H. Sehn,[1] Randy D. Gascoyne,[2] and Joseph M. Connors[1]

[1]Centre for Lymphoid Cancer and Department of Medical Oncology, British Columbia Cancer Agency and the University of British Columbia, Vancouver, BC; and
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The appropriate therapy for limited-stage nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is unclear. In contrast to classical Hodgkin lymphoma (CHL), chemotherapy is often omitted; however, it is unknown whether this impacts the risk of relapse. Herein, we compared the outcome of patients with limited-stage NLPHL treated in an era in which ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy was routinely incorporated into the primary therapy to an earlier era in which radiotherapy (RT) was used as a single modality. Using the British Columbia Cancer Agency Lymphoid Cancer Database, 88 patients with limited-stage NLPHL (stage 1A/1B or 2A, nonbulky disease < 10 cm) were identified. Treatment followed era-specific guidelines: before 1993, (n = 32) RT alone; and 1993 to present (n = 56), ABVD-like chemotherapy for 2 cycles followed by RT with the exception of 14 patients who received ABVD chemotherapy alone. Most patients were male (75%) with stage I disease (61%). In an era-to-era comparison, the 10-year time to progression (98% vs 76% $P = .0074$), progression-free survival (91% vs 65% $P = .0024$), and OS (93% vs 84%, $P = .074$) favored the ABVD treatment era compared with the RT alone era. Treating limited-stage NLPHL similarly to CHL may improve outcome compared with the use of radiation alone. (*Blood*. 2011;118(17): 4585-4590)

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BCCCA study

- Retrospective longitudinal cohort, mFU 6.4y
- 88 pts – over 43 ys (1966 – 2009):
  - 121 pts, 33 revised histology = 88
  - 88: 78 confirmed, 10 missing histology
  - <1993: RT alone =32
  - >1993: ABVDx2 +RT =56 (14 ABVD alone)
- Results (CMT v RT):
  - 10y PFS: 91 v 65% (p=0.002)
  - 10y OS: 93 v 84% (p=0.07)
- Problems:
  - Effect of improvements in staging, RT, overall care??
  - FU length

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Surgical resection + Observation

- Option for children
- 2 studies:

	EuroNET	COG
No of pts	57	52
	Stage 1A	Stage 1A, no bulk
Complete resection	86%	100%
Median FU	43m	26m
Relapse	27%	17%
Time to relapse	All within 26m	Median 10m
PFS	FFP 67%	2y EFS 80%

COG update
(Appel JCO 2016)
75% PFS for observation
> 90% PFS with chemo
100% OS.

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Summary of treatment of limited stage NLP

- Observation only:
  - Option in children + ? Adults (NCCN)
    - Single node
    - complete resection
- Radiotherapy:
  - Treatment of choice
  - Highly curative
- CMT:
  - B symptoms or Bulky disease ?

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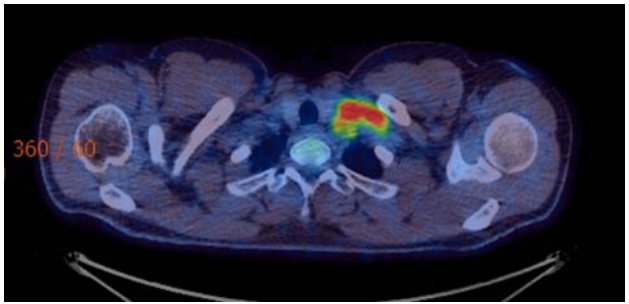
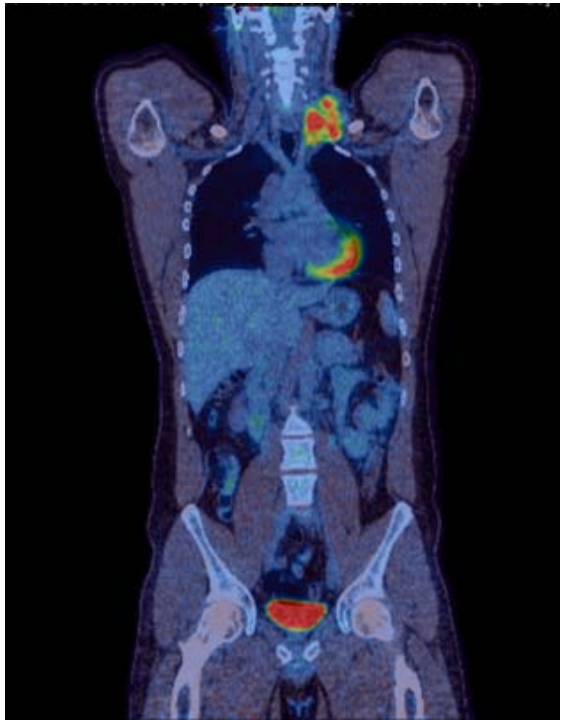
Radiotherapy

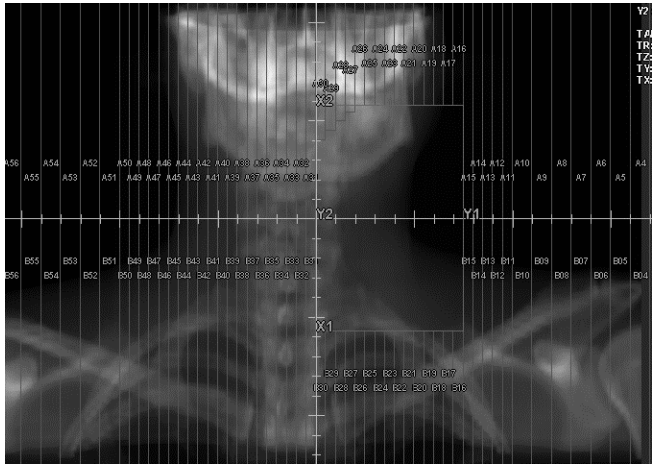
- ILROG guidelines: GTV, CTV, PTV
- PET / planning-CT image registration is ideal to outline GTV (as no prior chemo).
- Volume:
  - No chemo. RT needs to control *microscopic* disease
  - No benefit to EF over IFRT *(Nogova 2005, Eichenaeur 2015)*
  - IFRT / ISRT?

35 yo male
PMH stage 1 NLP
2007 30Gy L Neck



2014





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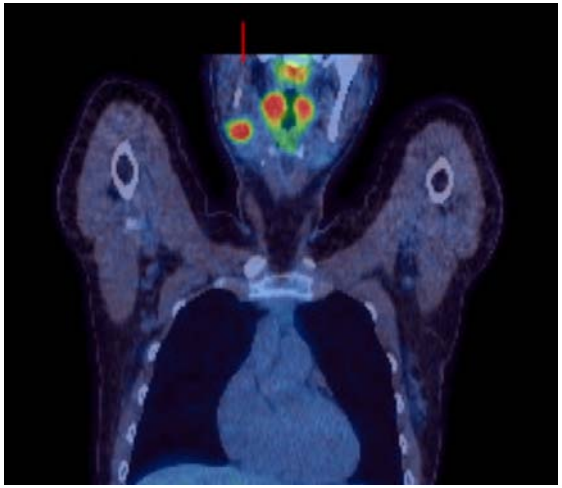
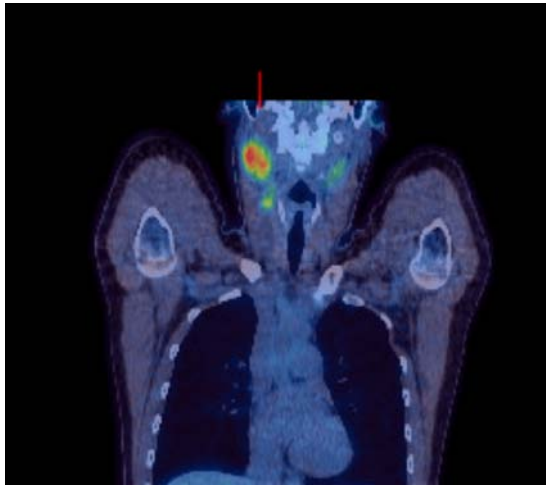
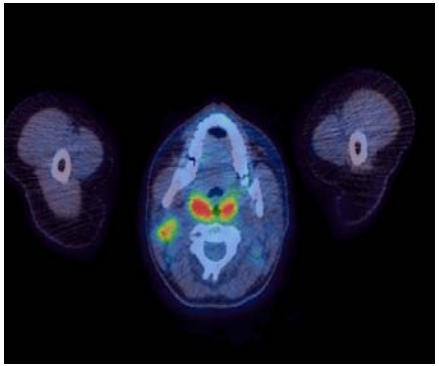
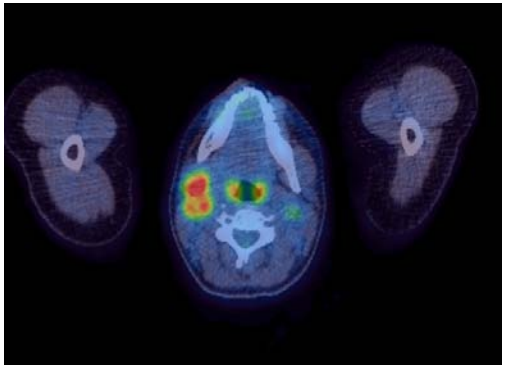
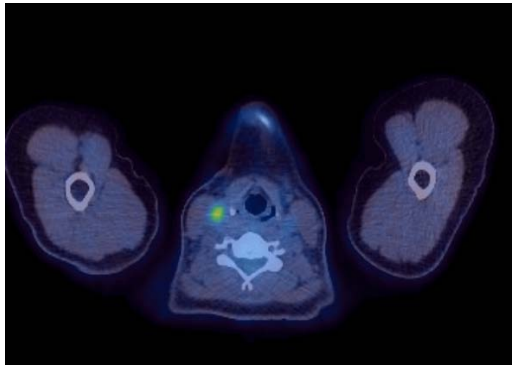

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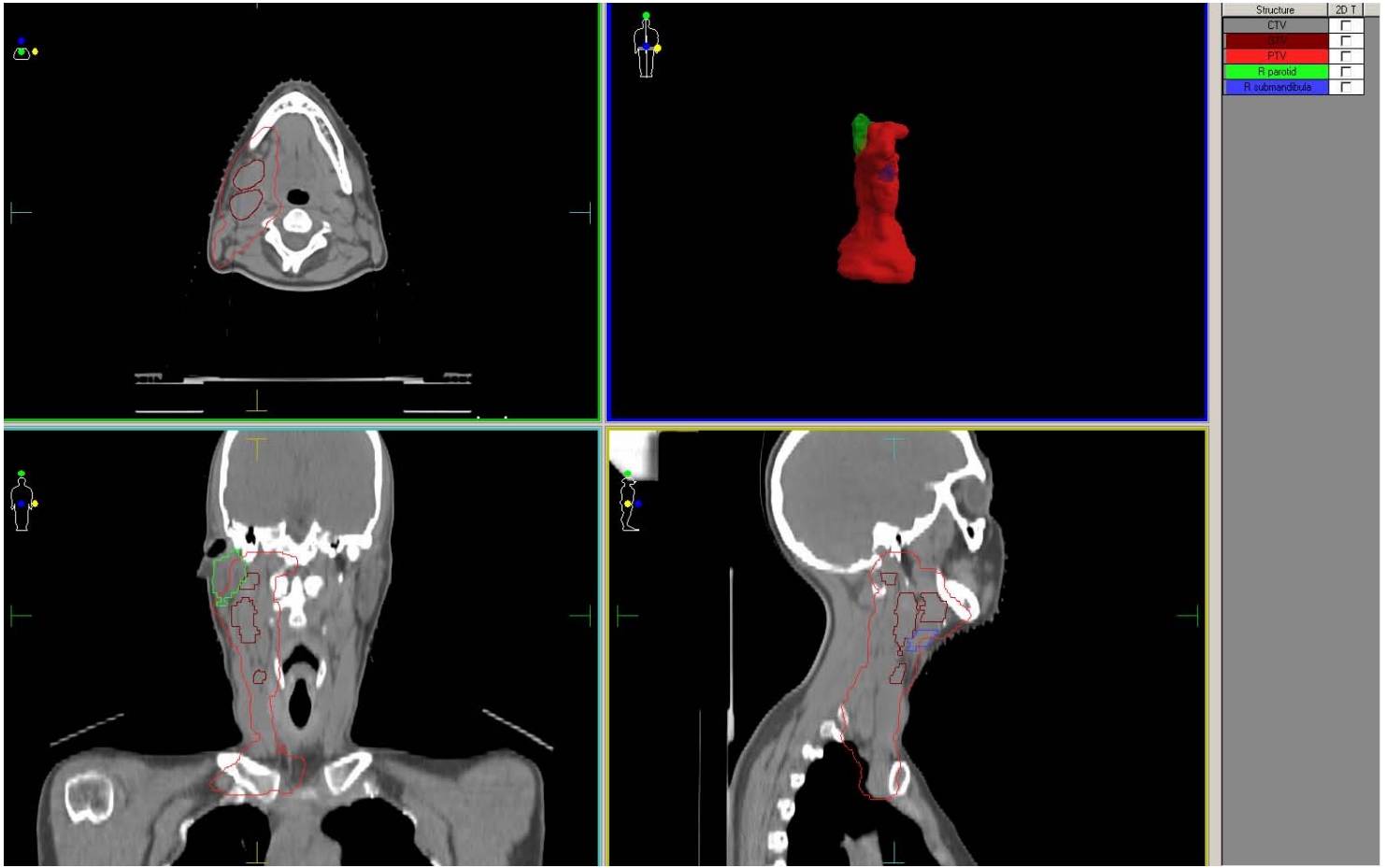

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Radiotherapy (cont.)

- Dose:
  - No conclusive evidence of benefit >30Gy
  - 4Gy: inferior outcome *(local relapse 5/8 pts)*
  - NCCN: 30-36 Gy, ESMO: 30 Gy
  - Standard: 30 Gy……36Gy for bulky disease? (uncommon)

Key points

- Rare, indolent
- Male predominance, mediastinal sparing
- Better prognosis than cHL, rarely cause of death.
- Tendency to transform
- RT alone for early stage: excellent outcome
- Generous ISRT (no chemo)
- Resection is an option only for children

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Thank you

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Aggressive Nodal NHL
RT for Relapsed / Refractory Disease

Prof George Mikhaeel

Professor of Radiation Oncology
King's College London
Consultant Clinical Oncologist
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Outline

- Definitions:
  - Primary Refractory: failure to achieve remission with 1st line treatment
  - Relapse: recurrence following remission

- Breakdown of clinical scenarios
  1. Persistent PET positivity after chemo
  2. Role in peri-transplant setting
  3. Role in patients who are transplant ineligible or relapsed after Tx

- RT details

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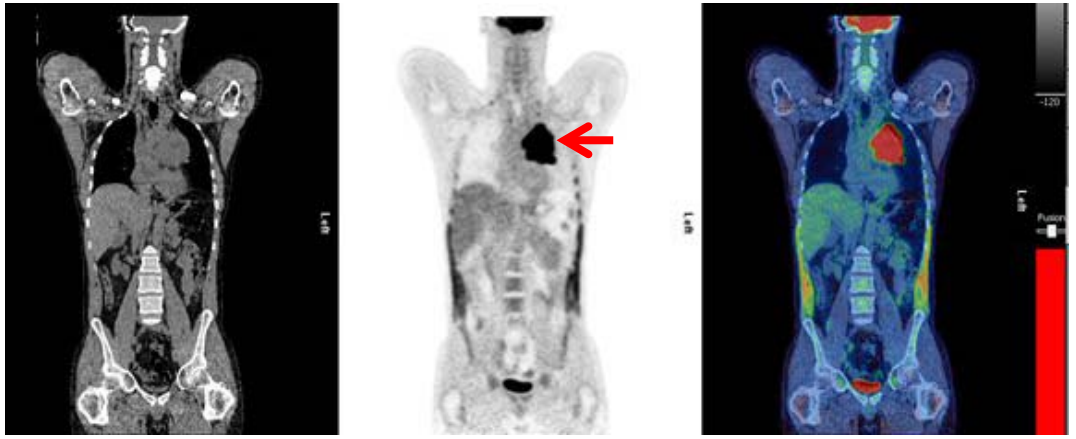
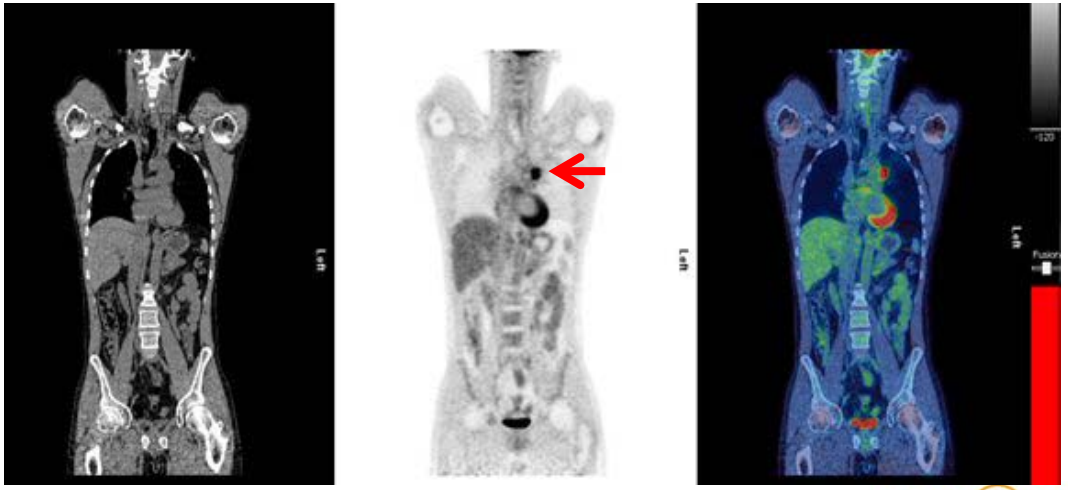
(1) Persistent PET positivity after Primary Chemo

Can RT Salvage these patients?

Baseline



Post chemo



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INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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original article

Annals of Oncology 22: 405–410, 2011
doi:10.1093/annonc/mdq389
Published online 30 July 2010

The impact of radiation therapy in patients with diffuse large B-cell lymphoma with positive post-chemotherapy FDG–PET or gallium-67 scans

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Received 9 December 2009; revised 25 May 2010; accepted 26 May 2010

Background: 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (PET) and gallium-67 citrate (gallium) response after chemotherapy are powerful prognostic factors in diffuse large B-cell lymphoma (DLBCL). However, clinical outcomes when consolidation radiation therapy (RT) is administered are less defined.

Patients and methods: We reviewed 99 patients diagnosed with DLBCL from 1996 to 2007 at Duke University who had a post-chemotherapy response assessment with either PET or gallium and who subsequently received consolidation RT. Clinical outcomes were estimated using the Kaplan–Meier method and compared using the log-rank test.

Results: Median follow-up was 4.4 years. Stage distribution was I–II in 70% and III–IV in 30%. Chemotherapy was R-CHOP or CHOP in 88%. Median RT dose was 30 Gy. Post-chemotherapy PET ($n = 79$) or gallium ($n = 20$) was positive in 21 of 99 patients and negative in 78 of 99 patients. Five-year in-field control was 95% with a negative PET/gallium scan versus 71% with a positive scan ($P < 0.01$). Five-year event-free survival (EFS; 83% versus 65%, $P = 0.04$) and overall survival (89% versus 73%, $P = 0.04$) were also significantly better when the post-chemotherapy PET/gallium was negative.

Conclusions: A positive PET/gallium scan after chemotherapy is associated with an increased risk of local failure and death. Consolidation RT, however, still results in long-term EFS in 65% of patients.

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Dorth et al

- 99 pts, 1996 – 2007, mFU 4.4y
- All had PET/Ga + RT
- 70% stage 1-2
- 88% CHOP/RCHOP
- 21% PET/Ga +ve

5y	In-field cont	EFS	OS
PET -ve	95%	83%	89%
PET +ve	71%	65%	73%
	P<0.01	*P=0.04*	*P=0.04*

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Factor	Positive ($n = 21$) PET/gallium (%)	Negative ($n = 78$) PET/gallium (%)	P value
Median age, years	54	62	0.03
Gender			1
Male	8 (38)	20 (38)	
Female	13 (62)	48 (62)	
Stage			0.76
I–II	16 (76)	62 (79)	
III–IV	5 (24)	16 (21)	
Performance status (ECOG)			0.58
0–1	19 (96)	75 (90)	
2–5	2 (4)	3 (10)	
Elevated LDH	12 (57)	24 (31)	0.03
B symptoms	6 (29)	16 (21)	0.55
IPI score (median)	1	1	0.95
>1 Extranodal sites	3 (14)	9 (12)	0.99
Median tumor diameter, cm	8	4.7	<0.05
Post-chemotherapy scan			1
PET	17 (81)	65 (83)	
Gallium	4 (19)	13 (17)	
Chemotherapy regimen			0.89
R-CHOP	12 (57)	47 (59)	
CHOP	6 (29)	22 (27)	
R-CNOP	1 (5)	2 (3)	
Other	2 (9)	9 (11)	
Chemotherapy cycles (median)	6	6	0.31
Radiation dose (Gy) (median)	36	30	<0.01

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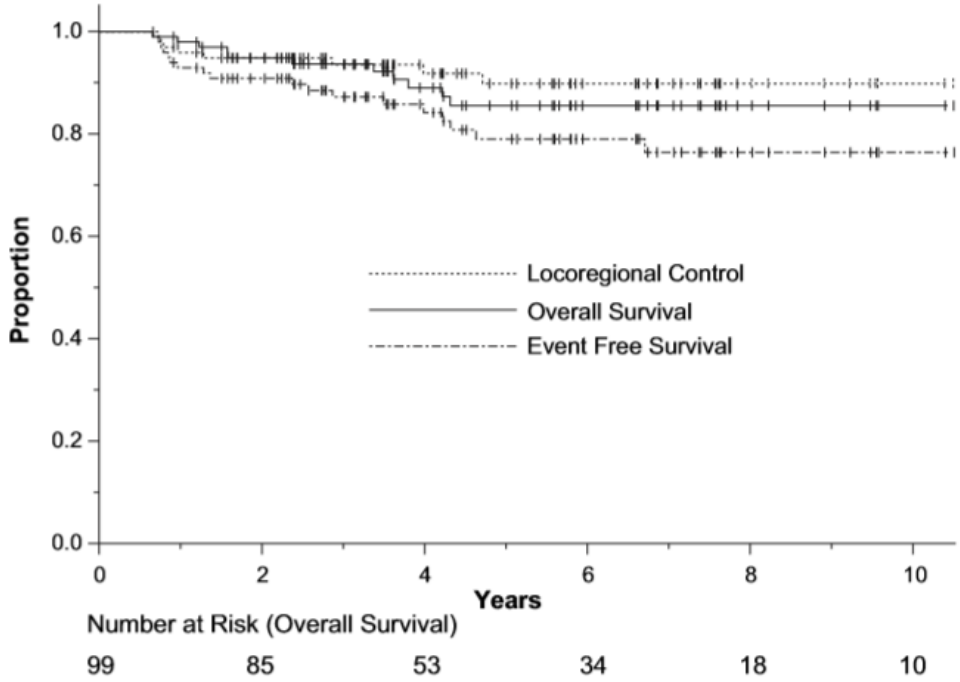

Figure 1. Local control, event-free survival, and overall survival for all patients.

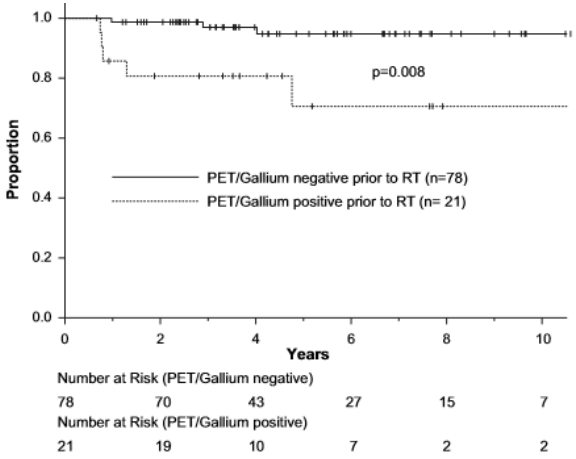

Figure 2. Local control by post-chemotherapy positron emission tomography (PET)/gallium status before radiation therapy (RT).

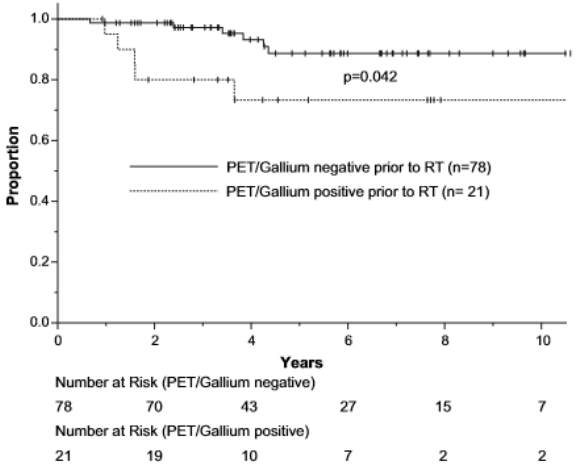

Figure 3. Overall survival by post-chemotherapy positron emission tomography (PET)/gallium status before radiation therapy (RT).

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Table 2. Multivariate analysis of factors associated with local (in-field) failure

Factor	HR	95% CI	*P*
Number of involved regions (per region)	1.14	0.7–1.84	0.6
IPI score (per point)	3.5	1.25–9.86	0.02
B symptoms	1.3	0.152–11.2	0.8
Size (per cm)	1.1	0.87–1.34	0.51
Number chemotherapy cycles (per cycle)	1.33	0.67–2.85	0.47
Use of rituximab	0.23	0.03–1.59	0.14
Radiation dose (per Gy)	1.13	0.99–1.85	0.1
Positive PET/gallium	9.64	1.44–64.5	0.02

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Clinical Investigation: Lymphoma

Combined Modality Treatment for PET-Positive Non-Hodgkin Lymphoma: Favorable Outcomes of Combined Modality Treatment for Patients With Non-Hodgkin Lymphoma and Positive Interim or Postchemotherapy FDG-PET

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Halasz et al

- 59 pts, 2001 – 2008, mFU 3.9y
- All had PET (interim=50 &/or end=28) + RT
- 83% stage 1-2
- 98% RCHOP
- 22 pts had +ve PET (7 iPET)

3y	LC	PFS	Death
PET -ve	100%	97%	1 (2nd lymphoma)
PET +ve	90%	90%	1 (relapse)

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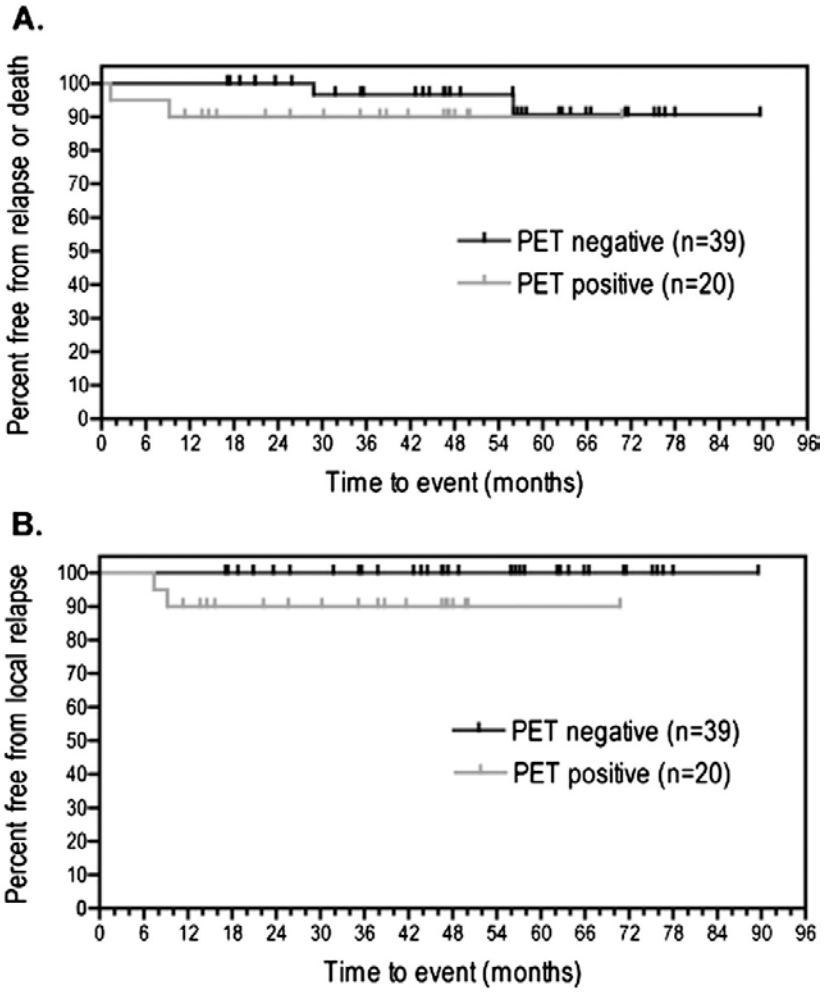
PFS

LC



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COMMENTS

Dorth

	In-field cont	5y-EFS	OS
PET -ve	95%	83%	89%
PET +ve	71%	65%	73%
	P<0.01	*P=0.04*	*P=0.04*

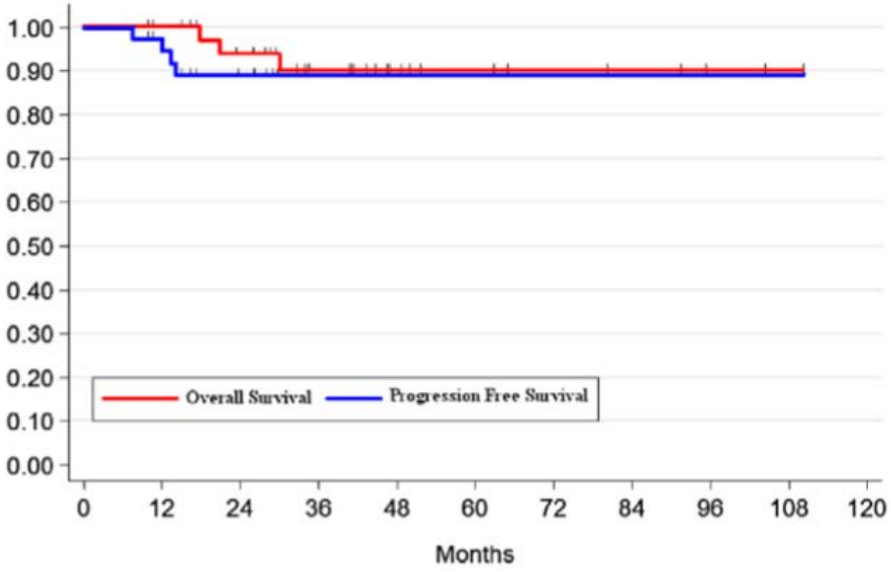
Halasz

	3y-LC	3y-PFS	Death
PET -ve	100%	97%	1 (2nd lymphoma)
PET +ve	90%	90%	1 (relapse)

- Better outcome than would be expected
- Majority early stage
- PET positivity defined by IHP criteria (~ DS 3-5)
- Do these patients need SCT?

Radiation Therapy in Primary Mediastinal B-Cell Lymphoma With Positron Emission Tomography Positivity After Rituximab Chemotherapy

Andrea Riccardo Filippi, MD,* Cristina Piva, MD,* Francesca Giunta, MD,† Marilena Bellò, MD,† Annalisa Chiappella, MD,§ Daniele Caracciolo, MD,§ Michela Zotta, MD,† Anastasios Douroukas, MD,‖ Riccardo Ragona, PhD,* Umberto Vitolo, MD,§ Gianni Bisi, MD,† and Umberto Ricardi, MD*



- 37 pts
- DS 1-3 = 51%
- DS 4 = 38%

1/33 relapsed

- DS 5 = 11%

3/4 relapsed

Int J Radiation Oncol Biol Phys, Vol. 87, No. 2, pp. 311–316, 2013

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PET +ve Post chemo

- Selected patients have good prognosis with RT alone (without ASCT):
  - Early stage
  - Advanced stage with a predominant site (+ other sites responded very early)
- PS:
  - PET +vity after chemo is related to bulk
  - PARMA study was relapse from remission

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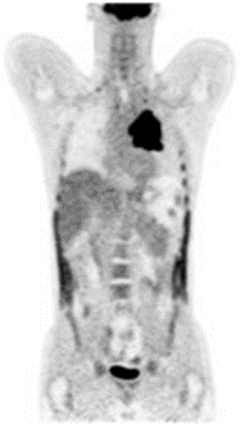
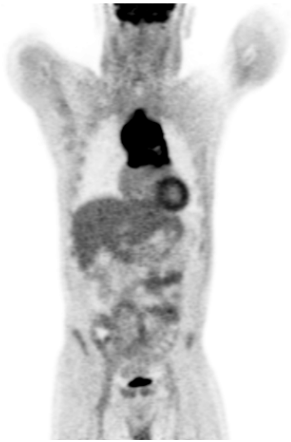
Which patient suitable for RT?

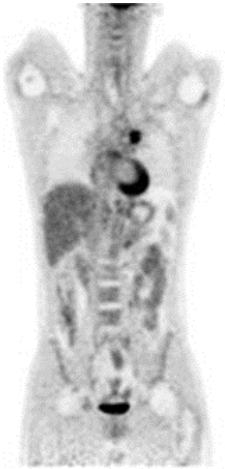
Baseline

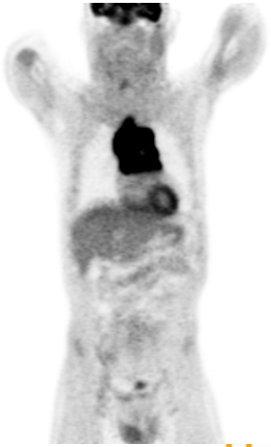




Baseline

Post chemo





Post chemo

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(2) Peri-transplant RT

Role & Timing

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2 Facts about ASCT salvage

- Results of salvage ASCT after "R" is worse
  - Relapse after RCHOP defines a worse prognostic group
- CORAL study:
  - RR 51% v 83%
  - 3y EFS 21% v 47%
  - Relapse < 1 year after Rituximab 1st line: particularly poor outcome

- Most recurrences after ASCT are in *previously involved sites*
- PARMA study results were obtained with IFRT

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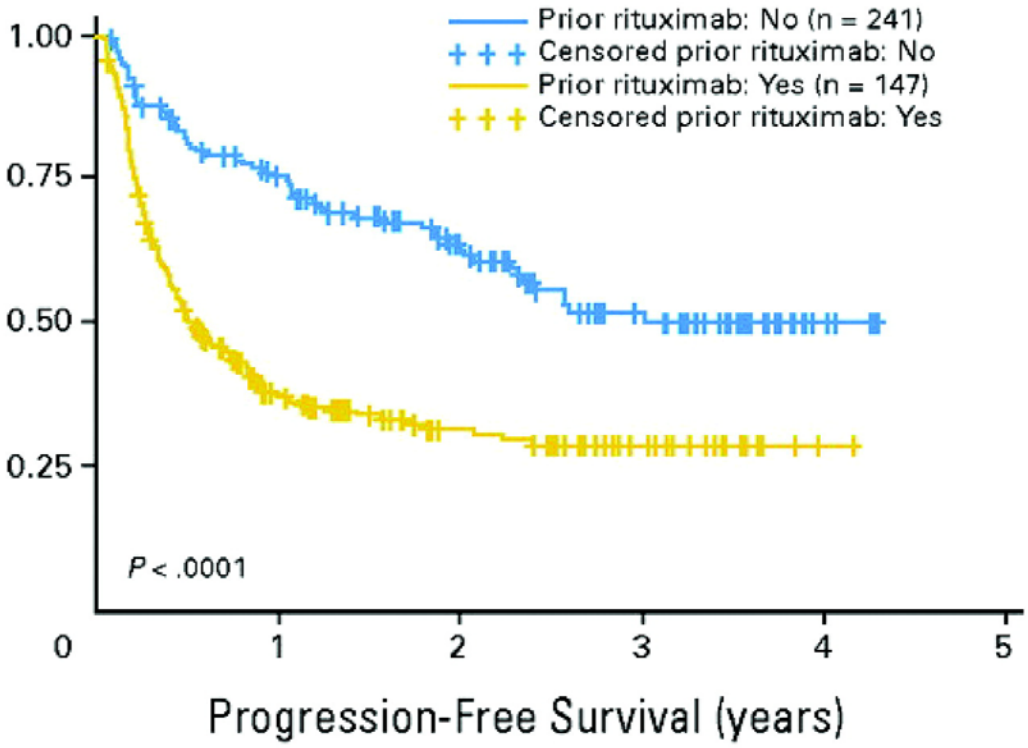
Salvage ASCT in Rituximab Era: CORAL study results.

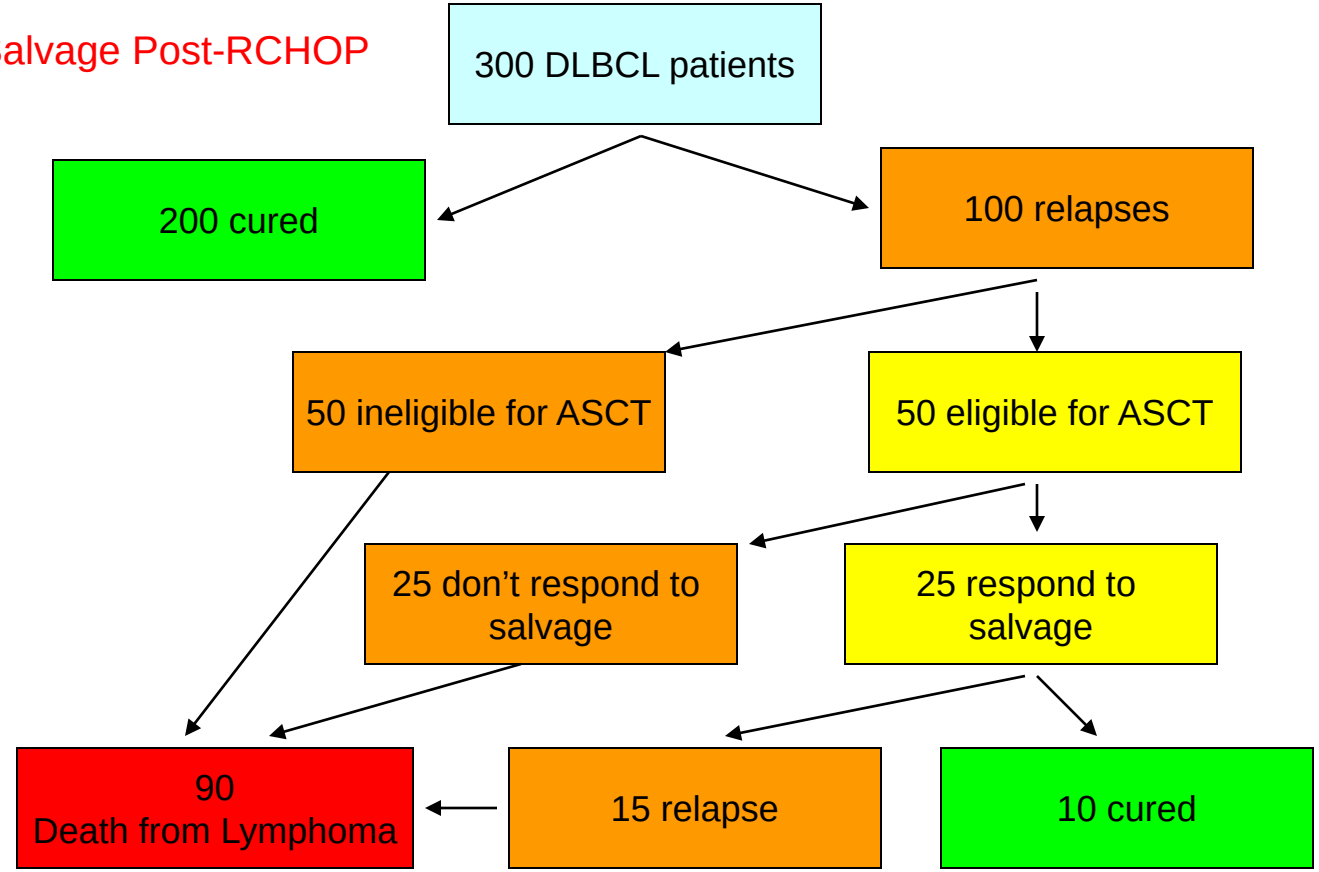


1/3 did not respond to salvage

½ did not get to ASCT

Friedberg J W Hematology 2011;2011:498-505

Salvage Post-RCHOP



Friedberg J W Hematology 2011;2011:498-505

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Role of Peri-transplant RT

	Patient No: Total (RT)		Important findings
Poen 1996	100 (24)	92% LC	RFS & OS better (SS) in RT naive
Mundt 1997	53		•2/3 of relapse in old sites •RT improves LC in: all sites, persistent >induction, persistent >ASCT
Rappaport 1997	136 (51)		RT ↑ RFS if >2cm residual at time of transplant
Vose 2001	184 1ry refractory		Registry data No RT was an adverse prognostic factor on MVA
Biswas 2010	164 (79)	10% better LC	•**Survival** benefit for RT •**Benefit in RCHOP > CHOP**

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Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 1, pp. 79–85, 2010

0360-3016/10/$–see front matter

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doi:10.1016/j.ijrobp.2009.04.036

CLINICAL INVESTIGATION **Lymphoma**

INVOLVED FIELD RADIATION AFTER AUTOLOGOUS STEM CELL TRANSPLANT FOR DIFFUSE LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA

TITHI BISWAS, M.D.,* SUGHOSH DHAKAL, M.D.,* RUI CHEN, PH.D.,† OLLIVIER HYRIEN, PH.D.,† STEVEN BERNSTEIN, M.D.,‡ JONATHAN W. FRIEDBERG, M.D.,‡ RICHARD I. FISHER, M.D.,‡ JANE LIESVELD, M.D.,‡ GORDON PHILLIPS, M.D.,‡ AND LOUIS S. CONSTINE*§

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Table 2. OS and DSS at 3-year and 5-year stratified by IFRT and rituximab

Period	R+/IFRT+ (n = 13)	R+/IFRT- (n = 20)	R minus/IFRT+ (n = 65)	R minus/no-IFRT (n = 66)
3-year OS	53%	21%	62%	50%
3-year DSS	50%	24%	64%	51%
5-year OS	53%	0%*	58%	41%
5-year DSS	50%	0%*	62%	46%

* 0% = At 5-years, patients were either censored or had died.

Timing of peri-transplant RT

PRE- transplant

Pros:

- Cytoreduction if poor salvage chemo response
- Less haematological toxicity
- Ensures administration

Cons:

- Higher risk of pneumonitis
- Delay of HD chemo
- Requires good co-ordination

POST- transplant

Pros:

- Less pneumonitis
- Less GI toxicity / VOD
- No delay in giving HD chemo

Cons:

- More haematological toxicity:
  - Irradiating regenerating marrow
  - MDS / leukemogenic risk
- May be delayed or omitted if recovery is prolonged

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Choice

- Local expertise and practice
- Disease status / response to salvage
- Type & pattern of disease
  - HL v NHL
  - Localised v disseminated
- Site of RT
- Previous chemo, HD chemo

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(3) Transplant-ineligible patients & Relapse after transplant

Palliative v Radical RT?

How radical should RT be?

Prognostic factors:

- Patient: age – comorbidities
- Initial disease: stage – B symp – EN sites
- Previous Rx: Rituximab - RT - ASCT
- Relapse:
  - Primary refractory v Relapse from remission
  - Disease-free interval
  - Extent of relapse
- Aim of salvage

Non transplant eligible

3 groups:

- Age / co-morbidities (up to ½ of relapses)
- Transplant eligible
  but poor response to salvage
  (salvage refractory)

Localised → Radical

Disseminated → Palliative

- Relapse after transplant (DFI, dis extent, previous RT)

e.g. late localised relapse - no RT vs early relapse after RT or disseminated

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What can RT achieve in refractory HG-NHL?

Without transplant:

- High response rate: 75-90%
- Durable LC: 50 – 65%
- Durable PFS in a small group, particularly localised disease and low IPI
- LC / cytoreduction may enable SCT in selected patients
- Excellent palliation with min toxicity

Salvage RT for *relapsed / chemorefractory* disease

Ref	No	patients	Local Control	PFS	Other findings
Aref 1999	35	chemoresitant	LC 47% @2y		Trend to better LC >39.6Gy
Martens 2006	34	Chemo-resistant Twice-daily RT	LC 73% @3y	PFS 15% @3y	ORR 97% (CR 24%, Cru 26%, PR 47%)
Halasz 2012	59	PET+ (interim or post-CT)	3y LC 90% v 100% In PET+ v PET-	3y PFS 90% v 97%	

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International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Rates and Durability of Response to Salvage Radiation Therapy Among Patients With Refractory or Relapsed Aggressive Non-Hodgkin Lymphoma

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110 pts, 121 sites. mFU 4.6y

IJROBP, 2015

Table 1 Patient demographic and disease characteristics among patients treated with curative (n=72, 76 sites) and palliative intent (n=38, 45 sites)

Characteristic	Treatment intent: Curative n	Curative %	Palliative n	Palliative %	Total n	Total %
Age at diagnosis (y)* (median and range)	54	19-88	62.5	32-86	55	19-88
Refractory/relapsed						
Refractory	45	63	30	79	75	68
Relapsed	27	38	8	21	35	32
Gender						
Female	28	39	16	42	44	40
Male	44	61	22	58	66	60
Histology						
Diffuse large B-cell lymphoma	56	78	29	76	85	77
Grade 3 follicular lymphoma	5	7	2	5	7	6
T cell lymphoma	3	4	2	6	5	5
Other†	8	11	5	13	13	12

2/3

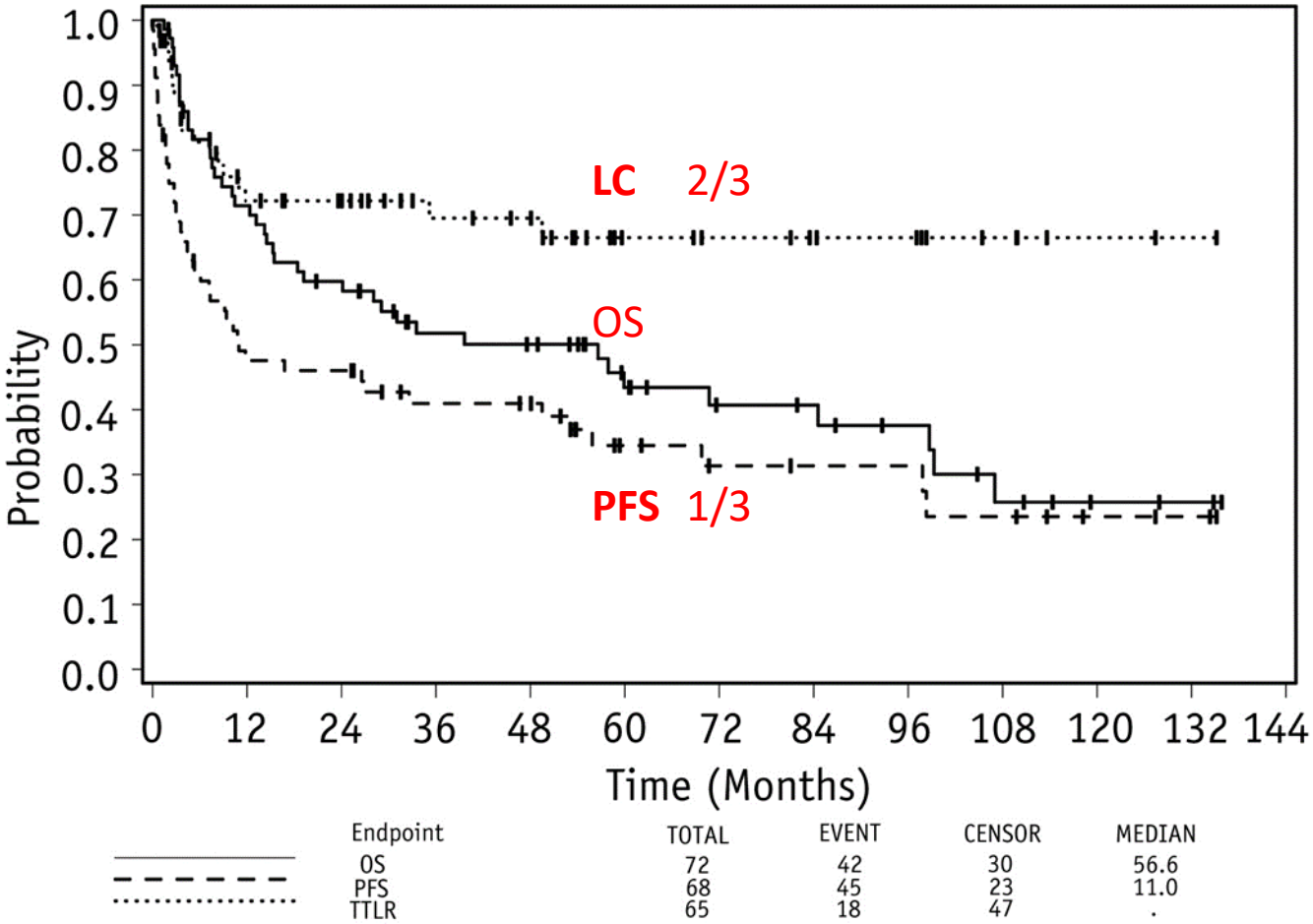
1/3

2/3

1/3

3/4

Median dose for curative = 40Gy



RR 85%

No dose response </> 40Gy

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Palliative low dose RT

Number of patients Number of sites	17 43
Histological subtype DLBCL MCL	 14 (37 sites) 3 (6 sites)
Median time from diagnosis to LDRT (months)	22 (0.23-195.1)
Median number of systemic therapies	3 (0-7)

- median OS 2.4 m (0.03-126.7)
- 4-8 Gy

Treatment outcome	ORR	CR	LR
All	91% (39/43)	49% (21/43)	10%
Site			
- Skin (23)	100% (23)	74%	4% (1/23)
- Nodal/EN (15)	87% (13)	27%	8% (1/13)
- Bone (5)	60% (3)	0	77% (2/3)
Dose			
- 4Gy (16)	88%	63%	14%
- 6-8Gy (27)	93%	41%	8%
Histology			
- DLBCL	92%	51%	12%
- MCL	83%	33%	0
No of previous lines of treatment			
- ≤2	86%	38%	17%
- >2	96%	59%	5%

- LC = 90%
- Patients surviving > 6m: 7 sites (3 pts) remaining controlled at 12 m
- Max response duration was 127 months (0.5-126.6)

Brady ESTRO 2016

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Key points

- Localised PET+ residual disease can be salvaged with RT in selected cases
- Consolidation RT is an option Peri-transplant for selected patients (improves PFS & ?OS)
- Salvage RT is an option for localised chemoresistant disease (durable LC 2/3, PFS 1/3)
- Higher doses are required for resistant disease
- Palliative RT is effective in chemoresistant disease (50 – 80% RR)

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Extranodal lymphomas:

Bone

Umberto Ricardi

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UNIVERSITY OF TURIN

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Introduction

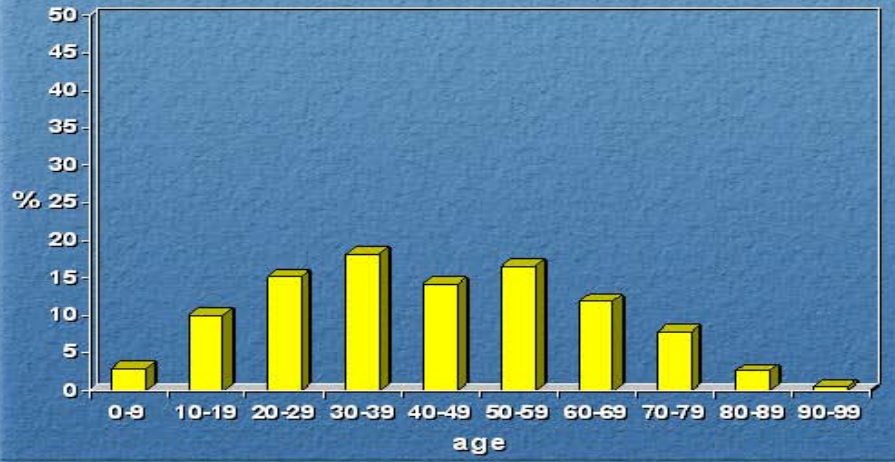
- Primary bone lymphoma (PBL) constitutes approximately 5% of all extranodal NHLs, <1% of all NHLs, and 3-7% of all malignant primary bone tumours
- Median age at diagnosis: 45 – 60 years old
- Slight preponderance of males over females (male/female ratio 1.5)

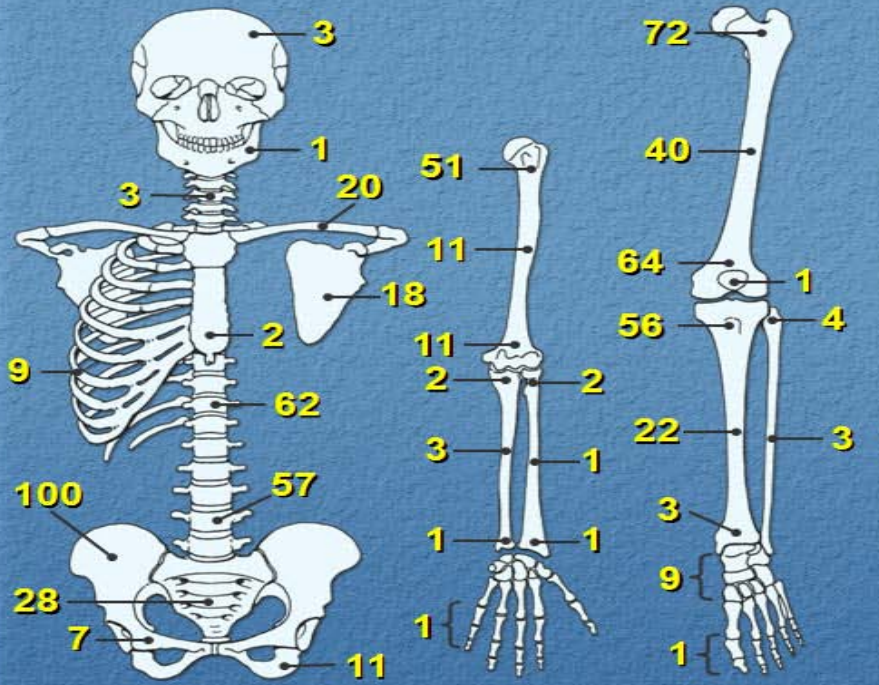
Introduction

- Most patients with bone lymphoma have DLBCL (80% of cases)
- Approximately 80% of patients present in stage IE (about 10% of patients have a polyostotic presentation)
- The most common involved bones are femur (most often diaphyseal involvement) and pelvis

Primary Lymphoma of Bone
620 cases

Average: 43 - Median: 42





27 multiple cases with 89 lesions

Clinical presentation

- Symptoms:
  - pain 80–95%
  - tumour mass 30–40%
  - pathological fracture 15–20%
- Mean time between symptoms and diagnosis: 8 months
- Spinal cord compression: 16%

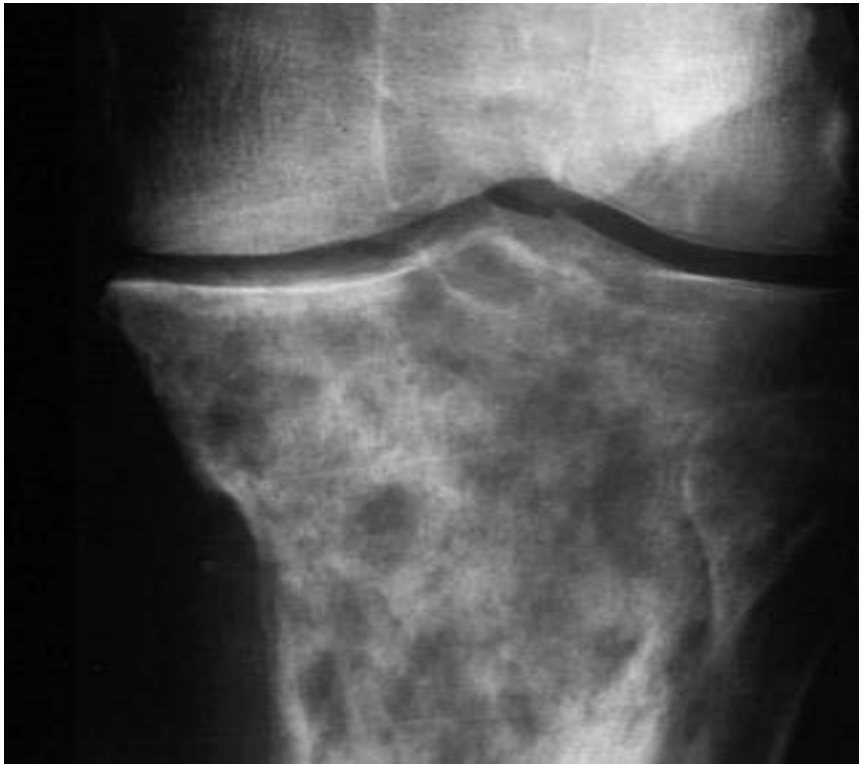
Staging

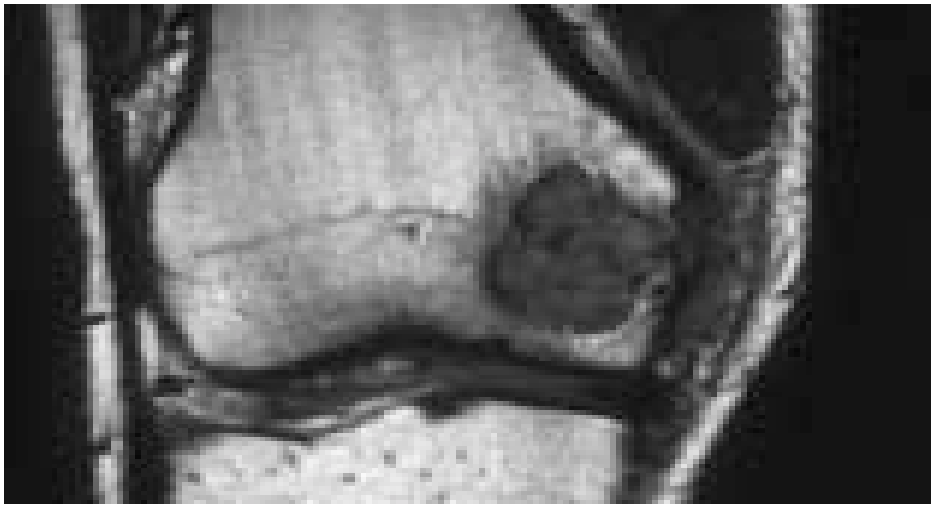
Staging procedures in patients with bone lymphoma.

Test/procedure
Demographics and medical history*
Physical examination
Blood tests#
Chest X-ray
Contrasted CT scan of the neck, chest, abdomen, and pelvis
MRI of bony lesions
^{18}FDG-PET
Bone marrow biopsy
In case of suspicion of involvement of particular organs
Cerebrospinal fluid (CSF) examination§
Gadolinium-enhanced brain MRI§
Gastrointestinal tract endoscopy
Blood smears

Radiographic findings

- **Rx:**
  - mostly lytic lesions
  - a mixture of permeative, moth-eaten or destructive patterns of the bone cortex
  - often reactive changes of the periosteum
- **contrast-enhanced CT scan:**
  - demonstrates the boundaries of any extraosseous extension
  - indicates cortical breakthrough by the tumour
  - detects osteolysis, osteosclerosis and fragments of bone sequestra
- **MRI:**
  - more detailed extension of disease
  - evidence of cortical changes, intratumoural fibrosis, replacement of trabecular bone and bone marrow by tumour
- **PET-CT:**
  - recommended for initial evaluation, staging and response assessment





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Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

U. Vitolo[1], J. F. Seymour[2], M. Martelli[3], G. Illerhaus[4], T. Illidge[5], E. Zucca[6], E. Campo[7] & M. Ladetto[8] on behalf of the ESMO Guidelines Committee*

Annals of Oncology 00: 1–12, 2016

Table 6. The International Extranodal Lymphoma Study Group (IELSG) staging system for DLBCL of the bone

Lymphoma extension	IELSG Stage
Single bony lesion	IE
Single bony lesion with involvement of regional lymph nodes	IIE
Multifocal disease in a single bone or lesions in multiple bones in a disease exclusively limited to the skeleton (without lymph nodal or visceral disease)[a]	IVE
Disseminated lymphoma with at least one bony lesion	IV

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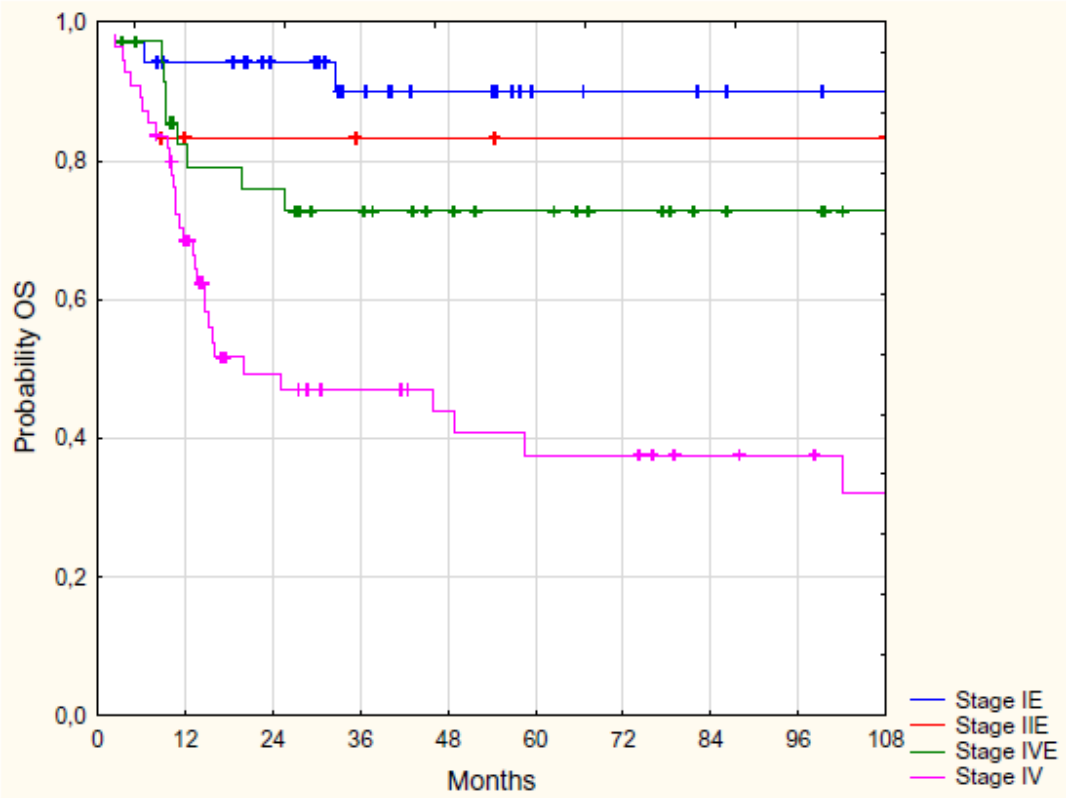
Prognosis according to stage



Messina et al, Cancer Treat Rev, 2015

DLBCL: combined modality treatment

- In aggressive DLCL, RT is used in combination with chemotherapy

- RT continues to have an important place in ensuring locoregional control and improving overall outcome in the combined modality treatment programs

Treatment

- *Combined modality therapy:*

R-CHOP x 6, followed by RT

Treatment: CMT as standard approach

• *Dosoretz et al.* treated 30 PBLs with RT alone

5 year-DFS: 53%; OS:63% Cumulative incidence of local recurrence: 14%

No local failures if dose up to 50 Gy

• *Fairbanks et al.* reported on 63 Stage IE PBLs

50 pts received RT alone, 10 CMT, 2 CT alone, 1 surgery alone

Univariate analysis: improved 5-year DFS with CMT vs RT alone (90% vs 57%) Doses over 40 Gy improved OS

• *Bacci et al.* 30 pts with localized PBL with 10 yrs follow-up

26 pts CT with anthracycline-chemo: 3 systemic relapses

4 RT only (30-45 Gy whole bone; 10-15 Gy boost): 1 local relapse

DFS 88 % at 87 months mean follow-up

Excellent cure rates with the addition of CT to RT

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Lymphoma

Clinical Features, Management, and Prognosis of an International Series of 161 Patients With Limited-Stage Diffuse Large B-Cell Lymphoma of the Bone (the IELSG-14 Study)

Marta Bruno Ventre,[a] Andrés J.M. Ferreri,[a] Mary Gospodarowicz,[b] Silvia Govi,[a] Carlo Messina,[a] David Porter,[c] John Radford,[d] Dae Seog Heo,[e] Yeon Park,[f] Giovanni Martinelli,[g] Emma Taylor,[h] Helen Lucraft,[i] Angela Hong,[j] Lydia Scarfò,[a] Emanuele Zucca,[k] David Christie,[l] on behalf of the International Extranodal Lymphoma Study Group (IELSG)

The Oncologist 2014;19:291–298

Implications for Practice: Patients with limited-stage diffuse large B-cell lymphoma of the bone exhibit a favorable prognosis when treated with primary anthracycline-based chemotherapy whether followed by radiotherapy or not. In patients treated with chemoradiotherapy, the use of larger radiation fields and doses are not associated with better outcome. Central nervous system dissemination is a rare event in these patients, suggesting that specific prophylaxis is superfluous.

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Parameter	Value
Patients, *n* (%)	161 (100)
Median age (yr) (range)	55 (18–99)
Age >60 years old, *n* (%)	62 (39)
Male gender, *n* (%)	90 (51)
Male/female ratio	1:2
Stage IIE, *n* (%)	20 (13)
B symptoms, *n* (%)	14 (9)
High LDH serum level, *n* (%)[a]	54/158 (34)
IPI risk group (score), *n* (%)	
Low (0–1)	113 (70)
Low intermediate (2)	36 (22)
High intermediate (3)	7 (4)
Unknown	5 (3)
Site, *n* (%)	
Femur	33 (20)
Spine	27 (17)
Pelvis	27 (17)
Skull	25 (15)
Lower limb, excluding femur	21 (13)
Upper limb, excluding humerus	11 (7)
Humerus	11 (7)
Others	6 (4)

Parameter	Combined treatment	Chemotherapy alone	Radiotherapy alone
Patients, *n*	125	13	23
Median age (yr) (range)	54 (18–99)	52 (27–68)	64 (27–85)
Age >60 years old, *n* (%)	43 (34)	2 (15)	14 (61)
Male gender, *n* (%)	66 (53)	9 (69)	14 (61)
Stage IIE, *n* (%)	15 (12)	2 (15)	3 (13)
B symptoms, *n* (%)	12 (10)	2 (15)	0 (0)
High LDH serum level[a]	46/123 (37)	6/12 (50)	2/23 (9)
IPI risk group (score), *n* (%)			
Low (0–1)	86 (69)	10 (77)	17 (74)
Low intermediate (2)	31 (25)	1 (8)	4 (17)
High intermediate (3)	4 (3)	1 (8)	2 (9)
Unknown	4 (3)	1 (8)	0 (0)

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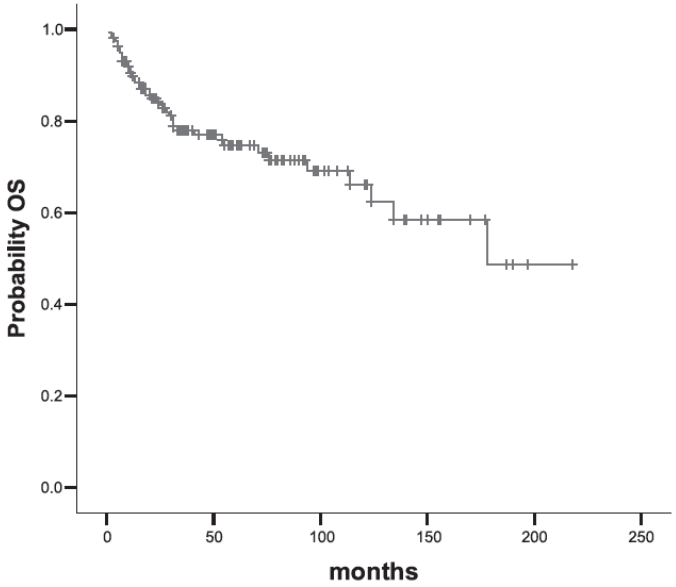

Table 4. Multivariate analysis

Variable	Subgroup	Odds ratio	95% CI	*p*
Age	Continuous	1.04	1.02–1.07	.0001
ECOG-PS	0–1	1.88	0.98–3.61	.057
	2–4			
Stage	I	1.27	0.44–3.67	.65
	II			
LDH	Normal	0.92	0.44–1.93	.83
	High			
B symptoms	No	1.25	0.37–4.27	.71
	Yes			
Fracture	No	0.87	0.41–1.85	.71
	Yes			
Primary chemotherapy	No	0.42	0.22–0.81	.009
	Yes			

Therapeutic issues

- Anthracycline-based chemotherapy as first line treatment for patients affected with primary bone DLBCL
- A survival benefit of the addition of the anti-CD20 monoclonal antibody rituximab to CHOP in primary bone DLBCL has not been demonstrated

- **The survival benefit of adjuvant irradiation after primary R-chemotherapy is a matter of debate**

- **Optimal radiation volumes and doses**

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Considerations on RT volumes

- IELSG-14 study:
  - primary bone DLBCL treated with CHOP followed by RT of the whole bone: 5-year PFS 76%
  - primary bone DLBCL treated with CHOP followed by RT of a part of the affected bone (IF-RT): 5-year PFS of 64%

Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Yahalom et al, IJROBP, 2015

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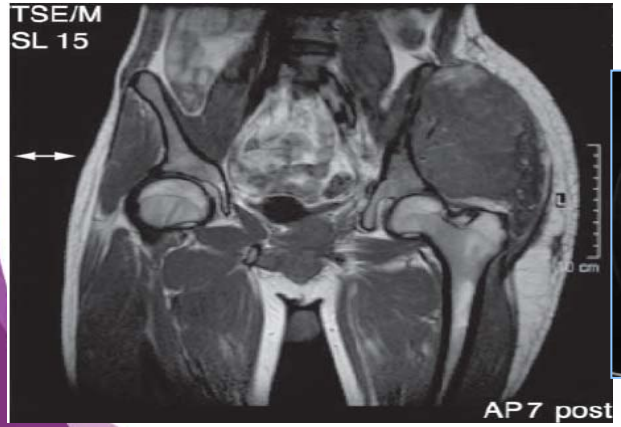
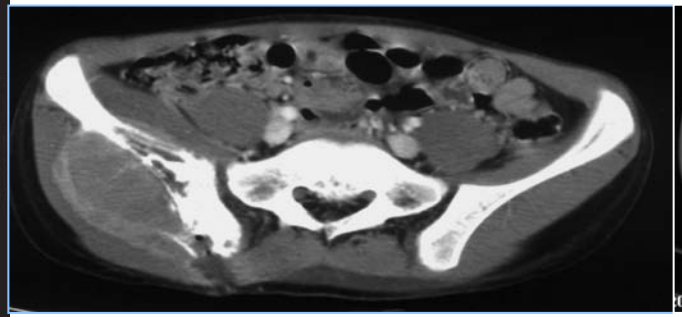
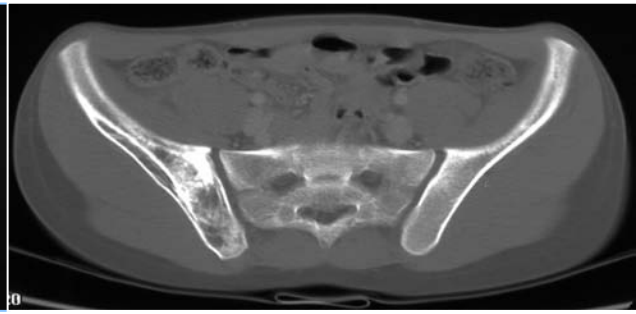
Radiation volumes

- CTV: Prechemotherapy GTV (preferably on MRI) with margins added to accommodate uncertainties in subclinical tumor extension and quality of imaging, and fusion into simulation CT

- PTV is between 0.5-1 cm, depending on site and immobilization







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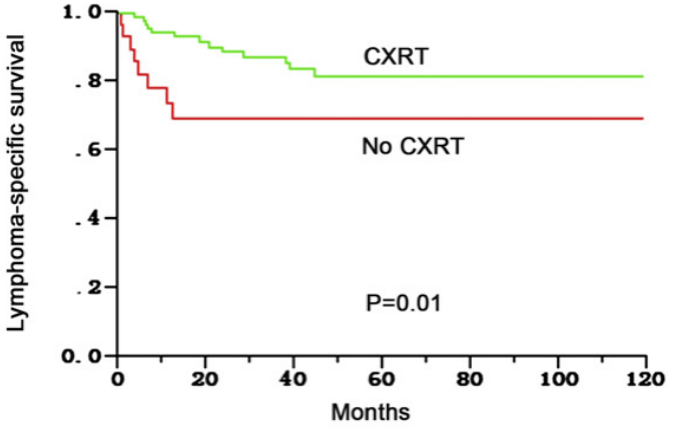
Considerations on RT dose

- Radiation dose depends on:
  - the size of the irradiated volume
  - the anatomical area
  - the response to primary chemotherapy

- IELSG-14 study:
  - 47 pts irradiated with a dose ≤ 36 Gy: 5-year PFS 72%
  - 58 pts irradiated with a dose > 36 Gy: 5-year PFS 75%

Rare Cancer Network study

116 PBL pts



CXRT = chemoradiotherapy

CXT = chemotherapy

RT = radiotherapy

Table 2 Univariate analyses (log–rank test)

Variable	*n*	5-y OS (%)	95% CI	*p*	5-y LSS (%)	95% CI	*p*	5-y LC (%)	95% CI	*p*
Treatment modality										
CXRT	87	79	69–89	0.001	81	72–90	<0.001	93	87–99	0.13
CXT	14	92	78–106		92	78–106		77	54–100	
RT	15	49	22–76		49	22–76		100	100	
CXRT vs. RT and CXT										
CXRT	87	79	69–89	0.05	81	72–90	0.01	93	87–99	0.66
RT and CXT	29	69	51–87		69	51–87		87	73–101	
Treatment modality of CXRT and RT vs. CXT										
CXRT and RT	102	75	66–84	0.27	94	89–99	0.08	94	89–99	0.08
CXT	14	92	78–106		77	54–100		77	4–100	
Treatment modality of CXRT and CXT vs. RT										
CXRT and CXT	101	80	71–89	0.004	82	73–91	<0.0001	91	85–97	0.24
RT	15	49	22–76		49	22–76		100	100	

Cai et al, IJROBP, 2011

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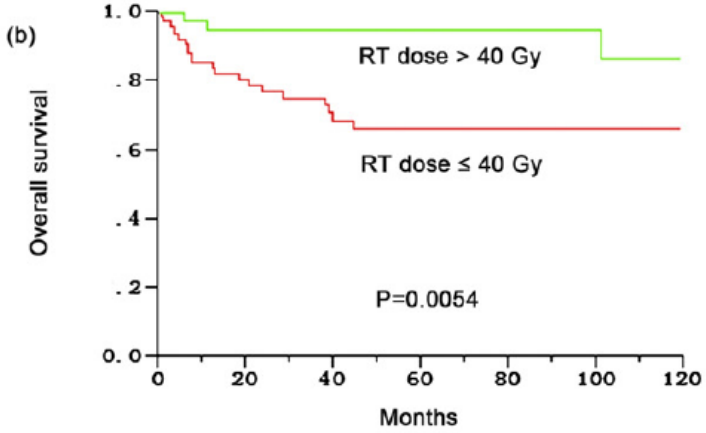
Early-Stage Primary Bone Lymphoma: A Retrospective, Multicenter Rare Cancer Network (RCN) Study

Ling Cai, M.D.,*,‡ Michael C. Stauder, M.D.,† Yu-Jing Zhang, M.D.,‡ Philip Poortmans, M.D.,§ Ye-Xiong Li, M.D.,¶ Nicolaos Constantinou, M.D.,‖ Juliette Thariat, M.D.,** Sidney P. Kadish, M.D.,†† Tan Dat Nguyen, M.D.,‡‡ Youlia M. Kirova, M.D.,§§ Pirus Ghadjar, M.D.,¶¶ Damien C. Weber, M.D.,‖‖ Victoria Tuset Bertran, M.D.,*** Mahmut Ozsahin, M.D., Ph.D.,* and René-Olivier Mirimanoff, M.D.*

Int J Radiation Oncol Biol Phys, Vol. 83, No. 1, pp. 284–291, 2012



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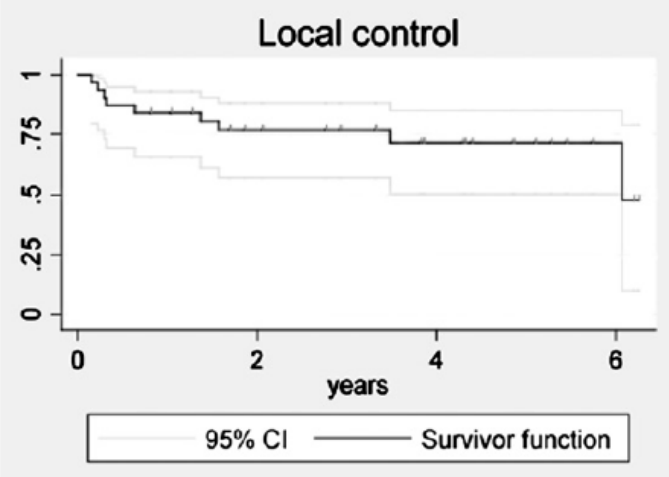
LIMITED CHEMOTHERAPY AND SHRINKING FIELD RADIOTHERAPY FOR OSTEOLYMPHOMA (PRIMARY BONE LYMPHOMA): RESULTS FROM THE TRANS-TASMAN RADIATION ONCOLOGY GROUP 99.04 AND AUSTRALASIAN LEUKAEMIA AND LYMPHOMA GROUP LY02 PROSPECTIVE TRIAL

DAVID CHRISTIE, F.R.A.N.Z.C.R.,* KEITH DEAR, M.STAT.,† THAI LE, B.H.B.,‡
MICHAEL BARTON, F.R.A.N.Z.C.R.,§ ANDREW WIRTH, F.R.A.N.Z.C.R.,‖ DAVID PORTER, F.R.A.C.P.,¶
DANIEL ROOS, F.R.A.N.Z.C.R.,# AND GARY PRATT, F.R.A.N.Z.C.R.**



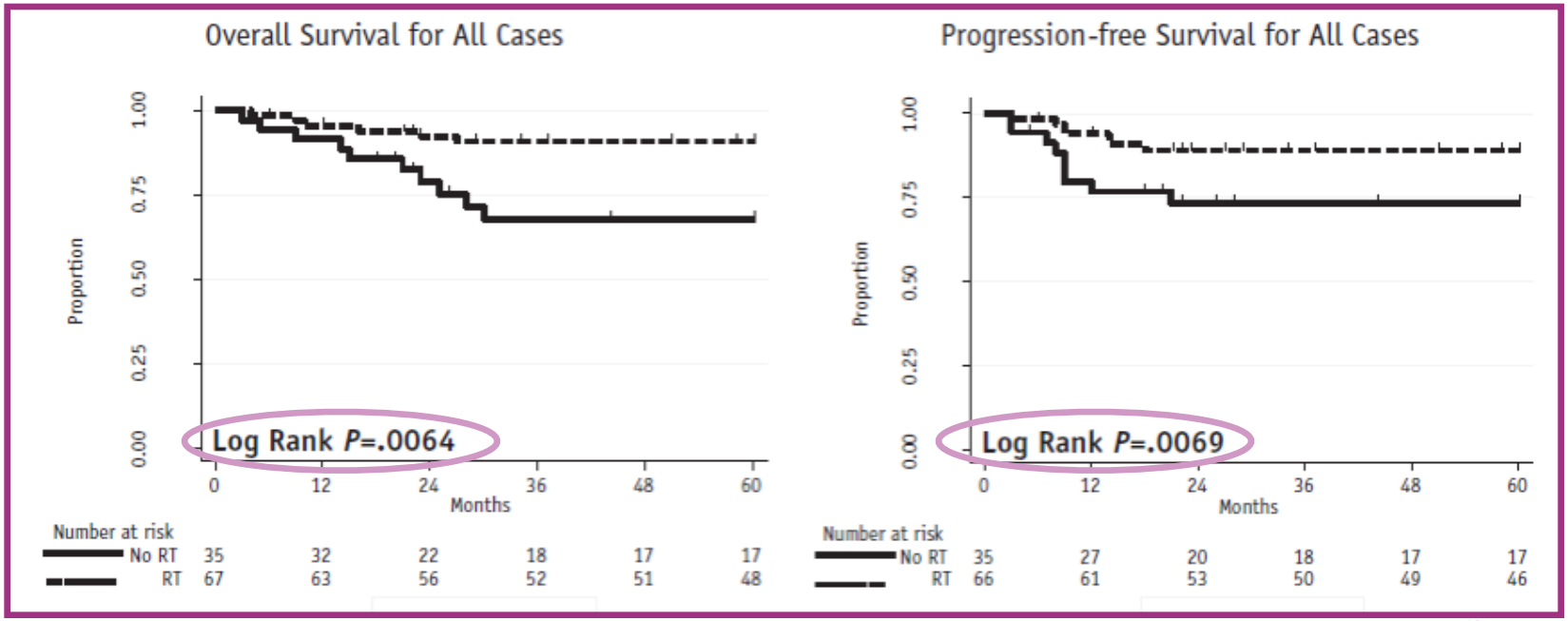
Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 4, pp. 1164–1170, 2011

radiation to a dose of 45 Gy in 25 fractions

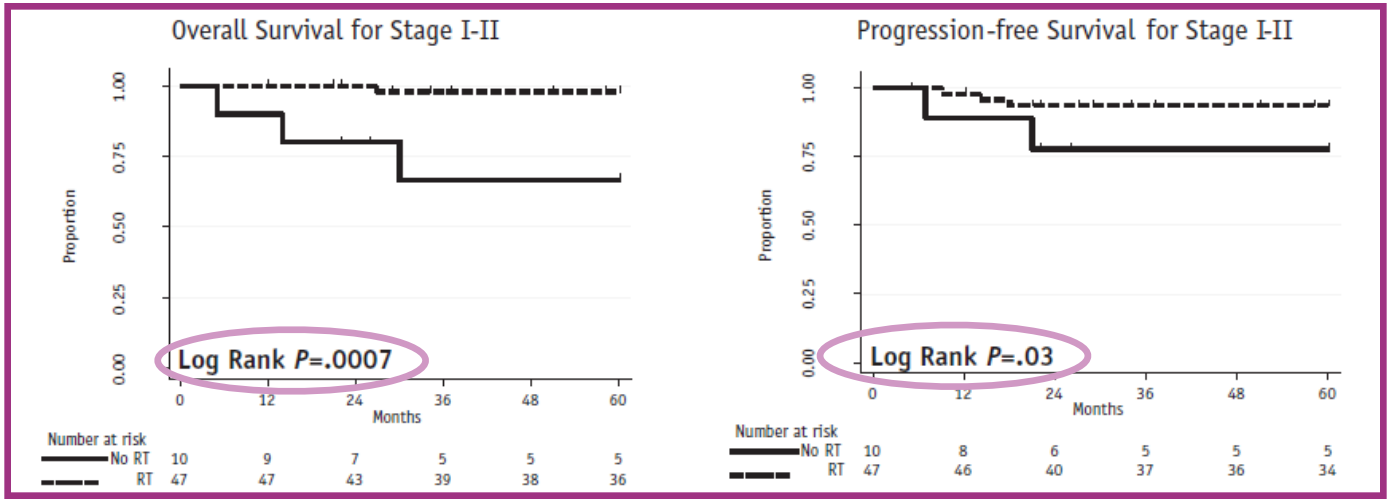
Conclusions: Relatively high rates of survival were achieved but the number of local failures suggests that the dose of radiotherapy should remain higher than it is for other types of lymphoma. Disability after treatment due to pathological fracture was not seen.

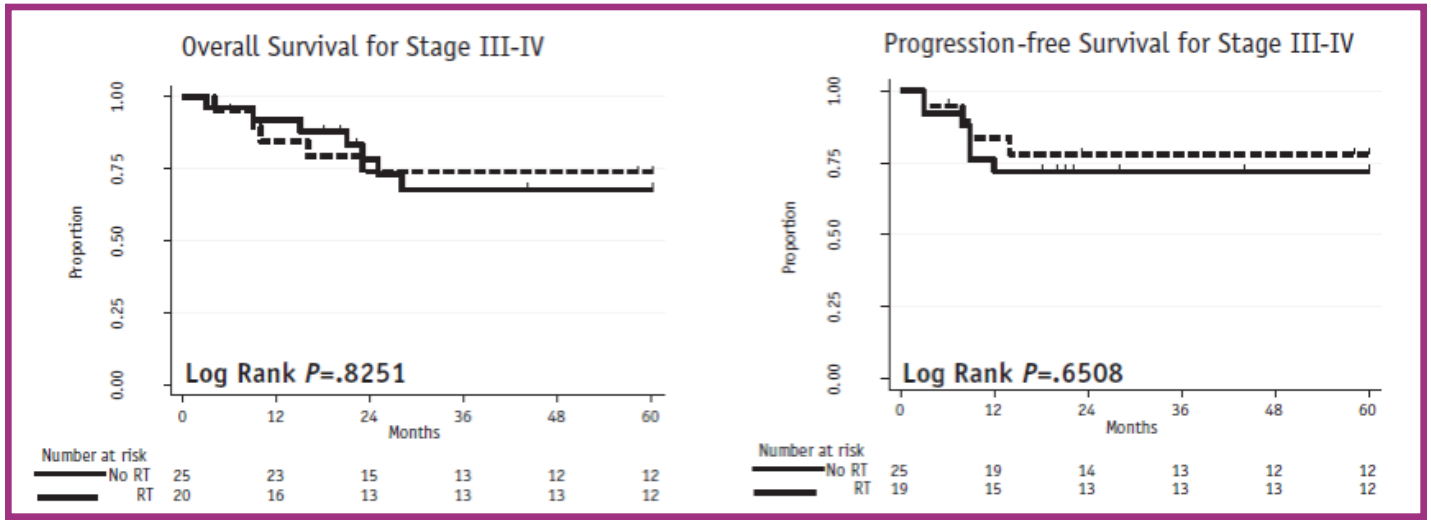
- 102 patients with primary bone DLBCL
- median age: 55 years (range, 16-87 years)
- most common site of presentation: long bones

- RT: 67 pts (66%)
  - 47 pts stage I – II
  - 20 pts stage III – IV
- median RT dose: 44 Gy



Tao et al, IJROBP, 2015





Tao et al, IJROBP, 2015

Table 3 Patient characteristics with overall and progression-free survival in multivariate Cox regression model

Characteristic	Overall survival		Progression-free survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
IPI score				
0-1	Ref		Ref	
2-3	2.1 (0.3-16.8)	.481	0.4 (0.06-2.4)	.303
4-5	13.5 (6.9-114.7)	.037	24.3 (3.3-178.2)	.002
Single or multiple bony sites				
Single	Ref		Ref	
Multiple	18.0 (2.1-157.4)	.035	11.7 (1.7-79.4)	.012
Response to chemotherapy				
Complete	Ref		Ref	
Partial	1.7 (0.4-7.2)	.075	4.5 (0.7-29.6)	.118
No response/progression	5.2 (1.3-19.8)	.003	30.8 (4.1-233.7)	.001
Radiation therapy				
No	Ref		Ref	
Yes	0.3 (0.09-1.01)	.053	0.14 (0.03-0.72)	.014

Abbreviations: CI = confidence interval; HR = hazard ratio; IPI = International Prognostic Index.

No significant difference in PFS or OS was found between patients treated with 30 to 35 Gy versus ≥ 36 Gy

Tao et al, IJROBP, 2015

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Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Dose range is 30 to 40 Gy, depending on the certainty that a CR has been obtained with systemic treatment

After chemotherapy, complete regression of PET uptake may not be clear at the time of RT

Yahalom et al, IJROBP, 2015

Treatment

- *Combined modality therapy:*

R-CHOP x 6 cycles followed by 30-40 Gy ISRT

Therapeutic issues

- Risk of CNS recurrence associated with skeletal involvement is a matter of debate, with rates of 4% and 0.6% respectively for DLCL patients with and without skeletal involvement

- In the IELSG-14 study, CNS involvement occurred in 2.5% of patients with primary bone DLCL

- Available evidence suggests that CNS prophylaxis is superfluous in primary bone DLCL

Therapeutic issues

Long-term bone health preventive measures should also be taken into account in patients with primary bone lymphoma, including evaluation and treatment of any underlying osteoporosis, and/or vitamin D deficiency

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Aggressive nodal non Hodgkin lymphoma

The role of radiation therapy

Early Stage

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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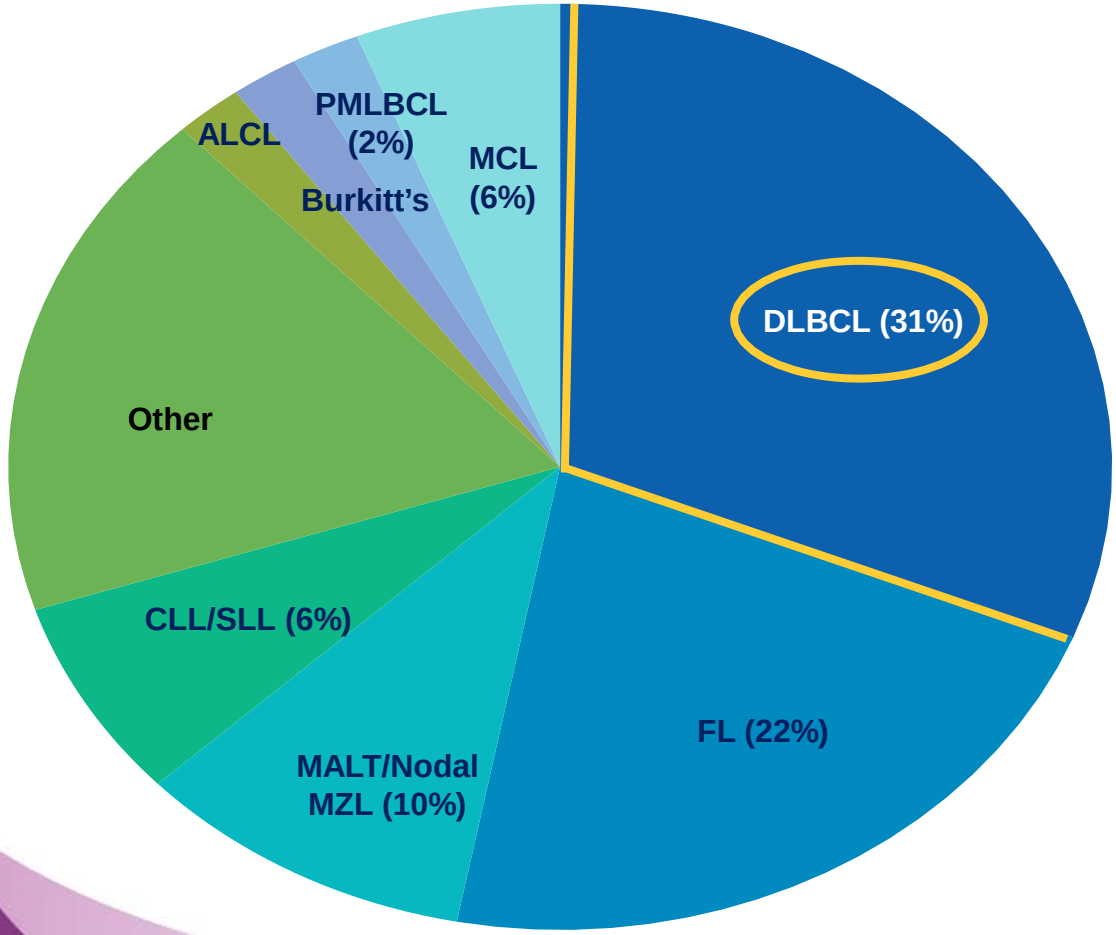
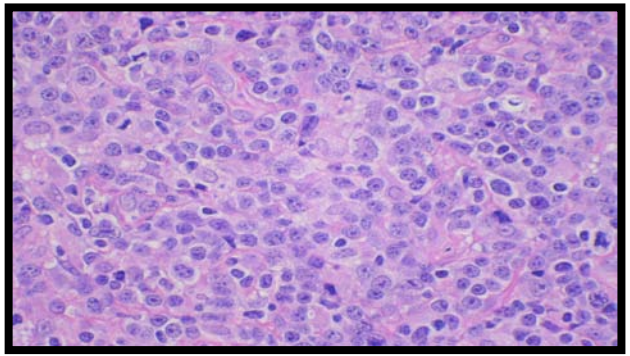
NHL: A Heterogeneous Disease



- 75% of aggressive NHL
- 40%: localized disease
- 40-50%: extranodal disease



- CMT has been the standard (with CHOP)

- Recent changes:
  - Rituximab improved PFS & OS
  - PET response assessment
  - Omitting RT in HL

- Need to revaluate role of RT in DLBCL

DLBCL is different from HL

- Prognosis:
  - HL is highly curable
  - DLBCL is curable in 60-65% in population-based studies
  - Salvage is more successful in HL > DLBCL (especially >RCHOP)

- Age: median age 60-65

- Late effects:
  - No evidence of increased risk of 2nd malignancy in NHL
  - Explanation:
    - 2nd malignancy risk is small > age 45
    - Competing causes of death: disease-related, co-morbidities

The main concern in DLBCL is curing the disease

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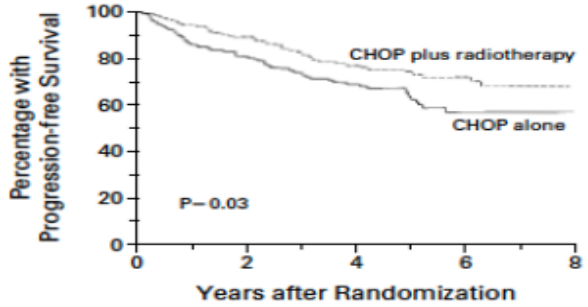
SWOG 8736

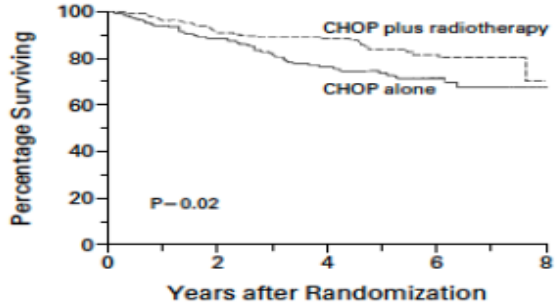
CHOP x 8 vs. CHOP x 3 + IFRT in Stage I/II DLBCL



No. at Risk					
CHOP alone	201	172	111	55	14
CHOP plus radiotherapy	200	178	119	70	17

Figure 1. Progression-free Survival of 201 Patients Receiving Eight Cycles of CHOP Alone and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

Sixty-five patients in the CHOP-alone group died or had progression of their disease, as compared with 45 patients in the CHOP-plus-radiotherapy group. The estimated rates of progression-free survival at five years were 64 percent and 77 percent, respectively.



No. at Risk					
CHOP alone	201	187	120	61	14
CHOP plus radiotherapy	200	185	128	75	17

Figure 2. Overall Survival of 201 Patients Receiving Eight Cycles of CHOP and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

There were 51 deaths in the CHOP-alone group, and 32 in the CHOP-plus-radiotherapy group. The estimated rates of survival at five years were 72 percent and 82 percent, respectively.

Miller et al NEJM 1998; 339:21

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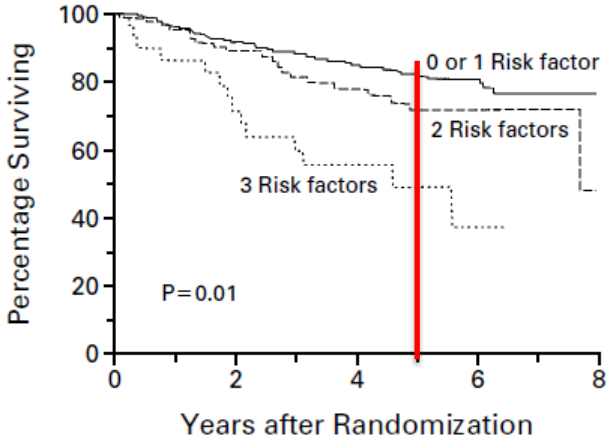
SWOG Contributions: Limited Stage DLBCL

- SWOG 8736
  - Established CHOP x 3+RT as standard of care
  - Introduced the stage-adjusted IPI:

Risk Factors
Age >60
Increased LDH
Stage II or IIE
ECOG Performance Status ≥ 2

Estimated 5-yr OS in S8736 By Risk Factors	
0-1	82% (95%CI 77-87%)
2	71% (95%CI 60-83%)
3	48% (95%CI 22-69%)
4	0%



(Miller, NEJM 1998)

Table 2. International prognostic index (IPI)

International prognostic index (IPI)			Estimated 3-year overall survival [26–29] (95% CI)
Risk factors	Age >60 years Serum LDH > normal Stage III–IV Performance status 2–4 Extranodal sites >1		
Risk categories	Low	0–1	91 (89–94)
	Low intermediate	2	81 (73–86)
	High intermediate	3	65 (58–73)
	High	4–5	59 (49–69)
Age-adjusted international prognostic index (aaIPI) in patients ≤60 years			
Risk factors	Serum LDH > normal Stage III–IV Performance status 2–4		
Risk categories	Low	0	98 (96–100)
	Low intermediate	1	92 (87–95)
	High intermediate	2	75 (66–82)
	High	3	

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v116–v125, 2015
doi:10.1093/annonc/mdv304

Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

H. Tilly[1], M. Gomes da Silva[2], U. Vitolo[3], A. Jack[4], M. Meignan[5], A. Lopez-Guillermo[6], J. Walewski[7], M. André[8], P. W. Johnson[9], M. Pfreundschuh[10] & M. Ladetto[11], on behalf of the ESMO Guidelines Committee*

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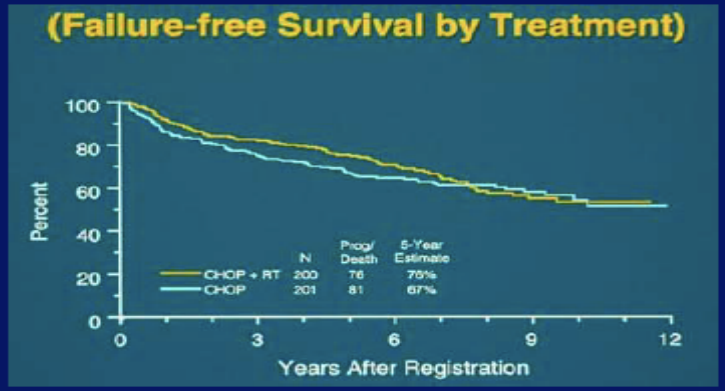
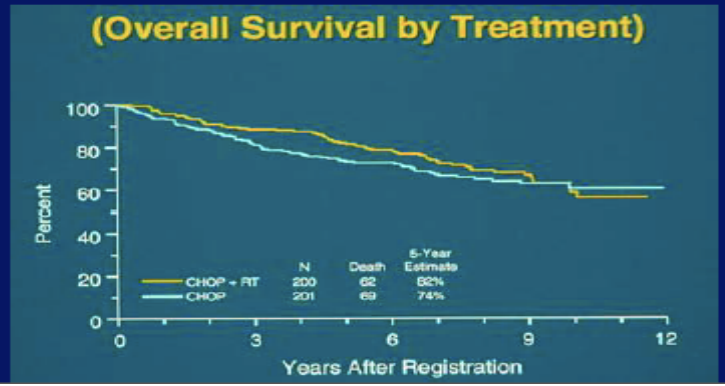
SWOG 8736: Updated Results





- Median f/u= 8.2 yrs
- FFS curves overlap at 7 years
- OS curves overlap at 9 years
- Late relapses and lymphoma deaths in CMT arm

Miller et al. ASH, 2001

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Cause Of Death S8736	CHOP8 (n = 92)	CHOP3+RT (n = 89)	Total (n = 181)
Relapse NHL	33	30	63
Cardiovascular	15	8	23
Congestive Heart Failure	7	1	8
Myocardial Infarction	3	1	4
Stroke	4	3	7
Other*	1	3	4
Secondary Malignancies	4	10	14
Lung	1	5	6
GI	2	3	5
Breast	1	0	1
Prostate	0	1	1
Melanoma	0	1	1
Infection	8	7	15
Miscellaneous**	10	14	24
Unknown	22	20	42

*AAA Rupture (1); Cardiac Arhythmia (2); PE (1)

**ALS (1); Alzheimers (2); COPD (2); Diabetes (2); Gastric Outlet Obstruction (1); Lewy Body

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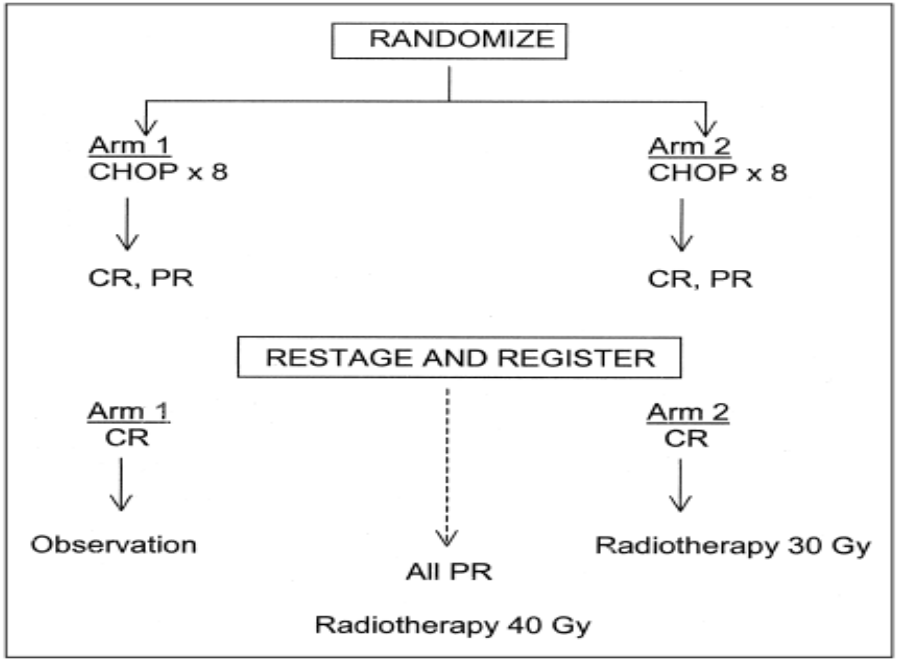
JOURNAL OF CLINICAL ONCOLOGY VOLUME 22 · NUMBER 15 · AUGUST 1 2004

Chemotherapy With or Without Radiotherapy in Limited-Stage Diffuse Aggressive Non-Hodgkin's Lymphoma: Eastern Cooperative Oncology Group Study 1484

Sandra J. Horning, Edie Weller, KyungMann Kim, John D. Earle, Michael J. O'Connell, Thomas M. Habermann, and John H. Glick



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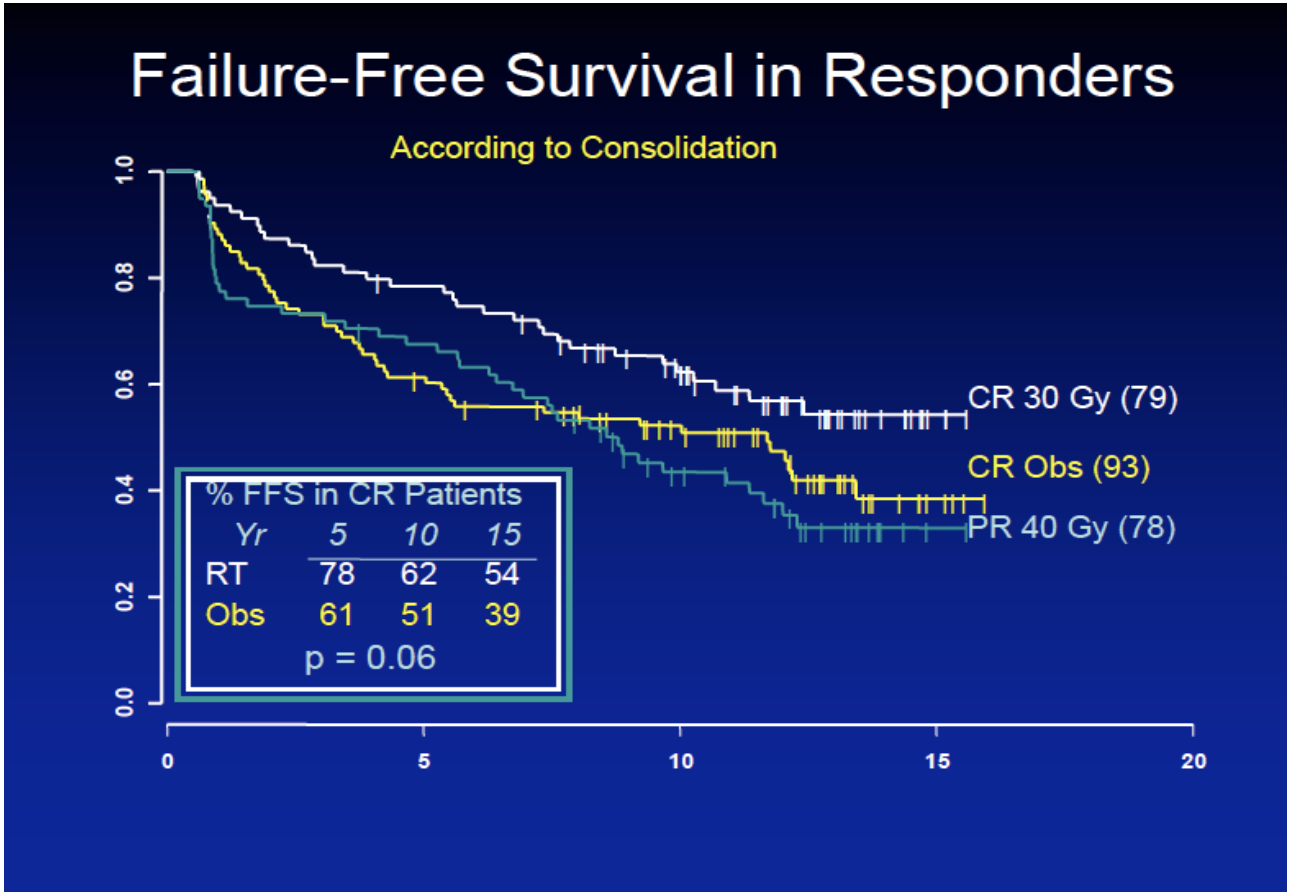
Failure-Free Survival in Responders



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2005;352:1197-205.

ACVBP versus CHOP plus Radiotherapy for Localized Aggressive Lymphoma

Félix Reyes, M.D., Eric Lepage, M.D., Gérard Ganem, M.D., Thierry J. Molina, M.D., Pauline Brice, M.D., Bertrand Coiffier, M.D., Pierre Morel, M.D., Christophe Ferme, M.D., Andre Bosly, M.D., Pierre Lederlin, M.D., Guy Laurent, M.D., and Hervé Tilly, M.D., for the Groupe d'Etude des Lymphomes de l'Adulte (GELA)*

GELA LNH 93-1

Age < 60, stage I-II, IPI 0

R
647 pts

ACVBP
318

3 x CHOP 21
+ IFRT (40 Gy)
329

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ACVBP vs CHOP + RT in Stage I/II aggressive Lymphoma

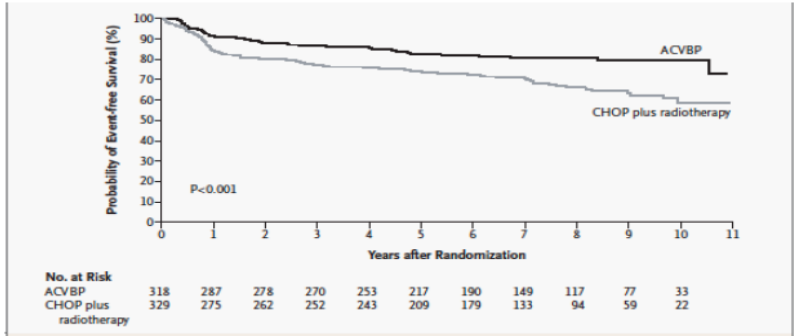

Figure 1. Event-free Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1197

Overall Survival

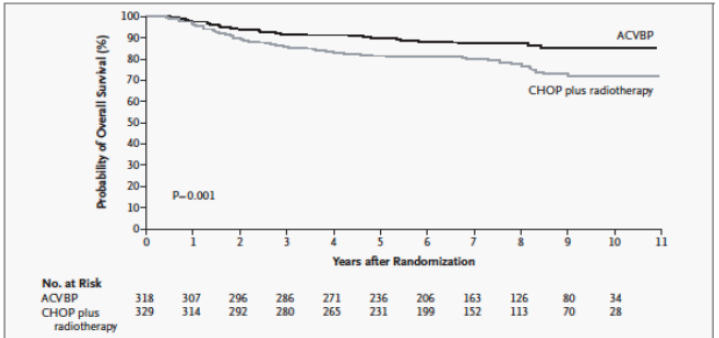

Figure 3. Overall Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1197

11% acute severe toxicity

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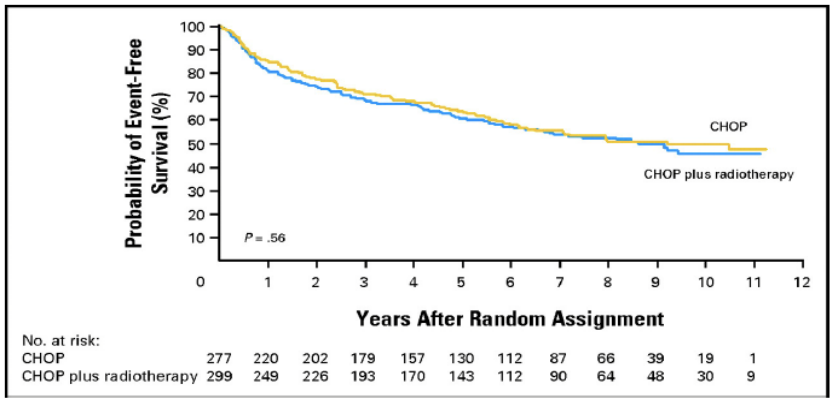
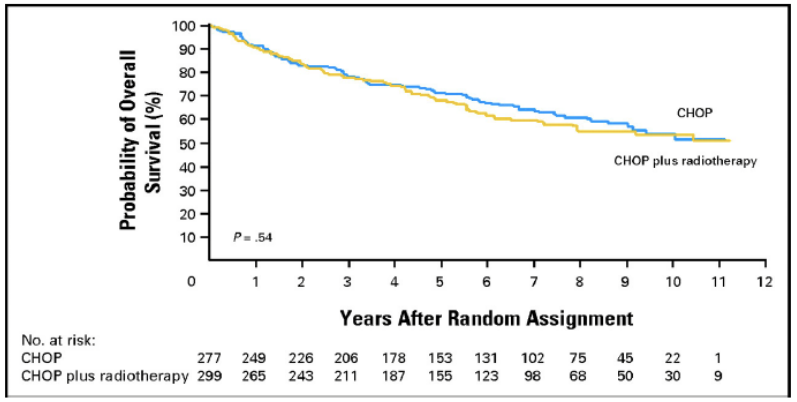
CHOP Alone Compared With CHOP Plus Radiotherapy for Localized Aggressive Lymphoma in Elderly Patients: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

Christophe Bonnet, Georges Fillet, Nicolas Mounier, Gérard Ganem, Thierry Jo Molina, Catherine Thiéblemont, Christophe Fermé, Bruno Quesnel, Claude Martin, Christian Gisselbrecht, Hervé Tilly, and Félix Reyes†



Age > 60 , stage I-II, IPI 0

Bonnet C et al. JCO 2007;25:787-792



Bonnet C et al. JCO 2007;25:787-792

GELA LNH 93-4

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GELA LNH 93-4: RESULTS

Both arms did significantly worse than CHOP x 3 cycles + IFRT in SWOG 8736 (5-ys OS 82%)

Limited Disease Radiotherapy Details

Treatment Parameter	SWOG 0014 [1]	BCCA	GELA 93-1 [2]	GELA 93-4 [3]
Recv'd RT	95%	90%	92%	88%
RT start < day 35	96%	- - -	- - -	50%
Doses	40-55	30-35	36-40	36-44
Recv'd Planned Doses	95%	96%	93%	
Relapse	0	18%	28%	34%

1. Miller et al, ASH 2003
2. Reyes et al, NEJM 2005
3. Bonnet et al, JCO 2007
4. Shenkier et al, JCO 2002

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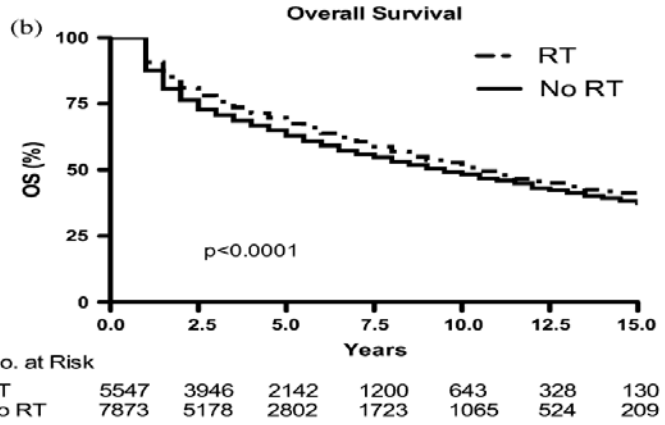
- Combined modality therapy has been the standard of care for most patients with localized diffuse large B-cell lymphoma (DLBCL), particularly those with limited stage low risk disease or bulky sites

OUTCOMES AND EFFECT OF RADIOTHERAPY IN PATIENTS WITH STAGE I OR II DIFFUSE LARGE B-CELL LYMPHOMA: A SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS ANALYSIS

Characteristic	*n* (%)
Patients	13,420 (100)
RT	
Yes	5,547 (41)
No	7,873 (59)
Age*	
≤60	6,121 (46)
>60	7,299 (54)
Extranodal disease	
No	6,368 (48)
Yes	7,052 (52)
Stage	
I	8,467 (63)
II	4,953 (37)
Gender	
Female	6,323 (47)
Male	7,097 (53)
Race	
White	11,556 (86)
Other	1,864 (14)

Abbreviation: RT = radiotherapy.
* Median, 60 y.



Variable	CHR*	95% CI	*p*†
DSS			
RT (yes vs. no RT)	0.86	0.80–0.93	0.0001
Age (≤60 vs. >60 y)	0.46	0.42–0.50	<0.0001
Extranodal disease (no vs. yes)	1.01	0.94–1.09	0.77
Stage (I vs. II)	0.76	0.70–0.81	<0.0001
Gender (female vs. male)	1.01	0.94–1.08	0.80
Race (white vs. other)	0.94	0.85–1.05	0.31
OS			
RT (yes vs. no)	0.89	0.84–0.94	<0.0001
Age (≤60 vs. >60 y)	0.41	0.38–0.43	<0.0001
Extranodal disease (no vs. yes)	0.92	0.87–0.97	0.0039
Stage (I vs. II)	0.87	0.82–0.92	<0.0001
Gender (female vs. male)	0.91	0.86–0.96	0.0007
Race (white vs. other)	0.99	0.91–1.08	0.81

- In the modern era the selection of appropriate patients for combined modality therapy has become increasingly complex over the last decade with the transition to

  - **immunochemotherapy (Rituximab)**

  - **emergence of functional imaging for response evaluation**

Is there (still) a role for Radiation Therapy in DLCL?

VOLUME 34 · NUMBER 13 · MAY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Re-Examining the Role of Radiation Therapy for Diffuse Large B-Cell Lymphoma in the Modern Era

Andrea K. Ng, *Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
Bouthaina Shbib Dabaja, *The University of Texas MD Anderson Cancer Center, Houston, TX*
Richard T. Hoppe, *Stanford University School of Medicine, Stanford, CA*
Timothy Illidge, *University of Manchester, Manchester Academic Health Sciences Centre, The Christie National Health Service Foundation Trust, Manchester, United Kingdom*
Joachim Yahalom, *Memorial Sloan Kettering Cancer Center, New York, NY*

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Radiation Therapy for Diffuse Large B-Cell Lymphoma: Indications, Outcomes, and Controversies

By Chelsea C. Pinnix, MD, PhD, *Associate Editor*

Received Dec 10, 2015. Accepted for publication Dec 15, 2015

STRO chool

Will Rituximab markedly change the results of CHOP+RT?

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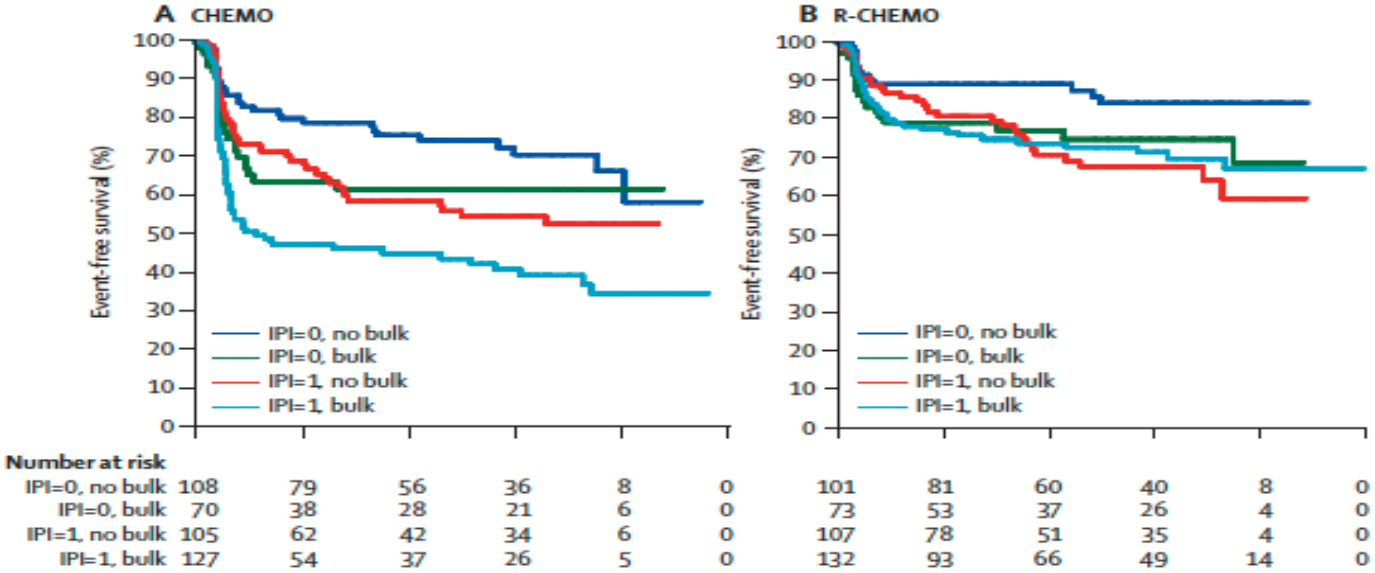
CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group

*Michael Pfreundschuh, Evelyn Kuhnt, Lorenz Trümper, Anders Österborg, Marek Trneny, Lois Shepherd, Devinder S Gill, Jan Walewski, Ruth Pettengell, Ulrich Jaeger, Pier-Luigi Zinzani, Ofer Shpilberg, Stein Kvaloy, Peter de Nully Brown, Rolf Stahel, Noel Milpied, Armando López-Guillermo, Viola Poeschel, Sandra Grass, Markus Loeffler, Niels Murawski, for the MabThera International Trial (MInT) Group**



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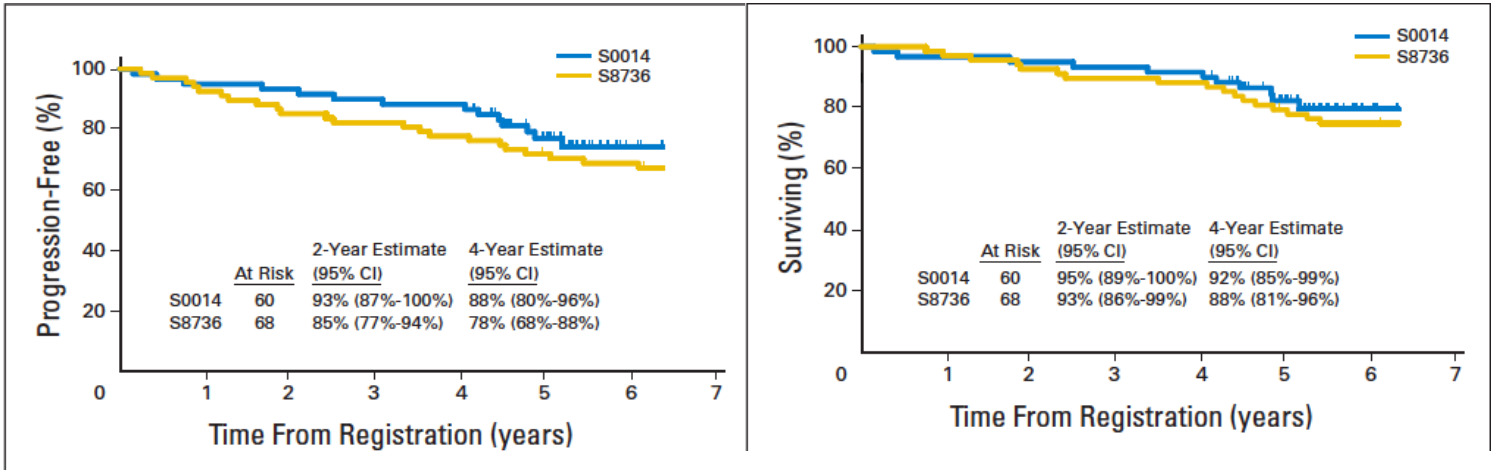
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Study of Rituximab Plus Three Cycles of CHOP and Involved-Field Radiotherapy for Patients With Limited-Stage Aggressive B-Cell Lymphoma: Southwest Oncology Group Study 0014

Daniel O. Persky, Joseph M. Unger, Catherine M. Spier, Baldassarre Stea, Michael LeBlanc, Matthew J. McCarty, Lisa M. Rimsza, Richard I. Fisher, and Thomas P. Miller



- Lower impact of R in limited stage ?
- Biological explanation : molecular fingerprint GC in 75% of cases (demonstrated lower benefit of R)

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VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Benefit of Consolidative Radiation Therapy in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP Chemotherapy

Jack Phan, Ali Mazloom, L. Jeffrey Medeiros, Tony G. Zreik, Christine Wogan, Ferial Shihadeh, Maria Alma Rodriguez, Luis Fayad, Nathan Fowler, Valerie Reed, Patrecia Horace, and Bouthaina Shbib Dabaja

Table 1. Demographic and Clinical Characteristics

Characteristic	No.	%
Sex		
Female	218	46.5
Male	251	53.5
Stage		
I	94	20.0
II	96	20.5
III	77	16.4
IV	202	43.1
Chemotherapy		
6-8 cycles of R-CHOP	327	69.7
Other	142	30.3
Radiotherapy		
Yes	142	30.3
No	327	69.7
Bulky disease status, cm		
≤ 5	260	55.4
> 5	207	44.1
Missing	2	0.4
PET standardized uptake values		
≤ 13	284	60.6
> 13	177	37.5
Missing	8	1.9

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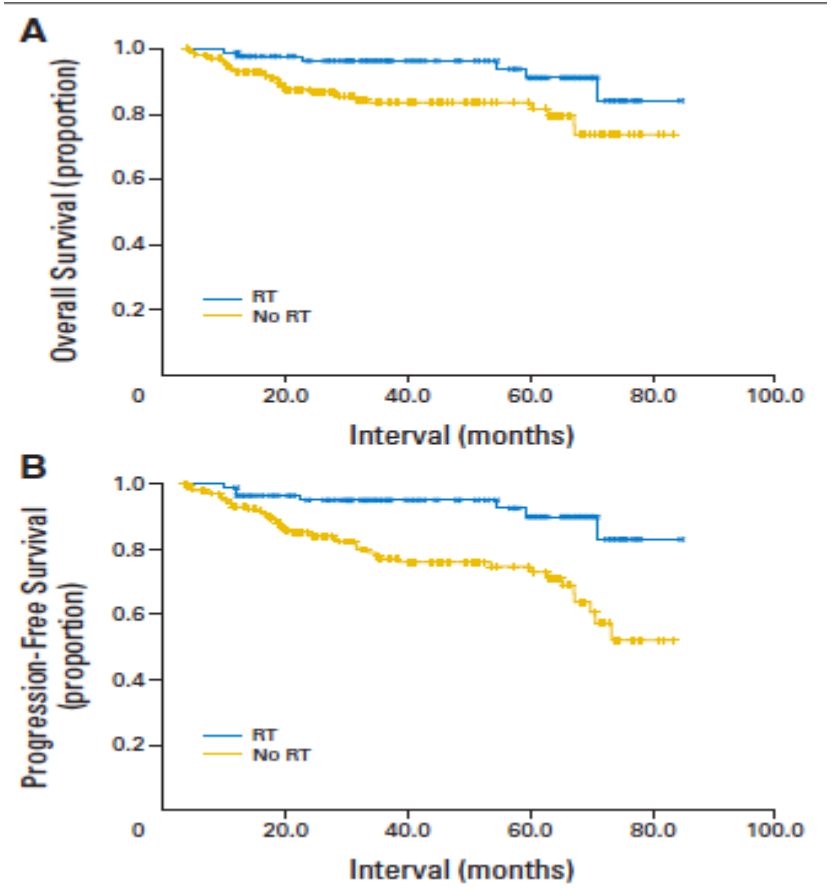

Table 5. Multivariate Analysis of Overall and Progression-Free Survival for All Patients

Variable	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Age, years						
≤ 60	1.00		.051	1.00		.010
> 60	1.34	0.98 to 2.02		1.42	1.00 to 2.15	
Chemotherapy						
6-8 cycles of R-CHOP	0.42	0.27 to 0.65	< .0001	0.57	0.39 to 0.84	.0050
Other	1.00			1.00		
Radiotherapy						
No	1.00		< .0001	1.00		< .0001
Yes	0.19	0.10 to 0.38		0.32	0.17 to 0.51	
Triple negative						
No	1.00		.025	1.00		.038
Yes	0.16	0.03 to 0.79		0.24	0.06 to 0.92	
Triple positive						
No	1.00		.006	1.00		.037
Yes	4.96	1.58 to 15.61		1.39	1.58 to 9.87	
IPI score						
0	1.00			1.00		
1-2	2.53	1.32 to 4.84	.005	2.12	1.34 to 3.69	.001
≥ 3	5.41	2.24 to 8.28	.001	6.03	3.11 to 9.19	.001
Response						
No response	1.00			1.00		
Partial remission	1.96	0.91 to 2.05	< .0001	0.27	0.16 to 0.56	< .0001
Complete remission	3.35	2.33 to 4.59	< .001	0.42	0.33 to 0.72	.0055

Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study

Michael Pfreundschuh, Anthony D Ho, Eva Cavallin-Stahl, Max Wolf, Ruth Pettengell, Ingrid Vasova, Andrew Belch, Jan Walewski, Pier-Luigi Zinzani, Walter Mingrone, Stein Kvaloy, Ofer Shpilberg, Ulrich Jaeger, Mads Hansen, Claudia Corrado, Adriana Scheliga, Markus Loeffler, Evelyn Kuhnt, for the MabThera International Trial (MInT) Group

Lancet Oncol 2008; 9: 435–44

- Linear prognostic effect of tumor diameter on OS, which is decreased (but not eliminated) by the addition of rituximab

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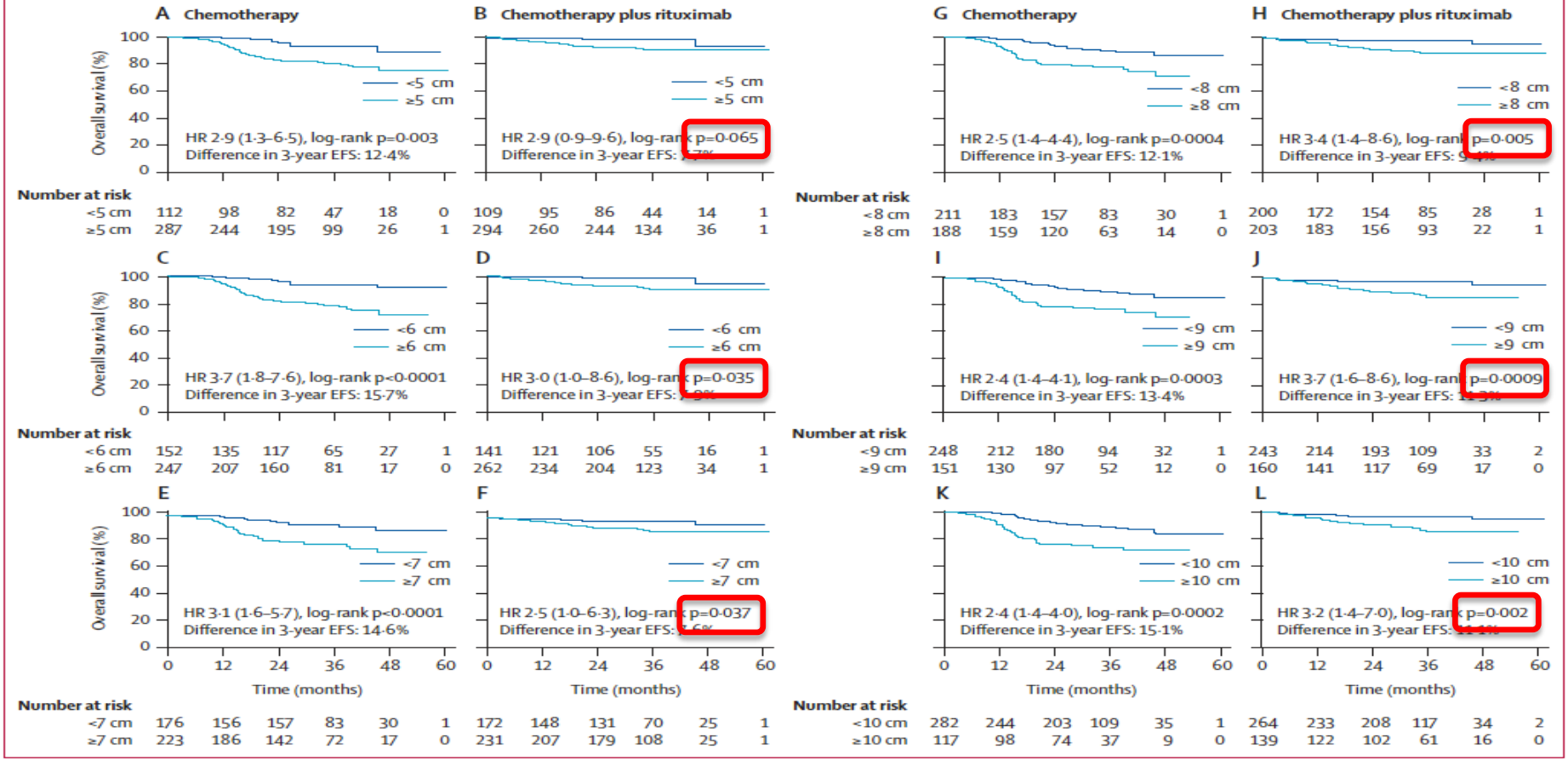
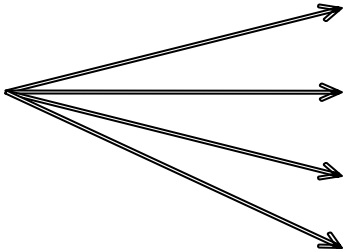

A Chemotherapy
B Chemotherapy plus rituximab
G Chemotherapy
H Chemotherapy plus rituximab
C
D
I
J
E
F
K
L
Overall survival (%)
<5 cm
≥5 cm
HR 2·9 (1·3–6·5), log-rank p=0·003
Difference in 3-year EFS: 12·4%
HR 2·9 (0·9–9·6), log-rank p=0·065
<8 cm
≥8 cm
HR 2·5 (1·4–4·4), log-rank p=0·0004
Difference in 3-year EFS: 12·1%
HR 3·4 (1·4–8·6), log-rank p=0·005
<6 cm
≥6 cm
HR 3·7 (1·8–7·6), log-rank p<0·0001
Difference in 3-year EFS: 15·7%
HR 3·0 (1·0–8·6), log-rank p=0·035
<9 cm
≥9 cm
HR 2·4 (1·4–4·1), log-rank p=0·0003
Difference in 3-year EFS: 13·4%
HR 3·7 (1·6–8·6), log-rank p=0·0009
<7 cm
≥7 cm
HR 3·1 (1·6–5·7), log-rank p<0·0001
Difference in 3-year EFS: 14·6%
HR 2·5 (1·0–6·3), log-rank p=0·037
<10 cm
≥10 cm
HR 2·4 (1·4–4·0), log-rank p=0·0002
Difference in 3-year EFS: 15·1%
HR 3·2 (1·4–7·0), log-rank p=0·002
Time (months)
Number at risk
<5 cm 112 98 82 47 18 0
≥5 cm 287 244 195 99 26 1
109 95 86 44 14 1
294 260 244 134 36 1
<8 cm 211 183 157 83 30 1
≥8 cm 188 159 120 63 14 0
200 172 154 85 28 1
203 183 156 93 22 1
<6 cm 152 135 117 65 27 1
≥6 cm 247 207 160 81 17 0
141 121 106 55 16 1
262 234 204 123 34 1
<9 cm 248 212 180 94 32 1
≥9 cm 151 130 97 52 12 0
243 214 193 109 33 2
160 141 117 69 17 0
<7 cm 176 156 157 83 30 1
≥7 cm 223 186 142 72 17 0
172 148 131 70 25 1
231 207 179 108 25 1
<10 cm 282 244 203 109 35 1
≥10 cm 117 98 74 37 9 0
264 233 208 117 34 2
139 122 102 61 16 0

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma (n=1,222)

RICOVER-60:



- CHOP- 14 x 8
- CHOP-14 x 6
- R-CHOP-14 x 8
- **R-CHOP-14 x 6**

Retrospective subgroup analysis of pts with bulky disease (≥7.5 cm) from the R-CHOP14 x 6 arm treated with or without RT (RICOVER-noRT)

Held et al, JCO 2014
Pfreundschuh. Lancet Oncol, 2008

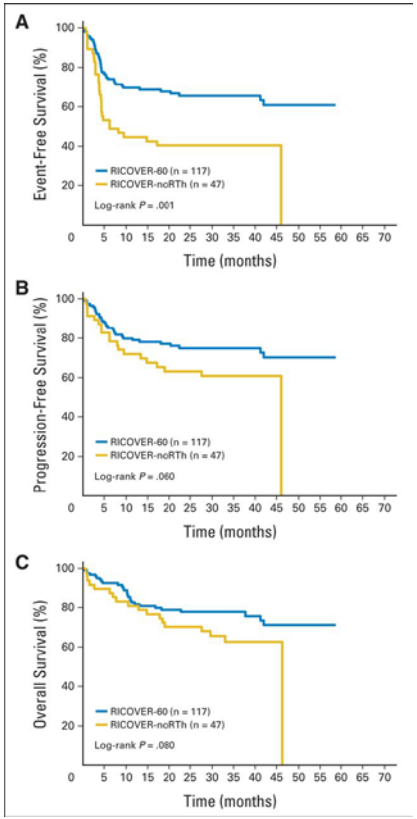
Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

Intent-To-Treat Analysis:

EFS

PFS

OS

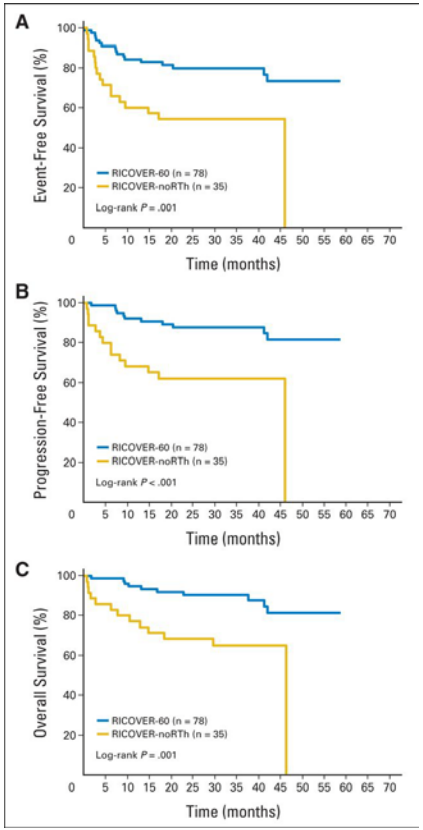


Per-Protocol Analysis:

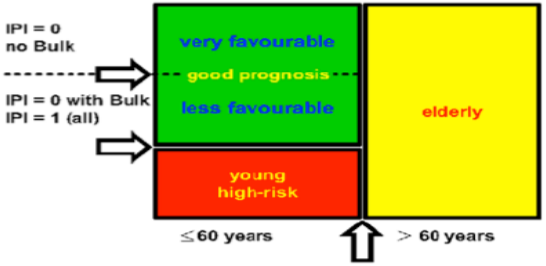
EFS

PFS

OS



Held et al, JCO 2014



GERMAN HIGH-GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP*

* (supported by Deutsche Krebshilfe)

Less Favorable
(IPI=1 and/or bulk)

DSHNHL 2004-2

6 R-CHOP 21 x 6
vs
6 R-CHOP 14 x 6

2nd Random

IFRT 30GY

NO IFRT

Patients with extranodal and/or bulky disease (>7.5 cm) were eligible for the RT randomization

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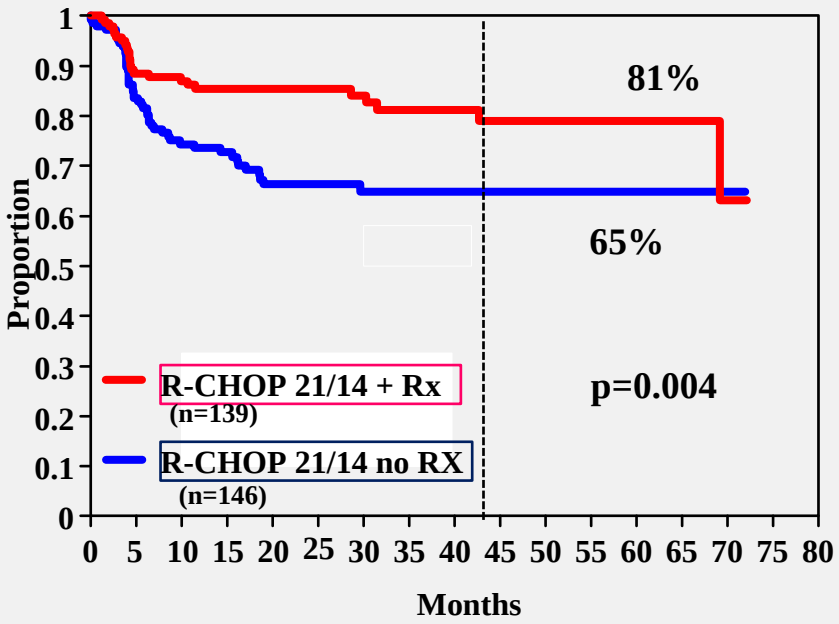
UNFOLDER phase 3 study: preliminary results

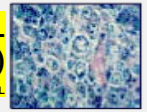
Patients 18- 60 years, aaIPI=0 with bulk or aaIPI=1, ITT (n=443)

Patients randomised to 4 arms (n=285)



GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)

www.lymphome.de/en/Groups/DSHNHL



~20% PMBCL

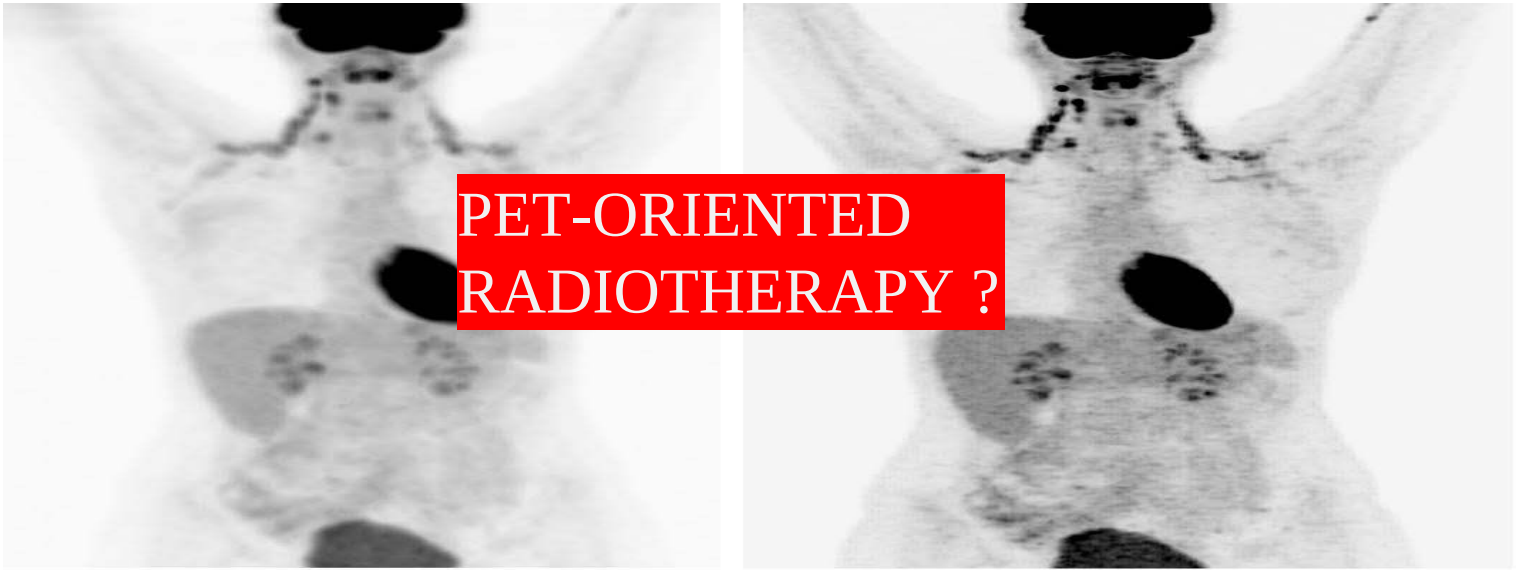
Patients randomized to receive or not IFRT irrespectively of PET response

Discontinuation of the no RT arms due to evident benefit for IFRT in bulky disease

DSHNHL 01.07.12

Courtesy of *M. Pfreundschuh , personal communication*

To irradiate or not to irradiate ?



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PET-oriented RT: BCCA experience

N=50 ; stage I-II ; no B symptoms; mass < 10 cm

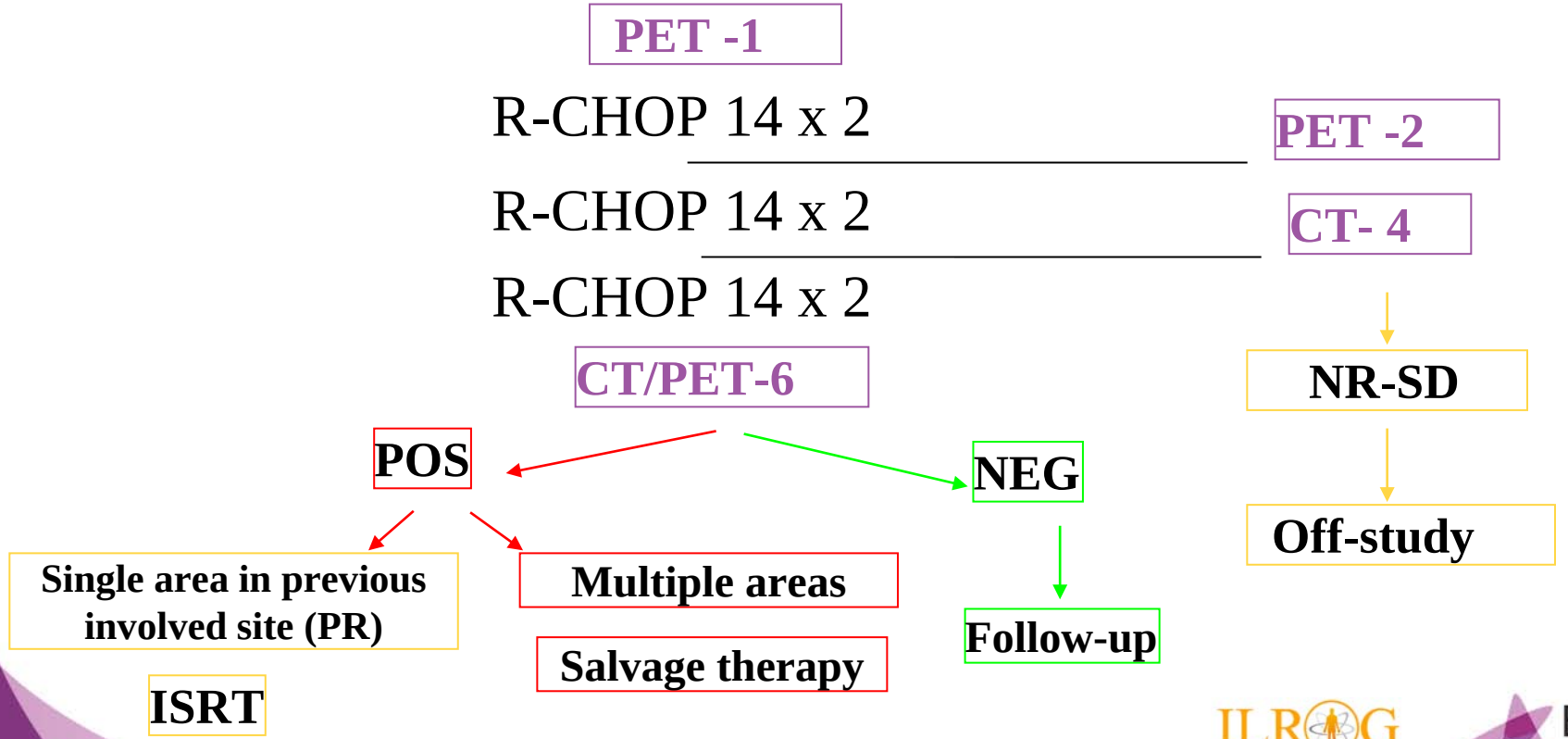
Median FU 17 months

R-CHOP 21 x 3 → PET

	N		Terapia	Recidive	2yFFP	*p*
PET neg →	37	→	CHOP x 1	1	97%	***.09***
PET pos →	13	→	IFRT	3	75%	

Sehn, ASH 2007

DLCL 10 IPI = 0 bulk, 1 and/or bulk (7.5 cm) (less favourable according MInT)



- The Lysa/Goelams Group recently presented preliminary results of a phase III trial comparing RT versus no RT after 4-6 cycles R-CHOP in patients with nonbulky (<7 cm), stages I and II DLBCL, showing no differences in 5-year event-free (91% v 87%) and OS rates (95% v 90%)

- However, patients with residual fluorodeoxyglucose-avid disease after four cycles of R-CHOP were recommended RT regardless of randomization

- These patients achieved similarly favorable outcome to those with a PET CR after R-CHOP with or without RT, suggesting a role for RT in patients who achieve only a PR to chemotherapy

Lamy, Abs., Blood 2014

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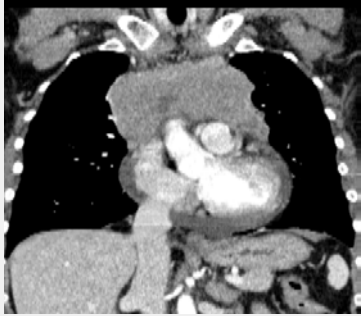
Background

- ***R-Chemotherapy plus mediastinal IFRT*** is considered the standard treatment for PMBCL (3-yrs PFS: 80-85%)

- Does mediastinal IFRT still improve the outcome in PMBCL patients treated with R-CHOP/R-CHOP like chemotherapy?

- Is a negative PET-CT scan a reliable indicator of cure following chemotherapy alone, making unnecessary consolidation RT?

IELSG 37: trial design



PMBCL diagnosis
basal PET-CT 1

Standard therapy
R-Chemo

*RCHOP 14-21; R-V/MACOP-B
DA-EPOCH-R; R-ACVBP;
R-CHO(E)P like

PET-CT 2
Central review

5-6 wks after R-Chemo

Positive not randomised pts will be followed for response, PFS and OS analysis of the chosen salvage strategy .

Positive

Negative

Random 1:1

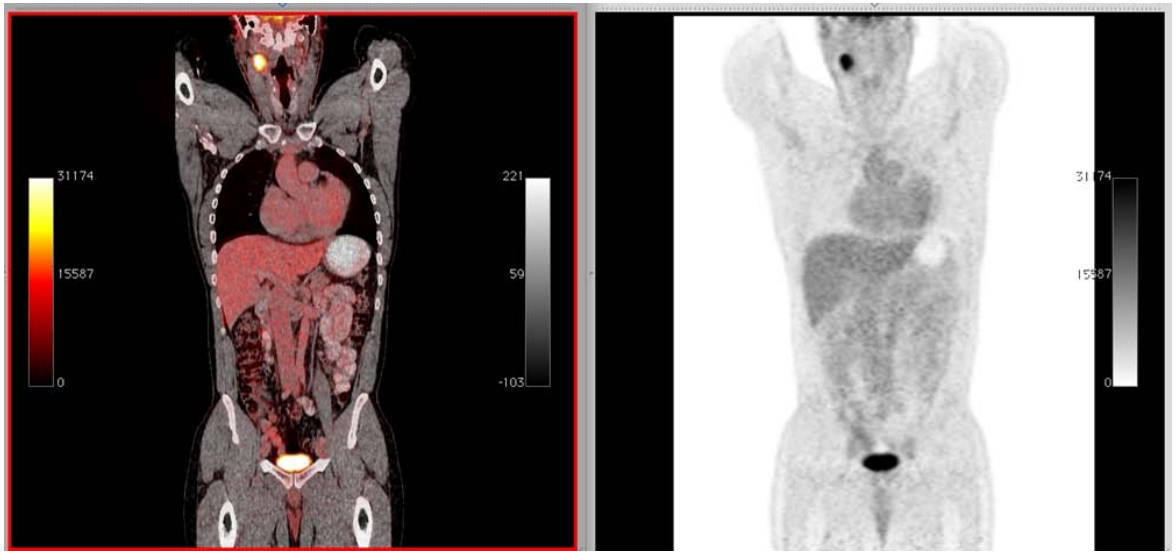
8 wks after R-Chemo

376 pts to randomize

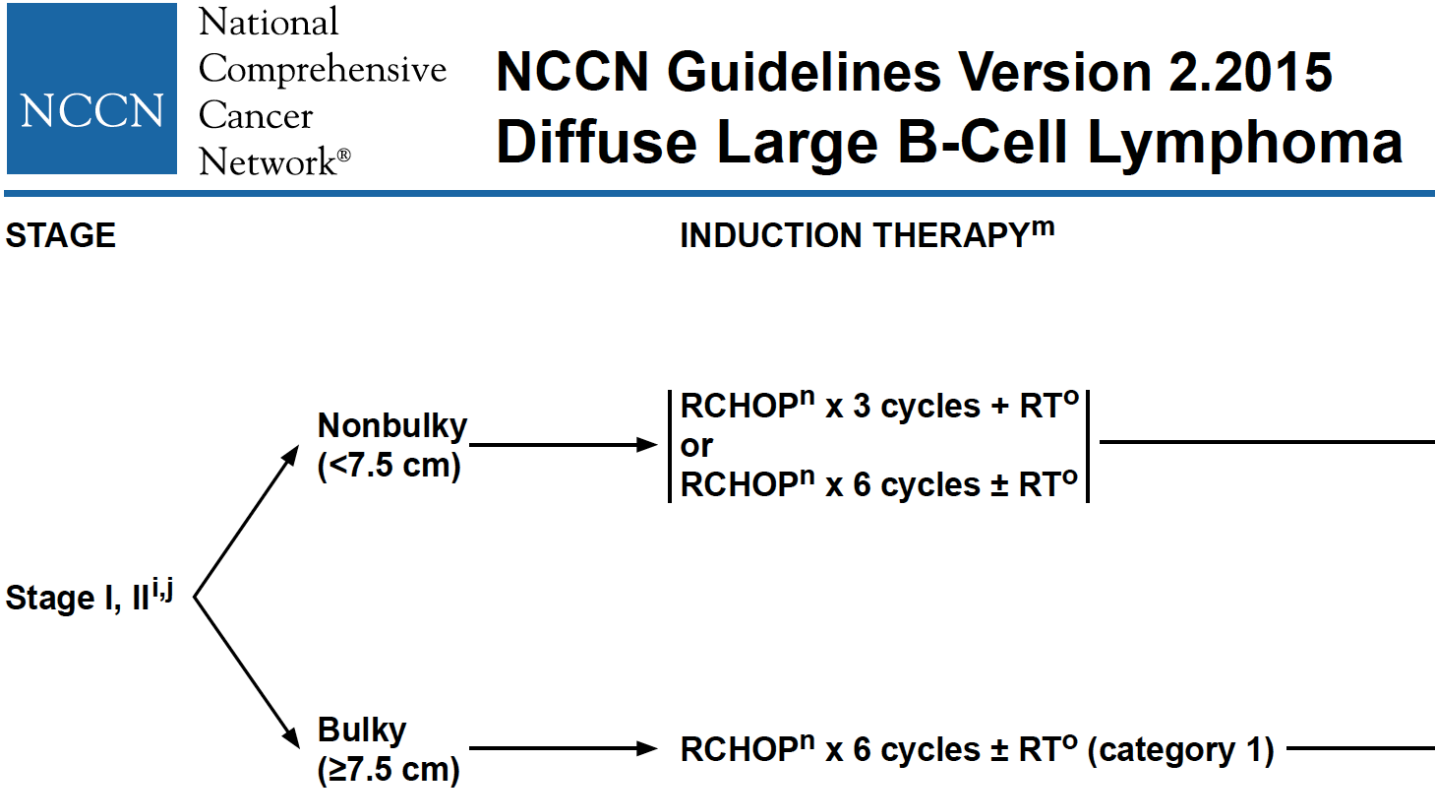
**Mediastinal RT
30 Gy**

Observation

Combined modality OR chemotherapy alone in early stage DLCL



Which is the current Treatment Strategy?



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JOURNAL OF CLINICAL ONCOLOGY

Radiation Therapy After R-CHOP for Diffuse Large B-Cell Lymphoma: The Gain Remains

Joachim Yahalom, *Memorial Sloan-Kettering Cancer Center, New York, NY*

- This variety of options in the NCCN guidelines may make everybody happy, but it could be confusing to the nonexpert

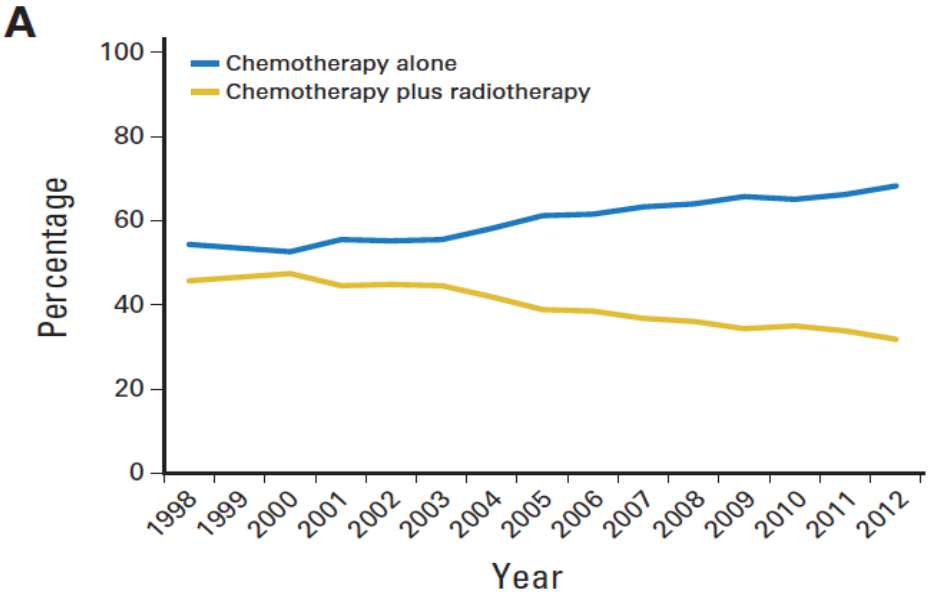
- In reality, many hematologists/oncologists simply extend the chemotherapy course and omit radiotherapy (RT)

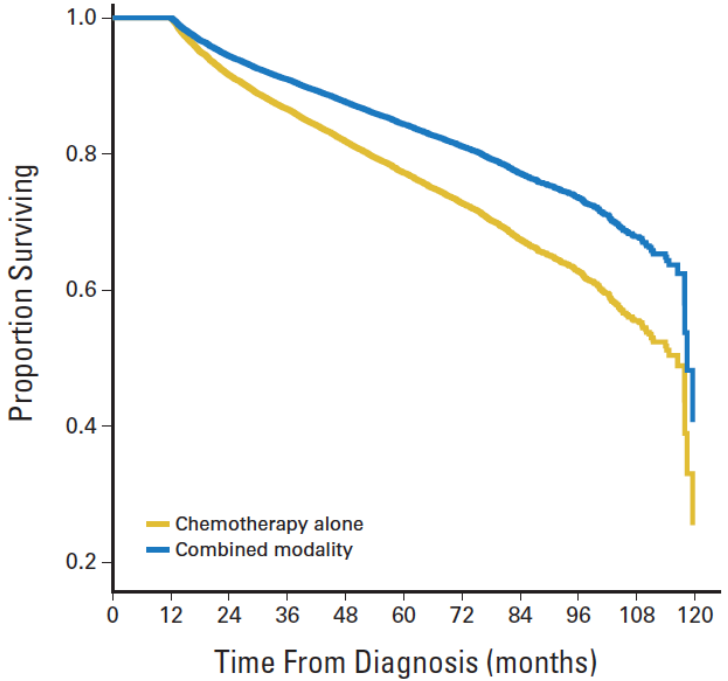
Published Ahead of Print on August 10, 2015 as 10.1200/JCO.2015.61.7654
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.61.7654

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Treatment Selection and Survival Outcomes in Early-Stage Diffuse Large B-Cell Lymphoma: Do We Still Need Consolidative Radiotherapy?

John A. Vargo, Beant S. Gill, Goundappa K. Balasubramani, and Sushil Beriwal





Combined-Modality Therapy for Early-Stage Diffuse Large B-Cell Lymphoma: Knowing When to Quit

Dan L. Longo, *Harvard Medical School, Brigham and Women's Hospital, Boston, MA*

See accompanying article doi:10.1200/JCO.2015.61.7654

Until we have better evidence for changing our current approach, oncologists should stop using radiation therapy as routine treatment in all patients with stage I and II diffuse large B-cell lymphoma

We should stop arguing and agree that current evidence does not support the use of radiation therapy in all of these patients

Rather, we should focus on conducting prospective clinical trials on selected subsets of patients for whom there may be a reasonable chance of demonstrating improved outcomes with radiation therapy

It is important to know when to quit

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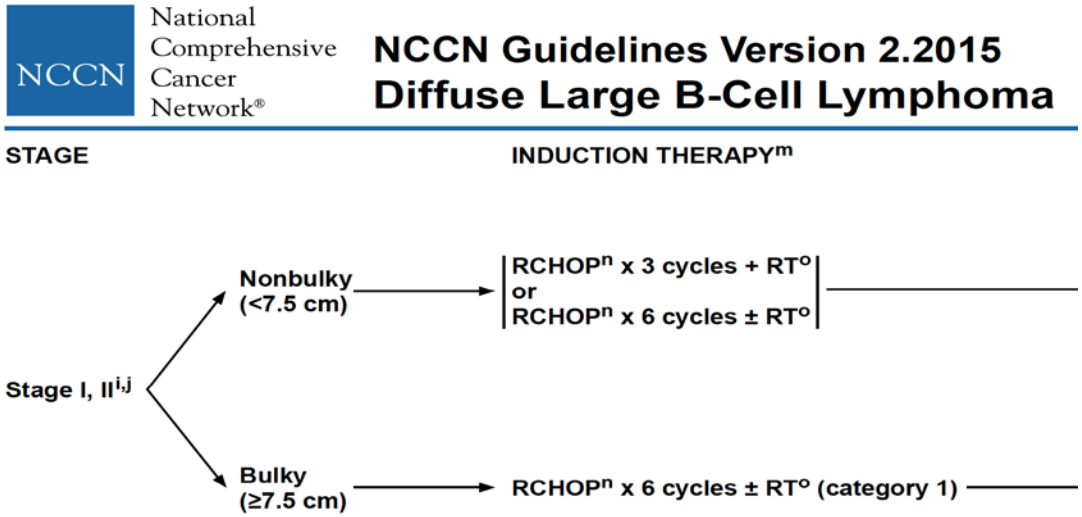
MODERN, BETTER TARGETED, SAFER, AND LOWER-DOSAGE, CONSOLIDATIVE RT

Therapeutic burden:

R-CHOP x 3 cycles followed by 30 Gy IS-RT probably better than R-CHOP x 6 cycles



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Is more of one modality better (and safer) than less of two?

CARDIAC MORTALITY IN PATIENTS WITH STAGE I AND II DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH AND WITHOUT RADIATION: A SURVEILLANCE, EPIDEMIOLOGY, AND END-RESULTS ANALYSIS

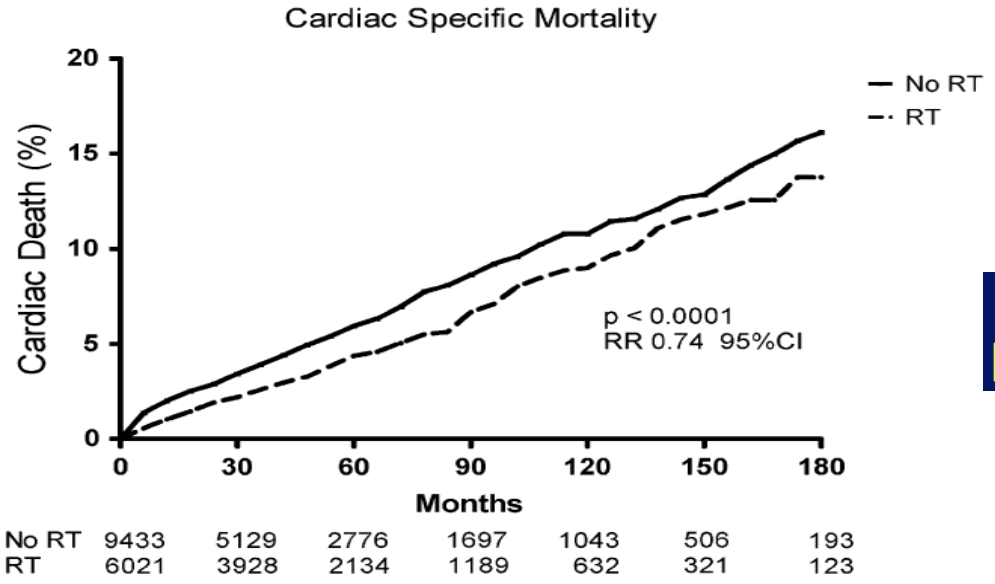

Fig. 1. Cardiac death in patients with stage I–II DLBCL. A comparison between patients treated with and without RT.

Increased Cardiac Death in Patients Treated without RT

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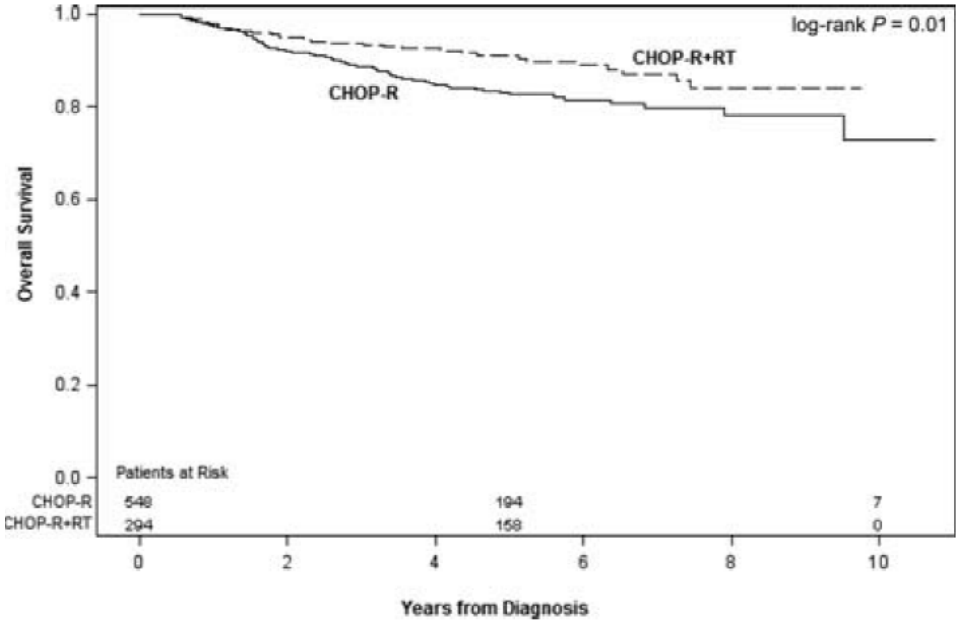
Radiation for Diffuse Large B-Cell Lymphoma in the Rituximab Era: Analysis of the National Comprehensive Cancer Network Lymphoma Outcomes Project

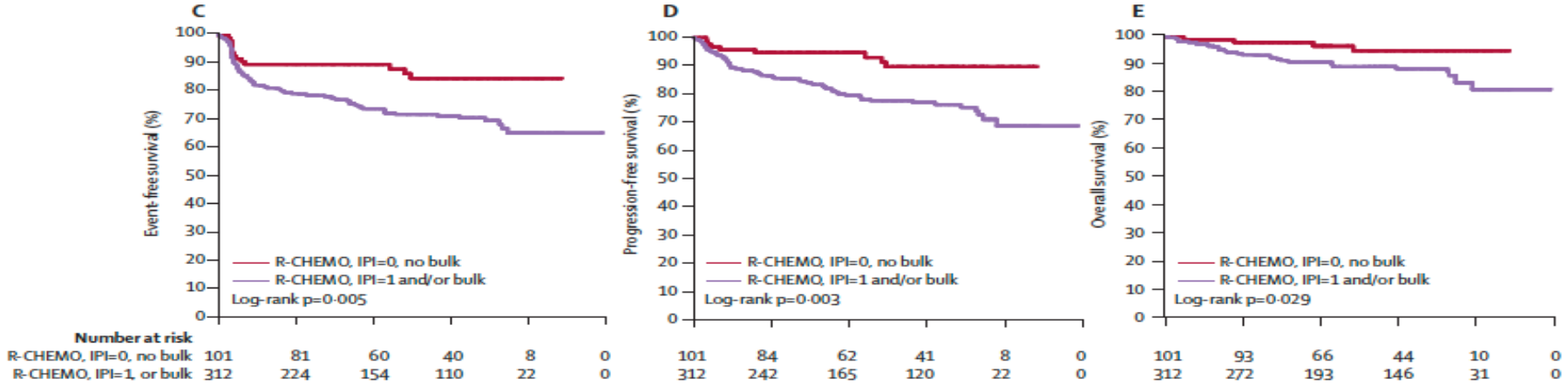
TABLE 2. Causes of Death

Coded Cause of Death	Treatment Group		
	All	R-CHOP	R-CHOP+RT
All deaths, n (%)	119	88 (73.9)	31 (26.0)
Missing, n (%)	3 (2.5)	2 (2.3)	1 (3.2)
Unknown, n (%)	22 (18.5)	17 (19.3)	5 (16.1)
Other, n (%)	18 (15.1)	14 (15.9)	4 (12.9)
Progressive disease, n (%)	66 (55.5)	49 (55.7)	17 (54.8)
Excessive toxicity, n (%)	3 (2.5)	2 (2.3)	1 (3.2)
Secondary malignancy, n (%)	6 (5.0)	3 (3.4)	3 (9.7)
Accidental death, n (%)	1 (0.8)	1 (0.8)	0



Dabaja B. et al Cancer 2014;121:1031-1039

- Given the favorable toxicity profile of RT to 30 Gy administered with modern RT techniques to involved sites, coupled with the suboptimal outcomes for patients with DLBCL, it is difficult to justify withholding a treatment that can positively influence PFS and possibly OS



- Late Effects of RT: Distinct Considerations for DLBCL

- General suggestions that RT no longer has a role in treating early-stage lymphomas should thus be reexamined carefully

Annals of Oncology 26 (Supplement 5): v116–v125, 2015
doi:10.1093/annonc/mdv304

Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

H. Tilly[1], M. Gomes da Silva[2], U. Vitolo[3], A. Jack[4], M. Meignan[5], A. Lopez-Guillermo[6], J. Walewski[7], M. André[8], P. W. Johnson[9], M. Pfreundschuh[10] & M. Ladetto[11], on behalf of the ESMO Guidelines Committee*

Patients with low risk disease may also benefit from abbreviated chemotherapy and RT instead of prolonged chemotherapy

Table 3. Recommended treatment strategies in diffuse large B-cell lymphoma

Patients ≤60 years		
IPI low risk (aaIPI = 0) and no bulk	IPI low risk (aaIPI = 0) with bulk or IPI low-intermediate risk (aaIPI = 1)	IPI intermediate-high risk or IPI high risk (aaIPI = 2, 3)
R-CHOP21 × 6	R-ACVBP and sequential consolidation or R-CHOP21 × 6 + IF-RT on bulk	R-CHOP21 × 6–8 or R-CHOP14 × 6 with 8 R Consider more intensive regimens in selected patients: R-CHOEP14 × 6 or R-CHOP or R-ACVBP plus HDCT with ASCT
Consider CNS prophylaxis in patients at risk for CNS progression		
Elderly >60 years		
Fit, 60–80 years	>80 years without cardiac dysfunction	Unfit or frail or >60 years with cardiac dysfunction
R-CHOP21 × 6–8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R	Attenuated regimens: R-miniCHOP21 × 6	Doxorubicin substitution with gemcitabine, etoposide or liposomal doxorubicin or others: R-C(X)OP21 × 6 or palliative care
Consider CNS prophylaxis in patients at risk		

Guidelines for the management of diffuse large B-cell lymphoma

Sridhar Chaganti,[1] Tim Illidge,[2] Sally Barrington,[3] Pam Mckay,[4] Kim Linton,[5] Kate Cwynarski,[6] Andrew McMillan,[7] Andy Davies,[8] Simon Stern,[9] Karl Peggs[10] and on behalf of the British Committee for Standards in Haematology

bjh guideline

Recommendations

- It is recommended that patients with non-bulky (<7·5 cm) stage IA DLBCL presenting at sites associated with low morbidity for radiotherapy (e.g. groin, neck or axilla), be treated with 3–4 cycles of R-CHOP chemotherapy followed by ISRT of 30 Gy (1B). Six cycles of R-CHOP is an alternative and should be the preferred option if disease involves a site where the acute and late complications of RT are better avoided (1A).
- Patients with non-bulky stage IIA DLBCL should be treated with 6 cycles of R-CHOP (1A).
- Patients with bulky stage IA/IIA DLBCL should be treated with 6 cycles of R-CHOP followed by ISRT of 30 Gy to initial sites of bulk (1B).

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- We eagerly await mature results of modern randomized trials that use contemporary immunochemotherapy and functional imaging for response assessment

The treatment of patients with DLBCL requires multidisciplinary collaboration to ensure optimal outcome

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Radiation therapy for cHL: volumes, doses and techniques

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

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HEMATOLOGICAL MALIGNANCIES (IN COLLABORATION WITH ILROG)

31 August-03 September, 2016
Vienna, Austria

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ESTRO Course on hematological malignancies:

London, September 4-6, 2015

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RT in classical Hodgkin Lymphoma

- In most HL patients, RT is used in combination with chemotherapy
- Chemotherapy has evolved with increasing efficacy to play a major role in the management of HL
- RT continues to have an important place in ensuring locoregional control and improving overall outcome in the combined modality treatment programs for HL

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Responsibilities of the radiation oncologist

- Ensure that the advantages that can be obtained with modern radiotherapy are used to the benefit of the patient:
  - Optimal target coverage (VOLUMES)
  - Lowest target dose necessary for the highest chance of local lymphoma control (DOSES)
  - Lowest possible risk of significant long-term side effects (TECHNIQUES)

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

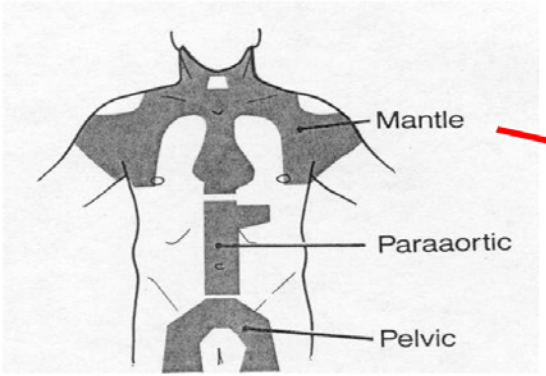
Early Stage classical Hodgkin Lymphoma

- Combined modality treatment

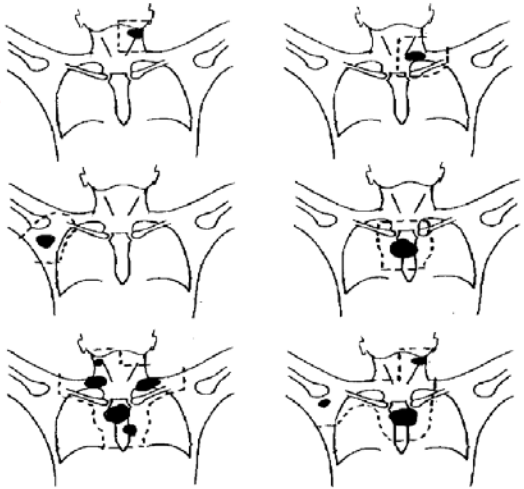
- Chemo followed by “modern” radiotherapy

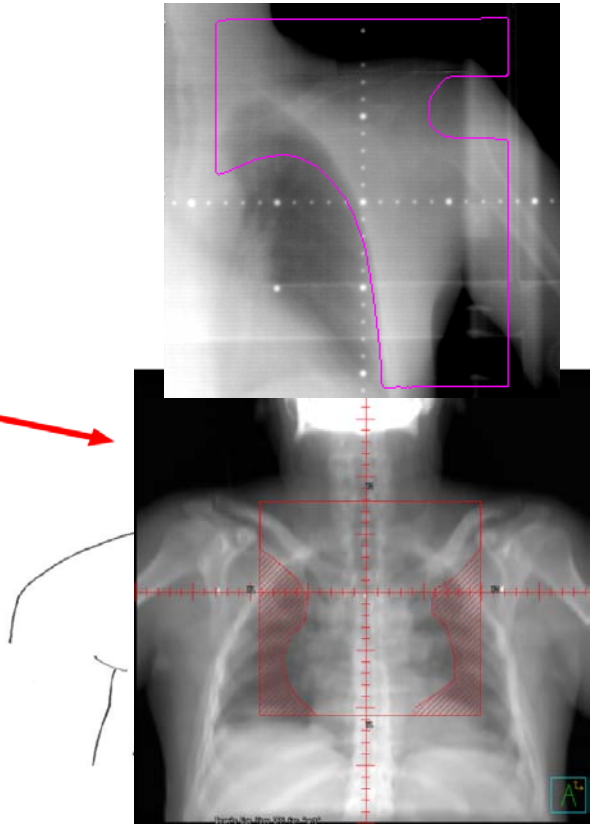
Radiotherapy for Hodgkin lymphoma:
from sole curative treatment to component in combined modality treatment (i.e. no prophylactic radiotherapy for microscopic disease)

EFRT



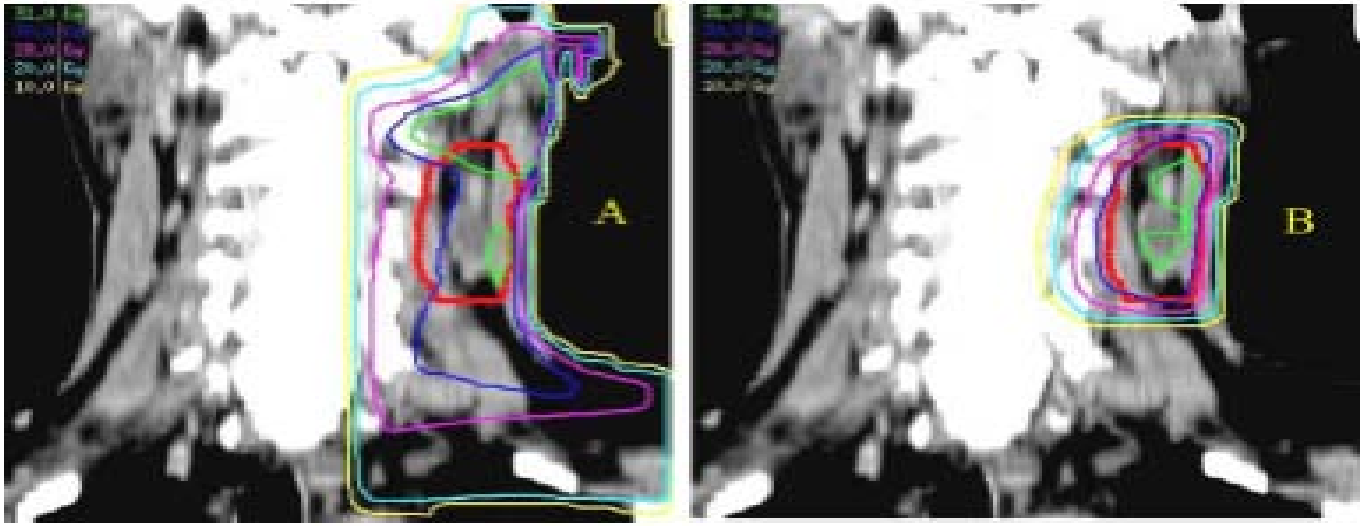
IFRT





In the era of combined modality treatment, bigger (radiation fields) is not better !

From IFRT to INRT/ISRT



•The concept of **IF-RT** which included the whole initially involved lymph node region can now be replaced by the concept of **involved-node/site RT**, which only includes the initially involved lymph node(s)

Critical Review

Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)

Lena Specht, MD, PhD,* Joachim Yahalom, MD,† Tim Illidge, MD, PhD,‡ Anne Kiil Berthelsen, MD,§ Louis S. Constine, MD,|| Hans Theodor Eich, MD, PhD,¶ Theodore Girinsky, MD,# Richard T. Hoppe, MD,** Peter Mauch, MD,†† N. George Mikhaeel, MD,‡‡ and Andrea Ng, MD, MPH††, on behalf of ILROG

The concepts of INRT and ISRT

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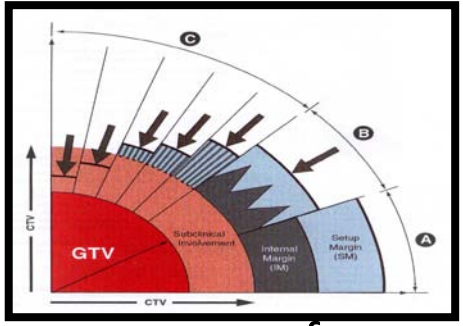
Treatment Volume Principles



- Modern RT planning in lymphoma incorporates the current concepts of volume determination as outlined by ICRU Report 83
- It is based on defining a gross tumor volume (GTV) and a clinical target volume (CTV), that is expanded to a planning target volume (PTV)
- The PTV is then used to define beam coverage
- This approach allows direct comparison with the diagnostic 3D-imaging, increasing the accuracy with which lymph node volumes are defined

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RT Planning for Lymphomas

- **Role of imaging in radiation planning**
  - 3D imaging (with CT supplemented by functional imaging: PET-CT)
  - The use of diagnostic contrast-enhanced CT is recommended to help to delineate nodal stations and differentiate nodes from vessels
  - Ideally, imaging studies with the patient in the treatment position and using the planned immobilization devices
  - Acquiring high-quality imaging is fundamental to high-quality RT planning

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Modern RT for lymphoma

- Radiation oncologists should be involved as part of the multidisciplinary team in the initial management plan and attempt to introduce imaging procedures upfront before the initiation of chemotherapy

Gross tumor volume (GTV) (ICRU 83)

- Gross demonstrable extent and location of the tumor (lymphoma)
- Original (before any treatment) lymphoma: pre-chemo GTV
  - Seen on CT: pre-chemo GTV(CT)
  - Seen on FDG-PET: pre-chemo GTV(PET)
- Residual (after systemic treatment) lymphoma: post-chemo GTV
  - Seen on CT: post-chemo GTV(CT)
  - Seen on FDG-PET: postchemo GTV(PET)

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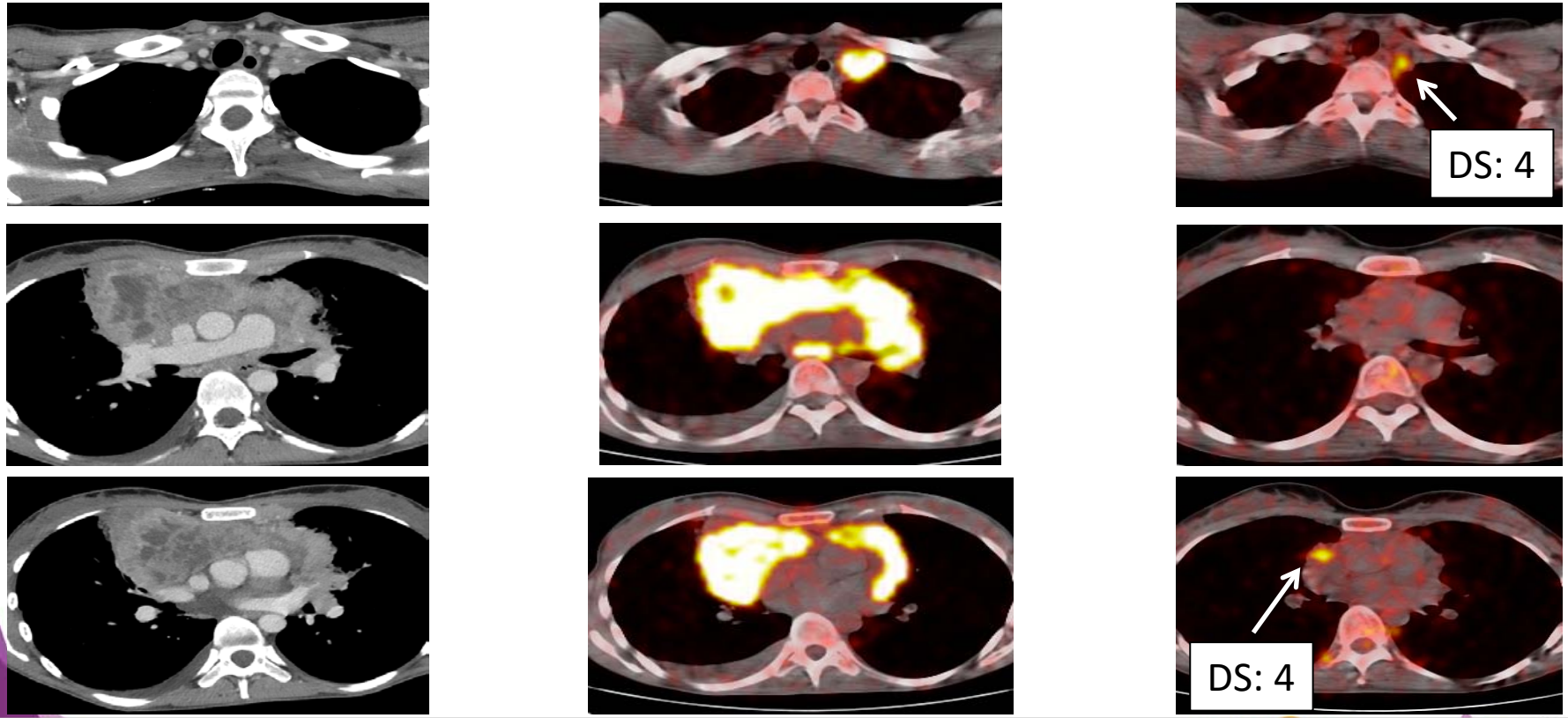
CT scan
(diagnosis)

PET/CT scan
(diagnosis)

PET/CT scan
(end of chemo)



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Clinical target volume (CTV) (ICRU 83)

- Volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy
- Encompasses the original (before any treatment) lymphoma (pre-chemo GTV), modified to account for anatomic changes if treated with chemotherapy up front
- Normal structures (e.g., lungs, kidneys, muscles) that were clearly uninvolved should be excluded
- Residual lymphoma (post-chemo GTV) is always part of the CTV

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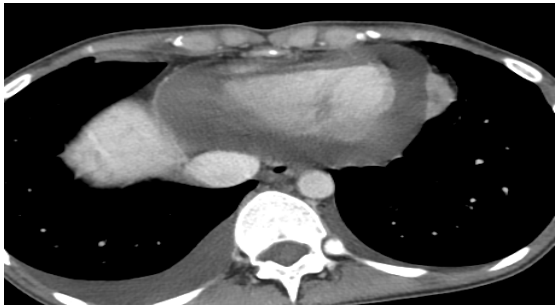
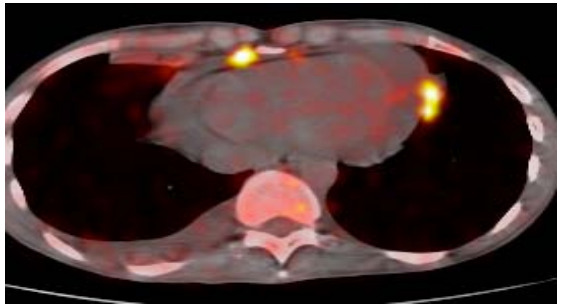
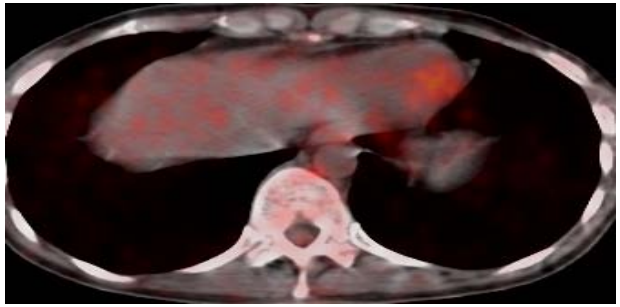
CT scan
(diagnosis)

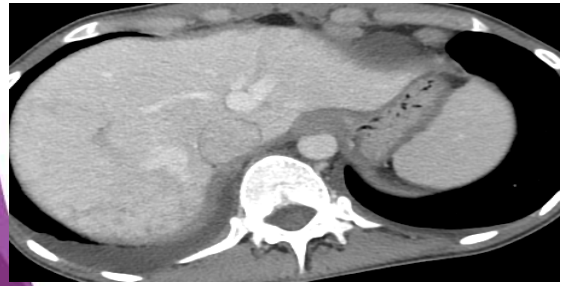
PET/CT scan
(diagnosis)

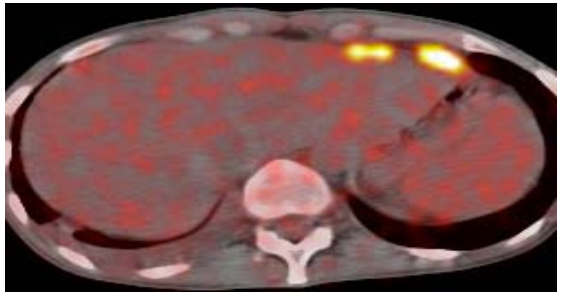
PET/CT scan
(end of chemo)

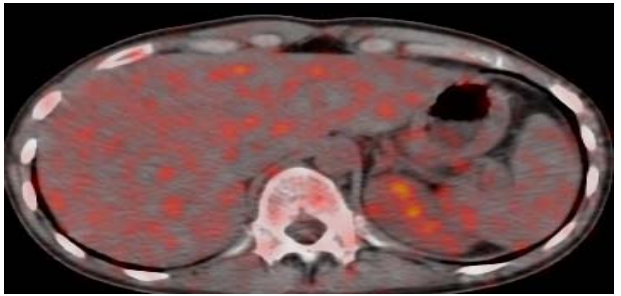












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Planning target volume (PTV) (ICRU 83)

- Accounts for set-up uncertainties in patient position and beam alignment during planning and through all treatment sessions
- Function of immobilization device, body site, and patient cooperation
- Geometrical concept introduced to ensure that CTV and/or ITV are properly covered
- Applied by clinician or treatment planner

- Depending on image-gudance in treatment delivery

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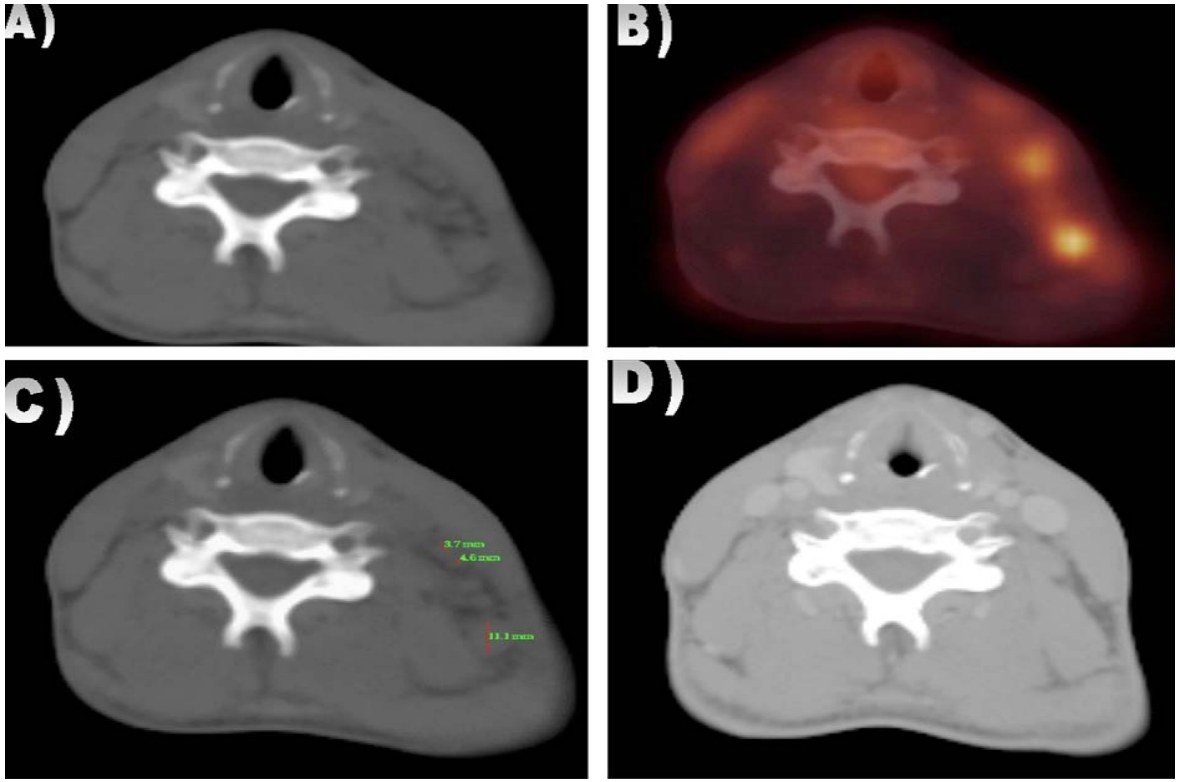
EORTC Lymphoma Group pioneered conformal RT for HL:

Involved node radiotherapy (INRT)

Requirements:

- Good pre-chemo imaging with PET/CT in treatment position
- Image fusion with post-chemo planning CT
- Contouring target volume of tissue which contained lymphoma at presentation

Assessment of initial lymph node involvement



Girinsky T, R&O 2008

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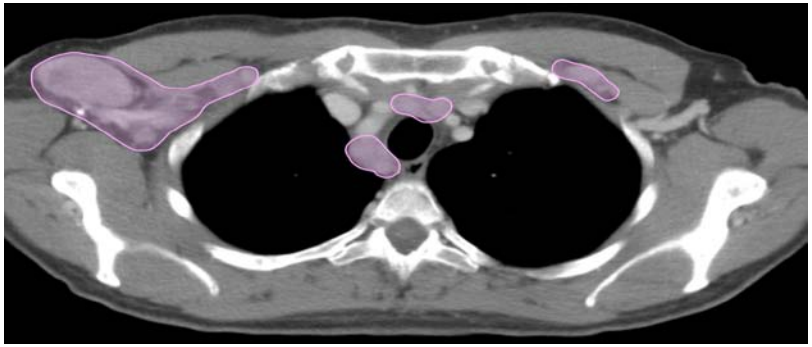
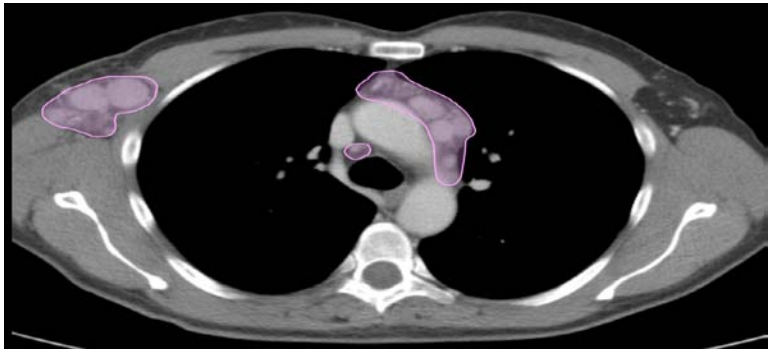
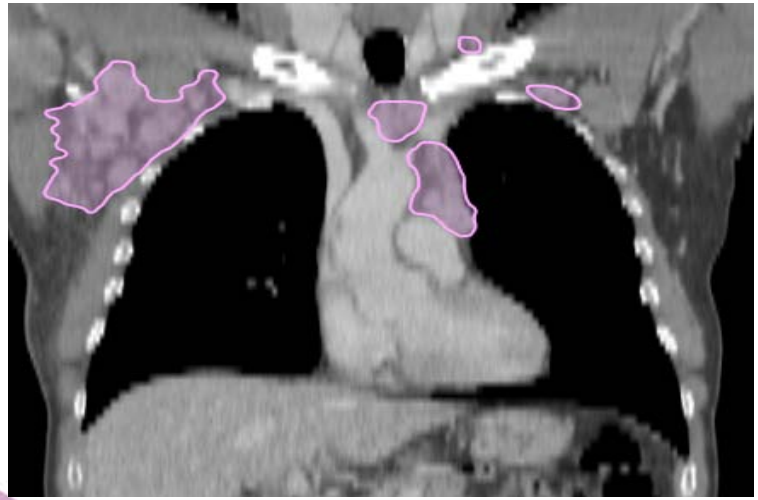
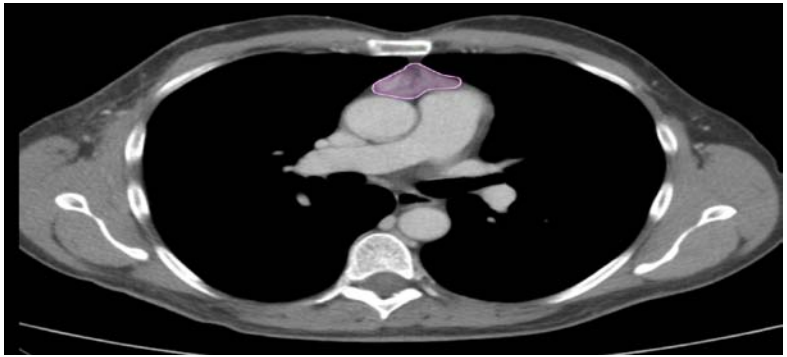
GTV on pre-chemotherapy CT









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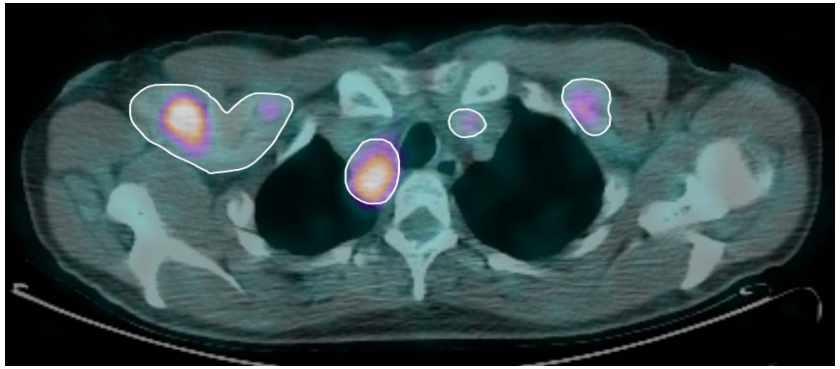
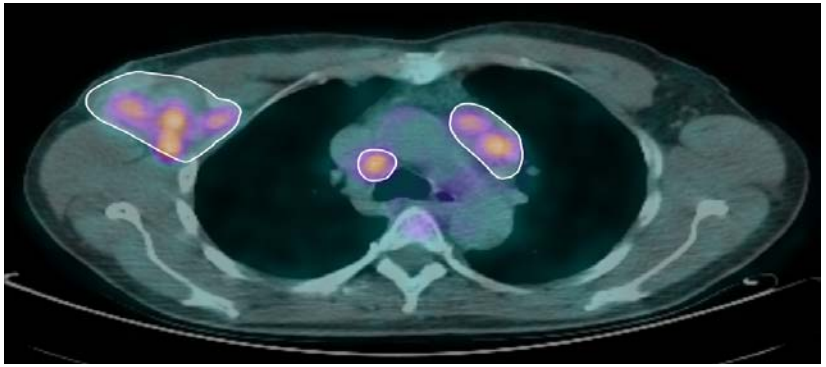
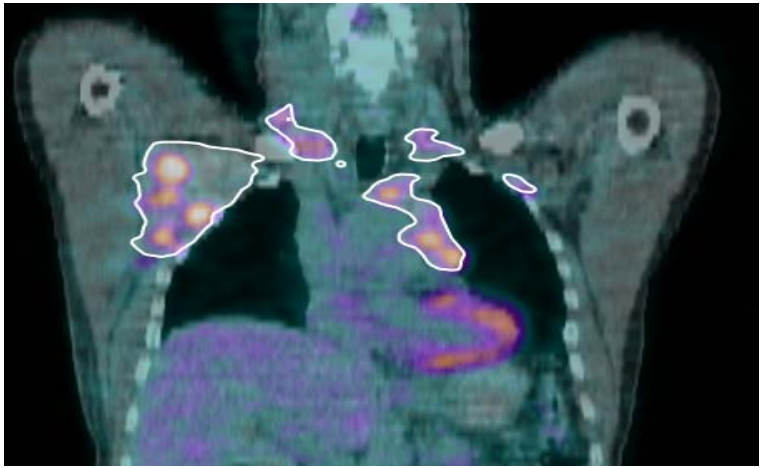
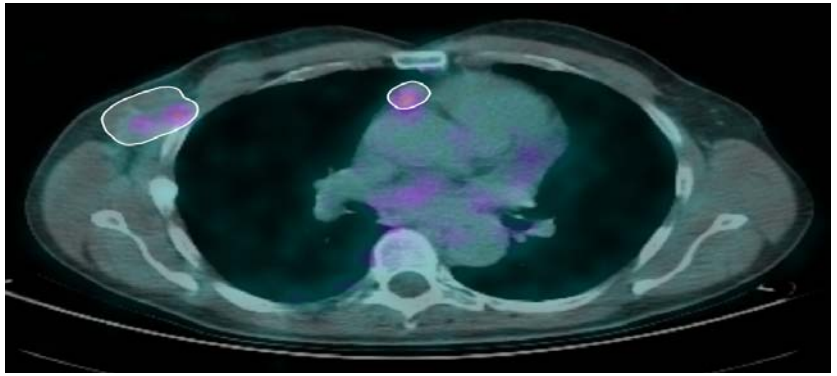
GTV on pre-chemotherapy PET









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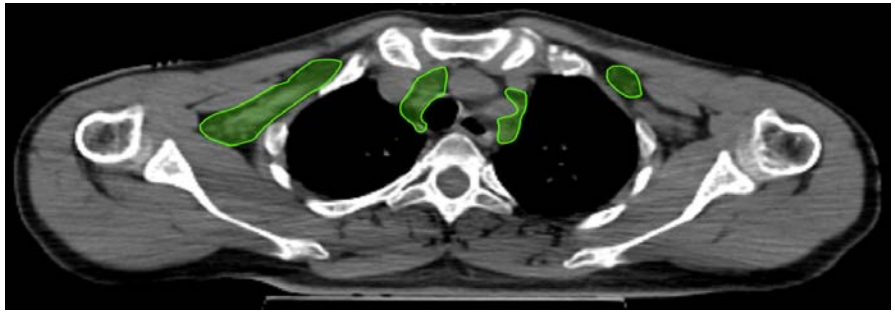
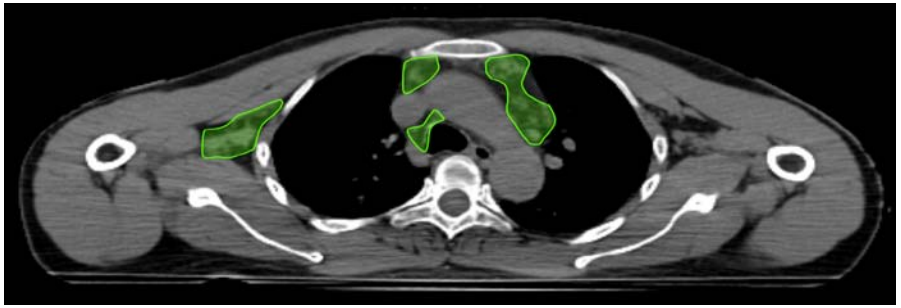
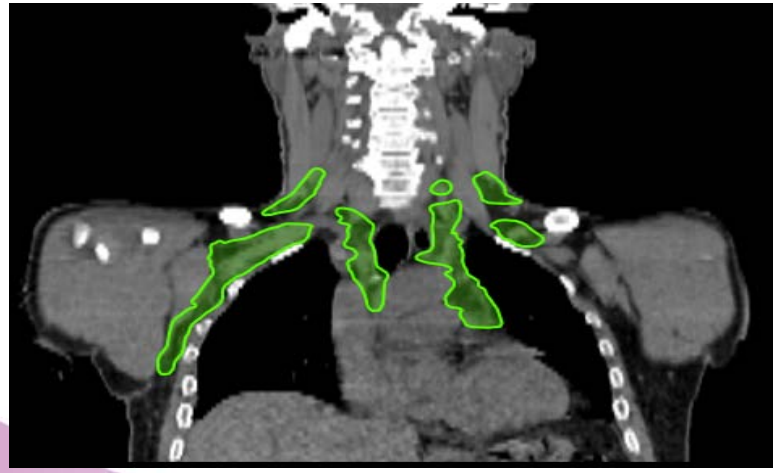
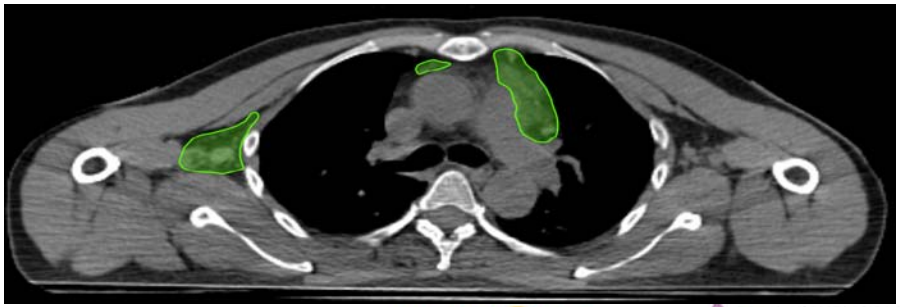
GTV_{CT} and GTV_{PET} import on planning CT→ CTV definition by modifying GTVs according to response and normal tissues displacement → **INRT**









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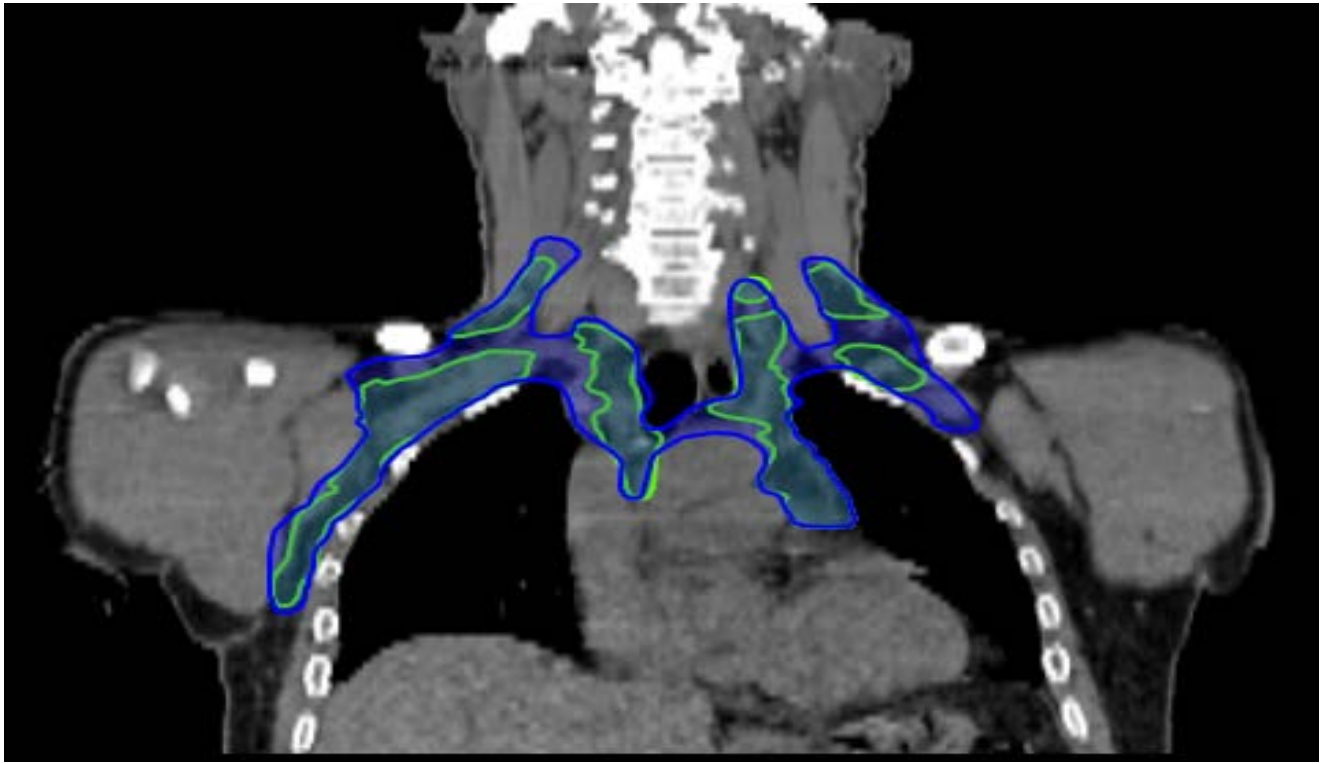
Involved Site Radiotherapy (ISRT)

- ISRT accomomodates cases in which optimal prechemotherapy imaging is not available to the radiation oncologist
- In these situations, it is not possible to reduce the CTV to the same extent as with INRT, because the prechemotherapy GTV information may not be optimal
- In ISRT, clinical judgment in conjunction with the best available imaging is used to contour a larger CTV that will be accommodate the uncertainties in defining the prechemotherapy GTV

INRT vs ISRT



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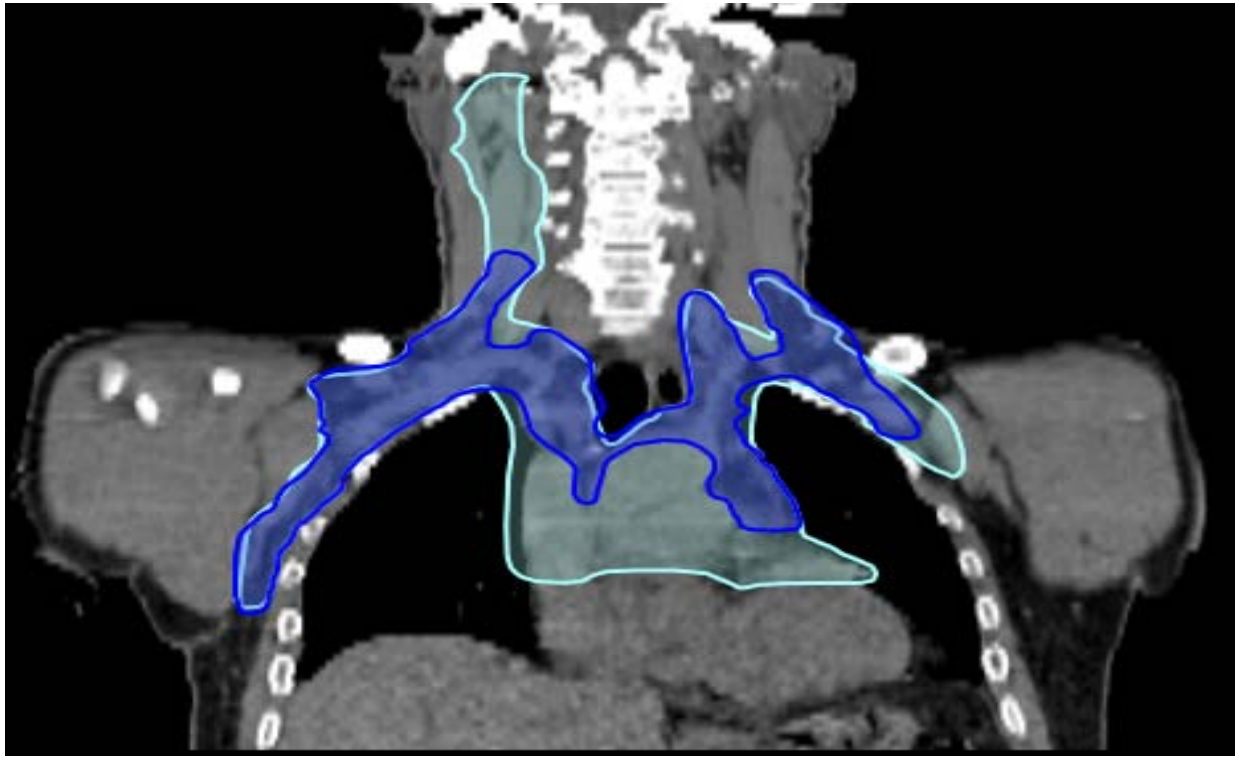
ISRT vs IFRT



In most situations, ISRT will include significantly smaller volumes than IFRT

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Guidelines

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 40–45, 2015

Expert Radiation Oncologist Interpretations of Involved-Site Radiation Therapy Guidelines in the Management of Hodgkin Lymphoma

Bradford S. Hoppe, MD, MPH,* and Richard T. Hoppe, MD†

Defining CTV relies upon

- the quality and accuracy of imaging;
- knowledge of the spread patterns of the disease, as well as potential subclinical extent of involvement, and adjacent organ at risk constraints

all of which depend on clinical judgment and experience

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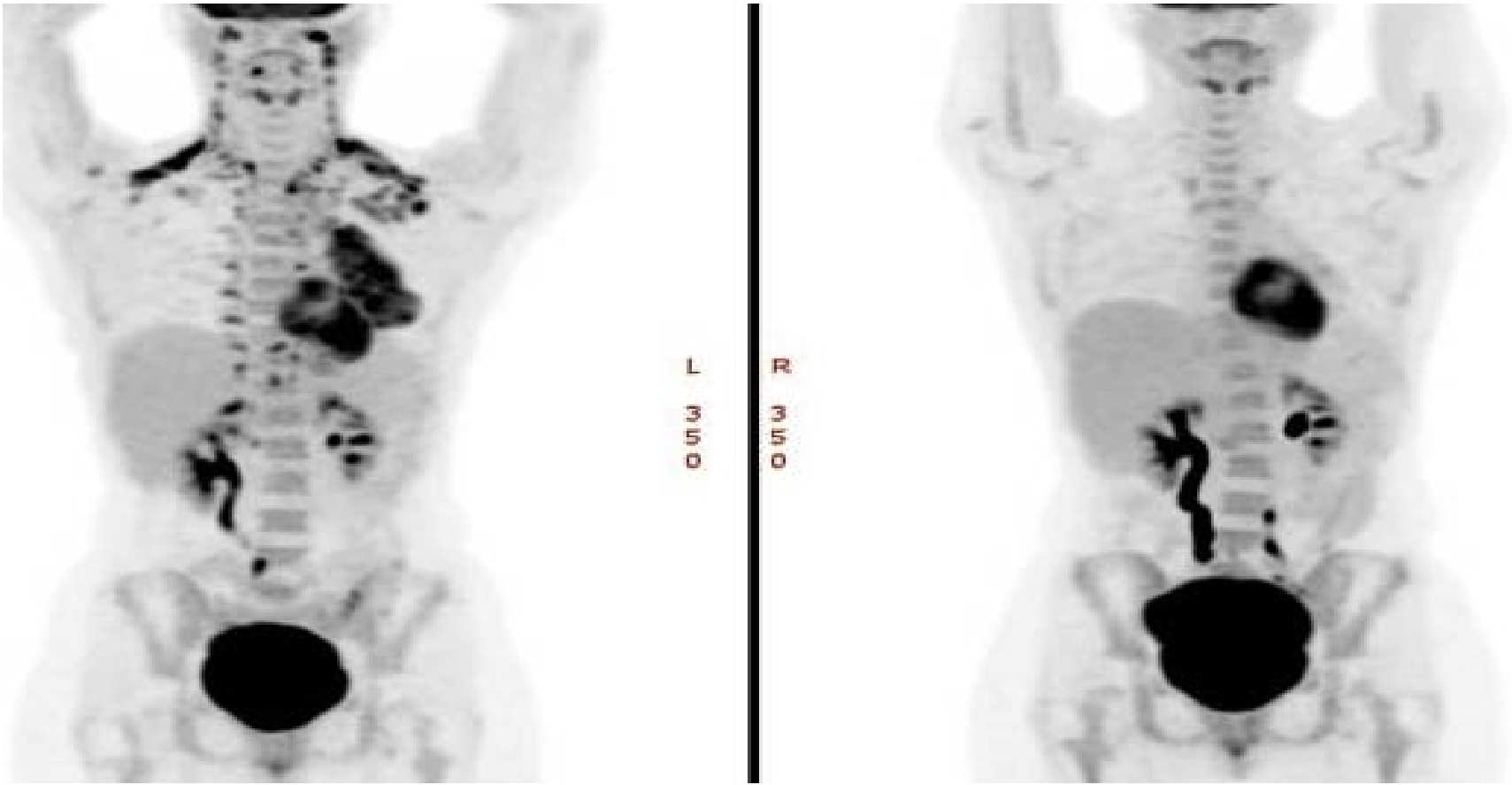
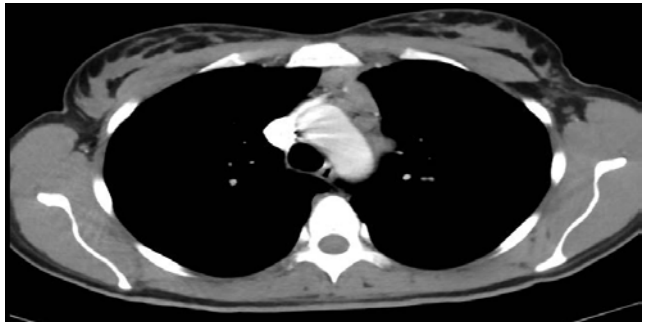
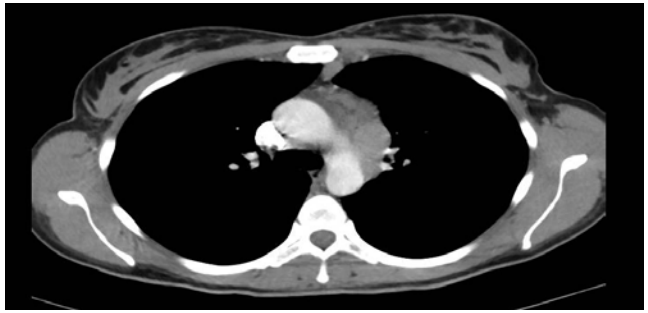
Baseline

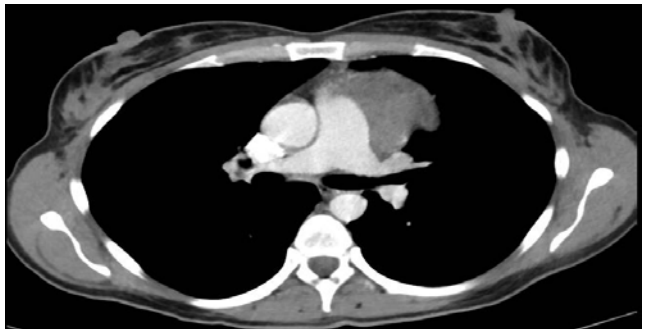
After ABVD



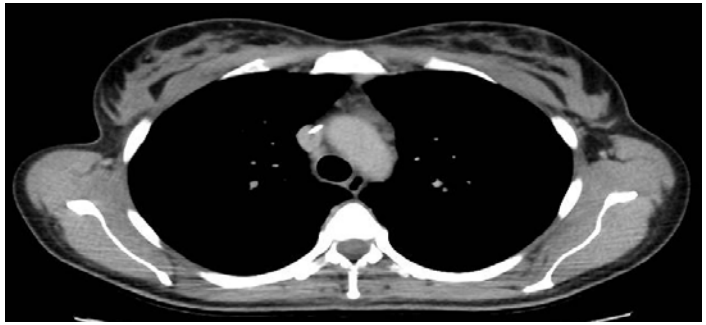
Baseline

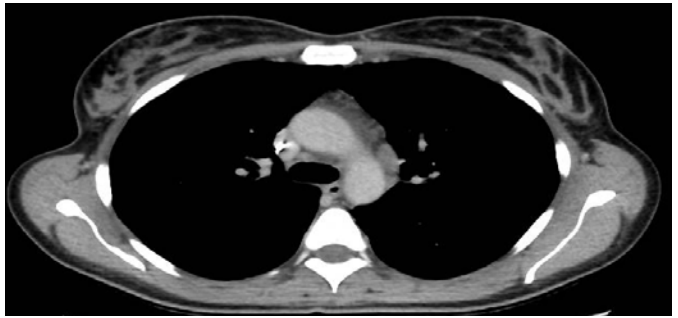


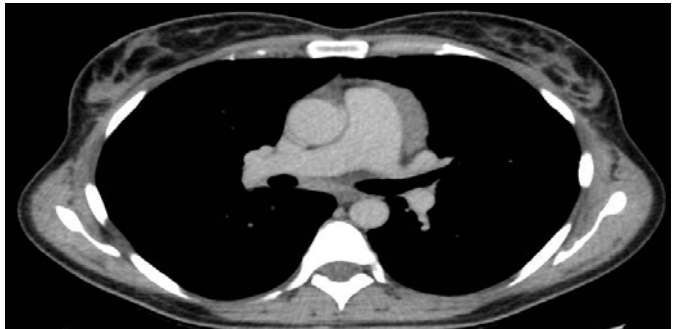




After 3 ABVD







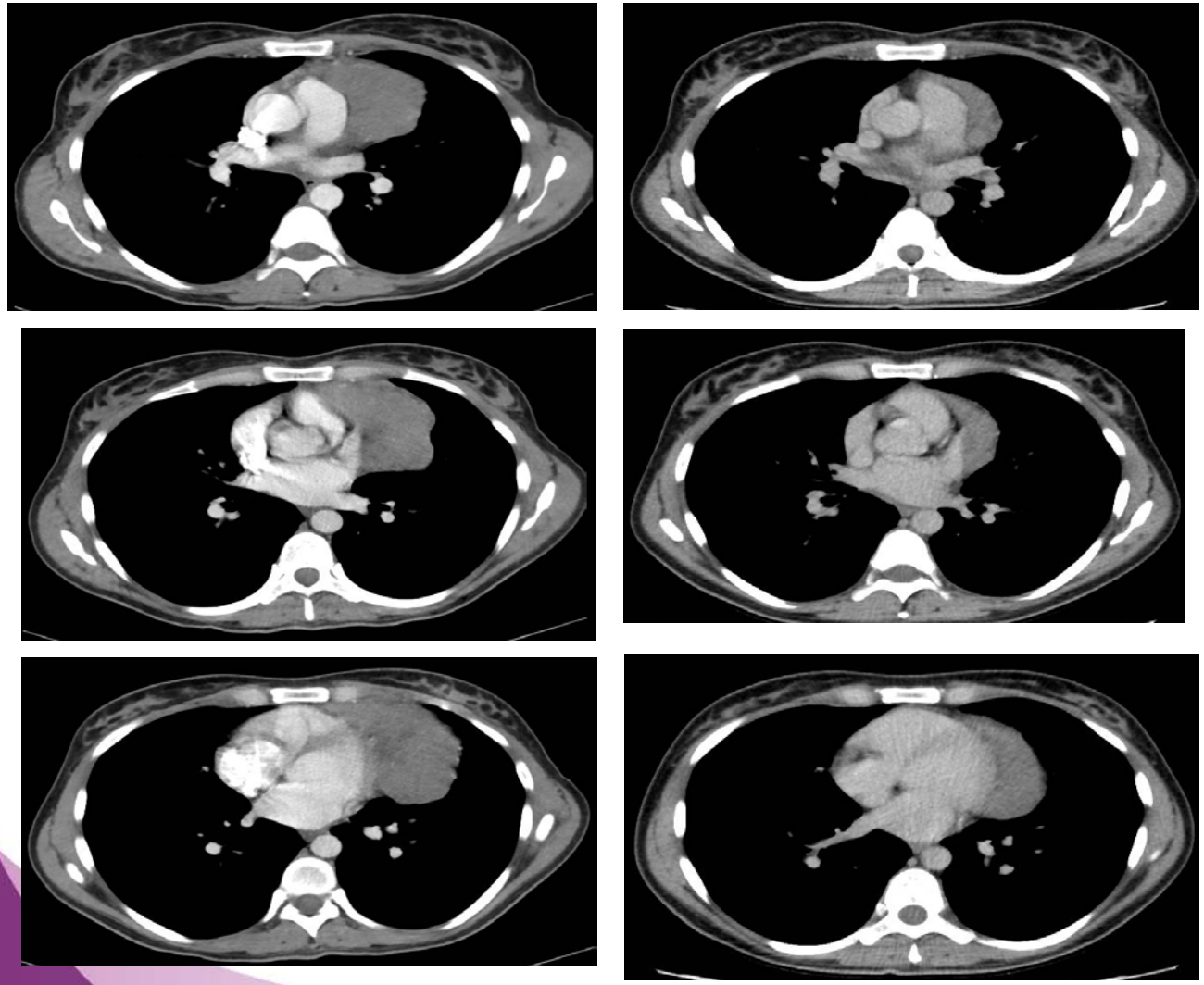


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Table 1 Survey results

Clinical scenario	Question	% of respondents who chose		
		A	B	Other
1	1	60	35	5
2	2	63	32	5
3	3	28	67	6
	4	67	28	6
4	5	11	89	0
5	6	56	28	17
	7	100	0	0
6	8	72	28	0
7	9	17	67	17

Conclusions: Even among expert radiation oncologists, interpretation of ISRT guidelines is variable. Further guidance for ISRT field design will be needed to reduce variability among practicing physicians.

Published Ahead of Print on March 17, 2014 as 10.1200/JCO.2013.51.9298
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.9298

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Omitting Radiotherapy in Early Positron Emission Tomography–Negative Stage I/II Hodgkin Lymphoma Is Associated With an Increased Risk of Early Relapse: Clinical Results of the Preplanned Interim Analysis of the Randomized EORTC/LYSA/FIL H10 Trial

John M.M. Raemaekers, Marc P.E. André, Massimo Federico, Theodore Girinsky, Reman Oumedaly, Ercole Brusamolino,† Pauline Brice, Christophe Fermé, Richard van der Maazen, Manuel Gotti, Reda Bouabdallah, Catherine J. Sebban, Yolande Lievens, Allessandro Re, Aspasia Stamatoullas, Frank Morschhauser, Pieternella J. Lugtenburg, Elisabetta Abruzzese, Pierre Olivier, Rene-Olivier Casasnovas, Gustaaf van Imhoff, Tiana Raveloarivahy, Monica Bellei, Thierry van der Borght, Stephane Bardet, Annibale Versari, Martin Hutchings, Michel Meignan, and Catherine Fortpied

Table 2. Results of Interim Analysis in Patients With Early PET-Negative Disease

Subset	No. of Patients	No. of Observed Events	HR	Adjusted CI*	*P*†	1-Year PFS	
						%	Adjusted CI*
Favorable					.017		
Standard	188	1	1.00			100.00	
Experimental	193	9	9.36	2.45 to 35.73		94.93	91.89 to 96.85
Unfavorable					.026		
Standard	251	7	1.00			97.28	95.17 to 98.48
Experimental	268	16	2.42	1.35 to 4.36		94.70	92.11 to 96.46

Abbreviations: HR, hazard ratio; PET, positron emission tomography; PFS, progression-free survival.
*Confidence level adjusted to significance level used in interim test: 79.6% CI for favorable group and 80.4% CI for unfavorable group.
†One-sided Wald-test *P* value of superiority test.

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Optimal radiation doses

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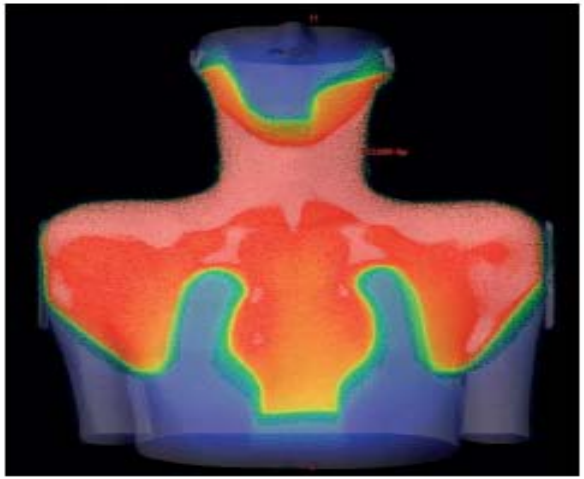
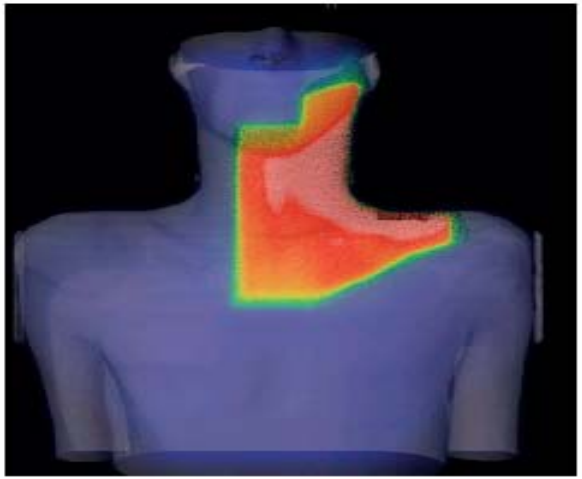
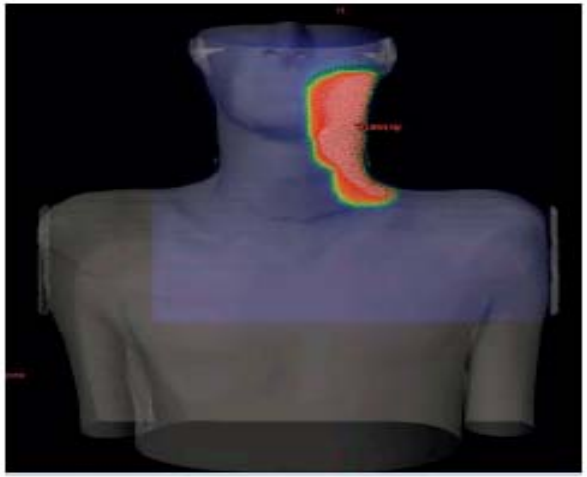
Mantle field, Involved field, Involved Node



40 Gy



36 Gy



20-30 Gy

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German HD 10 study: reducing therapy in early favourable disease

1370 pts 1998-2003

Early Favourable disease:

I_A/II_A

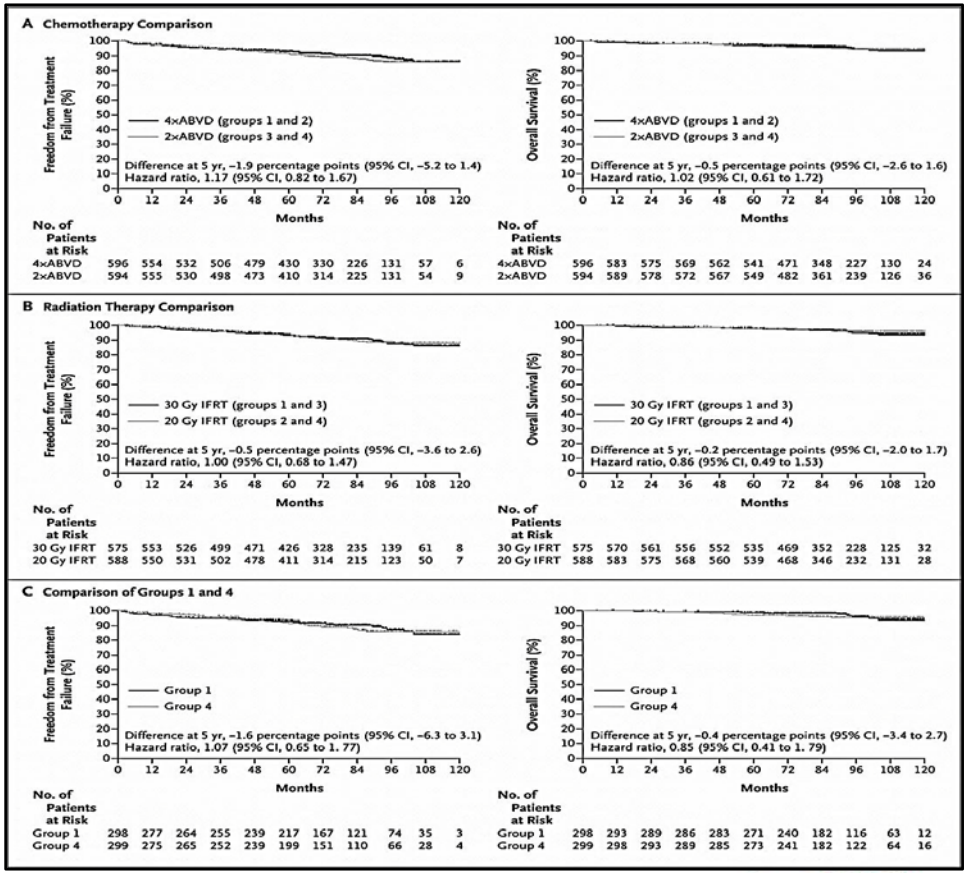
ABVD

2 cycles 4 cycles

Involved field RT

20 Gy 30 Gy

Results equivalent for all 4 arms: 5yr FFTF 92% OS 97%



Engert A et al. N Engl J Med 2010;363:640-652.

Hypothesis: Is more dose better?

German HD 11 Study:
Lower threshold of therapy for early unfavourable disease

1395 pts 1998-2003

Early Unfavourable disease

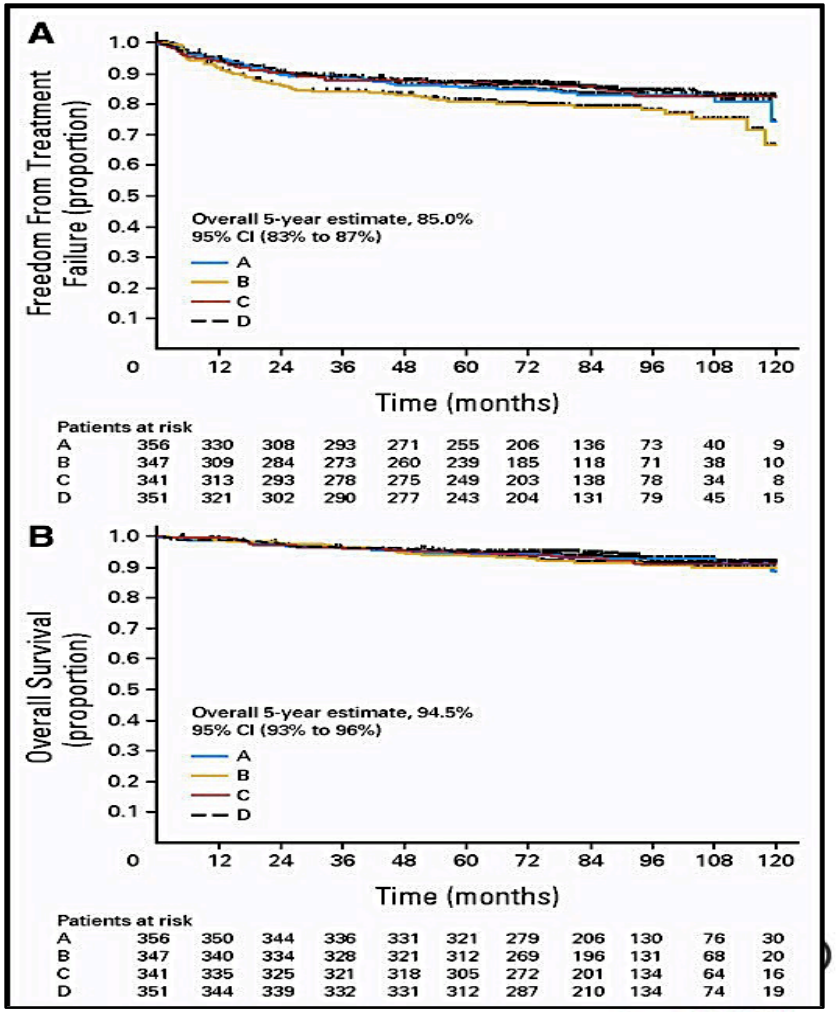
Chemotherapy

4 ABVD 4 BEACOPP

Involved field RT

20 Gy 30 Gy

ABVD x 4 + 20 Gy inferior on FFTF



Eich H T et al. J Clin Oncol 2010;28:4199-4206

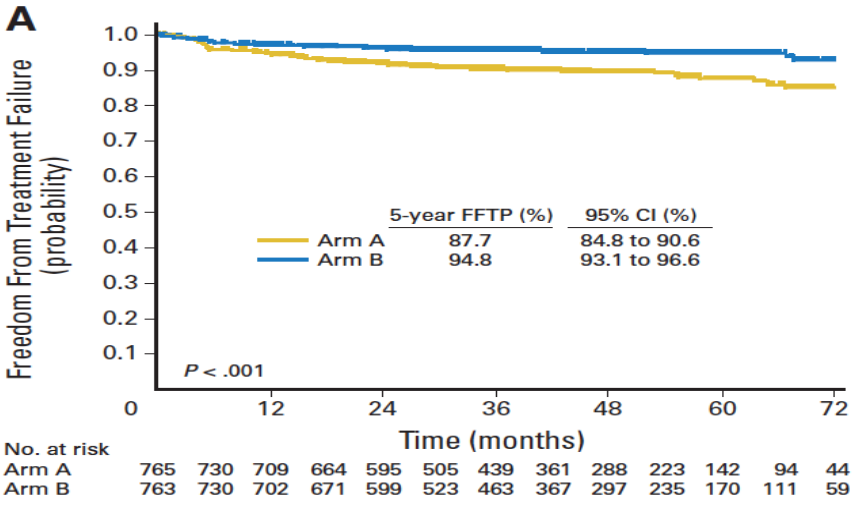
VOLUME 30 · NUMBER 9 · MARCH 20 2012

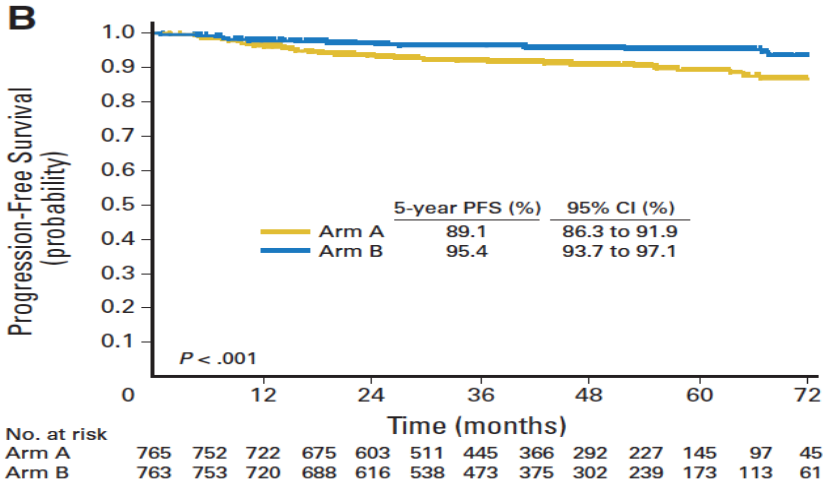
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial

Bastian von Tresckow, Annette Plütschow, Michael Fuchs, Beate Klimm, Jana Markova, Andreas Lohri, Zdenek Kral, Richard Greil, Max S. Topp, Julia Meissner, Josée M. Zijlstra, Martin Soekler, Harald Stein, Hans T. Eich, Rolf P. Mueller, Volker Diehl, Peter Borchmann, and Andreas Engert

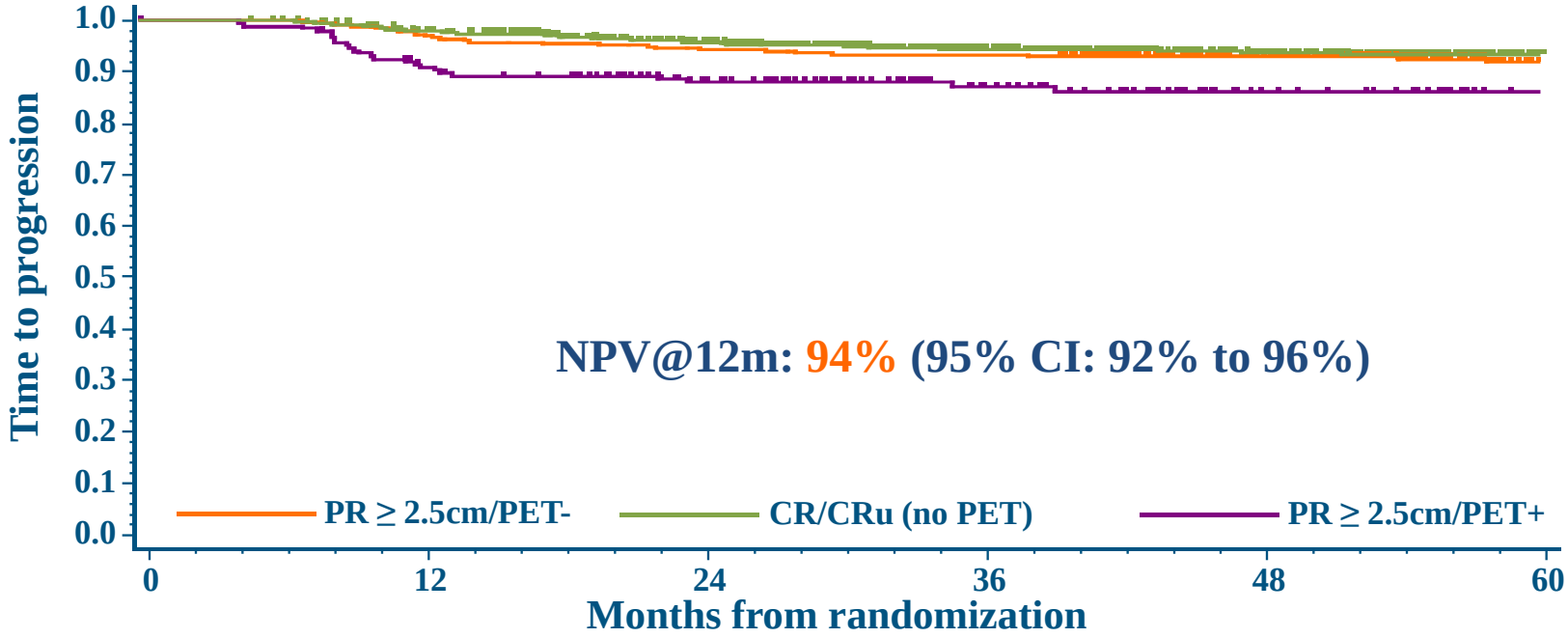




There was more acute toxicity associated with 2+2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies

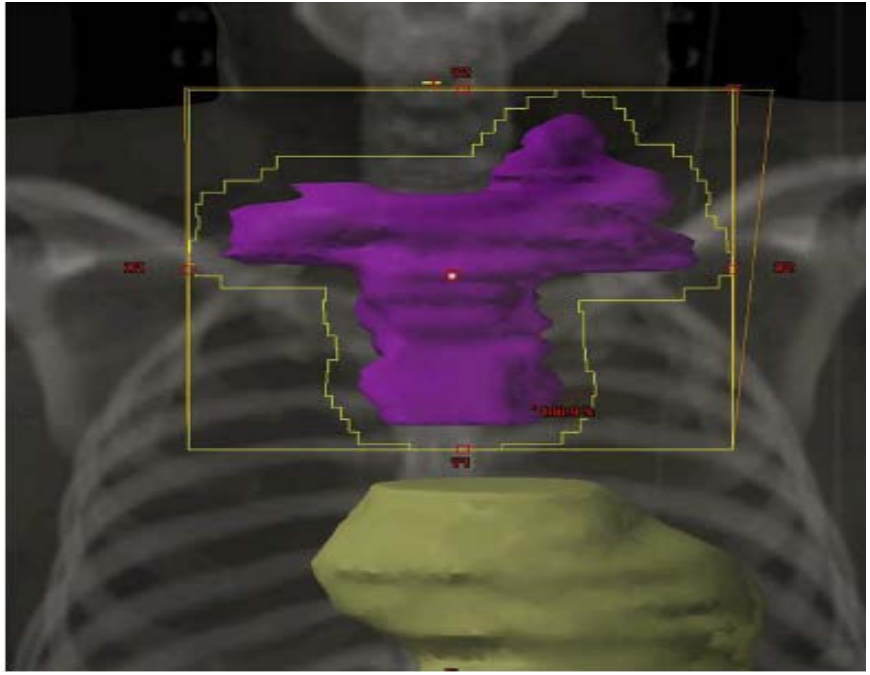
HD15-PET trial

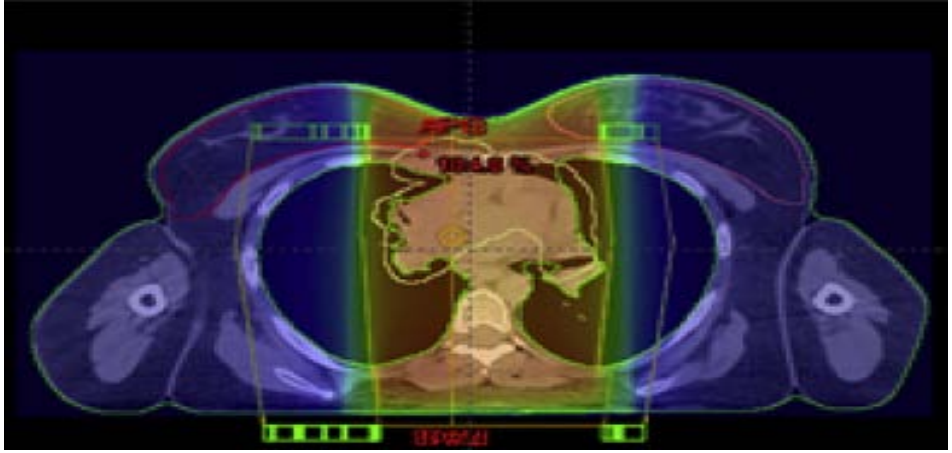
Impact of response and PET status (TTP)



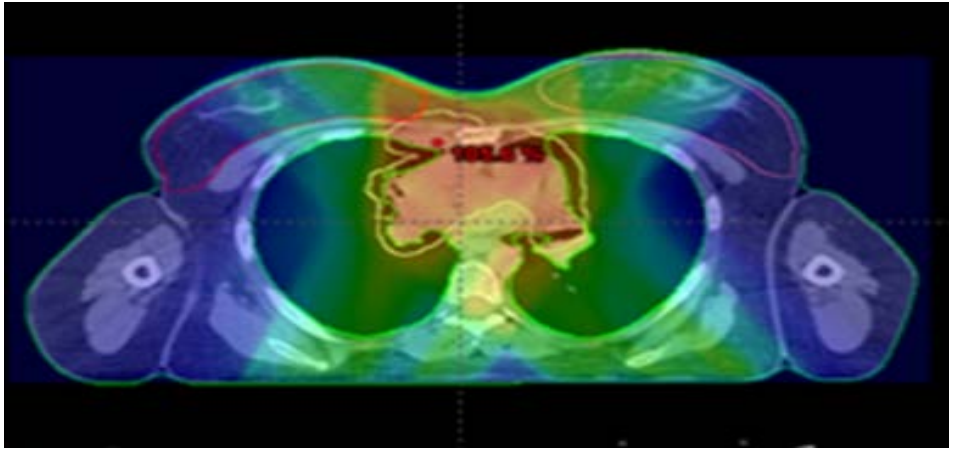
Pts. at Risk						
PET-	540	517	449	338	224	118
PET+	188	166	139	97	58	35
CR/CRu	854	811	690	482	303	155

New techniques in lymphoma RT





3D-CRT

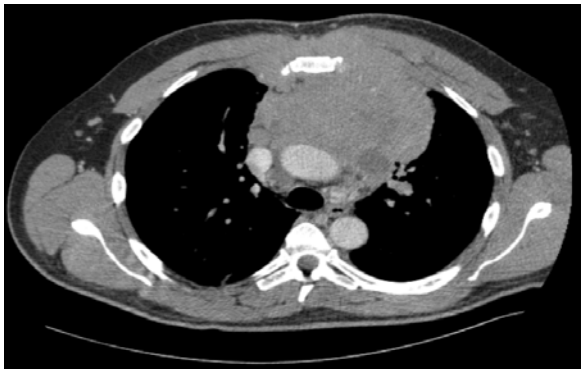


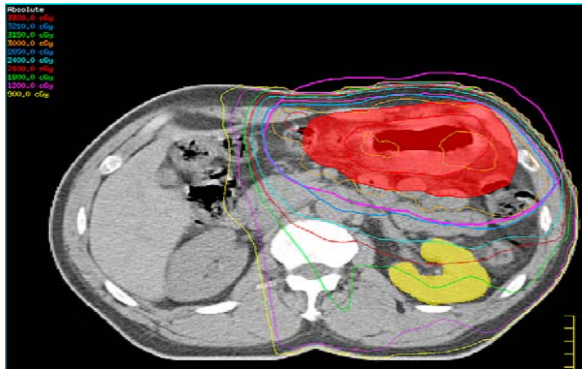
IMRT

Advanced conformal RT in lymphoma

- The question is whether modern highly conformal RT will lead to a further reduction in late toxicity

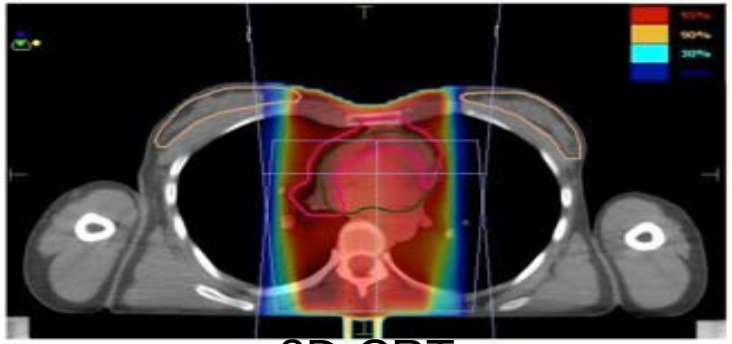
- This is especially relevant for patients receiving irradiation with target volumes in close proximity to critical organs at risk (heart, lung, liver, kidney)



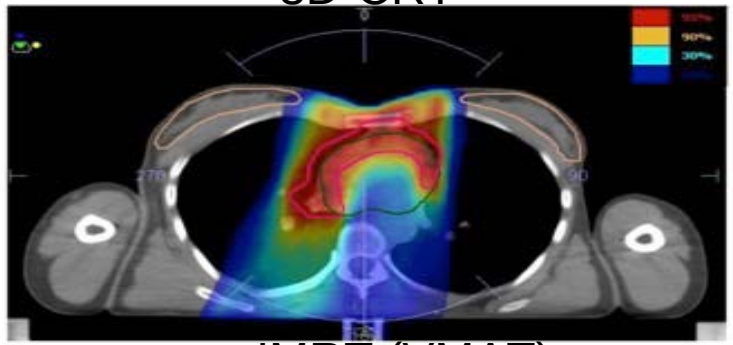


IMRT

- Only the target volume is treated to the full dose
- Better sparing of normal tissues



3D-CRT



IMRT (VMAT)

IMRT vs 3D-CRT in lymphoma

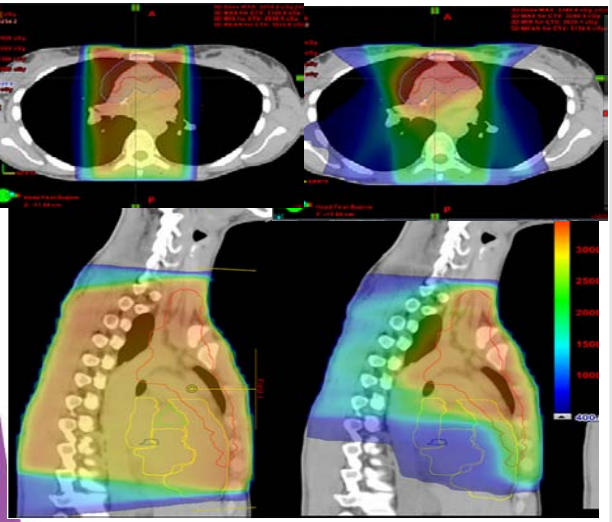
- Several published studies investigated the dosimetric profiles of IMRT compared to those of 3D-CRT

- They showed significantly better PTV coverage (V_{90}, V_{95}, conformity index) and/or significantly better sparing effect for different OAR

  - both for the traditional IFRT and for the more recent concept of limited volumes RT (INRT, ISRT)

Effective Dose Reduction to Cardiac Structures Using Protons Compared With 3DCRT and IMRT in Mediastinal Hodgkin Lymphoma

B. Hoppe, IJROBP 2012



3D-CRT IMRT

Cardiac subunit	3DCRT	IMRT
Heart	21 Gy (15–25)	12 Gy (10–19)
Left ventricle	13 Gy (8–21)	5 Gy (4–15)
Right ventricle	17 Gy (15–24)	11 Gy (8–18)
Left atrium	28 Gy (22–30)	15 Gy (11–21)
Right atrium	24 Gy (18–31)	17 Gy (11–25)
Mitral valve	28 Gy (20–30)	9 Gy (5–17)
Tricuspid valve	19 Gy (7–31)	13 Gy (6–26)
Aortic valve	30 Gy (26–31)	18 Gy (10–26)
Pulmonic valve	31 Gy (26–32)	28 Gy (19–31)
Left anterior descending artery	18 Gy (8–25)	10 Gy (4–21)
Left circumflex artery	30 Gy (21–31)	16 Gy (9–20)
Right circumflex artery	29 Gy (21–31)	22 Gy (11–30)
Pulmonary artery	31 Gy (28–32)	29 Gy (24–31)
Superior vena cava	31 Gy (31–32)	31 Gy (29–32)
Ascending aorta	31 Gy (27–32)	29 Gy (21–30)
Clinical target volume	107% (104–111)	105% (102–110)
Planned target volume	106% (103–110)	104% (102–108)

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IMRT in lymphoma RT

IMRT has been thought to be less useful and still not regarded as a standard option in hematological malignancies because:

- Lower prescribed doses, generally well below tolerance dose of normal tissues
- Fear of late effects secondary to low-dose exposure of larger volumes of healthy tissues
- Theoretical increased risk of geographic miss, as the dose gradients are steeper around the target volumes

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Dose constraints in lymphoma RT

- Even low doses to normal tissues, previously considered safe, may result in significant risks of morbidity and mortality in long-term survivors

- Doses to all normal structures should be kept as low as possible, but some structures are more critical than others

- Linear increase in risk of major cardiac events by 7.4% for every 1 Gy increase in mean heart dose
- No threshold dose

Darby et al NEJM 2013

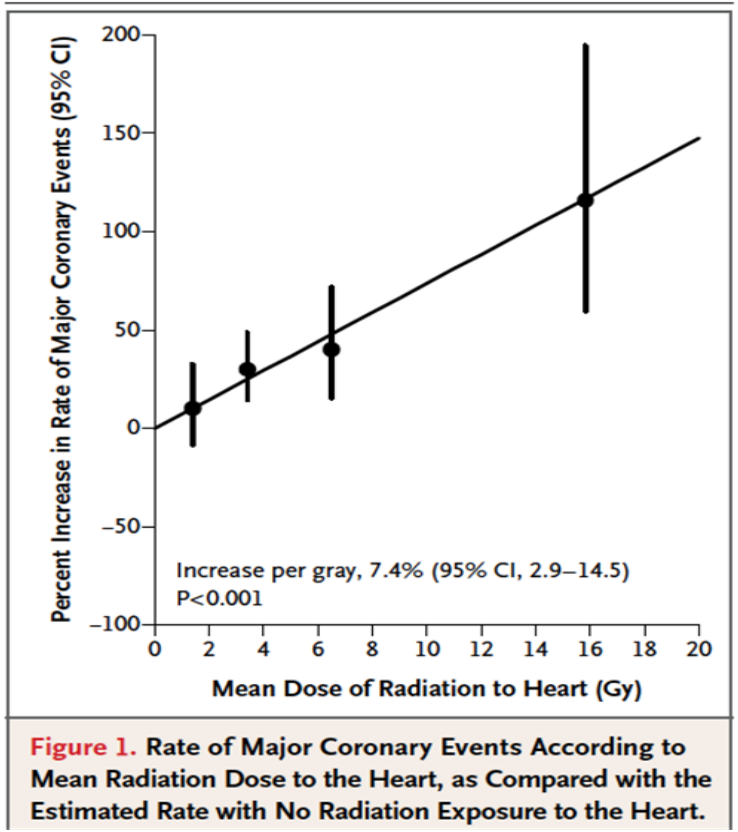
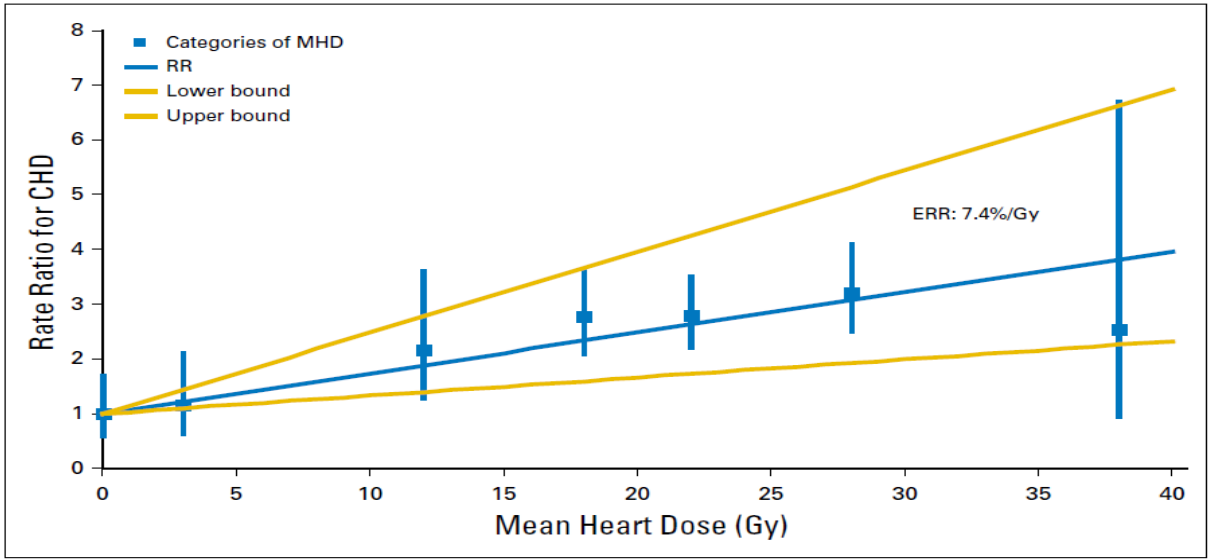


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma

Frederika A. van Nimwegen, Michael Schaapveld, David J. Cutter, Cècile P.M. Janus, Augustinus D.G. Krol, Michael Hauptmann, Karen Kooijman, Judith Roesink, Richard van der Maazen, Sarah C. Darby, Berthe M.P. Aleman, and Flora E. van Leeuwen

LINEAR "NO-THRESHOLD" CORRELATION BETWEEN MEAN HEART DOSE AND DEVELOPMENT OF CAD



J Clin Oncol 2016

Modern RT in lymphoma

- Specific dose constraints in lymphoma RT

Second Cancers: IMRT vs. 3D-CRT

- IMRT minimizes the amount of normal tissue getting high doses

- But IMRT does result in larger volumes of normal tissue getting lower doses (*more fields and more leakage*)

Which is preferable in terms of second cancers?

- Small volumes of normal tissue getting high doses (3D-CRT)
- Larger volumes of normal tissue getting low doses (IMRT)

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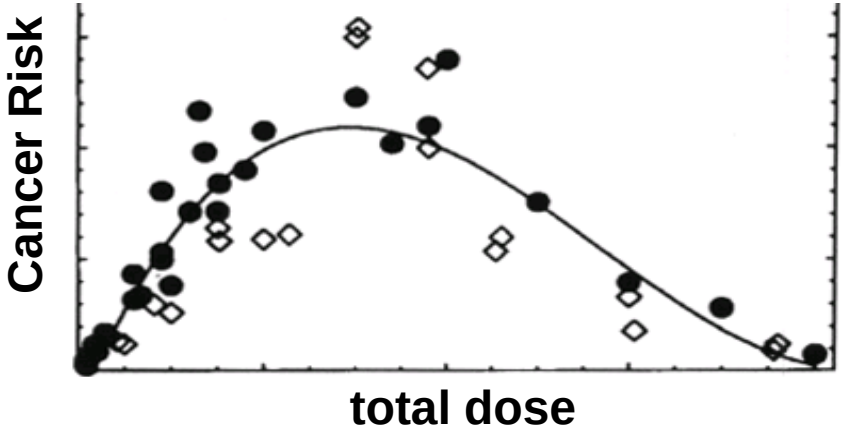
Second Cancers: IMRT vs. 3D-CRT

Key is the shape of the dose-response relationship for radiation-induced carcinogenesis...

High doses don't matter

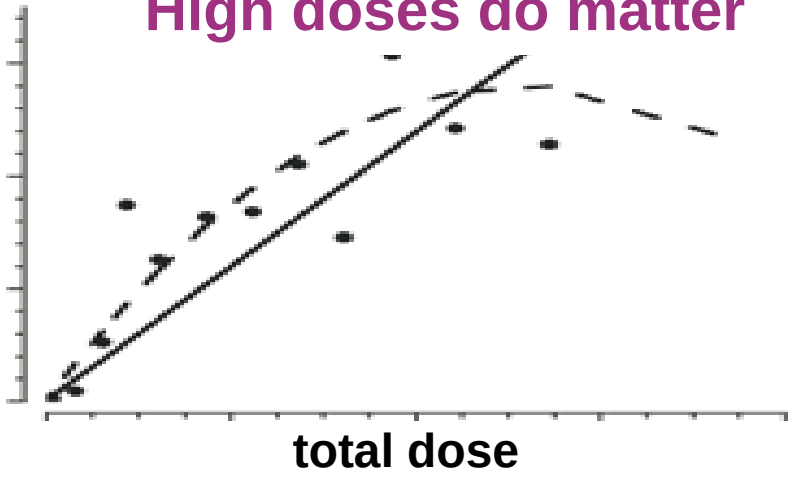


IMRT minimizing high doses doesn't help

IMRT's extra lower doses are bad

OR

High doses do matter



IMRT minimizing high doses helps

IMRT's extra lower doses less important

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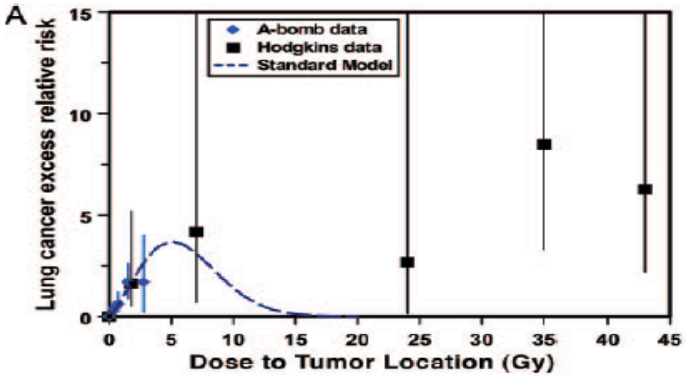
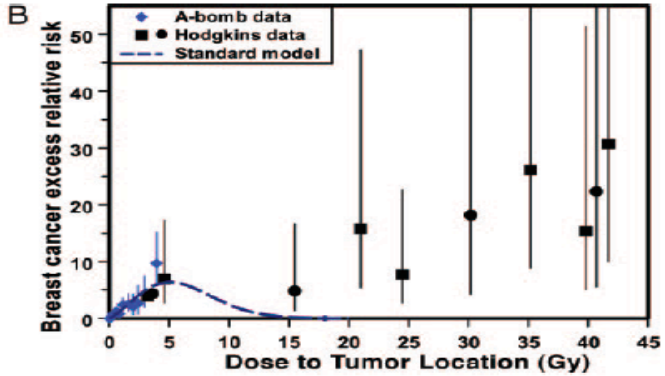
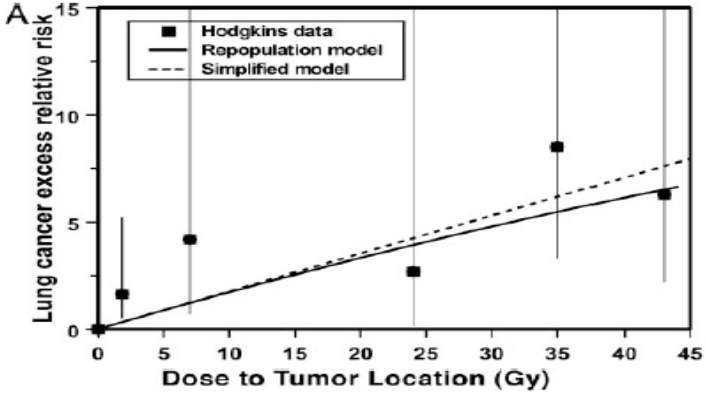
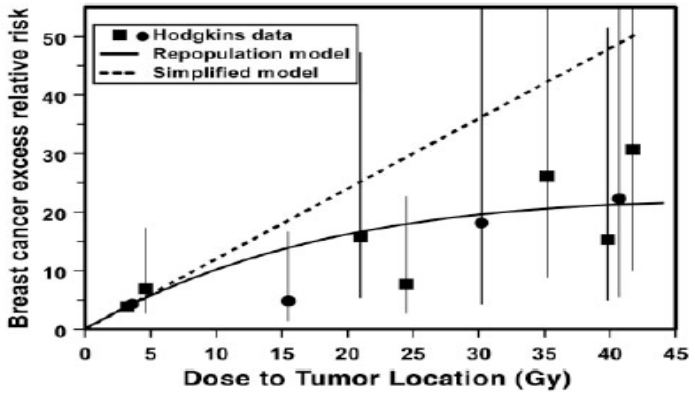
However, recent epidemiology suggests that the risks are not small at large doses









Sachs&Brenner, PNAS 2005

Secondary cancer risk models for RT optimization in HL

May IMRT be optimized taking into account secondary cancers risk?

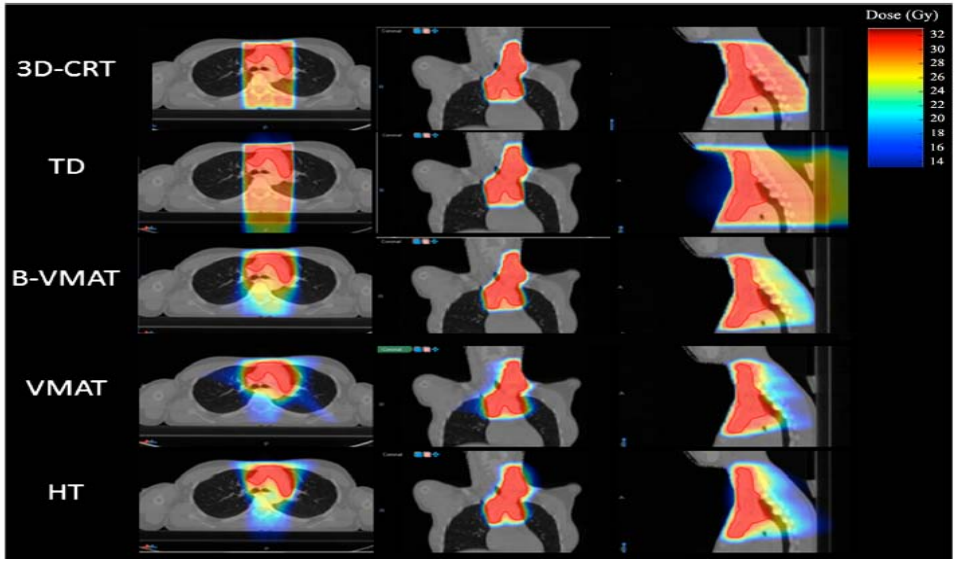
Fiandra *et al. Radiation Oncology* 2012, **7**:186
http://www.ro-journal.com/content/7/1/186

RADIATION ONCOLOGY

RESEARCH Open Access

Different IMRT solutions vs. 3D-Conformal Radiotherapy in early stage Hodgkin's lymphoma: dosimetric comparison and clinical considerations

Christian Fiandra[1*], Andrea Riccardo Filippi[1], Paola Catuzzo[3], Angela Botticella[1], Patrizia Ciammella[1], Pierfrancesco Franco[2], Valeria Casanova Borca[3], Riccardo Ragona[1], Santi Tofani[3] and Umberto Ricardi[1]



Optimizing IMRT with "intelligent" beam orientation

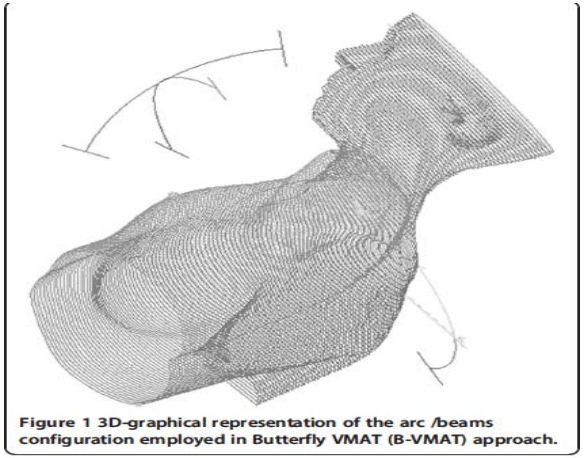


Figure 1 3D-graphical representation of the arc /beams configuration employed in Butterfly VMAT (B-VMAT) approach.

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Different IMRT solutions vs. 3D-Conformal Radiotherapy in early stage Hodgkin's lymphoma: dosimetric comparison and clinical considerations

Christian Fiandra[1*], Andrea Riccardo Filippi[1], Paola Catuzzo[3], Angela Botticella[1], Patrizia Ciammella[1], Pierfrancesco Franco[2], Valeria Casanova Borca[3], Riccardo Ragona[1], Santi Tofani[3] and Umberto Ricardi[1]

Radiation Oncology 2012, 7:186

Conclusions:

- Optimized multiarc VMAT able to achieve the most balanced compromise between higher conformation around the target and smaller volumes of OAR exposed to lower doses

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Original Report

Practical Radiation Oncology (2013)

Changes in breast cancer risk associated with different volumes, doses, and techniques in female Hodgkin lymphoma patients treated with supra-diaphragmatic radiation therapy

Andrea Riccardo Filippi MD*, Riccardo Ragona PhD, Marco Fusella PhD, Angela Botticella MD, Christian Fiandra PhD, Umberto Ricardi MD

practical radiation oncology pro

www.practicalradonc.org

10 young female pts

Different combined treatment solutions:

- IFRT vs INRT
- 30 Gy vs 20 Gy
- 3D-CRT (AP/PA) vs VMAT (2 coplanar arcs + 1 non-coplanar arc)

Table 5 Organ equivalent dose, mean, and SD values of the 10 patients; 3DCRT versus VMAT

IFRT				INRT			
	OED mean ± SD values		*P* value [a]		OED mean ± SD values		*P* value [a]
	3DCRT	VMAT			3DCRT	VMAT	
20 Gy	1.16 ± 0.37	1.23 ± 0.41	.203	20 Gy	0.50 ± 0.39	0.43 ± 0.37	.203
30 Gy	1.48 ± 0.45	1.65 ± 0.54	.093	30 Gy	0.65 ± 0.48	0.69 ± 0.46	.203

Optimized Volumetric Modulated Arc Therapy Versus 3D-CRT for Early Stage Mediastinal Hodgkin Lymphoma Without Axillary Involvement: A Comparison of Second Cancers and Heart Disease Risk

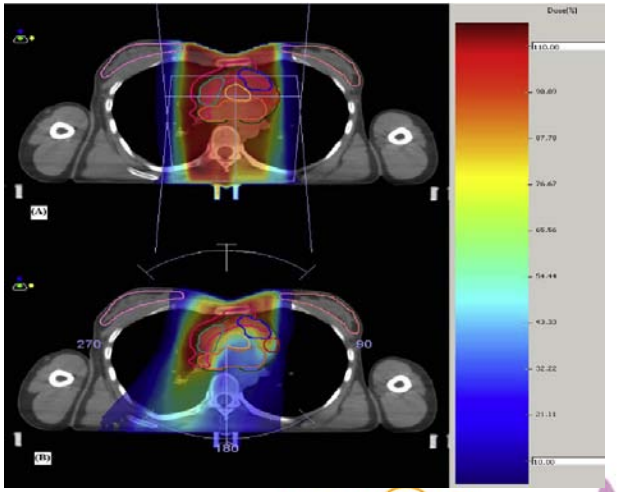
Andrea Riccardo Filippi, MD,* Riccardo Ragona, MSc,* Cristina Piva, MD,* Davide Scafa, MD,* Christian Fiandra, MSc,* Marco Fusella, MSc,† Francesca Romana Giglioli, MSc,† Frank Lohr, MD,‡ and Umberto Ricardi, MD*

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 161–168, 2015

Table 1 Patient characteristics

Characteristic	n	%
No. of patients	38	
Age (y)		
Range	15-43	
Median	30	
Sex		
Male	13	34.2
Female	25	65.8
Ann Arbor stage		
I	8	21.1
II	30	78.9
Bulky	5	13.1
EORTC prognostic groups		
Favorable	16	42.1
Unfavorable	22	57.9
Involved sites		
Mediastinum alone	8	21.1
Mediastinum and unilateral neck	19	50
Mediastinum and bilateral neck	11	28.9

Abbreviation: EORTC = European Organization for Research and Treatment of Cancer.



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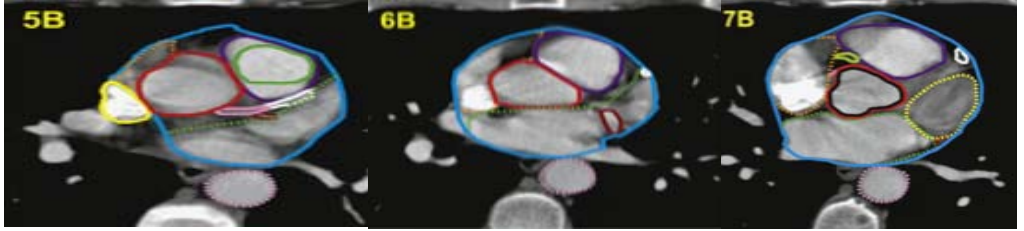
Optimized VMAT: cardiovascular disease



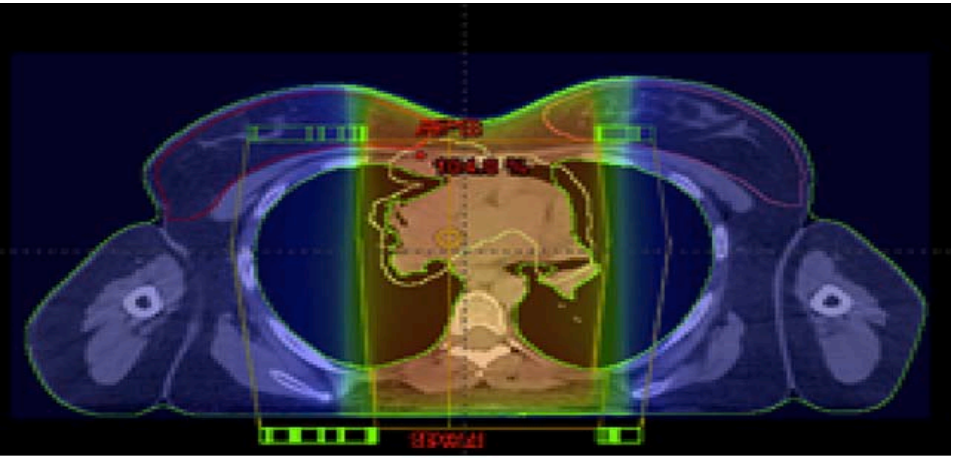
Cardiac subunits: heart atlas (Feng, 2011)

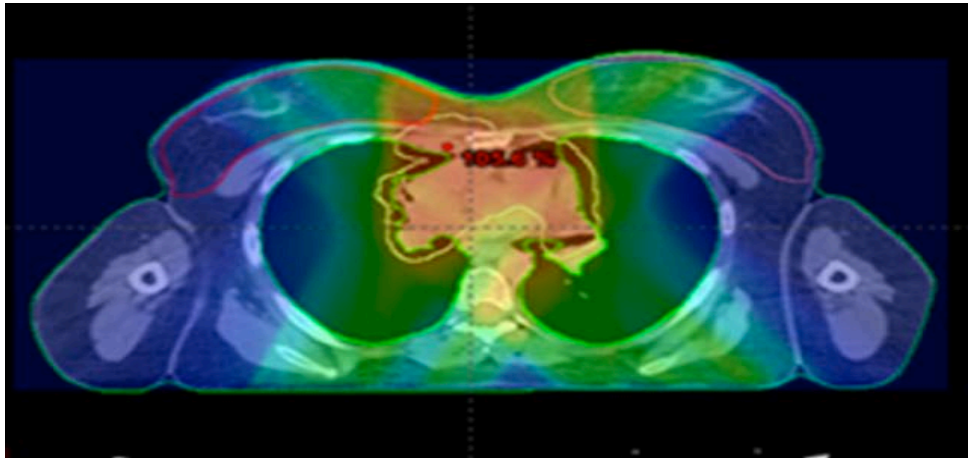
Absolute Excess Risk (AER)

	Mean AER and SD		
	3D-CRT	VMAT	*p* value
Cardiac diseases	0.74 ± 1.50	0.37 ± 0.45	0.038
Aortic valve	2.15 ± 2.27	0.26 ± 0.63	<0.0001
Pulmonic valve	3.13 ± 3.24	1.36 ± 1.88	<0.0001
Mitral valve	0.29 ± 1.10	0.003 ± 0.007	0.12
Tricuspid valve	0.73 ± 2.11	0.07 ± 0.36	0.045
All valves	1.57+/- 2.55	0.42+/- 1.14	<0.0001

Filippi et al, IJROBP 2015

The winner is....





Which technique is preferable?

- There is no single proven best planning and delivery RT technique
- No two lymphomas are the same with regard to localization and extent of disease
- The decision should be made at the individual patient level (i.e., what appears the optimal treatment plan for one patient may not be acceptable for another patient)

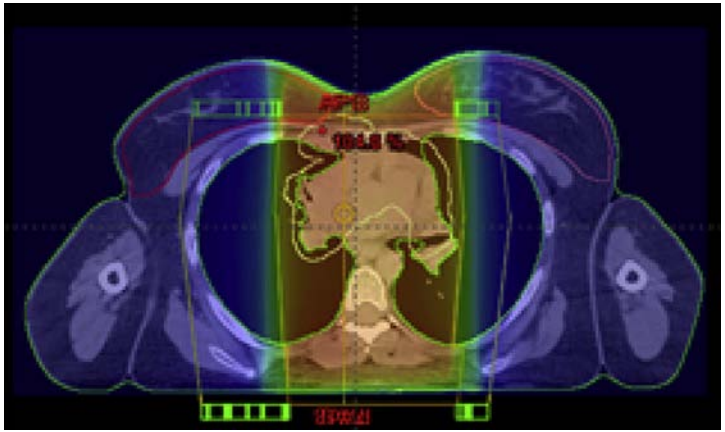
Which technique is preferable?

- The degree of modulation should be chosen based on individual treatment goals
- The benefits of advanced conformal radiotherapy techniques depend on the individual patient/target geometry
- Their use should therefore be decided case by case, with comparative treatment planning
  - 3D-CRT vs “optimized” VMAT
  - dose plans and DVHs for different alternatives should be compared

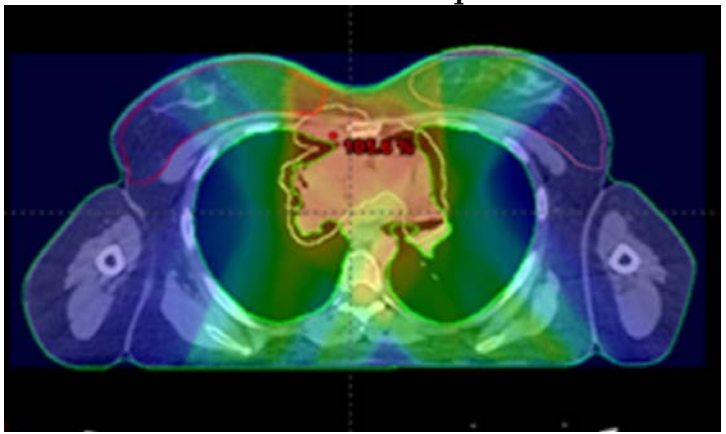
Choosing wisely

The treating radiation oncologist makes a clinical judgment as to which treatment technique to use, based on comparisons of treatment plans and DVHs with different techniques

3D conformal



IMRT technique



Which technique is preferable?

- Consideration for normal tissue toxicity varies between patients depending on:

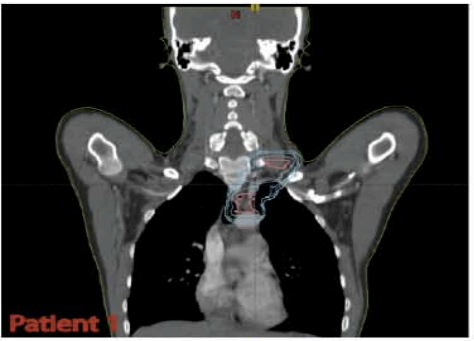
  - Age
  - Gender
  - Comorbidities and risk factors for other diseases
  - Dosimetric data adapted for lymphoma patients (lung, breast, thyroid, heart and cardiac structures)
  - Chemotherapy

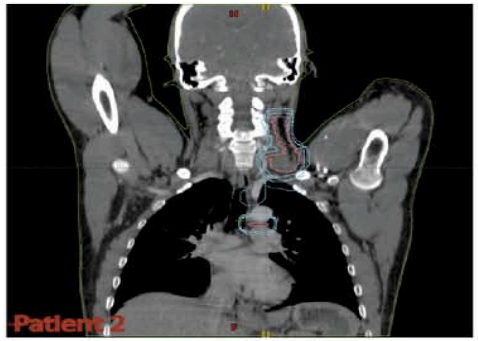
Radiation Therapy Planning for Early-Stage Hodgkin Lymphoma: Experience of the International Lymphoma Radiation Oncology Group

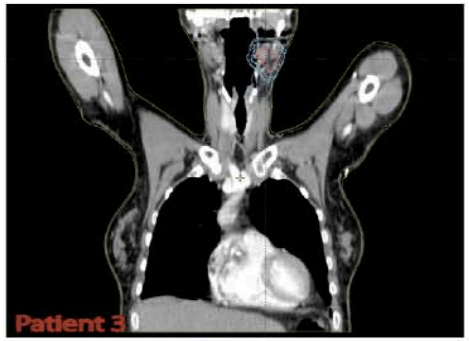
Methods: Ten patients with stage I-II classic HL with masses of different sizes and locations were selected. On the basis of the clinical information, 5 ILROG centers were asked to create RT plans to a prescribed dose of 30.6 Gy. A postchemotherapy computed tomography scan with precontoured clinical target volume (CTV) and OARs was provided for each patient. The treatment technique and planning methods were chosen according to each center's best practice in 2013.

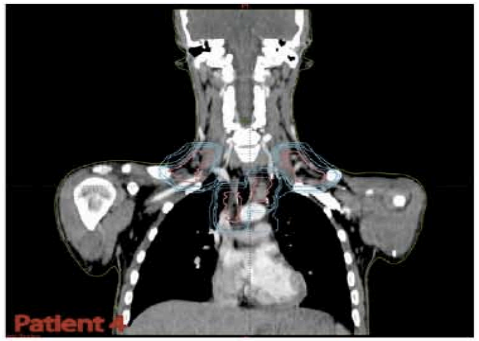
Results: Seven patients had mediastinal disease, 2 had axillary disease, and 1 had disease in the neck only. The median age at diagnosis was 34 years (range, 21-74 years), and 5 patients were male. Of the resulting 50 treatment plans, 15 were planned with volumetric modulated arc therapy (1-4 arcs), 16 with intensity modulated RT (3-9 fields), and 19 with 3-dimensional conformal RT (2-4 fields). The variations in CTV-to-planning target volume margins (5-15 mm), maximum tolerated dose (31.4-40 Gy), and plan conformity (conformity index 0-3.6) were significant. However, estimated doses to OARs were comparable between centers for each patient.

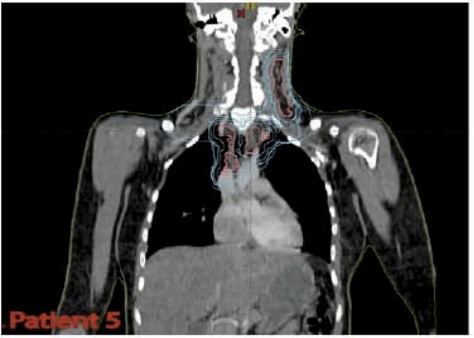
Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1—9, 2015

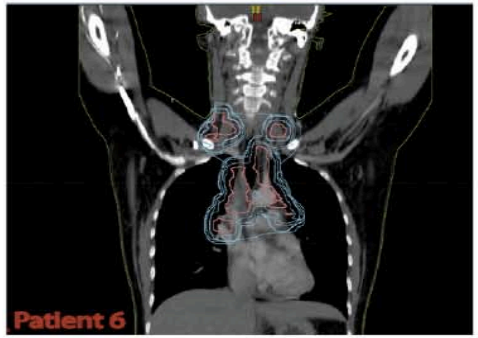


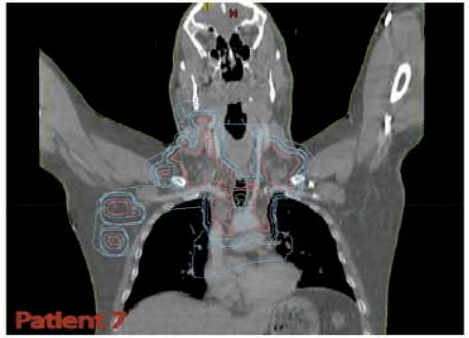


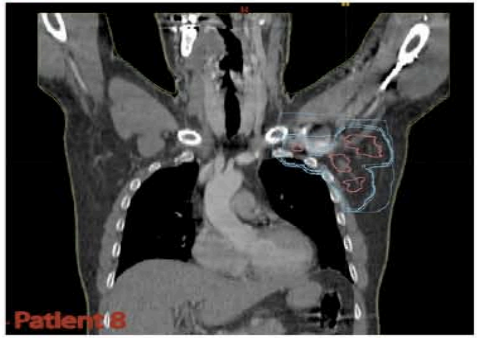


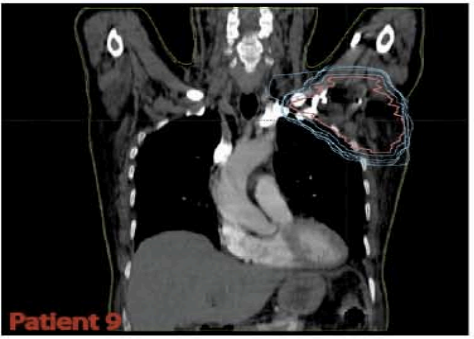


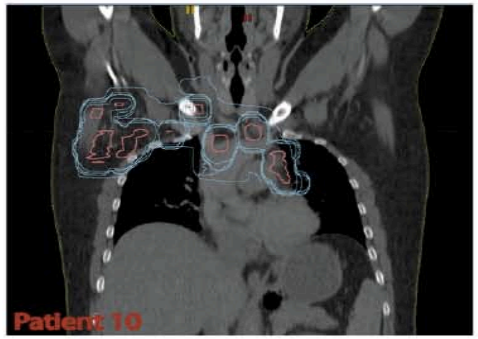








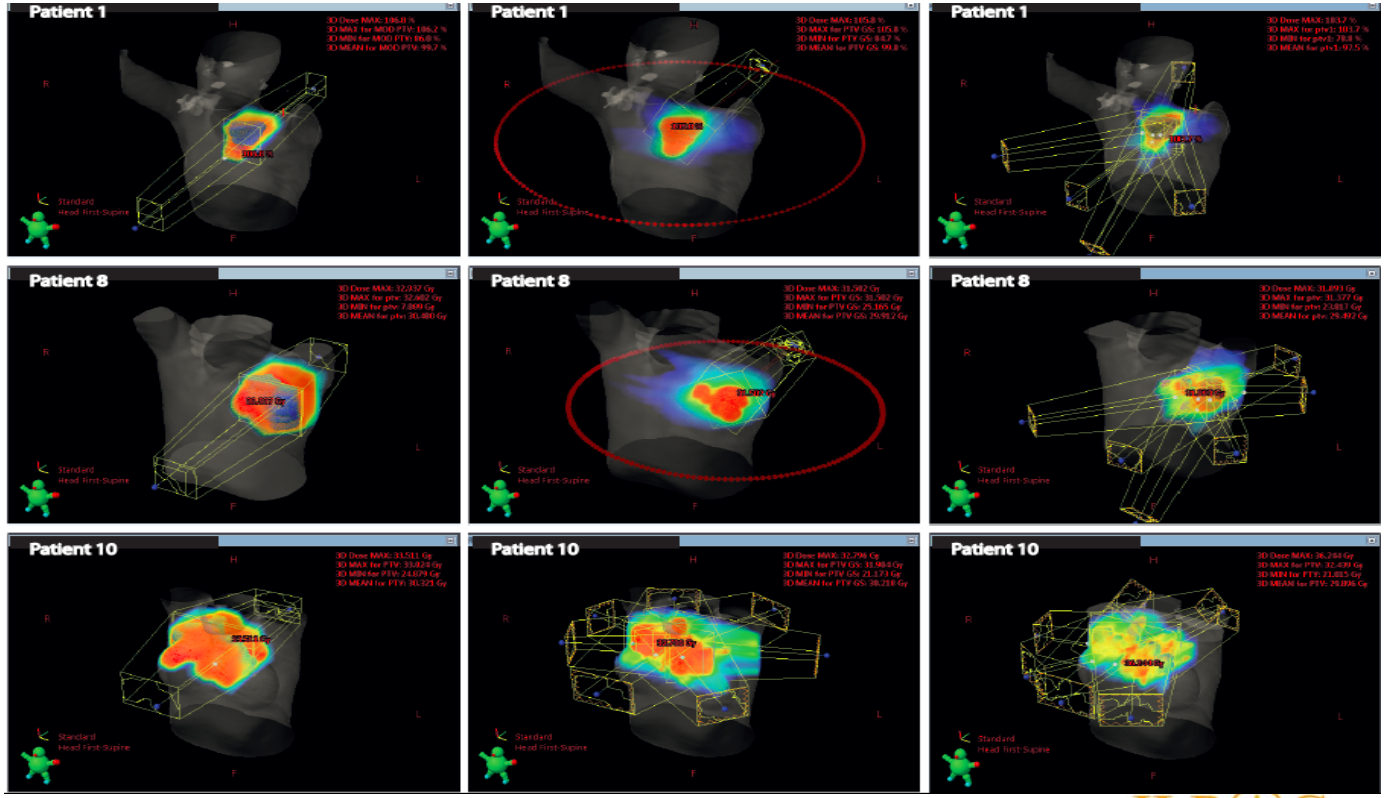




Of the resulting 50 treatment plans:

15 were planned with VMAT (1-4 arcs)
16 with IMRT (3-9 fields)
19 with 3D-CRT (2-4 fields)

Same patient, different solutions



Maraldo MV et a

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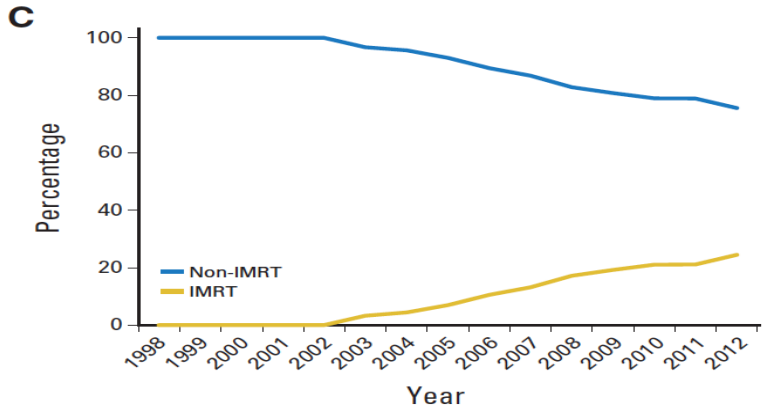
Big Data: National Cancer Database

Treatment Selection and Survival Outcomes in Early-Stage Diffuse Large B-Cell Lymphoma: Do We Still Need Consolidative Radiotherapy?

John A. Vargo, Beant S. Gill, Goundappa K. Balasubramani, and Sushil Beriwal



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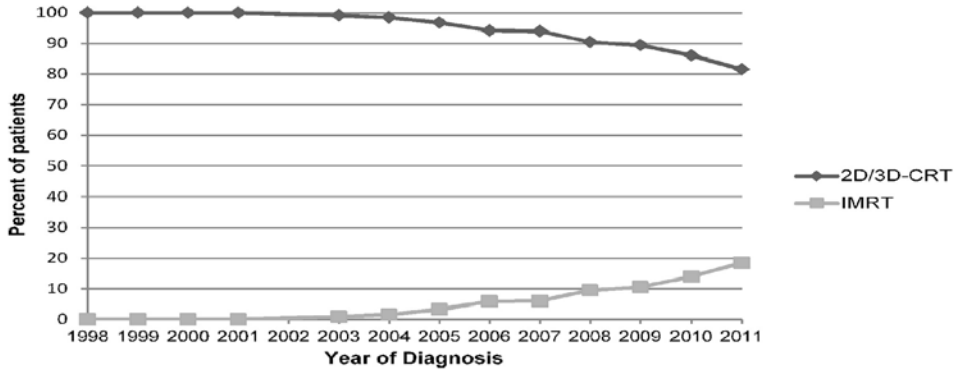
JOURNAL OF CLINICAL ONCOLOGY

Association of intensity-modulated radiation therapy on overall survival for patients with Hodgkin lymphoma

Rahul R. Parikh [a,*], Michael L. Grossbard [b], Louis B. Harrison [c], Joachim Yahalom [d]



Radiotherapy and Oncology 118 (2016) 52–59

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Modern RT in HL

- Radiation therapy has changed dramatically over the last few decades in terms of both irradiated volumes and dose

- Modern RT for HL is a highly individualized treatment restricted to limited treatment volumes

- Smaller treatment volumes, lower radiation dose and advanced conformal radiotherapy can certainly allow a safer radiation delivery, when/if needed (!!!)

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Radiation Therapy for Indolent Nodal non Hodgkin Lymphoma

Volumes, doses and techniques

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

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Indolent Lymphomas
Treatment of stage I and II

- Standard: Involved Field Radiotherapy (IFRT), historically 36-40 Gy
- The shape of the survival curve suggests a possible plateau in the potential for a cure
- Most relapses occur outside the radiation field

Results of radiotherapy in stage I/II:

	5 years	10 years	15 years	20 years
Survival	82%	64%	44%	35%
Relapse-free	55%	44%	40%	37%

Ref.: MacManus,MP et al.; JCO 14: 1282-90 (1996)

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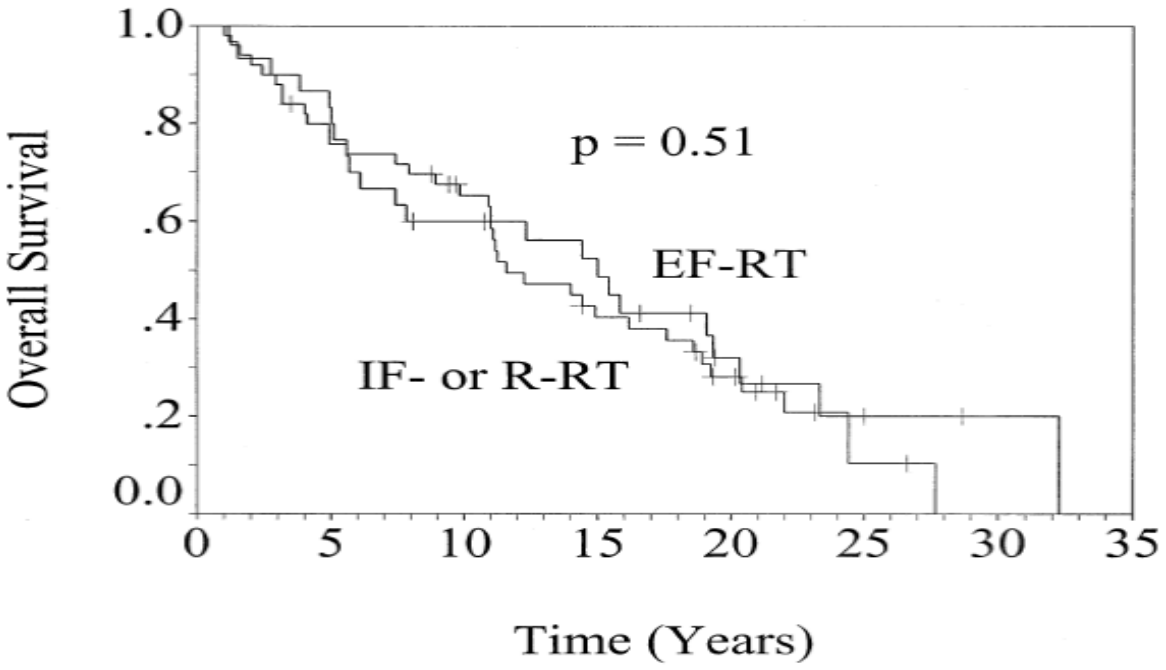
EFRT do not protect from relapses



Wilder et al, IJROBB, 2001

Modern RT in Indolent Lymphoma

- Advances in imaging, treatment planning, treatment delivery, enable irradiation of these volumes with great precision

- Guidelines for involved field RT based on anatomic landmarks and encompassing adjacent uninvolved lymph nodes are no longer appropriate for modern and more “targeted” RT delivery

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Clinical Investigation: Lymphoma and Leukemia

Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Tim Illidge, MD, PhD,* Lena Specht, MD,† Joachim Yahalom, MD,‡ Berthe Aleman, MD, PhD,§ Anne Kiil Berthelsen, MD,‖ Louis Constine, MD,¶ Bouthaina Dabaja, MD,# Kavita Dharmarajan, MD,‡ Andrea Ng, MD,** Umberto Ricardi, MD,†† and Andrew Wirth, MD,‡‡, on behalf of the International Lymphoma Radiation Oncology Group

Modern radiotherapy guidelines developed by

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- Previous wide field and involved field replaced by limited volumes based solely on detectable involvement at presentation
- ICRU concepts of GTV, CTV, ITV, and PTV are used
- New concept, Involved Site RadioTherapy (ISRT), defines CTV on this basis
- Previous doses were higher that necessary, replaced by lower doses in most lymphoma types

Indolent lymphomas

- In early stage disease, RT is the primary treatment
  - Target is the macroscopic lymphoma AND adjacent nodes in that site with a generous margin
- In advanced disease, RT is palliative
  - Target is localized symptomatic disease

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Role of Radiation Therapy in Indolent Nodal Lymphomas

- **Localized Indolent Lymphoma**

  - For the potentially curative treatment of localized early stage (I and II_1) disease, RT is used as the primary treatment approach

Gross tumor volume (GTV) (ICRU 83)

- Gross demonstrable extent and location of the tumor (lymphoma)

• **Determination of Gross Tumor Volume**

Imaging abnormalities obtained before any intervention should be outlined on the simulation study and included in the CTV

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Role of Radiation Therapy in Indolent Nodal Lymphomas

- **Localized Indolent Lymphoma**

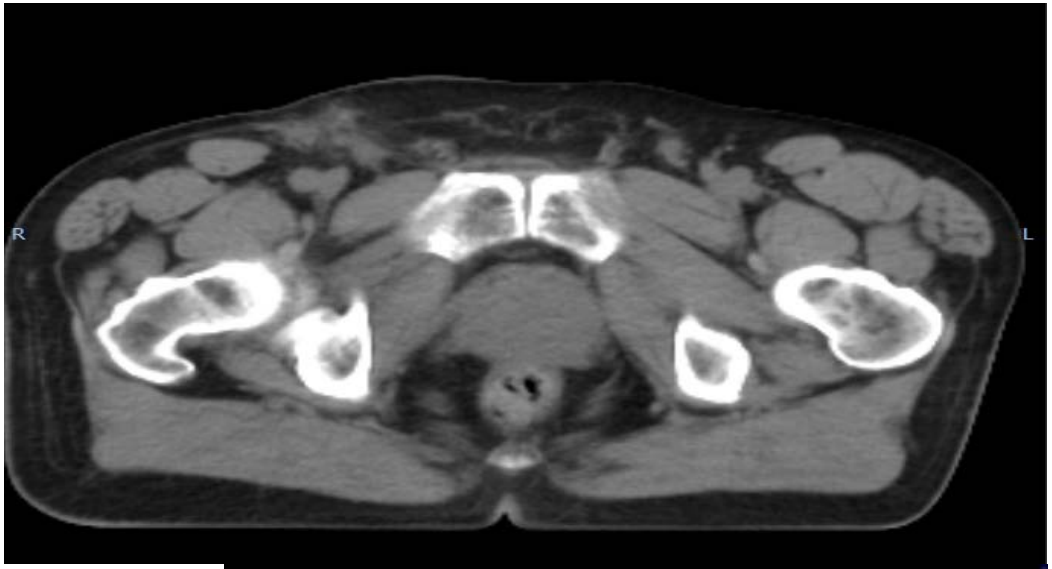
  - The CTV must be designed to encompass suspected subclinical disease based on preintervention GTV imaging

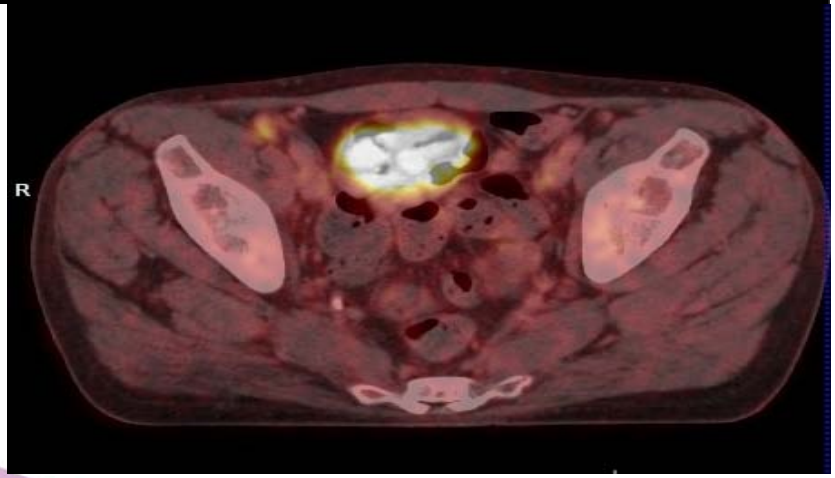
  - The CTV should incorporate GTV and include as a minimum adjacent lymph nodes potentially containing microscopic disease in that site, and a generous margin dictated by the clinical situation

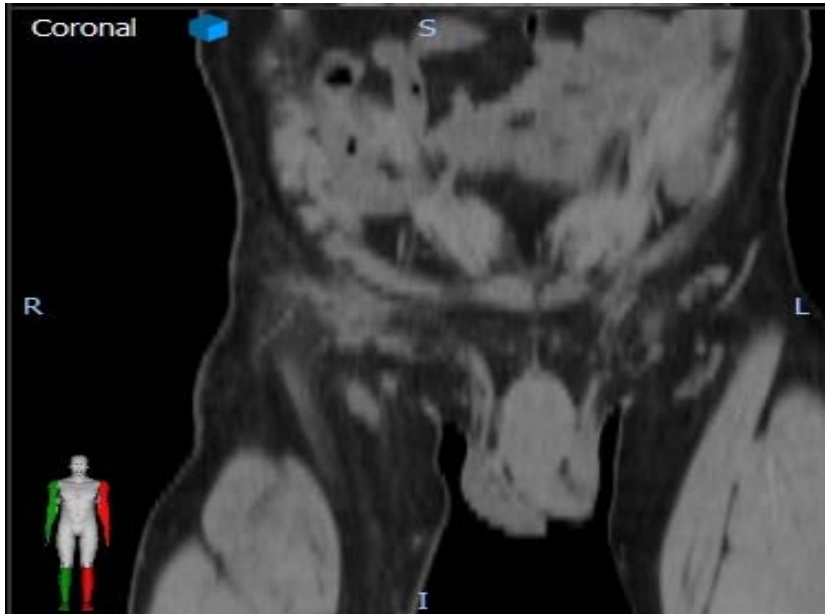
Radiation therapy as primary treatment

In most clinical situations that require RT as primary modality, the GTV should be readily visualized during treatment preparation

The CTV should be more generous in this clinical situation and encompass lymph nodes in the vicinity that, although of normal size, might contain microscopic disease that will not be treated when no chemotherapy is given







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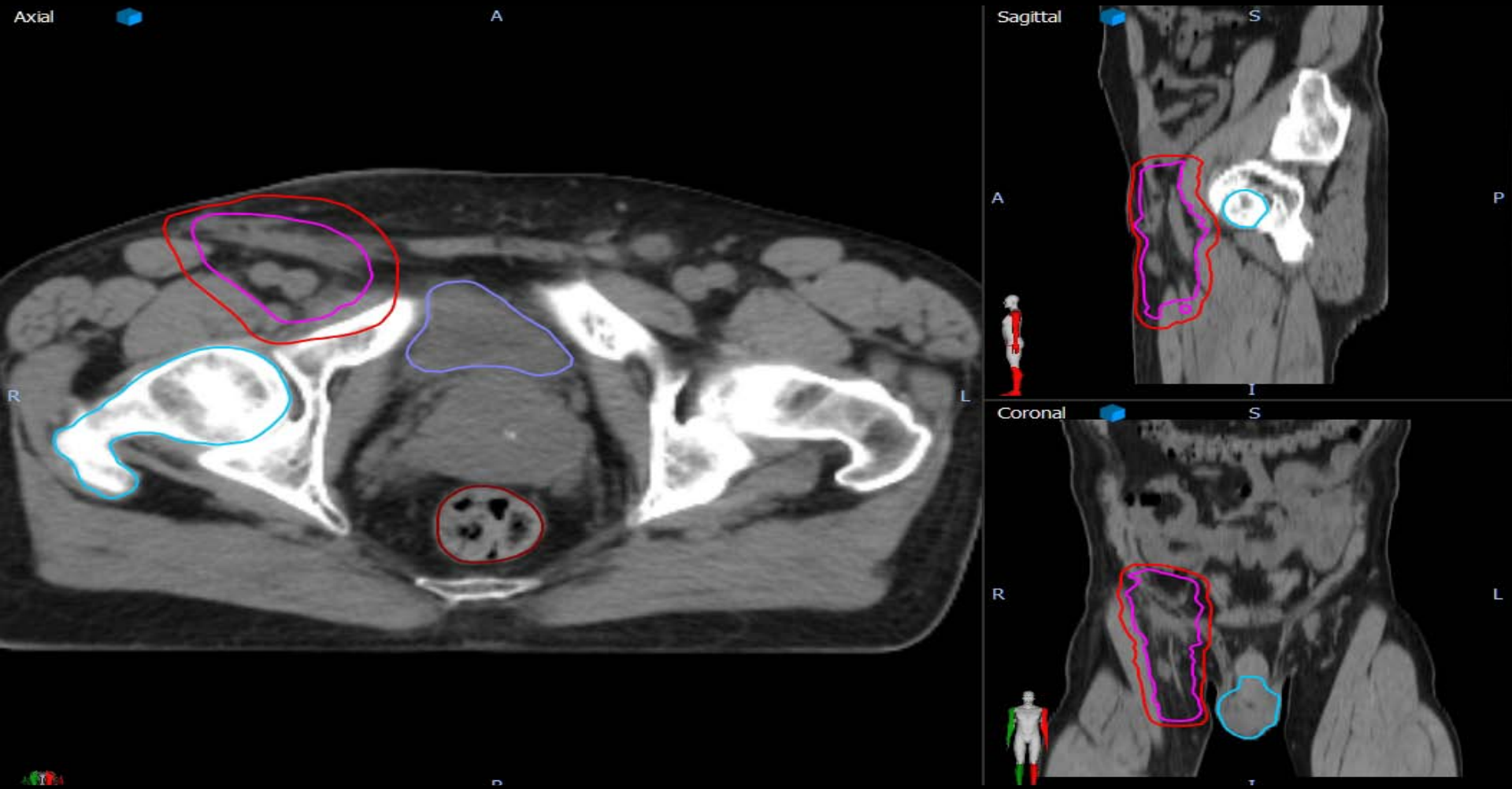
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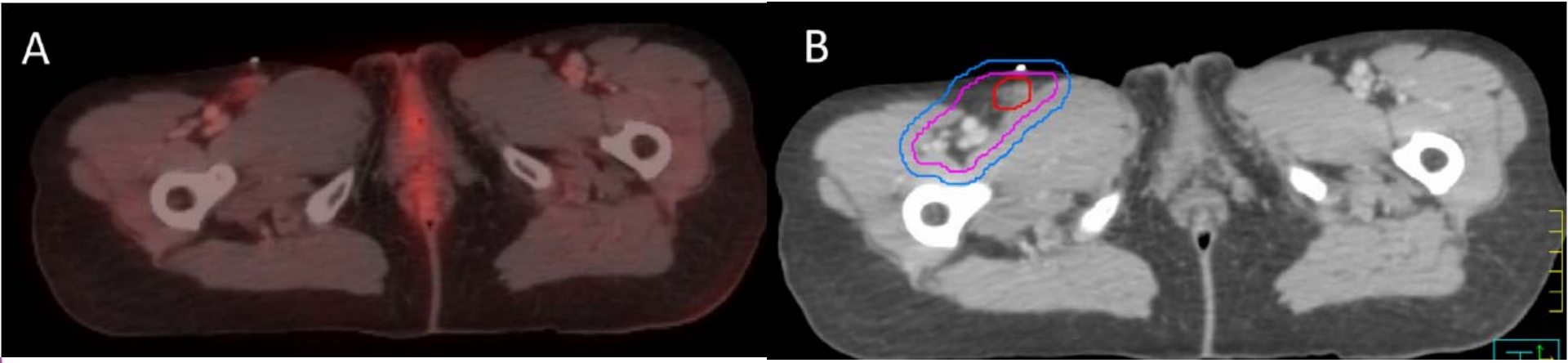
Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

ISRT: Localized indolent lymphoma



The CTV must be designed to encompass suspected subclinical disease based on the pre intervention GTV imaging

The CTV should incorporate GTV and include adjacent lymph nodes in that site and margin dictated by the clinical situation

Illidge et al, IJROBP, 2014

Defining CTV relies upon

- knowledge of the spread patterns of the disease
- potential subclinical extent of involvement
- adjacent organ(s) at risk constraints

all of which depend on clinical judgment and experience

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- “Rigorous staging” is required to determine appropriate patients to consider ISRT, including BM biopsy and FDG-PET scan

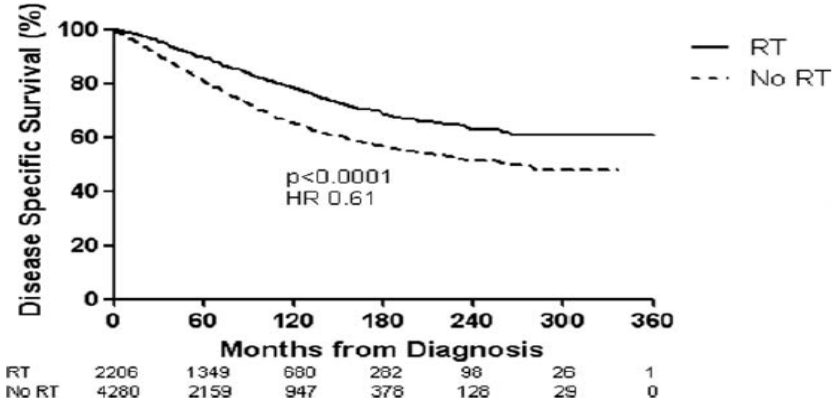
- ISRT remains treatment of choice for stage I/II indolent lymphomas and results in long term progression free survival and possible “cure” for patients still in remission past 10 years

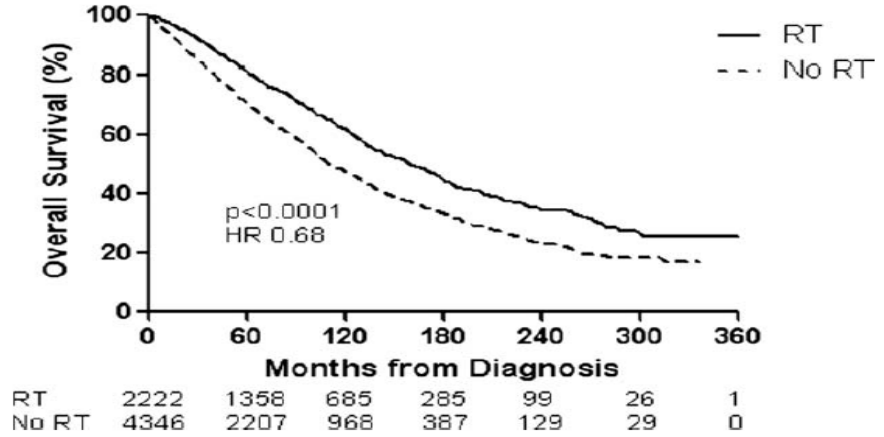
Improved Survival in Patients With Early Stage Low-Grade Follicular Lymphoma Treated With Radiation

Cancer 2010;116:3843–51

A Surveillance, Epidemiology, and End Results Database Analysis

Thomas J. Pugh, MD; Ari Ballonoff, MD; Francis Newman, MS; and Rachel Rabinovitch, MD





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Considerations on RT dose

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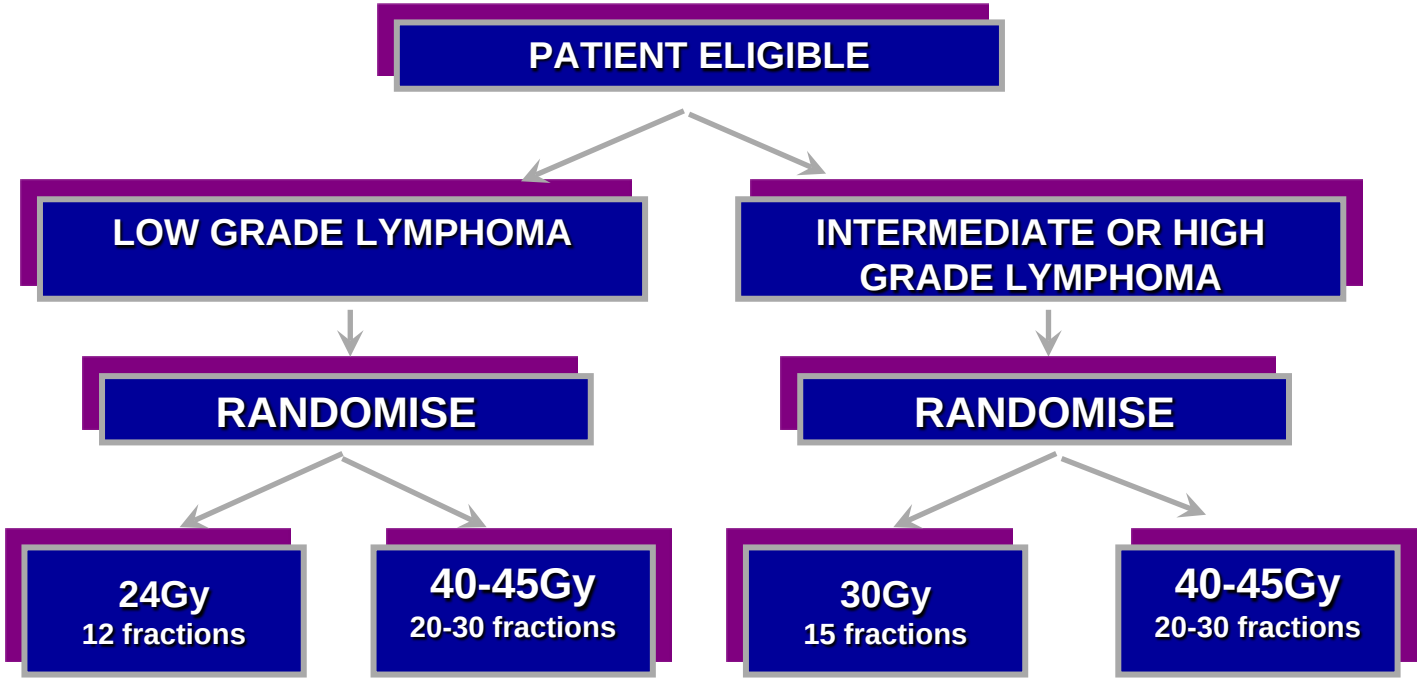
Reduced dose radiotherapy for NHL : A randomised phase III trial

Lowry L, Smith P, Qian W, Falk S, Benstead K, Illidge T, Linch D, Robinson M, Jack A, Hoskin P.

Radiother Oncol. 2011 Jun 9.



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Reduced RT dose in NHL

A randomised phase III trial

361 involved sites of patients with indolent lymphomas

(mostly FL and MZL in early stages)

Baseline characteristics and indications for therapy.

	Indolent	
	24 Gy *N* = 180	40–45 Gy *N* = 181
Age median (range)	62 (29–85)	64 (30–89)
Male gender N (%)	84 (47)	97 (54)
First-line treatment: stage N (%)		
I	69 (40)	72 (41)
IE	38 (22)	47 (27)
II/IIE	11 (6)	13 (7)
III/IV	6 (3)	12 (7)
Relapsed/refractory; any stage N (%)	50 (29)	30 (17)
Not known N	6	7
B symptoms N (%)	13 (8)	4 (2)
Time from diagnosis to randomisation; median months (range)	3.1 (0.2–220)	2.8 (0–179)
Indication for RT radical	119 (66)	130 (72)
Palliation	56 (31	46 (25)
Consolidation	5 (3)	5 (3)
Previous/contemporaneous chemotherapy N (%)	46 (26)	36 (20)
Previous radiotherapy N (%)	15 (8)	24 (13)
Previous rituximab exposure N (%)	2 (1)	2 (1)
Karnofsky scale N (%)		
60–80	16 (12)	16 (11)
90	44 (34)	34 (24)
100	70 (53)	90 (64)
Not known	50	41

Lowry et al, Radiother Oncol, 2011

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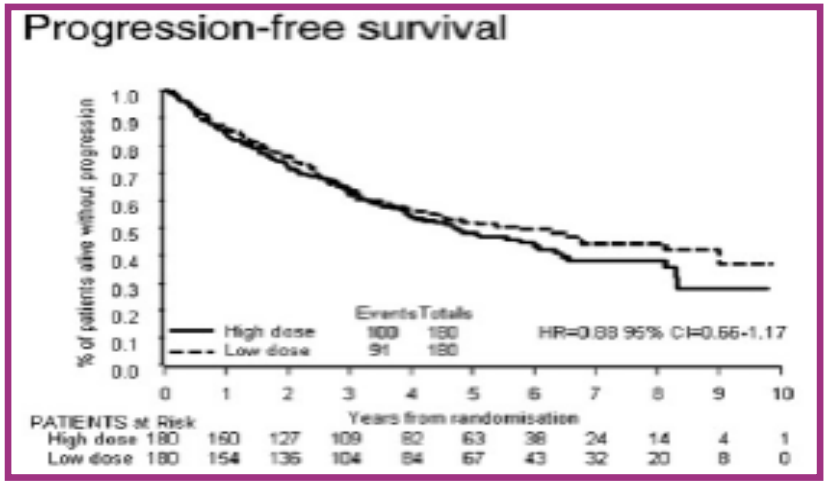
Reduced RT dose in NHL

A randomised phase III trial

Median follow-up time: 5.6 years

ORR: 92% in 24 Gy arm *vs* 93% in 40-45 Gy arm

Response	Indolent	
	24 Gy	40–45 Gy
CR	145 (82%)	138 (79%)
PR	18 (10%)	24 (14%)
SD/ progression	14 (8%)	12 (7%)
Death	0 (0%)	0 (0%)
Not assessable	2	2
No RT received	1	1
Missing	0	4
Total	180	181



Lowry et al, Radiother Oncol, 2011

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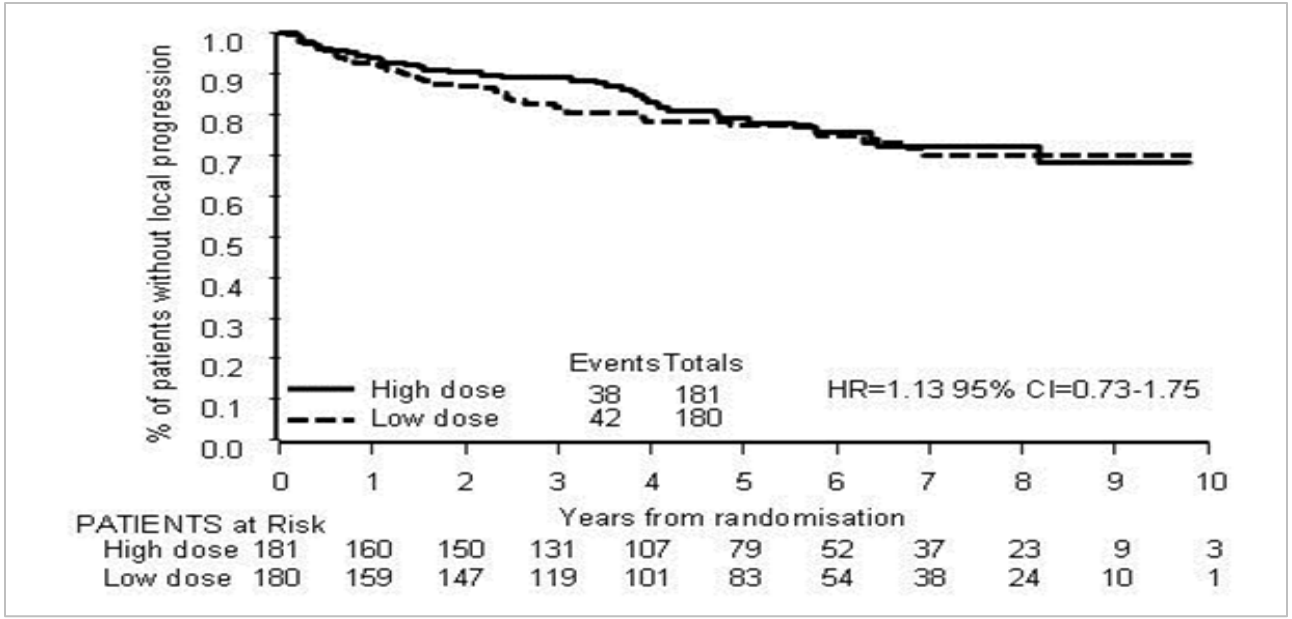
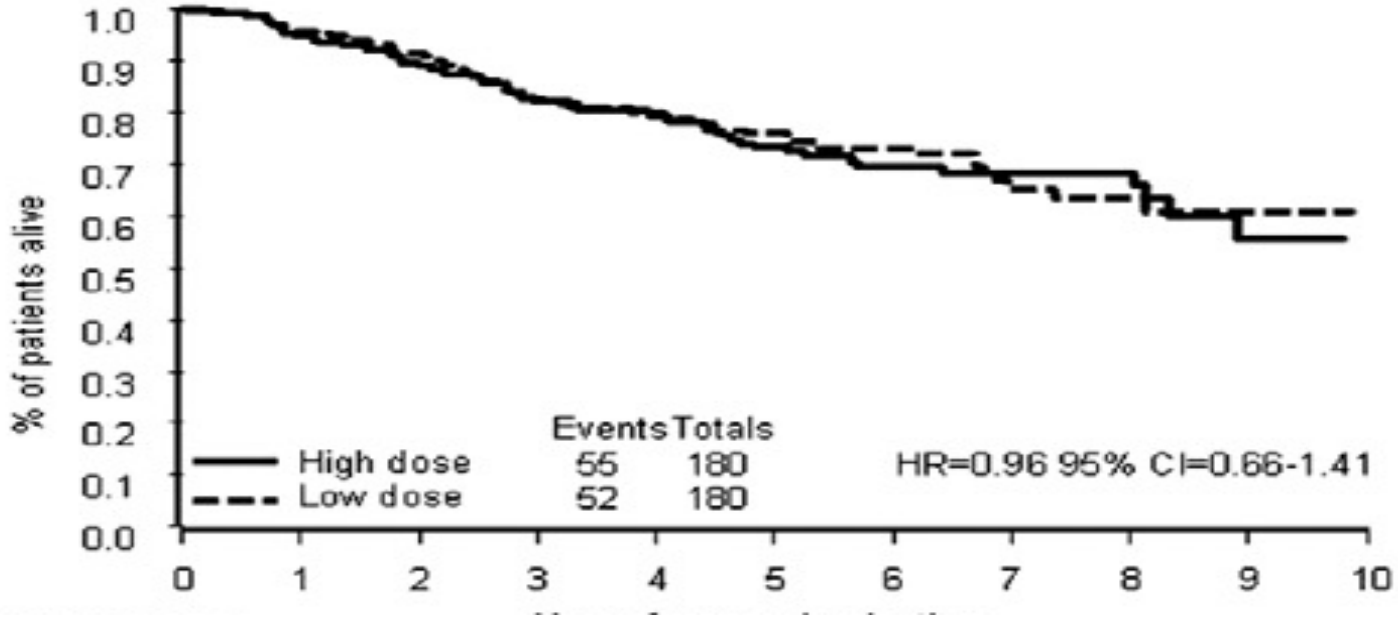
RT dose 24 Gy vs 40 Gy in indolent NHL



[1] Lisa Lowry, Paul Smith, Wendi Qian, Stephen Falk, Kim Benstead, Tim Illidge, David Linch, Martin Robinson, Andrew Jack, Peter Hoskin *'Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial'* Radiotherapy and Oncology 100 (2011) 86–92

INDOLENT LYMPHOMAS:
Overall Survival



Lowry et al. 2011

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BOOM BOOM

Basis for “Boom-Boom” Palliation

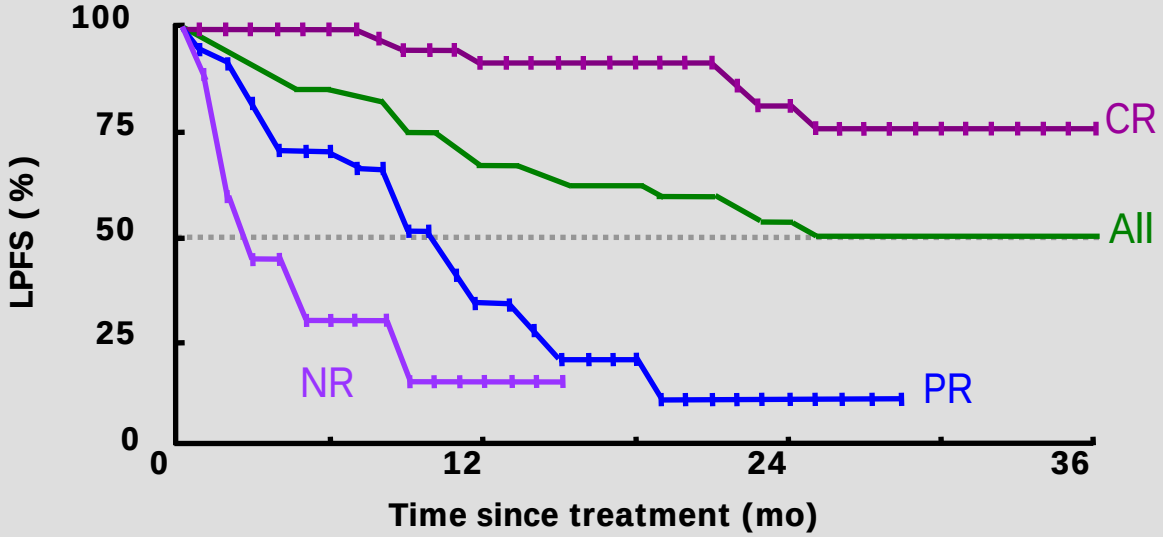
- Institute Gustave Roussy (IGR): patient refused additional palliative WAI after receiving 4 Gy

- At follow-up found to be in CR

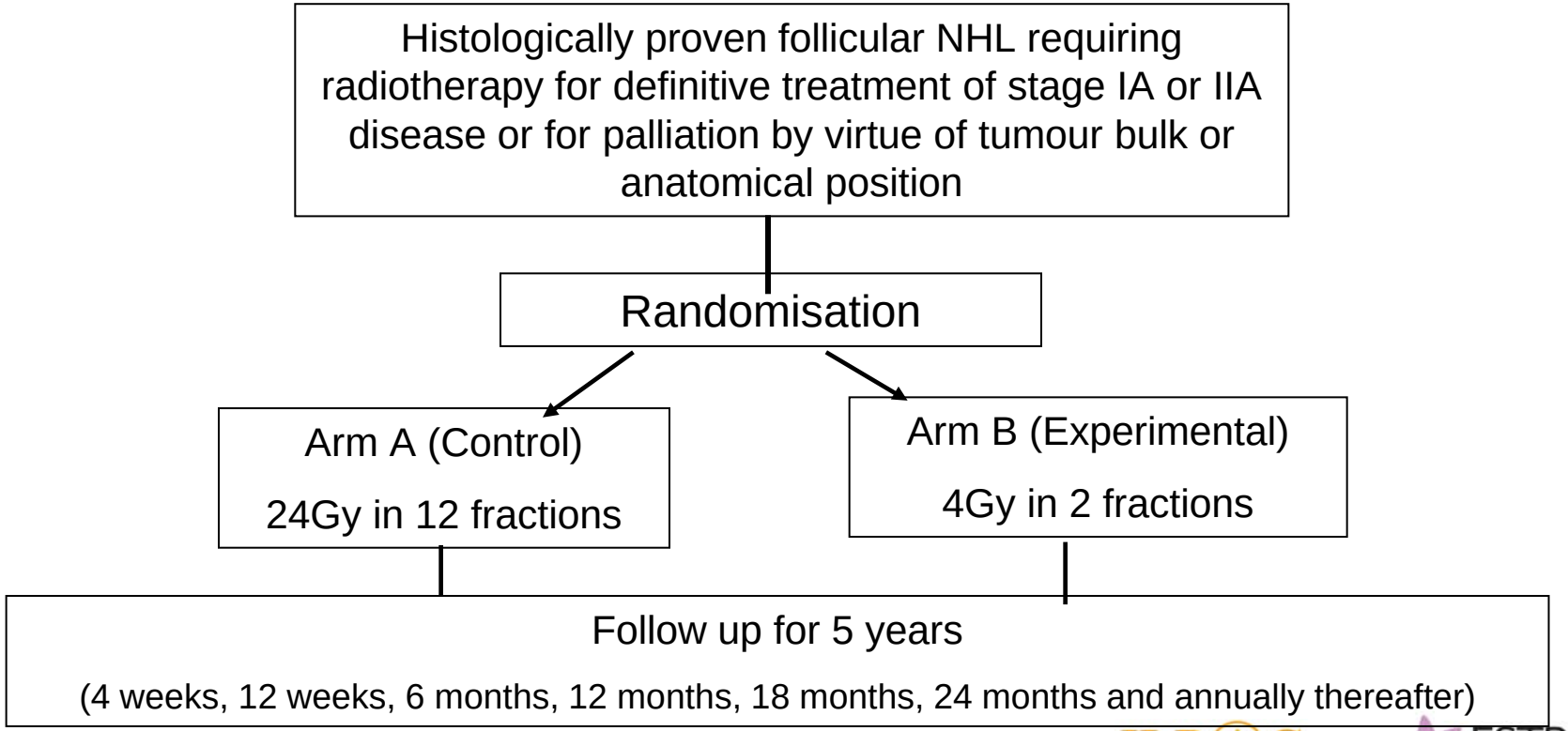
High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

Journal of Clinical Oncology, Vol 21, No 13 (July 1), 2003: pp 2474-2480

By R.L.M. Haas, Ph. Poortmans, D. de Jong, B.M.P. Aleman, L.G.H. Dewit, M. Verheij, A.A.M. Hart, M.H.J. van Oers, M. van der Hulst, J.W. Baars, and H. Bartelink



FoRT: Study design : A randomised trial of low dose radiotherapy for follicular lymphoma



Reduced RT dose in NHL

FORT trial: 4 Gy vs 24 Gy

614 sites in 548 pts with FL and some with MZL

Random to 24 Gy (299 sites) and 4 Gy (315 sites)

Median follow-up time: 26 months

	24 Gy		4 Gy		p value*
	Complete response (%)	Complete response plus partial response (%)	Complete response (%)	Complete response plus partial response (%)	
All patients	176/260 (68%)	236/260 (91%)	137/281 (49%)	227/281 (81%)	0·0095
Follicular lymphoma	152/226 (67%)	205/226 (91%)	116/243 (48%)	194/243 (80%)	0·0096
Marginal zone lymphoma	24/34 (71%)	31/34 (91%)	21/38 (55%)	33/38 (87%)	0·71
Stage I	78/102 (76%)	97/102 (95%)	62/115 (54%)	93/115 (81%)	0·0015
Stage II	21/50 (42%)	39/50 (78%)	22/48 (46%)	37/48 (77%)	0·91
Curative intent	71/95 (75%)	90/95 (95%)	57/105 (54%)	86/105 (82%)	0·0053
Curative intent, confirmed† follicular lymphoma only	38/46 (83%)	44/46 (96%)	35/60 (58%)	47/60 (78%)	0·011

*p value for responders (complete response plus partial response) versus non responders. †Confirmed by central review.

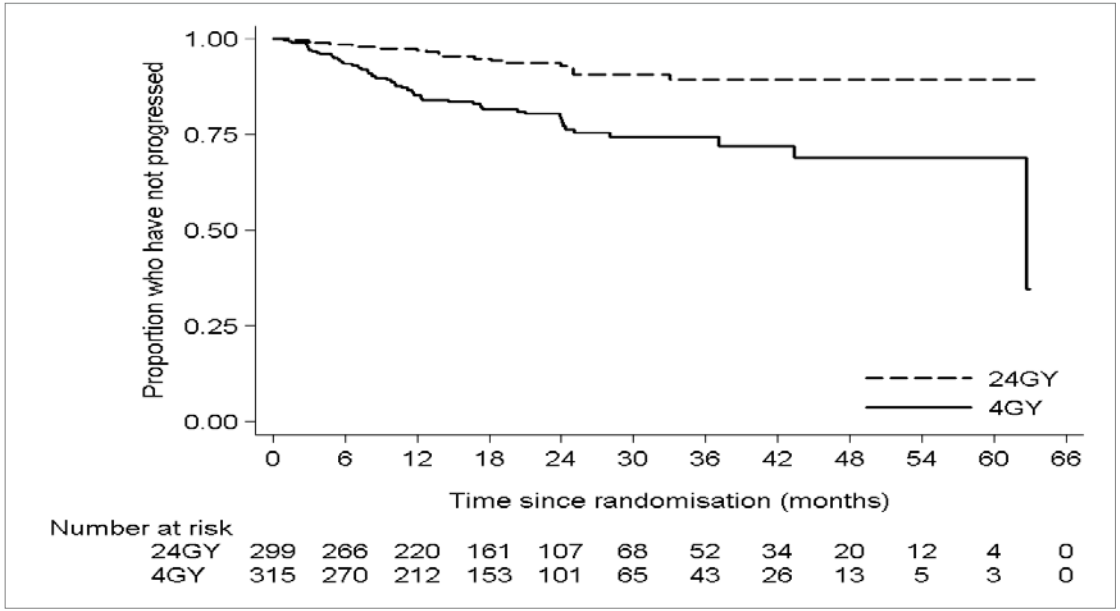
Table 3: **Response by subgroup**

Hoskin et al, Lancet Oncol, 2014

4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

Peter J Hoskin, Amy A Kirkwood, Bilyana Popova, Paul Smith, Martin Robinson, Eve Gallop-Evans, Stewart Coltart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

Lancet Oncol 2014; 15: 457–63



2 Year local progression free rate: 93.7% (24Gy) and 80.4% (4Gy) Hazard Ratio: 3.49 (95% CI: 2.06 - 5.90), p<0.001,

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4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

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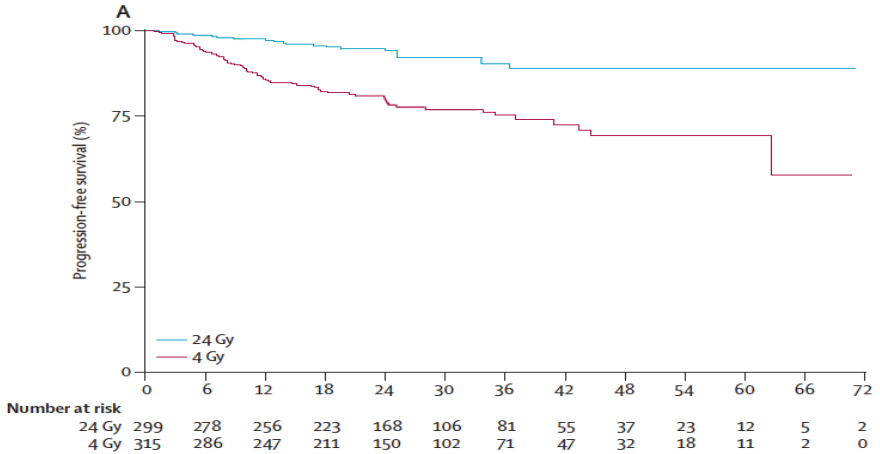
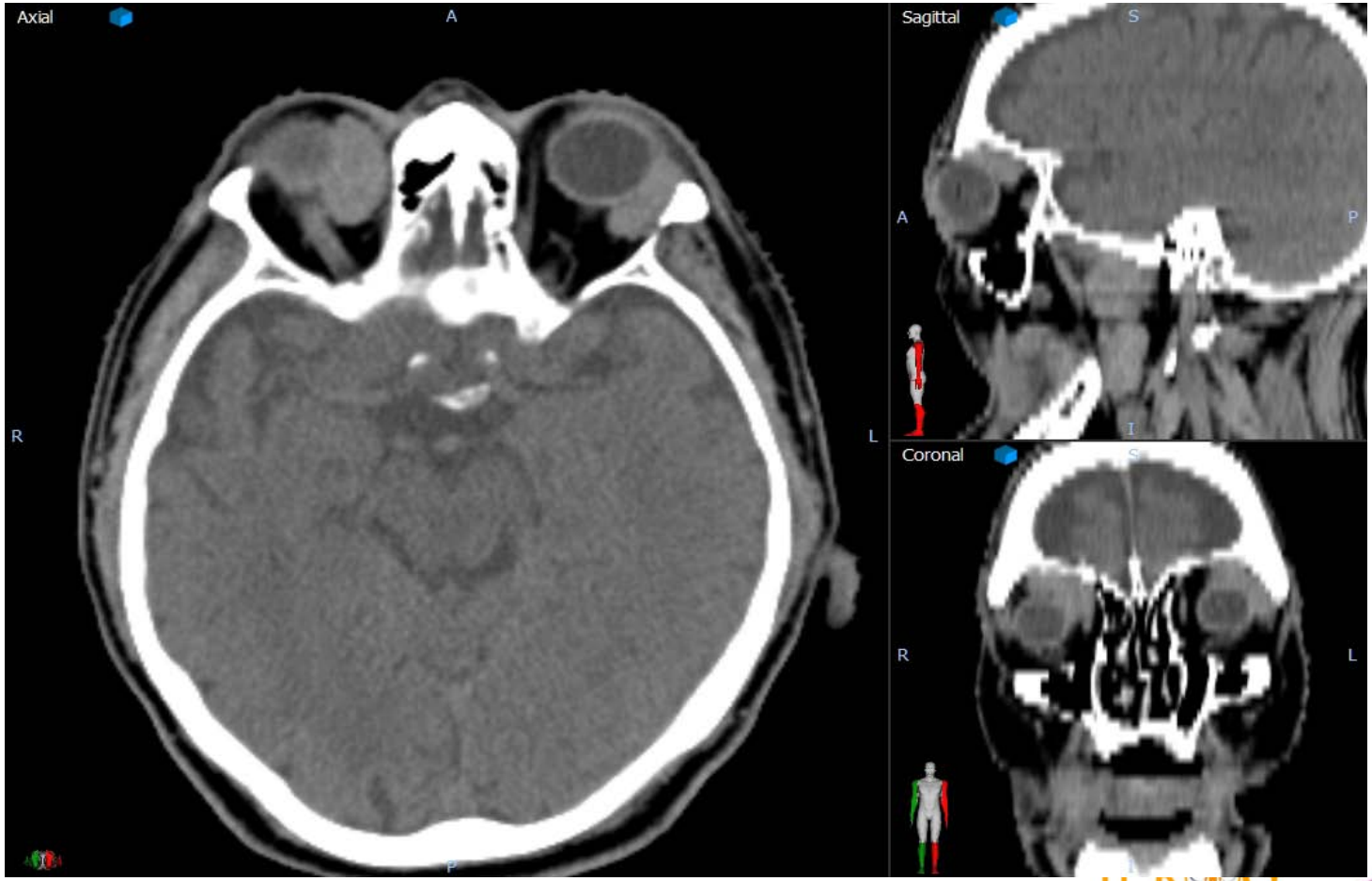
Lancet Oncol 2014; 15: 457–63

	24 Gy	4 Gy
All patients*		
Complete regression	176 (68%)	137 (49%)
Partial regression (>30%)	60 (23%)	90 (32%)
Stable disease (including <30% regression)	22 (8%)	44 (16%)
Progression	2 (<1%)	10 (4%)
Total	260	281



Interpretation 24 Gy in 12 fractions is the more effective radiation schedule for indolent lymphoma and should be regarded as the standard of care. However, 4 Gy remains a useful alternative for palliative treatment.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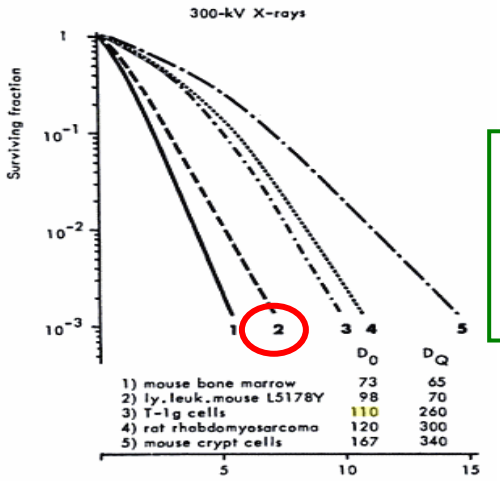
Role of Radiation Therapy in Indolent Nodal Lymphomas

- **Advanced-stage Indolent Lymphoma**
  - Patients with advanced or recurrent indolent disease treated with very low doses of only 4 Gy in 2 fractions achieve high response rates
  - RT provides effective palliation for localized symptomatic disease
  - RT to sites of bulky disease where monitoring clinical progression is challenging and progressive disease may lead to organ failure (such as within the retroperitoneum)

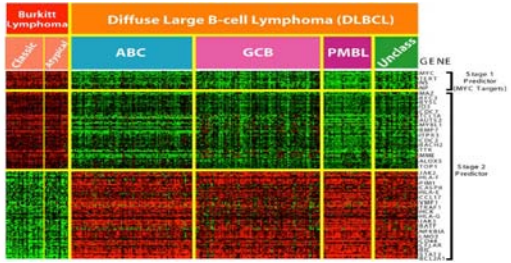
What Drives Radiation Sensitivity in Lymphoma?

The old radiobiology view of RT sensitivity in lymphoma

Lymphoma = Apoptosis = Radiosensitive



RT sensitivity in lymphoma, in the molecular age…



Lymphoma gene expression profiles may predict differences in radiosensitivity

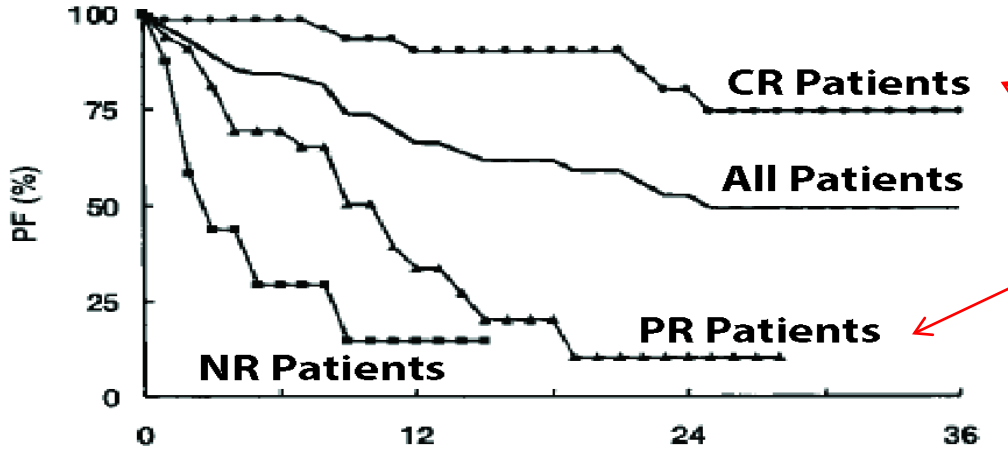
Wide spectrum of response to RT in lymphoma (4-40 Gy): Dramatic variations in radiosensitivity can be explained by molecular differences in the tumor

Figure from:
Radiobiology for the Radiologist
By Eric J. Hall, Amato J. Giaccia

Response to very low dose RT is variable

Our key questions:

1. **Are there molecular biomarkers that can predict these differences?**
2. **What about gene expression profiles?**



Can we identify these patients up-front?

RT techniques

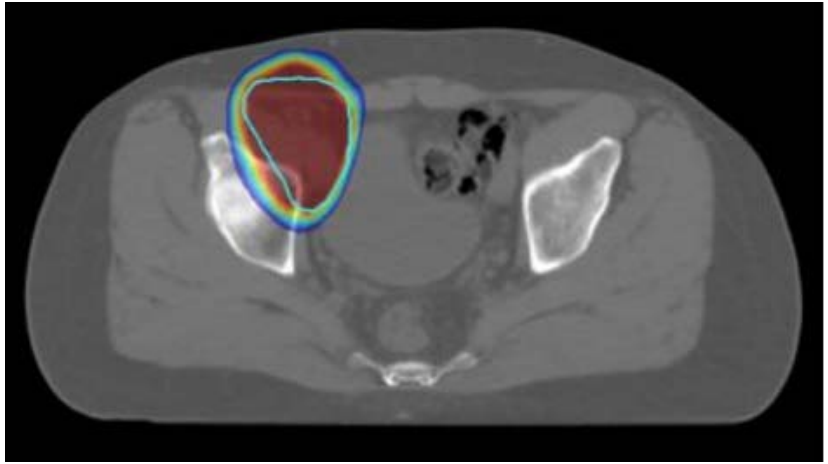
Dose constraints in lymphoma RT

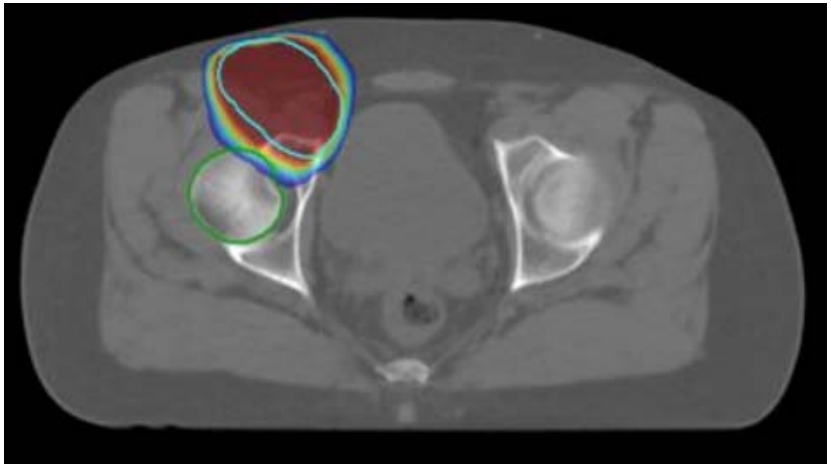
- The relatively low radiation doses needed result in most treatment plans being within the acceptable limits
- Even low doses to normal tissues, previously considered safe, may result in significant risks of morbidity and mortality in long-term survivors
- Doses to all normal structures should be kept as low as possible, but some structures are more critical than others

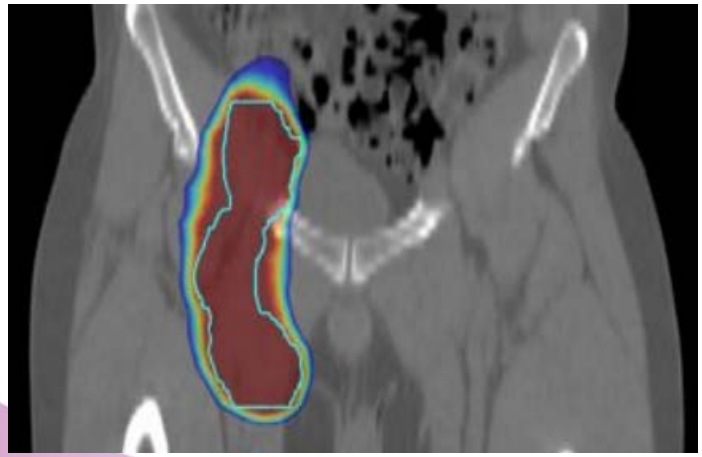
Which technique is preferable?

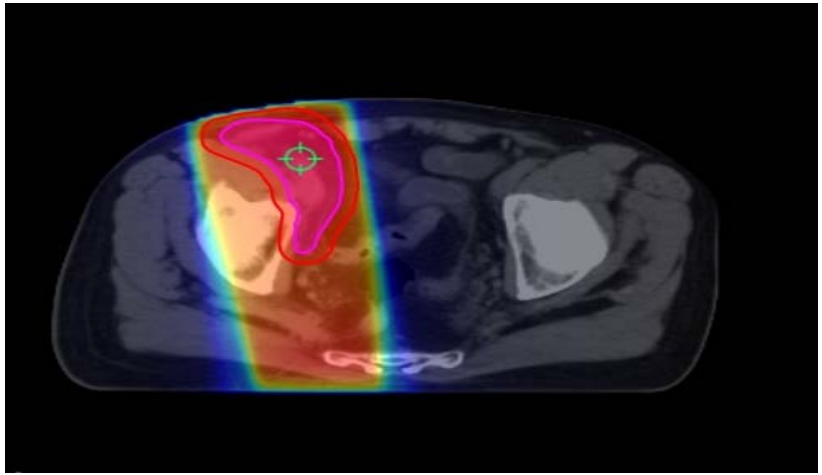
- There is no single proven best planning and delivery RT technique
- No two lymphomas are the same with regard to localization and extent of disease
- The decision should be made at the individual patient level (i.e., what appears the optimal treatment plan for one patient may not be acceptable for another patient)

M. L., 43 years old, follicular NHL, stage IA









Modern RT in indolent nodal lymphoma

- Radiation therapy has changed dramatically over the last few decades in terms of both irradiated volumes and doses

- Smaller treatment volumes, lower radiation dose and advanced conformal radiotherapy can certainly allow a safer radiation delivery

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Lung Lymphoma

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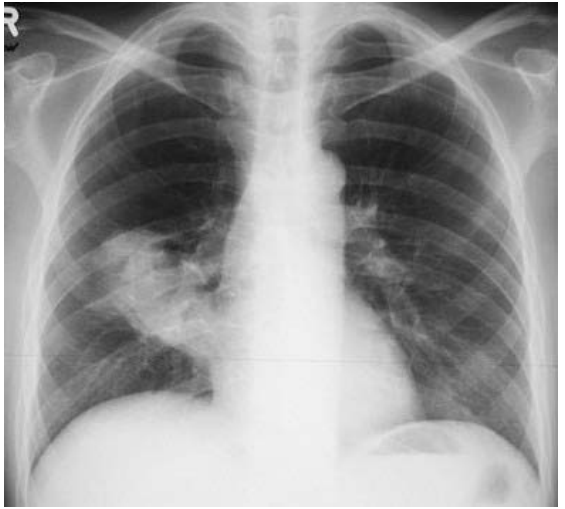
Background

- Primary pulmonary lymphoma is a very rare neoplasm, representing only 2-4% of extranodal non-Hodgkin lymphoma and only 0.4% of all malignant lymphomas

- Most cases are represented by MZL (80-90%); DLBCL very rare (10%)

- Primary pulmonary lymphoma is defined as a clonal lymphoma proliferation affecting one or both lungs in a patient with no detectable extrapulmonary involvement at diagnosis or during the subsequent 3 months



- The role of chronic infections, toxic exposure, or underlying autoimmune diseases in BALT lymphoma is unknown

- Achromobacter (Alcaligenes) xylosoxidans, a Gram negative bacterium with low virulence but with high resistance treatment, has been recently detected

- Whether this finding indicates a potential etiopathogenetic role of this bacterium in BALT lymphoma will however require further studies

Clinical characteristics and prognostic factors of pulmonary MALT lymphoma

Borie et al. Eur Respir J 2009;34:1408-1416

TABLE 1 Main clinical and biological characteristics of the 63 patients

Characteristics	Value
Age yrs	60 (24–83)
Females	29 (47)
Active or former tobacco use	24 (37)
Respiratory tract infection	6 (9)
Including tuberculosis	4 (6)
Autoimmune background	10 (16)
Respiratory symptoms	37 (58)
B symptoms	14 (22)
Cytopenia	12 (19)
LDH level more than twice the upper limit	2 (3)

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Clinical presentation

- Most patients (90%) are asymptomatic at diagnosis and disease is incidentally discovered

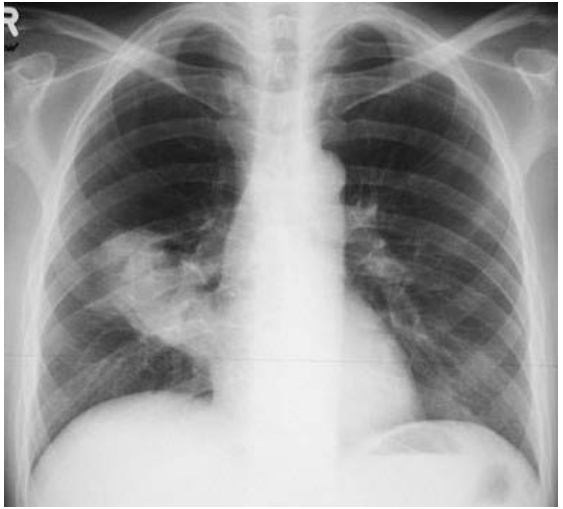
- When present, symptoms are unspecific, such as:
  - Cough
  - Mild dyspnea
  - Chest pain
  - Hemoptysis

- B symptoms are uncommon

Background

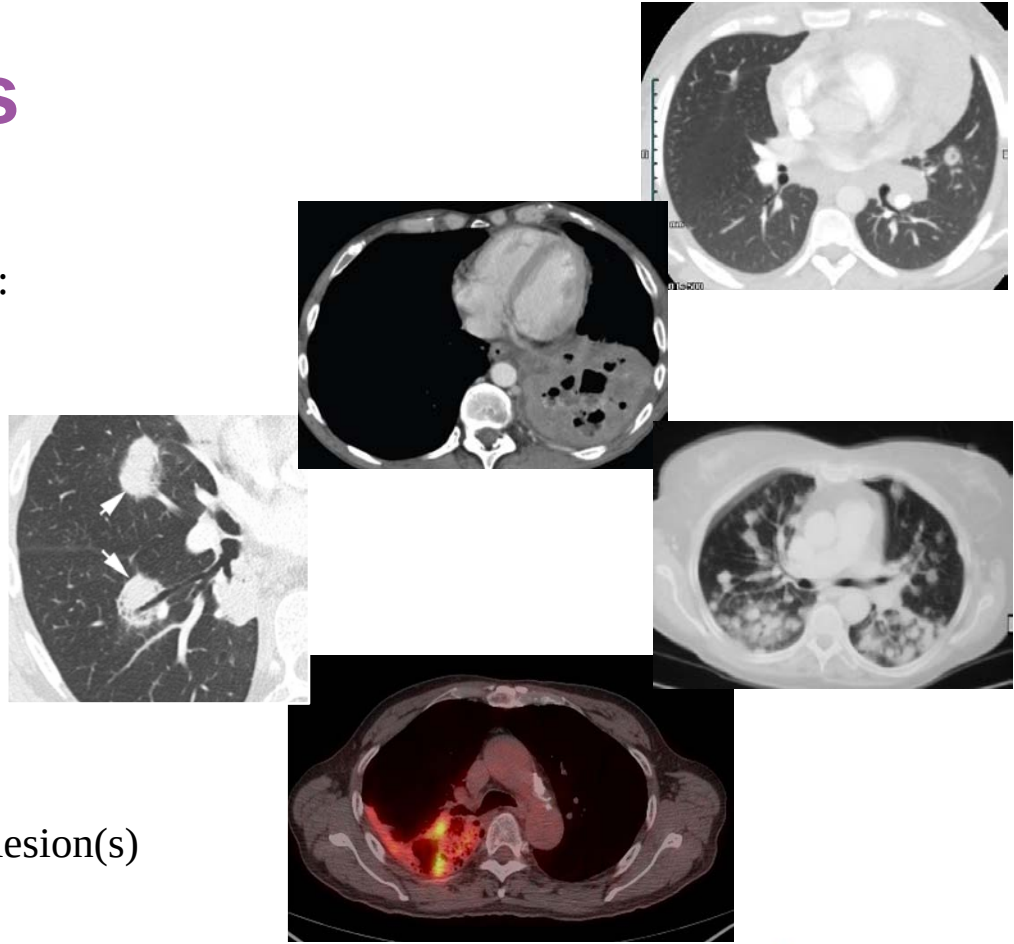
- MZL (bronchial associated lymphoid tissue lymphoma [BALT lymphoma]) may involve any element of the bronchial tree, often as an isolated lesion

- Surgery as first treatment: pulmonary lesion as a potential lung cancer

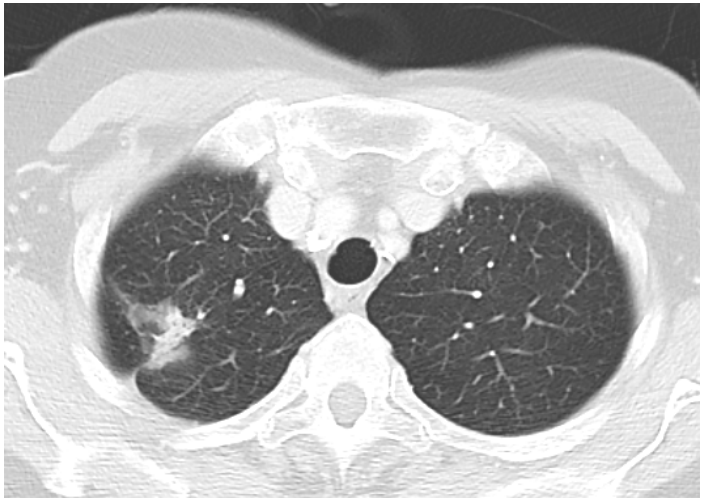
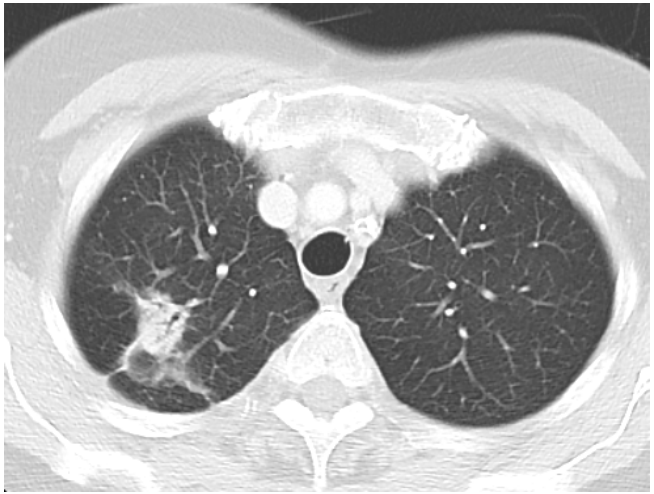
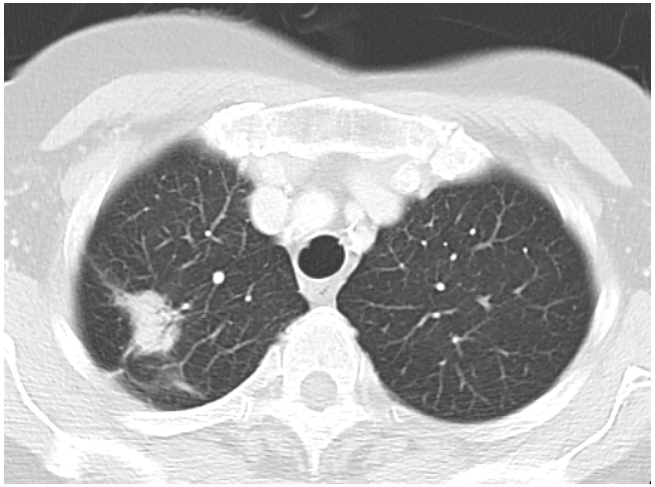
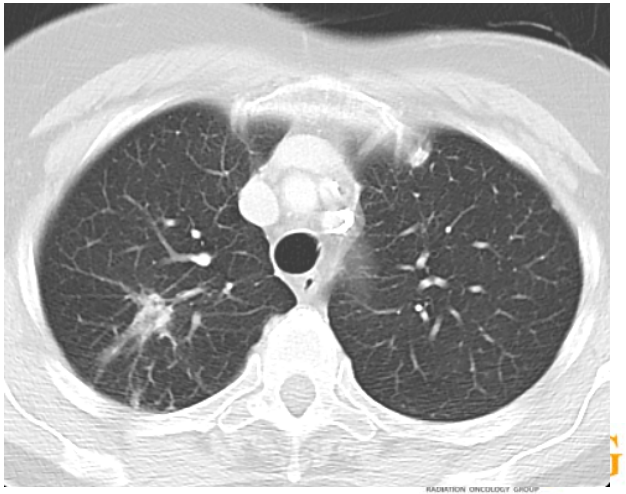


Diagnosis

- Radiologic findings are nonspecific and include:
  - Solitary nodule
  - Multiple ill-defined nodules
  - Mass with air bronchograms
  - Pleural effusion
  - Atelectasis
  - Cavities



- FDG-PET usually reports a mild uptake of the lesion(s)

Staging

Ann Arbor system modified by Ferraro

Stage	Description
I E	Unilateral or bilateral presentation of the lung
II 1E	Lung presentation with hilar lymph node involvement
II 2E	Lung presentation with mediastinal lymph node involvement
II 2EW	Lung presentation with chest wall or diaphragm involvement
III E	Lung presentation with abdominal lymph node involvement
IV E	Lung presentation with extra-lymphatic organs or tissue involvement

Ferraro et al. Ann Thorac Surg 2000;69:993-997

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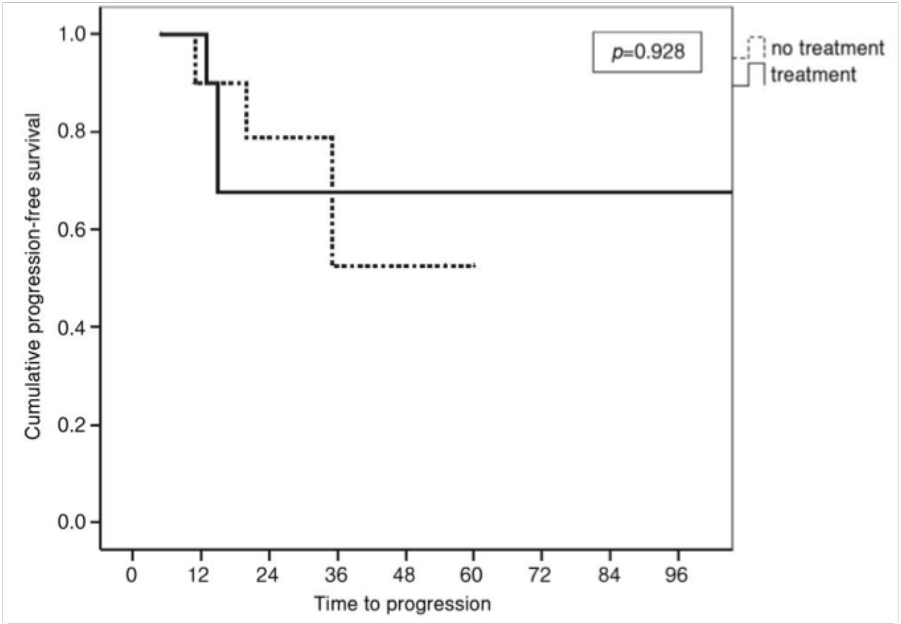
Treatment

Optimal treatment and prognostic factors are not well defined

- Surgery
- Watch and wait
- Chemotherapy
- Radiotherapy

Does MALT Lymphoma of the Lung Require Immediate Treatment? An Analysis of 11 Untreated Cases with Long-term Follow-up



"MALT lymphoma of the lung is a very indolent disease with the potential for spontaneous regression. For this reason, patients diagnosed with pulmonary MALT lymphoma might not require immediate treatment in the absence of symptoms and a watch-and-wait policy could be adopted."

Troch et al. Anticancer Research 2007;27:3633-3638

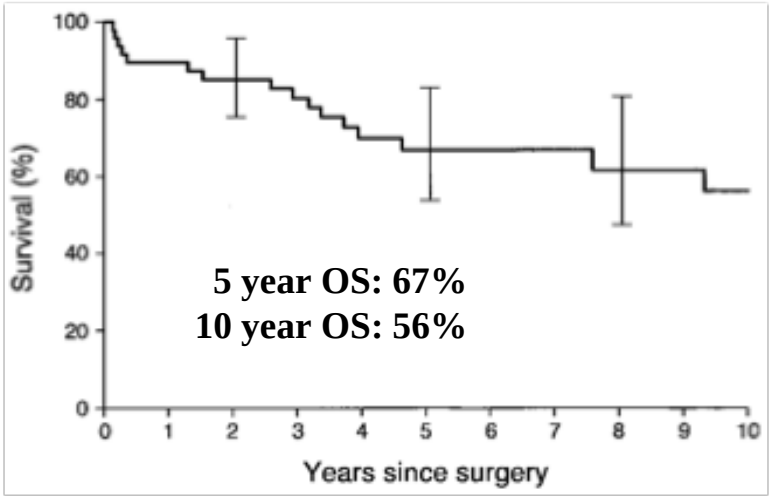
Surgical approach

Table 2. Diagnostic Procedures and Surgical Interventions[a]

Variable	No. of Patients
Bronchoscopy (n = 39)	
Biopsy positive for lymphoma	5 (10)
Washings positive for lymphoma	2 (4)
Normal or nonspecific findings	32 (67)
Not done	9 (19)
Open thoracotomy (n = 43)	
Biopsy	7 (16)
Wedge resection	21 (49)
Segmentectomy	2 (5)
Lobectomy	11 (26)
Pneumonectomy	2 (5)
VATS (n = 5)	
Diagnostic lymphoma	4 (80)
Converted to open procedure	1 (20)
Additional procedure	
Chest wall resection	1 (2)
Lymphadenectomy	27 (56)
Pleurodesis	8 (17)

[a] Numbers in parentheses are percentages.

- 48 patients
- 35 MALT lymphomas
- 13 Aggressive B cell lymphomas
- 1975-1995
- **All patients underwent surgical resection**



Ferraro et al. Ann Thorac Surg 2000;69:993-997

Surgical approach

Table 5. Influence of Prognostic Factors on Survival in Different Patient Groups

Prognostic Factor	All Patients (n = 48) 5-Year Survival (%)	All Patients (n = 48) *p* Value	Malt Lymphoma Only (n = 35) 5-Year Survival (%)	Malt Lymphoma Only (n = 35) *p* Value	Stage I Tumors Only (n = 37) 5-Year Survival (%)	Stage I Tumors Only (n = 37) *p* Value
Complete resection						
Chemotherapy postoperatively	75.0	0.35	66.7	0.56	66.7	0.55
No chemotherapy	57.5		62.9		53.5	
Incomplete resection						
Chemotherapy postoperatively	66.7	0.94	68.2	0.96	62.5	0.66
No chemotherapy	77.8		75.0		75.0	

MALT = mucosa-assisted lymphoid tissue.

Ferraro et al. Ann Thorac Surg 2000;69:993-997

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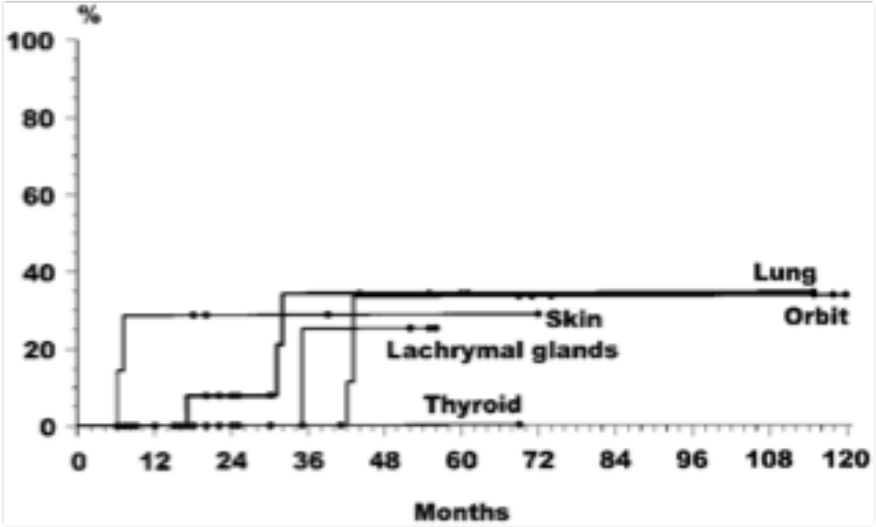
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Nongastrointestinal Low-Grade Mucosa-Associated Lymphoid Tissue Lymphoma: Analysis of 75 Patients

LUNG lymphoma

- 19 patients
- 17/19 treated with CT (as single agent or in combined modality schedules)
- 2/19 received surgery alone



- 100% ORR (79% CR and 21% PR)
- 3 relapses (15.7%)
- 100% OS at 5 years

Zinzani et al. JCO 1999;17:1254-1258

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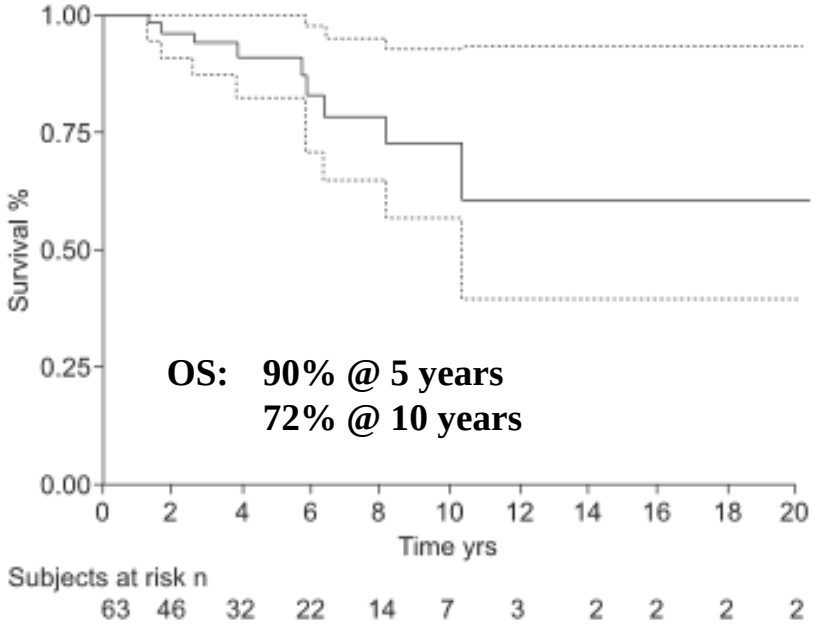
Clinical characteristics and prognostic factors of pulmonary MALT lymphoma

Borie et al. Eur Respir J 2009;34:1408-1416



OS: 90% @ 5 years
72% @ 10 years

TABLE 5 Hazard ratios for overall survival

	Univariate analysis	
	Hazard ratio (95% CI)	p-value
Age >60 yrs	12.5 (1.5–104.0)	0.02
Male sex	0.7 (0.2–2.5)	0.5
ECOG		
0	1	
1	20.3 (2.1–190.4)	0.008
2–3	38.6 (4–374)	0.002
Diagnosis delay (per 1 month increase)	1.0 (0.99–1.02)	0.8
Extrapulmonary location	2.2 (0.6–8.4)	0.2
Gastric	1.8 (0.4–7.8)	0.4
Nodal	6.0 (0.6–58.8)	0.1
Medullar		0.52#
Pulmonary extension		
Mediastinal adenopathy	2 (0.2–17.7)	0.5
Bilateral involvement	1.7 (0.4–6.4)	0.4
Pleural effusion	5.4 (0.9–30.6)	0.1
Treatment		
Chlorambucil	1	
Cyclophosphamide based chemotherapy	0.9 (0.1–6.6)	0.9
Anthracyclin- or fludarabine-based chemotherapy	2.6 (0.4–6)	0.3
Local therapy	0.2 (0.02–2.7)	0.2
Abstention	4.6 (0.4–54)	0.2

Favourable course of pulmonary MALT, with none of the lymphoma characteristics associated with worse clinical outcome

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A retrospective international study on primary extranodal marginal zone lymphoma of the lung (BALT lymphoma) on behalf of International Extranodal Lymphoma Study Group (IELSG)

Abstract

Primary lymphoma of the lung is a rare entity. Clinical features, optimal treatment, role of surgery and outcomes are not well defined, and the follow-up is variable in published data. Clinical data of 205 patients who were confirmed to have bronchus mucosa-associated lymphoid tissue lymphoma from December 1986 to December 2011 in 17 different centres worldwide were evaluated. Fifty-five per cent of the patients were female. The median age at diagnosis was 62 (range 28–88) years. Only 9% had a history of exposure to toxic substances, while about 45% of the patients had a history of smoking. Ten per cent of the patients had autoimmune disease at presentation, and 19% patients had a reported preexisting lung disease. Treatment modalities included surgery alone in 63 patients (30%), radiotherapy in 3 (2%), antibiotics in 1 (1%) and systemic treatment in 128 (62%). Patients receiving a local approach, mainly surgical resection, experienced significantly improved progression-free survival ($p = 0.003$) versus those receiving a systemic treatment. There were no other significant differences among treatment modalities. The survival data confirm the indolent nature of the disease. Local therapy (surgery or radiotherapy) results in long-term disease-free survival for patients with localized disease. Systemic treatment, including alkylating-containing regimens, can be reserved to patients in relapse after incomplete surgical excision or for patients with advanced disease. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: BALT lymphoma; marginal zone lymphoma; *Achromobacter* (*Alcaligenes*) *xylosoxidans*

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Sammassimo et al. Hematol Oncol 2015;DOI:10.1002/hon.2243

A retrospective international study on primary extranodal marginal zone lymphoma of the lung (BALT lymphoma) on behalf of International Extranodal Lymphoma Study Group (IELSG)

Table 2. Main clinical patients' characteristics

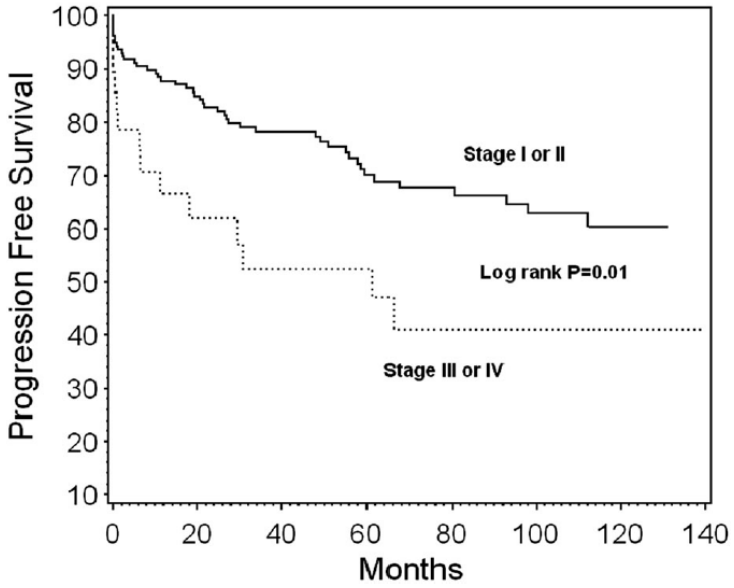
Characteristic	
All	205
Median age at diagnosis (range)	62 years (28–88)
	n (%)
Sex	
Male/female	91 (45)/114 (55)
Pre-existing risk factors	
Exposure to toxic substances	17/185 (9)
Smoking	88/197 (45)
Autoimmune disorders	19/184 (10)
Pre-existing lung disease	38/202 (19)
Stage	
I–II	169/197 (86)
III–IV	28/197 (14)
PS	
0–1	192/198 (97)
2–3	6/198 (3)
IPI score	
0–2	187/196 (95)
3–4	9/196 (5)
Constitutional symptoms	29/199 (15)
Respiratory symptoms	100/183 (55)

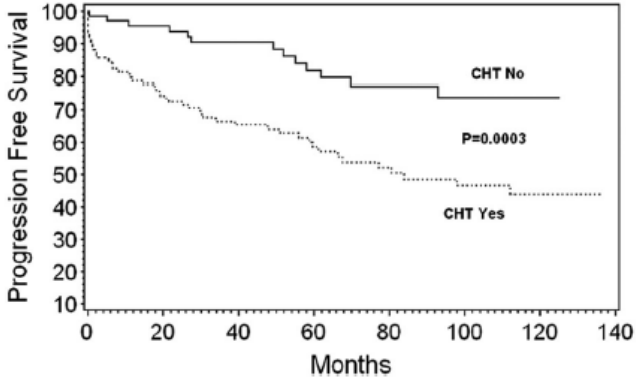
Table 3. Treatments, response and disease progression after first line treatment

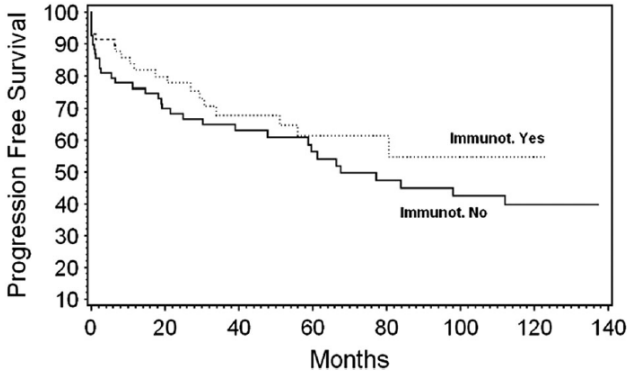
Treatment (*n*)	Response	*n* (%)	PFS (months)
Local treatment (67)			66
Surgery (63)	CR	58 (92)	
	PR	4 (6)	68
	UN	1 (2)	
Antibiotics (1)	SD	1 (100)	5
Radiotherapy (3)	CR	2 (67)	62
	PR	1 (33)	
Systemic treatment (128)			33
Immunochemotherapy (38)	CR	20 (53)	
	PR	13 (34)	
	SD	1 (3)	33
	PD	2 (5)	
	UN	2 (5)	
Immunotherapy — rituximab (20)	CR	4 (20)	
	PR	4 (20)	
	SD	10 (50)	24
	UN	2 (10)	
Chemotherapy (70)	CR	31 (44)	
	PR	25 (36)	
	SD	8 (11)	37
	PD	3 (4)	
	UN	1 (1)	
	NE	2 (3)	
Watch and wait (10)[a]	SD	8 (80)	26
	UN	2 (20)	

Sammassimo et al. Hematol Oncol 2015;DOI:10.1002/hon.2243

A retrospective international study on primary extranodal marginal zone lymphoma of the lung (BALT lymphoma) on behalf of International Extranodal Lymphoma Study Group (IELSG)







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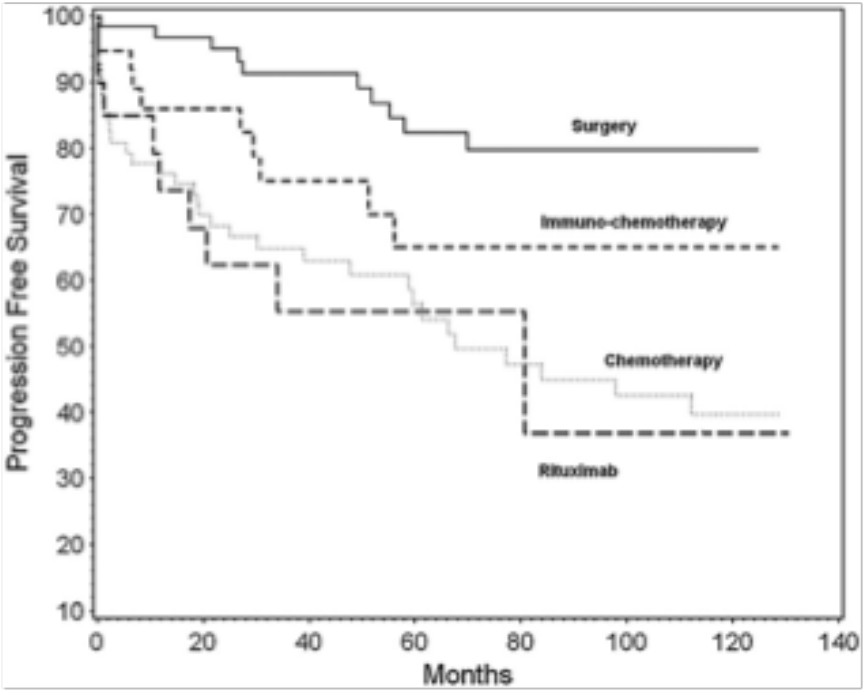

Conclusion:

Local therapy (surgery or radiotherapy) results in long-term disease-free survival for patients with localized disease.

Systemic treatment can be reserved for patients in relapse after incomplete surgical excision or for patients with advanced disease.

Sammassimo et al. Hematol Oncol 2015;DOI:10.1002/hon.2243

Radiotherapy

- Few retrospective studies with a limited number of patients

- Radiotherapy may play a role in the treatment of BALT lymphoma

Practice guidelines for the management of extranodal non-Hodgkin's lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. A project of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation

Zinzani et al. Haematologica 2008;93(9):1364-1371

Table 1. Case series including cases of primary pulmonary MALT lymphomas.

	Number of patients	Lung surgical resection	Chemotherapy	Rituximab	Radiotherapy	CR/PR	5 yr OS % (10 yr OS)	5 yr RFS %
Koss *et al.*, 1983[14]	44	NR	NR	NR	NR	NR	95 (85)	NR
Kennedy *et al.*, 1985[15]	32	10	18	NR	NR	NR	90 (78)	NR
Li *et al.*, 1990[16]	33	14	14	NR	5	NR	85 (75)	<54
Cordier *et al.*, 1995[17]	64	42	18	NR	5	NR	94 (50)	NR
Fiche *et al.*, 1995[18]	69	46	20	NR	6	NR	93.6% in low grades	NR
Wislez *et al.*, 1999[19]	13	3	10	NR	NR	7/5	100	NR
Ferraro *et al.*, 2000[20]	35	19	26	NR	2	NR	68 (53)	NR
Kurtin *et al.*, 2001[21]	50	NR	NR	NR	NR	NR	85 (72)	NR
Zinzani *et al.*, 2003[22]	12	4	10	NR	NR	12/0	100	>50
Zucca *et al.*, 2003[23]	15	NR	NR	NR	NR	NR	100	75
Ahmed *et al.*, 2004[24]	22	6	10	10	2	9/10	<100	<60
Graham *et al.*, 2005[25]	17	6	8	1	NR	NR	82%	NR

NR: not reported.

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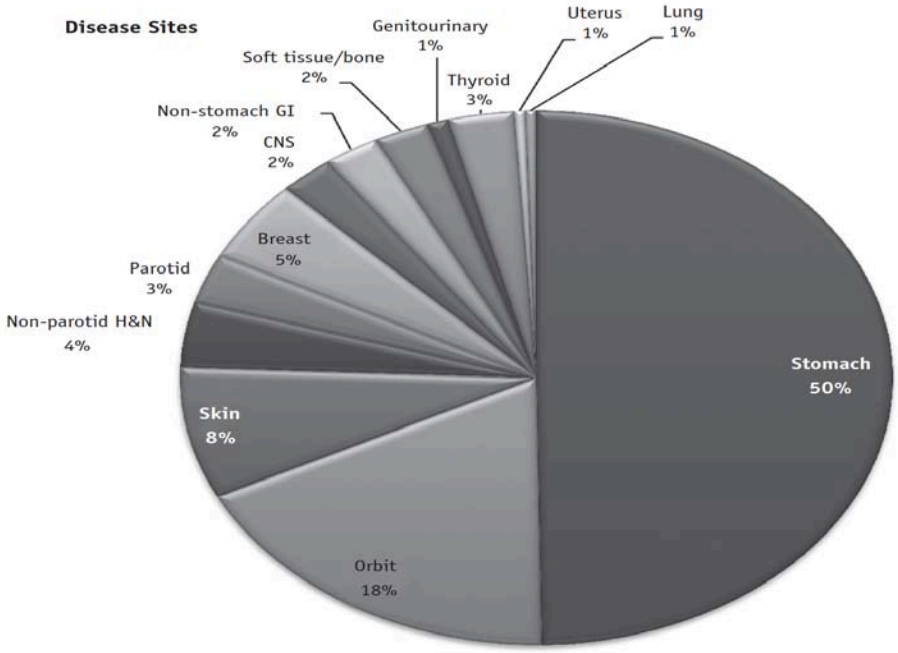
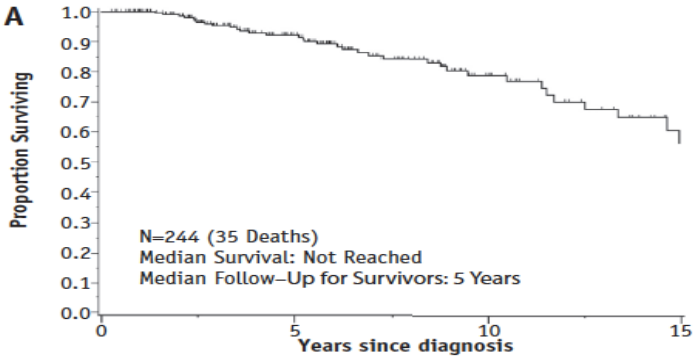
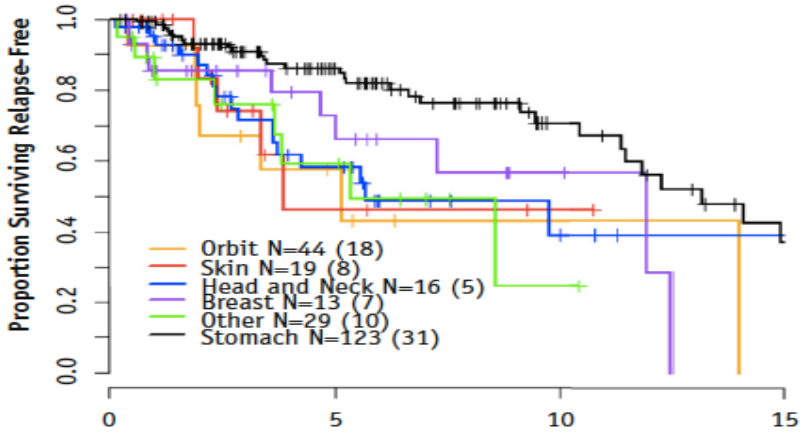
Long-Term Outcomes and Patterns of Relapse of Early-Stage Extranodal Marginal Zone Lymphoma Treated With Radiation Therapy With Curative Intent

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 130–137, 2015

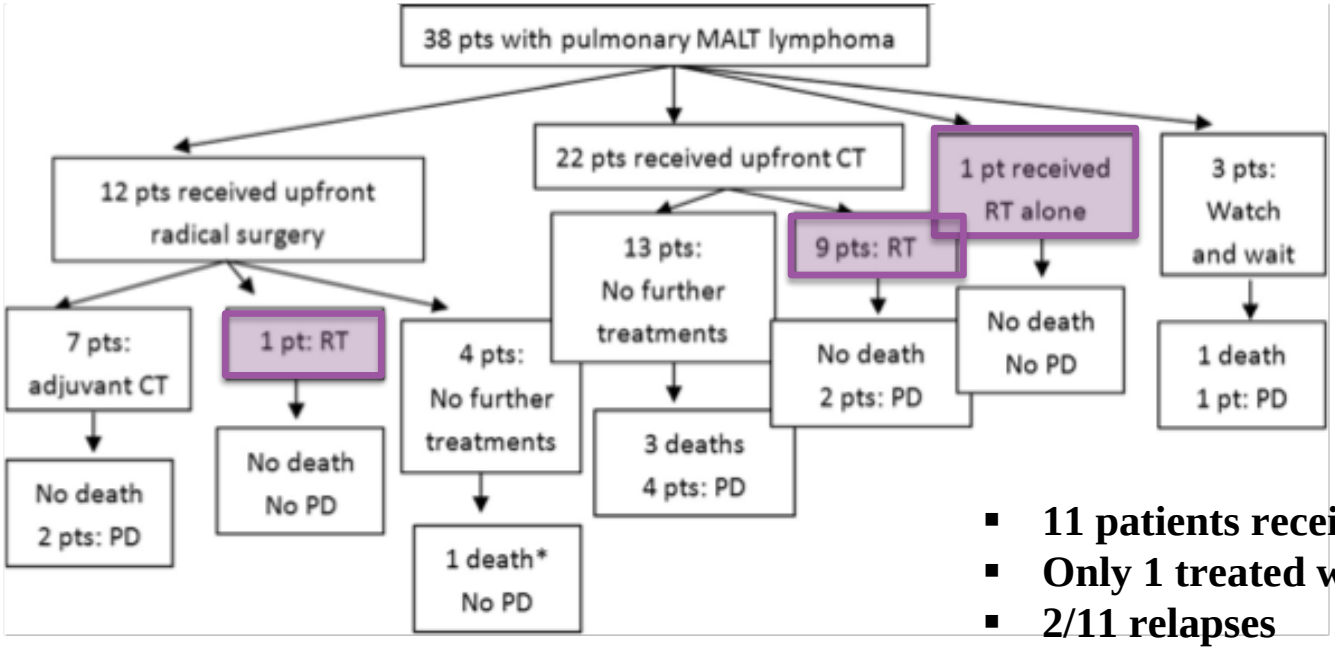
Sewit Teckie, MD,* Shunan Qi, MD,* Shona Lovie, MPH,* Scott Navarrett, BS,‡ Meier Hsu, MS,§ Ariela Noy, MD,|| Carol Portlock, MD,|| and Joachim Yahalom, MD*







Radical surgery may be not an optimal treatment approach for pulmonary MALT lymphoma

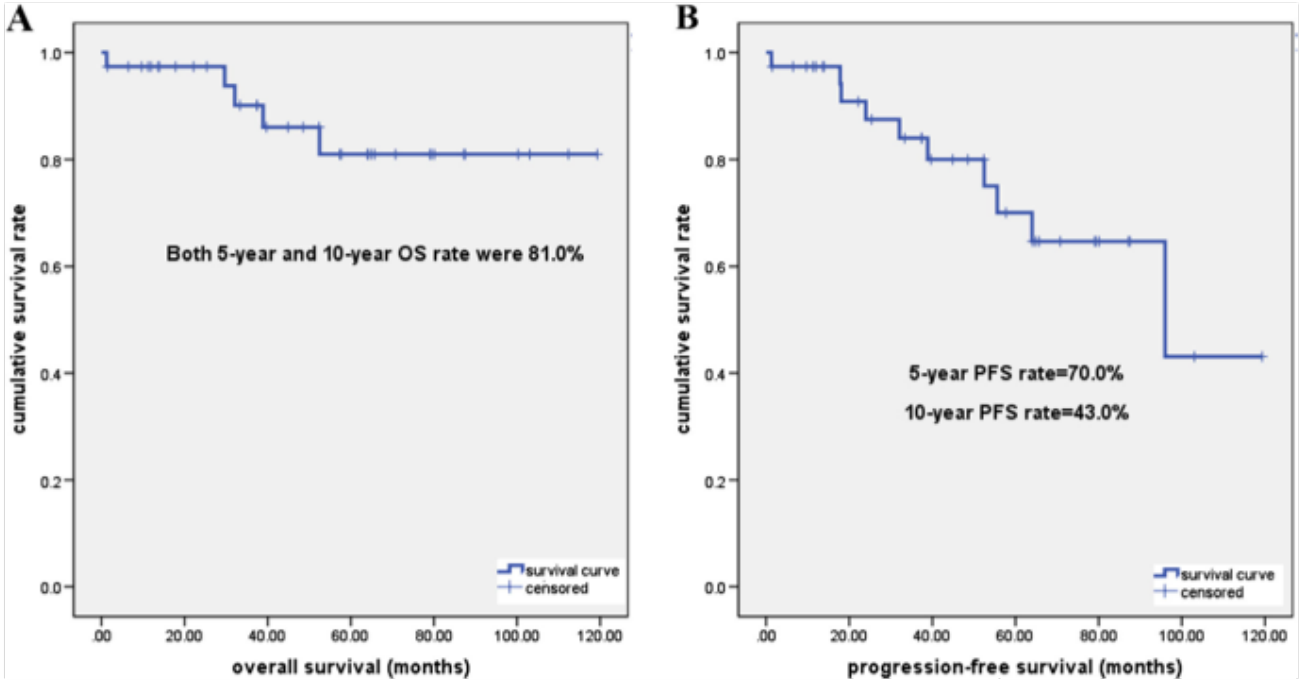


- **11 patients received RT**
- **Only 1 treated with RT alone**
- **2/11 relapses**
- **Median RT dose 30.6 (range 30-40 Gy)**

Wang et al. Tumor Biol. 2015;DOI10.1007/s13277-015-3329-y

Radical surgery may be not an optimal treatment approach for pulmonary MALT lymphoma

Overall Population



Wang et al. Tumor Biol. 2015;DOI10.1007/s13277-015-3329-y

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Long-Term Outcome in Localized Extranodal Mucosa-Associated Lymphoid Tissue Lymphomas Treated With Radiotherapy

Table 2. Radiation Doses with Respect to Anatomical Locations for MALT Lymphomas

Anatomic Site	No. of Patients	25 Gy	>25-30 Gy	35 Gy	Other[a]
Orbital adnexa	71	65	5	1	
Stomach	25	8	10	5	2
Salivary glands	28	2	24	1	1
Thyroid	21	1	12	8	
Other H & N sites	6	1	5		
Lung	3		2		1
Urinary bladder	4			2	2
Skin and soft tissue	3		3		
Breast	4		1	3	
Other GI sites (rectum)	1			1	
Meninges	1		1		

31 Gy

NO RELAPSES

Goda et al. Cancer 2010;116:3815-3824

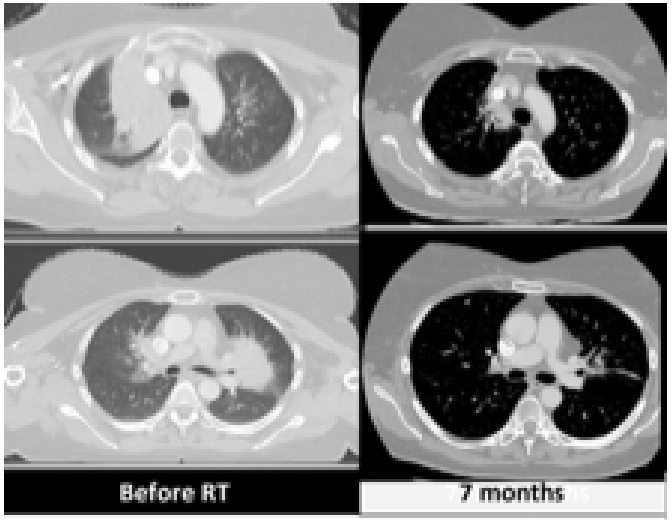
Low-Dose Radiation Treatment in Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma: A Plausible Approach? A Single-Institution Experience in 10 Patients

International Journal of Radiation Oncology biology • physics

BOOM-BOOM RADIOTHERAPY

- 4 Gy/2 fractions

Median follow up 56 months



Girinsky et al. IJROBP 2012;83(3): 385-389

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Table 2 Treatment outcome

Patient number, gender, and age (y)	Previous treatment	CT findings	Treatment response (2 mo)	Outcome	Follow-up (mo)
1. F, 45	6 mo of chlorambucil for a solitary pulmonary mass	Lobar consolidation	PR	Alive (CRu)	103
2. F, 51	CHOP therapy for Stage III disease (lung recurrence 5 y later)	Consolidation in each lung	PR	Alive (PR)	103
3. M, 46	None	Consolidations in the right lung	CR	Alive (CR)	84
4. M, 59	None	Consolidation	CRu	Alive (CRu)	75
5. F, 34	Initial wedge resection for a solitary mass in the upper left lobe (local relapse 6 mo later)	Nodule	PR	Alive (CRu)	56
6. F, 31	Rituximab (4 cycles) (PR) for tracheal infiltration	Infiltration of upper trachea	CR	Alive (CR)	56
7. M, 74	Pneumonectomy for a single pulmonary lesion (bronchial recurrence 3 mo later)	No visible lesion on CT	CR on fibroscopy	Alive (CR)*	28
8. M, 54	None	Bilateral diffuse involvement	CRu	Alive (CRu)	14–10†
9. F, 68	None	Single consolidation in each lung	CRu	Alive (CRu)	7
10. F, 45	R-CHOP chemotherapy for Stage IV disease (in CR except in the upper right lobe)	Consolidation in the upper right lobe	PR	Alive (PR)	6

Abbreviations: CR = complete response; CRu = unconfirmed CR; PR = partial response.

* Massive bilateral orbital relapses (possibly endangering patient's vision) were successfully treated with radiotherapy (30 Gy), and the patient is presently in CR.

† Different follow-ups because the left and right lung were treated separately. The left lung was treated first.

Girinsky et al. IJROBP 2012;83(3): 385-389

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Conclusions

- Most cases of primary lung lymphomas (80-90%) are MALT lymphoma

- BALT lymphoma tends to be an indolent disease with prolonged survival (70-80% @ 10 years), although with frequent relapses (30-40% @ 5 years)

- The optimal management of BALT lymphoma has yet to be clearly determined:

  - **Surgery** is preferable for localized disease
  - **Chemotherapy** is the treatment of choice for extensive disease
  - **Observation** is a good alternative for asymptomatic patients with localized disease

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Conclusions

- Data regarding a precise role for radiotherapy are lacking
- RT can be reserved for patients with a unique small lesion
- Planning procedures with 4D-CT is highly recommended to account for organ motion during the respiratory phases
- Modern radiation techniques (IMRT/IGRT) are recommended to reduce radiation exposure to ipsilateral and controlateral lung
- RT dose should be in the range of 24-30 Gy
- Low dose schedule (2 Gy x 2) has obtained promising results and could be argument of research in future trials

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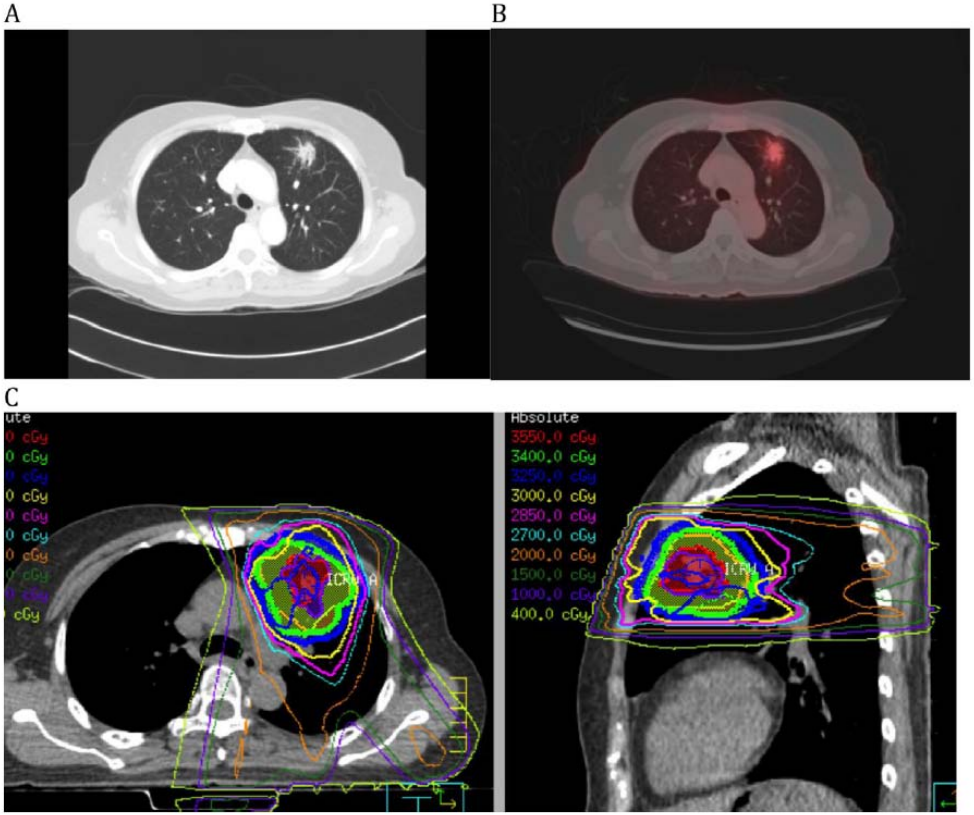
Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group



Yahalom et al. IJROBP 2015;92(1):11-31

Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

RECOMMENDATIONS FOR PLANNING AND TREATMENT

VOLUMES:

- CTV: preintervention (biopsy, surgery or systemic therapy) GTV, expanded by clinical judgment to accommodate imaging uncertainties and suspected adjacent microscopic infiltration
- ITV: expansion for respiratory motion (use 4DCT if available)

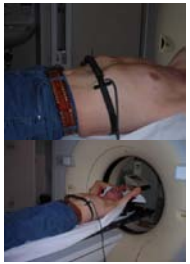
TECHNIQUE:

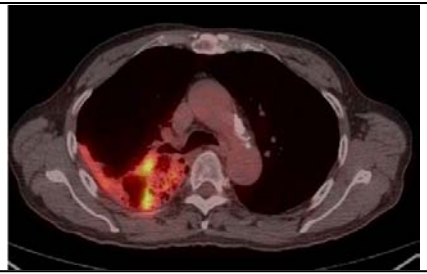
- 3D conformal or IMRT
- V20 and pulmonary function status should be taken into account

Yahalom et al. IJROBP 2015;92(1):11-31

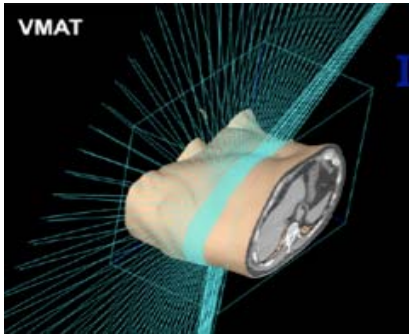
Modern RT for lung lymphoma

1. **Use of 4D-CT**: accounting for tumor motion during breathing (ITV)
2. **GTV-Definition**: minimization based on functional Imaging (PET-CT) and shift to smaller CTV volumes

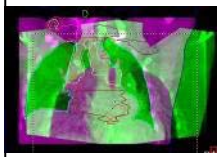


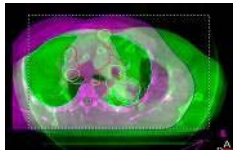


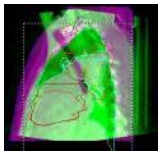
3. Treatment Planning as IMRT based on Monte-Carlo Dose calculation (dose-painting)



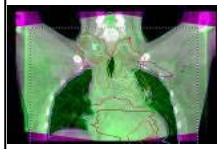
4. Image Guided Radiotherapy Treatment with Cone-Beam-CT at Linac for margins reduction

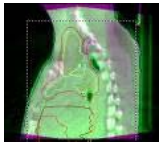






Suboptimal Positioning





Optimal Positioning

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Myeloma:
Solitary & Disseminated

Umberto Ricardi

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Multiple myeloma

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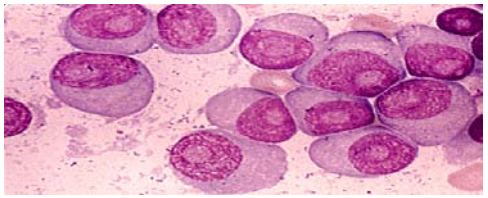
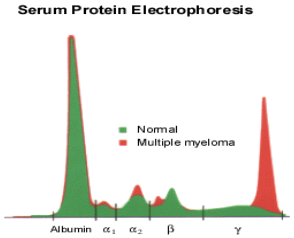


Multiple myeloma



Multiple myeloma is a neoplastic plasma-cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction

It accounts for approximately 1% of neoplastic diseases and 13% of hematologic malignancies

In Western countries, the annual age-adjusted incidence is 5.6 cases per 100,000 persons

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The median age at diagnosis is approximately 70 years; 37% of patients are younger than 65 years, and 37% are 75 years of age or older

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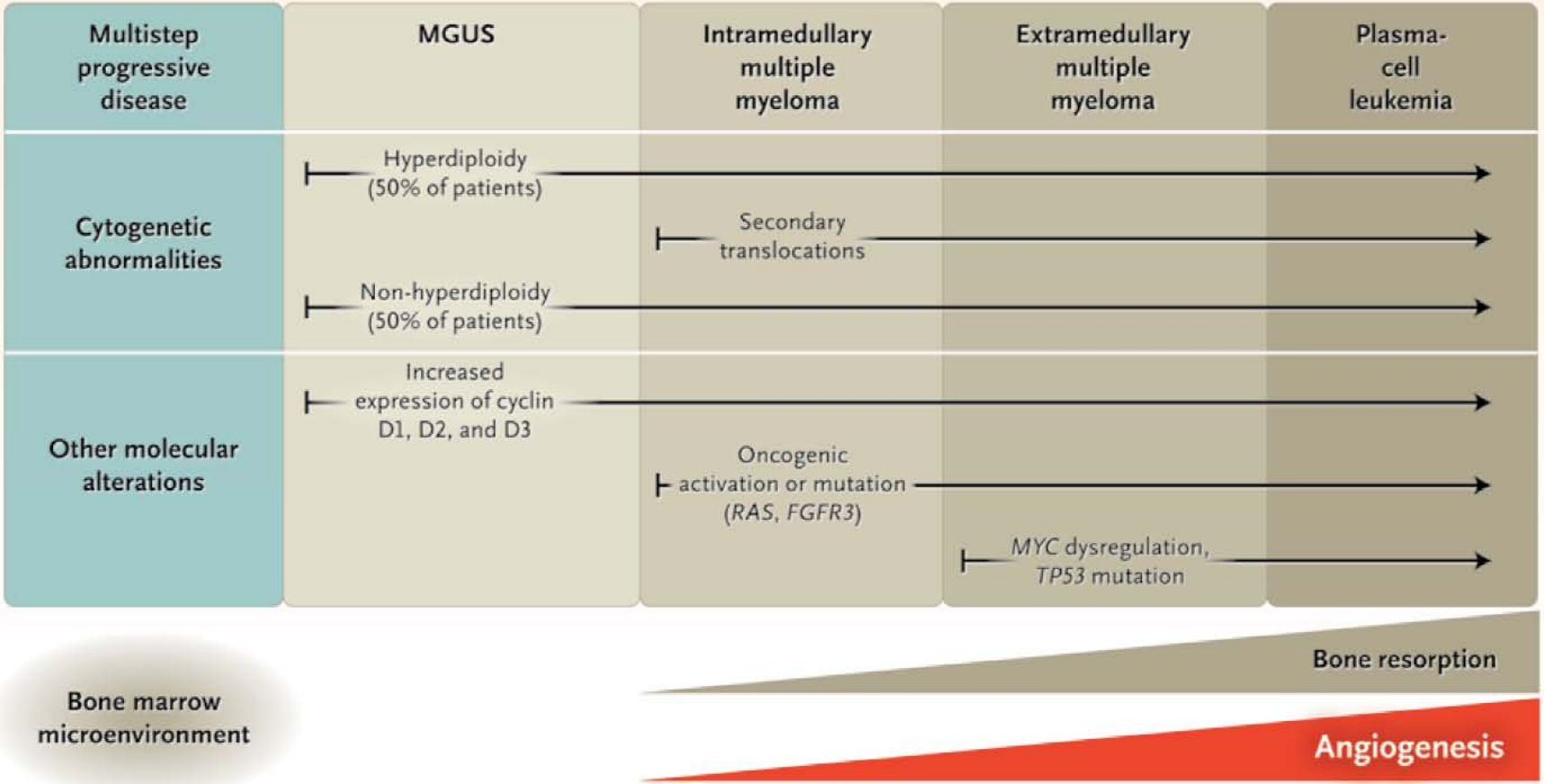
Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post-germinal-center B cells

Multistep genetic and microenvironmental changes lead to the transformation of these cells into a malignant neoplasm

Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance **(MGUS)** that progresses to **smoldering myeloma** and, finally, to **symptomatic myeloma**



Antonio Palumbo, M.D., and Kenneth Anderson, M.D. **N Engl J Med 2011;364:1046-60.**

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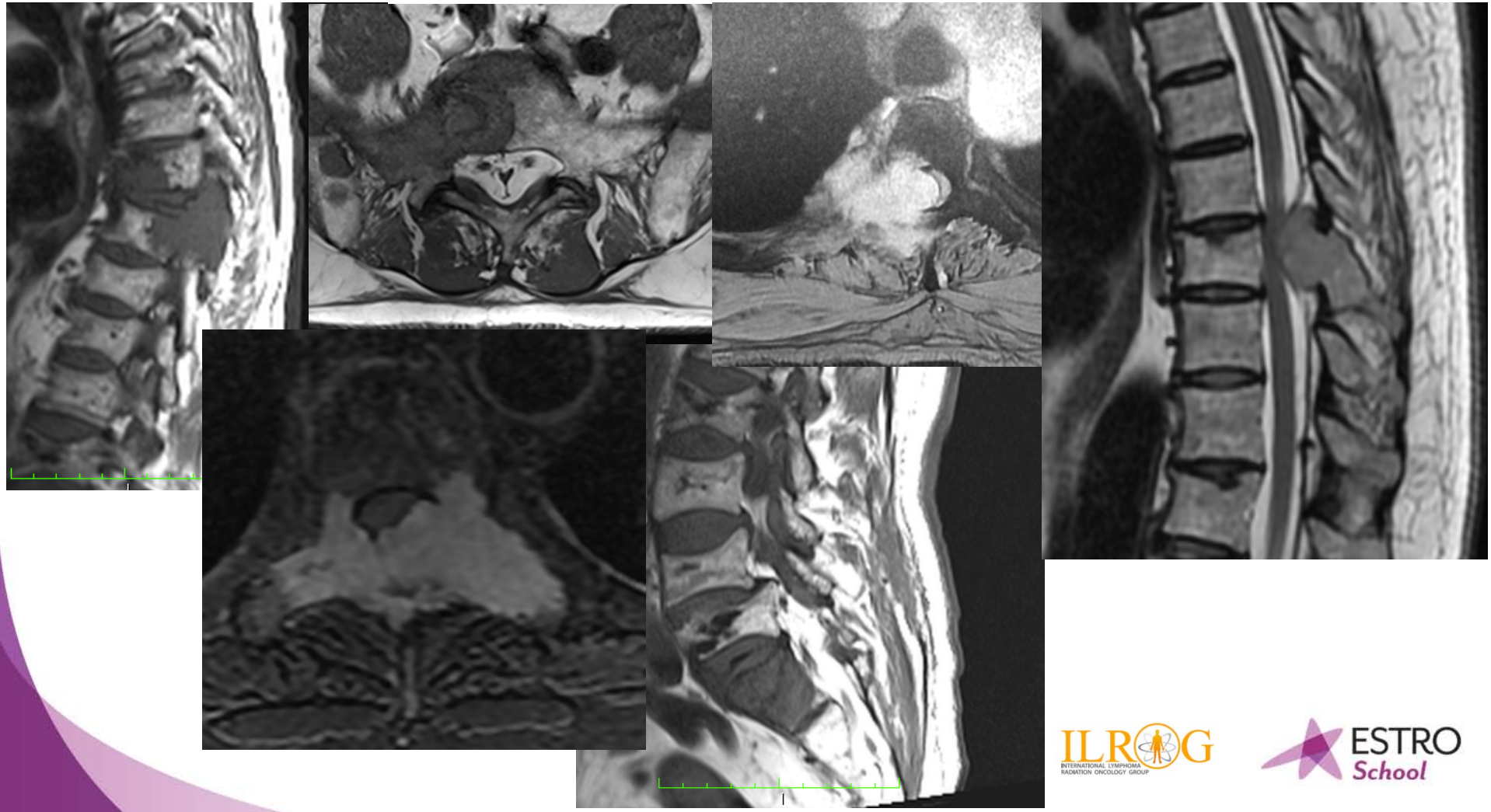
Clinical presentation, diagnosis and staging

Myeloma is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction, including:

- hypercalcemia
- renal insufficiency
- anemia
- bone disease

CRAB criteria



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Diagnostic evaluation

Diagnosis

- Medical history and physical examination
- Routine testing: complete blood count, chemical analysis with calcium and creatinine, serum and urine protein electrophoresis with immunofixation, quantification of serum and urine monoclonal protein, measurement of free light chains
- Bone marrow testing: trephine biopsy and aspirate of bone-marrow cells for morphologic features; cytogenetic analysis and fluorescence in situ hybridization for chromosomal abnormalities
- Imaging: skeletal survey, magnetic resonance imaging if skeletal survey is negative

Prognosis

- Routine testing: serum albumin, β_2-microglobulin, lactate dehydrogenase

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Stage	Durie-Salmon staging system (55)	International staging system (56)
I	All of the following: Hemoglobin >10 g/dl Serum calcium ≤12 mg/dl No myeloma-related bone lesions (solitary plasmacytoma excepted) Low M-protein concentration (IgG <5 g/dl, IgA <3 g/dl, and Bence Jones protein <4 g/24 h)	β_2-microglobulin <3.5 mg/L Albumin >3.5 g/dl
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: Hemoglobin <8.5 g/dl Serum calcium >12 mg/dl Extensive lytic bone lesions High M-protein concentration (IgG >7 g/dl, IgA >5 g/dl, or Bence Jones protein >12 g/24 h)	β_2-microglobulin >5.5 mg/L

Subclassification:

Normal renal function (serum creatinine <2.0 mg/dL)

Abnormal renal function (serum creatinine ≥2.0 mg/dL)

MST: **Stage I 62 months**
Stage II 44 months
Stage III 29 months

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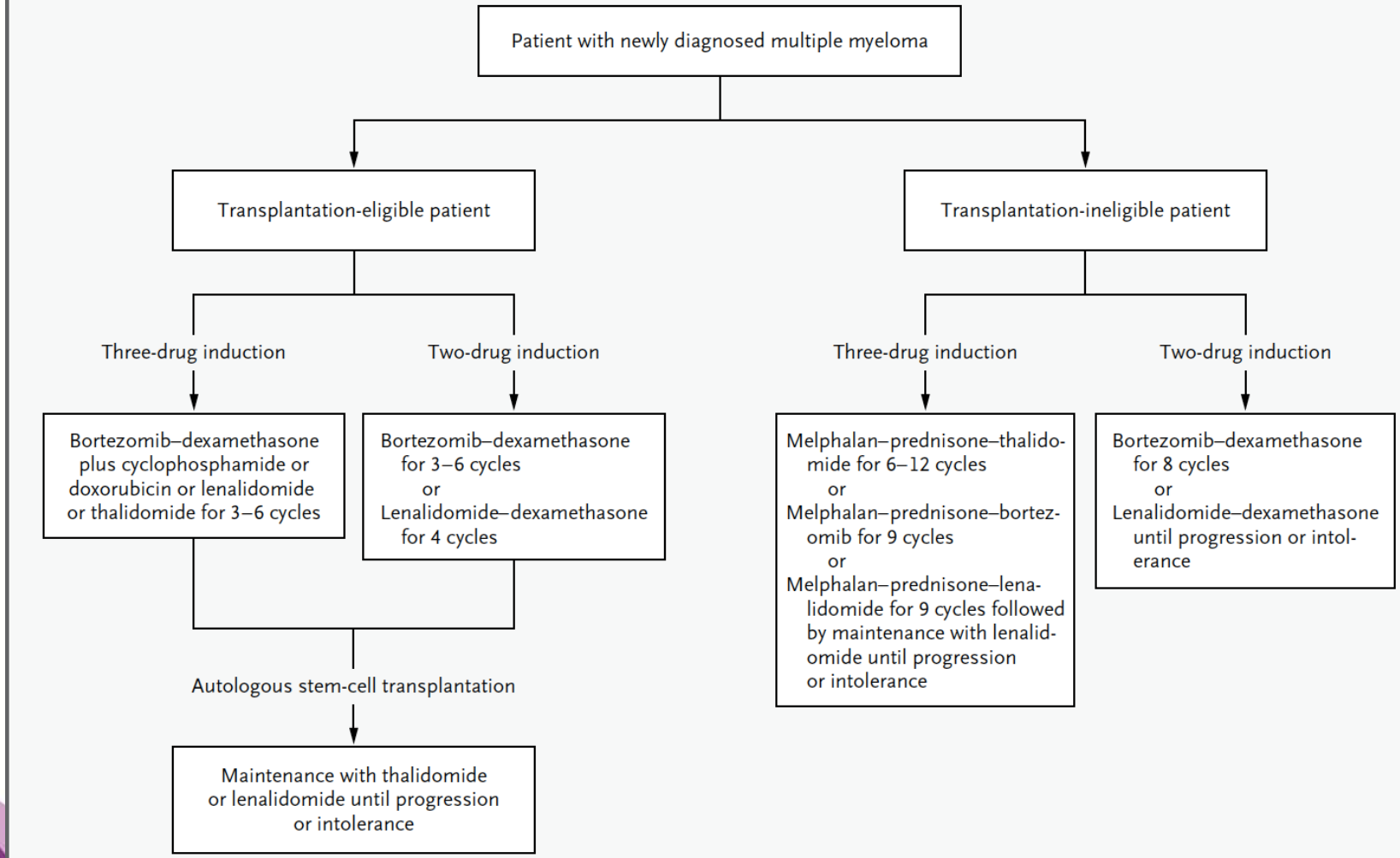
Treatment

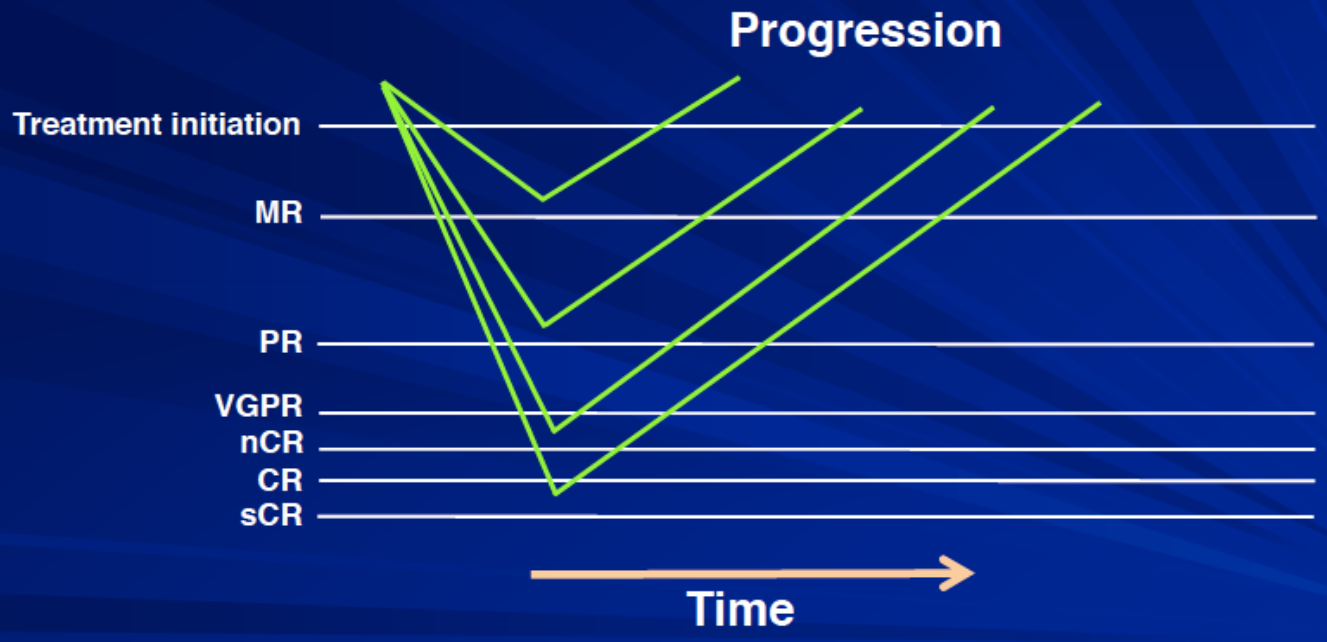
Symptomatic (active) disease should be treated immediately, whereas asymptomatic (smoldering) myeloma requires only clinical observation, since early treatment with conventional chemotherapy has shown no benefit

Investigational trials are currently evaluating the ability of immunomodulatory drugs to delay the progression from smoldering myeloma to symptomatic myeloma

The treatment strategy is mainly related to age


Patient with newly diagnosed multiple myeloma
Transplantation-eligible patient
Transplantation-ineligible patient
Three-drug induction
Two-drug induction
Three-drug induction
Two-drug induction
Bortezomib–dexamethasone plus cyclophosphamide or doxorubicin or lenalidomide or thalidomide for 3–6 cycles
Bortezomib–dexamethasone for 3–6 cycles or Lenalidomide–dexamethasone for 4 cycles
Melphalan–prednisone–thalidomide for 6–12 cycles or Melphalan–prednisone–bortezomib for 9 cycles or Melphalan–prednisone–lenalidomide for 9 cycles followed by maintenance with lenalidomide until progression or intolerance
Bortezomib–dexamethasone for 8 cycles or Lenalidomide–dexamethasone until progression or intolerance
Autologous stem-cell transplantation
Maintenance with thalidomide or lenalidomide until progression or intolerance

Depth of response



Depth of response is related to TTP

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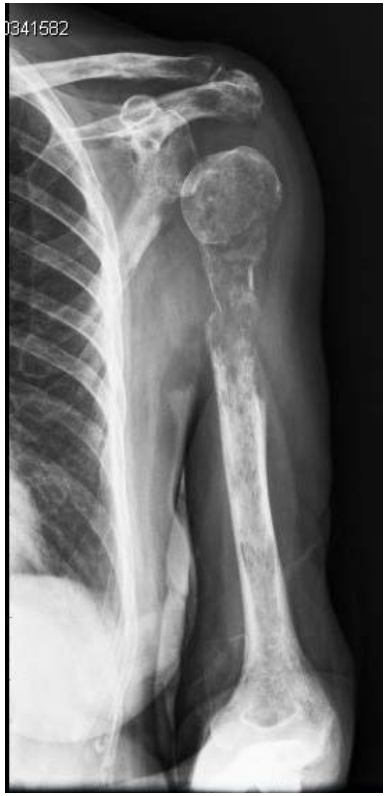
Role of Radiotherapy in MM

- Prompt and highly effective modality in the palliation of of painful bony lesions and mass effects from soft tissue extensions
- Efficacy in the control of lytic bone lesions and in reversing the morbidity of spinal cord and nerve root compression
- 30 Gy in 10 fractions or 40 to 45 Gy in 4 to 4.5 weeks to the lesions with generous margins; 8 Gy/1 fraction may be used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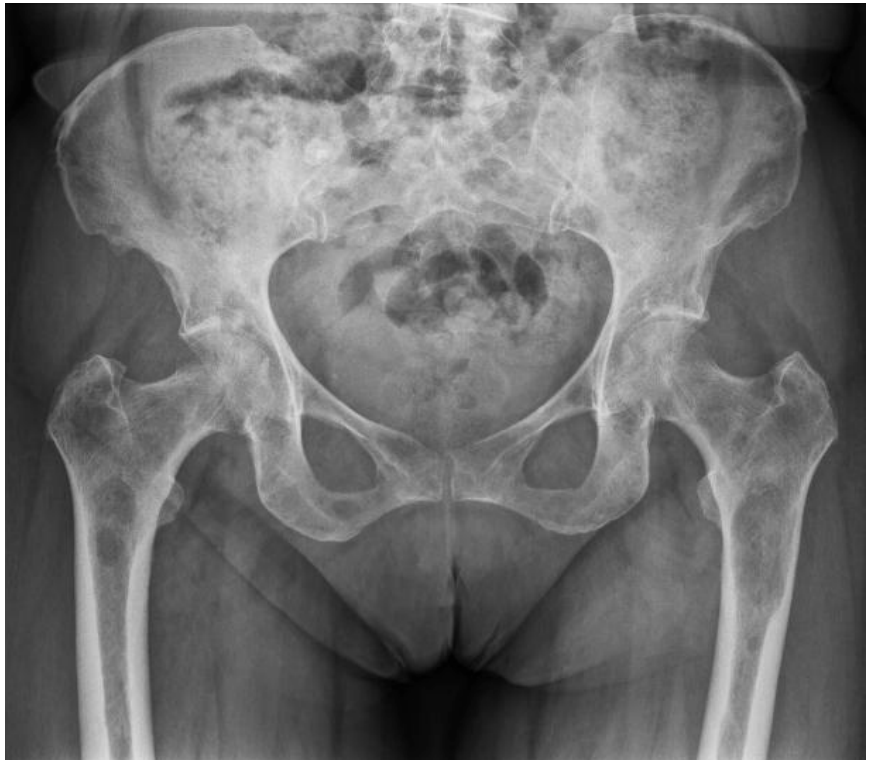
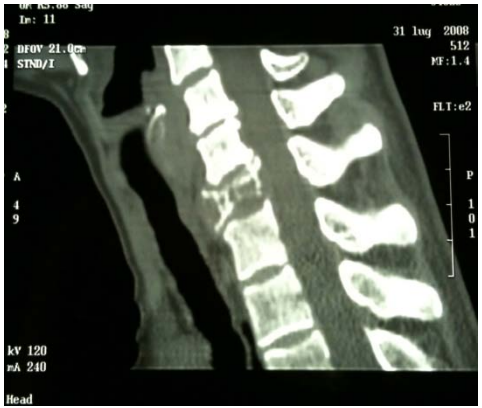
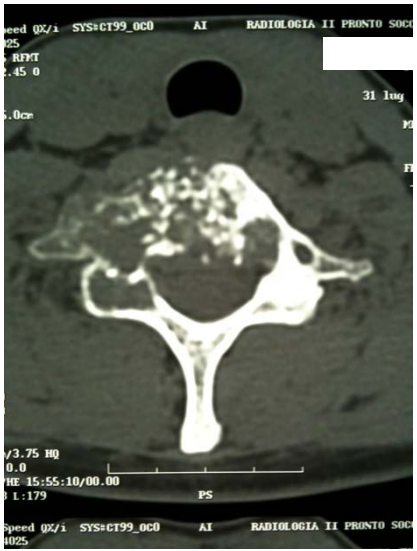
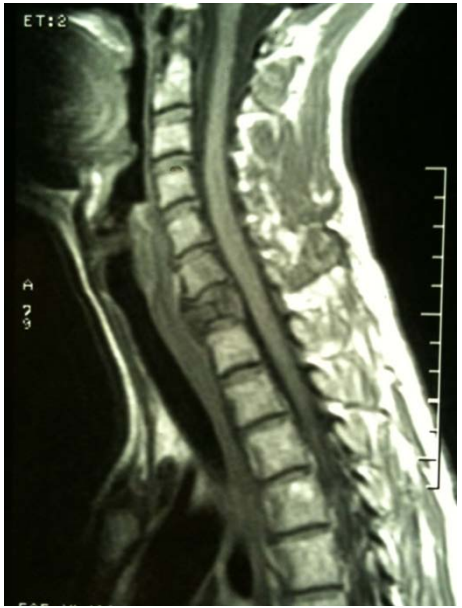


- solitary vertebral body lesion (C7) in MM







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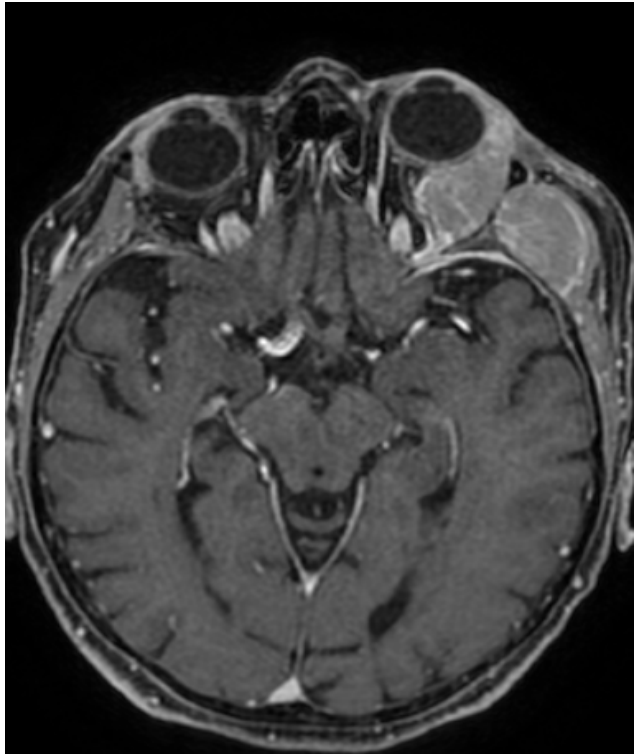
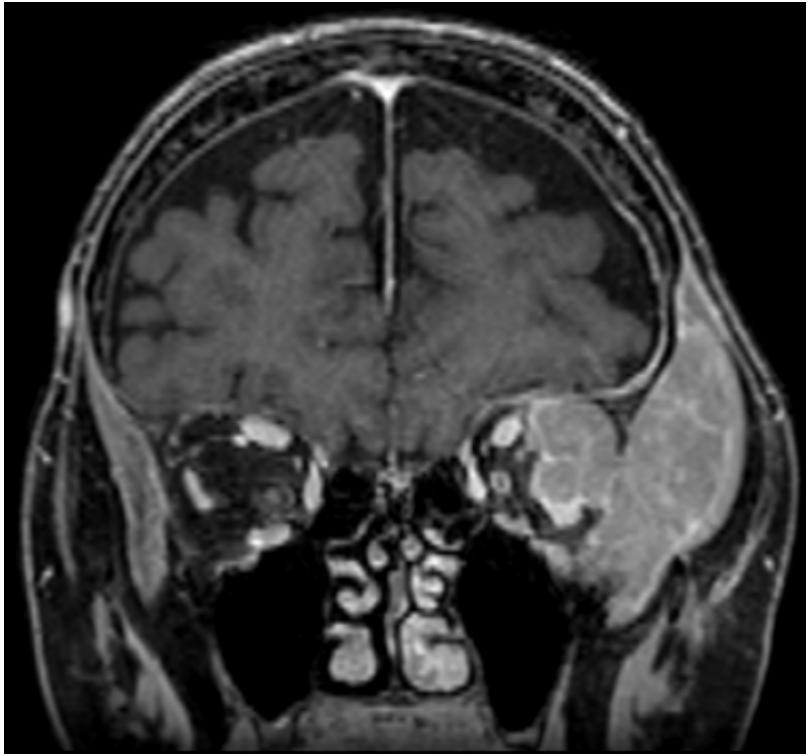
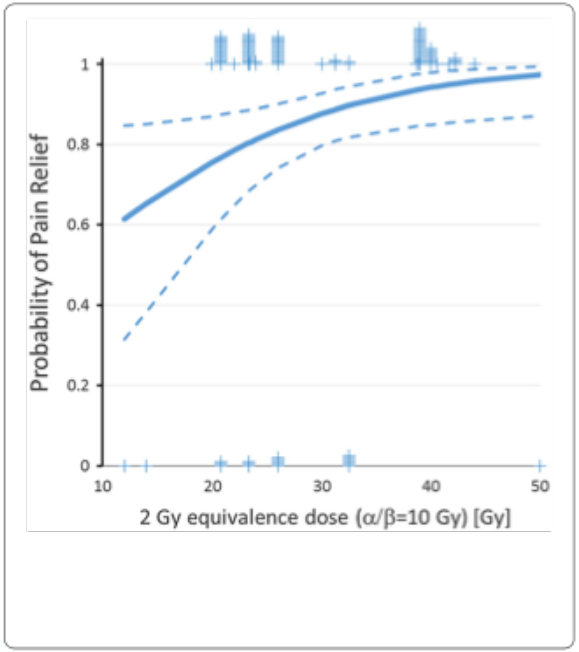




Effects of Radiotherapy in the treatment of multiple myeloma: a retrospective analysis of a Single Institution



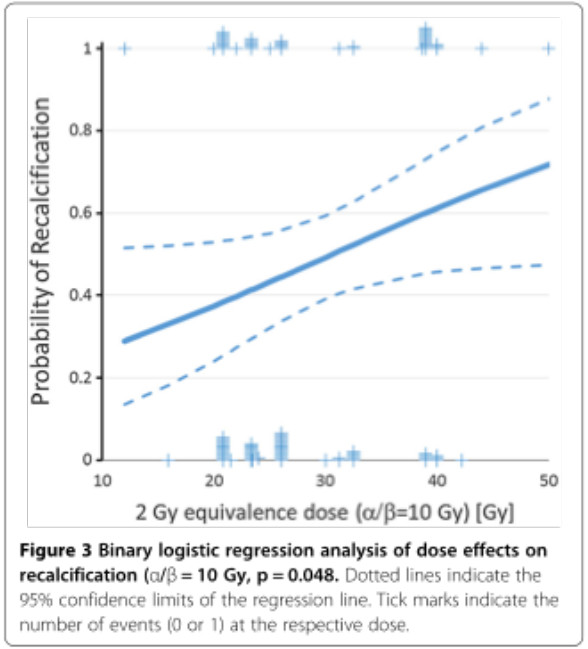


Figure 3 Binary logistic regression analysis of dose effects on recalcification (α/β = 10 Gy, **p = 0.048.** Dotted lines indicate the 95% confidence limits of the regression line. Tick marks indicate the number of events (0 or 1) at the respective dose.

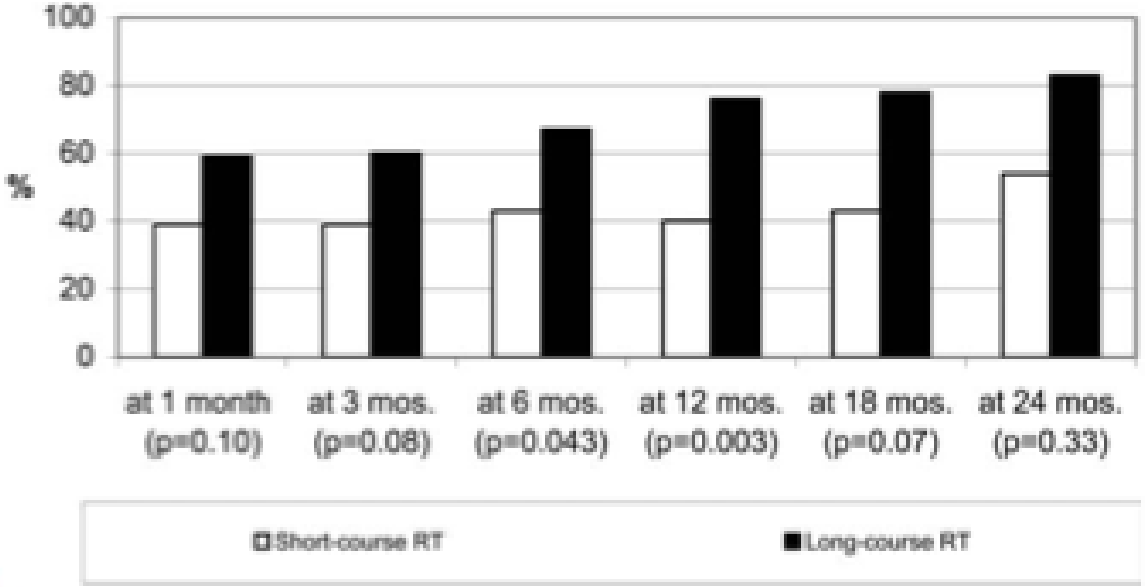
- 153 patients
- 1989-2013

Conclusions:
higher total biological RT dose were associated with better pain relief (**≥30 Gy**) and recalcification (**≥40 Gy**)

Matuschek et al Radiat Oncol 2015;10:71

SHORT-COURSE RADIOTHERAPY IS NOT OPTIMAL FOR SPINAL CORD COMPRESSION DUE TO MYELOMA

IMPROVEMENT OF MOTOR FUNCTION AFTER RADIOTHERAPY



- 172 patients
- 1994-2004

- Short course RT:
  - 8 Gy in single fraction
  - 20 Gy/5 fractions

- Long course RT:
  - **30 Gy/10 fractions**
  - **37.5 Gy/15 fractions**
  - **40 Gy/20 fractions**

Rades et al IJROBP 2006;64(5):1452-1457

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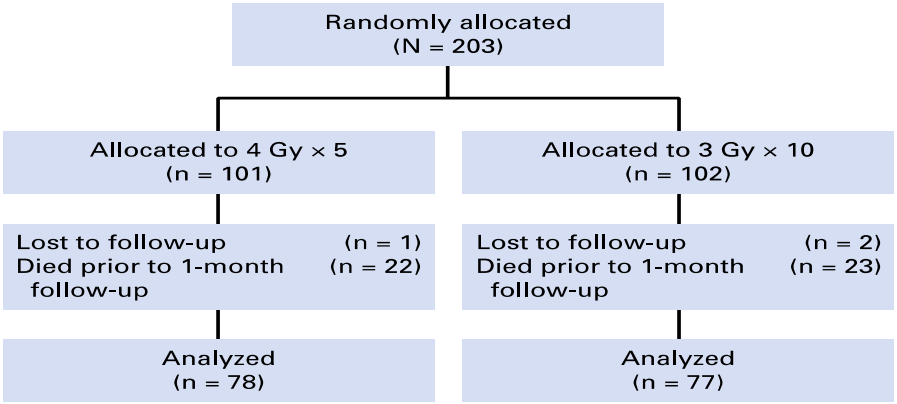
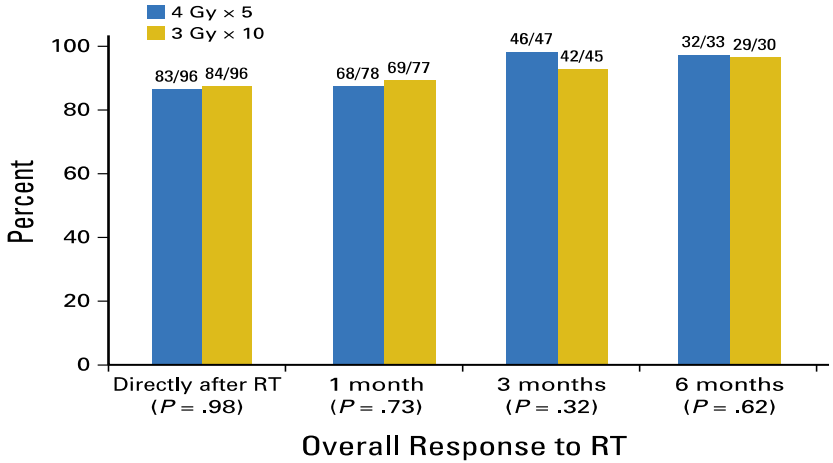
Radiotherapy With 4 Gy × 5 Versus 3 Gy × 10 for Metastatic Epidural Spinal Cord Compression: Final Results of the SCORE-2 Trial (ARO 2009/01)





Rades et al. JCO 2016

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Radiotherapy With 4 Gy × 5 Versus 3 Gy × 10 for Metastatic Epidural Spinal Cord Compression: Final Results of the SCORE-2 Trial (ARO 2009/01)

Table 1. Distribution of the Three Stratification Factors and Additional Characteristics

Stratification Factors and Additional Characteristics	Patients, n (%) 4 Gy × 5	3 Gy × 10	*P*
Stratification factor			
Ambulatory status before RT			
Ambulatory without aid (N = 52)	26 (25.7)	26 (25.5)	> .99
Ambulatory with aid (N = 65)	32 (31.7)	33 (32.4)	
Not ambulatory (N = 86)	43 (42.6)	43 (42.2)	
Time developing motor deficits before RT, days			
1-7 (N = 92)	46 (45.5)	46 (45.1)	> .99
8-14 (N = 53)	26 (25.7)	27 (26.5)	
> 14 (N = 58)	29 (28.7)	29 (28.4)	
Type of primary tumor			
Breast cancer (N = 32)	16 (15.8)	16 (15.7)	> .99
Prostate cancer (N = 32)	16 (15.8)	16 (15.7)	
Myeloma/lymphoma (N = 16)	8 (7.9)	8 (7.8)	
Lung cancer (N = 58)	29 (28.7)	29 (28.4)	
Other tumors (N = 65)	32 (31.7)	33 (32.4)	

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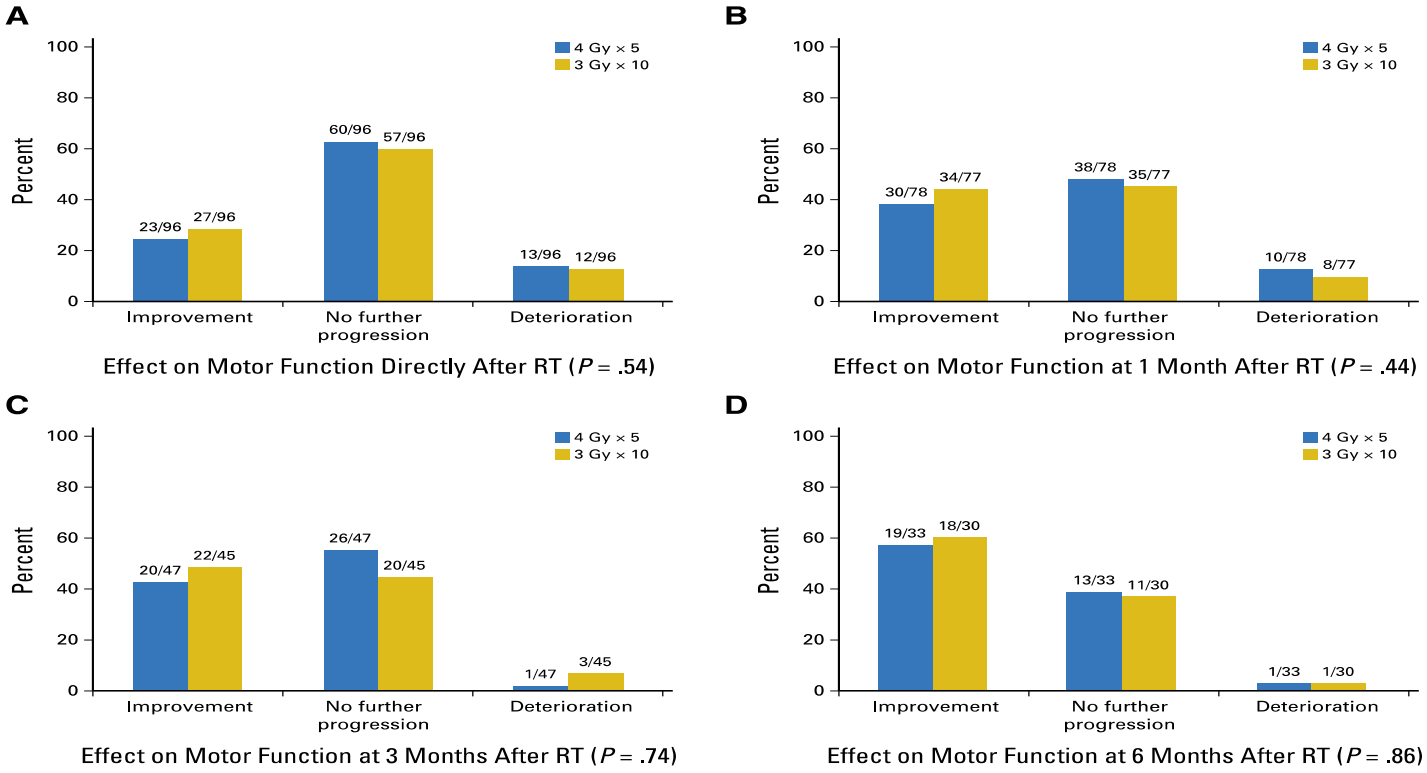
Radiotherapy With 4 Gy × 5 Versus 3 Gy × 10 for Metastatic Epidural Spinal Cord Compression: Final Results of the SCORE-2 Trial (ARO 2009/01)



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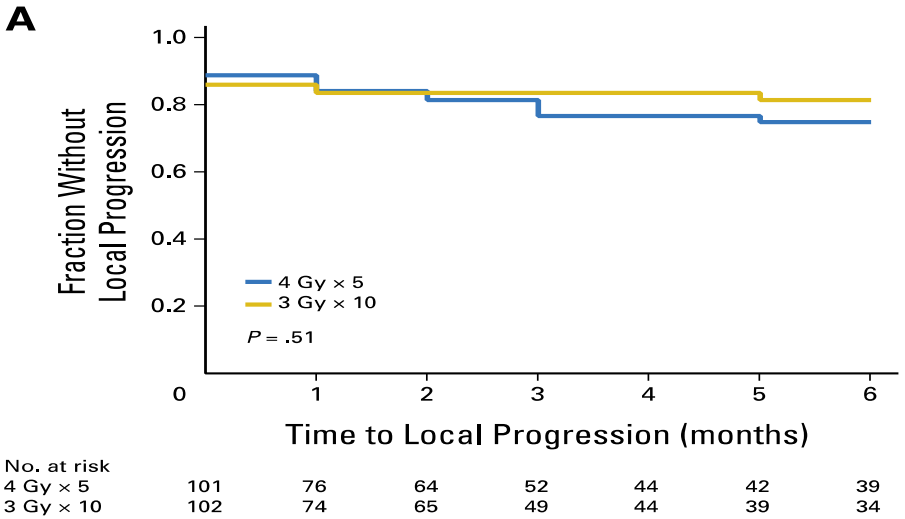
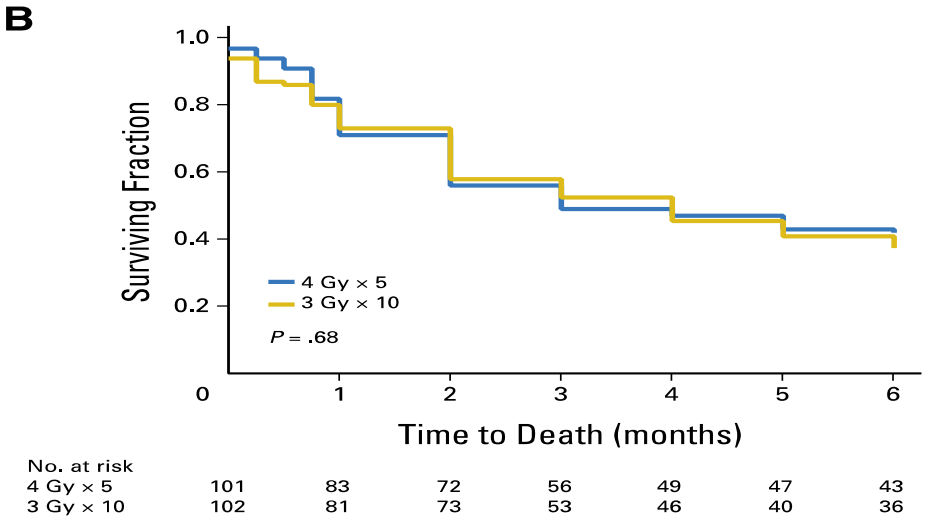
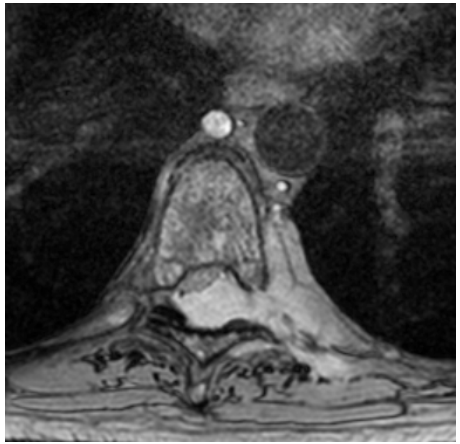
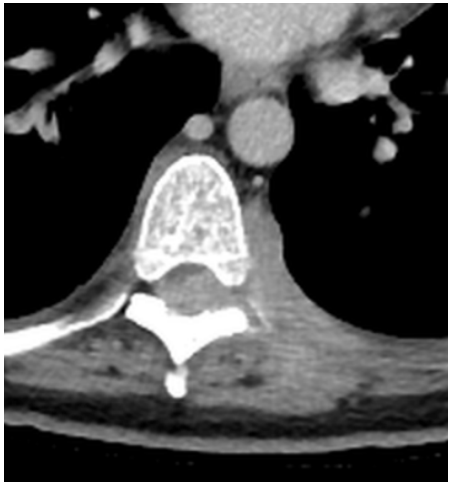


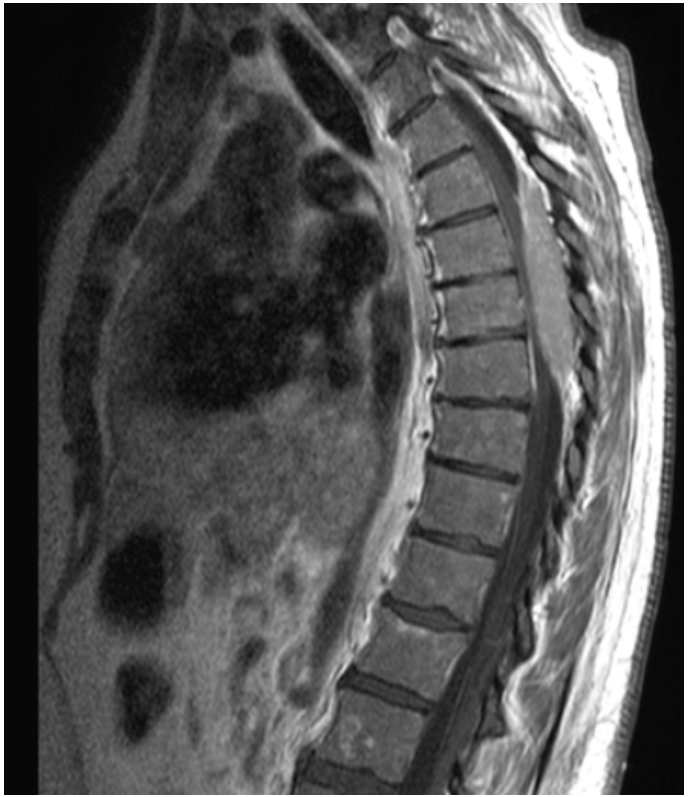


Rades et al. JCO 2016

RT for Multiple Myeloma @ University of Torino







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Systemic radiotherapy in MM:

TBI and HBI

- Bone marrow ablative (allo and/or auto) preparative regimens: drugs alone (Melphalan) (more toxicity with TBI)
- Non myeloablative allogeneic transplantations ("mini"-allo): single dose 2 Gy TBI, combined with various chemotherapy regimens
- HBI (mainly historical)

Solitary plasmacytoma

- Solitary or localized plasmacytomas are rare diseases that account for less than 10% of all plasma cell neoplasms

- Similar to MM but without infiltration of the bone marrow, these neoplasms are composed of sheets of plama cells involving bone or soft tissue

- When the lesion is isolated in bone, the disorder is called **Solitary Plasmacytoma of Bone (SPB)** [mostly occurs in the bones of the axial skeleton]

- When in soft tissues, the lesion is called **Extramedullary Plasmacytoma (EMP)**, and is found in the head and neck 80% of the time

- SPBs are found predominantly in men (male-to-female ratio of 2:1) and at a median age of 55 years (younger age than MM), and are slightly more common than EMPs

Diagnosis of SPB requires solitary bone lesion confirmed by skeletal survey, plasma cell infiltration proven by biopsy, normal bone marrow biopsy (< 10% plasma cells), and lack of myeloma-related organ dysfunction (CRAB)

Solitary Bone Plasmacytoma

- Treatment of SP is largely composed of retrospective studies on small number of patients

- Currently, the standard of care for SBP is definitive RT, being SBP a highly radiosensitive disease, for which excellent local control rates can be achieved with RT alone (lesion size as prognostic factor; cut off 5 cm)

- In some cases (bone instability, rapidly progressive neurological symptoms) surgical intervention may be required

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- Even though the optimal dose of RT has not yet established for SBP, it is recommended a radiation dose of at least 40 Gy in 20 fractions

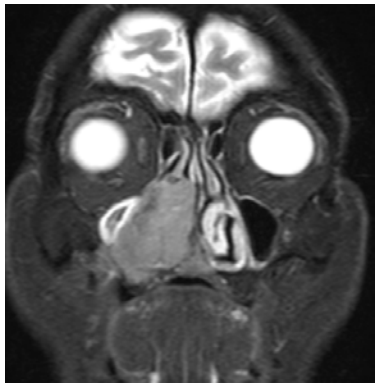
- Local control rates of 94% with doses over 40 Gy, dropped to 64% with doses lower than 40 Gy

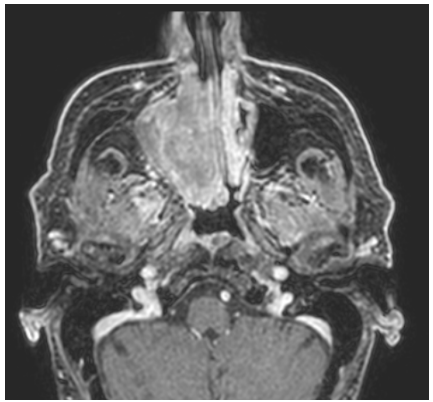
- In clinical practice, a radiation dose of 45-50 Gy with 2 Gy daily fractions is usually recommended

Extramedullary plasmacytoma

- Since the majority of EMP occurs in head and neck region and radical surgery with curative intent is often a mutilating procedure, radical RT should be preferred

- However, for patients with EMP in other sites, complete surgical removal should be considered, with adjuvant irradiation if appropriate (inadequate surgical margins)





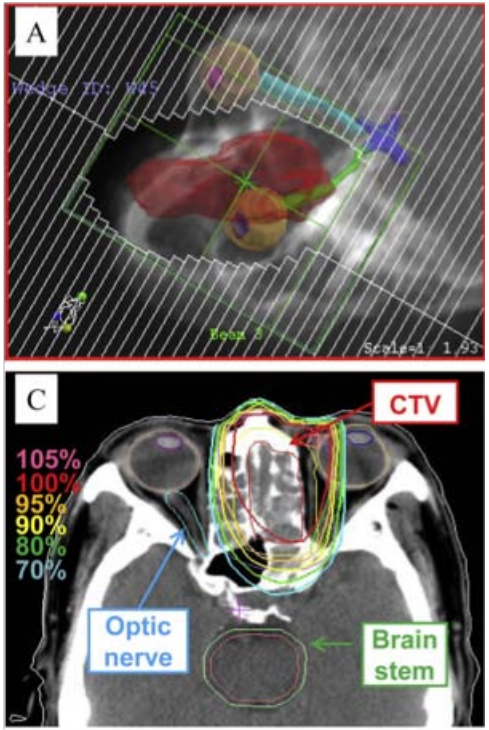
MULTI-INSTITUTIONAL ANALYSIS OF SOLITARY EXTRAMEDULLARY PLASMACYTOMA OF THE HEAD AND NECK TREATED WITH CURATIVE RADIOTHERAPY

- 67 patients
- 1983-2008
- Japanese cohort
- Median RT dose 50 Gy

Table 1. Patients and tumor characteristics

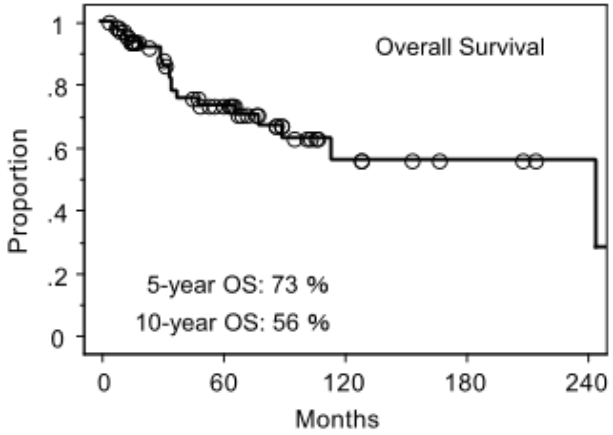
	Number	Percentage (%)
Age	12–83 (64)*	
Gender (M/F)	43/24	
ECOG performance status (0/1/2/unknown)	46/18/1/2	
Tumor size	1–10 cm (3.5)*	
Sites		
Nasal/paranasal	36	54
Oropharynx	9	13
Nasopharynx	7	10
Orbita	6	9
Larynx	3	5
Salivary glands	2	3
Lymph nodes	2	3
Middle ear	1	1.5
Thyroid	1	1.5
Positive for M protein	15/59	22
Positive for Bence-Jones proteins	2/56	4
Concomitant disease		
Amyloidosis	2/67	3

* median age, median tumor size.



Sasaky et al. IJROBP 2012;82(2):626-634

MULTI-INSTITUTIONAL ANALYSIS OF SOLITARY EXTRAMEDULLARY PLASMACYTOMA OF THE HEAD AND NECK TREATED WITH CURATIVE RADIOTHERAPY



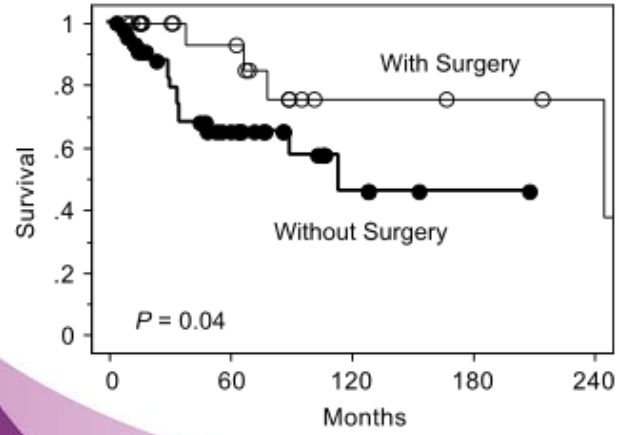


Table 5. Prognostic factors for overall survival

Prognostic factors	*p* value
Tumor size	
≤5 cm (*n* = 45) vs. >5 cm (*n* = 13)	0.59
Age	
≤50 (*n* = 15) vs. >51 (*n* = 52)	0.3
Gender	
Male (*n* = 43) vs. female (*n* = 24)	0.95
Radiation dose	
≤40 Gy (*n* = 13) vs. >40.1 Gy (*n* = 54)	0.82
≤45 Gy (*n* = 17) vs. >45.1 Gy (*n* = 50)	0.73
≤50 Gy (*n* = 56) vs. >50.1 Gy (*n* = 11)	0.72
Surgery	
With surgery (*n* = 23) vs. without surgery (*n* = 44)	0.04
Chemotherapy	
With chemotherapy (*n* = 9) vs. without chemotherapy (*n* = 58)	0.75

Sasaky et al. IJROBP 2012;82(2):626-634

Radiation volumes

- Current recommendations favor radiation fields encompassing only the primary lesion, with generous margins (1.5-2 cm) to cover both the osseous and soft tissue extensions of the tumor (other than the entire involved bone)

- Prophylactic regional nodes irradiation is not necessary in SPB, as isolated regional node failure is low after local RT without intentional coverage of adjacent nodes

- Elective nodal irradiation is not routinely indicated in EMP patients, unless regional nodes are clinically involved or considered at high risk

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Patterns of failure:

- local recurrence
- development of MM
- development of new bone lesions without MM

TABLE 1: Solitary plasmacytoma of bones: representative treatment results.

Author	*n*	f/u	LC (%)	PMM (%)	OAS (%)
Wilder et al. [35]	60	94 mo	90	62	59
Knobel et al. [25]	206	56 mo	79	51	50
Tsang et al. [32]	32	95 mo	87	64	65
Kilciksız et al. [24]	57	**2.4** y	94	4.1 y	68
Frassica et al. [23]	46	90	89	54	45
Bataille and Sany [33]	114	>10 y	88	58	68
Galieni et al. [40]	32	69 mo	91	68	49

mo: months, y: years f/u: Median followup, LC: Local control (10-year rate), PMM: progression to myeloma (10-year rate), and OAS: over all survival (10- year rate).

TABLE 2: Solitary Extramedullary Plasmacytoma: Representative Treatment Results.

Author	*n*	f/u	LC (%)	PMM (%)	OAS (%)
Kilciksiz et al. [24]	23	**2.4** y	95	7.4 y	89
Ozsahin et al. [3]	52	56	74	36	72
Galieni et al. [40]	46	118	92	15	78 (15 y)
Tournier-Rangeard [42]	17	80.5	88.2	63.8	63.4
Strojan et al. [43]	26	61	87	8	61
Leibross et al. [44]	22	—	95	32	56
Chao et al. [45]	16	66	100	31	54

- In comparison with EMP, SBP has worse prognosis, with a significantly higher risk for progression to myeloma (65-80% in 10 years), in spite of better local control rates

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- “Adjuvant” systemic treatments are not of convincing benefit in SBP and EMP

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Extranodal lymphomas: Orbital (ocular adnexal) lymphoma

Umberto Ricardi

DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

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ENL: Most common sites

- Primary CNS Lymphoma
- **Orbital (Ocular Adnexal) Lymphomas**
- Lymphomas of the Head and Neck
- Breast Lymphoma
- Lymphoma of the Lung
- Gastric Lymphoma
- Testicular Lymphoma
- Bone Lymphoma
- Skin Lymphomas

Orbital (ocular adnexal) Lymphoma

- 1-2% of all NHL
- 7-8% of extranodal lymphomas
- Ocular adnexa lymphomas (OAL) include:
  - orbit
  - extra ocular muscles
  - conjunctiva
  - eyelids
  - lacrimal gland
  - apparatus
- Most cases of extraocular orbital lymphoma are Marginal Zone Lymphoma (MZL)
- Approximately 15% of such cases are bilateral (synchronous or metachronous)

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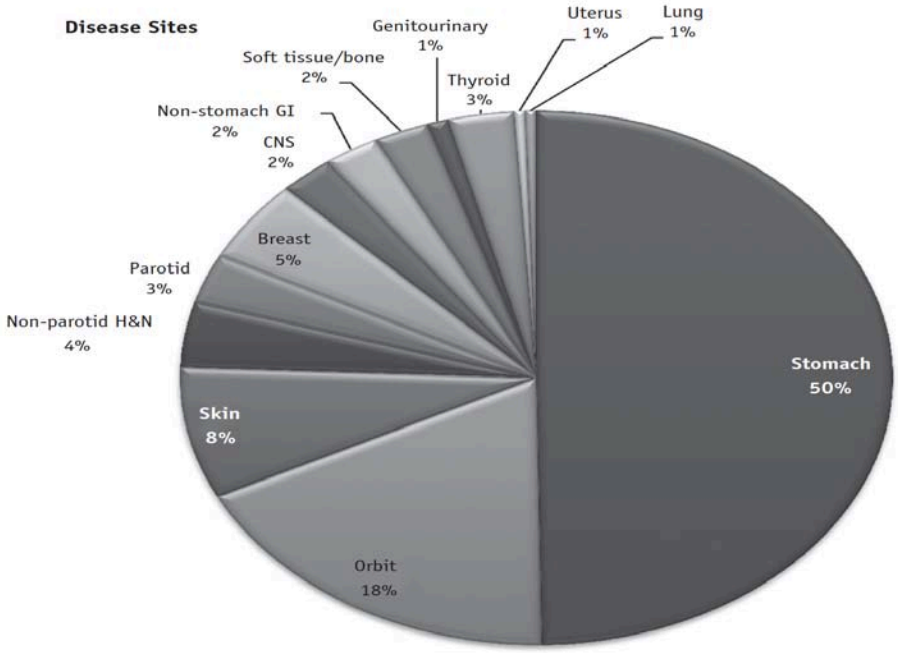
Introduction

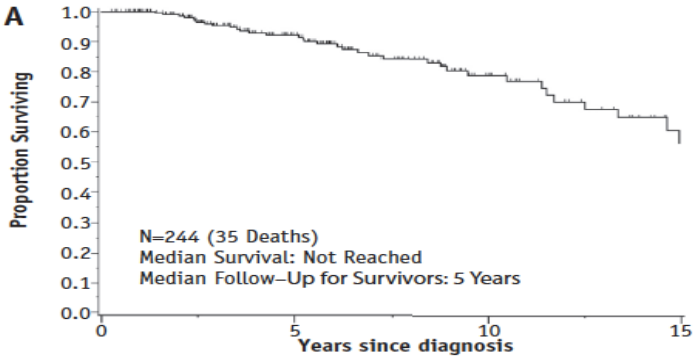
- 95% of OAL are B-cell neoplasms
  - Extranodular marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type = 35-80%
  - Follicular lymphoma = 20%
  - Diffuse large B-cell lymphoma = 8%
  - Mantle cell lymphoma, small lymphocytic lymphoma and lymphoplasmacytic lymphoma = less common

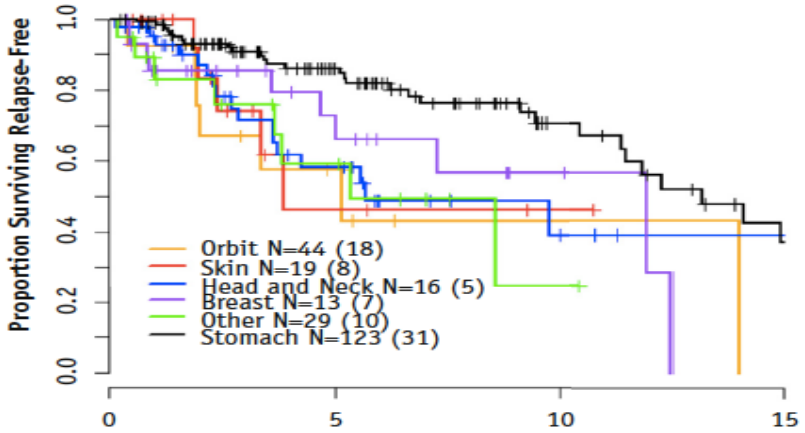
Long-Term Outcomes and Patterns of Relapse of Early-Stage Extranodal Marginal Zone Lymphoma Treated With Radiation Therapy With Curative Intent

Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 130–137, 2015

Sewit Teckie, MD,* Shunan Qi, MD,* Shona Lovie, MPH,* Scott Navarrett, BS,‡ Meier Hsu, MS,§ Ariela Noy, MD,|| Carol Portlock, MD,|| and Joachim Yahalom, MD*







Ocular adnexal marginal zone lymphoma (OAMZL)

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Clinical presentation

- 5^{th} - 7^{th} decade of life (median age, 65 years)
- female predominance (male:female = 1:1.5/2)
- Korean populations: younger age (median, 46 years) at the time of diagnosis, male rather than female predominance
- Site of origin:
  - orbit = 40%
  - conjunctiva = 35%-40%
  - lacrimal gland = 10%-15%
  - eyelid = 10%
- Bilateral involvement in 10% to 15% of cases (80% simultaneous, 20% sequential events)

Extranodal Lymphomas of Mucosa-associated Lymphoid Tissue

- Mainly indolent, composed of small cells
- Believed to be driven by host immune reactions to chronic infections or auto-immunity
- Form distinctive lympho-epithelial lesions

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Chlamydophila psittaci (Cp) infection

- **Cp** = etiologic agent of psittacosis, an infection caused by exposure to infected animals
- Cp infection is detected in tumor tissue in 11% of B-cell lymphomas
- In OAML Cp infection between 47% and 80% in countries like Austria, Germany, Italy and Korea

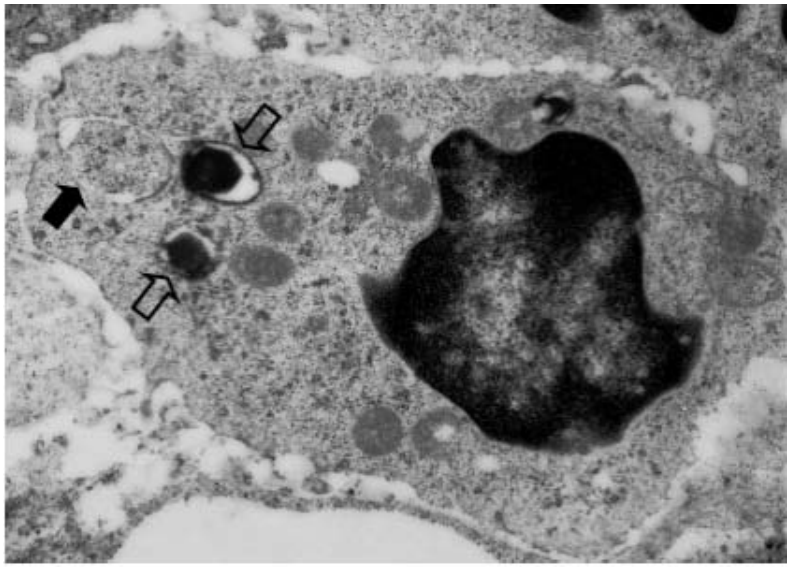

Fig. 2. Elementary bodies (CEB; open arrows) and reticulate body (CRB; full arrow) in an intratumor macrophage of a case of ocular adnexae MALT lymphoma assessed by electron microscopy. Chlamydial infection starts with attachment of a CEB to the host cell, followed by cell invasion. Within eukaryotic cells, chlamydia alternates from a metabolically inactive, highly infective form (*i.e.* the CEB), to a metabolically active, intracellular growing stage form (*i.e.* CRB). Under certain conditions, instead of dividing and differentiating into CEBs, CRBs retain a more stable association within the host cell forming the so-called persistent bodies, an important feature for better understanding the pathogenesis of chronic chlamydial infections.

Ferreri et al, Sem Cancer, 2013

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Clinical presentation

- Conjunctival lesions:

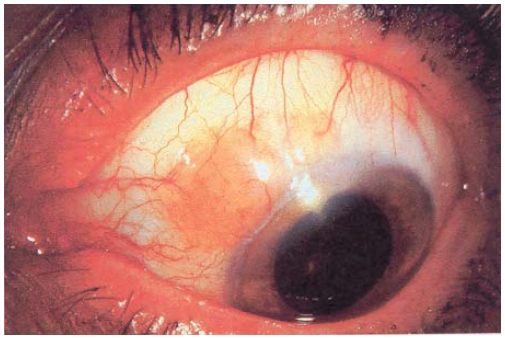
  mobile pink infiltrates in the substantia propria (“salmon-pink patch”), causing conjunctival swelling, redness, and irritation

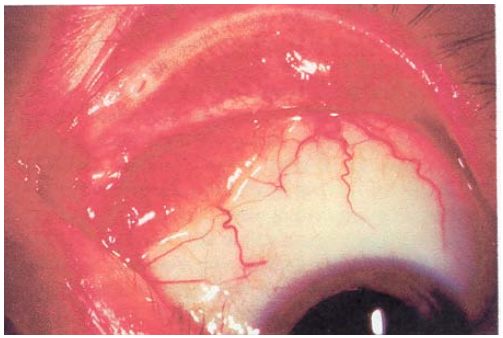
- Orbital lymphoid proliferations:

  palpable, firm or rubbery mass causing progressive proptosis, occasionally associated with periorbital edema, decreased visual acuity, motility disturbances, and diplopia

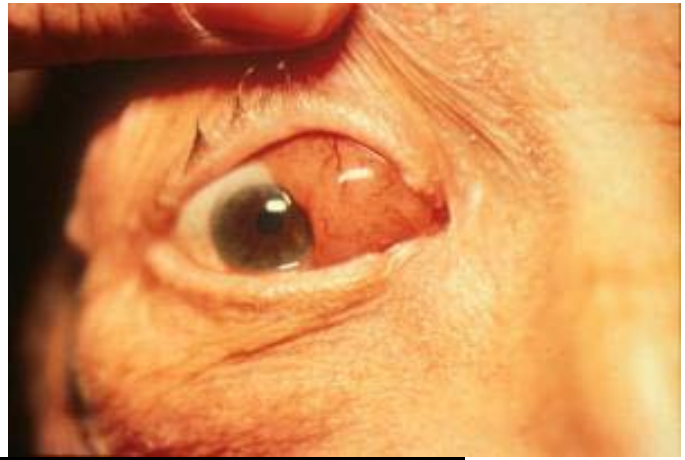
- Median interval between the onset of symptoms and time of diagnosis:

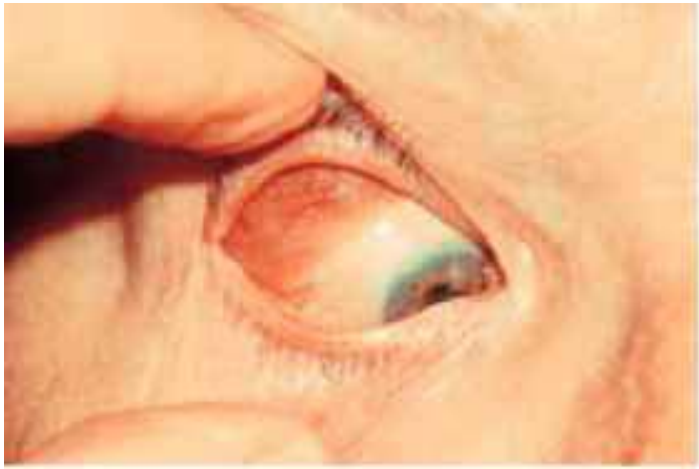
  7 months

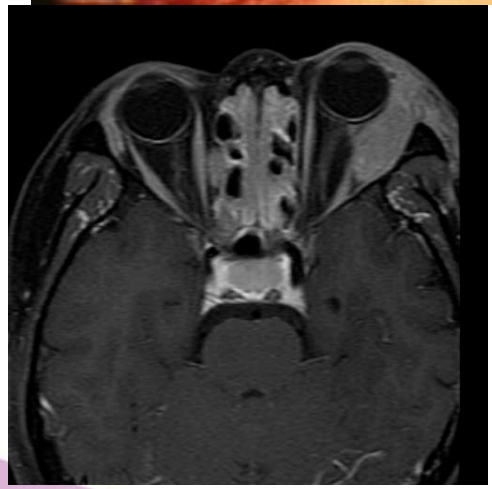


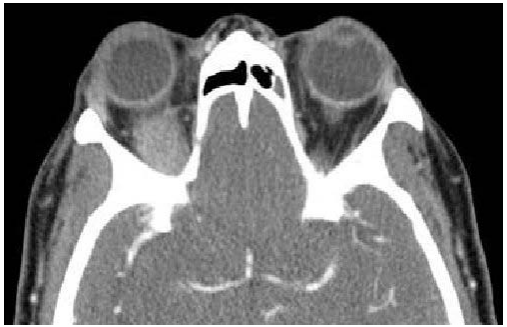


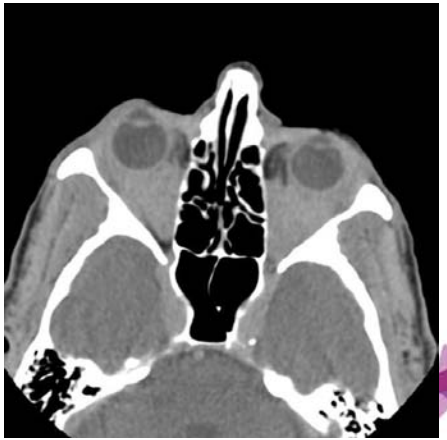
Clinical presentation











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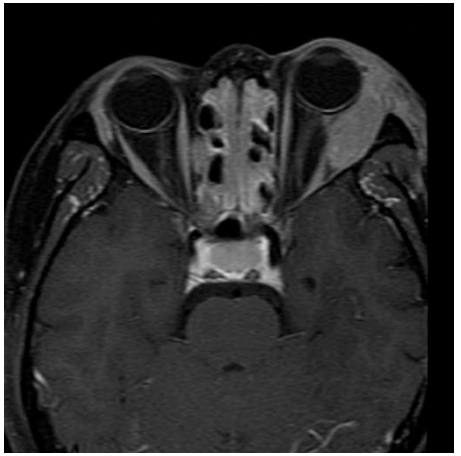
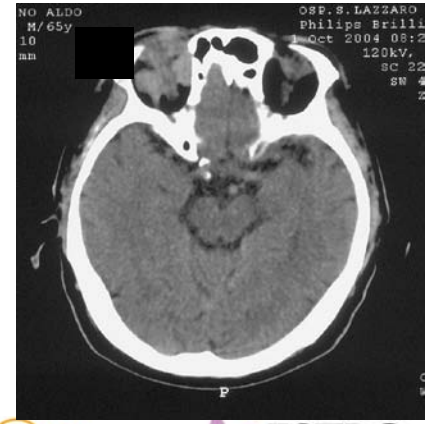
Diagnosis and staging

- Careful ophthalmologic examination
- Adequate tissue sampling
- Complete history and physical examination
- Routine laboratory studies, serum protein electrophoresis, serum LDH, β2-microglobulin
- Chest x-ray
- CT of chest, abdomen, and pelvis
- CT-PET
- Bone marrow biopsy (controversial)
- Orbital CT and MRI with contrast enhancement





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Diagnosis and staging

- Careful ophthalmologic examination:
  - To define the extent of conjunctival disease, which is often not fully appreciated on imaging
  - To assess ocular health before irradiation

Diagnosis and staging

- Ann Arbor system

- Localized disease (stage I) = 85%-90%
- Nodal involvement = 5%
- Bone marrow involvement = 5-8%

Treatment
Surgery

- Biopsy: mandatory for diagnosis and to determine the histologic subtype of OAL
- Incisional or excisional
- Local relapse has been reported more commonly in patients treated with surgery alone compared with those who also received RT *(Cho et al. 2003; Esik et al. 1996; Lee et al. 2005)*

Treatment

Surgical excision / “Watch and wait”

- 36 patients
- Observation for a median of 7.1 years
- 17 progression (47%)
- 11 required treatment

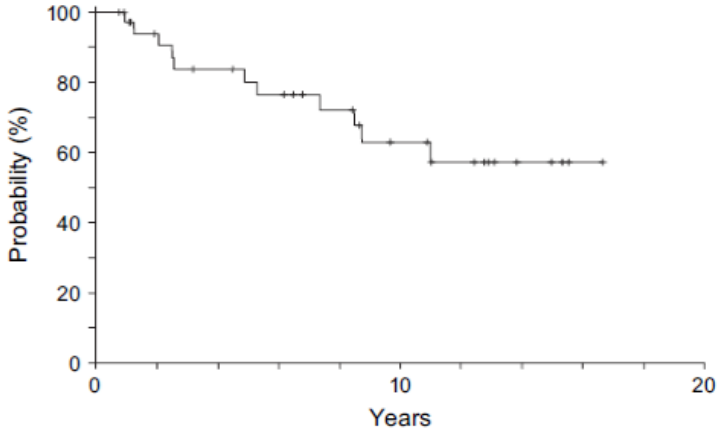

Figure 3. Freedom from requiring treatment. After 5, 10 and 15 years, freedom from requiring treatment was 80%, 63% and 57%, respectively.

This strategy may be appropriate in frail elderly patients with asymptomatic disease or in the setting of severe comorbidities that preclude an aggressive therapeutic approach

Tanimoto et al, Ann Oncol, 2006

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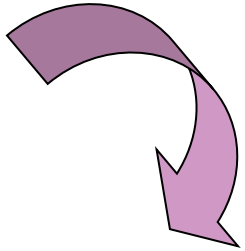
Treatment
Chemotherapy

- Limited data on chemotherapy for patients with OAML
- Different chemotherapy regimens:
  - COP/CVP
  - CHOP
  - C-MOPP
  - Chlorambucil (frail and/or elderly patients)



Complete response: 67-100%
BUT
Local recurrence: >29%

Treatment
Immunotherapy

- Single agent rituximab in previously untreated patients
  - overall response rates: 50-87%
  - median time to disease progression <1 year

Conconi et al. 2003; Ferreri et al. 2005; Benetatos et al. 2006; Heinz et al. 2007

- 90Y ibritumomab tiuxetan for front line treatment of stage IE indolent OAL in 12 patients:
  - complete response in 10 patients
  - partial response in 2 patients

Esmaeili et al. 2009; Shome and Esmaeili 2008

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Treatment
Cp-eradicating antibiotic therapy

- A prospective phase II clinical trial
- **27 patients** (15 newly diagnosed and 12 relapsed)
- Cp infection in 11 pts
- **Treatment:** doxycycline 100 mg orally twice daily for 3 weeks
- CR/PR in 7 of 11 Cp-positive and 6 of 16 Cp-negative patients
- ORR 48%
- 2-year FFS 66%

Ferreri et al, Ann Oncol, 2006

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Treatment

Cp-eradicating antibiotic therapy

IELSG 39

International prospective phase 2 trial addressing the efficacy of first-line *Chlamydophila psittaci*-eradicating therapy with protracted administration of doxycycline followed by eradication monitoring and antibiotic re-treatment at infection re-occurrence in patients with newly diagnosed Ocular Adnexal Marginal Zone Lymphoma (OAMZL)

44 patients (accrual completed)

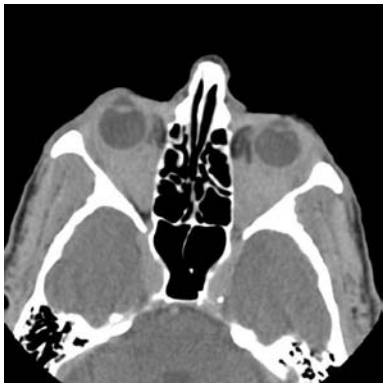
(A. Ferreri, E. Zucca, S. Govi)

Aim of the study is to establish in a prospective, multicentre phase 2 trial, the efficacy of an upfront targeted therapy consisting of *Cp*-eradicating therapy with prolonged administration of doxycycline followed by eradication monitoring and antibiotic re-treatment at infection re-occurrence in patients with newly diagnosed OAMZL.

Role of Radiotherapy

- Primary RT is considered to be the treatment of choice for indolent lymphomas

- Curative RT is appropriate even for bilateral presentations of indolent lymphomas



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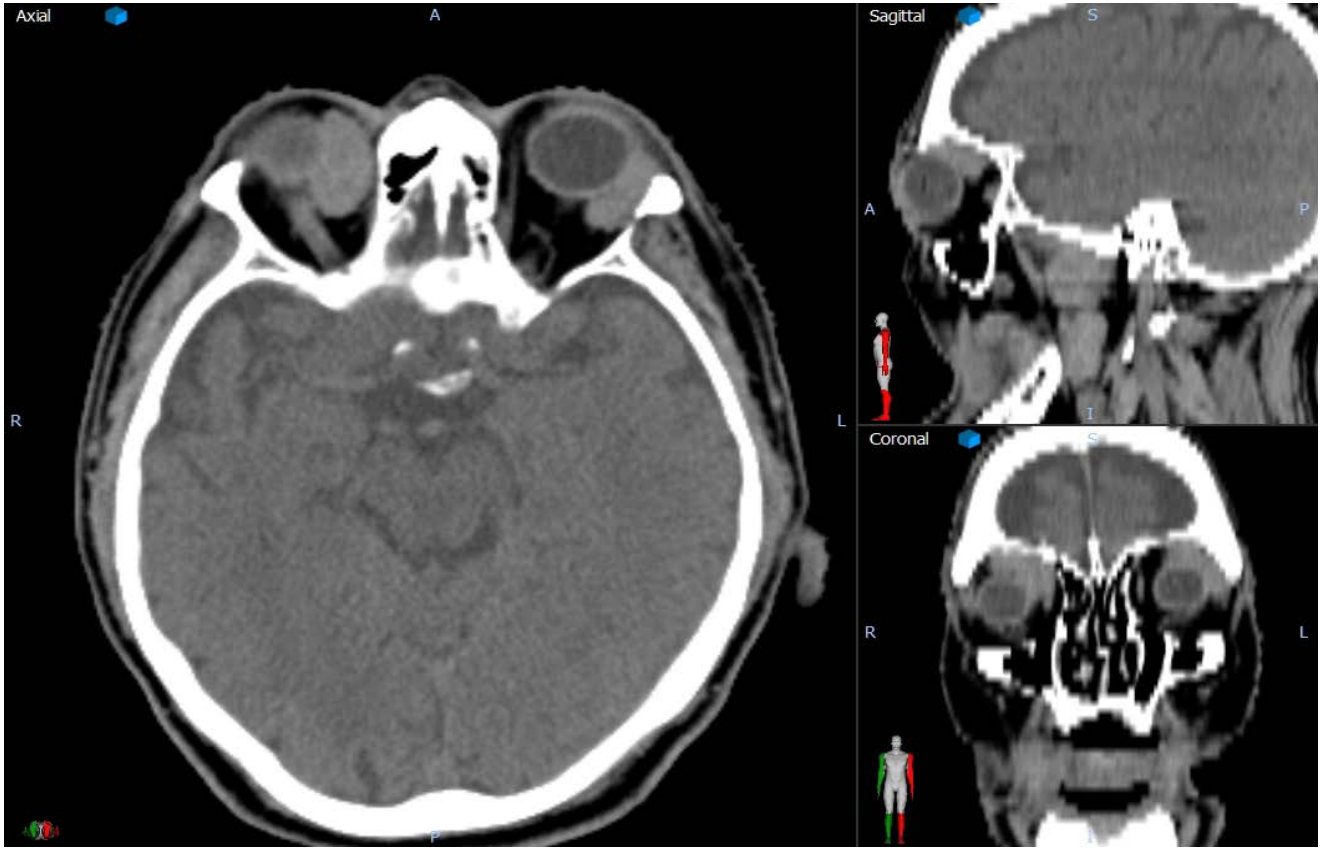

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Reference, year	No. of patients	Stage I, %	Gy	CR, %	LR, %	DR, %	Survival, %	LRM, %
Stafford et al. 2001	40	85	15-54	98	2	25	5-y RFS 88 5-y OS 74 5-y DSS 100	0
Le et al. 2002	31	100	30-40	100	0	16	10-y PFS 71 10-y OS 73	3
Fung et al. 2003	48	81	30.6	100	8	25	10-y OS 81 10-y DSS 100	0
Hasegawa et al. 2003	20	95	30	100	5	20	10-y PFS 70 10-y DSS 100	0
Tsang et al. 2003	30	97	25	97	17	10	5-y DFS 74 5-y OS 97	ND
Uno et al. 2003	50	100	20-46	98	6	6	5-y OS 91	2
Lee et al. 2005	29	100	30-45	100	3	0	3-y EFS 93 3-y OS 100	0
Ejima et al. 2006	42	100	30-36	84	10	10	5-y PFS 77 5-y DSS 100	0
Suh et al. 2006	48	96	30.6	96	6	0	10-y DFS 93 10-y DSS 98	2
Tanimoto et al. 2007	58	94	30-40	83	9	2	10-y PFS 72 10-y OS 92	0
Nam et al. 2009	66	100	20-45	97	3	7.5	5-y RFS 92 5-y OS 96.4	ND
Goda et al. 2011	89	100	25	99	2	22.5	7-y OS 91 7-y DSS 96% 7-y RFS 64%	4
Tran et al. 2013	25	92	24-25	100	4	8	5-y PFS 81 5-y OS 100	0

Role of RT

Local control: 85-100%

Distant recurrence: 10-25%

Long-term RFS or DFS: 70-90%

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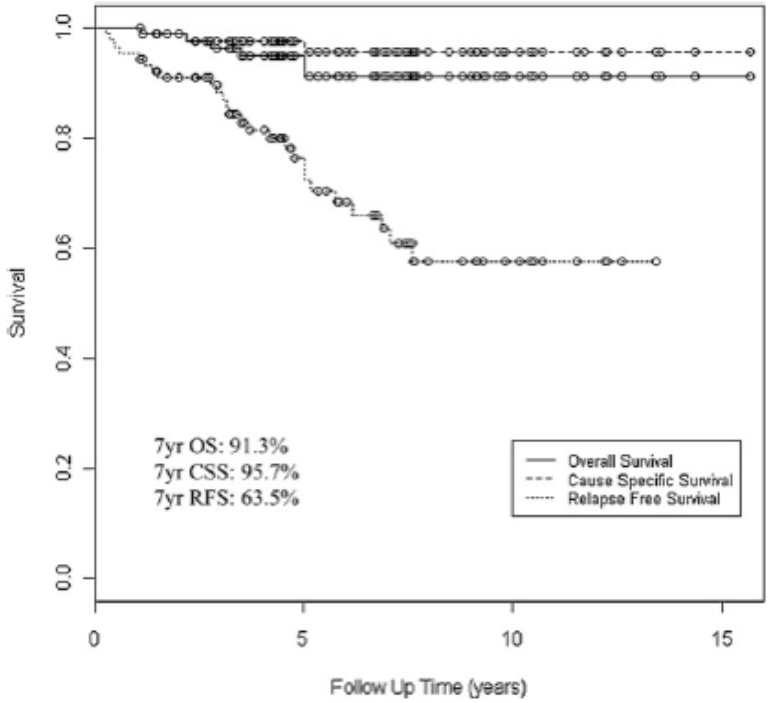
LOCALIZED ORBITAL MUCOSA-ASSOCIATED LYMPHOMA TISSUE LYMPHOMA MANAGED WITH PRIMARY RADIATION THERAPY: EFFICACY AND TOXICITY



89 pts with stage IE OAML treated with RT

Relapse: 22 pts (25%)

- local: 2 pts (9%)
- distant: 15 pts (68%)
- contralateral orbits: 5 pts (23%)

Goda et al, IJROBP, 2011

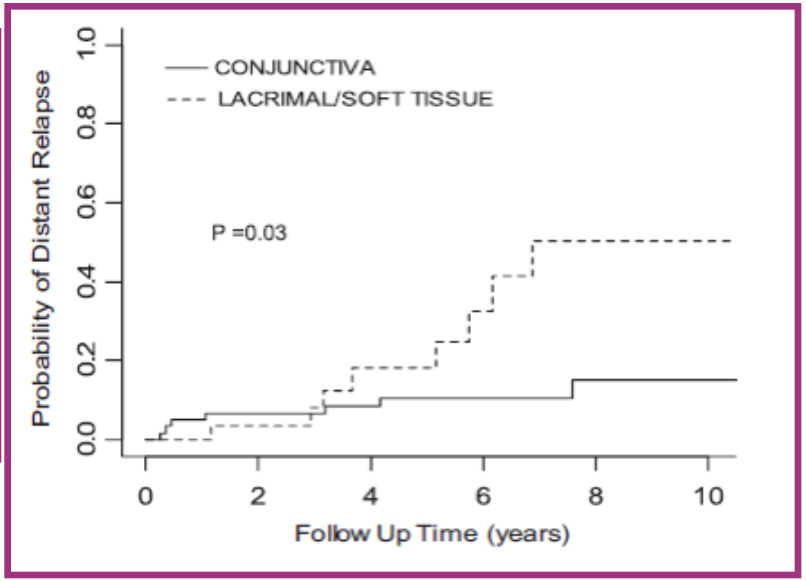
Disease subsite may be a significant prognostic factor

Table 4. Multivariate analysis (Cox model)

Factor	OS	DFS	FFTF
Age (<64 vs. ≥64 y)	<0.0001	0.002	NS
Grade (low vs. high)	0.05	0.02	NS
Response (CR vs. PR)	NS	0.004	0.002
Localization (conjunctiva vs. other)	NS	0.04	0.002
Complete staging (yes vs. no)	NS	0.01	0.03

Abbreviations: OS = overall survival; DFS = disease-free survival; FFTF = freedom from treatment failure; NS = not significant; CR = complete response; PR = partial response.

Martinet et al, IJROBP,2003



Goda et al, IJROBP,2011

Considerations on RT dose

- A dose of 24-25 Gy is required to provide optimal local control and minimize the rate of local failures in OAML

Principles of ISRT for Extranodal Sites

Site	Volume	Dose
Orbital	CTV = whole orbit	24-30 Gy (Indolent)
Tonsil	CTV=tonsil or tonsillar bed	Post-chemo CR = 30 Gy, PR = 40 Gy (DLBCL)
Salivary gland	CTV = superficial and deep lobe of the parotid Regional nodes if involved	24-30 Gy (Indolent) Post-chemo CR = 30 Gy, PR = 40 Gy (DLBCL)
Thyroid	CTV=Thyroid gland Consider including regional node (levels 3,4, and 6)	30 Gy (Indolent) Post-chemo CR = 30 Gy, PR = 40 Gy (DLBCL)
Breast	CTV = whole breast	30 Gy (Indolent) Post-chemo CR = 30 Gy, PR = 40 Gy (DLBCL)

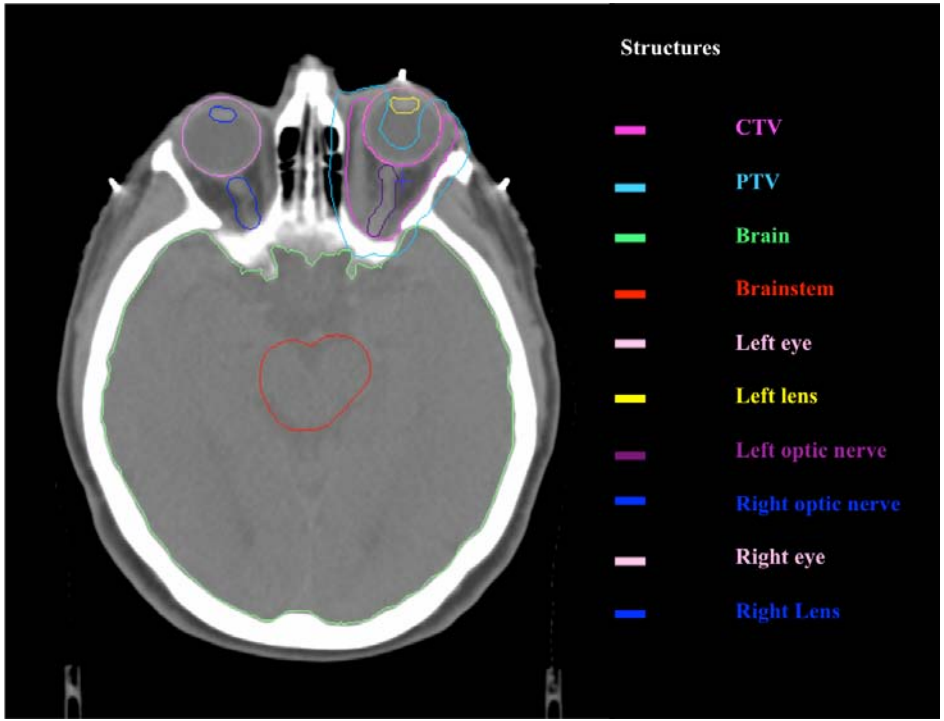
For most sites, the whole organ is the CTV

Considerations on RT volumes

For retrobulbar, lacrimal gland, and deep conjuctival lymphomas

The intent is to irradiate the whole orbit

CTV = outlined at the orbital bony borders and expanded to include any area of definite or suspected bony or extraorbital extension



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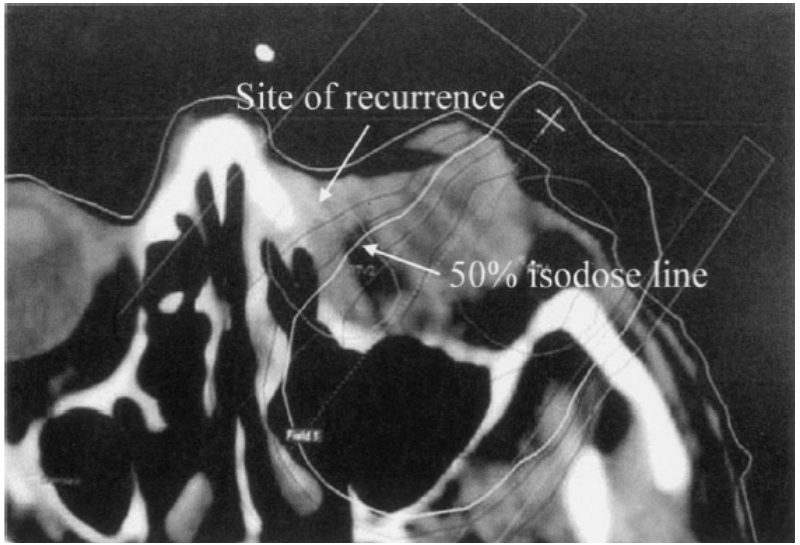
Is it necessary to treat the entire orbit?

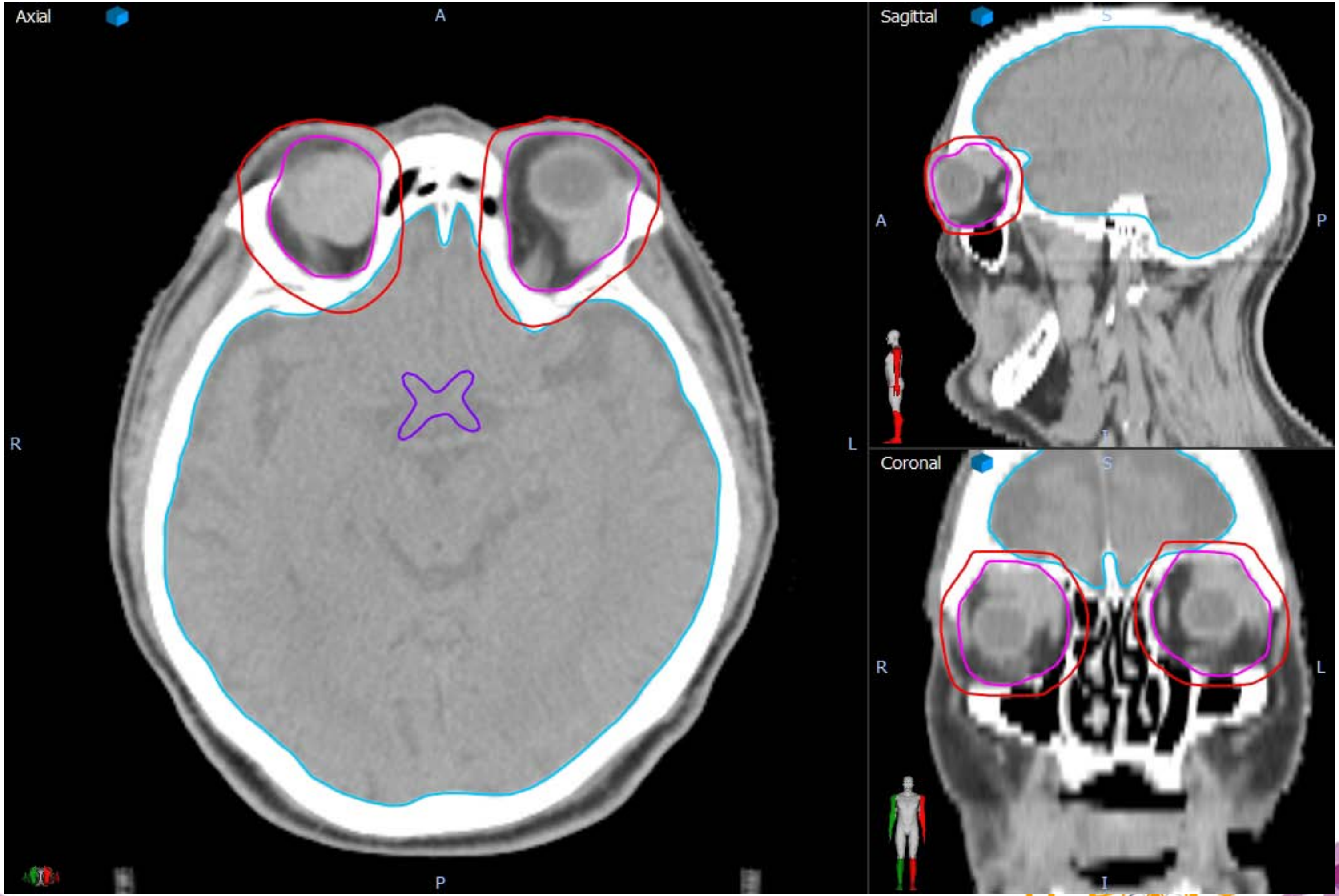
Characteristics	Whole orbit	Partial orbit
Patients (*n*)	11 (12 eyes)	12
Age (y)		
Range	40–82	34–81
Median (*n*)	55	70
Gender		
Male	2	8
Female	9	4
Grade (*n*)		
Low	8 (9 eyes)	10
Intermediate/high	3	2
Chemotherapy (n)	2	1
Stage (*n*)		
1E	9 (10 eyes)	11
IV	2	1
Dose (Gy)		
Low grade		
Range	20–30	20–27
Median	25.2	25.2
Intermediate/high grade		
Range	24–39.6	39.6–40
Median	39.6	

Pfeffer et al, IJROBP, 2004

- CR in all pts
- Intraorbital recurrence in previously uninvolved areas not included in the initial target volume: 4 pts (33%) with low-grade lymphoma treated with partial orbit RT



Partial orbital irradiation has been associated with higher risk of local failure

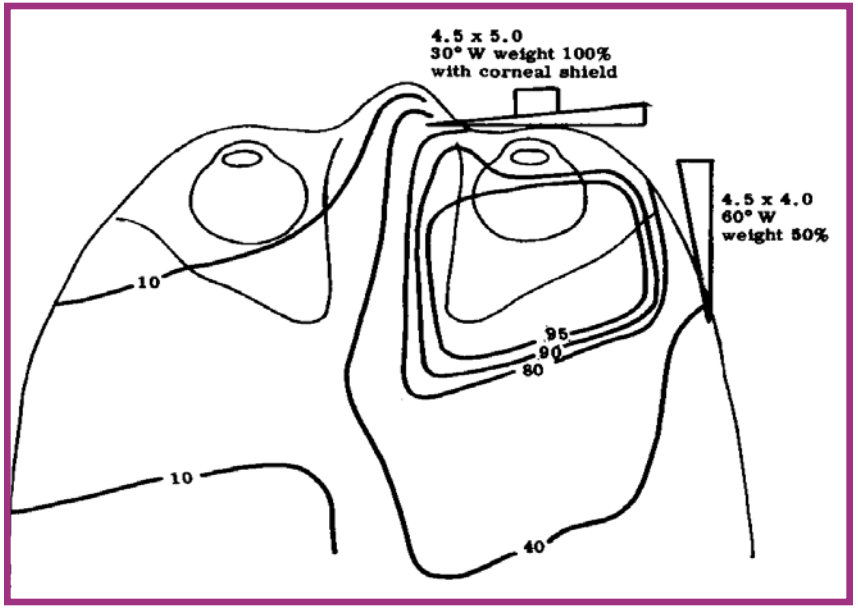


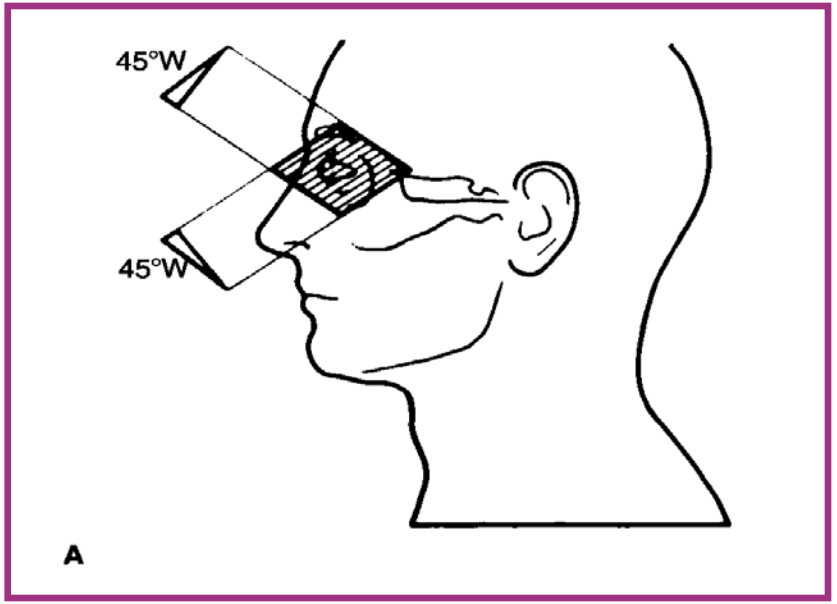
RT technique

- The whole orbit may be treated with 3D conformal or IMRT techniques
- The conjunctival sac and lacrimal gland may be treated with en face electrons
- Bolus should be used in all cases of conjunctival/superficial involvement or definite or suspected extension
- Lens shielding may be used for disease limited to conjunctiva/eyelid, if appropriate and only if there is confidence that disease will not be shielded

RT techniques (3D-CRT)

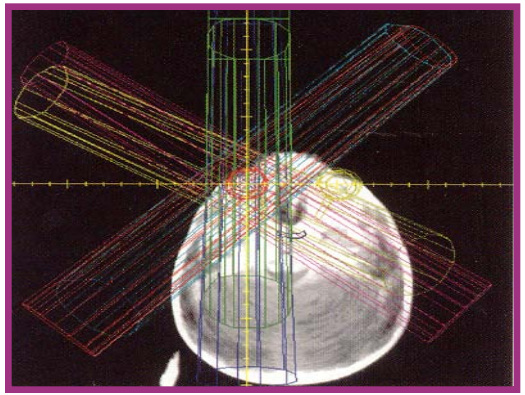
Whole orbit – wedge pair beams

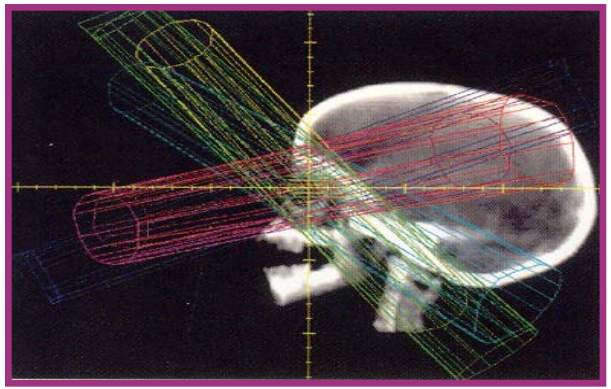


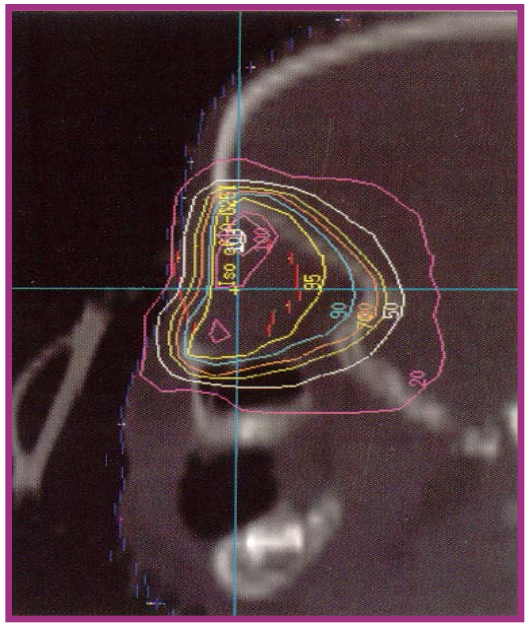


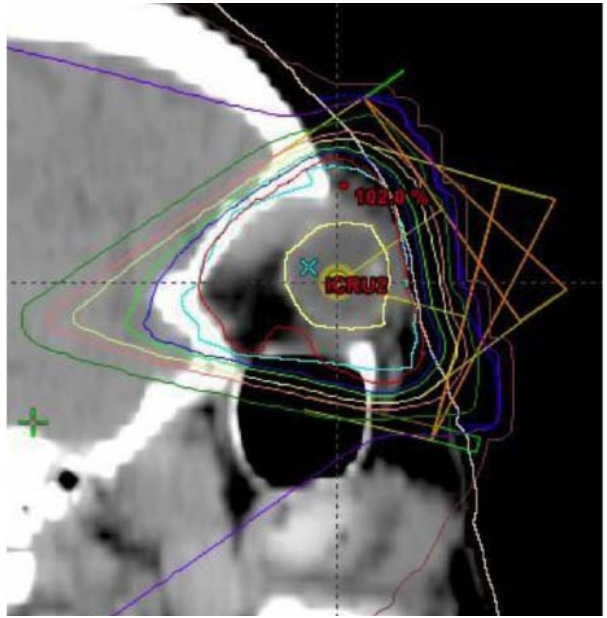
3D CRT

A technique such as a superior-inferior wedge pair has the advantage of sparing the controlateral orbit should metachronous controlateral disease require RT subsequently









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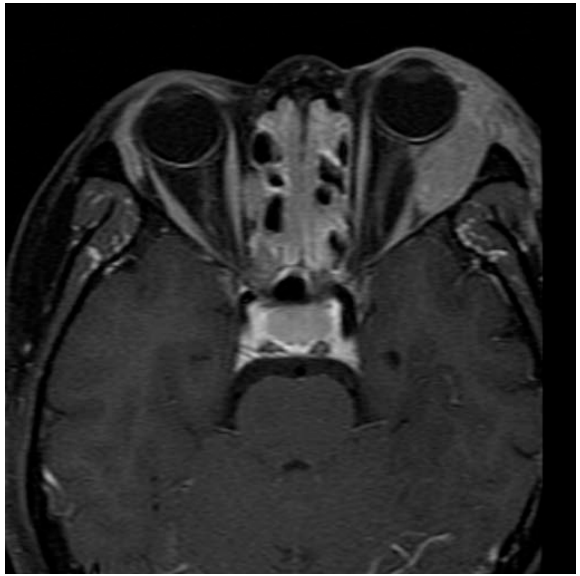
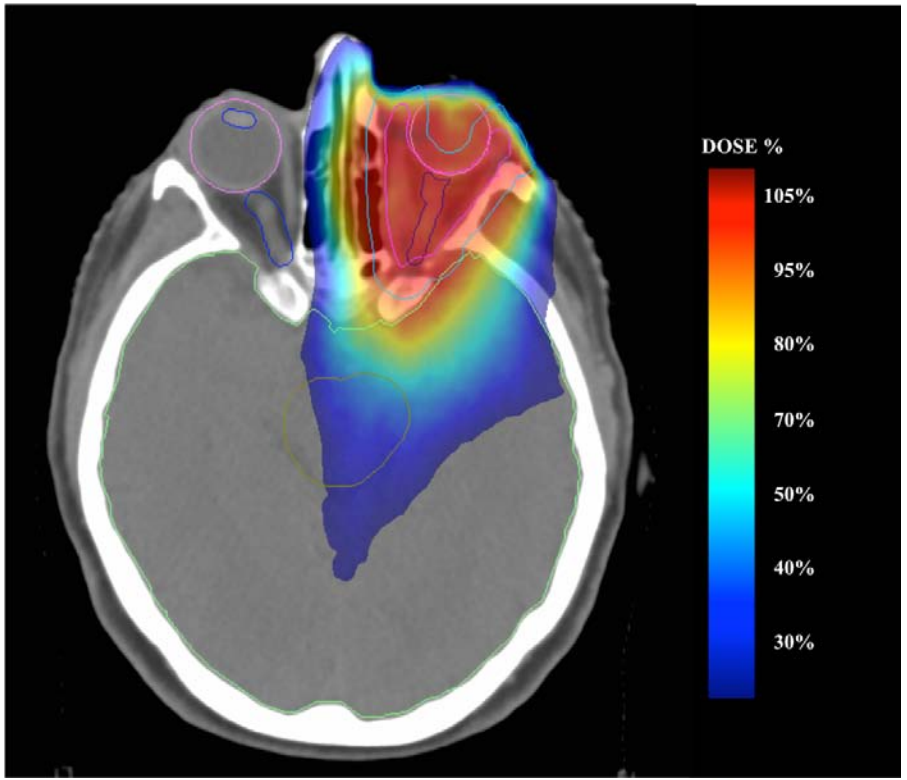
IMRT (VMAT)





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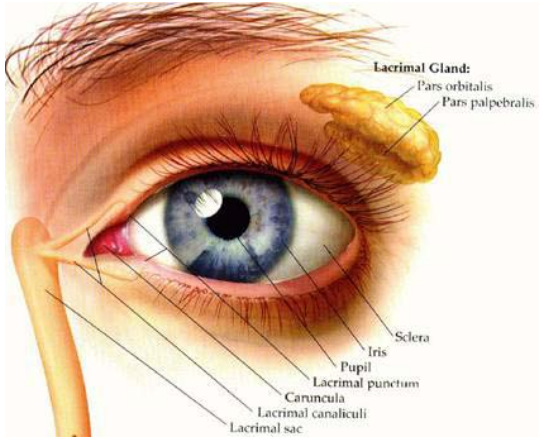
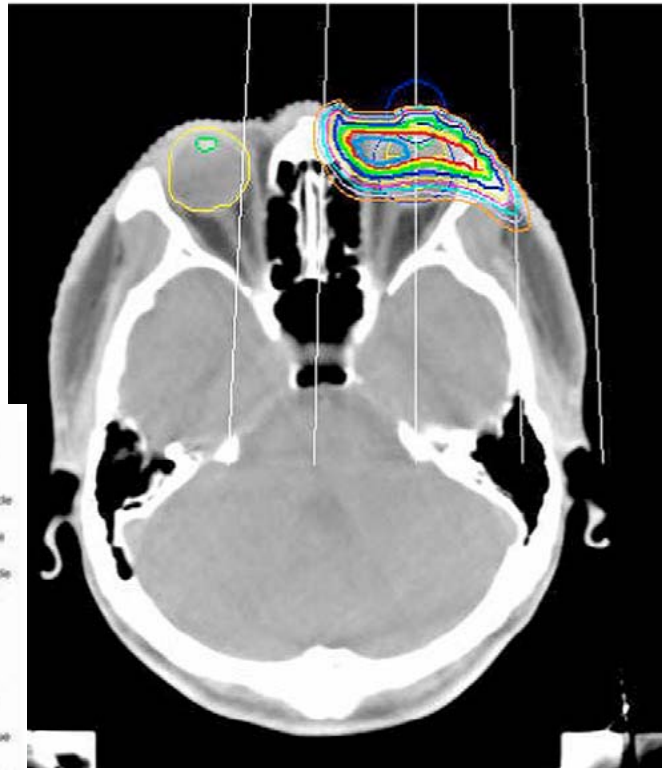
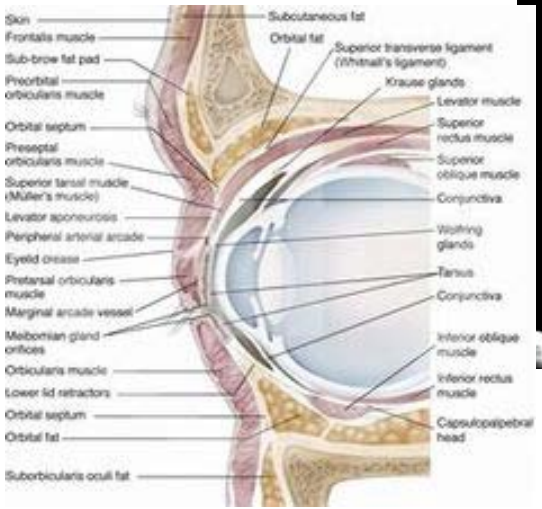
Tumors confined to the conjunctiva or eyelid

CTV = entire conjunctival reflection to the fornices (not to include the entire orbit)







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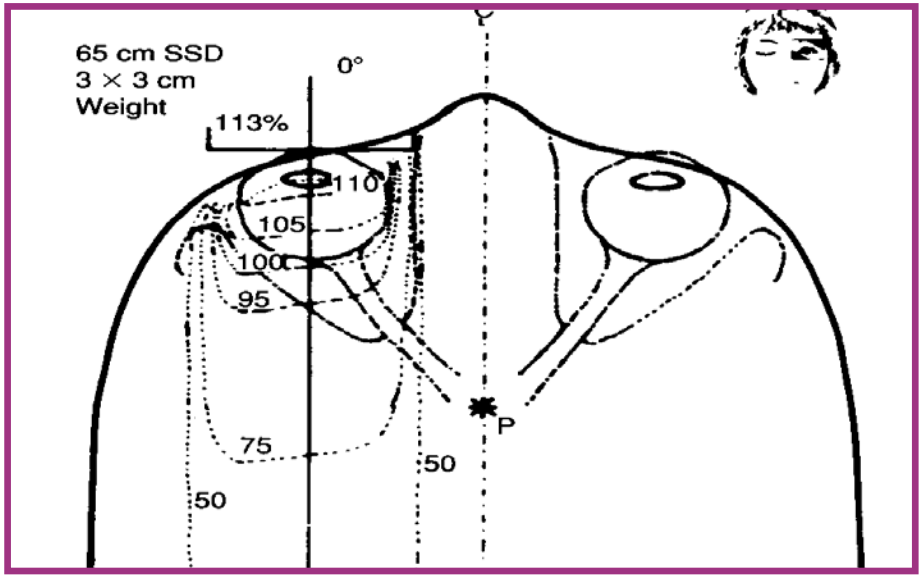
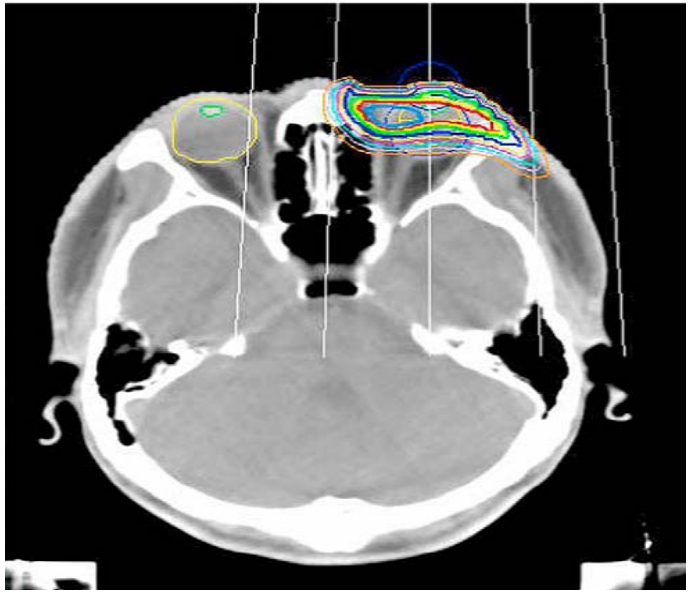
Tumors confined to the conjunctiva or eyelid (CTV = entire conjunctival reflection to the fornices)





- This situation is usually approached with a direct electron beam with bolus
- In selected cases, a lens shield may be used to reduce the risk of cataract formation
- Care must be taken not to shield parts of the conjunctiva because the whole conjunctival sac is the CTV

Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Volumes: indolent disease

- CTV: for most cases of indolent NHL, the entire bony orbit including definite or suspected extraorbital extensions. When disease is limited to the conjunctiva, the CTV includes the entire conjunctival sac and local extensions to eyelid.
- PTV margin is normally 5 mm.

Dose: indolent disease

Dose: 24 to 25 Gy in 1.5- to 2-Gy fractions.

Yahalom et al, IJROBP, 2015

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Lens shielding

- Aim: to reduce the incidence of cataract
- Caution: inadvertent tumor under dosing
- Some reports attributed local relapses to inadvertent partial shielding of tumor *(Uno et al. 2003; Fung et al. 2003)*
- Other reports suggest that the careful use doesn't lead to treatment failure *(Le et al. 2002; Martinet et al. 2003; Son et al. 2010; Tran et al. 2013)*
- ILROG guidelines: lens shielding may be used for disease limited to conjuctiva/eyelid, if appropriate and only if disease will not be shielded

Bolus

- Aim: to ensure that conjunctival tumors or other very superficially located lesions receive the full dose of radiation
- In most reports, local failure in superficial disease sites occurred with no mention of the use of bolus *(Uno et al. 2003; Yamashita et al. 2008; Son et al. 2010)*
- In another report bolus was not used routinely unless there was frank skin involvement, without an apparent increase in relapse rate *(Goda et al. 2011)*
- ILROG guidelines: bolus should be used in all cases of conjunctival/superficial involvement or definite or suspected extension

Ocular adnexae DLBCL

Role of RT

- Consolidation RT after R-chemotherapy

- Radical RT in patients “unfit” for chemotherapy

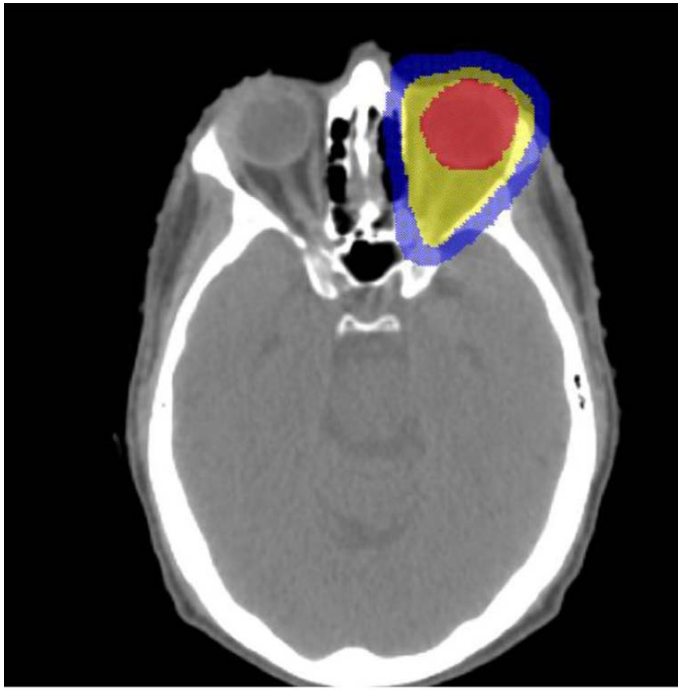
Considerations on RT volume

• **GTV** = residual disease after chemotherapy (if any) for a boost dose

• **CTV** = entire orbit

• **PTV** margin = normally 5 mm

• DLBCL of the lacrimal gland alone
→ CTV for consolidation RT limited to lacrimal gland



Yahalom et al, IJROBP, 2015

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Considerations on RT dose

- CR after chemotherapy → 30 Gy

- PR after chemotherapy
- Relapse
- RT alone (pts “unfit” for chemo)

→ 30 – 36 Gy to whole orbit and extensions

→ 40 – 45 Gy to residual GTV (depending on the volume and proximity to critical structures)

Yahalom et al, IJROBP, 2015

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Toxicity

- Immediate toxicity consists of mild to moderate cutaneous or conjunctival reactions
- Long-term complications are observed in up to 50% of patients
- The complications are relatively minor and include cataract formation (30-50%) and mild xerophthalmia (20-40%)
- RT doses above 36 Gy may result in deleterious ophthalmologic toxicity such as ischemic retinopathy, optic atrophy, corneal ulceration, neovascular glaucoma, associated with significant vision loss


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The role of the radiation oncologist in the multimodality treatment of lymphomas

Lena Specht MD DMSc
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Chief Oncologist, Depts. of Oncology and Haematology, Rigshospitalet, Copenhagen
Vice-chairman, International Lymphoma Radiation Oncology Group

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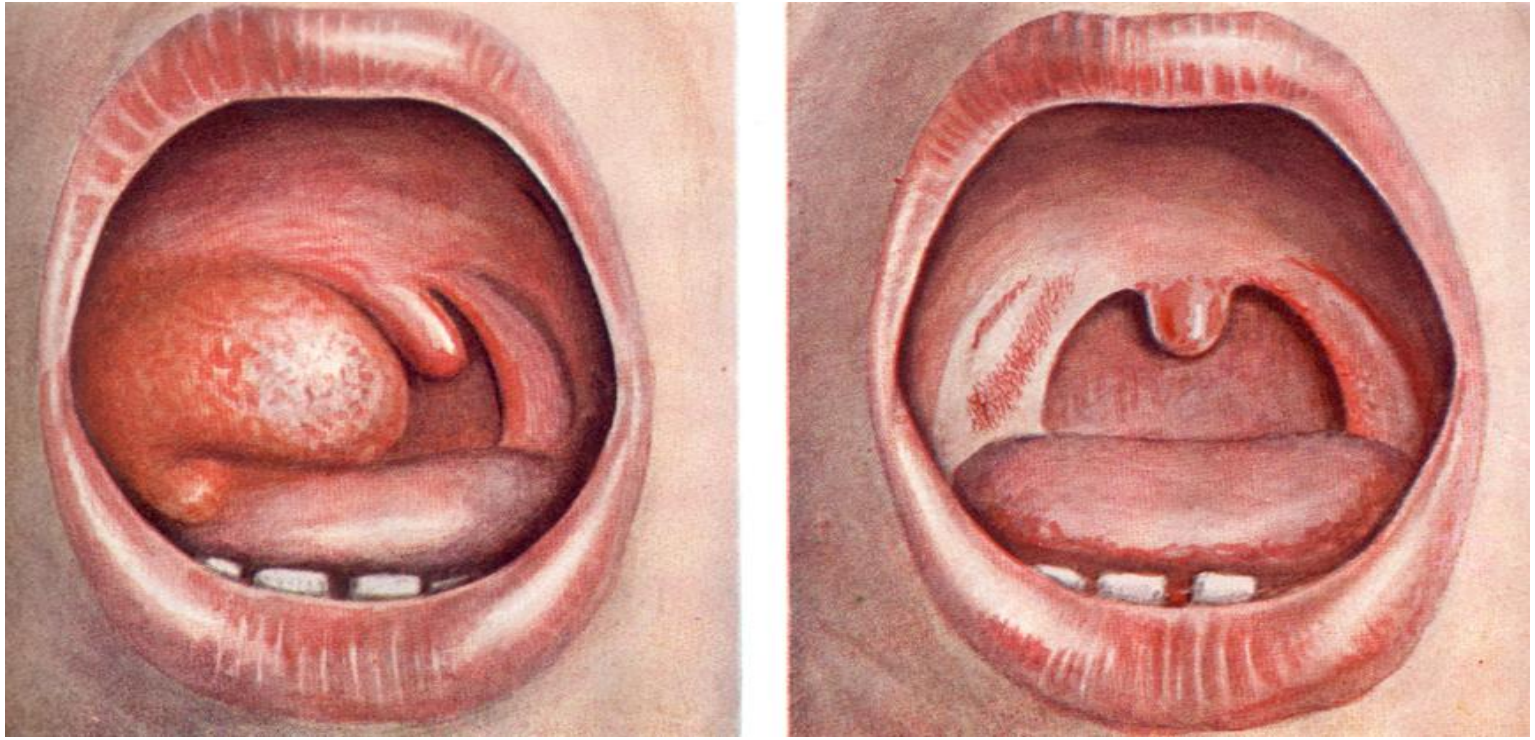
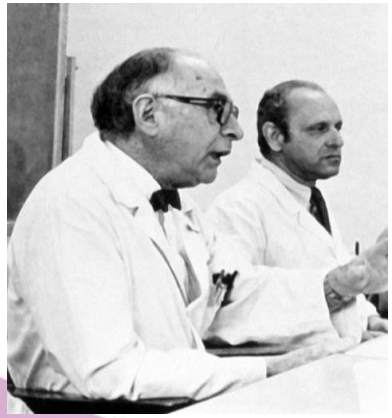
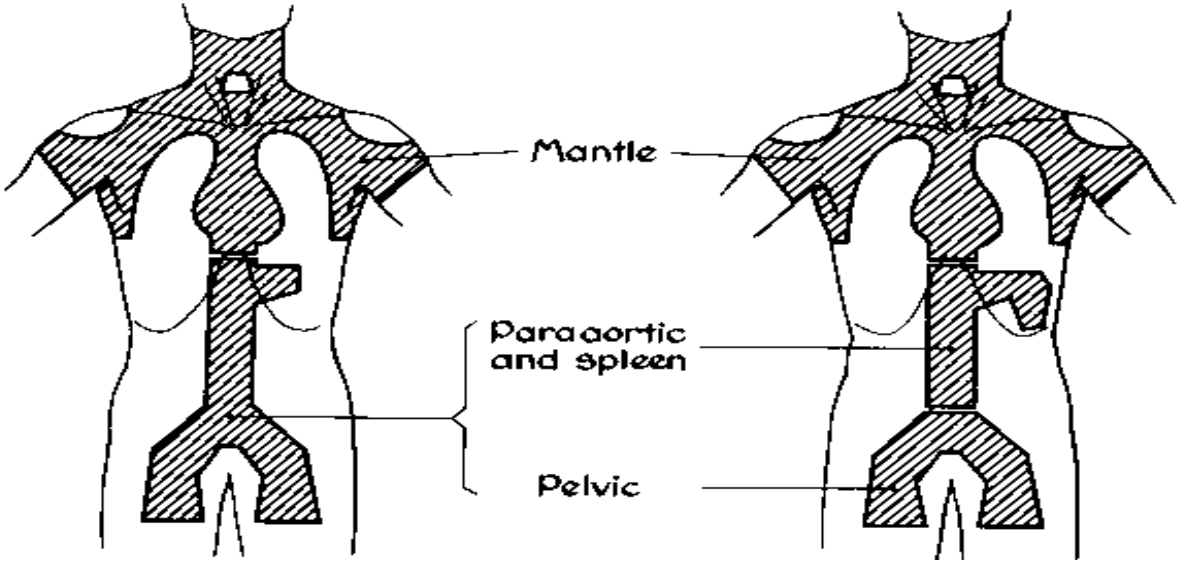


Lymphosarcoma of right tonsil, before treatment November 1916, alive and free of symptoms April 1930

Prophylactic irradiation of clinically uninvolved regions → extended field RT





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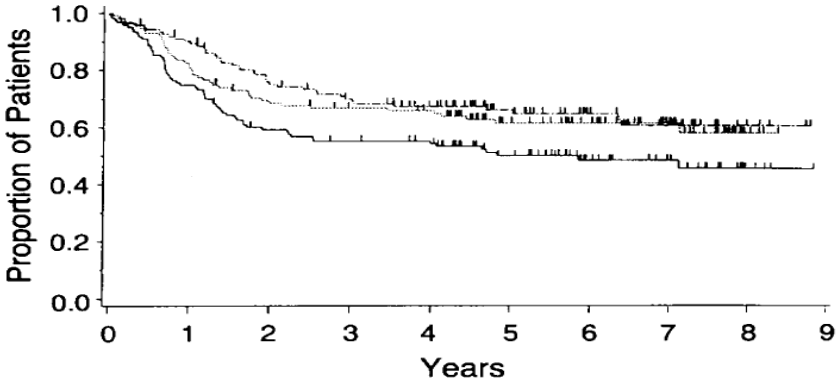
Effective chemotherapy was developed

Hodgkin lymphoma
Canellos et al. NEJM 1992; 327: 1478-84



Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
MOPP	123	62 (50)	4.84
ABVD	115	44 (38)	None
MOPP–ABVD	123	43 (35)	None
All	361	149 (41)	—

Figure 1. Failure-free Survival According to Primary Chemotherapeutic Regimen.

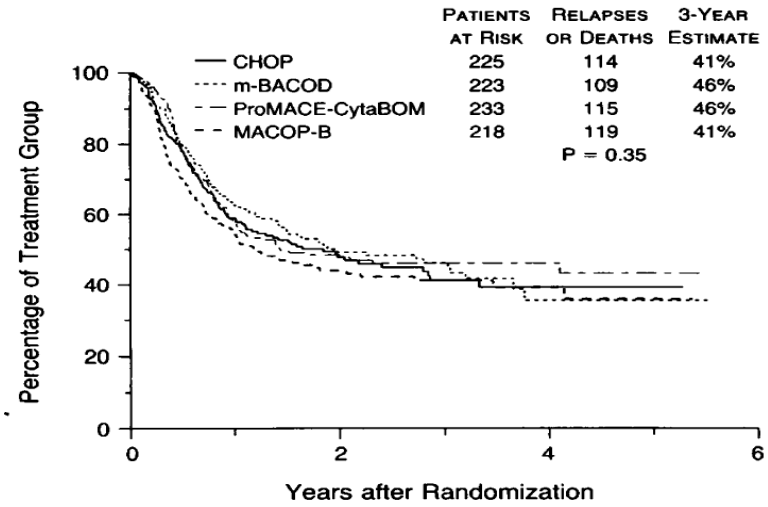


Figure 1. Time to Treatment Failure in the Treatment Groups. The three-year estimate is of survival without disease.

Aggressive non-Hodgkin lymphoma
Fisher et al. NEJM 1993; 328: 1002-6

”There is no doubt that radiation remains the most active single modality in the treatment of most types of lymphoma”

James O. Armitage

- Its role has changed
- Now part of combined modality treatment in most situations
- Often as consolidary treatment after primary chemotherapy

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Challenges in lymphoma treatment

- > 70 different diseases, classified on the basis of morphology, immunophenotype, genetic and clinical features:

  Expert pathology is needed

- The diseases may be localized or disseminated, nodal or extranodal, anywhere in the body:

  Expert imaging is needed

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Challenges in lymphoma treatment

- Modern treatment includes:
  - Radiotherapy
  - "Classical" chemotherapy
  - Antibodies
  - Small molecules

Expert radiation and medical oncology are needed

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Role of radiotherapy

Primary treatment for early stage indolent lymphomas

Consolidation therapy for early stage aggressive lymphomas (inc. HL)

Treatment of bulky or residual mass in advanced aggressive lymphoma

Treatment of recurrent disease +/- systemic treatment

Part of conditioning for autologous transplant for recurrent/refractory disease

Palliative treatment in advanced indolent lymphoma

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Role of radiation (and medical) oncology

- Close collaboration from the outset between systemic treatment (medical oncologist/ hematologist/clinical oncologist) and local treatment (radiation oncologist/clinical oncologist)
- The entire treatment strategy must be planned from the outset to allow optimal treatment
- Treatment modifications during treatment must be decided with due regard to both local and systemic treatment options
- Treatment interactions must be considered

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Multidisciplinary set-up

Haemato-pathology

Radiology,

Nuclear Medicine

Medical Oncology,
Haematology,
Clinical Oncology

Radiation Oncology,

Clinical Oncology

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Responsibilities of the radiation oncologist

- Ensure that all information necessary for optimal target definition is available for radiotherapy planning
- Relevant imaging of all lymphoma involvement before chemotherapy (and operation)
- Optimally see the patient before any treatment

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Responsibilities of the radiation oncologist

- Ensure that the advantages that can be obtained with modern radiotherapy are used to the benefit of the patient:
  - Optimal target coverage
  - Lowest target dose necessary for the highest chance of local lymphoma control
  - Lowest possible risk of significant long-term side effects

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Ensure that the unique biology of lymphoid malignancies is exploited in RT planning and delivery

In general no survival advantage has been demonstrated with the extended fields of the past

The unique radiosensitivity of lymphoid malignancies means that dose constraints for normal tissues used for solid tumours are not applicable

Modern conformal techniques should be used for lymphomas, not primarily as in solid tumours to allow a high target dose to be delivered, but to minimize the risk of long-term complications

Different techniques are applicable to different disease localizations and disease volumes, no two patients are the same

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Constraints, are they useful for lymphomas?

Organ at risk	Limiting dose/volume
Brain stem	If whole organ irradiated, $D_{max} < 54$ Gy to any part of the volume If partial volume irradiated, $D_{1-10\ cm^3} \leq 59$ Gy
Breast	Minimise volume inside PTV, particularly in young women ≤30 years. Mean dose ≤ 2 Gy
Cochlea	Mean dose ≤ 45 Gy
Coronary artery	Minimise volume inside treatment field and keep doses as low as possible without compromising on PTV coverage
Heart	Mean dose < 26 Gy; $D_{100} < 30$ Gy $V_{30} < 46\%$; $V_{33} < 60\%$, $V_{38} < 33\%$, $V_{42} < 20\%$
Kidney	Single kidney irradiated: V_{15} of 65–70%, Both kidneys irradiated: V_{15} of 20–25% for each kidney; mean dose < 18 Gy. Partial kidney irradiation (all constraints are for combined kidneys): mean dose < 18 Gy $V_{28} < 20\%$, $V_{23} < 30\%$, $V_{20} < 32\%$, $V_{12} < 55\%$. If mean dose to one kidney >18 Gy, V_6 for remaining kidney <30%
Lens	Maximum dose of 6 Gy to any part of the volume unless compromising PTV coverage
Liver	Mean dose < 32 Gy; V_{40} of 30–35%; D_{100} of 25 Gy, D_{66} of 28 Gy, D_{33} of 38 Gy
Lung (whole)	$V_{20} \leq 30\%$, Mean lung dose (MLD) ≤ 20 Gy
Oesophagus	Mean dose < 34 Gy, $V_{35} < 50\%$
Optic chiasm	$D_{max} < 55$ Gy to any part of the volume
Optic nerve	$D_{max} < 55$ Gy to any part of the volume
Ovary	D_{max} <10 Gy to any part of the volume outside PTV. If inside PTV discuss individual case with clinician
Parotid	Bilateral irradiation: mean dose < 25 Gy. Unilateral irradiation: mean dose < 20 Gy to the contralateral parotid
Small bowel	For individual loops $V_{15} < 120\ cm^3$ For whole peritoneal cavity $V_{45} < 195\ cm^3$
Spinal cord	$D_{max} \leq 50$ Gy to any part of the volume
Stomach	$D_{100} < 45$ Gy
Testis	Maximum dose of 2 Gy to any part of the volume
Thyroid	$D_{100} < 45$ Gy

Hoskin PJ et al, Clin Oncol 2013; 25: 49-58

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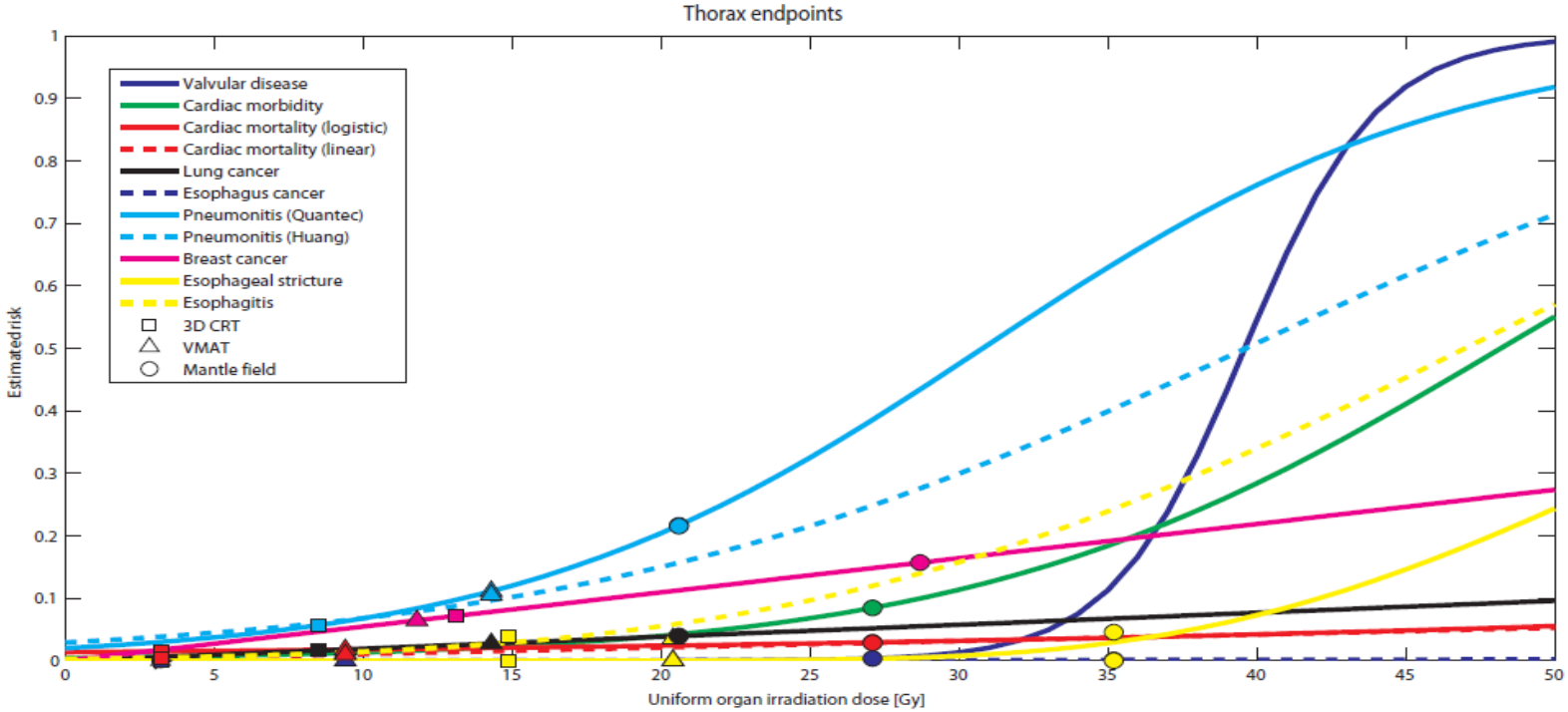
Ideally, normal tissue complication probability models for all relevant risk organs should be combined for each treatment plan



Brodin NP et al, IJROBP 2014;88:433-45

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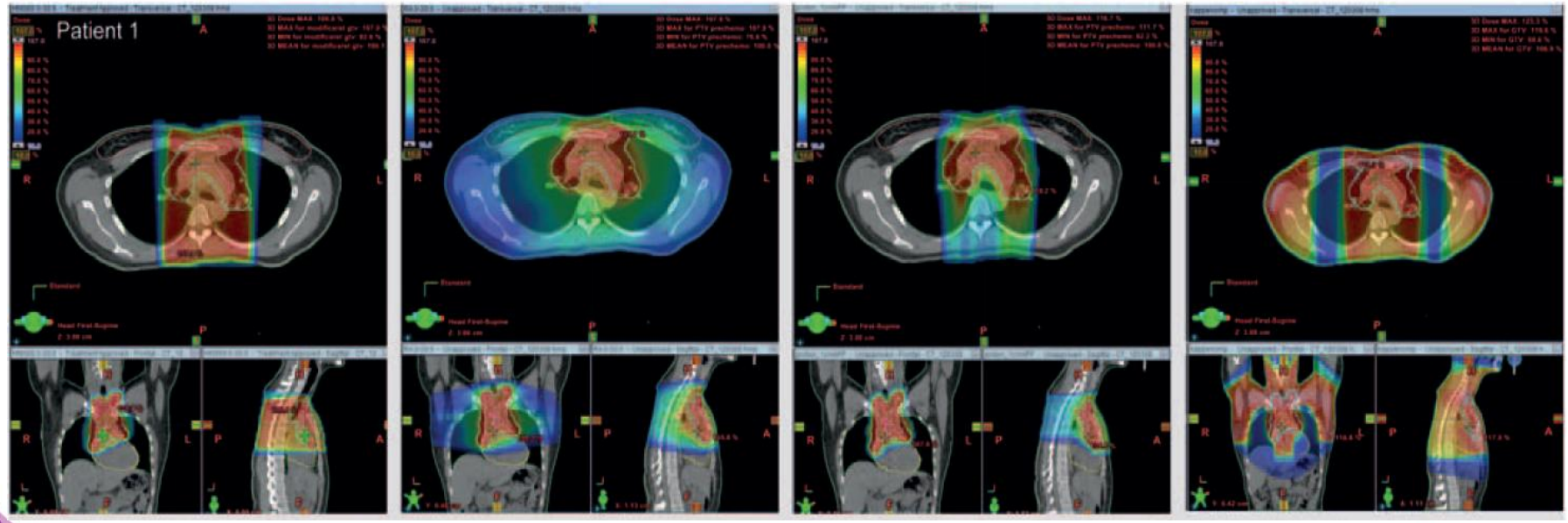
Different modern techniques vs. extended fields of the past

AP-PA IMRT IMPT Mantle field



Maraldo M et al. Ann Oncol 2013; 24: 2113-8

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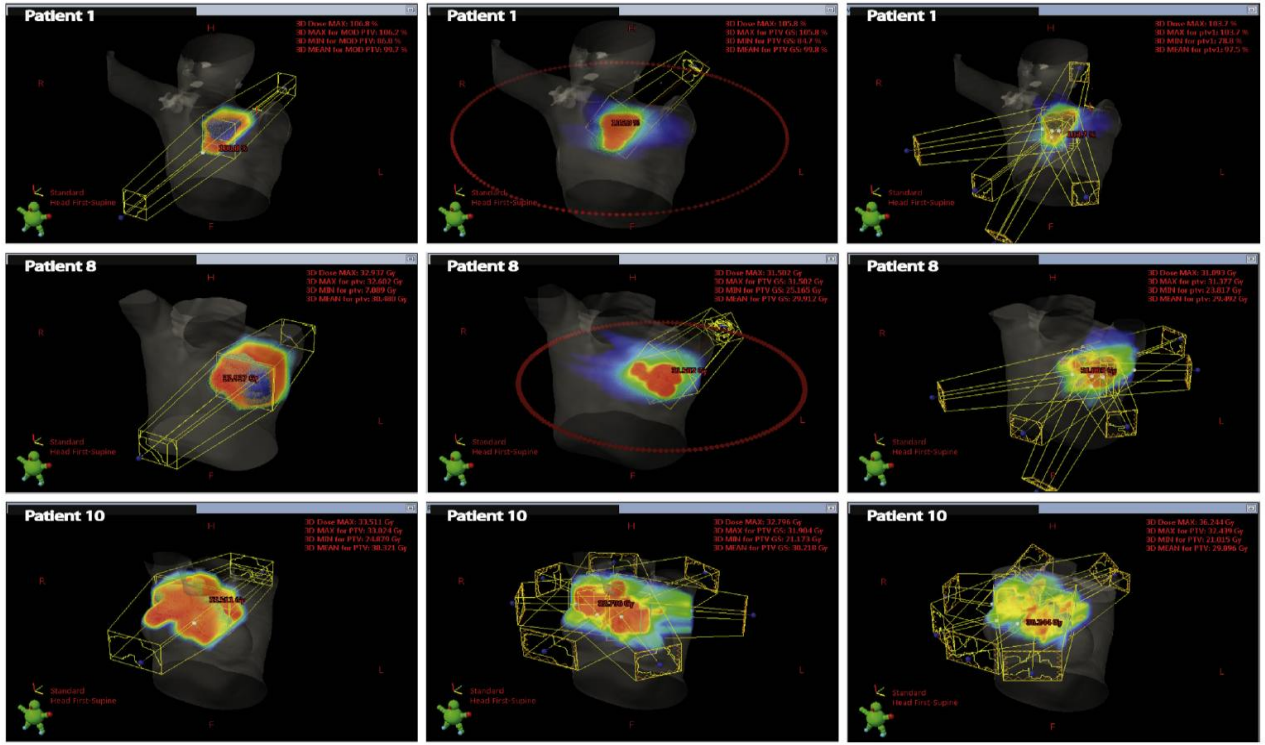
Same patient, different solutions



Maraldo M et al. IJROBP 2015; 92: 144-52

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Thank you for your attention

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Extranodal lymphomas: Skin

Lena Specht MD DMSc
Professor of Oncology, University of Copenhagen, Denmark
Chief Oncologist, Depts. of Oncology and Haematology, Rigshospitalet, Copenhagen
Vice-chairman, International Lymphoma Radiation Oncology Group

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Primary cutaneous lymphomas

- Heterogenous group of T- and B-cell lymphomas
- Natural history often more indolent than nodal lymphomas of same histologic subtype
- Solitary or localised skin lesions treated with involved field radiotherapy, long term local control rate generally 80-100 %

(Willemze et al, Blood 1997;90:354-71)

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European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas

Nancy J. Senff,[1] Evert M. Noordijk,[2] Youn H. Kim,[3] Martine Bagot,[4] Emilio Berti,[5] Lorenzo Cerroni,[6] Reinhard Dummer,[7] Madeleine Duvic,[8] Richard T. Hoppe,[9] Nicola Pimpinelli,[10] Steven T. Rosen,[11] Maarten H. Vermeer,[1] Sean Whittaker,[12] and Rein Willemze[1]

(Blood. 2008;112:1600-1609)

Table 1. Overview of previously and currently used classification systems for cutaneous lymphomas and clinicopathologic features of the different CBCL entities

	Previous and current classifications		
EORTC 1997	PCI/ PCMZL	PCFCCL	PCLBCL of the leg
WHO 2001	EMZL	cFCL	DLBCL
		DLBCL	
WHO-EORTC 2005	PCMZL	PCFCL	PCLBCL, LT
WHO 2008	EMZL	PCFCL	PCLBCL, LT
Clinicopathologic features			
Clinical features	Solitary or multiple papules, plaques, or nodules preferentially localized on the extremities	Solitary or grouped tumors presenting on the head or on the trunk	Solitary or multiple tumors presenting mainly on the leg(s) and rarely at other sites
	Sometimes associated with Borrelia burgdorferi infection	Cutaneous relapses in 20%	Frequent relapses and extracutaneous dissemination
	Frequent cutaneous relapses	Extracutaneous dissemination in 5% to 10%	
	Rarely extracutaneous dissemination		
Histopathology	Patchy or diffuse infiltrates composed of small B cells, including marginal zone (centrocyte-like) cells, lymphoplasmacytoid cells, and plasma cells	Follicular, follicular and diffuse, or diffuse infiltrates composed of neoplastic follicle center cells , usually a mixture of centrocytes and variable numbers of centroblasts	Diffuse infiltrates with a predominance or confluent sheets of of centroblasts and immunoblasts
Immunophenotype	Monotypic cIg, CD79a$^+$, Bcl-2$^+$, CD5$^-$, cyclin D1$^-$, Bcl-6$^-$, CD10$^-$, MUM-1$^+$ (on plasma cells)	Monotypic sIg or absence of sIg, CD20$^+$, CD79a$^+$, Bcl-6$^+$, Bcl-2$^-$, MUM-1$^-$, CD10±, FOXP1$^{-(\pm)}$	Monotypic sIg and/or cIg, CD20$^+$, CD79a$^+$, Bcl-6$^{+(-)}$, CD10$^-$, Bcl-2$^+$, MUM-1$^+$, FOXP1$^+$
Prognosis	5-year survival: > 95%	5-year survival: 95%	5-year survival: 50%

PCI indicates primary cutaneous immunocytoma; PCMZL, primary cutaneous marginal zone lymphoma; PCFCCL, primary cutaneous follicle center cell lymphoma; PCLBCL of the leg, primary cutaneous large B-cell lymphoma of the leg; EMZL, extranodal marginal zone lymphoma; cFCL, cutaneous follicle center lymphoma (for cases with a follicular or follicular-diffuse growth pattern); DLBCL, diffuse large B-cell lymphoma (for cases with a diffuse growth pattern); PCFCL, primary cutaneous follicle center lymphoma; and PCLBCL, LT, primary cutaneous diffuse large B-cell lymphoma, leg type.

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Table 4. Recommendations for initial management of the 3 main types of CBCL

Disease type and extent	First-line therapy	Alternative therapies
PCMZL		
Solitary/localized	Local radiotherapy Excision Antibiotics*	IFN-α i.l. Rituximab i.l. i.l. steroids
Multifocal	Wait-and-see Local radiotherapy Chlorambucil† Rituximab i.v. Antibiotics*	IFN-α i.l. Rituximab i.l. Topical or i.l. steroids
PCFCL		
Solitary/localized	Local radiotherapy Excision	IFN-α i.l. Rituximab i.l.
Multifocal	Wait-and-see Local radiotherapy Rituximab i.v.	R-CVP/CHOP‡
PCLBCL, LT		
Solitary/localized	R-CHOP ± IFRT	Local radiotherapy Rituximab i.v.
Multifocal	R-CHOP	Rituximab i.v.

IFRT indicates involved field radiotherapy; i.l., intralesional; and i.v., intravenous.
*In case of evidence for *B burgdorferi* infection.
†Or other single or combination regimens appropriate for low-grade B-cell lymphomas.
‡In exceptional cases or for patients developing extracutaneous disease.

ESMO guidelines, Ann Oncol 2013; 24 (Suppl 6): 149-54

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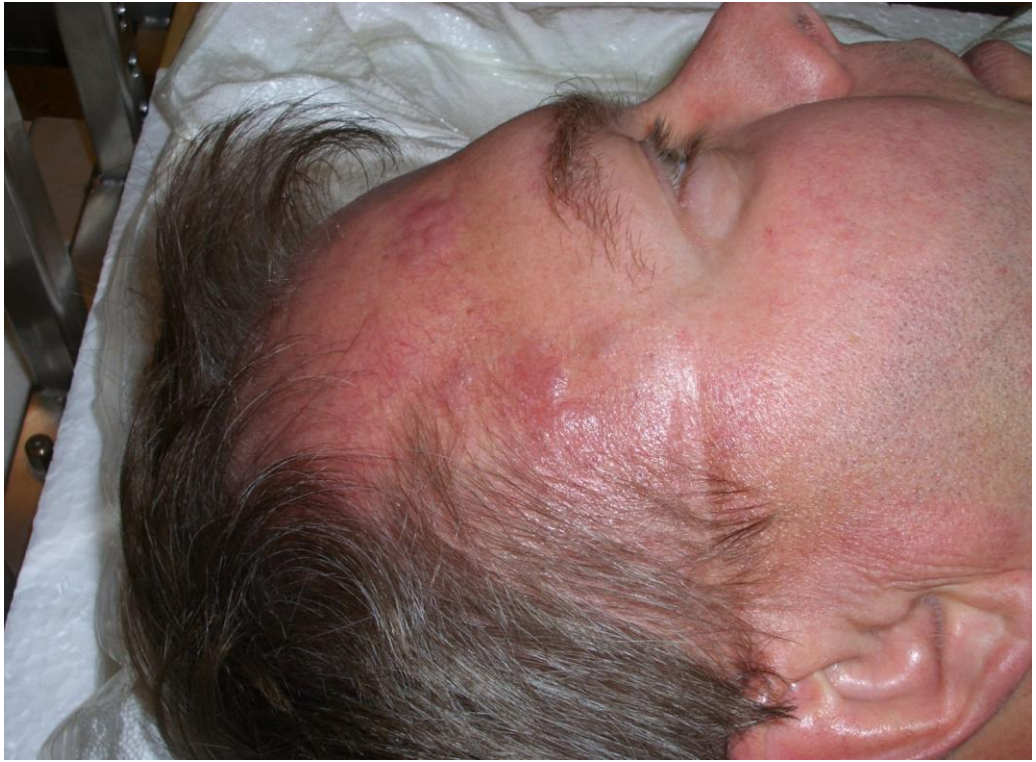
Guidelines

Modern Radiation Therapy for Primary Cutaneous Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Lena Specht, MD, PhD,* Bouthaina Dabaja, MD,† Tim Illidge, MD, PhD,‡ Lynn D. Wilson, MD,§ and Richard T. Hoppe, MD||, on behalf of the International Lymphoma Radiation Oncology Group

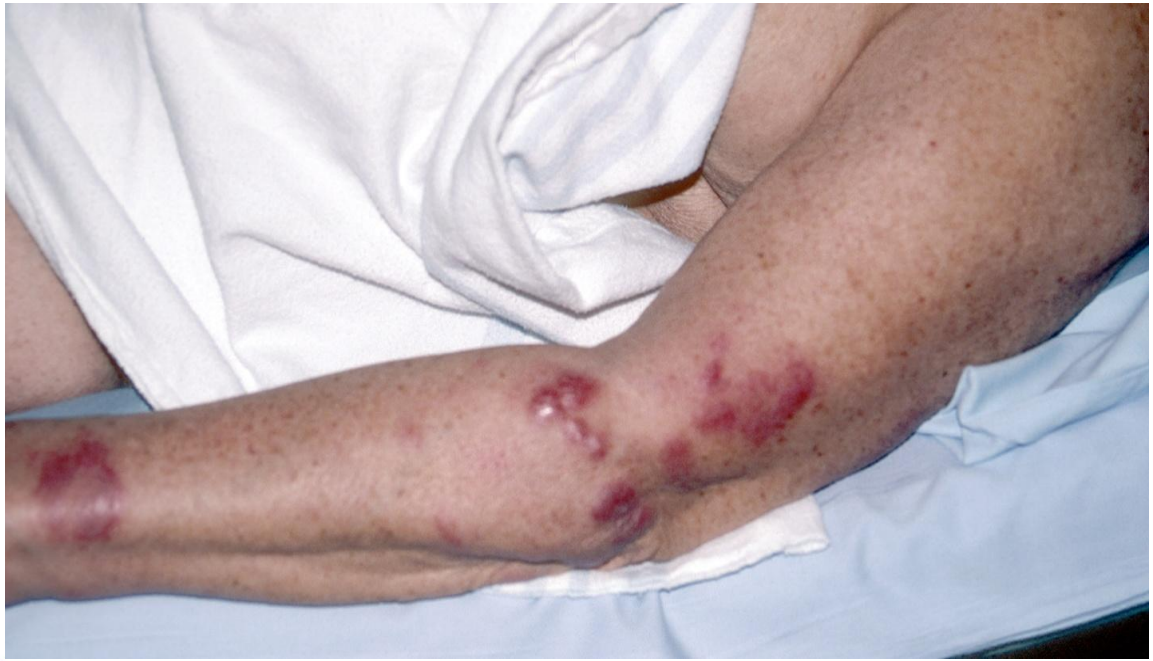
IJROBP 2015; 92: 32-39

Marginal zone lymfom



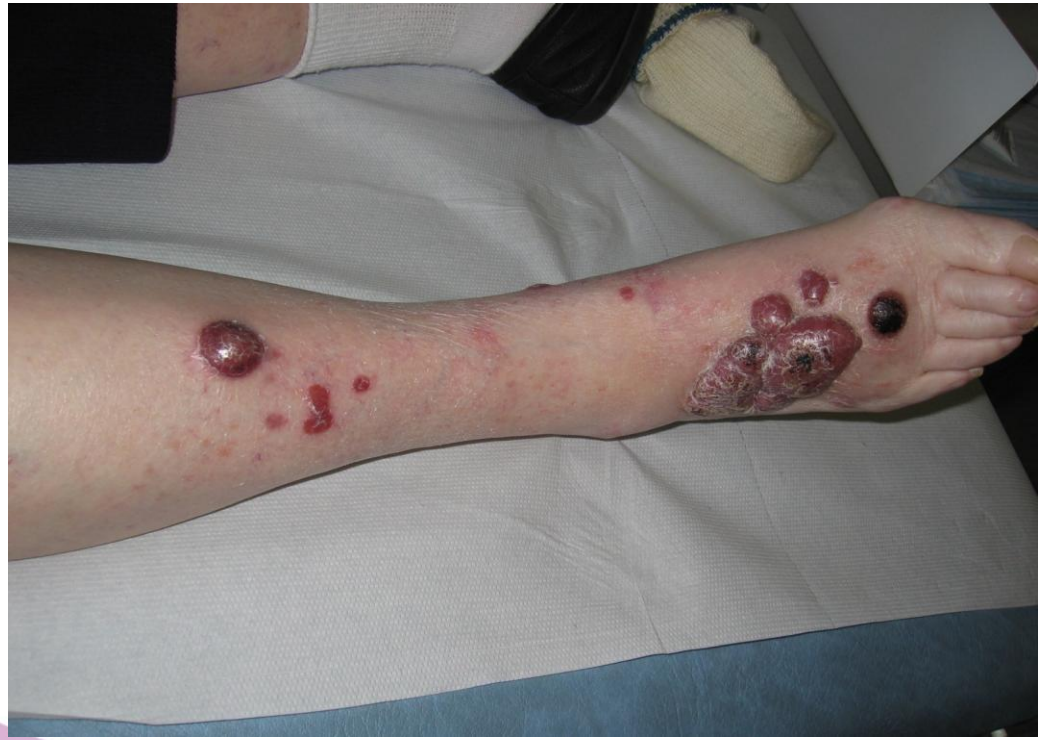
Dose for localized disease:
24-30 Gy

Primary cutaneous follicle center lymphoma PCFCL



Dose for localized disease:
24-30 Gy

Primary cutaneous diffuse large B-cell lymphoma, leg type



Dose for localized disease: 36-40 Gy

If no systemic treatment is given, 40 Gy is recommended

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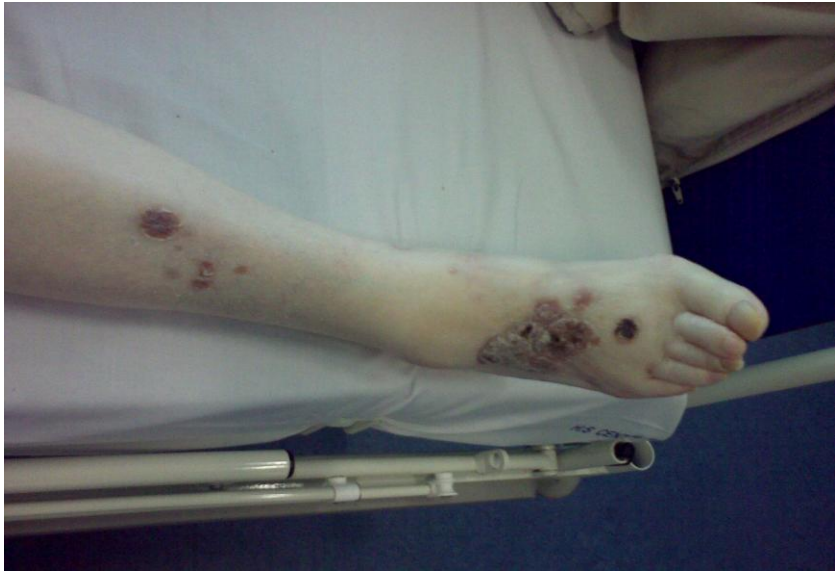
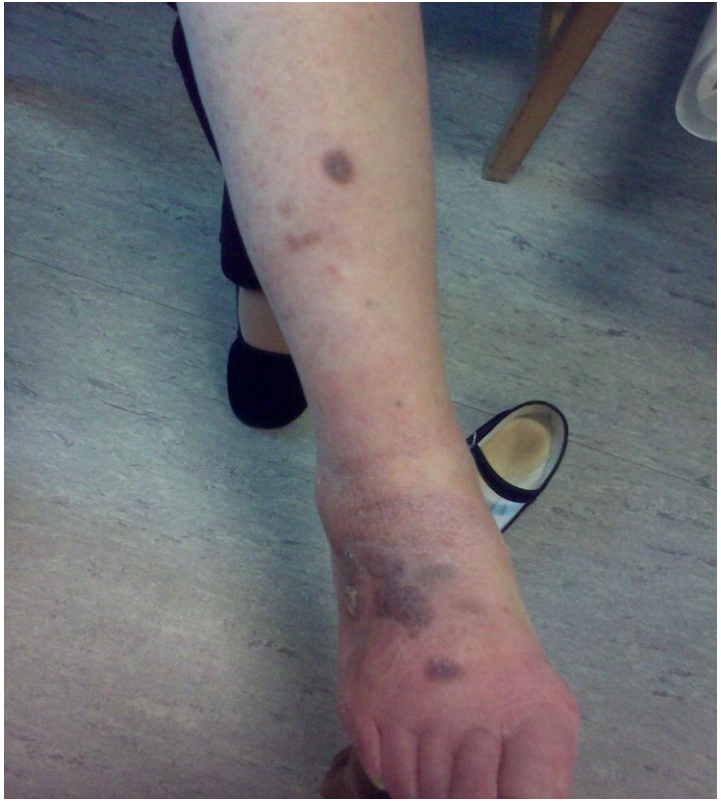


After 2 cycles R-CHOP21



After radiotherapy

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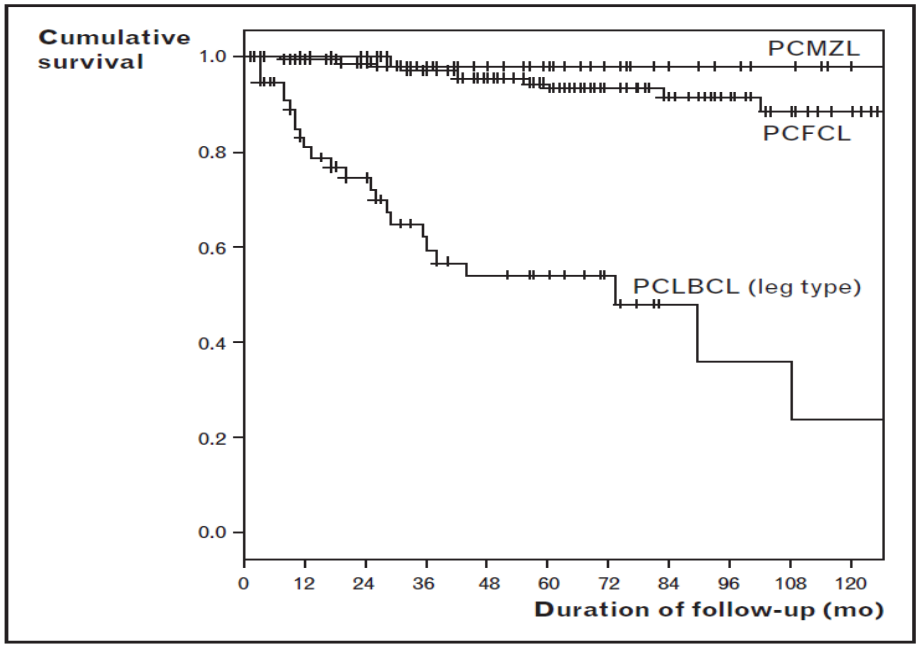
Figure 1 Disease-related 5-year-survivals of 280 Dutch patients with cutaneous B-cell lymphoma reclassified according to the World Health Organization–European Organization for the Research and Treatment of Cancer classification (N.J. Senff, unpublished data)



This group includes 64 primary cutaneous marginal zone B-cell lymphomas (PCMZL), 156 primary cutaneous follicle center lymphomas (PCFCL), and 60 primary cutaneous large B-cell lymphomas (PCLBCL) (leg type).

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WHO-EORTC classification for cutaneous lymphomas

Rein Willemze, Elaine S. Jaffe, Günter Burg, Lorenzo Cerroni, Emilio Berti, Steven H. Swerdlow, Elisabeth Ralfkiaer, Sergio Chimenti, José L. Diaz-Perez, Lyn M. Duncan, Florent Grange, Nancy Lee Harris, Werner Kempf, Helmut Kerl, Michael Kurrer, Robert Knobler, Nicola Pimpinelli, Christian Sander, Marco Santucci, Wolfram Sterry, Maarten H. Vermeer, Janine Wechsler, Sean Whittaker, and Chris J. L. M. Meijer

(Blood. 2005;105:3768-3785)

WHO-EORTC classification	No.	Frequency, %*	Disease-specific 5-year survival, %
Cutaneous T-cell lymphoma			
Indolent clinical behavior			
Mycosis fungoides	800	44	88
Folliculotropic MF	86	4	80
Pagetoid reticulosis	14	< 1	100
Granulomatous slack skin	4	< 1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	95
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T-cell lymphoma	18	1	82
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma†	39	2	75
Aggressive clinical behavior			
Sézary syndrome	52	3	24
Primary cutaneous NK/T-cell lymphoma, nasal-type	7	< 1	NR
Primary cutaneous aggressive CD8+ T-cell lymphoma†	14	< 1	18
Primary cutaneous γ/δ T-cell lymphoma†	13	< 1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified‡	47	2	16

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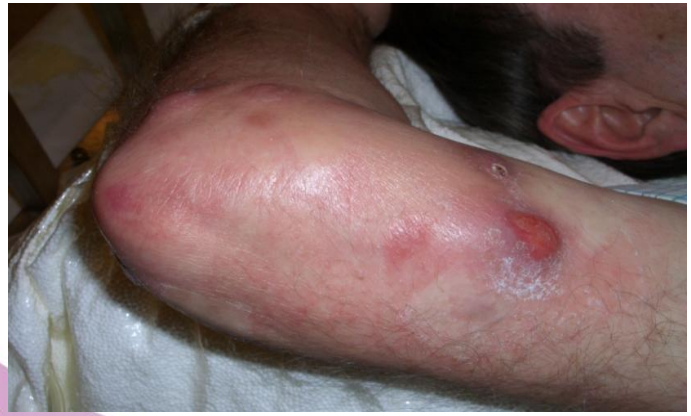
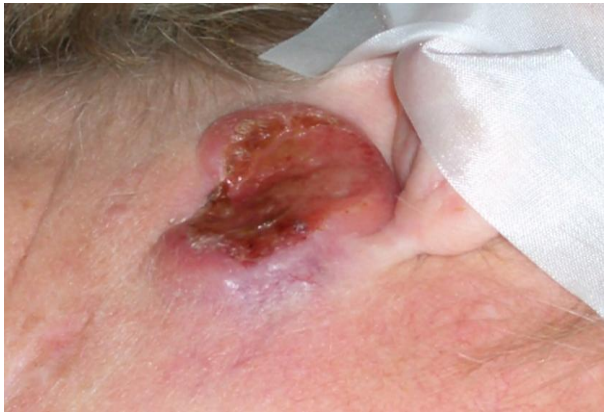
Primary Cutaneous CD30+ neoplasms (lymphomatoid papulosis, ALCL)

- LyP: Chronic, recurrent, self-healing
- In up to 20 % associated with other types of lymphoma



- C-ALCL: 80 % present with solitary or localized nodules
- Local radiotherapy, dose 24-30 Gy



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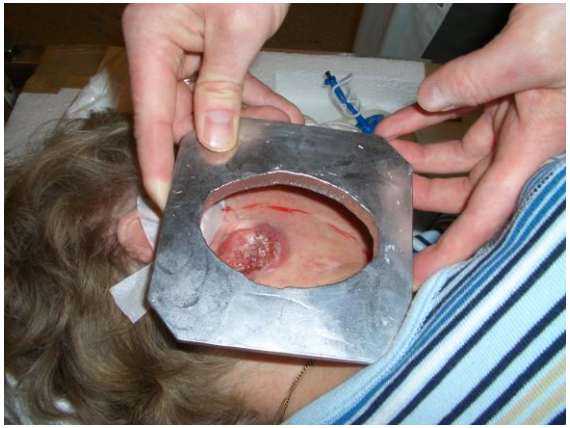
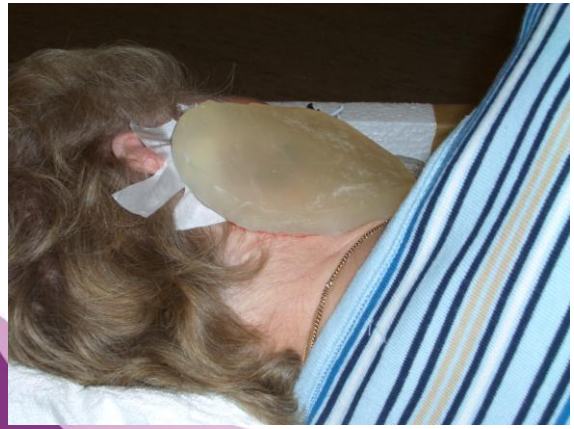
Localized skin lymphomas: ISRT





- Margin beyond clinically evident erythema/ induration 1-2 cm
- Thickness of lesion must be determined to ensure adequate coverage in depth
- Most lesions can be treated with electrons
- Bolus is required to avoid skin sparing
- Low energy X-rays (100 kV) may sometimes be used
- For deep, bulky or circumferential lesions photons may be needed

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Mycosis fungoides

- Most common cutaneous T-cell lymphoma
- 4 % of all lymphomas, 50 % of all cutaneous lymphomas
- Indolent clinical course
- Limited to the skin for many years
- Patches → Plaques → Tumors
- Skin directed therapies unless extracutaneous

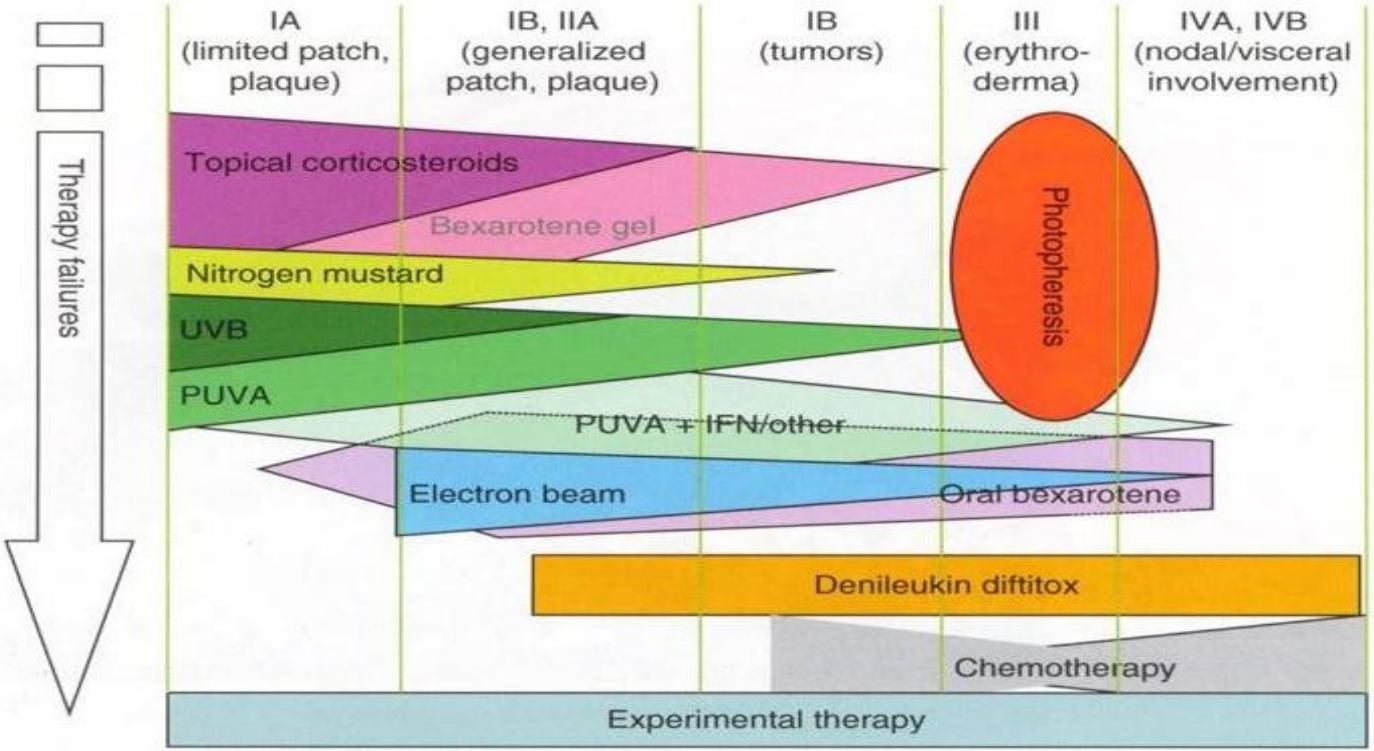
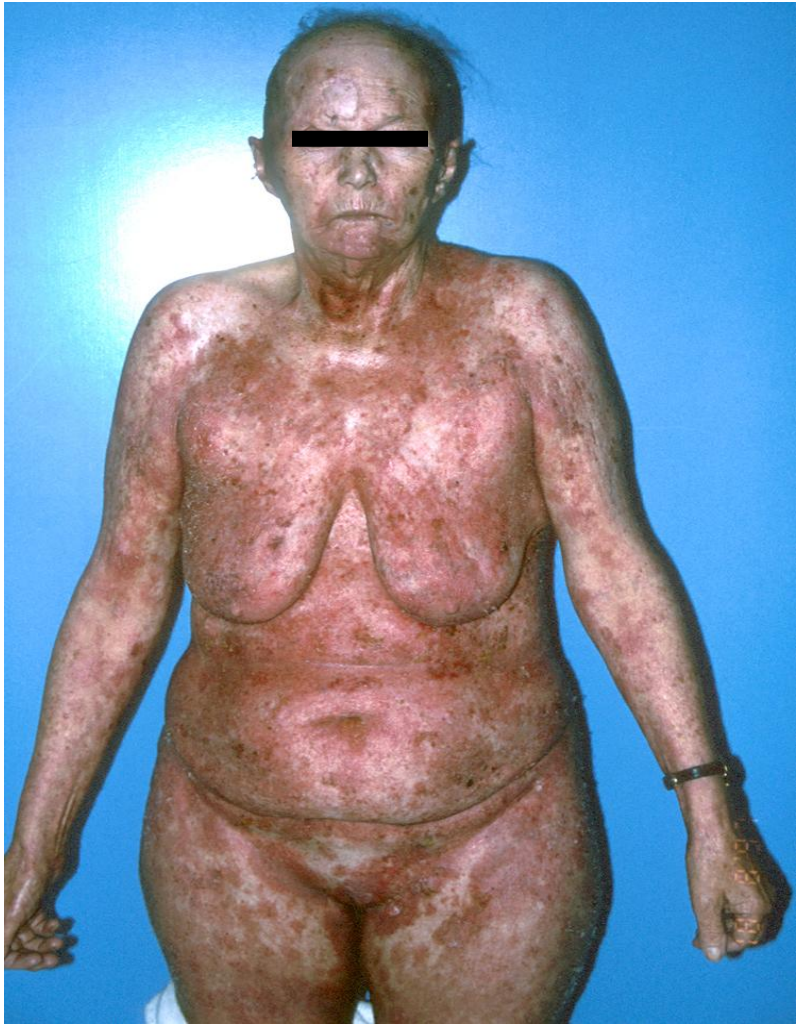


Fig. 19.3 Treatment of MF by stage. Stage is across the *top* of the diagram from T1 (*left*) to T4 (*right*)

+ HDAC inhibitors, low-dose Alemtuzumab, Adcetris,



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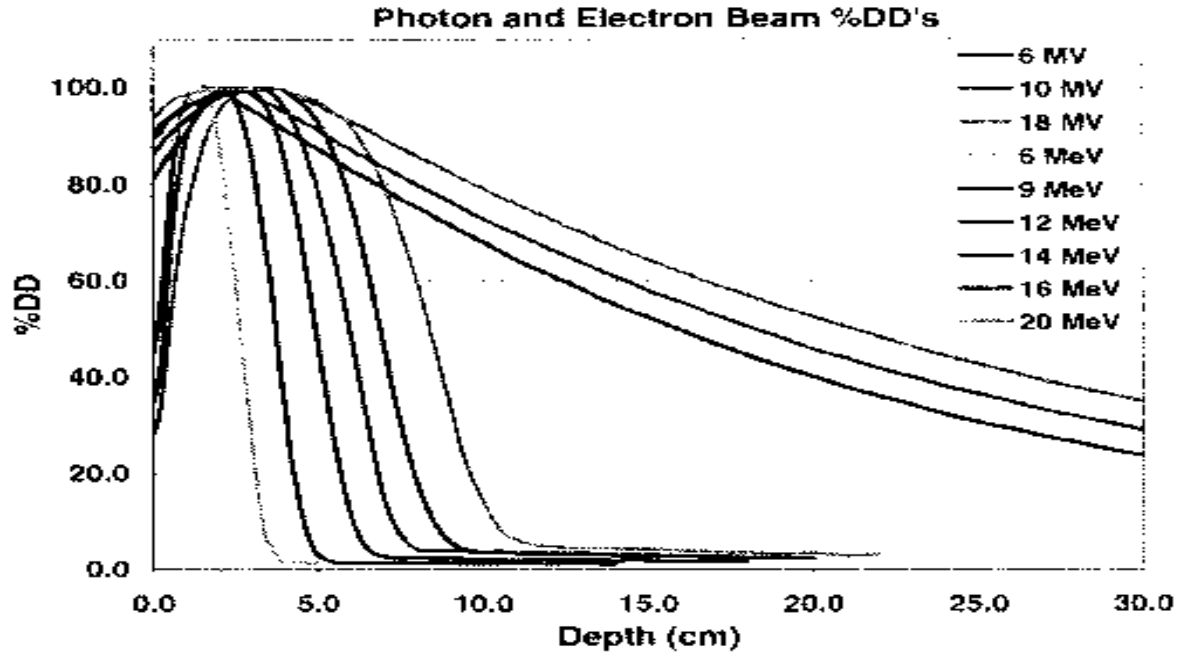
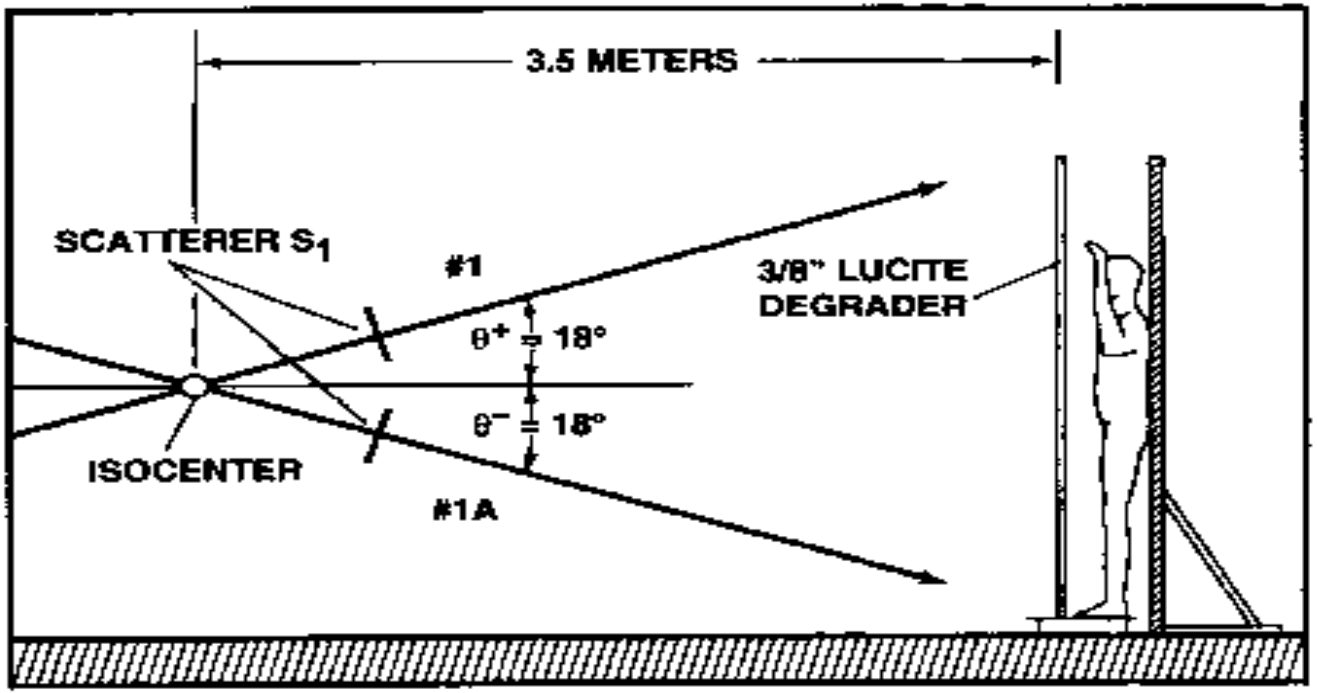
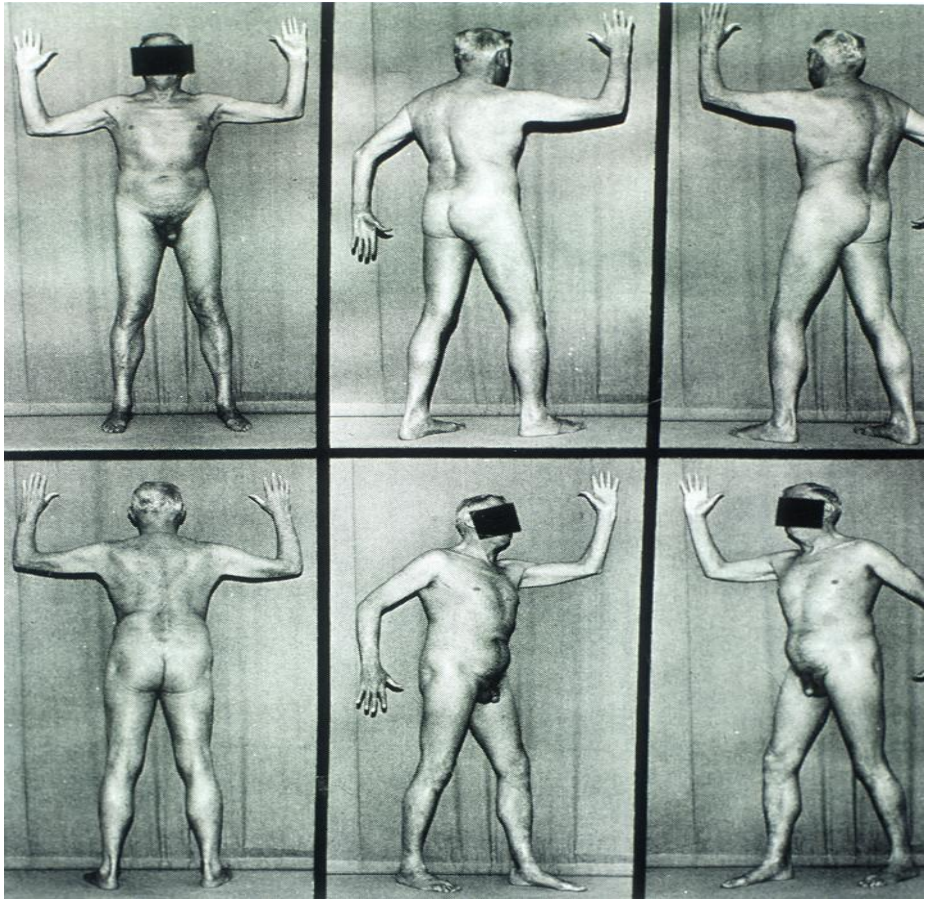
X-ray vs. electron depth-dose-curves



Total skin electron beam therapy (TSEBT)





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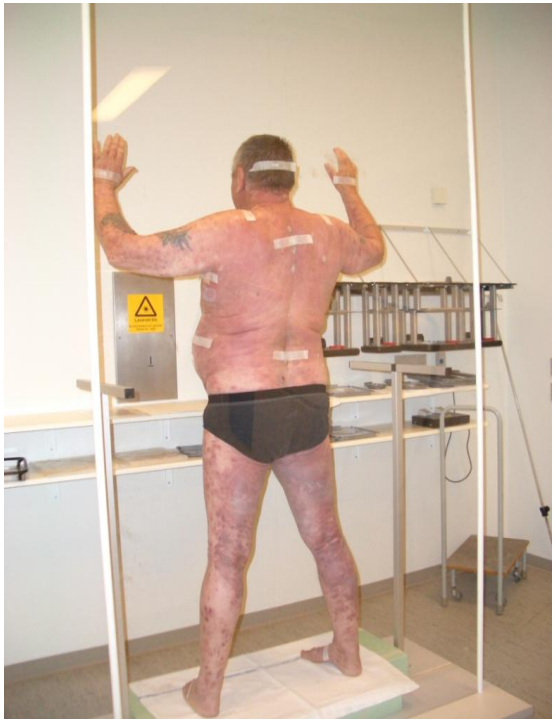
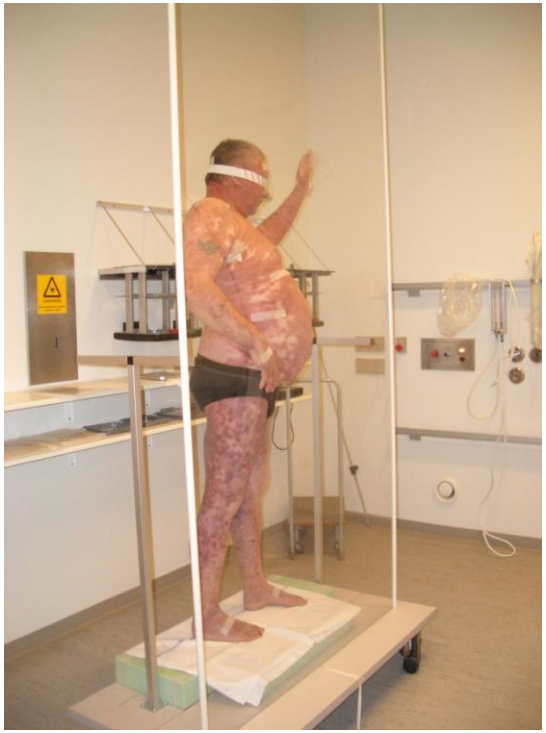
TSEBT





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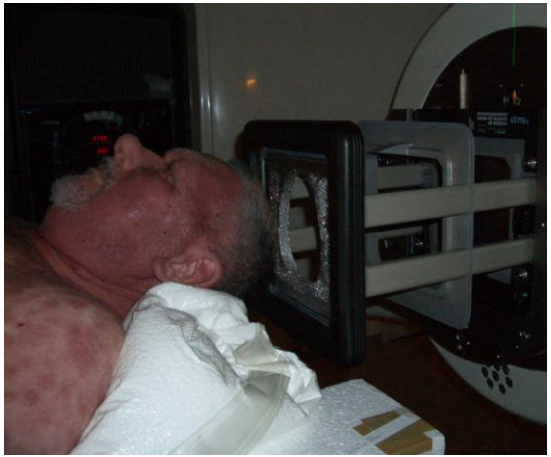
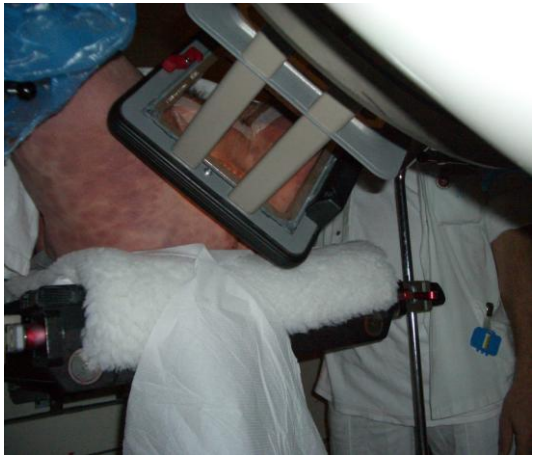
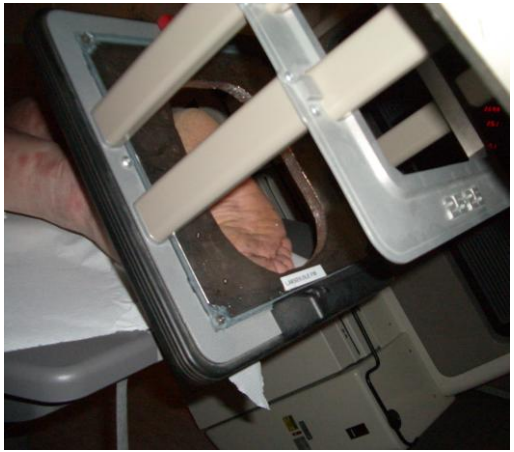
Additional treatment of ”shadowed areas”



Scalp

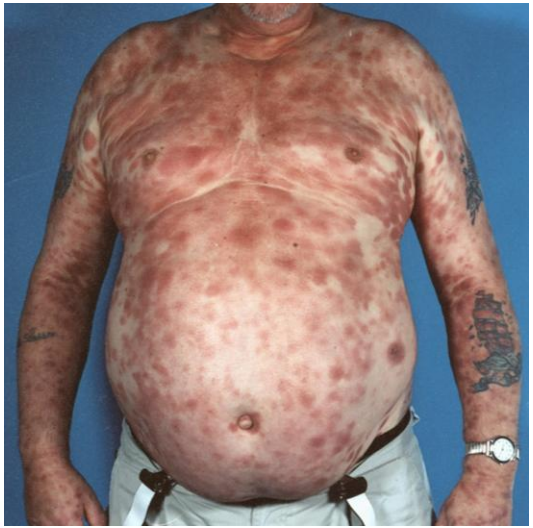


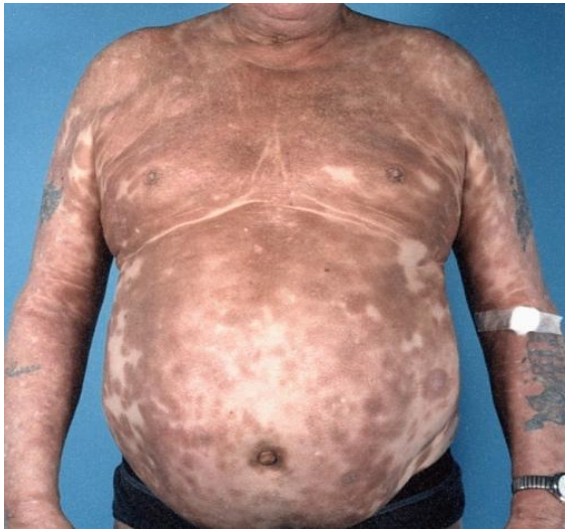
Perineum

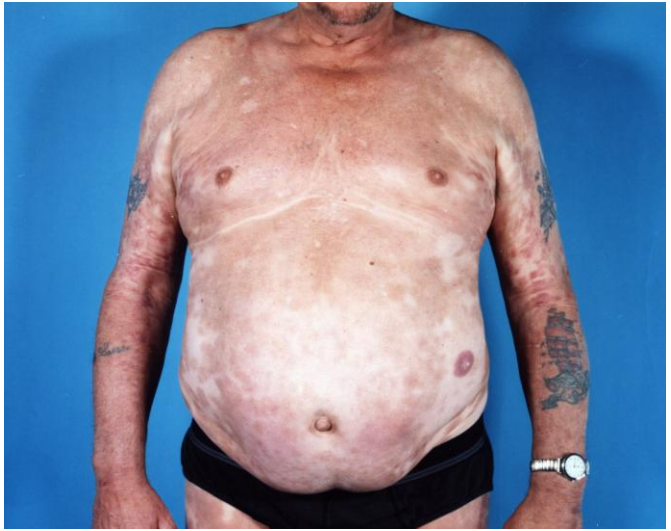


Soles

TSEBT, pt. with generalized plaques, before and 1 month after and 1 year after







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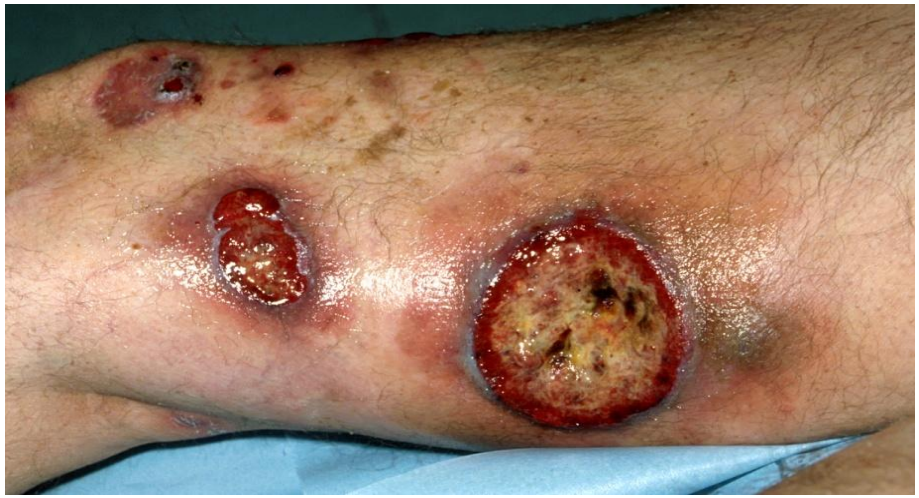
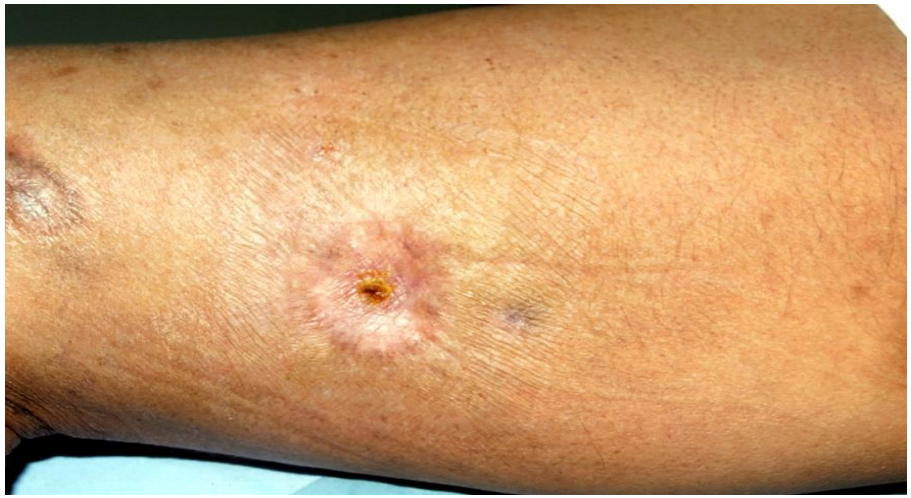
TSEBT, pt. with tumors, before and 6 months after





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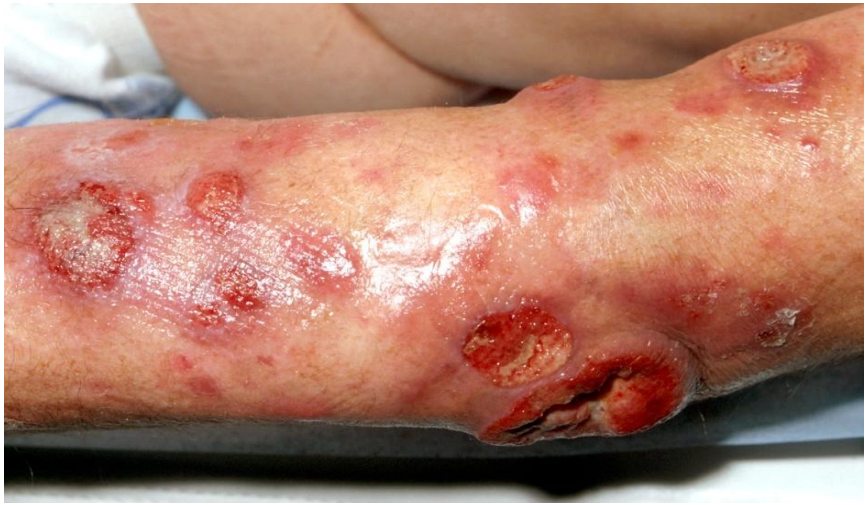
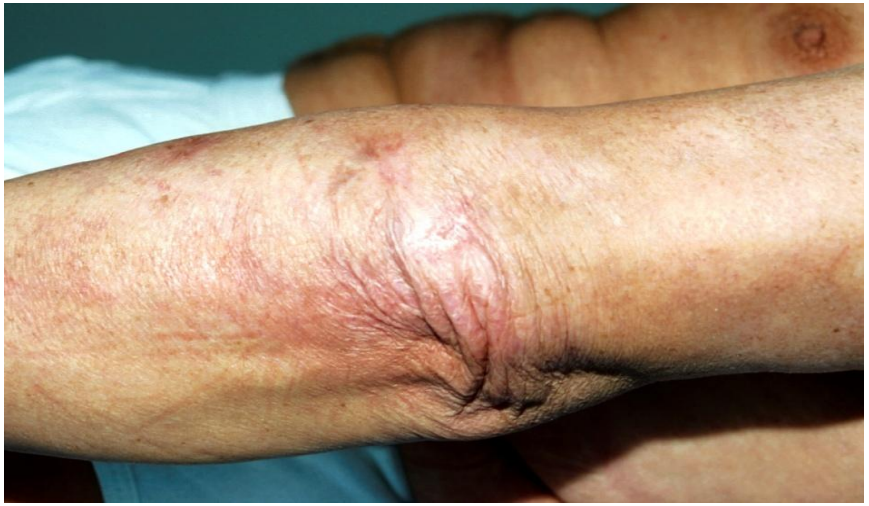
TSEBT, pt. with tumors, before and 6 months after





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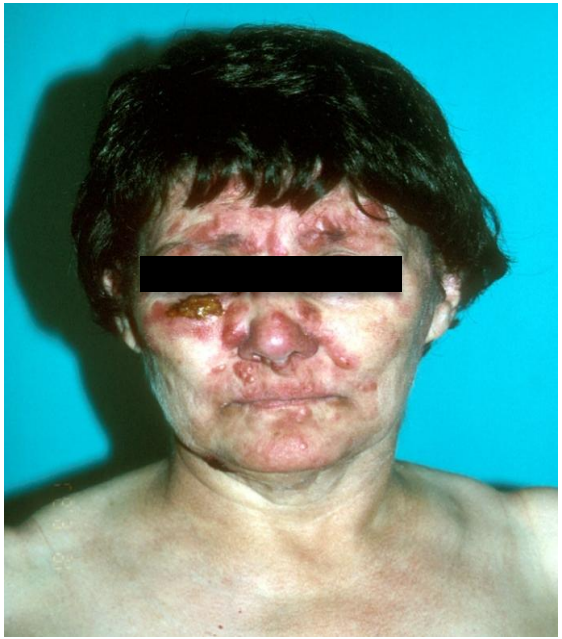
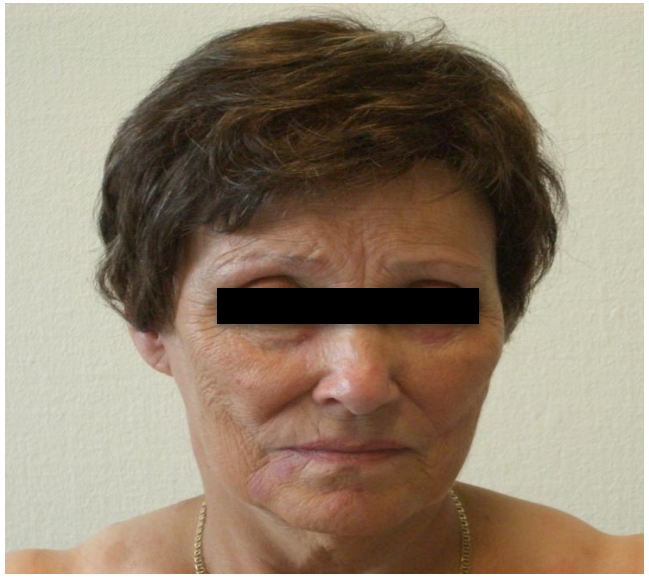
TSEBT, pt. with plaques and small tumors, before and 7 years after





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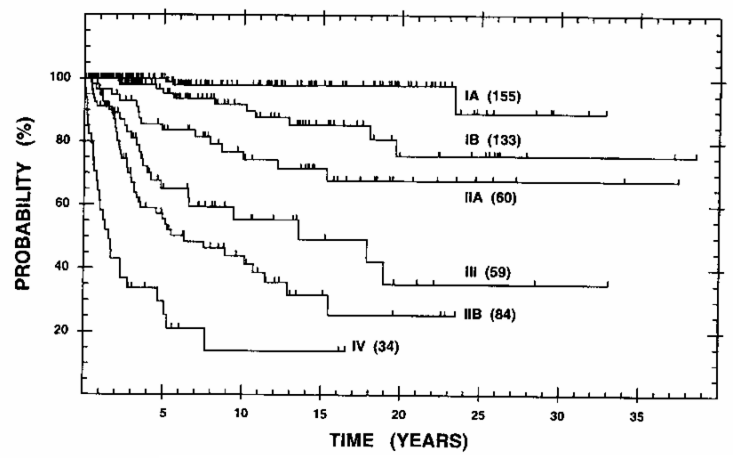
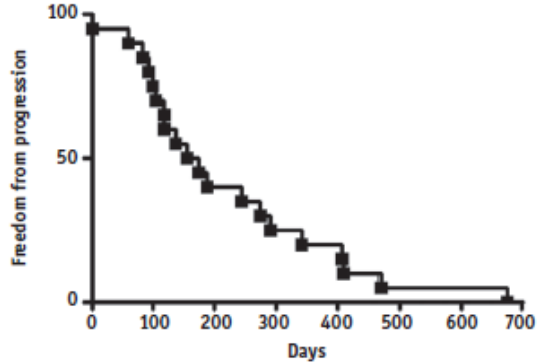
TSEBT outcome



Cause-specific survival after 30 Gy
(Stanford data)



PFS with low dose 10-12 Gy
(Kampstrup, IJROBP 2015; 92: 138-43

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Hypersplenism, splenomegaly

Lena Specht MD DMSc
Professor of Oncology, University of Copenhagen, Denmark
Chief Oncologist, Depts. of Oncology and Haematology, Rigshospitalet, Copenhagen
Vice-chairman, International Lymphoma Radiation Oncology Group

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Splenomegaly

- Seen in CML, CLL, myelofibrosis, other myeloproliferative disorders, hairy cell leukemia, splenic marginal lymphoma
- Caused by:
  - Leukemic infiltration
  - Extramedullary hematopoiesis
  - Important (but sometimes difficult) to tell the difference

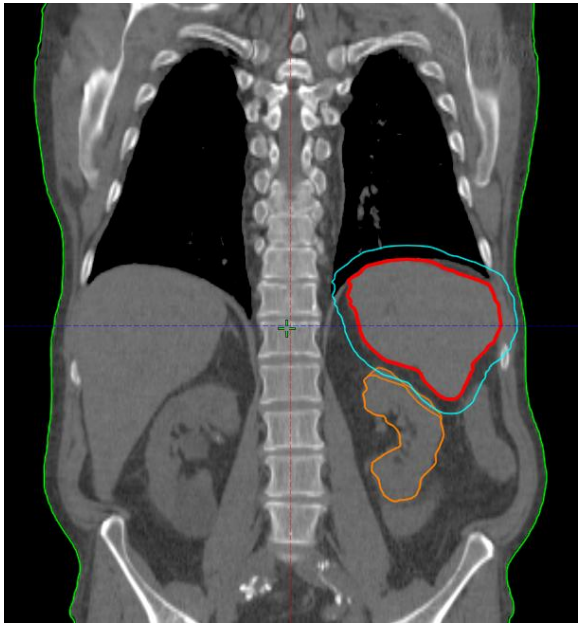
Splenic irradiation

- Used less often than in the past because of more effective systemic treatment
- Indications:
  - Palliative for pain and pressure symptoms
  - Reduction of tumor burden
  - Hypersplenism

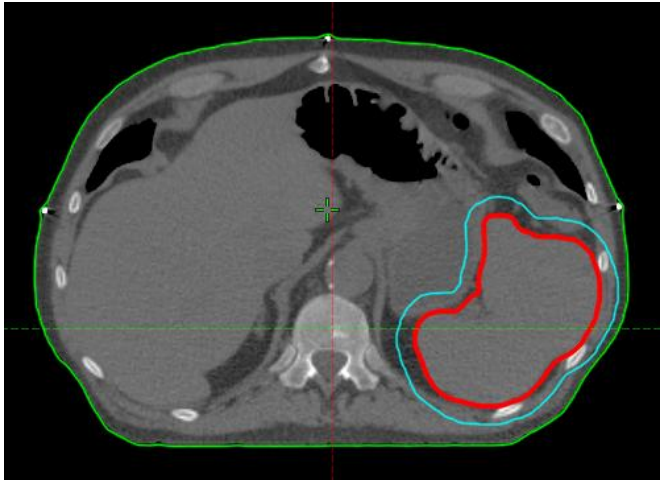
Splenic irradiation

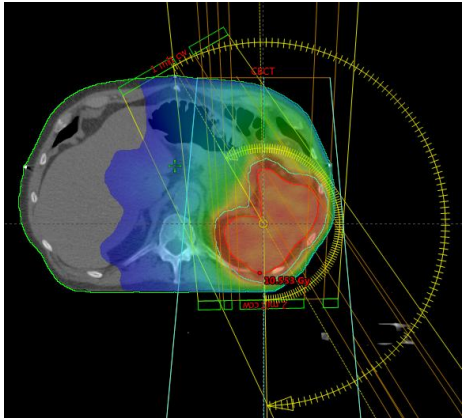
- Often significant extramedullary hematopoiesis in enlarged spleen
- Irradiation must be done with caution, risk of severe long-lasting pancytopenia
- E.g., 0.5 Gy x 20, 5 F/W
- Close monitoring of blood counts

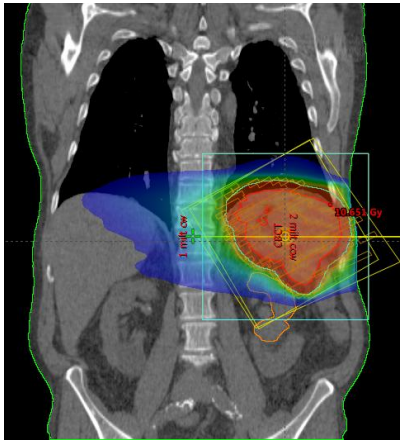
Splenic irradiation



70 year old male,
CMMOL, pain







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KING'S HEALTH PARTNERS

Pioneering better health for all

KING'S College LONDON

University of London

Guy's and St Thomas' NHS

NHS Foundation Trust

Thyroid Lymphoma

Prof George Mikhaeel

Professor of Radiation Oncology
King's College London
Consultant Clinical Oncologist
Guy's & St Thomas' Hospital
London, UK

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Incidence

- 5% of all thyroid malignancies
- 3% of all extra-nodal NHL
- 1-2 cases / million
- F:M = 3 : 1
- Peak: 7th decade
- 2 main subtypes:
  - DLBCL
  - MALT

Pathogenesis

- Link to autoimmune disease and chronic antigenic stimulation

- *Hashimoto's thyroiditis:*
  - Up to 80% of PTL have HT
  - PTL incidence is 40-80 times higher in HT
  - Typically 20-30 years after diagnosis
  - Only 0.6% of HT pts develop PTL

Histological types

- DLBCL 60-70%
- MALT 20-30%

- FL 3-5%
- cHL 2%
- SLL 2-3%
- T-cell very rare

Clinical Presentation

- *Enlarging painless goitre*:
  - days – 36 months
  - DLBCL : rapid course
- *Compressive symptoms* (1/3): dyspnoea, dysphagia and hoarseness. Rarely; stridor, SVCO
- *B symptoms*: not common (10-20%)
- Cervical LN
- Majority are euthyroid

Staging

- IE: Thyroid only 56%
- IIE: + LNs above diaphragm 32%
- IIIE: + LNs below diaphragm 2%
- IVE: + organ involvement 11%

88%

Based on 1048 cases: Graff-Baker, Surgery 2009

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Imaging

- US:
  - Modality of choice for thyroid assessment
  - Useful for DD of rapidly enlarging goitre:
    - Anaplastic thyroid carcinoma
    - Subacute thyroiditis
    - Haemorrhage into cyst or adenoma
  - 3 patterns: nodular, diffuse & mixed
  - Guides Bx

- Radionuclide scanning: not useful

- Cross-sectional imaging (CT + MRI)
  - Assessment of anatomical extent and airways
  - Staging

- FDG-PET/CT:
  - Standard imaging modality for staging

Biopsy

- FNAC
- Core Bx
- Surgical open biopsy

FNAC

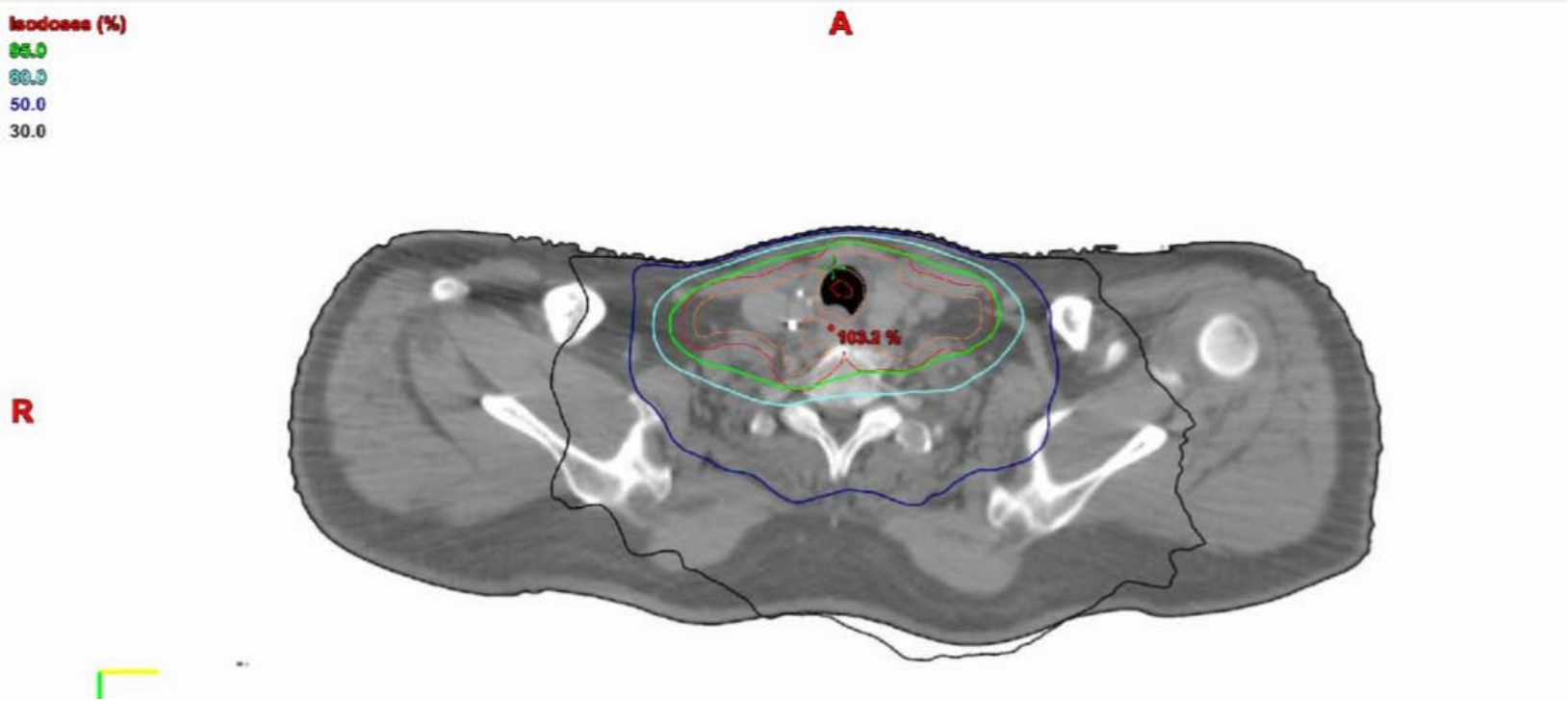
- Initial technique of choice for assessment of thyroid lesions
- simple, usually readily available with US
- Traditionally FNAC alone was considered inadequate
- Increasing accuracy with recent adjuncts: flow cytometry, immunoperoxidase studies & PCR.

Role of Surgery

- Primary role is to establish diagnosis
- Surgical resection is **not** a treatment option
- Airway compromise:
  - Tracheostomy
  - Steroids (after Bx + PET)

Treatment

- Indolent: Primary RT
- Aggressive: CMT
- CTV: whole thyroid + any involved nodes
- Dose:
  - Indolent 24Gy / 12#
  - Agg: 30 – 36 Gy according to response
- Technique:
  - 3D Conformal
  - IMRT / VMAT


Isodoses (%)
95.0
80.0
50.0
30.0
A
R
103.2 %

QUESTIONS?

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WELCOME

Second ESTRO – ILROG Course on Haematological Malignancies

Vienna, Austria, 31 August-3 September, 2016

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www.ilrog.com

Initiated 2010, Hodgkin Symposium in Cologne
First Steering Committee Meeting 2011 in Copenhagen

Goals:

- Advance optimal and evidence based care of lymphoma patients
- Improve the awareness of oncologists and patients of radiation benefits and reduce inappropriate scare from modern radiotherapy
- Improve the quality of radiotherapy for lymphoma patients
  - Guidelines, implementing modern radiation principles and techniques
  - Education of colleagues and trainees
  - Design and collaborate in research

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Multidisciplinary course

- Faculty medical oncologist/hematologists:
  - Professor Andreas Engert, University of Cologne, Chairman of the German Hodgkin Study Group, Honorary ILROG Steering Committee member
  - Dr. Andrew Davies, Cancer Research UK Senior Lecturer in Medical Oncology and Honorary Consultant, Southampton General Hospital

- Guest speaker, physicist:
  - Dr. Marianne Aznar, Associate Professor of Medical Physics, Rigshospitalet, University of Copenhagen

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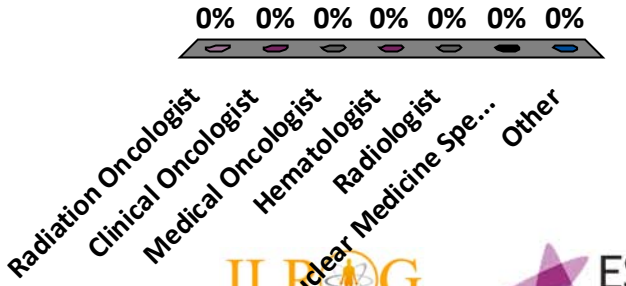
From ESTRO

- Carolina Goradesky, Miika Palmu, project managers
- Dr. Bernardino De Bari, Radiation Oncologist, University Hospital Lausanne, contouring administrator, FALCON

What is your specialty?

A. Radiation Oncologist
B. Clinical Oncologist
C. Medical Oncologist
D. Hematologist
E. Radiologist
F. Nuclear Medicine Specialist
G. Other



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How long in practice?

A. Trainee
B. < 10 years after specialist recognition
C. 10 – 20 years after specialist recognition
D. > 20 years after specialist recognition

Where do you practice?

A. Europe
B. Asia
C. Middle East
D. North America
E. South America
F. Australia/New Zealand
G. Africa

For those who have brought cases for the case discussion sessions

- We will include as many as possible, but may not be able to include all
- 5 min. presentation of case, discussion with faculty and participants
- Contact Lena
- Bring case on USB stick

RT for relapsed and refractory HL

Joachim Yahalom, M.D.
Memorial Sloan-Kettering Cancer Center
New York, NY, U.S.A.

Memorial Sloan Kettering Cancer Center

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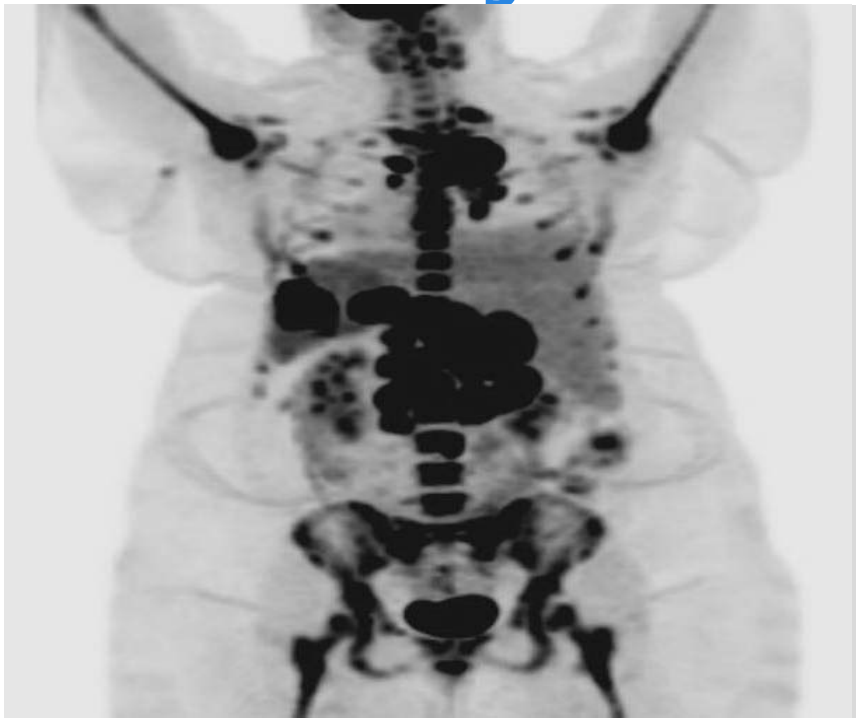
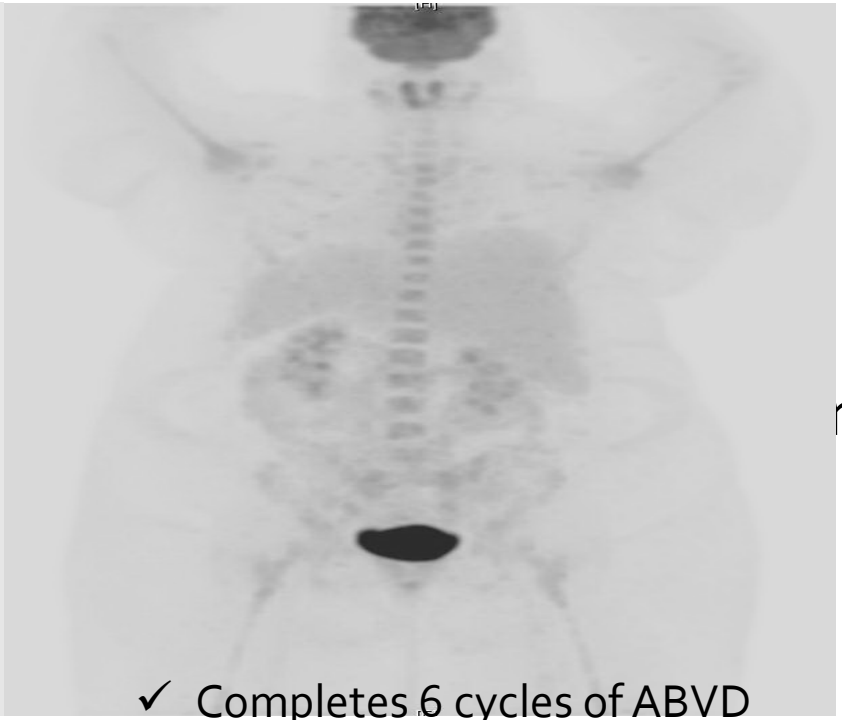
39 year old woman presented with abdominal pain - November 2013

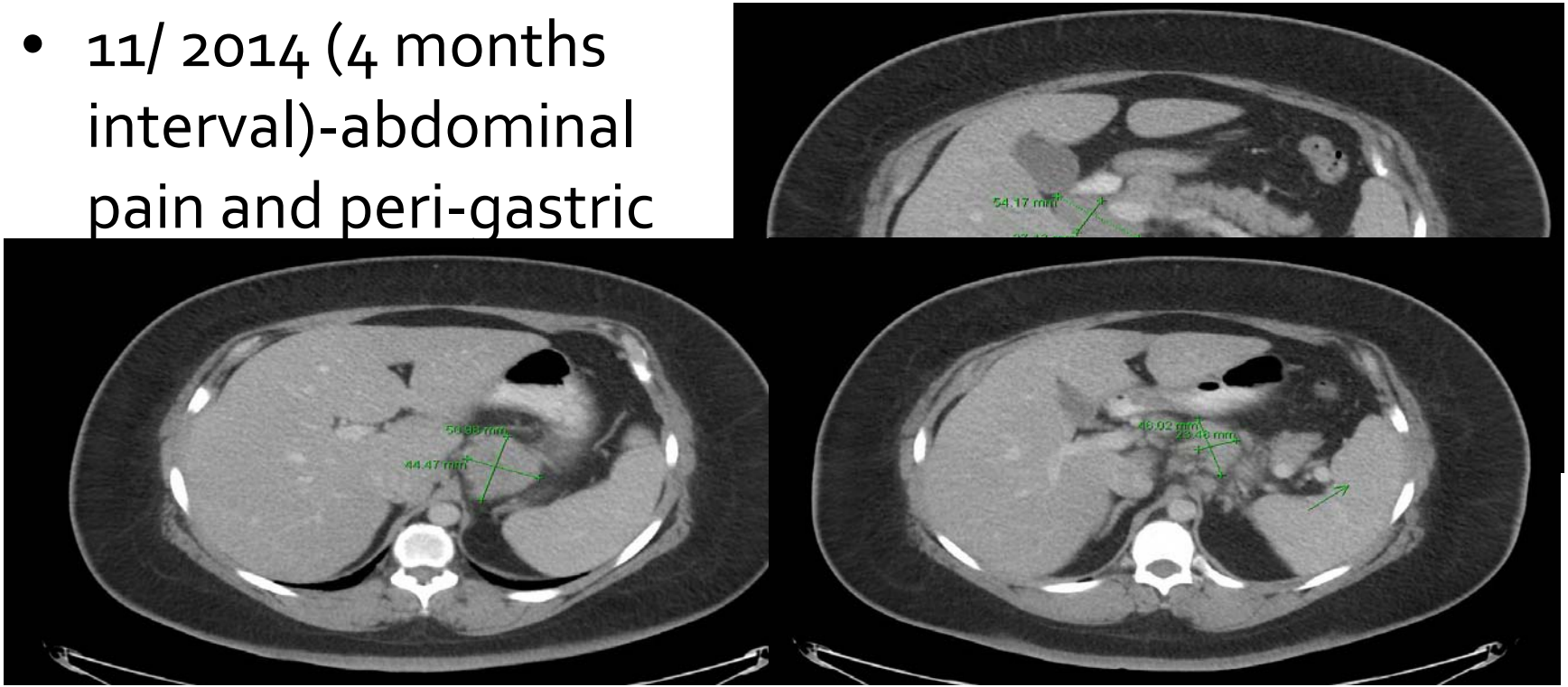




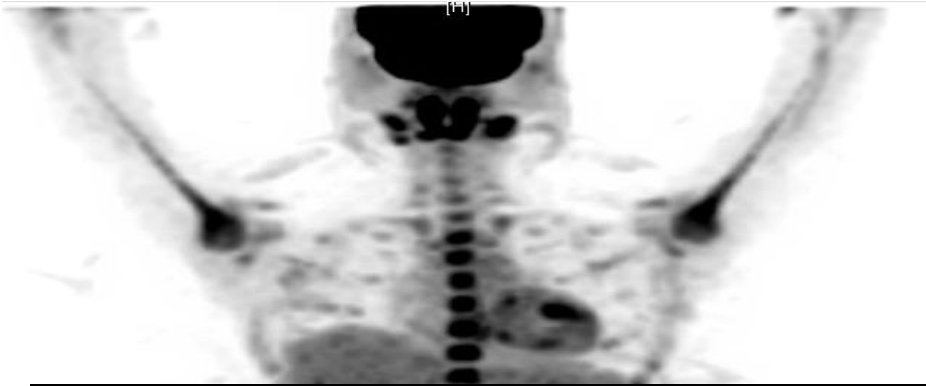
- ✓ Completes 6 cycles of ABVD
- ✓ PET in JUNE 2014- CR

39 yo woman in CR after ABVD X6 for HL

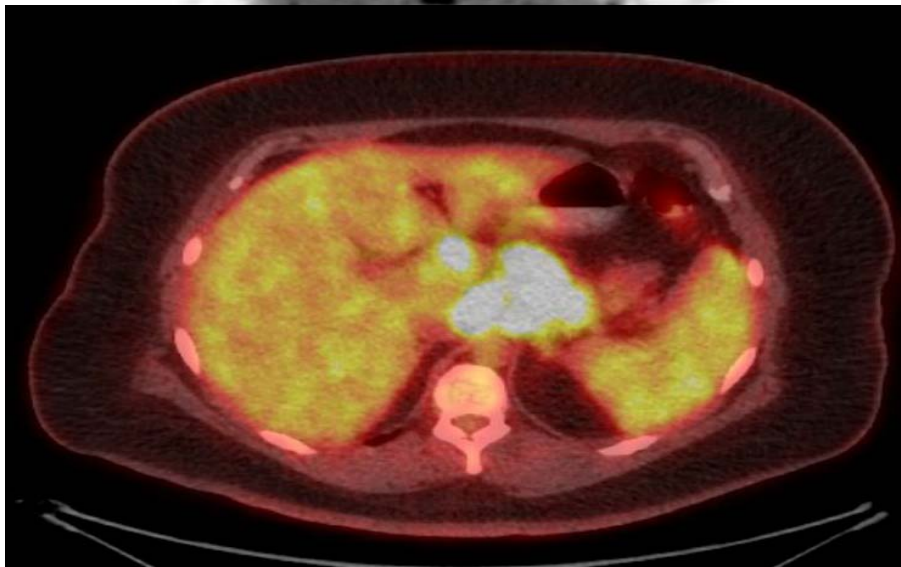
- 11/ 2014 (4 months interval)-abdominal pain and peri-gastric

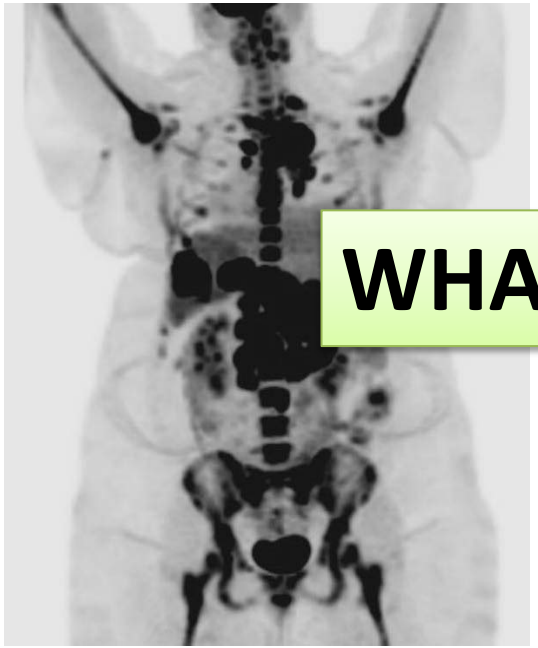


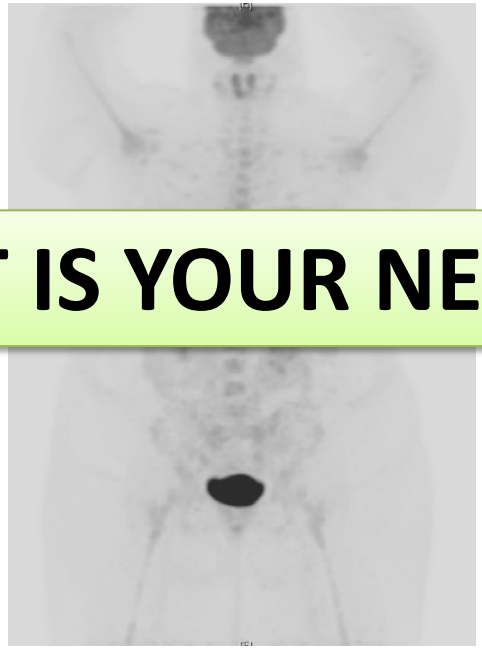
- 4/7/2015 CT
  - Mild to moderate size increase of retroperitoneal adenopathy
  - Upper abdominal adenopathy overall stable or decreased in size



- 4/14/2015 PET
  - New FDG avid nodes in left retrocrural, upper abdomen and retroperitoneum
  - Bilateral reactive vs lymphoma neck nodes







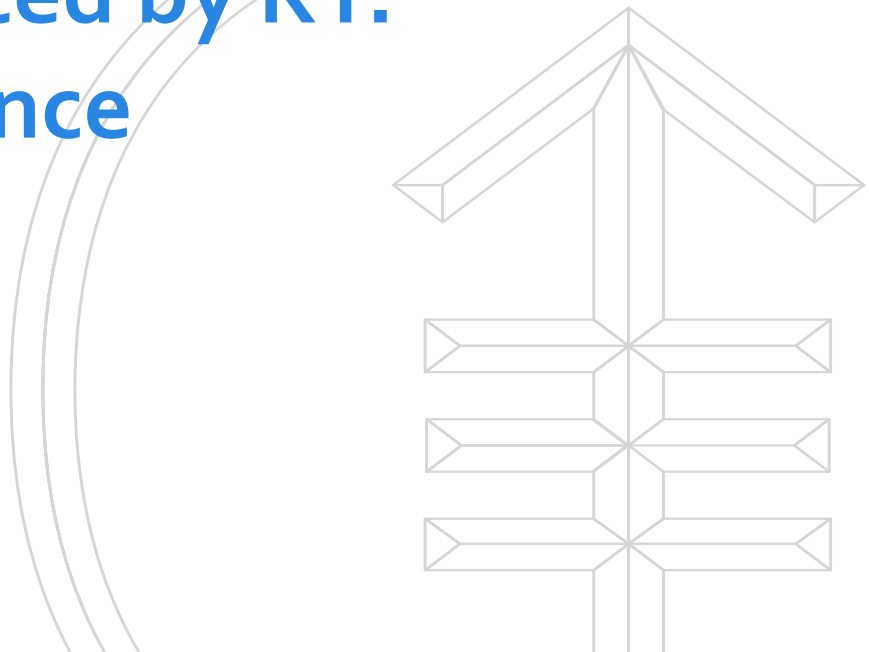
WHAT IS YOUR NEXT STEP?

11/2013: HL-IIIA 6/2014: CR post ABVD 11/2014: retroperitoneal relapse

a. Standard dose salvage chemotherapy (ICE)- PET CR?
b. Standard dose salvage chemotherapy (ICE)- PET PR?

Memorial Sloan Kettering
Cancer Center

High-Dose Therapy Salvage of Hodgkin Lymphoma Enhanced by RT: 30 Years of Experience



HL: the numbers

- 9200 cases in the US each year
- *Favorable ESHL: 1500 cases*
- *Unfavorable ESHL: 2500 cases*
- *Bulky stage II disease:1000 cases*
- *Favorable ASHL: 3200 cases*
- *Unfavorable ASHL: 1000 cases*

Recent Trends-increasing the role of RT in salvage of HL

- Radiation alone - obsolete
- Combined modality programs - **decreasing**
  - Radiation fields – markedly reduced (ISRT by ILROG)
  - Radiation dose – from 40 Gy to 20-30 Gy
- Chemotherapy alone -**increasing**
  - Advanced-stage
  - Early-stage **(>50% of U.S. patients, most women)**
- **New effective agents integrated in front line therapy**
  - **Brentuximab Vedotin**
  - **Check point inhibitors** `

MSKCC Salvage Program- Always Emphasizing RT

- Five consecutive prospective studies (1985, 1994, 1998, 2004, 2011)
- Approx. 500 patients (~18/year)
- Long-term and quality of life study

MSKCC HL- Salvage with Transplantation Program

- All progression/relapses- biopsy proven
- Two-step chemo salvage
  - *Standard dose re-induction*
  - ***High dose***
- Involved-field RT <u>always pre-transplant</u>
- TLI part of the conditioning regimen in previously unirradiated patients

Salvage Therapy of Hodgkin Lymphoma – Why RT?

- Chemotherapy failed in these patients
- Many patients had minimal or no exposure to radiation
- Chemotherapy failures remain responsive to RT
- Previously irradiated sites are amenable to meaningful additional RT by avoiding dose-limiting organs

Integrating Radiotherapy - *Rationale*

- Non-cross-resistant with chemotherapy
- Predictable pattern of relapse
- Unlimited penetration
- Selectivity of dose to site

Integrating Radiotherapy- *Concerns*

- Toxicity
- Treatment delay
- Availability and/or coordination of radiation oncology

Integrating Radiotherapy - *Options*

- ~~Total Body Irradiation~~
- **Post-transplantation RT** to selected sites / patients
  - Delayed or never happens
  - Less effective?
  - Toxic to regenerating marrow (MDS)

Integrating Radiotherapy - *Preferred*

- **Pre-transplantation RT** as part of the response-inducing regimen

✓ Induce maximal tumor reduction when it is most critical

✓ Differential dose to relapse/bulky site vs. all nodal sites (TLI)

✓ Completed within 10 days (36 Gy b.i.d program)

✓ Safe and rarely toxic

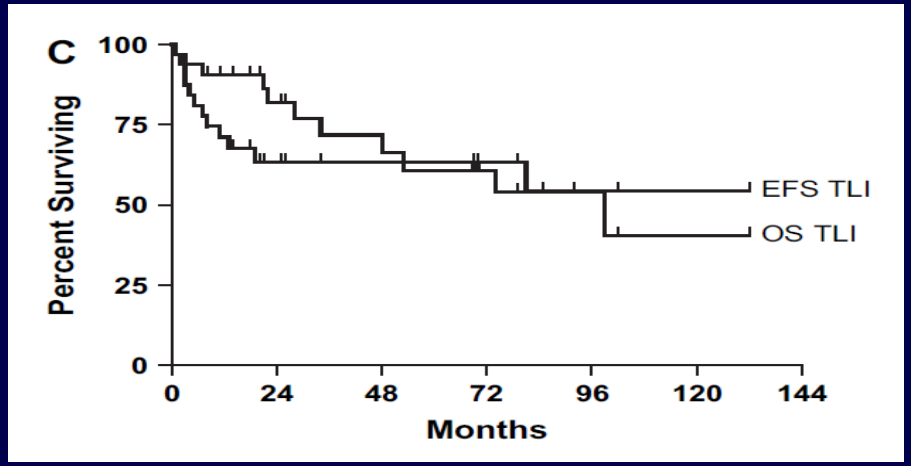
✓ Non-myelosuppressive or leukomogenic

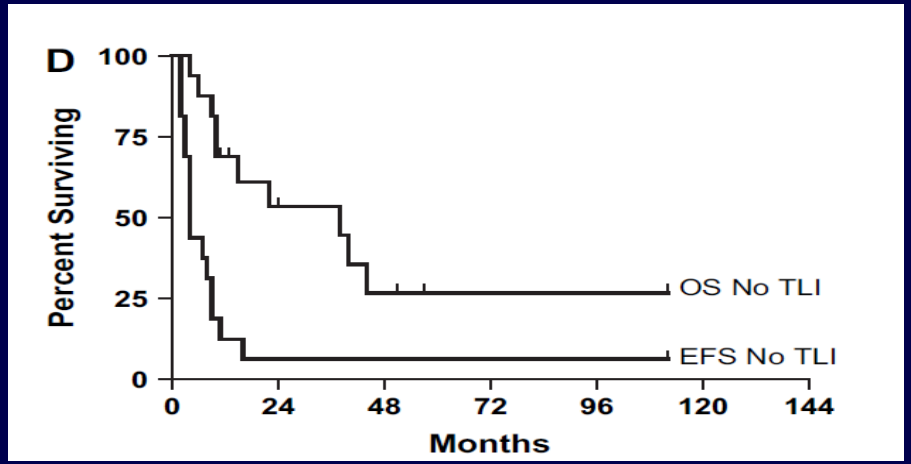
Phase I/II Trial of TLI vs High-Dose Chemotherapy Salvage Regimen

- Patients with primary refractory/relapsed HL (n=48; 1993-2005)
- Conditioning regimen:
  - TLI/chemotherapy
  - Chemotherapy-alone (if prior RT >2000cGy had been given)
- TLI details:
  - Accelerated hyperfractionated TLI 150cGy x10
  - Boost to previous and current disease to 150cGy x10
  - BID regimen
  - Pre-transplant
- Chemotherapy regimen:
  - Carboplatin
  - Cyclohosphamide
  - Etoposide

Evens et al., Ann Oncol 2007

Phase I/II Trial of TLI vs High-Dose Chemotherapy Salvage Regimen





5-year EFS for TLI/chemo vs chemo alone: 63 vs 6% (p<0.0001)

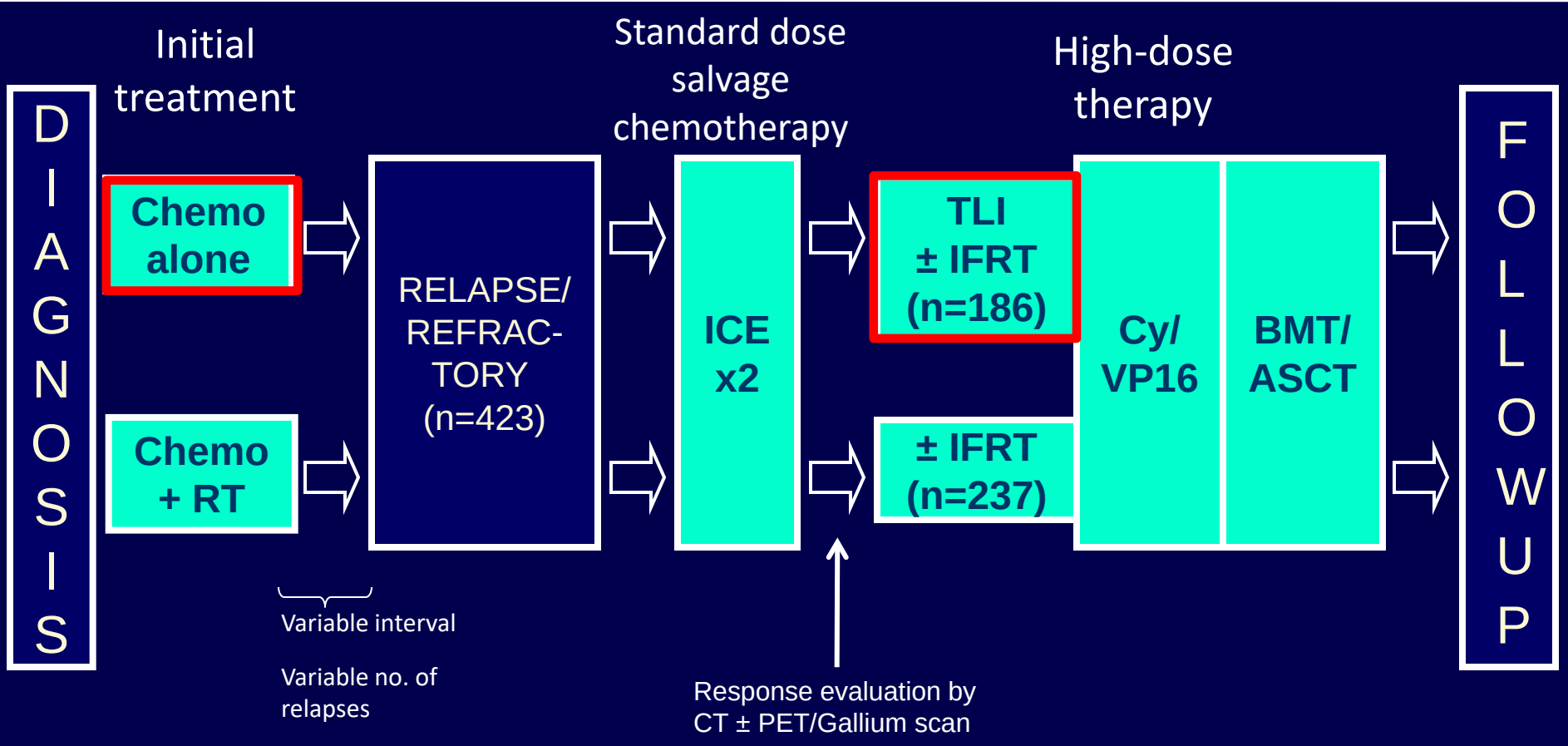
5-year OS for TLI/chemo vs chemo alone: 61 vs 27% (p=0.04)

Predictive factors for EFS: TLI/chemotherapy regimen

Prognostic factors for OS: B-symptoms at relapse

Evens et al., Ann Oncol 2007

Management of Relapsed HL



Advantages of Integrated RT in High-Dose Therapy Regimen

- Quick treatment (all treatment delivered over 10 days)
- No interference of RT with salvage chemotherapy and high-dose therapy
- Acute toxicity occurs when patients already admitted for transplantation
- RT pre-ASCT avoids irradiating newly engrafted cells

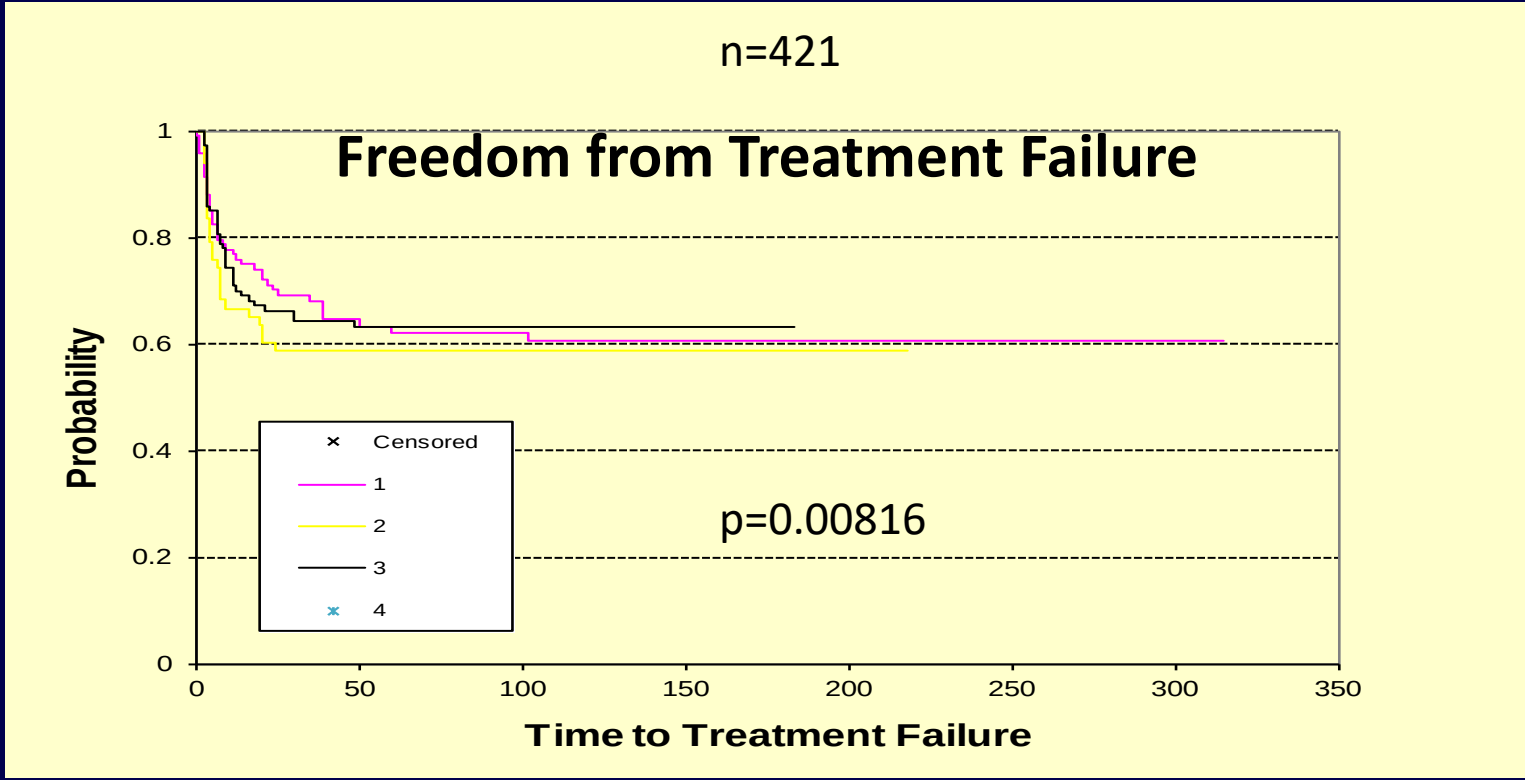
MSKCC Clinical Research Program of Salvage for Hodgkin Lymphoma 1985-2015

- First Generation (1985-1994): 146 pts.
  - Various salvage therapy
  - Pre-transplant IF-RT
  - TLI+CV or CBV/BMT
- Second Generation (1994-1998): 81 pts.
  - Intent to treat analysis
  - ICE salvage therapy
  - IF-RT
  - TLI+CV or CBV/ASCT
- Third Generation (1998- 2004): 105 pts.
  - Risk-adapted program
  - Same principles as 2nd
- Fourth Generation (2004- 2009 98 pts.
  - Achieve minimal disease state pre-ASCT
  - Add GND if PET remains positive
  - Same risk-related concept
- Fifth Generation (2011-2014)
  - Brentuximab followed by ICE—ISRT ± STLI – ASCT 45 pts.

Total = 475 pts.

ATHERA trial post-transplant BV maintenance (2010-2014)

Protocol Generation (1-85/86, 2-94, 3-98, 4-04/06)

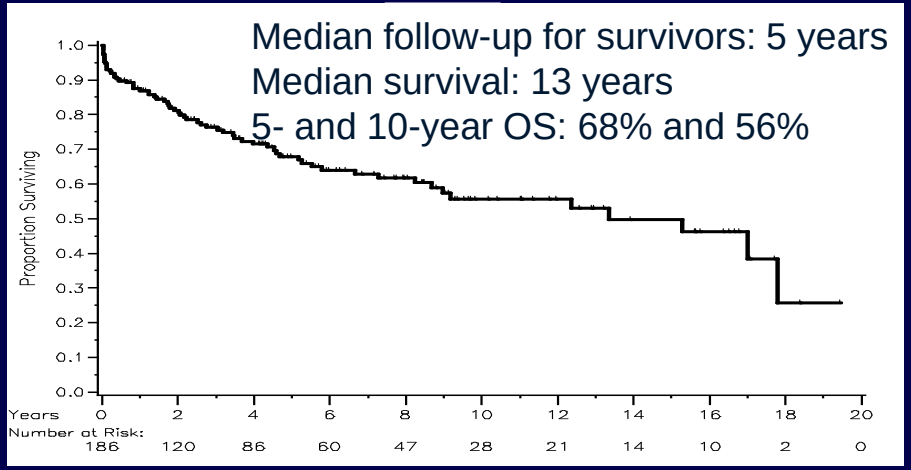


Protocol Generation (1-85/86, 2-94, 3-98, 4-04/06)

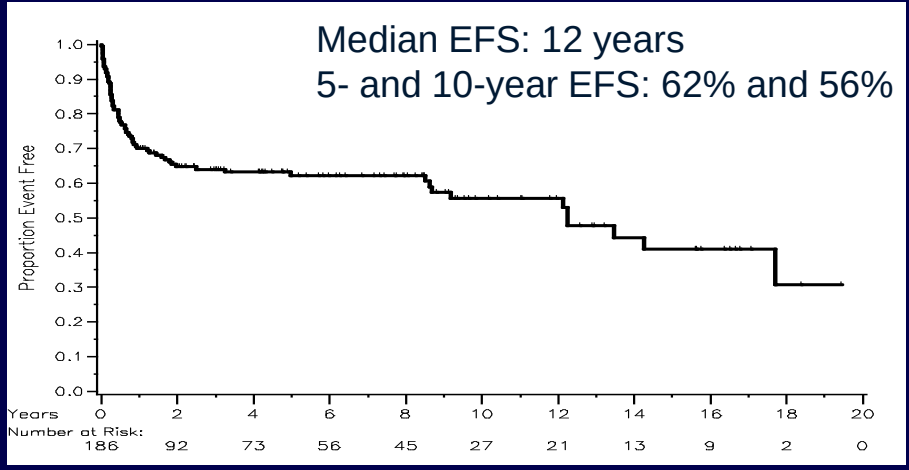
n=421

p=0.000885176

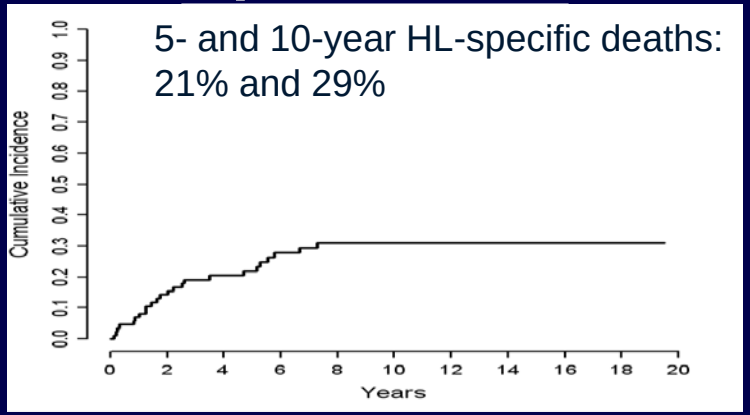
Overall Survival



Event-Free Survival



HL-Specific Deaths

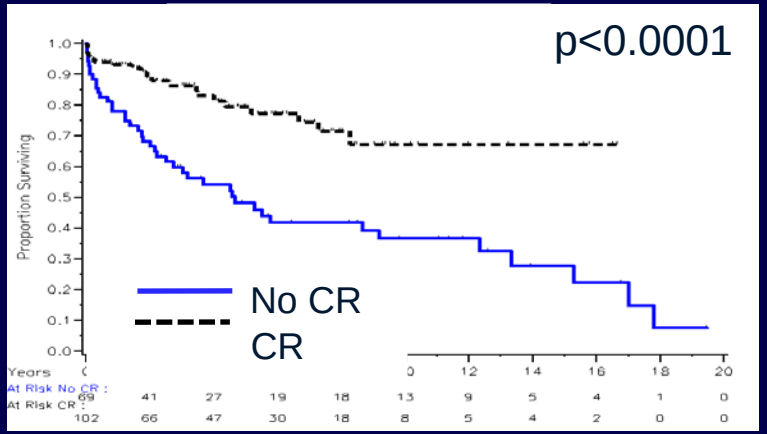


Multivariate Analysis

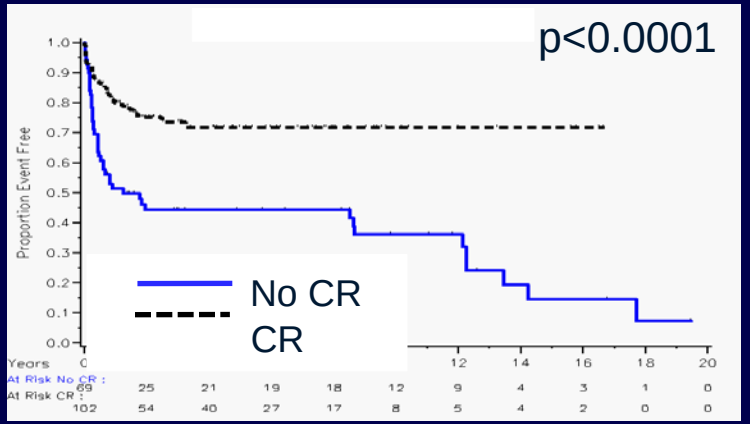
Variable	OS (HR + 95% CI)	p-value	EFS (HR + 95% CI)	p-value	DSS (HR + 95% CI)	p-value
CR to salvage therapy	0.31 (0.18 to 0.55)	<0.0001	0.34 (0.20 to 0.56)	<0.0001	0.55 (0.29 to 1.06)	0.076
Relapse vs refractory	-	-	0.57 (0.35 to 0.94)	0.029	0.39 (0.19 to 0.83)	0.01
Extranodal disease at relapse	-	-	1.67 (0.99 to 2.80)	0.05	-	-

Response to Salvage Therapy

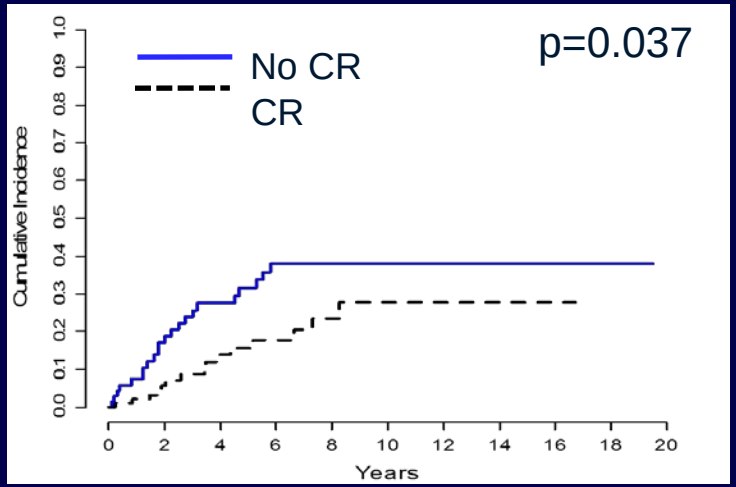
Overall Survival



Event-Free Survival



HL-Specific Deaths



Toxicity	Early ≥ grade 3 toxicity		Late ≥ grade 3 toxicity	
	n	(%)	n	(%)
Infection	108	(58%)	27	(15%)
Mucositis	41	(22%)	0	(0%)
Pulmonary	33	(18%)	19	(10%)
Other	30	(16%)	20	(11%)
Other GI	24	(13%)	12	(6%)
Esophagus	16	(9%)	6	(3%)
Cardiac	12	(6%)	13	(7%)
Hematologic	11	(6%)	6	(3%)
Renal	11	(6%)	3	(2%)
Skin	6	(3%)	4	(2%)
Thyroid	1	(0.5%)	0	(0%)

Second Malignancies

Number of deaths from second malignancies: 5

Total incidence of second malignancies: 11

- AML (2)
- MDS (1)
- DLBCL (1)
- NHL (1)
- Thyroid (1)
- Lung (1)
- Stomach (1)
- Colon (1)
- Unknown primary (1)

Summary

- Between 10 and 40% of patients with HL fail after initial therapy.
- Patients failing after chemotherapy alone are candidates for salvage RT.
- IFRT/ISRT followed by TLI integrated with high-dose chemotherapy is an effective, feasible and safe salvage therapy for patients with previously unirradiated, relapsed/ refractory HL.
- On multivariate analysis, CR to standard-dose salvage chemotherapy is the most important predictive factor for long-term OS, EFS and DSS after HDT.
- Primary refractory disease and extranodal disease at relapse are associated with worse outcome.
- Long-term morbidity and second malignancy rates are relatively low.

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NEW DIRECTIONS IN SALVAGE: MSKCC STUDIES

1. **Test Brentuximab as front-line salvage prior to ASCT**
2. **Test Brentuximab as "adjuvant"/maintenance post-ASCT**
3. **Avoid ASCT in selected patients with new check point inhibitors and ISRT**

THE LANCET Oncology

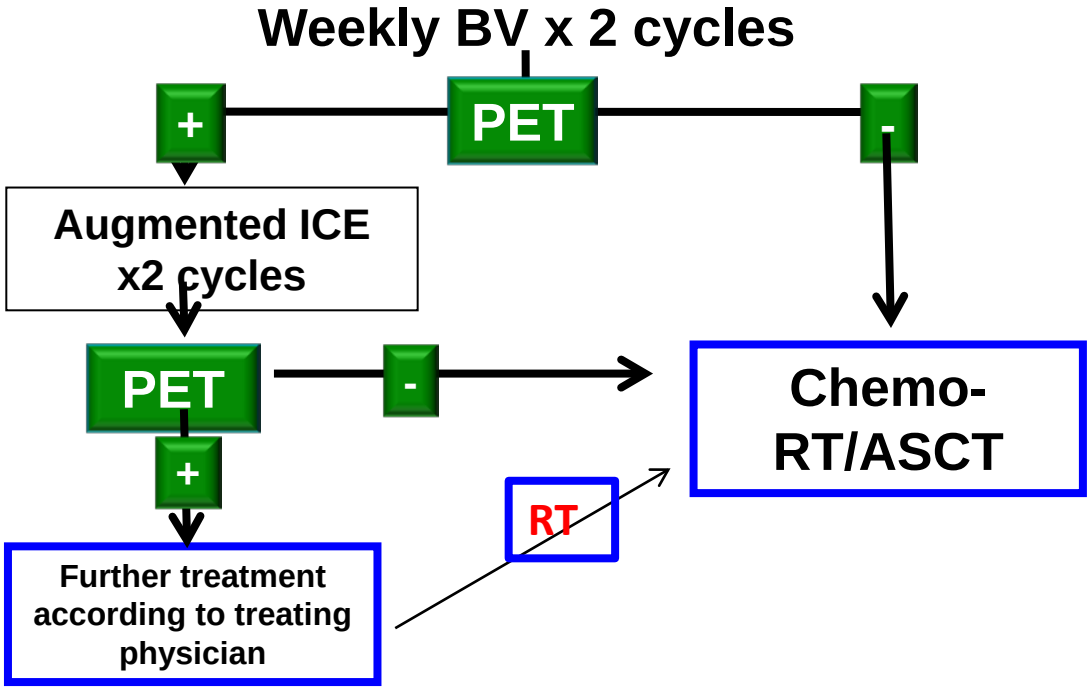
Volume 16, Issue 3, March 2015, Pages 284–292

Articles

PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study

Dr Alison J Moskowitz, MD[a], Prof Heiko Schöder, MD[a], Prof Joachim Yahalom, MD[a], Susan J McCall, NP[a], Stephanie Y Fox, BS[a], John Gerecitano, MD[a], Ravinder Grewal, MD[a], Paul A Hamlin, MD[a], Steven Horwitz, MD[a], Rachel Kobos, MD[a], Anita Kumar, MD[a], Matthew Matasar, MD[a], Ariela Noy, MD[a], M Lia Palomba, MD[a], Miguel-Angel Perales, MD[a], Prof Carol S Portlock, MD[a], Craig Sauter, MD[a], Neerav Shukla, MD[a], Prof Peter Steinherz, MD[a], Prof David Straus, MD[a], Tanya Trippett, MD[a], Prof Anas Younes, MD[a], Prof Andrew Zelenetz, MD[a],

PET-adapted therapy with BV followed by augICE

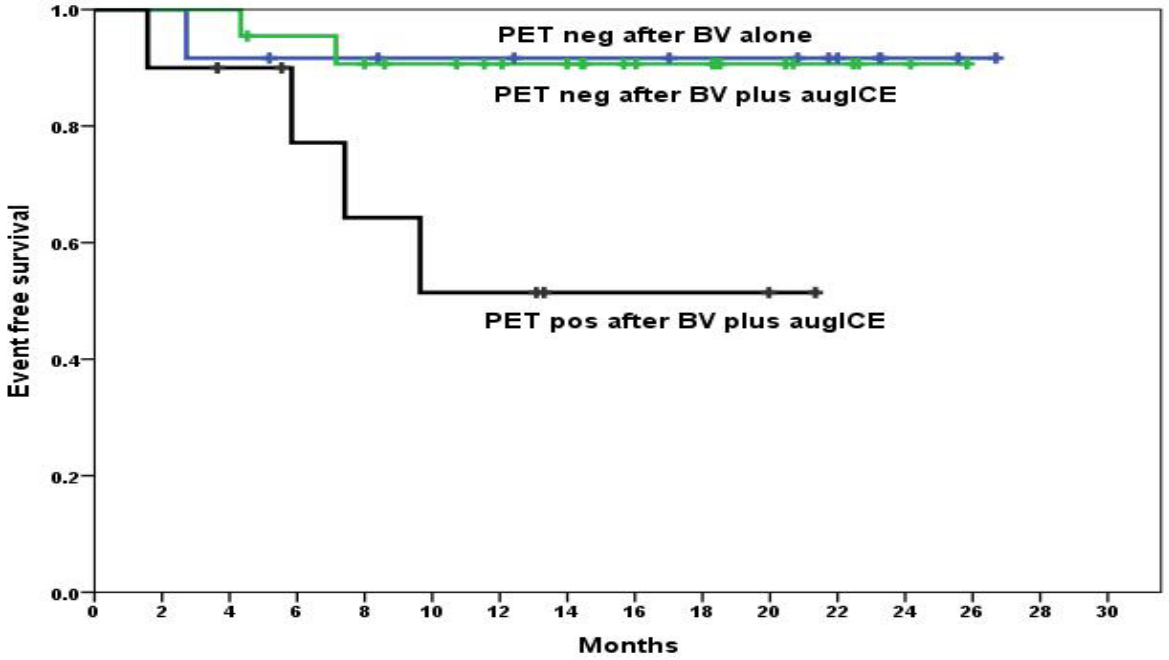


Summary:

- **45 patients enrolled**
- **27% PET negative after BV alone (avoided ICE)**
- **76% PET negative after whole treatment program**
- **All but 1 patient proceeded to ASCT**

Moskowitz, AJ, et al. Lancet Oncol 2015;16: 284-92

EFS according to treatment and PET status



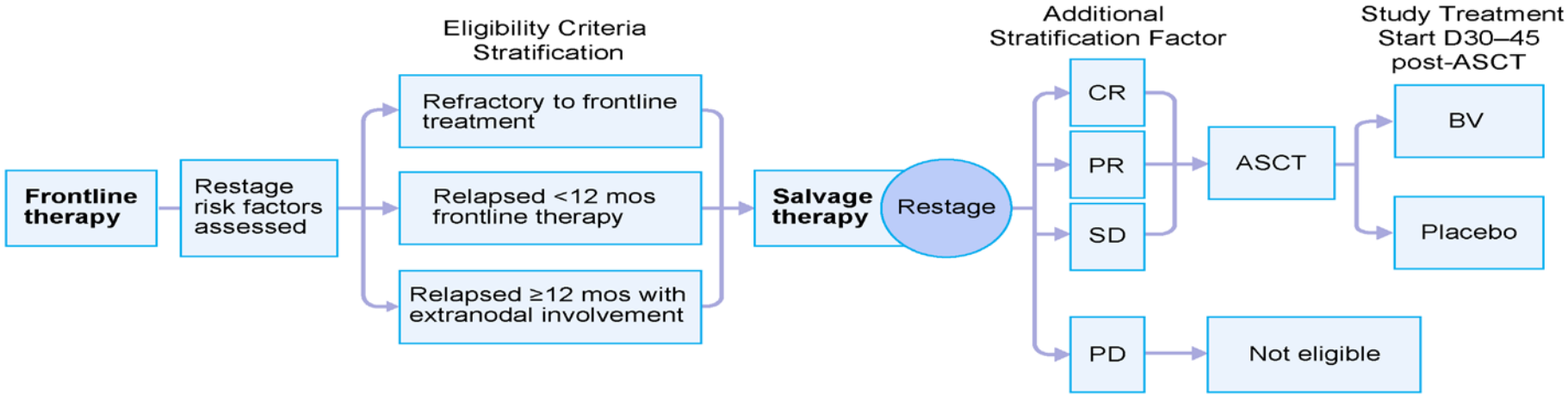
ATHERA Study- Lancet 2015

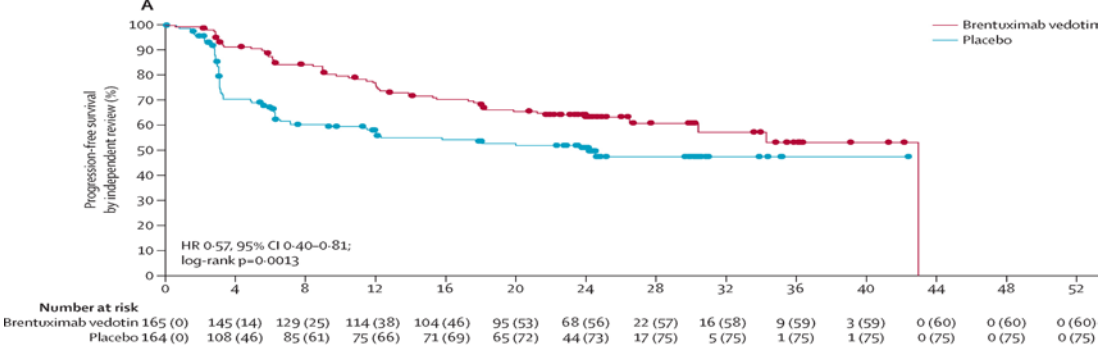
Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial

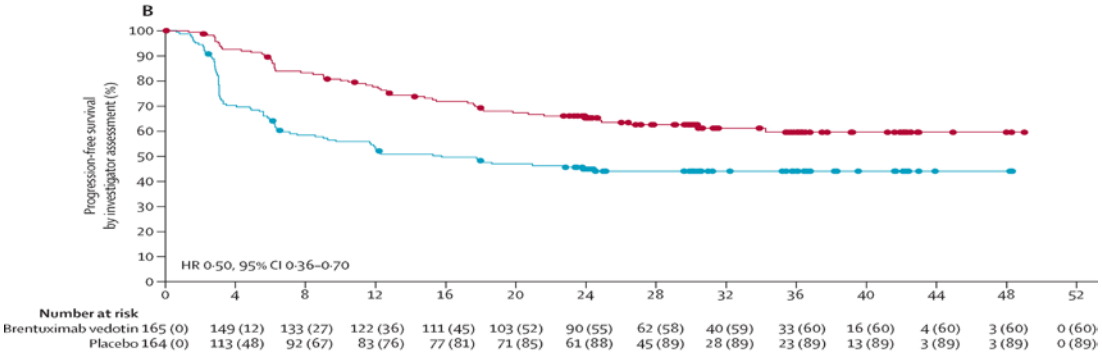
Craig H Moskowitz, Auayporn Nademanee, Tamas Masszi, Edward Agura, Jerzy Holowiecki, Muneer H Abidi, Andy I Chen, Patrick Stiff, Alessandro M Gianni, Angelo Carella, Dzhelil Osmanov, Veronika Bachanova, John Sweetenham, Anna Sureda, Dirk Huebner, Eric L Sievers, Andy Chi, Emily K Larsen, Naomi N Hunder, Jan Walewski, for the AETHERA Study Group

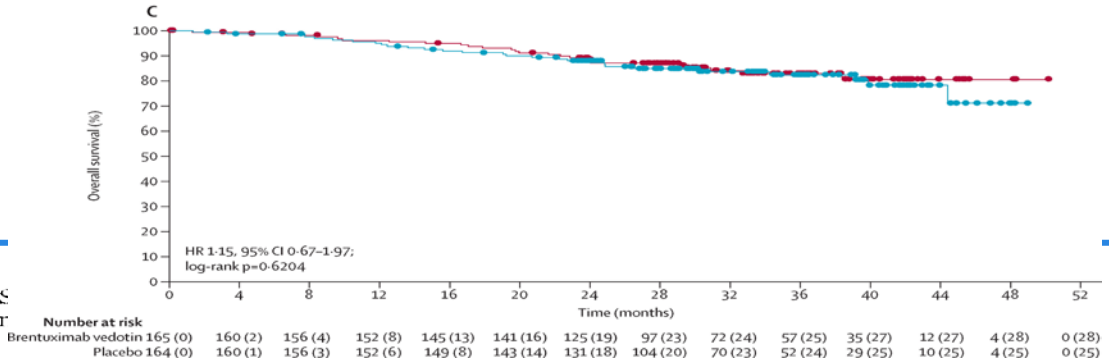
Study Design and Key Eligibility Criteria

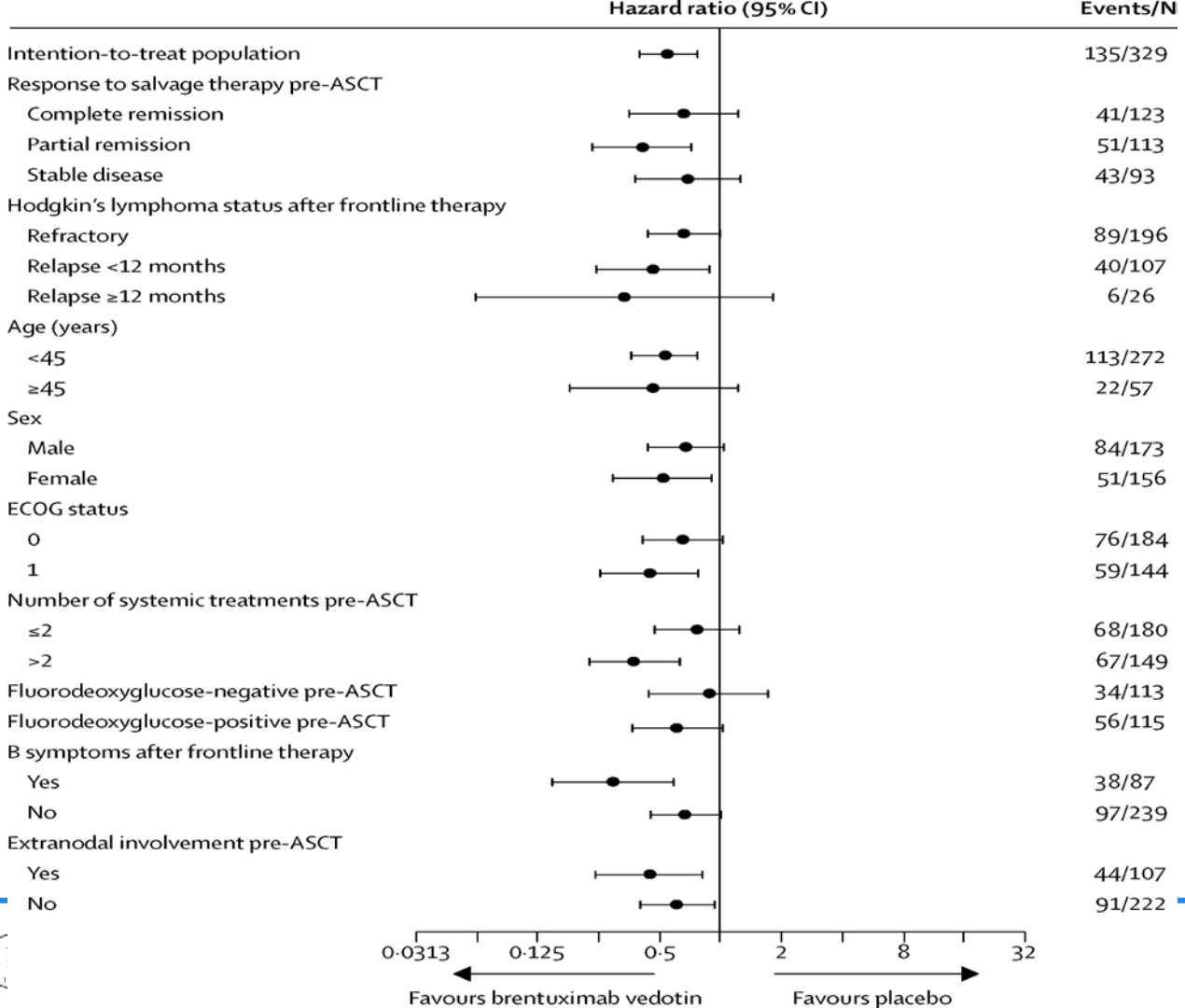
- 329 patients were randomized at 78 sites in North America and Europe




A
Brentuximab vedotin
Placebo
Progression-free survival by independent review (%)
HR 0·57, 95% CI 0·40–0·81;
log-rank p=0·0013
Number at risk
Brentuximab vedotin 165 (0) 145 (14) 129 (25) 114 (38) 104 (46) 95 (53) 68 (56) 22 (57) 16 (58) 9 (59) 3 (59) 0 (60) 0 (60) 0 (60)
Placebo 164 (0) 108 (46) 85 (61) 75 (66) 71 (69) 65 (72) 44 (73) 17 (75) 5 (75) 1 (75) 1 (75) 0 (75) 0 (75) 0 (75)


B
Progression-free survival by investigator assessment (%)
HR 0·50, 95% CI 0·36–0·70
Number at risk
Brentuximab vedotin 165 (0) 149 (12) 133 (27) 122 (36) 111 (45) 103 (52) 90 (55) 62 (58) 40 (59) 33 (60) 16 (60) 4 (60) 3 (60) 0 (60)
Placebo 164 (0) 113 (48) 92 (67) 83 (76) 77 (81) 71 (85) 61 (88) 45 (89) 28 (89) 23 (89) 13 (89) 3 (89) 3 (89) 0 (89)


C
Overall survival (%)
HR 1·15, 95% CI 0·67–1·97;
log-rank p=0·6204
Time (months)
Number at risk
Brentuximab vedotin 165 (0) 160 (2) 156 (4) 152 (8) 145 (13) 141 (16) 125 (19) 97 (23) 72 (24) 57 (25) 35 (27) 12 (27) 4 (28) 0 (28)
Placebo 164 (0) 160 (1) 156 (3) 152 (6) 149 (8) 143 (14) 131 (18) 104 (20) 70 (23) 52 (24) 29 (25) 10 (25) 4 (25) 0 (25)

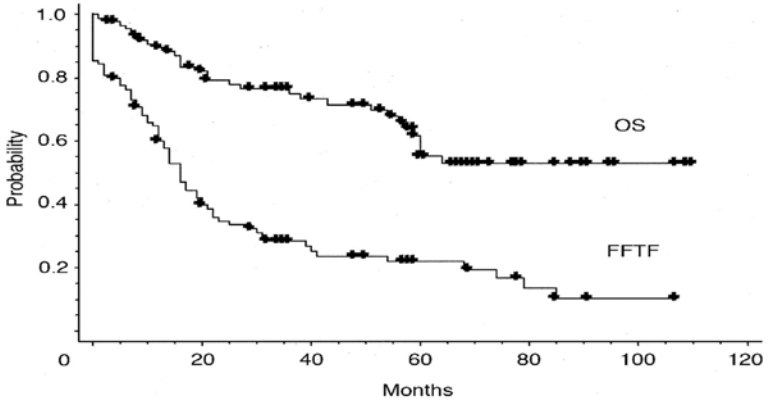

Hazard ratio (95% CI)
Events/N
Intention-to-treat population 135/329
Response to salvage therapy pre-ASCT
Complete remission 41/123
Partial remission 51/113
Stable disease 43/93
Hodgkin's lymphoma status after frontline therapy
Refractory 89/196
Relapse <12 months 40/107
Relapse ≥12 months 6/26
Age (years)
<45 113/272
≥45 22/57
Sex
Male 84/173
Female 51/156
ECOG status
0 76/184
1 59/144
Number of systemic treatments pre-ASCT
≤2 68/180
>2 67/149
Fluorodeoxyglucose-negative pre-ASCT 34/113
Fluorodeoxyglucose-positive pre-ASCT 56/115
B symptoms after frontline therapy
Yes 38/87
No 97/239
Extranodal involvement pre-ASCT
Yes 44/107
No 91/222
0·0313
0·125
0·5
2
8
32
Favours brentuximab vedotin
Favours placebo

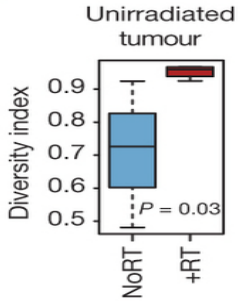
A Phase II Study of Pembrolizumab and Involved Site Radiation Therapy (ISRT) for Early Stage Relapsed or Primary Refractory Hodgkin Lymphoma

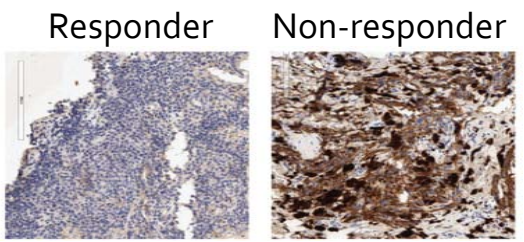
PI: Craig Moskowitz, MD
Co-PI: Joachim Yahalom, MD
Santosh Vardhana MD, PhD
Gunjan Shah MD, MS
August 17, 2016

Hypothesis

- HDT/ASCT may be overtreating a subset of patients who have excellent outcomes in relapsed HL
- Radiation therapy alone can induce durable remissions, particularly in patients with early stage disease at relapse
- Radiation therapy induces a diverse repertoire of anti-tumor T cells, but progression is associated with upregulation of the immune checkpoint PD-L1



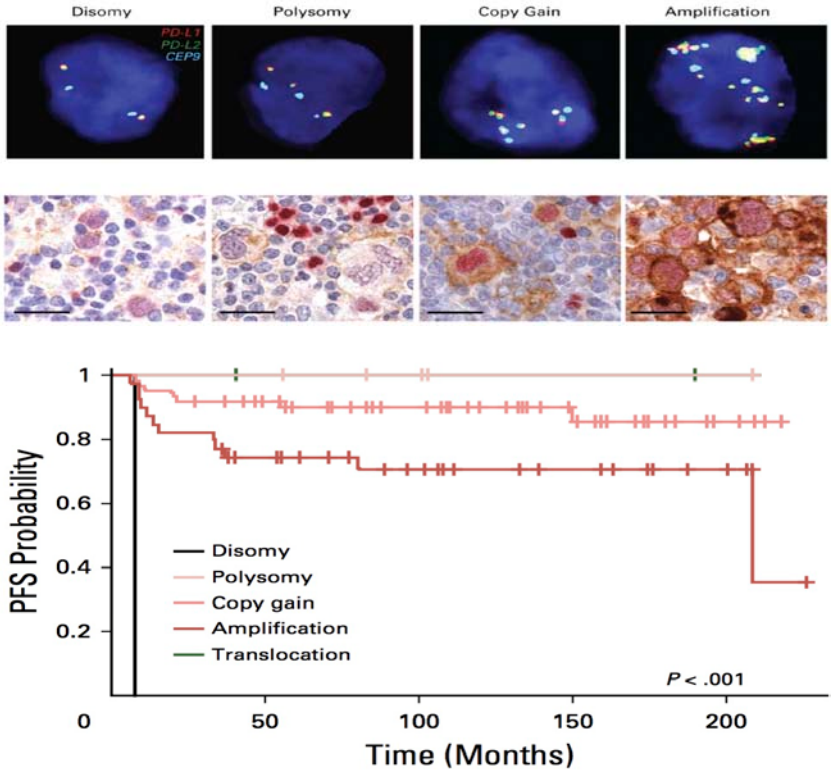




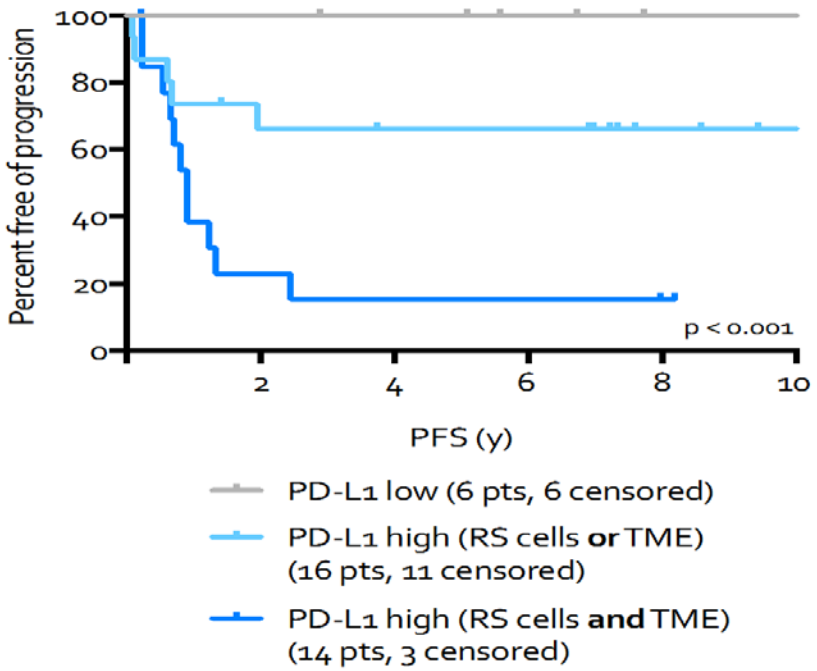
PD-L1 IHC

Josting et al, *J Clin Oncol* 2005
Twyman-Saint Victor, *Nature* 2015

PD-L1/L2 amplification is associated with poor prognosis in HL



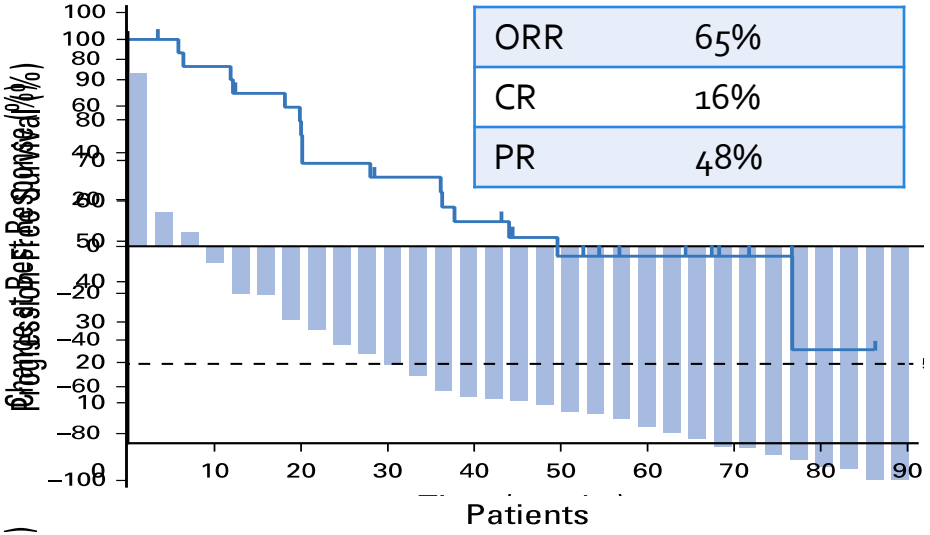
Relapsed HL patients



Roemer et al, *J Clin Oncol* 2016

Pembrolizumab is highly effective in heavily pre-treated HL patients

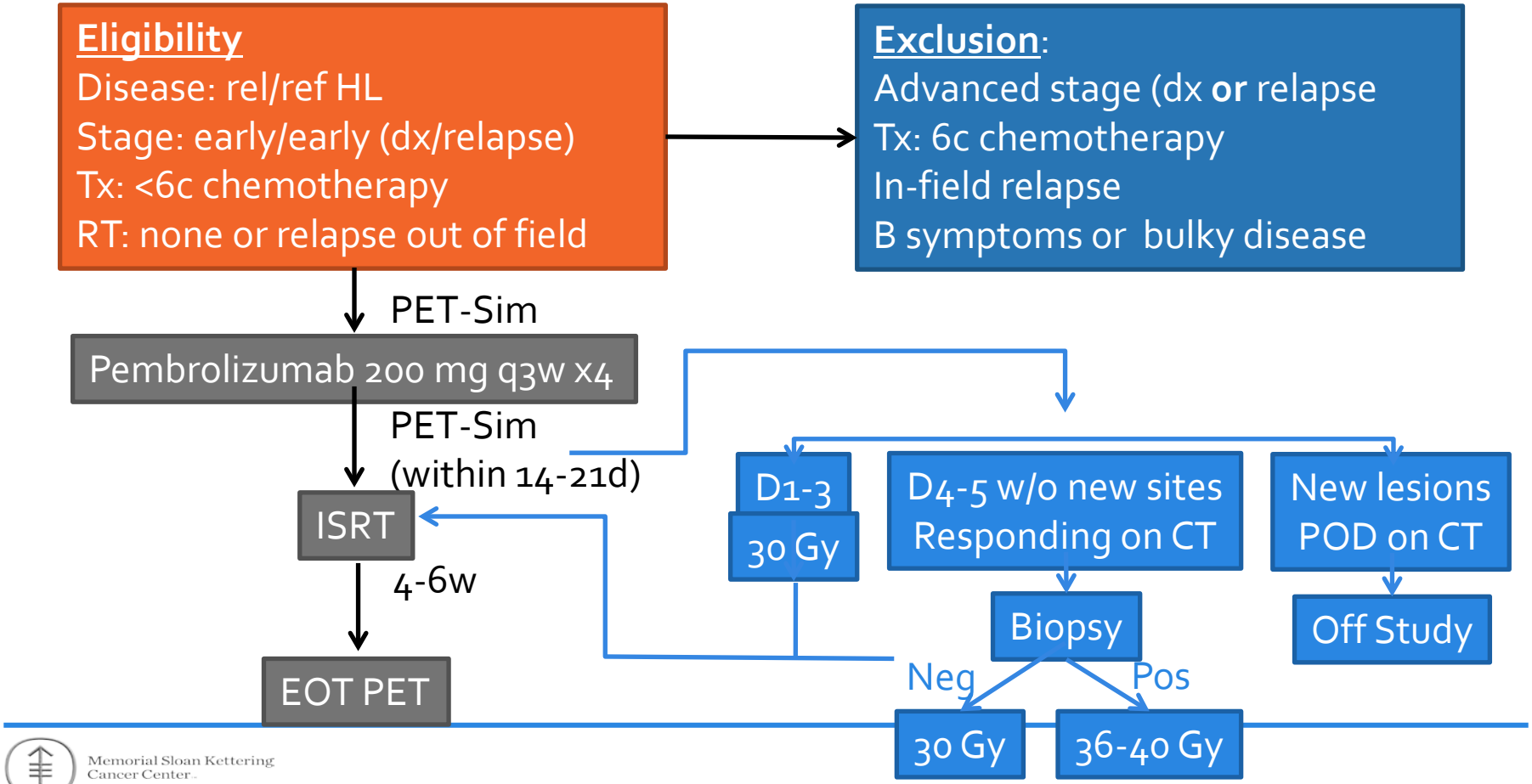
Patients	31
Age	32 (20-67)
Sex	M 58% F 42%
Histology	NS 97% MC 3%
Bulky disease	6%
Prior Tx	5+ 55%
Prior BV	100%
Prior auto-SCT	71%



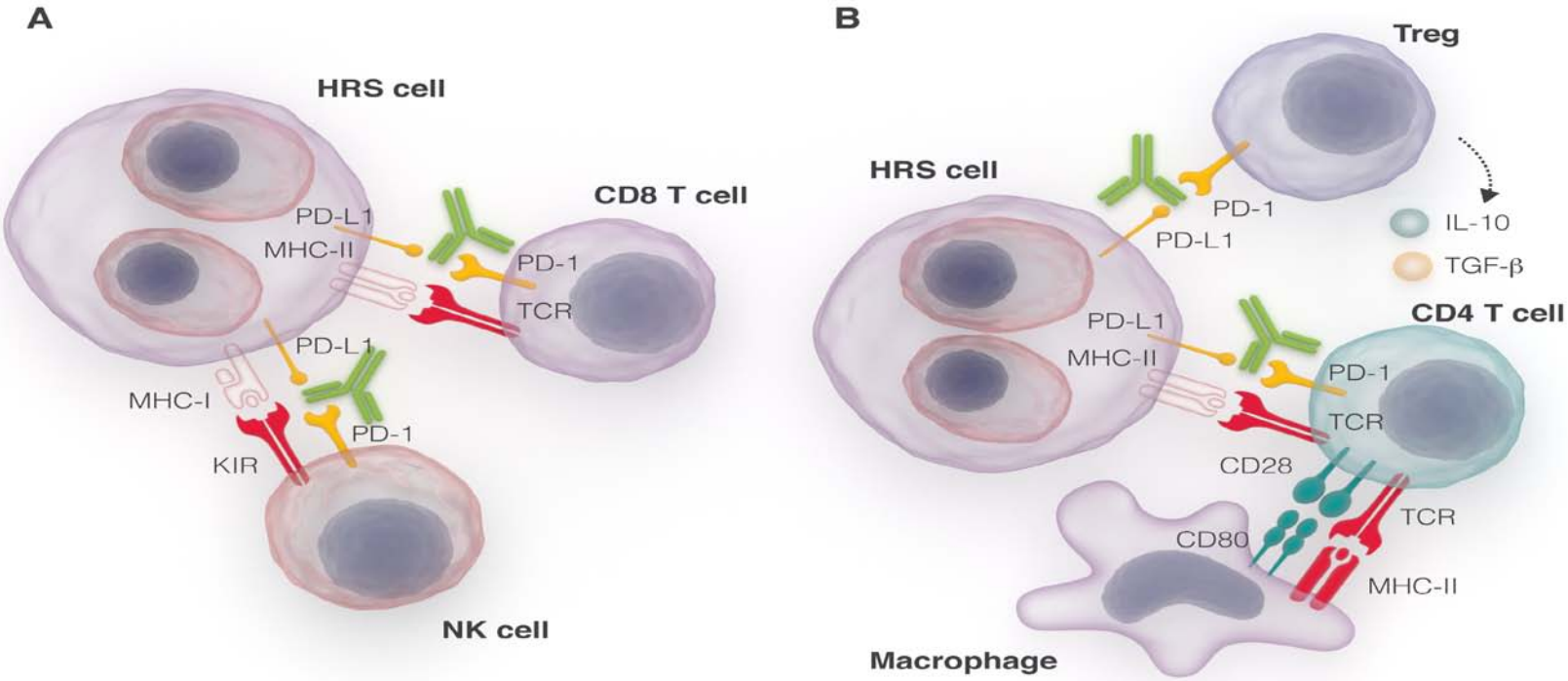
Ansell et al, *J Clin Oncol* 2016

Aims

1. Evaluate the **complete remission rate** of pembrolizumab combined with ISRT as an alternative to HDT/ASCT in early stage rel/ref HL patients
2. Determine the **single agent response rate** of pembrolizumab in this population
3. Determine the **toxicity and 2-year EFS** with this strategy
4. Evaluate **biological markers of response and resistance:**
    1. Tumor and TME immune evasion markers
    2. Development of anti-tumor T-cell clonal expansion
    3. T-effector:T-reg ratio
    4. Serum TARC


Eligibility
Disease: rel/ref HL
Stage: early/early (dx/relapse)
Tx: <6c chemotherapy
RT: none or relapse out of field
Exclusion:
Advanced stage (dx or relapse
Tx: 6c chemotherapy
In-field relapse
B symptoms or bulky disease
PET-Sim
Pembrolizumab 200 mg q3w x4
PET-Sim
(within 14-21d)
ISRT
4-6w
EOT PET
D1-3
30 Gy
D4-5 w/o new sites
Responding on CT
New lesions
POD on CT
Biopsy
Off Study
Neg
Pos
30 Gy
36-40 Gy

Anti-PD-1 works in HL…but how?



Vardhana and Younes, *Haematologica* 2016

Summary

- In most relapsed/refractory patients with HL or NHL ISRT is an important component of the salvage regimen
- In some HL cases with primarily nodal extensive disease we add STLI or TLI to the conditioning regimen
- We find using RT pre-transplant more logical, feasible and safe. It will practically engage more patients
- The program is safe short and long-term
- It requires involvement and coordination of the radiation oncology and medical oncology teams

Future Predictions for HL Salvage

- More patients that had chemotherapy alone.
- More patients that were exposed to Brentuximab early
- RT will remain a major player in salvage
- RT should be orchestrated optimally with old and new agents
- Not all chemo refractory patients will require high dose therapy and ASCT
- Standard allogeneic SCT will be replaced by other immunological interventions

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Marginal Gastric Zone Lymphoma: Role of RT

Joachim Yahalom, M.D.
Memorial Sloan Kettering Cancer Center
New York ,NY, USA

Memorial Sloan Kettering Cancer Center

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

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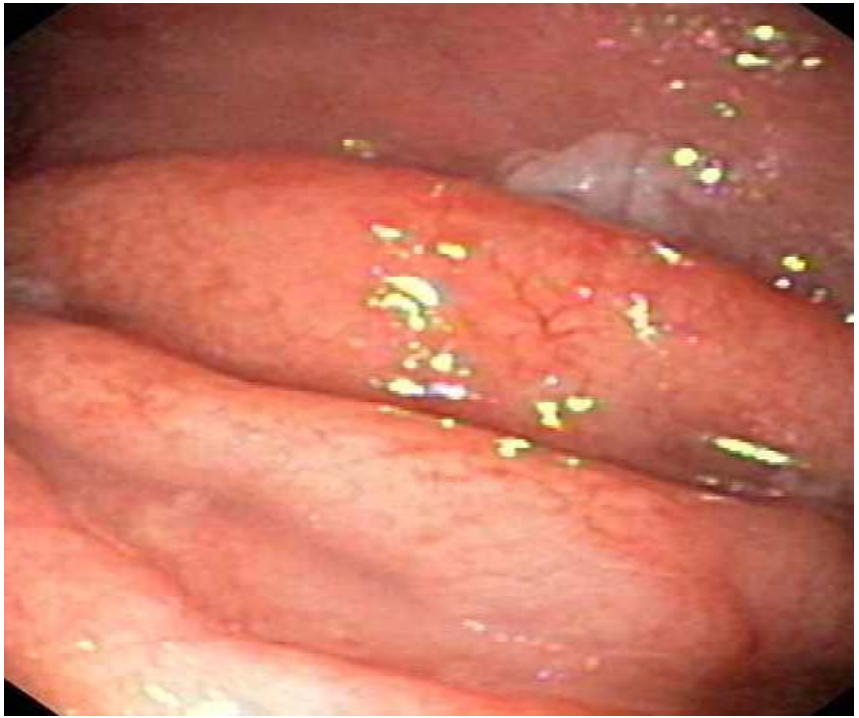

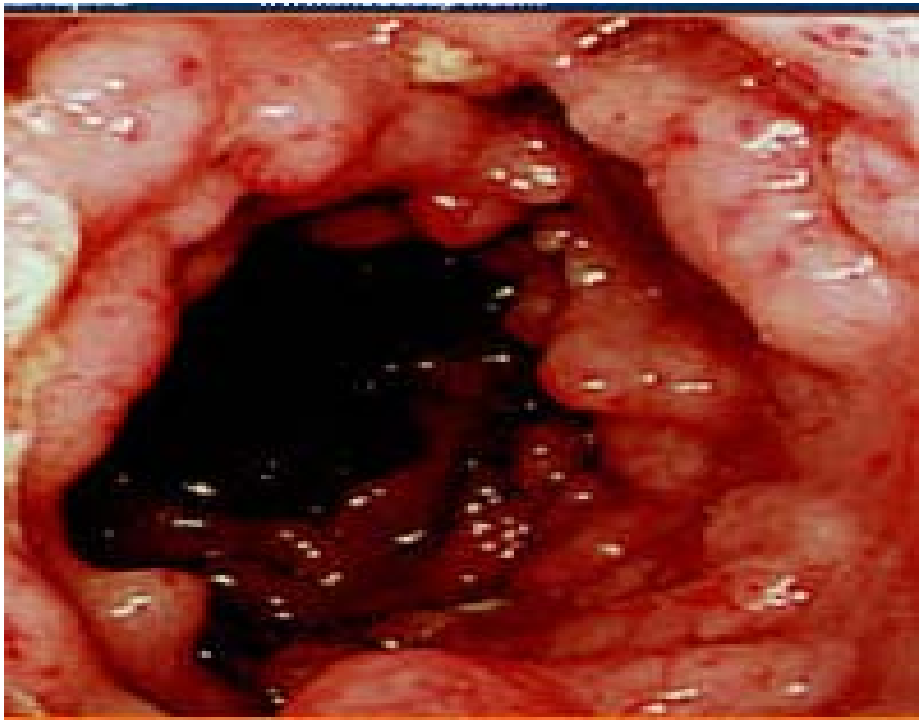

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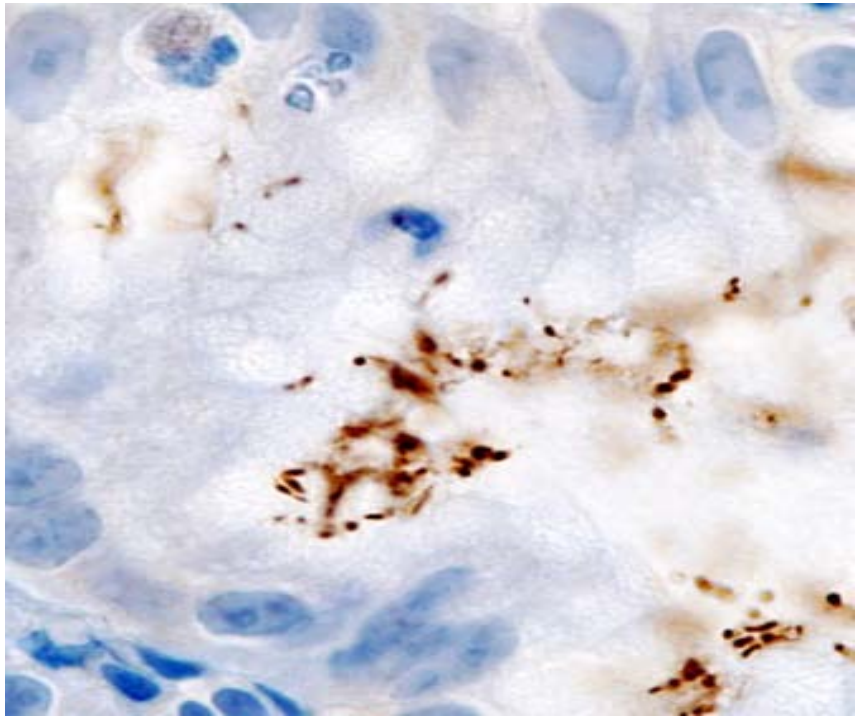
H. Pylori



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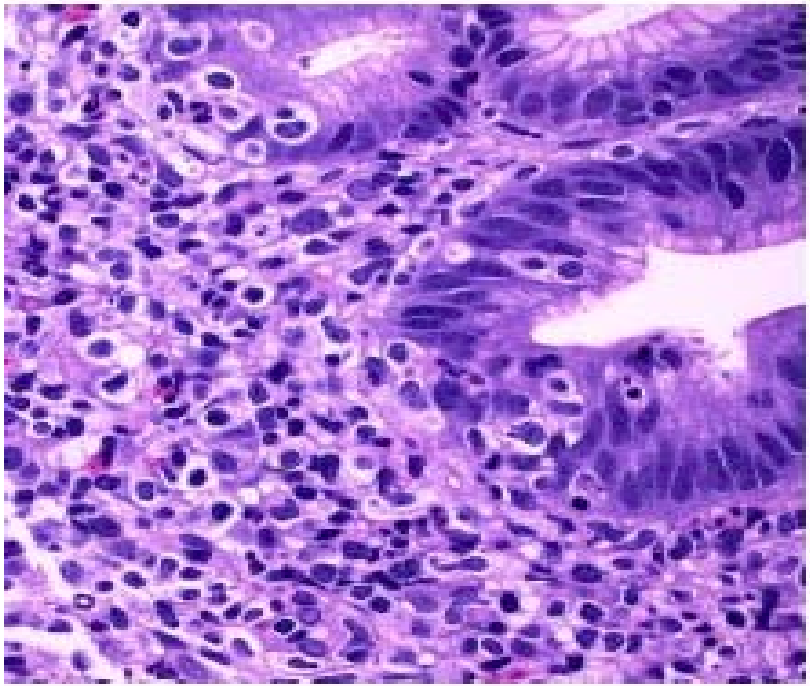

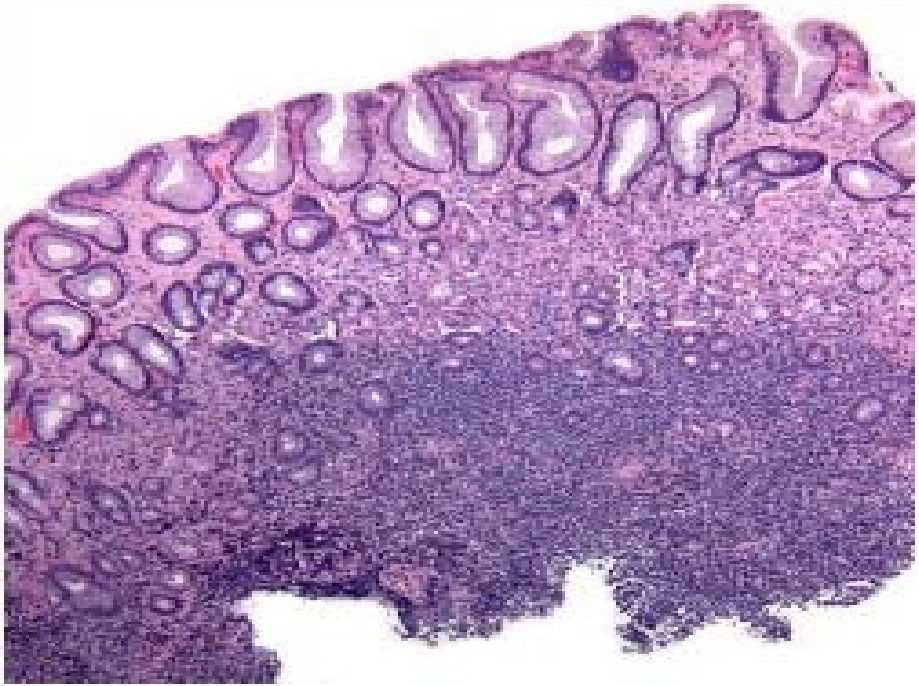

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RT of Gastric Lymphomas

- Marginal Zone Lymphoma (MZL) – Most common
  - RT is the standard treatment in North America for "H. Pylori-independent" Gastric MZL (or "MALT")
  - H. pylori –not present
  - H. pylori responded to antibiotics, but MZL persists for a long time
  - H. pylori resistant to multiple antibiotics, MZL persists
  - Failure of antibiotics - MZL progression
  - Failure of antibiotics - difficult symptoms
- **Diffuse Large B-Cell Lymphoma** (many are transformed MZL)
  - RT consolidation after R-CHOP induced CR

Involved-field Radiotherapy for H. pylori-independent Gastric Marginal Zone (MALT) Lymphoma:

23 years of experience with 131 patients

1991-2012 at MSKCC

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Patient Characteristics

Characteristic	# (range)
Median Age at Diagnosis	61 yrs (25-89)
Median Follow-up	4.4 yrs (0-19.9)
Characteristic	**N (%)**
Female	73 (56%)
Male	58 (44%)
Stage at diagnosis	
I	116 (89%)
II	6 (5)
III	0 (0) *
IV	9(5)

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Diagnostic/Staging Workup

Modality	N (%)	% +	% -
EGD	131 (100)	100	0 *
PET Scan	67 (51)	64	36
CT Scan	121 (92)	49	51
Bone Marrow Biopsy	83	99	1

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H. Pylori

Characteristic	N (%)
H. Pylori at Diagnosis	
No	107 (82)
Yes	21 (16)
Unknown	3 (2)
Antibiotics given	
No	71 (54)
Yes	60 (46)

Characteristic	N (%)
MALT response to abx	
No response	53 (40)
Relapse	3 (2)
Partial response → POD	1 (1)
Unknown	3 (2)

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Chemotherapy

Characteristic	N (%)
Chemotherapy Treatment	
No	124 (95)
Yes	7 (5)
Chemotherapy Regimens	
CHOP	2 (29)
Rituximab	2 (29)
Fludarabine	1 (14)
Chlorambucil and Prednisone	1 (14)
Multiple Regimens	1 (14)

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Radiotherapy

Characteristic	N (%)
RT Dose	
≤3000 cGy	120 (92)
>3000 cGy	11 (8)
Median Dose (cGy)	3000
Treatment Volume	
Stomach	121 (92)
Stomach + Duodenum	1 (1)
Duodenum only	4 (3)
Stomach + lymph nodes	5 (4)

Response to RT

Response to RT	N (%)
Complete response	127 (97)
Stable disease	3 (2)
POD	0
Other	1 (1)

Stomach relapse after RT

Median time to 1st relapse	13 months (0.0 – 148 months)

Relapses after RT	N (%)
No relapse	124 (95)
Refractory	2 (1.5)
Relapse	5 (4)

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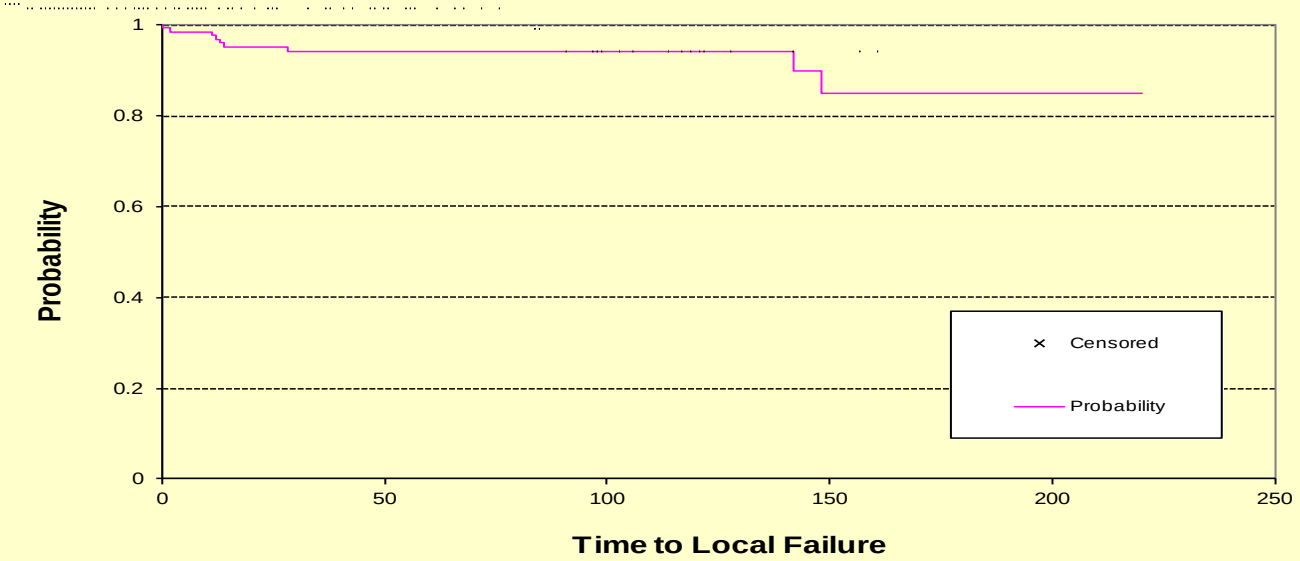
Freedom from Local Failure



5 years	10 years	15 years
94%	94%	85%

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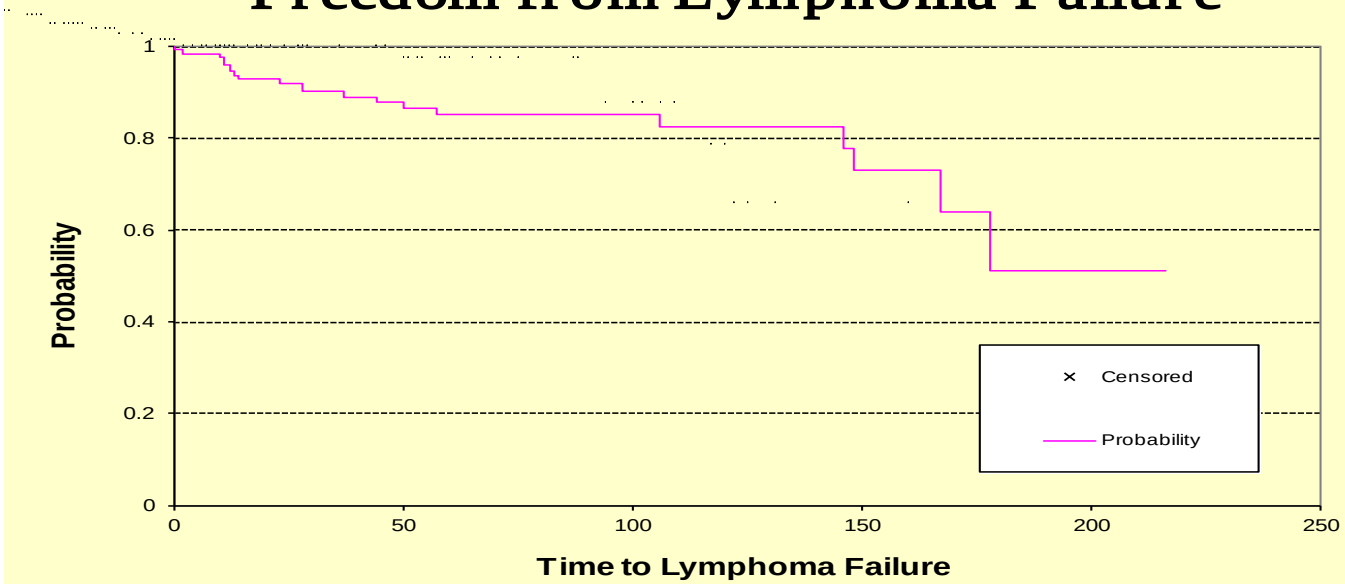
Freedom from Lymphoma Failure



5 years	10 years	15 years
85%	83%	51%

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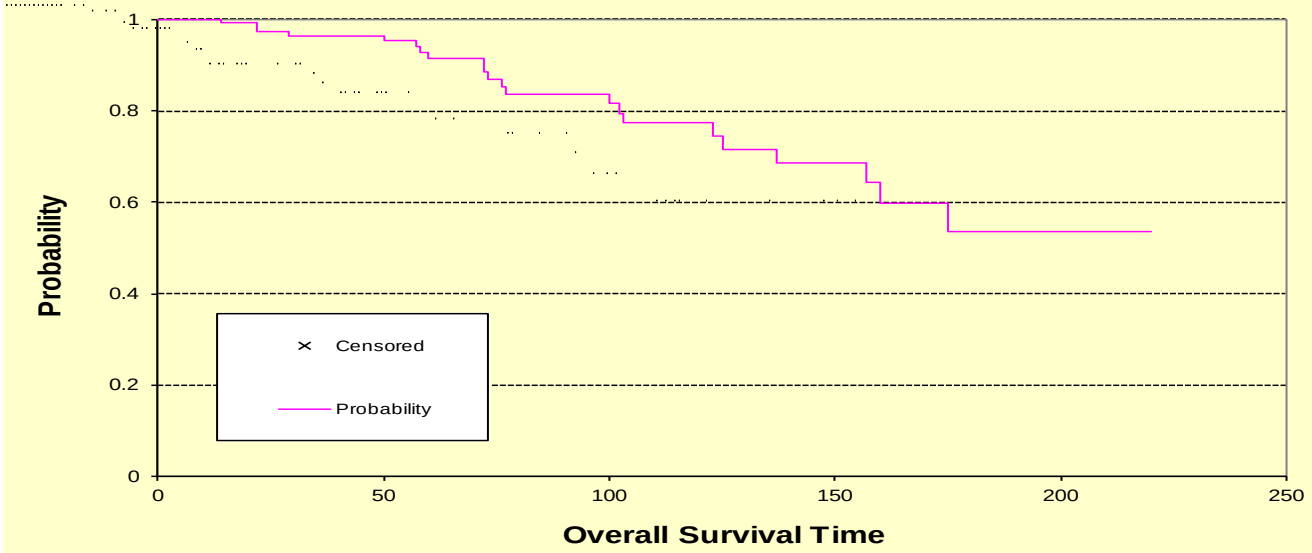
Overall Survival



5 years	10 years	15 years
91%	77%	54%

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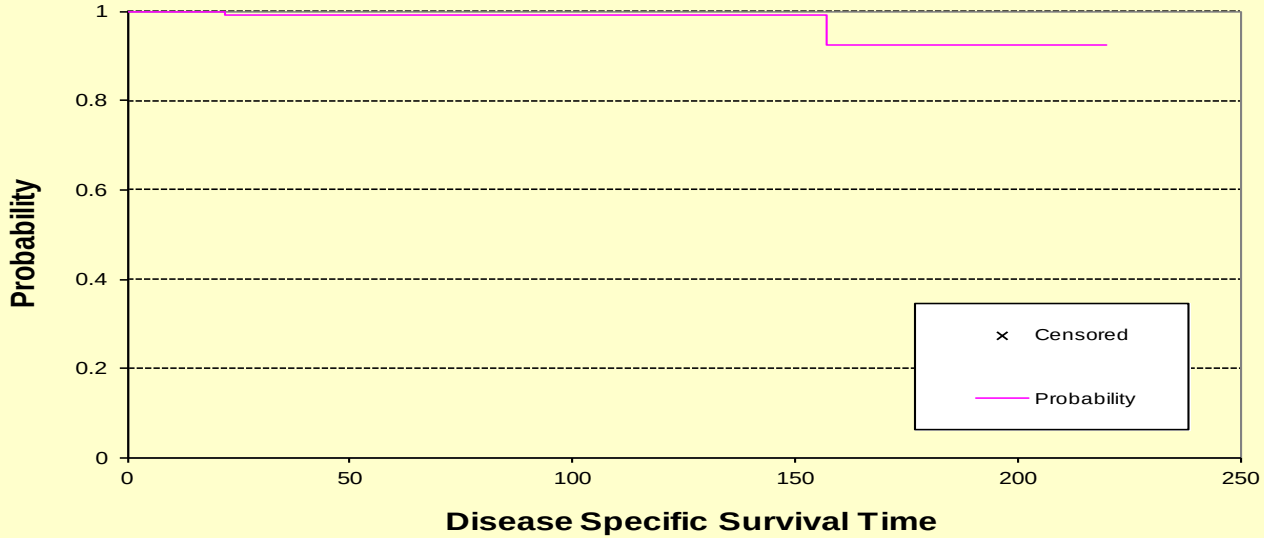
Disease Specific Survival



5 years	10 years	15 years
99%	99%	92%

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Principles of RT of Stomach

Principles of Gastric Lymphoma RT (1)

- For both MZL and DLBCL – The whole stomach constitutes the Clinical Target Volume (CTV)
- The duodenum is included is it was involved with the stomach
- Peri-gastric and adjacent lymph nodes are included only if suspicious by any imaging including endoscopic ultrasound

Principles of Gastric Lymphoma RT (2)

- The final volume also accounts for changes in stomach position during respiration
- The stomach is ideally treated while empty; but slight changes in volume should be accounted for
- The dose rarely exceeds 30 Gy; thus, acute or chronic complications are unlikely.
- Yet, RT exposure of kidneys, heart, lung and liver and bowl should be reduced as much as possible

Gastric Anatomy

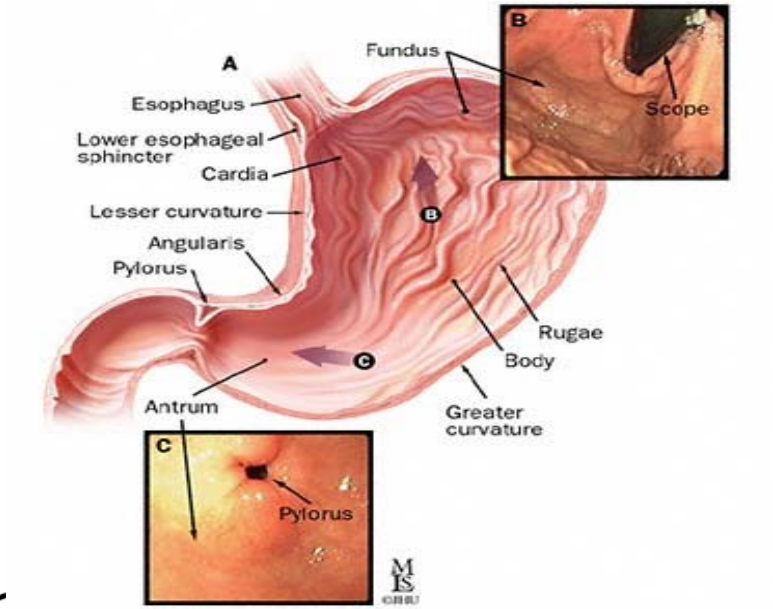

Figure 6. Normal internal anatomy of stomach **(A); B, C,** endoscopic views.

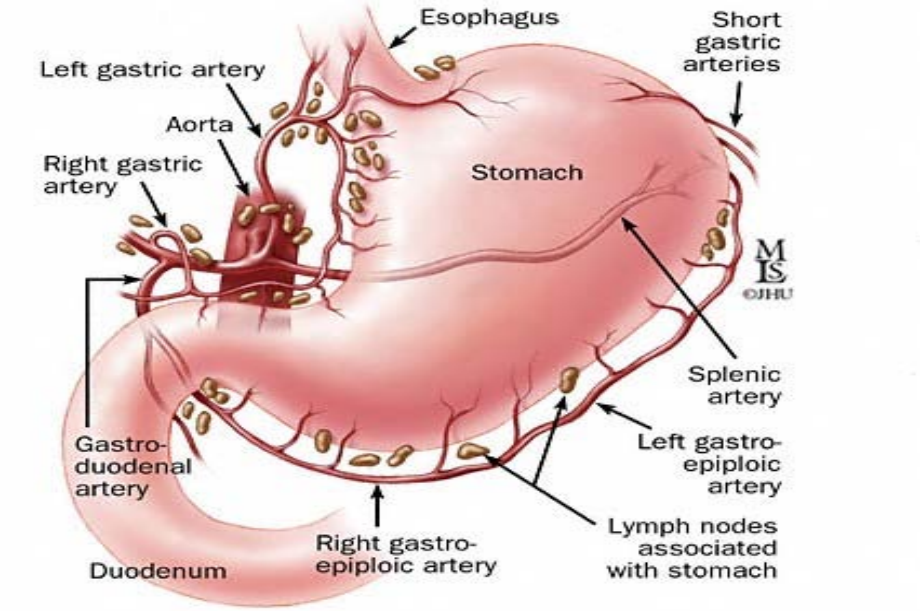

Figure 7. Normal external anatomy of the stomach with arteries and lymph nodes.

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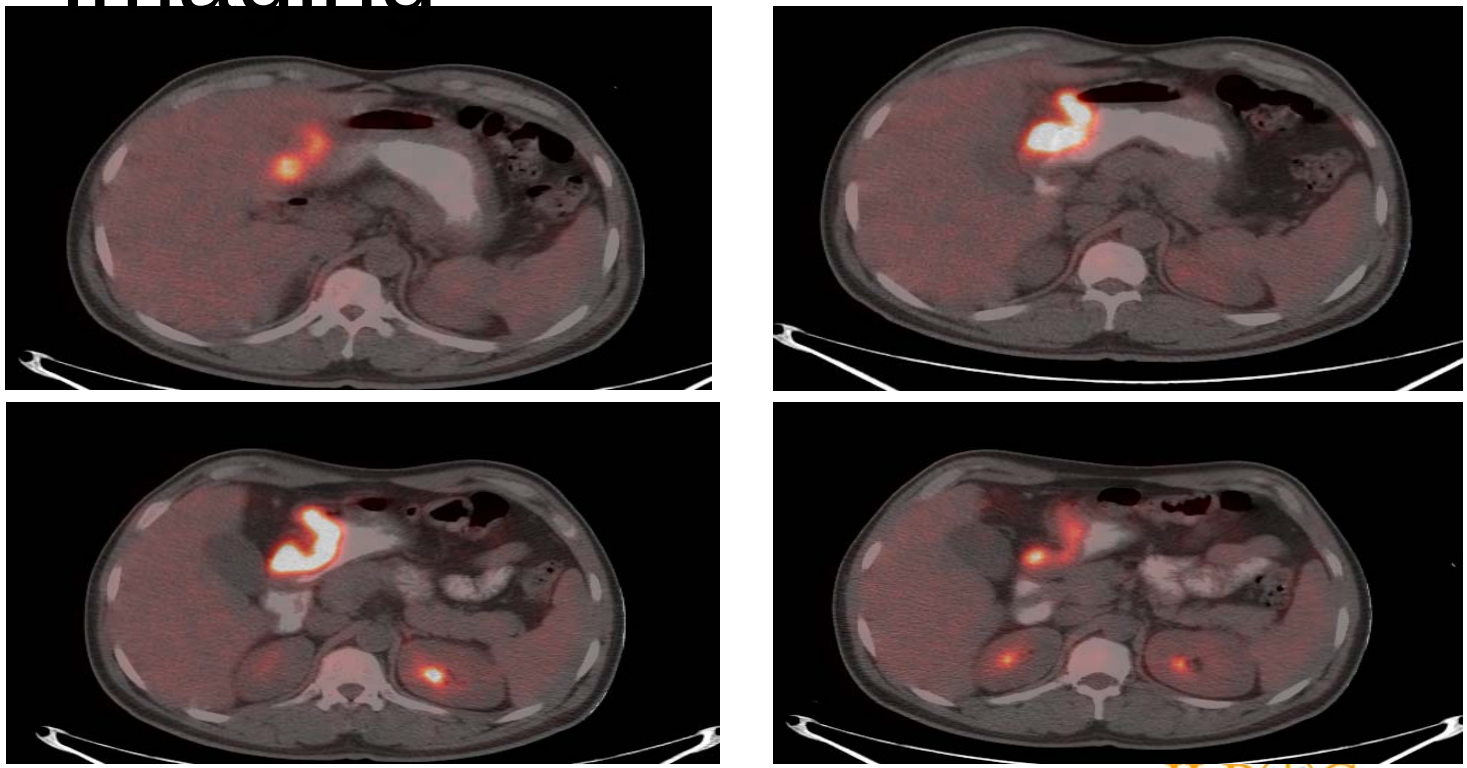
Imaging



*But in MZL often PET and CT may be negative

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RT of Stomach: Pre Planning Studies

- Details of endoscopic studies
- Endoscopic ultrasound and directed biopsy in case of thickened wall/suspected transformation
- In patients that may receive RT to large volume of one kidney, renal scan may provide important information

RT of Stomach: simulation

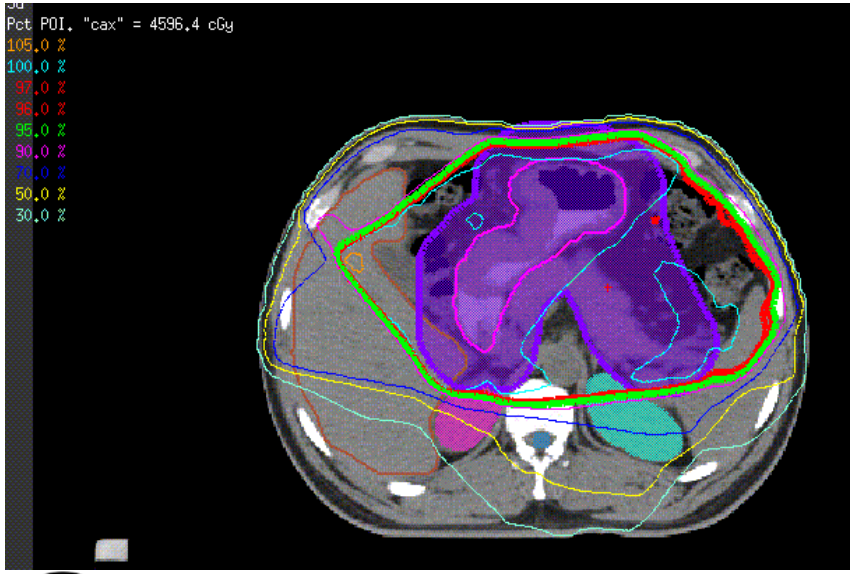
- The stomach volume and position is affected by ingestion of food or liquids. Patients are always simulated and treated with an empty stomach after at least 4 hours/overnight fast.
- Simulate the patient supine with arms up using customized immobilization device.
- A small volume (<50ml) of oral contrast (barium sulfate) should be used in all cases; IV contrast is recommended, if there are suspicious lymph nodes.
- Respiratory motion should be assessed using a 4D-CT scan or fluoroscopy

RT of Stomach: volumes

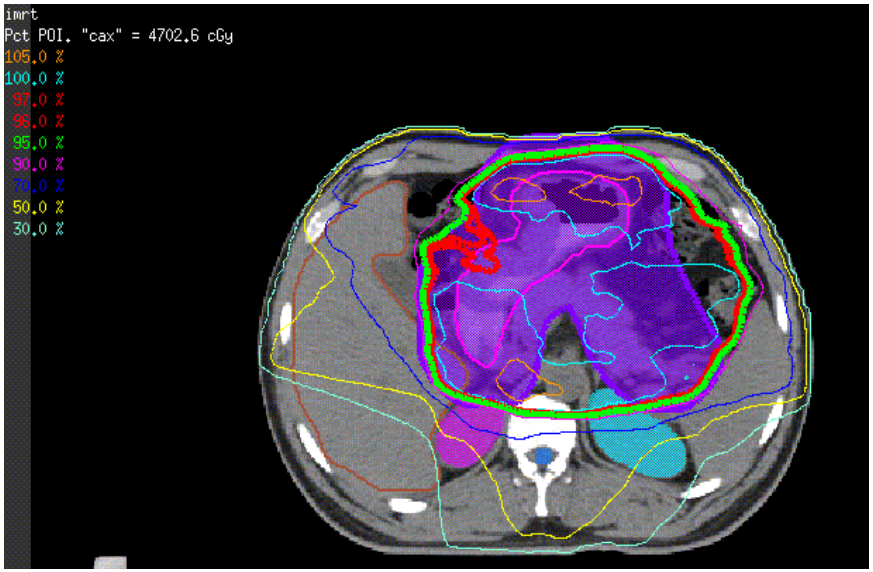
- **GTV:** Gross disease (if visualized on PET and/or CT) and pathologically enlarged lymph nodes
- **CTV**: GTV + stomach volume outlined from gastroesophageal junction to beyond the duodenal bulb; the whole wall is included (perigastric nodes are encompassed, if visible).
- **ITV** is determined by 4-D CT or by fluoroscopy to track variation of stomach position during respiration. An additional margin of at least 1-2 cm may be added to the CTV to accommodate stomach movement or internal volume changes.
- **PTV** is influenced by set-up variation; in the abdomen 1 cm over final ITV is advised.
- **OAR** volumes for consideration in planning include: kidneys, liver, heart. lungs, bowel, cord.

Treatment Planning

3D-CRT



IMRT



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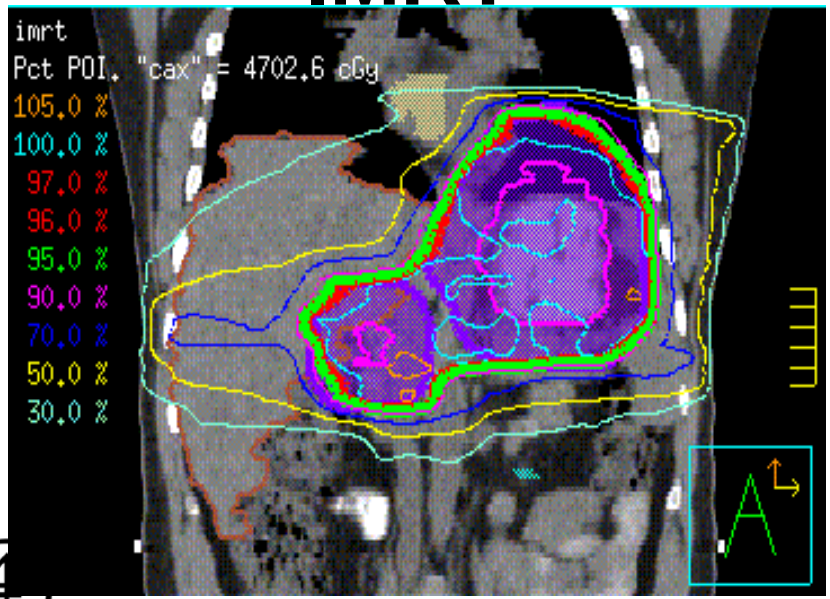
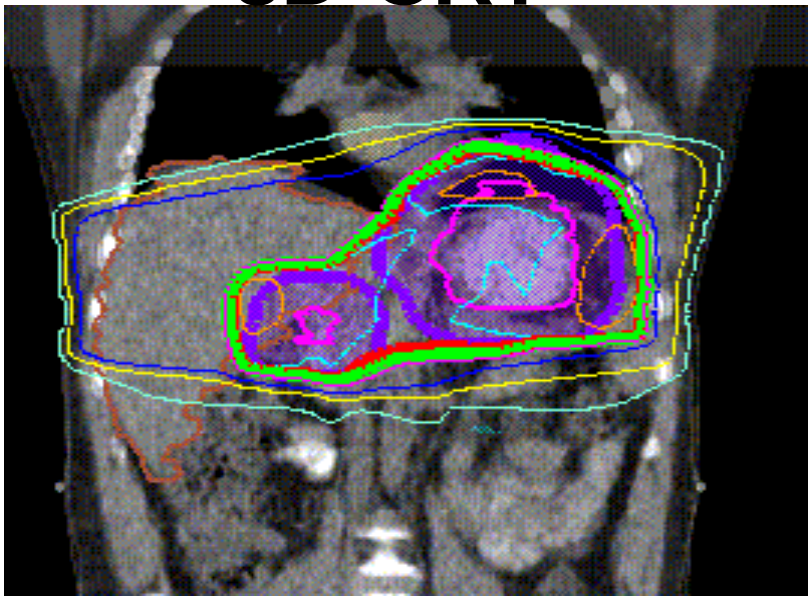
3D-CRT vs. IMRT

IMRT



3D-CRT



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Treatment Planning Goals

Conformal therapy is optimal

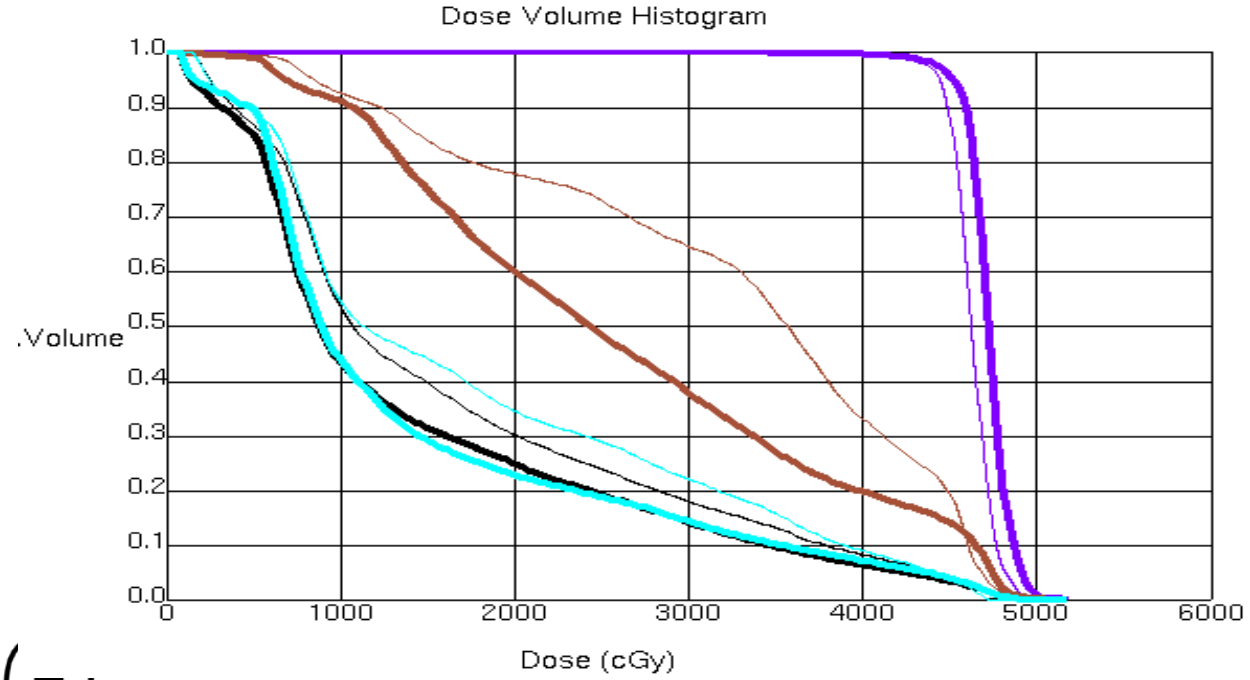
- Della-Bianca et al. compared AP/PA vs. 3D-CRT vs. IMRT
- Advantage to conformal therapy when PTV was in close proximity or overlapped with kidney
- IMRT led to further decrease in left kidney and liver dose

Potential advantages in some cases to IMRT over 3D-CRT
Goal of homogeneous dose delivery (D95 >95%)
Doses to normal structures as low as reasonably achievable (ALARA)

Sparing of kidney and liver

- Kidney dose: limited to <20 Gy to 2/3 of kidney
- Liver dose: Mean dose < 30 Gy

DVH: 3D-CRT vs. IMRT



--- Both Kidneys

--- Left Kidney

--- Liver

--- PTV

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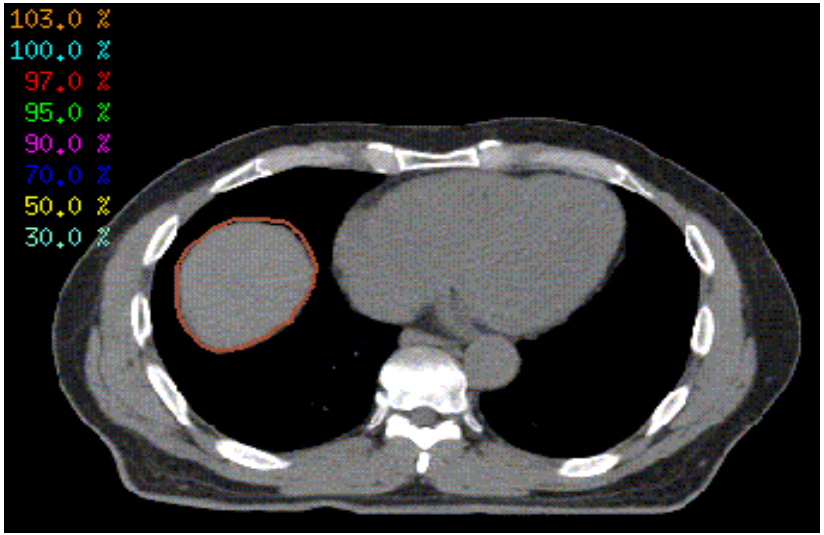
Respiratory Motion

Deep Inspiration



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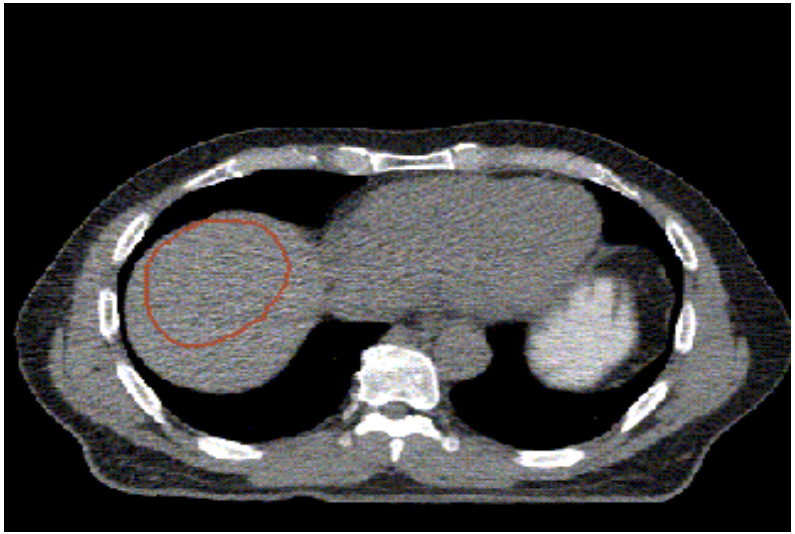

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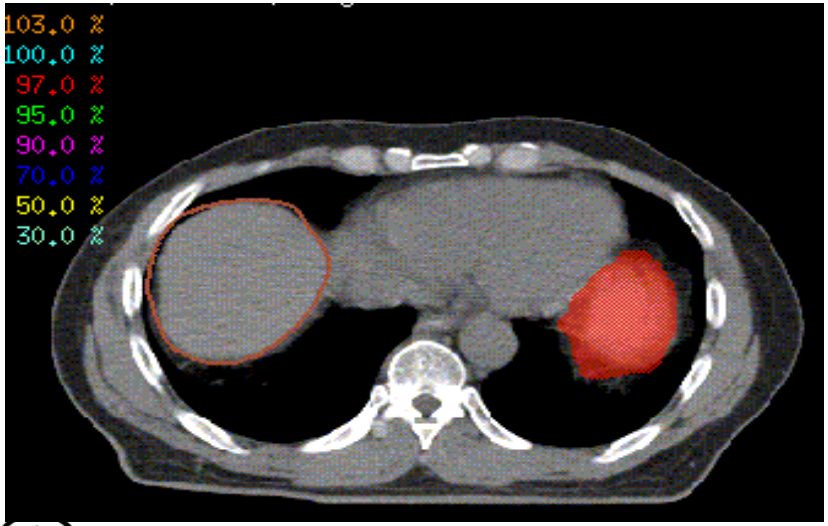
Respiratory Motion

Deep Inspiration



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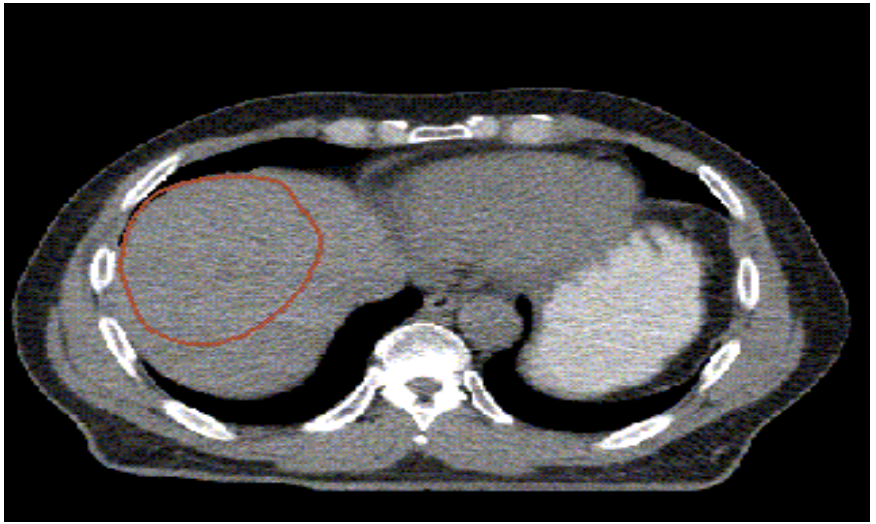

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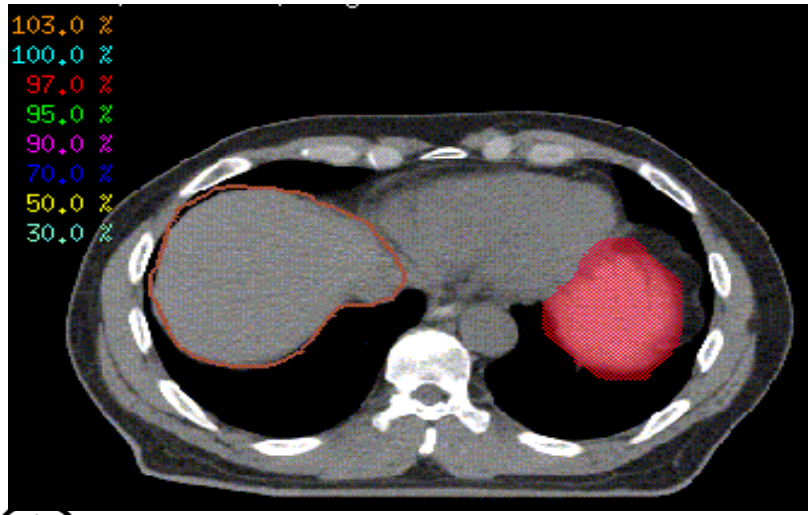
Respiratory Motion

Deep Inspiration



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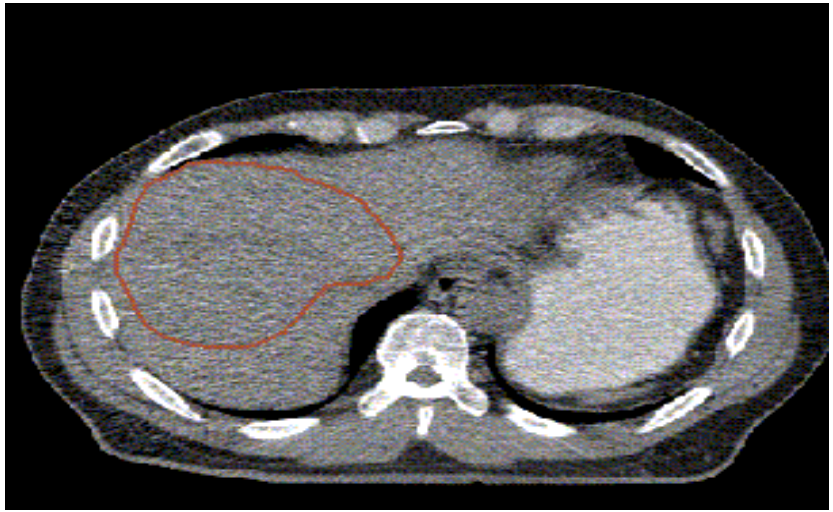

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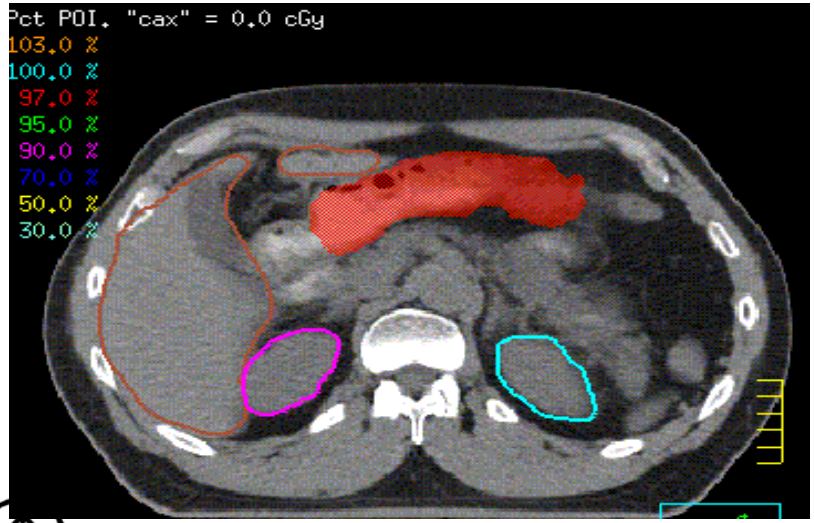
Respiratory Motion

Deep Inspiration



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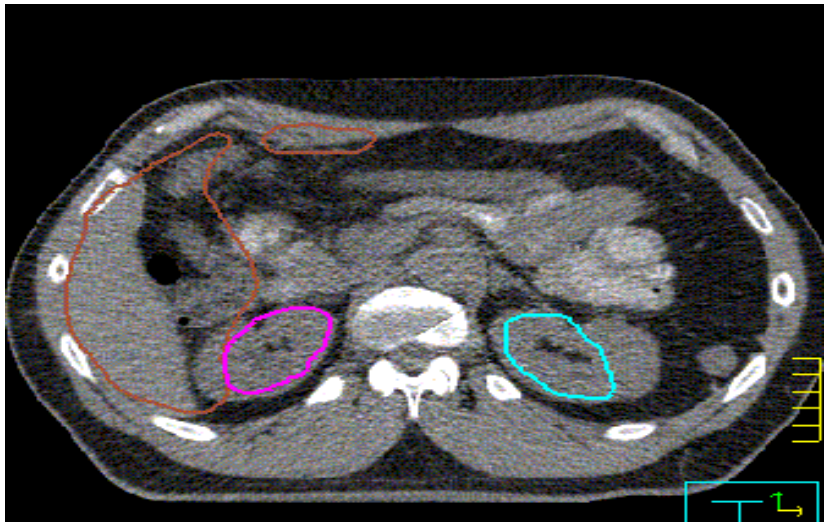

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Conclusions

- Recommend use of modern radiation techniques
- Target volume of stomach and perigastric nodes in gastric lymphoma
- Margin incorporating 4D CT scan for respiration motion assessment
- Radiation dose of : 30 Gy in 15-20 fractions for Gastric MALT and response-based for DLBCL
- Conformal radiation delivery techniques

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The Diminishing and Selective Role of RT in Advanced-stage Hodgkin Lymphoma (HL)

Joachim Yahalom, MD

Memorial Sloan-Kettering cancer Center,

New York City, NY, USA

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Who is an “advanced-stage” patient?

- Stage IV bulky/non-bulky/E site(s)
- Stage III bulky/non-bulky
- *Stage II bulky (with/without B symptoms)*

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The Evolution of Consolidation RT in Advanced-Stage HL

Type of Chemotherapy

- Standard Regimens (ABVD and similar)
- More Intensive Regimen (escalated BEACOPP)
- New Drug Combinations (Brentuximab-AVD)

The Evolution of Consolidation RT in Advanced-Stage HL

By Disease Parameters or by Response Criteria

- RT to All disease sites (EORTC H34)
- RT to Initial bulky by CT (Stanford V, U.S. Intergroup)
- RT to Initial bulk and residual CT (HD-9, UK LY09)
- **Interim PET Response (RATHL) – No RT (most)**
- **New Drug Combinations like Brentuximab-AVD (ECHELON)**

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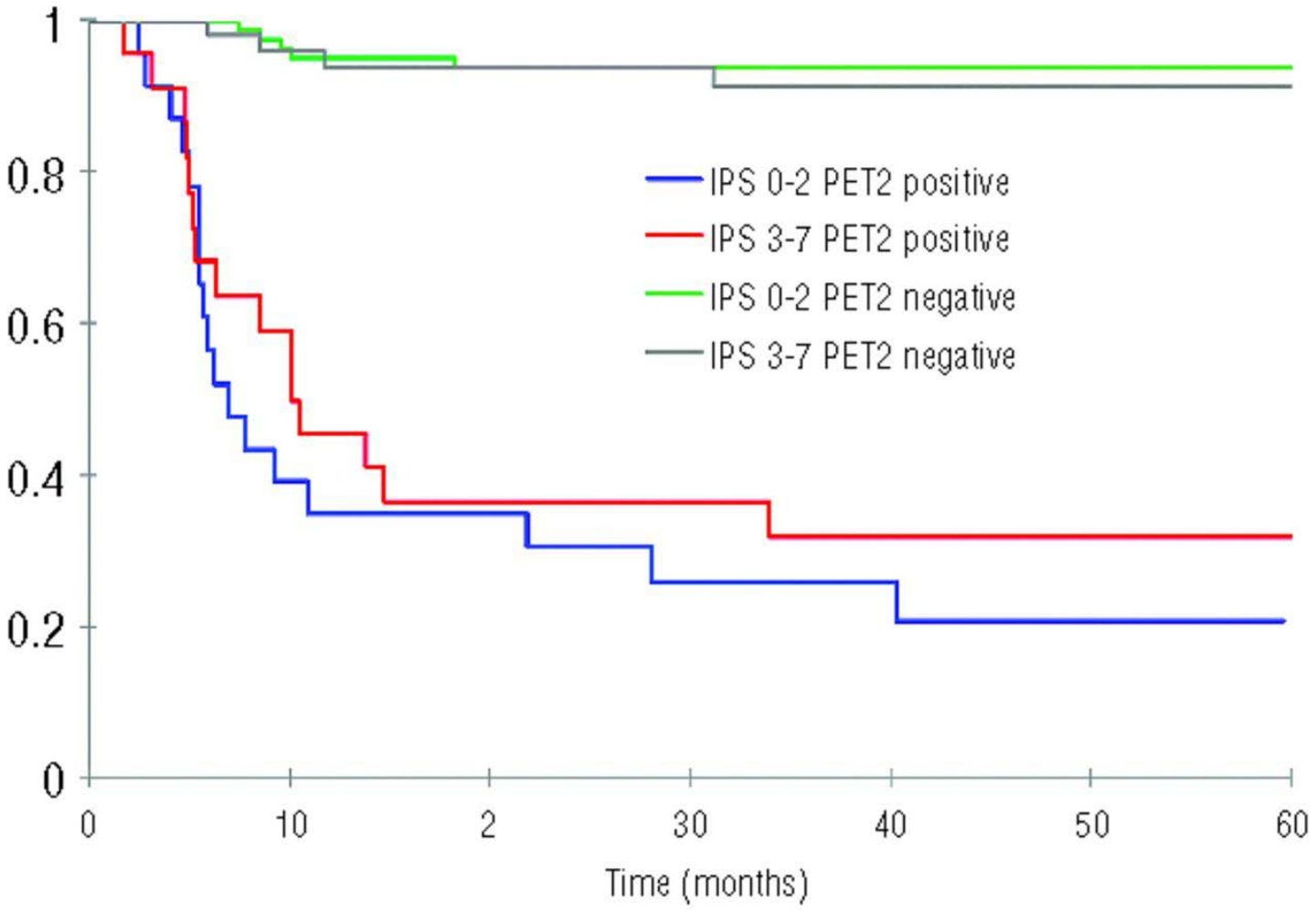
Hodgkin Lymphoma-Interim PET Progression-free Survival After Two Cycles Of ABVD.



Andrea Gallamini et al. Haematologica 2014;99:1107-1113

haematologica
the hematology journal

FDG-PET interim assessment

Deauville criteria or 5 point scale

Score	FDG-PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately more than liver uptake, at any site
5	Markedly increased uptake at any site or new sites of disease

- Score of 1 or 2 = PET negative

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Non-Adaptive Regimens: How RT was added or tested?

- MOPP/ABV hybrid-*EORTC* (obsolete)
  - Original volume IFRT 24 Gy (***vs* none**); 30 Gy for PR- response by CT
- ABVD (non-adaptive) 6-8 cycles
  - IFRT 36 Gy often to original, or CR?/PR (by CT)- to bulk or all sites
- Stanford V
  - IFRT 36 Gy to originally >5 cm disease sites or spleen
- Escalated BEACOPP (variety of schedules)
  - IFRT 30-40 Gy to bulky sites/residual sites (HD - landmark GHSG study)

“No Role” for Radiotherapy- The Primary Study

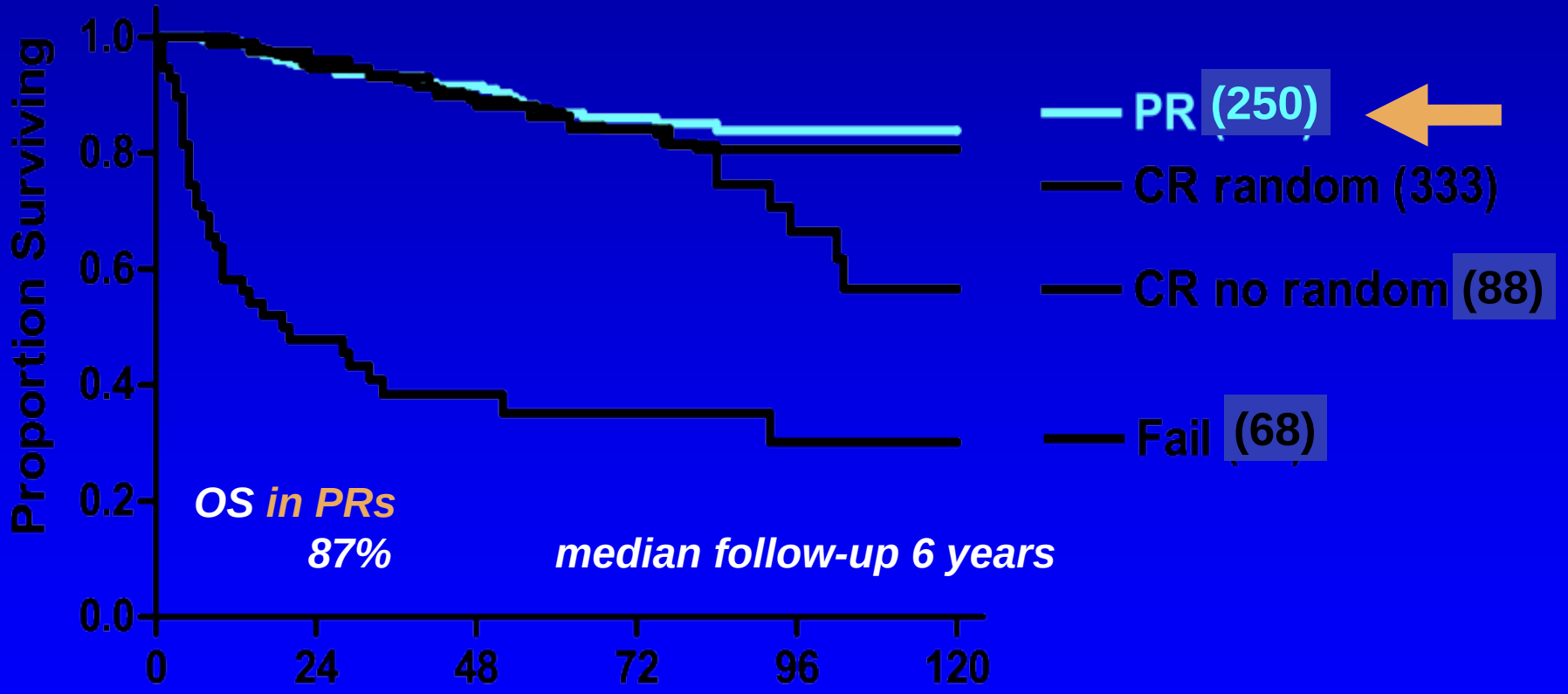
EORTC H34 (Aleman et al.) NEJM 248:24, 2003

739 Patients III-IV HD

MOPP-ABV x 6-8 (2 cycles after CR)

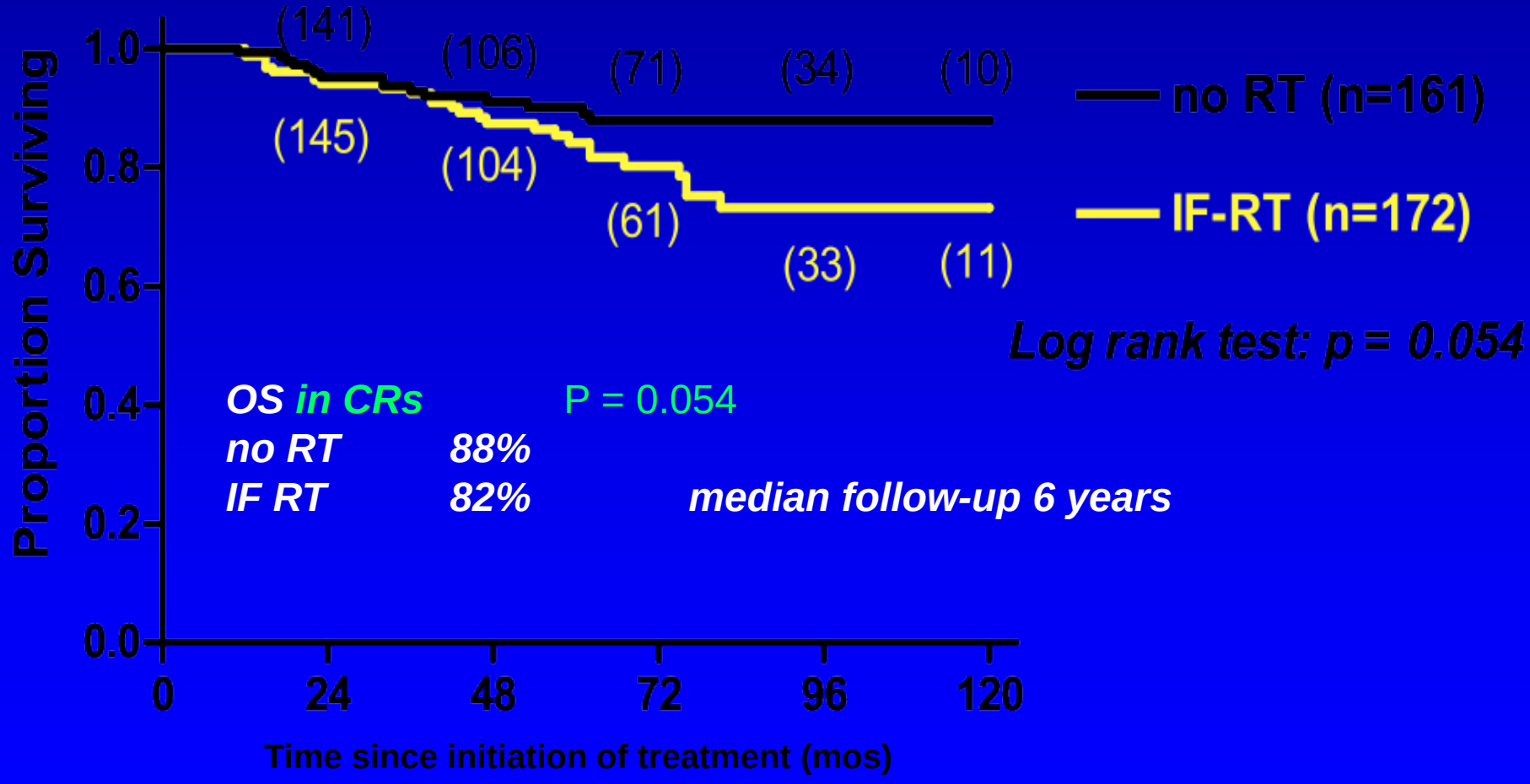
57% CR	34% PR
333 (45%) CR randomized:	227 (31%) PR
24 Gy IFRT or no RT	30 Gy RT

EORTC H34 Trial 1988-2001
PR →IF RT 30Gy Survival (n= 250)



Aleman *et al., NEJM* 2003; 348:2396-406

EORTC H34 Trial 1988-2001
Overall Survival n= 736



Aleman *et al., NEJM* 2003; 348:2396-406

Role of Radiotherapy

EORTC H34

Second Cancers and Treatment

		CR		PR
Second cancer * (N pt)	no RT(n=161)	RT(n=172)	NR**	RT (n=227)
Secondary AML (15)	1	8	4	2
NHL (3)	1	2	-	-
Solid tumor (19)	4	5	3	7

* Median FU = 6.5 Y; ** Not randomized

EORTC Study relevance concerns

- Obsolete Chemotherapy (with often 8 cycles)
- Strict CR definition (only 45%)
- Relatively small numbers for randomization
- Most bulky patients excluded

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Consolidation Radiotherapy in Patients With Advanced Hodgkin's Lymphoma: Survival Data From the UKLG LY09 Randomized Controlled Trial (ISRCTN97144519)

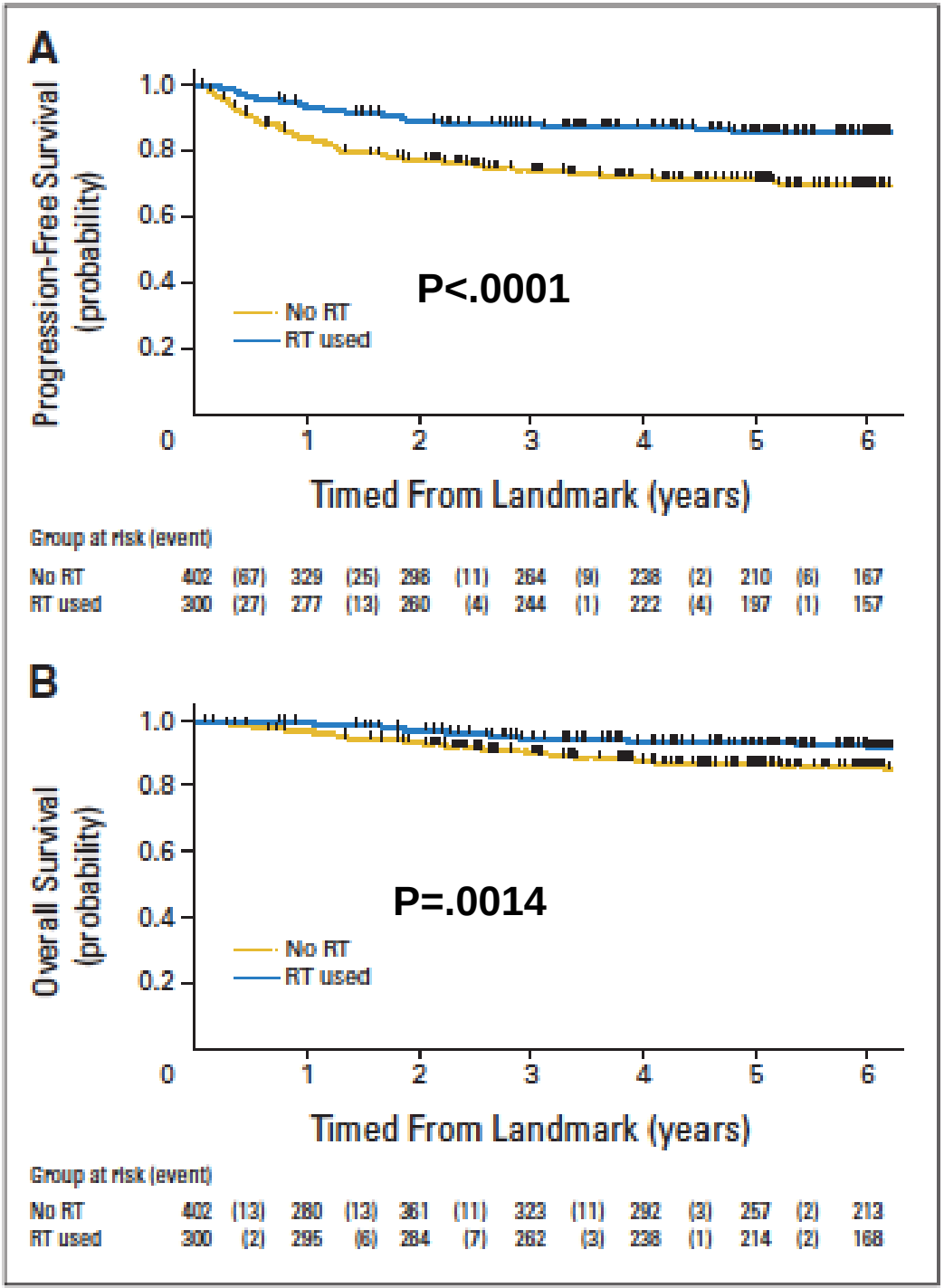
Peter W.M. Johnson, Matthew R. Sydes, Barry W. Hancock, Michael Cullen, John A. Radford, and Sally P. Stenning

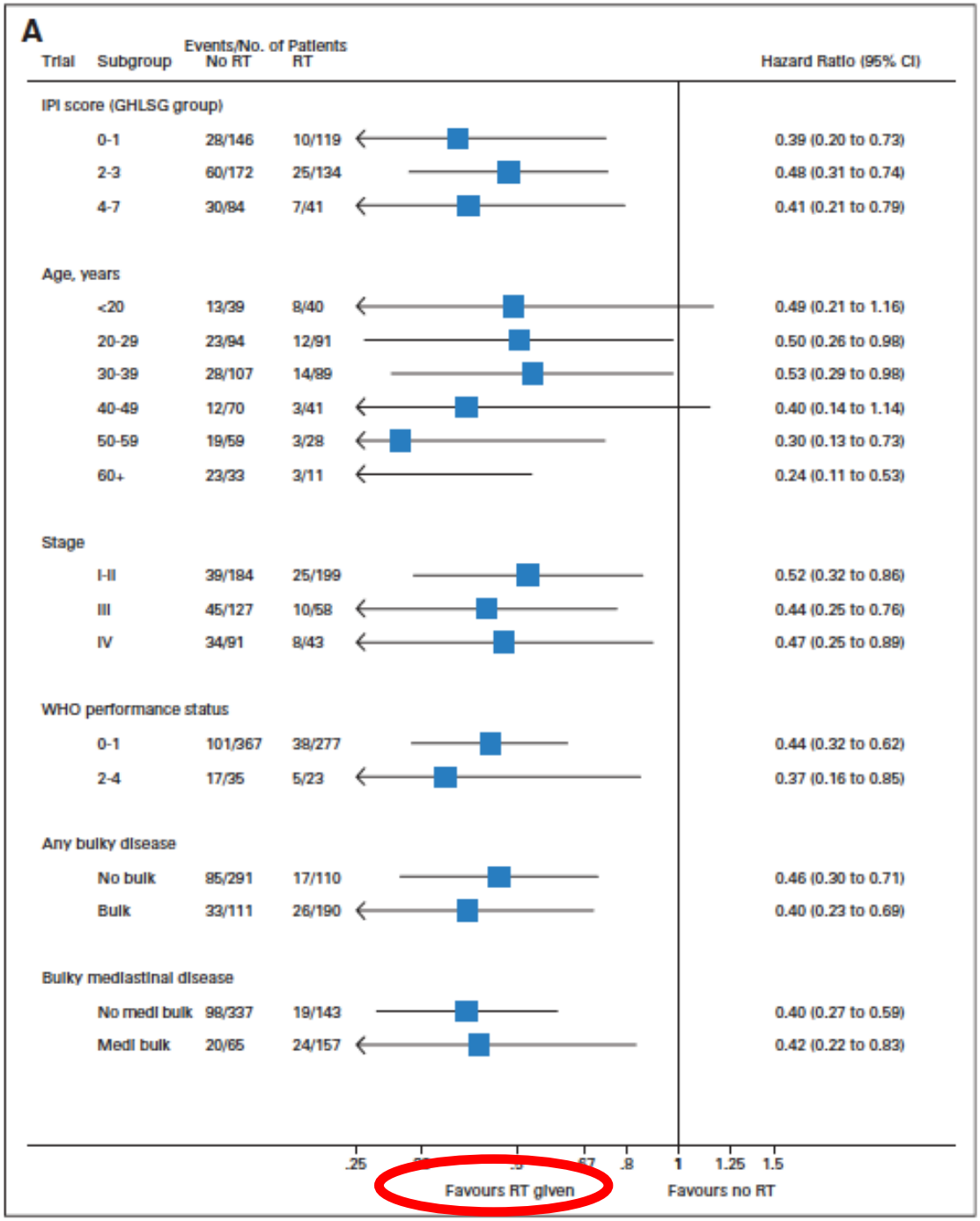
Patients and Methods

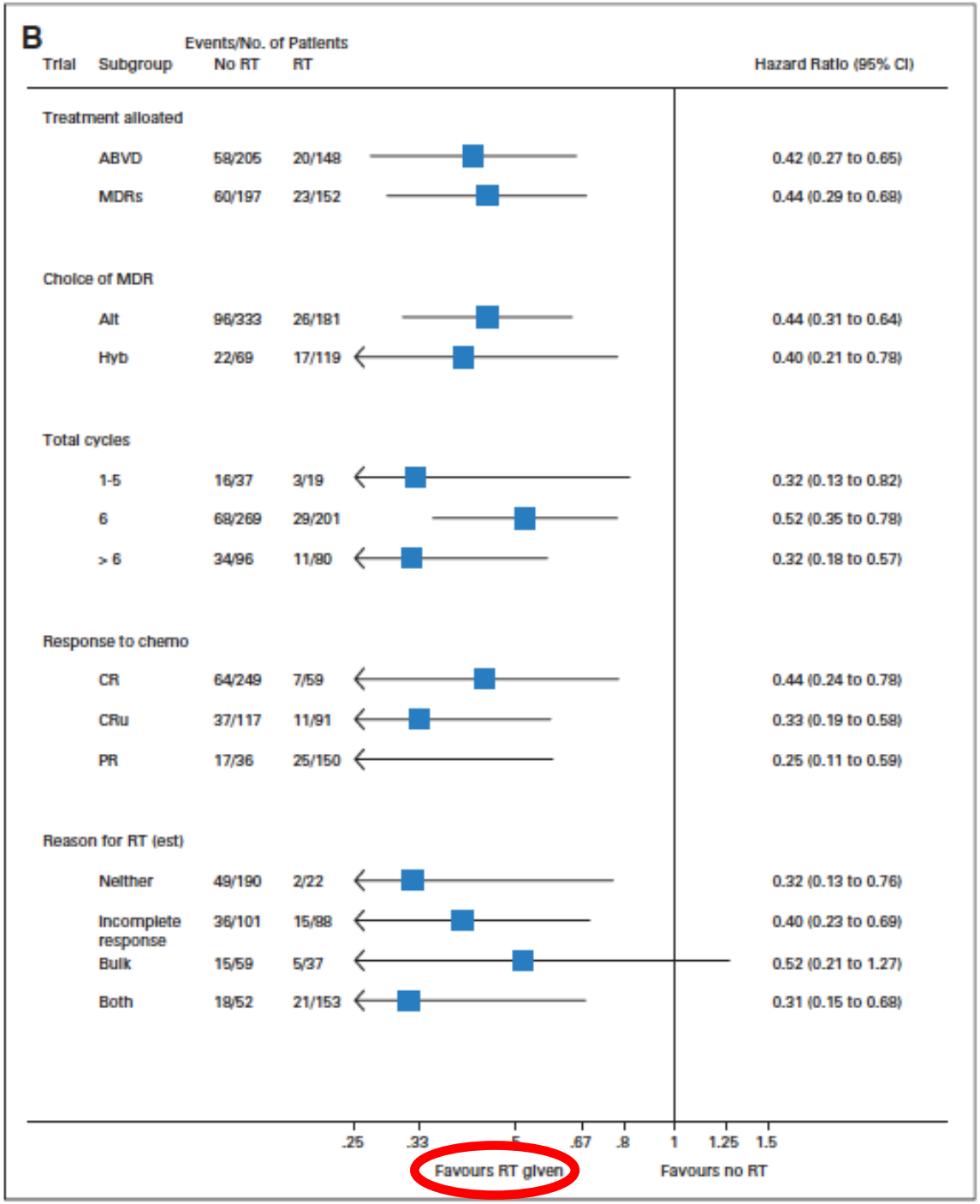
Patients were randomly assigned between doxorubicin, bleomycin, vinblastine, and dacarbazine and one of two prespecified multidrug regimens. At least six cycles of chemotherapy were planned, with up to eight for patients showing slower response. Involved-field RT was recommended for incomplete response to chemotherapy or bulk disease at presentation. The primary outcome measure was progression-free survival (PFS), landmarked from the end of chemotherapy.

Results

Among 807 patients randomly assigned, 702 achieved objective response. Postchemotherapy RT for consolidation was reported in 300 (43%). With median follow-up of 6.9 years, 161 PFS events and 83 deaths were reported. Baseline characteristics showed more patients with bulk disease having RT (190 [63%] *v* 111 [28%]) and only partial response after chemotherapy (150 [50%] *v* 36 [9%]). Other baseline characteristics were similar. PFS was superior for patients having RT (hazard ratio [HR], 0.43; 95% CI, 0.30 to 0.60) with 5-year PFS 71% without RT, 86% with RT. A similar advantage was seen for overall survival (HR, 0.47; 95% CI, 0.29 to 0.77). There was no evidence of heterogeneity of treatment effect across subgroups.


A
Progression-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
P<.0001
No RT
RT used
1
2
3
4
5
6
Timed From Landmark (years)
Group at risk (event)
No RT 402 (67) 329 (25) 298 (11) 264 (9) 238 (2) 210 (6) 167
RT used 300 (27) 277 (13) 260 (4) 244 (1) 222 (4) 197 (1) 157
B
Overall Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
P=.0014
No RT
RT used
1
2
3
4
5
6
Timed From Landmark (years)
Group at risk (event)
No RT 402 (13) 280 (13) 361 (11) 323 (11) 292 (3) 257 (2) 213
RT used 300 (2) 295 (6) 284 (7) 262 (3) 238 (1) 214 (2) 168


A
Trial
Subgroup
Events/No. of Patients
No RT
RT
Hazard Ratio (95% CI)
IPI score (GHLSG group)
0-1 28/146 10/119 0.39 (0.20 to 0.73)
2-3 60/172 25/134 0.48 (0.31 to 0.74)
4-7 30/84 7/41 0.41 (0.21 to 0.79)
Age, years
<20 13/39 8/40 0.49 (0.21 to 1.16)
20-29 23/94 12/91 0.50 (0.26 to 0.98)
30-39 28/107 14/89 0.53 (0.29 to 0.98)
40-49 12/70 3/41 0.40 (0.14 to 1.14)
50-59 19/59 3/28 0.30 (0.13 to 0.73)
60+ 23/33 3/11 0.24 (0.11 to 0.53)
Stage
I-II 39/184 25/199 0.52 (0.32 to 0.86)
III 45/127 10/58 0.44 (0.25 to 0.76)
IV 34/91 8/43 0.47 (0.25 to 0.89)
WHO performance status
0-1 101/367 39/277 0.44 (0.32 to 0.62)
2-4 17/35 5/23 0.37 (0.16 to 0.85)
Any bulky disease
No bulk 85/291 17/110 0.46 (0.30 to 0.71)
Bulk 33/111 26/190 0.40 (0.23 to 0.69)
Bulky mediastinal disease
No medi bulk 98/337 19/143 0.40 (0.27 to 0.59)
Medi bulk 20/65 24/157 0.42 (0.22 to 0.83)
.25
.8
1
1.25
1.5
Favours RT given
Favours no RT


B
Trial
Subgroup
Events/No. of Patients
No RT
RT
Hazard Ratio (95% CI)
Treatment alloated
ABVD 58/205 20/148 0.42 (0.27 to 0.65)
MDRs 60/197 23/152 0.44 (0.29 to 0.68)
Choice of MDR
Alt 96/333 26/181 0.44 (0.31 to 0.64)
Hyb 22/69 17/119 0.40 (0.21 to 0.78)
Total cycles
1-5 16/37 3/19 0.32 (0.13 to 0.82)
6 68/269 29/201 0.52 (0.35 to 0.78)
> 6 34/96 11/80 0.32 (0.18 to 0.57)
Response to chemo
CR 64/249 7/59 0.44 (0.24 to 0.78)
CRu 37/117 11/91 0.33 (0.19 to 0.58)
PR 17/36 25/150 0.25 (0.11 to 0.59)
Reason for RT (est)
Neither 49/190 2/22 0.32 (0.13 to 0.76)
Incomplete response 36/101 15/88 0.40 (0.23 to 0.69)
Bulk 15/59 5/37 0.52 (0.21 to 1.27)
Both 18/52 21/153 0.31 (0.15 to 0.68)
.25
.33
.67
.8
1
1.25
1.5
Favours RT given
Favours no RT

Consolidation Radiotherapy in Patients With Advanced Hodgkin's Lymphoma: Survival Data From the UKLG LY09 Randomized Controlled Trial (ISRCTN97144519)

Peter W.M. Johnson, Matthew R. Sydes, Barry W. Hancock, Michael Cullen, John A. Radford, and Sally P. Stenning

Table 2. Impact of RT on PFS in Unadjusted and Adjusted Cox Models

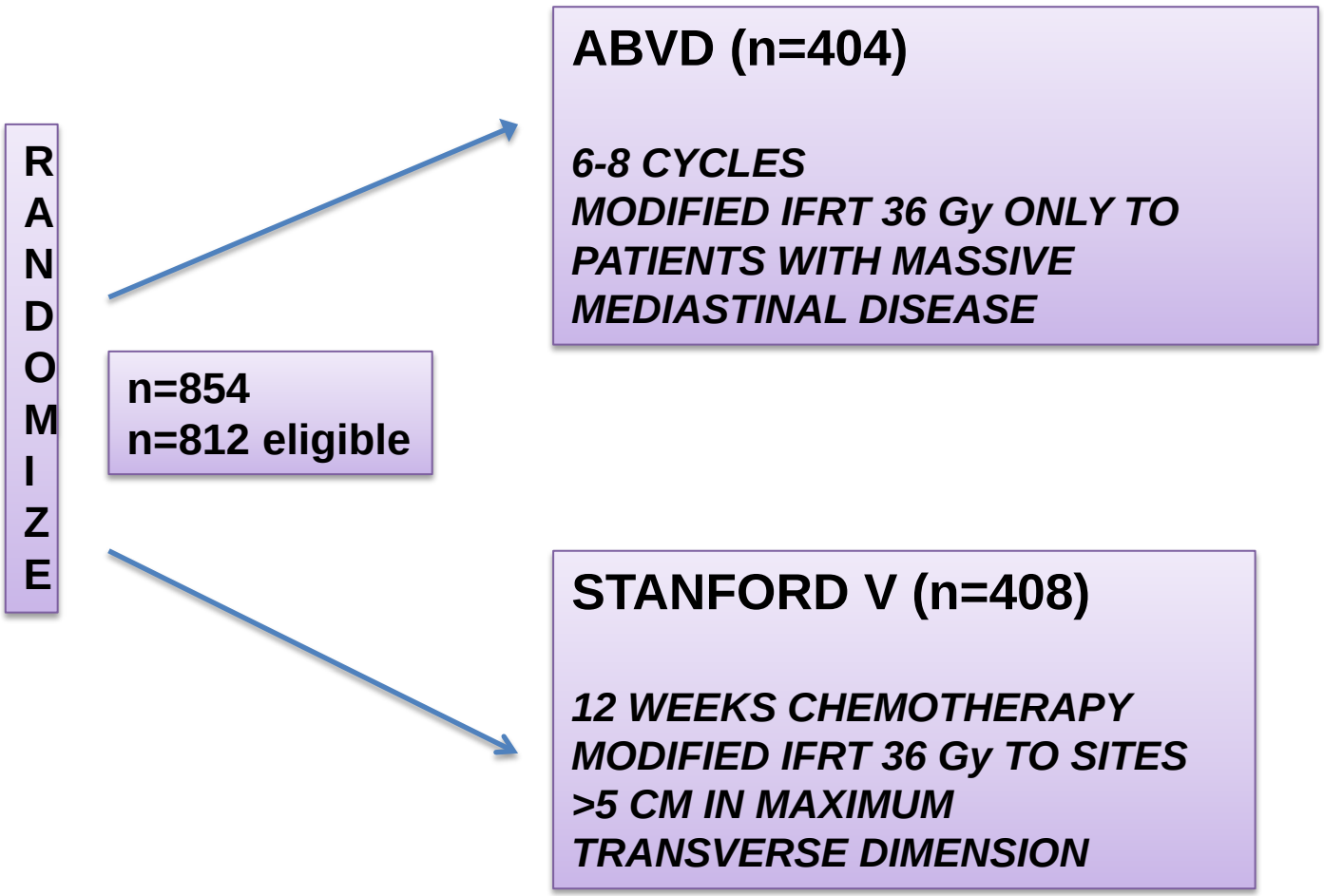
	Cox Model							
	Unadjusted		Stratification		IPS		Full	
Variable	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
RT given	0.43	0.30 to 0.61	0.50	0.35 to 0.72	0.44	0.31 to 0.63	0.33	0.22 to 0.51
WHO PS	—		1.54	0.97 to 2.46	—		1.54	0.96 to 2.47
Stage	—		1.31	1.08 to 1.59	—		—	
Age	—		1.46	1.05 to 2.04	—		—	
IPS	—		—		1.48	1.20 to 1.82	1.40	1.12 to 1.75
Allocated chemotherapy	—		—		—		1.05	0.77 to 1.44
MDR	—		0.97	0.67 to 1.41	1.09	0.75 to 1.57	1.03	0.71 to 1.51
Bulk disease	—		—		—		0.94	0.67 to 1.33
Response	—		—		—		1.40	1.12 to 1.76
Chemotherapy cycles	—		—		—		0.96	0.72 to 1.27

Conclusion

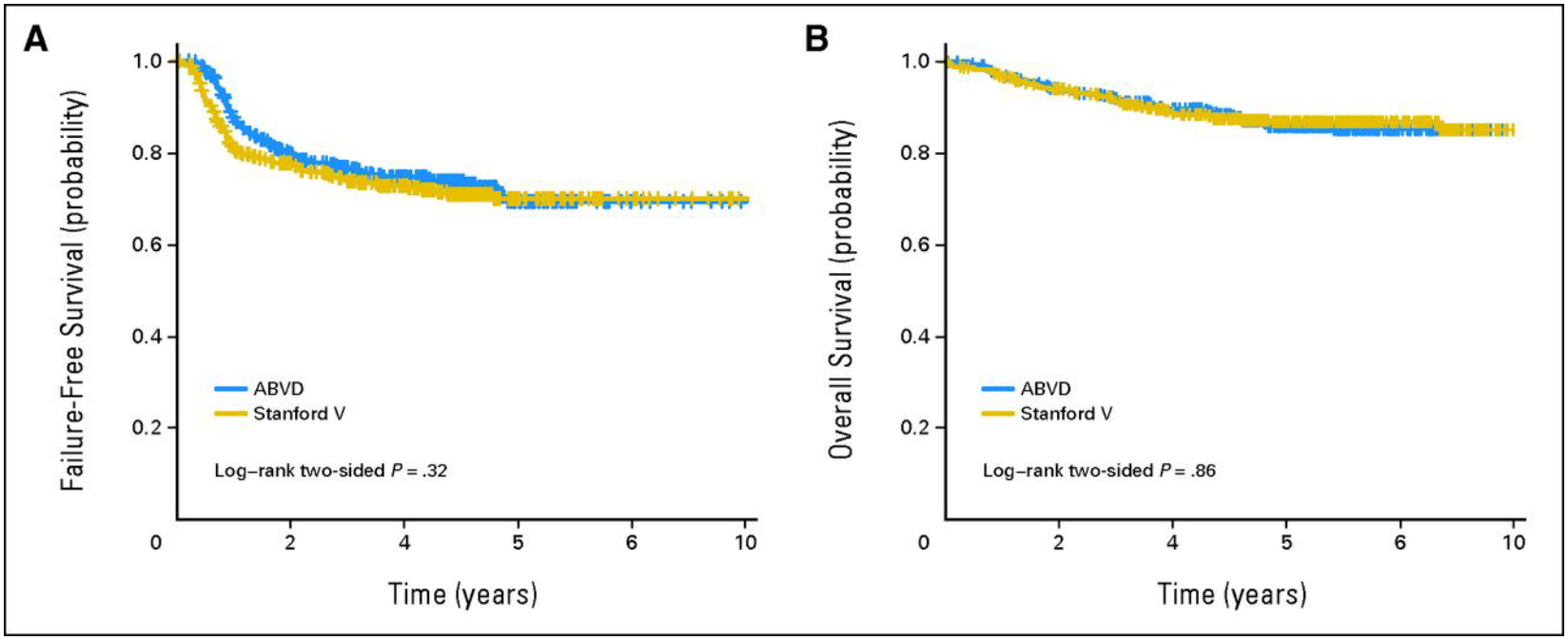
Patients who received consolidation RT apparently had better outcomes, consistently across all prognostic groups which persisted in multivariate analysis. This suggests that RT contributes significantly to the cure rate for advanced HL, although patient selection for combined modality treatment requires better definition in prospective trials.

J Clin Oncol 28:3352-3359. © 2010 by American Society of Clinical Oncology

A Randomized Phase III Trial of ABVD Vs. Stanford V +/- Radiation Therapy In Locally Extensive and Advanced Stage Hodgkin's Lymphoma: An Intergroup Study Coordinated by the Eastern Cooperative Oncology Group (E2496)
Gordon L et al. JCO 2013

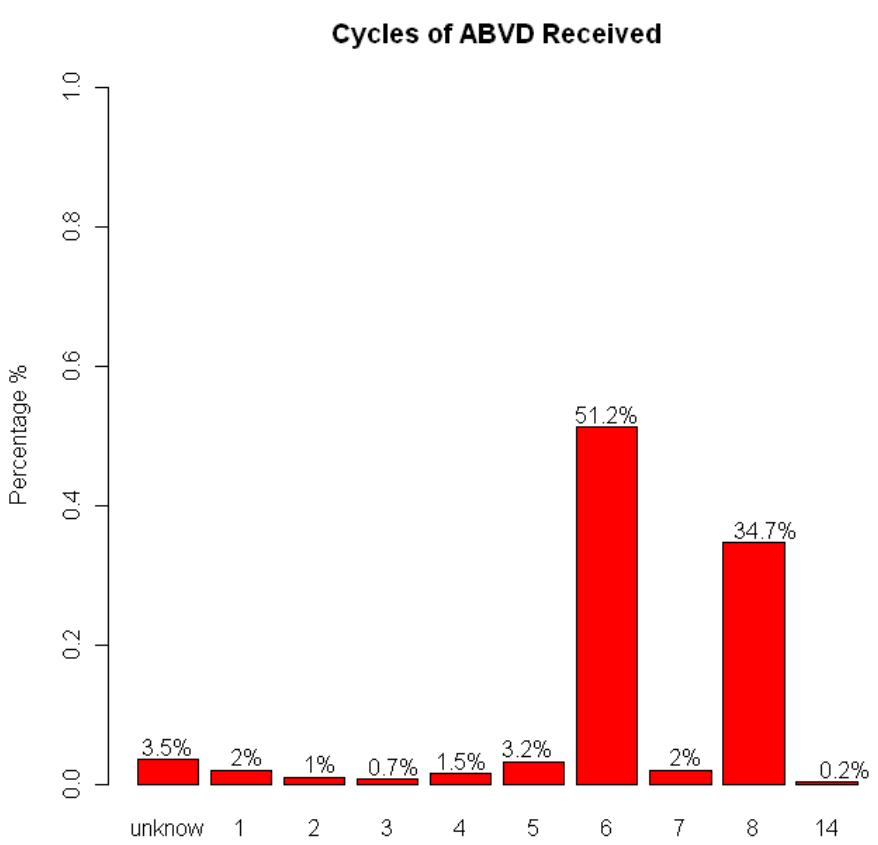


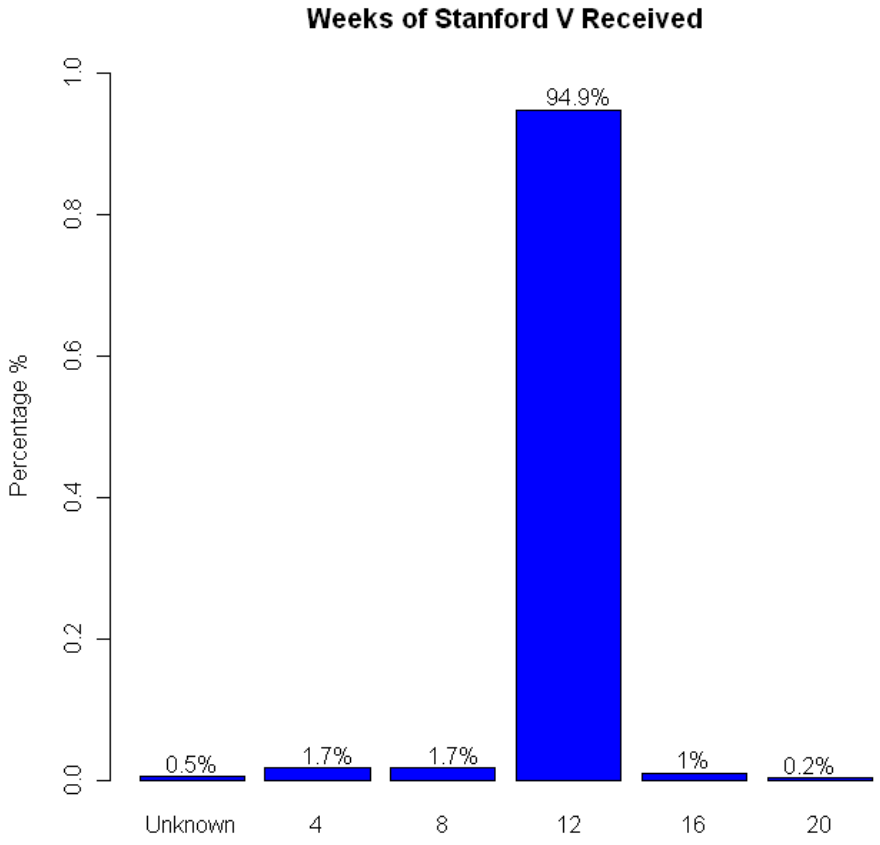
(A) Failure-free (P = .32) and (B) overall survival (P = .86) are shown for all patients, showing no difference between the two arms.



Gordon L I et al. JCO 2013;31:684-691

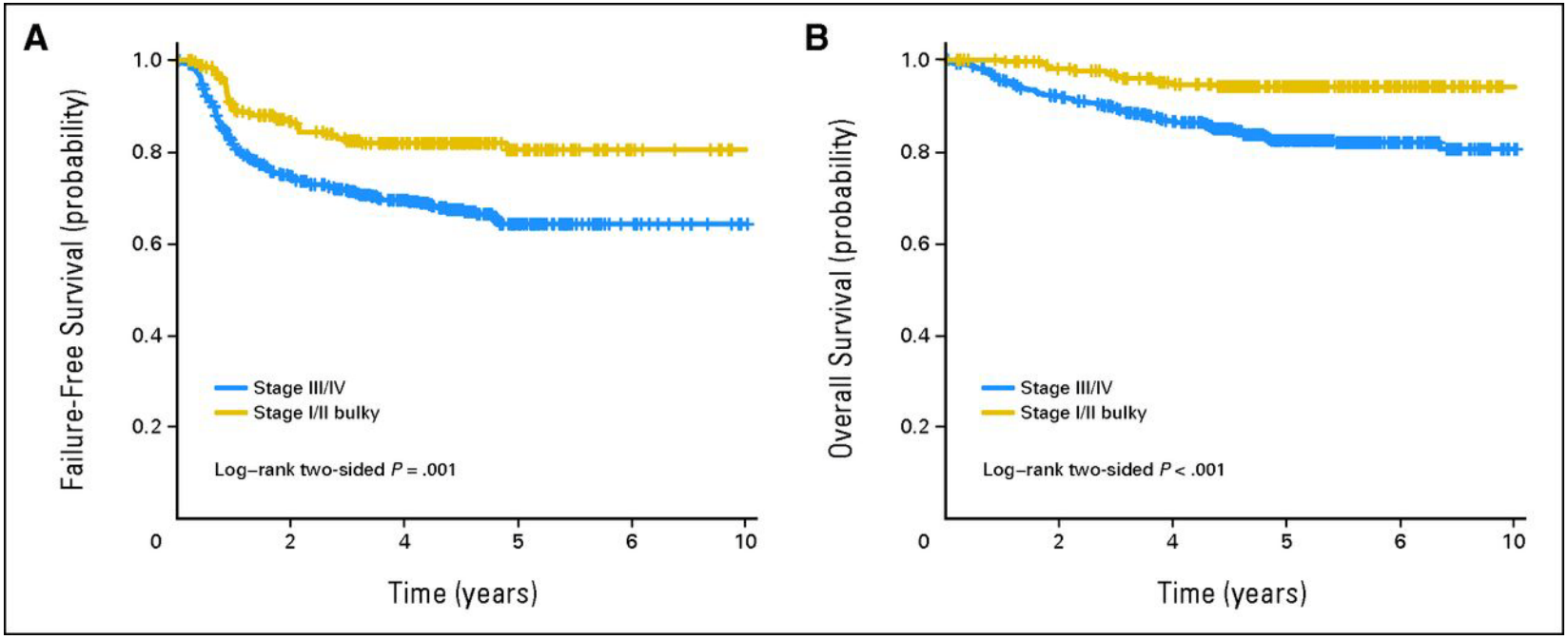
Intergroup Trial E2496: # of cycles





73% of patients had RT on Stanford V
40% of patients had RT on ABVD

Patients with locally extensive disease (stage I to II bulky) were compared with patients with advanced disease (stage III to IV); patients with locally advanced disease had better (A) failure-free survival (FFS; P = .001) and (B) overall survival (OS; P = ...



Gordon L I et al. JCO 2013;31:684-691

RT in GHSG BEACOPP Studies (1)

- **HD 9** established the advantage of escalated BEACOPP. It included 30-40 Gy IFRT to over 2/3 of patients (bulky and/or residual disease).
- In **HD 12** esc. BEACOPP cycle reduction and randomization to +/- RT were studied.
- Less esc. BEACOPP was inferior to 8 esc. BEACOPP, but not less toxic.
- FFTP was inferior with no RT particularly if residual CT abnormality. “Our results do not support the omission of consolidation RT for patients with residual disease”.

.

RT in GHSG BEACOPP Studies (2)

- **HD15** (Engert et al. Lancet 2012) showed that BEACOPP X6 was as effective and less toxic than BEACOPP X8. OS was better due to less treatment related toxic deaths.
- PET was used for post-chemo evaluation, if residual CT abnormality (39% of patients).
- There was no randomization to +/- IFRT.
- RT was given only to PET-positive patients (30% of those who had PET). Total receiving RT was 11% compared to 71% in HD9.
- PET- negative patients had outcome similar to CT evaluated CR/Cru and better that those with residual PET.
- PET (-) had a negative predictive value of 94%.

.

Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial

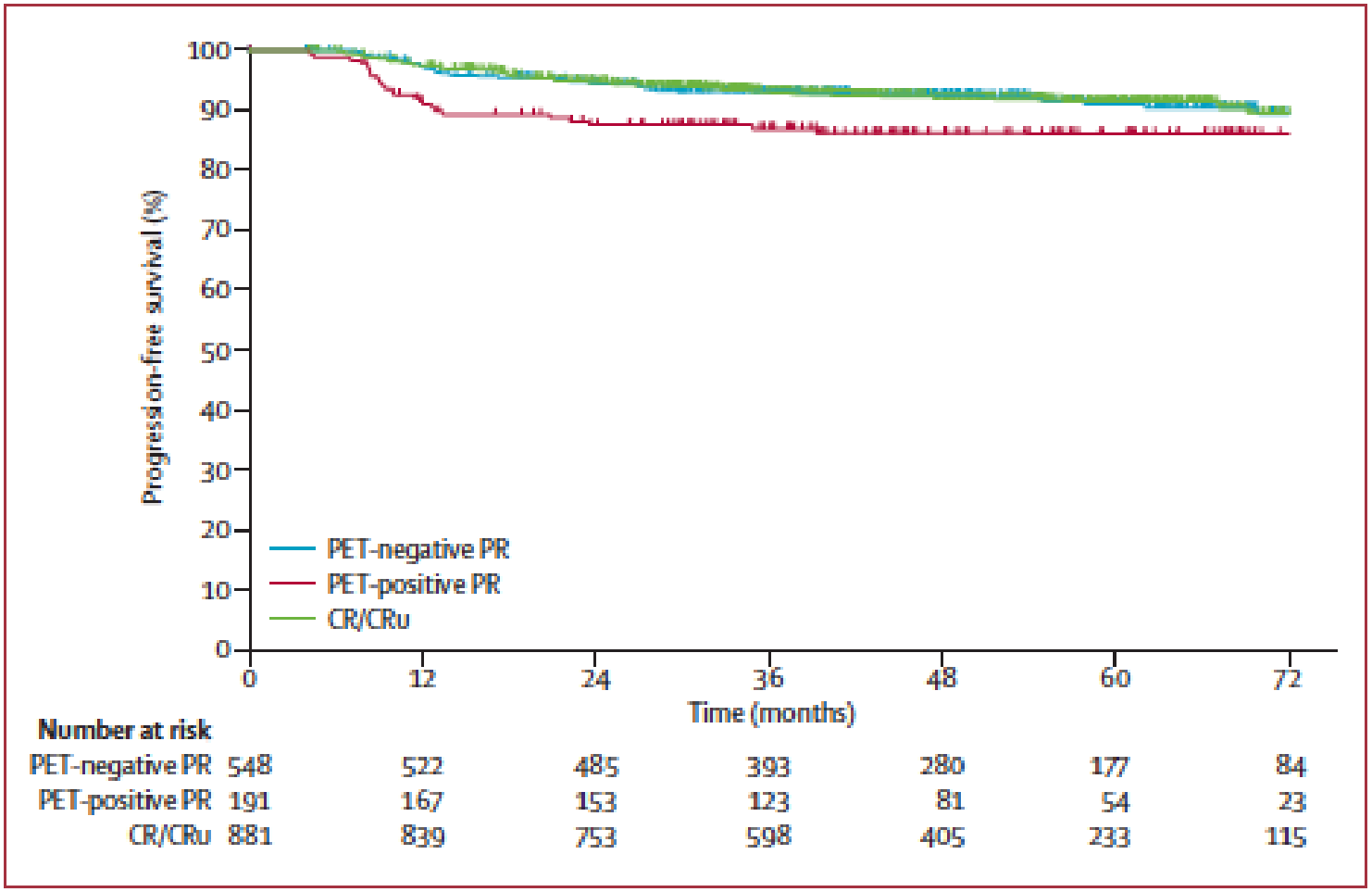


Figure 3: Progression free survival for PET study objective

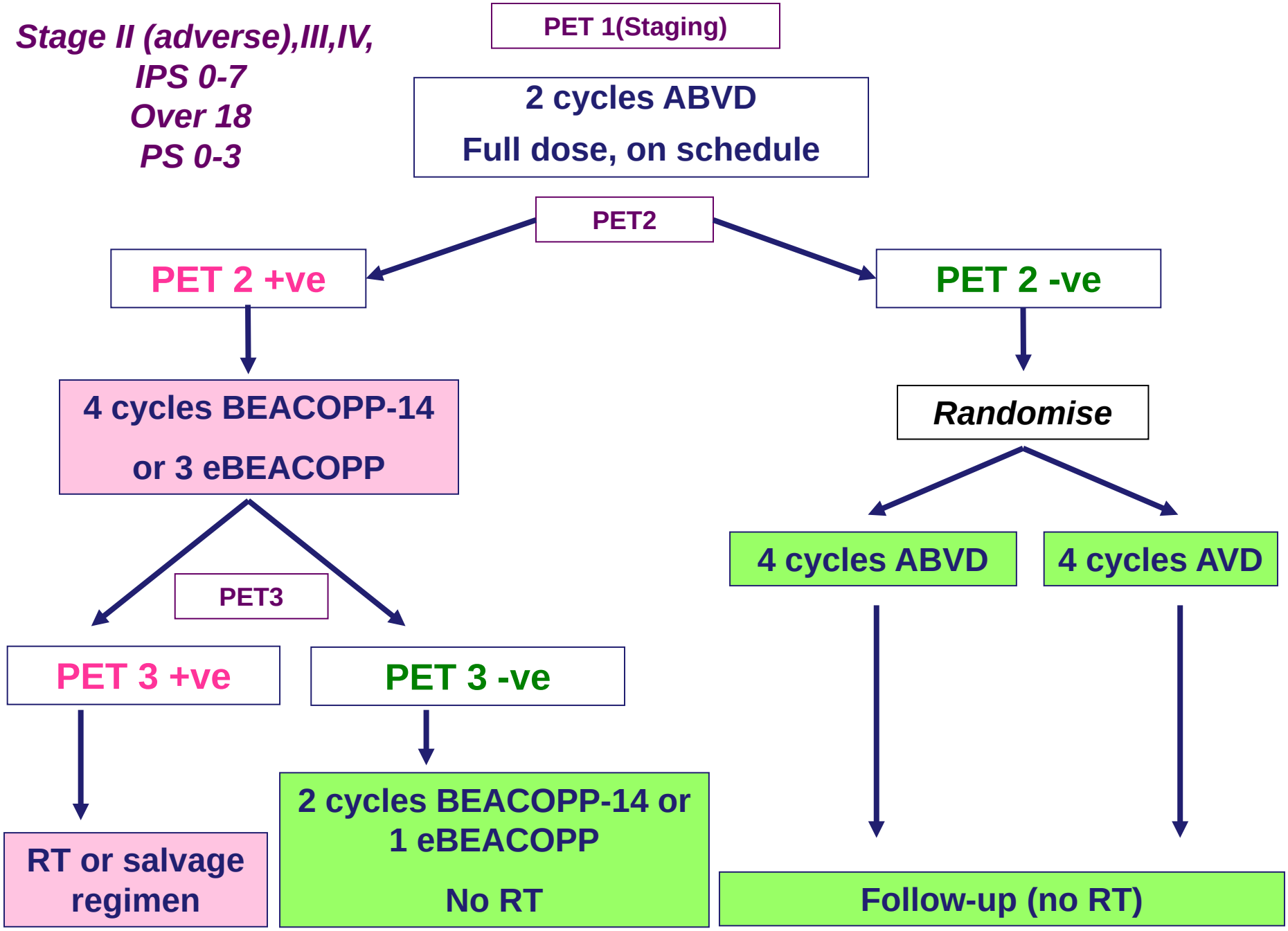
Original Article

Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma

Peter Johnson, M.D., Massimo Federico, M.D., Amy Kirkwood, M.Sc., Alexander Fosså, M.D., Leanne Berkahn, M.D., Angelo Carella, M.D., Francesco d'Amore, M.D., Gunilla Enblad, M.D., Antonella Franceschetto, M.D., Michael Fulham, M.D., Stefano Luminari, M.D., Michael O'Doherty, M.D., Pip Patrick, Ph.D., Thomas Roberts, B.Sc., Gamal Sidra, M.D., Lindsey Stevens, Paul Smith, M.Sc., Judith Trotman, M.D., Zaid Viney, M.D., John Radford, M.D., and Sally Barrington, M.D.

N Engl J Med
Volume 374(25):2419-2429
June 23, 2016

The NEW ENGLAND JOURNAL of MEDICINE


Stage II (adverse),III,IV,
IPS 0-7
Over 18
PS 0-3
PET 1(Staging)
2 cycles ABVD
Full dose, on schedule
PET2
PET 2 +ve
PET 2 -ve
4 cycles BEACOPP-14
or 3 eBEACOPP
Randomise
PET3
4 cycles ABVD
4 cycles AVD
PET 3 +ve
PET 3 -ve
2 cycles BEACOPP-14 or
1 eBEACOPP
No RT
RT or salvage
regimen
Follow-up (no RT)

Patient Characteristics/PET 2 Results

Characteristic	N=1214
Median age, years (range)	33 (18-79)
Male	55%
IPS	
0-1	34%
2-3	49%
≥4	18%
B symptoms	61%
Bulky	32%
Stage	
II	41%
III	31%
IV	28%

PET 2	N	%
1	114	10
2	493	43
3	347	31
4	145	13
5	38	3

Johnson PW, et al 13th ICML; 2015; Abst 008

Memorial Sloan Kettering Cancer Center

PET 2 Negative-Post randomization

	ABVD N=469	AVD N=466
CR/CRu	65%	69%
RT (N)	12	20
Deaths (N)	14	14
HL	1	7
3 yr PFS	85.4%	84.4%
3 yr OS	97.1%	97.4%
Respiratory AE (Gr 3-4)	3.6%	0.6% (p=.002)
Any non-heme AE (Gr 3-4)	31%	21% (p<0.001)

Johnson PW, et al 13th ICML; 2015; Abst 008

PET 2 Positive

	ALL N=174	BEACOPP-14 N=96	eBEACOPP N=78
CR/CRu	48%	43%	53%
RT (N)	43	23	20
Deaths (N)	21	9	12
HDT	18	6	12
3 yr PFS		66%	71%
3 yr OS		89.6%	82.8%

Johnson PW, et al 13th ICML; 2015; Abst 008

Conclusions: Authors

- After a negative interim FDG-PET scan it is safe to omit bleomycin from subsequent cycles without consolidation with radiotherapy.
- Omission of bleomycin reduces toxicity
- Escalated therapy for interim FDG-PET positive patients gives good subsequent response rates and promising PFS results (70 % 3 yr PFS for PET 3 negative)

- **Conclusions-mine**
- **This is a large study with good results that likely practice changing**
  - **Safely omitting bleo if concern**
  - **Guidance/strategy for interim PET positive**
  - **? True PFS of interim PET2+ with 4 more ABVD – many received RT**
  - **No guidelines for RT use**

Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma

Anita Kumar, Carla Casulo, Joachim Yahalom, Heiko Schöder, Paul M. Barr, Philip Caron, April Chiu, Louis S. Constine, Pamela Drullinsky, Jonathan W. Friedberg, John F. Gerecitano, Audrey Hamilton, Paul A. Hamlin, Steven M. Horwitz, Alexandra G. Jacob, Matthew J. Matasar, Gianna N. McArthur, Susan J. McCall, Alison J. Moskowitz, Ariela Noy, Maria L. Palomba, Carol S. Portlock, David J. Straus, Nicholas VanderEls, Stephanie L. Verwys, Joanna Yang, Anas Younes, Andrew D. Zelenetz, Zhigang Zhang, Craig H. Moskowitz

Blood 2016 :blood-2016-03-703470; doi:10.1182/blood-2016-03-703470

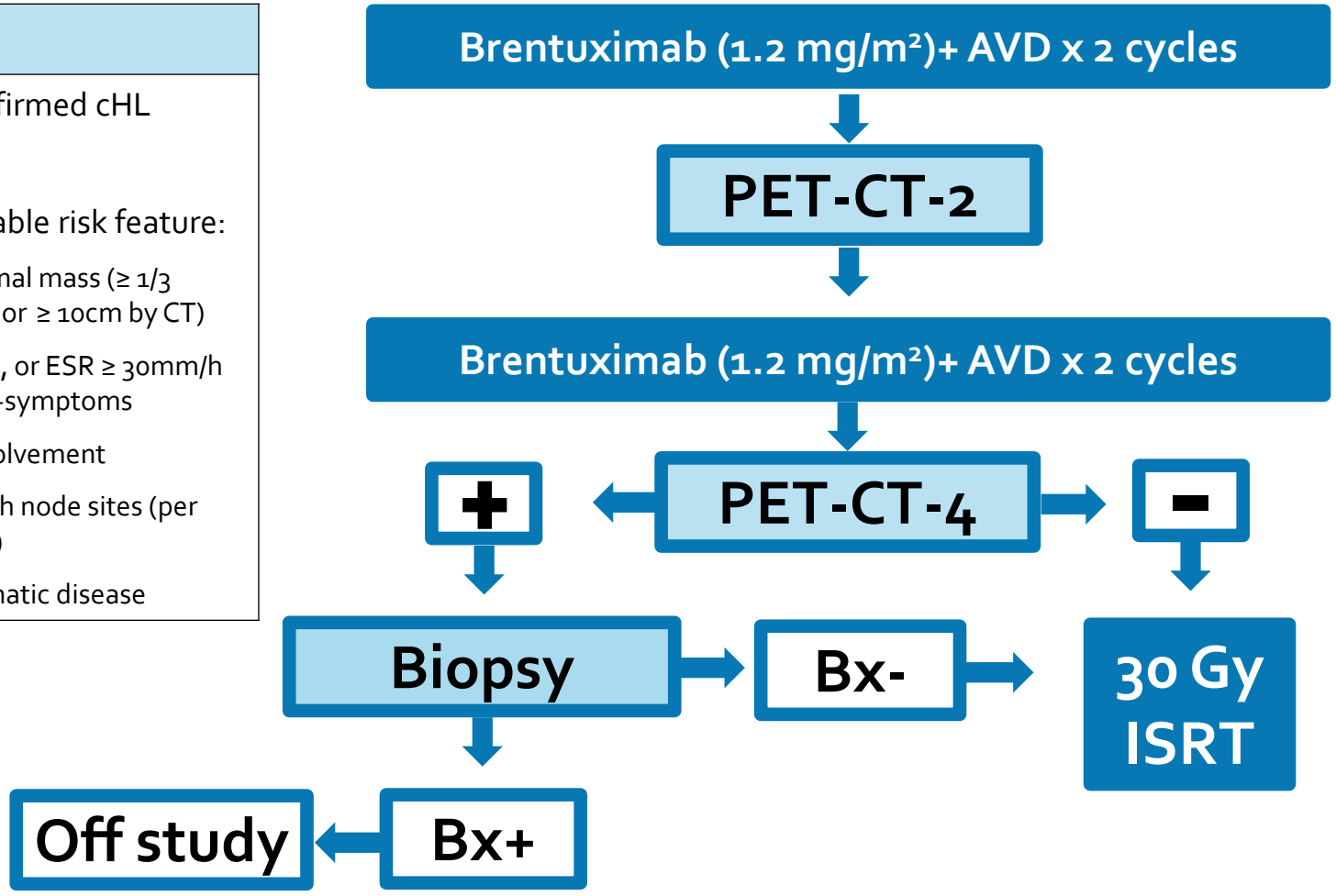
Overview: 4 Cohorts

Cohort	# of pts	Induction Chemotherapy	If PET-4 negative, then…
1	30	BV+AVD x 4 cycles	30 Gy ISRT
2	29	BV+AVD x 4 cycles	20 Gy ISRT
3	29	BV+AVD x 4 cycles	30 Gy Consolidation Volume Radiotherapy (CVRT)
4	29	BV+AVD x 4 cycles	No further treatment

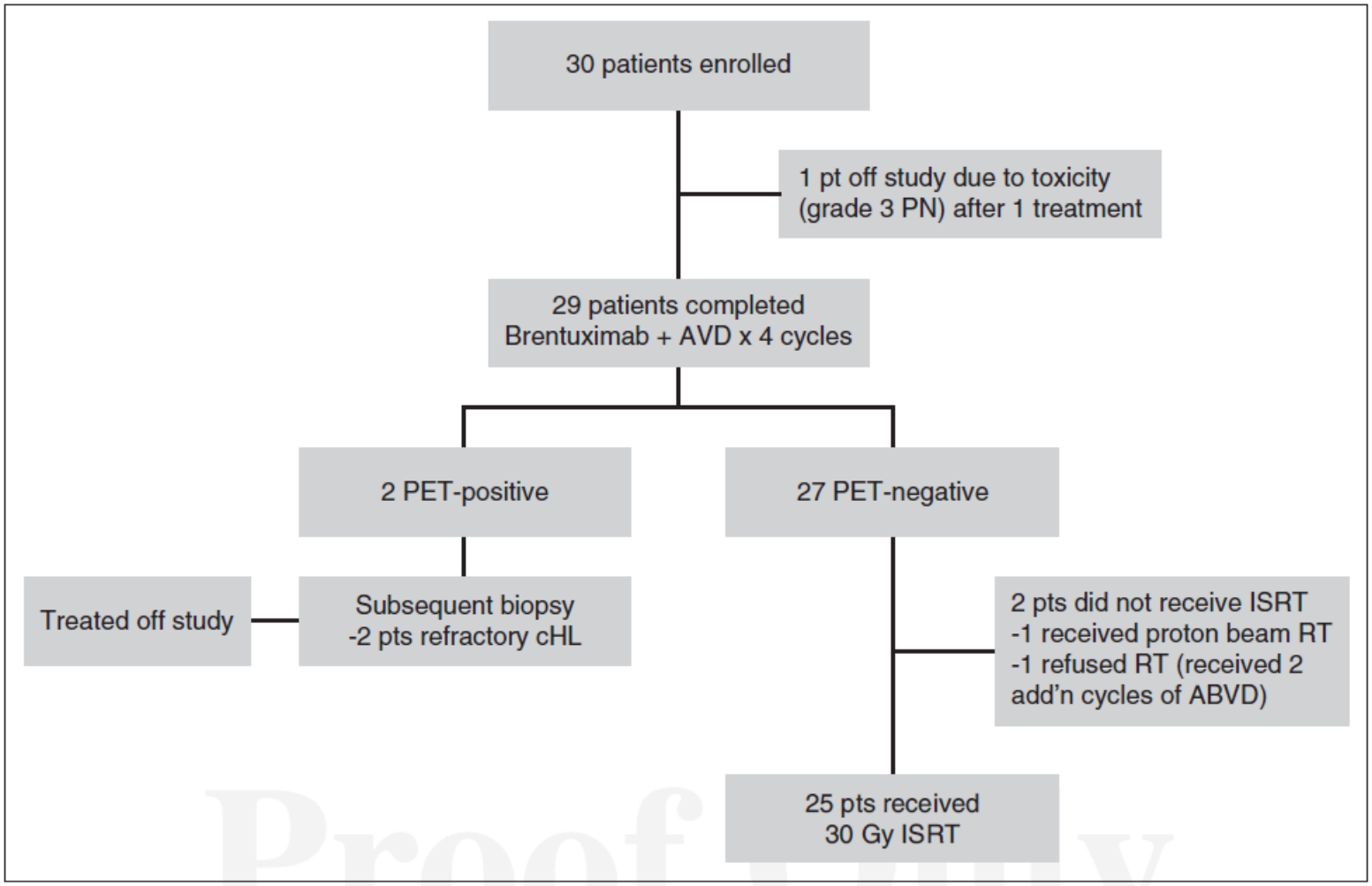
13-034 Cohort 1 Study Design

Eligiblity:

- Histologically confirmed cHL
- Stage I or II
- At least 1 unfavorable risk feature:
  - Bulky mediastinal mass (≥ 1/3 MMR on PA CXR or ≥ 10cm by CT)
  - ESR ≥ 50mm/h, or ESR ≥ 30mm/h in patient with B-symptoms
  - Extranodal involvement
  - 3 of more lymph node sites (per GHSG definition)
  - Infradiaphragmatic disease

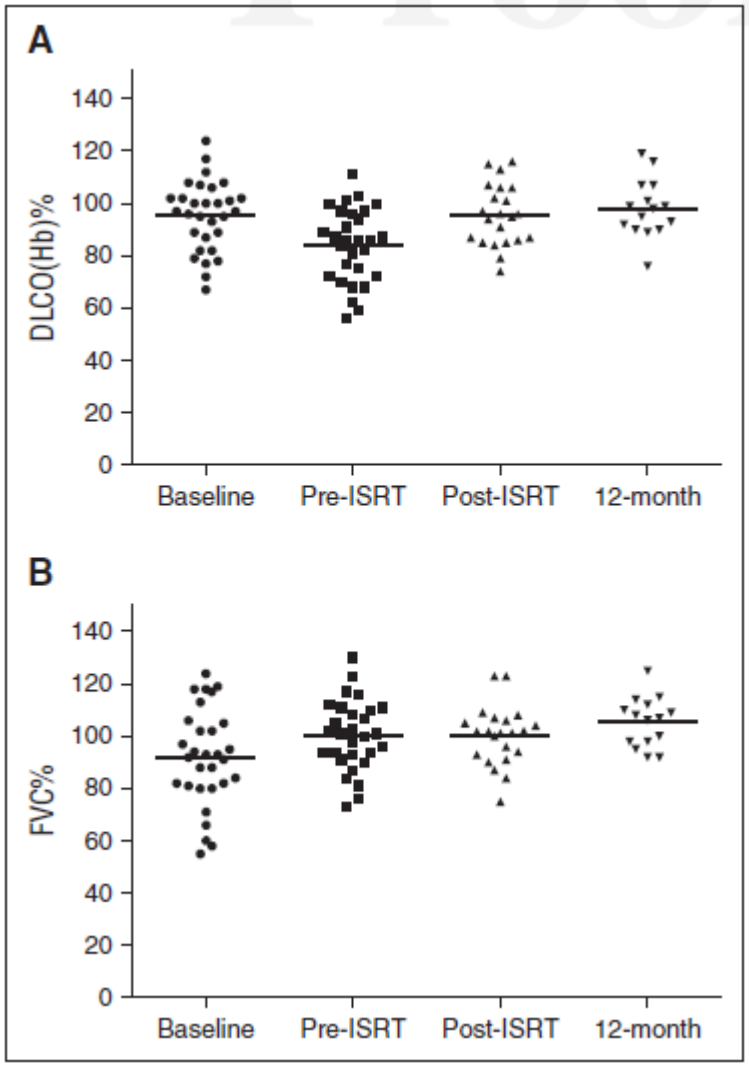


Clinical Trial Flowchart



Kumar et al, Blood 2016

No significant pulmonary toxicity



Kumar et al, Blood 2016

High rates of Interim PET-negativity

Deauville Score	PET-2 N(%) N=29	PET-4 N(%) N=29	Post tx N(%) N=25
1		3 (10)	5 (20)
2	14 (48)	21 (72)	16 (64)
3	12 (41)	3 (10)	2 (8)
4	3 (10)	2 (7)	2 (8)
5	0	0	0

89% PET Negative

93% PET Negative

All CRs

Kumar et al, Blood 2016

Promising Preliminary Efficacy

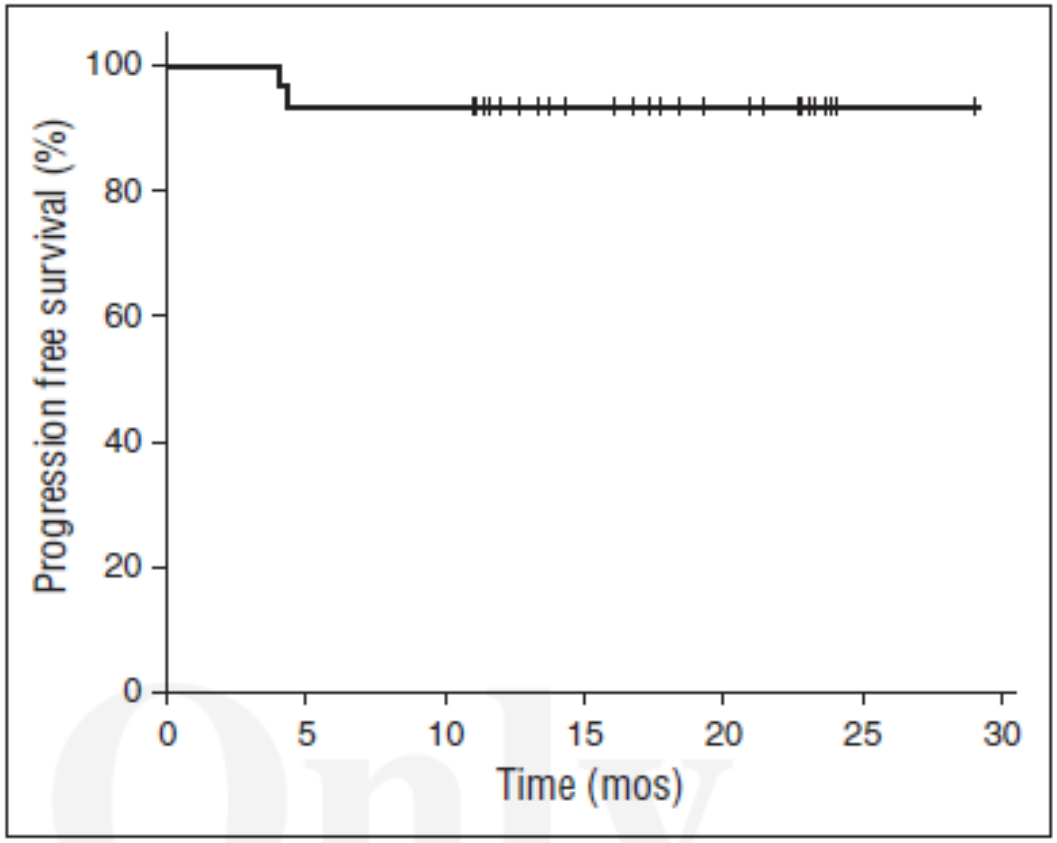


Figure 4. PFS by intent to treat (N = 30) with median follow up of 18.8 months.

Kumar et al, Blood 2016

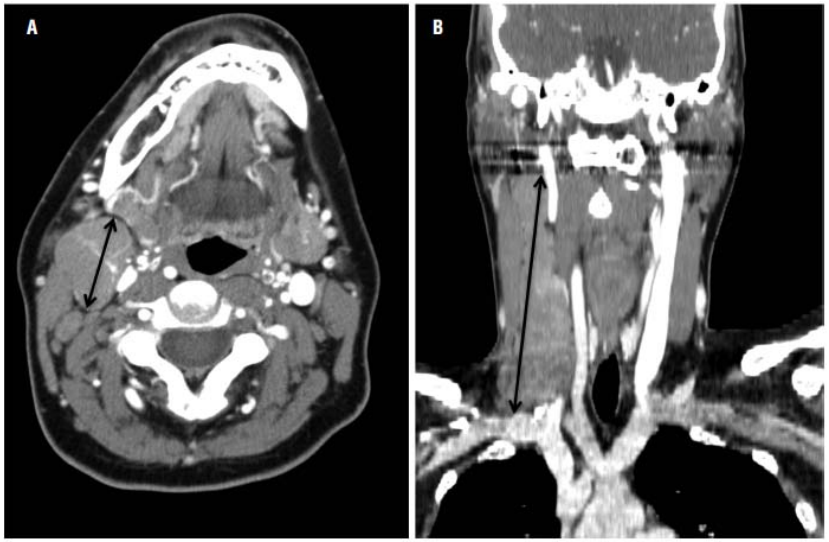
Overview: 4 Cohorts

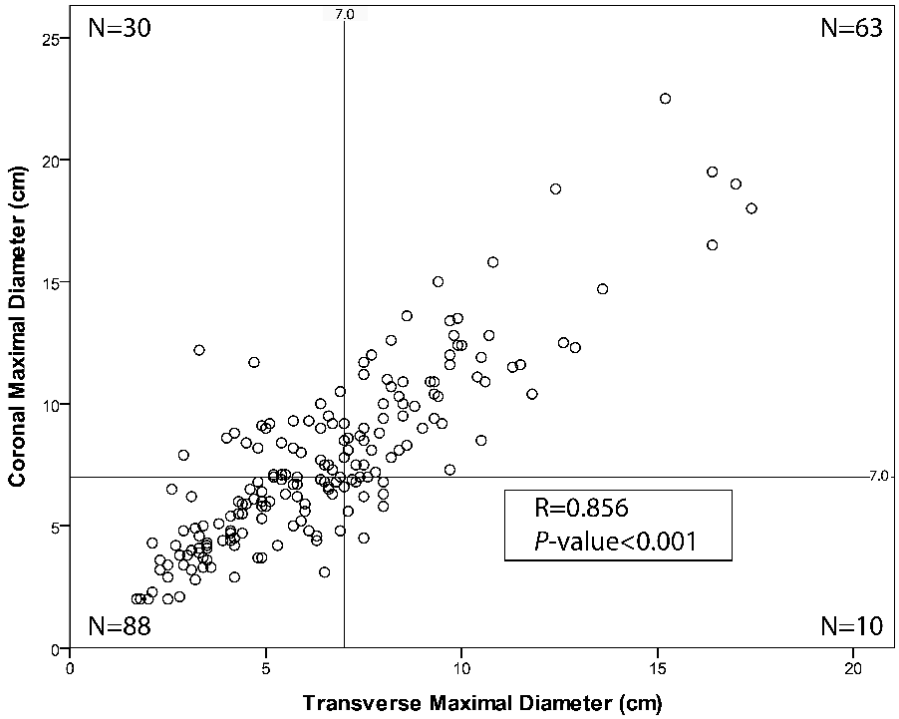
Cohort	# of pts	Induction Chemotherapy	If PET-4 negative, then…
1	30	BV+AVD x 4 cycles	30 Gy ISRT
2	29	BV+AVD x 4 cycles	20 Gy ISRT
3	29	BV+AVD x 4 cycles	30 Gy Consolidation Volume Radiotherapy (CVRT)
4	29	BV+AVD x 4 cycles	No further treatment

Multicenter collaboration

- **MSKCC, University of Rochester, Stanford University, City of Hope**

Cohorts 2-4: Definition of disease bulk





≥ 7 cm in maximal transverse or coronal dimension

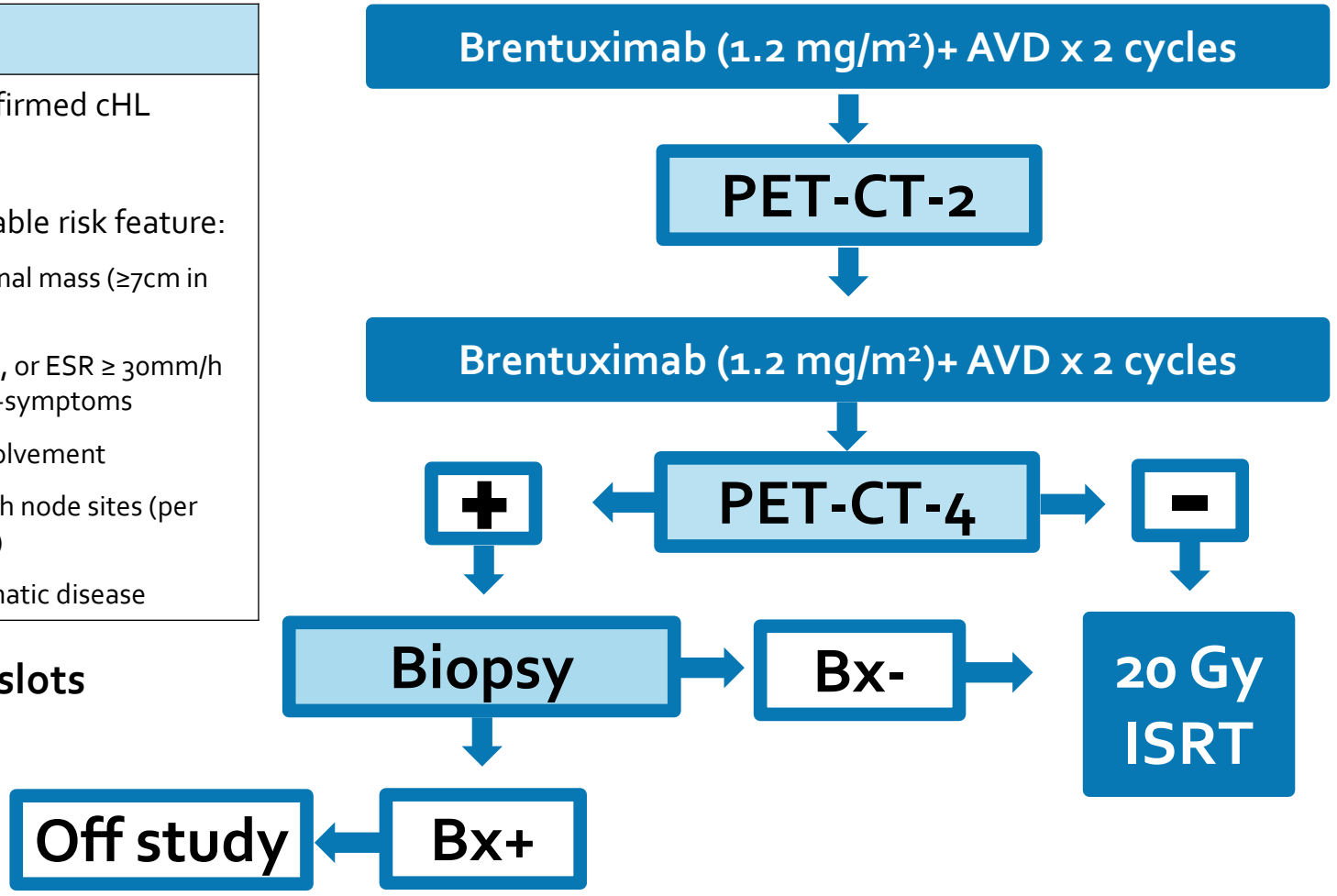
Kumar et al, Haematologica 2016

13-034 Cohort 2 Study Design, N=29

Eligiblity:

- Histologically confirmed cHL
- Stage I or II
- At least 1 unfavorable risk feature:
  - Bulky mediastinal mass (≥7cm in MTD or MCD)
  - ESR ≥ 50mm/h, or ESR ≥ 30mm/h in patient with B-symptoms
  - Extranodal involvement
  - 3 of more lymph node sites (per GHSG definition)
  - Infradiaphragmatic disease

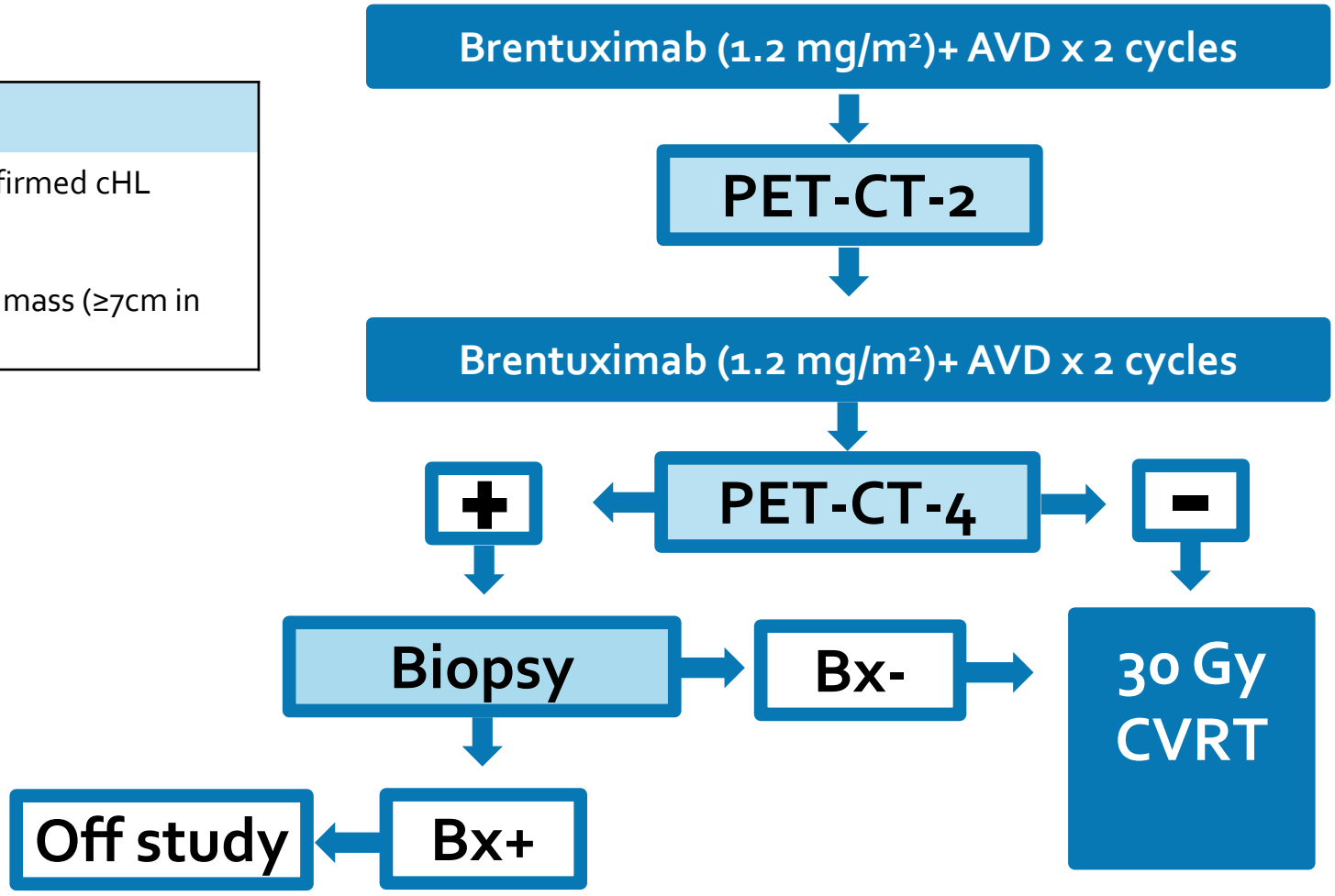
3 remaining slots



13-034 Cohort 3 Study Design, N=29

Eligiblity:

- Histologically confirmed cHL
- Stage I or II
- Bulky mediastinal mass (≥7cm in MTD or MCD)



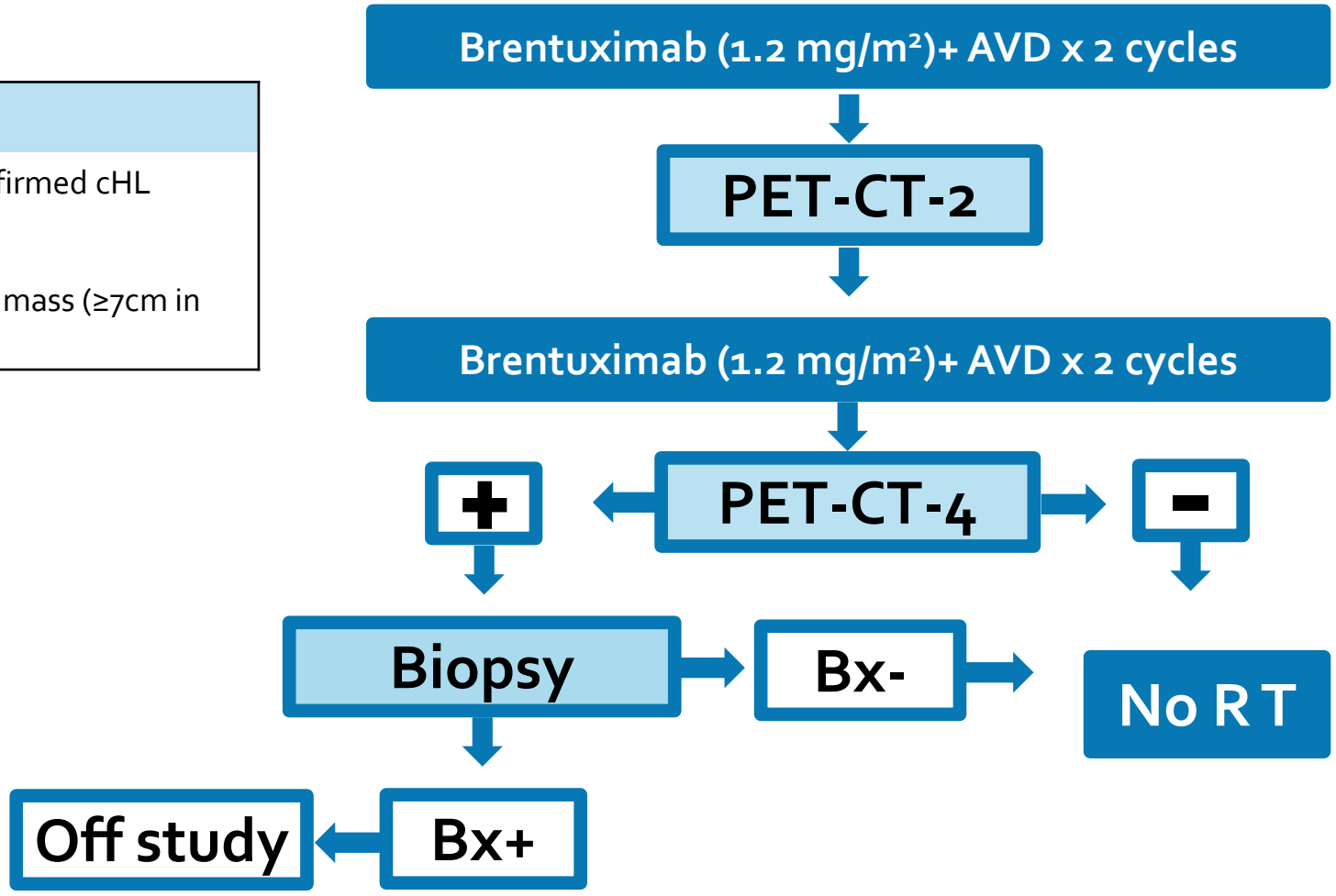
Consolidation Volume Radiotherapy / Residual Site Radiotherapy

- Deliver the radiation **only to the remaining CT abnormality** of a previously involved lymph nodes or organs that remain 1.5 cm or larger after BV-AVD
- Use high-quality CT scan with IV contrast
- Field is independent of the original size of the disease
- Lymph nodes that have resolved or are smaller than 1.5 cm will not be irradiated
- Volume definition-
  - GTV (gross tumor volume) is the post chemotherapy residual CT abnormality.
  - CTV (clinical target volume) is the GTV with minimal additional margins influenced by imaging uncertainty and motion.
  - PTV (planning target volume) is added if necessary for beam or plan qualities and influenced by patient immobilization.
- Dose prescribed to the to the PTV is 30.6 Gy (1.8 Gy daily X 17 fractions in 3.5 weeks).
- Either IMRT or 3-D conformal planning is allowed
- Deep Inspiration Breath Hold (DIBH) for mediastinal sites is encouraged

13-034 Cohort 4 Study Design

Eligiblity:

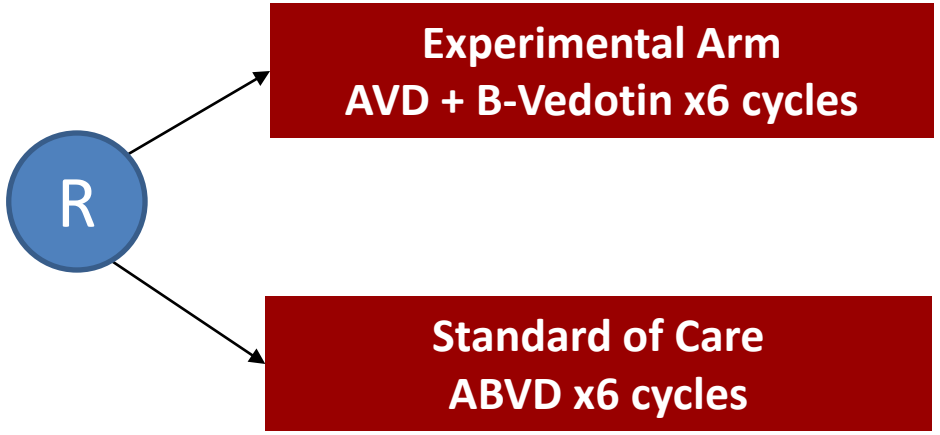
- Histologically confirmed cHL
- Stage I or II
- Bulky mediastinal mass (≥7cm in MTD or MCD)



Phase III Frontline HL (ECHELON-1)

- **Design**

Newly Diagnosed Advanced Stage cHL Patients ≥18 y

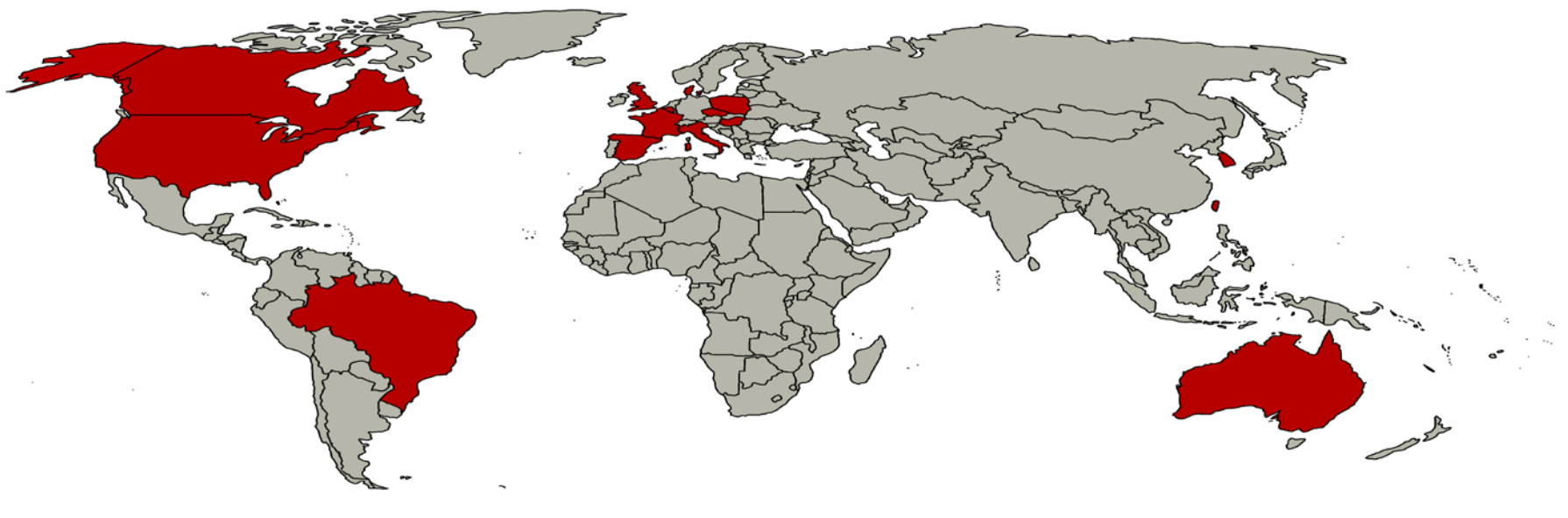


- **Target N=1240**
- **Primary outcome measure: Modified progression free survival (mPFS)**

Slide adapted from Takeda/Seattle Genetics

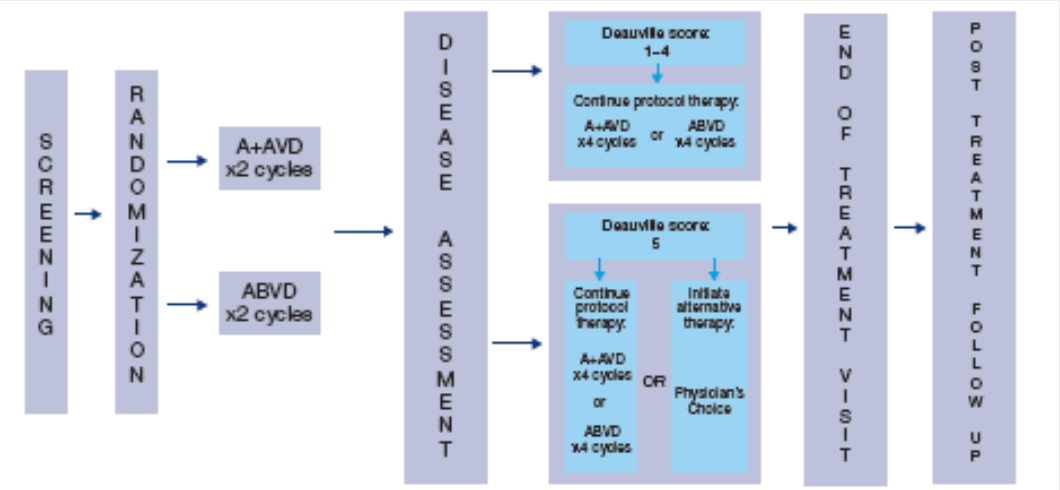
ECHELON-1 Highlights

- Improved treatment of FL HL would represent significant progress in an indication where treatment options have changed little in > 20 yrs
- Evaluation of brentuximab vedotin as a replacement for bleomycin in the AVD combination regimen is hypothesized to provide an improvement in PFS over the standard ABVD regimen, and eliminate the risk of bleomycin-associated pulmonary toxicity.
- Approximately 1040 patients at ~200 sites will be randomized to receive either A+AVD or ABVD; enrollment began in late 2012



ECHELON-1: Ongoing phase 3 trial of brentuximab vedotin and AVD vs. ABVD in frontline advanced HL

Schema:



Objectives:

- Primary: PFS
- Secondary:
  - Overall survival
  - Others: CR rate, safety, EFS, DFS, ORR, DOR, duration of CR, rate of irradiation for those not in CR, CR at the end of front-line therapy, rate of cycle 2 PET negativity, HRQOL, PK, immunogenicity

Treatment regimen:

- Brentuximab vedotin + AVD (up to 6 cycles):
  - Brentuximab vedotin 1.2 mg/kg IV infusion on days 1 and 15 of each 28-day cycle
  - Doxorubicin 25 mg/m^2 IV infusion on days 1 and 15 of each 28-day cycle
  - Vinblastine 6 mg/m^2 IV infusion on 1 days and 15 of each 28-day cycle
  - Dacarbazine (DTIC) 375 mg/m^2 on days 1 and 15 of each 28-day cycle
- ABVD (up to 6 cycles):
  - Doxorubicin 25 mg/m^2 IV infusion on days 1 and 15 of each 28-day cycle
  - Bleomycin 10 units/m^2 IV infusion on Days 1 and 15 of each 28-day cycle
  - Vinblastine 6 mg/m^2 IV infusion on 1 days and 15 of each 28-day cycle
  - Dacarbazine (DTIC) 375 mg/m^2 on days 1 and 15 of each 28-day cycle

PFS = Progression-free Survival, IRF = Independent review facility, EFS = Event-free survival, DFS= Disease-free survival, DOR= Duration of response, HRQOL= Health-related quality of life, PK= Pharmacokinetics

Younes A, et al. ASCO 2013; Chicago, US (Abstract #TPS8612)

When RT should be considered in “advanced-stage”?

- With regimens with less excessive chemotherapy (ABVD X6; BEACOPP X6, Stanford V)
- Older patients (>50) who tolerate intensive/long chemotherapy poorly.
- Patients with contra-indications for aggressive chemotherapy
- ~~Patients with predominantly bulky site(s) ????~~
- **Patients with residual disease that remain PET (+)**

- **Field: CTV is post-chemo volume**
- **Dose: 30 Gy (**36 Gy- 40 Gy under special circumstances)

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Primary CNS Lymphoma (PCNSL)

Joachim Yahalom, M.D.
Memorial Sloan Kettering Cancer Center
New York ,NY, USA

Memorial Sloan Kettering Cancer Center

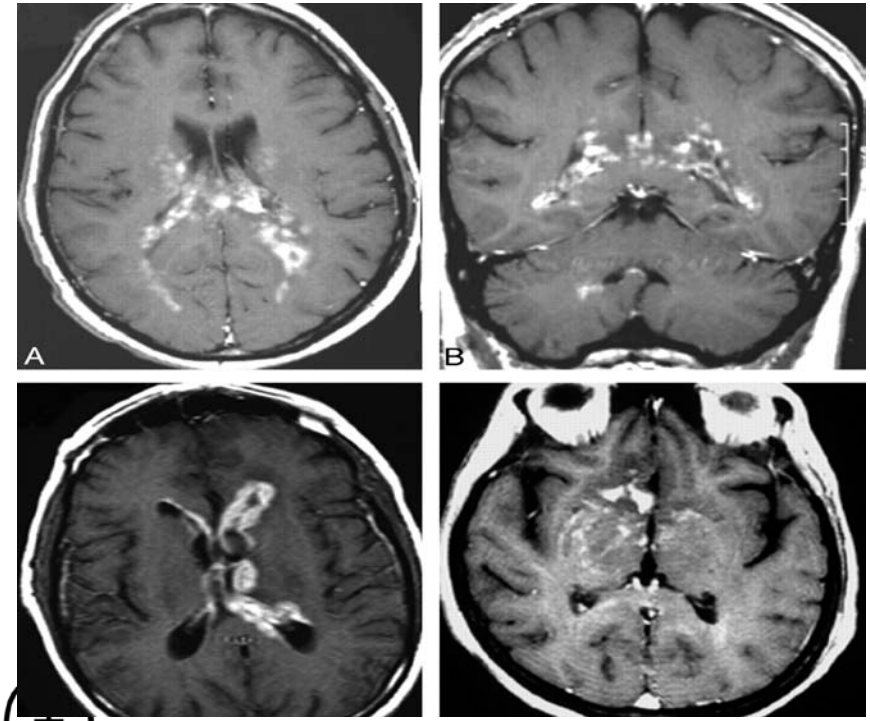
ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

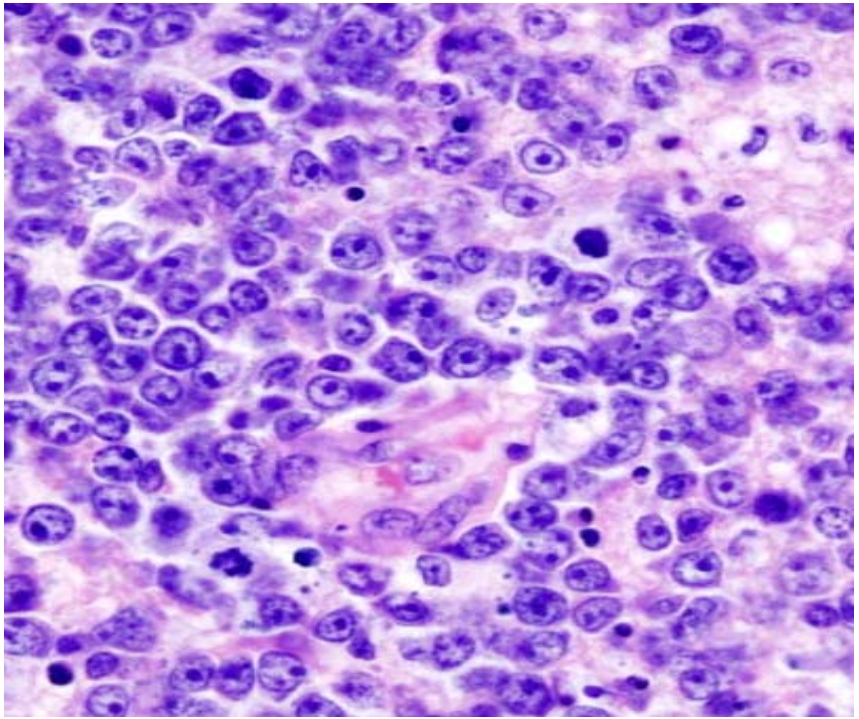
ESTRO School

Definitions

- **PCNSL -** Extranodal non-Hodgkin's lymphoma confined to the cranio-spinal axis without evidence of systemic involvement
- **Secondary Nervous System Lymphoma (SNSL)-** Systemic lymphoma with involvement of the nervous system

Primary CNS Lymphoma (PCNSL)





Memorial Sloan Kettering Cancer Center

ILROG International Lymphoma Radiation Oncology Group

ESTRO School

Primary CNS Lymphoma: A unique lymphoma entity

- Increasing incidence (immunocompetent, older)
- PCNSL- Confined to brain (occasionally to eyes and CSF)
- Systemic spread is very rare
- Multi-centric in the brain in presentation and in relapse (unlike gliomas)
- Resection is not associated with better outcome
- May initially improve and even temporarily disappear with steroids (may mask a diagnosis)

PCNSL

Epidemiology

- ***Central Brain Tumor Registry of the United States (CBTRUS), 1998-2002***
  - Brain Lymphoma
    - 3.1% of all primary CNS tumors
    - 0.46/100,000 person years
    - ~1000-1500 cases per year in the United States
    - Median age at diagnosis = 60
    - Incidence increased ~3-fold from 1973-1984 but recent SEER data suggests plateau of incidence

PCNSL

Epidemiology

- ***Risk Factors***
  - Immunosuppression
    - Congenital (SCID, Wiskott-Aldrich Syndrome)
    - Acquired (HIV)
      - The risk of PCNSL in HIV patients is 3600-fold higher than general population
      - Up to 2/100 HIV infected persons develop PCNSL
    - Iatrogenic (Organ allograft recipients)

PCNSL in “immunocompetent” hosts

(non-HIV)

Primary CNS Lymphoma

- Type

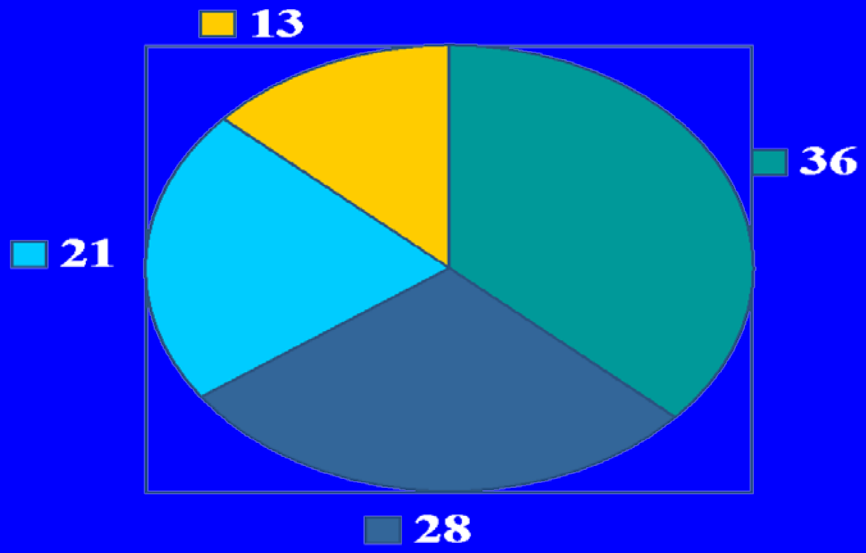
- Primary
  - Brain
  - Leptomeninges
  - Eye
  - Spinal cord
- Metastatic
  - Leptomeninges 4-11%
  - Epidural 3-5%
  - Brain 1%

- Clinical Features

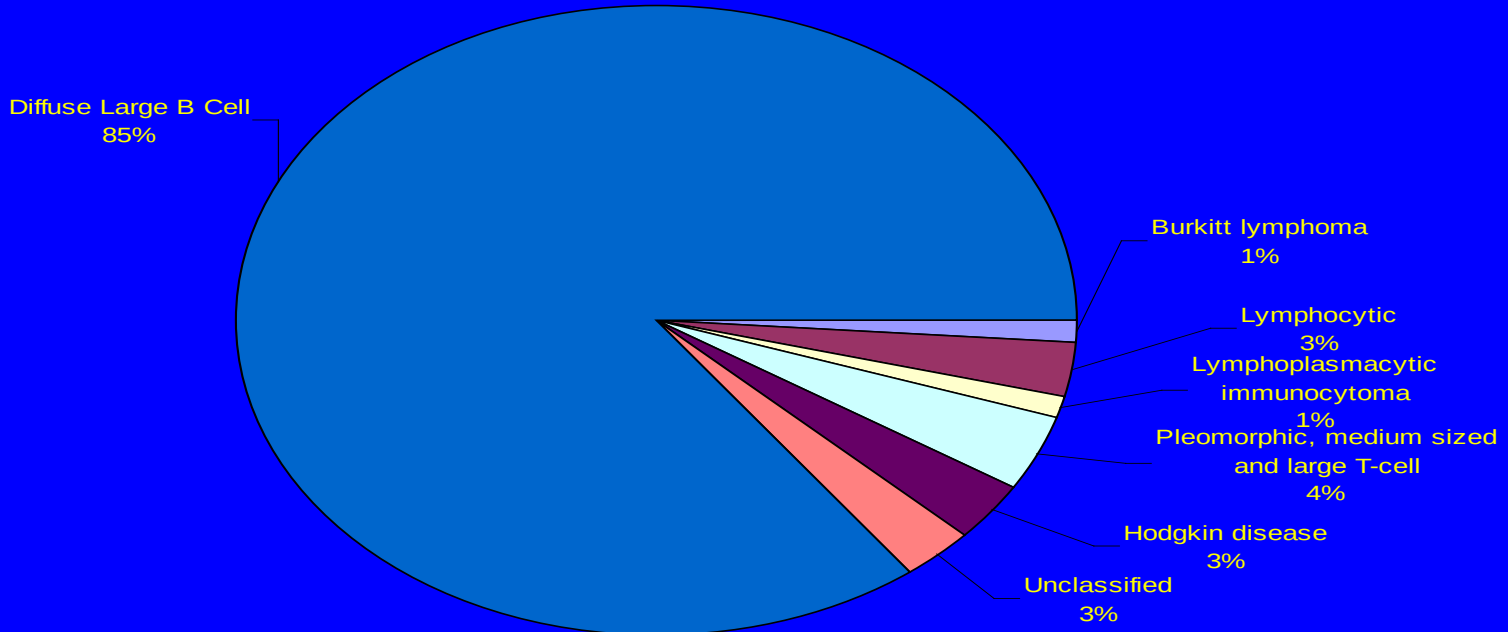
- Mean age = 60
- Gender: men: women - 1:1
- 23% ocular involvement
- 17% positive CSF cytology
- Clinical features
  - 51% behavioral/personality
  - 28% hemiparesis
  - 13% seizure
- DLBCL histology
  - ~85% Non-GC

PCNSL

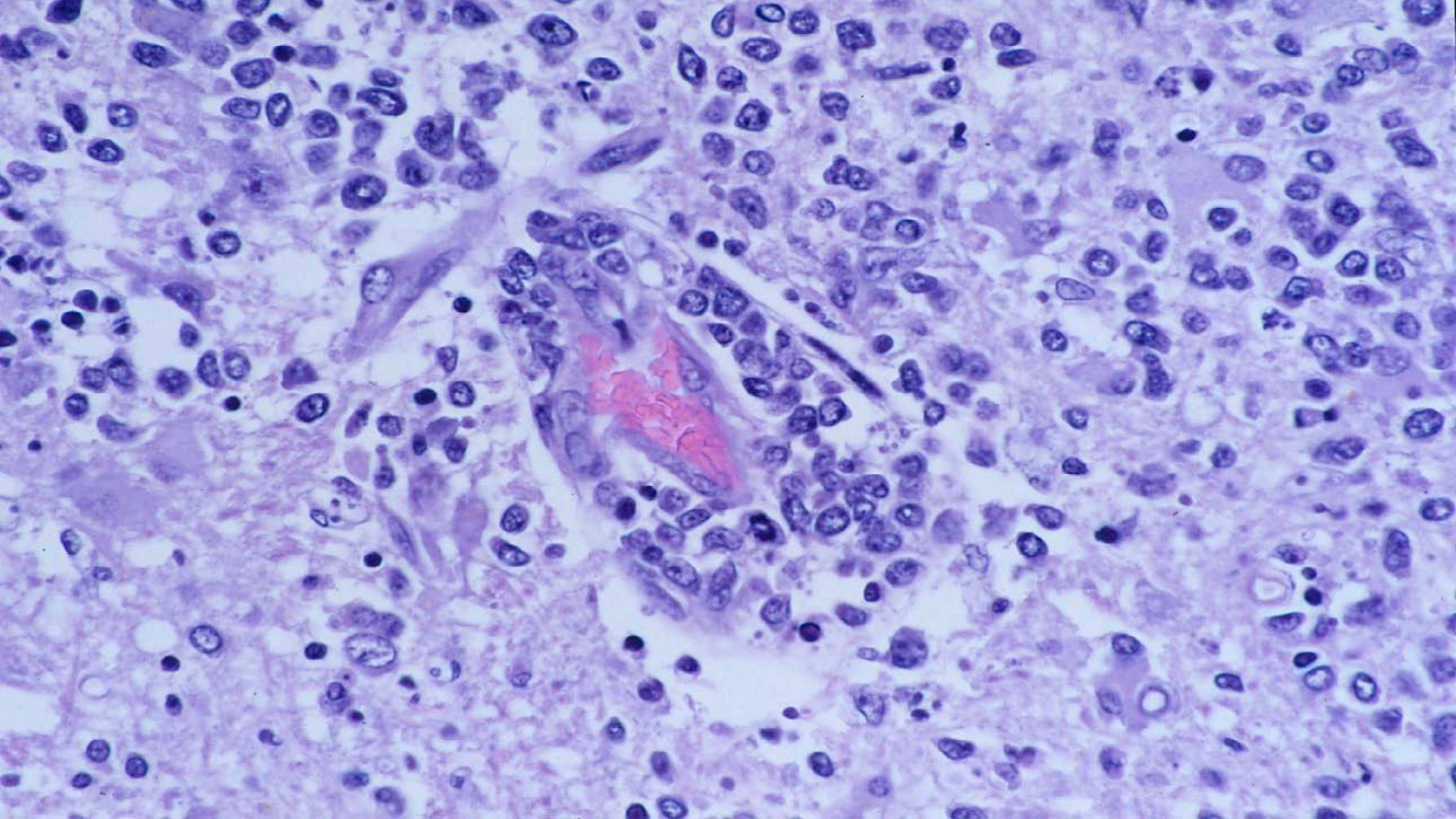
Symptoms

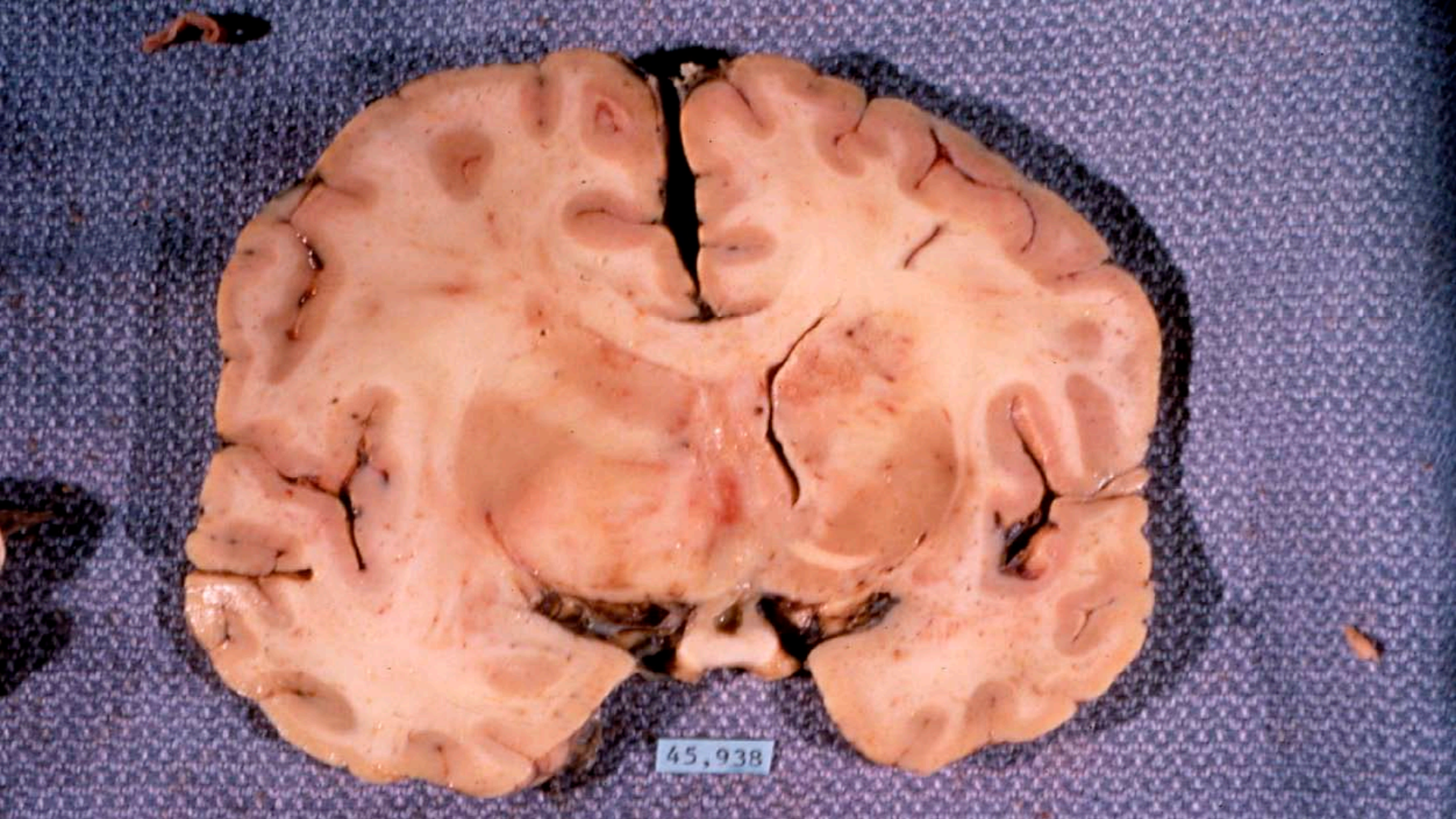


REAL classification of 72 Immunocompetent PCNSL Patients1



[1]*Am J Clin Pathol 1998;110:607-612.*

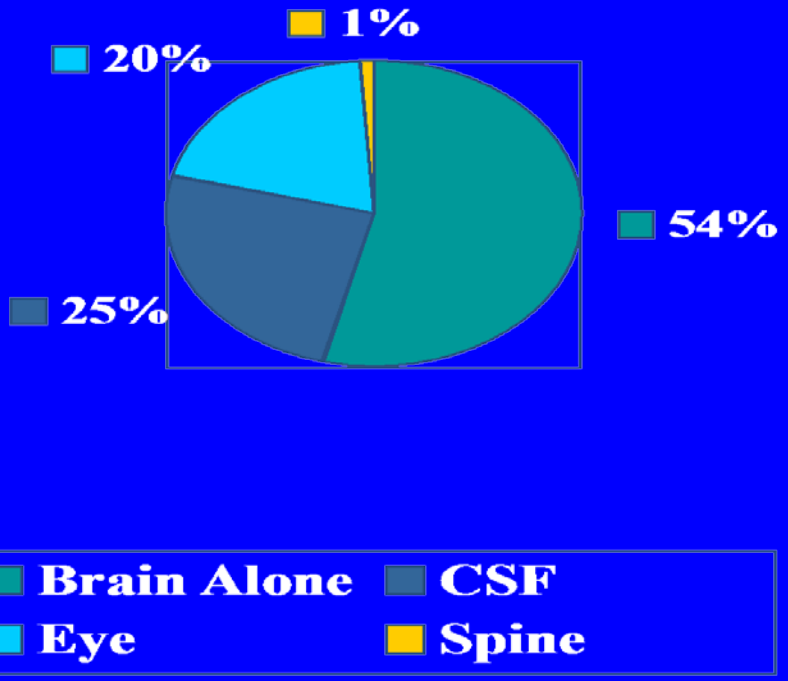



45.938

PCNSL

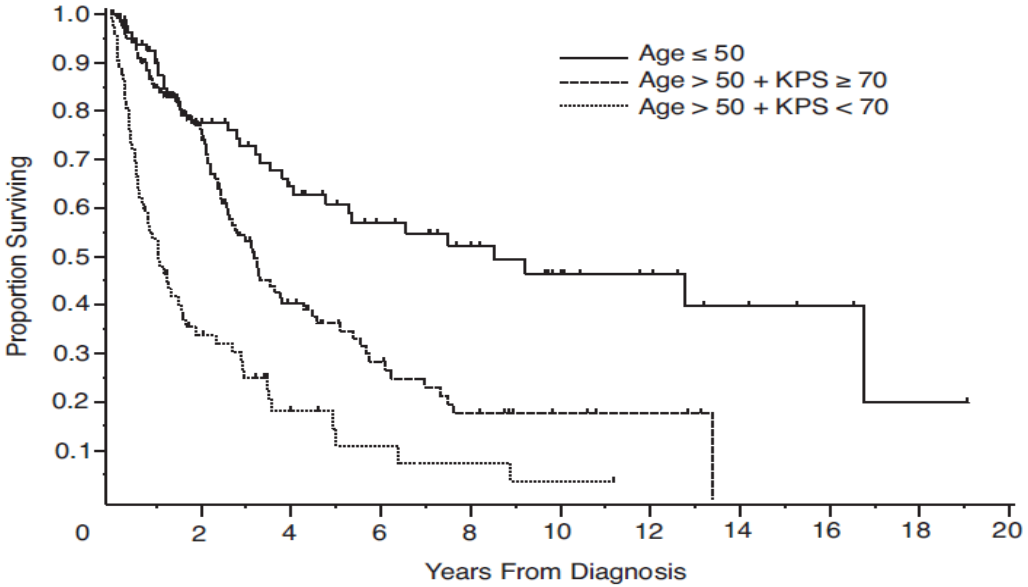
Extent of Disease

- Brain
  - 2/3 supratentorial, 1/3 infratentorial
  - 3/4 solitary, 1/4 multiple
- CSF (13-41%)
- Eye (5-20%)
- Spine (<1%)



Primary CNS Lymphoma

- Prognostic factors critical: age and KPS
- Prognostic model in pts treated with HD MTX-based Rx
- Pathologic subtype important?



(Abrey et al., JCO 2002)

Memorial Sloan Kettering Cancer Center

ILROG International Lymphoma Radiation Oncology Group

ESTRO School

PCNSL: A unique treatment challenge

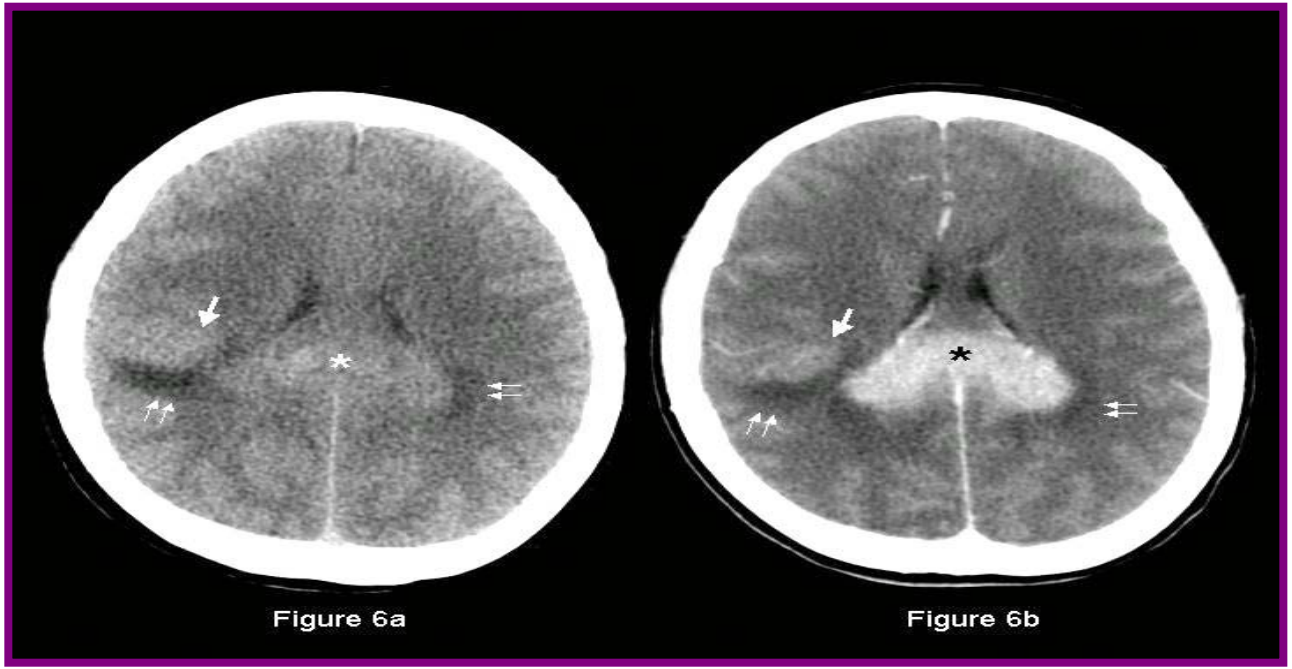
- Rapidly lethal if not treated or responsive
- **RT alone is effective**, but CRs are brief (median survival– 1 yr)
- Adding CHOP or CHOD does not improve RT alone results
- **High-Dose Methotrexate** is the mainstay of effective treatment best for inducing a complete response
- There may be a small benefit from adding rituximab
- High-dose ARA-C has also been used for consolidation and salvage
- High-dose chemotherapy with autologous stem cell rescue has been suggested as an alternative to RT consolidation for fit patients

PCNSL Baseline Evaluation

- **Pathologic Evaluation**
  - Centralized confirmation of pathology with immunopathology when possible
- **Clinical Evaluation**
  - Complete medical, neurological, cognitive examination
  - Determination of prognostic factors (age, PS)
- **Laboratory Evaluation**
  - HIV, lactate dehyrogenase, creatinine clearance
- **Extent of Disease Evaluation**
  - Brain- Contrast-enhanced cranial MRI
  - CSF- Cytology, flow cytometry, IgH PCR
  - Eye- Slit lamp evaluation
  - Body- CT of chest/abdomen/pelvis; BM biopsy + aspirate. Consider testicular US in older men

PCNSL

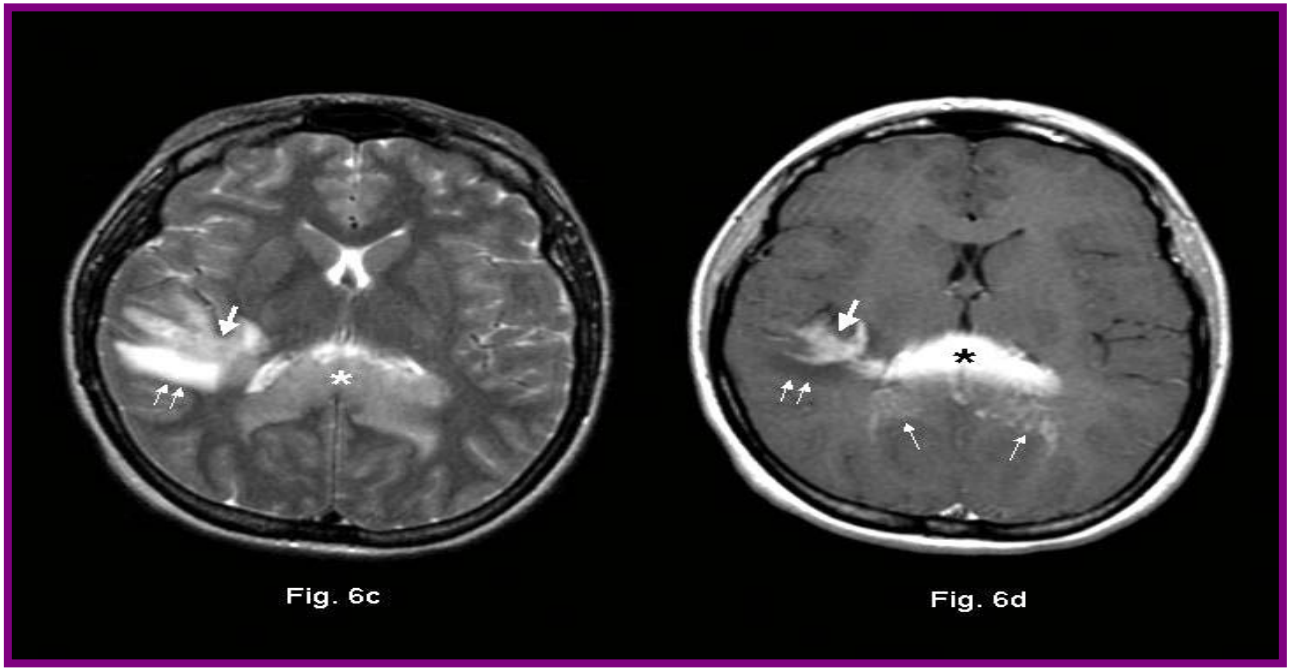
CT Appearance



From: Batchelor TT, Buchbinder BD, Harris NL. Case records of the Massachusetts General Hospital, A 32 year old woman with difficulty walking, headache and nausea. *N Engl J Med* 2005; 352: 185-194

PCNSL

MRI Appearance



From: Batchelor TT, Buchbinder BD, Harris NL. Case records of the Massachusetts General Hospital, A 32 year old woman with difficulty walking, headache and nausea. *N Engl J Med* 2005; 352: 185-194

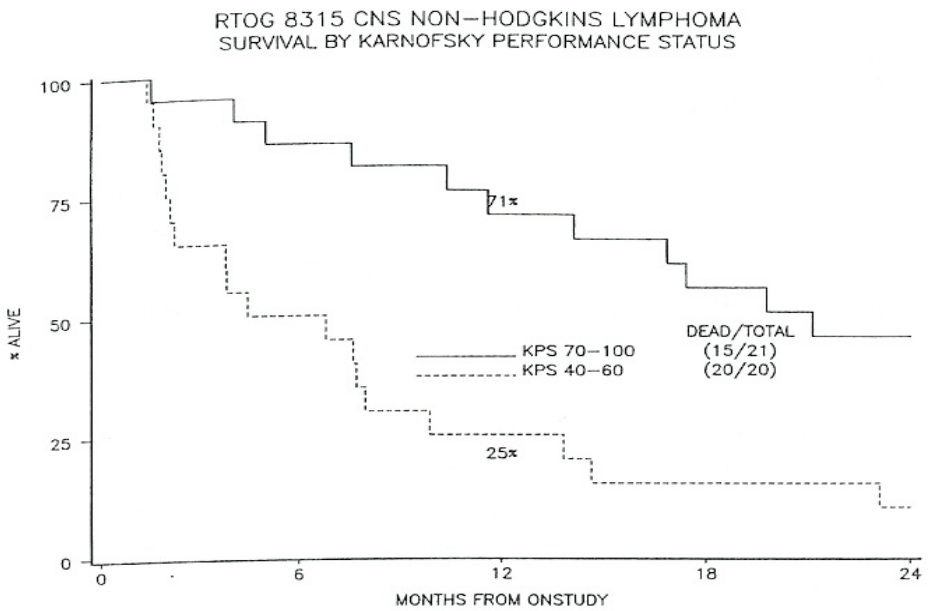
The debated role of RT consolidation

- A brief (forgotten) history of WBRT alone
- The breakthrough for cure with MTX followed by WBRT
- The great concern of post-MTX radiation-related neurotoxicity
- Efforts to match the results of combined modality with higher dose chemotherapy alone and effective salvage
- The controversial phase III study
- High-dose chemotherapy with autologous stem cell transplantation
- An alternative combined modality with low-dose RT and rare toxicity

RTOG 83-15 WBRT alone

- 41 patients
- WBRT of 20 RT of 40 Gy + boos
  Gy to lesion (+ 2 cm margin)

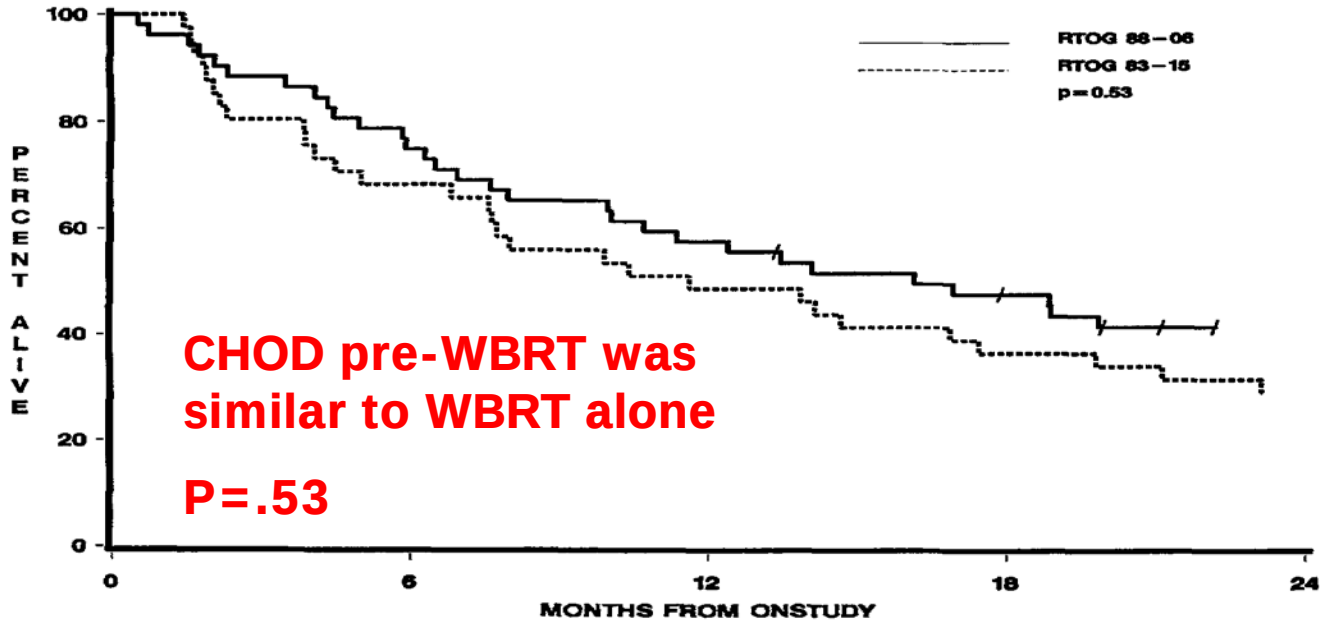
- **Overall median survival: 12 months**
  - <60 years: 23 months
  - ≥60 years: 8 months
  - KPS≥70: 21 month
  - KPS<70: 6 months
  - Relapses inside and outside the “boost” area



Nelson DF et al: IJROBP 1992; 23:9-17

Preirradiation Chemotherapy With Cyclophosphamide, Doxorubicin, Vincristine, and Dexamethasone for Primary CNS Lymphomas: Initial Report of Radiation Therapy Oncology Group Protocol 88-06

By Christopher Schultz, Charles Scott, William Sherman, Bernadine Donahue, Joseph Fields, Kevin Murray, Barbara Fisher, Ross Abrams, and Jeanne Meis-Kindblom



CHOD pre-WBRT was similar to WBRT alone

P=.53

JCO 1996;14:556-564

Diagnosis

↓

Dexamethasone 16mg/day

↓

Ommaya placement

↓

IV MTX (1 gm/M^2) Day 1,8

Intra-Ommaya MTX (12 mg/dose) Day 1,4,8,11,15,18

Taper dexamethasone (off by completion of RT)

↓

WBRT 200 cGyx20 (total 4000 cGy)

Coned-down 180 cGyx8 (total 1440 cGy)

↓

3 week rest

↓

IV cytosine arabinoside (3 gm/M^2/dose)

1 dose/day for 2 consecutive days

↓

3 week rest

↓

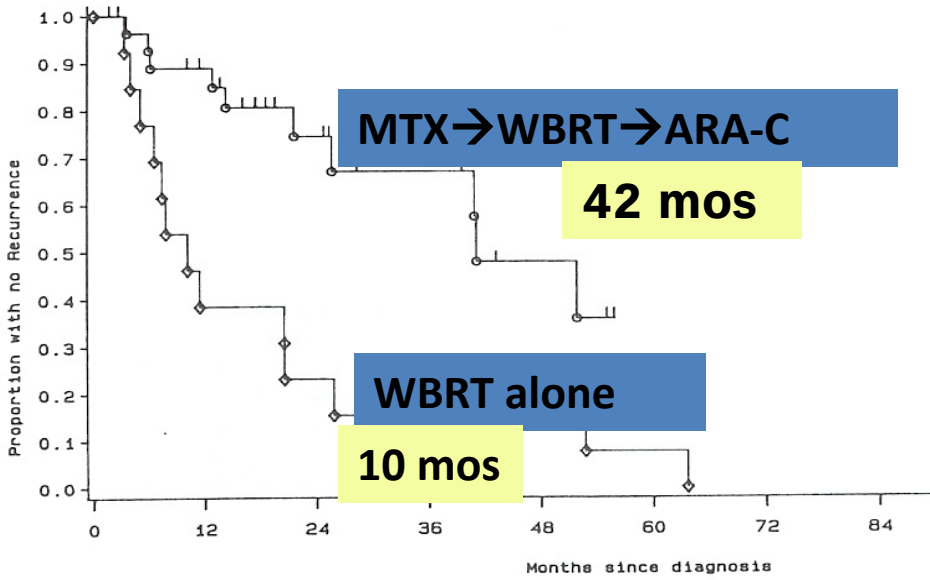
IV cytosine arabinoside (3 mg/M^2/dose)

Combined Modality Therapy for Primary CNS Lymphoma

By Lisa M. DeAngelis, Joachim Yahalom, Howard T. Thaler, and Uma Kher

Diagnosis
↓
Dexamethasone 16mg/day
↓
Ommaya placement
↓
IV MTX (1 gm/M^2) Day 1,8
Intra-Ommaya MTX (12 mg/dose) Day 1,4,8,11,15,18
Taper dexamethasone (off by completion of RT)
↓
WBRT 200 cGyx20 (total 4000 cGy)
Coned-down 180 cGyx8 (total 1440 cGy)
↓
3 week rest
↓
IV cytosine arabinoside (3 gm/M^2/dose)
1 dose/day for 2 consecutive days
↓
3 week rest
↓
IV cytosine arabinoside (3 mg/M^2/dose)
1 dose/day for 2 consecutive days

Fig 1. Outline of treatment protocol for PCNSL at MSKCC.



JCO 1992; 10:635-643

Long-Term Survival in Primary CNS Lymphoma

By Lauren E. Abrey, Lisa M. DeAngelis, and Joachim Yahalom

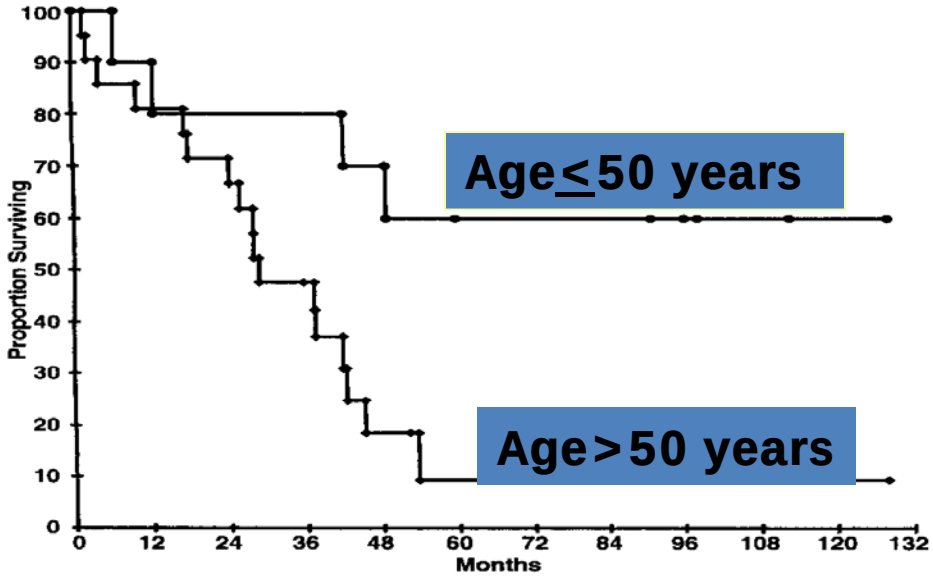
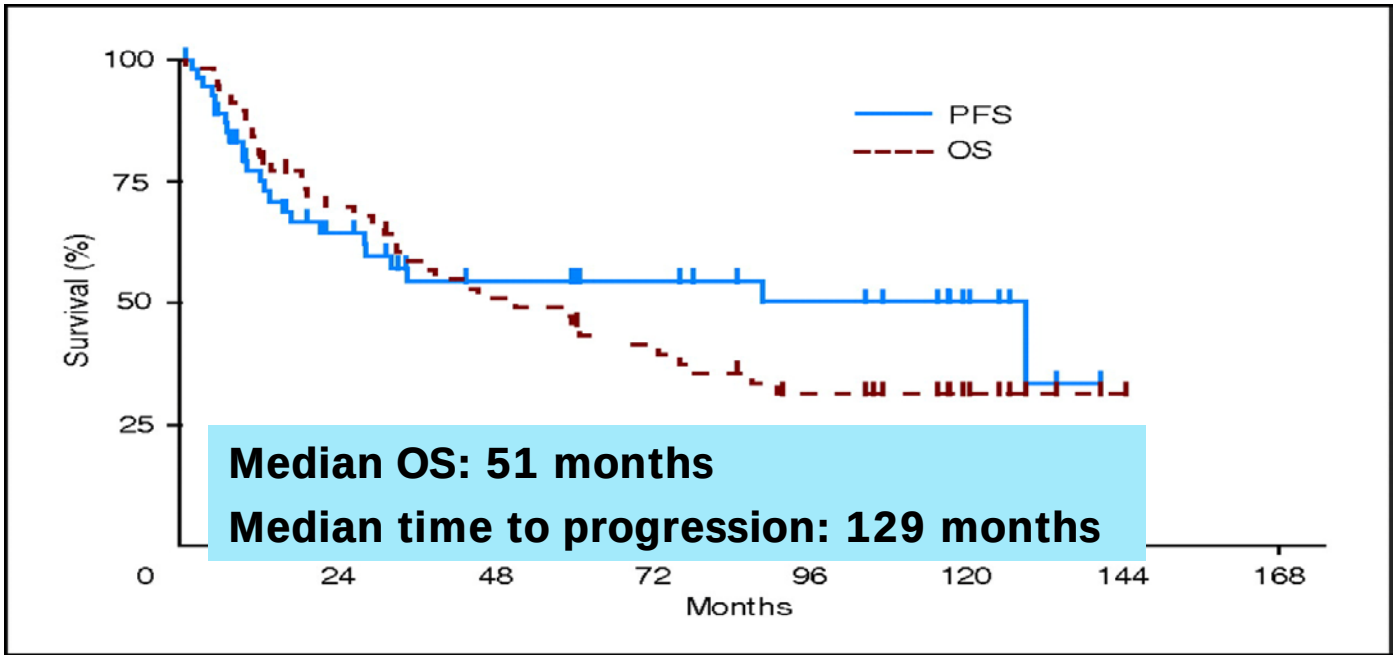


Fig 3. Kaplan-Meier plot: cause-specific survival comparing patients less than 50 years of age at diagnosis (circles) with patients aged more than 50 years (diamonds); $P = .01$ (Mantel-Cox method).

JCO 1992; 10:635-643

Overall survival (OS) and progression-free survival (PFS) for the entire cohort
Median follow-up of 115 months



Gavrilovic, I. T. et al. J Clin Oncol; 24:4570-4574 2006

JOURNAL OF CLINICAL ONCOLOGY

Neurotoxicity by Age

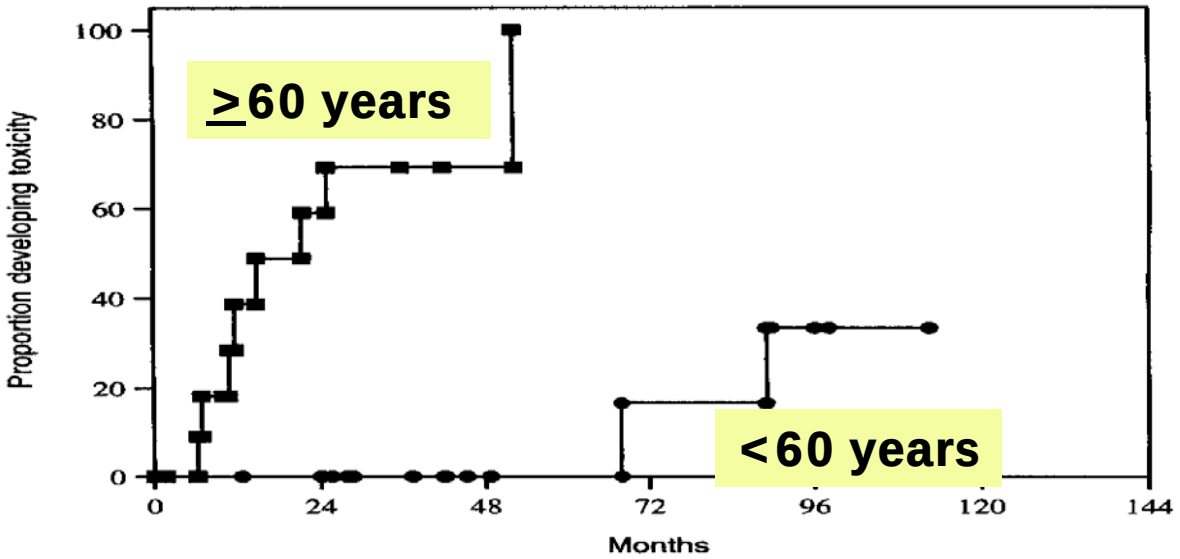
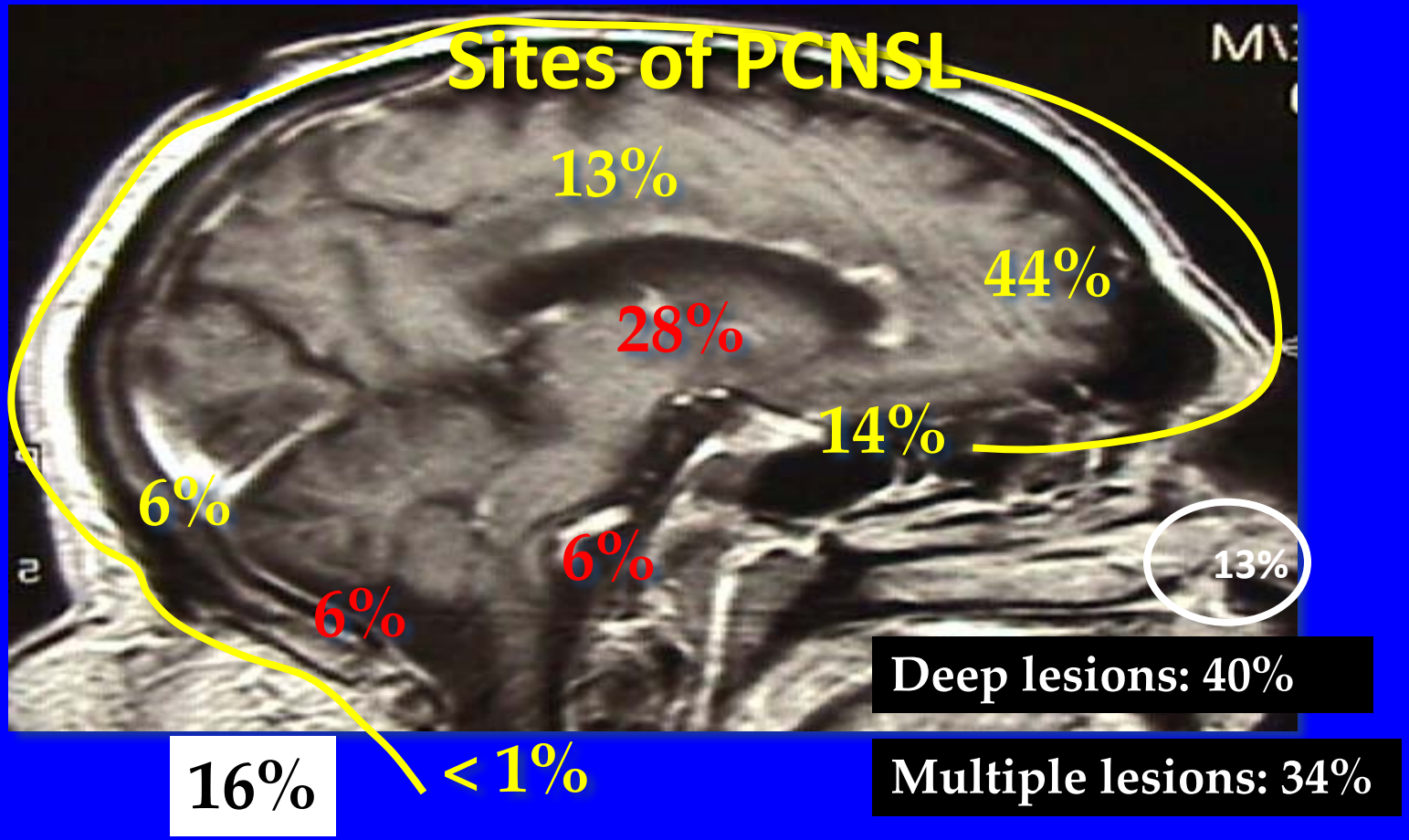
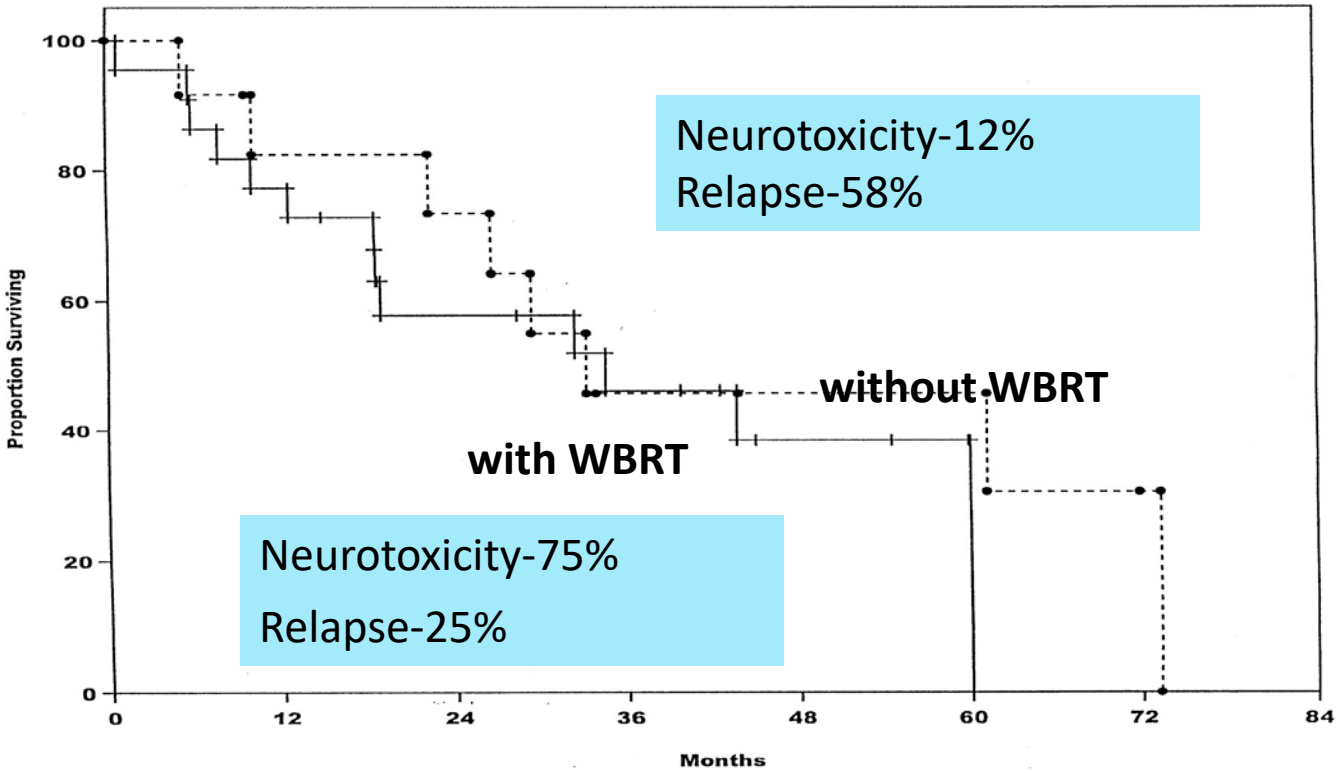


Fig 1. Proportion of patients who developed neurotoxicity with increasing duration of follow-up. Patients less than 60 years of age (circles) are compared with patients aged more than 60 years (squares); $P < .0001$ (Mantel-Cox method).


Sites of PCNSL
13%
44%
28%
14%
6%
6%
6%
13%
16%
< 1%
Deep lesions: 40%
Multiple lesions: 34%

Overall survival of patients ≥ 60 years who did (n = 12) or did not (n = 22) receive whole-brain RT



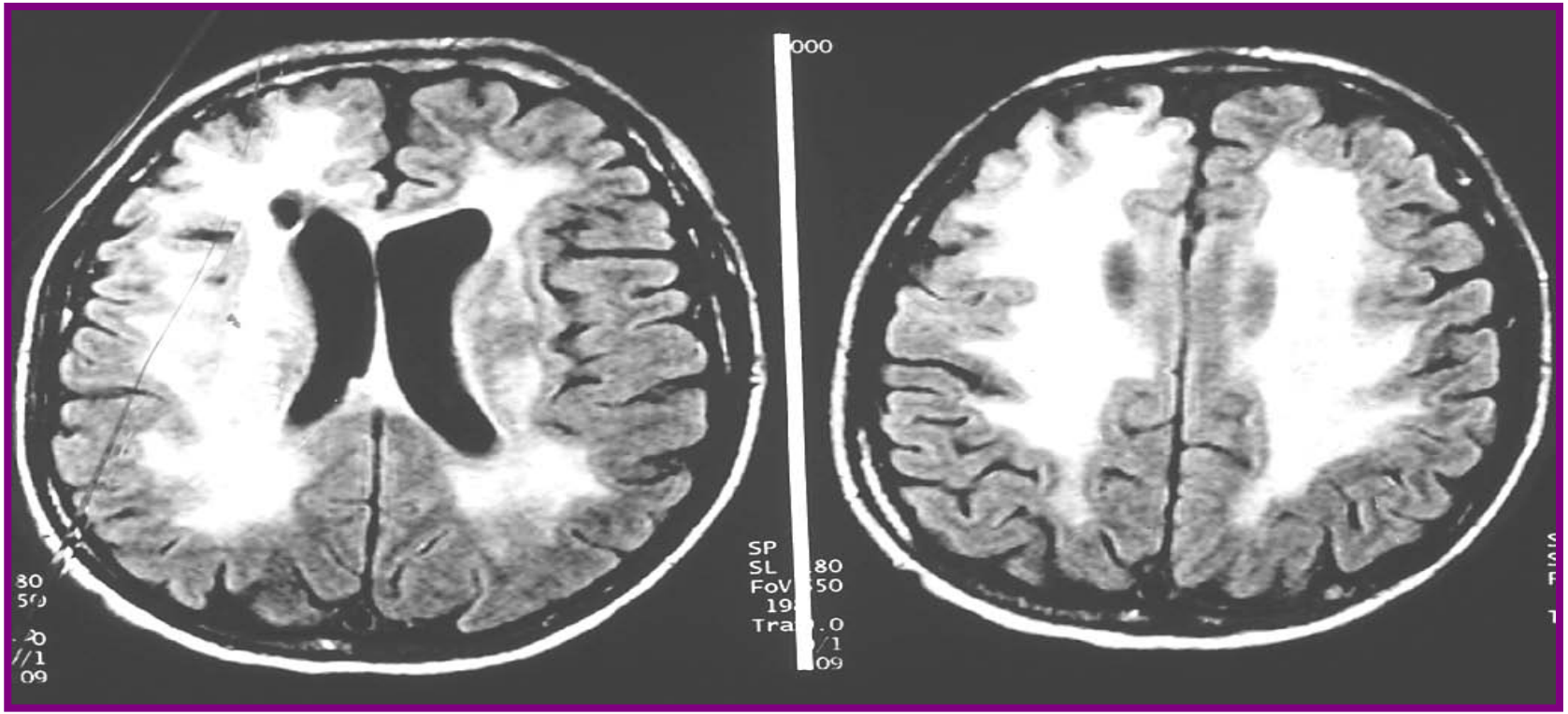
Abrey, L. E. et al. J Clin Oncol; 18:3144-3150 2000

JOURNAL OF CLINICAL ONCOLOGY

PCNSL - Neurotoxicity

- **Risk Factors**
  - Age > 60, MTX followed by full-dose whole brain RT
- **Clinical Features**
  - Imaging changes evident in most patients by 6 months after radiation
  - Clinical changes began at a median of 1 month in one study
  - Four domains most sensitive to disease and treatment
    - **Attention**
    - **Executive Functions**
    - **Memory**
    - **Psychomotor Speed**
  - **Occurs in many patients > 60 treated with MTX-WBRT (full dose)**

PCNSL- Neurotoxicity



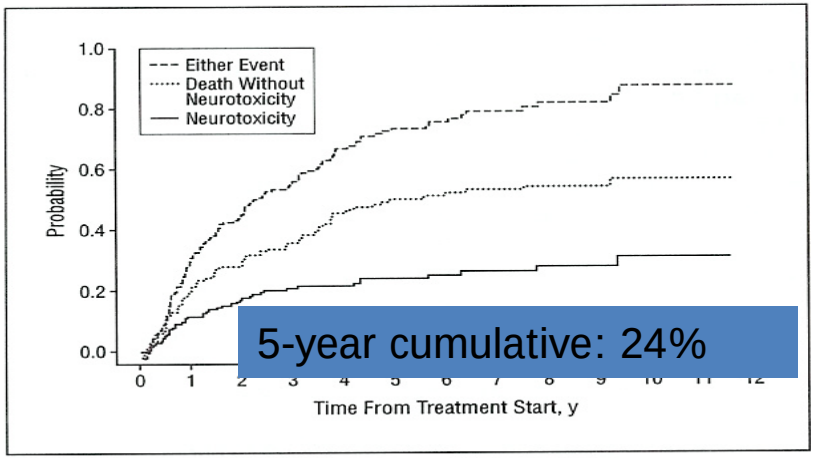
Increased T2 and FLAIR subcortical white matter signal abnormality associated with diffuse cerebral atrophy and ventricular enlargement

ORIGINAL CONTRIBUTION

Delayed Neurotoxicity in Primary Central Nervous System Lymphoma

Antonio M. P. Omuro, MD; Leah S. Ben-Porat, MS; Katherine S. Panageas, DrPH; Amy K. Kim, BA; Denise D. Correa, PhD; Joachim Yahalom, MD; Lisa M. DeAngelis, MD; Lauren E. Abrey, MD

MSKCC Experience: 185 pts (1985-2000)



5-year cumulative: 24%

Figure 1. Incidence of neurotoxicity, death, and either neurotoxicity or death (either event).

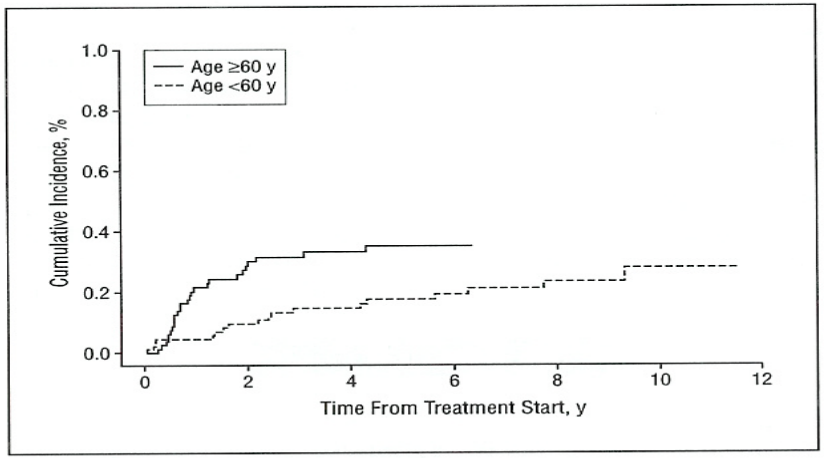


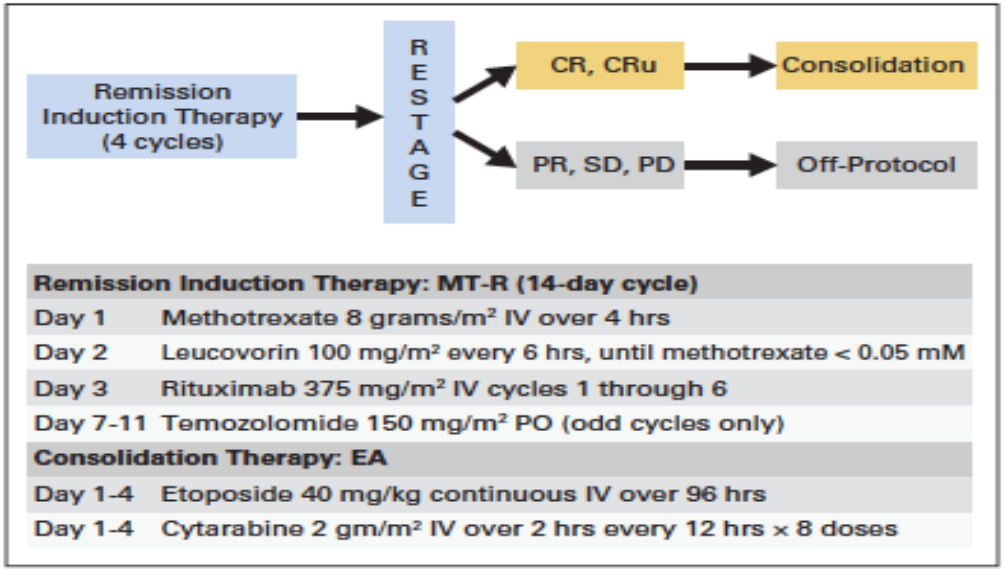
Figure 2. The incidence of neurotoxicity stratified by age, showing that although older patients are at a significantly higher risk, the development of neurotoxicity is also a concern in long-term survivors younger than 60 years.

Arch Neurol. **2005; 62:1-6**

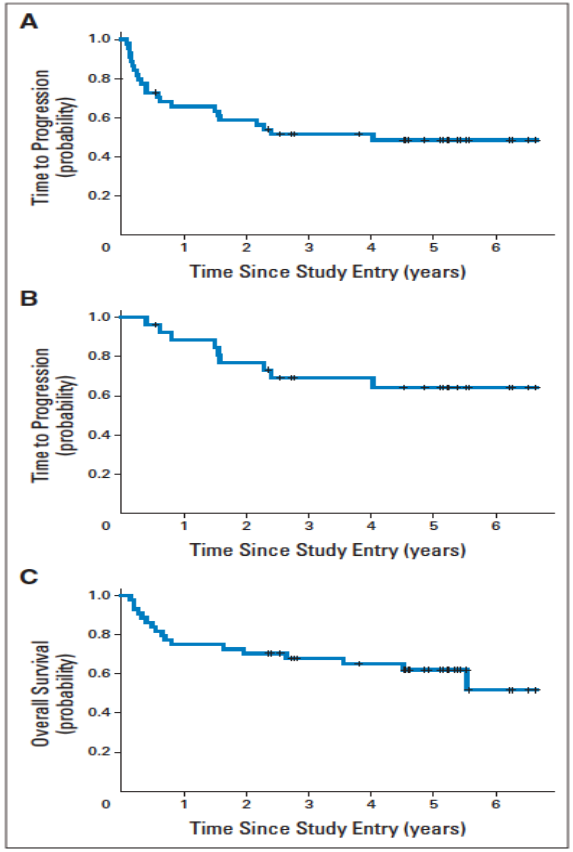
Intensive Chemotherapy and Immunotherapy in Patients With Newly Diagnosed Primary CNS Lymphoma: CALGB 50202 (Alliance 50202)

James L. Rubenstein, Eric D. Hsi, Jeffrey L. Johnson, Sin-Ho Jung, Megan O. Nakashima, Barbara Grant, Bruce D. Cheson, and Lawrence D. Kaplan

41 Patients- 26 completed treatment



Remission Induction Therapy: MT-R (14-day cycle)	
Day 1	Methotrexate 8 grams/m² IV over 4 hrs
Day 2	Leucovorin 100 mg/m² every 6 hrs, until methotrexate < 0.05 mM
Day 3	Rituximab 375 mg/m² IV cycles 1 through 6
Day 7-11	Temozolomide 150 mg/m² PO (odd cycles only)
Consolidation Therapy: EA	
Day 1-4	Etoposide 40 mg/kg continuous IV over 96 hrs
Day 1-4	Cytarabine 2 gm/m² IV over 2 hrs every 12 hrs × 8 doses



VOLUME 31 · NUMBER 25 · SEPTEMBER 1 2013
JOURNAL OF CLINICAL ONCOLOGY

High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial

Eckhard Thiel, Agnieszka Korfel*, Peter Martus, Lothar Kanz, Frank Griesinger, Michael Rauch, Alexander Röth, Bernd Hertenstein, Theda von Toll, Thomas Hundsberger, Hans-Günther Mergenthaler, Malte Leithäuser, Tobias Birnbaum, Lars Fischer, Kristoph Jahnke, Ulrich Herrlinger, Ludwig Plasswilm, Thomas Nägele, Torsten Pietsch, Michael Bamberg, Michael Weller*

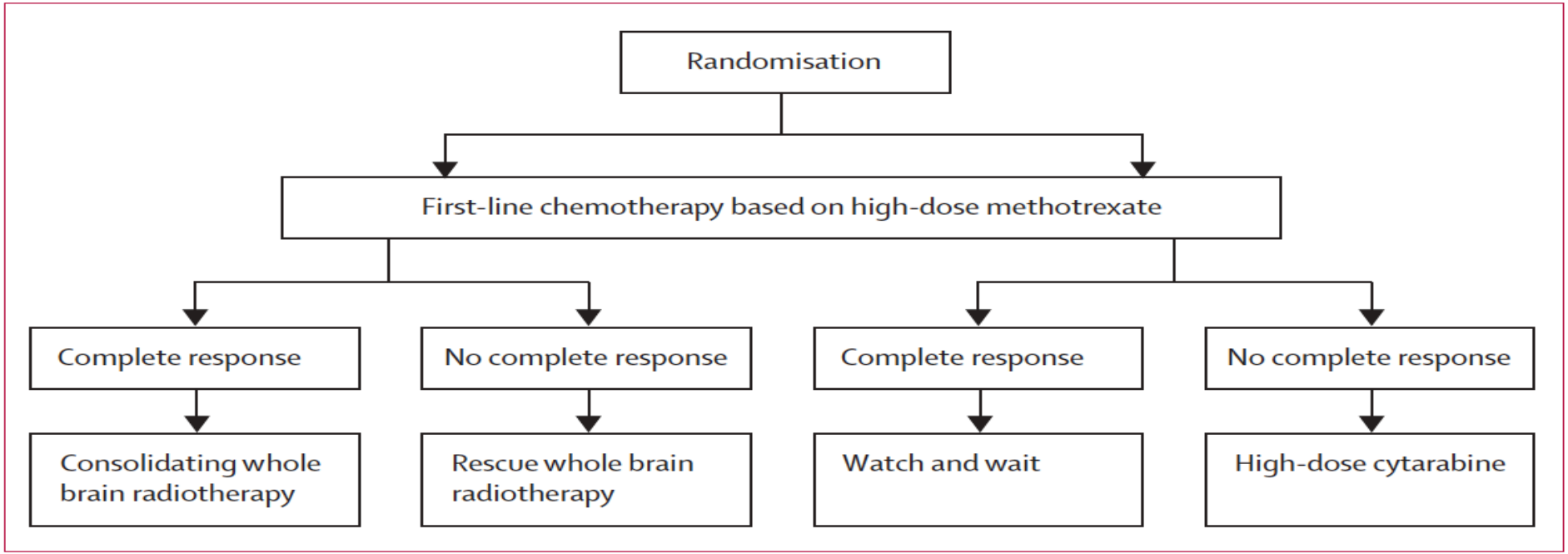
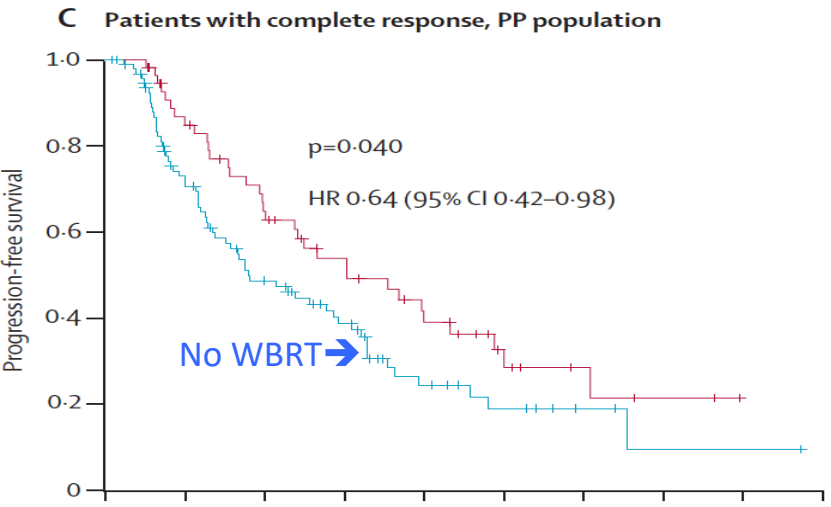
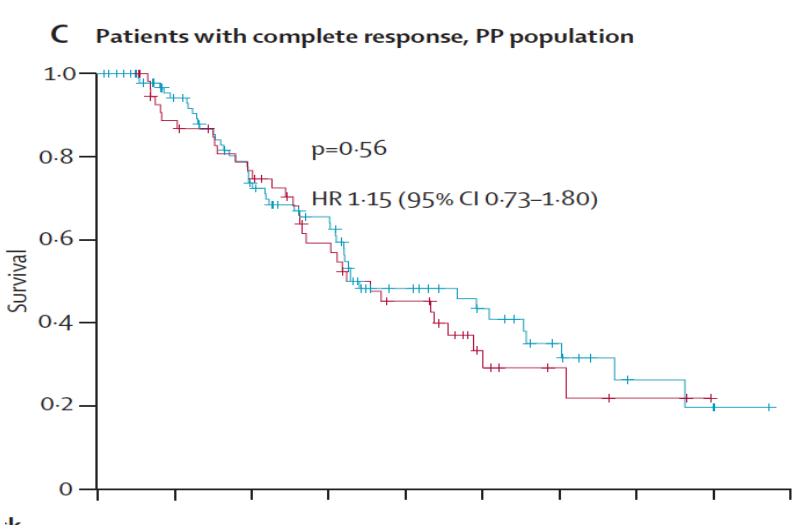


Figure 1: **Trial design**





Highly criticized:

- Poor protocol adherence
- Non-inferiority goal in OS not met
- Insufficient toxicity evaluation
- Overall poor results, sub-optimal chemo
- Neurotoxicity even with chemo alone (26%), with RT (49%)
- Salvage improved survival, but carries high QOL/toxicity cost

Hypothesis

Reduced-dose WBRT following effective immuno-chemotherapy will result in lower neurological toxicity while providing adequate disease control in all age groups

Chemotherapy Schedule

- **Day 1**
  - Rituximab 500 mg/m2
- **Day 2**
  - MTX 3.5 gm/m2
  - VCR 1.4 mg/m2
  - Procarbazine 100 mg/m2/d x 7 d. (cycles 1, 3, 5, 7)

X5 cycles (or X7, if PR)

- **Following WBRT**
  - ARA-C 3 gm/m2 (2 cycles)

RT Schedule

- **IF CR** after R-MVP X5 or X7 →**WBRT of 2340 cGy**

- **IF PR** after R-MVP X7 →**WBRT of 4500 cGy**

VOLUME 25 · NUMBER 30 · OCTOBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Combined Immunochemotherapy With Reduced Whole-Brain Radiotherapy for Newly Diagnosed Primary CNS Lymphoma

Gaurav D. Shah, Joachim Yahalom, Denise D. Correa, Rose K. Lai, Jeffrey J. Raizer, David Schiff, Renato LaRocca, Barbara Grant, Lisa M. DeAngelis, and Lauren E. Abrey

VOLUME 31 · NUMBER 31 · NOVEMBER 1 2013

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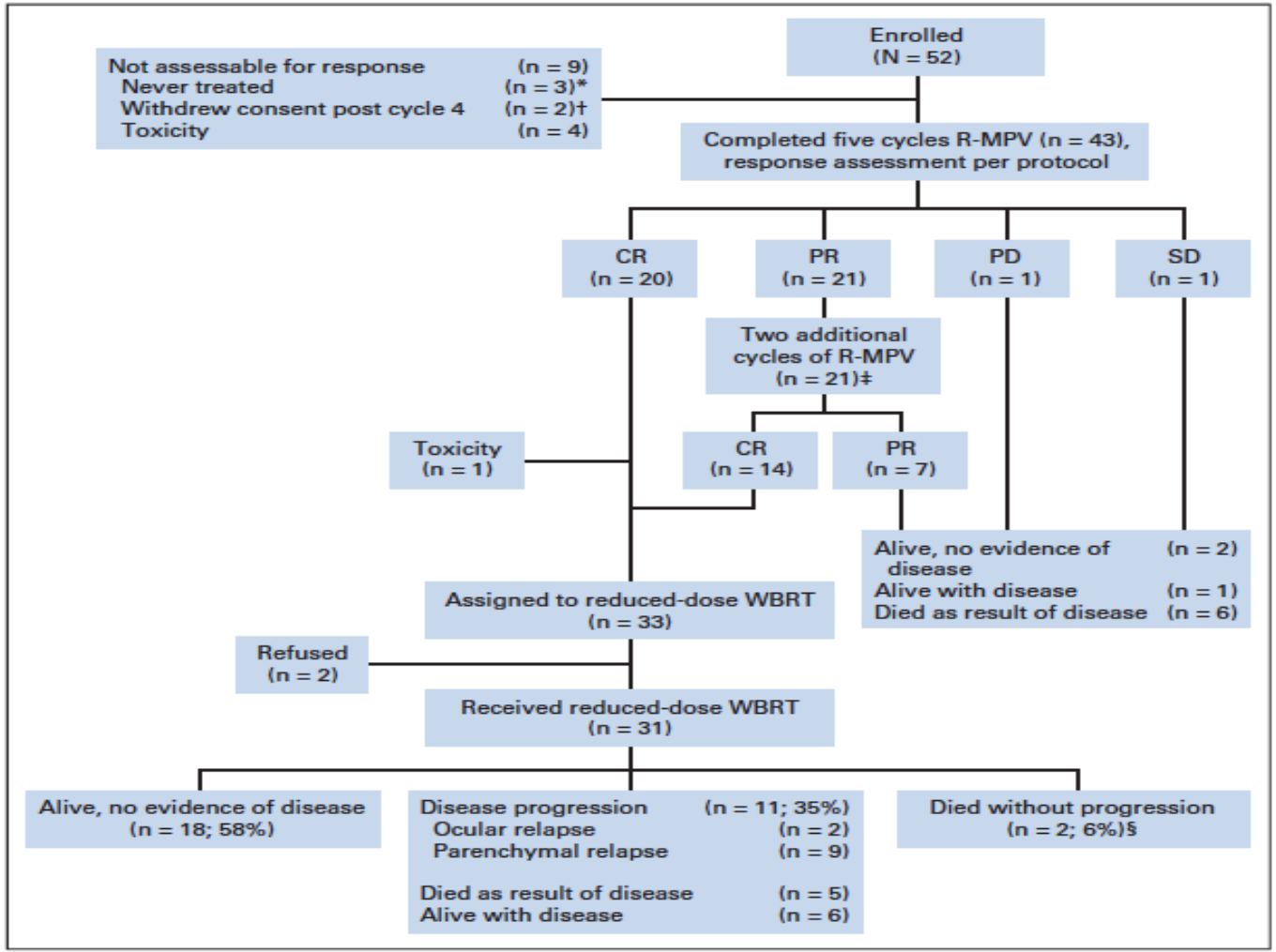
ORIGINAL REPORT

Rituximab, Methotrexate, Procarbazine, and Vincristine Followed by Consolidation Reduced-Dose Whole-Brain Radiotherapy and Cytarabine in Newly Diagnosed Primary CNS Lymphoma: Final Results and Long-Term Outcome

Patrick G. Morris, Denise D. Correa, Joachim Yahalom, Jeffrey J. Raizer, David Schiff, Barbara Grant, Sean Grimm, Rose K. Lai, Anne S. Reiner, Kathy Panageas, Sasan Karimi, Richard Curry, Gaurav Shah, Lauren E. Abrey, Lisa M. DeAngelis, and Antonio Omuro


Enrolled
(N = 52)
Not assessable for response (n = 9)
Never treated (n = 3)*
Withdrew consent post cycle 4 (n = 2)†
Toxicity (n = 4)
Completed five cycles R-MPV (n = 43), response assessment per protocol
CR
(n = 20)
PR
(n = 21)
PD
(n = 1)
SD
(n = 1)
Two additional cycles of R-MPV
(n = 21)‡
Toxicity
(n = 1)
CR
(n = 14)
PR
(n = 7)
Alive, no evidence of disease (n = 2)
Alive with disease (n = 1)
Died as result of disease (n = 6)
Assigned to reduced-dose WBRT
(n = 33)
Refused
(n = 2)
Received reduced-dose WBRT
(n = 31)
Alive, no evidence of disease
(n = 18; 58%)
Disease progression (n = 11; 35%)
Ocular relapse (n = 2)
Parenchymal relapse (n = 9)
Died as result of disease (n = 5)
Alive with disease (n = 6)
Died without progression
(n = 2; 6%)§

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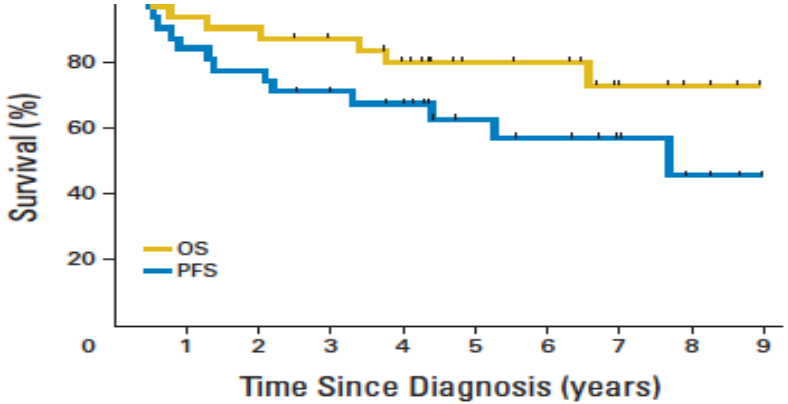

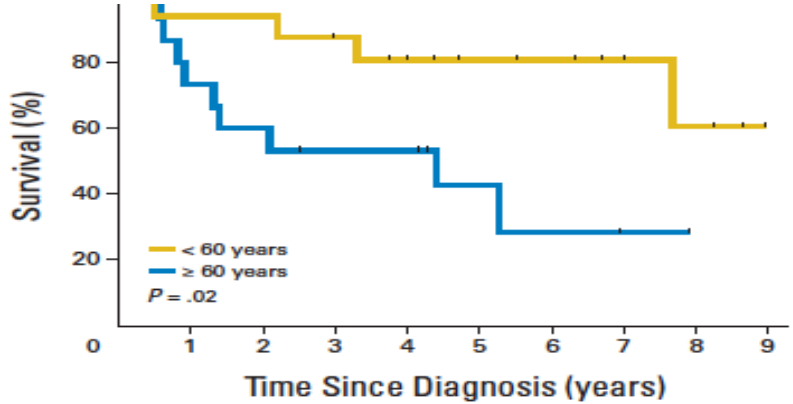

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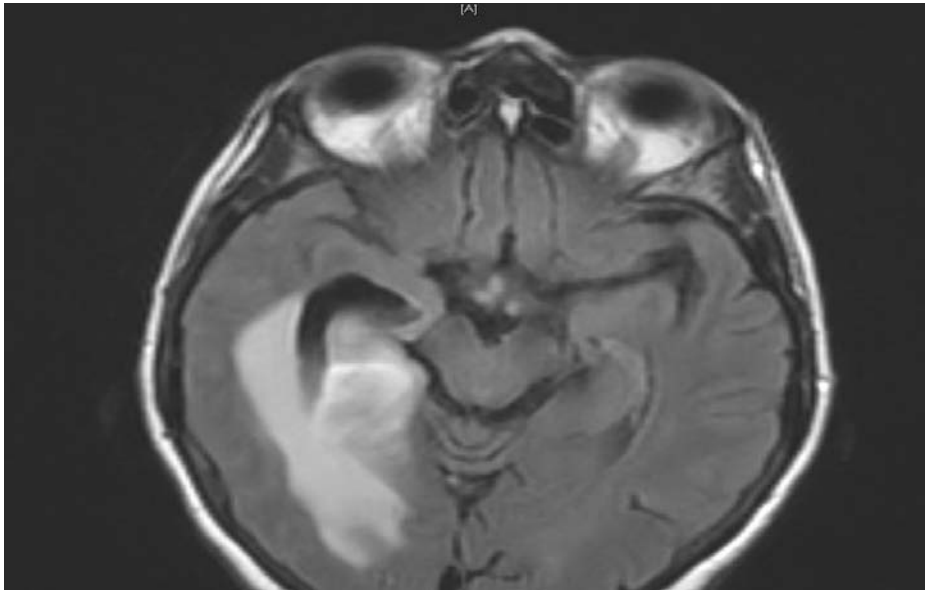
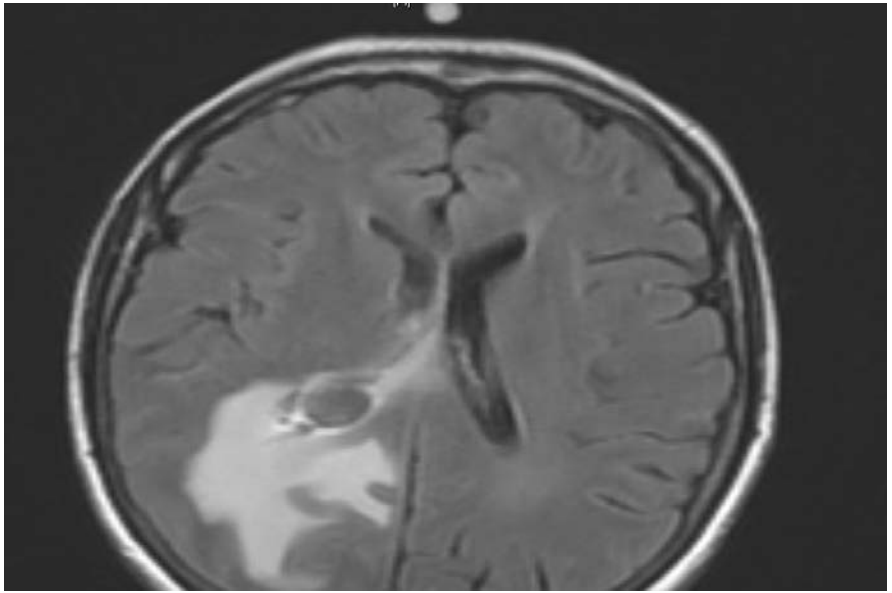
Patrick G. Morris, Denise D. Correa, Joachim Yahalom, Jeffrey J. Raizer, David Schiff, Barbara Grant, Ageas, Sasan Karimi, Richard Curry, Gaurav Shah, uro

Exploratory Neuropsychological and Imaging Correlates

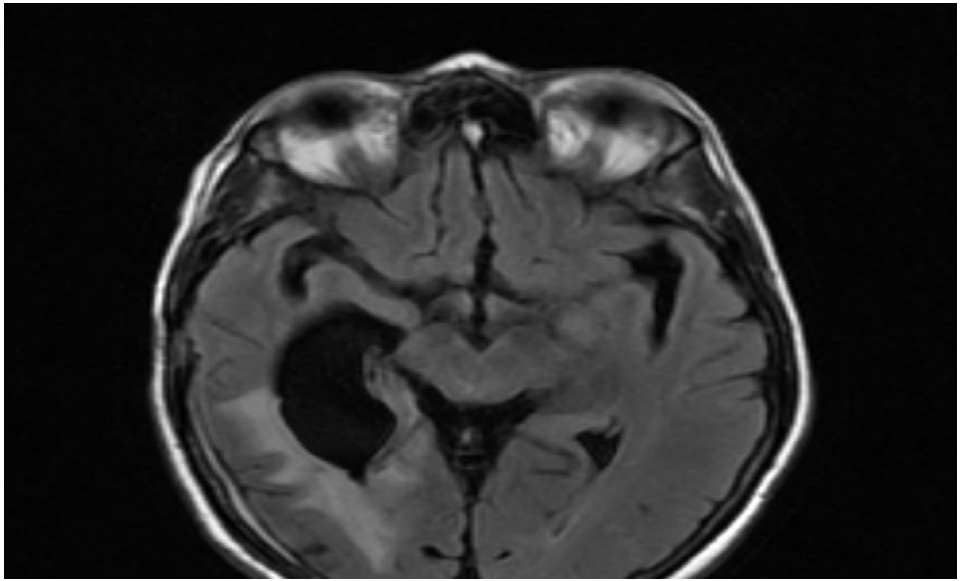
Among 31 patients who received rdWBRT, 12 patients (median age, 58 years, including three patients age ≥ 60 years) were progression-free and completed neuropsychological evaluations up to 48 months. At baseline, cognitive impairment was present in several domains. After induction chemotherapy, there was a significant improvement in executive ($P < .01$) and verbal memory ($P < .05$). There was no evidence of significant cognitive decline during the follow-up period, except for motor speed ($P < .05$). Minor fluctuations were observed on memory performance over time. There was no evidence of depressed mood, and self-reported quality of life remained stable during the follow-up period (Table 1).

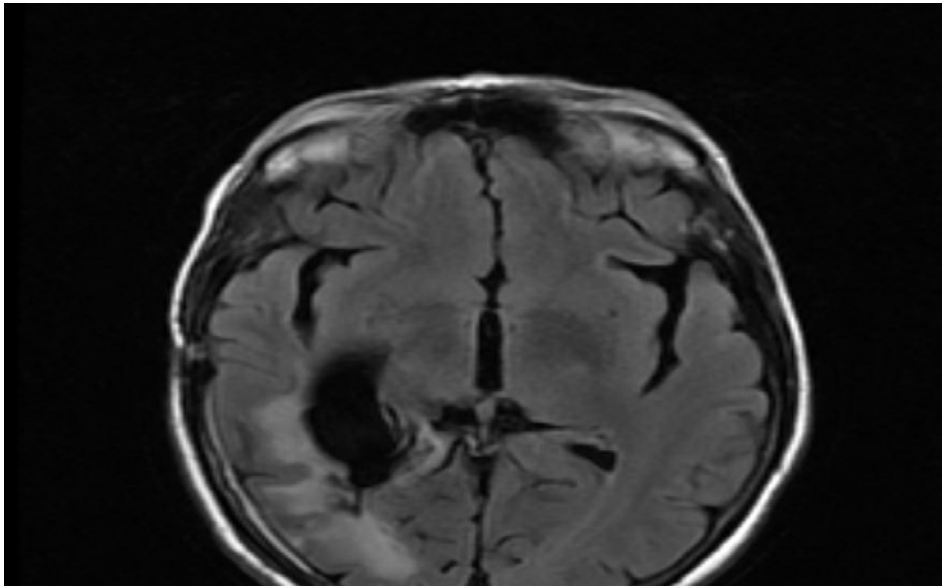
70 year old lady with severe headaches
Stereotactic biopsy- Diffuse large B-Cell Lymphoma



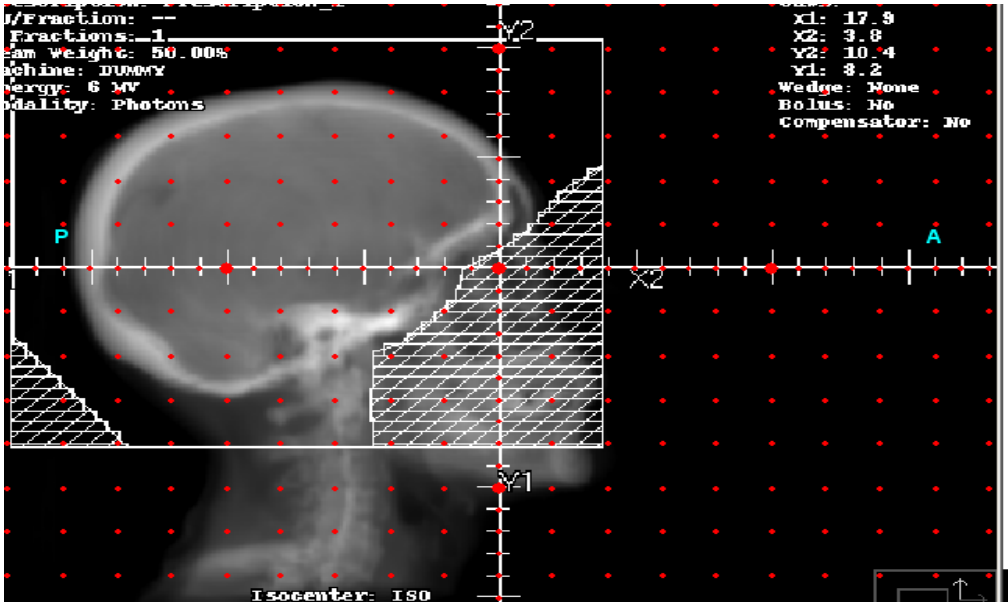


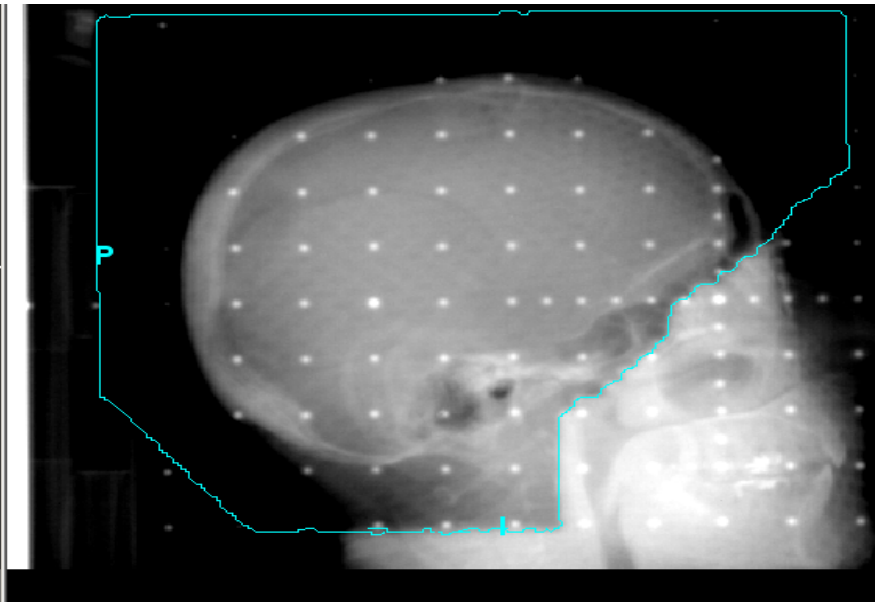
Randomized on RTOG-MSKCC protocol to receive low-dose RT after CR to R-MPV





RT Dose- 23.4 Gy (1.8 Gy X13)





Role of RT in PCNSL

- **Consolidation** after MTX-based chemo
  - Low dose after CR
  - Full dose after PR
- **Salvage** of chemotherapy alone failures (progression or relapse)
- **Palliation** of poor chemotherapy candidates

Salvage of chemotherapy alone failures **(MSKCC)**

- Progression- 24; relapse- 24 pts.
- WBRT- Median- 40 Gy (21-50 Gy)
- CR-58%; PR- 21%
- 15 pts (31%) remained in remission
- Median survival-16 months
- 54% survived >1 year
- Relapses 33 pts:
  - Brain- 22
  - Spine/lepto-8
  - Eyes- 3

Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma

Neurology® 2007;69:1178–1182

Andreas F. Hottinger, MD, PhD
Lisa M. DeAngelis, MD
Joachim Yahalom, MD
Lauren E. Abrey, MD

ABSTRACT

Background: High-dose methotrexate (MTX) and whole brain radiation therapy (WBRT) prolong survival in primary CNS lymphoma (PCNSL) patients but have been associated with delayed neurotoxicity. Consequently, patients are often treated with chemotherapy alone, and WBRT is deferred until relapse.

Methods: We performed a retrospective study to evaluate the safety and efficacy of salvage WBRT. Radiographic response, survival, and late neurotoxicity were assessed as the main endpoints.

Figure 1 Overall and progression-free survival (PFS) from start of whole brain radiation therapy

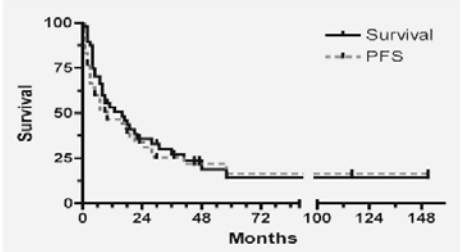
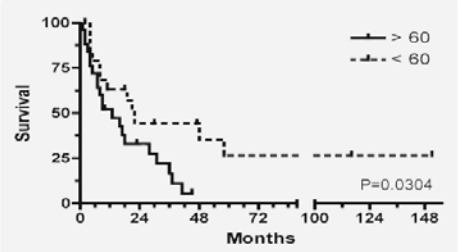


Figure 2 Survival from start of whole brain radiation therapy, separated by age group



Salvage of chemotherapy alone failures **(MGH)**

- Progression- 17; relapse- 10 pts.
- WBRT- Median- 36 Gy (28-45 Gy)
- CR-37%; PR- 37%
- Median survival- 9.7 from relapse
  - 29 mos from diagnosis
- 33% survived >1 year
- Relapses from CR- 8 pts:
  - Brain- 4
  - Systemic- 4

Results of Whole-Brain Radiation As Salvage of Methotrexate Failure for Immunocompetent Patients With Primary CNS Lymphoma

Paul L. Nguyen, Arnab Chakravarti, Dianne M. Finkelstein, Fred H. Hochberg, Tracy T. Batchelor, and Jay S. Loeffler

J Clin Oncol 23:1507-1513. © 2005

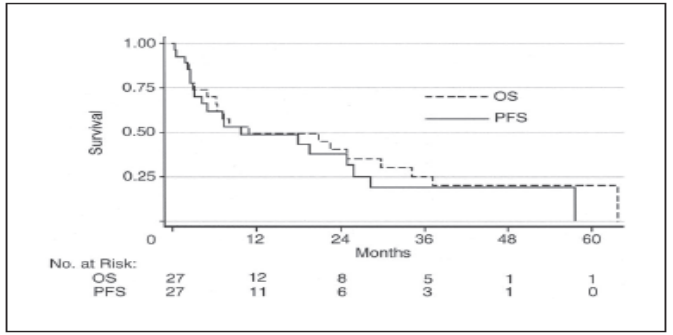


Fig 1. Overall survival (OS) and progression-free survival (PFS) from start of whole-brain radiotherapy.

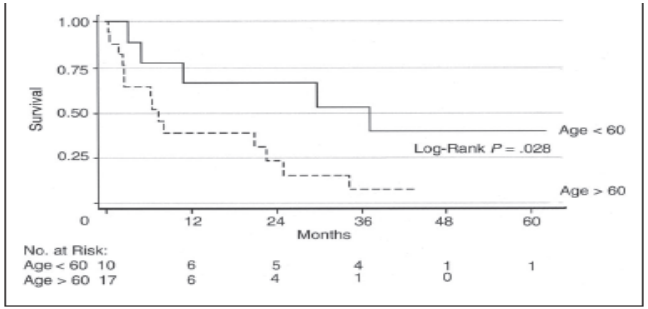


Fig 2. Survival from start of whole-brain radiotherapy, separated by age group.

RT in PCNSL: Field design

- **CTV**: Whole brain including C1 and C2 and the posterior aspect of the eyes.
- The iso-center is set anteriorly and bisects the bony canthi (to reduce divergence in possible future match to ocular field).
  - Alternatively, anterior border of PTV is set with the isocenter 5 mm behind the lens.
- If the eyes were originally involved, both eyes should be included in their entirety in WBRT field.
- The role of tumour site boost is uncertain and is not recommended by most experts
- It is not standard to irradiate the whole cranio-spinal axis

Is Whole-Brain Irradiation Necessary for Primary Central Nervous System Lymphoma?

Patterns of Recurrence after Partial-Brain Irradiation

Yuta Shibamoto, M.D.[1]
Naofumi Hayabuchi, M.D.[2]
Jun-ichi Hiratsuka, M.D.[3]
Sunao Tokumaru, M.D.[4]
Hiroki Shirato, M.D.[5]
Mitsuharu Sougawa, M.D.[6]
Natsuo Oya, M.D.[7]
Yuji Uematsu, M.D.[8]
Masahiro Hiraoka, M.D.[7]

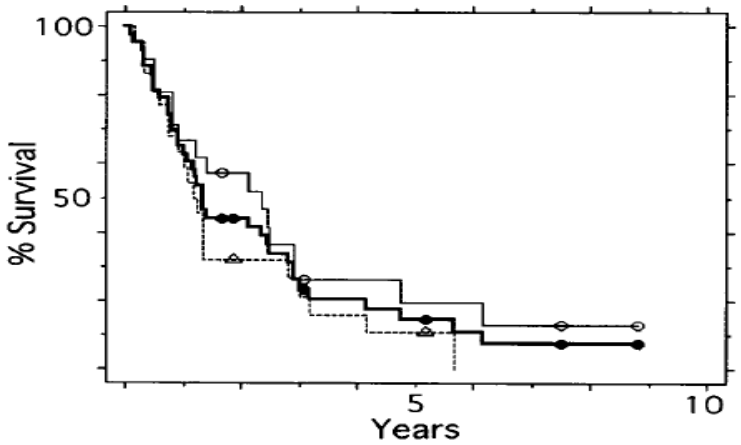


FIGURE 4. Overall survival curves for all 43 patients (—●—), for 21 patients treated with safety margins of ≥ 4 cm (—○—), and for 22 patients treated with safety margins of < 4 cm margins (--△--).

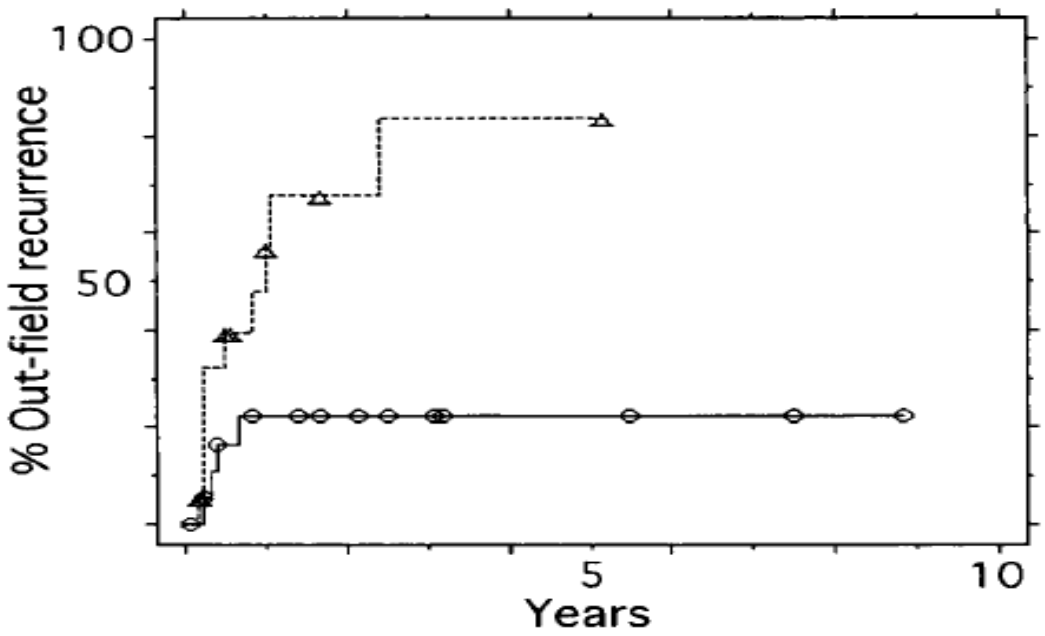
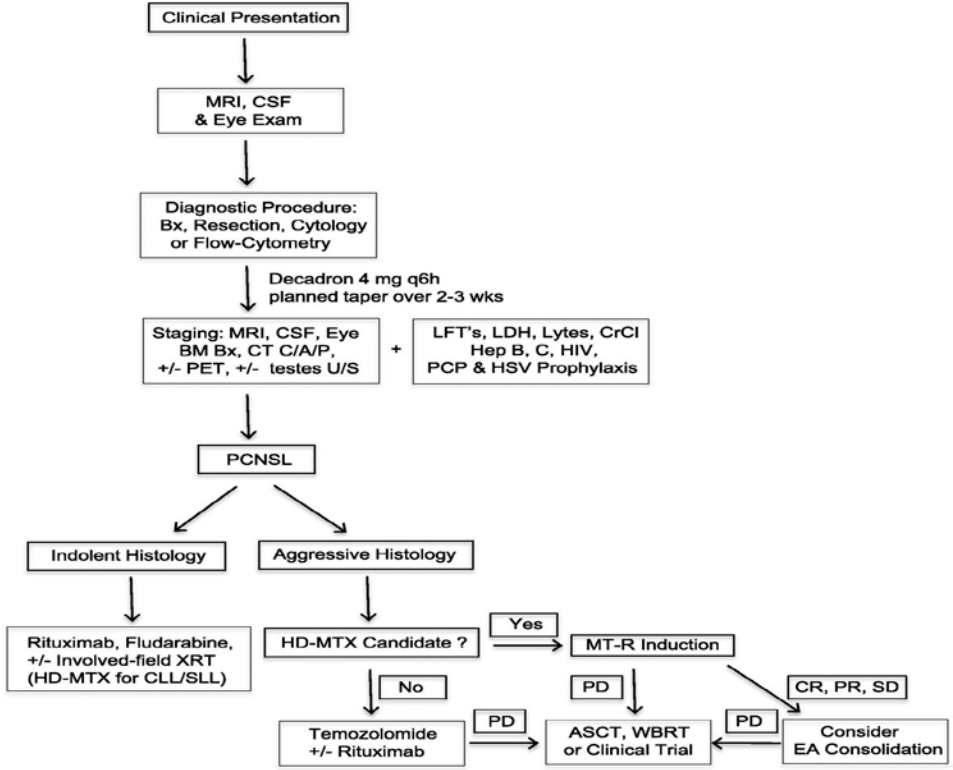


FIGURE 3. Cumulative incidence of out-field recurrences according to the safety margins of the radiation field. —○—: margins ≥ 4-cm; --△--: margins of < 4-cm.

RT in PCNSL: Dose

- Consolidation dose after MRI-CR to chemotherapy: 23.4 Gy in 1.8 Dose per fraction. (13 treatments)
- WBRT after incomplete response to chemotherapy: 36 Gy to 45 Gy (1.5 to 1.8 Gy/fraction)
- WBRT for salvage of chemotherapy failure (progression or relapse) 36 – 40 Gy (1.5 Gy-1.8 Gy/fraction)
- WBRT as primary treatment for non-candidates for chemotherapy: 40-50 Gy
- Whole orbit (if included)- only up to 36 Gy
- For palliation: WBRT dose is 30-36 Gy in 10 or 15 fractions.

How I treat PCNSL. In the diagnostic work-up, an MRI of the spine (± gadolinium) may be useful if warranted by neurologic symptoms or if CSF analysis is contraindicated.



James L. Rubenstein et al. Blood 2013;122:2318-2330

RT in PCNSL – Take home

- WBRT an effective tool in many stages of treatment
- Best use of RET is as low dose (24 Gy) after CR to MTX
- Full dose RT after MTX is toxic in age >60 years
- Chemotherapy alone in “full” MTX doses or with ASCT transplant is also toxic, but is often considered
- Patients respond (yet, temporarily) to salvage with RT alone or with chemotherapy

ESTRO School

WWW.ESTRO.ORG/SCHOOL

RT for relapsed indolent lymphomas

Joachim Yahalom, M.D.
Memorial Sloan-Kettering Cancer Center
New York, NY, U.S.A.

Memorial Sloan Kettering Cancer Center

ILROG INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

ESTRO School

General Treatment Options

- **Systemic**
  - REPEAT RITUXIMAB
  - ANOTHR CHEMOTHEAPY COMIBNATION
  - EXPERIMENTAL AGENTS
  - HIGH-DOSE WITH AUTOLOGOUS OR ALLOGENEIC TRANSPLANT
- **Observation**
- **Palliation and/or local control with RT**

Field Design Concept

- Involved site concept
- Limited to palliation need or local control concerns
- Dose and field considerations
- Toxicity to normal organs (including bone marrow reserve)

RT Dose for Palliation

- These are highly radio-responsive lymphomas
- Lower doses are effective
- Range of 4 Gy to 36 Gy (24 Gy commonly used)

Radiotherapy and Oncology 100 (2011) 86–92

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

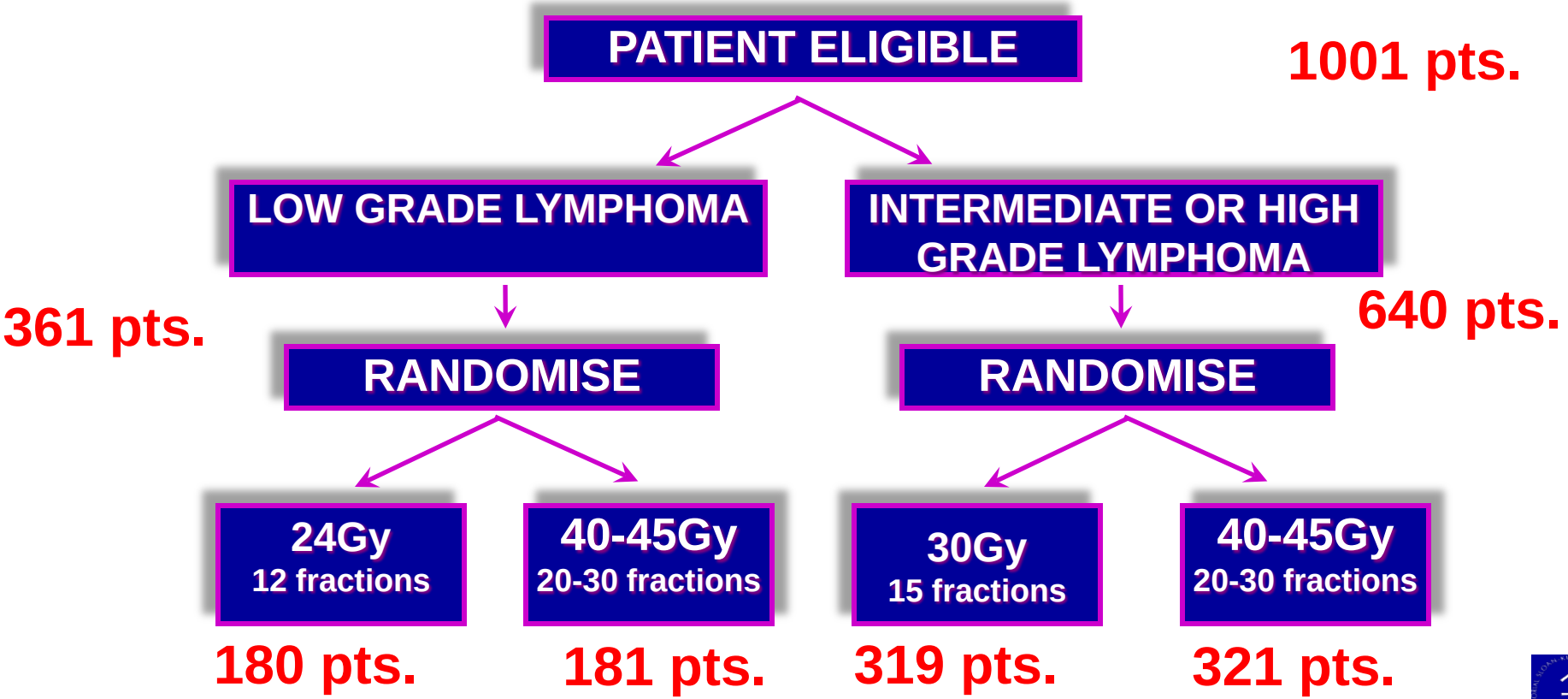
Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

Lisa Lowry [a], Paul Smith [a], Wendi Qian [b], Stephen Falk [c], Kim Benstead [d], Tim Illidge [e], David Linch [f], Martin Robinson [g], Andrew Jack [h], Peter Hoskin [i,*]

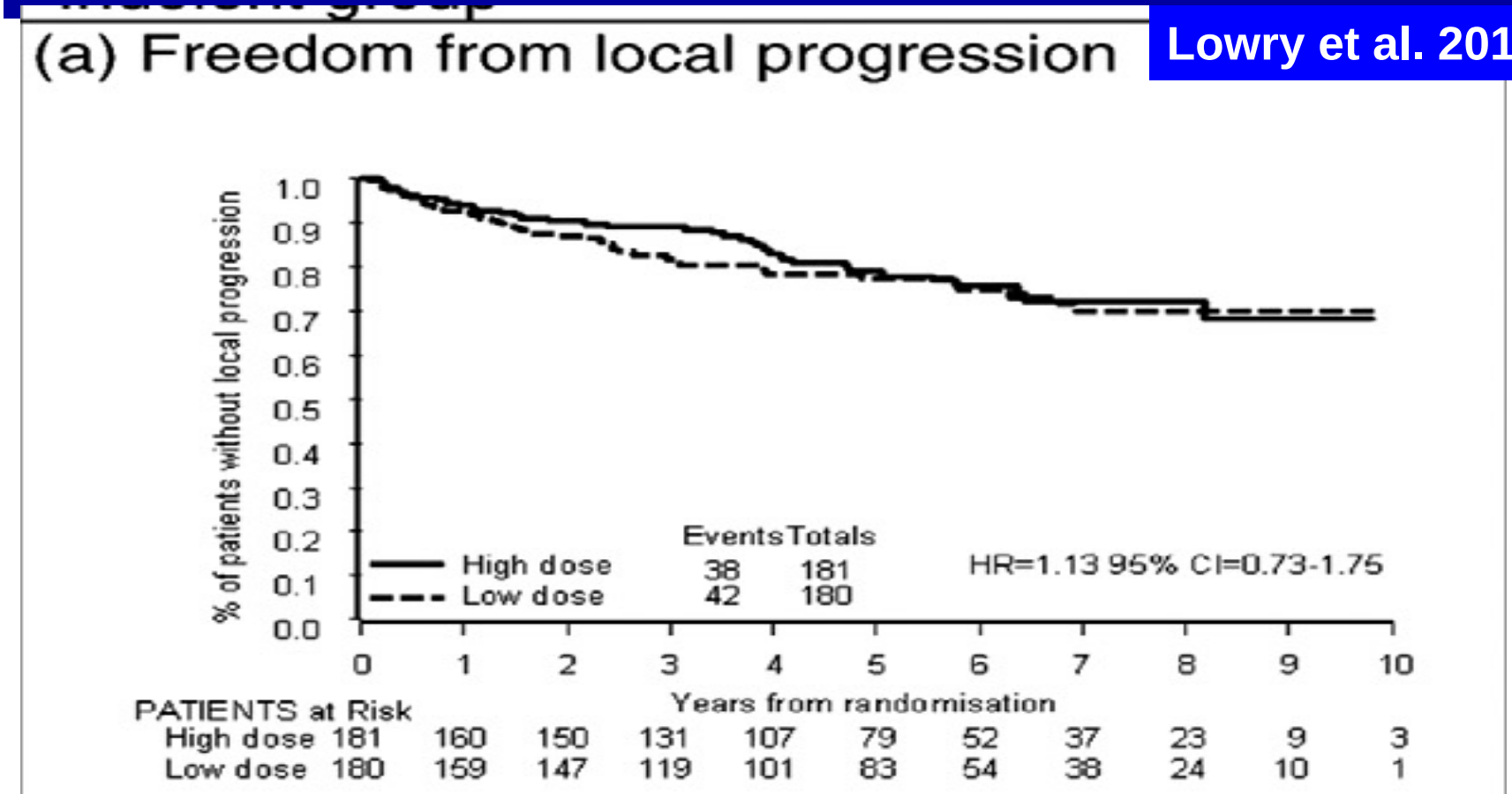
Lowry et al. 2011

STUDY DESIGN



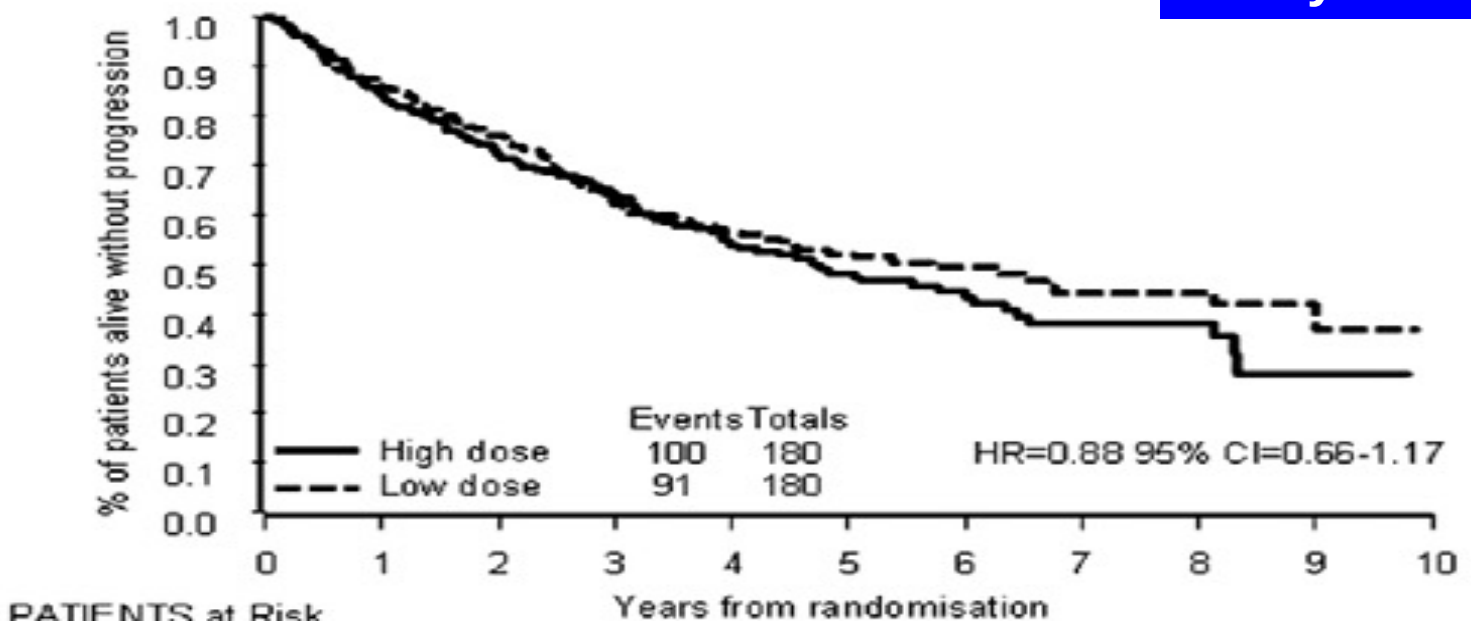
INDOLENT LYMPHOMAS: Local Control

Lowry et al. 2011



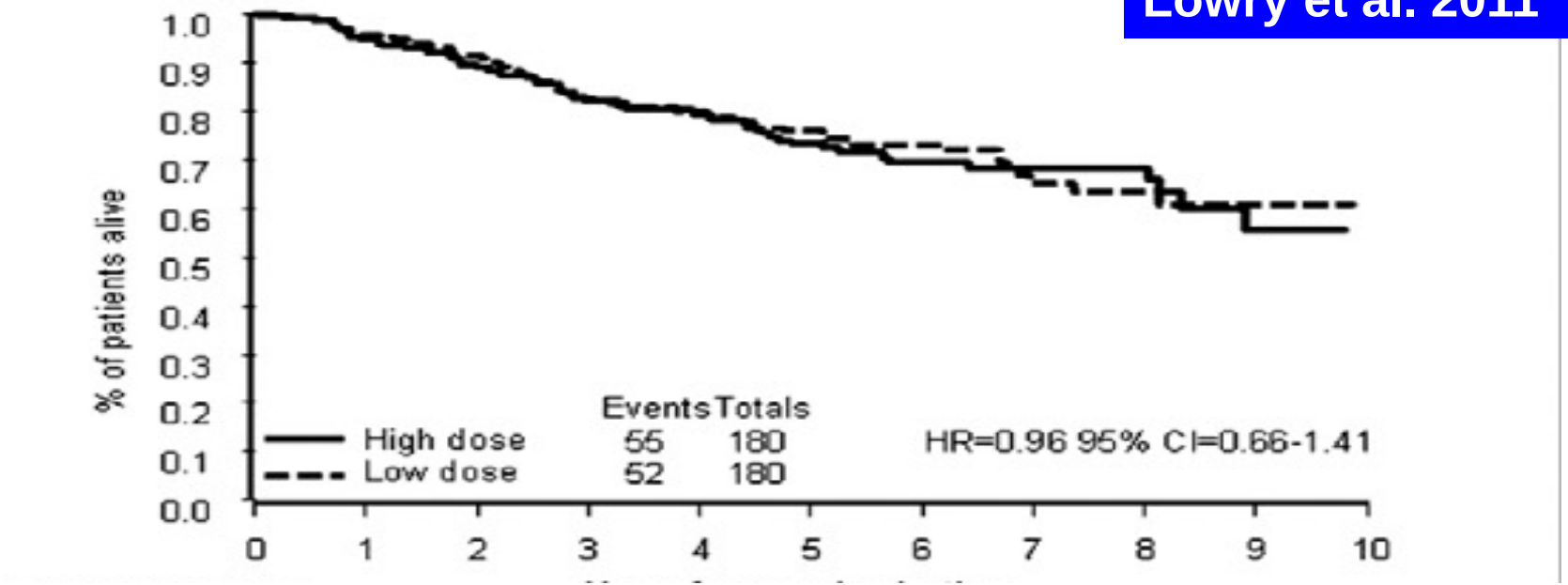
INDOLENT LYMPHOMAS: PFS

Lowry et al. 2011



INDOLENT LYMPHOMAS: Overall Survival

Lowry et al. 2011



BOOM BOOM

Basis for “Boom-Boom” Palliation

- **Institute Gustave Roussy (IGR) patient refused additional palliative WAI after receiving 4 Gy.**

- **At follow-up found to be in CR.**

“Boom-Boom” Palliation of Recurrent/Refractory NHL

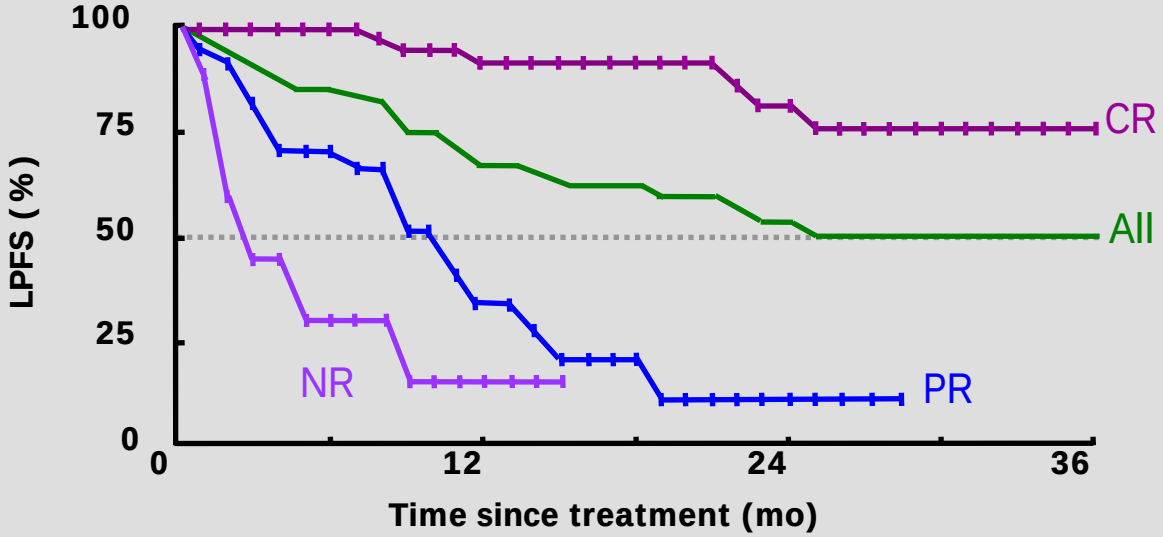
Study	N (pts)	N (sites)	PR	CR	Overall RR	Response duration	Comment
Ganem 1994	27	N/A	52%	37%	89%	Range: 4 – 35 mo	
Sawyer 1997	11	16	38%	56%	94%	Median: 7 mo	
Girinsky 2001	48	135	24%	57%	81%	2 yr actuarial: 56%	
Johannsson 2002	22	31	22%	65%	87%	Median: 22 mo	Prospective Phase II
Haas 2003	109	304	31%	61%	92%	Median: 25 mo	Prospective Phase II
Haas 2005†	71	177	39%	48%	87%	Median: 22 mo	Prospective Phase II
Summary			**34%**	**54%**	**88%**	**Median: 19 mo**	

†Includes 30 patients (42%) with aggressive NHL.

High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

Journal of Clinical Oncology, Vol 21, No 13 (July 1), 2003: pp 2474-2480

By R.L.M. Haas, Ph. Poortmans, D. de Jong, B.M.P. Aleman, L.G.H. Dewit, M. Verheij, A.A.M. Hart, M.H.J. van Oers, M. van der Hulst, J.W. Baars, and H. Bartelink



Prognostic Factors for Response to “Boom-Boom”

Haas 2003 - RR

Factor	p
CR	Not-tested
Size < 5cm	NS
# prior CTx regimens	NS
Age	NS
Sex	NS
Grade	NS
# positive sites	NS

- **Grinsky 2001 - FFLP**

Factor	p
CR	< 0.001
Size < 5cm	0.041
< 2 prior CTx regimens	< 0.001
Age ≤ 65 yrs	0.07
Histology	NS
Time from diagnosis	NS

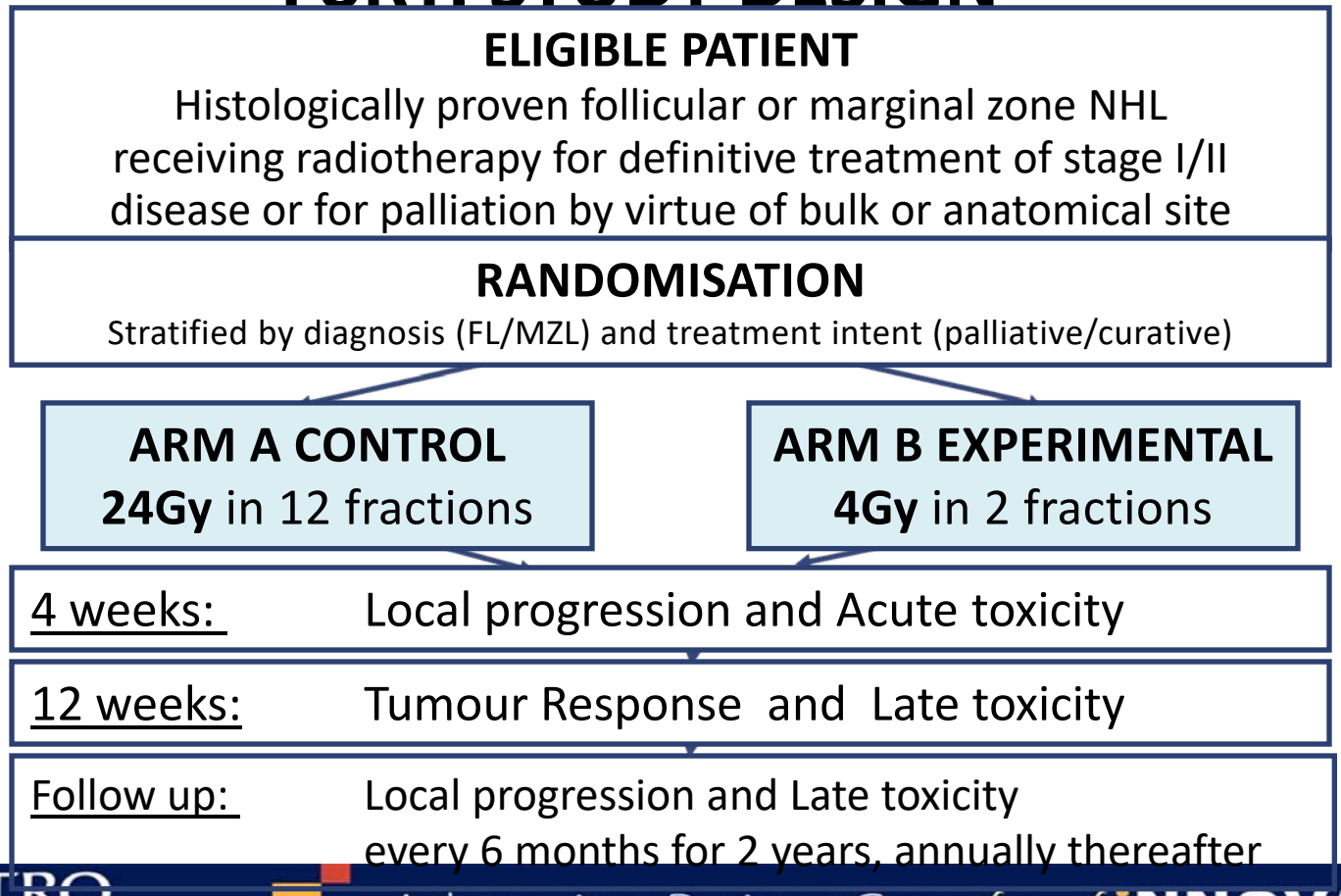
Advantages of “Boom-Boom”

- Short treatment duration.
- Minimal morbidity. No myelosuppression.
- High response rate similar to that obtained with primary therapy.
- Effective and simple re-treatment
- Rapid response onset.
- Significant LPFS interval.

FoRT: A phase III multi-centre randomised controlled trial of low dose radiotherapy for follicular and marginal zone lymphoma

Hoskin P, Kirkwood A, Popova B, Brammer C, Diez P, Gallop-Evans E, Jack A, Madhavan K, Robinson M, Syndikus I, Smith P

FoRT: STUDY DESIGN



FoRT: ENTRY CRITERIA

Patient inclusion criteria

- Patients aged over 18 with no upper age limit
- Histologically proven **follicular lymphoma** or **marginal zone lymphoma**
- Biopsy material available for histological review
- Radiation indicated for definitive treatment of stage IA or IIA disease or for palliation by virtue of tumour bulk or anatomical position
- Written informed consent

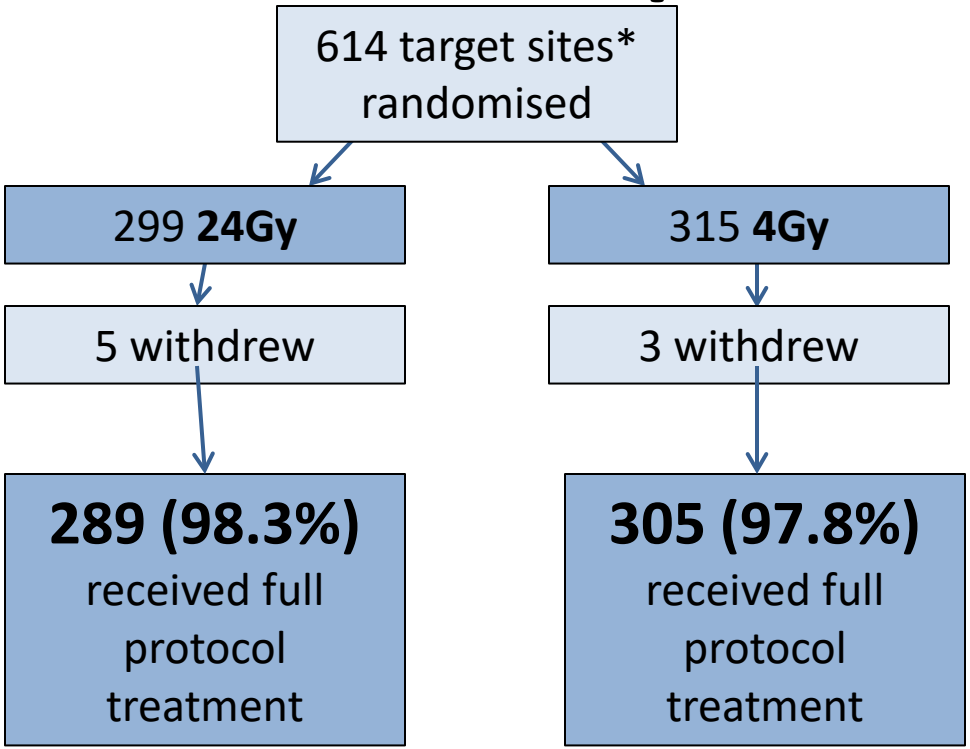
Patient exclusion criteria

- Histological subtypes other than **follicular lymphoma** or **marginal zone lymphoma**
- Predicted prognosis less than 3 months

Statistical considerations

- **Primary Endpoint**
  - Local progression free interval
    (*progression within the radiation field)*
- **Secondary Endpoints**
  - Acute toxicity
  - Late toxicity
  - RECIST response
  - Overall survival
  - Quality of life

Treatment Compliance



* 548 unique patients.

Response to radiotherapy[1]

Response	24Gy N(%)	4Gy N(%)
CR	175 (60.3)	137 (44.3)
PR	60 (20.7)	92 (29.8)
SD	22 (7.6)	44 (14.2)
No progression[2]	20 (6.9)	22 (7.1)
PD	2 (0.7)	9 (2.9)
Missing	11(3.8)	4 (1.3)

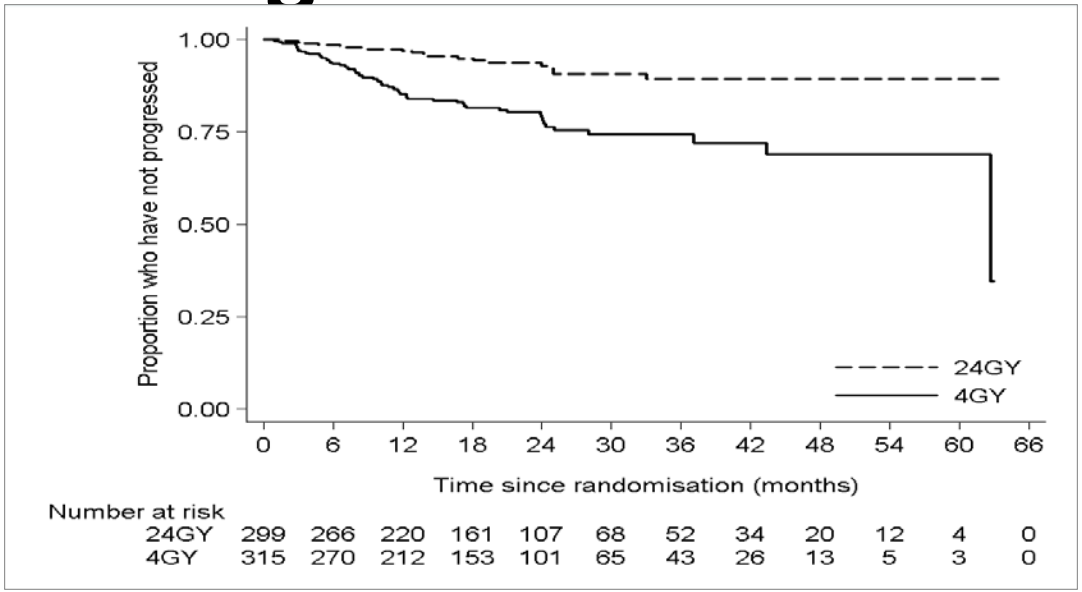
p=0.006

(Chi squared test, response (CR+ PR) vs. No response)

[1] Patients who started treatment only.

[2] No measurable disease at baseline.

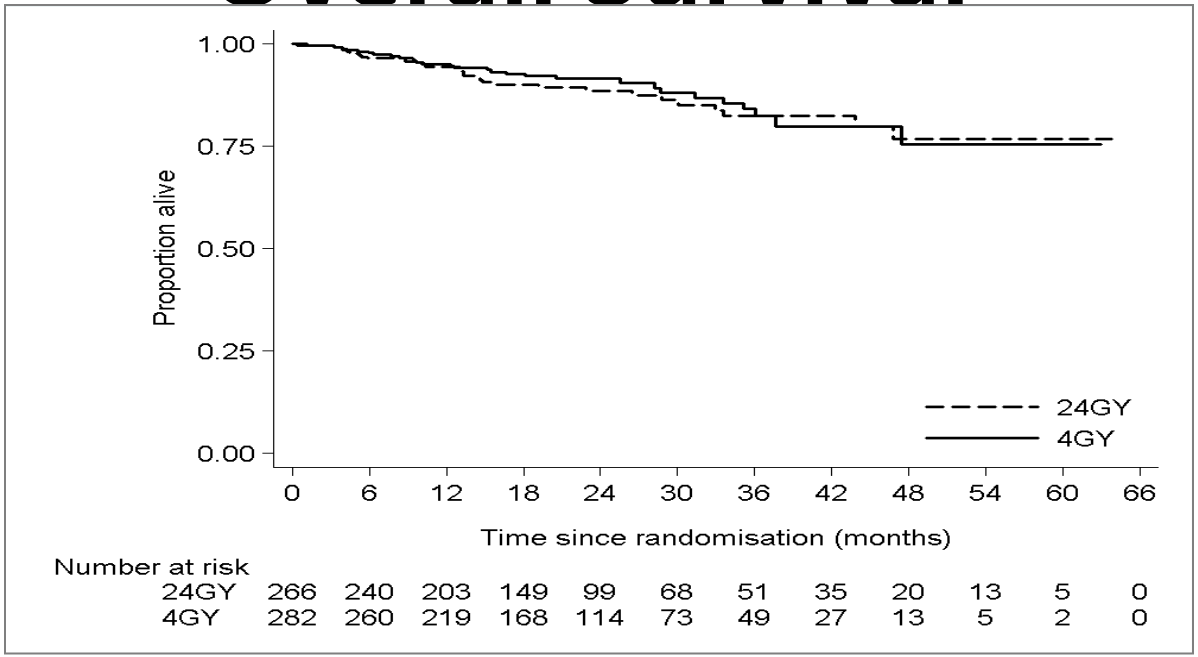
Local Progression Free Interval



Hazard Ratio: 3.49 (95% CI: 2.06 - 5.90), p<0.001

2 Year local progression free rate: 93.7% (24Gy) and 80.4% (4Gy)

Overall Survival



Hazard ratio (each patient counted once): 0.88 (95% CI: 0.53 - 1.46), p=0.61

Median Follow-up time: 22.8 months (0.39 -63.80)

Summary and conclusion

- 4Gy in 2 fractions was inferior to 24Gy in 12 fractions in achieving a durable local progression free interval in follicular and marginal zone NHL.
- 24Gy in 12 fractions should remain the standard schedule for indolent lymphoma.
- 4Gy in 2 fractions is effective (CR rate: 44.3%, PR rate: 29.8%) and may be considered for palliative treatment or retreatment.

Whom to Boom-Boom?

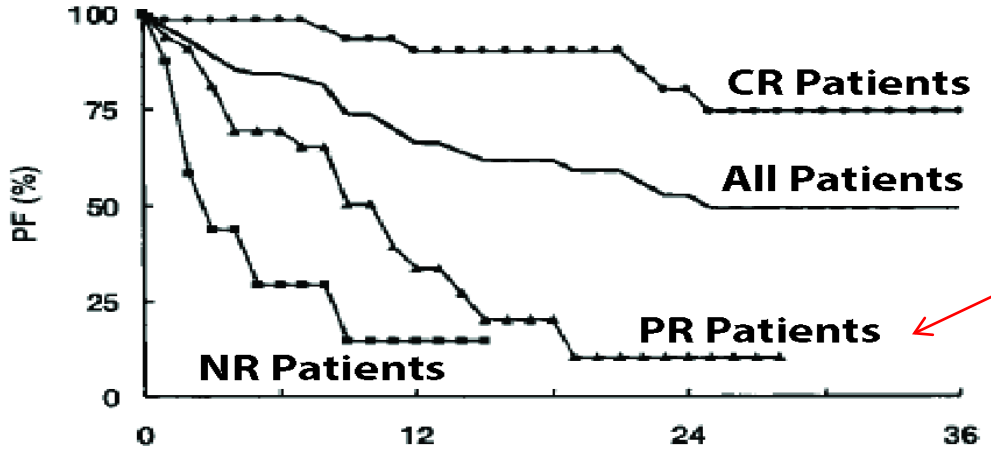
- **Follicular**
- **Mantle-cell**
- **CLL/SLL**
- **Marginal zone**

- **Relapsed, refractory to systemic therapy**
- **Not used as an alternative adequate first-line**

Response to very low dose RT is variable

Our key questions:

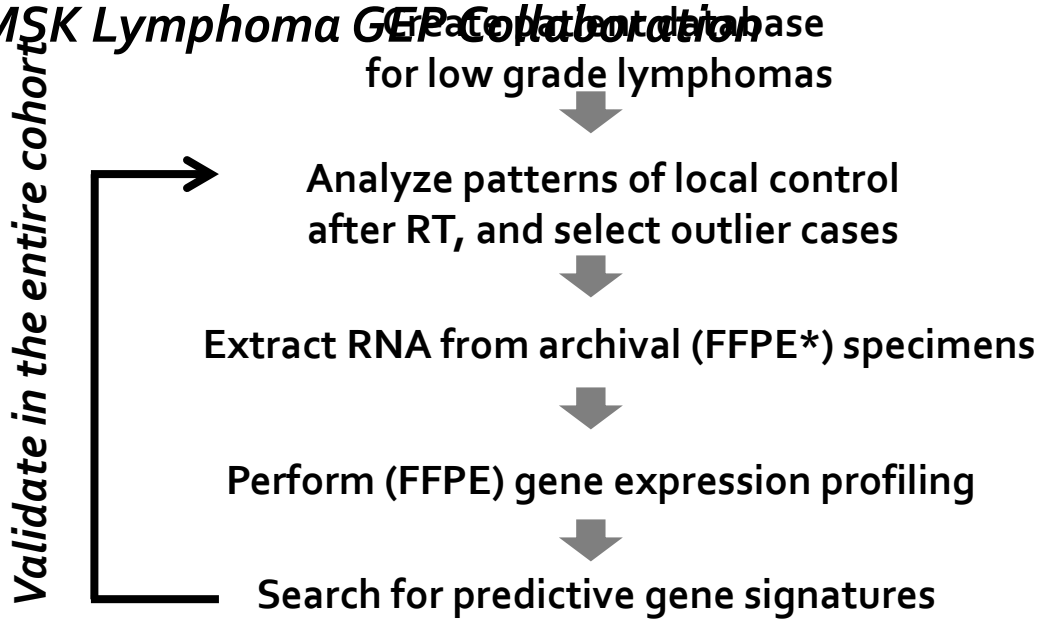
1. **Are there molecular biomarkers that can predict these differences?**
2. **What about gene expression profiles?**



Can we identify these patients up-front?

Materials and Methods: Our Approach

The Yale/MSK Lymphoma GEP Collaboration



*FFPE=Formalin-fixed, paraffin-embedded tissue

Database creation: Low grade lymphomas treated with 2 Gy x 2

- **90 sites in 68 patients**
- **2006-2012**
- **Initial responses assessed by imaging or PE**
  - CR
  - PR
  - NR
- **Local progression free survival**
  - estimated with K-M method
  - compared between response groups via log-rank

Median Age	68
Stage at treatment	
I	11
II	2
III	6
IV	31
Relapsed	40
Histology	
Follicular	62
Marginal Zone	14
Mantle Cell	6
SLL	6
MALT	1
Primary B Cell Cutaneous	1

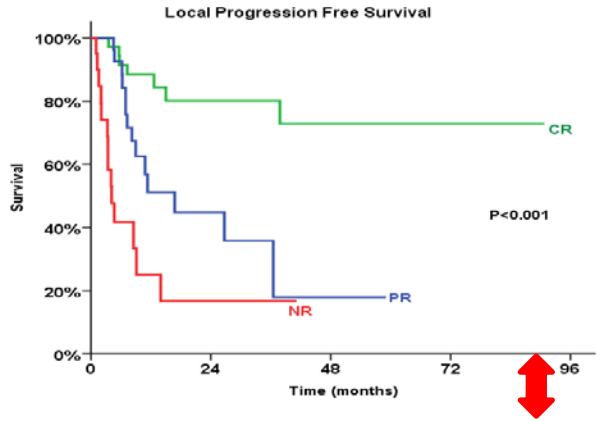
Initial response predicts local progression free survival

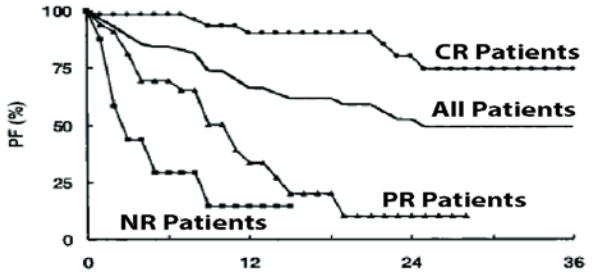
	All	CR	PR	NR
# Patients	67	34	22	21
# Sites	90	37	30	23
Median Follow up (mos)	20.1	30.4	14.6	11.1
Median Time to local progression (mos)	8.6	16.0	8.5	3.4
3 year LPFS	52.0%	80.1%	35.8%	16.7%

High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

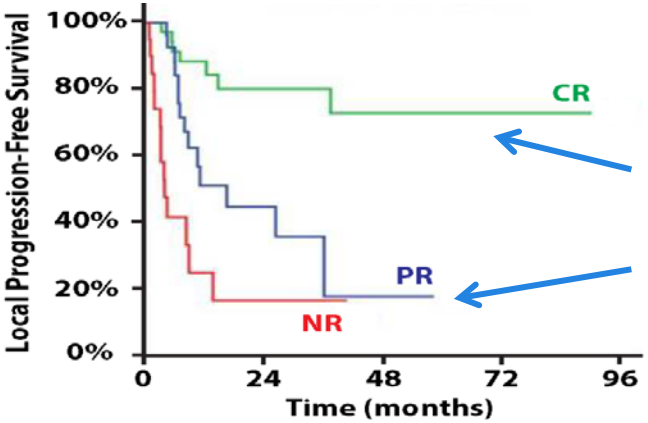
By R.L.M. Haas, Ph. Poortmans, D. de Jong, B.M.P. Aleman, L.G.H. Dewit, M. Verheij, A.A.M. Hart, M.H.J. van Oers, M. van der Hulst, J.W. Baars, and H. Bartelink

Journal of Clinical Oncology, Vol 21, No 13 (July 1), 2003: pp 2474-2480





Selection of outlier cases

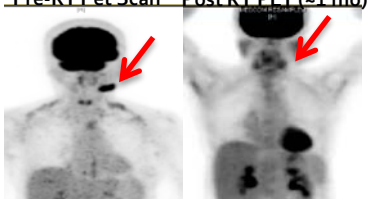


6 CR cases

6 NR/PR cases

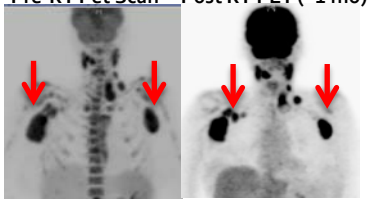
Complete Response

Pre-RT Pet Scan | Post RT PET (~1 mo)



Partial/No Response

Pre-RT Pet Scan | Post RT PET (~1 mo)



Patient Sample Summary by Type + Response

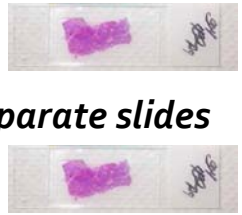
12 FFPE Samples

9 Follicular Lymphoma	
CR	S03 (7/15/13)
	S05 (7/15/13)
	S11-46296 1U1
	S13-62359
PR/NR	S06 (7/15/13)
	S08 (7/15/13)
	S08-1966 1U2
	S14-27031
	S14-62451

1 Low Grade BCL NOS	
CR	S12-16638

2 Marginal Zone	
CR	S01-41072
PR/NR	S12-52214 1U3

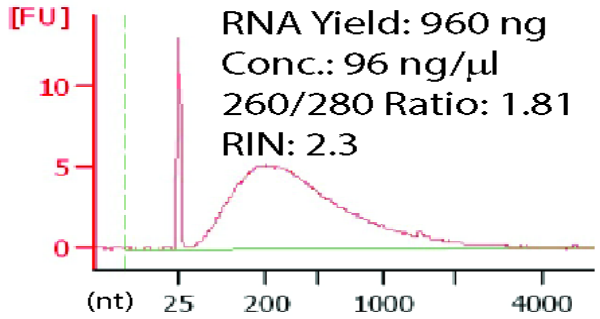
Whole transcriptome profiling with FFPE extracted RNA samples



2 separate slides

→ *Extract RNA* →

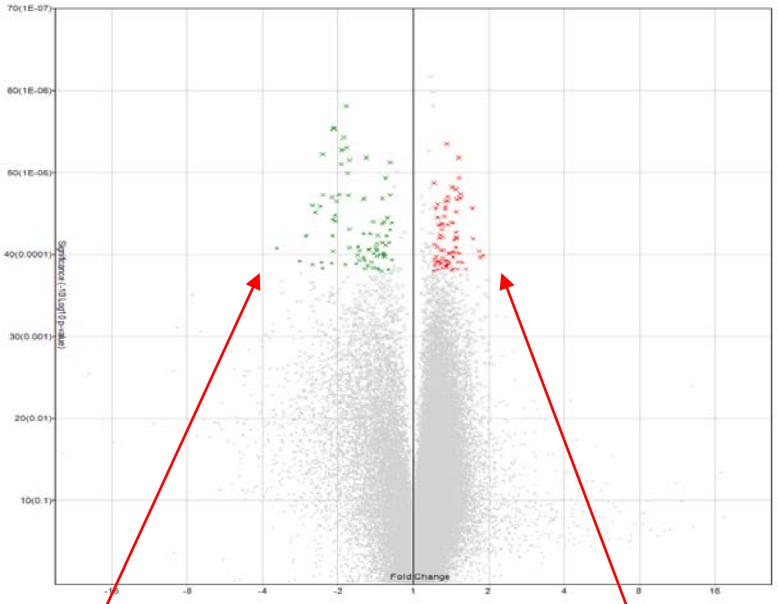
AFFYMETRIX®



RNA Yield: 960 ng
Conc.: 96 ng/µl
260/280 Ratio: 1.81
RIN: 2.3

Whole transcriptome profiling with FFPE extracted RNA samples

160 differentially expressed regions with FC > 1.2 and FDR < 0.055



Decreased in CR

Increased in CR

Increased expression in CR vs. PR/NR

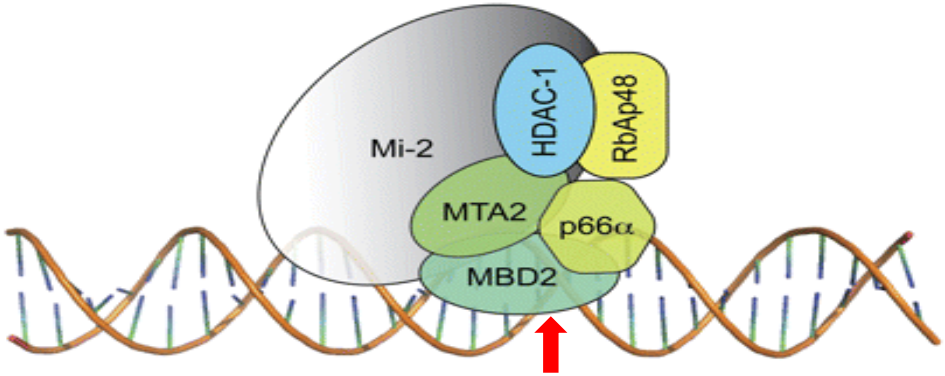
Gene	CR Avg Exp.	NR Avg. Exp	Fold Change	Gene Description
MIR517B	4.94	4.15	1.73	microRNA 517b
MGC13053	5.89	5.19	1.62	uncharacterized MGC13053
OR10J1	4.92	4.32	1.52	olfactory receptor, family 10, subfamily J, member 1
C17orf112	5.06	4.48	1.49	chromosome 17 open reading frame 112
PART1	5.99	5.42	1.48	prostate androgen-regulated transcript 1 (non-protein coding)
SNORD114-20	4.71	4.18	1.44	small nucleolar RNA, C/D box 114-20
TRDV1	6.23	5.71	1.44	T cell receptor delta variable 1
VHLL	5.44	4.96	1.39	von Hippel-Lindau tumor suppressor-like
RERG-AS1	5.46	5	1.37	RERG antisense RNA 1
NRXN1	5.51	5.07	1.36	neurexin 1
ZNF727	6.45	6.01	1.35	zinc finger protein 727
EFCAB1	5.54	5.12	1.34	EF-hand calcium binding domain 1
KLRD1	6	5.63	1.3	killer cell lectin-like receptor subfamily D, member 1
SORBS1	6.05	5.68	1.29	sorbin and SH3 domain containing 1
TRBV6-1	4.83	4.46	1.29	T cell receptor beta variable 6-1
ANGPTL7	6.34	5.99	1.28	angiopoietin-like 7
PCDH20	5.52	5.2	1.25	protocadherin 20
GABRA2	5.52	5.2	1.25	gamma-aminobutyric acid (GABA) A receptor, alpha 2

Decreased expression in CR vs. PR/NR

Gene	CR Avg Exp.	NR Avg. Exp	Fold Change	Gene Description
MBD2	8.95	10.76	-3.51	methyl-CpG binding domain protein 2
RBM6	7.7	9.2	-2.82	RNA binding motif protein 6
SYVN1	9.05	10.47	-2.68	synovial apoptosis inhibitor 1, synoviolin
SRGAP2B	7.87	9.22	-2.54	SLIT-ROBO Rho GTPase activating protein 2B (pseudogene)
EIF3C	8.7	10.03	-2.53	eukaryotic translation initiation factor 3, subunit C
ANKRD36	8.69	9.91	-2.33	ankyrin repeat domain 36; ankyrin repeat domain 36C
DNAJC10	7.48	8.69	-2.31	DnaJ (Hsp40) homolog, subfamily C, member 10
EIF3CL	8.66	9.86	-2.3	eukaryotic translation initiation factor 3, subunit C
ST6GAL1	7.5	8.58	-2.11	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1
LOC100996862	9.23	10.3	-2.1	ankyrin repeat domain-containing protein 36A-like
PSMC4	6.91	7.98	-2.1	proteasome (prosome, macropain) 26S subunit, ATPase, 4
SDHAP1	7.69	8.75	-2.09	succinate dehydrogenase complex, subunit A,
EAF2	6.7	7.73	-2.05	ELL associated factor 2
SEL1L3	8.85	9.88	-2.05	sel-1 suppressor of lin-12-like 3 (C. elegans)
NARS	7.61	8.56	-1.94	asparaginyl-tRNA synthetase
POU2AF1	7.72	8.67	-1.93	POU class 2 associating factor 1
HERC2P9	7.92	8.82	-1.87	hect domain and RLD 2 pseudogene 9
HERC2P2	8.14	9.01	-1.83	hect domain and RLD 2 pseudogene 2

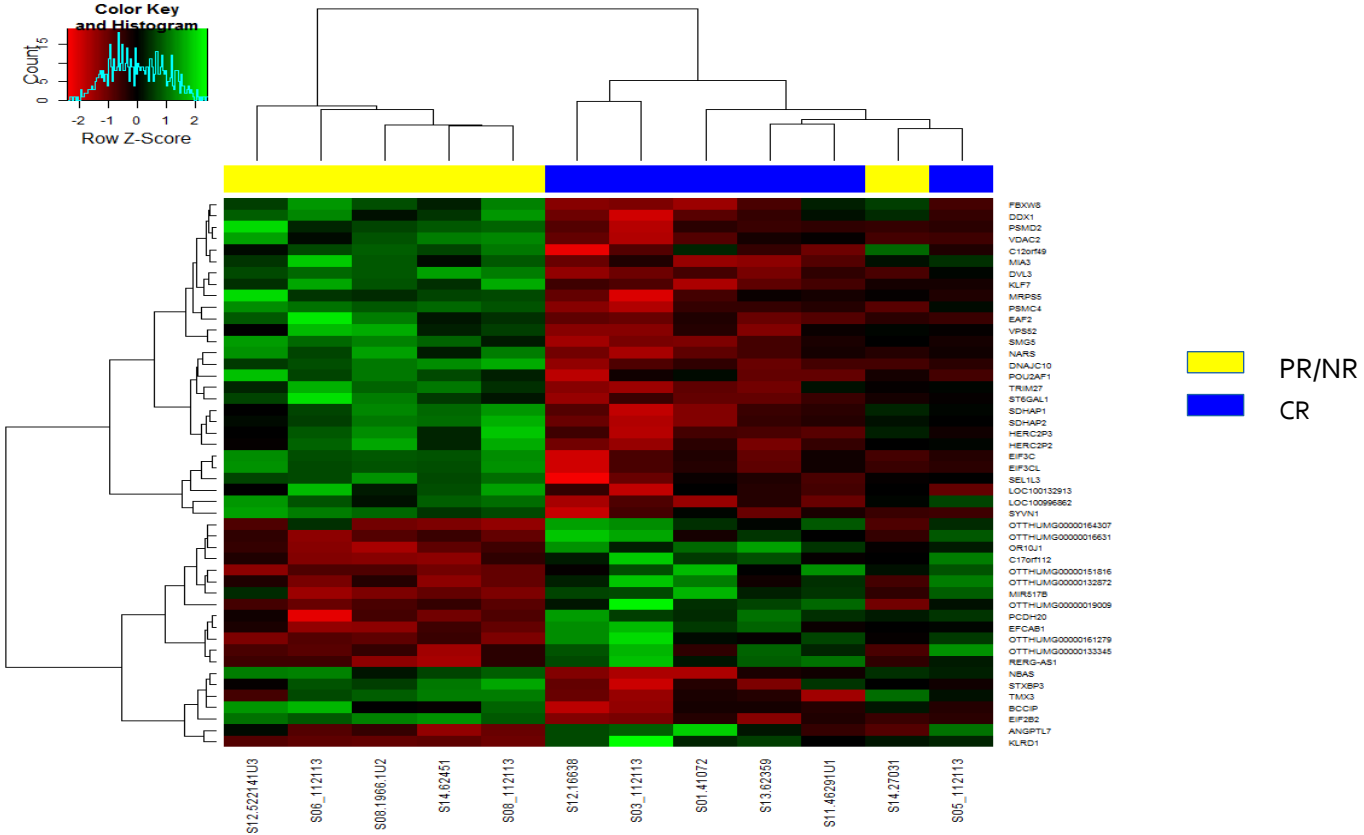
Associated with chromatin modification in cancers

Are the genes relevant to radiosensitivity?



4-fold reduction in MBD2 mRNA in CR patients

CR vs. PR/NR Gene Pathways



Conclusions

- **Very low dose RT for low grade lymphomas**
  - –Initial response predicts local progression free survival
- **Preliminary microarray profiling studies**
  - –Using FFPE specimens is feasible
  - –Initial studies showed statistically significant changes in relative gene expression between CR and NR groups

Future Directions

1. Expand and validate gene expression signatures in entire low grade lymphoma cohort
2. Translate signatures back to laboratory for functional studies
3. Expand collaboration to other centers/institutes
4. Adapt the proposed workflow to other lymphoma subtypes

Thank you!

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TBI and local RT in the conditioning regimen of BMT of Leukemia

Joachim Yahalom, M.D.
Memorial Sloan Kettering Cancer Center
New York ,NY, USA

Memorial Sloan Kettering Cancer Center

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Radiation therapy for leukemia

- Cranial irradiation for CNS disease in ALL
  - To prevent relapse in brain (12-18 Gy/6-12 fractions)
  - To treat disease in brain (18-24 Gy/10-16 fractions, with or without 6-12 Gy/3-8 fractions to spine)
- Testicular irradiation for disease in testes in ALL
  - 24-26 Gy/12-18 fractions
- Splenic irradiation in chronic leukemias
  - 1-10 Gy/10-100 fractions
- Total body irradiation as part of hematopoetic stem cell transplant (for any leukemia, and other diseases)
  - With or without any of the above

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Cranial irradiation for CNS leukemia

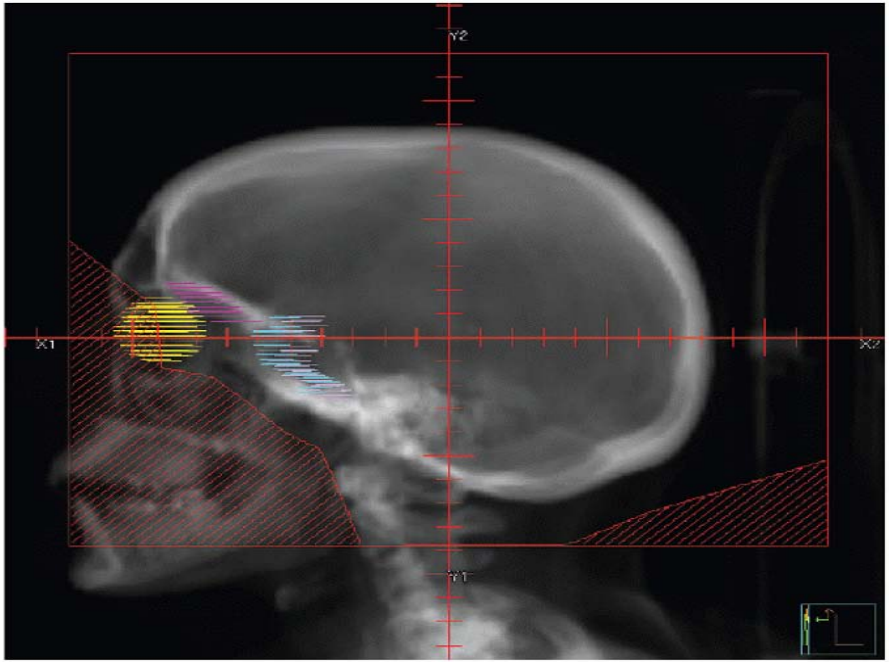

Figure 2.5 Lateral field for cranial irradiation in ALL. Note margin below cribriform plate (pink) and middle cranial fossa (blue). Targeted volume includes posterior eye (yellow) and orbit.

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Hematopoietic stem cell transplant (HSCT)

- HSCT: The transfer of hematopoietic stem cells (HSCs) between a donor and a recipient
  - HSCs are often referred to as “graft”
  - Successful transfer of HSCs requires “conditioning” recipient, otherwise rejection will occur
    - Myeloablative: capable of completely eliminating recipient blood system (lethal)
    - Non-myeloablative: not capable of completely eliminating recipient blood system (non-lethal)

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Types of HSCT

- Allogeneic: donor is a different person than the recipient
  - Require “matching” of human leukocyte antigen (HLA) markers
  - 25% chance of siblings being a “match”
  - Recipients without a related donor may have donor identified through National Marrow Donor Program
- Autologous: donor is the recipient
- Syngeneic: donor is identical twin of recipient

Types of HSCs/grafts

- Bone marrow: Taken directly from bone marrow of donor
- Peripheral blood: Taken from venous blood of donor
- Umbilical cord blood: Taken from umbilical cord of newborn baby

Process of HSCT

- Induction and consolidation therapy for leukemia
  - Until disease is in remission
- Conditioning: High dose chemotherapy with or without radiation therapy
- Hematopoietic stem cell transplant
  - Infusion of bone marrow, peripheral blood, or umbilical HSCs into recipient
- Immunosuppressive therapy (if needed) to prevent graft rejection

Total body irradiation as part of conditioning

- Non-myeloablative:
  - Commonly an outpatient procedure
- Myeloablative doses:
  - >5 Gy in a single fraction
  - >8 Gy in multiple fractions
  - Commonly an inpatient procedure (at MSKCC)
  - Can be performed as an outpatient (if patient is reliable)
  - Keep in mind, this is ***lethal*** therapy!

Indications for HSCT

- Center International Bone and Marrow Transplant most common indications for HSCT in 2005 (most to least common)
  - Multiple myeloma (MM)
  - Non-Hodgkin lymphoma (NHL)
  - Acute myelogenous leukemia (AML)
  - Hodgkin disease (HD)
  - Acute lymphoid leukemia (ALL)
  - Myelodysplastic and myeloproliferative disease (MDS)
  - Chronic myelogenous leukemia (CML)
  - Aplastic anemia (AA)
  - Various other leukemias, cancers, and non-malignant diseases

- National Comprehensive Cancer Network guidelines for HSCT (2009)
  - Acute myelogenous leukemia (AML)
  - Multiple myeloma (MM)
  - Myelodysplastic syndrome (MDS)
  - Chronic myelogenous (CML)
  - Hodgkin disease (HD)
  - Non-Hodgkin lymphoma (NHL)
  - Testicular cancer

Biology of TBI

- Normal and malignant blood cells are the major target in TBI
  - Very sensitive to radiation
  - D_0 of 0.5 – 1.5 Gy
  - Very small shoulder on cell survival curve
  - Other radiobiologic phenomena are ill-defined (repair, reoxygenation, repopulation, redistribution)

TBI effects on blood

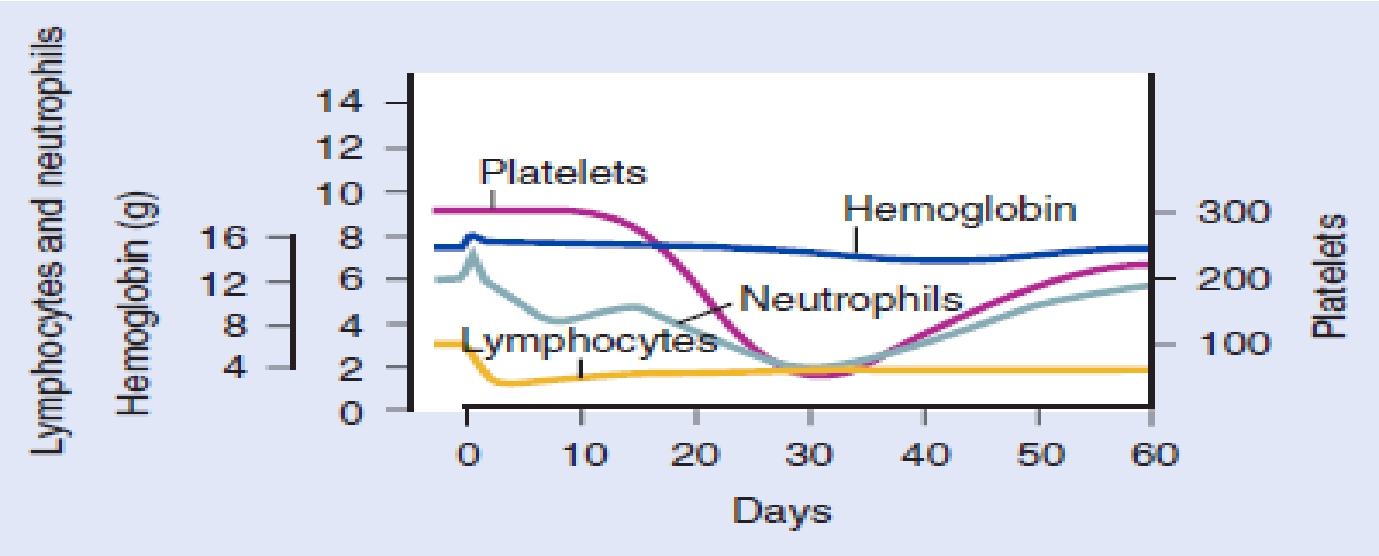

FIGURE 15-3 • Representative hematologic response to total body irradiation, given as a single fraction of 200 cGy on day 0. (From Andrews: Radiation accidents and their management, Radiat Res Suppl 7:390–397, ••••.)

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From *Textbook of Radiation Oncology*, 2010

Acute toxicity of TBI

- Side effects may be due to other components of HSCT

Table 15-1 Signs and Symptoms in Patients After Single-Dose or Fractionated Total Body Irradiation

Symptom/ Sign	Single Fraction TBI		Fractionated TBI
	% of Patients Experiencing **During** TBI	% of Patients Experiencing **After** TBI	% of Patients Experiencing During 3 Days of TBI
Nausea	90%	45%	43%
Vomiting	80%	23%	23%
Parotid gland pain	26%	74%	6%
Xerostomia	61%	58%	30%
Headache	42%	33%	15%
Fatigue	N/R	N/R	36%
Ocular dryness	None	16%	N/R
Esophagitis	N/R	N/R	4%
Loss of appetite	N/R	N/R	16%
Indisposition	N/R	N/R	25%
Erythema	None	None	41%
Pruritis	None	None	4%
Diarrhea	None	None	4%
No symptoms	N/R	N/R	17%
Fever (>38° C)	42%	97%	N/R
Hypertension	42%	None	N/R

Data from Chaillet et al.[86] and Buchali et al.[87]
N/R, Not reported; *TBI*, total body irradiation.

Prophylactic anti-emetics for TBI

Table 15-2 Randomized Controlled Trials of Prophylactic Antiemetics in Patients Undergoing Total Body Irradiation

Author [Reference]	Number of Patients	Total TBI Dose/ Number of Fractions	Experimental Antiemetic	Control Antiemetic	Outcome
Tiley et al. [90]	20	10.5 Gy/1	8 mg oral ondansetron at start of TBI + standard (metoclopramide, dexamethasone, lorazepam)	Placebo + standard (metoclopramide, dexamethasone, lorazepam)	Significantly fewer emetic events with ondansetron (60% versus 10%, $P < 0.03$) during TBI
Spitzer et al. [91]	20	13.2 Gy/11 (in 4 days)	8 mg oral ondansetron 1.5 hours prior to TBI thrice daily	Placebo	Significantly more patients had two or less episodes of emesis with ondansetron (60% versus 10%, $P < 0.03$); significantly longer time to first emetic episode ($P < 0.005$), and significantly fewer episodes of emesis during the first 24 hours and over the entire study period ($P < 0.05$) with ondansetron
Prentice et al. [92]	30	7.5 Gy/1	3 mg intravenous granisetron 1 hour prior to TBI	Metoclopramide, dexamethasone, and lorazepam 1 hour prior to TBI	Significantly greater rates of complete control of emesis within the first 24 hours with granisetron (53% versus 13%, $P = 0.02$) and significantly longer duration of emesis control ($P < 0.005$) with granisetron
Okamoto et al. [93]	58	6-12 Gy/1-6 (74% of patients received TBI)	40 mcg/kg intravenous granisetron twice daily 30 minutes prior to TBI	Various	Significantly greater rates of complete control of emesis within the first 24 hours with granisetron (92% versus 44%, $P < 0.01$) and throughout the duration of HSCT (68% versus 0%, $P < 0.001$) with granisetron in patients receiving TBI
Matsuoka et al. [94]	50	12 Gy/4-6 (64% of patients received TBI)	4 mg intravenous dexamethasone + 40 mcg/kg granisetron twice daily 30 minutes prior to treatment	40 mcg/kg intravenous granisetron twice daily 30 minutes prior to treatment	Significantly greater (100% versus 63%, $P = 0.02$) rates of complete emesis control within the first 24 hours with dexamethasone in patients receiving TBI; insomnia, headache, flushing, and hyperglycemia were more common in patients with corticosteroid

HSCT, Hematopoietic stem cell transplant; *TBI*, total body irradiation.

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From *Textbook of Radiation Oncology*, 2010

Late toxicity of TBI and HSCT

- Xerostomia
- Dental caries
- Pneumonopathy, pneumonitis, lung dysfunction – major dose-limiting toxicity
- Cardiovascular disease
- Hepatotoxicity
- Cataracts
- Nephropathy
- Endocrinopathy

Secondary Malignant Neoplasms after TBI and HSCT

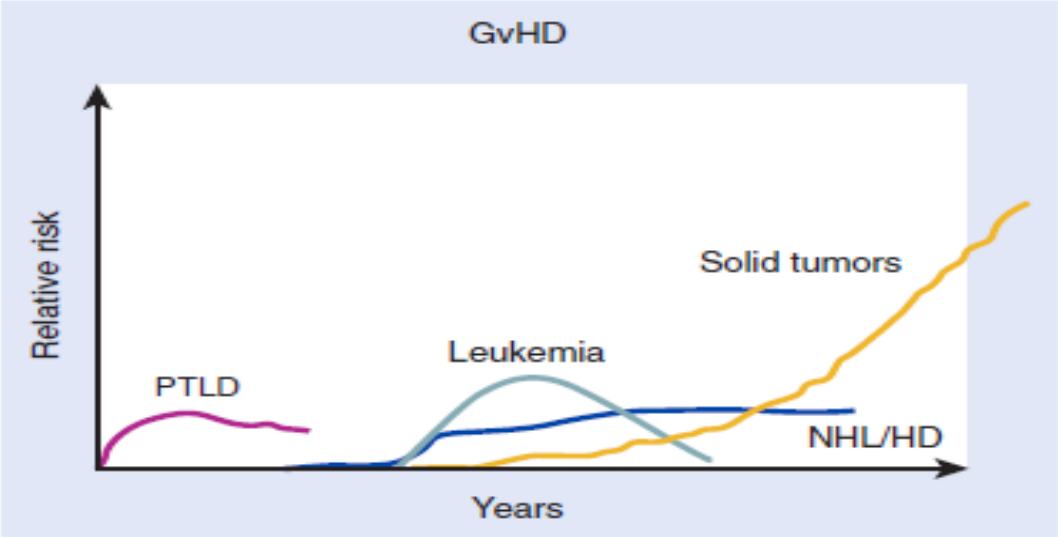

FIGURE 15-5 • Relative risk and chronology of second malignancies after allogeneic hematopoietic stem cell transplant. *GvHD,* Graft-verus-host disease; *HD,* Hodgkin disease; *NHL,* non-Hodgkin lymphoma. (From Adès et al: Second malignancies after allogeneic hematopoietic stem cell transplantation: new insight and current problems, Blood Rev 16:135–146.)

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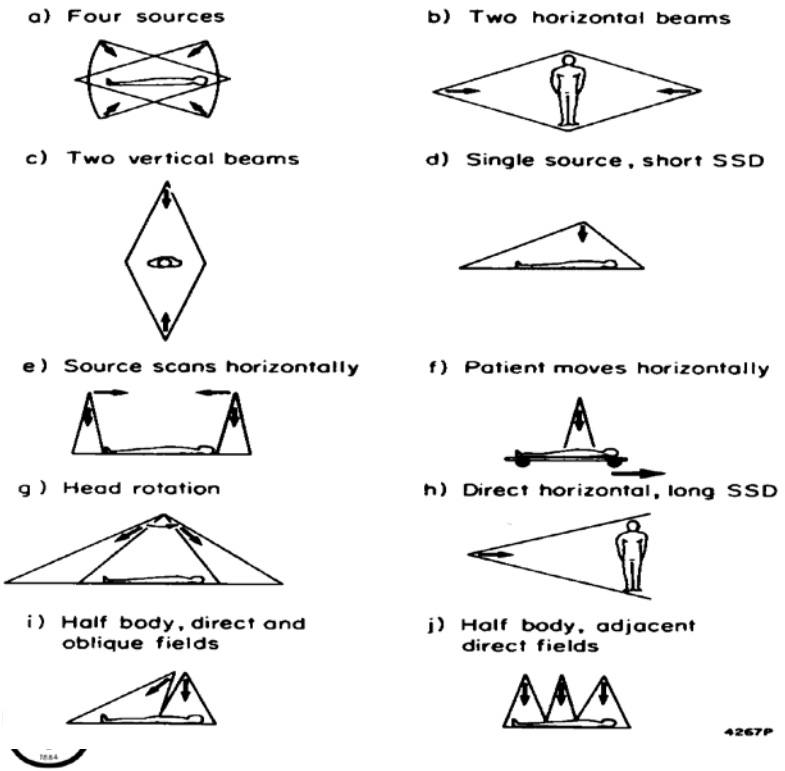
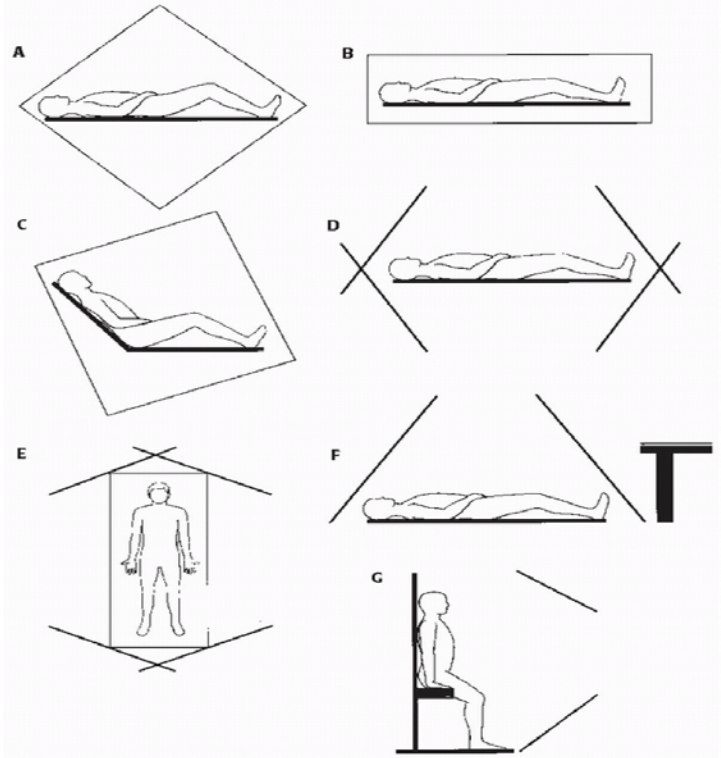
TBI: Techniques





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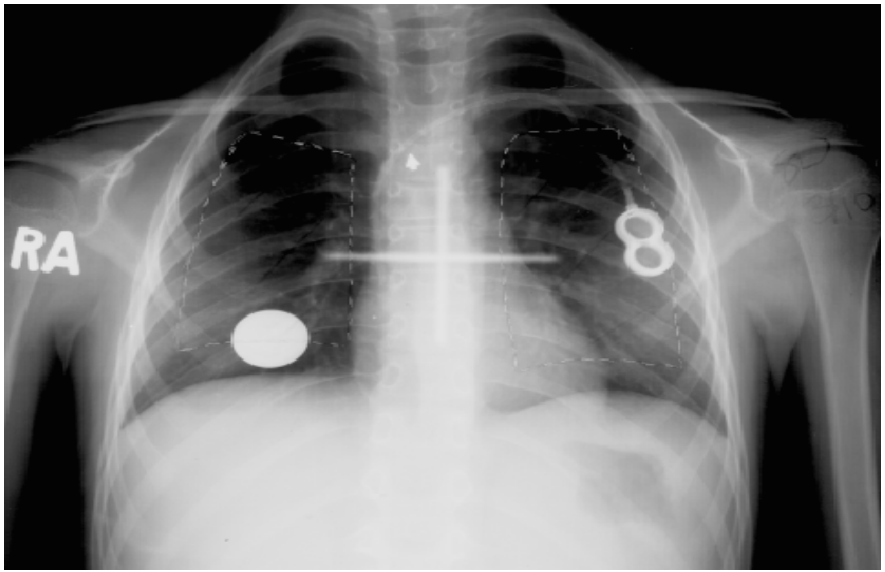
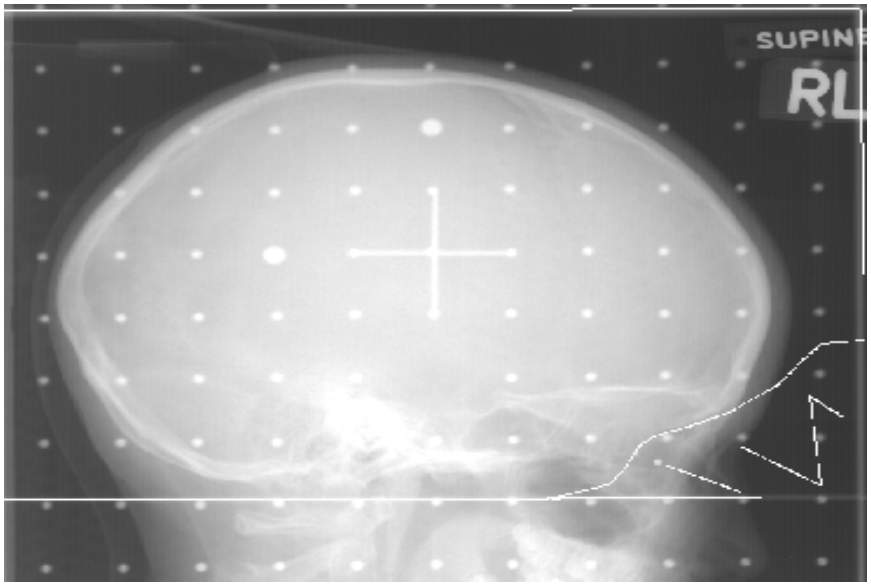
Courtesy of Tom LoSasso, MSKCC

TBI: Simulation Films





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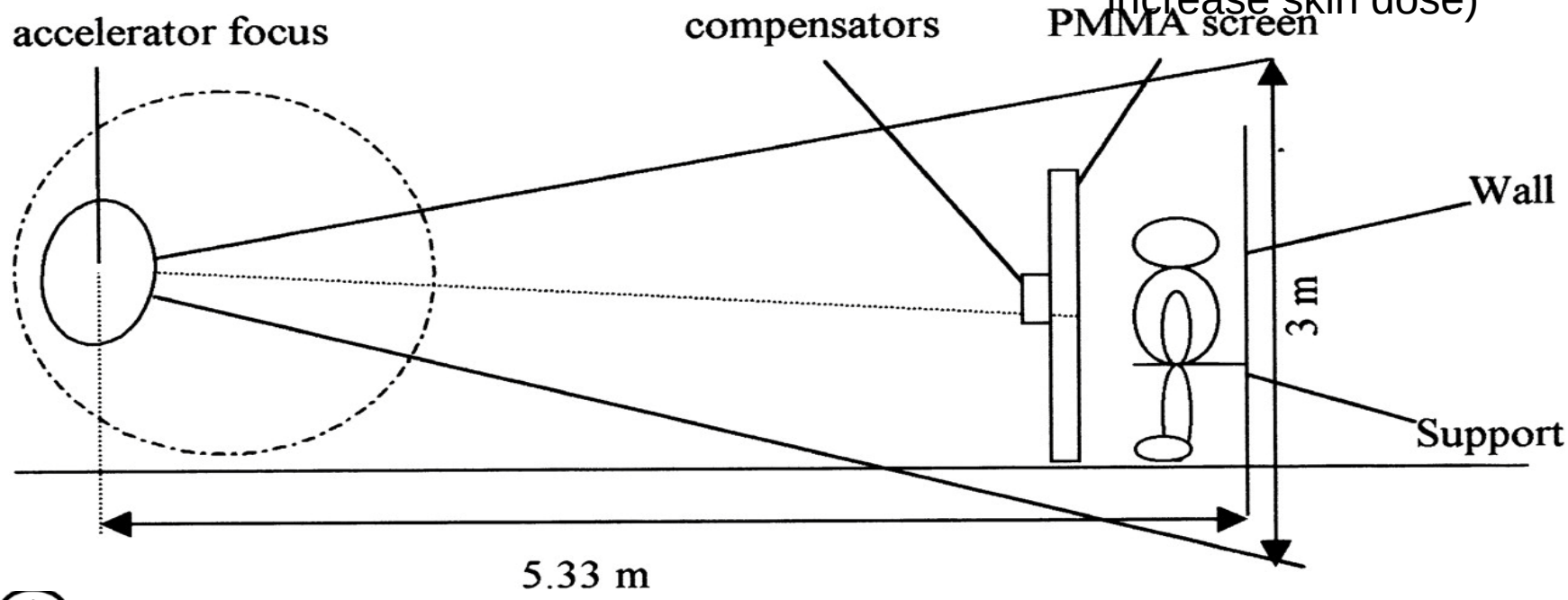
TBI: Technique

(beam spoilers used to increase skin dose)



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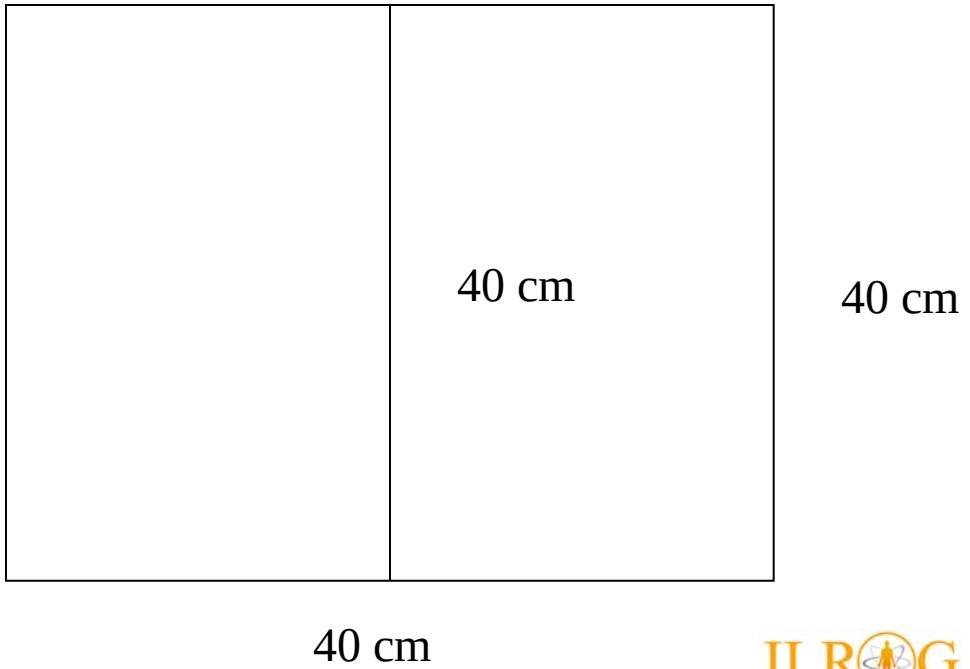
From *Br J Radiol*, 2001

TBI: Technique (patients <40 cm tall)



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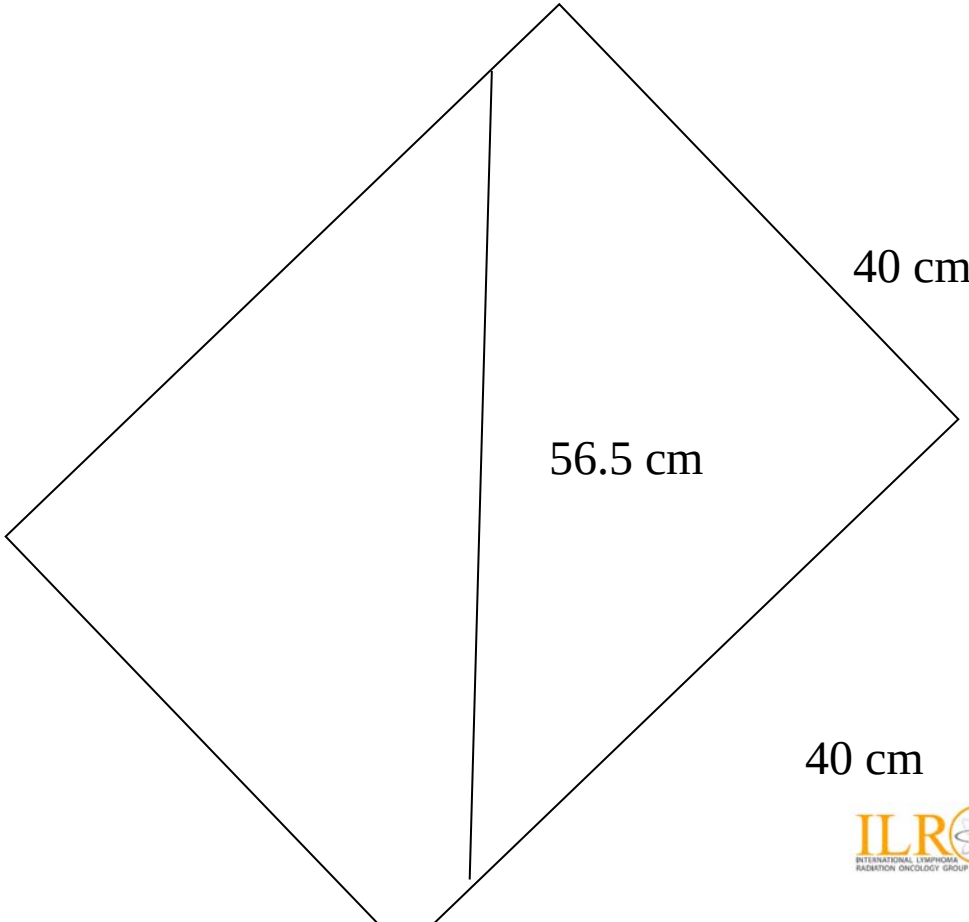
TBI: Technique (patients >40 cm tall)



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TBI: MSKCC Standing AP/PA Technique

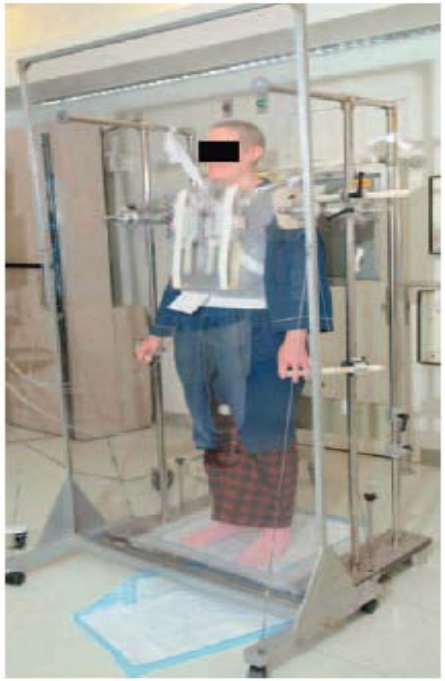

FIGURE 15-6 • Patient in position for total body irradiation using anteroposterior beam arrangement, with lung blocks in place.

Lung shielding used routinely for myeloablative TBI

Beam spoilers used to increase skin dose

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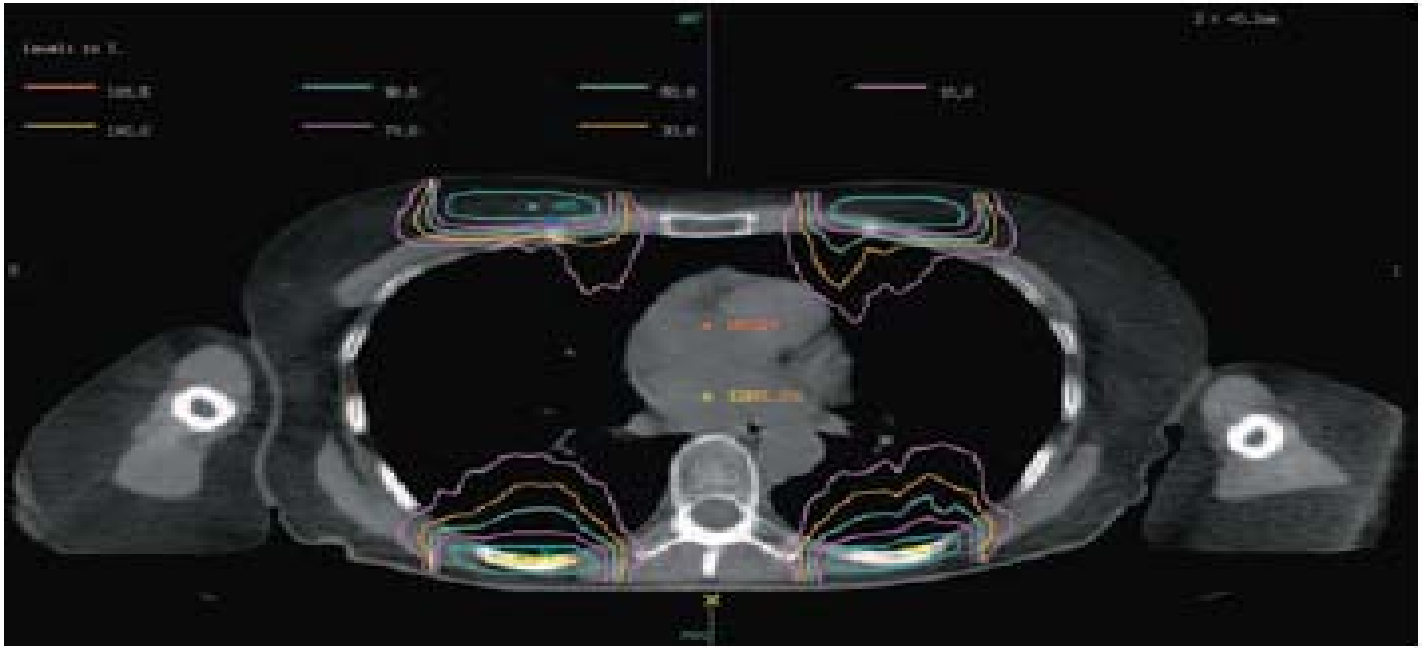
TBI: MSKCC Chest Wall Compensation



FIGUR E 15-7 • Computed tomography axial section demonstrating electron boost dose distribution.

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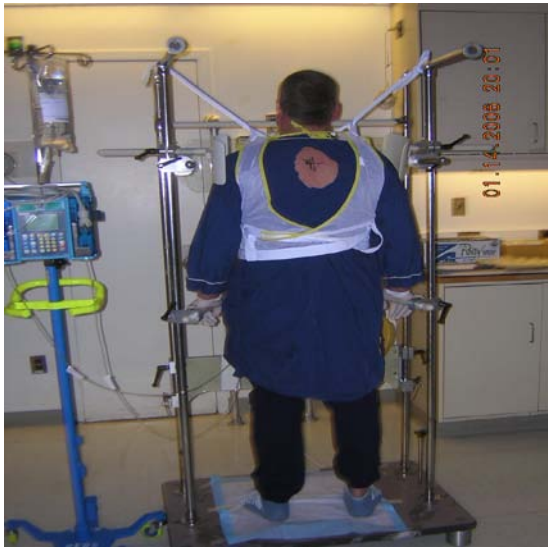
TBI: MSKCC Standing AP/PA Technique



Lung shielding not used for most non-myeloablative TBI regimens

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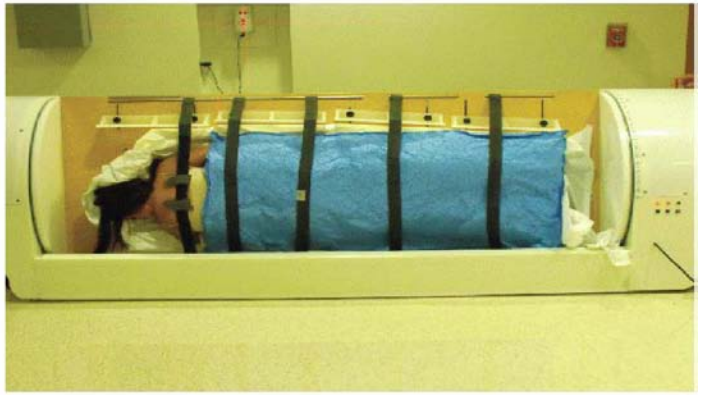
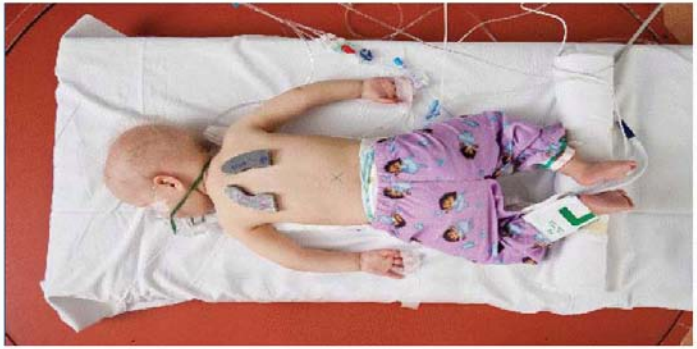
Courtesy of Tom Lo Sasso, MSKCC

TBI: Duke Pediatric Setup



A



B

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From *Pediatric Radiation Oncology*, 2011

TBI: MSKCC Techniques

	Standing (adults, children >3 years)	Lying on floor (children <3 years)
energy	15 MV	15/6 MV
SAD (cm)	440	220
CS	40x40	40x40
gantry / collimator	85º / 45º	0º / 45º
dose rate @ midplane (cGy/min)	10-13	13-17
Spoiler (25 cm from pt)	yes	yes
shielding / electrons	yes	yes
max. patient height (ft)	6	3.5

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Courtesy of Tom Lo Sasso, MSKCC

TBI: Prescription

Fields	01-02	03	04	05-06	07
Energy	15 MV photons	6 MeV electrons	6 MeV electrons	6 MV photons	6 MeV electrons
Site	TBI	Anterior chest wall	Posterior chest wall	Whole brain	Testes
Technique	AP-PA	Anterior	Posterior	Opposed laterals	en face
Rx Point	midplane	90% IDL	90% IDL	midplane	90% IDL
Dose/Fx	125 cGy	300 cGy	300 cGy	180 cGy	400 cGy
Fractions/Day	3	2	2	1	1
Total Dose	1500 cGy	600 cGy	600 cGy	900 cGy	400 cGy

TBI is associated with better survival

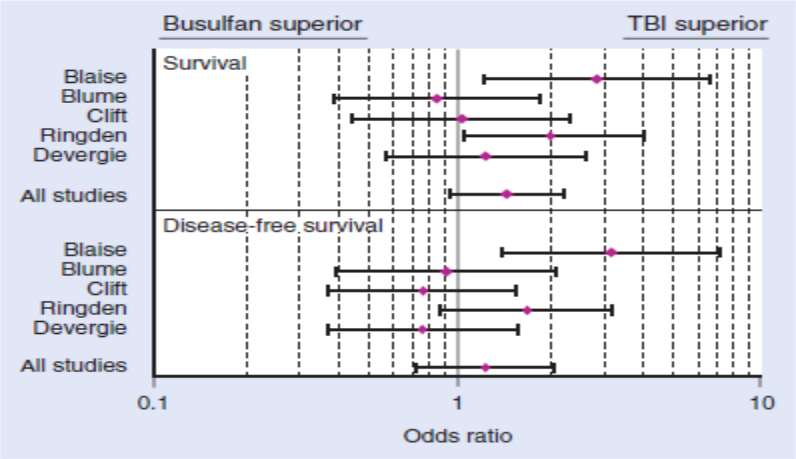

FIGURE 15-8 • Odds ratio and 95% confidence intervals of survival and disease-free survival in a meta-analysis of total body irradiation (TBI)–based conditioning versus non-TBI–based conditioning in five randomized controlled trials. (From Hartman et al: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: a meta-analysis, Bone Marrow Transplant 22:439–443.)

TBI associated with less veno-occlusive disease (liver complications)

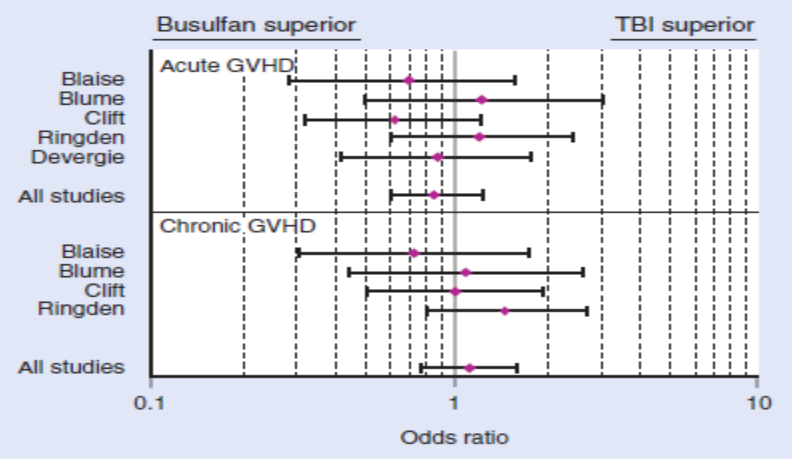

FIGURE 15-9 • Odds ratio and 95% confidence intervals of acute and chronic GVHD in a meta-analysis of total body irradiation (TBI)–based conditioning versus non-TBI–based conditioning in five and four randomized controlled trials, respectively. *GVHD,* Graft-versus-host disease. (From Hartman et al: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: a meta-analysis, Bone Marrow Transplant 22:439–443.)

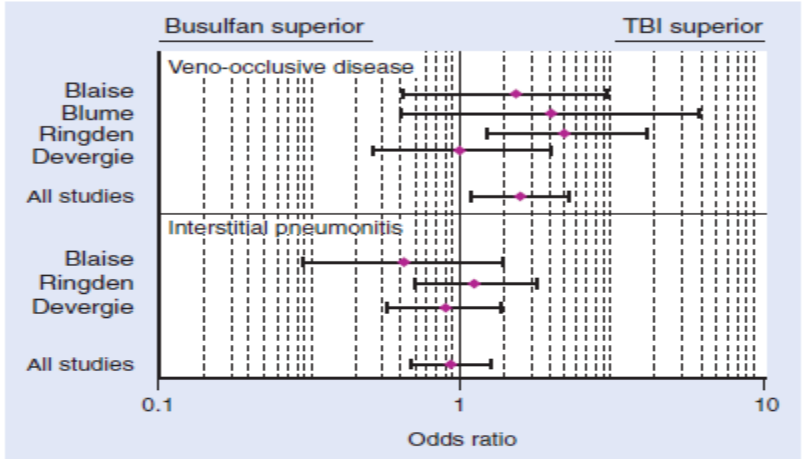

FIGURE 15-10 • Odds ratio and 95% confidence intervals of hepatic veno-occlusive disease and interstitial pneumonitis in a meta-analysis of total body irradiation (TBI)–based conditioning versus non-TBI–based conditioning in four and three randomized controlled trials, respectively. (From Hartman et al: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: a meta-analysis, Bone Marrow Transplant 22:439–443.)

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TBI associated with better outcomes in ALL & AML, but not MM

Table 15-3 Randomized Controlled Trials Comparing Hematopoietic Stem Cell Transplant Conditioning Regimens With and Without Total Body Irradiation

Disease	Author (Group) [Reference]	Number of Patients	Type of Transplant	TBI-Based Conditioning	Non-TBI-Based Conditioning	Total TBI Dose Number & Frequency of Fractions Dose Rate	Technique	Conditioning Regimen	OS	EFS	Relapse	Non-Relapse Mortality	TRM	Other Findings
ALL	Bunin et al. (PBMTC) [270]	43	Allogeneic marrow, cord, or peripheral blood	TBI, etoposide 40 mg/kg in 1 day, then Cy 120 mg/kg in 2 days	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	12 Gy 6 bid Dose rate not described	Not described	TBI Non-TBI	3 yr: 67% 3 yr: 47%	3 yr: 58%* 3 yr: 29%*	43%[1] 32%[1]	24%[1] 9%[1]		No significant difference in GVHD, or pulmonary, cardiac, or neurologic toxicity after HSCT; the TBI group had significantly better EFS among patients who received unrelated donor stem cells, and who were under 6 years
ALL AML CML lymphoma	Ringden et al. (NBMTG) [112, 172]	167	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-12.7 Gy 1-7 given ≥1 times daily 4-12.7 cGy/min	Varied All had lung blocks limiting dose to 9-10 Gy	TBI Non-TBI	7 yr: 63% 7 yr: 54%	7 yr: 62% 7 yr: 51%	7 yr: 29% 7 yr: 29%		7 yr: 14%* 7 yr: 34%*	No significant difference in immunosuppressant use, interstitial pneumonitis, or Karnofsky score, growth, renal, pulmonary, or thyroid function at follow-up; the TBI group had less hepatic VOD, hemorrhagic cystitis, chronic GVHD, death from GVHD, obstructive pronchiolitis, with more cataracts
ALL AML CML	Blume et al. (SWOG) [274]	122	Allogeneic marrow	TBI, then etoposide 60 mg/kg in 1 day	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	13.2 Gy 11 tid Dose rate not described	Not described	TBI Non-TBI	3 yr: ~24% (7 months[2]) 3 yr: ~28% (7 months[2])					No significant difference in GVHD, hemorrhage, sepsis, lung complications, infections, VOD, drug toxicity, relapse, disease free survival
AML	Dusenbery et al. (Minnesota) [261]	35	Autologous marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 200 mg/kg	13.2 Gy 8 bid (4.5 hr apart) 10 cGy/min	6-24 MV photons Bilateral parallel-opposed Head & neck,	TBI Non-TBI	2 yr: 46% 2 yr: 35%	2 yr: 50% 2 yr: 24%	2 yr: 43% 2 yr: 70%	Reported as "not different" Reported as "not different"		No significant difference in time to engraftment, GVHD, time in the hospital, infection, hepative VOD, hemorrhagic cystitis, pneumonitis
AML	Blaise et al. (GEGMO) [260, 262]	101	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-13.5 Gy 1-6 given 1-2 times daily (6 bid[2]) 3-25 cGy/min (5 cGy/min[2])	Varied All had lung blocks (8.8 Gy[2])	TBI Non-TBI	12 yr: 59%* 12 yr: 43%*	12 yr: 55%* 12 yr: 35%*	12 yr: 25% 12 yr: 37%		12 yr: 16% 12 yr: 27%	No significant difference in time to engraftment, GVHD; the TBI group had less chronic GVHD related mortality
CML	Clift et al. (Seattle) [265, 266]	142	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	12 Gy 6 qd 6-7 cGy/min	Dual opposed 60Co sources Geometry not described Blocks not described	TBI Non-TBI	9 yr: 65% 9 yr: 73%	9 yr: 48% 9 yr: 55%	9 yr: 22% 9 yr: 19%	9 yr: 25% 9 yr: 20%		No significant difference in the rate of engraftment, GVHD, hepatic VOD, number of fevers, deaths from infection, mean duration of first hospitalization; the TBI group did have significantly longer fevers, more blood cultures revealing bacteria or fungi, more than one hospitalization in the 100 days after transplant, and higher incidence of grade 2-4 GVHD
CML	Devergie et al. (SFGM) [267]	120	Allogeneic marrow	TBI, then Cy 120 mg/kg in 2 days	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-12 Gy 1-24 given 1-8 times daily (bid[2]) 3-25 cGy/min (8 cGy/min[2])	Varied All had lung blocks (8.8 Gy[2])	TBI Non-TBI	5 yr: 66% 5 yr: 61%	5 yr: 51% 5 yr: 59%	5 yr STBI: 11%* 5 yr FTBI: 31%* 5 yr: 4%*	Not reported Not reported	29%[1] 38%[1]	No significant difference in the rate of engraftment, GVHD, hepatic VOD, interstitial pneumonitis, hemorrhagic cystitis, GVHD
MM	Moreau et al. (IFM) [273]	282	Autologous peripheral blood	TBI, then Mel 140 in 1 day	Mel 200 in 1 day	8 Gy 4 qd Dose rate not described	Not described No lung blocks	TBI Non-TBI	3.75 yr: 45.5% 3.75 yr: 65.8%*	21 months[2] 20.5 months[2]			3.6%[1] 0%[1]	No significant difference in growth factor use, cardiac, pulmonary, renal, liver toxicity, or response rates; the TBI group had significantly higher rates of mucositis and hematologic toxicity, and longer hospitalizations

All drug doses given as mg/m² unless otherwise stated.
bid, Twice daily; *Bu*, busulfan; *Cy*, cyclophosphamide; *EFS*, even-free survival; *Mel*, melphalan; *OS*, overall survival; *tid*, three times daily; *TRM*, transplant related mortality; *qd*, once daily.
*Statistically significant difference; [1]observed incidence; [2]median.

TBI used in non-myeloablative regimens for various diseases

Table 15-4 Representative Total Body Irradiation–Based Reduced Intensity Conditioning Regimens for Allogeneic Hematopoietic Stem Cell Transplant

Disease	Author (Group) [Reference]	Number of Patients	Total TBI Dose Number & Frequency of Fractions Dose Rate	Additional Conditioning Therapy	Technique	Type of Transplant
AML	Hegenbart et al. (multicenter) [282]	122	2 Gy 1 ~~0.07 to 0.20 Gy~~/min	84% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic marrow (5%) and peripheral blood (95%)
AML	Stelljes et al. (COSTSG) [283]	71	8 Gy 4 given twice daily 8.9-30 cGy/min	TBI, then Flu 120 in 4 days +/- ATG	Not described	Allogeneic marrow (4%) and peripheral blood (96%)
AML	Hallemeier et al. (Washington U.) [284]	32	5.5 Gy 1 27.6-36.4 cGy/min	Cy 120 in 2 days, then TBI	6 MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
CLL	Sorror et al. (Seattle) [285]	64	2 Gy 1 7 cGy/min	83% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
CML	Kerbauy et al. (Seattle) [286]	24	2 Gy 1 7cGy/min	67% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
CML	Khoury et al. (Washington U.) [287]	30	5.5 Gy 1 26.4-36.0 cGy/min	Cy 120 in 2 days, then TBI	6 MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
Hematologic malignancy	McSweeney et al. (Seattle) [288]	45	2 Gy 1 7 cGy/min	None	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
Hematologic malignancy	Baron et al. (Seattle) [289]	221	2 Gy 1 7 cGy/min	77% received Flu 90 in 3 days, then TBI	Not described	97% allogeneic peripheral blood
Lymphoma	Tomblyn et al. (Minnesota) [290]	76	2 Gy 1 Dose rate not reported	Flu + Cy, then TBI or Flu + Bu, then TBI or Bu + Clad, then TBI	Not described	Allogeneic marrow (10%), peripheral blood (46%), and cord blood (43%)
Mantle cell lymphoma	Maris et al. (Seattle) [291]	33	2 Gy 1 7 cGy/min	Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic marrow (4%) and peripheral blood (96%)
MDS/AML	Schmid et al. (Wiesbaden) [292]	75	4 Gy 1 Dose rate not reported	TBI, then Cy 80-120 in 2 days, ATG	Not described	Allogeneic marrow (19%) and peripheral blood (81%)
MDS/MPD	Laport et al. (multicenter) [293]	148	2 Gy 1 7 cGy/min	97% received Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic marrow (2%) and peripheral blood (98%)
MDS/secondary AML	Hallemeier et al. (Washington U.) [294]	51	5.5 Gy 1 25.3-37.2 cGy/min	Cy 120 in 2 days, then TBI	6 MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
MM	Maloney et al. (Seattle) [295]	54	2 Gy 1 7 cGy/min	17% received Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
MM	Badros et al. (Arkansas) [296]	31	2.5 Gy 2 given twice in 1 day Dose rate not reported	TBI and Mel 100, then Flu 60 in 2 days	Not described	Allogeneic peripheral blood

All drug doses given in mg/kg unless otherwise stated.
AML, Acute myelogenous leukemia; ATG, antithymocyte globulin; Bu, busulfan; Clad, cladribine; CLL, chronic lymphoid leukemia; CML, chronic myelogenous leukemia; Cy, cyclophosphamide; Flu, fludarabine; melphalan; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPD, myeloproliferative disorder.

Memorial Sloan Kettering Cancer Center

From *Textbook of Radiation Oncology*, 2010

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Dutch HL case 29-year old male patient

Medical history:

- [7]2013 since 3-4 weeks swelling in right neck. No other complaints, especially no B-symptoms.
- No medication
- Smoking: sometimes. Alcohol: no

Dutch HL case

Physical examination:

WHO PS 0. Pathological lymph nodes right supraclavicular fossa. Largest node 2-3 cm. Presternal swelling (atheroma)

No other abnormalities on physical examination.

Lab:

ESR 11 mm/hour, Hb 8.9 mmol/l, leuco 5.6x10^9/l, lymfo 1.2 x10^9/l, LDH 158 U/l, albumin 48 g/l

Dutch HL case

Pathology

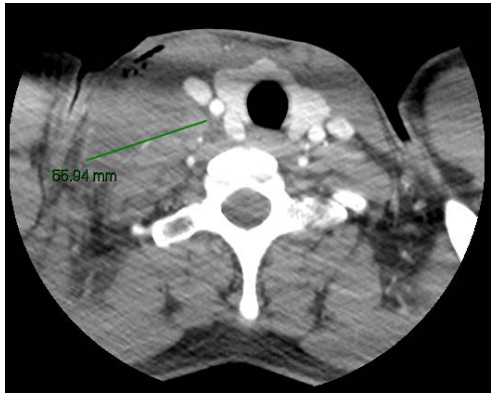
Biopsy right supraclavicular node:

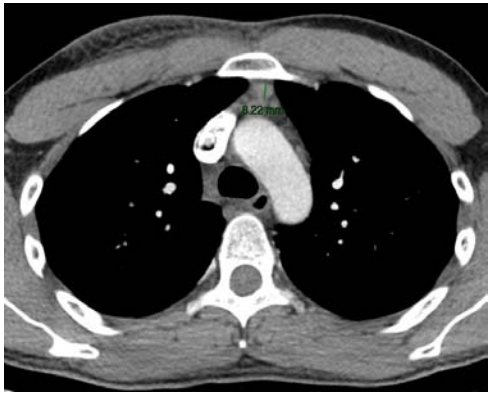
Classical Hodgkin lymphoma, nodular sclerosing

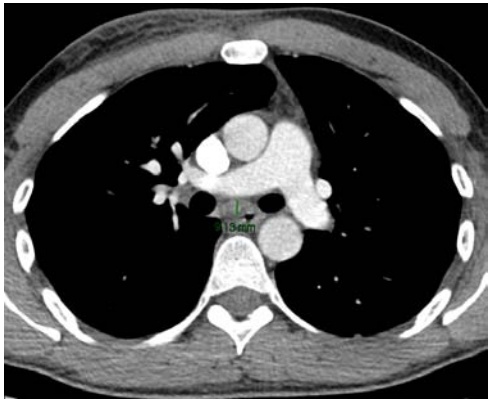
Bone marrow: no signs of Hodgkin lymphoma

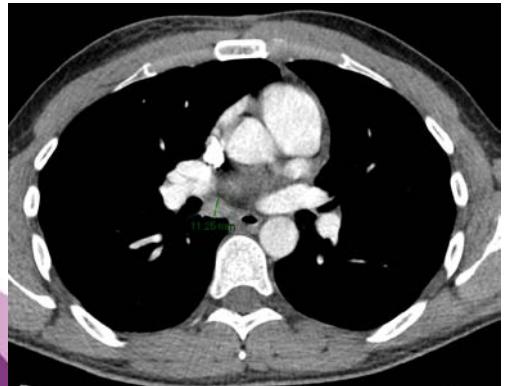
Dutch HL case

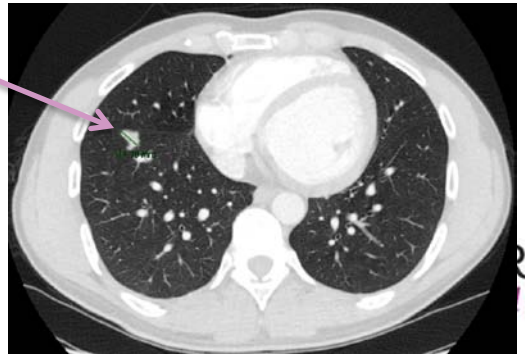
Post biopsy CT-scan





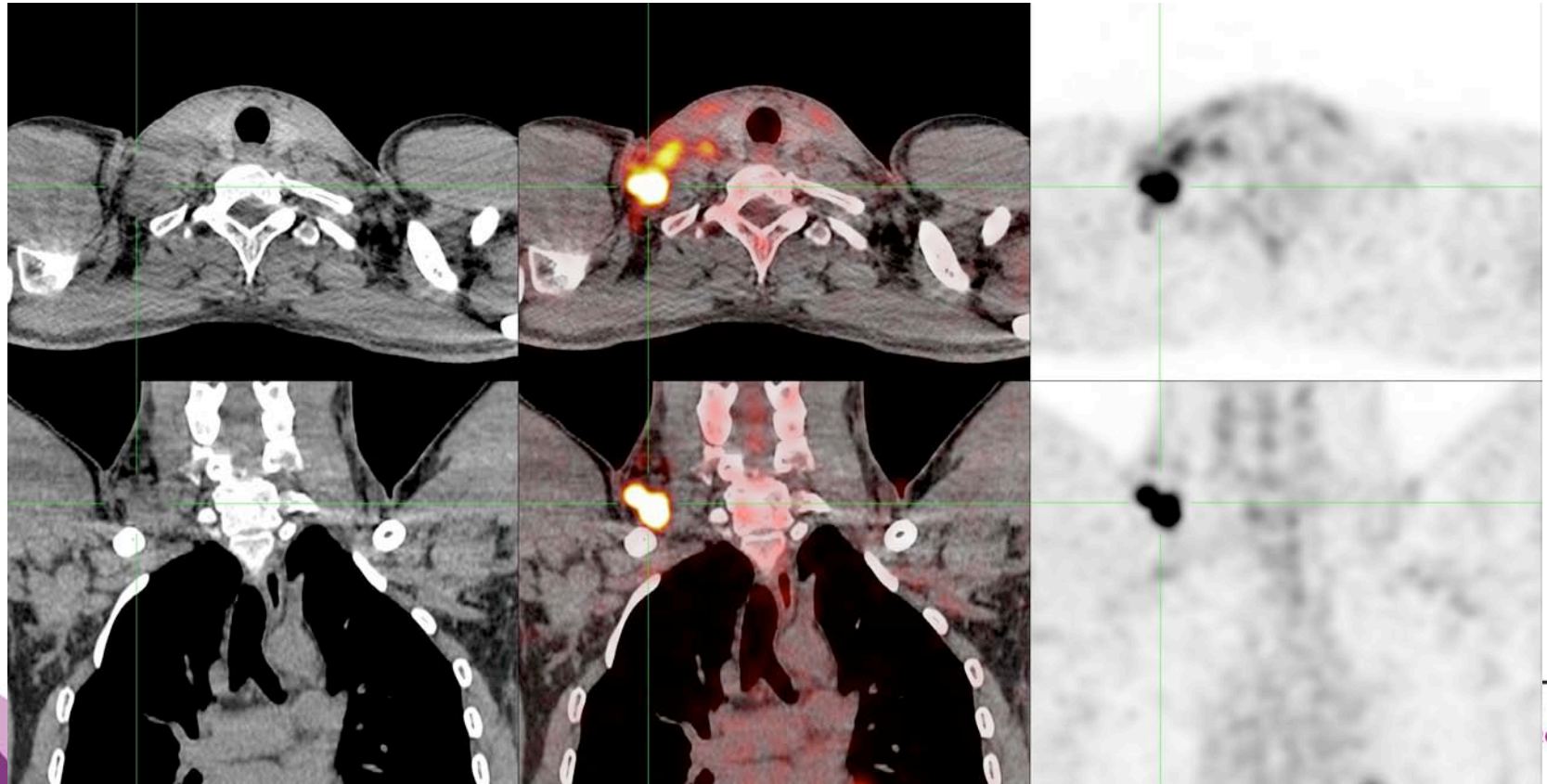






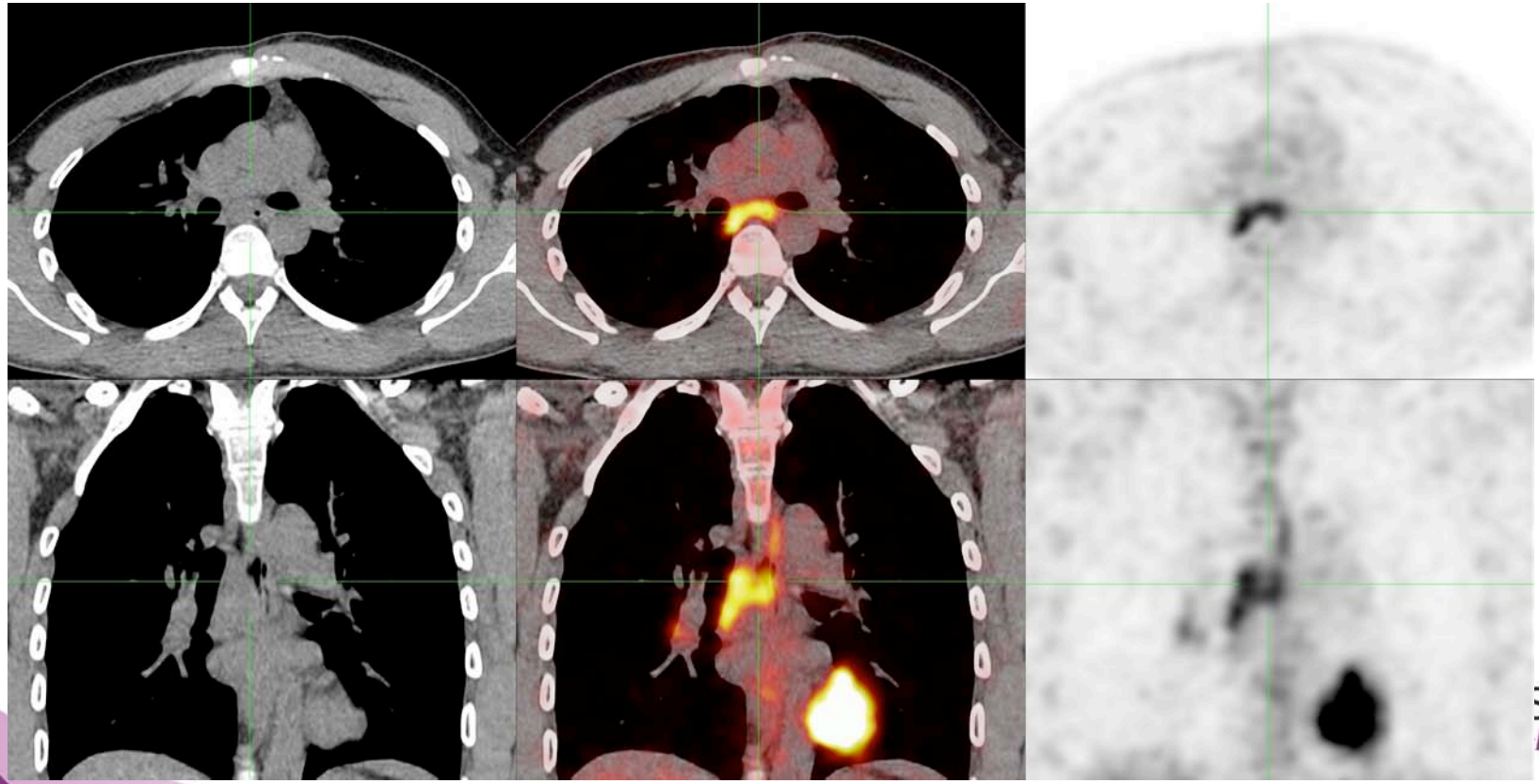
Dutch HL case

Post biopsy PETCT-scan



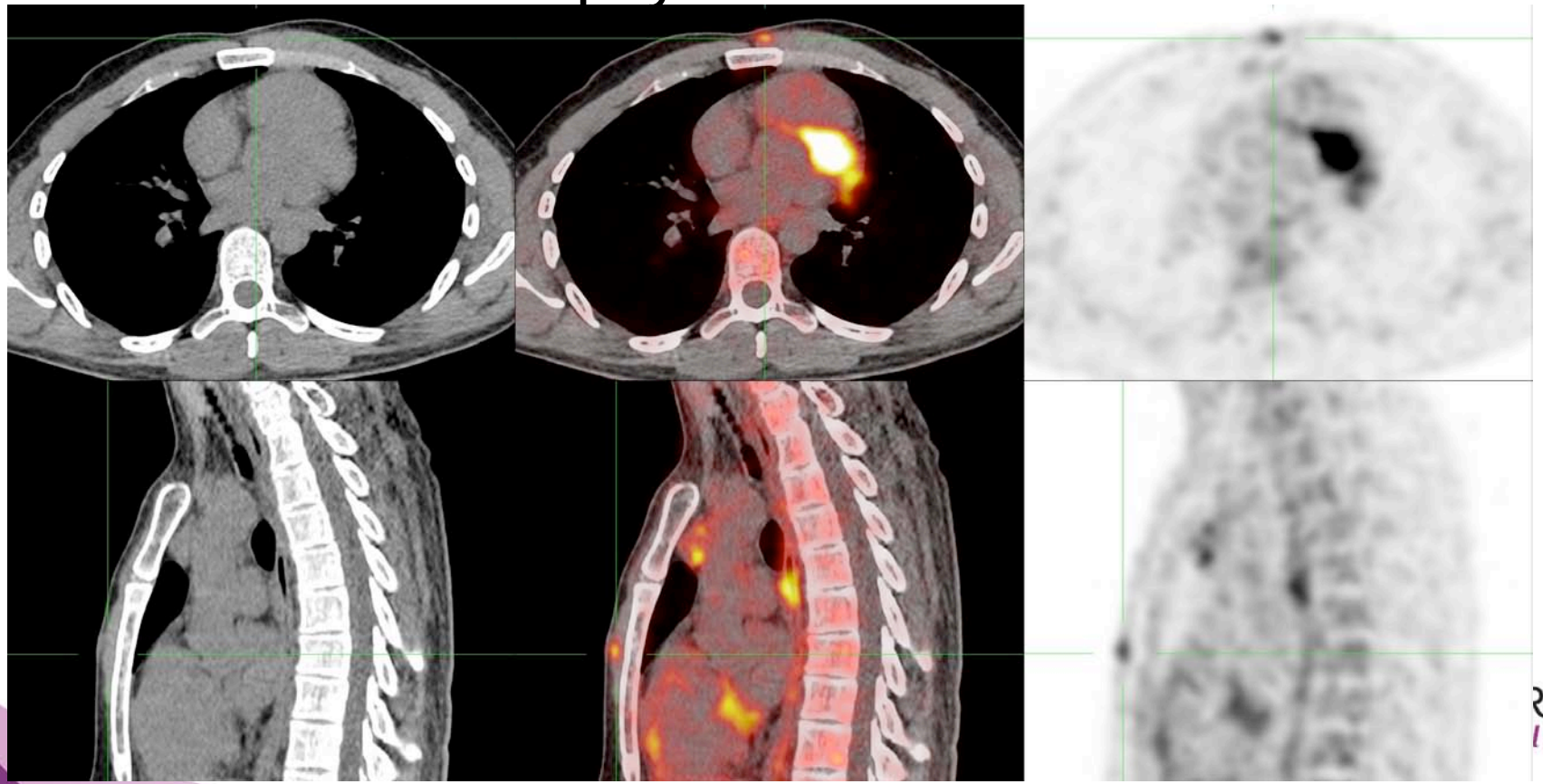
Dutch HL case

Post biopsy PETCT-scan



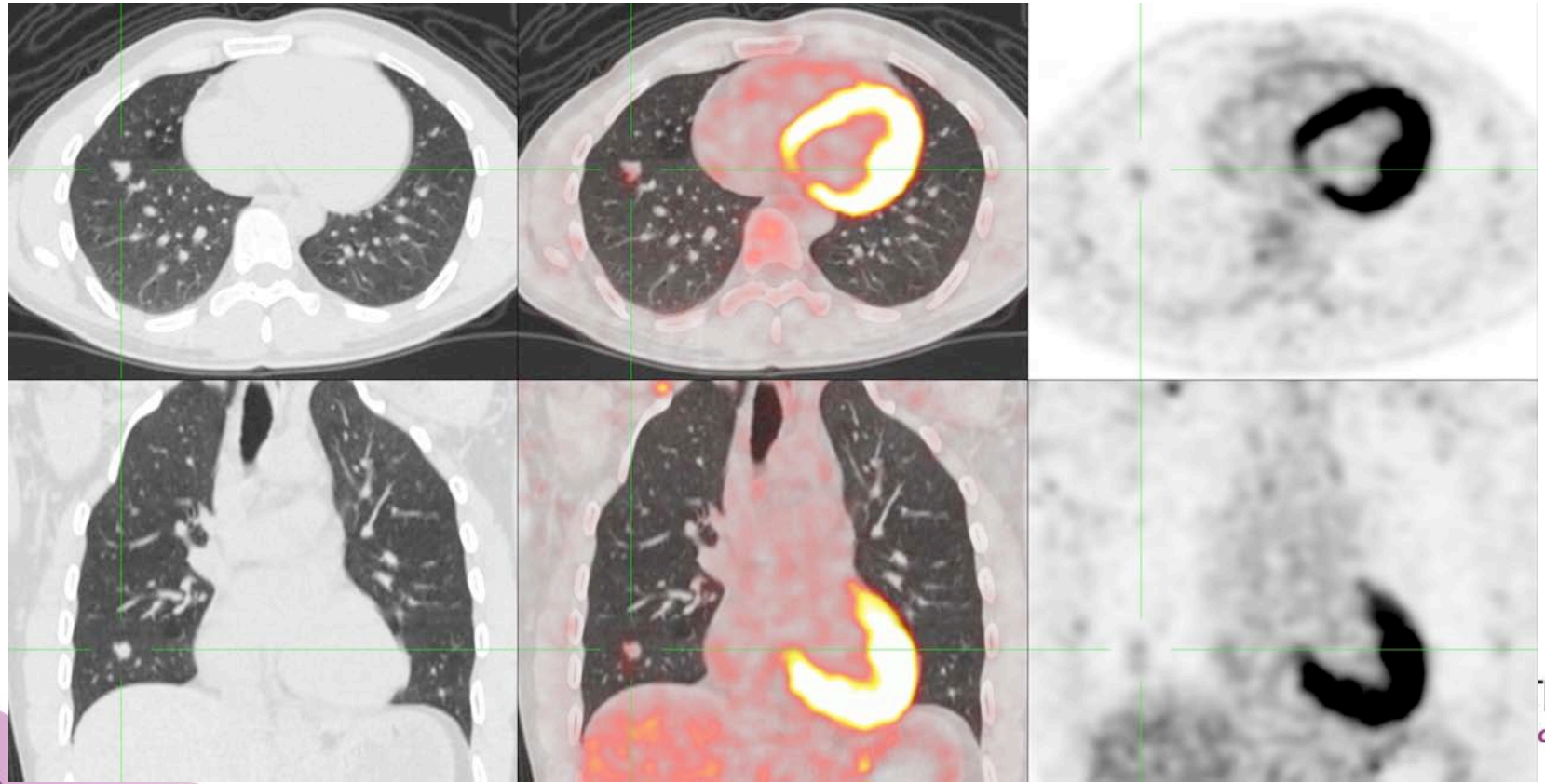
Dutch HL case

Post biopsy PETCT-scan



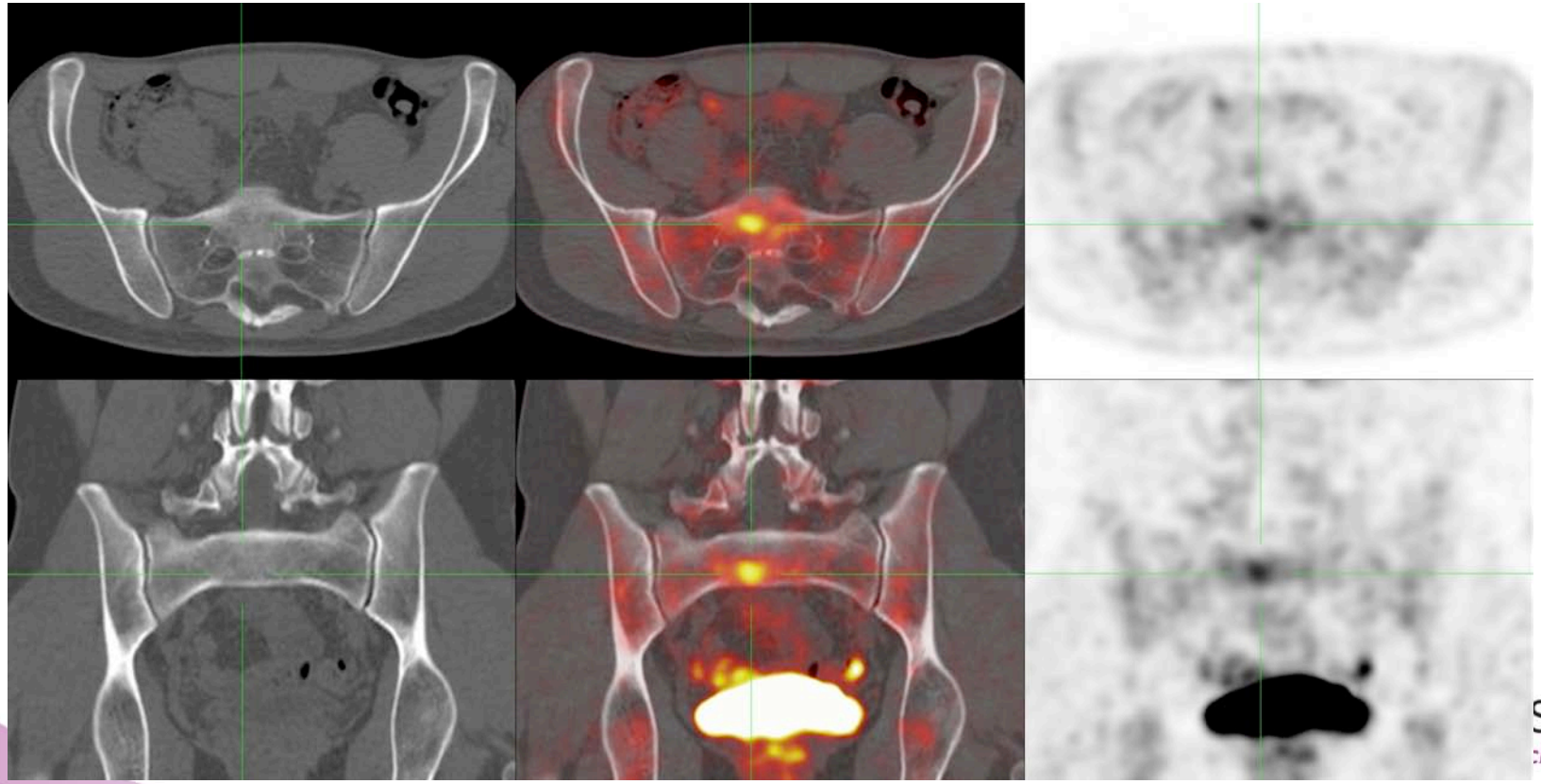
Dutch HL case

Post biopsy PETCT-scan



Dutch HL case

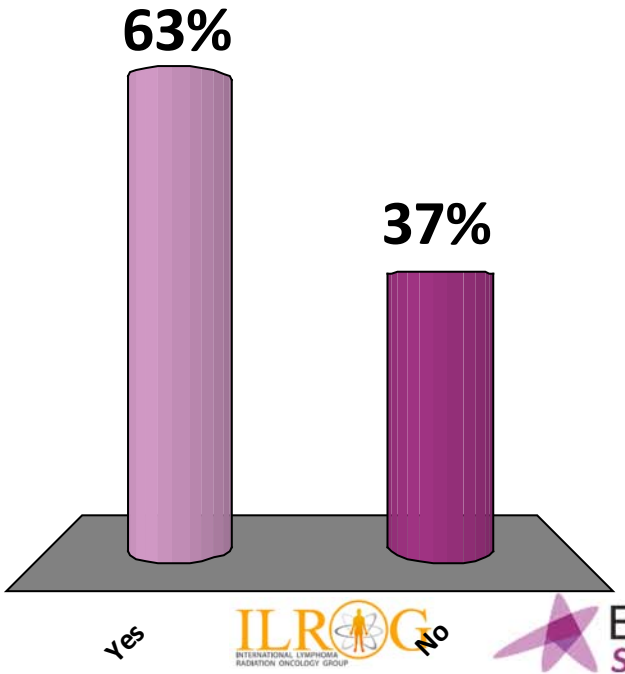
Post biopsy PETCT-scan



A bone marrow biopsy was performed, but was this indicated?

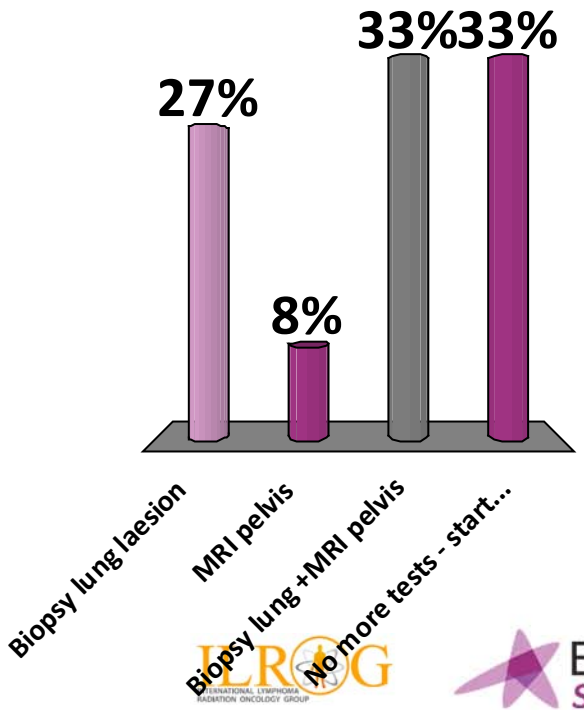
A. Yes

B. No



What would be your next step?

A. Biopsy lung laesion
B. MRI pelvis
C. Biopsy lung +MRI pelvis
D. No more tests - start treatment



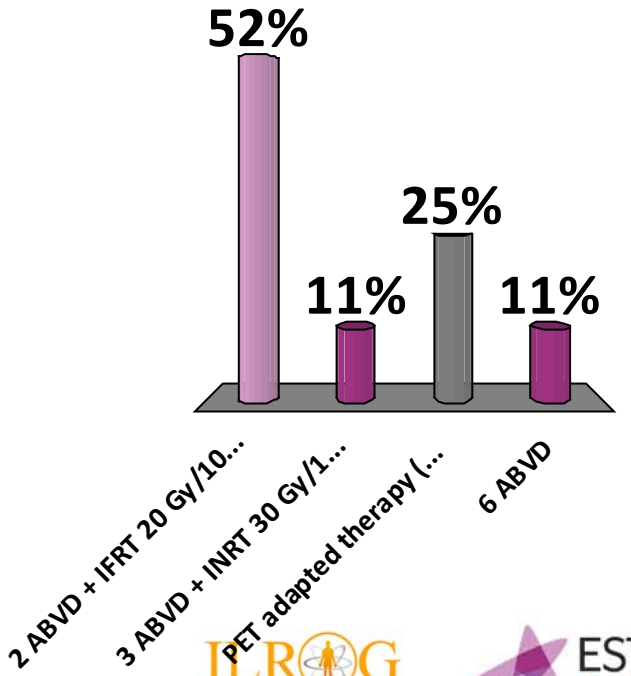
Dutch HL case

- Needle biopsies lung laesion: pulmonary tissue, no signs of malignancy

- MRI pelvis: no signs of tumor

Which treatment would you give?

A. 2 ABVD + IFRT 20 Gy/10 fractions
B. 3 ABVD + INRT 30 Gy/15 fractions
C. PET adapted therapy (i.e. 2 ABVD followed by 1 ABVD+INRT if PET2 negative or 2 escBEACOPP +INRT if PET2 positive)
D. 6 ABVD



Tabular List 1. Clinical Risk Factors

- Large mediastinal mass, size at least one third of the maximum thorax diameter
- Extra-nodal disease*
- Involvement of three or more nodal areas†
- Elevated erythrocyte sedimentation rate (≥ 50 mm/h for stages IA, IIA and ≥ 30 mm/h for stages IB, IIB)

Tabular List 2. Lymph Node Areas‡

- Area A: right cervical + right infra-/supra-clavicular/nuchal lymph nodes
- Area B: left cervical + right infra-/supra-clavicular/nuchal lymph nodes
- Area C: right/left hilar + mediastinal lymph nodes
- Area D: right axillary lymph nodes
- Area E: left axillary lymph nodes
- Area F: lymph nodes of the upper abdomen (spleen hilum, liver hilum, coeliacal)
- Area G: lymph nodes of the lower abdomen (spleen hilum, liver hilum, coeliacal)
- Area H: right iliac lymph nodes
- Area I: left iliac lymph nodes
- Area K: right inguinal + femoral lymph nodes
- Area L: left inguinal + femoral lymph nodes

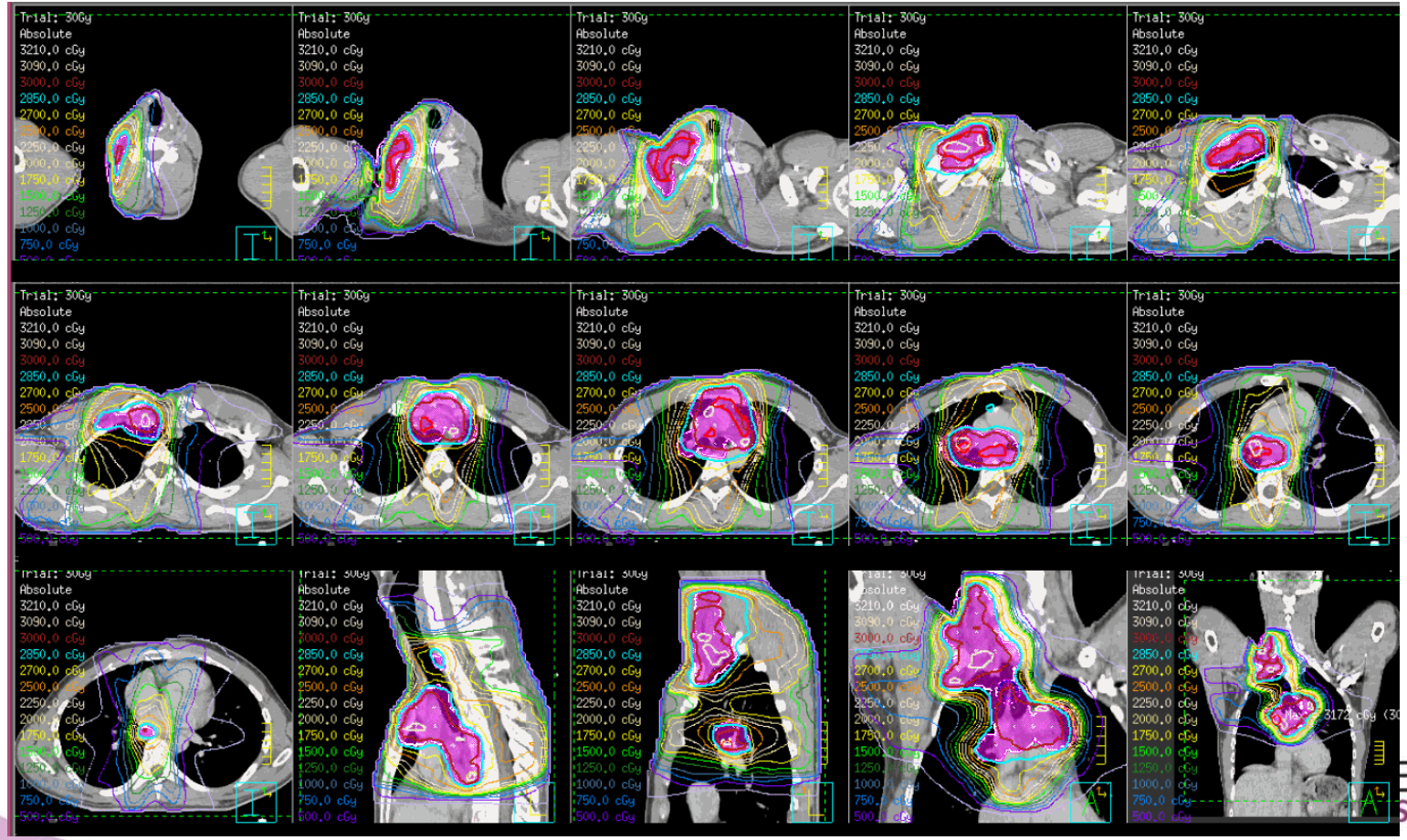
Dutch HL case

Conclusion: 29-year old man with stage II_2A favorable HL

Treatment: 3 ABVD + INRT 30 Gy/ 15 fractions

Chemotherapy and radiotherapy were well tolerated. Last RT on 24 March 2014.

Dutch HL case - IMRT plan



Dutch HL case - IMRT plan

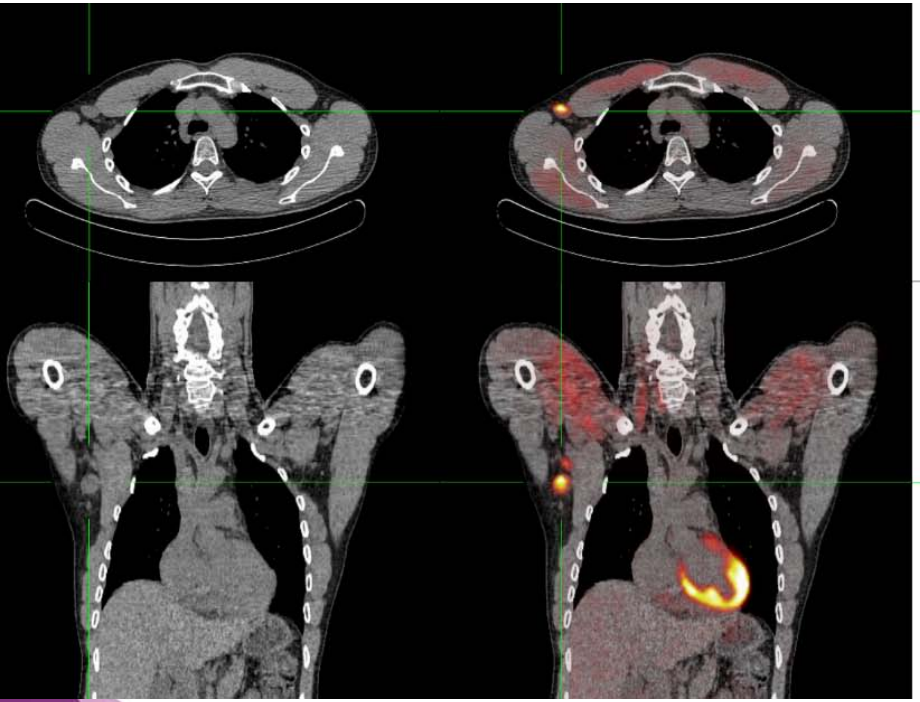
- Mean heart dose: 3.8 Gy
- Mean lung dose: 7.0 Gy

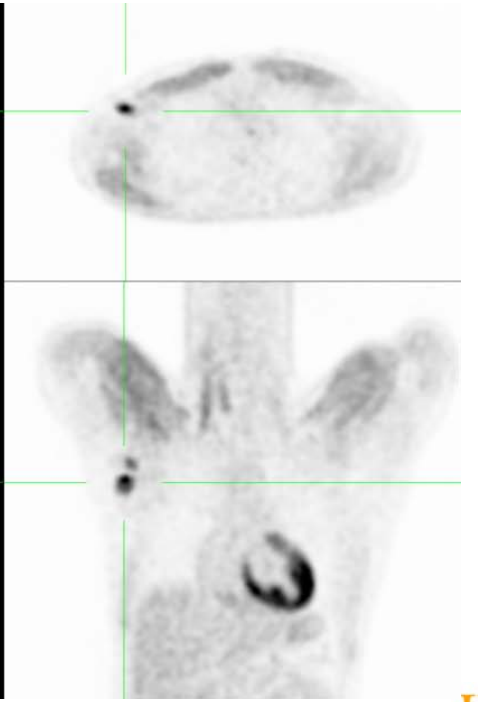
Dutch HL case - continued

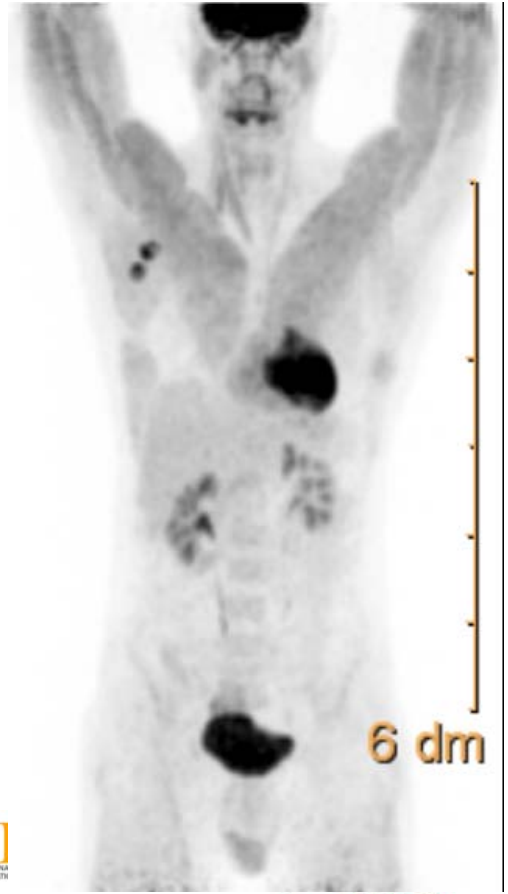
- Patient recovered normally after treatment

- [9]2014 patient discovered enlarged node in right axilla
- Ultrasound right axilla: multiple enlarged lymph nodes. Largest: 2 cm in diameter
- Cytology: tumor positive – consistent with Hodgkin lymphoma

Dutch HL case PETCT ^{9}2014

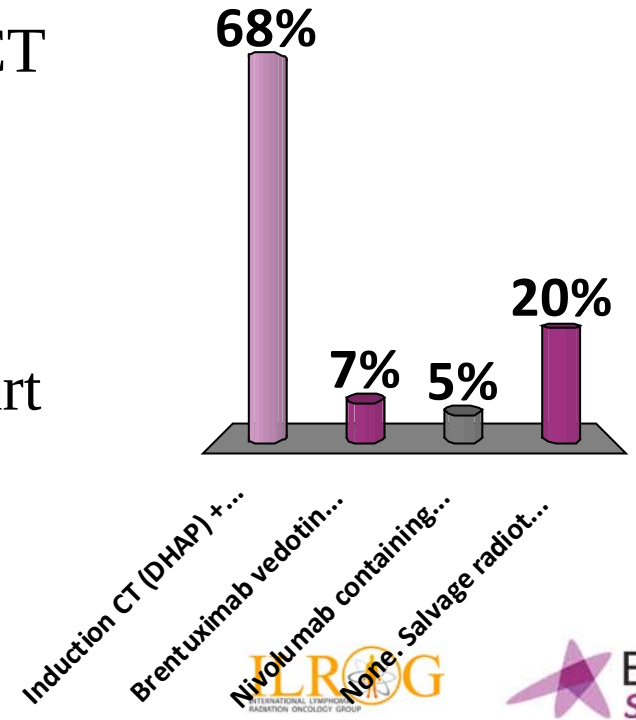






Which systemic treatment would you give for this localized recurrence 6 months after finishing primary treatment?

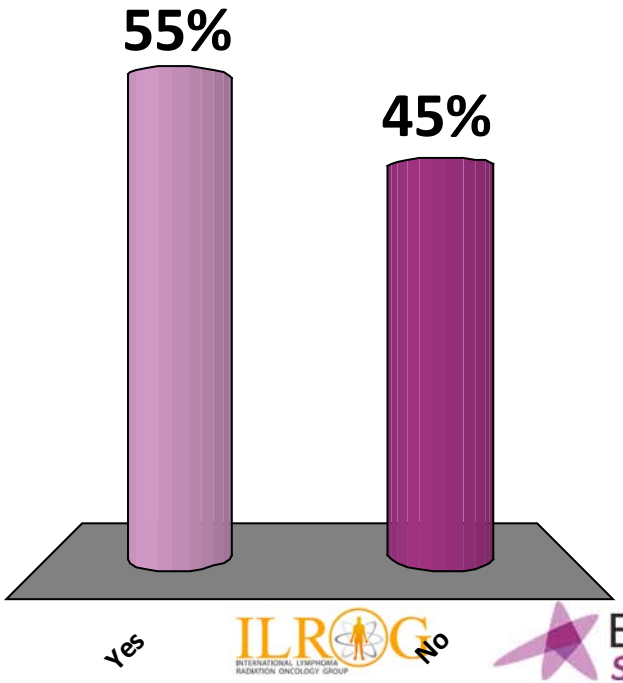
A. Induction CT (DHAP) + high dose CT + peripheral stem cell transplant
B. Brentuximab vedotin containing regimen
C. Nivolumab containing regimen as part of a trial
D. None. Salvage radiotherapy to axilla only



Would you give consolidation RT to right axilla?

A. Yes

B. No



Transplant BRAVE study

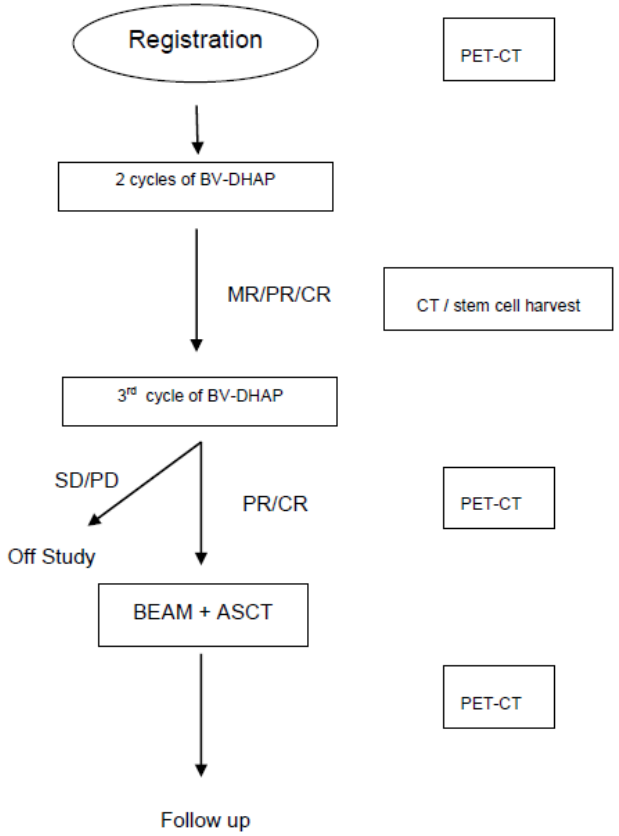
A prospective, multicenter, international phase I/II clinical trial consisting of a dose-finding phase 1 part, followed by a single-arm, non-randomized phase 2 part.

Rationale:

- Combining Brentuximab Vedotin with DHAP chemotherapy in patients with Hodgkin lymphoma (HL) refractory to first line chemotherapy or in first relapse is expected to induce a **significantly higher (metabolic) CR** rate prior to consolidation with BEAM
- Comparison with **published data on DHAP salvage only**.
- Increasing metabolic CR rate prior to consolidation with high dose chemotherapy and autologous SCT is expected to improve PFS and OS

Transplant BRAVE study

HL ≥18 yr, refractory to first line chemotherapy or first relapse



BV: Brentuximab Vedotin

ASCT: Autologous Stem Cell Transplantation

Dutch HL case - continued

- Patient achieved a CR after therapy
- Recovering. Physically OK, mentally a bit more difficult

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Case extranodal NHL woman born 1973

Medical history:

- 1996-08: Lump right breast. No other symptoms.
  Conclusion: diffuse large B-cellymphoma left breast stage IE.

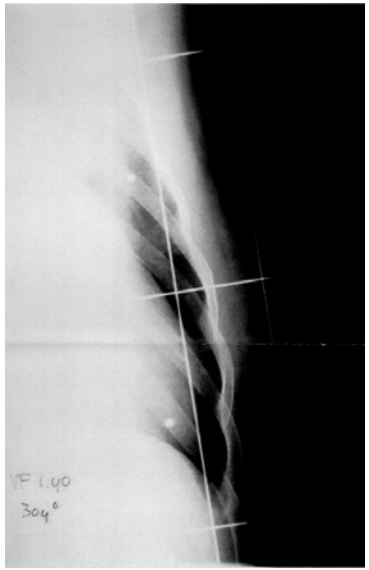
Treatment anno 1996 for 23-year old woman with stage IE DLBCL breast?

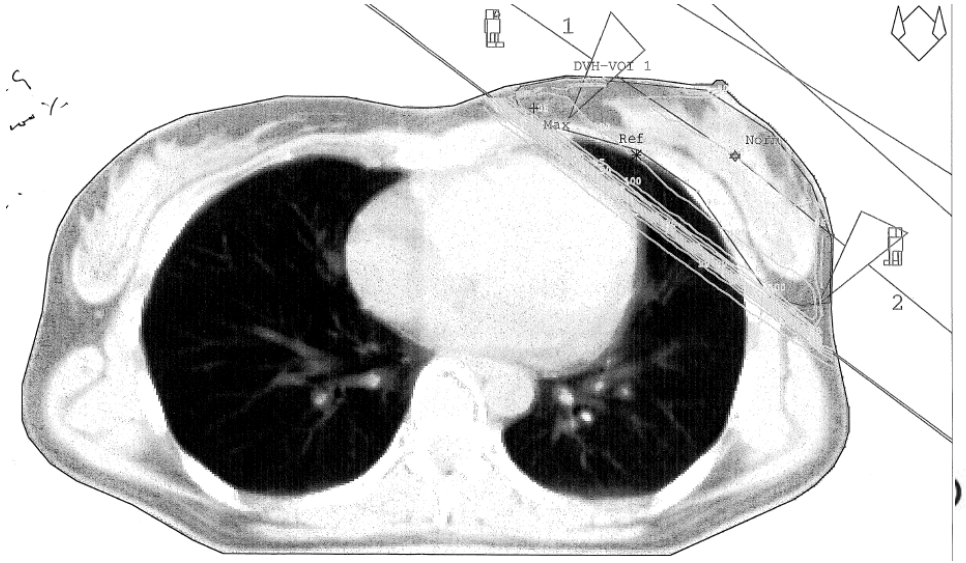
A. 6 x CHOP
B. 6 x R-CHOP
C. 3 x CHOP+radiotherapy to breast and axillary and supraclavicular nodes
D. 3 x CHOP+radiotherapy to breast and axillary nodes
E. 3 x CHOP+radiotherapy to breast only

Case extranodal NHL woman born 1973

Medical history:

- 1996-08: Diffuse large B-cellymphoma left breast stage IE. Treatment: 3xCHOP + radiotherapy 30 Gy/15 fractions to left breast using tangential fields with wedges





Case extranodal NHL woman born 1973

Medical history:

- 1996-08: Diffuse large B-cel lymphoma left breast stage IE. Treatment: 3xCHOP radiotherapy 30 Gy/15 fractions to left breast. Result: complete remission. Regular follow up
- 2002: Depression
- 2004: Artralgias
- 2014-07: Patient discovered lump right breast

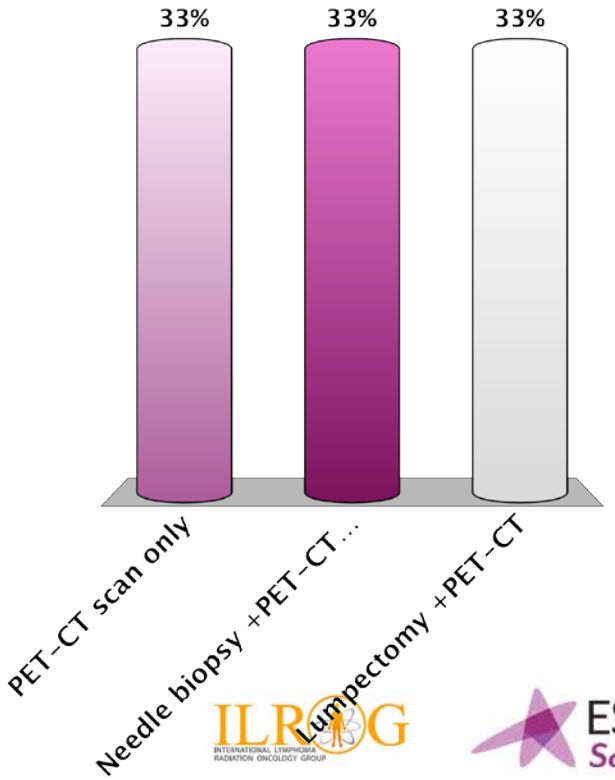
Case extranodal NHL woman 1973

Medical history:

- Physical examination:lump lower lateral quadrant right breast 1-1.5 cm
- Mammography: no abnormalities
- Ultrasound breast: cluster of 3 hypo-echoic laesions; total diameter: 3.5 cm
- Ultrasound axilla: multiple lymph nodes, 7.5 mm short axis, cortex >2.3mm in some.
- Cytology: possibly lymphoma in breast (monoclonal B-cel population); lymph node: no abnormalities.
- Lab: no abnormalities

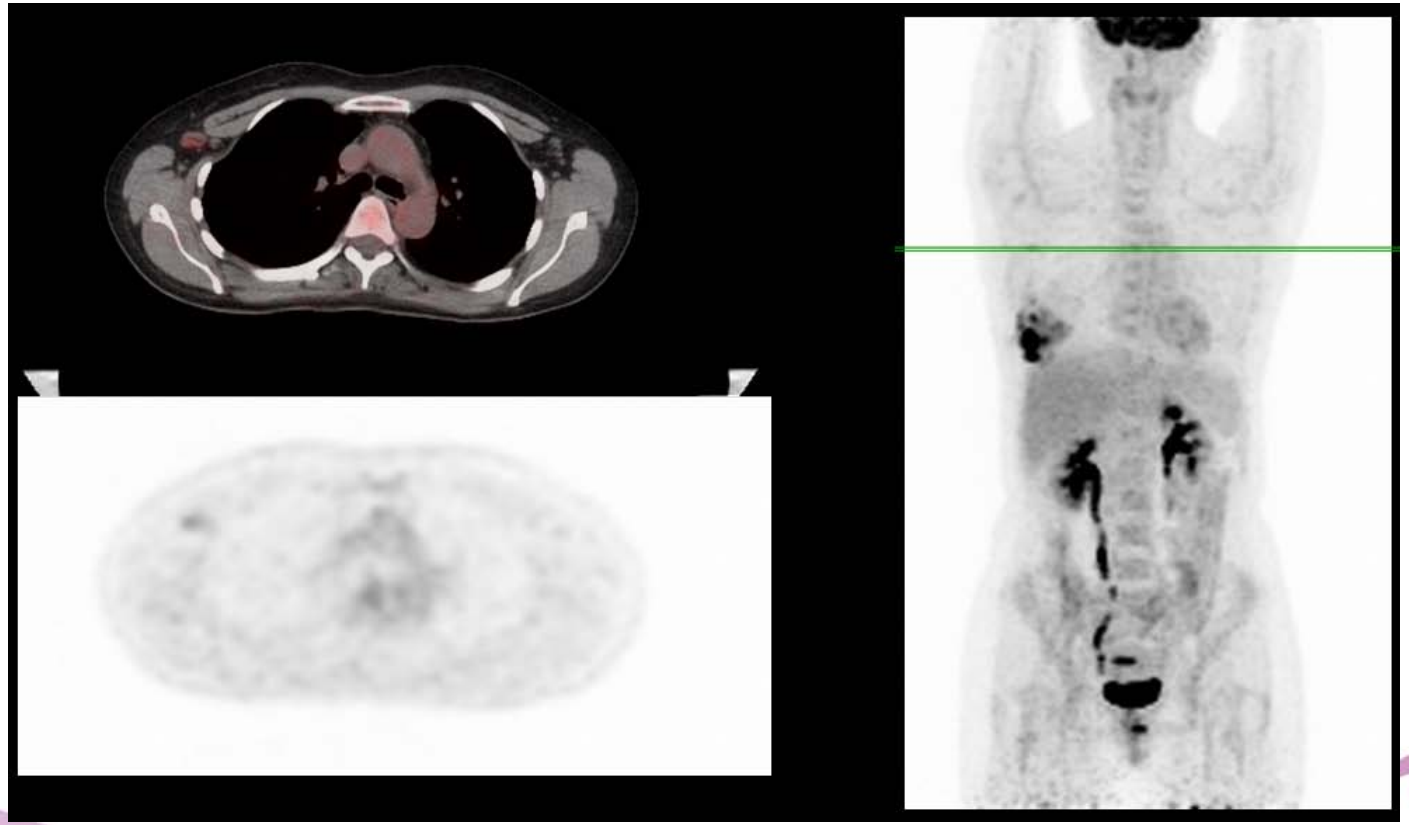
What would be your next step?

A. PET-CT scan only
B. Needle biopsy +PET-CT scan
C. Lumpectomy +PET-CT



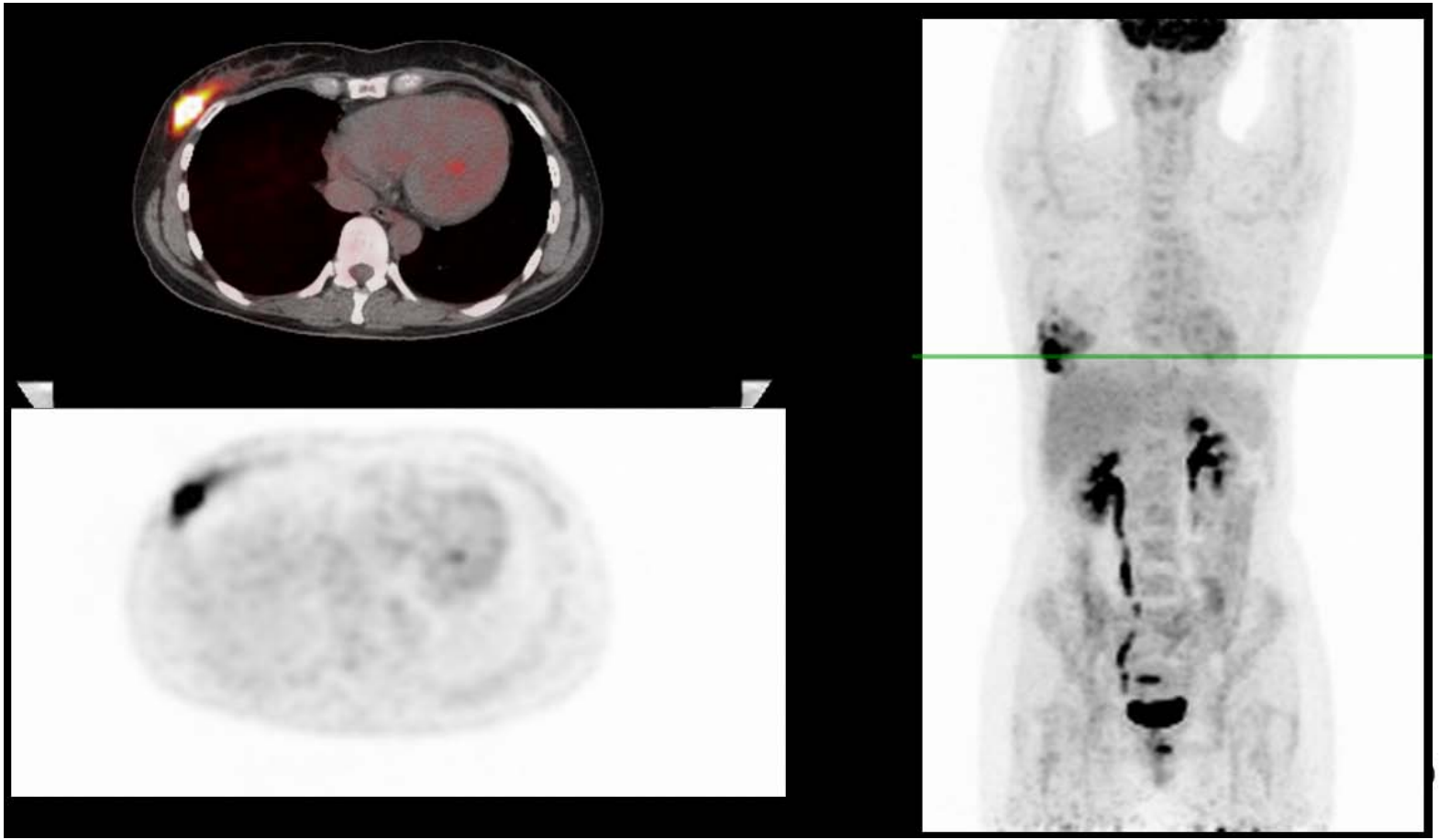
Case extranodal NHL woman born 1973

Pathology needle biopsy: diffuse large B-cellymphoma



Case extranodal NHL woman born 1973

PET-CT:



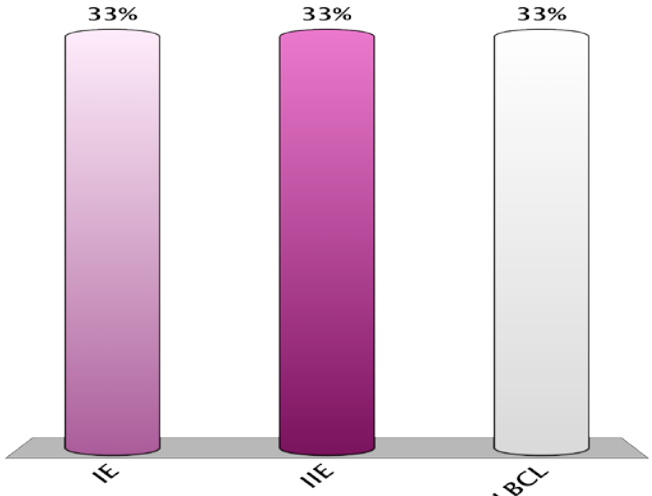
Conclusion:
Diffuse large B-cel lymphoma right breast with on PETCT some increase FDG uptake (IPI low).

What is the stage?

A. IE

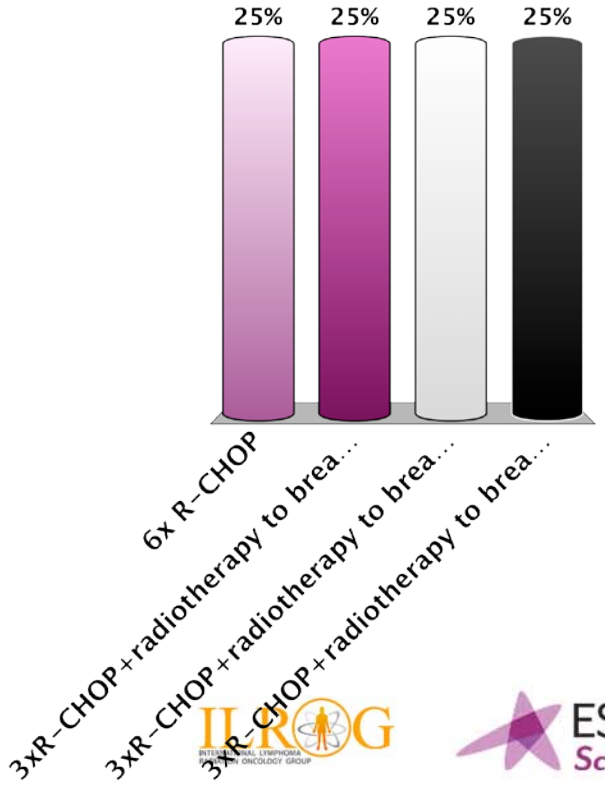
B. IIE

C. Relapse DLBCL



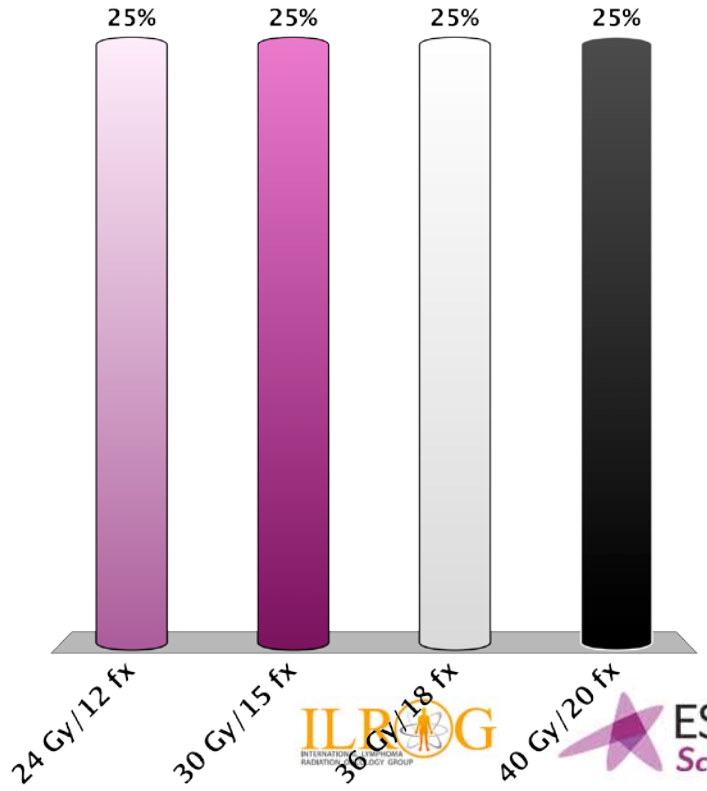
How would you treat this patient?

1. 6x R-CHOP
2. 3xR-CHOP+radiotherapy to breast and axillary and supraclavicular nodes
3. 3xR-CHOP+radiotherapy to breast and axillary nodes (level 1 and 2)
4. 3xR-CHOP+radiotherapy to breast only



RT dose in case of metabolic CR after 3 R-CHOP?

A. 24 Gy/12 fx
B. 30 Gy/15 fx
C. 36 Gy/18 fx
D. 40 Gy/20 fx

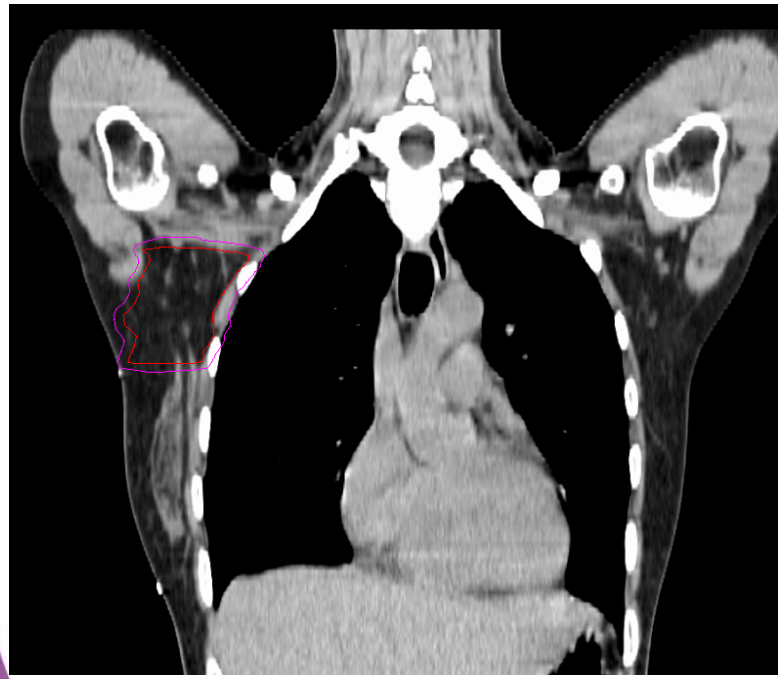


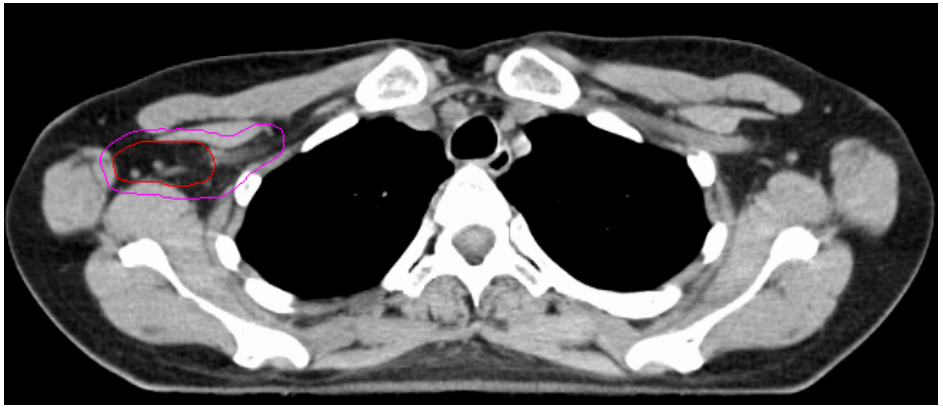
Case extranodal NHL woman born 1973

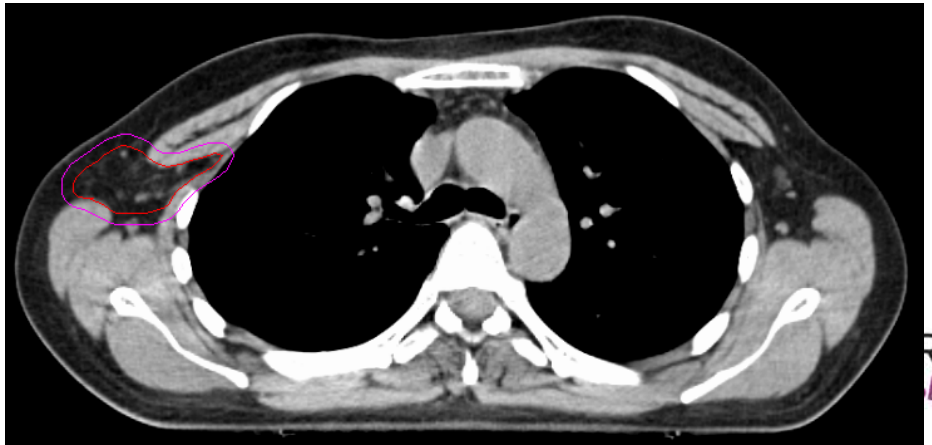
Conclusion:

- 2014-08: Diffuse large B-cel lymphoma right breast stage IE. Metabolic CR on 3xR-CHOP. Consolidation radiotherapy 30 Gy/15 fx to right breast including level 1 and 2

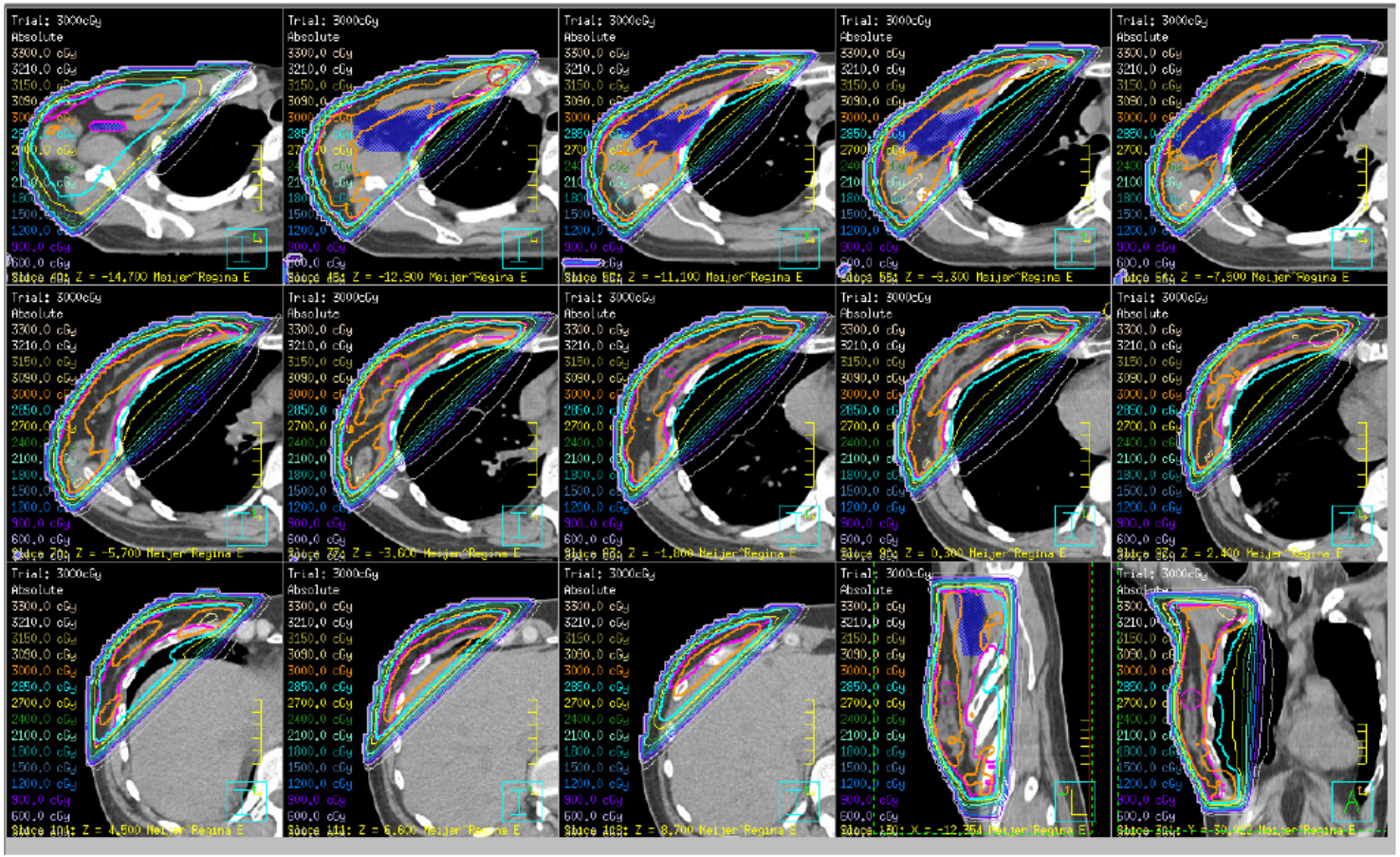
Case extranodal NHL woman born 1973







Case extranodal NHL woman born 1973



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Case extranodal NHL woman born 1981

Medical history:

2000 Breast enlargement

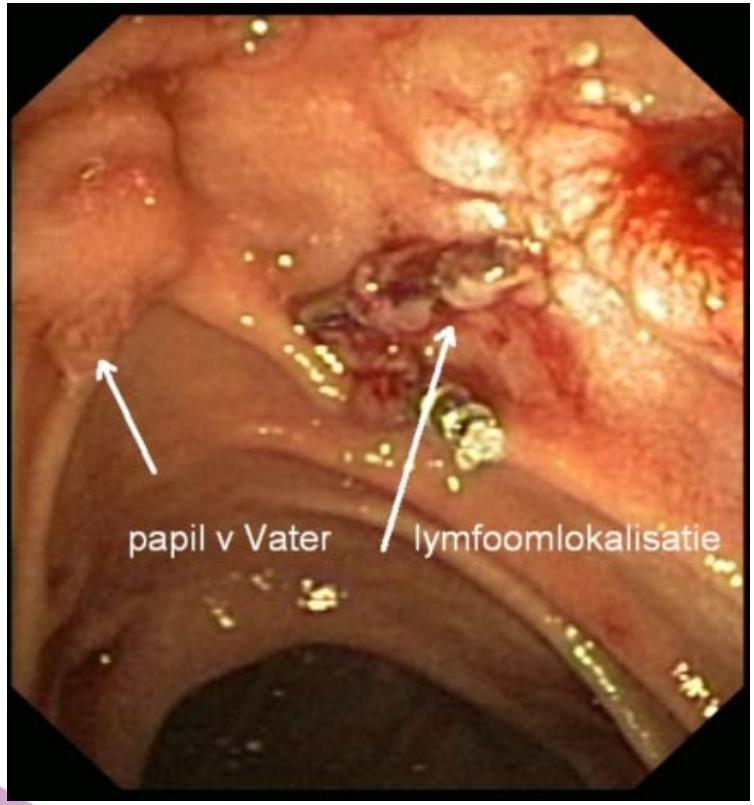
2012 Analysis of abdominal complaints (loss of appetite, sometimes pain upper abdomen, weight loss about 10 kg)

Physical examination: no abnormalities

Lab: no abnormalities

Gastroscopy: in duodenum at level of Vater's papilla irregular mucosa area with diameter of a couple of cm

Case extranodal NHL woman born 1981



PA: low grade NHL, best qualified as follicular lymphoma

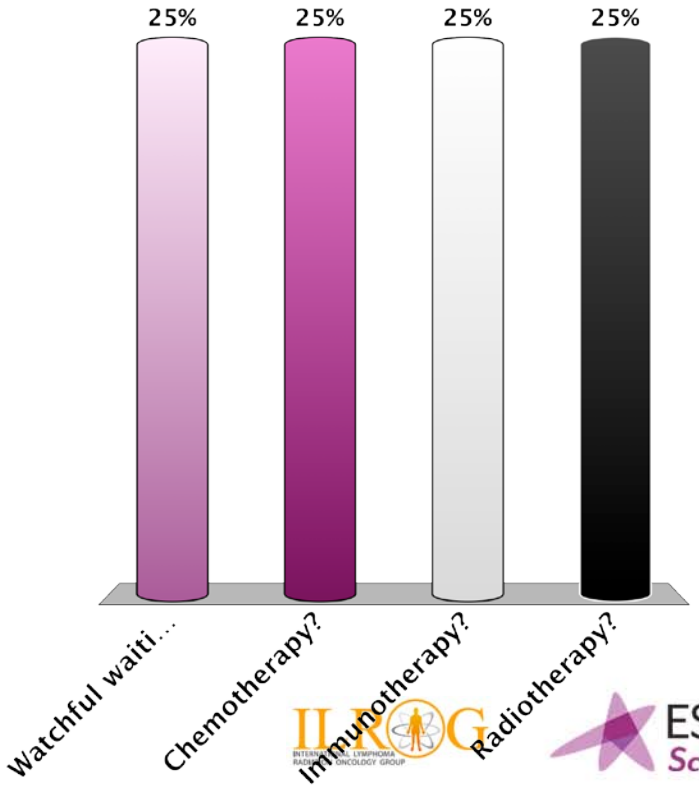
PET-CT scan: no abnormalities

CT-abdomen: no abnormalities

C: 31-year old woman with stage IE low grade NHL (follicular) in duodenum

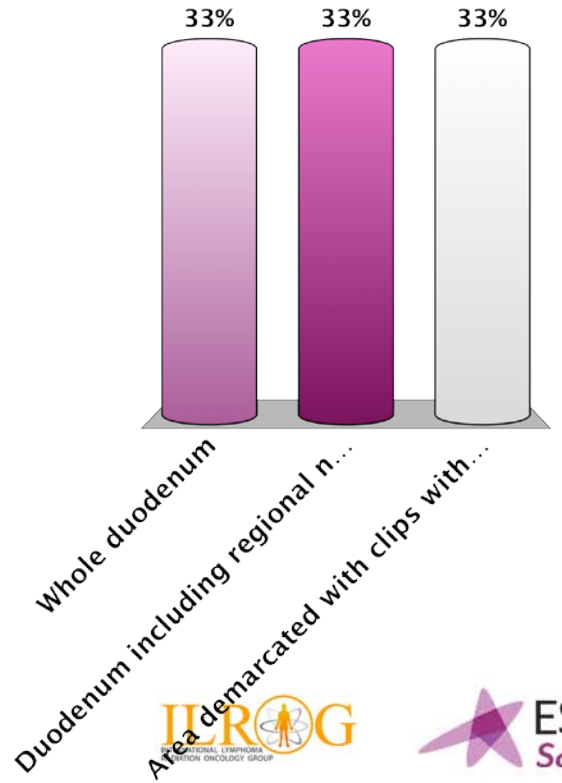
What would you do?

A. Watchful waiting?
B. Chemotherapy?
C. Immunotherapy?
D. Radiotherapy?



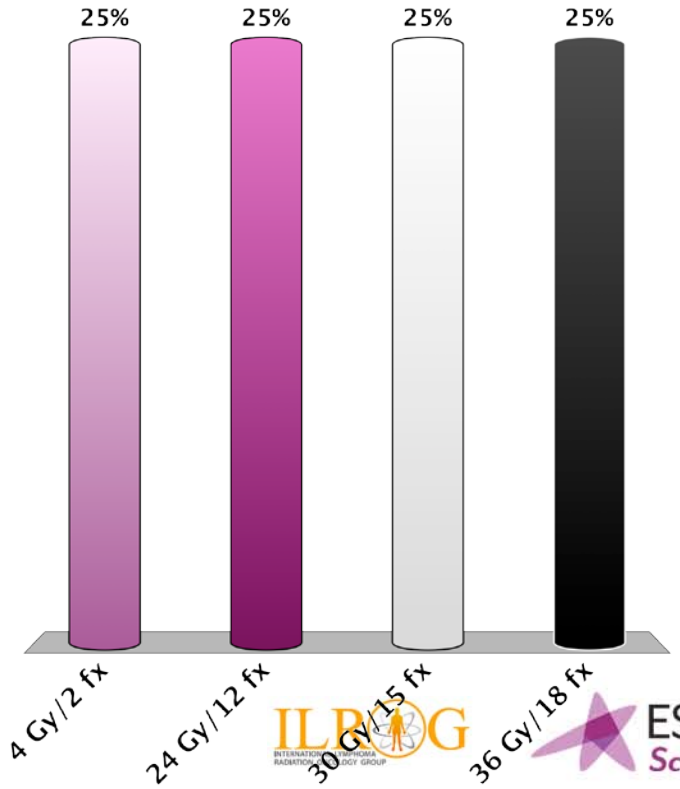
Target volume radiotherapy?

A. Whole duodenum
B. Duodenum including regional nodes
C. Area demarcated with clips with 2 cm margin

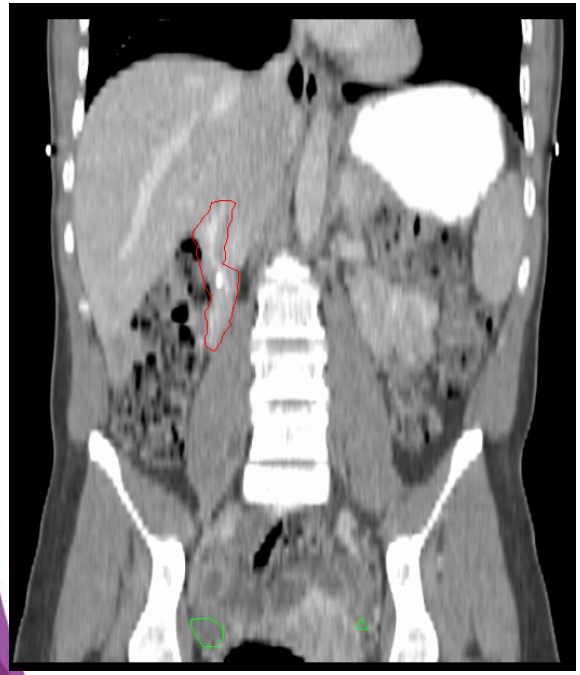


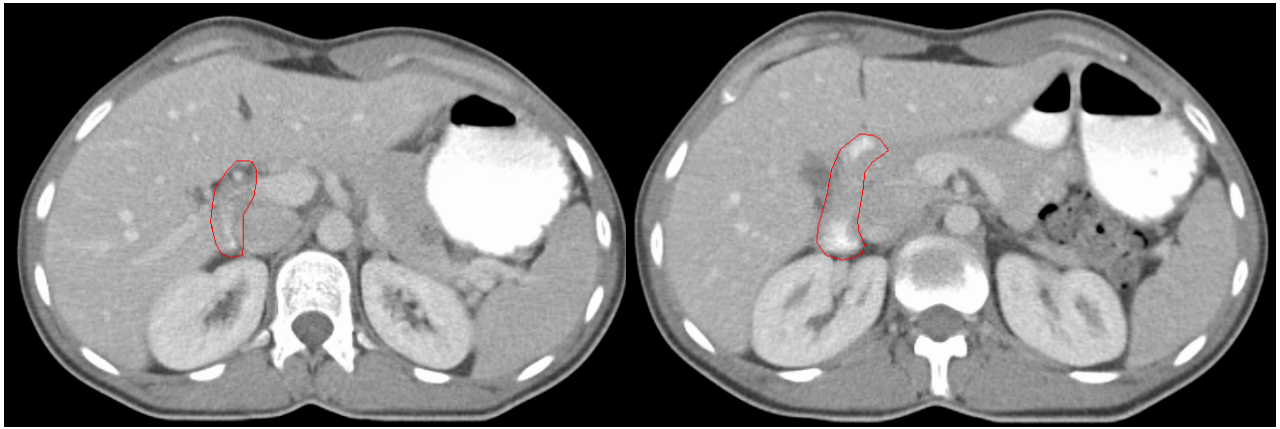
In case of RT what dose would you give?

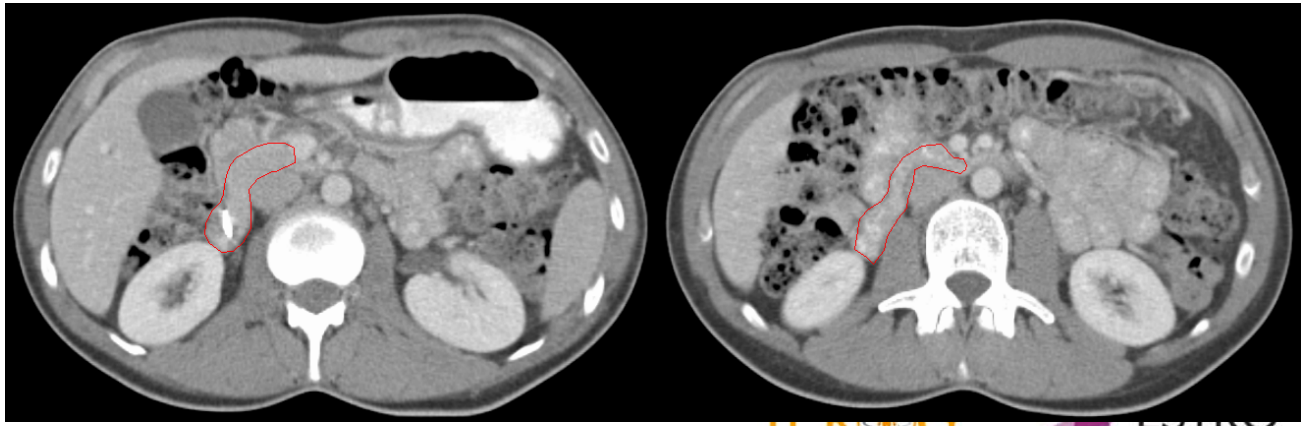
A. 4 Gy/2 fx
B. 24 Gy/12 fx
C. 30 Gy/15 fx
D. 36 Gy/18 fx



Case extranodal NHL woman born 1981

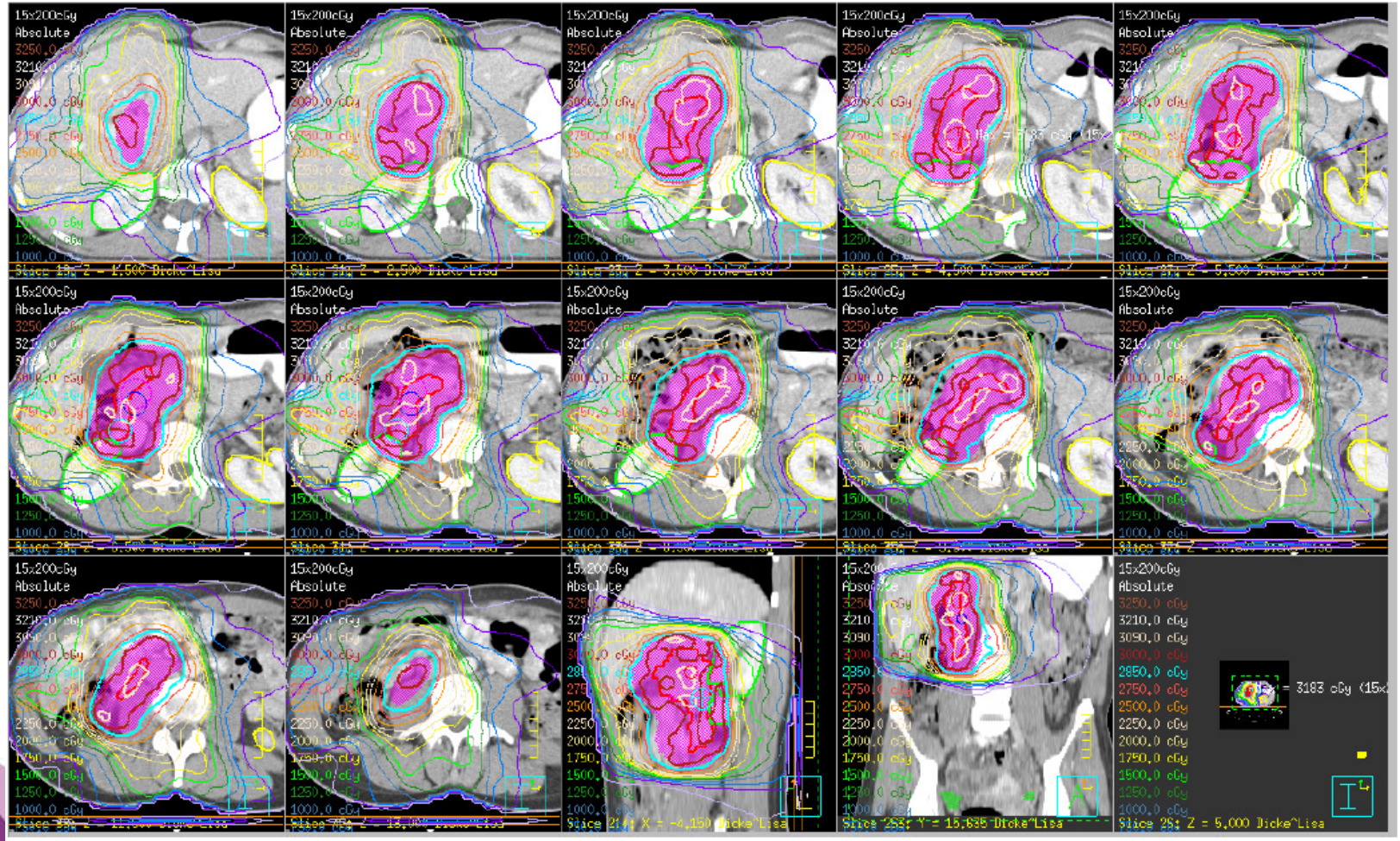






CTV in red

Case extranodal NHL woman born 1981



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Female 67

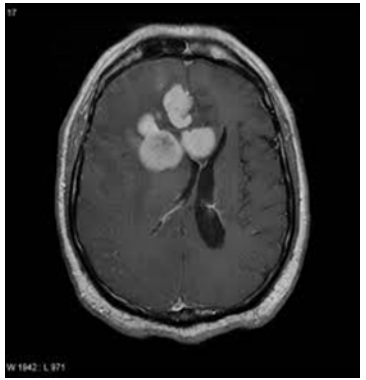
Long history of RhA. Multiple disease modifying agents

2010: IAE DLBCL breast.

R-CHOP x6 +IT MTX to CR

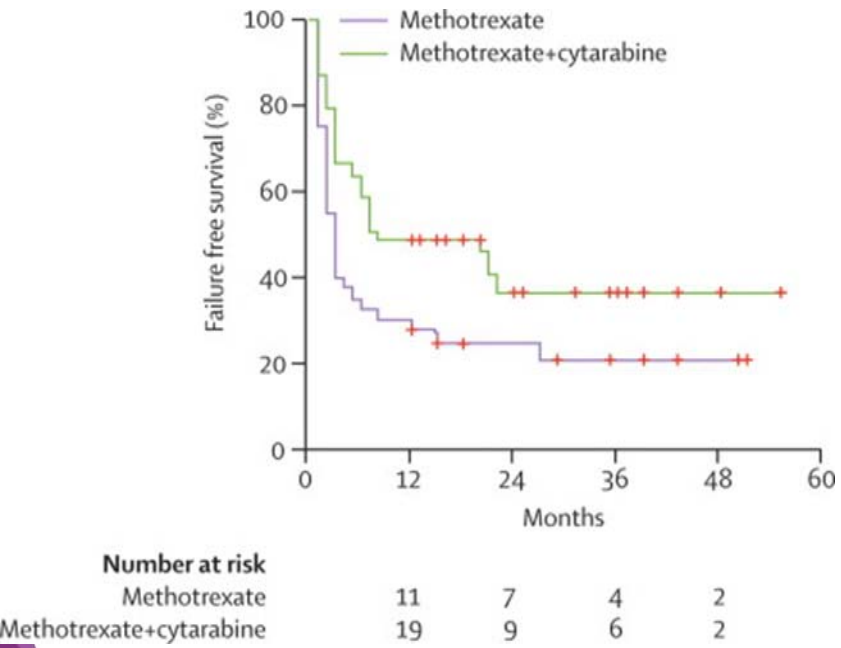
- Feb 2015: Confusion, disinhibition and left wakness. ECOG 3
- CT: multiple cerebral lesions suggestive of lymphoma
- Biopsy (eventually): DLBCL high proliferative fraction.

  ABC phenotype
- CT CAP: NAD



What therapy would you offer?

- WBRT
- Single agent methotrexate
- Methotrexate and cytarabine
- Rituximab, methotrexate and cytarabine
- Rituximab, methotrexate, cytarabine and thiotepa
- Other



	Methotrexate (n=40)	Methotrexate +cytarabine (n=39)	p value
Toxic deaths	1 (3%)	3 (8%)	0·35
Neutropenia	6 (15%)	35 (90%)	0·00001
Thrombocytopenia	3 (8%)	36 (92%)	0·00001
Anaemia	4 (10%)	18 (46%)	0·00001
Infective complications	1 (3%)	9 (23%)	0·0002
Hepatotoxicity	1 (3%)	4 (10%)	0·05
Nephrotoxicity	2 (5%)	1 (3%)	0·31
GI/mucositis	2 (5%)	1 (3%)	0·31
Cardiotoxicity	1 (3%)	1 (3%)	0·87
Neurotoxicity	0	1 (3%)	0·29
Coagulation/DVT	4 (10%)	1 (3%)	0·002

Ferreri et al. Lancet 2009

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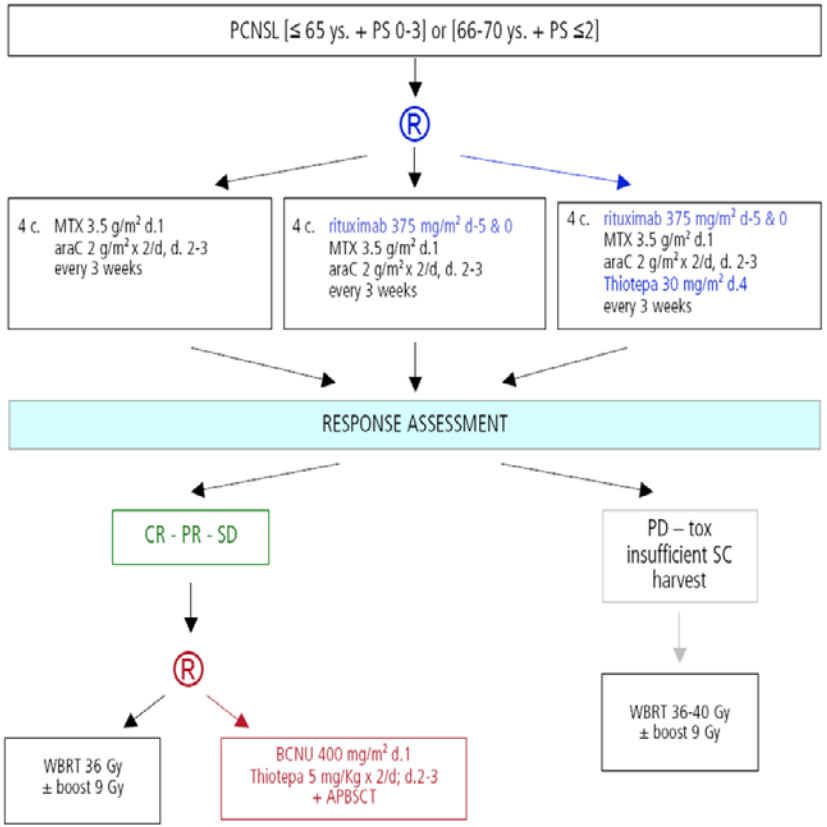
IELSG 32

- Rituximab improves outcomes for patients with systemic DLBCL but no randomised study has reported its impact on outcome of PCNSL
- Consolidation with WBRT improves survival but is associated with neurotoxicity and cognitive decline
- Single arm phase II data shows good outcomes with HDT and autologous PBSCT
- Could HDT+PBSCT replace WBRT?

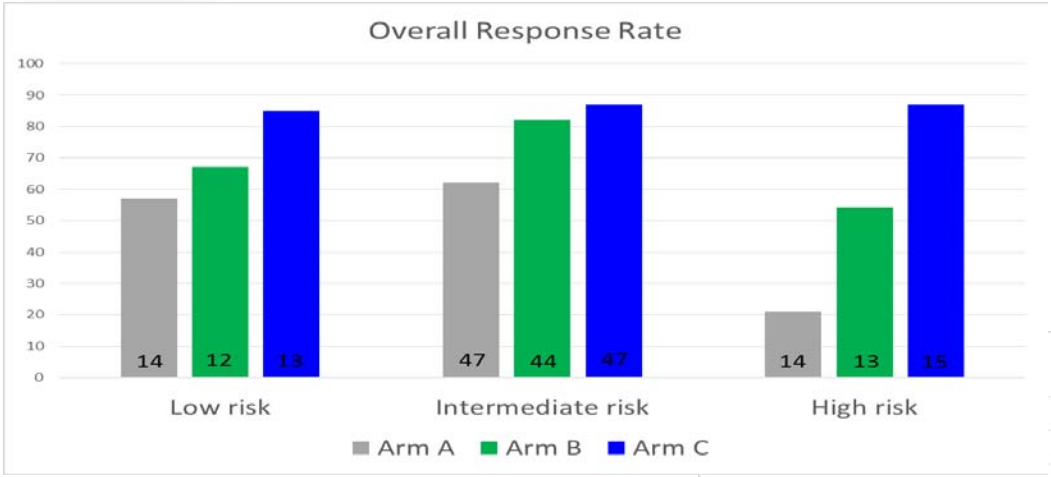
IELSG 32: Trial Design

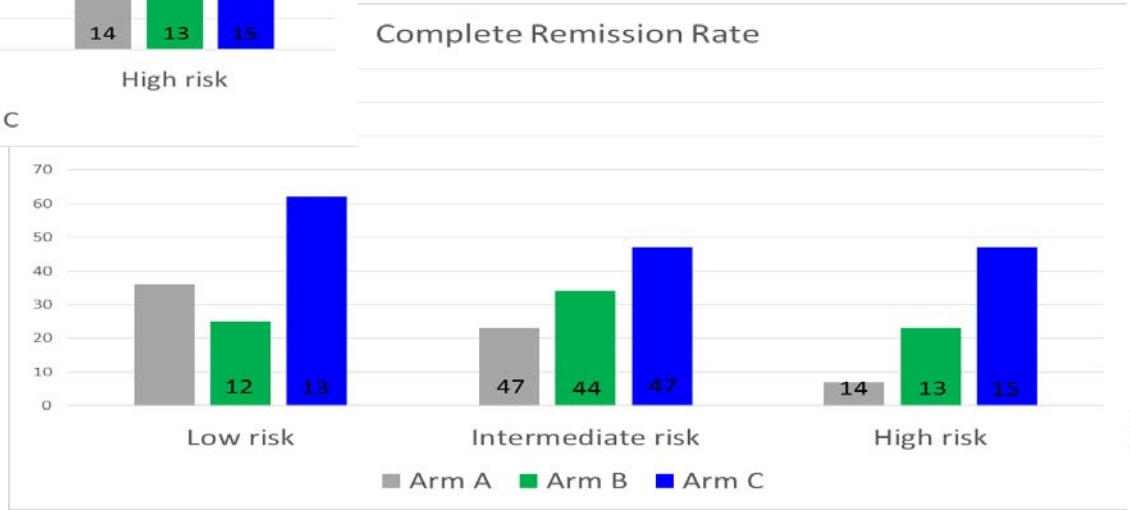


The addition of thiotepa and rituximab to MTX-ARAC (MATRIX) is associated with significantly improved CRR and ORR.

	A (n= 75)	B (n= 69)	C (n= 75)	p
CR	17 (23%) (95%CI= 14-31%)	21 (30%) (95%CI= 21-42%)	37 (49%) (95%CI= 38-60%)	A vs. B= 0.29 A vs. C= 0.0007 B vs. C= 0.02
PR	23 (31%)	30 (43%)	28 (37%)	
OR	40 (53%) (95%CI= 42-64%)	51 (74%) (95%CI= 64-84%)	65 (87%) (95%CI= 80-94%)	A vs. B= 0.01 A vs. C= 0.00001 B vs. C= 0.05
SD	6 (8%)	4 (6%)	1 (1%)	
PD	22 (29%)	11 (16%)	6 (8%)	
TD	7 (9%)	3 (4%)	3 (4%)	

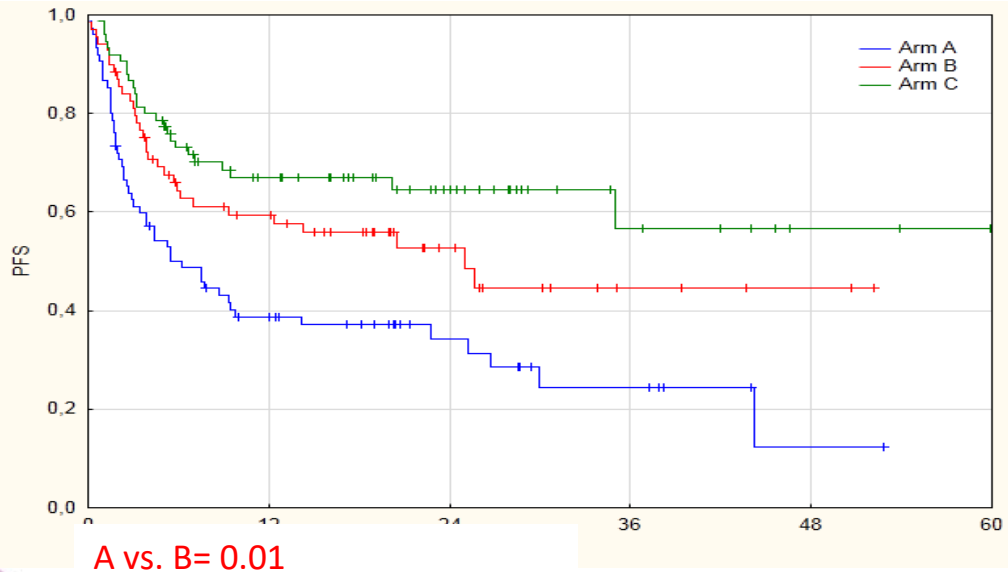
Positive effect was observed in all three IELSG risk groups





Preliminary results suggest a positive effect of these drugs on PFS

Median follow-up: 21 months (5-60)



A vs. B= 0.01
A vs. C= 0.00005
B vs. C= 0.13

110 (50%) pts remain failure-free
A: 24 (32%)
B: 37 (54%)
C: 49 (65%)

Failure: primary site involvement, usually the brain, in 97% of cases

Extra-CNS relapse in two pts.

No differences in salvage efficacy (65% of failed pts).

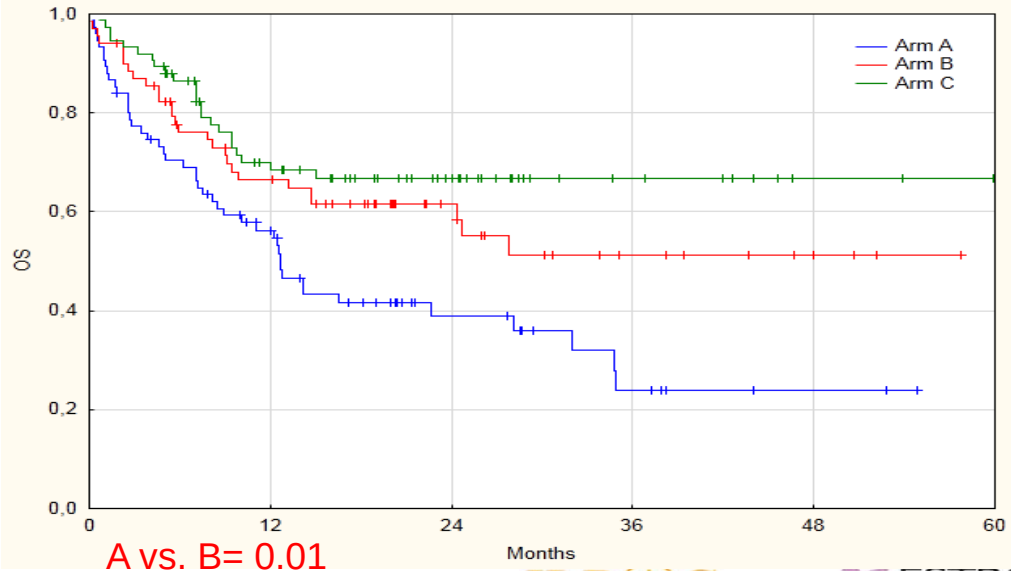
Addition of Rituximab + Thiotepa have a positive impact on OS

122 (56%) pts are alive
A: 29 (39%)
B: 41 (59%)
C: 52 (69%)

LTF: 6 pts (<3%)

Causes of death (n= 97):

- lymphoma	73
- toxicity (1° line)	15
- toxicity (salvage)	2
- neurotoxicity (rel-free)	2
- others while rel-free	4
- unknown	1



A vs. B= 0.01
A vs. C= 0.0005
B vs. C= 0.24

There is a good response to therapy.
Residual changes on imaging. CR(u)
ECOG 0 now

What next?

- Observation
- Consolidation with WBRT
- Consolidation with HDT

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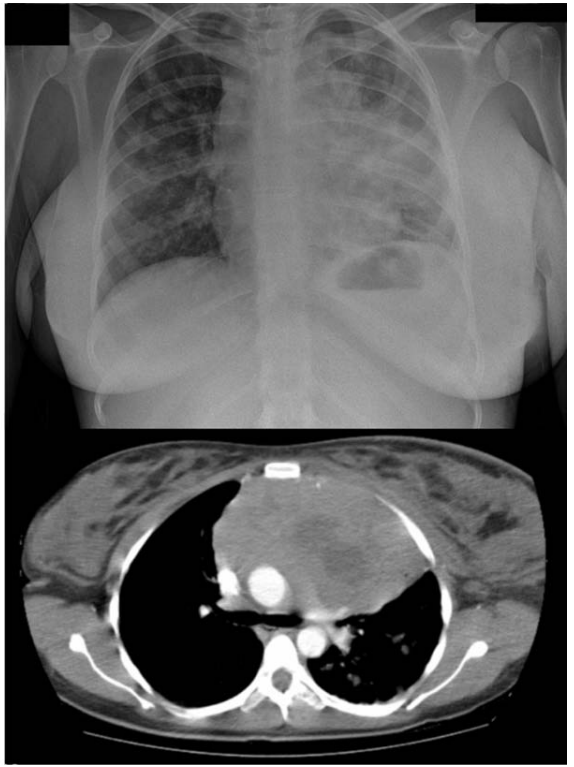
Primary Mediastinal B-Cell Lymphoma

Andy Davies
University of Southampton
a.davies@southampton.ac.uk
September 2016

Female 32 years old

- Presents with 6 week history of non-productive cough and progressive SOB
- In last 48 hours developed facial swelling and headache. ECOG 1
- Mediastinal mass on CXR
- CT: mediastinal mass with SVCO, breast oedma, small pleural effusions



- Percutaneous biopsy: Primary mediastinal B-cell lymphoma
- No B-symptoms
- LDH 1.5 xULN, FBC normal, normal renal and hepatic function. IPI 1

Clinical Features

- Rapidly growing mass of anterior mediastinum.
- Bulk common
- Young patient population
  (median age 35)
- Female predominance (2:1)
- Diagnosed as a result of symptoms compressing mediastinal structures.
  Superior vena caval obstruction present in 40%
- Recurrent laryngeal nerve palsy with resulting hoarse voice
- Breast swelling
- Cough/chest pain/dyspnoea
- Dysphagia

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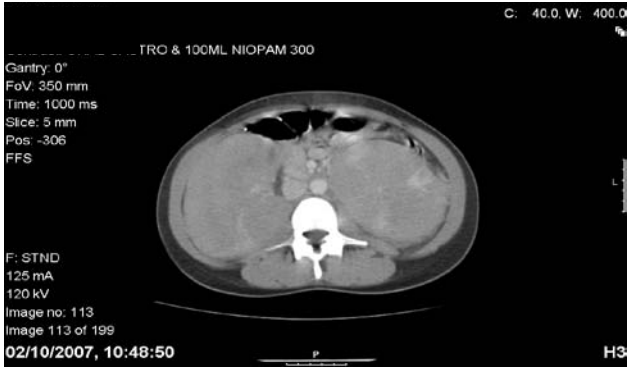
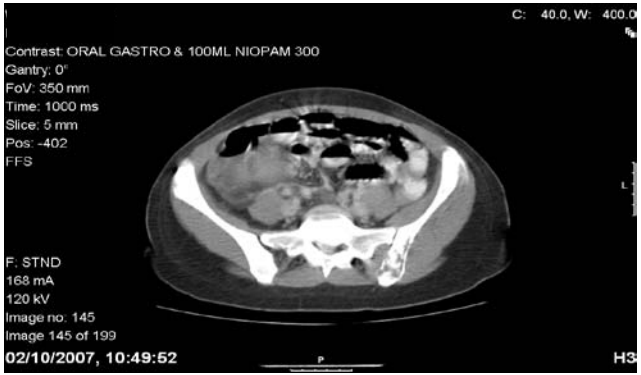
- Frequent invasion of local structures including pleura, pericardium and chest wall. Effusions common
- Involvement of bone marrow or extrathoraic structures uncommon.
- Usually stage I/II at presentation
- More typically at recurrence extranodal sites including kidney, adrenals, ovaries and CNS





Clinical Characteristics

Characteristic		Percentage (n=153)
Median age		37 years
Stage		
	I/II	74
	III/IV	26
Elevated LDH		77
Bulk (>10cm)		75
B symptoms		47
aaIPI		
	0	12
	1	49
	2	27
	3	12
Pleural or pericardial effusions		50

Savage et al. Ann Oncol. 2006 123-130

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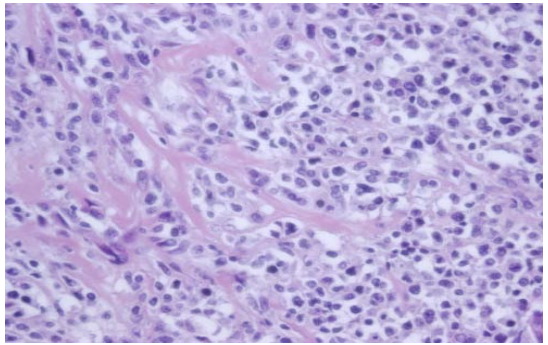
Pathology



Cytologically resembles many other large B cell lymphoma

Large transformed cells resembling centroblasts

Abundant pale cytoplasm

Diffuse involvement

marked areas of fine compartmentalising sclerosis

Expression of B-cell antigens:CD20 and CD79a positive, but lack sIg
CD30 may be present (>80%) although typically weak CD23: Frequent (73%)
BCL2: variable (50-80%, no t(14;18)
BCL6: variable (45-100%)
CD10: less common (8-30%)
Present: MAL (70%) – normal expression in thymic medullary cells, CD54, CD95, nuclear REL, TRAF
Evidence of somatic hypermutation

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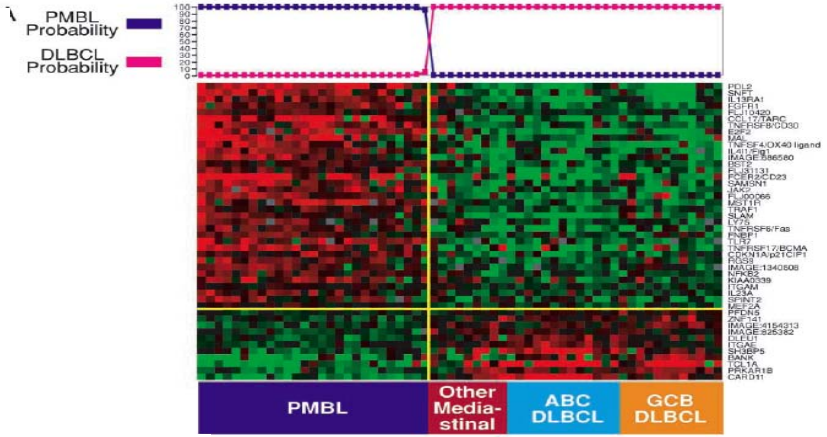
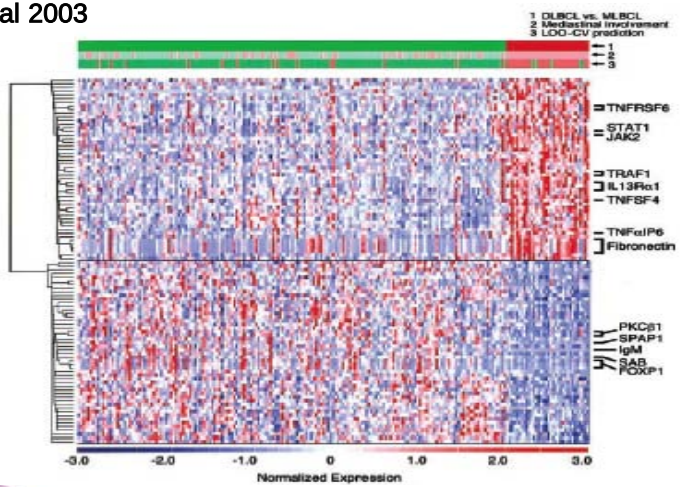
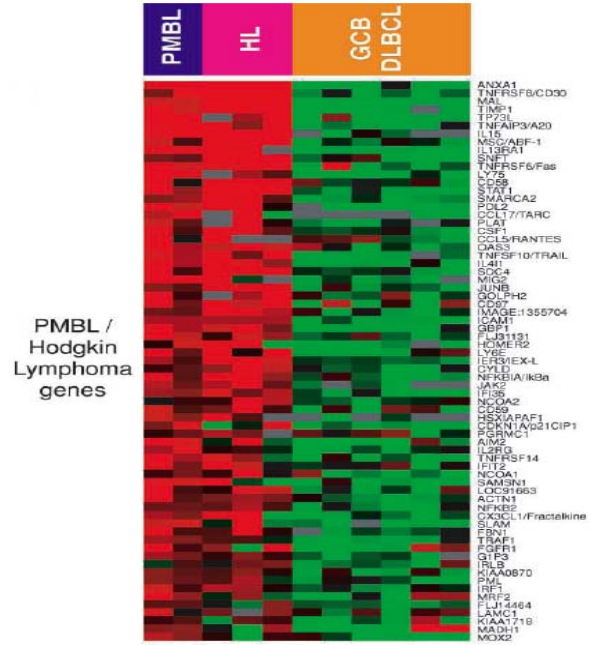
PMBL has a distinct pattern of gene expression



Rosenwald et al 2003



Savage et al 2003



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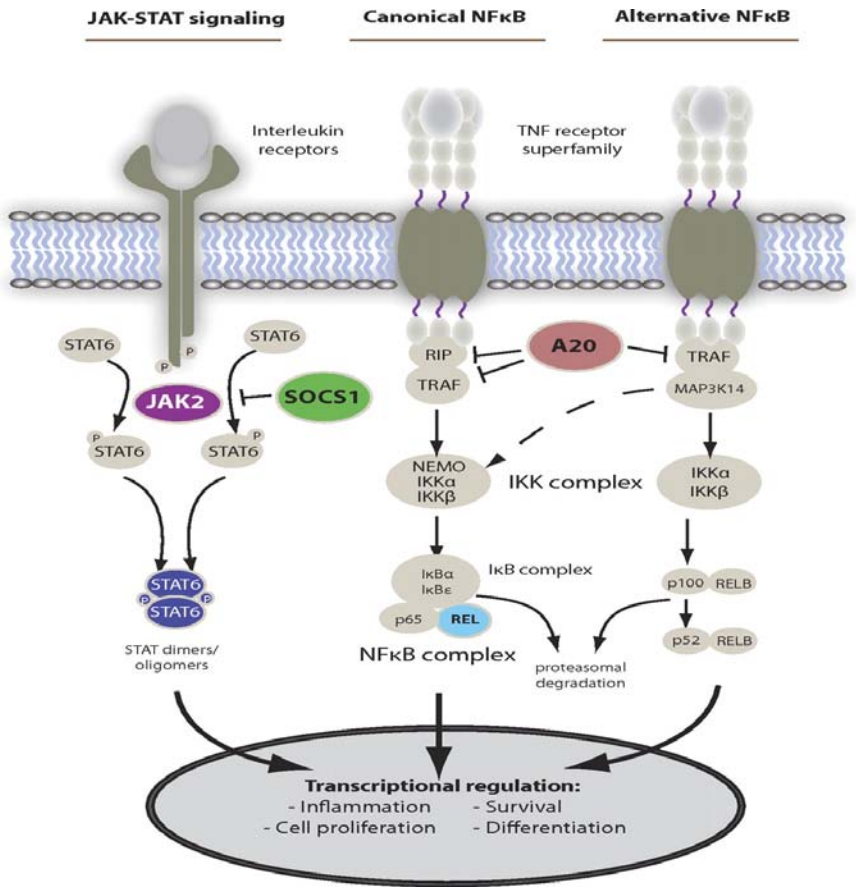
Aberration of two key pathways in PMBL

JAK-STAT



NF-κB

Steidl C , Gascoyne R D Blood 2011;118:2659-2669

Which immunochemotherapy would you offer?

A R-CHOP x6 -8

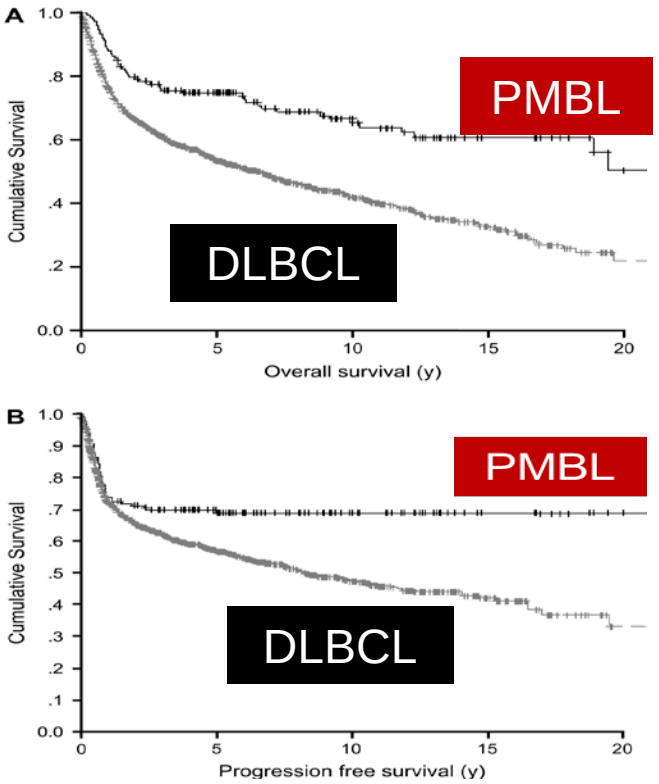
B DA-EPOCH-R

C R-MACOP-B/R-VACOP-B

D Induction followed by high-dose consolidation

Outcomes superior to DLBCL

Almost all recurrences within first 12-18 months



Savage, K. J. et al. Ann Oncol 2006 17:123-130

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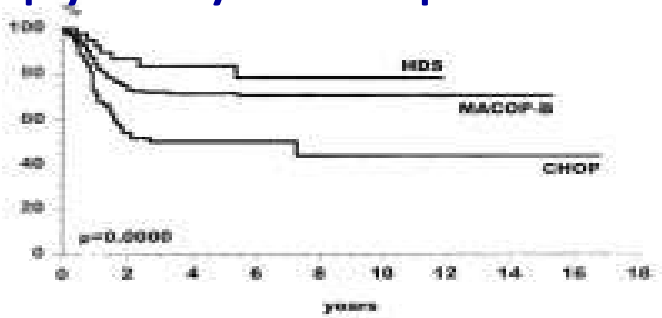
But…More intensive chemotherapy may be superior in PMBL

Zinzani et al 2002

Multinational retrospective (n=426), three different chemotherapeutic approaches

10yr OS	CHOP	44%
	3rd Generation	71%
	high-dose	77%

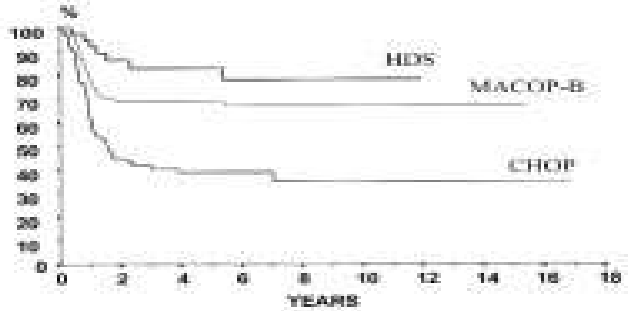


Overall survival with three different chemotherapeutic approaches

Todeschini *et al* 2004

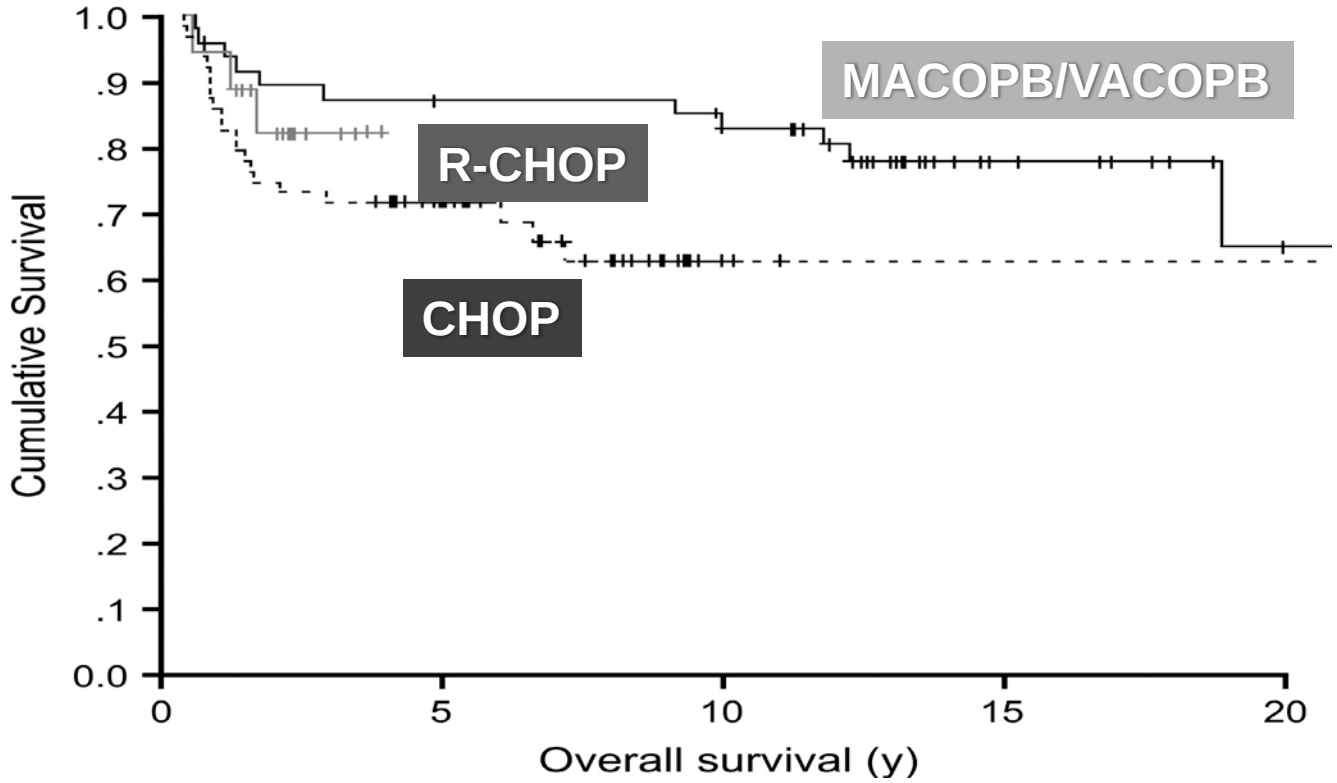
Italian multicentre retrospective (n=138)

CHOP (n=43)	CR 51%
MACOP-B (n=95)	CR 80%



Progression free survival with three different chemotherapeutic approaches

Zinzani et al 2002



Savage, K. J. et al. Ann Oncol 2006

CD20⁺ DLBCL
18-60 years
IPI 0,1
Stages II-IV,
I with bulk

Random.

6 x CHOP-like
+ 30-40 Gy (Bulk, E)

6 x CHOP-like
+ Rituximab
+ 30-40 Gy (Bulk, E)

Rieger M et al. Ann Oncol 2011;22:664-670

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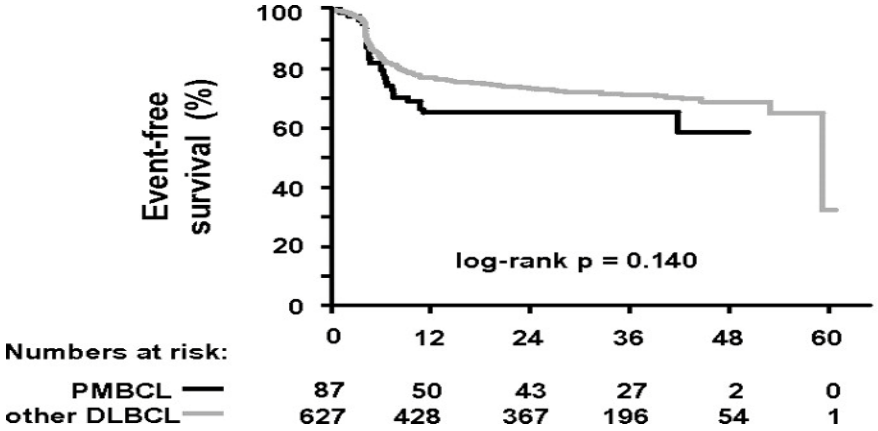
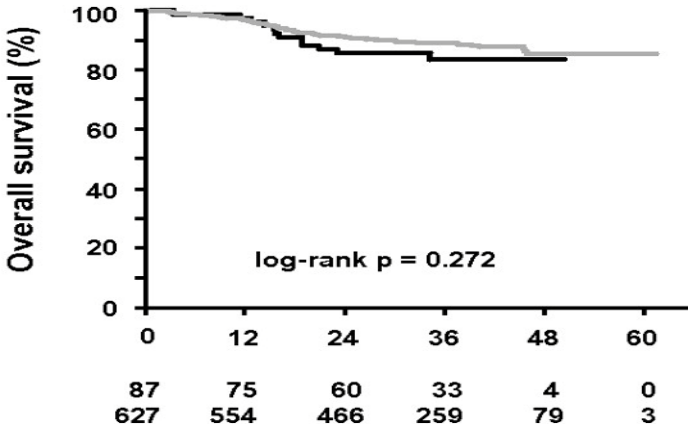
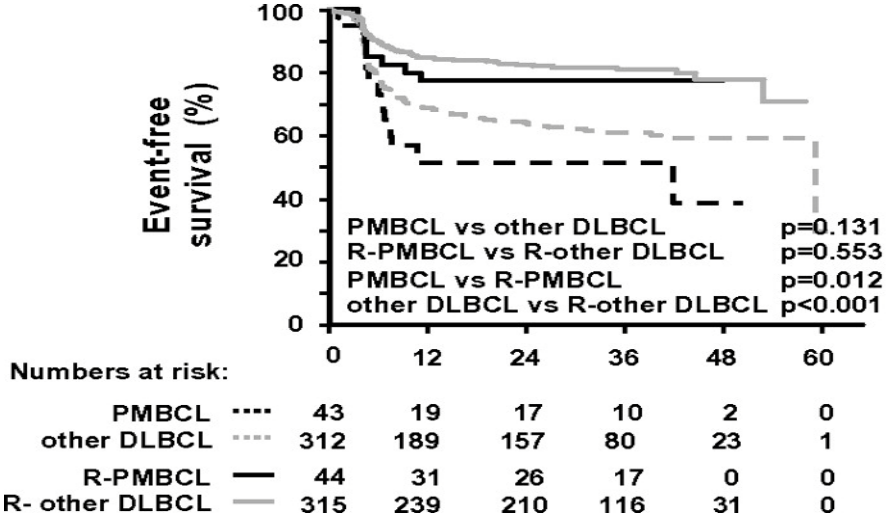
Characteristics	PMBCL patients (%)	DLBCL patients (%)	P value
n	87	627	
Age (years)			<0.001
Median (IQR)	36 (27–43)	46 (38–55)	
Range	19–59	18–60	
Sex			<0.001
Male	36 (41)	384 (61)	
Female	51 (59)	243 (39)	
Bulky disease	74 (85)	284 (45)	<0.001
B symptoms			
Yes	27 (31)	154 (25)	0.172
Extranodal sites			
>1	3 (3.4)	58 (9.3)	0.070
LDH			
> UNV	55 (63)	163 (26)	<0.001
>2 fold UNV	14 (16)	23 (3.7)	<0.001
ECOG performance status			
>1	3 (3.4)	3 (0.5)	0.027
Ann Arbor stage			
I/II	80 (92)	449 (72)	<0.001
BM involvement	2 (2.3)	36 (5.7)	0.303
IPI			<0.001
0	22 (25)	286 (46)	
1	65 (75)	341 (54)	

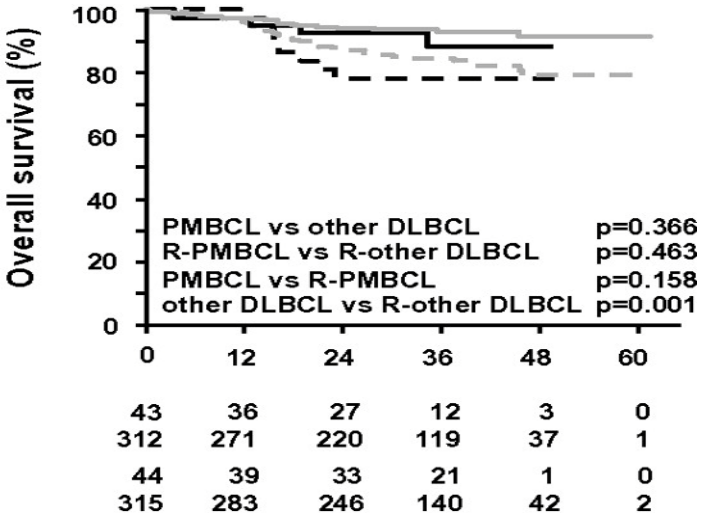
Survival of all patients with PMBCL and with DLBCL.





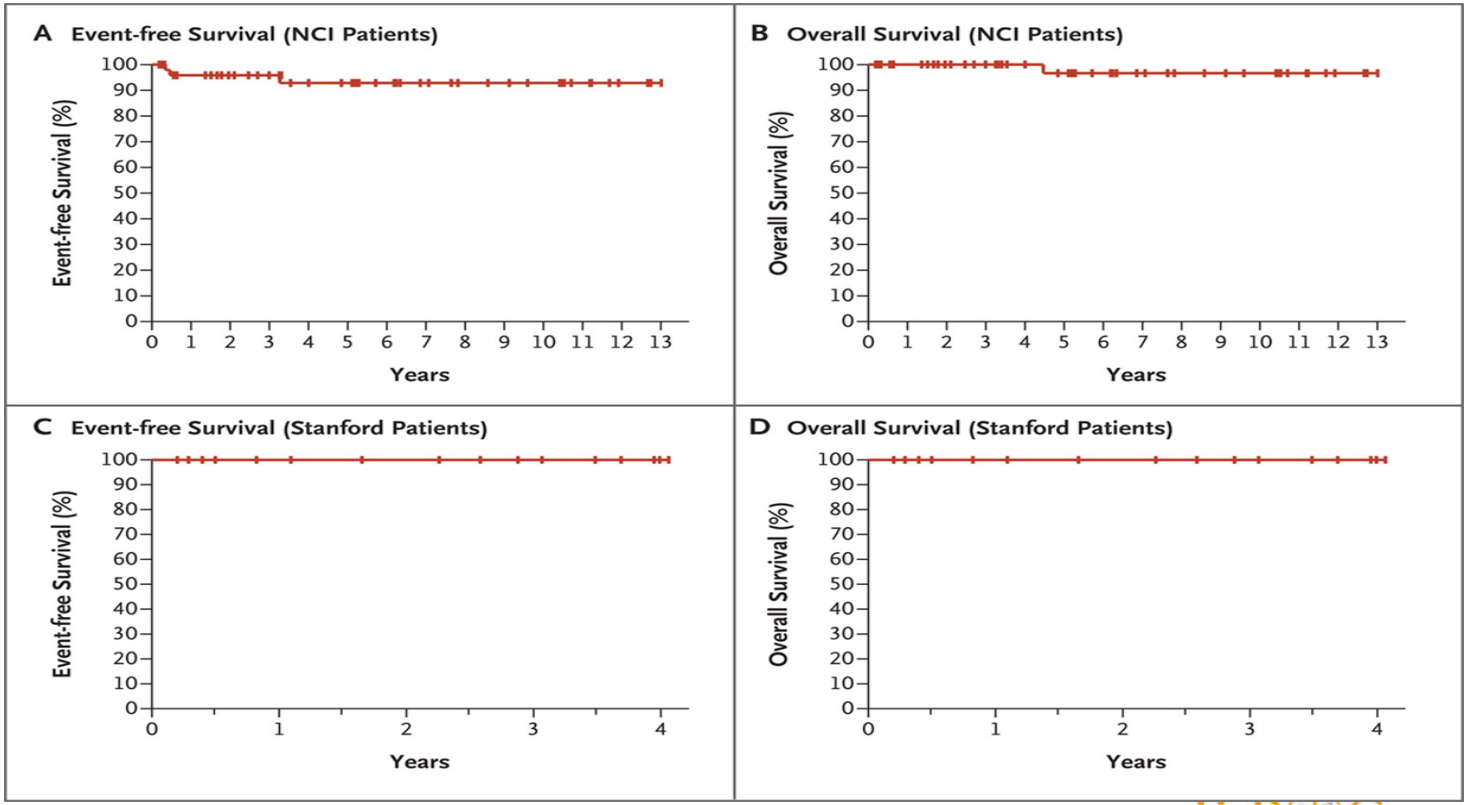
Rieger M et al. Ann Oncol 2011;22:664-670





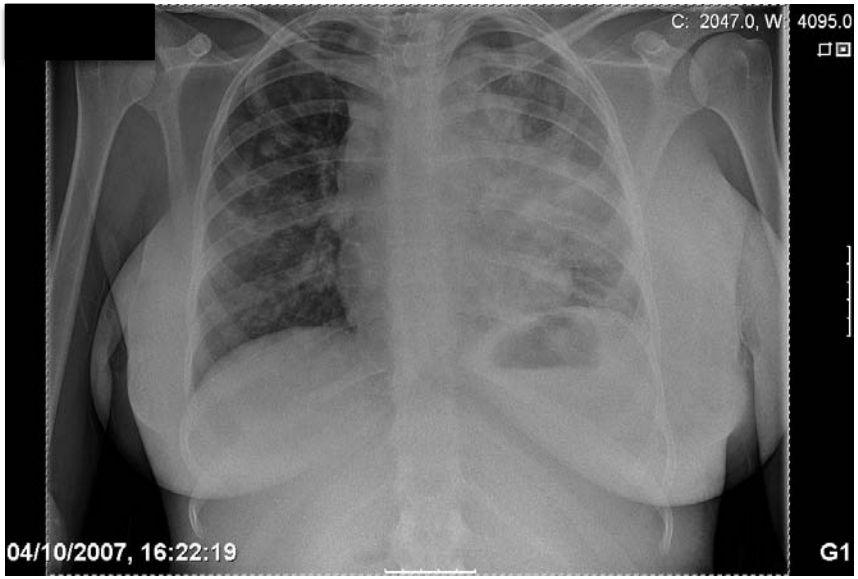
Rieger M et al. Ann Oncol 2011;22:664-670

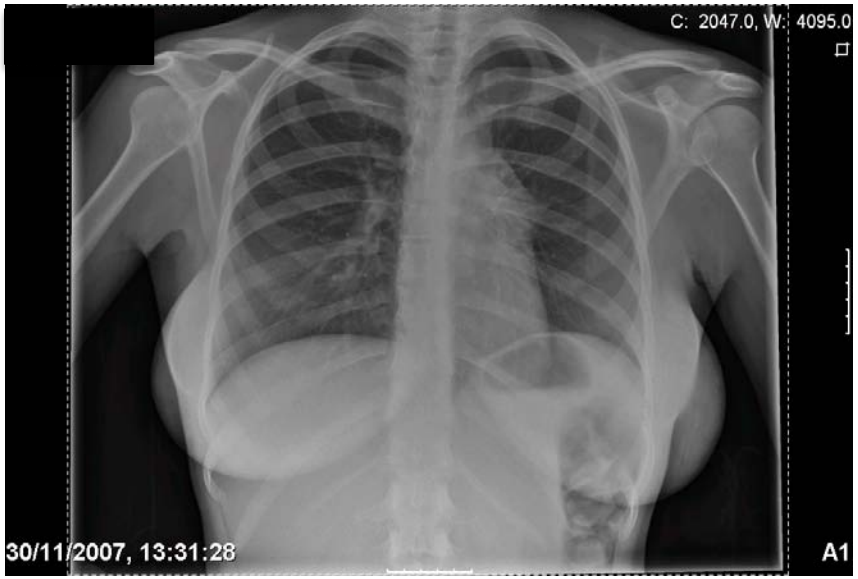
DA-EPOCH-R: Excellent results



Dunleavy K et al. N Engl J Med 2013;368:1408-1416.

What to do after chemotherapy?





Presentation

Post chemotherapy

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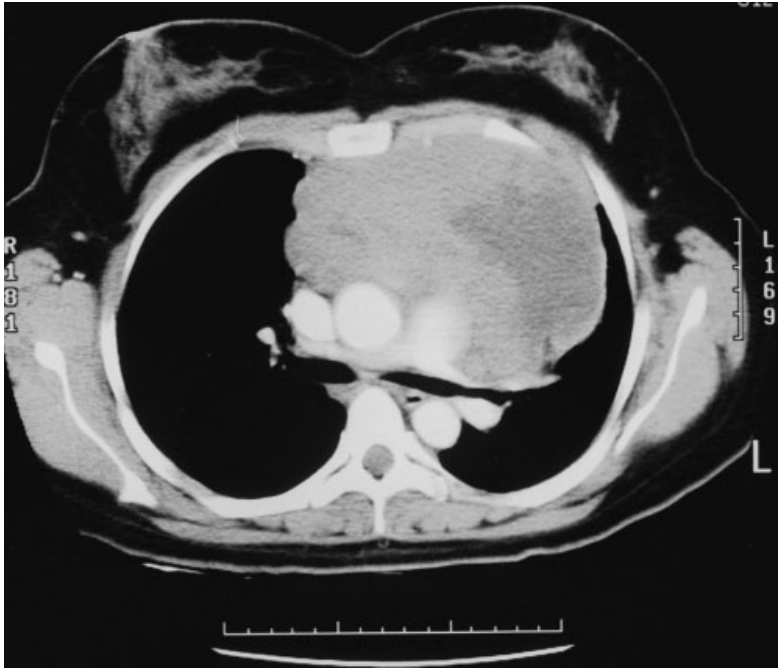
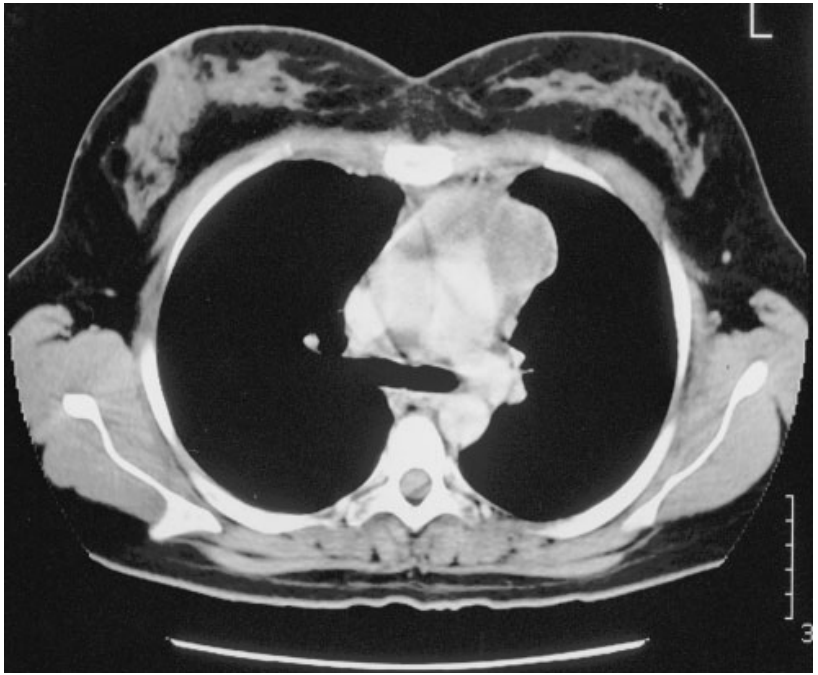


Diagnosis



Following chemotherapy

Assuming confined to mediastinum...what is your RT plan?

A no need...R-CHOP enough

B no need…DA-R-EPOCH enough

C no need…R-MACOP-B/R-VACOP-B enough

D R-CHOP + RT

E DA-R-EPOCH + RT

F R-MACOP-B/R-VACOP-B + RT

G Do a PET after immunochemotherapy… (i)RT if PET positive

(ii) HDT

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Is consolidation radiotherapy required?

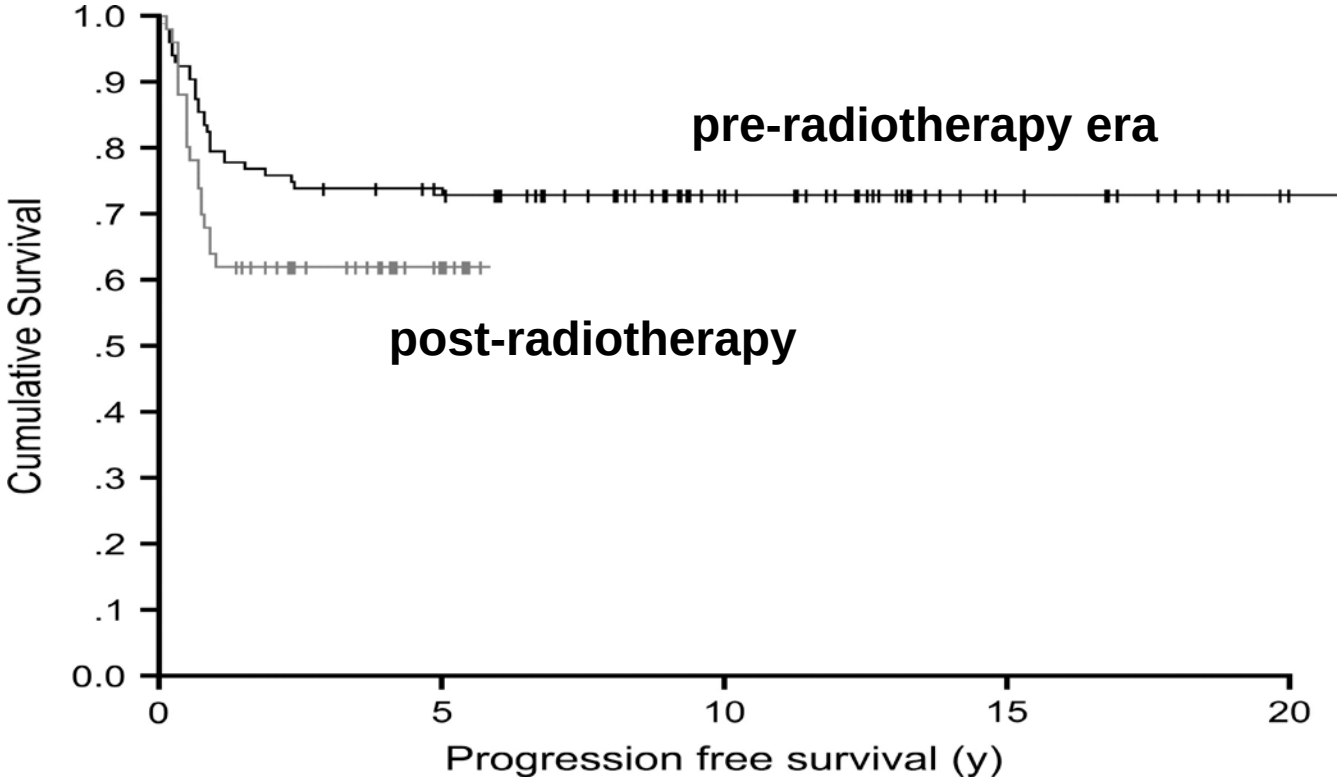
Radiotherapy may improve the quality of response

	CR after Chemo	PR to CR with RT	Global CR
First generation	49%	67%	61%
Third generation (*eg* MACOP-B)	51%	84%	79%
High-dose	53%	77%	75%
Overall	51%	81%	74%

Zinzani et al 2002

- The impact on cure rates is unclear, although several older series suggest that this is favourable
- Concerns regarding long term toxicity (cardiovascular and second malignancy)

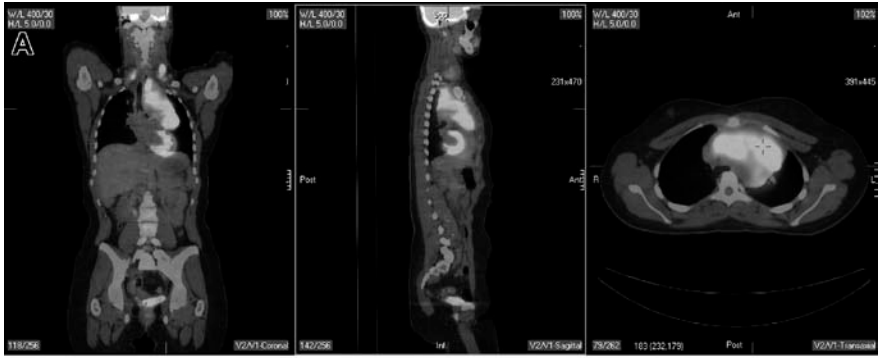
Impact of Radiotherapy: BC series

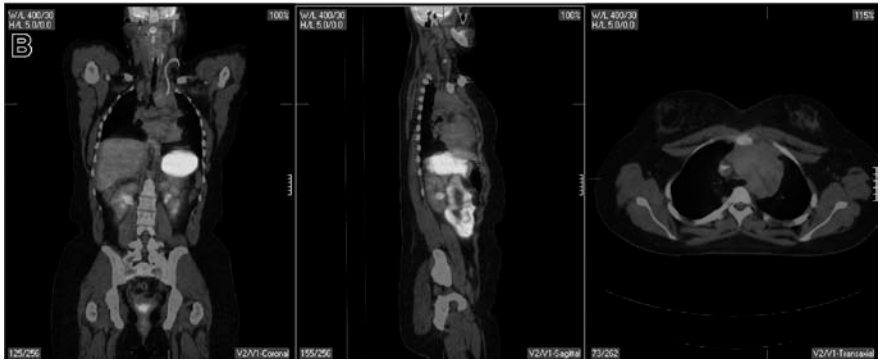


Savage, K. J. et al. Ann Oncol 2006 17:123-130; doi:10.1093/annonc/mdj030

Does the PET scan have a role in decision making ?

May be able to safely withhold RT without compromising cure?





IELSG 26:

Aim to collect prospective data in PET responses in PMBL after initial R-chemotherapy

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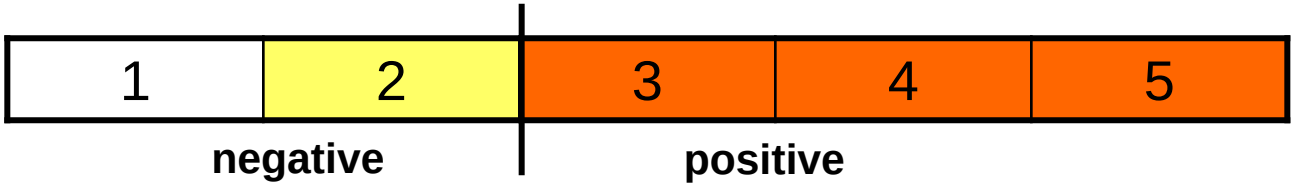
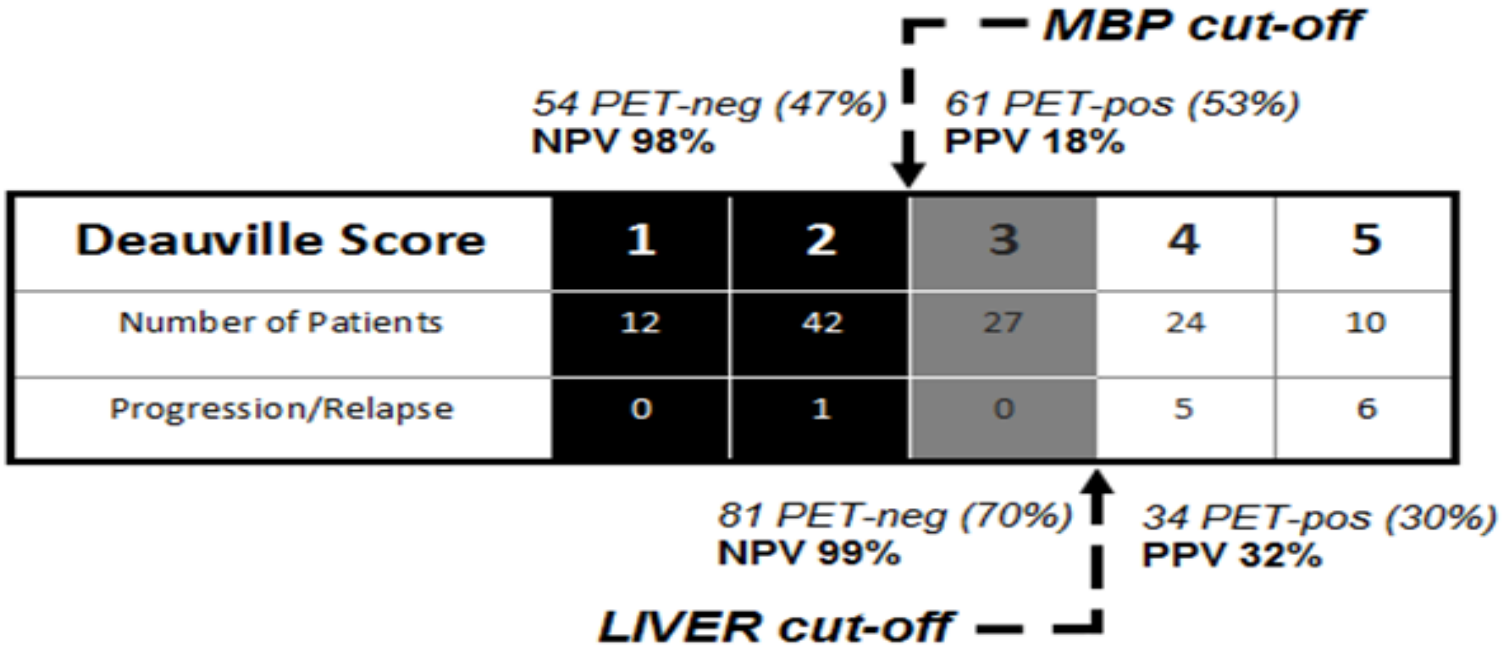
Visual analysis: the 5-point scale (Deauville criteria, 2009)

- 1. No uptake.
- 2. Uptake ≤ mediastinum.
- 3. Uptake > mediastinum but ≤ liver.
- 4. Uptake moderately more than liver uptake, at any site.
- 5. Markedly increased uptake at any site and new sites of disease.

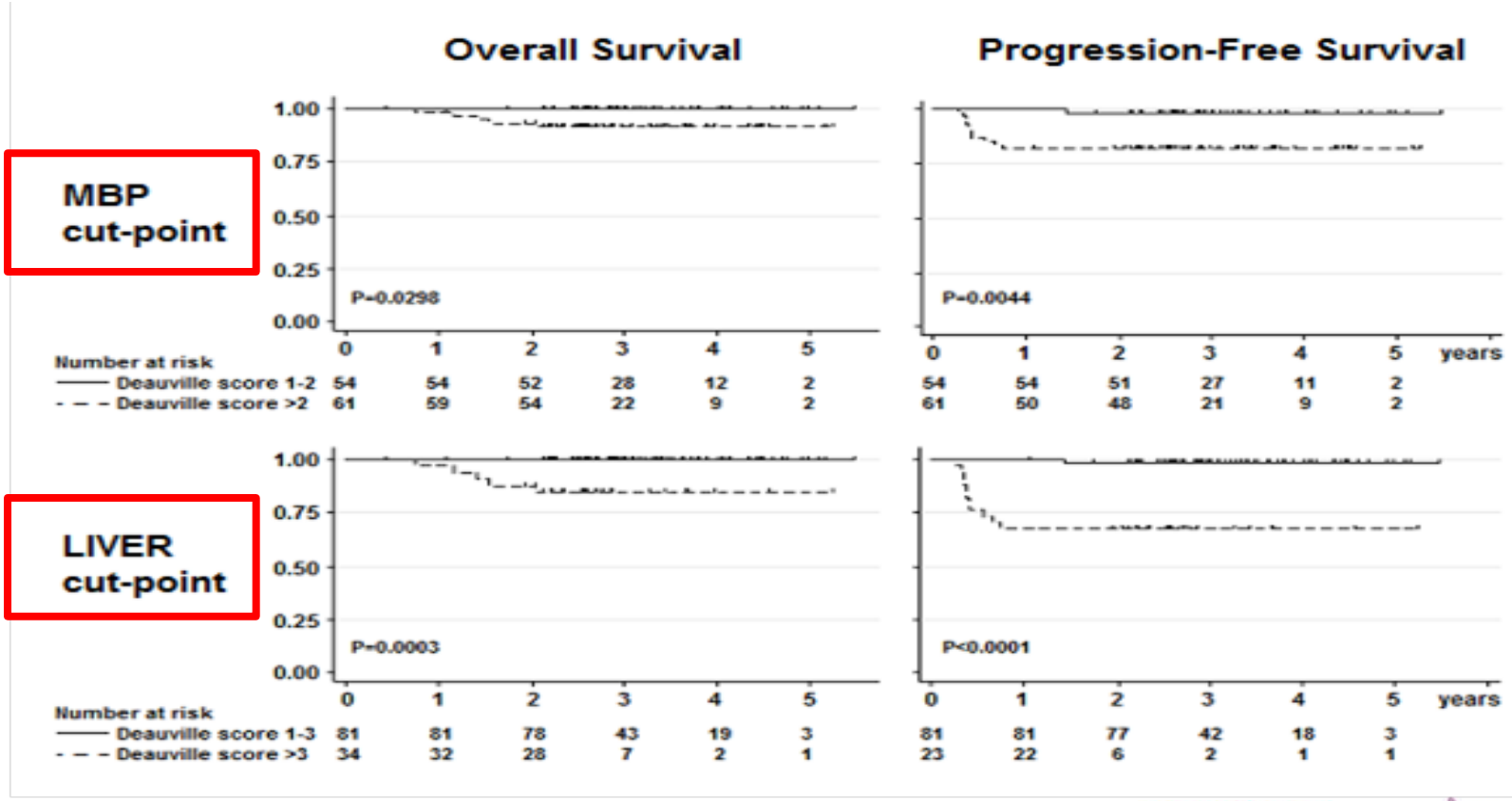


What is the impact of changing the cut point?



Deauville Score	1	2	3	4	5
Number of Patients	12	42	27	24	10
Progression/Relapse	0	1	0	5	6

Martelli *et al* JCO 2014



Martelli *et al* JCO 2014

Local diagnosis of PMBL
Registration
Baseline PET/CT

R-CHEMO
RCHOP 14-21; R-V/MACOP-B
DA R-EPOCH; R-ACVBP;R
mega-CHOP

Restaging PET/CT
Central Panel Review

PET/CT positive

Investigator choice of therapy (follow-up for PFS and OS)

PET/CT negative

Randomise (n=376)

Mediastinal IFRT

Observation

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ESMO Guideline

‘Primary mediastinal large B-cell lymphoma (PMBL) is probably a distinct entity. R-CHOP 21 is not established as the definitive treatment option and radiotherapy remains controversial.’

H. Tilly, M. Dreyling and On behalf of the ESMO Guidelines Working Group. Ann Oncol (2010) 21 (suppl 5): v172-v174.

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Summary: PMBL

- Thymic post-GC B-cell malignancy
- Good prognosis (>80% survival) with
  - R-CHOP
  - R-MACOP-B
  - DA-EPOCH-R
- Role of radiotherapy still controversial:
  - Excellent results in series with RT
  - Excellent results in a few series without
- CT-PET may be useful (especially when negative!)

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Case studies and interactive questions in Indolent lymphomas

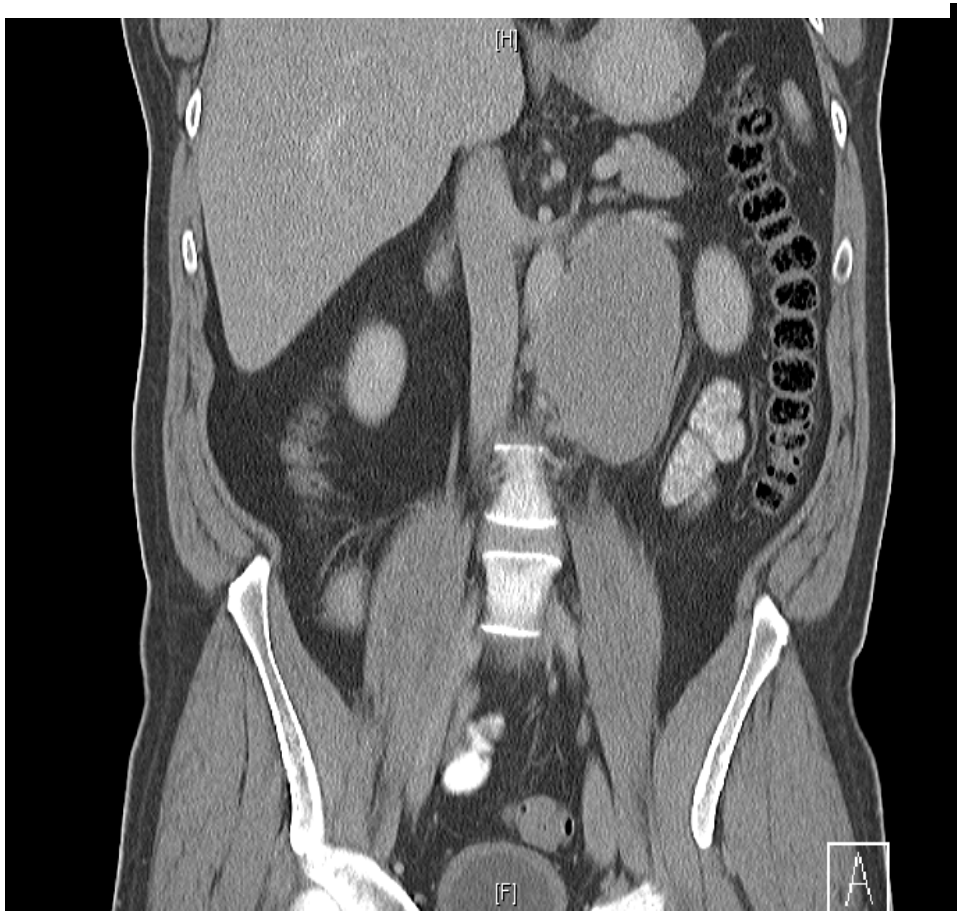
Tim ILLIDGE

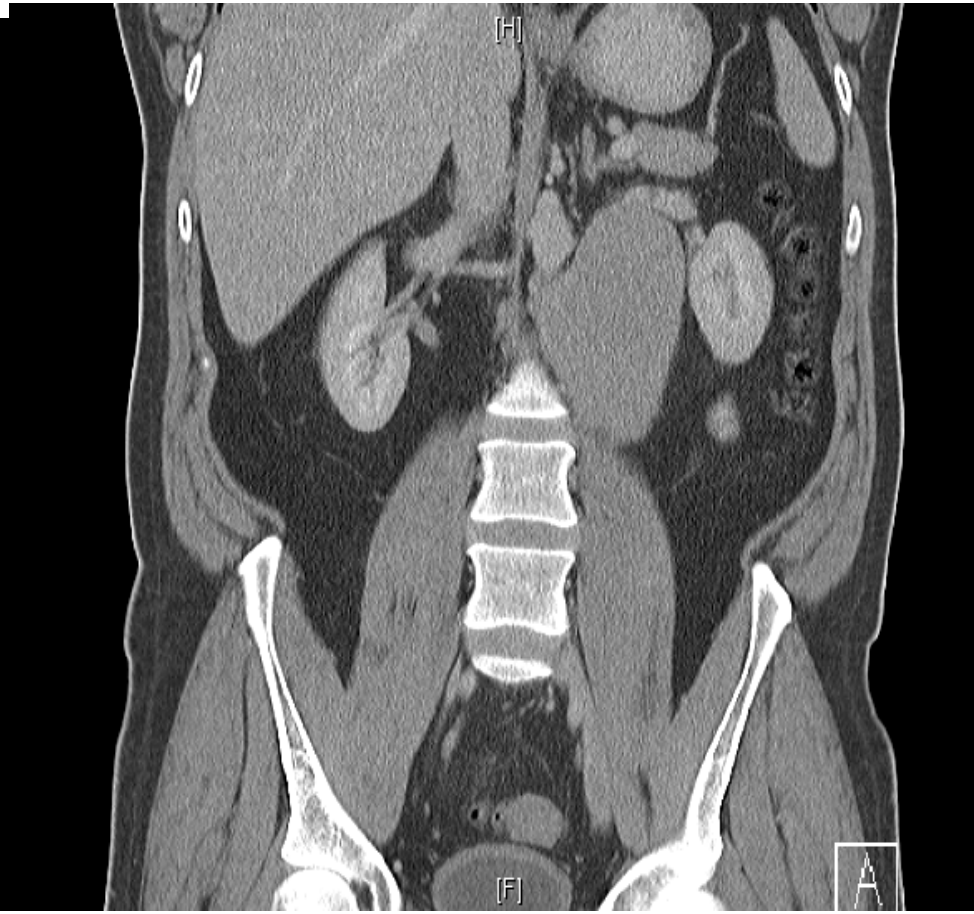
Follicular lymphoma nodal case presentation

- 45 year old train driver with a family history of aortic aneurysm rupture and therefore went to have a screening ultrasound - a mass around the abdominal aorta which was initially thought to be a saccular aneurysm but further assessment revealed it to be a distinct mass.

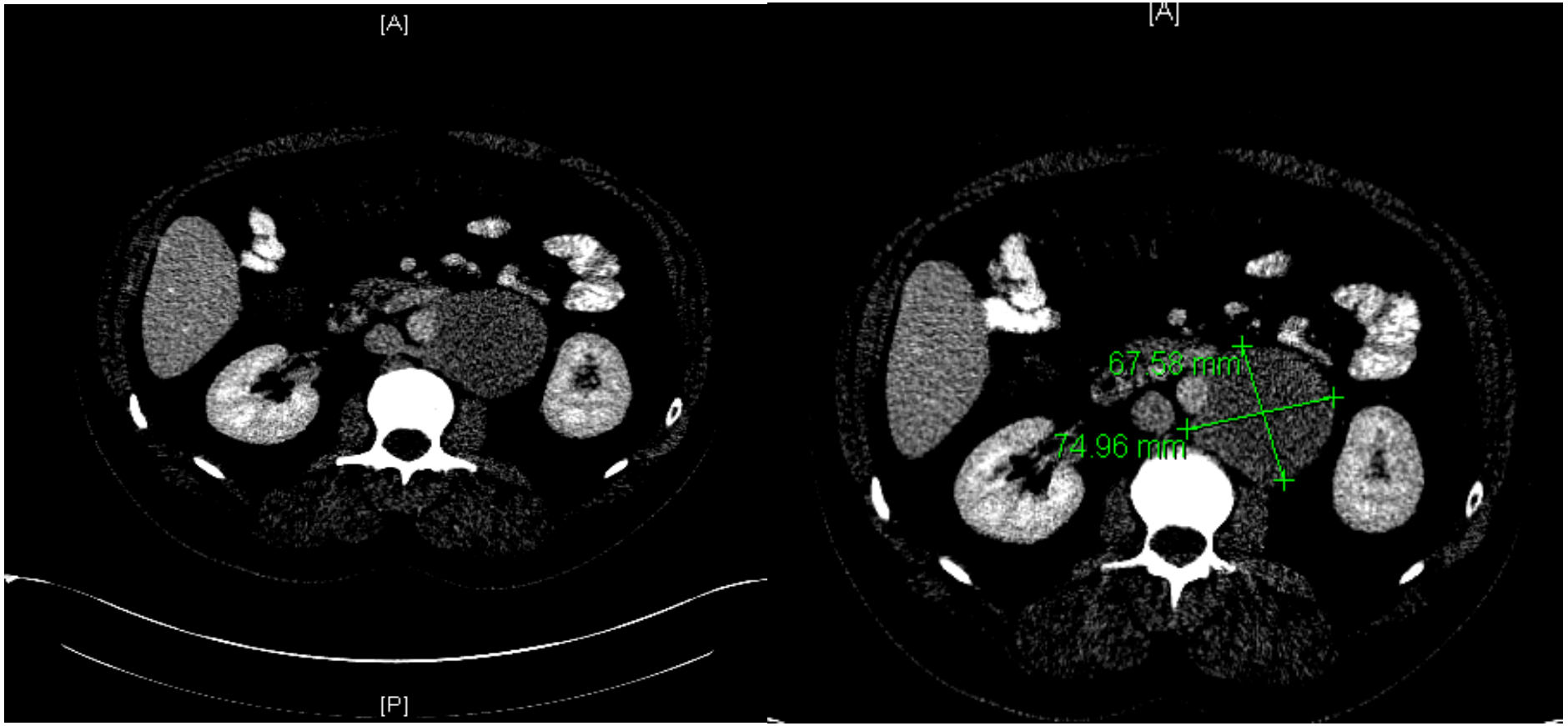
- Tru cut USS guided biopsy follicular lymphoma grade 1-2
- Well and asymptomatic – No B symptoms.
- Past medical history - Nil significant
- Examination Looks well ECOG 0. Weight 107.65kg. Height 187.3cm. Ill defined pulsatile abdominal mass palpable on deep palpation No palpable lymphadenopathy
- MRI of his abdomen which shows a left para-aortic solid lesion closely applied to the left side of the aorta. Dimensions are 65 x 59 mm in the axial plane and 92 mm craniocaudal extent.
- Ultrasound testes: no testicular abnormality.

45 year old man with retroperitoneal mass





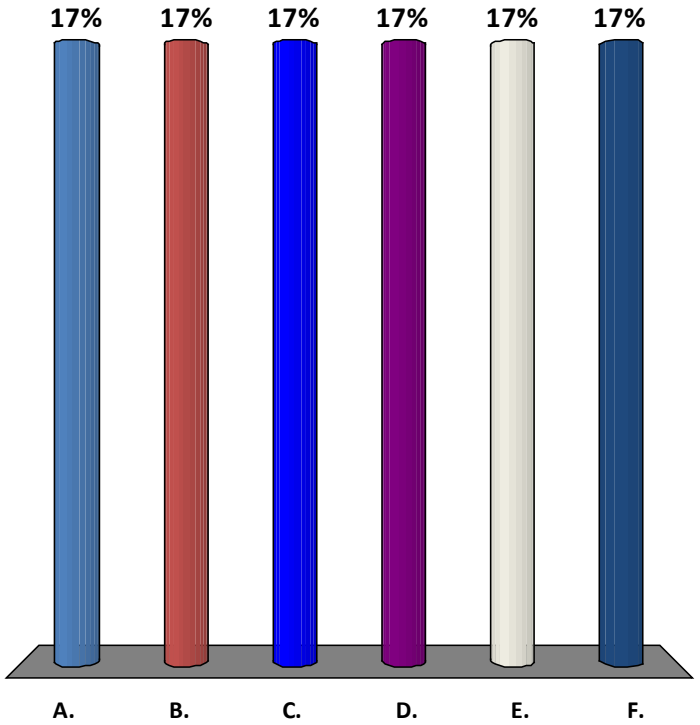
45 year old man with retroperitoneal mass



Solitary 7.5 x 6.8 cm left para aortic retroperitoneal lymph node inferior to the left renal vein. No other lymphadenopathy is seen. The liver, spleen, kidneys and rest of the abdominal organs are unremarkable. No pulmonary or skeletal infiltrates.

How would you treat this 45 year old man with retroperitoneal mass ?

A. Watch and wait
B. Single agent Rituximab
C. Involved Field Radiation Therapy (IFRT)
D. 6-8 cycles of Rituximab-Chemotherapy
E. 3 cycles of Rituximab-chemotherapy and consolidation Involved Site Radiation Therapy (ISRT)
F. 6-8 cycles of Rituximab chemotherapy and consolidation ISRT



How would you treat this 45 year old man with retroperitoneal mass ?

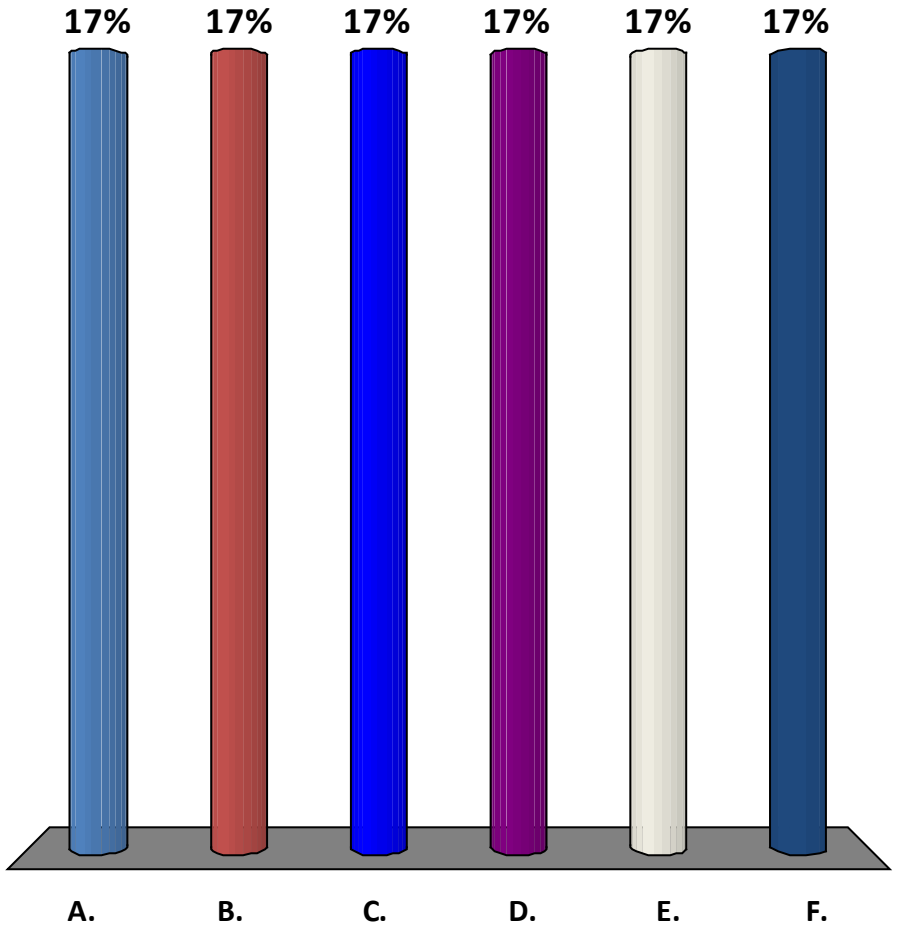
A. R-Chlorambucil

B. R-CHOP

C. R-CVP

D. R-Bendamustine

E. Other



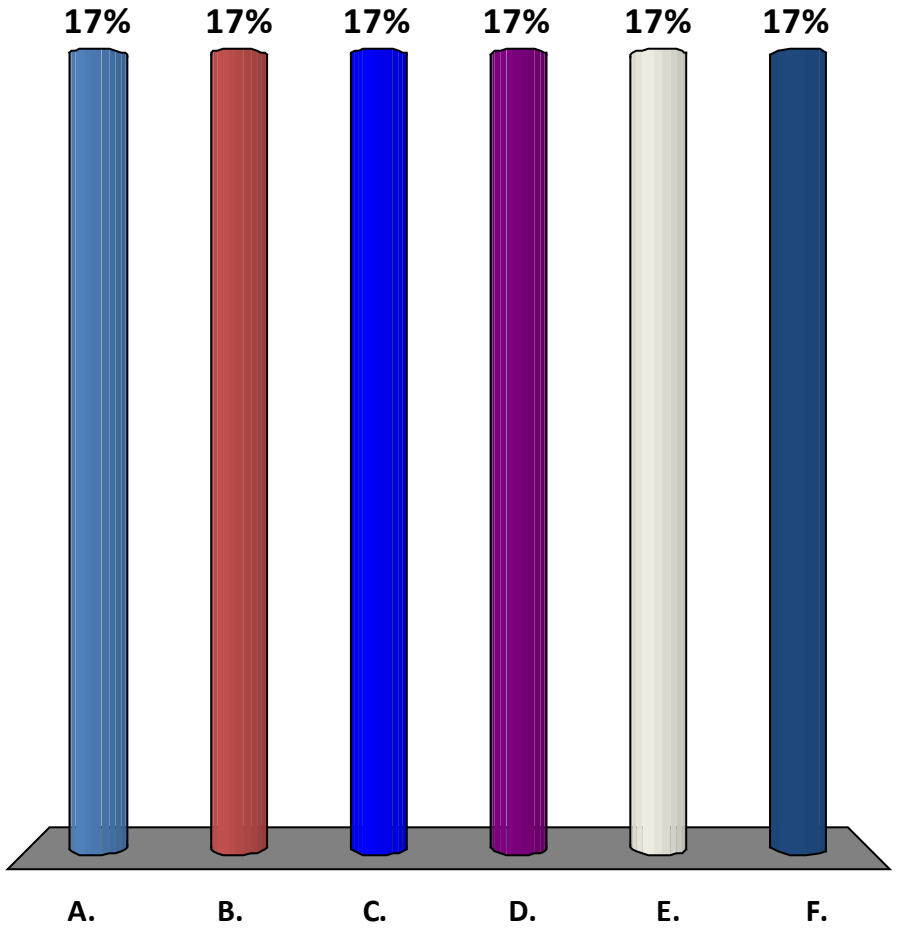
What ISRT does would you use to treat this retroperitoneal mass ?

A. 40 Gy

B. 30 Gy

C. 24 Gy

D. 4 Gy



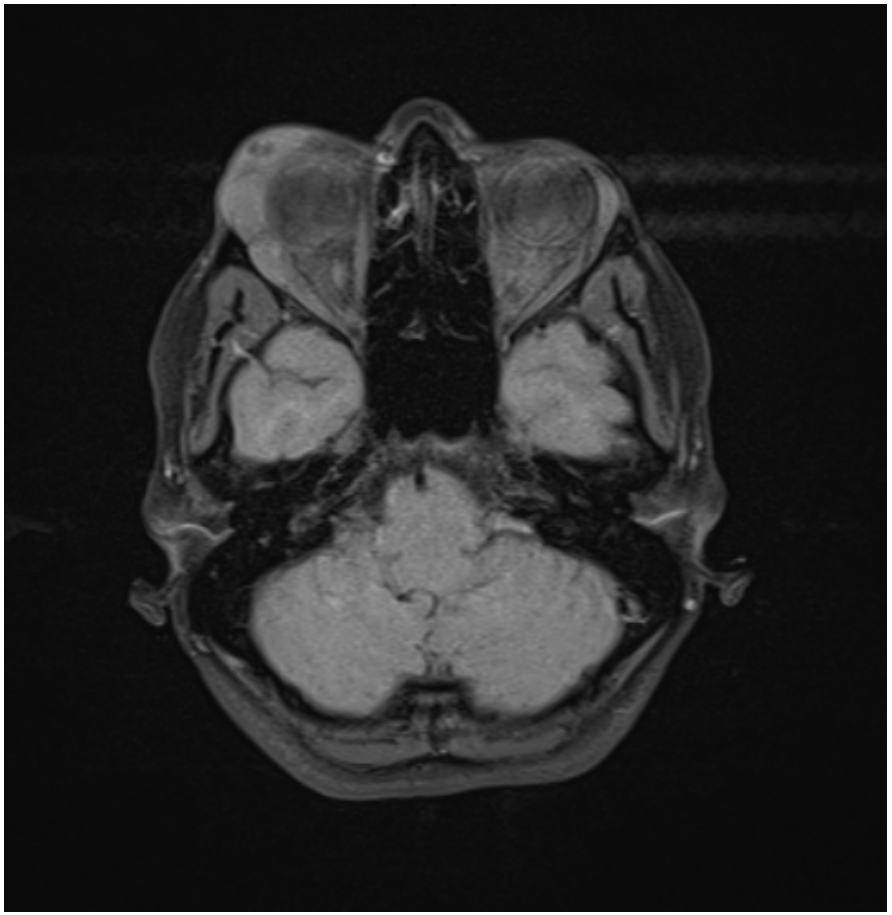
Case study orbital lymphoma

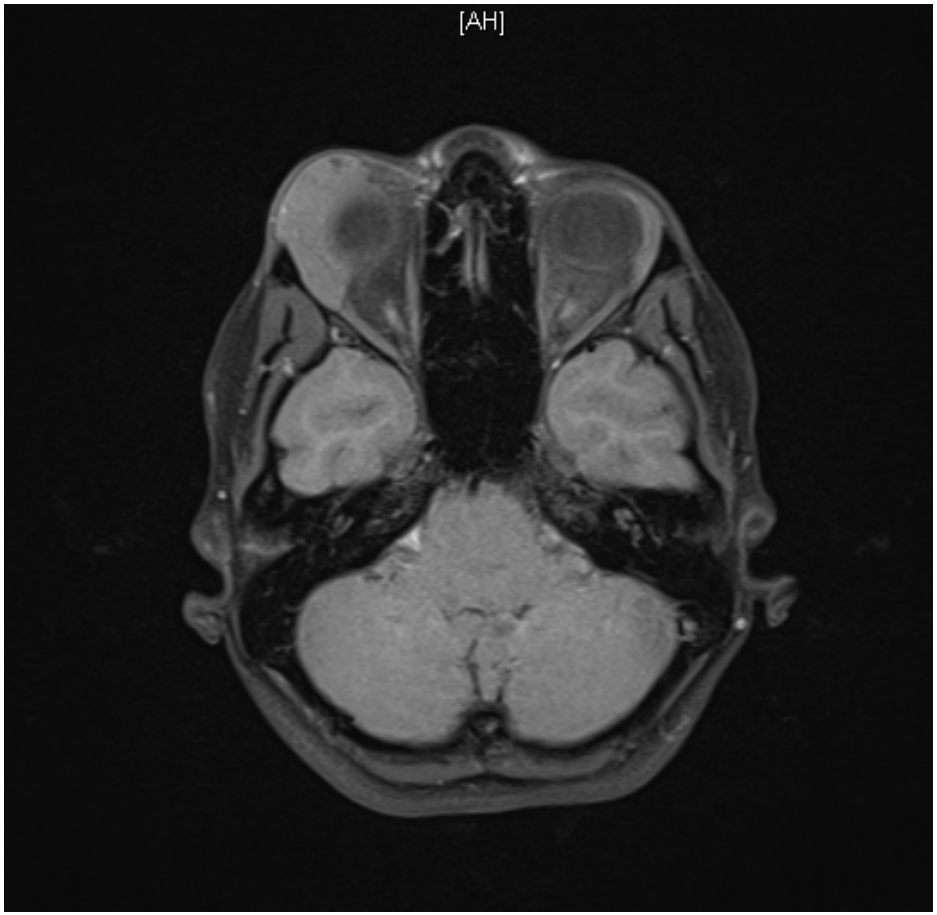
- 25 year old international business student presents with a 3 year history of swelling of her right upper eyelid and slowly enlarging mass. Referred to Consultant Ophthalmic Surgeon had a biopsy : confirmed the diagnosis of extra nodal marginal zone lymphoma.
- Occasional headaches, no B symptoms
- Past Medical History: nil relevant

- O/E 4 x 3cm superior orbital mass on the right hand side. On the left supero-orbital ridge a 2 x 1cm lump.

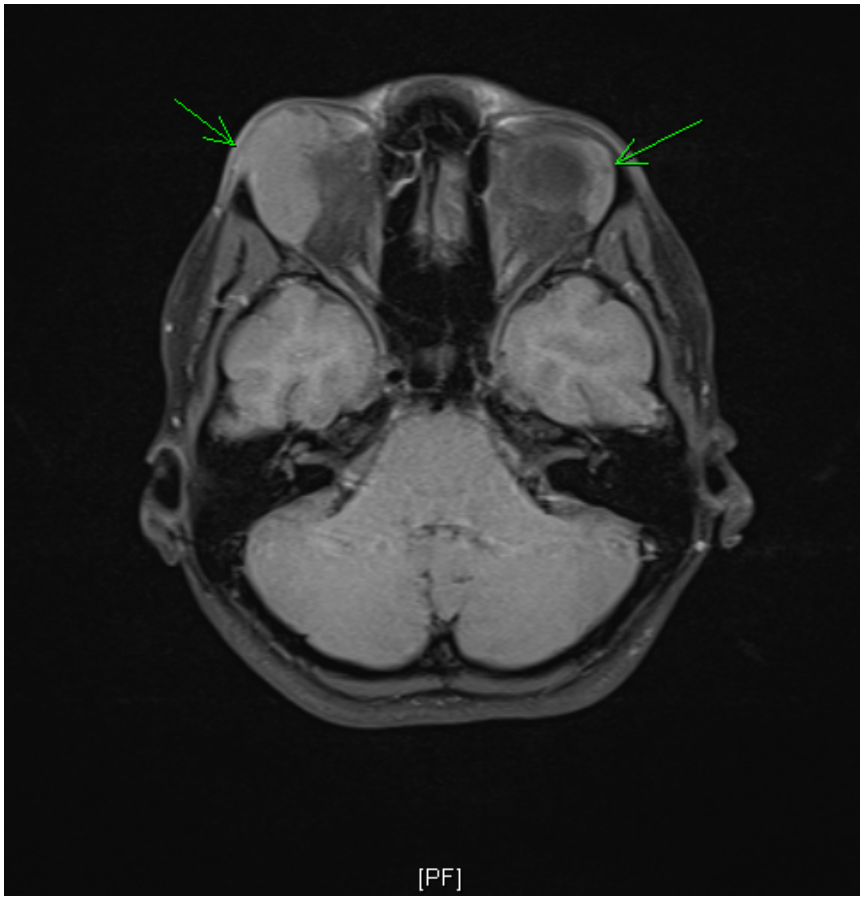
- CT Head , neck , thorax and abdomen – disease isolated to orbits only
- BM trephine biopsy – no involvement

Case study orbital lymphoma





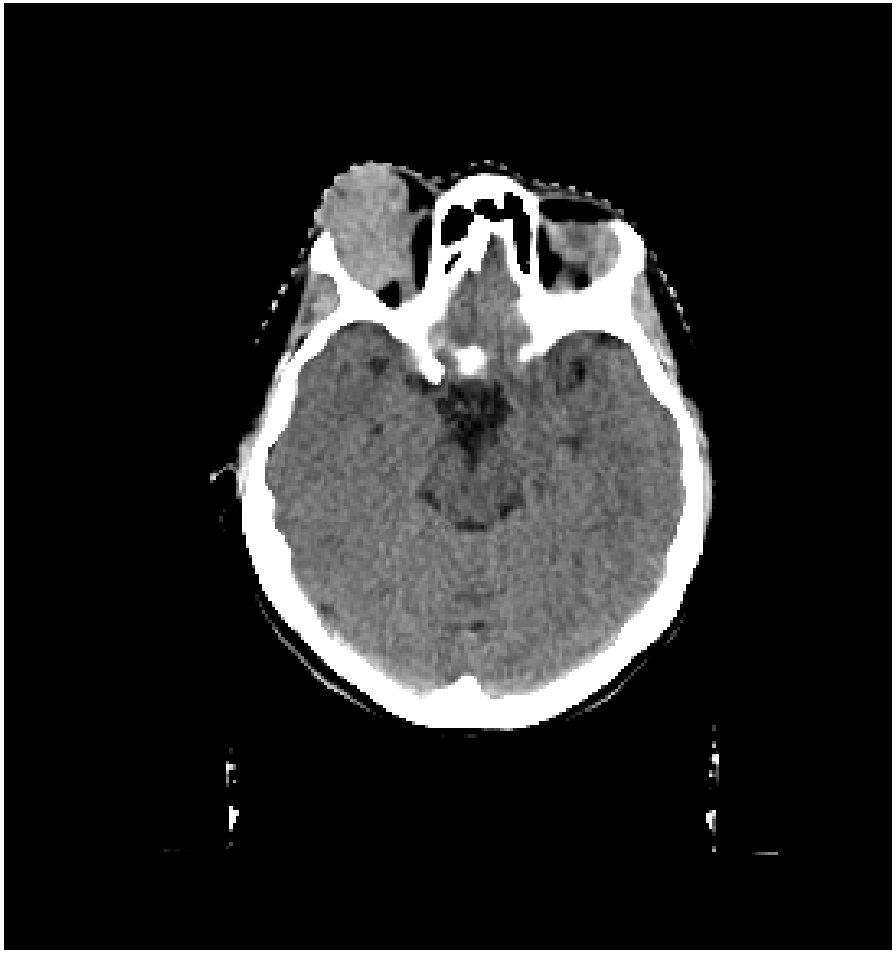
Case study orbital lymphoma

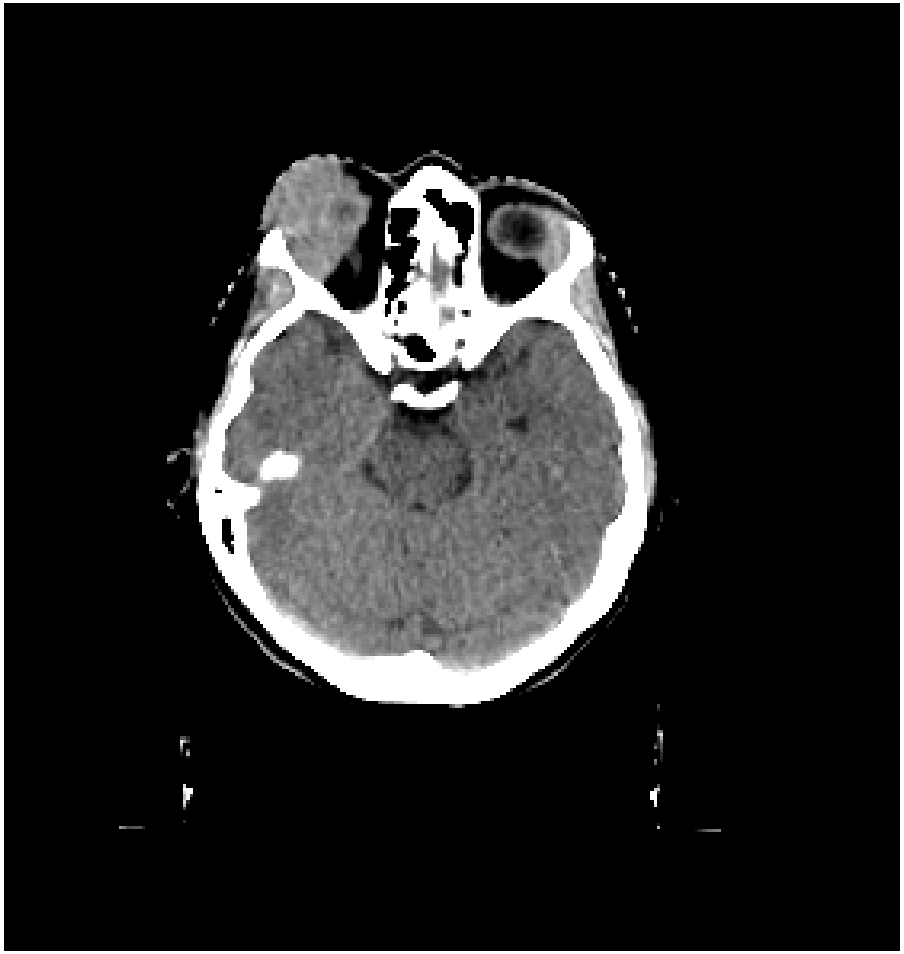


Lobulated fluid mass in the right superolateral orbit, measuring 3.8 x 2.6 cm transversely. The mass abuts and slightly displaces the globe and is inseparable from the lateral rectus and superior oblique muscles. The mass extends posteriorly along the lateral orbital wall, but does not encroach upon the orbital apex.

Smaller mass in the same position in the left orbit, measuring 2.2 x 1.1 cm, also unchanged from previously. No abnormality is seen elsewhere within the skull base or visualised brain.

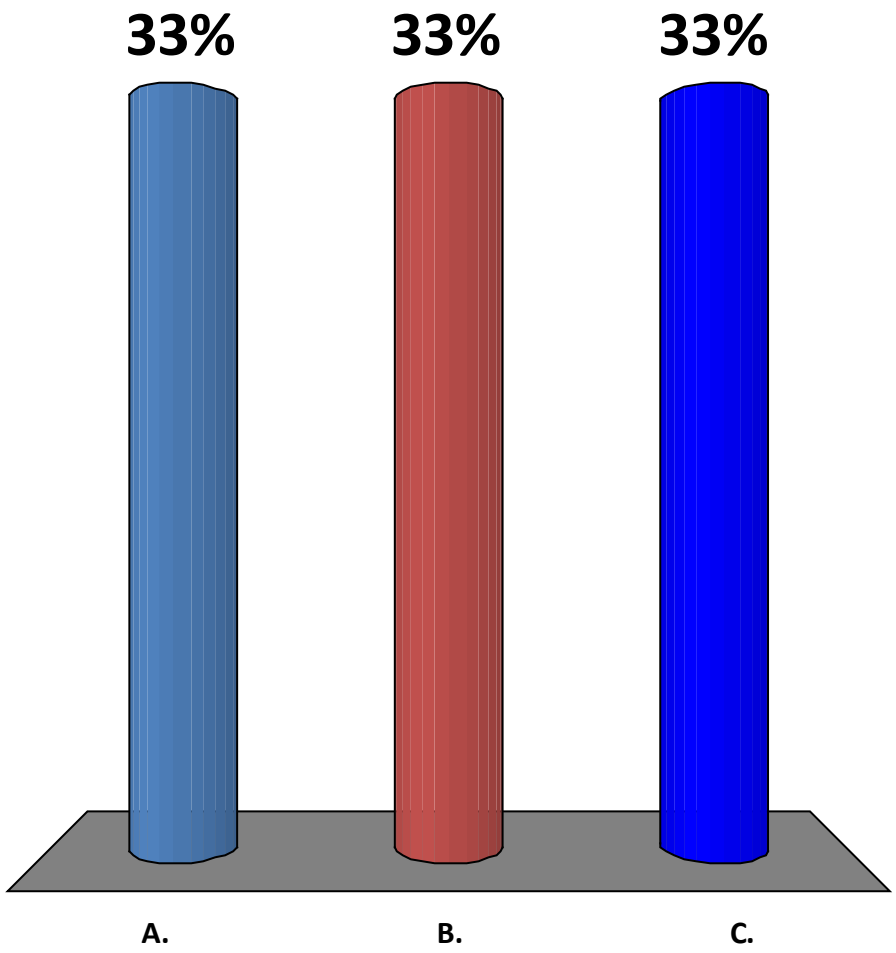
RTP scan for bilateral orbital lymphoma





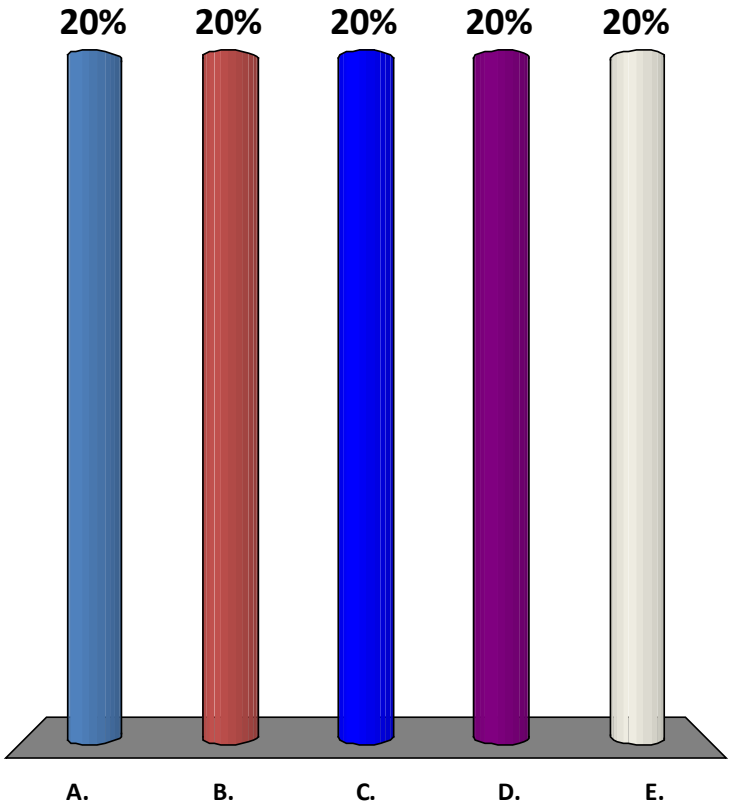
Staging confirms disease localised to orbits only – How would you treat ?

A. R-chemotherapy (R-CHOP, R-Benda, R-CVP
B. R-Chemo followed by RT
C. RT alone



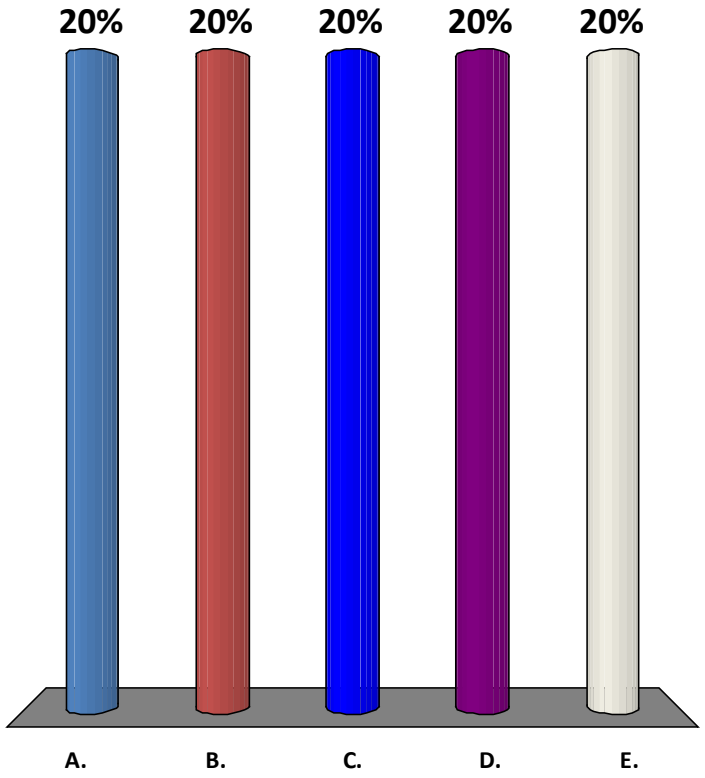
What radiotherapy technique would you use ?

A. RT alone - Bilateral lateral fields (both eyes together)
B. RT alone – superior and inferior oblique fields (both eyes together)
C. RT alone – superior and inferior oblique fields treat one eye and then treat contralateral eye later
D. Proton Beam Therapy
E. Another technique



Staging confirms disease localised to orbits only – what dose of RT?

A. 4 Gy in 2 fractions
B. 20 Gy in 10 fractions
C. 24 Gy in 12 fractions
D. 30 Gy in 15-20 fractions
E. 36 Gy in 18-20 fractions



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Pioneering better health for all

KING'S College LONDON
University of London

Guy's and St Thomas' NHS
NHS Foundation Trust

Aggressive Nodal NHL
Case discussion

Prof George Mikhaeel

Professor of Radiation Oncology
King's College London
Consultant Clinical Oncologist
Guy's & St Thomas' Hospital
London, UK

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Clinical History

- 22-year old male, no PMH.
- recent onset of cough, exertional dyspnea and fatigue.
- CXR: mediastinal mass, subsequently referred to the chest team.
- No B symptoms, no peripheral LN, infective screen negative.
- CT:
  - mediastinal mass 14.3x10.3cm (axial) &13cm (CC)
  - displacement of the heart and great vessels to the left.
  - External compression of the SVC without complete obstruction
  - R main bronchus: displaced posteriorly but not compressed

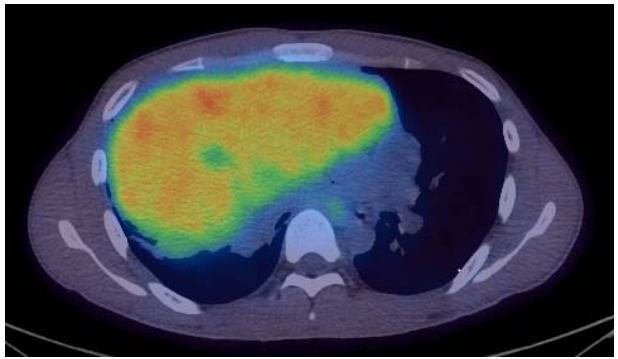
Diagnosis:

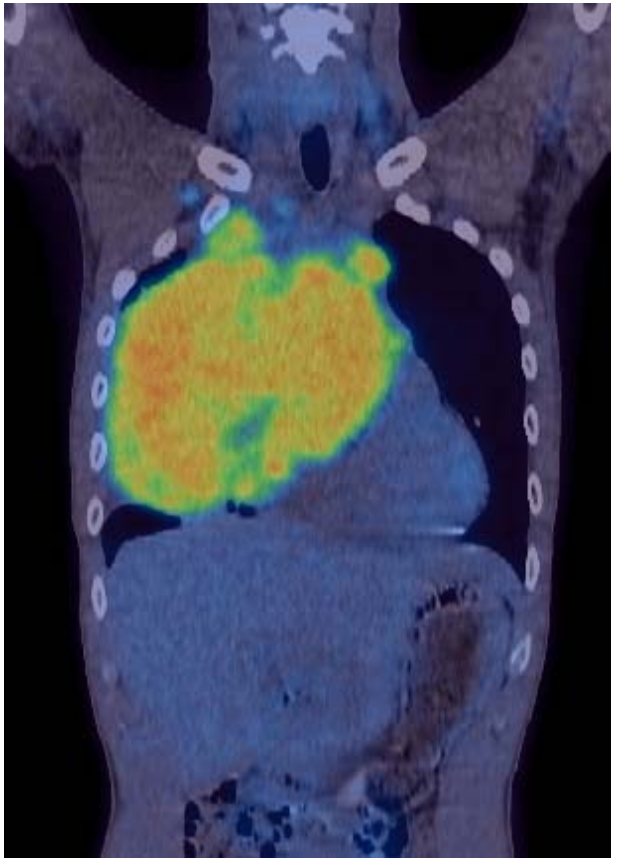
- A CT-guided percutaneous biopsy: DLBCL.
  - sheets of malignant large lymphocytes which were CD79a+, CD20+ confirming B-cell origin.
  - Further immunohistochemistry confirmed activated B-cell subtype of DLBCL, which is MUM1+, BCL2+, BCL6+, p53+, CD30+/-, CD10+/-
  - proliferation fraction (Ki67) > 90%.
  - In situ hybridization showed no MYC, IgH, BCL2, or BCL6 rearrangements.

Staging and prognostic factors

- Referred to the lymphoma team
- PET/CT:
  - stage II disease
  - large mediastinal mass (18 x 11cm) with increased FDG uptake (SUVmax 9.5)
  - small right infra-clavicular lymph node
  - no evidence of involvement below the diaphragm
- BMB: negative
- LDH: high
- IPI = 1, stage 2A bulky

Pre-treatment PET/CT





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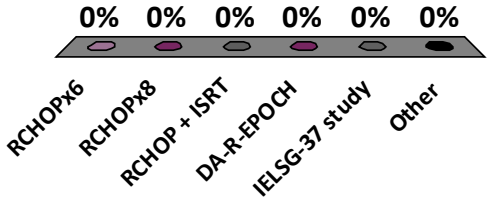
MDM & treatment plan

IPI = 1, stage 2A bulky

A. RCHOPx6
B. RCHOPx8
C. RCHOP + ISRT
D. DA-R-EPOCH
E. IELSG-37 study
F. Other



Points for discussion

- IPI=1, aaIPI=1, low risk group
- Bulky early stage require full course chemo (not eligible for abbreviated chemo + RT)
- CHOP-14 is superior to CHOP-21, the same is not true when Rituximab is added. A large phase 3 randomised study showed that there was no difference between RCHOP-21 and RCHOP-14 *(Cunningham, Lancet 2013).*
- 8 cycles have not been found to be better than 6 cycles *(Pfreundschuh, Lancet 2008).*
- RT for bulky site: most likely site of recurrence. Evidence from German trials. IELSG-37 testing PET-guided RT.
- MDM: RCHOPx6 + ISRT with close monitoring of response on PET/CT

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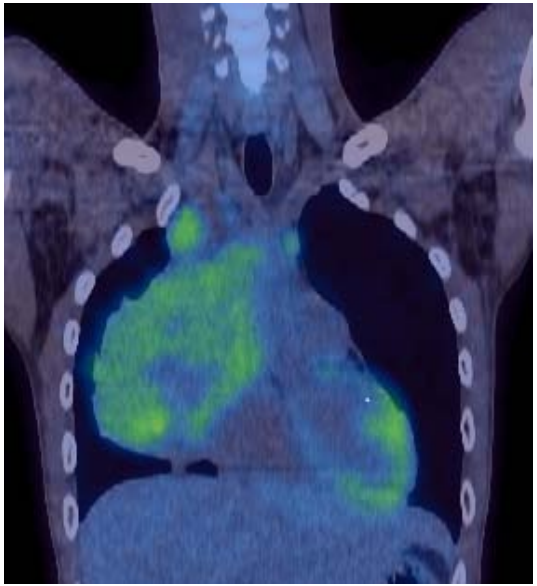
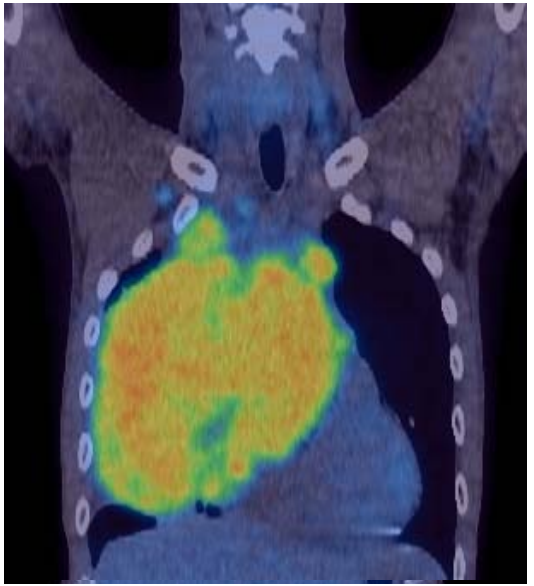


After 2 cycles:

- reduction of size and
- uptake (Deauville score 4, SUVmax = 5.7)

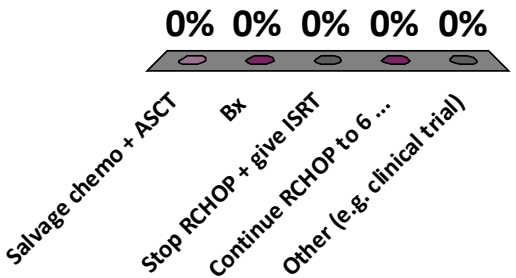


After 4 cycles:

- Pre-treatment
- further reduction of size and
- uptake (still DS 4, SUVmax = 5)

Further management

A. Salvage chemo + ASCT
B. Bx
C. Stop RCHOP + give ISRT
D. Continue RCHOP to 6 + repeat PET
E. Other (e.g. clinical trial)



Points for discussion

- Interim PET established in HL but controversial in DLBCL
- Interim assessment of response by imaging is better with PET/CT than CT
- No evidence to change treatment early on the basis of PET
  - No alternative option better than full course RCHOP
  - Several studies examined change of Rx with no benefit (although PET was prognostic):

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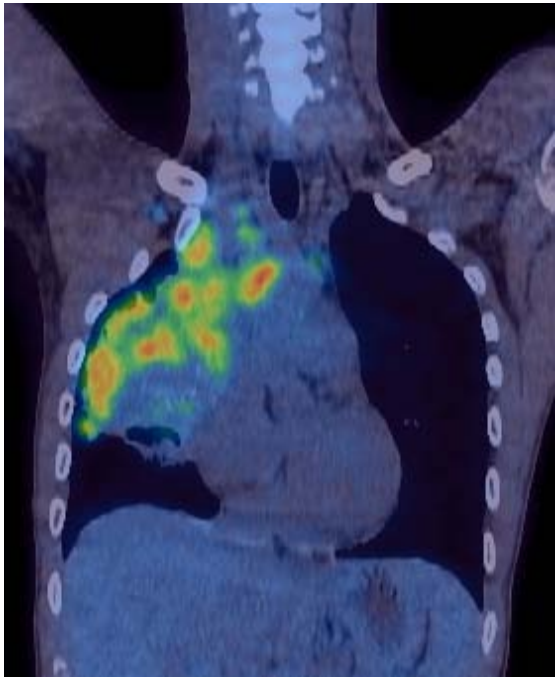
Change of RCHOP in DLBCL

Study	Pt no	iPET timing	Intervention	End point
Pradal (GELTAMO) 2015	71	>3 cycles MegaCHOP	-ve: 3 MegaRCHOP +ve: 2 RICE + BEAM ASCT (no info on RT)	3y PFS: -ve: 81%, +ve: 57% OS: -ve: 95%, +ve 33%
Swinnen (ECOG) 2014	74	> 3 RCHOP	-ve: 3 RCHOP +ve: 4 RICE (no RT)	2y PFS -ve: 76%, +ve: 42% OS -ve: 93%, +ve 69%
Duehrsen (PETAL) 2014	853 (926)	> 2 RCHOP	-ve: randomise to 4 RCHOP or 4 RCHOP + 2R +ve: randomise to 4 RCHOP or intensification	2 R: no difference (HR 1.2, 95%CI 0.8-2.1) Intensification: no difference (HR 1.6, 95%CI 0.9-2.7)
Sehn (BCCA) 2014	155	> 4 RCHOP	-ve: 2 RCHOP +ve: 4 RICE + RT for EOT PET +ve	4y PFS -ve: 91%, +ve: 59% OS -ve: 96%, +ve 73%
Kasamon 2009	59	> 2-3 RCHOP	-ve: continue RCHOP +ve: 2 ESHAP or ICE + ASCT RT permissible	2y EFS -ve: 89%, +ve: 67%

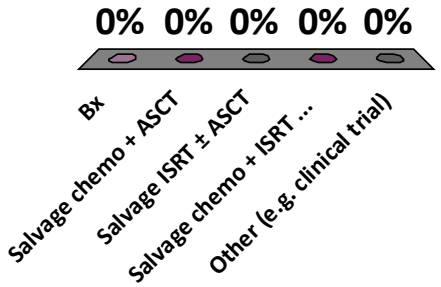


>6 cycles of R-CHOP: progression

- increase of size and
- uptake (DS 5, SUVmax = 11.5)

Further management

A. Bx
B. Salvage chemo + ASCT
C. Salvage ISRT ± ASCT
D. Salvage chemo + ISRT + ASCT
E. Other (e.g. clinical trial)



Points for discussion

- Bx was not done: course of disease (PET-2, PET-4, PET-6) + increase in size.
- Aim was to get CMR (-ve PET) prior to ASCT.
- Expected salvage chemo alone is not adequate:
  - Bulky disease
  - Primary refractory
  - CORAL data re poor salvage-ability >R
    - response rate 51% v 83%
    - 3y EFS of 21% v 47%
    - Primary refractory disease worse
- Retrospective evidence of benefit of peri-transplant RT, particularly after R
- Concern about pneumonitis?

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Timing of peri-transplant RT

PRE- transplant

Pros:

- Cytoreduction if poor salvage chemo response
- Less haematological toxicity
- Ensures administration

Cons:

- Higher risk of pneumonitis
- Delay of HD chemo
- Requires good co-ordination

POST- transplant

Pros:

- Less pneumonitis
- Less GI toxicity / VOD
- No delay in giving HD chemo

Cons:

- More haematological toxicity:
  - Irradiating regenerating marrow
  - MDS / leukemogenic risk
- May be delayed or omitted if recovery is prolonged

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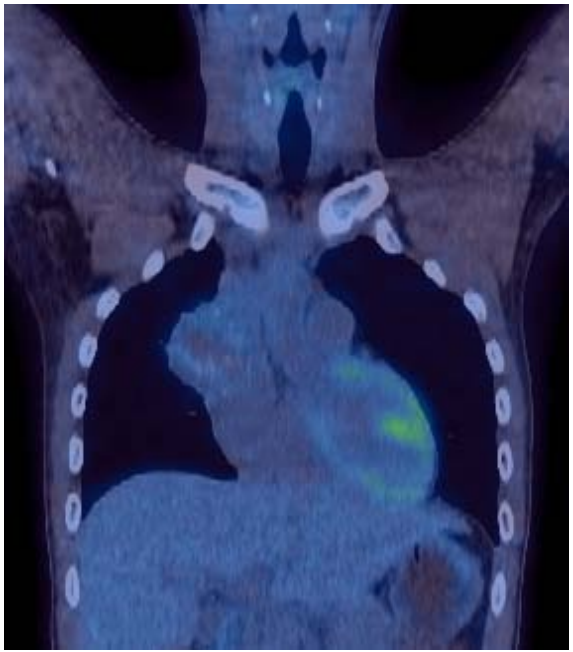
MDM decision

- R-DHAP + ISRT:
  - Best chance
  - Allows planning of RT
  - Stem cell harvest after DHAP

After R-DHAPx2 + ISRT:

- reduction of size (>50%) &
- uptake (DS 3)



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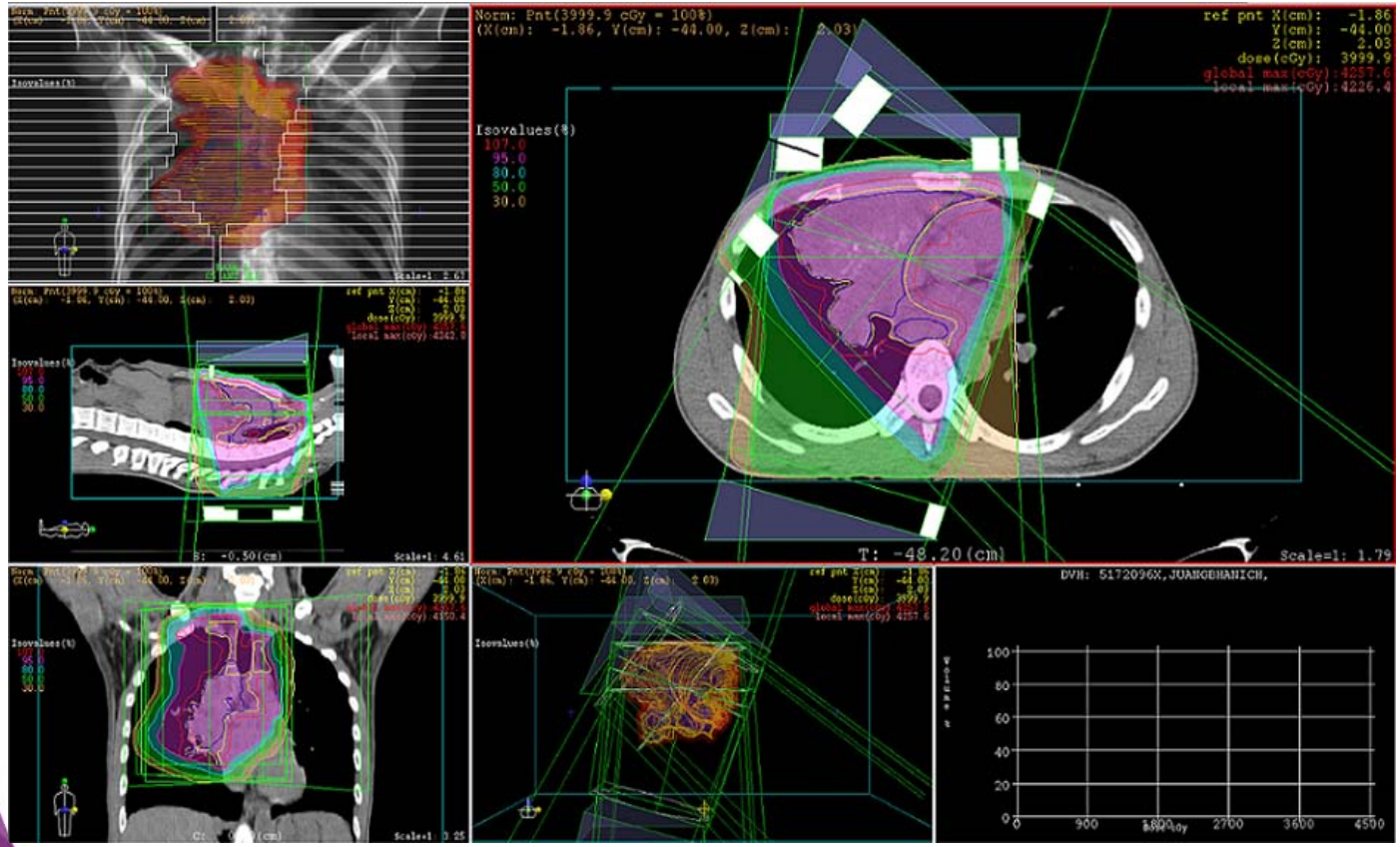
RT

- Planning CT, 2 weeks >1st R-DHAP + information from the PET/CT.
- Aim: to treat current extent of disease using ISRT
- Conformal plan:
  - 4 primary beams (anterior, R & L anterior obliques, and R posterior oblique) +
  - 2 segments (anterior and Ranterior oblique)
- 10 MV photons
- Dose: 40Gy / 20# / 4 weeks
  - Standard dose for consolidation RT is 30 Gy
  - Refractory disease usually requires higher dose to overcome the resistance.
  - Accept slightly higher doses for OAR (e.g. lung V20 <25%, mean heart dose <15 Gy).



Radiotherapy plan showing:

- GTV (dark blue)
- CTV (yellow)
- PTV (red)

And
beam arrangement

40Gy / 20# / 4 weeks

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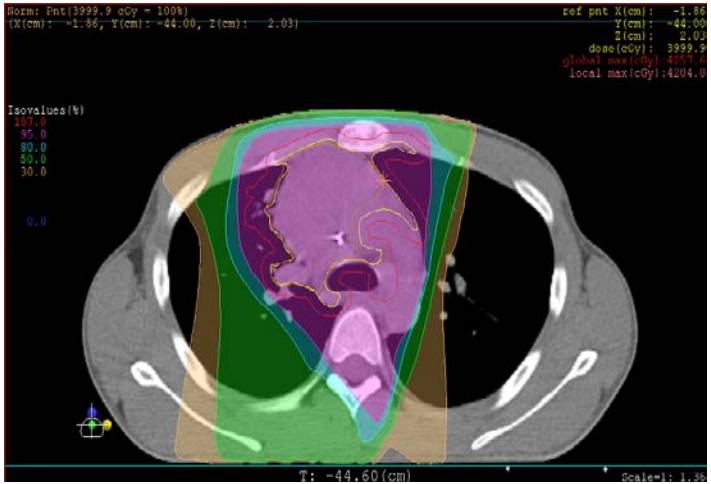
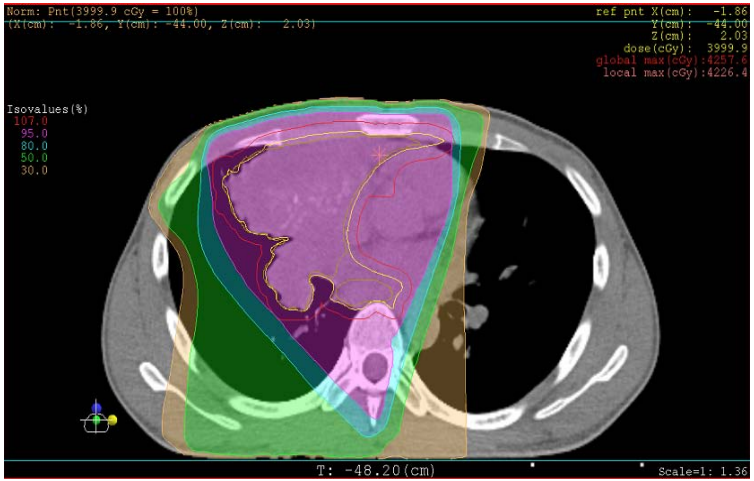
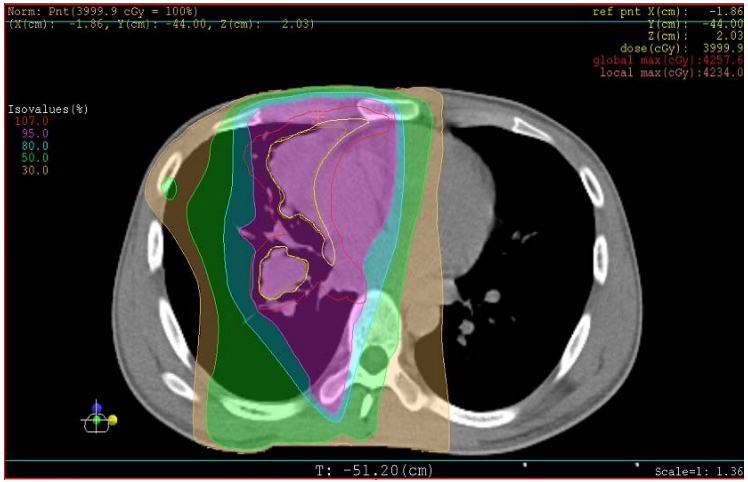
upper



middle



lower



Dose distribution

purple: 95%

blue: 80%

green: 50%

orange: 30%

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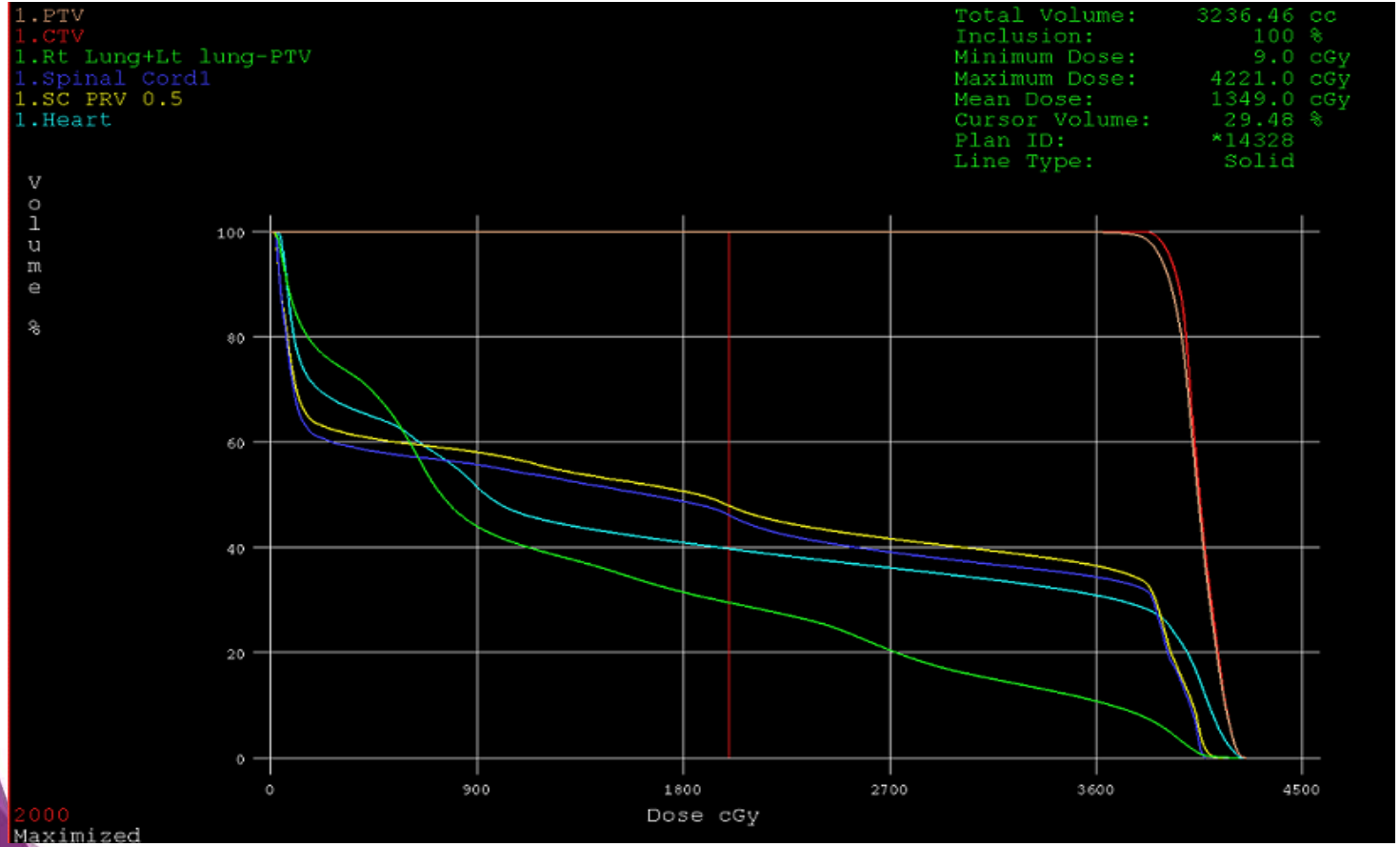

PTV:
V95: 98.9%

Lung:
V20 29.5%
mean: 13.5Gy

Heart :
V30 34.6%
mean 17.8 Gy
median 9.5 Gy

Sp cord max:
40.8 Gy

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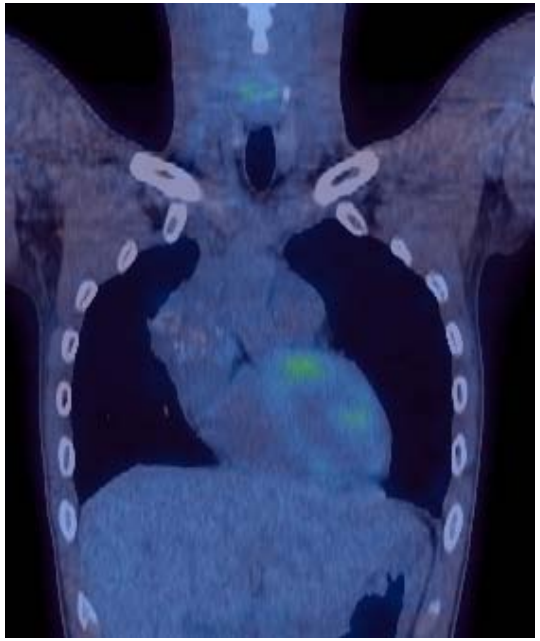

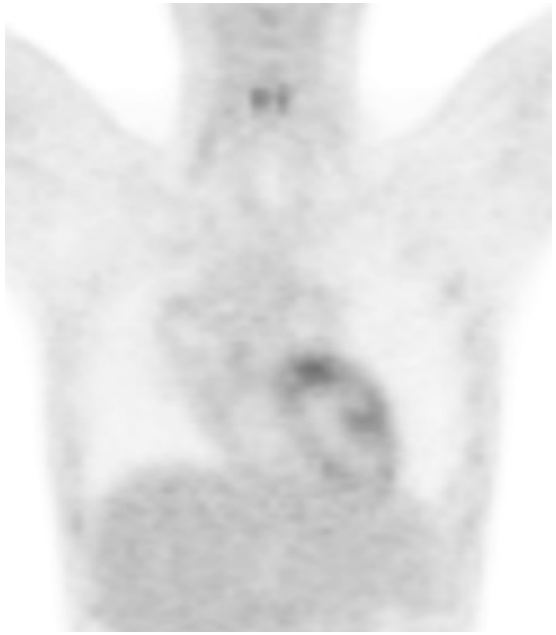

3 months >ASCT:

- continued CMR (DS 2; uptake <mediastinum)
- some calcification in the residual mass.

Last FU: NED (3.5 ys >ASCT), no late effects

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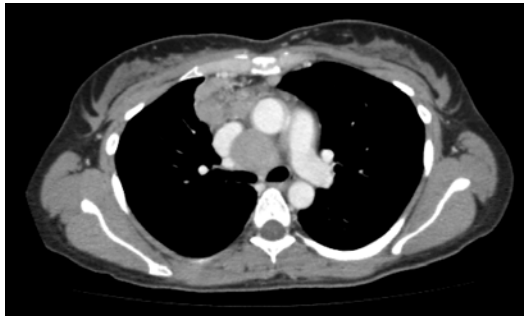
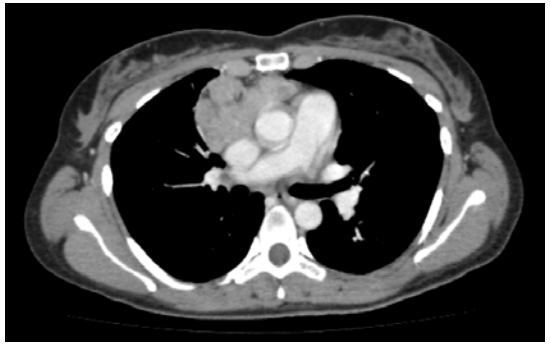
Early Stage Hodgkin Lymphoma

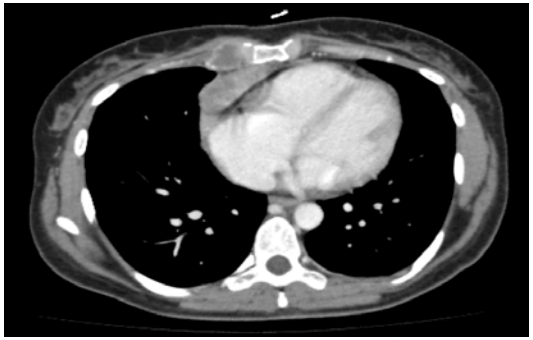
- M.C. 37 years old, female
- No significant past medical history
- October 2011: chest pain, weight loss (>10%), itching, cough, right parasternal lump
- Labs: normal CBC and chemistry; ESR: 45

Early Stage Hodgkin Lymphoma

- CT scan: involvement of mediastinum (bulky on chest X-ray) + right internal mammary region, with chest wall extension, and doubtful right supraclavicular lymph node; no other pathologic findings







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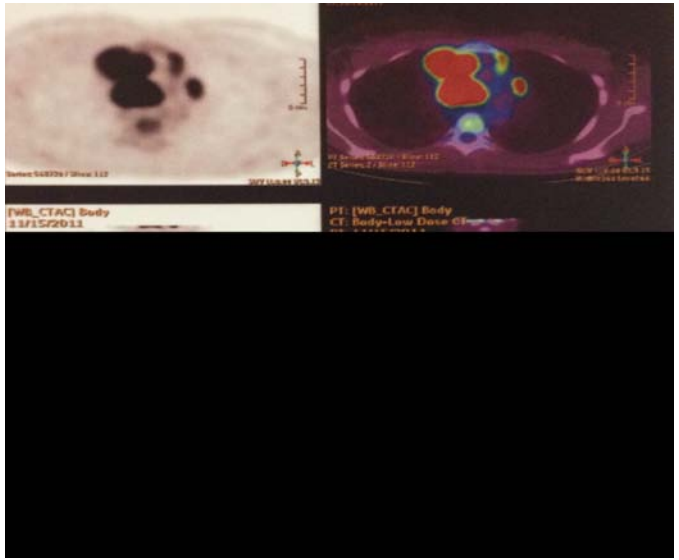
Early Stage Hodgkin Lymphoma

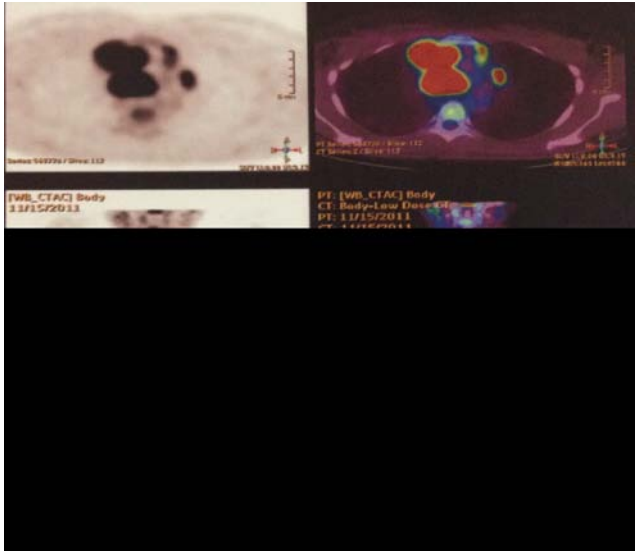
- Mediastinal biopsy (mediastinotomy):

classical HL, scleronodular subtype, CD45+, CD30+, CD20-, CD15-

Early Stage Hodgkin Lymphoma

- PET-CT scan:





- Bone marrow biopsy (2011): no evidence of disease

- **Stage IIB bulky mediastinum**

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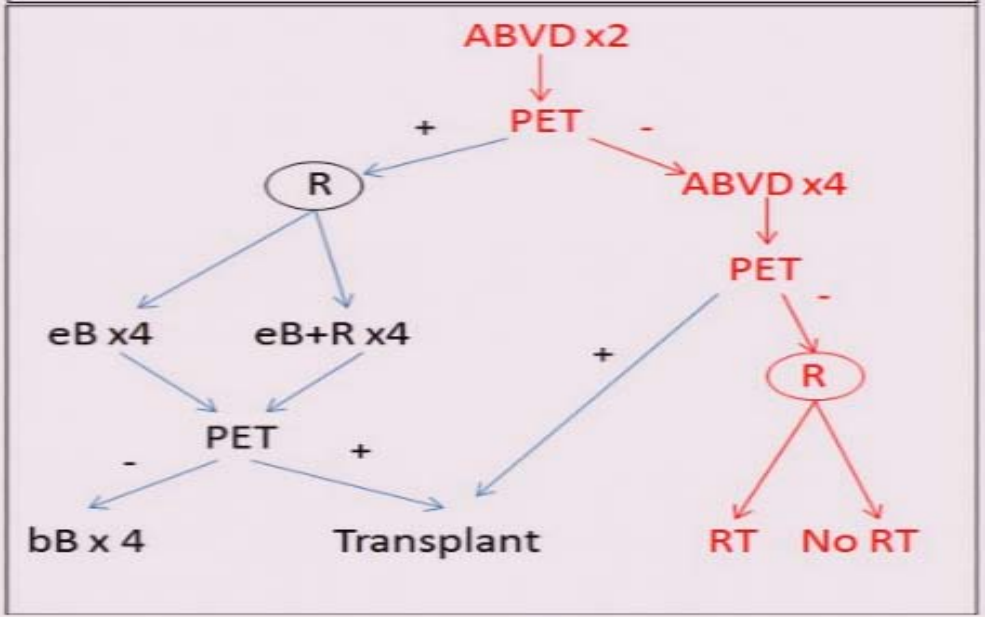
RT in Advanced HL Future Directions

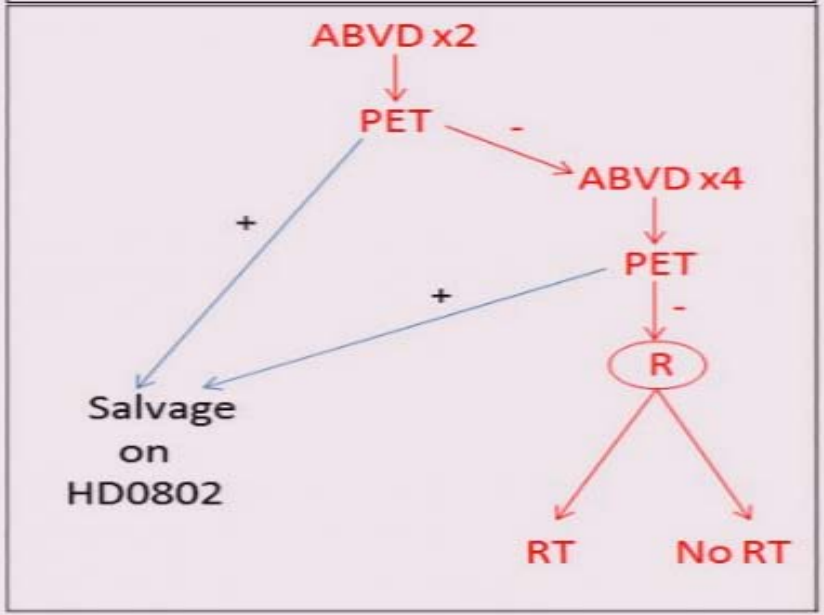
stage IIB-IV

2 ongoing trials addressing role of RT in patients with PET-CR after ABVD :

GITIL HD0607 Stage IIB-IV



FIL HD0801 Stage IIB-IV

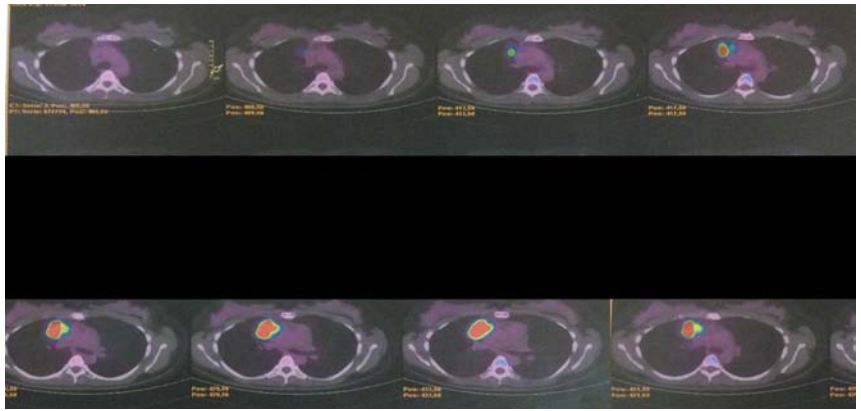


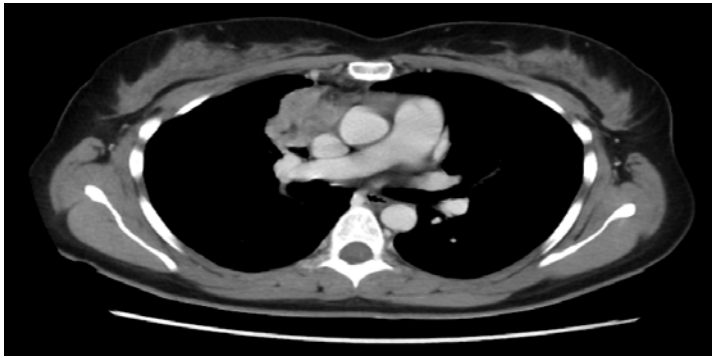
Early Stage Hodgkin Lymphoma

- November 2011: start of chemo (planned ABVD x 6)
- Interim PET: no evidence of disease (5PS score 1)
- CT scan after 6 cycles: residual mediastinal fibrotic tissue
- CT-PET: no pathologic uptake (5PS score 1) → CR
- Randomization arm: No RT on bulky disease
- Off therapy: April 2012

Early Stage Hodgkin Lymphoma

- Negative follow up till April 2014
- CT scan: PD of the mediastinal residue
- PET-CT: mediastinal pathologic uptake





- Mediastinal biopsy (April 2014): cHL

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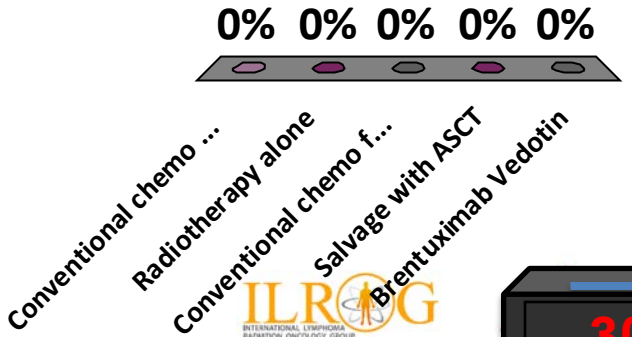
What to do now?

Limited stage relapse at > 12 months after end of treatment

(LYSA prognostic factors: standard risk)

Which salvage therapy?

A. Conventional chemo alone
B. Radiotherapy alone
C. Conventional chemo followed by RT
D. Salvage with ASCT ± RT
E. Brentuximab Vedotin



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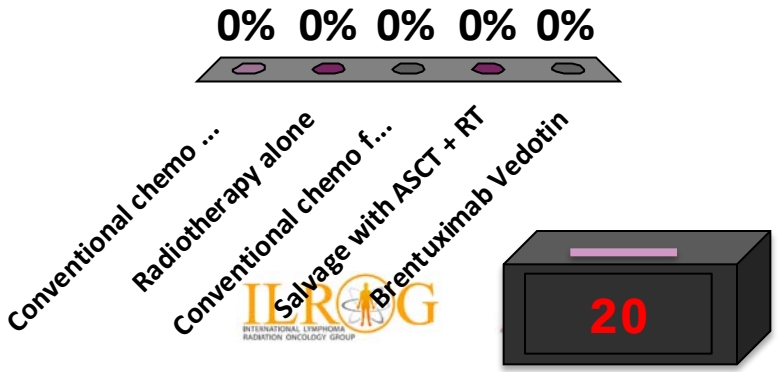
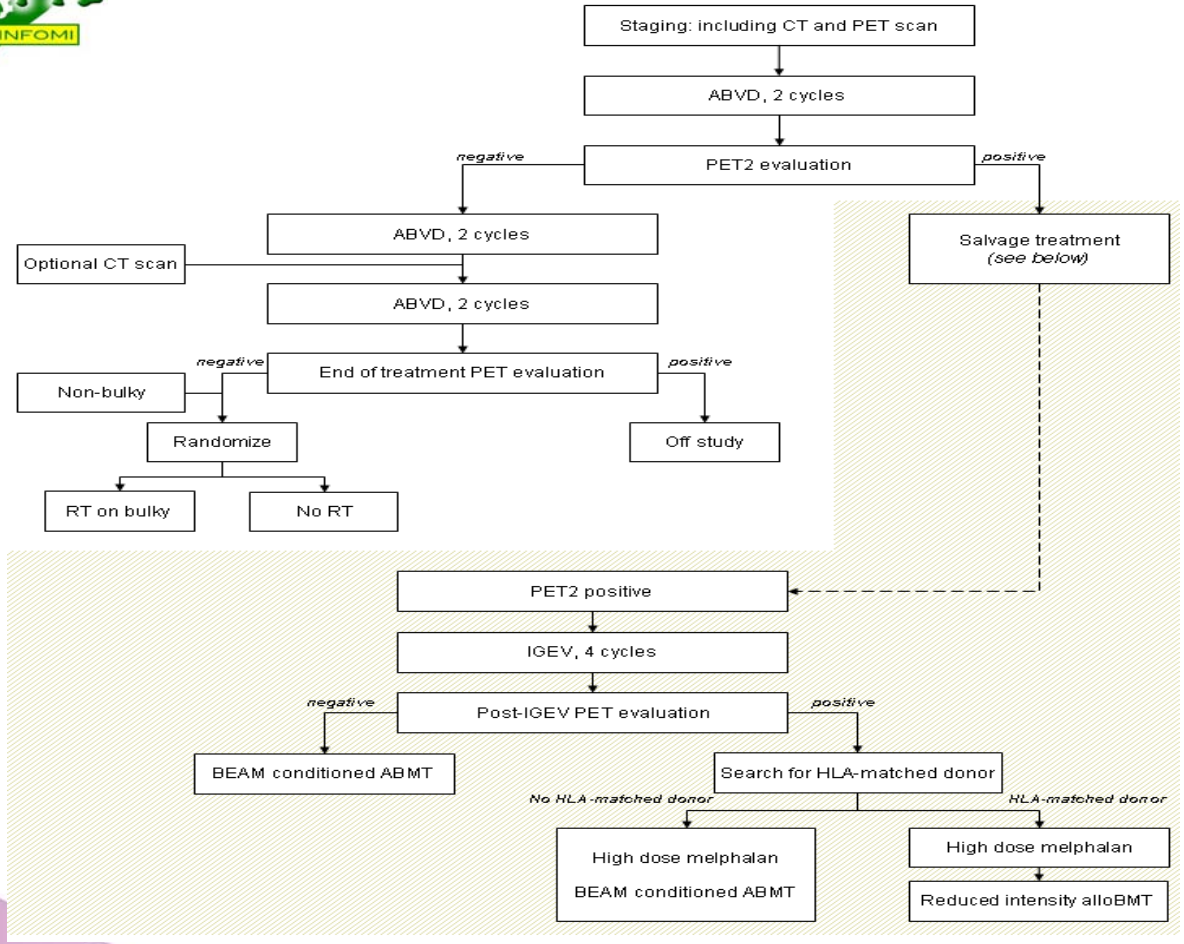


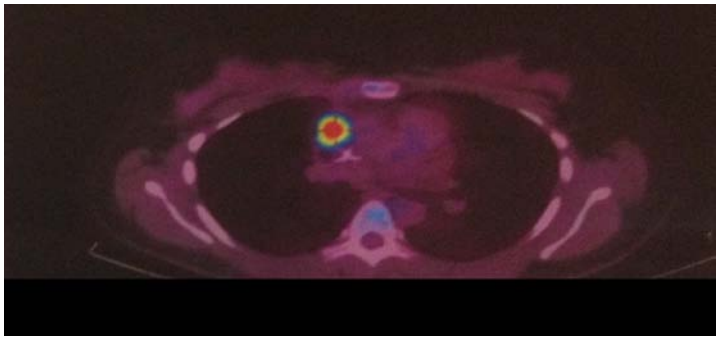
Study outline



Early Stage Hodgkin Lymphoma

- Planned salvage therapy: IGEV x 4, followed by ASCT
- PET after 2 IGEV: partial response (PR)

At relapse



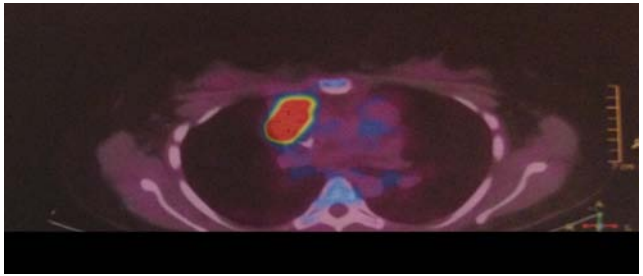
After 2 IGEV

Early Stage Hodgkin Lymphoma

- PET-CT after 4 IGEV: PD (increase in size and metabolic activity)

After 2 IGEV

After 4 IGEV



- High-dose therapy followed by autologous stem cell transplantation (ASCT) has been clearly identified as a reference treatment in relapsing/refractory patients compared to standard chemotherapy

- However, many questions still remain:

  - definition of subgroups with different risk
  - type and number of salvage chemotherapy cycles
  - use of metabolic imaging in response definition
  - place of double ASCT
  - need to consider allogeneic transplantation in selected patients
  - **role of radiotherapy**

- RT has been used for cytoreduction and consolidation therapy in the peri-transplant period

- Patients may benefit from RT either before (debulking) or after ASCT (consolidation) to sites of dominant local recurrence

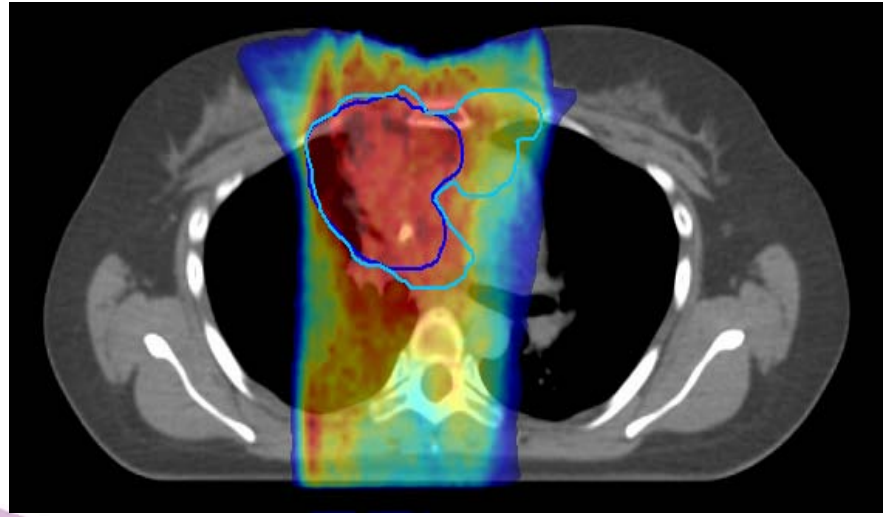
Early Stage Hodgkin Lymphoma

- MDT: mediastinal radiotherapy (ISRT) before ASCT

- RT treatment (October 2014)

  VMAT (SIB) →

  - 30 Gy/20 fractions to larger volumes
  - 40 Gy/20 fractions to PET+ sites after 4 IGEV



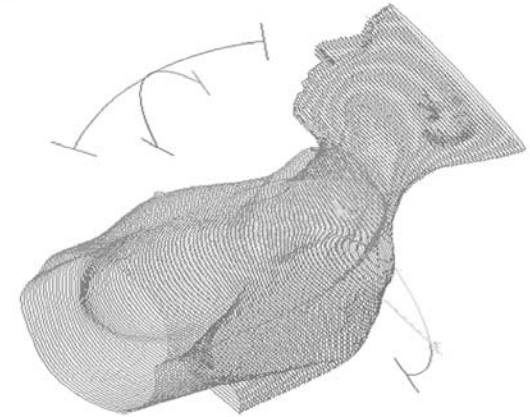


Figure 1 3D-graphical representation of the arc /beams configuration employed in Butterfly VMAT (B-VMAT) approach.

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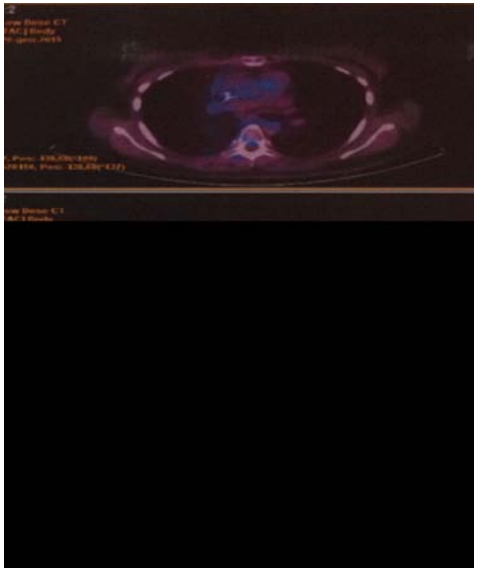
Early Stage Hodgkin Lymphoma

- Post RT CT scan: very good PR → FEAM ASCT (December 2014)
- PET evaluation 4 weeks after ASCT: complete metabolic response (CR)

After ASCT

After 4 IGEV

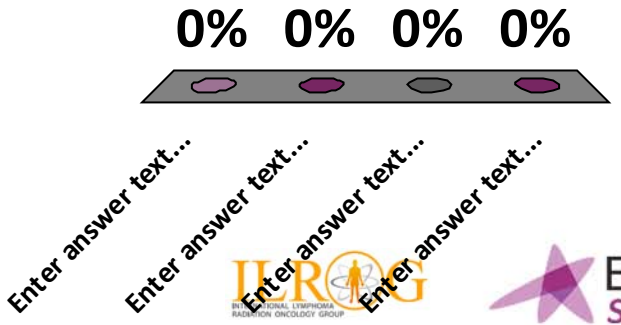
After 2 IGEV



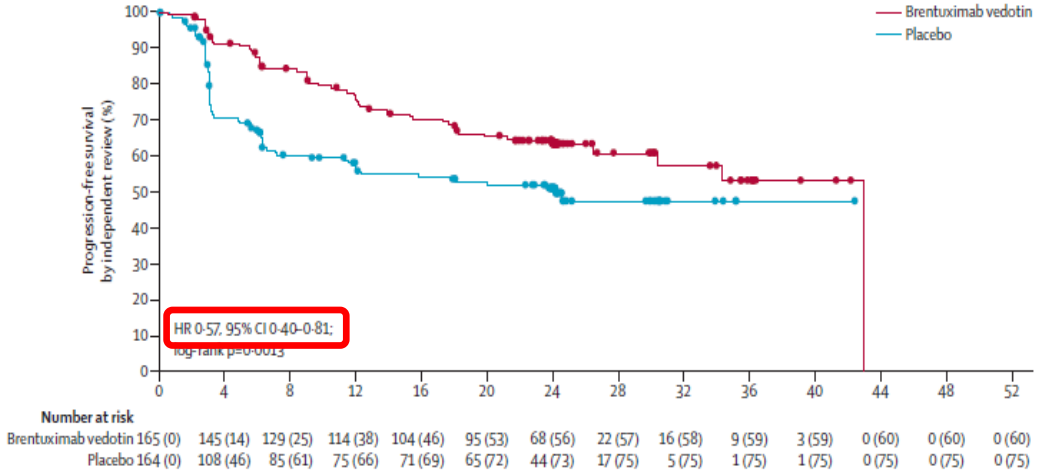
- Further therapy needed ?

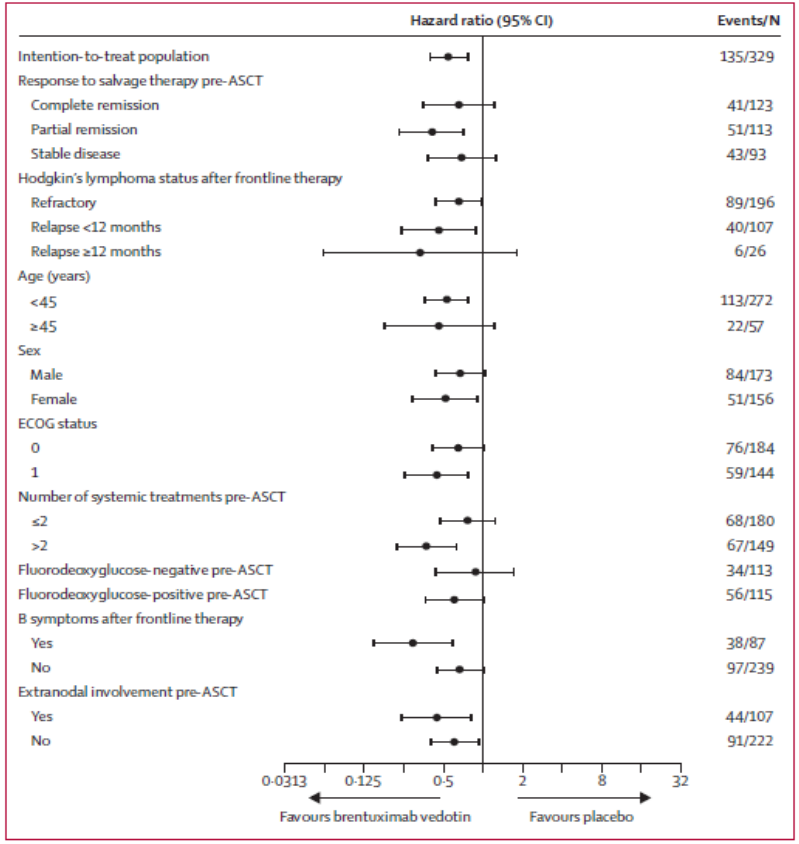
Further therapy needed?

A. No (just observation)
B. Brentuximab Vedotin
C. Anti-PD1



Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial





Moskowitz C.H. et al., The Lancet, 2015

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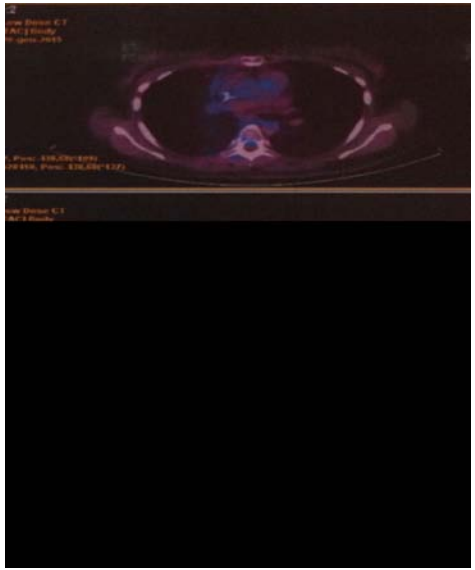
Early Stage Hodgkin Lymphoma

- Post-RT CT scan: very good PR → FEAM ASCT (December 2014)
- PET evaluation 4 weeks after ASCT: complete metabolic response (CR)

After ASCT

After 4 IGEV

After 2 IGEV



- Last follow-up (March 2016): cCR

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Case 1: Follicular lymphoma in inguinal lymph nodes

Lena Specht

48 year old male, March 2012

- Lymph nodes in right groin, increasing in size over 3-4 months
- FNA showed B-cell lymphoma, probably follicular
- No B-symptoms
- Blood tests normal (incl. LDH) except for low platelets, probably due to alcohol consumption

- Excisional biopsy of enlarged lymph node showed follicular lymphoma Grade 2, positive for CD20, CD79-alfa, CD10, bcl-2, negative for CD3 and CD5. Focal bcl-6 positivity, Ki-67 variable
- Bone marrow without lymphoma

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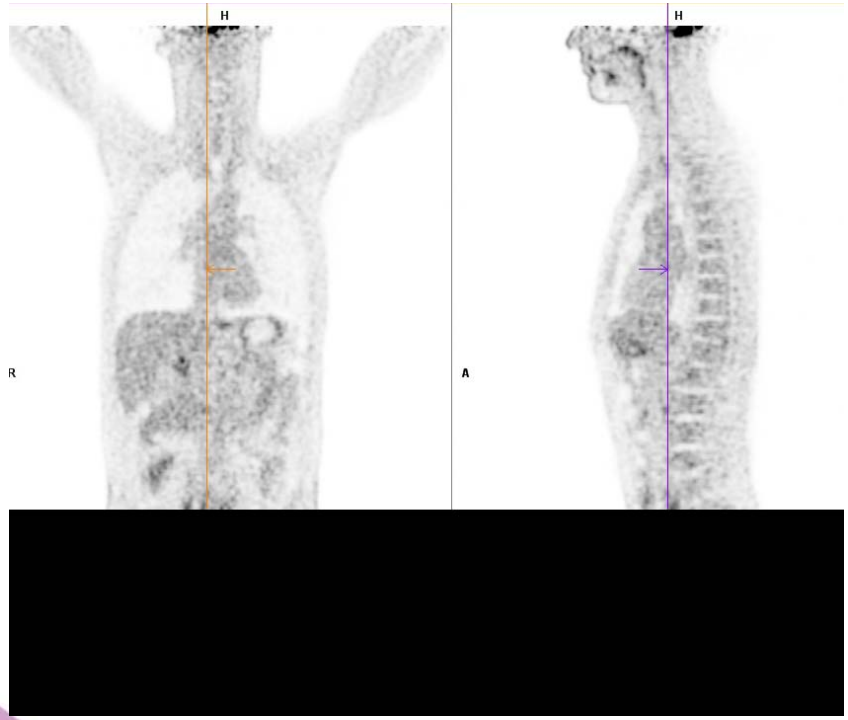
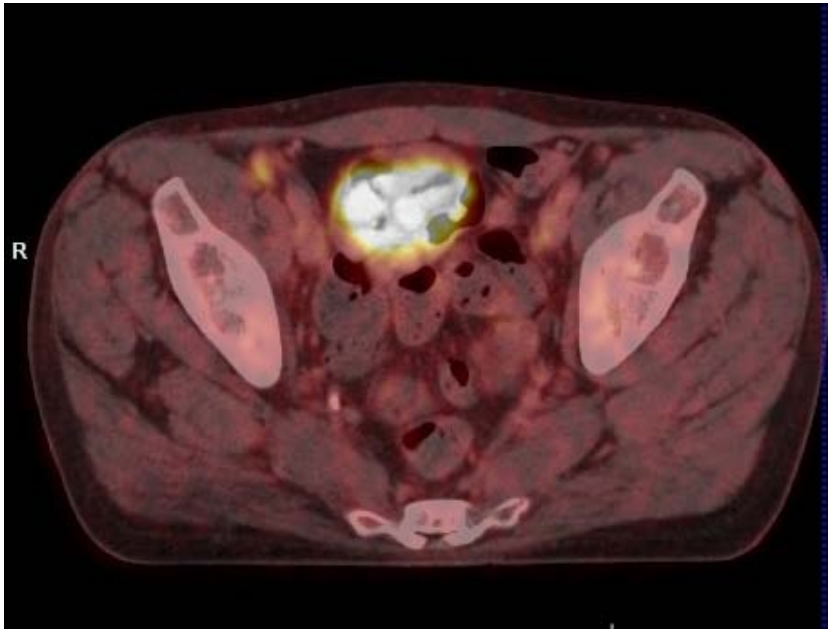
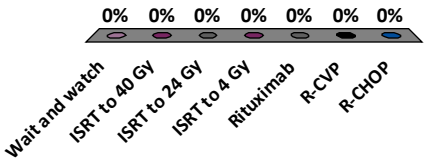
Staging PET/CT: CS IA (right groin)



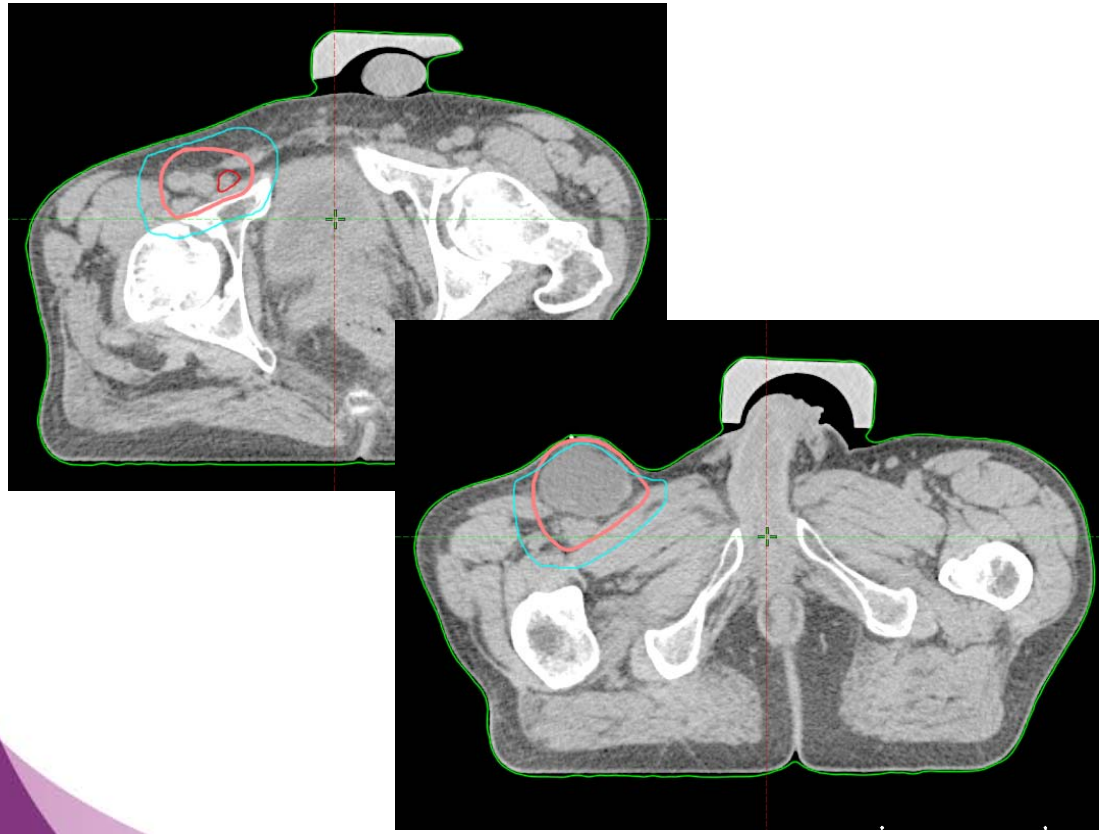


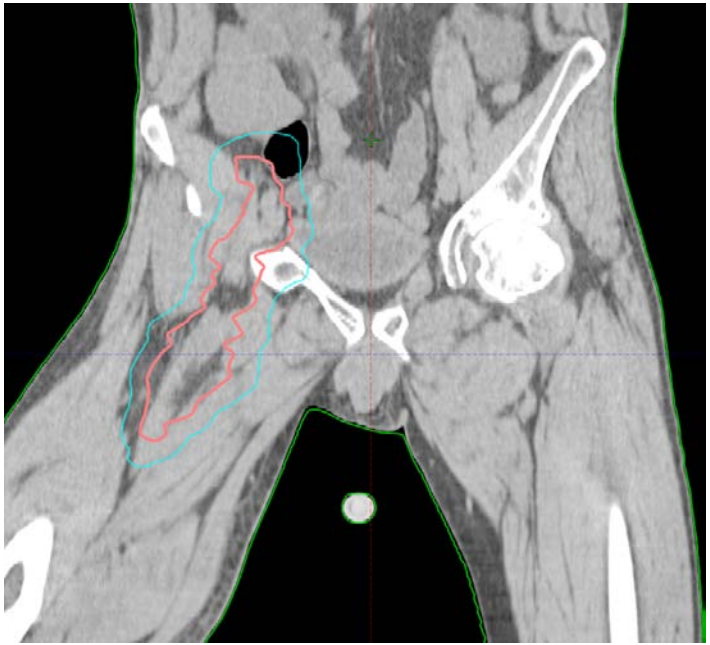
How would you treat this patient ?

A. Wait and watch
B. ISRT to 40 Gy
C. ISRT to 24 Gy
D. ISRT to 4 Gy
E. Rituximab
F. R-CVP
G. R-CHOP

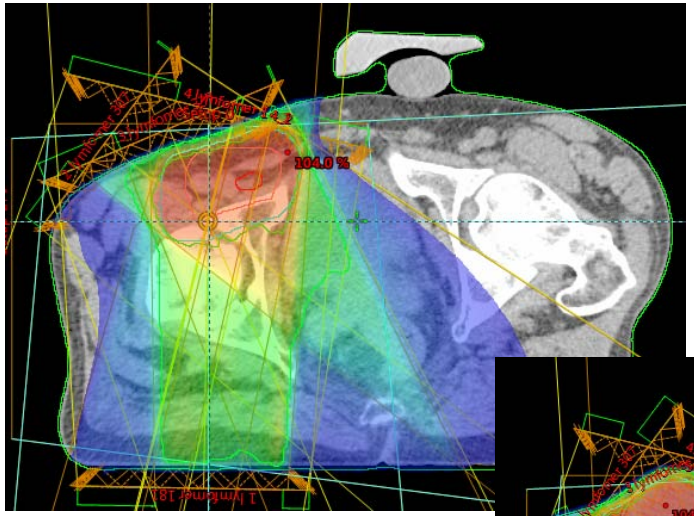


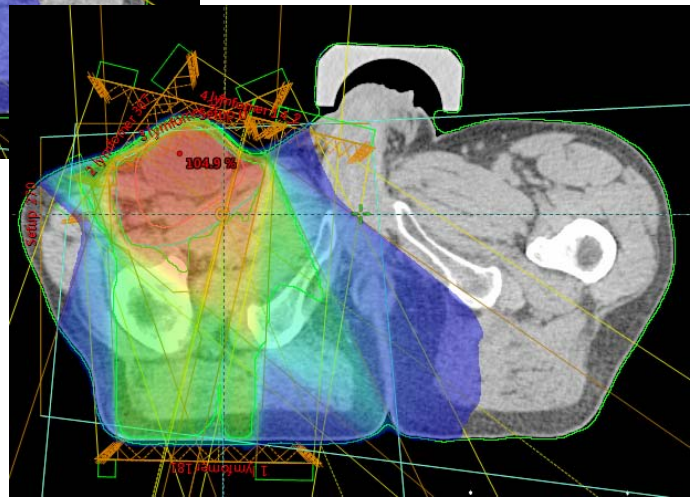
Contouring for ISRT

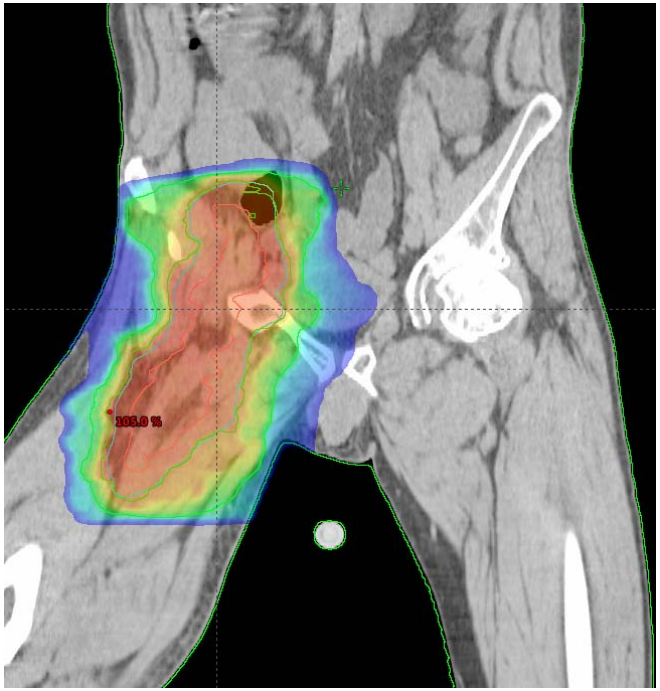




Treatment plan



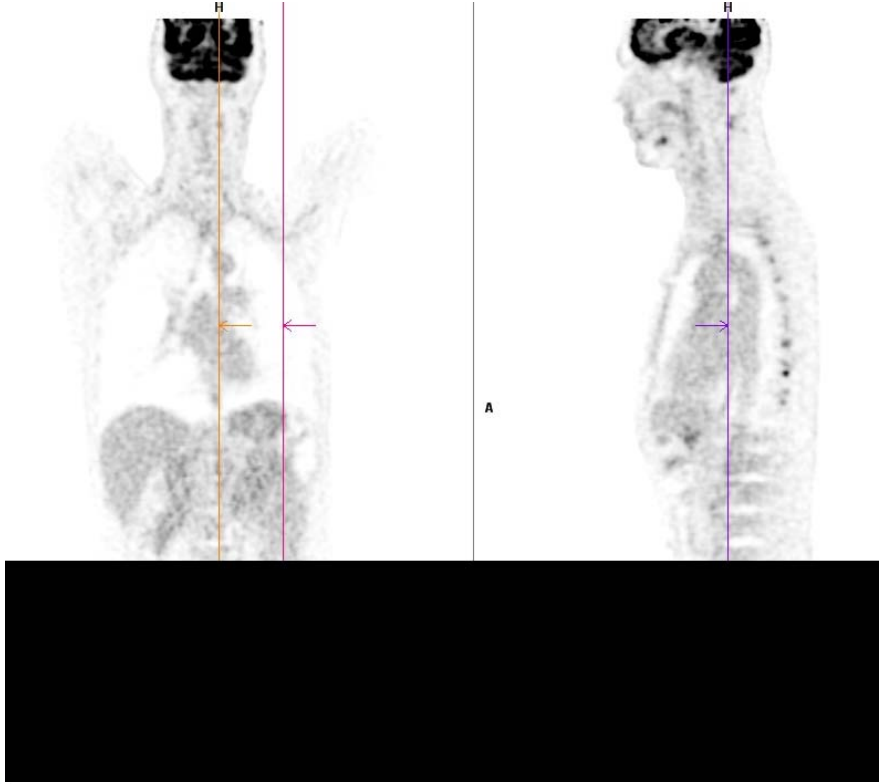


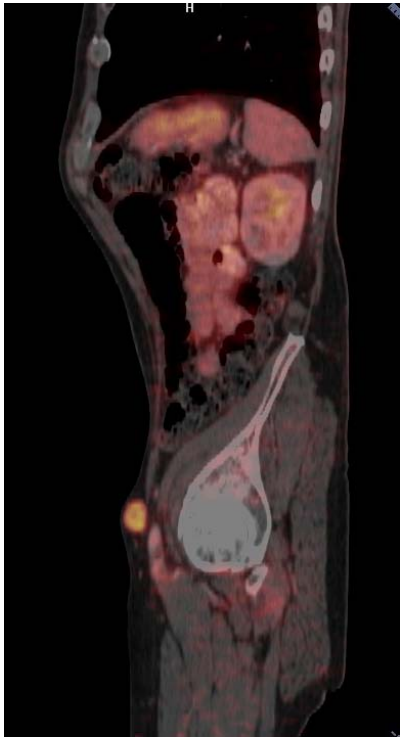


After radiotherapy

- PET/CT 2 months after RT: metabolic and structural CR
- September 2014: swelling in left groin
- No B-symptoms
- Blood tests normal, incl. normal LDH
- Bone marrow without lymphoma

PET/CT





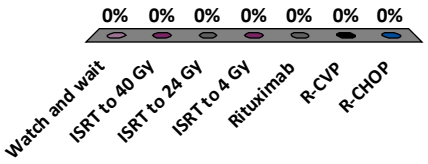
Relapse
stage IA
(left groin)

Excisional biopsy of enlarged PET+ lymph node

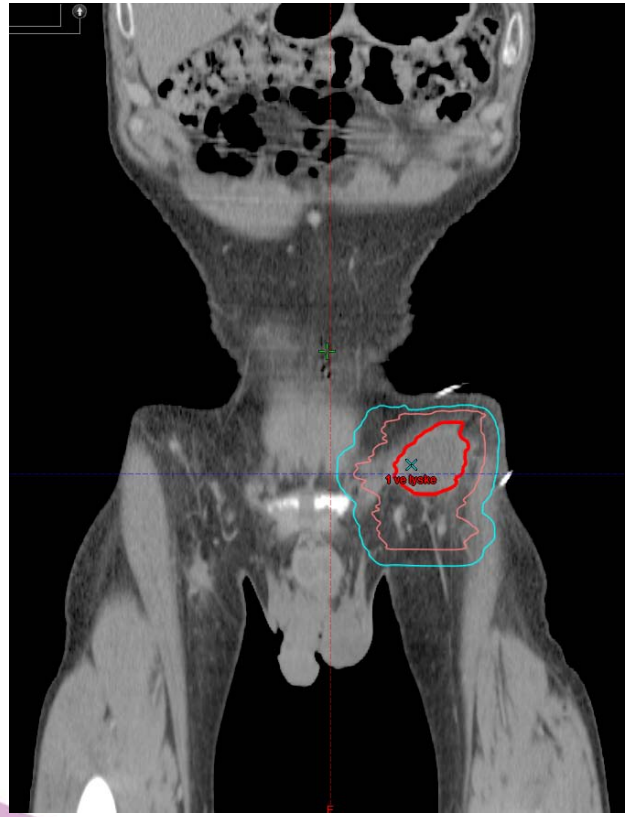
- Follicular lymphoma Grade 2, both follicular and diffuse areas
- Positive for CD20, CD10, bcl-6 and bcl-2
- High proliferation rate, Ki-67 60%

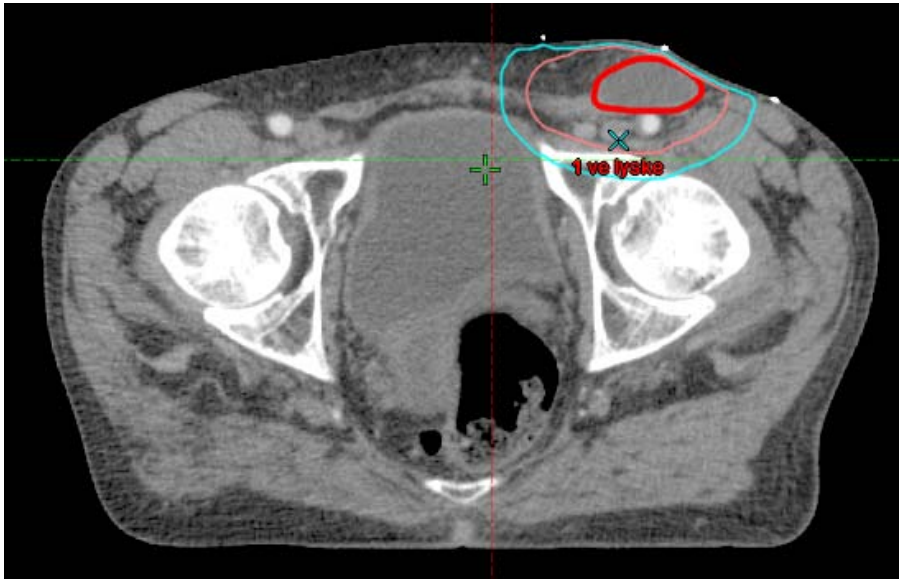
How would you treat this patient now?

A. Watch and wait
B. ISRT to 40 Gy
C. ISRT to 24 Gy
D. ISRT to 4 Gy
E. Rituximab
F. R-CVP
G. R-CHOP



Contouring for ISRT





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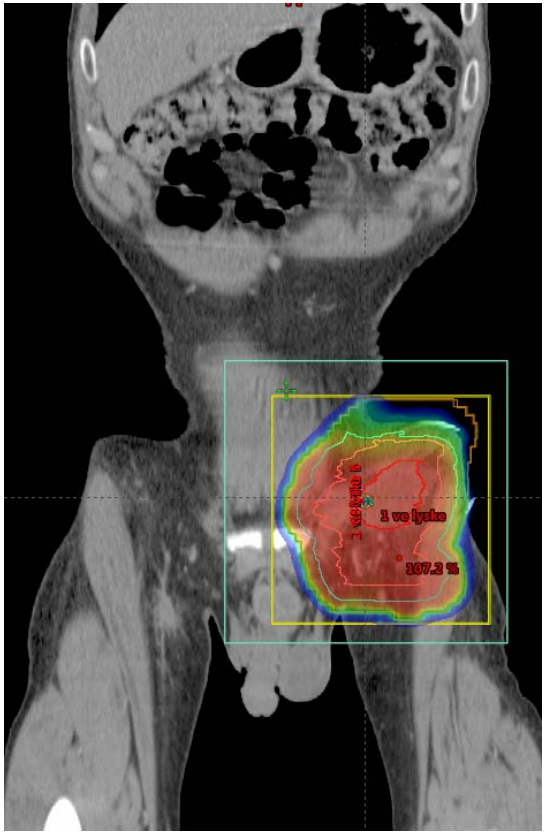
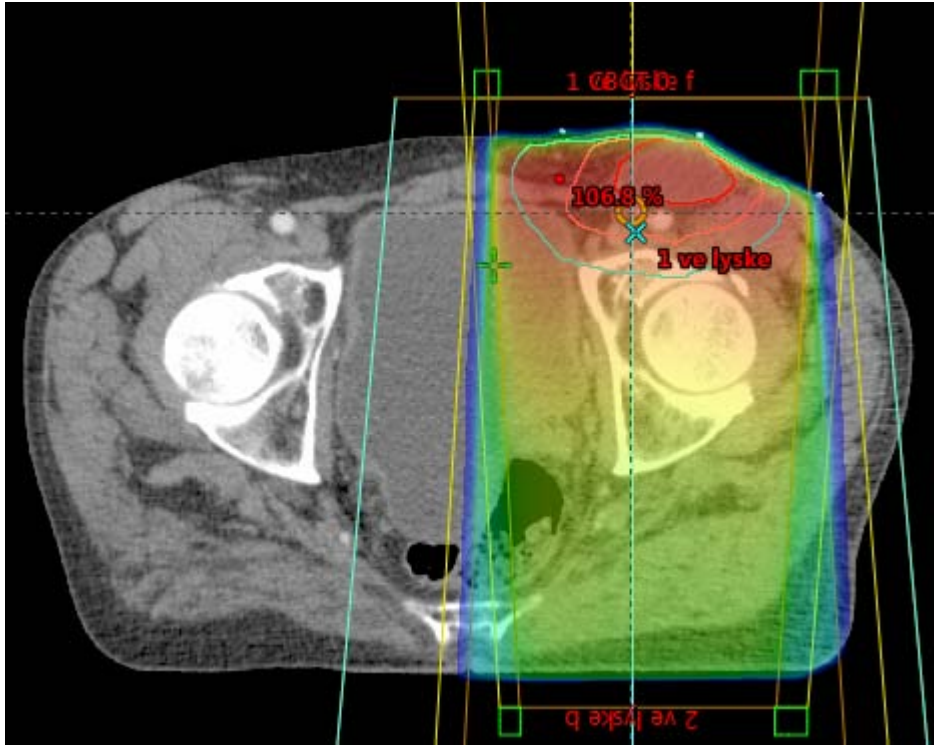
Treatment plan





After second radiotherapy

- In CR
- Informed about the risk of recurrence
- Regular follow-up
- No imaging except if recurrence is suspected

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Case 2; Marginal zone lymphoma in left lung

Lena Specht

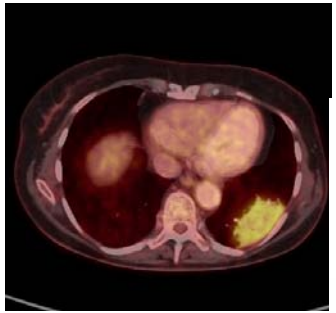
60 year old female from Greenland, February 2014

- 2009 pneumonia, after this left chest pain, subsequent CT-scan showed remaining left infiltrate, possible lung tumour, FNA negative.
- CT-scan October 2013 showed progression, 4,5 cm in diameter. Referred for examination for lung cancer
- CT-guided needle biopsy: Indolent B-cell lymphoma, positive for CD20, CD79a and bcl-2, negative for CD10, CD23, cyclinD1 and bcl-6. Low proliferation index < 5%
- Path diagnosis: Marginal zone lymphoma

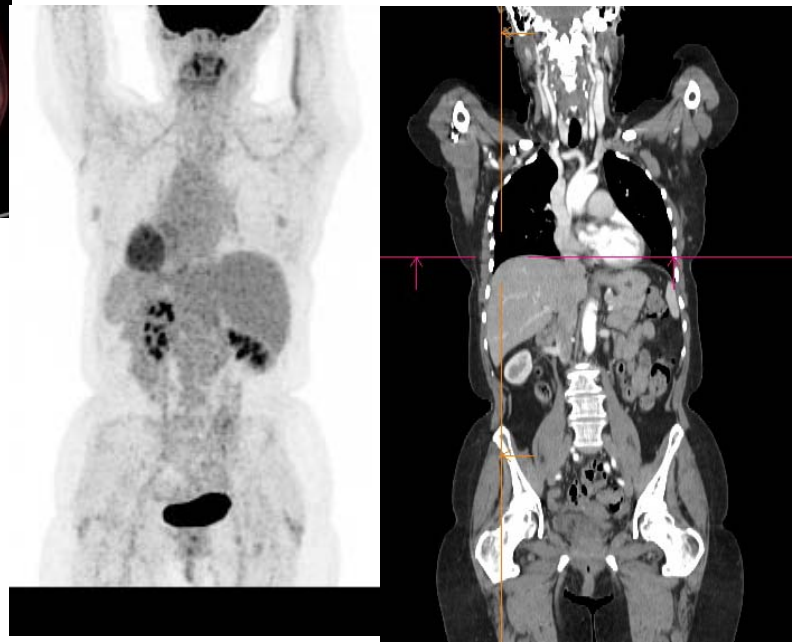
Staging

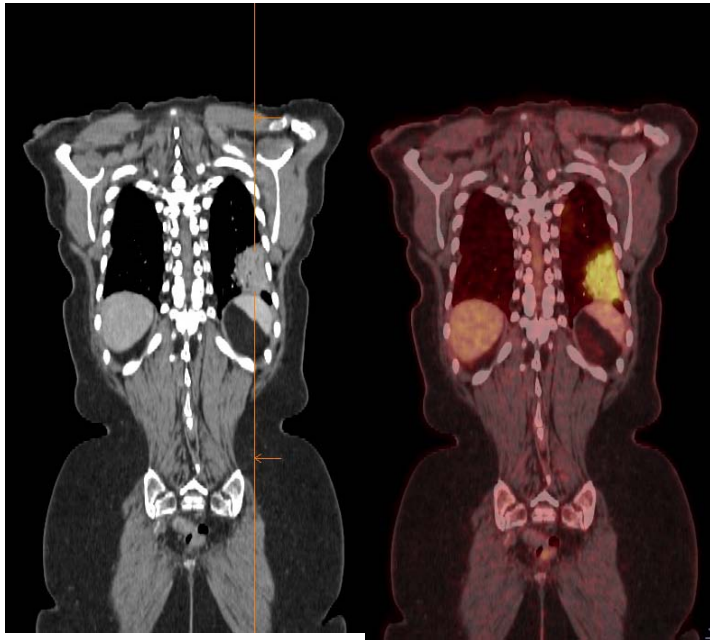
- No B-symptoms
- Normal blood tests, incl. LDH
- No bone marrow infiltration

PET/CT in deep inspiration breath hold



Free breathing





DIBH

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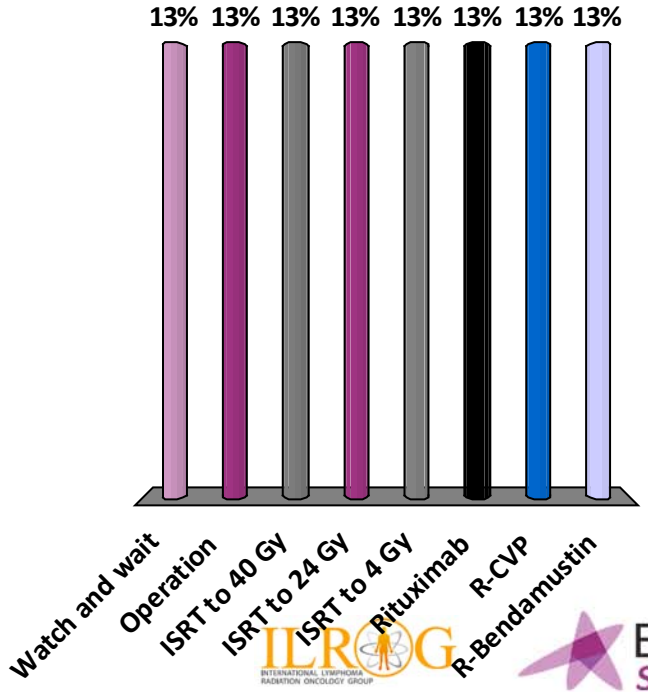
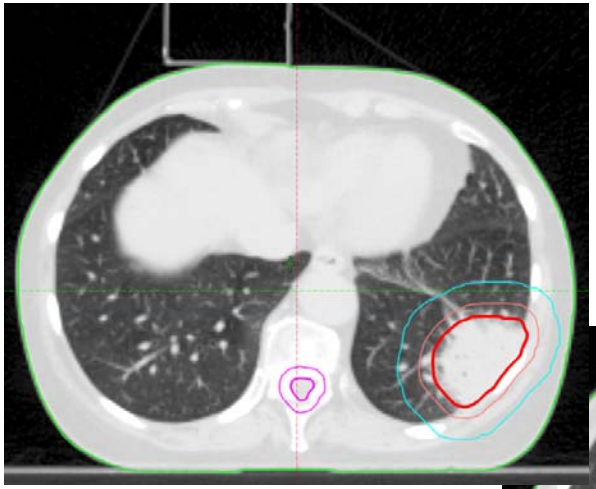
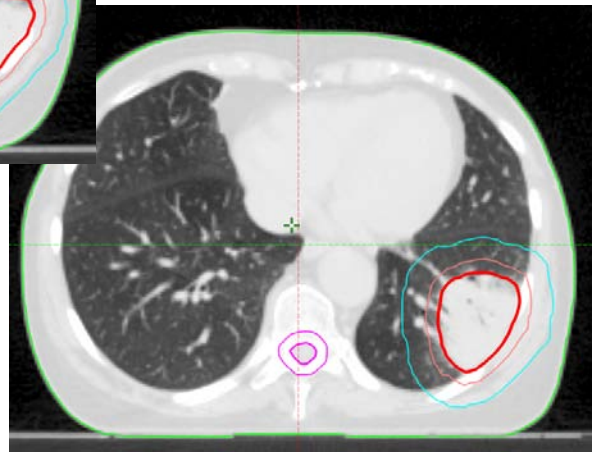
How would you treat this patient?

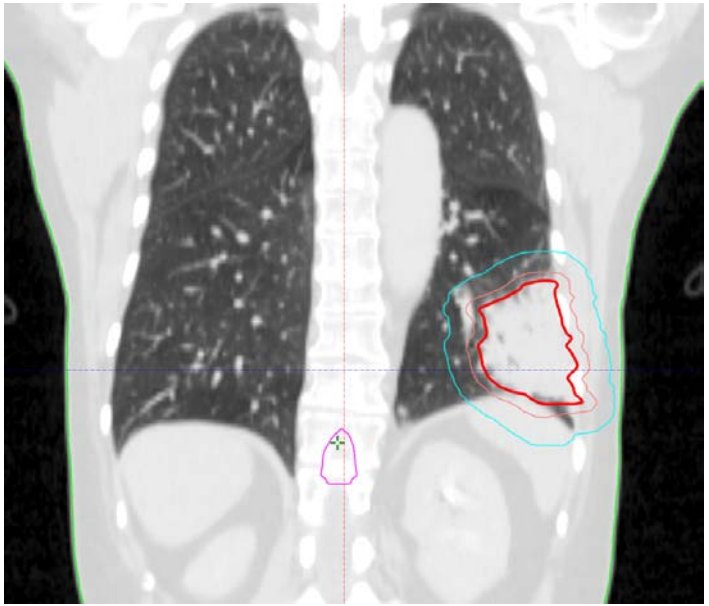
A. Watch and wait
B. Operation
C. ISRT to 40 Gy
D. ISRT to 24 Gy
E. ISRT to 4 Gy
F. Rituximab
G. R-CVP
H. R-Bendamustin



Contouring for ISRT in deep inspiration breath hold







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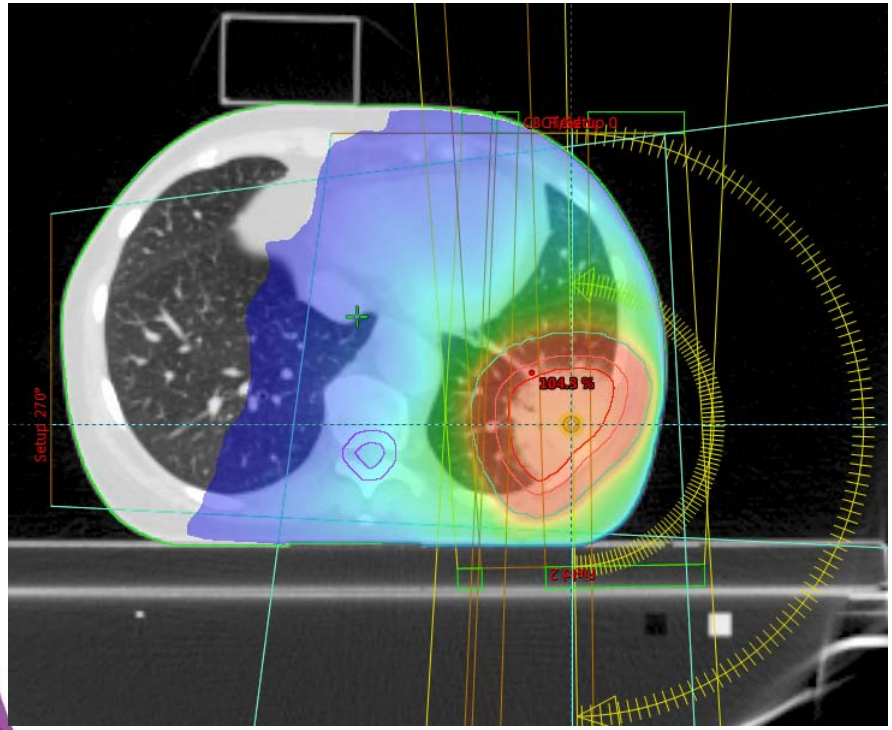
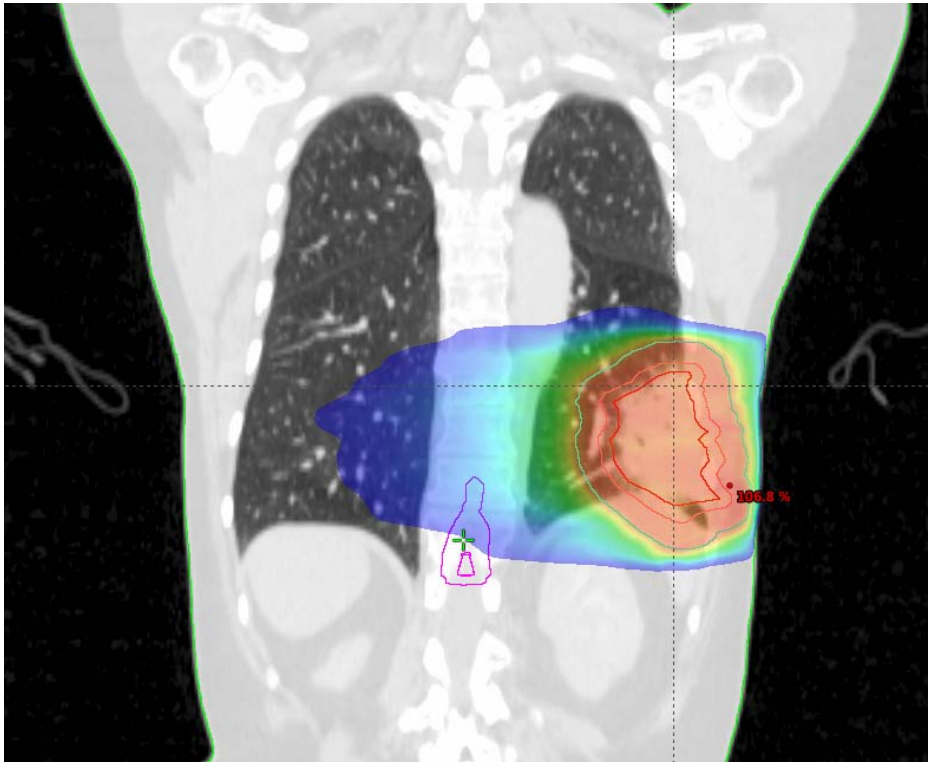
Treatment plan





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After radiotherapy

- PET/CT 2 months after radiotherapy: metabolic and structural regression, reactive changes in surrounding lung tissue with shrinkage and atelectasis
- Improved respiration, less pain
- Followed with CT-scans without signs of relapse

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Case 3: DLBCL in left maxilla

Lena Specht

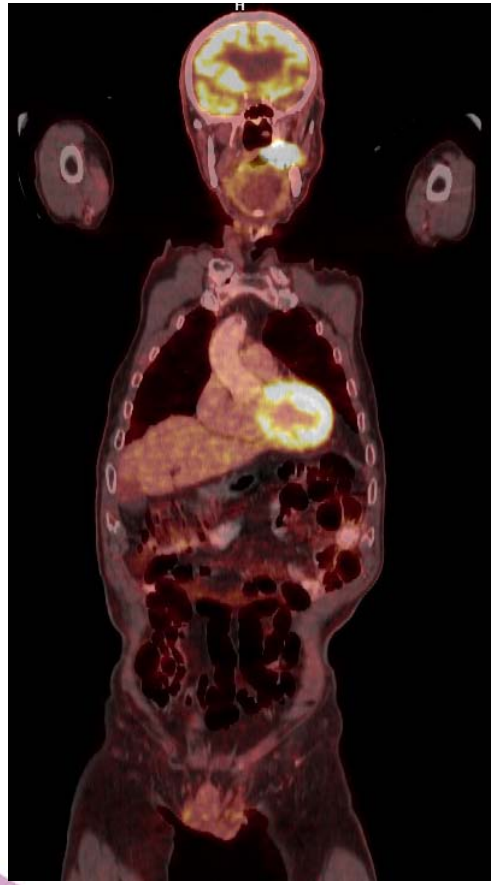
87 year old male, December 2014

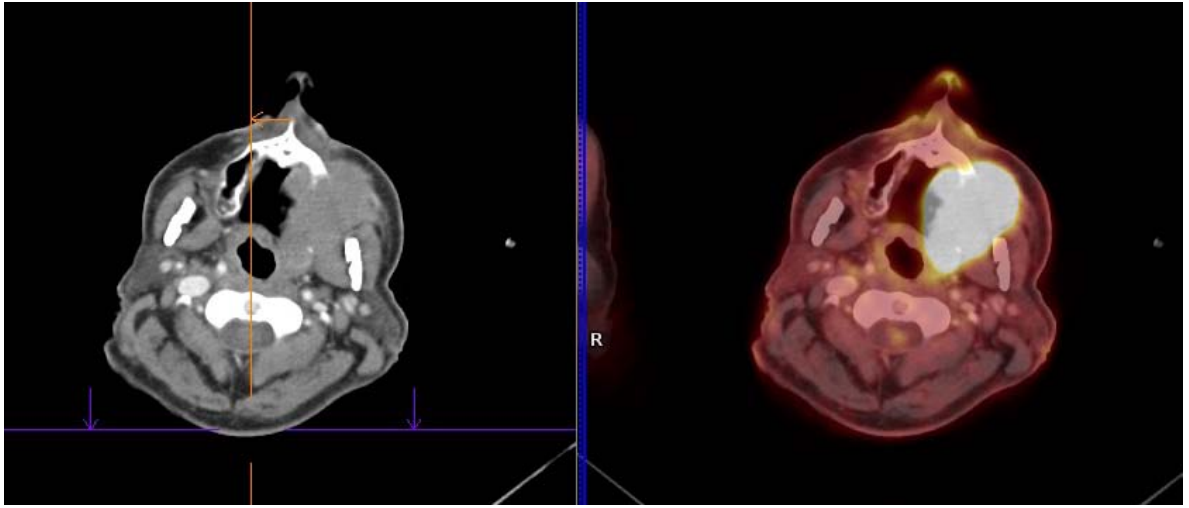
- Problems with upper dentures
- ENT surgeon found large tumour in left hard and soft palate
- Biopsy: Diffuse large B-cell lymphoma, positive for CD20, CD79a, bcl-2, bcl-6, MUM-1, negative for CD5, CD10, CD23 and cyclinD1. High proliferative index 80%

Staging

- Weight loss 7-8 kg over 3 months
- No other B-symptoms
- Normal LDH
- No bone marrow infiltration

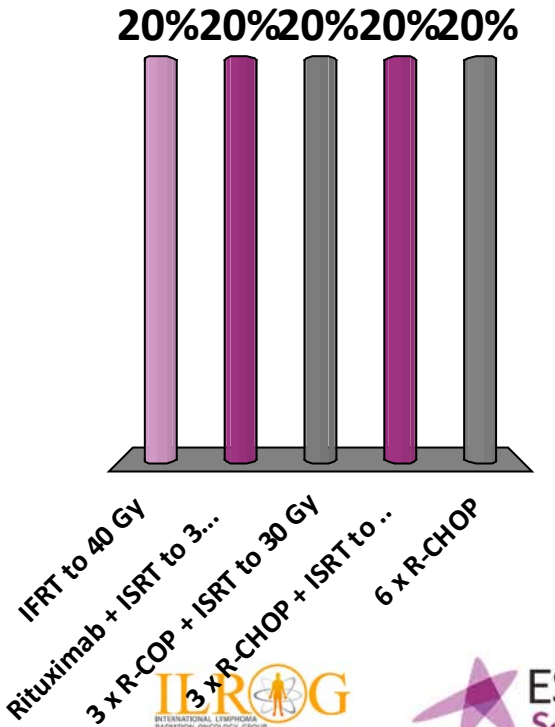
PET/CT: CS IEA





How would you treat this patient?

A. IFRT to 40 Gy
B. Rituximab + ISRT to 30 Gy
C. 3 x R-COP + ISRT to 30 Gy
D. 3 x R-CHOP + ISRT to 30 Gy
E. 6 x R-CHOP



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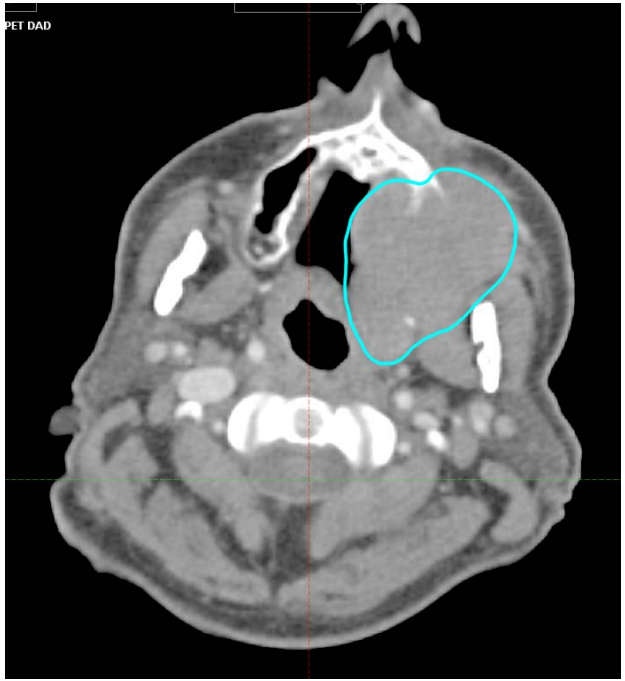
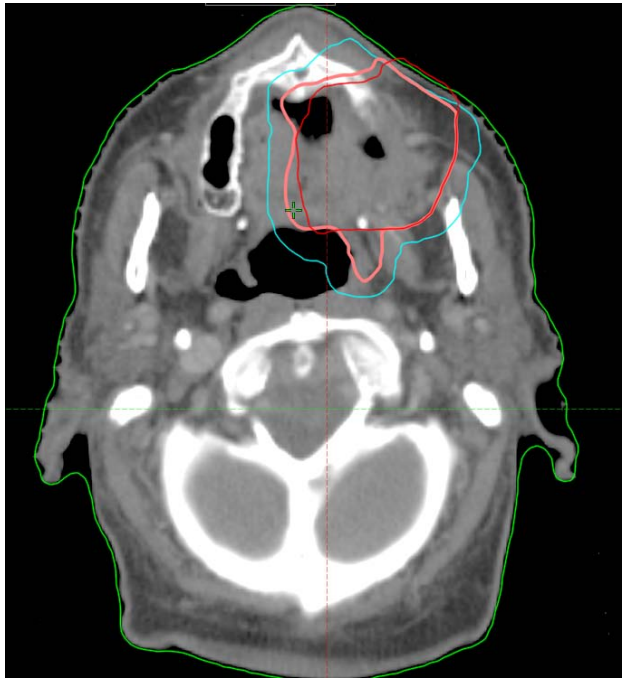
Treatment

- 3 cycles of R-CHOP21 (slightly reduced dose) with Neulasta
- Rapid tumour shrinkage
- Managed chemotherapy with few side effects
- ISRT 30 Gy

Contouring for ISRT

pre-chemo PET+ volume (left) and post-chemo CTV (right)





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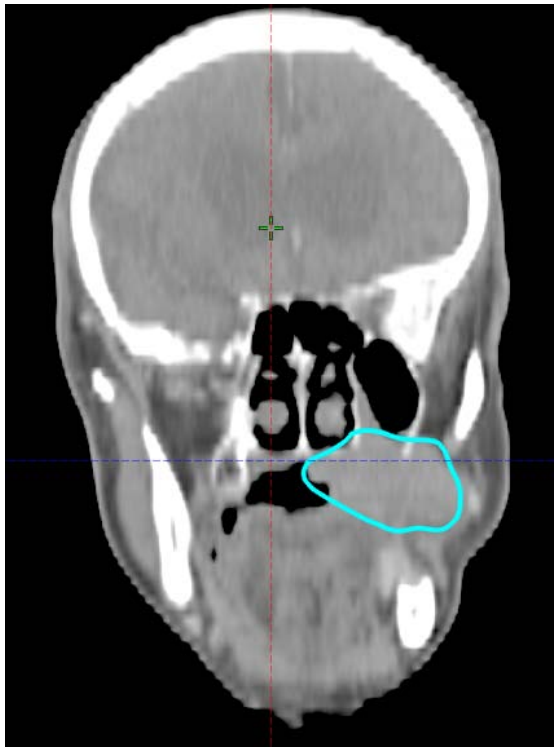
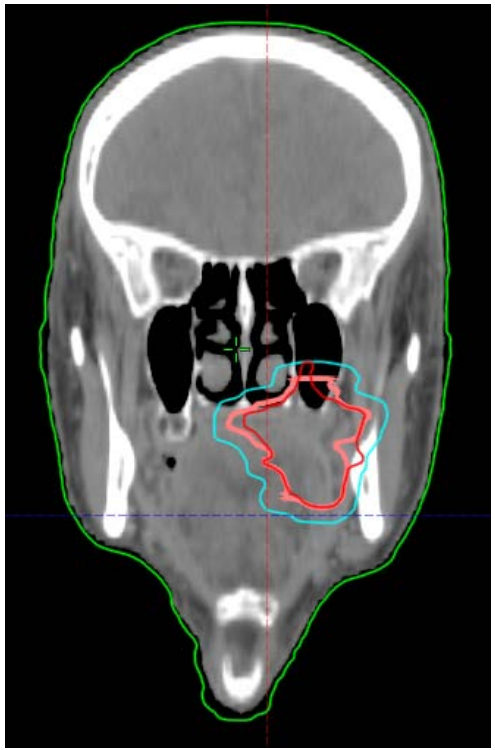
Contouring for ISRT

pre-chemo PET+ volume (left) and post-chemo CTV (right)





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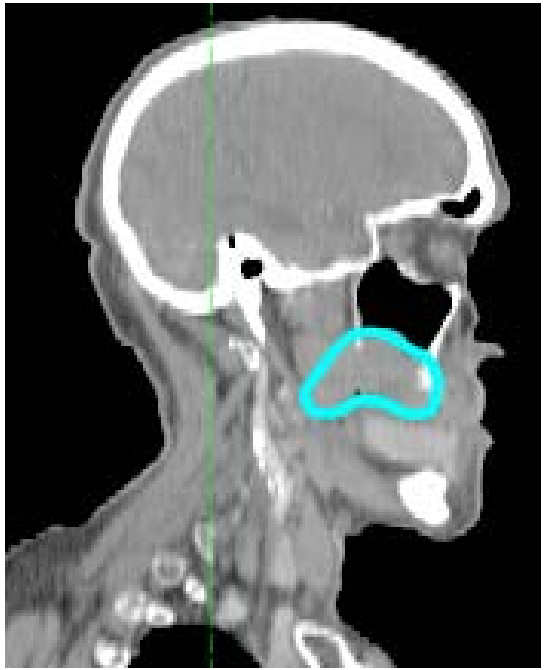
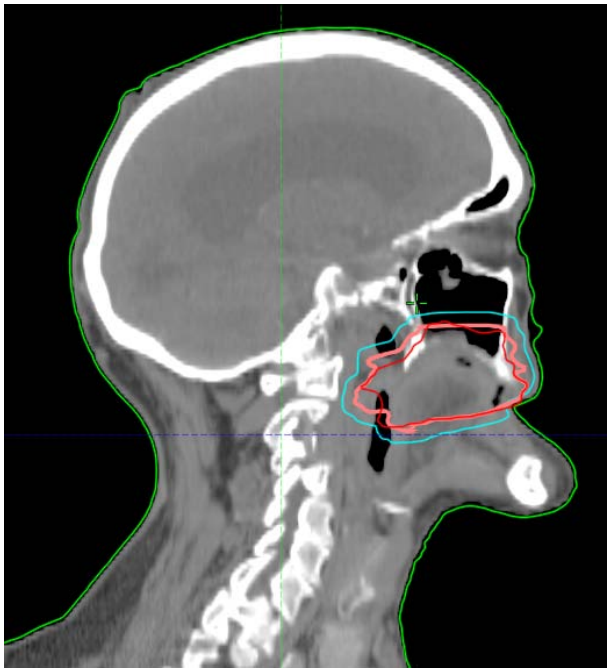
Contouring for ISRT

pre-chemo PET+ volume (left) and post-chemo CTV (right)





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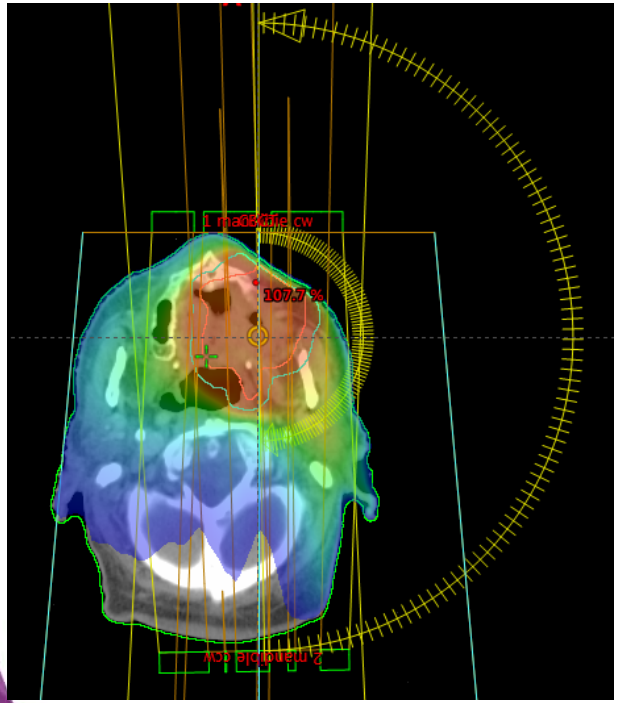
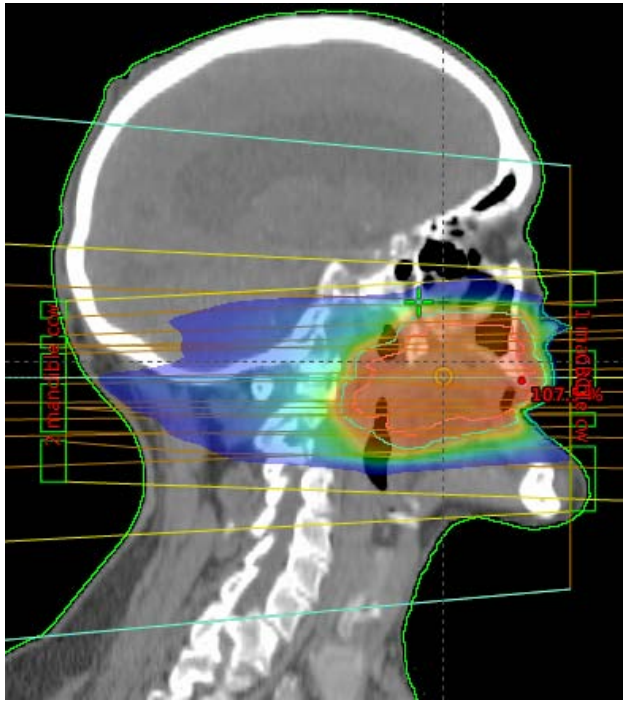
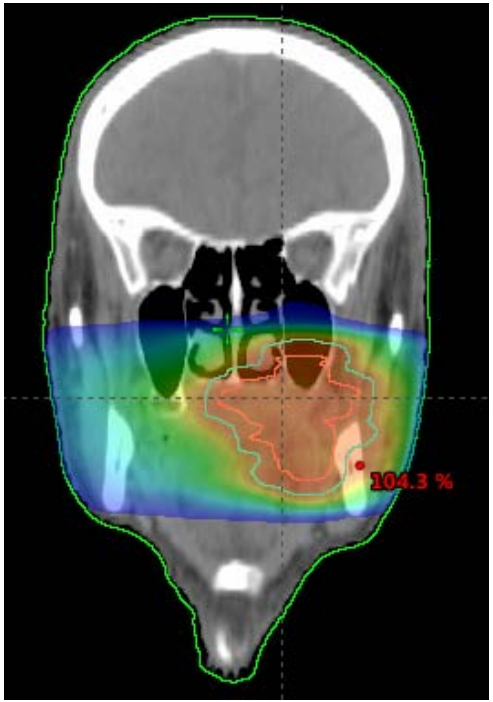
Treatment plan







After chemo-radiotherapy

- PET/CT 2 months after treatment: Complete metabolic and structural remission
- In PS 0

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Case 4: Mantle cell lymphoma in right tonsil and neck

Lena Specht

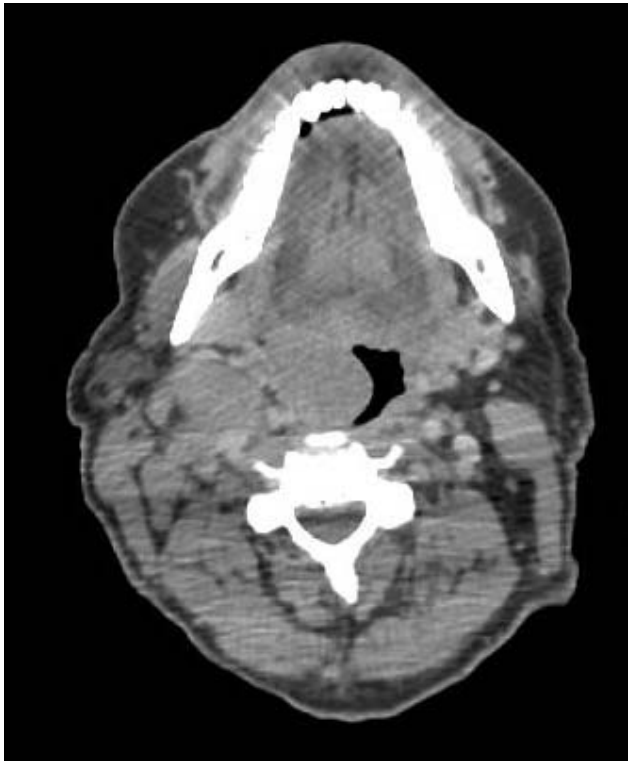
70 year old male, May 2014

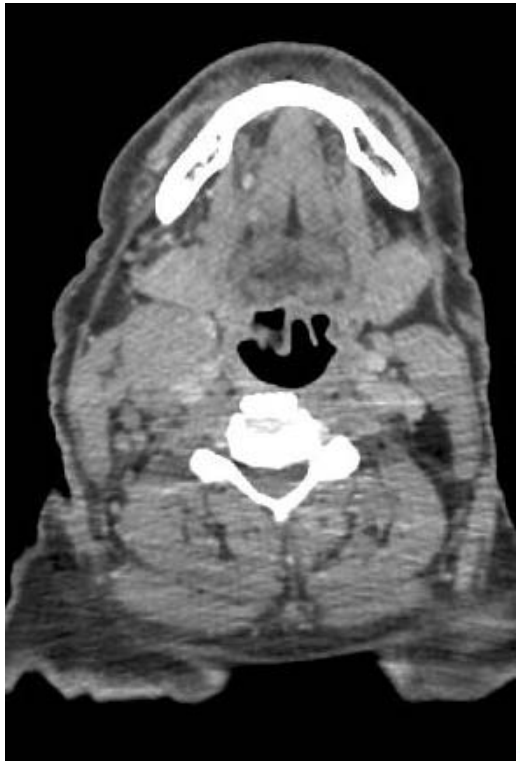
- Swelling right neck for 2 months
- Referred to ENT surgeon, who found enlarged right tonsil
- Biopsy: Classical mantle cell lymphoma, positive for CD20, CD79a, bcl-2, CD5, CyclinD1, negative for CD10 and CD23. Proliferation rate 5%

Staging: CS IIA

- CT-scan of neck, chest, abdomen and pelvis demonstrated right tonsillar mass, 8 x 5 x 3 cm, right neck lymph nodes, no other involvement
- No bone marrow involvement
- Normal LDH
- MIPI 5.7 (low-intermediate risk)

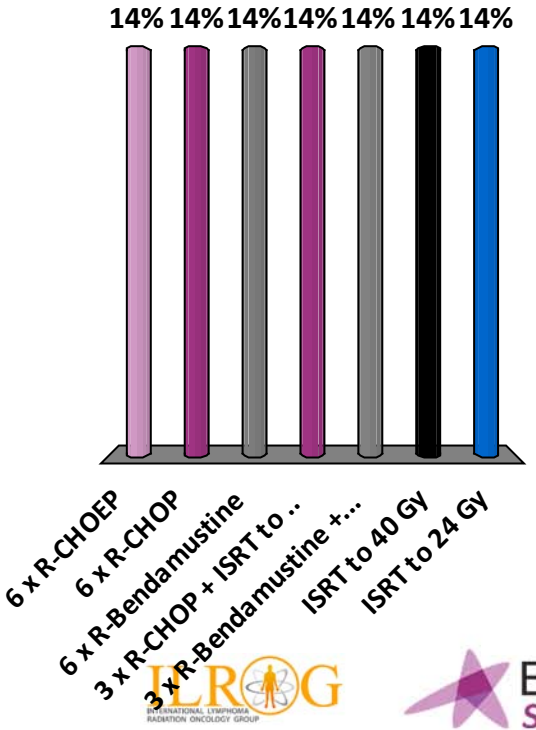
Staging CT-scan





How would you treat this patient?

A. 6 x R-CHOEP
B. 6 x R-CHOP
C. 6 x R-Bendamustine
D. 3 x R-CHOP + ISRT to 30 Gy
E. 3 x R-Bendamustine + ISRT to 30 Gy
F. ISRT to 40 Gy
G. ISRT to 24 Gy



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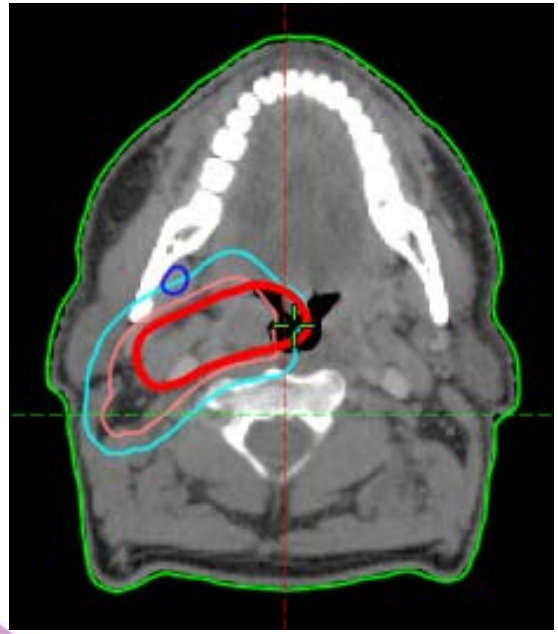
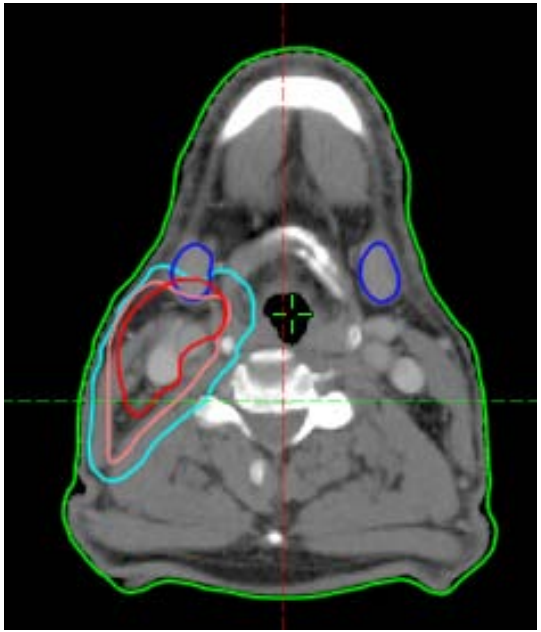
Treatment

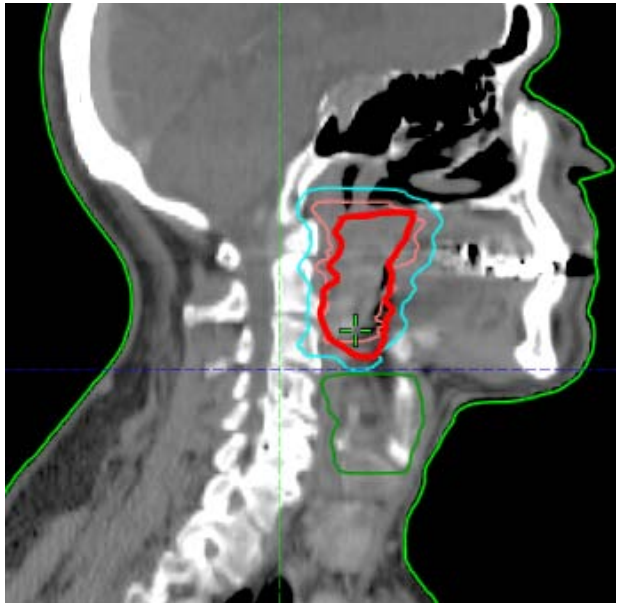
- 3 x R-Bendamustine
- Rapid tumour shrinkage
- ISRT to 30 Gy

Contouring for ISRT

pre-chemo GTV, post-chemo CTV







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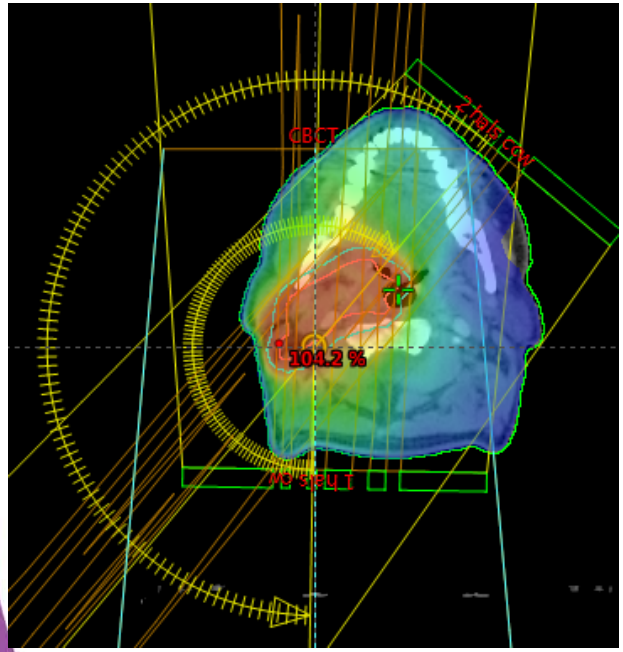
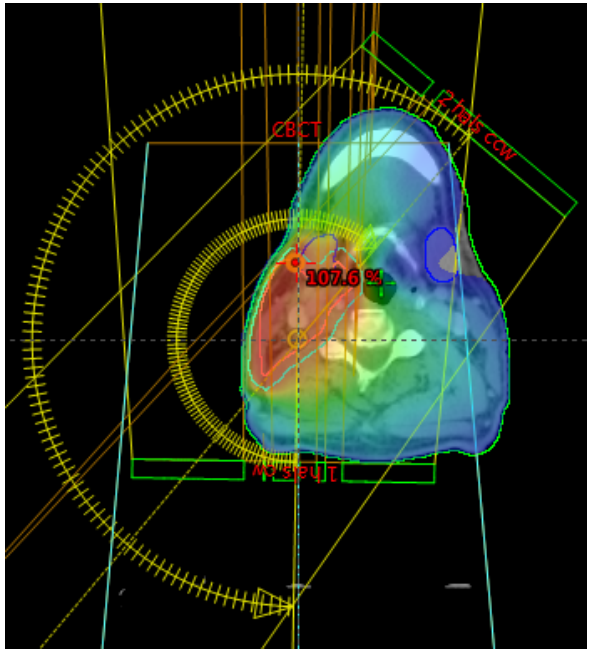
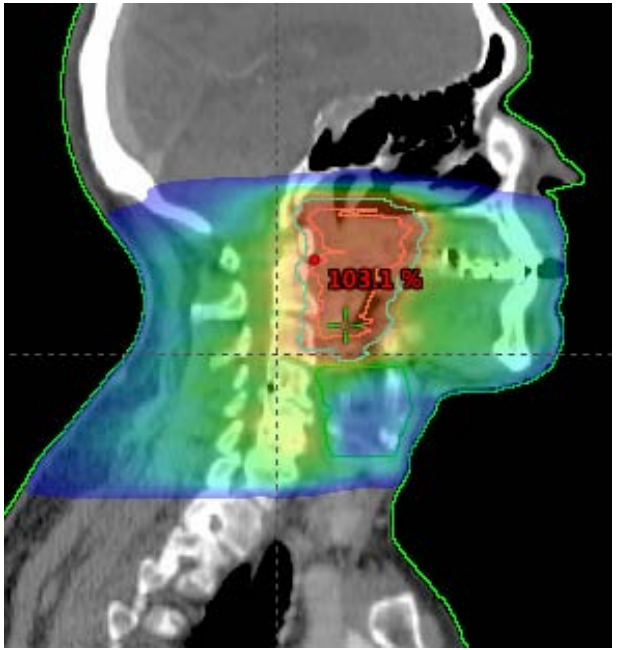
Treatment plan







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After chemo-radiotherapy

- CT 2 months after treatment: Complete remission
- In PS 0
- Some dryness of mouth, otherwise asymptomatic

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Case 5: DLBCL in right nasopharynx

Lena Specht

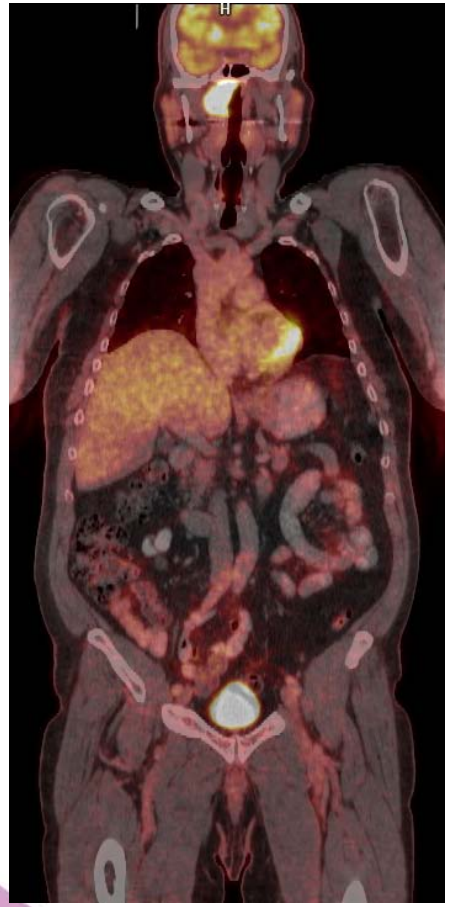
70 year old male, June 2014

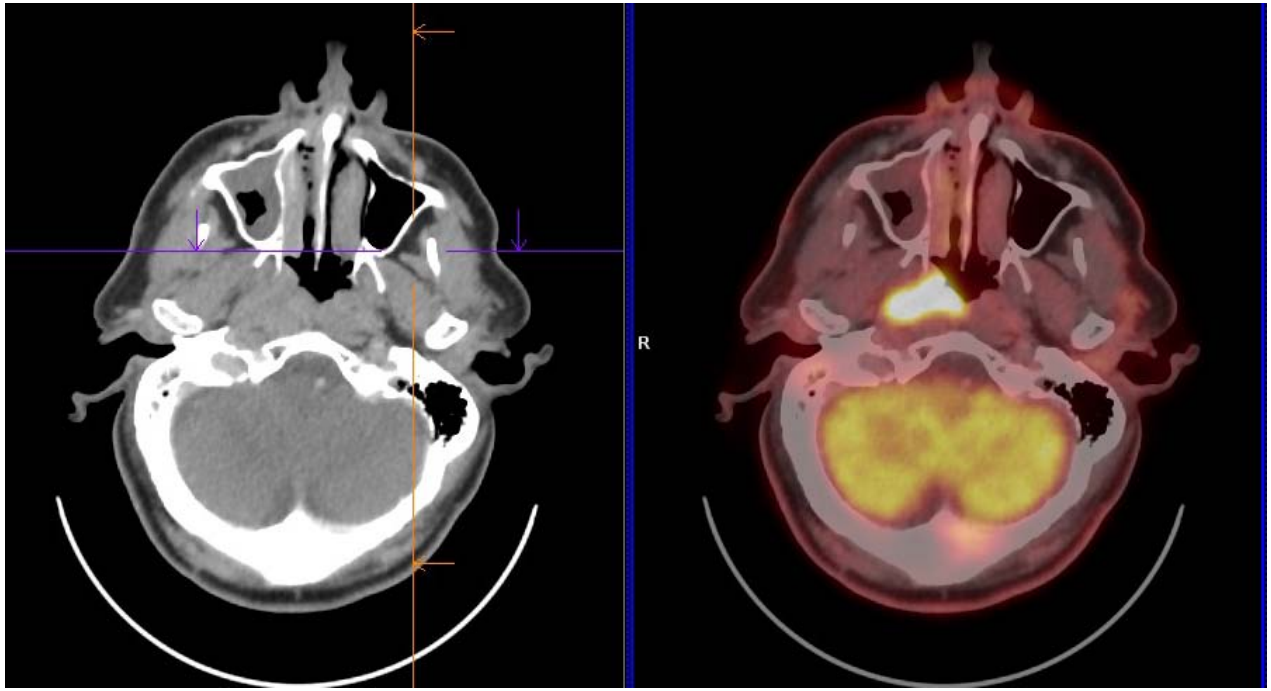
- Right otalgia and hearing loss, blocked nose of 6 months duration
- Referred to ENT dept., biopsy from nasopharynx showed DLBCL, GCB-type

Staging

- No B-symptoms
- Normal LDH
- No bone marrow infiltration

PET/CT: CS IEA





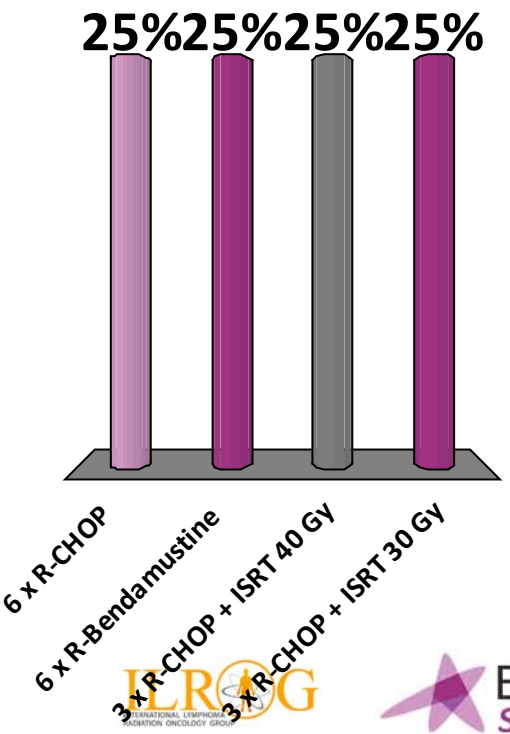
How would you treat this patient

A. 6 x R-CHOP

B. 6 x R-Bendamustine

C. 3 x R-CHOP + ISRT 40 Gy

D. 3 x R-CHOP + ISRT 30 Gy

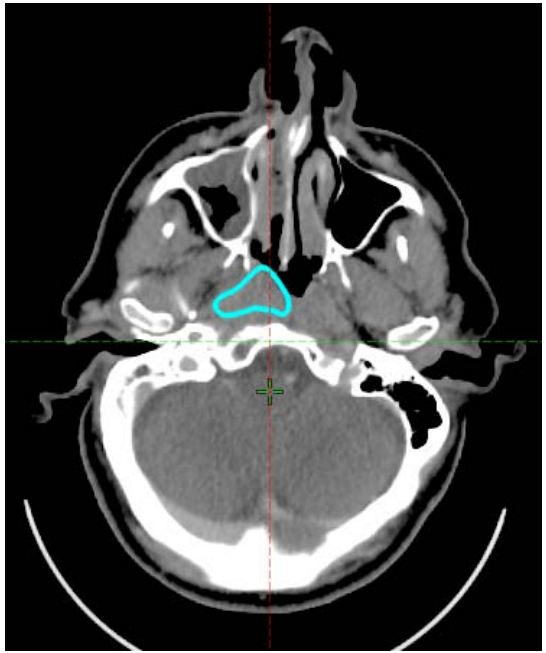


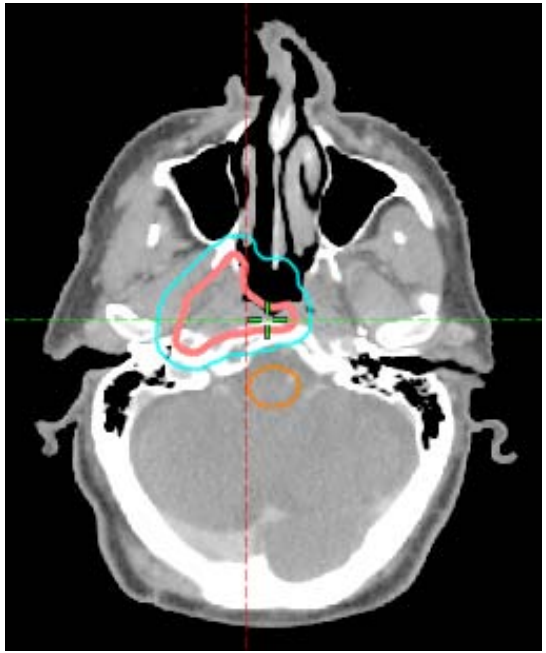
Treatment

- 3 cycles of R-CHOP21
- During chemotherapy improved hearing
- Managed chemotherapy with few side effects
- ISRT 30 Gy

Contouring for ISRT

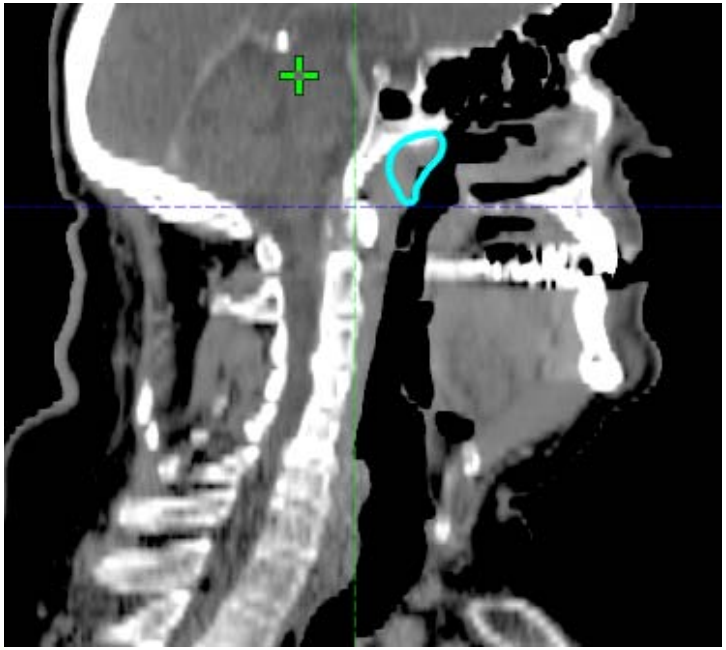
pre-chemo PET+ lymphoma and post-chemo CTV

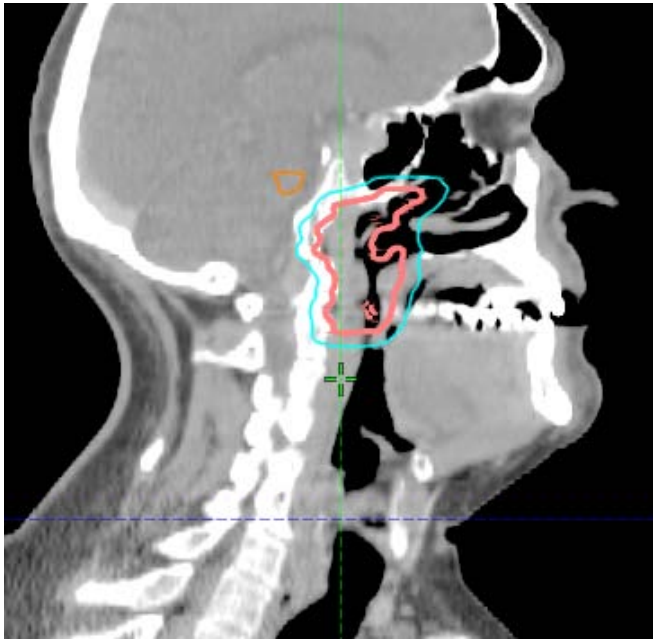




Contouring for ISRT

pre-chemo PET+ lymphoma and post-chemo CTV





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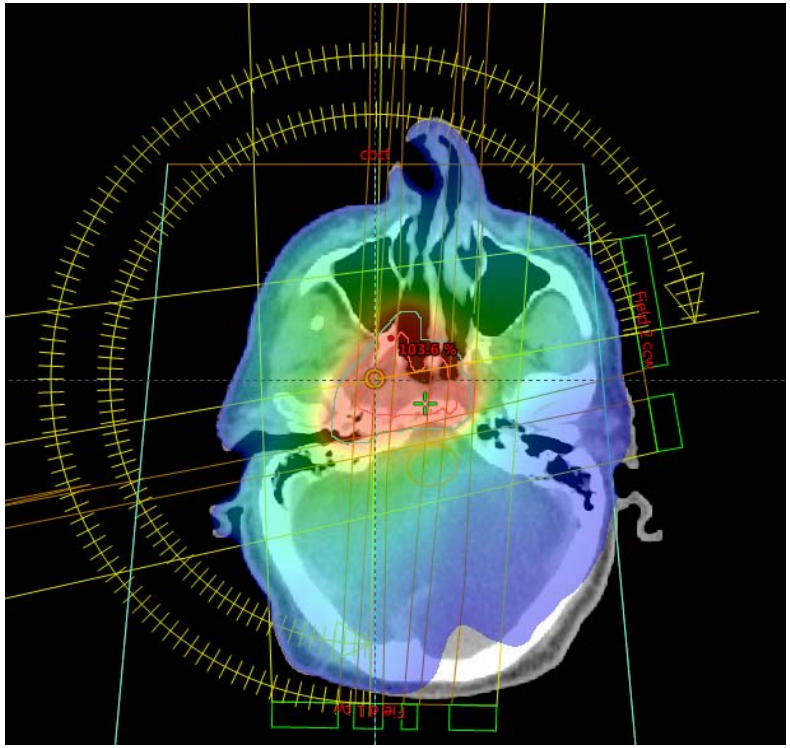
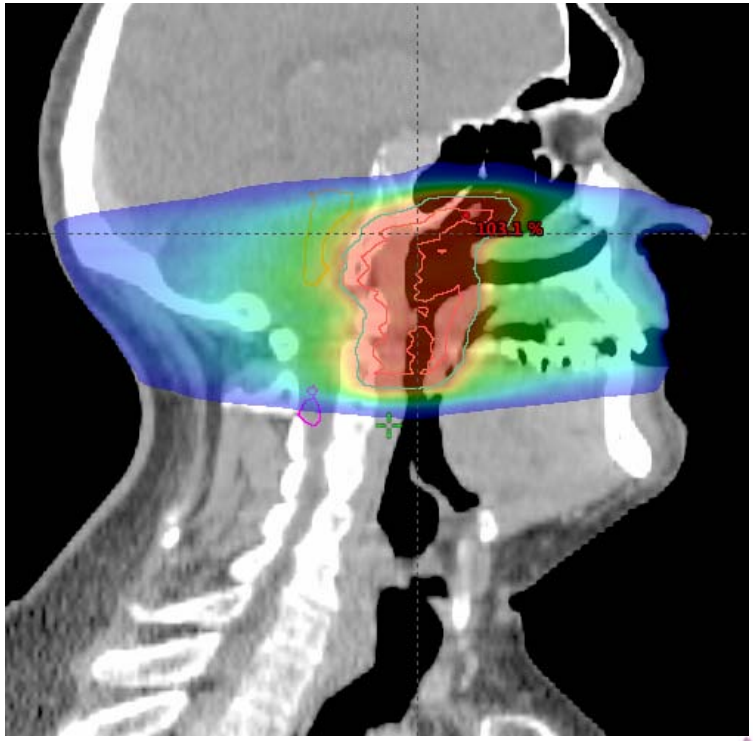
Treatment plan





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After chemo-radiotherapy

- PET/CT 2 months after treatment: Complete metabolic and structural remission
- In PS 0
- Slight dryness of mouth