WELCOME AND INTRODUCTION

UPPER GI: TECHNICAL AND CLINICAL CHALLENGES FOR RADIATION ONCOLOGISTS - FULLY BOOKED

25-28 March, 2017
Rome, Italy

ESTRO School

WELCOME AND INTRODUCTION

COURSE AIM

The aim of the course is to support an interactive educational environment by peer review of each step of radiation therapy practice (indication, prescription, delineation, planning, IGRT, outcome evaluation) according to the modern available technologies and knowledge and taking care of the clinician, physicist and RTT perspectives.

WELCOME AND INTRODUCTION

COURSE AIM

Specialists of different disciplines will support the radiation oncology audience in understanding the clinical needs, anatomic and pathologic details, and the therapeutic achievements needed to exploit the radiation technology at the best.

WELCOME AND INTRODUCTION

COURSE AIM

- Radiation Oncologists
Vincenzo Valentini (IT)
Marcel Verheij (NL)
Oscar Matzinger (CH)

- Physicist,
Dirk Verellen (BE)

- RTT
Lisa Wiersema (NL)

- Delineation Administrator
Francesco Cellini, RO (IT)

- Surgeon,
William Allum (UK)

- Medical oncologist
Florian Lordick (DE)
Nicola Silvestris (IT)

- Radiologist
Angela Riddell (UK)
Riccardo Manfredi (IT)

- Pathologist
Alexander Quaas (DE)

LEARNING OUTCOMES

By the end of this course, for each upper GI tumour site, participants should be able to practice:

- Proper indication for radiation therapy in a multidisciplinary perspective
- Prescription
- Tailored delineation according to tumour location and stage
- Dose distribution optimisation and comparison
- Optimal use of available IGRT technologies
- Proper monitoring of tumour response an control.

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COURSE CONTENT

Session 1: Prescription

Participants will be invited to make their prescription on cases, that will be afterward delineated and planned in the following sessions, by a monkey questionnaire. Lectures on imaging based staging and state of art of treatment will help the final discussion.

COURSE CONTENT

Clinical cases

Esophageal

- Mid third
- GEJ

Gastric

- Partial gastrectomy
- Total gastrectomy

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COURSE CONTENT

25 March (Saturday)			Speaker
	12.00 – 12.30	Registration	
	12.30 – 13.00	Welcome and Introduction Faculty and Participants	V.Valentini, Faculty, Participants
Esophageal cancer			
Session 1 Prescription	13.00-13.30	**Prescription interactive exercise**	All
	13.30-14.50	**Lecture (20'): imaging based staging and response evaluation**	A.Riddell
		Lecture (20'): state of art of surgery in a combined treatment perspective	W.Allum
		Lecture (20'): state of art of radiation therapy in a combined treatment perspective	V.Valentini
		Lecture (20'): state of art of chemotherapy in a combined treatment perspective	F.Lordick
	14.50-15.30	**Prescription interactive exercise**	All teachers

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COURSE CONTENT

27 March (Monday)			Speaker
Gastric cancer			
Session 7 Prescription	8.30-9.00	**Prescription interactive exercise**	All
	9.00-10.20	**Lecture (20'): Imaging based staging**	A.Riddel
		Lecture (20'): state of art of surgery in a combined treatment perspective	W.Allum
		Lecture (20'): state of art of radiation therapy in a combined treatment perspective	V. Valentini
		Lecture (20'): state of art of chemotherapy in a combined treatment perspective	N.Silvestris
	10.20-11.00	**Prescription interactive exercise**	All teachers

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COURSE CONTENT

Session 2: Delineation (Falcon session)

The previously discussed cases will be available for a tutored small working group delineation exercise. A video on surgical procedure highlighing the key surgical steps to better understand local anatomy will be commented by a surgeon.

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COURSE CONTENT

Session 2: Delineation (Falcon hands-on session)	16.00 – 16.45	**Hands-on: Group 1 delineation Middle Third**	Radiology anatomy: A.Riddell Tutors: M.Verhej, F.Cellini, L.Wiersema
		Hands-on: Group 2 video on surgical procedure (highlight of key surgical steps)	Surgical anatomy: W.Allum
	16.45 – 17.30	**Hands-on: Group 2 delineation Middle Third**	Radiology anatomy: A.Riddell Tutors: M.Verhej, F.Cellini, L.Wiersema
		Hands-on: Group 2 video on surgical procedure (highlight of key surgical steps)	Surgical anatomy: W.Allum

COURSE CONTENT

Session 3: Delineation

Lectures on primary tumour extension and nodal subsite involvement based on pathology evaluation and modern imaging will support the final recommendation for subsite delineation by stage and tumour position for the delineated cases.

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COURSE CONTENT

Session 2: Delineation (Falcon hands-on session)	16.00 – 16.45	**Hands-on: Group 1 delineation Middle Third**	Radiology anatomy: A.Riddell Tutors: M.Verhej, F.Cellini, L.Wiersema
		Hands-on: Group 2 video on surgical procedure (highlight of key surgical steps)	Surgical anatomy: W.Allum
	16.45 – 17.30	**Hands-on: Group 2 delineation Middle Third**	Radiology anatomy: A.Riddell Tutors: M.Verhej, F.Cellini, L.Wiersema
		Hands-on: Group 2 video on surgical procedure (highlight of key surgical steps)	Surgical anatomy: W.Allum

Session 9: Delineation	14.00 – 16.05	**Lecture (20'): Tumor growth and nodal spread**	A.Quaas
		Lecture (20'): Imaging of primary and nodal subsite boundaries?	R.Manfredi
		Lecture (20'): incidence and location of local recurrences after combined treatment	W.Allum
		Lecture (20'): recommendation for subsite delineation by stage and tumor position	F.Cellini
		Discussion on delineation exercises (45')	All teachers

COURSE CONTENT

Session 4: In room imaging guided radiotherapy

The choice among competitive plans for the cases by interactive systems will be supported by lectures on dose issues for tumour control and constrains for organ at risk.

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COURSE CONTENT

Session 4: Planning	11.00 – 12.20	**Lecture (20'): Dose issues in esophageal tumor control**	M. Verheij
		Lecture (20'): Dose constrains for organ at risk	O.Matzinger
		Interactive lecture (40'): choice among competitive plans for early and locally advanced esophageal cancer	D.Verellen

Session 4: Planning	11.00 – 12.20	**Lecture (20'): Dose issues in esophageal tumor control**	M. Verheij
		Lecture (20'): Dose constrains for organ at risk	O.Matzinger

COURSE CONTENT

Session 5: Planning

Drill and practice exercise in small working groups on how to determine PTV margin, and IGRT by portal imaging and CT cone beam will favor discussion on the daily dose delivery issues.

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COURSE CONTENT

27 March (Monday)			Speaker
Gastric cancer			
Session 5: In room imaging guided radiotherapy	14.00 – 14.45	Hands-on: Group 1 + Group 2 - How to determine PTV margin	D.Verellen
	14.45 – 15.30	Hands-on: Group 1 + Group 2 - Tips and tricks on in room IGRT	O.Matzinger, F.Cellini, L.Wiersema

28 March (Tuesday)			Speaker
Session 11: In room imaging guided radiotherapy	8.45 – 9.30	Hands-on: Group 1 + Group 2 - Re-irradiation: an exercise on dose accumulation	D.Verellen
	9.30 – 10.15	Hands-on: Group 1 + Group 2 - Tips and tricks on in room IGRT	O.Matzinger, F.Cellini, L.Wiersema

COURSE CONTENT

Session 6: What we learn by failure analysis and future perspective

The challenge of tumour recurrence will be addressed by lectures on how to distinguish primary recurrence vs nodal recurrence by imaging, on incidence and location of local recurrences and on the new treatment perspectives.

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COURSE CONTENT

26 March (Sunday)			Speaker
Session 6: what we learn by failure analysis and future perspective	15.50 – 17.15	Lecture (15'): Incidence and location of local recurrences after only surgery	W.Allum
		Lecture (15'): recurrence features by imaging	A.Riddell
		Lecture (15'): Palliative radiotherapy	M. Verheij
		Lecture (15'): Palliative chemotherapy	F.Lordick
		Discussion (10')	All teachers
		Lecture (15'): new perspectives in esophageal cancers	O.Matzinger

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COURSE CONTENT

28 March (Tuesday)			Speaker
Session 12 : what we learn by failure analysis and future perspective	10.45 – 11.40	Lecture (15'): recurrence features by imaging	A.Riddell
		Lecture (15'): Palliative chemotherapy	N.Silvestris
		Lecture (15'): new perspectives in gastric cancers	M. Verheij
		Discussion (10')	

WELCOME AND INTRODUCTION

47 participants

1

Republic of Korea

1

India

2

Australia

2

South Africa

1

New Zeland

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Imaging based staging and response evaluation in Esophageal Cancer

Dr Angela M Riddell

Royal Marsden, London. UK

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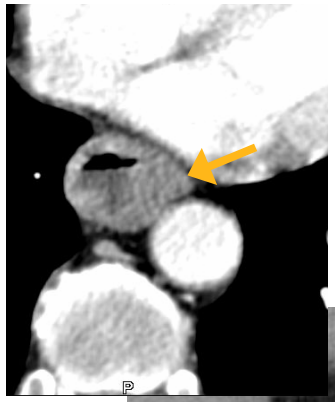
Esophageal Cancer - Current Staging Strategy

- Diagnosis – Endoscopic biopsy
- Initial Imaging:
  - MDCT
- Potentially curable disease:
  - PET/CT – exclude distant spread
  - Laparoscopy
  - EUS – Early disease, Proximal/ Distal Extent

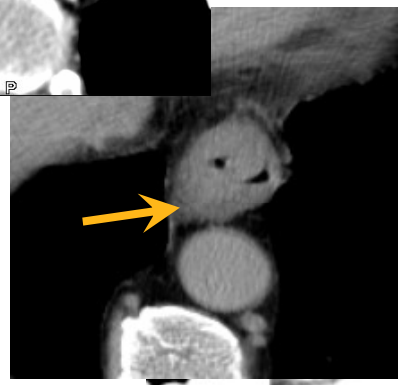
T staging - MDCT

Initial Staging

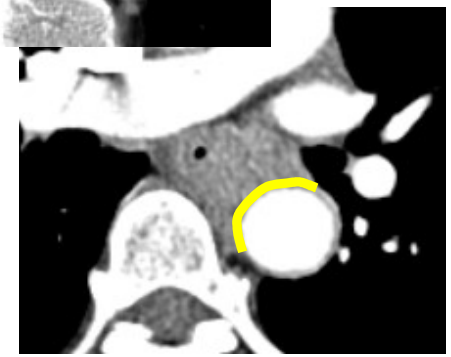
- T stage - based on wall thickness and outline
- Limited soft tissue contrast
- Poor for early tumours



pT2



pT3



pT4

T Stage	Wall thickness	Wall Contour
T2	>3mm, <5mm	Smooth
T3	5-15mm	Irregular
T4	>15mm	Contact with adjacent structure

T Staging Accuracy - 74%*

* Davies, A. R., D. A. Deans, et al. (2006). Dis Esophagus **19**(6): 496-503

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T staging - MDCT

2016 –

62 patients; Underwent primary surgery

Stage	Sensitivity	Specificity	Accuracy
T2	61%	68%	66%
T3	67%	56%	63%

Sultan R, Haider Z, Chawla TU et al. *J Pak Med Assoc.* 2016 Jan;66(1):90-2.

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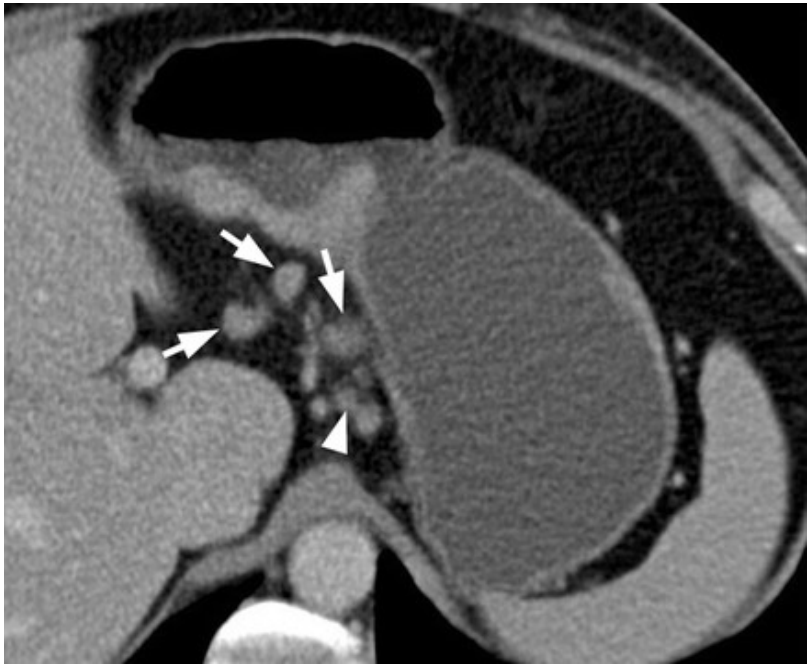
N Staging - MDCT

- CT - high specificity, but low sensitivity
- Based on size criteria (short axis):
  - ≥6mm perigastric
  - ≥ 8mm extra perigastric
  - ≥10mm mediastinum



Accuracy of N staging	
Oesophageal Cancer	68%*
Gastric Cancer	67%†

Stage	No of Regional Nodes
N1	≤2
N2	3-6
N3	≥7

* Davies, A. R., D. A. Deans, et al. (2006). Dis Esophagus **19**(6): 496-503
†Hur, J., M. S. Park, et al. (2006). J Comput Assist Tomogr **30**(3): 372-7.

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N staging - MDCT

2016 –

62 patients; Underwent primary surgery

Histopathology	CT		Total
	Node -ve	Node +ve	
Node -ve	15	5	20
Node +ve	17	25	42
	32	30	62

Stage	Sensitivity	Specificity	Accuracy
N Stage	59%	75%	65%

Sultan R, Haider Z, Chawla TU et al. *J Pak Med Assoc.* 2016 Jan;66(1):90-2.

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N Staging - MDCT

Tumour volume related to nodal burden*

Figure 1

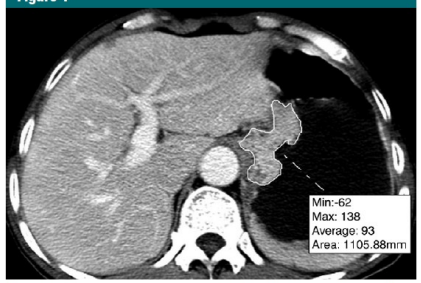

Figure 1: Transverse contrast-enhanced CT scan in 56-year-old man with AEG. Tumor area is manually drawn along margin of tumor, and value of this area (1105.88 mm) is automatically derived by software together with minimal, maximal, and average CT attenuation (in Hounsfield units).

Table 2

Gross Tumor Volume according to N Stage

N Stage	Stage T1–T3 (n = 216)	Stage T3 (n = 175)
N0	15.77 ± 6.95 (14.07, 17.48)	18.08 ± 10.00 (15.68, 20.49)
N1	27.01 ± 14.73 (23.11, 30.92)	28.83 ± 14.82 (24.62, 33.04)
N2	27.92 ± 14.49 (24.04, 31.85)	28.49 ± 14.15 (24.28, 32.69)
N3	38.62 ± 17.60 (32.83, 44.40)	38.82 ± 17.79 (32.89, 44.75)
N1–N2	27.46 ± 14.56 (24.74, 30.18)	28.66 ± 14.72 (25.74, 31.58)

Note.—Data are means ± standard deviations. Numbers in parentheses are 95% confidence intervals of the volume.

Table 3

ROC Analysis of Gross Tumor Volume in the Determination of N Stage

Gross Tumor Volume Cutoff	Comparison Groups	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Stage T1–T3 (n = 216)							
15.23 cm^3	N0 vs N1–N2	0.81	86 (96/112)	64 (42/66)	80 (96/120)	72 (42/58)	77 (138/178)
17.16 cm^3	N0 vs N1–N3	0.84	81 (122/150)	68 (45/66)	85 (122/143)	62 (45/73)	77 (167/216)
33.96 cm^3	N1–N2 vs N3	0.73	60 (23/38)	80 (90/112)	51 (23/45)	86 (90/105)	75 (113/150)
Stage T3 (n = 175)							
18.41 cm^3	N0 vs N1–N2	0.77	78 (78/100)	60 (23/38)	84 (78/93)	51 (23/45)	73 (101/138)
19.30 cm^3	N0 vs N1–N3	0.80	77 (105/137)	66 (25/38)	89 (105/118)	44 (25/57)	74 (130/175)
33.96 cm^3	N1–N2 vs N3	0.71	62 (23/37)	79 (79/100)	52 (23/44)	85 (79/93)	74 (102/137)

Note.—Numbers in parentheses are numbers of patients. AUC = area under the ROC curve, NPV = negative predictive value, PPV = positive predictive value.

*Li, R., T. W. Chen, et al. (2013) Radiology **269**(1): 130-138.

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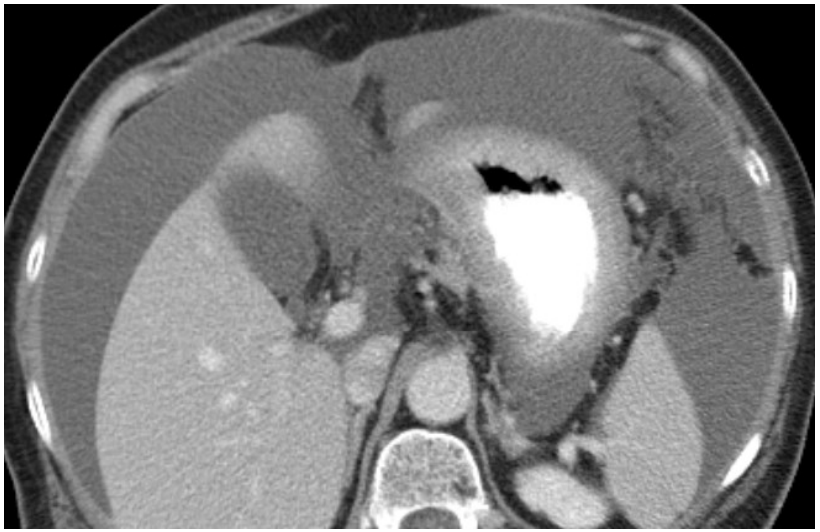
MDCT – M staging

- Detection of hepatic mets:
  - sens 88%, spec 99%*.
- Detection of peritoneal disease
  - No ascites: sens 30%†
  - In presence of ascites:
  - Sens 51%, Spec 97%*
- Laparoscopy for potentially operable patients



*Yajima, K., T. Kanda, et al. (2006). Am J Surg **192**(2): 185-90.

†D'Elia, F., A. Zingarelli, et al. (2000). Eur Radiol **10**(12): 1877-85.

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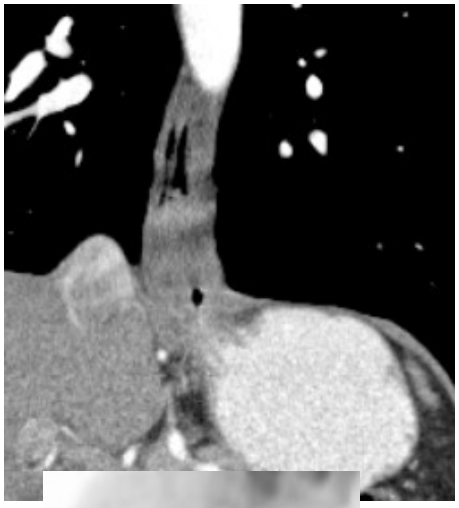
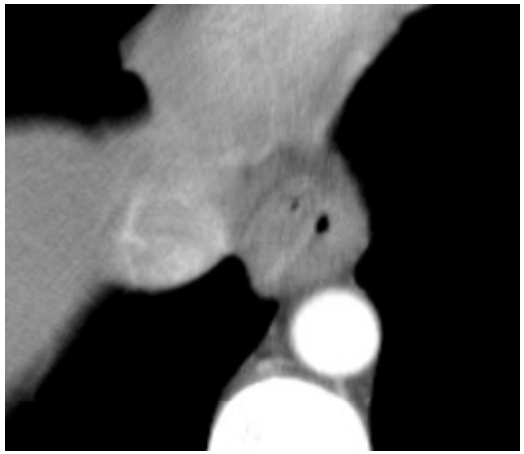
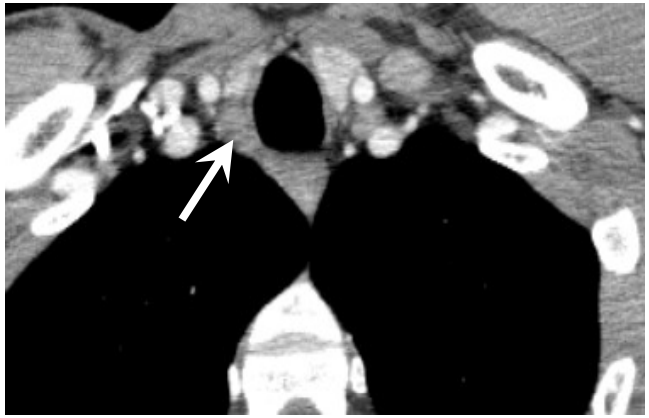
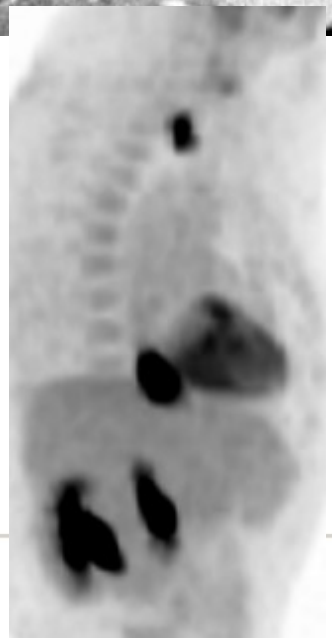
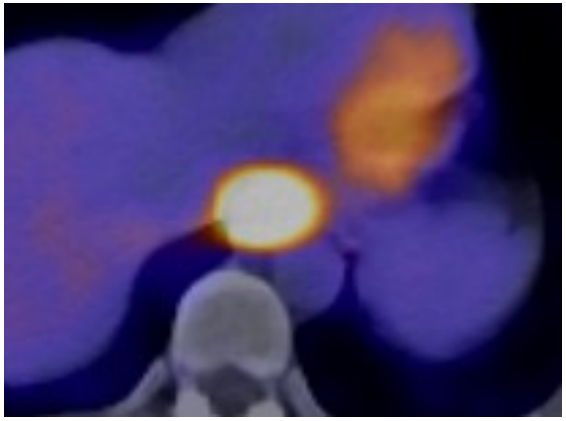
^{18}FDG-PET/CT – Staging

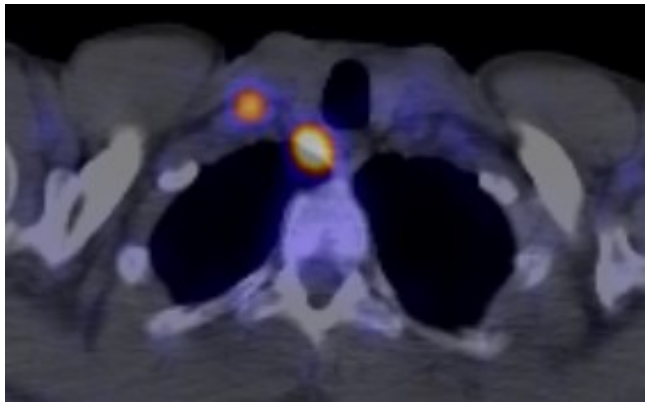






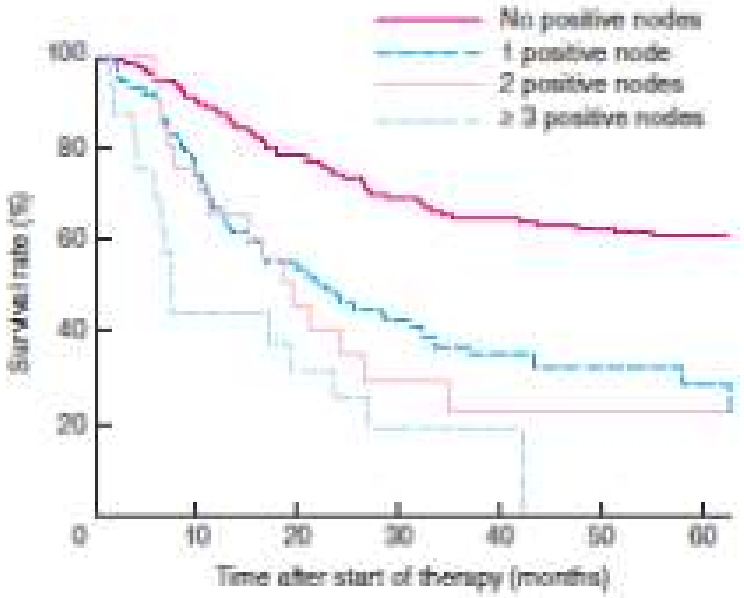






Importance of the number of nodes in prognosis

- No of PET-positive nodes before & after chemotherapy associated with survival*



p <0.001

*Miyat H, Yamasaki M, Makino T et al. 2015. BJS Oct 27. doi: 10.1002/bjs.9965. [Epub ahead of print]

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^{18}FDG-PET/CT – Staging

Detection of occult metastases

- Initial studies using FDG PET:
  - Metastatic disease detected in 15% patients considered potentially operable*.
- Prospective trial 187 patients showed confirmed up-staging in 9(4.8%) patients & 18 (9.5%) patients with unconfirmed metastases‡
- 25/156 (16%) patients up staged to M1b disease on PET-CT §
- False positive results on PET-CT ‡¥

*Flamen, P., A. Lerut, et al. (2000). J Clin Oncol **18**(18):

‡Meyers, B. F., R. J. Downey, et al. (2007). J Thorac Cardiovasc Surg **133**(3):

§ Purandare, N. C., C. S. Pramesh, et al. (2014). Nucl Med Commun **35**(8): 864-869

¥Adams, H. L. and S. S. Jaunoo (2014). Ann R Coll Surg Engl **96**(3): 207-210

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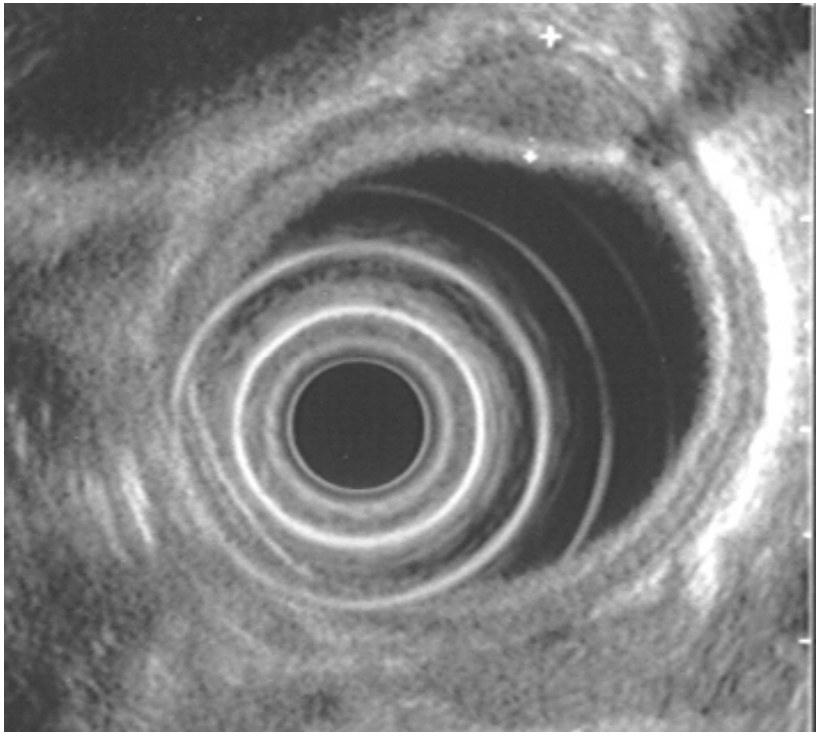
T staging - Endoscopic Ultrasound (EUS)

- Endoscopic Ultrasound is able to delineate the layers of the oesophageal wall
- More accurate staging of tumours confined within the wall (<T3)



pT1 tumour

Courtesy of Dr Martin Benson

Endoscopic Ultrasound – T & N Staging

Multi centre analysis*

- High frequency EUS (miniprobe)
- Pre therapeutic uT and uN compared to pT/pN classification obtained from esophagectomy (n = 93) or EMR (n = 50)

- Accuracy
  - T staging 60% & N Staging 74%
- 78% stratified to appropriate therapeutic regime
- 11% over-treatment & 11% under-treatment

*Meister, T., H. S. Heinzow, et al. (2013). Surg Endosc **27**(8): 2813-2819

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Endoscopic Ultrasound – T & N Staging

- Limitation: stenotic tumours
- These tumours are likely to be locally advanced*
- Such patients should be offered neoadjuvant therapy

*Worrell, S. G., D. S. Oh, et al. (2014). J Gastrointest Surg **18**(2): 318-320.

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Response to chemotherapy / CRT

Methods used for assessing response:

- MDCT: Response Evaluation Criteria in Solid Tumours (RECIST)

^{18}FDG-PET/CT:

Standardised Uptake Value (SUV mean / max)

Metabolic tumour volume (MTV)

Total lesion glycolysis (TLG)

MRI:

Apparent Diffusion Coefficient (ADC)

Response to chemotherapy / CRT

Predict outcome for OG patients

- responders to neoadjuvant therapy benefit most post surgery
- non-responders to neoadjuvant therapy have a poorer prognosis post op than those who have primary surgery alone*β
- Individualise patient care

*Ancona E, Ruol A et al. 2001. Cancer; 91:2165-2174

βLaw S, Fok M et al 1997. J Thorac Cardiovasc Surg; 14: 210-217

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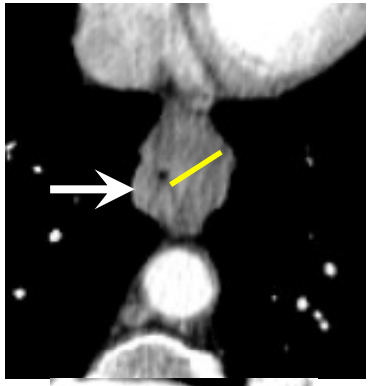
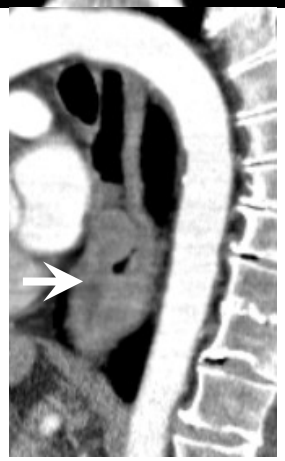
Response to chemotherapy / CRT

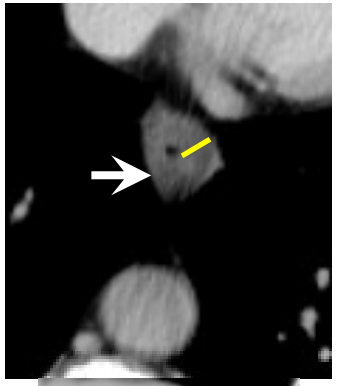
Multidetector Computed Tomography (MDCT)

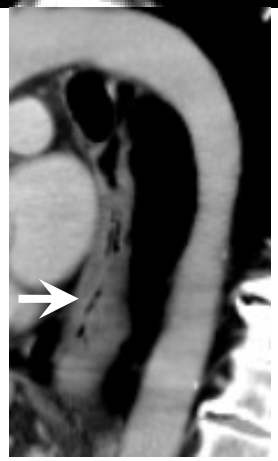




Sept 2012

3 cycles chemo





Dec 2012

Response by RECIST

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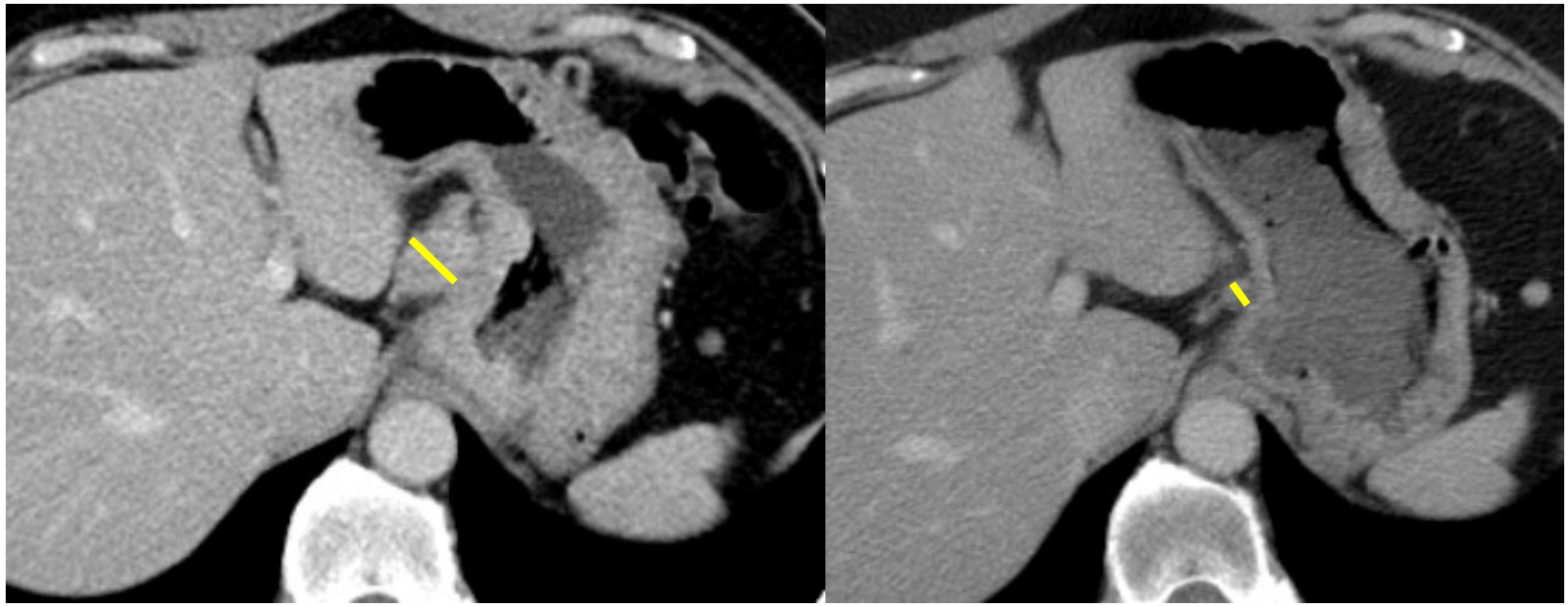
Response to chemotherapy / CRT



MDCT – measurement of lymph node size &/or metastases offer more consistent measures of response by RECIST

Response to chemotherapy / CRT

Challenges for MDCT

- Differences in luminal distension
- Lack of soft tissue contrast
- Unable to differentiate fibrosis & tumour

Detection of response by CT:

Sensitivity: 27 – 55%; Specificity: 50 – 91%*Ψ

*Cerfolio RJ, Bryant AS, Ohja B et al 2005. J Thorac Cardiovasc Surg; 129:1232-1241
ΨSwisher SG, Maish M, Erasmus JJ et al 2004. Ann Thorac Surg; 78: 1152 - 1160

MDCT - Restaging after neoadjuvant chemotherapy

- Predicted T stage correctly in 34 % (12/35)
- Overstaged 49 % (17/35)
- Understaged 17 % (6/35)*

- Accurate N stage was noted in 69 % (24/35)

- Assessment of oesophageal tumour response should focus on combined morphologic and metabolic imaging

*Konieczny, A., P. Meyer, et al. (2013). Eur Radiol 23(9): 2492-2502.

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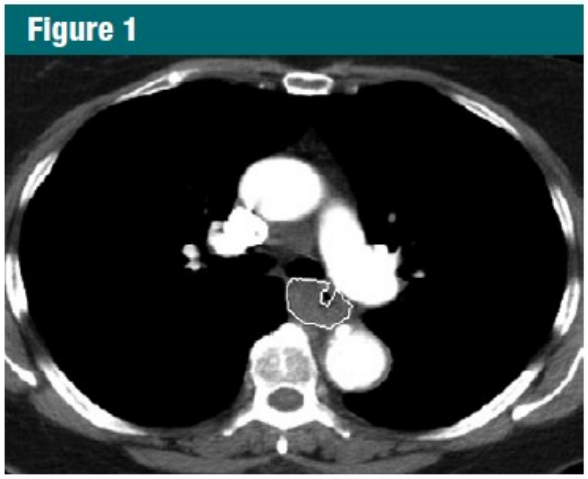
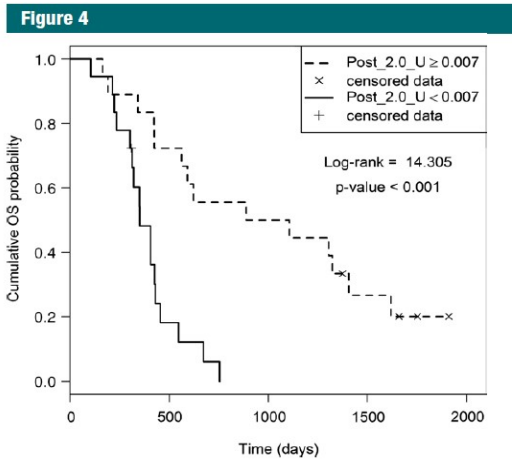
Response to chemotherapy / CRT

CT Textural analysis §



ROI placed round the tumour



Kaplan-Meier survival analysis stratified by the uniformity of distribution of grey levels

Post treatment uniformity of 0.007 or higher is a positive prognostic indicator (median survival 33.2 months vs 11.7 months) §

§ Yip C, Landau B et al 2014. Radiology 270;1: 141-148

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^{18}FDG-PET/CT - Response to chemotherapy / CRT

- Metabolic response occurs early
  - Studies (eg MUNICON*) have used a reduction in the standardised uptake value (SUV) at 14 days

- SUV_{max} reduction of 35-60% have been shown to correlate with pathological response §

*Lordick F, Ott K et al. 2007 Lancet Oncol 8;9:797-805

§ Bruzzi J, Munden R et al. 2007. Radiographics 27;1635 - 1652

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^{18}FDG-PET/CT

Meta analysis >1500 patients*

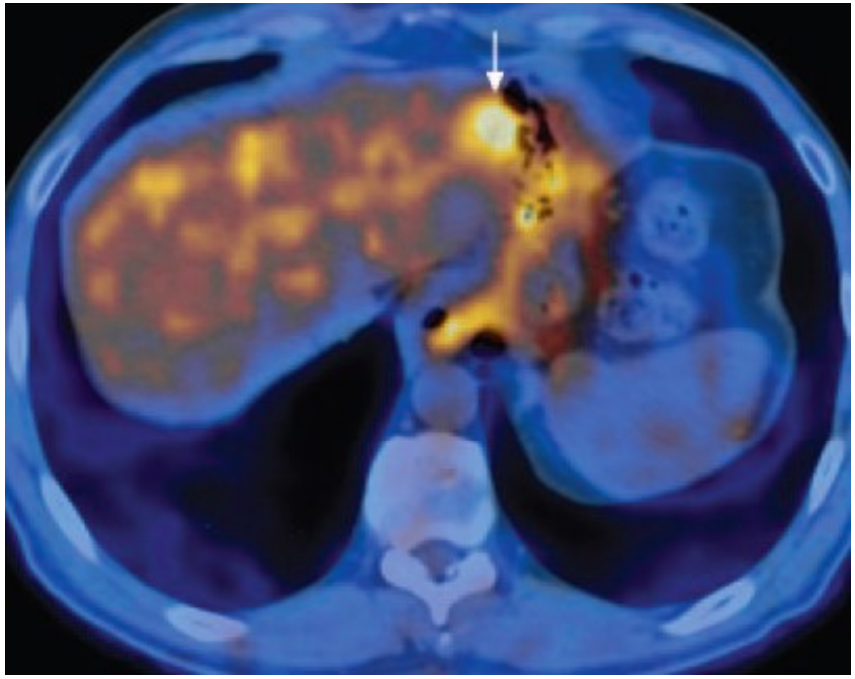
- Conclusion: metabolic response on ^{18}FDG-PET is a significant predictor of long-term survival data

*Schollaert, P., R. Crott, et al. (2014). J Gastrointest Surg 18(5): 894-905

Challenges for PET-CT

- False-positive interpretations
  - Post radiation therapy (due to inflammation/ulceration) – after 14/7 treatment
  - Change related to mucosal biopsy
  - Radiation damage to surrounding organs (eg liver)

Response to chemotherapy / CRT



Example of false positive PET-CT – area of increased FDG avidity in liver represents radiation induced necrosis/inflammation

Taken from: Bruzzi J, Munden R et al. 2007. Radiographics 27;1635 - 1652

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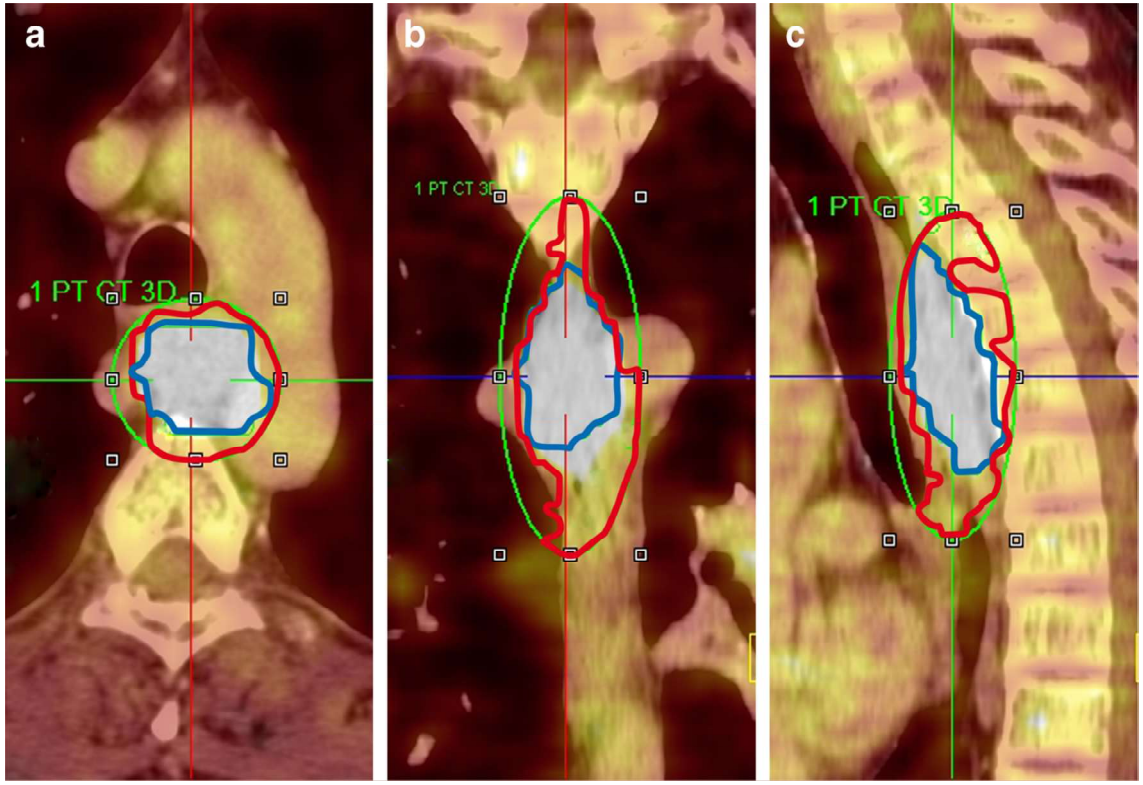
Response to chemotherapy / CRT

Current status for PET-CT

Recognised that PET SUV_{max} does not account for tumour heterogeneity

- Alternatives:
- Metabolic Tumour Volume (MTV)
  - Volume of tumour above a threshold of SUV_{max}
- Total Lesion Glycolysis (TLG)
  - MTV x SUV_{mean}

Response to chemotherapy / CRT



PET/CT images shown with delineation of MTV the SUV threshold of 40% SUV_{max} (Blue) and 25% SUV_{max} (red)

Tamandl D, Gore RM, Fueger B et al. 2015 Eur Radiol Jun 5 [Epub ahead of print]

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Response to chemotherapy / CRT

MTVratio & TLGratio shown to be independent predictors of OS following neoadjuvant chemoradiotherapy*

Table 2 Data are presented as medians with ranges in parentheses. *SUV* standard uptake value; *MTV* metabolic tumour volume; *TLG* total lesion glycolysis

Variable	Before chemotherapy	After chemotherapy	Ratio	*P* Value
CT volumetry (n=84)				
Tumour volume, mL	32.4 (4.6-278.3)	27.6 (0.0-210.6)	0.79 (0.0-2.65)	0.003
Maximum tumour thickness, mm	15 (6-29)	12 (5-27)	0.80 (0.38-1.85)	<0.001
PET metabolic parameters (SUV threshold 2.5, n=50)				
SUV_{mean}	5.2 (3.4-13.3)	3.5 (0.0-12.2)	0.65 (0.0-1.16)	<0.001
SUV_{max}	17.3 (6.2-63.8)	7.8 (0.0-56.4)	0.49 (0.0-1.93)	<0.001
MTV, mL	45.7 (4.0-242.3)	16.1 (0.0-358.7)	0.41 (0.0-7.65)	0.002
TLG, mL	272.5 (14.0-1491.6)	57.8 (0.0-1420.3)	0.31 (0.0-6.68)	<0.001
PET metabolic parameters (SUV threshold 4.0, n=50)				
SUV_{mean}	7.1 (4.6-17.7)	5.0 (0.0-16.3)	0.70 (0.0-1.22)	<0.001
SUV_{max}	18.6 (6.2-63.8)	8.2 (0.0-56.4)	0.49 (0.0-1.93)	<0.001
MTV, mL	22.0 (1.0-119.4)	4.1 (0.0-109.9)	0.20 (0.0-2.41)	<0.001
TLG, mL	171.8 (4.8-1177.2)	21.9 (0.0-654.9)	0.15 (0.0-2.68)	<0.001

Patients with a decrease in MTV of >50% or a decrease in TLG of >60% were shown to have superior overall survival

*Tamandl D, Gore RM, Fueger B et al. 2015 Eur Radiol Jun 5 [Epub ahead of print]

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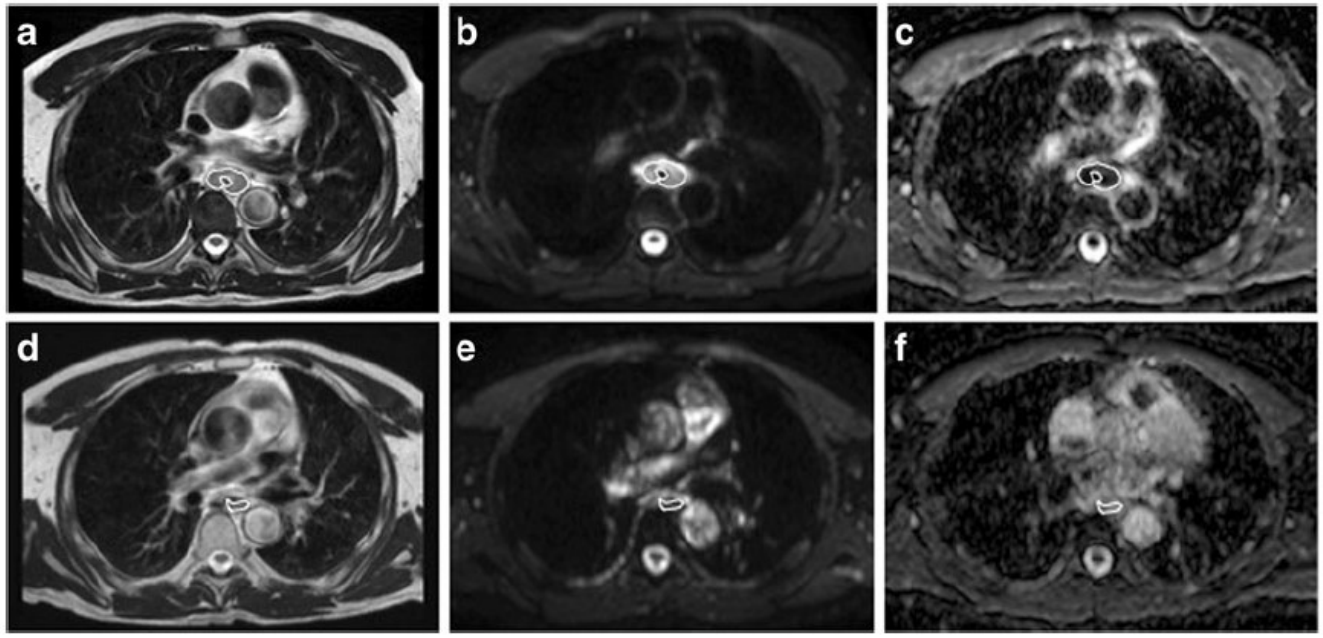
Response to chemotherapy / CRT

Current status for PET-CT

- Useful for response assessment, but consensus required for
  - timing of scan
  - optimised parameter to use to measure response (SUV_{max}, SUV_{mean} or MTV)
  - % change in the parameter that equates to response

Response to chemotherapy / CRT

Response assessment with Diffusion weighted MRI



Ax T2 DWI ADC

De Cobelli F, Giganti F et al 2013. Eur Radiol 23;2165-2174

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Response to chemotherapy / CRT

Responders

- Lower pre treatment ADC
- Higher post treatment ADC
- Change in ADC was inversely proportional to the pathology tumour regression grade

De Cobelli F, Giganti F et al 2013. Eur Radiol 23;2165-2174

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ADC as a prognostic biomarker

Limited small group studies

- Baseline ADC values ≤1.4 x$10^{-3}$$mm^2$/s were associated with poor prognosis

- ADC value correlated with tumour T stage[δ]

- Both for patients undergoing surgery alone & following neoadjuvant therapy*

*Giganti F, Salerno A, Ambrosi A et al. 2015 Radiol Med Sep 21 [Epub ahead of print]

[δ]Aoyagi T, Shuto K, Okazumi S et al. 2011 Dig Surg;28(4):252-7

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Response to chemotherapy / CRT

EUS – assessment of treatment response

•50% reduction in cross-sectional area or tumour thickness*β:

- response to treatment
- improved survival

*Willis J, Cooper GS et al 2002. Gastrointest Endosc 55;655-661

βOta M, Murata Y et al 2005. Dig Endosc 17; 59-63

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EUS - Reassessment after neoadjuvant chemotherapy (NAC)

Challenges for EUS post neoadjuvant therapy

- Unable to differentiate fibrosis / inflammation from tumour *(resulting in over-staging)*
- Unable to detect microscopic of viable tumour *(resulting in under-staging)*
- T staging accuracy 29%
  - Overstaged 23/45 (51%)
  - Understaged 7/45 (16%)
- N staging accuracy 62%
- Conclusion: EUS is an unreliable tool for staging esophageal cancer after NAC*

*Heinzow, H. S., H. Seifert, et al. (2013). J Gastrointest Surg **17**(6): 1050-1057.

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Summary

Initial Staging

- MDCT
- ^{18}FDG-PET/CT
- EUS (early tumours)

Provide

- TNM staging
- prognostic information

Individualise Patient care

Summary

Response Assessment

MDCT

•RECIST – relies on alteration in size; assumes reduction equates to response

PET-CT

•Useful for early response assessment

•Consensus required on technique & values used for response (SUV_{max}; MTV; TLG)

DW-MRI

•Potential to quantify response – further validation required to determine utility of ADC as a predictive biomarker

Thank you

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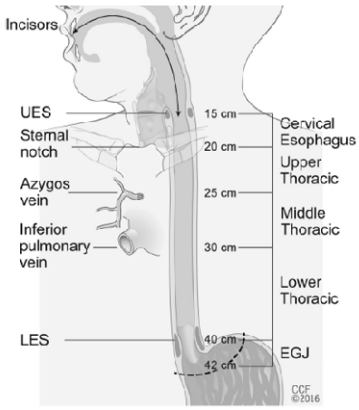
The Royal Marsden

State of Art of Surgery in a Combined Treatment Perspective: Oesophageal Cancer

William Allum

2



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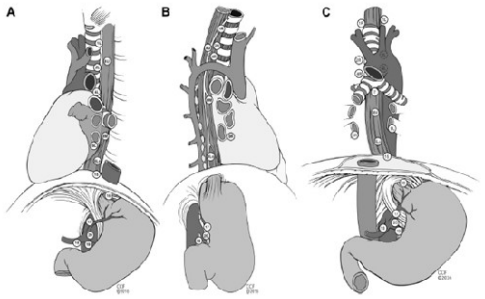
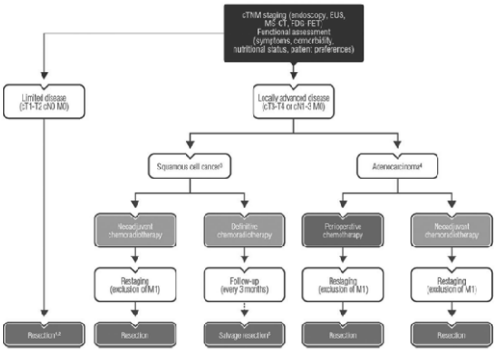


LEFT RIGHT ANTERIOR

4



The Royal Marsden

ENDOSCOPIC RESECTION

- **T1a**
- **pT1 sm1 <500 micro mm**
- well / moderately well differentiated adenocarcinoma
- no lymphatic or venous invasion
- intramucosal cancer regardless of size without ulceration
- minute submucosal penetration (sm1) and <20mm

EMR vs ESD

EMR	**ESD**
– Polypectomy	– En bloc
– Piecemeal	– Complications

Depth of invasion & nodal status

T Stage (n= 369)	N0	N1
T1a	147	2 (1.3%)
T1b	167	53 (24 %)
Total	314	55 (15%)

– Clark GWB. Oesophagogastric Surgery, Griffin SM & Raimes SA (ed); 1997: p108

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Endoscopic Resection vs Surgery

pT1m(1-3) Oesophageal ACA

ER plus APC 76
Oesophagectomy 38

Major complications
ER 0%
Surgery 32%

90 day mortality
ER 0%
Surgery 2.6%

4 year follow up
ER 1 patient local recurrence; 4 metachronous neoplasia

Pech et al 2001 Ann Surg 254:67

9 The Royal Marsden

Aim of Resection

Complete resection of primary tumour (R0)

Clear margins

Lymphadenectomy (>15 nodes)

10 The Royal Marsden

Aim of Resection

Complete resection of primary tumour (R0)

Clear margins

Lymphadenectomy (>15 nodes)

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Dutch Trial
Trans Hiatal Oesophagectomy vs Trans Thoracic Oesophagectomy

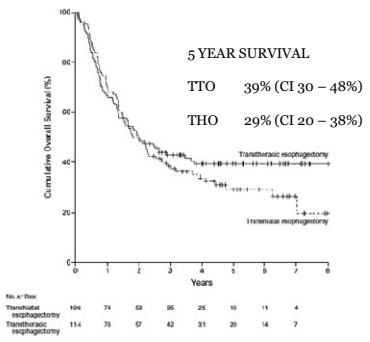
220 patients with mid and lower oesophageal ACA

THO
Lower morbidity

TTO
More nodes
More respiratory complications

Hulscher et lN Engl J Med 2002;347:1662-9.

12

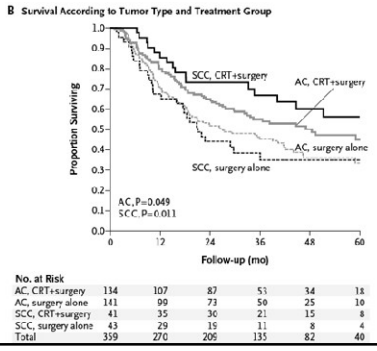


5 YEAR SURVIVAL

TTO 39% (CI 30 – 48%)

THO 29% (CI 20 – 38%)

13 CROSS Trial



14 The Royal Marsden

Minimally Invasive Oesophagectomy

101 open;
65 MIO;
9 Conversion

pT1a & pT1b. No

	Intraoperative	Morbidity	Medium Term
MIO	Less blood loss	Gastroparesis	Less pain
OPEN	Shorter time	Respiratory	More fatigued

Nafteux et al 2011 Eur J Cardio Surgery 40: 1455

15 Nutritional aspects of Enhanced Recovery

Minimally Invasive Oesophageal Resection

MIRO

	No.	Morbid.	Pulm Compl	30 day mort.
HMIO	103	35.9%	17.7%	4.9%
TTO	104	64.4%	30.1%	4.9%

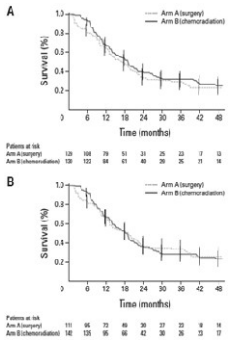
Mariette et al 2015 J Clin Onc 33: suppl 3: abstr 5

TIME

	No.	Pulm Compl	In Hosp Mort.
MIO	59	12%	3%
TTO	56	34%	2%

Biere et al 2012 Lancet Onc; 379:1887

16 Chemoradiation / Surgery vs Chemoradiation FFCD12



Survival ITT

Survival per protocol

Bedenne et al 2007 J Clin Oncol 25:1160

17 The Royal Marsden

Salvage Surgery after Definitive Chemoradiotherapy for SCC

Persistent disease - 234

Recurrent disease - 74

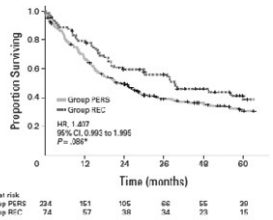
Anastomotic leak – 17.2%

Surgical site infection – 18.5%

Pulmonary complications – 42.9%

Markar et al 2015; J Clin Onc 33: 3866

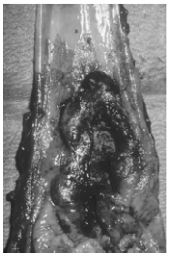
18 Salvage Oesophagectomy

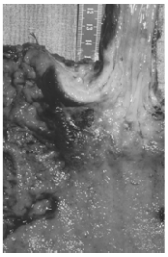


PERS – Persistent

REC - Recurrent

OESOPHAGO-GASTRIC JUNCTIONAL ADENOCARCINOMA





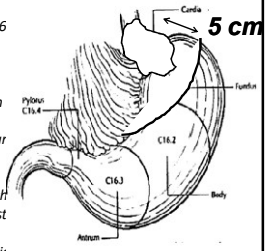
EGJ tumor (TNM 7th ed.)

Oesophagus
(ICD-O C15)
Includes Oesophagogastric junction (C16

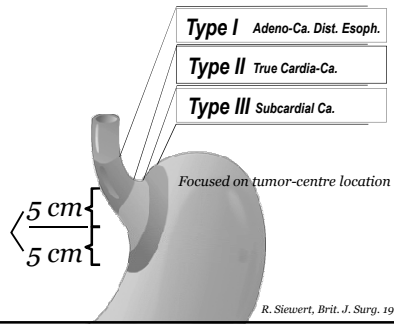
Rules for Classification

• A tumour the epicenter of which is within of the oesophagogastric junction and also extends into the oesophagus is classified ar staged using the oesophageal scheme.

• Tumours with an epicenter in the stomach greater than 5 cm from the oesophagogast junction or those within 5 cm of the oesophagogastric junction without extensi the oesophagus are classified and staged using the gastric carcinoma scheme.



SIEWERT AEG-Classification



R. Siewert, Brit. J. Surg. 1998

EORTC Consensus St Gallen 2012

- Type I – Oesophago-gastrectomy
- Type II – Oesophago-gastrectomy or
  - Extended Total Gastrectomy
- Type I & II – Mediastinal Lymphadenectomy
  – 2 field
- Type III - Extended Total Gastrectomy

Lutz et al *Eur J Cancer 2012; 48: 2941-53*

23 The Royal Marsden surgical audit group, January 2011

Type II Definition

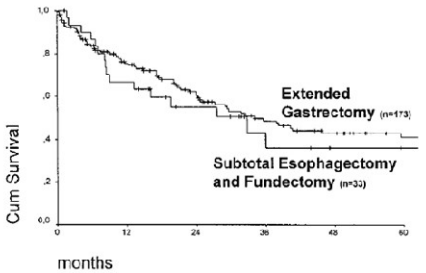
Centre of tumour 2cm above or below gastro-oesophageal junction

Defining the centre is NOT easy
- endoscopy
- imaging

Decisions based only on the centre ? Too simplistic

24

Survival in Type II according to surgery



Siewert et al Ann Surg 2002; 232: 353-61

25 The Royal Marsden surgical audit group, January 2011

Type II
French experience

500 cases (42% all EGJ cancers)	
Oesophagogastrectomy	292 (58%)
Extended total gastrectomy	203 (40%)
Other	5 (1%)

Sauvanet et al J Am Coll Surg 2005; 201: 253-62

26 The Royal Marsden surgical audit group, January 2011

Type II
French experience – Anastomotic leak

Overall (all OGJ cancer)	9%
Thoracic	10%
Abdominal	6%
Thoracic oesophago-jejunal	*14%*

Sauvanet et al J Am Coll Surg 2005; 201: 253-62

27 The Royal Marsden

Aim of Resection

Complete resection of primary tumour (R0)

Clear margins

Lymphadenectomy (>15 nodes)

28

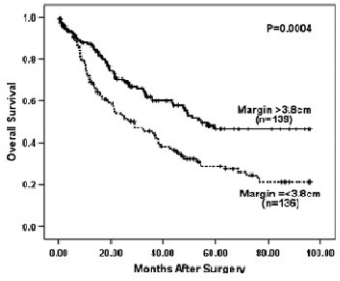
Proximal Margin according to surgery

Total Gastrectomy (n= 77)	**2.0cm (0.1 - 6.5cm)**
Oesophago-gastrectomy (n=199)	**5.5cm (0.3 - 16.0cm)**

Barbour et al Ann Surg 2007; 246: 1-8

29

Survival according to cephalad margin

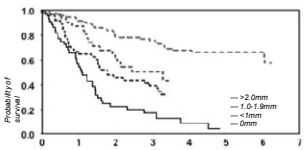


Barbour et al Ann Surg 2007; 246: 1-8

The Royal Marsden

Circumferential resection margin (CRM) size correlates with overall survival

Prospective database, single institution study, N = 229



CRM	n	Median Survival (95% CI)
Positive	**45**	**1.2 yrs** (0.9-1.4)
<1mm	**48**	**1.9 yrs** (1.4-3.2)
1.0-1.9mm	**31**	**3.5 yrs** (2.0–no upper CI)
≥ 2.0mm	**105**	**Not reached**

- *CRM size is a significant prognostic factor for overall survival*
- *40.6% of patients in this study had a CRM <1mm*
- *Post operative chemoradiation did not alter survival in patients with CRM <1mm*
- *BUT smaller CRM may just reflect a larger tumour*

Landau et al., ESMO 2010 (Abstract 711PD)

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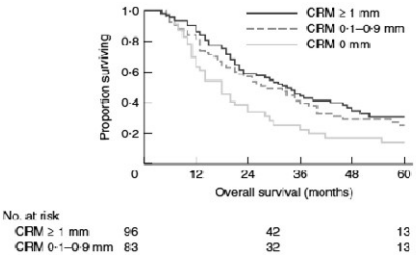
Survival by CRM



O'Neill et al. BJS 2013; 100:1055-63

CRM in Neoadjuvant Trials

	CS	S	CF	ECX	CXRT	S
OEO2	25%	28%				
OEO5			41%	33%		
CROSS					8%	30%

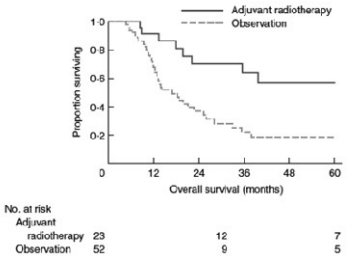
Radical Surgery – 13% - 2/62

The Royal Marsden

Positive margin vs negative margin

Pre-op Staging	Margin positive	Margin negative
T3N0	10%	T3N0 nor T1-2N0/1 40%
T3N1	40%	50%
T3N2	50%	10%
Median no +LN	5	0
Mean No +LN	6.3	1.6

Survival after Treatment for CRM+



O'Neill et al. BJS 2013; 100:1055-63

Aim of Resection

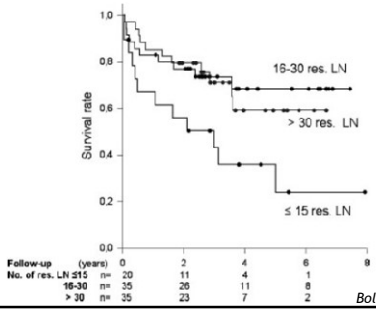
Complete resection of primary tumour (R0)

Clear margins

Lymphadenectomy (>15 nodes)

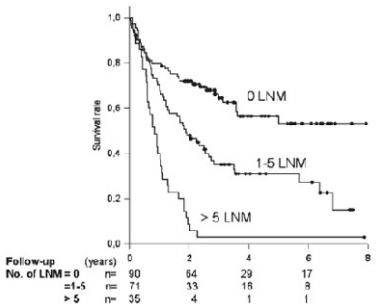
Survival by Number examined in N0 Disease

Bollschweiller et al 2006

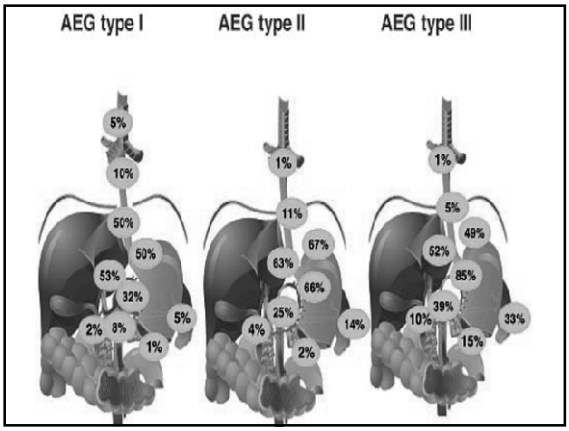


Bollschweiler et al 2006

Survival by Nodal Volume

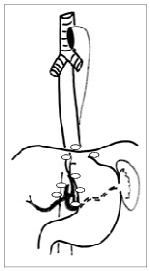


Bollschweiler et al 2006



Lymphadenectomy Common to Both Surgical Approaches

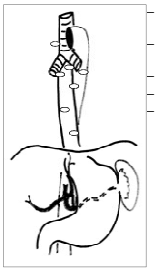
Oesophago-Gastrectomy & Total Gastrectomy



- Right paracardial
- Left paracardial
- Lesser curve
- Left gastric
- Coeliac
- Proximal splenic
- Common hepatic
- Lowest paraoesophageal

Difference in Lymphadenectomy

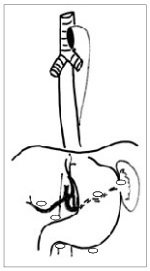
Oesophago-Gastrectomy



- Para-oesophageal
- Para-aortic / thoracic duct
- Carinal
- Bronchial
- Paratracheal

Total Gastrectomy

- Splenic hilum
- Distal splenic
- Right gastroepiploic
- Infra-pyloric
- Supra-pyloric
- Proper hepatic artery



3 Field Lymphadenectomy

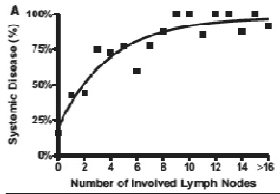
TABLE 2. Prevalence of Cervical Node Involvement by Tumor Site and Histologic Type

	All		Adeno		Squamous	
Site	No.	%	No.	%	No.	%
All	41/174	23.6	22/96	23.2	19/78	25.0
Proximal third	4/9	44.4	0/0	0.0	4/9	44.4
Middle third	11/42	26.2	0/0	0.0	11/42	26.2
Distal third	20/87	23.0	15/62	25.8	4/25	16.0
GEJ	6/36	16.7	5/34	17.6	0/2	0.0

Lerut et al 2004. Ann Surg 240: 962-72

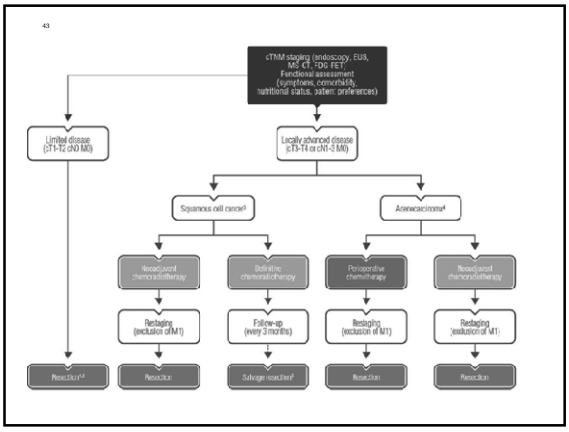
Risk of Systemic Disease and Number of Nodes Involved

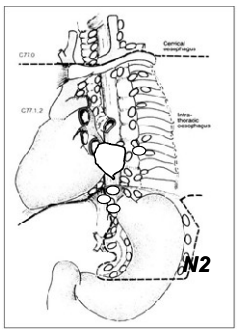
Peyre et al 2008



#Involved Nodes	0	1	2	3	4	5	6	7	≥8
# Patients	183	54	34	32	29	22	22	9	67

Peyre et al 2008 Ann Surg 248: 979-985





47 47

EGJ tumor (TNM 7th ed.)

Oesophagus
(ICD-O C15)
Includes Oesophagogastric junction (C16.0)

Rules for Classification

•A tumour the epicenter of which is within 5 cm of the oesophagogastric junction and also extends into the oesophagus is classified and staged using the oesophageal scheme.

•Tumours with an epicenter in the stomach greater than 5 cm from the oesophagogastric junction or those within 5 cm of the oesophagogastric junction without extension in the oesophagus are classified and staged using the gastric carcinoma scheme.

OEO2 update

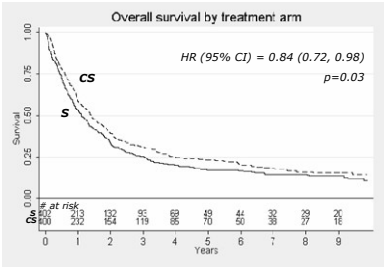
Resection Details

	CS	S
Number having surgery	**361**	**386**
Median time to surgery	**63 days**	**16 days**
Perioperative deaths	**36 (10%)**	**40 (10%)**
R0	**60%**	**55%**
R1	**18%**	**15%**
R2	**9%**	**13%**
Inoperable	**5%**	**14%**

ASGBI 2008

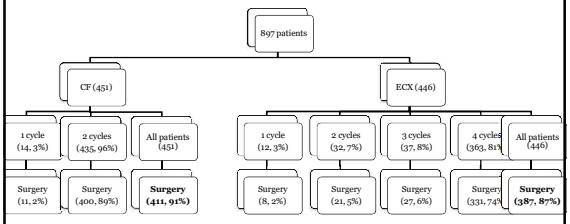
OE02 update

- Updated results
  - Overall survival (from randomisation)



ASGBI 2008

Treatment and Surgery



Of the 798 who had surgery, 47 (24 CF, 23 ECX) had an open and close operation.

Alderson, Cunningham et al ASCO 2015

Surgery

		CF (N=451)		ECX (N=446)		
		n	%	n	%	P-value
Surgery performed	Yes	411	91%	387	87%	0.043
	No	40	9%	59	13%	
Reason for no surgery	PD, inoperable, co-morbidity	37		44		
	Patient choice	2		7		
	Died	1		8		
Resection	Yes	387	94%	364	94%	1.000
	No	24	6%	23	6%	

Alderson, Cunningham et al ASCO 2015

Post-op complications

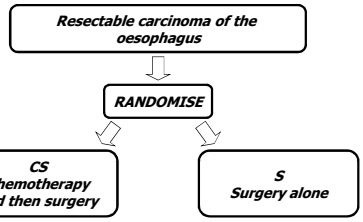
Complication	CF (N=397)		ECX (N=376)	
	n	%	n	%
Any complication	225	57%	234	62%
Respiratory	107	27%	126	34%
Thrombo-embolic	16	4%	17	5%
Infection	57	14%	56	15%
Cardiac	44	11%	45	12%
Surgery related	36	9%	42	11%
Haematological	18	5%	16	4%
Chylothorax	12	3%	15	4%
Anastomotic	44	11%	38	10%
Other	28	7%	28	7%
Required revisional operation	34	9%	30	8%
Died within 30 days	8	2%	10	2%
Died within 90 days	17	4%	20	5%

Alderson, Cunningham et al ASCO 2015

The Royal Marsden

OE02 update

Trial Design

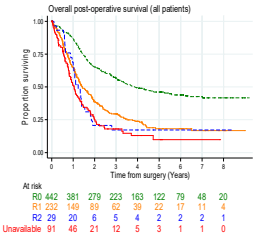


The Royal Marsden

2011-2015 update GOJ and oesophageal only

- 10/62 adenocarcinoma (16%)
- 8/62 circumferential, 2/62 distal/proximal
- 1 previously treated on advanced disease protocol + CRT
- 70% Siewert 1, 30% Siewert 2 (vs 36% Siewert 1 in margin negative)
- Pre-op CT demonstrated stable disease in 30%, partial response in 70%

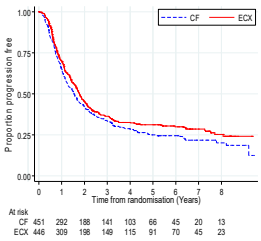
Survival by R0 status



3-year survival (95% CI)	
R0	57% (52%, 61%)
R1	30% (24%, 36%)
R2	17% (6%, 33%)
Unavailable	18% (11%, 27%)
HR (R0 vs others)	2.41 (2.02, 2.88)
P-value	<0.001

Alderson, Cunningham et al ASCO 2015

Progression free survival



Median PFS (95% CI)	
CF	1.53 (1.29, 2.74)
ECX	1.78 (1.61, 2.00)
HR	0.86 (0.74, 1.01)
P-value	0.0580

Alderson, Cunningham et al ASCO 2015

OEO2 update

Pathology of resected specimens

	CS	S
Total	342	327
Node +ve	195 (58%)	216 (68%)
Lateral resection margin +ve	78 (25%)	83 (28%)
Size < 4cm	184 (58%)	103 (34%)
Size 4.1 – 8.0cm	99 (31%)	161 (52%)

Allum et al J Clin Oncol 2009; 27:5062-7

Nodal Spread

Table 1 Epidemiological and morphological characteristics of the three differentiated tumour entities arising in the vicinity of the oesophagogastric junction

	Type I tumour (adenocarcinoma of the distal oesophagus) $n = 366$	Type II tumour (true carcinoma of the cardia) $n = 228$	Type III tumour (subcardial gastric s.str.) $n = 276$
Mean age at presentation (years)	60·6	63·2	62·0
Sex ratio (M:F)	8·2:1	5·1:1	2·4:1
Hiatus hernia (%)	72	89	21
History of GORD (%)	84	42	26
Prevalence of associated intestinal metaplasia in the distal oesophagus (Barrett's oesophagus) (%)	91	11	2
Prevalence of associated intestinal metaplasia at or below the gastric cardia (%)	75	32	9
Prevalence of G2/G4 (undifferentiated) tumours (%)	51	56	71
Prevalence of tumours with 'non-intestinal' growth pattern (%)	28	36	45
Primary direction of lymphatic spread	↑↓	↑↓	↓

Data based on an analysis of 815 patients undergoing resection at the Technischen Universität München between 1982 and 1997 (unpublished data). GORD, gastro-oesophageal reflux disease

MRC OEO 5 trial design

Patients with resectable adenocarcinoma of oesophagus or type 1 and 2 oesophagogastric junction

→ ***CF x2*** → ***Surgery***

TRIPLET vs. DOUBLET LONGER DURATION

→ ***ECX x4*** → ***Surgery***

- *Primary endpoint: overall survival*
- *Final recruitment: 897 patients (this will provide 74% power to detect a 7% improvement in 3 year survival (from 30% to 37%), or 84% power to detect an 8% improvement (to 38%)*
- *Recruitment completed 31st October 2011*

Alderson, Cunningham et al ASCO 2015

61 The Royal Marsden

Conclusions

Important factors

Longitudinal margin

Nodal dissection — total number harvested
thoracic and abdominal nodes

Similar morbidity and mortality

Selection based on patient factors

Pathology

Data		CF		ECX		
		n	%	n	%	P-value
Mandard TRG	1-3	43	15%	93	32%	<0.001
	4-5	244	85%	194	68%	
	Unavailable	99		75		
R0 resection	Yes	211	59%	222	67%	0.058
	No	144	41%	111	33%	
	Unavailable	32		29		

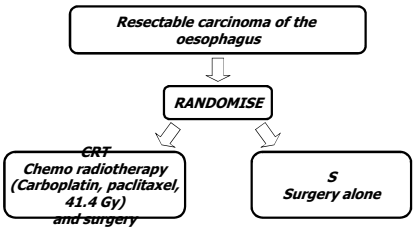
- *Mandard grade 1 rate was 9 (3%) CF vs 32 (11%) ECX.*
- *A central pathology review of all patients is currently ongoing.*

Alderson, Cunningham et al ASCO 2015

The Royal Marsden

CROSS Trial

Trial Design



Van Hagen et al NEJM 2012;366:2074-84

CROSS Trial

Pathologic findings in the resection specimen (n=161 in both arms).

	CRT + surgery (n=161)	Surgery alone (n=161)	p-value
Pathologic findings	No. of patients (percentage[a])		
pT-stage[b]			<0.001
pTis	1 (1%)	0 (0%)	
pT0	62 (39%)	0 (0%)	
pT1	15 (10%)	13 (8%)	
pT2	32 (20%)	19 (12%)	
pT3	49 (30%)	126 (78%)	
pT4	1 (1%)	3 (2%)	
Unknown	1 (1%)	0 (0%)	
pN-stage[b]			<0.001
pN0	111 (69%)	41 (26%)	
pN1	50 (31%)	120 (75%)	
No. of LNs resected			
Median (p25-p75)	15 (9-21)	18 (12.5-27)	0.77
No. of pos LNs			
Median (p25-p75)	0 (0-1)	2 (1-6)	<0.001
Radicality of resection[b]			<0.001
R0 resection	148 (92%)	111 (69%)	
R1 resection	13 (8%)	49 (30%)	
Not available	0 (0%)	1 (1%)	

The Royal Marsden

Health Related Quality of Life after Surgery for Junctional Cancer

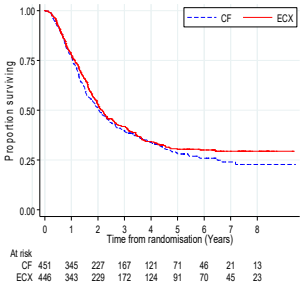
63 patients
20 Ext TG
43 TTO

Better baseline scores for TTO – fitter group

6/12 HQRL lower scores after TTO
Role and Social Function
Global Quality of Life
Fatigue

Barbour et al 2008, BJS 95: 80-4

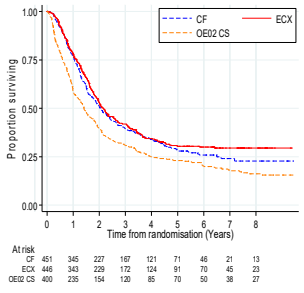
Overall survival



Median survival (95% CI)	
CF	2.02 (1.80, 2.38)
ECX	2.15 (1.93, 2.53)
HR	0.92 (0.79, 1.08)
P-value	0.8582
3-year survival (95% CI)	
CF	39% (35%, 44%)
ECX	42% (37%, 46%)

Alderson, Cunningham et al ASCO 2015

Overall survival



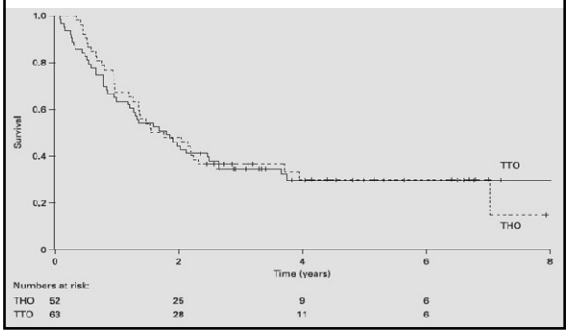
3-year survival (95% CI)	
CF	39% (35%, 44%)
ECX	42% (37%, 46%)
OE02 CS	31% (27%, 36%)

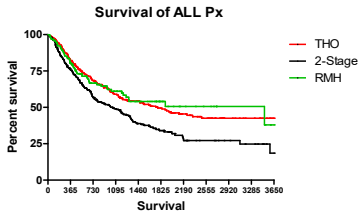
Alderson, Cunningham et al ASCO 2015

Dutch Trial
THO vs TTO

- TTO
  - More nodes
  - More respiratory complications
  - Lower oesophageal and LN 1-8 better outcome

Survival after TTO vs THO for Type II Tumours

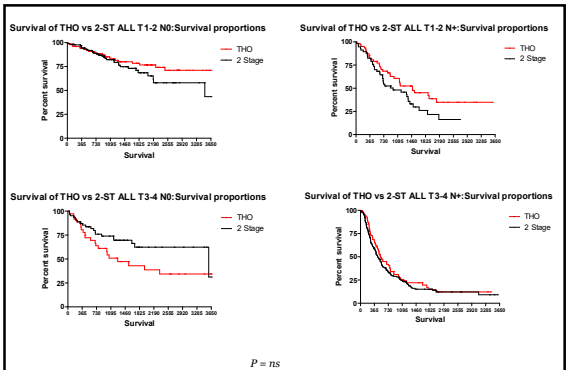




Median Survival

RMH	*54 months*
THO	*49 months*
2 ST	*34 months*

P < 0.0005



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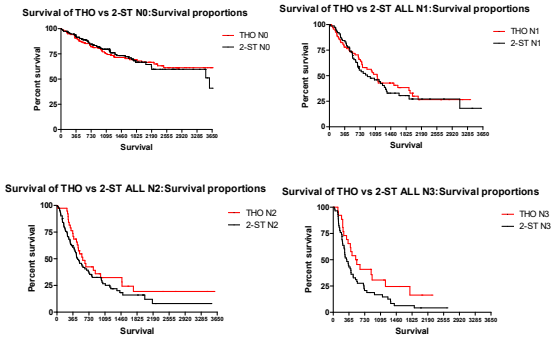
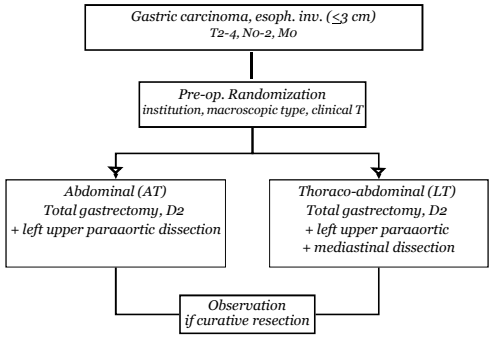


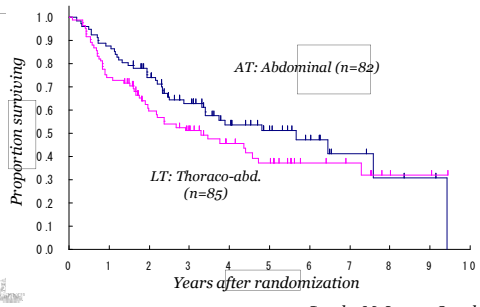
P = ns

JCOG 9502: Scheme



The Royal Marsden

Overall Survival



Sasako M. Lancet Oncol 2006

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Conclusions of JCOG 9502

Thoraco-abdominal approach is *not* recommended for tumors of Siewert's type 2 and 3.

The Royal Marsden

Health Related Quality of Life after Surgery for Junctional Cancer

63 patients
- 20 Ext TG
- 43 TTO

Better baseline scores for TTO – fitter group

6/12 HQRL lower scores after TTO
- Role and Social Function
- Global Quality of Life
- Fatigue

Barbour et al 2008, BJS 95: 80-

The Royal Marsden

Aim of Surgery for Junctional Cancer

R0 resection
Minimum 15 lymph nodes
5cm grossly normal in situ proximal oesophagus

The Royal Marsden

Surgical Options According to Type

Siewert Type I	TTO / THO
Siewert Type II	TTO / THO / Ext TG
Siewert Type III	Ext TG

The Royal Marsden

Resection Margin and Procedure

171 AEG Patients
- 16 Oesophagectomy
- 71 Left Thoraco-abdominal
- 84 Transhiatal

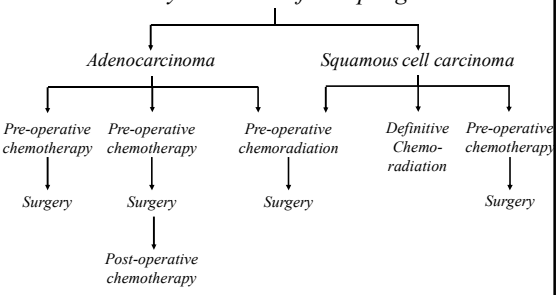
Margin: proximal limit of tumour above junction
- > 5cm – oesophagectomy
- 3 – 5cm – left thoraco-abdominal
- < 3cm - Transhiatal

Nakamura et al 2008, Hep Gastr 55: 1332-7

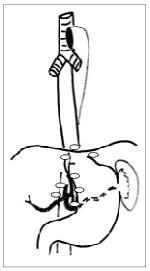
OPERATIVE MORBIDITY FOR JUNCTIONAL PROCEDURES

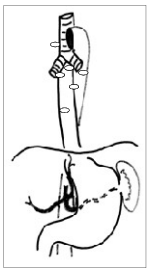
SERIES	PROCEDURE	NO.	OPERATIVE MORTALITY	OPERATIVE MORBIDITY	SPECIFIC MORBIDITY
Meyer et al (2002)	TTO LTA Ext TG	56 74	5.3% 1.4%	41%	Respiratory
Lerut et al (2004)	TTO 3 field	174	1.2%	58%	Respiratory 32.8% Arrythmia 10.9%
Internullo et al (2008)	LTA	94 (>75yrs)	7.4%	51.9%	Respiratory 37%
Ott et al (2009)	TTO	240	3.8%	17.9%	Respiratory
Li et al (2011)	LTA	135	0%	11%	Respiratory 6% Leak 1% Wound Infection 4%

Multimodality treatment of oesophageal cancer



Lymphadenectomy in Oesophago-Gastrectomy





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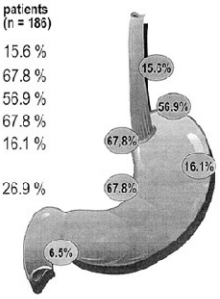
Nodal Distribution in Type II

Location	Number of patients with positive nodes		% of N+ patients (n = 185)
lower mediastinum	29		15.6 %
left paracardial	126		67.8 %
right paracardial	106		56.9 %
lesser curvature	126		67.8 %
greater curvature	30		16.1 %
left gastric artery	28		
splenic artery	9	50	26.9 %
celiac trunc	13		
parapyloric	3		
hepaduodenal ligament	9		
left renal hilus	6		



Siewert et al 2002

Frequency of Nodal Involvement

Pedrazzani et al 2007

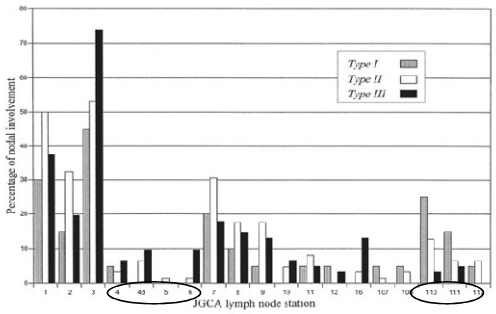


Figure 1. Percentage of nodal involvement to each Japanese Gastric Cancer Association (JGCA) lymph node station according to the tumor location (Siewert type I, type II, and type III) for the 143 patients under study.

Pedrazzani et al 2007

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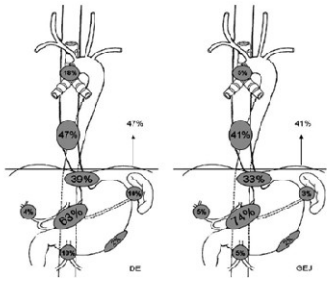
Pattern of lymph node spread En bloc resection



Leers et al. J Thor & Cardio 2009; 138: 594

The Royal Marsden

Operation Selection

Surgical Approach

Margins

Lymphadenectomy

The Royal Marsden

Operation Selection

Surgical Approach

Margins

Lymphadenectomy

Pattern of Recurrence of Type I & II Junctional Cancer

	Type I (*n*=55)	Type II (*n*=48)
Haematogenous	30	26
Local	18	14
Lymph node	10	12
Peritoneal	4	7

Site	Type I (n=10)	Type II (n=12)
Coeliac axis	4	3
Porta	3	4
Retrocrural/aortocaval	1	3
Supraclavicular	3	0

Wayman et al. Br J Cancer 2002, 86: 1223

The Royal Marsden

Lymph Node Spread from Type II

Right Cardiac	38.2%
Lesser Curve	35.1%
Left Cardiac	23.1%
Left Gastric Artery	20.9%

5 year Survival

N0 76.6%
N1 62.3%
N2 22.4%

Yamashita et al, 2011, Ann Surg 254: 274-80

Upper GI: technical and clinical challenges for RO

State of art of radiation therapy

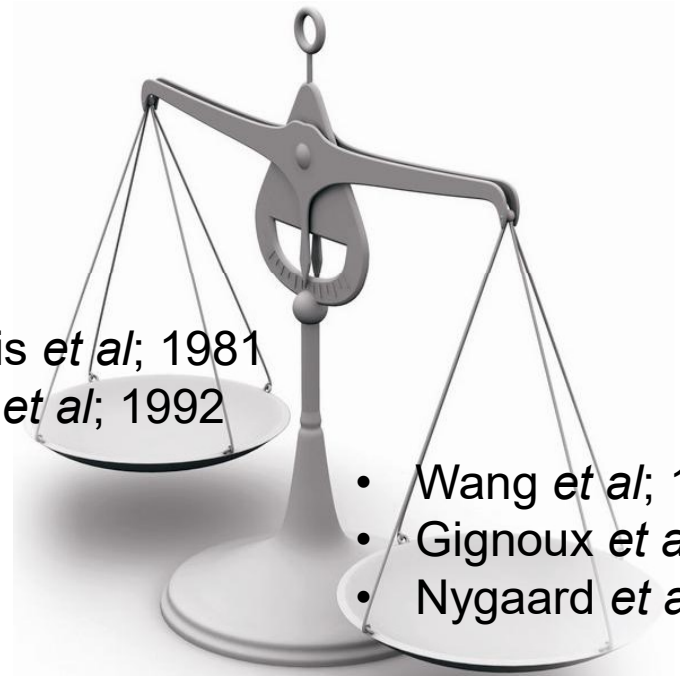
in a combined treatment perspective

State of art of radiation therapy in Esophageal Cancer

- ✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**
- ✓ **Definitive** Chemoradiation → **Salvage Esophagectomy**
- ✓ **Chemoradiation** → or **Selective Esophagectomy**

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- Phase III Trials RT(±CT)→Surg vs Surg alone



- Lanuois *et al*; 1981
- Arnott *et al*; 1992

- Wang *et al*; 1989
- Gignoux *et al*; 1987
- Nygaard *et al*; 1992

No Statistical Difference

✓ All SCC
✓ RT Doses: 20-40 Gy
✓ pCR ≈ 15%
✓ Local Failure (LF): 20-58%
✓ 5 yy SVV: 10-30%

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

• Walsh et al – 1996 (Trimodality)	Phase III Trial Chir ± Preop RTCT
• Urba et al – 2001 (Trimodality)	Phase III Trial Chir ± Preop RTCT
• Burmeister et al – 2005 (Trimodality)	Phase III Trial Chir ± Preop RTCT
• Tepper et al – 2008 (Trimodality)	Phase III Trial Chir ± Preop RTCT
• POET - 2009 (Trimodality)	Phase III Trial Chir + Preop CT ± RT
• FFCD 9901 - 2014 (Trimodality)	Phase III Trial Chir ± Preop RTCT
• CROSS - 2015 (Trimodality)	Phase III Trial Chir ± Preop RTCT

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- Walsh et al – 1996 (Trimodality) Stage n.a. Cardia 36%
  113 pts Adeno 100%

SVV Benefit

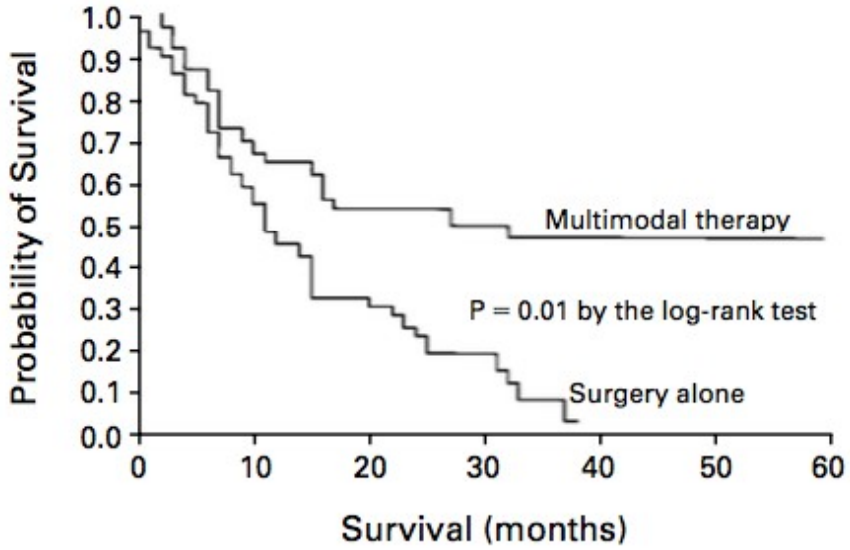


Figure 1. Kaplan–Meier Plot of Survival of Patients with Esophageal Adenocarcinoma, According to the Intention-to-Treat Analysis.

RTCT (3DCRT): 40 Gy (2.7 Gy fx) + 5Fu/CDDP EQD2: 42.33 Gy

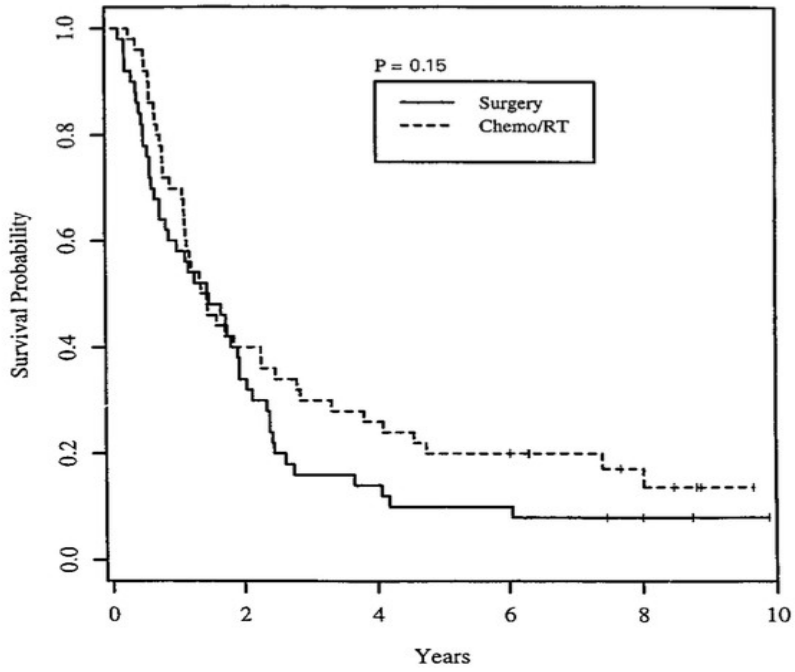
Walsh *et al*; N Engl J Med 1996
(Ireland)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- Urba et al – 2001 (Trimodality) Stage: n.a. Mid-Distal= 92%
  100 pts Adeno 75%

NO SVV Benefit



RTCT (3DCRT): 45 Gy (1.5 Gy fx x 2/day) + 5Fu/CDDP/Vimblastine EQD2: 48.75 Gy

Urba *et al*; JCO 2001
(USA)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- Burmeister et al – 2005 (Trimodality) 79%

Stage: n.a.
256 pts

Mid-Distal= Adeno 62%

NO SVV Benefit

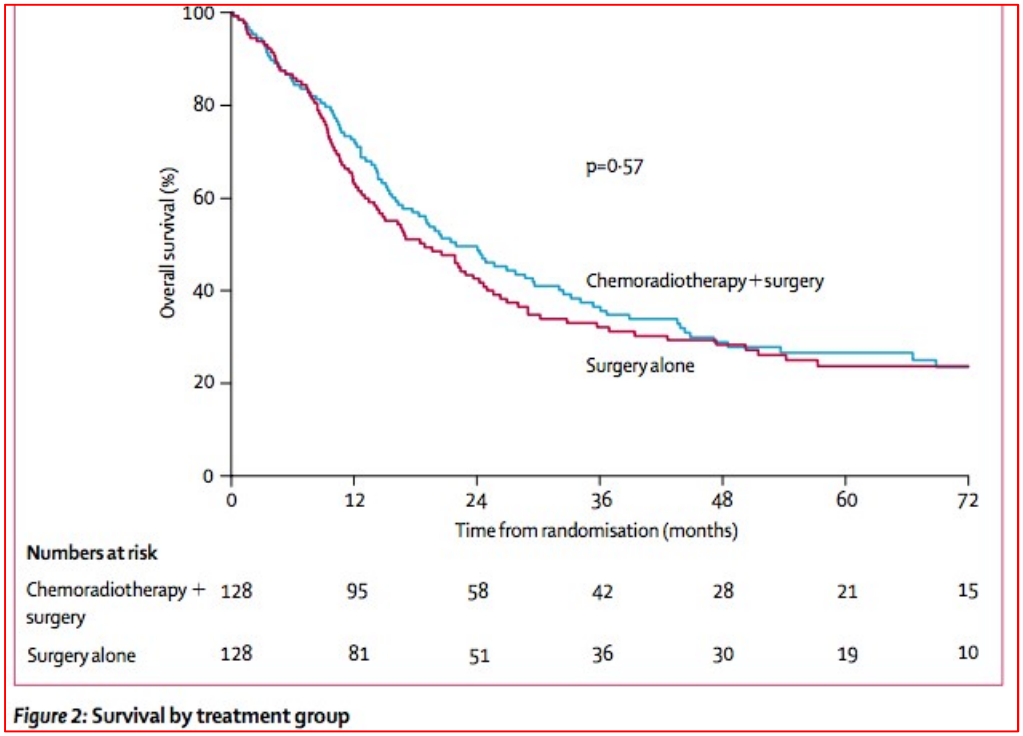


Figure 2: **Survival by treatment group**

RTCT (Simulator): 35 Gy (2.4 Gy fx) + 5Fu/CDDP

EQD2: 36.17 Gy

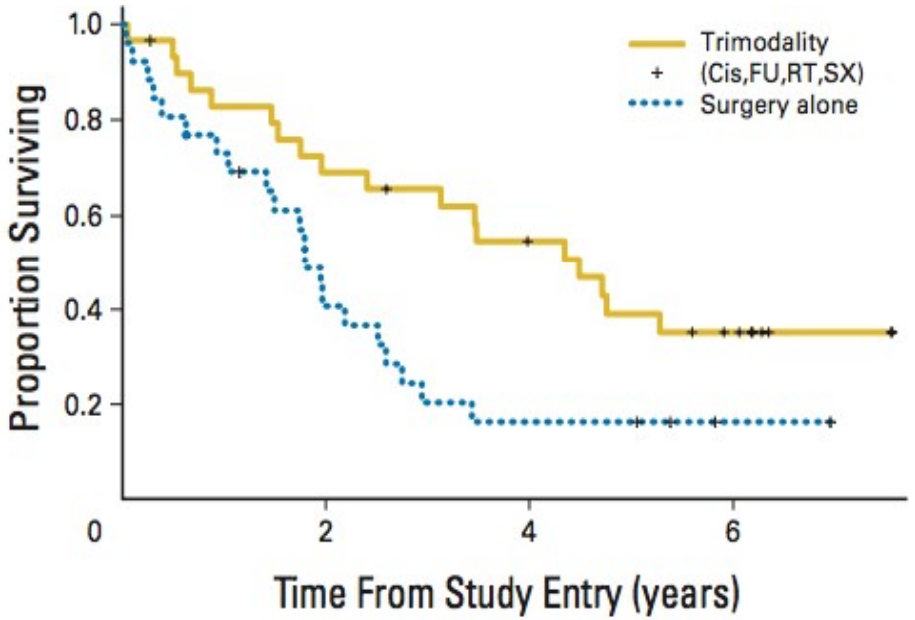
Burmeister *et al*; Lancet Oncol 2005 (Australia)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- Tepper et al – 2008 (Trimodality) Stage n.a. Low third n.a.
  56 pts Adeno 75%

SVV Benefit



RTCT: 50.4 Gy (1.8 Gy fx) + 5Fu/CDDP EQD2: 49.56 Gy

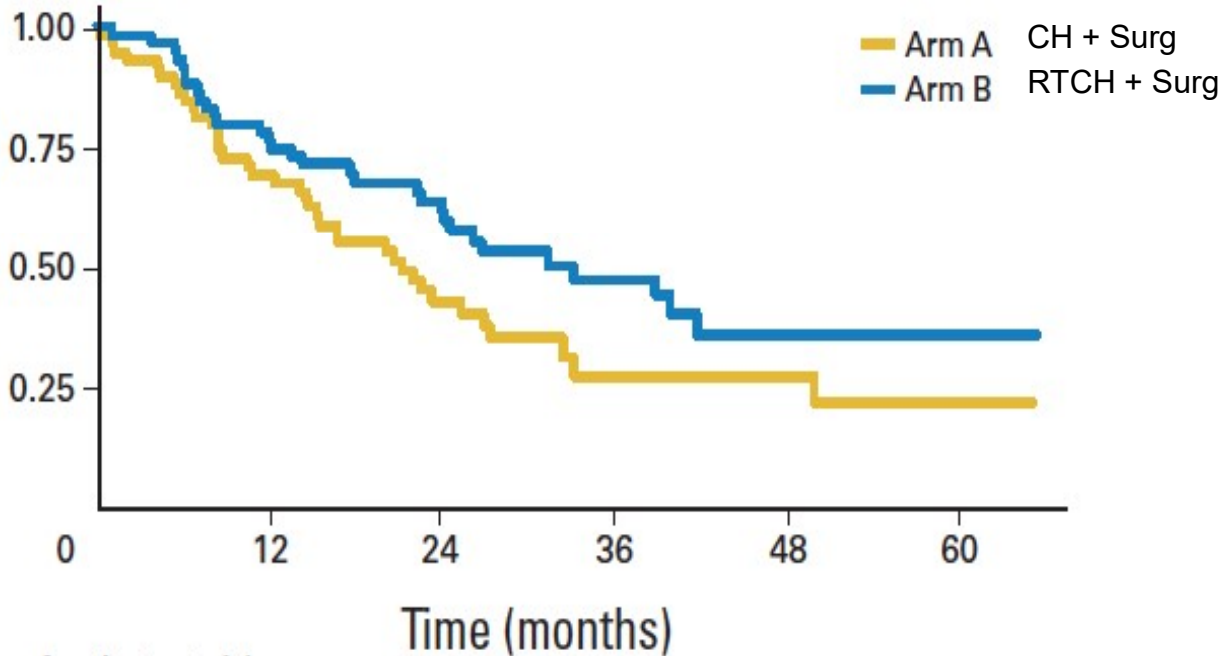
Tepper *et al*; JCO 2008
(USA)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- POET - 2009 (Trimodality) uT3-4NXM0 Siewert I-III= 100%
  126 pts **(326 planned)** Adeno 100%

NO SVV Benefit



RTCT (Simulator): 2PLF + 30 Gy (2 Gy fx) + CDDP/Etoposide EQD2: 30 Gy

Stahl *et al*; JCO – 2009
(Germany)

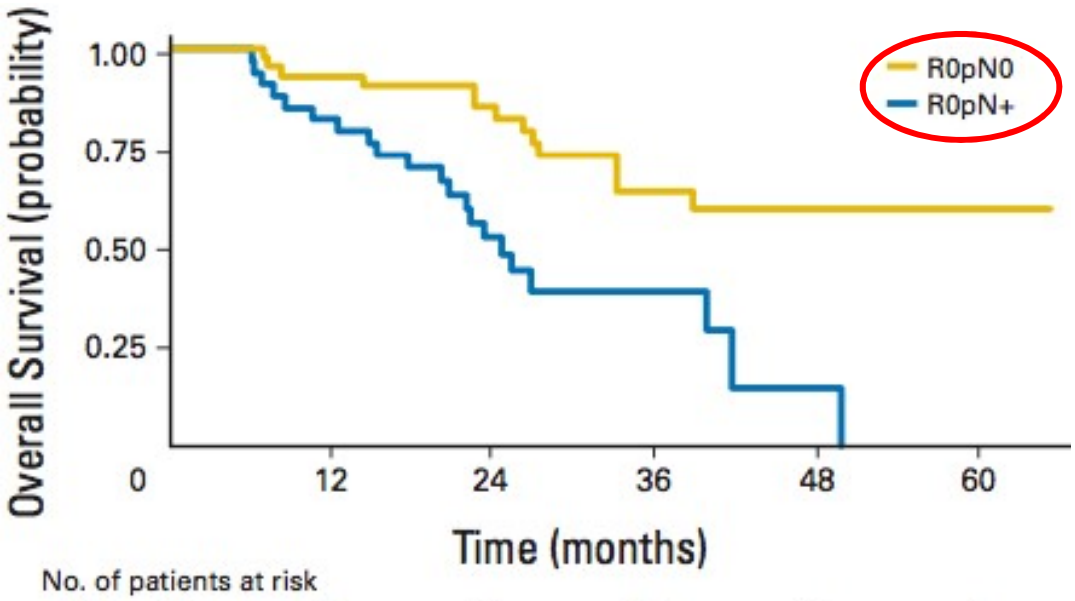
ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- POET - 2009 (Trimodality) uT3-4NXM0 Siewert I-III= 100%
  126 pts **(326 planned)** Adeno 100%

NO SVV Benefit

- Significant improvement of pCR (2 vs 15.6%; p=0.03) favoring RTCT



- Significant improvement of pN0 (36.7 vs 64.4%; p=0.03) favoring RTCT

Stahl *et al*; JCO – 2009
(Germany)

ESTRO School

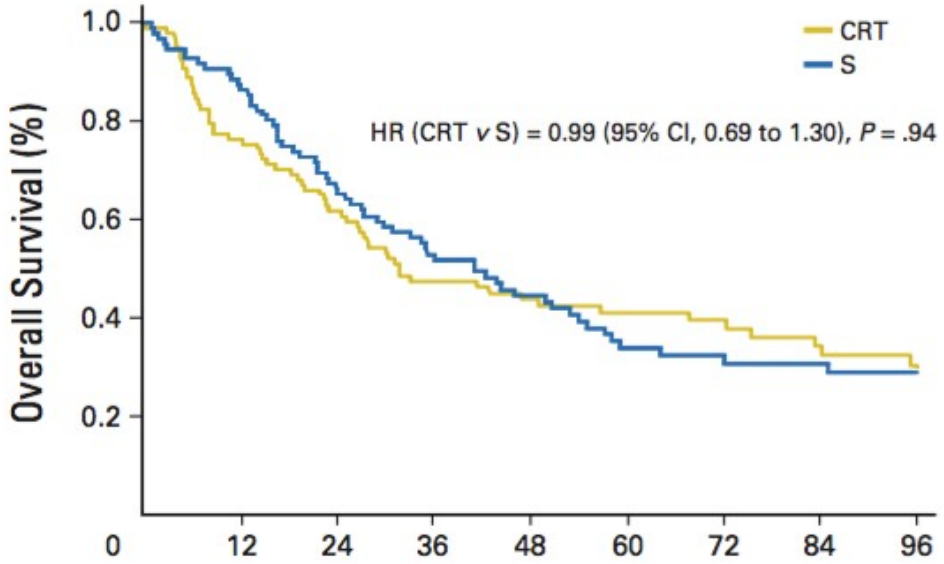
✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- FFCD 9901 - 2014 (Trimodality)

Stage I-II
194 pts

Below carina= 91%
Adeno 29%

NO SVV Benefit



RTCT: 45 Gy (1.8 Gy fx) + 5FU + Platinum

EQD2: 44.25Gy

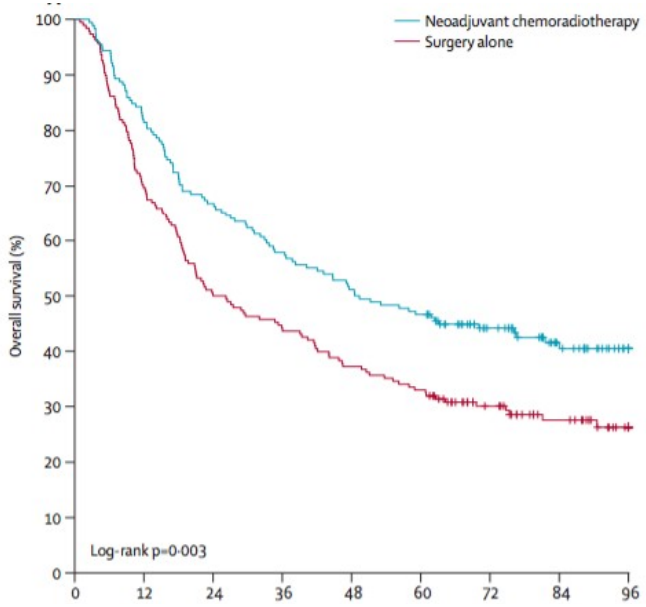
Mariette *et al*; JCO – 2014
(France)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- CROSS - 2015 (Trimodality) T1N1+T2-3N0-1M0 Junction= 24%
  366 pts Adeno 75%

Signif SVV Benefit



RTCT: 41.4 Gy (1.8 Gy fx) + Carbo/Paclitaxel EQD2: 40.71 Gy

Van Hagen *et al*; N Engl J Med 2012
Oppedijk *et al;* JCO 2014
Shapiro *et al*; Lancet Oncol 2015

The Netherlands

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

	Tumor site	N.	Histology	EQD2
• Walsh et al – 1996	**Cardia 36%**	**113 pts**	**Adeno 100%**	**EQD2: 42.33 Gy**
• Urba et al – 2001	Mid-Distal 92%	100 pts	Adeno 75%	EQD2: 48.75 Gy
• Burmeister et al – 2005	Mid-Distal 79%	256 pts	Adeno 62%	EQD2: 36.17 Gy
• Tepper et al – 2008	**Low third n.a.**	**56 pts**	**Adeno 75%**	**EQD2: 49.56 Gy**
• POET - 2009	Siewert I-III 100%	126 pts	Adeno 100%	EQD2: 30 Gy
• FFCD 9901 – 2014	Below carina 91%	194 pts	Adeno 29%	EQD2: 44.25Gy
• CROSS - 2015	**Junction 24%**	**366 pts**	**Adeno 75%**	**EQD2: 40.71 Gy**

Statistically in favour of Preop ChemoRT

Mod from Cellini *et al*; Radiat Oncol 2014 (Italy)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

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• FFCD 9901 – 2014	Below carina 91%	194 pts	Adeno 29%	EQD2: 44.25Gy
• CROSS - 2015	**Junction 24%**	**366 pts**	**Adeno 75%**	**EQD2: 40.71 Gy**

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Mod from Cellini *et al*; Radiat Oncol 2014 (Italy)

ESTRO School

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Statistically in favour of Preop ChemoRT

Mod from Cellini *et al*; Radiat Oncol 2014 (Italy)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

	Tumor site	N.	Histology	EQD2
• Burmeister et al – 2005	Mid-Distal 79%	256 pts	Adeno 62%	EQD2: 36.17 Gy
	Stage: T1–3, N0–1 M0			
	Stage: T1N1+T2-3N0-1M0			
• CROSS - 2015	**Junction 24%**	**366 pts**	**Adeno 75%**	**EQD2: 40.71 Gy**

Statistically in favour of Preop ChemoRT

Mod from Cellini *et al*; Radiat Oncol 2014 (Italy)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- **Propensity score match**

442 ptz available
multi-center (10 Europe)

resectable Esophageal or GEJ Siewert type I and II (stage II or III) , adenocarcinoma 100%

NCR+S (221ptz) = RTCT "CROSS" approach, followed by surgery.

NC+S (221ptz) = CT "MAGIC" approach, including surgery.

Evaluation period 2001-2012; follow-up until 2015

Markar SR et al – Ann Oncol - 2016
(Ireland)

ESTRO School

✓ Preoperative Chemoradiation → Planned Esophagectomy

- **Propensity score match**

442 ptz available
multi-center (10 Europe)

resectable Esophageal or GEJ Siewert type I and II (stage II or III) , adenocarcinoma 100%

- 3-year overall survival

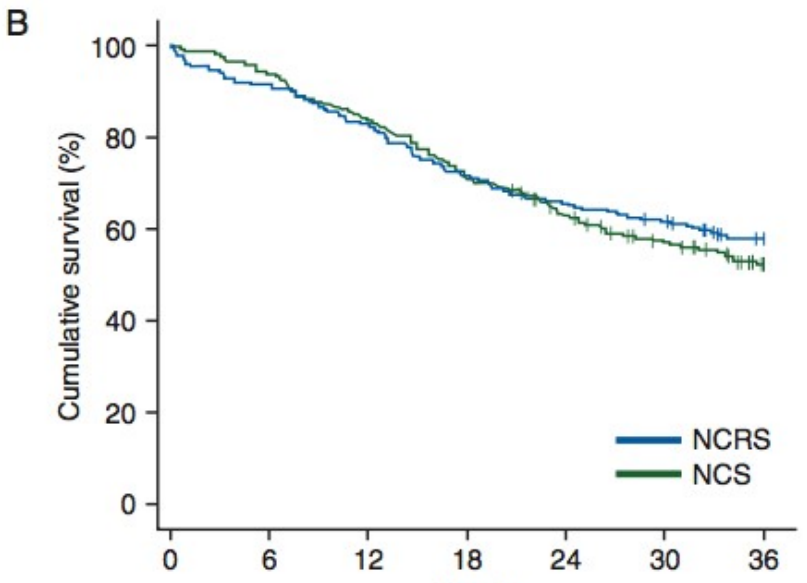
57.9% versus 53.4%;

HR= 0.89, 95%C.I. 0.67-1.17, p = 0.391

- disease-free survival

52.9% versus 48.9%;

HR = 0.90, 95%C.I. 0.69-1.18, p = 0.443



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Markar SR et al – Ann Oncol - 2016
(Ireland)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- **Propensity score match**

442 ptz available
multi-center (10 Europe)

resectable Esophageal or GEJ Siewert type I and II (stage II or III), adenocarcinoma 100%

- ypT0= NCR+S= 26.7% versus NC+S= 5%; p<0.001;
- R1/2 resection margins= NCR+S= 7.7% versus NC+S= 21.8%; p<0.001;

- ypN0= NCR+S= 63.3% versus NC+S= 32.1%; p<0.001;
- lymph node harvest= NCR+S= 14% versus NC+S= 27%; p<0.001;

- 30+90-day mortality= No sign diffs
- anastomotic leak= NCR+S= 23.1% versus NC+S= 6.8%; p<0.001;

Evaluation period 2001-2012; follow-up until 2015

Markar SR et al – Ann Oncol - 2016
(Ireland)

ESTRO School

State of art of radiation therapy in Esophageal Cancer

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- Walsh et al – 1996 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- Urba et al – 2001 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- Burmeister et al – 2005 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- Tepper et al – 2008 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- POET - 2009 (Trimodality) — Phase III Trial Chir + Preop CT ± RT
- FFCD 9901 - 2014 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- CROSS - 2015 (Trimodality) — Phase III Trial Chir ± Preop RTCT

✓ **Definitive** Chemoradiation → **Salvage Esophagectomy**

- RTOG 85-01 - 1999 — Phase III Trial RT vs RTCT
- INT 0123 - 2002 — Phase III Trial RTCT (50Gy) vs RTCT (65Gy)

✓ **Definitive** Chemoradiation → **Salvage Esophagectomy**

- RTOG 85-01 - 1999 — Phase III Trial RT (64Gy) vs RTCT (50Gy)
- RTOG 85-01 – 1999 — T1-3 N0-1M0 — Low third: n.a.
- RTOG 85-01 – 1999 — 129 pts — Adeno 21.4%
- RTOG 85-01 – 1999 — **SVV Benefit** (RTCT vs RT Alone)

50 Gy- EQD2: 49.17 Gy

- INT 0123 - 2002 — Phase III Trial RTCT (50Gy) vs RTCT (65Gy)
- INT 0123 – 2002 — T1-T4 N0-1M0 — Low third: n.a.
- INT 0123 – 2002 — 218 pts — Hystotype: n.a.
- INT 0123 – 2002 — **NO SVV Benefit**

Cooper *et al*; - JAMA – 1999
Minsky *et al;* JCO 2002

USA

ESTRO School

State of art of radiation therapy in Esophageal Cancer

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- Walsh et al – 1996 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- Urba et al – 2001 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- Burmeister et al – 2005 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- Tepper et al – 2008 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- POET - 2009 (Trimodality) — Phase III Trial Chir + Preop CT ± RT
- FFCD 9901 - 2014 (Trimodality) — Phase III Trial Chir ± Preop RTCT
- CROSS - 2015 (Trimodality) — Phase III Trial Chir ± Preop RTCT

✓ **Definitive** Chemoradiation → **Salvage Esophagectomy**

- RTOG 85-01 - 1999 — Phase III Trial RT vs RTCT
- INT 0123 - 2002 — Phase III Trial RTCT (50Gy) vs RTCT (65Gy)

✓ **Chemoradiation** → or **Selective Esophagectomy**

- ESSEN Trial - 2005 — Phase II Trial RTCT ± Selective Chir
- FFCD 9102 - 2015 — Phase III Trial RTCT in > PR RTCT vs Selective Chir

ESTRO School

✓Chemoradiation → or Selective Esophagectomy

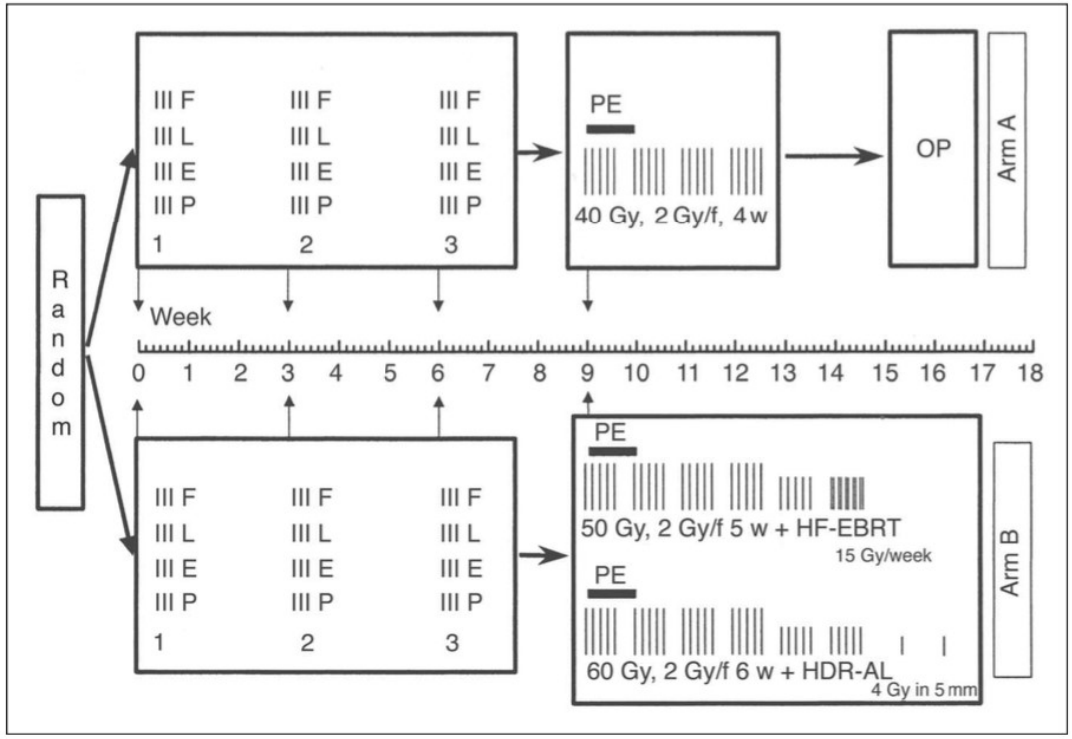
- ESSEN Trial – 2005

T3-4, N0-1, M0

172 pts

Low third: 0%

Adeno 0%



EQD2: 40 Gy

EQD2: 50 Gy

EQD2: 60 Gy

Stahl *et al*; JCO 2005
(Germany)

ESTRO School

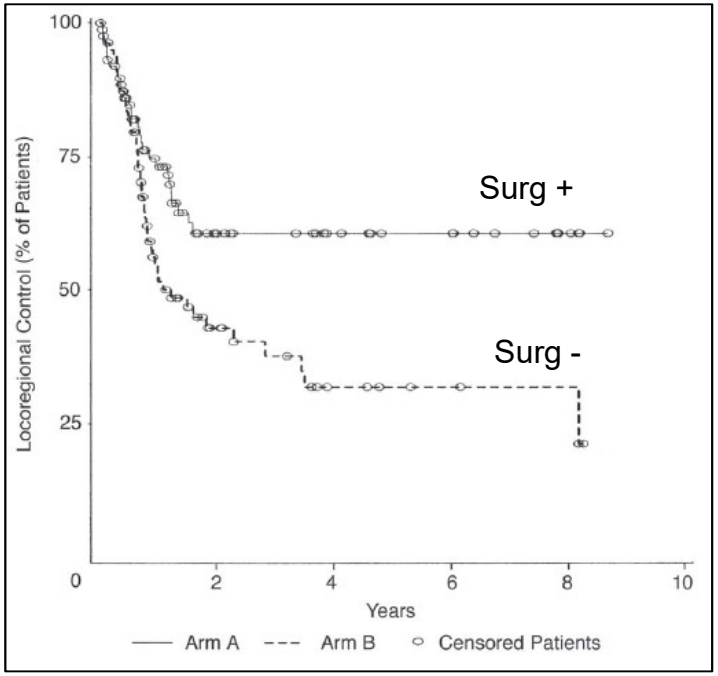
✓Chemoradiation → or Selective Esophagectomy

- ESSEN Trial – 2005

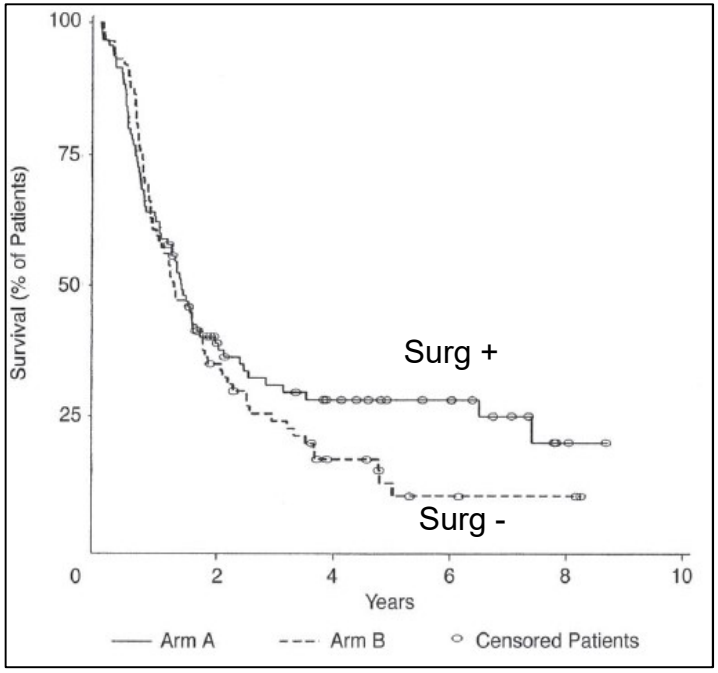
T3-4, N0-1, M0
172 pts

Low third: 0%
Adeno 0%

Local control



Survival



Stahl *et al*; JCO 2005
(Germany)

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✓Chemoradiation → or Selective Esophagectomy

- ESSEN Trial – 2005

T3-4, N0-1, M0
172 pts

Low third: 0%
Adeno 0%

Treatemet related mortality

chemoradiotherapy + surgery: **12.8%**

chemoradiotherapy alone: **3.5%**

p=0.03

Stahl *et al*; JCO 2005
(Germany)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- FFCD 9901 - 2014 (Trimodality) — Stage I-II, 194 pts — Below carina= 91%, Adeno 29%

Treatemet related mortality

chemoradiotherapy + surgery: **11.1%**

surgery alone: **3.5%**

p=0.04

Mariette *et al*; JCO – 2014
(France)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- CROSS - 2015 (Trimodality) T1N1+T2-3N0-1M0 366 pts — Junction= 24% Adeno 75%

Treatemet related mortality

chemoradiotherapy + surgery: **4%**

surgery alone: **4%**

p=ns

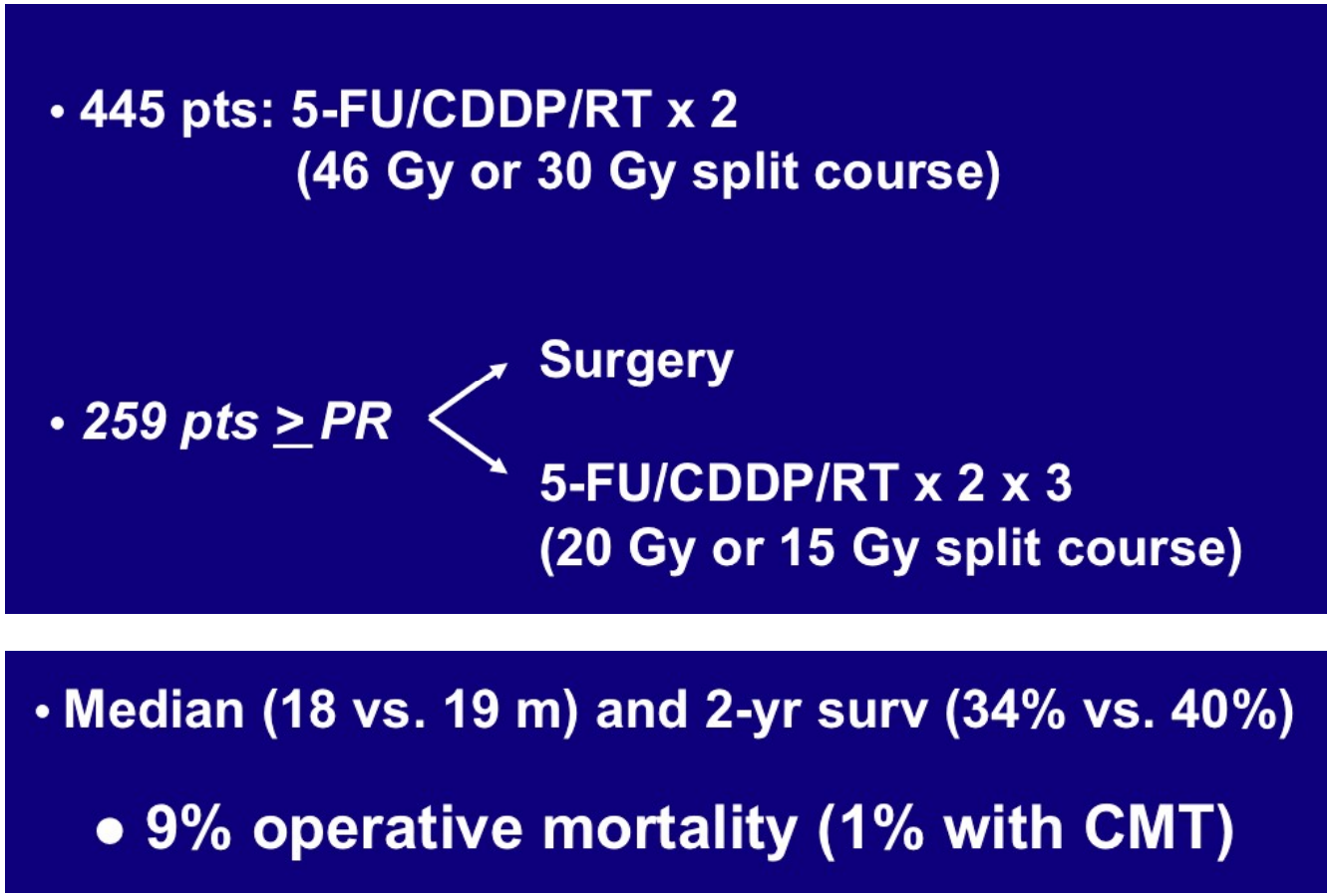
Van Hagen *et al*; N Engl J Med 2012
Oppedijk *et al;* JCO 2014
Shapiro *et al*; Lancet Oncol 2015

The Netherlands

ESTRO School

✓Chemoradiation → or Selective Esophagectomy

- FFCD 9102 – 2015 T3-N0/N1-M0 thoracic adeno 11%



Bedenne *et al*; - JCO– 2007
(France)

ESTRO School

✓Chemoradiation → or Selective Esophagectomy

- FFCD 9102 – 2015 T3-N0/N1-M0 thoracic adeno 11%

  Median OS **non-randomised** (**11.5** months) vs **randomised** (**18.9** months; p=0.0024).

  In 112 non-randomised who underwent **surgery**, median OS was **17.3** versus **18.9** months in randomised : (p=0.58)

Mariette *et al*; - EJC – 2015
(France)

ESTRO School

State of art of radiation therapy in Esophageal Cancer

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

- Walsh et al – 1996 (Trimodality) — **SVV Benefit**
- Urba et al – 2001 (Trimodality) — **NO SVV Benefit**
- Burmeister et al – 2005 (Trimodality) — **NO SVV Benefit**
- Tepper et al – 2008 (Trimodality) — **SVV Benefit**
- POET - 2009 (Trimodality) — **NO SVV Benefit**
- FFCD 9901 - 2014 (Trimodality) — **NO SVV Benefit**
- CROSS - 2015 (Trimodality) — **SVV Benefit**

✓ **Definitive** Chemoradiation → **Salvage Esophagectomy**

- RTOG 85-01 - 1999 — **SVV Benefit**
- INT 0123 - 2002 — **NO SVV Benefit**

✓ **Chemoradiation** → or **Selective Esophagectomy**

- ESSEN Trial - 2005 — **NO SVV Benefit**
- FFCD 9102 - 2015 — **NO SVV Benefit**

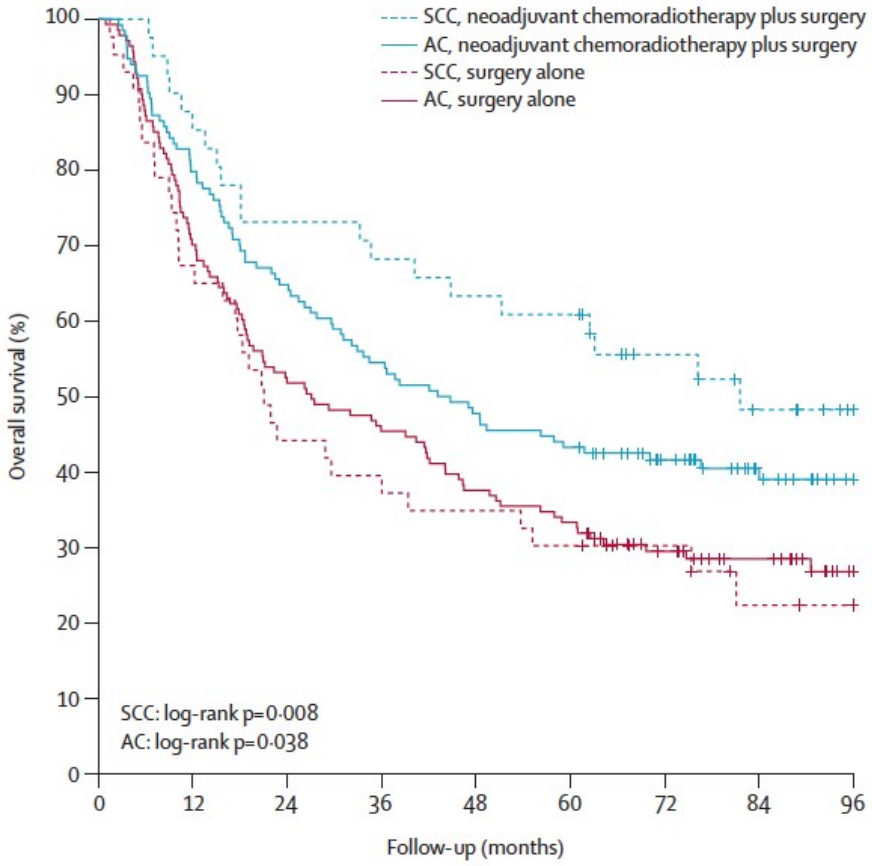
ESTRO School

State of art of radiation therapy in Esophageal Cancer

- ✓ Does **histology** affect radiotherapy **response?**
- ✓ Does dose **impact long term outcome?**
- ✓ Is there any role for **Brachytherapy in palliation**?

✓Does **histology** affect radiotherapy **response?**

- CROSS - 2015 (Trimodality) T1N1+T2-3N0-1M0 Junction= 24%
  366 pts Adeno 75%



Shapiro *et al*; Lancet Oncol 2015
(The Netherlands)

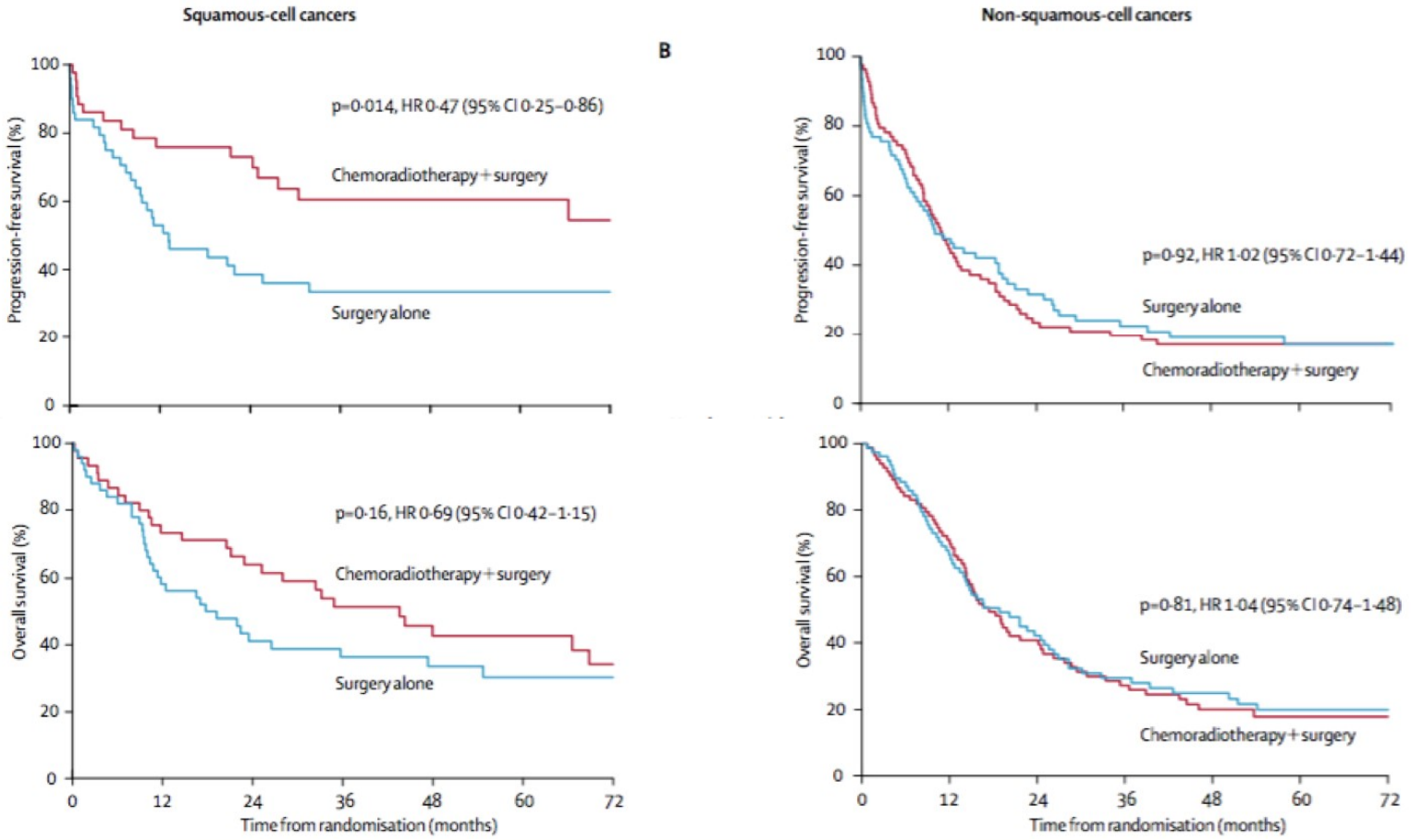
ESTRO School

✓Does **histology** affect radiotherapy **response?**

- Burmeister et al – 2005 (Trimodality) 79%

Stage: n.a. 256 pts

Mid-Distal= Adeno 62%

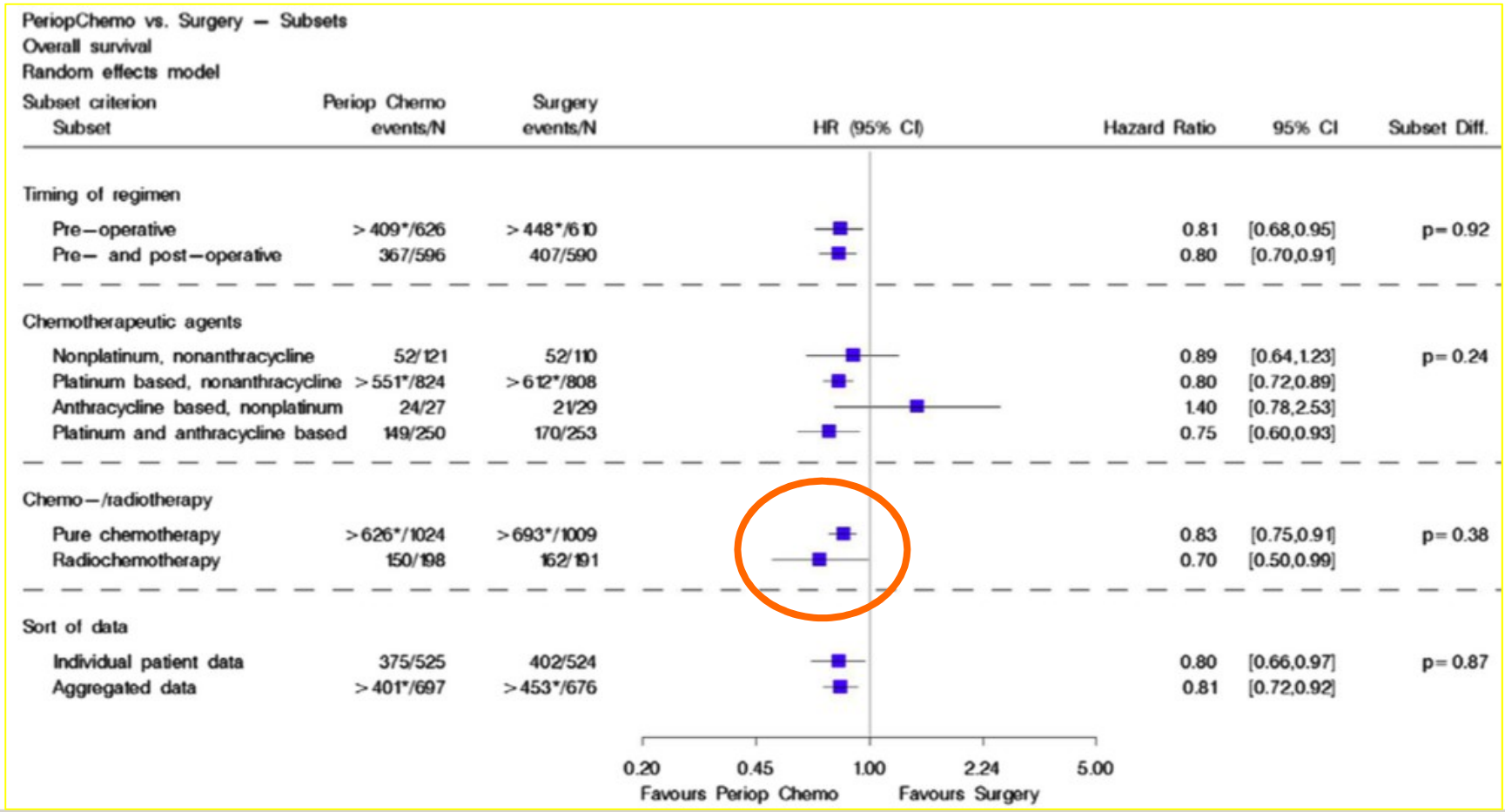


Burmeister *et al*; Lancet Oncol 2005 (Australia)

ESTRO School

✓Does **histology** affect radiotherapy **response?**

Systematic review with meta-analysis combining individual patient and aggregate data

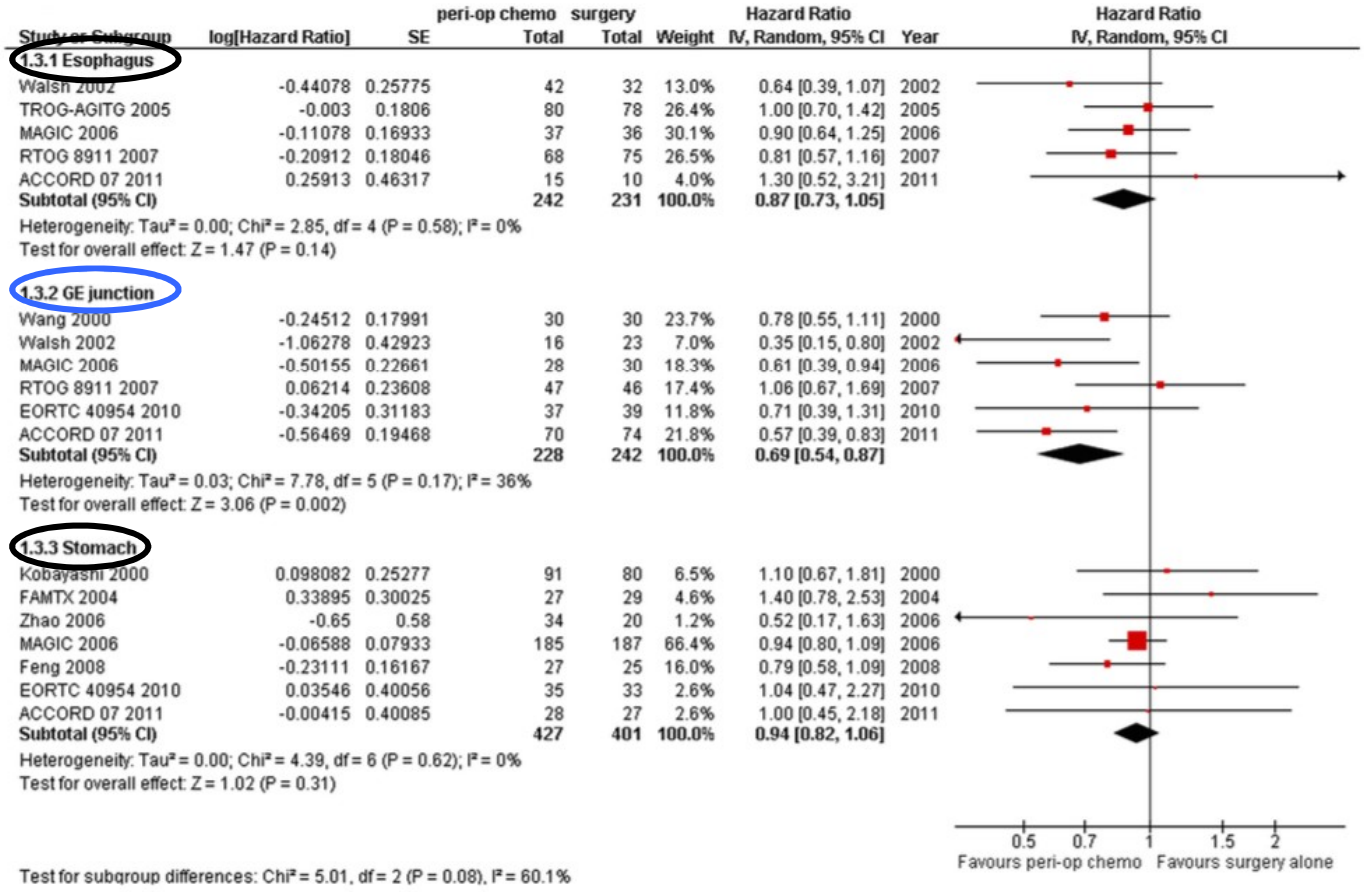


Ronellenfitsch *et al*; Eur J Cancer – 2013 (Germany)

ESTRO School

✓Does **histology** affect radiotherapy **response?**

Systematic review with meta-analysis combining individual patient and aggregate data



Ronellenfitsch *et al*; Eur J Cancer – 2013

ESTRO School

State of art of radiation therapy in Esophageal Cancer

- ✓ Does **histology** affect radiotherapy **response?** **YES/NO**
- ✓ Does dose **impact long term outcome?**
- ✓ Is there any role for **Brachytherapy in palliation**?

✓Does dose **impact long term outcome?**

- RTOG 85-01 - 1999 — Phase III Trial RT (64Gy) vs RTCT (50Gy)
- RTOG 85-01 – 1999 — T1-3 N0-1M0 — Low third: n.a.
- RTOG 85-01 – 1999 — 129 pts — Adeno 21.4%
- RTOG 85-01 – 1999 — **SVV Benefit** (RTCT vs RT Alone)

- INT 0123 - 2002 — Phase III Trial RTCT (50Gy) vs RTCT (65Gy)
- INT 0123 – 2002 — T1-T4 N0-1M0 — Low third: n.a.
- INT 0123 – 2002 — 218 pts — Hystotype: n.a.
- INT 0123 – 2002 — **NO SVV Benefit**

Cooper *et al*; - JAMA – 1999 (USA)
Minsky *et al;* JCO 2002 (USA)

ESTRO School

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

	N.	Histology	EQD2	pCR
• Walsh et al – 1996	113 pts	Adeno 100%	EQD2: 42.33 Gy	25 %
• Urba et al – 2001	100 pts	Adeno 75%	EQD2: 48.75 Gy	28 %
• Burmeister et al – 2005	256 pts	Adeno 62%	**EQD2: 36.17 Gy**	**16 %**
• Tepper et al – 2008	56 pts	Adeno 75%	EQD2: 49.56 Gy	40 %
• FFCD 9901 – 2014	194 pts	Adeno 29%	EQD2: 44.25Gy	33 %
• CROSS - 2015	366 pts	Adeno 75%	EQD2: 40.71 Gy	29 %

Mod from Cellini *et al*; Radiat Oncol 2014 (Italy)

ESTRO School

State of art of radiation therapy in Esophageal Cancer

- ✓ Does **histology** affect radiotherapy **response?** **YES/NO**
- ✓ Does dose **impact long term outcome?** **NO but**
- ✓ Is there any role for **Brachytherapy in palliation**?

✓Is there any role for **Brachytherapy in palliation**?

Conventional stents versus stents loaded with ^{125}iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial

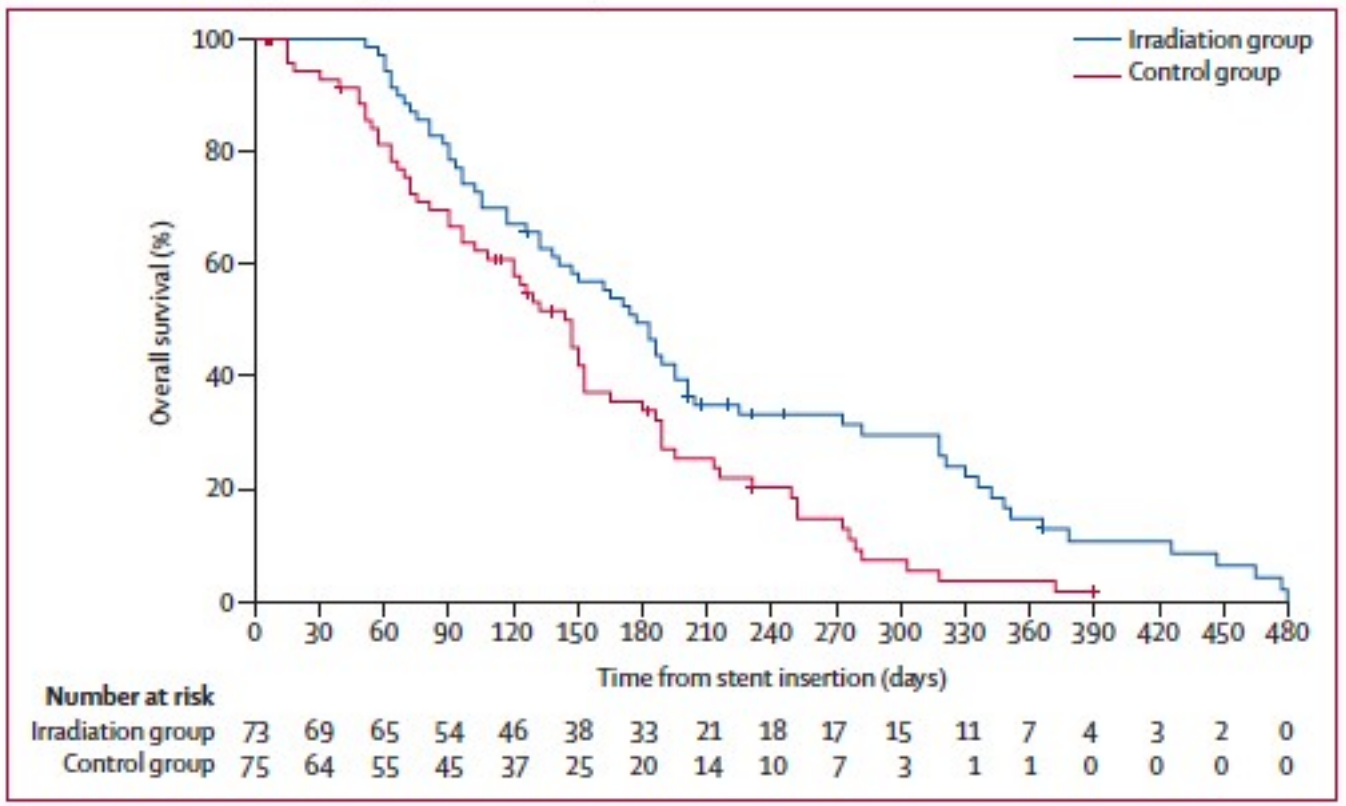
Hai-Dong Zhu, Jin-He Guo*, Ai-Wu Mao*, Wei-Fu Lv*, Jian-Song Ji*, Wen-Hui Wang, Bin Lv, Rui-Min Yang, Wei Wu, Cai-Fang Ni, Jie Min, Guang-Yu Zhu, Li Chen, Mei-Ling Zhu, Zhen-Yu Dai, Peng-Fei Liu, Jian-Ping Gu, Wei-Xin Ren, Rui-Hua Shi, Gao-Feng Xu, Shi-Cheng He, Gang Deng, Gao-Jun Teng*

Zhu *et al*; Lancet Oncol 2014
(China)

ESTRO School

✓Is there any role for **Brachytherapy in palliation**?

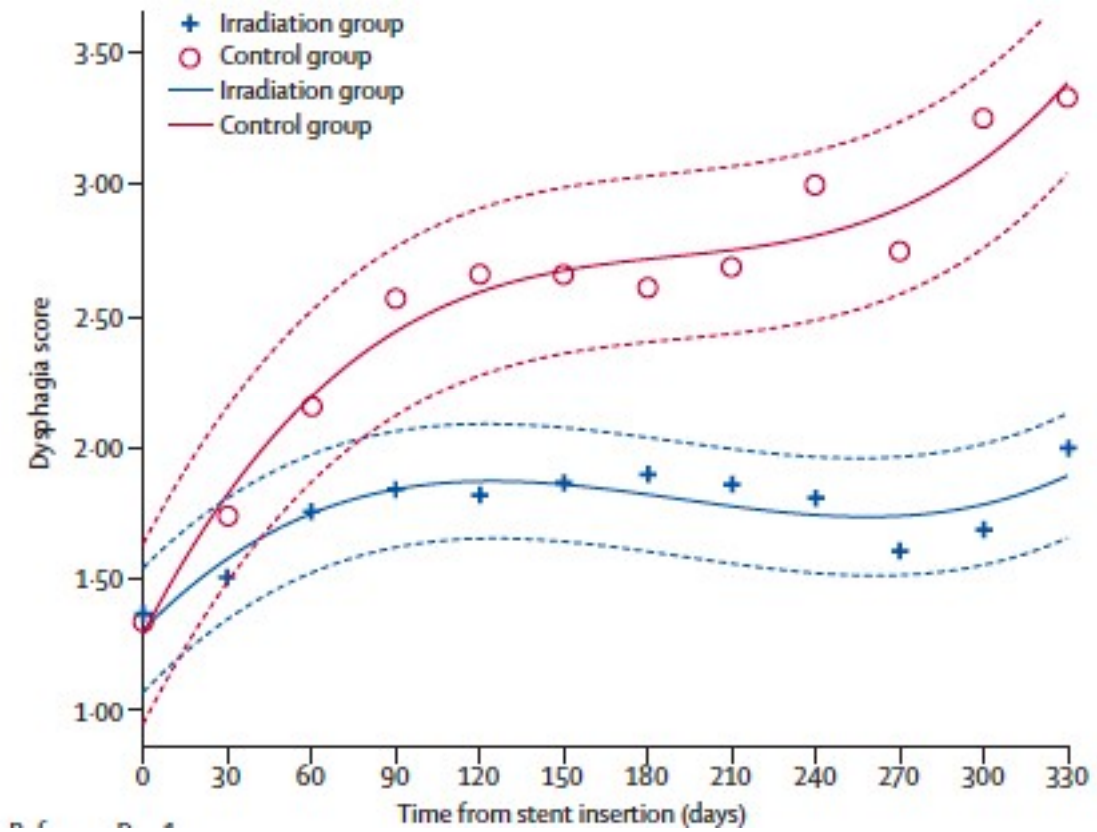
Survival



Zhu *et al*; Lancet Oncol 2014

ESTRO School

✓Is there any role for **Brachytherapy in palliation**?



Zhu *et al*; Lancet Oncol 2014

ESTRO School

State of art of radiation therapy in Esophageal Cancer

- ✓ Does **histology** affect radiotherapy **response?** **YES/NO**
- ✓ Does dose **impact long term outcome?** **NO but**
- ✓ Is there any role for **Brachytherapy in palliation**? **YES**

UNIVERSITÄT LEIPZIG

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Medizin ist unsere Berufung.

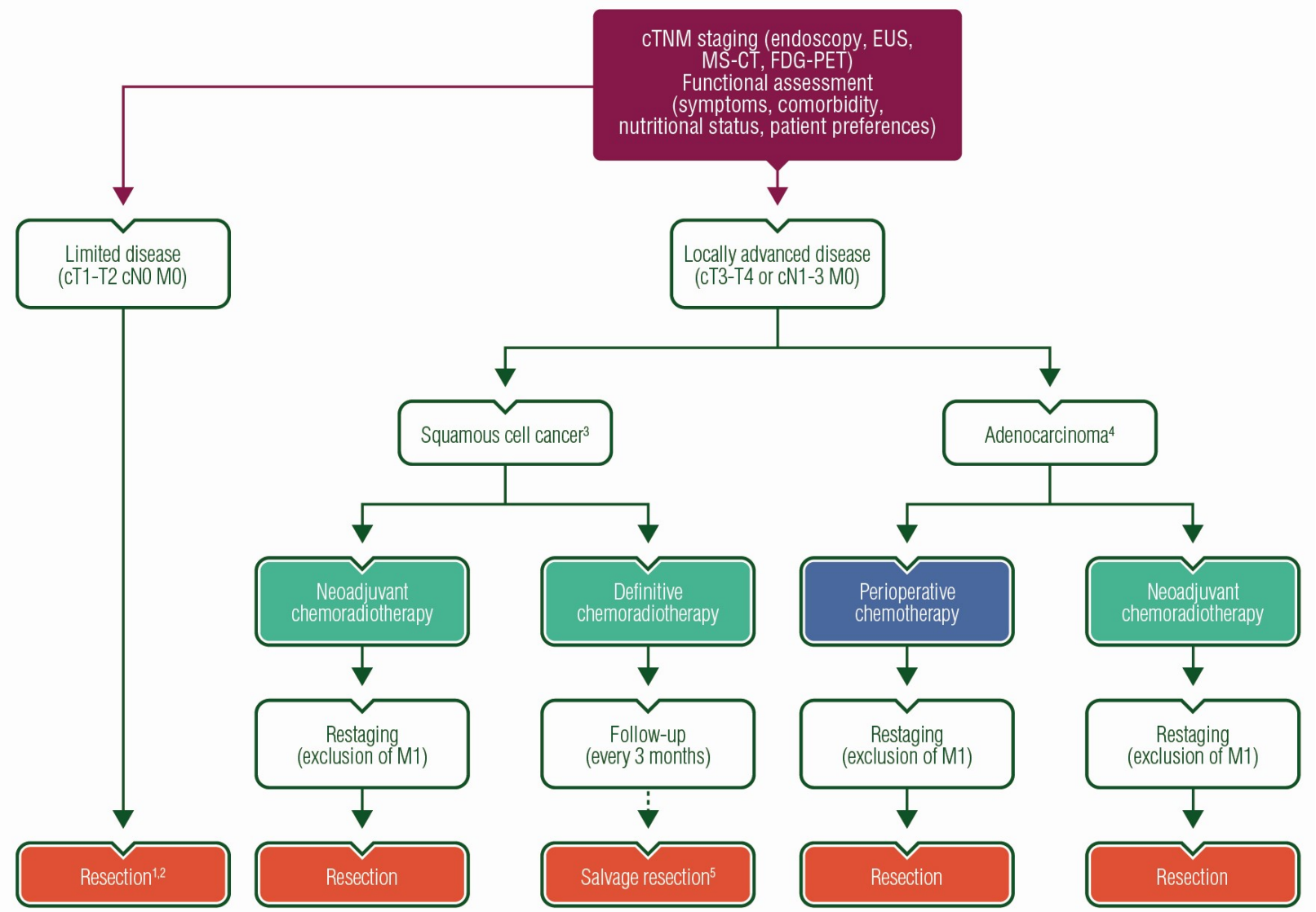
UCCL UNIVERSITÄRES KREBSZENTRUM

Upper GI: technical and clinical challenges for radiation oncologists
25 March 2017, Rome

State of art of chemotherapy in a combined treatment perspective

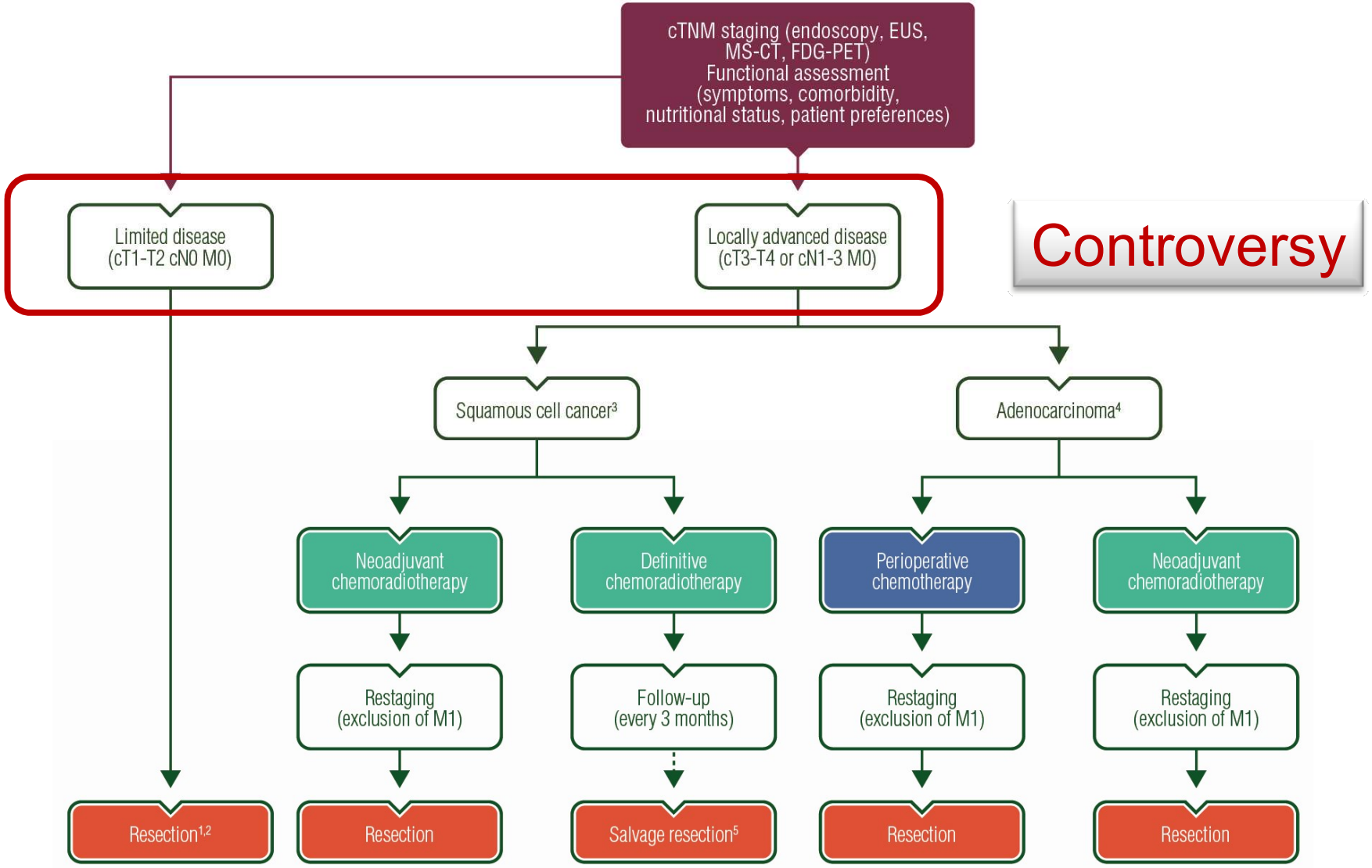
Prof. Dr. med. Florian Lordick
Director
University Cancer Center Leipzig
UCCL

ESMO Guidelines Oesophageal Cancer 2016



Lordick et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

ESMO Guidelines Oesophageal Cancer 2016



Lordick et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

ESMO Guidelines Oesophageal Cancer 2016

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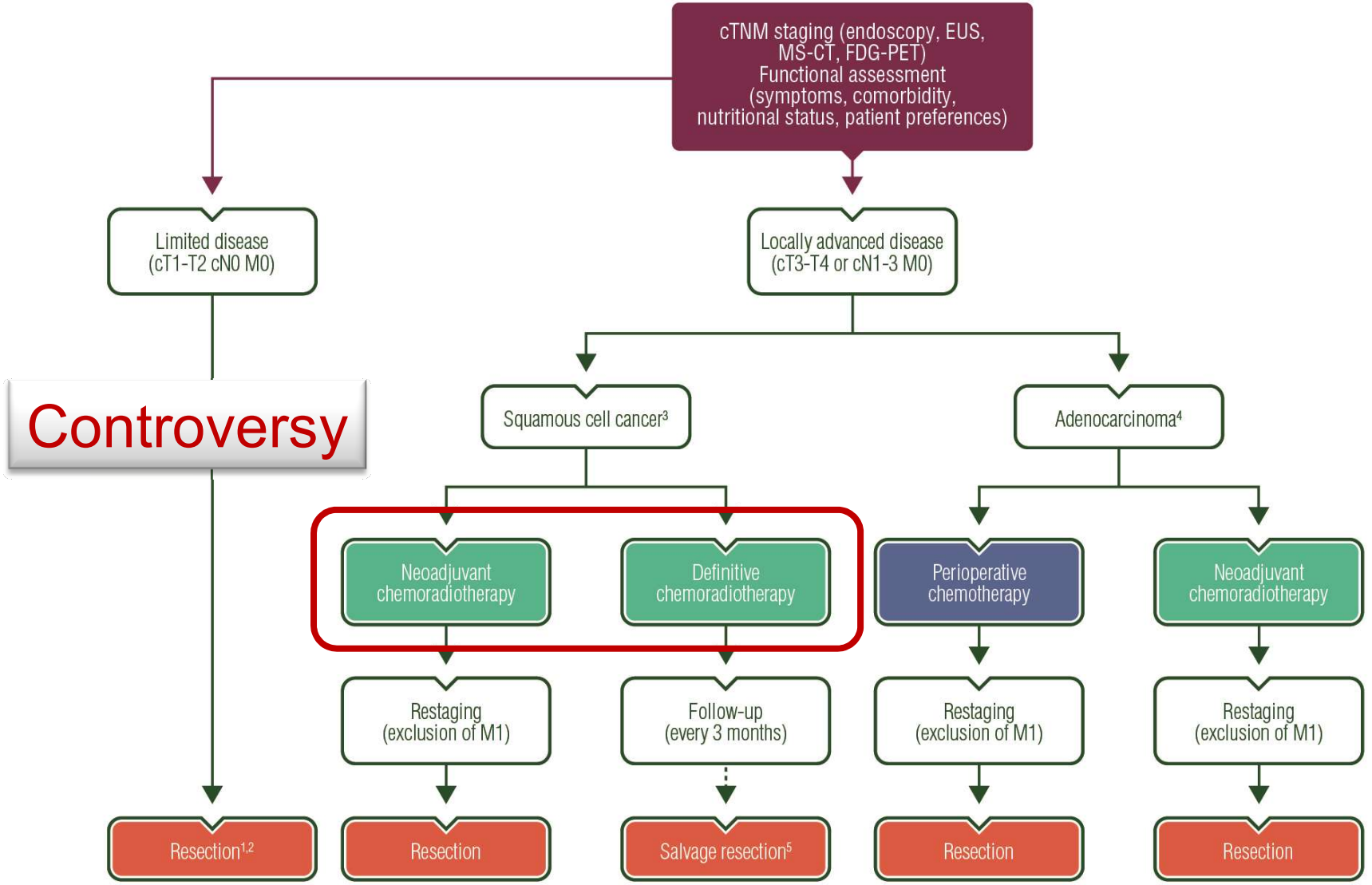
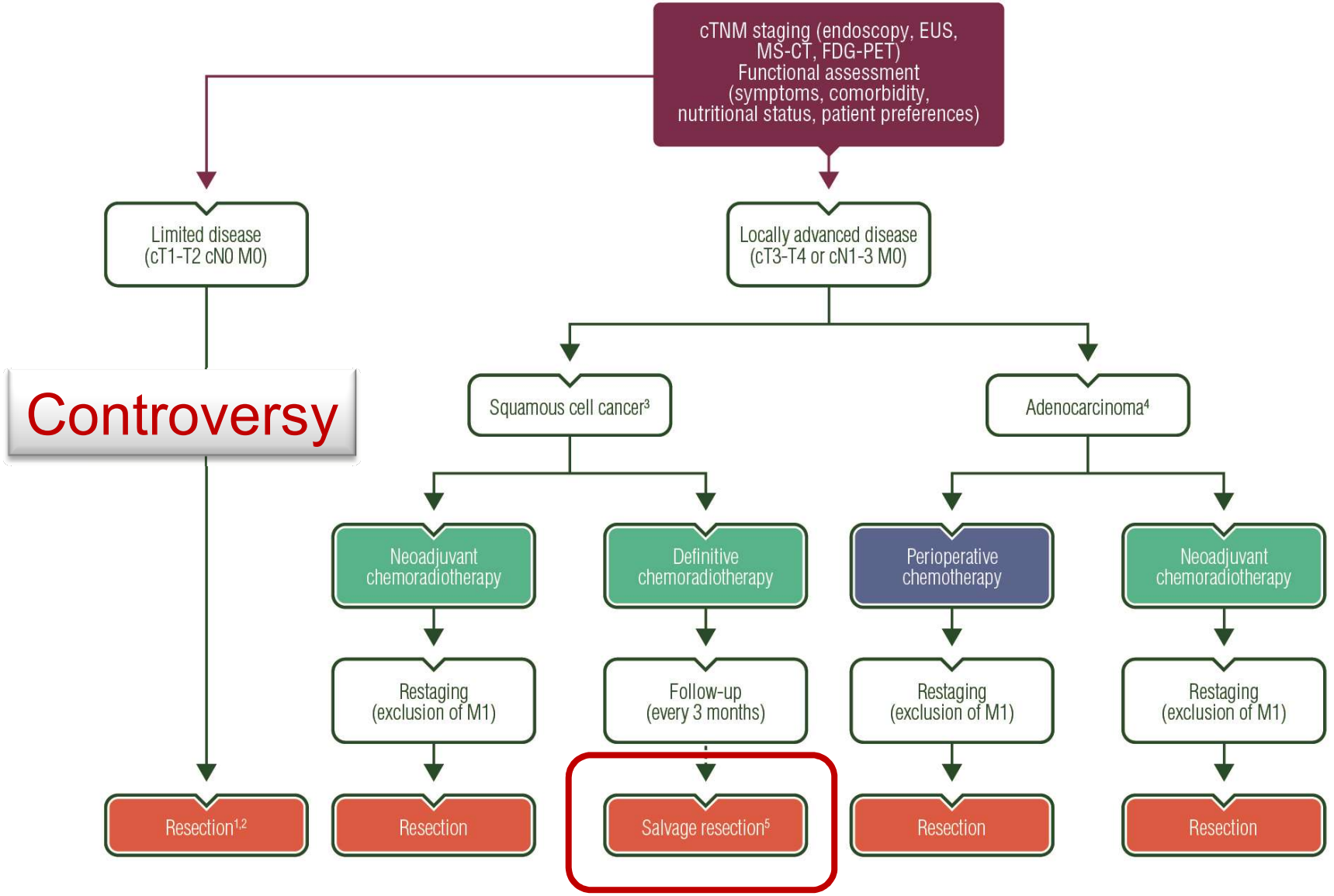


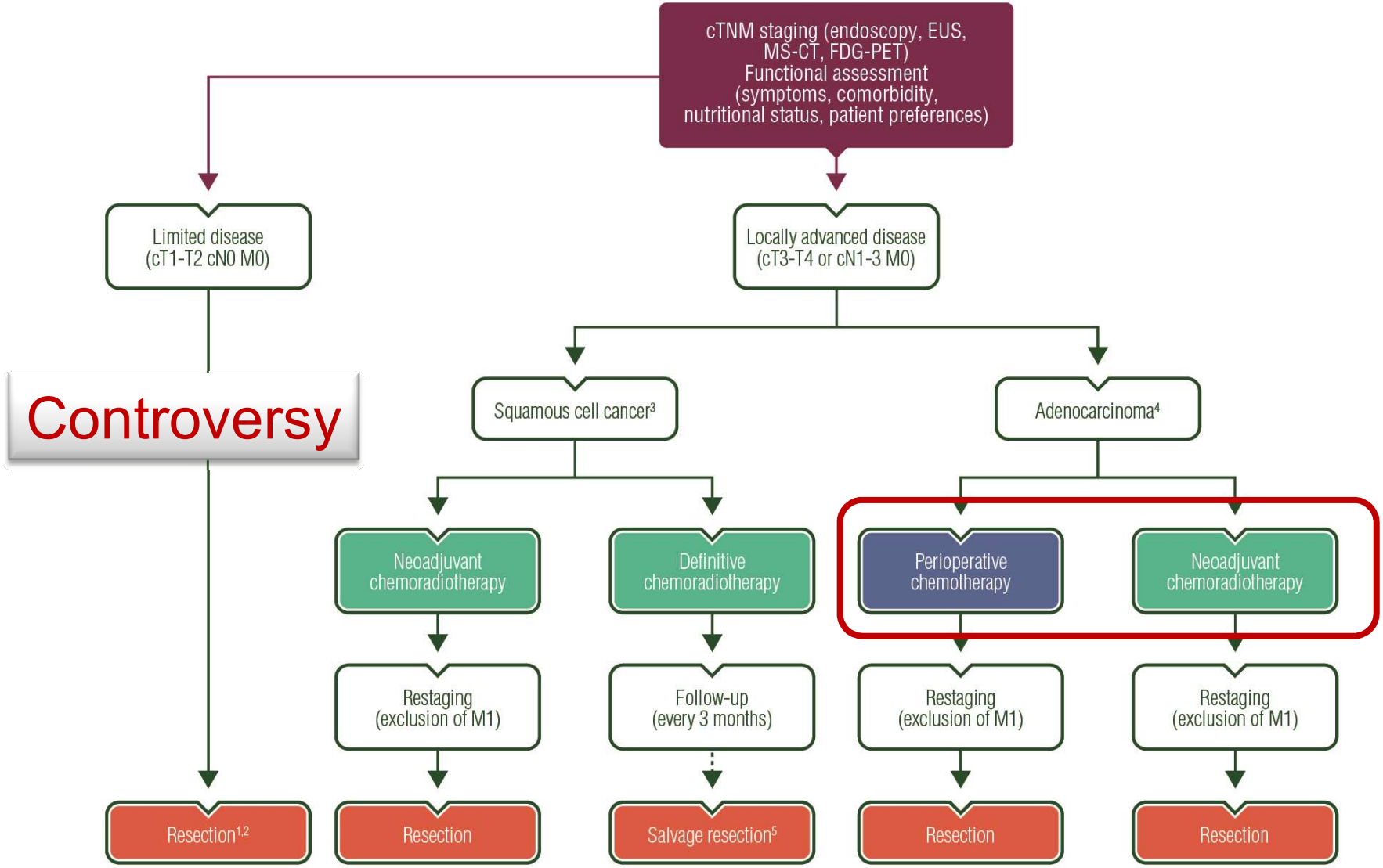
Lordick et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

ESMO Guidelines Oesophageal Cancer 2016



Lordick et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

ESMO Guidelines Oesophageal Cancer 2016



Lordick et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

Oesophageal Cancer – CROSS Study

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N=363

T1N1M0
or
T2–3N0–1M0

AC*
SCC**

RANDOM

Neoadjuvant R-CTX. 41,4 Gy:
Carbo AUC2 + Paclitaxel 50mg/m² weekly
RESECTION

Primary endpoint: overall survival

RESECTION

*AC: Adenocarcinoma
**SCC: Squamous cell cancer

Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084
Shapiro J et al., *Lancet Oncol* 2015; 16: 1090–98

Oesophageal Cancer – CROSS Study

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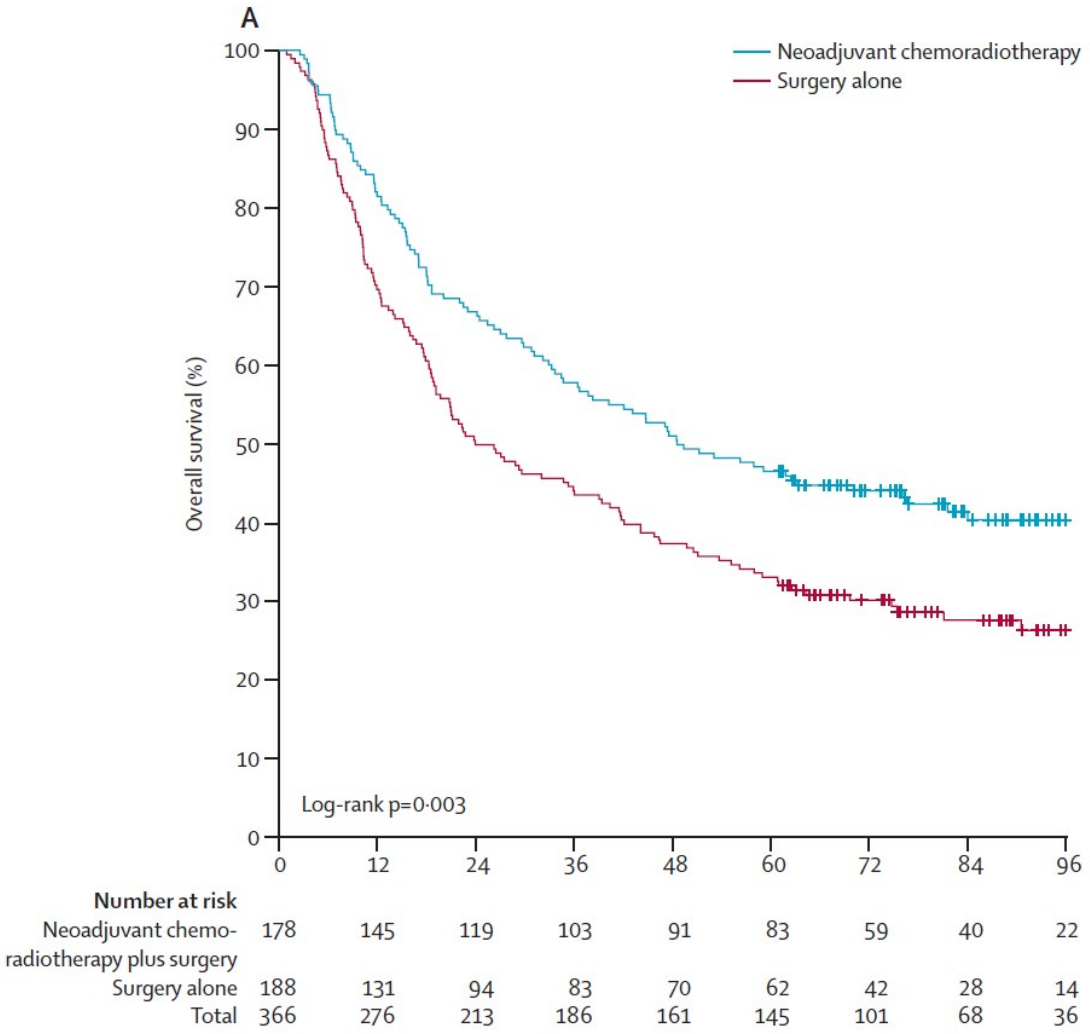
	RCTX + Surgery	Surgery alone	
Hospital mortality	4%	4%	
R0 Resection	92%	69%	
pCR rate	29%		
Median survival	49.4 months	24 months	HR 0.657 p = 0.003
5-year-survival	47%	34%	

Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084

Oesophageal Cancer – CROSS Study



Median follow-up for surviving patients: 84·1 months
(HR 0·68 [95% CI 0·53–0·88]; log-rank p=0·003)

Shapiro J et al., *Lancet Oncol* 2015; 16: 1090–98

Oesophageal Cancer – CROSS Study (I+II)

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VOLUME 32 · NUMBER 5 · FEBRUARY 10 2014
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials

Vera Oppedijk, Ate van der Gaast, Jan J.B. van Lanschot, Pieter van Hagen, Rob van Os, Caroline M. van Rij, Maurice J. van der Sangen, Jannet C. Beukema, Heidi Rütten, Patty H. Spruit, Janny G. Reinders, Dick J. Richel, Mark I. van Berge Henegouwen, and Maarten C.C.M. Hulshof

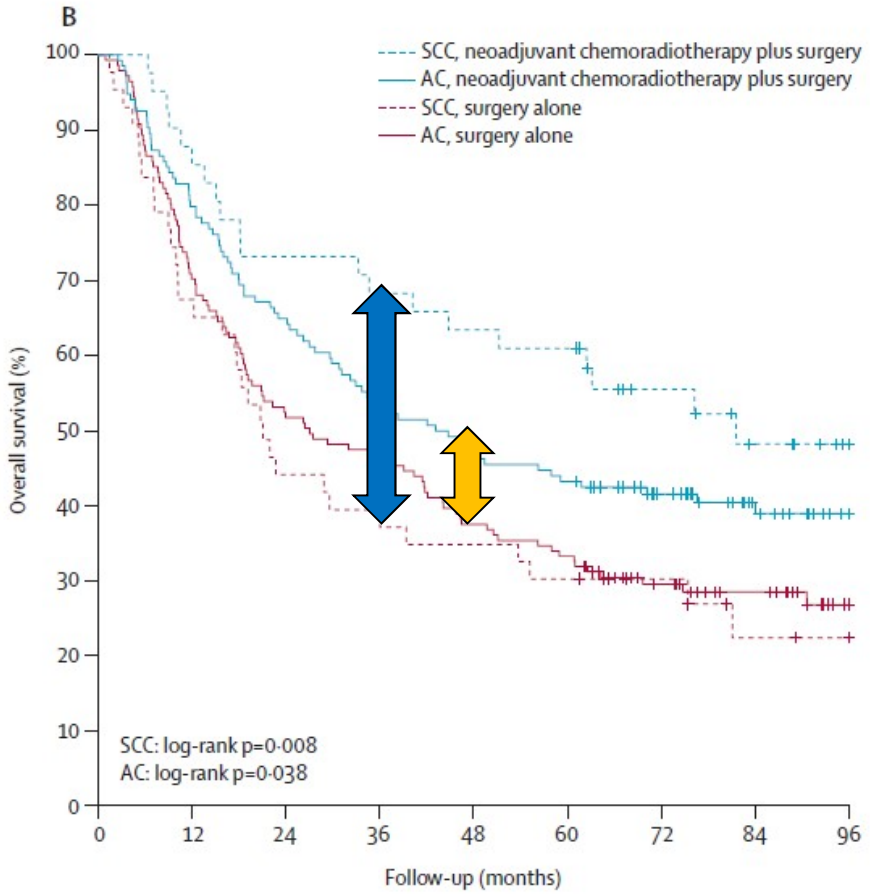
CROSS I and II study
(n=418)

Relapse	After Resection (n=161) n	%	After RCTx+ Resection (n=213) n	%	HR	P-value
Mediastinum	33	**20.5%**	15	**7.0%**	0.29	<0.001
Hematogenous	57	**35.4%**	61	**28.5%**	0.67	0.03

Distant disease control is still not optimal with the CROSS regimen

Oppedijk et al. *J Clin Oncol* 2014; 32:385-391

Oesophageal Cancer – CROSS Study



Number at risk									
SCC, neoadjuvant chemo-radiotherapy plus surgery	41	35	30	28	26	25	17	11	6
SCC, surgery alone	43	29	19	17	16	13	9	5	4
AC, neoadjuvant chemo-radiotherapy plus surgery	134	107	87	73	64	58	42	29	16
AC, surgery alone	141	99	73	64	53	47	32	23	10
Total	359	270	209	182	158	143	100	68	36

Adeno-CA

Squamous-CA

SCC: HR 0·48 [95% CI 0·28–0·83]; log-rank p=0·008
AC: HR 0·73 [95% CI 0·55–0·98]; log-rank p=0·038

Shapiro J et al., *Lancet Oncol* 2015; 16: 1090–98

Oesophageal Adenocarcinoma
CROSS Study Comparison

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MAGIC[1] - 2006 Periop. chemo (n=503)	FNCLCC[2] - 2011 Periop. chemo (n=224)	OE-2[3] - 2009 Pre-op. chemo (n=802)	CROSS[4] - 2015 Chemorad. (n=275)
ECF SURG	CF SURG	CF SURG	RCTx SURG
HR=0.75 (95% CI 0.60; 0.93)	**HR=0.69** (95% CI 0.50; 0.96)	**HR=0.84** (95% CI, 0.72; 0.98)	**HR=0.73** (95% CI 0.55; 0.98)

CI: Confidence Interval; CF: Cisplatin, 5-FU; ECF: Epirubicine, Cisplatin, 5-FU; RCTx: Chemoradiation, SURG: Surgery

[1]**Cunningham D et al.,** *NEJM* 2006 [2]**Ychou M et al.,** *J Clin Oncol* 2011 [3]**Allum B et al.,** *J Clin Oncol* 2009 [4]**Shapiro J et al.,** *Lancet Oncol* 2015

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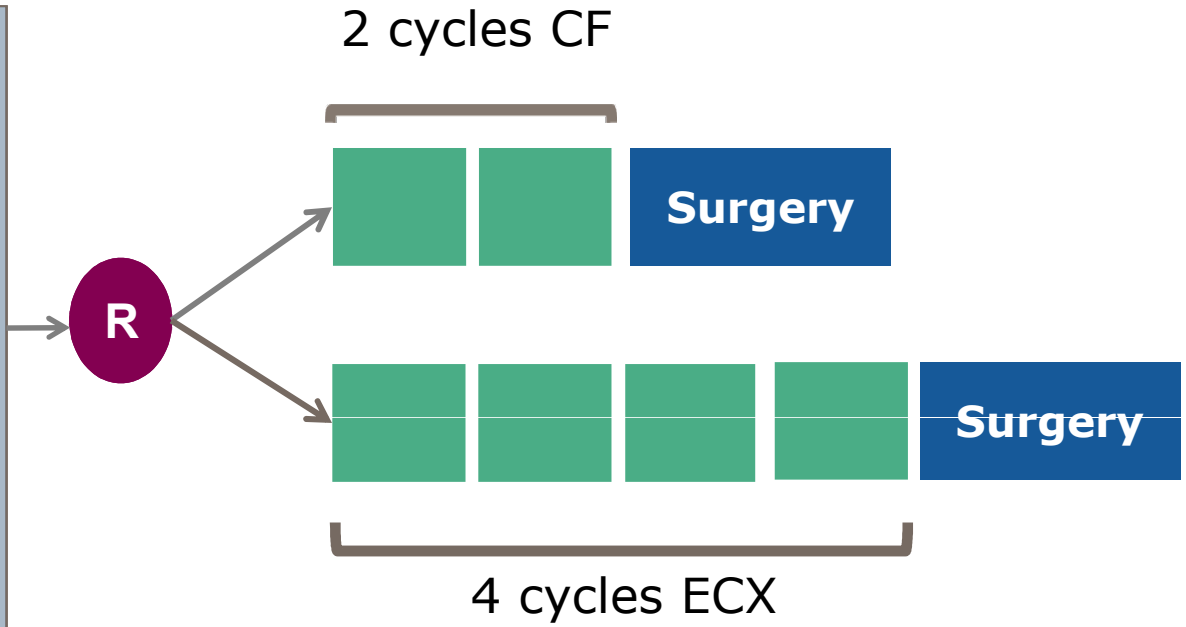
OE-5-Study

Histologically confirmed adenocarcinoma lower oesophagus and GOJ (Type I and II)

MDT - resectable following EUS and CT

(excluded T1/2 N0)



- **CF:** Two 3-weekly cycles of cisplatin (80mg/m^2 D1) and 5FU (1g/m^2 D 1-4)
- **ECX**: Four 3-weekly cycles of epirubicin (50mg/m^2 D1), cisplatin (60mg/m^2 D1) and capecitabine (1250mg/m^2 daily)

Alderson D et al. *ASCO* 2015; #4002

OE-5 Study

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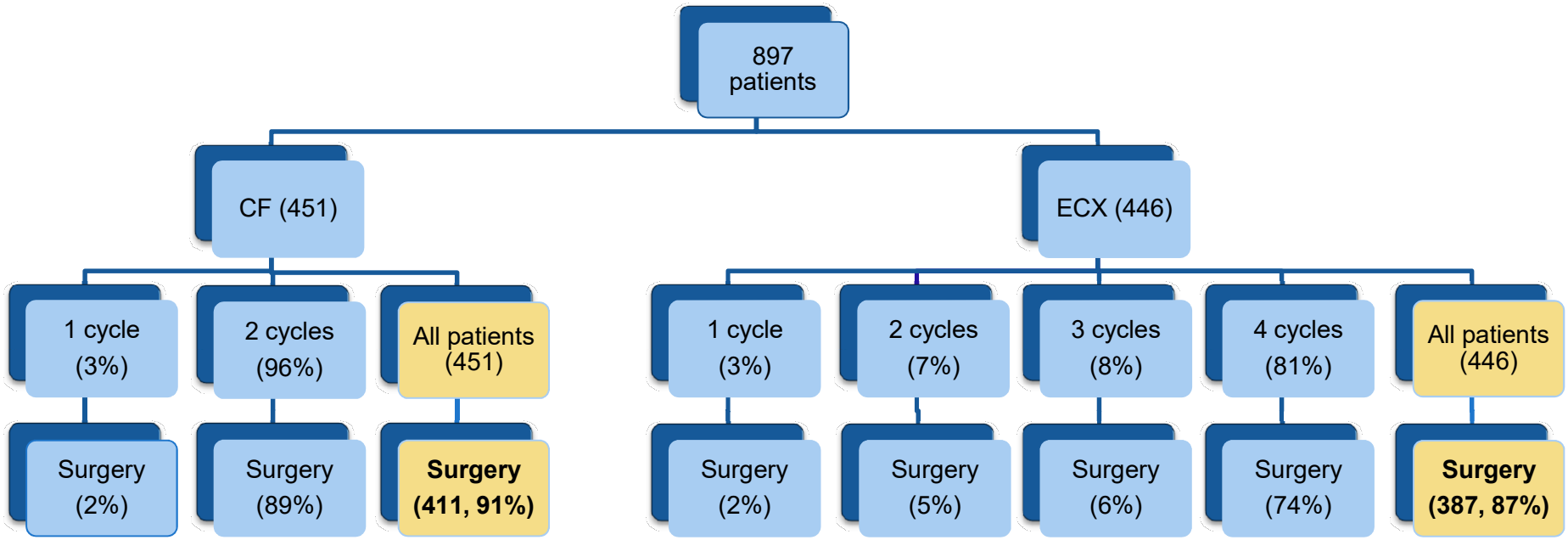
897 patients, Jan 2005 – Oct 2011 72 UK centres		CF (N=451) %	ECX (N=446) %
Age (years)	Median (Range)	62 (27 – 81)	62 (33 – 80)
Sex	Male	91%	89%
WHO PS	0	69%	65%
	1	31%	35%
Stage (TNM6)	T1 N1	1%	1%
	T2 N1	11%	9%
	T3 N0	22%	22%
	T3 N1	64%	65%
	T4 N0	1%	<1%
	T4 N1	3%	2%
Laparoscopy	Yes	48%	48%
PET	Yes	60%	61%

Alderson D et al. *ASCO* 2015; #4002

OE-5 Study



Of the 798 who had surgery, 47 (24 CF, 23 ECX) had an open and close operation.

Alderson D et al. *ASCO* 2015; #4002

OE-5 Study

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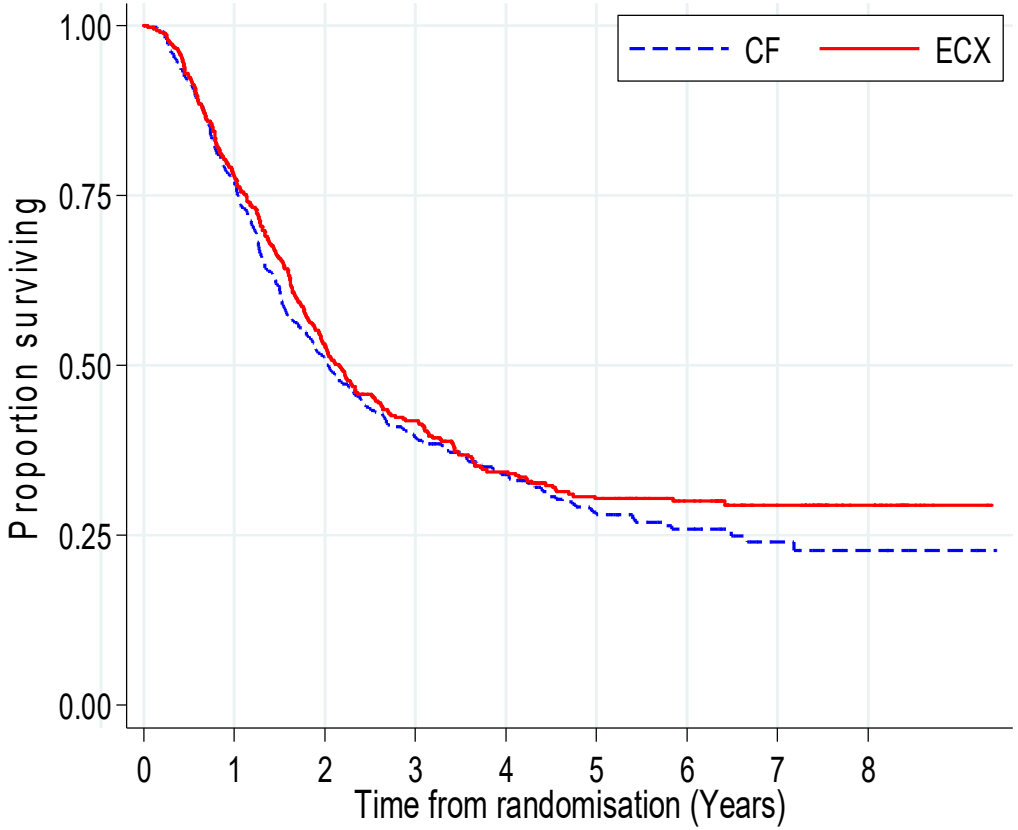
Data		CF		ECX		
		n	%	n	%	P-value
Mandard TRG	**1-3**	**44**	**15%**	**93**	**32%**	**<0.001**
	4-5	244	85%	196	68%	
	Unavailable	99		75		
R0 resection	**Yes**	**212**	**60%**	**223**	**67%**	**0.059**
	No	144	40%	112	33%	
	Unavailable	31		29		

- **Mandard grade 1 rate was 9 (3%) CF vs 32 (11%) ECX.**
- A central pathology review of all patients is currently ongoing.

Alderson D et al. *ASCO* 2015; #4002

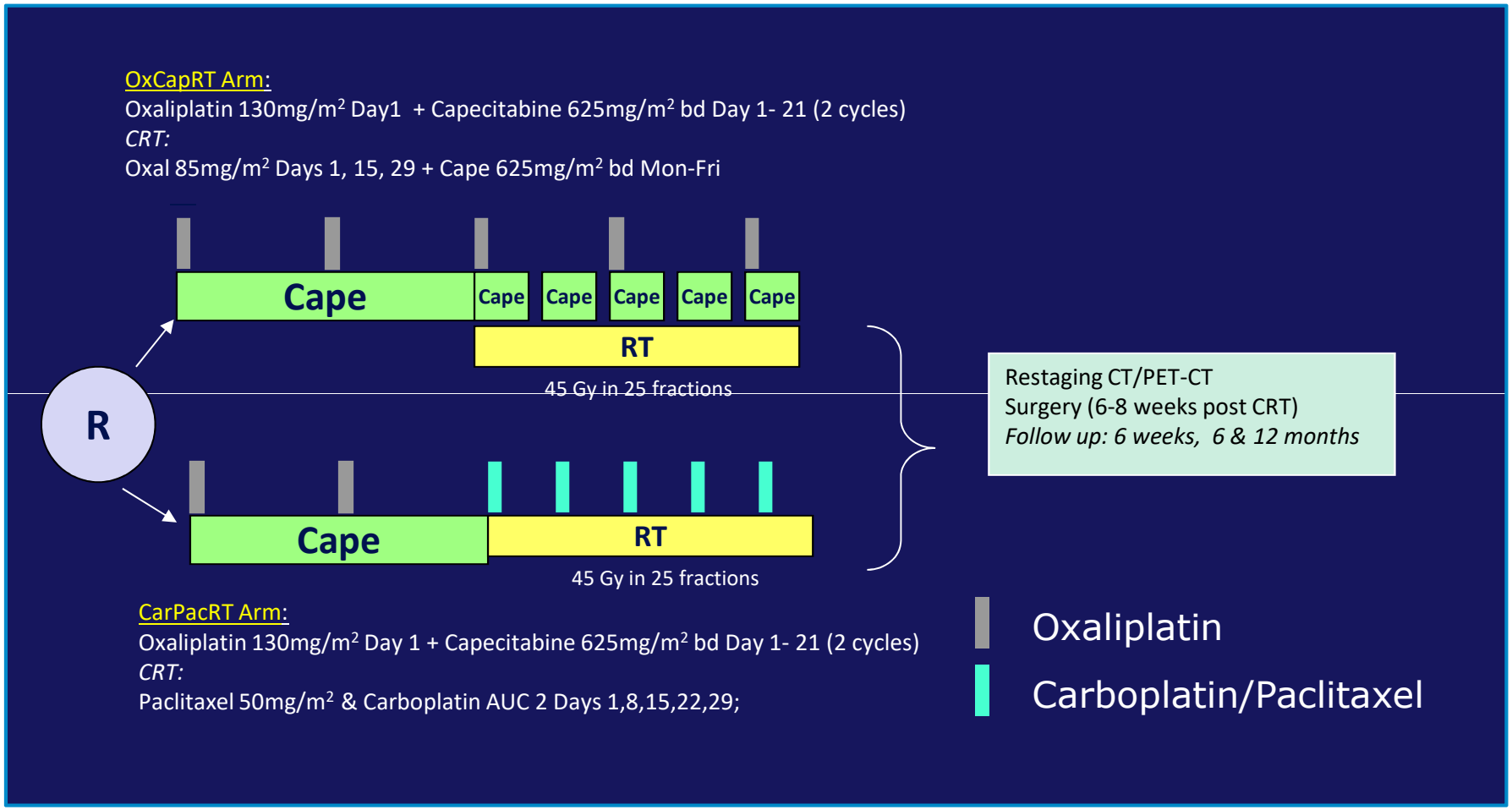
OE-5 Study



Median survival (95% CI)	
CF	2.02 (1.80, 2.38) ys
ECX	2.15 (1.93, 2.53) ys
HR	0.92 (0.79, 1.08)
P-value	0.8582
3-year survival (95% CI)	
CF	39% (35%, 44%)
ECX	42% (37%, 46%)

Alderson D et al. *ASCO* 2015; #4002

Neoscope Study – Trial Design



Mukherjee S et al. *ASCO-GI* 2016

Neoscope Study – Tumor Regression (Primary Endpoint)

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	OxCapRT (n=42)		CarPacRT (n=43)	
	n	%	n	%
1 (pCR)	**5**	**11.9***	**12**	**27.9***
2	13	31.0	16	37.2
3	13	31.0	10	23.3
4	4	9.5	3	7.0
5	0	0.0	0	0.0
Missing TRG data	1	2.4	0	0.0
No surgery	6	14.3	2	4.7

* 13.9% and 29.3% respectively of those undergoing surgery

10 of first 38 patients in the CarPacRT arm attained pCR, thereby meeting pre-specified criteria of success

Mukherjee S et al. *ASCO-GI* 2016

Neoscope Study – Cross Trial Comparison

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		OE05 (n= 897)		CROSS (n=368)	NEOSCOPE (n=85)	
		CF	ECX	CarPacRT	CarPacRT	OxCapRT
Grade 3/4 toxicity (any)		30%	47%	**Haem 7%** **Other 13%**	**52.4%**	42.1%
Surgical complications		Resp:27% Cardiac: 11% Chylothx:3% Anas Leak:11%	Resp: 34% Cardiac: 12% Chylothx:4% Anas Leak:10%	Resp: 46% Cardiac: 21% Chylothx:10% Anas Leak:22%	Resp: 36.6% Cardiac: 9.8% Chylothx:4.9% Anas Leak:7.3%	Resp: 38.9% Cardiac: 25% Chylothx:2.8% Anas Leak:0%
Post op Mortality		30 day:2% 90 day:4%	30 day:2% 90 day:5%	**30 day:4% (4% in S)** >30 day:2% (3% in S)	**30 day: 2.4%** 90 day:	30 day: 2.8% 90 day:
TRG	1	3%	11%	**29% (ACA23%; SC:49%)**	**27.9%**	11.9%
	2	3%	6%	32%	37.2%	31%
R0		60%	67% (p=0.059)	**92% (69% in S)**	**80.5%**	72.2%

Mukherjee S et al. *ASCO-GI* 2016

Neoscope Study – What Can We Conclude?

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- **CarPacRT** passed the pre-specified efficacy criteria for taking forward to phase III trial.
  OxCapRT failed to meet the same criteria

- **CarPacRT** can be taken forward to phase III.

Oesophageal CA – neo Chemoradiation or Chemo?

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Annals of Oncology 27: 660–667, 2016
doi:10.1093/annonc/mdw010
Published online 17 January 2016

A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction

F. Klevebro[1]*, G. Alexandersson von Döbeln[2], N. Wang[3], G. Johnsen[4], A.-B. Jacobsen[5], S. Friesland[2], I. Hatlevoll[6], N. I. Glenjen[7], P. Lind[8], J. A. Tsai[1], L. Lundell[1] & M. Nilsson[1]

[1]Division of Surgery, Department of Clinical Science Intervention and Technology, Karolinska Institutet and Centre for Digestive Diseases, Karolinska University Hospital, Stockholm; Departments of [2]Oncology; [3]Pathology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; [4]Department of Gastrointestinal Surgery, St Olavs Hospital, Trondheim University Hospital, Trondheim; [5]Department of Oncology, Oslo University Hospital, Oslo; [6]Department of Oncology, St Olavs Hospital, Trondheim University Hospital, Trondheim; [7]Department of Oncology, Haukeland University Hospital, Bergen, Norway; [8]Department of Oncology, Mälarsjukhuset Eskilstuna, Karolinska Institutet, Stockholm, Sweden

Klevebro F et al., *Ann Oncol* 2016; 27: 660-667

Oesophageal CA – neo Chemoradiation or Chemo?

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N=180

T1N1M0
or
T2–3N0–1M0

AC*
SCC**

RANDOM

Neoadjuvant R-CTX 40,0 Gy (20 x 2Gy)
Cisplatin 100mg/m²d1 + 5FU 750mg/m² d1-5 x3
RESECTION

Primary endpoint:
Histologic complete response (pCR)

Neoadjuvant CTX
Cisplatin 100mg/m²d1 + 5FU 750mg/m² d1-5 x3
RESECTION

*AC: Adenocarcinoma (73%)
**SCC: Squamous cell cancer (27%)

Klevebro F et al., *Ann Oncol* 2016; 27: 660-667

Oesophageal CA – neo Chemoradiation or Chemo?

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	Neo Radiochemo	Neo Chemo	P-Wert
pCR	**28%**	**9%**	**0.002**
N+	35%	65%	0.001
R0	87%	74%	0.04

Klevebro F et al., *Ann Oncol* 2016; 27: 660-667

Oesophageal CA – neo Chemoradiation or Chemo?

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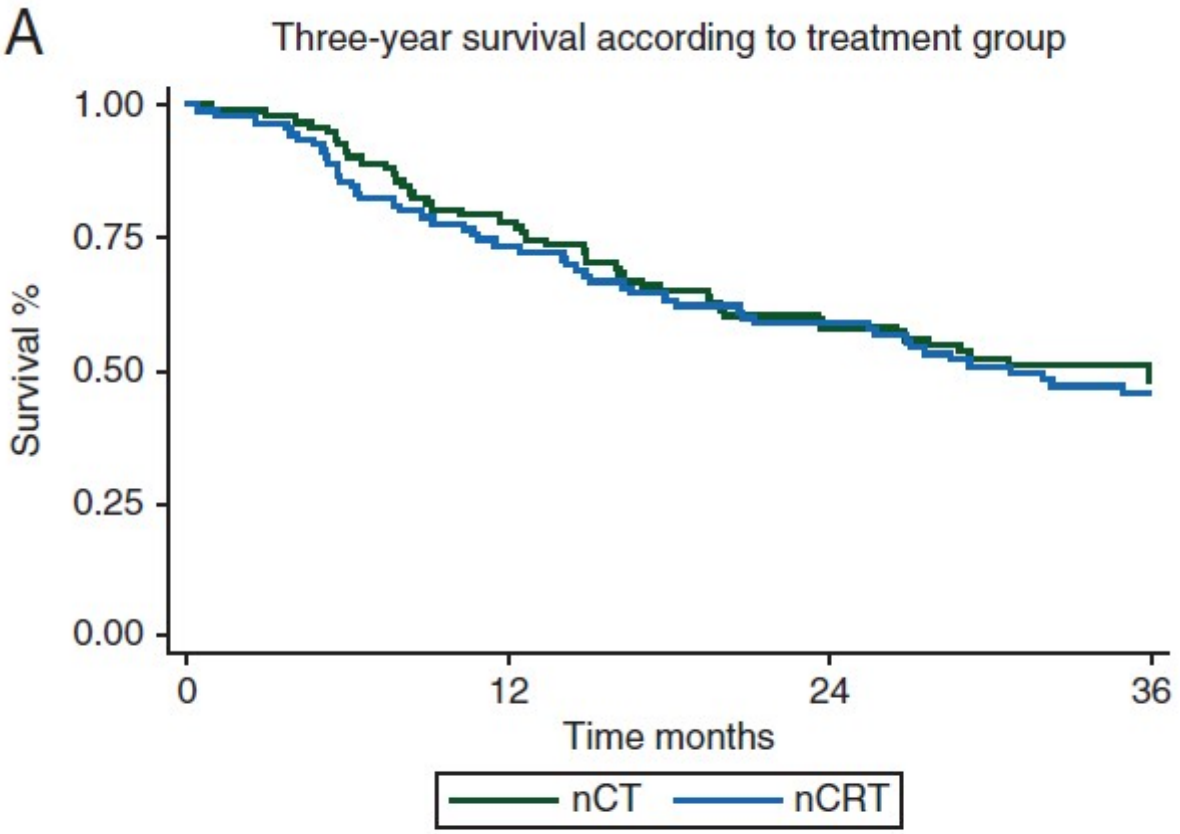

Number at risk

Follow up (months)	0	12	24	36
nCT	91	71	53	45
nCRT	90	66	53	42

Klevebro F et al., *Ann Oncol* 2016; 27: 660-667

Oesophageal CA – neo Chemoradiation or Chemo?

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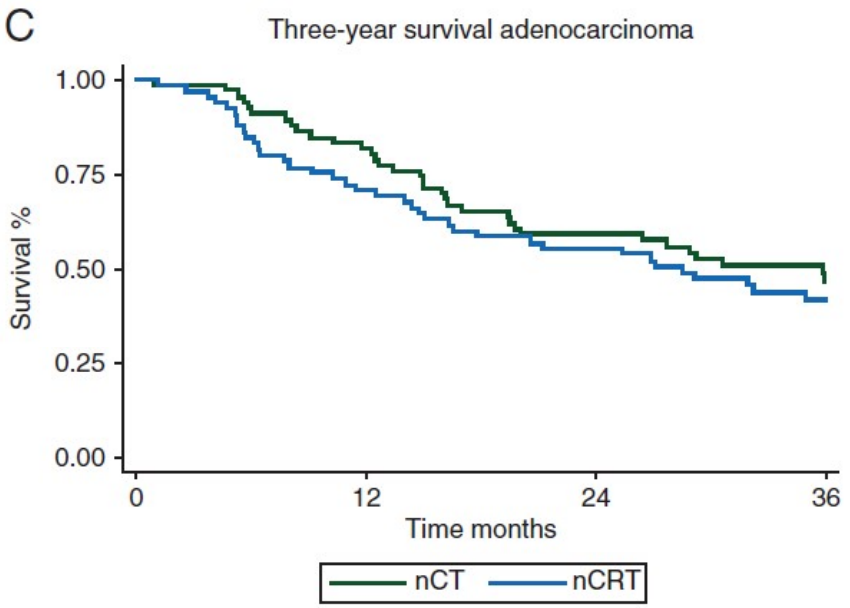
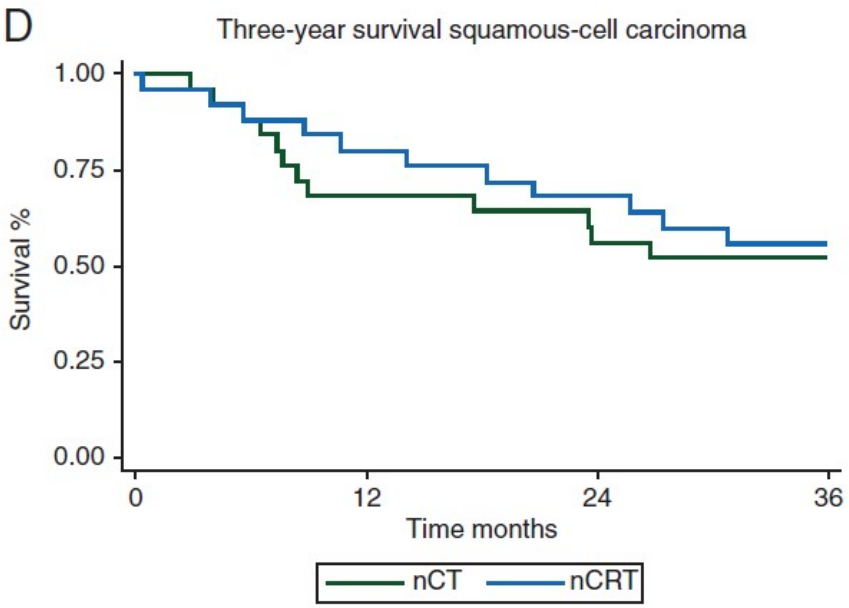
Adeno



Number at risk

Follow up (months)	0	12	24	36
nCT	66	54	39	32
nCRT	65	46	36	28

Squamous



Number at risk

Follow up (months)	0	12	24	36
SCC and nCT	25	17	14	13
SCC and nCRT	25	20	17	14

Klevebro F et al., *Ann Oncol* 2016; 27: 660-667

Current study- ESOPEC (Germany)

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ESOPEC

DFG Deutsche Forschungsgemeinschaft

N=438

T1N1M0
or
T2–4aN0–1M0

R A N D O M

Neoadjuvant **Radio-CTX** – **CROSS Regimen**
RESECTION

Primary endpoint: survival
3-year-OS-rate
55% CROSS vs. 68% FLOT)

Perioperative **CTX**: **FLOT* 4 x pre and post**
RESECTION

*FLOT = 5-Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel

Hoeppner J et al. *BMC Cancer.* 2016 Jul 19;16:503.

Early Detection of Non-Response

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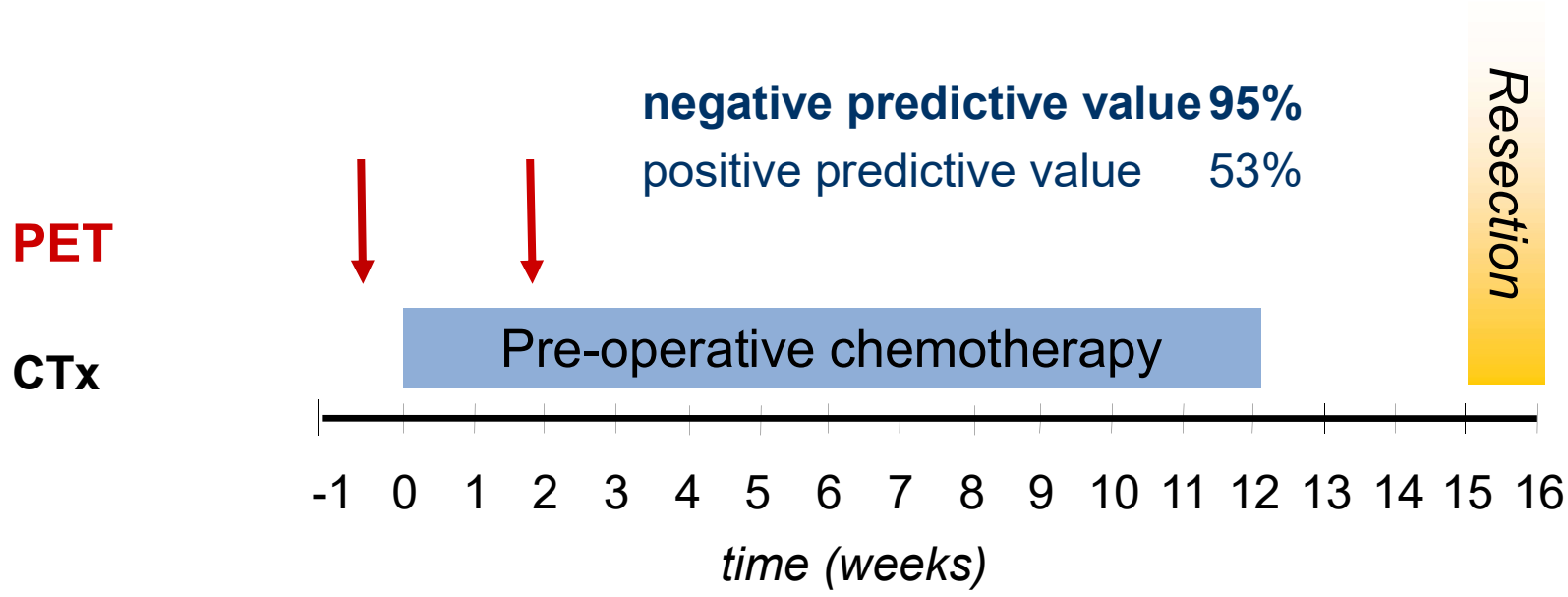
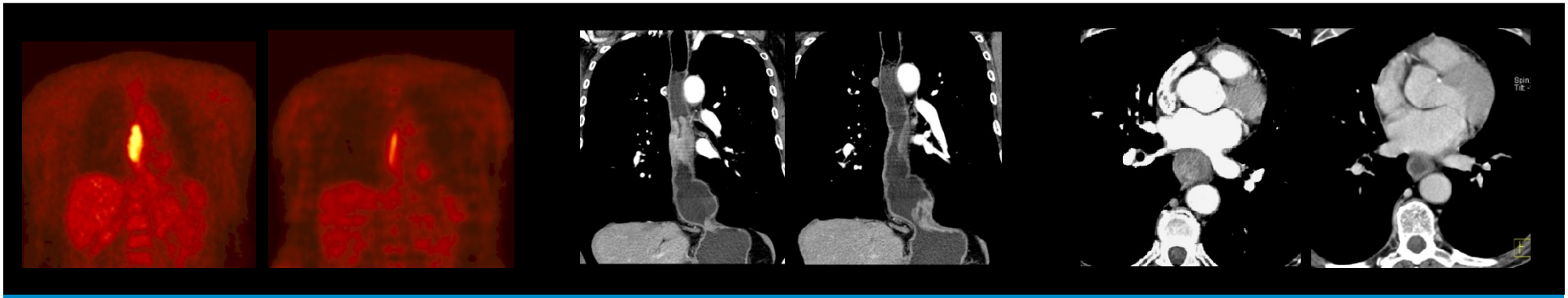
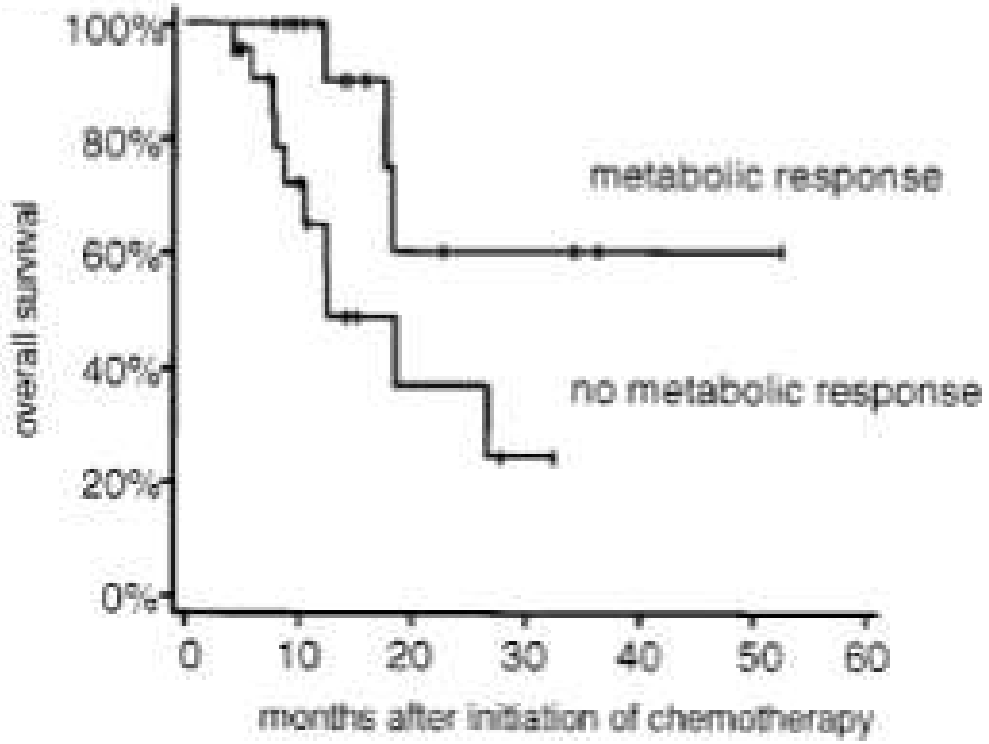


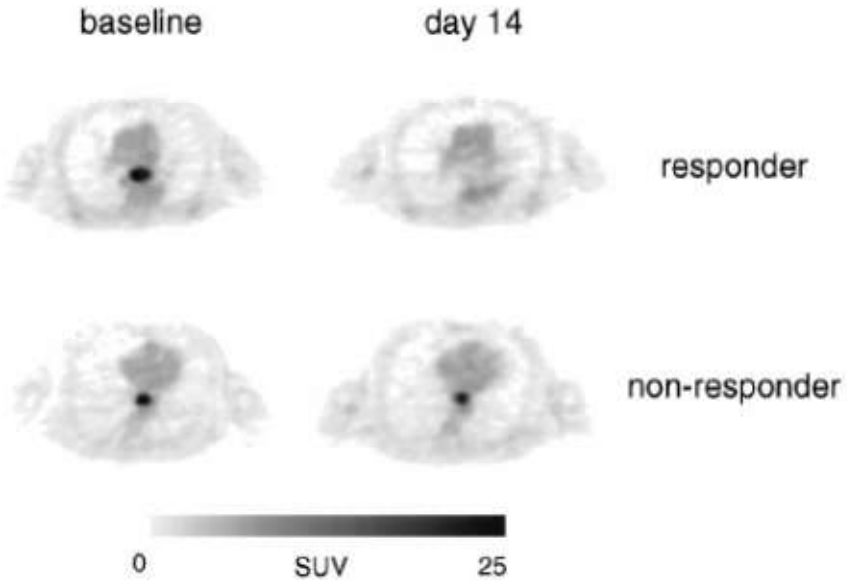
Can PET help to tailor treatment according to response?



Early Detection of Non-Response

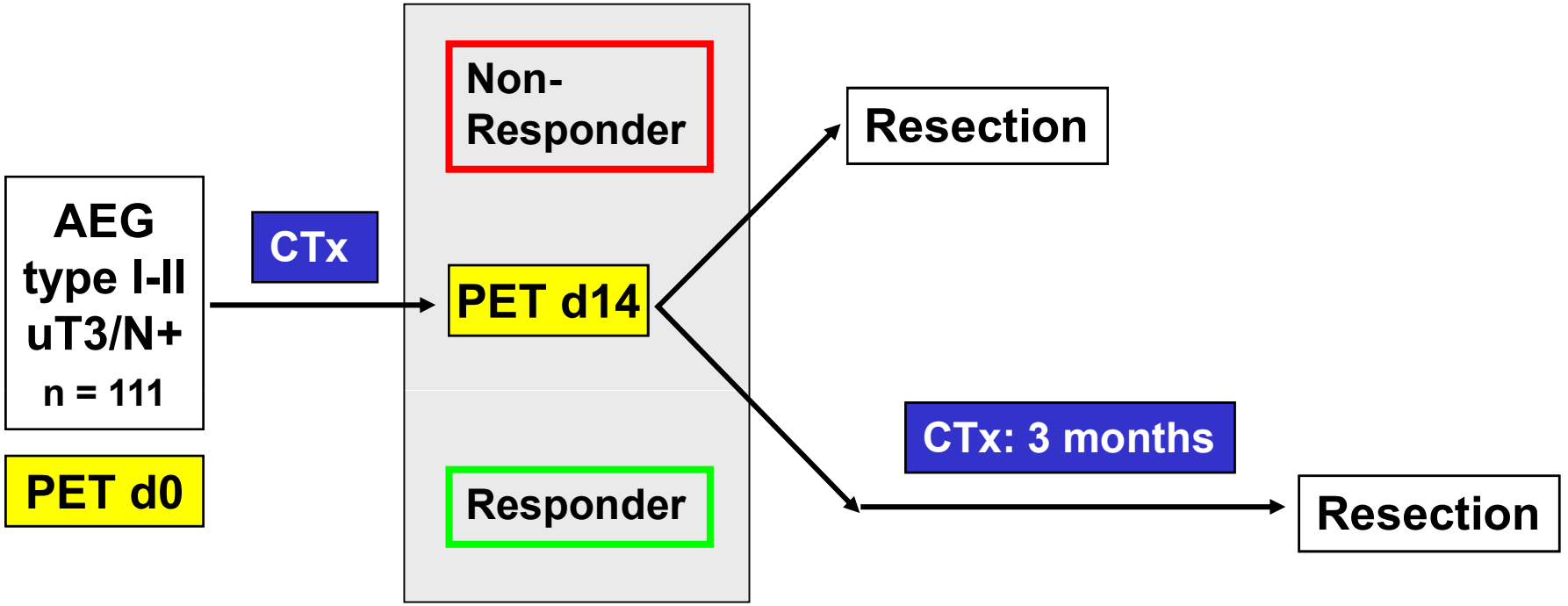
Determination of a „cut-off“: -35% decrease of SUV





Weber et al. *J Clin Oncol*, 2001; 19:3058-3065

Early Response PET – MUNICON I



Response definition: **Decrease of the SUV_{mean} PET_{d14} / $PET_{baseline}$ ≥ 35%**

Weber et al. *J Clin Oncol* 2001;19:3058-65 Ott et al. *J Clin Oncol* 2006;24:4692-8

AEG: adenocarcinoma of the esophago-gastric junction; C: cisplatinum; d: day
CTX: chemotherapy PET: positron emission tomography; SUV: standard uptake value

Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

Early PET Response is Prognostic

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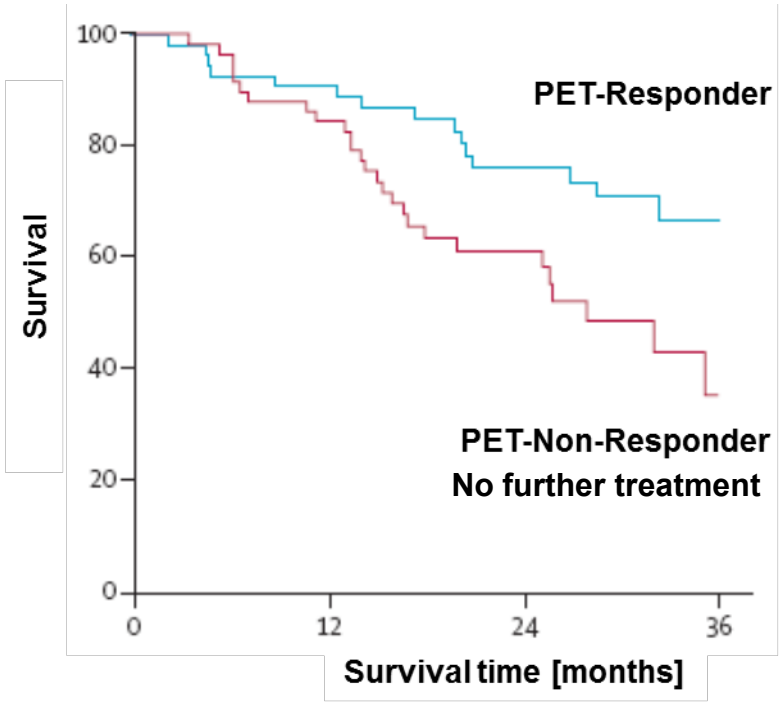
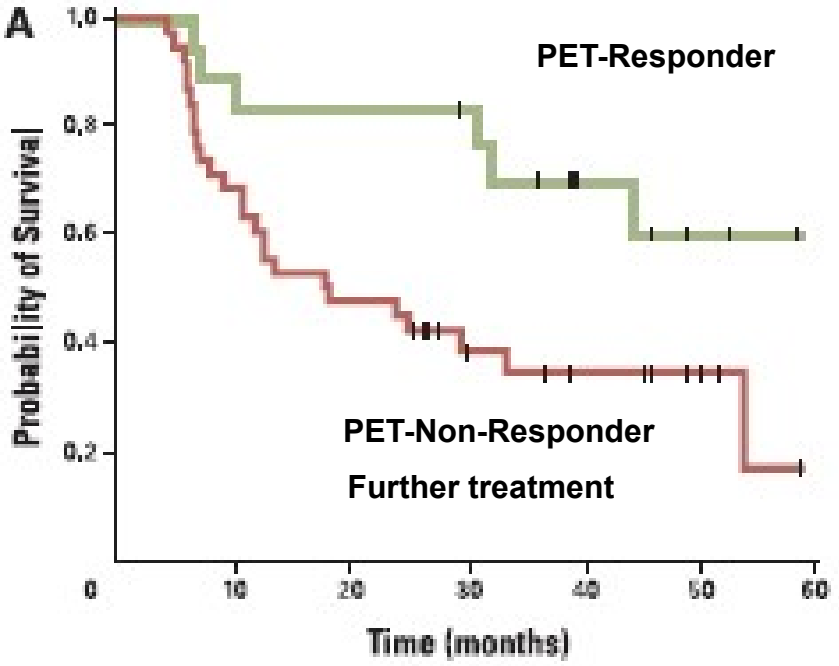
MUNICON 1 Study



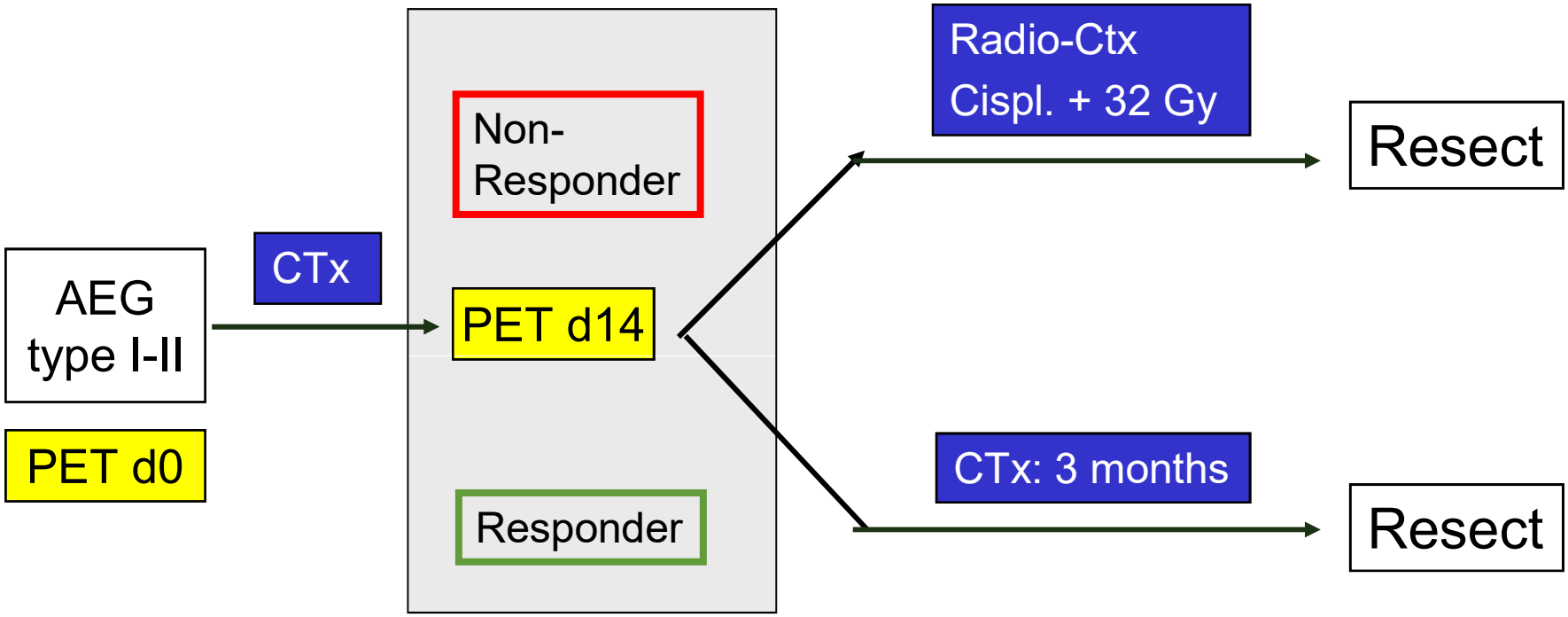
Pre MUNICON Experience



Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

Ott et al. *J Clin Oncol* 2006; 10;24:4692-8

Early Response PET – MUNICON II



Response definition: Decrease of the SUV_{mean} PET_{d14} / $PET_{baseline}$ ≥ 35%

Weber et al. *J Clin Oncol* 2001;19:3058-65 Lordick et al. *Lancet Oncol* 2007;8:797-85

AEG: adenocarcinoma of the esophago-gastric junction; C: cisplatinum; d: day
CTX: chemotherapy PET: positron emission tomography; SUV: standard uptake value

M z Bueschenfelde et al. *J Nuc Med* 2011

Early PET Response is Prognostic

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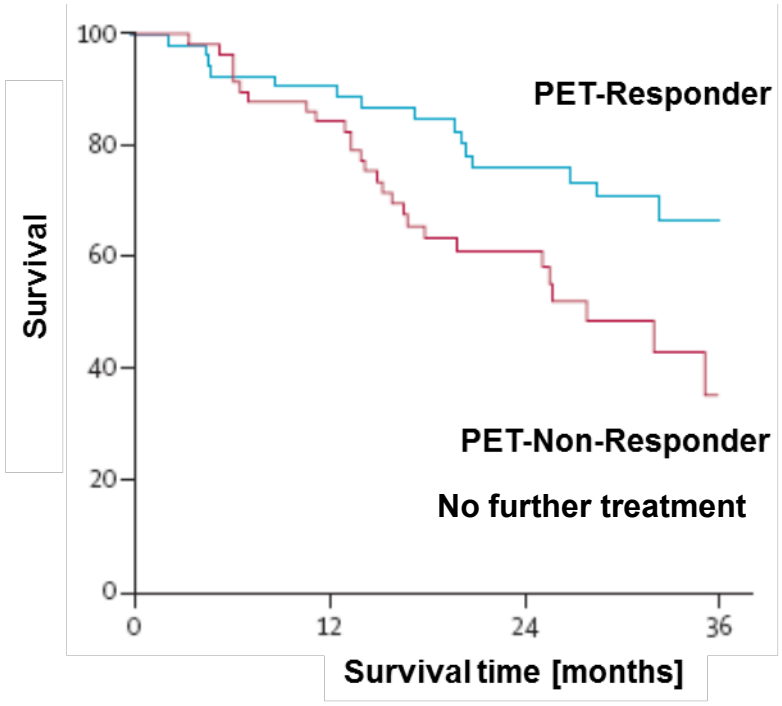
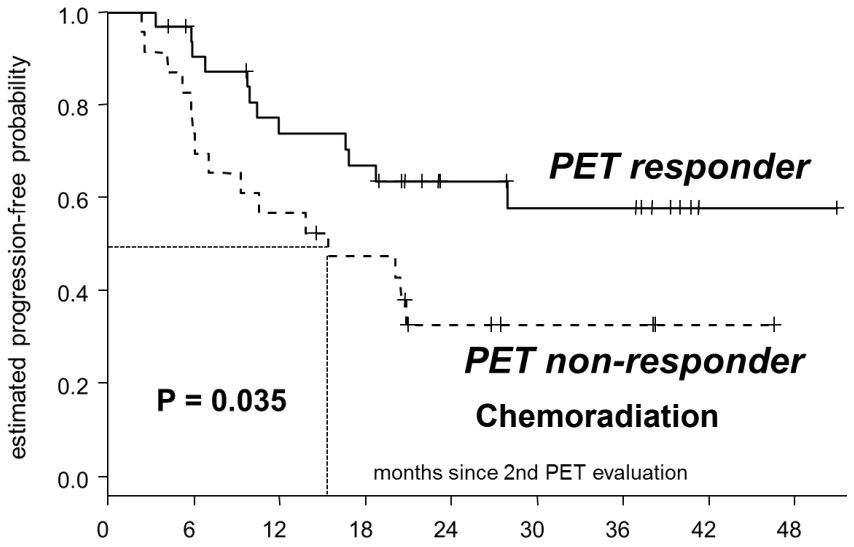
MUNICON 1 Study



Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805

MUNICON 2 Study



M z Bueschenfelde et al. *J Nuc Med* Aug;52(8):1189-96

USA – CALGB 80803

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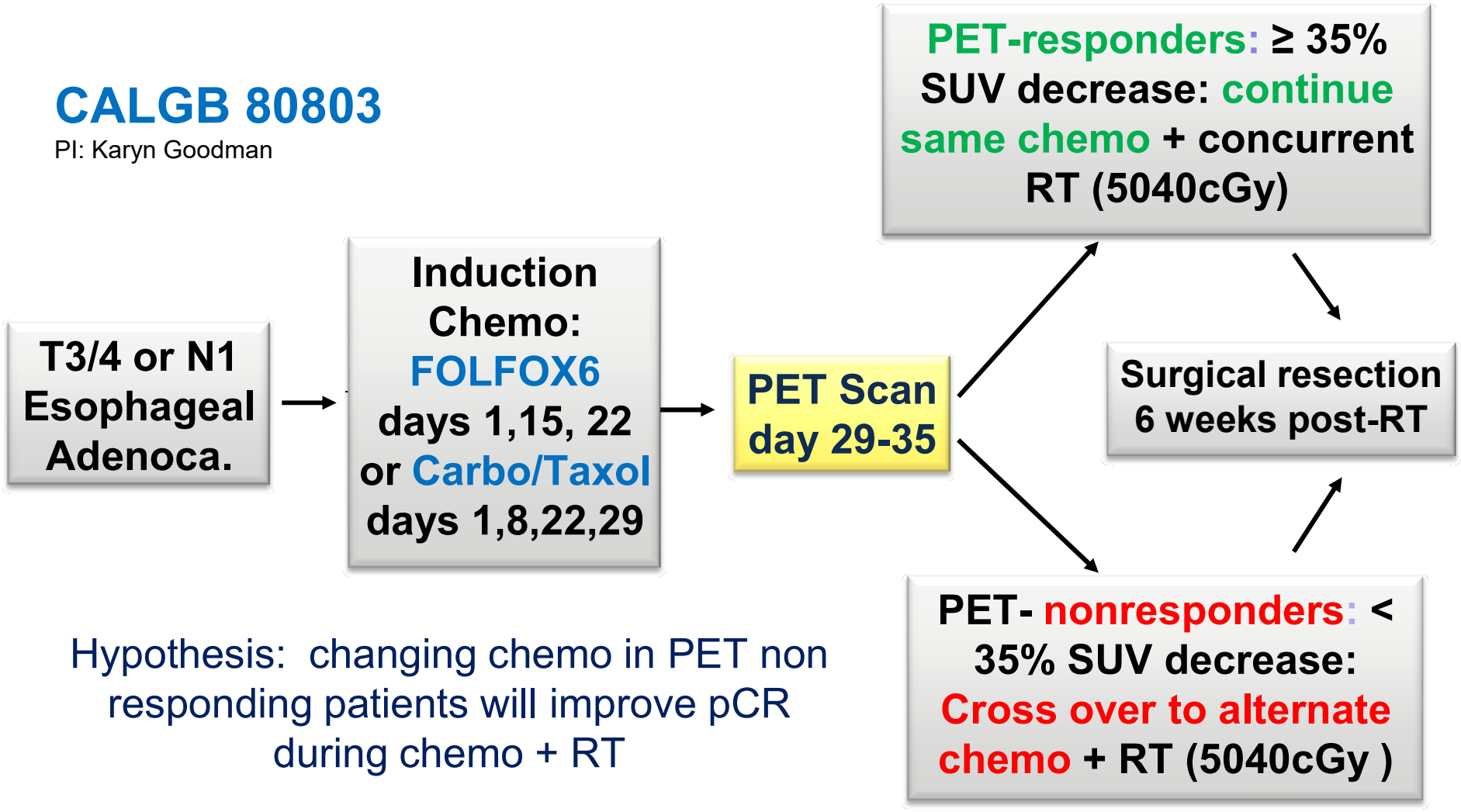
CALGB 80803

PI: Karyn Goodman



Hypothesis: changing chemo in PET non responding patients will improve pCR during chemo + RT

By courtesy of David Ilson, New York

Goodman KA, et al. J Clin Oncol 2017; 35 (suppl 4): abstr 1

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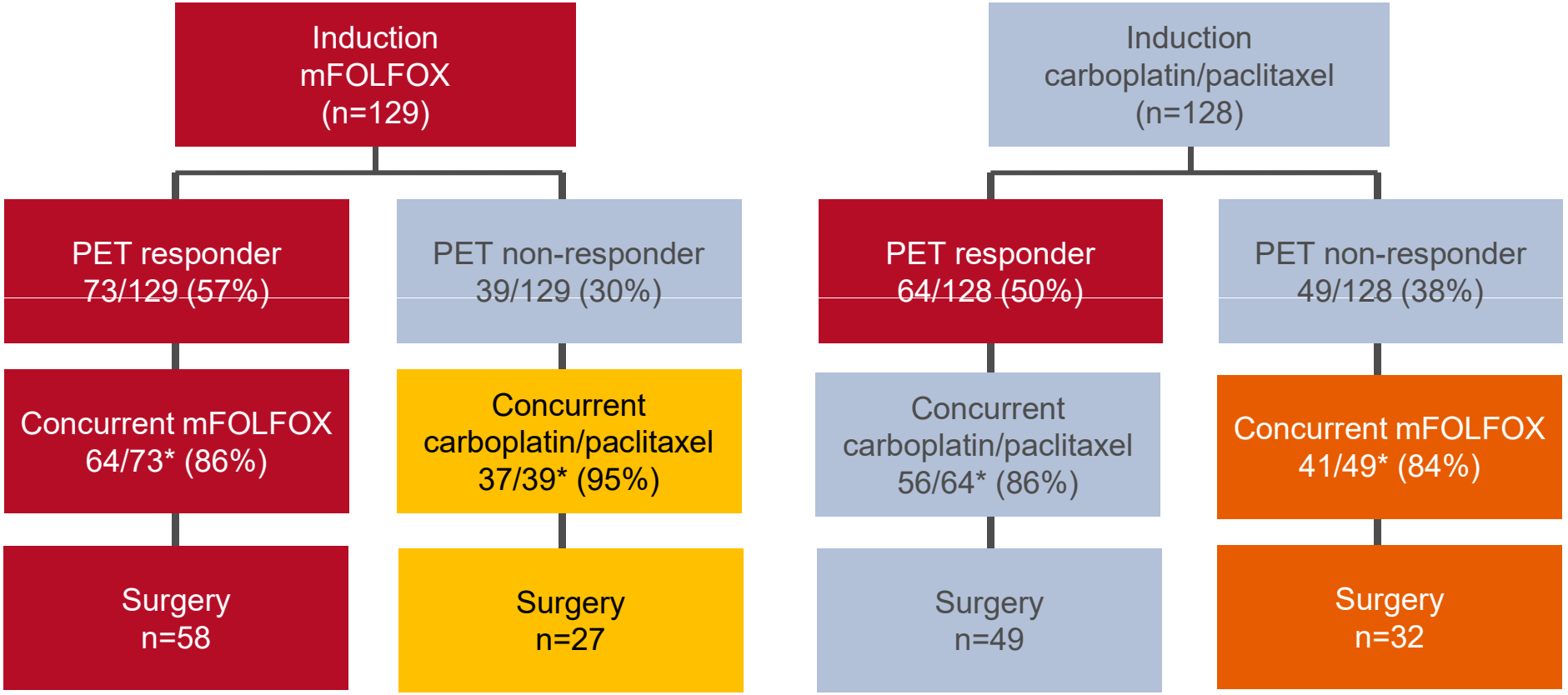
Key results

Treatment course by induction therapy



*Evaluable patients

Goodman KA, et al. J Clin Oncol 2017; 35 (suppl 4): abstr 1

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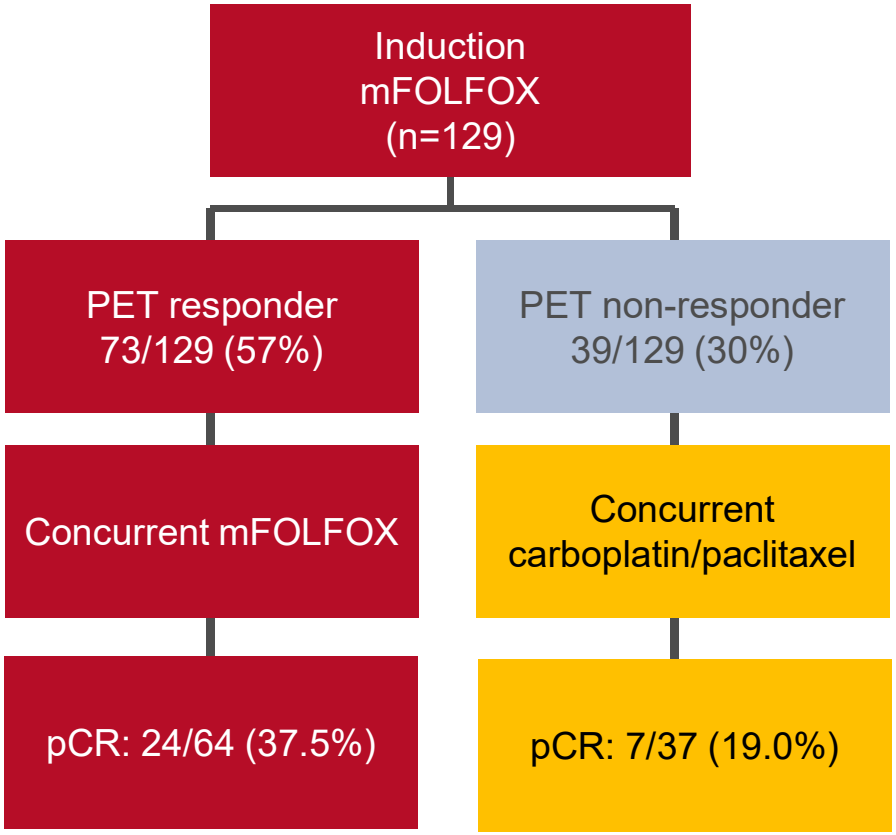
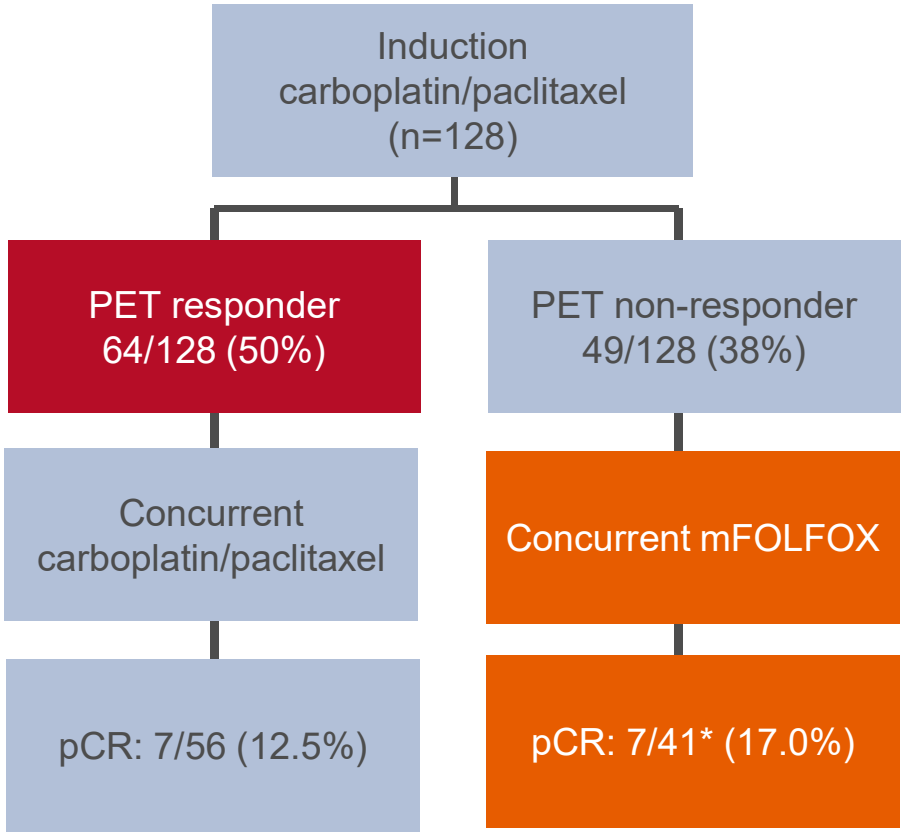
Key results (cont.)

pCR rates





*One ypTON1 excluded

Goodman KA, et al. J Clin Oncol 2017; 35 (suppl 4): abstr 1

The Future – Molecular Signatures

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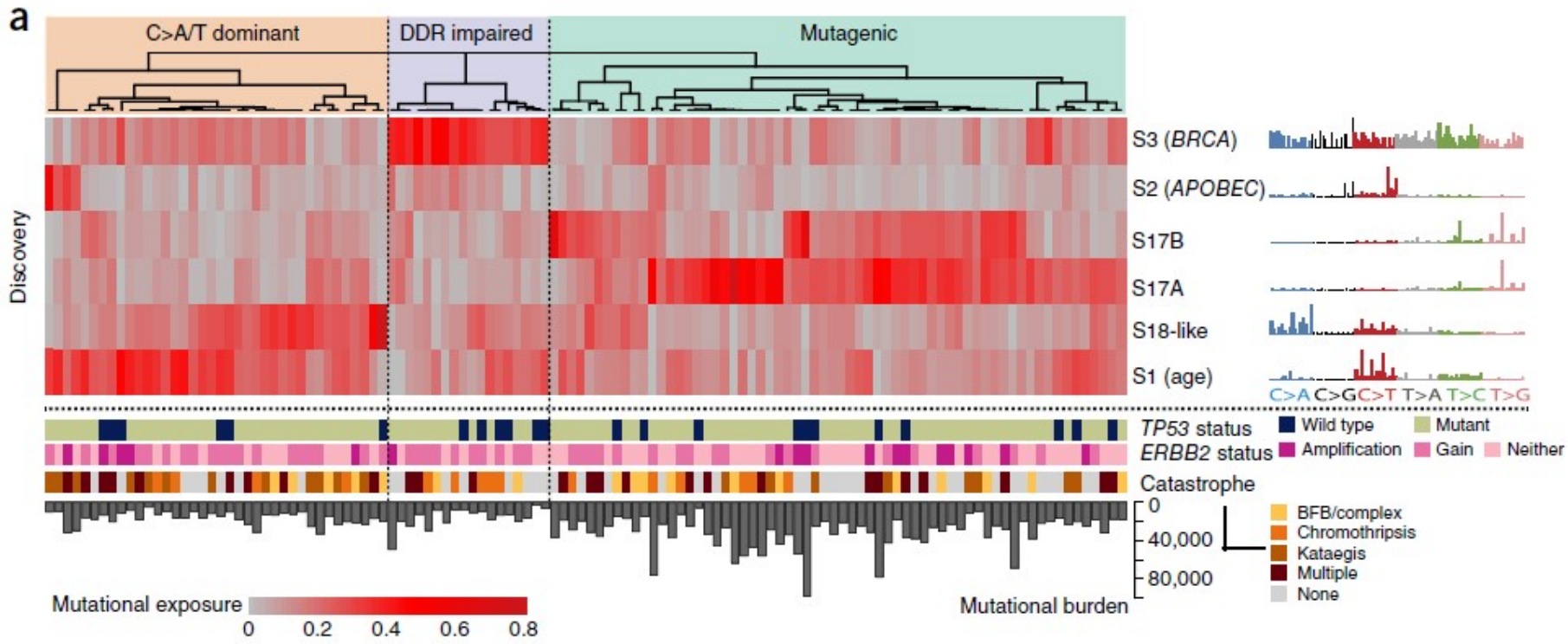
nature genetics

Mutational signatures in esophageal adenocarcinoma define etiologically distinct subgroups with therapeutic relevance

Maria Secrier[1,13], Xiaodun Li[2,13], Nadeera de Silva[2], Matthew D Eldridge[1], Gianmarco Contino[2], Jan Bornschein[2], Shona MacRae[2], Nicola Grehan[2], Maria O'Donovan[2,3], Ahmad Miremadi[2,3], Tsun-Po Yang[2], Lawrence Bower[1], Hamza Chettouh[2], Jason Crawte[2], Núria Galeano-Dalmau[2], Anna Grabowska[4], John Saunders[5], Tim Underwood[6,7], Nicola Waddell[8], Andrew P Barbour[9,10], Barbara Nutzinger[2], Achilleas Achilleos[1], Paul A W Edwards[11], Andy G Lynch[1], Simon Tavaré[1] & Rebecca C Fitzgerald[2] on behalf of the Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) Consortium[12]

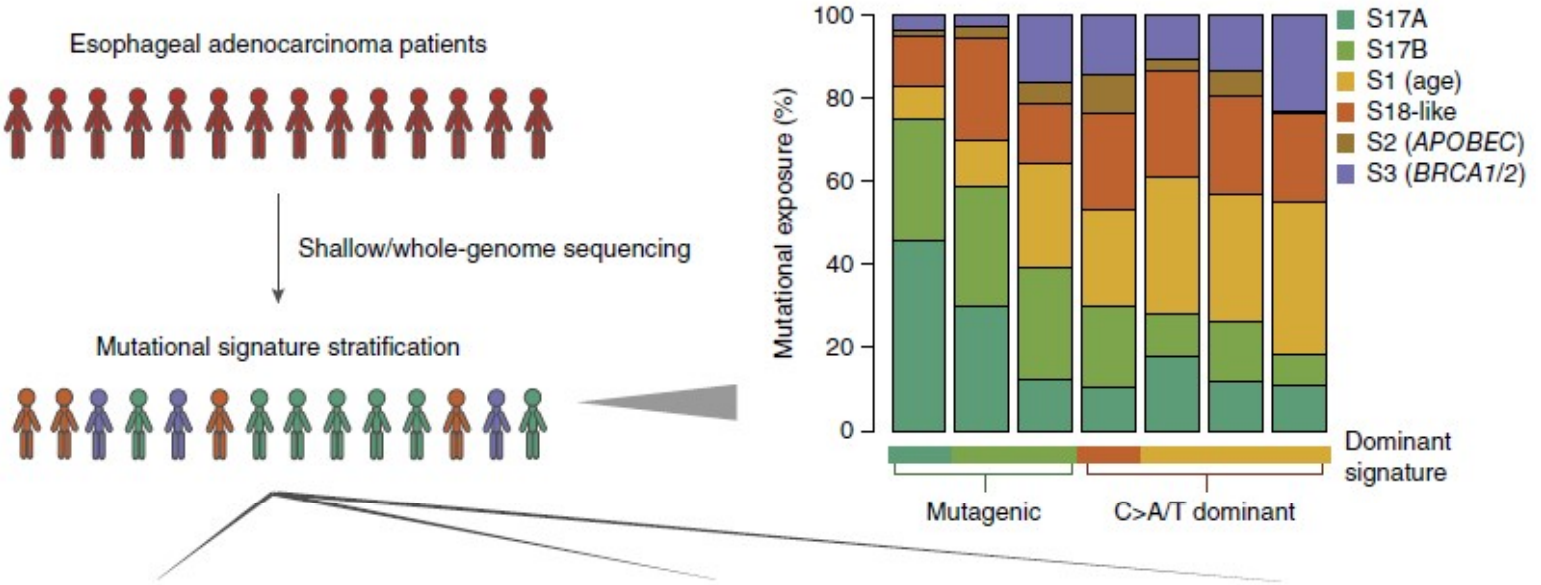
Secrier M et al. *Nature Genetics* 2016; 5 Sep 2016 ([epub ahead of print]

The Future – Molecular Signatures



Secrier M et al. *Nature Genetics* 2016; 5 Sep 2016 ([epub ahead of print]

The Future – Molecular Signatures



	C>A/T dominant (29%)	DDR impaired (18%)	Mutagenic (53%)
Etiology			
Description	• Dominant C>A/T mutational pattern • Aging as a pervasive risk factor • Fewer unstable genomes and large duplication events	• Prevalent defects in homologous recombination and chromosome segregation pathways	• Dominant T>G mutational pattern • Highest mutational burden • Highest neoantigen load
Therapy	• Conventional chemotherapy • Tailored ERBB2/MET inhibition	• DNA-damaging agents combined with PARPi • Proton irradiation • Photon irradiation with PARPi	• CHK/WEE1 inhibition • Immunotherapy: ◦ CTLA4-targeting agents ◦ PD-1\PD-L1-targeting agents

Secrier M et al. *Nature Genetics* 2016; 5 Sep 2016 ([epub ahead of print]

8–11 May 2019, Prague, Czech Republic

Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

13th INTERNATIONAL
GASTRIC CANCER CONGRESS IGCC 2019

INTERNATIONAL GASTRIC CANCER CONGRESS PRAGUE 2019

Photos ©CzechTourism.com

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- Contacts

Welcome

Dear Participants of the International Gastric Cancer Congress 2019,

With great pleasure we announce the **2019 International Gastric Cancer Congress to be held in Prague**. Gastric Cancer continues to be a major health problem in Europe, in the Asian-Pacific Region, in America, Middle East and Africa. From a worldwide perspective, almost 1 Mio patients are diagnosed with gastric cancer / year and 750.000 die from this aggressive cancer.

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Upper GI: technical and clinical challenges
for Radiation Oncologists

Primary tumor extension – pathology evaluation
Role of pathologist for treatment decisions in esophageal carcinoma

Alexander Quaas
Institute of Pathology
University of Cologne

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Road map

- Facts – carcinoma of the oesophagus in Germany
- Tumor extension evaluation – using UICC-TNM 8th edition (2017)
- Patho-anatomical basics, reportings and technical workflow
- How pathologists can help in personalized treatment decisions

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Facts

- Germany 2017: 5.600 men /1.600 women
- 80% will die carcinoma-releated in following 5 years
- 85% are diagnosed in advanced disease (cT2 and more)
- 60% squamous cell carcinoma (ESCC)
- 40% adenocarcinoma (EAC)
- In Cologne: 75% adenocarcinoma

From: krebsdaten.de (Robert-Koch-Institut)

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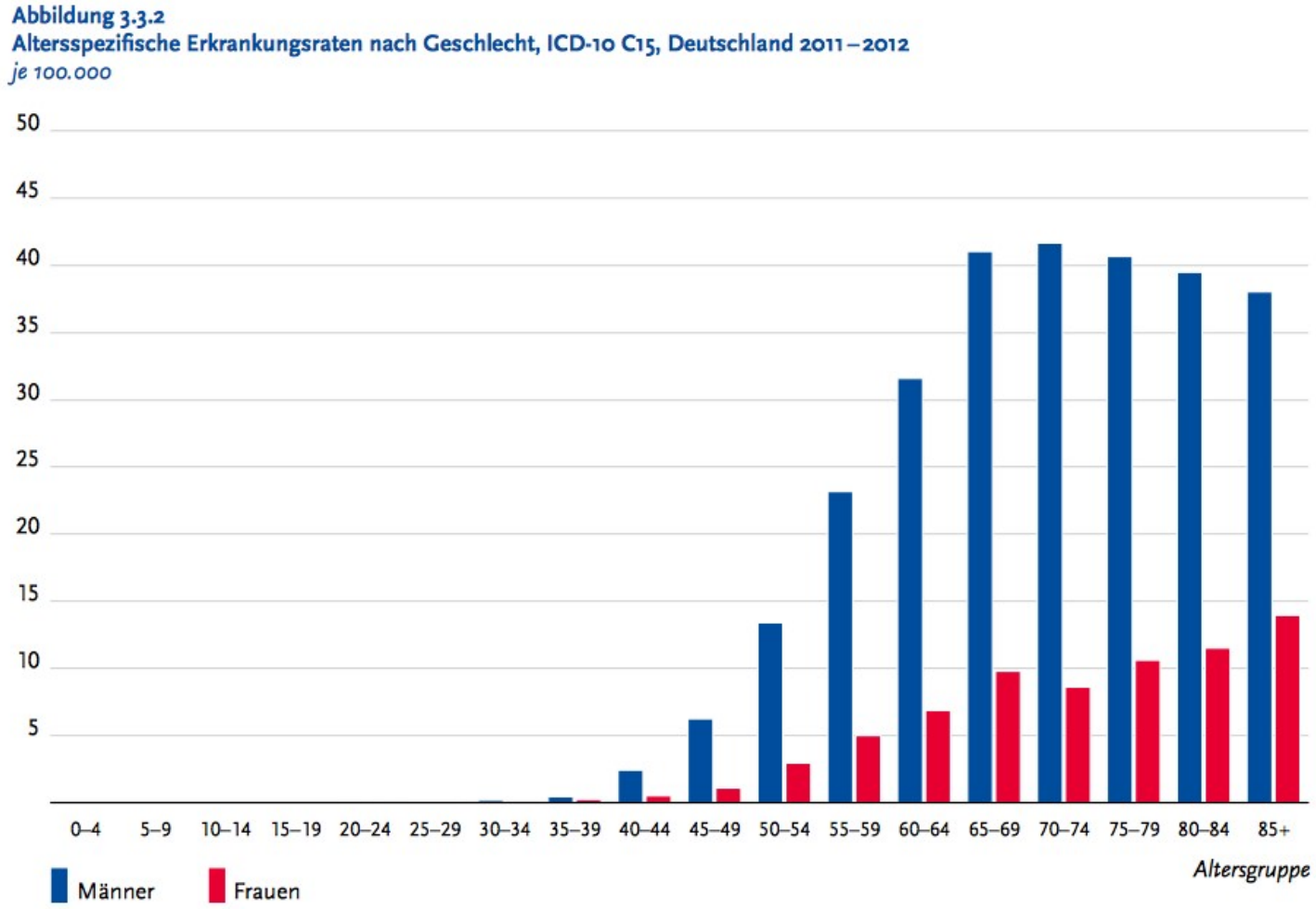
Facts – age distribution



From: krebsdaten.de (Robert-Koch-Institut)

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Usually: ESCC or EAC

WHO classification[a] of tumours of the oesophagus

Epithelial tumours	
Premalignant lesions	
Squamous	
Intraepithelial neoplasia (dysplasia), low grade	8077/0*
Intraepithelial neoplasia (dysplasia), high grade	8077/2
Glandular	
Dysplasia (intraepithelial neoplasia), low grade	8148/0*
Dysplasia (intraepithelial neoplasia), high grade	8148/2
Carcinoma	
Squamous cell carcinoma	8070/3
Adenocarcinoma	8140/3
Adenoid cystic carcinoma	8200/3
Adenosquamous carcinoma	8560/3
Basaloid squamous cell carcinoma	8083/3
Mucoepidermoid carcinoma	8430/3
Spindle cell (squamous) carcinoma	8074/3
Verrucous (squamous) carcinoma	8051/3
Undifferentiated carcinoma	8020/3
Neuroendocrine neoplasms[b]	
Neuroendocrine tumour (NET)	
NET G1 (carcinoid)	8240/3
NET G2	8249/3
Neuroendocrine carcinoma (NEC)	8246/3
Large cell NEC	8013/3
Small cell NEC	8041/3
Mixed adenoneuroendocrine carcinoma	8244/3

Mesenchymal tumours	
Granular cell tumour	9580/0
Haemangioma	9120/0
Leiomyoma	8890/0
Lipoma	8850/0
Gastrointestinal stromal tumour	8936/3
Kaposi sarcoma	9140/3
Leiomyosarcoma	8890/3
Melanoma	8720/3
Rhabdomyosarcoma	8900/3
Synovial sarcoma	9040/3
Lymphomas	
Secondary tumours	

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {904A}. Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for carcinoma *in situ* and grade III intraepithelial neoplasia, and /3 for malignant tumours.
[b] The classification is modified from the previous (third) edition of the WHO histological classification of tumours {691} taking into account changes in our understanding of these lesions. In the case of neuroendocrine neoplasms, the classification has been simplified to be of more practical utility in morphological classification.
* These new codes were approved by the IARC/WHO Committee for ICD-O at its meeting in March 2010.

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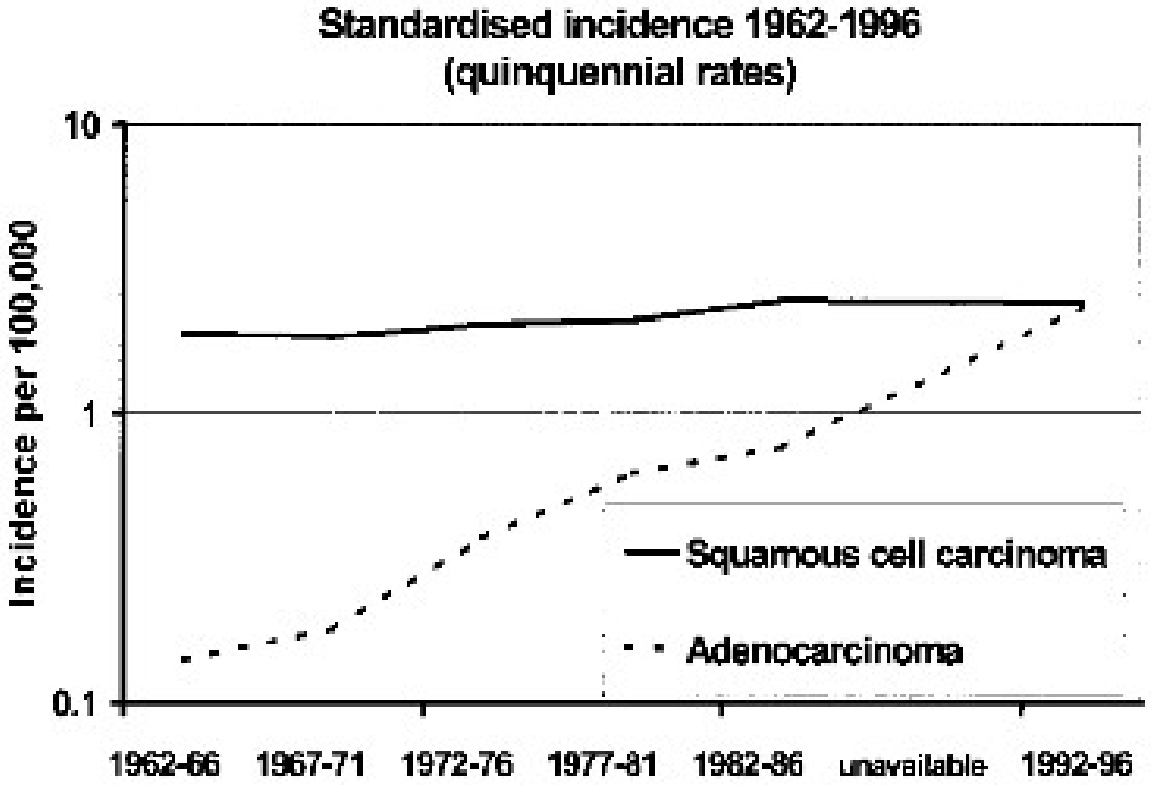
EAC
Incidence continues to increase



From: Powell et al. Int J Cancer 2003

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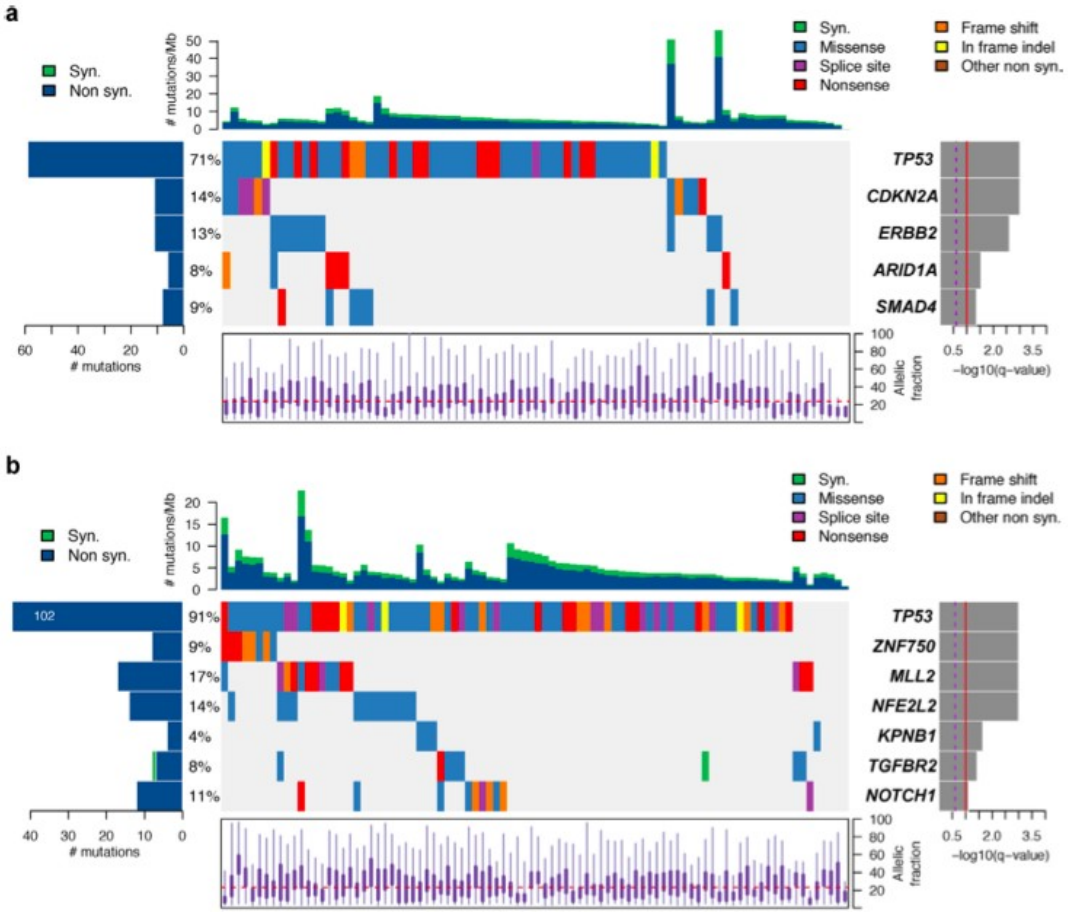
Molecular features
Comparison: EAC vs. ESCC

EAC

ESCC



From: Cancer Genome Atlas Research Network Group:
Integrated molecular characterization of esophageal carcinoma, Nature 2017

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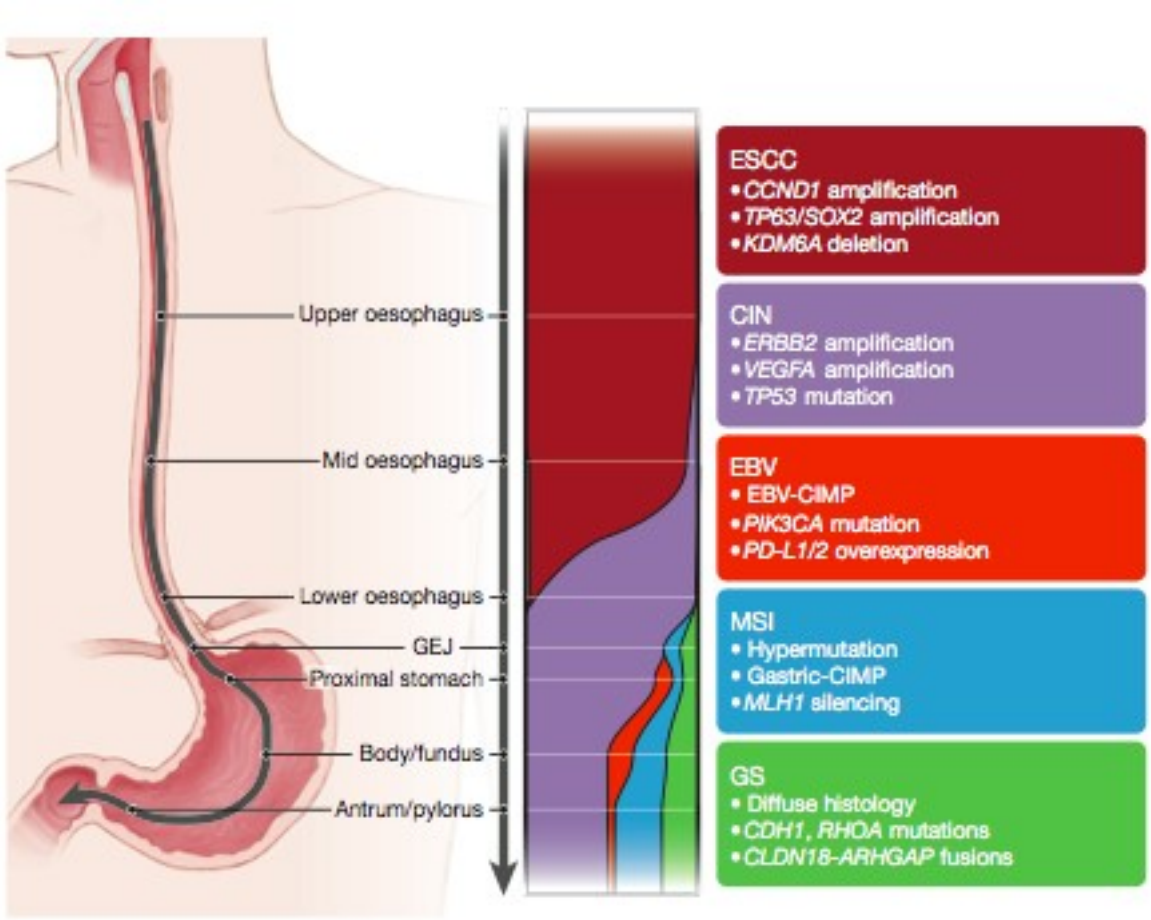
Molecular features: Main distribution/differences



gastric adenocarcinoma:

1) Chromosomal instable (CIS) 49,8%
2) Microsatellite-instable (MSI) 21,7%
3) Genomic stable (GS) 19,6%
4) EBV-induced (EBV) 8,9%

esophageal adenocarcinoma:

1) **EAC = CIS**
   ERBB2 amplification
   (like in gastric carcinoma)

2) **MSI and EBV very rare**

From: Cancer Genome Atlas Research Network Group:

1) Integrated molecular characterization of esophageal carcinoma, Nature 2017

2) Epstein-Barr Virus Infection and Mismatch Repair Deficiency in Esophageal Cancer: Clinical Implication for Potential Treatment with PD1/PD-L1 Blockade Therapy; *L.C. Hewitt, I.Z Inam, A. Quaas…. and H.Grabsch*

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Prognosis and Treatment decisions

- PD-L1 expression is rare
- MSI-subtypes nearly non-existent
- EBV-subtypes non-existent

Checkpoint-inhibition in ESCC and EAC perhaps less effective than in lung cancer

- Her2/neu amplification/overexpression: about 15%

Trastuzumab in Her2-positive adenocarcinoma

- TP53 wildtype carcinoma: favourable prognosis?

Determination of TP53 helpful?

1) PD-L1 in esophageal carcinoma – different expression pattern on mRNA and protein level; *L. Tharun.....and A. Quaas*
2) Epithelial PD-L2 expression marks Barrett's Esophagus and Esophageal Adenocarcinoma; *S. Derks..... and A. Bass*
3) The prognostic value of TP53 mutations in oesophageal adenocarcinoma: a systematic review and meta-analysis; *O. M Fisher.... and R. V Lord* - „patients with OAC and TP53 gene mutations have reduced overall survival compared with patients without these mutations, and this effect is independent of tumour stage".
4) Radiation sensitivity in a preclinical mouse model of medulloblastoma relies on the function of the intrinsic apoptotic pathway; A.J. Crowther.....and T.R Gershon

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Anatomical subsites

1. Cervical oesophagus (C15.0)

begins: lower border of the cricoid cartilage

ends: thoracic inlet (suprasternal notch). 18 cm distal upper incisor teeth

2. Intrathoracic oesophagus (C15.3-5)

- Upper: begins: thoracic inlet (about 18 cm) ends: tracheal bifurcation (about 24 cm)
- Mid: begins: tracheal bifurcation (about 24 cm) ends: 32 cm distal upper incisor teeth
- Lower: About 8 cm long and includes abdominal oesophagus. Ends about 40 cm.

3. Oesophago-gastric junction (C16.0)

Definition of oesophago-gastric junction: There is no universally agreed definition!

For histologists: junction of squamous epithelial cells to cylindric epithelial cell of the stomach

For surgeons: passage through the diaphragm

For gastroenterologists: junction at the beginning of proximal gastric folds

In Japan: at the distal end of palisade venes

Japanese Classification of Esophageal Cancer, 11 edition Esophagus, (2017) 14:1-65

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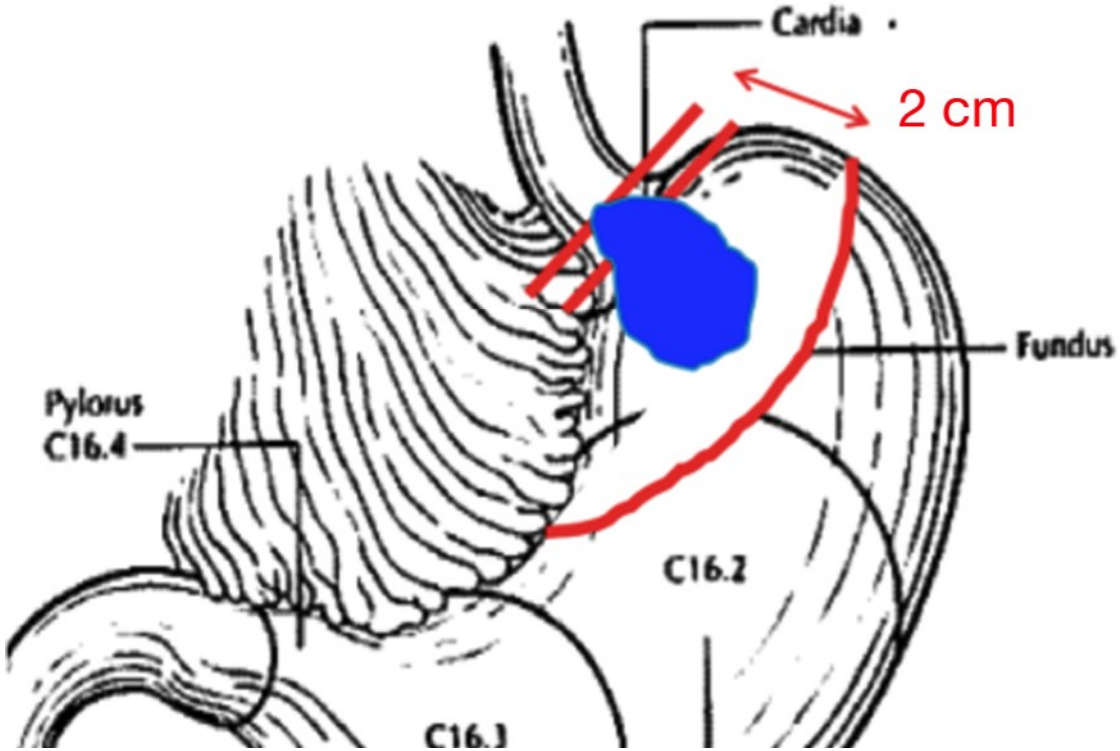
Definition oesophageal/ gastric adenocarcinoma

Definition changed 2017



A tumour of epicentre of which is within **2 cm** of the oesophagogastric junction and also extends into the oesophagus is classified and staged using the oesophageal scheme. Tumours with an epicentre in the stomach greater than 2 cm from the oesophagogastric junction or those within 2 cm of the oesophagogastric junction without extension in the oesophagus are classified and staged using the gastric carcinoma

Modified from: Wittekind and Schmiegel

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Staging: UICC

Oesophagus 8th edition, 2017

TNM definitions: AJCC = UICC

Tis: High grade intraepithelial neoplasia/dysplasia
T1: T1a: lamina propria or muscularis mucosae
T1b: submucosa
T2: mucularis propria
T3: adventitia
T4: T4a: pleura, pericardium, diaphragm, peritoneum
T4b: other adjacent structures (e.g. aorta, trachea)

N1: 1-2 regional lymph node(s)
N2: 3-6
N3: >6

M1: Distant metastasis

Applies to carcinoma (ICD-0 C15) and includes adenocarcinoma of the oesophagogastric junction (ICD-0 C16.0)

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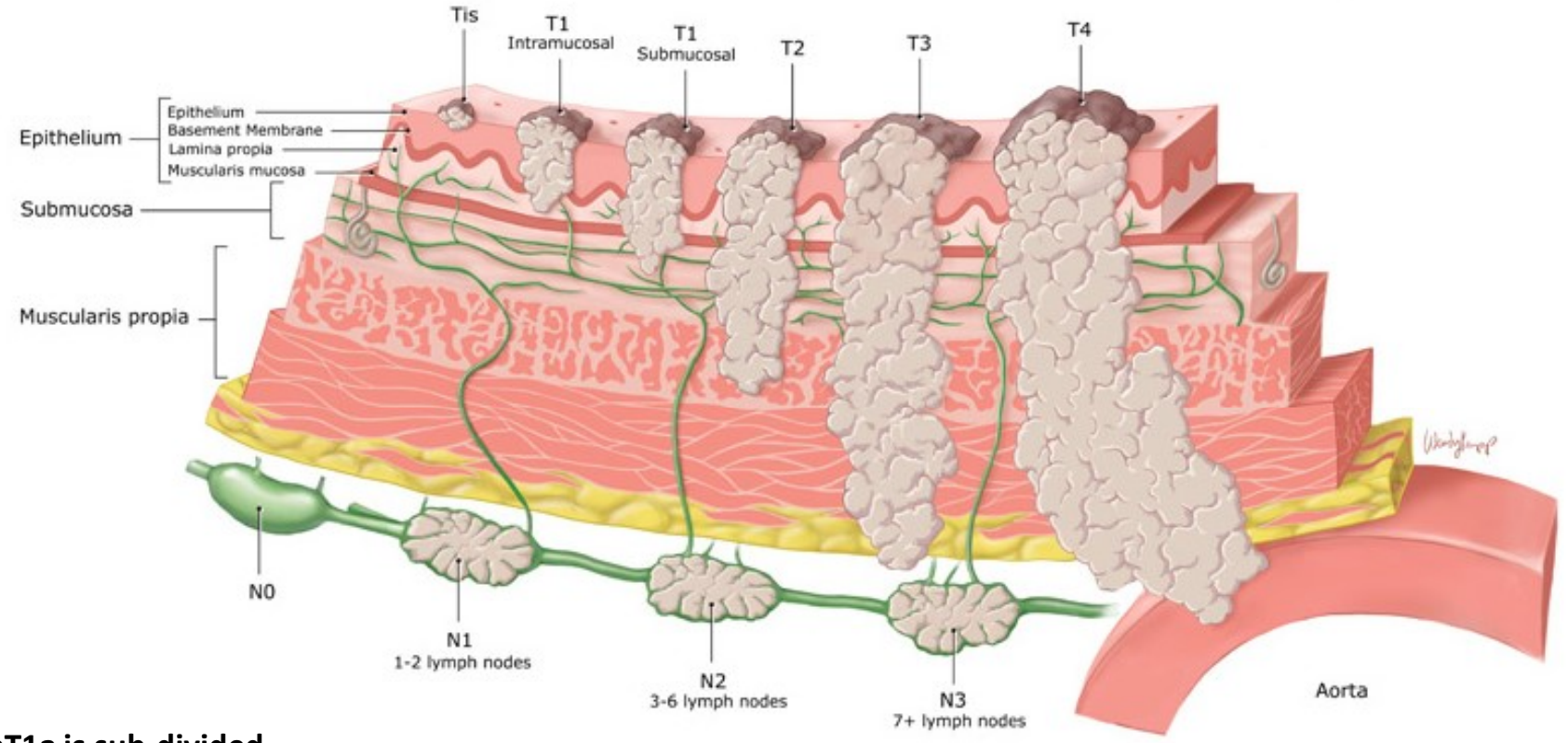
Staging: UICC
Esophageal Cancer Staging



pT1a is sub-divided

- m1 – into the lamina propria
- m2 – into the superficial/inner muscularis mucosae
- m3 – into the space between the layers of the muscularis mucosae
- m4 – into the outer/true muscularis mucosae

T1b is sub-divided as SM1-3 as follows

- sm1 – superficial 1/3 submucosa
- sm2 – intermediate one third of submucosa
- sm3 – outer one third of submucosa

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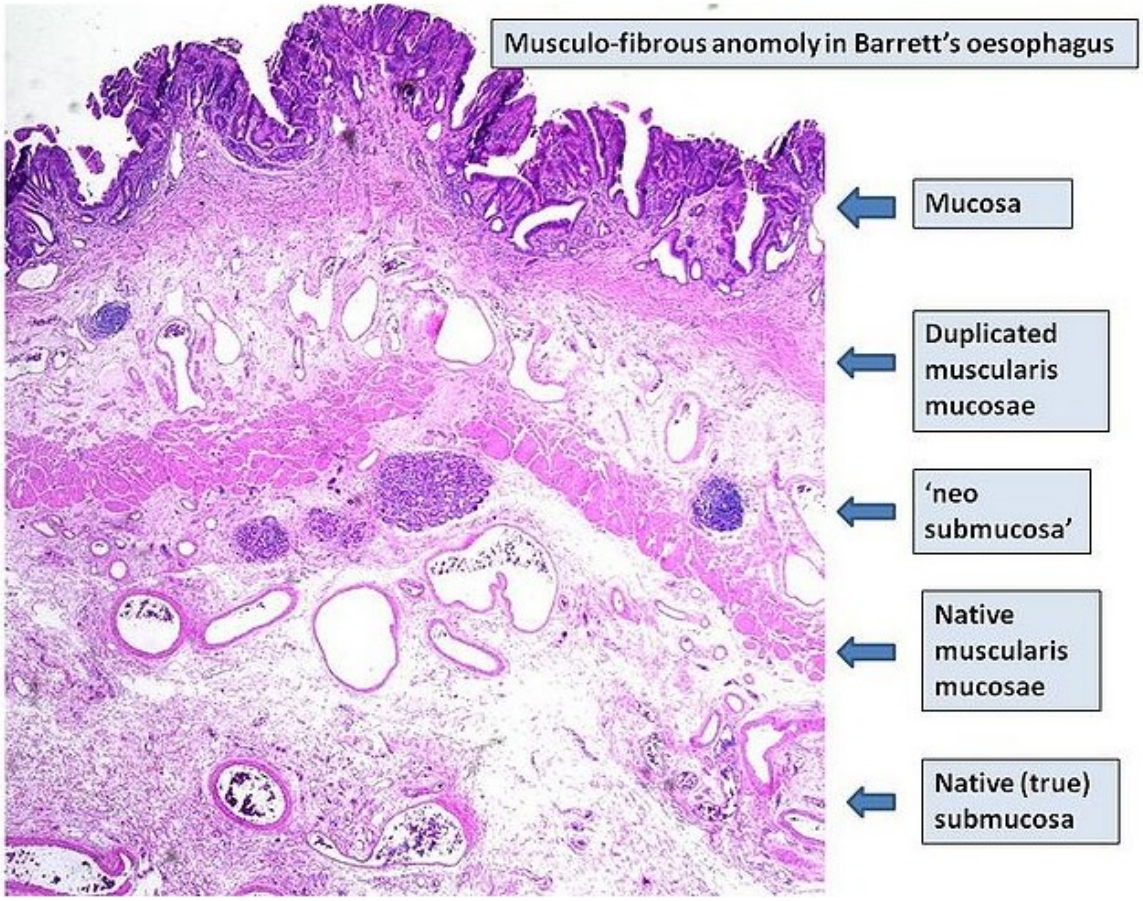
Double layer of muscularis mucosae in Barrett (pT1a; m1-m4)



Bobryshev, Y, Brown, I, Clouston, A, Cancer Council Australia Barrett's Oesophagus Guidelines Working Party. What are the histological features of early adenocarcinoma of the oesophagus?

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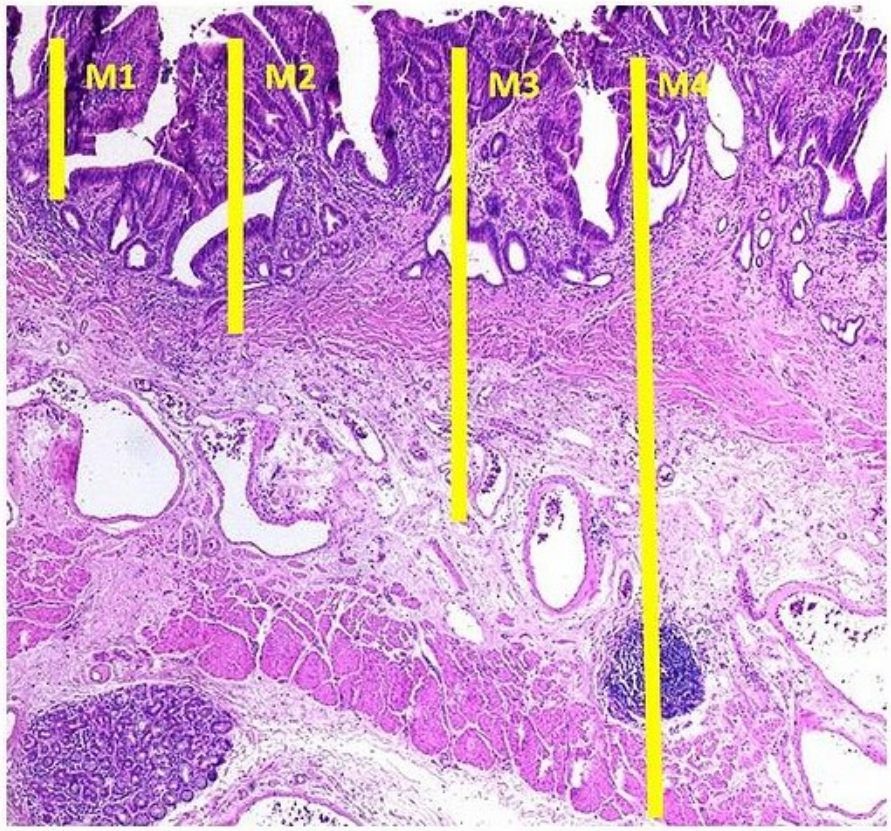
Double layer of muscularis mucosae in Barrett (pT1a; m1-m4)

Stolte staging system (mucosa)



Stolte

m1 - into the lamina propria

m2 - into the superficial/inner muscularis mucosae

m3 - into the space between the layers of the muscularis mucosae

m4 - into the outer/true muscularis mucosae

Bobryshev, Y, Brown, I, Clouston, A, Cancer Council Australia Barrett's Oesophagus Guidelines Working Party. What are the histological features of early adenocarcinoma of the oesophagus?

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Prognostic factors

Univariable analysis of factors influencing survival

Variable	χ^2	DF	*P*-value
Age	48.020	41	0.210
Gender	1.039	1	0.308
Histological cell type	2.250	2	0.308
Histological tumour grade	10.260	2	0.006
Operative approach (TT *vs* TH)	0.795	1	0.373
Neoadjuvant therapy	0.627	1	0.429
T stage (same in TNM6 and TNM7)	21.514	3	<0.0001
N stage (TNM6)	21.499	1	<0.0001
N stage (TNM7)	37.509	3	<0.0001
Number of lymph node metastases	61.677	12	<0.0001
Stage groupings (TNM6)	36.587	4	<0.0001
Stage groupings (TNM7)	50.531	7	<0.0001
Prognostic groupings (TNM7)	47.147	7	<0.0001

Most important:

- Depth of invasion (primary tumor extension)
- Lymph node involvement
- Stage/prognostic groupings

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Prognostic factors – Lymph nodes metastasis indicate poor prognosis

Extensive interconnecting lymphatic channels
High risk of skip areas (high risk of local recurrence)
Drain into lymph nodes: paraoesophageal, paratraechael, dorsal mediastinum, lung hilum, inferior thyroid artery, left gastric artery (celiac axis), paraesophageal in the neck.

Risk to develop nodal mets: T1b: 20%
T2: 60%
T3: 90%
T4: 100%

Biggest problem in oesophageal carcinoma:
- Often: locally advanced tumors (85% in T2 or more)
- Metastasizes early

From: neoadjuvant.wikidot.com staging and krebsdaten.de (Robert-Koch-Institut)

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Regional Lymph Nodes

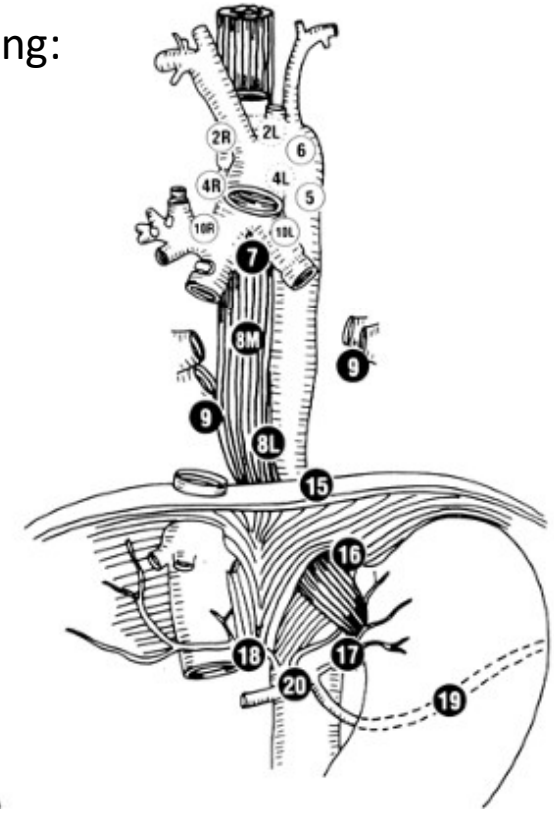
Localisation using TNM 8th edition

Regional lymph nodes, irrespective of the site of the primary those in the oesophageal drainage – including:

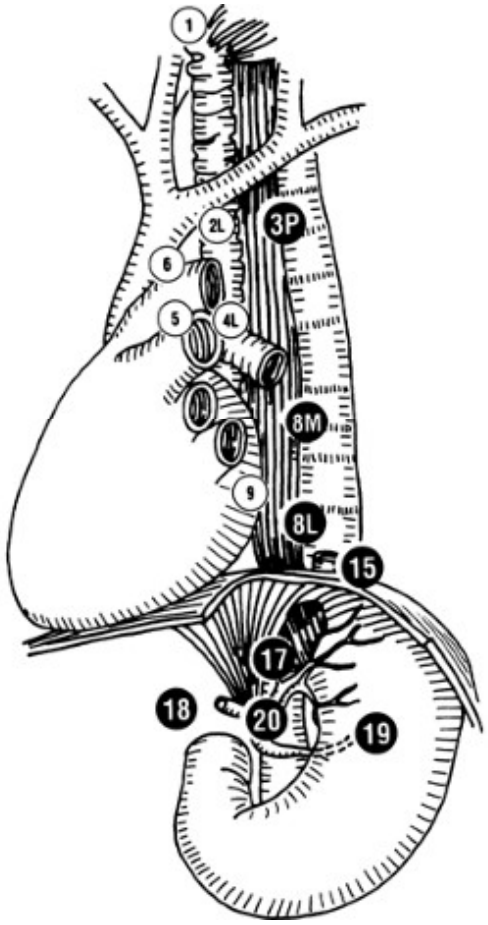
- paraoesophageal
- paratraechael
- dorsal medistinum
- lung hilum
- inferior thyroid artery
- left gastric artery (celiac axis) paraesophageal in the neck

How many we need

>7 lymph nodes

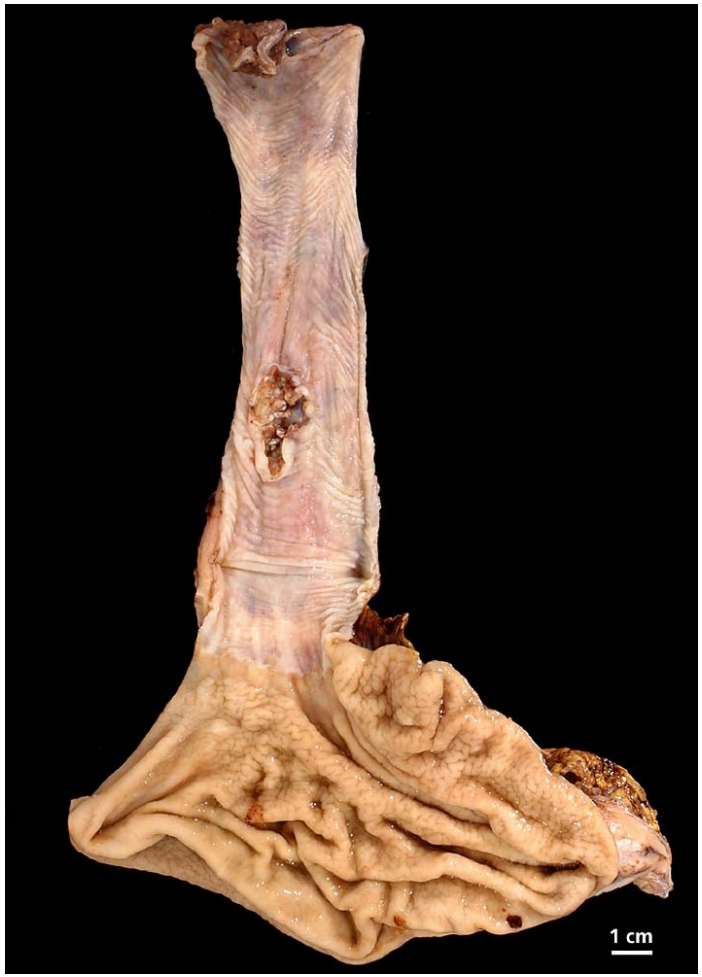


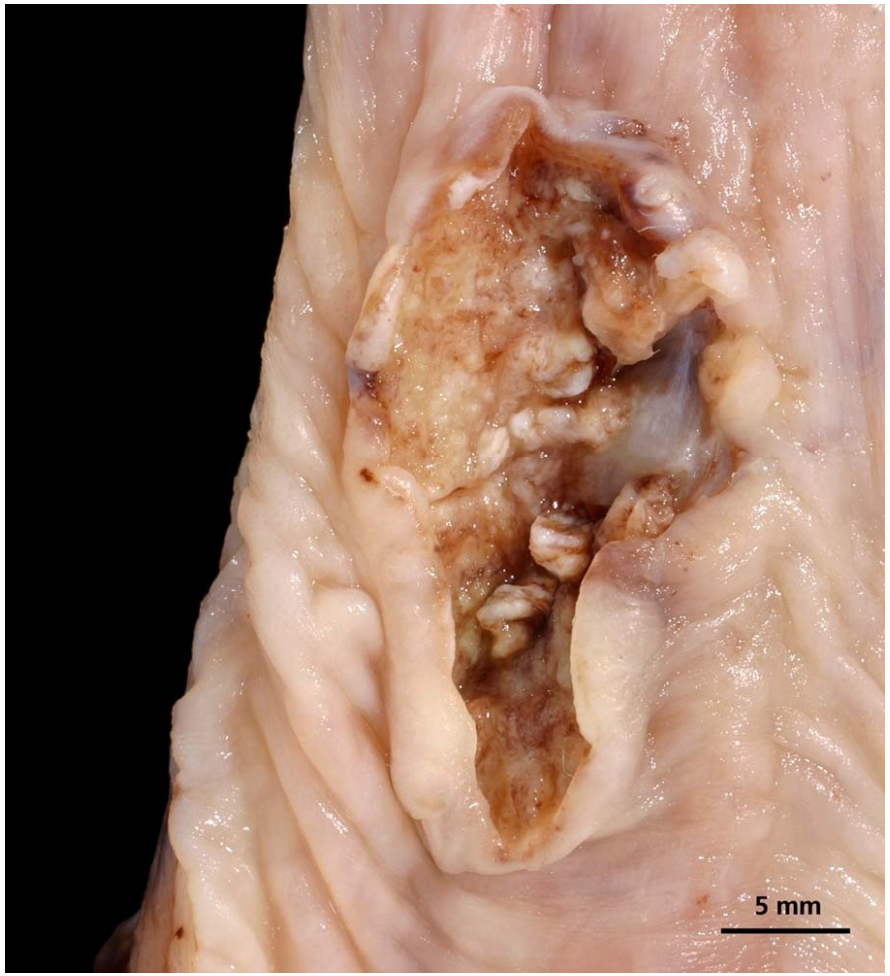
A



B

ESCC





Localisation: Whole oesophagus including distal parts; more often: middle third

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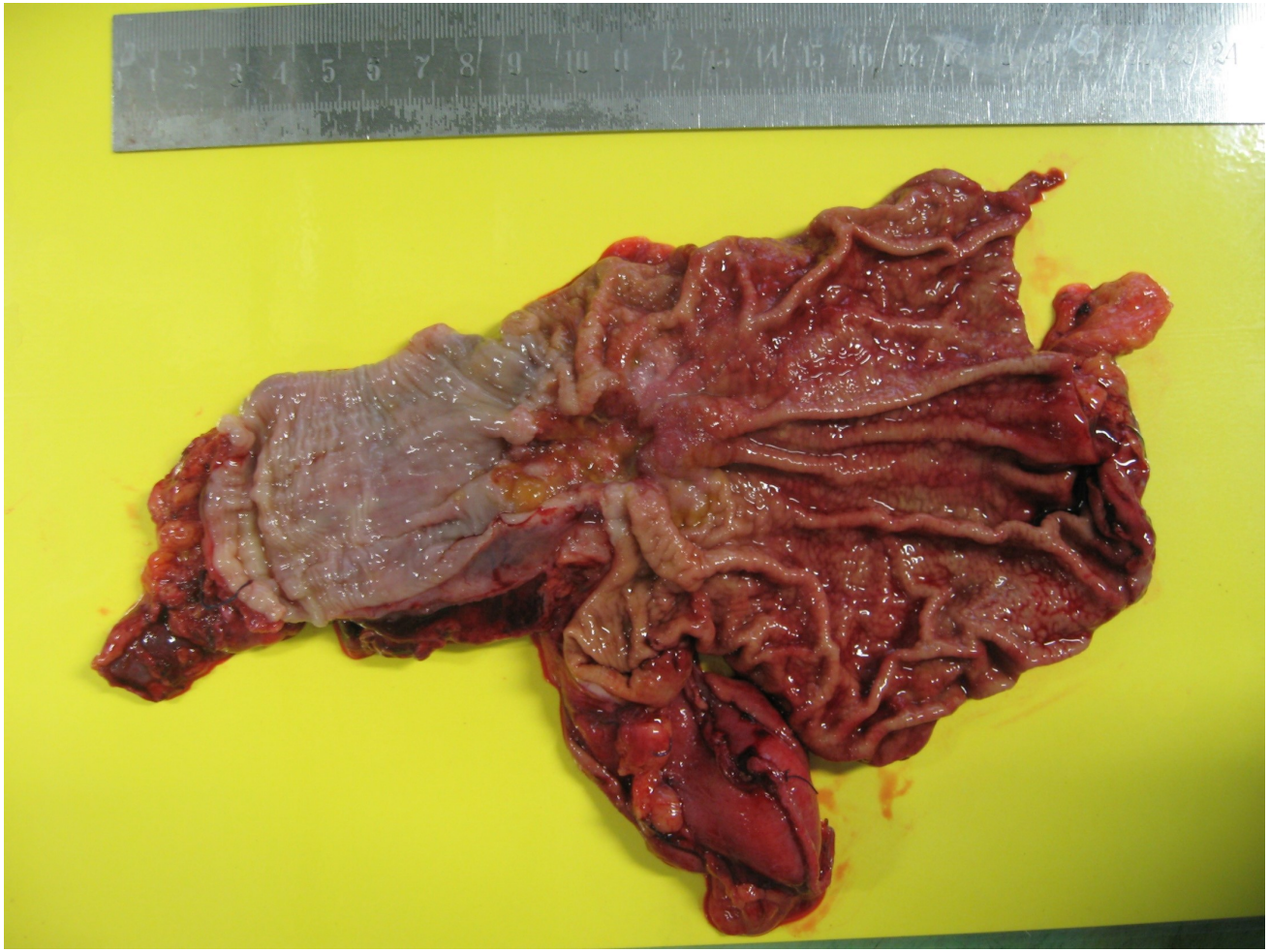
EAC



Localisation: distal parts of oesophagus/oesophgeal-gastric junction

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Regression-Scores after neoadjuvant therapy

According to Becker et al:

Morphological regressions signs:

- oedema
- foamy histiocytes
- necrosis
- fibrosis and hyalinosis

Grading of Histophathologic Regression in the Primary Tumor Bed	
Grade	**Description**
1a	No residual tumor / tumor bed
1b	< 10% residual tumor / tumor bed
2	10-50% residual tumor / tumor bed
3	> 50% residual tumor / tumor bed

From: Becker et al. Ann Surg 2011 or Becker et al. Cancer 2003

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Regression-Scores

Response Classification System

Scheme	Characteristic
Class I	Minor histomorphologic regression
a	With lymph node metastases
b	Without lymph node metastases
Class II	Major histomorphologic regression
a	With lymph node metastases
b	Without lymph node metastases

Major responder
Minor responder
Cut-off: 10% vital tumour

Cologne Regression Classification System

- Grade I indicates minimal/no regression, with more than 50% vital tumor remaining;
- Grade II indicates partial regression, with less than 50% and more than 0% vital tumor remaining;
- Grade III indicates sub-total regression, with 0% vital tumor remaining;
- Grade IV indicates complete regression, with no vital tumor remaining.[22,23]

Response grades I and II are classified as 'minor response,' and grades III and IV as 'major response.'

From: Schneider et al. Ann Surg 2005 Nov; 242(5):684-692

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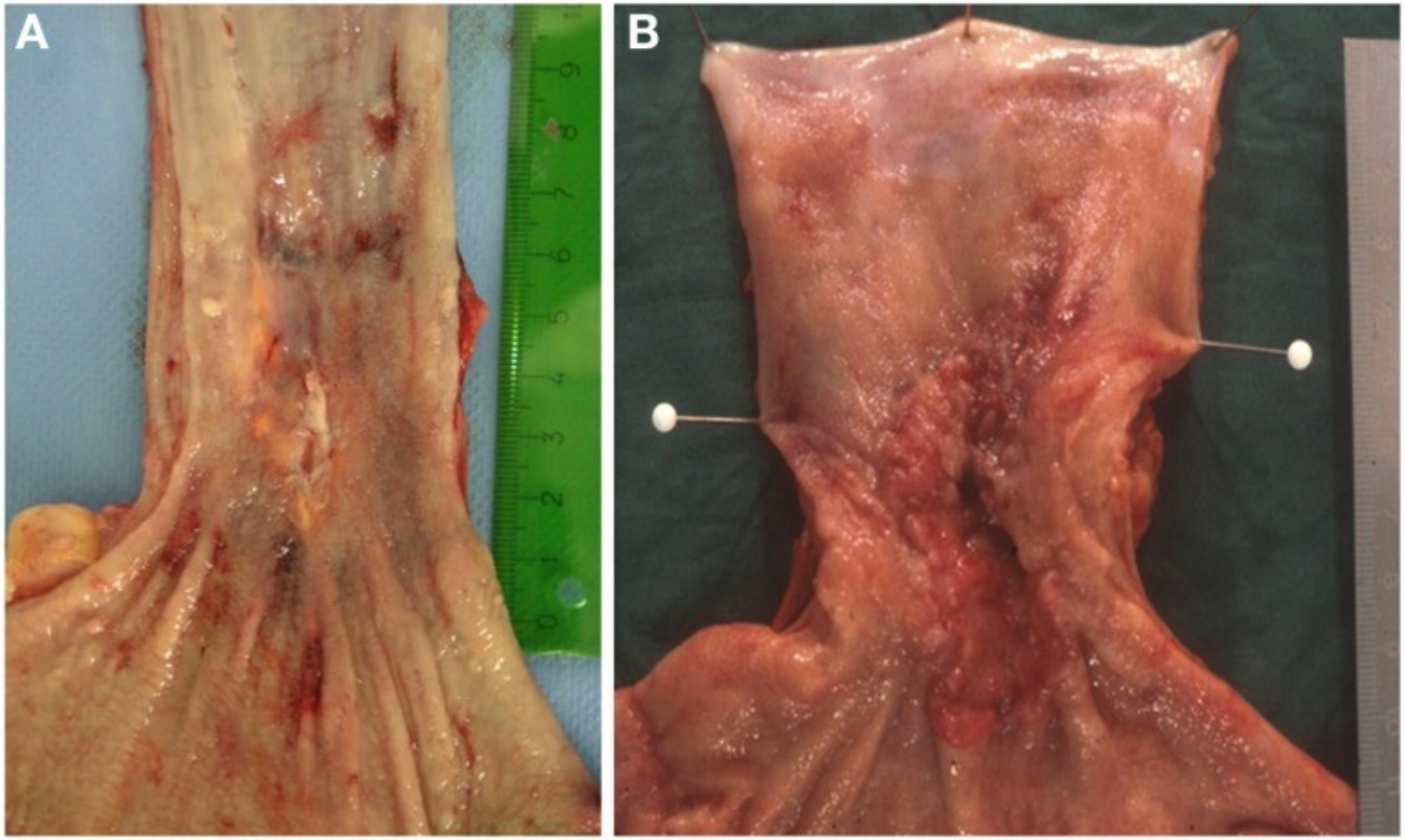
Photographic documentation Adenocarcinoma



From: Front Oncol. 2013; 3: 262. Thies, Langer **Gross images of esophageal adenocarcinomas with (A) macroscopic significant regression and (B) no macroscopic significant regression after neoadjuvant chemotherapy**.

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Work-flow in Cologne

1) Photographic documentation of all surgical specimens

2) Macroscopically

- Tumor size (if possible in three dimension)
- Tumor localisation
- Tumor extension
- Distance to margins (oral, aboral, circumferential)
- Complete embedding of the tumor from oral to aboral (CRM is included and colourmarked)
- Lymph nodes are completely embedded

3) Reporting

- Histological types (adenocarcinoma, squamous cell carcinoma)
- UICC staging (y) pT pN (including ece+) L V Pn (=perineural invasion)
- Margins (free; distance; oral, aboral, circumferential)
- Grading (in case of neoadjuvant chemo-/radiotherapy: no grading)
- Regression grade (in case of neoadjuvant therapy using Becker and Cologne Score)

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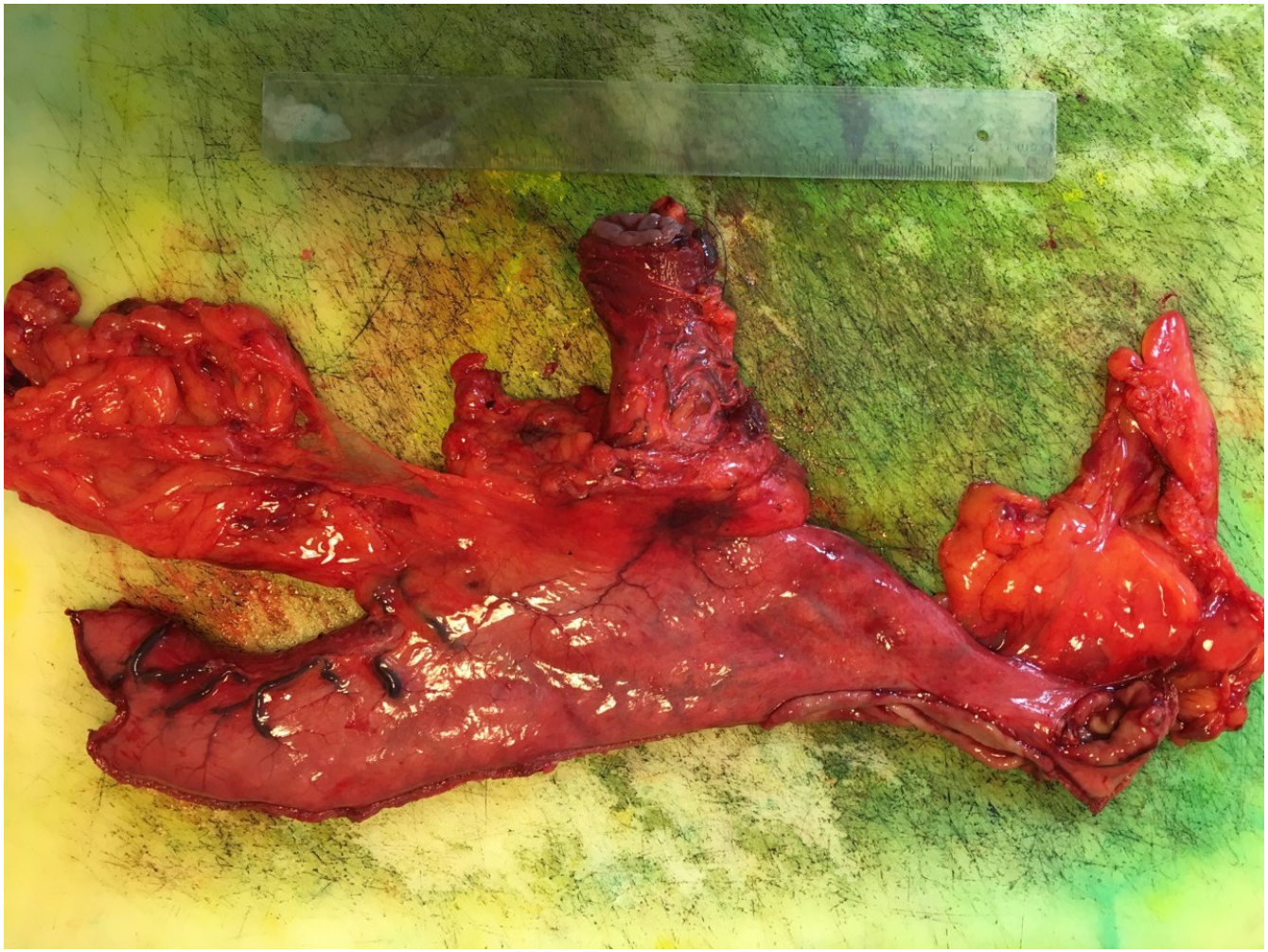
Surgical specimens
Adenocarcinoma of GEJ



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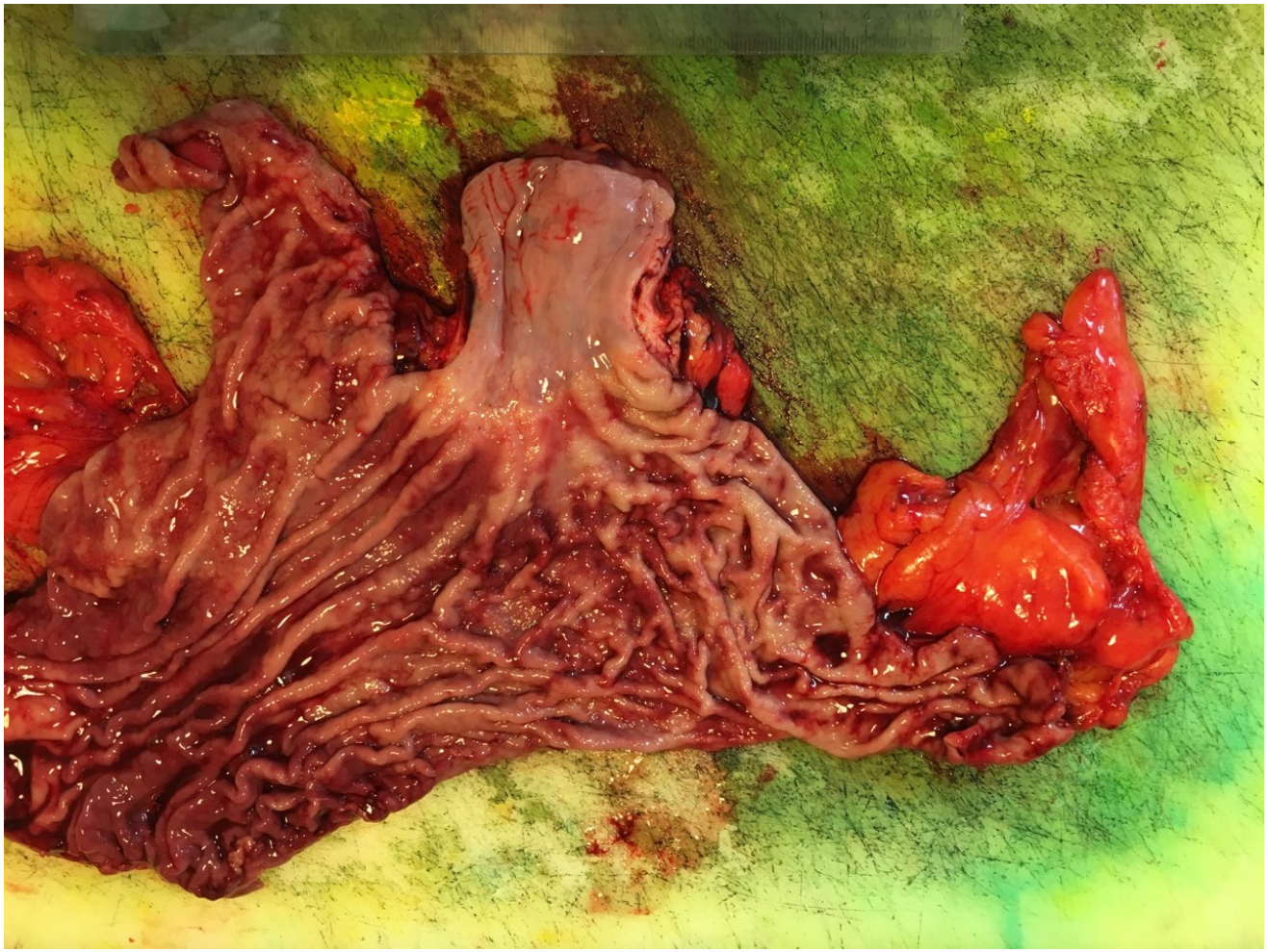
Surgical specimens
Adenocarcinoma of GEJ



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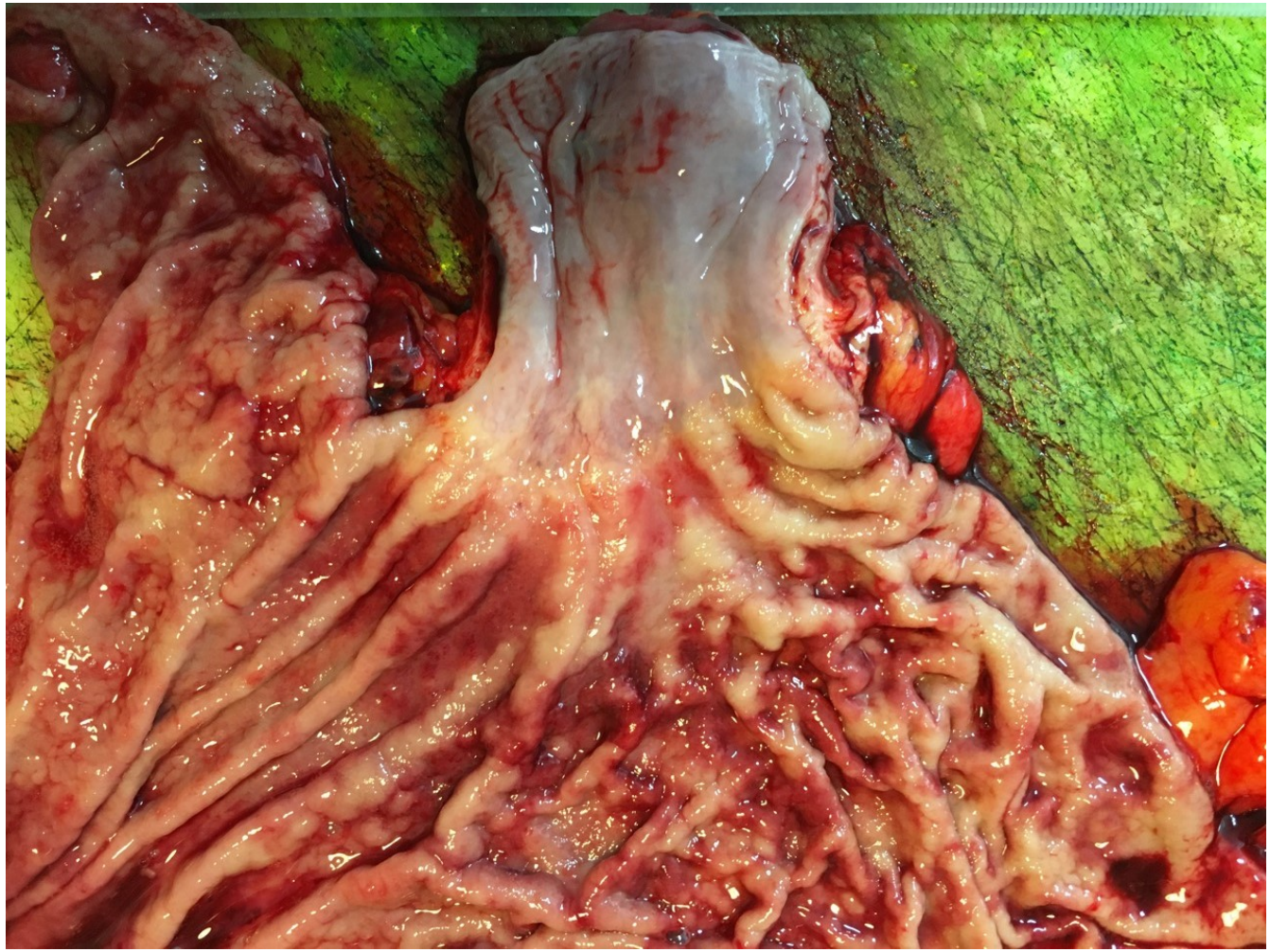
Surgical specimens
Adenocarcinoma of GEJ



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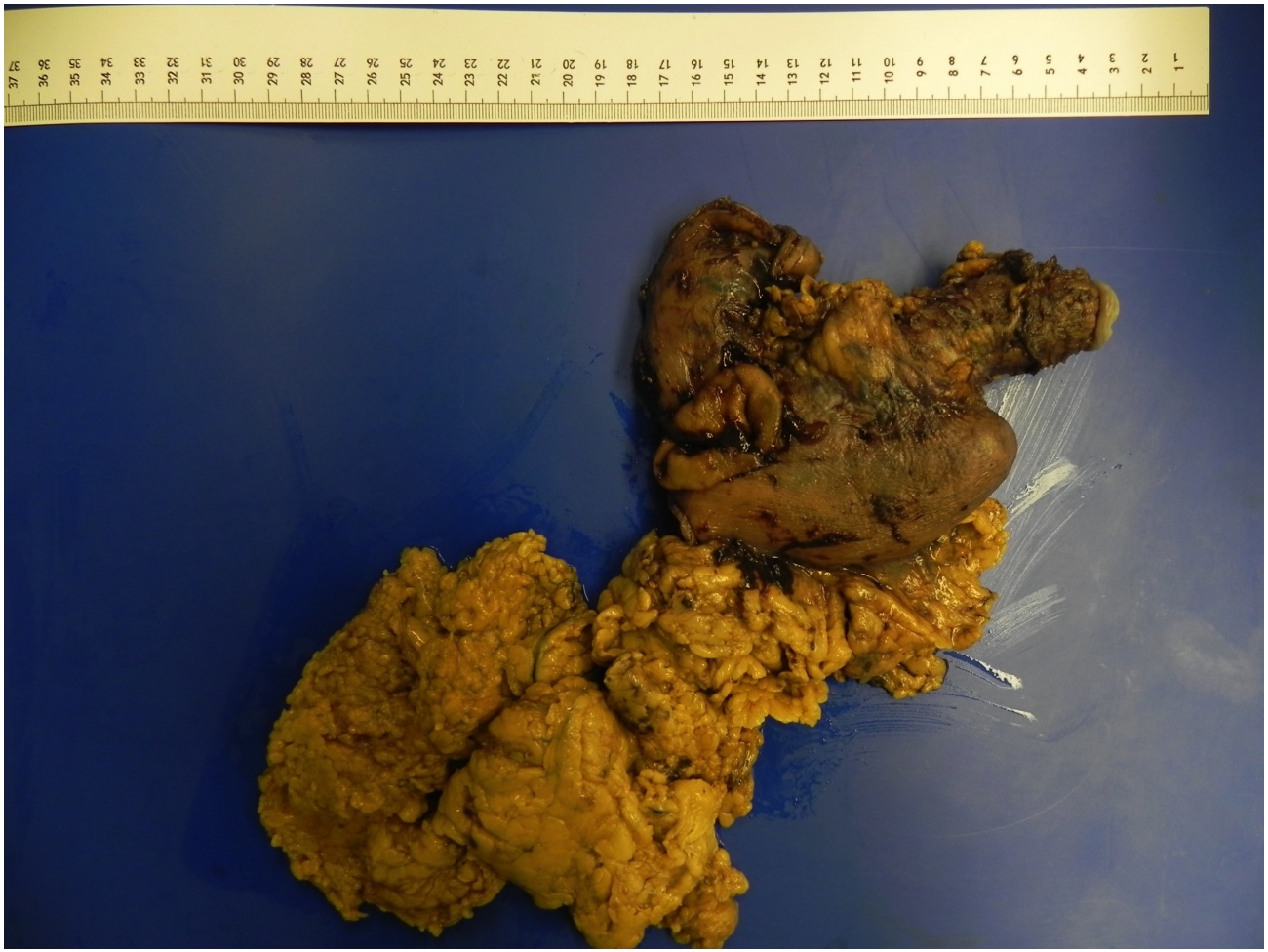
Surgical specimens
Adenocarcinoma of GEJ



distal oesophagus/proximal stomach incl. omentus majus
After neodjuvant treatment

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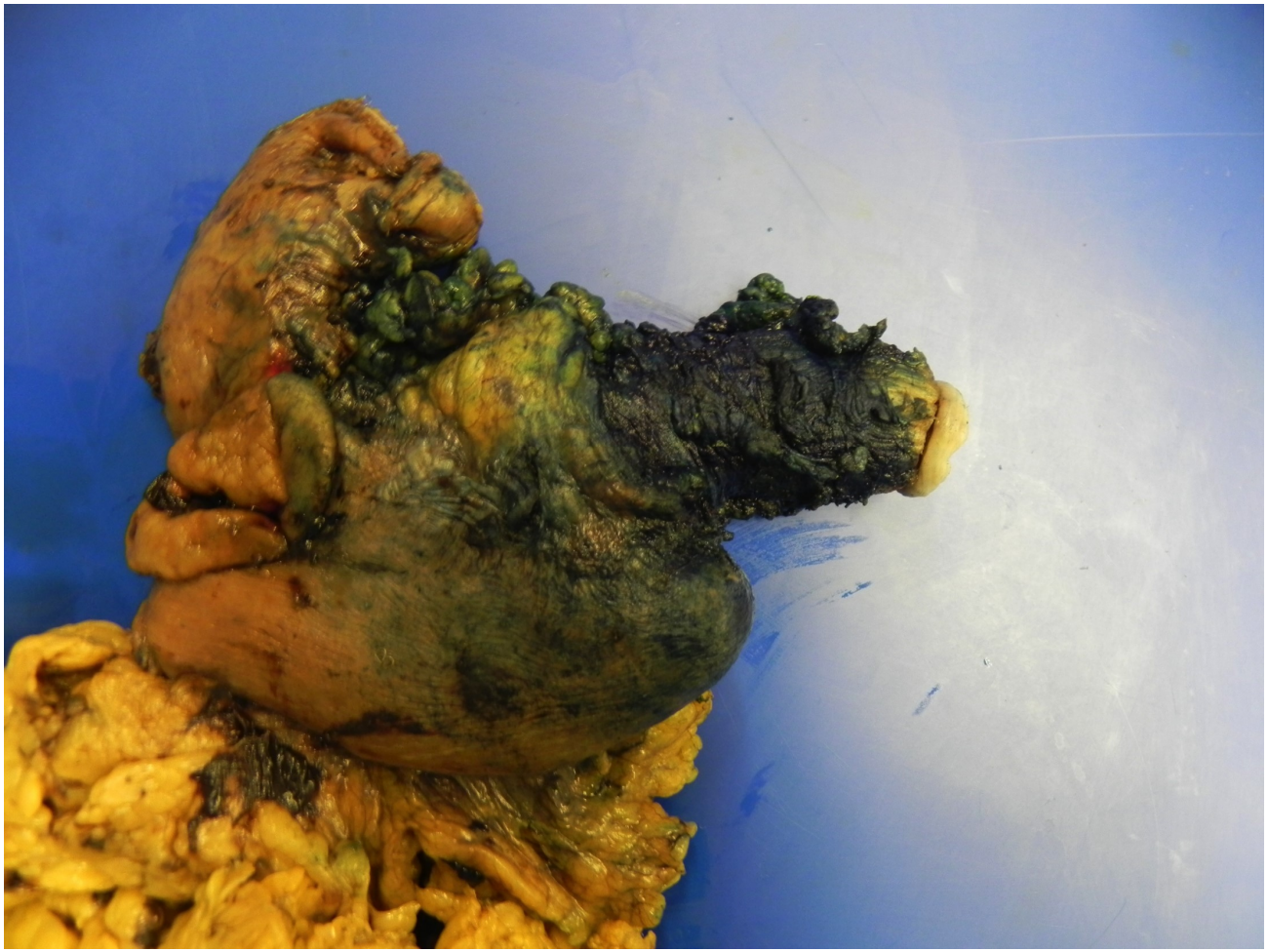
Surgical specimens
Adenocarcinoma of GEJ



Colour-marked circumferential margin

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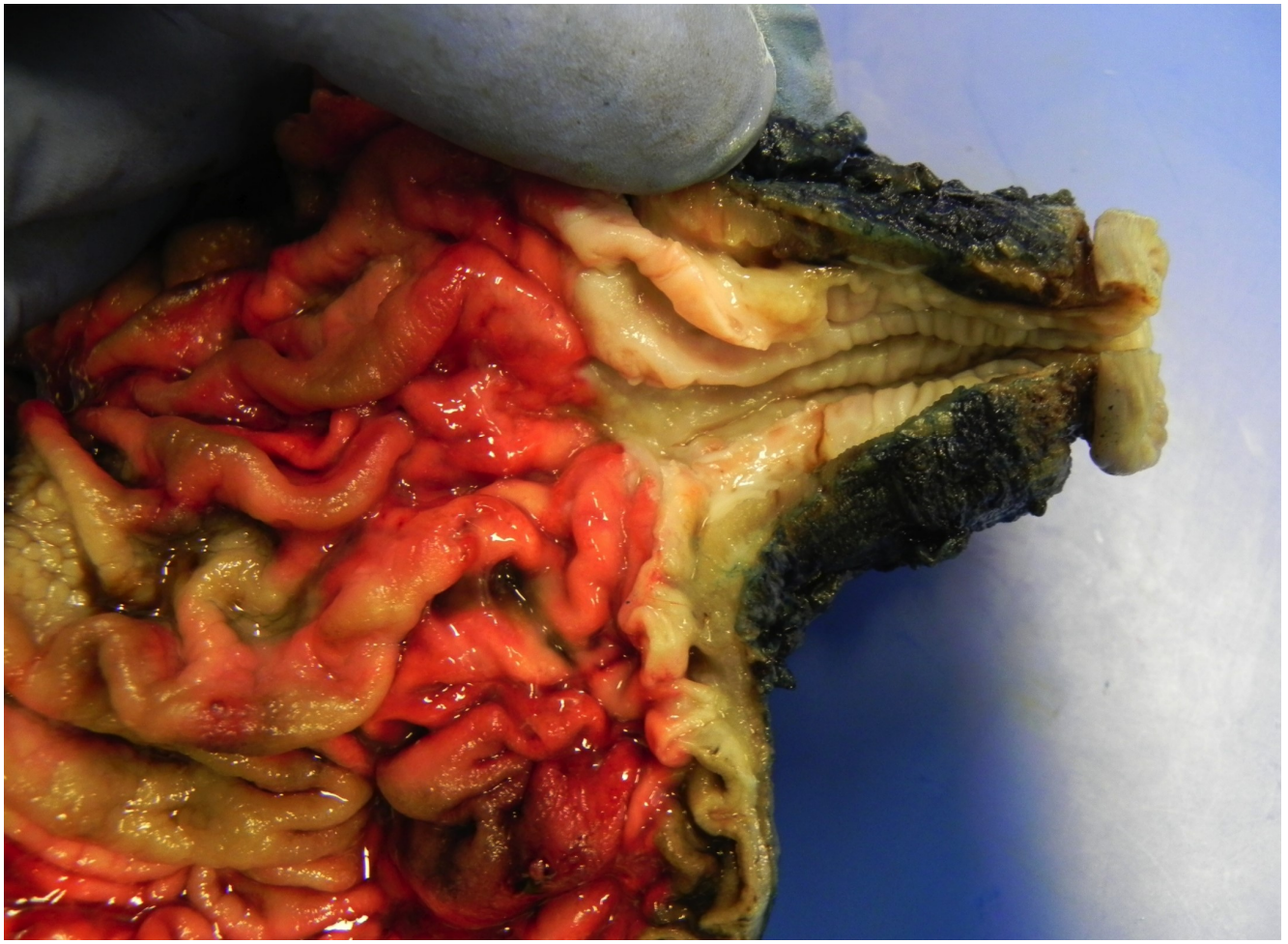
Surgical specimens
Adenocarcinoma of GEJ



Macroscopically just small residual tumor

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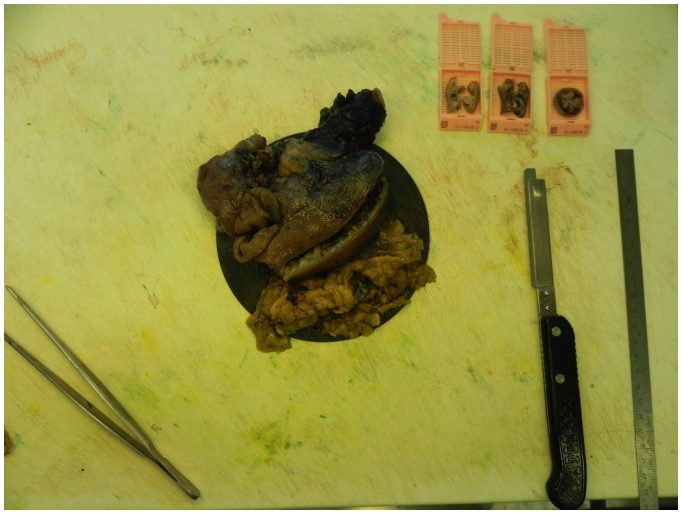
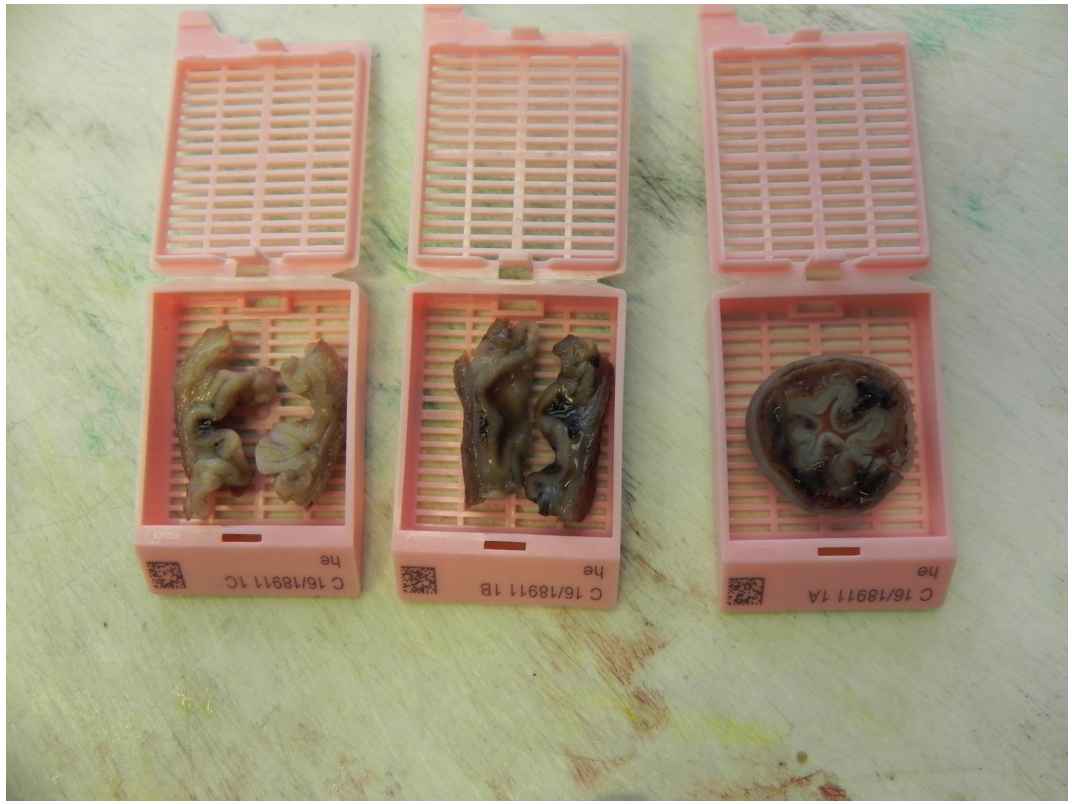
Surgical specimens





Starting with oral and aboral surgical margins

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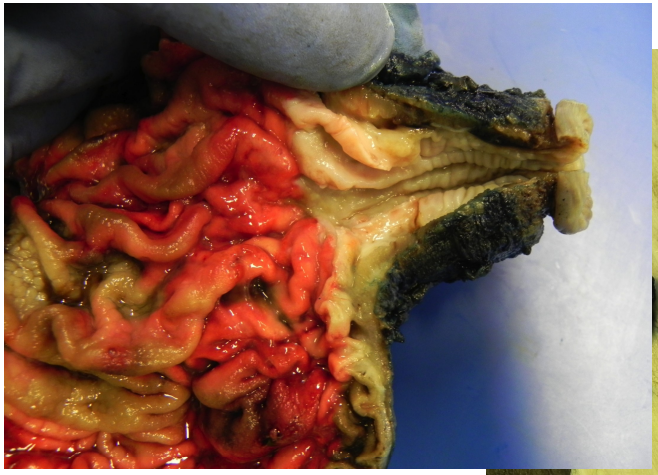
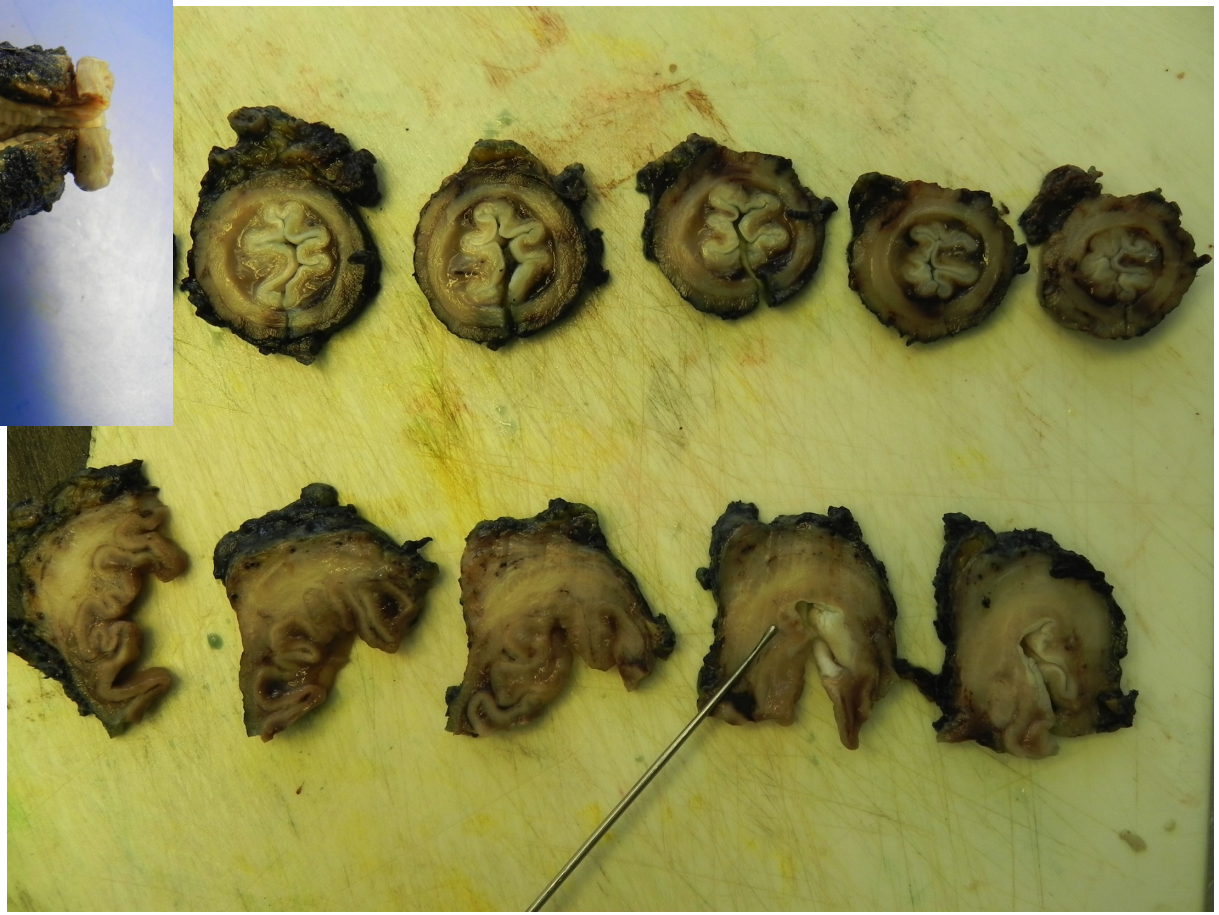
Surgical specimens





Embedding of whole specimen/whole tumor bed coming for oral to aboral.
Every tissue block is 3-4 mm thick

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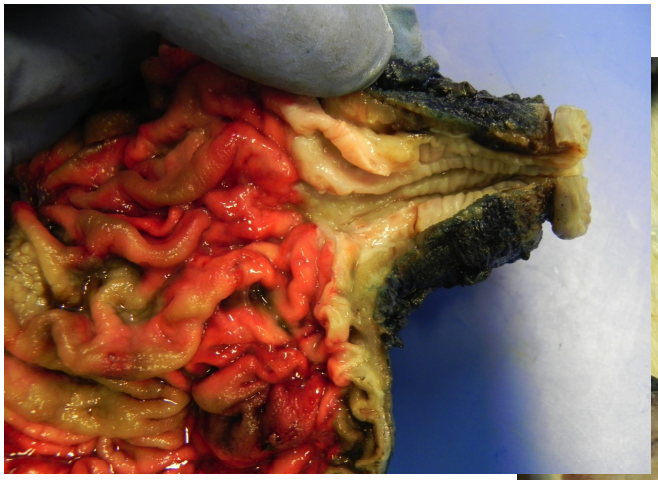
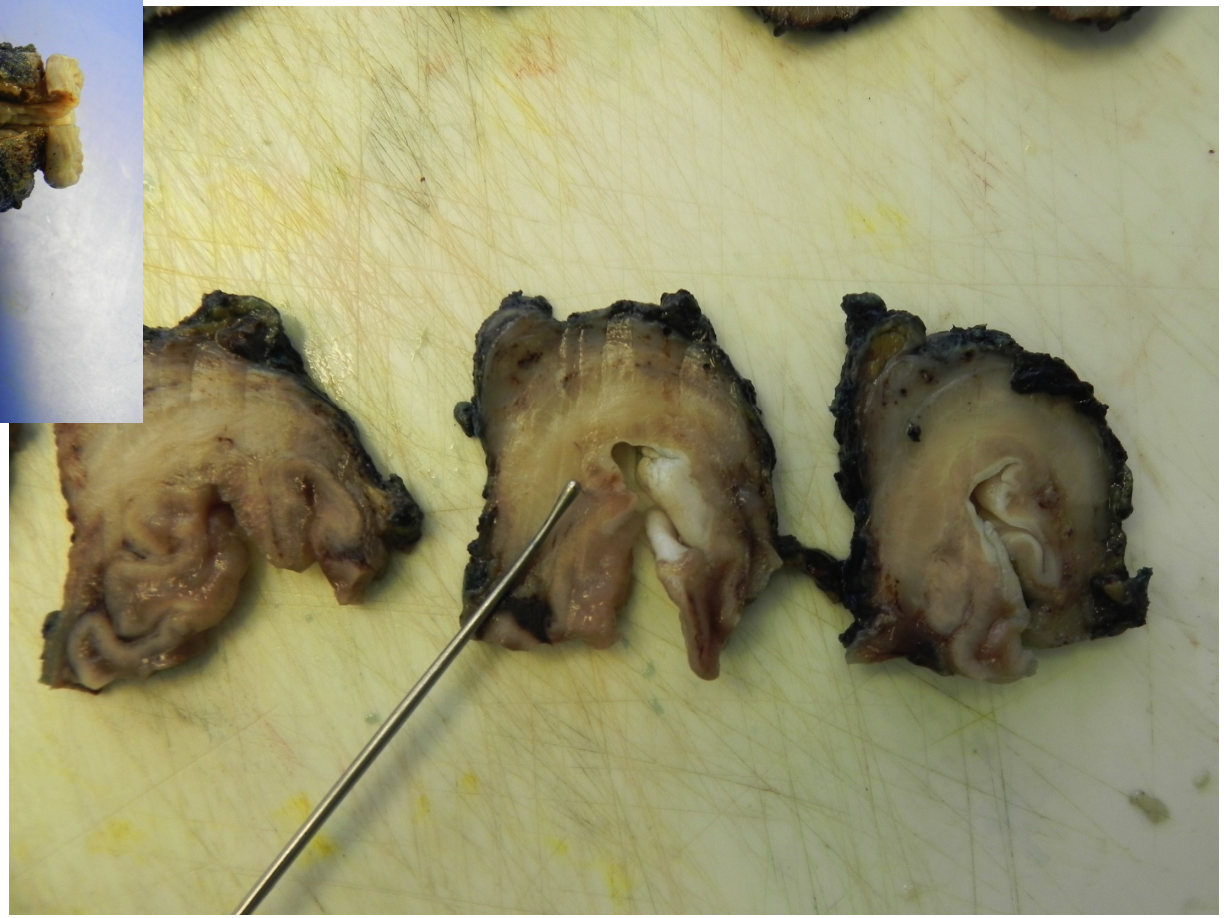
Surgical specimens





White mucosa: squamous cell mucosa of oesophagus with suspected residual tumor

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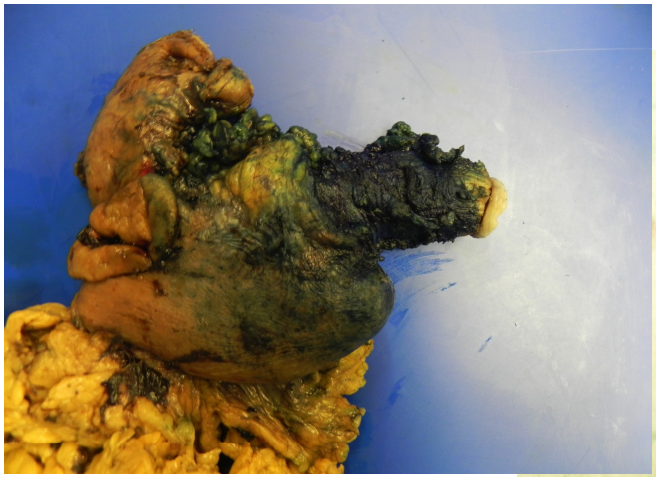
Surgical specimens



Lymph nodes preparation

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Surgical specimens

Up to four lymph nodes in one tissue block

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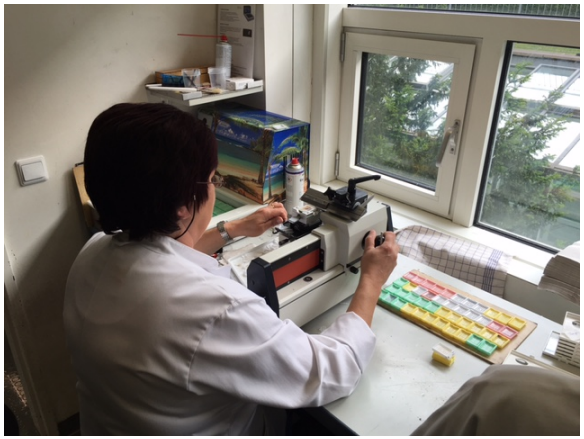
Last steps



From three-dimensional surgical specimen to two-dimensional slides

Stainings: HE, PAS

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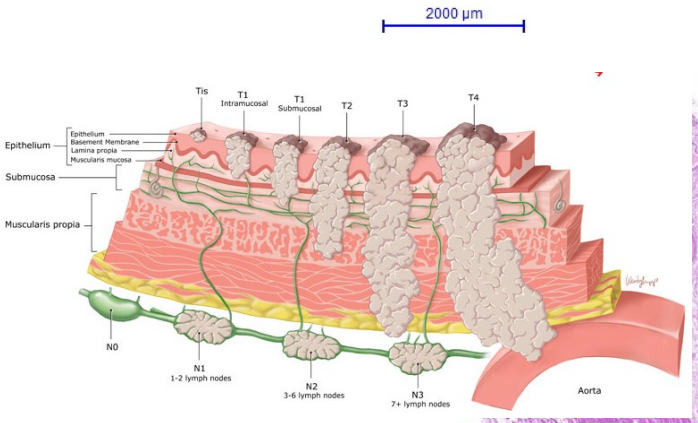
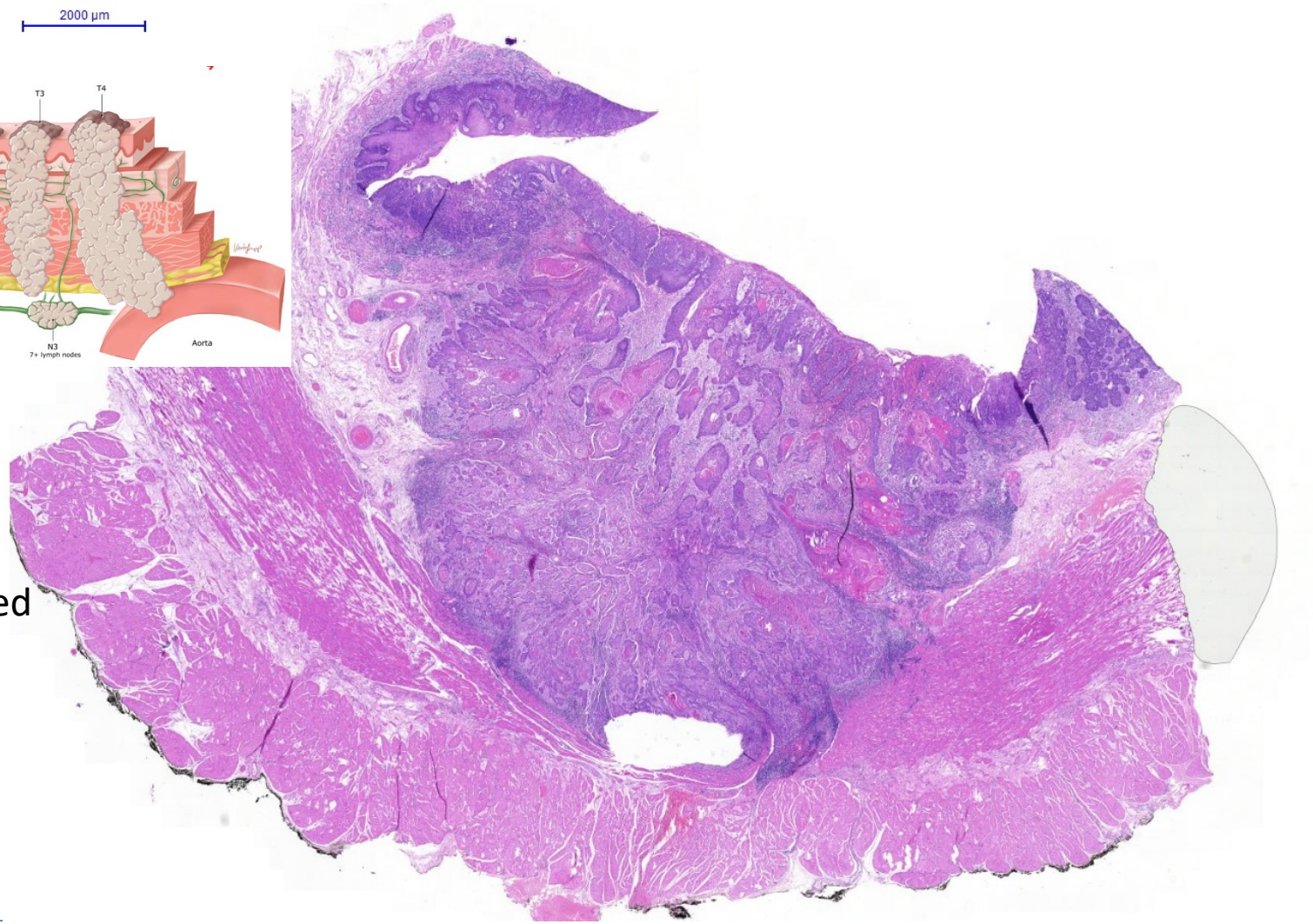
ESCC – pT?





Coloured margin

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Summary

- Incidence of adenocarcinoma is increasing
- Overall prognosis is dismal (despite some advances), mainly due to:
  - locally advanced disease (we diagnose too late)
  - early lymph nodes metastasis (intense network of lymph vessels)
  - no well defined subtypes
  - treatment options are still insufficient (personalized: Herceptin only)
- No EBV and MSI subtypes
- PDL1-checkpoint-inhibition less effective?
- HER2/neu still the only personalized treatment option
- >7 regional lymph nodes
- Standardized work flow in pathology embedding of whole tumor bed
- Regression scores after neoadjuvant treatment

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Questions

- Why do we have differences in responding to treatment (major and minor responder)?
- How important is the TP53 wildtype group?
- Can liquid biopsies be helpful in detection early recurrences?

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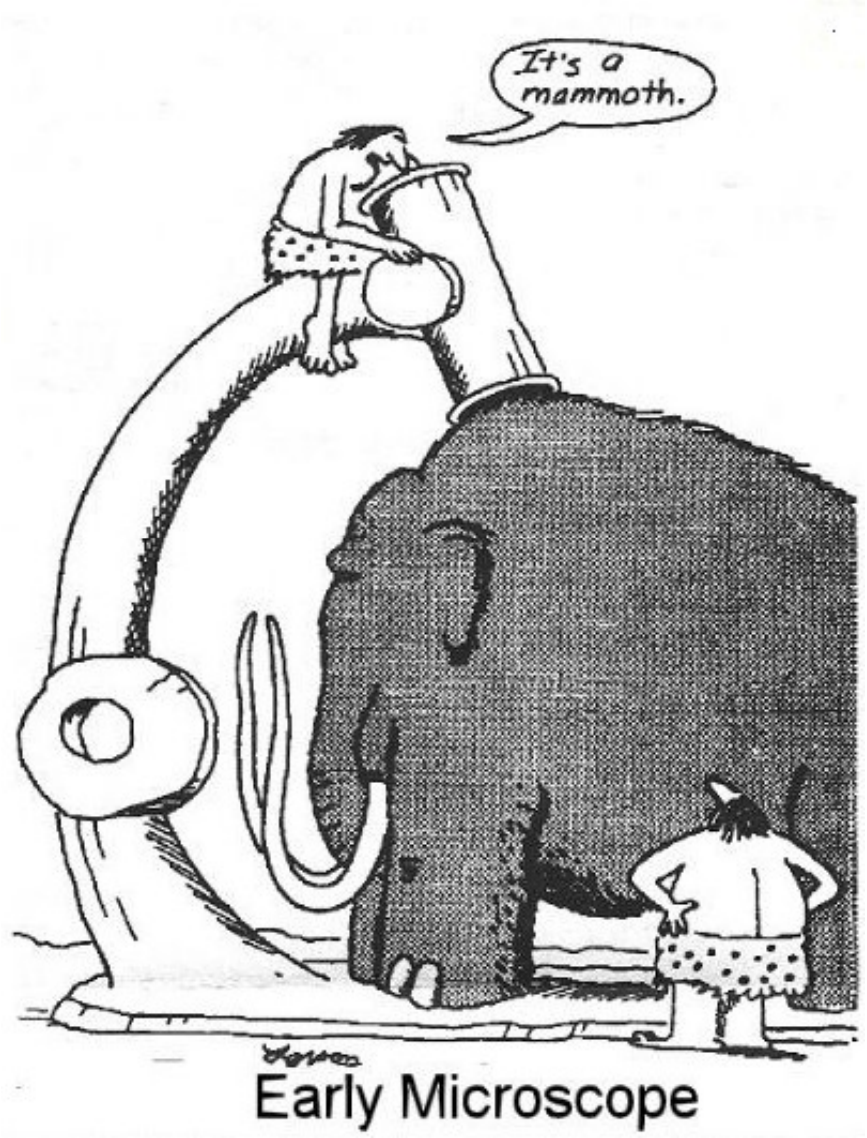
Thank you for your attention



Early Microscope

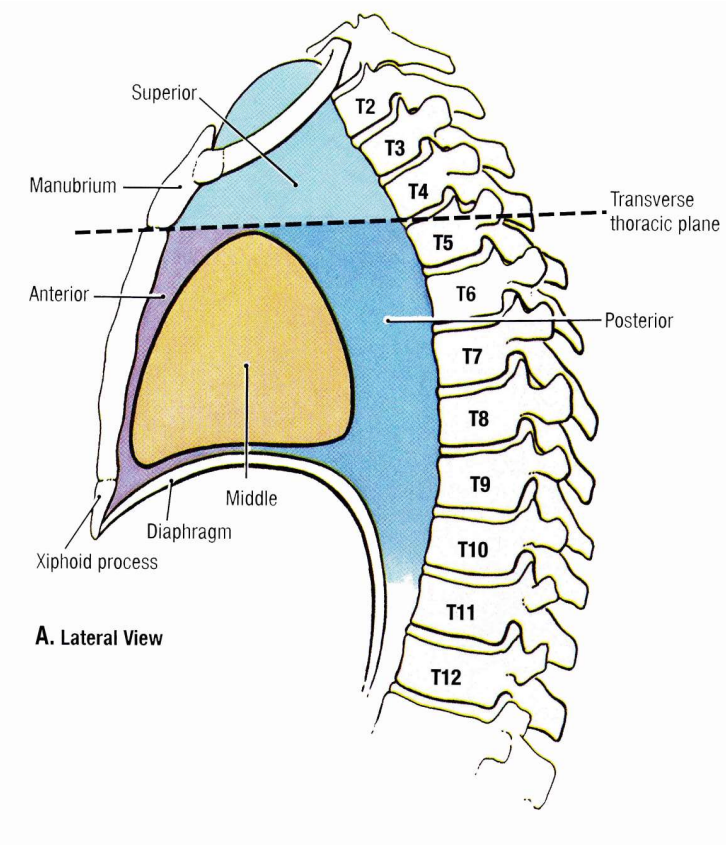
Imaging of primary and nodal subsite boundaries in Esophageal Cancer

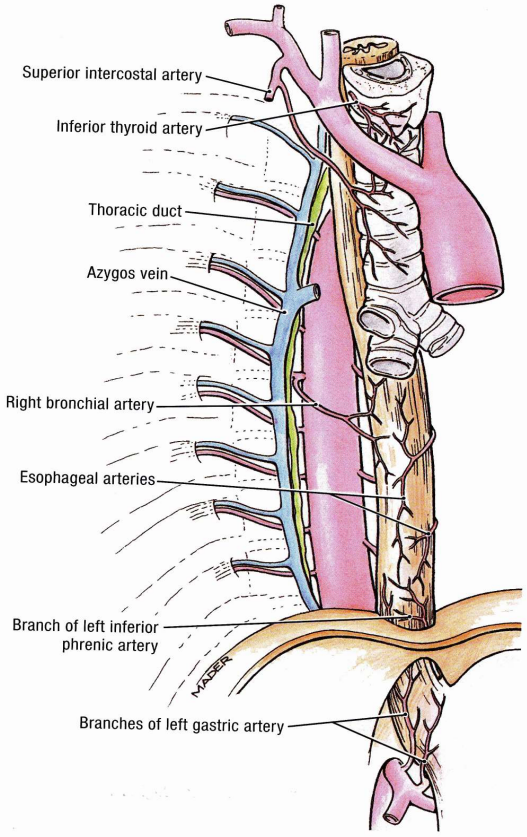
Dr Angela M Riddell

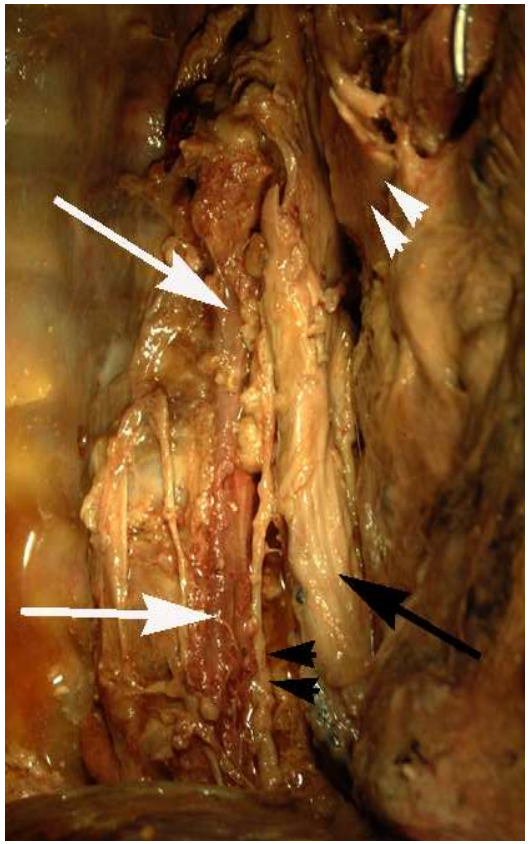
Royal Marsden, London. UK

ESTRO School

Anatomy







Grant's Atlas of Anatomy: Agur AM, Dalley AF. 11th Edition, 2005. Baltimore: Lippincott Williams and Wilkins

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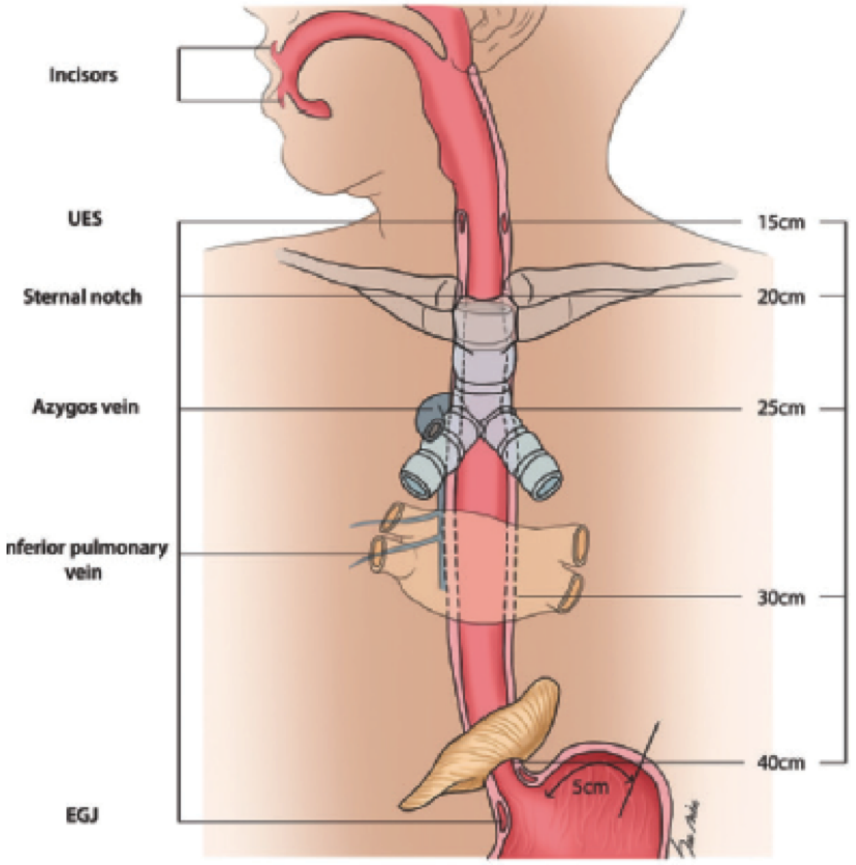
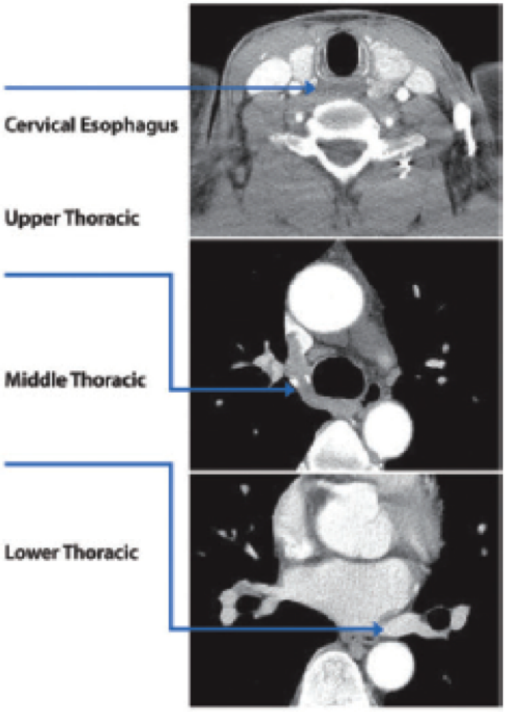
Anatomy: Oesophagus





Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740

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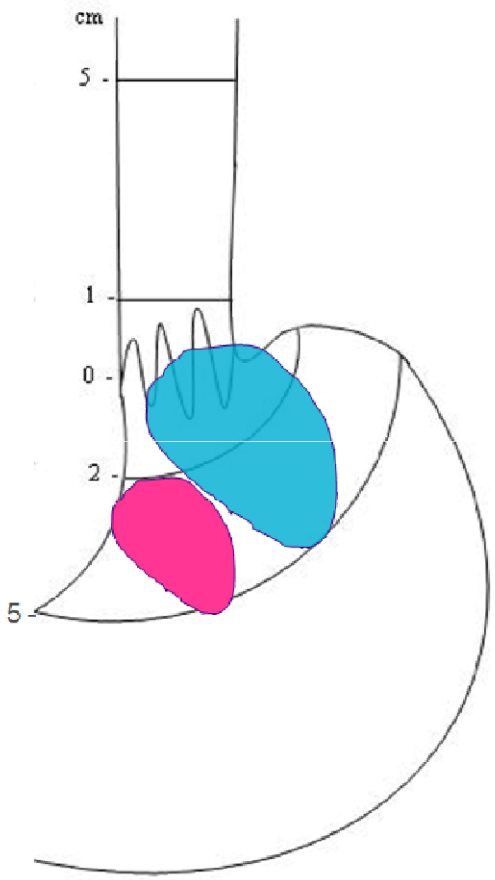
Anatomy: Gastro-oesophageal junction (GOJ)

- Tumours arising at the gastro-oesophageal junction, or arising in the stomach ≤ 5 cm from the GOJ and also extending into the oesophagus are classified and staged as ***oesophageal*** cancers [1]
- All other tumours with an epicentre in the stomach greater than 5 cm from the gastro-oesophageal junction or those within 5 cm of the GOJ but without extension into the oesophagus are staged as ***gastric*** cancers [1]
- ***7th Edition AJCC Staging manual***



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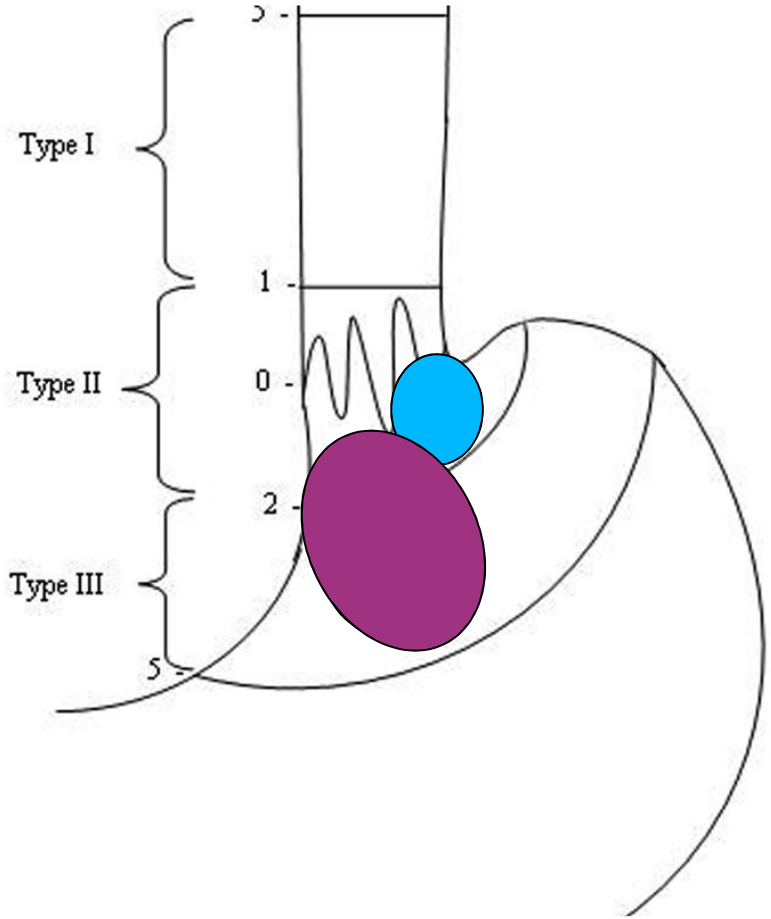
Anatomy: Gastro-oesophageal junction (GOJ)

- Tumours involving the OGJ whose epicentre is within the proximal 2cm of cardia (Siewert I & II) staged as ***oesophageal***
- Tumours with epicentre greater than 2cm from GOJ staged as ***gastric*** *even if OGJ is involved*
- ***8th Edition AJCC Staging manual***



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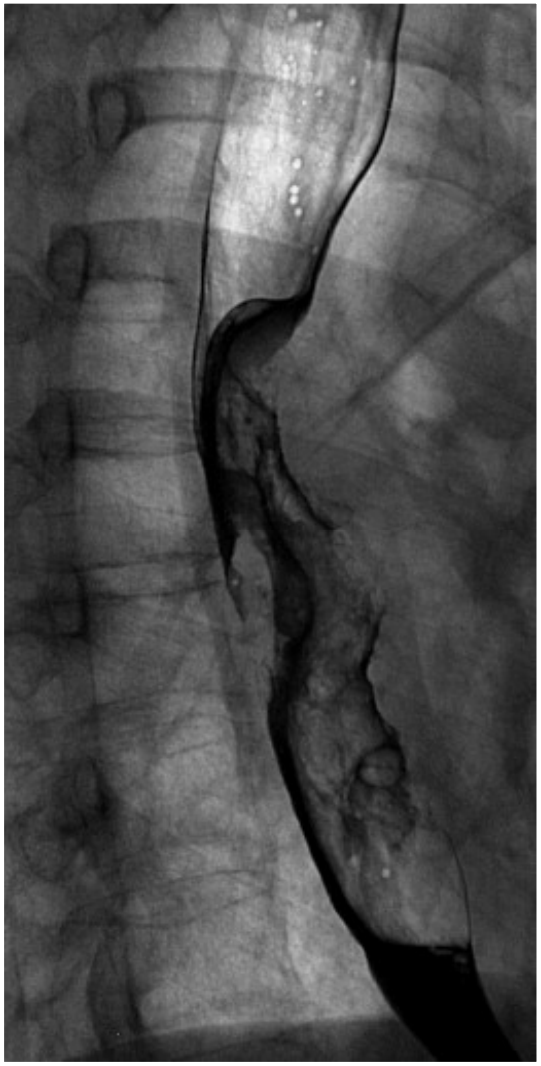
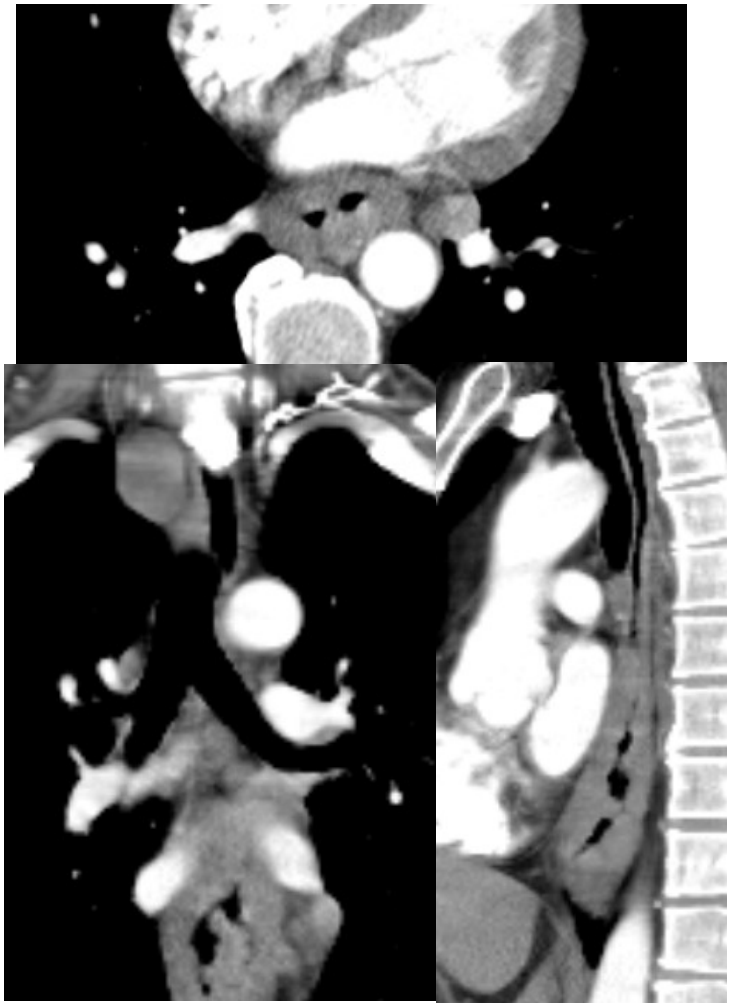
Imaging the primary



Double contrast barium swallow

- tumour length & location

Imaging the primary



Double contrast barium swallow

- tumour length & location

MDCT

- relationship to surrounding structures

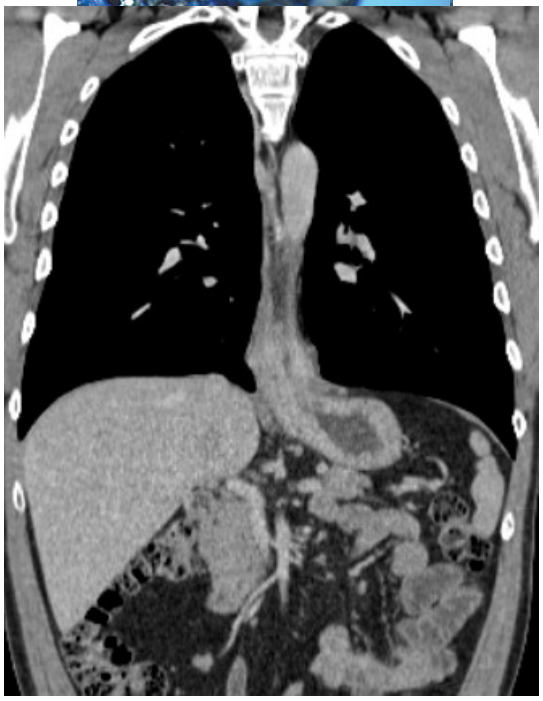
MDCT Technique

Oral contrast – 500mls

+/- carbon dioxide granules

+/- hyoscine butylbromide (Buscopan)

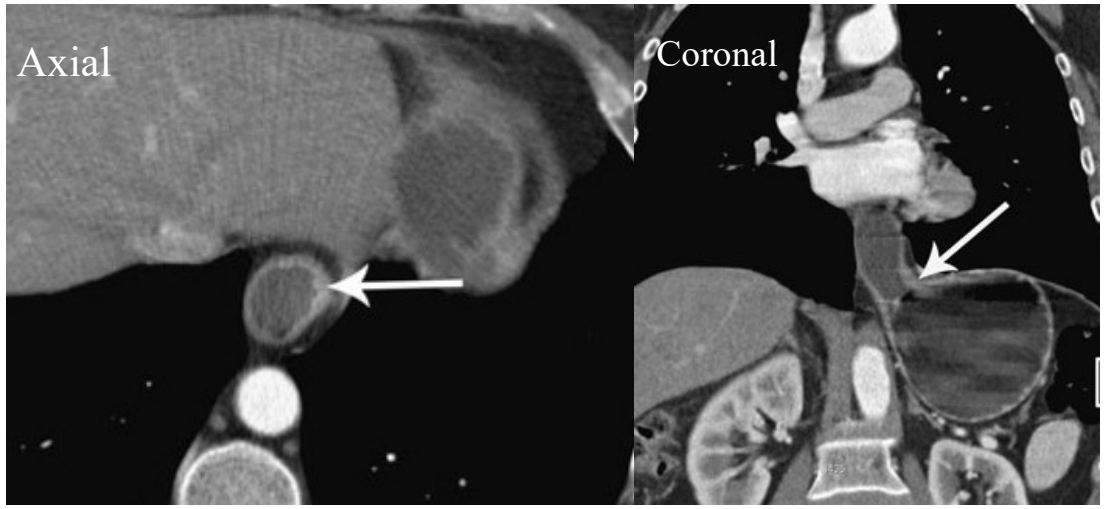
100mls water sol IV contrast 3mls/sec,
hepatic parenchymal phase



Chest & abdomen (pelvis)

Staging the primary: Hydro-MDCT

Patient preparation	Fasting
Oral contrast material	1,000–1,500 mL of water was administered slowly within 1 hour and two 3 g packets of gas-producing effervescent granules (Duplotrast, Gerot, Vienna Austria) were given immediately prior to the scanning
Hypotonia	20 mg of intravenous scopolamine
Patient position	Prone



T1 tumour correctly staged

Overall T staging accuracy 76.3%

Ba-Salamah, A., W. Matzek, et al. (2011). Eur Radiol **21**(11): 2326-2335

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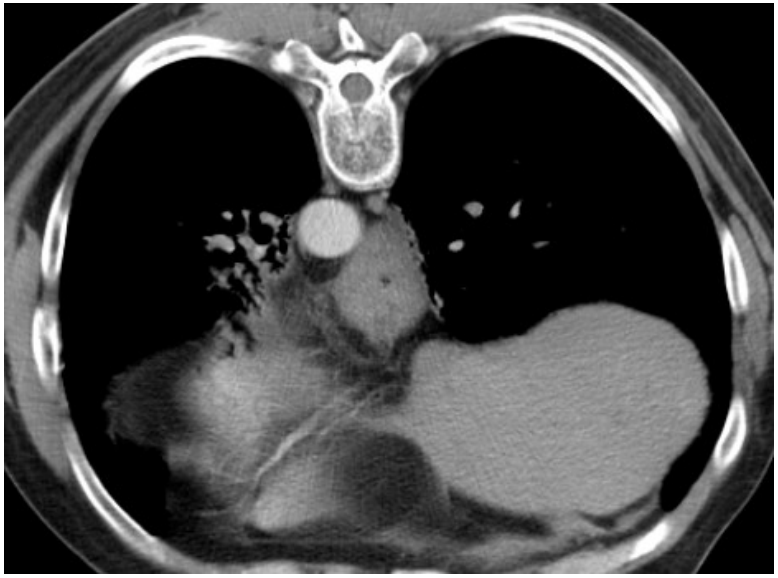
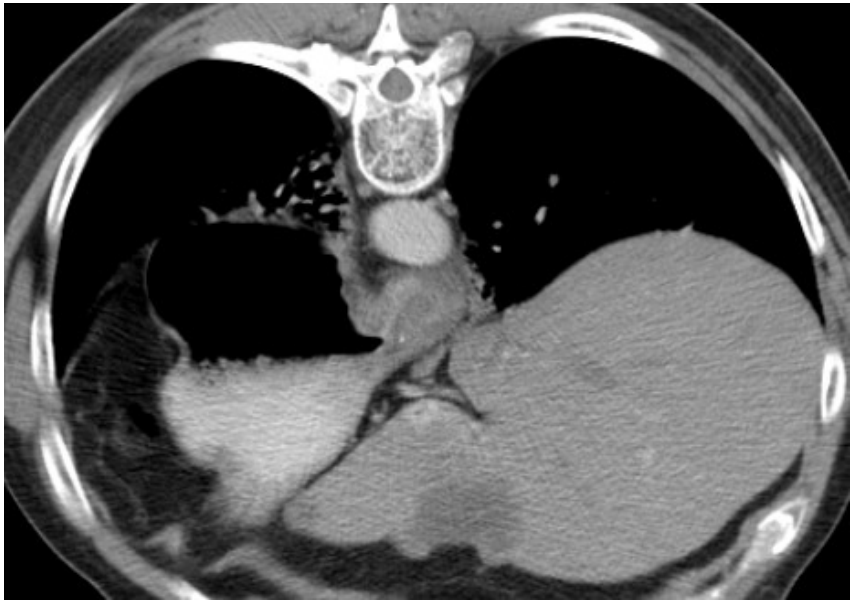
Prone imaging



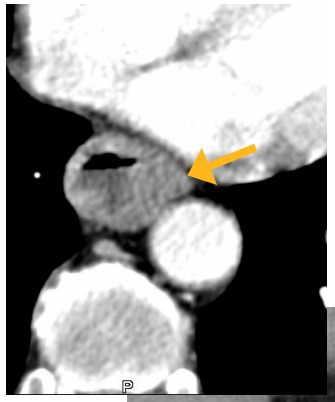


Contact versus invasion of aorta

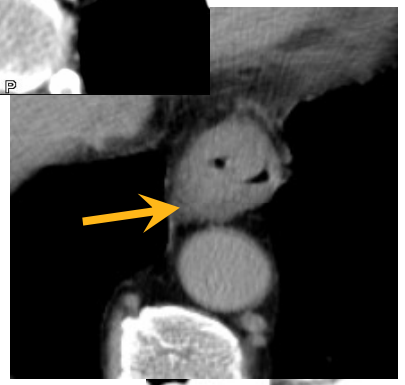
Staging the primary

Initial Staging

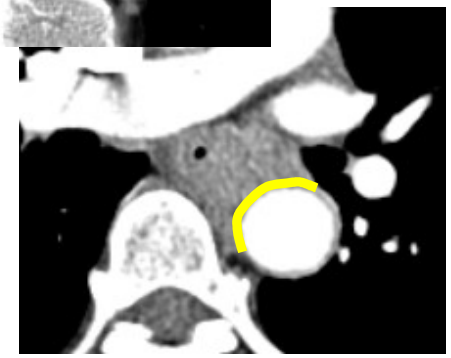
- T stage - based on wall thickness and outline
- Limited soft tissue contrast
- Poor for early tumours



pT2



pT3



pT4

T Stage	Wall thickness	Wall Contour
T2	>3mm, <5mm	Smooth
T3	5-15mm	Irregular
T4	>15mm	Contact with adjacent structure

T Staging Accuracy - 74%*

* Davies, A. R., D. A. Deans, et al. (2006). Dis Esophagus **19**(6): 496-503

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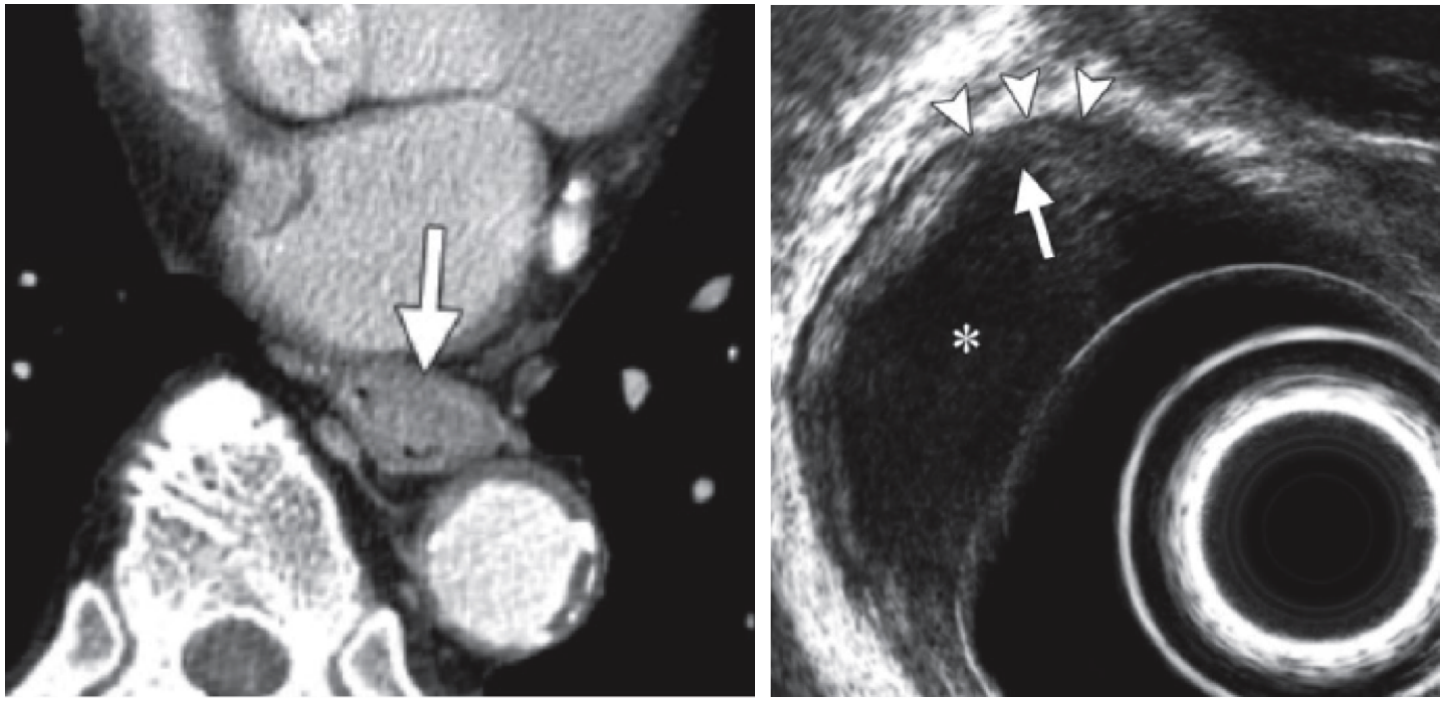
Imaging the primary

- Endoscopic Ultrasound (EUS) delineates the layers of the oesophageal wall



Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740

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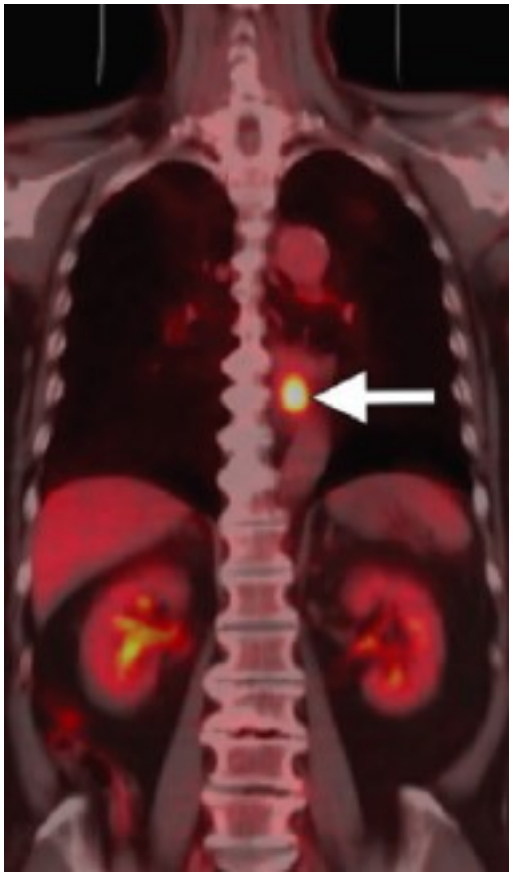
Imaging the primary – PET-CT

- 78-95% sensitivity for detecting primary tumour
- False positive due to oesophagitis & GORD
- T staging limited
- Provides information for tumour delineation
- Controversy remains over optimum segmentation method for determining target volume



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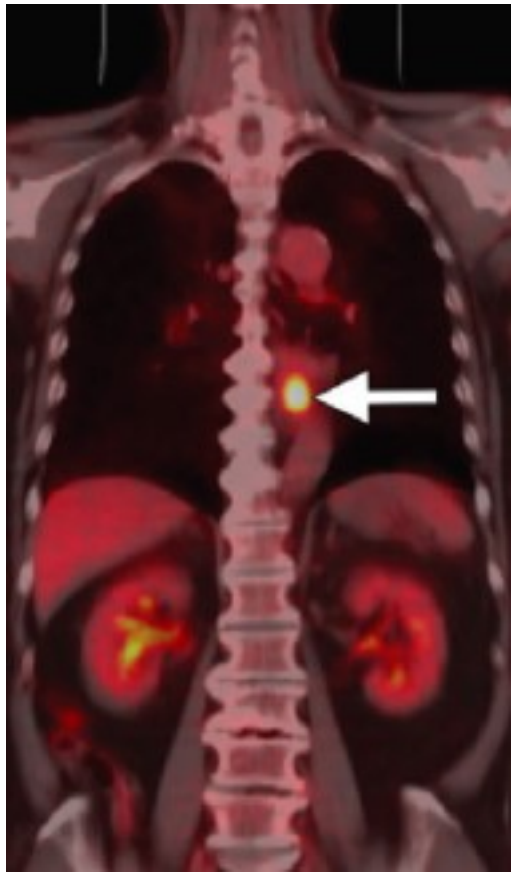
Imaging the primary – PET-CT

Utility for Radiotherapy planning

Systematic review*:

- 3/50 studies demonstrated positive correlation of PET-CT length with path
- 1/50 showed improved inter & intra observer variability
- No studies demonstrated improved locoregional control



*Muijs CT, Beukema JC, Pruim J 2010. Radiother Oncol. Nov;97(2):165-71

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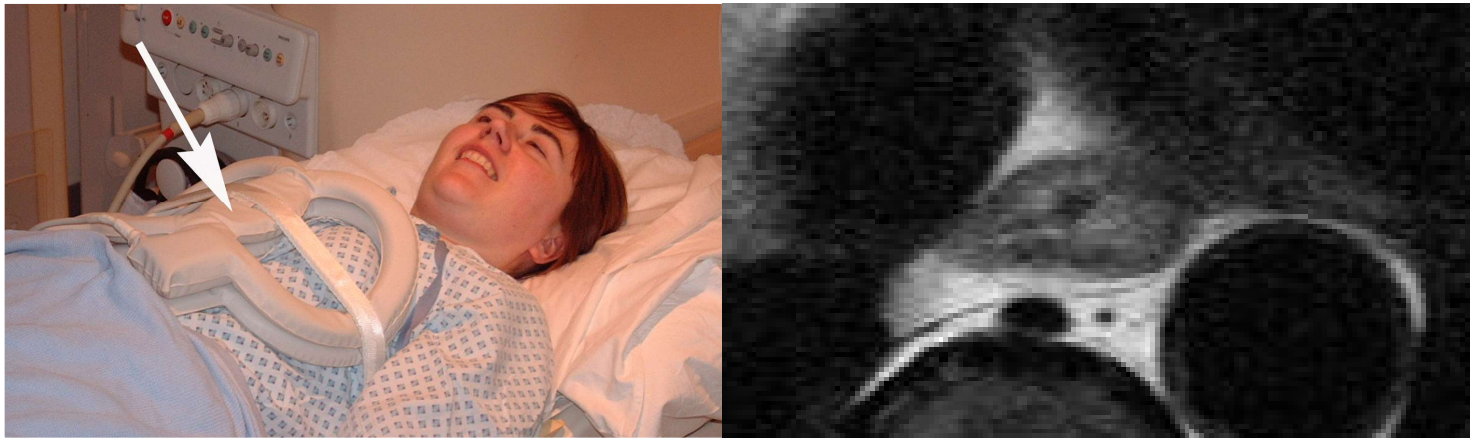
Imaging the primary: High Resolution MRI

- Advances in surface coil technology & fast imaging techniques
- Improved signal to noise
- Small field of view
- Thin slice imaging
- High Resolution Images = Voxel size 1-2mm^3

- Enables demonstration of the esophageal wall layers, allowing for local staging.

MRI Technique

External Surface coil MRI



Patient preparation

Starve for 2 hours

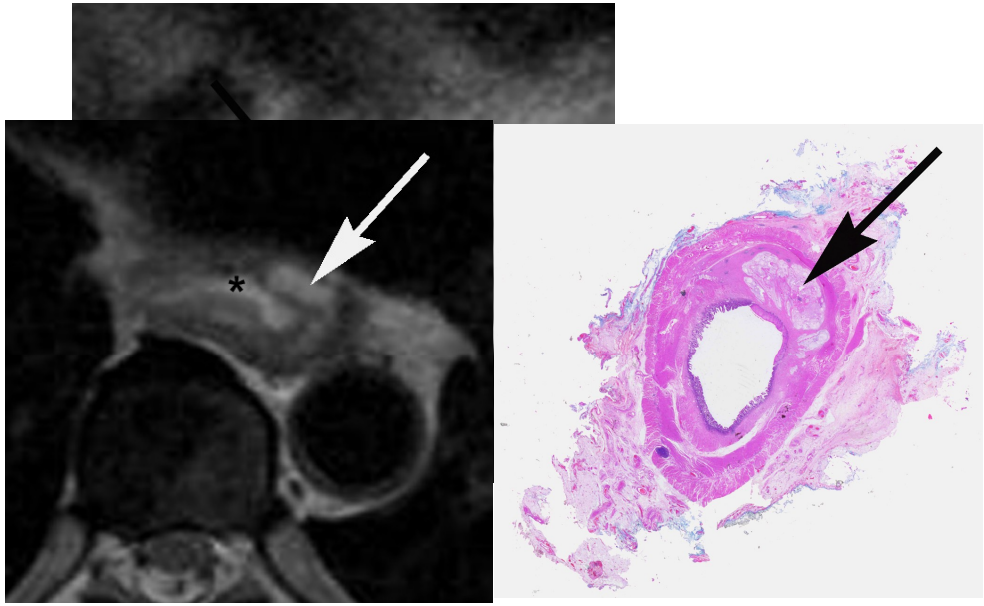
Antispasmodic

400mls water prior to scan

No requirement for IV contrast

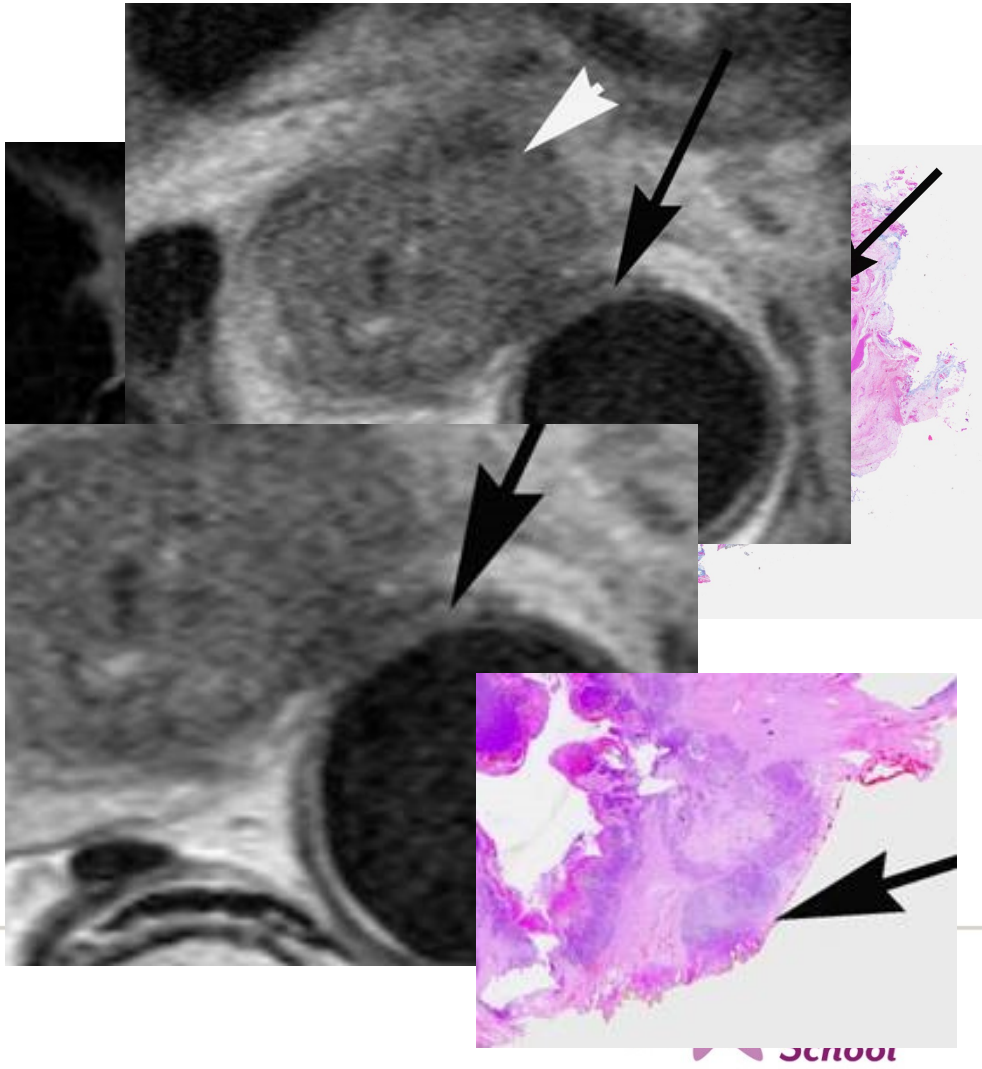
Potential advantages of MRI over MDCT

- Superior soft tissue contrast
  - Local staging
  - Tumour characterisation



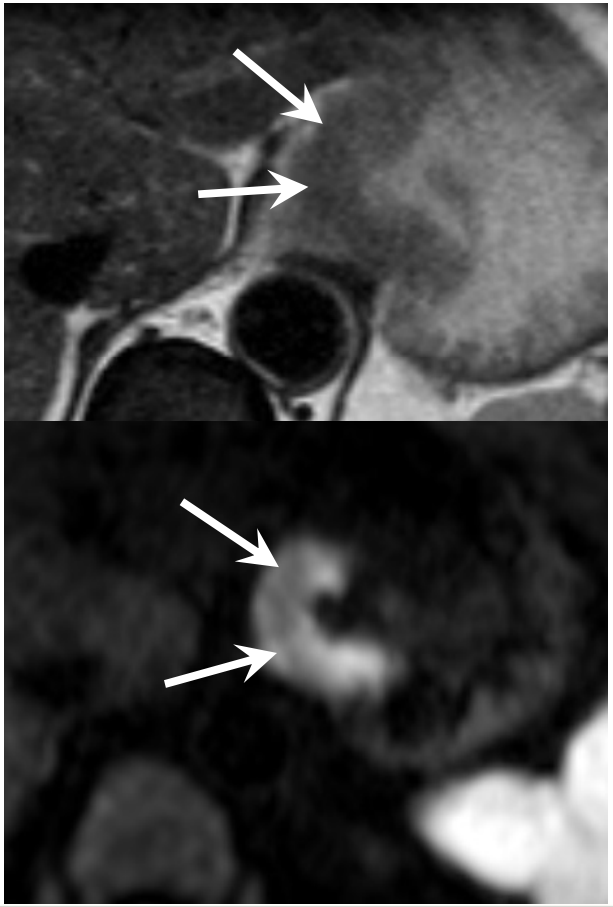
Potential advantages of MRI over MDCT

- Superior soft tissue contrast
  - Local staging
  - Tumour characterisation
- Improved assessment of the circumferential resection margin (CRM)

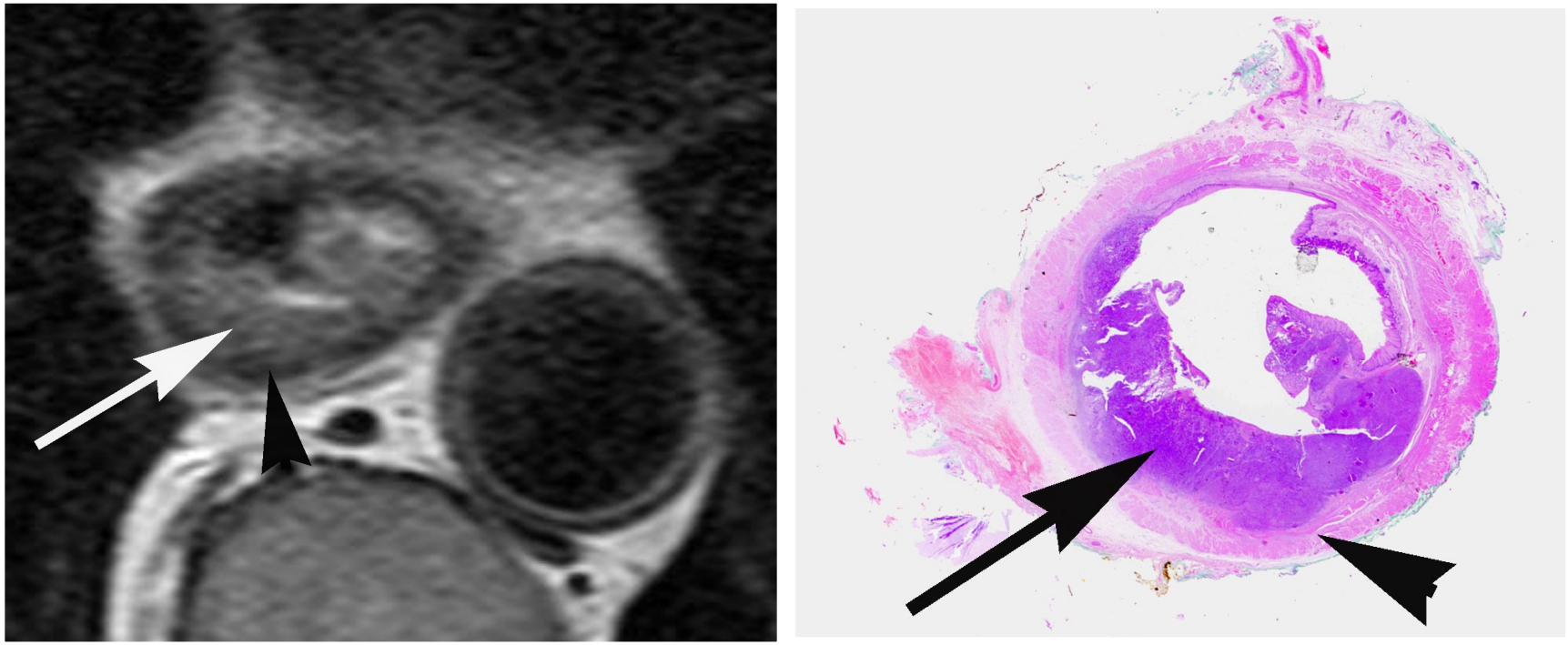


Potential advantages of MRI over MDCT

- Superior soft tissue contrast
  - Local staging
  - Tumour characterisation
- Improved assessment of the circumferential resection margin (CRM)
- Functional Information
  - Diffusion Weighted Imaging



High Resolution MRI



T2 tumour

Riddell A M, Allum W H, Thompson J N et al 2007. European Radiology: 17(2); 391-399

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MRI -T Staging

- Spatial resolution of MRI insufficient to accurately stage early tumours
- Good level of agreement with histology for ≤T2 vs ≥T3

	Path		
MRI	T= 0-2	T= 3-4	
T= 0-2	26	5	31 (44.3%)
T = 3-4	5	34	39 (55.7%)
	31 (44.3%)	39 (55.7%)	70

- Kappa for MRI 0.71
- Kappa for EUS 0.57 (post chemotherapy)

MRI - Prediction of Resectability

	Path Margin		
	Positive (no resection)	Negative	Total
MRI Positive	17(5)	5	22
Negative	9	44	53
Total	26	49	75

Correlation with Path for resected tumours:

Sensitivity	65%
Specificity	90%
PPV	77%
NPV	83%

Accuracy with MRI = 61/75, 81%

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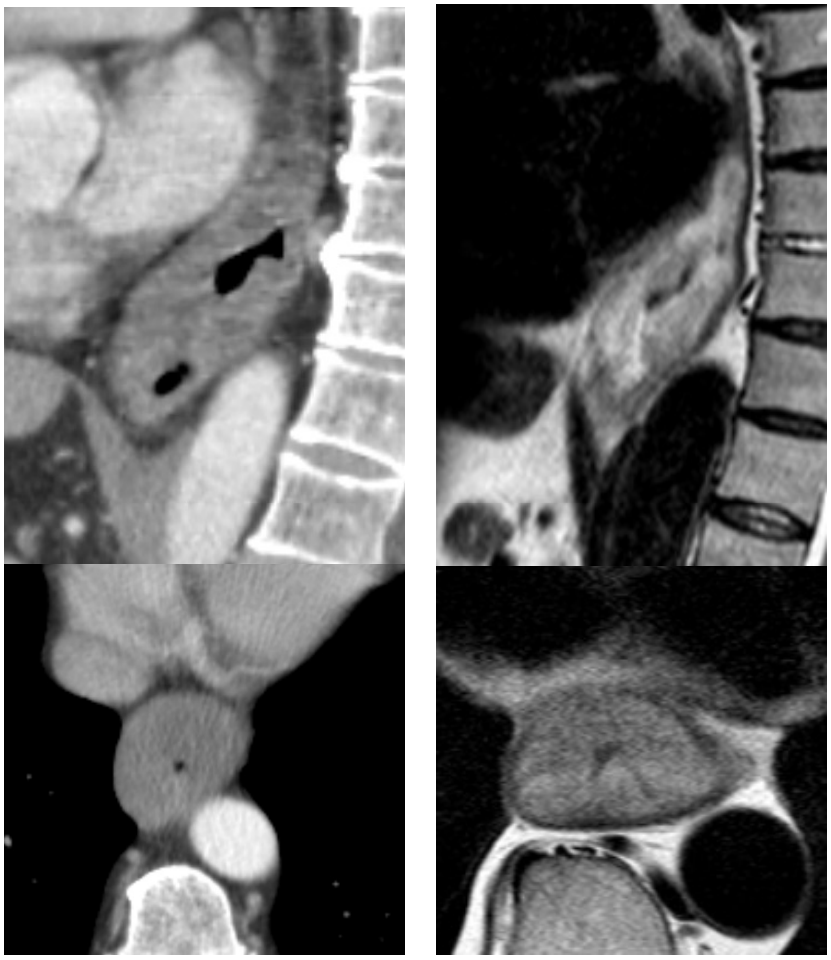
Imaging the primary

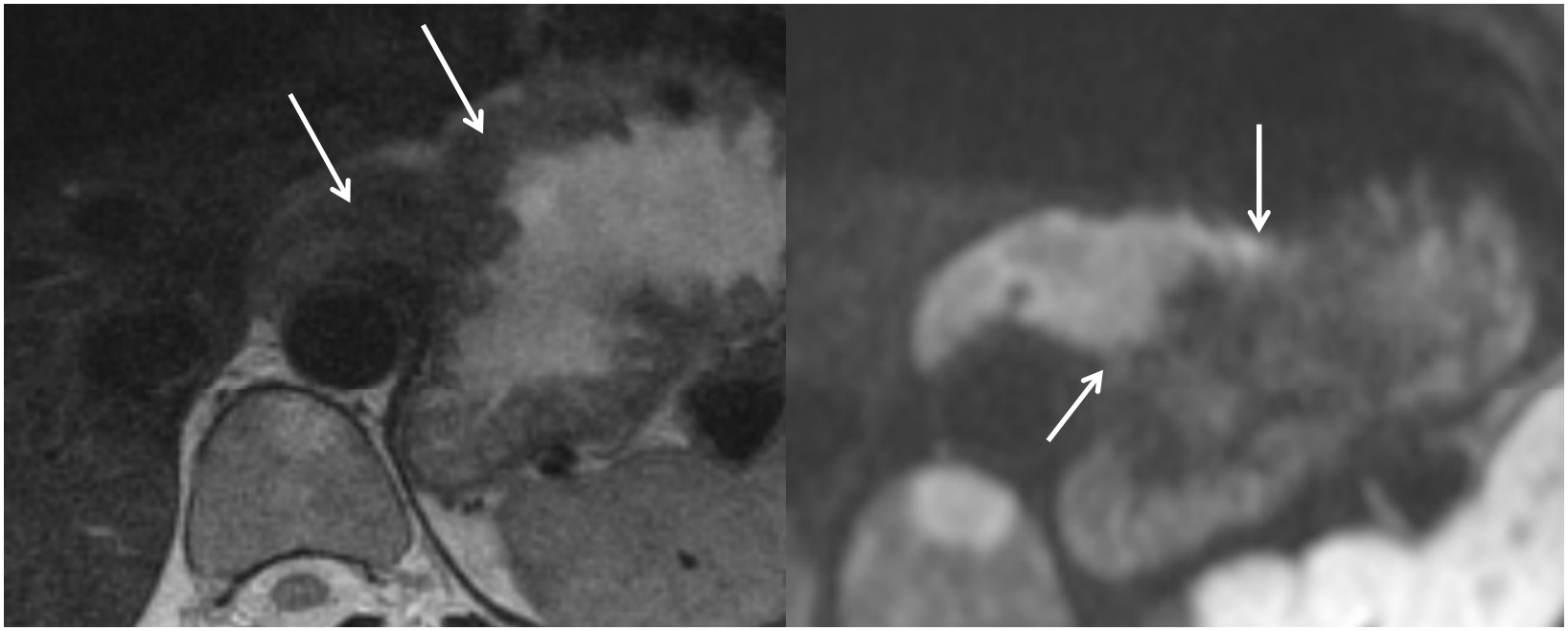
Tumour delineation

- Radiotherapy & Surgical planning



CT T2W MRI

Tumour delineation – DWI MRI

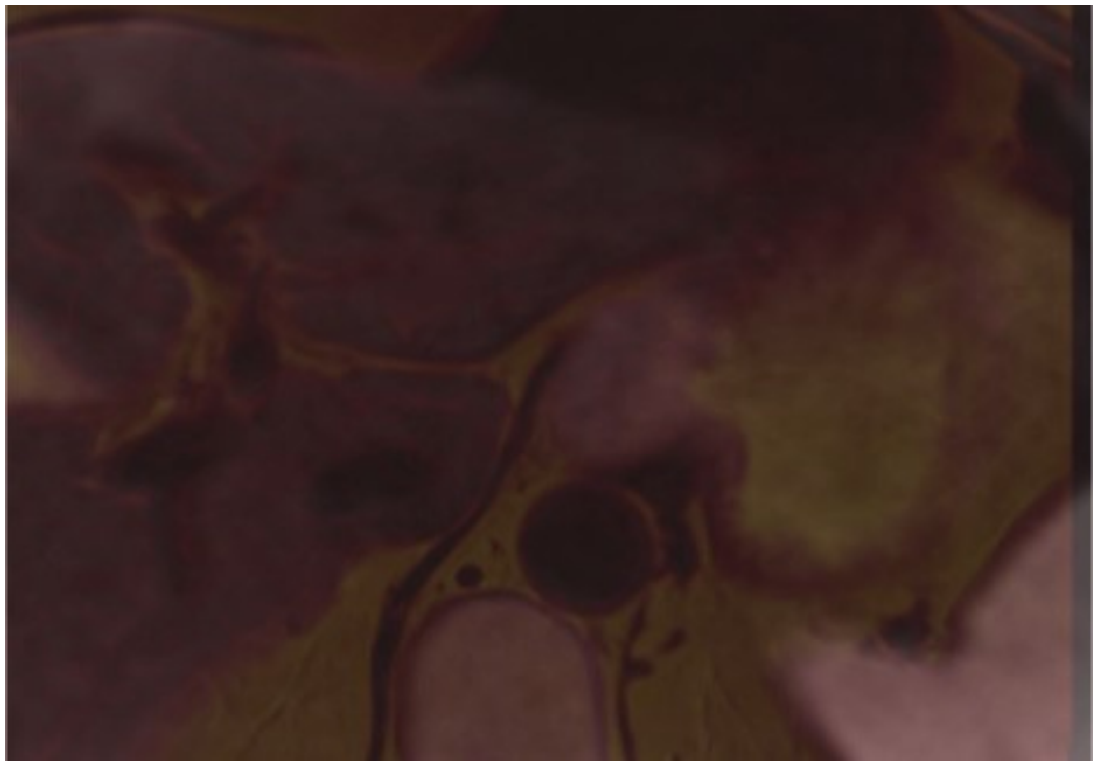


T2W

DWI, b= 500

DWI Sequence demonstrates areas of increased cellularity

Tumour delineation – Fused MRI



Fused T2W MRI with DWI

LYMPH NODES

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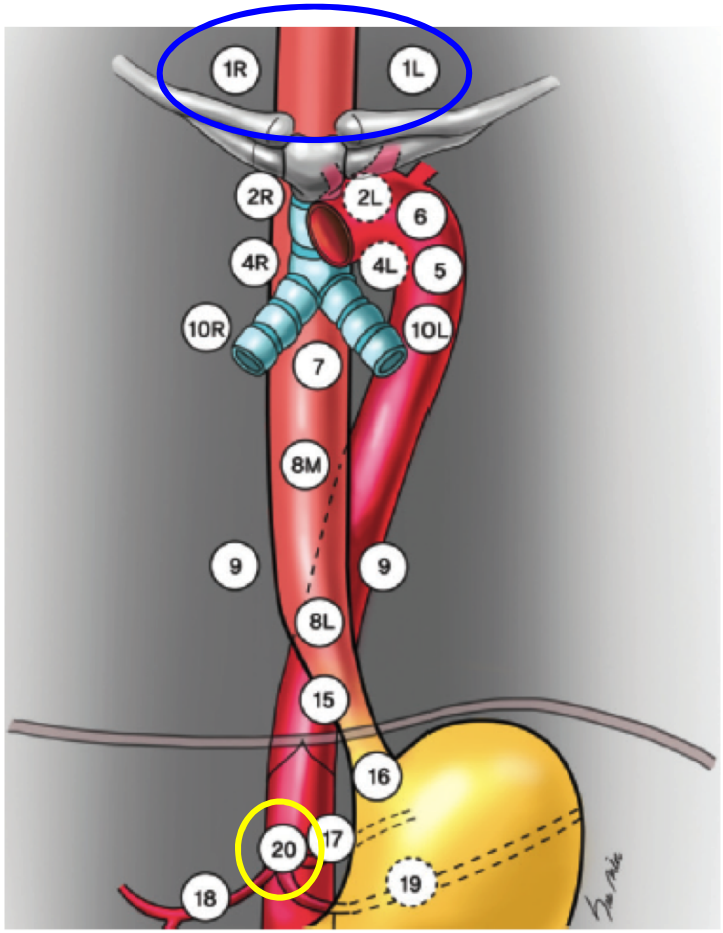
Anatomy: regional nodal stations



- Important prognostic factor
- Extensive submucosal network of lymphatics leads to potential early longitudinal spread to lymph nodes
- TNM7 – includes supraclavicular lymph nodes as regional nodes
- *TNM8 – excludes supraclavicular*
- TNM7 – includes coeliac axis nodes as regional
- *TNM8 – includes coeliac nodes*

Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740

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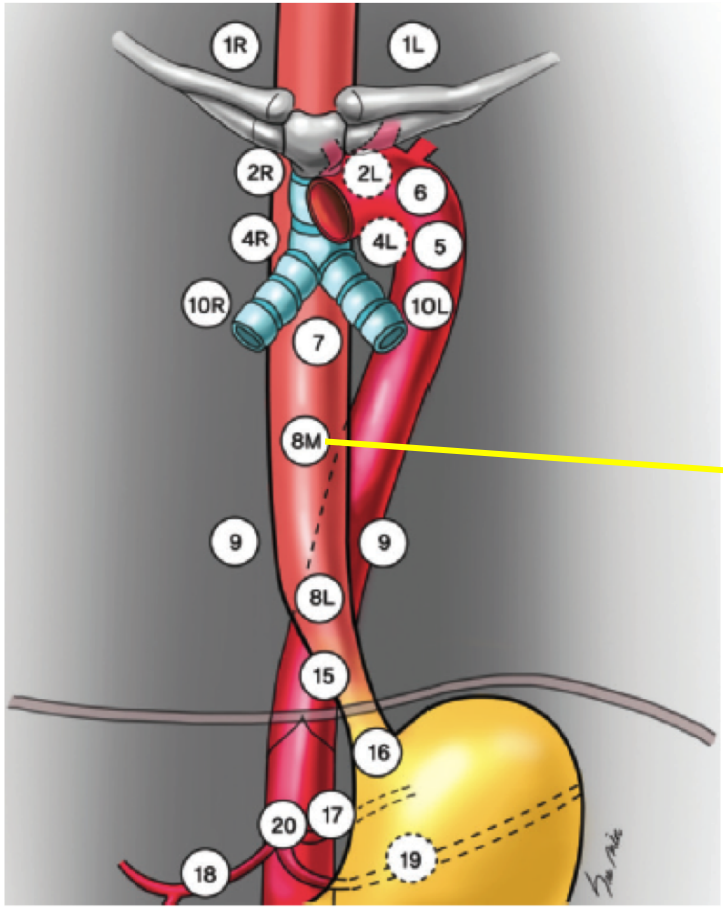
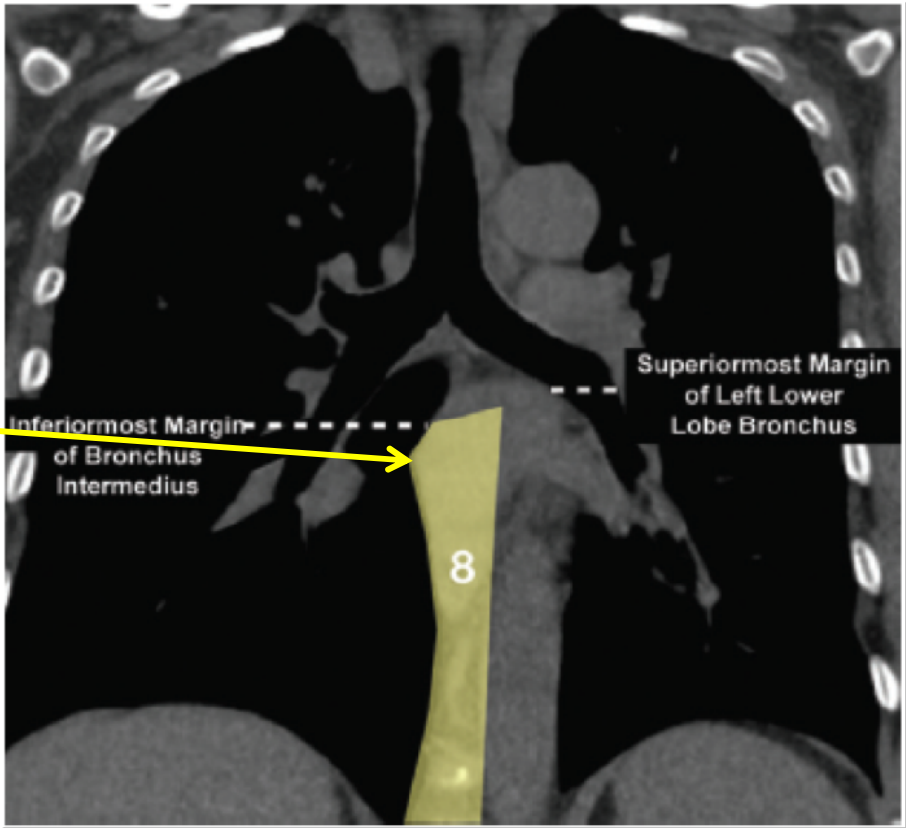
Anatomy: regional nodes





Peri-oesophageal lymph nodes – station 8

Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740
El-Sherief, Lau C, Wu C et al. 2014 Radiographics; 34:1680-1691

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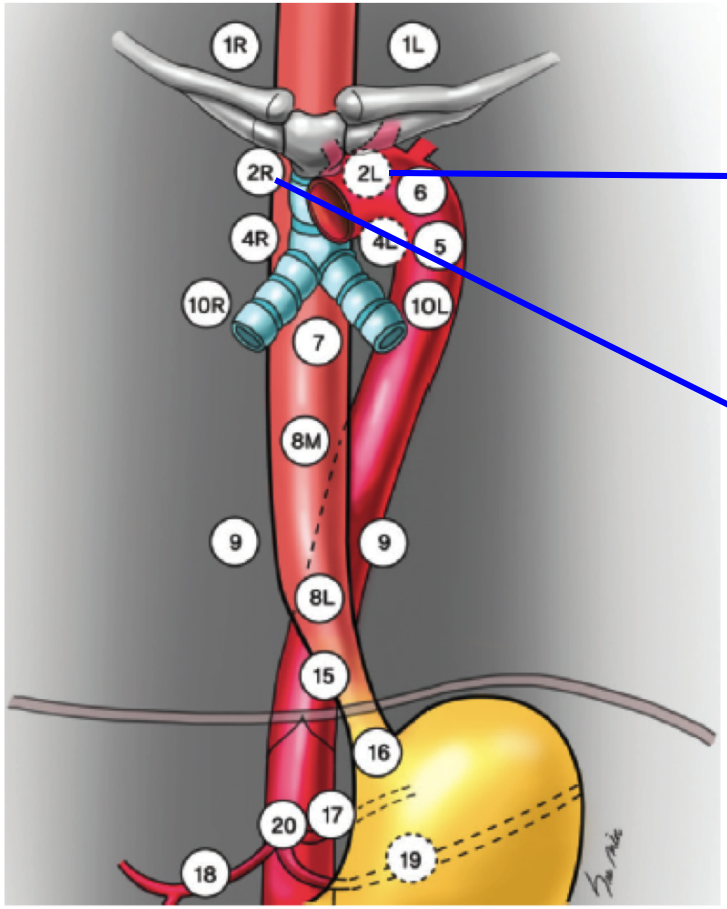
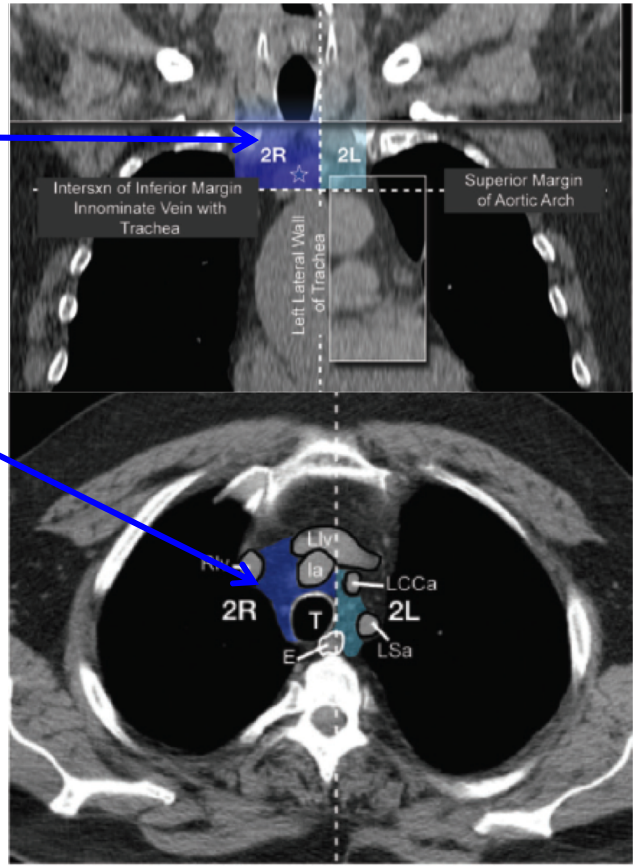
Anatomy: regional nodes





Thoracic Inlet: Level of the Brachiocephalic vein / sternoclavicular joint

Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740
El-Sherief, Lau C, Wu C et al. 2014 Radiographics; 34:1680-1691

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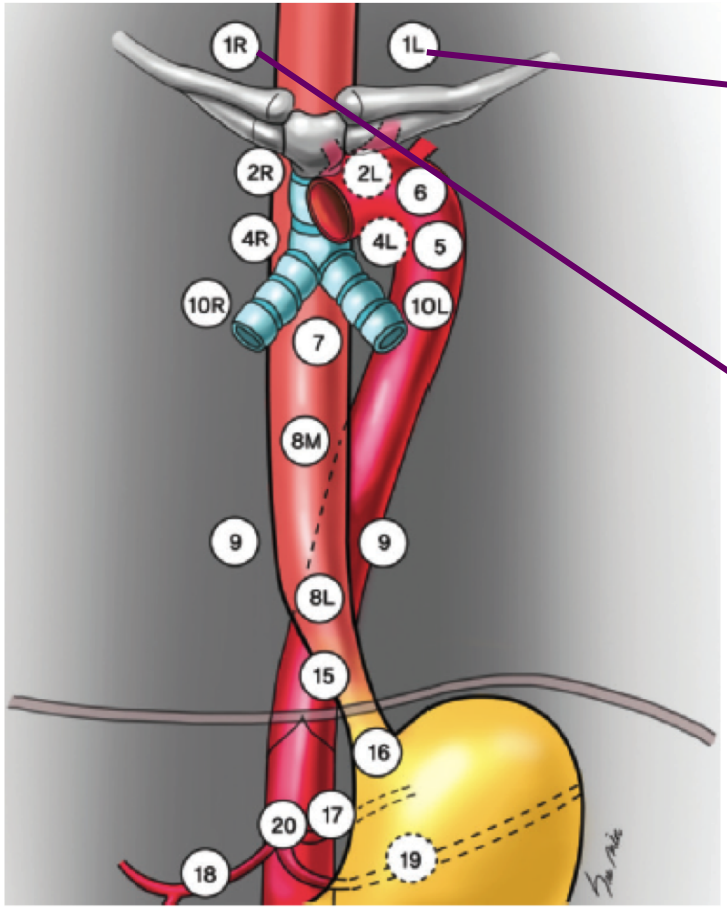
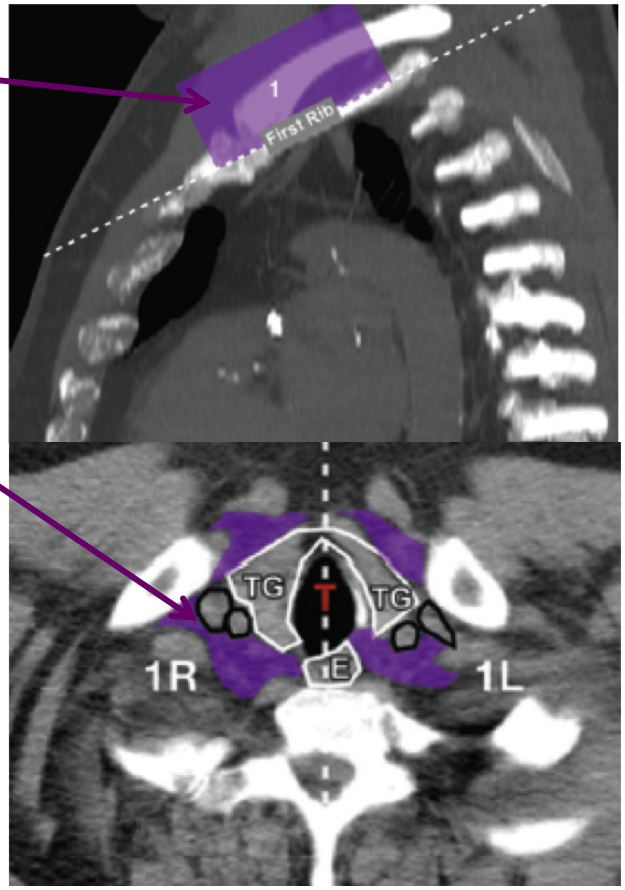
Anatomy: regional nodes





Supraclavicular fossa: Level of the Thyroid Cartilage

Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740
El-Sherief, Lau C, Wu C et al. 2014 Radiographics; 34:1680-1691

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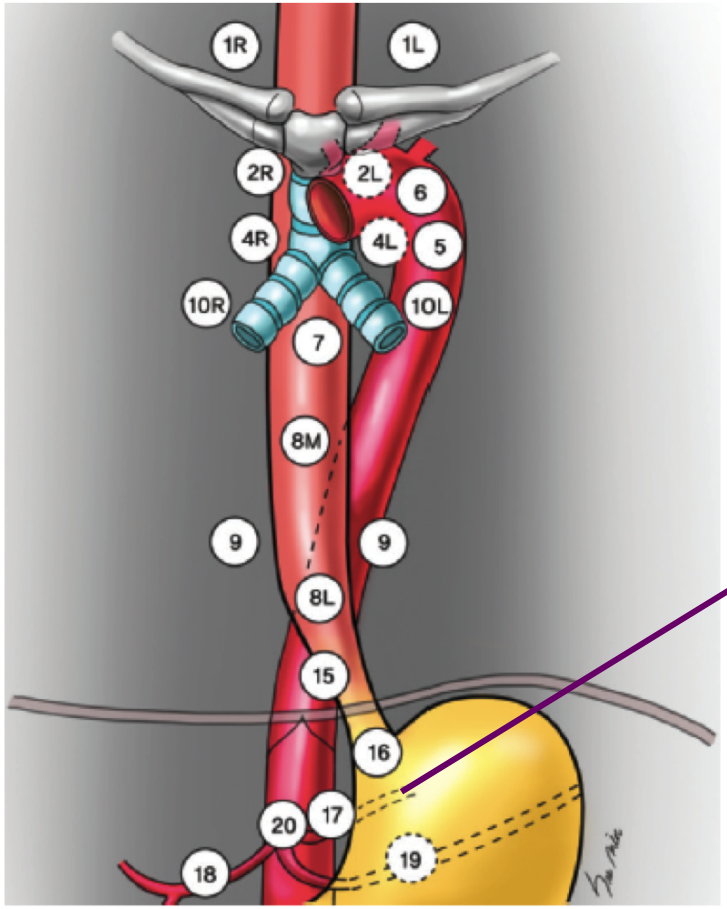
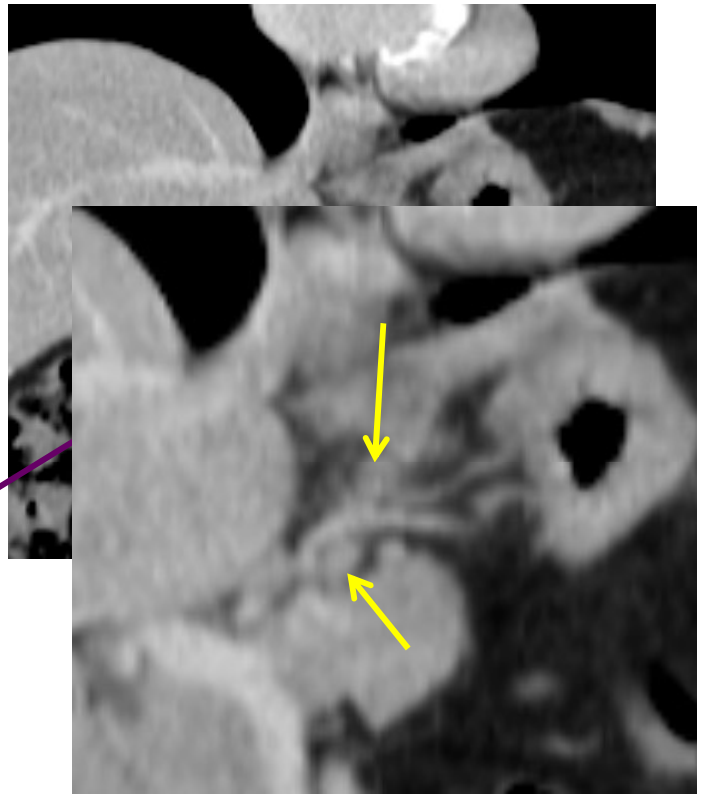
Anatomy: regional nodes



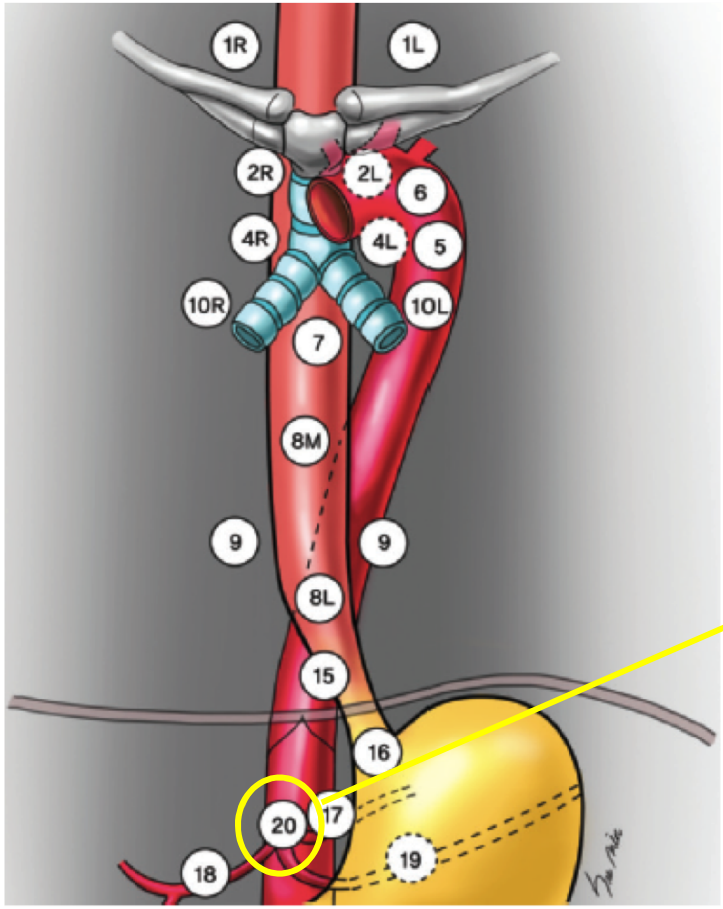


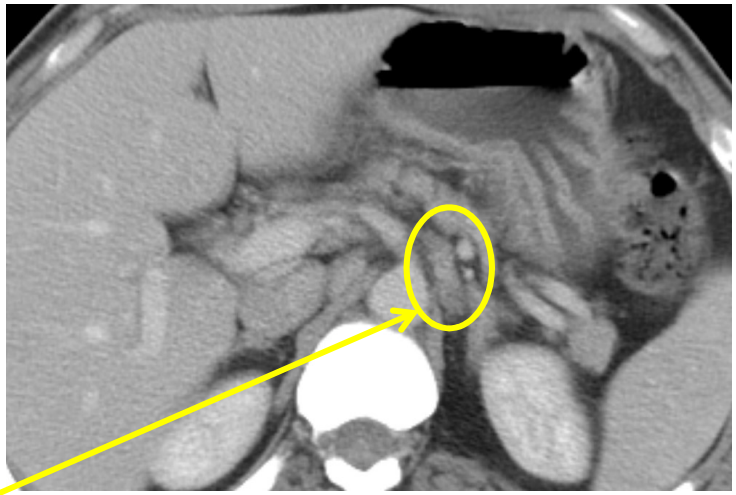
Left gastric artery node

Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740

ESTRO School

Anatomy: regional nodal stations





Coeliac axis lymph node

Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740

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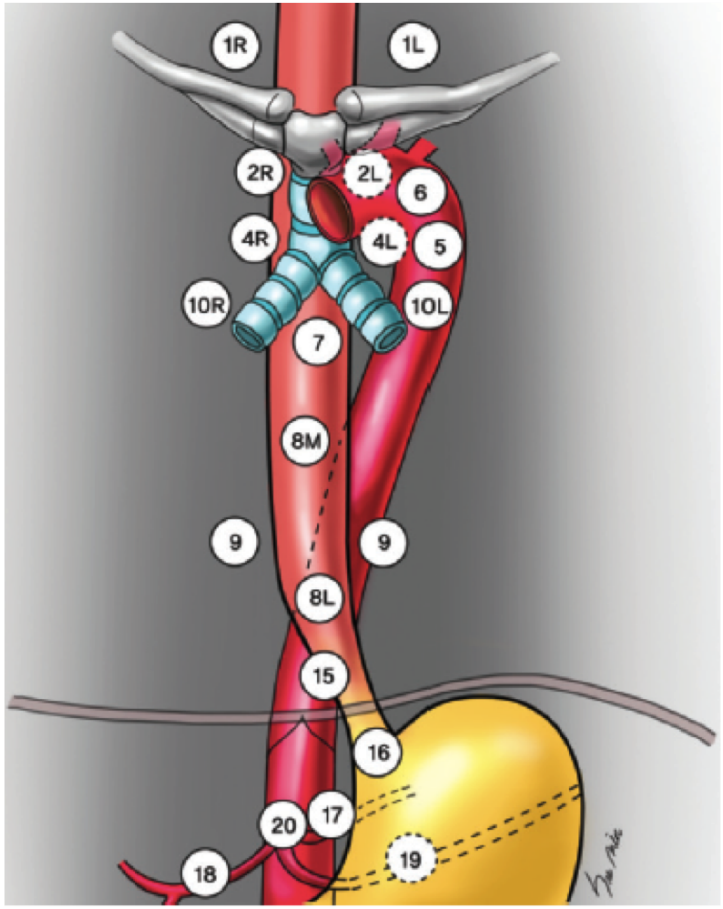
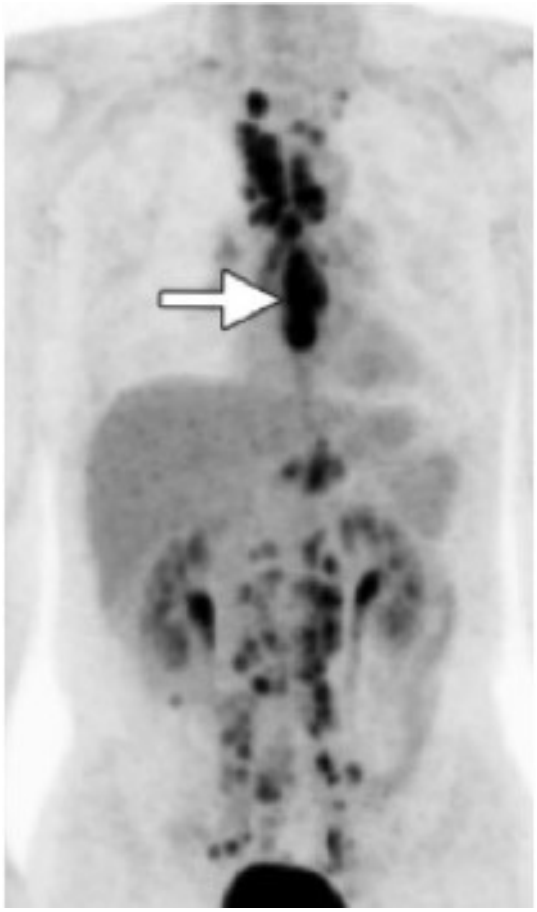
Anatomy: regional nodal stations – PET-CT





Hong SJ, Kim T J, Nam KB 2014. Radiographics; 34:1722-1740

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Summary

Identification of anatomical landmarks

- Enables accurate location of primary & involved nodal stations

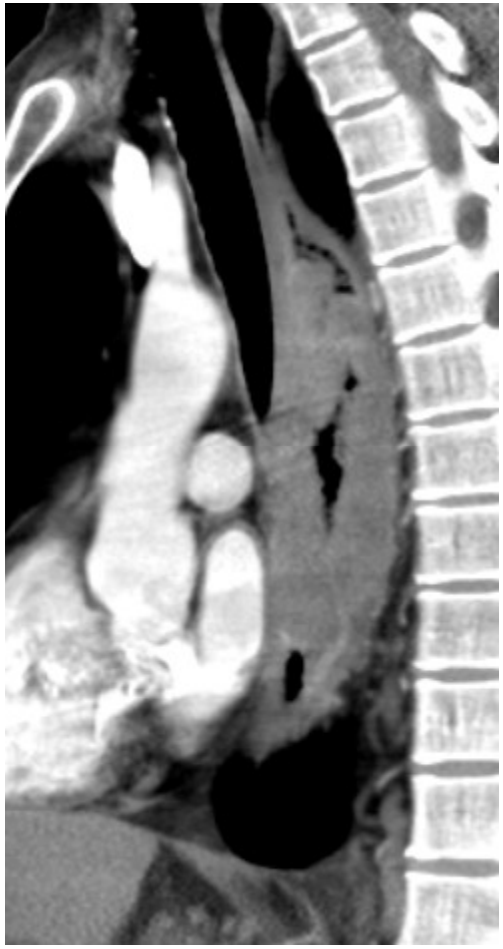
Multimodality approach to imaging

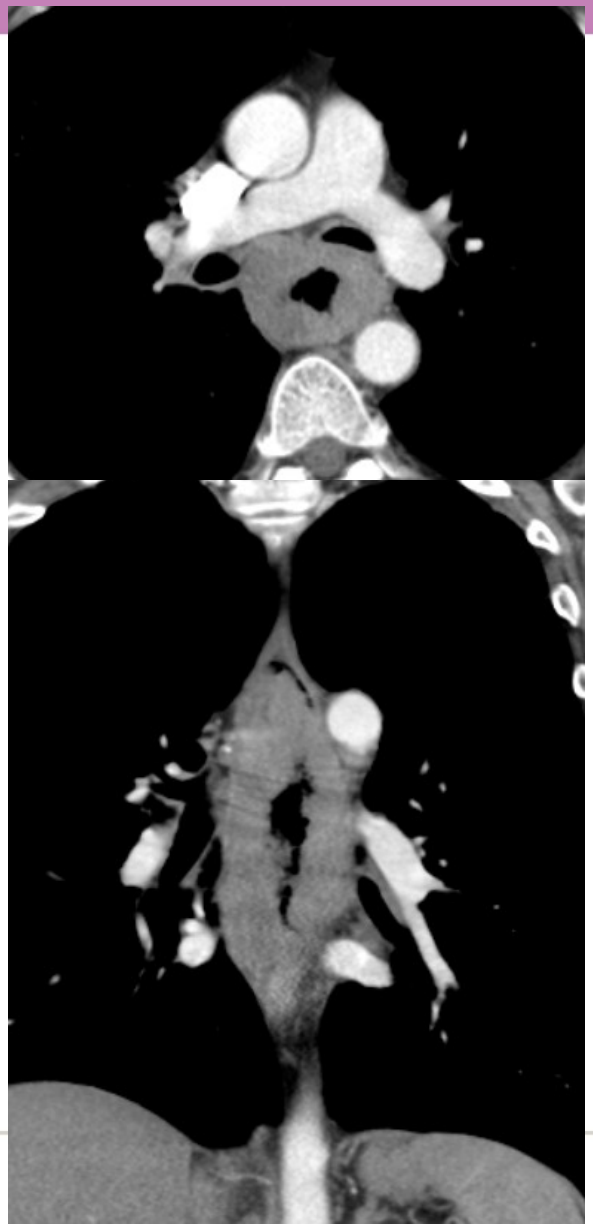
- MDCT
- PET-CT can refine identification and staging
- MRI likely to be used increasingly in the future

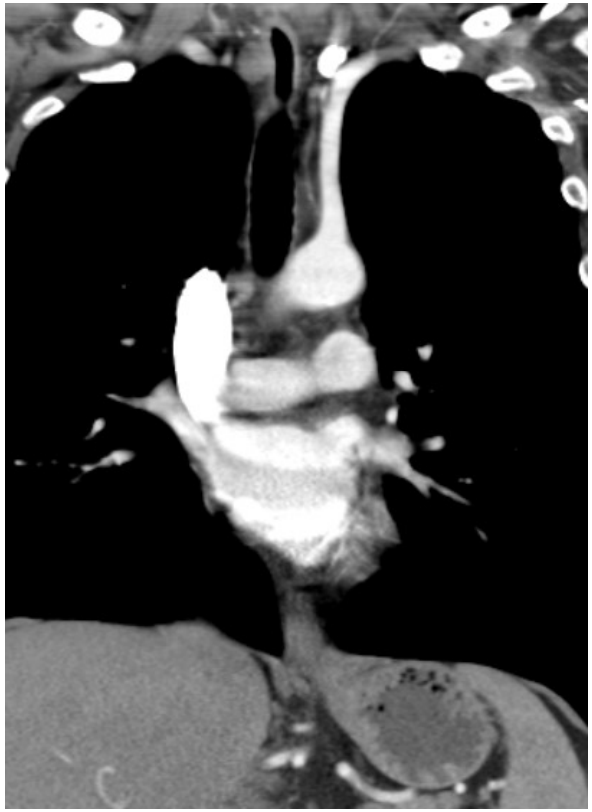
Quiz

Male patient presenting with dysphagia

Quiz







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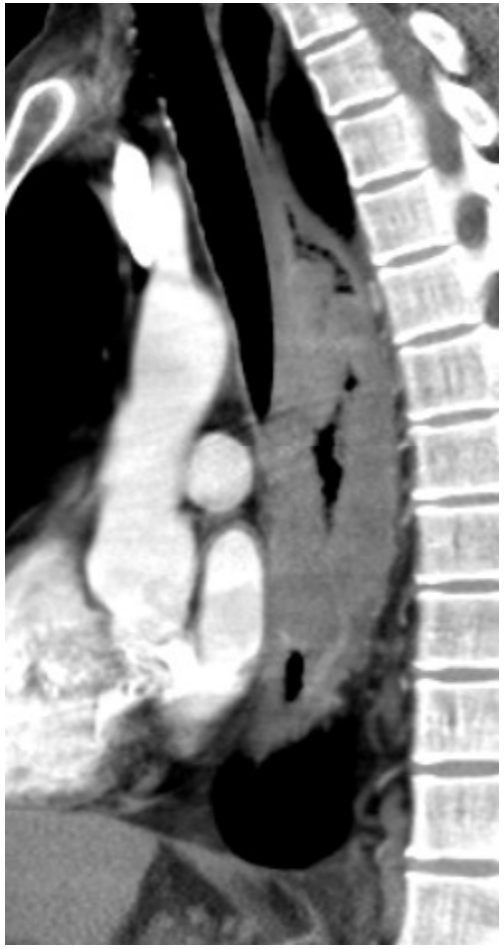
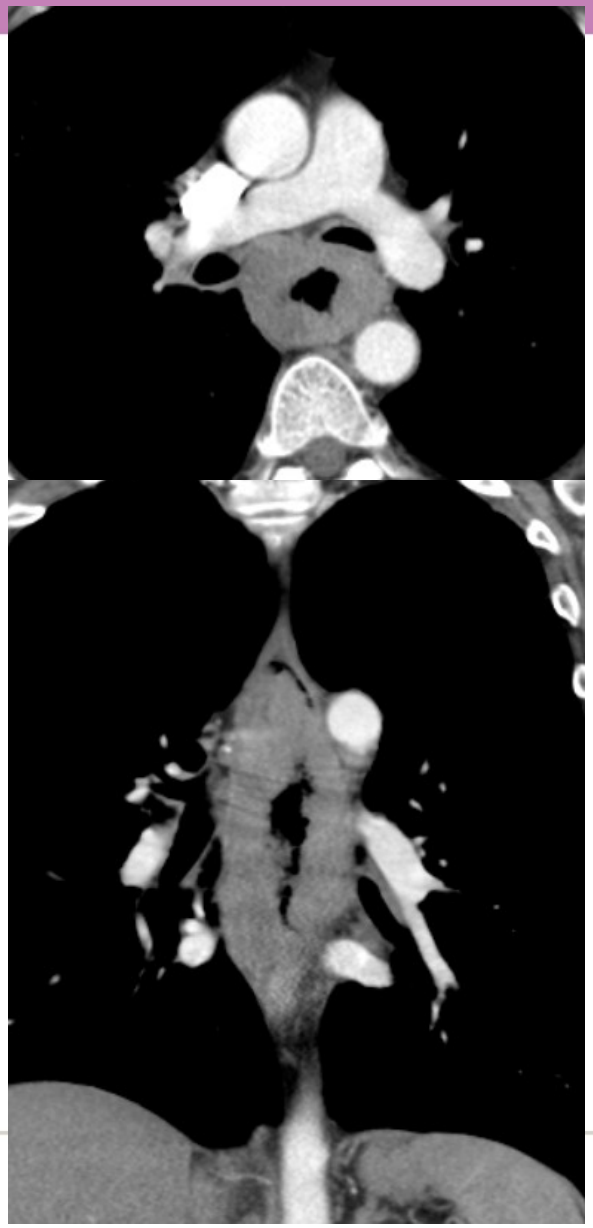
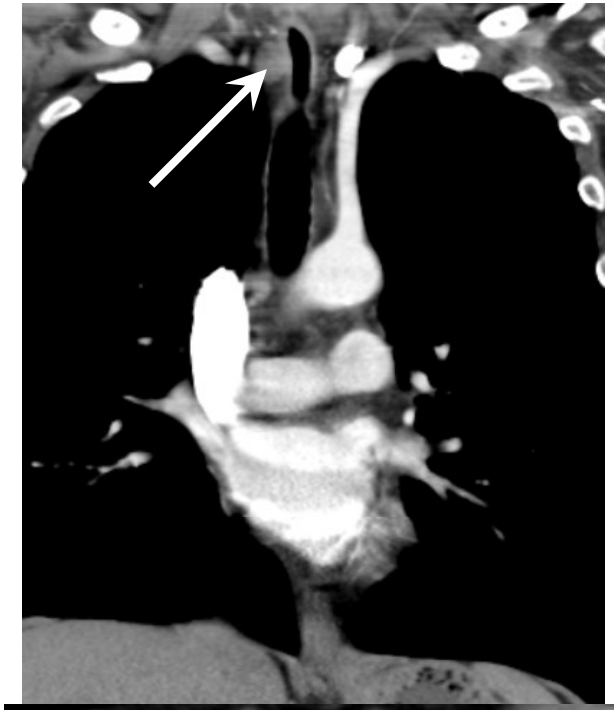
Quiz

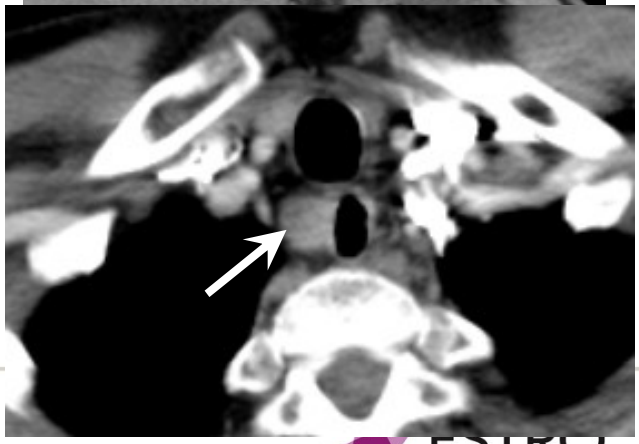
- Describe the location of the tumour
- Stage the tumour

Quiz









Quiz

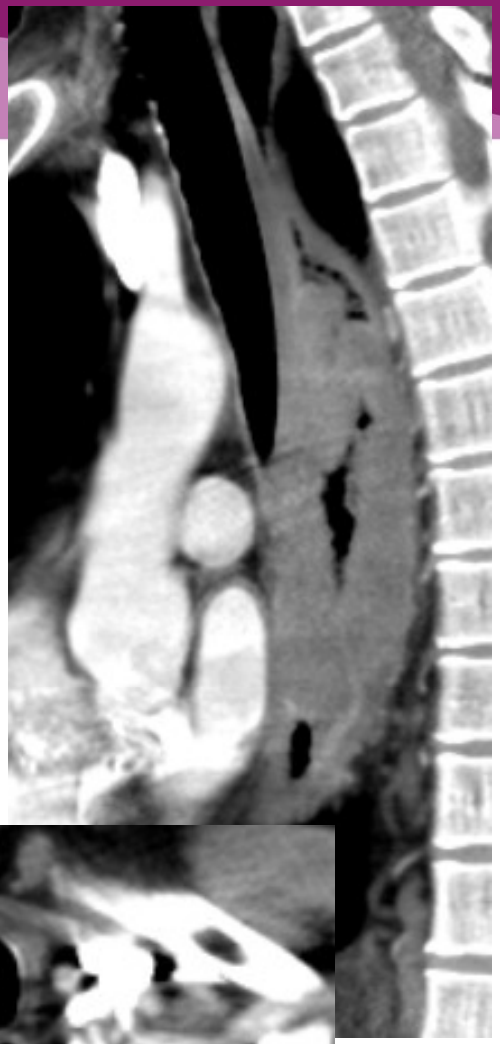
Location

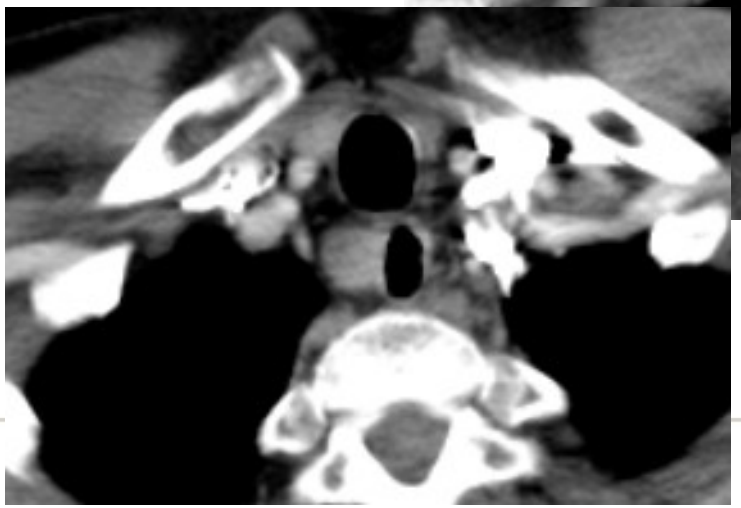
mid & lower oesophagus

Tumour Stage

Bulky T3 N1

Node at station 1





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Thank You

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Recommendation for sub-site delineation by stage and tumor position

Prof Oscar Matzinger
Chef de service, service interdisciplinaire de cancérologie, Vevey, Switzerland
Médecin Agréé, service de radio-oncologie, CHUV

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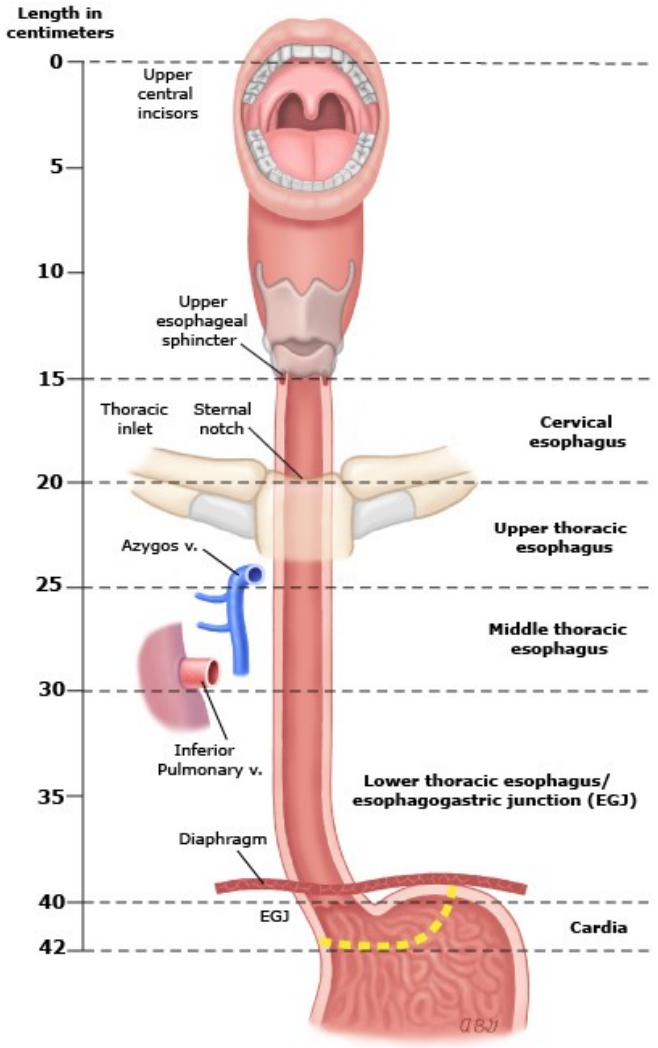
Sub-site Anatomy Oesophagus



Exact measurements depend on body size and height

AJCC: American Joint Committee on Cancer

Rice TW, Kelsen D, Blackstone EH, et al. Esophagus and esophagogastric junction. In: AJCC Cancer Staging Manual, 8th Ed, Amin MB (ed), Springer Science+Business Media, LLC, New York, 2017.

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Sub-site Anatomy Oesophagus

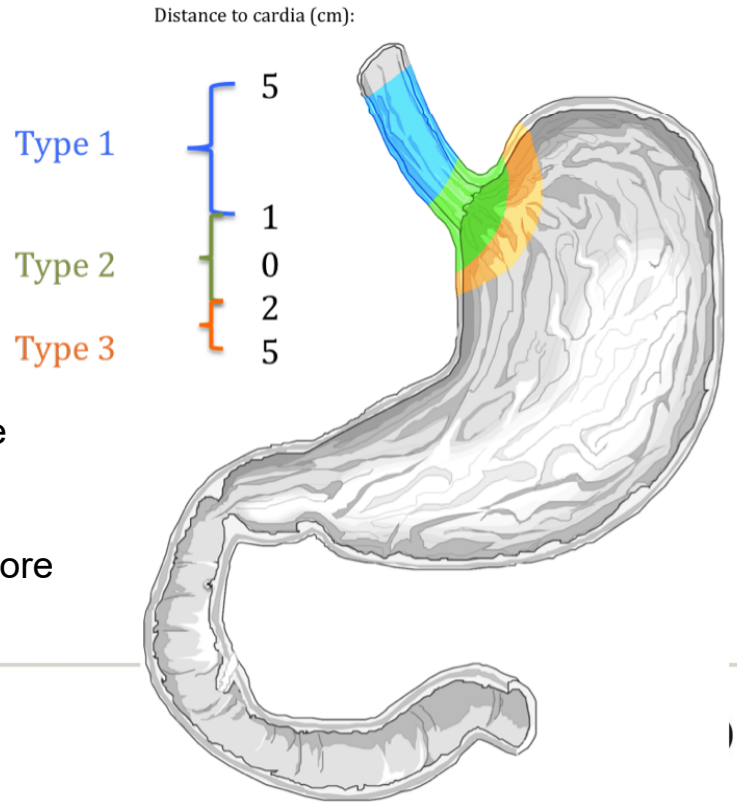
Gastroesophageal junction

Based on the anatomic location of the tumour centre three subtypes can be defined :

Type I tumours have their tumour centres more than 1 cm above the anatomical gastroesophageal junction.

Type II tumours are the true carcinomas of the cardia and have their tumour centres located within 1 cm oral and 2 cm aboral of the anatomical gastroesophageal junction.

Type III tumours have their tumour centre more than 2 cm but not more than 5 cm below the anatomical gastroesophageal junction.



AJCC: staging scheduled in the US on 01.2018.
UICC: January 1, 2017

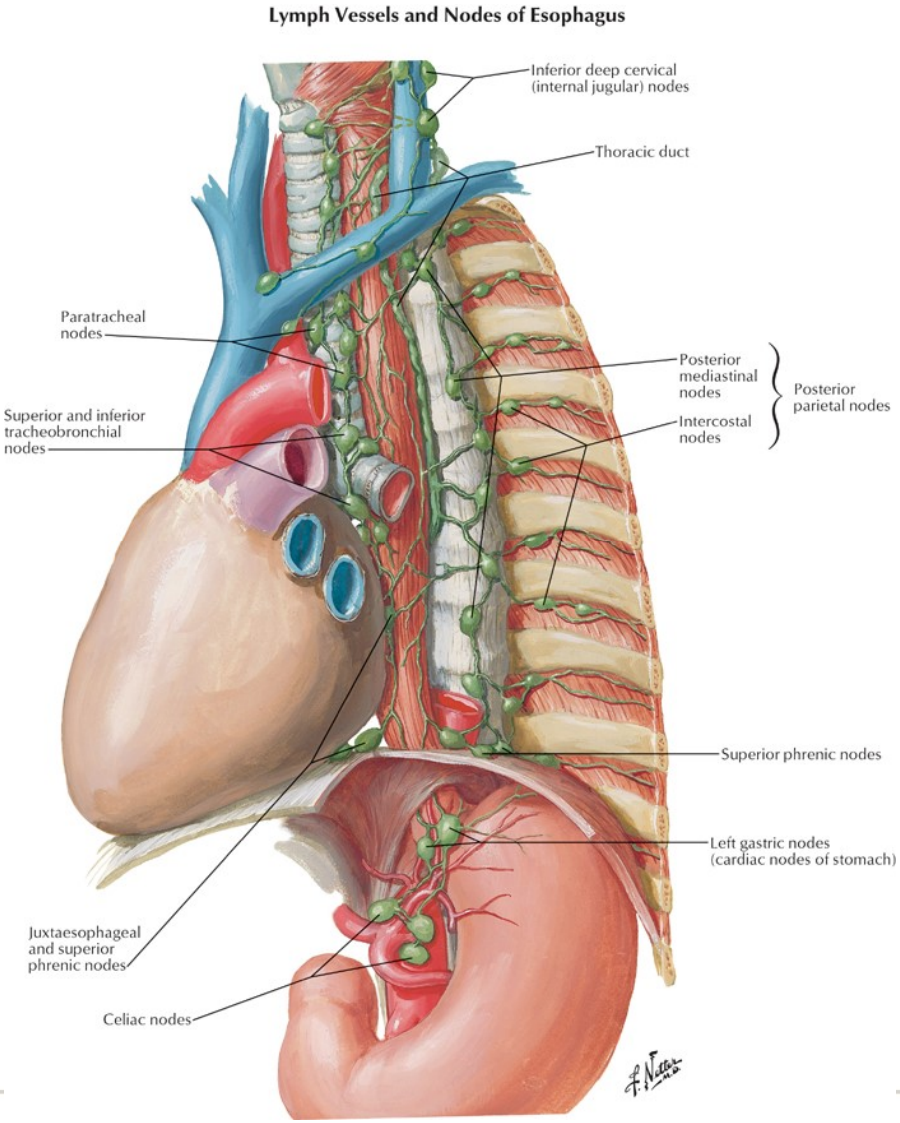
EGJ tumors:

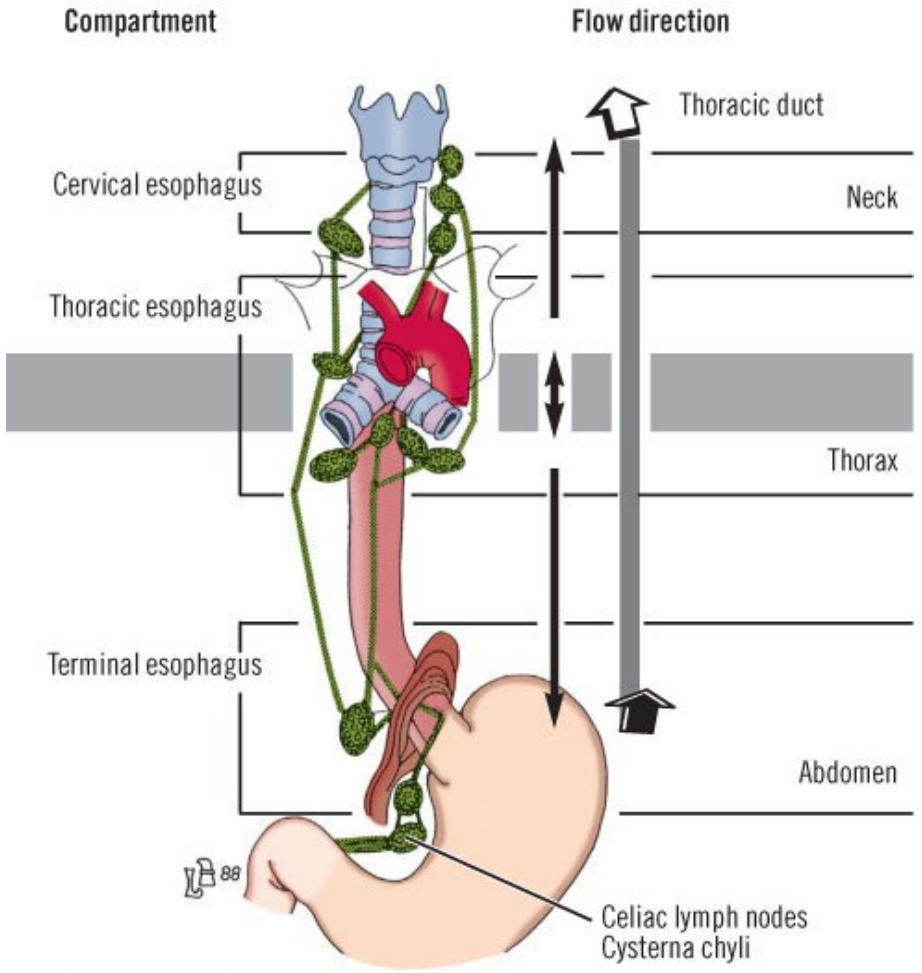
tumor epicenter no more than 2 cm into the proximal stomach are staged as
➔ esophageal cancers

epicenter located more than 2 cm into the proximal stomach are staged as
➔ stomach cancers

all cardia cancers not involving the EGJ, even if within 2 cm of the EGJ
➔ stomach cancers

Lymphatic drainage





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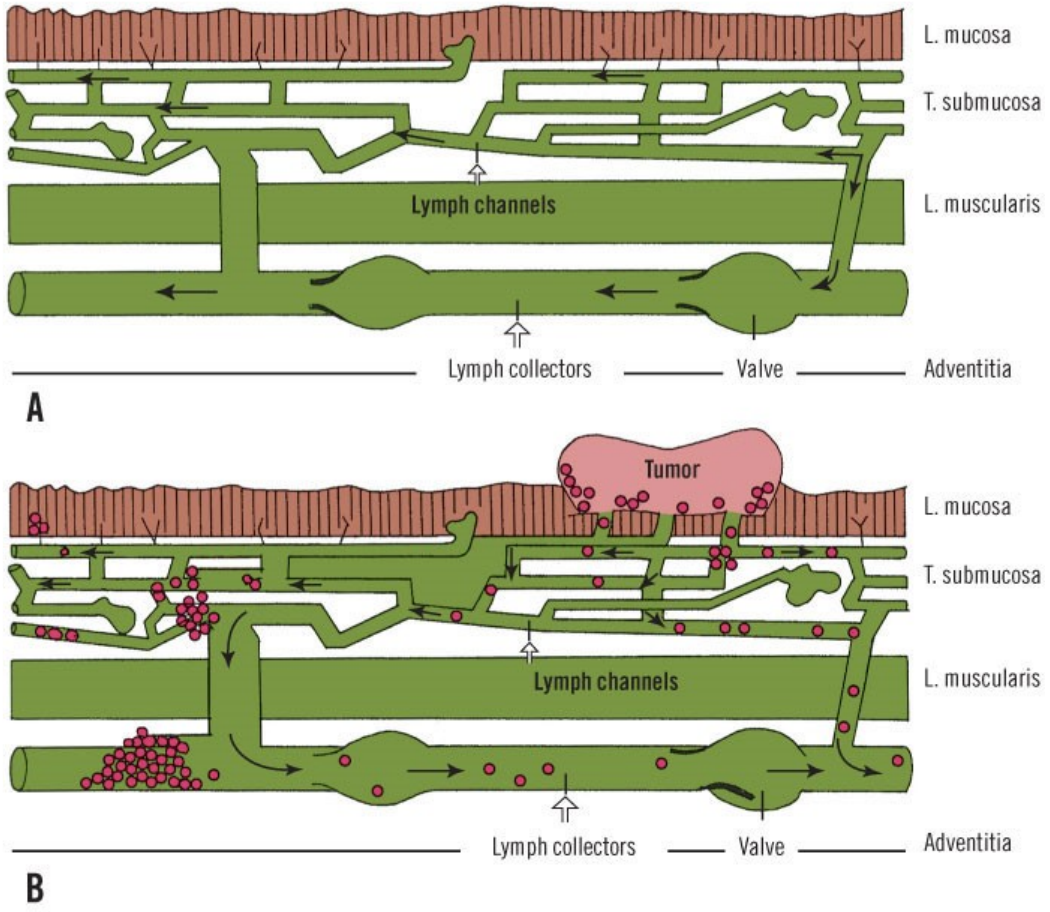
Lymphatic drainage (2)



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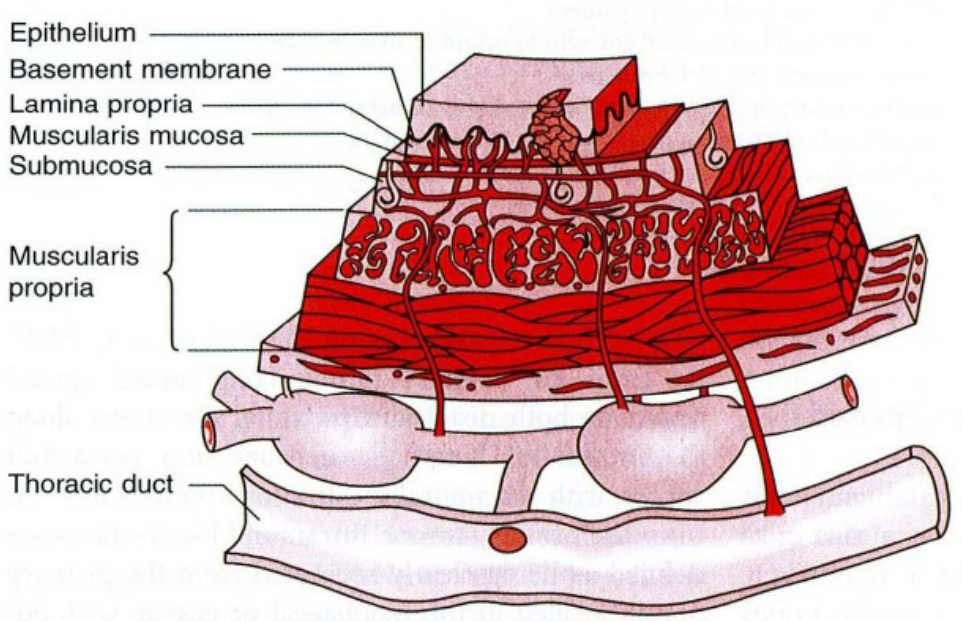
Regional lymph node involvement and CTV

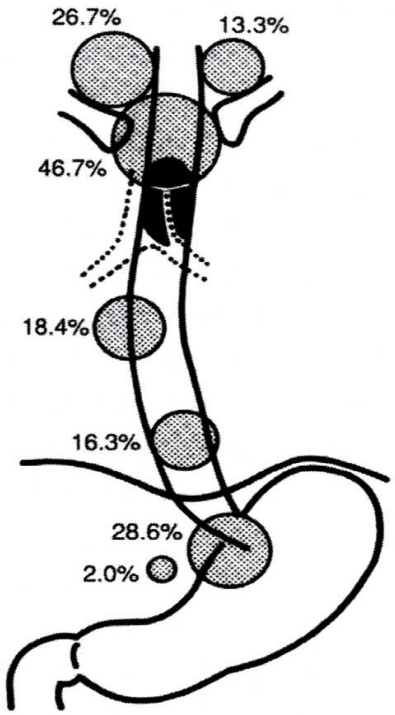
Tis	0%
T1b	31-56%
T2	58-78%
T3	83-100%



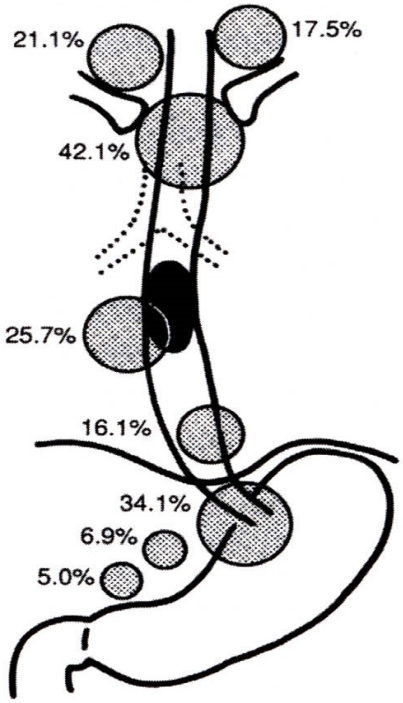
Distant lymph node metastasis

'Skip metastasis'

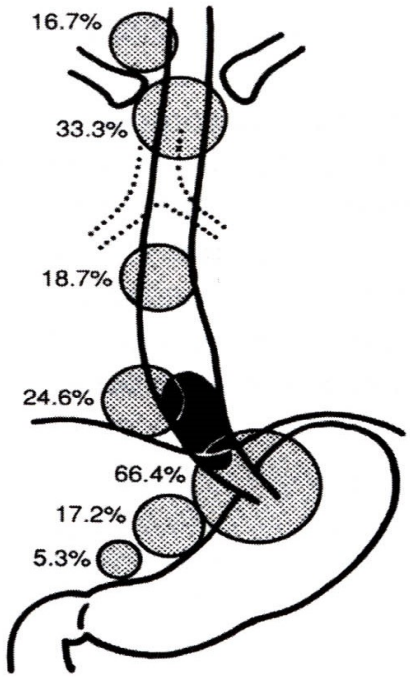
A COMPLEX LYMPHATIC NETWORK



Upper esophageal cancer
(n*=15)
(n=49)



Middle esophageal cancer
(n*=57)
(n=261)



Lower esophageal cancer
(n*=24)
(n=134)

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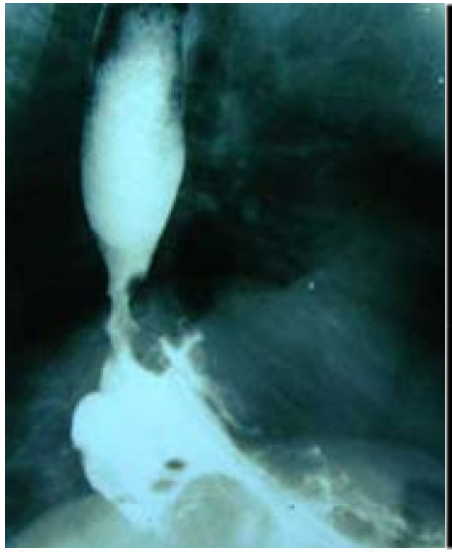
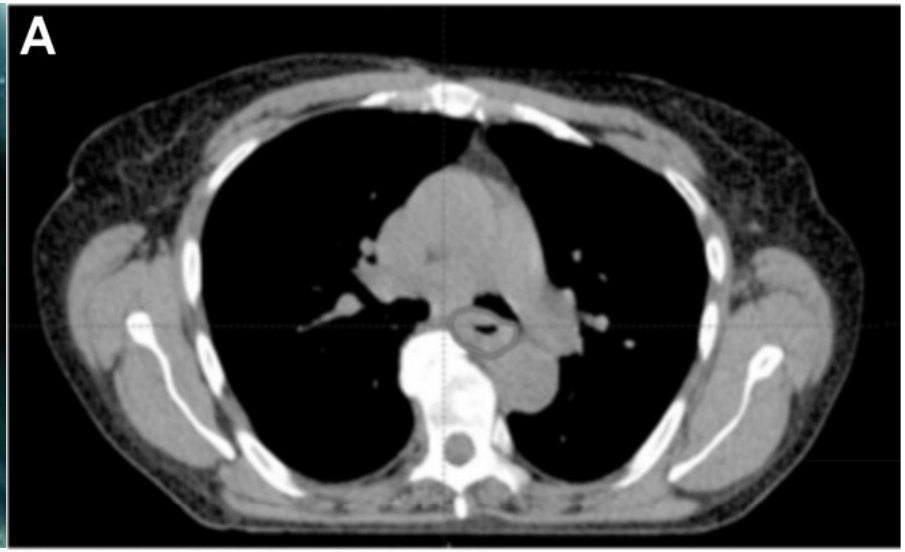
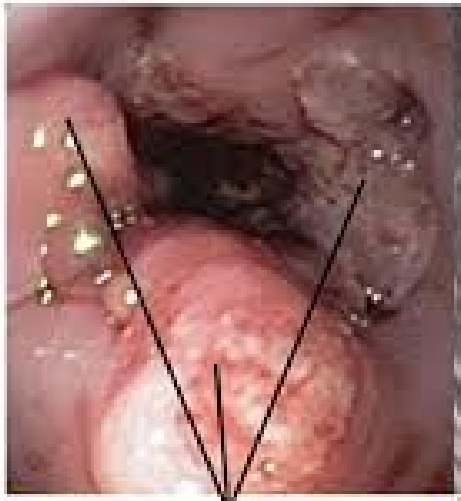
GTV

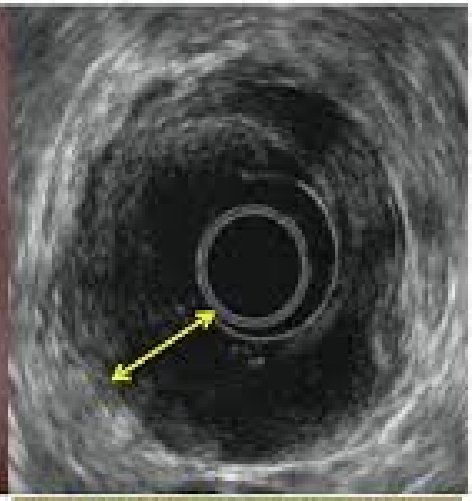




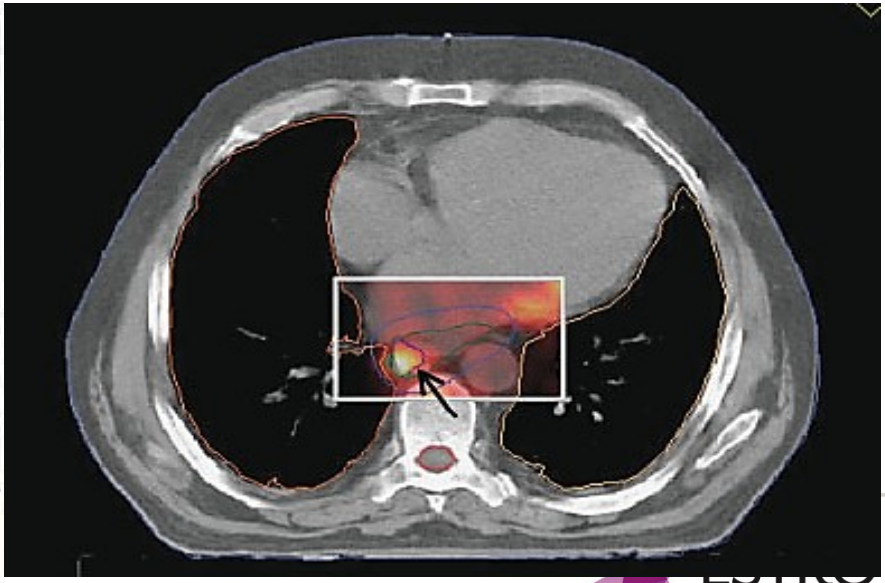
- Barium swallow
- CT-Scan
- Endoscopy
- EUS
- PET - CT



Circumferential esophageal cancer



EUS showing the cancer invading the inner layers of the esophagus



Resection versus PET scan

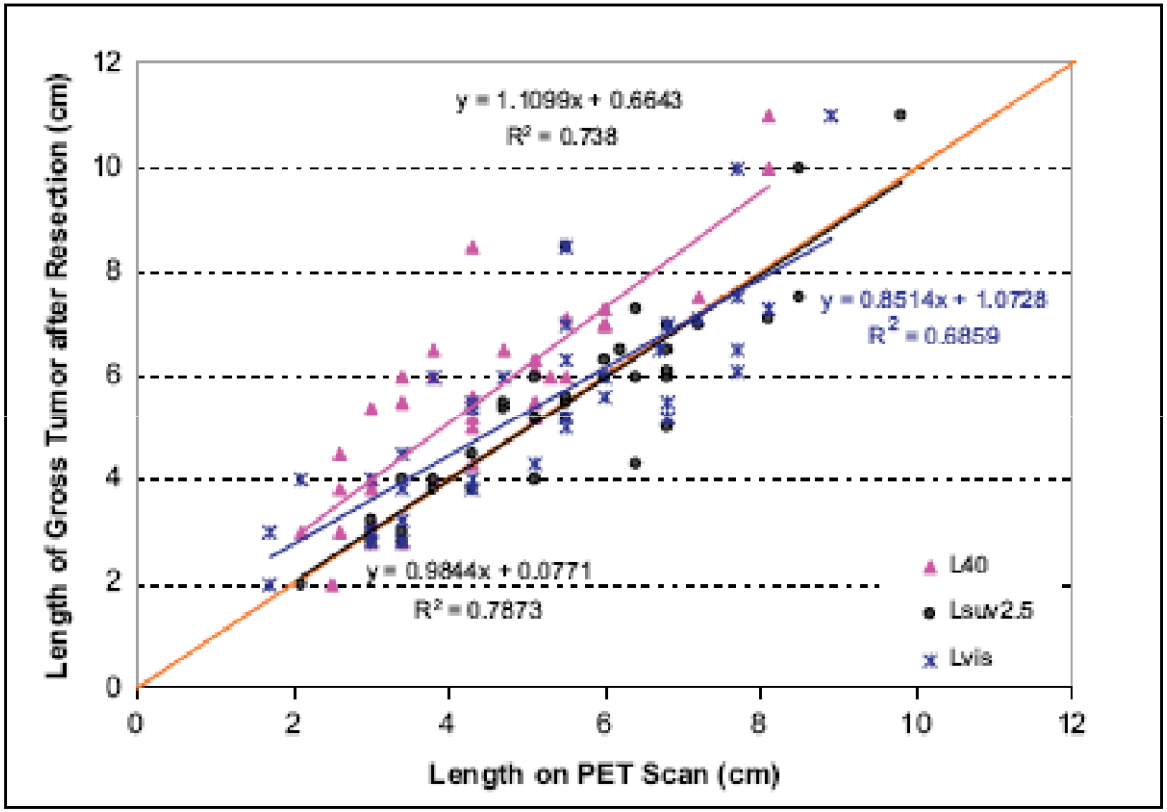


Fig. 2. Image–pathology correlations.

Xiaojun Zhong IJROBP 2009;73:136-141

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Integrated PET - CT

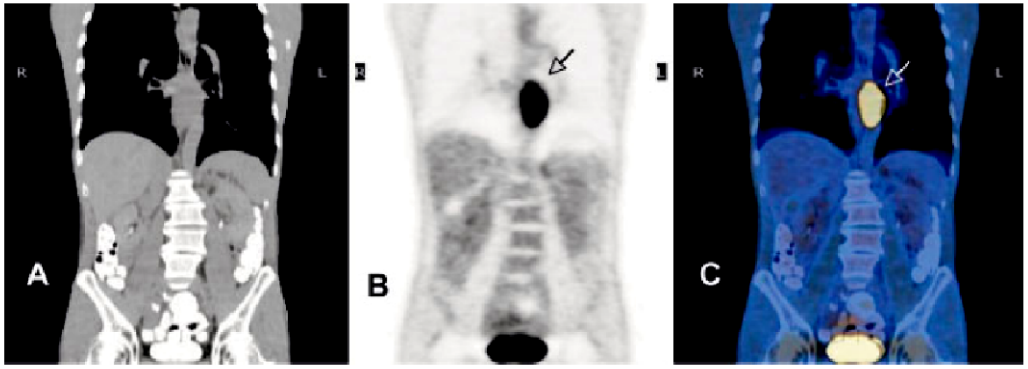

FIGURE 1. Integrated PET/CT of a patient showing NPA = 1 in the primary (arrow). (A) CT scan; (B) PET scan; (C) integrated image.

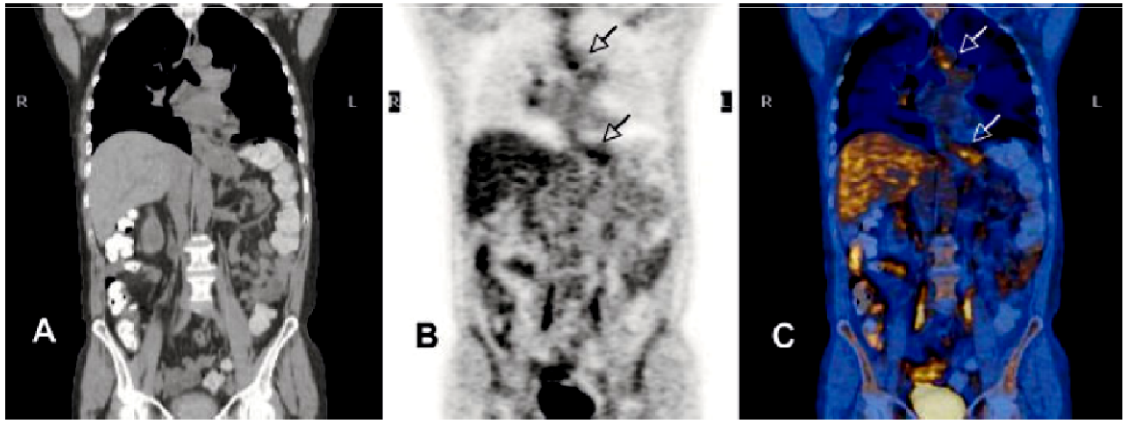

FIGURE 2. Integrated PET/CT of a patient showing NPA = 2 in the primary and mediastinum (arrows). (A) CT scan; (B) PET scan; (C) integrated image.

Hong D. Cancer 2005;104:1620-6

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Esophageal cancers

- PET can improve the RT planning

- PET is more accurate for nodal assessment
- Distant lymph nodes and distant metastasis
- PET shows the longitudinal extent better than CT
- PET may be the only way to visualize the lower border of the tumor

Duong Eur J Nucl Med Imaging 2006

Van Westreneen JCO 2004

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CTV

Generally applied margins for esophageal cancer

ICRU 50 Definitions: GTV plus areas at risk of microscopic extension

CTV: Gross tumor (GTV)
+ 3 to 5 cm margin craniocaudal
+ extension to involved nodes

+1 to 2 cm circumferential margin

CTV to PTV: 1 cm

i.e.: field border 5 cm craniocaudal from GTV

LNM distribution

TABLE 3. Rate of LNM to Different Regions According to the Location of the Primary Tumor

Location	Cervical	Um	Mm	Lm	Abdominal
Ut	12/82 (14.6)	24/82 (29.3)	7/82 (8.5)	8/82 (9.8)	6/82 (7.3)
Mt	55/1266 (4.3)	63/1266 (5.0)	417/1266 (32.9)	32/1266 (2.5)	189/1266 (14.9)
Lt	11/545 (2.0)	12/545 (2.2)	84/545 (15.4)	208/545 (38.1)	150/545 (27.5)
Total	78/1893 (4.1)	99/1893 (5.2)	508/1893 (26.8)	248/1893 (13.1)	345/1893 (18.2)

LNM, lymph node metastasis; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Um, upper mediastinal; Mm, middle mediastinal; Lm, lower mediastinal.

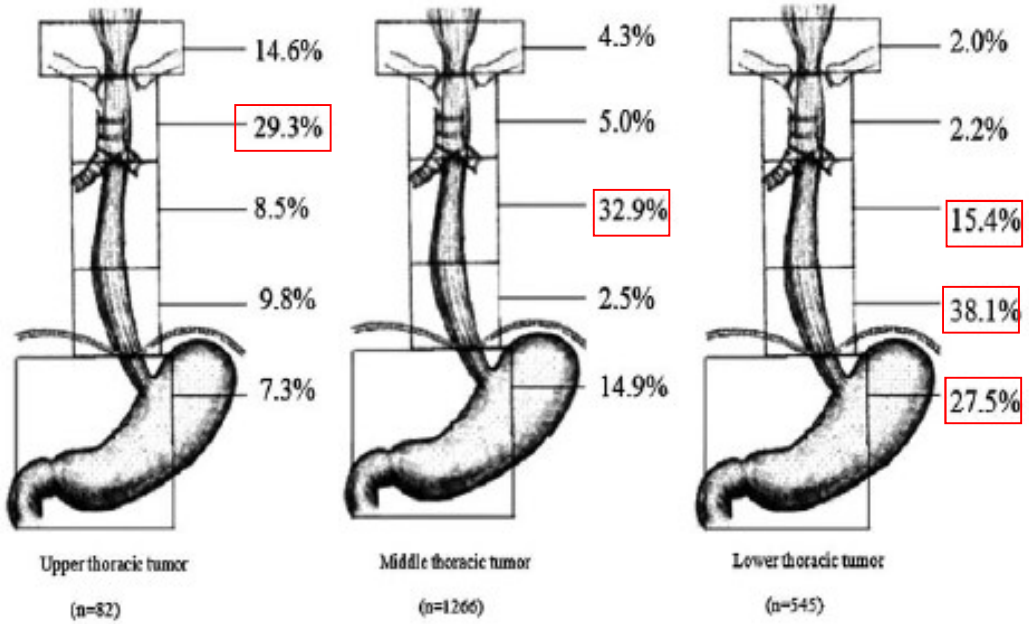

FIGURE 1. Rate of LNM in different regions according to the location of the primary tumor. LNM, lymph node metastasis.

J Thorac Oncol. 2013;8: 359-365

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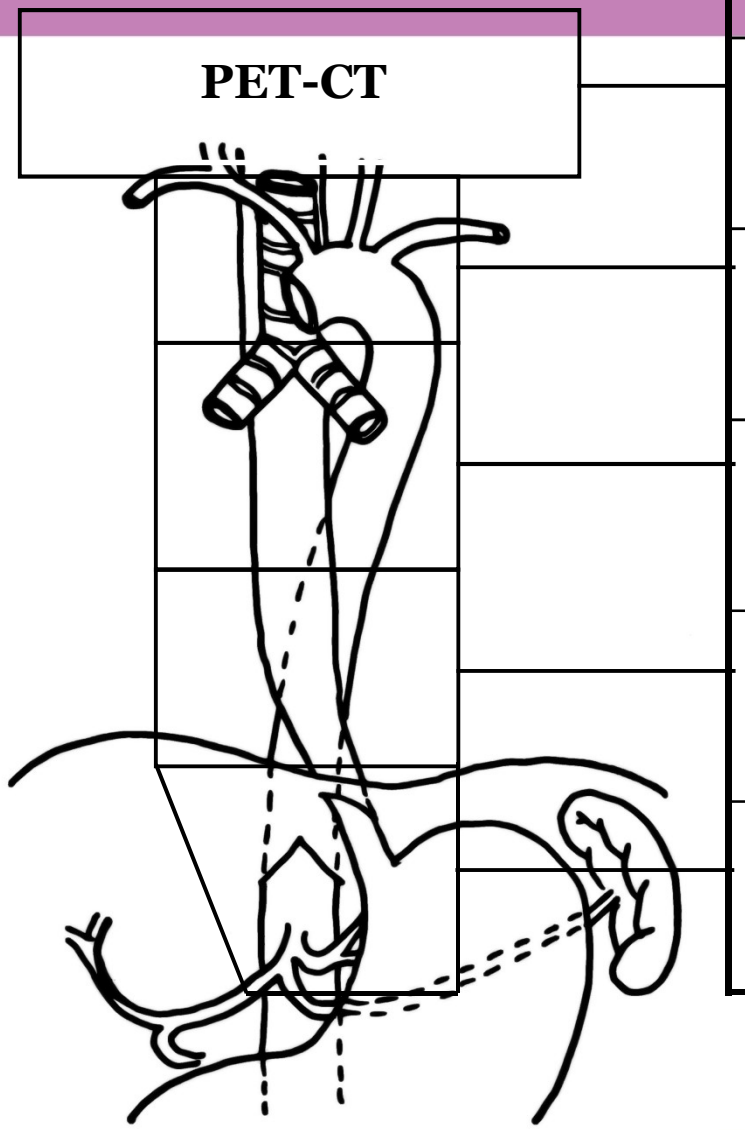

proximal	mid-	distal	total
66,7%	48,1%	20,7%	37,4%
52,4%	51,9%	22,4%	36,4%
28,6%	25,9%	32,8%	29,9%
23,8%	18,5%	15,5%	17,8%
19,0%	25,9%	48,3%	37,4%

Wouterse et al. Distribution of PET positive nodes in dCRT oesophageal patients

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Control

On surgical specimens: n= 34 SCC/32ADK

Lateral (mean value) =

- SCC : 10.5 ± 13.5 mm SUP et 10.6 ± 8.1 mm INF
- ADK : 10.3 ± 7.2 mm SUP et 18.3 ± 16.3 mm INF

➔ 50mm = 100% in field

➔ 30mm = 94% in field

Gao S et al., IJROBP 2007

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Elective CTV

For cervical tumors:

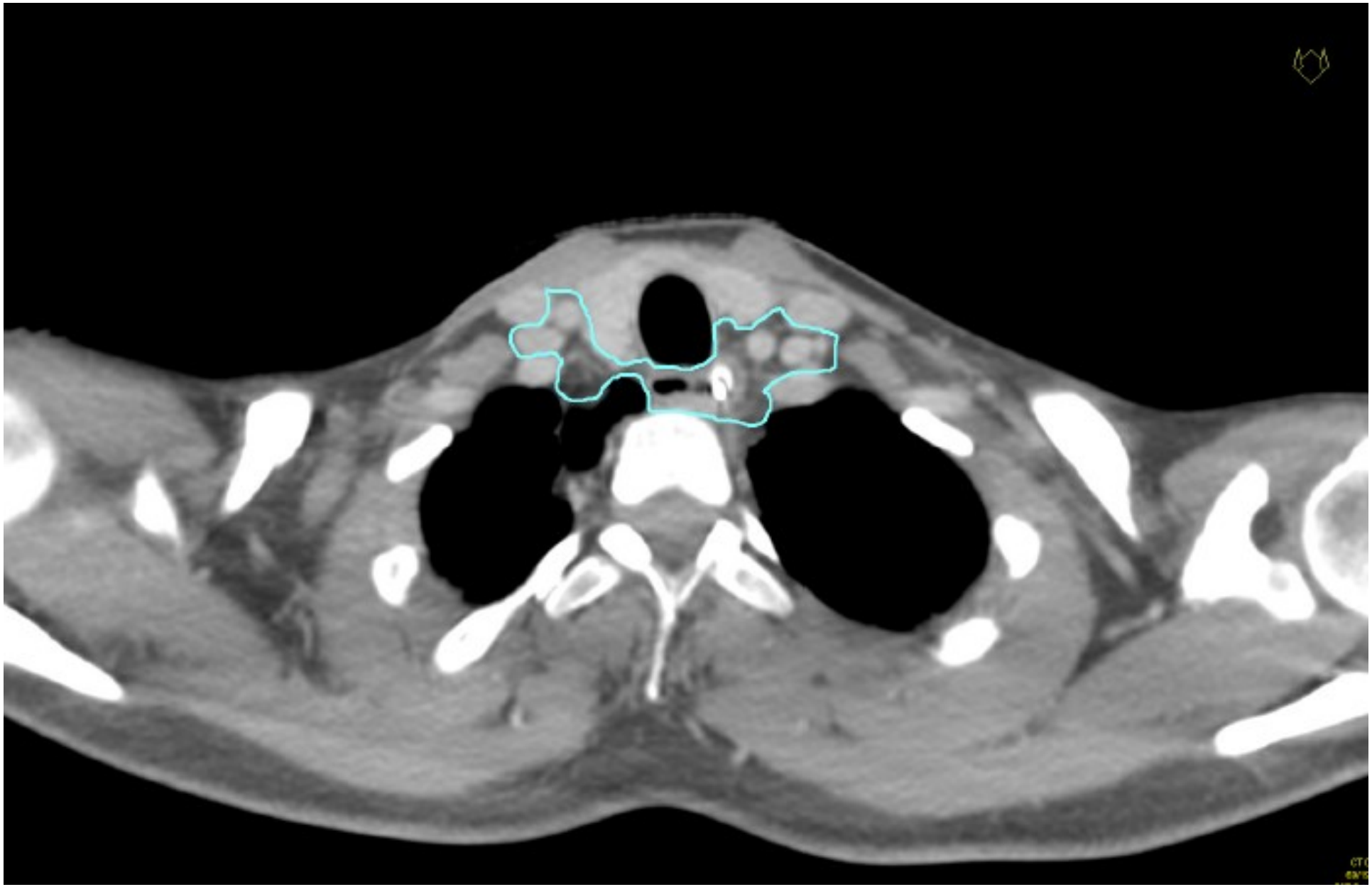
➔ supraclavicular, para esophageal, pretracheal and a-p fenestra

For proximal tumors:

➔ supraclavicular, para esophageal, pretracheal and a-p fenestra,(- pre and subcarinal)

For mid esophageal tumors:

➔ para and pretracheal, a-p fenestra, pre and subcarinal and higher and lower para esophageal



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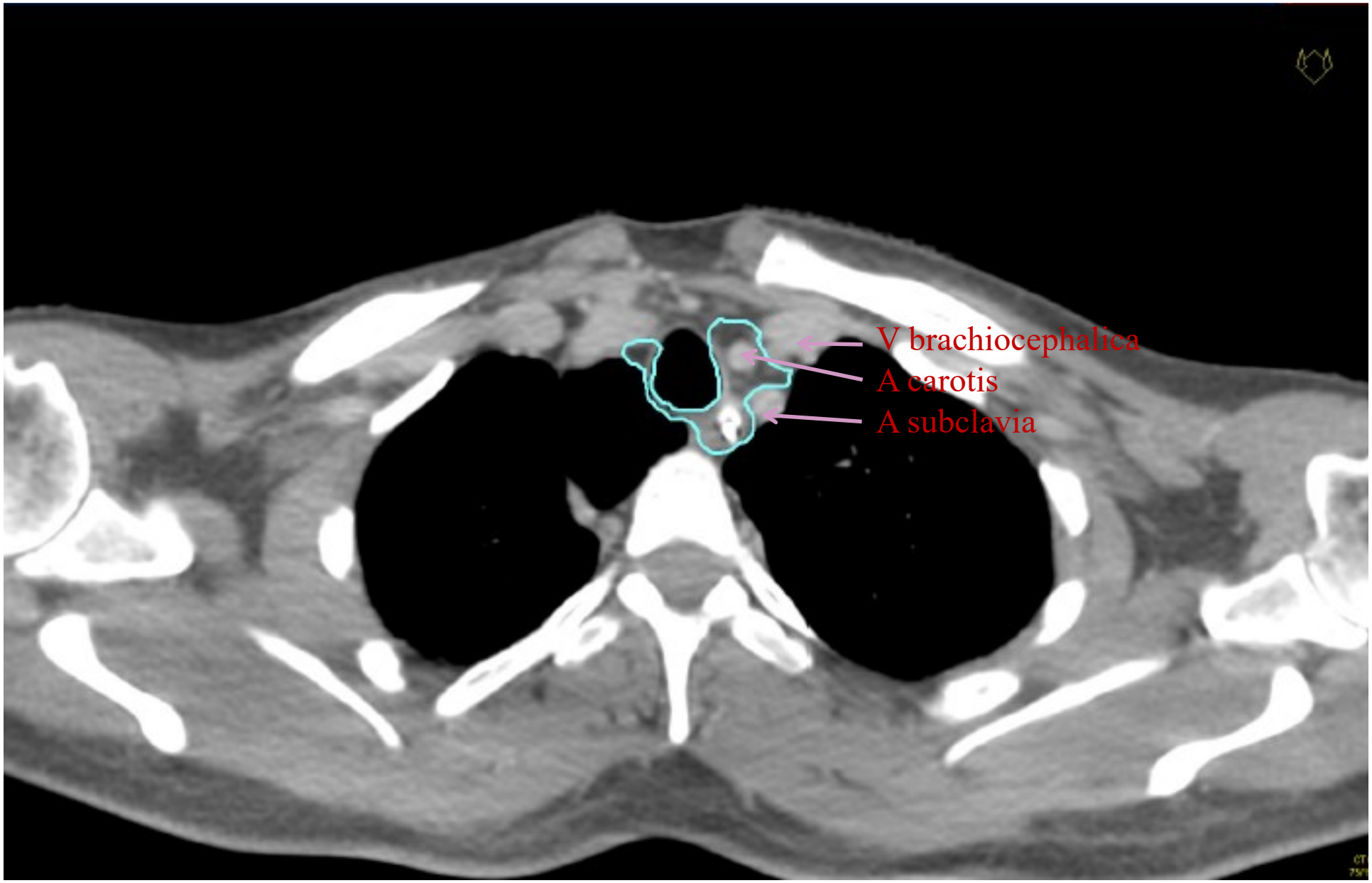
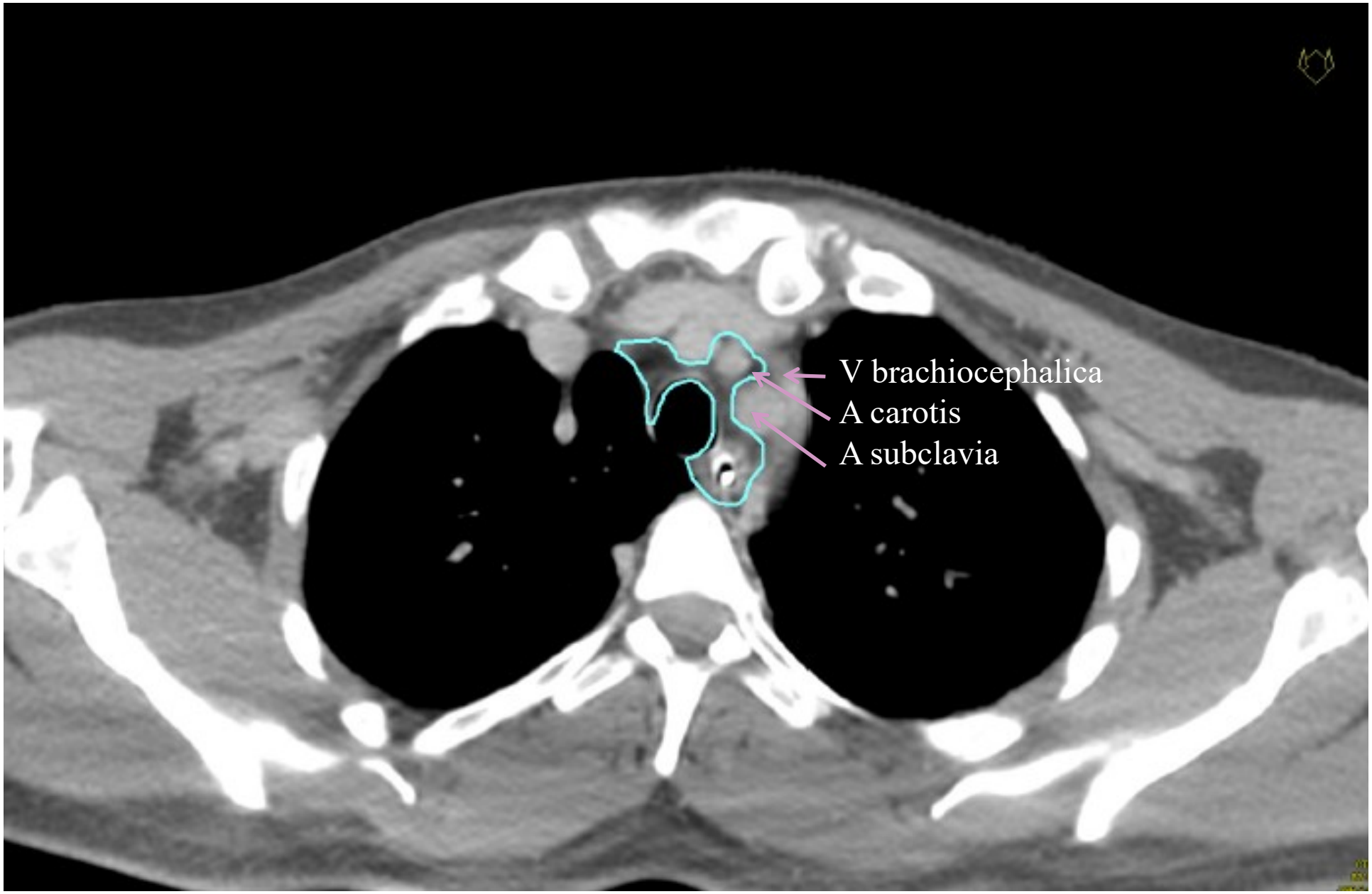

V brachiocephalica
A carotis
A subclavia



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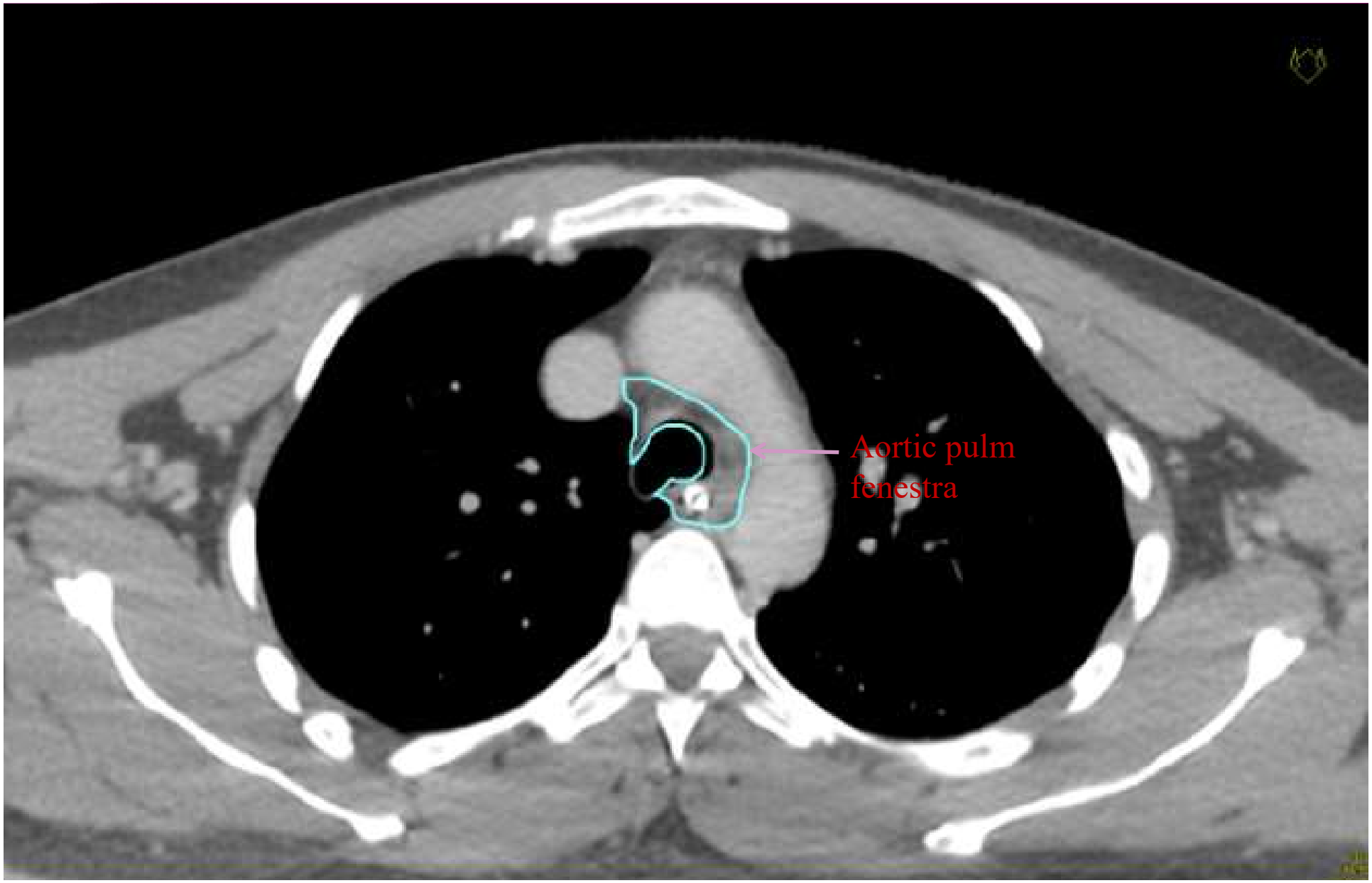
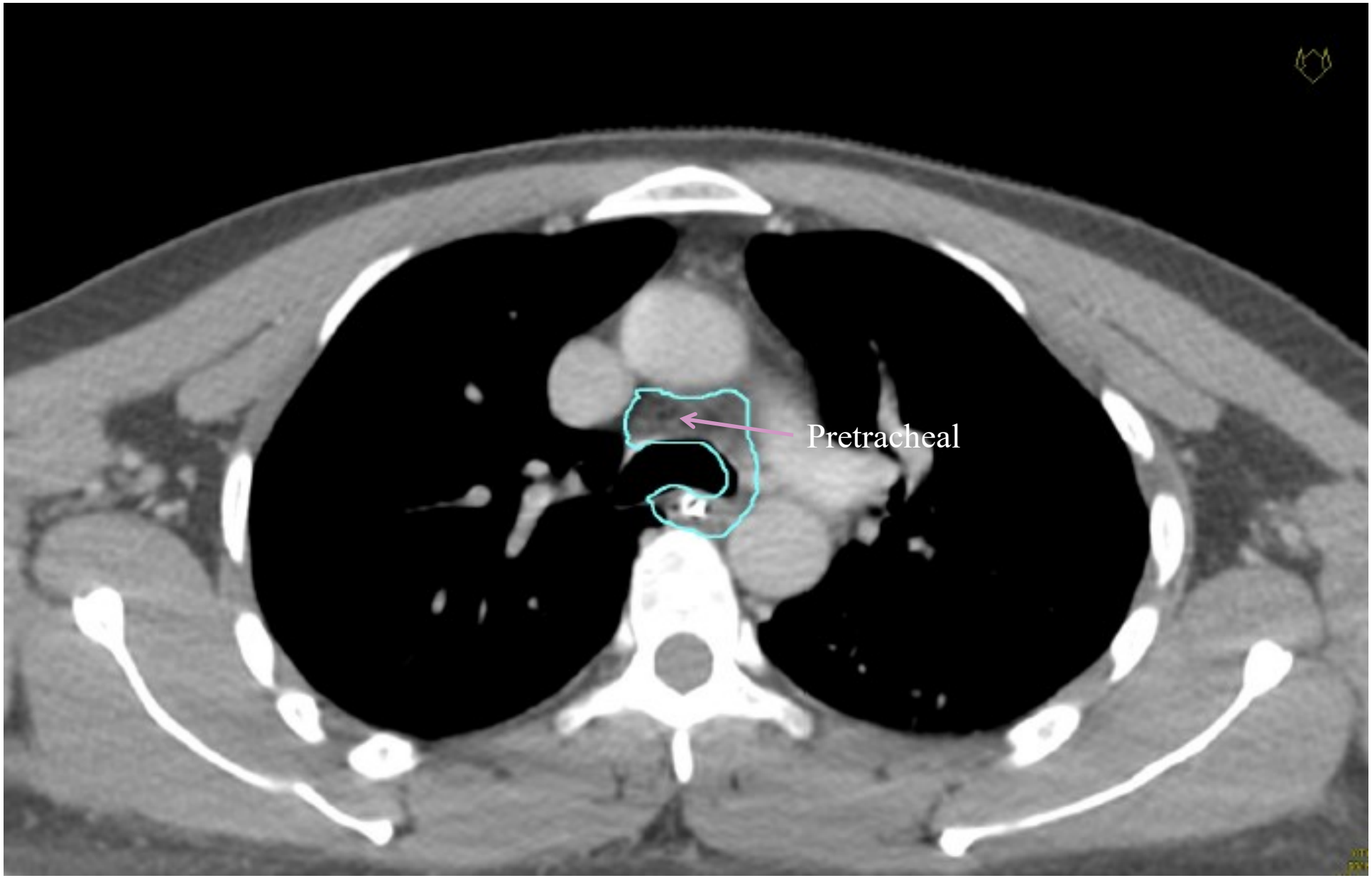

Aortic pulm
fenestra



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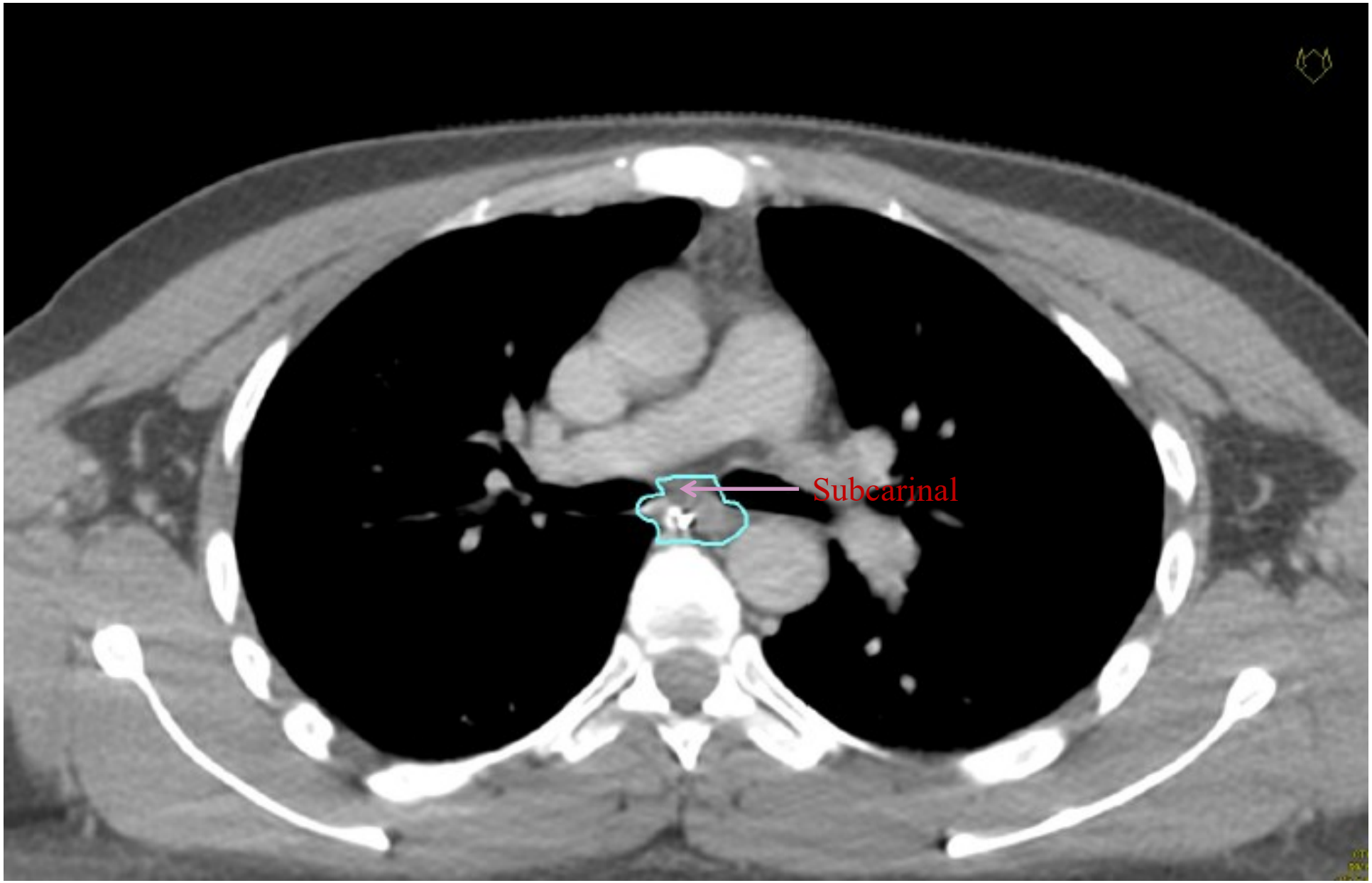
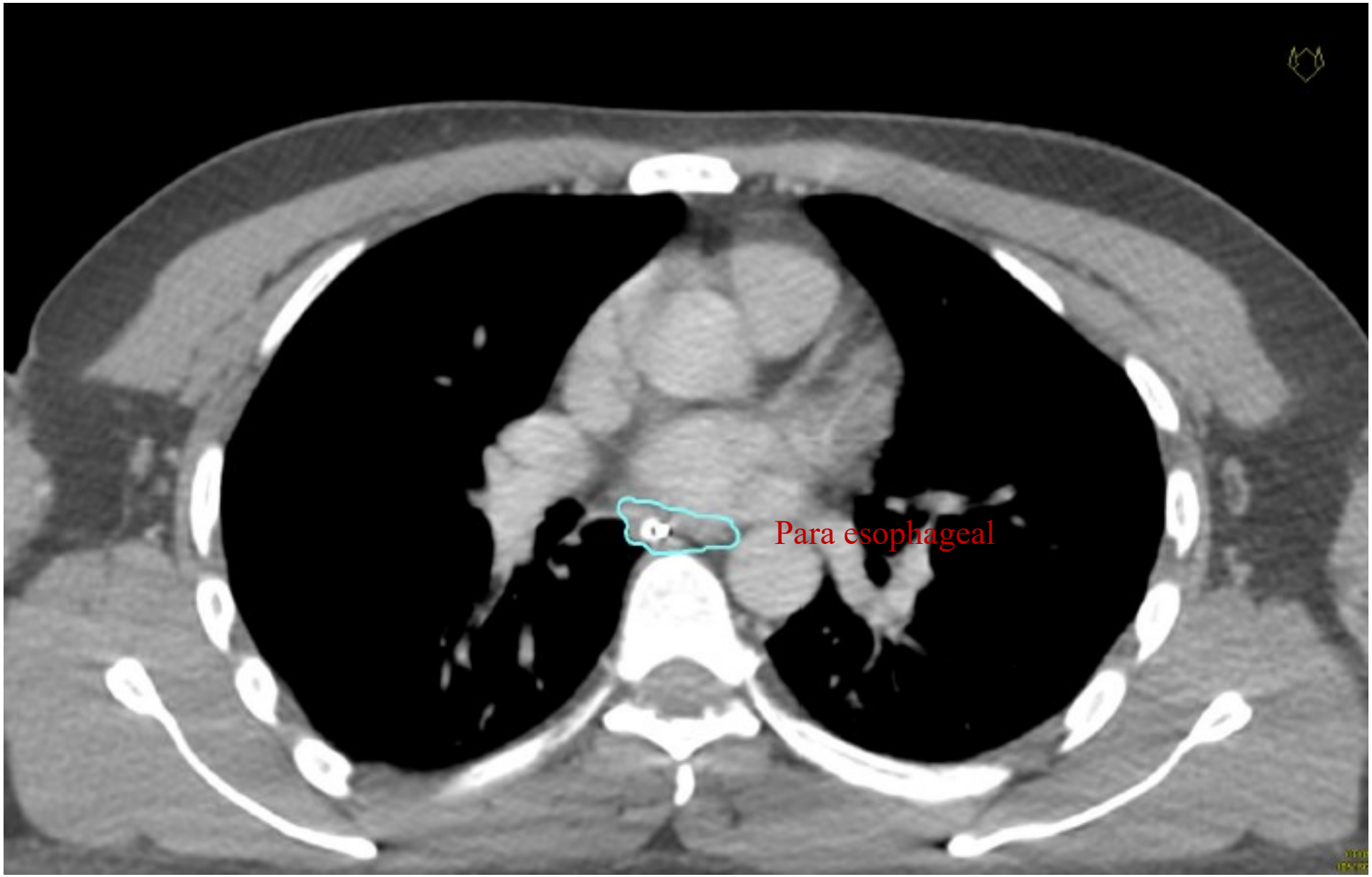
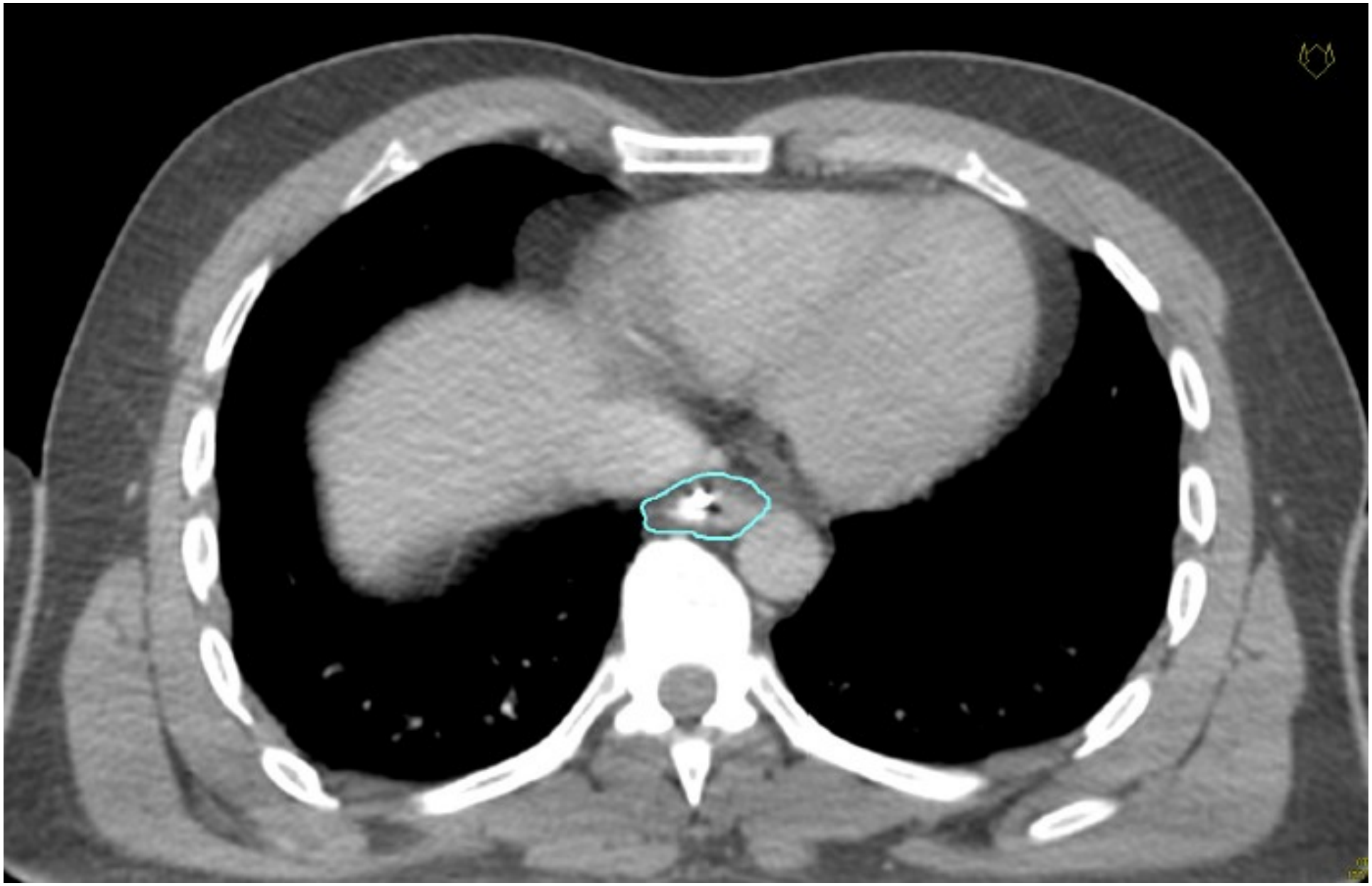

Subcarinal


Para esophageal



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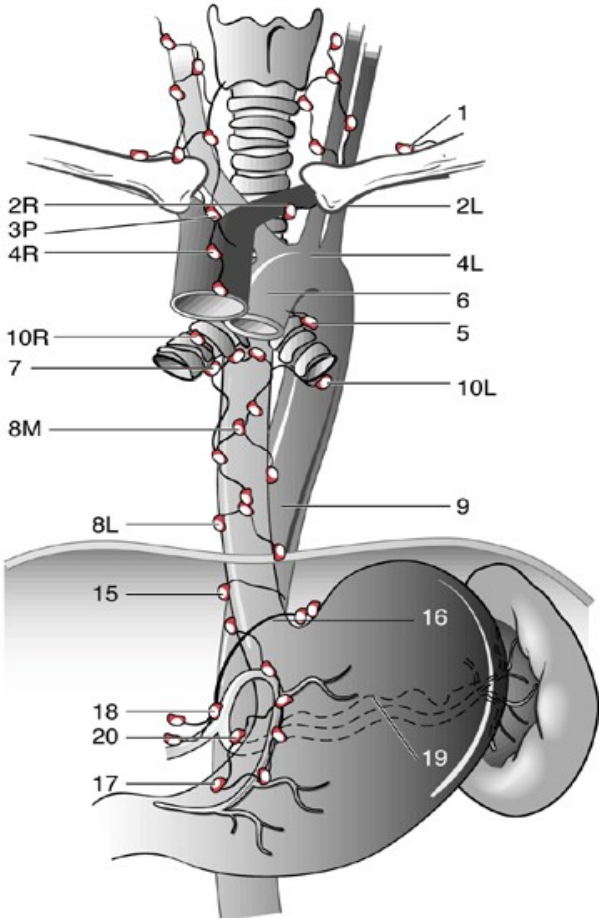
RTOG Staging system



	1	Supraclavicular nodes
	2R	Right upper paratracheal nodes
	2L	Left upper paratracheal nodes
●	3P	Posterior mediastinal nodes
	4R	Right lower paratracheal nodes
	4L	Left lower paratracheal nodes
	5	Aortopulmonary nodes
	6	Anterior mediastinal nodes
●	7	Subcarinal nodes
●	8M	Middle paraesophageal lymph nodes
●	8L	Lower paraesophageal lymph nodes
●	9	Pulmonary ligament nodes
	10R	Right tracheobronchial nodes
	10L	Left tracheobronchial nodes
●	15	Diaphragmatic nodes
●	16	Paracardial nodes
●	17	Left gastric nodes
●	18	Common hepatic nodes
●	19	Splenic nodes
●	20	Celiac nodes

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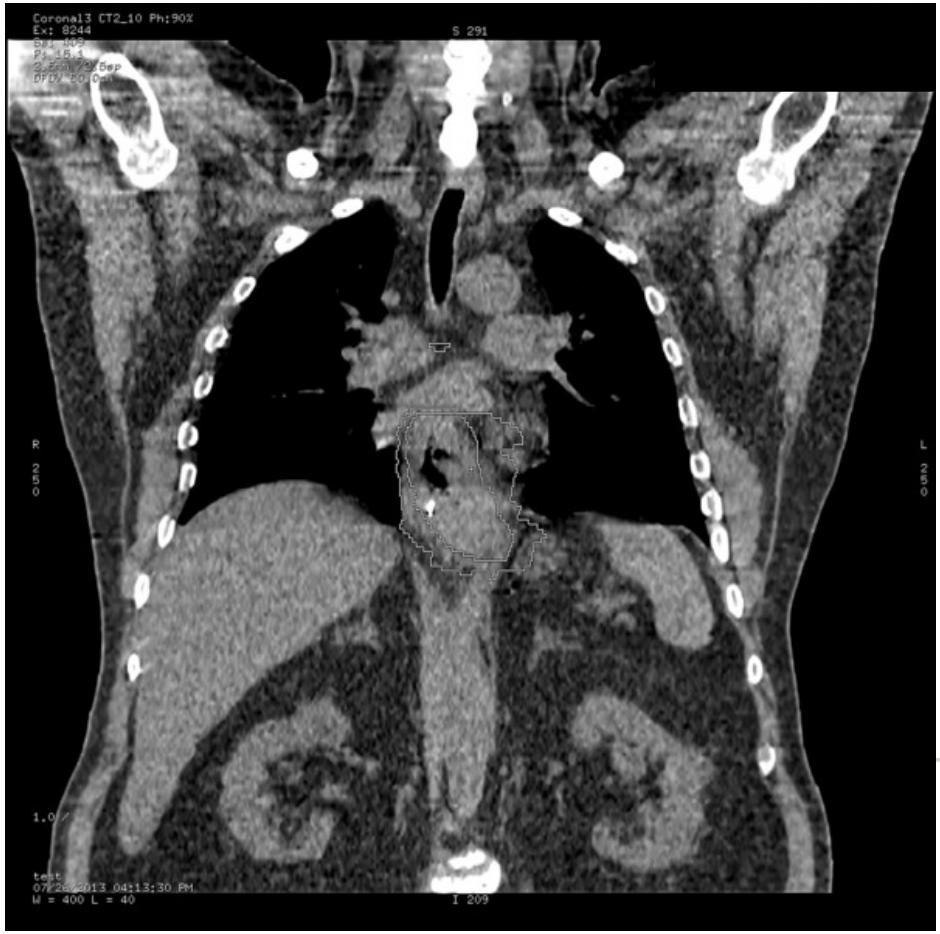
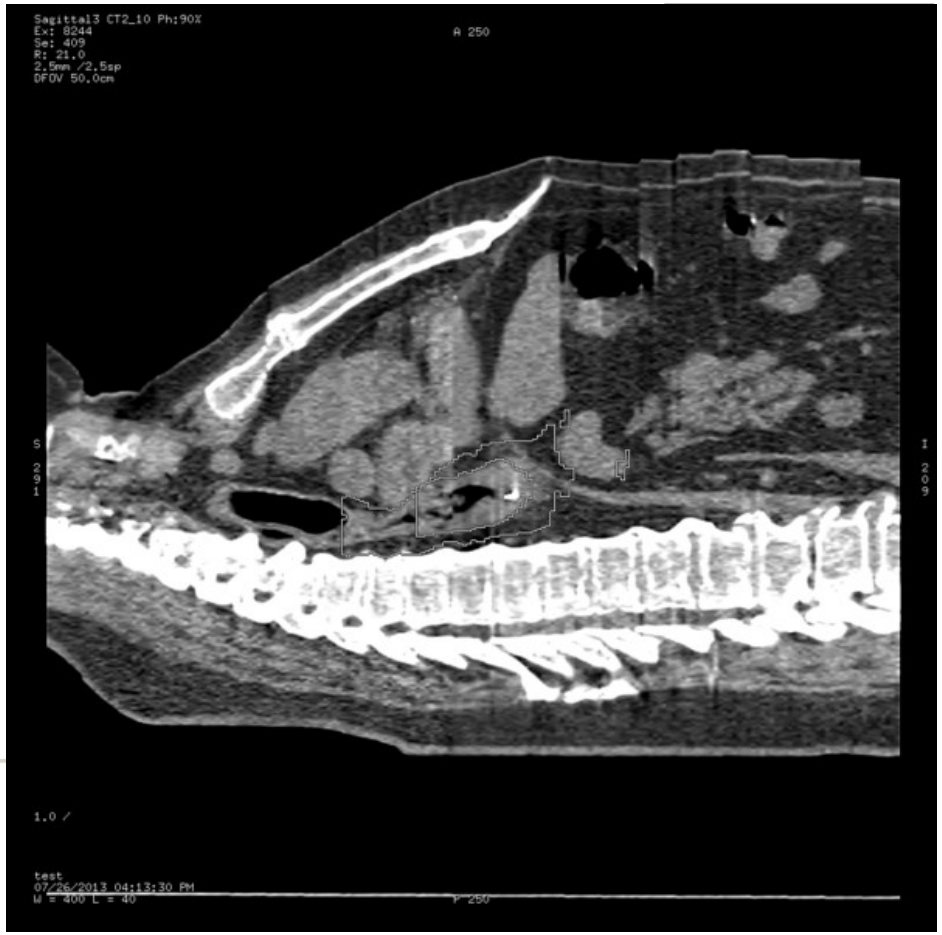
Levels	Cervical	Upper	Middle	Lower	ADC Distal	Siewert I	Siewert II
1	×	×					
2R/2L	×	×	×				
3P	×	×					
4R/4L	×	×					
5		×	×				
6	Anterior Mediastinal						
7		×	×				
8M			×				
8L			×	×	×	×	×
9			×	×			
10R/10L			×				
15				×	×	×	×
16				×	×	×	×
17			×	×	×	×	×
18	Common Hepatic						
19	Splenic						
20			×	×	×	×	×

RTOG recommandations

Mobility of oesophagus

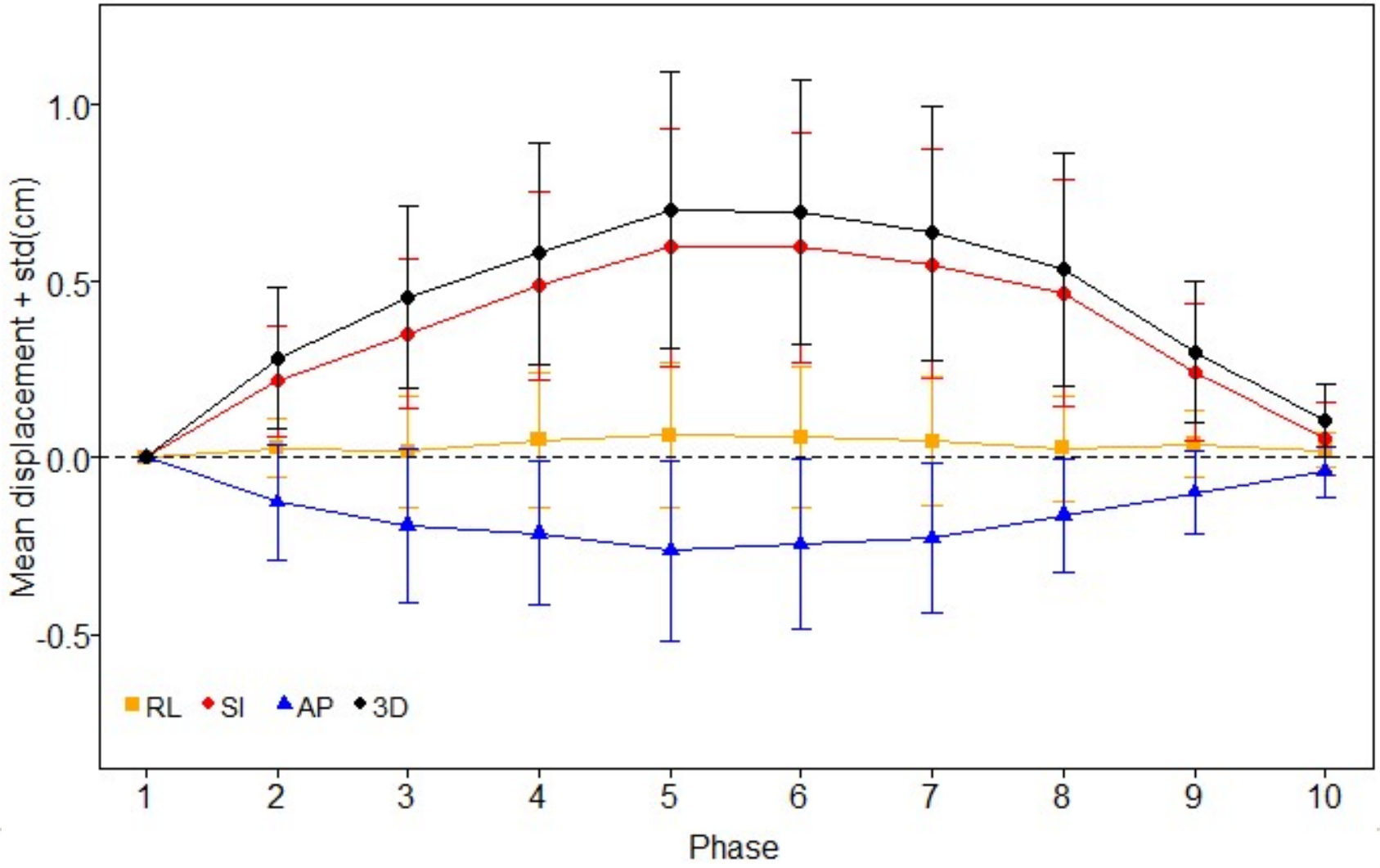




Effect of breathing on oesophagus

	Thoracic part	Abdominal part
Yaremko 2008	8 mm	10 mm
Welch 1982	4 mm	6 mm
Dieleman 2007	7 mm	9 mm

Relative marker displacement during breathing



Courtesy from Maarten C C M Hulshof

Results

Motion in each phase

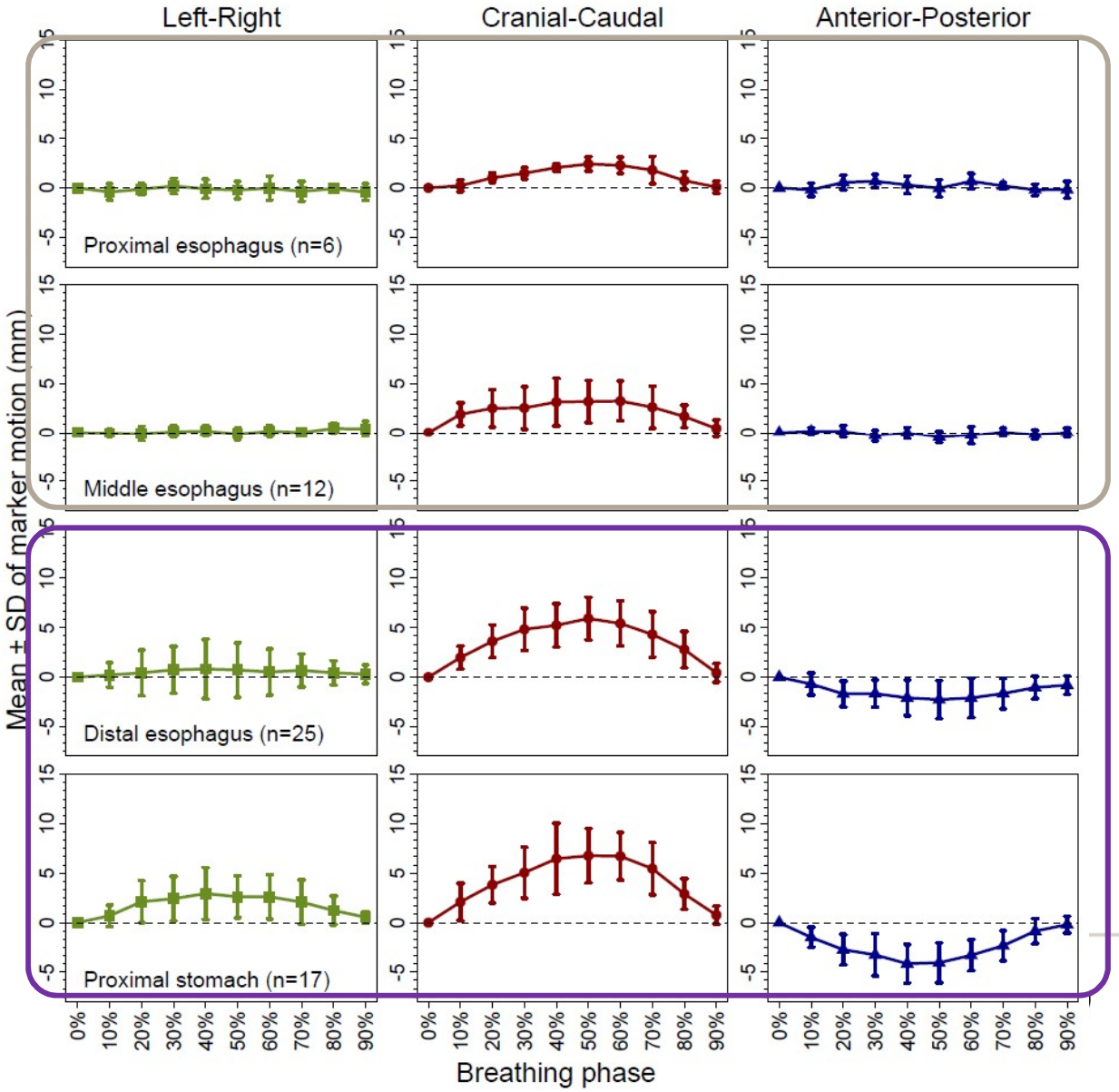
CC > LR & AP

Lower > Upper

Exhalation

- To left
- To cranial
- To posterior

Induced by respiration



CTV-ITV margin proximal and mid- esophageal tumors

APPA:	7-8 mm
Lateral:	5-7 mm
Craniocaudal:	10 mm

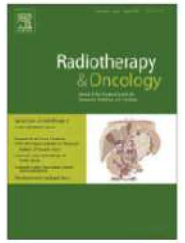
Target Volume definition oesogastric junction tumor

Radiotherapy and Oncology 92 (2009) 164–175

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Guidelines

EORTC-ROG expert opinion: Radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach

Oscar Matzinger [a,b,*], Erich Gerber [c], Zvi Bernstein [d], Philippe Maingon [e], Karin Haustermans [f], Jean François Bosset [g], Akos Gulyban [a], Philip Poortmans [h], Laurence Collette [a], Abraham Kuten [d]

[a] EORTC Headquarters, Brussels, Belgium
[b] CHU Vaudois, Department of Radiation Oncology, Lausanne, Switzerland
[c] Radiation Oncologist, Vienna, Austria
[d] Rambam Health Care Campus, Oncology Department, Haifa, Israel
[e] Centre Georges-Francois Leclerc, Department of Radiation Oncology, Dijon, France
[f] U.Z. Gasthuisberg, Department of Radiation Oncology, Leuven, Belgium
[g] CHR de Besancon, Department of Radiation Oncology, Besancon, France
[h] Dr. Bernard Verbeeten Institute, Department of Radiation Oncology, Tilburg, The Netherlands

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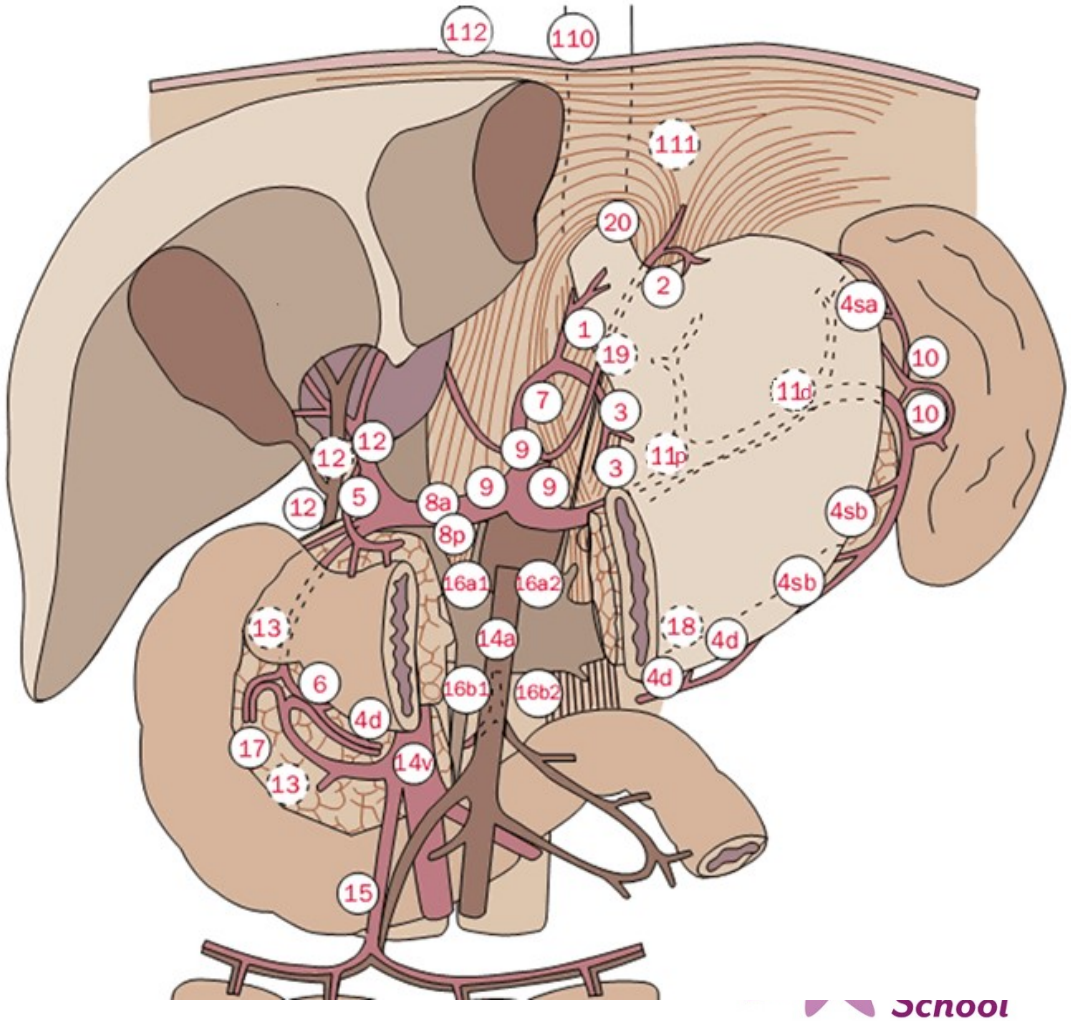
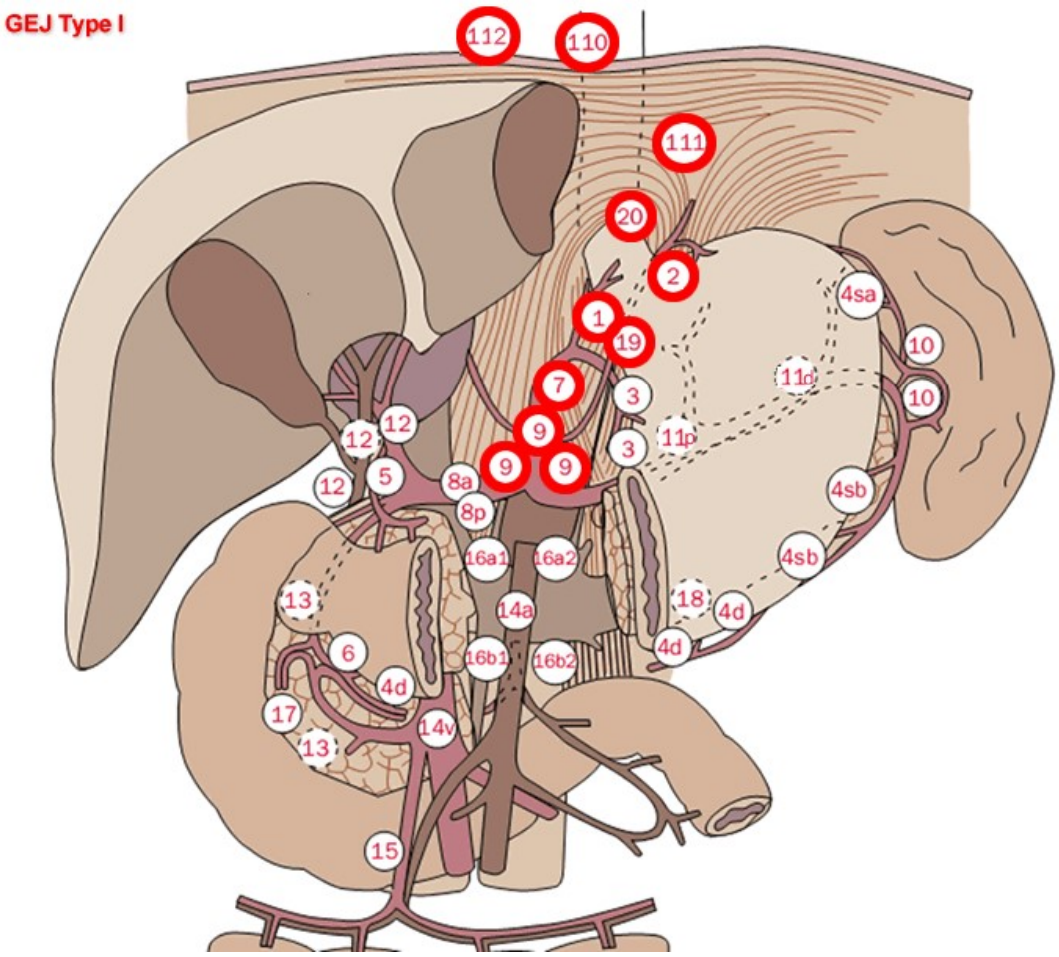
The classification of the lymph node stations of the stomach and the perigastric region according to the JGCA

No. 1	Right paracardial LN
No. 2	Left paracardial LN
No. 3	LN along the lesser curvature
No. 4sa	LN along the short gastric vessels
No. 4sb	LN along the left gastroepiploic vessels
No. 4d	LN along the right gastroepiploic vessels
No. 5	Suprapyloric LN
No. 6	Infrapyloric LN
No. 7	LN along the left gastric artery
No. 8a	LN along the common hepatic artery (Anterosuperior group)
No. 8p	LN along the common hepatic artery (Posterior group)
No. 9	LN around the celiac artery
No. 10	LN at the splenic hilum
No. 11p	LN along the proximal splenic artery
No. 11d	LN along the distal splenic artery
No. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
No. 12b	LN in the hepatoduodenal ligament (along the bile duct)
No. 12p	LN in the hepatoduodenal ligament (behind the portal vein)
No. 13	LN on the posterior surface of the pancreatic head
No. 14v	LN along the superior mesenteric vein
No. 14a	LN along the superior mesenteric artery
No. 15	LN along the middle colic vessels
No. 16a1	LN in the aortic hiatus
No. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
No. 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
No. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
No. 17	LN on the anterior surface of the pancreatic head
No. 18	LN along the inferior margin of the pancreas
No. 19	Infradiaphragmatic LN
No. 20	LN in the esophageal hiatus of the diaphragm
No. 110	Paraesophageal LN in the lower thorax
No. 111	Supradiaphragmatic LN
No. 112	Posterior mediastinal LN



Lymph node stations of gastroesophageal junction

1 Right paracardial LN
2 Left paracardial LN
7 LN along the left gastric artery
9 LN around the celiac artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN
112 Posterior mediastinal LN



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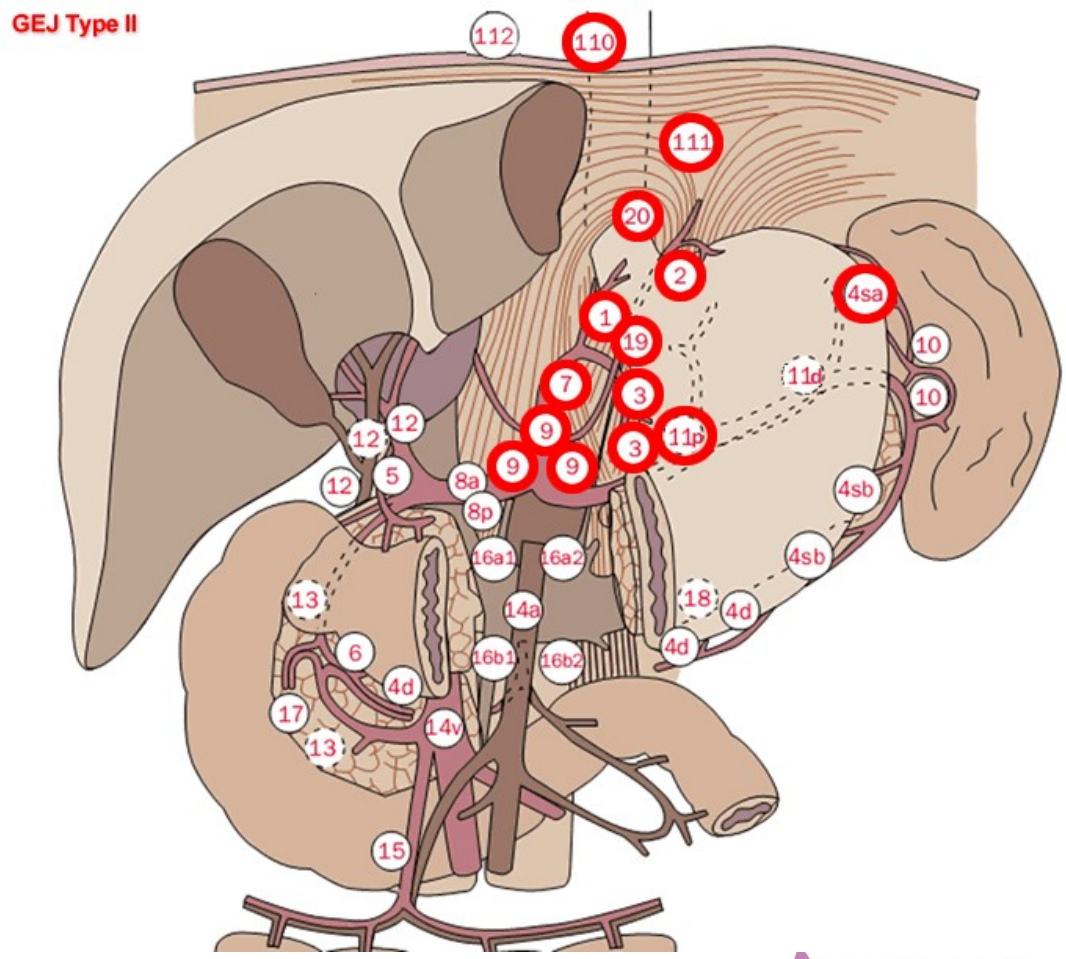
Lymph node stations of gastroesophageal junction tumors: Type II

1 Right paracardial LN
2 Left paracardial LN
3 LN along the lesser curvature
4sa LN along the short gastric vessels
7 LN along the left gastric artery
9 LN around the celiac artery
11p LN along the proximal splenic artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN



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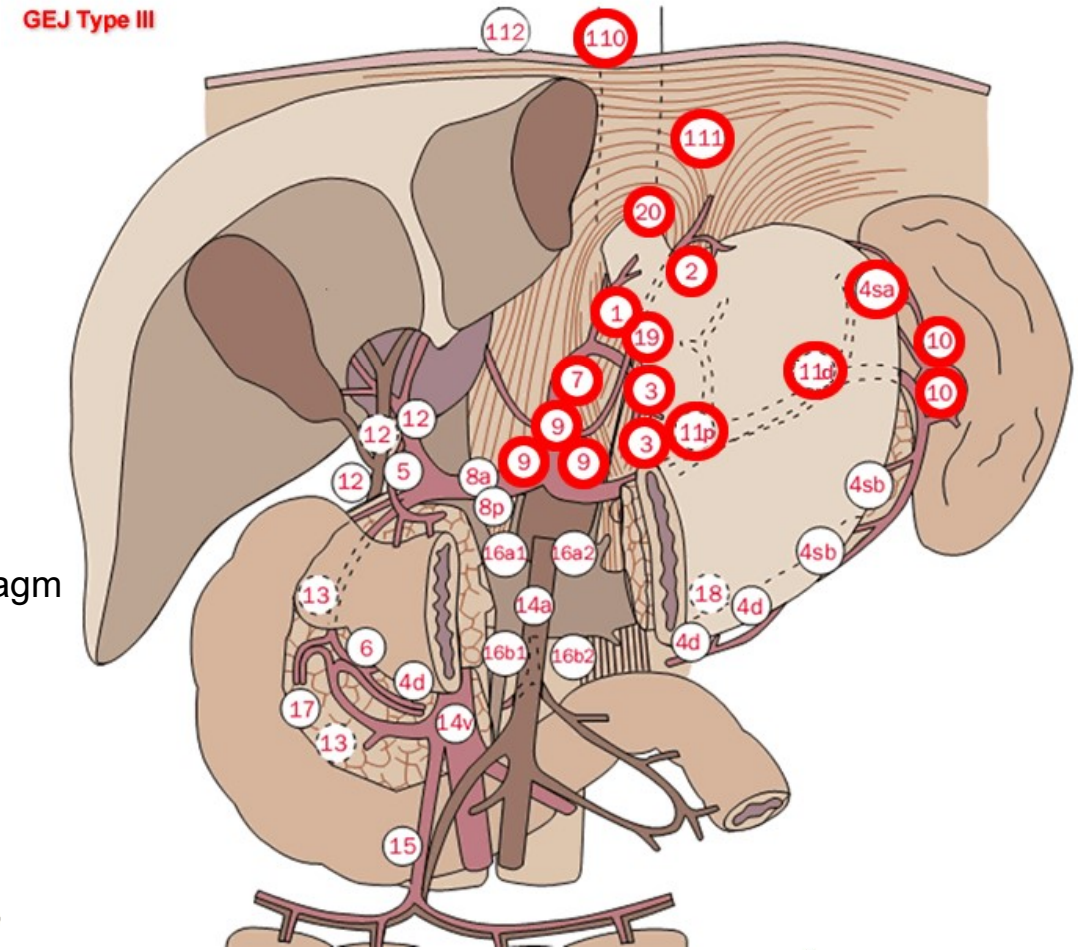
Lymph node stations of gastroesophageal junction tumors: Type III

1 Right paracardial LN
2 Left paracardial LN
3 LN along the lesser curvature
4sa LN along the short gastric vessels
7 LN along the left gastric artery
9 LN around the celiac artery
10 LN at the splenic hilum
11p LN along the proximal splenic artery
11d LN along the distal splenic artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN



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Other consensus atlas US

Clinical Investigation

Expert Consensus Contouring Guidelines for Intensity Modulated Radiation Therapy in Esophageal and Gastroesophageal Junction Cancer

Abraham J. Wu, MD,* Walter R. Bosch, DSc,† Daniel T. Chang, MD,‡ Theodore S. Hong, MD,§ Salma K. Jabbour, MD,‖ Lawrence R. Kleinberg, MD,¶ Harvey J. Mamon, MD, PhD,# Charles R. Thomas Jr, MD,** and Karyn A. Goodman, MD*

**Memorial Sloan-Kettering Cancer Center, New York, New York; †Washington University, St. Louis, Missouri; ‡Stanford Cancer Institute, Stanford, California; §Massachusetts General Hospital, Boston, Massachusetts; ‖Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey; ¶Johns Hopkins Medical Center, Baltimore, Maryland; #Brigham and Women's Hospital, Boston, Massachusetts; and **Knight Cancer Institute, Oregon Health & Sciences University, Portland, Oregon*

Received Nov 16, 2014, and in revised form Mar 24, 2015. Accepted for publication Mar 26, 2015.

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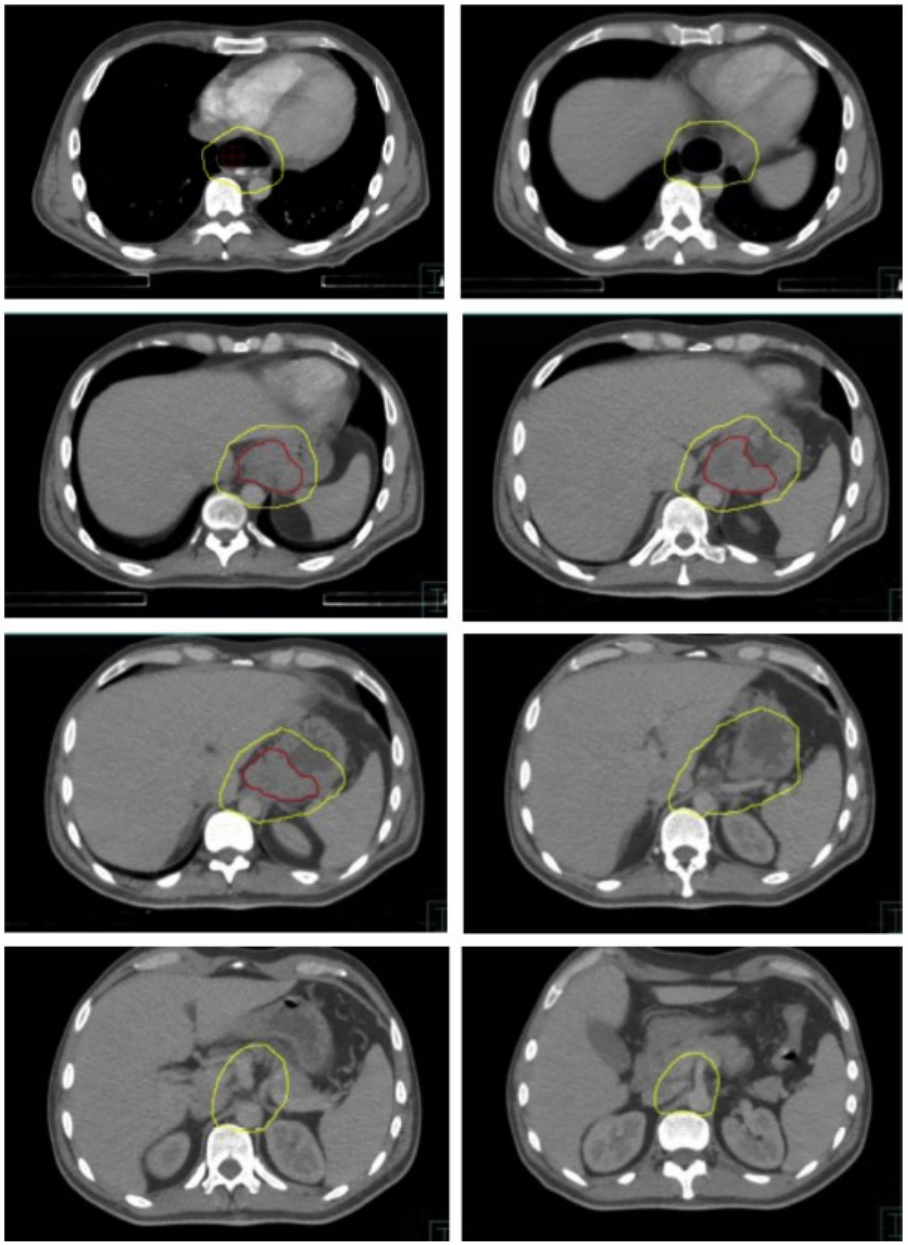

Fig. 3. Consensus contours for case 1: T3N0, Siewert II gastroesophageal junction cancer, gross tumor volume in red. A color version of this figure is available at www.redjournal.org.

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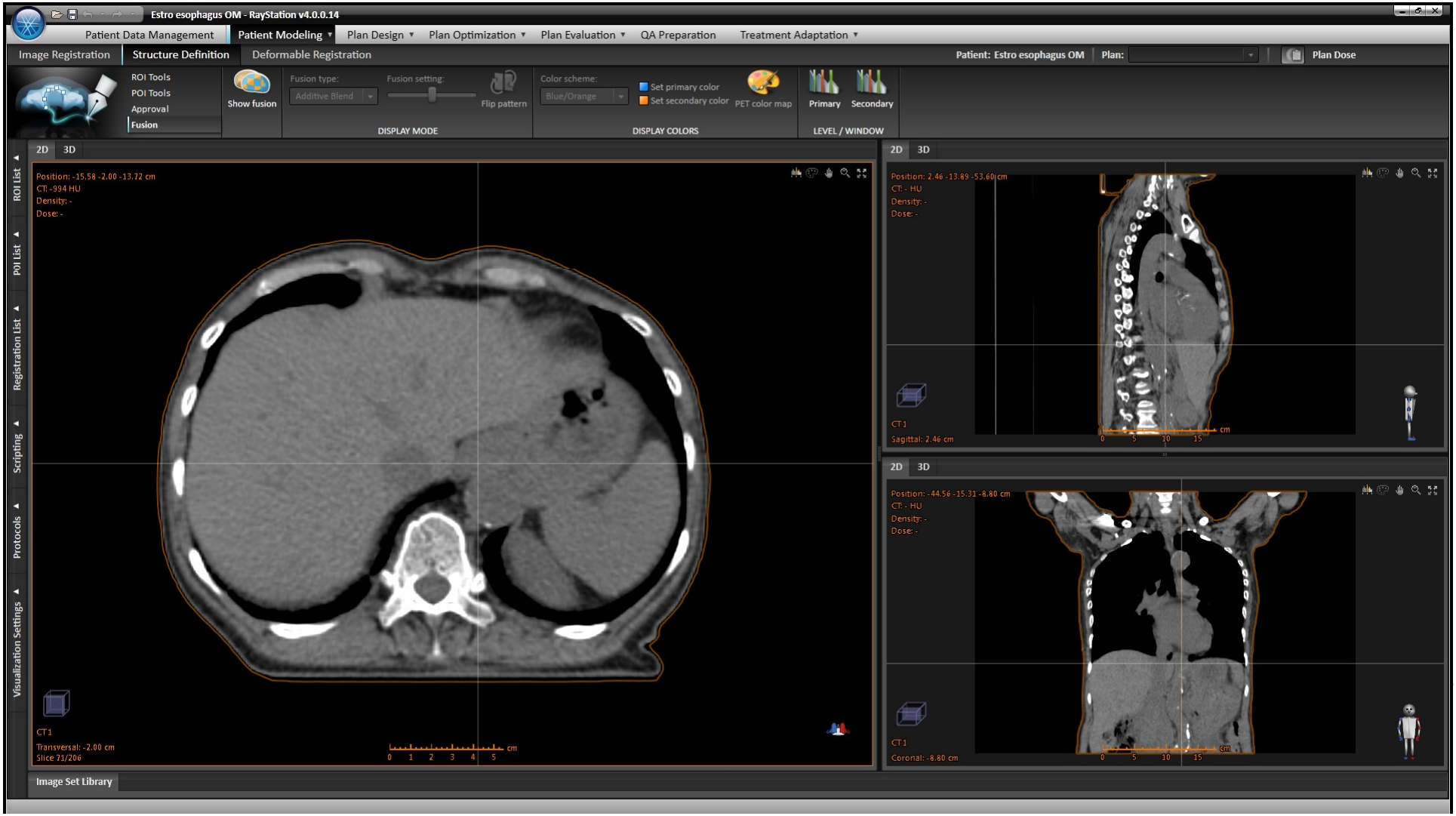
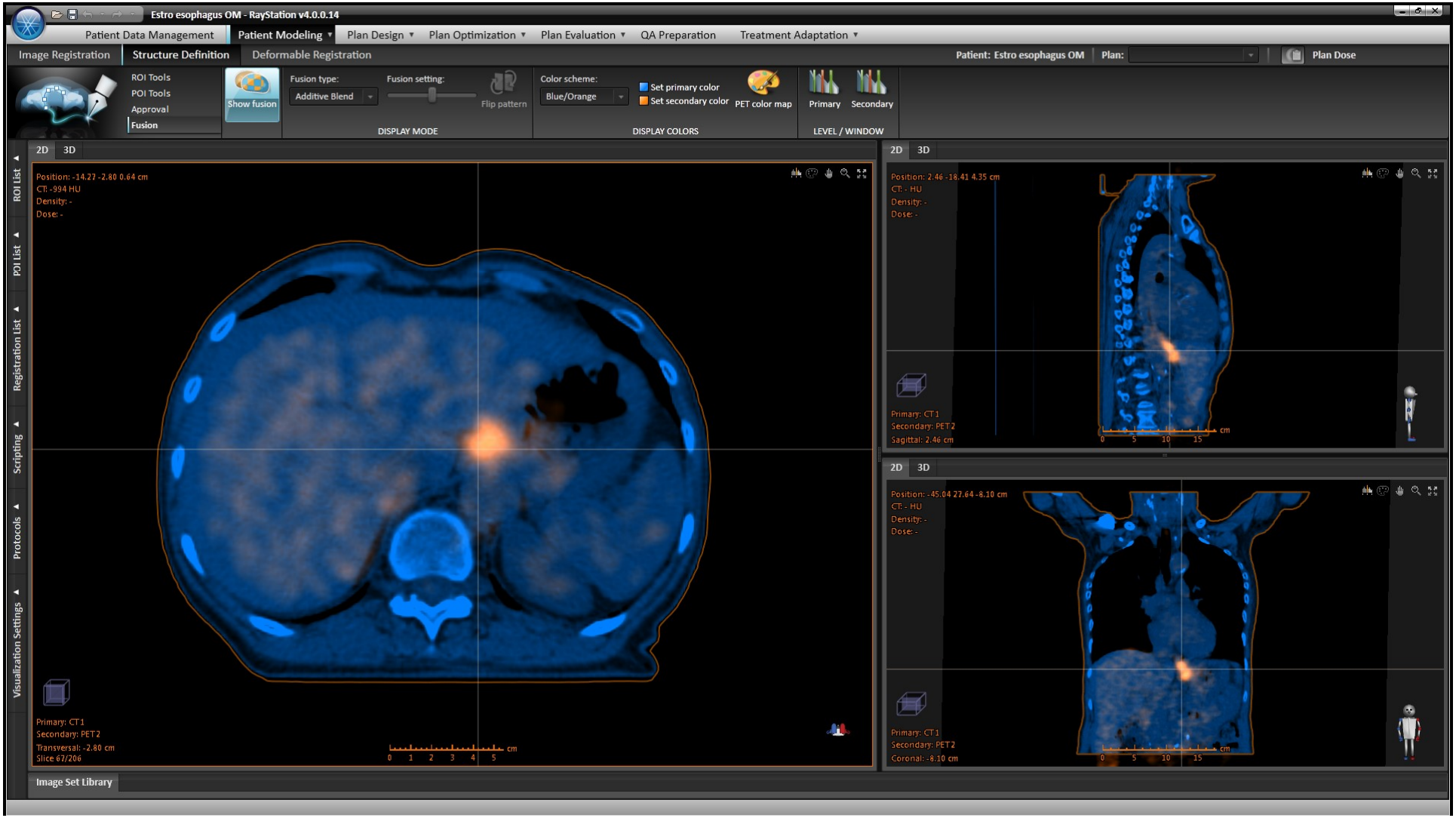
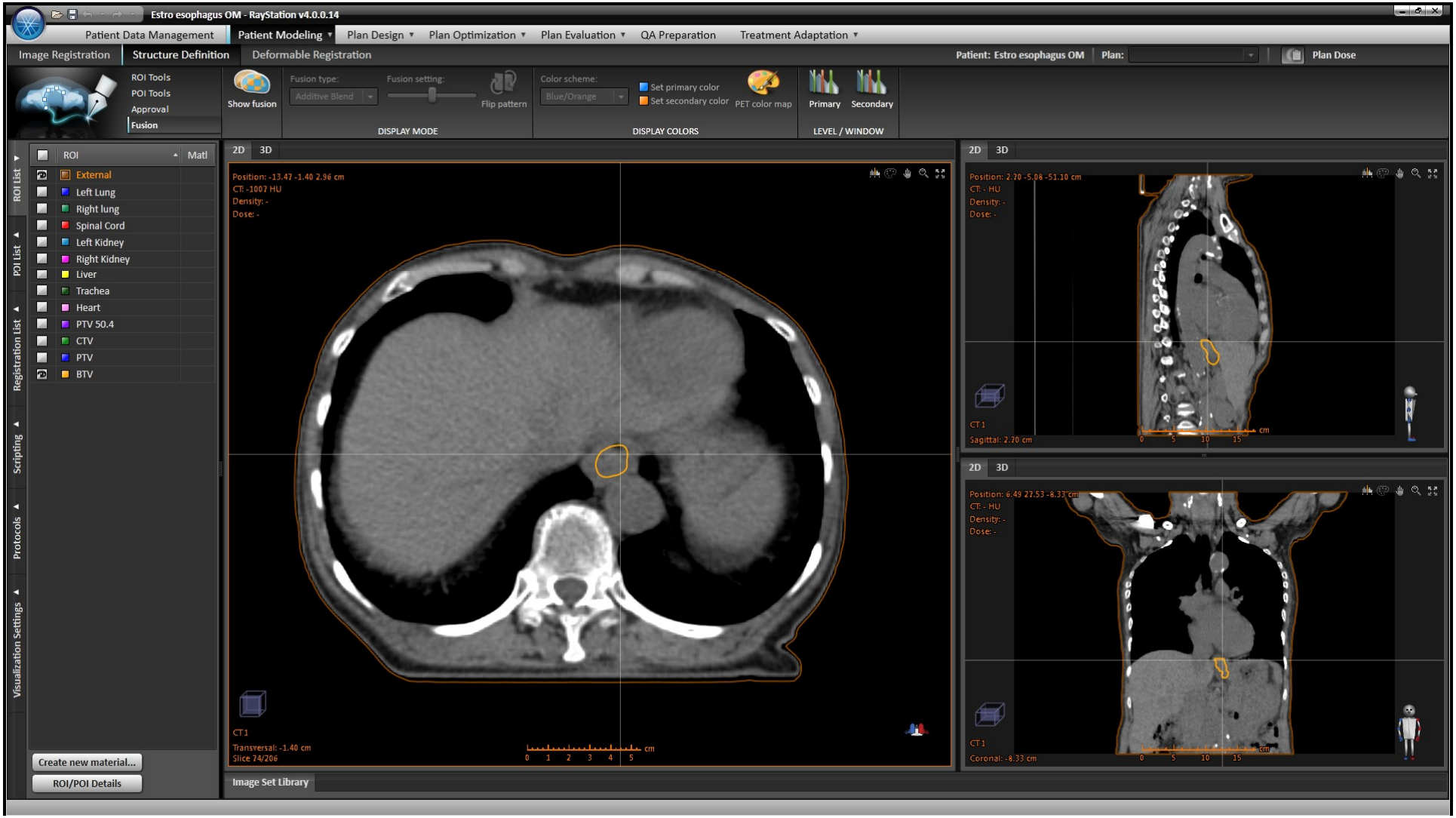
Clinical case: GTV?



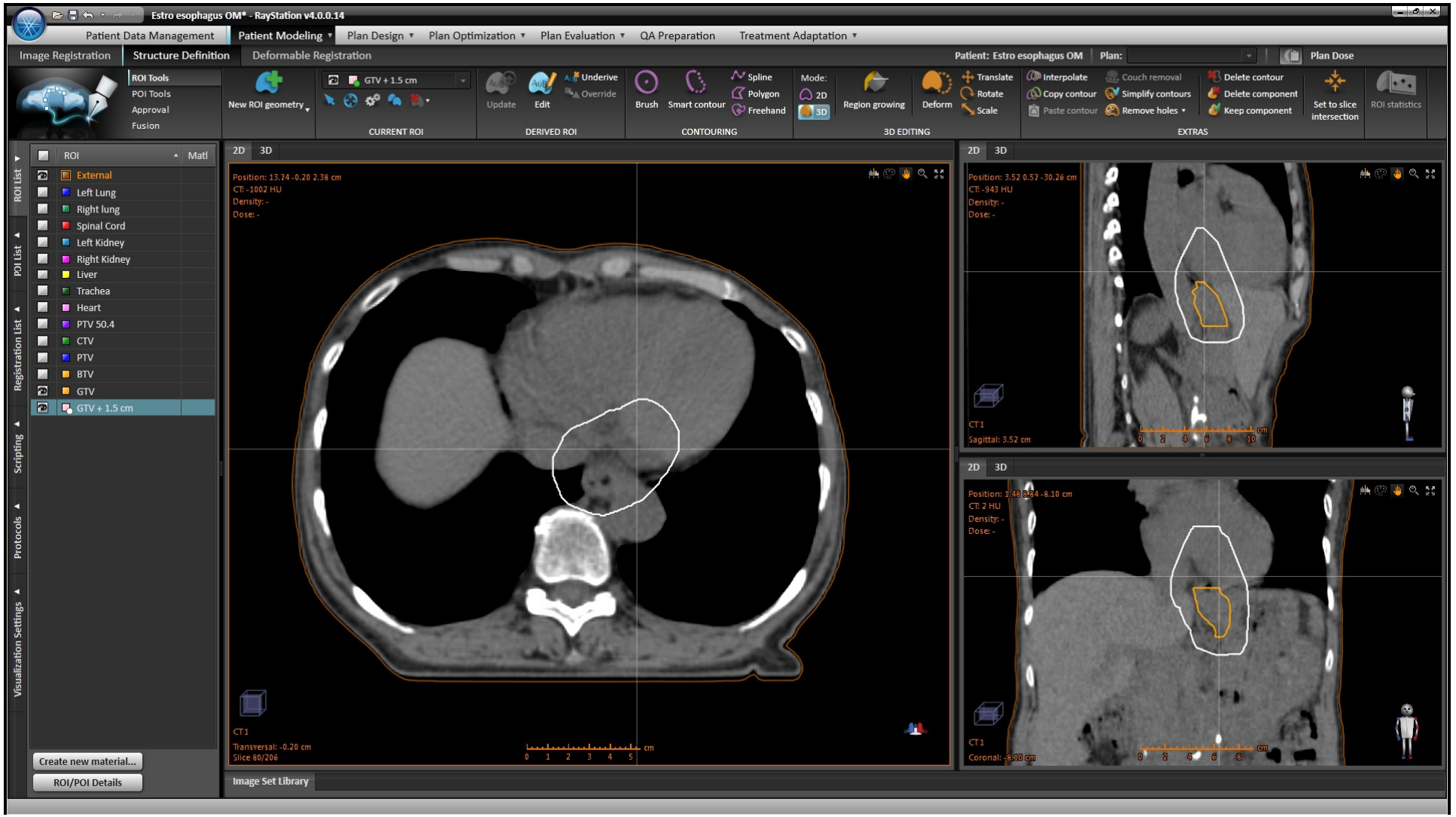
BTV?


Estro esophagus OM - RayStation v4.0.0.14
Patient Data Management
Patient Modeling
Plan Design
Plan Optimization
Plan Evaluation
QA Preparation
Treatment Adaptation
Image Registration
Structure Definition
Deformable Registration
Patient: Estro esophagus OM
Plan:
Plan Dose
ROI Tools
POI Tools
Approval
Fusion
Show fusion
Fusion type:
Additive Blend
Fusion setting:
Flip pattern
DISPLAY MODE
Color scheme:
Blue/Orange
Set primary color
Set secondary color
PET color map
DISPLAY COLORS
Primary
Secondary
LEVEL / WINDOW
ROI List
POI List
Registration List
Scripting
Protocols
Visualization Settings
2D
3D
Position: -14.27 -2.80 0.64 cm
CT: -994 HU
Density: -
Dose: -
Primary: CT 1
Secondary: PET 2
Transversal: -2.80 cm
Slice 67/206
Position: 2.46 -18.41 4.35 cm
CT: - HU
Density: -
Dose: -
Primary: CT 1
Secondary: PET 2
Sagittal: 2.46 cm
Position: -45.04 27.64 -8.10 cm
CT: - HU
Density: -
Dose: -
Primary: CT 1
Secondary: PET 2
Coronal: -8.10 cm
Image Set Library

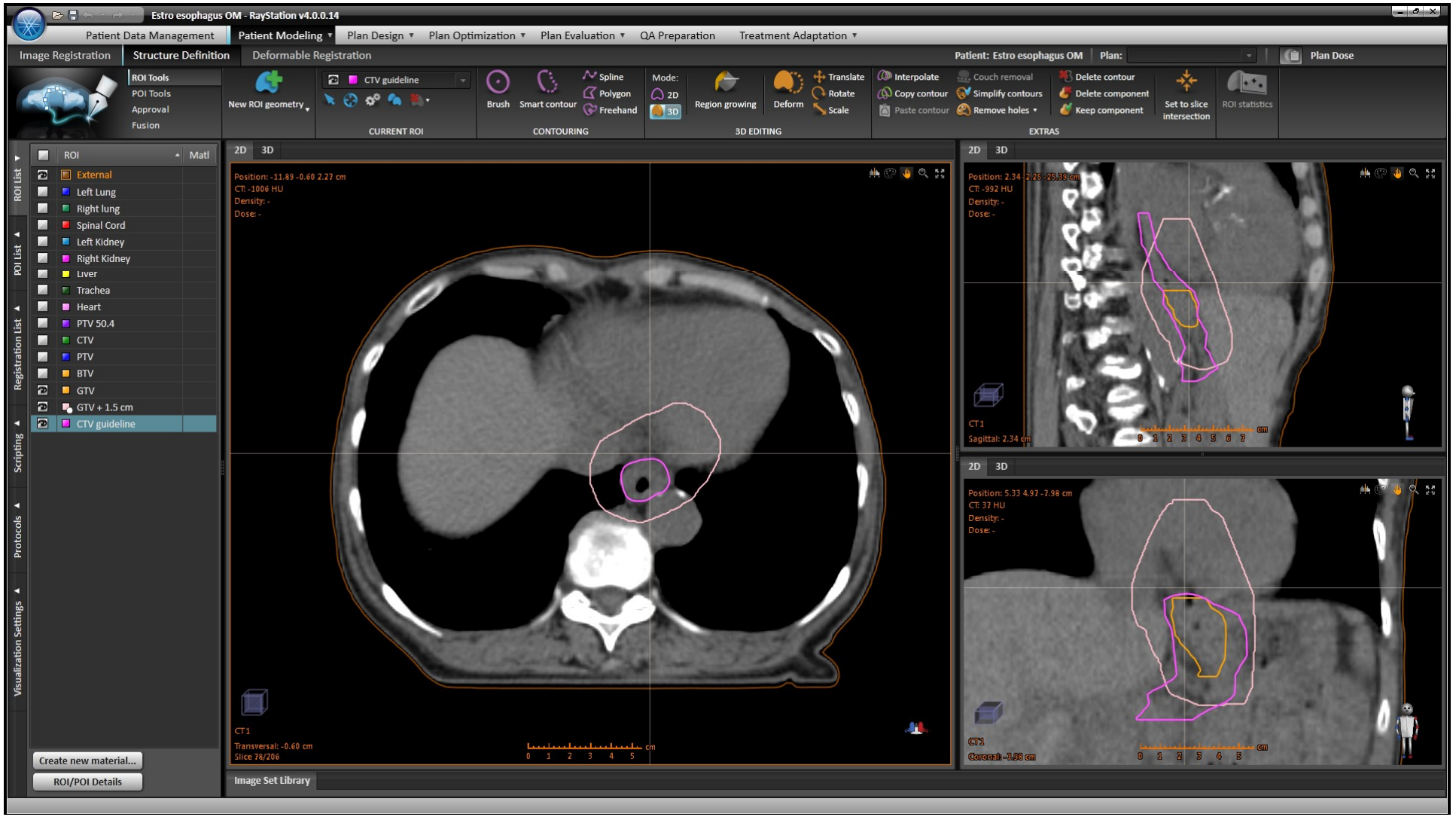
BTV ? CAVEAT…
SUV & registration



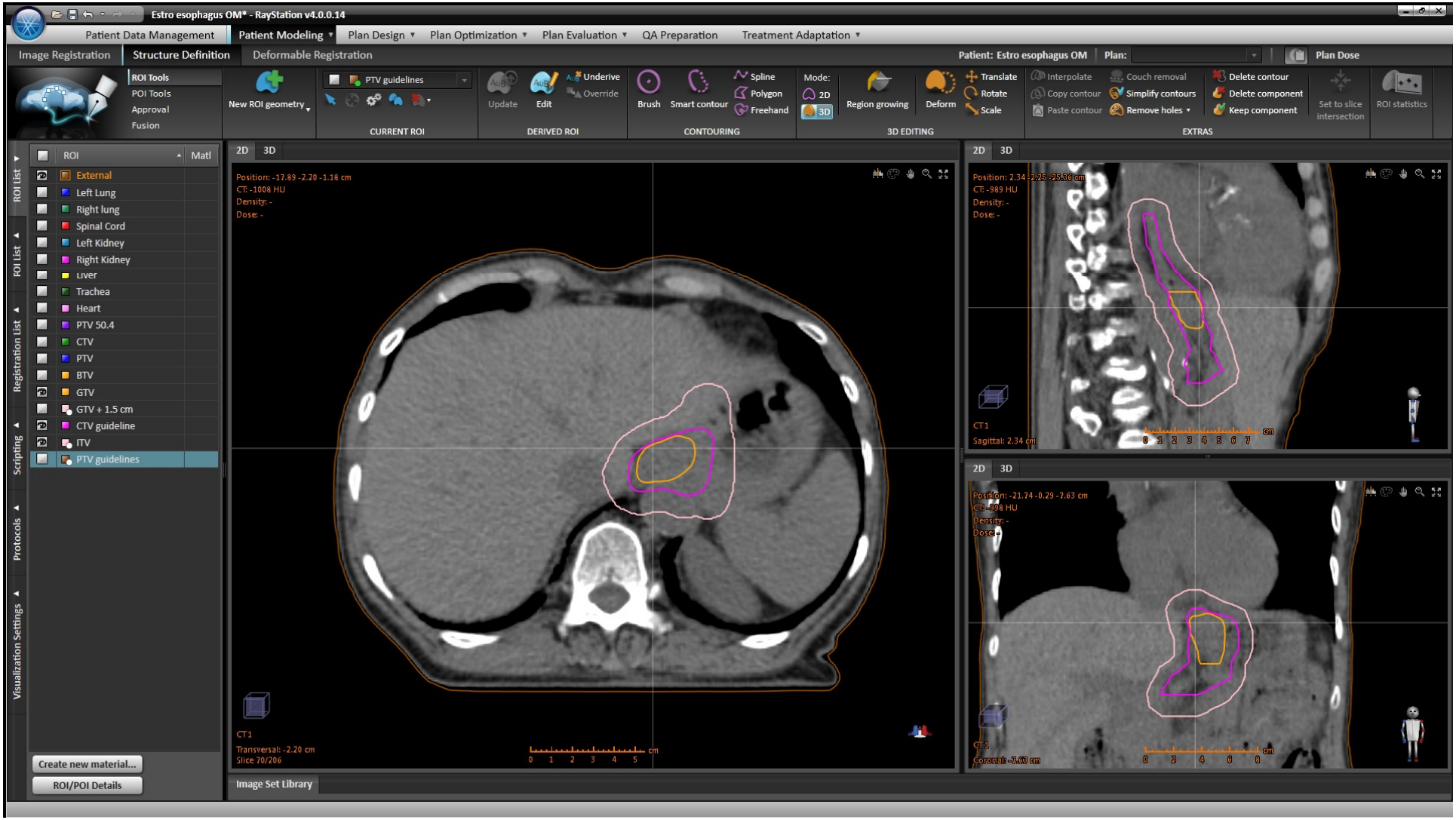
CTV margins: (1,5 cm; 5cm)?



CTV margins: anatomic corrections



ITV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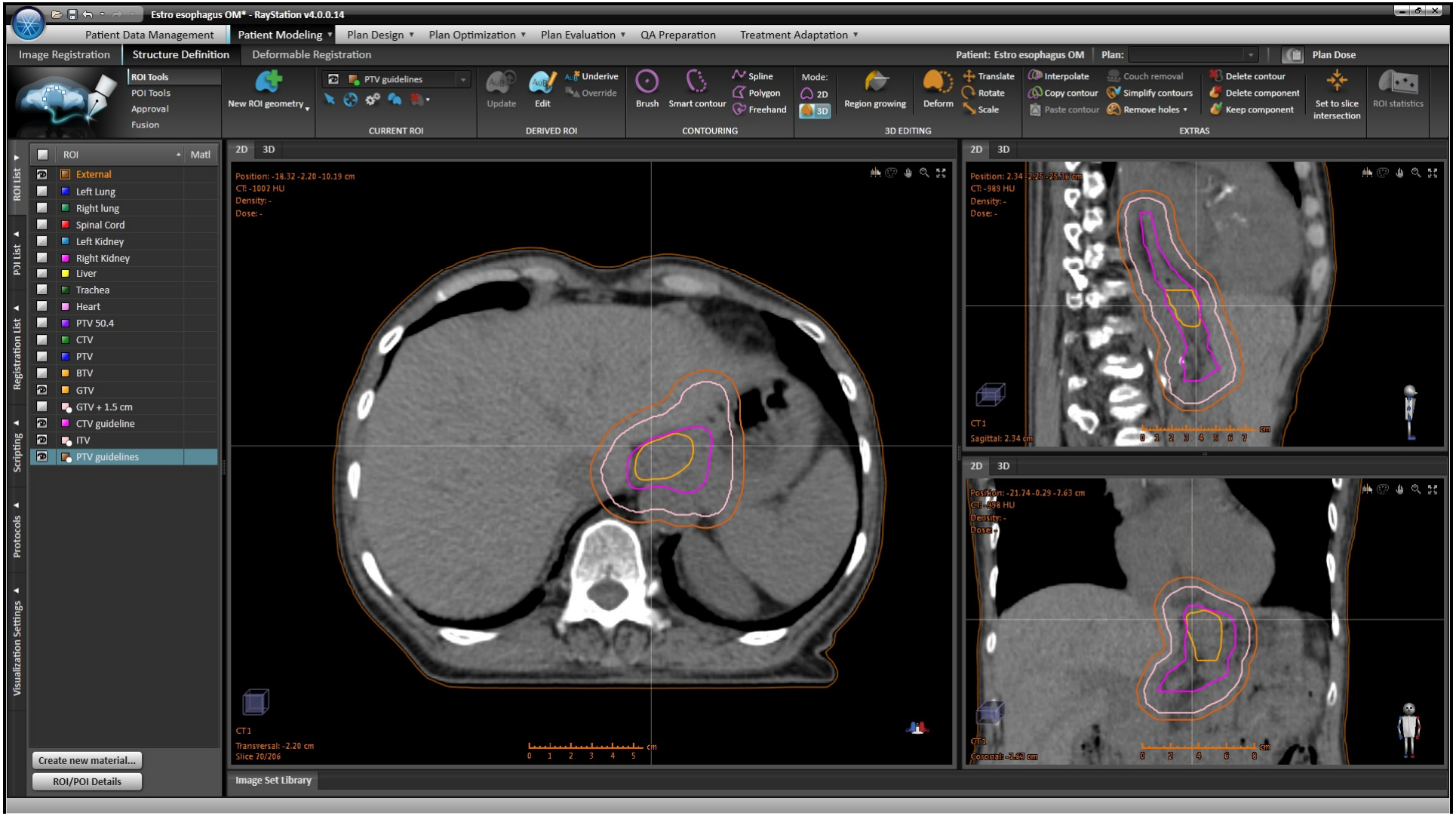
Structure Definition
Deformable Registration
Patient: Estro esophagus OM
Plan:
Plan Dose
ROI Tools
POI Tools
Approval
Fusion
New ROI geometry
PTV guidelines
Update
Edit
Underive
Override
CURRENT ROI
DERIVED ROI
Brush
Smart contour
Spline
Polygon
Freehand
CONTOURING
Mode:
2D
3D
Region growing
Deform
Translate
Rotate
Scale
3D EDITING
Interpolate
Copy contour
Paste contour
Couch removal
Simplify contours
Remove holes
Delete contour
Delete component
Keep component
EXTRAS
Set to slice intersection
ROI statistics
ROI
Matl
External
Left Lung
Right lung
Spinal Cord
Left Kidney
Right Kidney
Liver
Trachea
Heart
PTV 50.4
CTV
PTV
BTV
GTV
GTV + 1.5 cm
CTV guideline
ITV
PTV guidelines
Create new material...
ROI/POI Details
ROI List
POI List
Registration List
Scripting
Protocols
Visualization Settings
2D
3D
Position: -17.89 -2.20 -1.18 cm
CT: -1008 HU
Density: -
Dose: -
CT 1
Transversal: -2.20 cm
Slice 70/206
Position: 2.34 -2.25 -25.36 cm
CT: -989 HU
Density: -
Dose: -
CT 1
Sagittal: 2.34 cm
Position: -21.74 -0.29 -7.63 cm
CT: -998 HU
Density: -
Dose: -
CT 1
Coronal: -7.63 cm
Image Set Library

Planning Target Volume (PTV)

According to the ICRU 50 and 62 report

> PTV will then be defined as the ITV-volume plus a 3-D margin of ***5 mm*** (except if the centre has defined its own measures of positioning inaccuracy).

PTV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Copy contour
Paste contour
Couch removal
Simplify contours
Remove holes
Delete contour
Delete component
Keep component
EXTRAS
Set to slice intersection
ROI statistics
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Left Lung
Right lung
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3D
Position: -18.32 -2.20 -10.19 cm
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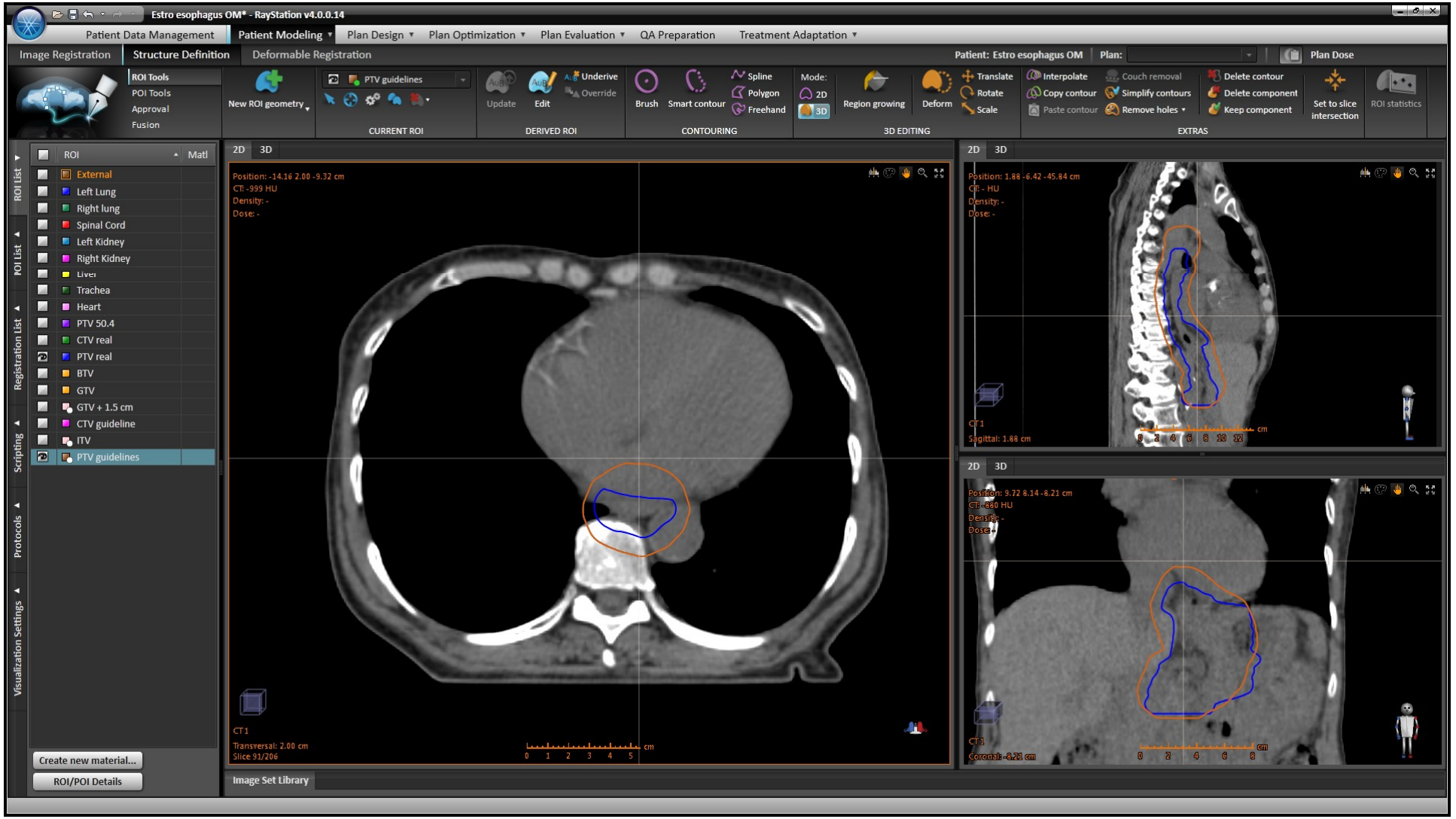
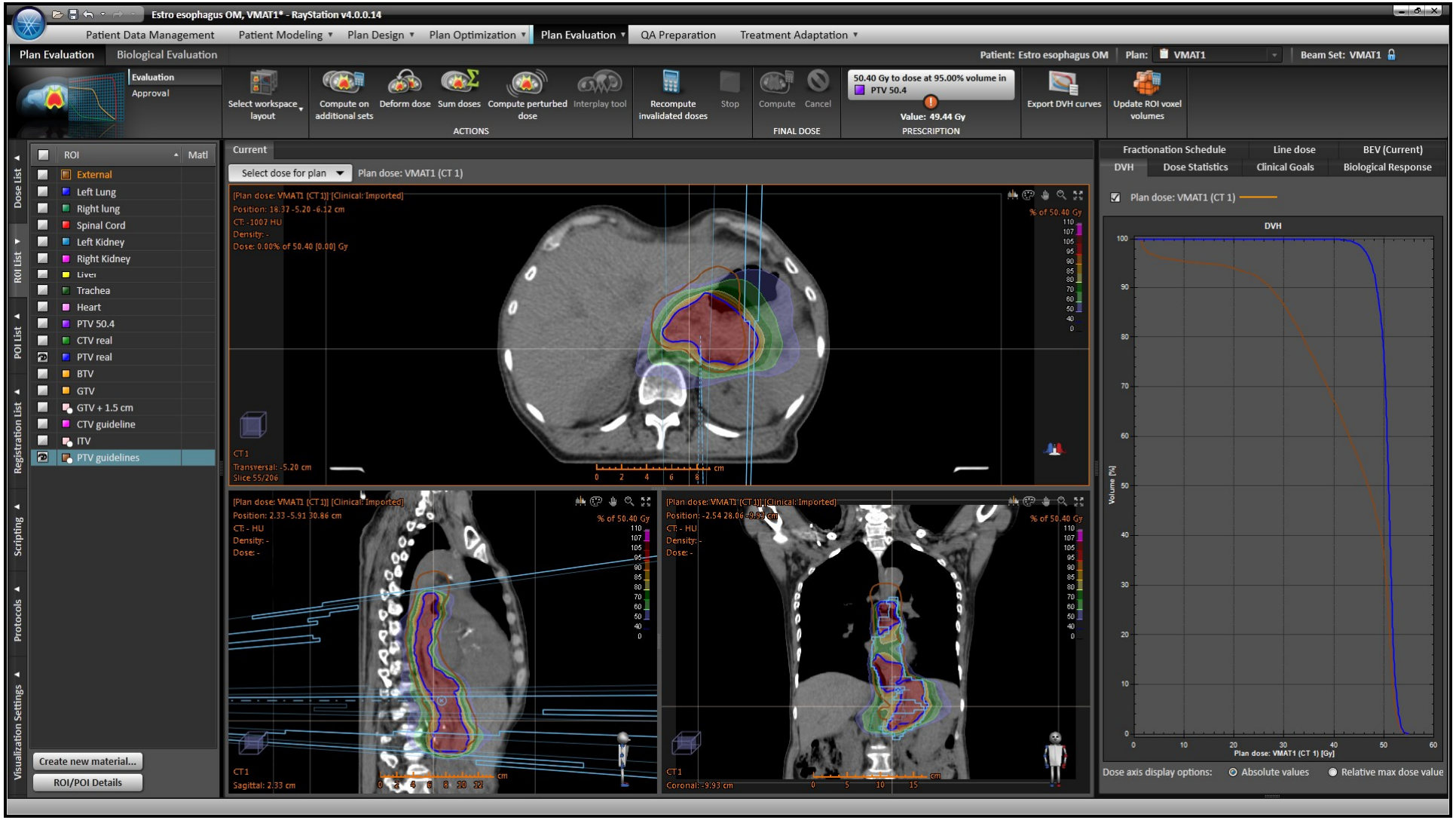
Slice 70/206
Position: 2.34 -2.25 -25.56 cm
CT: -989 HU
Density: -
Dose: -
CT 1
Sagittal: 2.34 cm
Position: -21.74 -0.29 -7.63 cm
CT: -998 HU
Density: -
Dose: -
CT 1
Coronal: -7.63 cm
Image Set Library

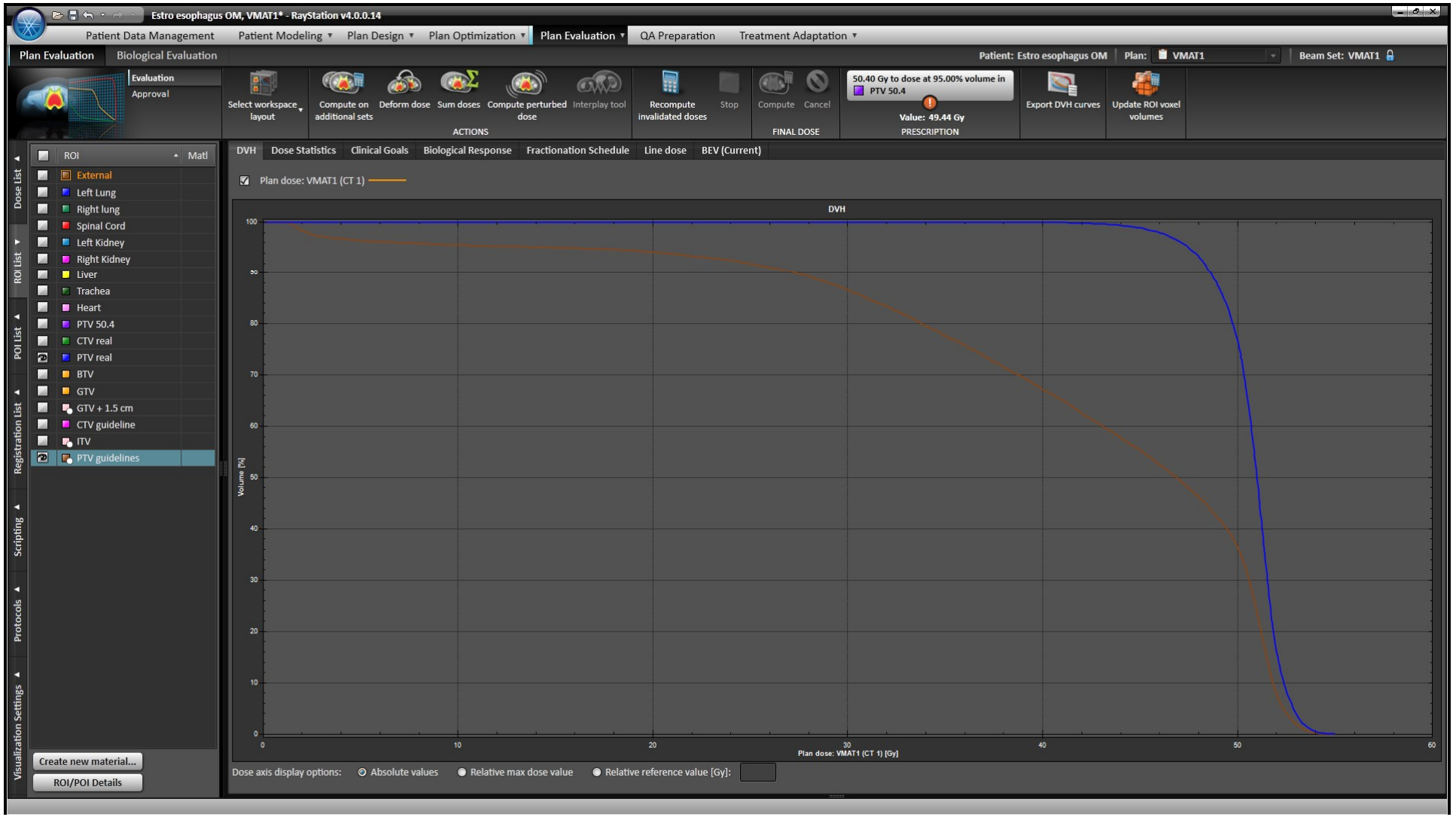
Reality vs guidelines (I)



Reality vs guidelines (II)



Reality vs guidelines (II)
does it matter?



Questions and doubts ?

Oesophageal cancer

Dose issues in esophageal tumor control

Marcel Verheij MD PhD
Department of Radiation Oncology
NKI, Amsterdam

ESTRO School

Contents

- Introduction
- Treatment options
- Radiotherapy: dose escalation

Epidemiology of esophageal cancer

- 2012: Europe ~46,000 cases/year; ~39,500 deaths
- 6th leading cause of cancer-related mortality
- 8th most common cancer worldwide
- Worldwide >450,000 people are affected
- Incidence is increasing rapidly
- Overall 5-year survival 15-25%
- Diagnosis at advanced (metastatic) stages
- 30-40% present with resectable disease
- SCC is predominant type; in some western European countries adenocarcinoma exceeds SCC

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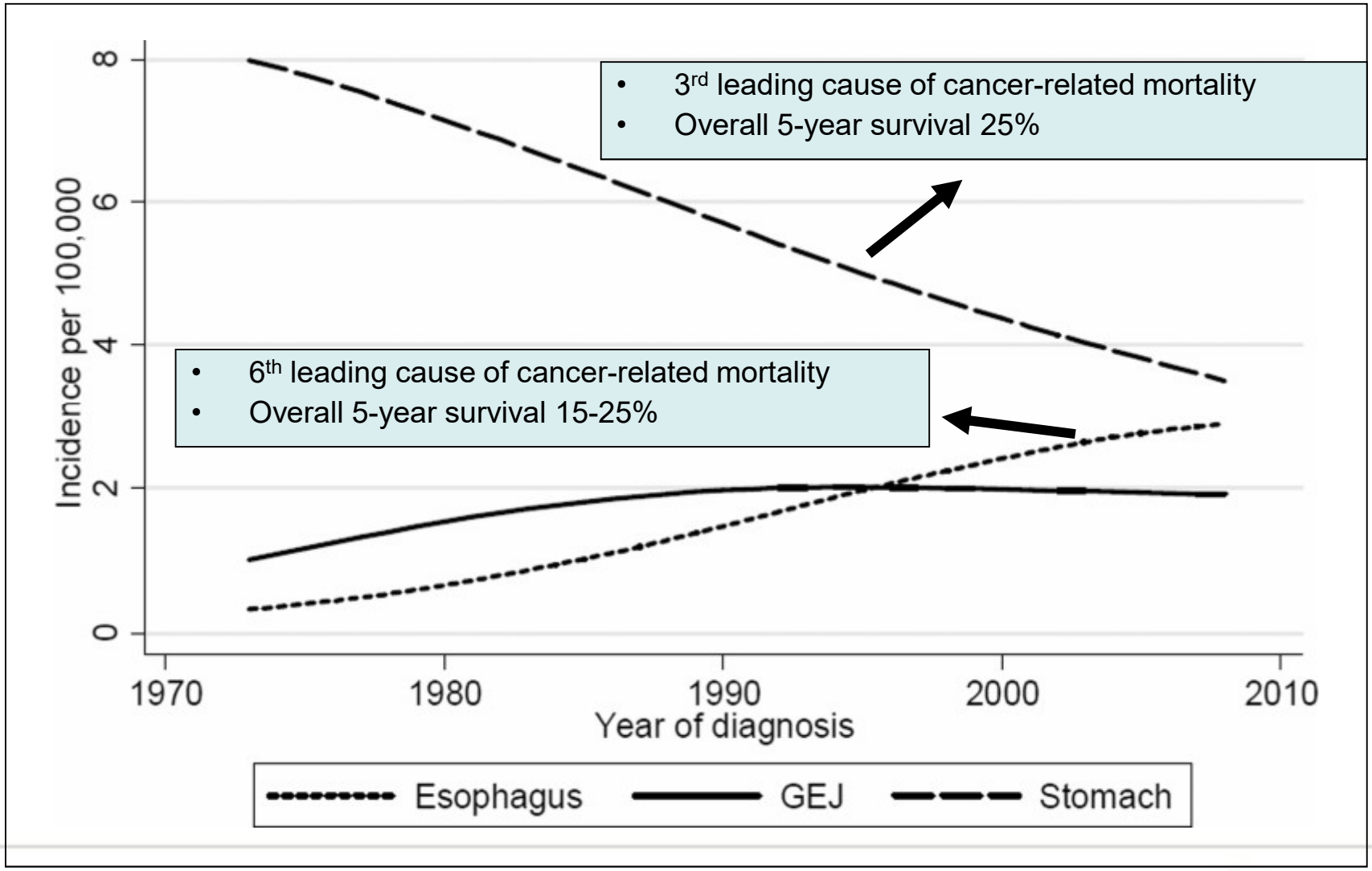
Incidence of adenocarcinoma of the esophagus, GEJ and stomach 1973 - 2008, United States



Buas et al, Semin Radiat Oncol 2013

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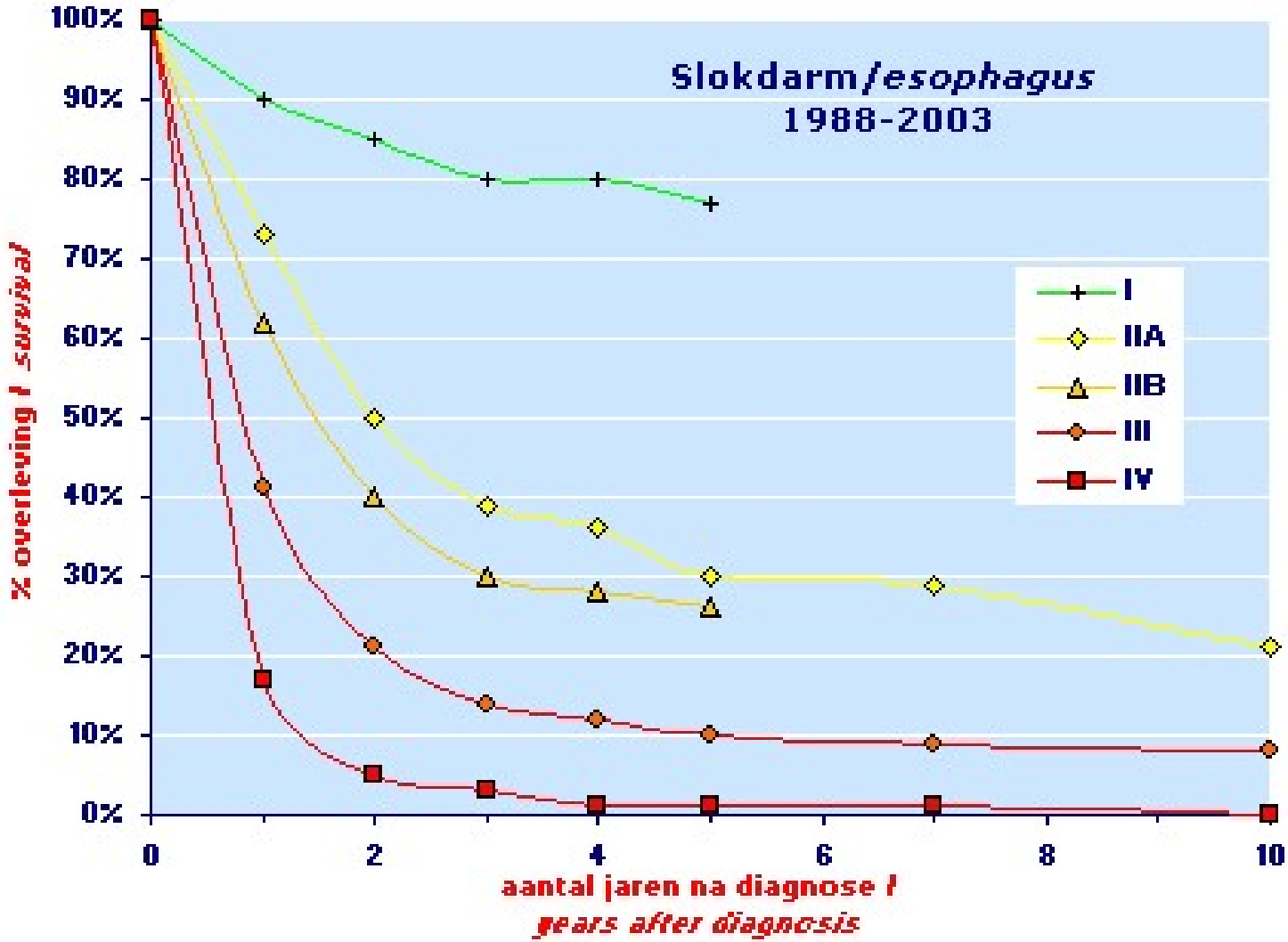
Relative survival according to stage in The Netherlands 1988 - 2003



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Esophageal cancer: risk factors

Oesophageal SCC

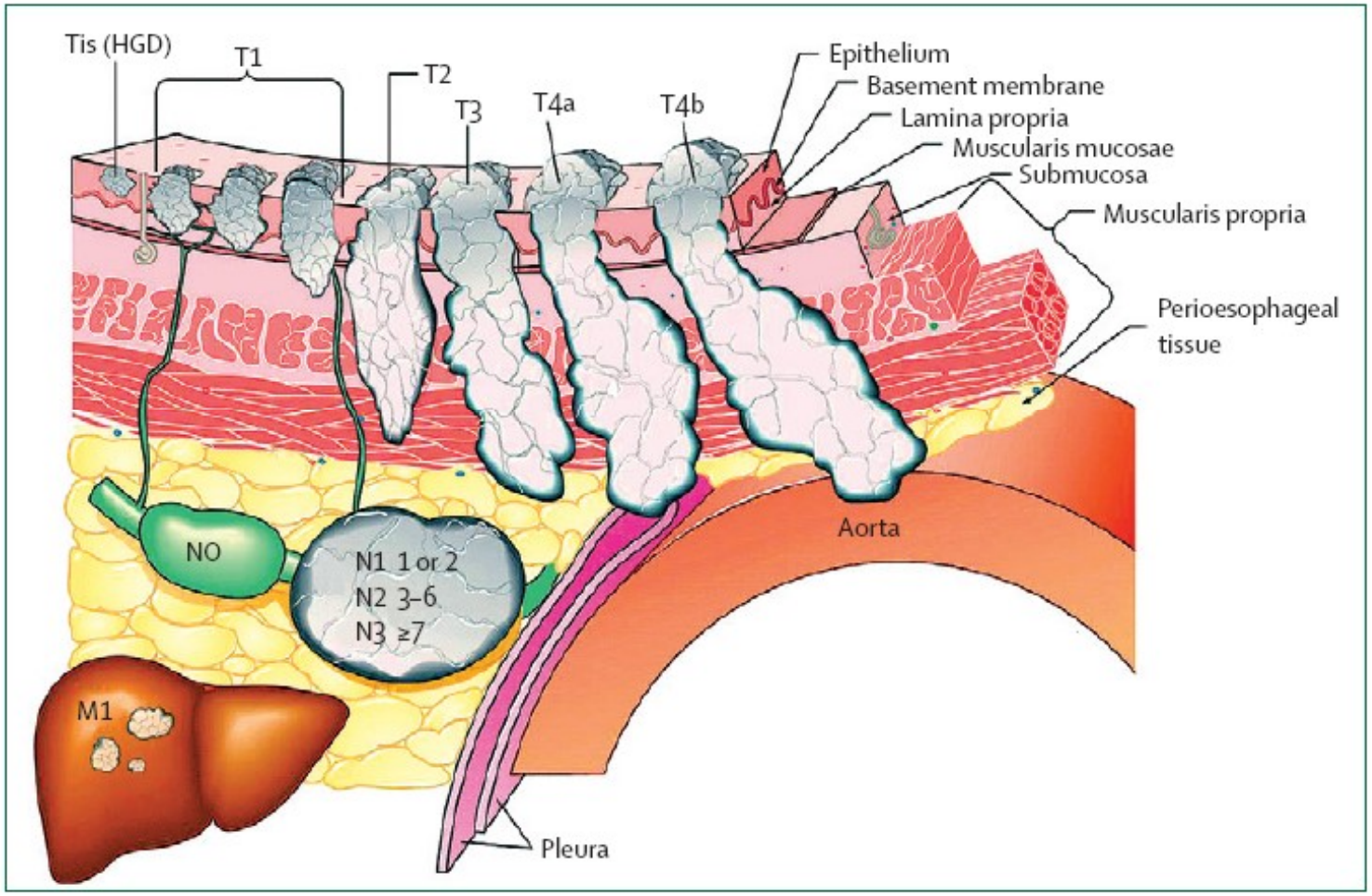
- Tobacco use
- Alcohol consumption
- Mutations of enzymes that metabolise alcohol
- Achalasia
- Caustic injury
- History of thoracic radiation
- Low socioeconomic status
- Poor oral hygiene
- Nutritional deficiencies
- Non-epidermolytic palmoplantar keratoderma

Oesophageal adenocarcinoma

- Symptomatic gastro-oesophageal reflux disease
- Barrett's oesophagus
- Obesity
- Tobacco use
- History of thoracic radiation
- Diet low in vegetables and fruits
- Increased age
- Male sex
- Medications that relax the lower oesophageal sphincter
- Familial history (rare)

TNM esophageal cancer 7th edition

(including esophagogastric junction)



Pennathur et al, Lancet 2013

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Treatment options

- Operable/resectable vs. inoperable/irresectable
- Surgery vs. neoadjuvant chemotherapy + surgery
- Neoadjuvant chemoradiotherapy with surgical resection
- Surgery with adjuvant chemotherapy, radiotherapy, or chemoradiotherapy
- Definitive (chemo-) radiotherapy

Surgery vs. neoadjuvant chemotherapy + surgery

	Number of patients	Study treatments	Chemotherapy regimen	Histology	Median survival (months)	Overall survival (%)
Kelsen et al, 1998[91]	440	Surgery vs surgery and chemotherapy	Cisplatin+fluorouracil for three cycles before surgery	204 (46%) SCC, 236 (54%) adenocarinoma	14·9 vs 16·1	(3-year) 26% vs 23%
MRC, 2002[92] and Allum et al, 2009*	802	Surgery vs surgery and chemotherapy	Cisplatin+fluorouracil for two cycles before surgery	247 (31%) SCC, 533 (66%) adenocarcinoma, 24 (3%) undifferentiated or unknown	13·3 vs 16·8	(5-year) 17% vs 23%†
Cunningham et al, 2006[93]	503	Surgery vs surgery and chemotherapy	Epirubicin+cisplatin+ fluorouracil for three cycles before and after surgery	503 (100%) adenocarcinoma (372 [74%] gastric, 131 [26%] oesophageal)	NR	(5-year) 23% vs 36%†

SCC=squamous-cell carcinoma. MRC=Medical Research Council Oesophageal Cancer Working Group. NR=not reported. *Appendix p 7. †Significant difference in favour of the neoadjuvant chemotherapy group.

Table 2: **Results of randomised trials of neoadjuvant chemotherapy**

- Rationale: control early spread of systemic disease
- Results not consistent
- MAGIC study (Cunningham) may not be generalisable to all esophageal adenocarcinoma (26% EGJ/adeno)

Pennathur et al, Lancet 2013

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Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

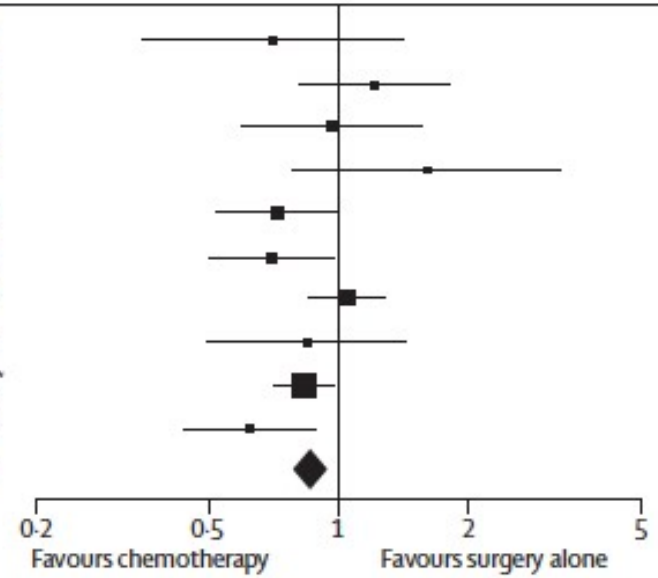
Katrin M Sjoquist, Bryan H Burmeister, B Mark Smithers, John R Zalcberg, R John Simes, Andrew Barbour, Val Gebski, for the Australasian Gastro-Intestinal Trials Group

A

	Chemotherapy (total)	Surgery alone (total)	Hazard ratio (95% CI)
Roth[23]	19	20	0·71 (0·36–1·43)
Nygaard[9]	56	25	1·22 (0·82–1·81)
Schlag[19]	22	24	0·97 (0·60–1·57)
Maipang[24]	24	22	1·61 (0·79–3·27)
Law[20]	74	73	0·73 (0·53–1·00)
Boonstra[37]	85	84	0·71 (0·51–0·98)
Kelsen[8]	233*	234	1·05 (0·86–1·28)
Ancona[21]	48	48	0·85 (0·50–1·44)
Allum[1]	400†	402*	0·84 (0·72–0·98)
Ychou[7]	85	84	0·63 (0·45–0·89)
Total	**1046**	**1016**	**0·87 (0·79–0·96)**

Heterogeneity: χ^2=15·77, df=9 (p=0·07); I^2=43%

Test for overall effect: Z=2·83 (p=0·005)



Sjoquist et al. Lancet Oncol 2011

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Surgery vs. neoadjuvant chemoradiotherapy + surgery

	Number of patients	Study treatments	Regimen	Histology	Median survival (months)	Overall survival (%)
Le Prise et al, 1994[94]	86	Surgery vs surgery and CRT	Sequential cisplatin+fluorouracil and RT to 20·0 Gy	86 (100%) SCC	10·0 vs 10·0	(1-year) 47% vs 47%
Walsh et al, 1996[98]	103	Surgery vs surgery and CRT	Concurrent cisplatin+fluorouracil and RT to 40·0 Gy	103 (100%) adenocarcinoma	11·0 vs 16·0	(3-year) 6% vs 32%*
Bosset et al, 1997[95]	282	Surgery vs surgery and CRT	Sequential interrupted cisplatin and RT to 37·0 Gy	282 (100%) SCC	18·6 vs 18·6	(3-year) 34% vs 36%
Urba et al, 2001[96]	100	Surgery vs surgery and CRT	Concurrent cisplatin+fluorouracil +vinblastine and RT to 45·0 Gy	25 (25%) SCC, 75 (75%) adenocarcinoma	17·6 vs 16·9	(3-year) 16% vs 30%
Burmeister et al, 2005[100]	256	Surgery vs surgery and CRT	Concurrent cisplatin+fluorouracil and RT to 35·0 Gy	95 (37%) SCC, 158 (62%) adenocarcinoma, 3 (1%) mixed or other	22·2 vs 19·3	NR
Tepper et al, 2008[99]	56	Surgery vs surgery and CRT	Concurrent cisplatin+fluorouracil and RT to 50·4 Gy	14 (25%) SCC, 42 (75%) adenocarcinoma	21·5 vs 53·8	(5-year) 16% vs 39%*

CRT=chemoradiotherapy. RT=radiotherapy. SCC=squamous-cell carcinoma. NR=not reported. *Significant difference in favour of neoadjuvant chemoradiotherapy.

***Table 3*: Results of randomised trials of neoadjuvant chemoradiotherapy**

- Rationale: downstaging, improve resectability (R0), survival benefit
- Results not consistent
- CROSS study and meta-analysis show benefit for preoperative CRT

Pennathur et al, Lancet 2013

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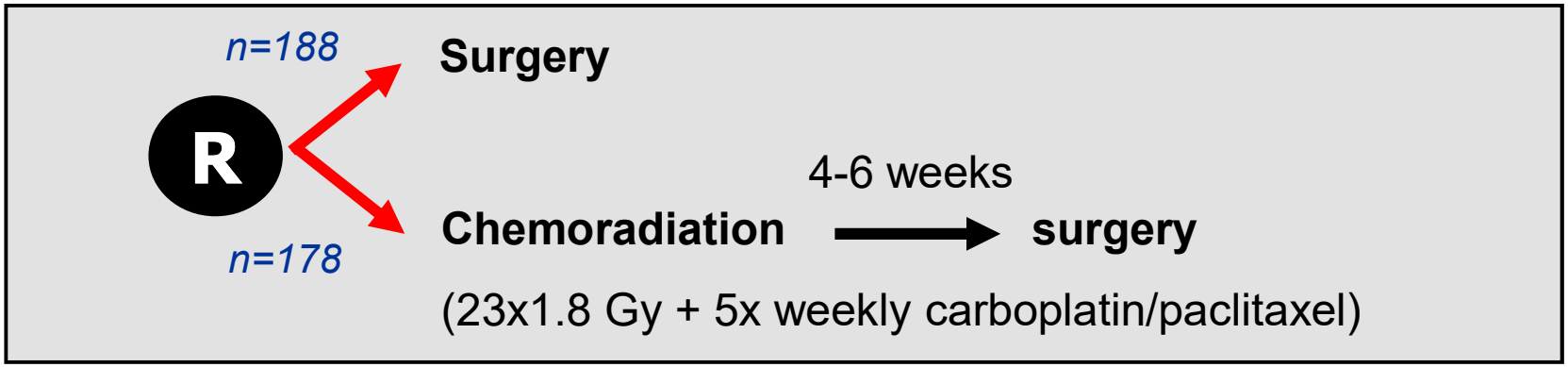
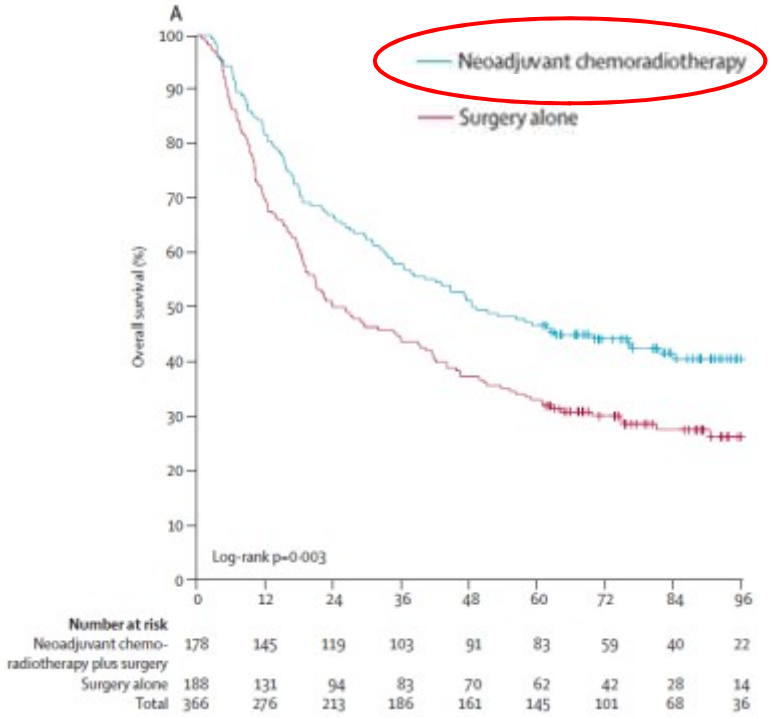
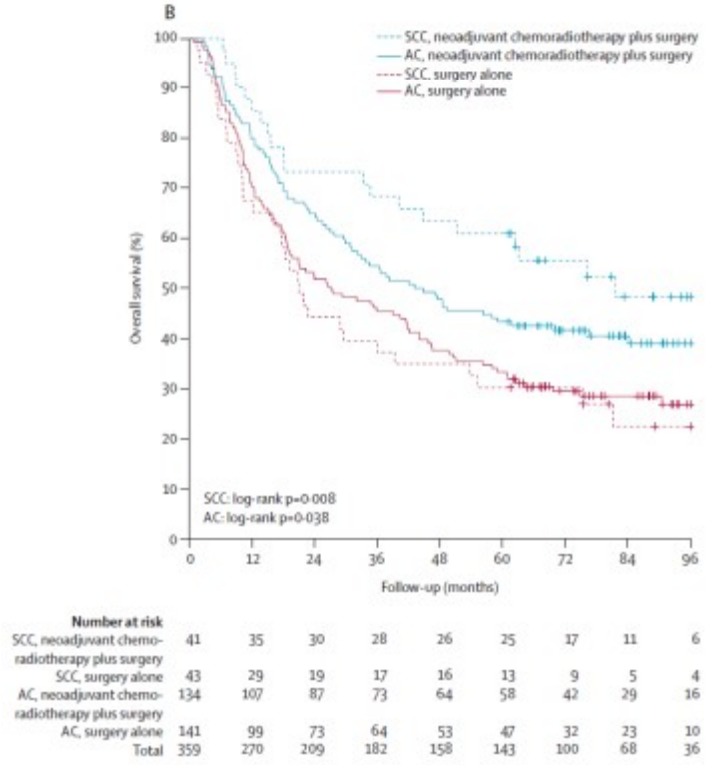
Pre-operative chemoradiation improves outcome in esophageal and junctional cancer: the CROSS trial







Shapiro et al. Lancet Oncol 2015 (median FU 84.1 months)

Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

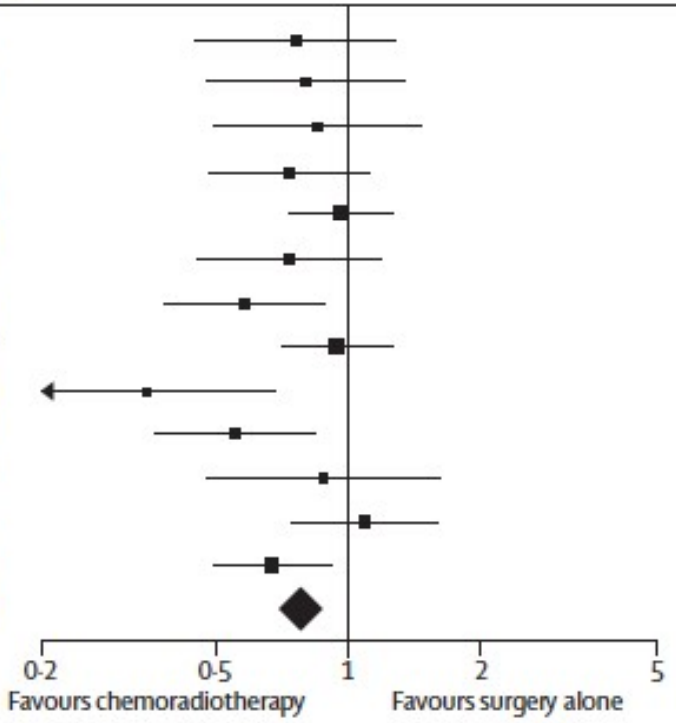
Katrin M Sjoquist, Bryan H Burmeister, B Mark Smithers, John R Zalcberg, R John Simes, Andrew Barbour, Val Gebski, for the Australasian Gastro-Intestinal Trials Group

A

	Chemoradiotherapy (total)	Surgery alone (total)	Hazard ratio (95% CI)
Nygaard[9]	53	25	0·76 (0·45–1·28)
Apinop[39]	35	34	0·80 (0·48–1·34)
Le Prise[10]	45*	41	0·85 (0·50–1·46)
Urba[40]	50	50	0·74 (0·48–1·12)
Bosset[12]	148	145	0·96 (0·73–1·27)
Walsh (SCC)[13]	29	32	0·74 (0·46–1·18)
Walsh (adenocarcinoma)[14]	58	55	0·58 (0·38–0·88)
Burmeister[22]	128†	128‡	0·94 (0·70–1·26)
Tepper[43]	30	26	0·35 (0·18–0·68)
Lv[41]	80	80	0·55 (0·36–0·84)
Lee[17]	51	50	0·88 (0·48–1·62)
Mariette[11]	97	98	1·09 (0·74–1·59)
van der Gaast[42]	176	188	0·67 (0·49–0·91)
Total	**980**	**952**	**0·78 (0·70–0·88)**

Heterogeneity: χ^2=18·04, df=12 (p=0·11); I^2=33%

Test for overall effect: Z=4·28 (p<0·0001)



Sjoquist et al. Lancet Oncol 2011

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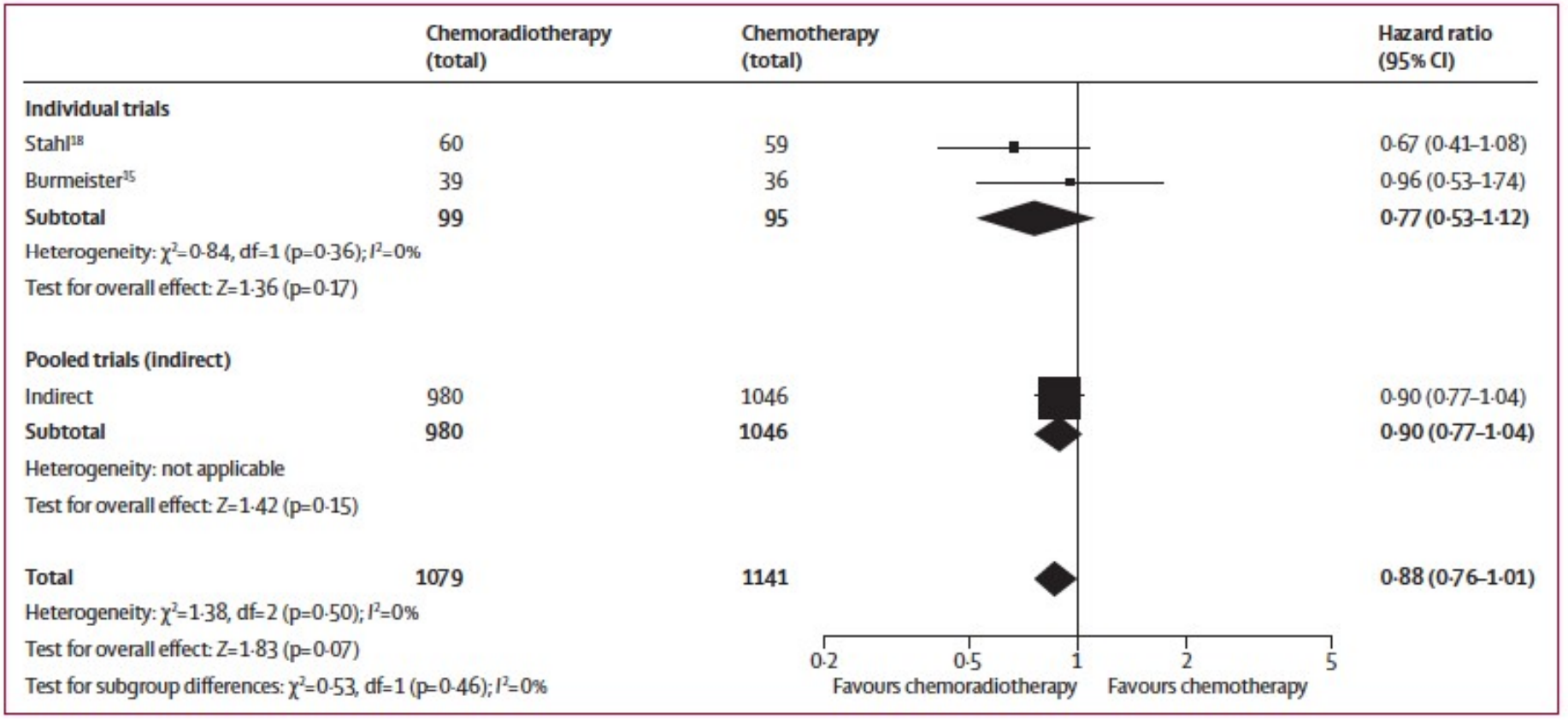

Sjoquist et al. Lancet Oncol 2011

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Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

	Year started	Radiotherapy schedule	Chemotherapy schedule	Concurrent or sequential	Tumour type	Sample size	Median follow-up (months)*
Chemoradiotherapy *vs* surgery alone							
Nygaard[9]	1983	35 Gy, 1·75 Gy per fraction over 4 weeks	Two cycles: cisplatin 20 mg/m² days 1–5; bleomycin 5 mg/m² days 1–5	Sequential	SCC	78	18†
Apinop[39]	1986	40 Gy, 2 Gy per fraction over 4 weeks	Two cycles: cisplatin 100 mg/m² day 1; fluorouracil 1000 mg/m² days 1–4	Concurrent	SCC	69	12†
Le Prise[10]	1988	20 Gy in 10 fractions over 12 days	Two cycles: cisplatin 100 mg/m² day 1; fluorouracil 600 mg/m² days 2–5 and 22–25	Sequential	SCC	86	12
van der Gaast[42]‖	2004	41·4 Gy, 1·8 Gy per fraction over 4·6 weeks	5 weeks concurrent chemotherapy: carboplatin area under curve=2 and paclitaxel 50 mg/m² on day 1 weekly	Concurrent	SCC and adenocarcinoma	364	32

Different neoadjuvant schedules:

- 20-50.5 Gy in 10-28 Fx
- 5FU/cis; bleo/cis; paclitaxel/cis; paclitaxel/carbo
- Sequential/concurrent

Sjoquist et al. Lancet Oncol 2011

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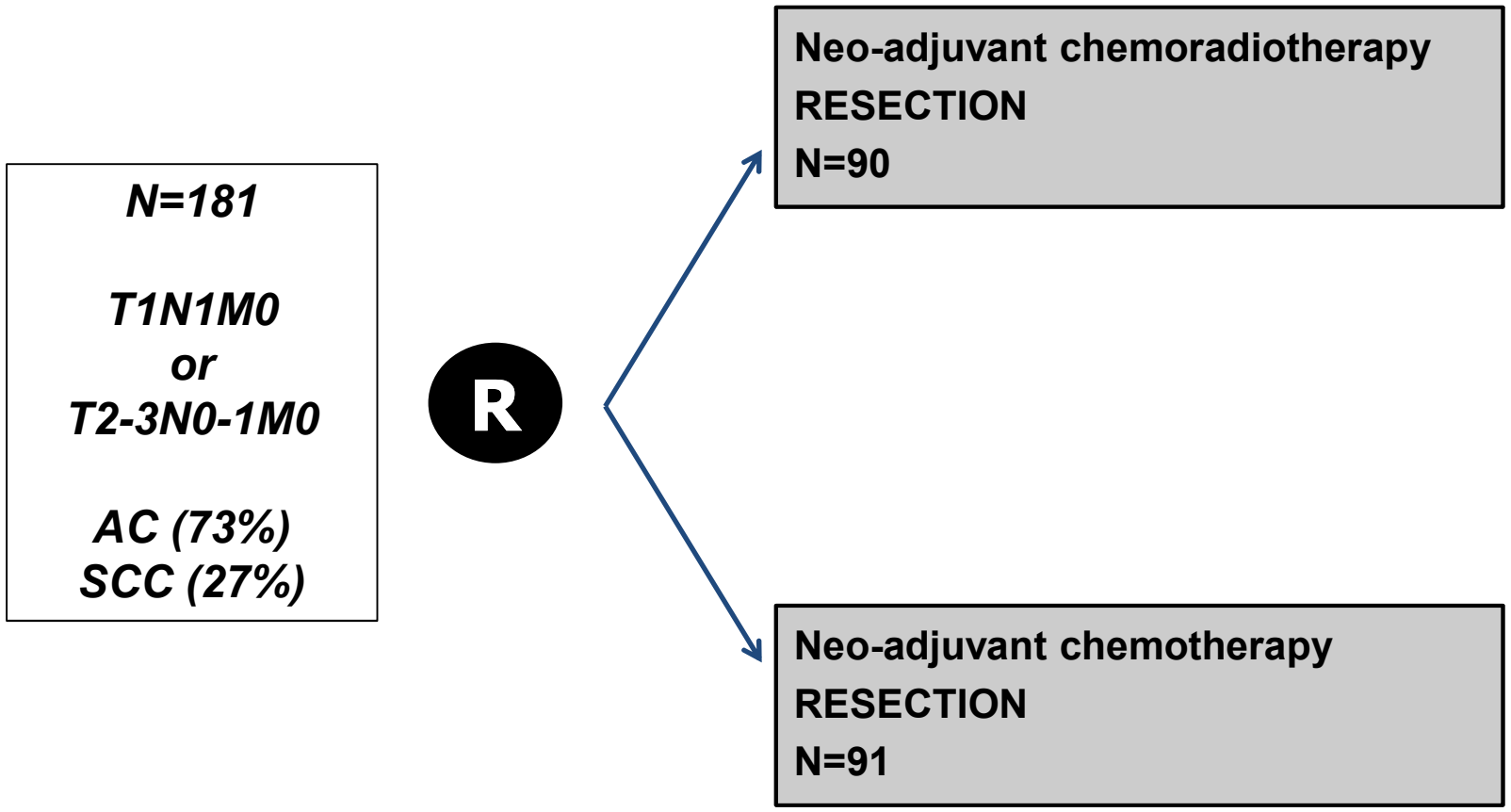
Neo-adjuvant chemoradiotherapy vs. chemotherapy



Klevebro et al. Ann Oncol 2016

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Neo-adjuvant chemoradiotherapy vs. chemotherapy

Primary endpoint: Histological complete response (pCR)

	Neo-adjuvant Chemoradiotherapy	Neo-adjuvant Chemotherapy	p-value
pCR	28%	9%	0.002
N+	35%	65%	0.001
R0	87%	74%	0.04

Klevebro et al. Ann Oncol 2016

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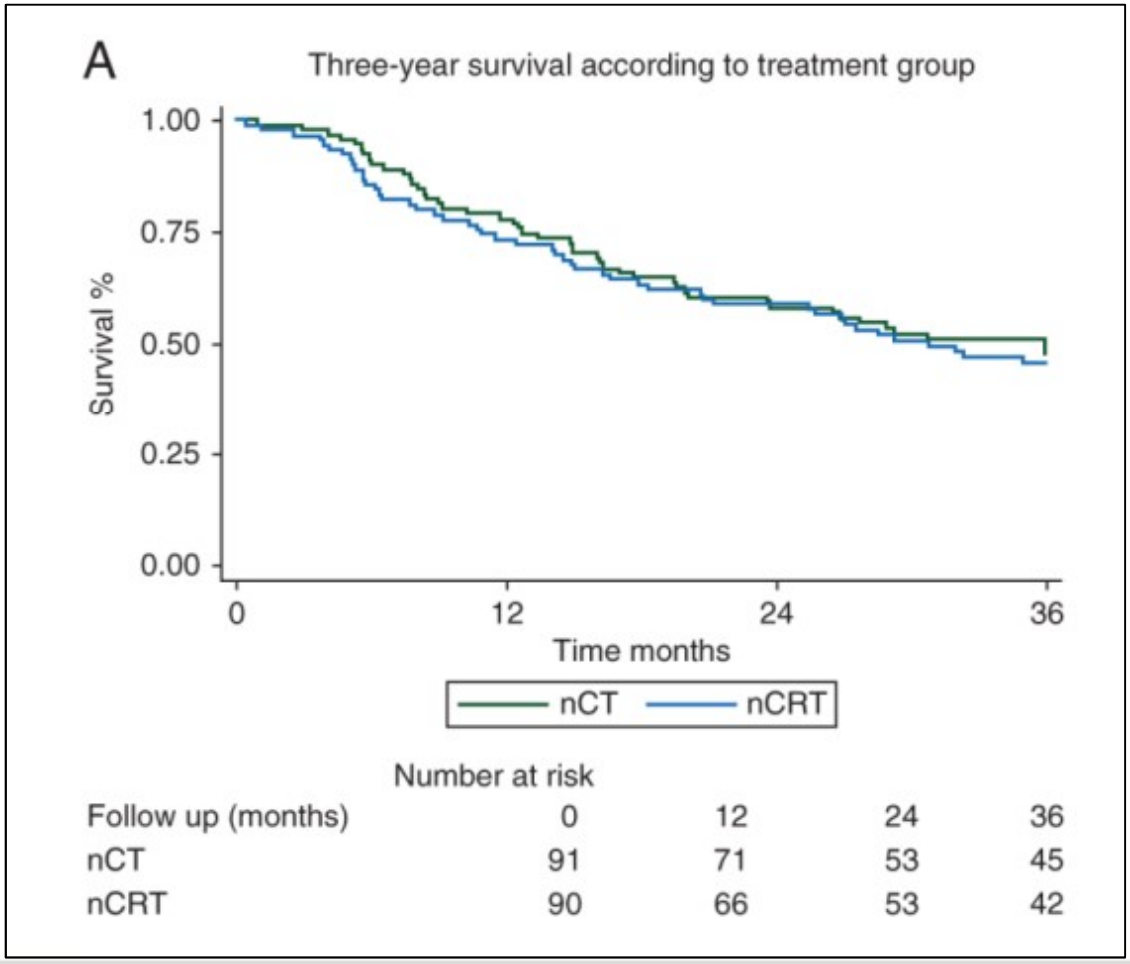
Neo-adjuvant chemoradiotherapy vs. chemotherapy



Klevebro et al. Ann Oncol 2016

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Surgery vs. surgery + adjuvant chemotherapy, radiotherapy, CRT

	Number of patients	Study treatments	Regimen	Histology	Median survival (months)	Overall survival (%)
Macdonald et al, 2001[106]	556	Surgery vs surgery and adjuvant CRT	Sequential and concurrent CRT with fluorouracil	556 (100%) adenocarcinoma (445 [80%] stomach, 111 [20%] gastro-oesophageal junction)	27 vs 36	(3-year) 41% vs 50%*
Ando et al, 2003[105]	242	Surgery vs surgery and adjuvant chemotherapy	Fluorouracil+ cisplatin	242 (100%) SCC	NR	(5-year) 52% vs 61%†
Armanios et al, 2004[103]‡	55	Surgery and adjuvant chemotherapy	Cisplatin+ paclitaxel	55 (100%) adenocarcinoma	31·2	(3-year) 42%
Xiao et al, 2003§	495	Surgery vs surgery and adjuvant RT	50·0–60·0 Gy in 25–30 fractions	495 (100%) SCC	NR	(5-year) 31·7% vs 41·3%
Ténière et al, 1991§	221	Surgery vs surgery and adjuvant RT	45·0–55·0 Gy	221 (100%) SCC	18 vs 18	(5-year) 17·6% vs 18·6%
Fok et al, 1993§	130	Surgery vs surgery and adjuvant RT	49·0–52·5 Gy in 14 fractions	104 (80%) SCC, 26 (20%) adenocarcinoma	15·2 vs 8·7¶	NR
Zieren et al, 1995§	68	Surgery vs surgery and adjuvant RT	Up to 30·6 Gy	68 (100%) SCC	NR	(3-year) 20% vs 22%

CRT=chemoradiotherapy. RT=radiotherapy. SCC=squamous-cell carcinoma. NR=not reported. *Difference significant for overall survival. †Although overall survival did not differ (p=0·13), disease-free surival was improved with adjuvant chemotherapy (45% vs 55%, p=0·037). ‡Phase 2 non-randomised, non-controlled trial. §Appendix pp 7–8. ¶Difference significant for median survival.

Table 4: **Results of trials of adjuvant chemotherapy, radiotherapy, and chemoradiotherapy** *Pennathur et al, Lancet 2013*

- Rationale: may be beneficial for specific subgroups (node-positive disease; positive margins)
- No consistent benefits

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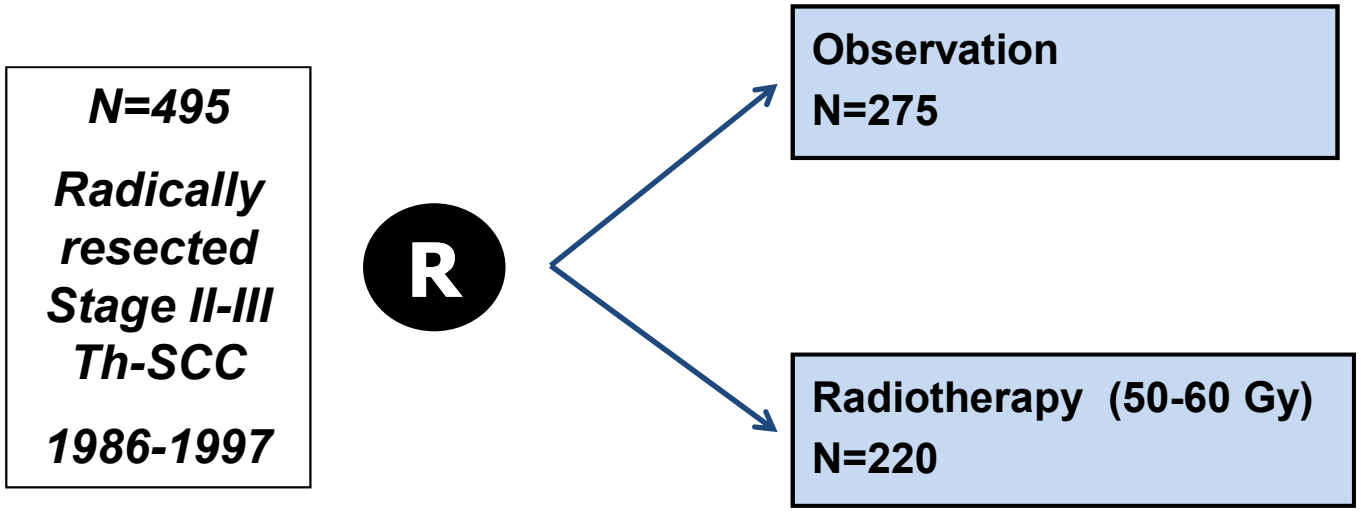
Post-operative Radiotherapy



Primary endpoint: Survival

Xiao et al. Ann Thorac Surg 2003

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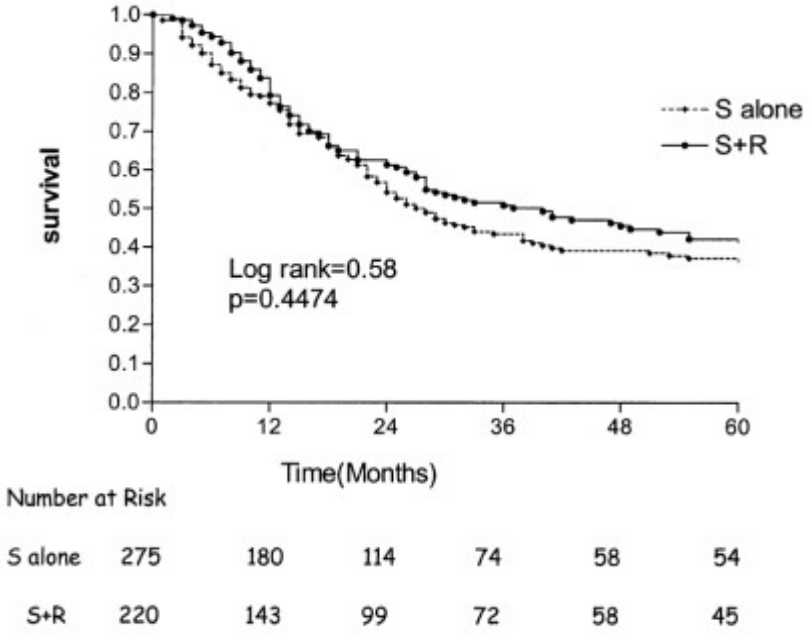
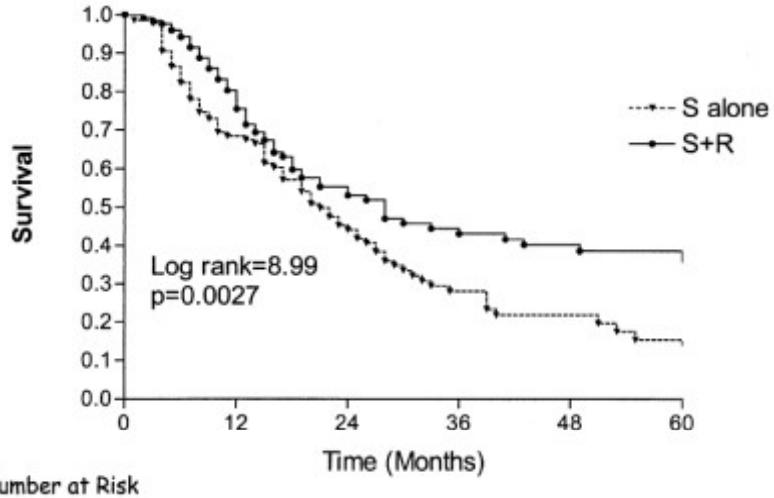
Post-operative Radiotherapy

All stages



Number at Risk						
S alone	275	180	114	74	58	54
S+R	220	143	99	72	58	45

Stage III



Number at Risk						
S alone	143	69	39	15	9	6
S+R	129	78	47	32	24	10

Table 2. Cause of Failure as Related to Treatment

	S (n = 243)		S+R (n = 191)			
	n	%	n	%	χ^2	*p*
Intrathoracic lymph node metastasis	63	25.0	31	16.2	5.925	0.015
Anastomotic recurrence	14	5.8	1	0.5	8.793	0.003
Supraclavicular lymph node metastasis	38	13.2	6	3.1	13.439	0.000
Intraabdominal metastasis	24	9.9	14	7.3	0.868	0.351
Hematogenous metastasis	44	18.1	45	23.6	1.951	0.162

S = surgery alone; S+R = surgery plus radiotherapy.

Xiao et al. Ann Thorac Surg 2003

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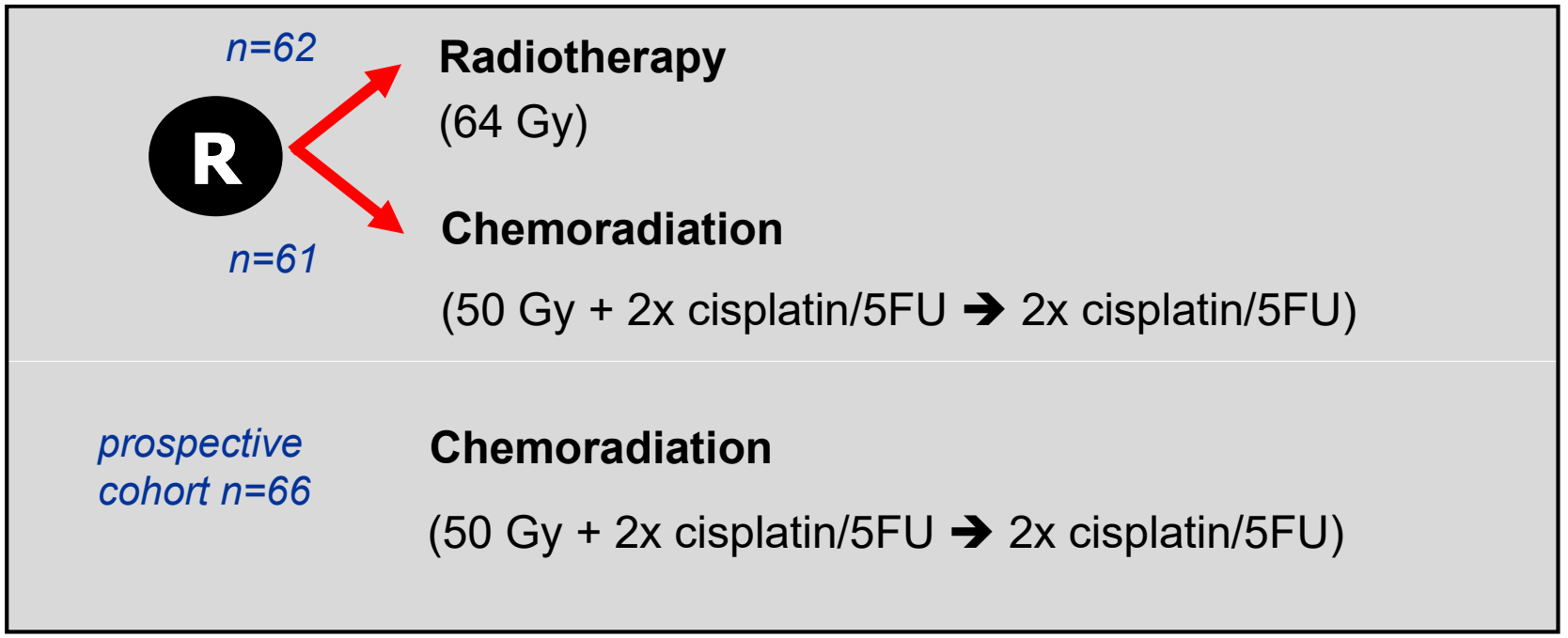
Definitive chemoradiotherapy vs. radiotherapy in locally advanced esophageal cancer: RTOG 85-01



Al-Sarraf et al. J Clin Oncol 1997

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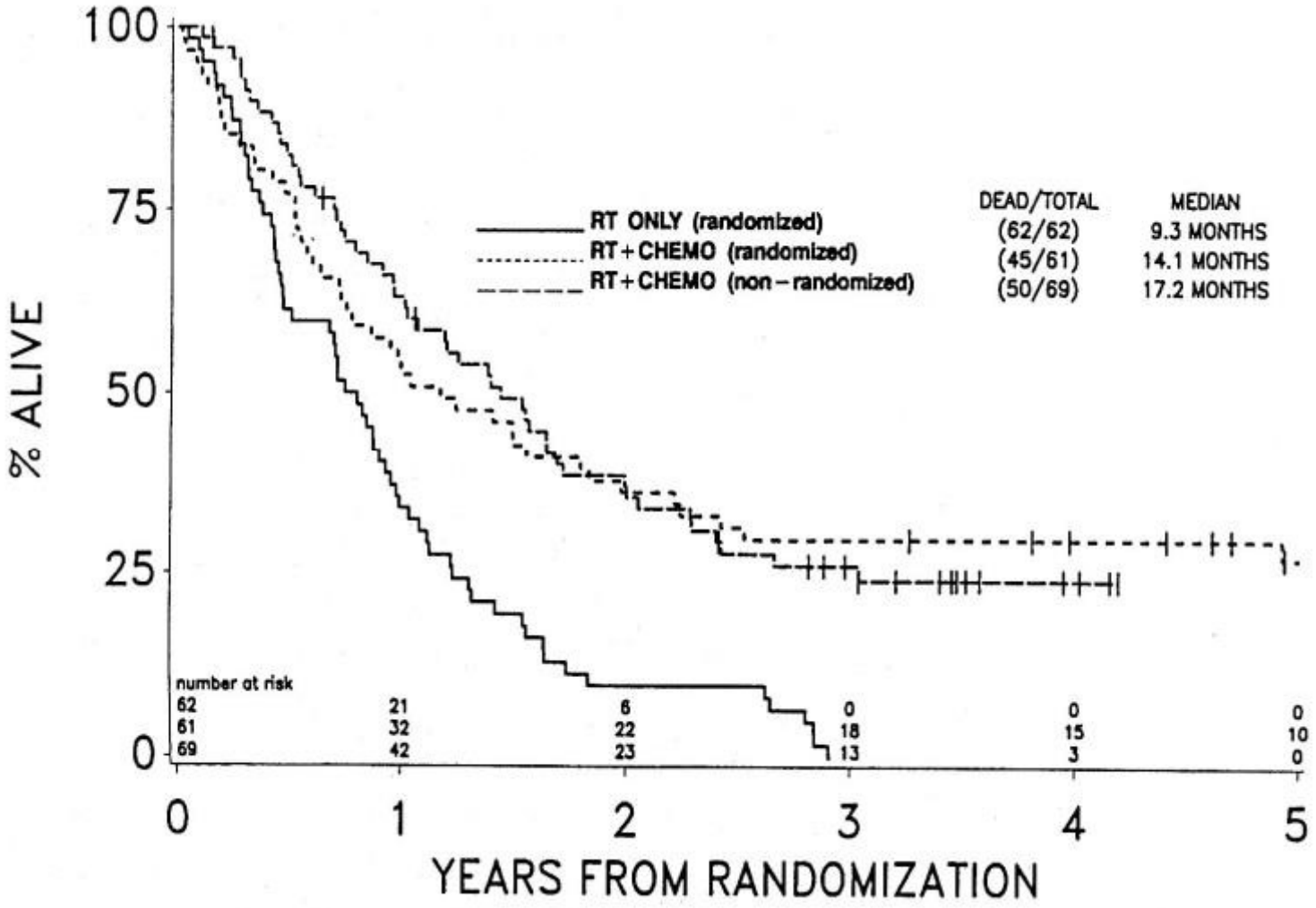
Definitive chemoradiotherapy is superior to radiotherapy in locally advanced esophageal cancer: RTOG 85-01



Al-Sarraf et al. J Clin Oncol 1997

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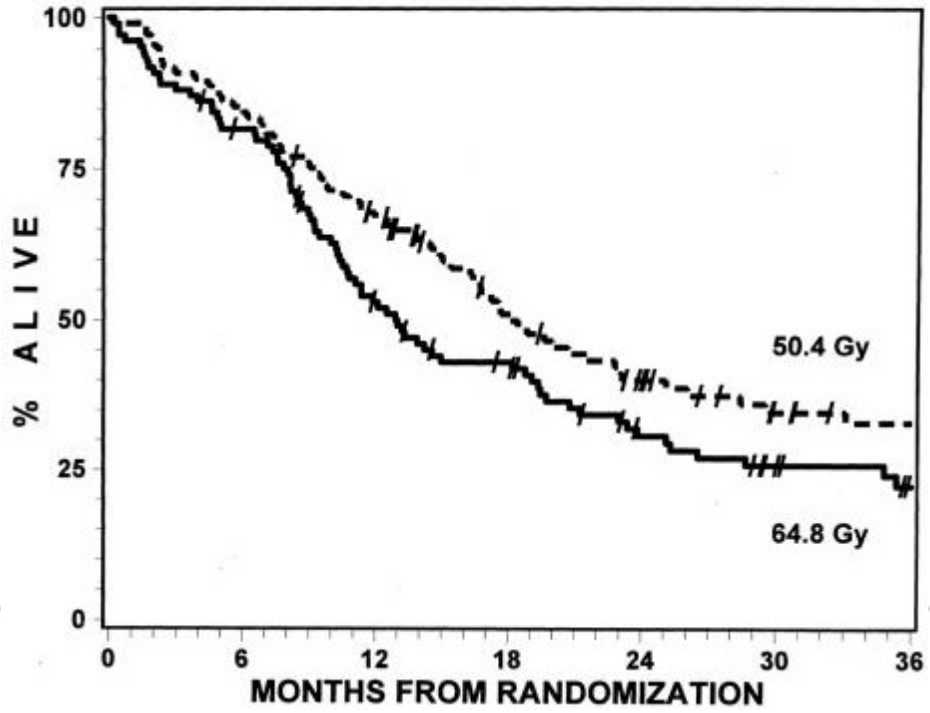
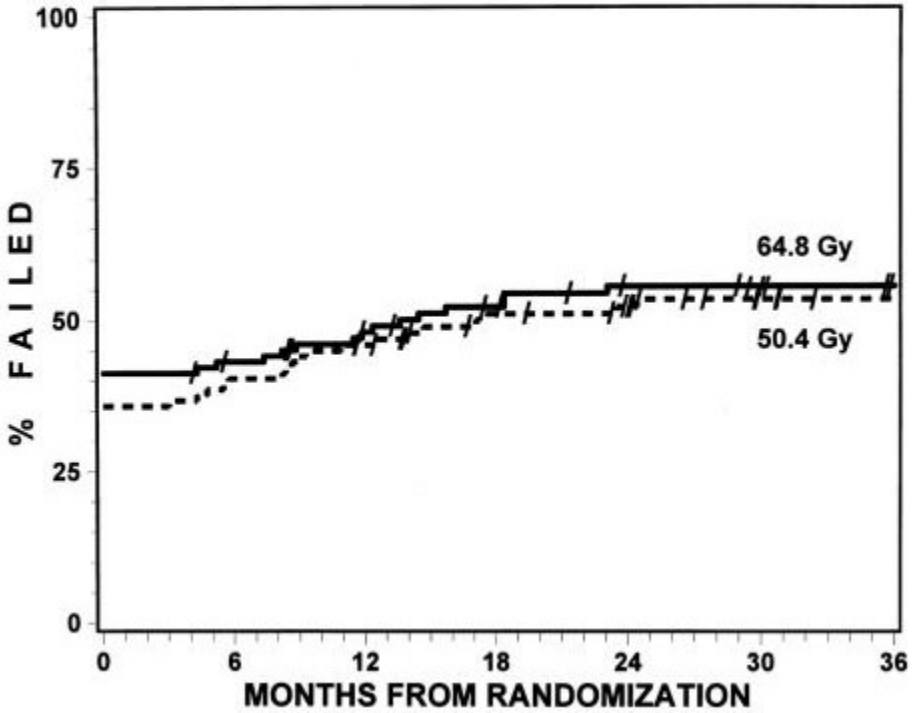
Definitive chemoradiotherapy in esophageal cancer: higher radiation dose does not improve outcome: RTOG 94-05





Minsky et al. J Clin Oncol 2002

Treatment-related deaths

Table 4. Treatment-Related Deaths (grade 5)

Dose Received	Toxicity
High dose (64.8 Gy)	
5.4 Gy	Cardiac
5.4 Gy	Cardiac, genitourinary
9.0 Gy	Cardiac, hematologic
37.8 Gy	Respiratory
43.2 Gy	Hematologic, infection, genitourinary
50.4 Gy	Infection
50.4 Gy	Genitourinary
54.0 Gy	Infection
61.2 Gy	Hematologic
64.8 Gy	Infection
64.8 Gy	Fistula, gastrointestinal
Standard dose (50.4 Gy)	
50.4 Gy	Infection
50.4 Gy	Infection

Minsky et al. J Clin Oncol 2002

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Adding surgery to chemoradiotherapy improves local control, but not survival (LA-SCC)

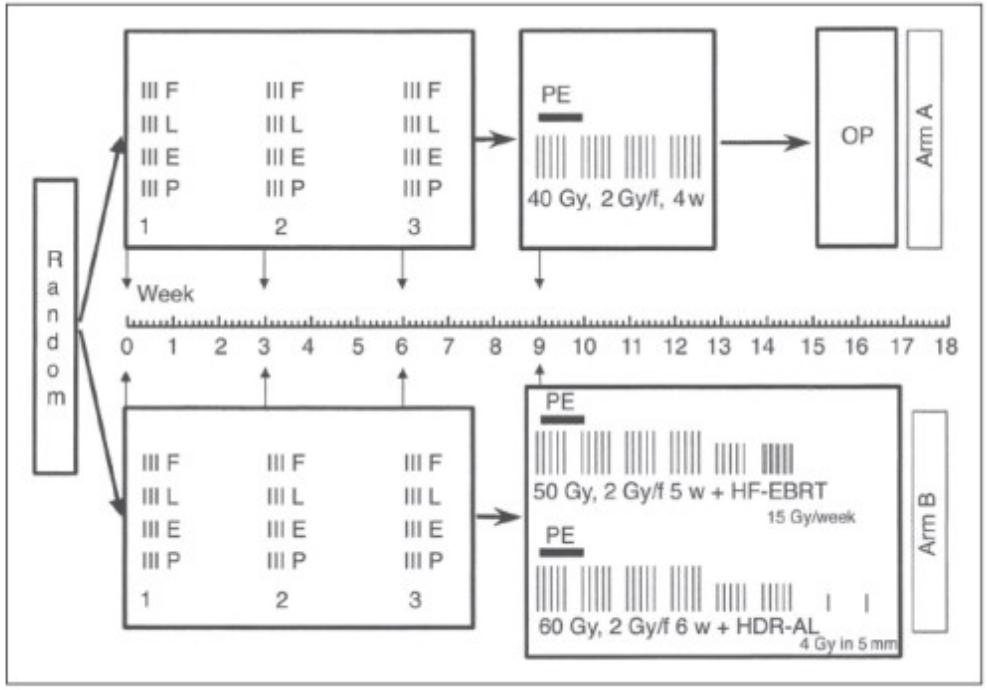
n=86

R

n=86

Chemotherapy ➔ chemoradiotherapy (40 Gy) ➔ surgery

Chemotherapy ➔ chemoradiotherapy (>65 Gy)



Stahl et al. J Clin Oncol 2005

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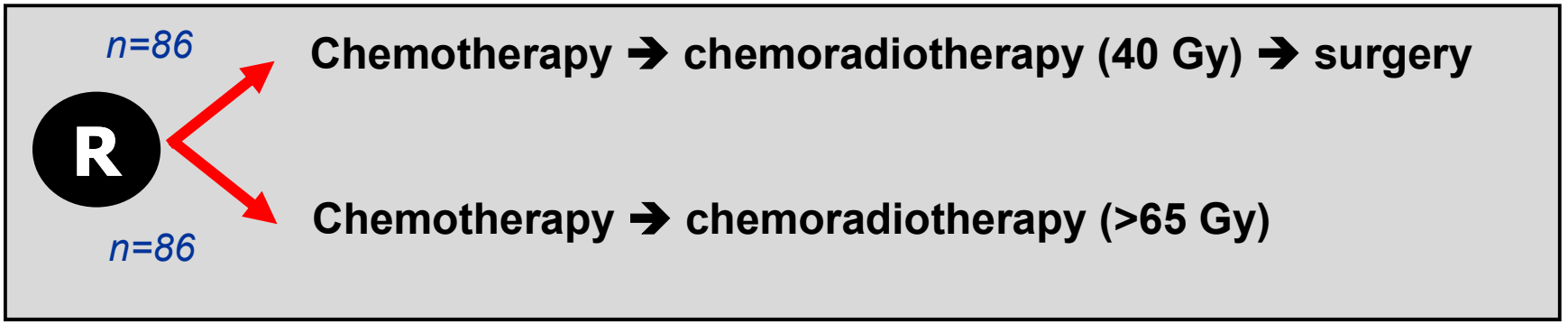
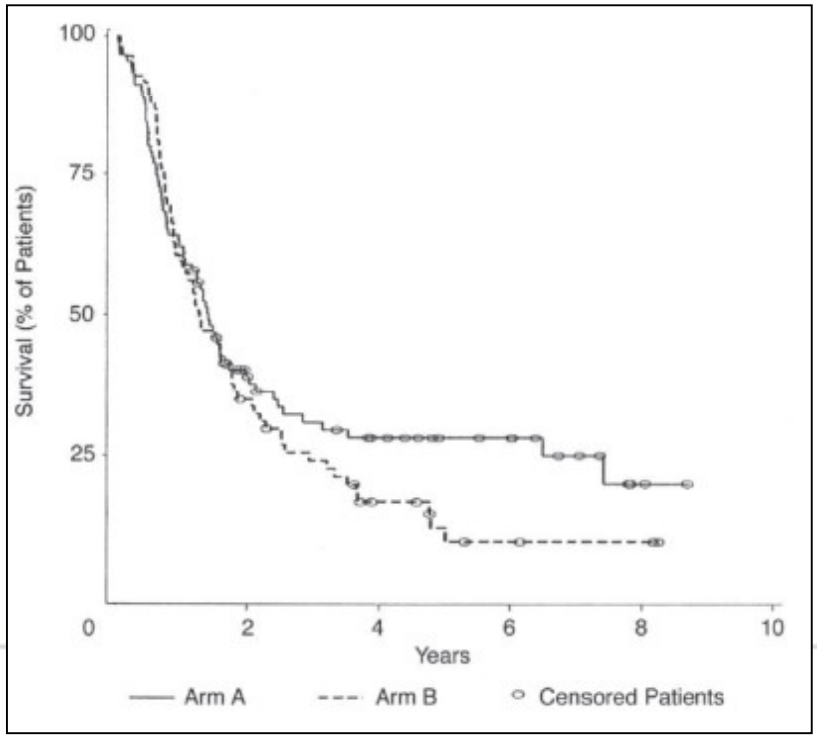
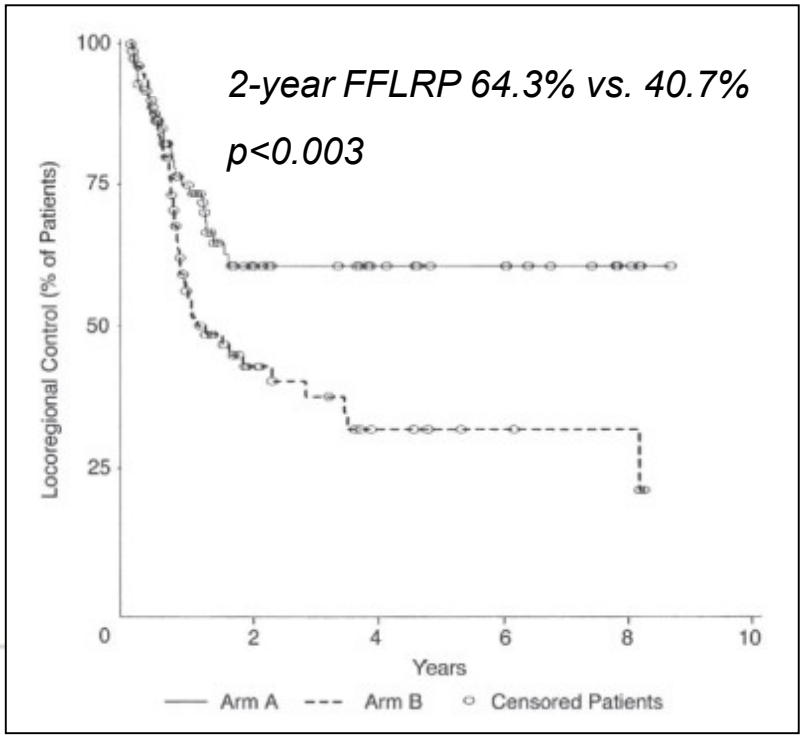
Adding surgery to chemoradiotherapy improves local control, but not survival (LA-SCC)



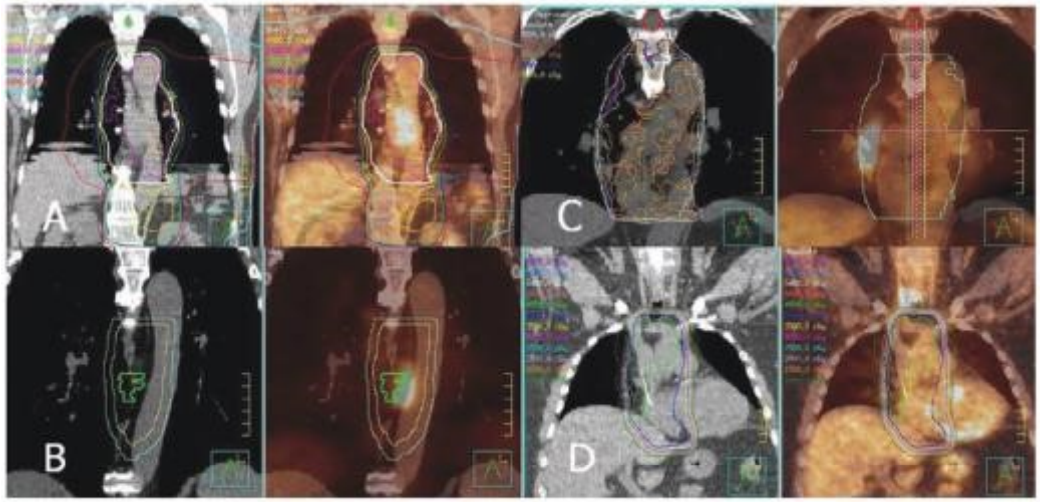


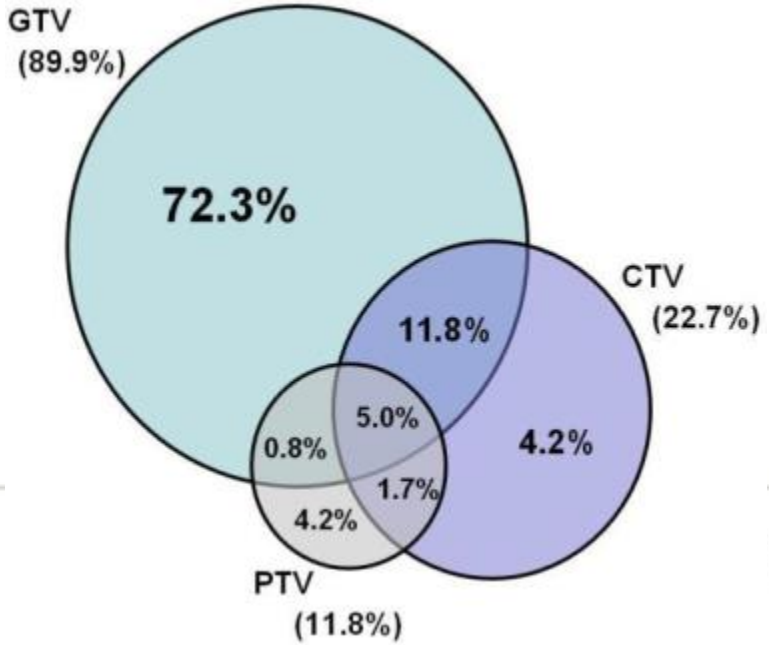


Stahl et al. J Clin Oncol 2005

Failure patterns in patients with esophageal cancer treated with definitive chemoradiation

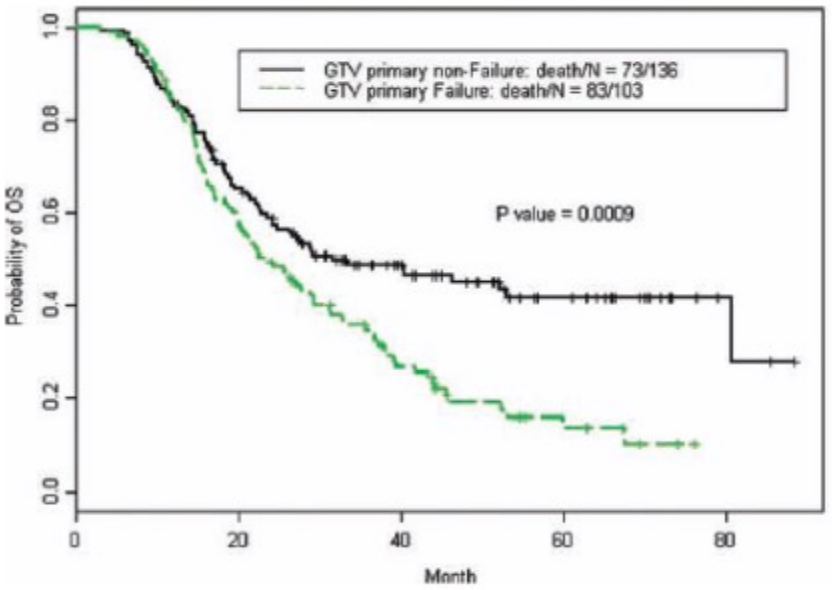
- 239 patients dCRT
  - 87% T3/T4
  - 50.4Gy/28 fr + 5FU
- median FU 52.6 months
  - 50% (n=119) local failure
  - 48% (n=114) distant failure
  - 31% (n= 74) NED
  - Local failure (n=119)
    - 90% GTV failure(107/119)
    - 23% CTV failure (27/119)
    - 12% PTV failure (14/119)

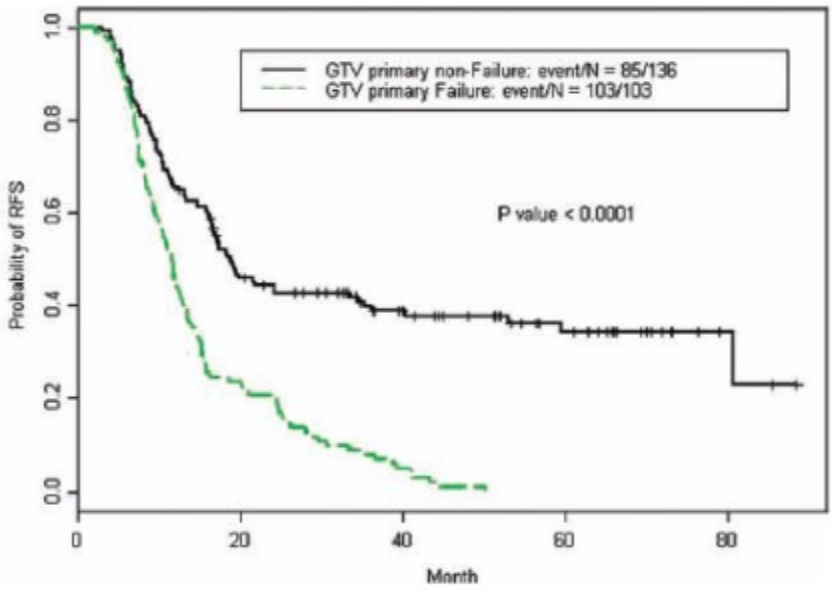




Welsh, Cancer 2012

Failure patterns in patients with esophageal cancer treated with definitive chemoradiation





Welsh, Cancer 2012

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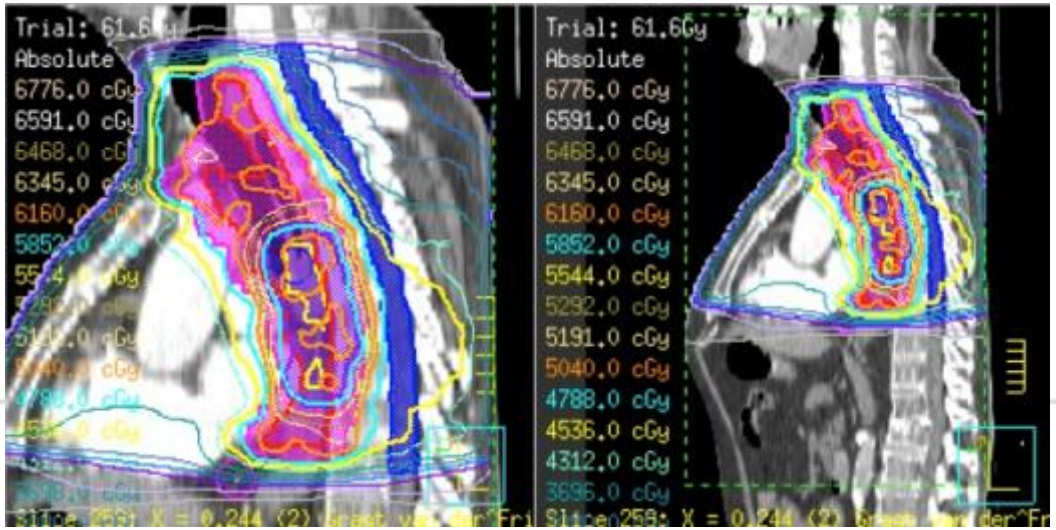
Dose escalation in definitive CRT

ART-DECO: Dutch dose escalation trial in patients with locally irresectable or medically inoperable carcinoma of the esophageal or GEJ treated with definitive CRT

R

Standard: 50.4 Gy/28 fr + weekly carboplatin/paclitaxel

Experimental: 61.6 Gy/28 fr (SIB boost GTV_{oes}) + weekly C/P



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Conclusions

- *Incidence of esophageal cancer is increasing*
- *Prognosis is poor due to advanced stages at diagnosis*
- *Treatment is challenging and requires multidisciplinary approach*
- *Largest gain is obtained in neo-adjuvant setting (CRT>CT?)*
- *Whether there is room for RT dose escalation remains unanswered (subgroups? Better/safer RT techniques?)*

ESOPHAGUS:

Dose constraints for Organs at Risk

Prof Oscar Matzinger
Chef de service, service interdisciplinaire de cancérologie, Vevey, Switzerland
Médecin Agréé, service de radio-oncologie, CHUV, Lausanne

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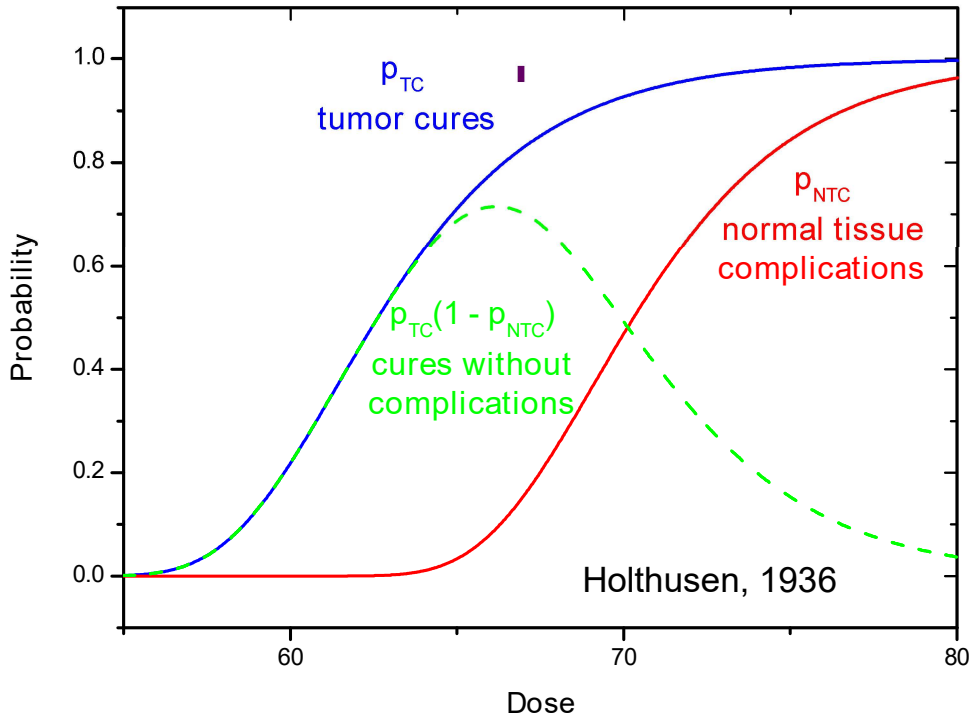
Introduction

Radiation therapy affects both tumor cells and uninvolved normal cells



Introduction

- 1972: First formal attempt to address normal tissue tolerance to radiation

Rubin P, Cassarett G. A direction for clinical radiation pathology. In: Vaeth JM, et al., eds. Frontiers of radiation therapy and oncology VI. Baltimore, MD: University Park Press, 1972:1–16.

- 1991: A committee reviewed available published data
  - ➔ but much of the data was nonexistent
  - ➔ rely on experience of 8 clinicians from major institutions in the US

CAVE:

- *Literature review up to 1991.*
- *Pre-dated the 3D-CRT, IMRT- IGRT era.*
- *Dose-volume histograms were not in routine clinical use.*
- *Arbitrary decision: organs be divided into one-third, two-thirds, and whole organ volumes*
- *It was only for external beam radiation with conventional fractionation.*
- *Only one severe complication was chosen as an endpoint*

Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21(1):109–122.

2007: Milano & al.

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Seminars in RADIATION ONCOLOGY

Normal Tissue Tolerance Dose Metrics for Radiation Therapy of Major Organs

Michael T. Milano, MD, PhD, Louis S. Constine, MD, and Paul Okunieff, MD

Table 2 Summary of Dosimetric Parameters for Clinical Toxicity

Organ	Emami[2] TD 5/5	Emami[2] TD 50/5	Endpoints	Dosimetric Parameters	Endpoints
Brainstem	1/3: 60 Gy 2/3: 53 3/3: 50	1/3: - 2/3: - 3/3: 65 Gy	Necrosis, infarction	V60 <0.9 mL	<5% grade≥1 toxicity
Spinal cord	5 cm: 50 Gy 10 cm: 50 20 cm: 47	5 cm: 70 Gy 10 cm: 70 20 cm: -	Myelitis, necrosis	max <50 Gy	<5% grade≥3 toxicity
Cervical spinal cord	—	—	—	EUD <52 Gy, max. <55 Gy	<5% grade≥3 toxicity
Parotid	1/3: - 2/3: 32 Gy 3/3: 32	1/3: - 2/3: 46 Gy 3/3: 46	Xerostomia	Mean dose <26 Gy	Late grade 2 xerostomia resulting from >75% functional loss
Lung	1/3: 45 Gy 2/3: 30 3/3: 17.5	1/3: 65 Gy 2/3: 40 3/3: 24.5	Pneumonitis	V13<40% V20<25-30% V30<10-15% MLD<10-20 Gy	Late grade 2 in <10-20% Late grade 3 in <5-10%
Heart	1/3: 60 Gy 2/3: 45 3/3: 40	1/3: 70 Gy 2/3: 55 3/3: 50	Pericarditis	V33 <60%, V38 <33% V42 <20%	5% excess cardiac mortality
Esophagus	1/3: 60 Gy 2/3: 58 3/3: 55	1/3: 72 Gy 2/3: 70 3/3: 68	Clinical stricture/ perforation	V50 and S50 <30%	5% risk of late toxicity
Rectum	1/3: 60 Gy 2/3: 60 3/3: 60	1/3: 80 Gy 2/3: 80 3/3: 80	Proctitis, necrosis, fistula, stenosis	V70-80 ≤15 cc V70≤20-25%	Late grade 2 in <5-10%
Liver	1/3: 50 Gy 2/3: 35 3/3: 30	1/3: 55 Gy 2/3: 45 3/3: 40	Liver failure	1/3: 40-80 Gy 2/3: 30-50 3/3: 25-35	Late grade 3-4 liver toxicity <5%
Kidney	1/3: 50 Gy 2/3: 30 3/3: 23	1/3: - 2/3: 40 Gy 3/3: 28	Clinical nephritis	median dose <17.5 Gy	anemia, azotemia, hypertension and edema

Dose (Gy) 0 20 40 60 70

Spinal Cord

Volume			
0-20%	<1%	<5%	10-50%
20-40%			
40-60%			
60-80%			
80-100%			

Lung

Volume					
0-20%	<5%	<5%	<10%	<20%	>20%
20-40%					
40-60%		10-20%	30-50%		>75%
60-80%		>50%			
80-100%					

Parotid

Volume			
0-20%	<5%	5-10%	>25%
20-40%			
40-60%		10-20%	>50%
60-80%			
80-100%			

Heart

Volume				
0-20%	<5%	<5%	5-10%	10-25%
20-40%				
40-60%		10-15%	<15-20%	25-40%
60-80%			15-25%	25-40% >40%
80-100%				

Liver

Volume			
0-20%	<1%	<5%	<25%
20-40%			
40-60%		5-25%	>75%
60-80%		>50%	
80-100%			

Rectum

Volume				
0-20%	<1%	5-10%	<10%	<20%
20-40%				
40-60%			>25%	~50%
60-80%				
80-100%				

Esophagus

Volume				
0-20%	<1%	5-10%	<10%	<20%
20-40%				
40-60%			>30%	>50%
60-80%				
80-100%				

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2010: Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S10–S19, 2010

0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.07.1754

INTRODUCTORY PAPER

USE OF NORMAL TISSUE COMPLICATION PROBABILITY MODELS IN THE CLINIC

LAWRENCE B. MARKS, M.D.,* ELLEN D. YORKE, PH.D.,† ANDREW JACKSON, PH.D.,†
RANDALL K. TEN HAKEN, PH.D.,‡ LOUIS S. CONSTINE, M.D.,§ AVRAHAM EISBRUCH, M.D.,‡
SØREN M. BENTZEN, PH.D.,‖ JIHO NAM, M.D.,* AND JOSEPH O. DEASY, PH.D.¶

*Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC; †Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY; ‡Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; §Department of Radiation Oncology, University of Rochester Cancer Center, Rochester, NY; ‖Department of Human Oncology, University of Wisconsin School of Medicine, Madison, WI; and ¶Department of Radiation Oncology, Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)*

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated
	Whole organ	3D-CRT	Symptom			
	Whole organ	3D-CRT	Symptom			
	Whole organ	SRS (single fraction)	Symptom			
Brain stem	Whole organ	Whole organ	Permanen neuropath			
	Whole organ	3D-CRT	Permanen neuropath			
	Whole organ	3D-CRT	Permanen neuropath			
	Whole organ	SRS (single fraction)	Permanen neuropath			
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neu			
	Whole organ	3D-CRT	Optic neu			
	Whole organ	3D-CRT	Optic neu			
	Whole organ	SRS (single fraction)	Optic neu			
Spinal cord	Partial organ	3D-CRT	Myelopath			
	Partial organ	3D-CRT	Myelopath			
	Partial organ	3D-CRT	Myelopath			
	Partial organ	SRS (single fraction)	Myelopath			
	Partial organ	SRS (hypofraction)	Myelopath			
Cochlea	Whole organ	3D-CRT	Sensory n			
	Whole organ	SRS (single fraction)	Sensory n			
Parotid	Bilateral whole parotid glands	3D-CRT	Long term function r pre-RT le			
	Unilateral whole parotid gland	3D-CRT	Long term function r pre-RT le			

Table 1. QUANTEC Summary: Appro

Organ	Volume segmented
	Bilateral whole parotid glands
Pharynx	Pharyngeal constrictors
Larynx	Whole organ
	Whole organ
	Whole organ
	Whole organ
Lung	Whole organ
	Whole organ
	Whole organ
	Whole organ
	Whole organ
	Whole organ
Esophagus	Whole organ
	Whole organ
	Whole organ
	Whole organ
Heart	Pericardium
	Pericardium
	Whole organ

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Liver	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD‖	Mean dose <30-32	<5	Excluding patients with pre-existing liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <42	<50	
	Whole liver – GTV	3D-CRT or Whole organ	Classic RILD	Mean dose <28	<5	In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding hepatitis B reactivation
	Whole liver – GTV	3D-CRT	Classic RILD	Mean dose <36	<50	as an endpoint
	Whole liver –GTV	SBRT (hypofraction)	Classic RILD	Mean dose <13	<5	3 fractions, for primary liver cancer
				<18	<5	6 fractions, for primary liver cancer
	Whole liver – GTV	SBRT (hypofraction)	Classic RILD	Mean dose <15	<5	3 fractions, for liver metastases
				<20	<5	6 fractions, for liver metastases
	>700 cc of normal liver	SBRT (hypofraction)	Classic RILD	D_{max} <15	<5	Critical volume based, in 3–5 fractions
Kidney	Bilateral whole kidney‡	Bilateral whole organ or 3D-CRT	Clinically relevant renal dysfunction	Mean dose <15–18	<5	
	Bilateral whole kidney‡	Bilateral whole organ	Clinically relevant renal dysfunction	Mean dose <28	<50	
	Bilateral whole kidney‡	3D-CRT	Clinically relevant renal dysfunction	V12 <55% V20 <32% V23 <30% V28 <20%	<5	For combined kidney
Stomach	Whole organ	Whole organ	Ulceration	D100§ <45	<7	
Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity§	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity§	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity

(*Continued*)

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Normal tissue tolerance dose

Table 2 Summary of Dosimetric Parameters for Clinical Toxicity

Organ	Emami[2] TD 5/5	Emami[2] TD 50/5	Endpoints	Dosimetric Parameters	Endpoints
Brainstem	1/3: 60 Gy 2/3: 53 3/3: 50	1/3: - 2/3: - 3/3: 65 Gy	Necrosis, infarction	V60 <0.9 mL	<5% grade≥1 toxicity
Spinal cord	5 cm: 50 Gy 10 cm: 50 20 cm: 47	5 cm: 70 Gy 10 cm: 70 20 cm: -	Myelitis, necrosis	max <50 Gy	<5% grade≥3 toxicity
Cervical spinal cord	—	—	—	EUD <52 Gy, max. <55 Gy	<5% grade≥3 toxicity
Parotid	1/3: - 2/3: 32 Gy 3/3: 32	1/3: - 2/3: 46 Gy 3/3: 46	Xerostomia	Mean dose <26 Gy	Late grade 2 xerostomia resulting from >75% functional loss
Lung	1/3: 45 Gy 2/3: 30 3/3: 17.5	1/3: 65 Gy 2/3: 40 3/3: 24.5	Pneumonitis	V13<40% V20<25-30% V30<10-15% MLD<10-20 Gy	Late grade 2 in <10-20% Late grade 3 in <5-10%
Heart	1/3: 60 Gy 2/3: 45 3/3: 40	1/3: 70 Gy 2/3: 55 3/3: 50	Pericarditis	V33 <60%, V38 <33% V42 <20%	5% excess cardiac mortality
Esophagus	1/3: 60 Gy 2/3: 58 3/3: 55	1/3: 72 Gy 2/3: 70 3/3: 68	Clinical stricture/ perforation	V50 and S50 <30%	5% risk of late toxicity
Rectum	1/3: 60 Gy 2/3: 60 3/3: 60	1/3: 80 Gy 2/3: 80 3/3: 80	Proctitis, necrosis, fistula, stenosis	V70-80 ≤15 cc V70≤20-25%	Late grade 2 in <5-10%
Liver	1/3: 50 Gy 2/3: 35 3/3: 30	1/3: 55 Gy 2/3: 45 3/3: 40	Liver failure	1/3: 40-80 Gy 2/3: 30-50 3/3: 25-35	Late grade 3-4 liver toxicity <5%
Kidney	1/3: 50 Gy 2/3: 30 3/3: 23	1/3: - 2/3: 40 Gy 3/3: 28	Clinical nephritis	median dose <17.5 Gy	anemia, azotemia, hypertension and edema

Milano MT, Semin Radiat Oncol 2007:17;131-40

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Oesophagus: OAR…

- Heart
- Lungs
- Spinal cord
- Vertebrae
- Thyroïd
- Brachial plexus
- Stomach
- Liver
- Biliary tract
- Pancreas
- Spleen
- Kidneys

- Vessels, pericarde, coronary arteries
- Esophagus

- Patient at risk

OAR: Spinal cord

Spinal cord injury rare but extremely debilitating

➔ paralysis, sensory, deficits, pain, and bowel/bladder incontinence (10,30)

Schultheiss review:

risk of myelopathy to be 0.2% at 50 Gy and 5% at 59.3 Gy

Similar conclusions published by QUANTEC

CAVE: α/β ratio of 0.87 < the values frequently used in the literature

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	

Schultheiss TE, Kun LE, Ang KK, et al. Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 1995;31:1093–1112.

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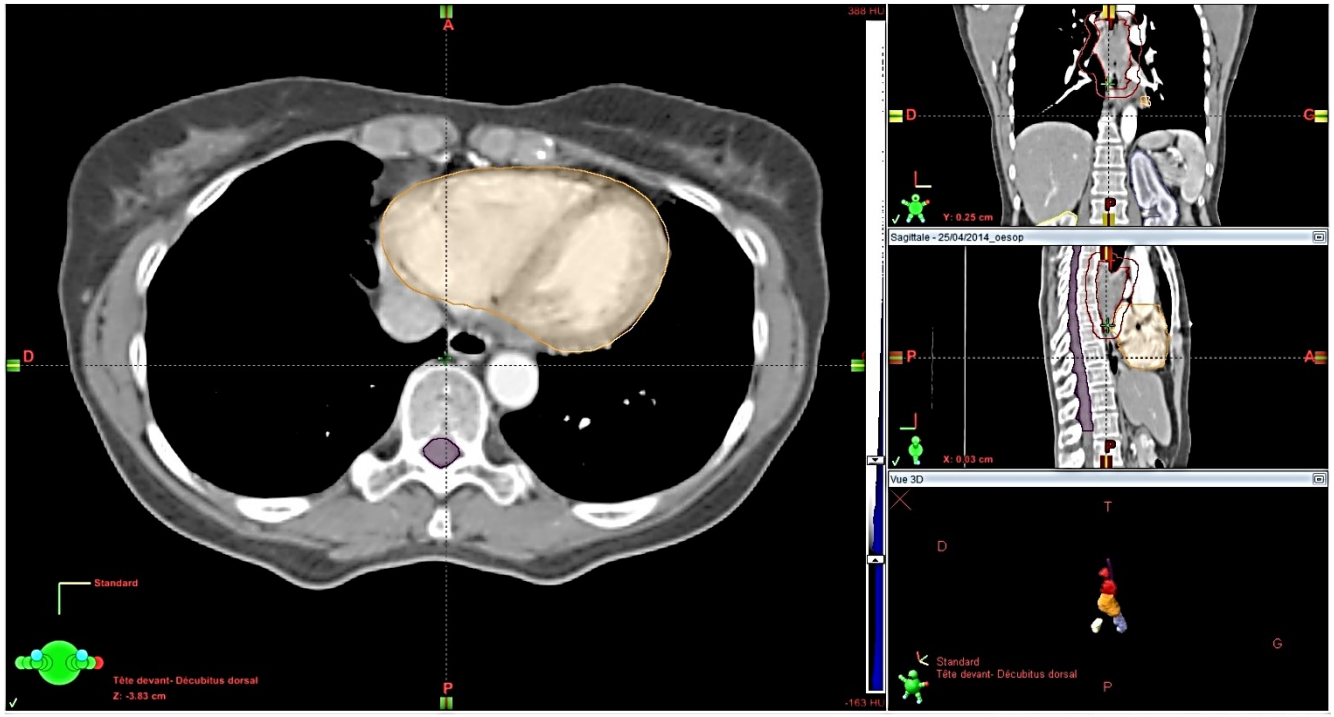
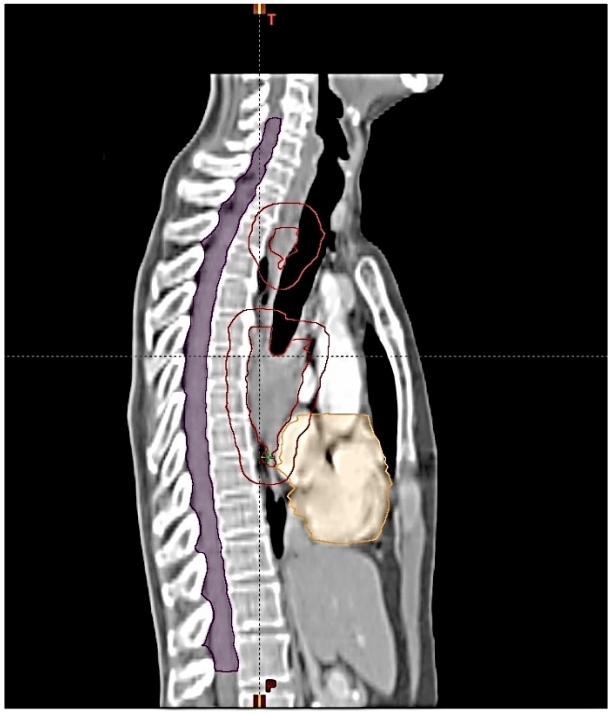
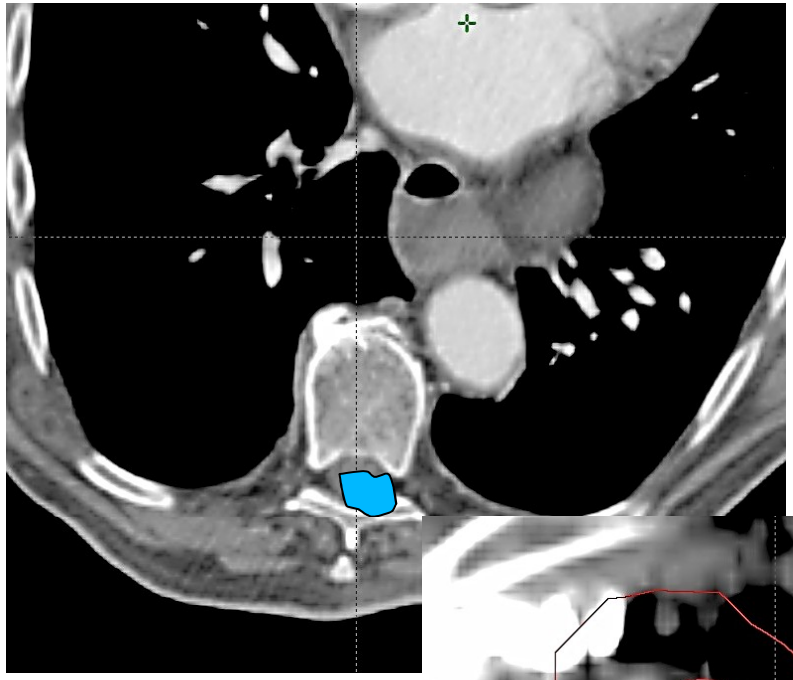
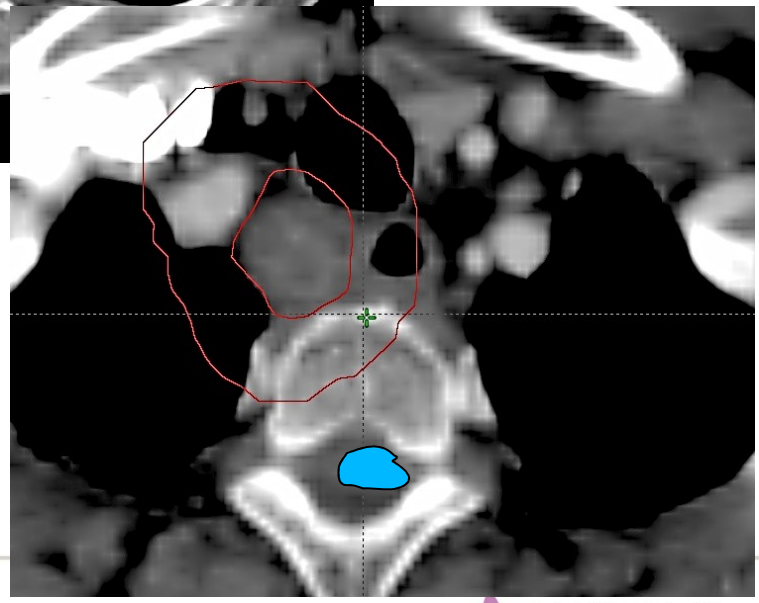
Spinal cord …


A
D
P
Standard
Tête devant- Décubitus dorsal
Z: -3.83 cm
Y: 0.25 cm
Sagittale - 25/04/2014_oesop
X: 0.03 cm
Vue 3D
T
D
G
Standard
Tête devant- Décubitus dorsal
P

Spinal cord … Which one ?







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Dose volume effect in the heart

Most relevant cardiac toxicities

- Clinical pericarditis
- Long-term cardiac mortality

Long-term cardiac mortality

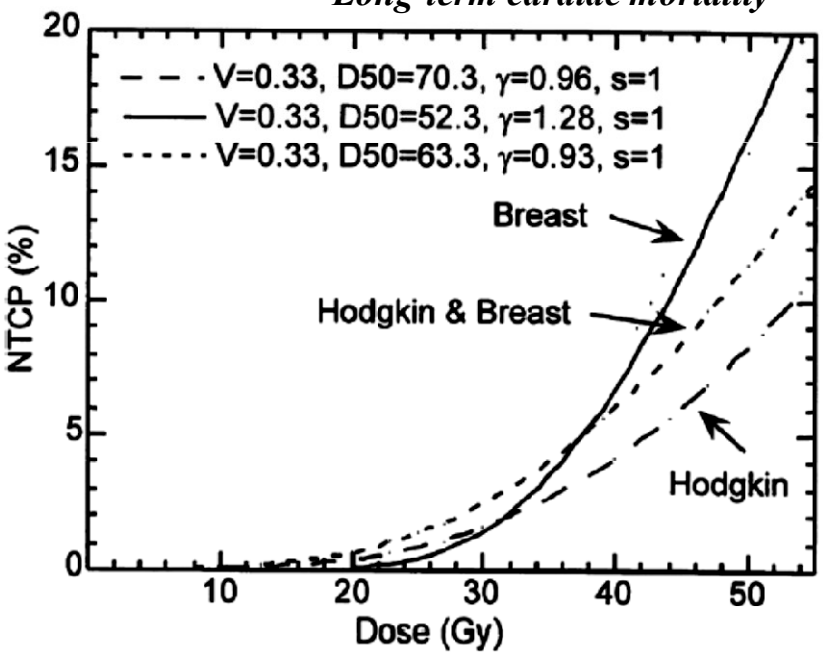

Table 2. Pericarditis/pericardial effusion: Dose–volume predictors and NTCP parameters

Authors, Year, Reference	Diagnosis, No. of patients, Years of treatment	OAR	Fractionation schedule, dose data	Predictive parameters	NTCP parameters
Carmel and Kaplan* 1976 (3)	Hodgkin's 377 Patients 1964–1972	Pericardium		$D_{pericardium} > 30$ Gy 50% pericarditis, 36% requiring treatment	
Cosset *et al.* 1991 (65)	Hodgkin's 499 Patients 1971–1984		35–43 Gy/ 2.5–3.3 Gy/fraction pre-3D dose data	$D_{Mediastinum} \geq 41$ Gy d/ fraction ≥ 3 Gy (marginal significance)	
Burman *et al.* 1991 (66)	Historical data				LKB† *TD50* = 48 Gy *m* = 0.10 *n* = 0.35
Martel *et al.* 1998 (26)	Esophagus 57 Patients 1985–1991	Pericardium	37.5–49 Gy/ 1.5–3.5 Gy / fraction 3D data	$D_{mean} > 27.1$ Gy† $D_{max} > 47$ Gy† d/ fraction 3.5 Gy	LKB (95% CI) *TD50* = 50.6 Gy (–9; 23.1) *m* = 0.13 (–0.07; 0.13) *n* = 0.64 (–0.58; 3)
Wei *et al.* 2008 (27)	Esophagus 101 Patients 2000–2003	Pericardium	45–50.4 Gy 1.8–2.0 Gy/fraction 3D data	D_{mean}pericardium > 26.1 Gy $V_{30} < 46\%$	

Gagliardi G. IJROBP 2010

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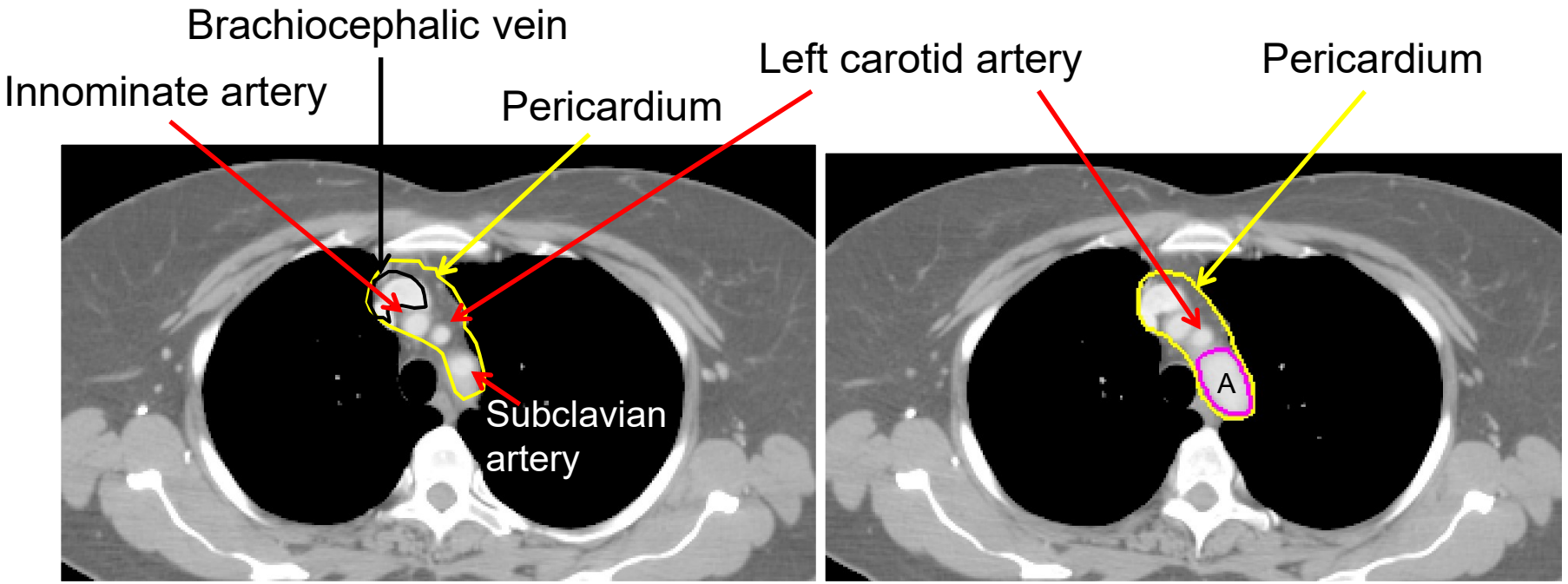
Dose volume effect in the heart

QUANTEC:

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Heart	Pericarditis	<15	V30 <46%		<26
	Long-term cardiac mortality	<1	V25 <10%		

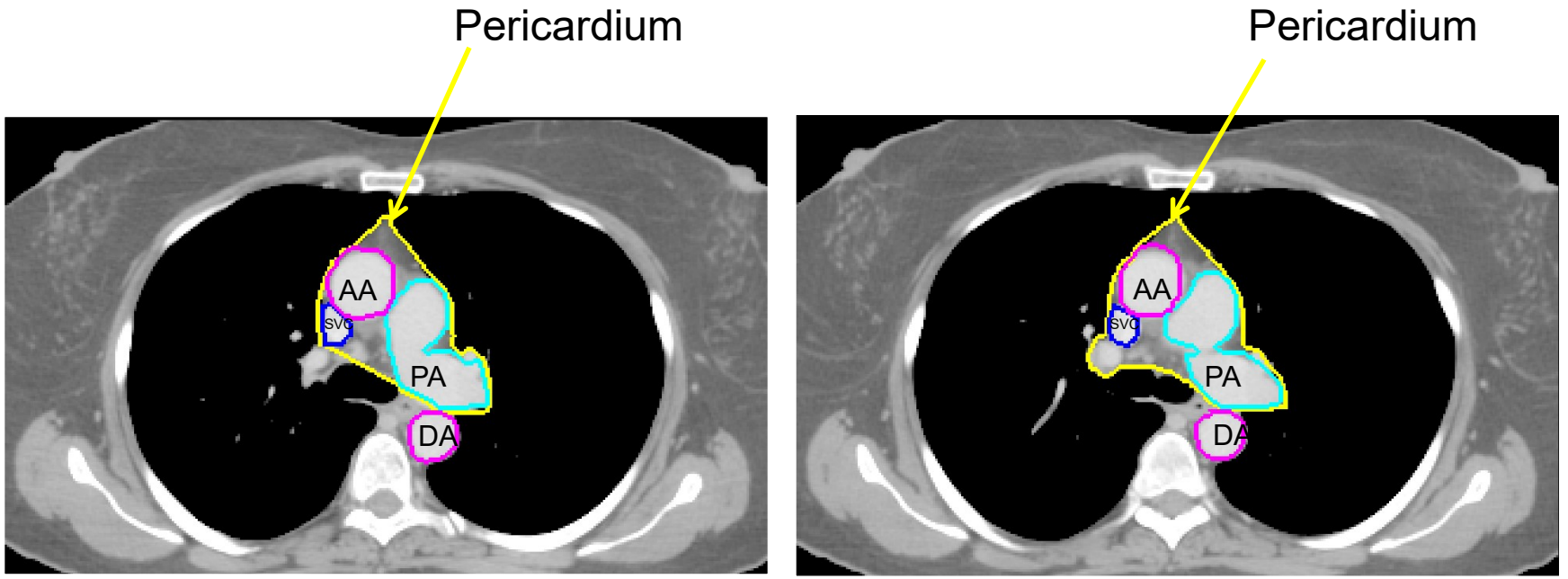
CAVE: ALARA left ventricule

Pericardium starts …



Pericardium starts at 1-2 slices (5-6 mm) above the superior end of the aortic arch

Pericardium Continues…



SVC=Superior vena cava
PA=Pulmonary artery
AA=Ascending aorta
DA=Descending aorta

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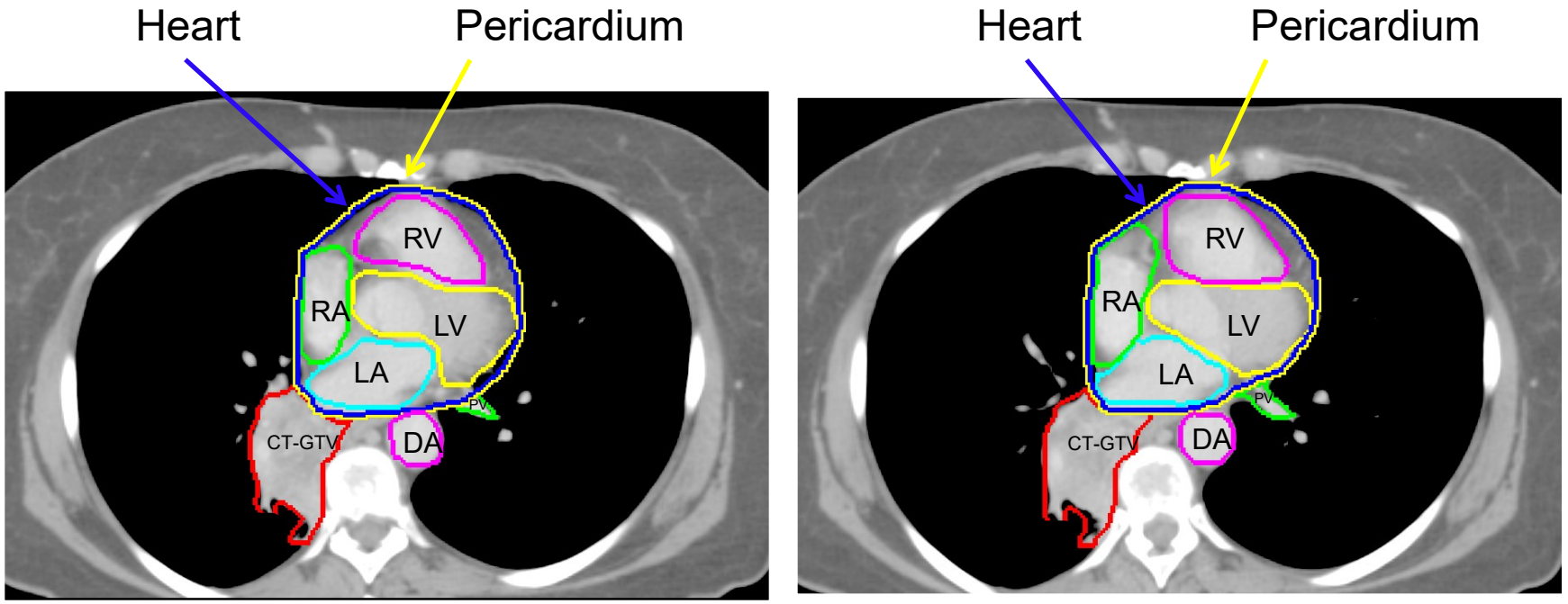
Heart and pericardium continue…



RA=right atrium, RV=right ventricle
LV=left ventricle, LA=Left atrium
DA=descending aorta

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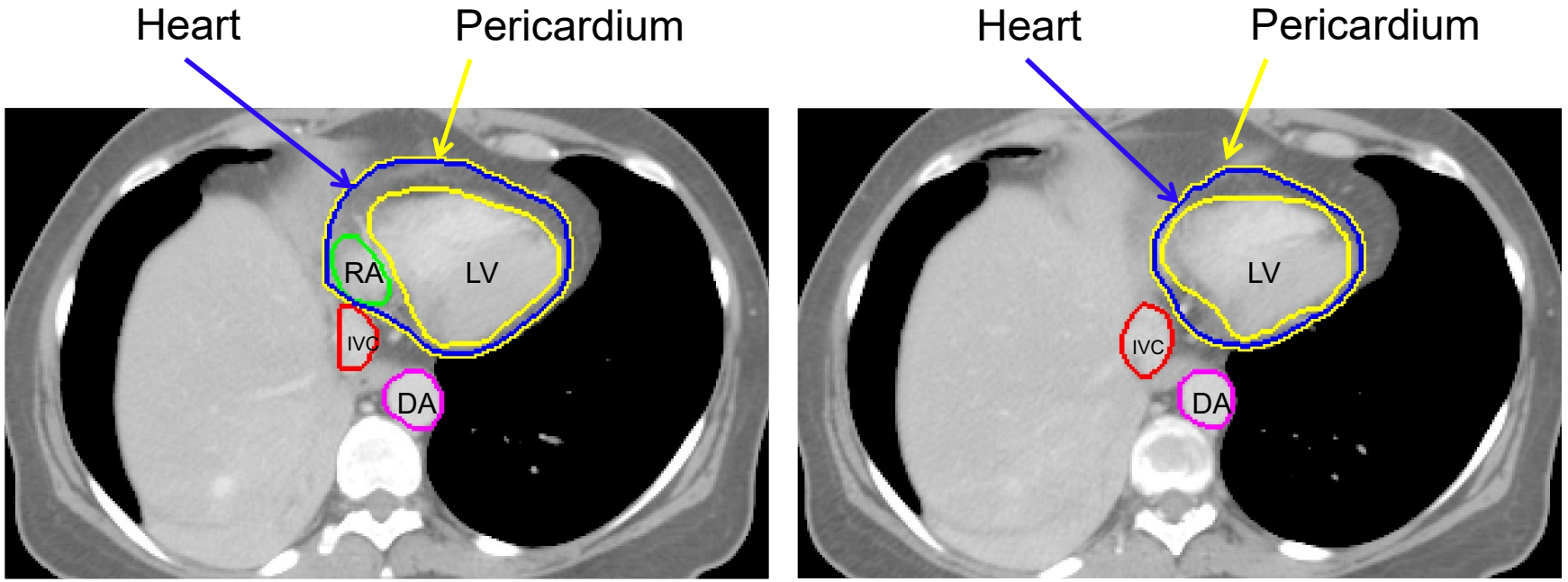
Heart and pericardium continue…



IVC=inferior vena cava
RA=right ventricle
LV=left ventricle
DA=descending aorta

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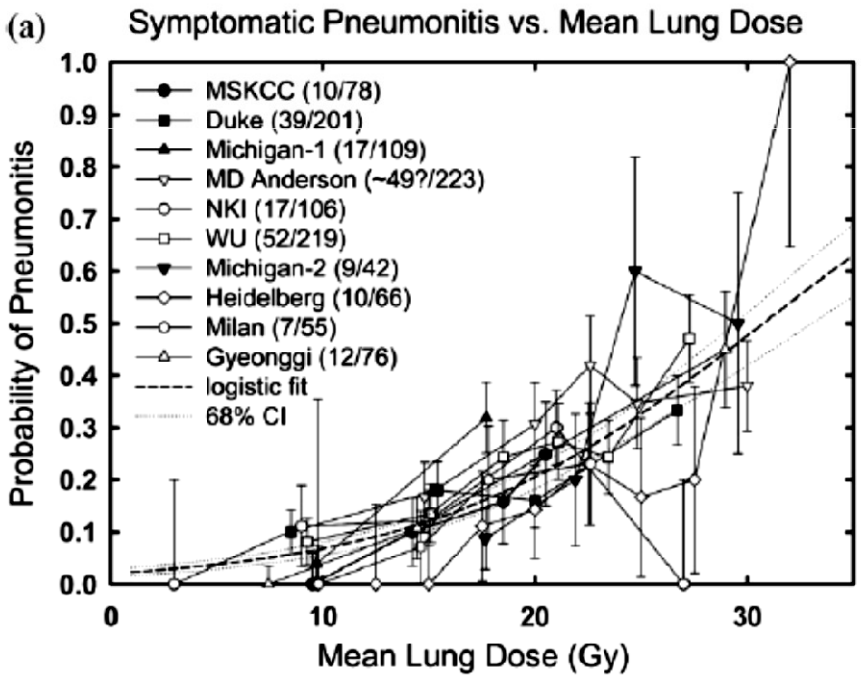
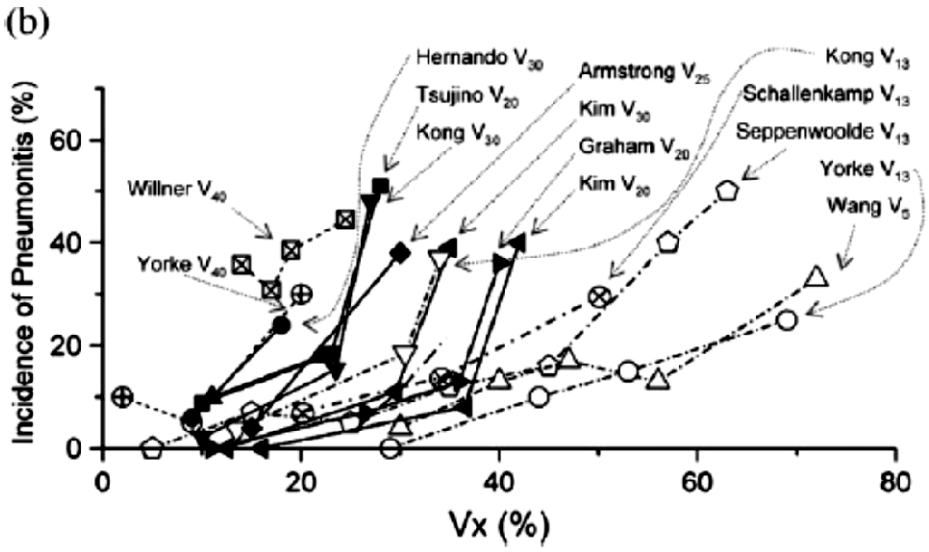
Radiation Dose-Volume effect in the lung

QUANTEC review >70 articles: mean lung doses & Vx parameters

➔ no clear threshold dose

➔ 20% risk of pneumonitis for a **mean lung dose** of 20 Gy
➔ **V20** most useful parameter





Marks L. IJROBP 2010

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OAR: lung

QUANTEC:

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Lung	Symptomatic pneumonitis	5	V5 <42%, V20 <22%		7
		10	V20 <31%		13
		20	V20 <40%		20
		30			24
		40			27

NCCN guidelines

National Comprehensive Cancer Network (NCCN) Guidelines

- Spinal cord Dmax = 45Gy
- Heart 1/3 < 40Gy, ALARA left ventricule
- Lungs D max normal lung (2 cm outside PTV) < 40 Gy
  V 20 Gy < 25%; V5 Gy < 50 %

- Liver V60% < 30Gy; 25 Gy mean
- Kidney 2/3 ≤ 20Gy

National Comprehensive Cancer Network guidelines, Clinical practice guidelines in oncology, Esophageal cancer, 02.2016.

http:// www.nccn.org. Accessed 11.03.2017

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Last, but … Esophagus

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Esophagus	Grade ≥2 esophagitis	<30	V35 <50% V50 <40% V70 <20%	<74 Point	
	Grade ≥3 esophagitis	≤10	V60 <30%		<34

- Dose limit = 50 Gy Mean dose > 34 Gy *Sing IJROBP 2003*
- Lenght of esophagus receiving more than 55 Gy *Maguire IJROBP 1999*
- Acute esophageal toxicity is the greatest predictor of late toxicity

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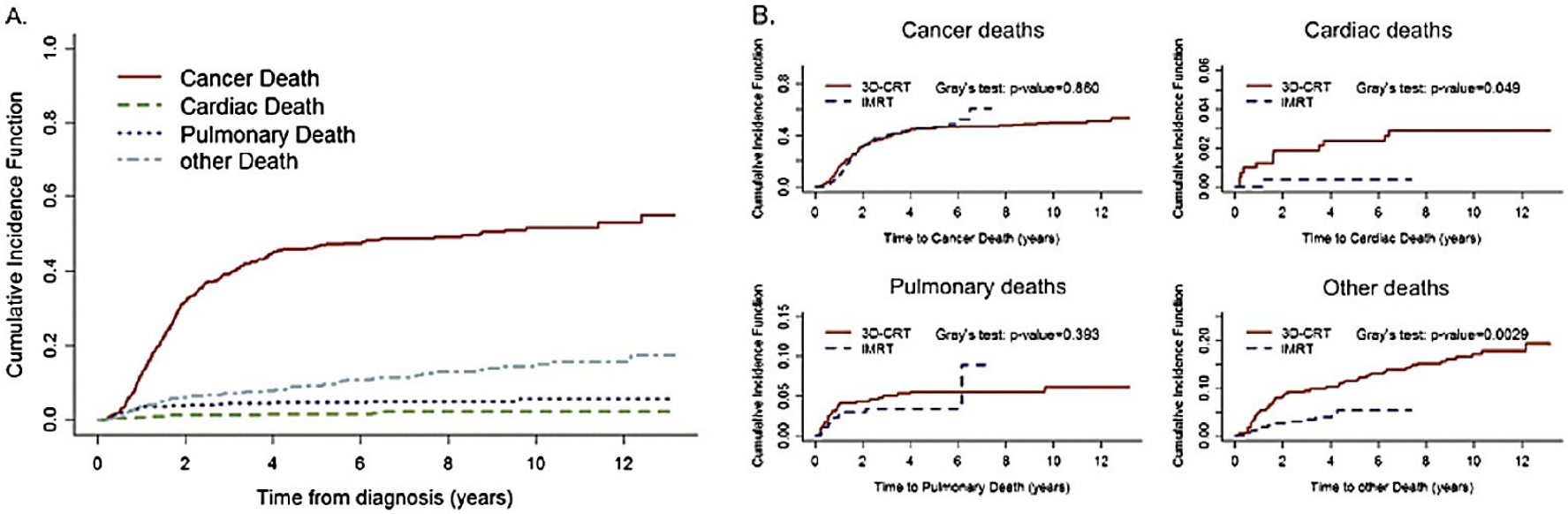
IMRT : Evolution or Revolution?

Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer.



Int J Radiat Oncol Biol Phys. 2012 Dec 1;84(5):1078-85. doi: 10.1016/j.ijrobp.2012.02.015.

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CONCLUSIONS

- IMRT should be favored in the treatment of esophageal cancer
- The inverse treatment planning is asking for contraints to the tumor as well as for organs at risk
- The constraints to OARs should minimize the dose delivered to critical structures which could be associated to acute toxicities and poor compliance
- The ALARA principle should be applied to all thoracic irradiated organs.

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“Competitive” plans

Dirk Verellen

DV is involved in an on-going scientific collaboration with RaySearch

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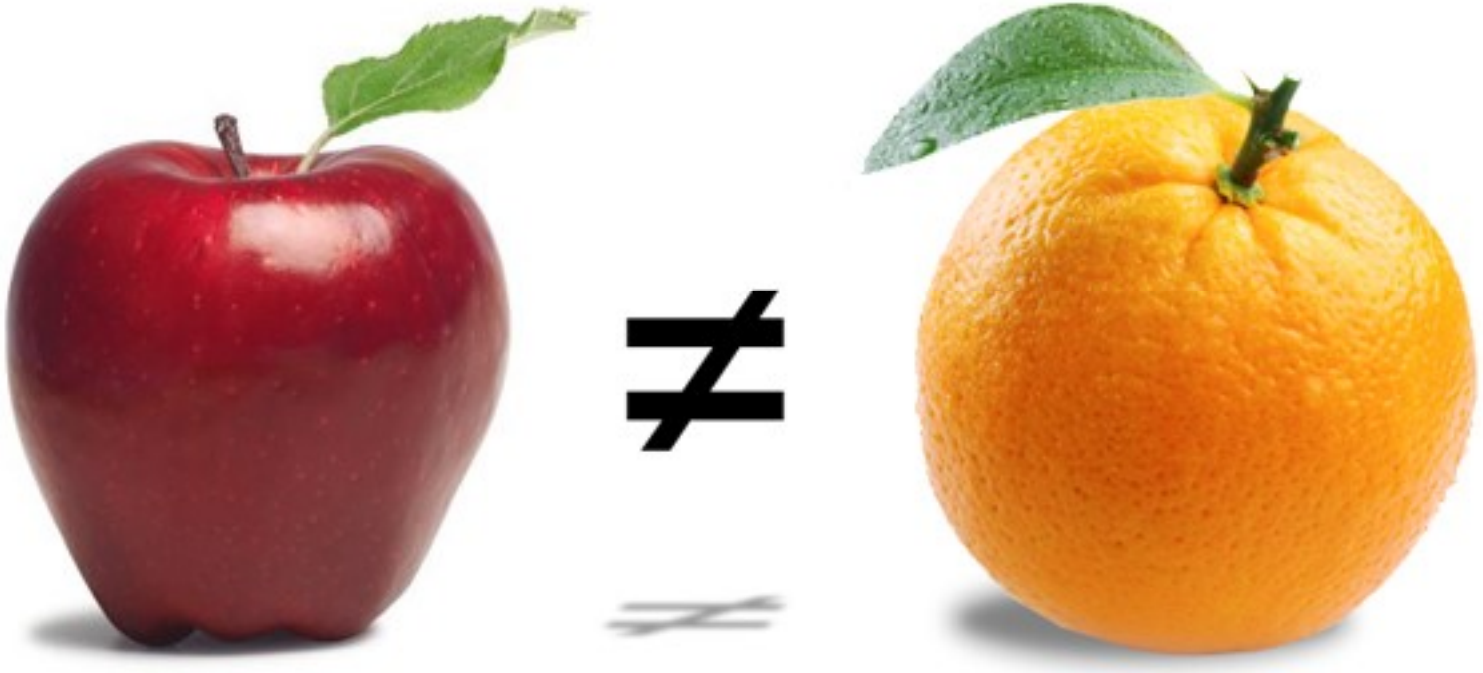
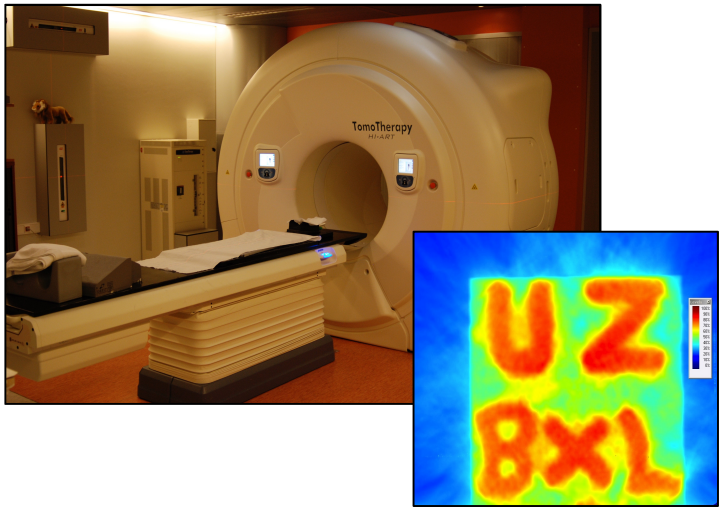
Outline

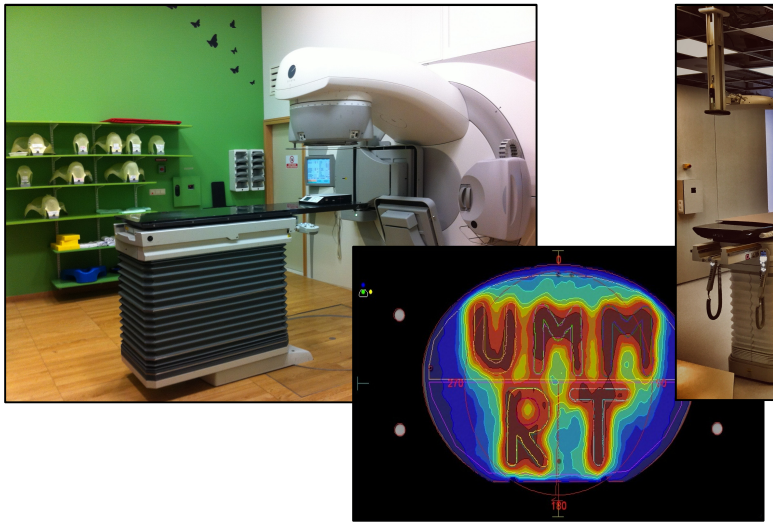
- How to compare plans?
- Oesophagus: 3D-CRT versus VMAT
- Oesophagus: 3D-CRT versus Helical TomoTherapy
- Partial gastrectomy: 3D-CRT versus Helical TomoTherapy

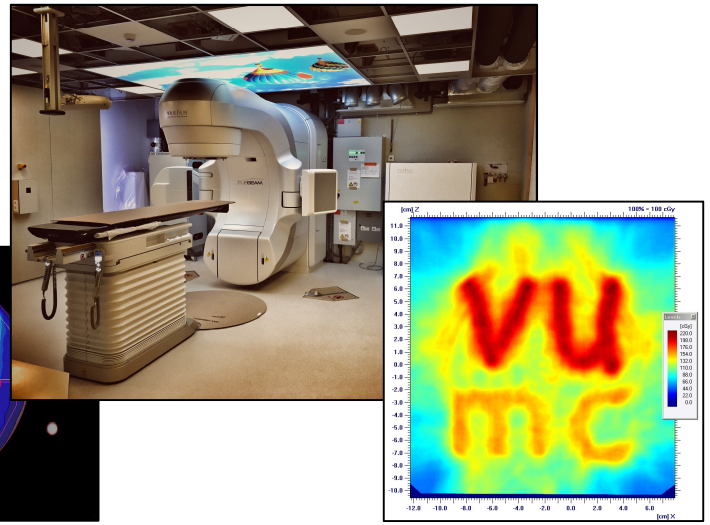


A few disclaimers

- Unlike the title suggests, this exercise is not trying to show superiority of a technology







- The plans shown in this presentation are typical plans as they would be performed in clinic, generated by a dosimetrist.
  - eg focus on a certain constraint in the optimizer could drive the IMRT plan to outperform another on that particular variable … bias, selectivity ….
  - The acceptance criteria, were: “the plan being clinically acceptable, presenting a good compromise.”

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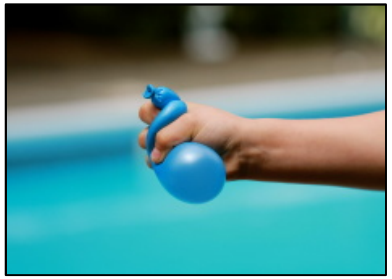
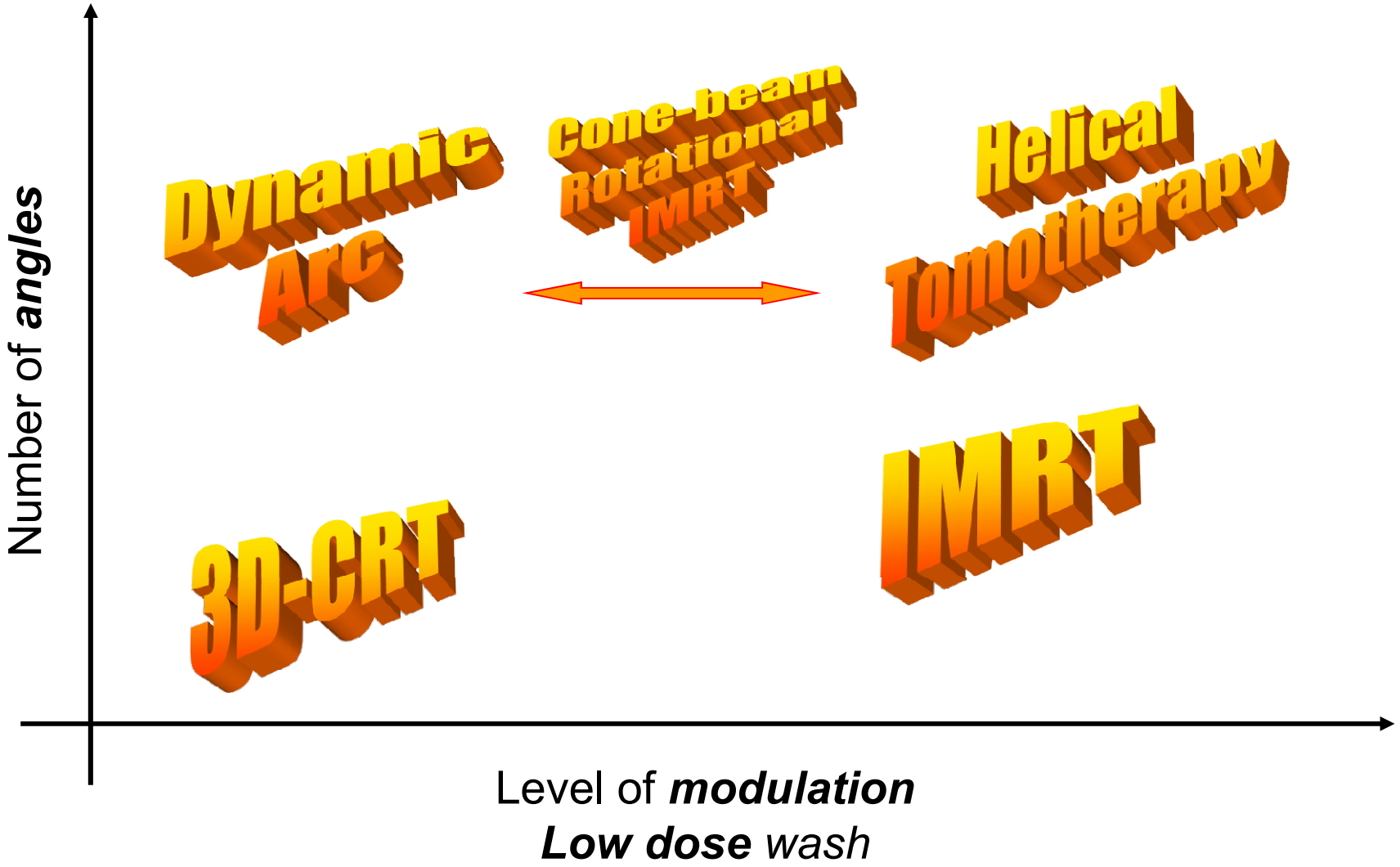
A few disclaimers

- We're limiting ourselves to photon treatment
  - … for obvious reasons

- From 3D-CRT to IMRT to rotational IMRT: "**re-distribution of dose**"
  - Simplistic: "if you want more conformality, you'll sacrifice on homogeneity and *vice versa*."
  - The clinical choice is: "delivering more dose to *some* normal tissues and sparing *others* completely" versus "distributing low dose values uniformly within large volumes of normal tissues (***low dose wash***)."



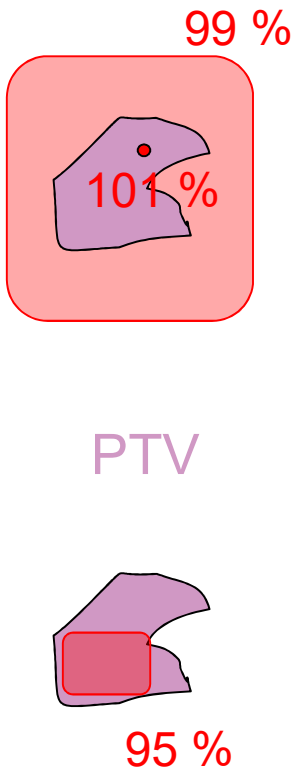
You get what you pay for



Dose homogeneity & Conformity

Tumor dose inhomogeneity, $TDI = (D_{max} - D_{min})/D_{median}$
Conformity Index, $CI_{95} = V_{NonTargetTissue}/V_{CTV}$

Technique	TDI	CI
Tomotherapy	**0.38**	**0.35**
IMRT opposing	**0.26**	**2.33**
IMRT non opposing	**0.25**	**0.33**
Dynamic Arc	**0.26**	**0.51**
IMRS opposing	**0.30**	**0.43**
IMRS non opposing	**0.26**	**0.29**



TDI ++

CI ++

Dose homogeneity & Conformity

- Paddick Conformity Index:
  - simultaneously takes into account irradiation of the target volume and irradiation of the healthy tissue

$$\frac{TV_{PI}}{PIV} \times \frac{TV_{PI}}{TV}$$

  - TV_{PI} is the target volume (TV) within the prescribed isodose volume (PIV)
  - **Part 1**: Healthy tissue receiving dose > PI (ideally ➔ 1)
  - **Part 2**: Quality of target coverage (ideally ➔ 1)
  - Ideally, **should be close to 1**.

Dose homogeneity & Conformity

- Homogeneity Index:

$$HI = \frac{D_2 - D_{98}}{D_P}$$

  - D_2: represents maximum dose, dose to 2% of the PTV
  - D_{98}: represents minimum dose, dose to 98% of the PTV
  - D_p: prescription dose
  - **Lower values indicate more homogeneity**.

Dose homogeneity & Conformity

- Gradient Index:
  - A measure for dose fall-off

$$GI = \frac{PIV_{50}}{PIV}$$

  - PIV: Prescription isodose volume, in this case PIV_{95}
  - PIV_{50}: Volume that receives half of prescription dose
  - **The lower the better** (eg for SRS a GI less than 3 is suggested).

Oesophagus, a case study (1)

- An 83 year old male patient
- Adenocarcinoma of oesophagus, distal 1/3 (GEJ)
- T3N1M0

- Radiochemotherapy: 25 x 1.6/2.0 Gy = **40/50 Gy**, concommitant carbotaxol.

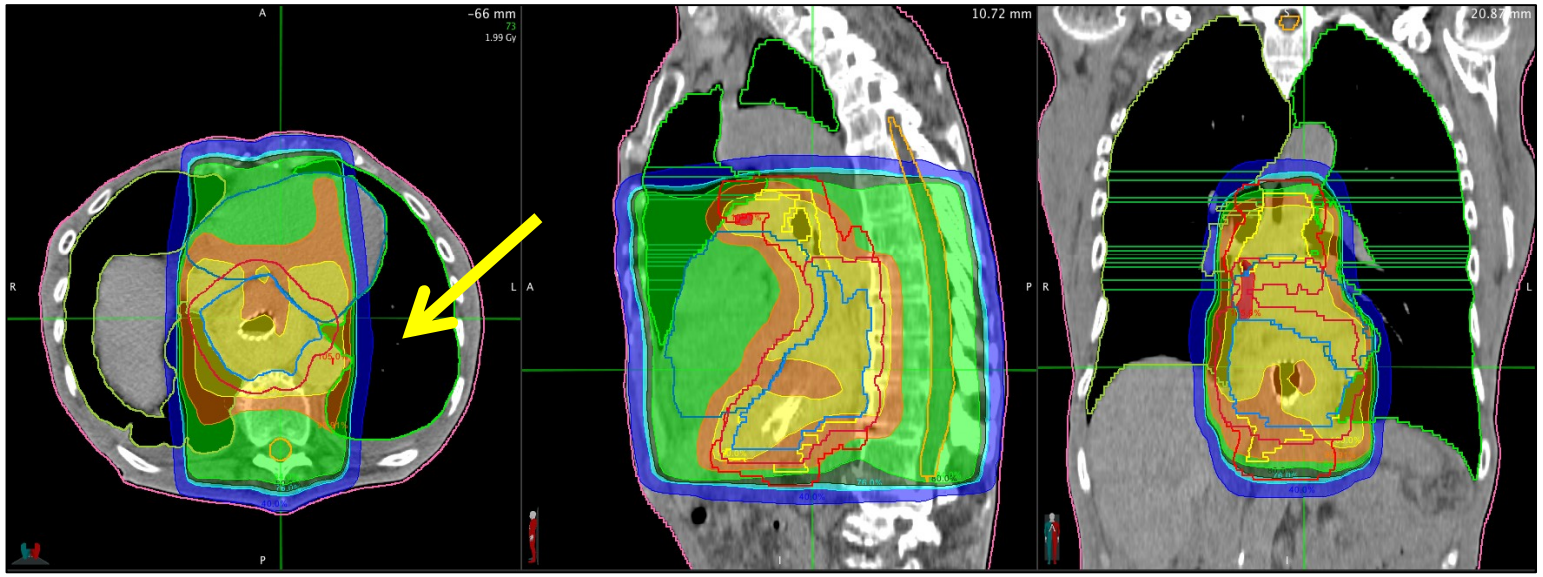
- **Treatment objectives**:
  - PTV: 95% of PTV to receive 95% of D_p
  - Lung: MLD: 19Gy, $V_{20} \leq 20\%$, $V_5 \leq 70\%$
  - Heart: $V_{30} \leq 46\ \%$
  - Myelum: $D_{2\%}$: 30Gy

Oesophagus, a case study (1)

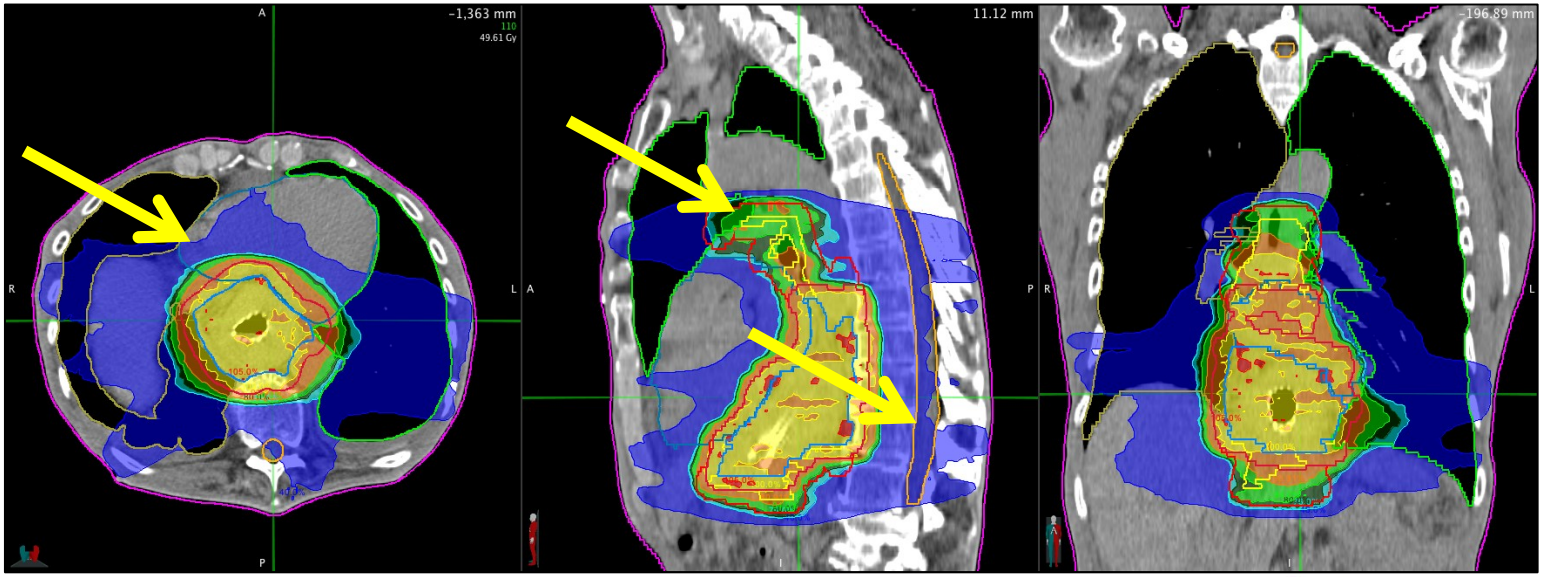
- 3D-CRT:
  - Elekta Infinity
  - AP-PA opposing beams
    + 1 dynamic conformal arc
  - TPS: XiO CMS
- VMAT:
  - Elekta Infinity
  - 1 VMAT
  - TPS: MONACO

Oesophagus, a case study (1)

- 3D-CRT



- VMAT



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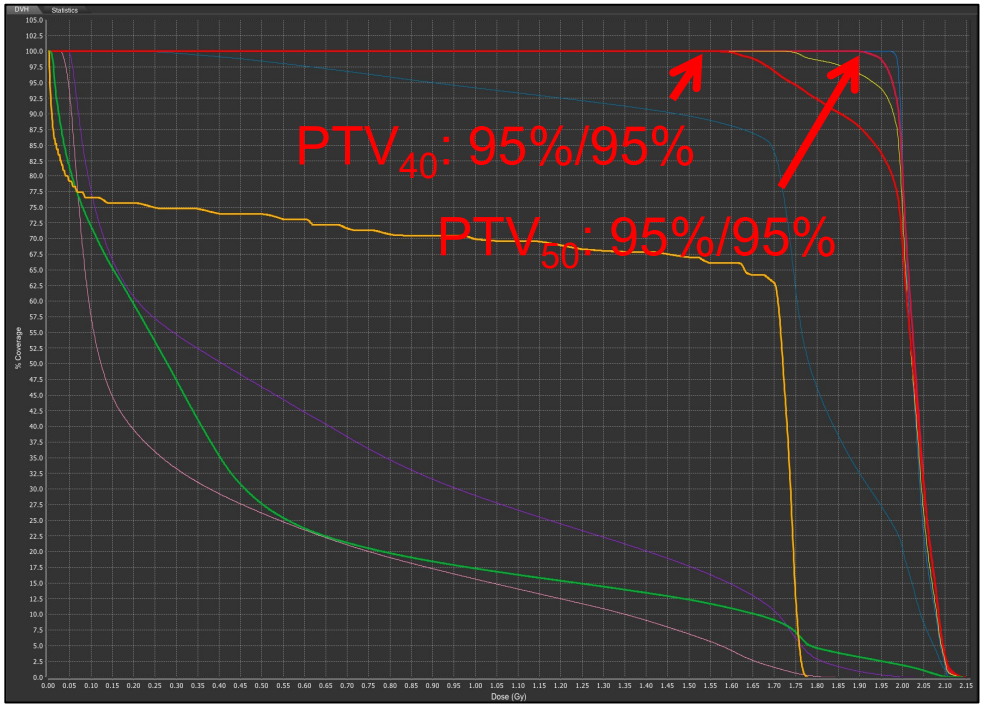
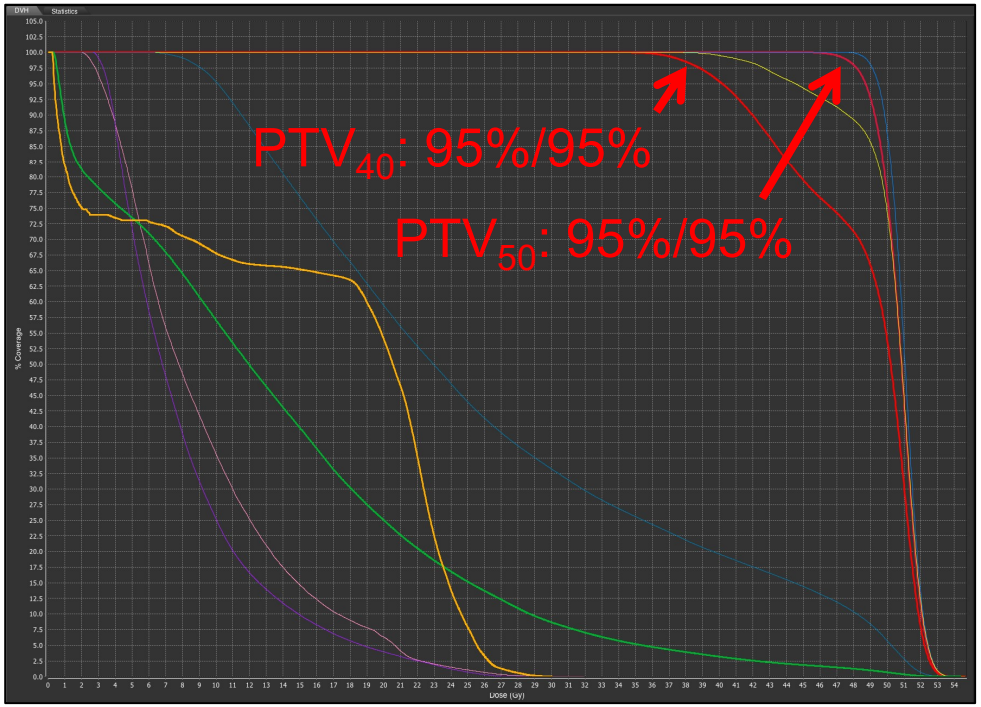
Oesophagus, a case study (1)

3D-CRT



VMAT



3D-CRT		
	40 Gy	**50 Gy**
PI	0.25	0.69
HI	**0.38**	**0.14**
GI	**1.45**	**5.57**

more homogenous

VMAT		
	40 Gy	**50 Gy**
PI	0.70	1.18
HI	**0.54**	**0.21**
GI	**3.70**	**6.16**

low dose wash

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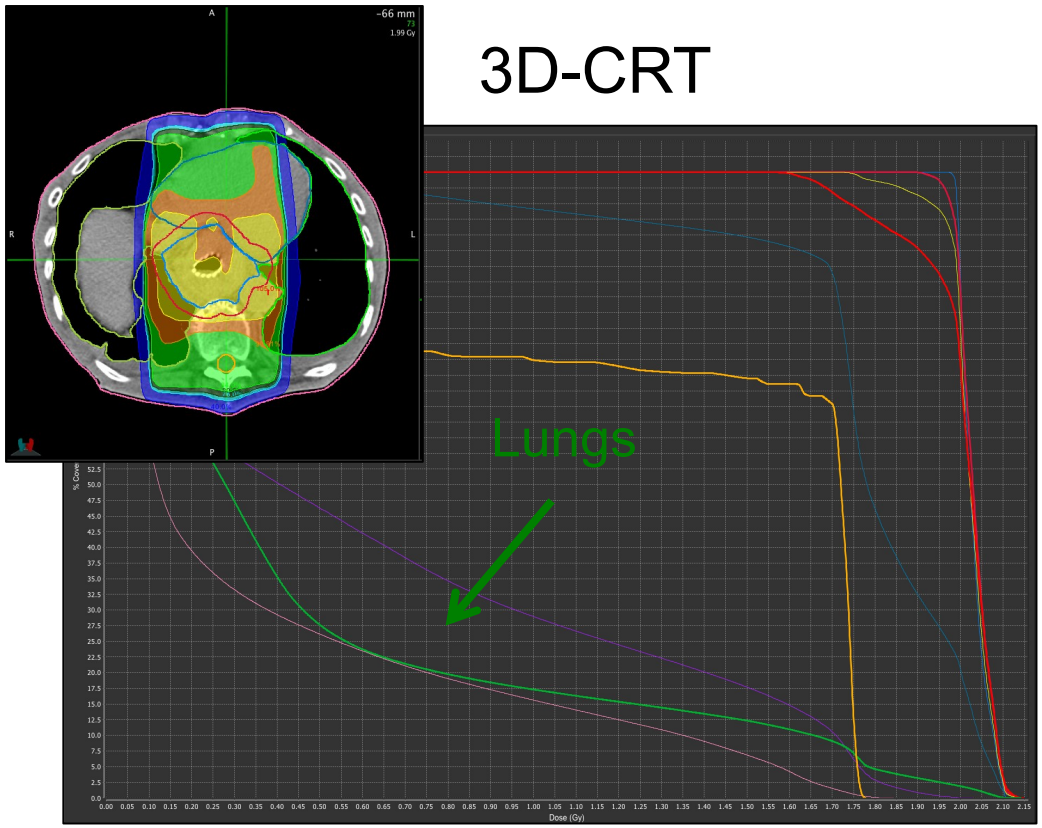
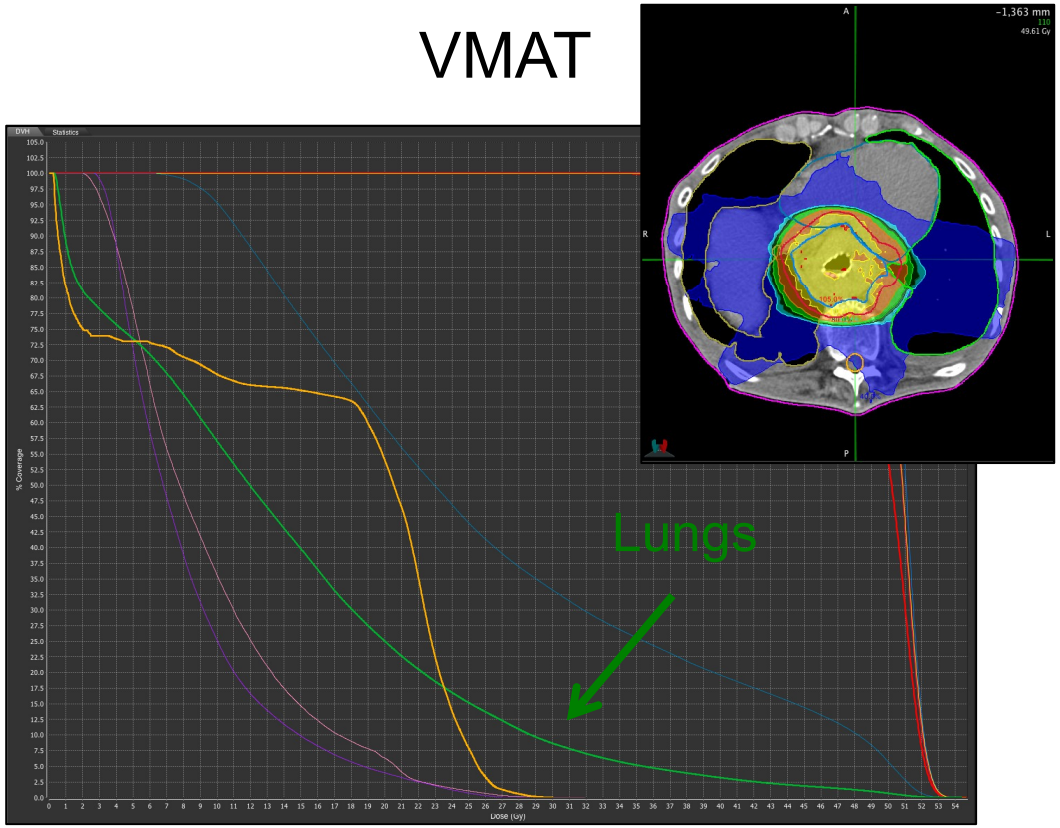
Oesophagus, a case study (1)

3D-CRT



VMAT

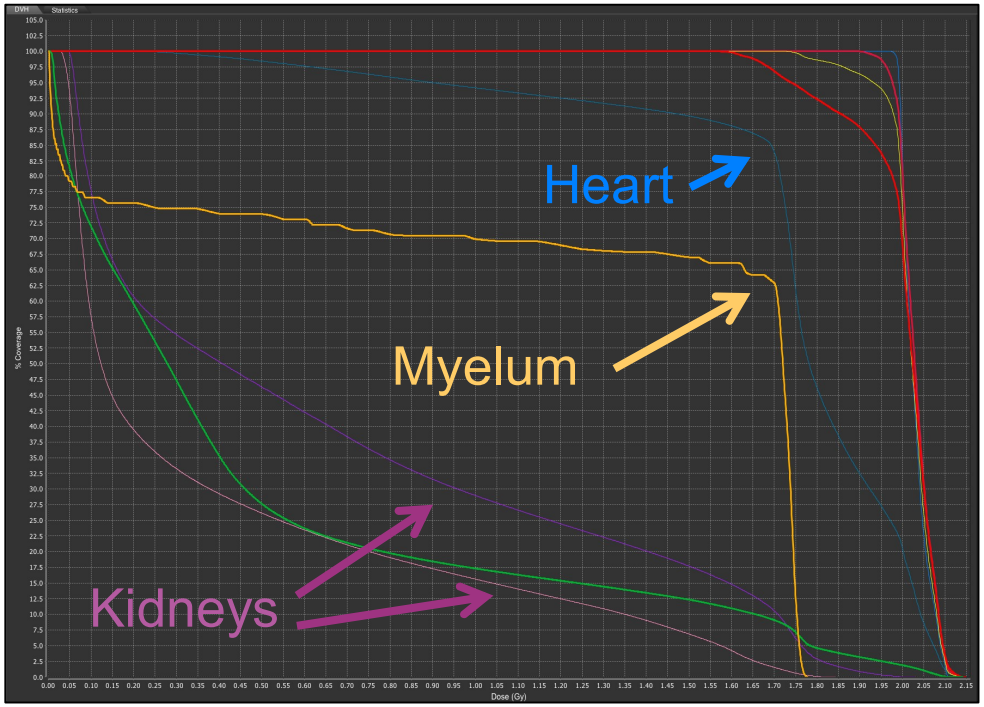


Lungs		
	objective	3D-CRT
V_{20}	< 20%	20
V_5	< 70%	60
MLD	< 19Gy	12

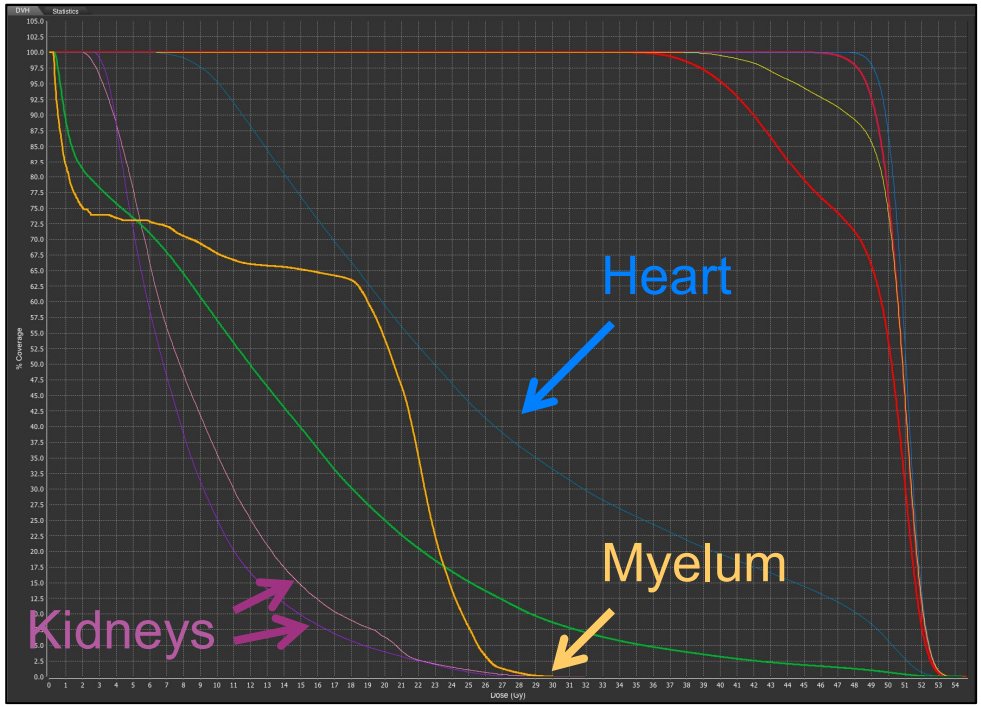
Lungs		
	objective	VMAT
V_{20}	< 20%	25
V_5	< 70%	73
MLD	< 19Gy	14

Oesophagus, a case study (1)

3D-CRT



VMAT

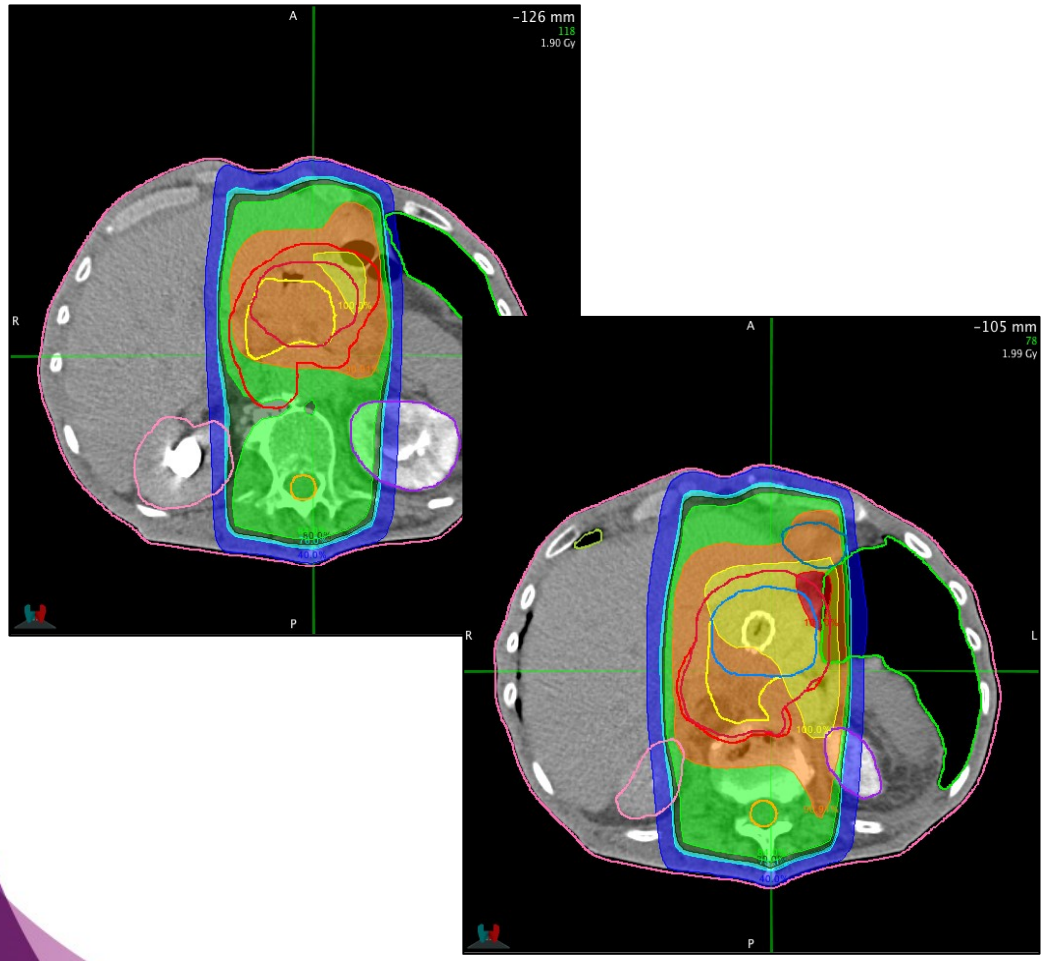


	objective	3D-CRT
Heart	$V_{30} < 46\%$	**93%**
Myelum	$D_{2\%} < 30Gy$	**45%**
Kidney L	Mean dose	**10Gy**
Kidney R	Mean dose	**17Gy**

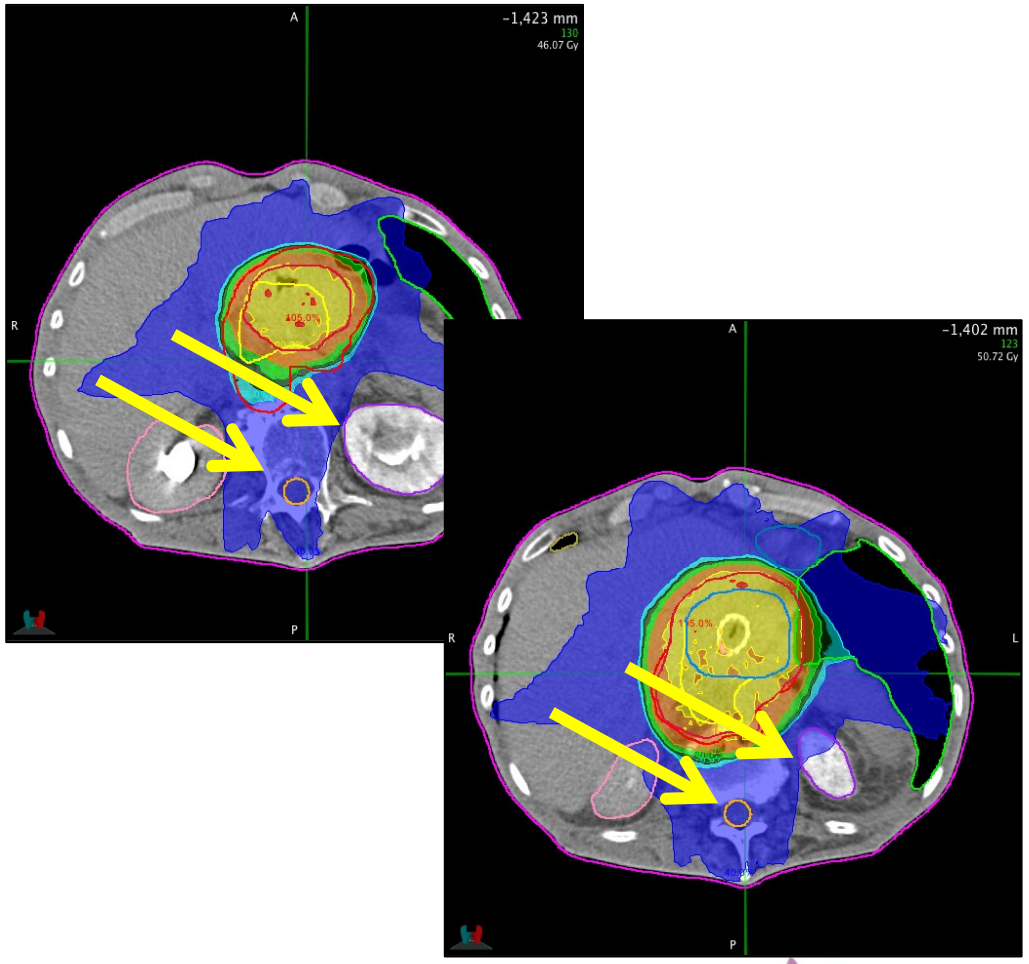
	objective	VMAT
Heart	$V_{30} < 46\%$	**33%**
Myelum	$D_{2\%} < 30Gy$	**30%**
Kidney L	Mean dose	**8gy**
Kidney R	Mean dose	**9Gy**

Oesophagus, a case study (1)

3D-CRT



VMAT



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Oesophagus, a case study (2)

- An 58 year old male patient
- Squamous cell carcinoma of oesophagus, distal 1/3 (GEJ)
- T1N0M0

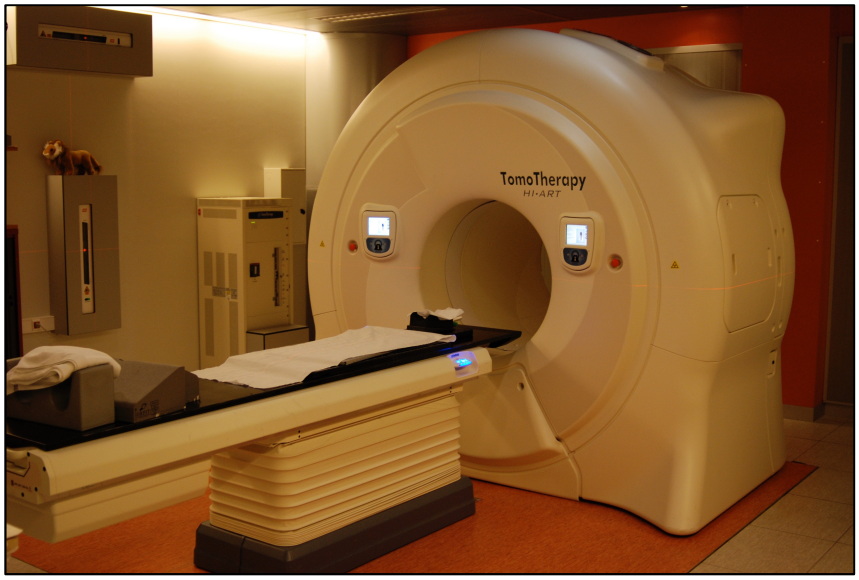
- Radiochemotherapy: 25 x 1.6/2.0 Gy = **40/50 Gy**, concommitant carbotaxol.

- **Treatment objectives**:
  - PTV: 95% of PTV to receive 95% of D_p
  - Lung: MLD: 19Gy, $V_{20} \leq 20\%$, $V_5 \leq 70\%$
  - Heart: $V_{30} \leq 46\ \%$
  - Myelum: $D_{2\%}$: 30Gy

Oesophagus, a case study (2)

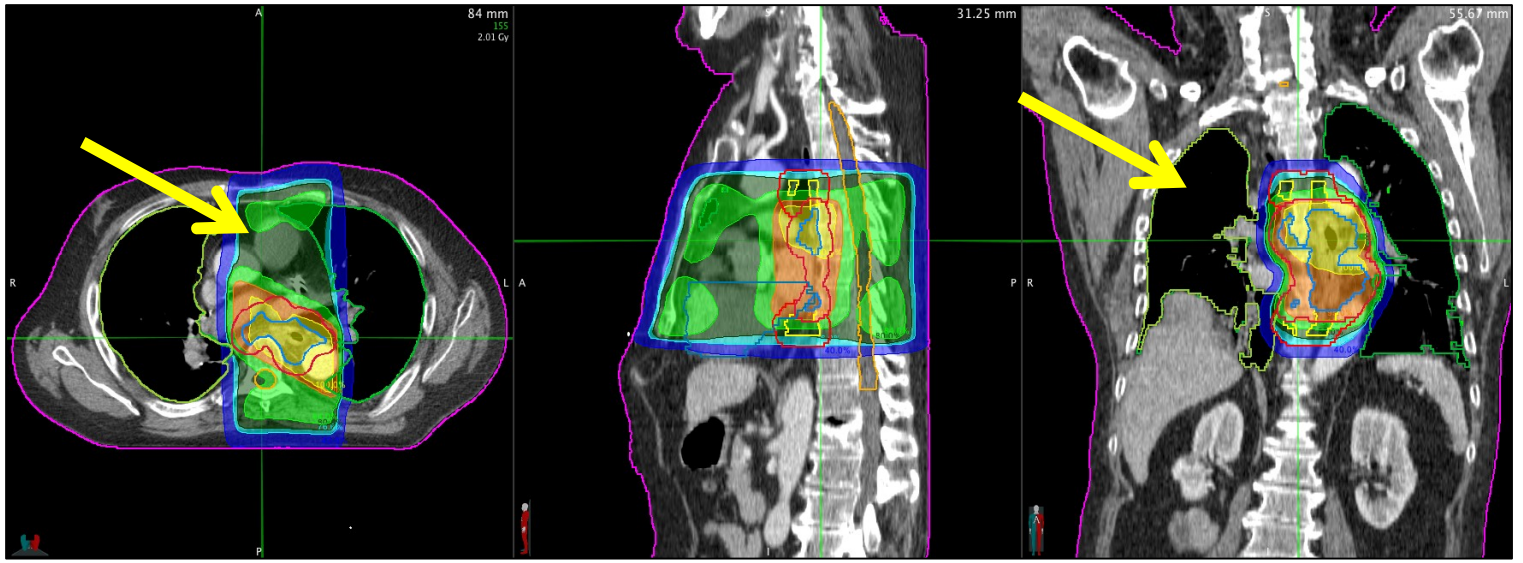
- 3D-CRT:
  - Elekta Infinity
  - 4 beams, box technique (6 and 15MV)
  - TPS: XiO CMS

- Tomo:
  - TomoTherapy
  - Helical tomotherapy
  - TPS: Hi-Art

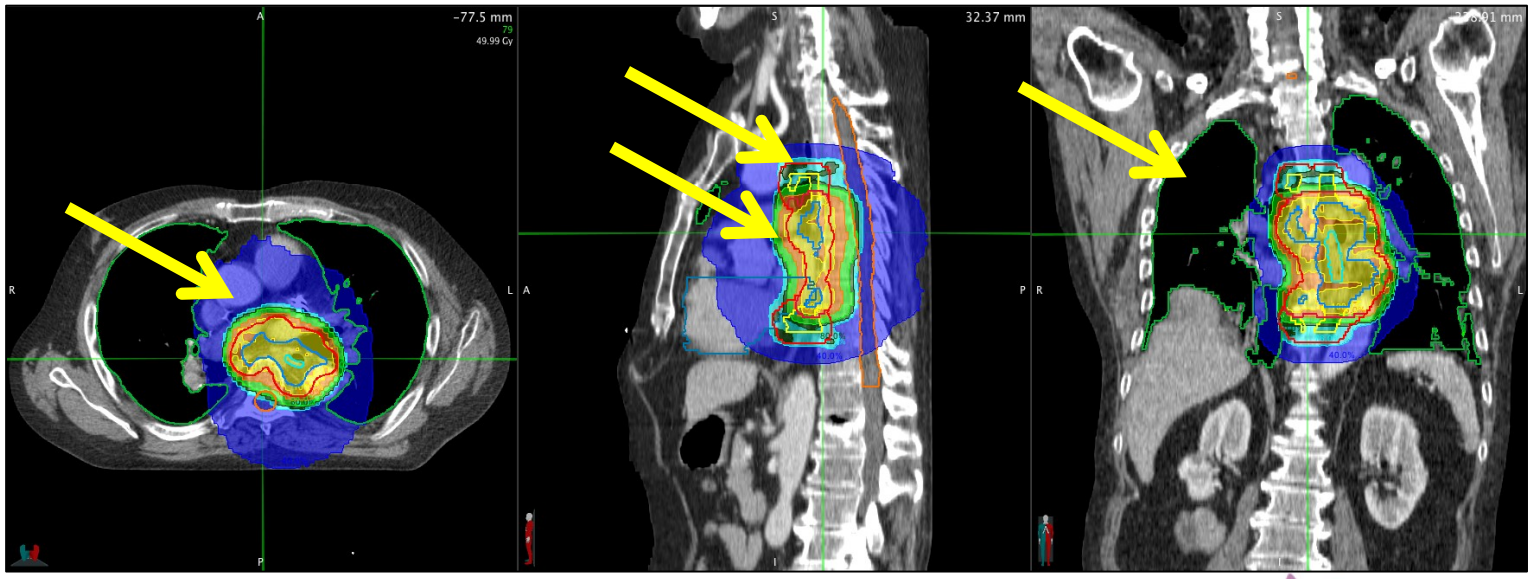


Oesophagus, a case study (2)

- 3D-CRT



- Tomo



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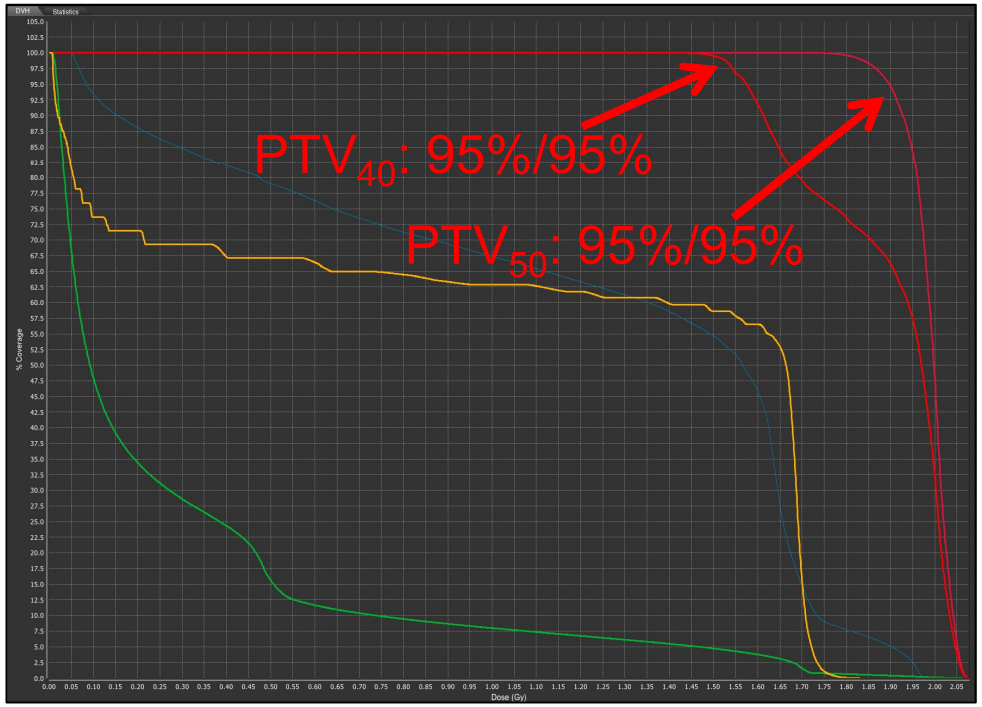
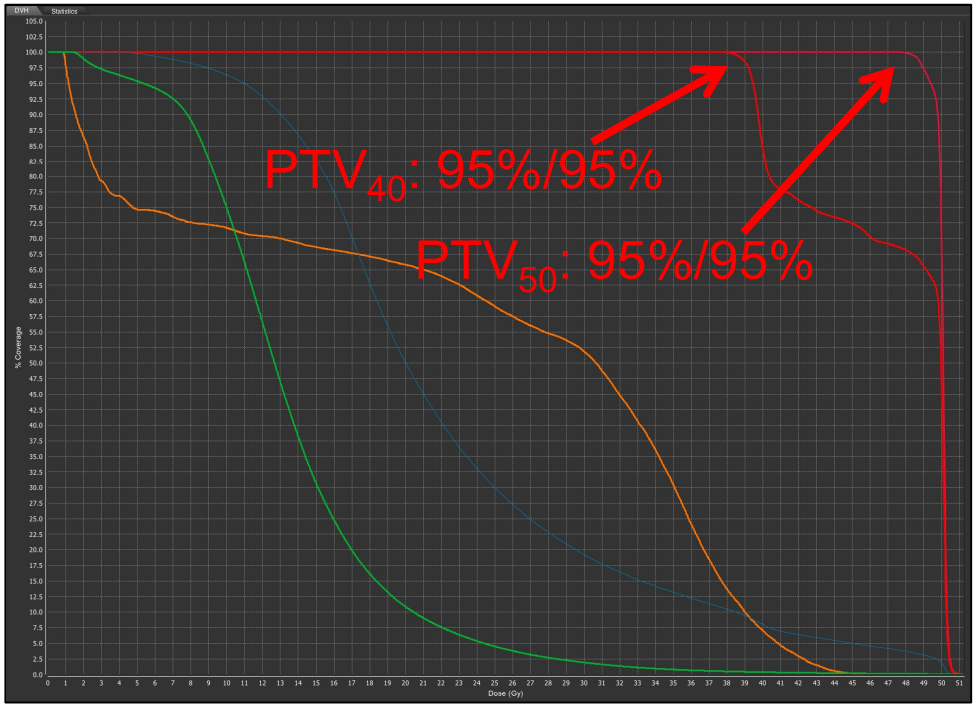
Oesophagus, a case study (2)

3D-CRT



Tomo



3D-CRT	40 Gy	50 Gy
PI	0.20	1.78
HI	**0.42**	**0.19**
GI	**1.71**	17.83

Tomo	40 Gy	50 Gy
PI	0.64	1.15
HI	**0.36**	**0.08**
GI	**4.26**	7.41

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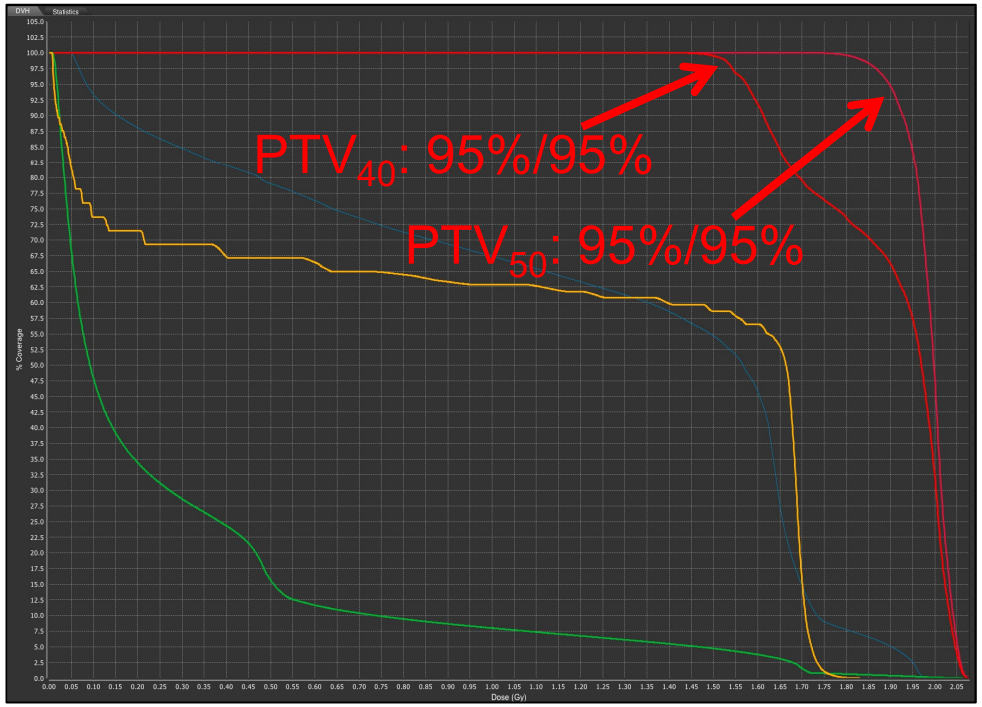
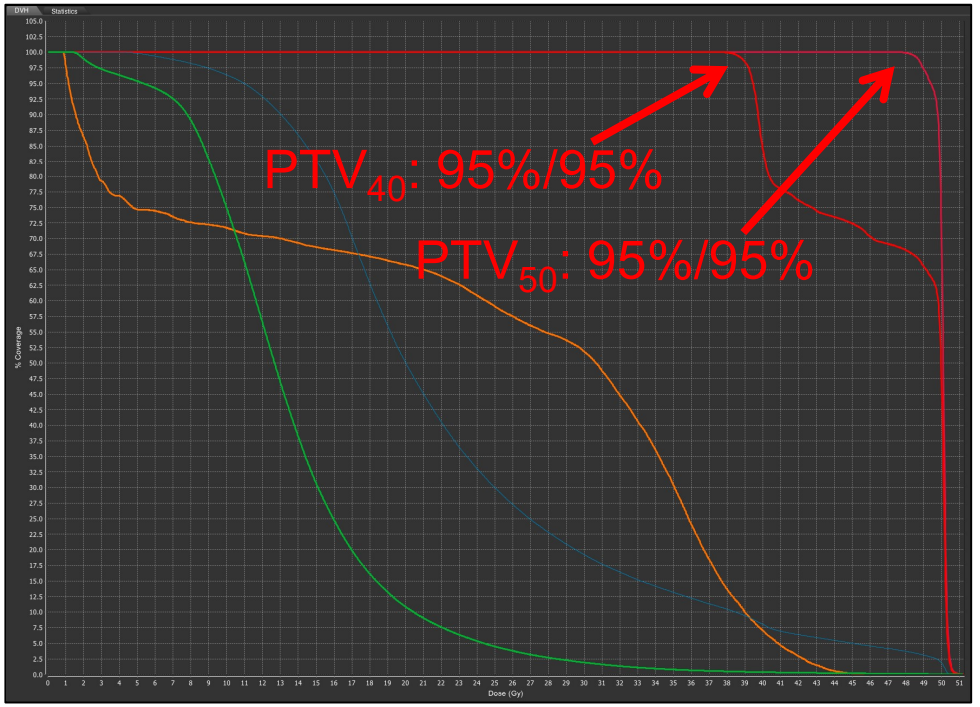
Oesophagus, a case study (2)

3D-CRT



Tomo



3D-CRT		
	40 Gy	**50 Gy**
PI	**0.20**	**1.78**
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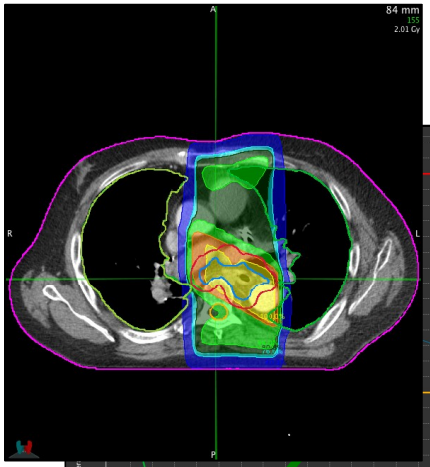
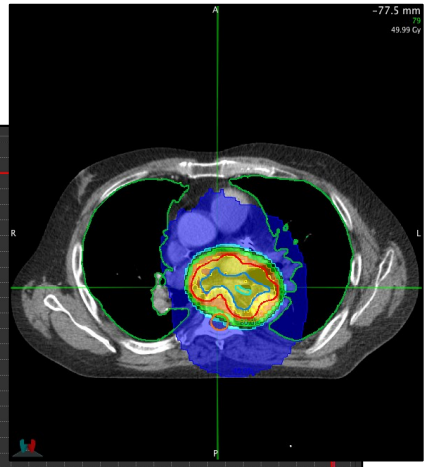
Tomo		
	40 Gy	**50 Gy**
PI	**0.64**	**1.15**
HI	0.36	0.08
GI	4.26	7.41

Oesophagus, a case study (2)



3D-CRT



Tomo

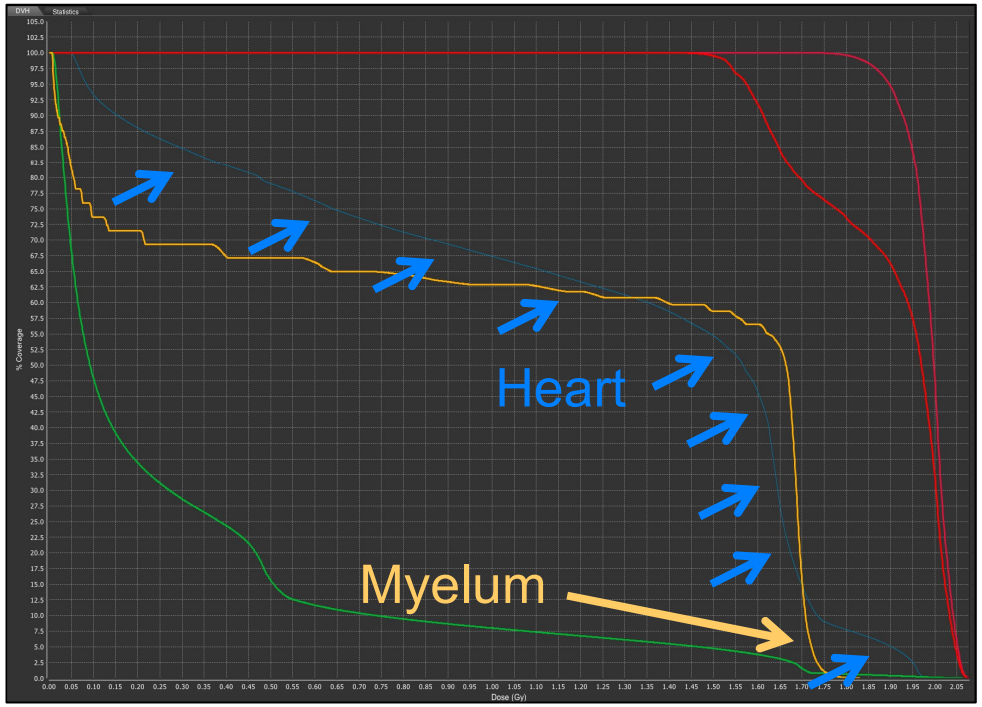
Lungs		
	objective	3D-CRT
V_{20}	< 20%	9
V_5	< 70%	34
MLD	< 19Gy	7

Lungs		
	objective	Tomo
V_{20}	< 20%	11
V_5	< 70%	95
MLD	< 19Gy	14

low dose wash

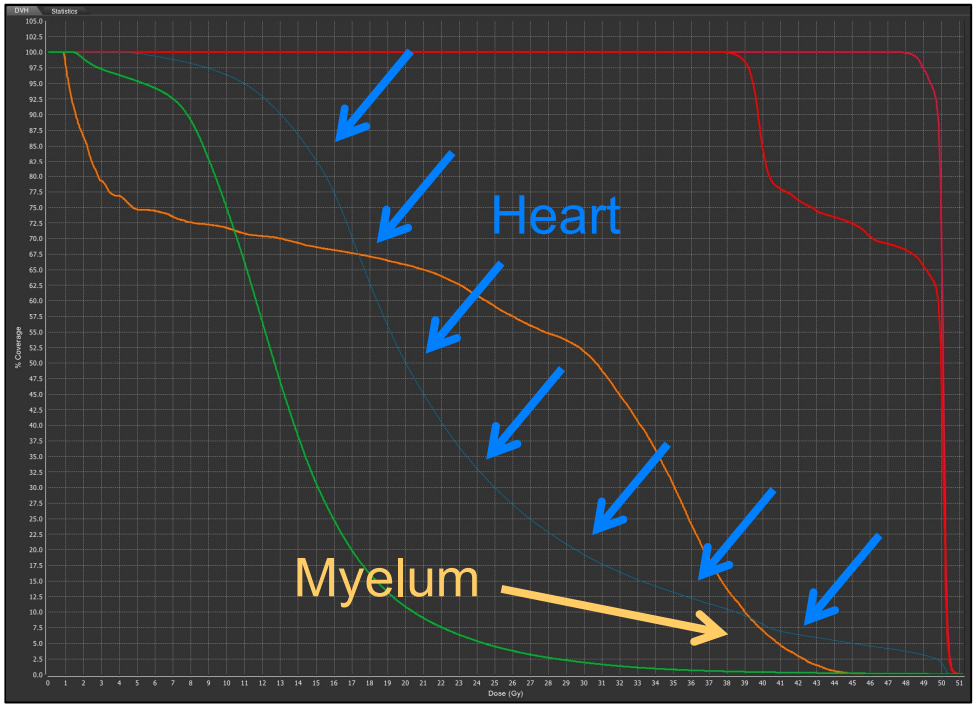
Oesophagus, a case study (2)

3D-CRT



	objective	3D-CRT
Heart	$V_{30} < 46\%$	**63%**
Myelum	$D_{2\%} < 30Gy$	46%

Tomo



	objective	Tomo
Heart	$V_{30} < 46\%$	**19%**
Myelum	$D_{2\%} < 30Gy$	46%

Stomach, a case study (3)

- An 70 year old male patient
- Adenocarcinoma of stomach, “subtotal” gastrectomy
- pT3pN1M0

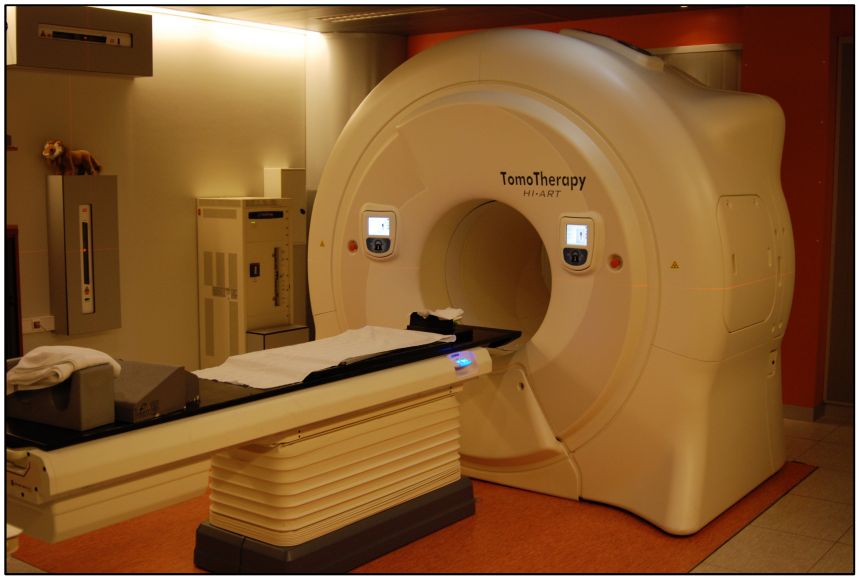
- Radiochemotherapy: 25 x 1.8 Gy = **45 Gy**, concommitant 5-FU (Post op MacDonald).

- **Treatment objectives**:
  - PTV: 95% of PTV to receive 95% of D_p
  - Liver: V_{30}
  - Heart: V_{30}
  - Myelum: $D_{2\%}$

Stomach, a case study (3)

- 3D-CRT:
  - Elekta Infinity
  - Dynamic conformal arc + posterior beam (15MV)
  - TPS: XiO CMS

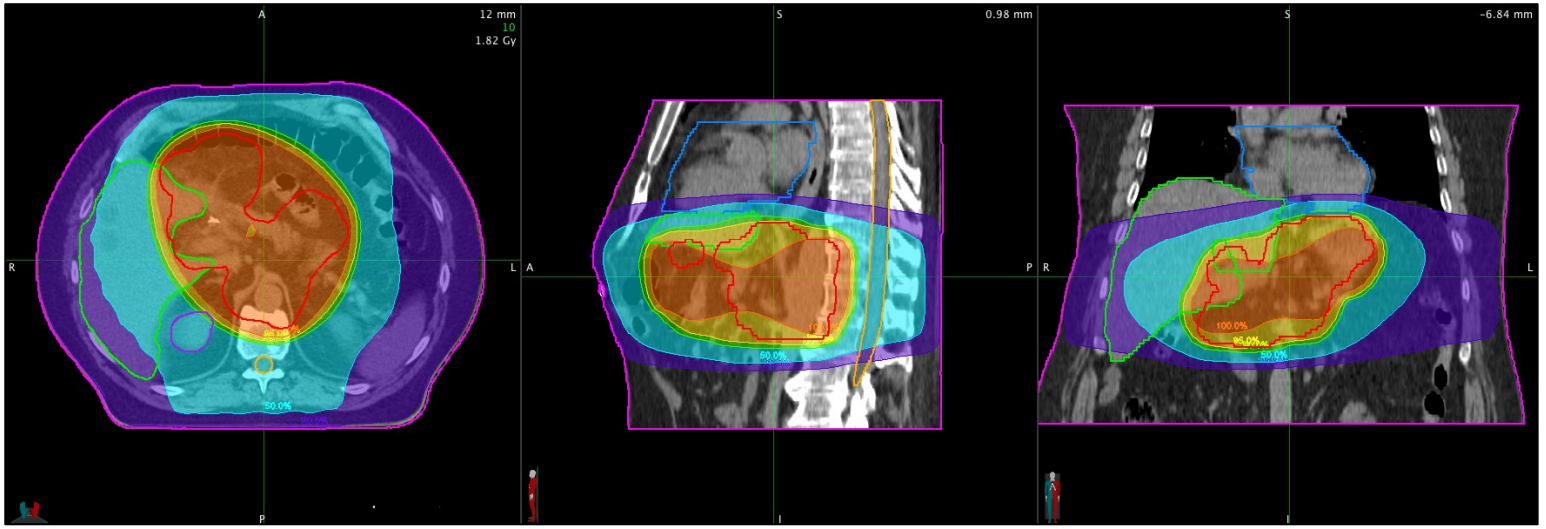
- Tomo:
  - TomoTherapy
  - Helical tomotherapy
  - TPS: Hi-Art



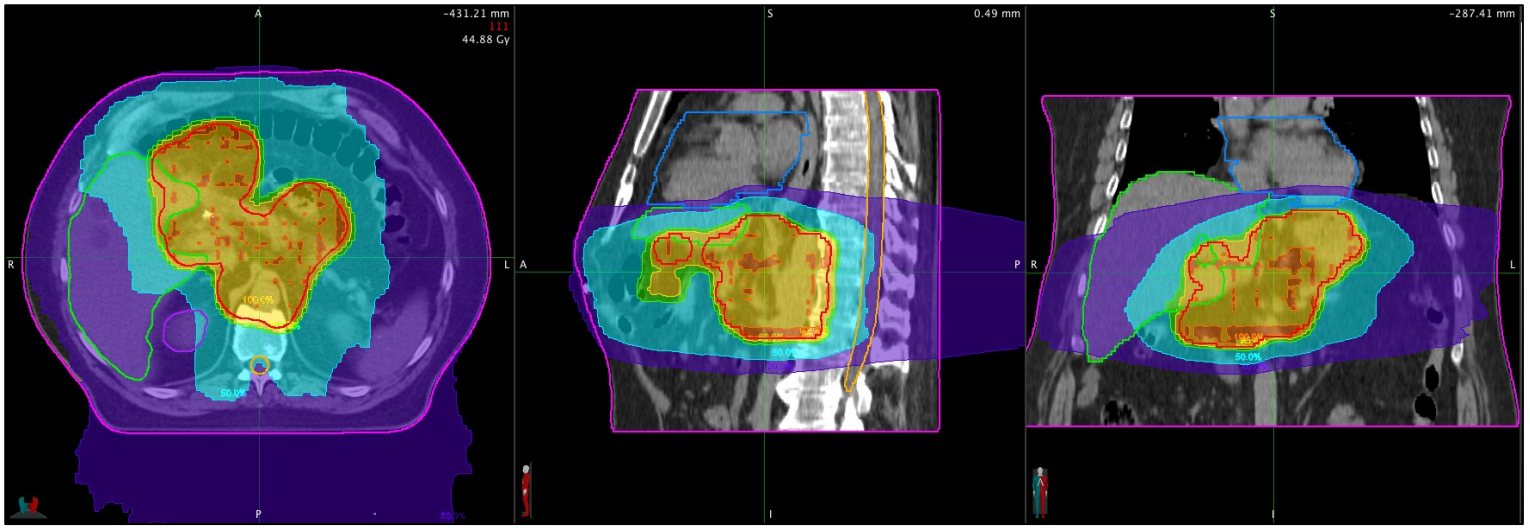
Stomach, a case study (3)

- 3D-CRT

1 105.00 (%)	47.25 (Gy)
1 100.00 (%)	45.00 (Gy)
1 95.00 (%)	42.75 (Gy)
1 90.00 (%)	40.50 (Gy)
1 50.00 (%)	22.50 (Gy)
1 20.00 (%)	9.00 (Gy)



- Tomo



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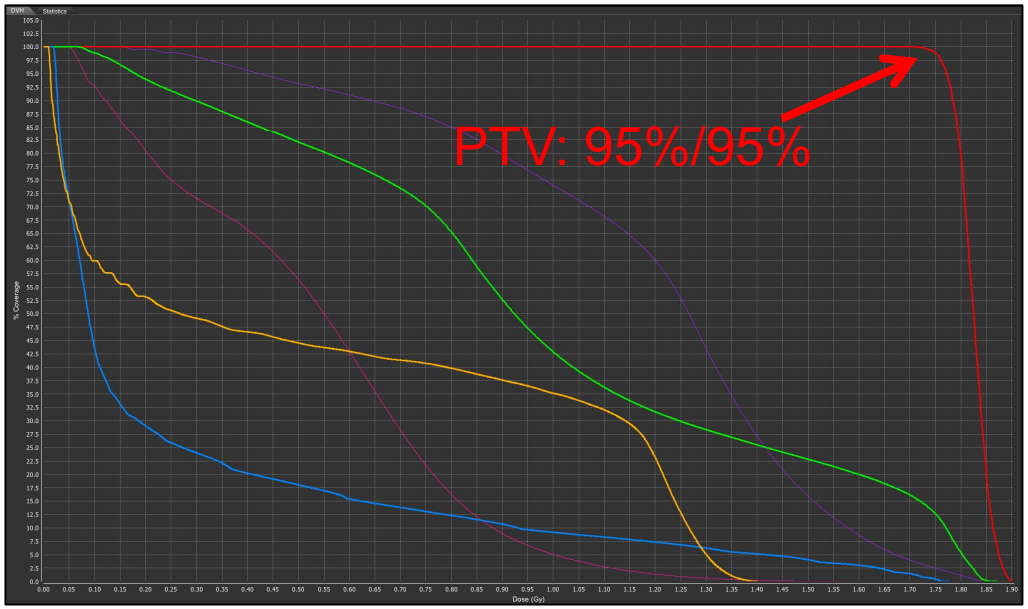
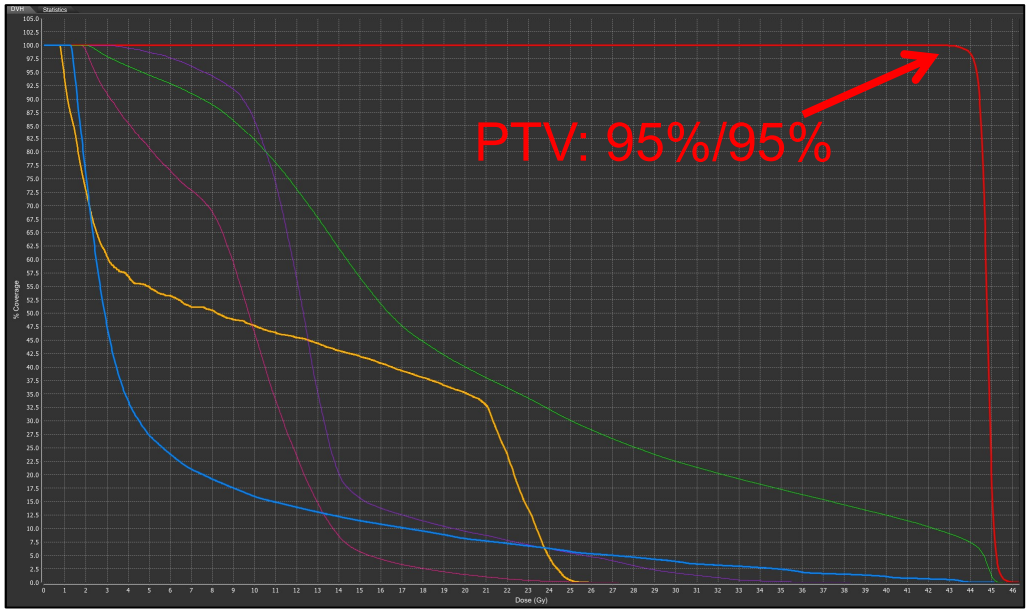
Stomach, a case study (3)

3D-CRT



Tomo

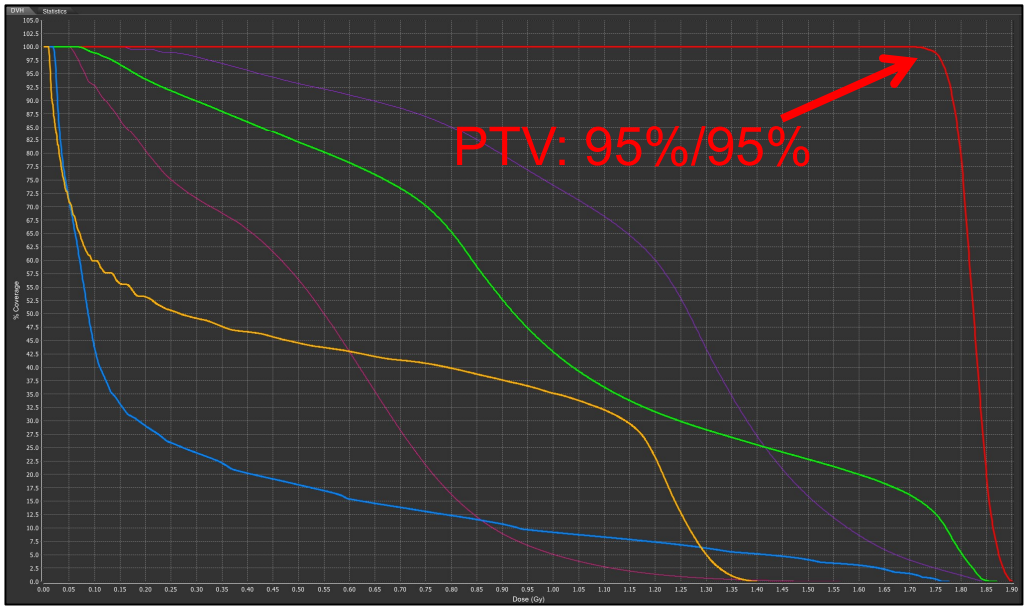


3D-CRT	
PI	0.57
HI	**0.11**
GI	**2.78**

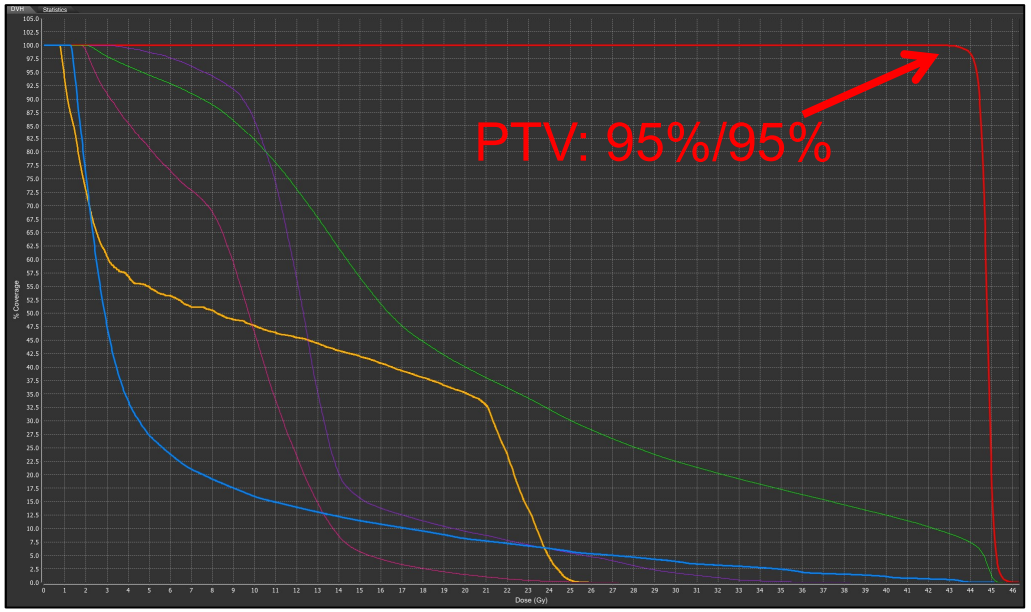
Tomo	
PI	0.84
HI	**0.10**
GI	**3.29**

Stomach, a case study (3)

3D-CRT



Tomo



3D-CRT	
PI	**0.57**
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Tomo	
PI	**0.84**
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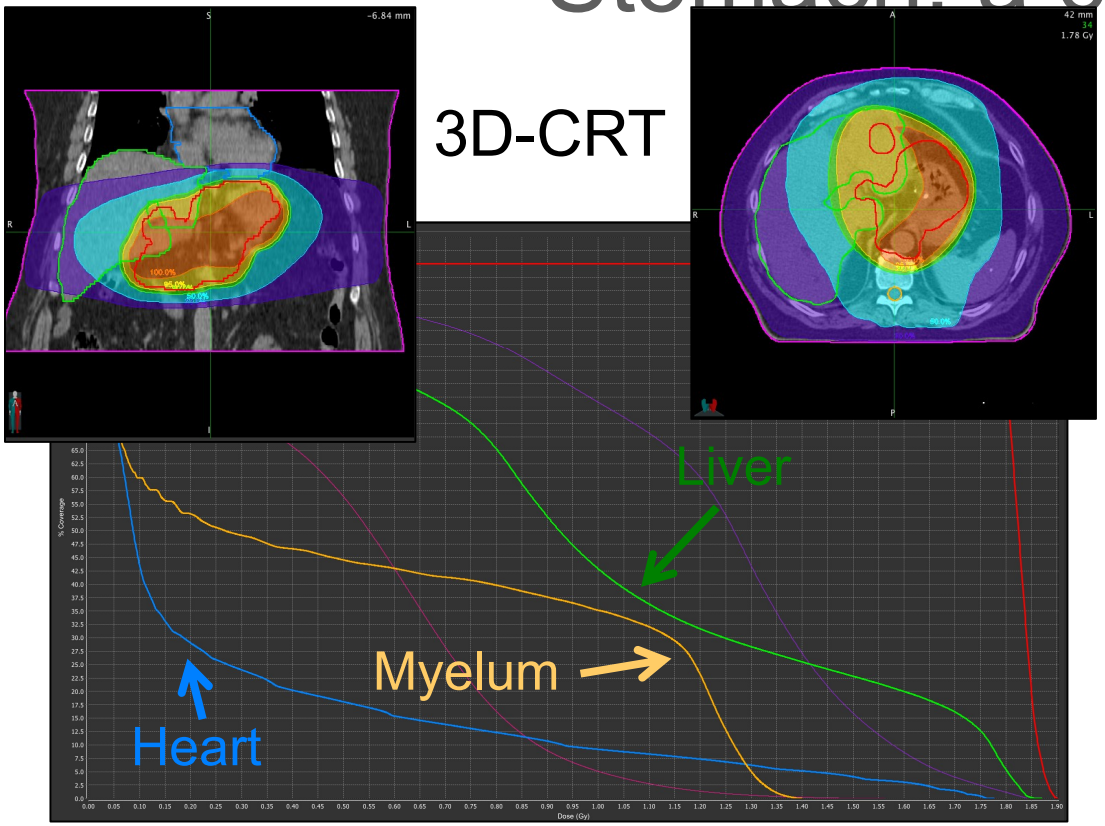
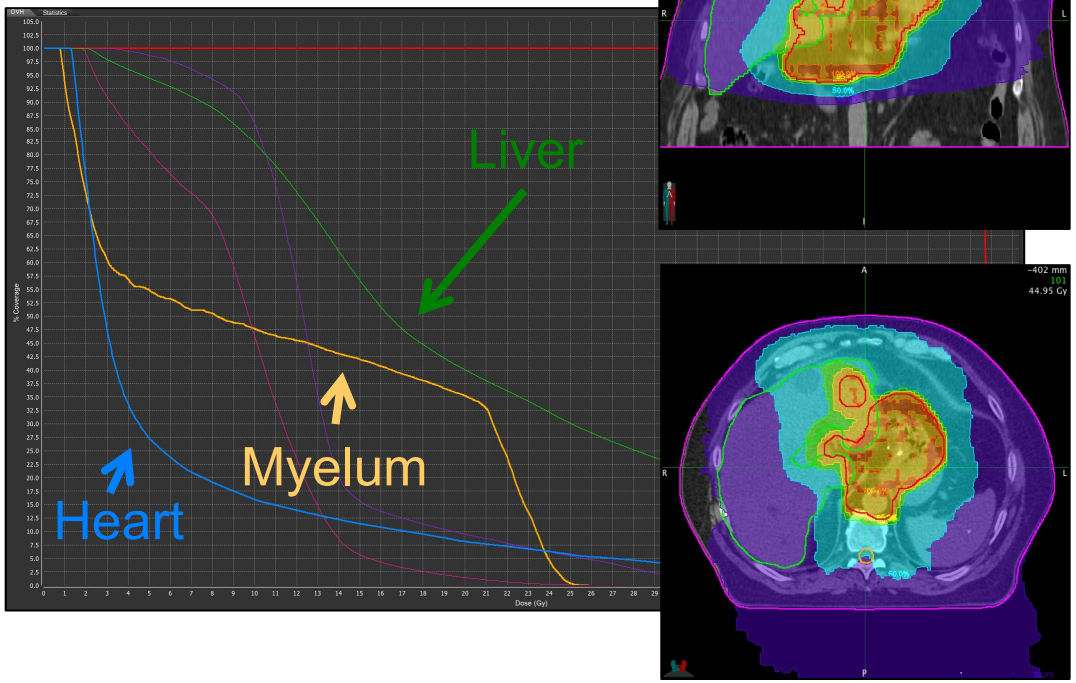
GI	3.29

Stomach, a case study (3)

3D-CRT



Tomo

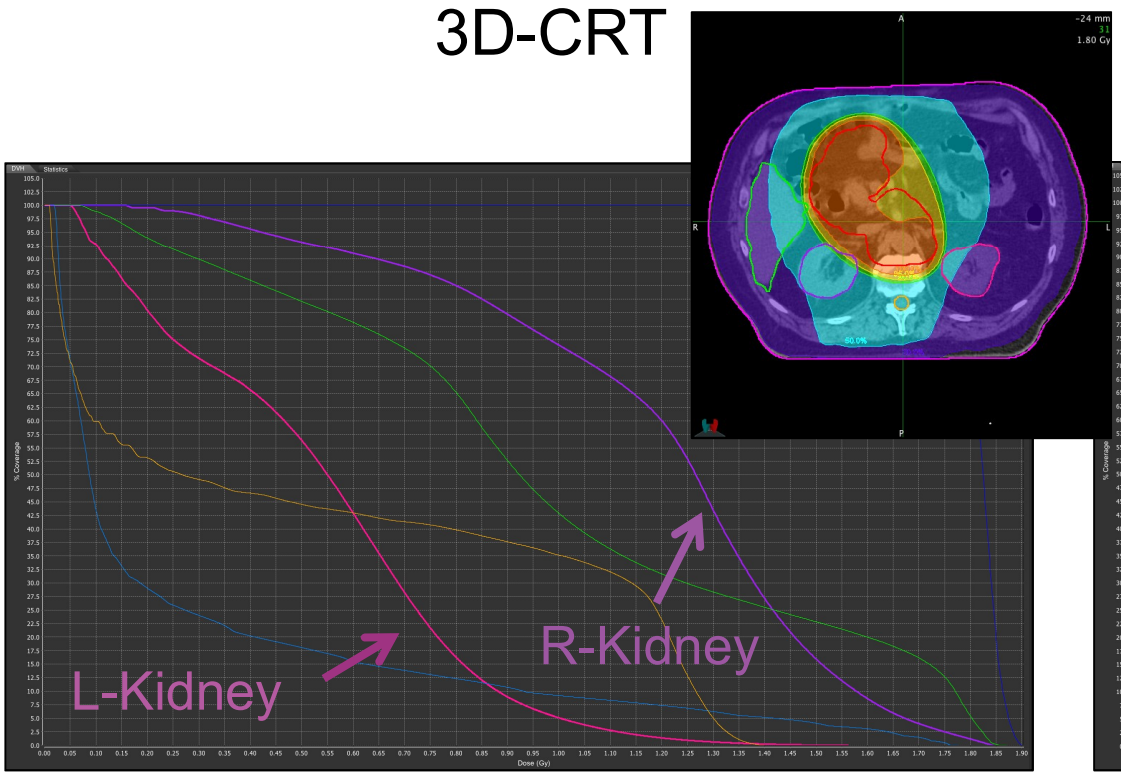


3D-CRT		
	objective	
Liver	V_{30}	31.7%
Heart	V_{30}	7.3%
Myelum	$D_{2\%}$	35.0Gy

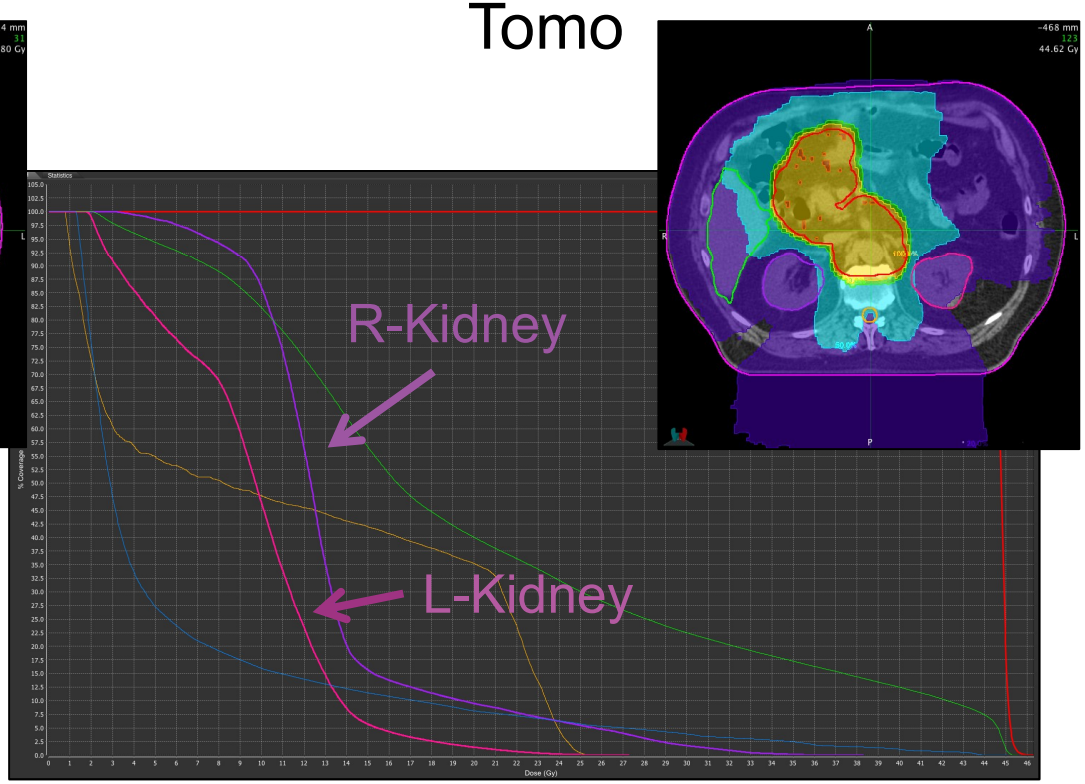
Tomo		
	objective	
Liver	V_{30}	**22.5%**
Heart	V_{30}	**3.9%**
Myelum	$D_{2\%}$	**25.8Gy**

Stomach, a case study (3)

3D-CRT



Tomo



Kidneys		
	Left	**Right**
D_{mean}	13.0Gy	29.5Gy
V_{15}	42.8%	91.0%

Kidneys		
	Left	**Right**
D_{mean}	9.3Gy	13.3Gy
V_{15}	5.7%	15.6%

Acknowledgements

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PTV margins: The “paranoid target volume”

Dirk Verellen

DV is involved in an on-going scientific collaboration with RaySearch

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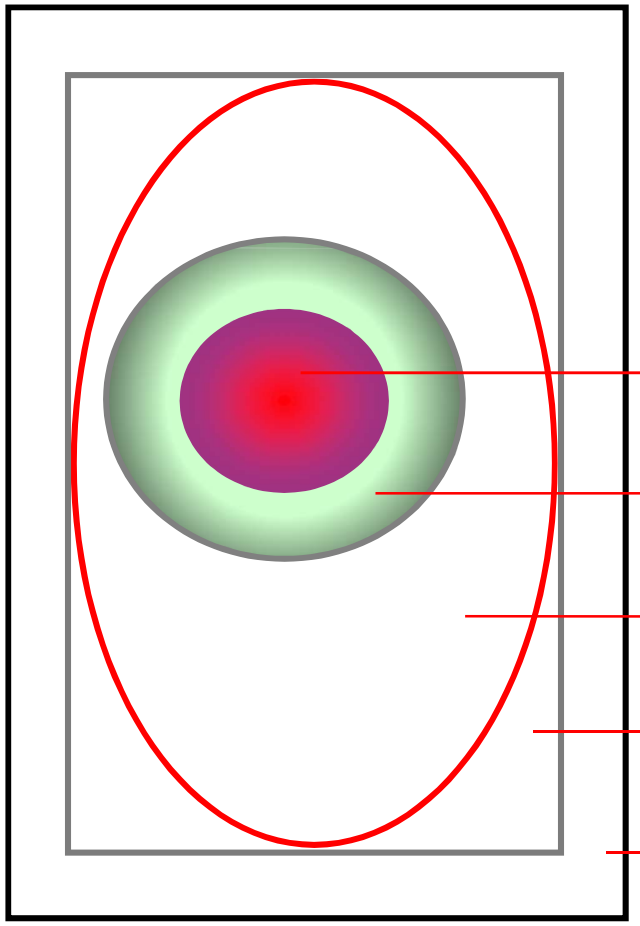
Outline

- PTV as a pragmatic solution
- Is there still room for the concept PTV when we evolve to BCRT, ART, … particle therapy?

Let's start with the definition



GTV

CTV

PTV

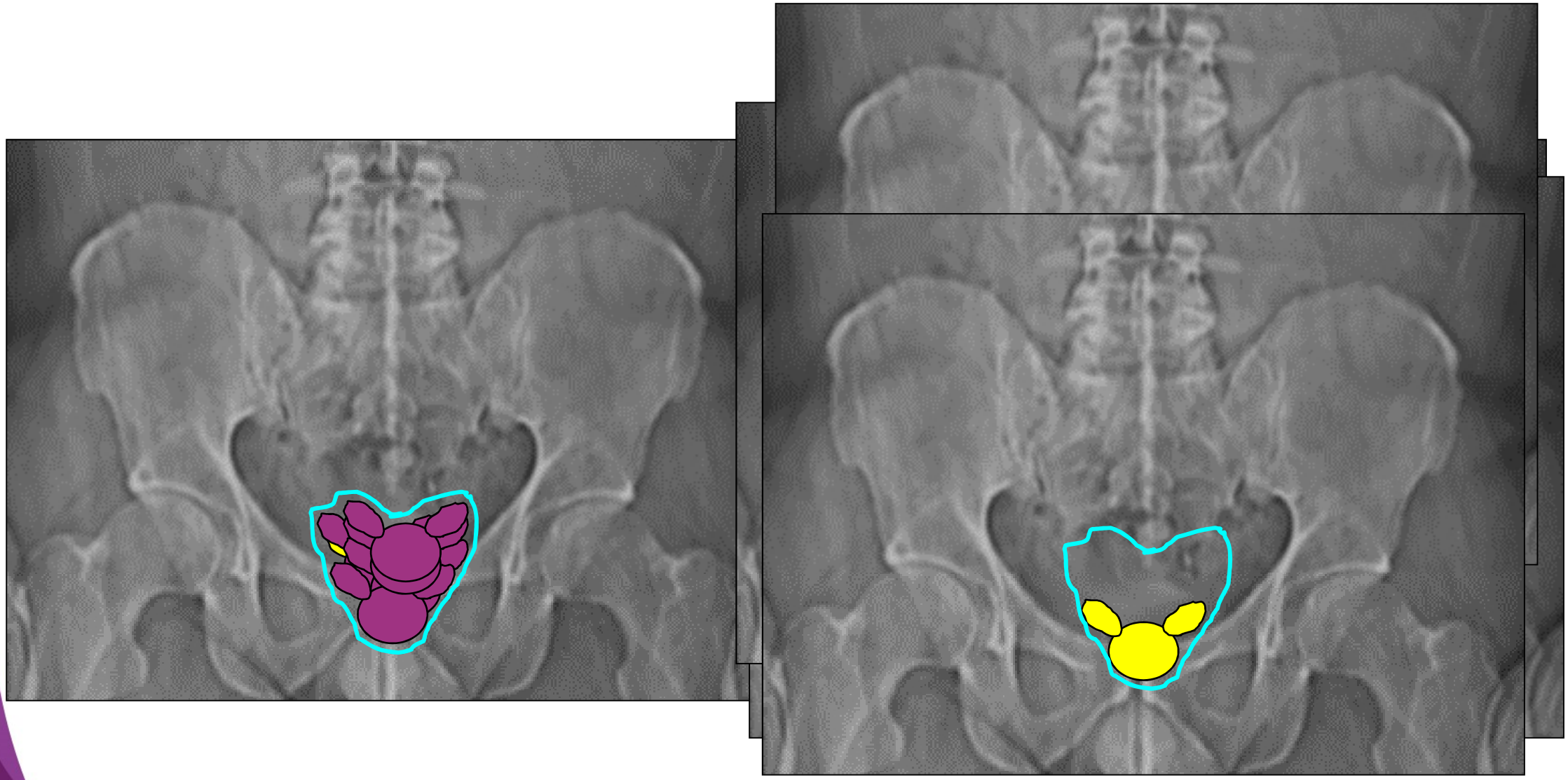
TV

IV

Clinically determined

"statistical box" representing a volume with a high probability of containing the CTV

Let’s start with the definition



“The dancing prostate”

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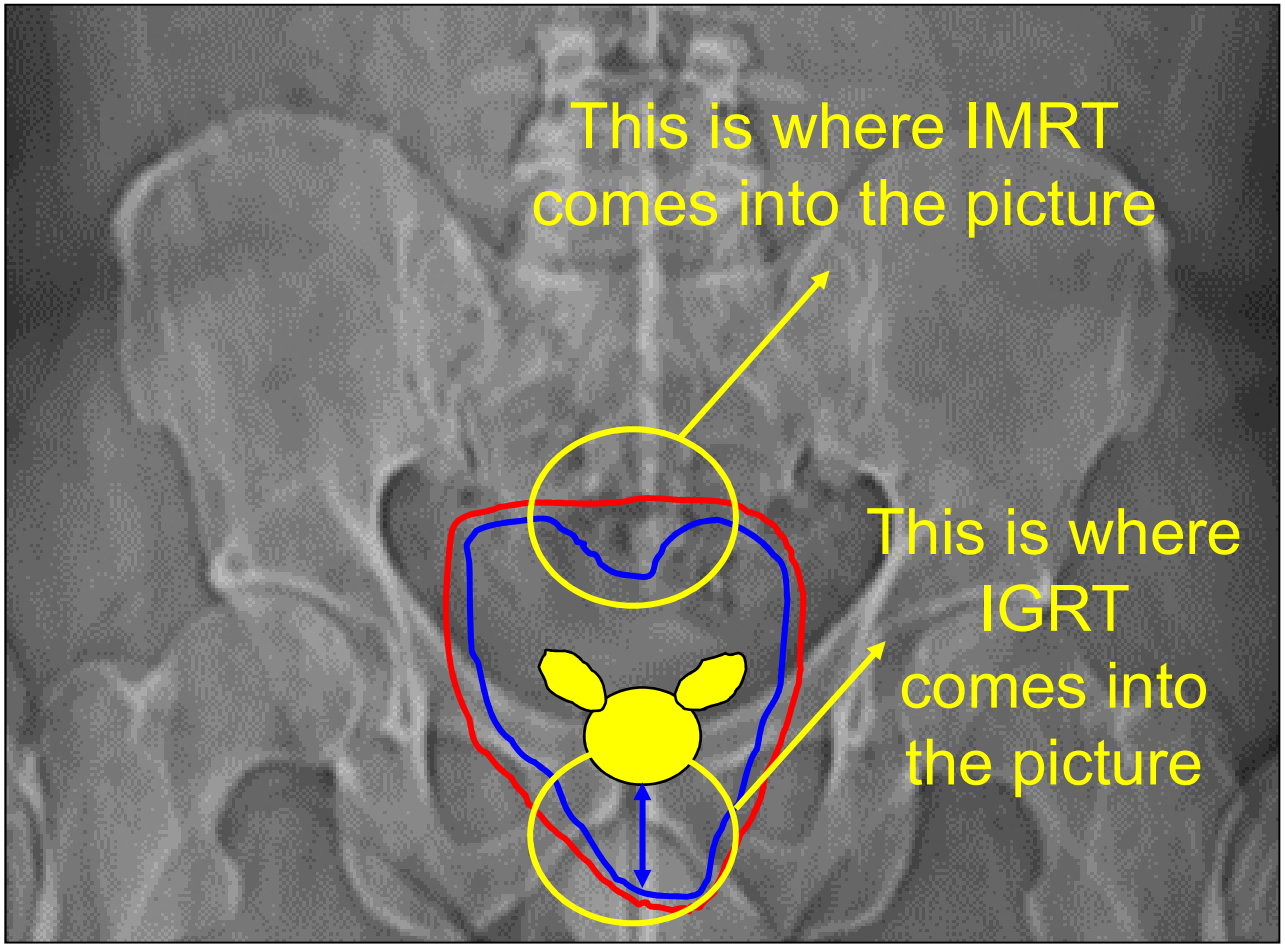
Let's start with the definition



Set up Margin

+

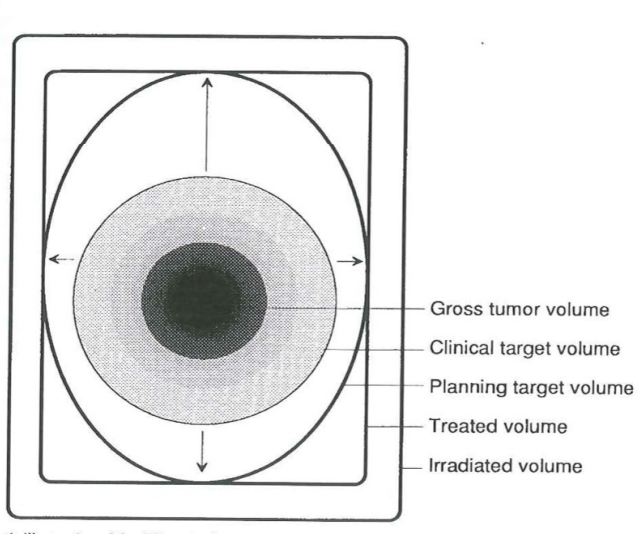
Internal Margin

Irradiated Volume

"The dancing prostate"

Let's start with the definition

- ICRU 50



- ICRU 62

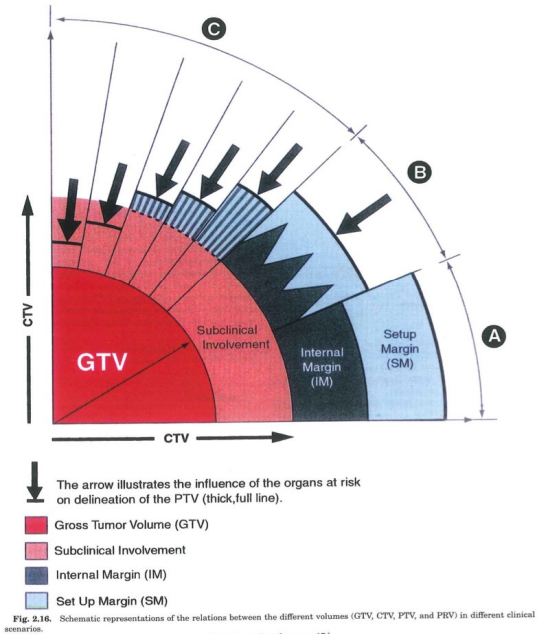


Fig. 2.16. Schematic representations of the relations between the different volumes (GTV, CTV, PTV, and PRV) in different clinical scenarios.

- … ICRU 83 …

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Let's start with the definition

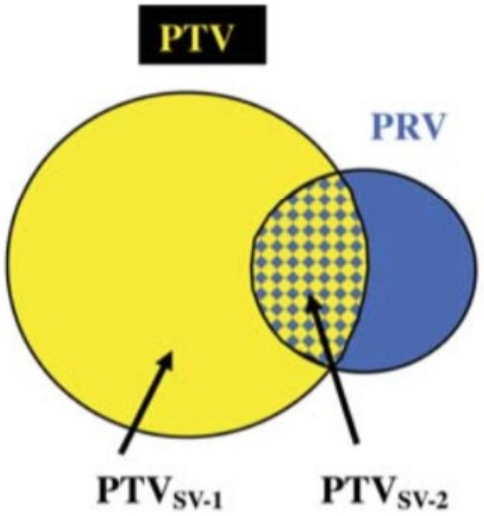
- **ICRU 83**:
  - The PTV is **A GEOMETRICAL CONCEPT** introduced for treatment planning and evaluation. **It is the recommended tool to shape absorbed-dose distributions to ensure that the prescribed absorbed dose will actually be delivered to all parts of the CTV with a clinically acceptable probability**, despite geometrical uncertainties such as organ motion and setup variations
  - It surrounds the representation of the CTV with a margin such that the planned absorbed dose is delivered to the CTV
  - This margin takes into account both the **internal** and the **setup** uncertainties
  - **Although the delineation of the GTV and the CTV is independent of the irradiation technique, the delineation of the PTV is dependent on the technique and is part of the treatment prescription**.
  - A margin must be added to the CTV taking into account uncertainties and variations in (1) position, size, and shape of the CTV (internal variations), and (2) patient and beam positioning (external variations)

Let's start with the definition

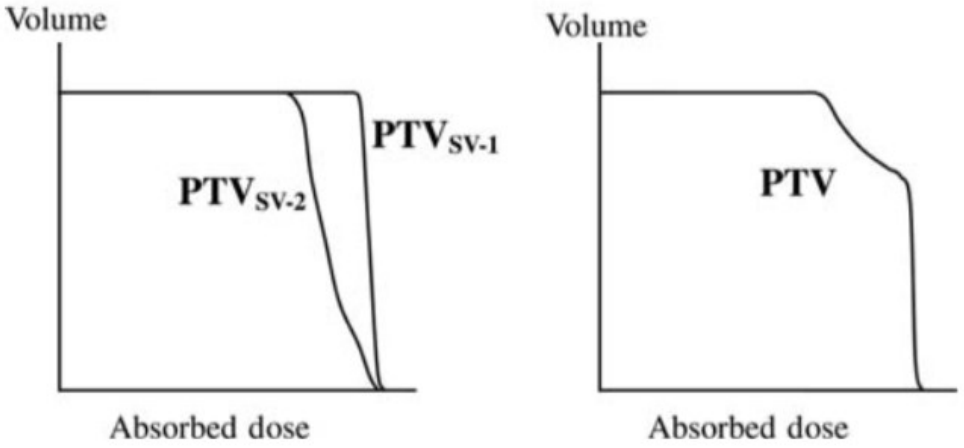
- **ICRU 83**:
  - In earlier ICRU documents, the possibility of **compromising** the margins of the PTV if they encroached on **OAR** was suggested (ICRU, 1999; 2004; 2007), but is **no longer recommended**. To reduce the CTV-to-PTV margin has always been a temptation. As an example, the CTV-to-PTV margin between the prostate and rectum is often 1 cm, except in the anterior – posterior direction for which it is reduced to spare the rectum
  - To ensure accurate reporting of absorbed dose to the PTV in cases for which the PTV encroaches or overlaps another PTV, OAR, or PRV, it is now recommended that the delineation of the primary PTV margins should not be compromised. Developments in treatment-planning software now make it possible to achieve sufficient dose sparing of the OAR by **using priority rules in optimizer** planning systems (see Section 2). Alternatively, subdivision of the PTV into regions with different prescribed absorbed doses (so-called **PTV-subvolumes**, PTVSV) may be used.

Let's start with the definition

- **ICRU 83**:

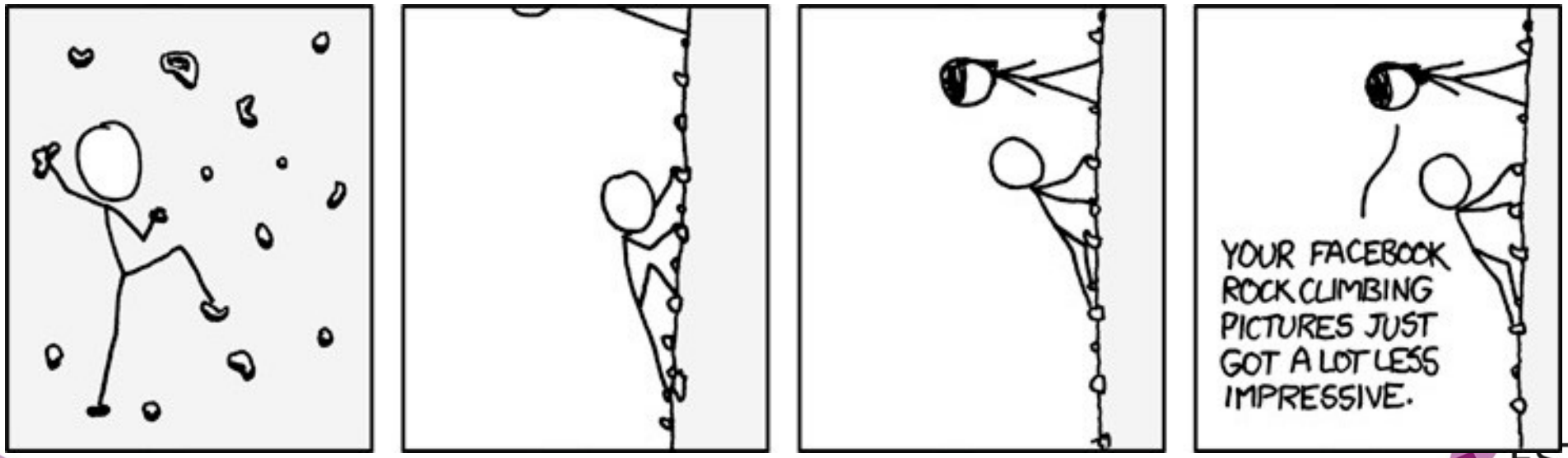


$$PTV = PTV_{SV-1} + PTV_{SV-2}$$



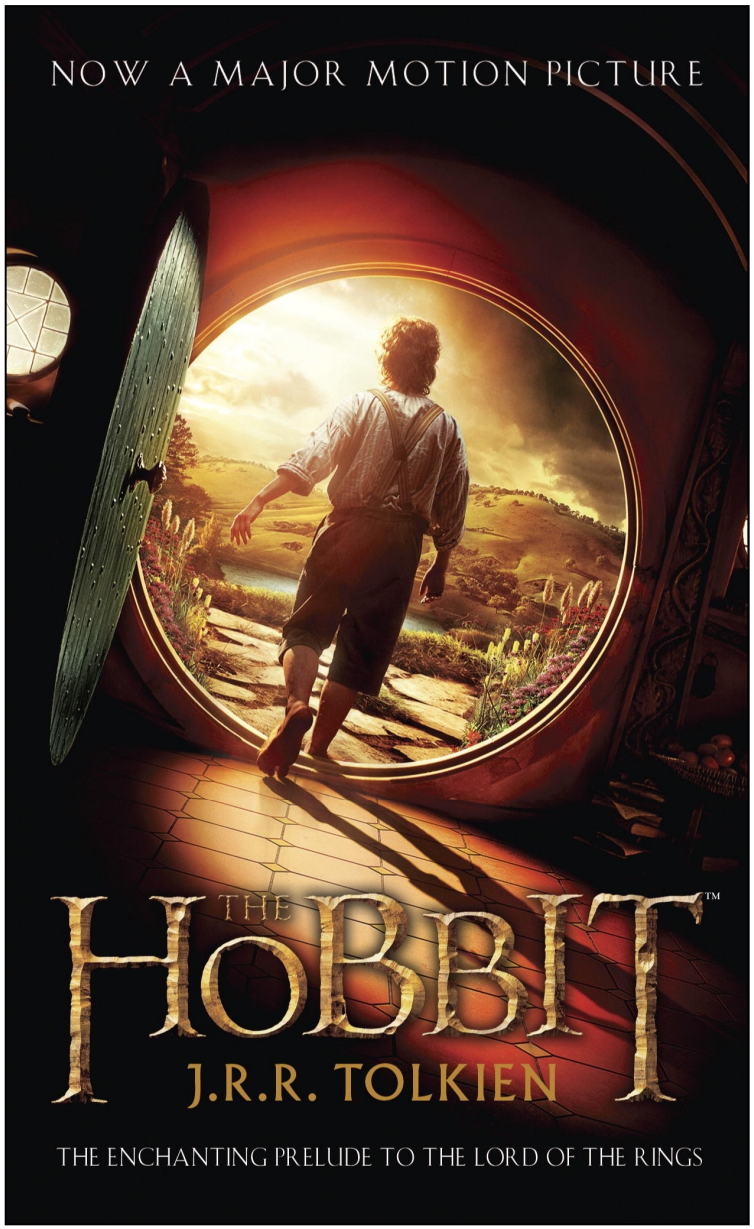
That was easy …

- What about clinical practice?
  - Requiring 100 % confidence for adequately treating the CTV would result in unreasonably large margins.
  - To quote ICRU 83, case number B3. Adenocarcinoma of the Prostate: "*The PTV-T was defined by adding an anisotropic margin to the CTV. This margin was 7 mm posteriorly, and 10 mm in all other directions …*"
- **But where does the 7 mm come from**??????



The PTV

- There and back again



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PTV in literature

PRESCRIBING, RECORDING, AND REPORTING PHOTON-BEAM IMRT

Table 4.4. Summary of various published recommendations for margins around target volumes (CTV) and OAR (modified from van Herk, 2004).

Author	Region	Recipe	Comments
Bel *et al.* (1996)	PTV	0.7σ	Statistical uncertainties only (linear approximation)—Monte Carlo.
Antolak and Rosen (1999)	PTV	1.65σ	Statistical uncertainties only, block margin?
Stroom *et al.* (1999a)	PTV	$2\,\Sigma + 0.7\sigma$	95 % absorbed dose to on average 99 % of CTV tested in realistic plans.
van Herk *et al.* (2000)	PTV	$2.5\,\Sigma + 0.7\,\sigma$ (or more correctly): $2.5\Sigma + 1.64$ $(\sigma - \sigma_e)$	Minimum absorbed dose to CTV is 95 % for 90% of patients. Analytical solution for perfect conformation.
McKenzie (2000)	PTV	$2.5\,\Sigma + \beta + (\sigma - \sigma_e)$	Extension of van Herk *et al.* (2000) for fringe dose due to limited number of beams. The factor β depends on the beam organization.
Parker *et al.* (2002)	PTV	$\Sigma + \sqrt{(\sigma^2 + \Sigma^2)}$	95 % minimum absorbed dose and 100 % absorbed dose for 95 % of volume. Probability levels not specified.
van Herk *et al.* (2002)	PTV	$2.5 + \Sigma + 0.7\sigma + 3$ mm (or more correctly): $\sqrt{2.7^2\Sigma^2 + 1.6^2\sigma^2} - 2.8$ mm	Monte Carlo based test of 1 % TCP loss due to geometrical errors for prostate patients, fitted for various σ and Σ.
Ten Haken *et al.* (1997), Engelsman *et al.* (2001a, 2001b)	PRV (liver and lung)	0	No margin for respiration, but compensation by absorbed-dose escalation to iso-NTCP, reducing target-dose homogeneity constraints.
McKenzie *et al.* (2000)	PRV	A	Margin for respiration on top of other margins when respiration dominates other uncertainties.
van Herk *et al.* (2003)	PRV (lung)	0.25 A (caudally); 0.45 A (cranially)	Margin for (random) respiration combined with random setup error of 3 mm SD, when respiration dominates other uncertainties ($A > 1$ cm).
McKenzie *et al.* (2002)	PRV	$1.3\,\Sigma \pm 0.5\,\sigma$	Margins for small and/or serial organs at risk in low (+) or high (−) absorbed-dose region.

Symbols: Σ, standard deviation of systematic uncertainties; σ, standard deviation of statistical (random) uncertainties; σ_e, describes width of beam penumbra fitted with a Gaussian function; A, peak-to-peak amplitude of respiration.

PTV in practice?

- … Use **coverage probabilities** to derive margins …
- … This idea is limited to effects expressed in terms of physical dose, biological response parameters are not included …
  - Stroom *et al.*: 99% of target volume receives 95% of the prescribed dose or more
  - Van Herk *et al.*: 90% of patients in the population receives a minimum cumulative CTV dose of at least 95 % of the prescribed dose.
- … Not all patients will be treated to 100% of the prescription dose in all fractions!!!

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 4, pp. 1121–1135, 2000

0360-3016/00/$–see front matter

PII S0360-3016(00)00518-6

PHYSICS CONTRIBUTIONS

THE PROBABILITY OF CORRECT TARGET DOSAGE: DOSE-POPULATION HISTOGRAMS FOR DERIVING TREATMENT MARGINS IN RADIOTHERAPY

MARCEL VAN HERK, PH.D., PETER REMEIJER, PH.D., COEN RASCH, M.D, AND JOOS V. LEBESQUE, M.D., PH.D.

Radiotherapy Department, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands

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Margins and the "van Herk recipe"

- A short refreshment on the "philosophy"
  - "**Blur**" the planned dose distribution using ***all execution (random) errors*** (i.e. set-up, inter/intra fraction motion, penumbra, …) to estimate the cumulative dose distribution: **σ**
  - **Shift** the blurred dose with the ***preparation*** error (***systemetic error***): **Σ**
  - Use a probability distribution of preparation errors to compute the fraction of patients that receive a certain dose to the CTV:
  - For a given dose level:
    - Find the region of space where the cumulative dose exceeds the given dose level.
    - Compute the ***probability*** that the CTV is in that region
  - … this gives you the required margin.

$$\mathbf{M}_{ptv} = \alpha\sqrt{(\boldsymbol{\Sigma}^2{}_i + \boldsymbol{\Sigma}^2{}_e)} + \beta\sqrt{(\boldsymbol{\sigma}^2{}_i + \boldsymbol{\sigma}^2{}_e + \boldsymbol{\sigma}^2{}_p)} - \beta\boldsymbol{\sigma}_p, \quad (13)$$

Margins and the “van Herk recipe”

- So, don’t use

Simplified PTV margin recipe for dose - probability

To cover the CTV for 90% of the patients with the 95% isodose (analytical solution) :

PTV margin = 2.5 Σ + 0.7 σ

Σ = quadratic sum of SD of all preparation (systematic) errors
σ = quadratic sum of SD of all execution (random) errors

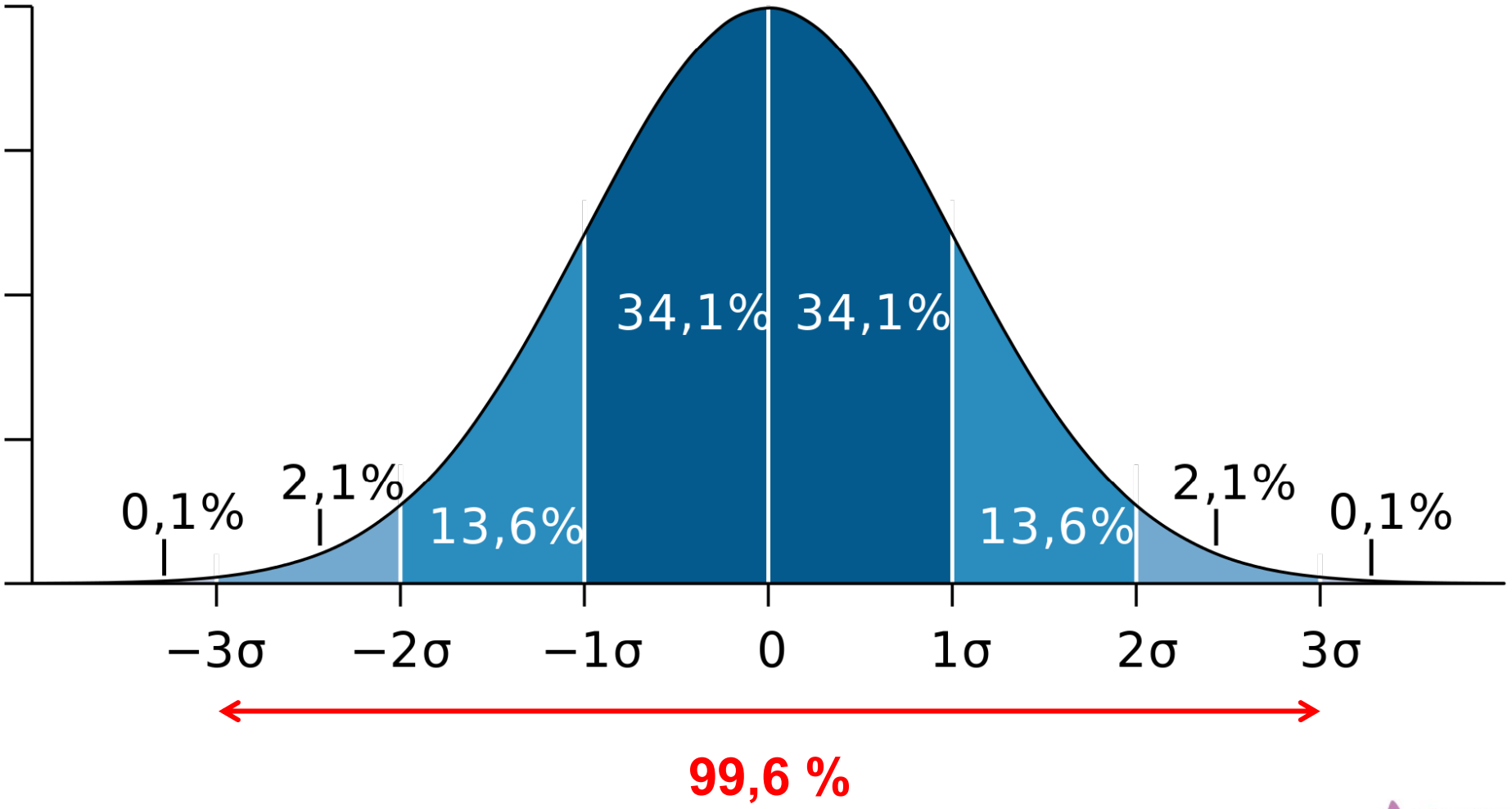
(van Herk et al, IJROBP 47: 1121-1135, 2000)

*For a big CTV with smooth shape, penumbra 5 mm

- Without knowing what it’s about

It’s all about probabilities

- This idea assumes Normal Distributions!



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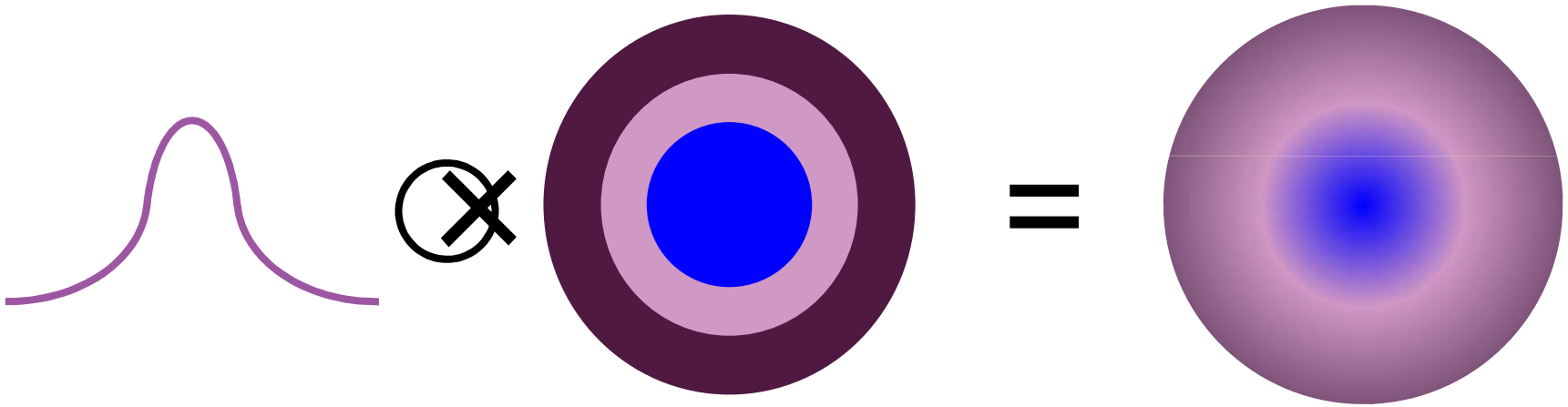
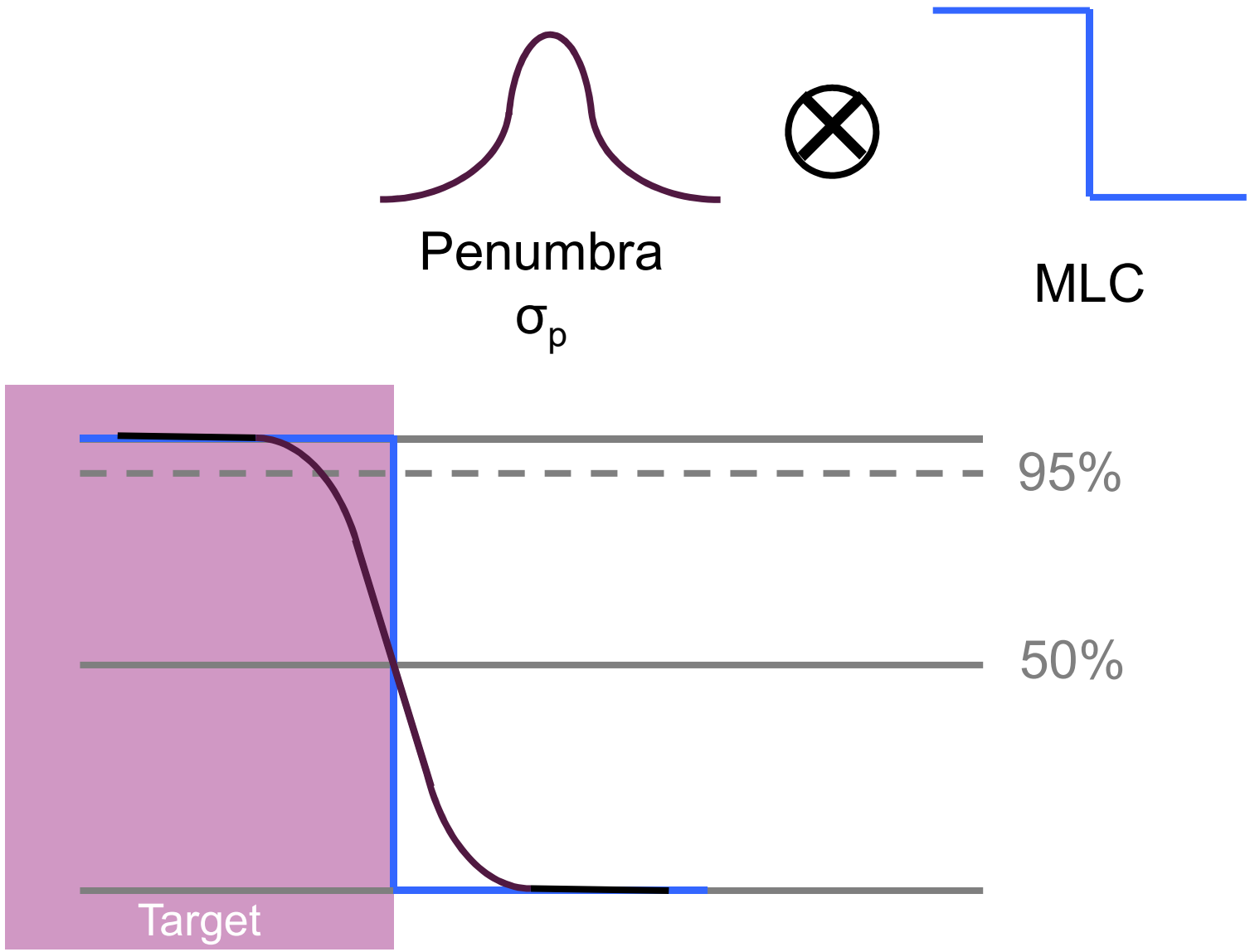
The “blurring” part: random

- “Daily” random variations in alignment of dose distribution with CTV cause a blurring effect of the delivered dose distribution.
- This blurring can be described by convolving a random distribution (normal) with the planned dose distribution



The “blurring” part: random

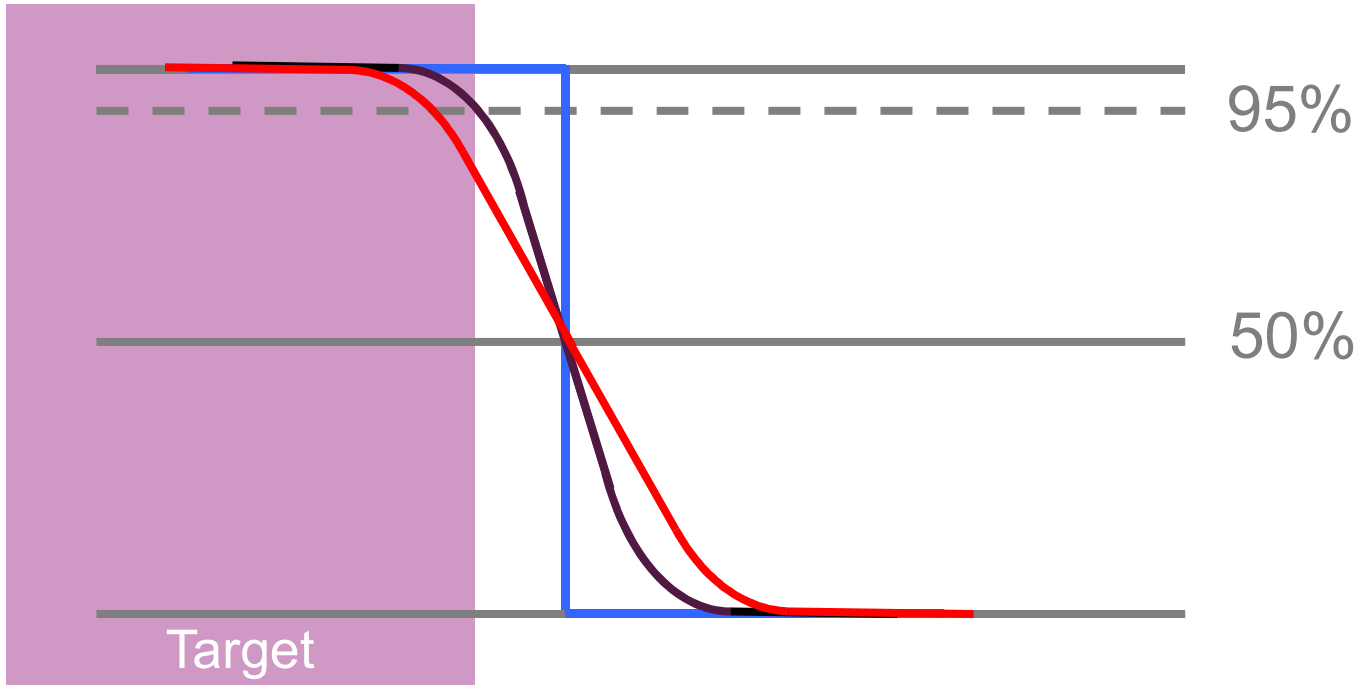


The “blurring” part: random

Random uncertainties
σ

Penumbra
σ_p

MLC



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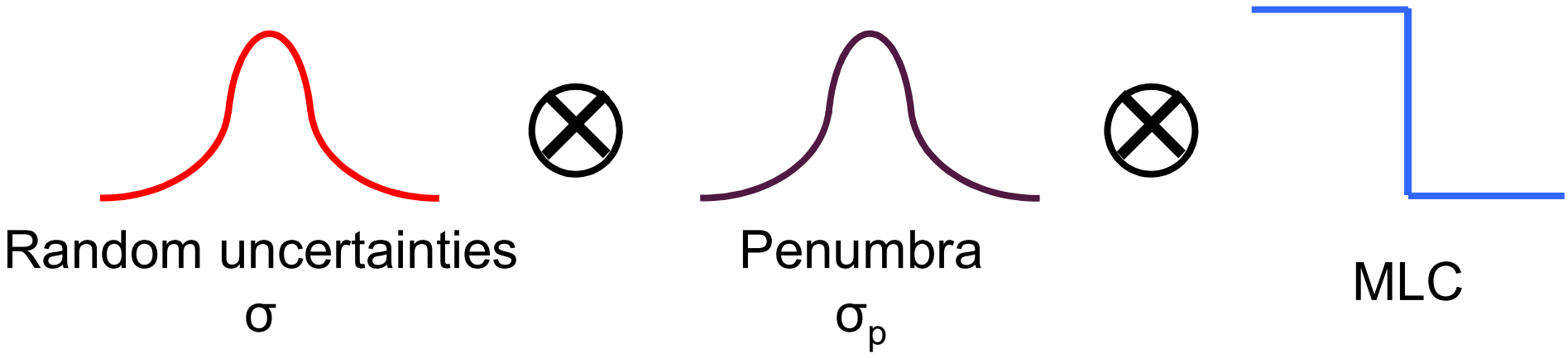
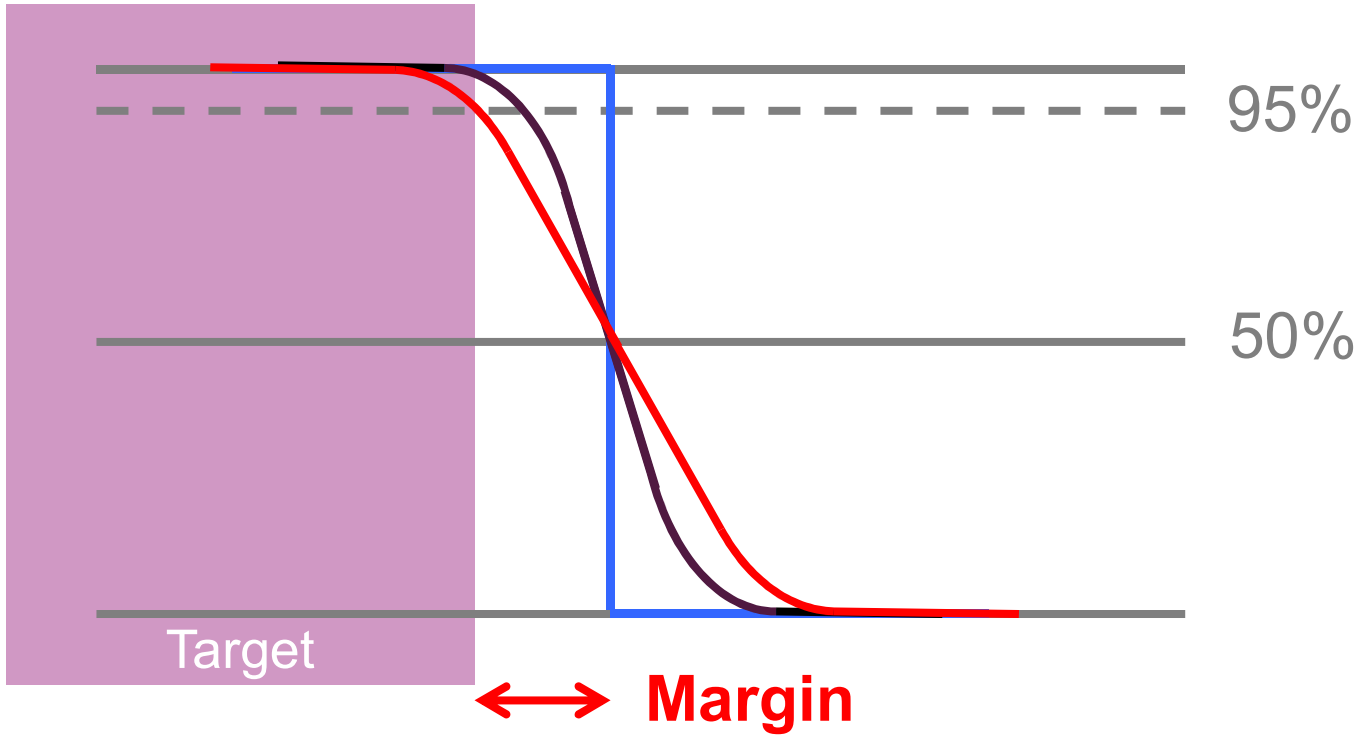
The “blurring” part: random



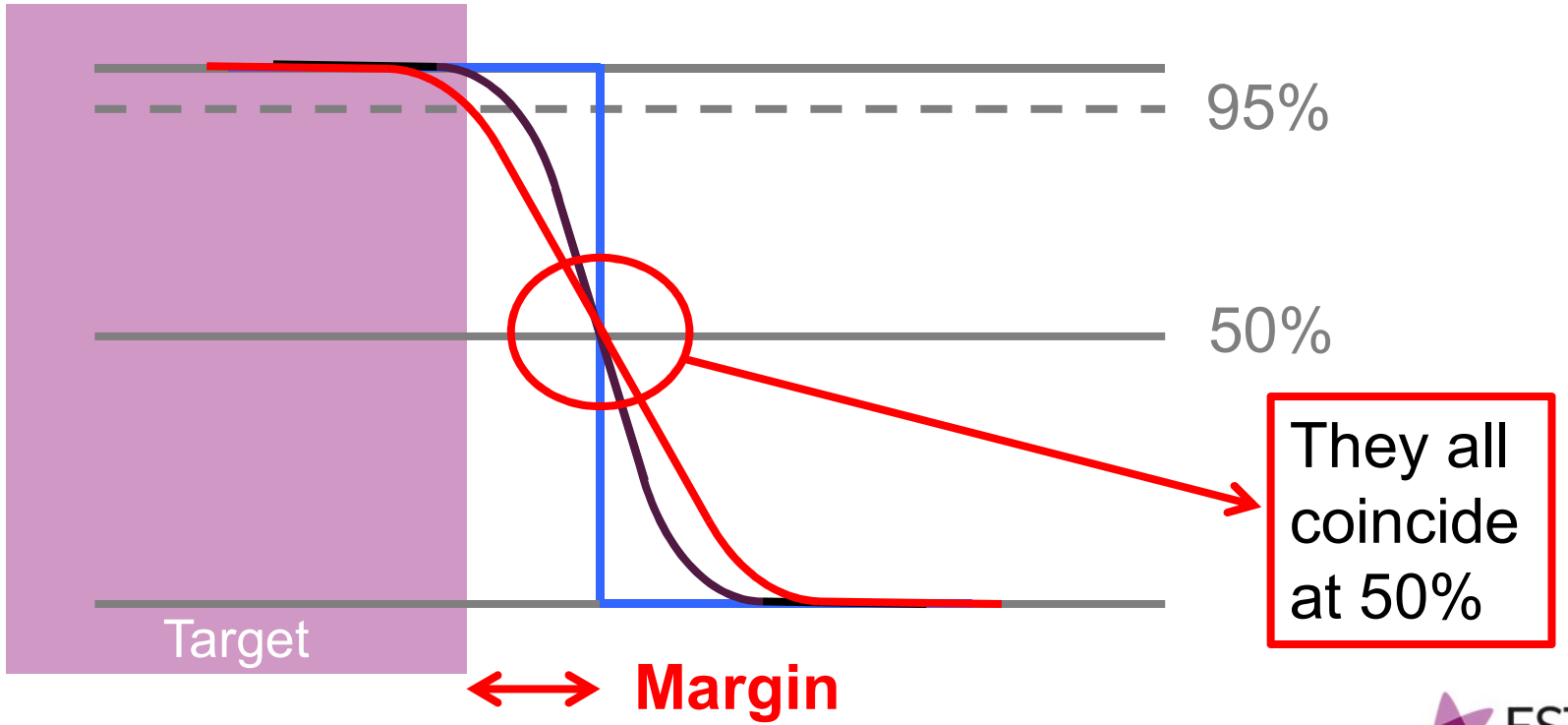


Dose prescription and margins

Random uncertainties
σ

Penumbra
σ_p

MLC



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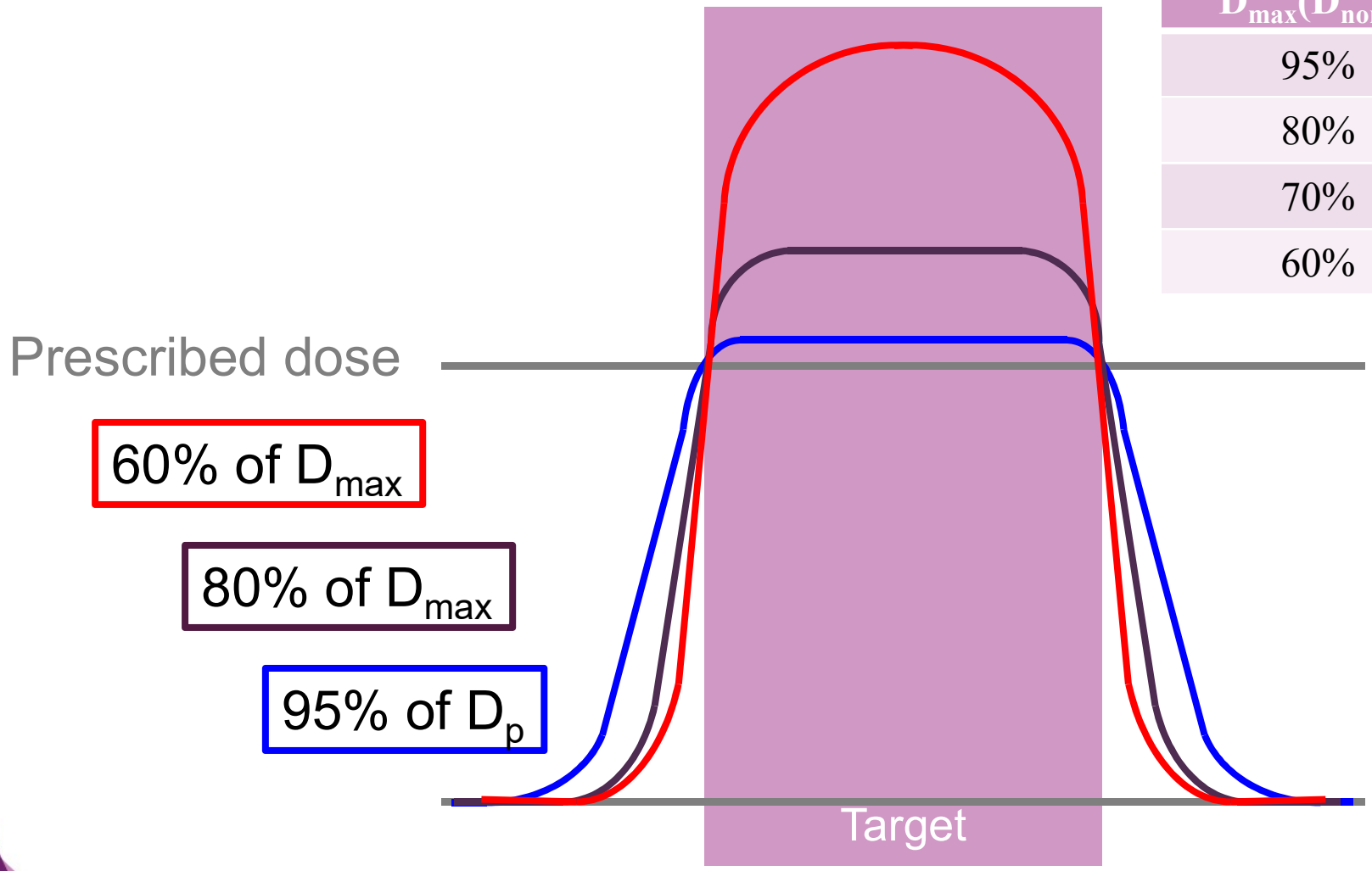
Dose prescription and margins

% of $D_{max}(D_{norm})$	β
95%	1.64
80%	0.84
70%	0.52
60%	0.25



The “blurring” part: random

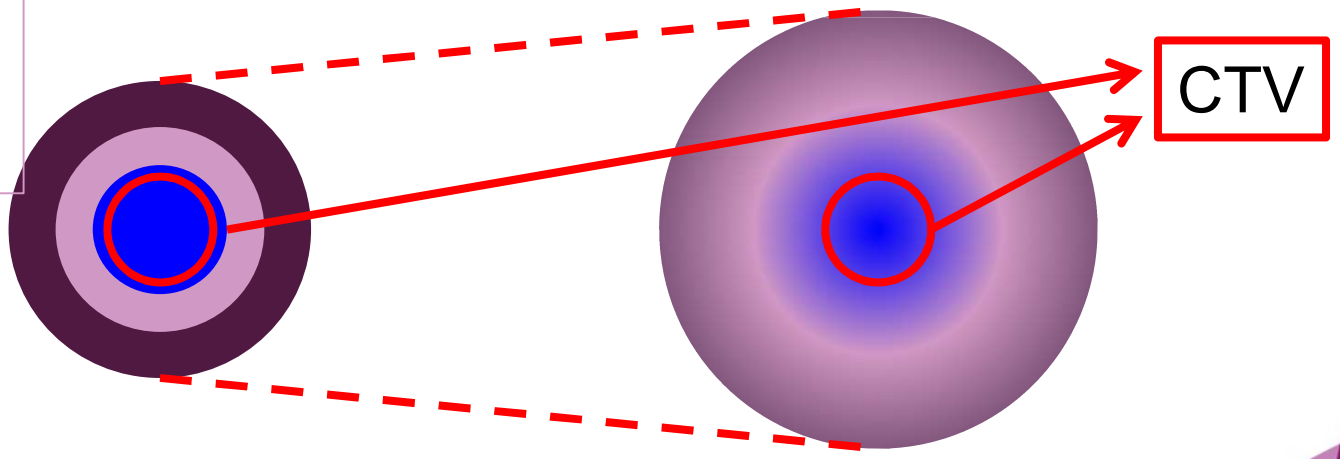
- Cumulative minimum dose to CTV ≥ 95% of prescription dose

	σ_p
Water	3.2
Lung	6.4

$$M_r = \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

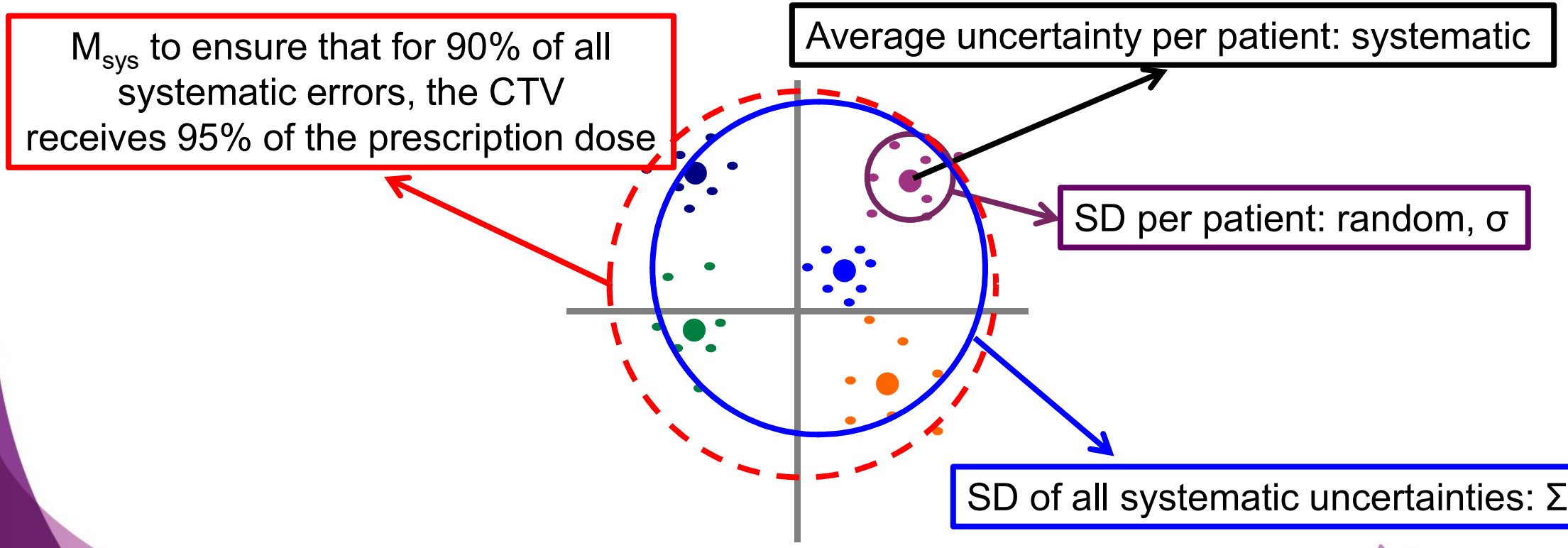
% of D_{norm}	β
95%	1.64
80%	0.84
70%	0.52
60%	0.25

But, what about:
IMRT, VMAT,
Helical TomoTherapy?



The “shift” part: systematic

- Systematic uncertainties (typically preparation errors) cause a **shift** of the (blurred) dose distribution.
- Again, we assume the systematic uncertainties within a certain population of patients to be described by a normal distribution



The “shift” part: systematic

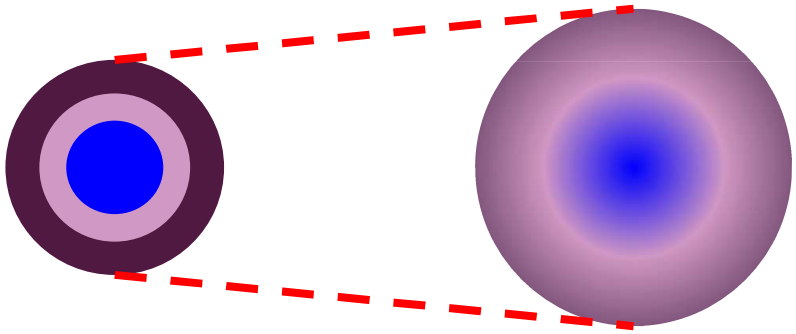
- Assuming a “spherical” target

$$\int_0^{M_{sys}} p(\Sigma)\,dr = 0.9 \quad \Rightarrow \quad M_{sys} = 2.5\Sigma$$

confidence	α
80%	2.16
90%	2.50
95%	2.79
99%	3.36

Margins and the “van Herk recipe”

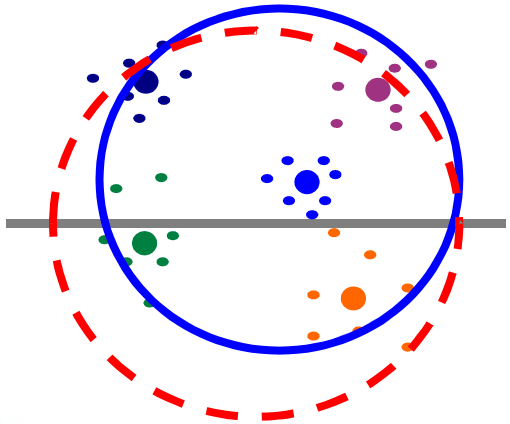
- “Blurring” part: cumulative minimum dose ≥ 95% of D_p



$$M_r = \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

$$\beta = 1.64$$

- “Shifting part: ≥90% of population receives a cumulative CTV dose ≥ 95% of D_p



$$M = \alpha\Sigma + M_r$$

$$\alpha = 2.5$$

Total systematic and random uncertainties

- Why "quadratic sum"?

  - For a simple criterion such as probability level of minimum dose, random and systematic uncertainties could be added linearly.

$$M = M_{sys} + M_r$$

  - For the separate systematic and random uncertainties a **quadratic sum** is required:

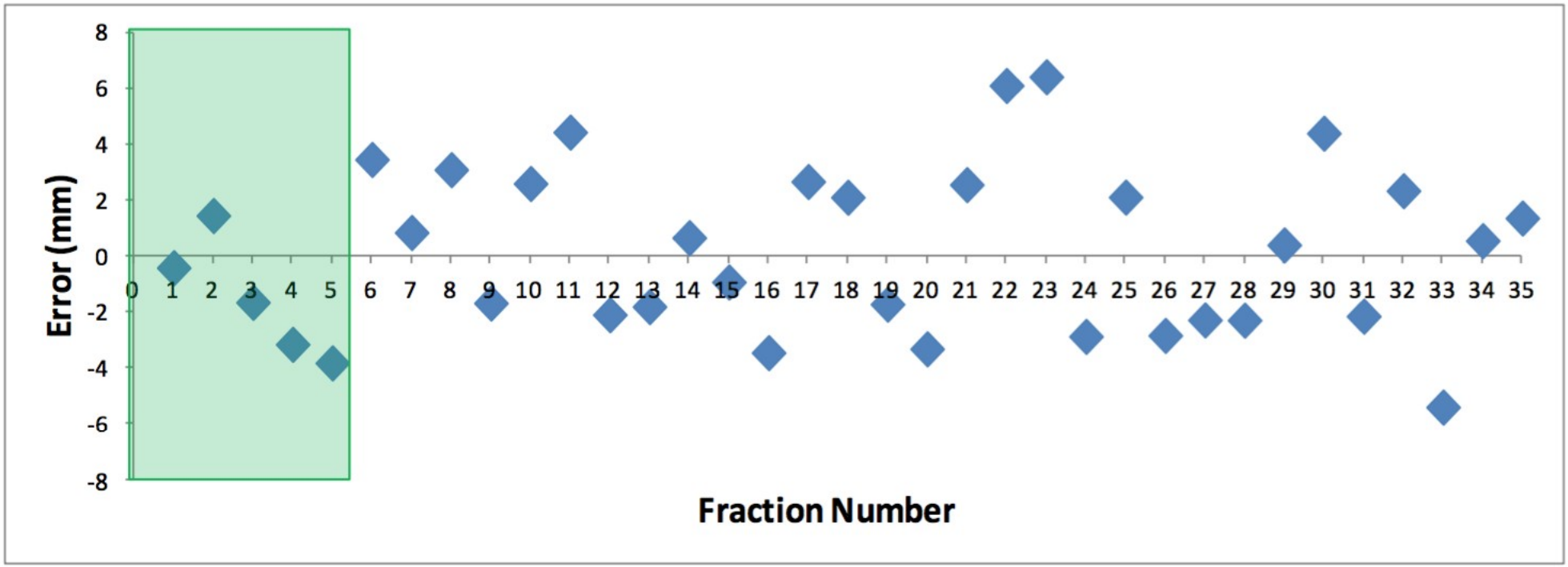
$$\Sigma = \sqrt{\Sigma_a^2 + \Sigma_b^2 + \Sigma_c^2}$$

$$\Sigma = \sqrt{10^2 + 3^2 + 3^2} = 10.9$$

  - **It emphasizes the large uncertainties**!!! (see example)

Margins and number of fractions

- If the number of fractions decreases (eg HYPOFRACTIONATION) the “random” component becomes more “systematic” (ie a “shift”)



- Uncertainty after 35 fractions: 0.1mm
- Uncertainty after 5 fractions: -1.6mm

Margins and number of fractions

- If the number of fractions decreases (eg HYPOFRACTIONATION) the "random" component becomes more "systematic" (ie a "shift")

- Effective systematic uncertainty (shift)

$$\Sigma_{eff} = \sqrt{\Sigma^2 + \frac{1}{N}\sigma^2}$$

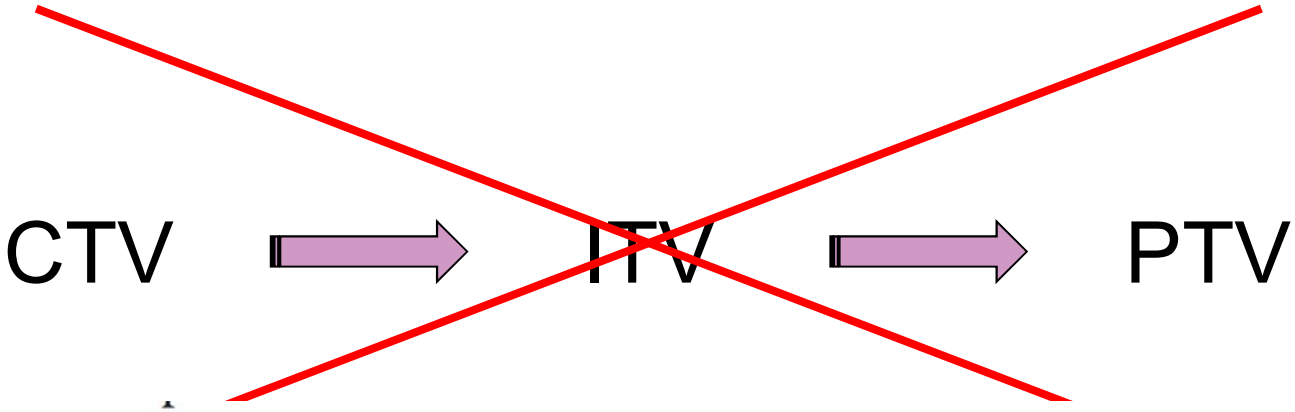
- Effective random uncertainty (blur)

$$\sigma_{eff} = \sqrt{\left(1 - \frac{1}{N}\right)\sigma^2}$$

$N \to 1$

… and motion management

- Based on the previous, it is obvious that



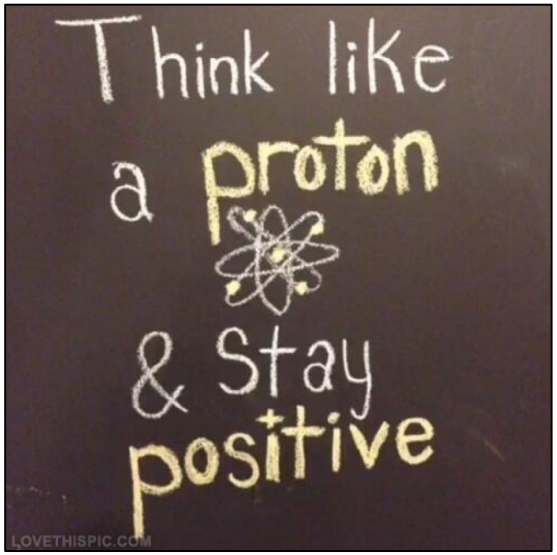
$$\mathbf{M}_{ptv} = \alpha\sqrt{(\boldsymbol{\Sigma}^2{}_i + \boldsymbol{\Sigma}^2{}_e)} + \beta\sqrt{(\boldsymbol{\sigma}^2{}_i + \boldsymbol{\sigma}^2{}_e + \boldsymbol{\sigma}^2{}_p)} - \beta\boldsymbol{\sigma}_p, \quad (13)$$

- For more details: see ESTRO course

  "Clinical Practice & Implementation of Image-Guided Stereotactic Body Radiotherapy"

… and particle therapy

- Don’t even think of using a PTV!!



- Halperin’s rule:
  - Most tumours are radioresistent if you miss them …
  - Proton therapy offers many new and expensive ways of missing the tumour.

Validity of the margin recipe

- Assumes **homogeneous patient population** (identical SD)
- Assumes **many fractions**
- Assumes **spherical symmetry**
  - More or less OK if CTV >> σ
- Assumes **"ideal" conformation**
  - ie preparation errors have the same impact in all directions
- **Rotations and shape variations** have been ignored
- Uncertainties were assumed to be isotropic
  - The concept can be generalized to 3D by separating x, y, and z directions.
- The different sources of uncertainties are assumed to be **statistically independent**
  - As most of the uncertainties are introduces at different stages of the treatment, this assumption seems OK
- And again: **normal probability distributions** are assumed.

PTV in practice: oesophagus

- In this exercise we will work out the antero-posterior margin only, the latero-lateral and cranio-caudal margins can be deduced in a similar way.
- 3D (isotropic) margins assume a ball rolling along the 3D CTV … sounds easier than it is.

- **As this is an example based on a particular patient population using a particular IGRT workflow, this data is NOT TO BE USED in an other setting**.

PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT		
Delineation (intra observer)		
Interfraction setup (laser)		
Interfraction setup (IGRT) (intra observer registration)		
End2end IGRT (eg PentaCheck)		
…		
QUADRATIC SUM		
Σ		

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility		
Interfraction setup (laser)		
Intrafraction patient motion		
σ_p	3.2	
…		
QUADRATIC SUM		
σ		
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

α=2.5
β=1.64

PTV margin (mm)	

CT snapshot and mobility

- Try to obtain the data from your own patient population, using your own technology and workflows!
- If this is not practical, refer to relevant literature.

- Example mobility oesophagus:
  - Welch *et al.* (Gastroentrology 1982), Dieleman *et al.* (IJROBP 2007)

	Amplitude (mm)		SD (mm)	
	Upper & mid 1/3	GEJ	Upper & mid 1/3	GEJ
Welch	4	1	6	2
Dieleman	3	1	4	1

  - Snapshot CT: $\Sigma = 0.33 * \text{amplitude} = 0.33 * 4 = 1.32$ mm
  - Intrafraction organ mobility: $\sigma = 1.00$

PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT	1.32	
Delineation (intra observer)		
Interfraction setup (laser)		
Interfraction setup (IGRT) (intra observer registration)		
End2end IGRT (eg PentaCheck)		
…		
QUADRATIC SUM		
Σ		

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility	1.00	
Interfraction setup (laser)		
Intrafraction patient motion		
σ_p	3.2	
…		
QUADRATIC SUM		
σ		
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

α=2.5
β=1.64

PTV margin (mm)	

Patient setup

- In-house study on 10 patients, followed for 10 fractions each.
- Patient set-up on laser and skin marks, daily CBCT and appropriate correction pre-treatment, daily post-treatment CBCT.

  ➢ Interfraction systematic and random uncertainty based on laser setup (i.e. difference between laser setup and CBCT)

	Pat 1	Pat 2	…	Pat 10
Fraction 1				
Fraction 2				
…				
Fraction 25				
Average				
SD				

SD (averages) = $\Sigma_{interfr}$ = 19.13 mm

average (SD) = $\sigma_{interfr}$ = 4.52 mm

Patient setup

- In-house study on 10 patients, followed for 10 fractions each
- Patient set-up on laser and skin marks, daily CBCT and appropriate correction pre-treatment, daily post-treatment CBCT.

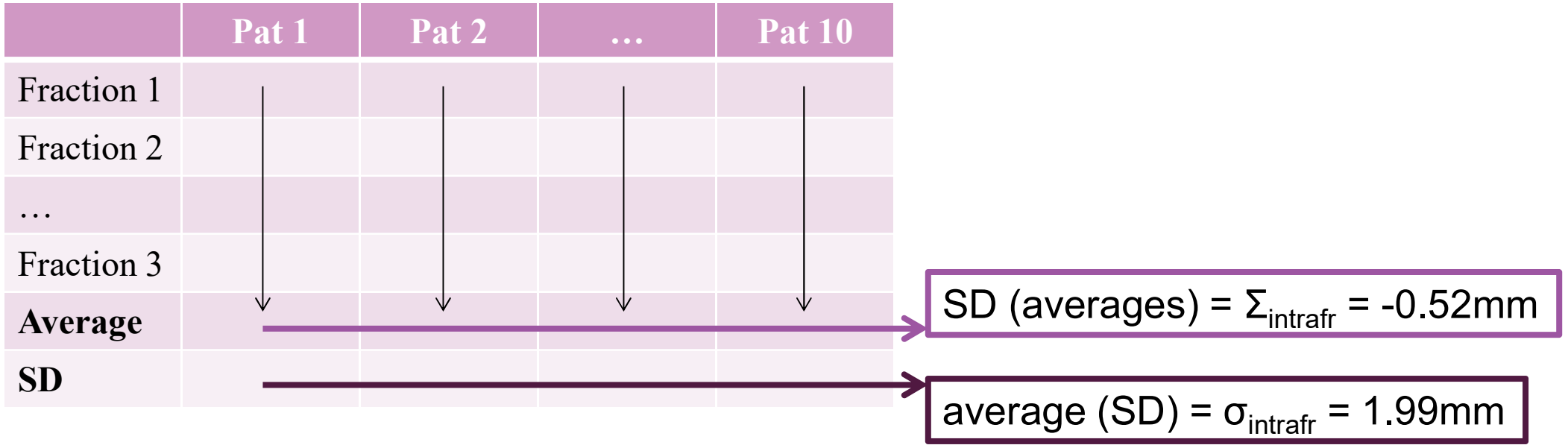
  ➢ Automated registration was performed 3 consecutive times (assessment of registration error, intra observer variation):

Interfraction setup (IGRT)	**0.3 mm**

Patient setup

- In-house study on 10 patients, followed for 10 fractions each
- Patient set-up on laser and skin marks, daily CBCT and appropriate correction pre-treatment, daily post-treatment CBCT.

➢ Intrafraction motion (difference between pre- and post CBCT):



PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT	1.32	
Delineation (intra observer)		
Interfraction setup (laser)	19.13	
Interfraction setup (IGRT) (intra observer registration)	0.3	
End2end IGRT (eg PentaCheck)		
…		
QUADRATIC SUM		
Σ		

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility	1.00	
Interfraction setup (laser)	4.52	
Intrafraction patient motion	1.99	
σ_p	3.2	
…		
QUADRATIC SUM		
σ		
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

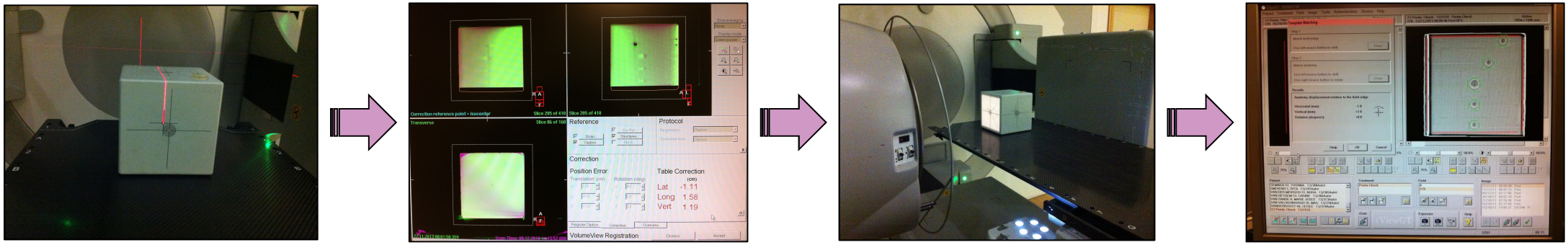
α=2.5
β=1.64

PTV margin (mm)	

Patient setup

- Systematic uncertainty related to IGRT workflow, in this particular case the CBCT – CT registration and automated set-up.
- The registration uncertainty was already accounted for.
- The positioning uncertainty after automated couch movement can be assessed by the weekly QA (alternative: an extra CBCT)
  - ➢ in this case the so-called PentaCheck: data from January 2016-May 2016.

Laser setup → CBCT → Couch correction → EPID verification



- ➢ Average uncertainty antero-posterior: -1.08mm (SD: 0.80mm)

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PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT	1.32	
Delineation (intra observer)		
Interfraction setup (laser)	19.13	
Interfraction setup (IGRT) (intra observer registration)	0.3	
End2end IGRT (eg PentaCheck)	1.08	
…		
QUADRATIC SUM		
Σ		

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility	1.00	
Interfraction setup (laser)	4.52	
Intrafraction patient motion	1.99	
σ_p	3.2	
…		
QUADRATIC SUM		
σ		
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

α=2.5
β=1.64

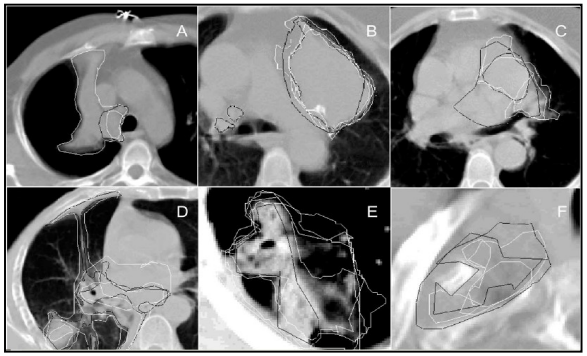
PTV margin (mm)	

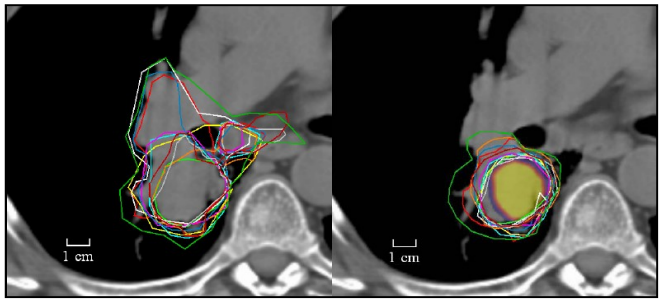
Delineation

- Again, ideally an intra-observer study should be performed in combination with MRI and pathology data to assess the treatment volumes.
- In this exercise we will start with a conservative systematic "guestimate" of 4mm.

- Food for thought:
  - The well cited paper from Steenbakkers *et al.* comparing delineation in lung without and with help from PET:
  - Observer variations (1 SD) without PET 10 mm, with PET … 4 mm!!

Van de Steene *et al.* Radiother Oncol 2002





Steenbakkers *et al.* Radiother Oncol 2005

PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT	1.32	
Delineation (intra observer)	4.00	
Interfraction setup (laser)	19.13	
Interfraction setup (IGRT) (intra observer registration)	0.3	
End2end IGRT (eg PentaCheck)	1.08	
…		
QUADRATIC SUM		
Σ		

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility	1.00	
Interfraction setup (laser)	4.52	
Intrafraction patient motion	1.99	
σ_p	3.2	
…		
QUADRATIC SUM		
σ		
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

α=2.5
β=1.64

PTV margin (mm)	

PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT	1.32	1.74
Delineation (intra observer)	4.00	16.00
Interfraction setup (laser)	19.13	365.96
Interfraction setup (IGRT) (intra observer registration)	0.3	0.09
End2end IGRT (eg PentaCheck)	1.08	1.17
…		
QUADRATIC SUM		384.96
Σ		19.62

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility	1.00	1.00
Interfraction setup (laser)	4.52	20.43
Intrafraction patient motion	1.99	3.96
σ_p	3.2	10.24
…		
QUADRATIC SUM		35.63
σ		5.97
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

α=2.5
β=1.64

PTV margin (mm)	53.59

PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT	1.32	1.74
Delineation (intra observer)	4.00	16.00
Interfraction setup (laser)	0	0
Interfraction setup (IGRT) (intra observer registration)	0.3	0.09
End2end IGRT (eg PentaCheck)	1.08	1.17
…		
QUADRATIC SUM		19.00
Σ		4.36

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility	1.00	1.00
Interfraction setup (laser)	0	0
Intrafraction patient motion	1.99	3.96
σ_p	3.2	10.24
…		
QUADRATIC SUM		15.20
σ		3.90
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

α=2.5
β=1.64

PTV margin (mm)	12,04

PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT	1.32	1.74
Delineation (intra observer)	0	0
Interfraction setup (laser)	0	0
Interfraction setup (IGRT) (intra observer registration)	0.3	0.09
End2end IGRT (eg PentaCheck)	1.08	1.17
…		
QUADRATIC SUM		3.00
Σ		1.73

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility	1.00	1.00
Interfraction setup (laser)	0	0
Intrafraction patient motion	1.99	3.96
σ_p	3.2	10.24
…		
QUADRATIC SUM		15.20
σ		3.90
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

α=2.5
β=1.64

PTV margin (mm)	5.48

PTV in practice: oesophagus

Systematic uncertainty (confidence level)	Σ (mm)	Σ^2
Snapshot CT	1.32	1.74
Delineation (intra observer)	2	4
Interfraction setup (laser)	0	0
Interfraction setup (IGRT) (intra observer registration)	0.3	0.09
End2end IGRT (eg PentaCheck)	1.08	1.17
…		
QUADRATIC SUM		7.00
Σ		2,65

Random uncertainty (dose blurring)	σ (mm)	σ^2
Intrafraction organ mobility	1.00	1.00
Interfraction setup (laser)	0	0
Intrafraction patient motion	1.99	3.96
σ_p	3.2	10.24
…		
QUADRATIC SUM		15.20
σ		3.90
σ_p	3.2	

$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

α=2.5
β=1.64

PTV margin (mm)	7.76

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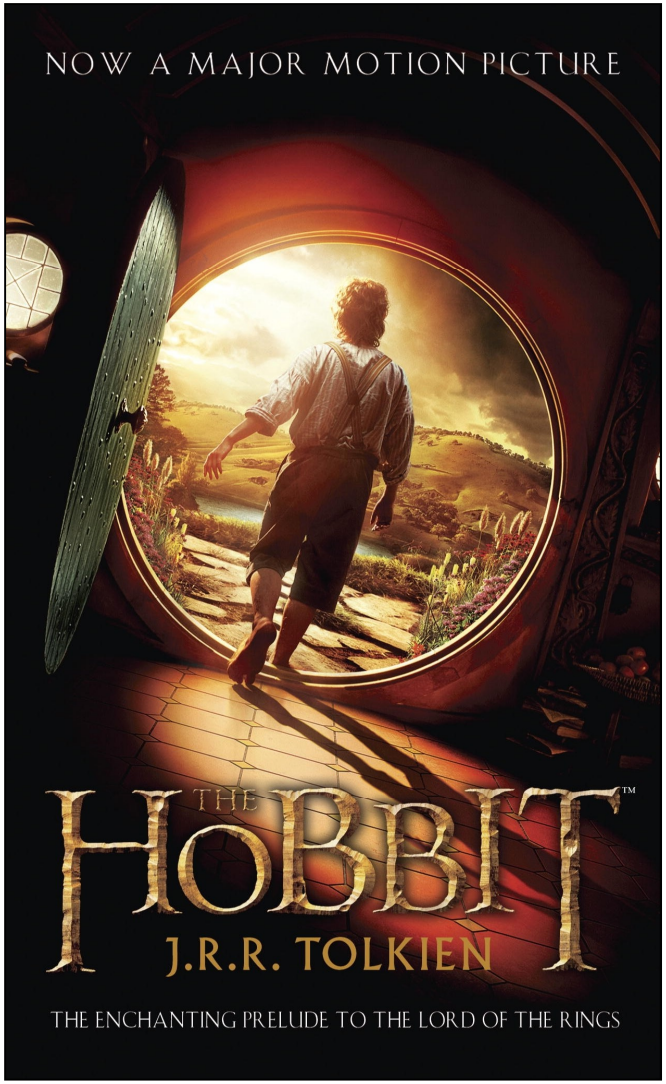
PTV in practice: oesophagus

- Margins used in clinical practice at UZ Brussel:
  - Helical TomoTherapy
  - Delineation on CT, PET-CT and MRI (MIM software environment)
  - Daily MV-CT
  - **Antero-posterior: 8mm (upper and mid 1/3), 10mm (GEJ)**



There and back again

Margin reduction …

IGRT does **NOT** mean that
margins can converge to zero!!!!!!!!

margin recipes are still a necessity,
especially to cope with uncertainty in CTV

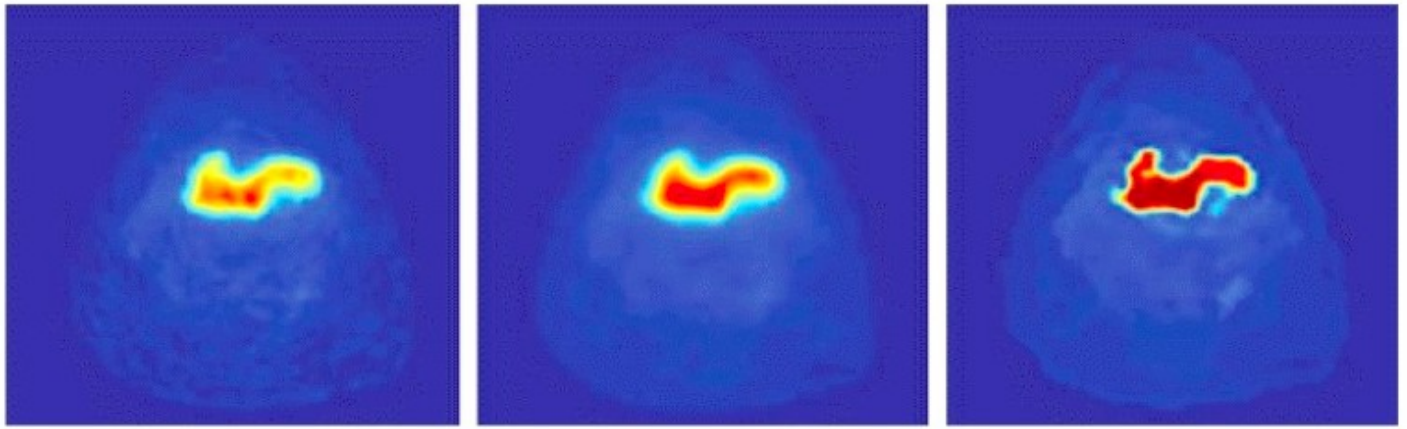
Engels B, Soete G, Verellen D, Storme G.

Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distened rectum on the planning CT in spite of image guidance by implanted markers.

Int J Radiat Oncol Biol Phys 2009

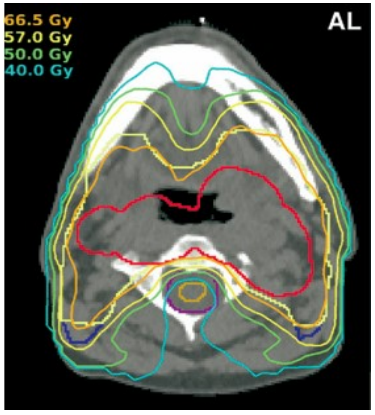
Dose painting by numbers …

Courtesy
X. Geets

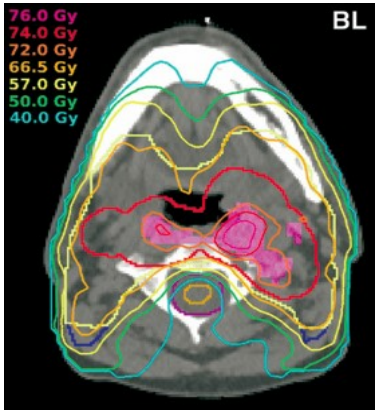


Dose painting by numbers …

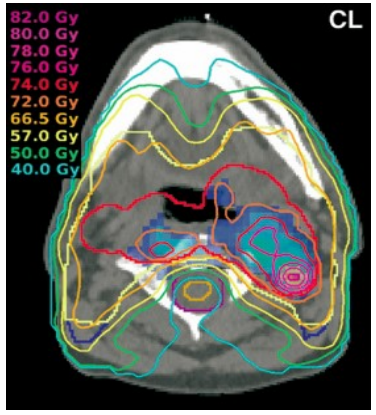
- … we don't know what the numbers stand for
- … our painting brush does not match the required resolution … yet



"conventional IMRT"
or
dose sculpting

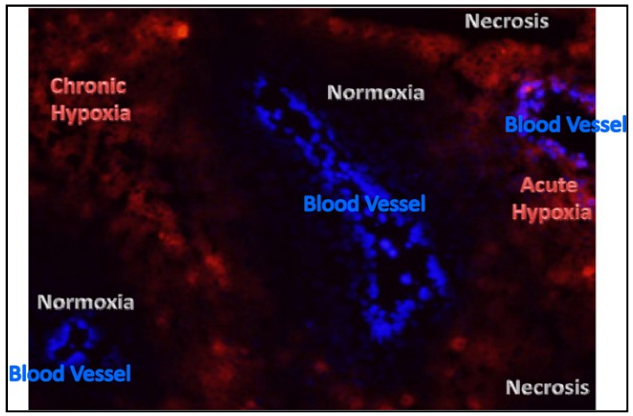


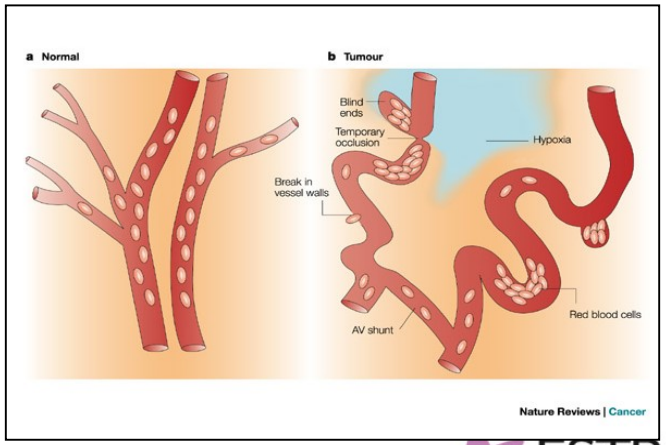
Dose escalation
based on
FDG-PET



Dose-painting
Based on
Dynamic F-MISO

Courtesy Thorwarth *et al.*





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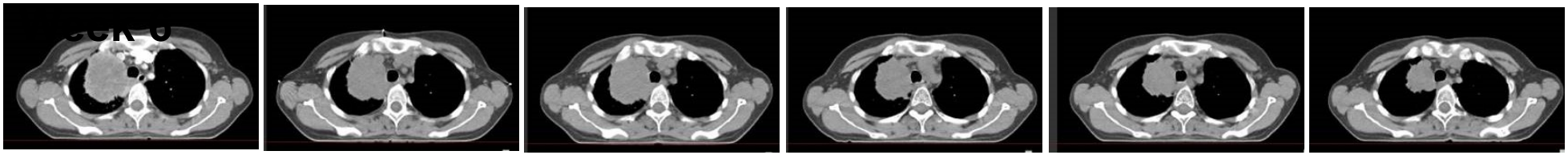
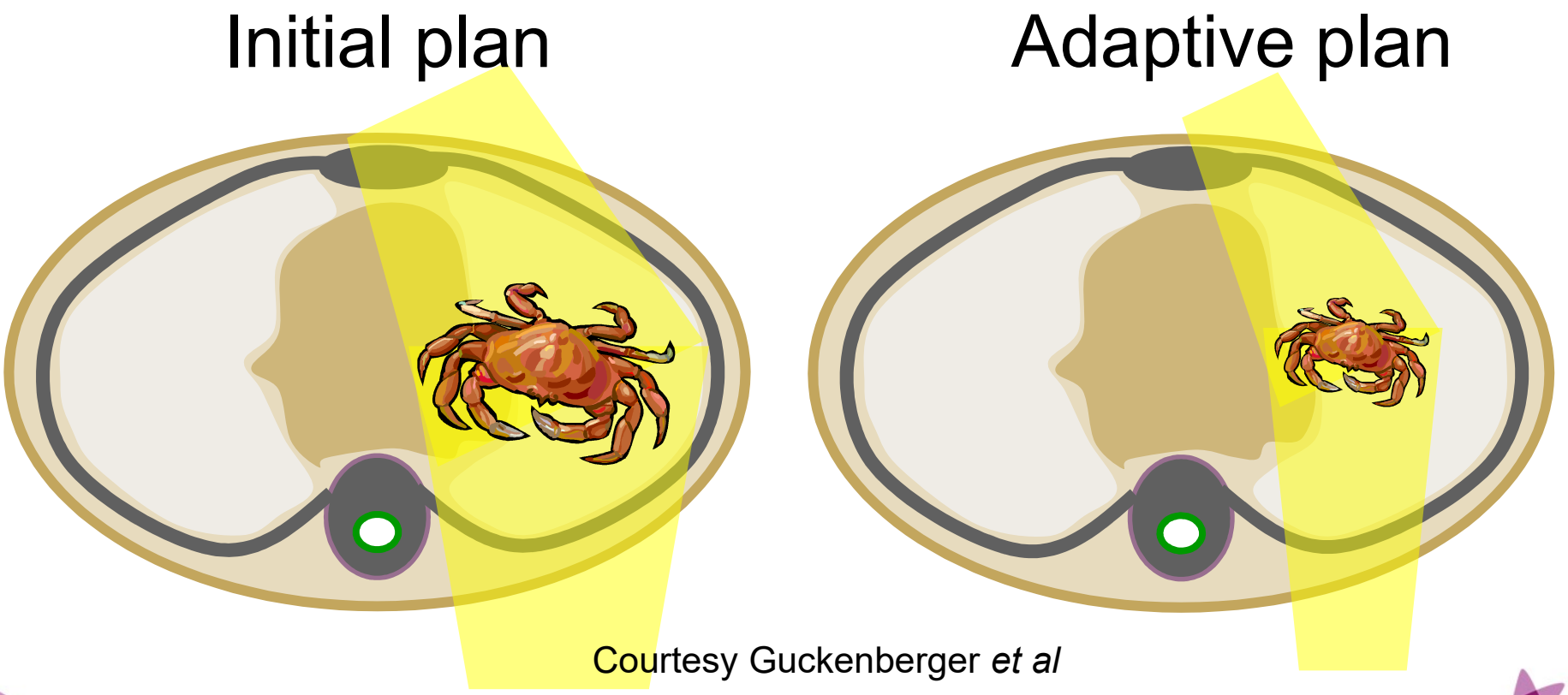
Adaptive radiotherapy …

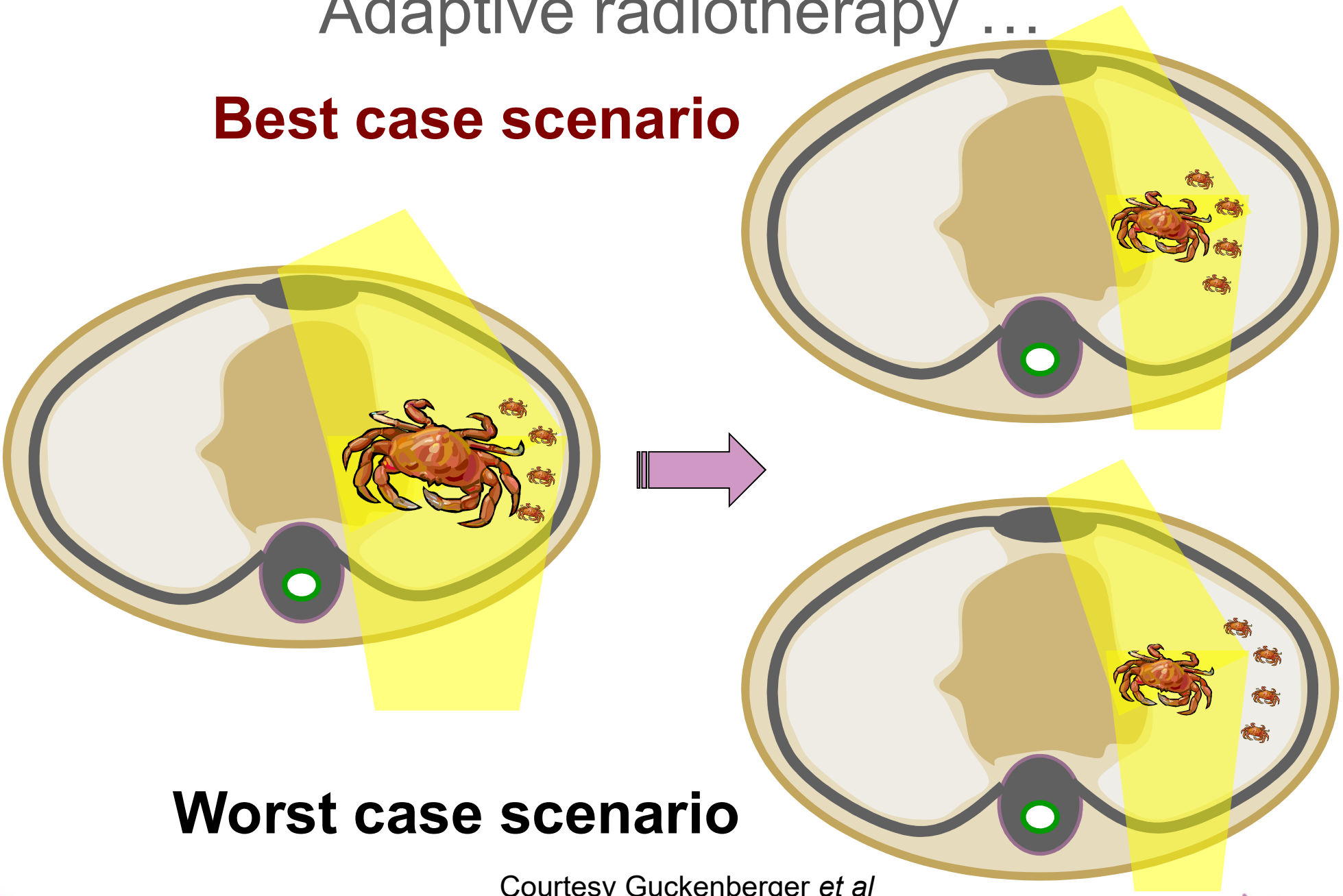




Courtesy Guckenberger *et al*

Adaptive radiotherapy …

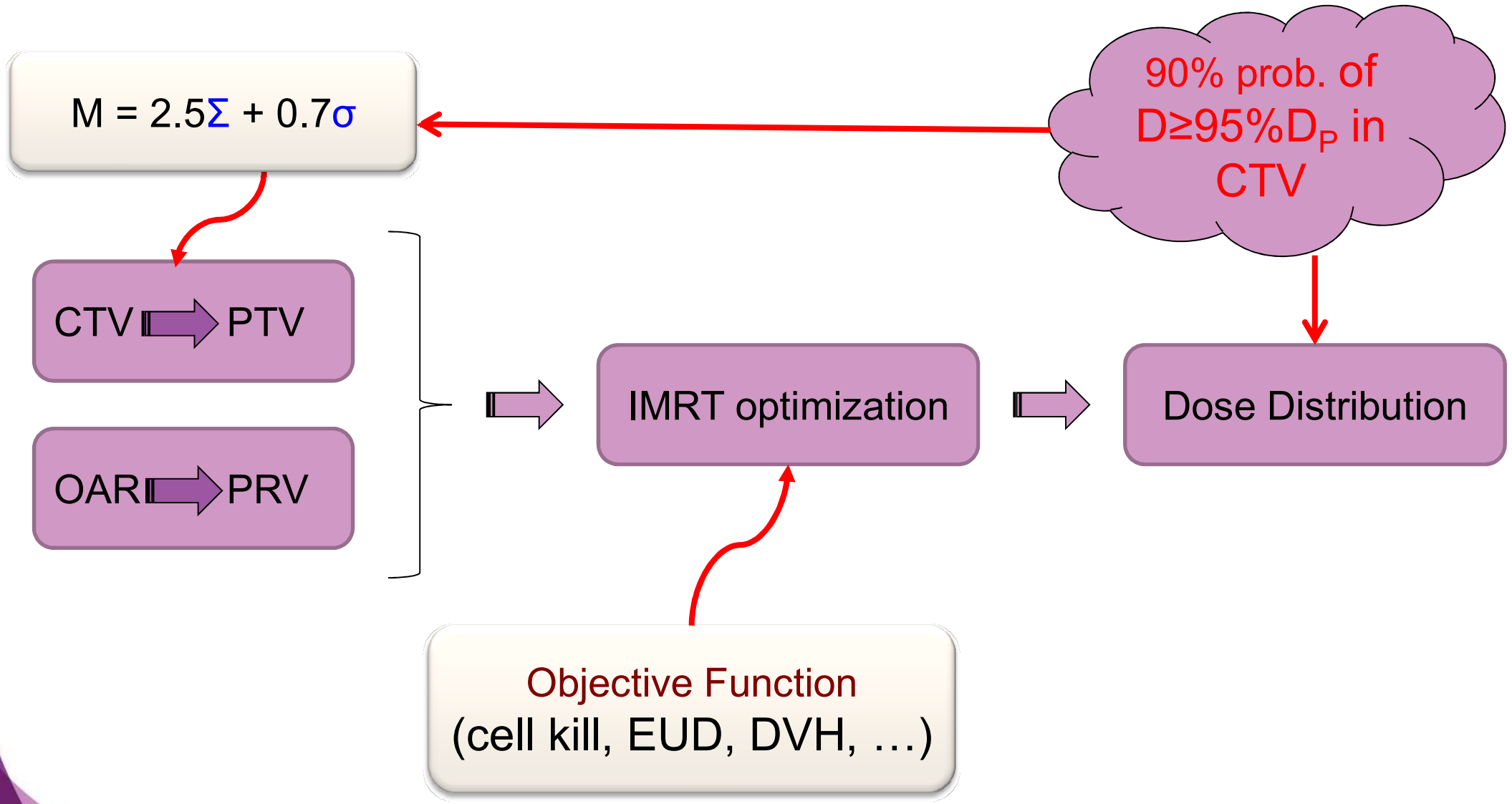
Best case scenario



Worst case scenario

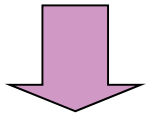
Courtesy Guckenberger *et al*

“Conventional” IMRT planning

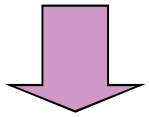


Motion compensation techniques

Knowledge on organ motion
(clinical studies, multiple CT scans, 4D CT)

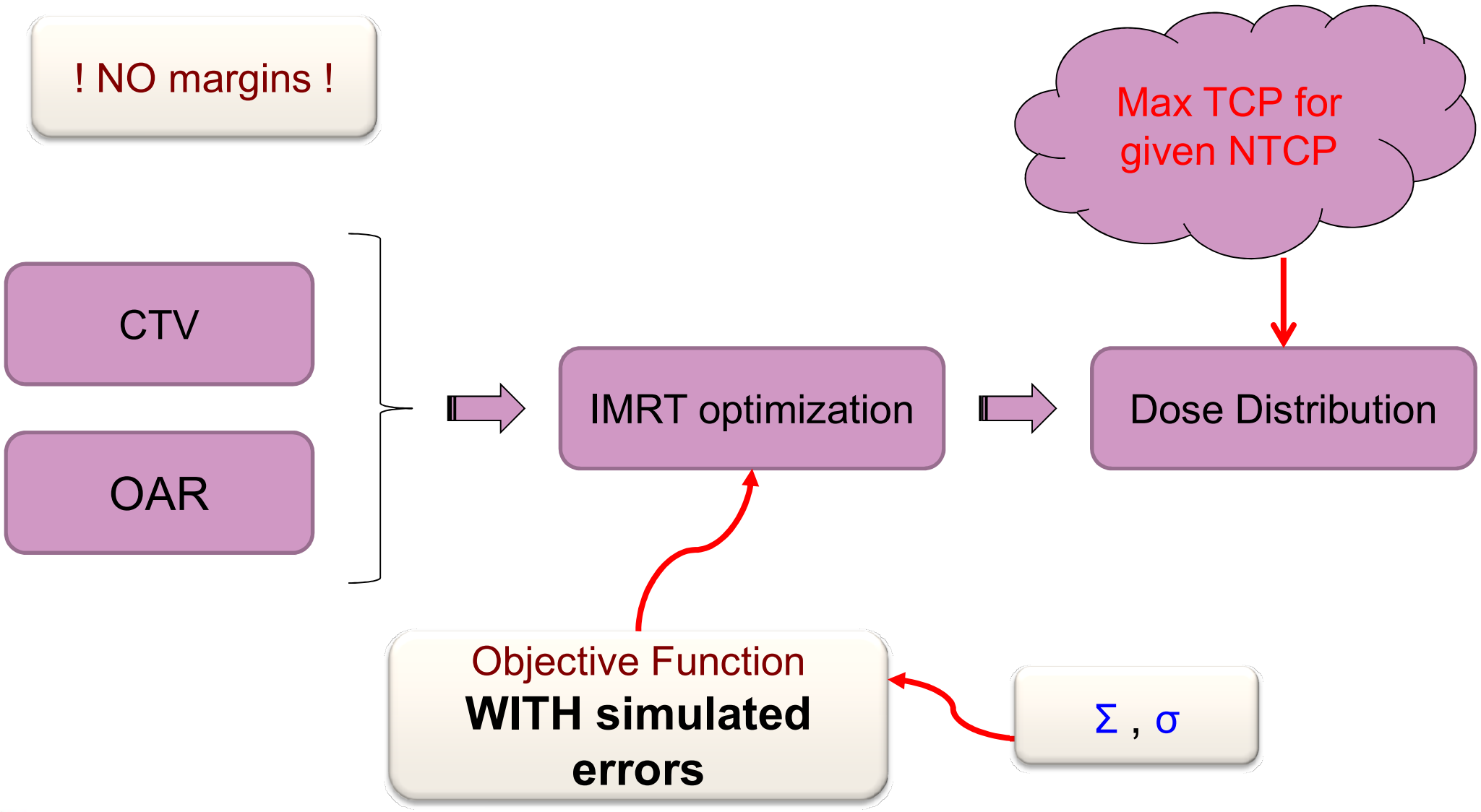


Mathematical model to describe organ motion induced geometric changes
Probability distribution of patient geometries



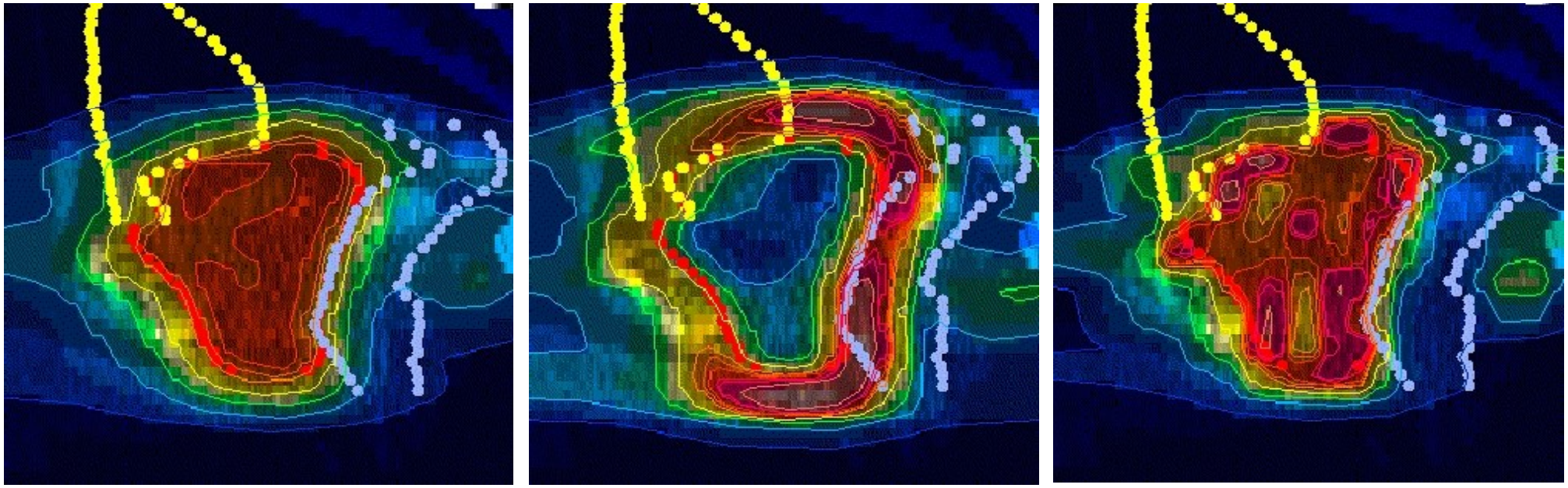
Probabilistic IMRT optimization

“Probabilistic” IMRT planning



“Probabilistic” IMRT planning

Expectation value | Dose variance per voxel | Risk, ‘static’ dose

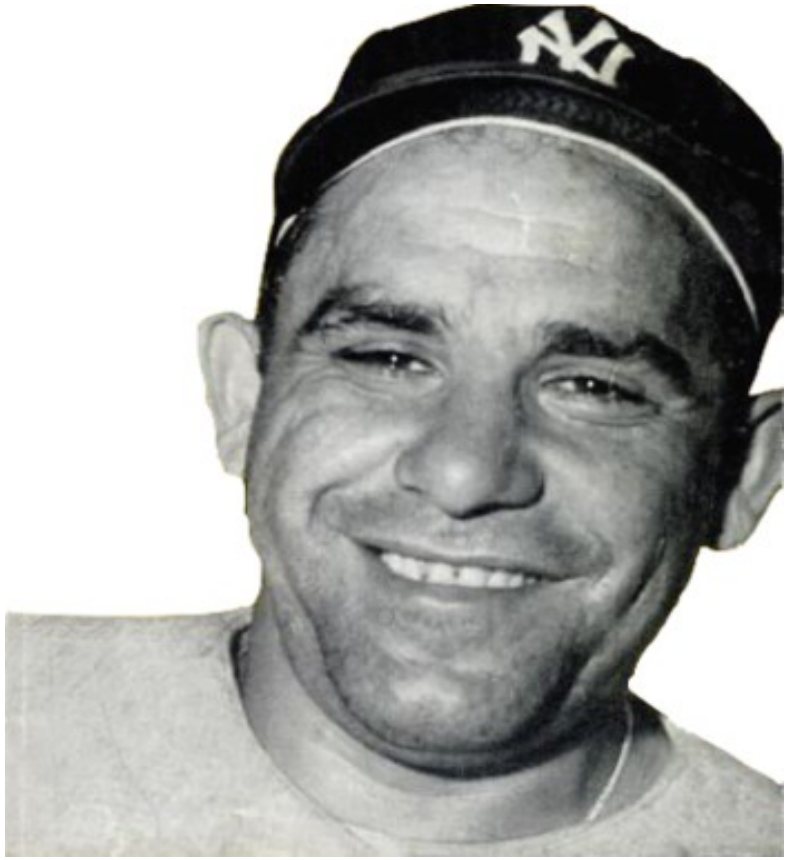


Courtesy U. Oelfke

- These probabilistic approaches, require some prior knowledge of patient motion and tumor mobility, and assume a ‘reasonable’ reproducible, predictive breathing pattern

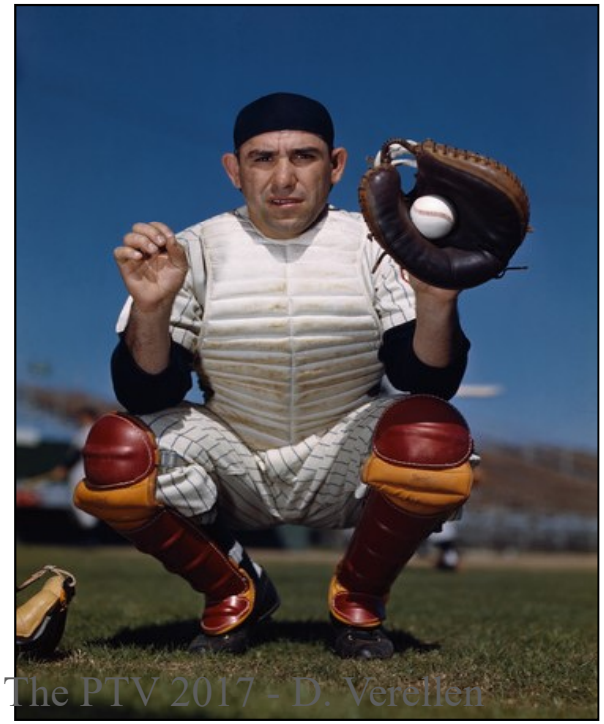
Let’s start with some Yogi wisdom …

- Quoting the famous Yogi Berra:
  - “If you don't know where you're going, you might not get there.”



Let's start with some Yogi wisdom …

- … he also said:
  - "I knew the record would stand until it was broken."
- … free translated, by yours truly:
  - "**I knew the PTV would remain in use until it became useless.**"



The ROYAL MARSDEN
NHS Foundation Trust

Incidence and Location of Local Recurrences after Only Surgery for Oesophageal Cancer

William Allum

NHS

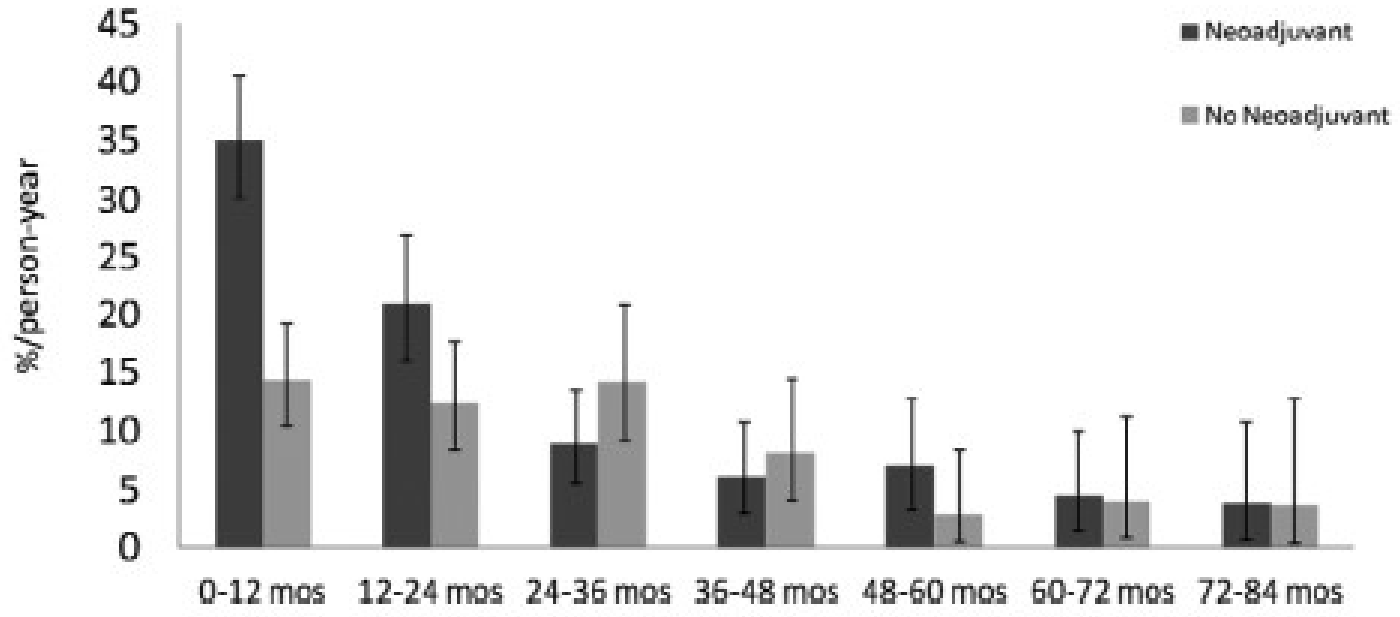
Incidence

Author	Sample size	Rate
De Manzoni EJSO 2003; 29: 506–510	92	71% at 5 years
Hulscher J Am Coll Surg 2000;191: 143–148.	137	52.6% - median FU 24mo
MSKCC J Thorac Oncol. 2013;8: 1558–1562	1147	38% - median FU 46mo
Mariette Cancer 2003;97:1616–23	439	54% - median FU 37mo
Moorcraft BMC Cancer 2016 16:112-121	214	47% - median FU 62 months

Relapse Free Interval

Author	Rate	Local	Haematogenous	Peritoneal
De Manzoni	80% < 24mo	12mo	12mo	10mo
Hulscher	50% by 11mo	11mo	11mo	
Mariette	46% by 12mo	14mo	11mo	13.5mo
Moorcraft	82% by 24mo			

Recurrence Rates with and without neoadjuvant therapy



Neo. # at risk	723	400	274	209	162	132	98
No Neo # at risk	424	278	201	155	116	91	71

Pattern of Recurrence

Author	Local / Regional only	Systemic only	Both
Hulscher	46%	30%	24%
MSKCC	28%	55%	17%
Mariette	44%	40%	16%
Moorcraft	7%	79%	14%

Site of Relapse

Lymph nodes	**52 (52%)**
Anastomosis	**21 (21%)**
Peritoneum	**16 (16%)**
Liver	**18 (18%)**
Bone	**12 (12%)**
Abdominal wall	**3 (3%)**
Lung	**10 (10%)**
Brain	**10 (10%)**
Mediastinum	**9 (9%)**
Other	**8 (8%)**

Moorcraft et al BMC Cancer 2016 16:112-121

Pattern of Recurrence of Type I & II Junctional Cancer

	Type I (*n*=55)	Type II (*n*=48)
Haematogenous	30	26
Local	18	14
Lymph node	10	12
Peritoneal	4	7

Site	Type I (*n*=10)	Type II (*n*=12)
Coeliac axis	4	3
Porta	3	4
Retrocrural/aortocaval	1	3
Supraclavicular	3	0

Wayman et al. Br J Cancer 2002, 86: 1223

Histological Subtype

Histology	Local	Regional	Distant
Adenocarcinoma	23%	23%	55%
Squamous Cell Carcinoma	23%	43%	34%

Prediction of Relapse

Author	
De Manzoni	Lymph node +ve >6 LN +ve – all relapsed in 2 years
Hulscher	Lymph node +ve R1 resection
Mariette	T stage
Moorcraft	Differentiation T stage N stage R1 resection

Detection of Relapse RMH

Elevated tumour markers at relapse	
Yes	**63 (63%)**
No	**24 (24%)**
Unknown	**13 (13%)**
Symptoms at time of relapse	
Yes	67 (67%)
How relapse was first detected in asymptomatic patients	(n = 33)
Routine tumour markers	22 (67%)
Routine CT	6 (18%)
Concurrent routine CT/ markers	1 (3%)
Endoscopy	2 (6%)
Other	2 (6%)

Detection of Recurrence MSKCC

Method of Detection	*n* (%)
Clinical (symptoms)[a]	217 (49.9)
Computed tomography	194 (44.6)
Upper endoscopy	6 (1.4)
Other[b]	2 (0.5)
Unknown	16 (3.7)

[a]Clinical detection includes symptoms and/or abnormal physical examinations.

[b]Other detection methods include tests not routinely performed at Memorial Sloan-Kettering Cancer Center: positron emission tomography/computed tomography, carcinoembryonic antigen level, chest radiograph, and magnetic resonance imaging.

Detection of Relapse MSKCC

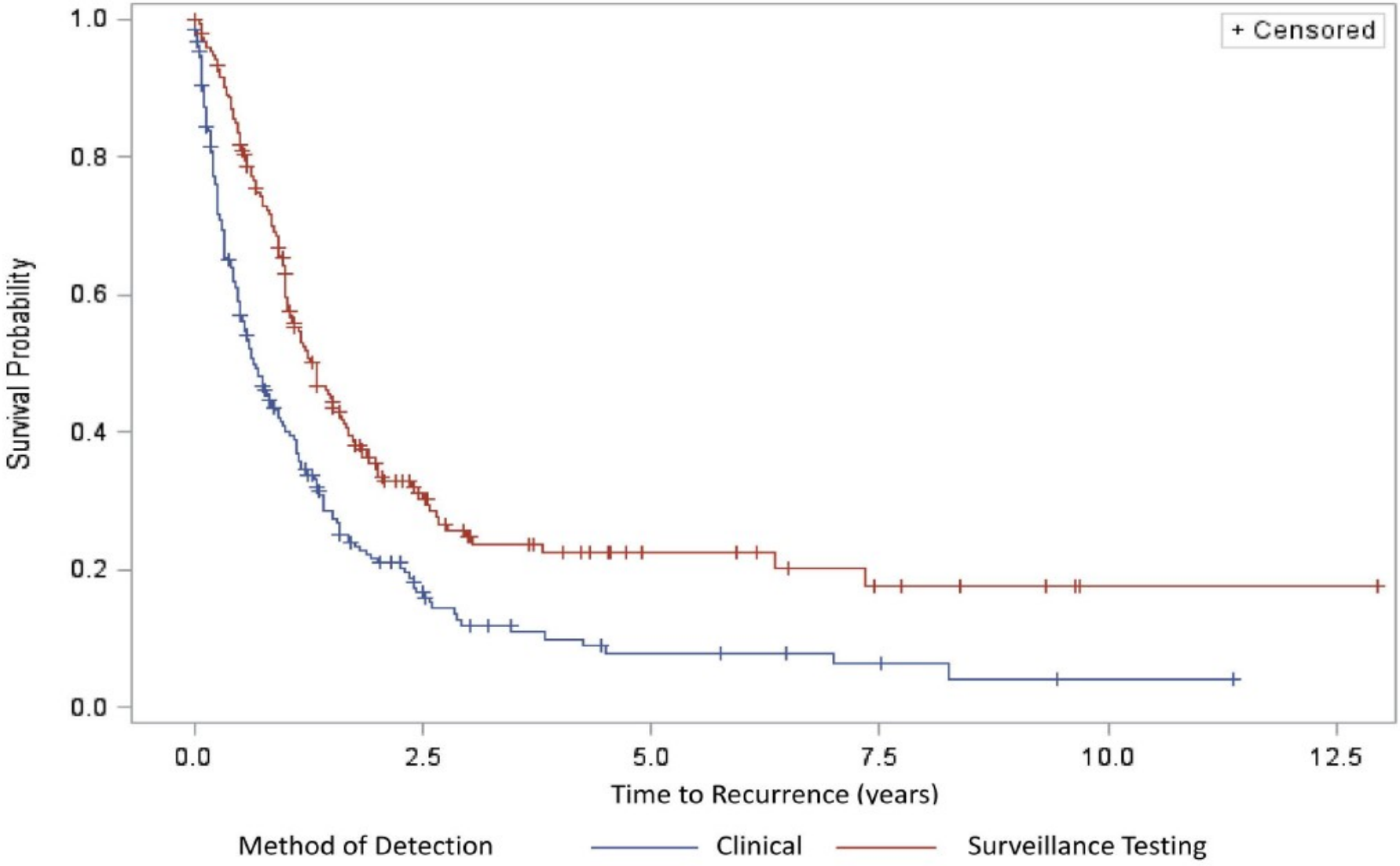
Symptomatic – 50%

CT – 45%

27 / 100 person years in year 1

4/100 person years in year 6

Survival according to method of detection of recurrence



Treatment of Relapse RMH

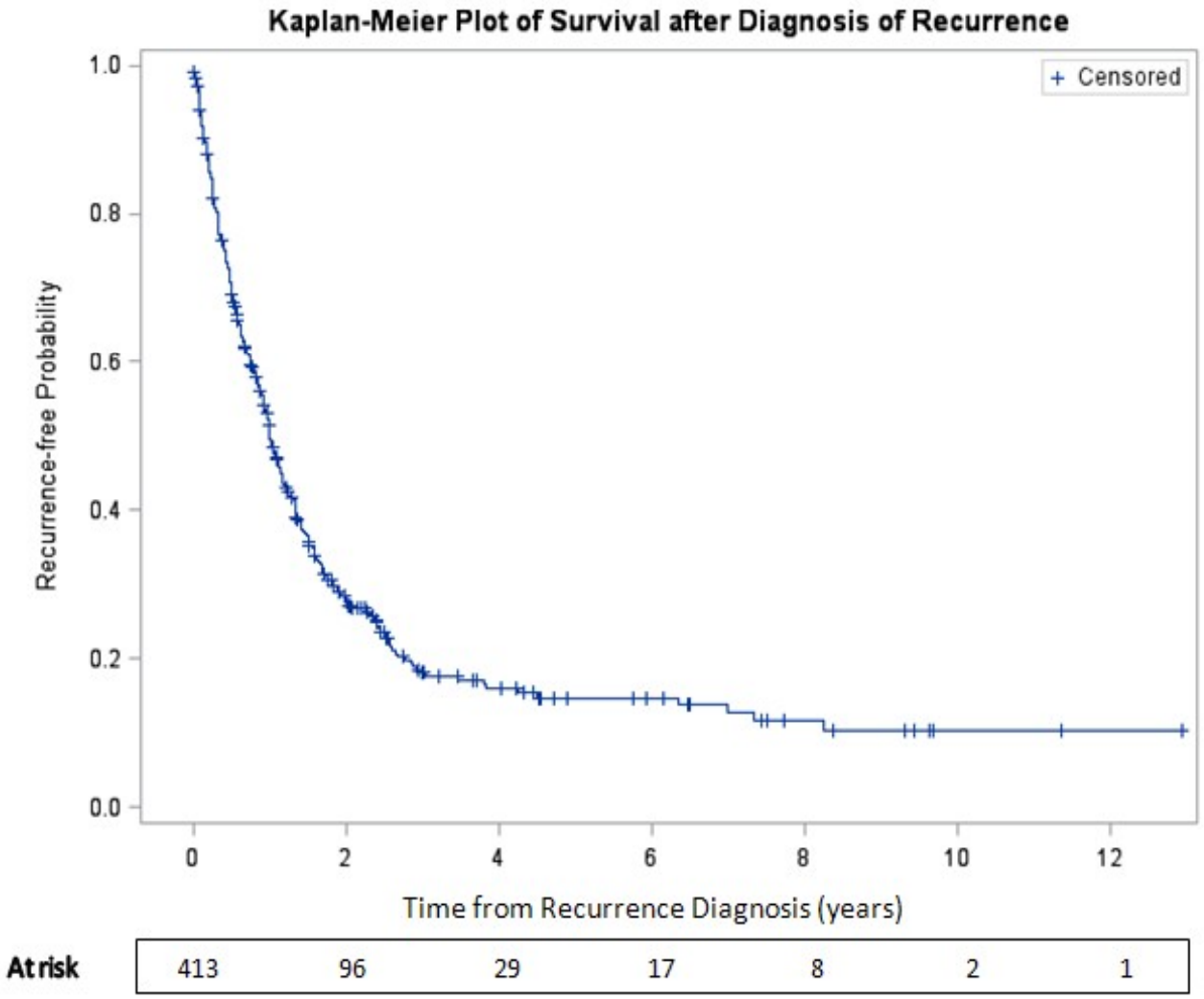
Further treatment for recurrent disease **Yes**	**72 (72%)**
Type of treatment for recurrent disease	
Chemotherapy	63 (88%)
Radiotherapy	21 (29%)
Chemoradiotherapy	1 (1%)
Surgery	5 (7%)

Survival (Mariette)

Median survival after relapse

7 months

Survival MSKCC



Survival longer:

Local recurrence
Detected after 2 years

Esophageal Cancer: Recurrence features by imaging

Dr Angela M Riddell

Royal Marsden, London. UK

ESTRO School

When to Image for surveillance

Questions:

- When to perform surveillance imaging?
  - Perform routine / Wait until symptomatic?
- Where is recurrence likely to occur ?
  - Locoregional / distant sites?

Esophageal Cancer Recurrence Patterns and Implications for Surveillance

Feiran Lou, MD, MS, Camelia S. Sima, MD, MS, Prasad S. Adusumilli, MD, Manjit S. Bains, MD, Inderpal S. Sarkaria, MD, Valerie W. Rusch, MD, and **Nabil P. Rizk, MD, MS**
Thoracic Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

J Thorac Oncol. 2013 8(12):1558-1562

When to Image for surveillance

>1000 patients, retrospective review

Clinical review & CT every 4-6 months for 2 years; CT annually after

Endoscopy every 6 months for 2 years then annually

- Distant failure more common than locoregional
- 75% recurrences occurred within the first 2 years
- 50% patients were asymptomatic at time of diagnosis of relapse
- CT detected 45% of all recurrences
- Endoscopy only identified 65% symptomatic & 15% asymptomatic patients
- Symptomatic patients had worse prognosis

J Thorac Oncol. 2013 8(12):1558-1562

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Patterns of relapse in Esophageal Cancer

CROSS I & II Trials* 418 patients

Table 2. Results of Univariable Cox Regression Analysis of RFS Time per Treatment Arm in Patients Undergoing Resection (n = 374)

	S Arm (n = 161)		CRT + S Arm (n = 213)				
Site of Recurrence	No.	%	No.	%	HR	95% CI	*P*
Anastomosis	14	8.7	6	2.8	0.28	0.11 to 0.72	**.008**
Mediastinum	33	20.5	15	7.0	0.29	0.16 to 0.53	**< .001**
Supraclavicular	7	4.3	9	4.2	0.83	0.31 to 2.2	.71
Celiac axis	11	6.9	8	3.8	0.42	0.17 to 1.04	.06
Para-aortic	17	10.6	14	6.6	0.53	0.26 to 1.1	.08
Peritoneal carcinomatosis	22	13.7	9	4.2	0.27	0.12 to 0.58	**.01**
Hematogenous	57	35.4	61	28.6	0.67	0.46 to 0.96	**.03**

NOTE. Bold font indicates significance.
Abbreviations: CRT, chemoradiotherapy; HR, hazard ratio; RFS, recurrence-free survival; S, surgery.

- Most patients had distant failure (22%) or combined locoregional (LRR) and distant failure (16.5%)
- Isolated locoregional recurrence 9.3% surgery & 3.3% CRT+S
- Majority of LRR developed within 2 years & none after 30 months

Oppedijk V, van der Gaast A, van Lanschot J et al. 2014 JCO doi:10.1200/JCO.2013.51.2186

Patterns of relapse in Esophageal Cancer

Relapse related to radiation target volume

Table 3. Tumor Recurrences in Relation to Radiation Target Volumes in Patients Undergoing CRT Plus Surgery (n = 213)

Recurrence	Infield	Outfield	Borderline	Unknown	Total
LRR only	2	2	2	1	7
Distant only	0	43	0	1	44
LRR plus distant	9	11	3	0	23
Total	11	56	5	2	74

Abbreviations: CRT, chemoradiotherapy; LRR, locoregional recurrence.

Oppedijk V, van der Gaast A, van Lanschot J et al. 2014 JCO doi:10.1200/JCO.2013.51.2186

Detection of relapse CT vs PET-CT

Modality	Sensitivity	Specificity
Conventional CT	65-89%	79-91%
FDG PET & PET-CT	96%	78%

- Authors recommend histopathological confirmation of FDG PET suspected lesions; due to high false positive rate.

Goense L, van Rossum P, Reitsma J et al. J Nucl Med 2015; 56:995–1002

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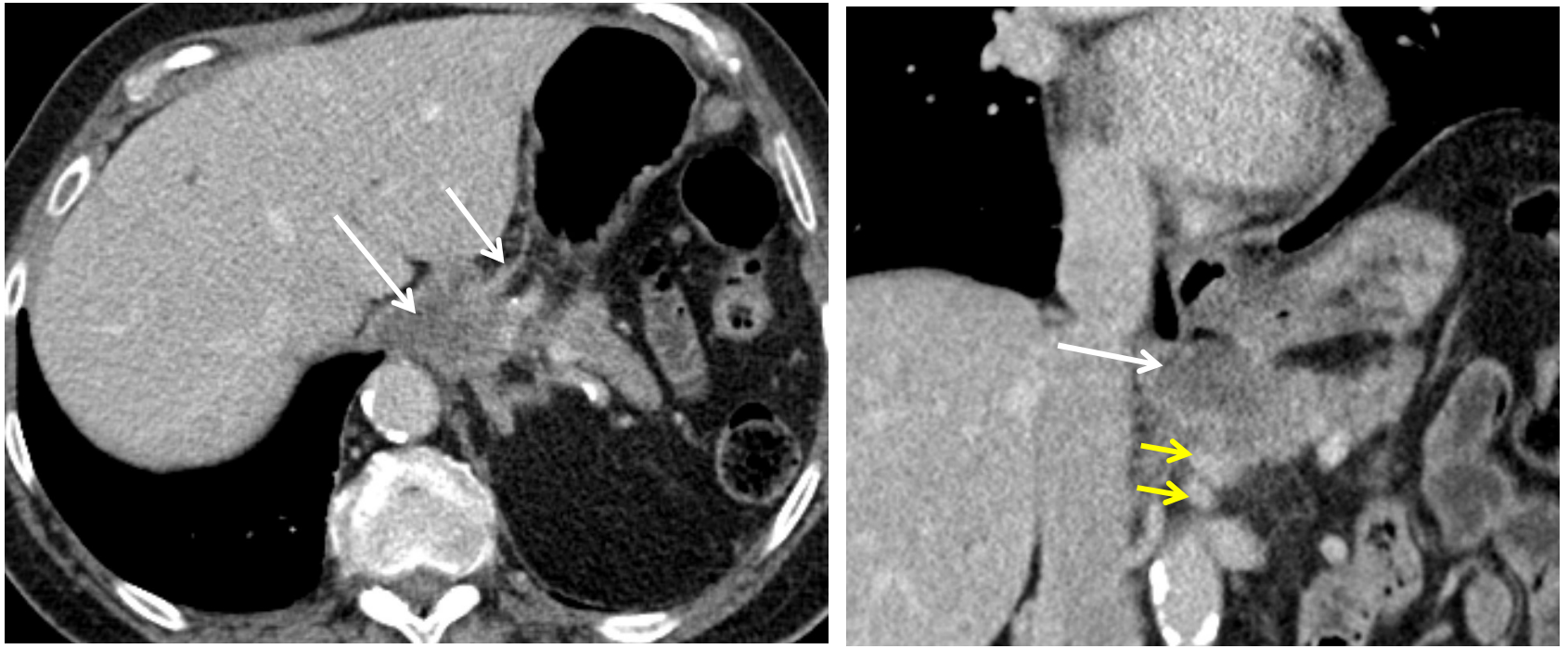
Locoregional relapse

81 female. Previous CRT for SCC at 31cm

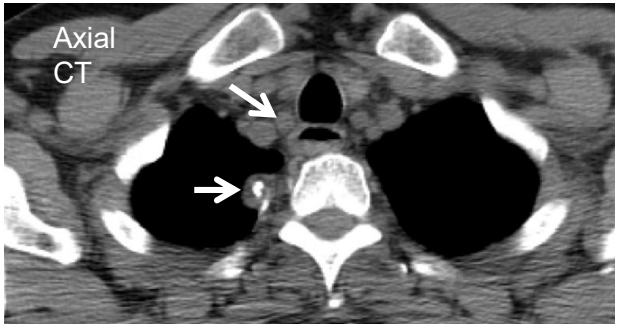


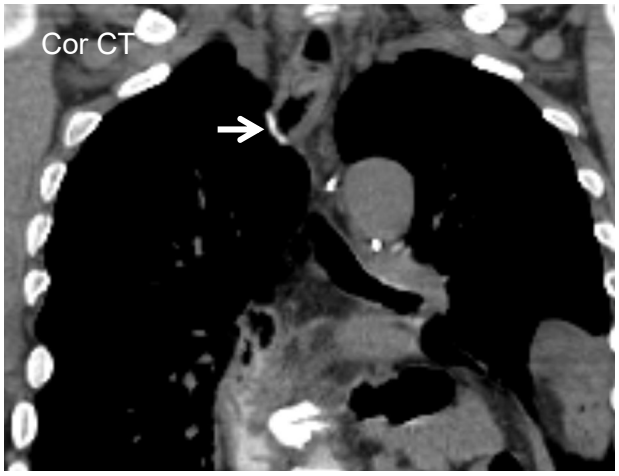
Nodal relapse centred on left gastric territory extending to coeliac (Stations 7 & 9)

Locoregional relapse

69 year old male diagnosed with adenocarcinoma in 2008. Underwent perioperative chemotherapy & surgery (Ivor Lewis)

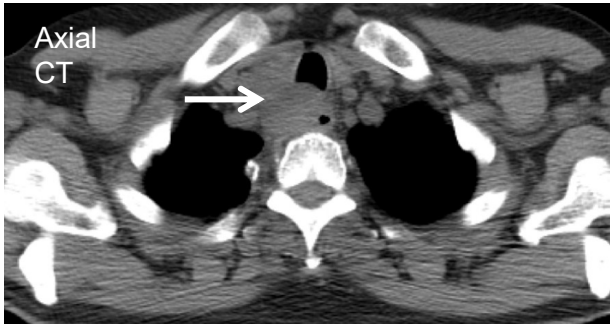
25.02.2010

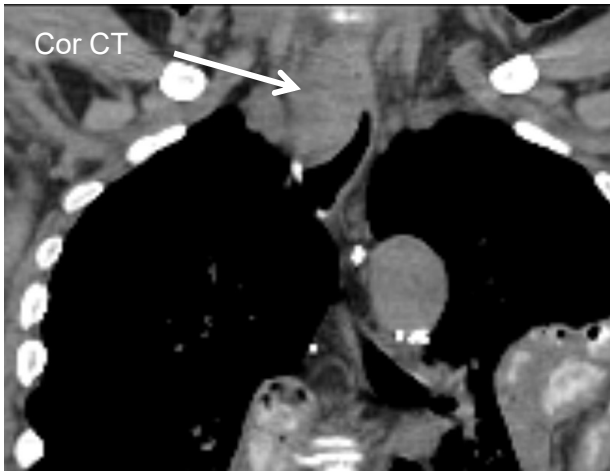




Baseline post op

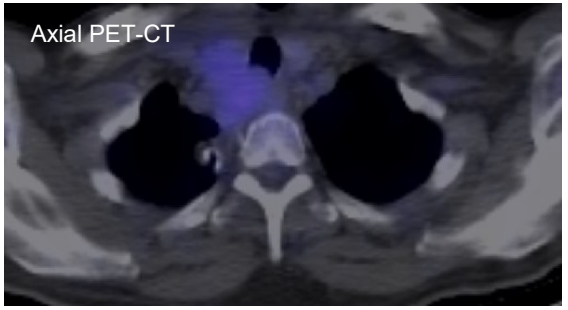
11.07.2011



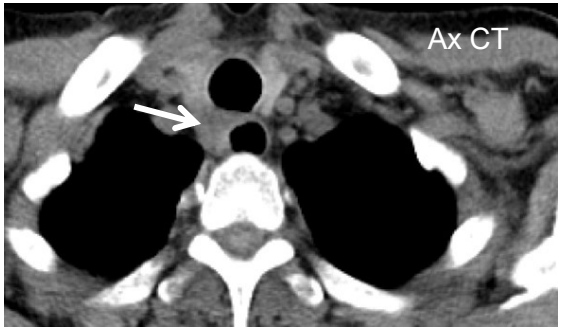


Recurrence eccentric to oesophageal anastomosis

01.07.2011



12.04.2012



Response post 8♯ chemotherapy

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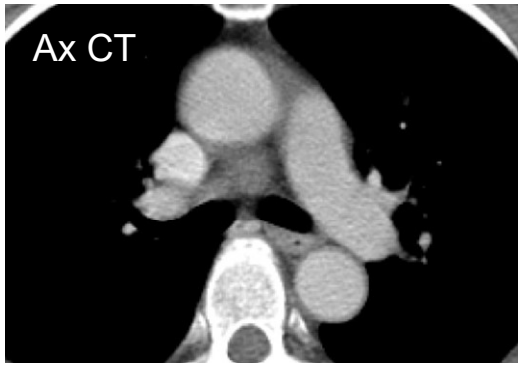
Locoregional relapse

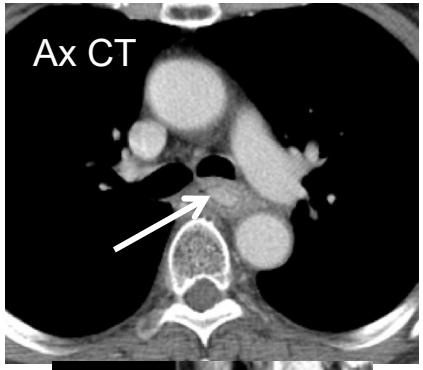
69 year old female with SCC mid oesophagus. Diagnosed March 2015 and underwent ECX & CRT; completed in August 2015

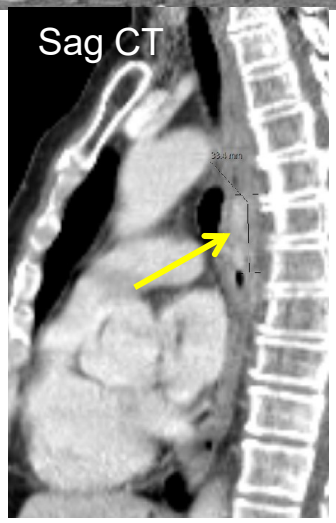
18.06.2015



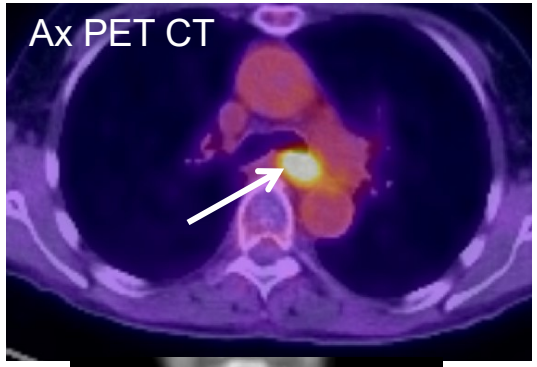
Baseline

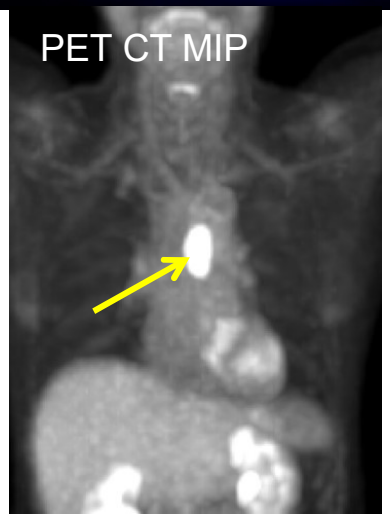
17.02.2016





18.02.2016





Relapse: epicentre in oesophageal wall.
Endoscopy biopsy positive

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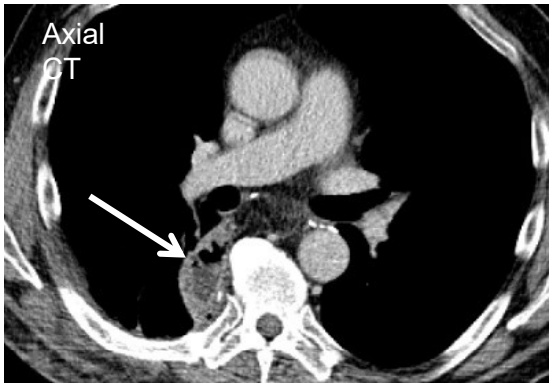
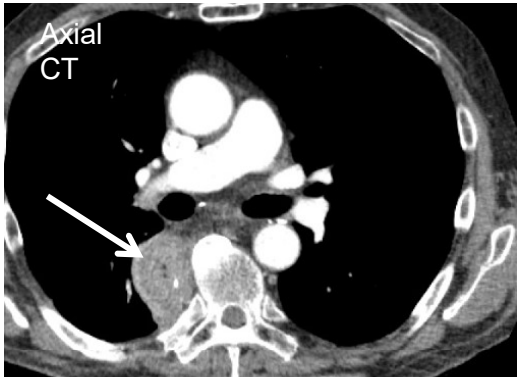
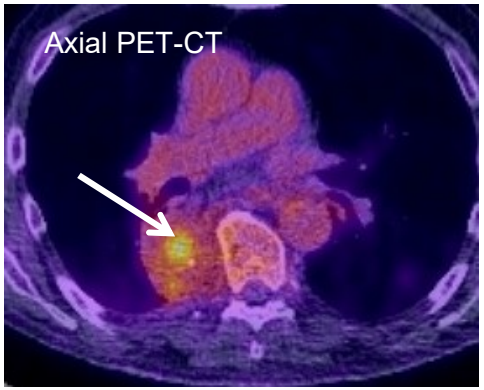
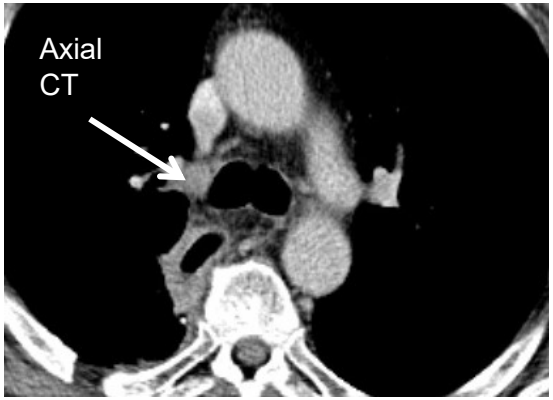
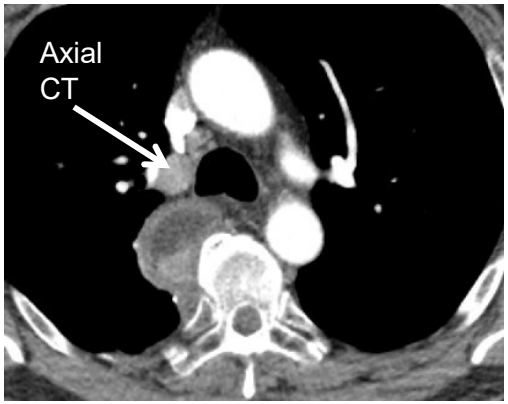
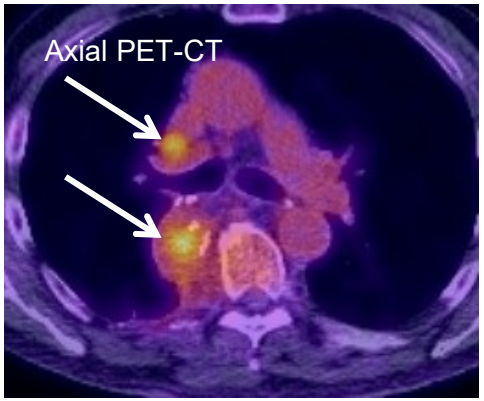
Locoregional relapse

72 year old male patient. Post oesophagectomy, with new dysphagia

30.04.2012	22.10.2015	04.11.2015
		
		

Baseline

Relapse: epicentre in oesophageal wall.
Endoscopy biopsy positive

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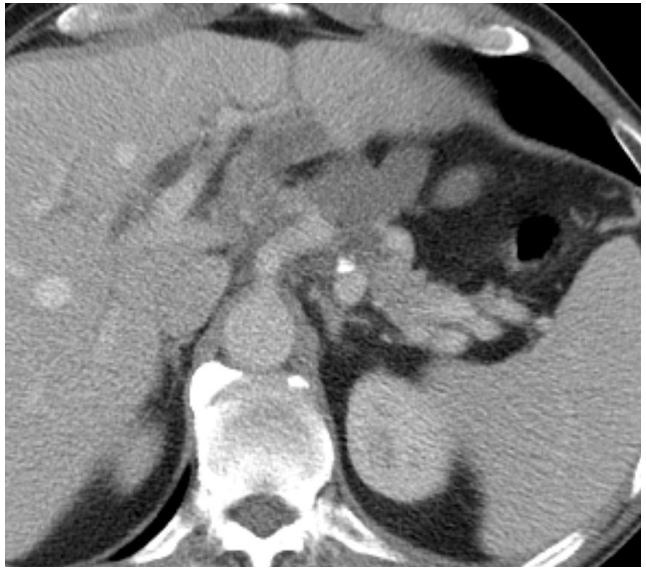
Locoregional relapse

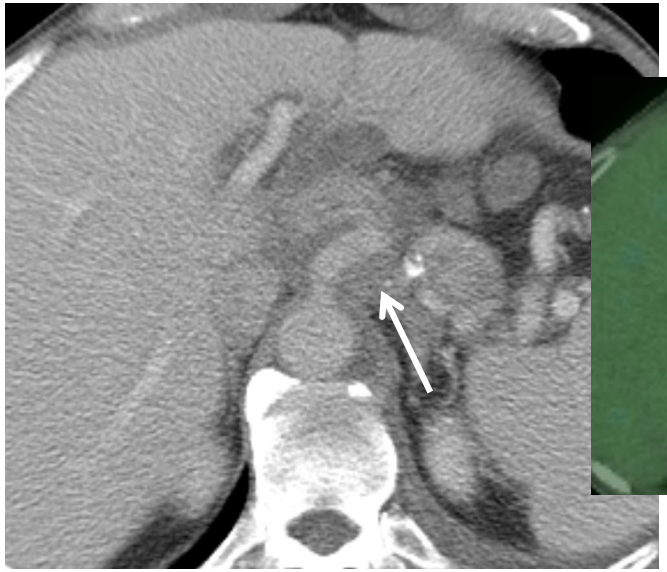
52 year old male patient T3N1 ACA of GOJ – Type II.

04.03.2009



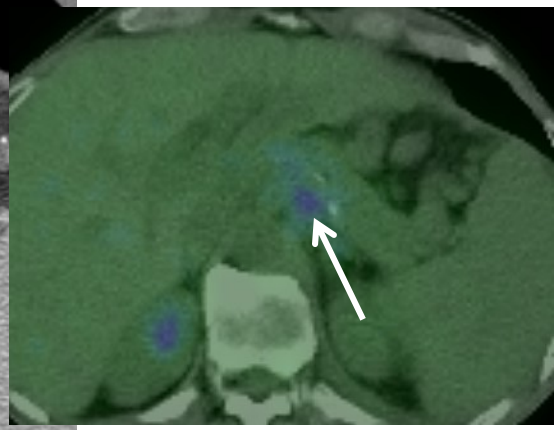
Baseline post op

17.07.2009



Increase in soft tissue adjacent to coeliac axis

28.07.2009



Area FDG avid on PET-CT

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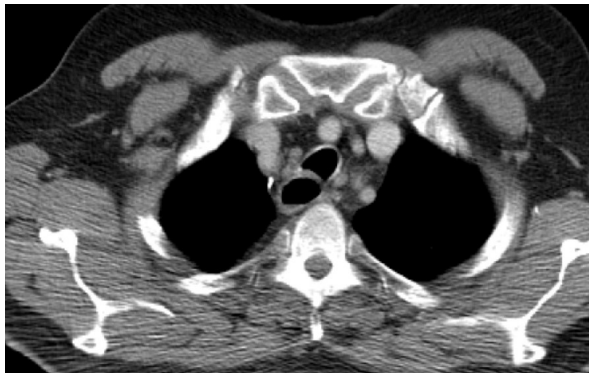
Locoregional relapse

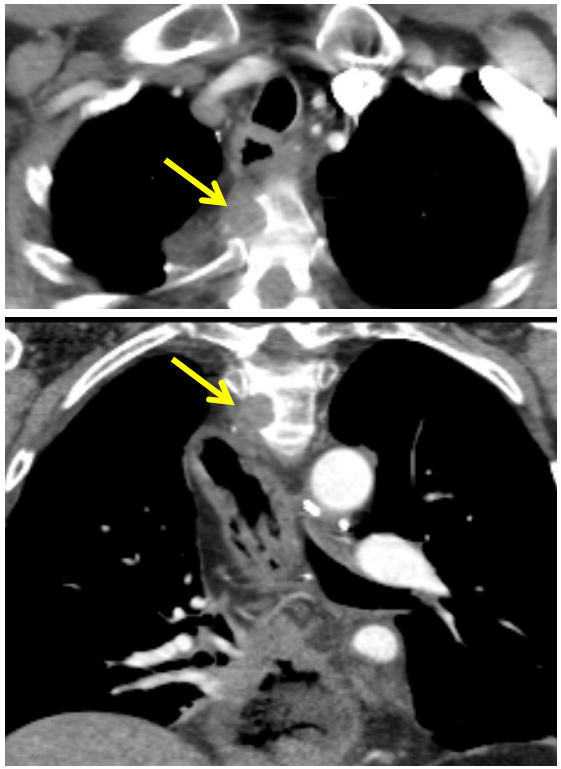
74 year old male patient underwent Ivor Lewis oesophagectomy following perioperative chemotherapy. 1 year post op he developed back pain.

30.05.2014



Baseline

08.10.2014



Bone involvement due to direct extension from LRR, not haematogenous spread

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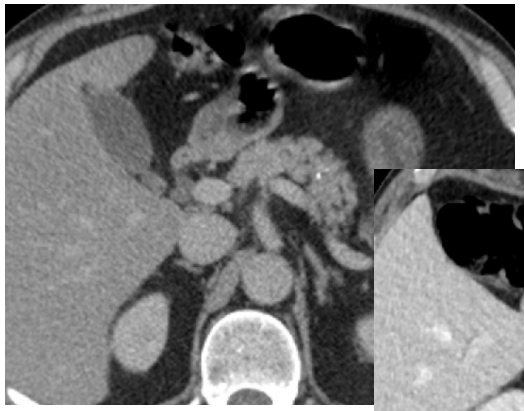
Local & distant spread

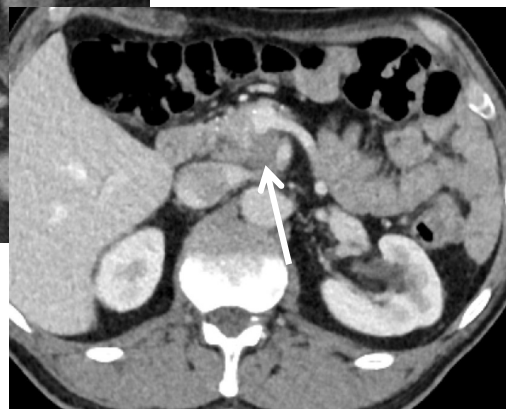
60 year old male patient. Underwent preoperative ECX x4 followed by surgery for pT3N2M0 R0 TRG4 GOJ tumour. Post op he had 54Gy in 30♯ completed Feb 2015. Presented with rectal bleeding

10.02.2014



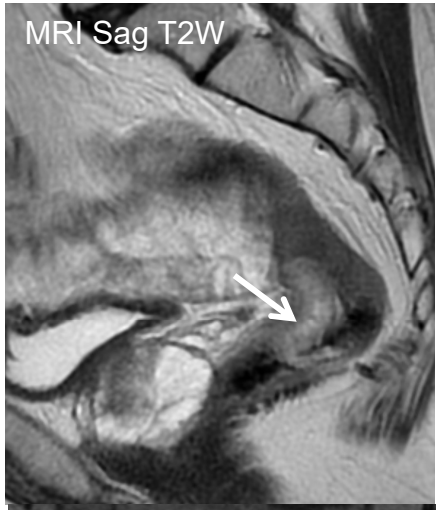
Baseline

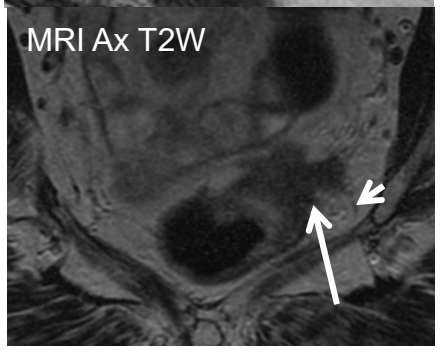
13.04.2016



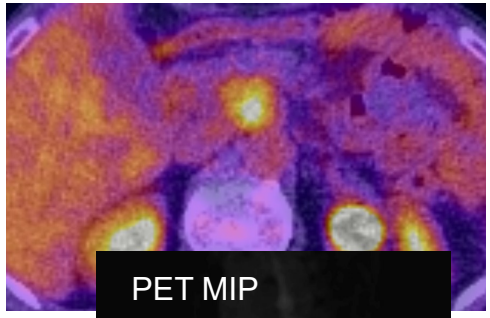
SMA Nodal relapse

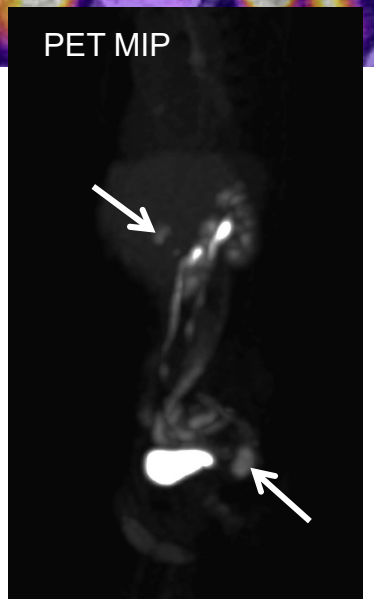
13.04.2016





24.05.2016





Biopsy showed adenocarcinoma with immunohistochemistry profile consistent with an oesophageal primary similar to original primary

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Summary

- Recurrence occurs within 2 years of definitive therapy.
- Distant failure is more common than locoregional recurrence
- MDCT will identify a majority of relapse; PET-CT should be considered if conventional CT is negative.
- Patients who are asymptomatic at time of relapse have better prognosis – therefore imaging surveillance is recommended

Thank you

Oesophageal cancer
- Palliative radiotherapy -

Marcel Verheij MD PhD
Department of Radiation Oncology
NKI, Amsterdam

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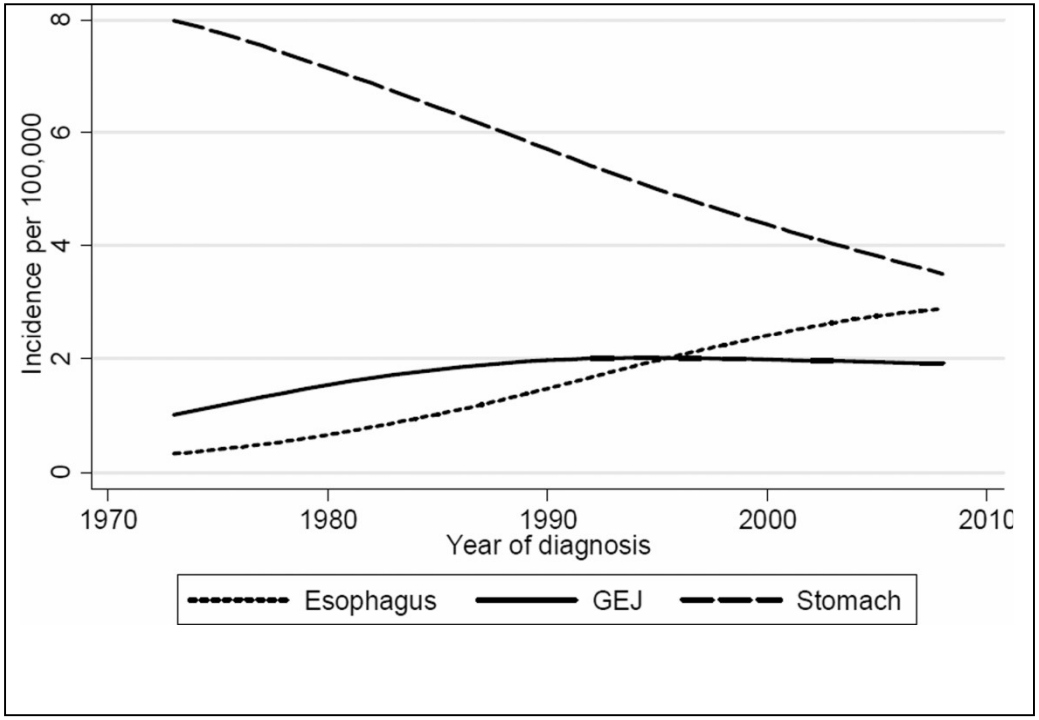
Contents

- Introduction
- Treatment options
- Summary

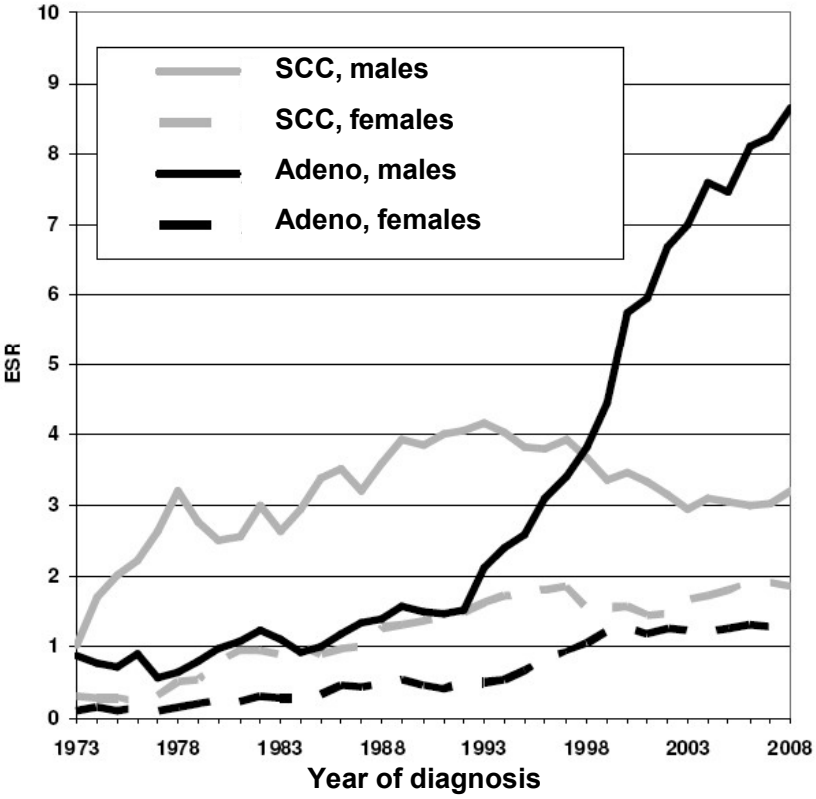
Introduction

Incidence of adenocarcinoma of the esophagus, GEJ, and stomach 1973-2008, United States



Buas et al, Semin Radiat Oncol 2013

Incidence of esophageal cancer in The Netherlands 1973-2008



www.cijfersoverkanker.nl

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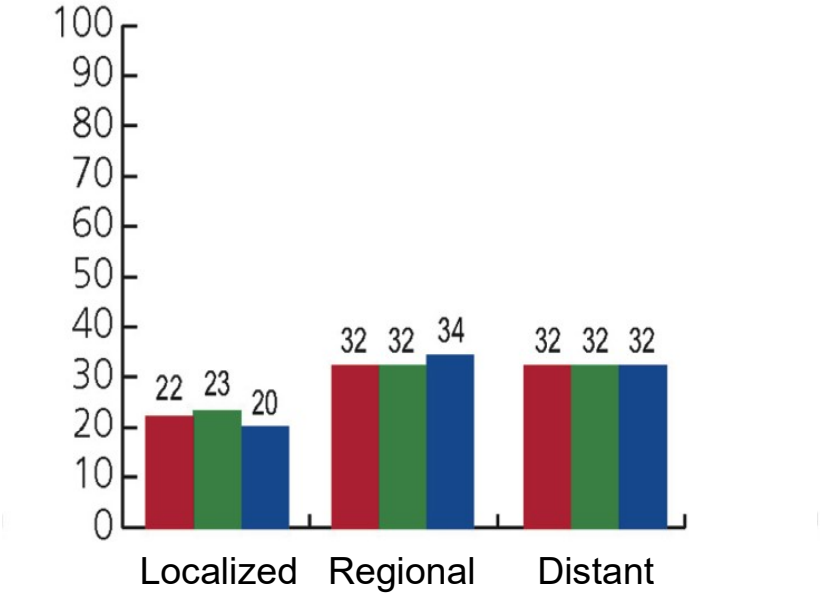
Introduction

Distribution by stage at diagnosis



5-year survival by stage

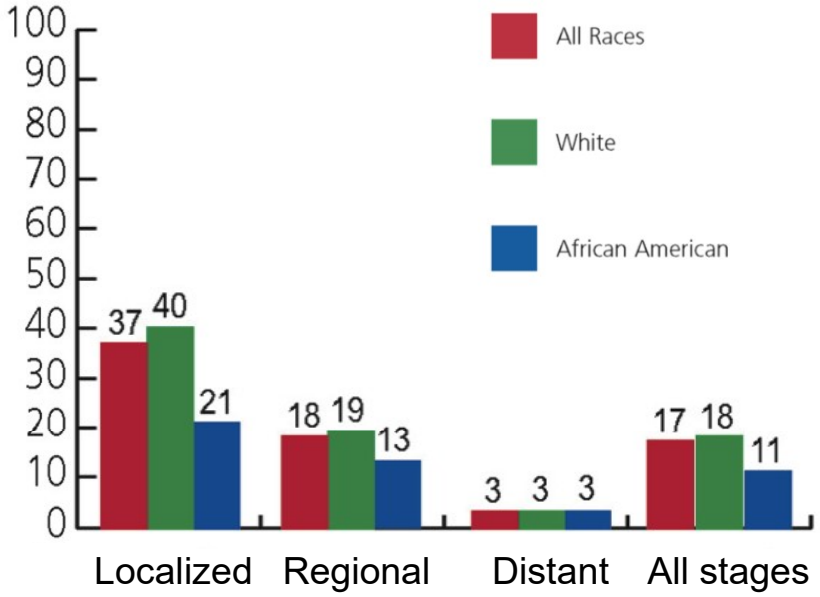


TABLE 6. Percentage of Patients' Stage at Diagnosis According to Time of Diagnosis

Stage	In Situ (%)	Local (%)	Regional (%)	Metastatic (%)
1970s	0.4	29	37	34
1980s	1	26	37	36
1990s	1.6	30	35	33
2000s	2	27	34	37

TABLE 4. Percentage of Cured Patients with Esophageal Cancer Through the Decades

Stages	In Situ	Local	Regional	Metastatic	All
1970s	19	9	4	0.6	5
1980s	50	18	6	0.8	8
1990s	63	26	10	1	13
2000s	73	37	12	2	18

Cancer Statistics 2012, CA Cancer J Clin 2012
SEER Database Analysis 2012, J Thor Oncol 2012

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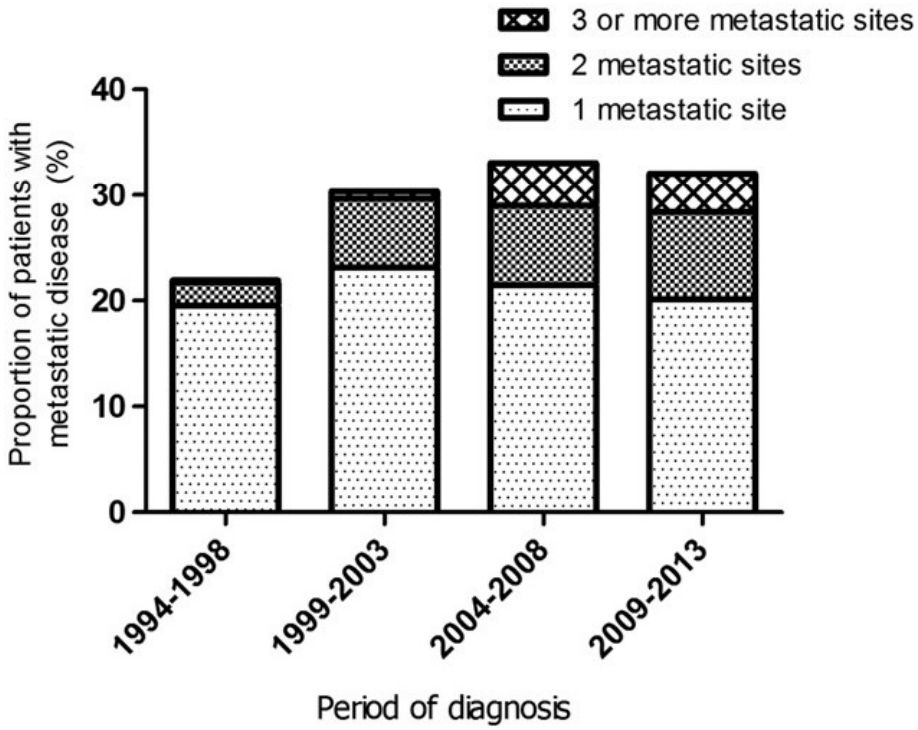
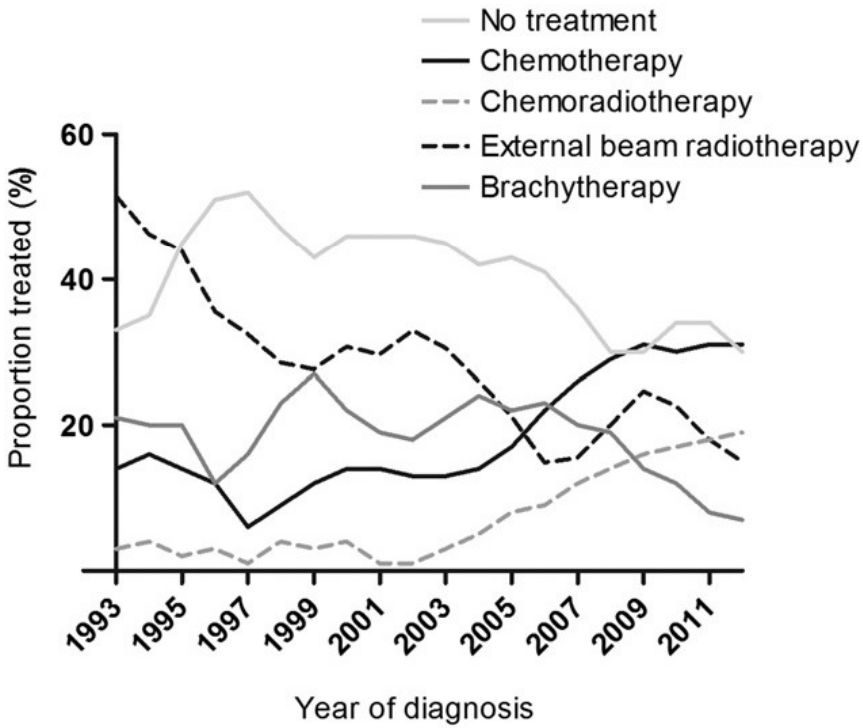
Introduction

Use of EBRT, brachytherapy, chemoradiotherapy and chemotherapy in patients with metastatic esophageal cancer and the effect on overall survival South of the Netherlands 1994 - 2013 (n=1020)





Bernards et al. Acta Oncol 2016

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Introduction

Use of EBRT, brachytherapy, chemoradiotherapy and chemotherapy in patients with metastatic esophageal cancer and the effect on overall survival South of the Netherlands 1994 - 2013 (n=1020)

Table 3. Crude median overall survival, crude 1-year survival and risk of dying (hazard ratios) of patients with metastatic esophageal cancer, diagnosed between 1994 and 2013 in the Southern Netherlands (N = 1020).

	Crude median survival (weeks)	Crude 1-year survival (%)	HR (95% CI) Without treatment	HR (95% CI) Including treatment
Period of diagnosis				
1994–1998	18.3	14.4	1.00 (reference)	1.00 (reference)
1999–2003	19.2	13.1	0.96 (0.75–1.21)	0.99 (0.78–1.25)
2004–2008	19.3	15.0	0.85 (0.68–1.06)	0.93 (0.74–1.17)
2009–2013	25.1	22.4	0.63 (0.50–0.79)	0.87 (0.68–1.10)
Treatment				
No treatment	9.4	4.6	not applicable	2.46 (2.05–2.96)
External beam radiotherapy	23.3	15.0	not applicable	1.00 (reference)
Brachytherapy	20.7	9.4	not applicable	1.23 (0.97–1.57)
Chemoradiotherapy	50.6	50.0	not applicable	0.40 (0.29–0.56)
Chemotherapy	41.9	36.0	not applicable	0.63 (0.50–0.80)
BRT and EBRT	29.6	26.2	not applicable	0.87 (0.62–1.23)
BRT and CT	32.4	27.3	not applicable	0.75 (0.47–1.20)
CRT and CT	40.4	34.2	not applicable	0.49 (0.23–1.05)

EBRT: external beam radiotherapy; BRT: brachytherapy; CRT: chemoradiotherapy; CT: chemotherapy.

Bernards et al. Acta Oncol 2016

- *Median survival of M+ EC improved from 18 (1994-1998) to 25 wks (2009-2013)*
- *Contributing factors: major changes in treatment strategies and better pt selection*

Introduction

- More than 50% of patients have inoperable disease at presentation
- Around 35% of patients with EC present with metastatic disease
- These patients have an extremely poor prognosis:
  - 1-yr survival rate 18%
  - Median survival 3-5 months
- In 80-90% of LA-EC dysphagia is predominant symptom
- There are different modalities to achieve adequate locoregional palliation:
  - EBRT
  - Brachytherapy
  - Chemoradiotherapy
  - Chemotherapy
  - Endoscopic stent placement
- There is no consensus on which regimen should be used in first line

Introduction

Adequate local/locoregional palliation should be:

- Delivered in short treatment time
- Fast
- Effective (dysphagia, pain, QOL)
- Sustained
- Well-tolerated
- Cost-effective

Brachy vs. stent

Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial

*Marjolein Y V Homs, Ewout W Steyerberg, Wilhelmina M H Eijkenboom, Hugo W Tilanus, Lukas J A Stalpers, Joep F W M Bartelsman, Jan J B van Lanschot, Harm K Wijdeman, Chris J J Mulder, Janny G Reinders, Henk Boot, Berthe M P Aleman, Ernst J Kuipers, Peter D Siersema, for the Dutch SIREC study group**

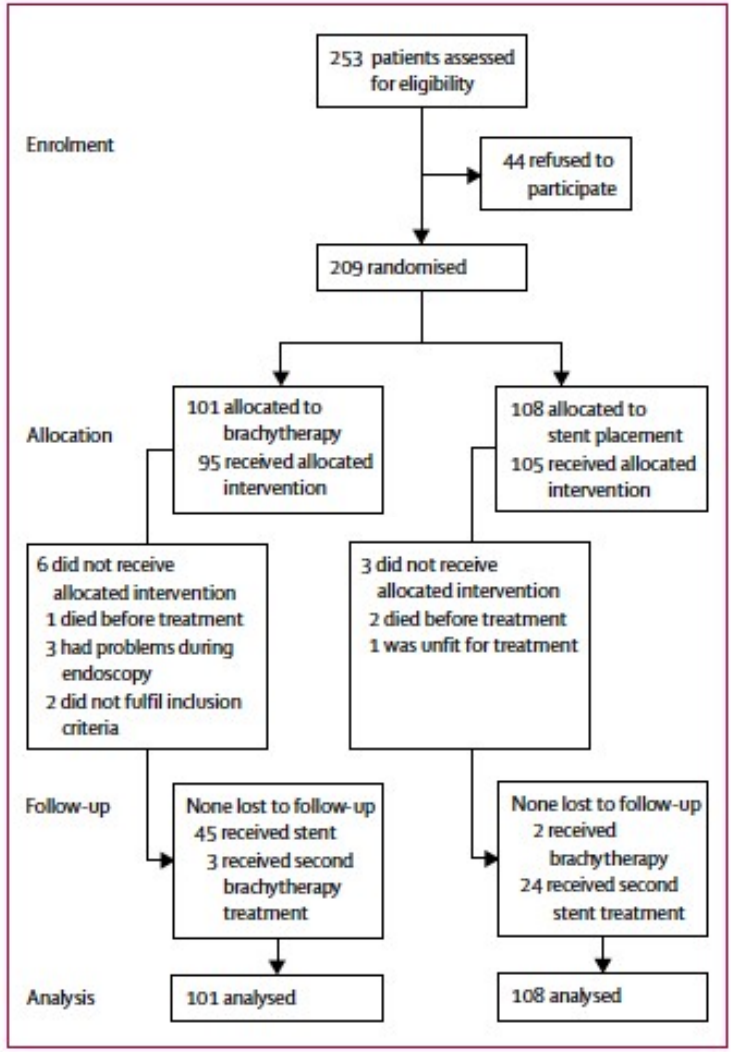
Lancet 2004; 364: 1497–504

*Participating investigators and centres listed at end of report

	Brachytherapy (n=101)	Stent placement (n=108)
Age (years, mean [SD])	69 (13)	69 (11)
Men/women	76/25	86/22
Dysphagia score before treatment (mean [SD])	2·8 (0·9)	2·8 (0·7)
Tumour length (cm, mean [SD])	7·5 (2·6)	7·5 (2·8)
Indications for palliative treatment		
Metastases	66 (65%)	68 (63%)
Poor medical condition	23 (23%)	28 (26%)
Both	12 (12%)	12 (11%)
Location of tumour		
Oesophagus	86 (85%)	93 (86%)
Oesophagogastric junction	15 (15%)	15 (14%)
Tumour histology		
Squamous-cell carcinoma	29 (29%)	29 (27%)
Adenocarcinoma	69 (68%)	75 (69%)
Other	3 (3%)	4 (4%)
Previous chemotherapy	13 (13%)	17 (16%)

Data are number (%) unless otherwise specified.

Table 1: **Baseline characteristics**



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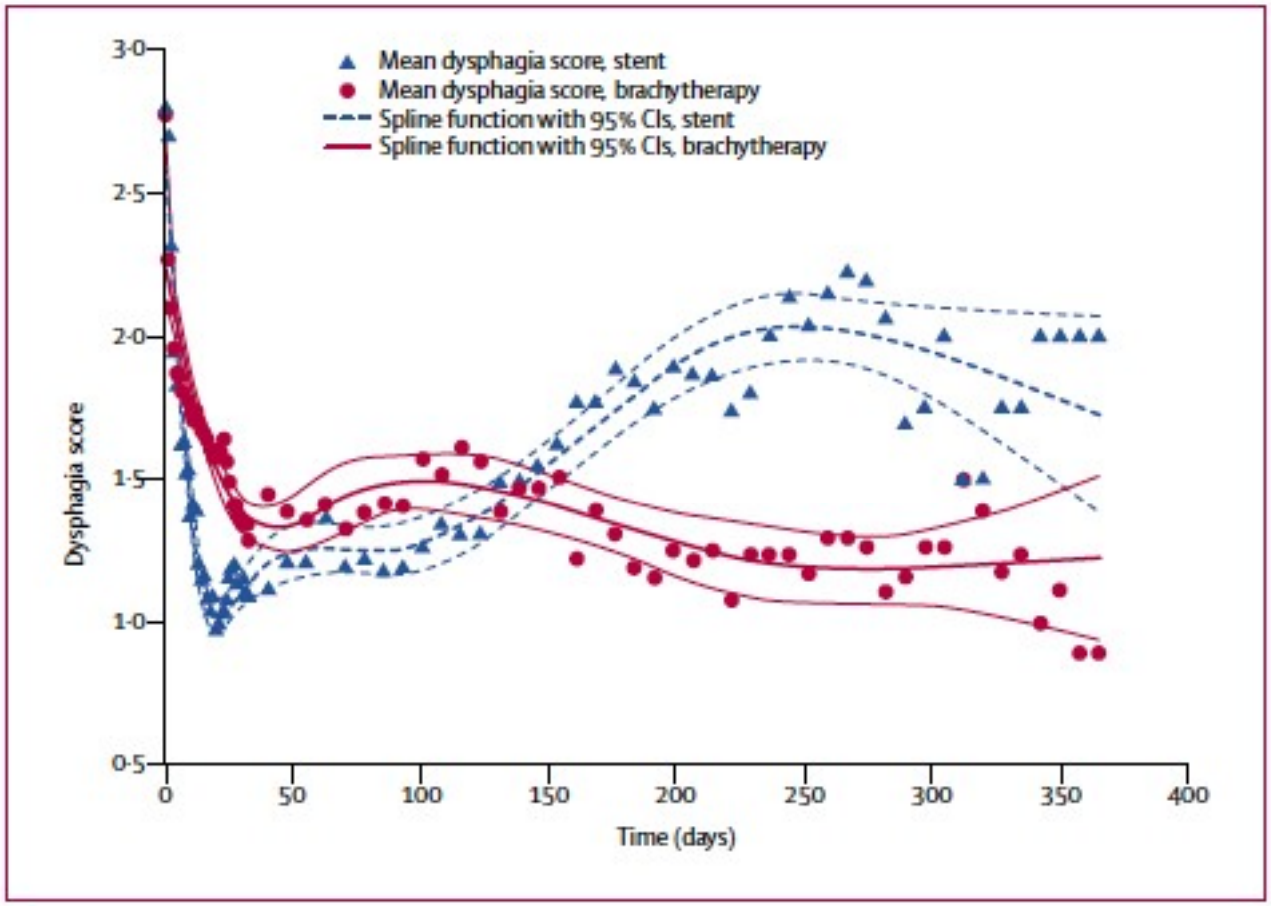
Brachy vs. stent



	Brachytherapy (n=101)	Stent placement (n=108)	p*
Total complications†	21 (21%)	36 (33%)	0·02
Major complications†	13 (13%)	27 (25%)	0·02
≤7 days			
Perforation	1	2	–
Fever	1	1	–
Severe pain	0	2	–
(Aspiration) pneumonia	1	1	–
>7 days			
Perforation	1	0	–
Fever	1	0	–
Haemorrhage	5	14	–
Fistula formation	3	3	–
Severe pain	1	1	–
Pressure necrosis	0	3	–
Pre-stenotic dilation	0	1	–
Minor complications†	8 (8%)	16 (15%)	0·08
Mild retrosternal pain	5	9	–
Gastro-oesophageal reflux	1	5	–
Radiation oesophagitis	1	0	–
Candida or infestation	1	2	–
Persistent/recurrent dysphagia†	43 (43%)	43 (40%)	0·81
Tumour persistence	18	0	–
Tumour regrowth	26	16	–
Stent migration	3‡	18	–
Food-bolus obstruction	5	16	–
Fracture of stent	0	2	–
Oblique-position stent	1‡	0	–

*Log-rank test for time to first complication. †More than one complication arose in some patients. ‡Some patients randomly assigned to brachytherapy later received a stent for various reasons.

Table 2: **Complications and persistent or recurrent dysphagia, after brachytherapy and stent placement**

Compared to stent, single-dose (12 Gy) brachy resulted in:

- *slower, but better long-term dysphagia relief*
- *fewer complications*
- *better HR-QOL*
- *similar costs*

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Brachy vs. stent

Stent placement or brachytherapy for palliation of dysphagia from esophageal cancer: a prognostic model to guide treatment selection (CME)

Volume 62, No. 3 : 2005 GASTROINTESTINAL ENDOSCOPY

Ewout W. Steyerberg, PhD, Marjolein Y. V. Homs, PhD, Annemieke Stokvis, BSc, Marie-Louise Essink-Bot, MD, PhD, Peter D. Siersema, MD, PhD, for the SIREC Study Group

Rotterdam, The Netherlands

Capsule Summary

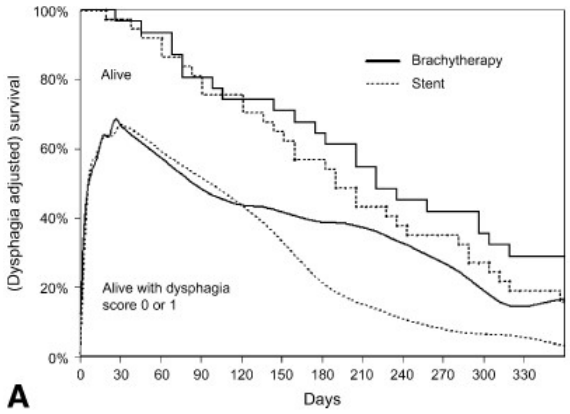
What is already known on this topic

- Single-dose brachytherapy is preferable to stent placement in patients with dysphagia due to inoperable cancer of the esophagus or GE junction.
- Stent placement may be reserved for dysphagic patients with short life expectancy or with persistent or recurrent tumor growth after brachytherapy.

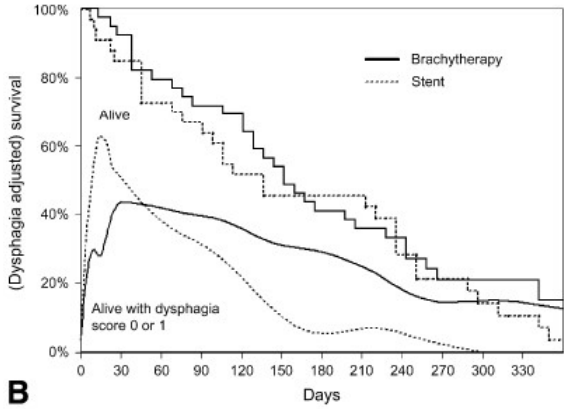
What this study adds to our knowledge

- In a regression analysis model of patients' data from a multi-center, randomized, controlled trial and a consecutive series, a simple prognostic score could identify patients in whom stent placement would be at least equivalent to brachytherapy.

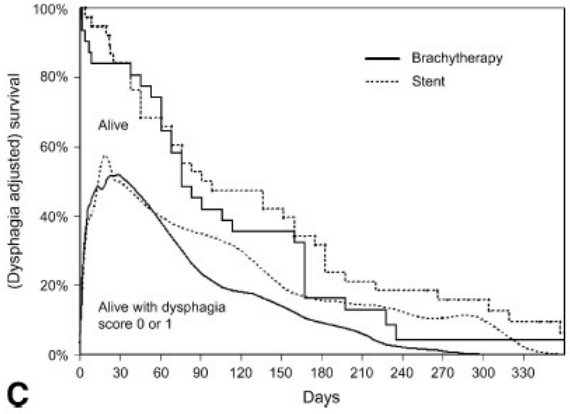
Brachy vs. stent



Good prognosis score <3.5



Intermediate prognosis score 3.5-5



Poor prognosis score >5

TABLE 3. Score chart for survival

Characteristic	Score*
Male gender	1
Age (y)	
40	−1
50	−0.5
60	0
70	0.5
80	1
Tumor length > 10 cm	2
Metastases	2
WHO performance score	
1	1
2	2
3+	3

WHO, World Health Organization.
*A higher score corresponds to shorter survival.

Steyerberg et al. Gastrointest Endosc 2005

- *In patients with poor prognosis stent and brachytherapy are equivalent*

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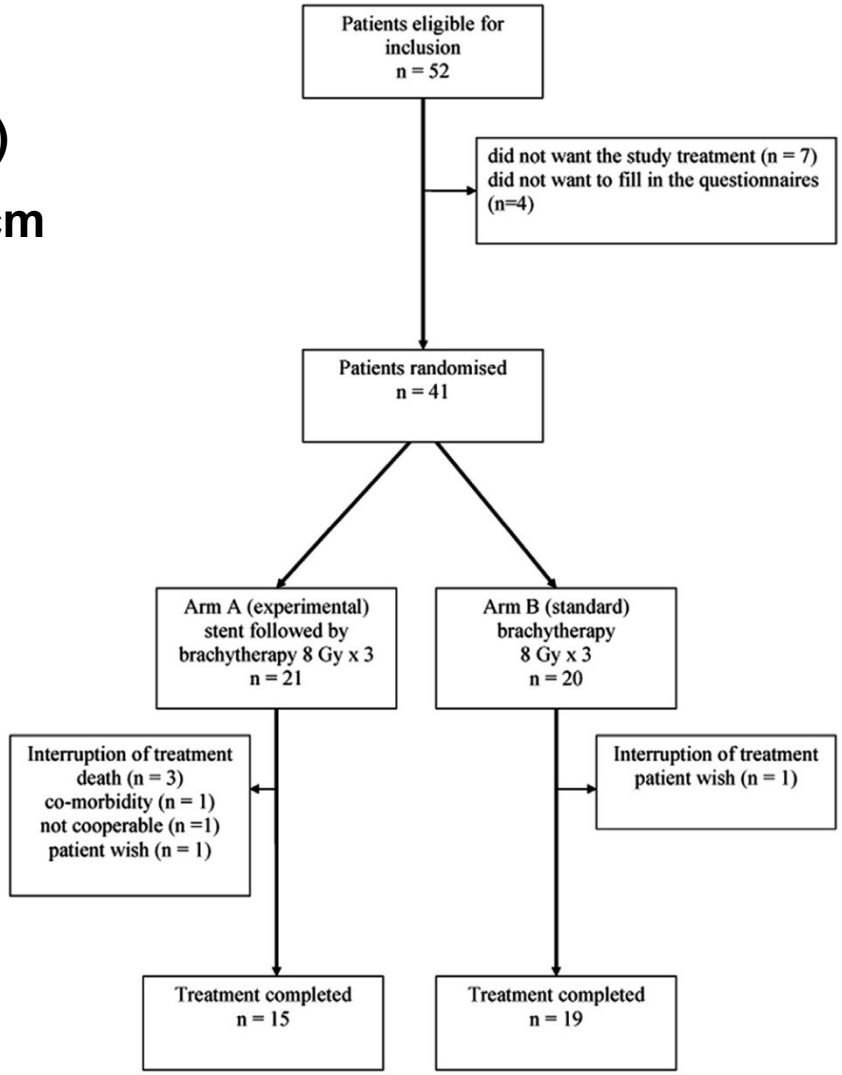
Brachy w/wo stent

N=41

LA-EC (61% AC)

Tumor length 7 cm



Amdal et al. R&O 2013

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Brachy w/wo stent

Change in patient-reported dysphagia and pain from baseline to FU1 (week 3) and from baseline to FU2 (week 7).[a]

FU1 evaluation		Change score	Stent + brachytherapy $n = 17$	Brachytherapy alone $n = 18$	p-Value[b]
Dysphagia	Mean change (range)		1 (−1, 3)	0 (−1, 1)	
Proportion of patients	Improved	3	1/17	0/18	
		2	4/17	0/18	
		1	7/17	7/18	0.02
	Unchanged	0	4/17	9/18	
	Worse or always full stop	−1	1/17	2/18	
Pain	Mean change (range)		1 (0, 9)	1 (−2, 3)	
Proportion of patients	Improved		0/17	1/18	
	Always no pain		7/17	7/18	0.3
	Unchanged		6/17	5/18	
	Worse		4/17	5/18	
FU2 evaluation		Change score	Stent + brachytherapy $n = 9$	Brachytherapy alone $n = 12$	
Dysphagia	Mean change (range)		1 (−1, 3)	1 (0, 4)	
	Improved	1–3	7/9	10/12	
Proportion of patients	Unchanged	0	1/9	2/12	
	Worse or always full stop	−1	1/9	0/12	
Pain	Mean change (range)		2 (−1,8)	1 (−1,4)	
	Always no pain		2/9	4/12	
Proportion of patients	Improved		0/9	0/12	
	Unchanged		3/9	5/12	
	Worse		4/9	3/12	

Amdal et al. R&O 2013

- *Stent followed by brachy is preferable for patients in need for <u>immediate</u> dysphagia relief*

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Brachy w/wo EBRT

N=60

St III AEC-SCC

Tumor length 8.1 cm

HDR-BT

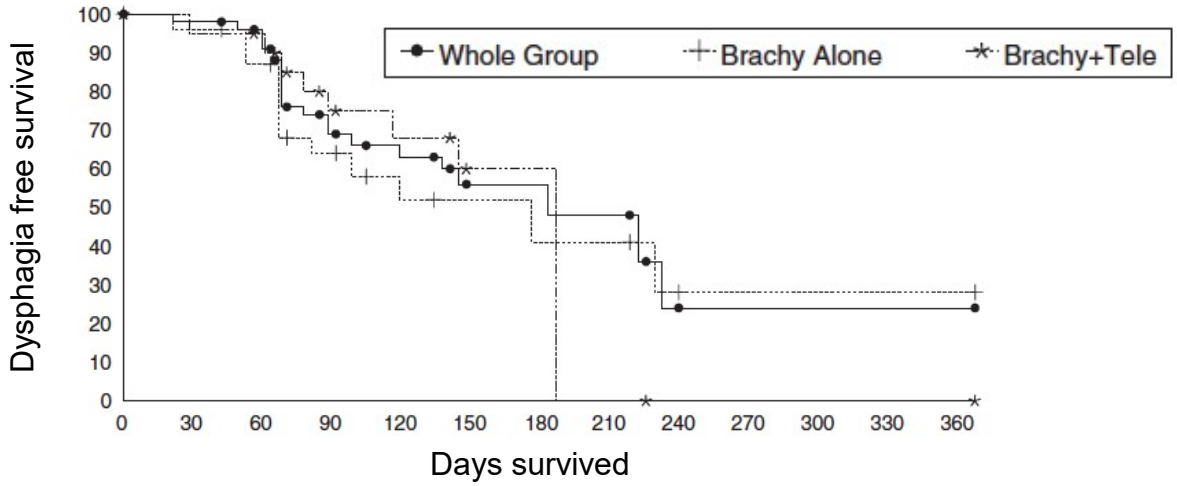
2x8 Gy (<1 wk)

R

No further treatment (N=30)

Primary endpoint: Dysphagia Relief

EBRT 10x3 Gy (N=28)



Sur et al. Brachytherapy 2004

- *HDR-BT + EBRT does not improve DFS/OS compared to HDR-BT*

ESTRO School

Brachy w/wo EBRT

N=219

65% St IIA
80% distal

SCC

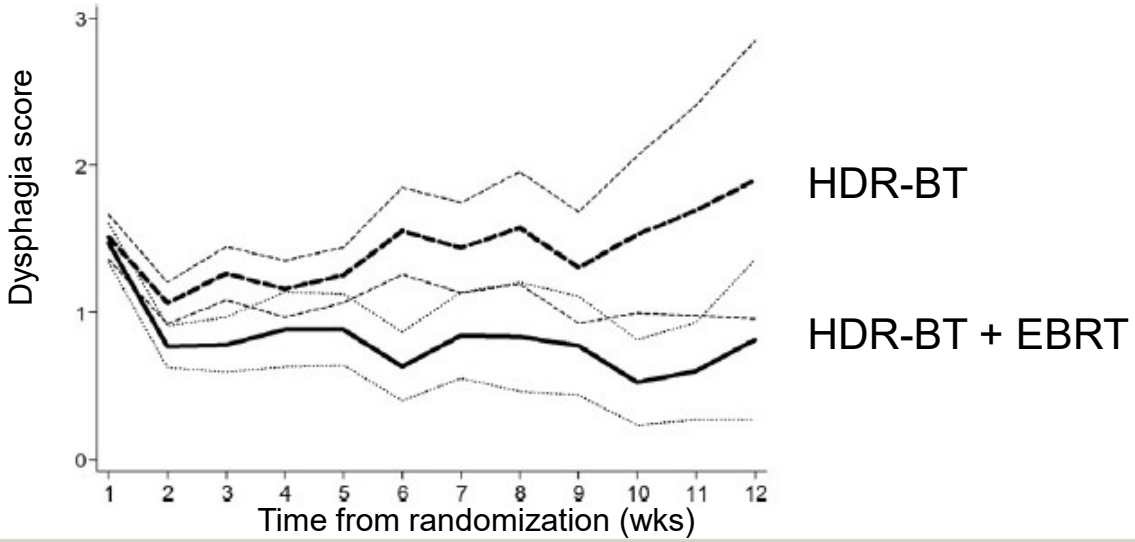
Tumor length
6.7 cm

R

HDR-BT (N=109)
2x8 Gy (<1 wk)

Primary endpoint: Dysphagia Relief Experience

HDR-BT + EBRT (N=110)
2x8 Gy + 10x3 Gy



Rosenblatt et al. R&O 2010

- *Symptom improvement occurs when EBRT is added to HDR-BT*
- *Combined treatment is well tolerated and relatively safe (similar OS)*

ESTRO School

Brachy: fractionation

N=232

Inoperable

SCC

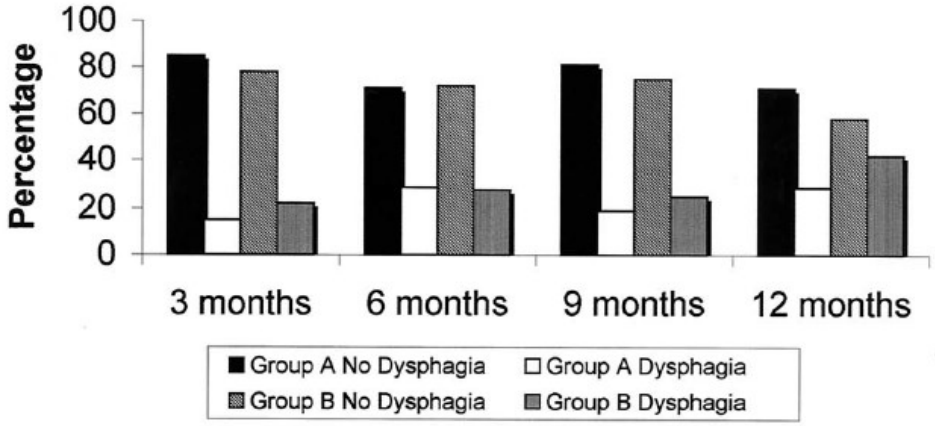
Tumor length 9.9 cm

R

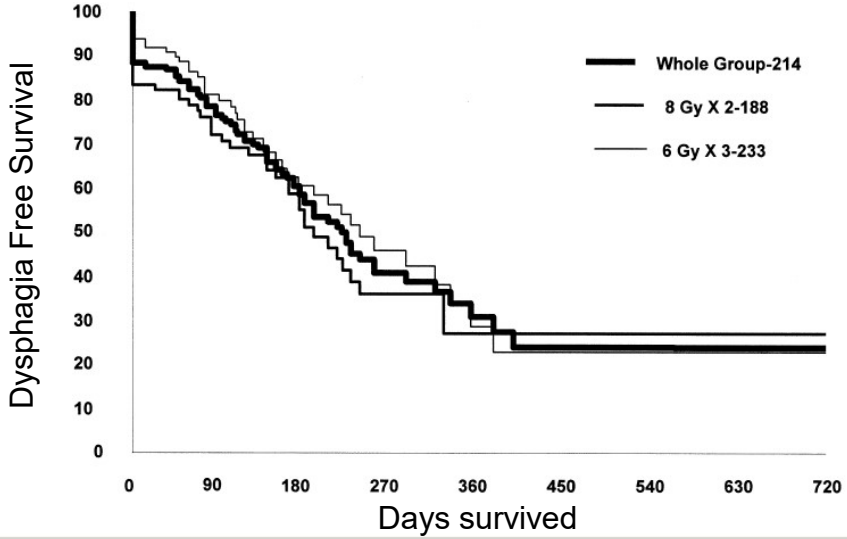
A. HDR-BT (N=112)
3x6 Gy

B. HDR-BT (N=120)
2x8 Gy

Primary endpoint: Dysphagia Free Survival



Sur et al. IJROBP 2002



- *Fractionated HDR-BT is effective palliation*
- *No difference in dose fractionation (fractionated vs. single dose BT?)*

ESTRO School

Stent w/wo EBRT

N=84

71% LA-EC
84% SCC

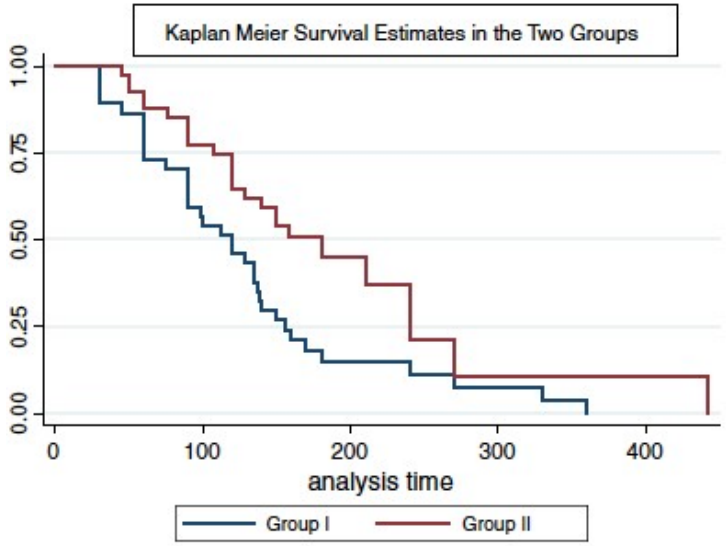
Tumor length
7 cm

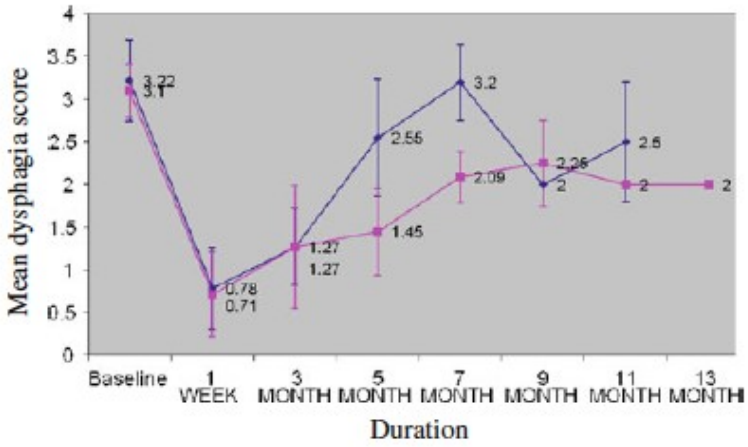
R

I. Stent (N=42)

Primary endpoint: Dysphagia Relief

II. Stent + EBRT (N=42)
10x3 Gy (<4-6 wks)



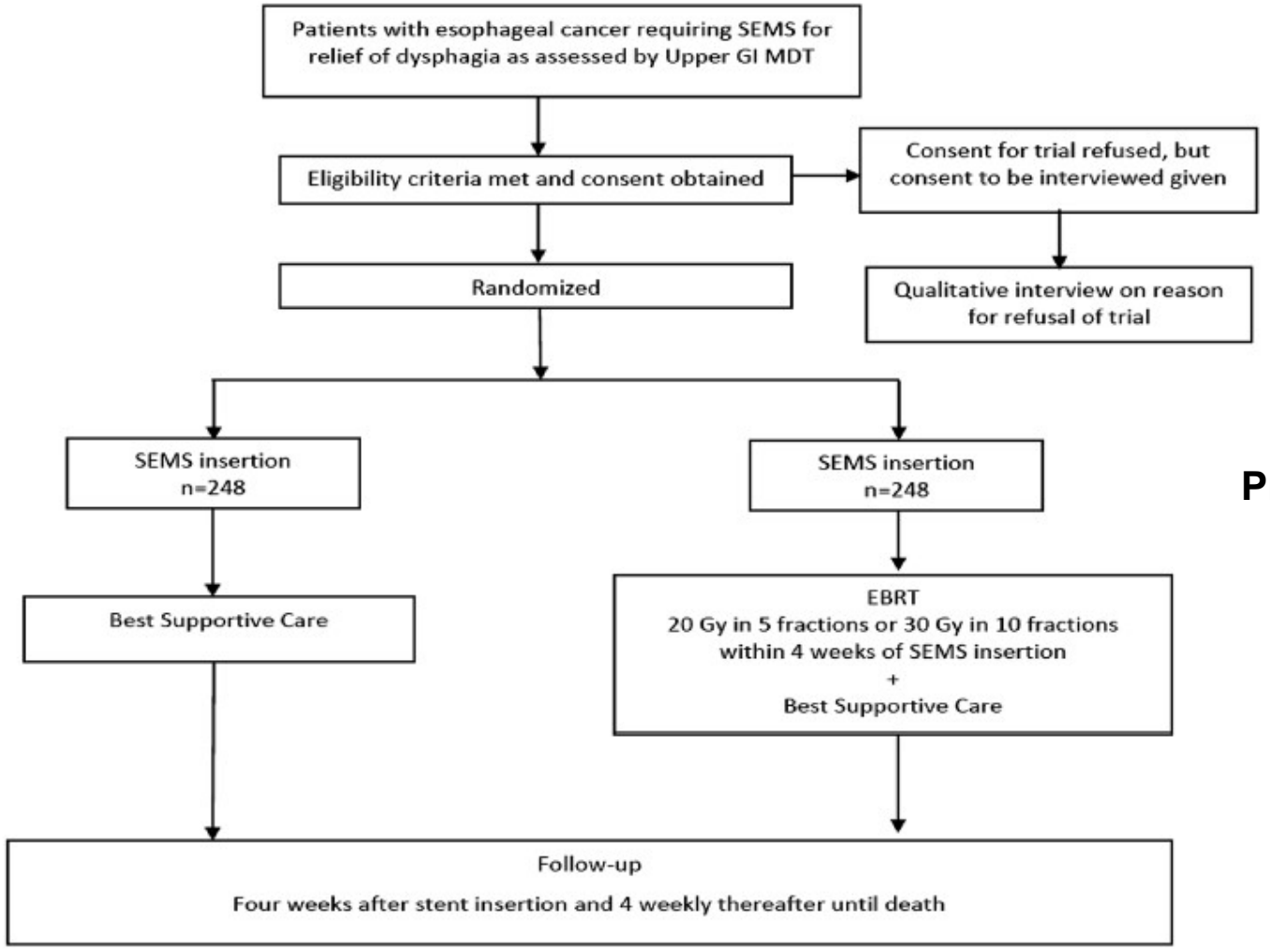


Javed et al. J Gastrointest Canc 2012

- *Post-stenting EBRT prolongs dysphagia relief and improves OS*
- *Major complications in 35% (p=ns)*

ESTRO School

Stent w/wo EBRT



ROCS trial

Primary endpoint: TTP of patient-reported dysphagia

Adamson et al. Trials 2014

Integrated pilot phase aims: that at least 70% of patients referred for SEMS are eligible for the study and that at least 50% consent to randomisation

ESTRO School

Summary

Use of brachytherapy and EBRT as palliative strategy in esophageal cancer

NKI 2007 - 2016 (n=335)

Treatment modality	N (%)
Brachytherapy	**67 (20)**
EBRT	**268 (80)**
13x3 Gy	153 (57)
10x3 Gy	81 (30)
5x4 Gy	19 (7)
4x6 Gy	2 (<1)
Not finished	13 (5)

Summary

- There are different strategies to alleviate dysphagia in LA-EC
- There is no consensus on the optimal intervention
- Systematic comparisons of different modalities are rare
- Chemotherapy can provide palliation, improve QOL and prolong OS
- Chemoradiotherapy is more effective than radiotherapy in terms of locoregional control
- Clinical benefit from chemotherapy, chemoradiotherapy and EBRT is slow in onset, and most patients are unfit

Summary

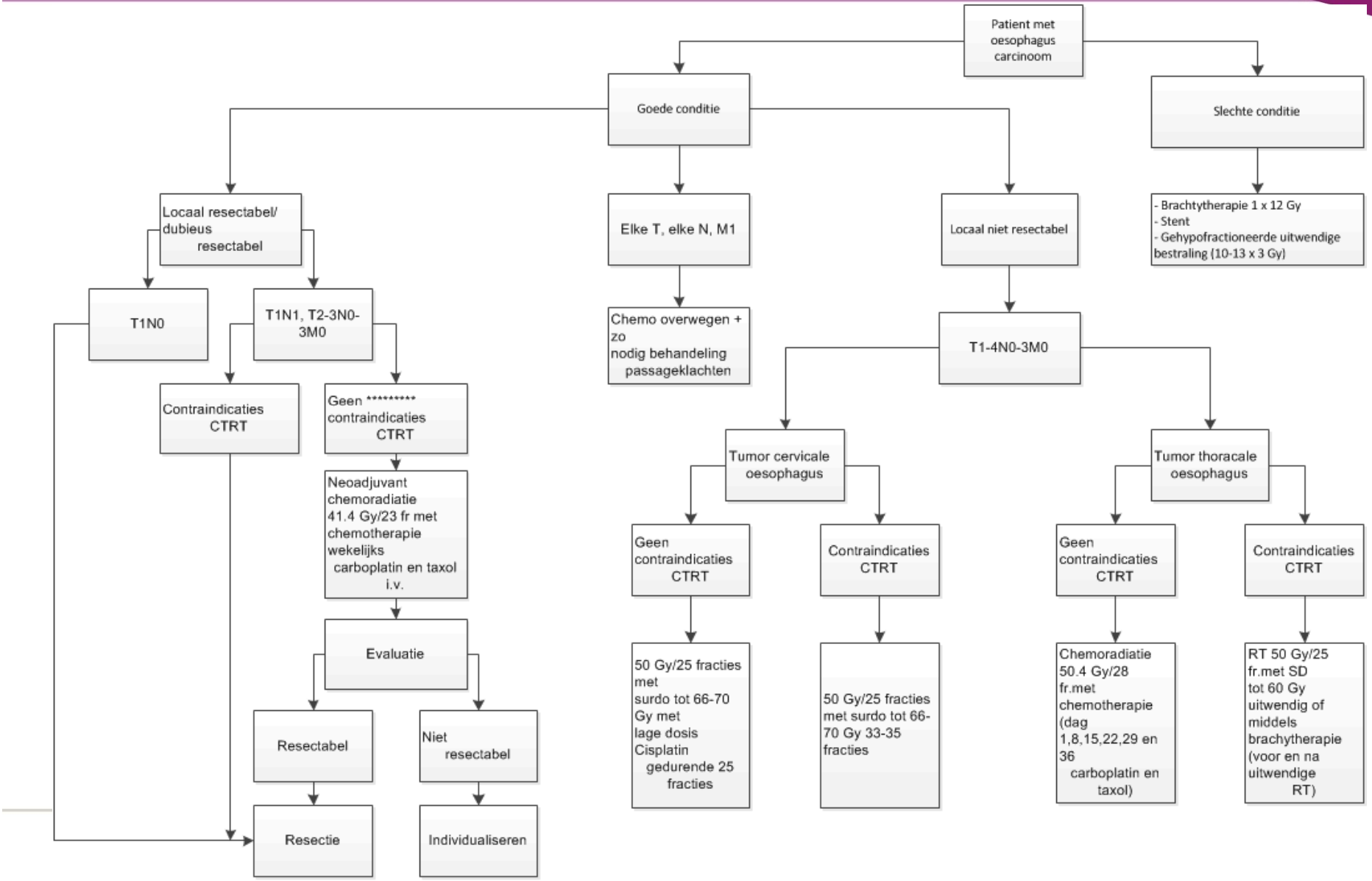
- More rapid relief of dysphagia can be obtained by SEMS or brachy
- SEMS improve dysphagia more rapidly than brachy
- Brachy (fractionated and single dose) effect is more sustained, less toxic and associated with better QOL than SEMS
- Adding EBRT to SEMS or brachy may improve/prolong dysphagia relief, but is intensive and associated with significant toxicity
- EBRT provides durable and effective relief of dysphagia, but reaches optimal effect up to 6 weeks after treatment

Summary

The regimen of choice depends on patient-, disease- and treatment-related factors:

- Chemoradiotherapy could be considered for patients in good condition, with a relatively good prognosis and oligometastatic disease
- Chemotherapy could be considered for patients in relatively good condition, with a life expectancy >6 months and metastatic disease
- EBRT is recommended for patients with a life expectancy between three and six months, when there is no need for immediate relief
- Brachytherapy is recommended for patients with a life expectancy between three and six months, where EBRT would take too long
- In patients with a shorter life expectancy or those with severe dysphagia/stenosing tumor, endoscopic stent placement is preferred, which offers instant relief of symptoms

Flow diagram



NB. TNM classificatie 7e editie

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UCCL UNIVERSITÄRES KREBSZENTRUM

Upper GI: technical and clinical challenges for radiation oncologists
26 March 2017, Rome

Systemic palliative chemotherapy of oesophageal cancer

Prof. Dr. med. Florian Lordick
Director
University Cancer Center Leipzig
UCCL

Oesophageal Cancer Chemotherapy in Metastatic Disease?

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v50–v57, 2016
doi:10.1093/annonc/mdw329

Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Lordick[1], C. Mariette[2], K. Haustermans[3], R. Obermannová[4] & D. Arnold[5] on behalf of the ESMO Guidelines Committee*

[1]University Cancer Centre Leipzig, University Hospital Leipzig, Leipzig, Germany; [2]Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Lille, France; [3]Department of Radiation Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; [4]Clinic of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute and Faculty of Medicine, Masaryk University, Brno, Czech Republic; [5]Instituto CUF de Oncologia, Lisbon, Portugal

Management of advanced/metastatic disease

Patients with metastatic oesophageal cancer can be considered for different options of palliative treatment depending on the clinical situation. Single-dose brachytherapy may be a preferred option even after external RT, since it provides better long-term relief of dysphagia with fewer complications than metal stent placement [I, B].

Chemotherapy is indicated for palliative treatment in selected patients, particularly for patients with AC who have a good PS [III, B].

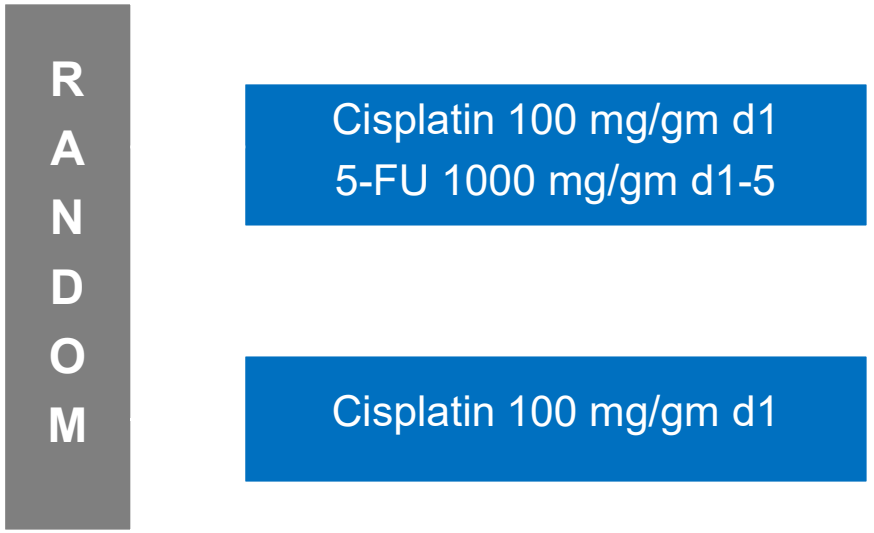
In squamous cell oesophageal cancer, the value of palliative combination chemotherapy is less proved. Therefore, BSC or palliative monotherapy should also be considered [II, B].

Lordick F et al. *Ann Oncol.* 2016; 27 (Supplement 5): v50–v57

Oesophageal Cancer „Standard Therapy“

- Phase II

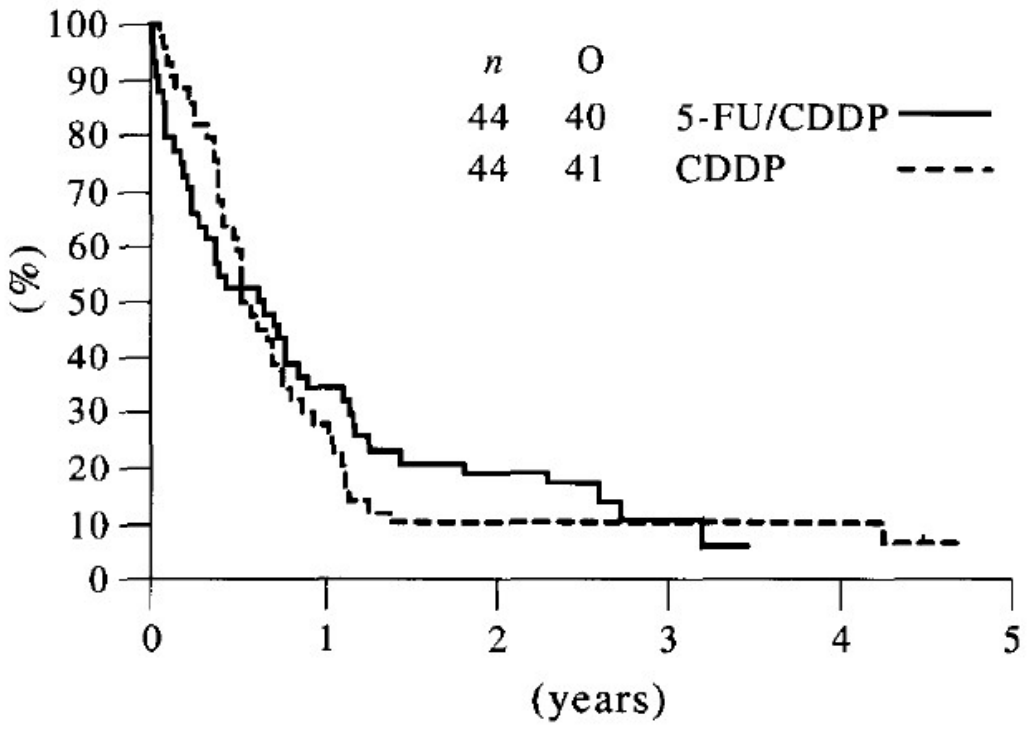
88 patients
Stage IV



	n Pat.	Response rate	Median survival
CDDP/5-FU	44	35%	33 weeks
CDDP mono	44	19%	28 weeks

Bleiberg et al. *Eur J Cancer* 1997; 33: 1216-20

Oesophageal Cancer „Standard Therapy“



Number of patients at risk:

44	15	8	3	0	5-FU/CDDP
44	12	3	2	2	CDDP

Figure 3. Overall survival.

Bleiberg et al. *Eur J Cancer* 1997; 33: 1216-20

Oesophageal Cancer
„Standard Therapy“

7 treatment-associated deaths (16%) in arm A (CDDP+5FU)

“The severe side-effects induced by the combination suggest that, currently, no standard chemotherapy can be recommended for patients with advanced squamous cell oesophageal cancer…“

and

“…chemotherapy should not be given to patients with advanced squamous cell oesophageal cancer outside of prospective studies.”

Bleiberg et al. *Eur J Cancer* 1997; 33: 1216-20

Oesophageal Cancer
Potential Alternatives (Low Evidence)

Cisplatin-Vinorelbin

Conroy et al. *Ann Oncol* 2002; 13: 721-9

Cisplatin-Irinotecan

Ilson et al. *J Clin Oncol* 1999; 17: 3270-5

Docetaxel-Capecitabin

Lorenzen et al. *Brit J Cancer* 2005; 92: 2129-33

Oesophageal Cancer „Personalized Medicine“

Only one positive approach thus far: Trastuzumab in HER2+++ adenocarcinoma

Trastuzumab in Oesophageal Adenocarcinoma (Toga)

Bang et al. *Lancet* 2010

Anti-EGFR antibodies (Cetuximab, Panitumumab)

Lordick et al. *Lancet Oncol* 2013
Waddell et al. *Lancet Oncol* 2013

EGFR-directed tyrosine kinase inhibitors (Gefitinib)

Dutton et al. *Lancet Oncol* 2014

MET / HGF directed antibodies (Onartuzumab, Rilotumumab)

Shah et al. *JAMA Oncol* 2016
Cunningham et al. ASCO 2015

Case Report

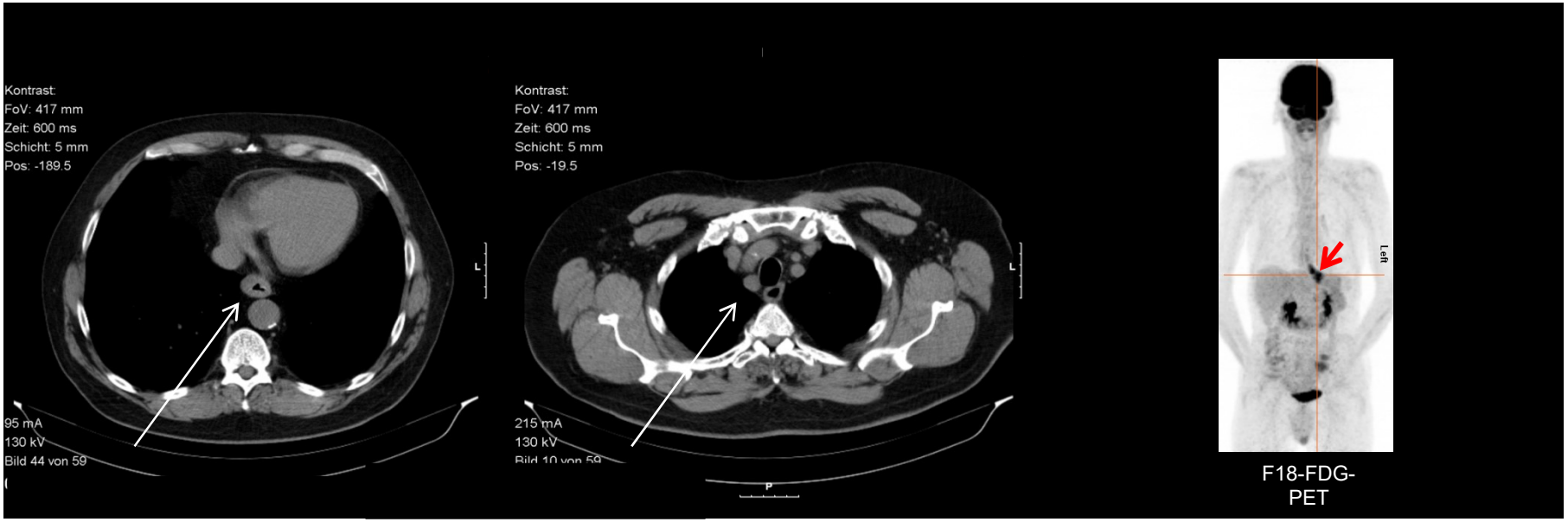
63 year old caucasian male, overweighed (BMI 30), arterial hypertension, diabetes

Adenocarcinoma of the Esophago-Gastric junction (AEG) type I (Siewert)

uT3, N+, cM0

Endoscopy: prominent 40-43cm from the incisors, circular growth pattern

Biopsy: highly differentiated, ulcerated adenocarcinoma



F18-FDG-PET

Case Report

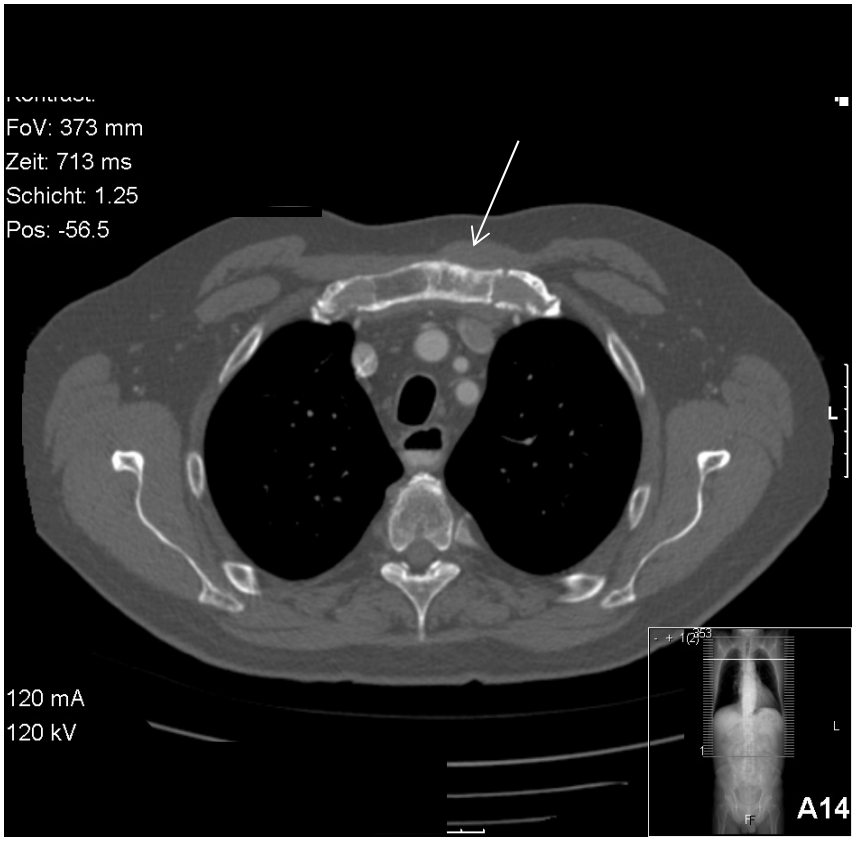
Tumor board decision and clinical course:

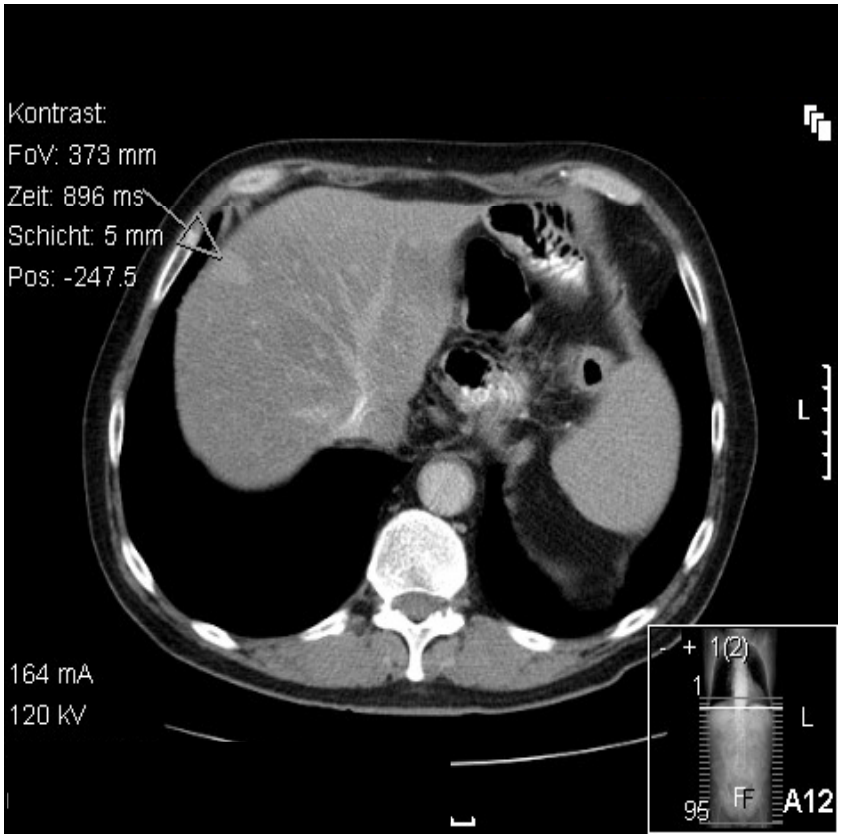
03-05/2015	3 x ECX (d1 epirubicin 50mg/m^2, cisplatin 60mg/m^2, d1-21 capecitabine 2x 625mg/m^2)
	during neoadjuvant chemotherapy, some episodes of dyspnoea
04/2015	cardiac catheterization, to rule out unstable angina
	CT-scan, to rule out pulmonary embolism
06/2015	surgery: extended gastrectomy with transhiatal
	resection of the distal esophagus and D2(?)-lymphadenectomy ypT_3, $pN_{1(1/14)}$, G_1, L_1, R_0,
	reconstruction: end-to-side esophagojejunostomy with
	roux-en-Y reconstruction
	histology showed no regression (Becker score 3)
07/2015	follow-up, no adjuvant chemotherapy

Case Report

09/15 suspected early relapse:

CT-scan: new liver lesion, enlargement of lymph nodes
(right upper mediastinum) and bone (sternum)

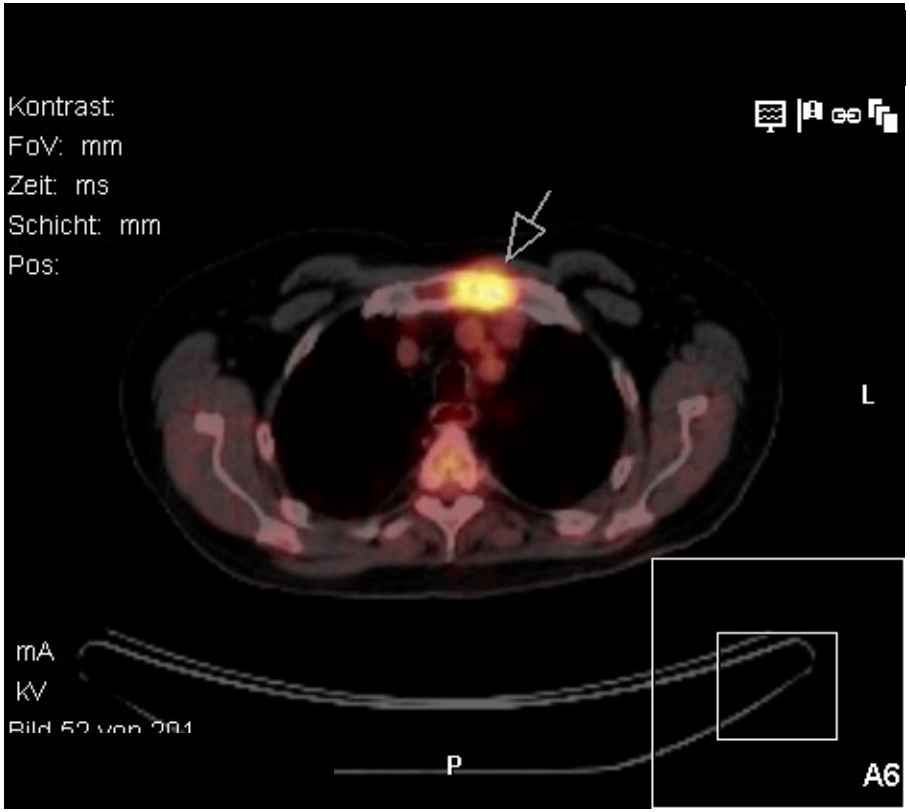


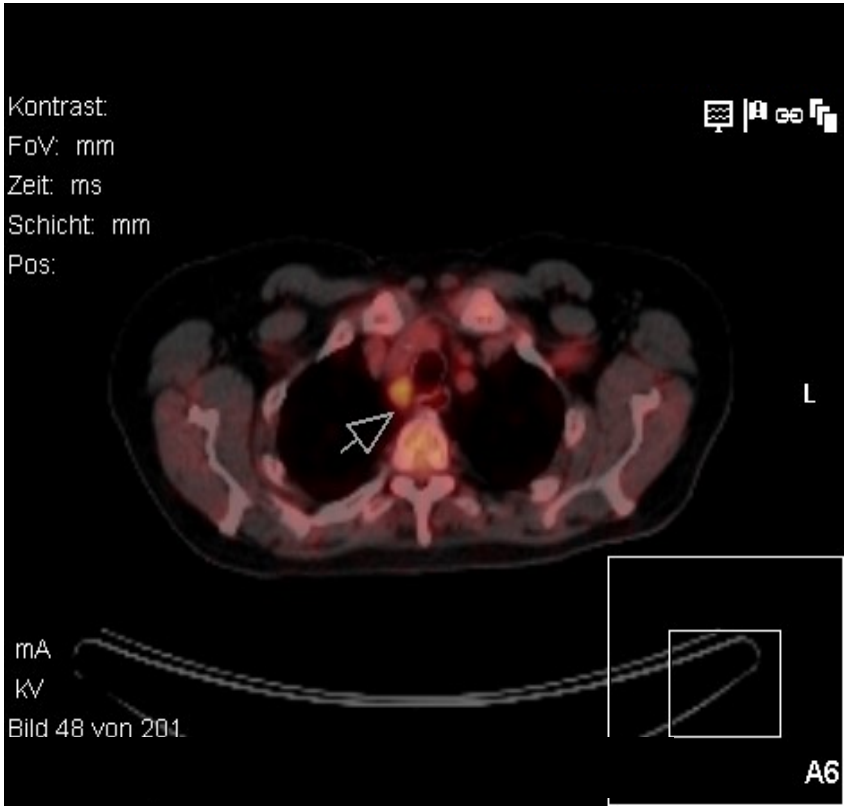


Case Report

Further evaluation

09/15 PET-CT-scan: enhanced FDG uptake sternum, lymph nodes, and liver SVIII,



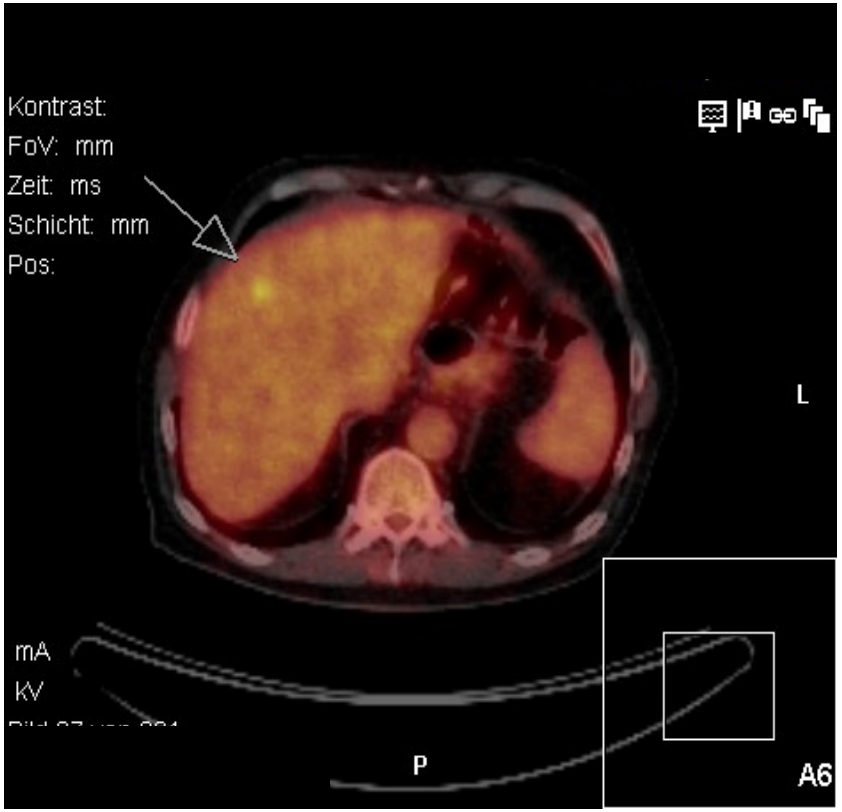


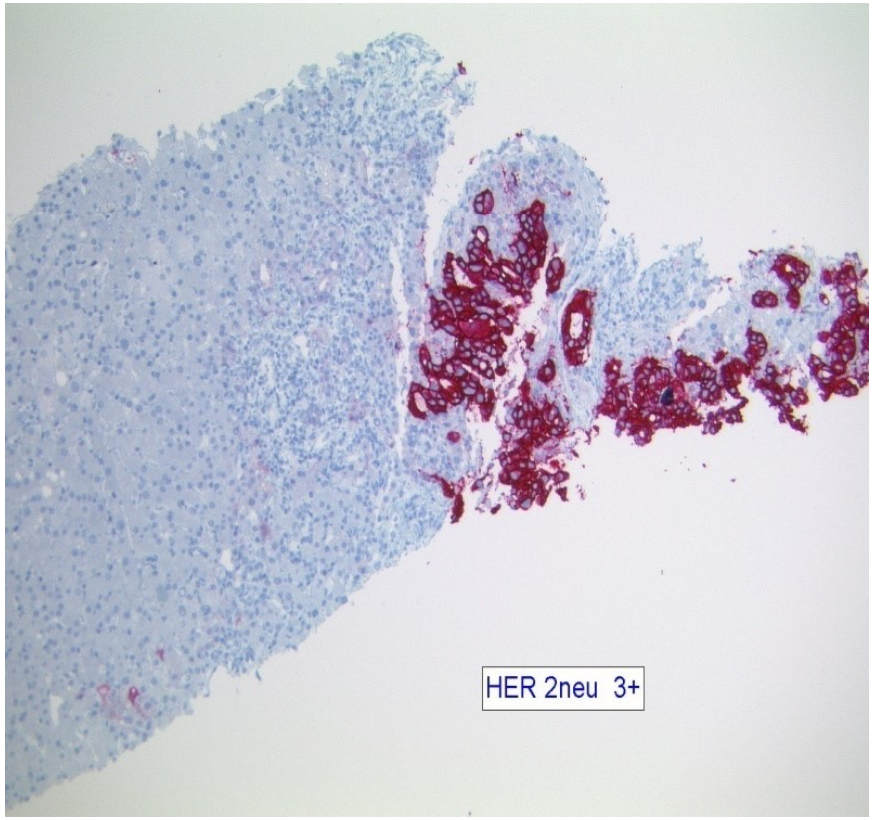
Case Report

Her2 assessment

Liver biopsy: Hercep-Score 3+

(strong and homogenous staining; FISH high amplification, ratio HER2:CEP17 = 9.7)





The removed primary tumor was also tested with a Hercep-Score 3+

Case Report

Clinical course

10/15-02/16	6 x CX (Cisplatin and Capecitabine)
	+ Trastuzumab (d1 8mg/kg / 6mg/kg) repeat d21
	+ Zoledronic acid
12/15	Very good remission (formally PR)
	Parenteral nutrition due to weight loss
01/16	Oesophagitis I°-II°
02-04/16	5 x Trastuzumab 6mg/m^2 repeat d22
05/16	Stopped because of polyneuropathy grade 3
	„Drug holiday“
08/16	Radiotherapy because of progressive pain (sternum)
02/17	Still in remission

Case Report

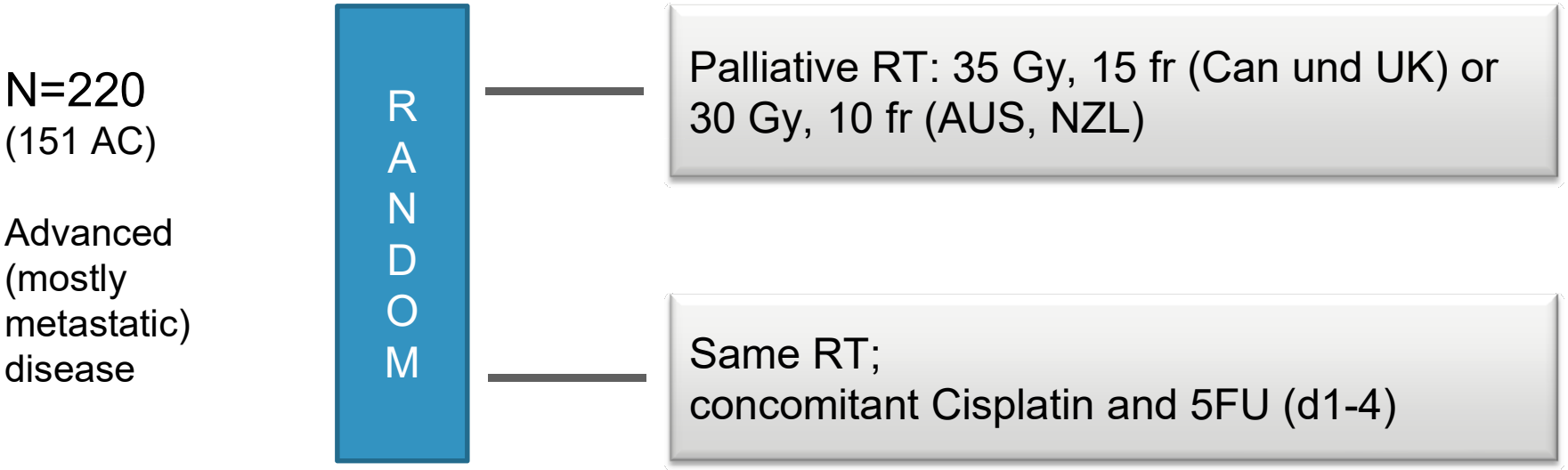
Summary

Locally advanced AEG type I (Siewert), Her2 positive

- 3x ECX + resection (extended gastrectomy)
- distant relapse 4 months after surgery
- 6 x CX + 11 x Trastuzumab
- 18 months after starting palliative chemotherapy
  the disease is well controlled (in durable remission)
- the symptomatic bone metastasis treated with radiotherapy

How to Control the Primary Tumor in Metastatic Disease

Prospective randomised study (AUS, NZL, CAN & UK)



Primary endpoint: improvement of dysphagia (≥1 pt on Mellow scale)

Penniment MG et al. *ASCO-GI* 2015; abstract 06

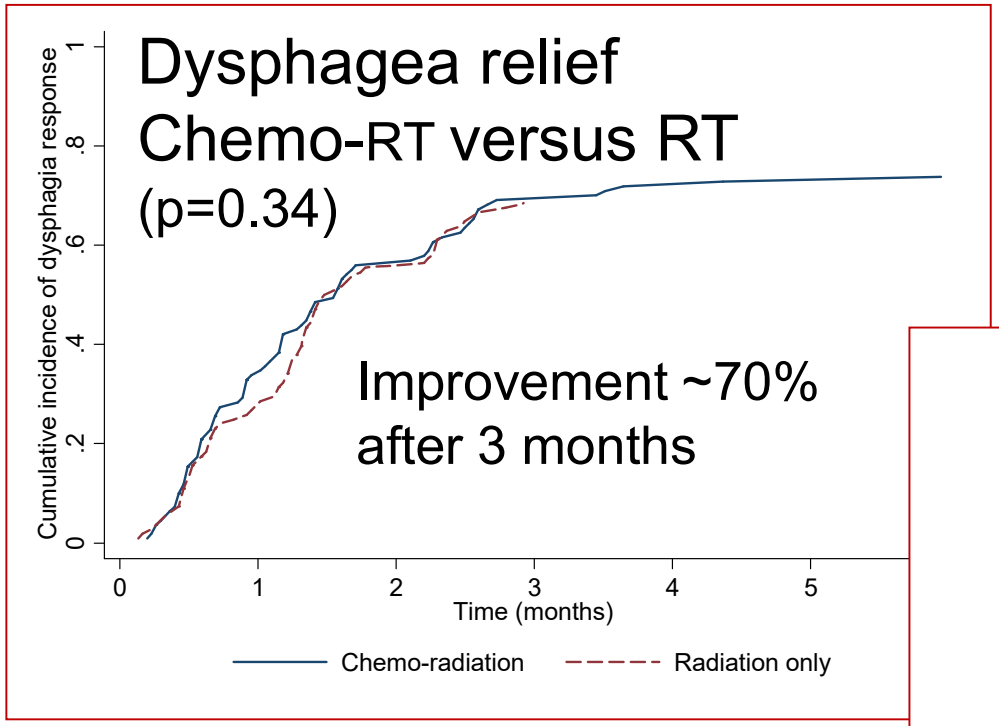
How to Control the Primary Tumor in Metastatic Disease

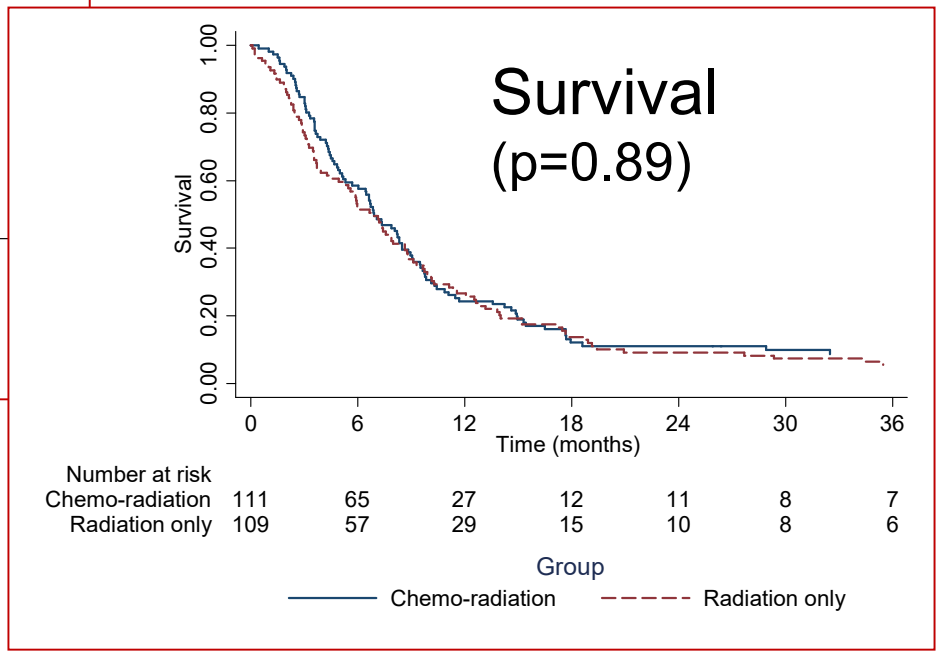
Combined radiochemotherapy is more toxic

Toxicity	Chemo-RT n (%)	RT n (%)
Oesophagitis	102/111 (92%)	94/109 (87%)
Skin toxicity	75/111 (67%)	62/109 (56%)
Mucositis	32/111 (29%)	11/109 (10%)
Intestinal side effects	54/111 (48%)	22/109 (20%)
Fever	22/111 (19%)	12/109 (11%)
Nausea & emesis	103/111 (92%)	85/109 (78%)
Other side effects	79/111 (71%)	61/109 (56%)

Penniment MG et al. *ASCO-GI* 2015; abstract 06

How to Control the Primary Tumor in Metastatic Disease





Radiatio without chemo sufficient for control of dysphagia

Penniment MG et al. *ASCO-GI* 2015; abstract 06

ARTICLE

OPEN

doi:10.1038/nature20805

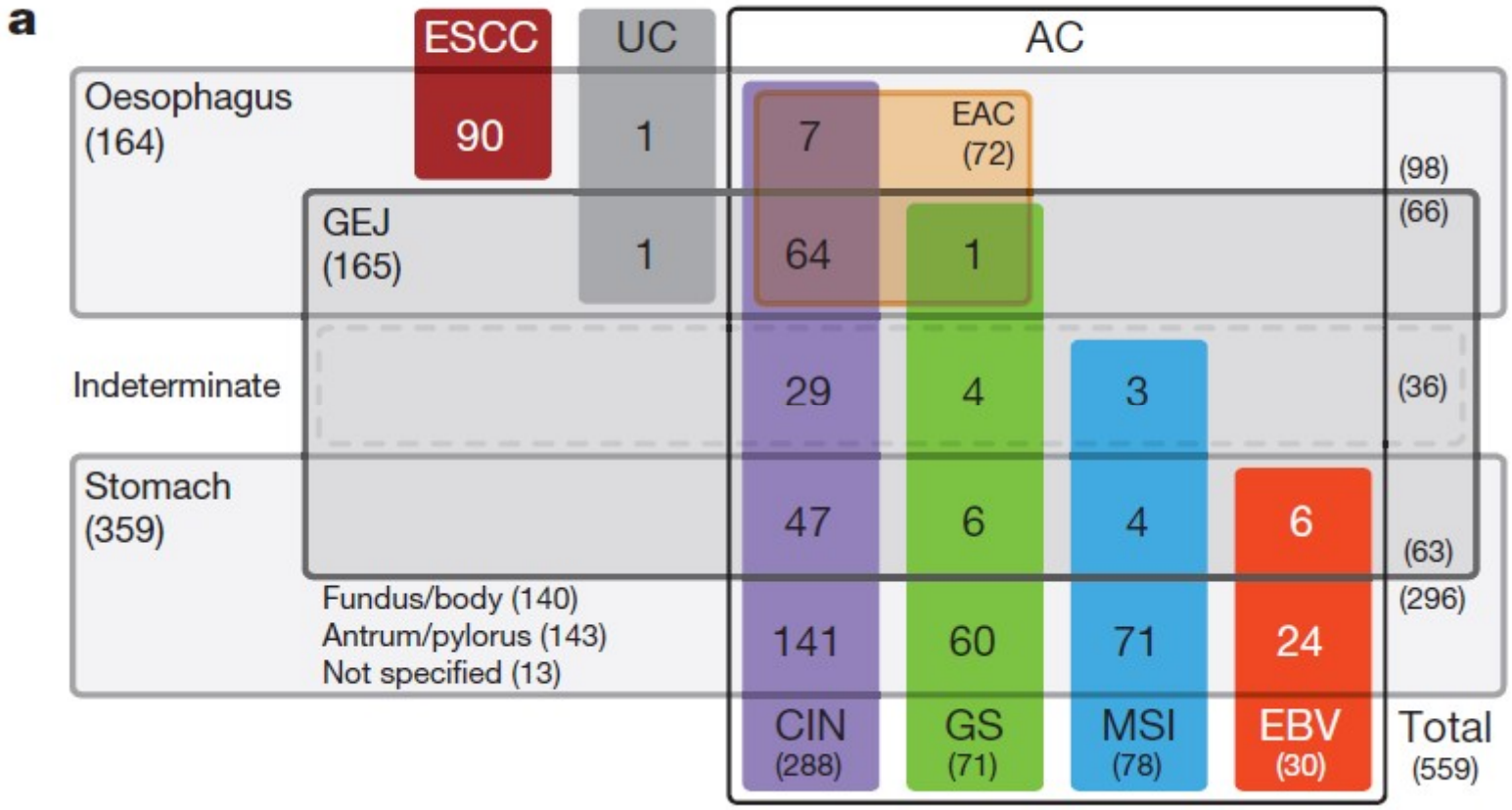
Integrated genomic characterization of oesophageal carcinoma

The Cancer Genome Atlas Research Network*

Oesophageal cancers are prominent worldwide; however, there are few targeted therapies and survival rates for these cancers remain dismal. Here we performed a comprehensive molecular analysis of 164 carcinomas of the oesophagus derived from Western and Eastern populations. Beyond known histopathological and epidemiologic distinctions, molecular features differentiated oesophageal squamous cell carcinomas from oesophageal adenocarcinomas. Oesophageal squamous cell carcinomas resembled squamous carcinomas of other organs more than they did oesophageal adenocarcinomas. Our analyses identified three molecular subclasses of oesophageal squamous cell carcinomas, but none showed evidence for an aetiological role of human papillomavirus. Squamous cell carcinomas showed frequent genomic amplifications of *CCND1* and *SOX2* and/or *TP63*, whereas *ERBB2*, *VEGFA* and *GATA4* and *GATA6* were more commonly amplified in adenocarcinomas. Oesophageal adenocarcinomas strongly resembled the chromosomally unstable variant of gastric adenocarcinoma, suggesting that these cancers could be considered a single disease entity. However, some molecular features, including DNA hypermethylation, occurred disproportionally in oesophageal adenocarcinomas. These data provide a framework to facilitate more rational categorization of these tumours and a foundation for new therapies.

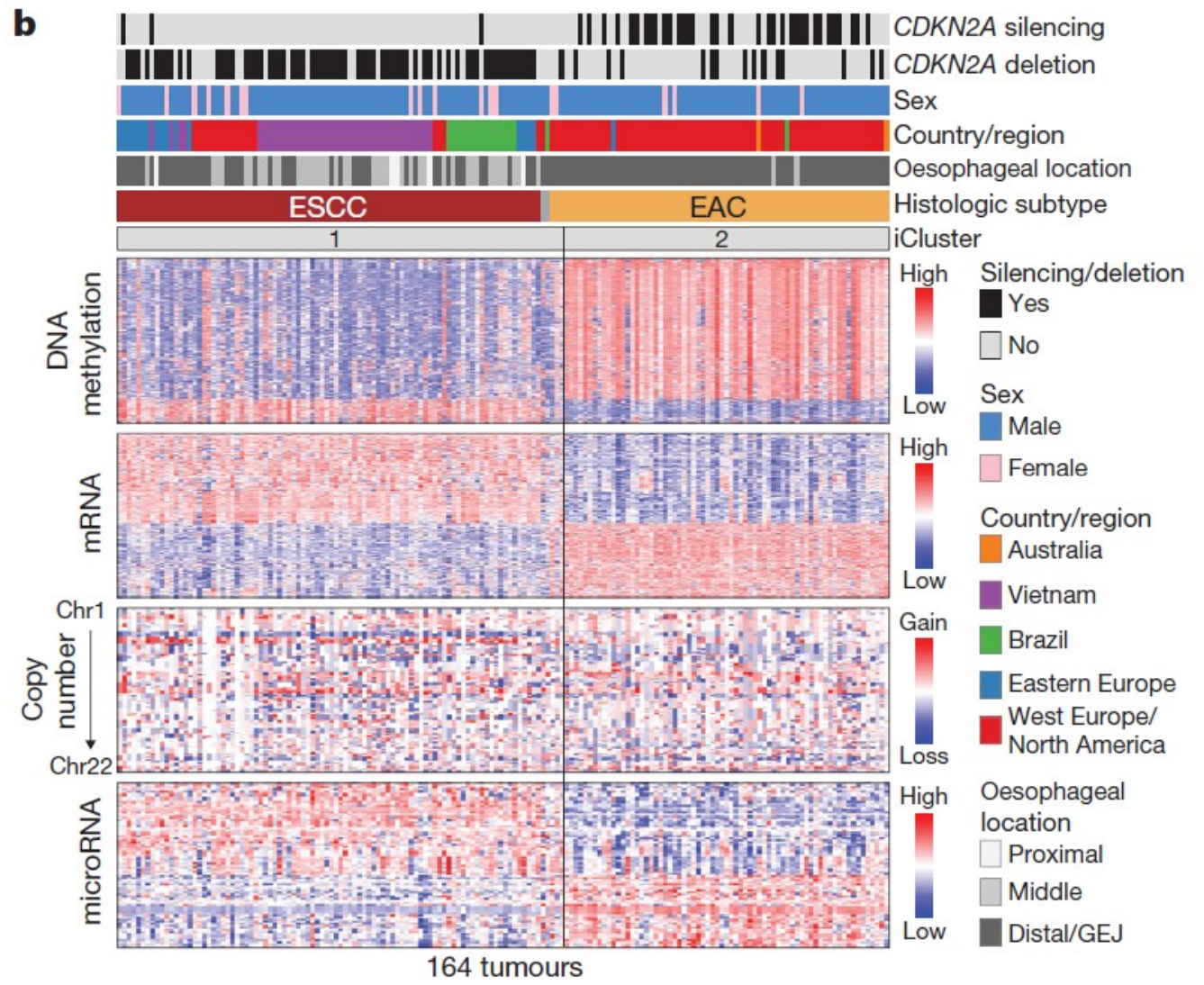
TCGA *Nature* 2017; 541: 169ff.

The Future – Molecular Characterisation



TCGA *Nature* 2017; 541: 169ff.

The Future – Molecular Characterisation



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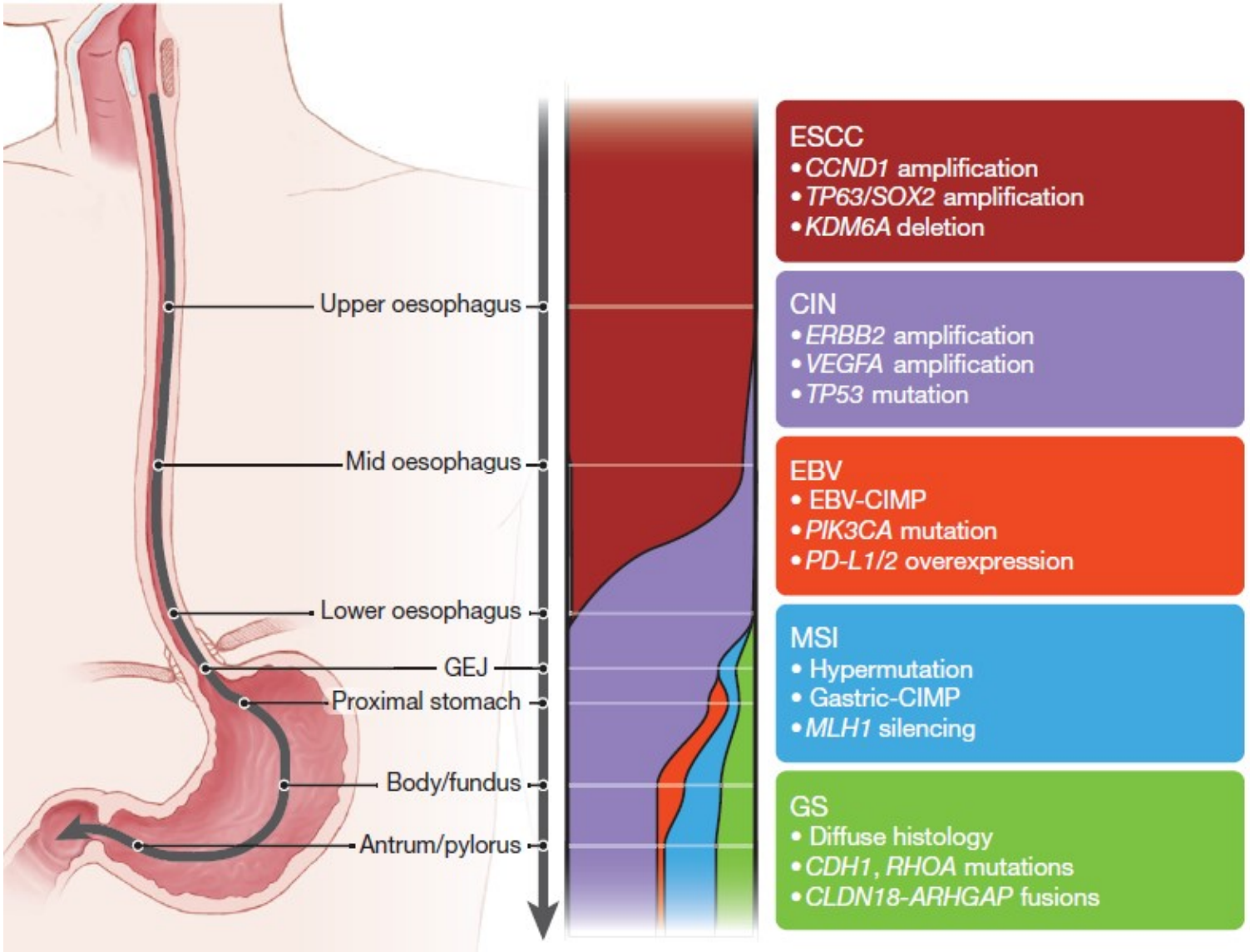
The Future – Molecular Characterisation



TCGA *Nature* 2017; 541: 169ff.

8–11 May 2019, Prague, Czech Republic

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13th INTERNATIONAL
GASTRIC CANCER CONGRESS IGCC 2019

INTERNATIONAL GASTRIC CANCER CONGRESS PRAGUE 2019

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Welcome

Dear Participants of the International Gastric Cancer Congress 2019,

With great pleasure we announce the **2019 International Gastric Cancer Congress to be held in Prague**. Gastric Cancer continues to be a major health problem in Europe, in the Asian-Pacific Region, in America, Middle East and Africa. From a worldwide perspective, almost 1 Mio patients are diagnosed with gastric cancer / year and 750.000 die from this aggressive cancer.

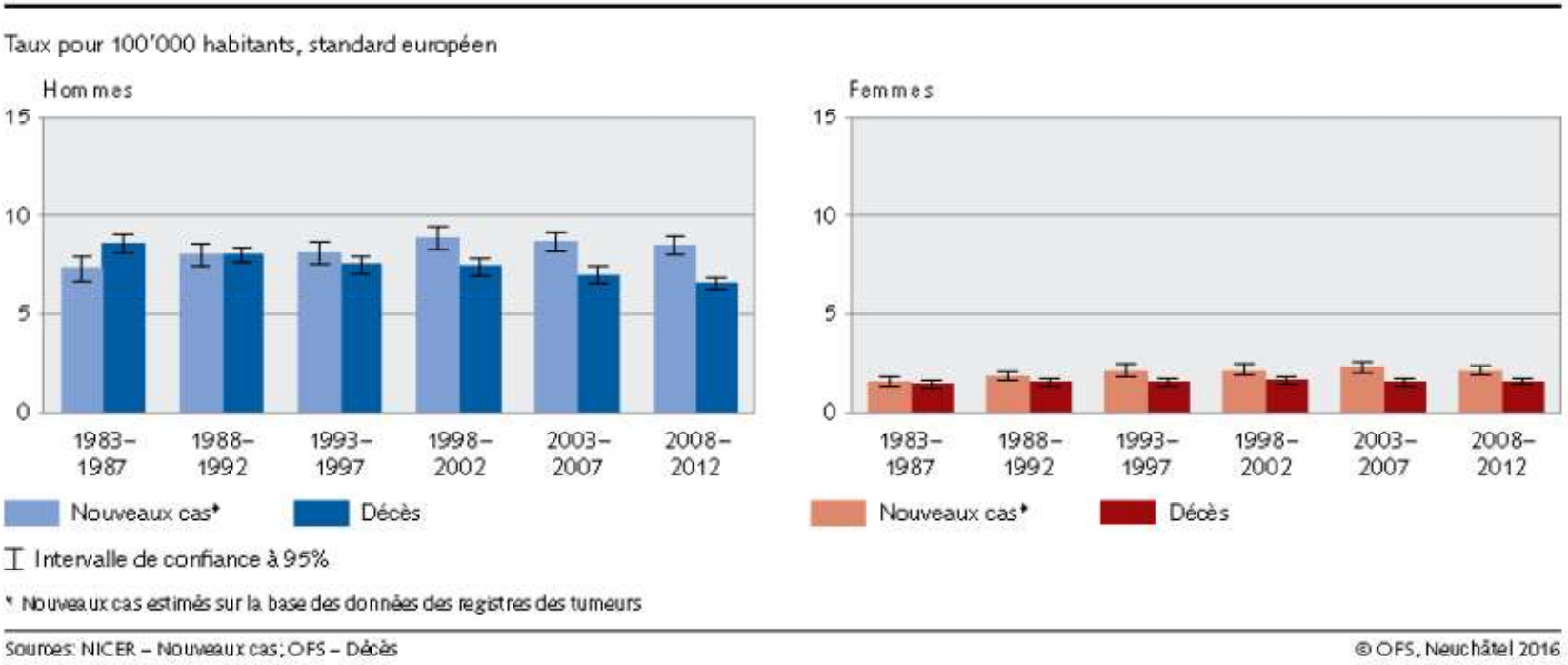
New perspectives in esophageal cancers

(Radiation-Oncologist perspective)

Prof Oscar Matzinger
Chef de service, service interdisciplinaire de cancérologie, Vevey, Switzerland
Médecin Agréé, service de radio-oncologie, CHUV, Lausanne

ESTRO School

Incidence (CH)



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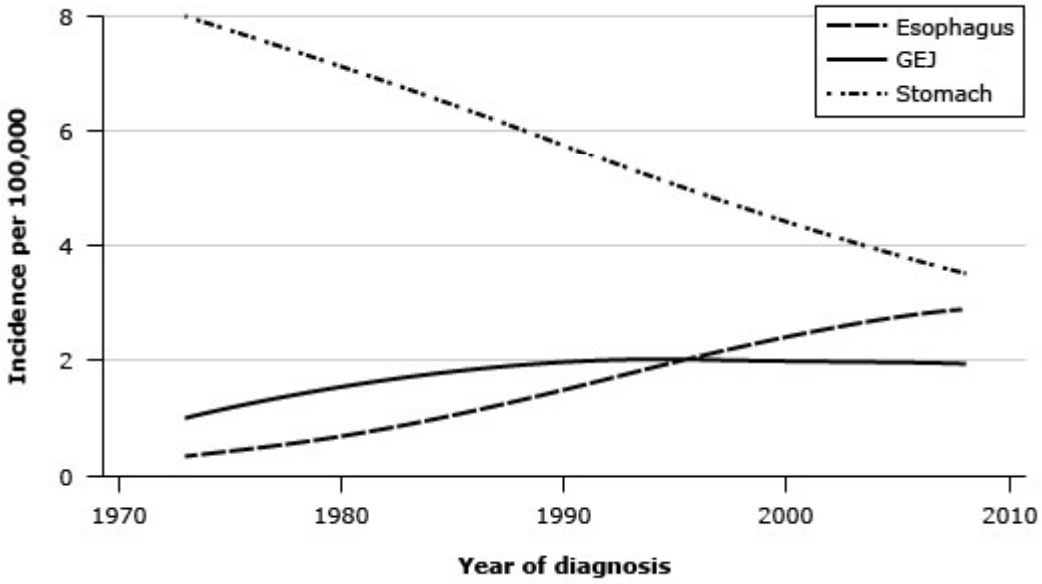
Incidence of carcinoma of the stomach, esophagus, and GEJ, 1973-2008

- *incidence of squamous cell carcinoma (SCC) is decreasing*
- *incidence of adenocarcinoma arising is rising*

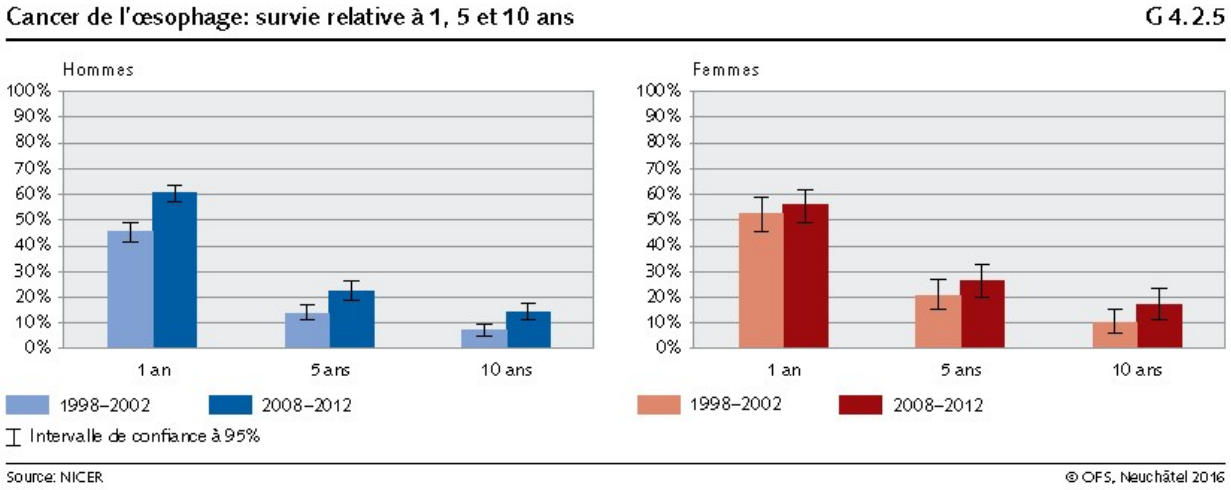


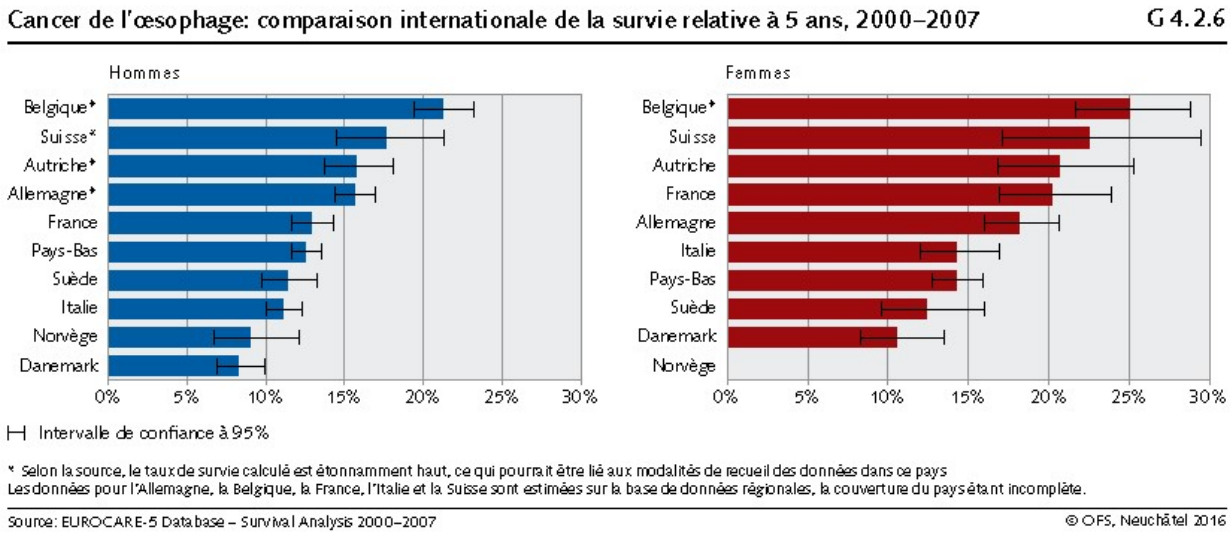
Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. Semin Radiat Oncol 2013; 23:3

ESTRO School

Survival

5-year survival rates of 12–20% in Western populations





Historical Perspective

For over a century, ***surgical resection***:
key modality for the treatment of EC

But ***outcomes*** with surgery were ***poor***

- High rates of postoperative complications
- High local and distant failure

Taylor, H. Oesophageal carcinoma treated by resection and presternal oesophago-gastrostomy. Proc. R. Soc. Med. 1947, 40, 465–466

Garlock, J.H. Progress in the Treatment of Carcinoma of the Oesophagus and Upper Stomach. Ann. R. Coll. Surg. Engl. 1948, 2, 183–188.

Garlock, J.H. Progress in the Treatment of Carcinoma of the Oesophagus and Upper Stomach. Surgery 1948, 23, 906–911.

Earlam, R.; Cunha-Melo, J.R. Oesophageal squamous cell carcinoma: I. A critical review of surgery. Br. J. Surg.1980, 67, 381–390.

Historical Perspective (2)

Improve local control (LC) after surgery ➔ ***postoperative radiotherapy***:

- improved LC
- patterns of failure shifted towards distant metastasis

- local failures were still not uncommon

The rise of radiosensitizing chemotherapy revolutionized care for EC

Scheel, A. The results of radiation treatment of esophageal cancer at Det Norske Radiumhospital. Acta Chir. Scand. **1952**, 103, 425–429.

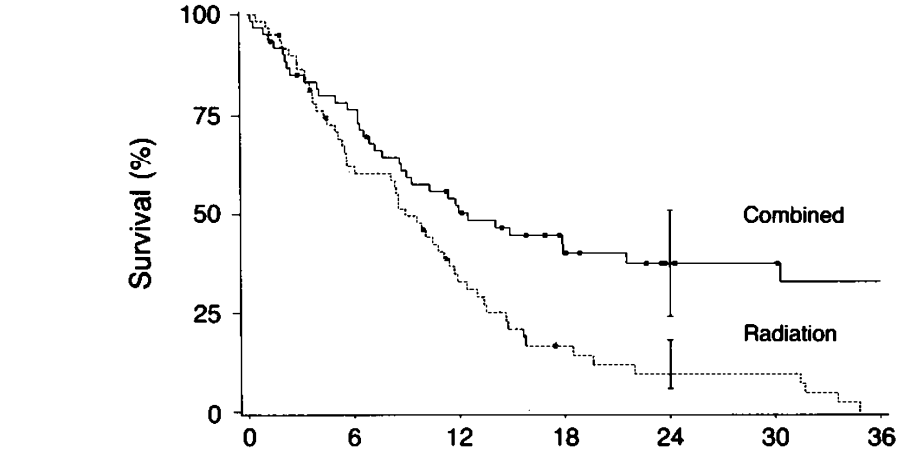
Davis,W.; Larionov, L.F. Progress in chemotherapy of cancer. Bull. World Health Organ. **1964**, 30, 327–341

Historical Perspective (3)

1992: Randomized trial

CRT versus RT alone

➔ aborted early owing to overall survival (OS) benefit for CRT



Patients at risk							
Combined therapy	61	45	28	18	10	9	7
Radiation therapy	60	35	17	7	4	4	0

Figure 1. Kaplan–Meier Plot of Survival in Patients with Esophageal Carcinoma Treated with Radiation Alone or with Radiation and Chemotherapy Combined.
Bars indicate 95 percent confidence intervals at 24 months.

Herskovic, A.; Martz, K.; Al-Sarraf, M.; Leichman, L.; Brindle, J.; Vaitkevicius, V.; Cooper, J.; Byhardt, R.; Davis, L.; Emami, B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N. Engl. J. Med. 1992, 326, 1593–1598

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Historical Perspective (4)

Many randomized studies comparing surgical resection with or without preoperative CRT

Table 1. Selected randomized trials examining neoadjuvant chemoradiation followed by surgery versus surgery alone.

Study	Groups	Chemotherapy	RT	Follow-up	Postoperative Complications	Mortality	L(R)R	Hospital Stay	Median OS
Walsh et al. * [9]	S (n = 55) vs. CRT + S (n = 58)	Cisplatin/5FU	40 Gy	0.8 years	Pulm: 58% vs. 48% Cardio: 24% vs. 24%	90 days: 4% vs. 9%	-	-	11 months vs. 16 months (p = 0.01)
Bosset et al. [15]	S (n = 139) vs. CRT + S (n = 143)	Cisplatin	18.5 + 18.5 split-course	4.6 years	General: 26% vs. 33% (p = 0.25)	Postoperative: 4% vs. 12% (p = 0.01)	RR 0.6, favoring CRT + S (p = 0.01)	24 days vs. 24 days (p > 0.05)	19 months vs. 19 months (p = 0.78)
Urba et al. [10]	S (n = 50) vs. CRT + S (n = 50)	Cisplatin/5FU/ vinblastine	45 Gy	8 years	Wound/GI: 10% vs. 14% (p > 0.05)	Postoperative: 4% vs. 2% (p > 0.05)	42% vs. 19% (p = 0.02)	-	18 months vs. 17 months (p = 0.15)
Burmeister et al. [11]	S (n = 128) vs. CRT + S (n = 128)	Cisplatin/5FU	35 Gy	5.4 years	Pulm: 28% vs. 20% Cardio: 11% vs. 12% GI: 5% vs. 5%	Postoperative: 5% vs. 4% (p > 0.05)	19% vs. 15%	14 days vs. 14 days (p > 0.05)	19 months vs. 22 months (p = 0.57)
Tepper et al. * [12]	S (n = 26) vs. CRT + S (n = 30)	Cisplatin/5FU	45 Gy	6 years	Pulm: 54% vs. 54% Cardio: 13% vs. 4% GI: 29% vs. 29%	Postoperative: 4% vs. 0% (p > 0.05)	15% vs. 13%	10 days vs. 12 days (p > 0.05)	21 months vs. 54 months (p = 0.002)
Van Hagen et al. [14]	S (n = 188) vs. CRT + S (n = 178)	Carboplatin/paclitaxel	41.4 Gy	3.8 years	Pulm: 44% vs. 46% Cardio: 17% vs. 21% GI: 30% vs. 22%	In-hospital: 4% vs. 4% (p = 0.70)	-	-	24 months vs. 49 months (p = 0.003)
Mariette et al. [16]	S (n = 97) vs. CRT + S (n = 98)	Cisplatin/5FU	45 Gy	7.8 years	Pulm: 53% vs. 40% Surg: 32% vs. 31% Infection: 11% vs. 18%	Postoperative: 3% vs. 11% (p = 0.05)	29% vs. 22% (p = 0.02)	15 days vs. 18 days (p = 0.80)	41 months vs. 32 months (p = 0.94)

RT, radiation therapy; L(R)R, loco(regional) recurrence; OS, overall survival; S, surgery; CRT, chemoradiotherapy; 5FU, 5-fluorouracil; Gy, Gray; RR, relative risk; GI, gastrointestinal (most commonly referring to anastomotic complications); * Denotes use of two-dimensional radiotherapy planning; remainder utilized three-dimensional conformal radiotherapy.

Historical Perspective (5)

Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS)

Large sample size

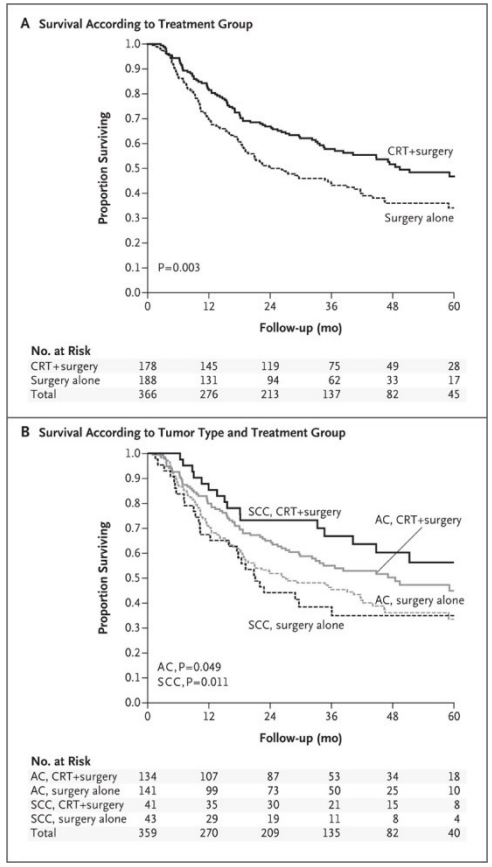
Most patients had adenocarcinoma, anatomically lower tumors

Chemotherapy regimen (carboplatin/paclitaxel)
Lower RT dose (41.4 Gy)

➔

Doubling OS: 48.6 months vs. 24.0 months.

There was also no observed increase in perioperative complications from neoadjuvant CRT



Van Hagen, P.; Hulshof, M.C.; van Lanschot, J.J.; Steyerberg, E.W.; van Berge Henegouwen, M.I.; Wijnhoven, B.P.; Richel, D.J.; Nieuwenhuijzen, G.A.; Hospers, G.A.; Bonenkamp, J.J.; et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N. Engl. J. Med. ***2012****, 366, 2074–2084.*

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Historical Perspective (6)

The success of combined CRT ➔
investigations if surgical resection is needed after CRT.

three prospective randomized trials:

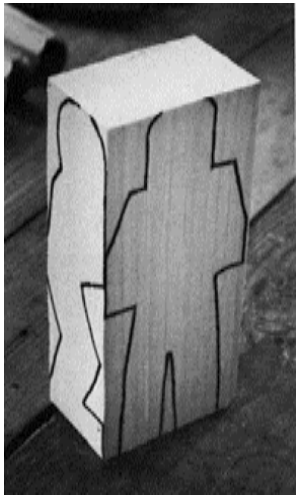
- No OS benefit
- Improved LC but higher mortality

Table 2. Randomized evidence comparing chemoradiation and surgery.

Study	Groups	Chemotherapy	RT	Follow-up	Mortality	LC	Hospital Stay	Median OS
Chiu et al. [17]	CRT (n = 36) vs. S (n = 44)	5FU, cisplatin	50-60 Gy	1.5 years	Operative: 7%	44% vs. 41% (p = 0.77)	41 days vs. 27 days (p = 0.02)	21 months vs. 24 months (p = 0.34)
Stahl et al. [18]	IC + CRT (n = 86) vs. IC + CRT + S (n = 86)	IC: 5FU, VP16, cisplatin CRT: cisplatin, VP16	65 + Gy (no S), 40 Gy (with S)	6 years	Postoperative: 4% vs. 13% (p = 0.03)	43% vs. 62% (p < 0.05)	-	15 months vs. 16 months (p > 0.05)
Bedenne et al. [19]	CRT (n = 130) vs. CRT + S (n = 129)	5FU, cisplatin	46 Gy continuous or 15 + 15 Gy split-course	4 years	3 months: 1% vs. 9% (p = 0.002)	57% vs. 66% (p < 0.05)	52 days vs. 68 days (p = 0.02)	19 months vs. 18 months (p = 0.49)

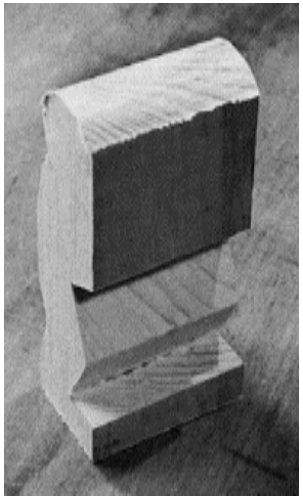
RT, radiation therapy; LC, local control; OS, overall survival; CRT, chemoradiotherapy; S, surgery; 5FU, 5-fluorouracil; Gy, Gray; IC, induction chemotherapy; VP16, etoposide.

Radiotherapy: 2D-CRT → IMRT



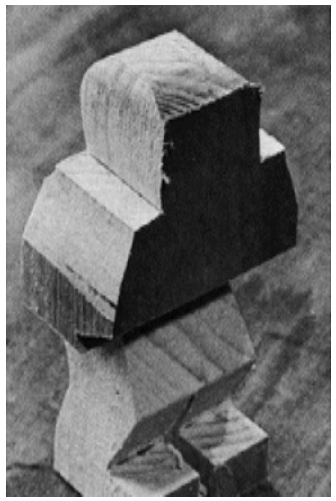
1950-1970

RT 2D



1970-1990

RT 3D



1990-2000

IMRT

Many trials in EC have utilized 3DCRT, including the CROSS trial

No randomised study…

Dose to organs at risk correlate with postoperative complications

Lee, H.K.; Vaporciyan, A.A.; Cox, J.D.; Tucker, S.L.; Putnam, J.B., Jr.; Ajani, J.A.; Liao, Z.; Swisher, S.G.; Roth, J.A.; Smythe,W.R.; et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: Correlation with pulmonary dose-volume histogram parameters. Int. J. Radiat. Oncol. Biol. Phys. **2003**, 57, 1317–1322.

Wang, J.; Wei, C.; Tucker, S.L.; Myles, B.; Palmer, M.; Hofstetter, W.L.; Swisher, S.G.; Ajani, J.A.; Cox, J.D.; Komaki, R.; et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. Int. J. Radiat. Oncol. Biol. Phys. **2013**, 86, 885–891.

Tucker, S.L.; Liu, H.H.; Wang, S.; Wei, X.; Liao, Z.; Komaki, R.; Cox, J.D.; Mohan, R. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int. J. Radiat. Oncol. Biol. Phys. 2003, 66, 754–761.

Dose to organs at risk correlate with outcome

Lin, S.H.;Wang, L.; Myles, B.; Thall, P.F.; Hofstetter,W.L.; Swisher, S.G.; Ajani, J.A.; Cox, J.D.; Komaki, R.; Liao, Z. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy for esophageal cancer. Int. J. Radiat. Oncol. Biol. Phys. 2012, 84, 1078–1085.

Retrospective, IMRT-based treatment for EC

Table 3. Selected retrospective studies examining neoadjuvant intensity-modulated radiotherapy and chemotherapy followed by surgery.

Study	*N*	Chemotherapy	RT	Follow-up	Postoperative Complications	L(R)R	DM (+/− LR)	Median OS
La et al. [28]	30	Various	50.4 Gy	24 months	-	37%	40%	-
Wang et al. [26]	164	Various	50.4 Gy		Pulm: 24% Cardio: 17% GI: 18% Wound: 12% Death: 2% Hospital stay: 10 d	-	-	-
Shridhar et al. [29]	58	Cisplatin/5FU	50.4 Gy	19 months	Death: 5%	-	-	33 months
Preilich et al. [30]	138	Cisplatin/5FU	50.4 Gy	19 months	-	12%	26%	31 months
Zeng et al. [31]	17	Cisplatin/5FU	50.4 Gy; boost to 56 Gy	54 months	Surgical leak: 24%	11%	40%	29 months

N, sample size; RT, radiation therapy; L(R)R, loco(regional) recurrence; DM, distant metastasis; OS, overall survival; Gy, Gray; GI, gastrointestinal; 5FU, 5-fluorouracil.

MD Anderson, retrospective

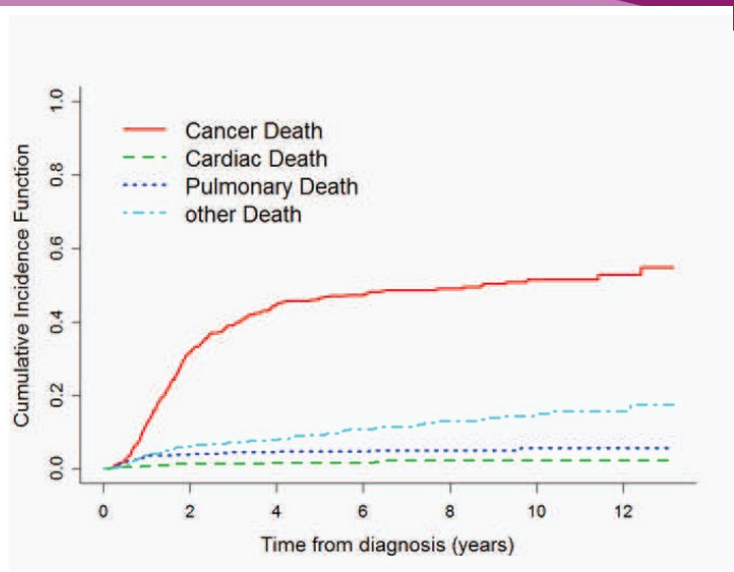
676 patients

- 413 3DCRT
- 263 IMRT

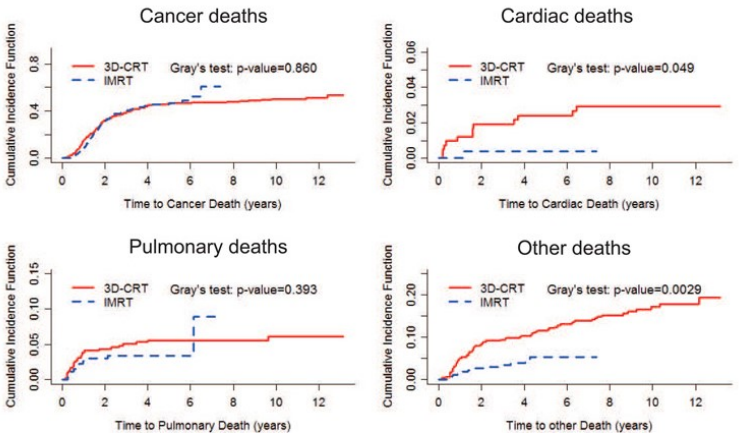
IMRT worse performance status

➔ *3DCRT modality independent predictor of all-cause mortality*
➔ *fewer postsurgical gastrointestinal and pulmonary complications with IMRT*

A.



B.



Lin, S.H.;Wang, L.; Myles, B.; Thall, P.F.; Hofstetter,W.L.; Swisher, S.G.; Ajani, J.A.; Cox, J.D.; Komaki, R.; Liao, Z. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy for esophageal cancer. Int. J. Radiat. Oncol. Biol. Phys. **2012**, 84, 1078–1085.

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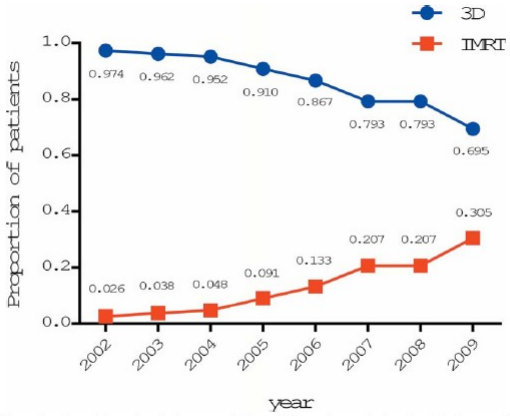
Analysis of two large cancer registries

2 databases:

- Surveillance, Epidemiology End Results (SEER)-Medicare
- Texas Cancer Registry-Medicare

2553 patients aged>65 years with nonmetastatic EC

- diagnosed between 2002 and 2009 and were
- treated with either 3D (2240 patients) or IMRT (313 patients)



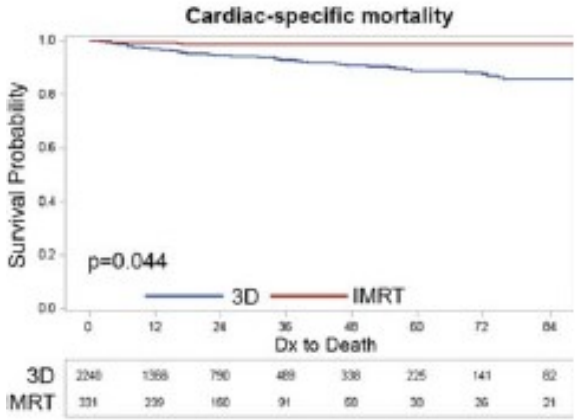


Figure 1. The use of 3-dimensional conformal radiotherapy (3D) and intensity-modulated radiotherapy (IMRT) for the treatment of esophageal cancer from 2002 to 2009.

Lin, S.H.; Zhang, N.; Godby, J.; Wang, J.; Marsh, G.D.; Liao, Z.; Komaki, R.; Ho, L.; Hofstetter, W.L.; Swisher, S.G.; et al. Radiation modality use and cardiopulmonary mortality risk in elderly patients with esophageal cancer. Cancer **2016**, 122, 917–928.

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Protons ?

- Proximity of esophagus, lungs, and heart

&

- Operative procedure in the chest after CRT

➔

Dosimetric advantage:

Decreasing doses to surrounding areas may prove clinically advantageous in terms of overall toxicities and postoperative complications

Chuong, M.D.; Hallemeier, C.L.; Jabbour, S.K.; Yu, J.; Badiyan, S.; Merrell, K.W.; Mishra, M.V.; Li, H.; Verma, V.; Lin, S.H. Improving outcomes for esophageal cancer using proton beam therapy. Int. J. Radiat. Oncol. Biol. Phys. **2016**, 95, 488–497.

Proton, clinical results

2 series from ***Japan*** and ***MD Anderson Cancer Center***

Table 4. Selected retrospective studies examining concurrent proton beam therapy and chemotherapy.

Study	*N*	Chemotherapy	RT	Follow-up	Postoperative Complications	L(R)R	DM (+/− LR)	3-Year OS
Ishikawa et al. [42]	40	Cisplatin/5FU	60 GyE	24 months	-	34%	-	70%
Lin et al. [43]/ Wang et al. [39]	62	Various	50.4 GyE	20 months	Pulm: 14% GI: 18% Death: 0% Hospital stay: 9 d	31%	26%	52%

N, sample size; RT, radiation therapy; L(R)R, loco(regional) recurrence; DM, distant metastasis; OS, overall survival; 5FU, 5-fluorouracil; GyE, Gray-equivalent; GI, gastrointestinal.

MD Anderson: 47% post-CRT resection

➔ pCR 28%
➔ Postoperative wound complication 3%, cardiac complication 8%, pulmonary complication 7%
➔ 3 year OS 52%.

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Prospective trials and PBT

- Phase II trial being conducted at Loma Linda Medical Center: evaluate outcomes in a targeted population of 38 resectable patients undergoing carboplatin/paclitaxel and PBT

  (NCT01684904)

- Randomized phase IIB trial by MD Anderson is targeting 180 patients to compare chemo-PBT versus chemo-IMRT

  (NCT01512589)

Targeted therapies?

EGFR:

The SCOPE1 trial: addition of cetuximab to standard chemoradiation for localized esophageal cancers

Stop before phase 3 chemoradiation plus cetuximab ➔ shorter median OS and more grade 3 and 4 toxicities

Crosby T, Hurt CN, Falk S, Gollins S, Mukherjee S, Staffurth J, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): A multicentre, phase 2/3 randomised trial. Lancet Oncol. 2013;14(7):627–37

HER2:

Overexpressed in gastric & GEJ tumor ➔ Positive TOGA trial

➔ RTOG 1010 ongoing

VEGF:

AVAGAST trial randomized inoperable locally advanced or metastatic gastric or GEJ adenocarcinomas to bevacizumab or placebo with capecitabine and cisplatin

➔Survival did not reach statistical significance

Shen L, Li J, Xu J, Pan H, Dai G, Qin S, et al. Bevacizumab plus capecitabine and cisplatin in chinese patients with inoperable locallyadvanced or metastatic gastric or gastroesophageal junction cancer: Randomized, double-blind, phase III study (AVATAR study). Gastric Cancer. 2015;18(1):168–76

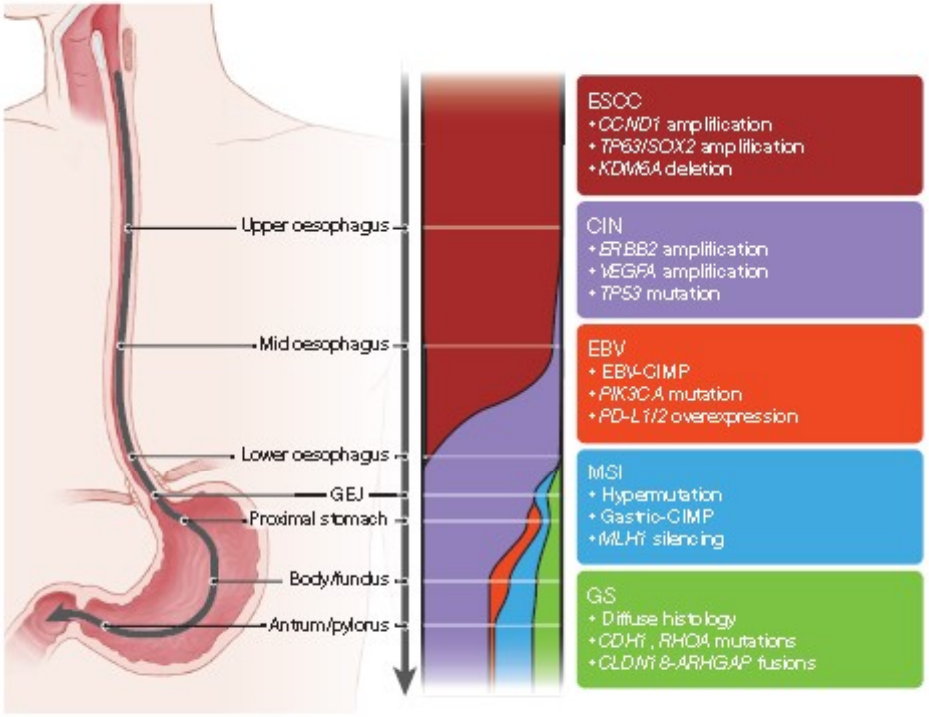


Figure 6 | Gradations of molecular subclasses of gastroesophageal carcinoma. Schematic representing shifting proportion of subtypes of gastroesophageal carcinoma from the proximal oesophagus to the distal stomach. The widths of the colour bands represent the proportion of the subtypes present within anatomic regions. Key features of subtypes are indicated in associated text.

Ongoing trials:

Other avenues currently being explored:

- immune checkpoint inhibitors:
  PD-L1 and PD-1 (pembrolizumab and nivolumab)
- c-MET
- heat shock protein
- Hedgehog pathways.
- …

Post-induction therapy FDG PET

clinically useful in the selection of subsequent therapy?:

➔identify CR ➔ avoid surgery

Outcomes of patients with esophageal cancer staged with [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? Monjazeb AM, Riedlinger G, Aklilu M, Geisinger KR, Mishra G, Isom S, Clark P, Levine EA, Blackstock. J Clin Oncol. 2010;28(31):4714

But: not confirmed in

Utility of (18)F-FDG PET for Predicting Histopathologic Response in Esophageal Carcinoma following Chemoradiation. Arnett AL, Merrell KW, Macintosh EM, James SE, Nathan MA, Shen KR, Ravi K, Neben Wittich MA, Haddock MG, Hallemeier. J Thorac Oncol. 2017 Jan;12(1):121-128

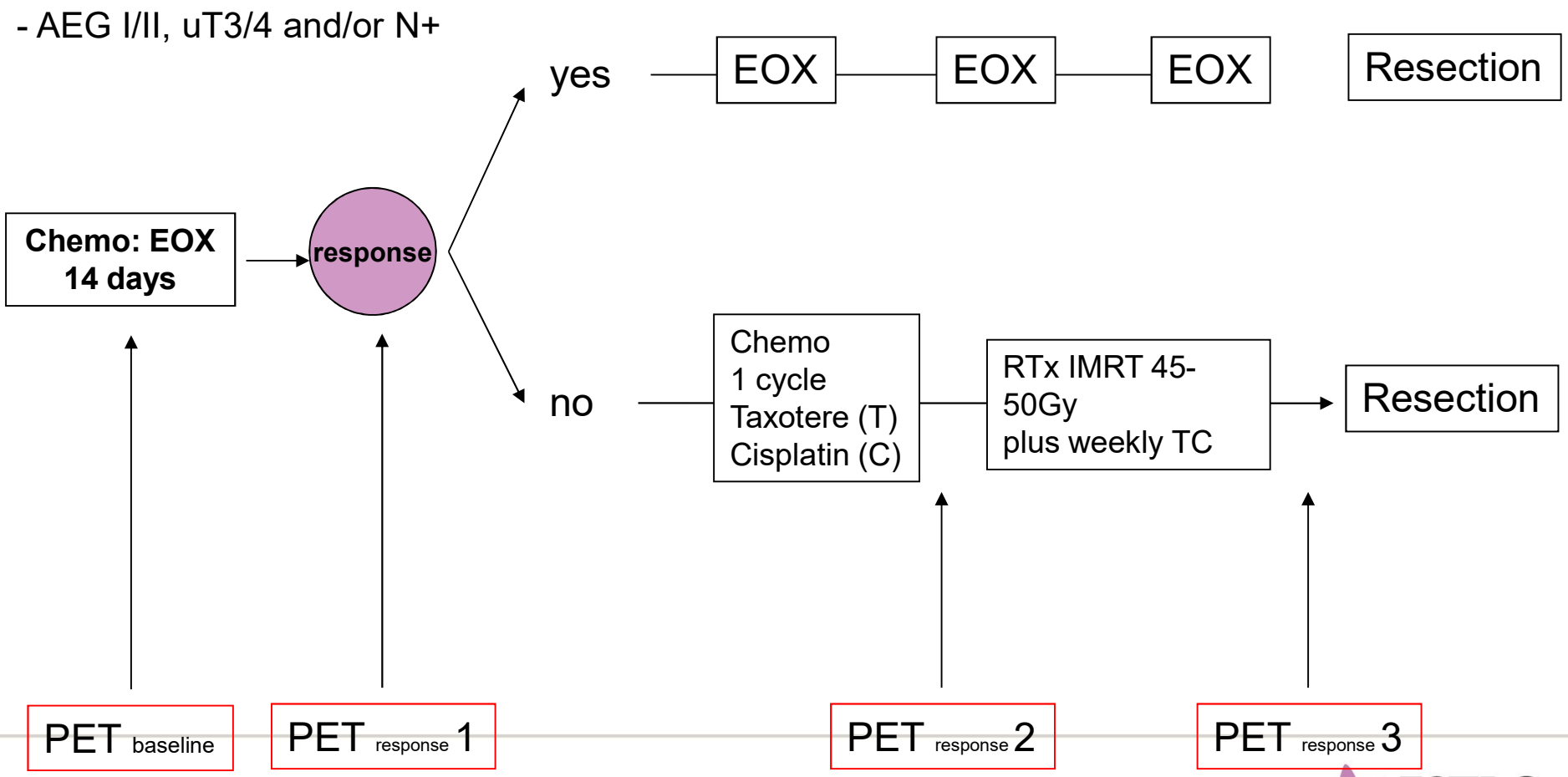
➔Identify non responders:

MUNICON study:metabolic responders had a significantly better prognosis than did non responders

PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial.AULordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR SOLancet Oncol. 2007;8(9):797

Metabolic response?

Munich II study



BMC Cancer. Published online 2011 Jun 24. doi: 10.1186/1471-2407-11-266

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Ongoing trial

CALGB 80803, NCT01333033

Post-induction chemotherapy PET

➔ choice of the chemotherapy regimen during subsequent chemoradiotherapy followed by surgery

Preliminary report presented at the 2017 ASCO GI Cancers Symposium

- PET non responders who crossed over to an alternative chemotherapy regimen had a higher pathologic complete response (CR) rate than did those who continued the same regimen

Goodman KA, Niedzwiecki D, Hall N, et al. Initial results of CALGB 80803 (Alliance): A randomized phase II trial of PET scan-directed combined modality therapy for esophageal cancer (abstract). J Clin Oncol 35, 2017 (suppl 4S; abstract 1)

RT Dose escalation?

- CAVE Minsky !

- ART-DECO ongoing

  - Inoperable carcinoma

  - Radio-chemotherapy (50.4 Gy) + weekly carbo/paclitaxel
  - SIB (61.6 Gy GTV tumor) + weekly carbo/paclitaxel

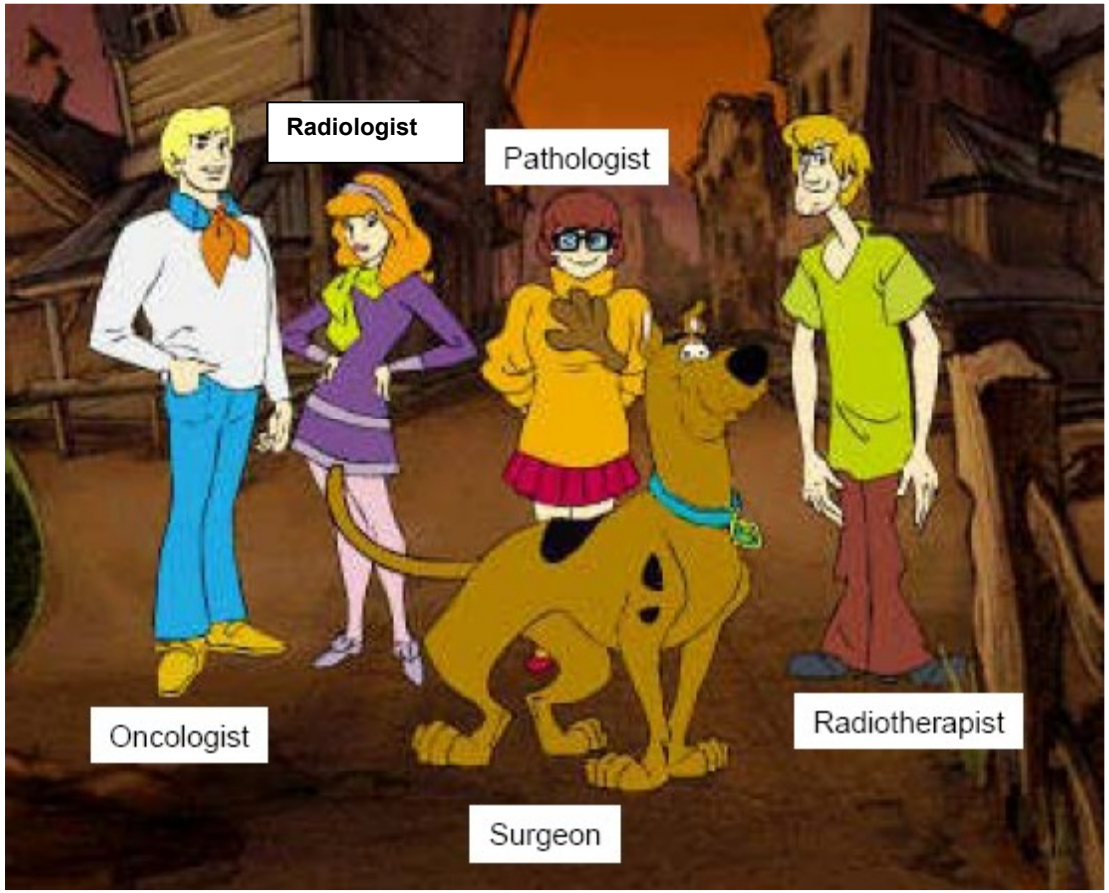
Conclusion:
Perspectives in esophageal cancers

- RT:
  - dose (escalation? Differentiation?)
  - volumes (need for universal guidelines ➔ TCP/NTCP)
  - Delivery & IGRT

- Differentiation:
  - oesophagus/GEJ/gastric
  - histologic
  - molecular differentiation

- Oncological strategy & response assessment
  - de-escalate
  - intensify treatment

Pluridisciplinarity!!!



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Gastric Cancer – Imaged based staging

Dr Angela M Riddell

Royal Marsden, London. UK

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STOMACH 8TH EDITION - AJCC

Primary Tumor

- TX — Primary tumour cannot be assessed
- T0 — No evidence of primary tumour
- Tis — Carcinoma in situ
- T1 — Lamina propria or submucosa
  - T1a — Lamina propria or muscularis mucosae
  - T1b — Submucosa
- T2 — Muscularis propria
- T3 — Subserosa
- T4 — Adjacent structures
  - T4a — Perforates serosa
  - T4b — Other adjacent structures

Regional Lymph Nodes

- NX — Lymph nodes cannot be assessed
- N0 — No regional lymph node metastasis
- N1 — 1 to 2 regional lymph nodes
- N2 — 3 to 6 nodes
- N3 — ≥ 7 nodes
  - N3a — 7 to 15 nodes
  - N3b — ≥16 nodes

Distant Metastasis

- M0 — No distant metastasis
- M1 — Distant metastasis

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Staging of Gastric Cancer

Two main categories:

Early gastric cancer

Malignant invasion confined to the mucosa & submucosa

Advanced gastric cancer

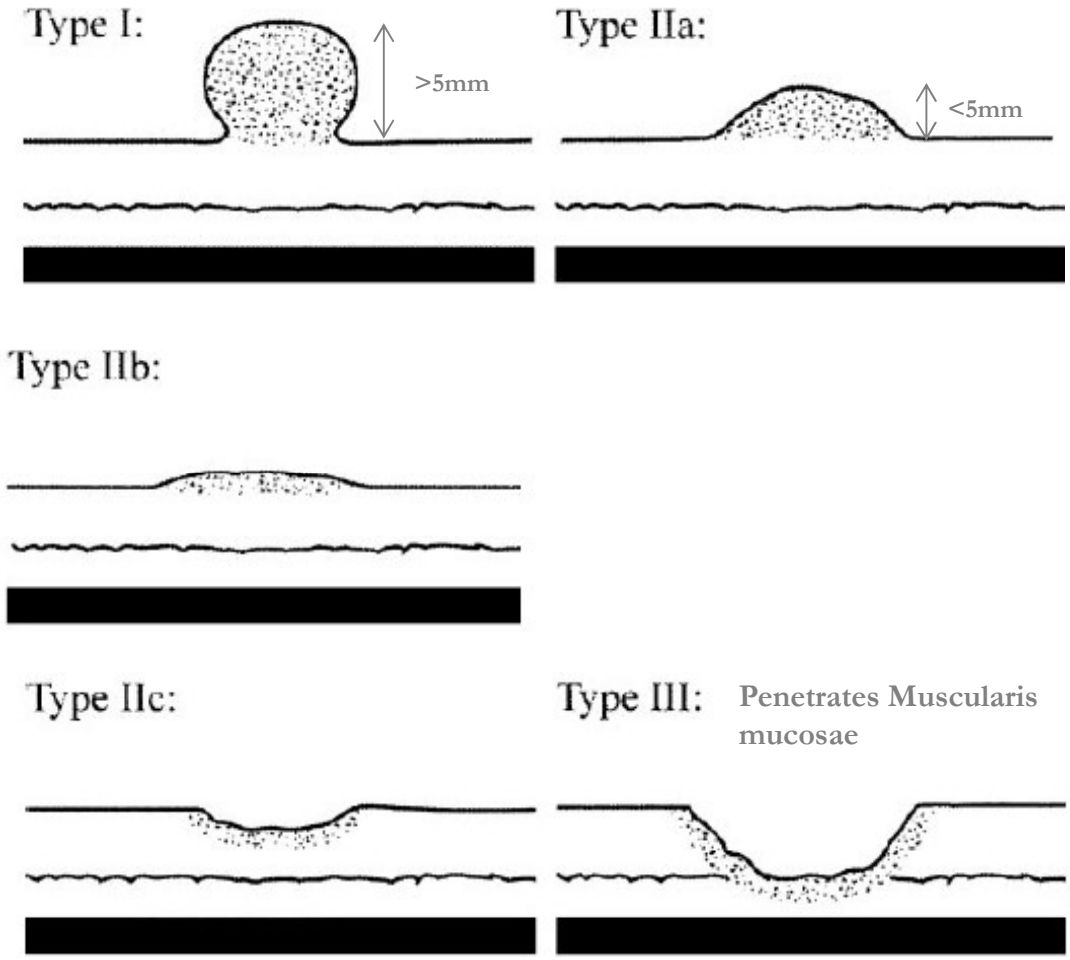
Malignant invasion into the muscularis propria

Early Gastric cancer

Elevated

Flat

Depressed



Adapted from: Ba-Ssalamah A, Prokop M et al. Radiographics 2003; 23:625-644

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Advanced Gastric Cancer Staging

Diagnosis – Endoscopic biopsy

Initial Imaging

MDCT

Potentially operable disease

- PET/CT – exclude distant spread
- Laparoscopy

Other imaging modalities

- EUS – Early disease, Proximal/ Distal Extent
- MRI – Trouble shooting

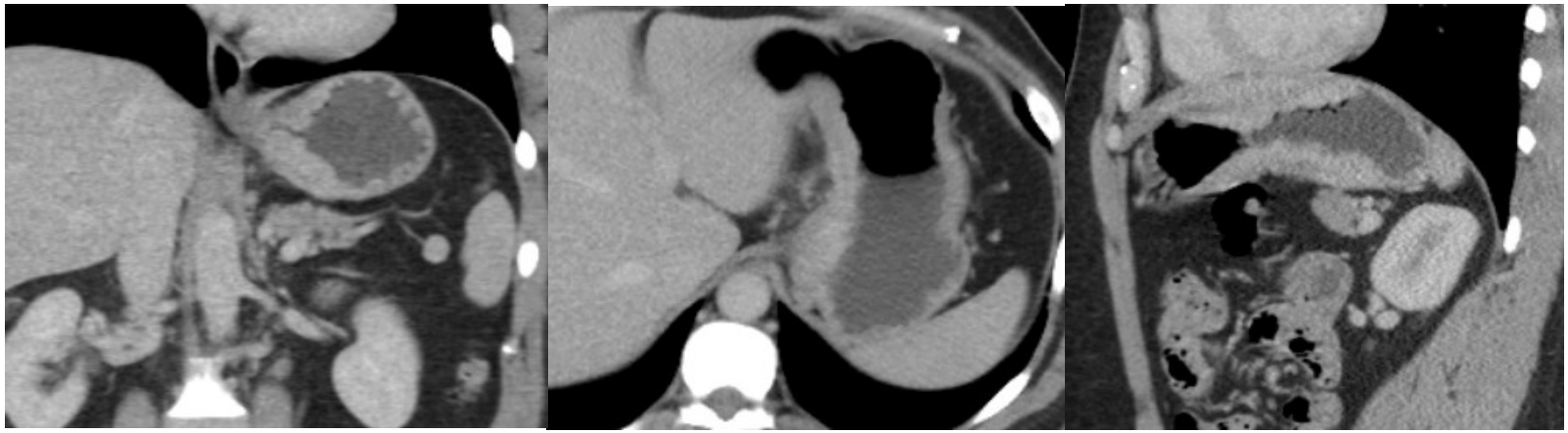
MDCT - Patient preparation

- Fasted for 6hrs
- Gastric distension
  - Anti spasmodic –Buscopan®
  - Oral contrast – water
- Position
  - Supine
  - Prone
  - Oblique angle to improve regional gastric distension

MDCT - Scan Technique

Protocol:

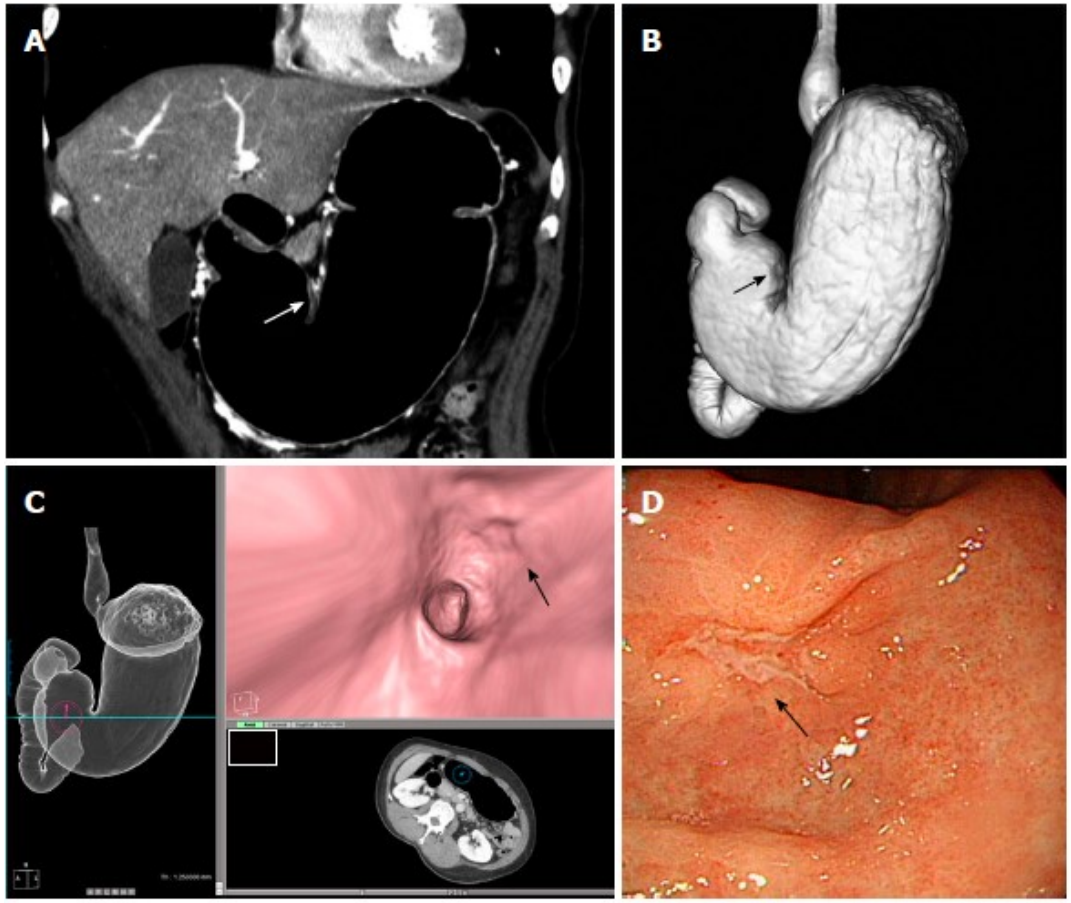
- Oral contrast – water: 500mls over 45 mins. 200mls prior to scan
- IV contrast: Portal venous phase imaging (70 second delay)
- Thorax, abdomen & pelvis



Scan parameters aim to achieve resolution that can enable MPR post-processing using isotropic voxels

MDCT - Scan Technique

Virtual gastroscopy



Useful to detect mucosal / early lesions.

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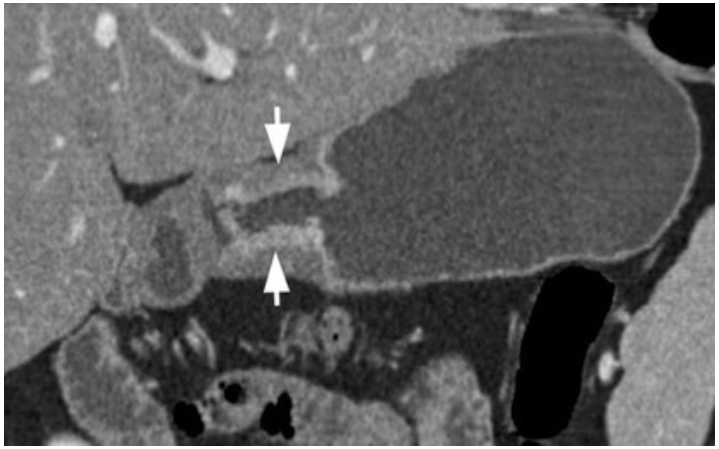
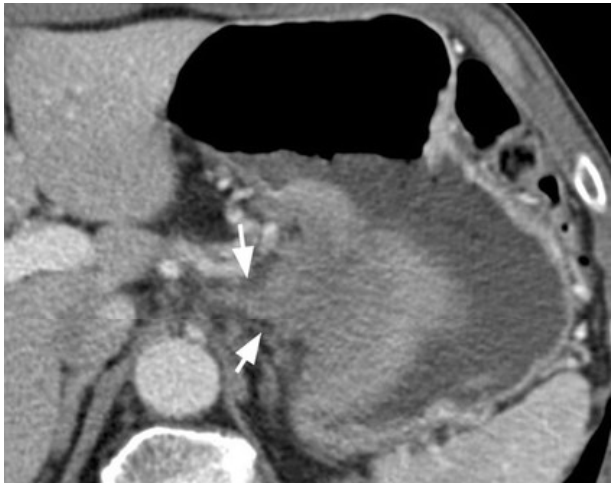
MDCT - T Staging



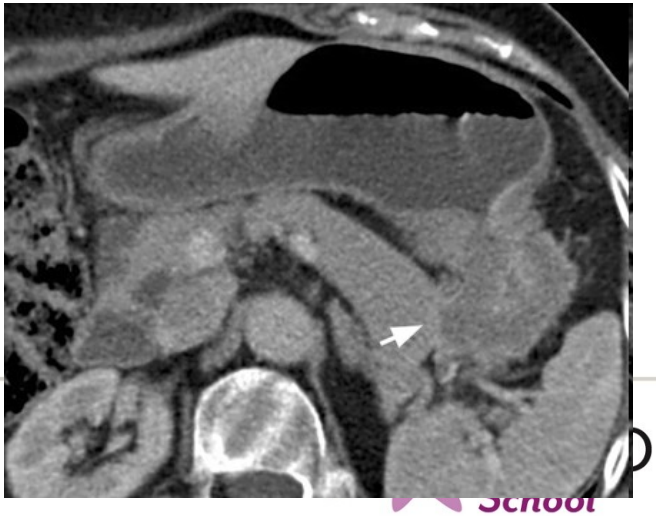
pT2



pT3

Parameter	Percentage range
Accuracy	77 - 89%
Sensitivity	83-100%
Specificity	80 -97%

pT4



Choi J, Joo I, Lee, J 2014 WJG 20;16: 4546 - 4557

MDCT - N Staging

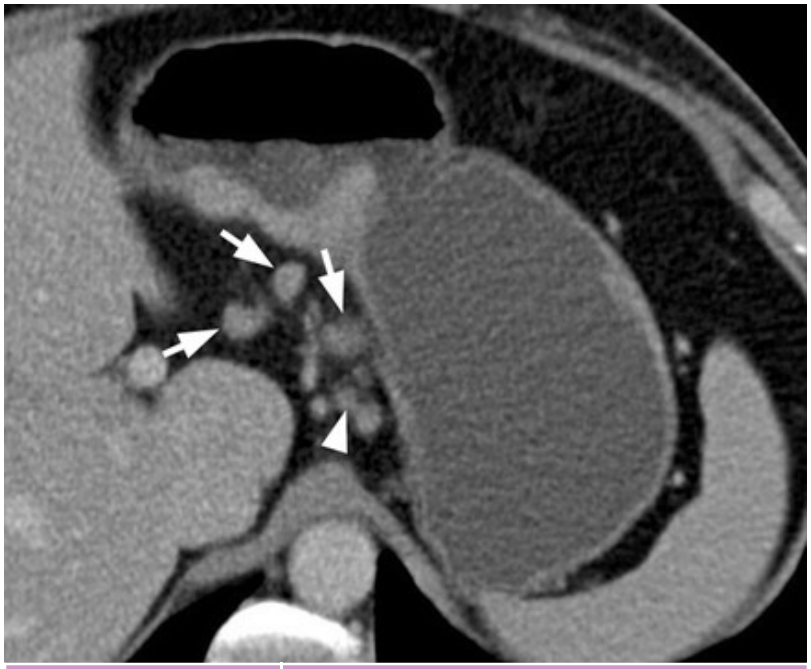
Lymphatic spread is found in 74%–88% of patients

N staging depends on the number of lymph nodes involved

Based on size criteria (short axis):

≥6mm perigastric

≥ 8mm extra perigastric

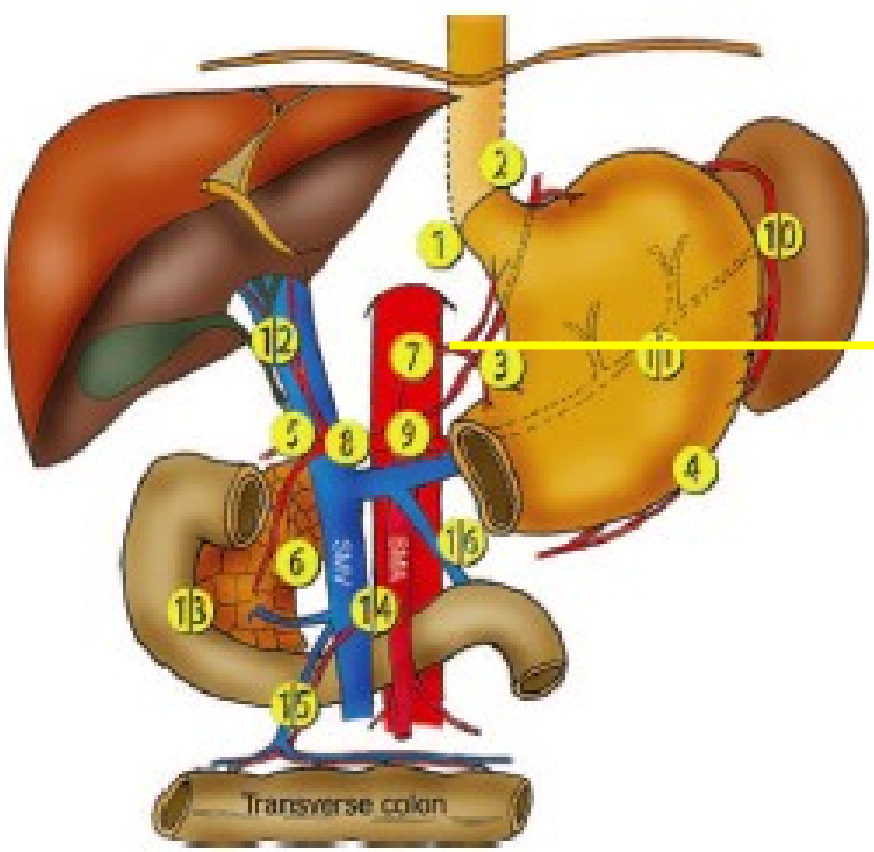


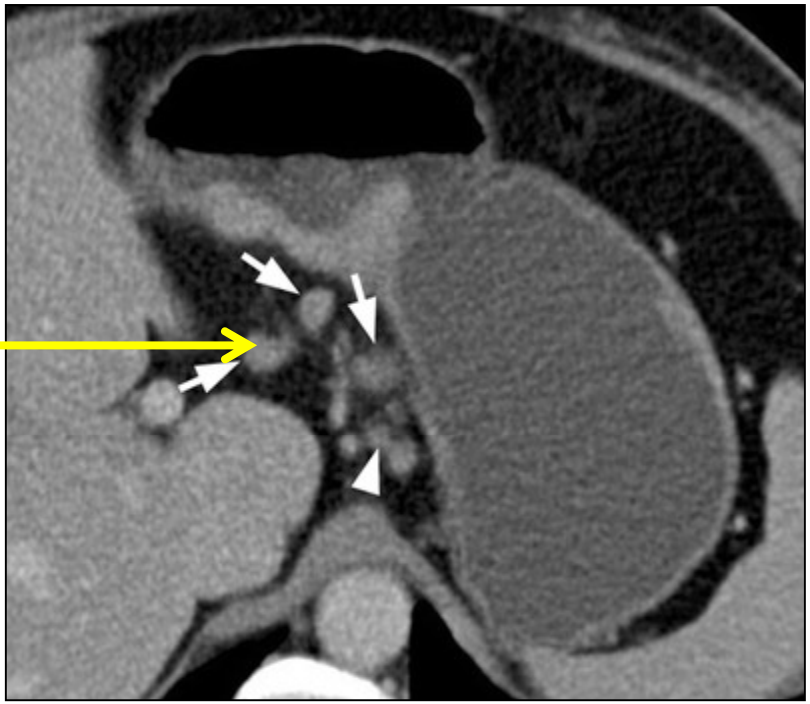
Parameter	Percentage range
Sensitivity	62.5 - 91.9%
Specificity	50 - 87.9%

Stage	No of Regional Nodes
N1	≤2
N2	3-6
N3a	7 - 15
N3b	≥16

Kwee RM, Kwee TC. 2009 Gastric cancer; 12: 6-22

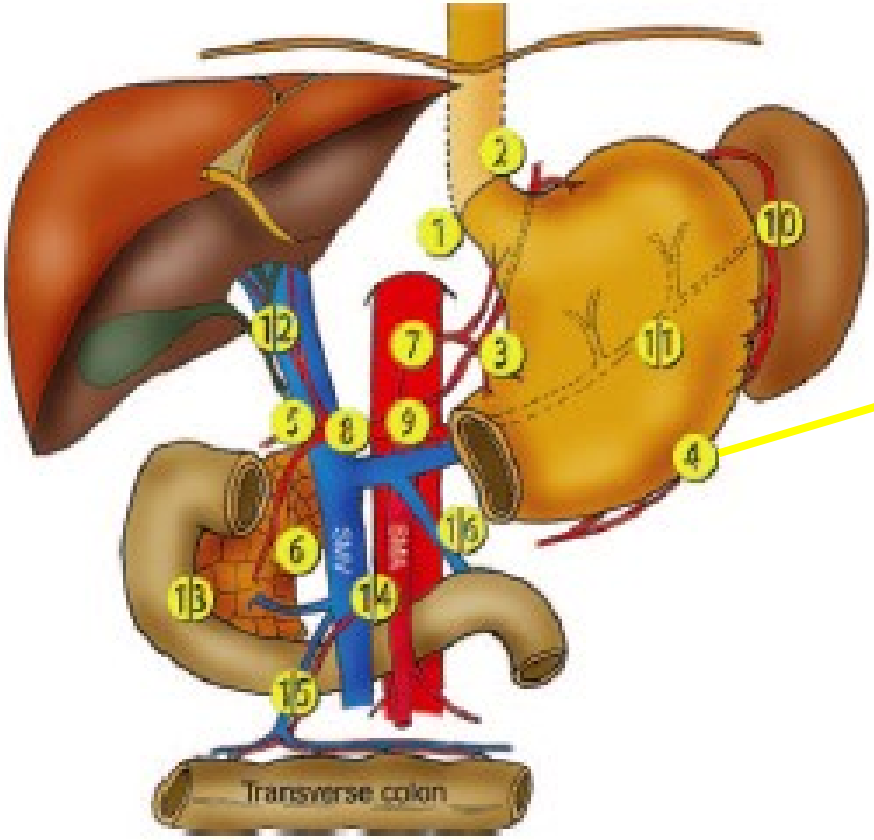
Upper Abdominal Lymph nodes groups

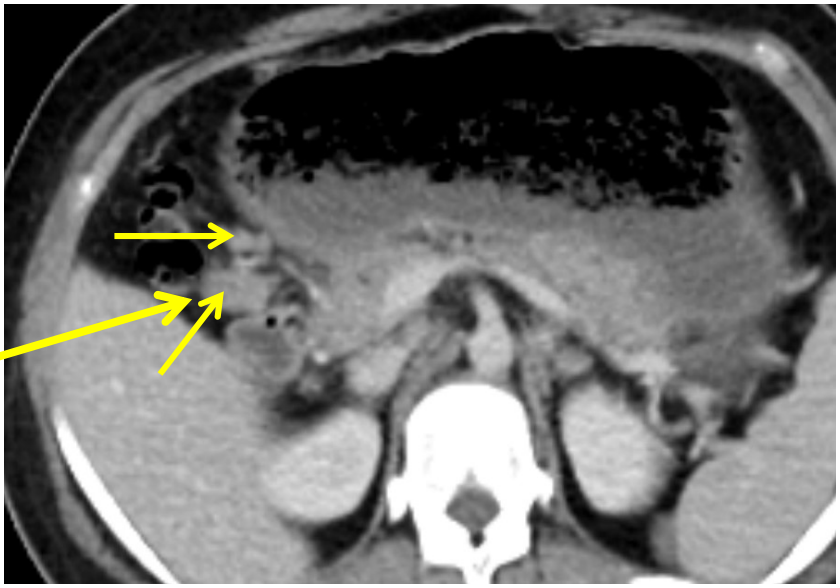




Station 7
Left gastric artery territory

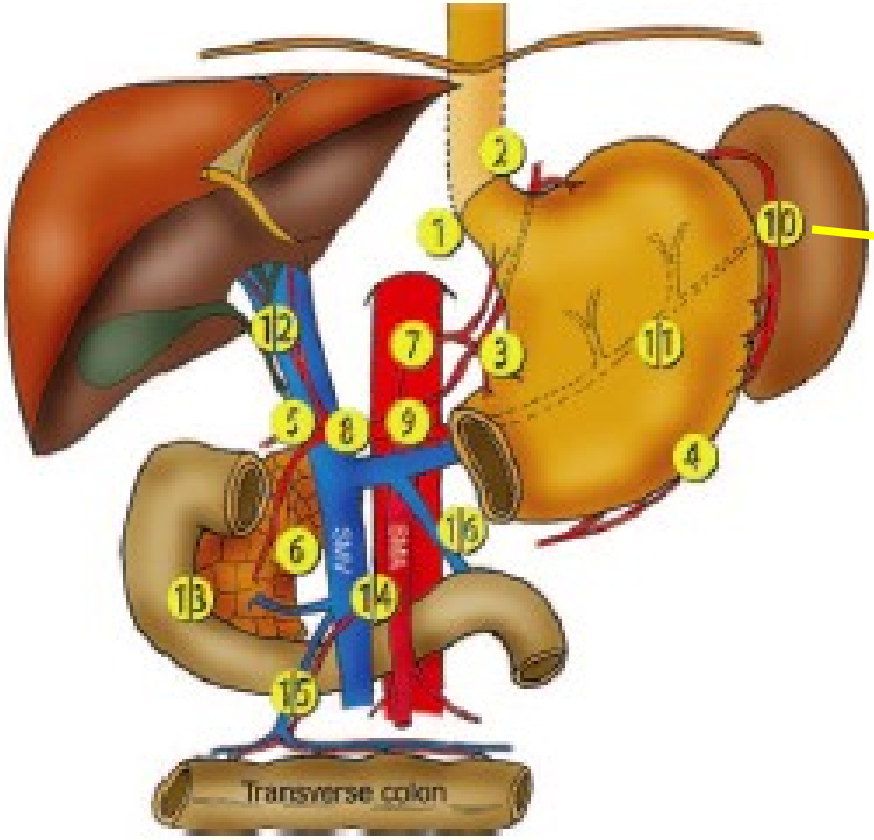
Upper Abdominal Lymph nodes groups

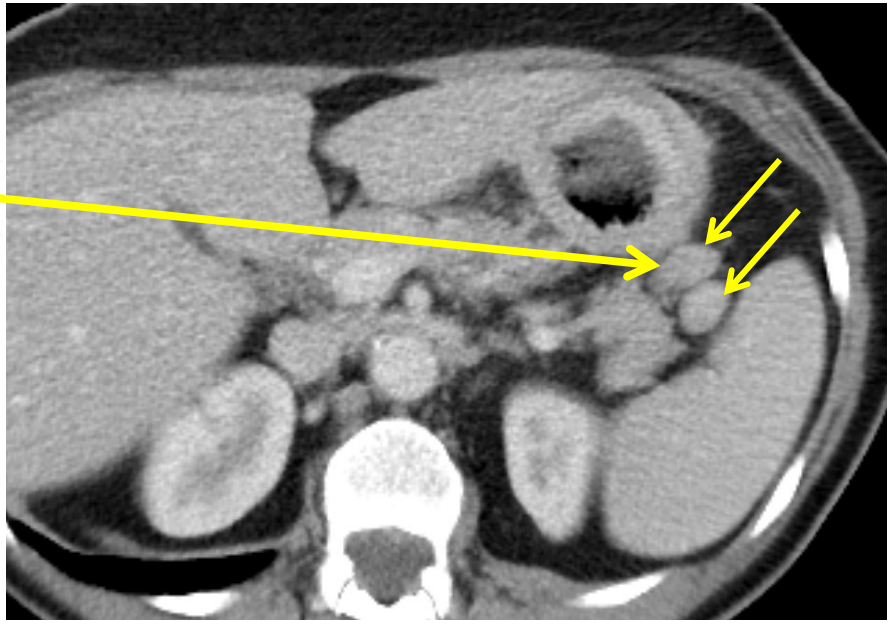




Station 4
Gastroepiploic artery

Upper Abdominal Lymph nodes groups

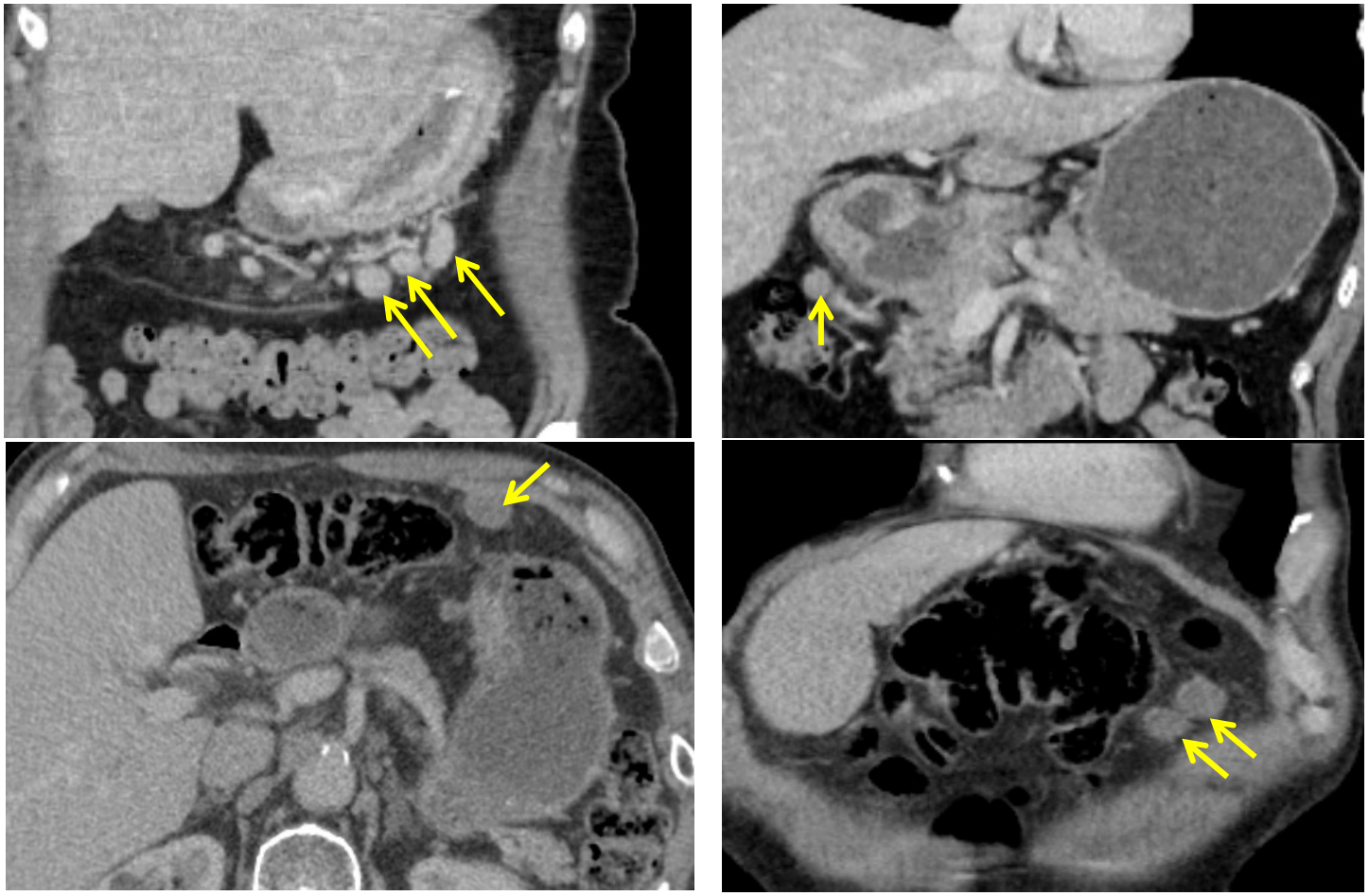




Station 10 Splenic hilum

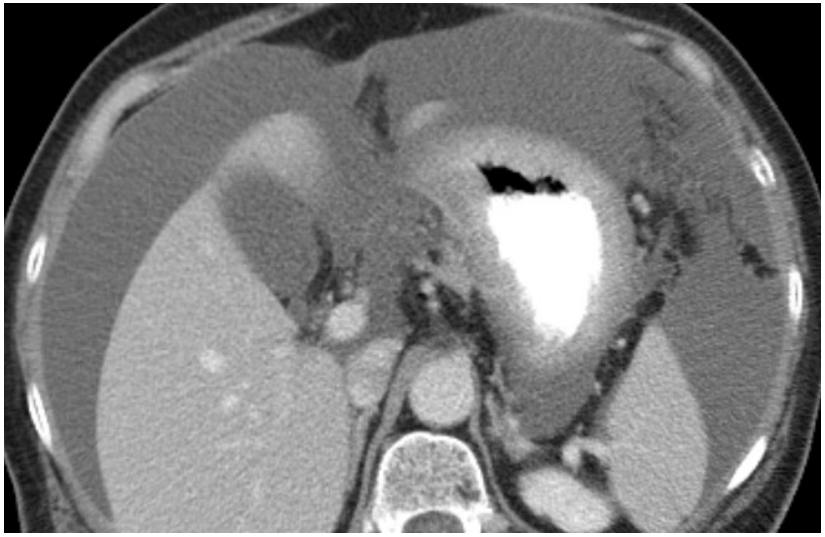
Upper Abdominal Lymph nodes groups

Difficulty distinguishing Gastroepiploic nodes from peritoneal disease



MDCT – M staging

- Detection of hepatic mets:
  sens 88%, spec 99%*.
- Detection of peritoneal disease
  No ascites: sens 30%†
  In presence of ascites:
  Sens 51%, Spec 97%*



Laparoscopy for potentially operable patients

*Yajima, K., T. Kanda, et al. (2006). Am J Surg **192**(2): 185-90.
†D'Elia, F., A. Zingarelli, et al. (2000). Eur Radiol **10**(12): 1877-85.

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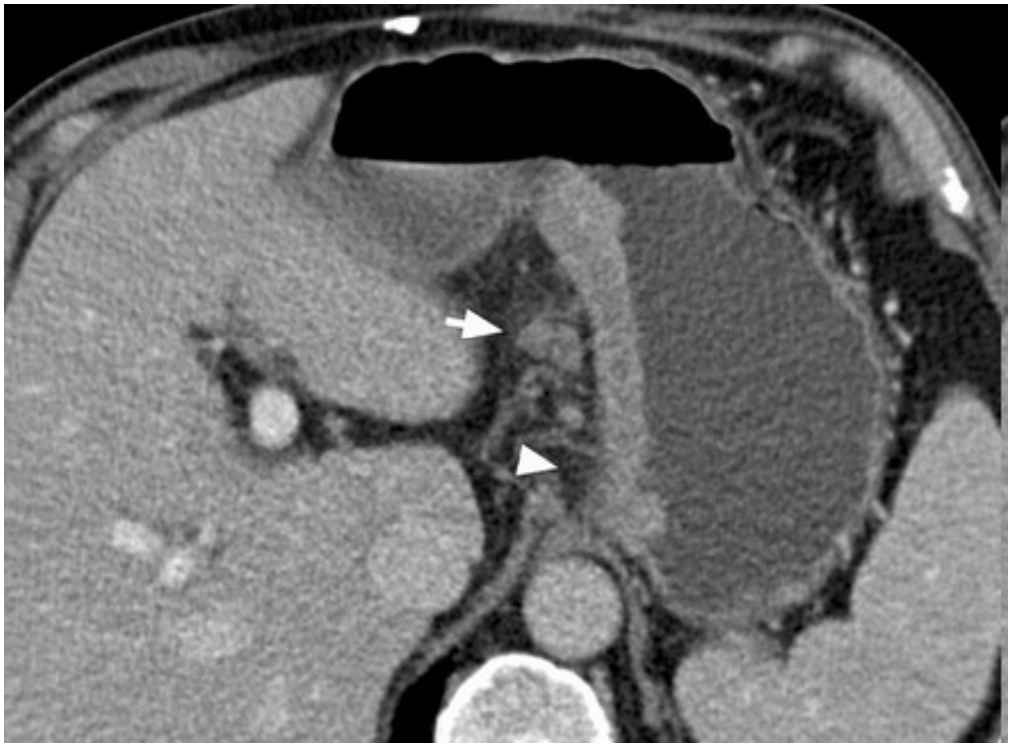
Gastric Cancer staging



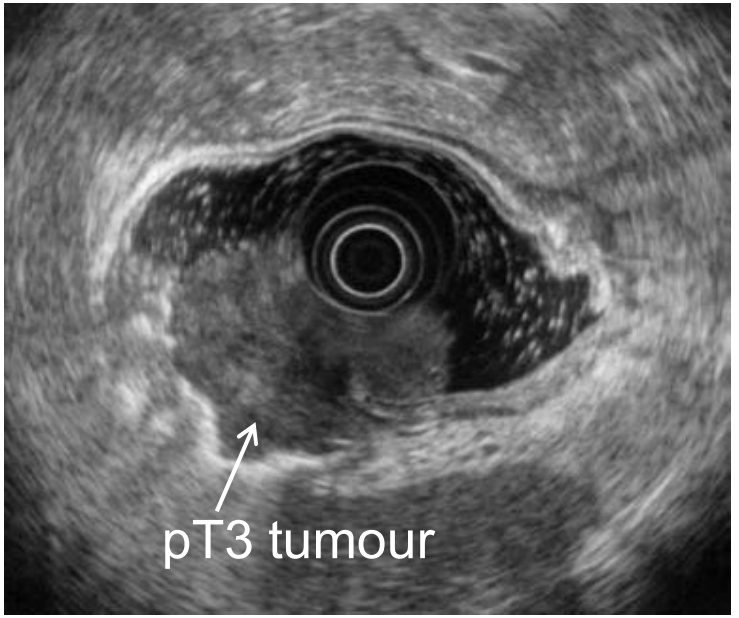
CT Report:

- Length
- Location
- T Stage
- N & M Stage

EUS - T Staging

5-20mHz probes

- High spatial resolution enables visualization of individual wall layers
- EUS T staging more accurate than MDCT



Wide variation in accuracy in literature (65-92%)

Overstaging early tumours

Image from: Bohle W et al. 2011 J Gastrointestin Liver Dis; Vol. 20 No 2, 135-139

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EUS - N Staging

Provides morpholgical information

- Malignant nodes: round, hypoechoic, lose echogenic hilum
- Fine needle aspiration (FNA) possible

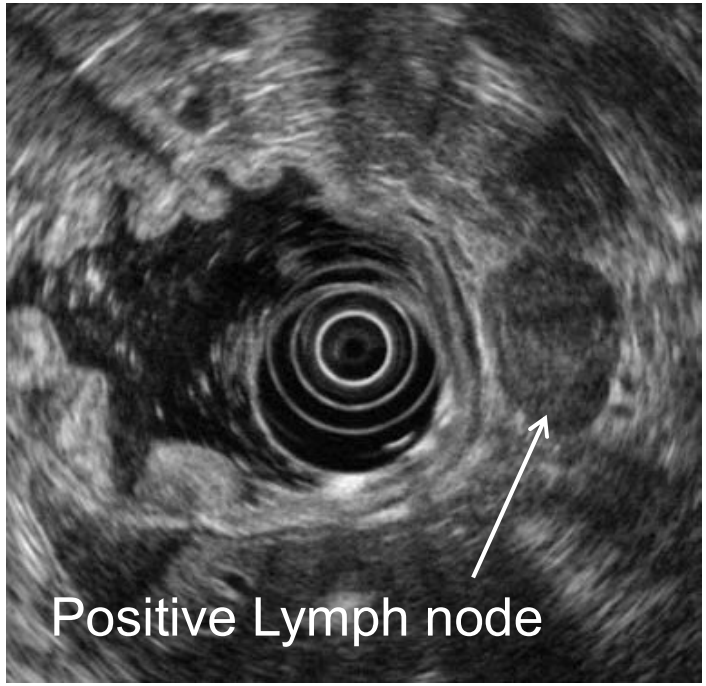

Image from: Bohle W et al. 2011 J Gastrointestin Liver Dis; Vol. 20 No 2, 135-139

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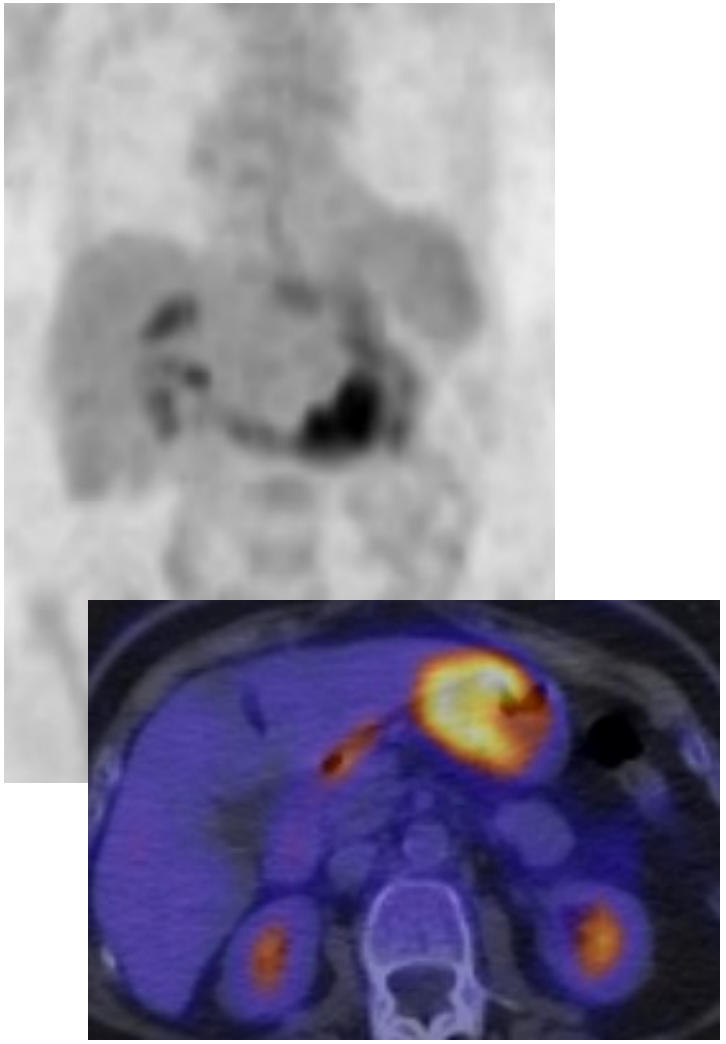
^{18}FDG-PET/CT

Gastric Cancer

- Variable ^{18}FDG avidity dependent upon tumour subtype
- Intestinal-type have greater FDG avidity
- Limited uptake in diffuse-type

  ~30% tumours not visualised



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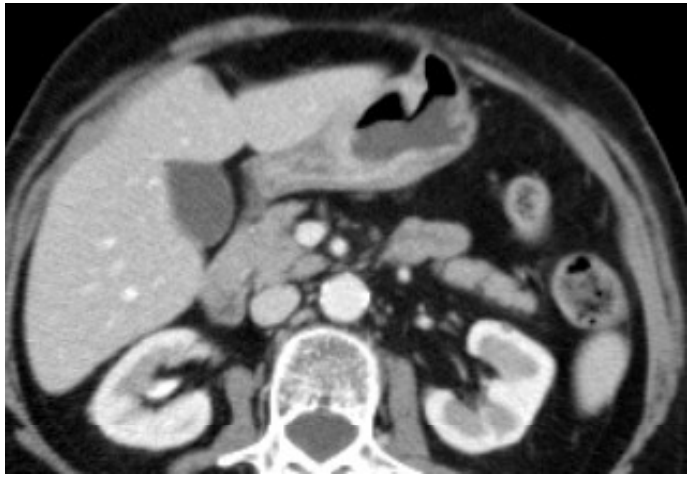
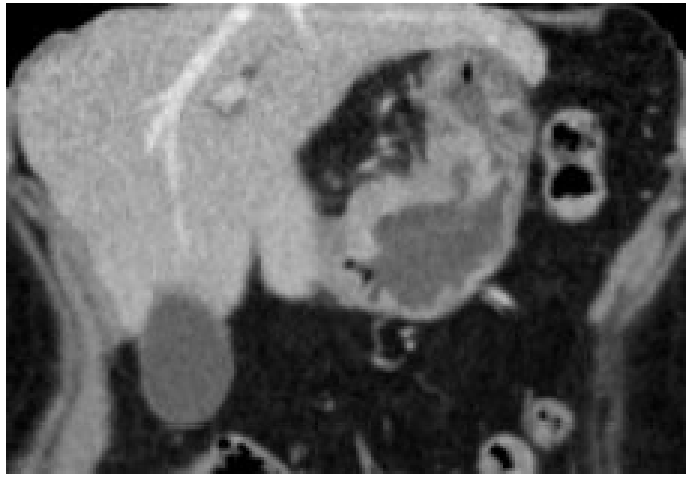
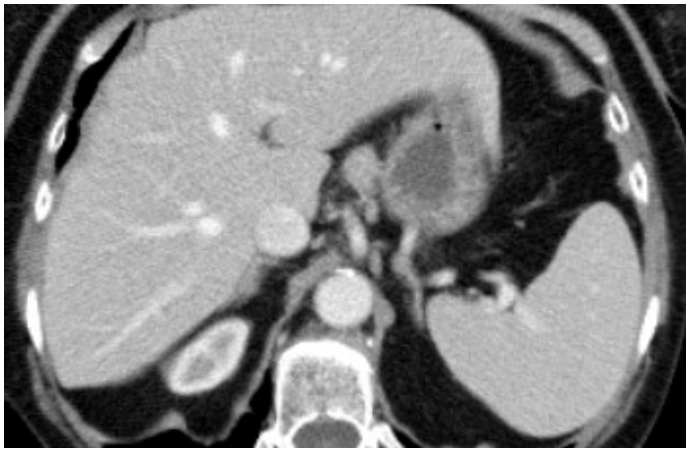
Challenges of nodal staging

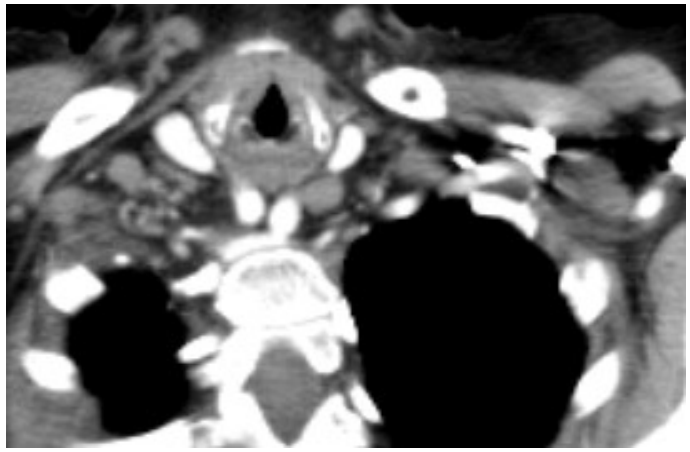
72 year old female with weight loss and anaemia

Case

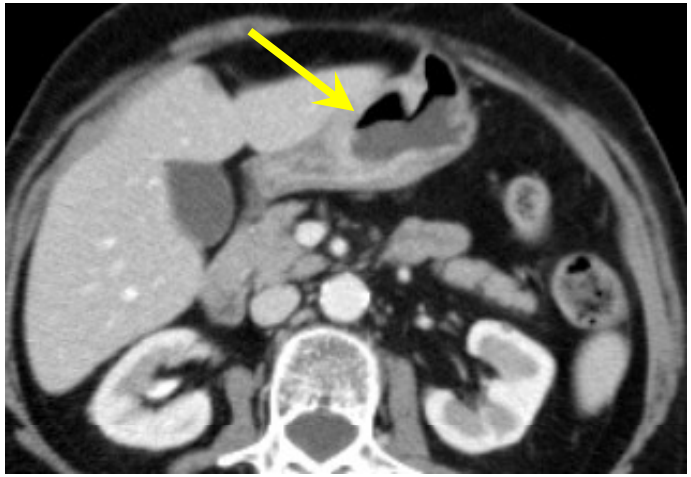


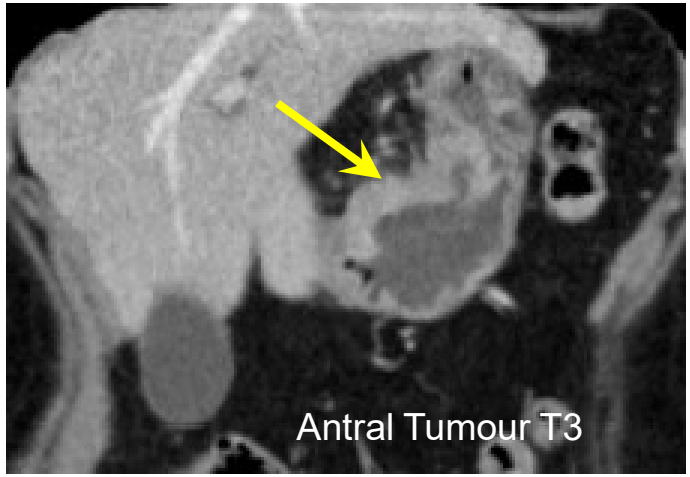


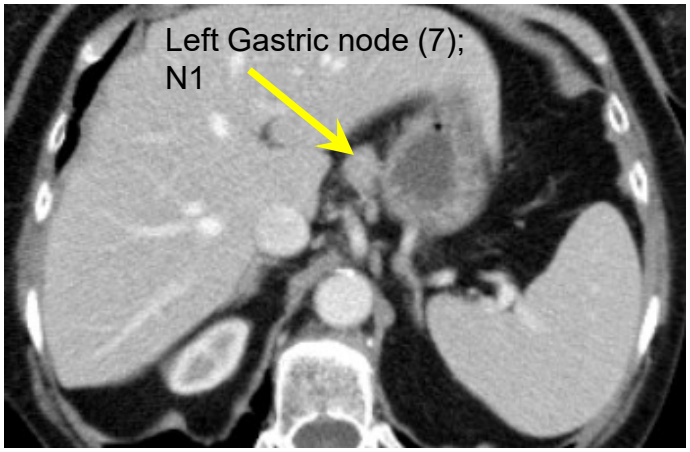


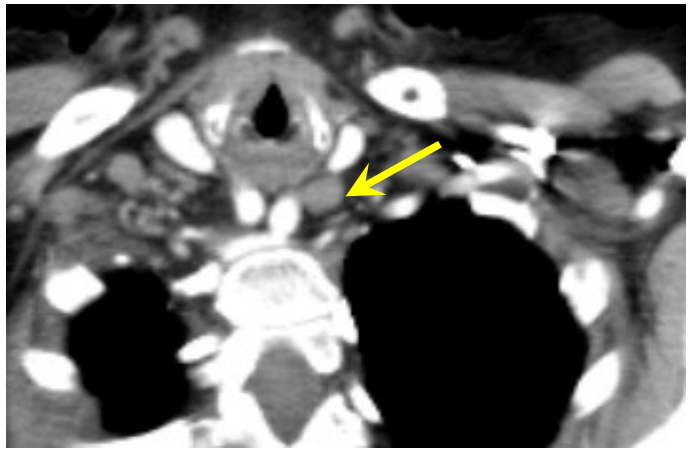


Case









T3N1 ?? M1 – Supraclavicular node…

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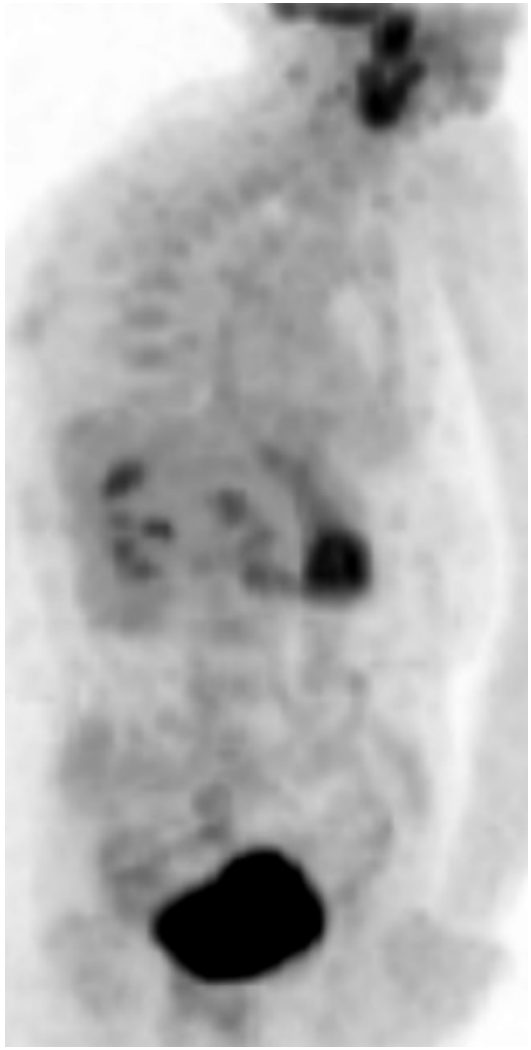
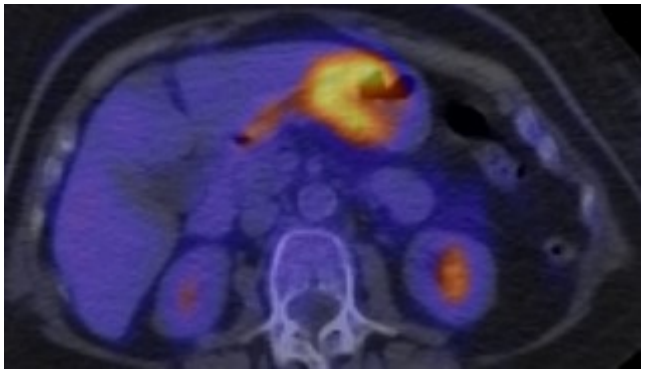
Case

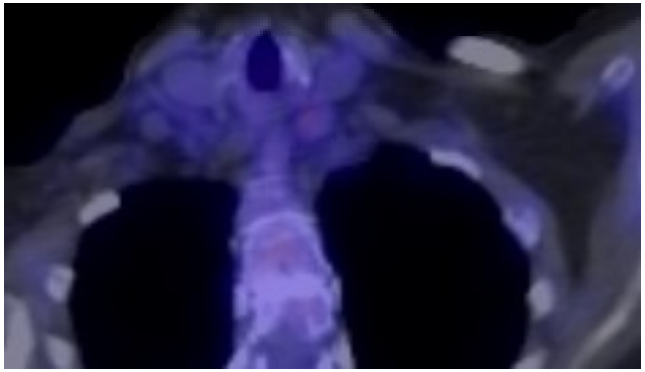
What to do next?

- Consider supraclavicular node positive based on size (9mm)?
- Arrange a PET-CT scan
- Arrange an U/S +/- FNA

Case







Moderate FDG avidity in node ‘equivocal’ on PET-CT

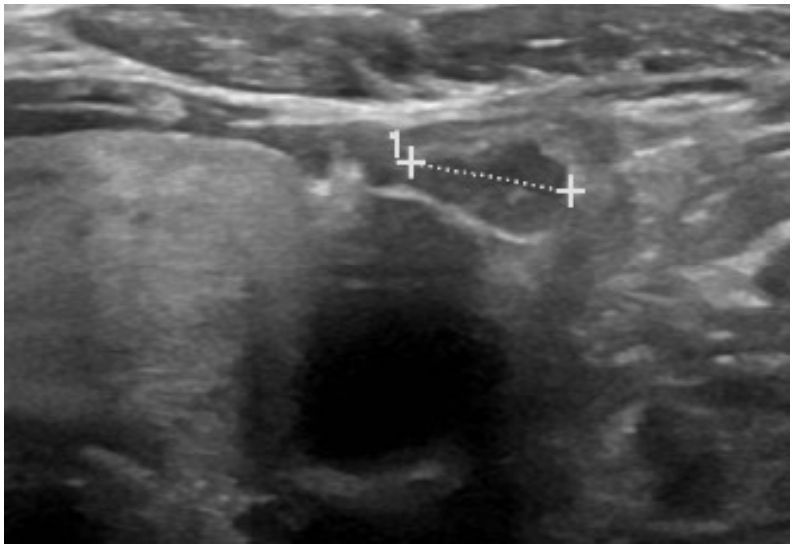
Case

What to do next?

- Consider supraclavicular node positive based on PET-CT findings
- Arrange an U/S +/- FNA
- Consider PET-CT findings as negative in the node & proceed with neoadjuvant therapy followed by surgery

Case

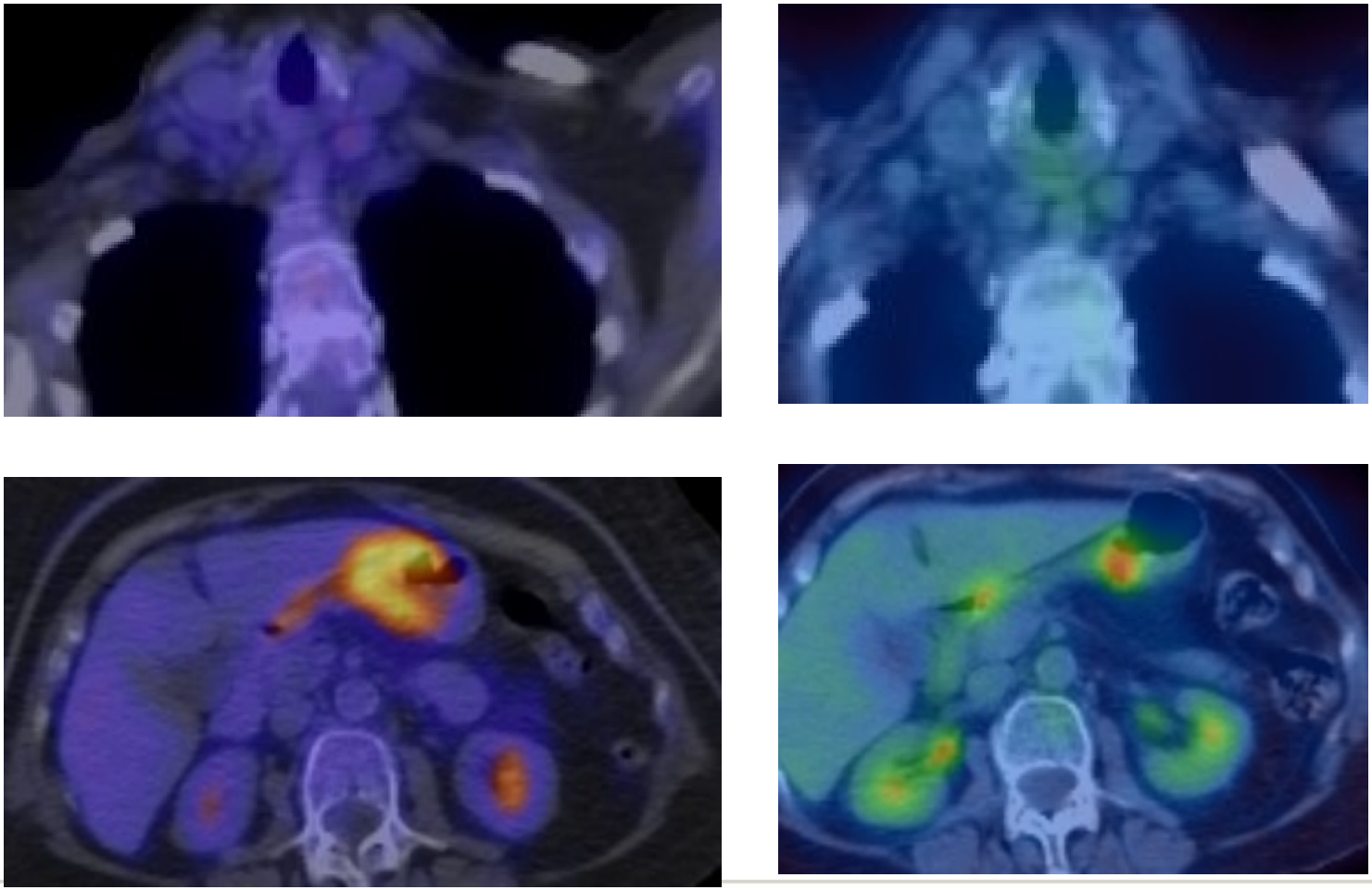
- An U/S with FNA was arranged
- Sonographic appearance in keeping with a reactive node.
- Cytology – C1



Case

The patient was given neoadjuvant therapy

Case



Post x2 Chemo cycles - PR

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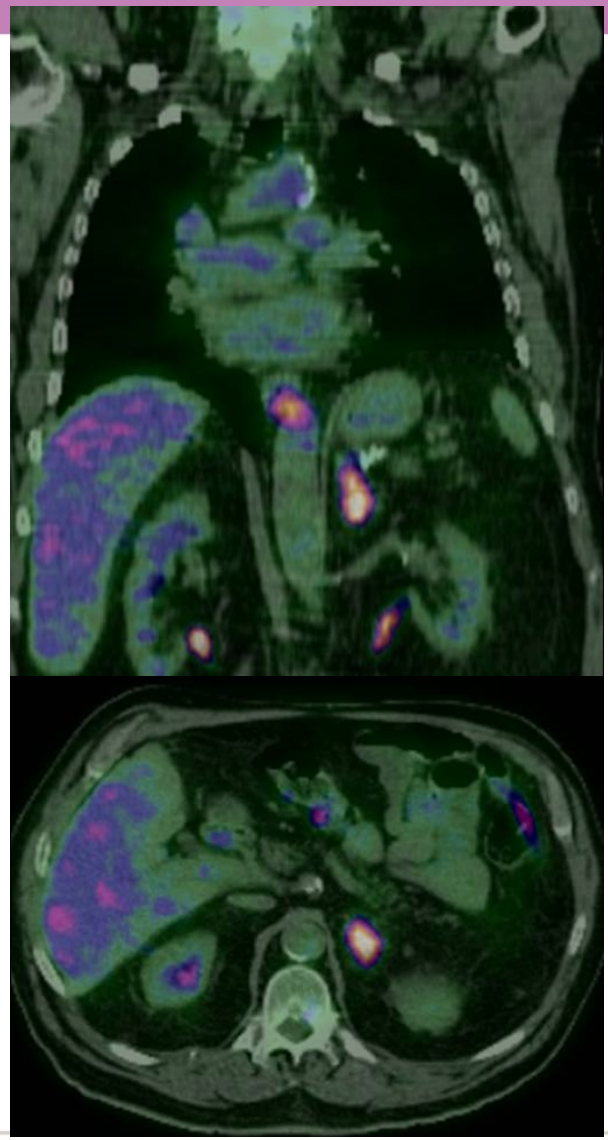
Case

- Had second laparoscopy – no metastases
- Went on to have total gastrectomy in Dec 2009.
- Well with no recurrence
- Patient opted for no further treatment post op.

^{18}FDG-PET/CT

Main advantage

Identification of occult metastatic disease*



*Kinkel K, Ying L et al (2002) Radiology 224:748–756

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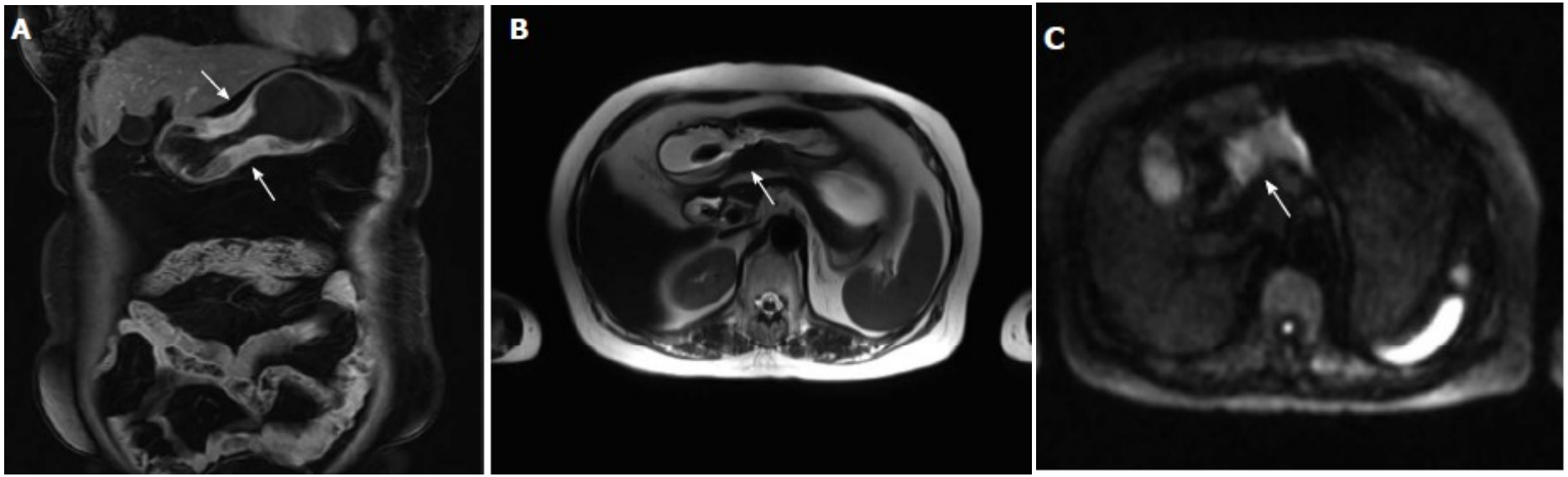
Gastric Cancer Staging - MRI



Limited studies

- In vitro studies – demonstrate individual layers of the oesophageal wall. High level of accuracy for staging all tumours
- In vivo studies – T & N staging similar to MDCT

Choi J, Joo I, Lee, J 2014 WJG 20;16: 4546 - 4557

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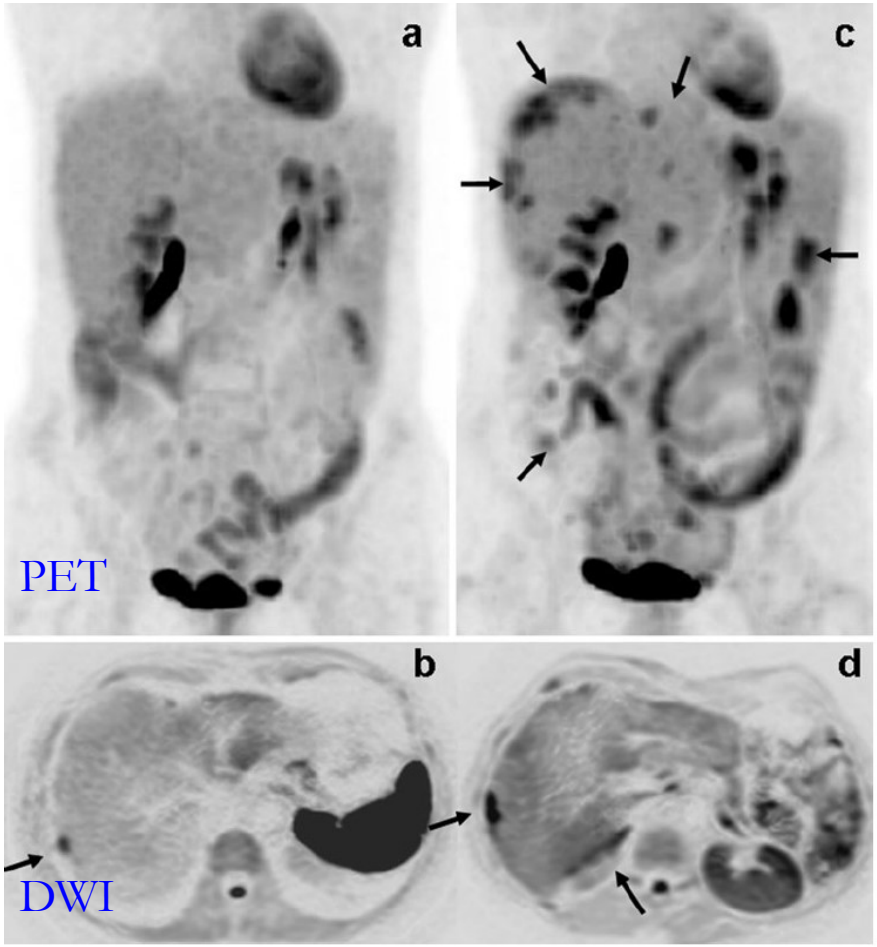
M Staging – Peritoneal disease

MDCT

Accuracy 25-90% dependent on site, size & morphology of disease

Functional imaging

PET-CT & Diffusion Weighted MRI (DW-MRI) have similar improved accuracy, but falls for foci <1cm*



*Soussan M, Des Guetz G et al. (2012) Eur Radiol 22:1479 - 1487

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Summary – Imaging for Gastric Cancer staging

Staging

- MDCT T & N staging & exclude metastatic disease
- PET-CT refine staging & localise tumour
  - False negative with diffuse type

- EUS – defining prox / distal extent.
- MRI – Trouble shooting & clinical research

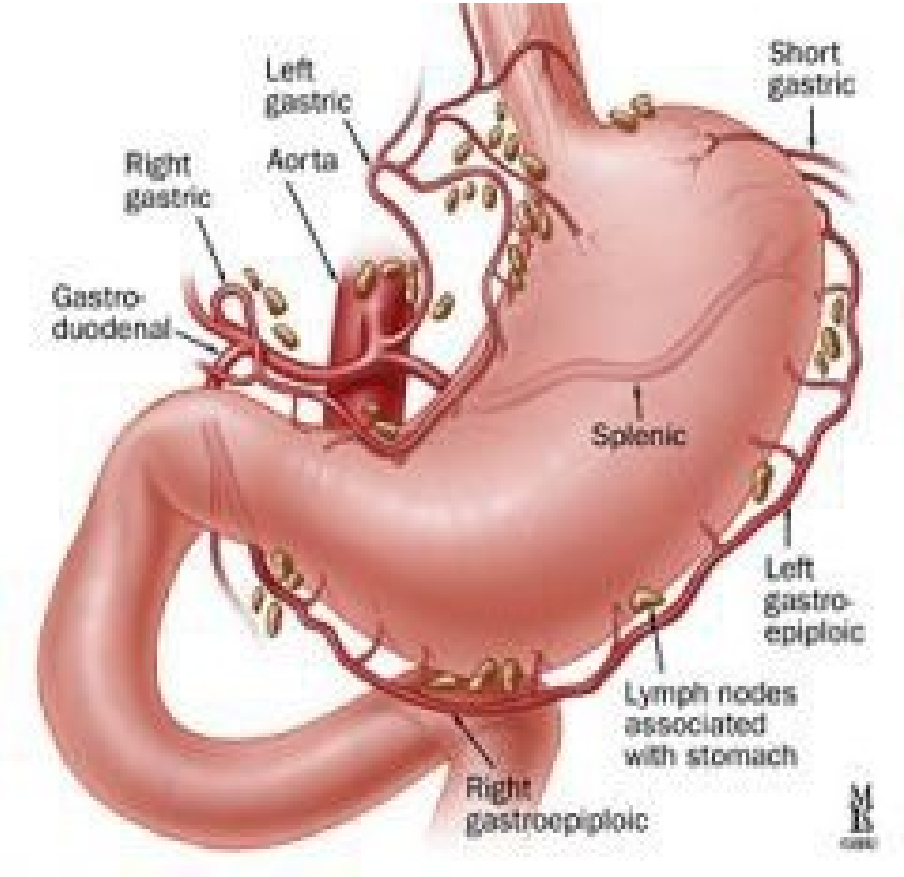
Thank you

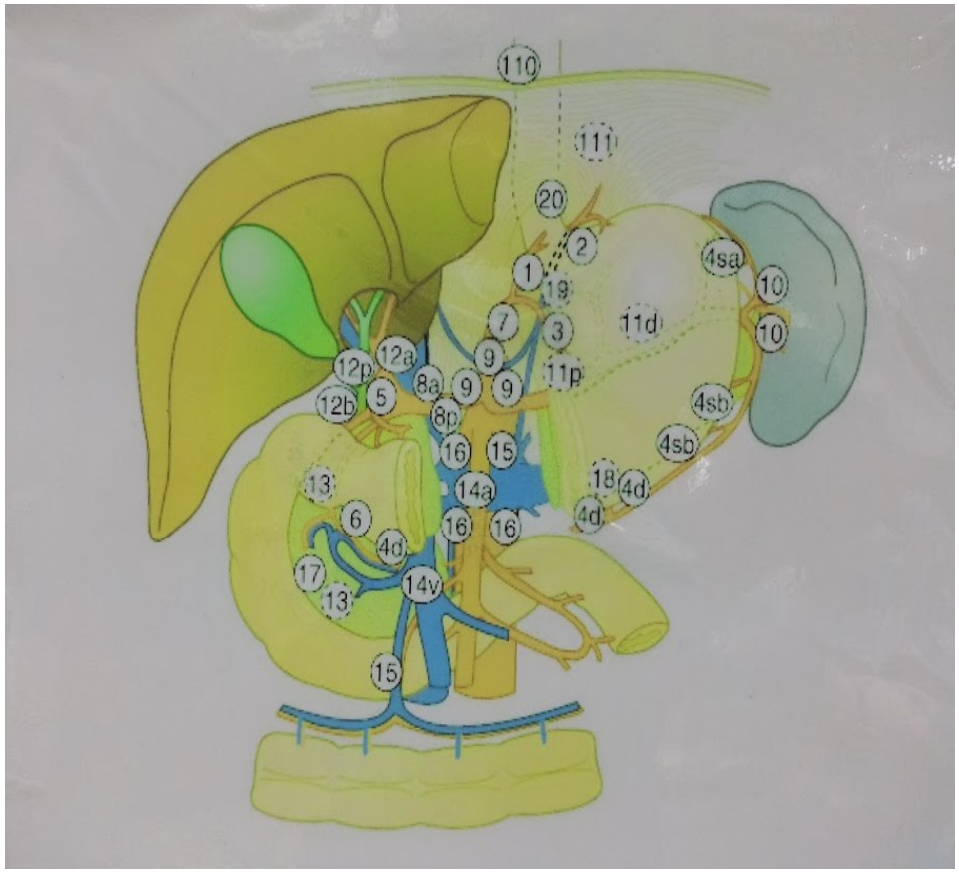
The ROYAL MARSDEN
NHS Foundation Trust

State of Art of Surgery in a Combined Treatment Perspective: Gastric Cancer

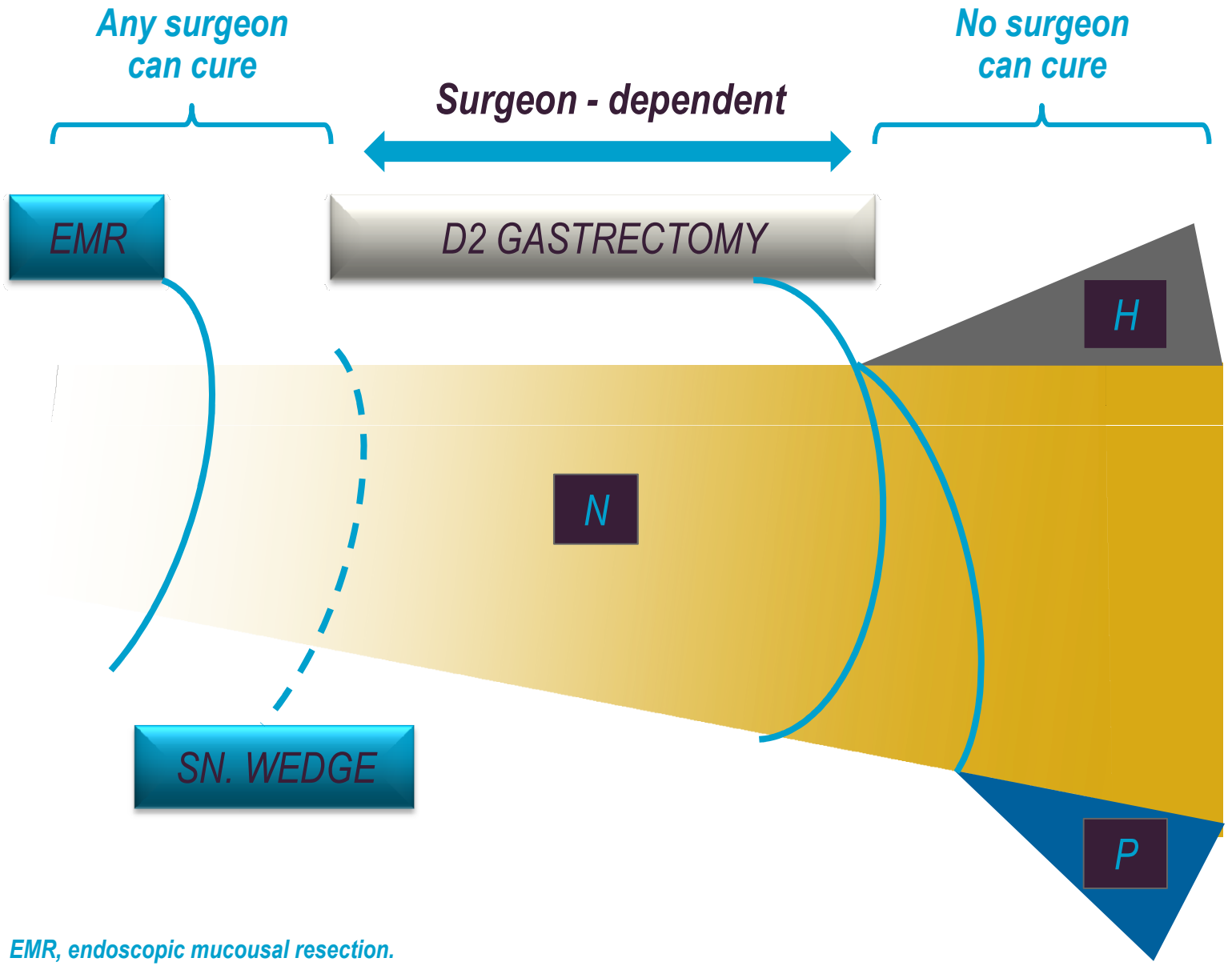
William Allum
Consultant Surgeon
Royal Marsden NHS Foundation Trust
London, UK

NHS





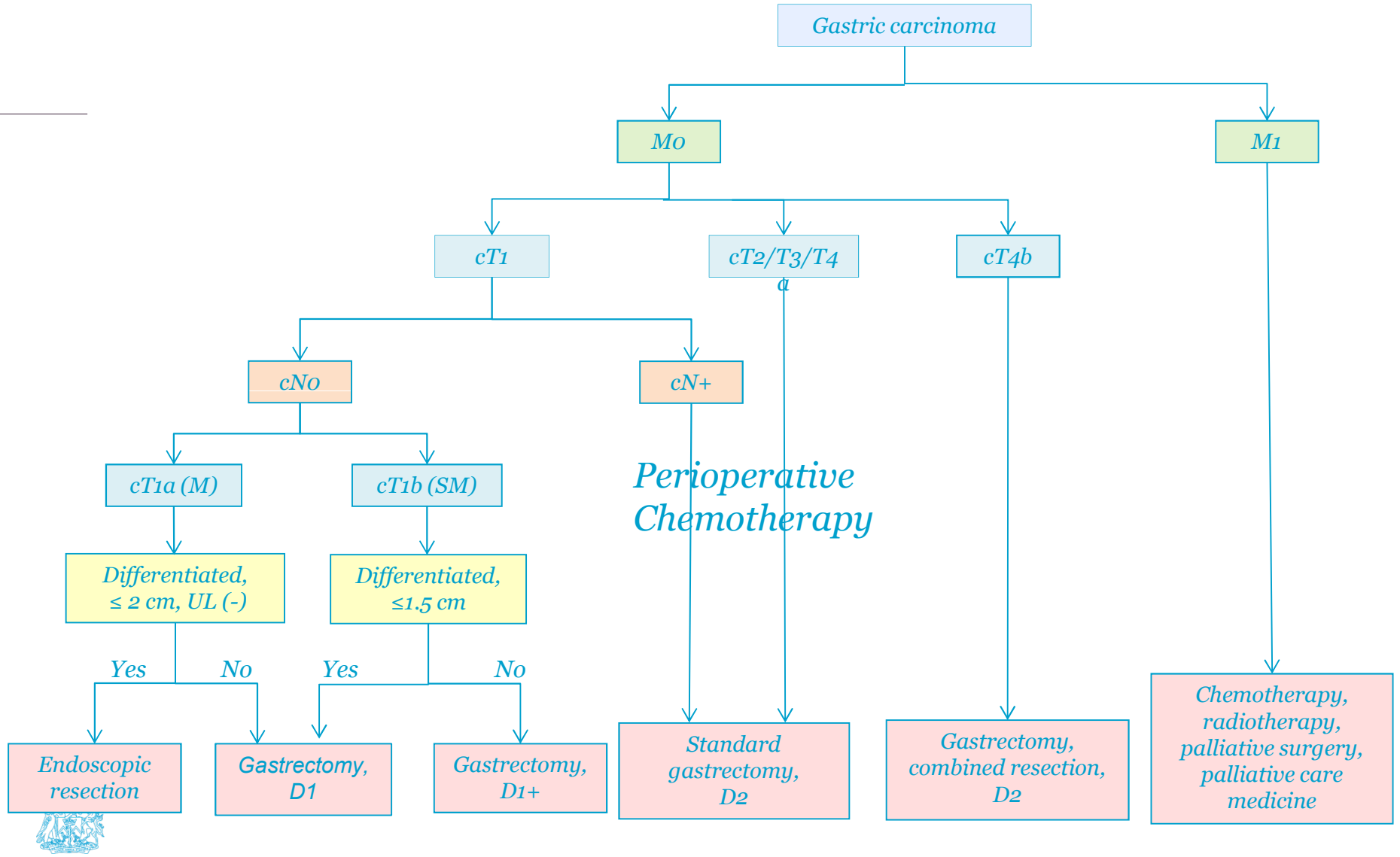
Gastric Vascular and Lymphatic Anatomy



EMR, endoscopic mucousal resection.

The Royal Marsden

Algorithm of Standard Treatment



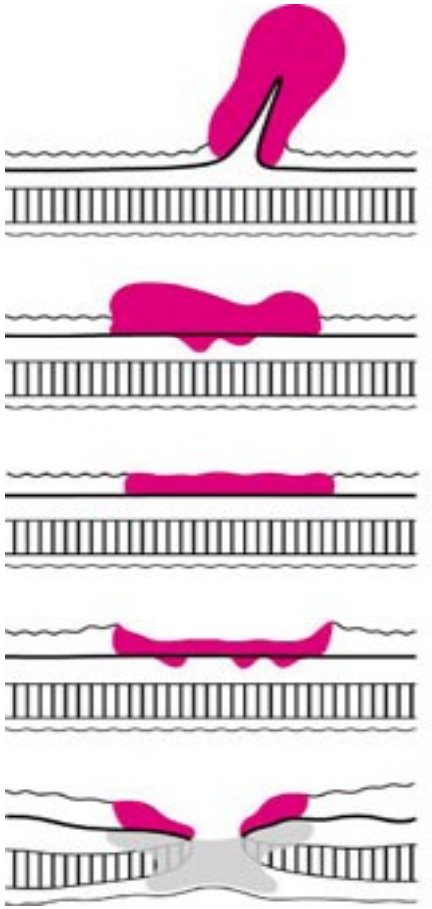
Early Disease

Locally Advanced

Surgical Trials

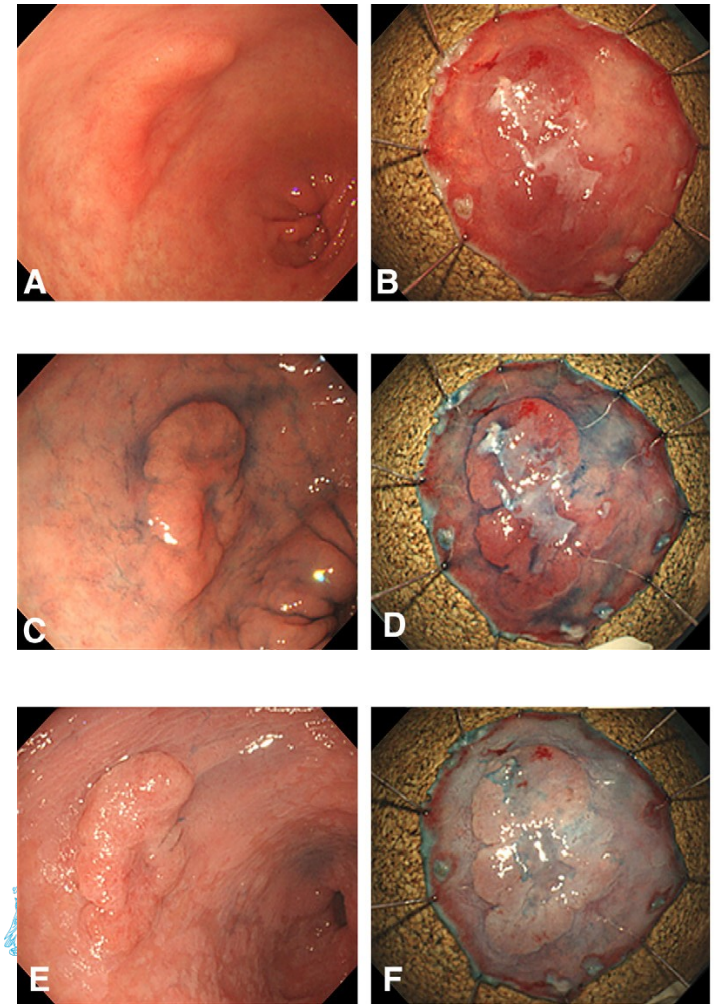
Surgery Quality Assurance

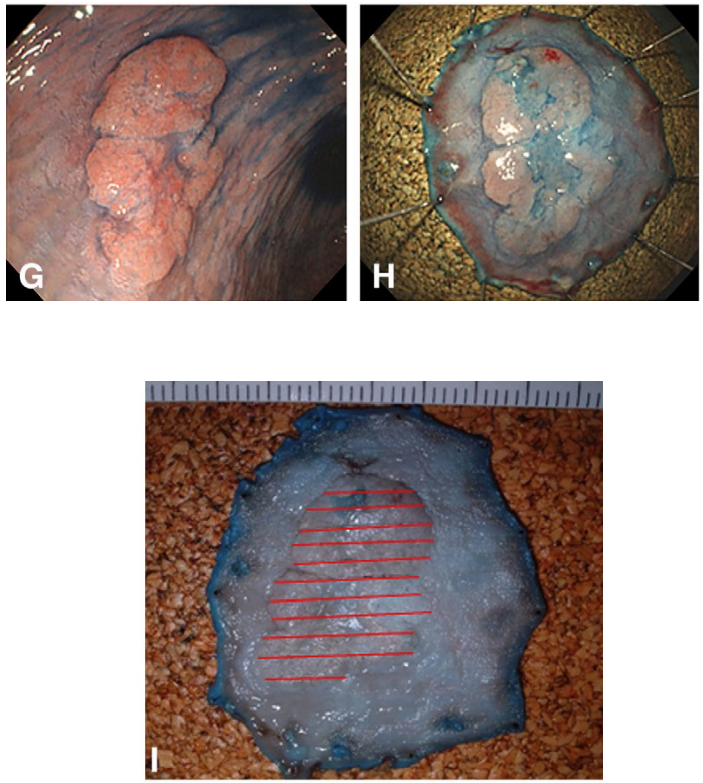
T1 TUMOURS



- Protruding
- Superficial Elevated
- Superficial Flat
- Superficial Ulcerated
- Excavated

Endoscopic Diagnosis
Indigo carmine + Acetic Acid





Sakai et al, GIE 2008

ENDOSCOPIC RESECTION

well differentiated adenocarcinoma

no lymphatic or venous invasion

intramucosal cancer regardless of size without ulceration

intramucosal cancer <30mm with ulceration

minute submucosal penetration (sm1) and <30mm

LN Metastasis from EGC

About 10% of EGC

3% of M cancer

20% of SM cancer

5% of SM has N2

Multiple sections of the primary tumor detect SM

Multiple sections of LN detects metastasis

SURGERY FOR EARLY GASTRIC CANCER

T1 m	D1 alpha (Stations 7 & 8)
T1 sm	D1 beta (D1 alpha + station 9 & 11p)

Function preserving gastrectomy

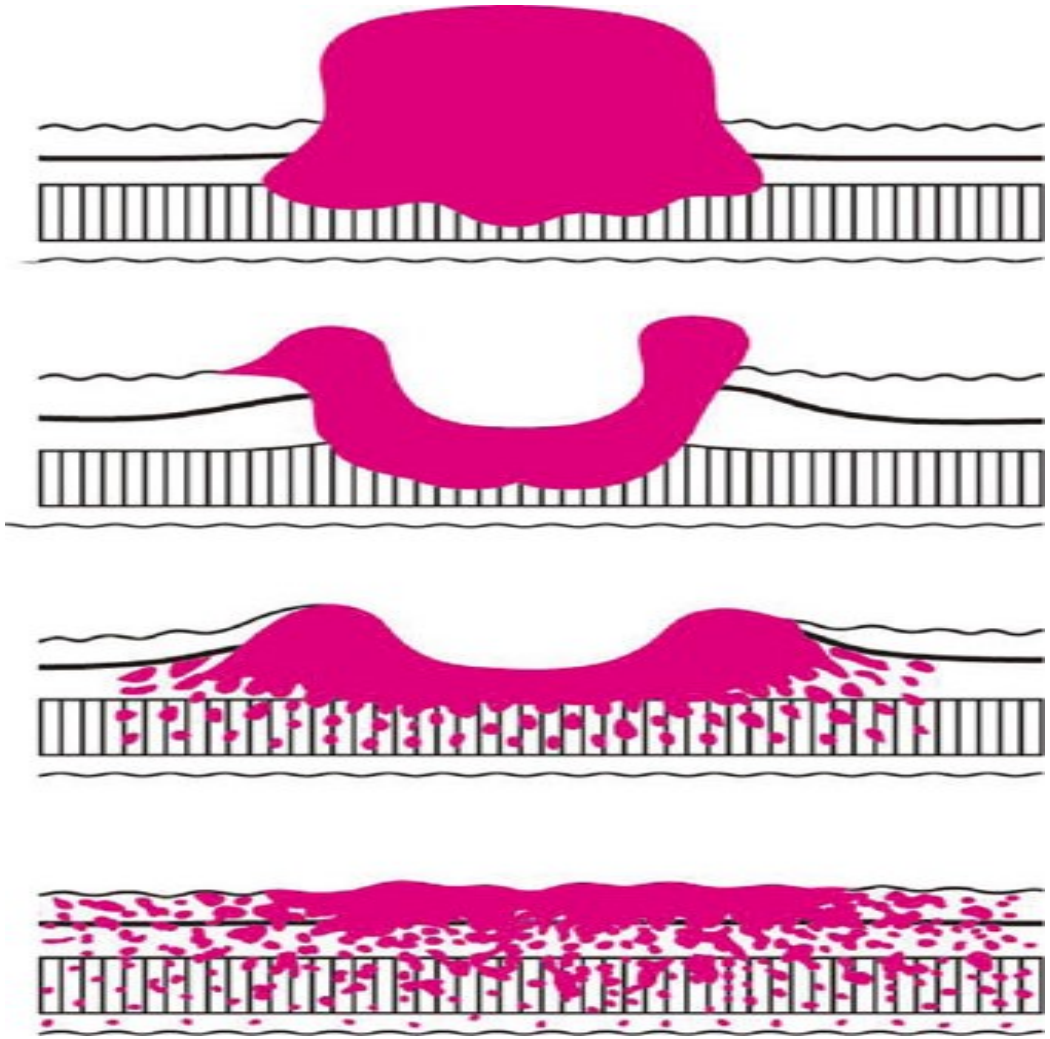
Early Disease

Locally Advanced Disease

Surgical Trials

Surgery Quality Assurance

LOCALLY ADVANCED GASTRIC CANCER



Mass

Ulcerative

Infiltrative, ulcerative

Infiltrative, diffuse

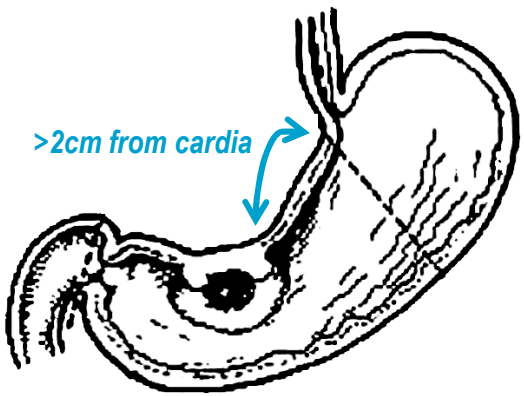
R0 Resection

A surgical procedure in which there is no evidence of macroscopic residual tumour in the tumour bed, lymph nodes and/or distant sites with microscopic negative resection margins

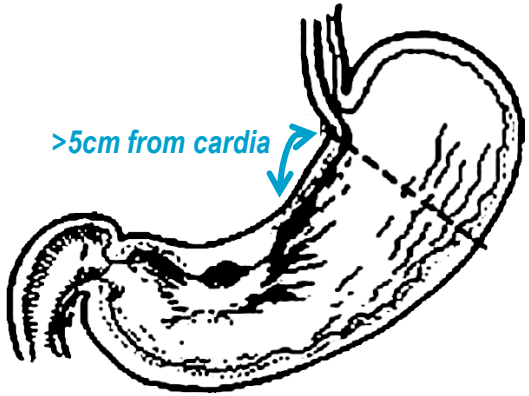
Hermanek P, Wittekind C. Pathol Res Pract. 1994;190(2):115-123.

Indication and Division Lines for Distal Subtotal and Total Gastrectomy

Distal subtotal gastrectomy

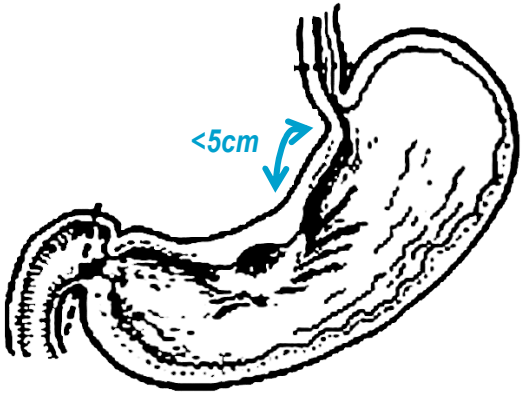


Early cancer or well-circumscribed advanced cancer

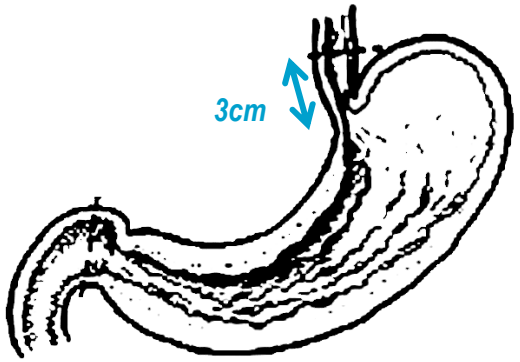


Infiltrative advanced cancer

Total gastrectomy

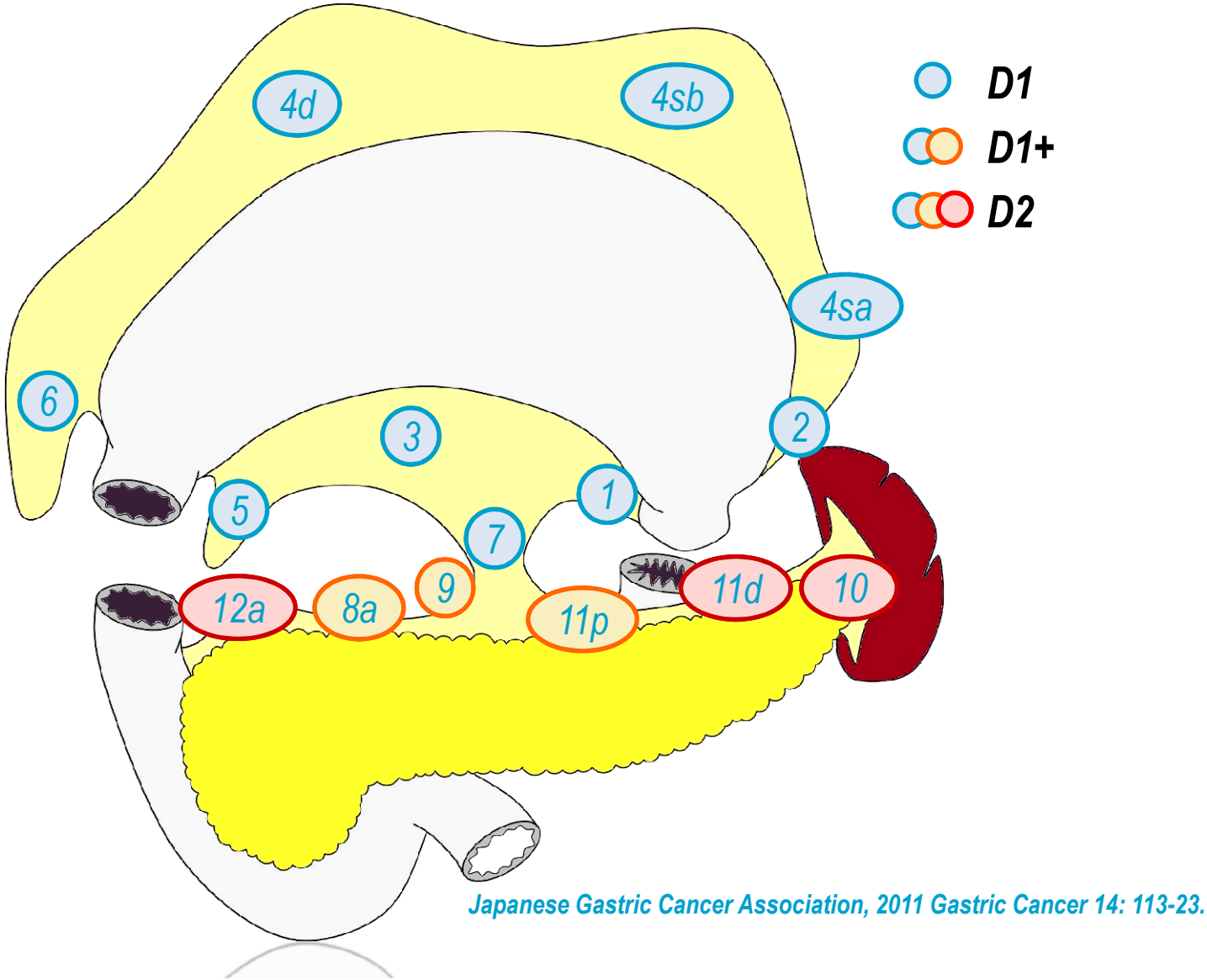


When the proximal distance from the cardia is less than the required length, total gastrectomy is indicated



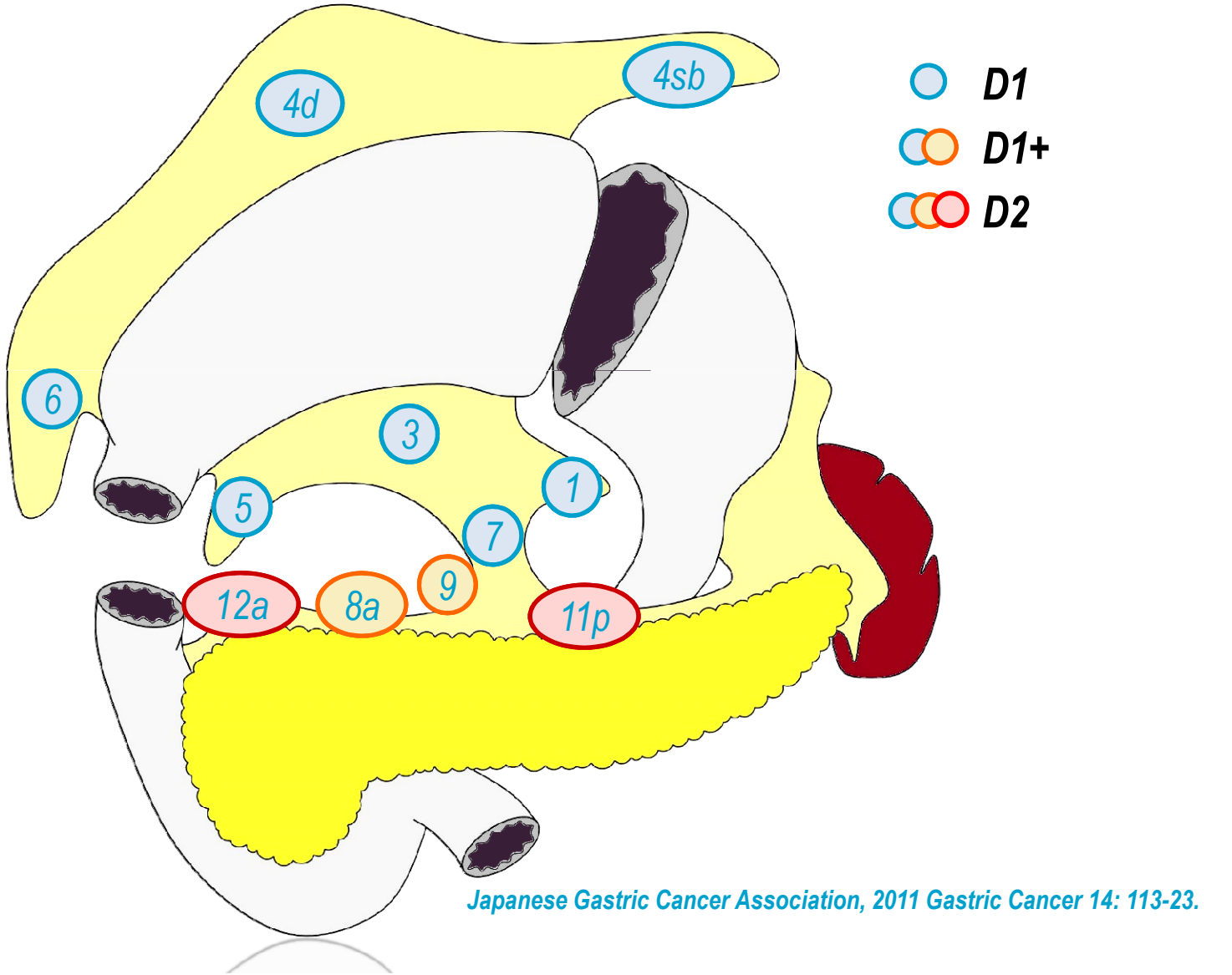
Total gastrectomy is always indicated in diffuse carcinoma (Borrmann type 4) regardless of its size

Total Gastrectomy and Lymph Node Dissection



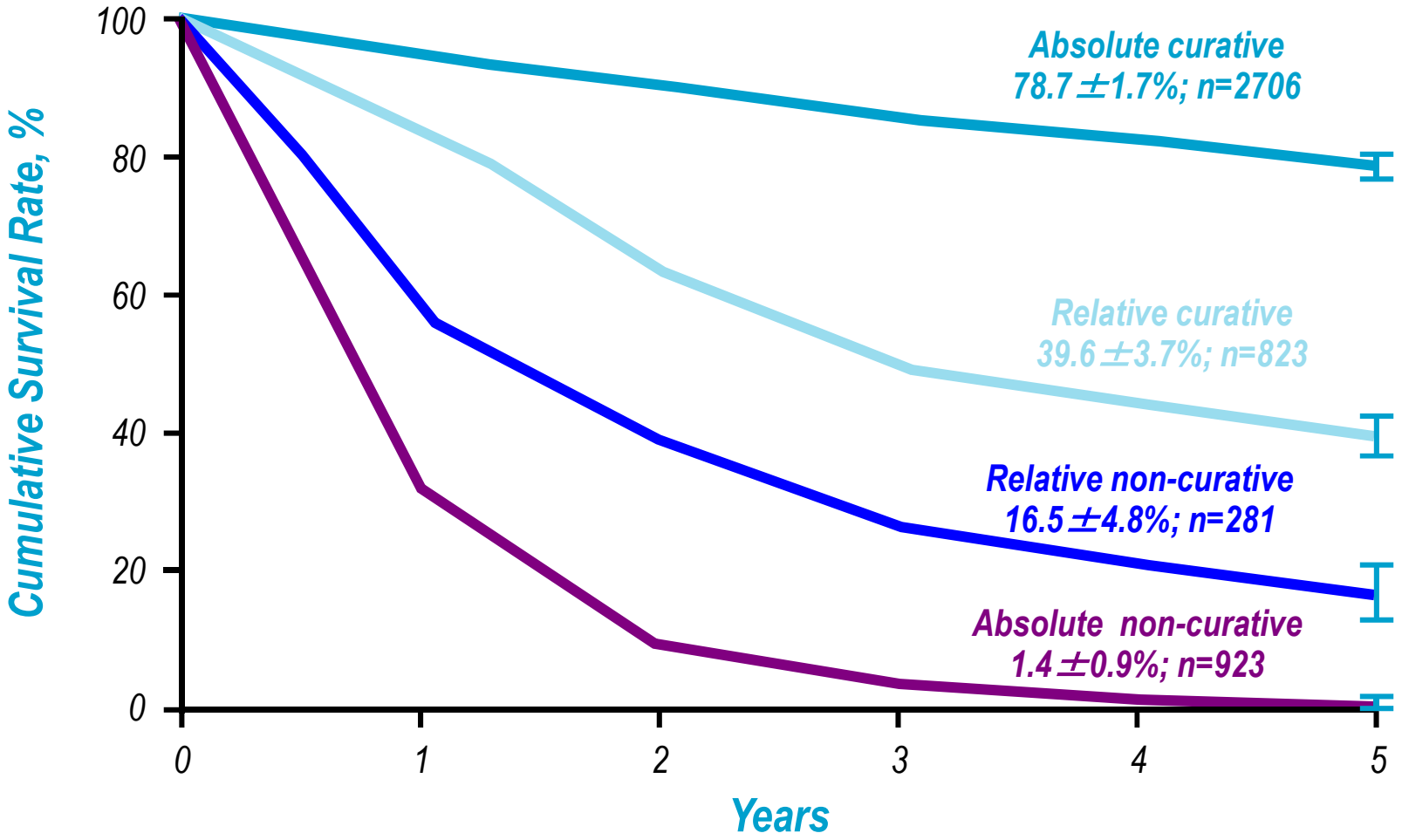
Japanese Gastric Cancer Association, 2011 Gastric Cancer 14: 113-23.

Distal Gastrectomy and Lymph Node Dissection



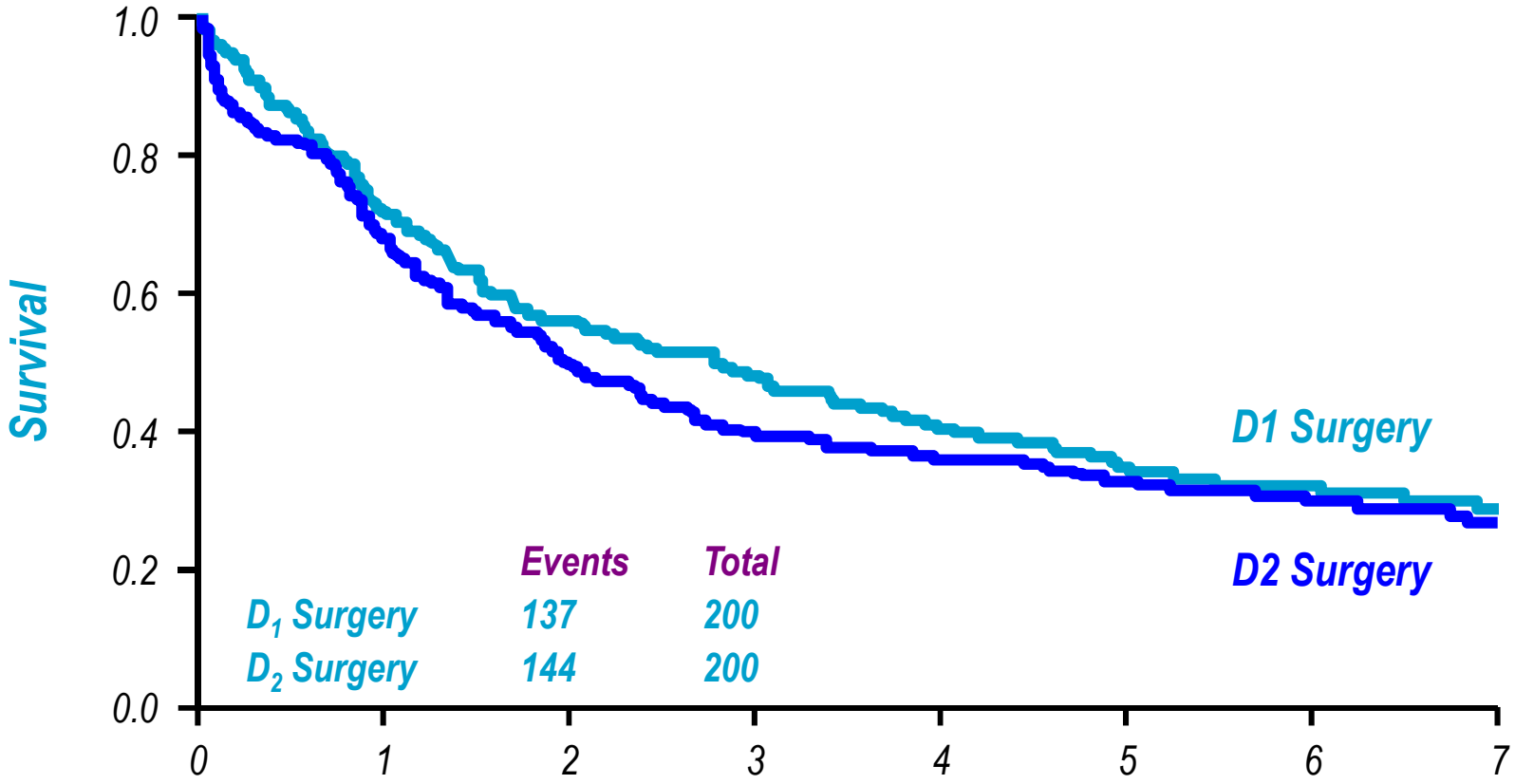
Japanese Gastric Cancer Association, 2011 Gastric Cancer 14: 113-23.

Japanese Rules
End Results of Surgical Resection



Maruyama 1981. Jpn J Surg 11: 127-45

Medical Research Council
D1 vs D2



Patients at risk	Events															
D_1 Surgery	200	(58)		142	(30)	108	(15)	87	(13)	66	(8)	48	(3)	35	(3)	27
D_2 Surgery	200	(68)	132	(34)	97	(19)	76	(6)	65	(5)	54	(4)	36	(3)	26	

Cuschieri A, et al. Br J Cancer. 1999;79(9-10):1522-1530.

Dutch Gastric Cancer Trial Results

N = 711	D_1	D_2	*P* value
Morbidity, %	25	43	<0.001
Mortality, %	4	10	0.004
5-year survival, %	45	47	NS
11-year survival, %	30	35	NS
15-year survival, %	21	29	NS
Gastric Cancer Deaths	48	37	0.01

NS, not significant.

Songun I, et al. Lancet Oncol. 2010;11(5):439-449.

Italian Gastric Cancer Study Group
D1 vs D2 trial

	D1	D2
Operative Mortality	3.0%	2.2%
5 year Survival	66.5%	64.2%
pT1 (p=0.015)	98%	83%
pT2-4 N+ (p=0.055)	38%	59%

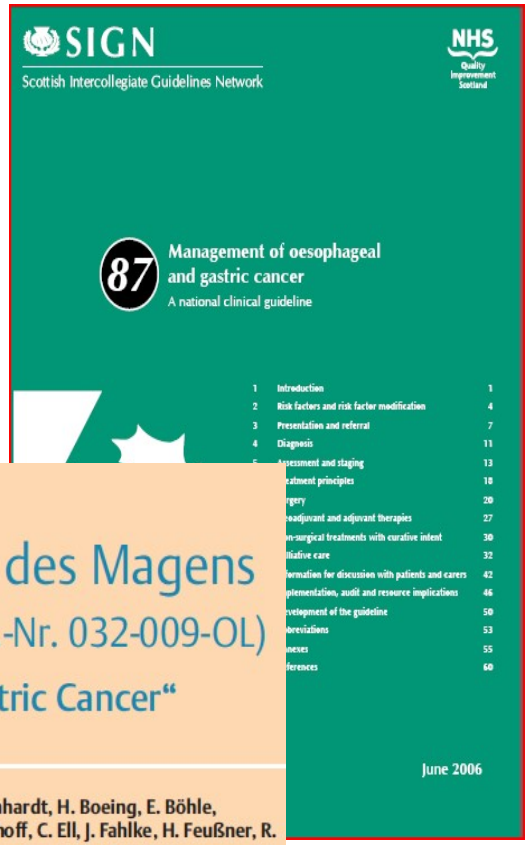
Degiuli M, et al. Br J Surg. 2014; 101:23-31

Gut 2011;**60**:1449-1472 doi:10.1136/gut.2010.228254

Guidelines

Guidelines for the management of oesophageal and gastric cancer

William H Allum[1], Jane M Blazeby[2], S Michael Griffin[3], David Cunningham[4], Janusz A Jankowski[5], Rachel Wong[4] On behalf of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncolo



S3-Leitlinie „Magenkarzinom" –

Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs (AWMF-Regist.-Nr. 032-009-OL)

German S3-Guideline „Diagnosis and Treatment of Esophagogastric Cancer"

Authors M. Moehler, S.-E. Al-Batran, T. Andus, M. Anthuber, J. Arends, D. Arnold, D. Aust, P. Baier, G. Baretton, J. Bernhardt, H. Boeing, E. Böhle, C. Bokemeyer, J. Bornschein, W. Budach, E. Burmester, K. Caca, W. A. Diemer, C. F. Dietrich, M. Ebert, A. Eickhoff, C. Ell, J. Fahlke, H. Feußner, R. Fietkau, W. Fischbach, W. Fleig, M. Flentje, H. E. Gabbert, P. R. Galle, M. Geissler, I. Gockel, U. Graeven, L. Grenacher, S. Groß, J. T. Hartmann, M. Heike, V. Heinemann, B. Herbst, T. Herrmann, S. Höcht, R. D. Hofheinz, H. Höfler, T. Höhler, A. H. Hölscher, M. Horneber, J. Hübner, J. R. Izbicki, R. Jakobs, C. Jenssen, S. Kanzler, M. Keller, R. Kiesslich, G. Klautke, I. Körber, B. I. Krause, C. Kuhn, F. Kullmann, H. Lang, H. Link, F. Lordick, Porschen, berger, . Seufferlein, gelsang, D. Wagner,

Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer – Differential treatment strategies for subtypes of early gastroesophageal cancer

Manfred P. Lutz[a,*], John R. Zalcberg[b], Michel Ducreux[c], Jaffer A. Ajani[d], William Allum[e], Daniela Aust[f], Yung-Jue Bang[g], Stefano Cascinu[h], Arnulf Hölscher[i], Janusz Jankowski[j], Edwin P.M. Jansen[k], Ralf Kisslich[l], Florian Lordick[m], Christophe Mariette[n], Markus Moehler[l], Tsuneo Oyama[o], Arnaud Roth[p], Josef Rueschoff[q], Thomas Ruhstaller[r], Raquel Seruca[s], Michael Stahl[t], Florian Sterzing[u], Eric van Cutsem[v], Ate van der Gaast[w], Jan van Lanschot[x], Marc Ychou[y], Florian Otto[z]

European Guidelines
Surgery

Guideline	Gastric Resection	Lymphadenectomy
SIGN	R0 (proximal, distal circumferential margins)	D2 ≥ 25 lymph nodes
	R0 (proximal, distal circumferential margins)	D2 > 25 lymph nodes
German S3	5cm intestinal 8cm diffuse	> 16 nodes for TNM No pancreatectomy/splenectomy
UK	R0	D2 for stage II & III – if fit > 15 nodes for TNM
St Gallen	cT1 diffuse – resect R0	D2 – without pancreatectomy or splenectomy

SIGN, Scottish Intercollegiate Guidelines Network; TNM, tumour node metastases..

Allum W et al Gut 2011; 60:1449-72; Lutz MP, et al. Eur J Cancer. 2012;48(16):2941-2953; Moehler M, et al. Z Gastroenterol. 2011;49(4):461-531; Scottish Intercollegiate Guidelines Network. Management of oesophageal and gastric cancer: a national clinical guideline. http://www.sign.ac.uk/pdf/sign87.pdf. Published June 2006. Accessed September 9, 2013.

Early Disease

Locally Advanced

Surgical Trials

Surgery Quality Assurance

The Royal Marsden

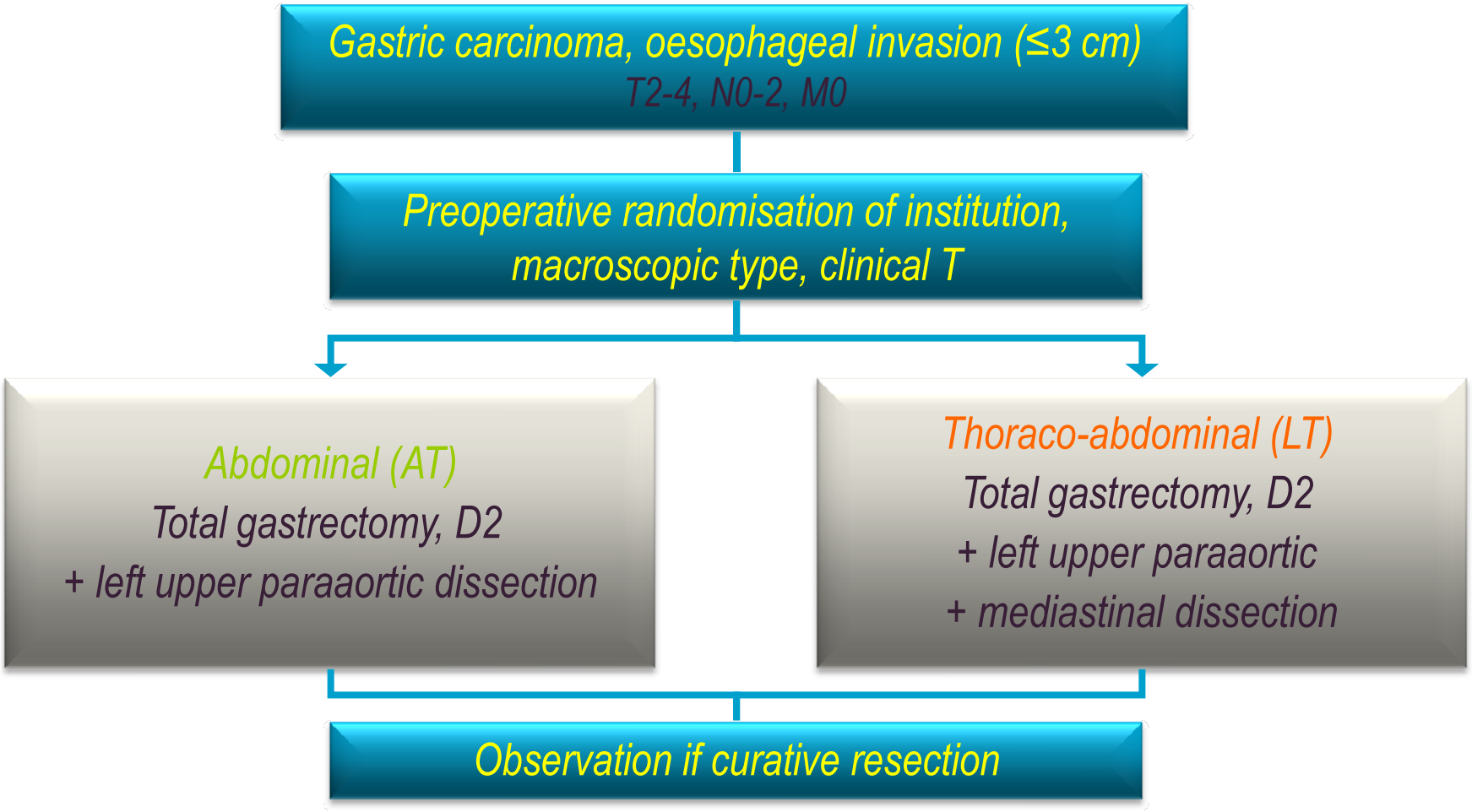
JCOG 9502

Randomized trial in Siewert type II and III cancers

Left thoraco-abdominal approach versus abdominal transhiatal approach

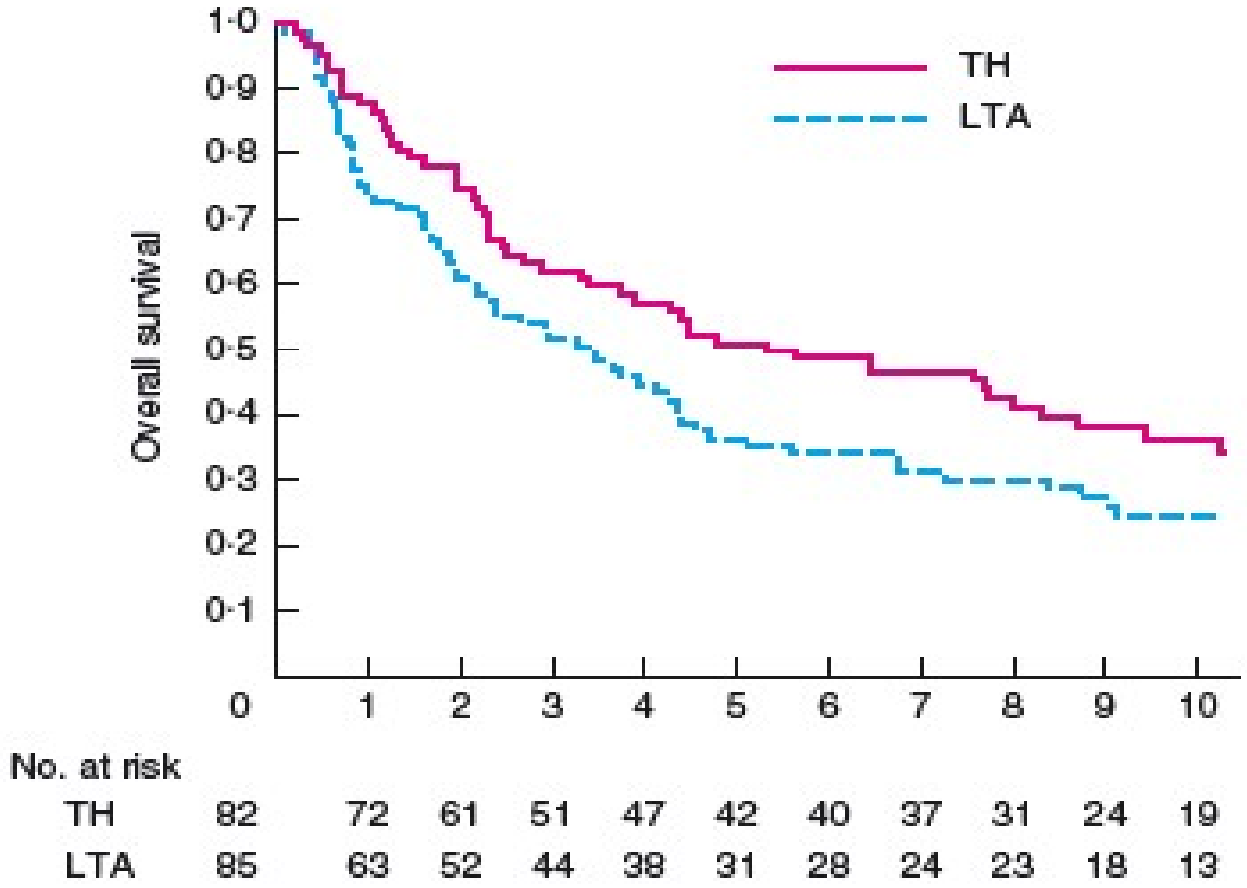
JCOG, Japan Clinical Oncology Group.
Sasako et al. Lancet Oncol. 2006;7(8):644-651; BJS 2015; 102:341-8.

JCOG 9502
Scheme



AT, abdominal transhiatal; LT, left thoraco-abdominal.
Sasako et al. Lancet Oncol. 2006;7(8):644-651.

JCOG 9502
Overall Survival



Kurokawa et al Br J Surg 2015 102:341-348.

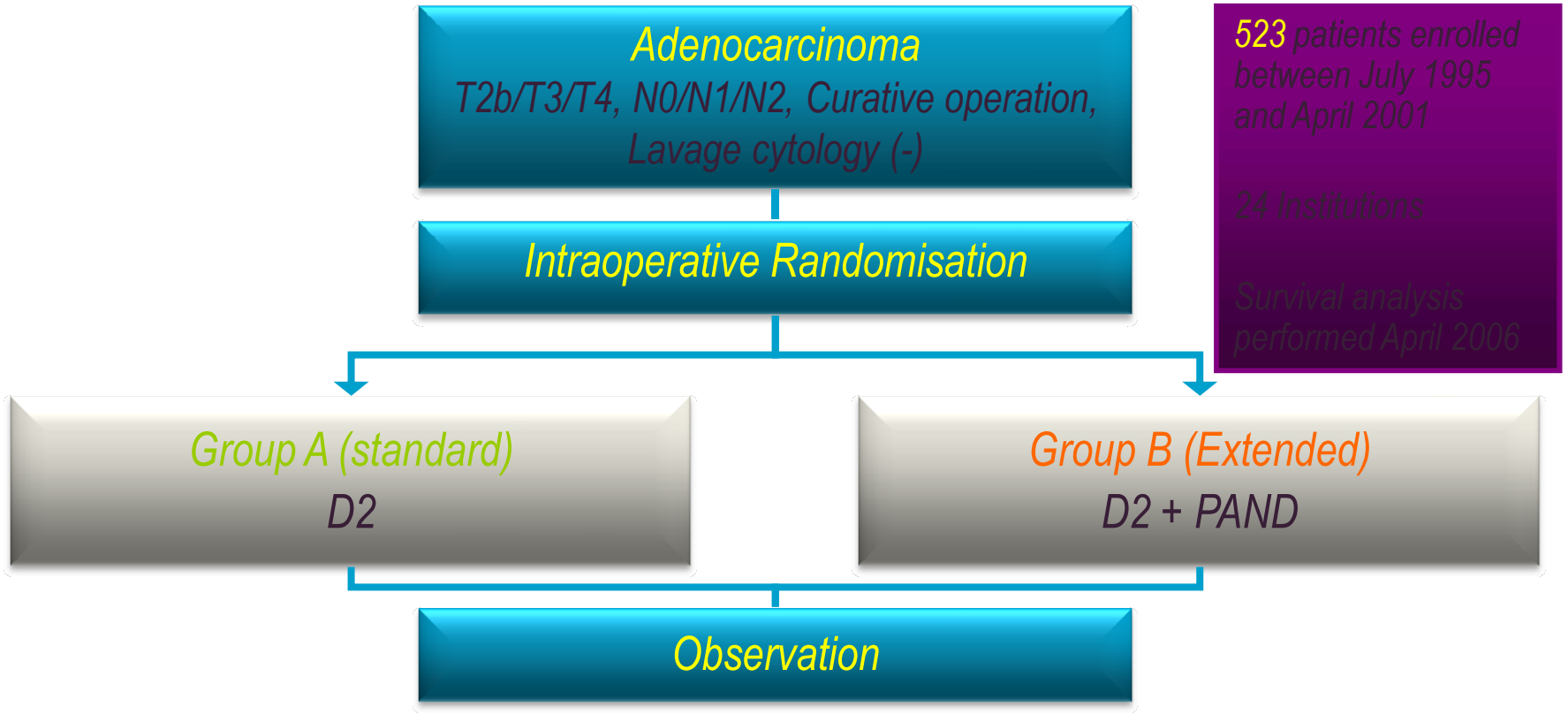
The Royal Marsden

JCOG 9501

D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer

Sasako M, et al. N Eng J Med. 2008;359(5):453-462.

JCOG 9501
Scheme



523 patients enrolled between July 1995 and April 2001

24 Institutions

Survival analysis performed April 2006

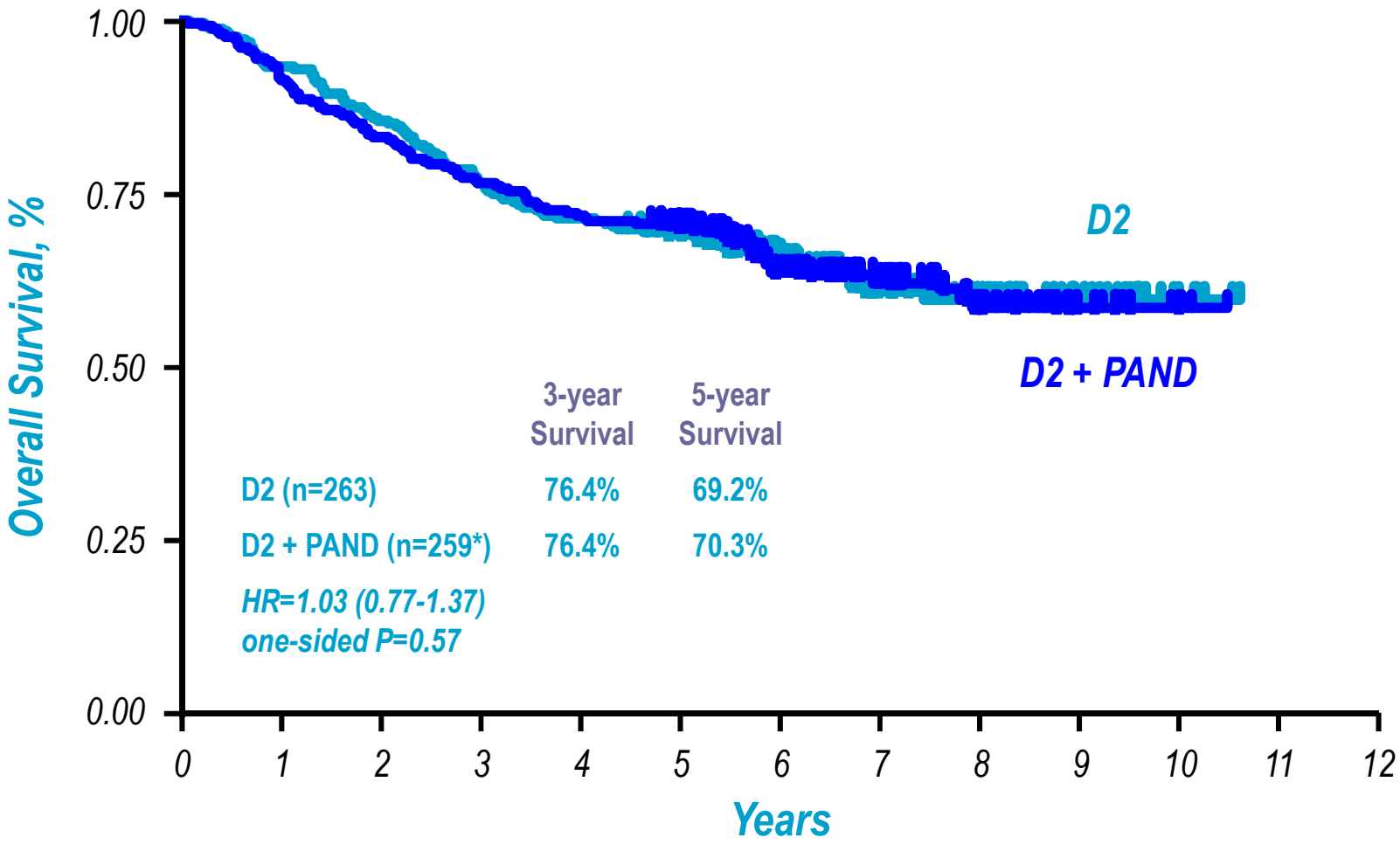
Endpoints

1. Overall survival
2. Recurrence-free survival, morbidity/mortality

PAND, para-aortic nodal dissection.

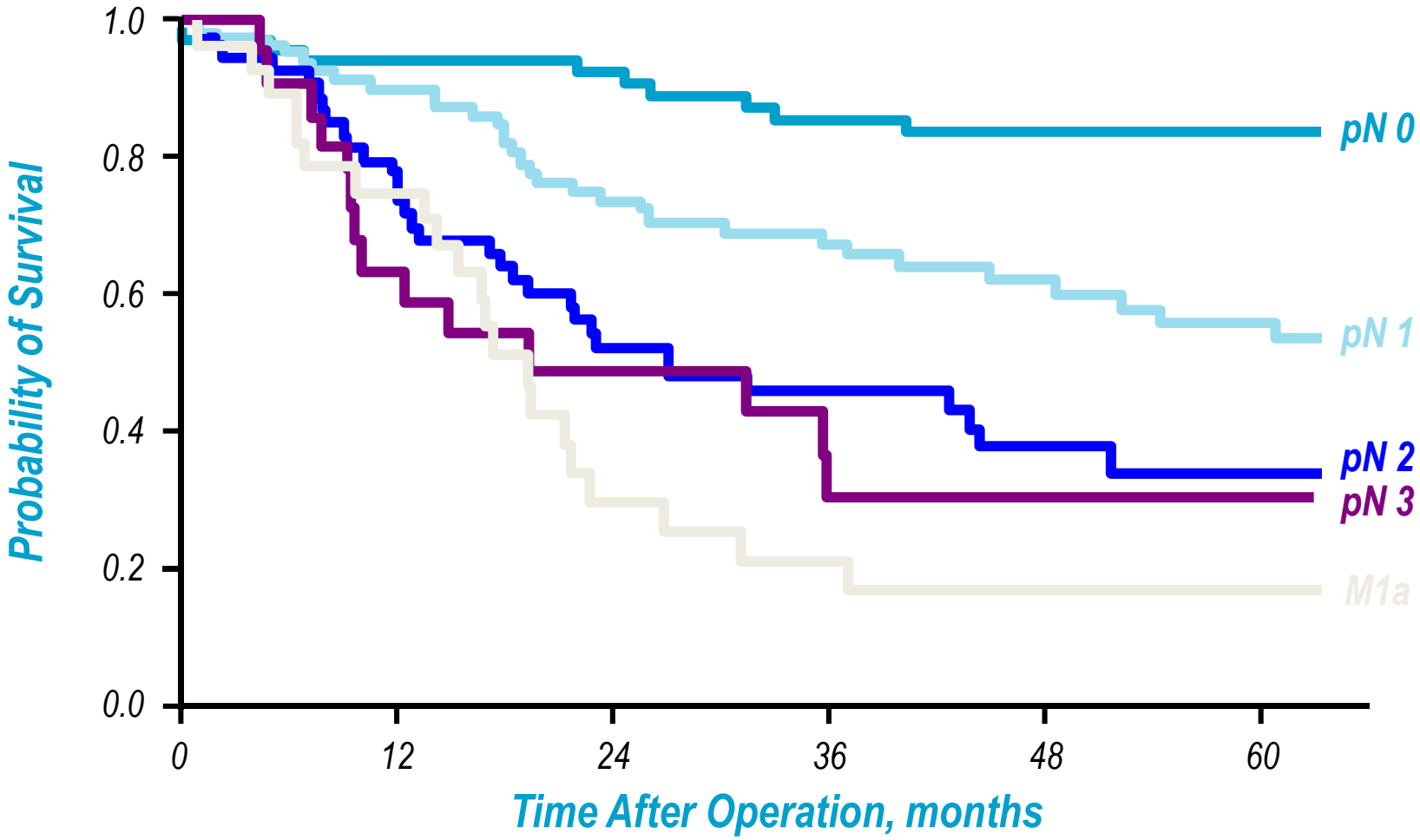
Sasako M, et al. N Eng J Med. 2008;359(5):453-462.

JCOG 9501
Overall Survival



HR, hazard ratio.
**One case was ineligible because of changed histologic diagnosis.*
Sasako M, et al. N Engl J Med. 2008;359(5):453-462.

Extended Lymphadenectomy



Roviello F, et al. Eur J Surg Oncol. 2010;36(5):439-446.

Extended Lymphadenectomy

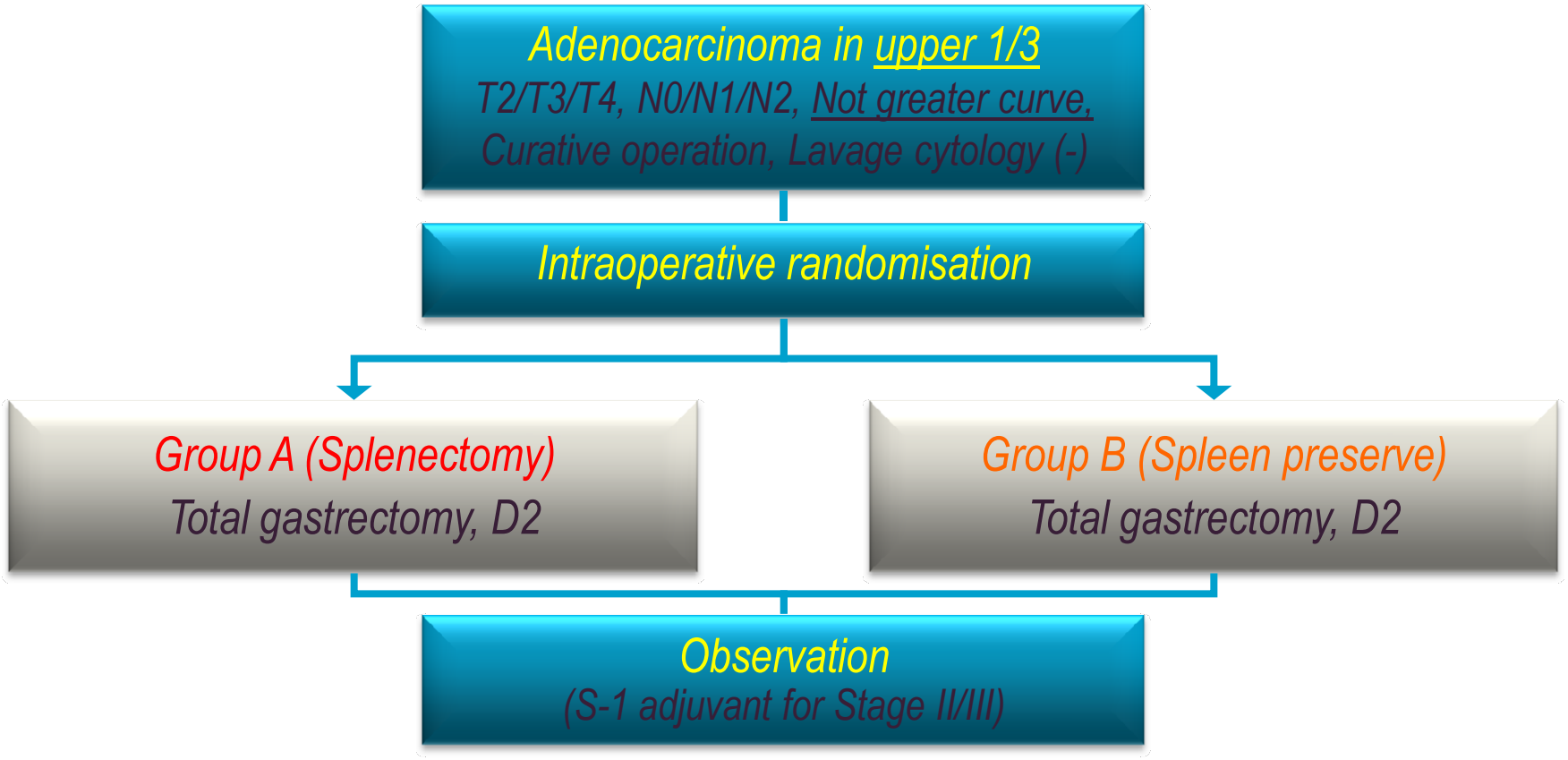
T3/4 cancers

Mixed or diffuse histology

Upper third of the stomach

De Manzoni G, et al. Ann Surg Oncol. 2011;18(8):2273-2280.

JCOG 0110 “Splenectomy or Not”



Endpoints *1. Overall survival*

2. Morbidity, operation time, blood loss

Sano T, et al. J Clin Oncol. 2010;28(15 Suppl):abstract 4020.

JCOG 0110 “Splenectomy or Not”

505 patients

Similar operative mortality with or without splenectomy

Greater postoperative morbidity with splenectomy

Greater intraoperative blood loss with splenectomy

5 year survival

Splenectomy	75.1%
Splenic preservation	76.4%

Sano T, et al. J Clin Oncol. 2010;28(15 Suppl):abstract 4020; GI ASCO 2015.

Minimally Invasive Surgery

Shorter inpatient stay

Less blood loss

Quicker return to GI function

? Anastomotic leak rates

Intraluminal bleeding

Minimally Invasive Surgery
Total Gastrectomy

Variables	Extent of LND		*P* value
	D1 + ß (n=103)	D2 (n=19)	
Operating time, mean, min ± SD	277 ± 86	350 ± 76	0.001
EBL, mean, mL ± SD	231 ± 190	350 ± 250	0.019
Harvested lymph nodes, mean, n ± SD	42 ± 16	44 ± 16	0.484
Morbidity, n %	19 (18.4)	10 (52.6)	0.003
Mortality, n %	0	2 (10.5)	<0.001
Hospital stay, mean, d ± SD	10.8 ± 9.1	17.1 ± 20.8	0.032

EBL, estimated blood loss; LND, lymph node dissection; SD, standard deviation.
Jeong O, et al. J Am Coll Surg. 2013;216(2):184-191.

Minimally Invasive Surgery

Early gastric cancer

Distal Gastrectomy

KLASS Trial

Comparison of laparoscopic vs open gastrectomy for gastric cancer: a prospective randomized trial

JCOG 0912

Phase III study of laparoscopy-assisted vs open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric cancer: a multicenter study

KLASS, Korea Laparoscopic Gastrointestinal Surgery Study Group.
Kim HH, et al. Ann Surg. 2010;251(3):417-420; Nakamura K, et al. Jpn J Clin Oncol. 2013;43(3):324-327.

Early Disease

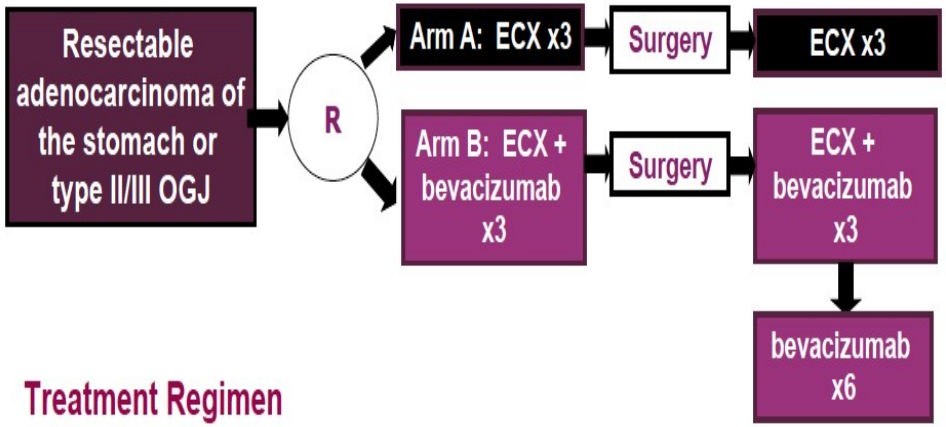
Locally Advanced

Surgical Trials

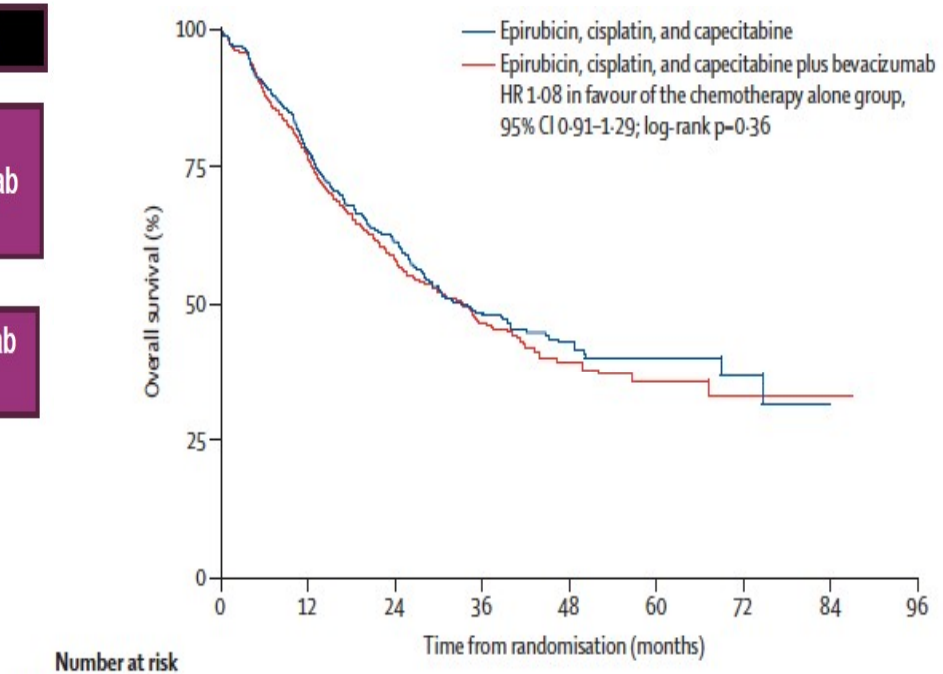
Surgery Quality Assurance

STO3 Trial

Perioperative ECX +/- bevacizumab in patients with gastric or oesophagogastric junction adenocarcinoma



Treatment Regimen



Number at risk (number censored)									
Epirubicin, cisplatin, and capecitabine	533 (11)	404 (52)	271 (85)	135 (59)	65 (31)	30 (20)	9 (8)	1 (0)	0 (0)
Epirubicin, cisplatin, and capecitabine plus bevacizumab	530 (11)	397 (52)	254 (69)	142 (71)	57 (27)	26 (12)	13 (13)	1 (0)	0 (0)

Cunningham et al 2017, Lancet Oncol. 18: 357-70

Surgery in ST03
Radicality of Resection

		ECX (n=533)	ECX+B (n=530)	p-value
Extent of resection	R0	315 (74%)	301 (75%)	0.844
	R1	108 (26%)	100 (25%)	
	No resection	86	105	
	Unavailable	24	24	
Lymph node dissection	<15 nodes	79 (19%)	62 (15%)	
	15-24 nodes	143 (34%)	134 (33%)	
	25+ nodes	204 (48%)	206 (51%)	
	Unavailable	21	23	

Post-operative Morbidity & Mortality

	ECX		ECX+B		Total	
	Overall	LT	Overall	LT	Overall	LT
Any complication	**48%**	**7%**	**56%**	**8%**	**52%**	**8%**
Revisional operation	**8%**		**9%**		**9%**	
Wound healing complications	7%	<1%	12%	1%	10%	<1%
Wound infection (superficial)	8%	<1%	9%	<1%	9%	<1%
Cardiac complications	5%	2%	7%	1%	6%	2%
Intra-abdominal sepsis	4%	1%	4%	2%	4%	1%
Wound infection (deep)	3%	1%	3%	1%	3%	1%
Haemorrhage requiring transfusion	3%	1%	3%	2%	3%	1%
PE	1%	0%	2%	0%	2%	0%
DVT	1%	0%	2%	0%	1%	0%
TOTAL	**440**		**426**		**866**	

LT = life-threatening

Post-operative mortality	Death within 30 days	14 / 447 (3%)	10 / 425 (2%)
	Death within 90 days	21 / 447 (5%)	21 / 425 (5%)

The Royal Marsden

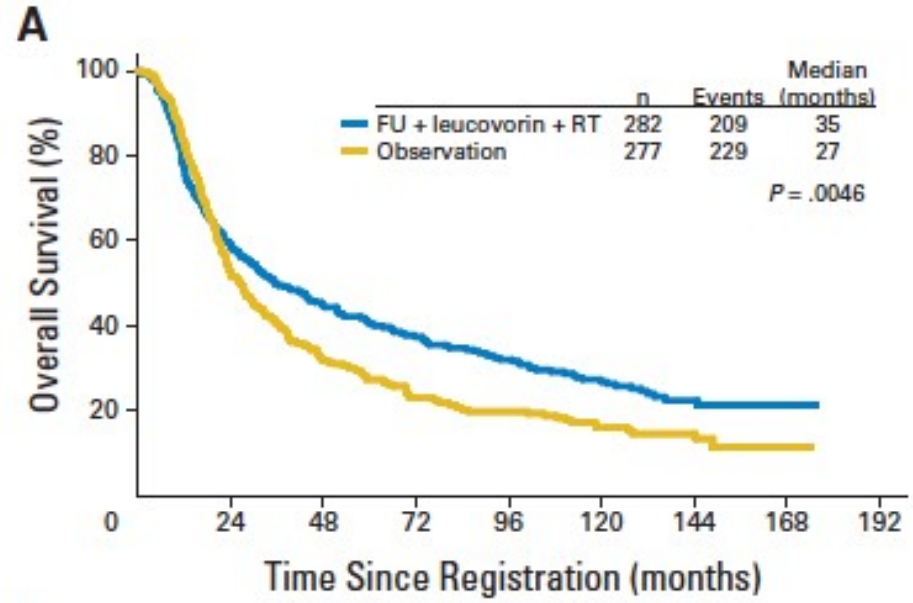
Anastomotic leaks

Surgical procedure	ECX		ECX+B		Total	
	Leaks / Patients	(%)	Leaks / Patients	(%)	Leaks / Patients	(%)
Oesophago-gastrectomy	20 / 229	(9%)	51 / 218	(23%)	71 / 447	(16%)
Total gastrectomy	17 / 137	(12%)	19 / 129	(15%)	36 / 266	(14%)
Sub-total gastrectomy	0 / 15	(0%)	1 / 16	(6%)	1 / 31	(3%)
Distal gastrectomy	1 / 43	(2%)	2 / 41	(5%)	3 / 84	(4%)
Other procedures	1 / 16	(6%)	2 / 22	(9%)	3 / 38	(8%)
TOTAL	**39 / 440**	**(9%)**	**75 / 426**	**(18%)**	**114 / 866**	**(13%)**

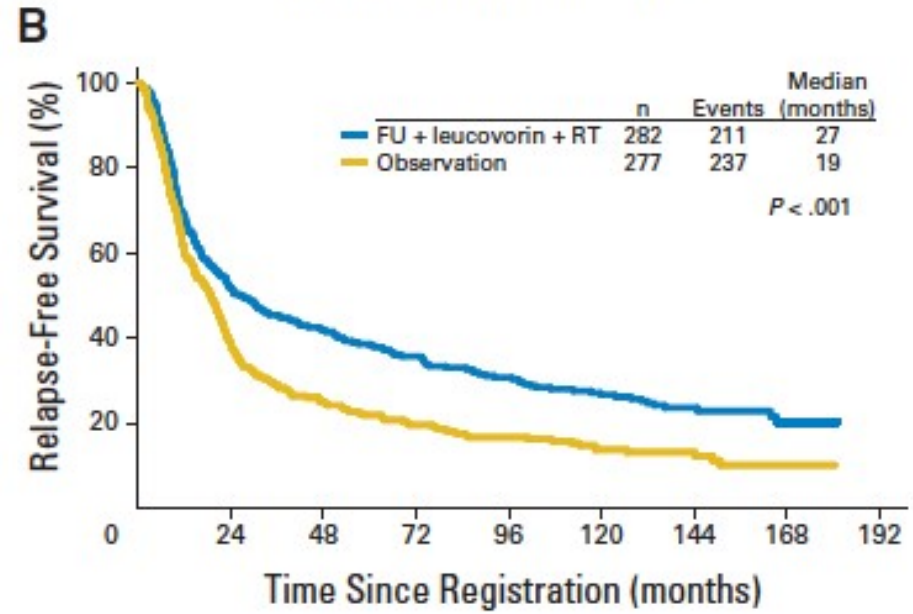
- 30-day mortality: 2 / 39 ECX (5%), 8 / 75 ECX+B (11%)
- Revisional operations: 20 / 39 ECX (51%), 24 / 75 ECX+B (32%)
- 39% occurred within 5 days of surgery, 78% within 10 days

- No other clinical factors identified (no centre/surgeon effect)

Intergroup 0116 chemoradiation in resected gastric cancer



A: Overall Survival



B: Relapse free survival

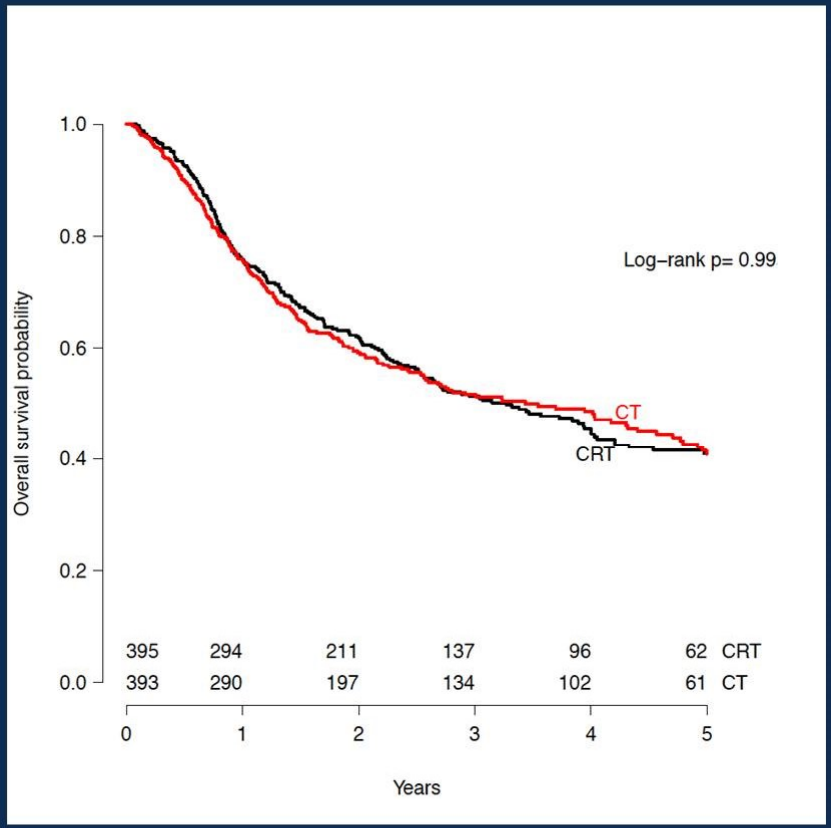
Smalley et al 2012

Intergroup 0116
Gastric Resection

PROCEDURE	PROPORTION IN STUDY
D0	54%
D1	36%
D2	10%

CRITICS Trial

Results: Overall Survival



	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Marcel Verheij at 2016 ASCO Annual Meeting

CRITICS

Surgical Compliance

D1+	40.8%	
	Non-compliance	35.6% (nodal resection)

Surgical – pathological compliance

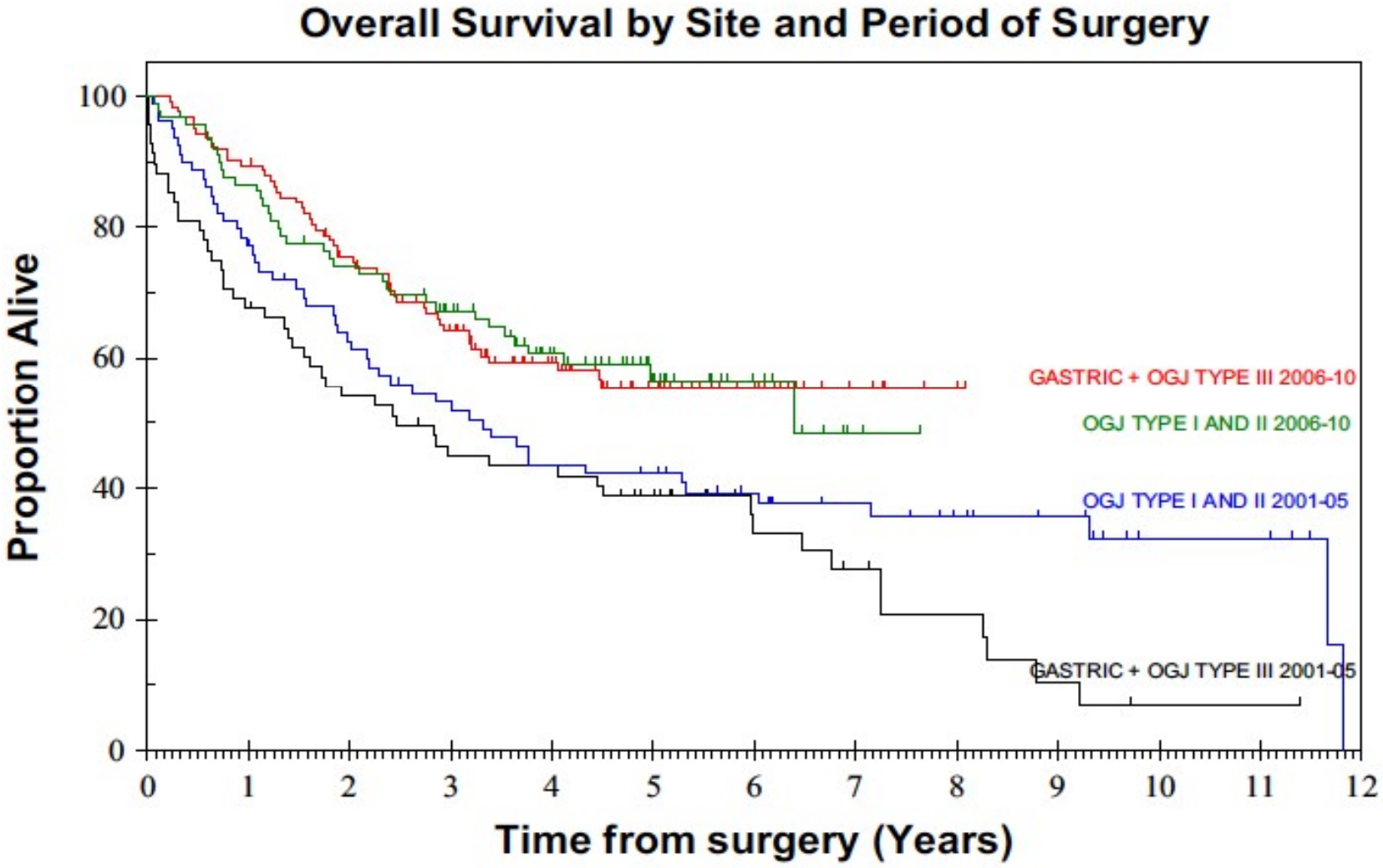
>15 LN	73.3%	
	2007	55.0%
	2015	90.0%

Claassen et al 2017 ECCO

Completion of Planned Adjuvant Treatment

	Proportion
MAGIC	Chemo 41%
FFCD	Chemo 50%
ST03	Chemo 37%; Chemo +Bevacizumab 37%
INT 0116	CRT 65%
ARTIST	Chemo 75%; CRT 81.7%
CRITICS	Chemo 47%; CRT 52%

RMH Overall Survival 2001-2010



Fontana et al 2016 *In Press*

Tailored Treatment

Treatment modality varies:

- Stage
- Patient risk
- Surgical volume
- Available chemotherapy
- Quality of radiotherapy

"the result of treatment for locally advanced gastric cancer is the sum of the effect of local tumour control by surgery, with or without radiotherapy and / or systemic chemotherapy"

Takeshi Sano 2007


Thank you for your attention
FULHAM ROAD

The Royal Marsden

The Royal Marsden

Multipurpose device

Surgery

	CSC		S	
	N	**%**	**N**	**%**
Proceeded to surgery	219	88%	240	95%
Resection outcome:				
'Curative' operation	169	-	166	-
Palliative operation	44	-	70	-
Laparotomy but no resection	1	-	0	-
Resection performed but outcome unknown	5	-	4	-
Never had surgery	15	6%	6	2%
Incomplete surgical data	16	6%	4	2%
Median time to surgery	99 days		14 days	

In patients who proceeded to resection with known outcome, a significantly higher proportion of patients in the CSC arm (79% vs 70%; p=0.029, χ^2 test) had resections which were deemed curative by the surgeon.

Postoperative morbidity/mortality

	CSC	S
Postoperative deaths	6% (14/219)	6% (15/240)
Postoperative complications	46%	46%
Median duration of post-operative hospital stay	13 days	13 days

Pathology staging following surgery

	CSC	S	p-value
Maximum tumour diameter			
Median (IQR)	3.cm (2.0-5.0)	5.0cm (3.5-7.5)	<0.001, Mann-Whitney U test
Extent of tumour (gastric only)			
T1/T2	52%	38%	0.009, χ^2 test (trend)
T3/T4	48%	62%	
Nodal status (gastric only)			
N0/N1	84%	76%	0.01, χ^2 test (trend)
N2/N3	16%	29%	

The EURECCA Project Upper GI

Survey of variations of curative treatment of oesophageal and gastric cancer among 5 european countries

Gastric Cancer
Neoadjuvant - Results

	Treated	Control	Treated	Control
MAGIC	79%	70%	T1/2: 52% N0/1: 84%	T1/2: 38% N0/1: 76%
FFCD 9703	87%	74%	T1/2: 39% N0: 33%	T1/2: 32% N0: 20%
EORTC 40954	82%	67%	T1/2: 66% N0: 38.6%	T1/2: 50% N0: 19%

NUMBER OF CASES TREATED RADICALLY

	Oesophagus Oesophago-Gastric Junction	Stomach
Netherlands	697	465
France	348	266
Spain	207	456
UK	1219	747
Ireland	196	68

NEOADJUVANT CHEMOTHERAPY

	Oesophagus	Oesophago-Gastric Junction	Stomach
Netherlands	6%	27%	51%
France	38%	24%	34%
Spain	8%	18%	22%
UK	47%	59%	29%
Ireland	5%	30%	38%

SURGERY STOMACH

	Proximal Gastrectomy	Total Gastrectomy	Distal Gastrectomy	Laparotomy only
Netherlands		33%	54%	12%
France	23%	49%	28%	
Spain	1%	38%	61%	
UK	3%	39%	44%	5%
Ireland		42%	57%	1%

Upper GI: technical and clinical challenges for RO

State of art of radiation therapy

in a combined treatment perspective

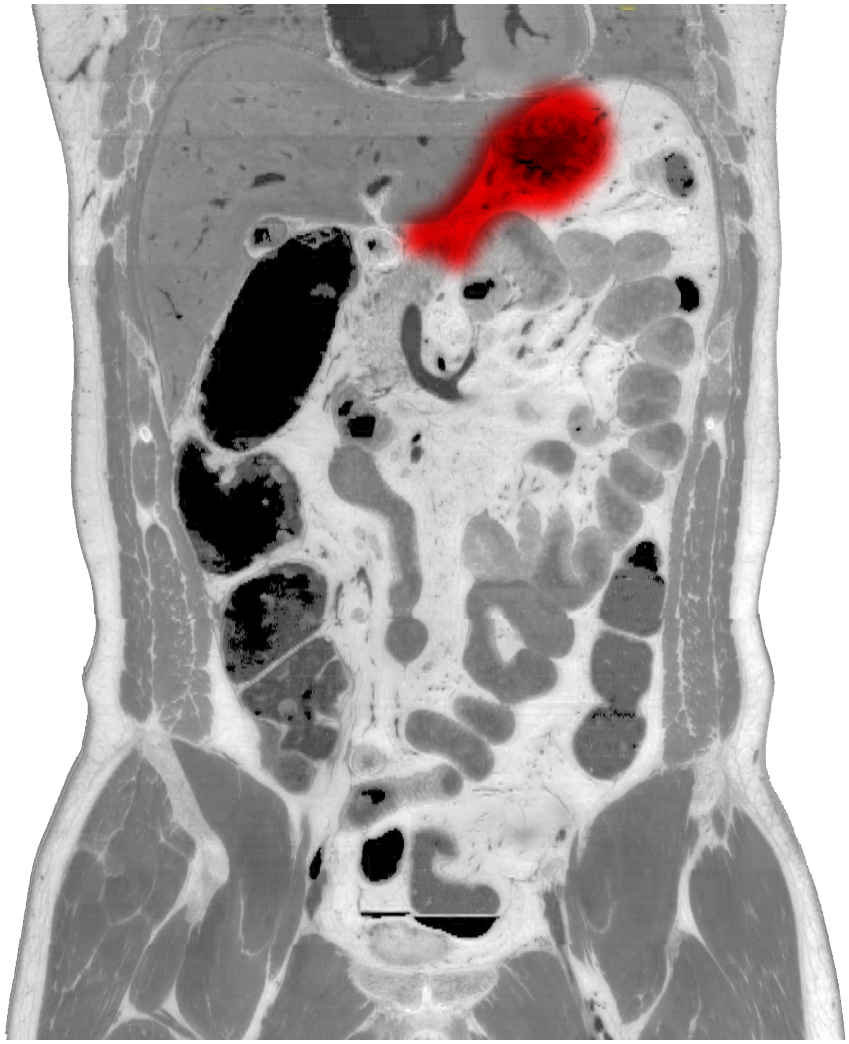
State of art of radiation therapy in Gastric Cancer

- ✓ **Background** and **assumptions**
- ✓ **Post-operative** Chemoradiation
- ✓ **Pre-operative Chemoradiation**
- ✓ **Intra-operative RT**

✓Background and assumptions: the challenge

Sites of Recurrence

Only Failure	Any Component
23%	69%
21%	42%
5%	23%



Gunderson LL Sosin H – IJROBP – 1982 (USA)

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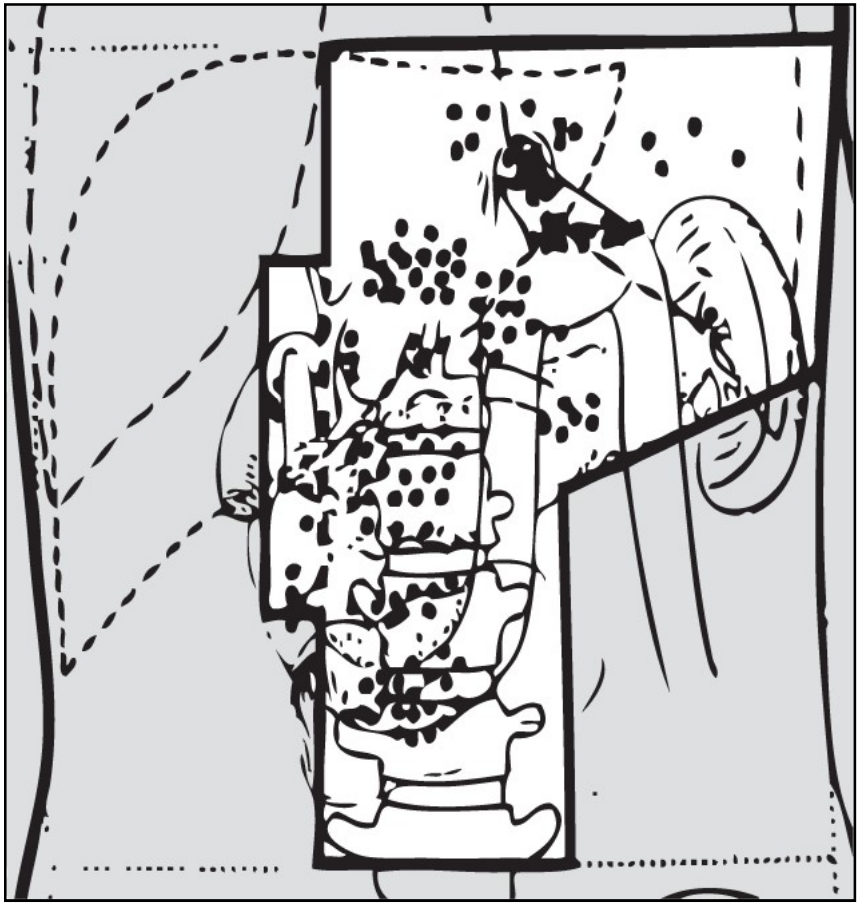
Target volume based on second look



Gunderson LL Sosin H – IJROBP - 1982

✓Background and assumptions: the challenge

Author	Year	Pts	Relapse (%)	Single Site (%)	Multiple Sites (%)	Locoregional Relapse (%) Remnant Stomach Duodenal Stump Regional Nodes	Sistemic Relapse (%)		
							Peritoneal	Hematogenous	Lymphatic
Yoo Median F-up 68 months	2000	2328	45.7	83.7	16.3	19.3	33.9	26.2	4.3
Maehara Median F-up 24.3 months	2000	939	62.8	74.6	24.4	17.5	34.0	44.3	4.1
Cordiano Median F-up 42 months	2002	412	50.2	93.2	7.0	3.5	30.5	30.9	-
Ohno Median F-up 17.2 months	2003	709	18.5	79.2		5.8	44.2	30.8	19.2
Wu Median F-up 76.8 months	2003	631	40.1	50.2	49.8	26.0	38.2	26.8	8.9

Average

22.3%

Valentini V et Al – Exp Rev – 2007
(Italy)

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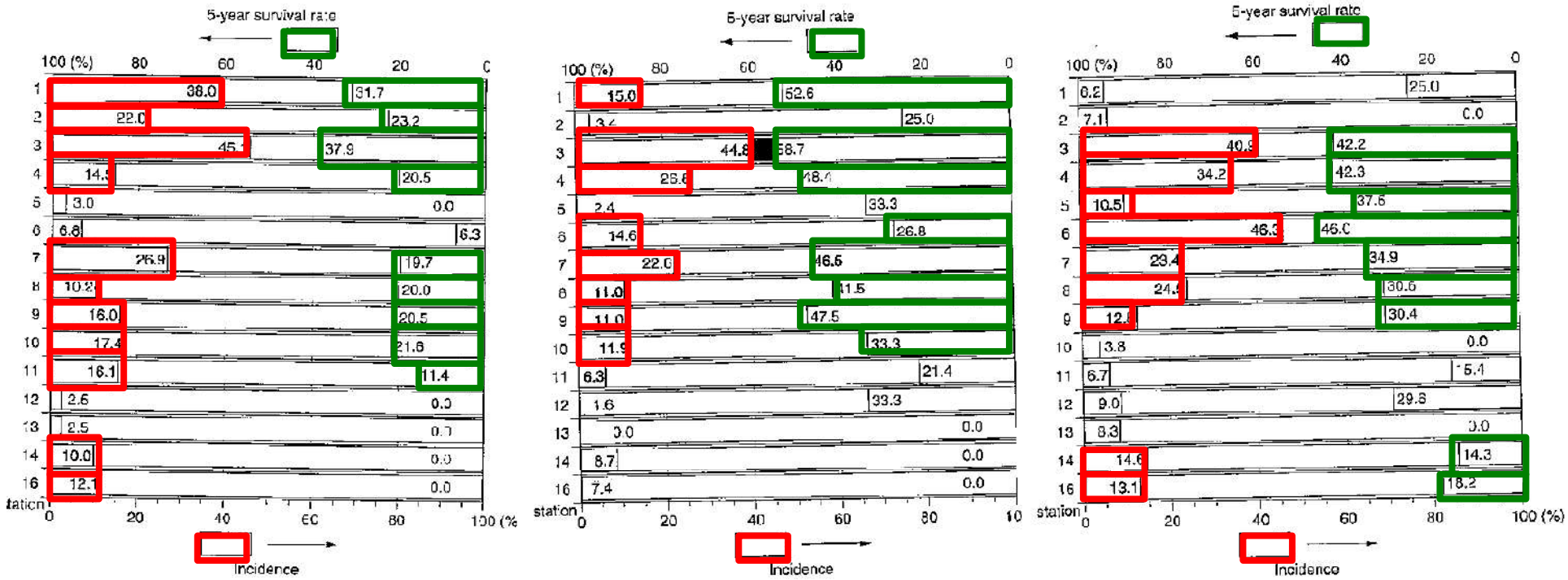
✓Background and assumptions: the challenge

4683 patients



proximal **middle** **distal**

Sasako M – Gastric Cancer – 1999
(Japan)

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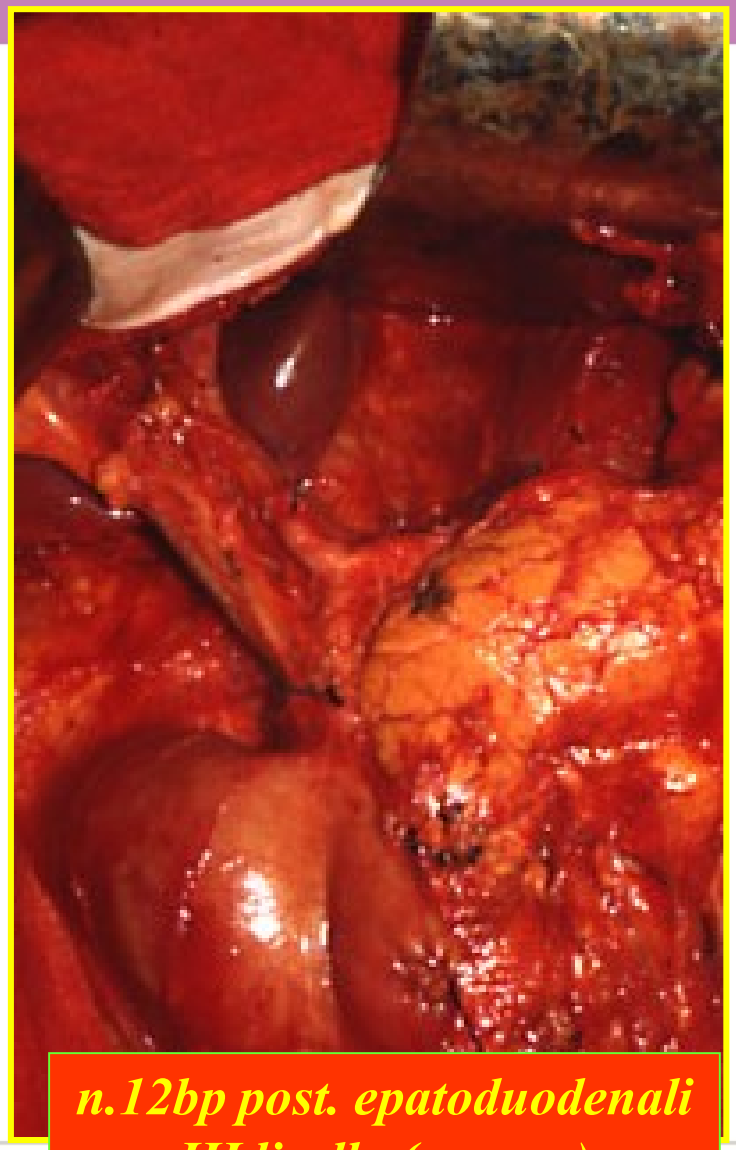
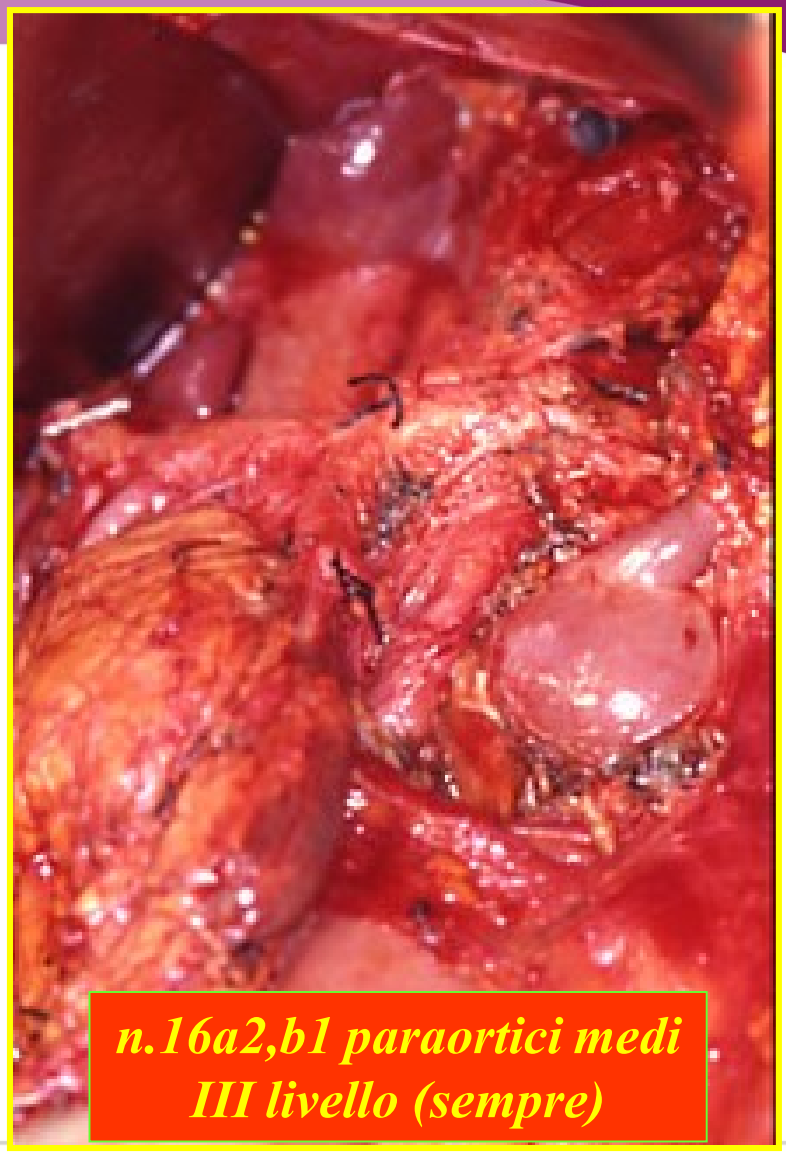
CANCRO GASTRICO T2-T3 *Chirurgia estesa (D3)*



n.12bp post. epatoduodenali
III livello (sempre)



n.16a2,b1 paraortici medi
III livello (sempre)

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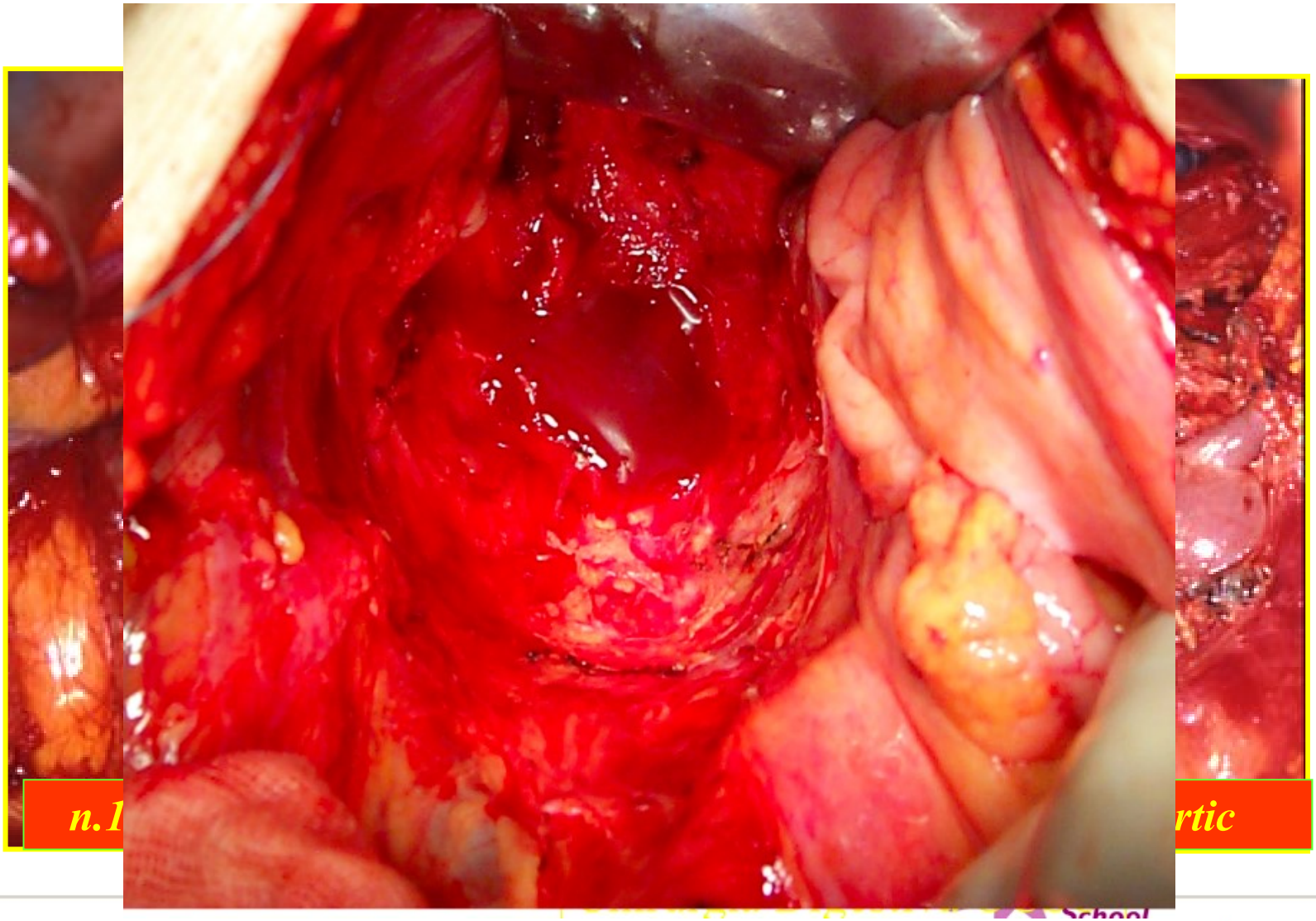
✓Background and assumptions: the challenge



By the courtesy of F. Pacelli, UCSC, Rome

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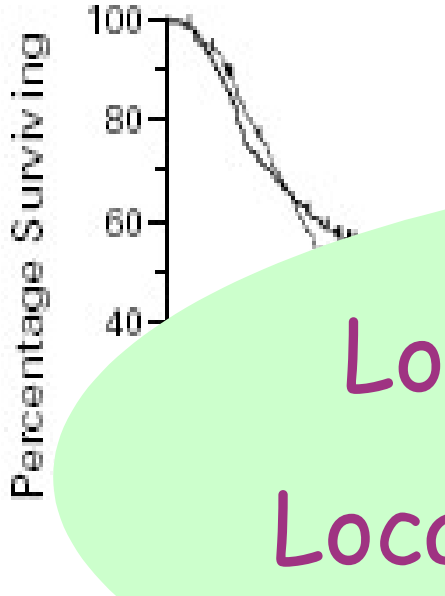
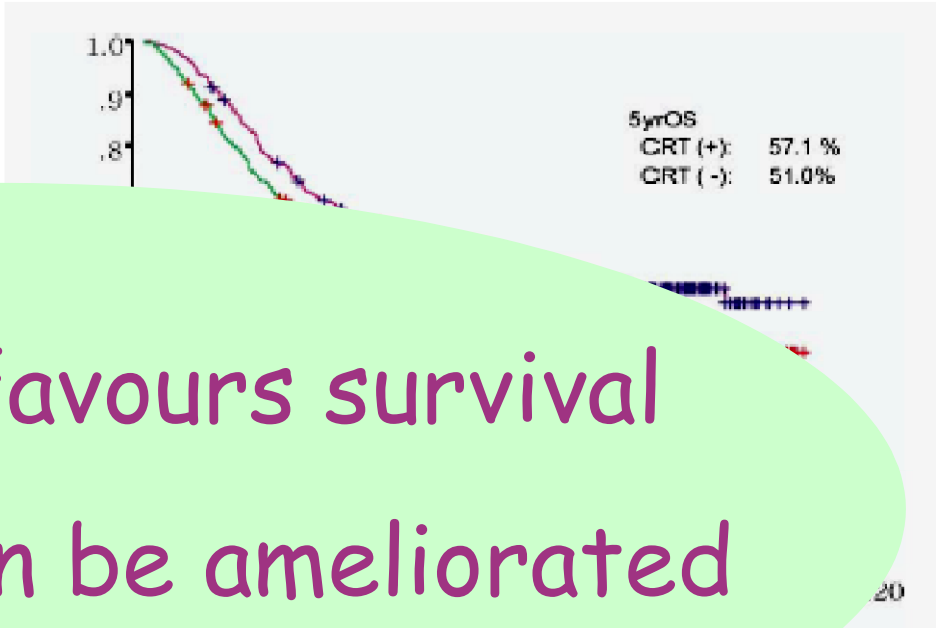
✓Background and assumptions: the challenge

EQD2: 44.25 Gy



EQD2: 44.25 Gy



N.Pat. ... t. 990

Local control favours survival

Local control can be ameliorated

INT-0116

D2 = 10%

Korean study

D2 = 87%

Macdonald JS et Al – NEJM -2001
Kim S, Macdonald JS et Al – IJROBP – 2005

(USA)

ESTRO School

✓Background and assumptions: the challenge

Cessation of chemioradiotherapy

TABLE 2. REASONS FOR THE CESSATION OF CHEMORADIOTHERAPY AMONG THE 281 PATIENTS IN THE CHEMORADIOTHERAPY GROUP.

REASON FOR CESSATION	NO. OF PATIENTS (%)
Protocol treatment completed	181 (64)
Toxic effects	49 (17)
Patient declined further treatment	23 (8)
Progression of disease	13 (5)
Death	3 (1)
Other	12 (4)

Side effects (Grade 3-4 WHO)

TABLE 3. MAJOR TOXIC EFFECTS OF CHEMORADIOTHERAPY.*

TYPE OF TOXIC EFFECT†	NO. OF PATIENTS (%)
Hematologic	148 (54)
Gastrointestinal	89 (33)
Influenza-like	25 (9)
Infection	16 (6)
Neurologic	12 (4)
Cardiovascular	11 (4)
Pain	9 (3)
Metabolic	5 (2)
Hepatic	4 (1)
Lung-related	3 (1)
Death†	3 (1)

Macdonald JS et Al – NEJM -2001

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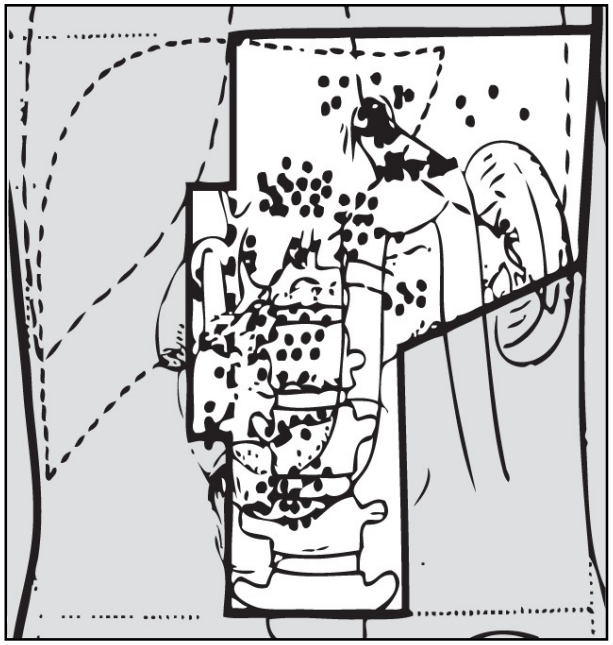
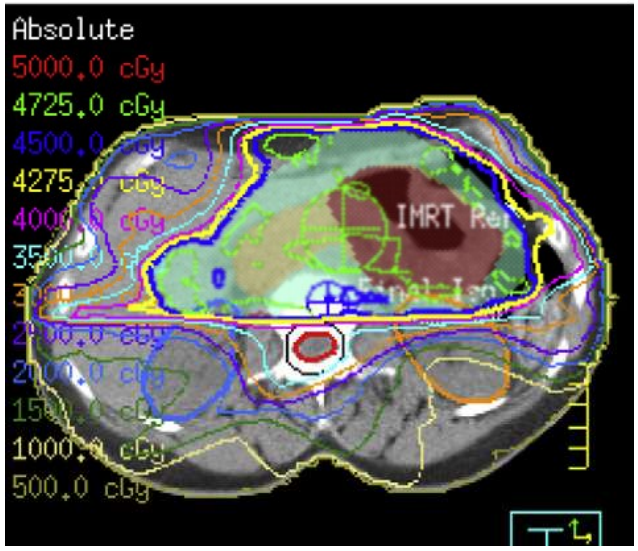
✓Background and assumptions: the challenge





2D 3D IMRT

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✓Background and assumptions: the challenge

Postop CT vs IMRT RTCT After D2 for locally advanced

Selection criteria:

- T3-T4 and/or N+ M0
- D2 lymphadenectomy

EQD2: 44.25 Gy

Treatment arms:

- CT-RTCT (IMRT)-CT-CT
- CT arm = same regimen

Zhu W-g el al – *Radiother and Oncol*– 2012 (China)

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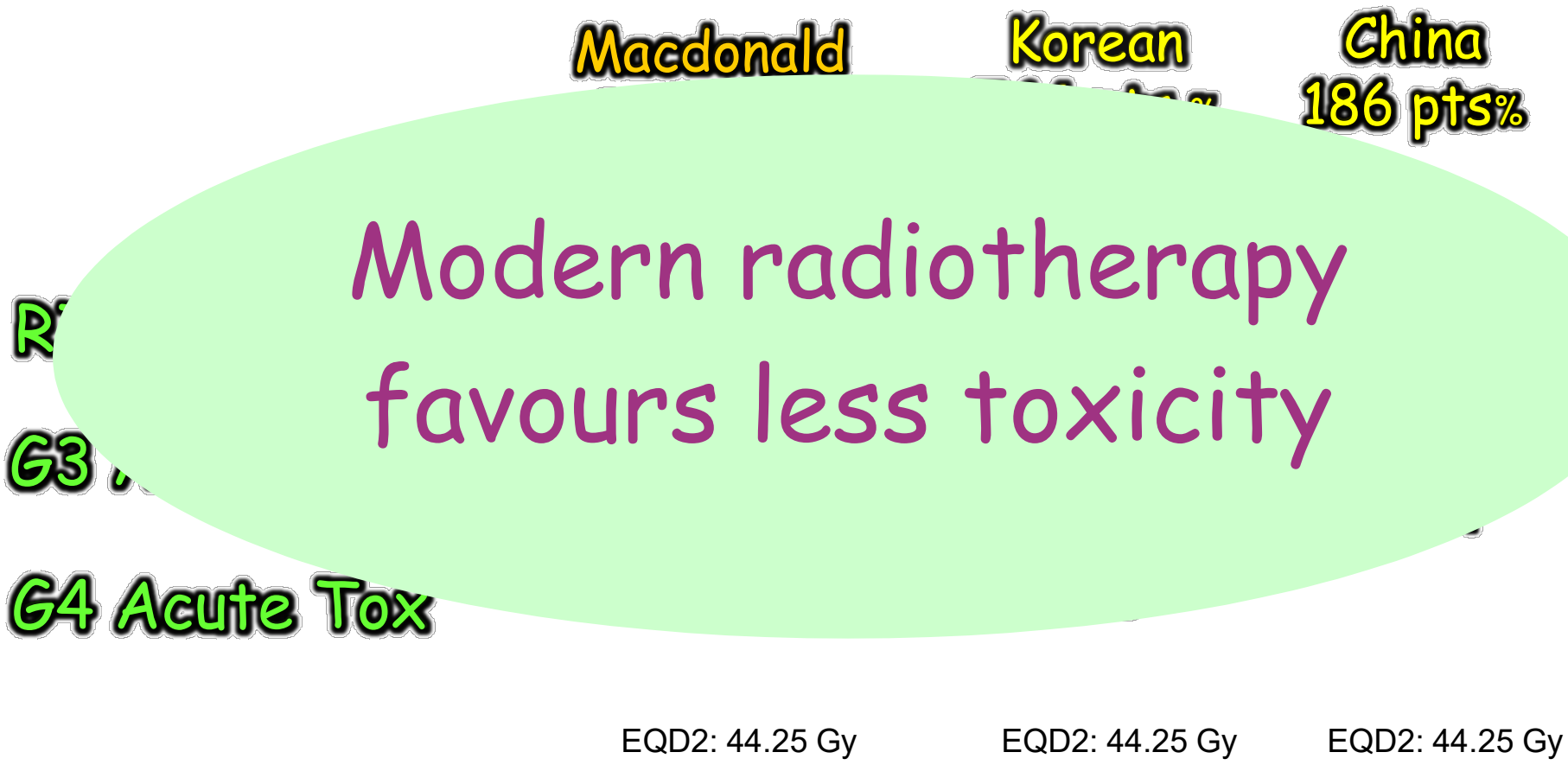
✓Background and assumptions: the challenge



Modern radiotherapy favours less toxicity

Macdonald JS et Al – NEJM -2001
Kim S, Macdonald JS et Al – IJROBP – 2005
Zhu W et Al – Radioth Oncol - 2012

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State of art of radiation therapy in Gastric Cancer

- ✓ **Background** and **assumptions**

  Local control favours survival
  Local control can be ameliorated
  Modern radiotherapy favours less toxicity

- ✓ **Post-operative** Chemoradiation

✓Post-operative Chemoradiation

THE LANCET, OCTOBER 25, 1969

COMBINED 5-FLUOROURACIL AND SUPERVOLTAGE RADIATION THERAPY OF LOCALLY UNRESECTABLE GASTROINTESTINAL CANCER

CHARLES G. MOERTEL DONALD S. CHILDS, JR.
RICHARD J. REITEMEIER MALCOLM Y. COLBY, JR.
MARGARET A. HOLBROOK

Section of Oncology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901

Moertel *et al*; Lancet Oncol 1969
(USA)

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✓Post-operative Chemoradiation

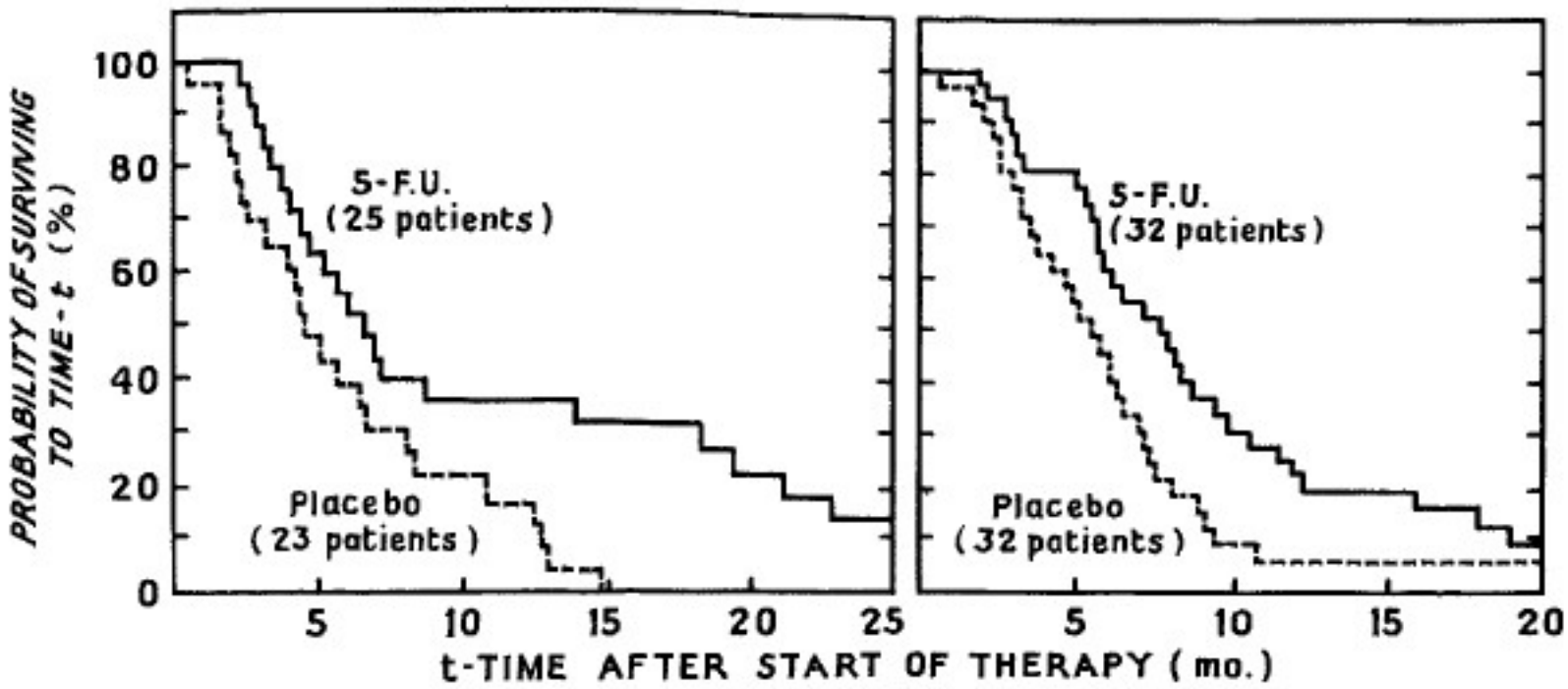


Fig. 1—Survival curves for patients with unresectable adenocarcinoma of stomach.

Fig. 2—Survival curves for patients with unresectable adenocarcinoma of pancreas.

RTCT (2D): 35-40 Gy (1.8-2.2 Gy fx) + 5Fu EQD2: 34.42- 40.67 Gy

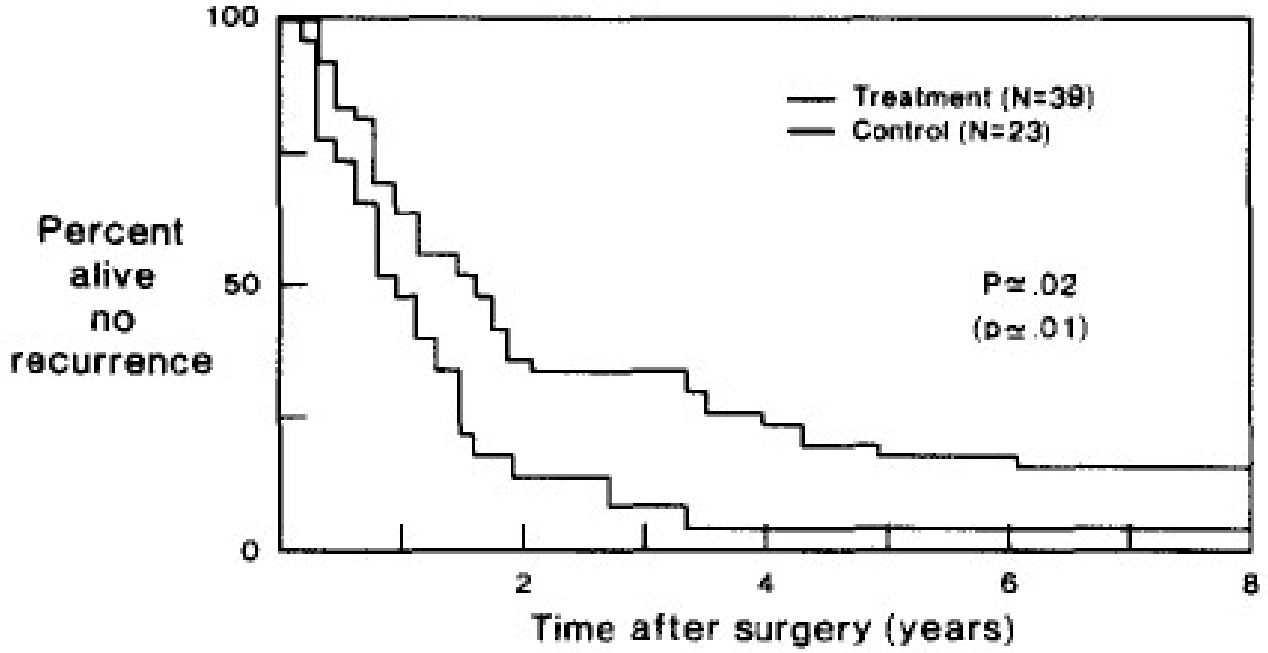
Moertel *et al*; Lancet Oncol 1969

ESTRO School

✓Post-operative Chemoradiation

- Moertel et al – 1984 Stage Resectable 39 pts

SVV Benefit



RTCT (2D): 37.5 Gy (1.5 Gy fx) + 5Fu EQD2: 35.94 Gy

Moertel *et al*; JCO 1984

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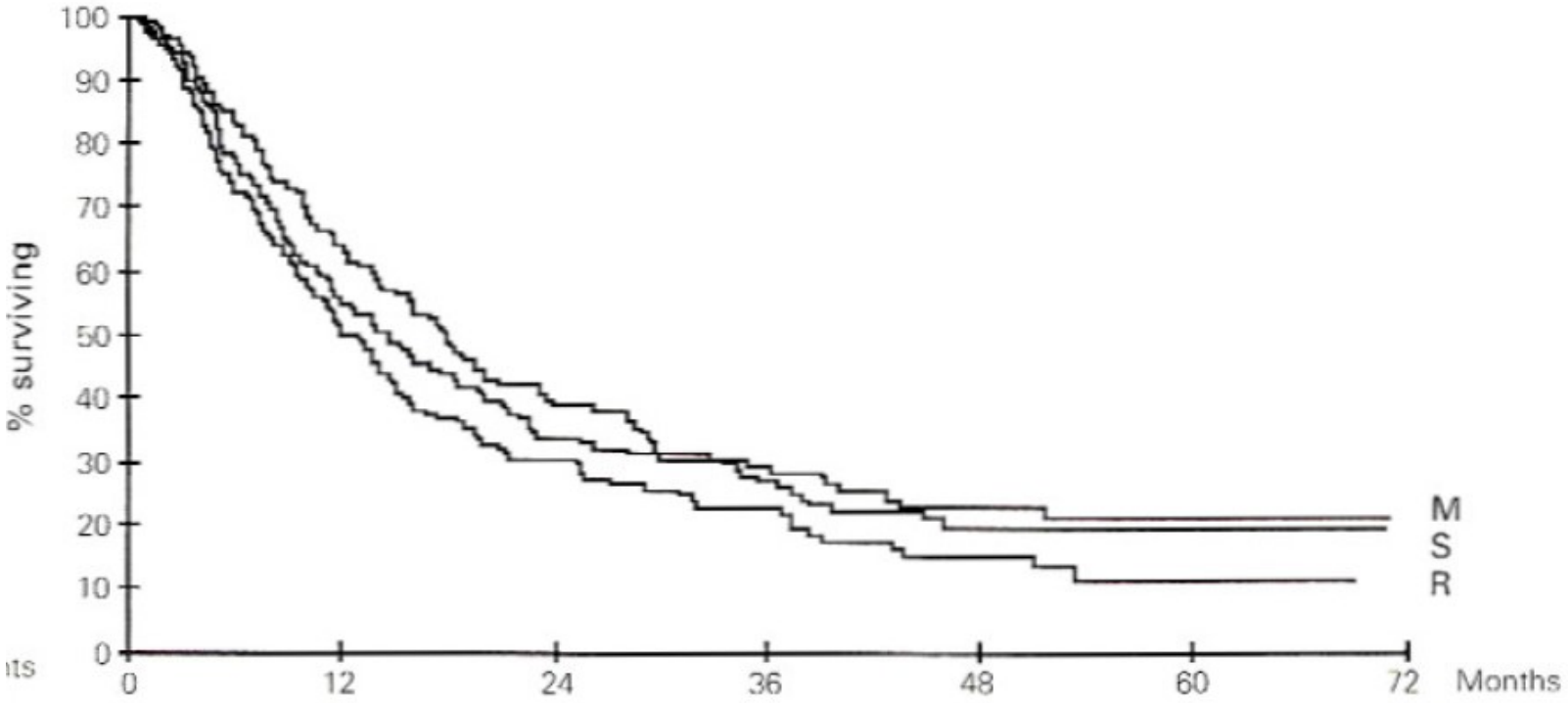
✓Post-operative Chemoradiation

- Allum et al – 1989 Stage Resectable 436 pts

Surgery vs MAF vs RT

NO SVV Benefit



RT (2D): 45 + 5 Gy (2 Gy fx) EQD2: 50 Gy

Allum *et al*; JCO 1989
(UK)

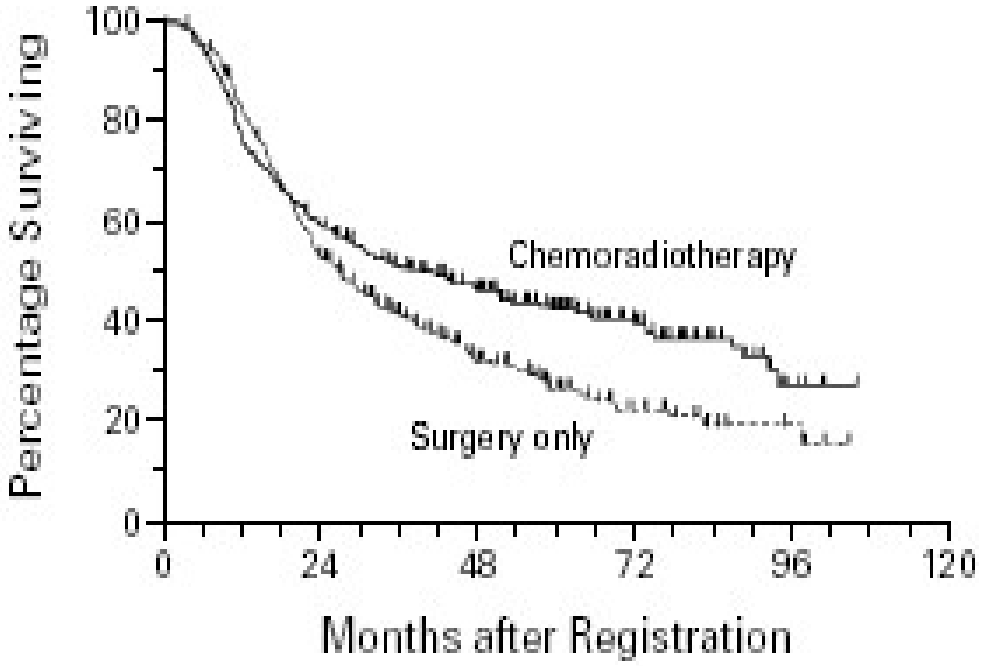
ESTRO School

✓Post-operative Chemoradiation

- Macdonald et al – 2001 Stage IB through IVM0, R0 556 pts

  Surg vs Surg + Ch / RTCH / 2Ch

  SVV Benefit



RT (2D): 45 Gy (1.8 Gy fx) EQD2: 44.25 Gy

Macdonald *et al*; NEJM 2001
Smalley *et al*: JCO 2011

(USA)

ESTRO School

✓Post-operative Chemoradiation

- MacDonald et al – 2001 Stage IB through IVM0, R0 556 pts

D2 Lymphnode dissection was recommended

D0: 54%
Incomplete resection of perigastric nodes

D1: 36%
Complete resection of perigastric nodes

D2: 10%
Extended resection of vascular nodes

D0 vs D2
No significant difference in survival by Cox multivariate analysis
RTCHEM

All subgroups had a survival benefit

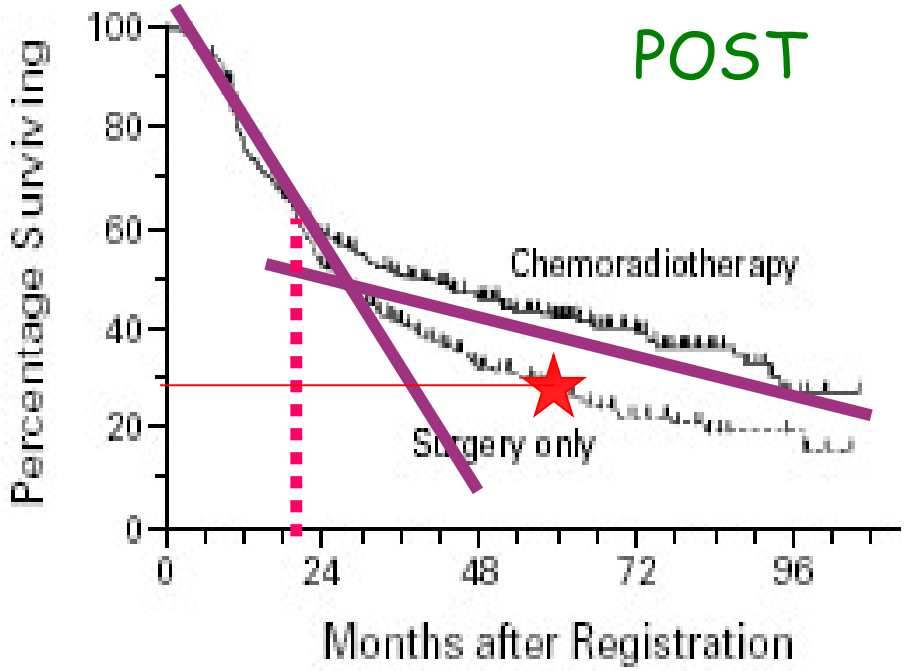
MacDonald *et al*; NEJM 2001
Minsky B– personal communication – 2005

(USA)

ESTRO School

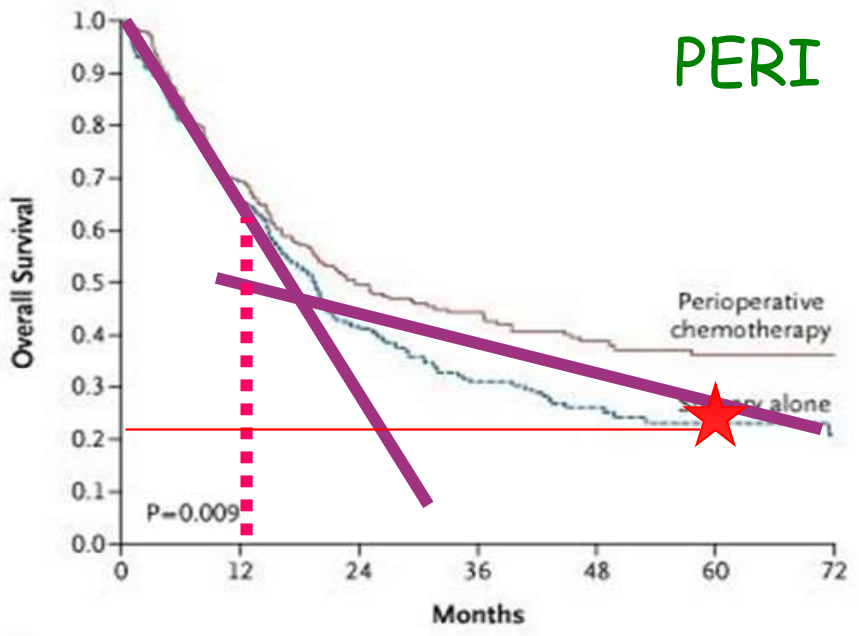
✓Post-operative Chemoradiation

INT-0116



D2 = 10%

Magic



D2 = 41%

Macdonald JS et Al – NEJM -2001 (USA)
Cunningham D et Al – NEJM – 2006 (UK)

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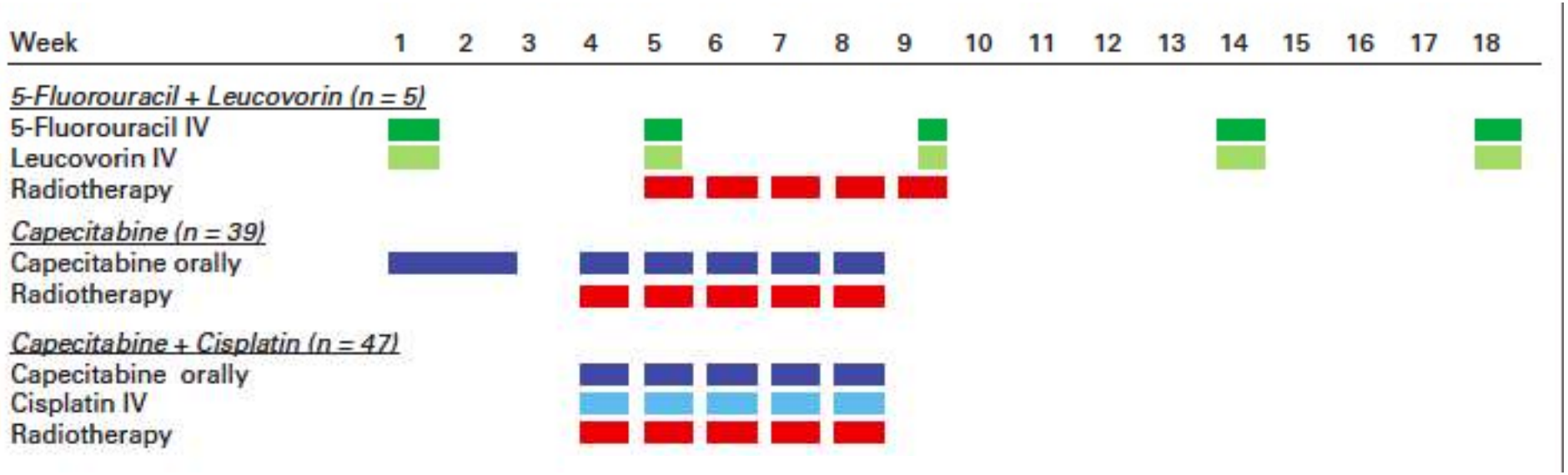
✓Post-operative Chemoradiation

- Dikken et al – 2010 Stage IB to IV 113 pts
- Bonenkamp et al – 1999 Stage IB to IVMO 1098 pts



RT : 45 Gy (1.8 Gy fx) EQD2: 44.25 Gy

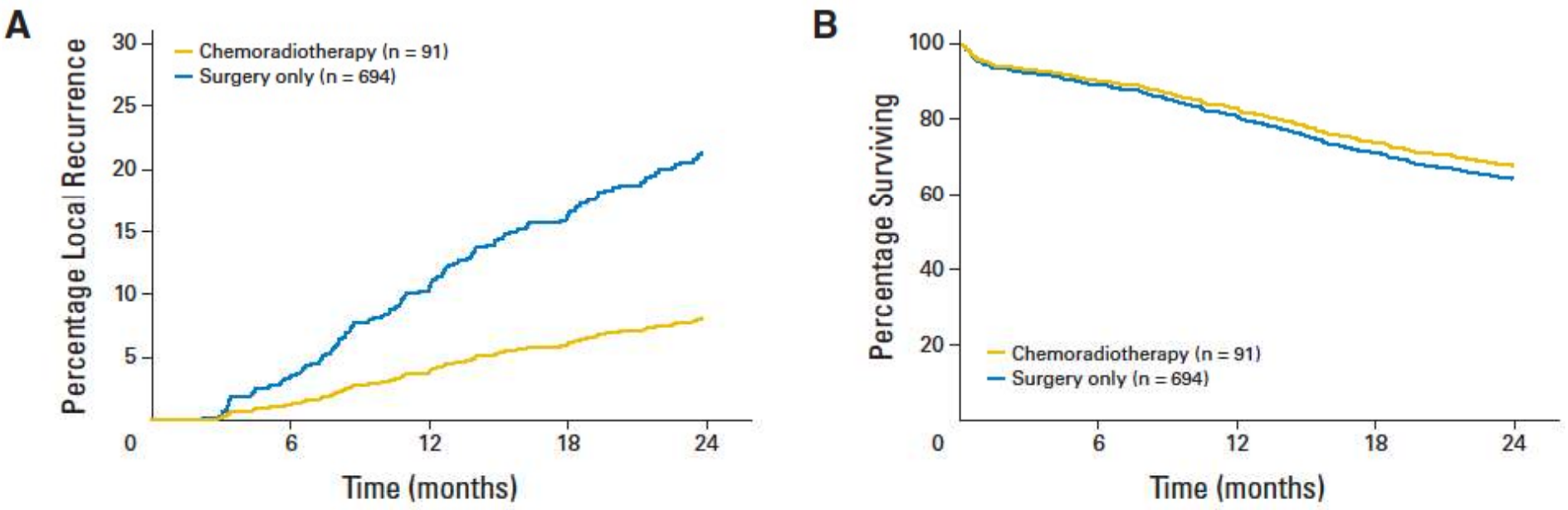
Dikken *et al*: JCO 2010
Bonenkamp JJ et al: NEJM 1999

(the Netherlands)

ESTRO School

✓Post-operative Chemoradiation

- Dikken et al – 2010 Stage IB to IV 113 pts
- Bonenkamp et al – 1999 StageIB to IVMO 1098 pts



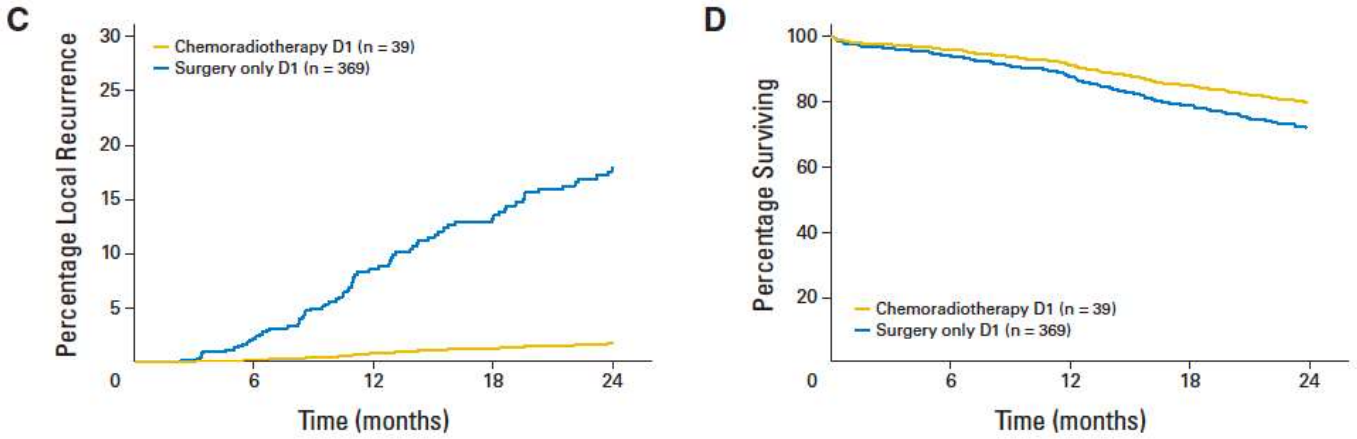
Dikken *et al*: JCO 2010
Bonenkamp JJ et al: NEJM 1999

ESTRO School

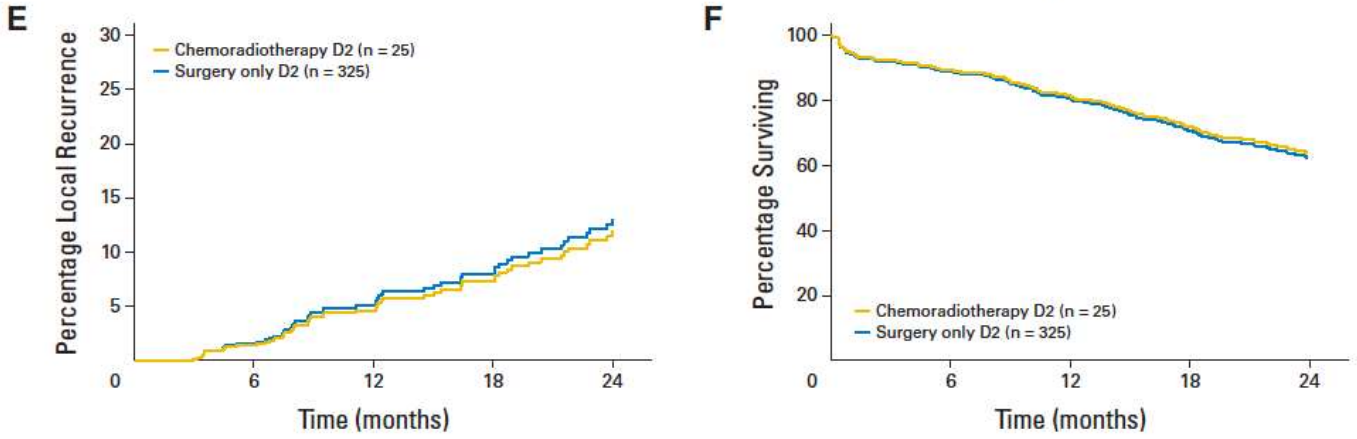
✓Post-operative Chemoradiation

- Dikken et al – 2010 — Stage IB to IV(M0) — 113 pts
- Bonenkamp et al – 1999 — Stage IB to IVMO — 1098 pts

D1



D2



Dikken *et al*: JCO 2010
Bonenkamp JJ et al: NEJM 1999

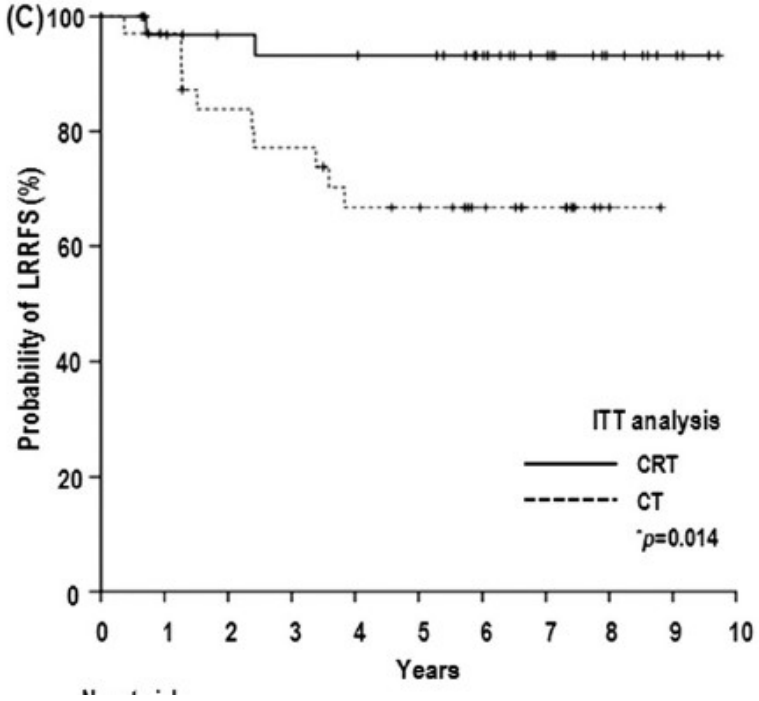
ESTRO School

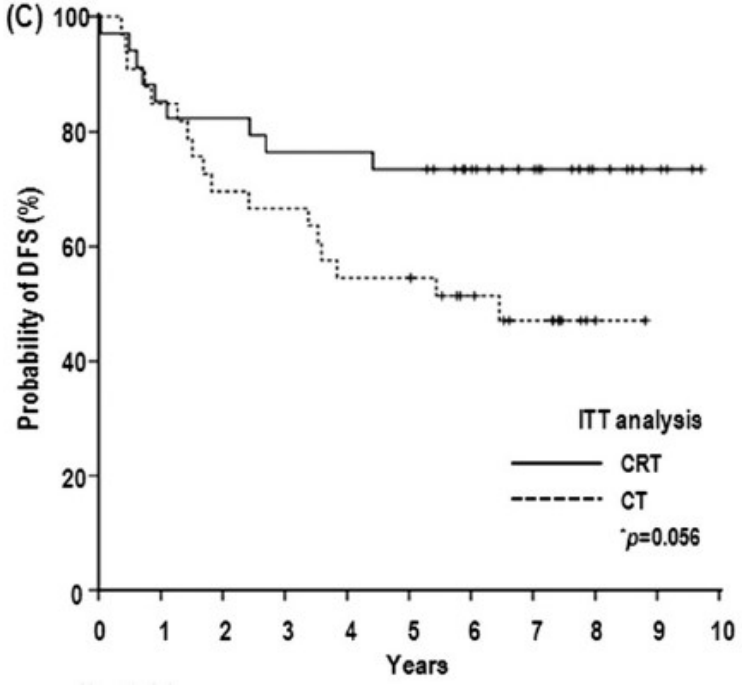
✓Post-operative Chemoradiation

- Kim et al – 2012 Stage III and IV(M0) 90 pts

  D2 5 folowed by FUL vs FUL RT+FU 2FUL

Stage III





RT (3D) : 45 Gy (1.8 Gy fx) EQD2: 44.25 Gy

Kim *et al*: IJROBP 2012
(Korea)

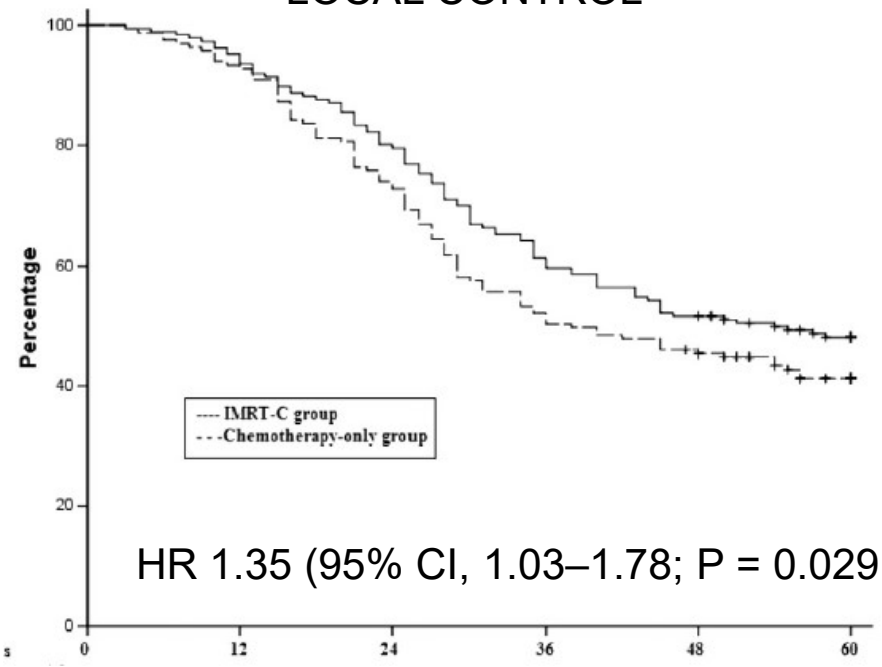
ESTRO School

✓Post-operative Chemoradiation

- Zhu et al – 2012 Stage T3 or T4 and (or) N positive(M0) 404 pts

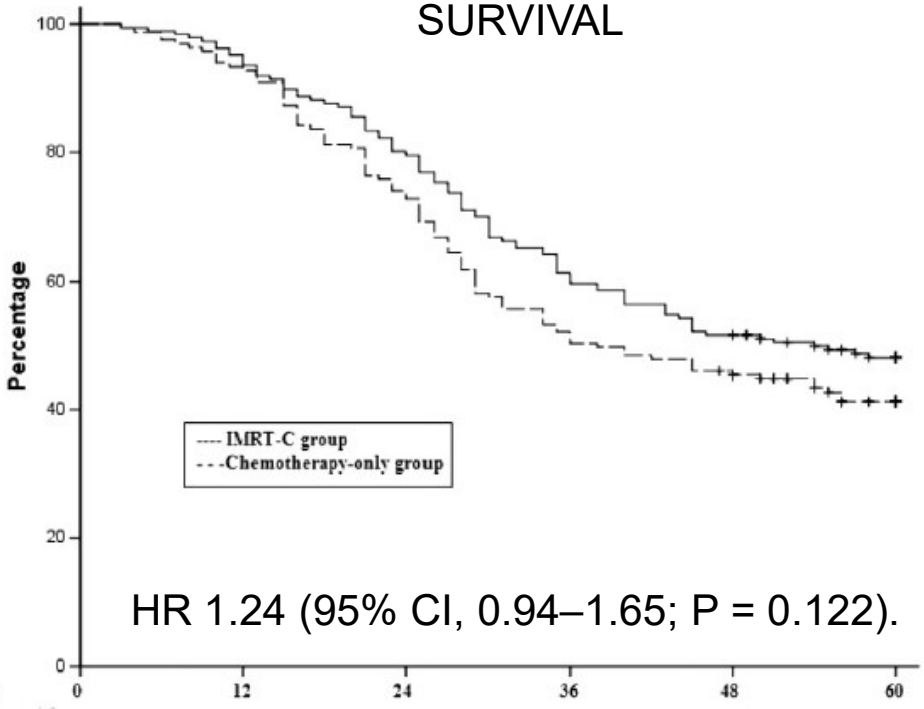
  D2 5 folowed by FUL vs FUL RT+FU 2FUL

LOCAL CONTROL



HR 1.35 (95% CI, 1.03–1.78; P = 0.029

SURVIVAL



HR 1.24 (95% CI, 0.94–1.65; P = 0.122).

RT (IMRT) : 45 Gy (1.8 Gy fx) EQD2: 44.25 Gy

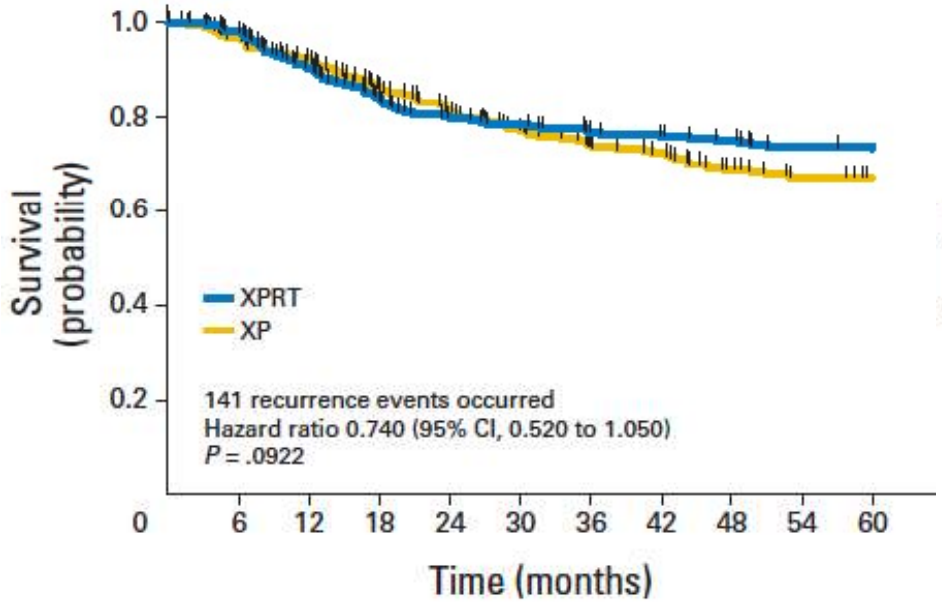
Zhu *et all*: Radiot Oncol 2012
(China)

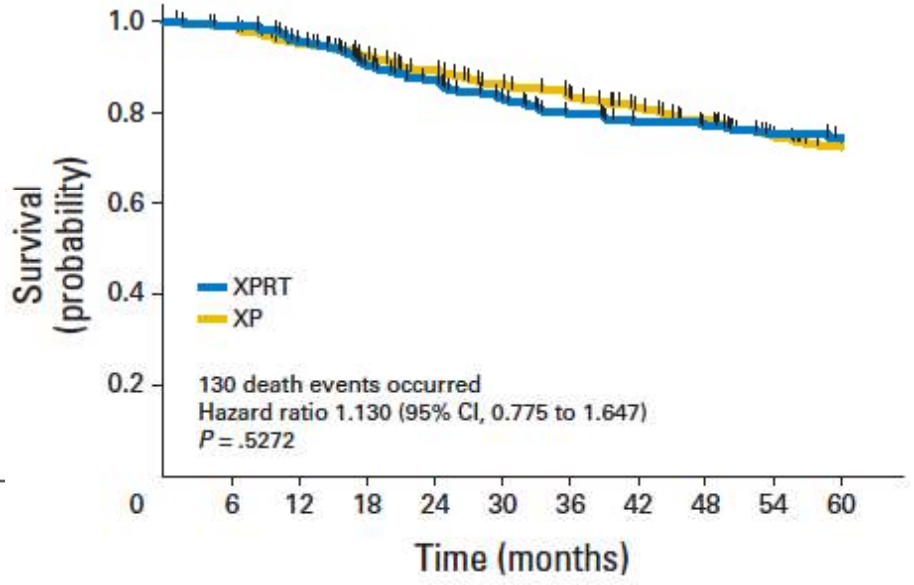
ESTRO School

✓Post-operative Chemoradiation

- Park et al – 2015 Stage IB to IV (M0, R0) 458 pts

  D2 folowed by 6 XP vs 2XP + RT+X + 2XP





RT (3D) : 45 Gy (1.8 Gy fx) EQD2: 44.25 Gy

Lee *et al*. JCO 2012
Park *et all*: JCO 2015

(Korea)

ESTRO School

✓Post-operative Chemoradiation

- Park et al – 2015 Stage IB to IV (M0, R0) 458 pts

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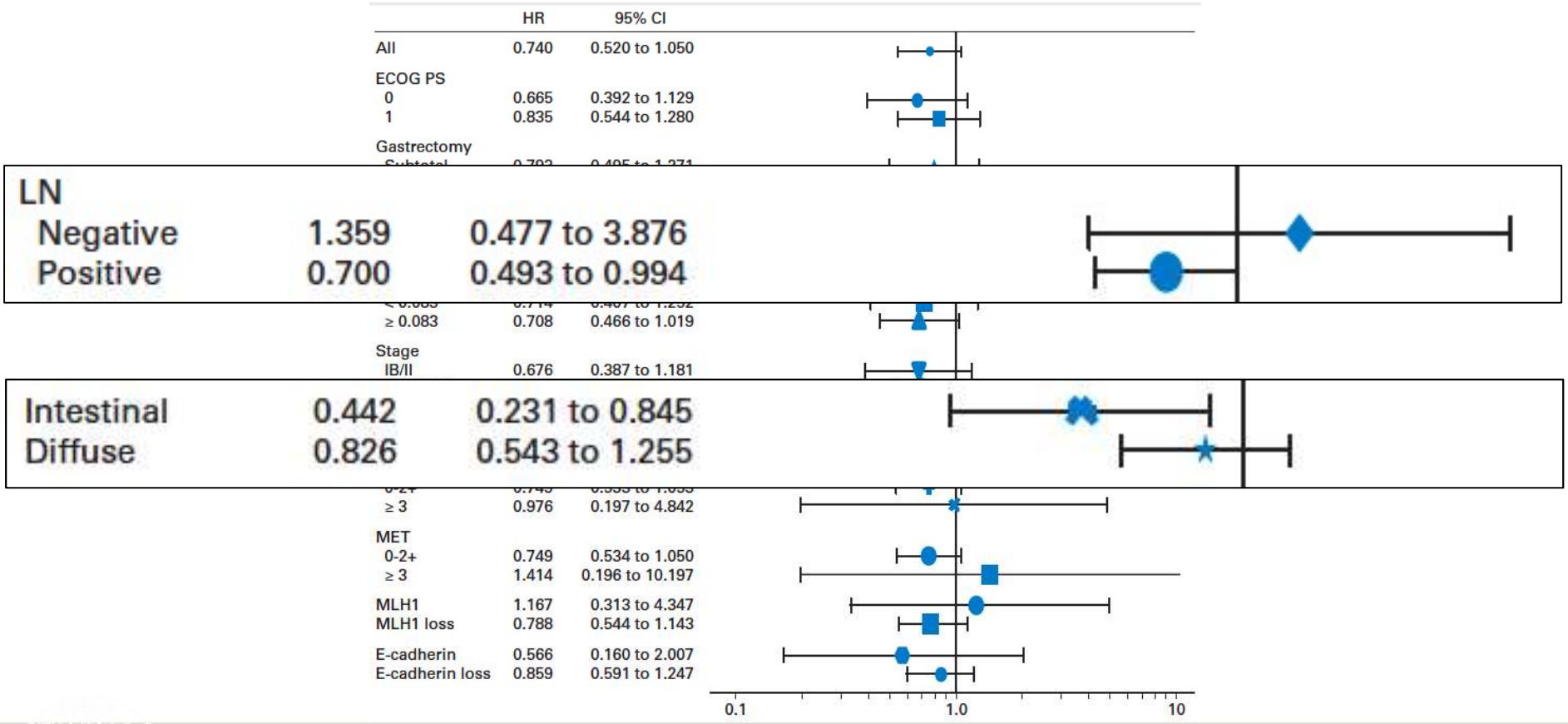


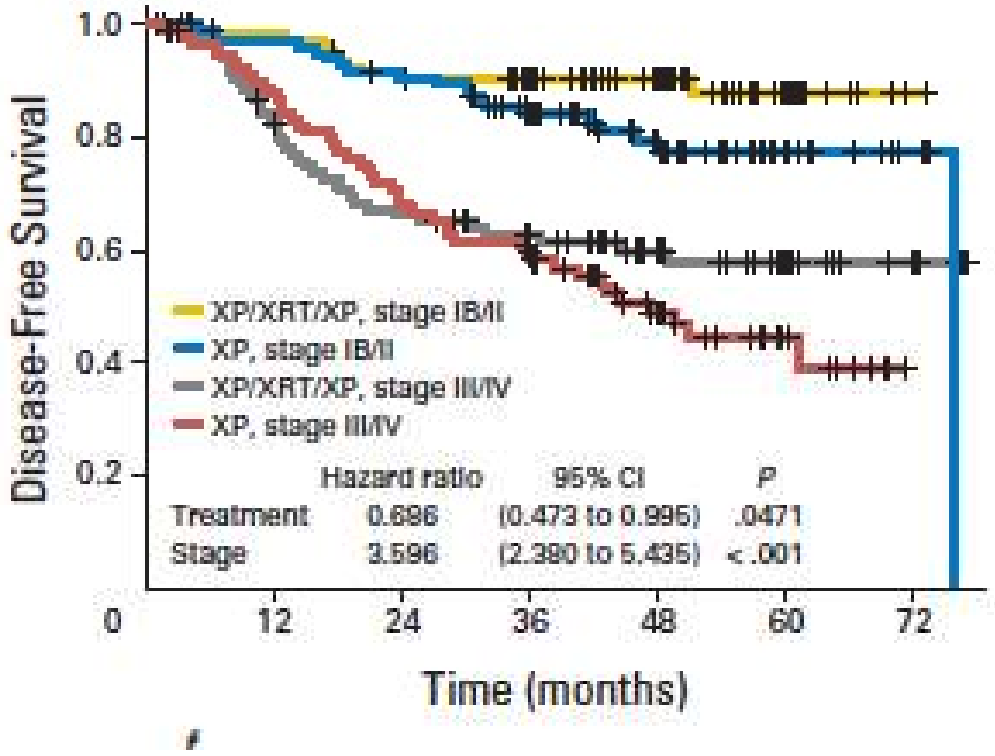
Lee *et al*. JCO 2012
Park *et al*: JCO 2015

ESTRO School

✓Post-operative Chemoradiation

- Park et al – 2015 Stage IB to IV (M0, R0) 458 pts

D2 folowed by 6 XP vs 2XP + RT+X + 2XP

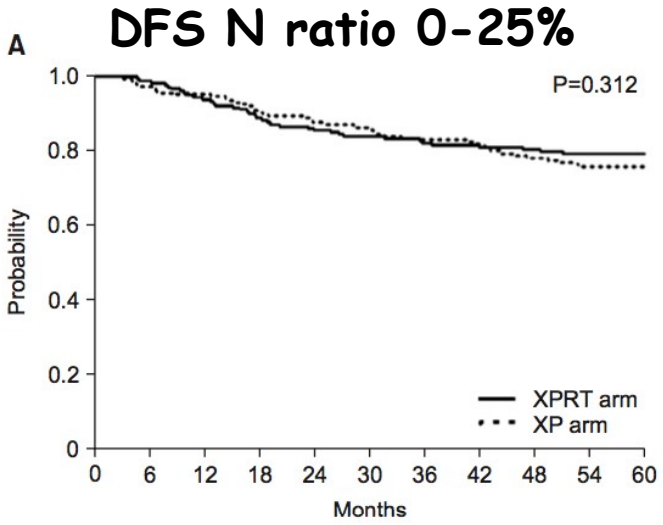


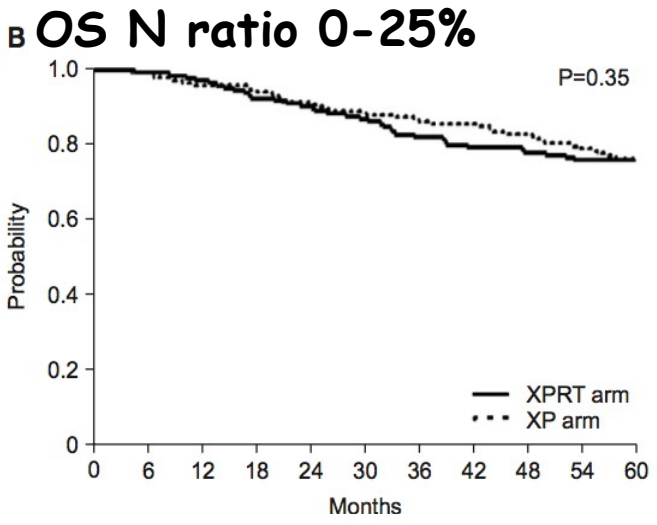
RT (3D) : 45 Gy (1.8 Gy fx)

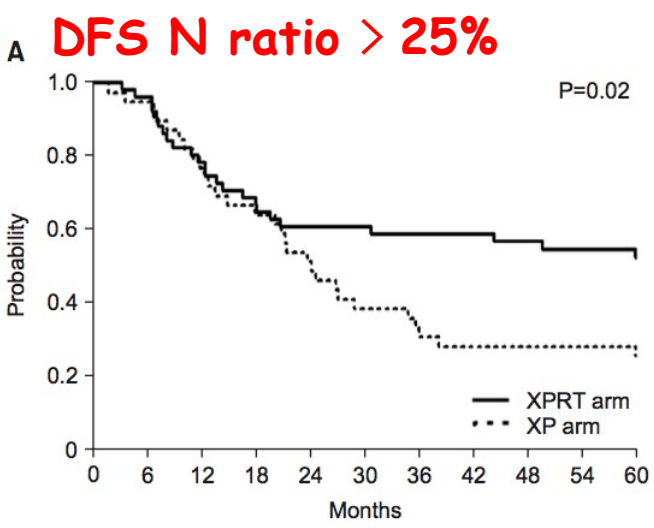
Lee *et al*. JCO 2012
Park *et al*: JCO 2015

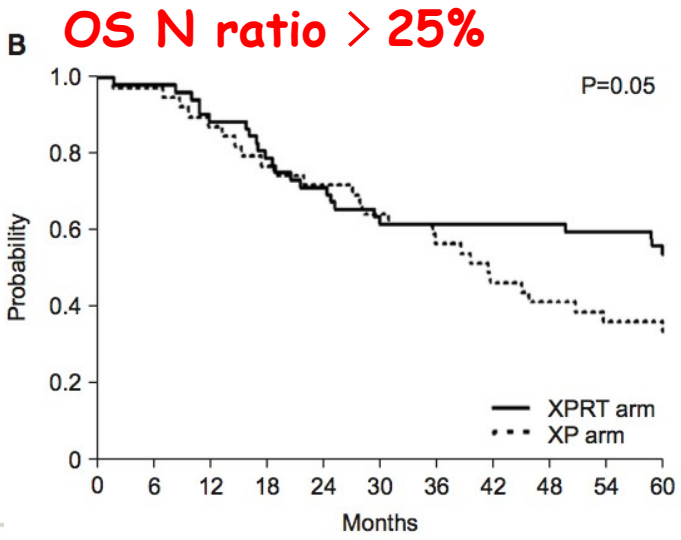
ESTRO School

✓Post-operative Chemoradiation









Kim J et al – J Gastric Cancer - 2016

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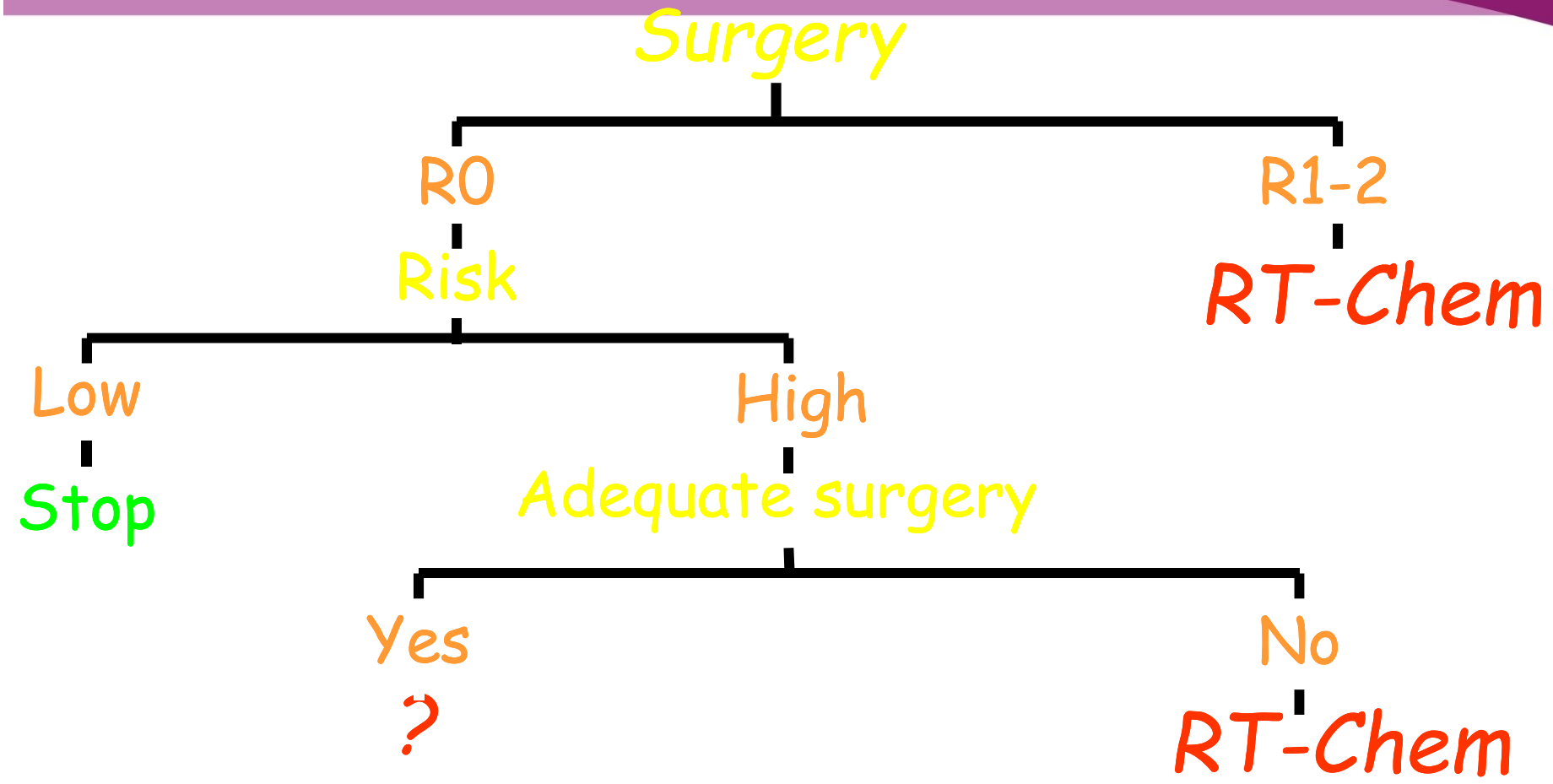
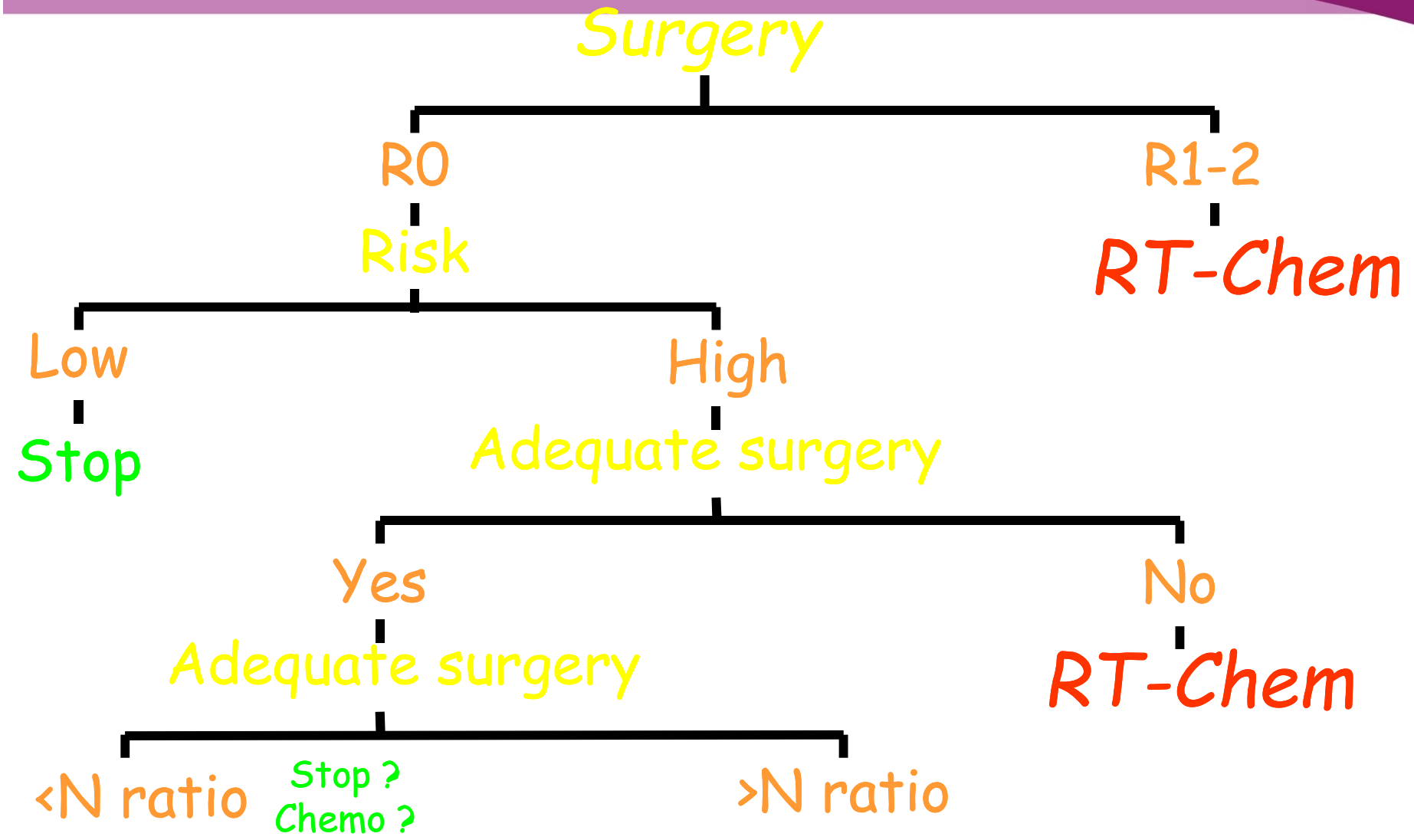
✓Post-operative Chemoradiation

✓Post-operative Chemoradiation



✓Post-operative Chemoradiation



✓Post-operative Chemoradiation

CRITICS trial

(ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach).

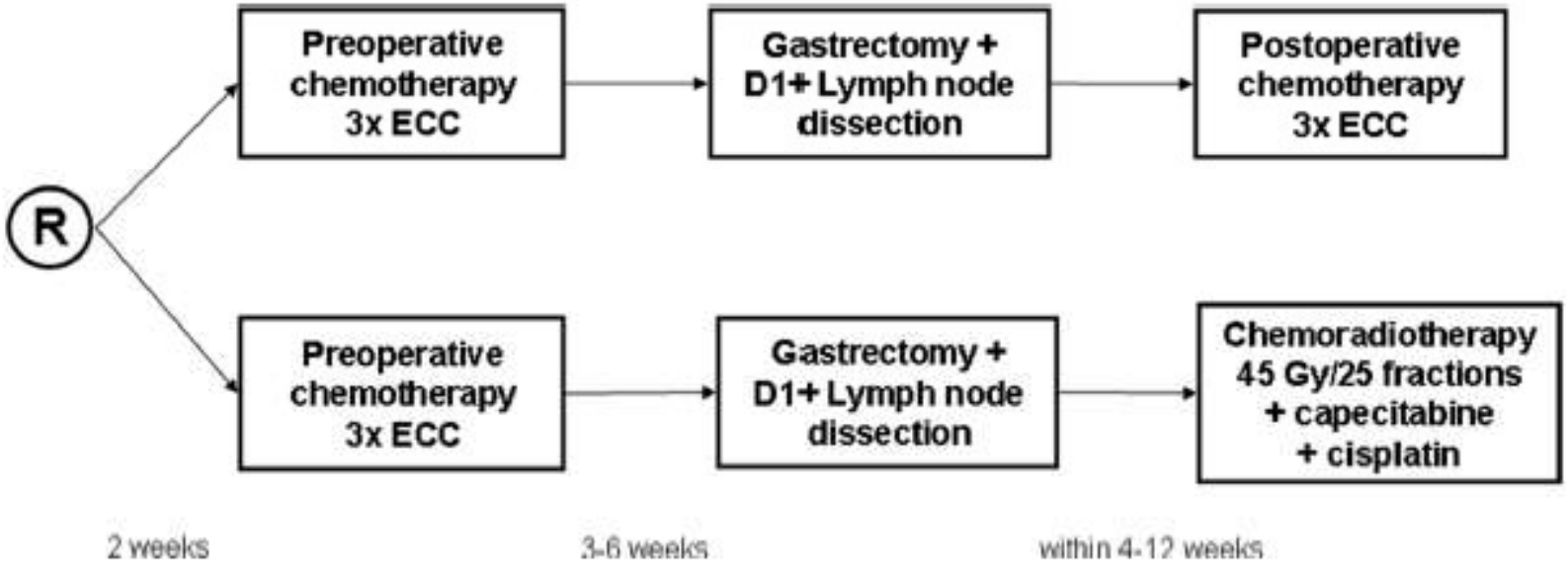


Figure 1 Randomization scheme. R: randomization. ECC: epirubicin, cisplatin, capecitabine.

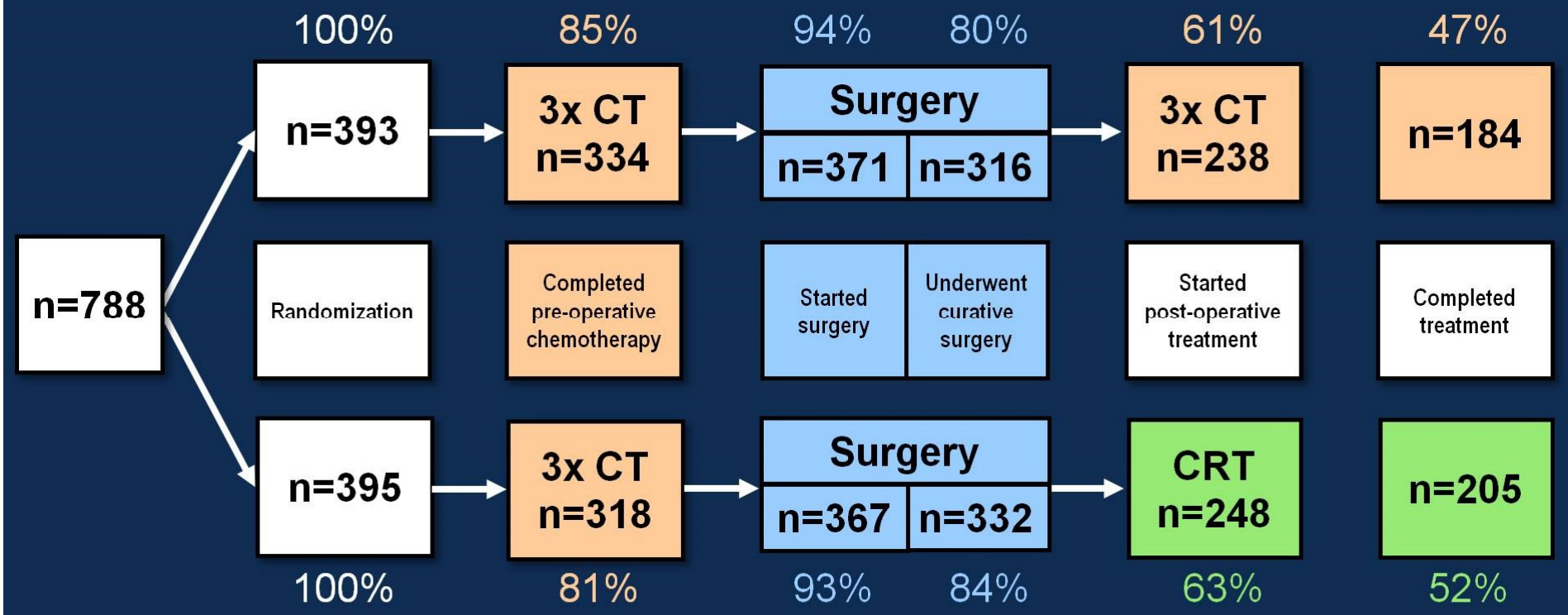
EQD2: 44.25 Gy

Dikken *et al*: BMC 2011 (the Netherlands)

ESTRO School

✓Post-operative Chemoradiation

Results: Study Profile



PRESENTED AT: ASCO ANNUAL MEETING '16

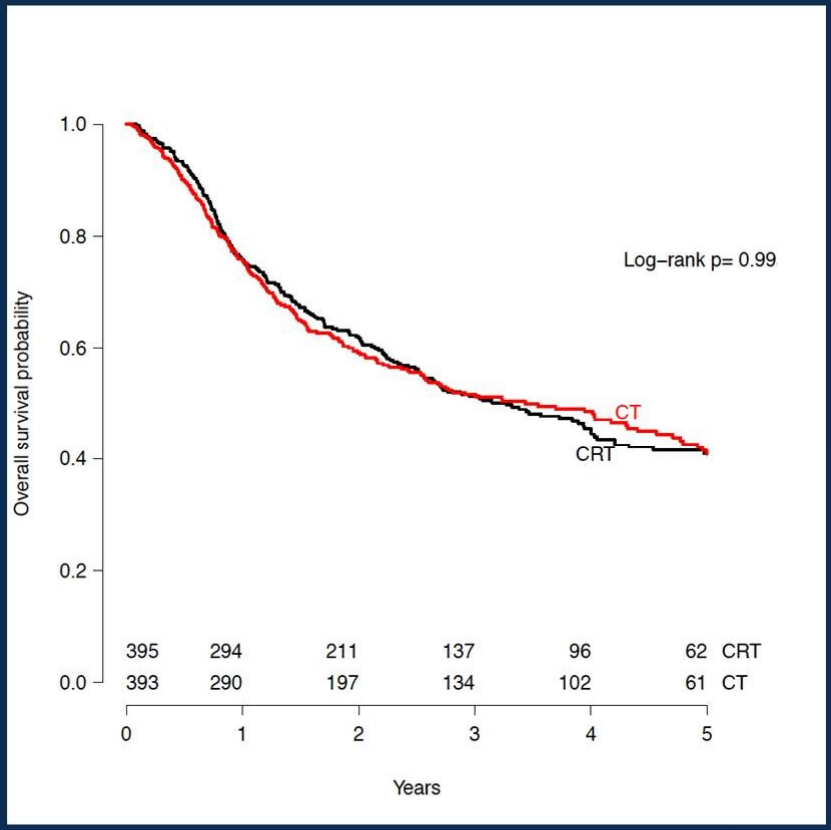
By the courtesy of Prof M.Verheij

Dikken JL et al.; BMC Cancer 2011, 11:329
Verheij M et al.; J Clin Oncol 34, 2016 (suppl; abstr 4000)

ESTRO School

✓Post-operative Chemoradiation

Results: Overall Survival



	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3

PRESENTED AT: ASCO ANNUAL MEETING '16

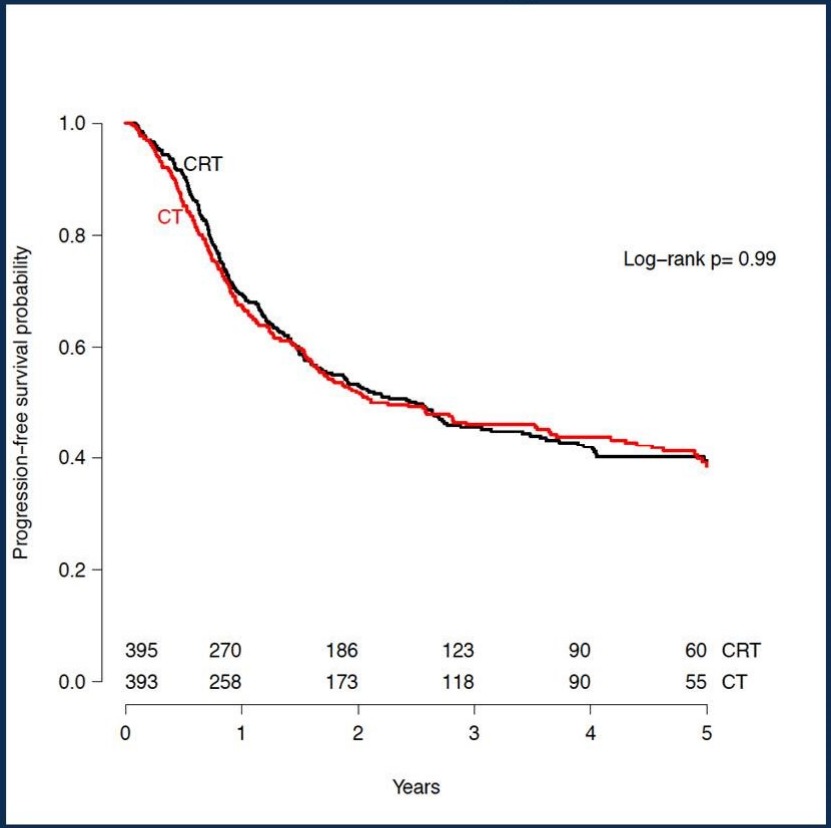
By the courtesy of Prof M.Verheij

Dikken JL et al.; BMC Cancer 2011, 11:329
Verheij M et al.; J Clin Oncol 34, 2016 (suppl; abstr 4000)

ESTRO School

✓Post-operative Chemoradiation

Results: Progression-Free Survival



	CT	CRT
5-year PFS (%)	38.5	39.5
Median PFS (yrs)	2.3	2.5

PRESENTED AT: ASCO ANNUAL MEETING '16

By the courtesy of Prof M.Verheij

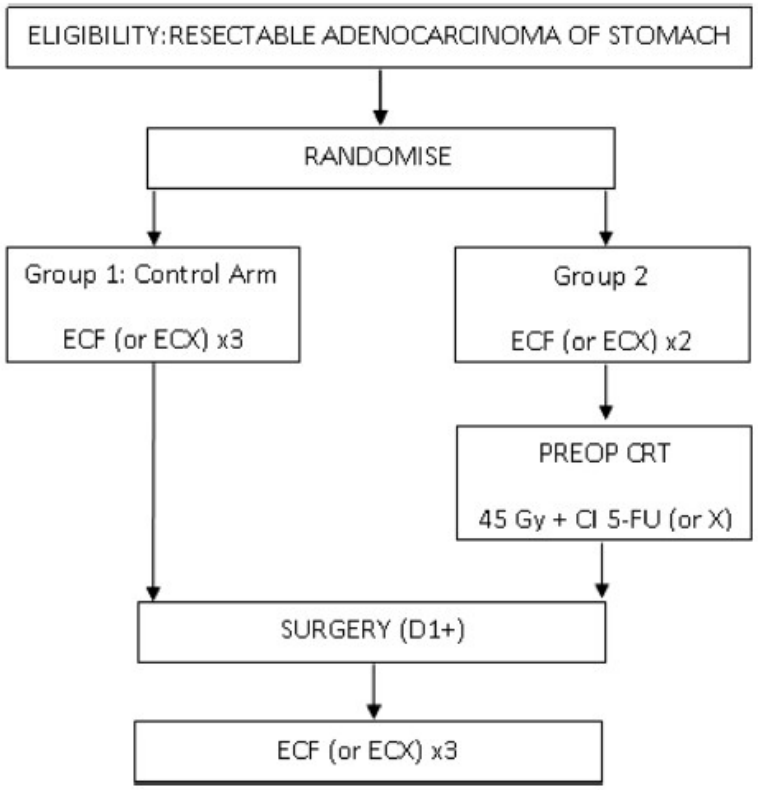
Dikken JL et al.; BMC Cancer 2011, 11:329
Verheij M et al.; J Clin Oncol 34, 2016 (suppl; abstr 4000)

ESTRO School

✓Post-operative Chemoradiation

TOPGEAR

(Trial Of Preoperative therapy for Gastric and Esophagogastric junction AdenocaRcinoma)



EQD2: 44.25 Gy

Leong *et al*: BMC 2015
(Australia)

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✓Post-operative Chemoradiation

ARTIST II

- Histologically proven gastric or gastroesophageal adenocarcinoma
- ≥ D2 lymph node dissection, curative gastrectomy
- Stage II, III (AJCC 2010) with any N (any stage with N0 will be excluded)

•**Arm A**: S-1 40-60mg BID (4weeks - 2weeks off) x 8 cycles

•**Arm B**: S-1 40-60mg BID (2weeks - 1week off) + Oxaliplatin 130mg/m2 q 3 week x 8 cycles

•**Arm C**: "Arm B" x 2 cycles → S-1 40mg BID (2weeks - 1week off - 2weeks)+ RT 45 Gy (5weeks) → Rest for 4 weeks → "Arm B" x 4 cycles

www.clinicaltrials.gov

State of art of radiation therapy in Gastric Cancer

✓ **Background** and **assumptions**

Local control favours survival
Local control can be ameliorated
Modern radiotherapy favours less toxicity

✓ **Post-operative** Chemoradiation

Moertel 1969	Favour RTCHEM
Moertel 1984	Favour RTCHEM
Allum 1989	No benefit
Macdonald 2001	Favour RTCHEM + D2(?)
Kim 2012	Trend RTCHEM vs Chem
Zhu 2012	Trend RTCHEM vs Chem
Park 2015	No benefit RTCHEM but
Verheij 2016 (abs)	No benefit RTCHEM but

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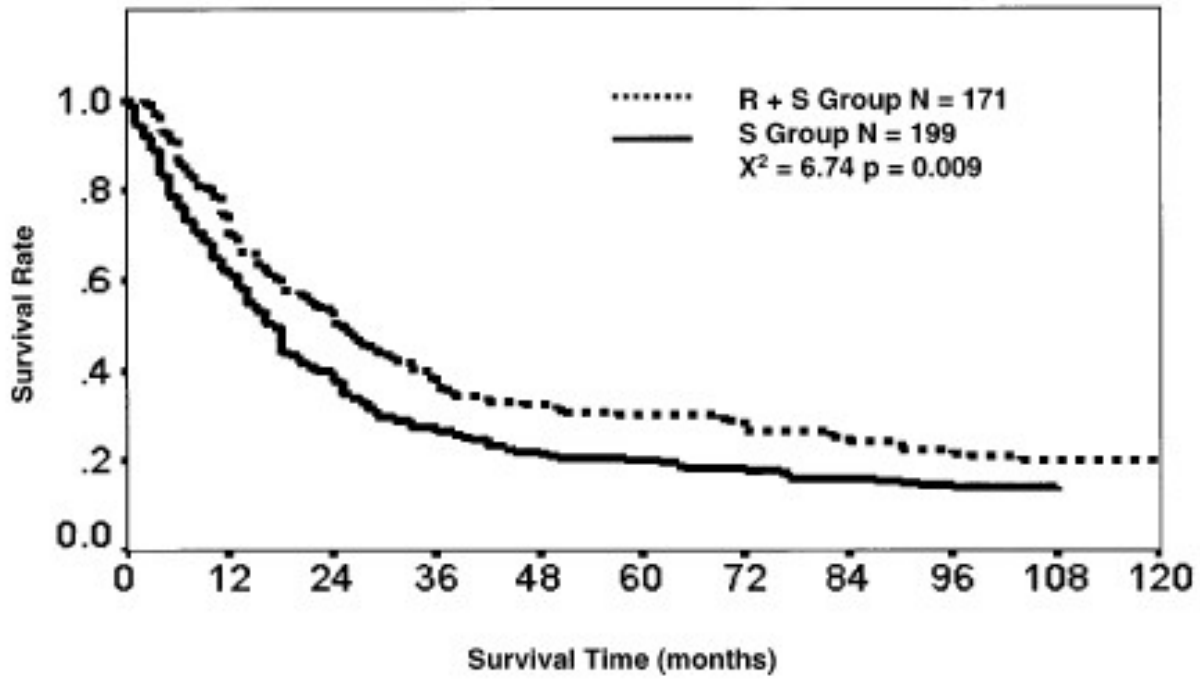
✓Pre-operative Chemoradiation

- Zhang et al – 1998 Stage not contraindicated for surgery (M0) 370 pts

RT + Surg vs Surg



RT (2D) : 40 Gy (2.0 Gy fx) EQD2: 40 Gy

Zhang *et al*. IJROBP 1998
(China)

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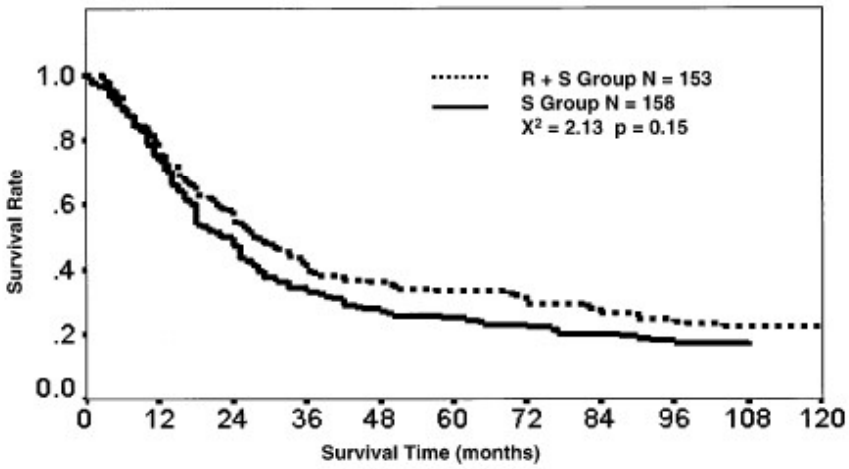
✓Pre-operative Chemoradiation

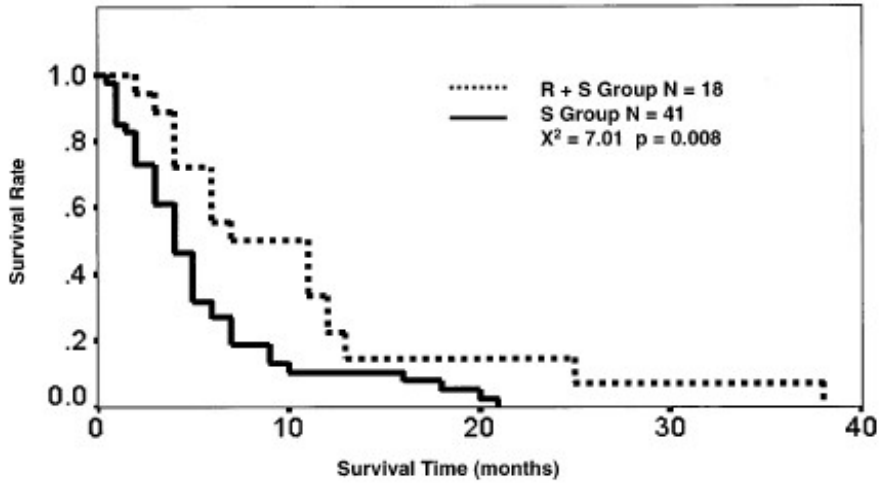
- Zhang et al – 1998 Stage not contraindicated for surgery (M0) 370 pts

RT + Surg vs Surg

Radical Surgery



Palliative Surgery



RT (2D) : 40 Gy (2.0 Gy fx)

Zhang *et al*. IJROBP 1998

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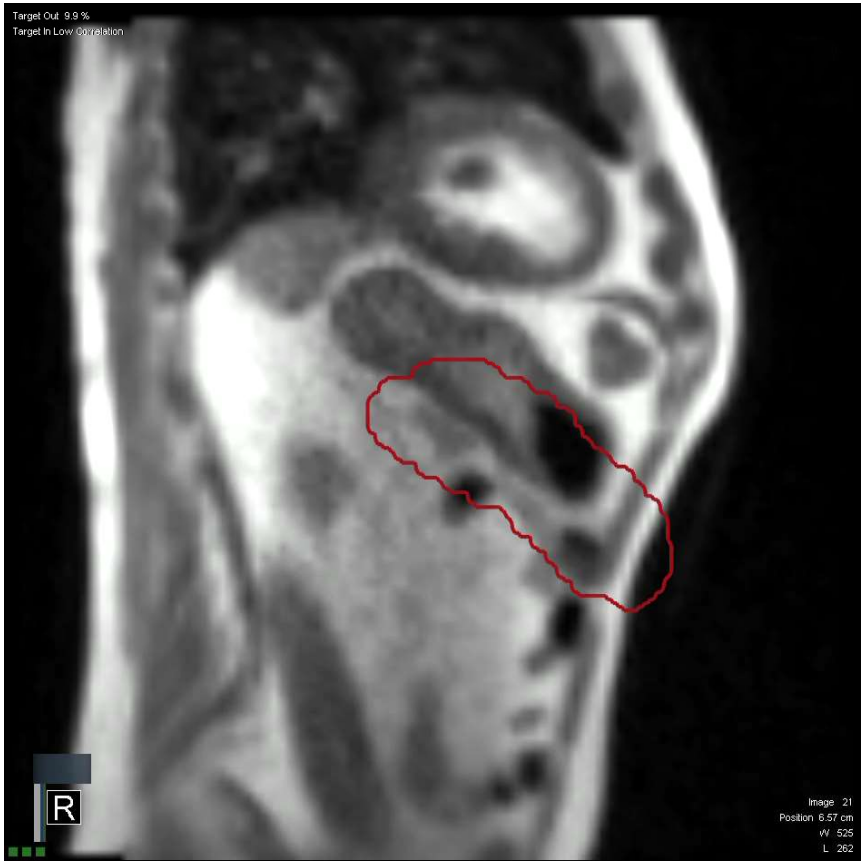
✓**Pre-operative** Chemoradiation

MRI based IGRT



State of art of radiation therapy in Gastric Cancer

- ✓ **Background** and **assumptions**

  Local control favours survival
  Local control can be ameliorated
  Modern radiotherapy favours less toxicity

- ✓ **Post-operative** Chemoradiation

Kim 2012	Trend RTCHEM vs Chem
Zhu 2012	Trend RTCHEM vs Chem
Park 2015	No benefit RTCHEM but
Verheij 2016 (abs)	No benefit RTCHEM but

- ✓ **Pre-operative Chemoradiation**

Zhang 1998	Seeding perspective

- ✓ **Intra-operative RT**

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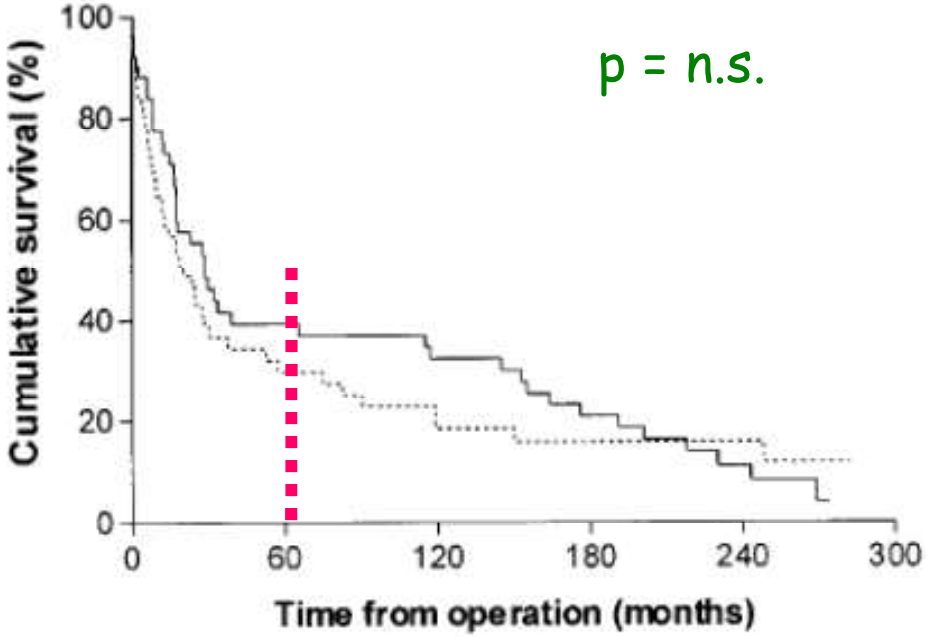
✓Intra-operative Radiotherapy

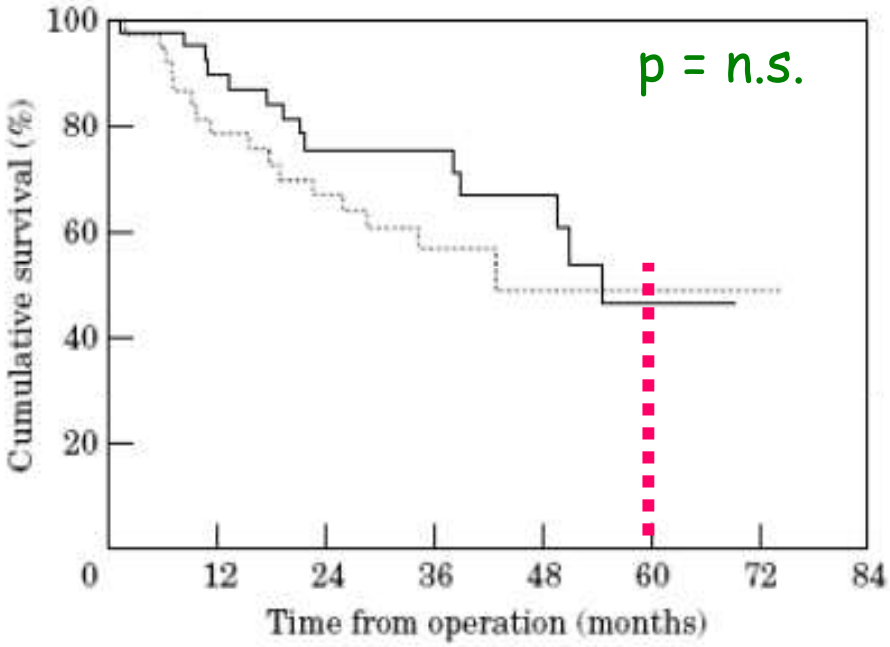
112 patients

p = n.s.



PreopRT vs Surg

p = n.s.



PreopRT vs Surg + IORT

RT (2D) : 20 Gy 4.00 Gy fx) + IORT 20 EQD2: 23.33 Gy

Skoropad VJ et Al – EJSO - 2000
Skoropad VJ et Al – JSO – 2002

Russia

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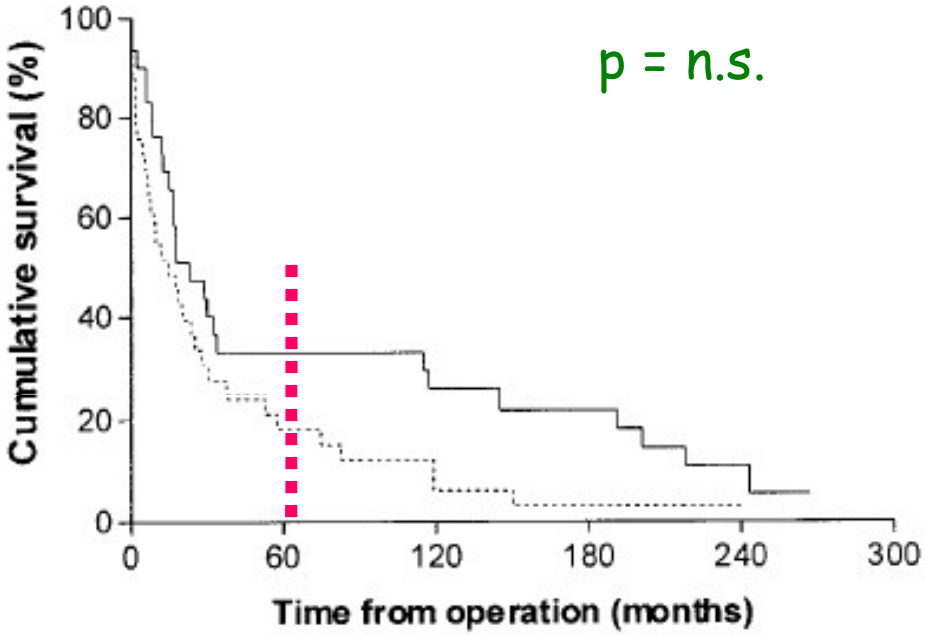
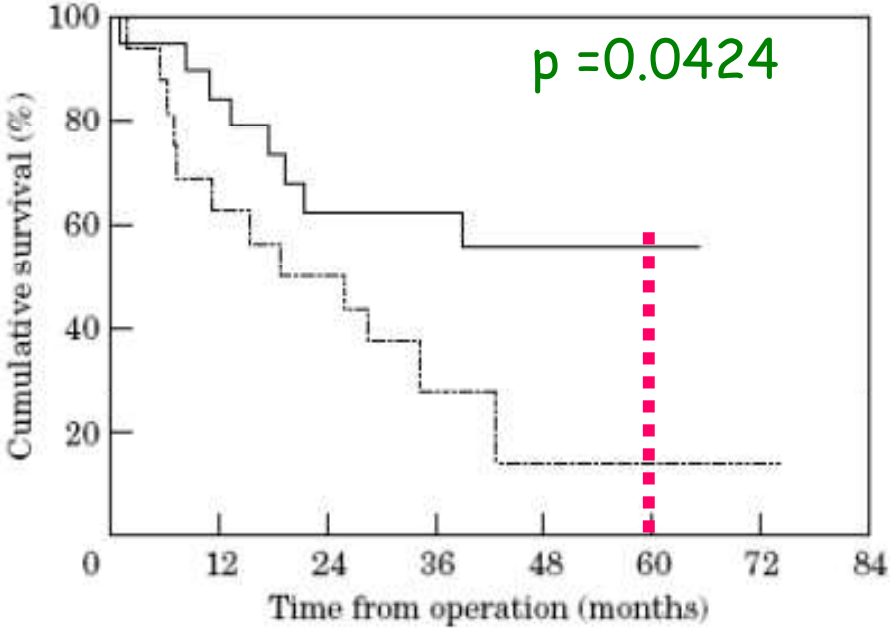
✓Intra-operative Radiotherapy

pT3-T4



PreopRT vs Surg



PreopRT vs Surg + IORT

RT (2D) : 20 Gy 4.00 Gy fx) + IORT 20

Skoropad VJ et Al – EJSO - 2000
Skoropad VJ et Al – JSO – 2002

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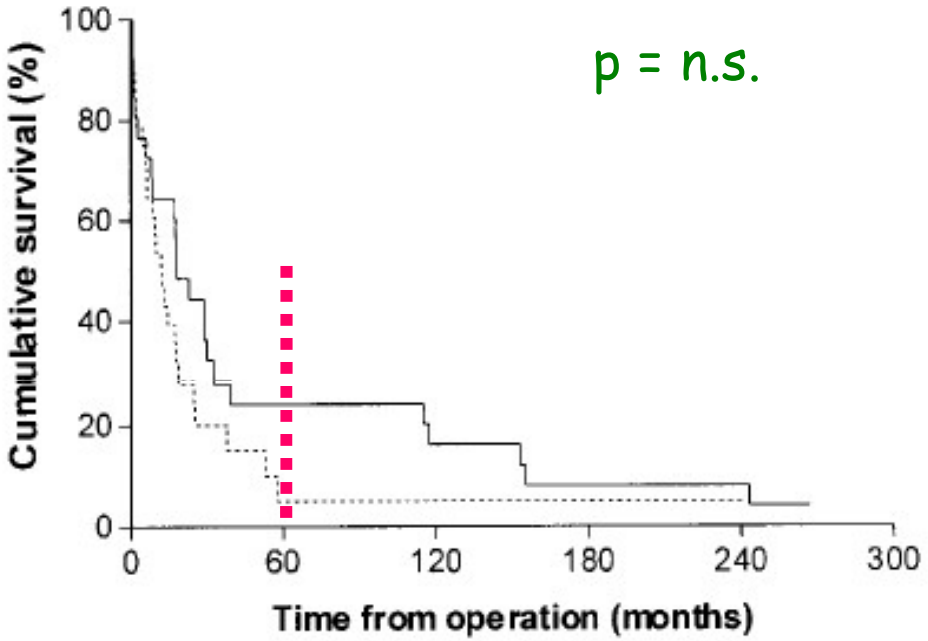
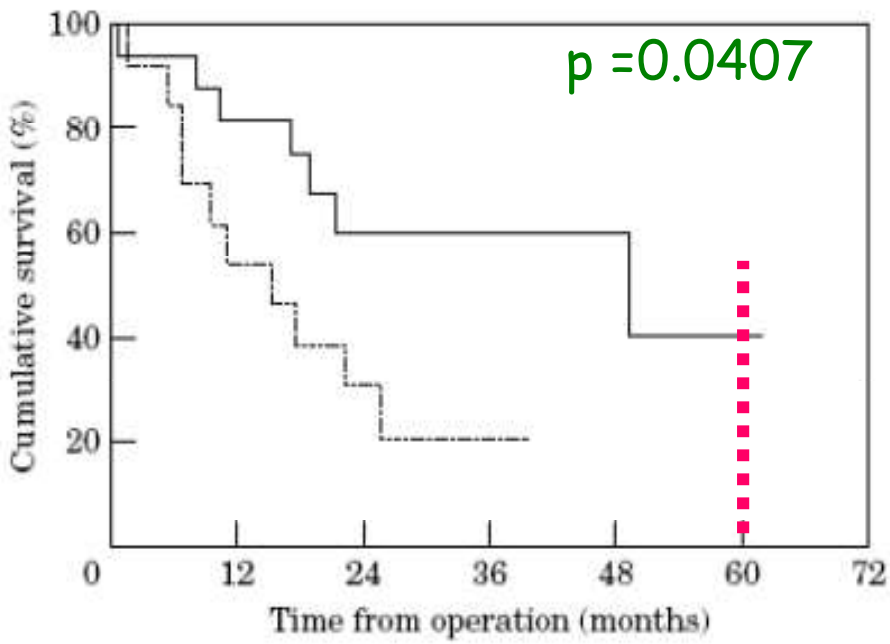
✓Intra-operative Radiotherapy

pN+



PreopRT vs Surg



PreopRT vs Surg + IORT

RT (2D) : 20 Gy 4.00 Gy fx) + IORT 20

Skoropad VJ et Al – EJSO - 2000
Skoropad VJ et Al – JSO – 2002

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State of art of radiation therapy in Gastric Cancer

- ✓ **Background** and **assumptions**

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- ✓ **Post-operative** Chemoradiation

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- ✓ **Intra-operative RT**

Skoropad 2002	Seeding perspective

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ESTRO School

Rome, Italy, 25-28 March 2017

Vincenzo Valentini and Laura La Porta

UPPER GI: TECHNICAL AND CLINICAL CHALLENGES FOR RADIATION ONCOLOGISTS - FULLY BOOKED

27 March (Monday)

Gastric cancer

Lecture (20'): state of art of chemotherapy in a combined treatment perspective

Nicola Silvestris
Medical Oncology Unit
Cancer Institute "Giovanni Paolo II" Bari

n.silvestris@oncologico.bari.it

ESTRO School

27 March (Monday)

Gastric cancer

Lecture (20'): state of art of chemotherapy in a combined treatment perspective

Perioperative chemotherapy

- ✓ *What is the impact of preoperative chemotherapy alone?*
- ✓ *Should perioperative chemotherapy be considerd a standard?*
- ✓ *What could be the reasons of the undertreatment of gastric cancer patients despite available high quality evidence?*
- ✓ *Has preoperative treatment a negative impact on post-operative outcomes?*
- ✓ *What are potential prognostic markers?*
- ✓ *How can we treat non-responding patients?*
- ✓ *More is better?*

Adjuvant chemotherapy

- ✓ *More is better?*
- ✓ *Is it better late than ever?*

Perioperative or adjuvant chemotherapy

- ✓ *What is better?*

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Comparison of Neoadjuvant Versus a Surgery First Approach for Gastric and Esophagogastric Cancer

Journal of SURGICAL ONCOLOGY
2016;114:296–303

Preoperative Chemotherapy

- **Meta-analysis of 12 trials** with 1,800 patients with resectable gastric or gastroesophageal cancer: ***neoadjuvant chemotherapy*** *could significantly* ***downstage tumors*** *and* ***improve R0 resection*** *while* ***slightly improving the overall survival*** (*Xiong et al., Eur J Surg Oncol, 2014*)

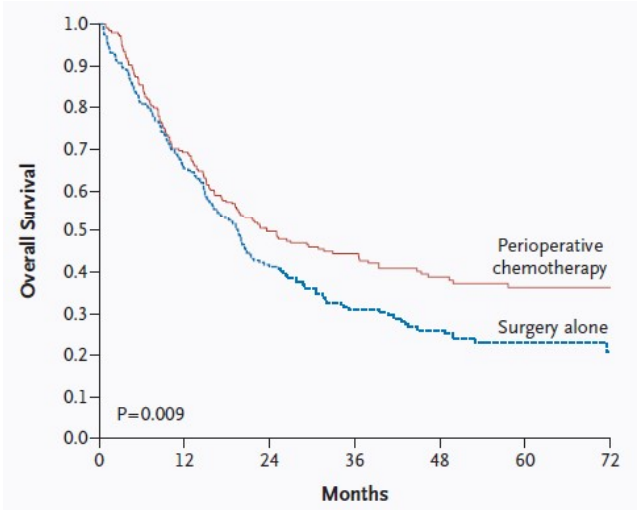
- **Additional meta-analysis** comparing neoadjuvant chemotherapy with surgery alone: *the* ***only significant finding*** *is that there were* ***significantly fewer negative lymph nodes after neoadjuvant treatment*** (*Xu et al., PLoS One, 2014*)

Neoadjuvant chemotherapy does not improve OS

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

The NEW ENGLAND JOURNAL of MEDICINE 2006;355:11-20.

3 preoperative and 3 postoperative cycles of ***ECF***
Primary endpoint: ***OS***



The perioperative-chemotherapy group had a ***higher likelihood of overall survival*** (hazard ratio for death, 0.75; 95 percent confidence interval, 0.60 to 0.93; P = 0.009; ***five-year survival rate, 36% vs 23%***)

Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial

VOLUME 29 · NUMBER 13 · MAY 1 2011
JOURNAL OF CLINICAL ONCOLOGY

2-3 preoperative cycles and 3-4 cycles of postoperative ***CF***
Primary endpoint: ***OS***

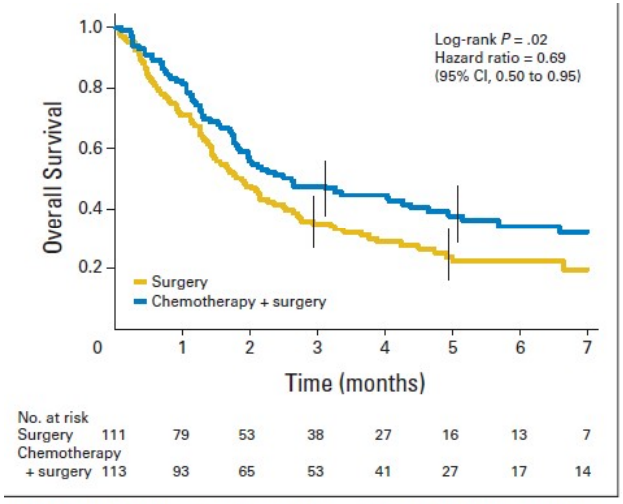


Fig 2. Kaplan-Meier curve showing overall survival from date of random assignment.

The CS group had a better OS (***5-year rate 38% vs 24%***; hazard ratio [HR] for death: 0.69; 95% CI, 0.50 to 0.95; *P* <0.02)

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Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

ANNALS OF ONCOLOGY
27 (Supplement 5): v38–v49, 2016

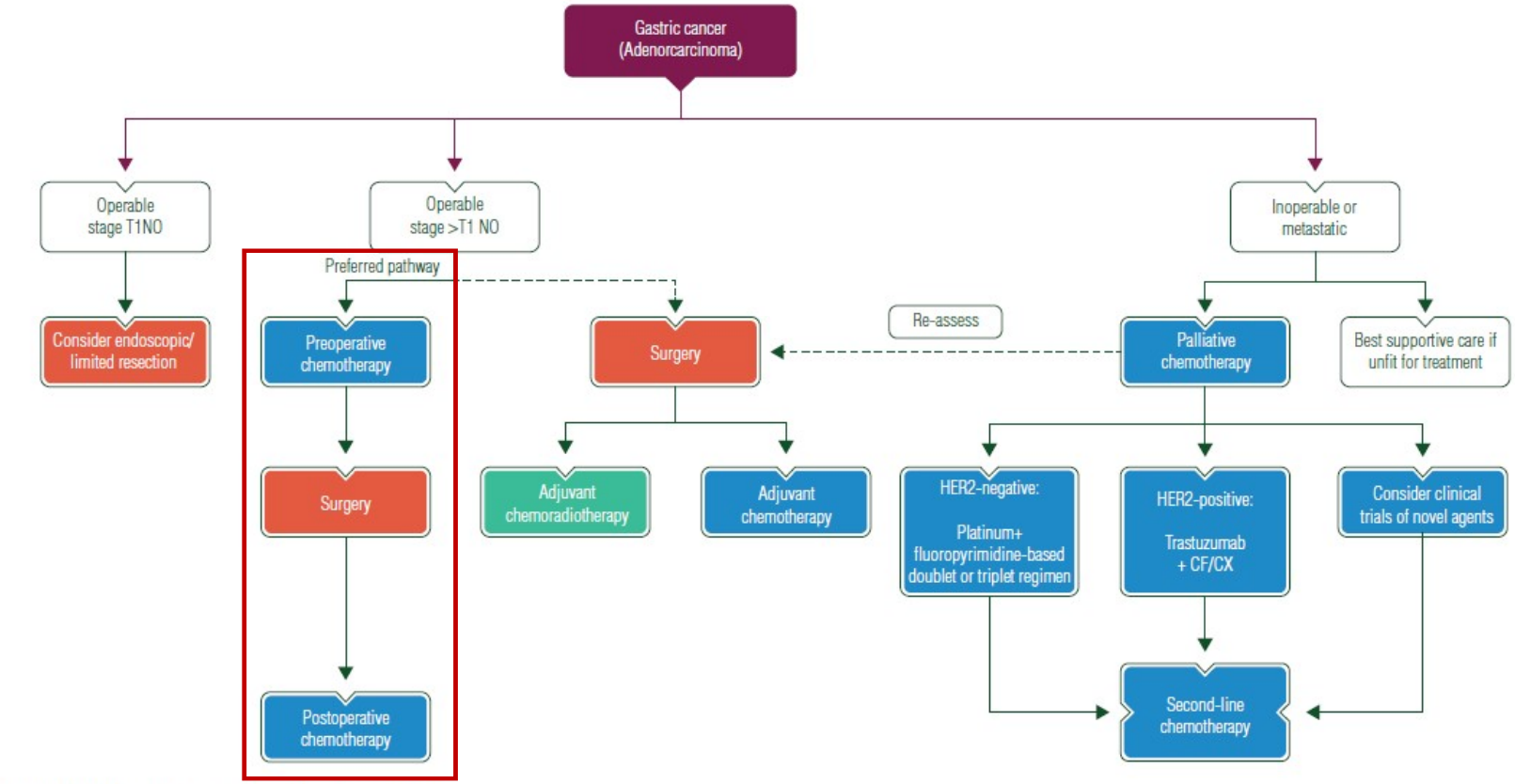

Figure 1. Gastric cancer treatment algorithm.

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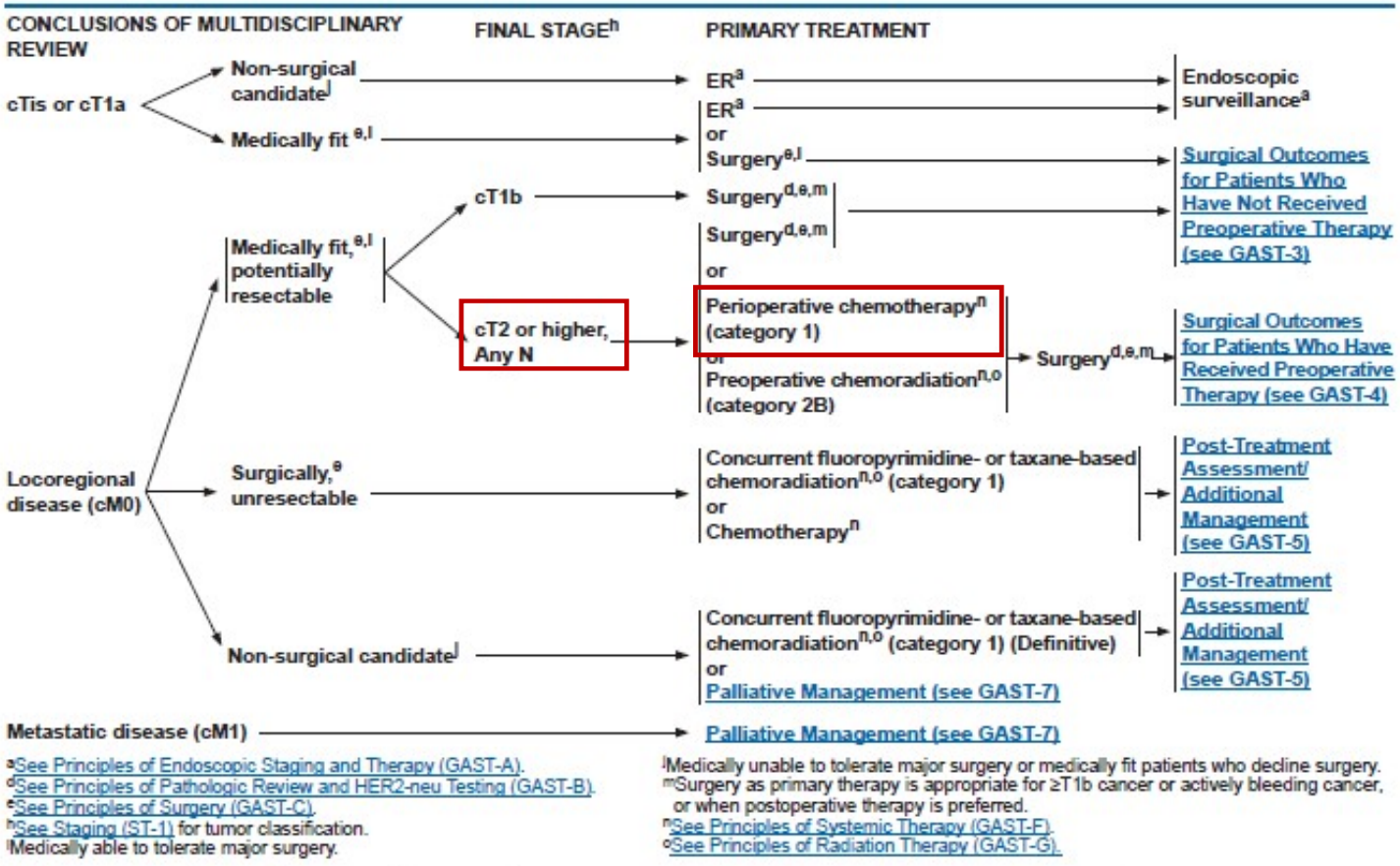
National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Gastric Cancer

NCCN Guidelines Index
Gastric Cancer Table of Contents
Discussion



[a] See Principles of Endoscopic Staging and Therapy (GAST-A).
[d] See Principles of Pathologic Review and HER2-neu Testing (GAST-B).
[e] See Principles of Surgery (GAST-C).
[h] See Staging (ST-1) for tumor classification.
[l] Medically able to tolerate major surgery.
[j] Medically unable to tolerate major surgery or medically fit patients who decline surgery.
[m] Surgery as primary therapy is appropriate for ≥T1b cancer or actively bleeding cancer, or when postoperative therapy is preferred.
[n] See Principles of Systemic Therapy (GAST-F).
[o] See Principles of Radiation Therapy (GAST-G).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Trends in the Use of Evidence-Based Therapy for Resectable Gastric Cancer

Journal of SURGICAL ONCOLOGY
2014;110:285–290

We performed a retrospective cohort study of patients with ***Stage IB–IV (M0) gastric adenocarcinoma*** who underwent resection ***from 1991 to 2009*** using the linked ***SEER–Medicare database***

TABLE I. Trends in Use of Multimodality Therapy Over Time (N = 4841)

	1991–2001	2002–2005	2006–2009	*P*-Value
Any preoperative chemotherapy	0.8% (18)	1.5% (20)	4.7% (52)	<0.001
Post-operative chemoradiation	13.0% (310)	24.8% (333)	25.4% (282)	<0.001
Surgery alone	68.7% (1641)	55.5% (746)	50.4% (559)	<0.001
Other	17.6% (419)	18.2% (245)	19.5% (216)	0.386
Total	100% (2,388)	100% (1,344)	100% (1,109)	—

Only 19.1% of patients received post-operative chemoradiation therapy (CRT), and ***1.9% received peri-operative chemotherapy***; most patients underwent surgery alone (60.9%)

The proportion of patients treated with postoperative CRT increased significantly after trial publication as did the ***proportion of patients treated with peri-operative chemotherapy***

There are a number of ***hypotheses that might explain*** the undertreatment of gastric cancer patients despite high quality evidence supporting its use:

- ✓ *timeliness of information dissemination*
- ✓ *economic impact of treatment*
- ✓ *availability of resources and multidisciplinary expertise*

Trends in the use and impact of neoadjuvant chemotherapy on perioperative outcomes for resected gastric cancer: Evidence from the American College of Surgeons National Cancer Database

SURGERY
2016;159:1099-112

Using the ***American College of Surgeons National Cancer Database***, 16,128 patients underwent gastrectomy for cancer ***from 2003 to 2012***

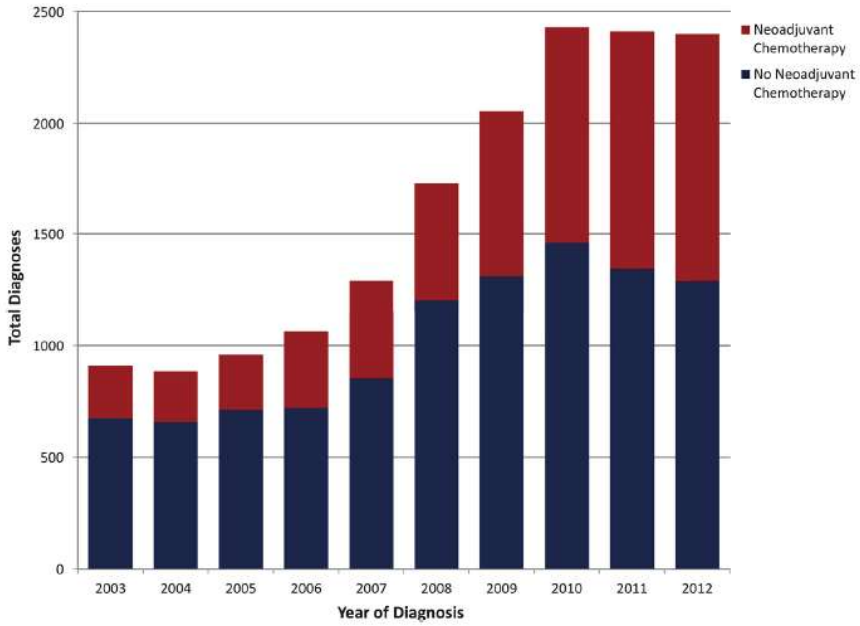

Fig 1. Use of neoadjuvant chemotherapy, by year.

- ***36.6%*** received ***NAC*** and 63.4% did not receive chemotherapy in the neoadjuvant setting.
- ***Patients who received NAC*** were more frequently ***younger***, male, white, ***privately insured***, with ***fewer comorbidities***, and ***treated at an academic center*** (all P <.0001).
- Over time, the use of NAC increased annually, from ***25.9%*** in ***2003*** to ***46.3%*** in ***2012***

Trends in the use and impact of neoadjuvant chemotherapy on perioperative outcomes for resected gastric cancer: Evidence from the American College of Surgeons National Cancer Database

SURGERY
2016;159:1099-112

- Patients who received NAC had a ***postoperative duration of stay 0.43 days shorter than patients who did not receive chemotherapy*** (5.79 vs 6.22 days; P = .050)

- They had a ***36% lower odds of 30-day mortality*** (odds ratio, 0.64, P<.0001) but nonsignificant lower odds of 90-day mortality

Conclusion. *With concerns regarding the toxicity of NAC, these findings suggest that NAC is not associated with worse postoperative outcomes. In light of evidence touting the benefits of NAC, its adoption as a component in the multimodality care of gastric cancer is slowly increasing, although use of NAC remains poor overall. (Surgery 2016;159:1099-112.)*

27 March (Monday)

Gastric cancer

Lecture (20'): state of art of chemotherapy in a combined treatment perspective

Perioperative chemotherapy

- ✓ *What is the impact of preoperative chemotherapy alone?* — *Modest*
- ✓ *Should perioperative chemotherapy be considerd a standard?* — *YES!*
- ✓ *What could be the reasons of the undertreatment of gastric cancer patients despite available high quality evidence?* — *Lack of multidisciplinary expertise*
- ✓ *Has pre-operative treatment a negative impact on post-operative outcomes?* — *No*
- ✓ *What are potential prognostic markers?*
- ✓ *How can we treat non-responding patients?*
- ✓ *More is better?*

Adjuvant chemotherapy

- ✓ *More is better?*
- ✓ *Is it better late than ever?*

Perioperative or adjuvant chemotherapy

- ✓ *What is better?*

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Significance of Histopathological Tumor Regression After Neoadjuvant Chemotherapy in Gastric Adenocarcinomas

A Summary of 480 Cases

ANNALS OF SURGERY

(*Ann Surg* 2011;253:934–939)

Evaluation of ***histopathological tumor regression*** in 480 surgical resection specimens ***after NA cisplatin-based CT***

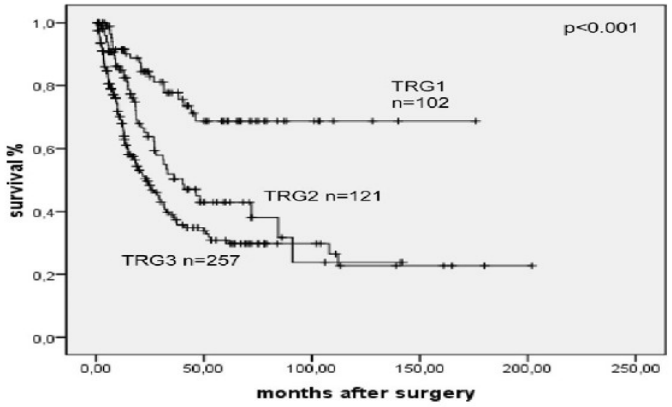

FIGURE 2. Histopathological Tumor Regression Grade (TRG) and survival. $P < 0.001$ for TRG1 vs. TRG2 and TRG3.

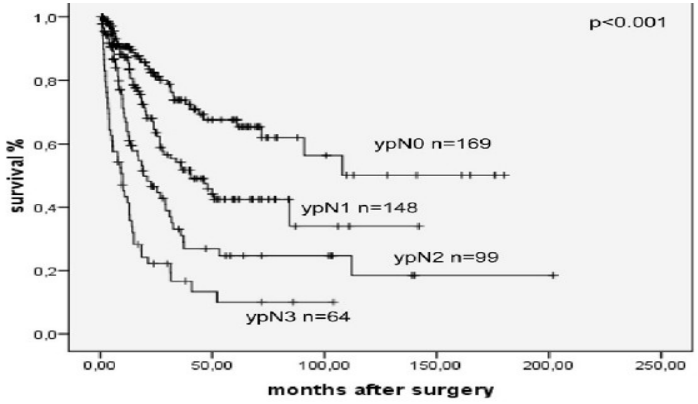

FIGURE 1. Postoperative Lymph node status (UICC 2002 ypN category) and survival.

Tumor regression ($P = 0.009$) and postoperative Lymph node status ($P < 0.001$) were independent prognostic factors for survival in a multivariate analysis

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Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial

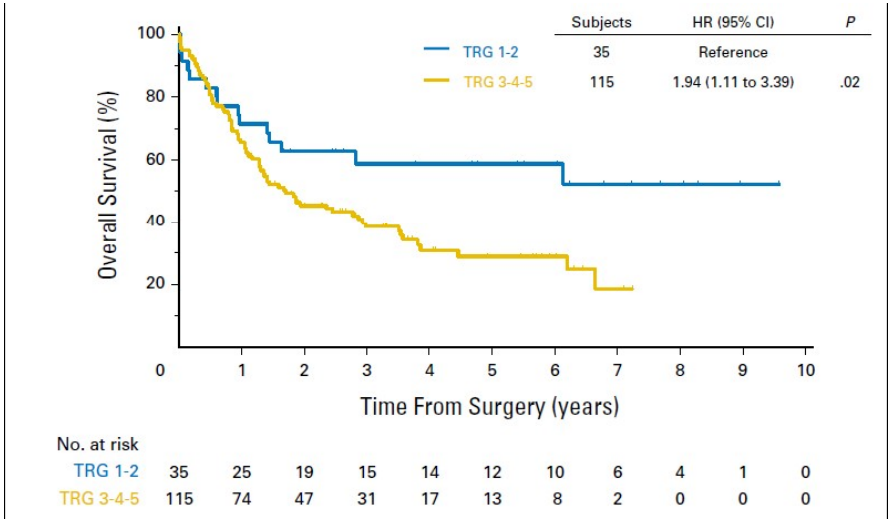
VOLUME 34 · NUMBER 23 · AUGUST 10, 2016
JOURNAL OF CLINICAL ONCOLOGY

We evaluated ***whether pathologic response and lymph node status after neoadjuvant chemotherapy*** are ***prognostic*** in patients treated in the ***MAGIC trial***

Table 2. Overall Survival From Surgery Stratified by Mandard TRG in Patients Treated With Chemotherapy Plus Surgery

Mandard TRG	Median Survival	HR (95% CI)	P*
Mandard TRG (1 and 2 *v* 3 *v* 4 *v* 5)			
1-2	Not reached†		.098
3	22.51	1.86 (1.01 to 3.43)	
4	20.47	1.84 (0.97 to 3.49)	
5	19.15	2.43 (1.17 to 5.04)	
Mandard TRG (1 and 2 *v* 3 and 4 and 5)			
1-2	Not reached†	1.94 (1.11 to 3.39)	.0209
3-5	20.47		

Abbreviations: HR, hazard ratio; TRG, tumor regression grade.
*Cox regression method.
†Greater than last censoring time.



In chemotherapy-treated patients with a ***tumor regression rate (TRG) of 1 or 2***, ***median OS was not reached***, whereas for patients with a ***TRG of 3, 4, or 5***, ***median OS was 20.4 months***

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Effect of Pathologic Tumor Response and Nodal Status on Survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial

VOLUME 34 · NUMBER 23 · AUGUST 10, 2016
JOURNAL OF CLINICAL ONCOLOGY

Table A3. Univariate Analysis of Factors Affecting Overall Survival in Patients Treated With Chemotherapy Plus Surgery (n = 150)

Variables	HR (95% CI)	P
Age, years		
< 60		.122
60 to < 70	1.42 (0.88 to 2.30)	.150
≥ 70	1.70 (1.00 to 2.90)	.051
MI + diff/other	1.10 (0.14 to 8.41)	.928
Not assessed	3.12 (0.40 to 24.2)	.276
TRG score		
1-2		
3-5	1.94 (1.11 to 3.39)	.021
N stage		
Node-negative		
Node-positive	3.63 (1.88 to 7.00)	< .001

Table A4. Multivariate Analysis of Factors Affecting Overall Survival in Patients Treated With Chemotherapy Plus Surgery (n = 110)

Conclusion

Prospective evaluation of whether omitting postoperative chemotherapy and/or switching to a noncross-resistant regimen in patients with lymph node-positive disease whose tumor did not respond to preoperative epirubicin, cisplatin, and fluorouracil may be appropriate.

On *univariate analysis*, ***high TRG and lymph node metastases*** were ***negatively related to survival***

On *multivariate analysis*, ***only lymph node status*** was ***independently predictive of OS***

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Mismatch Repair Deficiency, Microsatellite Instability, and Survival

An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial

JAMA Oncology

JAMA Oncol. doi:10.1001/jamaoncol.2016.6762

IMPORTANCE Mismatch repair (MMR) deficiency (MMRD) and microsatellite instability (MSI) are prognostic for survival in many cancers and for resistance to fluoropyrimidines in early colon cancer. However, the effect of MMRD and MSI in curatively resected gastric cancer treated with perioperative chemotherapy is unknown.

Figure 1. Overall Survival by Microsatellite Instability (MSI) Status and Treatment Arm in the Study Patients

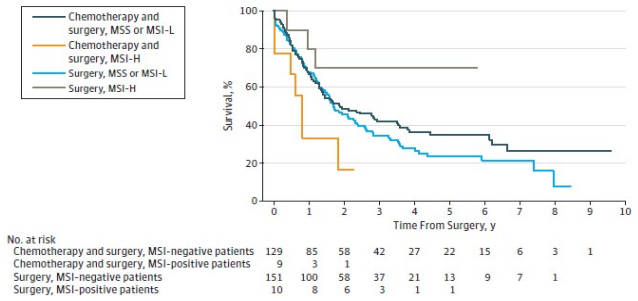
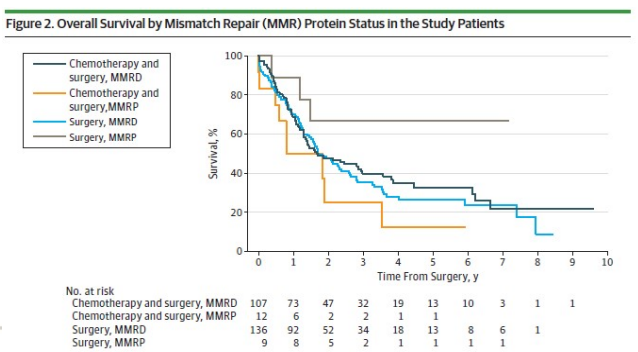


Figure 2. Overall Survival by Mismatch Repair (MMR) Protein Status in the Study Patients



We found that patients with MSI-H or MMRD tumors have superior survival compared with patients with MSS/MSI-L or MMRP tumors when treated with surgery alone and conversely have inferior survival to patients with MSS/MSI-L or MMRP tumors when treated with perioperative chemotherapy plus surgery. These findings are significant, because if validated, they suggest that patients with MSI-H or MMRD may not benefit (or may experience a detrimental effect) from perioperative chemotherapy and may be better served by a surgery-only approach. Because MSI or MMRD tumors comprise up to 10% to 20% of stomach cancers in some series, this finding has the potential to affect large numbers of patients.[15]

27 March (Monday)

Gastric cancer

Lecture (20'): state of art of chemotherapy in a combined treatment perspective

Perioperative chemotherapy

- ✓ *What is the impact of preoperative chemotherapy alone?* — *Modest*
- ✓ *Should perioperative chemotherapy be considerd a standard?* — *YES!*
- ✓ *What could be the reasons of the undertreatment of gastric cancer patients despite available high quality evidence?* — *Lack of multidisciplinary expertise*
- ✓ *Has pre-operative treatment a negative impact on posto-operative outcomes?* — *No*
- ✓ *What are potential prognostic markers?* — *Lymph node status; TRG, MMRD, MSI (?)*
- ✓ *How can we treat non-responding patients?* — *Clinical trials*
- ✓ *More is better?*

Adjuvant chemotherapy

- ✓ *More is better?*
- ✓ *Is it better late than ever?*

Perioperative or adjuvant chemotherapy

- ✓ *What is better?*

ESTRO School

Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

ANNALS OF ONCOLOGY
27 (Supplement 5): v38–v49, 2016

Table 5. Summary of recommendations

Management of local/locoregional disease
Perioperative chemotherapy
• Perioperative (pre- and postoperative) chemotherapy with a platinum and fluoropyrimidine combination is recommended for patients with ≥stage IB resectable gastric cancer [I, A]
• Since capecitabine avoids the need for an indwelling central venous access device, and is non-inferior to 5-FU in the advanced disease setting, capecitabine-containing regimens can also be suggested in the perioperative setting [IV, C]

Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial

THE LANCET Oncology

Lancet Oncol 2016; 17:1697-708

- Patients with resectable gastric or gastro-oesophageal junction cancer who had ***clinical stage cT2 or higher***, ***nodal positive (cN+)*** disease, ***or both***

- 3 preoperative and 3 postoperative 3-week cycles of ***ECF/ECX*** or 4 preoperative and 4 postoperative ***FLOT*** (2-week cycles of *docetaxel* 50 mg/m², intravenous *oxaliplatin* 85 mg/m², intravenous *leucovorin* 200 mg/m², and *5-FU* 2600 mg/m² as a 24 h infusion, all on day 1)

- **Primary endpoint**: ***pathological complete regression*** (***TRG1a***: *equivalent to pathological complete regression; no residual tumour cells*)

Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial

THE LANCET Oncology

Lancet Oncol 2016; 17:1697-708

	ECF/ECX (n=137)	95% CI	FLOT (n=128)	95% CI	p value*
Complete (TRG 1a)†	8 (6%)	2·8–11·3%	20 (16%)	10·3–23·0%	0·02
Subtotal (TRG 1b)	23 (17%)	11·4–24·0%	27 (21%)	14·9–29·0%	..
Complete or subtotal (TRG 1a/b)	31 (23%)	16·4–30·4%	47 (37%)	28·9–45·4%	0·02
Partial (TRG 2)	28 (20%)	14·5–28·0%	23 (18%)	12·2–25·6%	..
Minimal or none (TRG 3)	52 (38%)	30·3–46·3%	49 (38%)	30·3–46·9%	..
No surgery	26 (19%)	13·2–26·4%	9 (7%)	3·6–13·0%	..

Data are n (%). ITT=intention-to-treat. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. TRG=tumour regression grade. *ECF/ECX compared with FLOT. †TRG1a was achieved in eight (7%) of 111 patients who had ECF/ECX and 20 (17%) of 119 patients who had FLOT (p=0·03) in the per-protocol population (resected patients).

Table 3: Histopathological tumour regression in the modified ITT population according to Becker

- A ***significantly higher proportion of patients achieved a pathological complete regression (TRG1a) in the FLOT group than in the ECF/ECX group*** (20 [***16%***; 95% CI 10 · 3–23 · 0] of 128 patients in the FLOT group *vs* eight [***6%***; 2 · 8–11 · 3] of 137 patients in the ECF/ECX group; p=0 · 02)
- The proportion of patients who achieved ***complete and subtotal regression (TRG1a/b)*** was also higher with FLOT (47 [***37%***] of 128 patients, 95% CI 28 · 9–45 · 4%) than with ECF/ECX (31 [***23%***] of 137 patients, 16 · 4–30 · 4%; p=0.02)

Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial

THE LANCET Oncology

Lancet Oncol 2016; 17: 1697–708

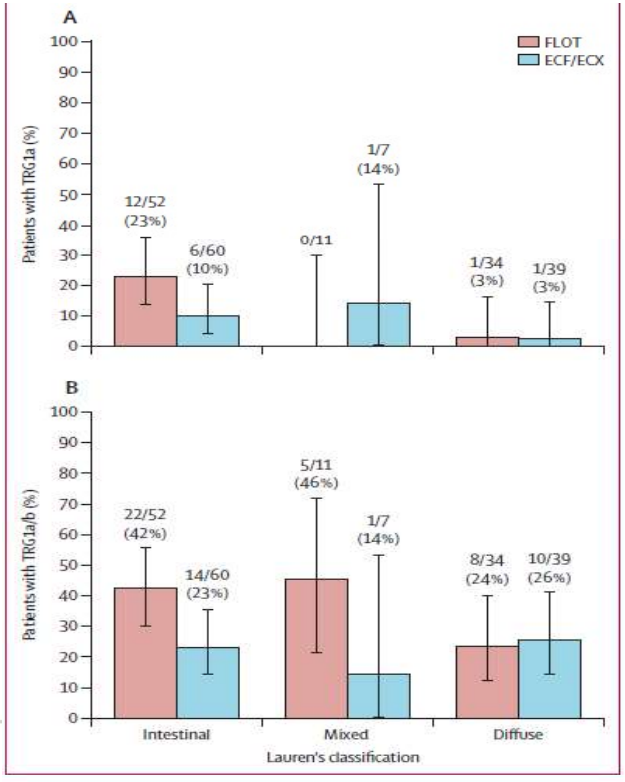


Figure 2: Histopathological regression by Lauren's classification

- ***TRG1a status was most frequent in patients with intestinal type tumours*** (18 [***16%***] of 112 patients) and ***least frequent in patients with the diffuse type histology*** (two [***3%***] of 73 patients; p=0.004), whereas one (6%) of 18 patients had TRG1a in the mixed type histology (p=0・47)

ESTRO School

27 March (Monday)

Gastric cancer

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Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer

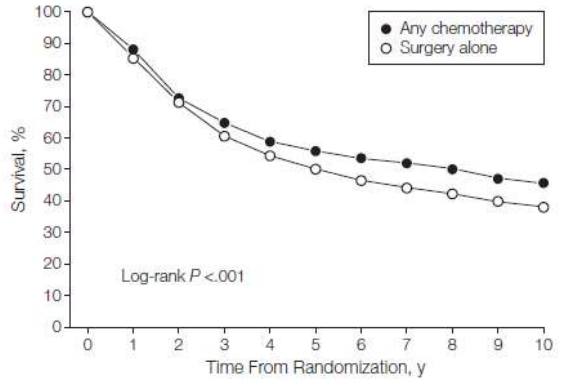
A Meta-analysis

The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group*

JAMA

May 5, 2010—Vol 303, No. 17

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years



No. at risk

Any chemotherapy	1924	1688	1385	1217	1080	929	709	526	390	297	243
Surgery alone	1857	1568	1300	1092	952	782	583	407	267	172	138

The estimates of the survival curves use an actuarial approach as described in the Methods.

- Adjuvant chemotherapy was associated with a ***statistically significant benefit in terms of overall survival*** (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.76-0.90; *P*.001)
- The estimated ***median OS was 4.9 years*** (95% CI, 4.4-5.5) ***in the surgery-only group*** vs ***7.8 years*** (95% CI, 6.5-8.7) in the group receiving ***adjuvant chemotherapy***
- ***Absolute benefits*** were ***5.8% at 5 years*** (from 49.6% to 55.3%) and ***7.4% at 10 years*** (from 37.5% to 44.9%)

Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer

A Meta-analysis

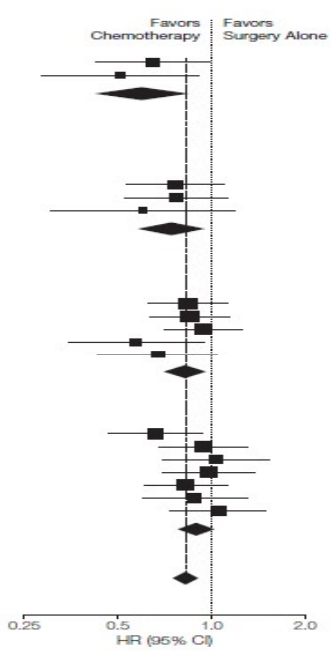
The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group*

JAMA

May 5, 2010—Vol 303, No. 17

Figure 2. Individual Trial and Overall Hazard Ratio for Overall Survival When Comparing Any Adjuvant Chemotherapy vs Surgery Alone

	Events, No./Patients, No.			
	Any Chemotherapy	Surgery Alone	Hazard Ratio (95% CI)	Observed Events–Expected Events (Variance)
Monochemotherapy				
Grau et al,[19] 1993	42/64	49/63	0.65 (0.43-0.99)	−9.4 (21.8)
Nakajima et al,[20] 2007	18/95	30/95	0.51 (0.29-0.90)	−7.9 (11.7)
Subtotal	60/159	79/158	0.60 (0.42-0.84)	−17.3 (33.5)
Heterogeneity: $\chi^2_1=0.44$; $P=.51$				
Polychemotherapies				
Fluorouracil + Mitomycin C + Other Without Anthracyclines				
Nakajima et al,[21] 1984	102/156	52/72	0.77 (0.54-1.09)	−8.3 (31.1)
Nakajima et al,[22] 1999	47/288	60/285	0.77 (0.53-1.12)	−7.0 (26.7)
Nashimoto et al,[23] 2003	13/128	21/124	0.60 (0.31-1.18)	−4.3 (8.5)
Subtotal	162/572	133/481	0.74 (0.58-0.95)	−19.7 (66.4)
Heterogeneity: $\chi^2_2=0.43$; $P=.81$				
Fluorouracil + Mitomycin C + Anthracyclines				
Coombes et al,[24] 1990	86/133	102/148	0.85 (0.64-1.13)	−7.8 (46.7)
Lise et al,[25] 1995	88/152	99/154	0.85 (0.64-1.14)	−7.5 (46.6)
Macdonald et al,[26] 1995	90/109	96/112	0.94 (0.71-1.26)	−2.7 (46.4)
Tsavaris et al,[27] 1996	25/44	38/43	0.57 (0.35-0.94)	−8.7 (15.6)
Popiela et al,[28] 2004	42/69	47/62	0.67 (0.44-1.04)	−8.0 (20.2)
Subtotal	331/491	382/509	0.82 (0.71-0.95)	−34.6 (175.5)
Heterogeneity: $\chi^2_4=3.82$; $P=.43$				
Other				
Douglass and Stablein,[29] 1982	64/88	73/82	0.66 (0.47-0.93)	−13.7 (33.0)
Engstrom et al,[30] 1985	73/91	72/89	0.94 (0.68-1.30)	−2.3 (36.0)
Krook et al,[31] 1991	51/63	50/64	1.04 (0.70-1.53)	0.9 (25.1)
Bajetta et al,[32] 2002	67/135	69/136	0.98 (0.70-1.37)	−0.7 (34.0)
Bouché et al,[33] 2005	79/133	90/138	0.82 (0.61-1.11)	−8.2 (42.1)
Nitti et al,[34] 2006	50/103	55/103	0.88 (0.60-1.29)	−3.3 (26.2)
Nitti et al,[34] 2006	63/89	64/97	1.05 (0.74-1.49)	1.6 (31.6)
Subtotal	447/702	473/709	0.89 (0.78-1.02)	−25.8 (228.0)
Heterogeneity: $\chi^2_8=5.10$; $P=.53$				
Overall	1000/1924	1067/1857	0.82 (0.76-0.90)	−97.4 (503.3)
Heterogeneity: $I^2=0\%$; $\chi^2_{15}=15.03$; $P=.49$				
Test for 4 regimens' heterogeneity: $\chi^2_3=5.59$; $P=.13$				



Conclusion Among the RCTs included, postoperative adjuvant chemotherapy based on fluorouracil regimens was associated with reduced risk of death in gastric cancer compared with surgery alone.

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Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial

THE LANCET Oncology

Lancet Oncol 2014; 15: 1389–96

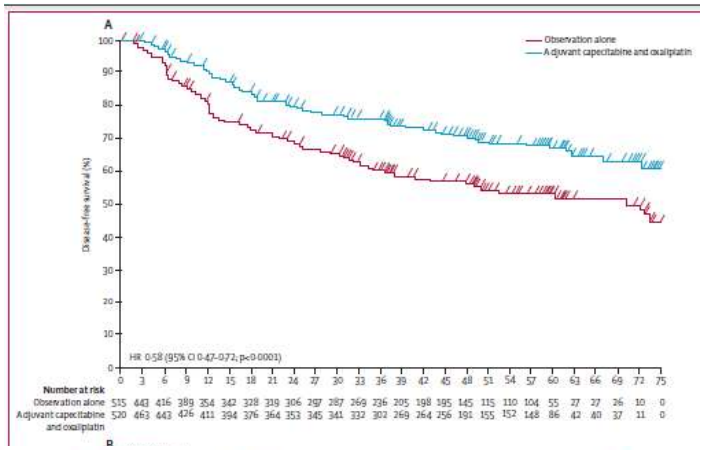

Figure 2: Disease-free survival (A) and overall survival (B) in the intention-to-treat population

- 139 (***27%***) patients had ***DFS events*** in the adjuvant ***capecitabine and oxaliplatin*** group versus 203 (***39%***) patients in the ***observation group*** (stratified hazard ratio [HR] 0·58, 95% CI 0·47–0·72; p<0·0001).
- Estimated ***5-year DFS*** was ***68%*** (95% CI 63–73) in the adjuvant ***capecitabine and oxaliplatin*** group versus ***69%*** (64–73) in the ***observation group***
- Estimated ***5-year OS*** was ***78%*** (95% CI 74–82) in the

Interpretation Adjuvant treatment with capecitabine plus oxaliplatin after D2 gastrectomy should be considered for patients with operable stage II or III gastric cancer.

Randomized trial on adjuvant treatment with FOLFIRI followed by docetaxel and cisplatin versus 5-fluorouracil and folinic acid for radically resected gastric cancer

ANNALS OF ONCOLOGY

Annals of Oncology 25: 1373–1378, 2014

Conclusions: A more intensive regimen failed to show any benefit in disease-free and OS versus monotherapy.

Sequential paclitaxel followed by tegafur and uracil (UFT) or S-1 versus UFT or S-1 monotherapy as adjuvant chemotherapy for T4a/b gastric cancer (SAMIT): a phase 3 factorial randomised controlled trial.

THE LANCET Oncology

2014 Jul;15(8):886-93.

INTERPRETATION: Sequential treatment did not improve disease-free survival.

Two large randomized trials ***failed to report an evidence of superiority of sequential polichemotherapy over single agent CT with fluoropyrimidine***, since none of them met the primary endpoint in terms of DFS

Combination or single-agent chemotherapy as adjuvant treatment of gastric cancer
A systematic review and meta-analysis of published trials

98 (2016) 24–28

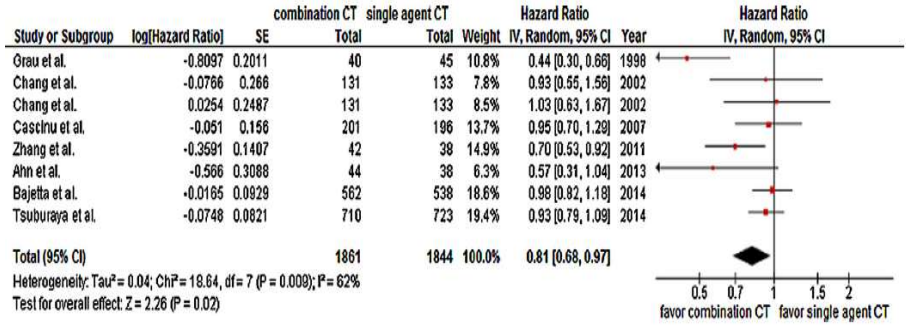

Fig. 2. Overall survival in the overall population.

- In the overall population, ***combination CT decreased the risk of death by 13%*** (HR = 0.87; 95% CI, 0.79–0.95; p = 0.004)
- When analysis was ***limited to studies with D2 lymphadenectomy***, a ***significant reduction of the risk of death was also found*** in favor of combination CT (HR = 0.86; 95%CI, 0.76–0.98; p = 0.02)

Conclusions: This analysis reported that adjuvant combination CT decreases the risk of death over single agent therapy in patients with non-metastatic GC.

- When analysis was ***limited to studies with D2 lymphadenectomy***, a ***non-significant reduction of the risk of relapse*** was found in favor of combination CT

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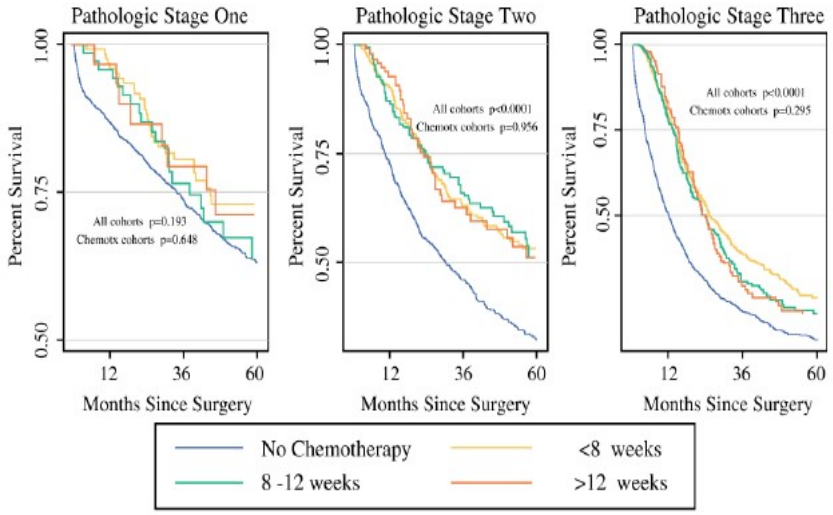
Timing of Adjuvant Chemotherapy and Impact on Survival for Resected Gastric Cancer

Annals of SURGICAL ONCOLOGY
(2016) 23:4203–4213



	Time to adjuvant chemotherapy				*p* Value	
	<8wk	8-12 wk	>12 wk	No Chemotx	Chemotx cohorts	All cohorts
Overall	37.97	34.98	32.39	48.06	0.759	0.405
Pathologic Stage						
1	113.96	ϕ	ϕ	98.79	0.648	0.193
2	74.08	64.96	65.27	29.90	0.956	<0.001
3	24.88	22.92	23.41	11.68	0.295	<0.001

FIG. 1 Kaplan-Meier estimates of overall postoperative survival of patients undergoing definitive resection for pathologic stages 1–3 gastric cancer, stratified by time to initiation of adjuvant chemotherapy

Median survival was longer for chemotherapy cohorts when compared with the no chemotherapy cohort, specifically in patients with pathologic stages 2 and 3 disease

Conclusions. Time to initiation of AC does not impact survival. With improved survival over patients who did not receive AC, even delayed initiation of chemotherapy should be offered, when appropriate.

ESTRO School

27 March (Monday)

Gastric cancer

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- ✓ *More is better?* — *Probably YES (FLOT4)*

Adjuvant chemotherapy

- ✓ *More is better?* — *May be - Selection of patients is crucial*
- ✓ *Is it better late than ever?* — *Yes*

Perioperative or adjuvant chemotherapy

- ✓ *What is better?*

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

The NEW ENGLAND JOURNAL of MEDICINE 2006;355:11-20.

- The ***completion rate*** of the whole protocol treatment was only ***41.6%***, while the ***completion rate of preoperative chemotherapy*** was ***over 80%***

Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial

VOLUME 29 · NUMBER 13 · MAY 1 2011
JOURNAL OF CLINICAL ONCOLOGY

- The ***completition rate*** of the whole protocol treatment was only ***47.8%***, whereas that of the ***preoperative chemotherapy*** was ***97%***

Both these trials demonstrated that ***the survival benefit seemed attributable to the effects of the preoperative chemotherapy***

Adjuvant Therapy Completion Rates in Patients with Gastric Cancer Undergoing Perioperative Chemotherapy Versus a Surgery-First Approach

Journal of Gastrointestinal Surgery

J Gastrointest Surg (2016) 20:172–179

Clinicopathologic and treatment variables of 155 patients undergoing potentially curative gastrectomy for stages Ib–IIIc gastric adenocarcinoma from 2001 to 2014 were analyzed, and rates of receipt of chemotherapy and radiotherapy in patients treated with either a surgery-first approach (SURG) or neoadjuvant therapy followed by surgery followed by postoperative therapy (PERIOP) were compared.

Fig. 1 Therapy completion rates in the surgery-first (SURG) group

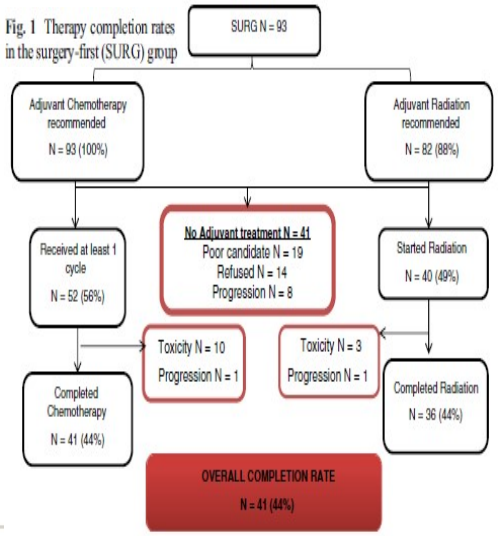
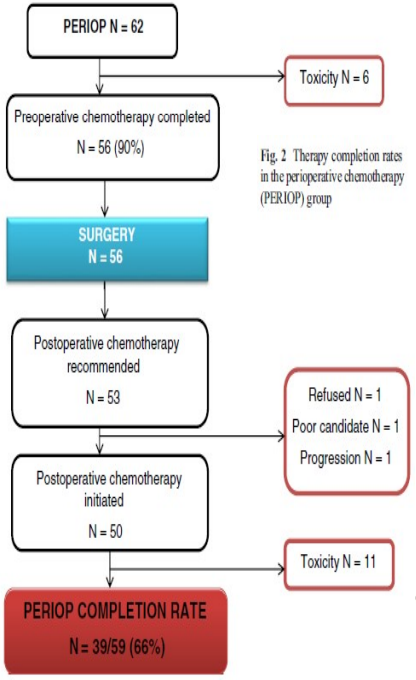


Fig. 2 Therapy completion rates in the perioperative chemotherapy (PERIOP) group



Conclusions

A significantly higher percentage of gastric cancer patients treated with perioperative chemotherapy receive some or all of the recommended multimodality therapy than do patients treated with a surgery-first approach. Strategies designed to deliver *all* (or as much as possible) chemotherapy and radiotherapy *prior to* surgery should be pursued in order to ensure the optimal treatment, and thus the best outcomes, for patients with high-risk gastric cancers.

ESTRO School

Adjuvant therapy for locally advanced gastric cancer

DOI 10.1007/s00595-017-1493-y

- Although the MAGIC and FNCLCC/FFCD trials showed that preoperative chemotherapy was effective for locally advanced gastric cancer, ***whether perioperative chemotherapy is effective when combined with D2 dissection is unclear***
- D2 gastrectomy was performed in ***only 42.5%*** of the patients in the perioperative chemotherapy arm in the ***MAGIC trial*** and the extent of dissection was ***not described in the FNCLCC/FFCD trial***

Perioperative chemotherapy more of a benefit for overall survival than adjuvant chemotherapy for operable gastric cancer: an updated Meta-analysis

SCIENTIFIC REPORTS

| 5:12850 | DOI: 10.1038/srep12850

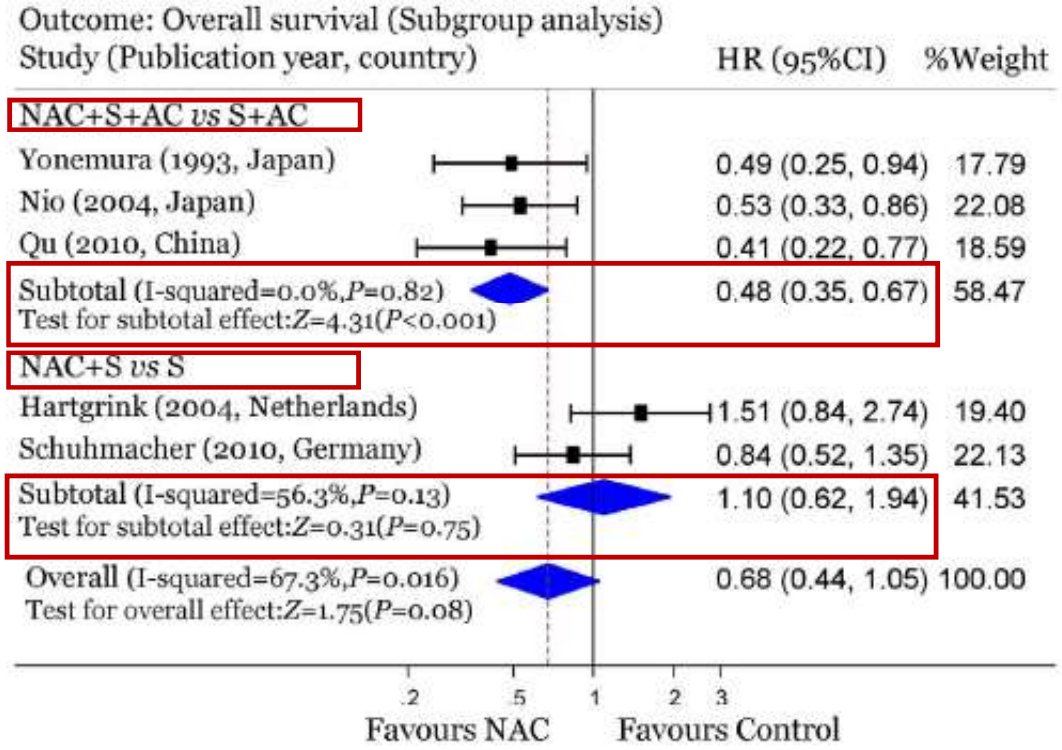
- Would ***NAC alone*** have survival benefits for operable gastric cancer patients, or ***should it be combined with AC***?
- Or ***is AC itself sufficient to improve the survival*** in gastric cancer patients and ***NAC is not useful***?

- The key question is that ***we still don't know if PC exactly has an extra advantage than AC*** in the treatment of operable gastric cancers

- Updated meta-analysis involving 2,093 patients from 14 different trials between 1966 and June, 2014, comparing ***NAC-containing strategies*** with ***NAC-free strategies***, mainly in terms of OS of patients with resectable gastric cancer

Perioperative chemotherapy more of a benefit for overall survival than adjuvant chemotherapy for operable gastric cancer: an updated Meta-analysis

SCIENTIFIC REPORTS
| 5:12850 | DOI: 10.1038/srep12850



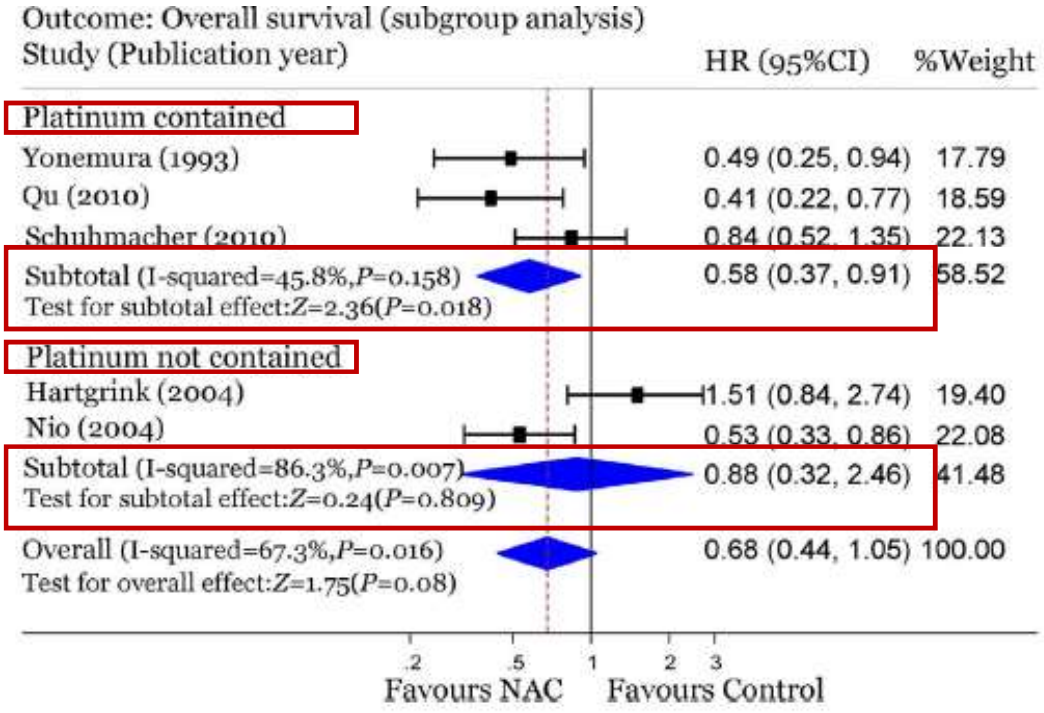
- The OS of the treatment arm that involved ***both AC and NAC*** was significantly improved over the control arm (***AC only***) (HR = 0.48, 95% CI: 0.35–0.67; P < 0.001)

- ***NAC alone plus surgery*** did ***not*** show ***any survival benefit over surgery alone***

Perioperative chemotherapy more of a benefit for overall survival than adjuvant chemotherapy for operable gastric cancer: an updated Meta-analysis

SCIENTIFIC REPORTS

| 5:12850 | DOI: 10.1038/srep12850



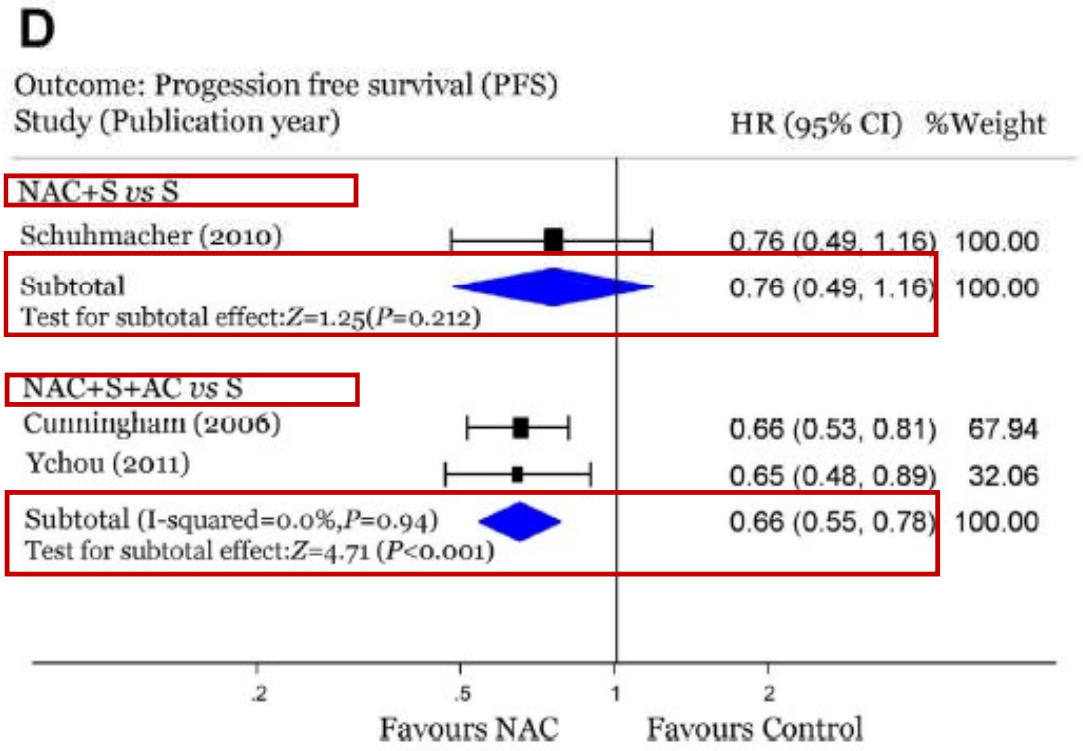
- The ***platinum-containing regimens*** showed ***better efficacy*** in improving OS ***than other regimens***

ESTRO School

Perioperative chemotherapy more of a benefit for overall survival than adjuvant chemotherapy for operable gastric cancer: an updated Meta-analysis

SCIENTIFIC REPORTS

| 5:12850 | DOI: 10.1038/srep12850

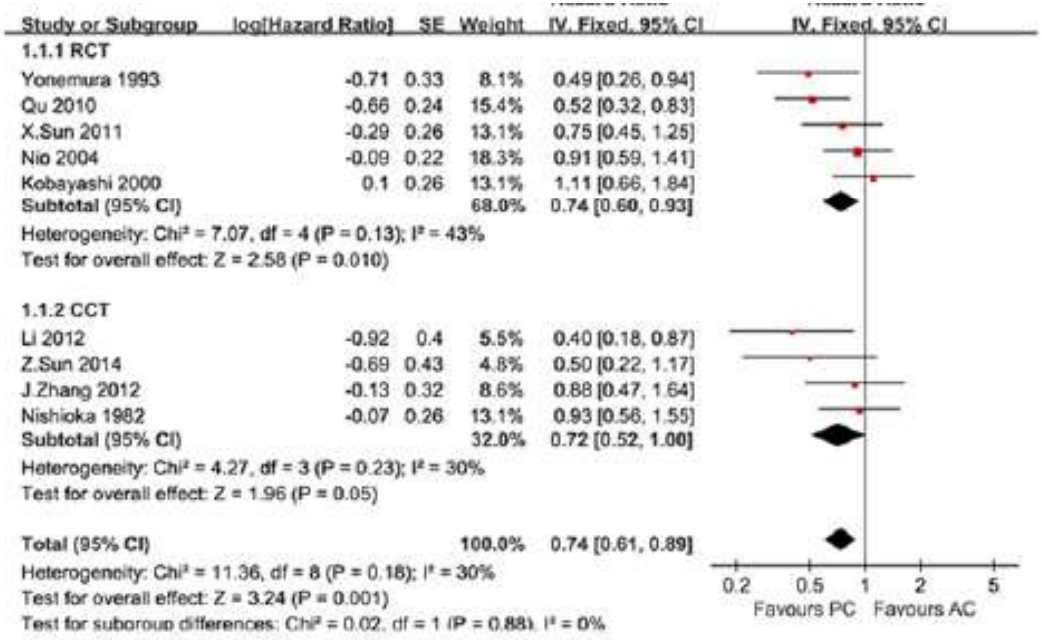


- The results of the perioperative subgroup showed a significant ***increase in PFS***

Which is better for gastric cancer patients, perioperative or adjuvant chemotherapy: a meta-analysis

BMC Cancer

Zhao *et al. BMC Cancer* (2016) 16:631



- Compared with the adjuvant chemotherapy group, the ***perioperative chemotherapy group had significantly better prognosis*** (HR, 0.74; 95 % CI, 0.61 to 0.89; P < 0.01).

ESTRO School

27 March (Monday)

Gastric cancer

Lecture (20'): state of art of chemotherapy in a combined treatment perspective

ESTRO School

Perioperative chemotherapy

- ✓ *What is the impact of preoperative chemotherapy alone?* — *Modest*
- ✓ *Should perioperative chemotherapy be considerd a standard?* — *YES!*
- ✓ *What could be the reasons of the undertreatment of gastric* — *Lack of multidisciplinary expertise*
- ✓ *cancer patients despite available high quality evidence?*
- ✓ *Has pre-operative treatment a negative impact on posto-operative outcomes?* — *No*
- ✓ *What are potential prognostic markers?* — *Lymph node status; TRG*
- ✓ *How can we treat non-responding patients?* — *Clinical trials*
- ✓ *More is better?* — *Probably YES (FLOT4)*

Adjuvant chemotherapy

- ✓ *More is better?* — *May be - Selection of patients is crucial*
- ✓ *Is it better late than ever?* — *Yes*

Perioperative or adjuvant chemotherapy

- ✓ *What is better?* — *NAC alone is not enough and AC alone is not good enough to definitely improve the OS (after D2 dissection?)*
- *AC is inferior to PC*

Thanks!

n.silvestris@oncologico.bari.it

Primary tumor extension – pathology evaluation
Role of pathologist for treatment decisions in gastric carcinoma

Alexander Quaas
Institute of Pathology
University of Cologne

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Road map

- Facts – gastric carcinoma in Germany
- Morphology based and molecular based diagnostics
- Tumorsubtypes
- Tumor extension evaluation – using UICC- TNM 8th edition (since 2017)
- Patho-anatomical basics and reportings
- Tumormicroenviroment

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Facts

- Germany 2016: 9.200 men / 6.400 women
- 60-70% will die carcinoma-releated in following years
- In metastasis/recurrence: dismal prognosis (8 months median survival)

From: gekid.de (Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.) and krebsdaten.de (Robert-Koch-Institut)

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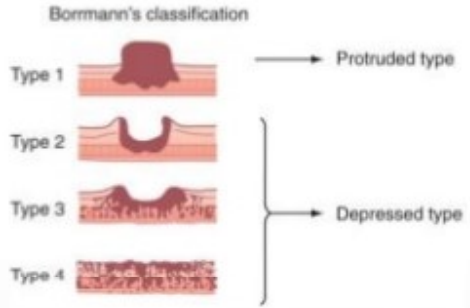
Traditional morphology based diagnostics

Classifications

- 1926-



- 1942- **Border**'s classification- degree of cellular differentiation.
- 1965- **Lauren**- Intestinal, Diffuse types.
- 1990- **WHO**- Adeno Ca., AdenoSq., SqCC, Small cell Ca., Undifferentiated Ca.

From: Dr. D. Guin, St. John's Medical College Hospital

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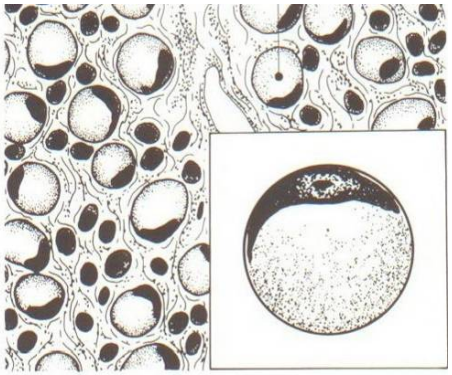
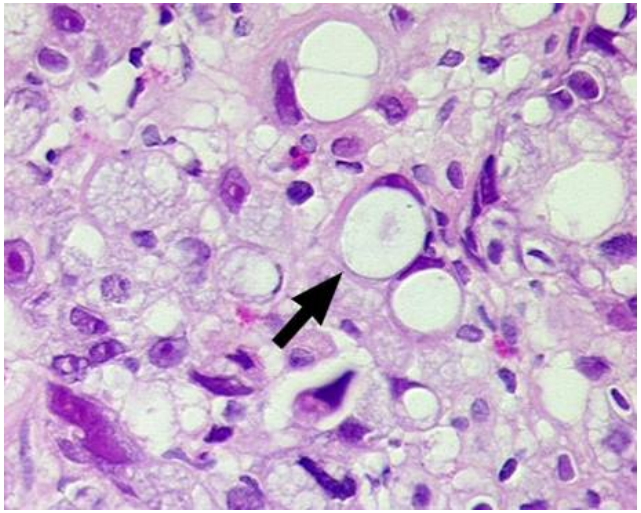
Traditional morphology based diagnostics

Table 1 Gastric adenocarcinoma classification systems

WHO (2010)	Lauren (1965)
Papillary adenocarcinoma Tubular adenocarcinoma Mucinous adenocarcinoma	Intestinal type
Signet-ring cell carcinoma And other poorly cohesive carcinoma	Diffuse type
Mixed carcinoma	Indeterminate type
Adenosquamous carcinoma	
Squamous cell carcinoma	
Hepatoid adenocarcinoma	
Carcinoma with lymphoid stroma	
Choriocarcinoma	
Carcinosarcoma	
Parietal cell carcinoma	
Malignant rhabdoid tumor	
Mucoepidermoid carcinoma	
Paneth cell carcinoma	
Undifferentiated carcinoma	
Mixed adeno-neuroendocrine carcinoma	
Endodermal sinus tumor	
Embryonal carcinoma	
Pure gastric yolk sac tumor	
Oncocytic adenocarcinoma	

"Carcinomas of the stomach are a heterogeneous group of lesions in terms of architecture, pattern of growth, cell differentiation, and histogenesis..."





From: Bing Hu, Gastric cancer: Classification, histology and application of molecular pathology, J Gastrointest Oncol 2012;3(3):251-261
Hye Seung Han and Gregory Y. Lauwers, Connection 2010

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Molecular subtypes

1) Chromosomal instable 49,8%
2) Microsatellite-instable 21,7%
3) Genomic stable 19,6%
4) EBV-induced 8,9%

Microsatellite-instable carcinoma and EBV-positive carcinoma: more antigenes/highly inflammed: probably immunocheckpoint inhibition (and perhaps radiation) more effective

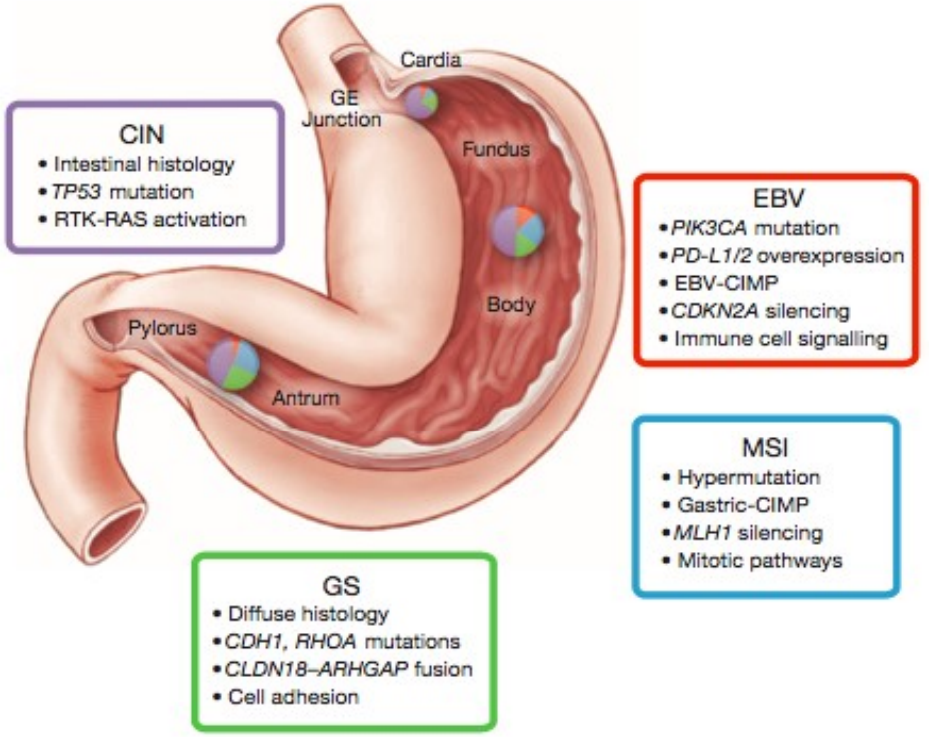

Figure 6 | Key features of gastric cancer subtypes. This schematic lists some of the salient features associated with each of the four molecular subtypes of gastric cancer. Distribution of molecular subtypes in tumours obtained from distinct regions of the stomach is represented by inset charts.

From: CancerGenomeAtlasResearchNetwork, „comprehensive molecular characterization of gastric adenocarcinoma“ Nature 2014

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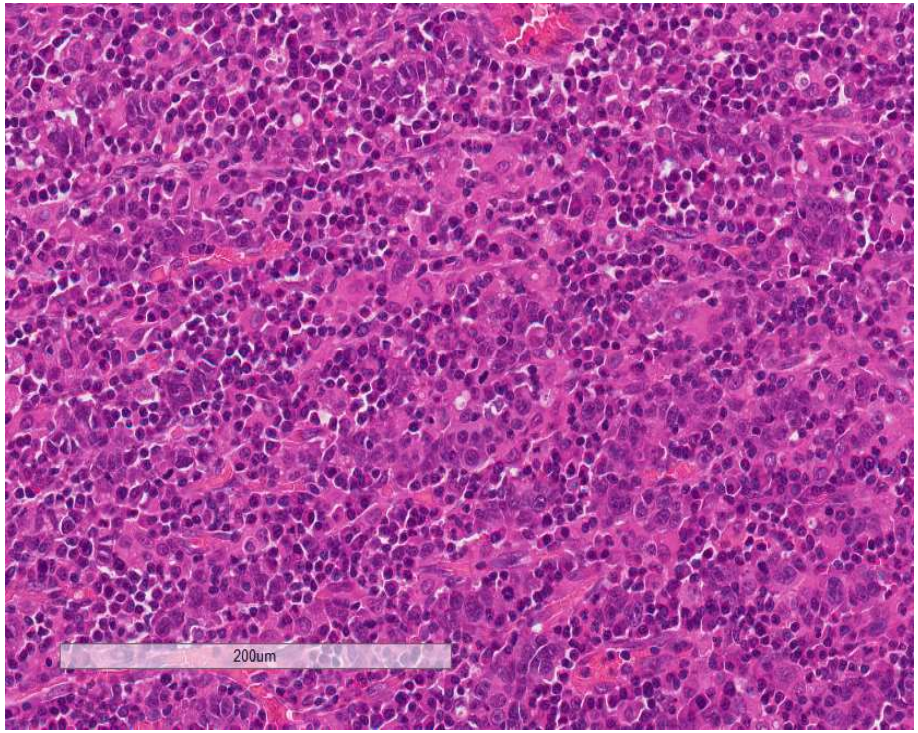
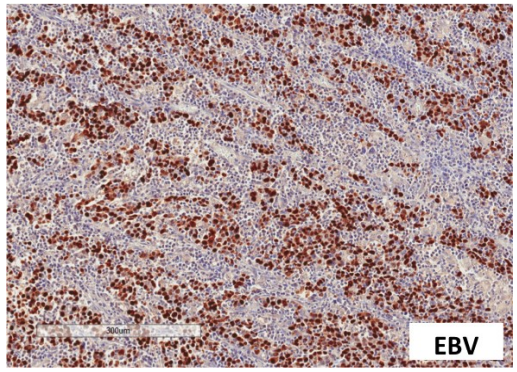
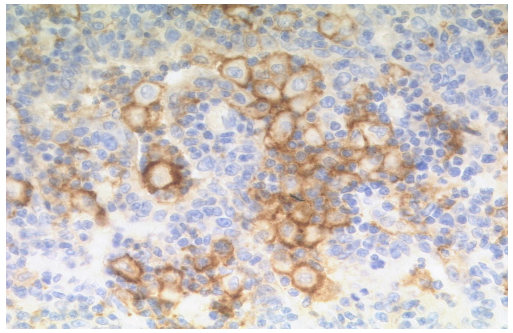
EBV+ gastric carcinoma



WHO: Gastric carcinoma with lymphoid stroma (medullary or lymphoepithelioma-like carcinoma)



EBV-encoded RNA (EBER) in-situ hybridization (ISH)



PD-L1 Immunohistochemistry, Dako-clone 28-8

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Classifications

WHO (2010)	Lauren (1965)	Goseki (1992)	Ming (1992)	Molecular (2014)
Papillary adenocarcinoma	Intestinal type		(expanding type)	Chromosomal instable, MSI*
Tubular adenocarcinoma		type 1, (type 2, type 3)	(infiltrating type)	
Mucinous adenocarcinoma				
Signet-ring cell carcinoma	Diffuse type	type 4		Genomic stable
And other poorly cohesive carcinoma				
Mixed carcinoma	Indeterminate type			
Adenosquamous carcinoma				
Squamous cell carcinoma				
Hepatoid adenocarcinoma				
Carcinoma with lymphoid stroma				EBV-related; MSI*
Choriocarcinoma				
Carcinosacrcoma				
Parietal cell carcinoma				
Malignant rhabdoid tumor				
Mucoepideroid carcinoma				
Paneth cell carcinoma				
Undifferentiated carcinoma				
Mixed adeno-neuroendocrine carcinoma				
Endodermal sinus tumor				
Embryonal carcinoma				
Pure gastric yolk sac tumor				
Oncocytic adenocarcinoma				

The correlation between the different classification systems is relatively. The Ming classification can not be assigned to the other classifications.

* MSI = Microsatellite instable

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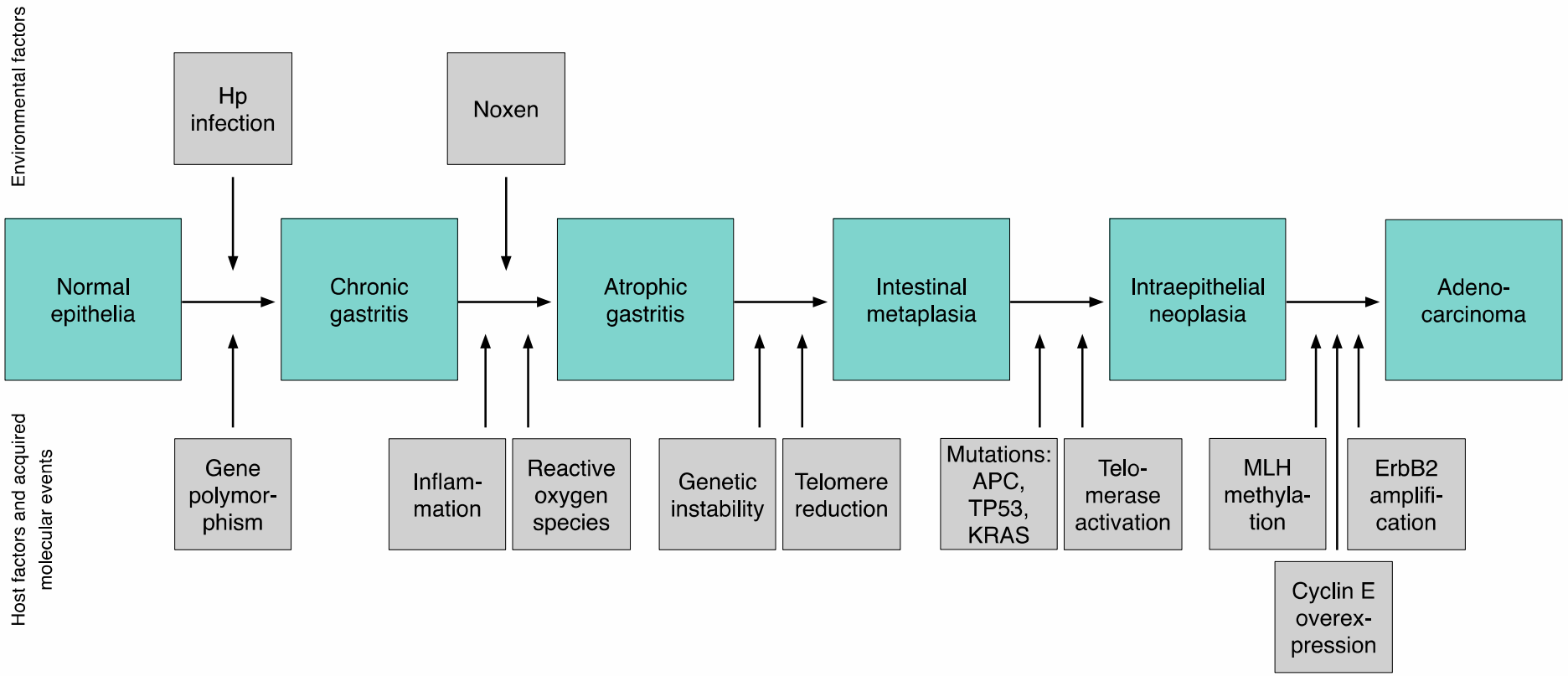
Pathogenesis „intestinal“ type



Simplified schema of pathogenesis of the intestinal type gastric adenocarcinoma. According to: P. Tan, K.G. Yeoh “Genetic and Molecular Pathogenesis of gastric adenocarcinoma”; Gastroenterology 2015; 149:1157-1162

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Practical and cost-effective subtyping of gastric carcinoma

Molecular subtype	Cost-effective
• CIS	• Intestinal • Her2 + • P53 + (IHC-based)
• GS	• Diffuse (includ. signet cell) • Her2 -
• MSI	• MLH1 - (IHC-based)
• EBV	• EBER-ISH +

Cologne Panel analysis: p53, Her2/neu, MLH1, PD-L1 and EBER-ISH = 85 Euro

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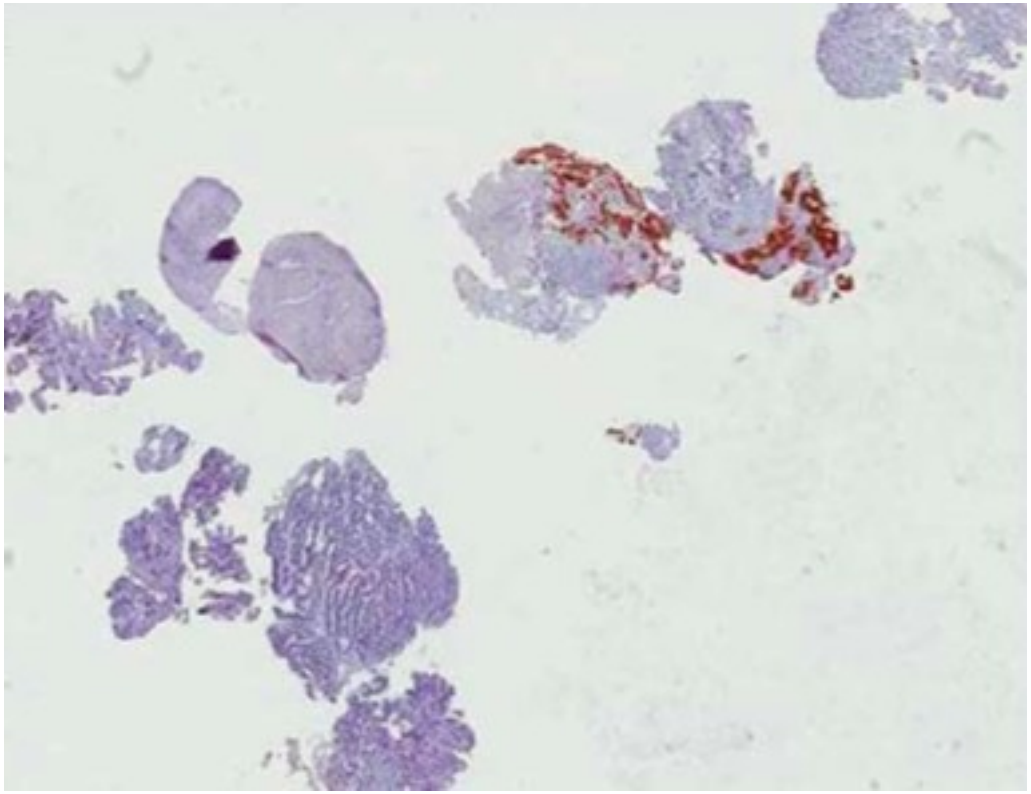
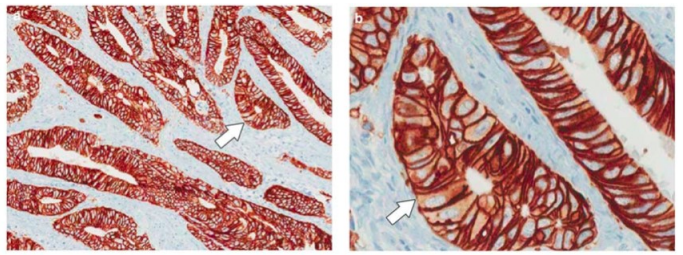
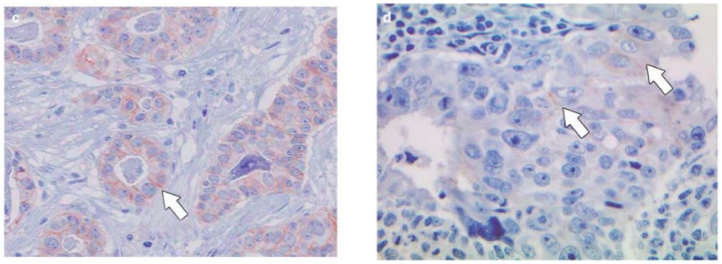
Her2+ gastric carcinoma





Magnification rule: 2,5-5X easy to see: 3+



Magnification rule: 20x : 2+ - (F) ISH and 1+ is negative

Positivity: baso-lateral or circumferential staining
Highly heterogenous distribution
Use other staining protocols: breast/gastric

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other subtypes

- BRCA mutated adenocarcinoma (BRCA1: 1,2% und BRCA2: 3,7%*)
- ATM deficient adenocarcinoma
- Small bowel adenocarcinoma harbour PARP-inhibitor-sensitive BRCA-mutations as well

→ PARP-inhibition and Checkpoint-inhibition (probably) effective in **DNA-repair-deficient** upper GI-tumors as well

Quaas, A et al.: Pathogenic BRCA mutation in small bowel adenocarcinoma – successfully treatable with the PARP-inhibitor Olaparib, Clin Cancer Res, 2017 subm.
Kubot, E et al.: Low ATM protein expression and depletion of p53 correlates with olaparib sensitivity in gastric cancer cell lines. Cell Cycle 2014
Higuchi T et al. CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer.
Cancer Immunol Res. 2015 Nov;3(11):1257-68

*according: Zhen DB, Hruban RH et al, Genet Med 2014

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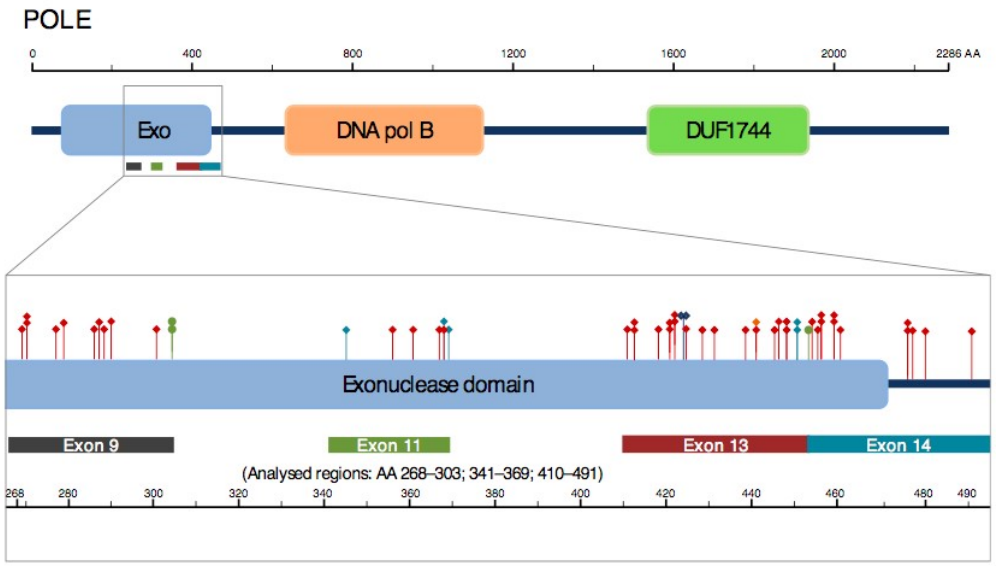
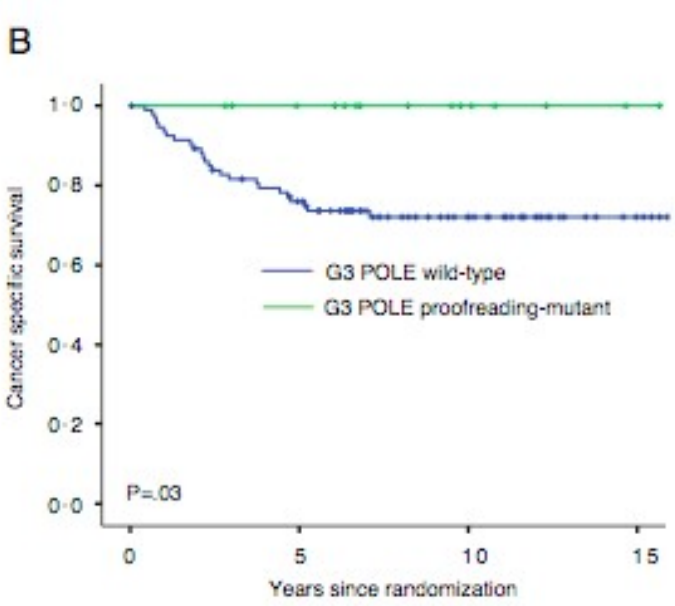
POLE-mutated gastric carcinoma about 5%





- G3 morphology?
- Good prognosis?
- Highly sensitive to chemotherapy?

From: Church, DN Prognostic significance of POLE proofreading mutations in endometrial cancer, J Natl Cancer Inst 2015
Stenzinger A Mutations in POLE and survival of colorectal cancer patients – link to disease stage and treatment, Cancer Med. 2014

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Pan-Cancer-All-In One-Panel= 83 Genes

Gene	target	Gene	target	Gene	target
ABL1	exons	IDH1	exons	RHOA	Exon 2,3
ALK	breakpoints and exons	IDH2	exons	RICTOR	exons
APC	exons	IGF2R	exons	ROS1	breakpoints and exons
AR	exons	JAK2	exons	RPTOR	exons
ARAF	exons	KDR	exons	SMO	exons
ATM	exons	KEAP1	exons	STK11	exons
ATR	exons	KIF5B	breakpoint only	TGFBR2	exons
BCL6	exons	KIT	exons	TP53	exons
BRAF	breakpoints and exons	KNSTRN	Exon1	TSC1	exons
BRCA1	exons	KRAS	exons	TSC2	exons
BRCA2	exons	MAP2K1	Exon 2	VHL	exons
CCND1	exons	MDM2	exons		
CCNE1	exons	MET	whole gene		
CD74	breakpoints	MSH3	exons		
CDK4	exons	MTOR	exons		
CDK6	exons	MYC	exons		
CDKN2A	exons	MYCL1	exons		
CDKN2B	exons	MYCN	exons		
CTNNB1	exons	NF1	exons		
EGFR	whole gene	NF2	exons		
EML4	breakpoint	NFE2L2	exons		
ERBB2	exons	NOTCH 1	exons		
FGFR1	whole gene	NOTCH 2	exons		
FGFR2	breakpoints and exons	NOTCH 3	exons		
FGFR3	whole gene	NRAS	exons		
FLT1	exons	NRG1	breakpoint only		
FLT4	exons	NTRK1	breakpoints and exons		
GNA11	exons	OXA1L	Exon 1		
GNA13	exons	PDGFRa	breakpoints and exons		
GNAI2	exons	PDGFRb	breakpoints and exons		
GNAQ	exons	PIK3CA	exons		
GNAS	exons	PTCH1	exons		
GNAT2	exons	PTEN	exons		
GNG2	exons	RAC1	Exon2		
HDAC2	exons	RB1	exons		
HRAS	exons	RET	breakpoints and exons		

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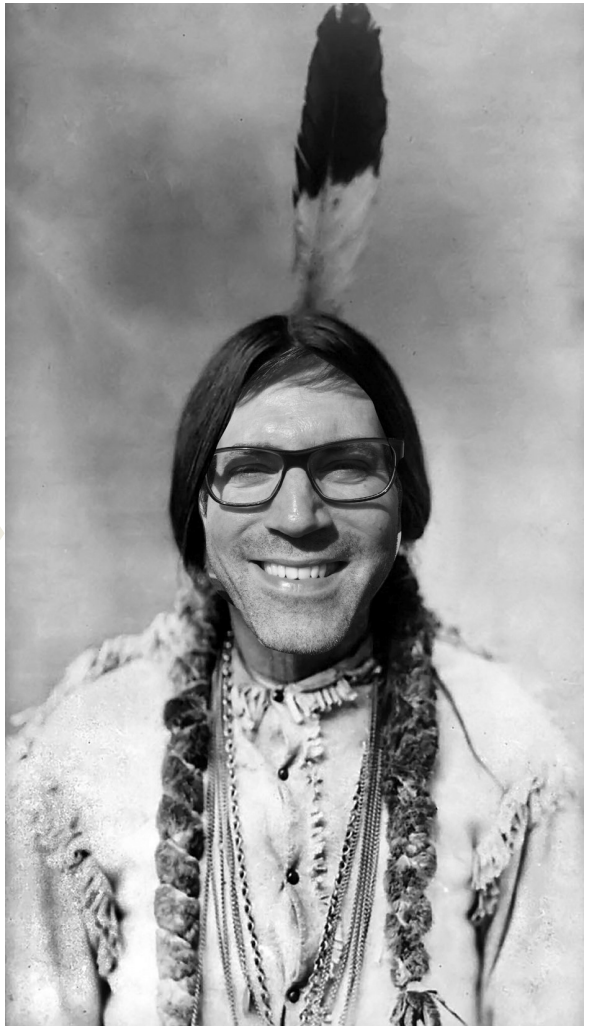
„the new pathologist“

1997: deliverer of diagnosis



2020: „Chief Treating Bull“

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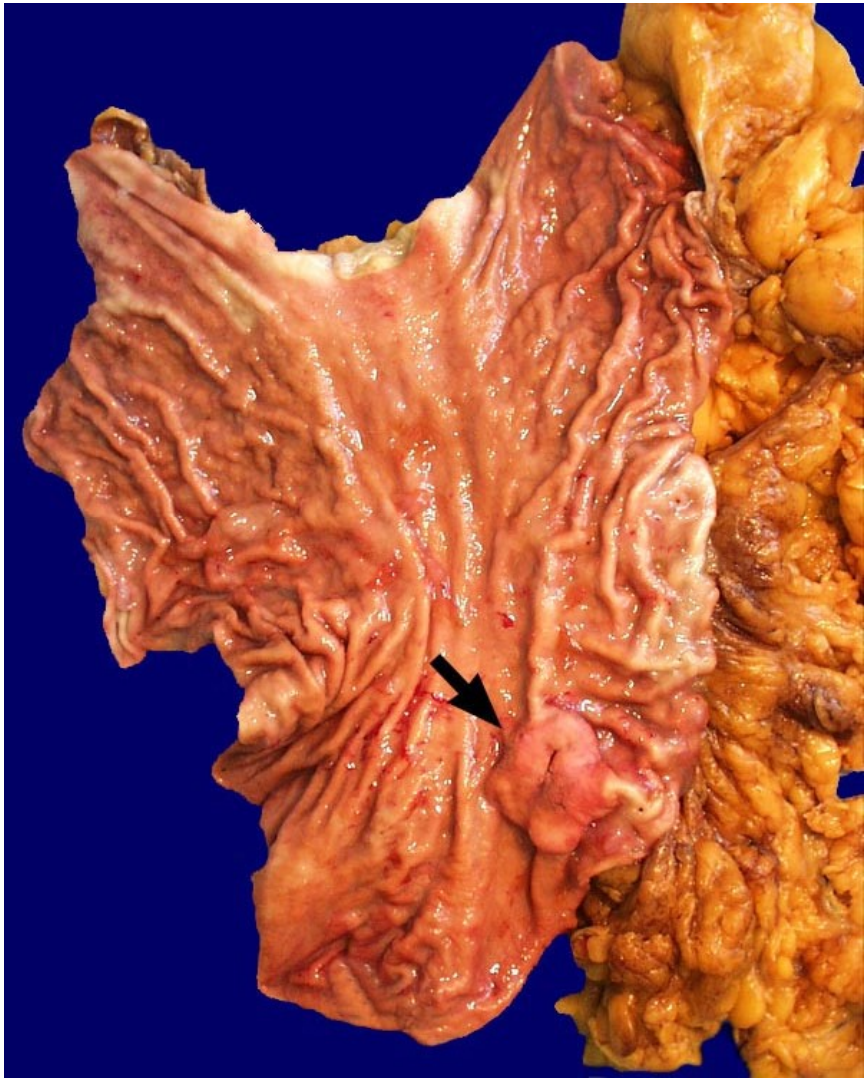
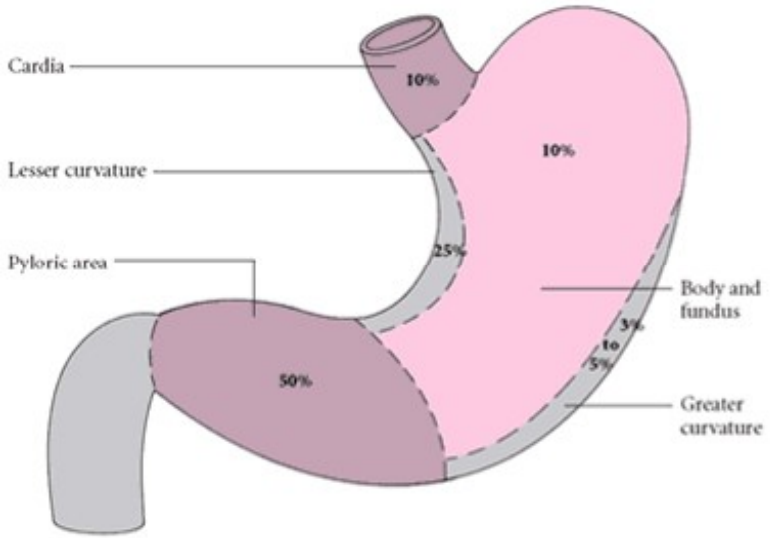
Distribution





But: increased incidence of cardia carcinoma/GEJ Carcinoma. „Intestinal type“ carcinoma, more often Her2/neu positive

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Staging: UICC

Stomach 8th edition, 2017

Tis: High grade intraepithelial neoplasia/dysplasia without infiltration of l. propria
T1: T1a: lamina propria or muscularis mucosae
T1b: submucosa
T2: mucularis propria
T3: sub-serosa
T4: T4a: perforation of serosa
T4b: other adjacent structures (e.g. spleen, colon)

N1: 1-2 regional lymph node(s)
N2: 3-6
N3: 3a:7-15
3b:16 and more

M1: Distant metastasis

Applies to carcinoma (ICD-0 C15) and includes adenocarcinoma of the oesophagogastric junction (ICD-0 C16.0)

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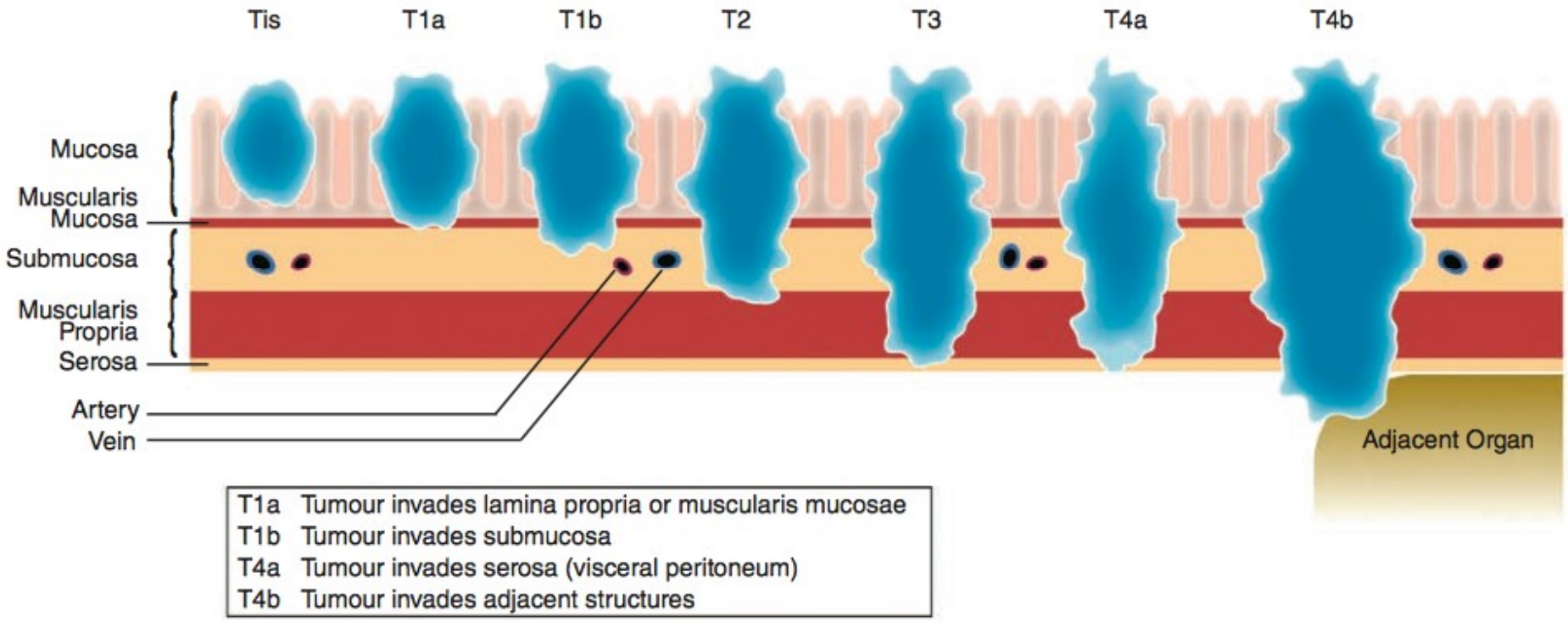
TNM



From: Hye Seung Han and Gregory Y. Lauwers, Connection 2010

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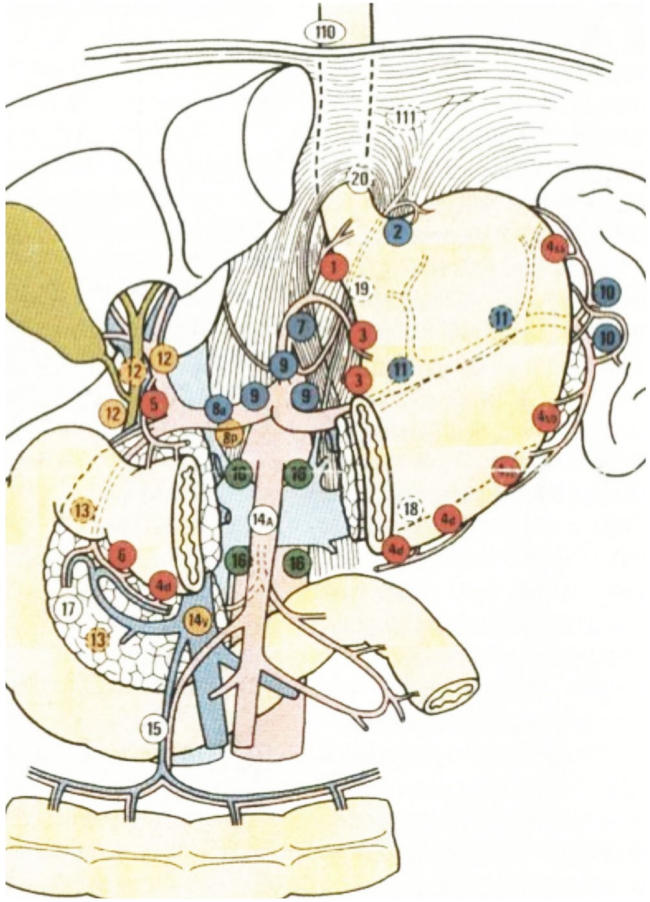
Lymphnodes stations

16 different LN stations surround the stomach (D1-D4)



D1 dissections:
LN stations 1-6; N1 level
1 Right cardia
2 Left cardia
3 along lesser curvatur
4 along right curvatur
5 suprapyloric
6 infrapyloric

D2 dissections:
LN stations 7-11; N2 level
7 left gastric artery
8 common hepatic artery
9 celiac trunk
10 splenic hilus
11 splenic artery

D3 dissections:
LN stations 12-14; N3 level
12 hepatoduodenal ligament
13 posterior surface of pancreas head
14 root of the mesentery/ artery/vein

D4 dissections:
LN stations 15-16; N4 level
15 paraaortic
16 paracolic

From: Hong JK et al: Standardization of the extent of lymphadenoectomy for gastric cancer: impact on survival. Advances in Surgery, Vol. 35, 2001 pp 203-223; S3-Leitlinie Magenkarzinom; Springer Science, Business Media ; Siewert et al Praxis der Viszeralchirurgie. Onkologische Chirurgie – 3.Auflage2010(541): Abb.40.12.

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Regression-Scores after neoadjuvant therapy

According to Becker et al:

Morphological regressions signs:

- oedema
- foamy histiocytes
- necrosis
- fibrosis and hyalinosis

Grading of Histophathologic Regression in the Primary Tumor Bed	
Grade	**Description**
1a	No residual tumor / tumor bed
1b	< 10% residual tumor / tumor bed
2	10-50% residual tumor / tumor bed
3	> 50% residual tumor / tumor bed

From: Becker et al. Ann Surg 2011 or Becker et al. Cancer 2003

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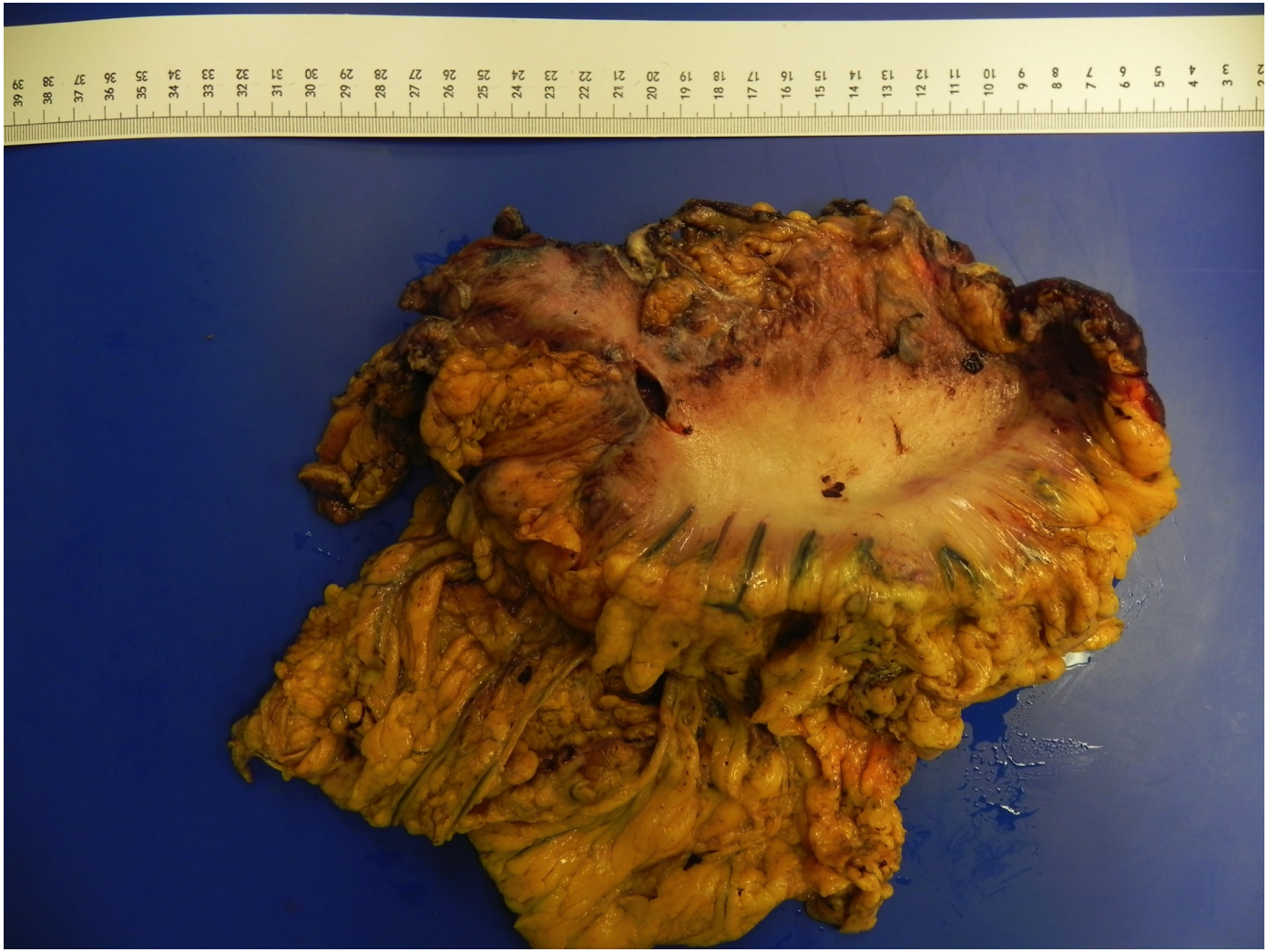
Surgical specimens



Gastrectomy

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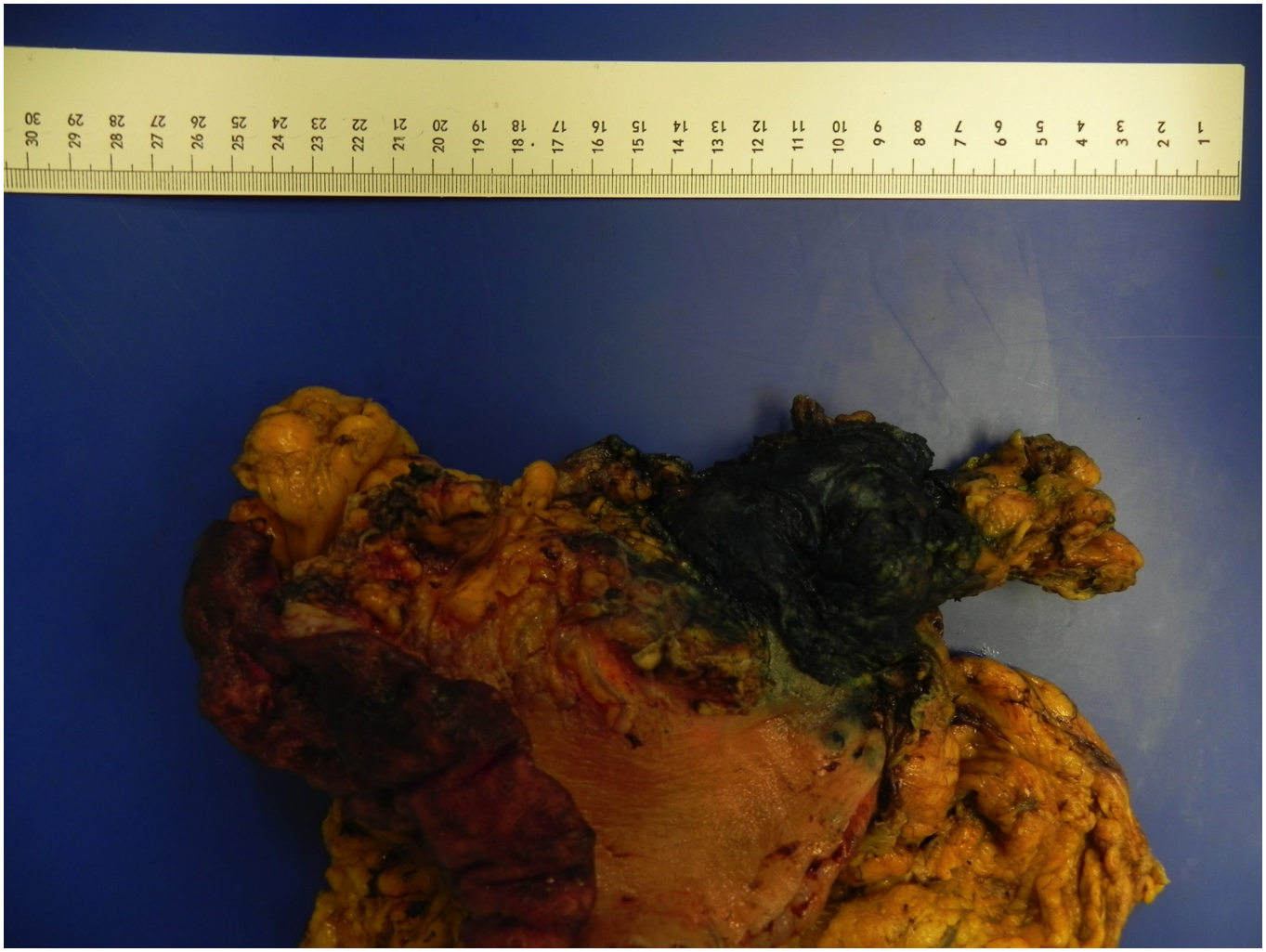
Surgical specimens



Colour-marked serosa

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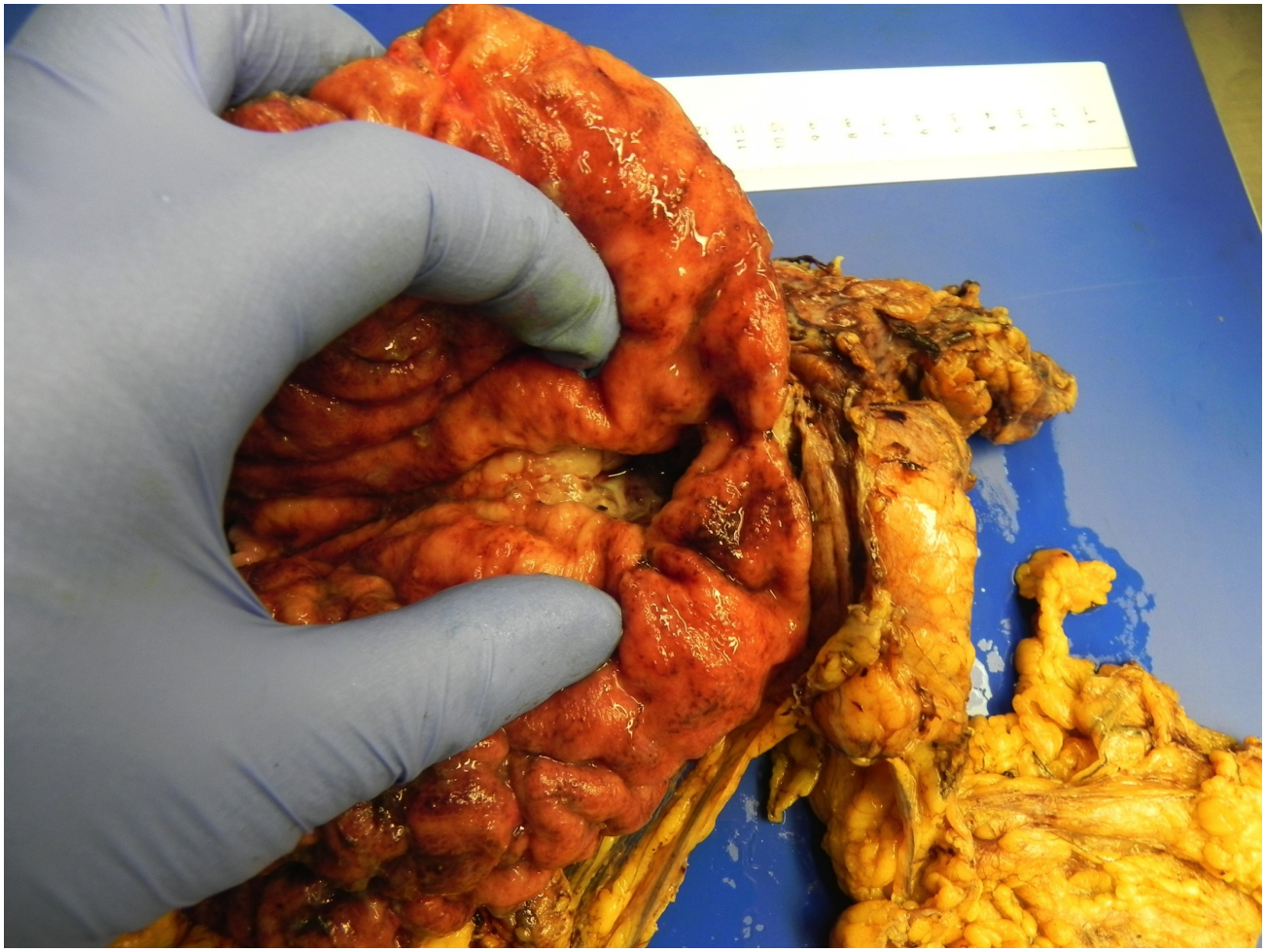
Surgical specimens



Ulcerated tumor

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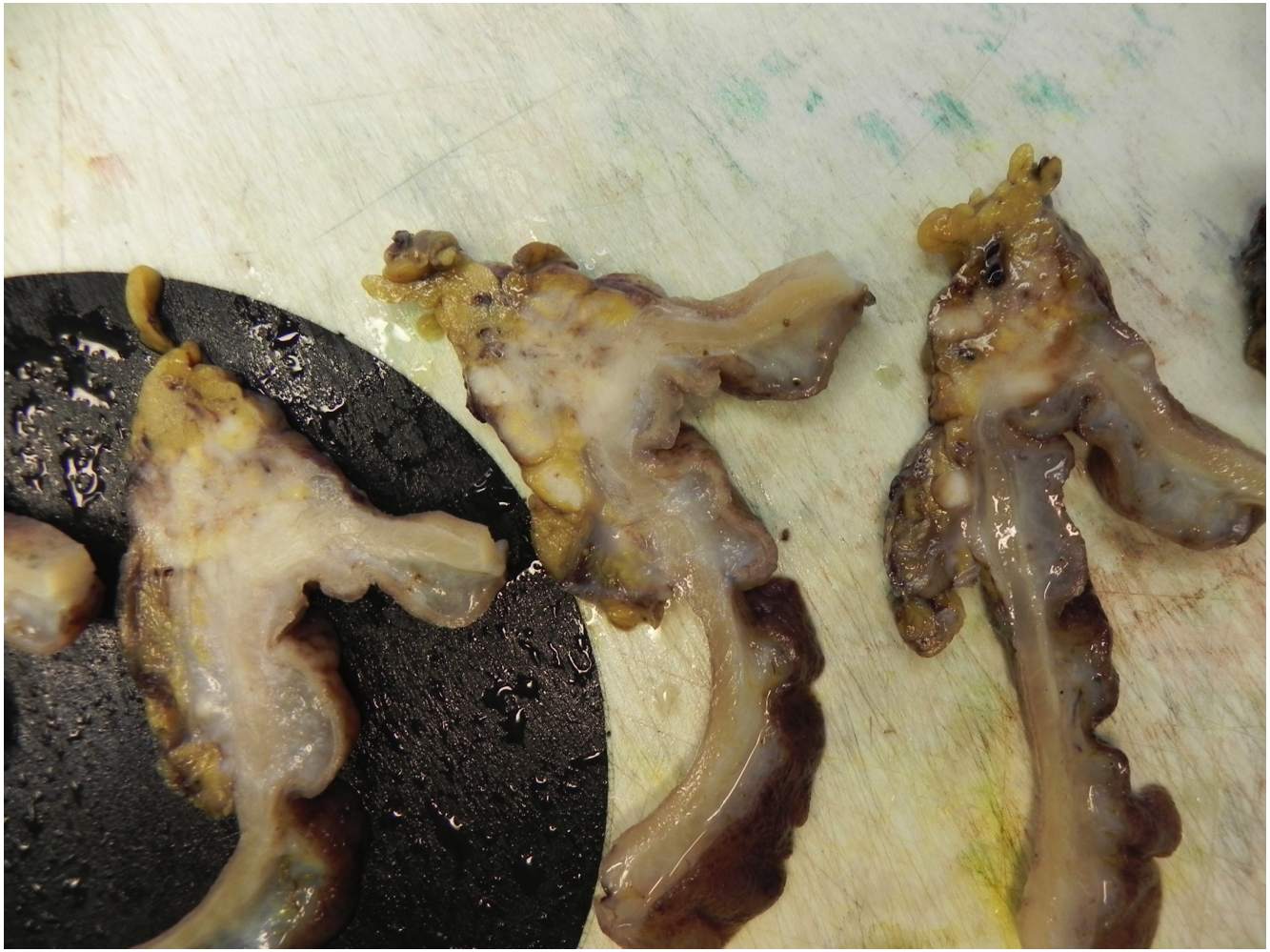
Surgical specimens



Probably already lymph nodes metastasis

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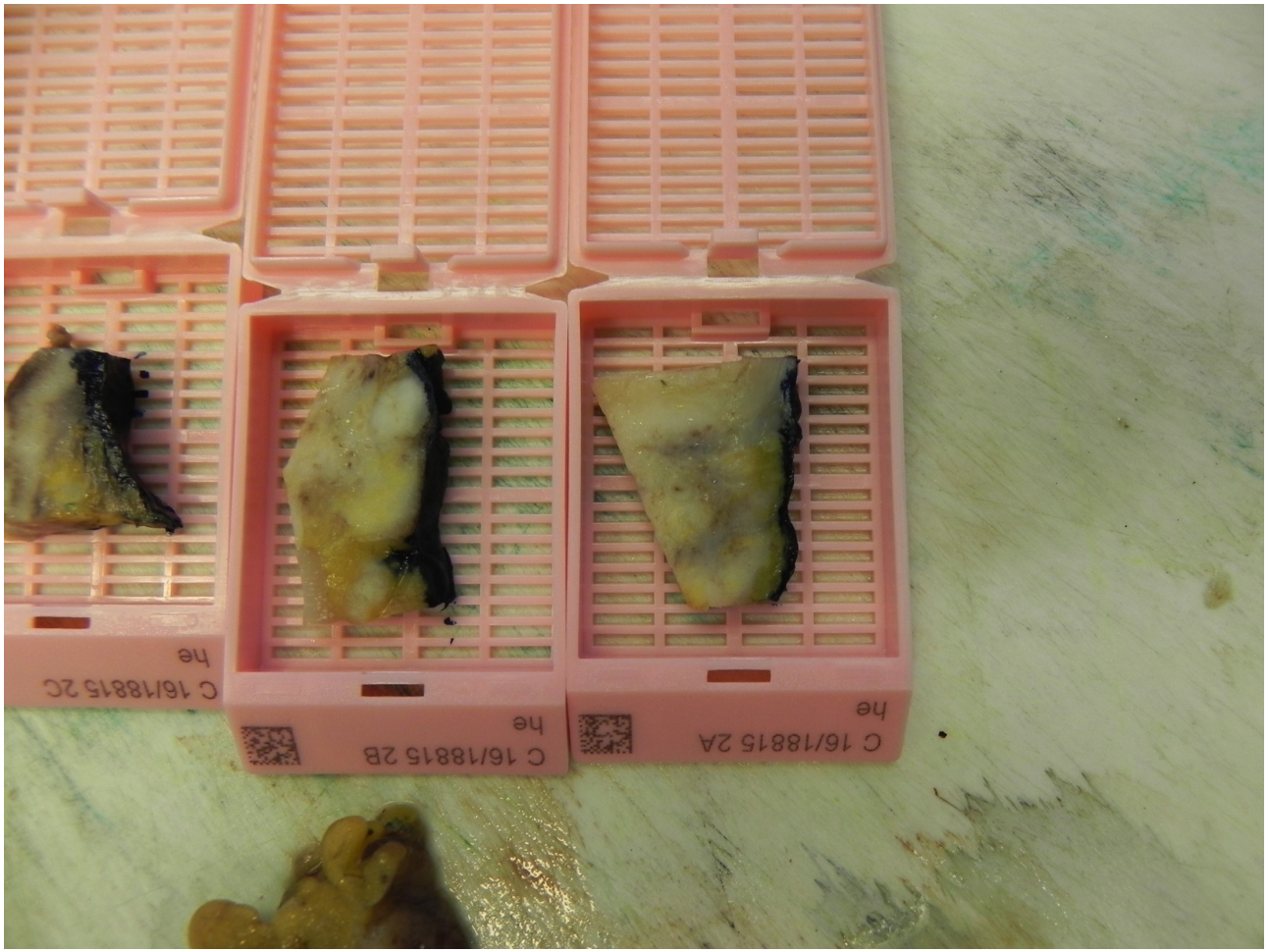
Surgical specimens



Tumor in close contact to serosa – probably pT4a

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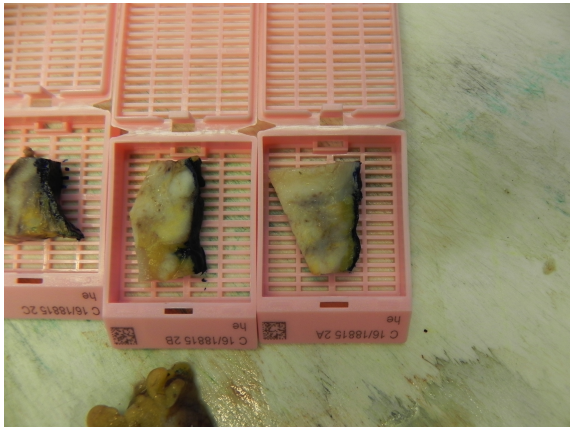
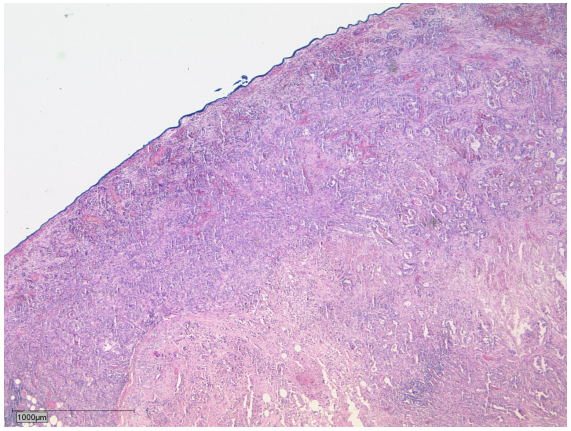
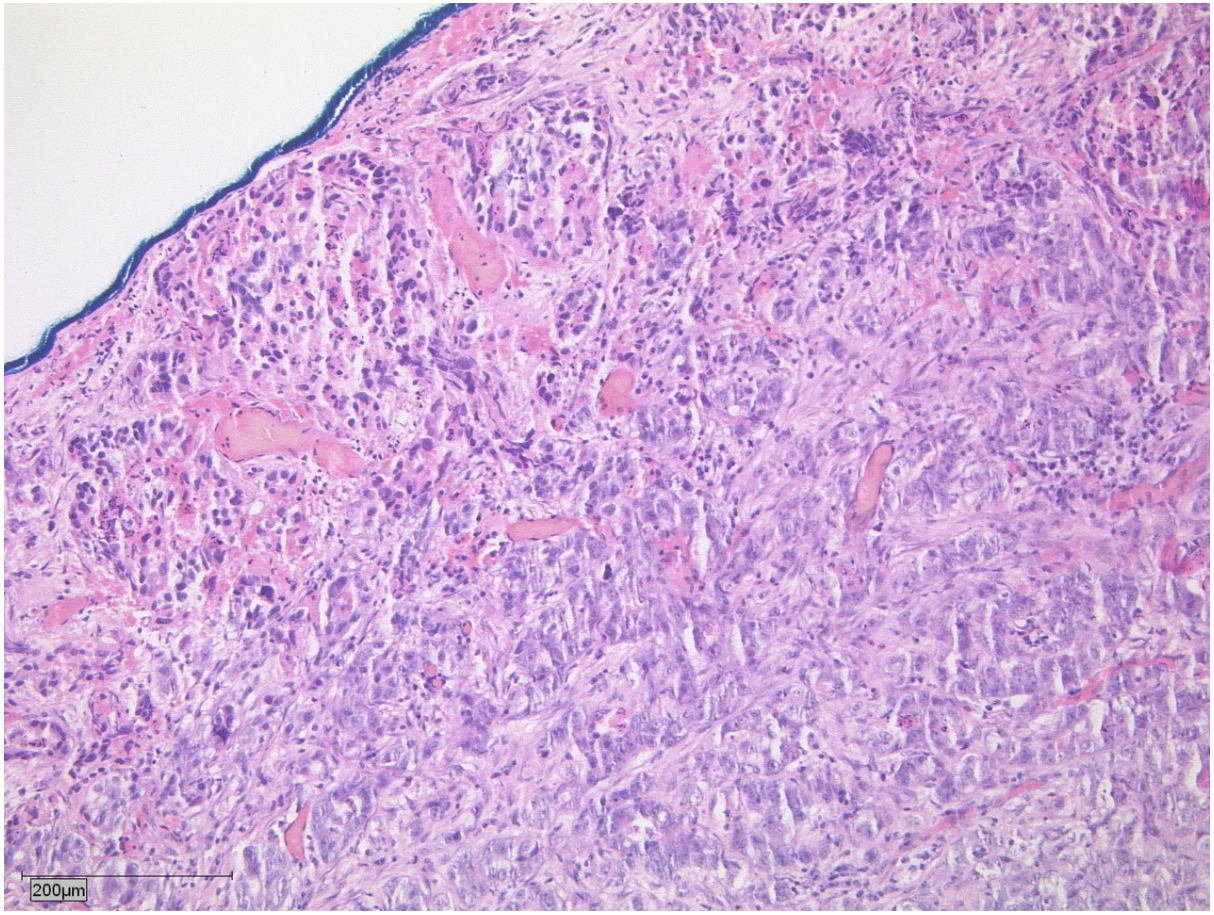
Surgical specimens







Tumor in contact to serosa
–pT4a

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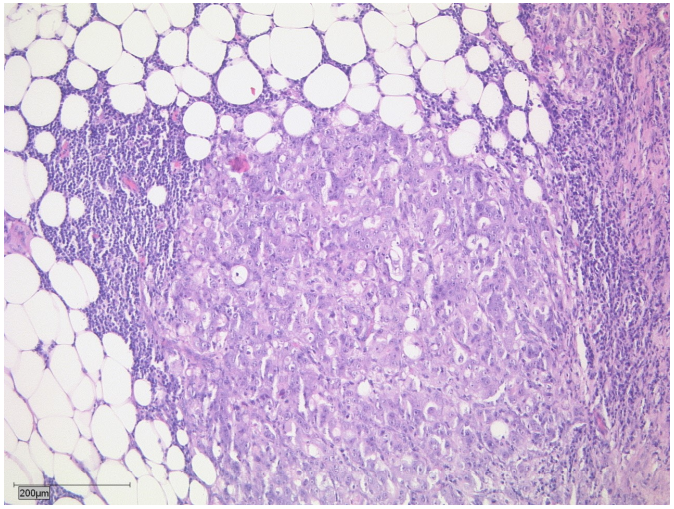
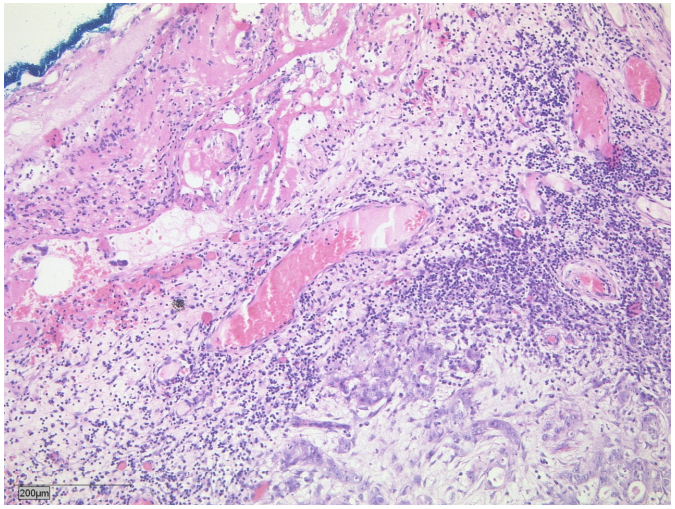
Tumormicroenviroment





www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 3), pp: 3933-3945

Research Paper

The role of tumor microenvironment in therapeutic resistance

Beomseok Son[1,*], Sungmin Lee[1,*], HyeSook Youn[2,*], EunGi Kim[1], Wanyeon Kim[3,4] and BuHyun Youn[1,4]

Yang and Zhang *Journal of Hematology & Oncology* (2017) 10:58
DOI 10.1186/s13045-017-0430-2

Journal of Hematology & Oncology

REVIEW Open Access

Tumor-associated macrophages: from basic research to clinical application

Li Yang[1,2] and Yi Zhang[1,2,3*]

Interaction of CAFs and CAMs
with carcinoma cells
(using exosomes and mi-RNA)
Inflammatory reaction
Checkpointmarker other than PD-L1/PD1:
e.g CTLA4, CTXR4, VISTA, IDO, TIM3, LAG3

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Summary

- Two main types: intestinal and diffuse adenocarcinoma
- Many (and rare) special types according to WHO
- Heterogeneity of tumors is a big problem (morphology-based and molecular-based; Her2/neu only focally expressed
- Some progress in molecular subtyping
  - MSI and EBV related: checkpoint inhibition effective?
  - rare other subtypes (BRCA, ATM, POLE)
- >16 regional lymph nodes
- Regression scores after neoadjuvant treatment (e.g. Becker et.al)
- Tumormicroenviroment

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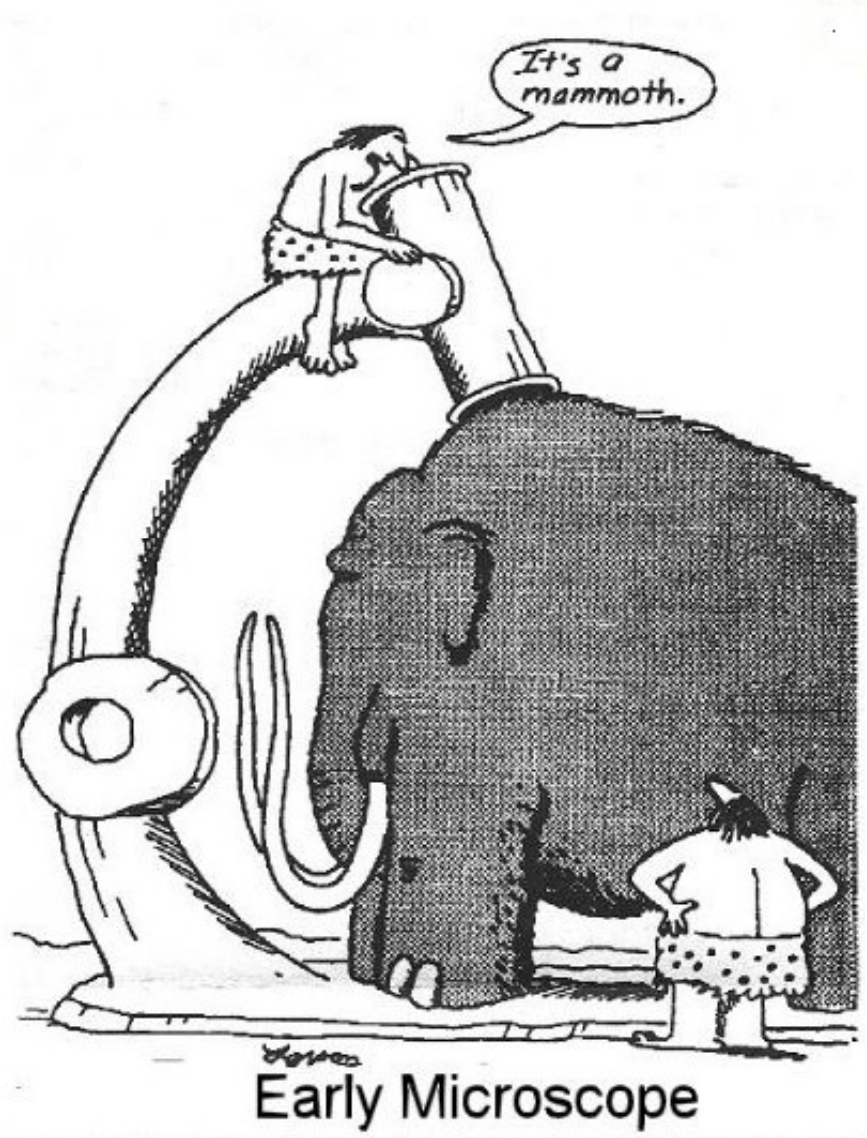
Thank you for your attention



Early Microscope

The ROYAL MARSDEN
NHS Foundation Trust

Incidence and Location of Local Recurrences after Combined Treatment Gastric Cancer

William Allum
Consultant Surgeon
Royal Marsden NHS Foundation Trust
London, UK

NHS

Incidence

Author	Sample size	Rate
Moorcraft BMC Cancer 2016 16:112-121	146	32% - median FU 62 months
Roviello Br J Surg 2003; 90: 1113–1119	215	49% - median FU 48mo
Wu World J Surg 2003;27:153-158.	611	40.1%
MSKCC Ann Surg 2004;240: 808–816	1172	42% - median FU 22mo
US GC Collaborative J Am Coll Surg 2014;219:664-675.	817	30% - median FU 29mo

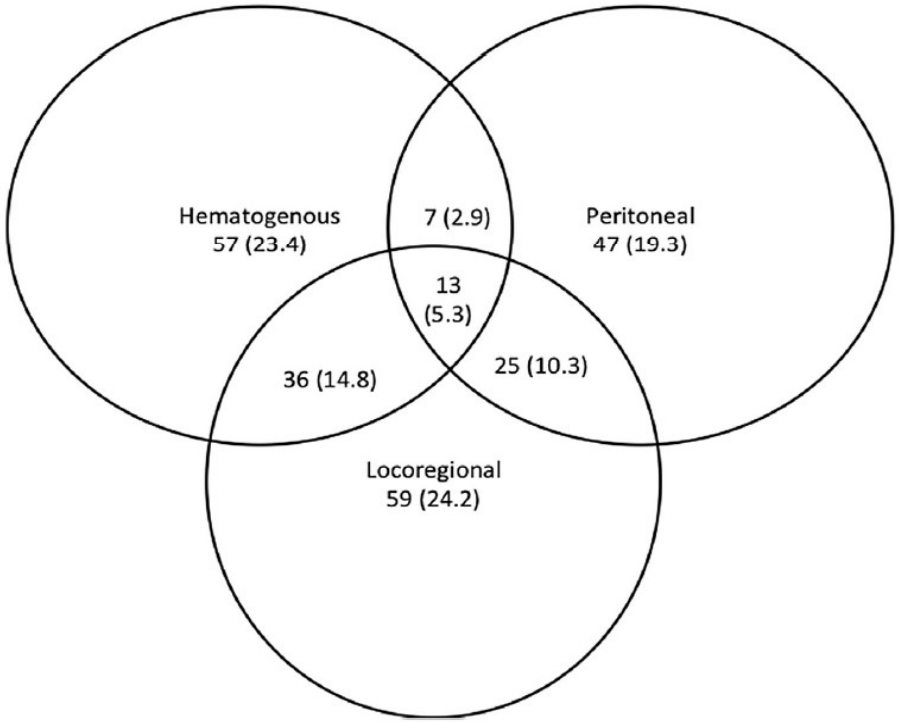
Time to Recurrence

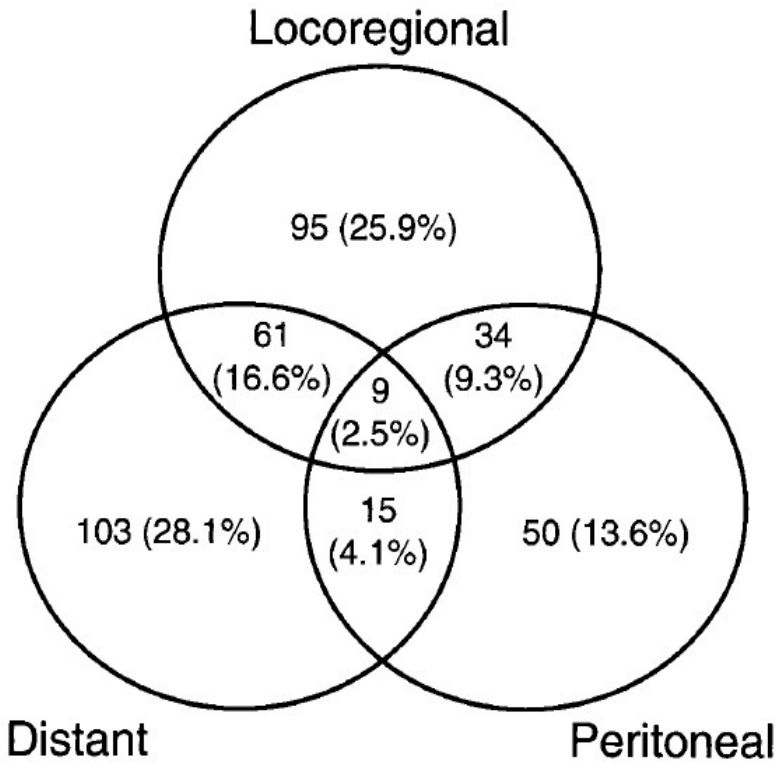
Author	
Moorcraft	80% by 2 years
Roviello	81% by 2 years
MSKCC	79% by 2 years
Wu	80% by 2 years

Pattern of Recurrence

Author	Local / Regional only	Systemic only	Peritoneal	Both
Roviello	45%	35%	36%	
MSKCC	54%	51%	29%	
Wu	45%	87%	53%	80%
Moorcraft	9%	79%		13%

Pattern of Recurrence





US Gastric Cancer Collaborative Group

MSKCC

Site of Relapse

Lymph nodes	**14 (30%)**
Anastomosis	**10 (21%)**
Peritoneum	**18 (38%)**
Liver	**9 (19%)**
Bone	**4 (9%)**
Abdominal wall	**5 (11%)**
Lung	**2 (4%)**
Brain	**0 (0%)**
Mediastinum	**1 (2%)**
Other	**5 (11%)**

Specific Sites of Recurrence

Locoregional (199 patients, 215 specific sites)	
Lymph nodes	103 (48%)
Anastomosis	69 (32%)
Gastric bed	43 (20%)
Distant (188 patients, 245 specific sites)	
Liver	90 (37%)
Lung	39 (16%)
Bone	39 (16%)
Lymph nodes	35 (14%)
Brain	15 (6%)
Adrenal	8 (3%)
Pleura	6 (2%)
Subcutaneous	5 (2%)
Breast, Kidney, Bone marrow, pericardium, wound, spine	<2% each

There were 109 patients who had peritoneal recurrence that was not subspecified.

Percentages are calculated from the total number of sites in each area.

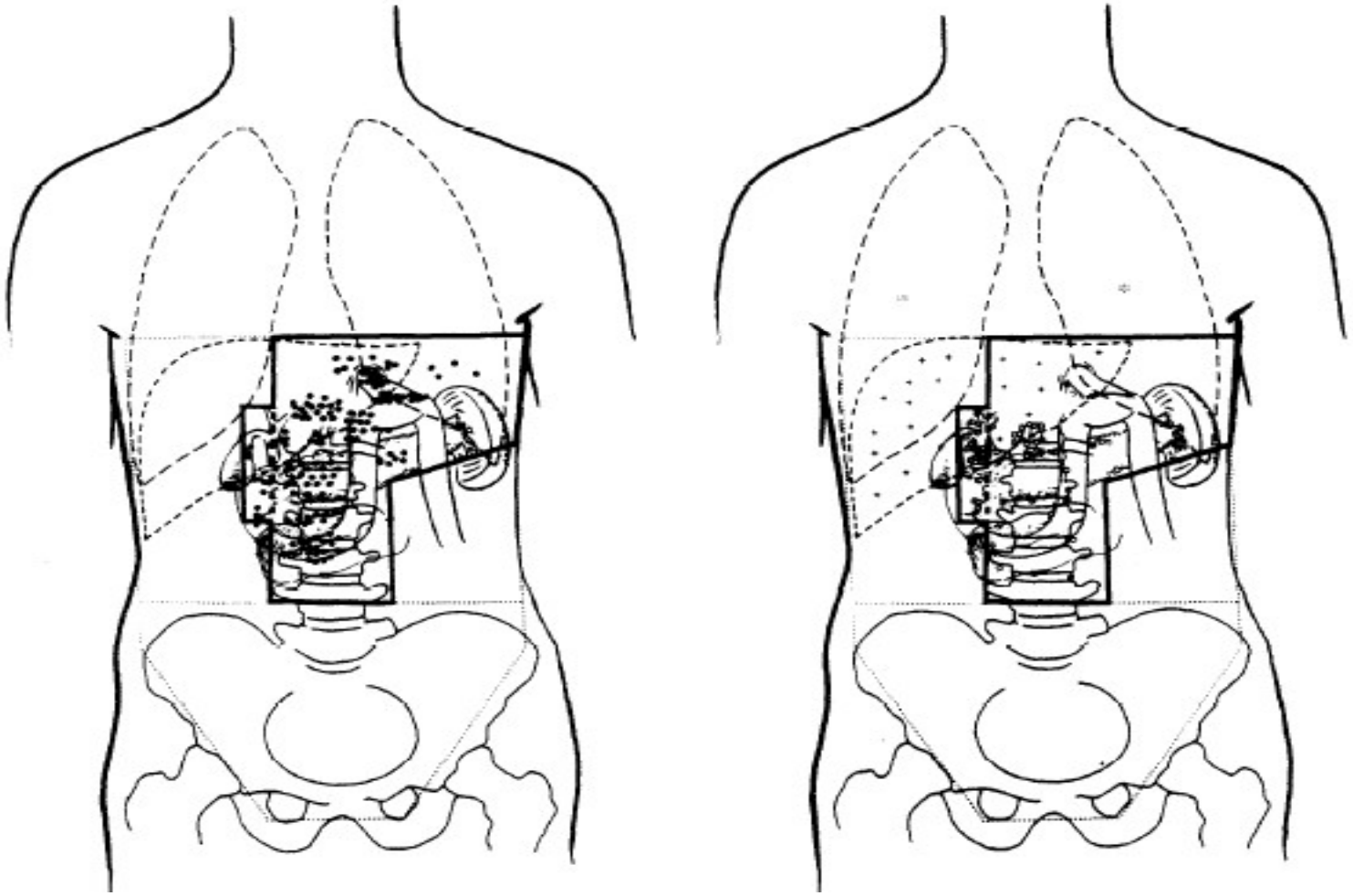
Follow-up and patterns of recurrence - MAGIC

Median follow-up time for survivors = 3 years

90% of patients followed to death or minimum of 2 years

Patients where site of recurrence was identified	CSC (N=250)		S (N=253)	
	N	%	N	%
Locoregional only	27	11%	45	18%
Systemic only	32	13%	47	19%
Both	46	18%	65	26%
TOTAL	105	42%	157	62%

Sites of Recurrence
Second Look Laparotomy



Gunderson & Sosin 1982 Int J Rad Oncol Biol Phys 8:1-11

Prediction of Relapse

Author	Overall Risk	Local / Regional	Distant	Peritoneal
MSKCC		Male Proximal	Proximal Early T stage Intestinal	Female T stage Distal Diffuse
US GC Collaborative	Young T stage Diffuse type Signet ring LVI / PNI Lymph node +ve	Proximal T stage LN +ve D2	T stage LN +ve LVI PNI	Grade T stage LVI PNI Chemo

Detection of Relapse

Elevated tumour markers at relapse	
Yes	**24 (51%)**
No	**16 (34%)**
Unknown	**7 (15%)**
Symptoms at time of relapse	
Yes	34 (72%)
How relapse was first detected in asymptomatic patients	(n = 12)
Routine tumour markers	4 (33%)
Routine CT	4 (33%)
Concurrent routine CT/ markers	3 (25%)
Endoscopy	1 (8%)
Other	0 (0%)

Treatment of Relapse

Further treatment for recurrent disease **Yes**	**22 (47%)**
Type of treatment for recurrent disease	
Chemotherapy	19 (86%)
Radiotherapy	3 (14%)
Chemoradiotherapy	0 (0%)
Surgery	1 (5%)

Survival

Median survival after relapse

5 months (US GC Collaborative)

6 months (MSKCC)

Survival by Detection

	Symptomatic	Asymptomatic
Kodera	40 mo	51.7 mo
Bennett	21.6 mo	29.4 mo
	Intensive FU	Regular FU
Tan	49.2 mo	45.6 mo

Kodera et al 2003; Ann Surg Oncol: 10: 898
Bennett et al 2005; J Am Coll Surg 201: 503
Tan et al 2007; J Surg Oncol 96: 503

Recommendation for subsite delineation by stage and tumor position

Francesco Cellini MD, EF

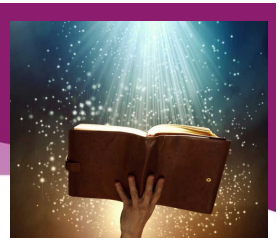
Gemelli ART
Radiotherapy Department
Fondazione Policlinico A. Gemelli
Università Cattolica S. Cuore
Roma

Outline

- CTV Definition: Background and Issues
- CTV Selection
- CTV Identification

} Preoperative Setting
} Postperative Setting

CTV Definition: Background



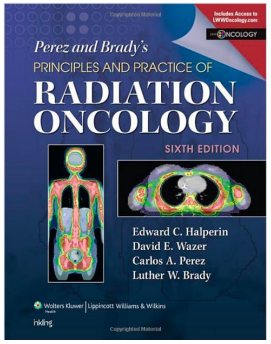


TABLE 58.6 PATTERNS OF LOCOREGIONAL FAILURE AFTER RESECTION OF GASTRIC CANCER

Failure Area	Incidence (%) Clinical[a]	Reoperation[b]	Autopsy[c]
Gastric bed	21	54	52–68
Anastomosis or stumps	25	26	54–60
Abdominal or stab wound	–	5	–
Lymph node(s)	8	42	52

[a] 130 patients at risk [97].
[b] 107 patients at risk [38].
[c] 92 patients at risk [93] and 28 patients at risk [96].

McNeer *et al.; Ann Surg* - 1957
Gunderson *et al; IJROBP* - 1981
Gilbertsen et al; Cancer - 1969

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Perez and Brady's – Principles and Practice of Radiation Oncology- Lippincott Williams- 6th Ed; 2013

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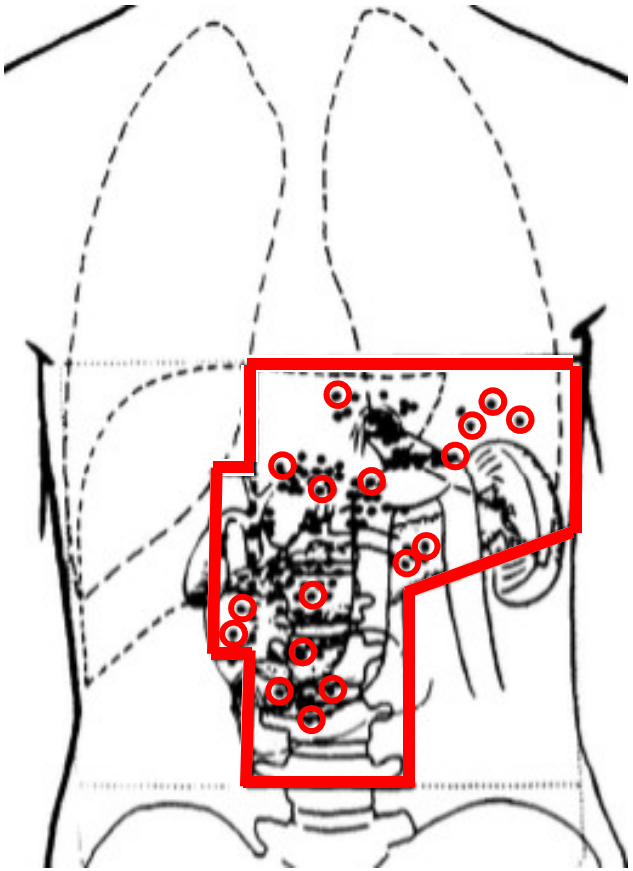
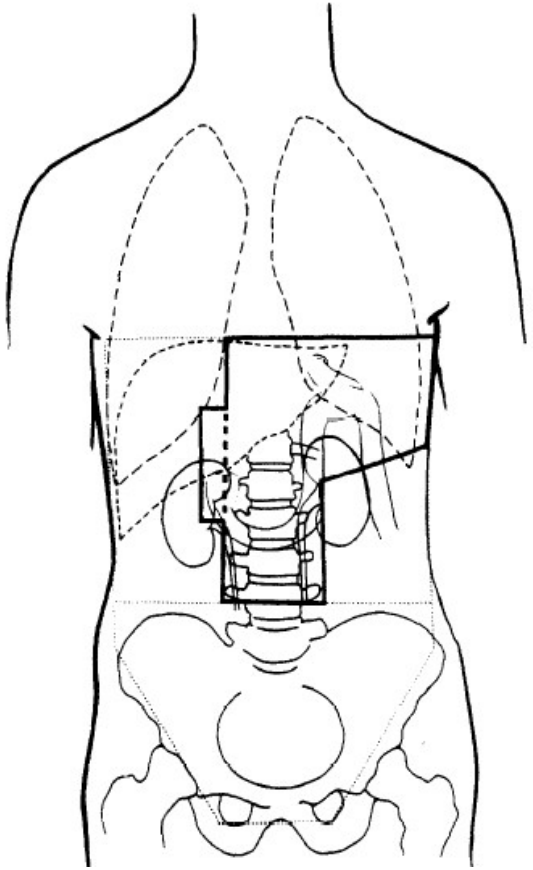
CTV Definition: Background



Gunderson *et al.; IJROBP* -1981

CTV Definition: Background



Gunderson *et al.; IJROBP* -1981

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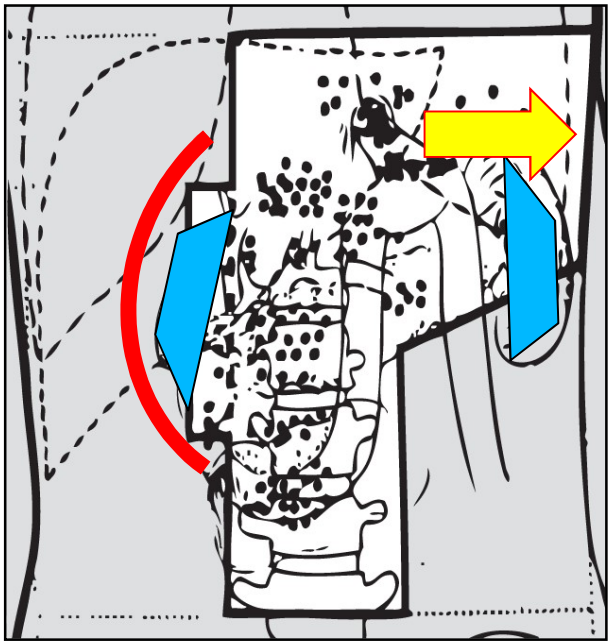
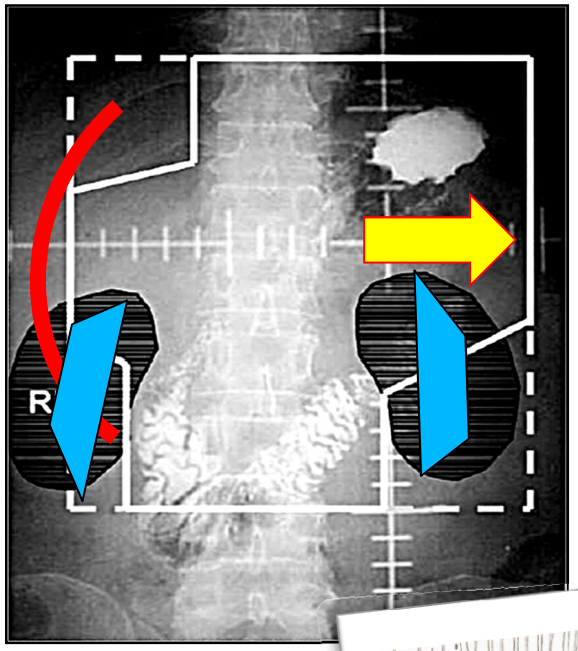
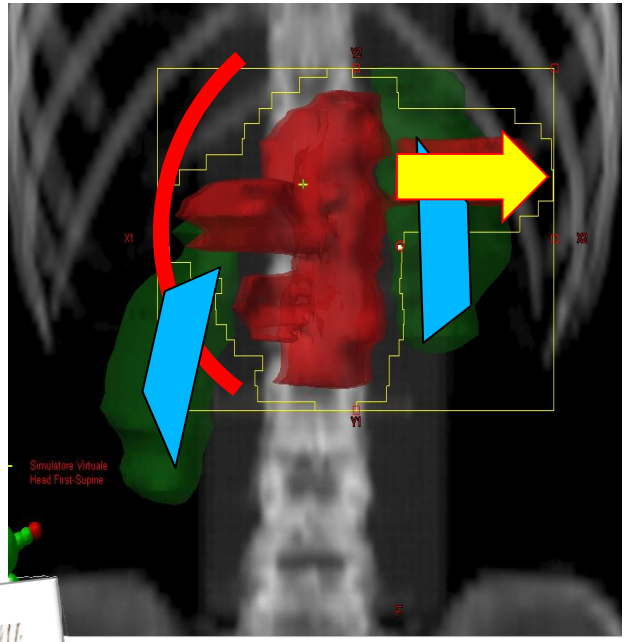
CTV Definition: Background

Radiotherapy Planning

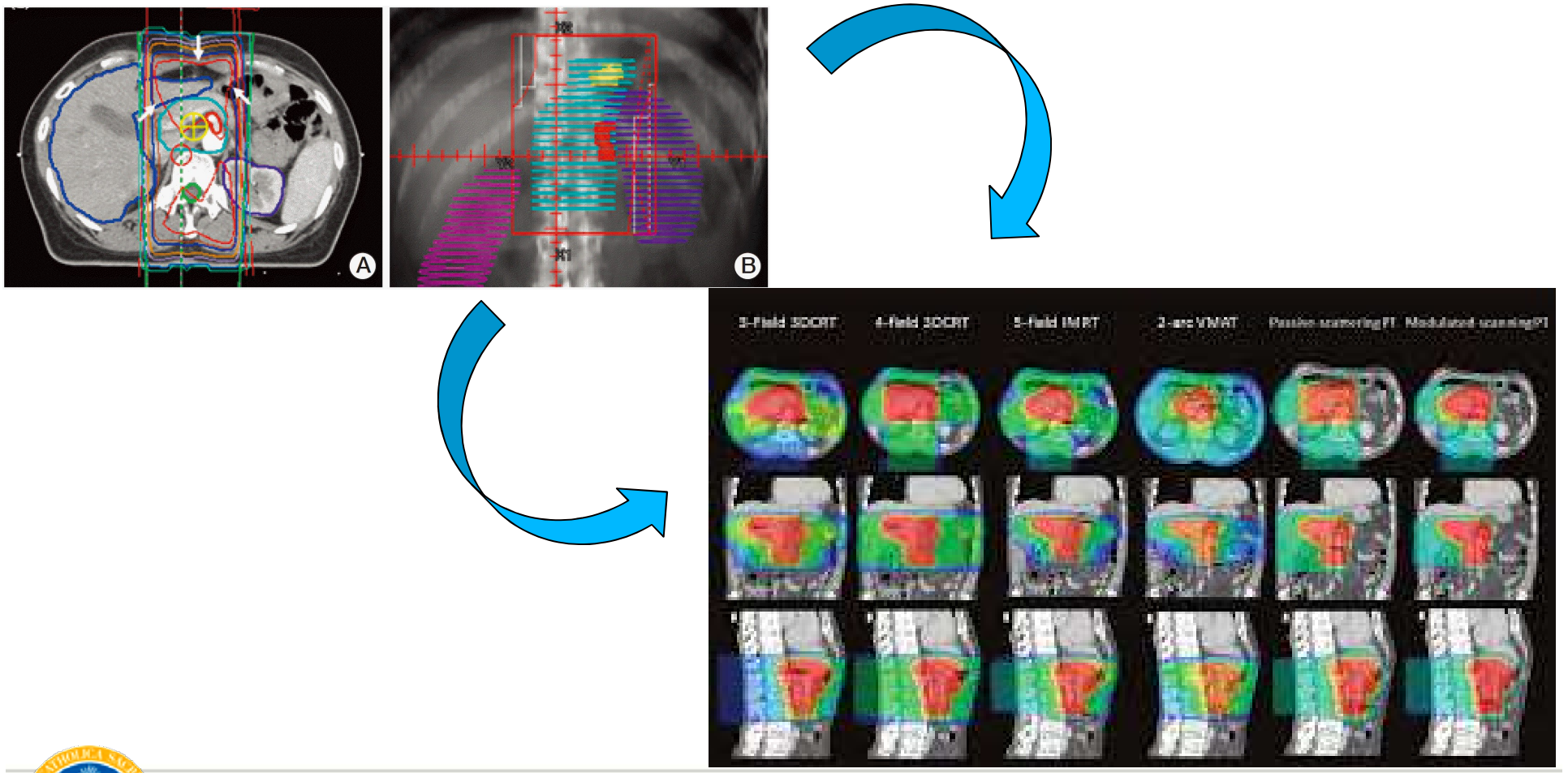






CTV Definition: Background

Radiotherapy Targeting

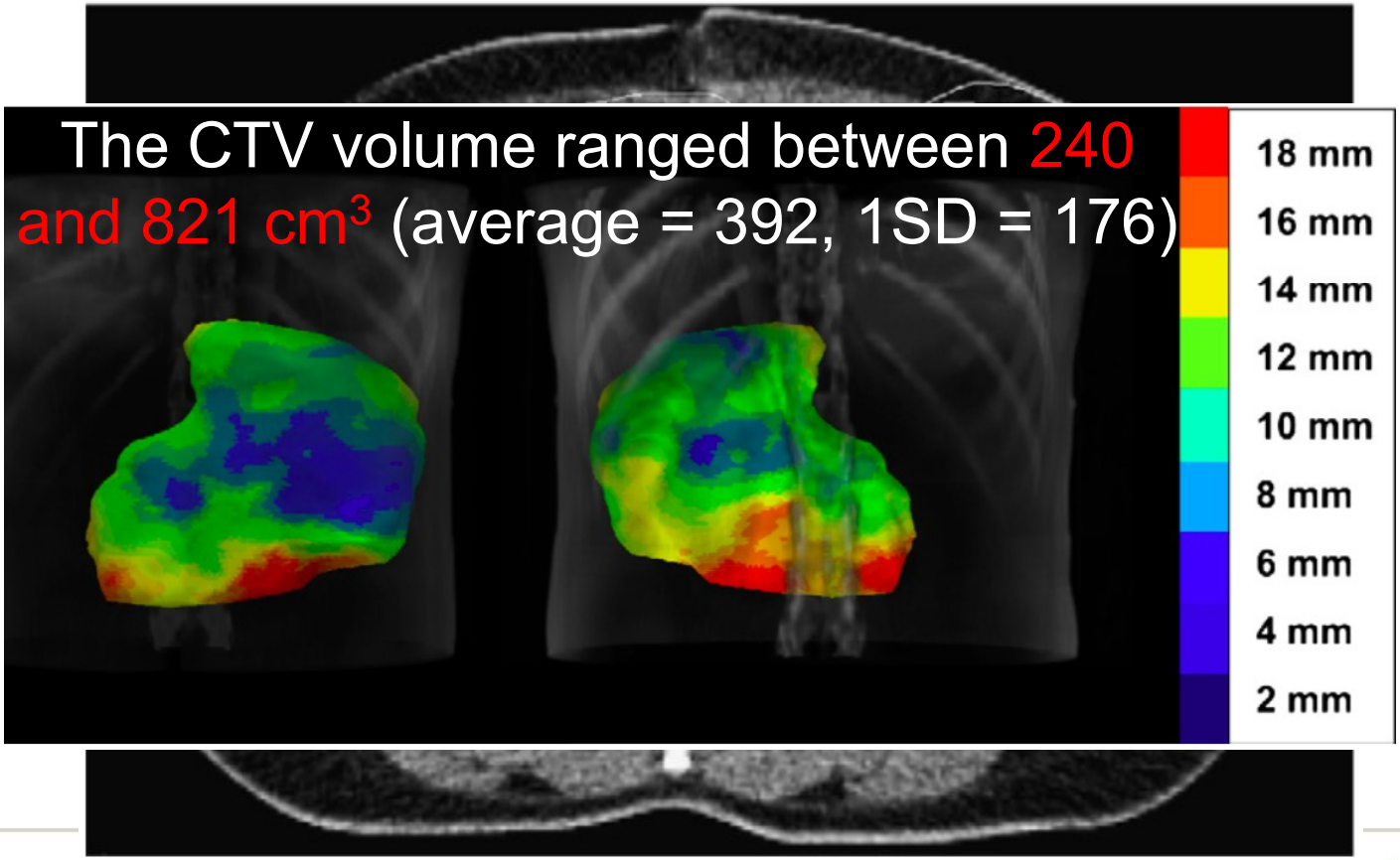


CTV Definition: Issues

CLINICAL INVESTIGATION Stomach

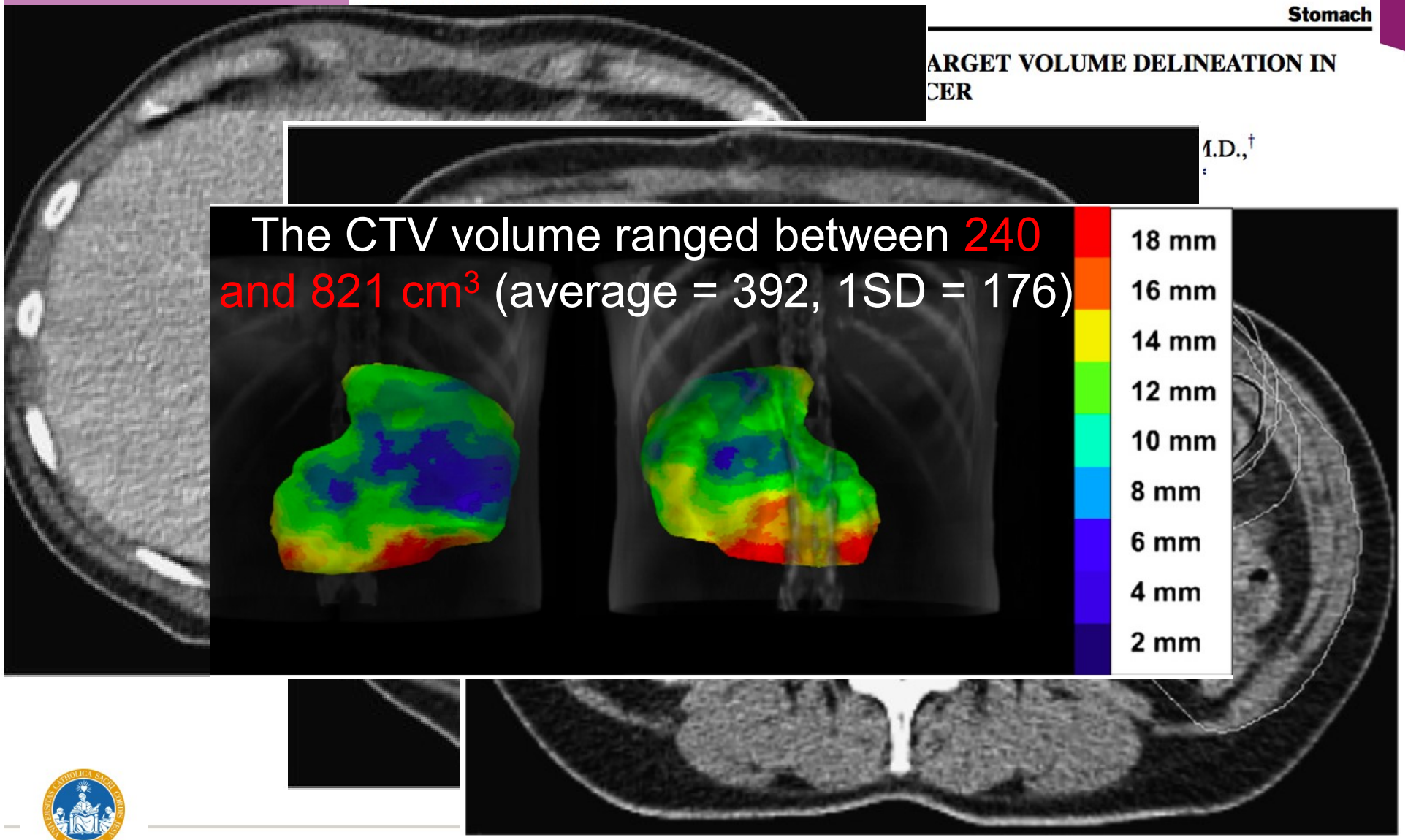
INTEROBSERVER VARIATION OF CLINICAL TARGET VOLUME DELINEATION IN GASTRIC CANCER

EDWIN P. M. JANSEN, M.D.,* JASPER NIJKAMP, M.SC.,* MICHAEL GUBANSKI, M.D.,†
PEHR A. R. M. LIND, M.D., PH.D.,† AND MARCEL VERHEIJ, M.D., PH.D.*



Jansen *et al.; IJROBP* -2010

CTV Definition: Issues



Jansen *et al.; IJROBP* -2010

CTV DEFINITION: Issues

CTV Selection

CTV Identification

CTV DELINEATION: Preoperative Setting

Contents lists available at ScienceDirect

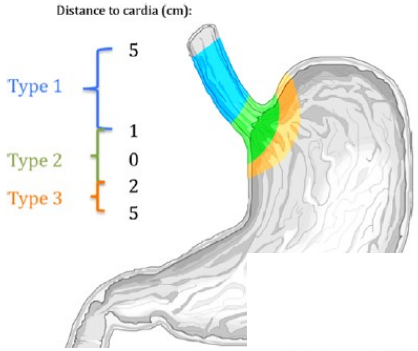
Radiotherapy and Oncology

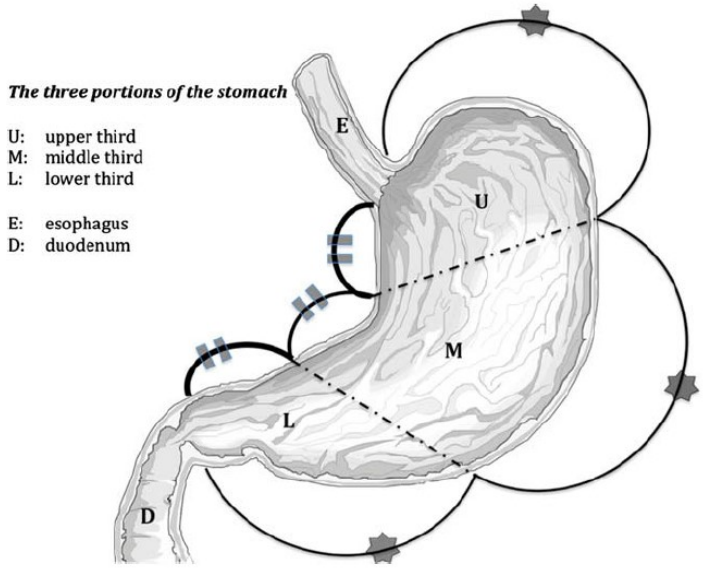
journal homepage: www.thegreenjournal.com

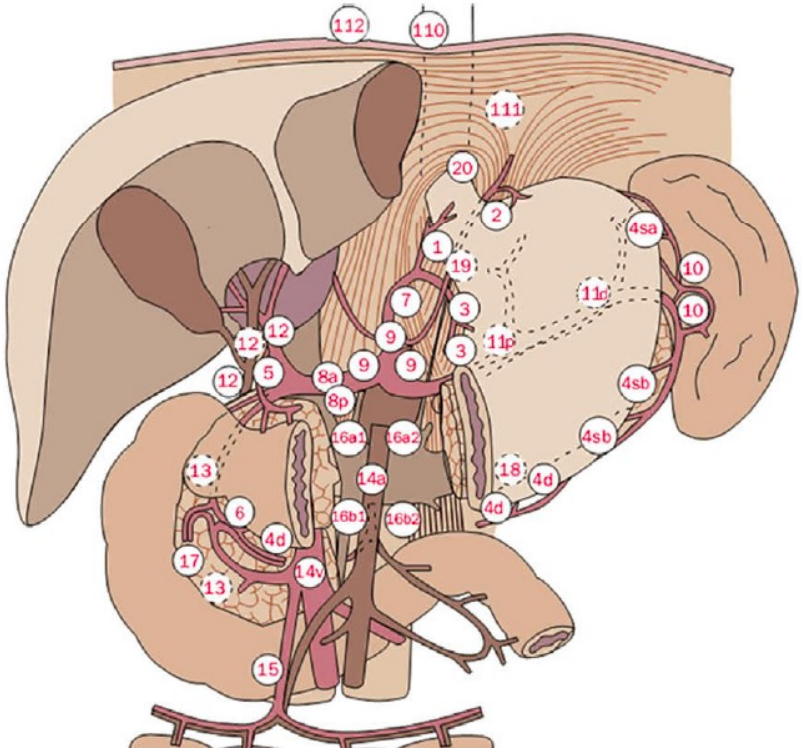
Guidelines

EORTC-ROG expert opinion: Radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach

Oscar Matzinger [a,b,*], Erich Gerber [c], Zvi Bernstein [d], Philippe Maingon [e], Karin Haustermans [f], Jean François Bosset [g], Akos Gulyban [a], Philip Poortmans [h], Laurence Collette [a], Abraham Kuten [d]







Matzinger *et al.; Radiother Oncol* -2009

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CTV DELINEATION: Preoperative Setting

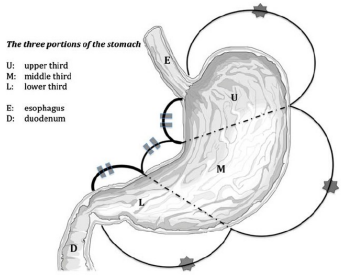
GTV tumor + GTV nodal

↓ ↓

+ 1.5 cm= CTV tumor + 0.5 cm= CTV nodal

+

CTV Gastric



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Matzinger *et al.; Radiother Oncol* -2009

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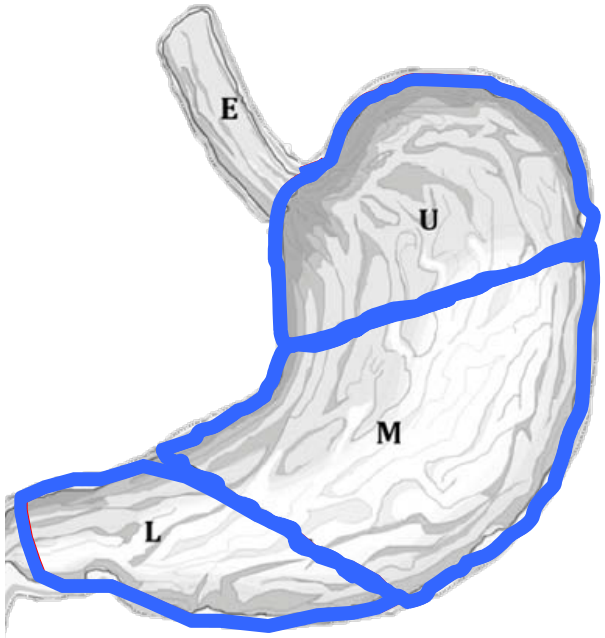
CTV DELINEATION: Preoperative Setting



UP ⅓ = Stomach wo Pylorus + Antrum
(CTV= GTV + 5 cm minimum)

MID ⅓ = Whole Stomach

LOW ⅓ = Stomach wo Cardias + Fundus
(CTV= GTV + 5 cm minimum)
(If Pylorus or Duodenum "+": Include 3 cm Duodenum)

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Matzinger *et al.; Radiother Oncol* -2009

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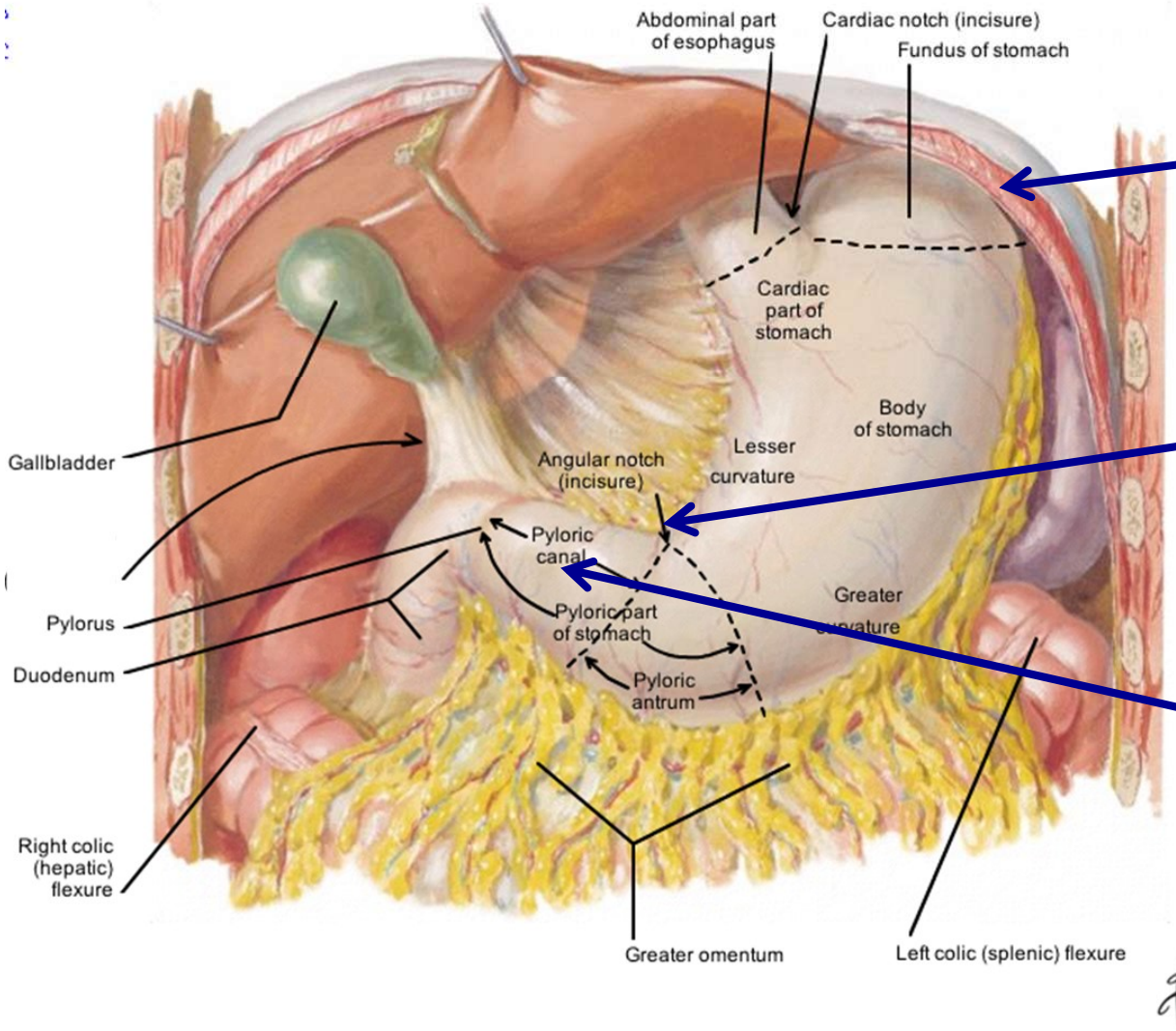
CTV DELINEATION: Preoperative Setting

Stomach CT Anatomy



FUNDUS

CARDIAS

GREATER CURVATURE

ANGULUS

LESSERE CURVATURE

ANTRUM

BULB

PYLORUS

F. Netter M.D.

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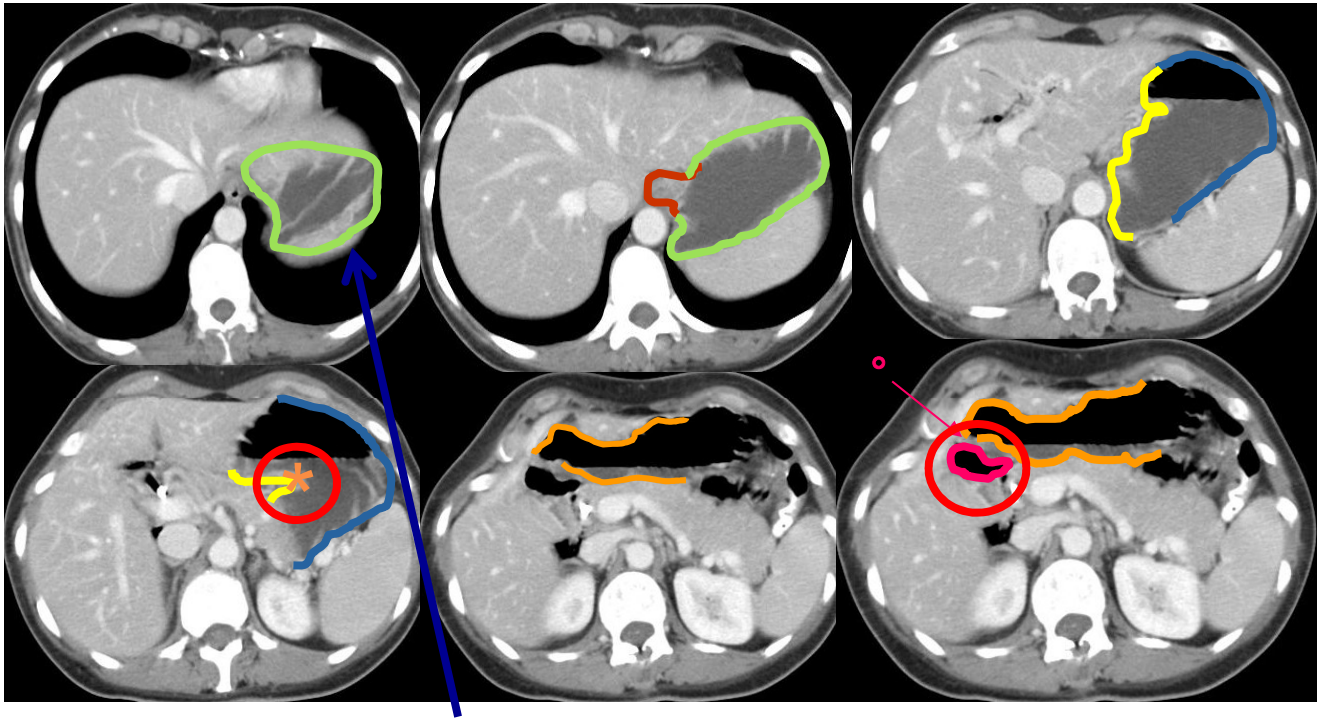
CTV DELINEATION: Preoperative Setting

Stomach CT Anatomy



FUNDUS
CARDIAS
GREATER CURVATURE
* ANGULUS
LESSERE CURVATURE
ANTRUM
BULB
° PYLORUS

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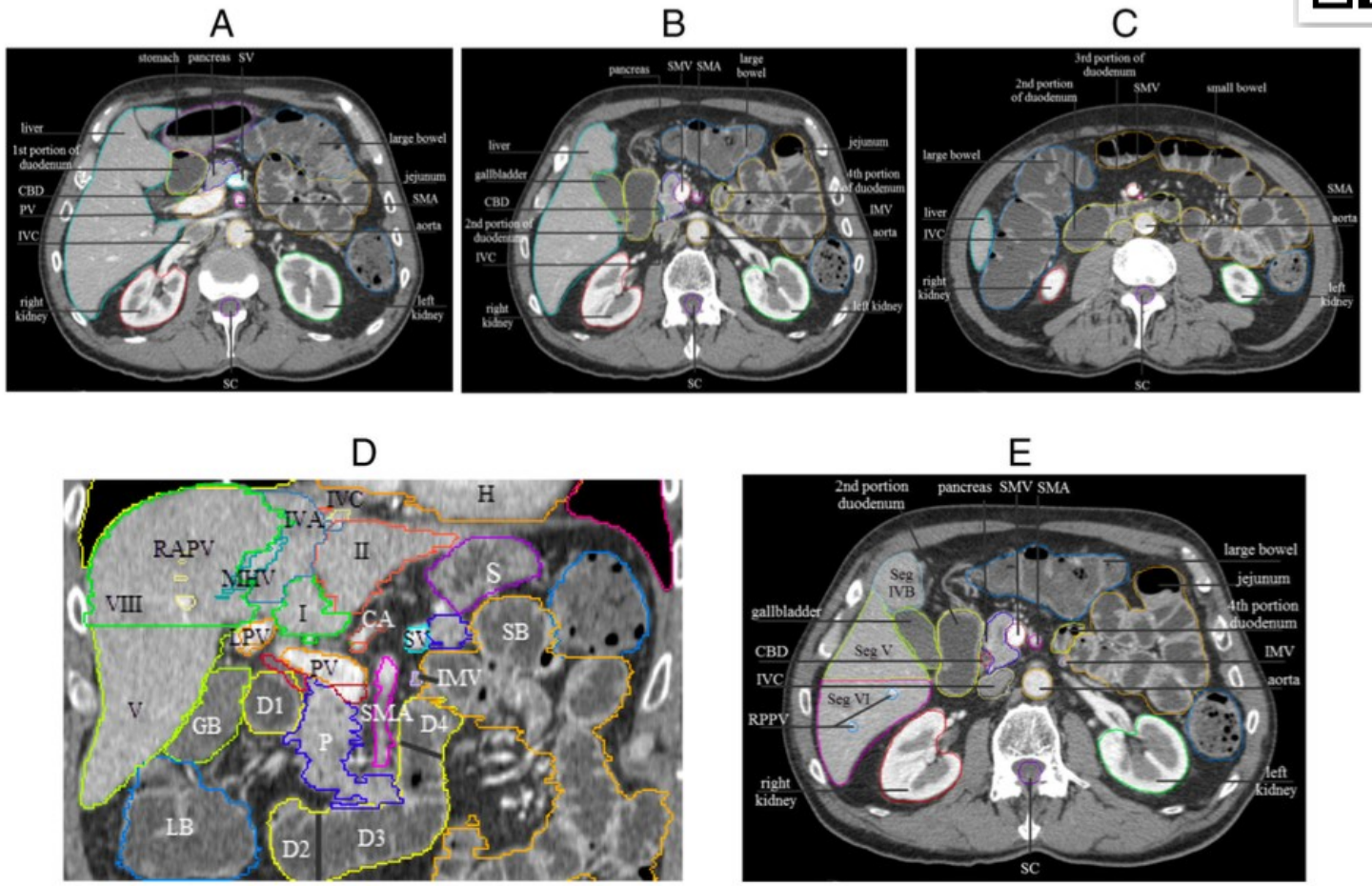
OAR/CTV DELINEATION: Preop./Postop. Setting

Organs Anatomy



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Jabbour *et al.; PRO* -2014

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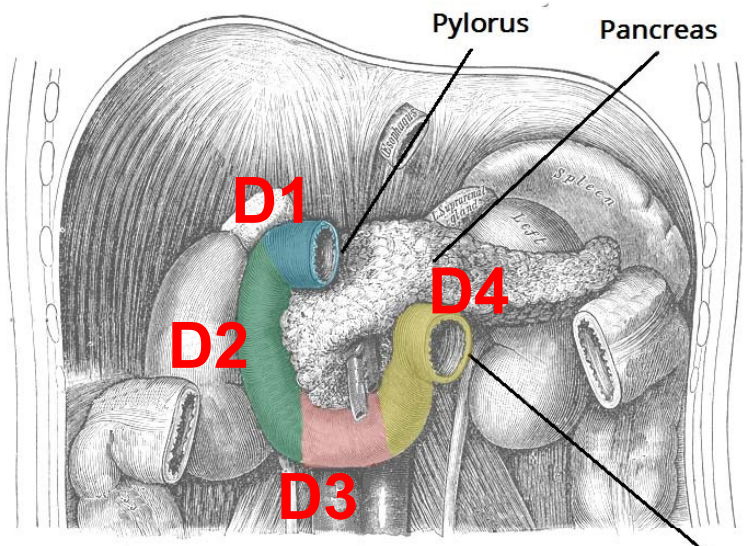
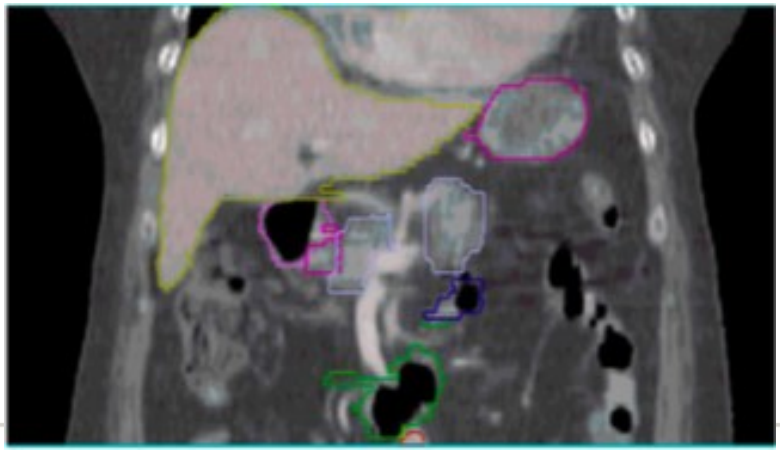
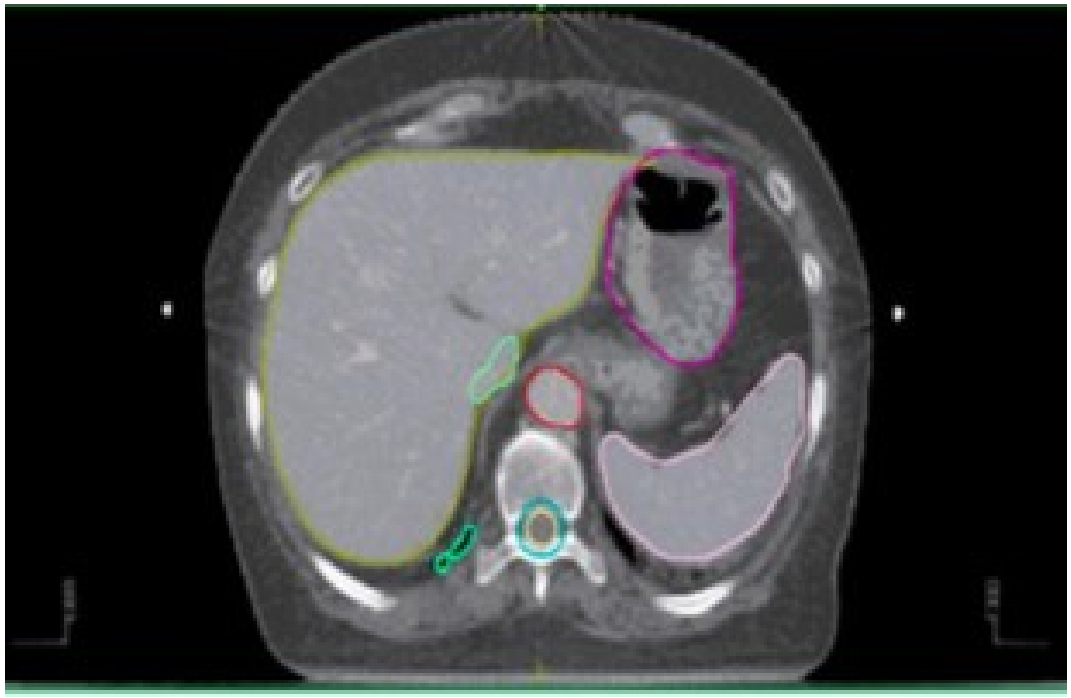
OAR/CTV DELINEATION: Preop./Postop. Setting

Parts of the Duodenum
- Superior
- Descending
- Inferior
- Ascending

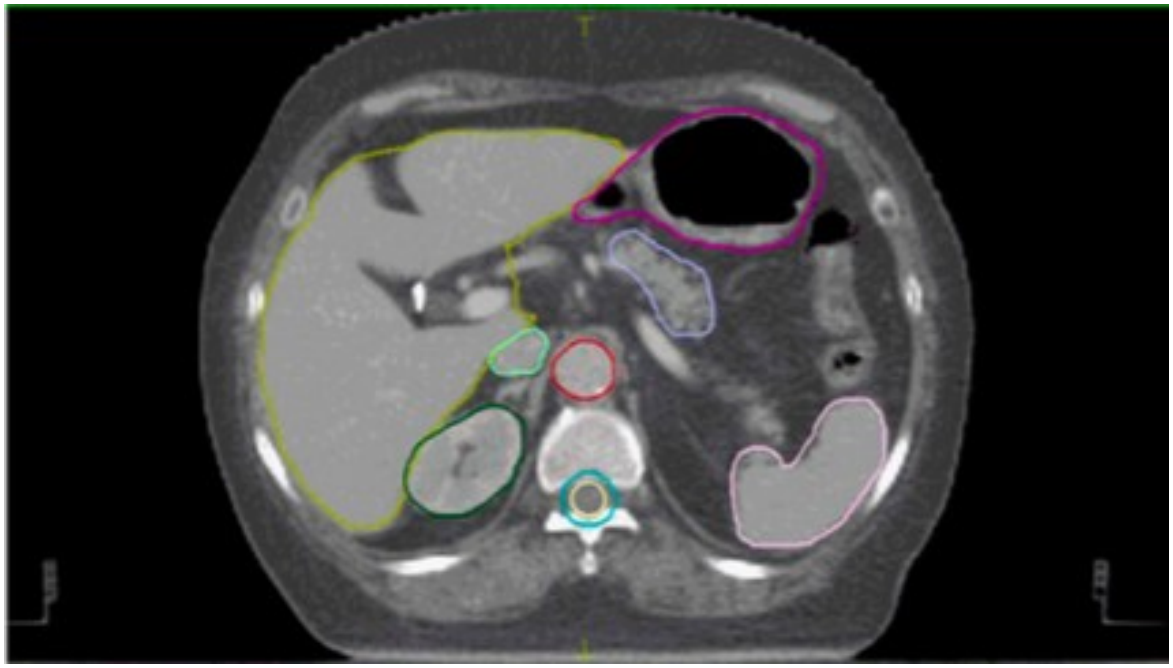




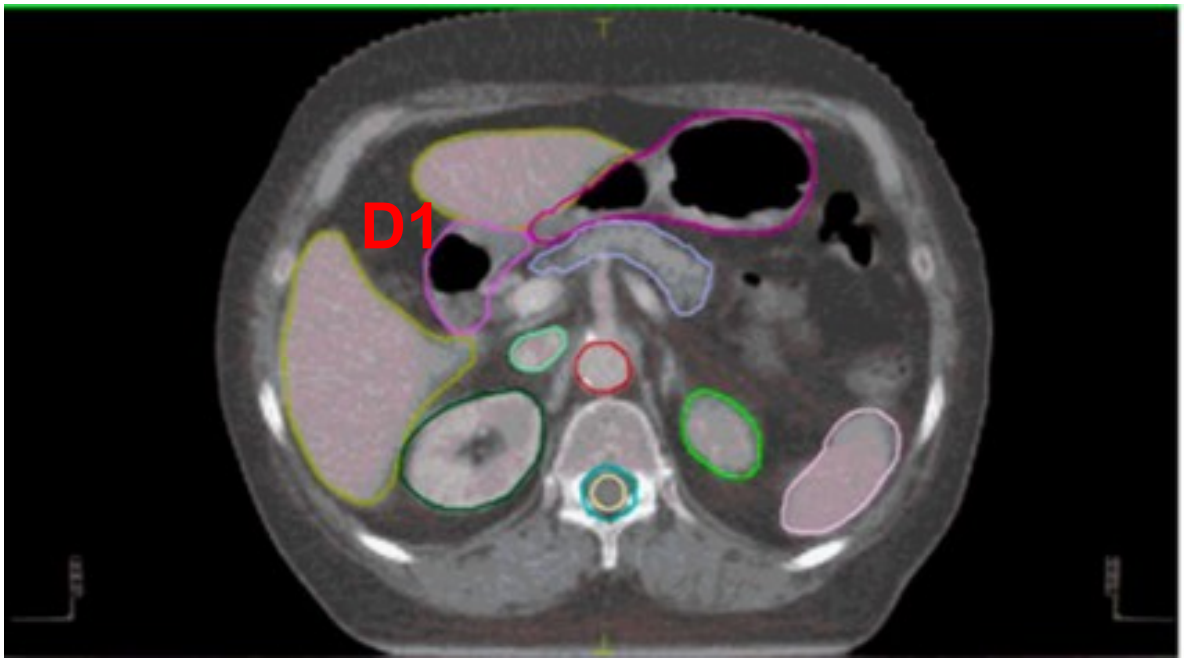
Kataria *et al.; Br J Radiol*-2016



Kataria *et al.; Br J Radiol*-2016



Kataria *et al.; Br J Radiol*-2016



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Kataria *et al.; Br J Radiol*-2016

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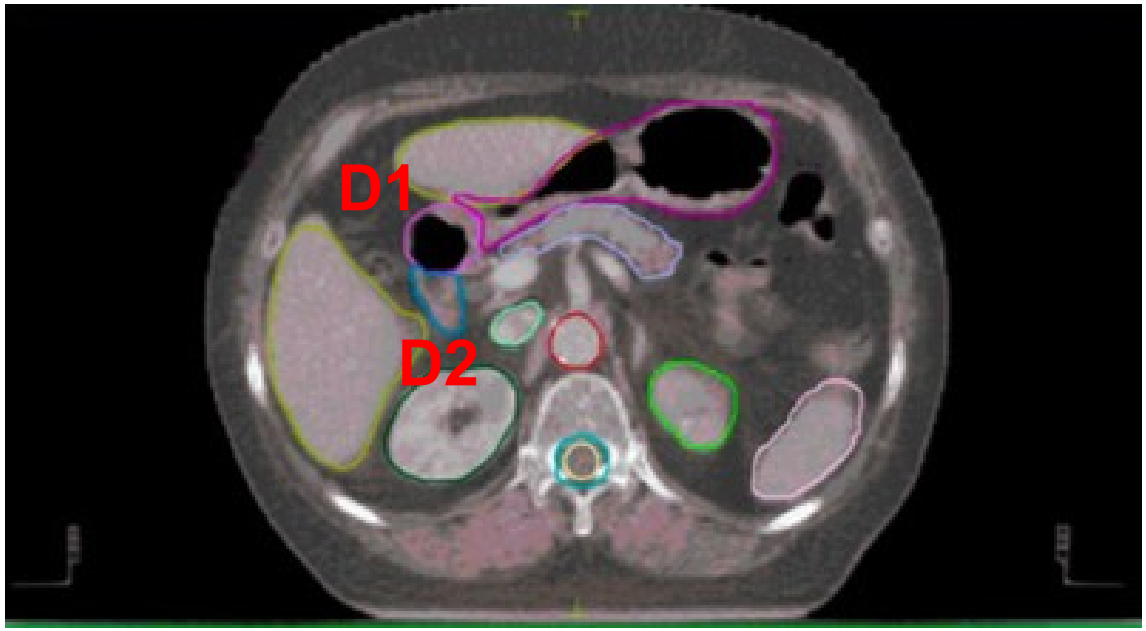
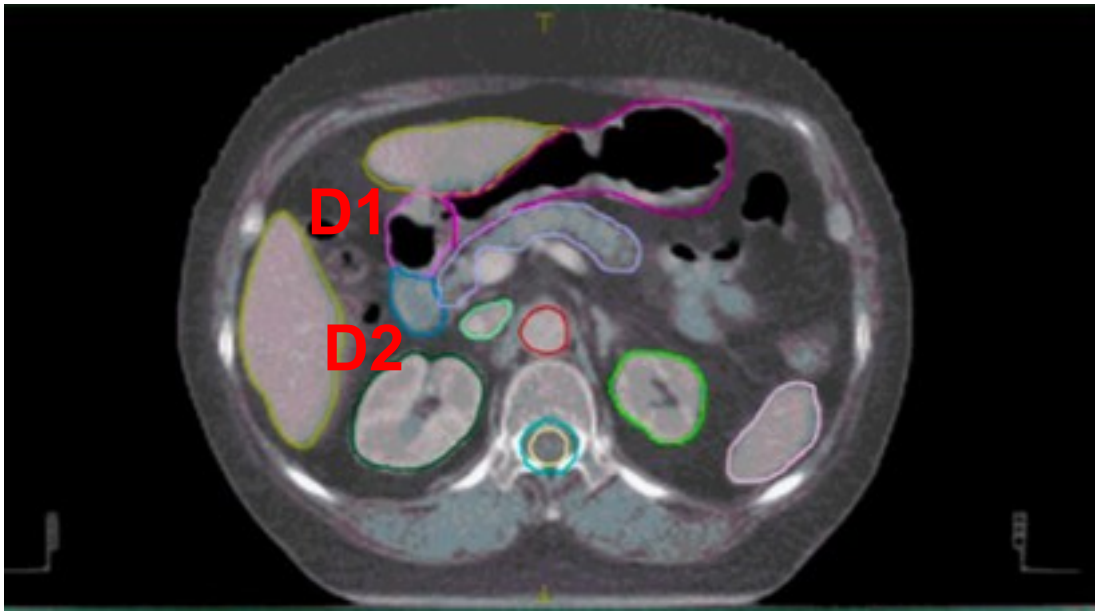
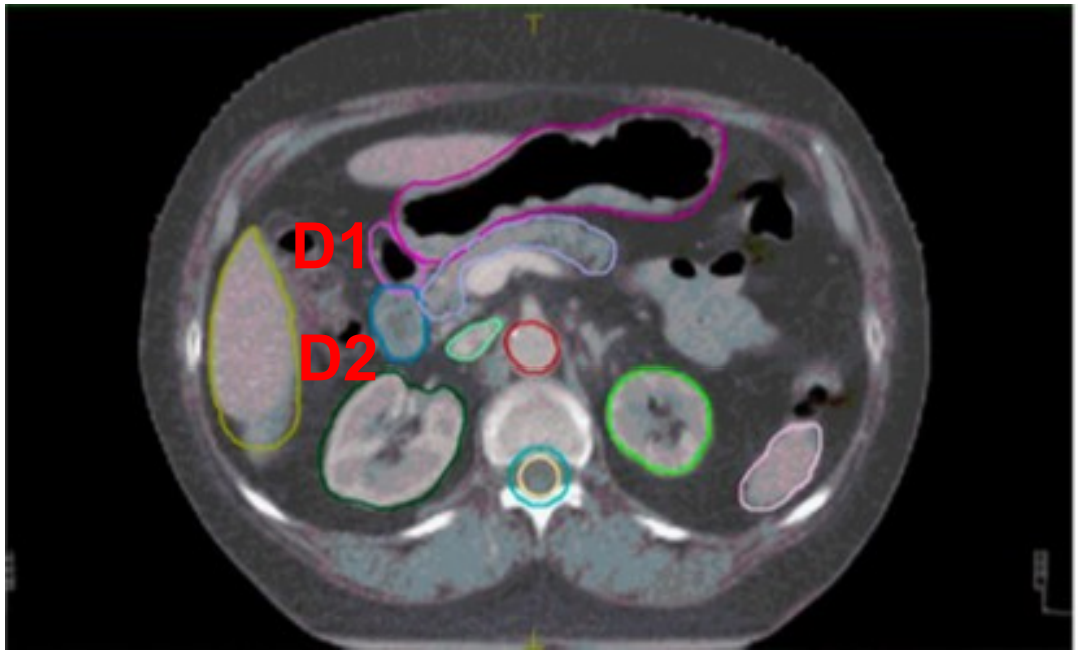


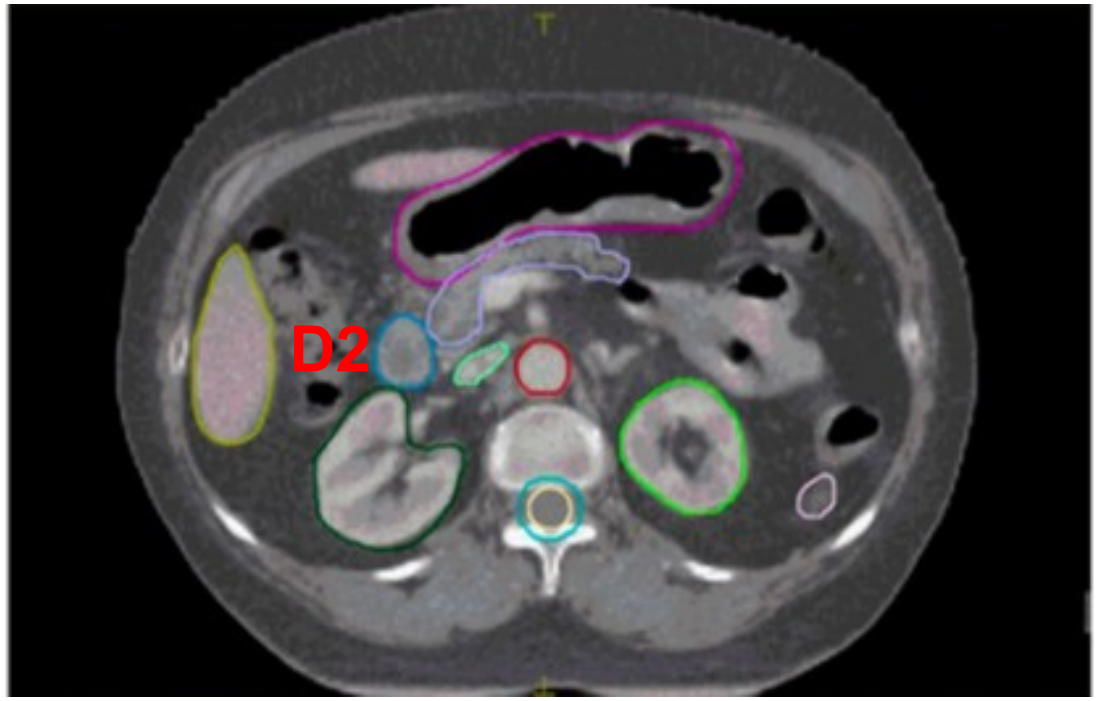
Kataria *et al.; Br J Radiol*-2016



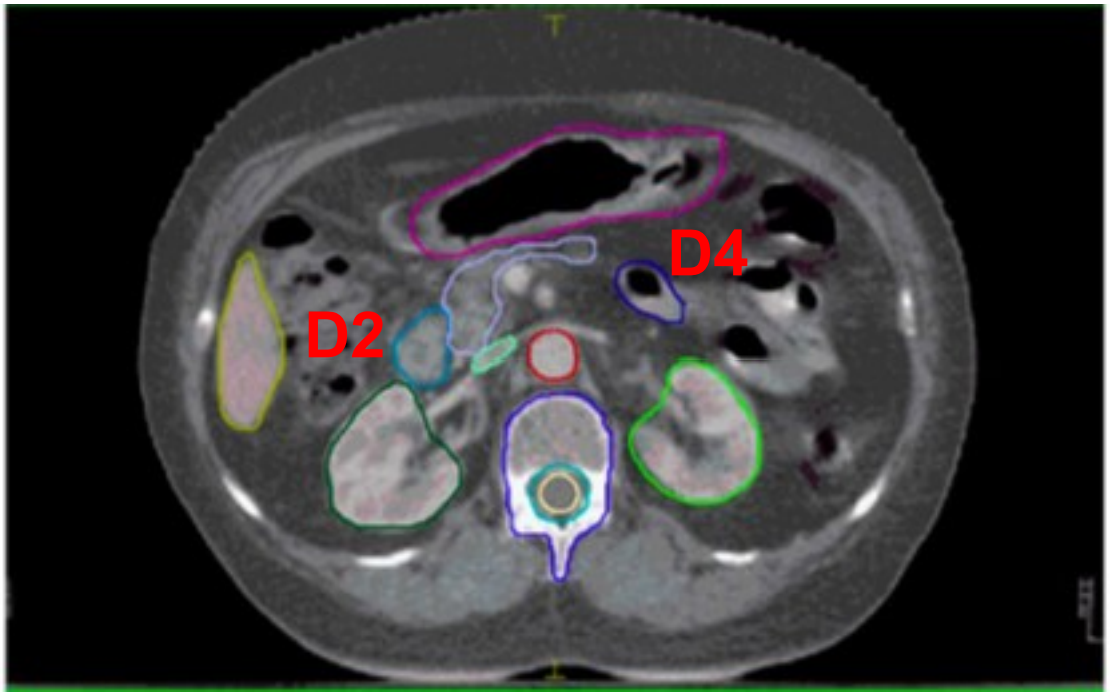
Kataria *et al.; Br J Radiol*-2016



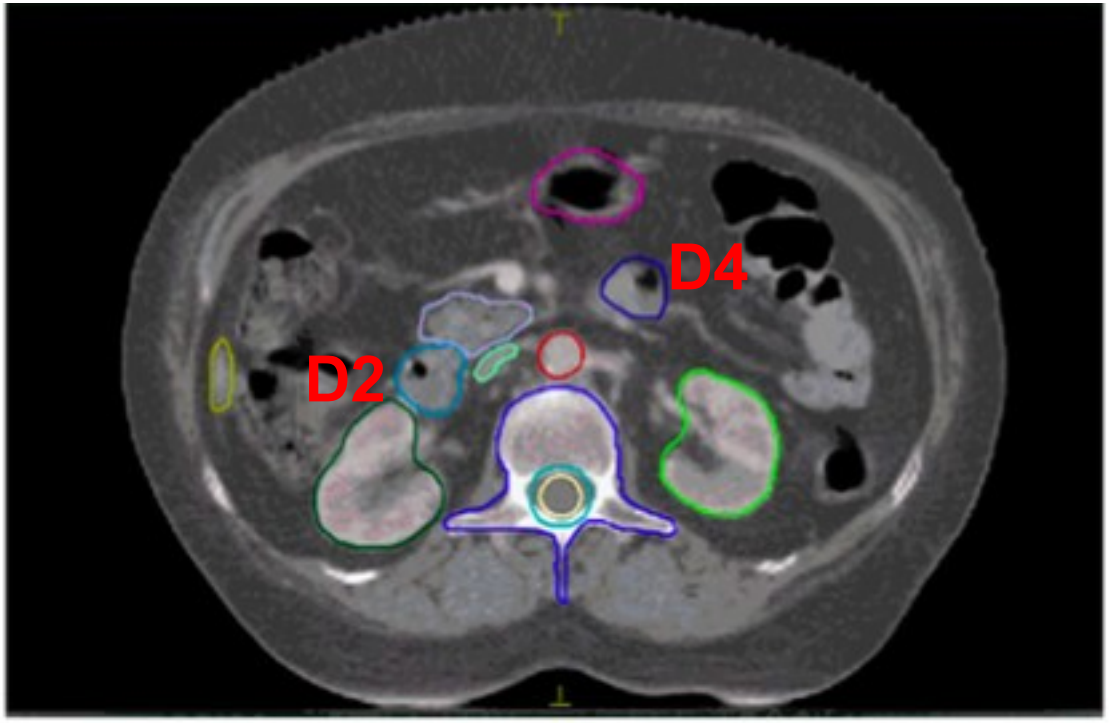
Kataria *et al.; Br J Radiol*-2016



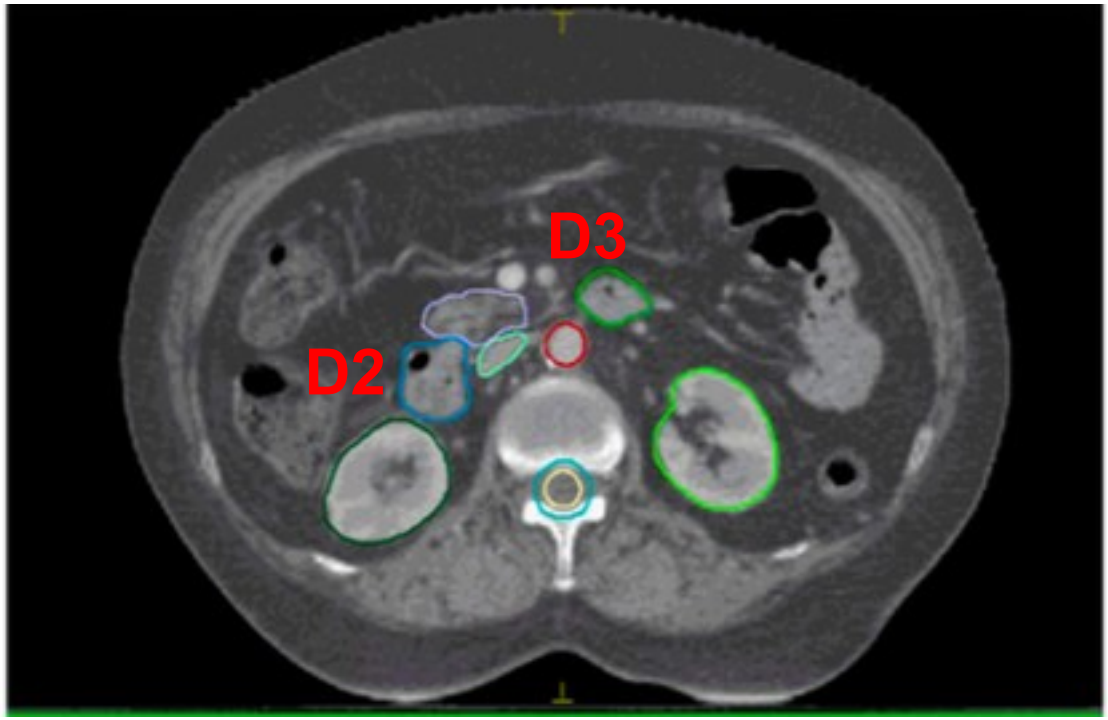
Kataria *et al.; Br J Radiol*-2016



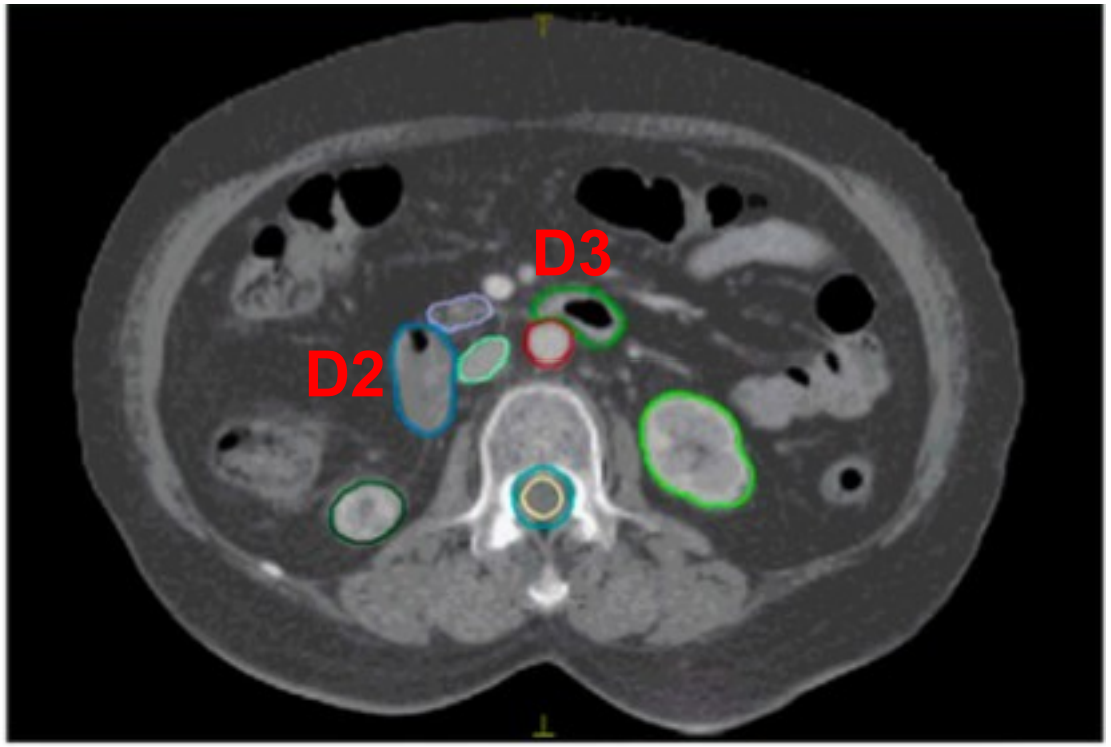
Kataria *et al.; Br J Radiol*-2016



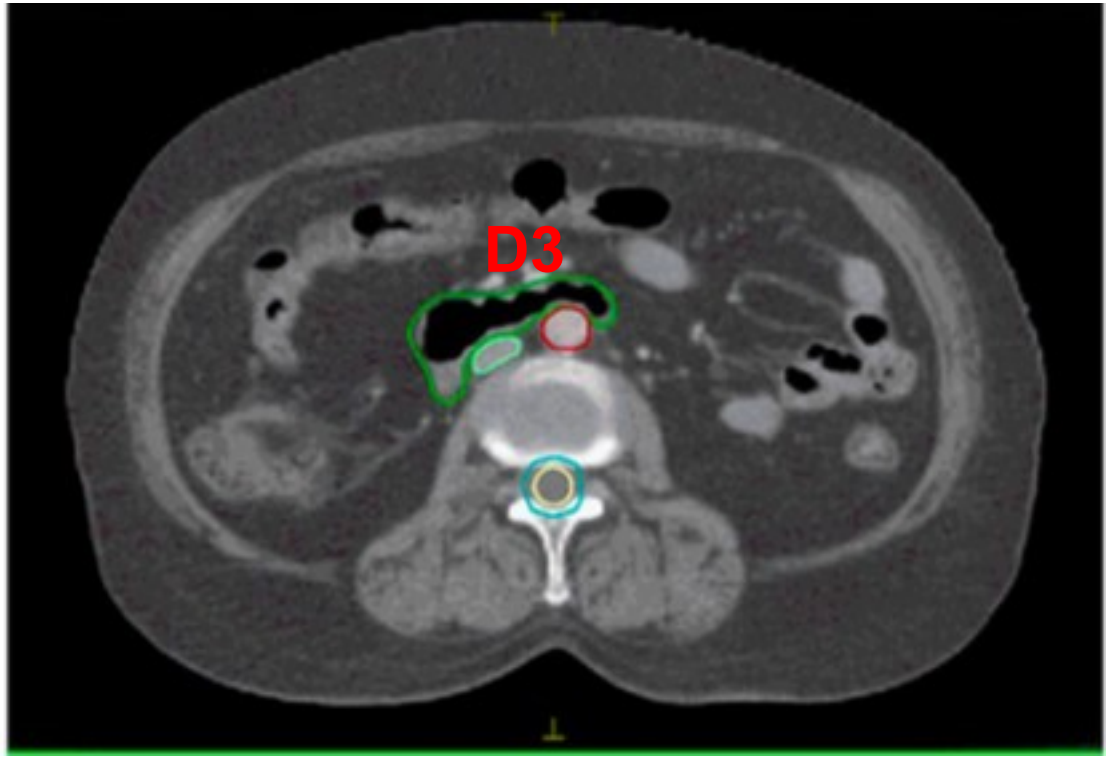
Kataria *et al.; Br J Radiol*-2016



Kataria *et al.; Br J Radiol*-2016



Kataria *et al.; Br J Radiol*-2016



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Kataria *et al.; Br J Radiol*-2016

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CTV DELINEATION: Preoperative Setting

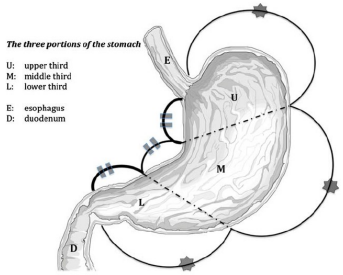
GTV tumor + GTV nodal

+ 1.5 cm= CTV tumor

+ 0.5 cm= CTV nodal

+

CTV Gastric



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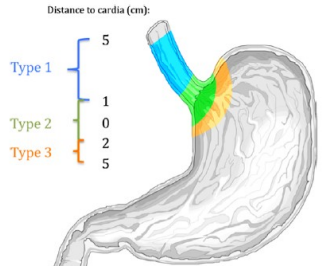
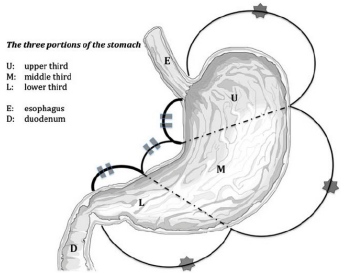


CTV Elective



Matzinger *et al.; Radiother Oncol* -2009

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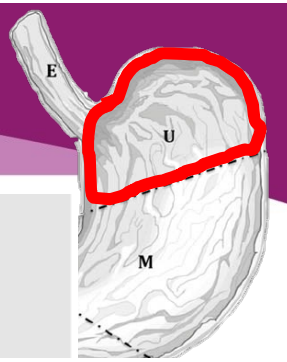
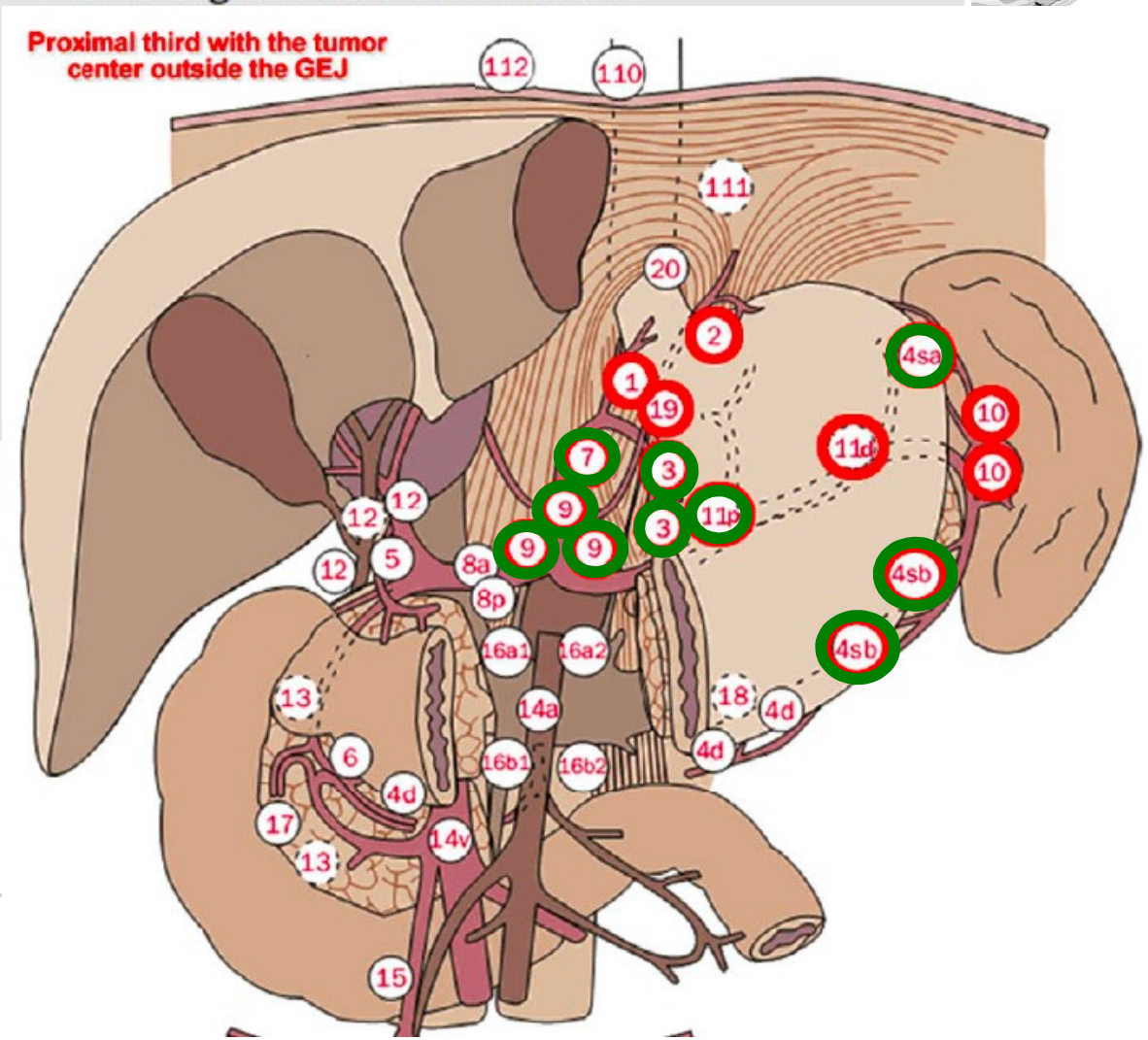
CTV DELINEATION: Preoperative Setting



GC: proximal third	1	Right paracardial LN
	2	Left paracardial LN
(Figs. 3, 7 and 10)	3	LN along the lesser curvature
	4sa	
	4sb	
	7	
	9	
	10	
	11p	
	11d	
	19	



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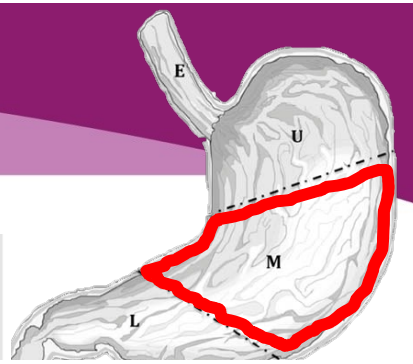
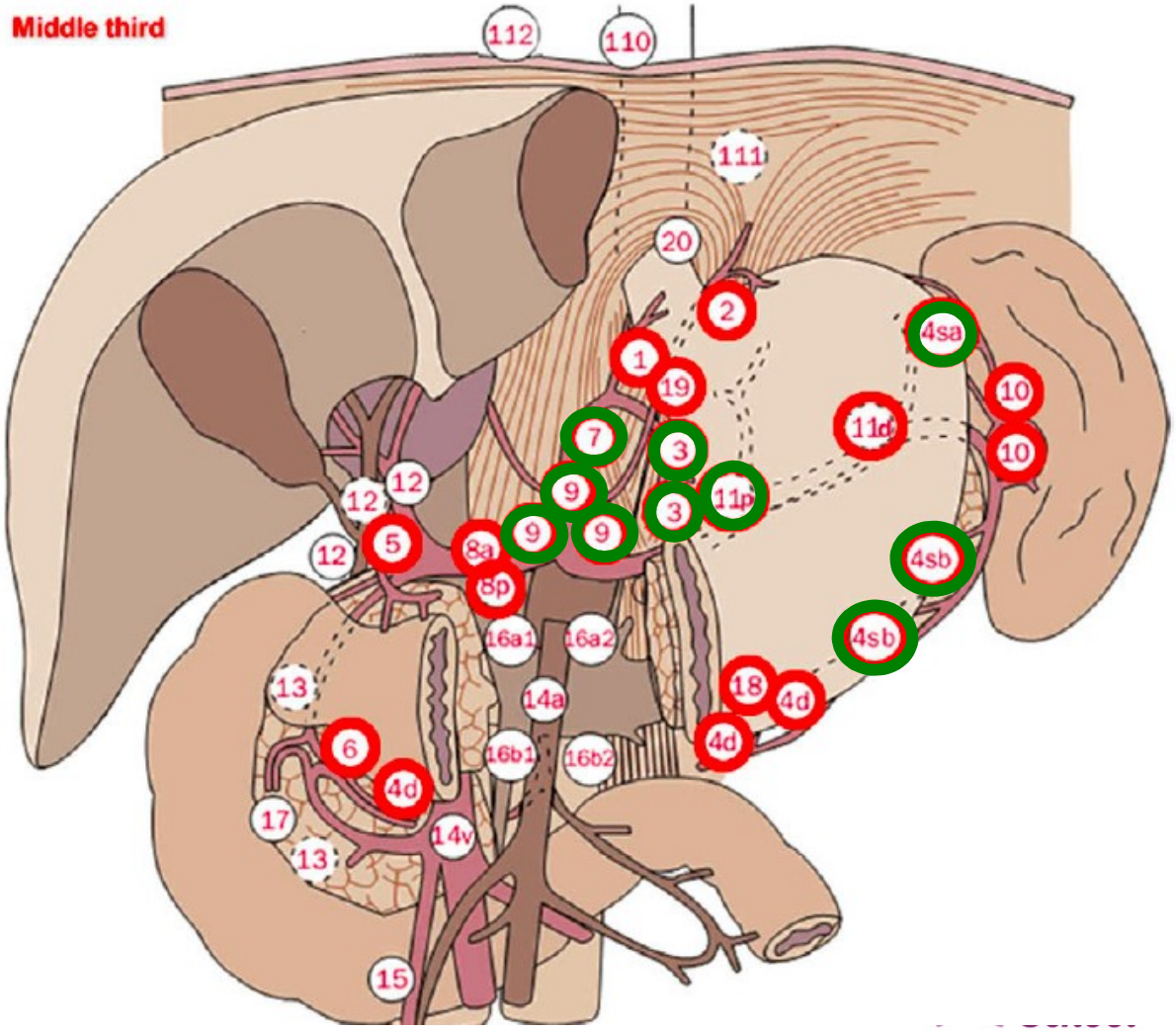
CTV DELINEATION: Preoperative Setting



GC: middle third	1	Right paracardial LN
	2	Left paracardial LN
(Figs. 3, 8 and 10)	3	LN along the lesser curvature
	4sa	L
	4sb	L
	4d	L
	5	S
	6	In
	7	L
	8a	L
		(A
	8b	L
		g
	9	L
	10	L
	11p	L
	11d	L
	18	L
	19	in



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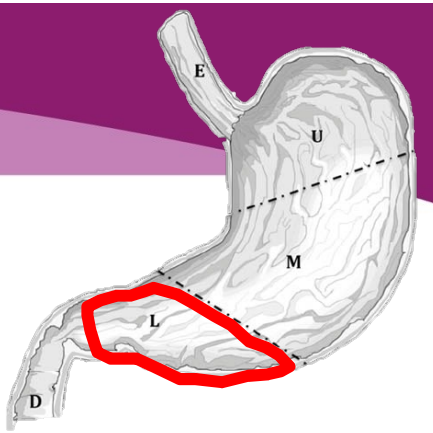
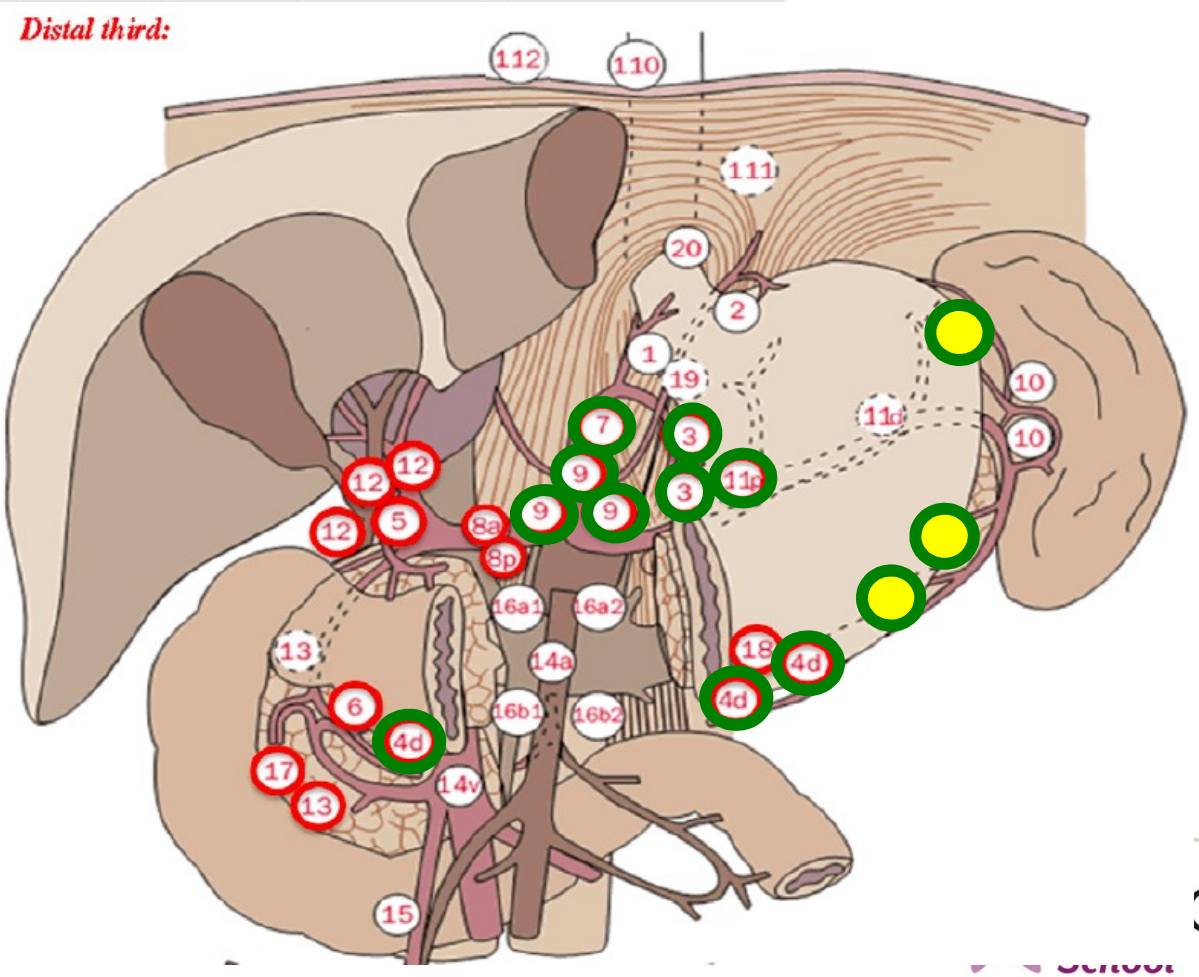
CTV DELINEATION: Preoperative Setting

GC: distal third	3	LN along the lesser curvature
	4d	LN along the right gastroepiploic vessels
(Figs. 3, 9 and 10)	5	Suprapyloric LN
	6	Infrapyloric LN
	7	LN along the left gastric artery
	8a	
	8b	
	9	
	11p	
	12a	
	12b	
	12p	
	13	
	17	
	18	





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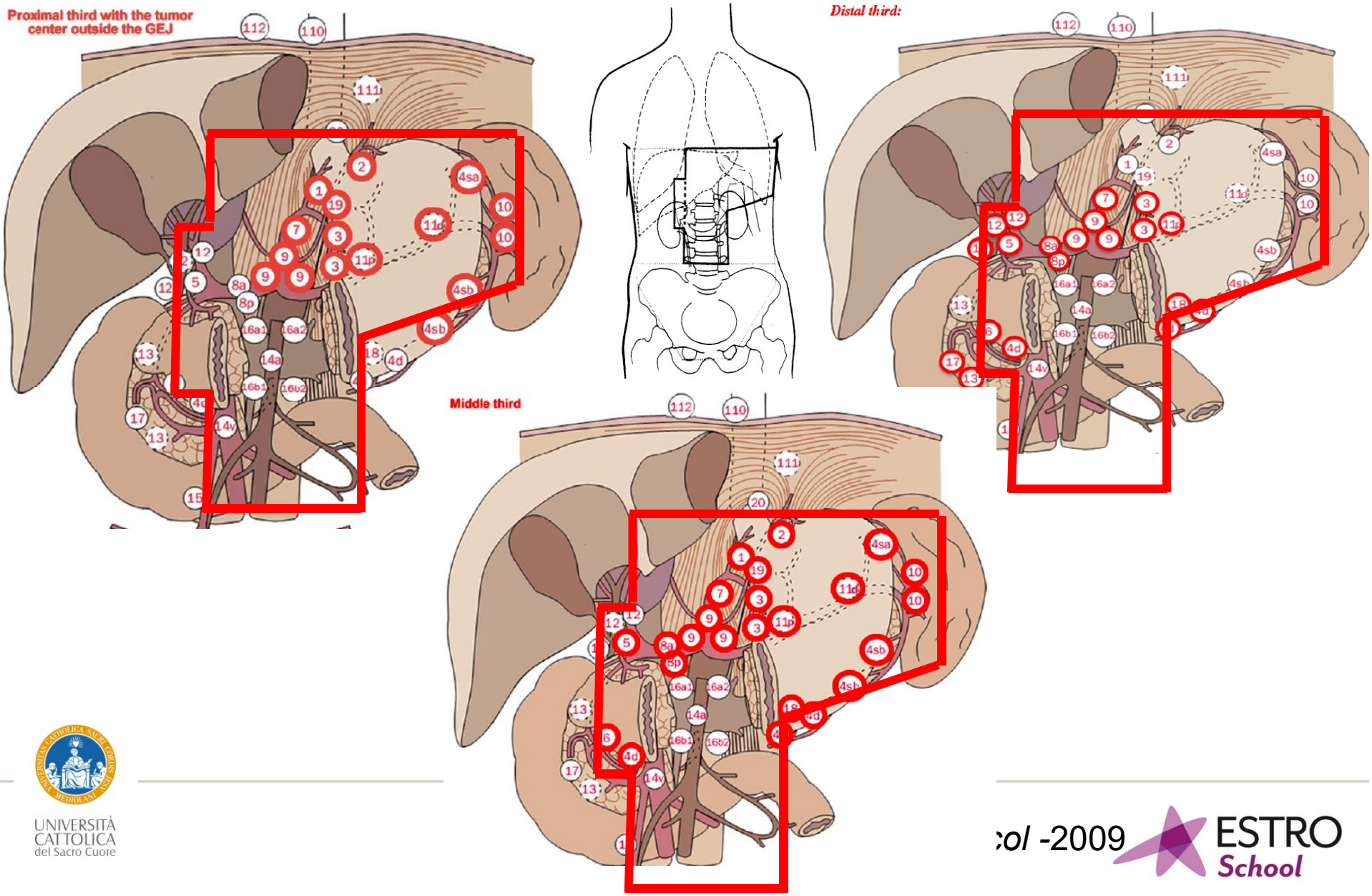
CTV DELINEATION: Preoperative Setting



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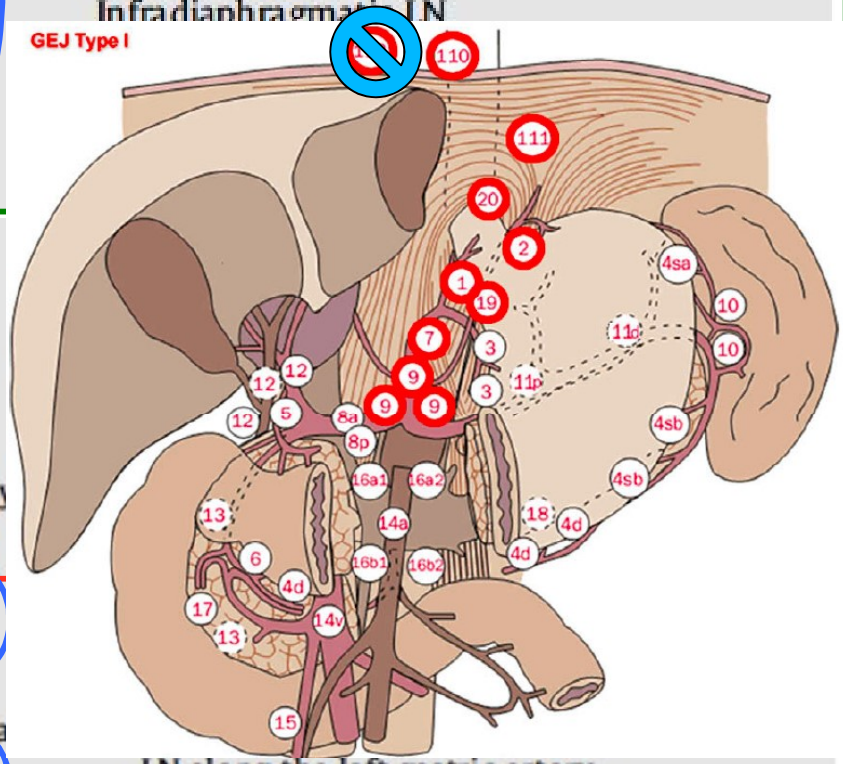
CTV DELINEATION: Preoperative Setting

GEJ type I (Figs. 3, 4 and 10)	1	Right paracardial LN
	2	Left paracardial LN
	7	LN along the left gastric artery
	9	LN around the celiac artery
	19	Infradiaphragmatic LN
	20	
	110	
	111	
	112	



GEJ type II (Figs. 3, 5 and 10)	1	Right paracardial LN
	2	Left paracardial LN
	3	LN along the lesser curvature
	4sa	LN along the short gastric vessels
	7	LN along the left gastric artery
	9	LN around the celiac artery
	11p	LN along the proximal splenic artery
	19	Infradiaphragmatic LN
	20	LN in the oesophageal hiatus of the
	110	Paraoesc
	111	Supradia

GEJ type III (Figs. 3, 6 and 10)	1	
	2	
	3	
	4sa	
	7	LN along the left gastric artery
	9	LN around the celiac artery
	10	LN at the splenic hilum
	11p	LN along the proximal splenic artery
	11d	LN along the distal splenic artery
	19	Infradiaphragmatic LN
	20	LN in the oesophageal hiatus of the diaphragm
	110	Paraoesophageal LN in the lower thorax
	111	Supradiaphragmatic LN

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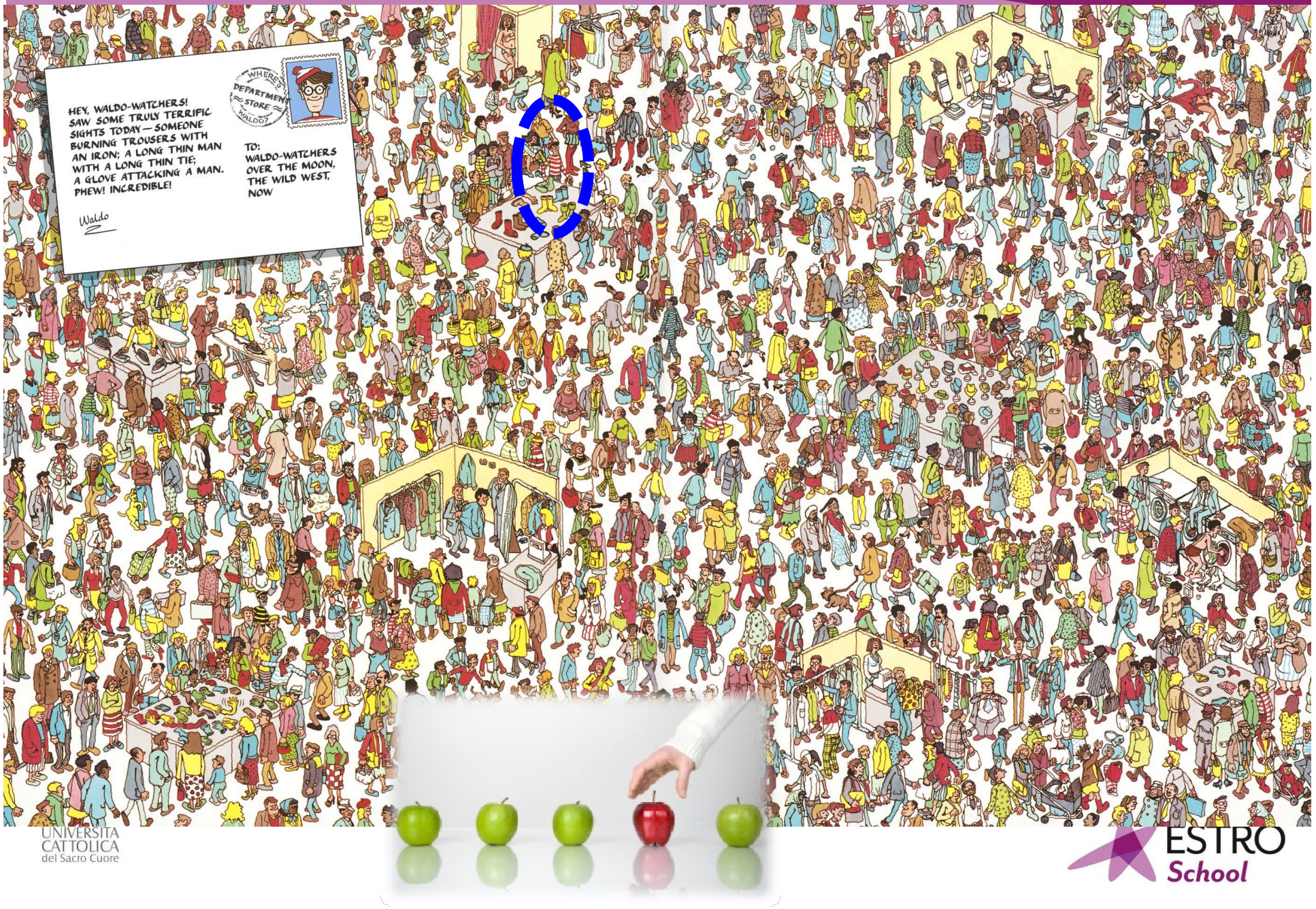

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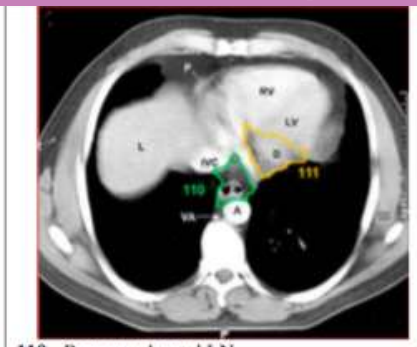
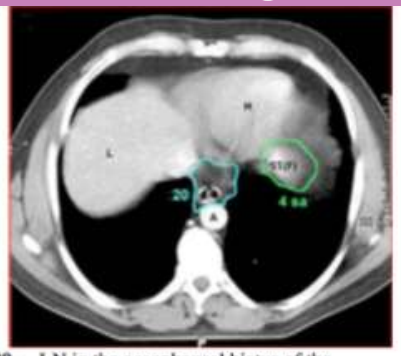
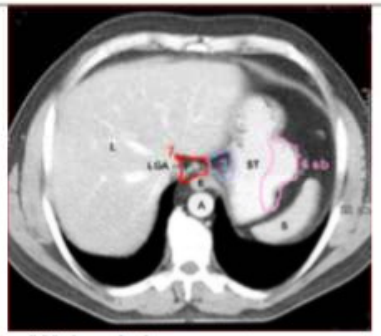
CTV DELINEATION: Preoperative Setting



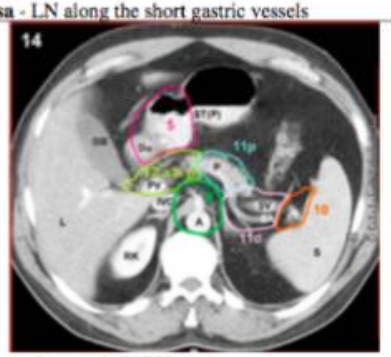
110 - Paraoesophageal LN
111 - Supradiaphragmatic LN



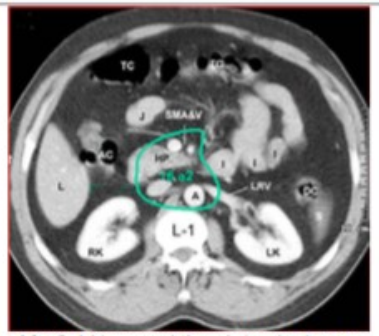
20 - LN in the oesophageal hiatus of the diaphragm
4sa - LN along the short gastric vessels



3 - LN along the lesser curvature
4sb - LN along the left gastroepiploic vessels
7 - LN along the left gastric artery

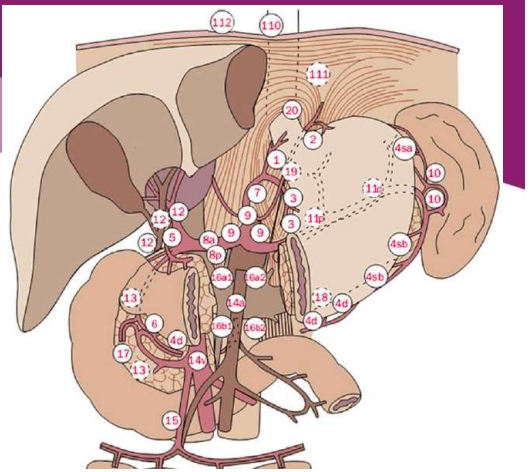


5 - Suprapyloric LN,
9 - LN around the celiac artery
10 - LN at the splenic hilum
11p - LN along the proximal splenic artery
11d - LN along the distal splenic artery
12 a, b, p - LN in the hepatoduodenal ligament



16 a2 LN around the abdominal aorta

LEGEND:
A – Aorta; AC – Ascending Colon; D - Diaphragma; DC – Descending Colon; Du – Duodenum; E – Oesophagus; GB – Gall Bladder; I – Ilium; H – Heart; J – Jejunum; IVC – Inferior Cava Vein; L – Liver; L-1 – First Lumbar Vertebra; LK – Left Kidney, LRV – Left Renal Vein; LV – Left Ventricle; P – Pancreas; PV – Portal Vein; RGA – Right Gastric Artery; RK – Right Kidney; RV – Right Ventricle; S – Spleen; SA – Splenic Artery; SMA&V – Superior Mesenteric Artery and Vein; SV – Splenic Vein; ST – Stomach; ST(F) – Stomach Fundus; ST(P) – Stomach Pylorus; TC - Transverse Colon; VA – Azygos Vein



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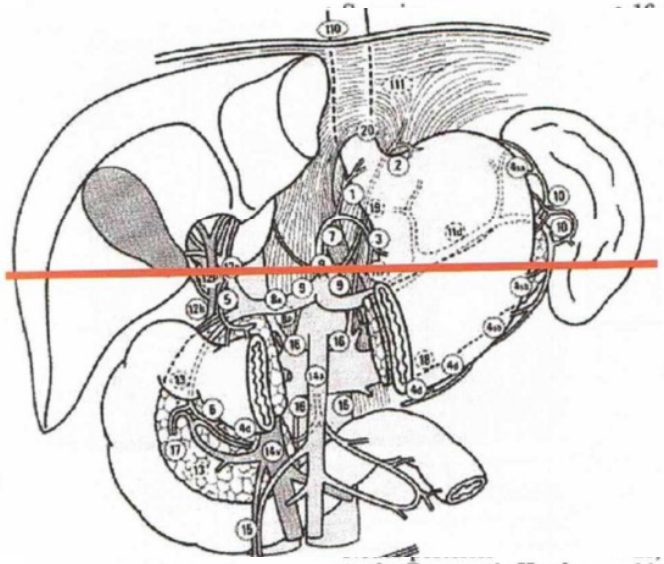
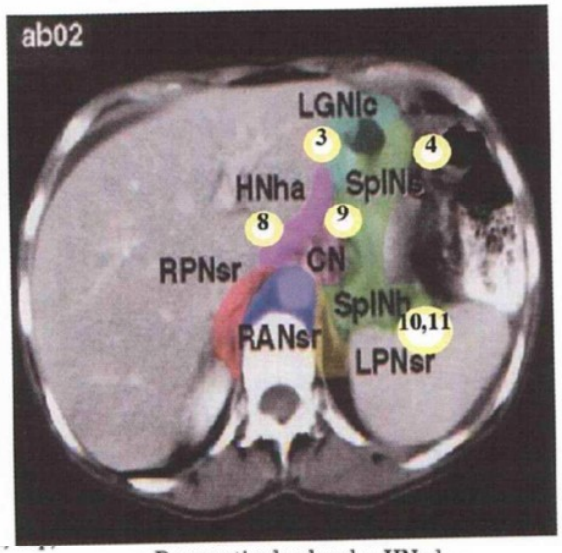
CTV DELINEATION: Preoperative Setting

CTV	***Middle Third or Multiple Gastric Subsite Primaries***	• Perigastric lymph nodes of the: – Cardia – Lesser Curvature – Greater Curvature – Antrum and Pylorum	• 1, 2, 3, 4, 5, 6, 7	Juxtacardiac = LGNc Lesser Curvature = LGNlc Suprapancreatic (Gastric Greater SplNs Curvature) = Right Gastroepiploic = HNrg Suprapyloric = HNp Infrapyloric = HNp
TION		• Splenic Hilum and Splenic Artery	• 10, 11	• Splenic Hilum = SplNh
		to the Pancreatic Head and Superior Portion of the Pancreas	14, 16a	Pancreaticoduodenal = HNpd Splenic Hilum = SplNh Superior Mesenteric Nodes = SMN Retroaortic nodes = RANs, RPNs, LPNs





Cellini *et al.; Rays* -2003

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CTV DELINEATION: Preoperative Setting

Rafael Martinez-Monge, MD
Patrick S. Fernandes, MD
Nilendu Gupta, PhD
Reinhard Gahbauer, MD

Index terms:
Computed tomography (CT), three-dimensional, 99.12917, 99.92
Lymphatic system, 99.12917, 99.92
Special reports

Cross-sectional Nodal Atlas: A Tool for the Definition of Clinical Target Volumes in Three-dimensional Radiation Therapy Planning[1]

TABLE 4
Gastrointestinal Lymphatic System (I)

Anatomic Site	First Echelon Nodal Group	Subgroup	Category	Abbreviation
Gastric cardia	Left gastric nodes	Juxtacardiac	Main	LGNc
Gastric lesser curvature	Left gastric nodes	Gastropancreatic	Main	LGNlc
		Lesser curvature	Main	LGNlc
Gastric antrum and pylorus	Hepatic nodes	Right gastroepiploic	Main	HNrg
		Infrapyloric	Main	HNp
		Suprapyloric	Main	HNp
Greater omentum	Hepatic nodes	Right gastroepiploic	Main	HNrg
		Infrapyloric	Main	HNp
		Suprapyloric	Main	HNp
Gastric greater curvature	Splenic nodes	Suprapancreatic	Main	SplNs
Duodenum	Hepatic nodes	Infrapyloric	Main	HNp
		Retropyloric	Main	HNp
		Pancreaticoduodenal	Main	HNpd
	Superior mesenteric nodes	Postpancreaticoduodenal	Main	SMN
Pancreas	Hepatic nodes	Infrapyloric, suprapyloric	Main	HNp
		Pancreaticoduodenal	Main	HNpd
		Hepatic artery	Main	HNha
	Splenic nodes	Suprapancreatic	Main	SplNs
		Splenic hilum	Main	SplNh
	Left gastric nodes	Gastropancreatic	Main	LGNlc
	Superior mesenteric nodes	Root of mesentery	Main	SMN
		Middle colic	Main	SMN
		Postpancreaticoduodenal	Main	SMN
	Right paraaortic nodes	Superior	Main	RPNs
	Left paraaortic nodes	Superior	Main	LPNs
Spleen	Splenic nodes	Splenic hilum	Main	SplNh
Liver	Hepatic nodes	Gallbladder, hepatic artery	Main	HNha
	Celiac axis nodes		Main	CN
	Left gastric nodes	Lesser curvature	Main	LGNlc
	Diaphragmatic nodes	Anterior, lateral	Main	DNa, lat
	Paraesophageal nodes	Inferior	Main	PENi
	Renal hilum nodes		Main	RRH, LRH
Gallbladder and cystic duct	Hepatic nodes	Gallbladder	Main	HNha
		Foramen of Winslow	Main	HNha
Hepatic duct	Hepatic nodes	Foramen of Winslow	Main	HNha
Common bile duct	Hepatic nodes	Foramen of Winslow	Main	HNha
		Postpancreaticoduodenal	Main	HNpd

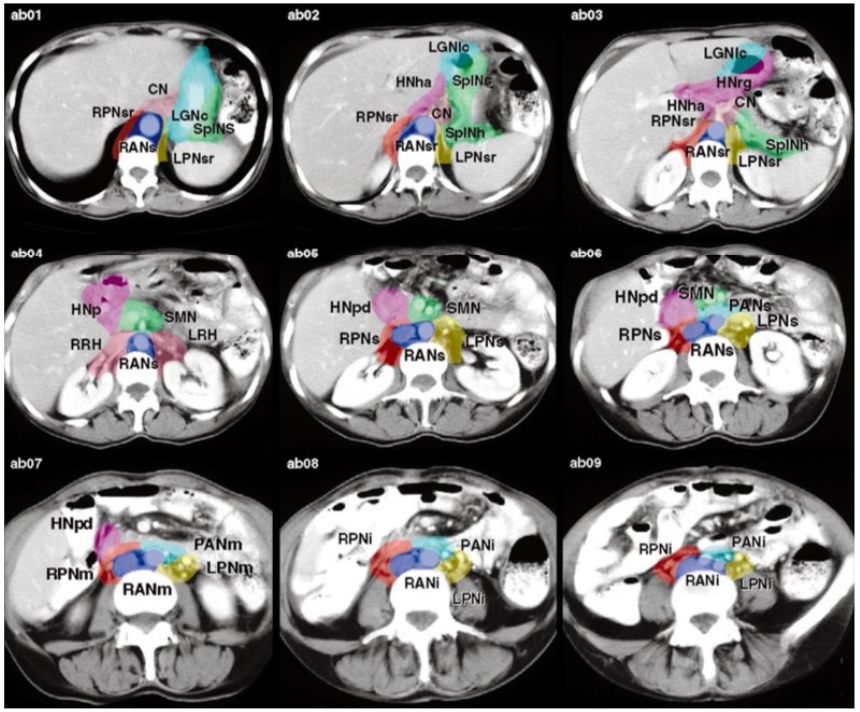

Figure 4. CT images depict the nodal stations in the abdomen (*ab*).

Martinez-Monge *et al.; Radiology. 1999*

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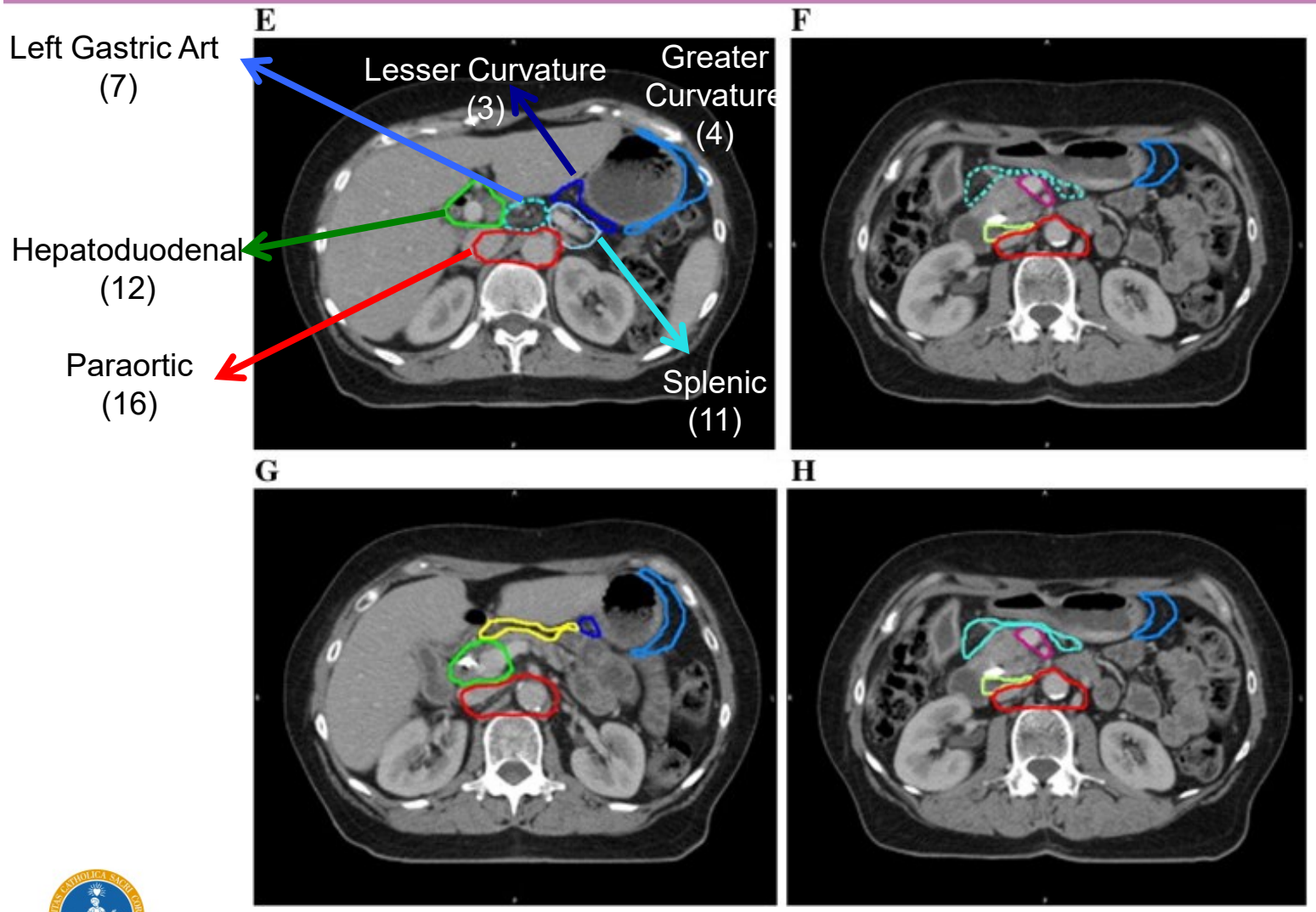
CTV DELINEATION: Preoperative Setting



Wo *et al.; PRO* - 2013

Splenic LN (11)

"The splenic artery LN basin surrounds the splenic artery.

It is bordered anteriorly by the posterior aspect of the gastric body, posteriorly by the left kidney, laterally by the splenic hilum LNs, and medially by the celiac axis LNs"

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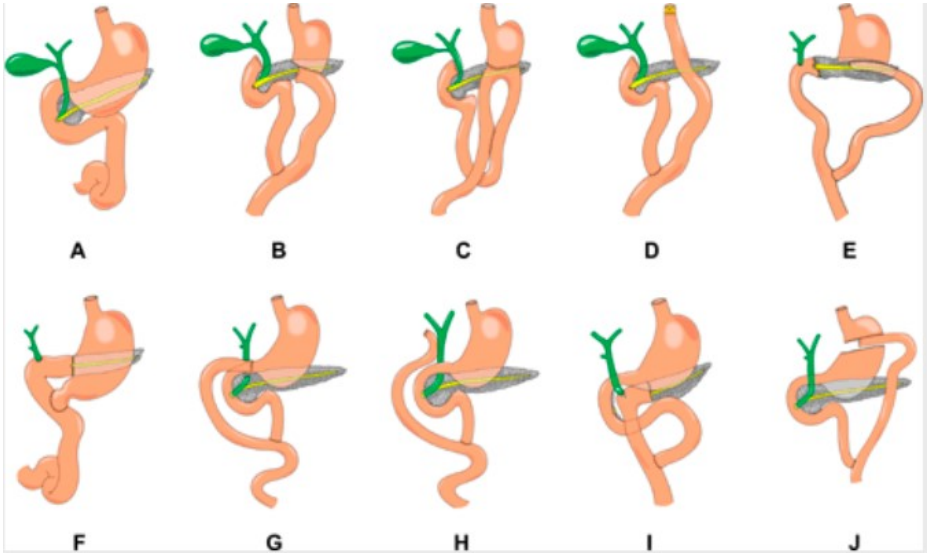
CTV DELINEATION: Postoperative Setting



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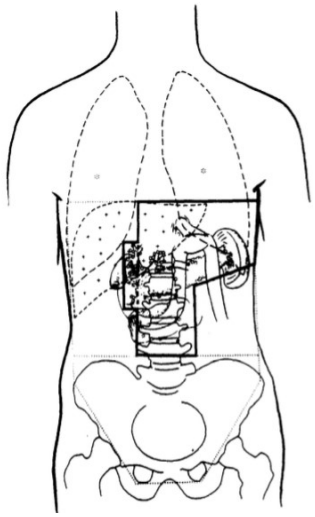
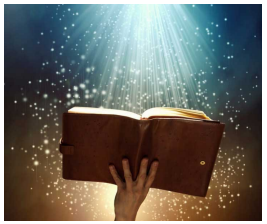
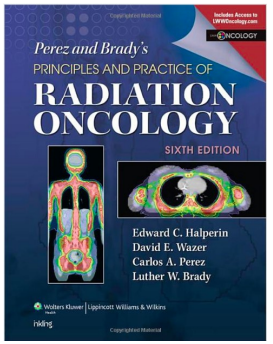
CTV DELINEATION: Postoperative Setting



CTV Definition:

- Post-surgical gastric remnant;
- Gastric Bed structure;
- Anastomoses;
- Duodenal Stump;
- Major nodal chains at risk;





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Perez and Brady's – Principles and Practice of Radiation Oncology- Lippincott Williams- 6th Ed; 2013

Gunderson *et al.; IJROBP* -1981

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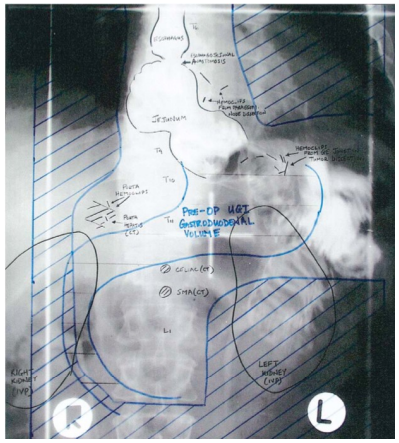
CTV DELINEATION: Postoperative Setting

CTV Definition: Tumor bed and longitudinal surgical margins

GEJ- UP ⅓



- Paraesophageal;
- Perigastric nodes (if subtotal surg)
- Subpyloric is optional

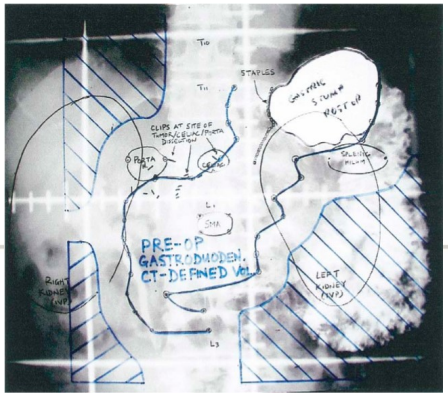
LNs: 1,2,3,4,(5,6),19-20? 110-111?

MID ⅓

- Perigastric lymph nodes (cardia, lesser and greater curvature);
- Splenic hilus and splenic artery;
- Infrapyloric area;
- Superior retropancreatic chain;
- Hepatoduodenal ligament;

LNs: 1,2,3,4,5,6,7; 10, 11, 12, 13

Antral Lesion- Low ⅓



- Subpyloric;
- Pancreaticoduodenal;
- Splenic hilar is optional

LNs: 6,7; (10), 11, 13

Smalley *et al.; IJROBP* -2002

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CTV DELINEATION: Postoperative Setting

Table 3. Impact of Site of Primary Lesion and TN Stage on Irradiation Treatment Volumes—EG Junction (General Guidelines)

Site of Primary and TN Stage	*Remaining Stomach*	*Tumor Bed Volumes***	*Nodal Volumes*	*Tolerance Organ Structures*
1) EG junction	If allows exclusion of 2/3 R kidney	T-stage dependent	N-stage dependent	Heart, lung, spinal cord, kidneys,
T2N0 with invasion of subserosa	Variable dependent on surgical-pathologic findings*	Medial left hemidiaphragm; adjacent body of pancreas	None or perigastric, periesophageal***	
T3N0	Variable dependent on surgical-pathologic findings*	Medial left hemidiaphragm; adjacent body of pancreas	None or perigastric, periesophageal mediastinal, celiac***	
T4N0	Preferable but dependent on surgical-pathologic findings*	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site of adherence, +/− perigastric, periesophageal mediastinal, celiac	
T1-2 N+	Preferable	Not indicated for T1, as above for T2 into subserosa	Periesophageal, mediastinal, prox perigastric, celiac	
T3-4 N+	Preferable	As for T3, T4N0	As for T1-2N+ and T4N0	

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Tepper *et al.; Sem Radiat Oncol* -2002

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CTV DELINEATION: Postoperative Setting

Table 4. Impact of Site of Primary Gastric Lesion and TN Stage on Irradiation Treatment Volumes—Cardia/ Proximal One Third of Stomach (General Guidelines)

Site of Primary and TN Stage	*Remaining Stomach*	*Tumor Bed Volumes***	*Nodal Volumes*	*Tolerance Organ Structures*
2) Cardia/ prox 1/3 of stomach	Preferred, but spare 2/3 of one kidney (usually R)	T-stage dependent	N-stage dependent	kidneys, spinal cord, liver, heart, lung
T2N0 with invasion of subserosa	Variable dependent on surgical-pathologic findings*	Medial L hemidiaphragm, adjacent body of pancreas (+/− tail)	None or perigastric†	
T3N0	Variable dependent on surgical-pathologic findings*	Medial L hemidiaphragm, adjacent body of pancreas (+/− tail)	None or perigastric: optional: periesophageal, mediastinal, celiac#†	
T4N0	Variable dependent on surgical-pathologic findings*	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site of adherence, +/− perigastric, periesophageal, mediastinal, celiac	
T1-2N+	Preferable	Not indicated for T1, as above for T2 into subserosa	Perigastric, celiac, splenic, suprapancreatic, +/− periesophageal, mediastinal, panc-duod, porta hepatis***	
T3-4 N+	Preferable	As for T3, T4N0	As for T1-2N+ and T4N0	

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Tepper *et al.; Sem Radiat Oncol* -2002

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CTV DELINEATION: Postoperative Setting

Table 5. Impact of Site of Primary Gastric Lesion and TN Stage on Irradiation Treatment Volumes—Body/Middle One Third of Stomach (General Guidelines)

Site of Primary and TN Stage	*Remaining Stomach*	*Tumor Bed Volumes**	*Nodal Volumes*	*Tolerance Organ Structures*
3) Body/mid-1/3 of stomach	Yes, but spare 2/3 of one kidney	T-stage dependent	N-stage dependent, spare 2/3 of one kidney	Kidneys, spinal cord, liver
T2N0 with invasion of subserosa—esp. post wall	Yes	Body of pancreas (+/− tail)	None or perigastric; optional: celiac, splenic, supra-pancreatic, pancreatico-duodenal, portahepatis**	
T3N0	Yes	Body of pancreas (+/− tail)	None or perigastric; optional; celiac, splenic, supra-pancreatic, pancreatico-duodenal, portahepatis**	
T4N0	Yes	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site of adherence +/− perigastric, celiac, splenic, supra-pancreatic, pancreatico-duodenal, portahepatis	
T1-2 N+	Yes	Not indicated for T1	Perigastric, celiac, splenic, supra-pancreatic, pancreatico-duodenal, porta hepatis	
T3-4N+	Yes	As for T3, T4N0	As for T1-2N+ and T4N0	

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Tepper *et al.; Sem Radiat Oncol* -2002

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CTV DELINEATION: Postoperative Setting

Table 6. Impact of Site of Primary Gastric Lesion and TN Stage on Irradiation Treatment Volumes—Antrum/Pylorus/Distal One Third of Stomach (General Guidelines)

Site of Primary and TN Stage	*Remaining Stomach*	*Tumor Bed Volumes***	*Nodal Volumes*	*Tolerance Organ Structures*
4) Pylorus/distal 1/3 stomach	Yes, but spare 2/3 of one kidney (usually L)	T-stage dependent	N-stage dependent	Kidneys, liver, spinal cord
T2N0 with invasion of subserosa	Variable dependent on surgical-pathologic findings*	Head of pancreas, (+/− body), 1st and 2nd duodenum	None or perigastric; optional: pancreatico-duodenal, porta hepatis, celiac, supra-pancreatic***	
T3N0	Variable dependent on surgical-pathologic findings*	Head of pancreas, (+/− body), 1st and 2nd duodenum	None or perigastric; optional: pancreatico-duodenal, porta hepatis, celiac, supra-pancreatic***	
T4N0	Preferable but dependent on surgical-pathologic findings*	As for T3N0 plus site(s) of adherence with 3-5 cm margin	Nodes related to site(s) of adherence +/− perigastric, pancreatico-duodenal, portahepatis, celiac, supra-panc	
T1-2N+	Preferable	Not indicated for T1	Perigastric, pancreatico-duodenal, portahepatis, celiac, supra-pancreatic; Optional splenic hilum***	
T3-4N+	Preferable	As for T3, T4N0	As for T1-2N+ and T4N0	

Tepper *et al.; Sem Radiat Oncol* -2002

CTV DEL

Author (yy)	DOSE	CTV Definition	CTV T	CTV Nodal	Nodal Identification	Subsite UP 1/3	Subsite MID 1/3	Subsite LOW 1/3
Macdonald et al. (2001)	45 Gy (1.8 Gy/fx)	- T. Bed - Regional LN + 2 cm beyond prox/distal resec. margs	- T. Bed (Preop Imaging + surgical clips)	- Perigastric, - Celiac, - Local Paraaortic, - Splenic, - Hepatoduodenal or Hepaticportal, - Pancreaticoduodenal	Japanese Research Society for Gastric Cancer	GEJ: - Paracardial + -Paraesophageal; - Pancreaticoduodenal excluded - UP 1/3: Medial left hemidiaphragm		Antral lesions: Excluding splenic nodes allowed in patients if necessary spare the left kidney.
Kim *et al.* (2012)	45 Gy (1.8 Gy/fx)	- Anastomosis - Duod. Stump - Regional LN + OVER 2 cm beyond prox/distal resec. margs	- Tumor Bed NOT included (due R0 Surg, Apart for T4 lesions) - Remnant Stomach (but protect Left Kidney)	Not Specified	Not Specified			
Yu *et al.* (2012)	IMRT 45 Gy (1.8 Gy/fx)	- T. Bed, - Stroma, - Regional LN	"Based on the intraoperative situation and the silver-clip"	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified
Zhu *et al.* (2012)	IMRT 45 Gy (1.8 Gy/fx)	"LNs delineated by different sites of the primary lesions"	Not Specified	Detailed	Not Specified	- Paraesophagus 5.0 cm upper GEJ, - Para-GEJ, - Greater curvature, - Lesser curvature, - Left gastric artery, - Splenic artery/splenic hilar lymph node	- Para-GEJ, - Greater curvature, - Lesser curvature, - Left gastric artery, - Splenic artery/splenic hilar lymph node - Posterior pancreaticoduodenal artery, - Hepatoduod.	- Greater curvature, - Lesser curvature, - Left gastric artery, - Common hepatic artery, - Posterior pancreaticoduodenal artery, - Celiac artery, - Hepatoduodenal ligament, - Exclude: splenic artery/splenic hilum and para- GEJ
Lee et al. (2012) ARTIST	45 Gy (1.8 Gy/fx)	- T. Bed - Anastomosis - Duod. Stump - Regional LN + 2 cm beyond prox/distal resec. margs	- Tumor Bed NOT included (due R0 Surg, Apart for T4 lesions) - Remnant stomach not routinely included in RT-field		- Common hepatic, - Celiac, - Splenic, - Hepatoduodenal			- Exclude: Splenic hilar

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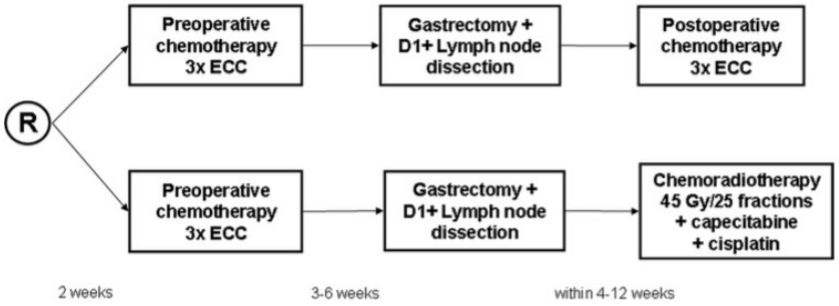
CTV DELINEATION: Postoperative Setting



CTV consists of 3 parts:

1. Anastomoses
2. Gastric Bed/Remnant
3. Lymphnodes (at risk)

CTV DELINEATION: Postoperative Setting

1. Anastomoses

- for tumors of the proximal stomach or GE- junction, the oesophagojejunal anastomosis has to be treated
- duodenal stump has to be treated in tumors of the distal stomach

CTV DELINEATION: Postoperative Setting

2. Gastric Bed/Remnant

- GEJ and proximal tumors at least 2/3-3/4 of the left medial hemidiaphragm
- T1-2 tumors: tumor bed not necessarily
- Hepatogastric ligament (i.e. part of lesser omentum between liver and lesser curvature, which contains peri-gastric nodes)
- Anterior abdominal wall: only in T3-4 tumors with invasion or a close relationship with the anterior abdominal wall on pre-operative imaging or when described by the surgeon during surgery

CTV DELINEATION: Postoperative Setting

3. Lymphnodes

- **GE-Junction/ Cardia/proximal 1/3**: para-oesophageal, perigastric, hepatogastro lig, perigastric, ,celiac (left gastric artery, celiac axis), splenic hilum, suprapancreatic, porta hepatis, pancreaticoduodenal **[Stations 1-4;7,9-13]**

- **Corpus/middle 1/3:** perigastric, suprapyloric, infrapyloric, celiac (left gastric artery, common hepatic artery and celiac axis), splenic hilum, suprapancreatic, porta hepatis, pancreaticoduodenal **[Stations 3-13]**

- **Antrum/distal 1/3:** perigastric, suprapyloric, infrapyloric, splenic artery, pancreaticoduodenal, porta hepatis, celiac (left gastric artery, common hepatic artery and celiac axis), suprapancreatic **[Stations 3-9;11-13]**

CTV DELINEATION: Postoperative Setting

3. Lymphnodes

- **GE-Junction/ Cardia/proximal 1/3**: para-oesophageal, perigastric, hepatogastro lig, perigastric, ,celiac (left gastric artery, celiac axis), splenic hilum, suprapancreatic, porta hepatis, pancreaticoduodenal **[Stations 1-4;7 9-13]**

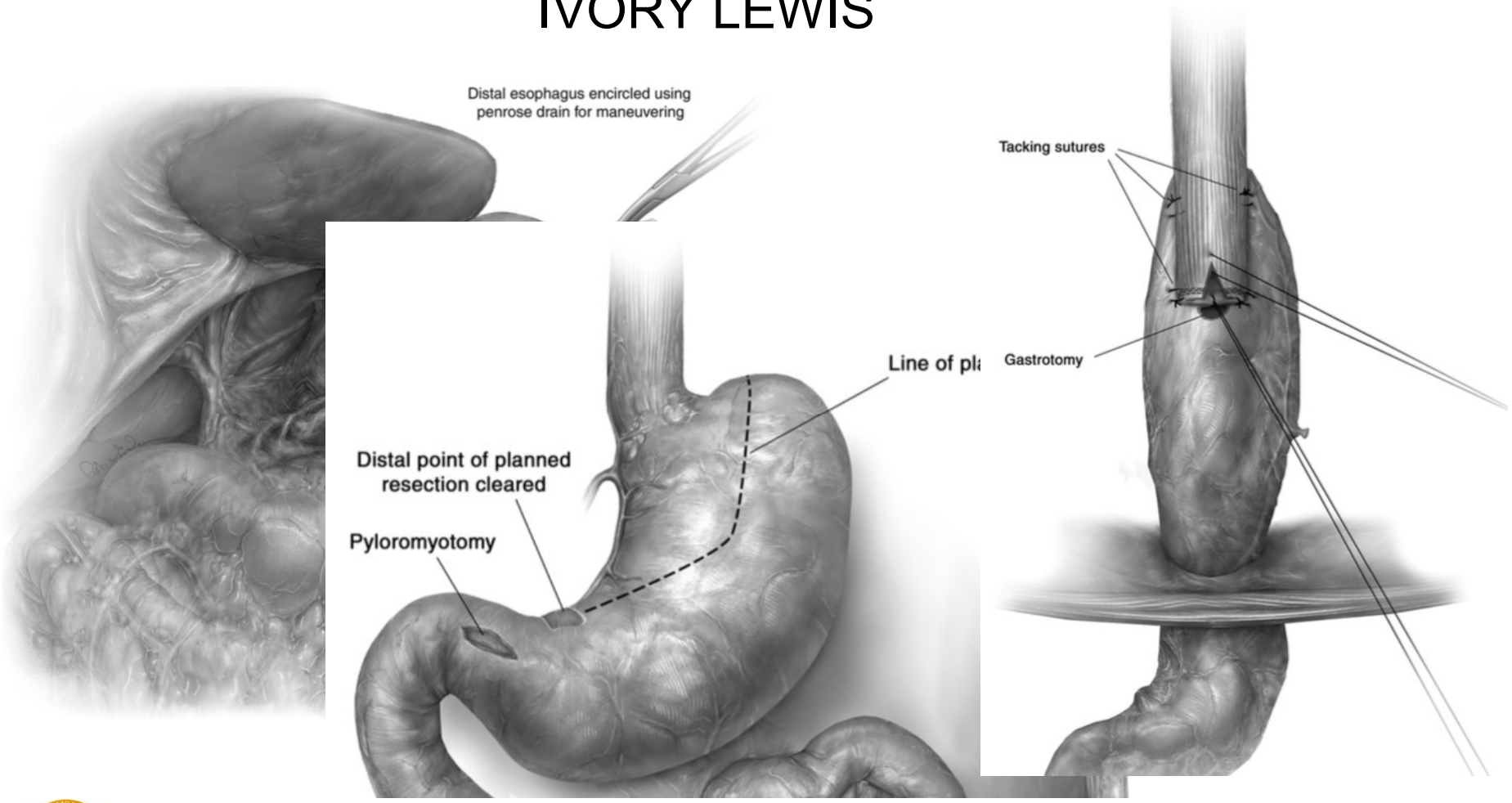
+ all combinations when tumor invaded more than one part of the stomach before start of treatment

- **Corpus/m**eliac (left gastric art ic hilum, suprapancreatic, porta hepatis, pancreaticoduodenal **[Stations 3-13]**

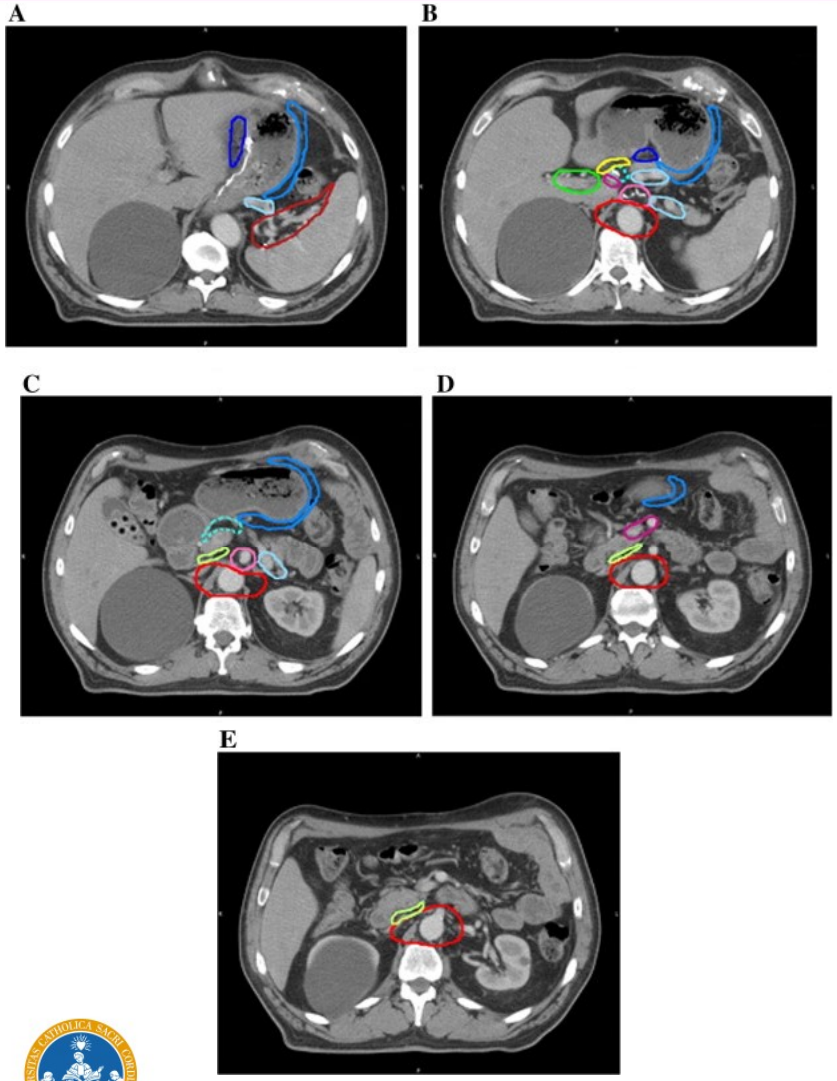
- **Antrum/distal 1/3:** perigastric, suprapyloric, infrapyloric, splenic artery, pancreaticoduodenal, porta hepatis, celiac (left gastric artery, common hepatic artery and celiac axis), suprapancreatic **[Stations 3-9;11-13]**

CTV DELINEATION: Postoperative Setting – Surgical Approach

IVORY LEWIS



CTV DELINEATION: Postoperative Setting – Surgical Approach



IVORY LEWIS

- Paracardial LN are tipically dissected;
- Perigastric LN may be transposed into thoracic cavity;
- Splenic artery not routinely dissected;
- Left gastric artery can be taken at its origin (clips?);
- Kocher maneuver: medially and superiorly shifting duodenum along with supra/infra-pyloric LN

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Wo *et al.; PRO* - 2013

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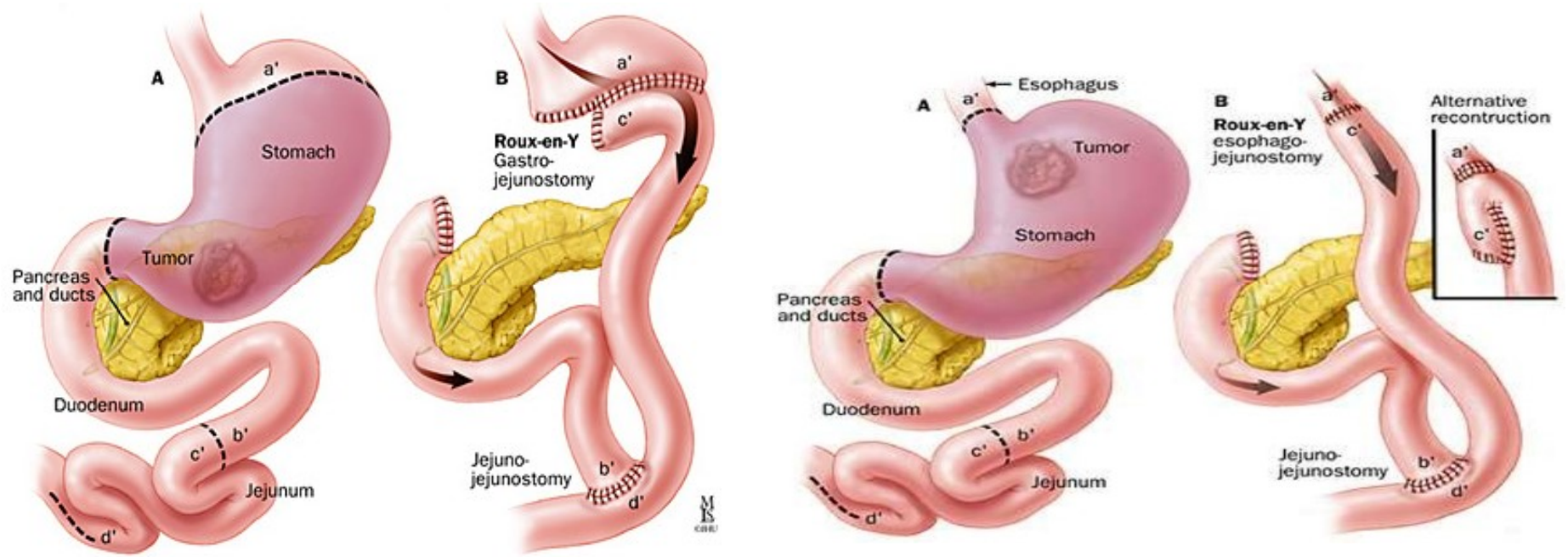
CTV DELINEATION: Postoperative Setting – Surgical Approach

Roux-En-Y



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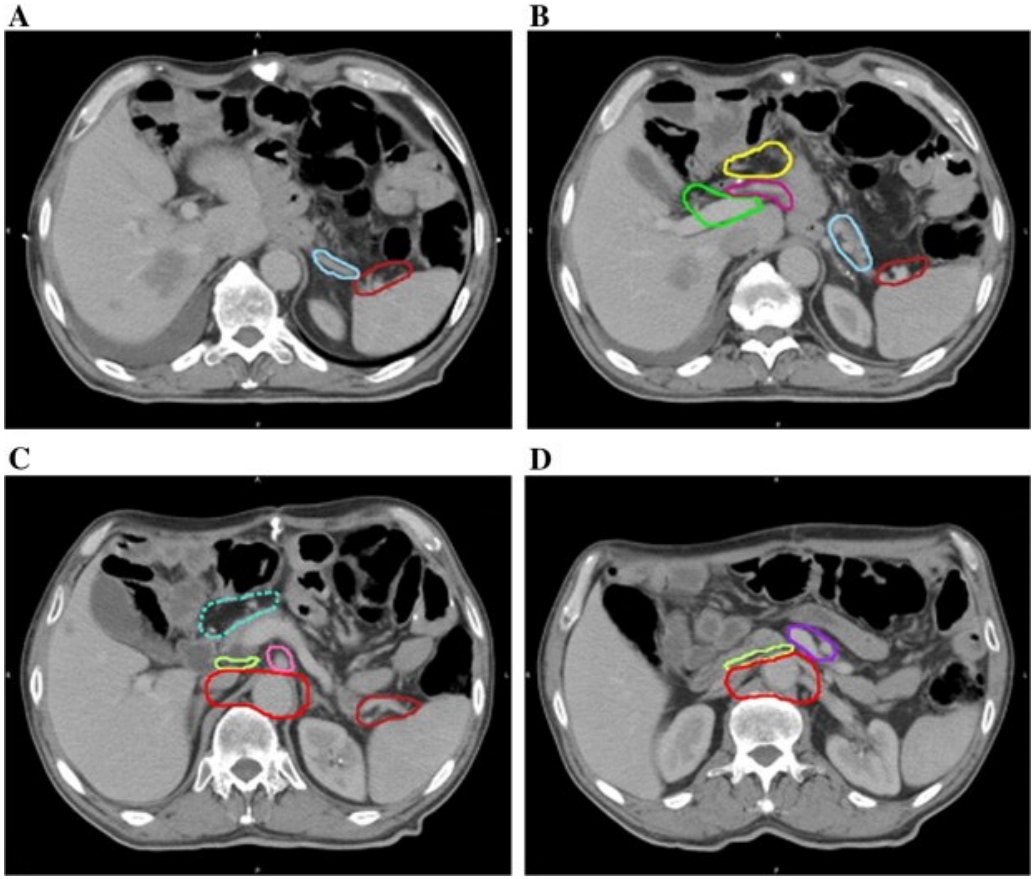
CTV DELINEATION: Postoperative Setting – Surgical Approach

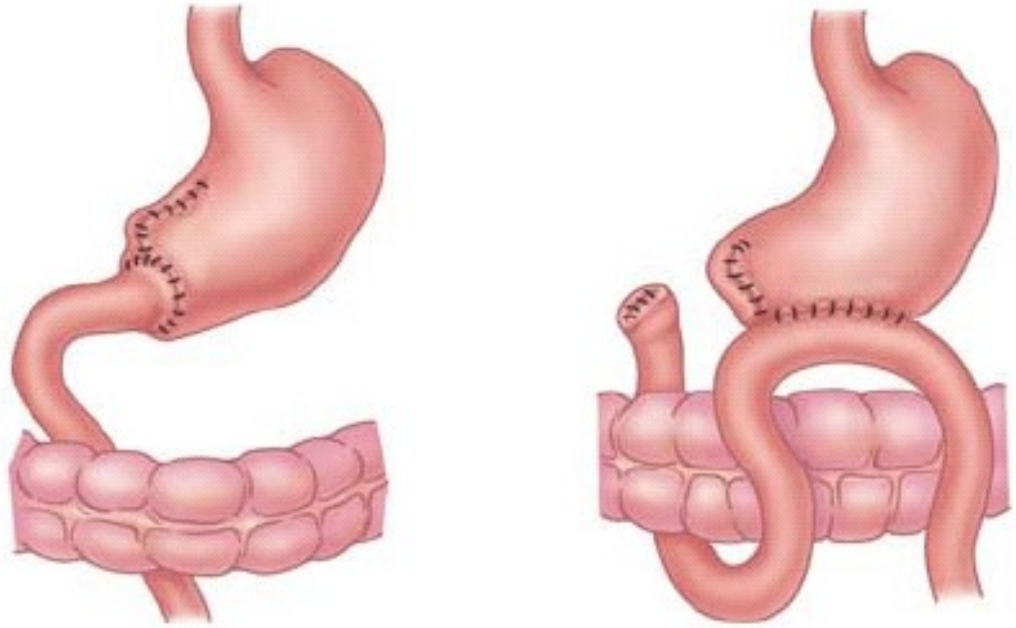


Roux-En-Y

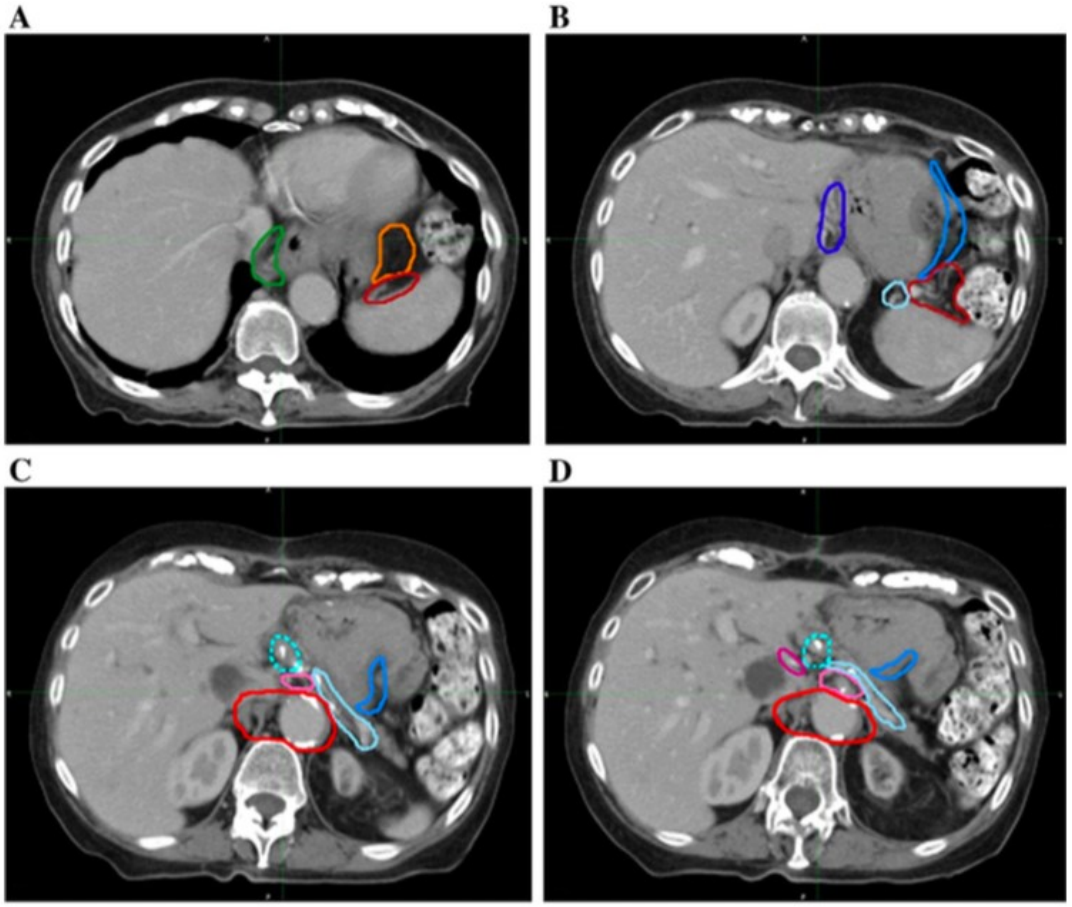
- Stomach removed (completely or partially) along with paracardial, lesser, greater curvature
- Supra- and infrapyloric LN should be identified

CTV DELINEATION: Postoperative Setting – Surgical Approach

Subtotal Gastrectomy



CTV DELINEATION: Postoperative Setting – Surgical Approach



Subtotal Gastrectomy

- Paracardial and portions of the lesser and greater nodes not dissected
- Infrapyloric and suprapyloric ideally removed

CTV DELINEATION: Guidelines

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Gastric Cancer

Proximal One-Third/Cardia/Esophagogastric Junction Primaries

- **Preoperative and Postoperative**
  - **With proximal gastric lesions or lesions at the esophagogastric junction (EGJ), a 3- to 5-cm margin of distal esophagus and nodal areas at risk should be included. Nodal areas at risk include: perigastric, celiac, splenic hilar, porta hepatic, and lymph nodes. Coverage of nodal areas may be modified based on clinical circumstances and the risks of toxicity.**

Middle One-Third/Body Primaries

- **Preoperative and Postoperative**
  - **Nodal areas at risk include: perigastric, suprapancreatic, celiac, splenic hilar, porta hepatic, and pancreaticoduodenal lymph nodes.**

Distal One-Third/Antrum/Pylorus Primaries

- **Preoperative**
  - **First and second part of duodenum should be included if the gross lesion extended to the gastroduodenal junction. Nodal areas at risk include: perigastric, suprapancreatic, celiac, porta hepatic, and pancreaticoduodenal lymph nodes.**
- **Postoperative**
  - **A 3- to 5-cm margin of duodenal stump should be included if the gross lesion extended to the gastroduodenal junction. Nodal areas at risk include: perigastric, suprapancreatic, celiac, porta hepatic, and pancreaticoduodenal lymph nodes.**

CTV DELINEATION: CONCLUSION

- Main setting of Target delineation is defined but still some issues remaining
- Refer to available Consensus recommendations
- Refer to Atlas to identify normal structures and target
- Refer to Surgeon and Radiologist into Multidisciplinar frame

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Dose issues in gastric tumor control

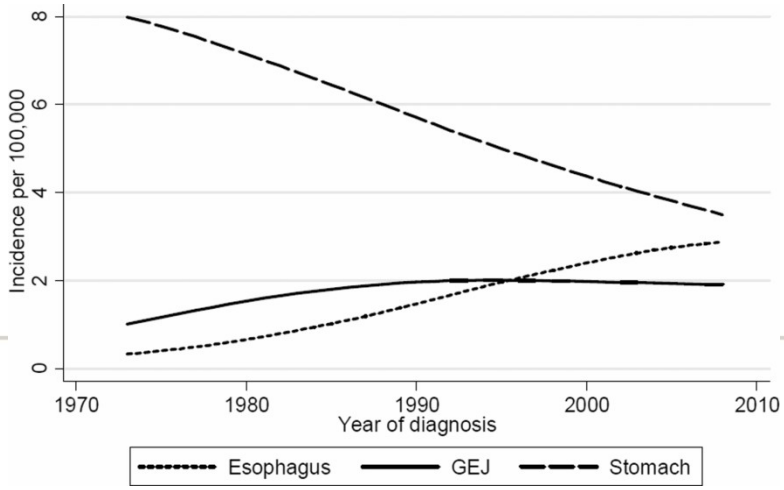
Marcel Verheij MD PhD
Department of Radiation Oncology
NKI, Amsterdam

Contents

- Introduction
- Current evidence-based treatment strategies
- Dose issue 1: efficacy
- Dose issue 2: toxicity

Epidemiology of gastric cancer

- Europe ~140,000 cases/year; ~107,000 deaths
- The Netherlands >2,000 cases/yr; ~1,000 deaths
- 3rd cause of death from cancer worldwide
- Distal cancers decreasing; tumors of cardia or GEJ increasing
- Proximal gastric cancer associated with reflux disease
- Distal gastric cancer associated with *H. pylori*
- 65% T3-T4; 85% N+; 30% liver metastases



Buas et al. Semin Radiat Oncol 2013

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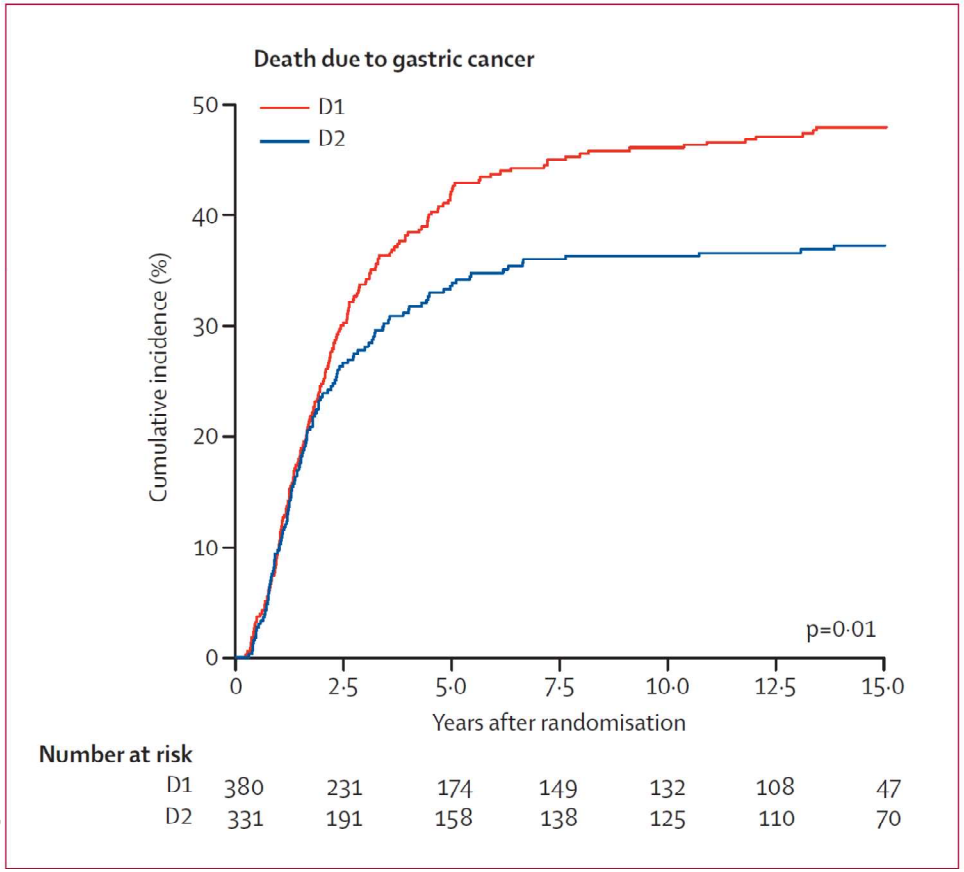
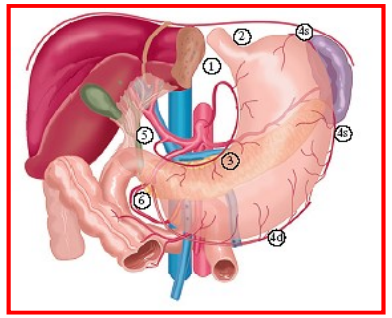
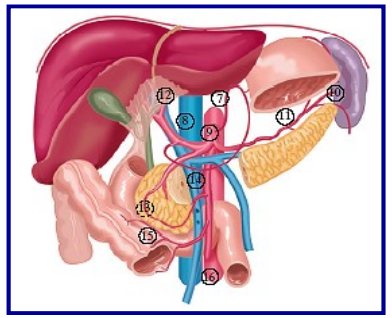
Surgical treatment of gastric cancer

15 years follow-up results D1-D2 study

D2 dissection (>15 ln) is the recommended surgical approach
(no splenectomy or pancreatectomy in specialized high-volume centers)







Songun et al. Lancet Oncol 2010

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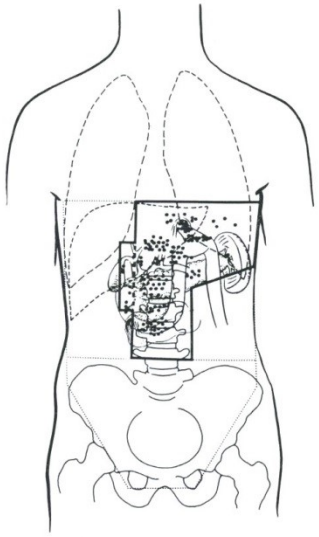
High locoregional failure rates after curative resection

Recurrences	Mean	Range
Locoregional - only	54%	(29-72%)
Locoregional - total	88%	(38-94%)
Distant - only	25%	(18-35%)



Gunderson et al. 1982; Smalley et al. IJROBP 2002; Lim et al. Br J Cancer 2004

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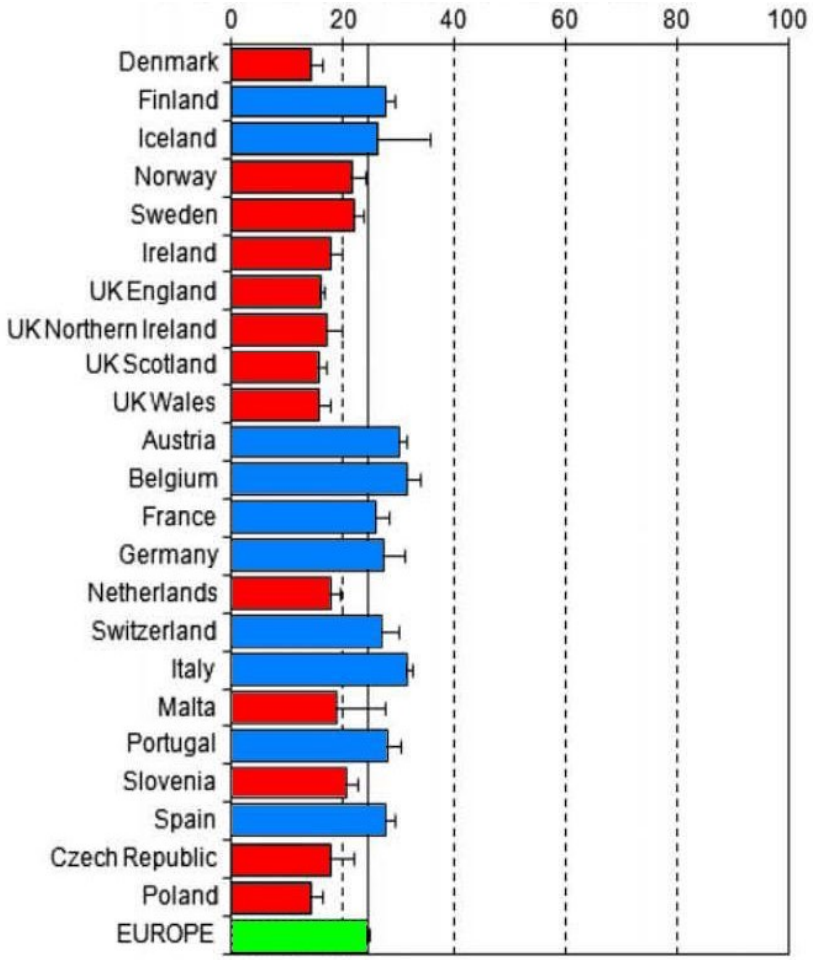
Survival of gastric cancer patients in Europe

Age-standardized 5-year relative survival (%)

1995-1999: EUROCARE-4



Sant et al. Eur J Cancer 2009

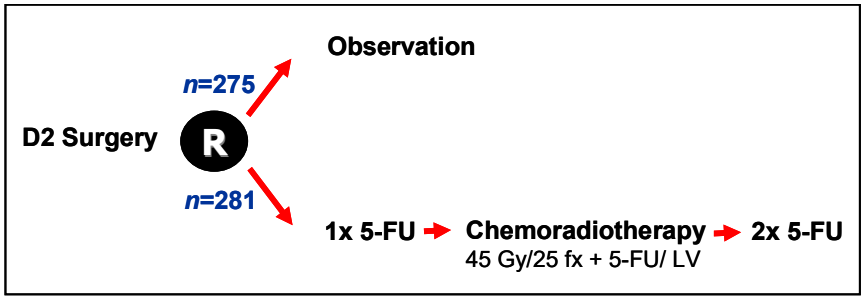
1999-2007: EUROCARE-5

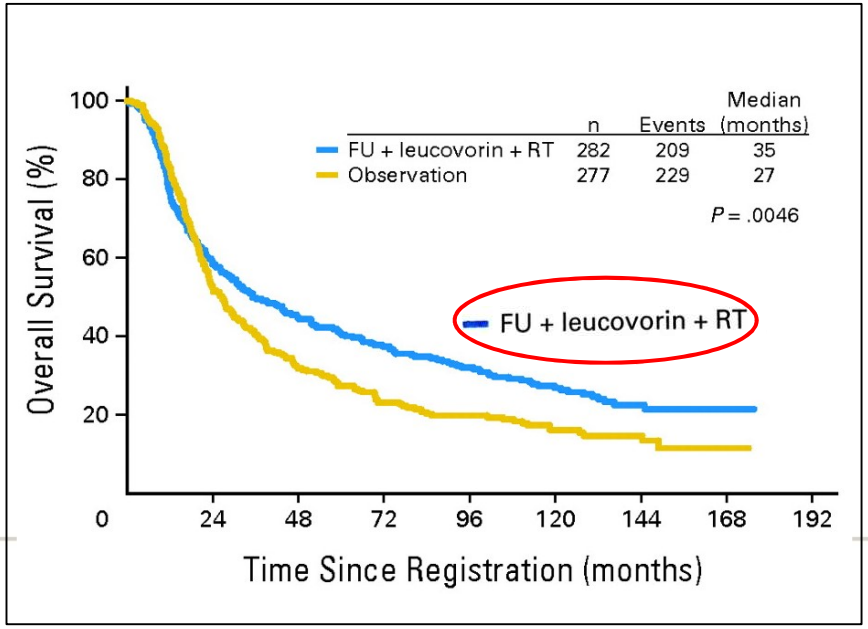
	Stomach cancer
European mean	25·1 (24·8–25·4)
Central Europe	28·1 (27·6–28·5)
Austria	31·0 (29·9–32·2)
Belgium*	30·5 (29·1–32·0)
France*	26·3 (24·9–27·6)
Germany*	31·3 (30·6–32·0)
Switzerland*	31·6 (29·2–34·1)
Netherlands	20·4 (19·7–21·2)

De Angelis et al. Lancet Oncol 2014

Evidence-based (neo-)adjuvant strategies (1)

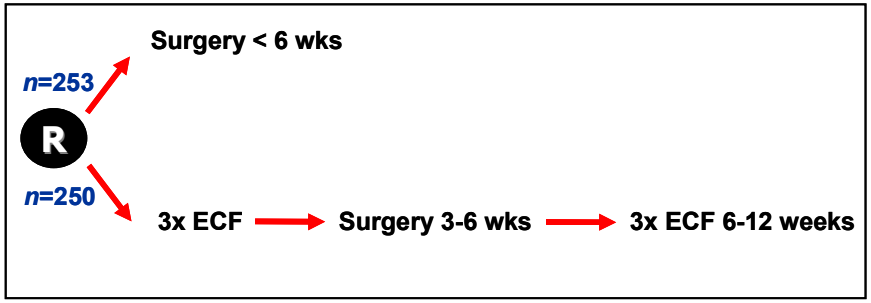
SWOG-Intergroup 0116 Trial

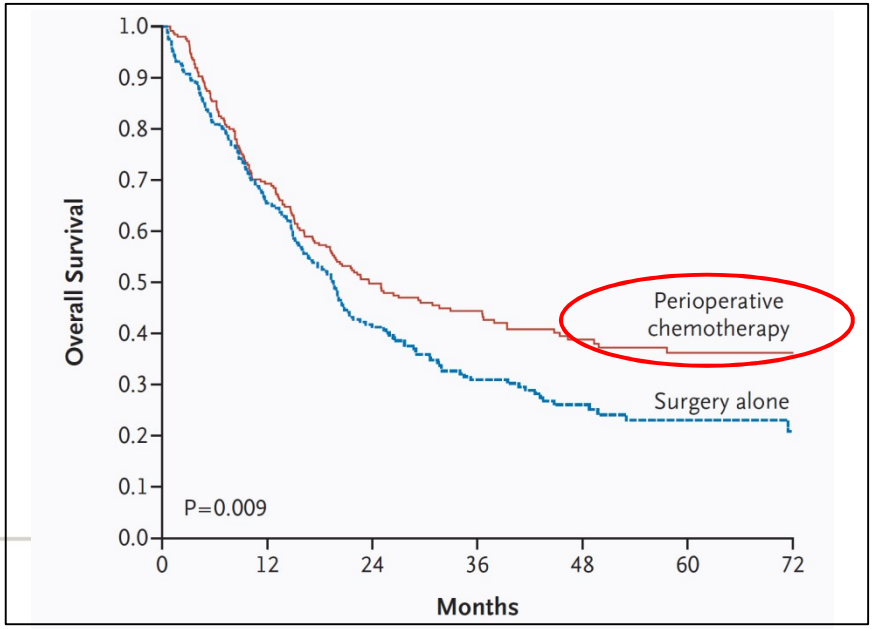




Macdonald et al. NEJM 2001; Smalley et al. JCO 2012

MAGIC Trial

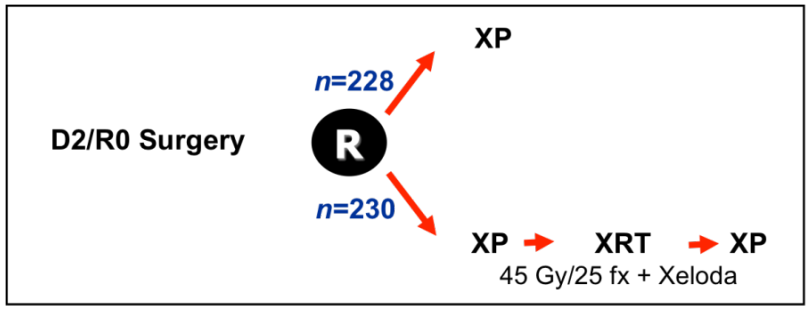


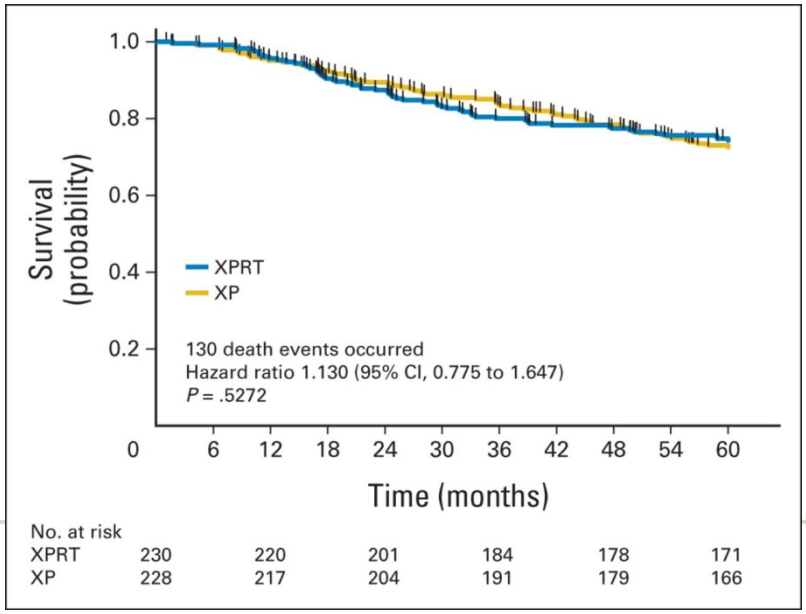


Cunningham et al. NEJM 2006

Evidence-based (neo-)adjuvant strategies (2)

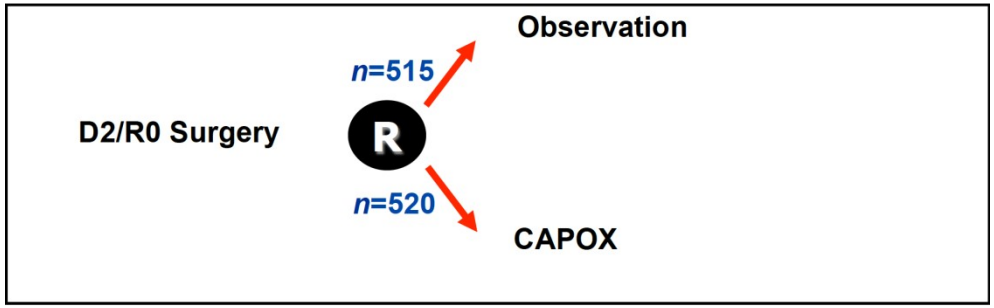
ARTIST Trial

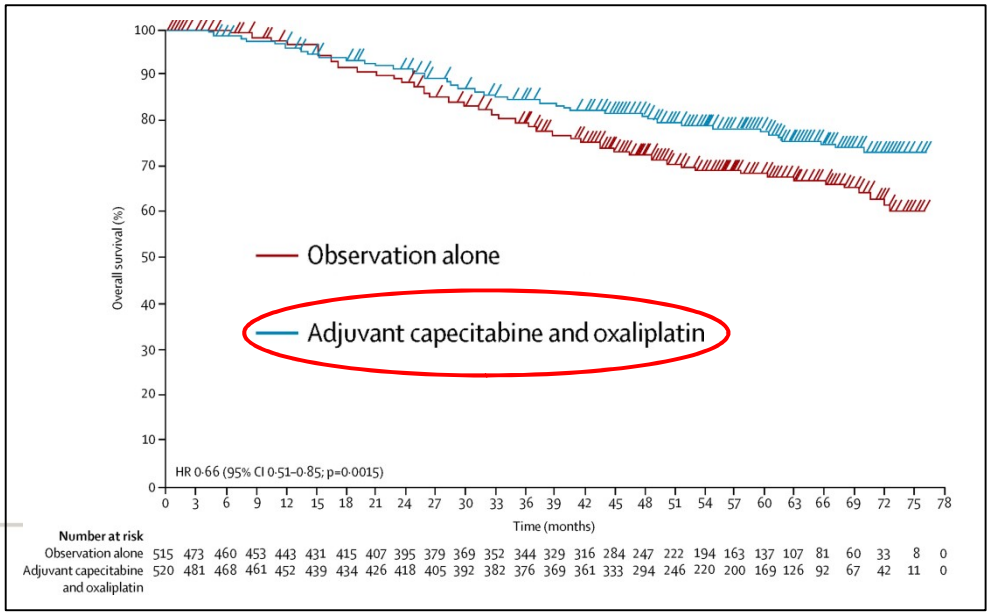




Lee et al. J Clin Oncol 2012; Park et al. J Clin Oncol 2015

CLASSIC Trial

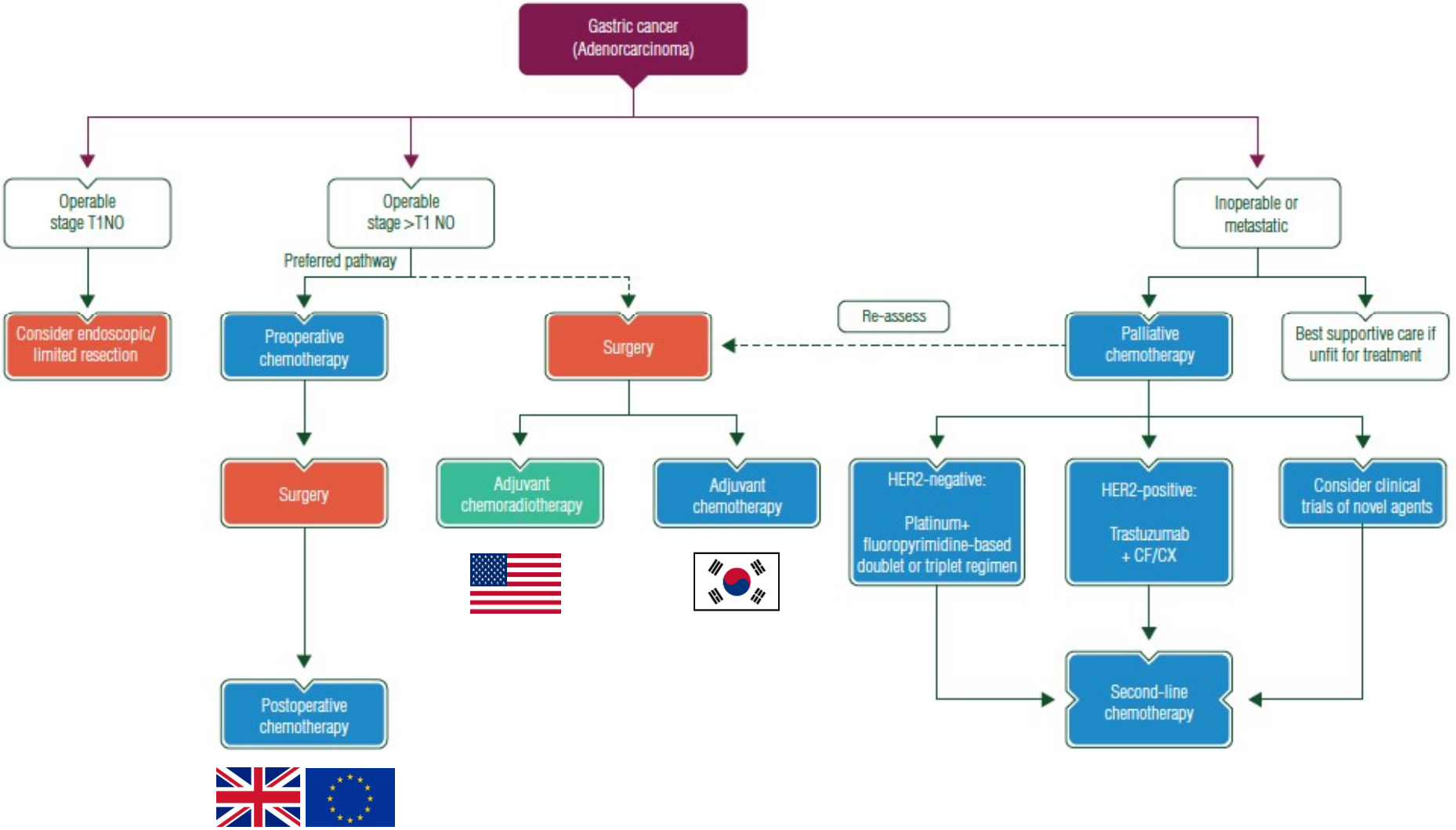




Bang et al. Lancet 2012; Noh et al. Lancet Oncol 2014

Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

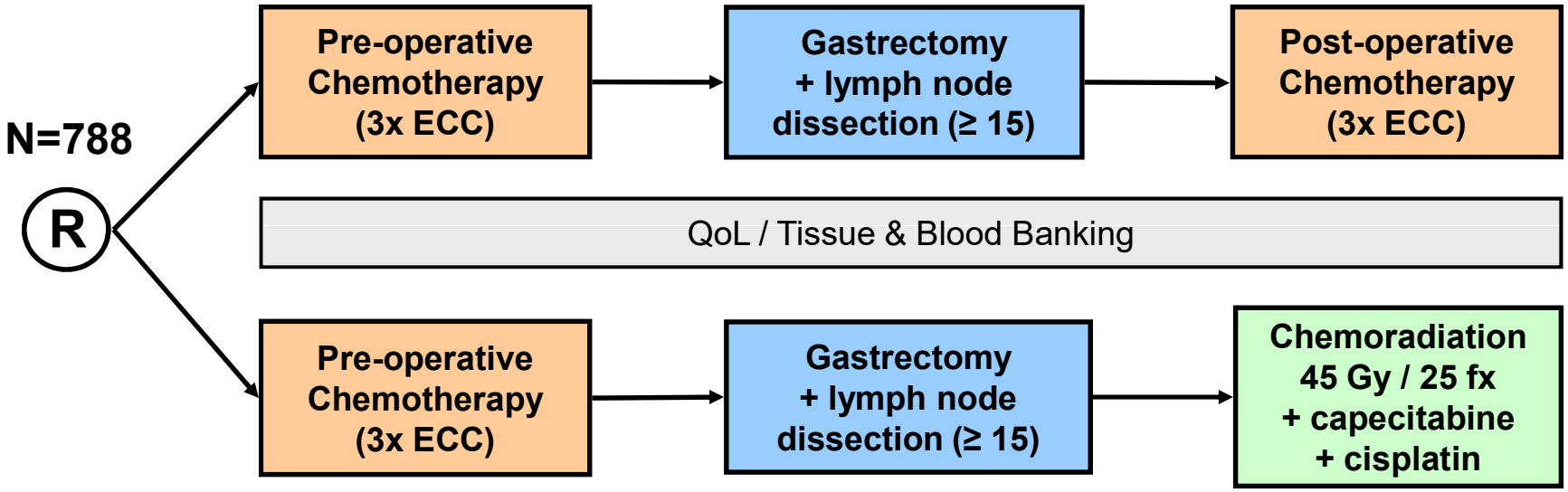
E. C. Smyth[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6] on behalf of the ESMO Guidelines Committee*



Ann Oncol 2016

CRITICS trial

- Study design -



www.CRITICS.nl; Dikken et al. BMC Cancer 2011

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CRITICS trial

- Baseline characteristics -

	CT n=393	CRT n=395	Total (%) n=788 (100)
Gender			
male	264	265	529 (67)
female	129	130	259 (33)
Age: median (IQR)	62 (54;69)	63 (56;68)	62 (55;69)
WHO			
0	260	273	533 (68)
1	103	106	209 (26)
unknown	30	16	46 (6)
Localization			
GE-junction	68	67	135 (17)
proximal	79	84	163 (21)
middle	120	117	237 (30)
distal	126	127	253 (32)
Lauren classification			
intestinal	127	126	253 (32)
diffuse	116	117	233 (30)
mixed	20	22	42 (5)
unknown	130	130	260 (33)

CRITICS trial

- Results: surgery -

Curative resection	CT n=316	CRT n=332	Total (%) n=648 (100)
Type of gastrectomy			
total	163	164	327 (51)
distal/subtotal	141	159	300 (46)
esophageal-cardia	12	9	21 (3)
Type of lymph node dissection*			
D1+	149	167	316 (49)
D2	123	116	239 (37)
D3	5	4	9 (1)
none	6	5	11 (2)
unknown	33	40	73 (11)
Splenectomy			
yes	22	17	39 (6)
Pancreatectomy			
yes	7	11	18 (3)

**Median Maruyama Index: 1 (n=610, 0-136)*

CRITICS trial

- Results: pathology -

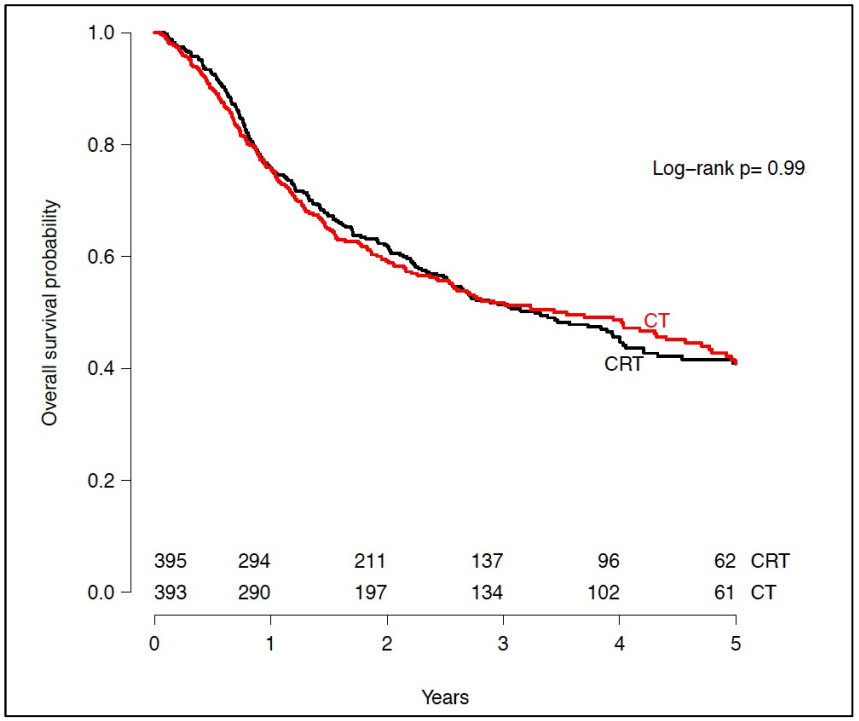
	CT n=316	CRT n=332	Total (%) n=648 (100)
Pathological T-stage			
pT0	18	21	39 (6)
pTis	0	5	5 (1)
pT1	41	45	86 (13)
pT2	111	112	223 (34)
pT3	113	108	221 (34)
pT4	30	35	65 (10)
unknown	3	6	9 (1)
Pathological N-stage			
pN0	149	158	307 (47)
pN1	111	108	219 (34)
pN2	37	43	80 (12)
pN3	15	19	34 (5)
unknown	4	4	8 (1)
Number of lymph nodes (median, range)	21 (0 - 72)	19 (0 - 71)	20 (0 - 72)

Central review in progress

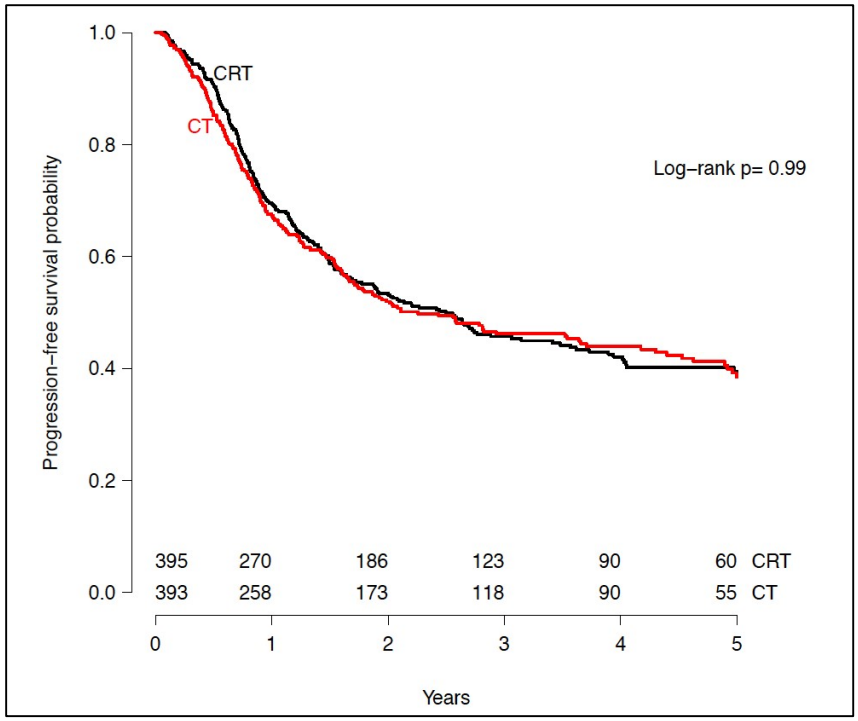
Verheij et al. ASCO 2016

CRITICS trial

- Results -



	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3



	CT	CRT
5-year PFS (%)	38.5	39.5
Median PFS (yrs)	2.3	2.5

Verheij et al. ASCO 2016

Summary (1): general

- *Gastric cancer has a poor outcome*

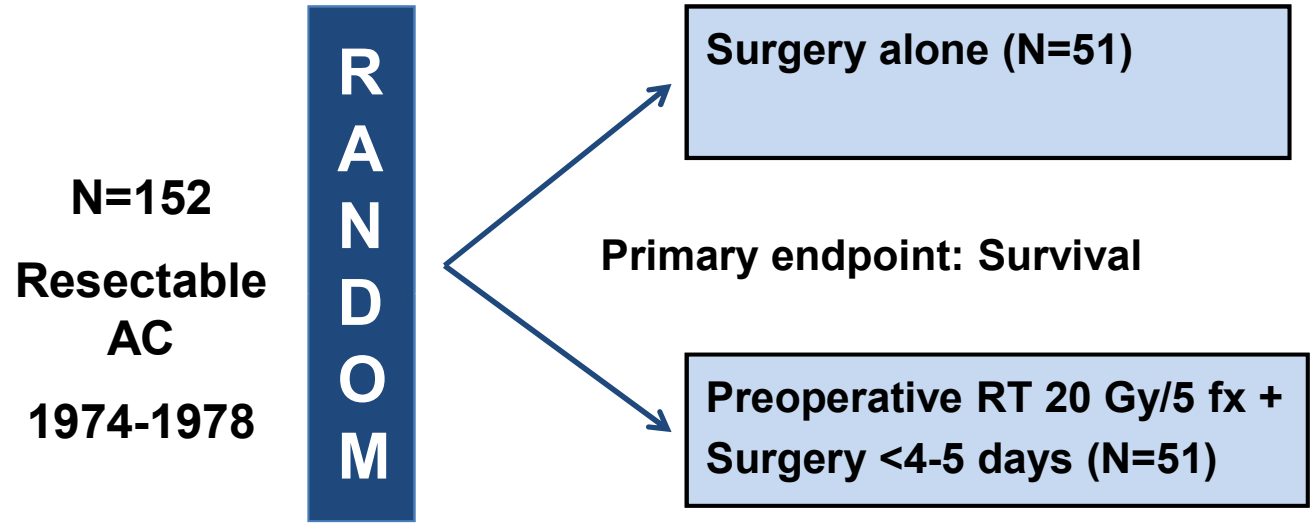
- *Despite adequate surgery (D2; ≥15 ln), local-regional recurrence rates remain high*

- *Evidence-based strategies to improve surgical results are:*

  - *post-operative chemoradiation (SWOG/US)*
  - *peri-operative chemotherapy (MAGIC/EU)*
  - *adjuvant chemotherapy (ARTIST, CLASSIC/Asia)*

- *CRITICS showed no difference between post-operative chemotherapy and post-operative chemoradiation after adequate surgery and pre-operative chemotherapy*

Pre-operative Radiotherapy



Skoropad et al. J Surg Oncol 2002

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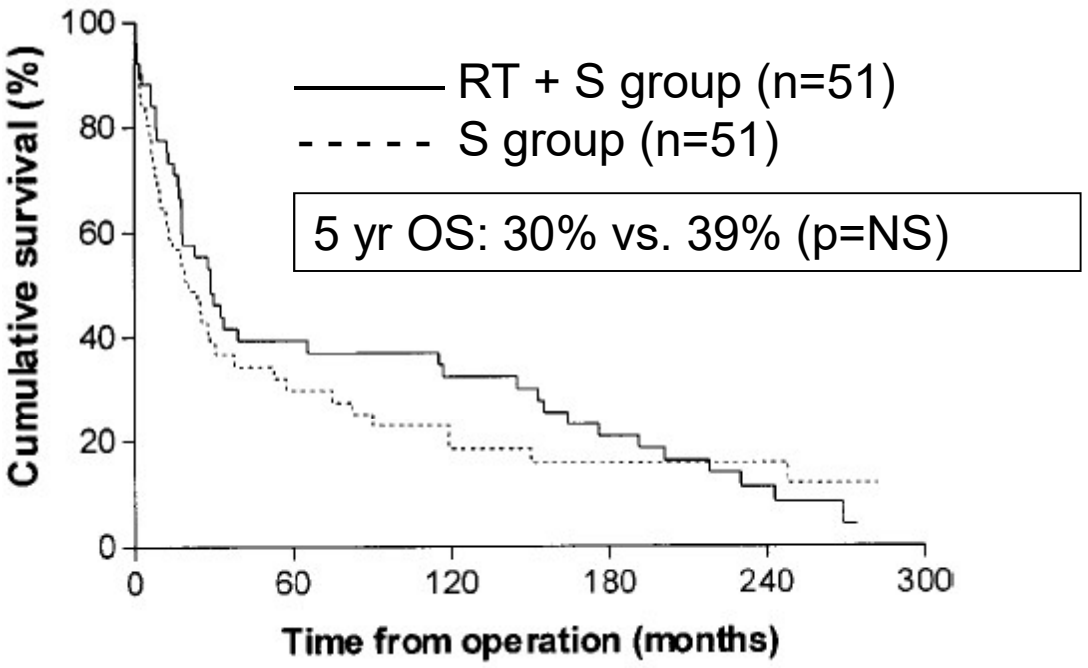
Pre-operative Radiotherapy

TABLE III. Early Postoperative Complications and Death*

Complications	Experimental group No.	Experimental group %	Control group No.	Control group %
Oesophago-jejunal anastomotic leakage	4 (3)	8 (6)	2 (1)	4 (2)
Oesophago-gastric anastomotic leakage	1	2	1 (1)	2 (2)
Duodenal stump leakage	2	4	1	2
Abdominal sepsis/abscess	6 (4)	12 (8)	6 (3)	12 (6)
Wound infection/dehiscence	1	2	1 (1)	2 (2)
Hemorrhage	2 (1)	4 (2)	4	8
Intestinal obstruction	0	0	1 (1)	2 (2)
Postoperative pancreatitis	4	8	9	18
Pleural/pulmonary	17	33	11	22
Myocardial infarction	1	2	0	0
Other	3 (1)	6 (2)	4 (1)	8 (2)
No. of patients with complications	29	57	25	49
No. of postoperative deaths	5	9.8	6	11.8

*Those requiring re-operation are in parentheses.



"Probably preoperative radiotherapy at a dose of 20 Gy is not sufficient to provide effective locoregional control (...)".

Skoropad et al. J Surg Oncol 2002

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Pre-operative Radiotherapy

N=370

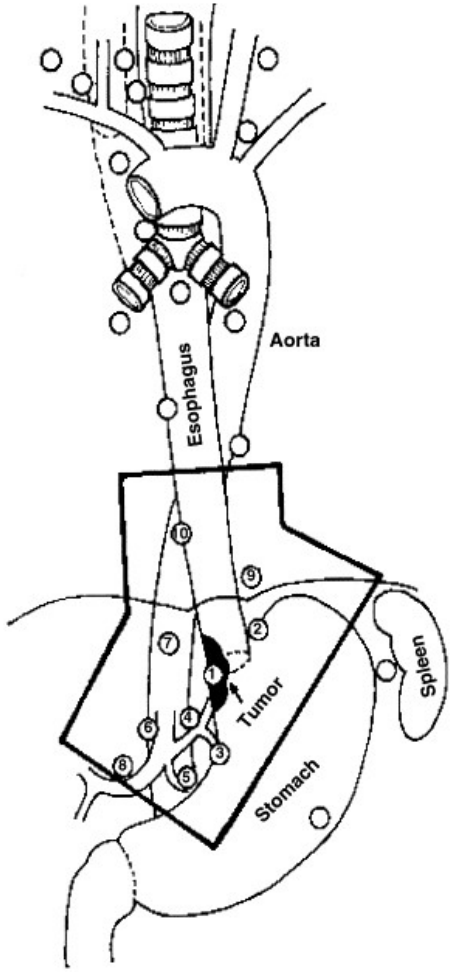
Gastric cardia

RANDOM

Surgery alone (N=199)

Primary endpoint: Survival

Preoperative RT 40 Gy/20 fx + Surgery <2-4 wks (N=171)



Zhang et al. IJROBP 1998

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Pre-operative Radiotherapy

Table 2. Immediate results of preoperative radiotherapy for AGC

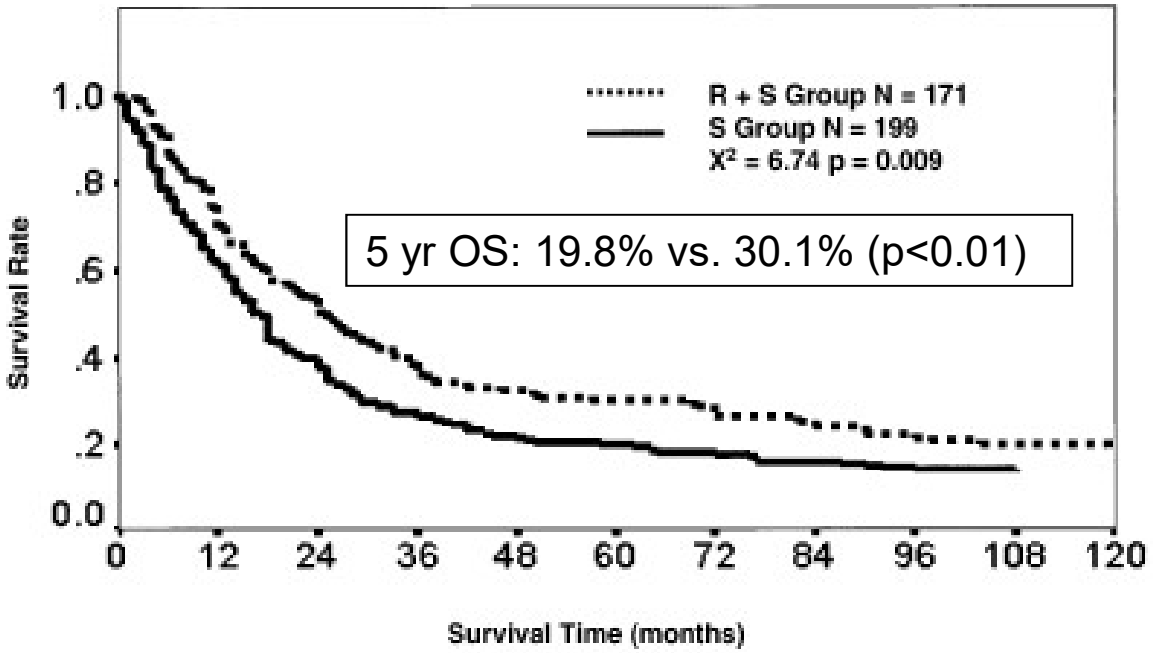
	R+S (n = 171) n (%)	S (n = 199) n (%)	Chi-square test, p value
Resectability	153 (89.5)	158 (79.4)	< 0.01 $\chi^2 = 6.97$
Radically resected	137 (80.1)	123 (61.8)	< 0.001 $\chi^2 = 15.80$
Palliatively resected	16 (9.4)	35 (17.6)	< 0.025 $\chi^2 = 5.24$
Explored only	18 (10.5)	41 (20.6)	< 0.01 $\chi^2 = 6.97$
Positive stump	8 (4.7)	8 (4.0)	$= 0.75$ $\chi^2 = 0.10$
T classification			
T_1	1 (0.6)		
T_2	22 (12.9)	9 (4.5)	< 0.01 $\chi^2 = 8.34$
T_3	79 (46.2)	88 (44.2)	
T_4	69 (40.3)	102 (51.3)	< 0.05 $\chi^2 = 4.40$
Lymph node metastasis by No. of patient	110 (64.3)	169 (84.9)	< 0.001 $\chi^2 = 21.04$
by No. of node	375 of 1486 (25.24)	900 of 2565 (35.10)	< 0.0001 $\chi^2 = 42.35$

Table 3. Complications of surgery for AGC

Complications	R+S (n = 171) n (%)	S (n = 199) n (%)	Chi-square test p value
Operative mortality	1 (0.6)	5 (2.5)	> 0.05 $\chi^2 = 2.14$
Anastomotic leak	3 (1.8)	8 (4.0)	$= 0.2$ $\chi^2 = 1.64$

Zhang et al. IJROBP 1998

Pre-operative Radiotherapy



"To further improve the results (...), increase of the preoperative radiation dose to 45 or 50 Gy may be feasible".

Zhang et al. IJROBP 1998

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Pre-operative Radiotherapy

Neoadjuvant Radiation Therapy Does Not Increase Perioperative Morbidity Among Patients Undergoing Gastrectomy for Gastric Cancer

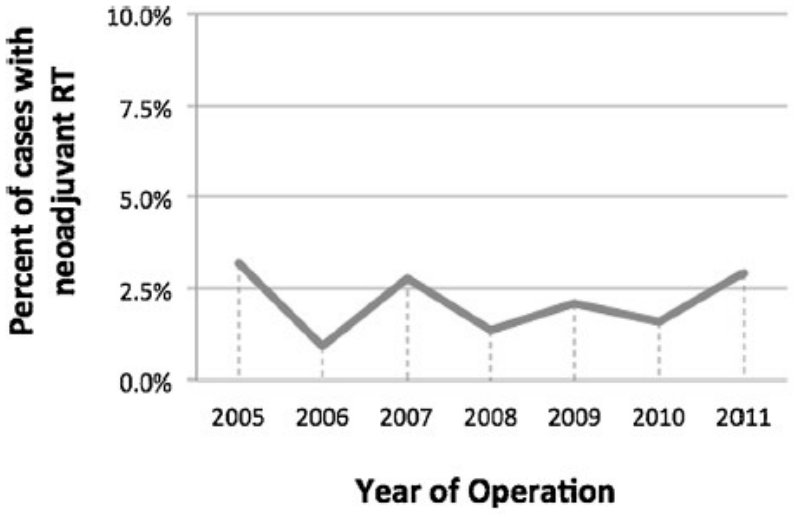
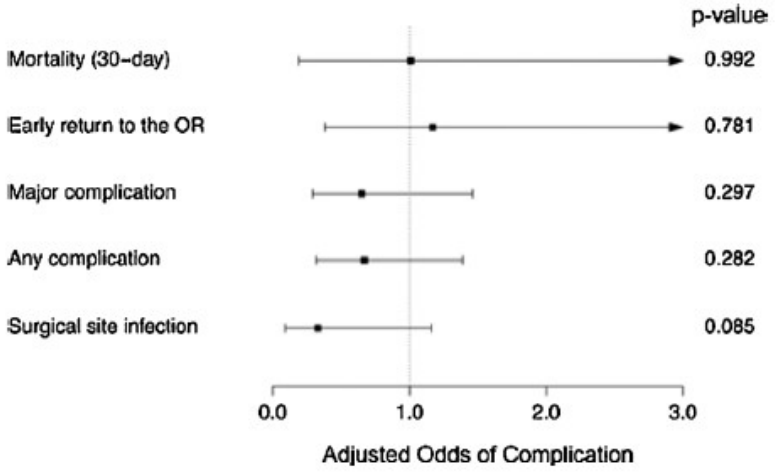


TABLE III. Adjusted Outcomes After Propensity Matching Between Patients Who Did and Did Not Receive Neoadjuvant Radiation Therapy (RT)

Variable	No RT n = 165	Preop RT n = 55	*P*-value
Mortality (30d)	6 (3.6%)	2 (3.6%)	0.99
Overall complication rate	49 (29.7%)	13 (23.6%)	0.48
Major complication rate	38 (23%)	10 (18.2%)	0.57



Sun et al. J Surg Oncol 2015

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Pre-operative chemoradiotherapy: phase I-II studies

Authors	Patients	RT	Chemotherapy	Surgery	Outcome
Allal et al. IJROBP 2005; Ann Oncol 2003	N=19 T3-4 or N+	Median dose 38.4 Gy (hyperfx)	2 cycles of Cisplatin (100 mg/m^2) d1; 5FU (800 mg/m^2) d1-4; leucovorin (60 mg bid) d1-4 Second cycle during RT	D2 with (sub) total gastric resection	R0 resection 100% pCR+pPR 47% 2yr OS 71%
Ajani et al. JCO 2004	N=34 T2-3, Nany or T1N1	45 Gy/25 fx	2 cycles of Cisplatin (20 mg/m^2) d 1-5; 5FU (200 mg/m^2) 21 days; leucovorin (20 mg^2) d1, 8, 15 During RT: 5FU (300 mg/m^2) dd conti. iv	D2 Median number lymph nodes examined: 16	R0 resection 70% pCR+pPR 54% 2yr OS 54%
Lowy et al. Ann Surg Oncol 2001	N=24 ≥T2 and/or N+	45 Gy/25 fx 10 Gy intra-operative	5FU c.i. (300 mg/m^2)	83% D2 Rest PD	11% pCR 63% sign treatment effect
Ajani et al. JCO 2005	N=41 T2-3N0-1 T1N1	45 Gy/25 fx	2 induction courses of fluorouracil, paclitaxel and cisplatin; 5FU and paclitaxel concurrent with RT	98% S 78% R0	pCR 20% pPR 15%
Ajani et al. JCO 2006	N=43 assessable [20 institutions] T2-3N0-1 or T1N1	45 Gy/25 fx	2 induction courses with 5FU, leucovorin and cisplatin; fluorouracil and paclitaxel concurrent with RT	50% D2	pCR 26% R0 77% Med surv 23.2 m 1yr surv 72%
Wydmanski et al. R&O 2007	N=40 TNM??	45 Gy/25 fx	4 5FU and LV based schedules (1st and last week of RT)	80% S (D2)	R0 94% pCR 17.5% pPR 20% 2yr surv 63%
Saikawa et al. IJROBP 2008	N=29 evaluable	40 Gy/20 fx	S1 (60 mg/m2/d) and Cisplatin (6 mg/m^2/d)	33% S D2; > 10 months	R0: 100% pCR: 4/30 (13.3%) Med surv 25 m
Trip et al. R&O 2014	N=25 II-IV (M0)	45 Gy/25 fx	weekly carboplatin and paclitaxel concurrent with RT	84% D1+	R0: 72% pCR: 16%
Combined	***19 - 43 pts***	***40 - 45 Gy***	***5FU/cis-/carboplatin/ paclitaxel***	***D2***	***R0: 70 - 100%*** ***pCR: 11 - 26%***

From: Trip et al. Transl Gastrointest Cancer 2015

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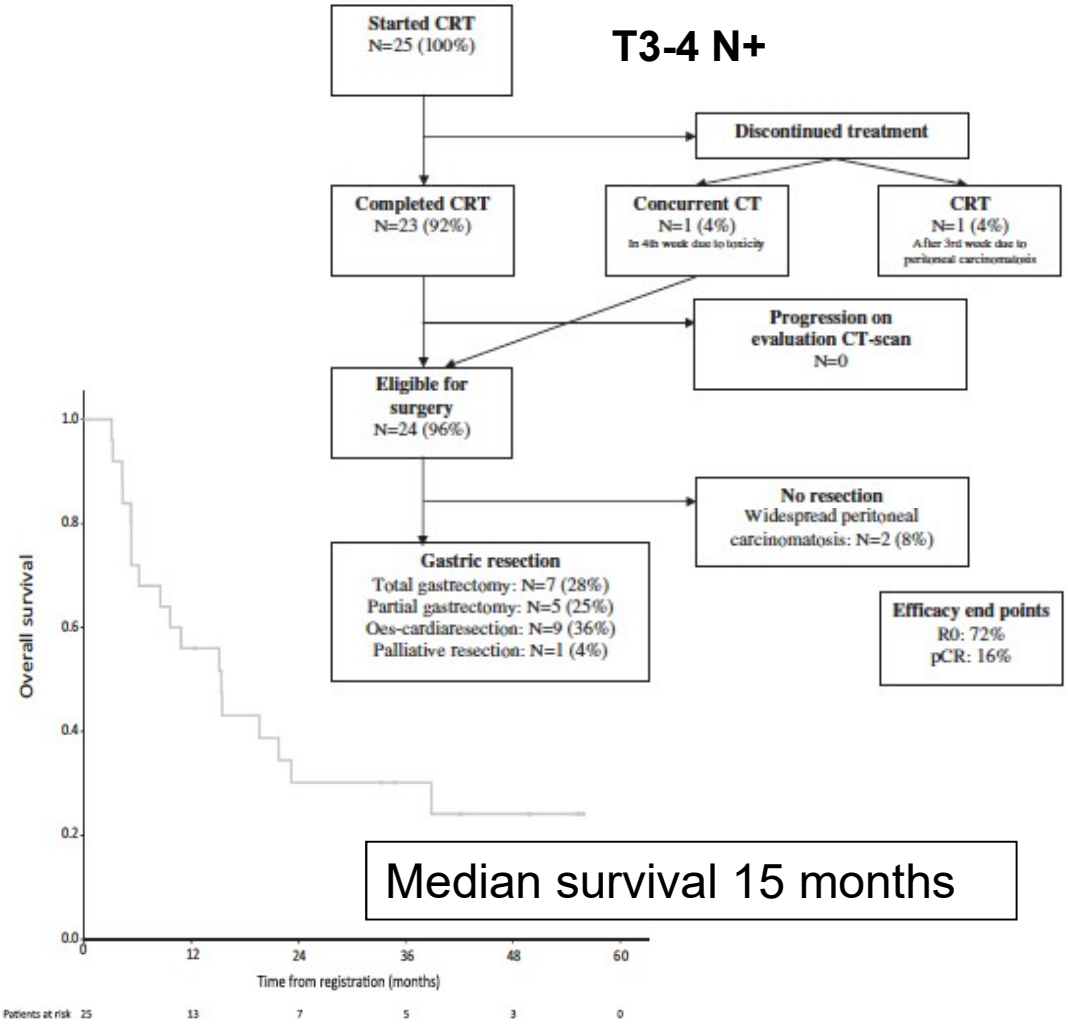
Pre-operative chemoradiotherapy: phase I-II study



Toxicity of chemoradiotherapy until surgery, and postoperative complications.

Toxicity of chemoradiotherapy $N = 25$	
Grade III adverse event	N (%)
Gastro-intestinal	
Oesophagitis	1 (4)
Anorexia	1 (4)
Nausea	1 (4)
Haematological/vascular	
Leucopenia	3 (12)
Febrile neutropenia	1 (4)
Thrombosis	1 (4)
Constitutional	
Fatigue	1 (4)
Postoperative complications $N = 22$	
Postoperative complications	N (%)
General complications	
Cardiac	5 (20)
Infectious complications	
Urinary tract infection	1 (4)
Pneumonia	3 (12)
Sepsis	3 (12)
Surgery related complications	
Anastomotic leakage	3 (12)
Bowel perforation	2 (8)
Death	
In-hospital and 30-day	1 (4)

Trip et al. R&O 2014

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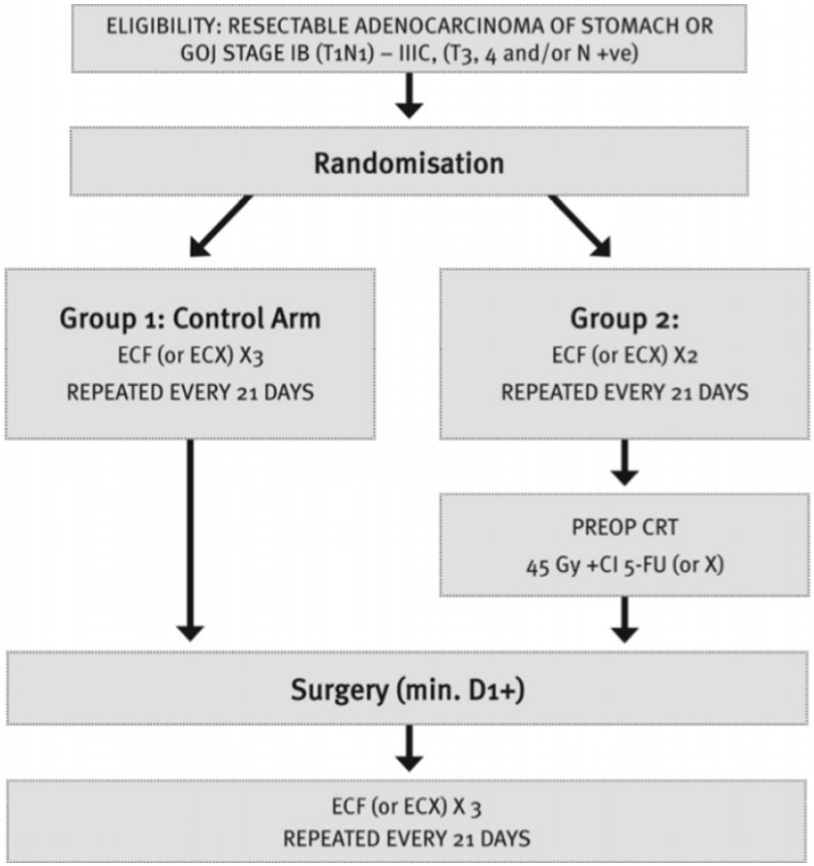
Pre-operative chemoradiotherapy is feasible and safe: early results from the TOPGEAR study

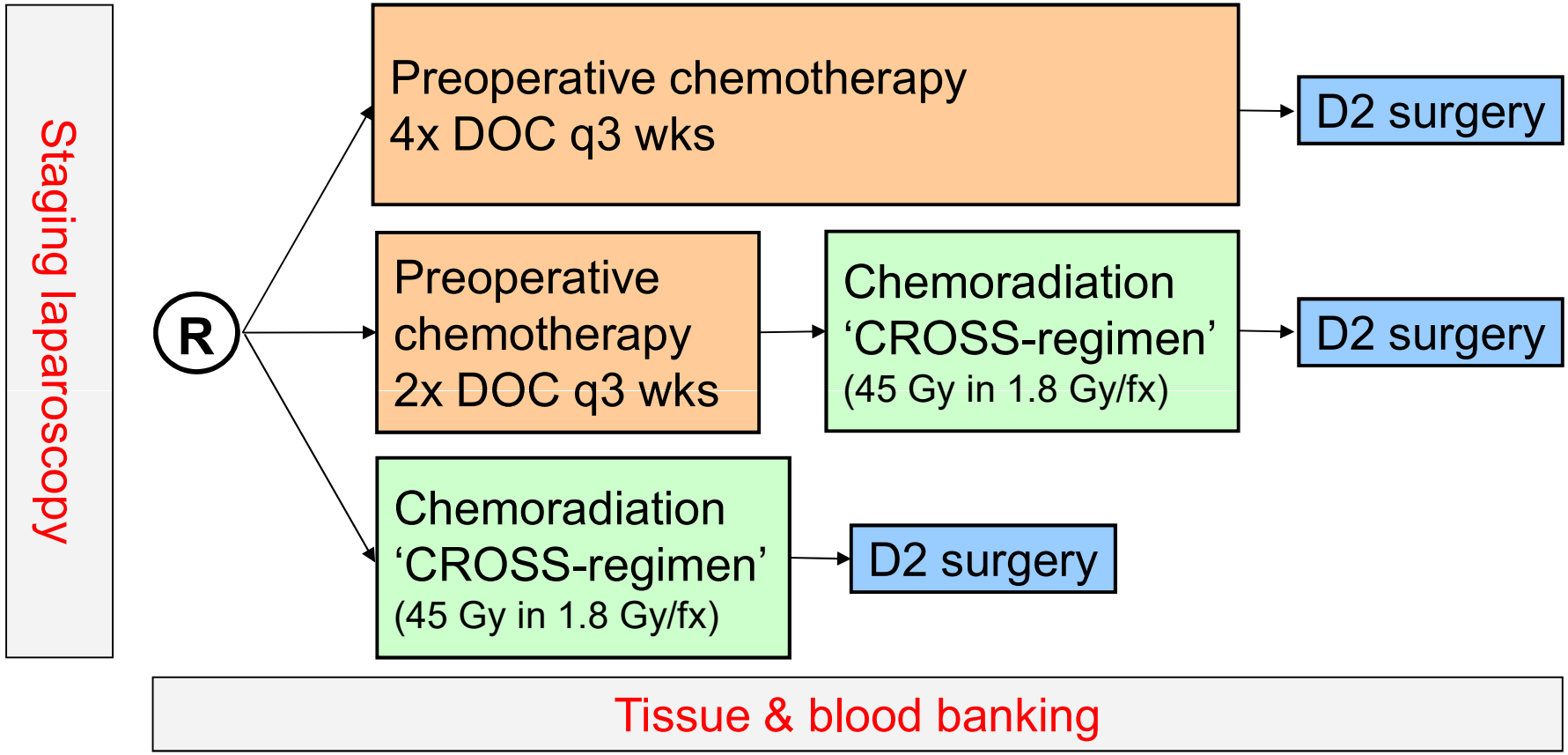


PART 1 (n=120):

- Grade ≥3 anastomotic leakage: 5.6% vs. 7.8%
- Grade ≥3 intra-abdominal sepsis: 7.4% vs. 5.9%

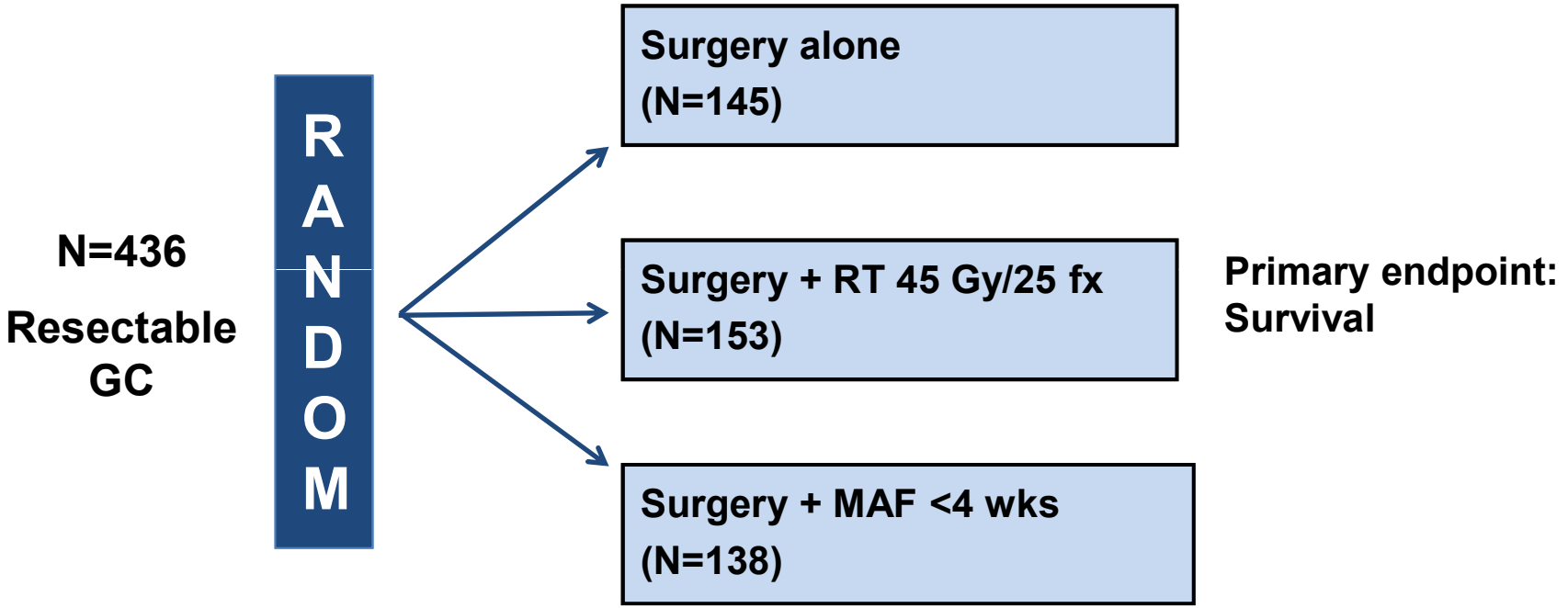
Leong et al. BMC Cancer 2015, ECC Vienna 2015

Design CRITICS-II



Post-operative Radiotherapy

British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer



Hallissey et al, Lancet 1994

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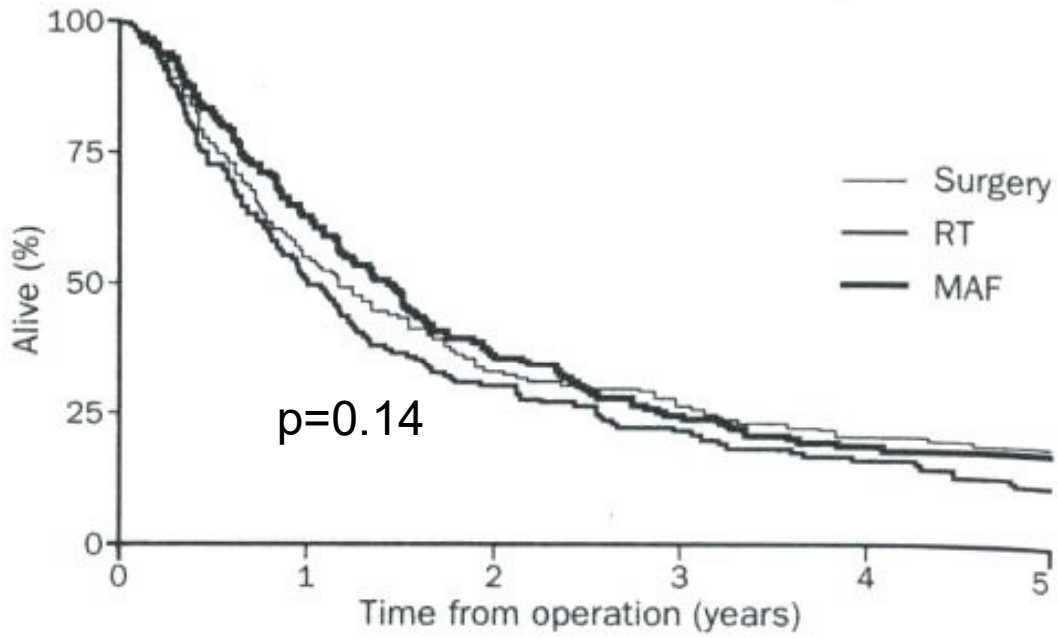
Post-operative Radiotherapy

British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer



No survival benefit

Treatment	No at risk						5 year OS	No adj Tx
S	145	81	49	40	31	29	20%	
RT	153	79	47	34	26	18	12%	24%
MAF	138	88	50	35	27	26	19%	17%

Hallissey et al, Lancet 1994

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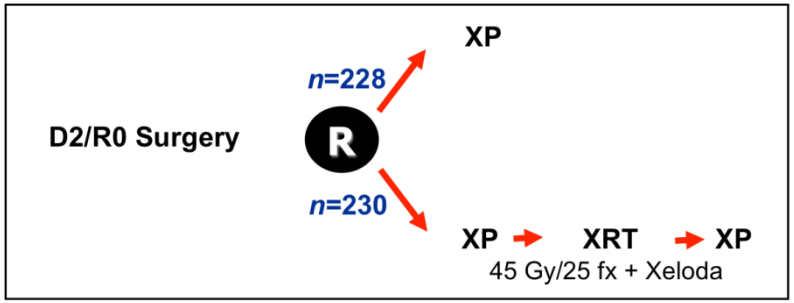
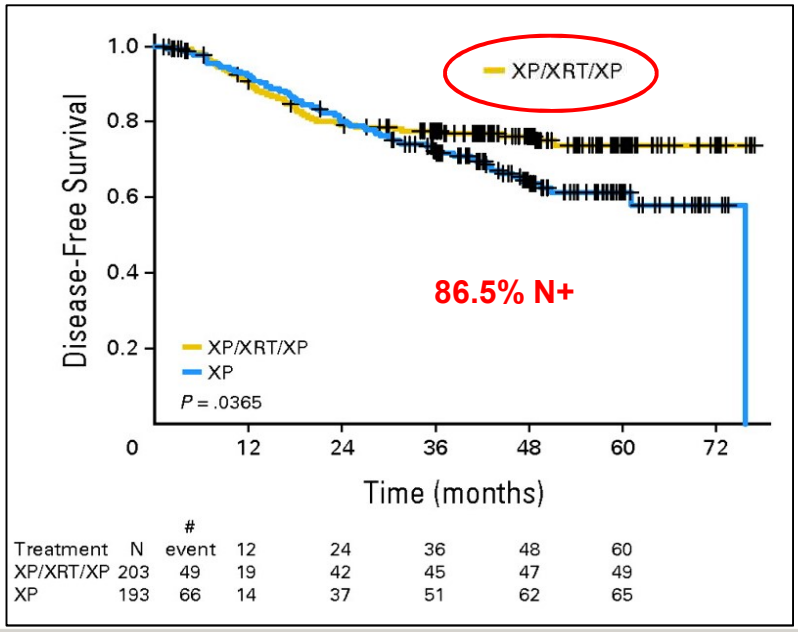
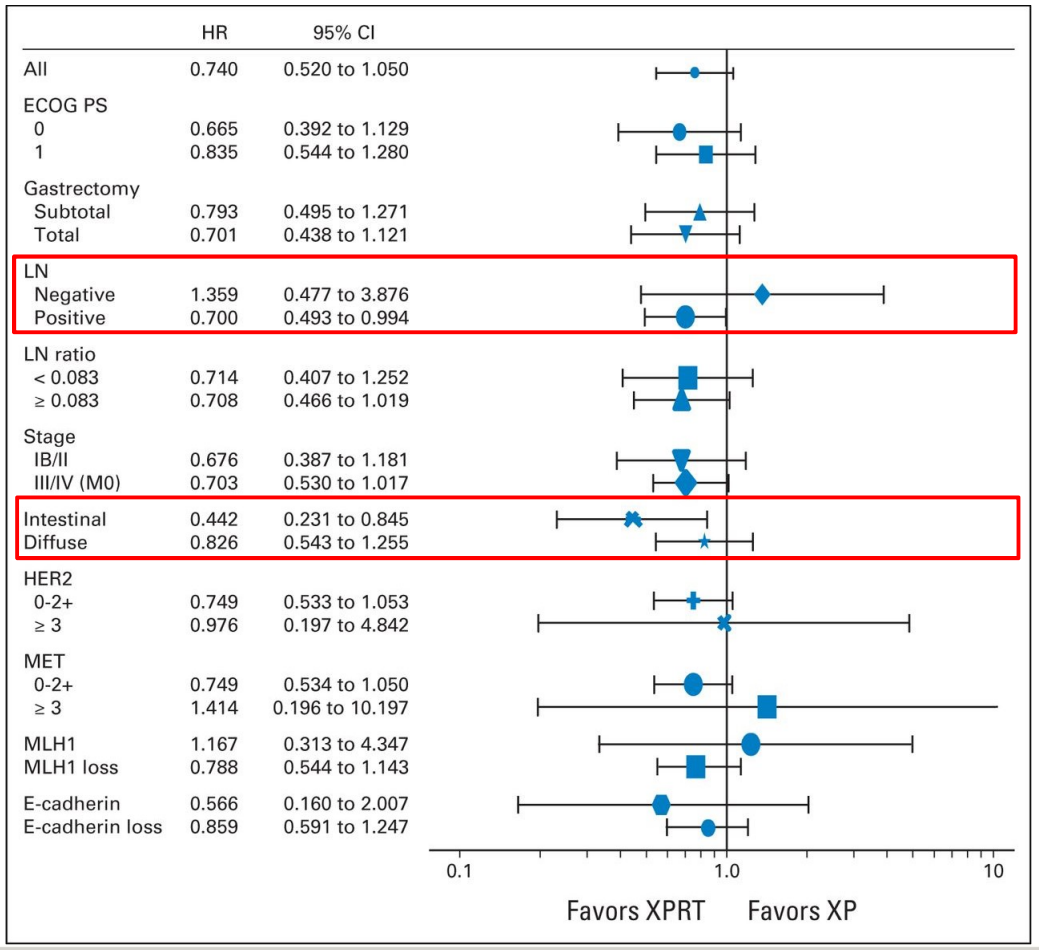
ARTIST Trial: Post-operative chemoradiotherapy improves DFS in lymph node-positive patients







Lee et al. JCO 2012

Park et al. JCO 2015

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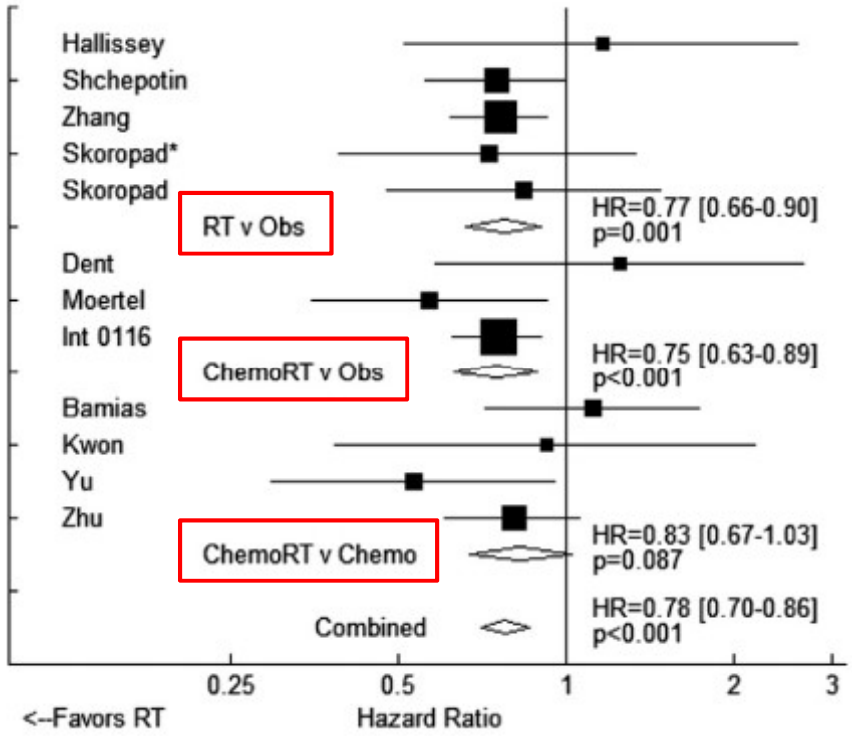
Who benefit from (neo)adjuvant (chemo-)radiation for gastric cancer? A meta-analysis (n=2811)



Ohri et al. IJROBP 2013

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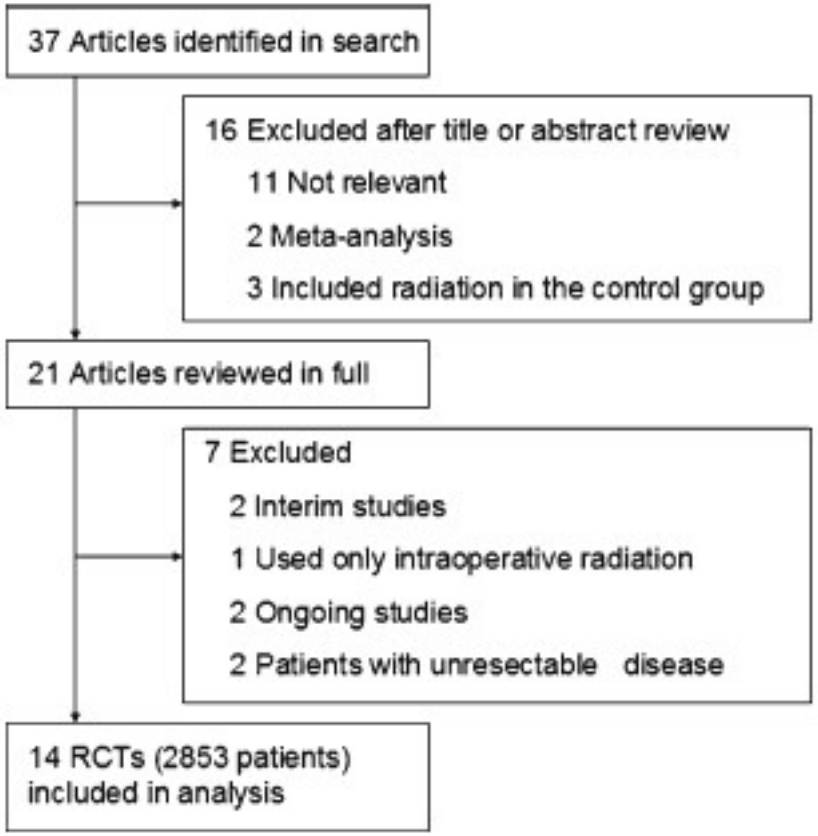
Benefit of Radiotherapy

Benefit of radiotherapy on survival in resectable gastric carcinoma: a meta-analysis



- Total dose range 20-45 Gy
- Daily dose range 1.56-5 Gy
- 5 preop; 9 postop

Li et al. Tumor Biol 2014

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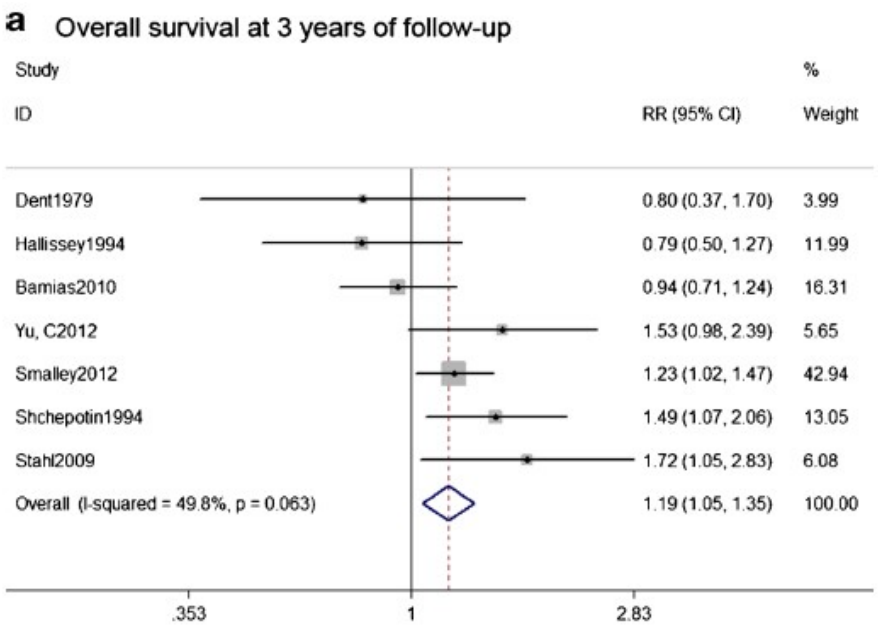
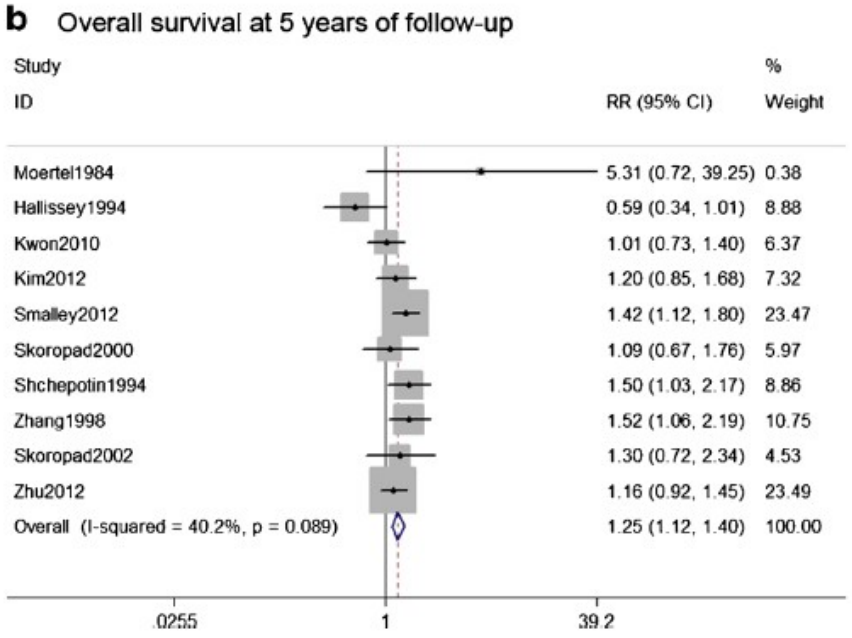
Benefit of Radiotherapy





- Adjuvant RT improves 3- and 5-year survival
- Trend favoring preoperative RT over postoperative RT

Li et al. Tumor Biol 2014

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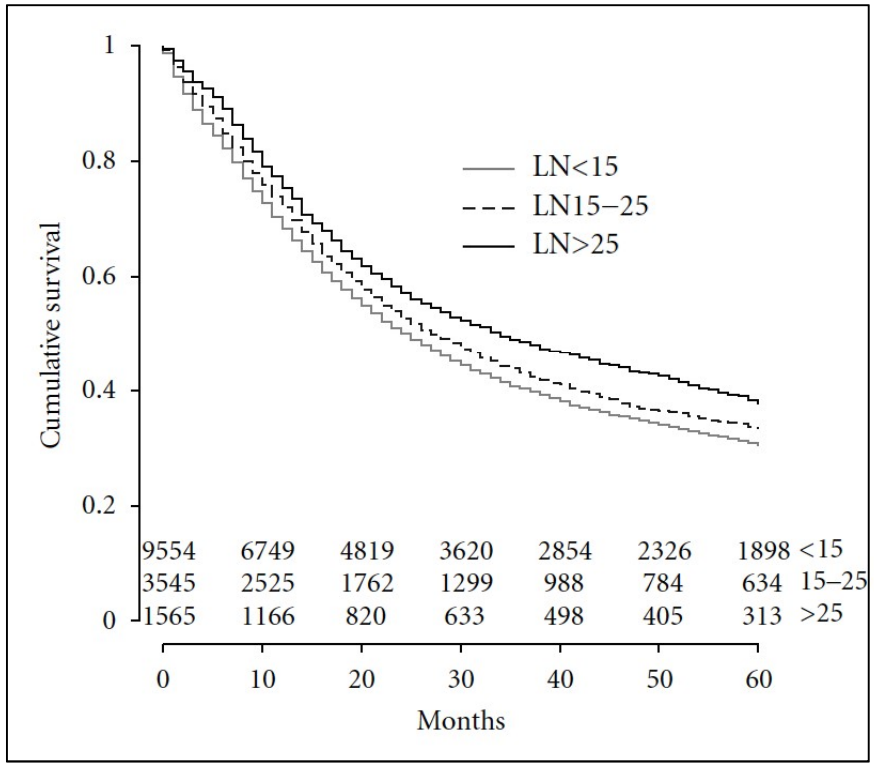
Benefit of Radiotherapy

SEER registry: Survival benefit of adjuvant chemoradiotherapy following gastrectomy persists after extended lymphadenectomy



Variable	HR	*P* value
No XRT	1.00	<0.001
Adjuvant XRT	0.67	
Age		
≤60	1.00	<0.001
>60	1.49	
Gender		
Male	1.00	<0.001
Female	0.88	
Race		
White	1.00	
Black	1.06	0.075
Other	0.77	<0.001
Lymph nodes		
LN <15 : >25	0.65	<0.001
LN 15–26 : >25	0.84	<0.001
Stage		
IA	1.00	
IB	1.689	0.004
II	3.08	<0.001
IIIA	4.44	<0.001
IIIB	6.02	0.003
IV (M0)	7.14	<0.001

Snyder et al. Int J Surg Oncol 2012

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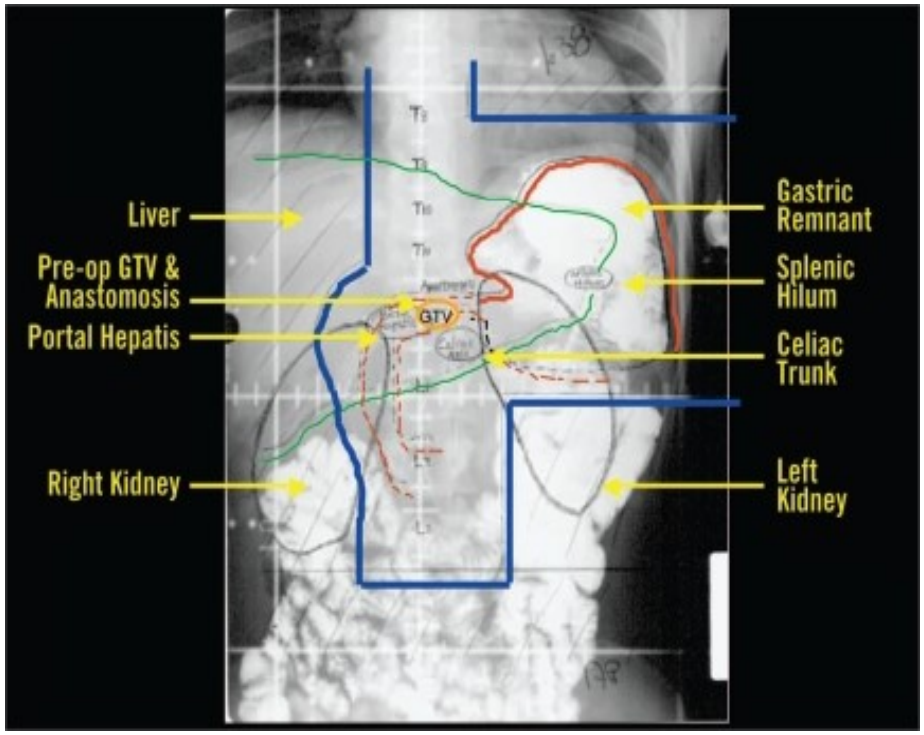
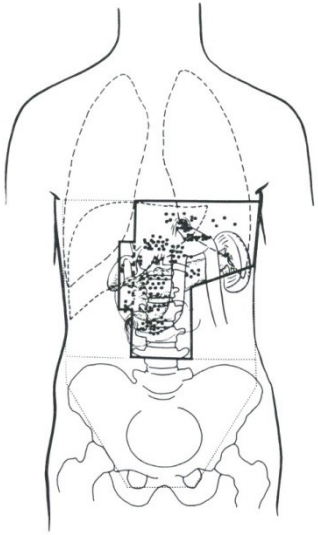
Summary (2): efficacy

- *Gastric cancer is relatively radioresistant and has a high tendency to recur locoregionally after surgery*
- *To obtain disease control, high radiation doses (>40-50 Gy) are required*
- *Radiotherapy alone in the pre- or post-operative setting is well-tolerated, but shows limited benefit*
- *Chemoradiotherapy shows the largest benefit*
- *Pre-operative chemoradiotherapy has advantages over post-operative treatment*

Radiotherapy-technique according to the SWOG protocol (2001)

2D AP-PA





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Adjuvant chemoradiotherapy vs. surgery

SWOG-Intergroup 0116 Trial: comments

Suboptimal surgery:

- only 10% underwent the advised D2 dissection; 54% < D1

Suboptimal radiotherapy:

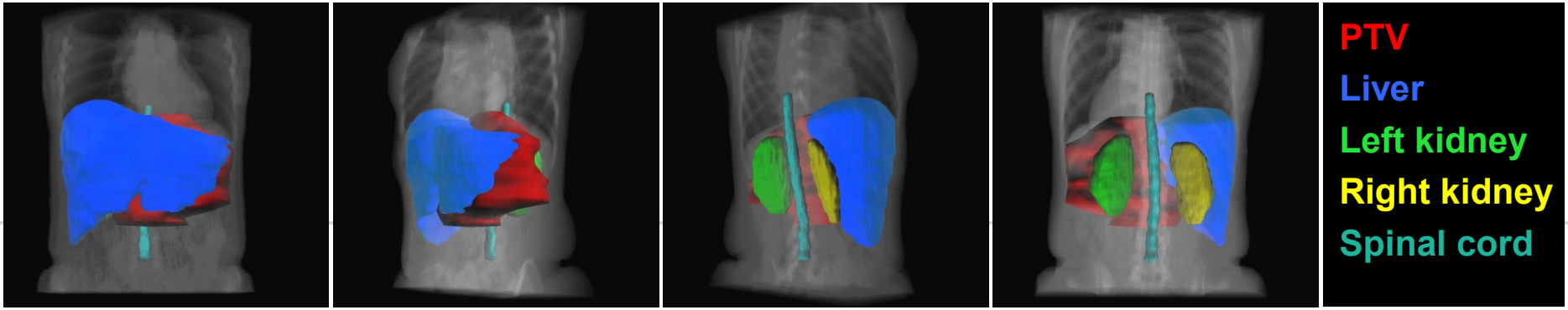
- 34% had major radiation treatment plan deviation
- outdated radiation techniques; no data on late toxicity (kidney)

Suboptimal chemotherapy:

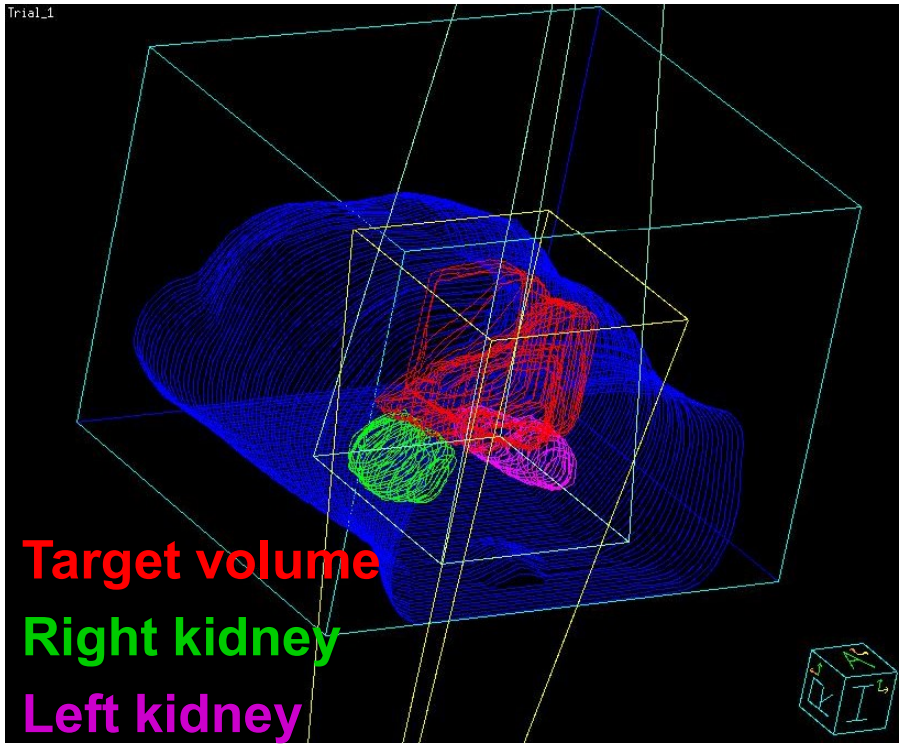
- according to present standard, chemotherapy was suboptimal and the interaction with radiation limited

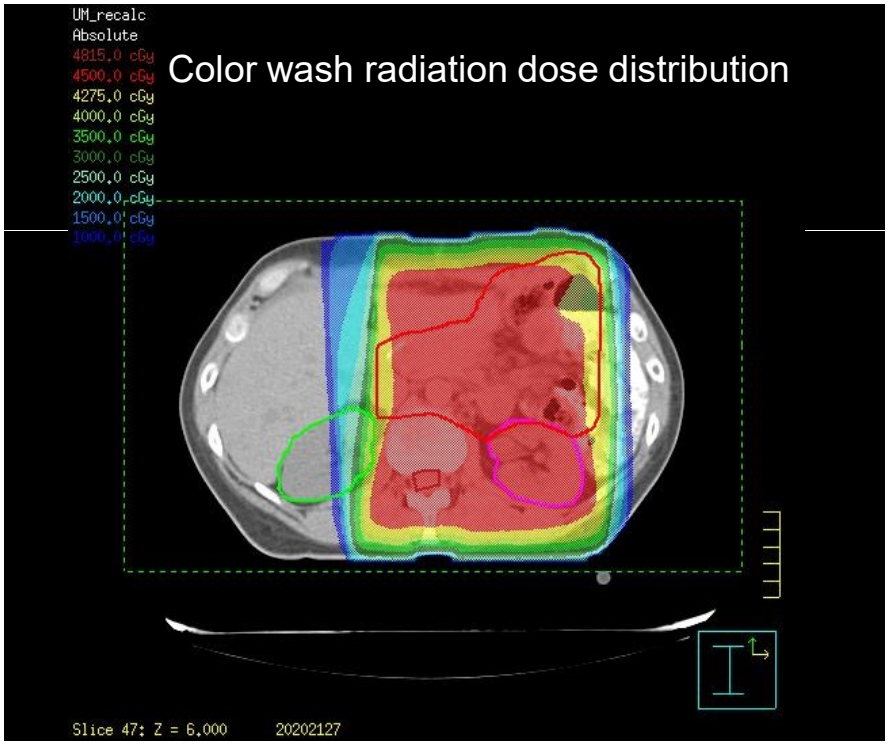
Critical structures and dose constraints

- Kidneys: at least 2/3 of the volume of 1 (right) normally functioning kidney should receive less than 18 Gy (i.e. 40% of the prescribed physical dose)
- Liver: EQD2 D_{mean} < 30 Gy (α/β=3)
- Heart: 3/3 <40 Gy; 2/3 <50 Gy; 1/3 < 66 Gy
  (<30% cardiac silhouette may receive 40 Gy)
- Spinal cord: EQD2 D_{max} ≤ 50 Gy (α/β=2)
- Spleen: ?



Late renal toxicity following postoperative chemoradiotherapy in gastric cancer





Jansen et al. IJROBP 2007

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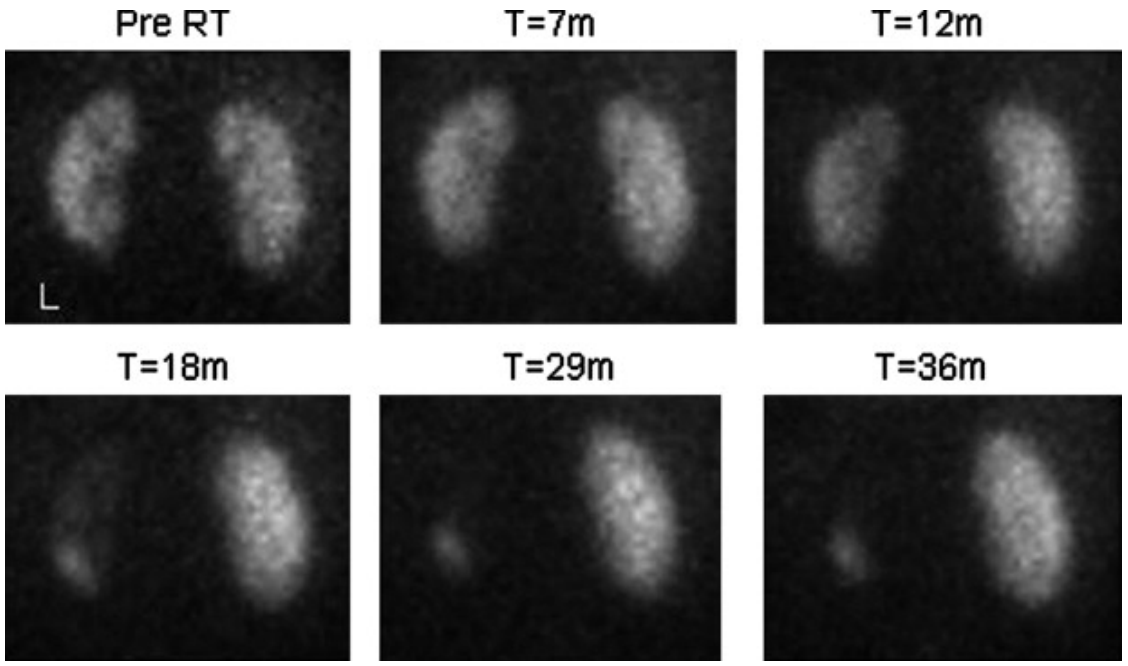
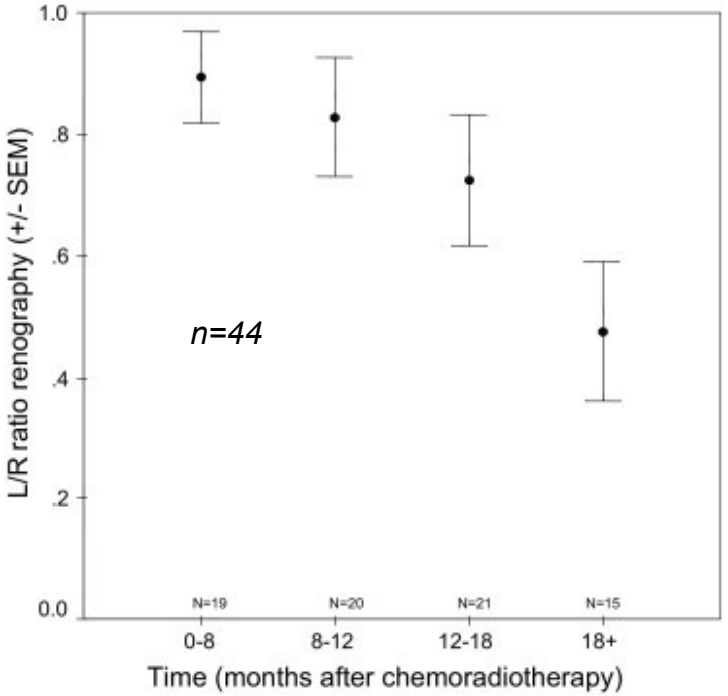
Late renal toxicity following postoperative chemoradiotherapy in gastric cancer





30-50% of patients with radiation nephropathy are at risk for (renovasular) hypertension (Verheij et al. IJROBP 1994)

Compensatory renal response after unilateral partial and whole volume high-dose irradiation of the human kidney (Dewit et al. Eur J Cancer 1993

Jansen et al. IJROBP 2007

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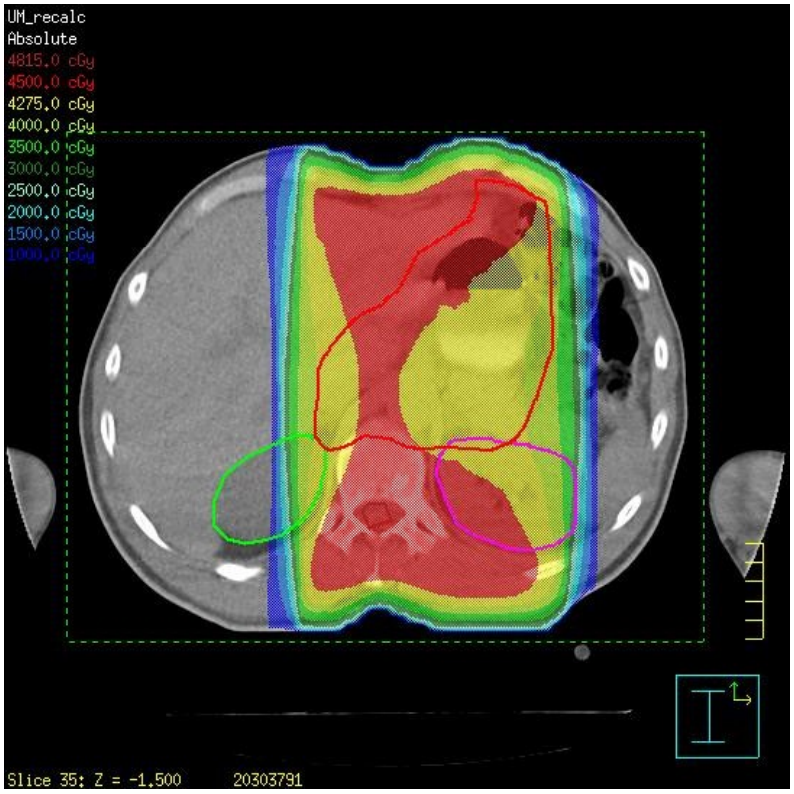
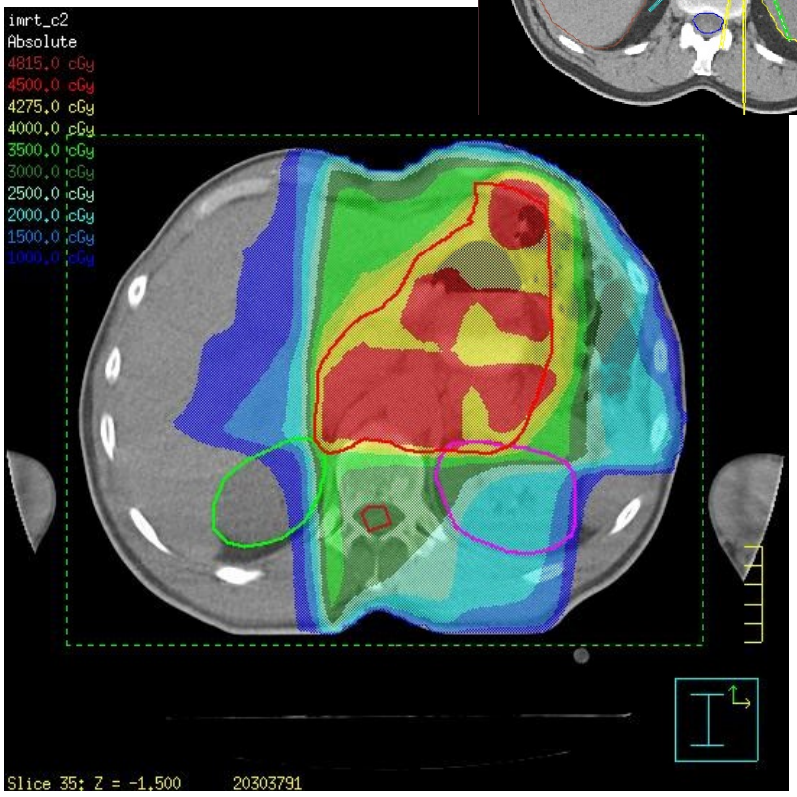
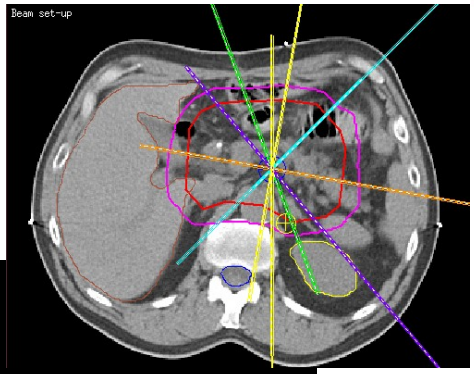
Advanced radiation techniques reduce the dose to both kidneys







Conventional AP-PA

IMRT

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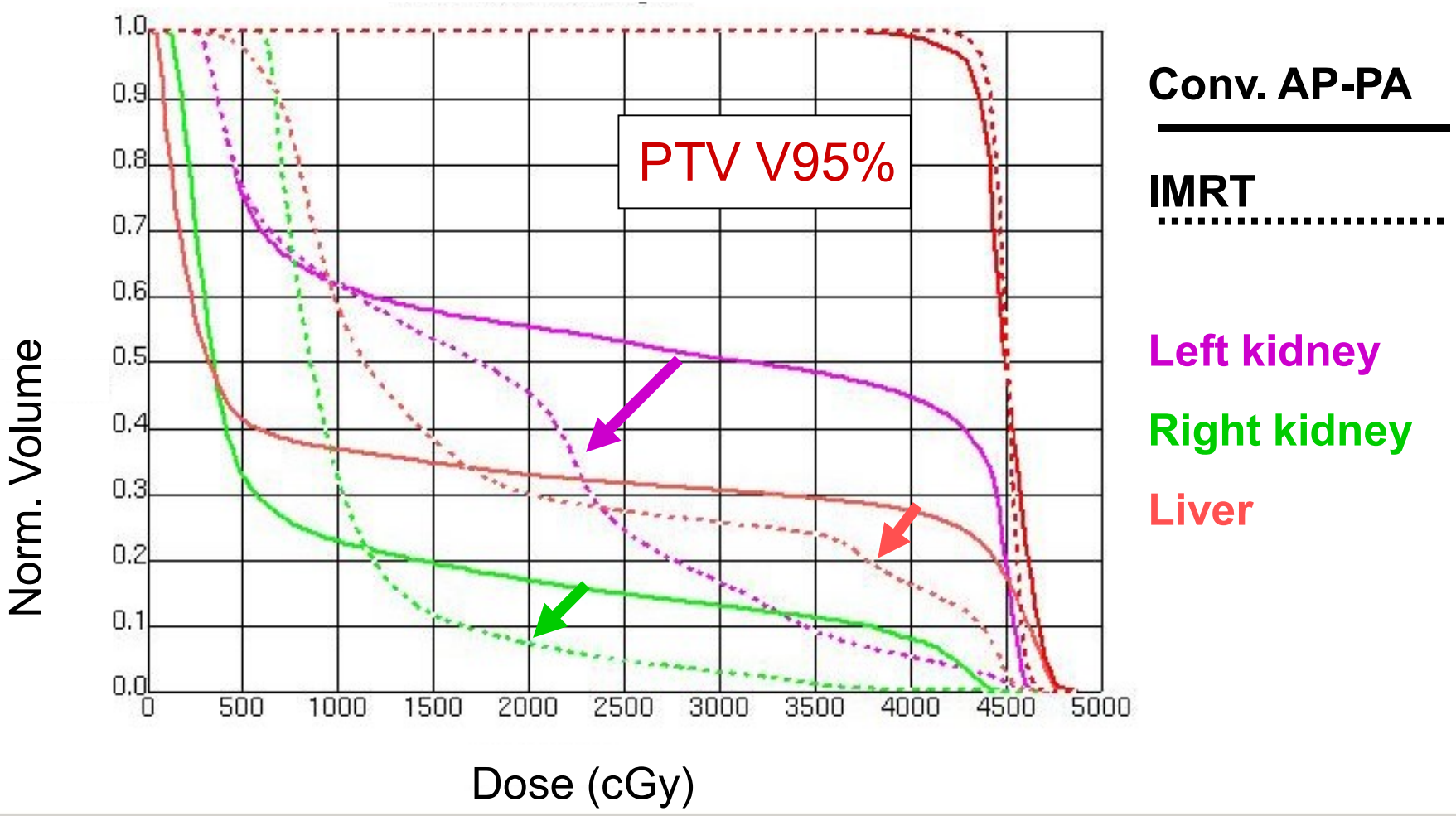
Advanced radiation techniques reduce the dose to both kidneys



Advanced radiation techniques reduce the dose to both kidneys

Organ/ROI	Conventional (AP-PA)	IMRT
Left kidney Mean dose (± SD)	34 ± 8 Gy	22 ± 3 Gy*
Left kidney V20Gy (± SD)	77 ± 19 %	54 ± 11 %**
Right kidney Mean dose (± SD)	10 ± 5 Gy	11 ± 2 Gy
Right kidney V20Gy (± SD)	17 ± 11 %	9 ± 5 %

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Liver Mean dose (± SD)	15 ± 3	18 ± 2
Liver V30Gy (± SD)	26 ± 6	21 ± 5
PTV V95% (± SD)	95 ± 3	98 ± 2

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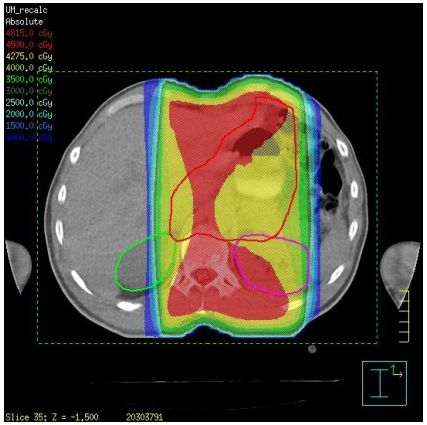
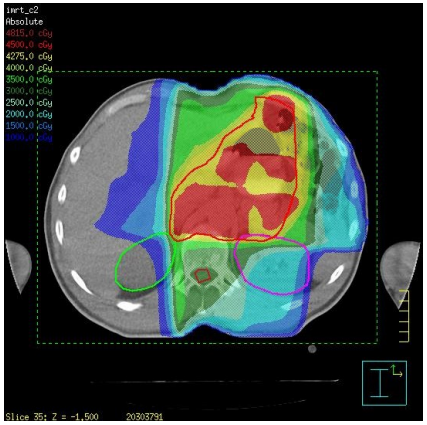
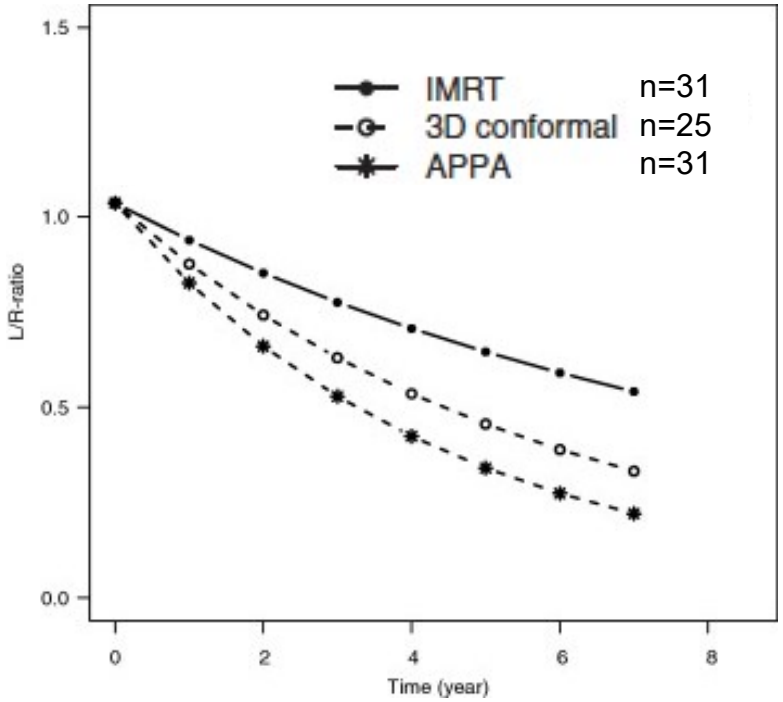
IMRT limits nephrotoxicity after chemoradiotherapy for gastric cancer



AP-PA



IMRT



Trip et al. Radiother Oncol 2014

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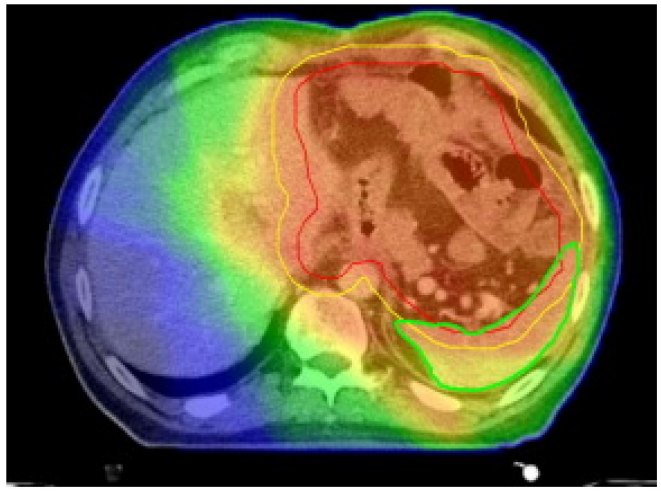
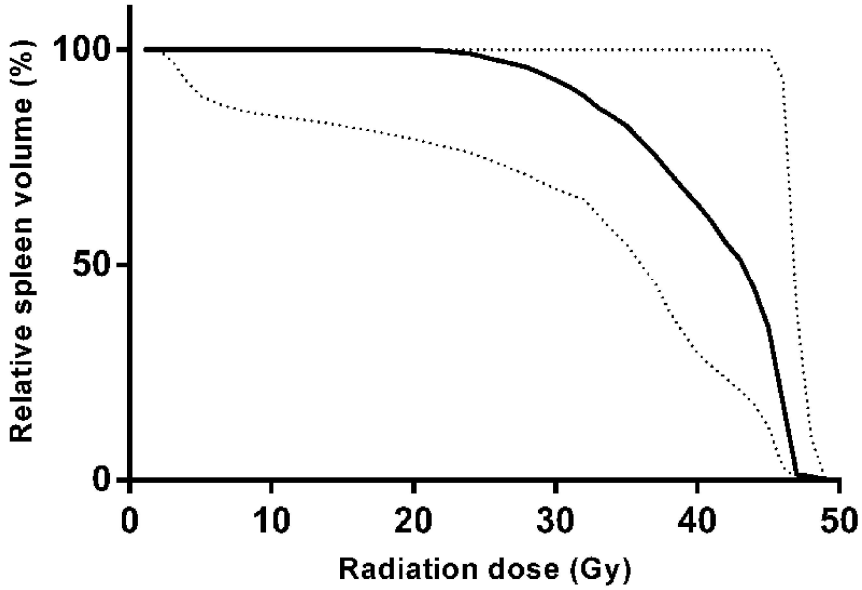
Late splenic toxicity following postoperative chemoradiotherapy in gastric cancer





Trip et al. Radiother Oncol 2015

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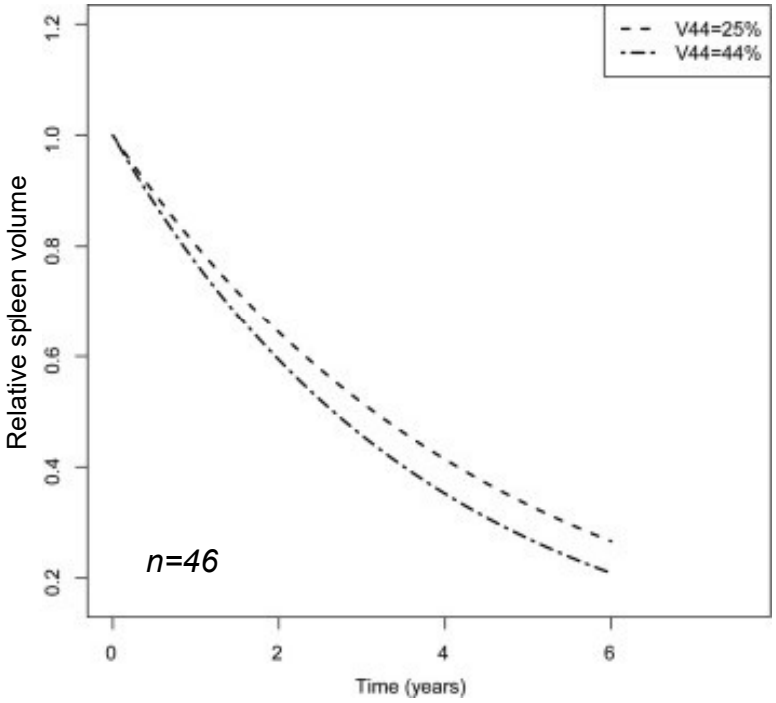
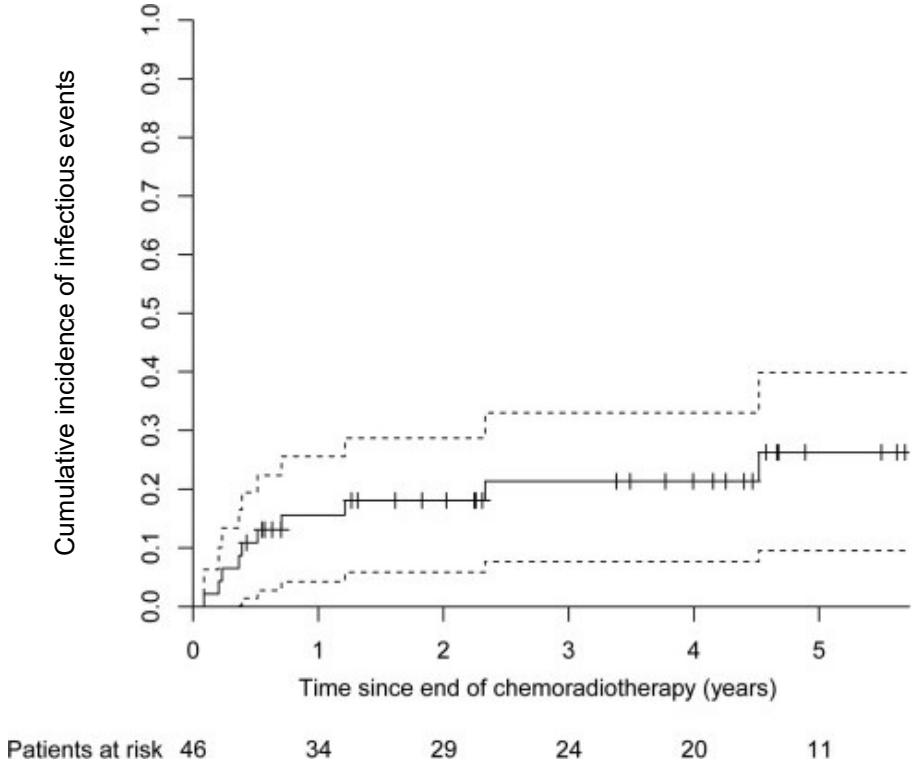
Late splenic toxicity following postoperative chemoradiotherapy in gastric cancer





Trip et al. Radiother Oncol 2015

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Summary (3): toxicity

- *Kidney and spleen are important dose-limiting OAR in post-operative (chemo-)radiotherapy for gastric cancer*
- *State-of-the-art radiation technology limits (late) side effects*
- *Pre-operative (chemo-)radiotherapy may reduce dose to OAR*

GASTRIC TUMORS:

Dose constraints for Organs at Risk

Prof Oscar Matzinger
Chef de service, service interdisciplinaire de cancérologie, Vevey, Switzerland
Médecin Agréé, service de radio-oncologie, CHUV, Lausanne

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Organs at Risk …

- Heart
- Lungs
- Spinal cord
- Vertebrae
- Thyroïd

- Stomach
- Liver
- Biliary tract
- Pancreas
- Spleen
- Kidneys

- Vessels, pericarde, coronary arteries
- Esophagus

- Patient at risk

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- Patient at risk

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 52, No. 2, pp. 283–293, 2002

0360-3016/02/$–see front matter

PII S0360-3016(01)02646-3

CLINICAL INVESTIGATION **Stomach**

GASTRIC SURGICAL ADJUVANT RADIOTHERAPY CONSENSUS REPORT: RATIONALE AND TREATMENT IMPLEMENTATION

STEPHEN R. SMALLEY, M.D.,* LEONARD GUNDERSON, M.S., M.D.,† JOEL TEPPER, M.D.,‡ JAMES A. MARTENSON, JR., M.D.,† BRUCE MINSKY, M.D.,§ CHRISTOPHER WILLETT, M.D.,‖ AND TYVIN RICH, M.D.¶

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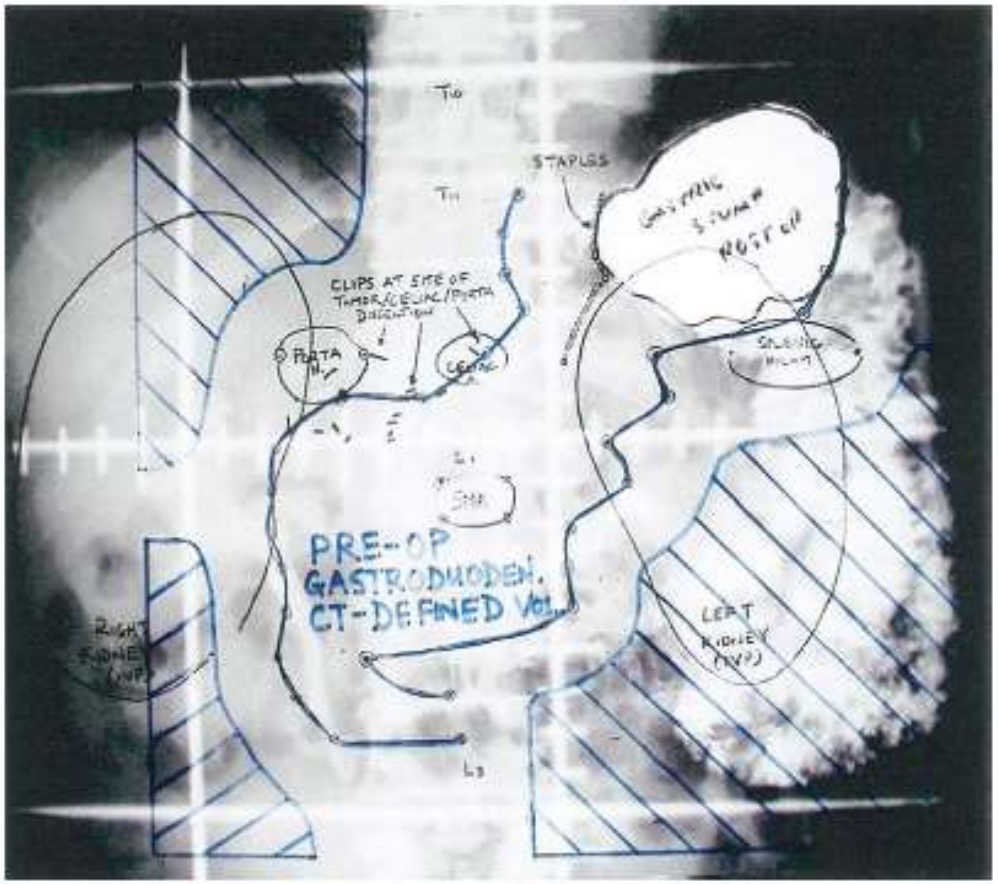

Smalley SR IJROBP 2002;52:283-93

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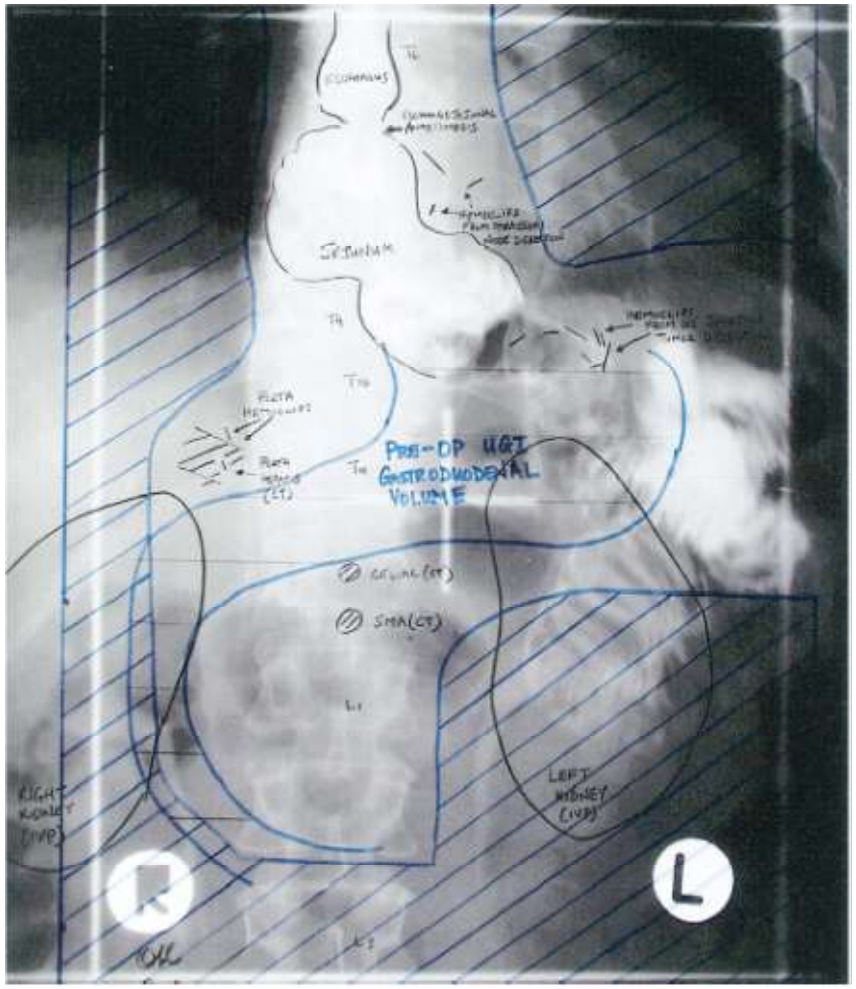

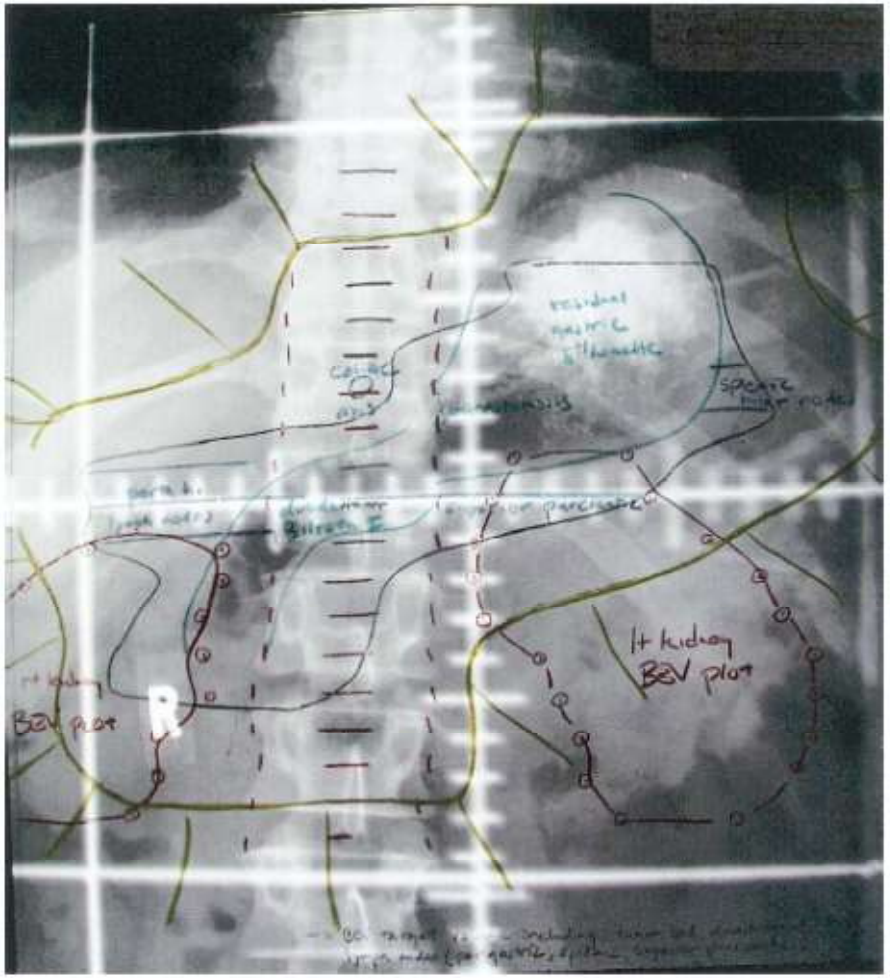

Smalley SR IJROBP 2002;52:283-93

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Normal tissue tolerance dose

Table 2 Summary of Dosimetric Parameters for Clinical Toxicity

Organ	Emami[2] TD 5/5	Emami[2] TD 50/5	Endpoints	Dosimetric Parameters	Endpoints
Brainstem	1/3: 60 Gy 2/3: 53 3/3: 50	1/3: - 2/3: - 3/3: 65 Gy	Necrosis, infarction	V60 <0.9 mL	<5% grade≥1 toxicity
Spinal cord	5 cm: 50 Gy 10 cm: 50 20 cm: 47	5 cm: 70 Gy 10 cm: 70 20 cm: -	Myelitis, necrosis	max <50 Gy	<5% grade≥3 toxicity
Cervical spinal cord	—	—	—	EUD <52 Gy, max. <55 Gy	<5% grade≥3 toxicity
Parotid	1/3: - 2/3: 32 Gy 3/3: 32	1/3: - 2/3: 46 Gy 3/3: 46	Xerostomia	Mean dose <26 Gy	Late grade 2 xerostomia resulting from >75% functional loss
Lung	1/3: 45 Gy 2/3: 30 3/3: 17.5	1/3: 65 Gy 2/3: 40 3/3: 24.5	Pneumonitis	V13<40% V20<25-30% V30<10-15% MLD<10-20 Gy	Late grade 2 in <10-20% Late grade 3 in <5-10%
Heart	1/3: 60 Gy 2/3: 45 3/3: 40	1/3: 70 Gy 2/3: 55 3/3: 50	Pericarditis	V33 <60%, V38 <33% V42 <20%	5% excess cardiac mortality
Esophagus	1/3: 60 Gy 2/3: 58 3/3: 55	1/3: 72 Gy 2/3: 70 3/3: 68	Clinical stricture/ perforation	V50 and S50 <30%	5% risk of late toxicity
Rectum	1/3: 60 Gy 2/3: 60 3/3: 60	1/3: 80 Gy 2/3: 80 3/3: 80	Proctitis, necrosis, fistula, stenosis	V70-80 ≤15 cc V70≤20-25%	Late grade 2 in <5-10%
Liver	1/3: 50 Gy 2/3: 35 3/3: 30	1/3: 55 Gy 2/3: 45 3/3: 40	Liver failure	1/3: 40-80 Gy 2/3: 30-50 3/3: 25-35	Late grade 3-4 liver toxicity <5%
Kidney	1/3: 50 Gy 2/3: 30 3/3: 23	1/3: - 2/3: 40 Gy 3/3: 28	Clinical nephritis	median dose <17.5 Gy	anemia, azotemia, hypertension and edema

Milano MT, Semin Radiat Oncol 2007:17;131-40

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OAR: Stomach

Late radiation-induced toxicity:

- Dyspepsia
- Ulceration

Since Emami publication:

- Few studies have reported severe RT-related gastric toxicity

Quantec Review:

whole organ dose: 50 Gy ➔ 2% to 6% risk of severe late toxicity

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Stomach	Ulceration		D100 <50 Gy		

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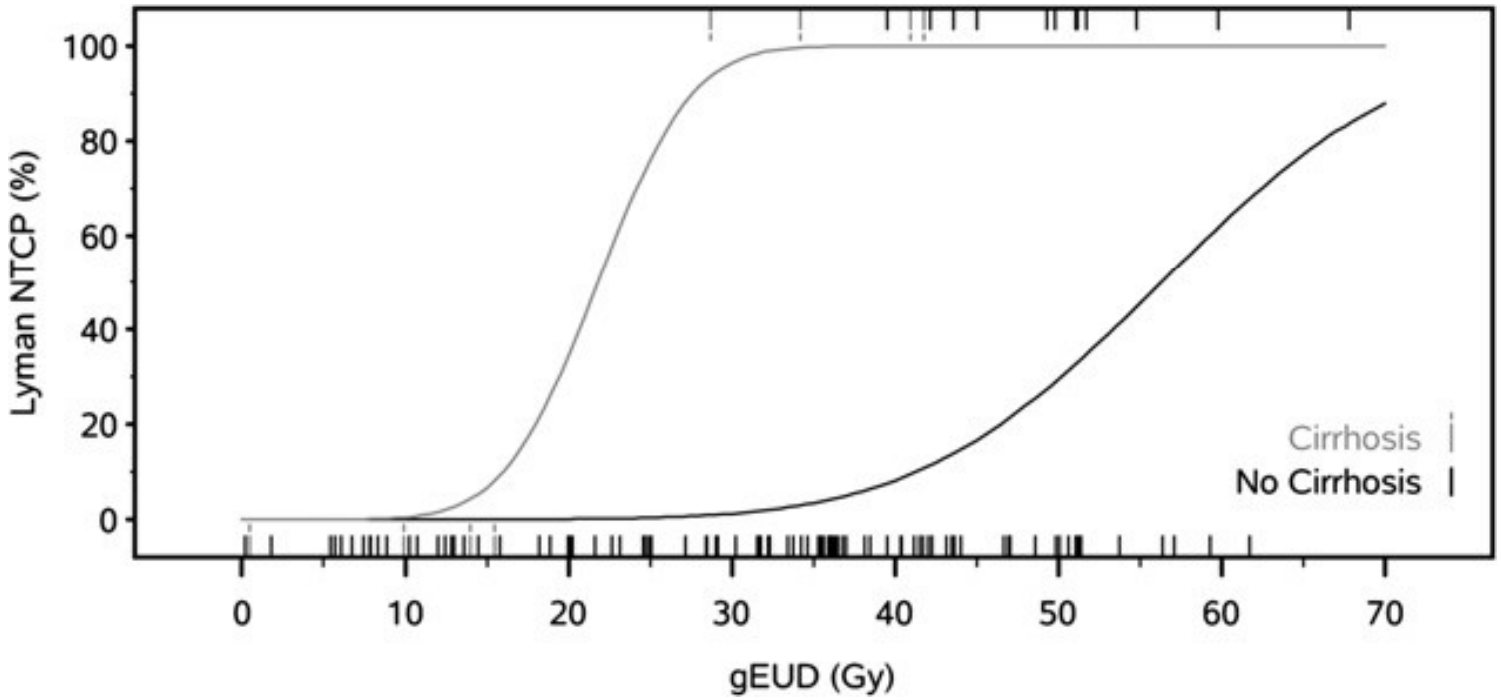
NTCP model 2012

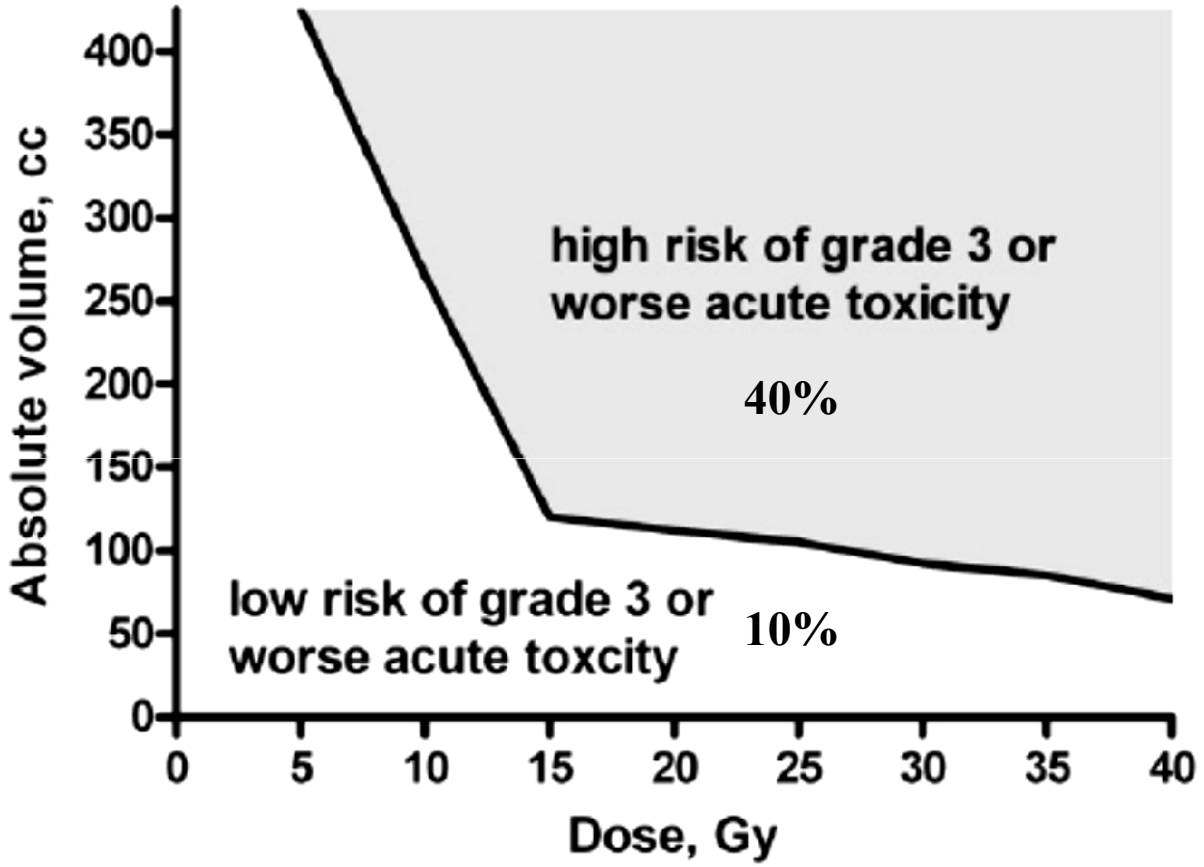


Dosimetric analysis of radiation-induced gastric bleeding. Feng M, Normolle D, Pan CC, Dawson LA, Amarnath S, Ensminger WD, Lawrence TS, Ten Haken RK. Int J Radiat Oncol Biol Phys. 2012 Sep 1;84(1):e1-6. doi: 10.1016/j.ijrobp.2012.02.029.

Small bowel: QUANTEC, dose-volume effects in

Volume of individual bowel loops

NOT the peritoneal space …



Baglan – Robertson Threshold model

Kavanagh B. IJROBP 2010

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OAR: small bowel

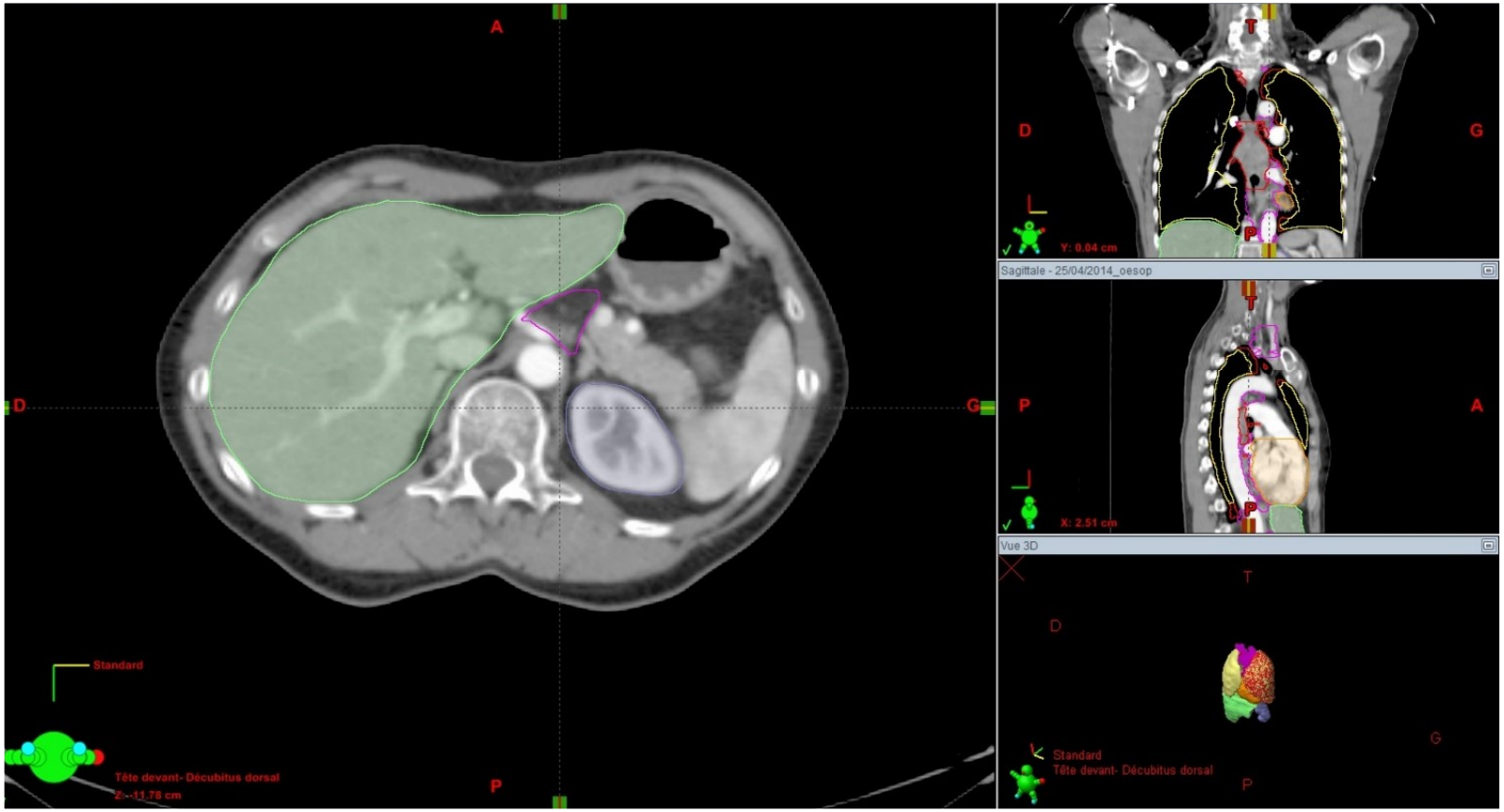
The volume receiving relatively low doses of radiation plays a significant role in the rate of acute toxicity.

When contouring individual bowel loops, the most robust dose-volume metric is the V15

The rate of grade ≥3 acute toxicity is <10% when the V15 <120 cc

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Small Bowel	Acute grade ≥3 toxicity Late obstruction/perforation	<10 <5	V15 <120 cc V50 <5%		

OAR: LIVER


A
D
G
P
Standard
Tête devant- Décubitus dorsal
T
D
G
P
Y: 0.04 cm
Sagittale - 25/04/2014_oesop
T
P
A
P
X: 2.51 cm
Vue 3D
T
D
G
P
Standard
Tête devant- Décubitus dorsal

QUANTEC: Radiation-induced liver toxicity

Table 2. Series of fractionated partial liver irradiation and rates of RILD

Study group	*n*	Diagnosis	Baseline Child-Pugh score	Prescription dose fractionation	Crude percent RILD	Mean normal liver dose in patients with vs. without RILD	Factors associated with RILD
Michigan (8, 23)	203*	PLC + LMC	203 A	1.5 Gy twice daily	9.4% (19/203)	37 Gy vs. 31.3 Gy	PLC vs. LMC mean liver dose
Taipei (20)	89†	HCC	68 A 21 B	1.8–3.0 Gy	19% (17/89)	23 Gy vs. 19 Gy	HBV, liver cirrhosis
Shanghai (3, 18)	109†	PLC	93 A 16 B	4–6 Gy	15.6% (17/109)	24.9 Gy vs. 19.9 Gy	Liver cirrhosis
Guangdong (20)	94**	HCC	43 A 51 B	4–8 Gy	17% (16/94) Note: 4 fatal	Not stated	Liver cirrhosis
S. Korea (Seong, Park) (21)	158†	HCC	117 A 41 B	1.8 Gy	7% (11/158)	Not stated	Dose
S. Korea (Kim) (4)	105†	HCC	85 A 20 B	2.0 Gy	12.3% (13/105)	25.4 Gy vs. 19.1 Gy	Total liver volume receiving 30 Gy or more above 60%

Pan C. IJROBP 2010

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OAR: liver

Radiation-induced liver disease (RILD):

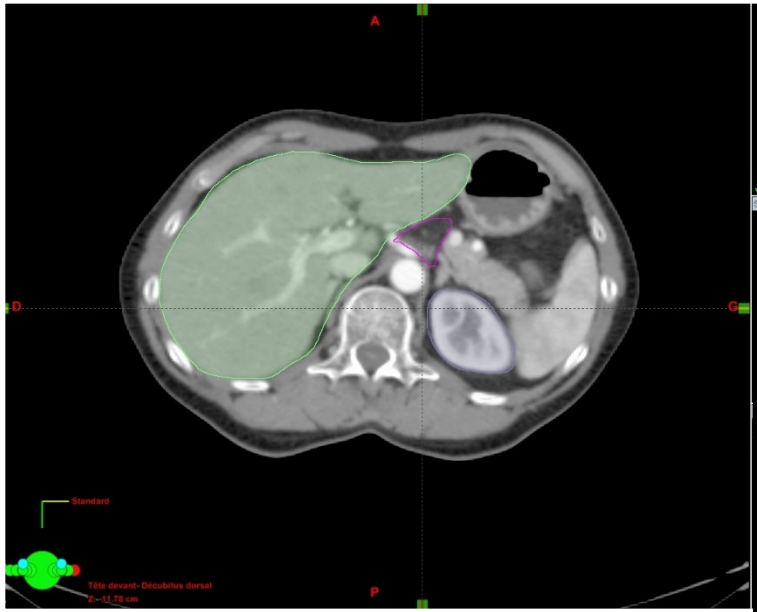
➔ between 2 weeks and 3 months after radiotherapy

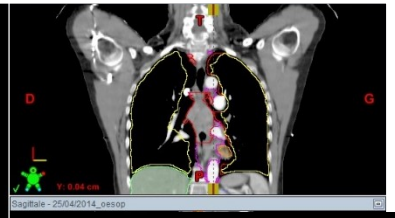
➔ Preexisting liver disease may render patients more susceptible

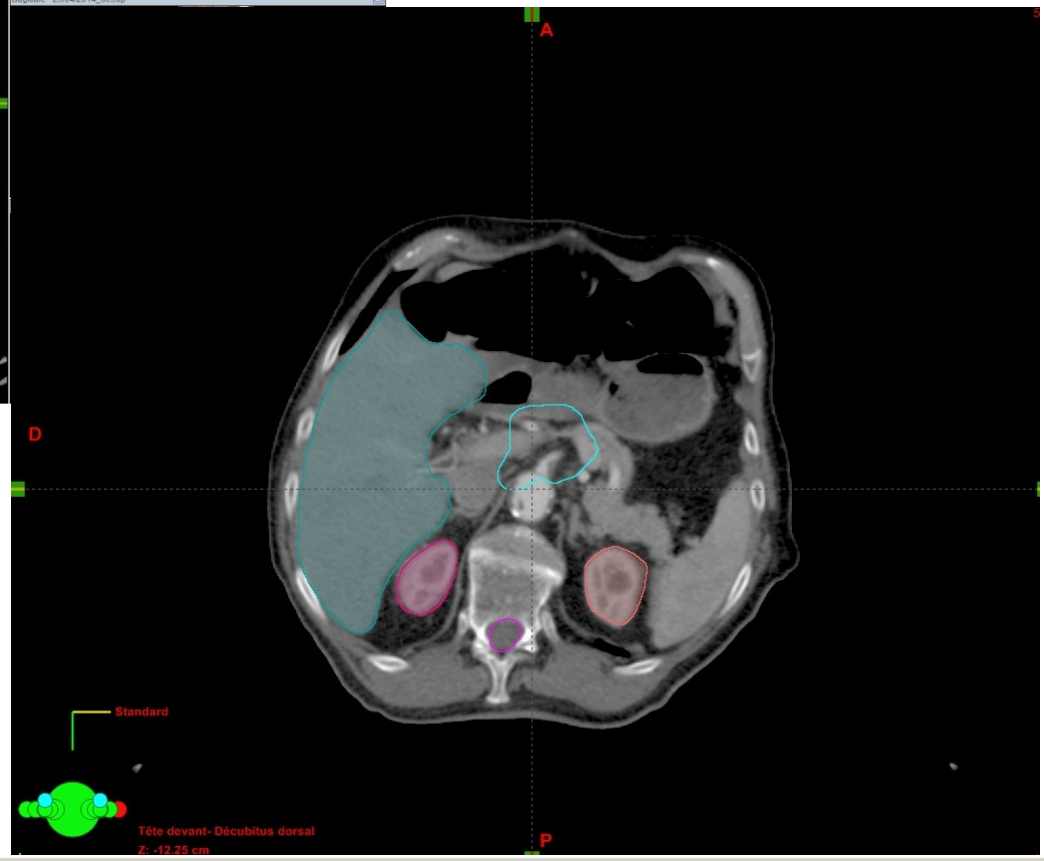
Findings by QUANTEC are very similar to the original estimates by Emami

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Liver	RILD, normal liver	<5			≤30
	RILD, liver disease	<5			≤28

Kidneys







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Kidney

- Radiation-induced renal dysfunction:
  - wide array of endpoints (creatinine clearance to renal failure)

- Bilateral ***whole kidney*** irradiation: pooled analysis by Cassady:
  - mean dose of 18 Gy corresponded to a 5% risk of injury at 5 years.
- For bilateral ***partial kidney*** irradiation, the data is less clear
- Small volumes of the kidney can tolerate relatively high doses of radiation

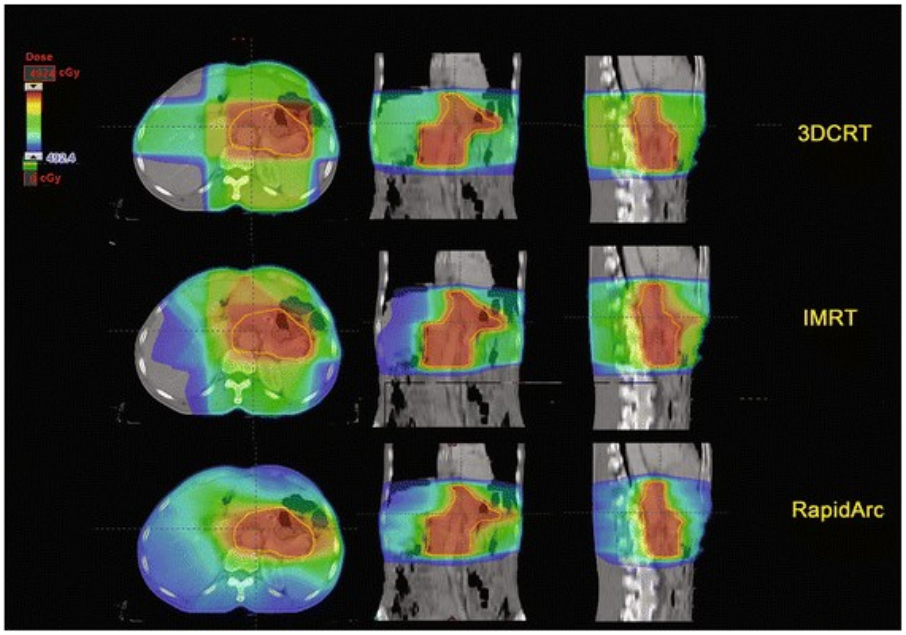
QUANTEC:

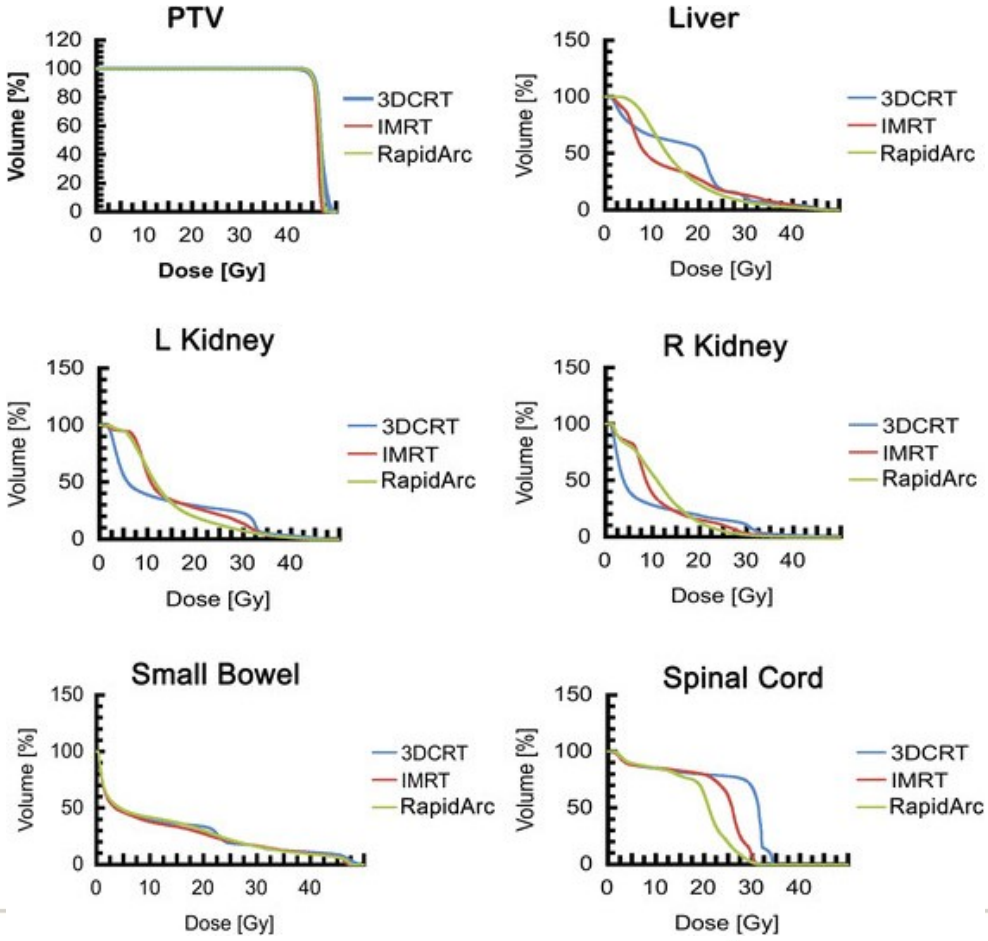
- <5% risk of injury when the mean kidney dose is limited to <18 Gy.
- Current common practice of limiting the equivalent of one kidney to <20 Gy

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Kidney 1	Renal dysfunction	<5	Equivalent of 1 kidney <18 Gy		
Kidney 2	Renal dysfunction	<5			<18

Cassady JR. Clinical radiation nephropathy. Int J Radiat Oncol Biol Phys 1995;31:1249–1256

Double-arc volumetric modulated therapy improves dose distribution compared to static gantry IMRT and 3D conformal radiotherapy for adjuvant therapy of gastric cancer





Zhang Radiat Oncol 2015;10:114

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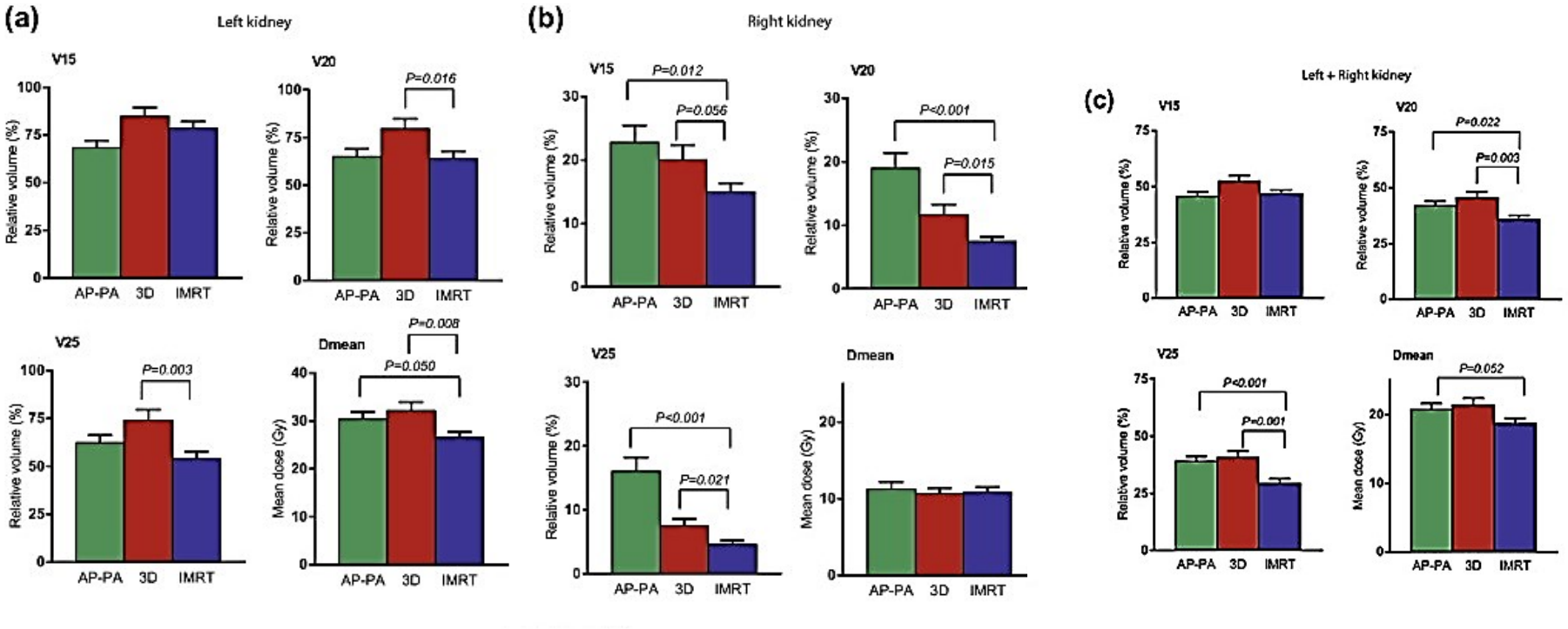
IMRT limits nephrotoxicity after chemoradiation for gastric cancer



Trip A. Radiother Oncol 2015;114:421-426

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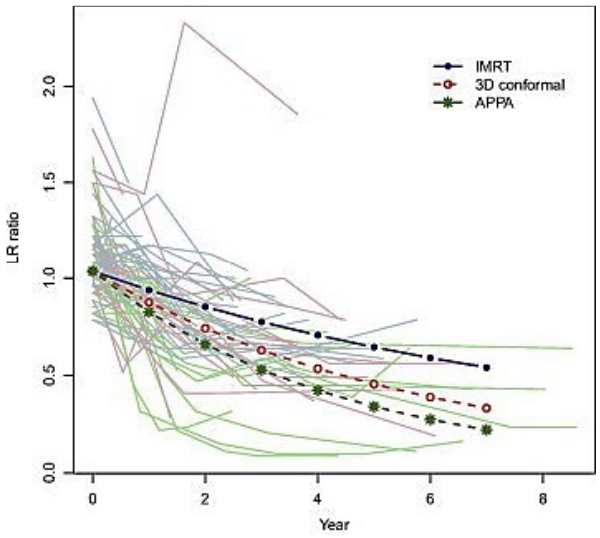
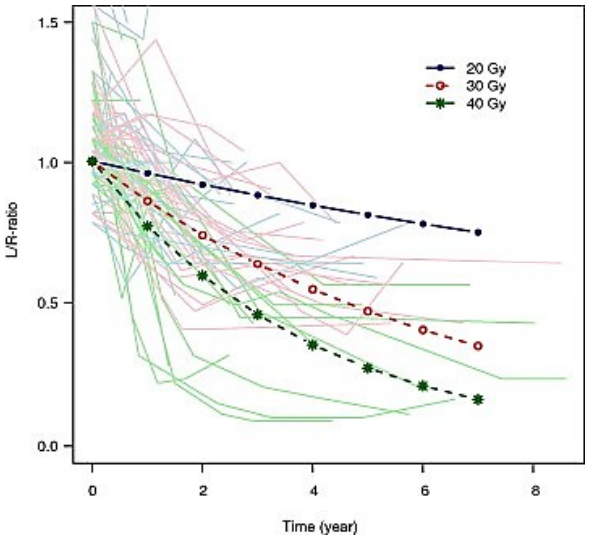
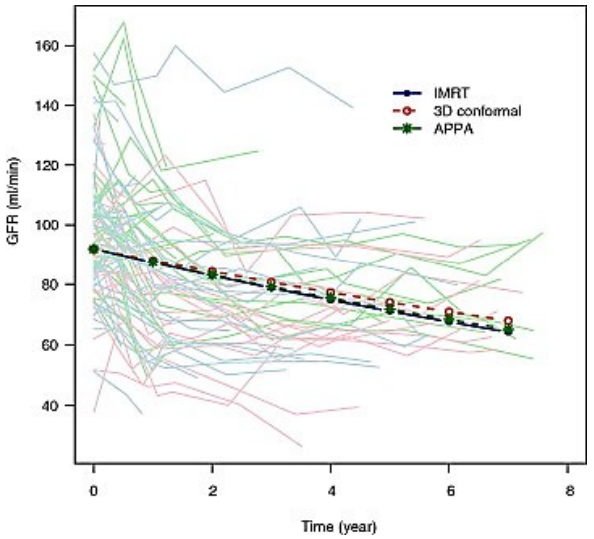


Left renal function
Mixt effect model



Dose effect relationship
D mean
Tc99m-mAG3-renography



GFR
Cockcroft-Gauss formula

Trip A. Radiother Oncol 2015:114:421-426

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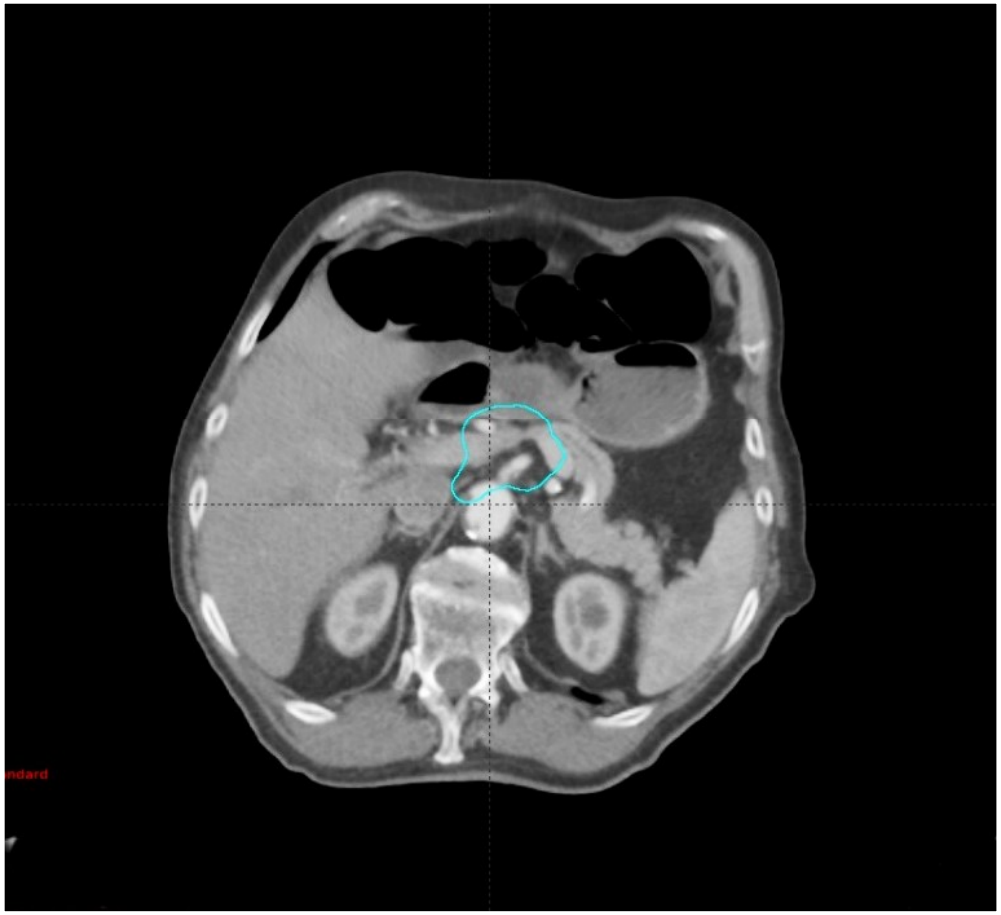
NCCN guidelines

Normal Tissue Tolerance Dose-Limits

- **Treatment planning is essential to reduce unnecessary dose to organs at risk including liver (60% of liver <30 Gy, ≤25 Gy mean dose to liver), kidneys (at least 2/3 of one kidney <20 Gy), spinal cord (<45 Gy), heart (1/3 of heart <40 Gy, effort should be made to keep the left ventricle doses to a minimum), and lungs.[a]**
- **It is recognized that these dose guidelines may be appropriately exceeded based on clinical circumstances**

Liver:	60% < 30 Gy; mean dose < 25 Gy
Kidneys:	2/3 of one Kidney < 20 Gy
Spinal cord:	< 45 Gy
Heart:	1/3 heart < 40 Gy; left ventricle ALARA
Lungs	

Others … ?



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Re-irradiation and “modern” treatment planning

Dirk Verellen

DV is involved in an on-going scientific collaboration with RaySearch

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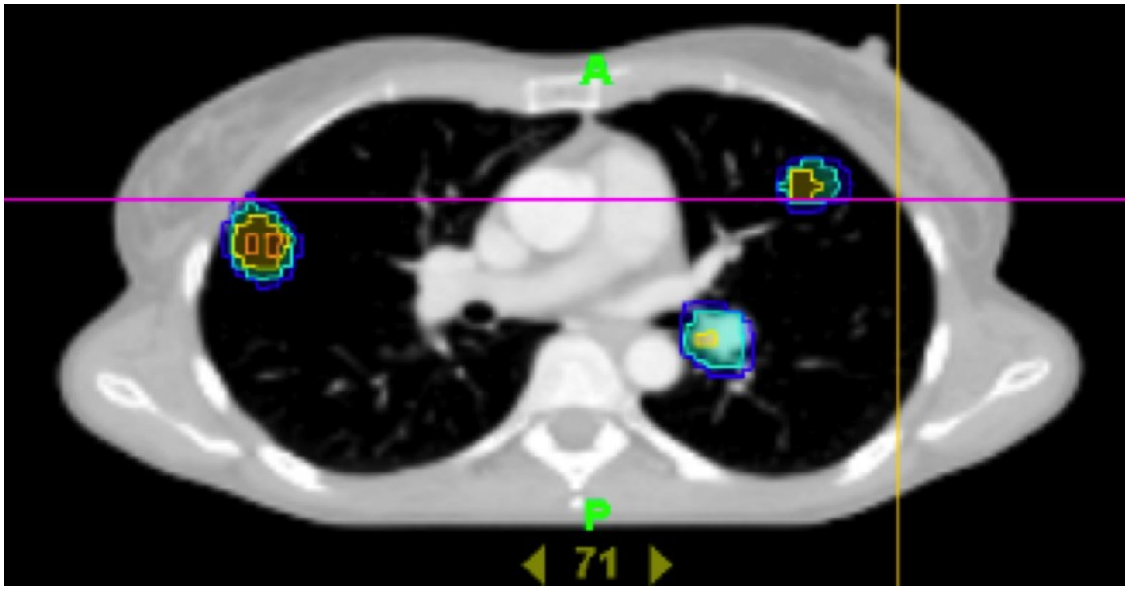
Outline

- Where do we come from?
  - Intra-departmental
  - Inter-departmental

- A few examples:
  - "poor man's solution": breast as example
  - Dose accumulation, with different fractionations: Oesophagus
    - Level 1: manually assessing EQD2
    - Level 2: rescaling both dose distributions to EQD2 and accumulate
    - Level 3: rescaling dose distributions taking into account the different α/β (and recovery …) of all OAR's and accumulate.
  - SBRT oligometastases: mixing fractionations and treatment machines
- Some remaining challenges
- Conclusions

Palliation and QoL: a case study



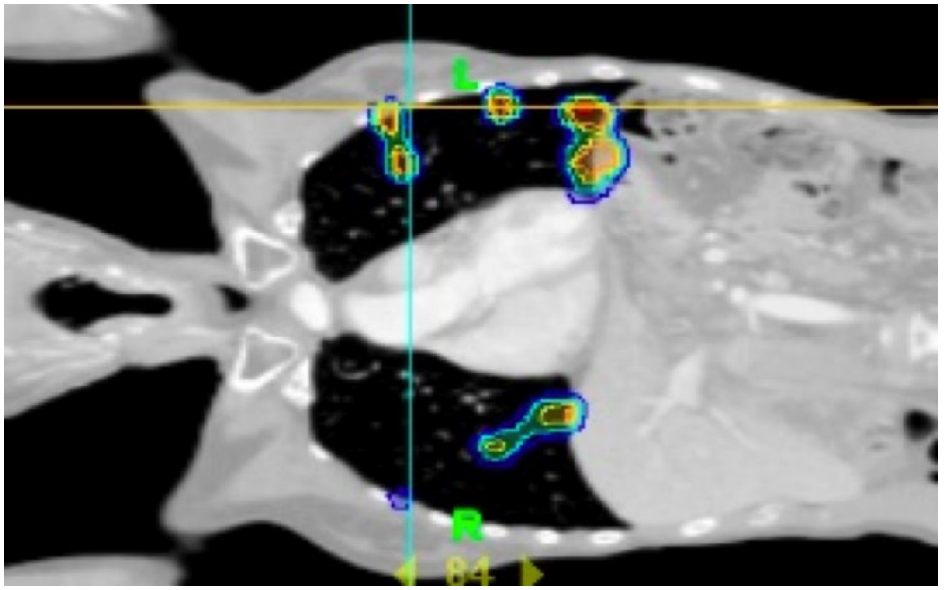
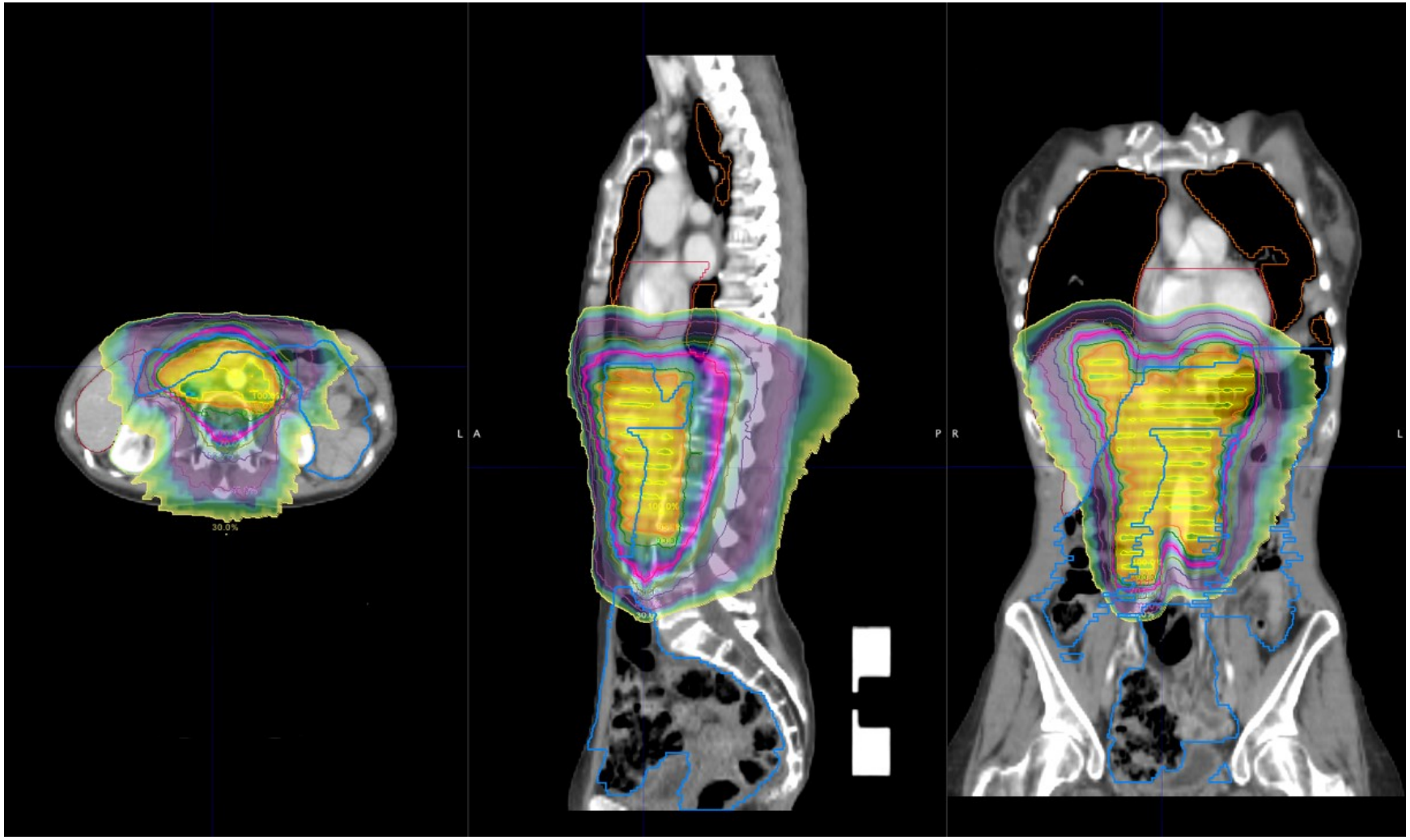


Illustration of a palliative setting in radiotherapy. The patient previously treated for a nasopharyngeal carcinoma presented multiple (17) metastasis not responding after several cycles of chemotherapy, and was treated on all lesions with 10 times 4 Gy with helical tomotherapy in **July 2008**, early 2012 the patient was still in good overall condition.

Accumulated dose: 2007



Total Accumulated Dose 40Gy

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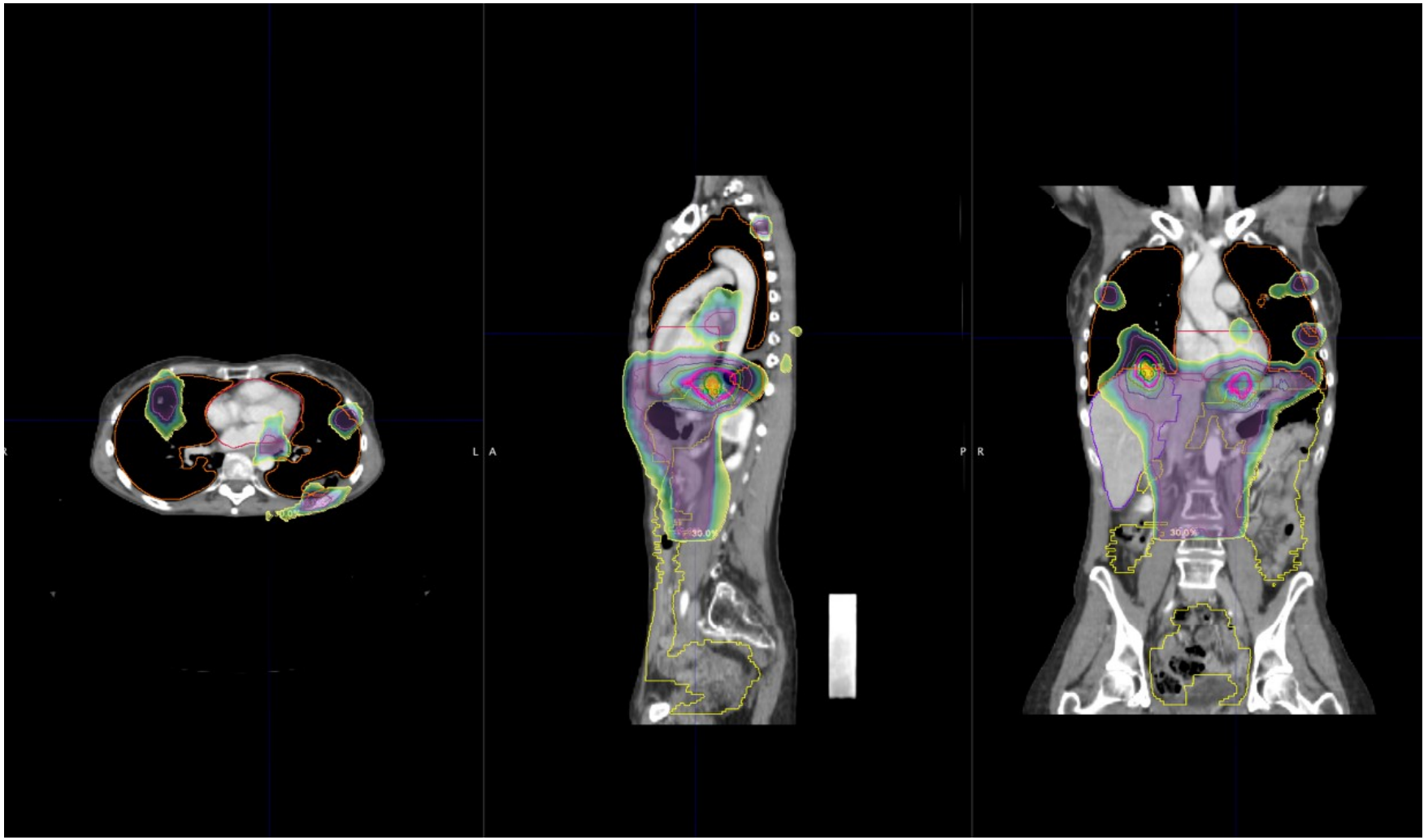
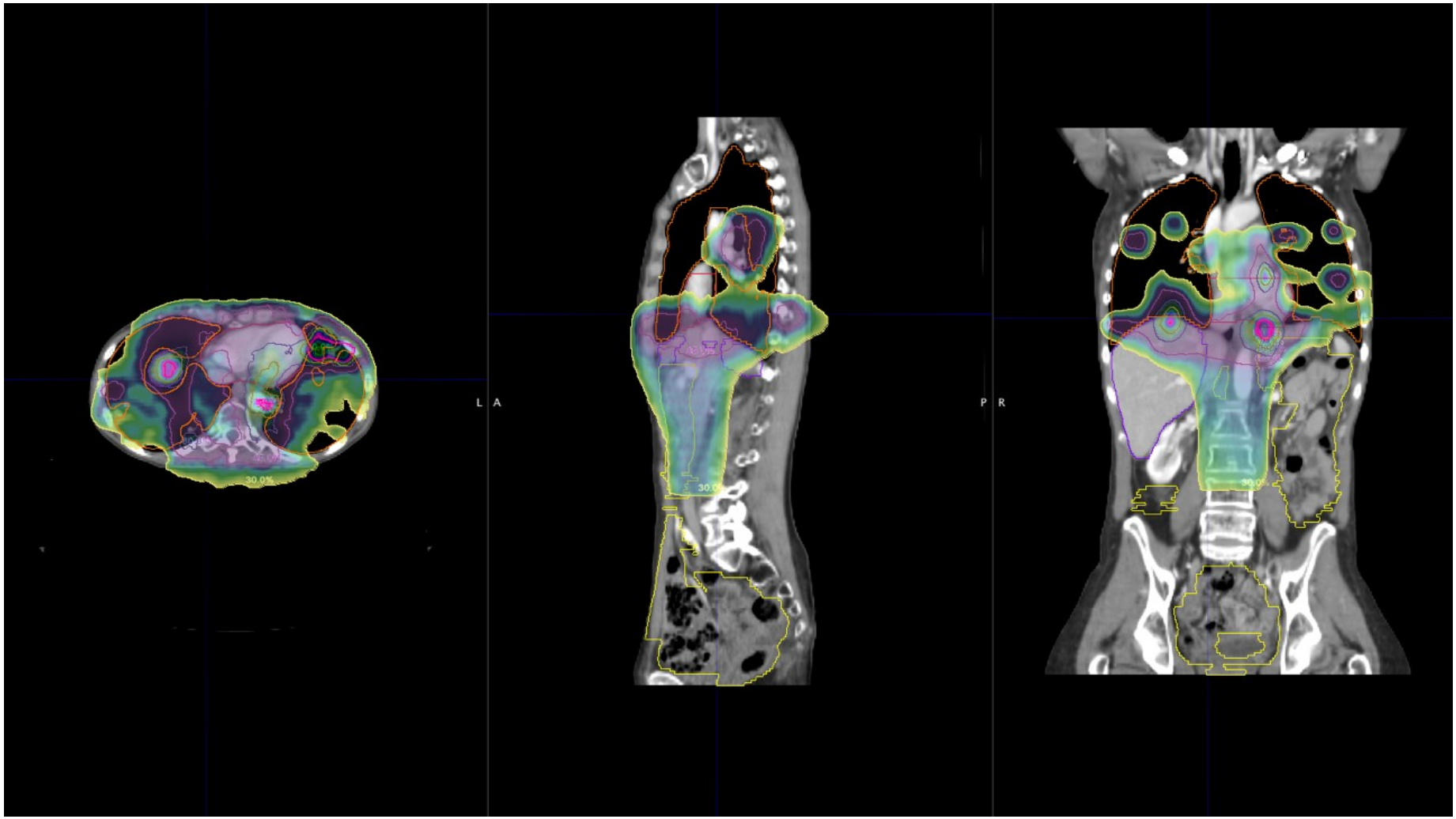
Accumulated dose: 2007-2008



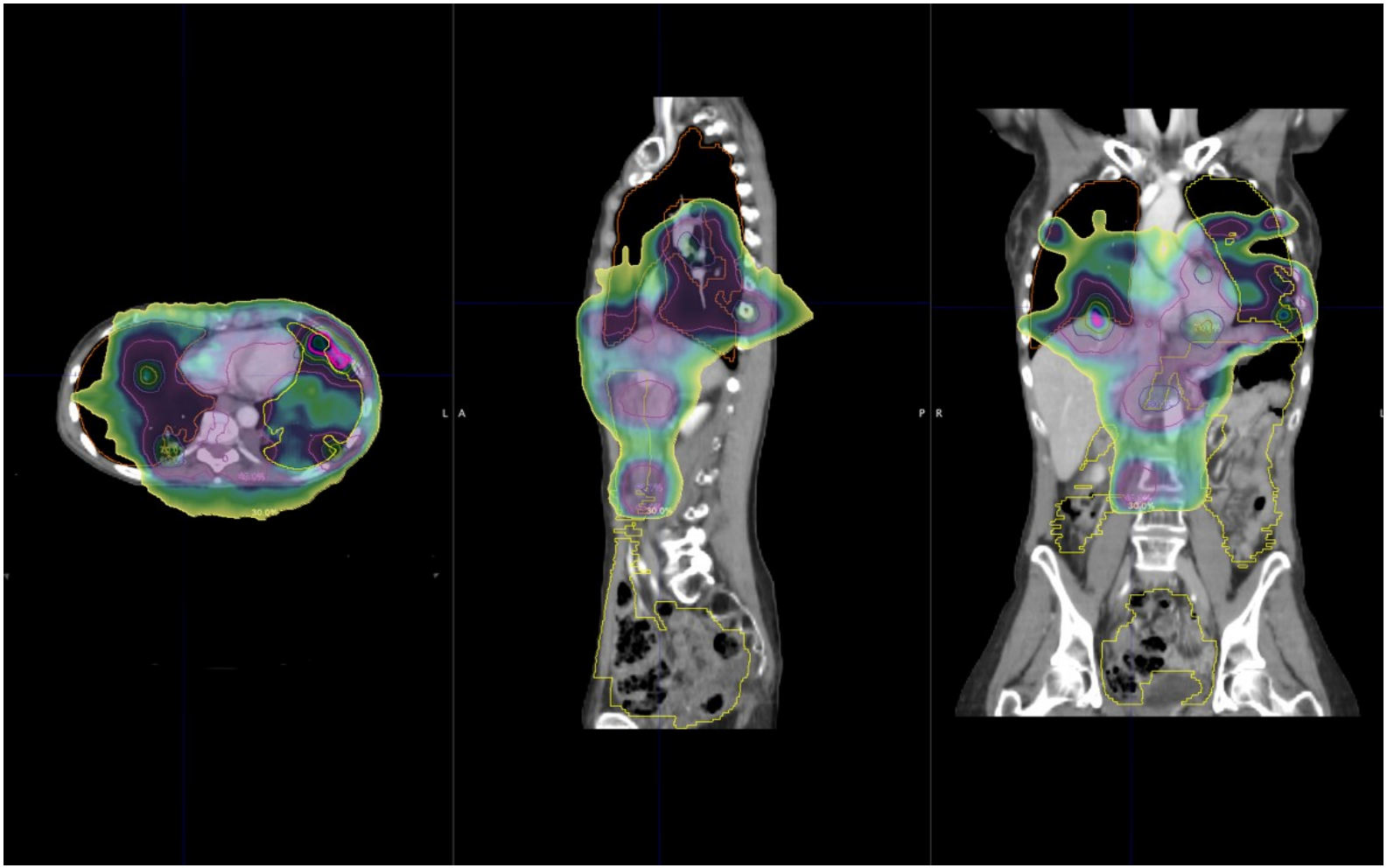
Total Accumulated Dose 76Gy

Accumulated dose: 2007-2009



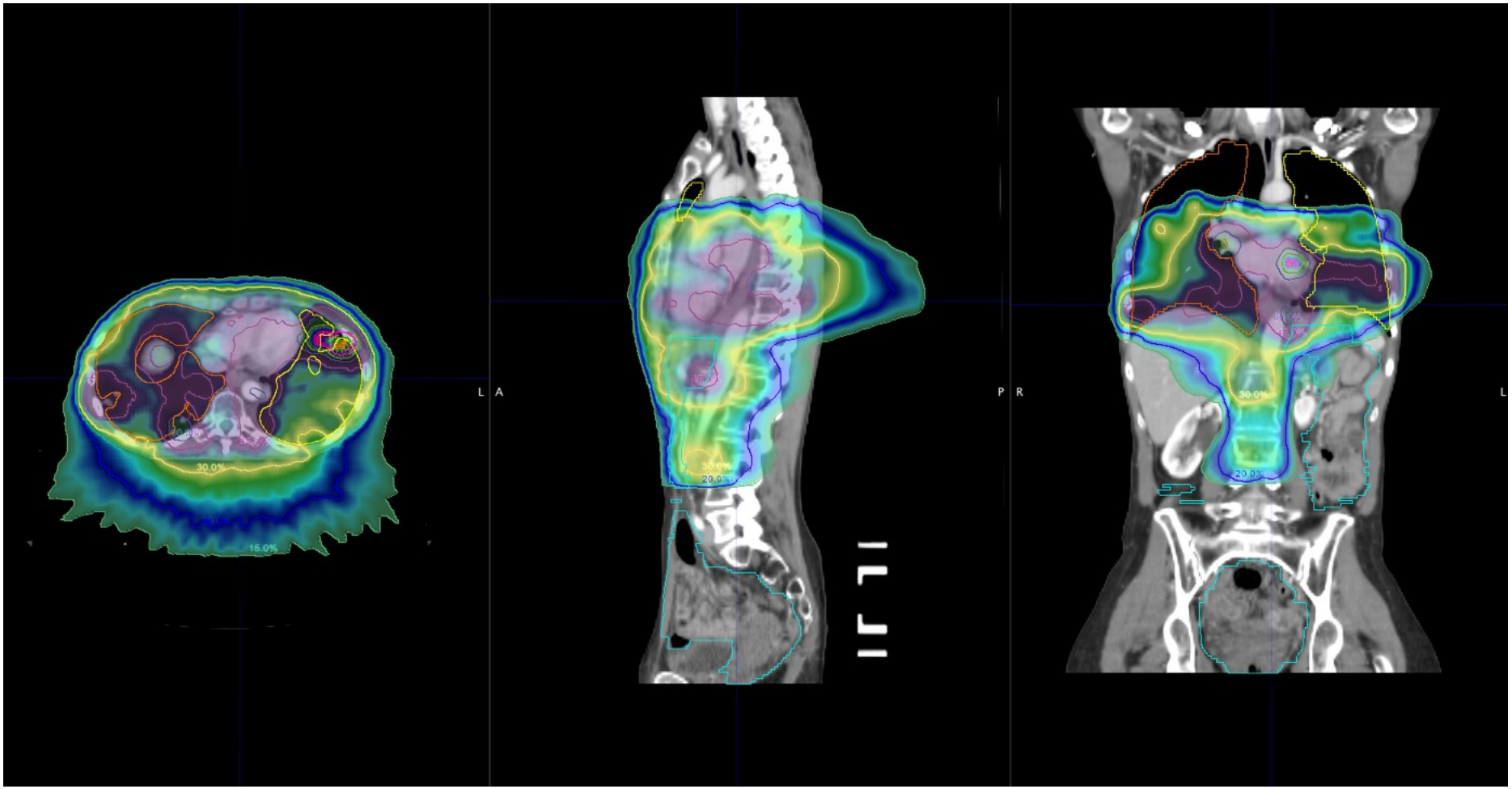
Total Accumulated Dose 102Gy

Accumulated dose: 2007-2010



Total Accumulated Dose 120Gy

Accumulated dose: 2007-2011



Total Accumulated Dose 160Gy

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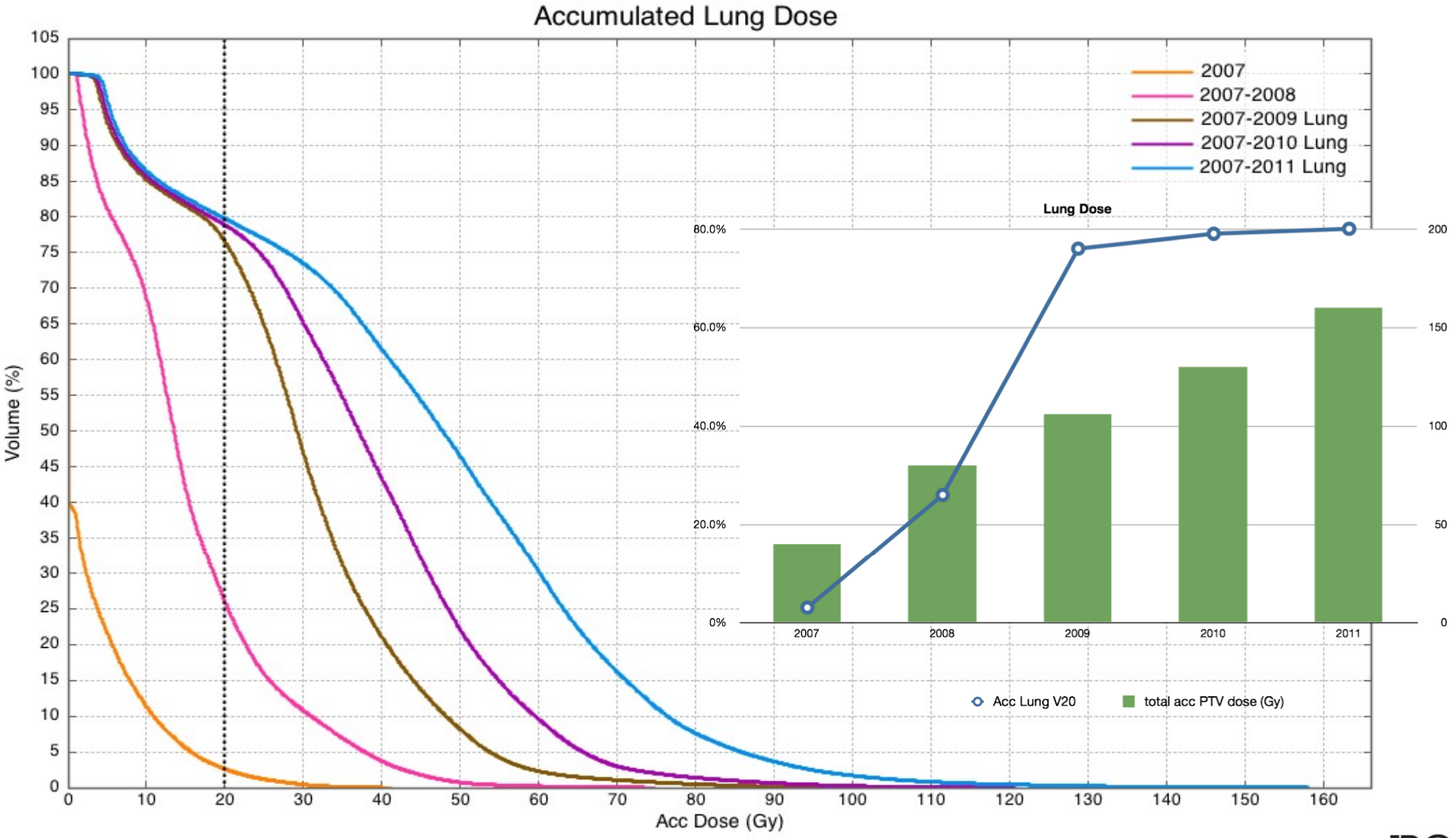
Accumulated lung dose



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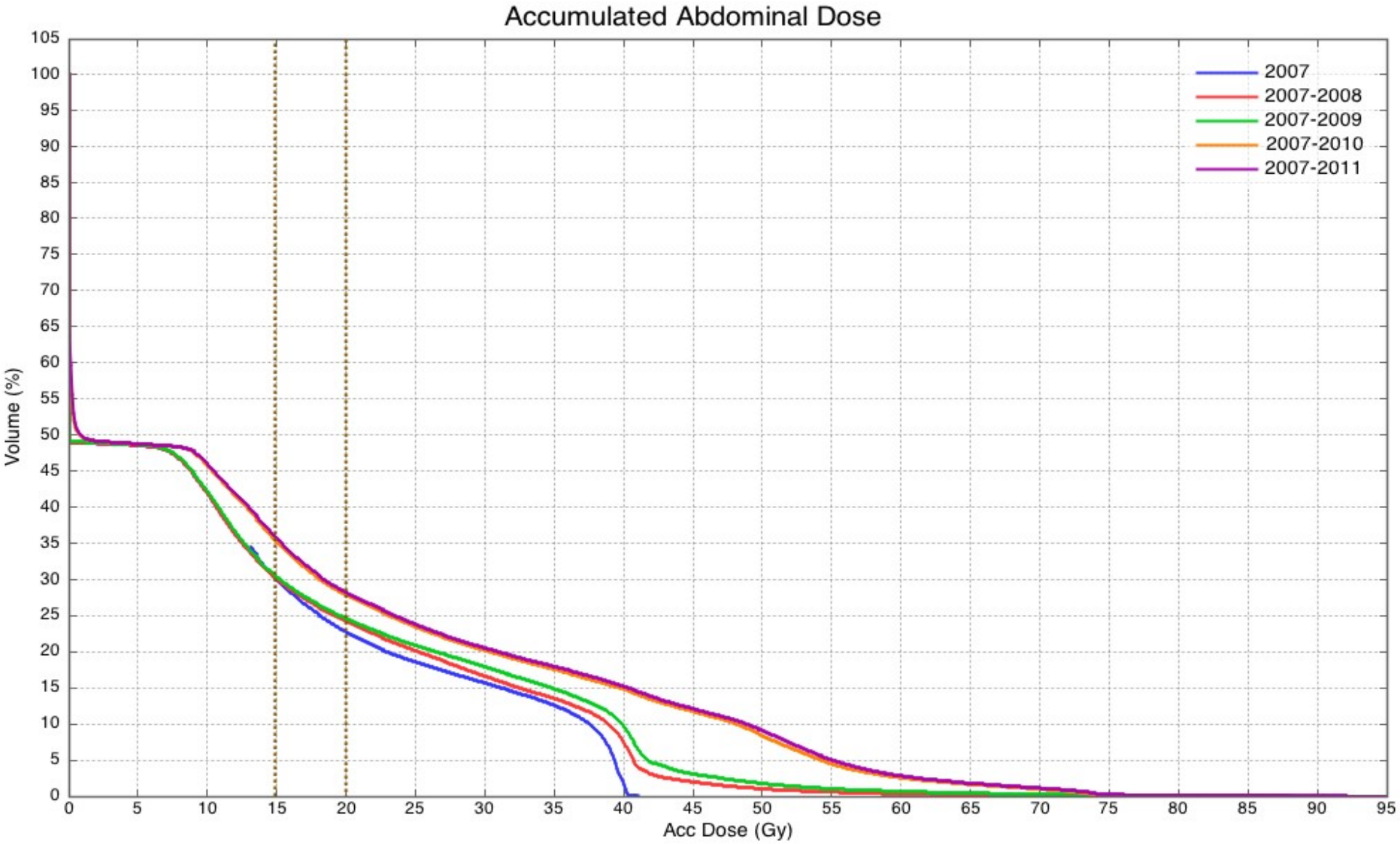
Accumlated abdominal dose



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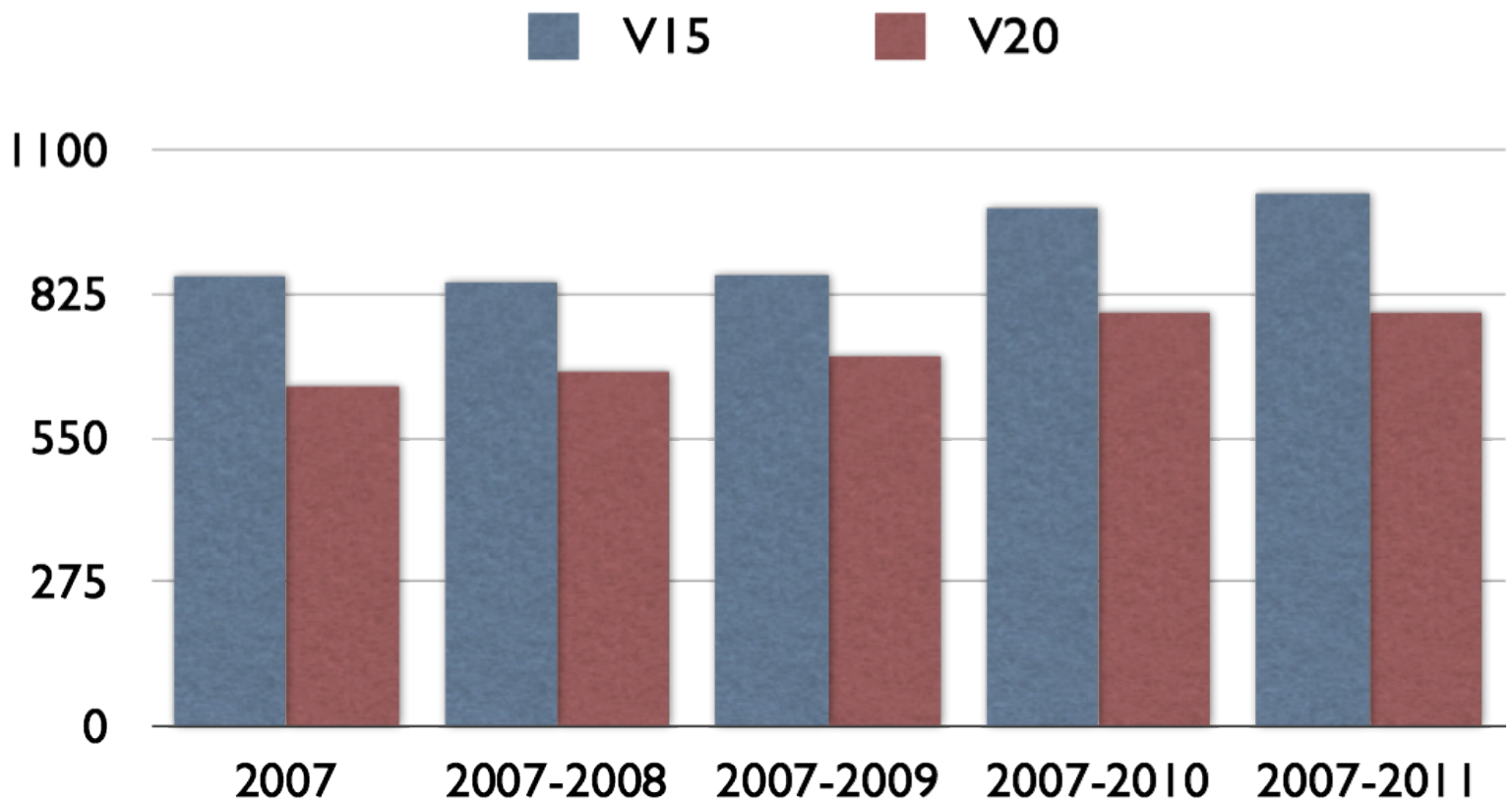
Abdomen

Period	V15(cc)	V20(cc)
07	860	650
07-08	848	678
07-09	862	707
07-10	989	791
07-11	1017	791

100% = 2826cc

Abdomen



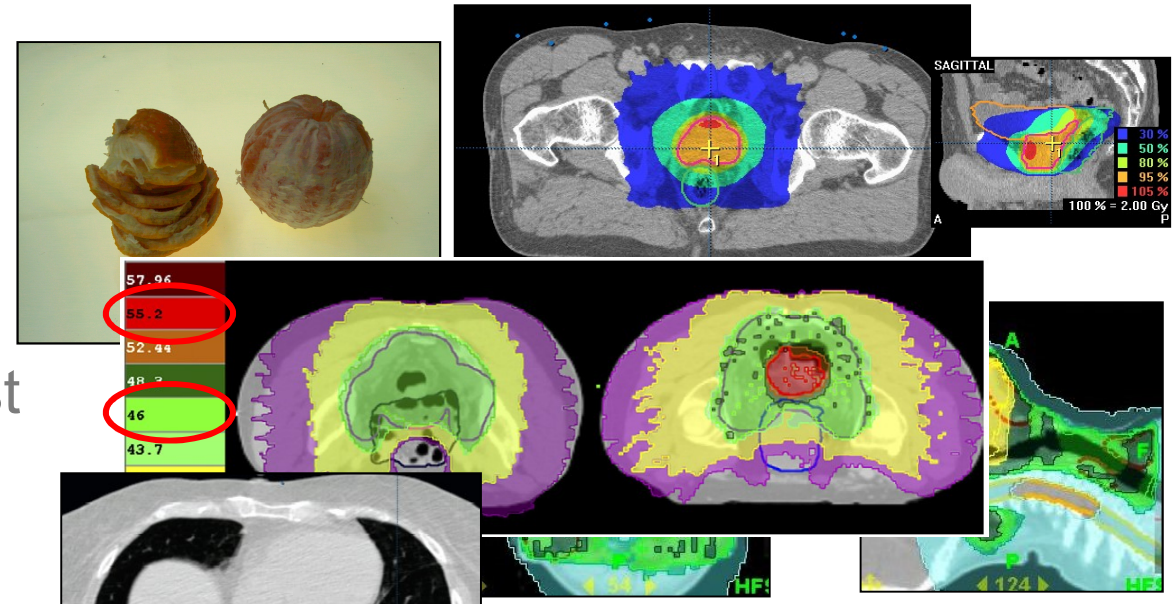
Palliation and QoL: a case study

4 January, 2011

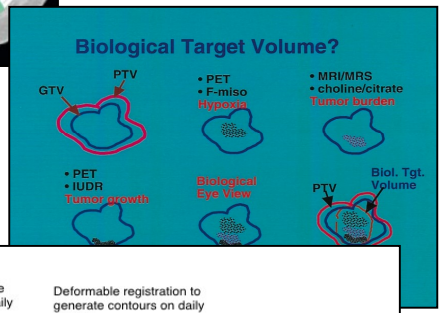
“...et les 2500m d'altitude ne m'ont posé aucun trouble particulier au plan respiratoire ni cardiaque, juste quelques courbatures aux mollets le lendemain.....”

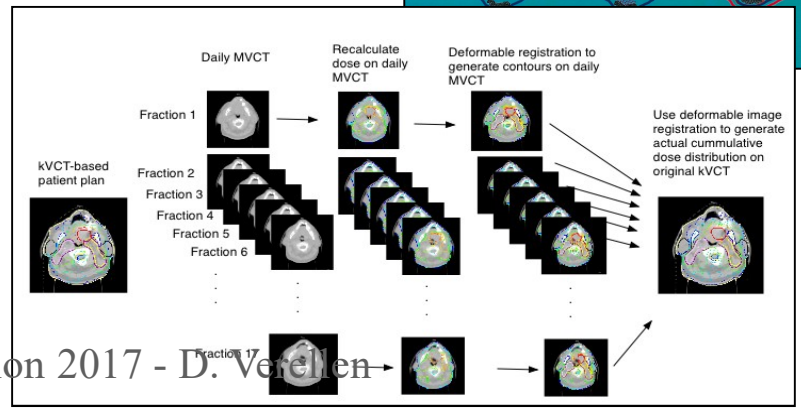
Possibilities created by IGRT/IMRT

- Margin reduction:
  - Dose escalation
  - Conformal avoidance
- Simultaneous Integrated Boost (SIB)
- Reviewed dose fractionation (SBRT)
- Biological Conformal Radiation Therapy (BCRT)
- Adaptive Radiation Therapy (ART)



Paint by numbers, Warhol 1962





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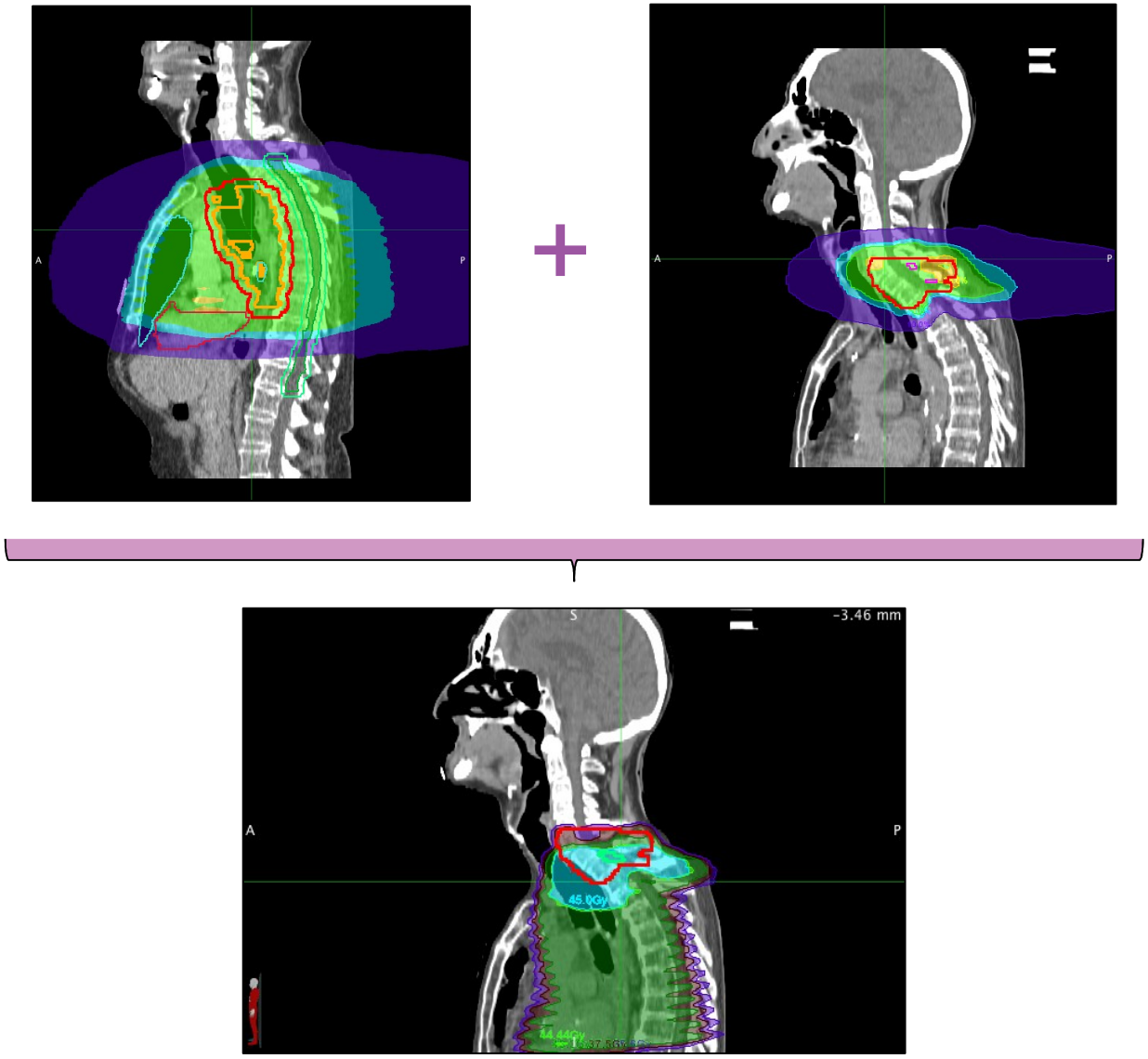
Possibilities created by IGRT/IMRT and modern treatment planning

- Re-irradiation



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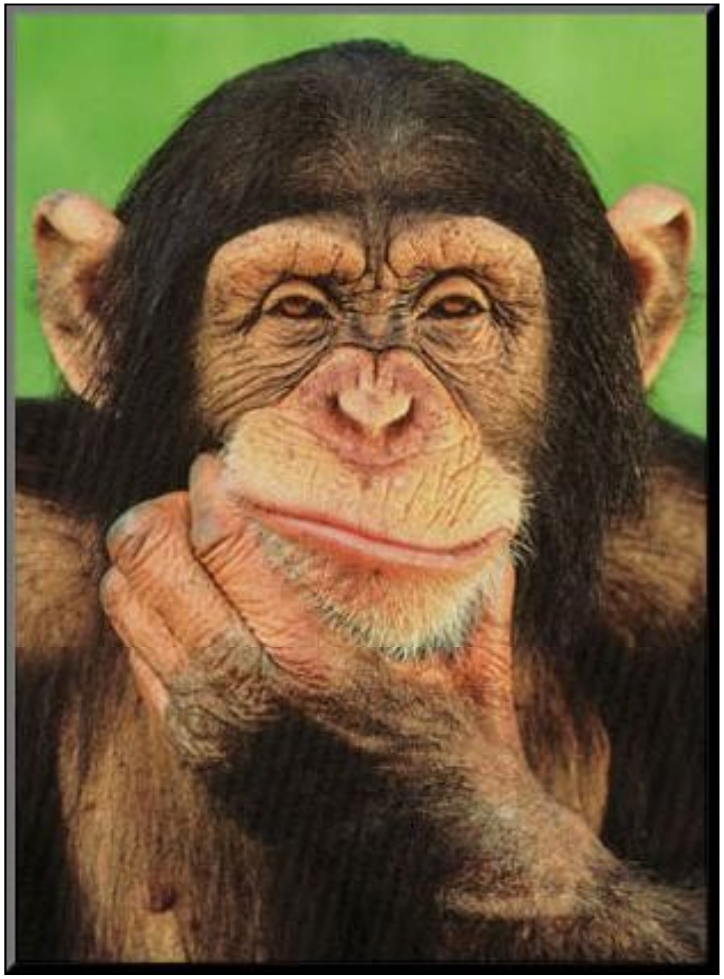
Is it that simple?

- **Requirements for dose accumulation**?
  - Adding dose distributions from different treatment planning systems
  - Adding dose distributions originating from different fractionations schemes
  - Including α/β for different OARs and PTVs, and rescaling dose distribution dynamically (… what α/β will we use?)
  - Including the recovery factors …
  - Assessing accuracy of deformable registration?
  - Applying the information in optimization
  - Is the planned dose equal to the delivered dose?
  - … what is the tolerance dose?????



The QUANTEC Report 2010

I. J. Radiation Oncology ● Biology ● Physics Volume 76, Number 3, Supplement, 2010

Introductory Papers
History/Overview/Scientific Issues
Application of QUANTEC metrics/models into clinical practice

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.
3. **Challenges Defining Volumes**- Describes how the organ is typically defined (or segmented) on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Fig. 1. Outline of the issue: the first section consists of Introductory Papers; the second section consists of Organ-Specific Papers, each containing 10 topic sections; and the third section consists of Vision Papers.

- Useful guidelines for normal tissue tolerances in the **primary** situation
- Very limited information concerning **re-irradiation**

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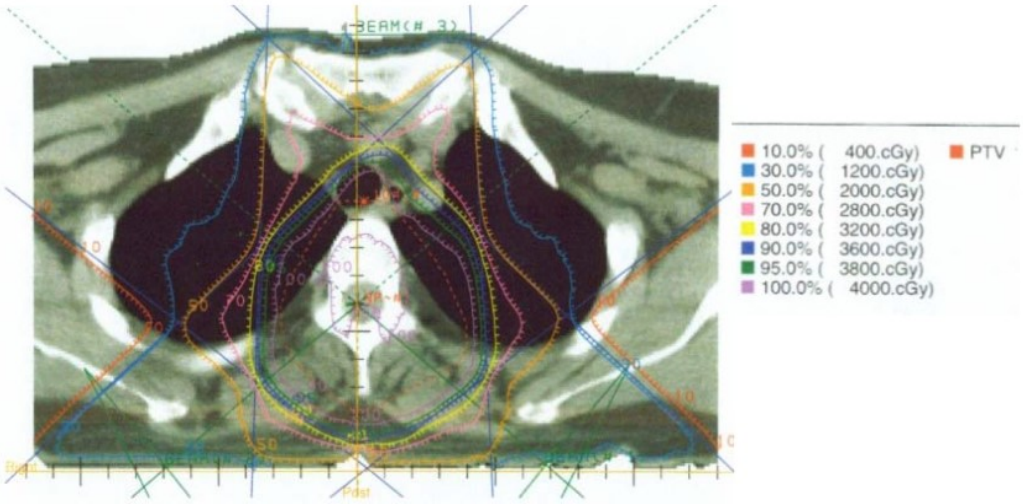
The QUANTEC Report 2010

- Very limited information concerning re-irradiation
- Maybe, because reliable data is limited …
  - Even in a so-called intra-departmental situation, using the same treatment planning system for years, it '*was*' difficult to accumulate dose.
  - In an inter-departmental situation, with patients being referred from other centres, compatibility issues made it impossible to accurately assess the previous dose, let alone accumulate dose accurately.
  - Even when dose matrices can be accumulated, using deformable registration algorithms some issues remain to be solved:
    - Accuracy of deformable registration algorithm
    - Assessing differences in dose fractionation
    - Accounting for different sensitivities and different doses delivered to OAR's
    - Type A or B dose calculation algorithm?

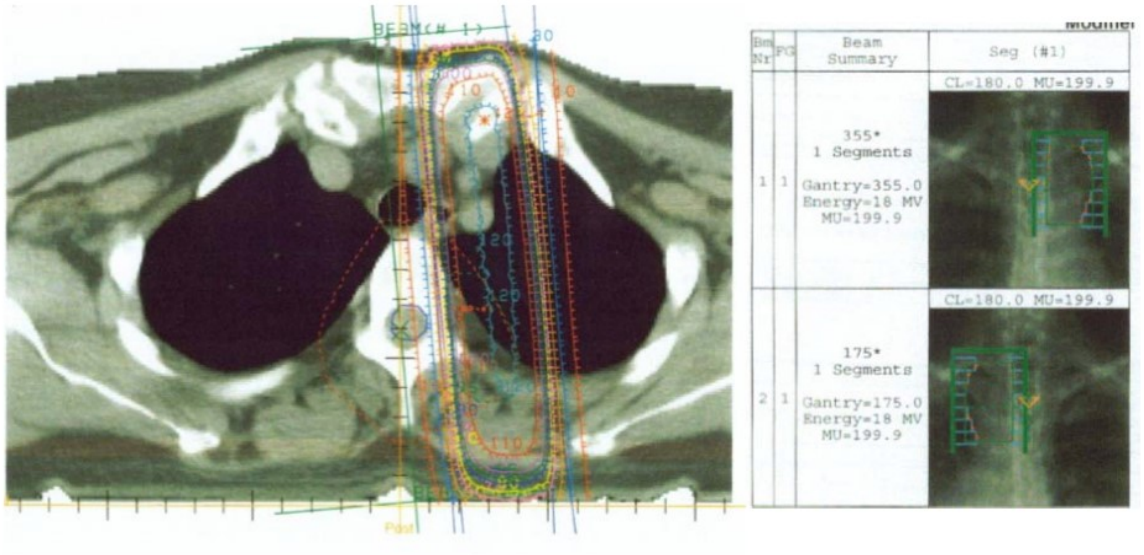
The past …?

- An example of re-irradiation for vertebral metastases

20 Gy wedged fields



20 Gy AP-PA with spinal cord sparing



- … in short: common sense

Courtesy M. Guckenberger ESTRO SBRT course

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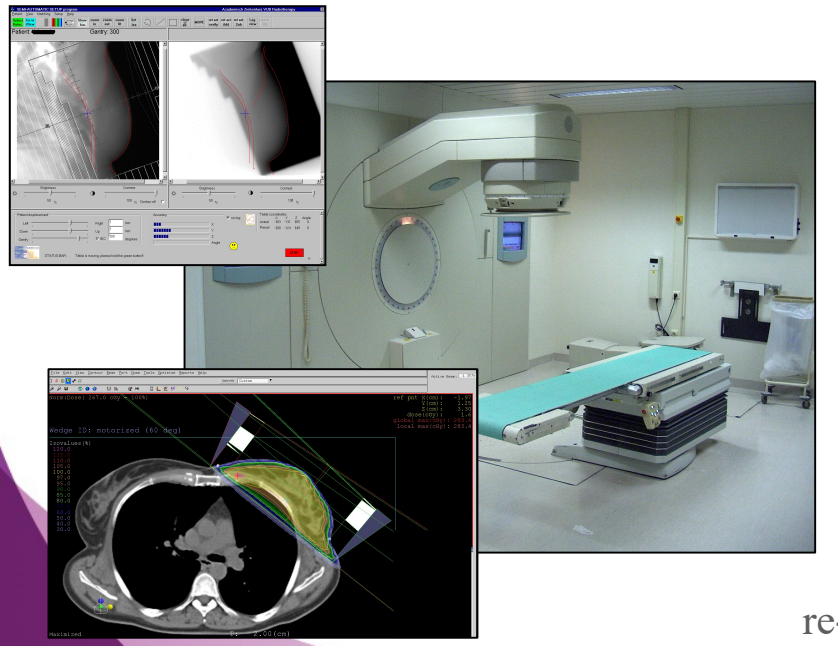
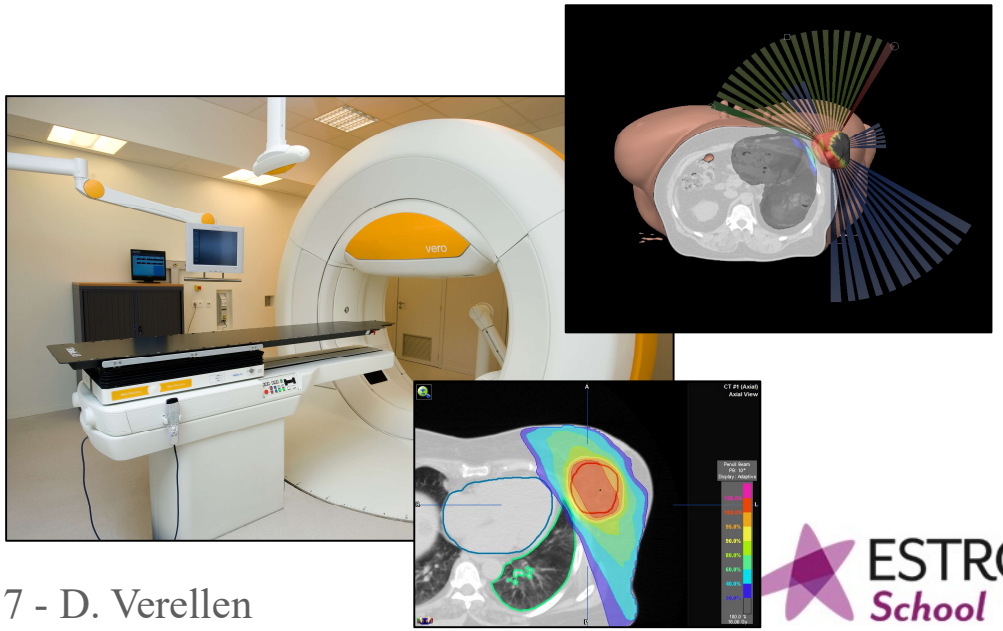
Dose accumulation … an example

- Sequential breast boost to illustrate the principle

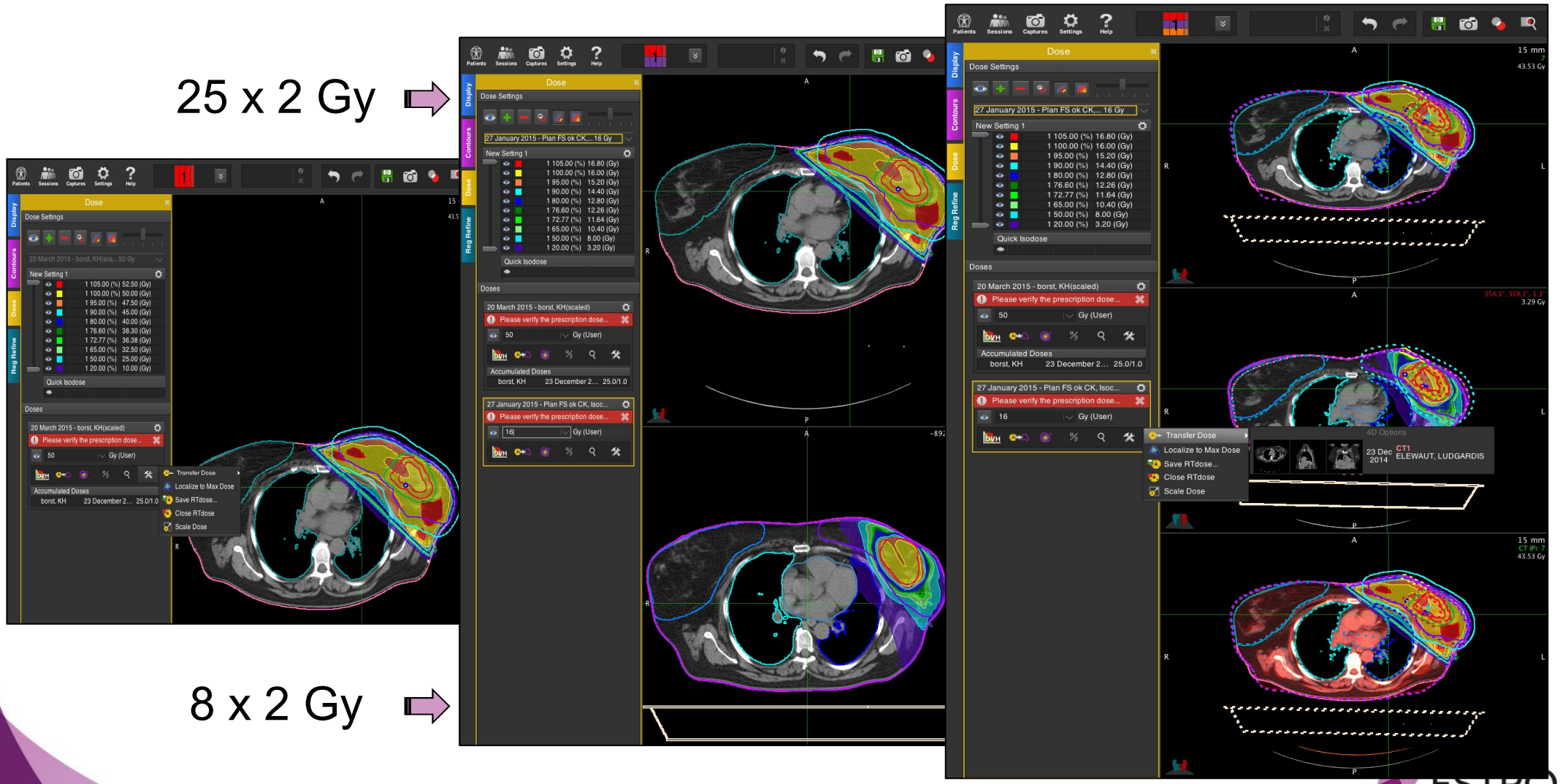
- As a temporary solution
  (in attendance of purchasing new treatment machine)
  - Whole breast irradiation is delivered on Elekta SLiPlus (without CBCT) / TPS: XiO CMS
  - Sequential boost is delivered on VERO system (CBCT) / TPS: iPlan





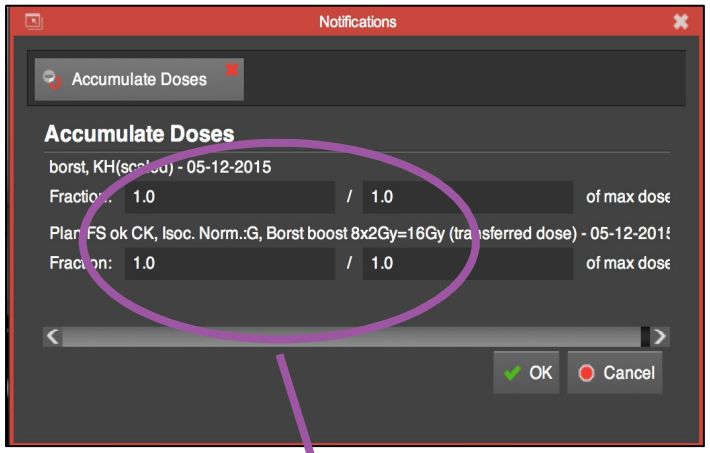
Dose accumulation … an example

- Sequential breast boost to illustrate the principle

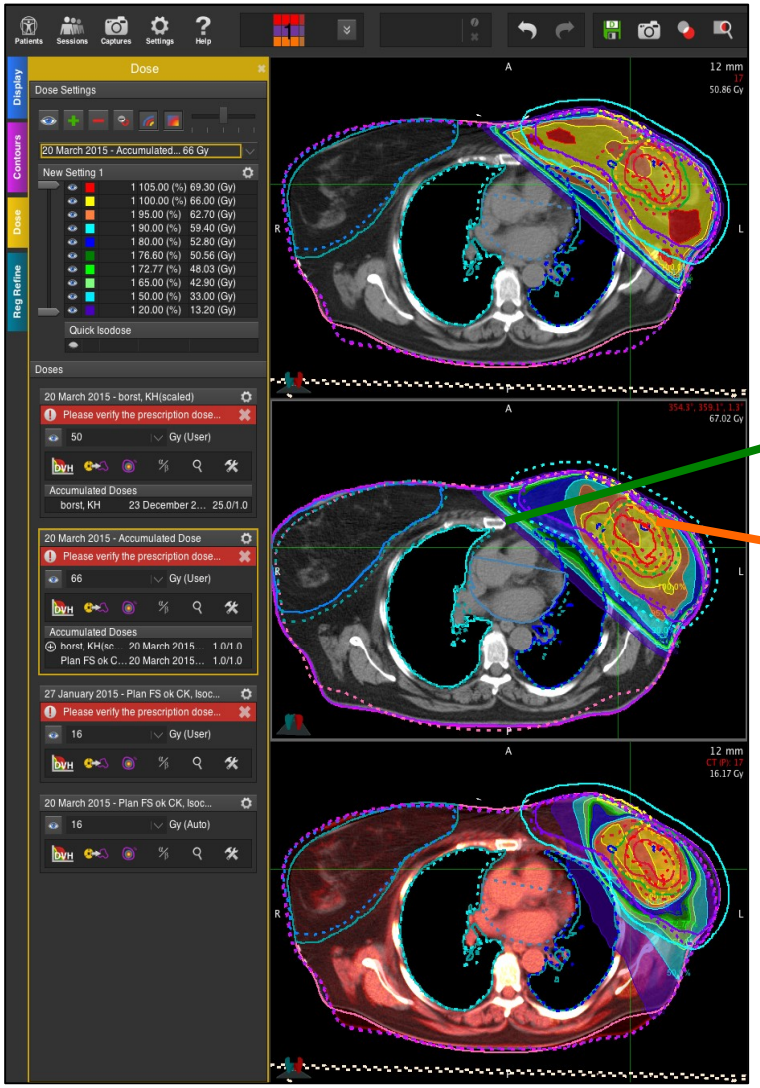


Dose accumulation … an example

- Sequential breast boost to illustrate the principle



Both 2 Gy equivalent



- **Accumulated**
- 95% D_p: 50Gy
- 95% D_p:66Gy

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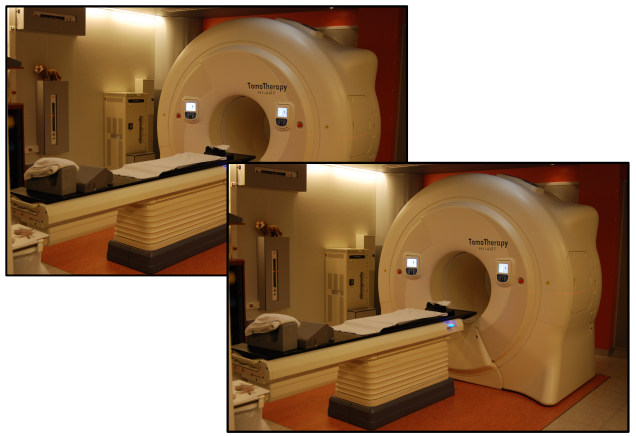
Accumulated dose a case study (1)

- A 75 year old, male patient
- 2012:
  - Prostate cancer
  - TUR + 39x2Gy + androgen deprivation
- 2014:
  - **Adenocarcinoma oesophagus**
  - Surgery
- 2015:
  - Recurrence of adenocarcinoma
  - Surgery + neo adjuvant Radio-chemotherapy (41.4 Gy)
- 2016:
  - Metastases (liver + cervical vertebra C7, overlapping with primary)
  - C7: 15x2.5 Gy (original protocol: 15x 3Gy)

Accumulated dose a case study (1)



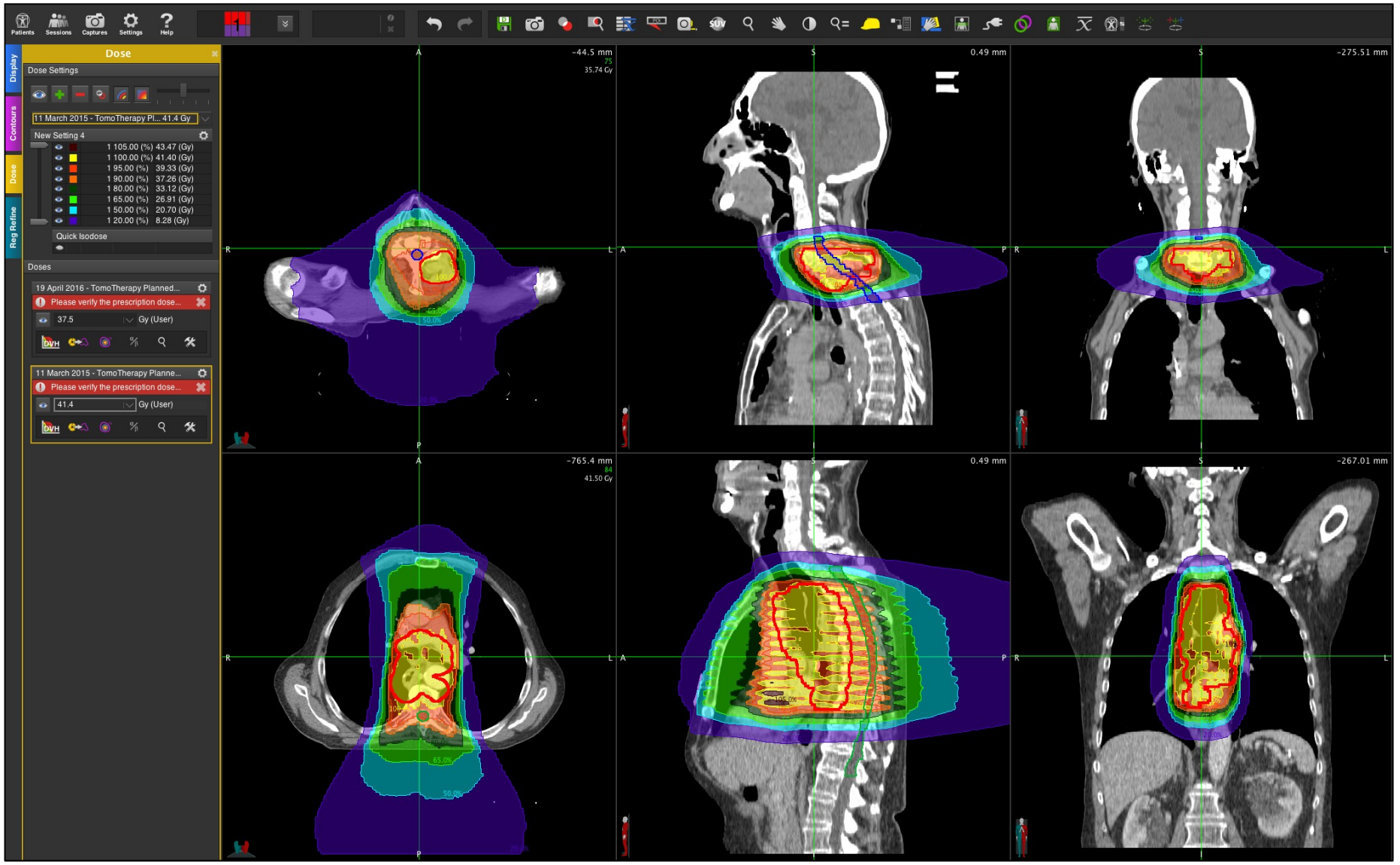
- Treatment approach re-irradiation:

- Previous irradiation (TomoTherapy): **23 x 1.8 Gy = 41.4 Gy**
- Re-irradiation (TomoTherapy): **15 x 2.5 Gy = 37.5 Gy**

- Dose distribution adapted/compromised based on accumulated dose accounting for spinal cord tolerances.

- **Assumption**s:
  - No recovery (previous irradiation late 2015, re-irradiation early 2016)
  - Spinal cord tolerance: **50 Gy $EQD_{2/2}$** ($EQD_{2/2} = D \times \frac{d + \alpha/\beta}{2 + \alpha/\beta}$)
    (2 Gy equivalent dose with $\alpha/\beta = 2$:

Accumulated dose
a case study (1)



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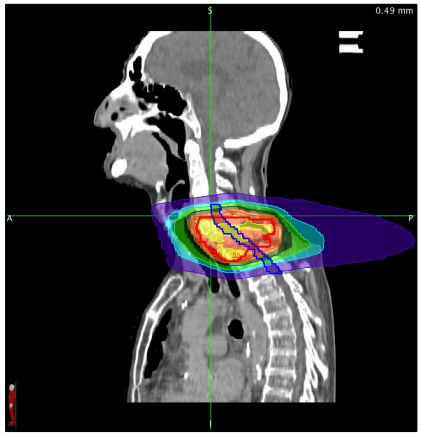
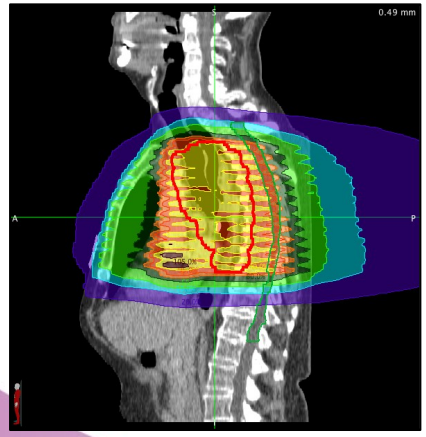
Accumulated dose
a case study (1)

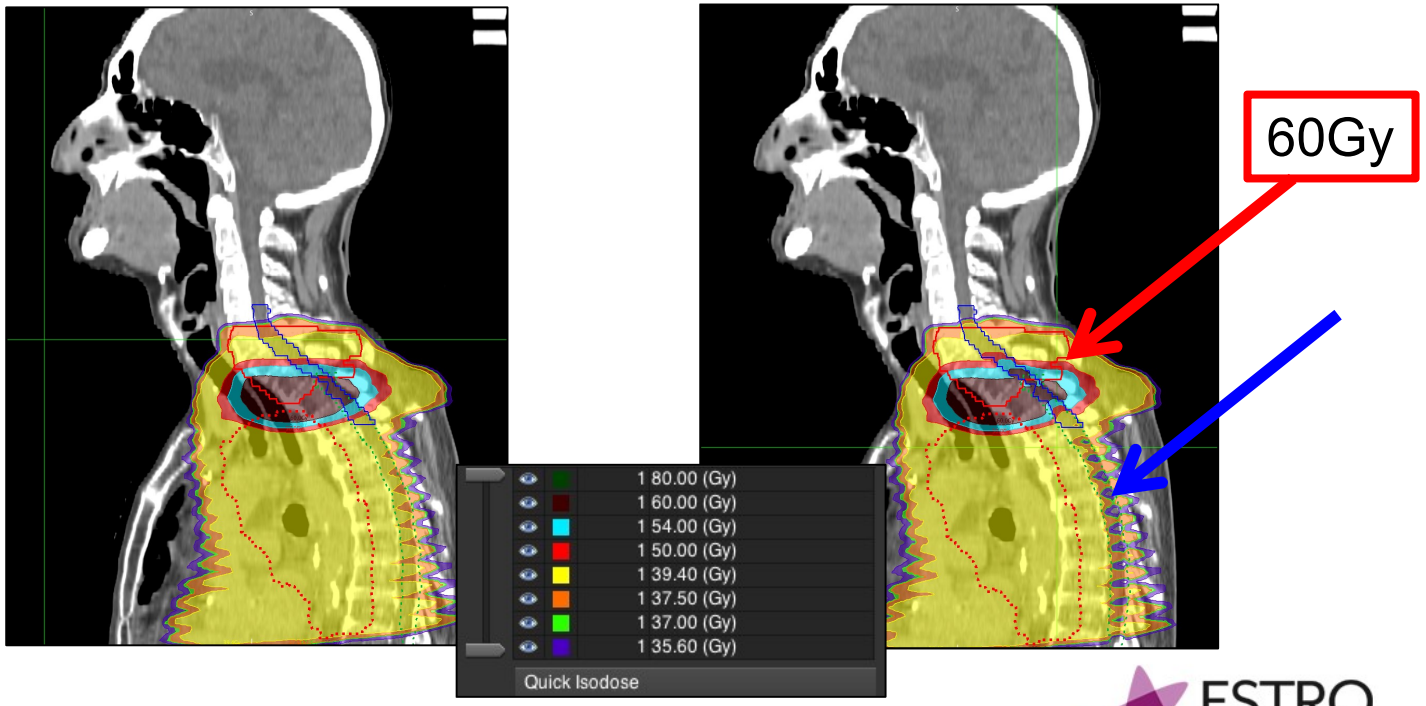
- Just adding the treatments, ignoring previous treatment **is not an option**:
  - In this particular case the dose distributions overlap due to the "TomoTherapy over-travel" although both PTV's do not overlap!!!





Total Dose

EQD2/2 (spinal cord only)



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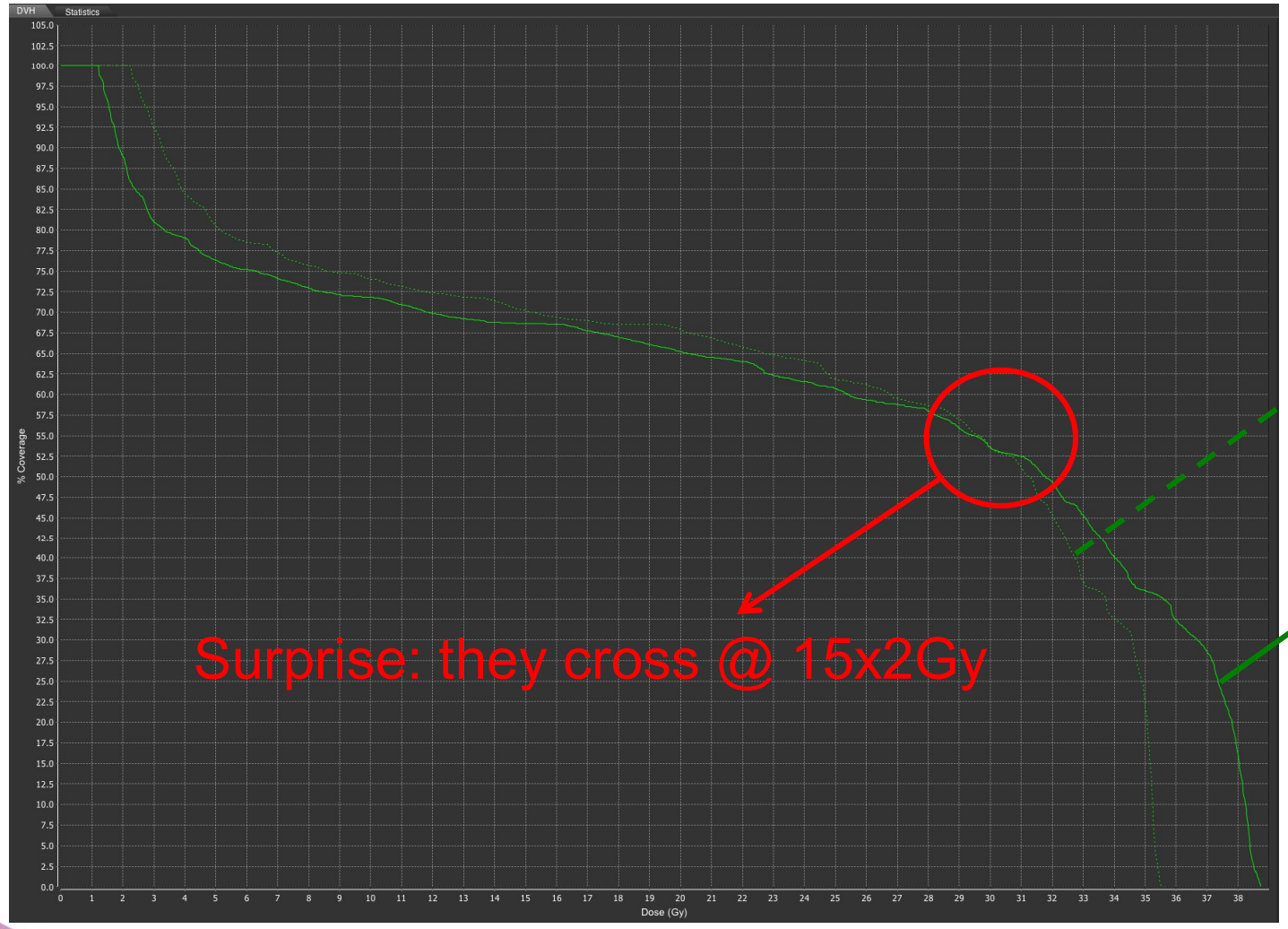
Accumulated dose a case study (1)

- For illustration purposes we will only focus on the spinal cord



D_p = 15 x 2.5 Gy

Dose Re-irradiation

EQD2/2 Re-irradiation

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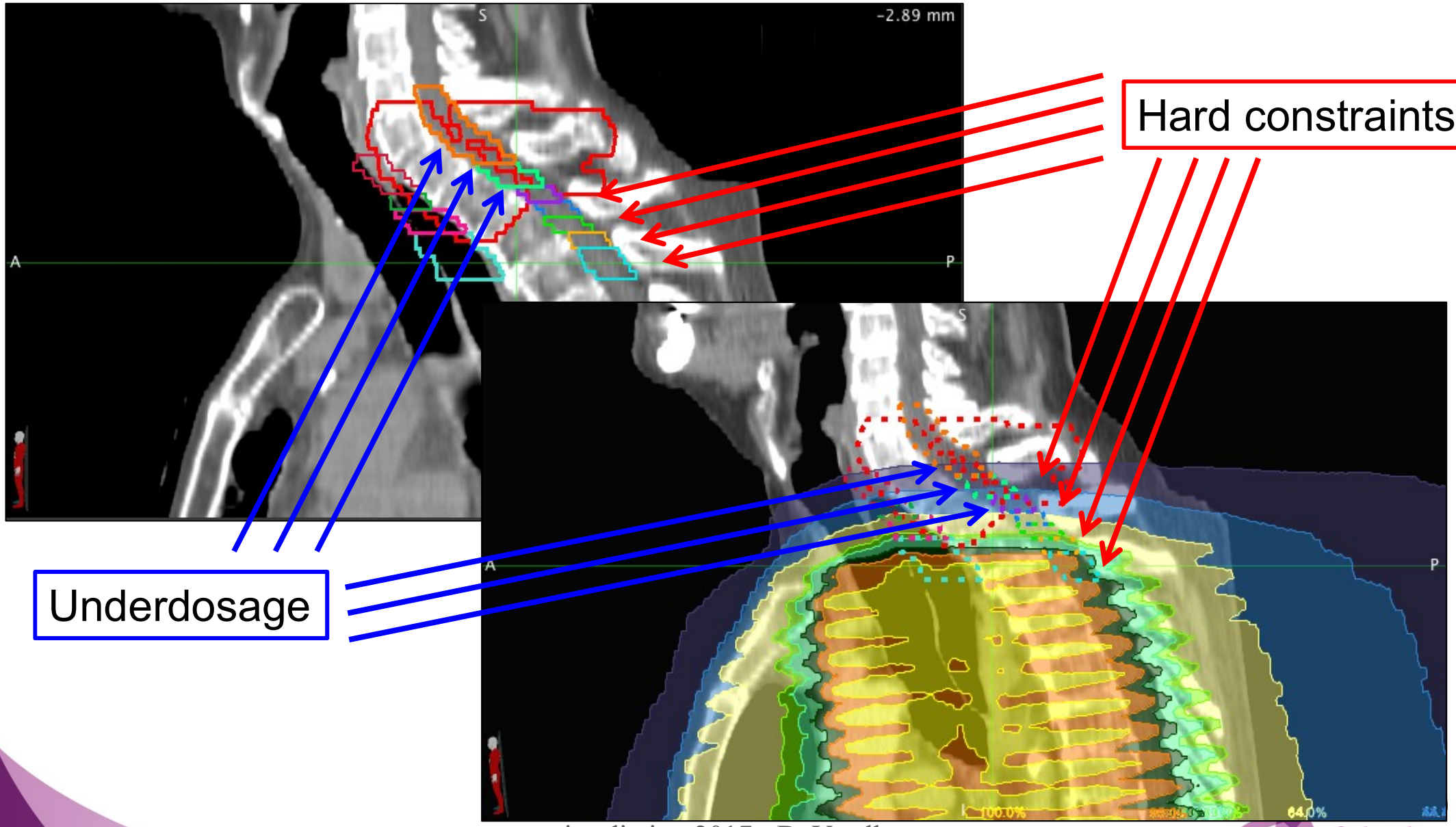
Accumulated dose a case study (1)

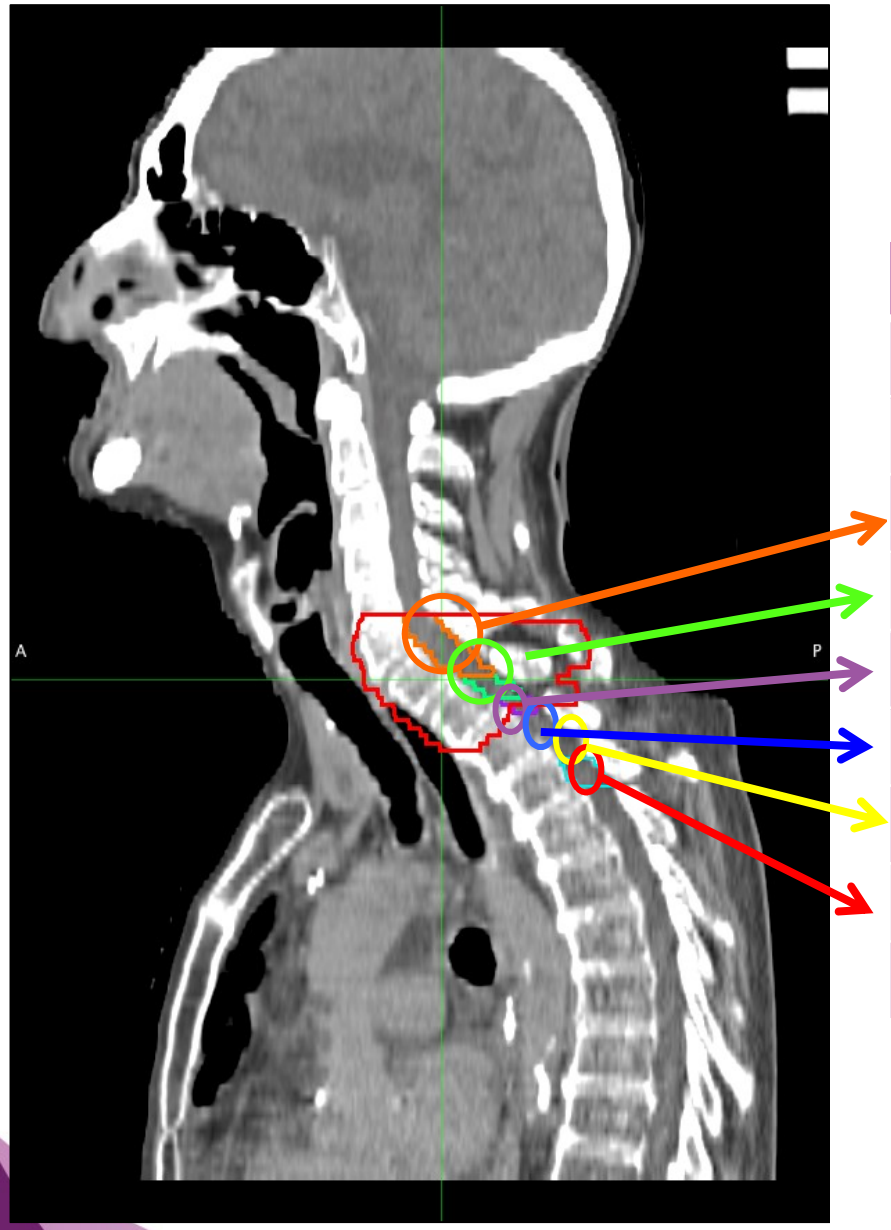
- **3 different scenario's will be illustrated**:

- (**1**) Accumulate (physical) dose of primary and re-irradiation
  - Evaluate the dose received to different regions of the spinal cord, correct for EQD2/2
  - Define tolerance dose for re-irradiation to these different regions using EQD2/2, translate to physical dose, and use this in the optimization algorithm
- (**2**) Accumulate dose distribution of primary and re-irradiation, but rescaled to EQD2/2 to assess dose to spinal cord.
- (**3**) Recalculate both dose distributions with EQD2/2 in spinal cord only, physical dose everywhere else, and accumulate.
- *… Recalculate dose distribution with EQD2/2 in all OARs* ***and*** *PTV, and accumulate … include recovery factors …*

Accumulated dose
a case study (1)



Accumulated dose a case study (1)



D_P = 23 x 1.8 Gy		D_P = 15 x 2.5 Gy	
$D_{received}$	$EQD_{2/2}$	$EQD_{2/2}$	$D_{tolerated}$
16.4	11.1	38.9	35.6
21.0	15.3	34.7	33.0
25.7	20.0	30.0	30.0
31.7	26.8	23.2	25.2
34.6	30.3	19.7	22.5
37.4	33.9	16.1	19.5
	Tolerance $EQD_{2/2}$ = 50.0 Gy		

Into the optimization

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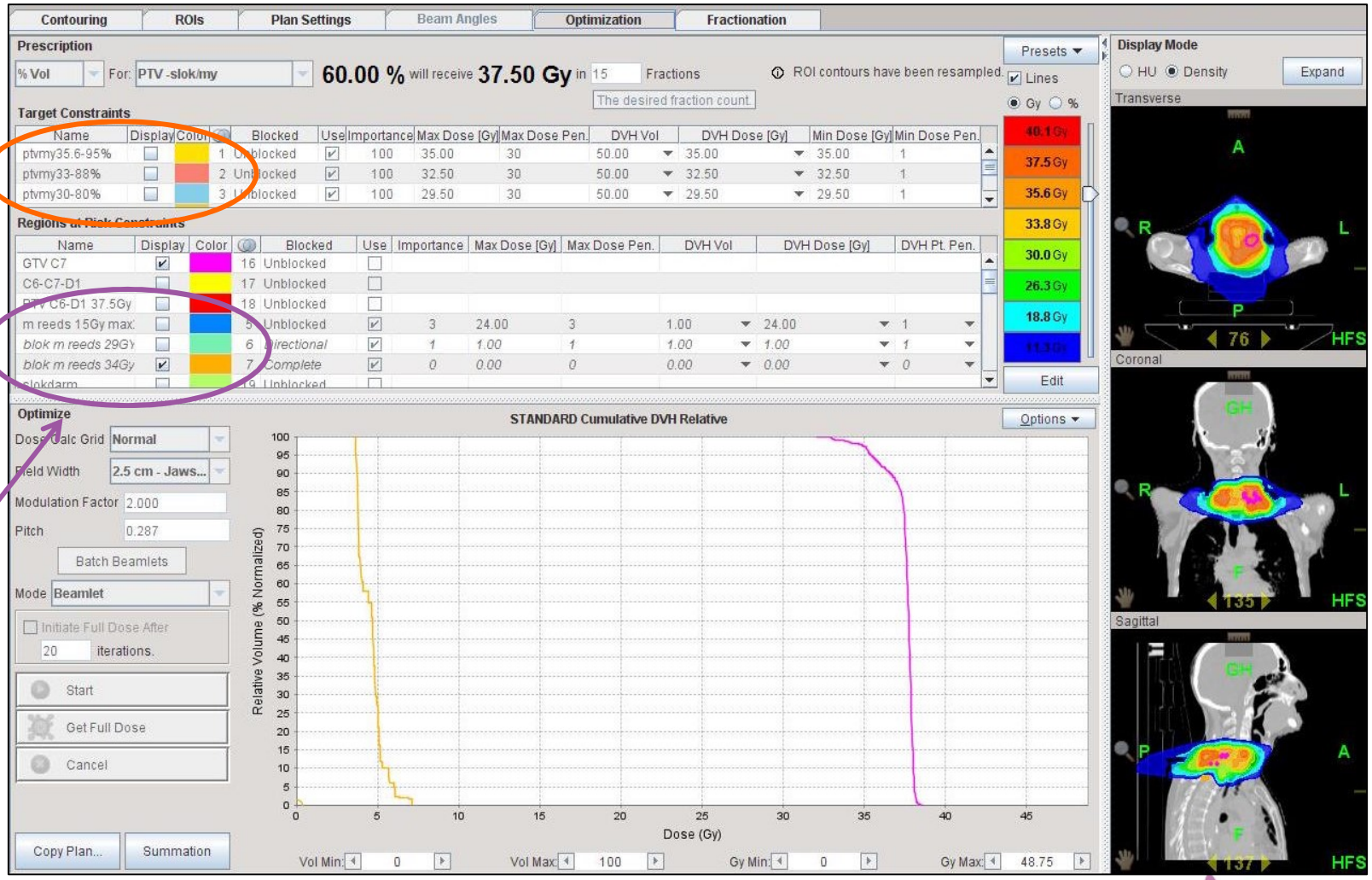
Accumulated dose a case study (1)

- Dose optimization

Spinal cord inside PTV: defined as Sub-PTV's

Spinal cord outside PTV: defined as OARs



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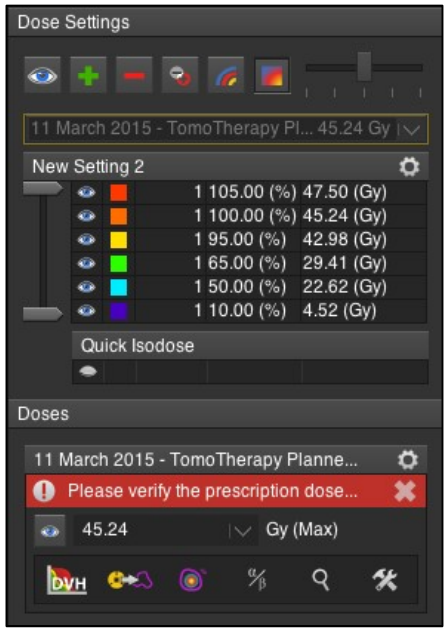
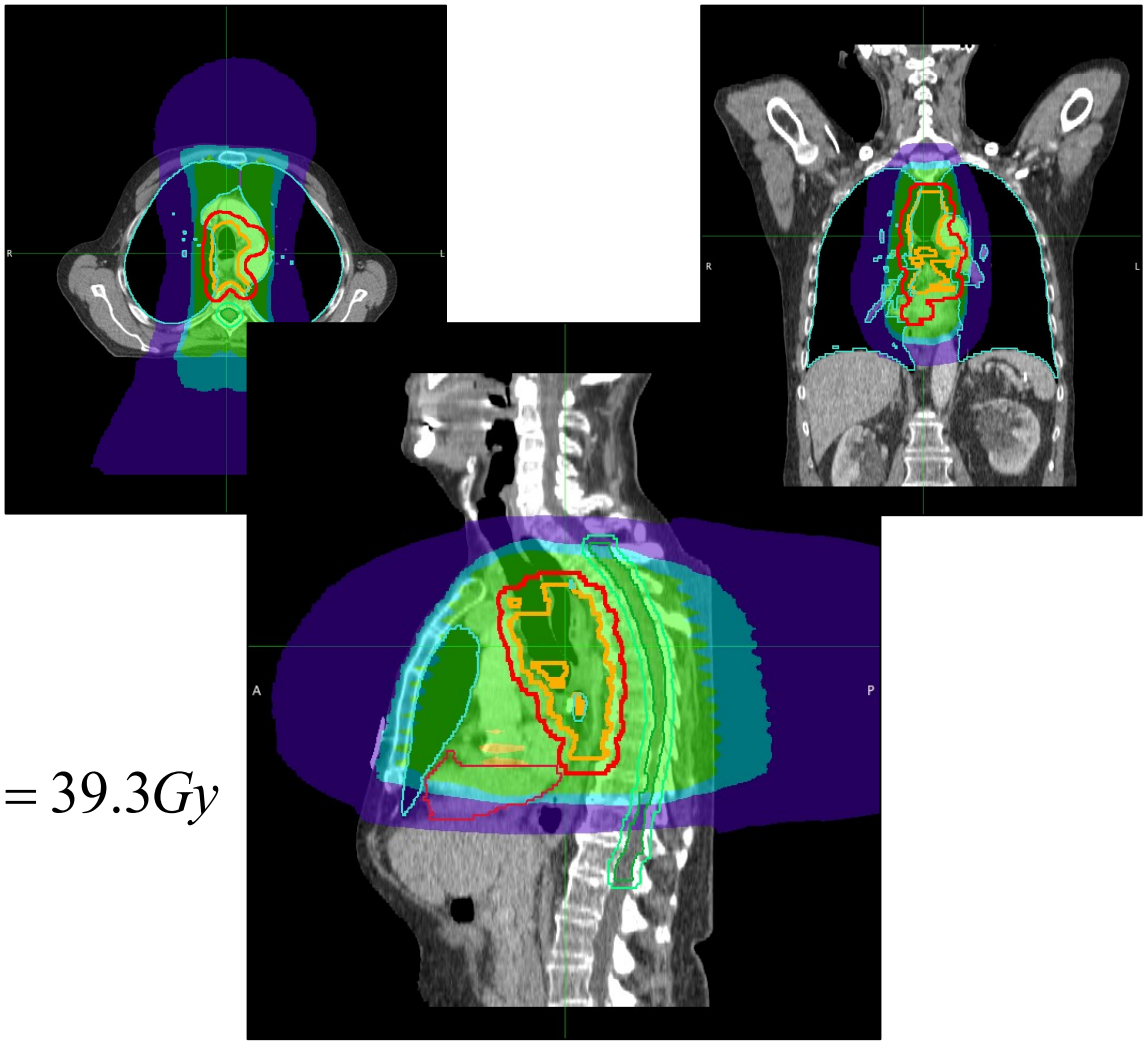
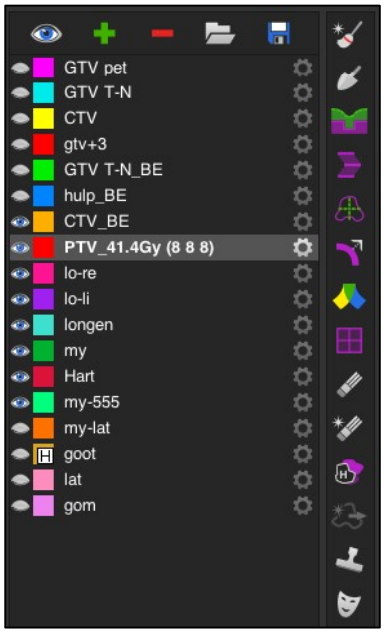
Accumulated dose a case study (1)

- Previous irradiation: 23 x 1.8 Gy = 41.4 Gy







$$EQD_{2/2} = 41.4 \times \frac{1.8+2}{2+2} = 39.3Gy$$

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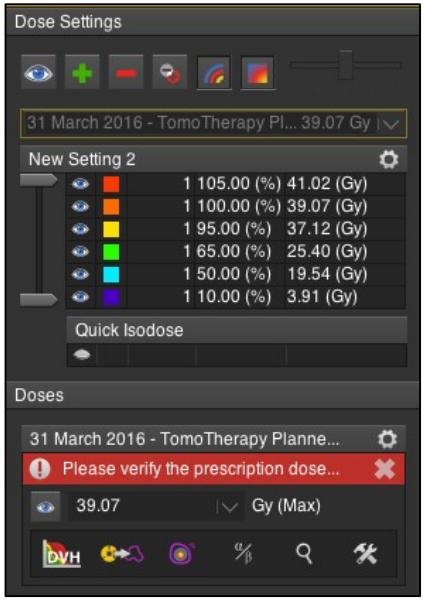
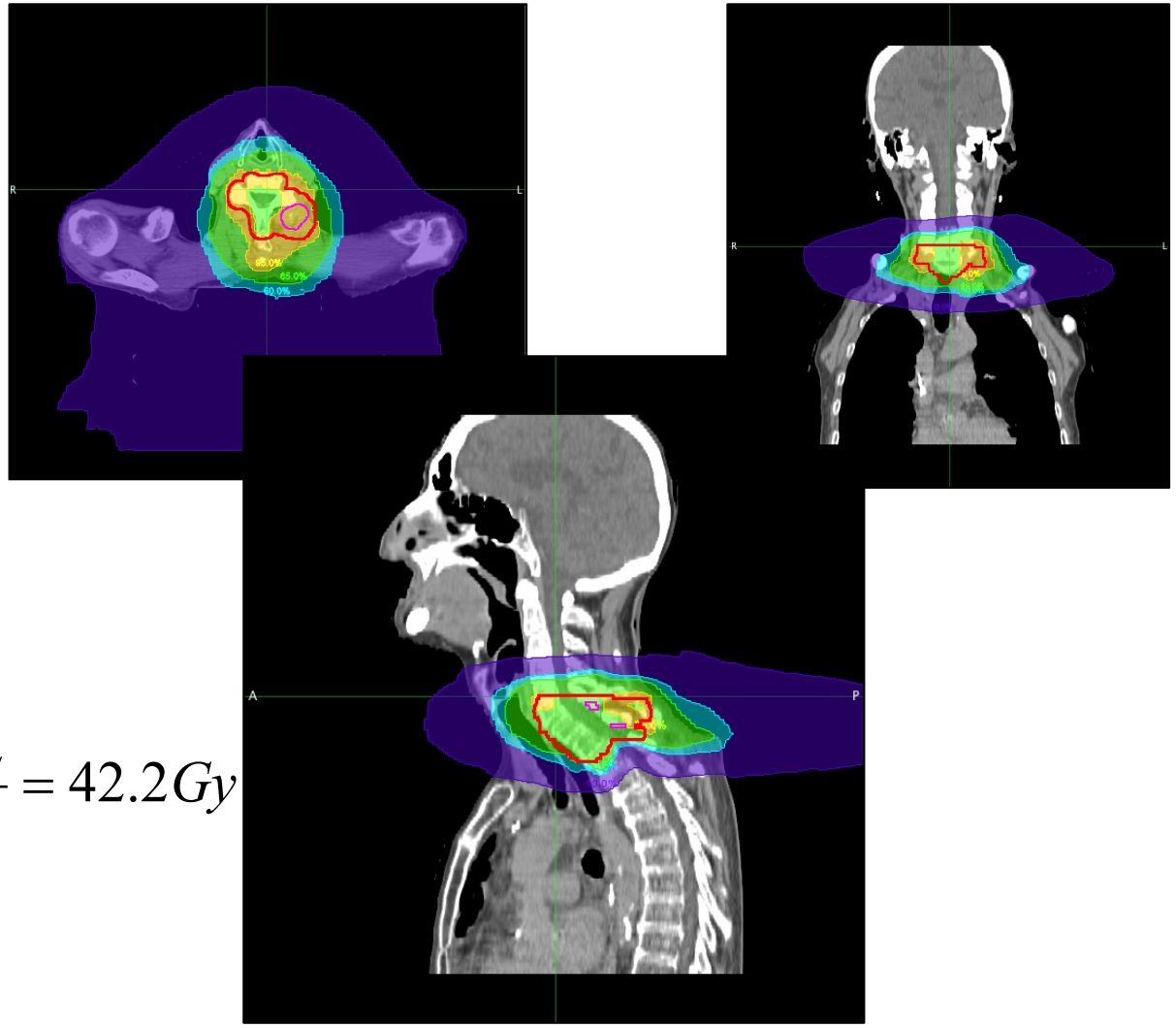
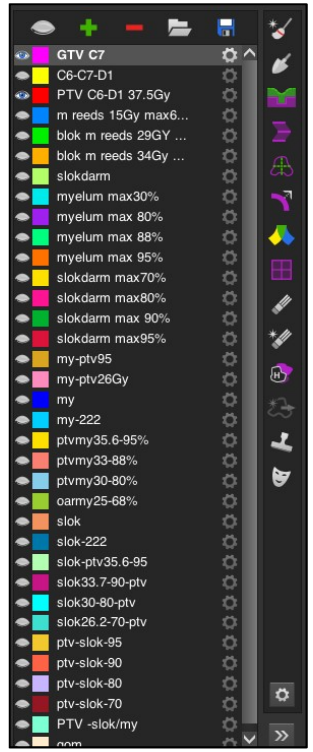
Accumulated dose
a case study (1)

- Re-irradiation: 15 x 2.5 Gy = 37.5 Gy (optimized based on tolerances)







$$EQD_{2/2} = 37.5 \times \frac{2.5+2}{2+2} = 42.2Gy$$

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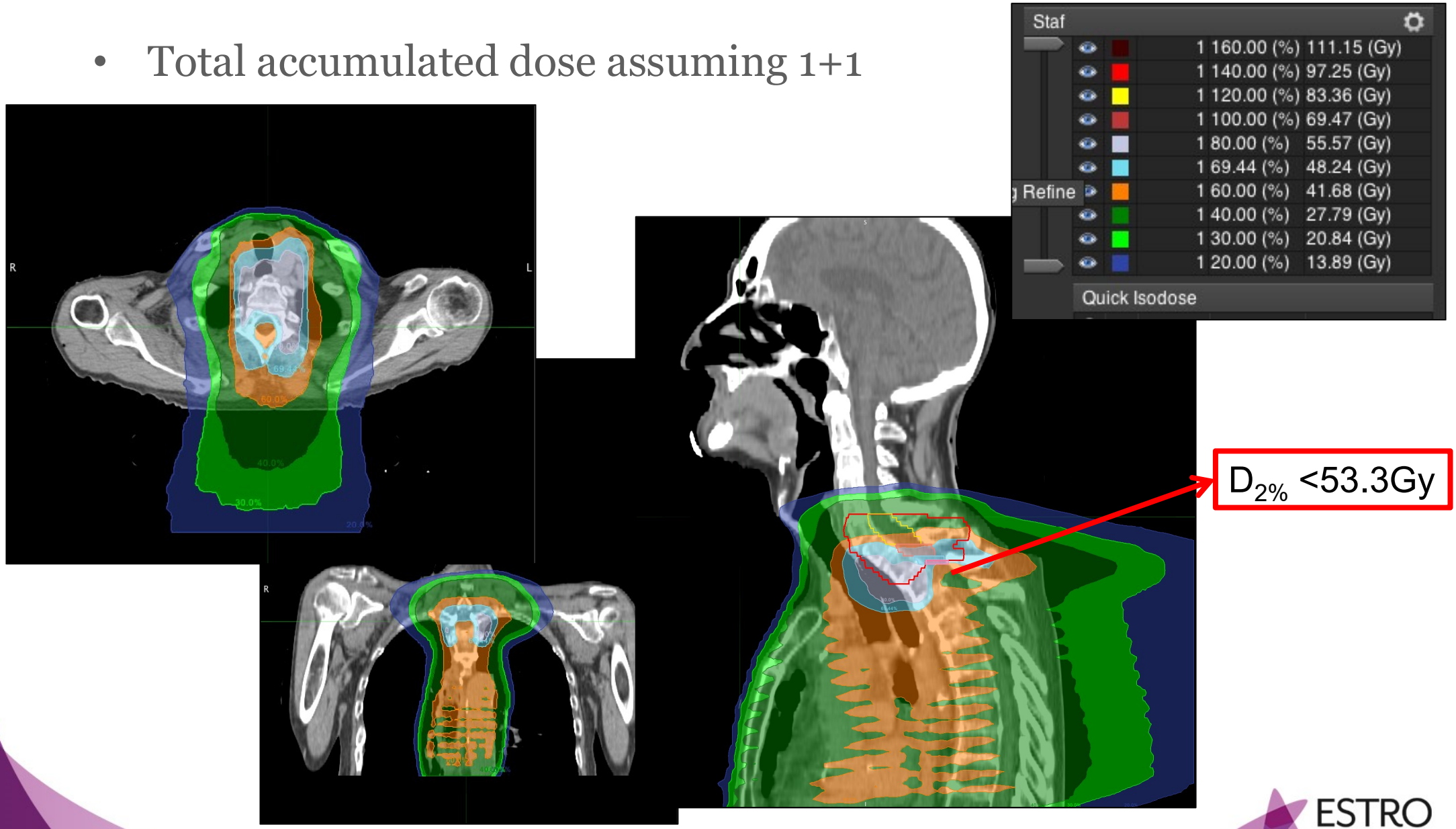
Accumulated dose a case study (1)

- Total accumulated dose assuming 1+1



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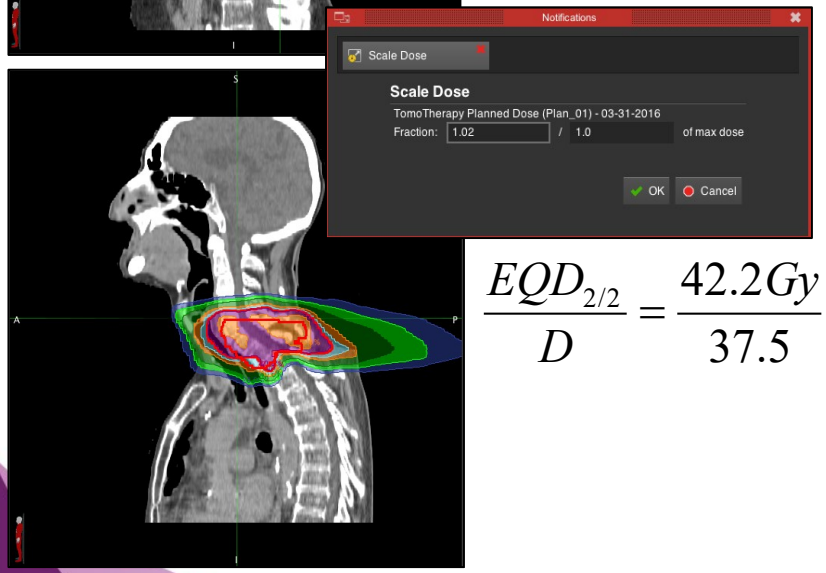
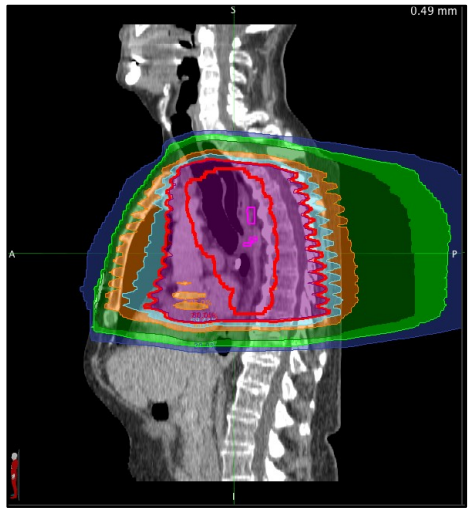
Accumulated dose a case study (1)

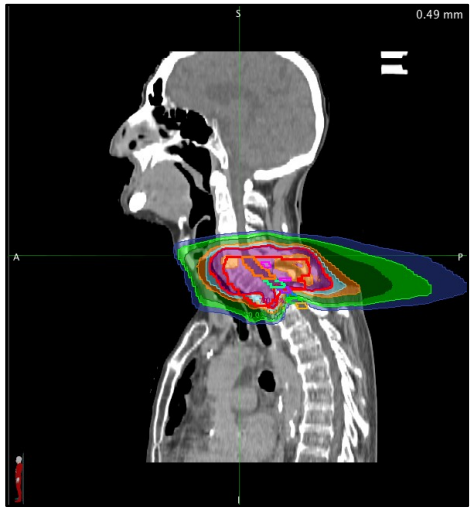
- Rescaling entire dose distribution for $EQD_{2/2}$, and accumulating rescaled doses

$$\frac{EQD_{2/2}}{D} = \frac{39.3Gy}{41.4}$$

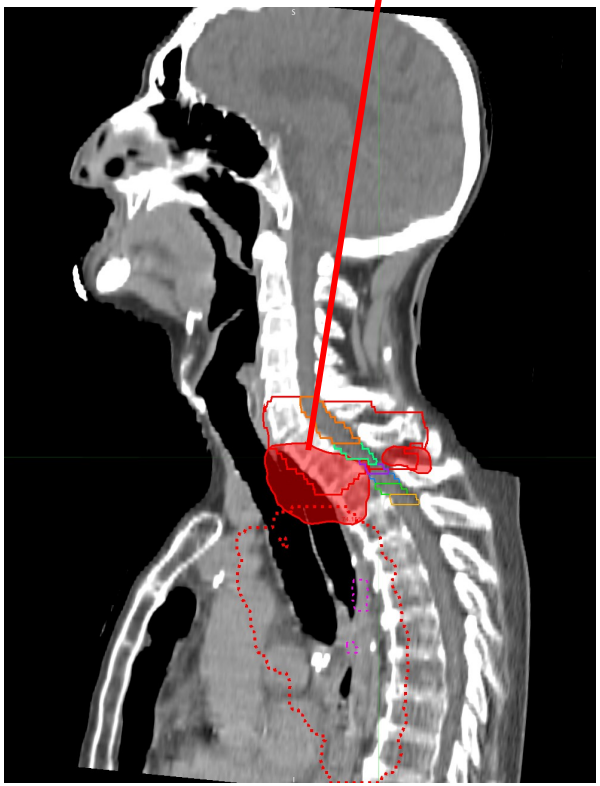


$$\frac{EQD_{2/2}}{D} = \frac{42.2Gy}{37.5}$$





$EQD_{2/2}$: 50 Gy



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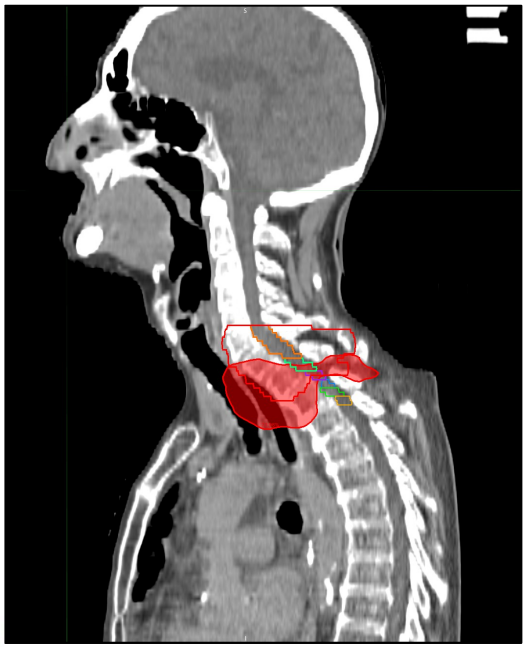
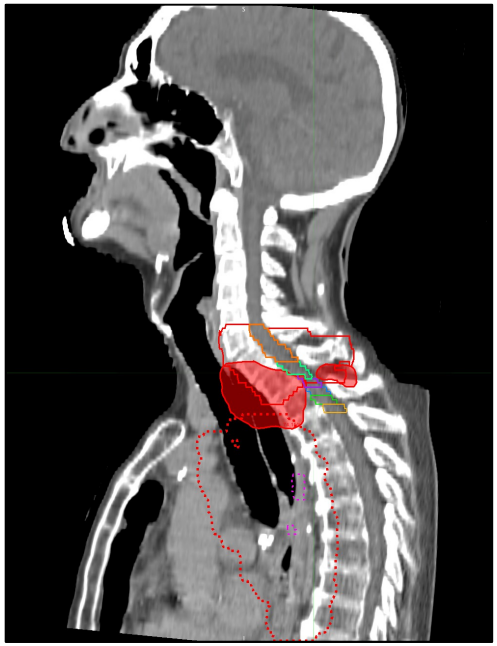
Accumulated dose a case study (1)

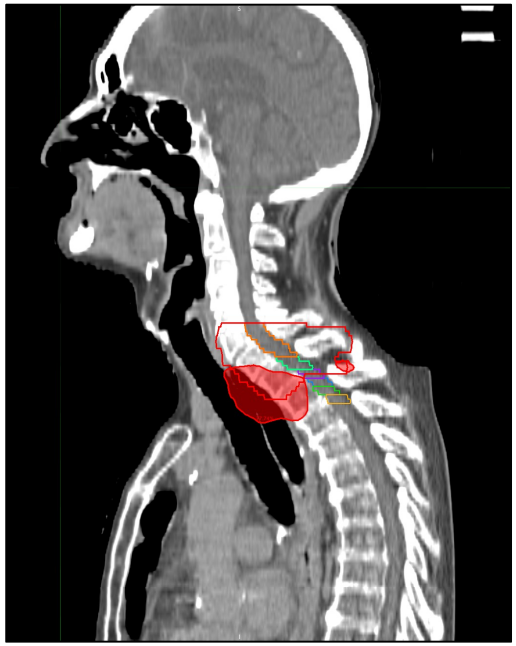
- Rescaling entire dose distribution for $EQD_{2/2}$, and accumulating rescaled doses



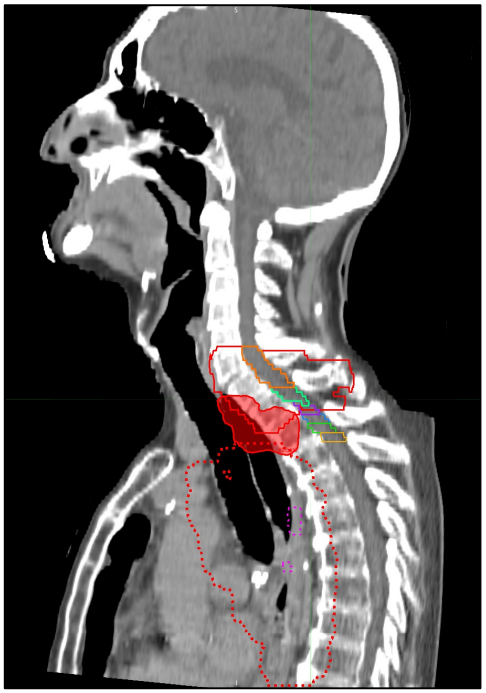
Dose: 50 Gy



$EQD_{2/2}$: 50 Gy



Dose: 54 Gy



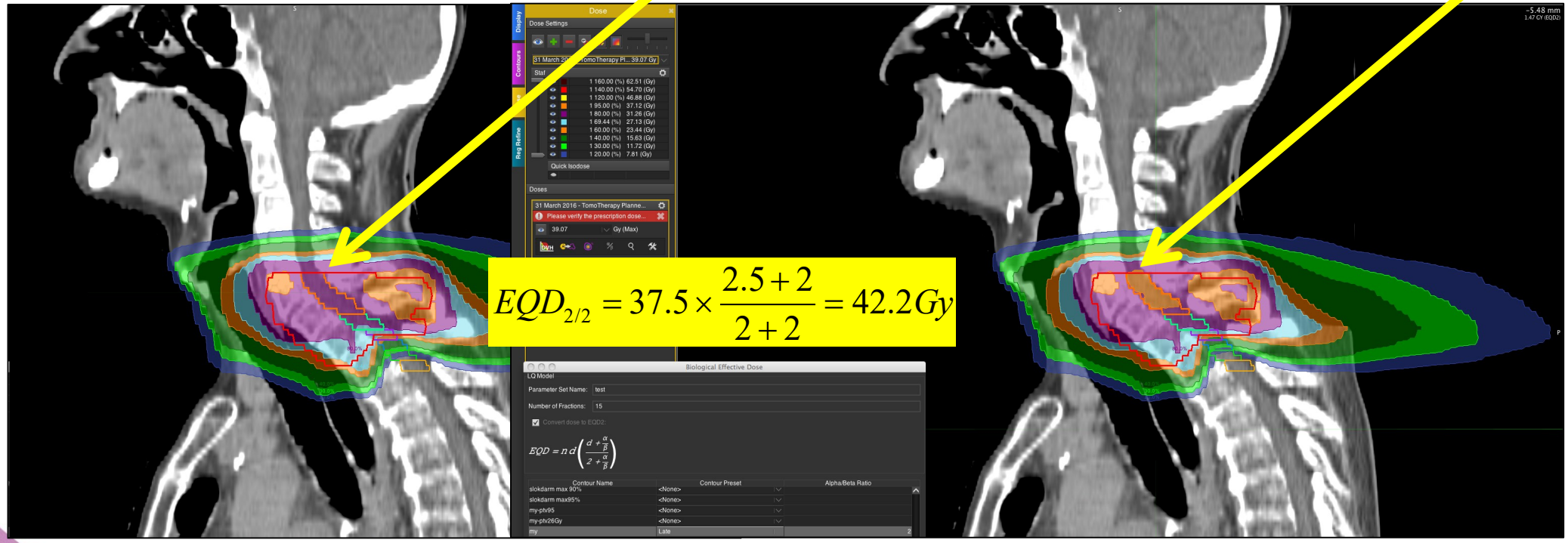
$EQD_{2/2}$: 54 Gy

Accumulated dose a case study (1)

- Dose corrected for $EQD_{2/2}$ in spinal cord (displayed dose outside spinal cord is uncorrected physical dose)

Re-irradiation Dose (uncorrected)

Re-irradiation $EQD_{2/2}$



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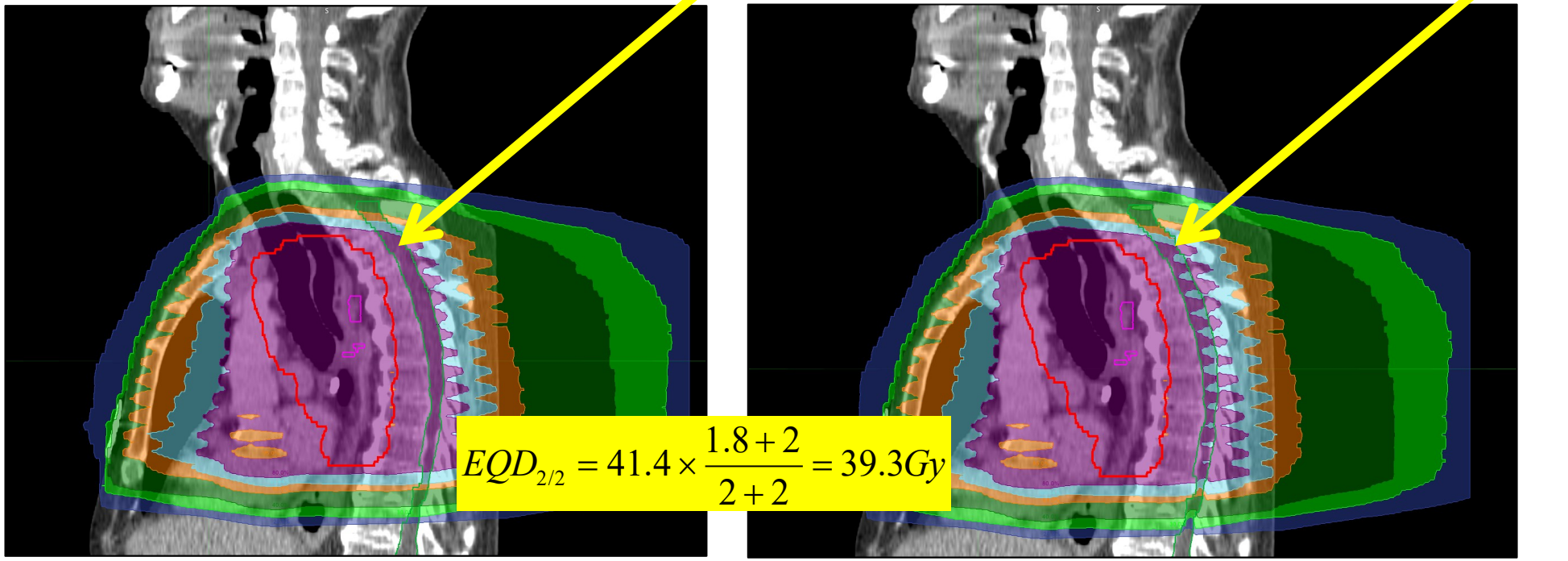
Accumulated dose a case study (1)

- Dose corrected for $EQD_{2/2}$ in spinal cord (displayed dose outside spinal cord is uncorrected physical dose)

Previous Dose (uncorrected)

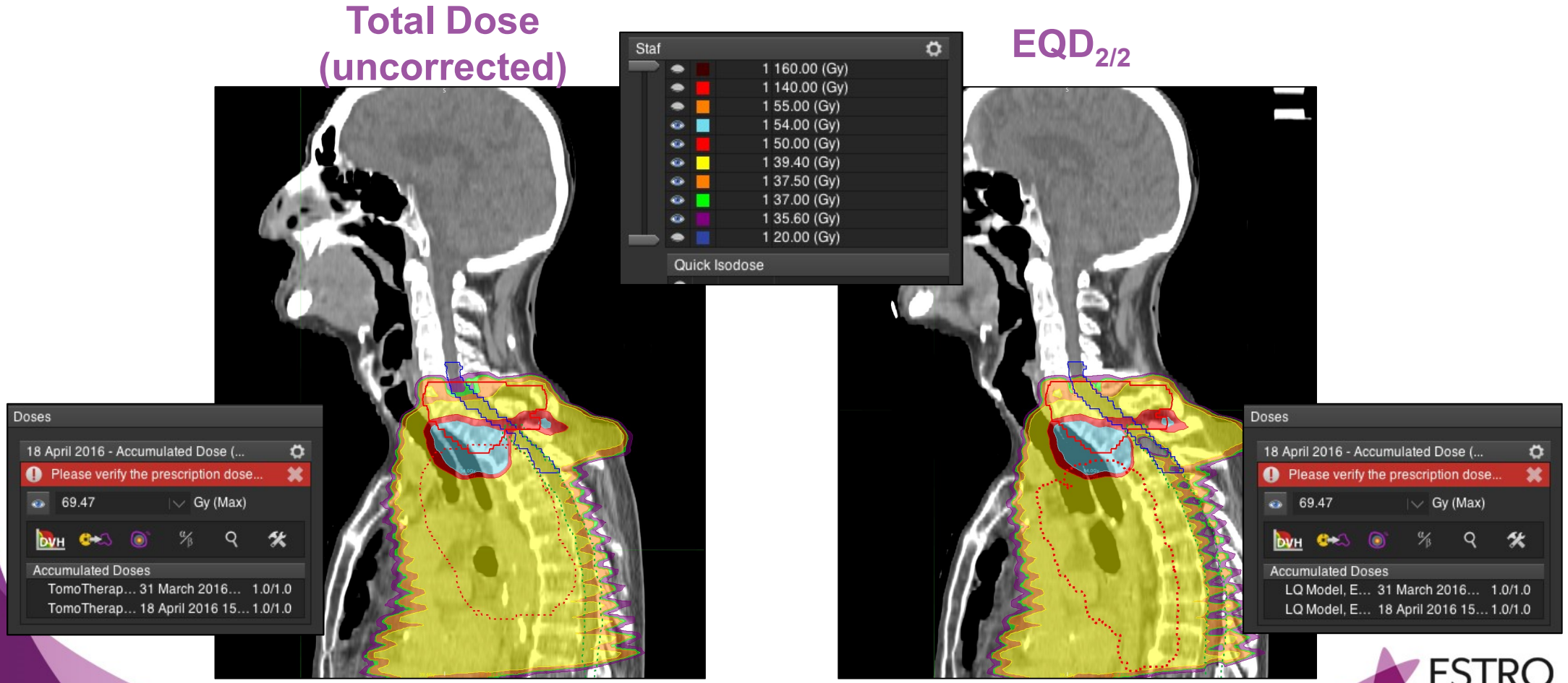
Previous $EQD_{2/2}$



$$EQD_{2/2} = 41.4 \times \frac{1.8+2}{2+2} = 39.3Gy$$

Accumulated dose
a case study (1)

- Dose corrected for $EQD_{2/2}$ in spinal cord and then accumulated (displayed dose outside spinal cord is uncorrected physical dose)



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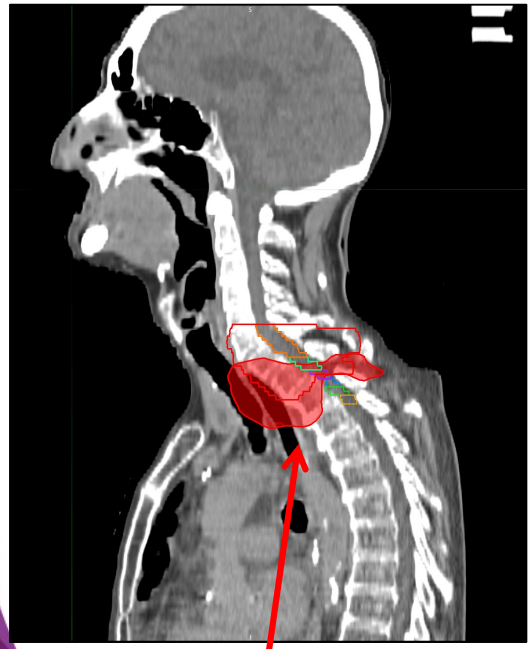
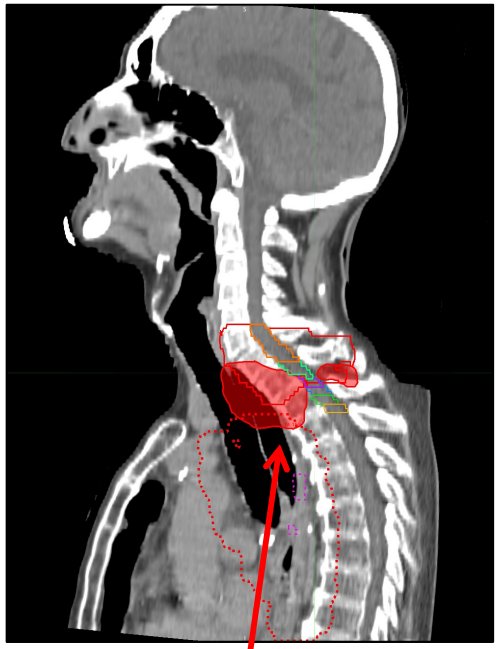
Accumulated dose a case study (1)

- 1st scenario:
  - Re-irradiation optimized using $EQD_{2/2}$ constraints, but accumulated dose = physical dose
  - $D_{2\%}$(spinal cord) = 53.3Gy (physical dose)

- 2nd scenario:

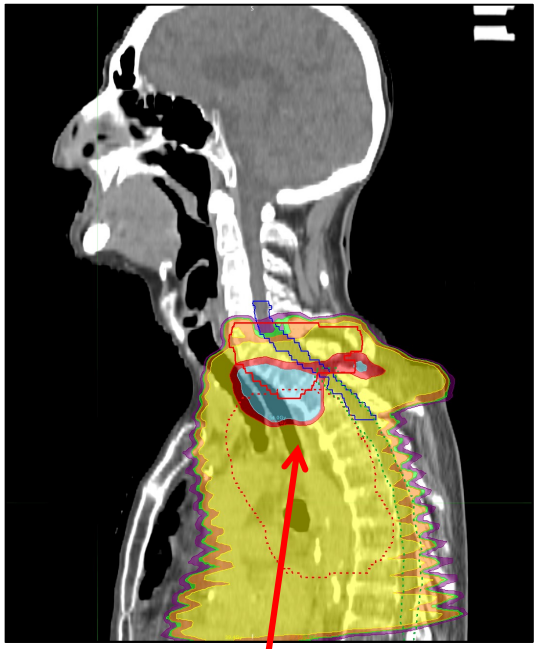


Dose: 50 Gy

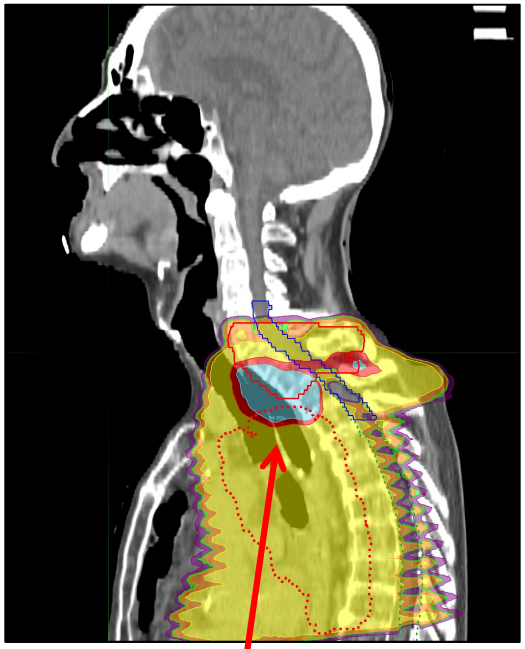


$EQD_{2/2}$: 50 Gy

- 3rd scenario:

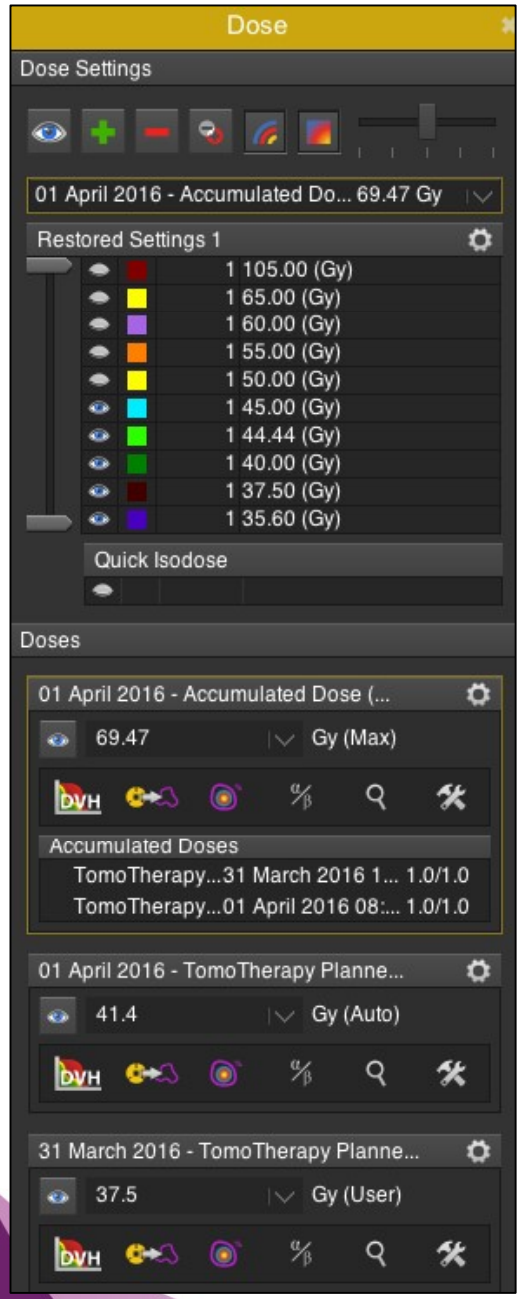


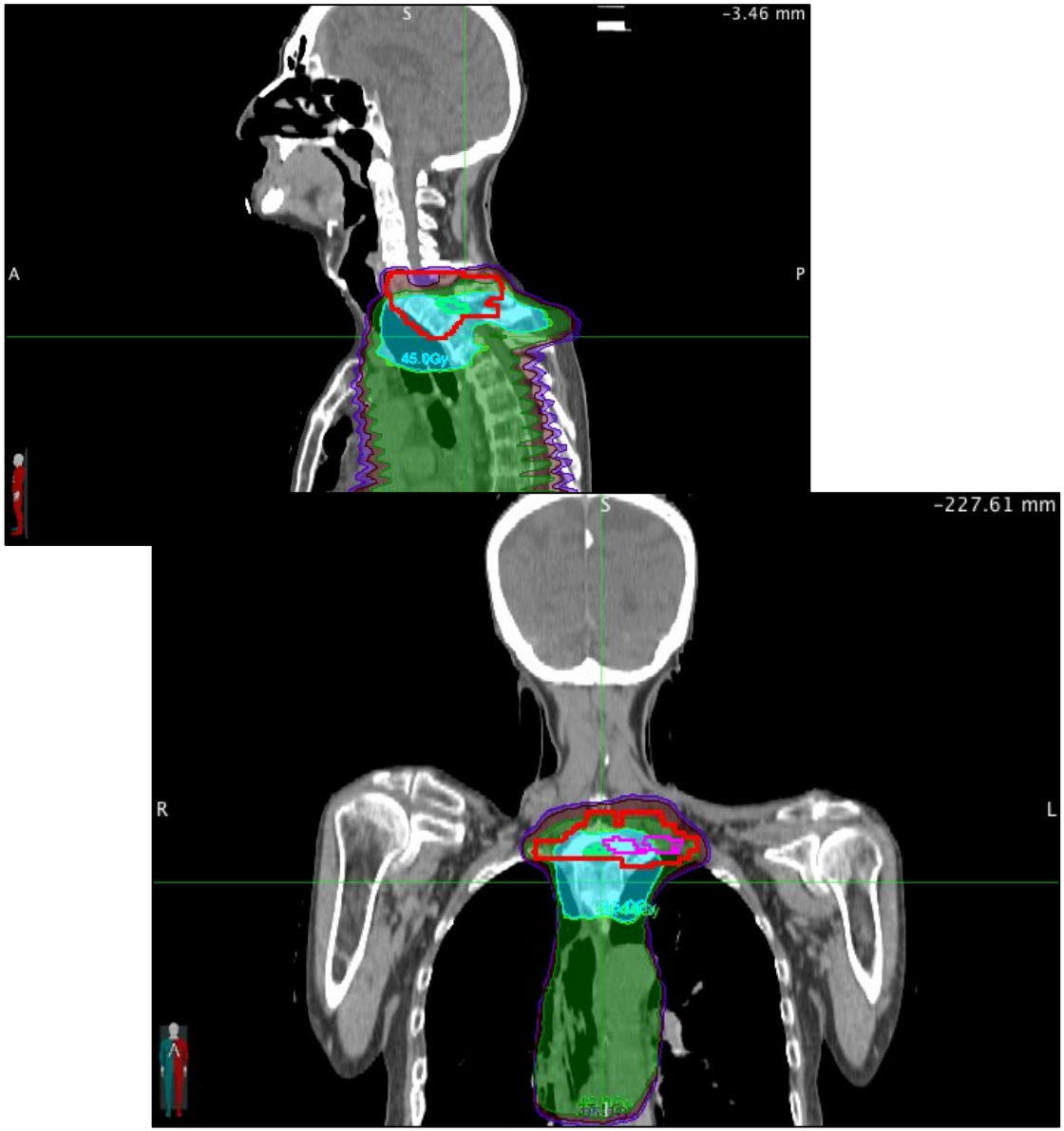
Dose: 50 Gy

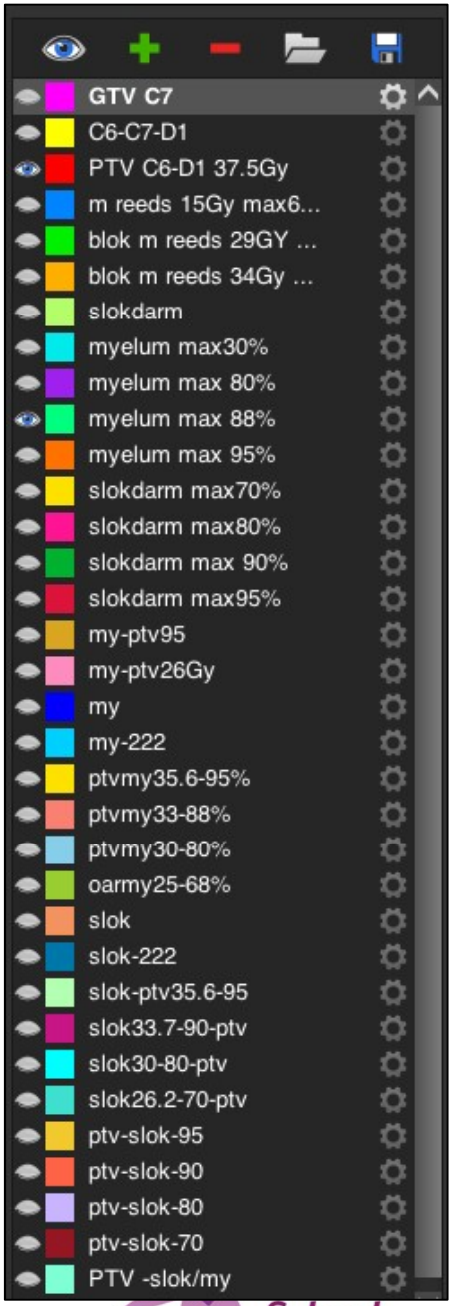


$EQD_{2/2}$: 50 Gy

Accumulated dose a case study (1)

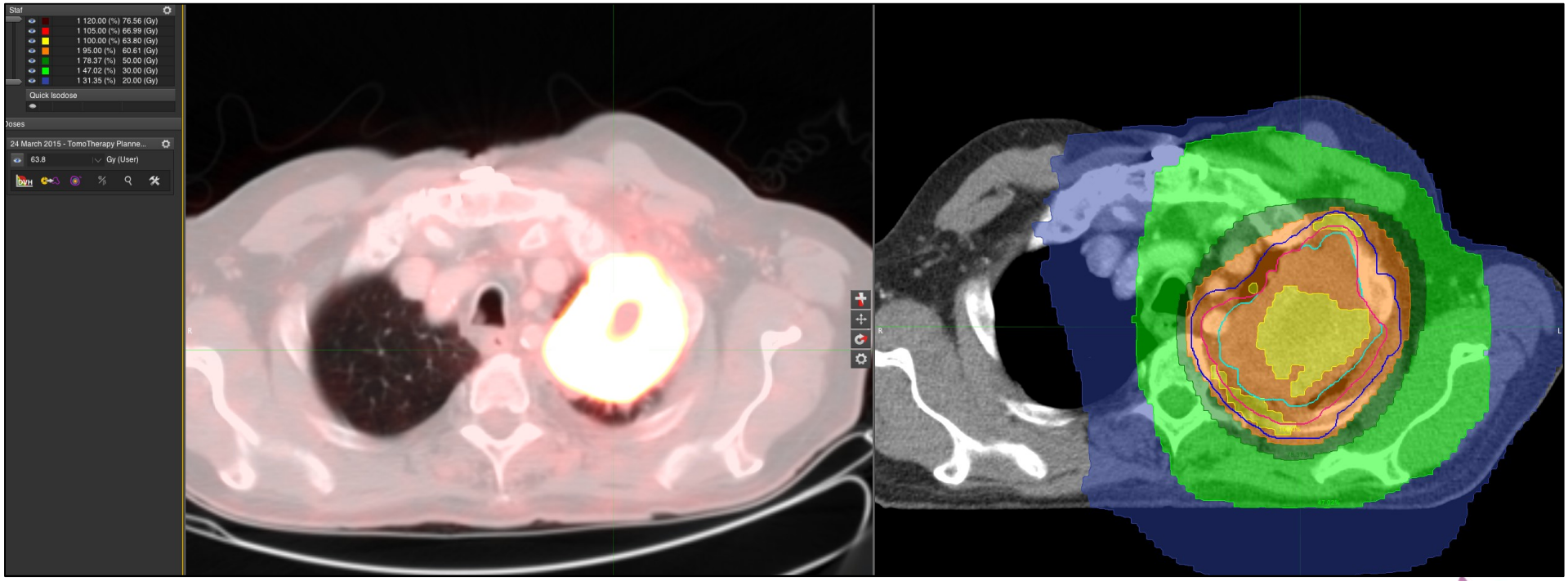






Accumulated dose a case study (2)

- A 75 year old, male patient
- February 2015:
  - NSCLC (squamous cell) grade3, $cT_3N_0M_0$
  - Left upper lobe
  - Radiochemotherapy, TomoTherapy: 30 x 2.13 Gy = 63.9 Gy



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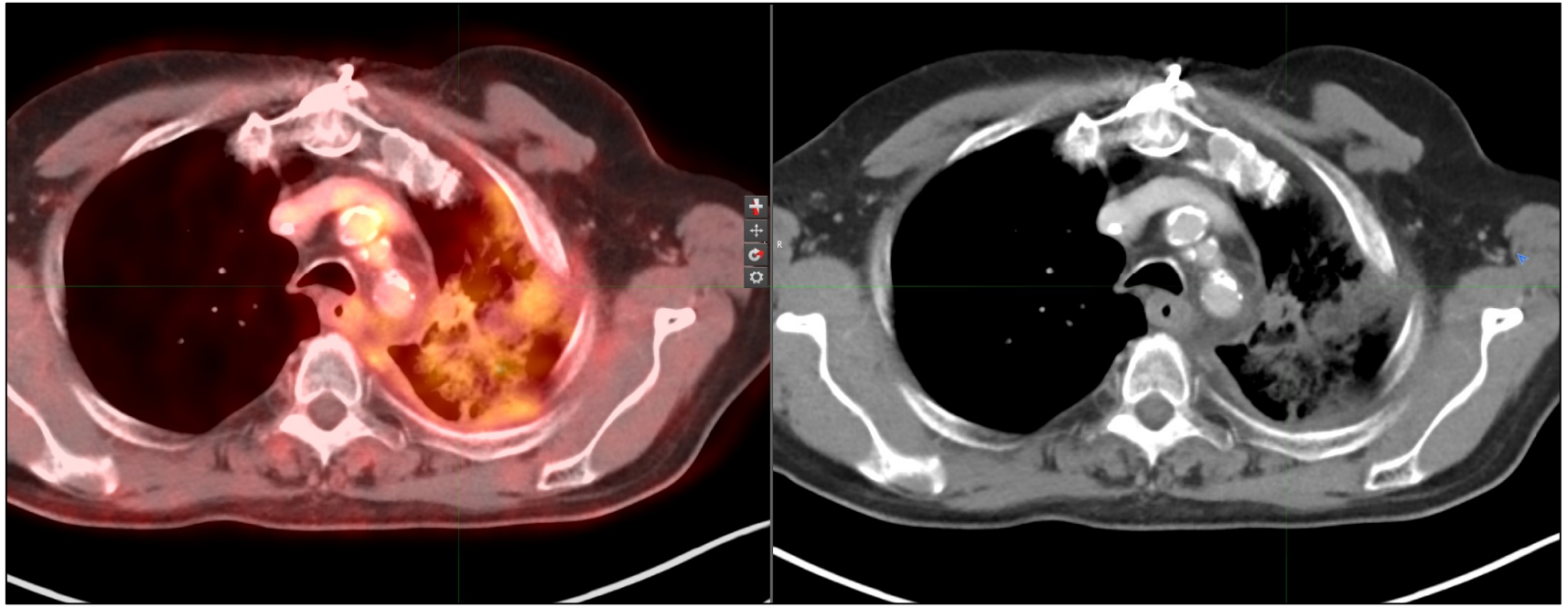
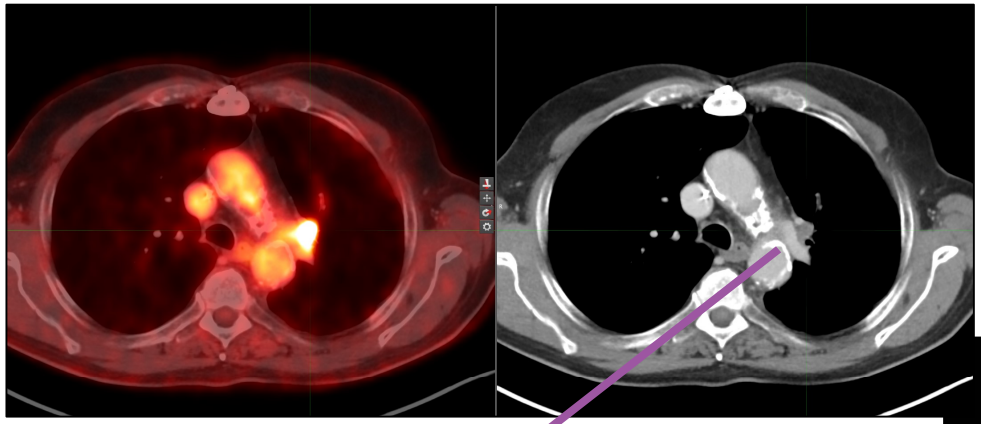
Accumulated dose a case study (2)

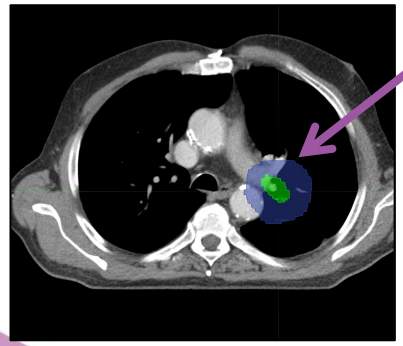
- A 75 year old, male patient
- March 2016:
  - NSCLC (squamous cell) grade3, $cT_3N_0M_0$
  - Left upper lobe
  - Feb 2015: Radiochemotherapy, TomoTherapy: 30 x 2.13 Gy = 63.9 Gy



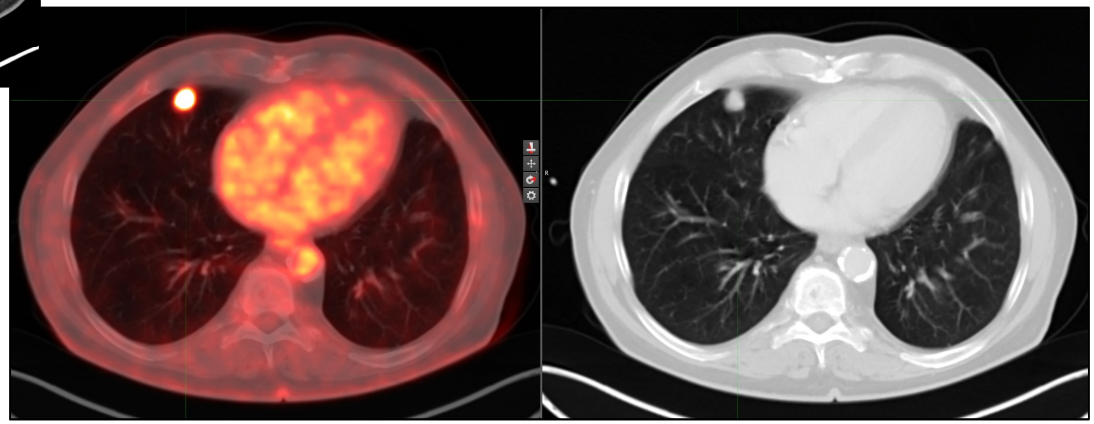
Accumulated dose
a case study (2)

- A 75 year old, male patient
- September 2015:
  - New small mediastinal hypermetabolic lesion
  - watch-and-wait

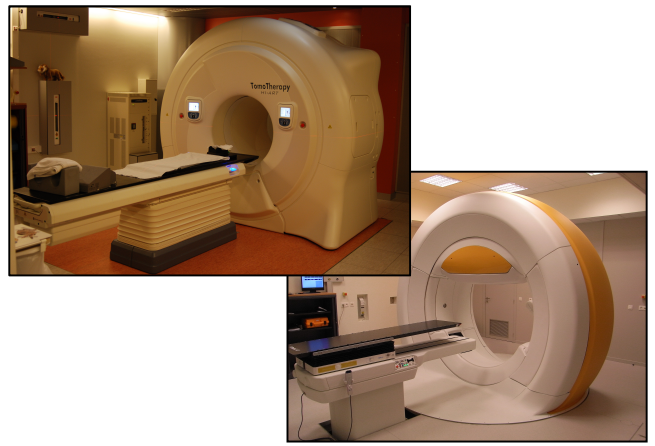




- January 2016:
  - New nodule, right middle lobe



Accumulated dose a case study (2)



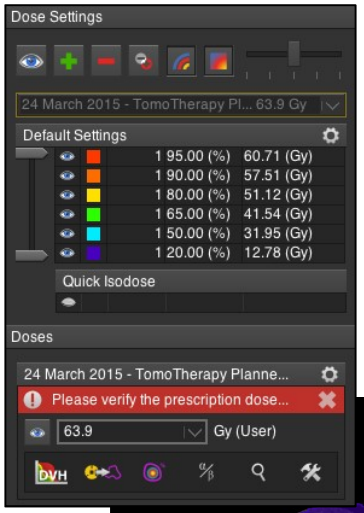
- Treatment approach re-irradiation:

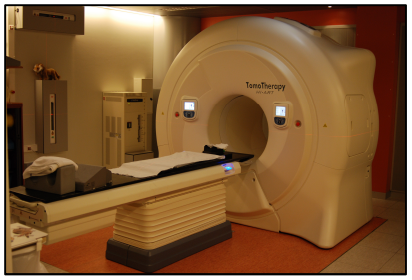
- Previous irradiation (TomoTherapy): **30 x 2.13 Gy = 63.9 Gy**
- Re-irradiation (VERO):
  - Mediastinal: **10 x 4 Gy = 40 Gy**
  - Right Middle Lobe: **10 x 5 Gy = 50 Gy**

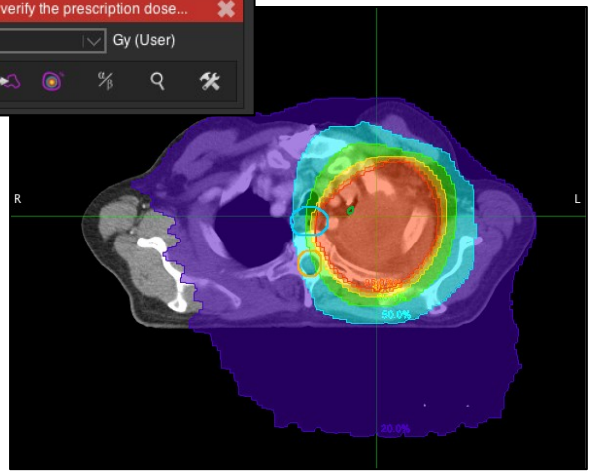
- **Assumption**s:
  - Acute toxicity for lungs and oesophagus less relevant considering gap of 1 year.
  - For both oesophagus and lungs an $\alpha/\beta = 3$ is assumed for late toxicity
    - Lungs: $V_{20} < 40\%$
    - Oesophagus: $D_{2\%} < 68$ Gy (ie maximum 10Gy with re-irradiation)

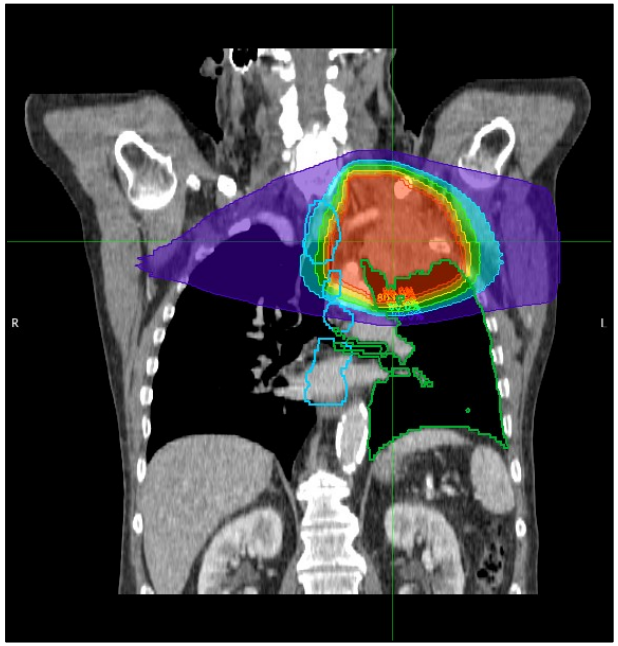
Accumulated dose
a case study (2)

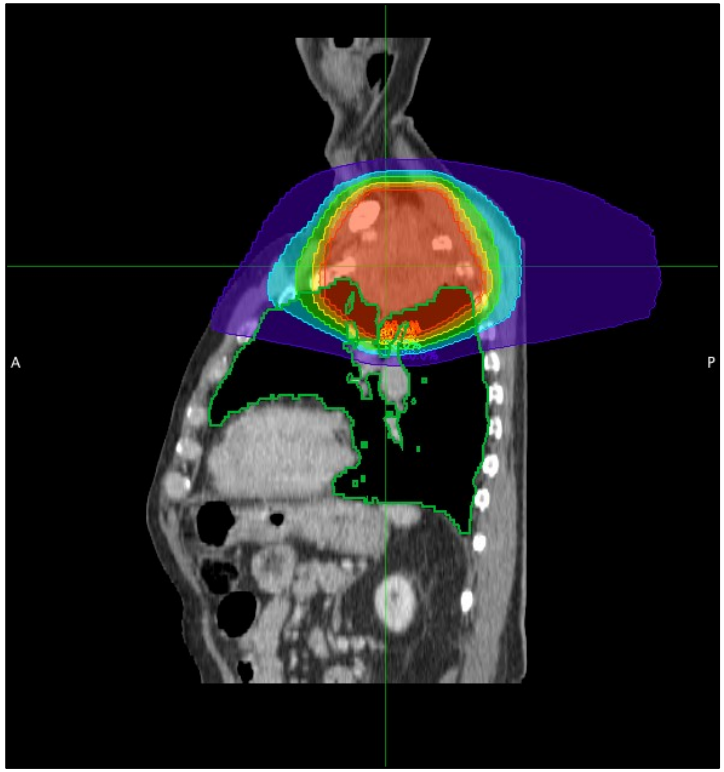
- Previous irradiation (TomoTherapy): **30 x 2.13 Gy = 63.9 Gy**











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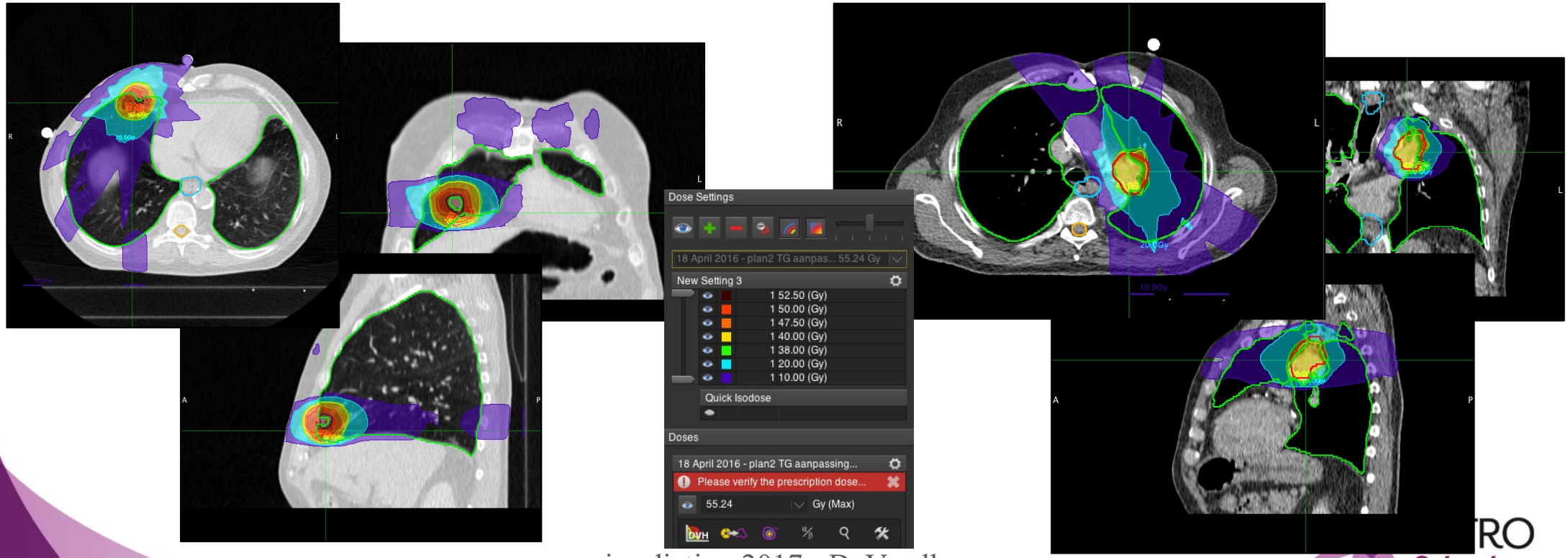
Accumulated dose
a case study (2)

- Re-irradiation (VERO):

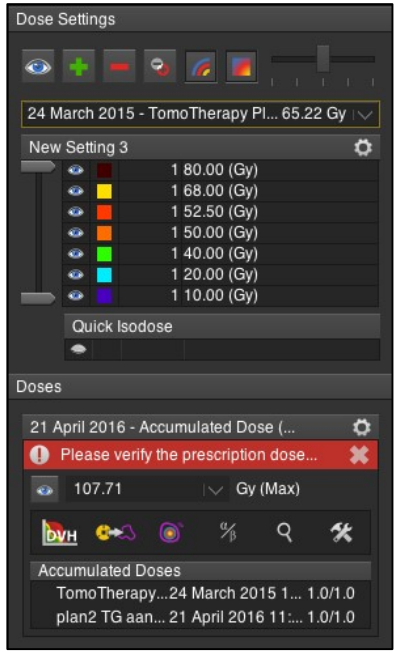
➢ Right Middle Lobe:
10 x 5 Gy = 50 Gy

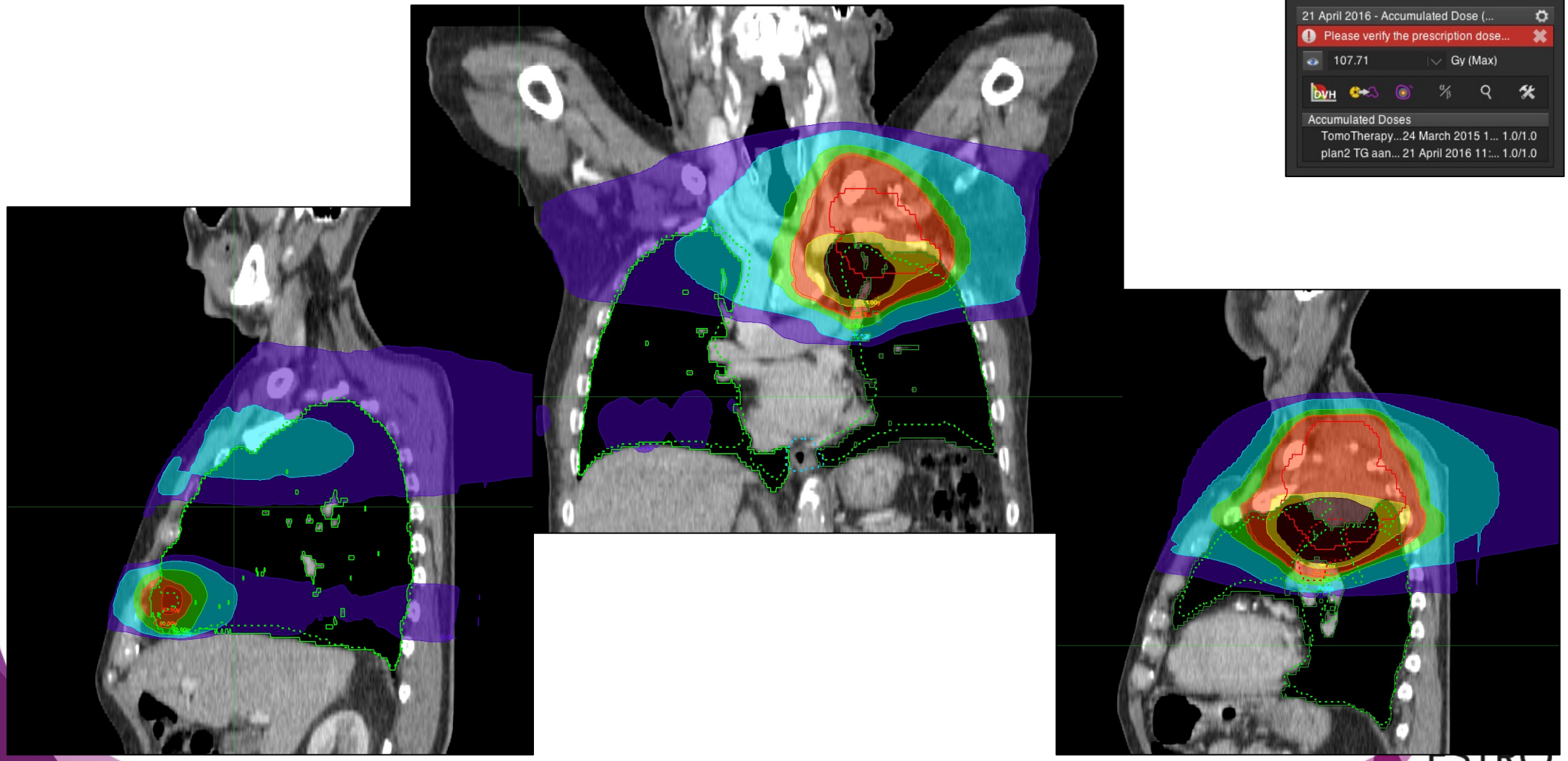
➢ Mediastinal:
10 x 4 Gy = 40 Gy



Accumulated dose a case study (2)

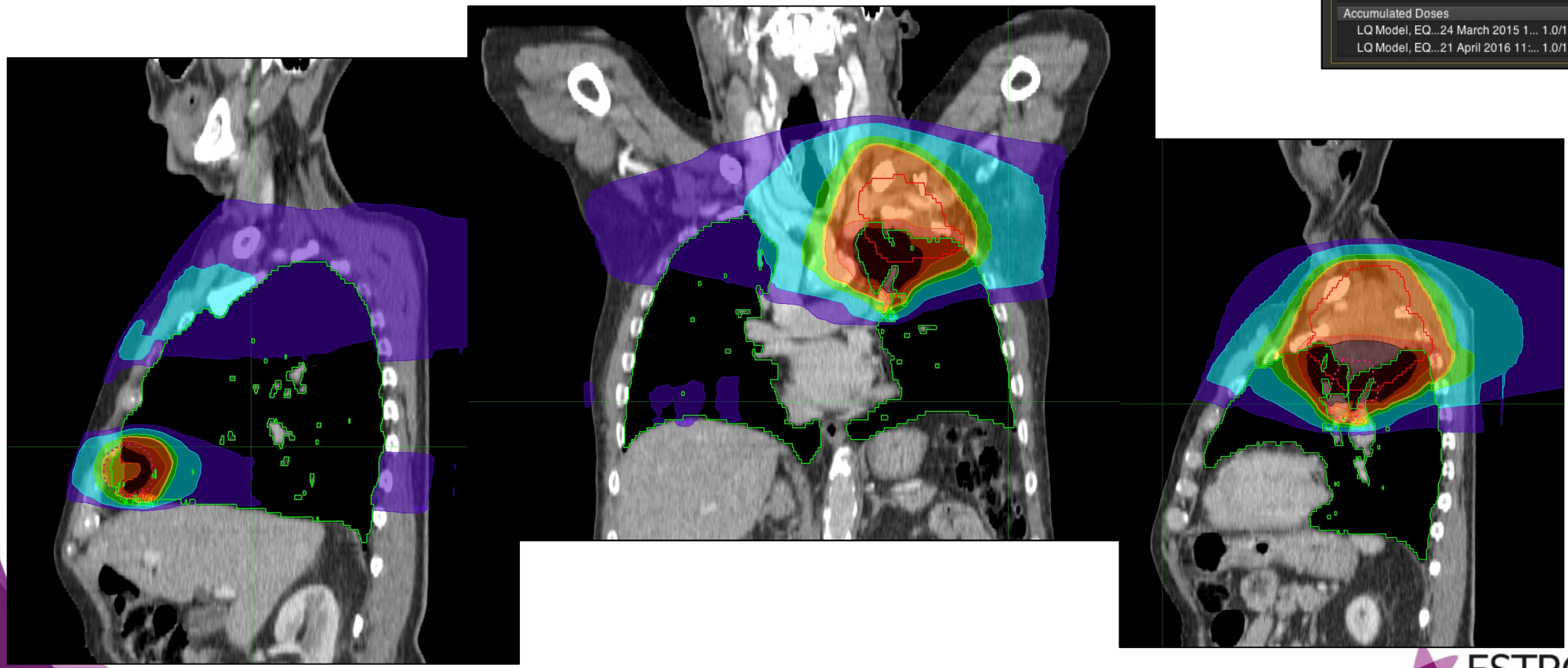
- Total accumulated dose assuming 1+1





Accumulated dose a case study (2)

- Total accumulated dose:
  - $EQD_{2/3}$ (oesophagus, lung)
  - $EQD_{2/2}$ (spinal cord)



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Accumulated dose a case study (2)

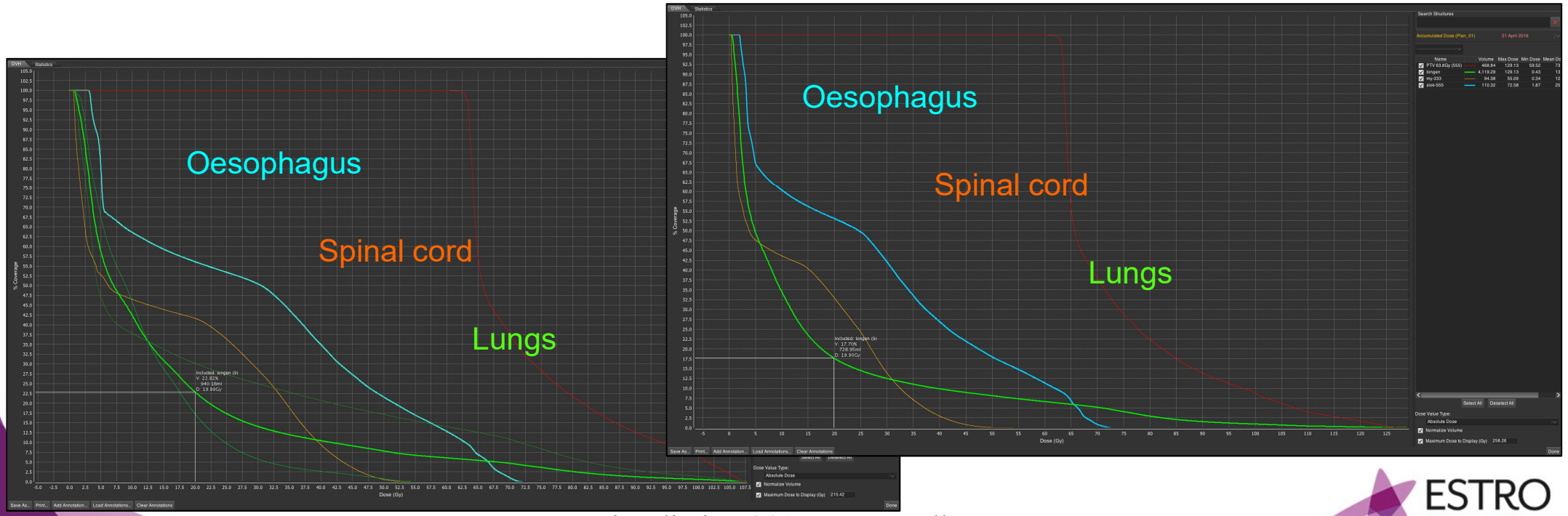
- Total accumulated dose: comparison

Total Dose (uncorrected)

- V_{20} (lungs): 22.8%
- $D_{2\%}$ (Oesophagus: 68.9Gy
- $D_{2\%}$ (spinal cord): 47.5 Gy

$EQD_{2/2}$

- V_{20} (lungs): 17.6%
- $D_{2\%}$ (Oesophagus: 68.5 Gy
- $D_{2\%}$ (spinal cord): 42.0 Gy



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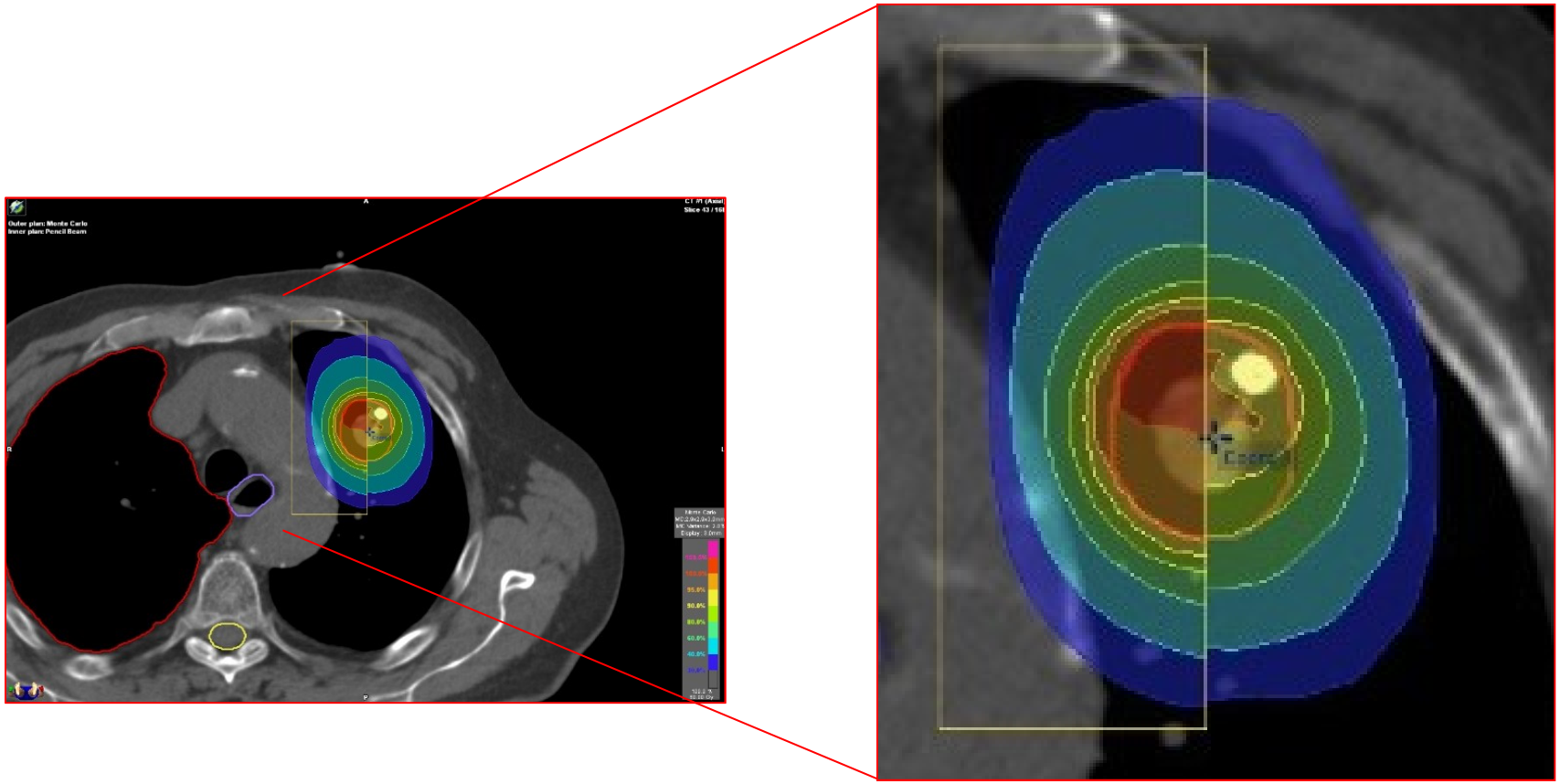
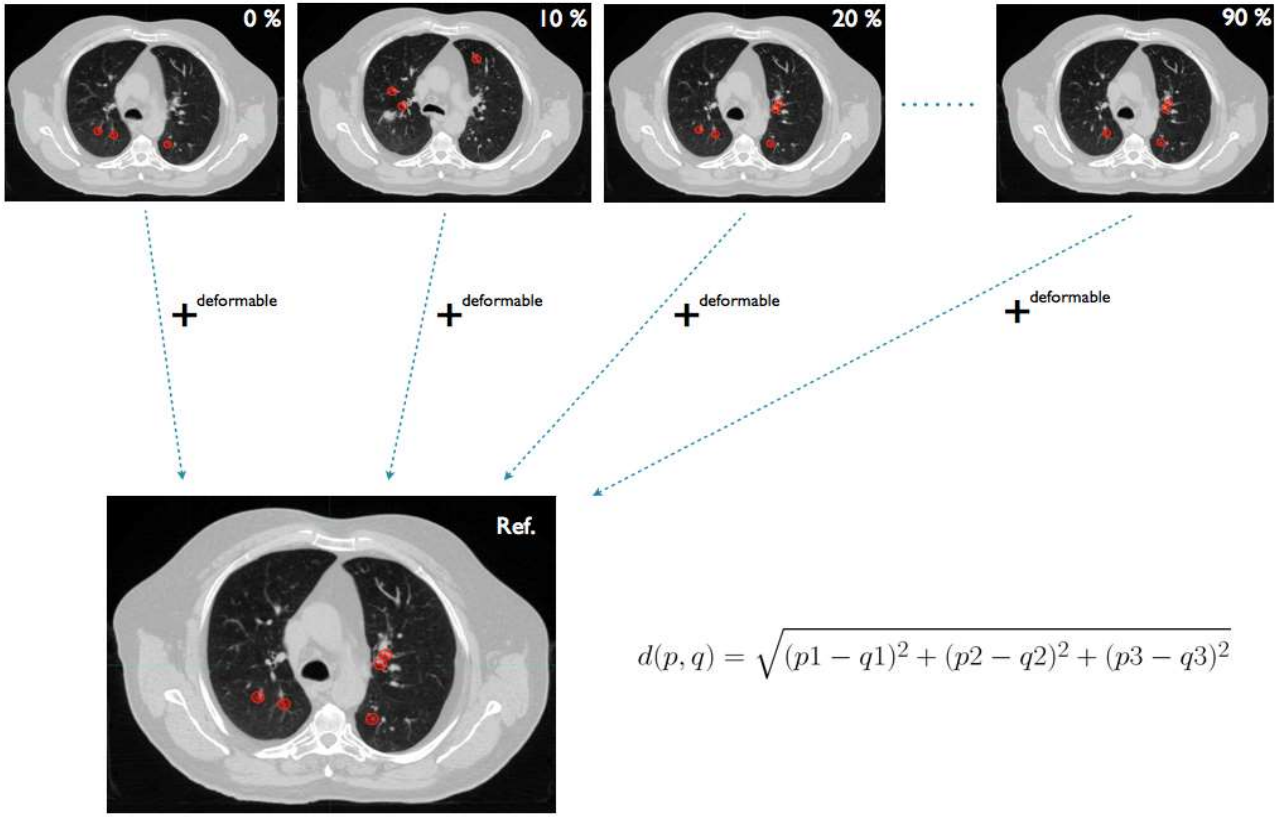
Dose calculation algorithm?

- Type A or B?



Deformable registration …???

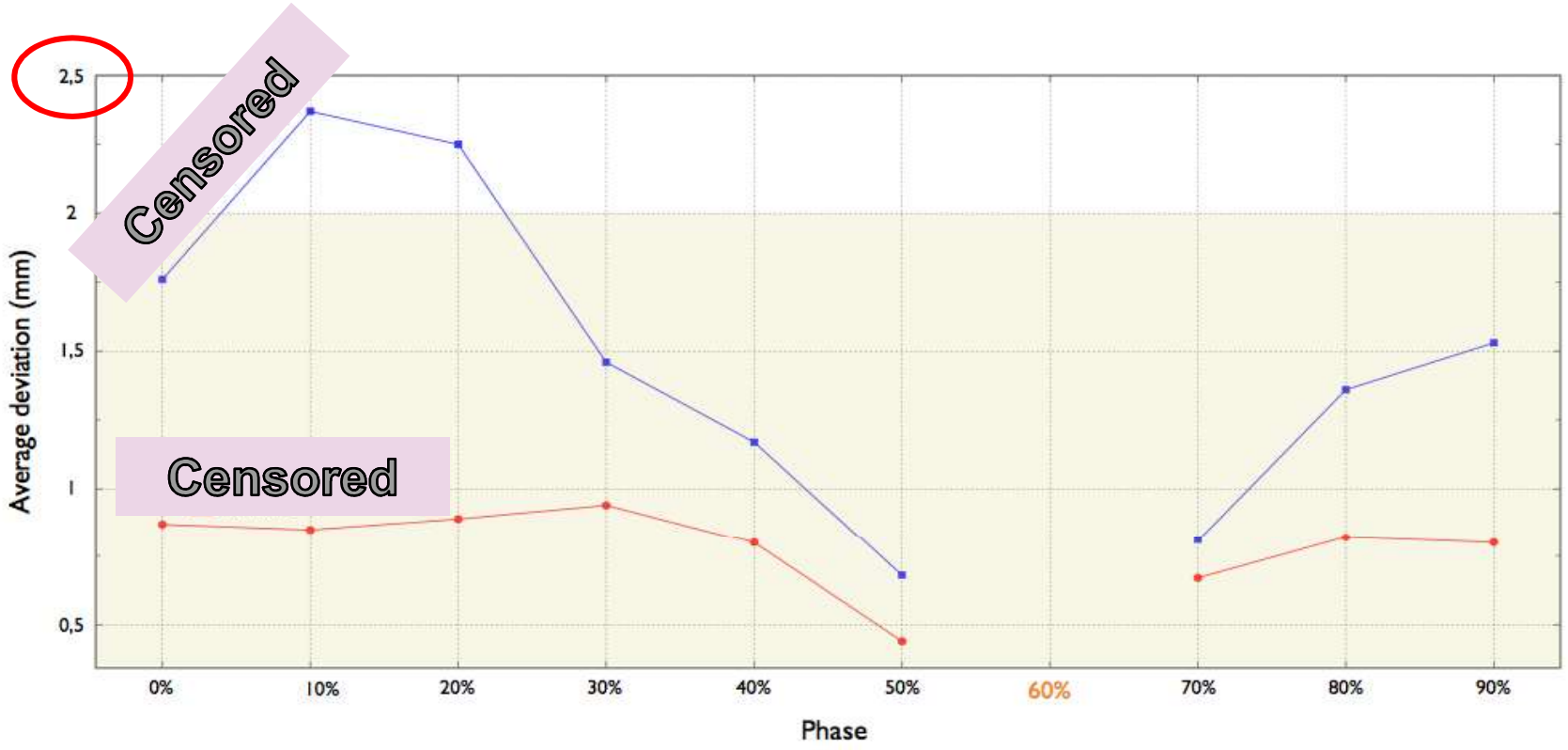
- http://www.creatis.insa-lyon.fr/rio/popi-model
- 4D-CT datasets, with 100 POIs on vessel and bronchial bifurcations



$$d(p,q) = \sqrt{(p1-q1)^2 + (p2-q2)^2 + (p3-q3)^2}$$

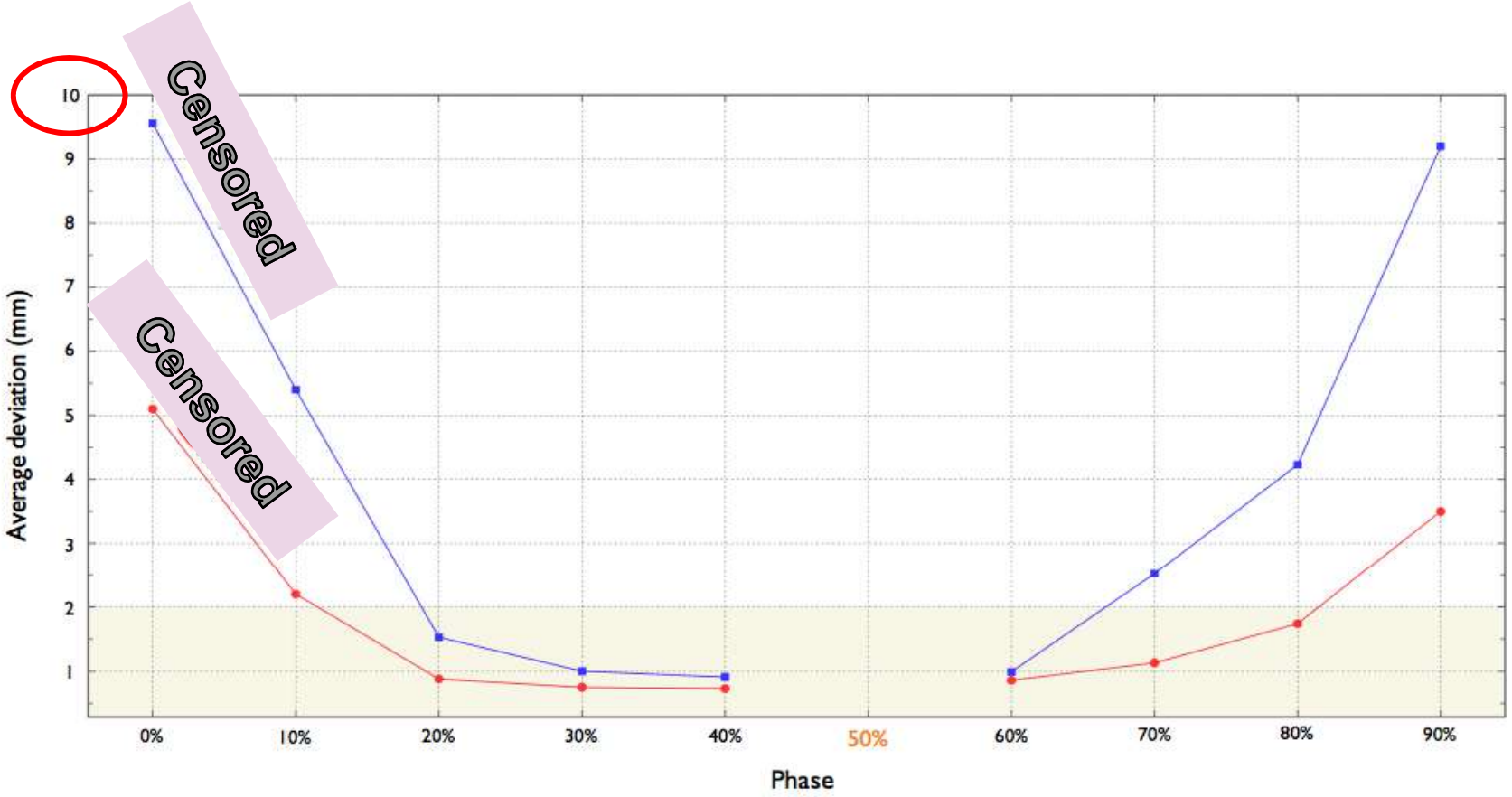
Deformable registration …???

- "Easy" case

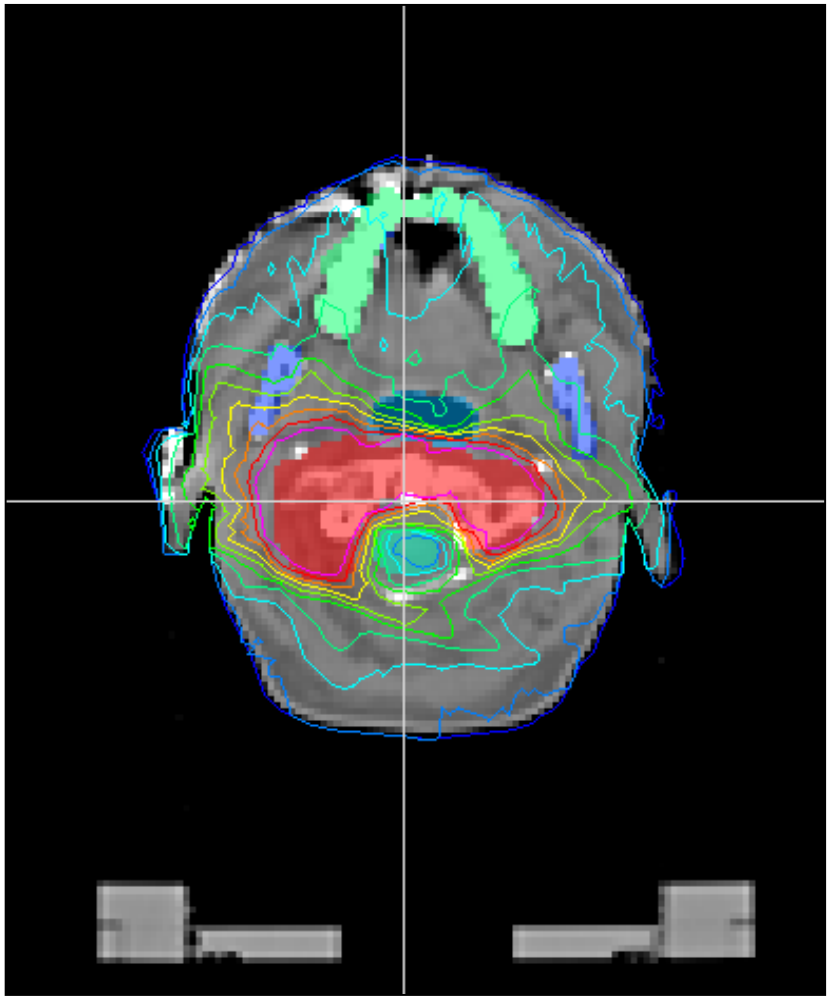


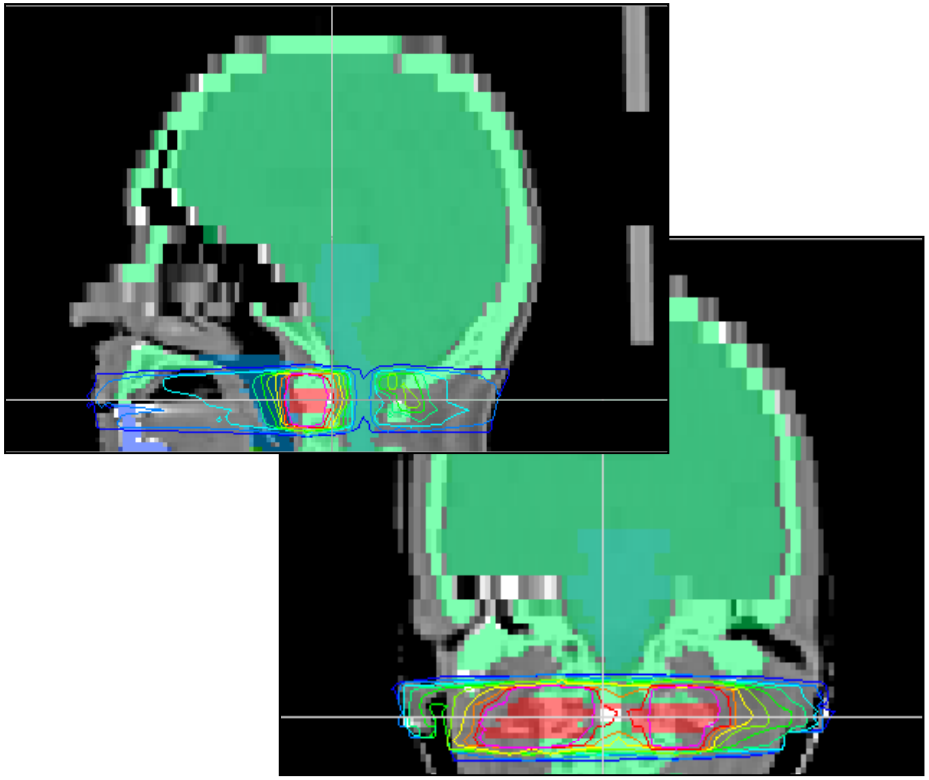
Deformable registration …???

- “Difficult” case



Should we refrain from irradiation?





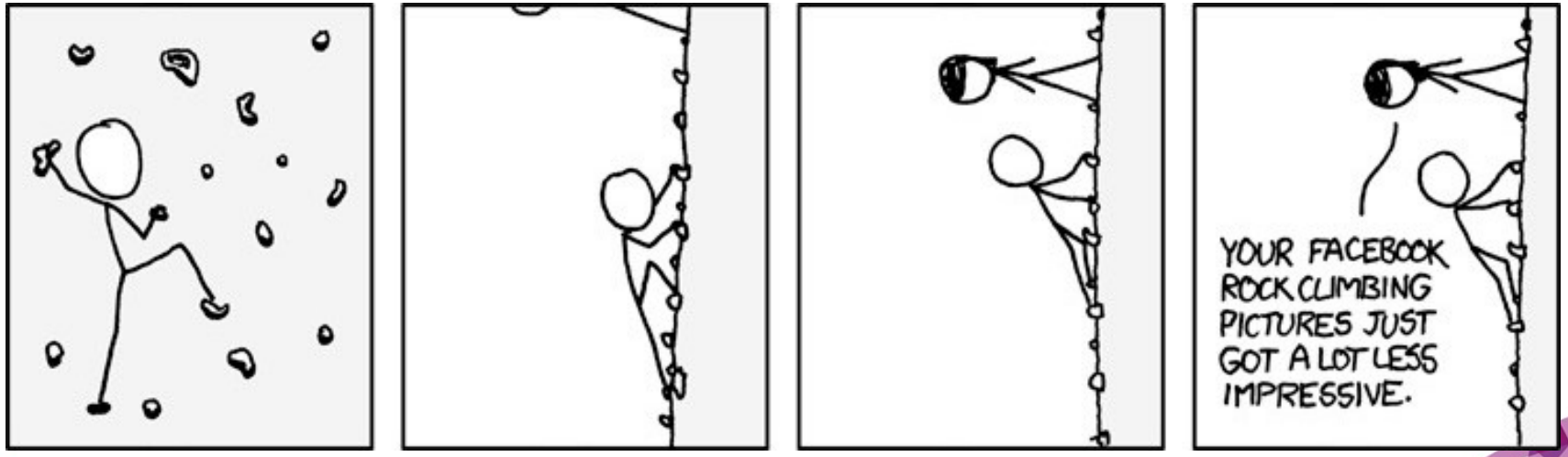
Second IMRT treatment at AZ-VUB, using sequential tomotherapy: 1995

Conclusions

- If the TPS does not allow for dose accumulation
  - Rescale the primary dose to EQD2 and assess tolerance dose for OAR, use these tolerances as dose constraints in the optimization …
- If the TPS allows for dose accumulation, but not for EQD2 recalculation
  - Rescale primary and re-irradiation to EQD2 and accumulate dose
- If TPS allows for dose accumulation, EQD2, recovery, …
  - Use it … but how?

Conclusions cont'd

- Today it would **be unethical not to have** an open system that allows import and export of RT-structures and RT-Dose!!!
- UNIFORM REPORTING is key for the future … a new ICRU report?
- Accuracy of deformable image registration??
- Accuracy of dose calculation should no longer be an issue Today, but might be an issue when previous irradiation dates from the type A era!!!



Acknowledgements

Special thanks to:

- Peter De Coninck
- Robbe Van den Begin
- Benedikt Engels
- Koen Tournel

Gastric Cancer: Recurrence features by imaging

Dr Angela M Riddell

Royal Marsden, London. UK

ESTRO School

Patterns of relapse

Retrospective review

- 1985 -2000
- 1172 patients; R0 resection
- 492 (42%) recurrence
- Locoregional recurrence – surgical bed; upper abdominal retroperitoneal lymph nodes; anastomotic recurrence

Location of recurrence	Number
Locoregional	199 (54%)
Distant	188 (51%)
Peritoneal	108 (29%)

79% recurred within 2 years

D'Angelica M, Gonen M, Brennan M et al 2004 Ann of Surg; 240:808-816

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Role of imaging for detection of relapse

Surveillance imaging may be:

- Directed within a clinical trial protocol
- Local protocols
- Response to development of clinical symptoms
- Response to rising tumour markers
- No standard recommendations

Detecting relapse

- Challenging!
- Extremely difficult sometimes to identify relapse
- Post op – anatomy no longer predictable
- Mobile tissues, appearances vary on sequential imaging
- No specific rules….
- Important to discuss with operative procedure with surgeon
- Discuss pathological findings
- Multi-disciplinary effort

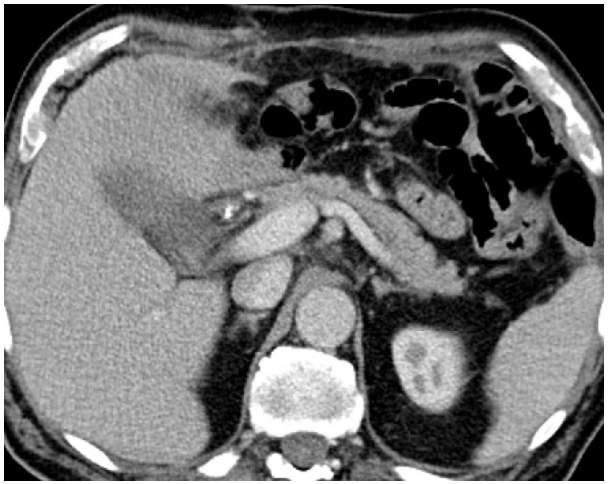
Gastric cancer patterns of disease relapse

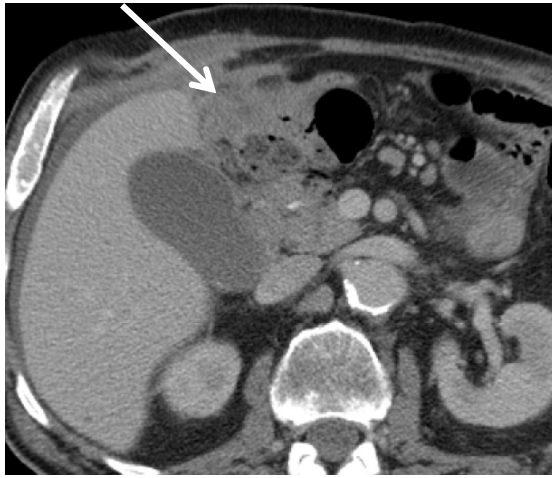
Male patient underwent a total gastrectomy on 09.09.2014 post neoadjuvant chemotherapy. The path staging was pT3bN1 R0 (3/40 nodes positive).

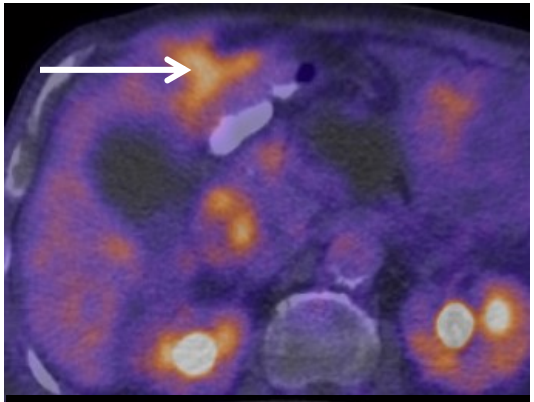
29.10.2014

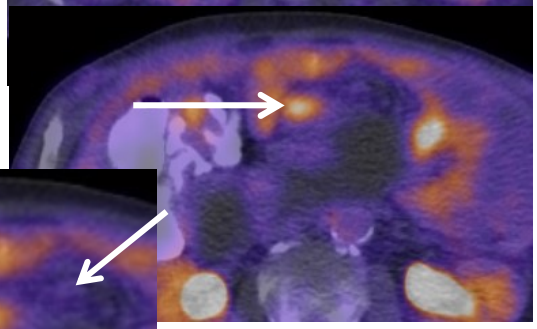
12.02.2015

06.03.2015

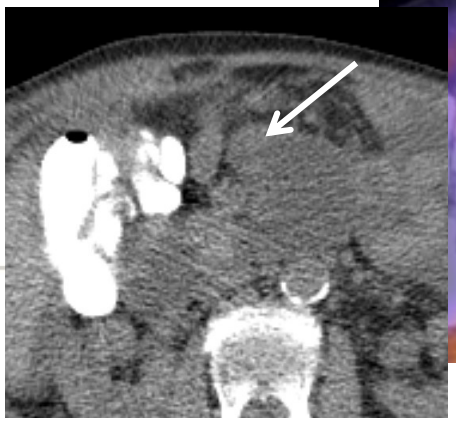


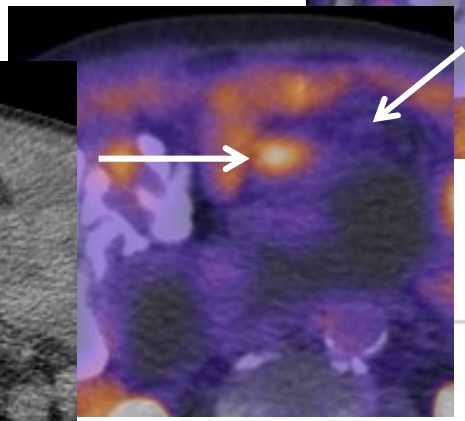






Baseline





Serosal disease causing small bowel obstruction

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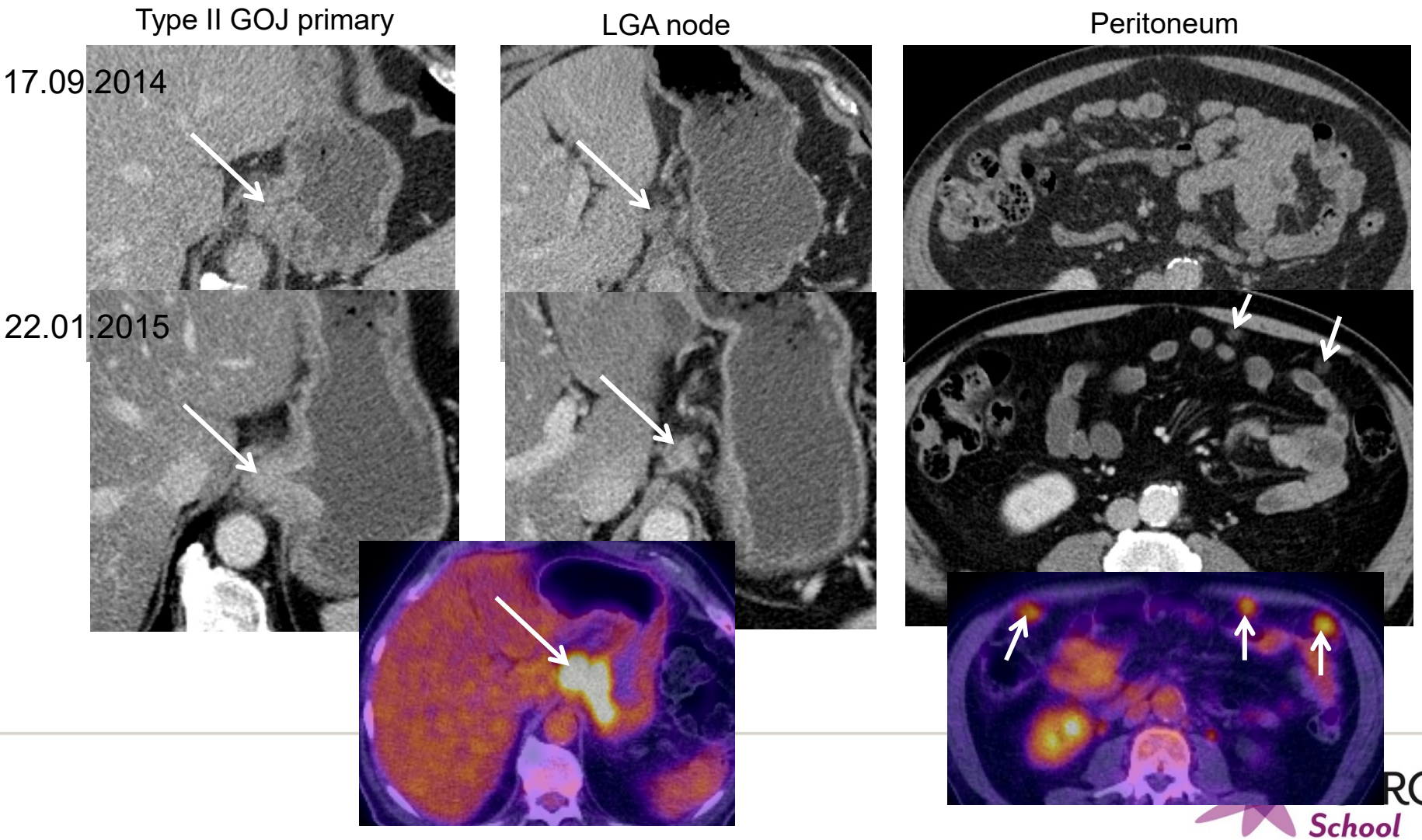
Locoregional and distant relapse

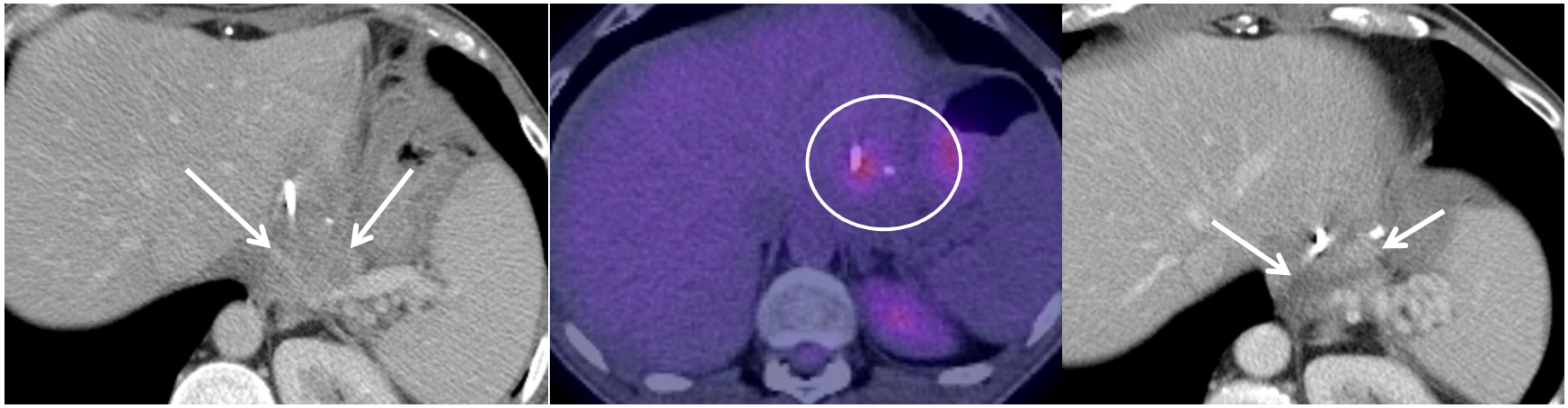
Type II GOJ tumour staged as T3N2. Commenced chemo. Progressive symptoms of dysphagia.



Challenging anatomy

44 year old male with familial E-cadherin CDH1 gene +ve; poorly differentiated signet ring cell gastric carcinoma. Total gastrectomy 27.04.2010. pT3N1 (1/31 nodes)

10.12.2014 | 10.12.2014 | 19.03.2015

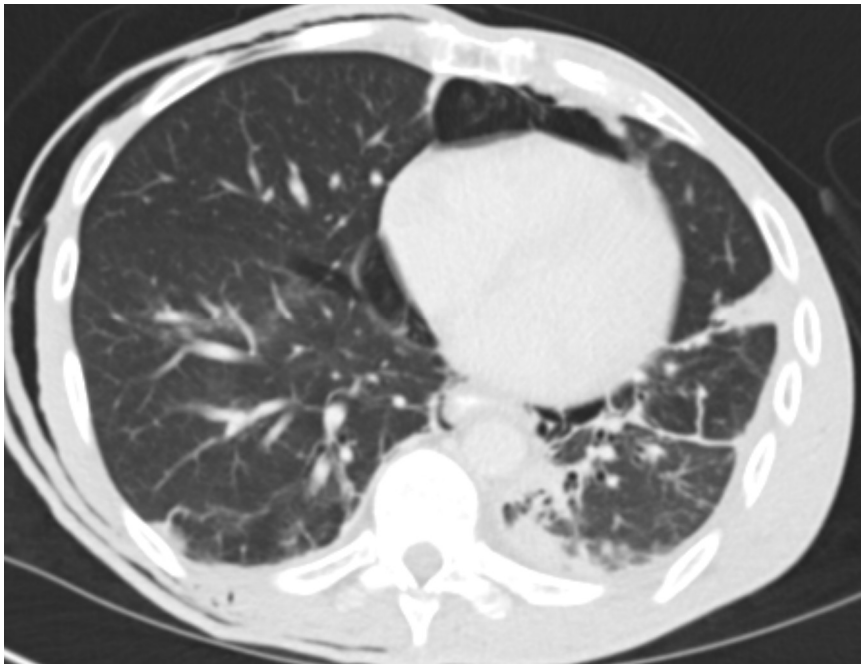


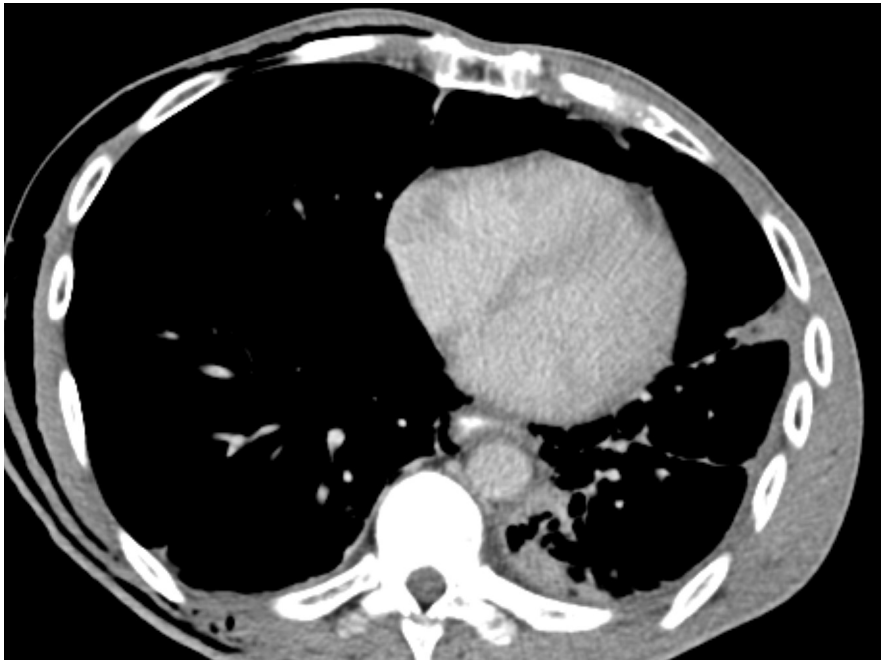
Likely locoregional relapse?? PET-CT not avid…….

Partial response post chemotherapy

Example of False positive PET-CT

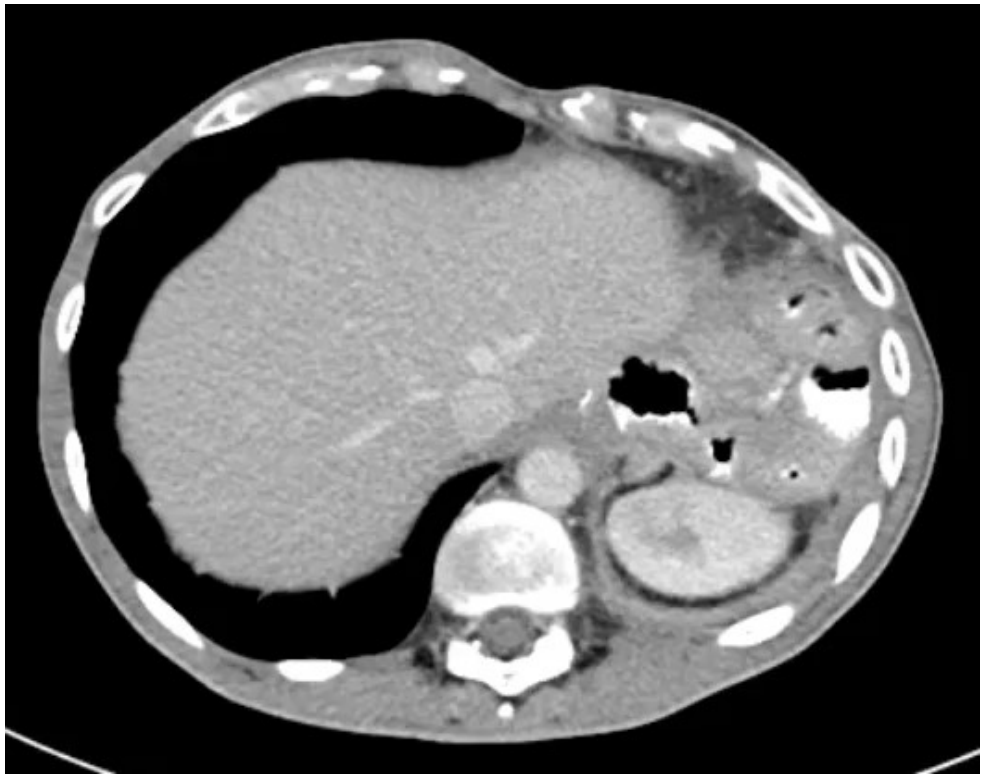
45 yr old male total gastrectomy in 2010. Relapse in 2015 treated with CRT and surgery (refashioning oesophago-jejunal anastomosis). Required dilatation of anastomosis due to recurrent strictures; complicated by perforation





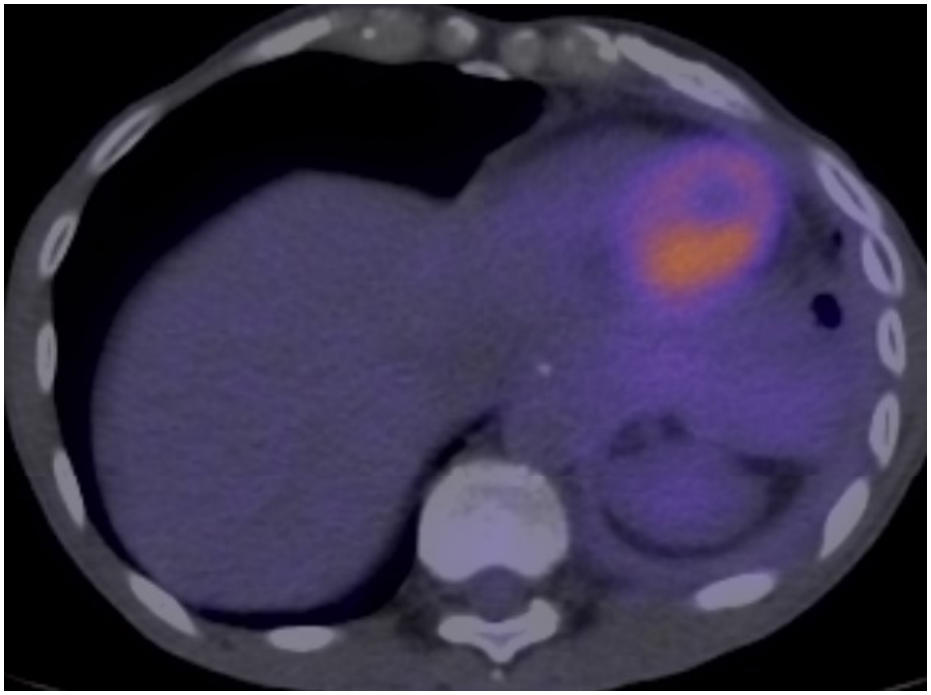
28.06.2016 – post dilatation of anatomotic stricture.

Example of False positive



CT 11.07.2016 Follow up. Patient clinically improving

Example of False positive



03.08.2016 PET-CT reported as recurrent disease

Summary

Detecting relapse following gastric surgery is challenging

- Unfamiliar anatomy
- Lack of intra abdominal fat
- False negative CT
- PET-CT may assist in detection of relapse
- Advise follow up if symptoms persist & imaging is negative

Thank you

ESTRO School

Rome, Italy, 25-28 March 2017

Vincenzo Valentini and Laura La Porta

UPPER GI: TECHNICAL AND CLINICAL CHALLENGES FOR RADIATION ONCOLOGISTS - FULLY BOOKED

28 March (Tuesday)

Lecture (15'): Palliative chemotherapy

Nicola Silvestris
Medical Oncology Unit
Cancer Institute "Giovanni Paolo II" Bari

n.silvestris@oncologico.bari.it

ESTRO School

Lecture (15'): Palliative chemotherapy

First line

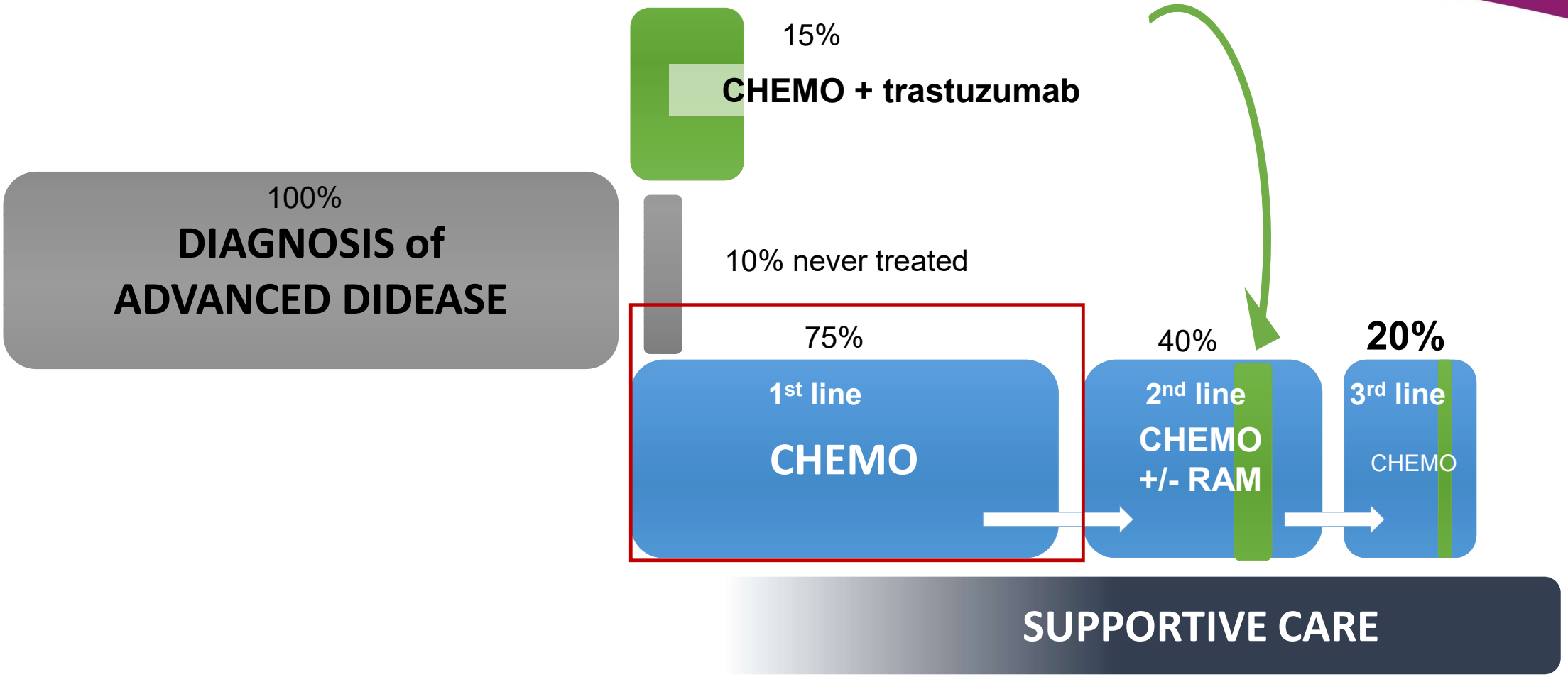
- ✓ *Doublets or triplets?*

Second line

- ✓ *What should be a standard?*
- ✓ *Are all patients candidated to a second line therapy?*

Molecular classification

- ✓ *Do we have distinct treatment choices for these different molecular pathways?*
- ✓ *How can we address tumor heterogenity when we design GC clinical trials?*



MODIFIED FROM LINEE GUIDA AIOM, UPDATE OCTOBER 2016

Annals of Oncology 8: 163–168, 1997.

Original article

Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer

British Journal of Cancer (1995) 71, 587–591

Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer

J Clin Oncol 15:261-267. © 1997

Randomized Trial Comparing Epirubicin, Cisplatin, and Fluorouracil Versus Fluorouracil, Doxorubicin, and Methotrexate in Advanced Esophagogastric Cancer

- The ***first*** chemotherapeutic agent against mGC was ***5-FU***, either ***alone*** or ***in combination*** with various reagents (***FAM, FAMTX***)
- In the late 1990s, a randomized trial showed that ***epirubicin, cisplatin and venous infusion of 5-FU*** (***ECF***) was better than FAMTX

Chemotherapy in Advanced Gastric Cancer: A Systematic Review and Meta-Analysis Based on Aggregate Data

Anna D. Wagner, Wilfried Grothe, Johannes Haerting, Gerhard Kleber, Axel Grothey, and Wolfgang E. Fleig

JOURNAL OF CLINICAL ONCOLOGY

J Clin Oncol 24:2903-2909. © 2006

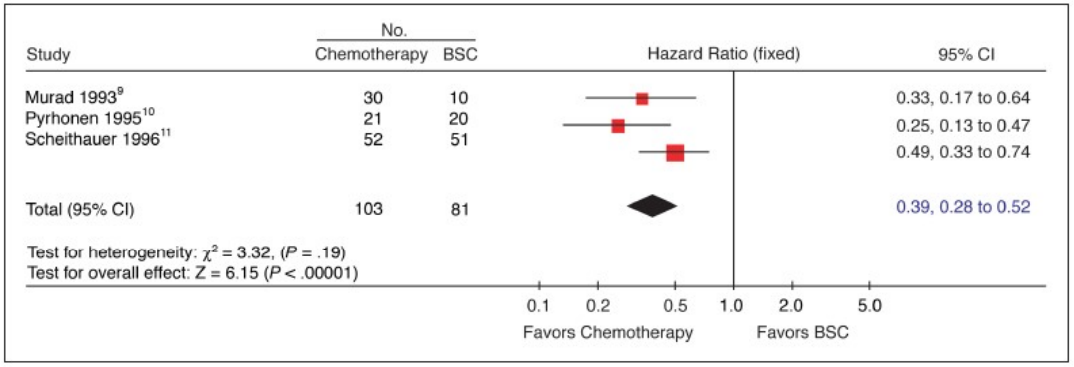


Fig 1. Effect of chemotherapy versus best supportive care (BSC) on overall survival. Hazard ratios were analyzed with the fixed-effect model (reproduced with permission[8]).

A meta-analysis of ***first-line chemotherapy versus best support care*** studies reported a hazard ratio (HR) of 0.39 (95% CI, 0.28 to 0.52; *P*.001) for OS in favor of chemotherapy, translating to ***a benefit in weighted median average survival of approximately 6 months***

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Chemotherapy in Advanced Gastric Cancer: A Systematic Review and Meta-Analysis Based on Aggregate Data

Anna D. Wagner, Wilfried Grothe, Johannes Haerting, Gerhard Kleber, Axel Grothey, and Wolfgang E. Fleig

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J Clin Oncol 24:2903-2909. © 2006

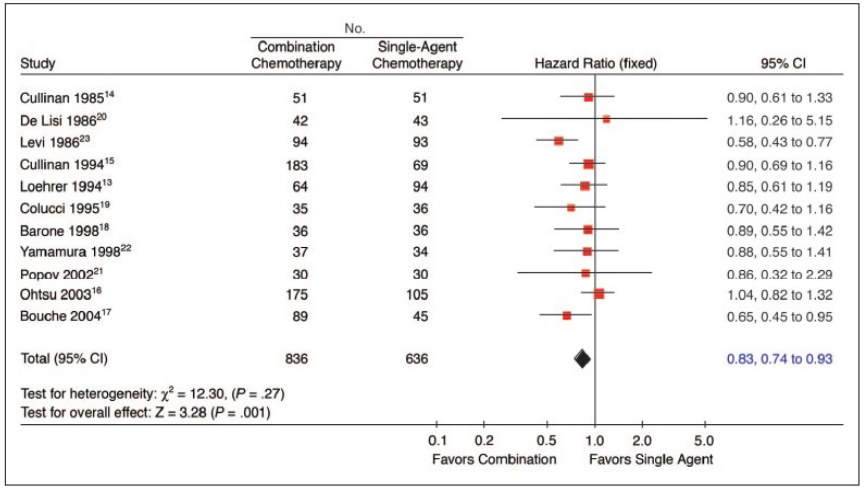

Fig 2. Effect of combination versus single-agent chemotherapy on overall survival. Hazard ratios were analyzed with the fixed-effect model.

Analysis of ***combination chemotherapy versus single agent***, mainly fluorouracil (FU) -based chemotherapy (HR 0.83; 95% CI 0.74 to 0.93) showed ***significant overall survival benefits in favor of combination chemotherapy***

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Phase III Trial in Metastatic Gastroesophageal Adenocarcinoma with Fluorouracil, Leucovorin Plus Either Oxaliplatin or Cisplatin: A Study of the Arbeitsgemeinschaft Internistische Onkologie

JOURNAL OF CLINICAL ONCOLOGY

J Clin Oncol 26:1435-1442. © 2008 ı

Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer

David Cunningham, M.D., F.R.C.P., Naureen Starling, M.R.C.P., Sheela Rao, M.R.C.P., Timothy Iveson, M.D., F.R.C.P., Marianne Nicolson, M.D., F.R.C.P., Fareeda Coxon, F.R.C.P., Gary Middleton, M.D., F.R.C.P., Francis Daniel, M.B., Ch.B., R.C.S.I., F.F.R., Jacqueline Oates, and Andrew Richard Norman, Ph.D.,

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2008;358:36-46.

original article

Annals of Oncology 20: 666–673, 2009
doi:10.1093/annonc/mdn717
Published online 19 January 2009

Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial

Y.-K. Kang[1]*, W.-K. Kang[2], D.-B. Shin[3], J. Chen[4], J. Xiong[5], J. Wang[6], M. Lichinitser[7], Z. Guan[8], R. Khasanov[9], L. Zheng[10], M. Philco-Salas[11], T. Suarez[12], J. Santamaria[13], G. Forster[14] & P. I. McCloud[15]

Oxaliplatin and capecitabine are noninferior to cisplatin and fluorouracil, respectively, with ***perhaps a more manageable toxicity profile***, and both of these agents are now established in combination chemotherapy regimens for metastatic disease

ESTRO School

Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group

Eric Van Cutsem, Vladimir M. Moiseyenko, Sergei Tjulandin, Alejandro Majlis, Manuel Constenla, Corrado Boni, Adriano Rodrigues, Miguel Fodor, Yee Chao, Edouard Voznyi, Marie-Laure Risse, and Jaffer A. Ajani

JOURNAL OF CLINICAL ONCOLOGY

J Clin Oncol 24:4991-4997. © 2006

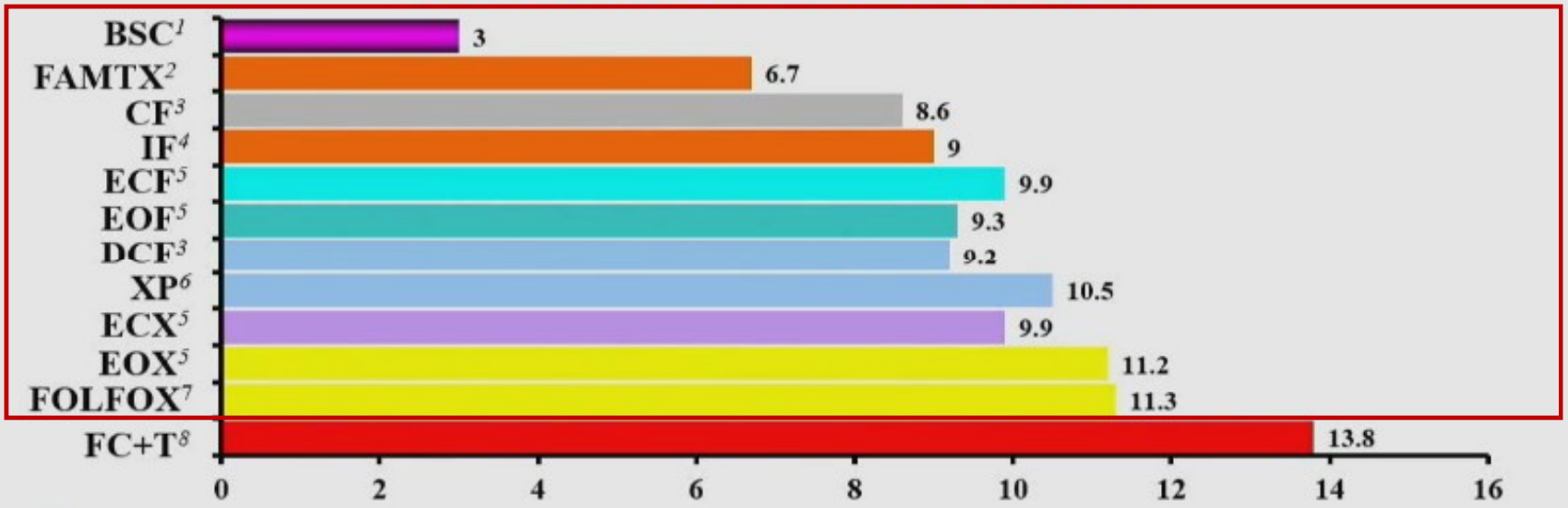
Randomized Multicenter Phase II Study of Modified Docetaxel, Cisplatin, and Fluorouracil (DCF) Versus DCF Plus Growth Factor Support in Patients With Metastatic Gastric Adenocarcinoma: A Study of the US Gastric Cancer Consortium

Manish A. Shah, Yelena Y. Janjigian, Ronald Stoller, Stephen Shibata,† Margaret Kemeny, Smitha Krishnamurthi, Yungpo Bernard Su, Allyson Ocean, Marinela Capanu, Bhoomi Mehrotra, Paul Ritch, Charles Henderson, and David P. Kelsen

JOURNAL OF CLINICAL ONCOLOGY

J Clin Oncol 33:3874-3879. © 2015

Overall survival with chemotherapy in advanced OG cancer



THE ROYAL MARSDEN

[1]Murad et al. Cancer 1993; [2]Vanhoefer et al. J Clin Oncol 2000; [3]Van Cutsem et al. J Clin Oncol 2006; [4]Dank et al. Ann Oncol 2008; [5]Cunningham et al. N Engl J Med 2008; [6]Kang et al. Ann Oncol 2009; [7]Shah et al JAMA Oncol 2016; [8]Bang et al. Lancet 2010

Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet *versus* doublet chemotherapy: a systematic literature review and meta-analysis

CANCER METASTASIS REVIEWS

Cancer Metastasis Rev (2015) 34:429–441
DOI 10.1007/s10555-015-9576-y

There is a debate whether triplet or doublet chemotherapy should be used as a first-line treatment in patients with advanced or metastatic esophagogastric cancer. Therefore, here we will review the available literature to assess the efficacy and safety of triplet *versus* doublet chemotherapy as a first-line treatment in patients with advanced esophagogastric cancer.

Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet *versus* doublet chemotherapy: a systematic literature review and meta-analysis

CANCER METASTASIS REVIEWS

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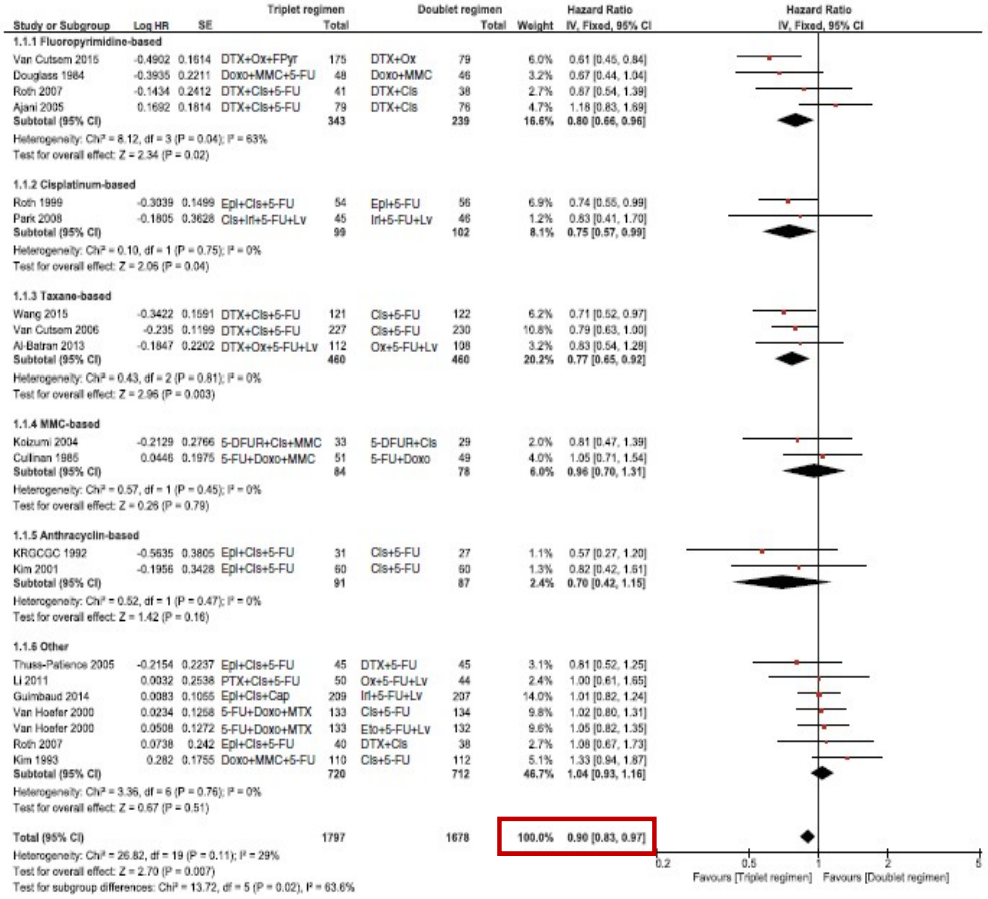
DOI 10.1007/s10555-015-9576-y



3.2 Overall survival, progression-free survival, and objective response rate

A significant improvement in OS with a low heterogeneity was observed in favor of a triplet (HR 0.90, 95 % confidence interval (CI) 0.83–0.97, I^2=29 %). When examining the subgroups, especially the triplets with fluoropyrimidine, taxane and cisplatin showed a significant benefit (Fig. 2.).

Although the survival of patients treated with a triplet significantly outweighed the survival of patients treated with a doublet, overall, ***the survival gain was modest with a hazard ratio of 0.90 of which the clinical relevance may be questioned***

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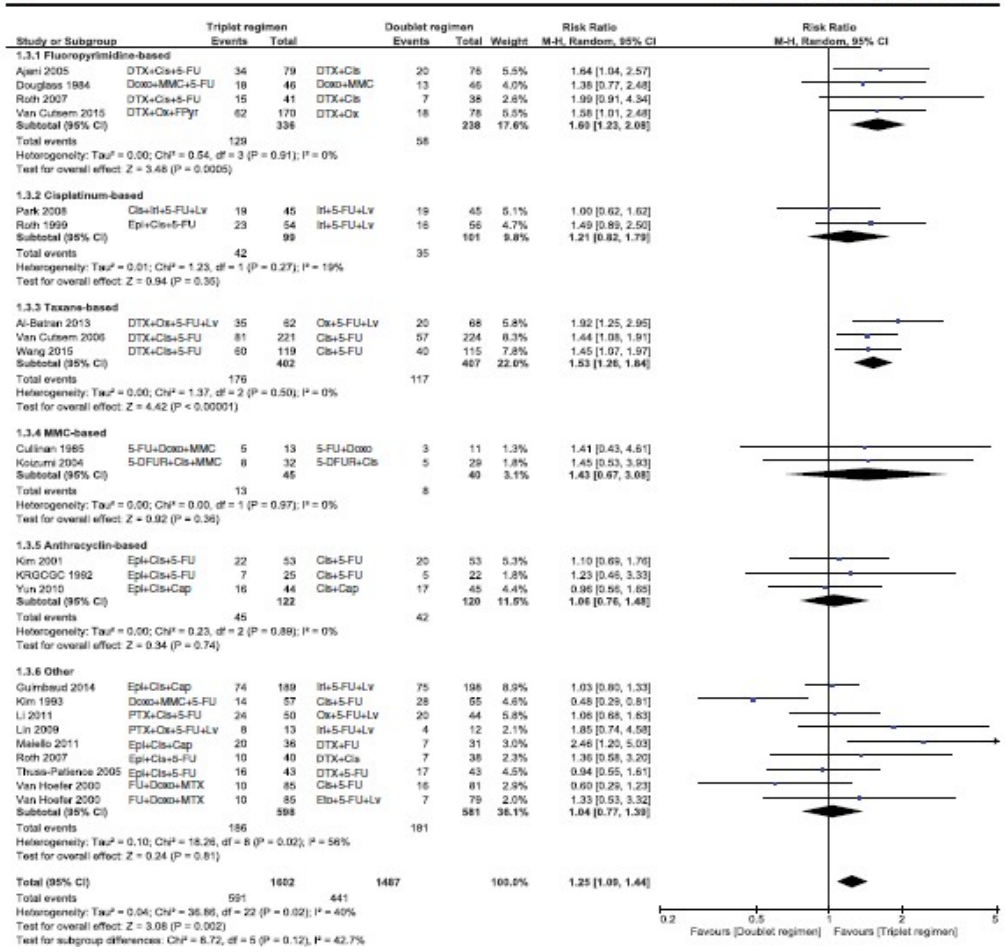
Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet *versus* doublet chemotherapy: a systematic literature review and meta-analysis

CANCER METASTASIS REVIEWS

Cancer Metastasis Rev (2015) 34:429–441
DOI 10.1007/s10555-015-9576-y



3.2 Overall survival, progression-free survival, and objective response rate

In addition, the use of a triplet was associated with a better ORR compared to a doublet (risk ratio=1.25, 95 % CI 1.09-1.44). This was mainly due to triplets with a fluoropyrimidine or taxane (Fig. 4.)

3.4 Toxicity

The risk of grade 3–4 thrombocytopenia (6.2 vs 3.7 %), infection (10.2 vs 6.4 %), and mucositis (9.7 vs 4.7 %) was significantly increased with a triplet compared to a doublet

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Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet *versus* doublet chemotherapy: a systematic literature review and meta-analysis

CANCER METASTASIS REVIEWS

Cancer Metastasis Rev (2015) 34:429–441
DOI 10.1007/s10555-015-9576-y

Although in general in metastatic disease ORR is not considered to be the most robust outcome measure, in advanced esophagogastric cancer, ORR may be a clinically relevant end point, given the high symptom burden that patients may suffer from that may be alleviated by response to treatment [1].

It Is Time to Stop Using Epirubicin to Treat Any Patient With Gastroesophageal Adenocarcinoma

VOLUME 35 · NUMBER 4 · FEBRUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

However, considering the overall poor performance of epirubicin combinations in the many trials we have described (in which it never showed benefit against two-drug combinations or even single-agent FU), we cannot justify the use of precious resources to launch a new trial to address this issue. We do not recommend epirubicin-based treatment for any patient with GEAC.

Elena Elimova
University of Texas MD Anderson Cancer Center, Houston, TX

Yelena Y. Janjigian
Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Mary Mulcahy
Feinberg School of Medicine, Lurie Comprehensive Cancer Center, Chicago, IL

Daniel V. Catenacci
University of Chicago, Chicago, IL

Mariela A. Blum
University of Texas MD Anderson Cancer Center, Houston, TX

Khaldoun Almhanna
H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

J. Randolph Hecht
David Geffen School of Medicine, University of California Los Angeles, Santa Monica, CA

Jaffer A. Ajani
University of Texas MD Anderson Cancer Center, Houston, TX

Lecture (15'): Palliative chemotherapy

First line

✓ *Doublets or triplets?*

- *Triplets only in patients with high symptom burden*
- *Stop using epirubicin*

Second line

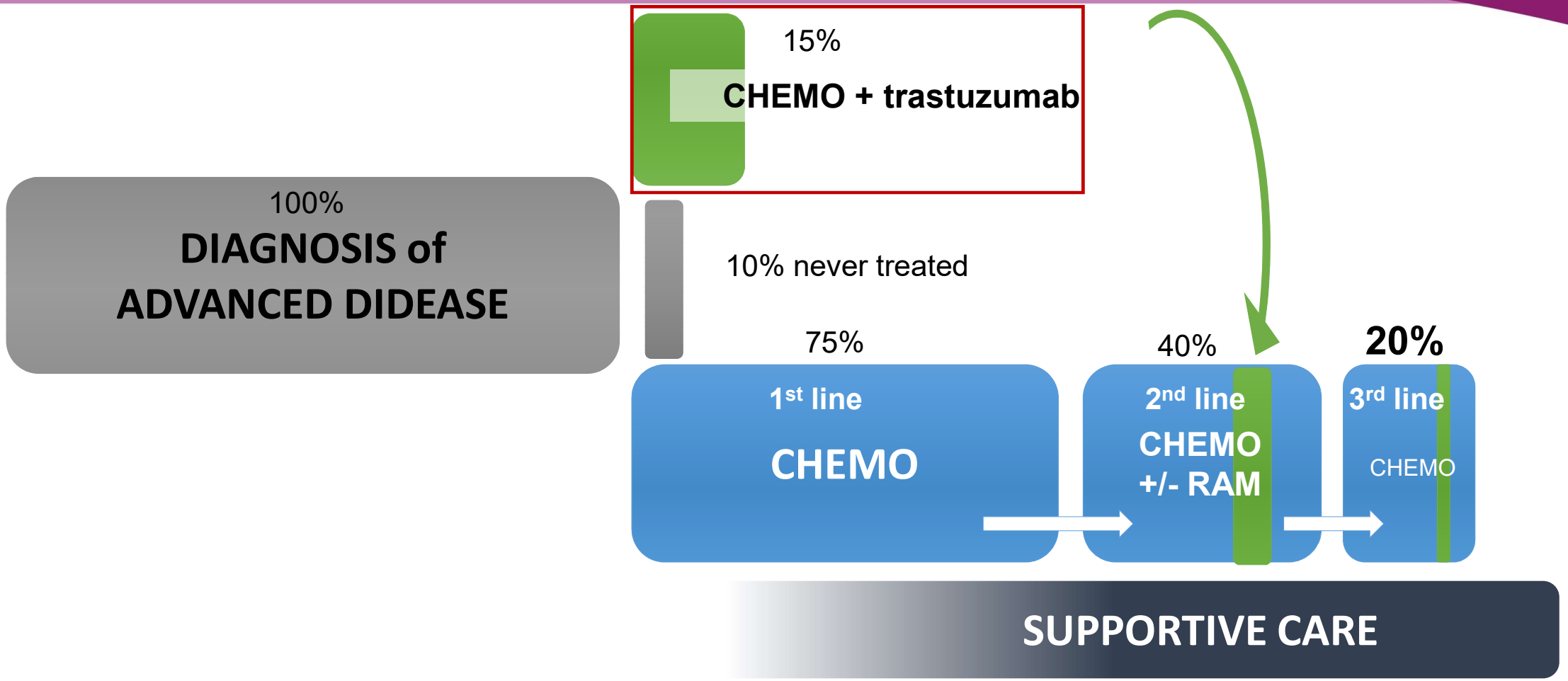
✓ *What should be a standard?*

✓ *Are all patients candidated to a second line therapy?*

Molecular classification

✓ *Do we have distinct treatment choices for these different molecular pathways?*

✓ *How can we address tumor heterogenity when we design GC clinical trials?*



MODIFIED FROM LINEE GUIDA AIOM, UPDATE OCTOBER 2016

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Yung-Jue Bang, Eric Van Cutsem,* Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Satoh, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang, for the ToGA Trial Investigators†*

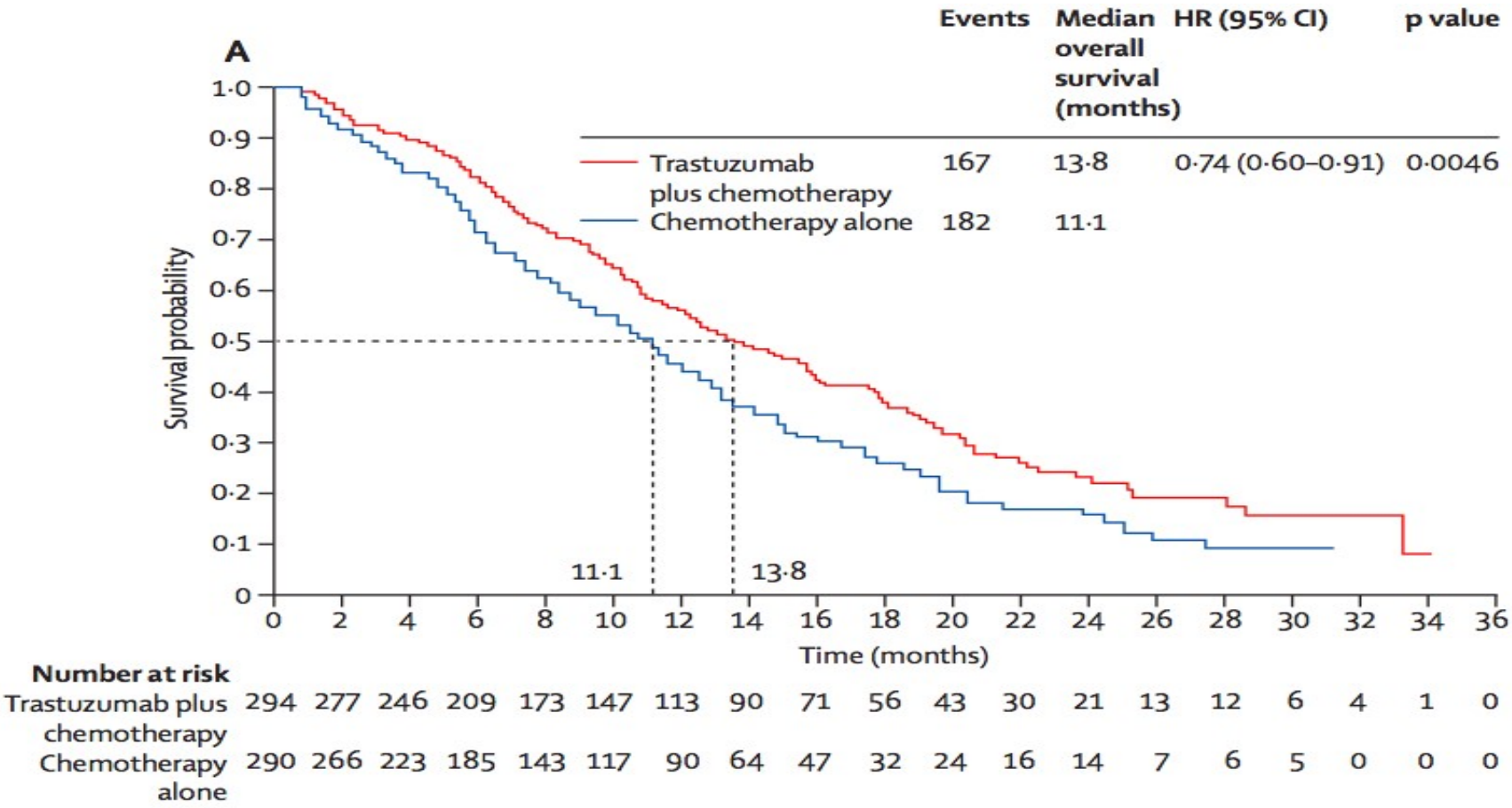
Summary

Background Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2; also known as ERBB2), was investigated in combination with chemotherapy for first-line treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer.

Lancet 2010; 376: 687–97
Published Online
August 20, 2010
DOI:10.1016/S0140-

ESTRO School

The ToGA TRIAL: Primary Endpoint OS



Bang et al; Lancet 2010

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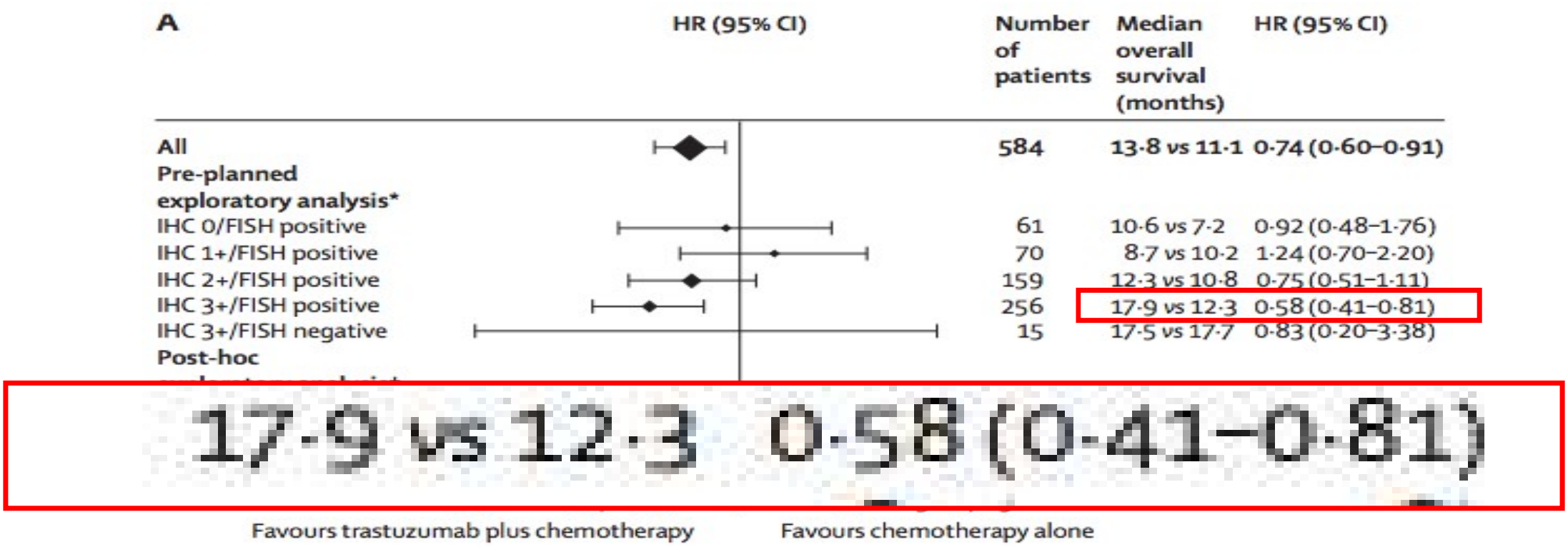
The ToGA TRIAL: OS by HER-2 status



The cohort of patients that were IHC 3+ or IHC 2+/FISH positive, the "***strongly HER2-positive***" group, exhibited the ***greatest benefit from trastuzumab in the ToGA trial***

Bang et al; Lancet 2010

ESTRO School

Lecture (15'): Palliative chemotherapy

First line

✓ *Doublets or triplets?*

- *Triplets only in patients with high symptom burden*
- *Stop using epirubicin*

Second line

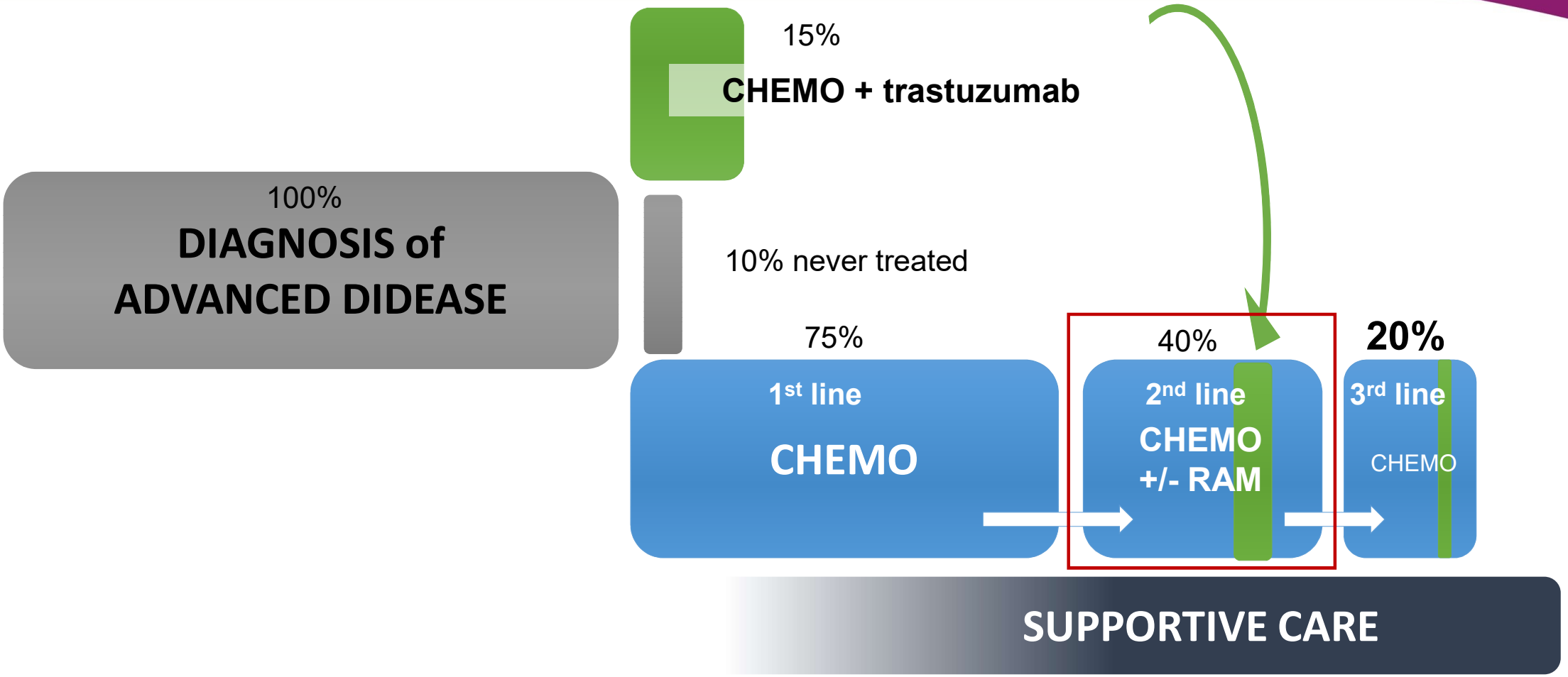
✓ *What should be a standard?*

✓ *Are all patients candidated to a second line therapy?*

Molecular classification

✓ *Do we have distinct treatment choices for these different molecular pathways?*

✓ *How can we address tumor heterogenity when we design GC clinical trials?*



MODIFIED FROM LINEE GUIDA AIOM, UPDATE OCTOBER 2016

Chemotherapy *vs* supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data

BJC
British Journal of Cancer (2016) 114, 381–387

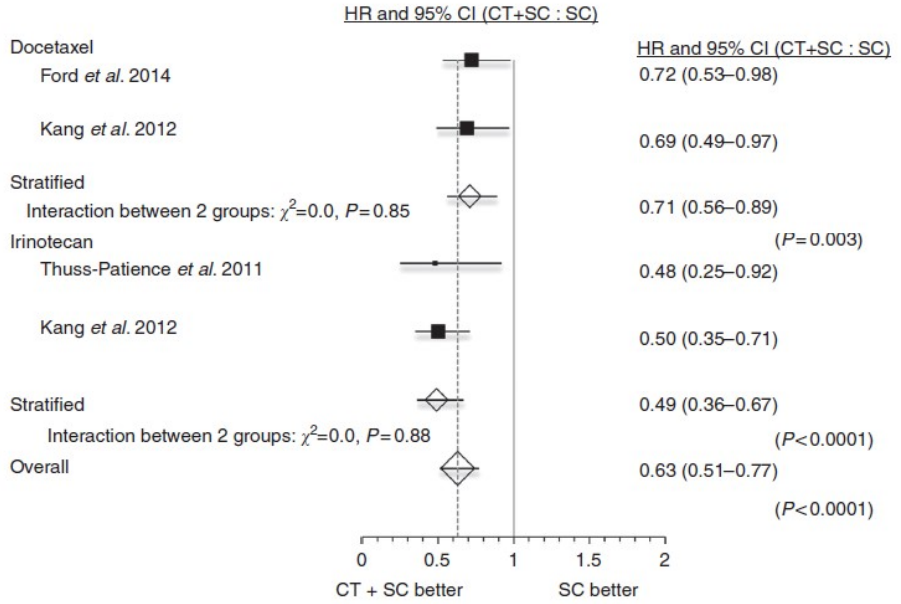


Figure 2. Forest plot of the hazard ratio (HR) for death with chemotherapy and supportive care (CT + SC) compared with supportive care (SC) alone for trials using docetaxel and those using irinotecan separately. Overall HR from a one-stage random effects Cox regression model.

Chemotherapy significantly reduced the risk of death

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Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO)

EUROPEAN JOURNAL OF CANCER 47 (2011) 2306–2314

Salvage Chemotherapy for Pretreated Gastric Cancer: A Randomized Phase III Trial Comparing Chemotherapy Plus Best Supportive Care With Best Supportive Care Alone

VOLUME 30 · NUMBER 13 · MAY 1 2012
JOURNAL OF CLINICAL ONCOLOGY

Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial

THE LANCET Oncology
Volume 15, Issue 1, January 2014, Pages 78–86

Randomized, Open-Label, Phase III Study Comparing Irinotecan With Paclitaxel in Patients With Advanced Gastric Cancer Without Severe Peritoneal Metastasis After Failure of Prior Combination Chemotherapy Using Fluoropyrimidine Plus Platinum: WJOG 4007 Trial

VOLUME 31 · NUMBER 35 · DECEMBER 10 2013
JOURNAL OF CLINICAL ONCOLOGY

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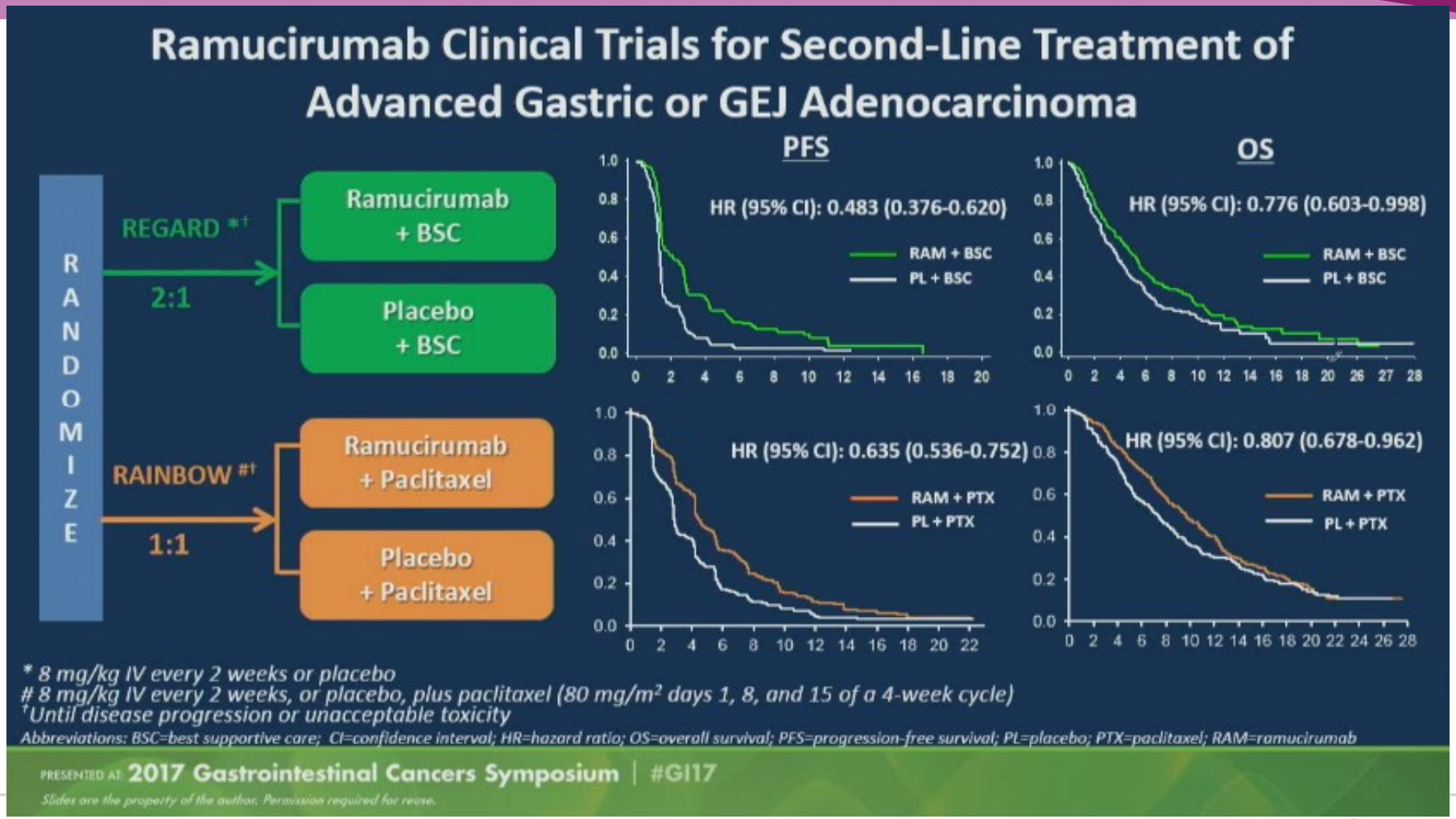
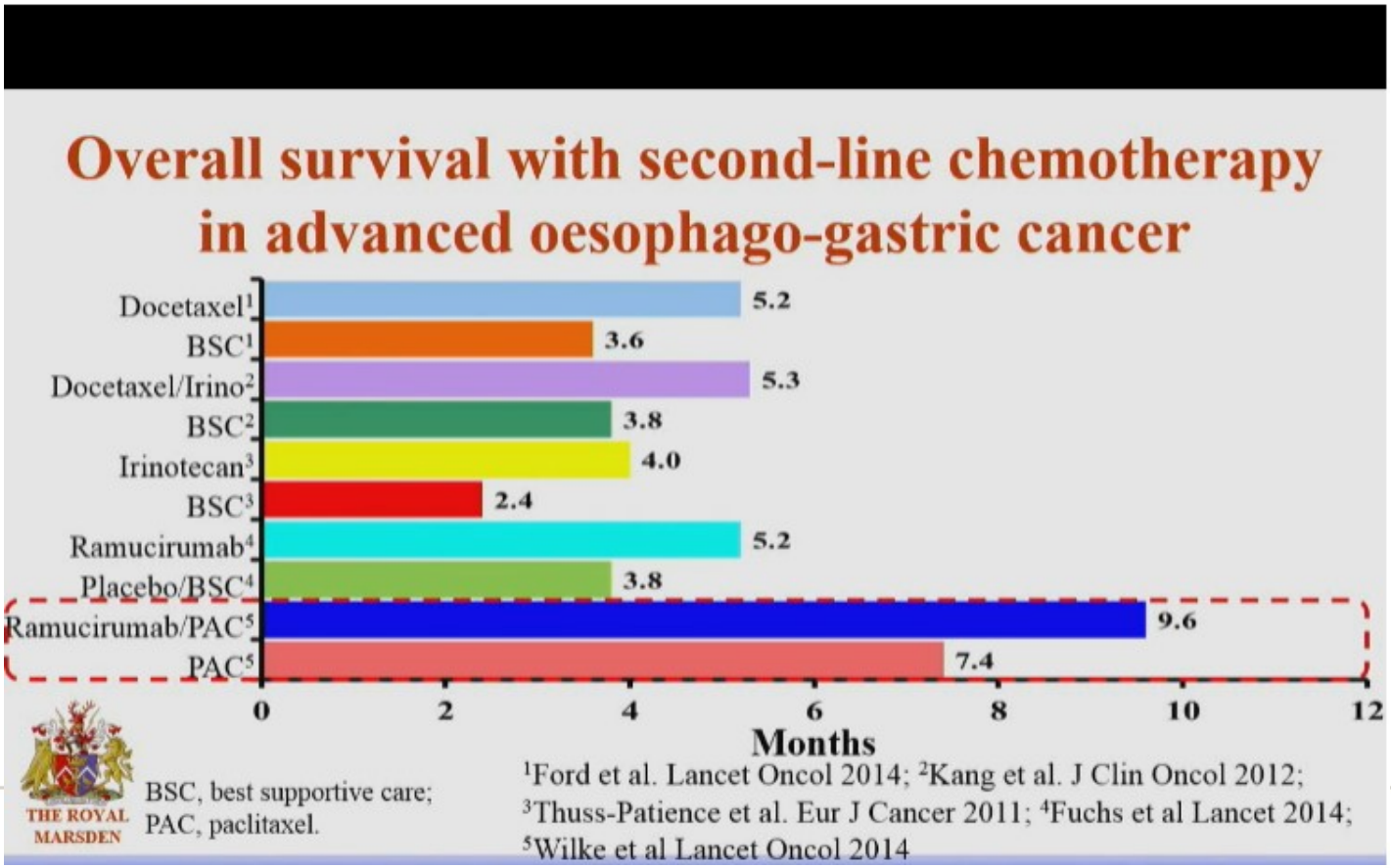

Ramucirumab Clinical Trials for Second-Line Treatment of Advanced Gastric or GEJ Adenocarcinoma
RANDOMIZE
REGARD *†
2:1
Ramucirumab + BSC
Placebo + BSC
RAINBOW #†
1:1
Ramucirumab + Paclitaxel
Placebo + Paclitaxel
PFS
HR (95% CI): 0.483 (0.376-0.620)
RAM + BSC
PL + BSC
OS
HR (95% CI): 0.776 (0.603-0.998)
RAM + BSC
PL + BSC
HR (95% CI): 0.635 (0.536-0.752)
RAM + PTX
PL + PTX
HR (95% CI): 0.807 (0.678-0.962)
RAM + PTX
PL + PTX
* 8 mg/kg IV every 2 weeks or placebo
# 8 mg/kg IV every 2 weeks, or placebo, plus paclitaxel (80 mg/m² days 1, 8, and 15 of a 4-week cycle)
†Until disease progression or unacceptable toxicity
Abbreviations: BSC=best supportive care; CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; PL=placebo; PTX=paclitaxel; RAM=ramucirumab
PRESENTED AT 2017 Gastrointestinal Cancers Symposium | #GI17
Slides are the property of the author. Permission required for reuse.

Current Systemic Treatment Options for Esophageal and Gastric Cancer

Ian Chau MD, FRCP

General Session 2: Advances in Systemic Therapy for Esophageal and Gastric Cancer (ARS)
Cancers of the Esophagus and Stomach Track



Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis

Annals of Oncology

Annals of Oncology 24: 2850–2854, 2013

Although the benefit of second-line chemotherapy is evident***, the disease control rate is just above 40%***. In other words, ***almost half of patients do not benefit from second-line chemotherapy and suffer from chemotherapy toxic effect***. Therefore, it is ***important to predict whether patients can benefit from second line chemotherapy*** treatment

Chemotherapy *vs* supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data

BJC
British Journal of Cancer (2016) 114, 381–387

Predictors of OS.

- ***PS 0–1*** compared with PS 2 and ***locally advanced disease*** compared with metastatic disease were ***significant predictors of improved OS***
- ***Progression of disease during first-line treatment or within the first 3 months of completion of first-line*** treatment were ***predictors of an increased risk of death*** compared with progression between 3 and 6 months

Lecture (15'): Palliative chemotherapy

First line

- ✓ *Doublets or triplets?*
  - *Triplets only in patients with high symptom burden*
  - *Stop using epirubicin*

Second line

- ✓ *What should be a standard?*
  - *Ramucirumab-paclitaxel*
- ✓ *Are all patients candidated to a second line therapy?*
  - *PS 0-1; PFS > 3-6 months*

Molecular classification

- ✓ *Do we have distinct treatment choices for these different molecular pathways?*
- ✓ *How can we address tumor heterogenity when we design GC clinical trials?*

TABLE 1. Major Clinical Trials in Gastric Adenocarcinoma With Targeted Agents

Target	Trial	Type of Study/Line	Patient Selection Method	Regimen	Results (Primary Endpoint)	Reference
HER2	ToGa	Phase III/first	HER2 IHC	5-FU/capecitabine + cisplatin ± trastuzumab	Positive (OS)	Bang et al 2010[5]
HER2	LOGIC	Phase III/first	HER2 amplification	Lapatinib + XELOX	Negative (OS)	Hecht et al[16]
				XELOX		
HER2	TYTAN	Phase III/second	HER2 amplification	Paclitaxel + lapatinib vs. paclitaxel	Negative (OS)	Bang et al (2013)[17]
EGFR	EXPAND	Phase III/first	All comer	Cetuximab/XP vs. placebo/XP	Negative (OS)	Lordick et al[18]
EGFR	REAL-III	Phase III/first	All comer	Panitumumab/EOC vs. EOC	Negative (OS)	Waddell et al[19]
EGFR	Nimotuzumab	Phase II/second	All comer	Nimotuzumab/irinotecan vs. irinotecan	Negative	Kim et al[20]
VEGF	AVAGAST	Phase III/first	All comer	XP/bevacizumab vs. XP	Negative (OS)	Van Cutsem et al[21]
MET	RILOMET-1	Phase III/first	MET IHC	Rilotumumab/ECX vs. ECX	Negative (OS)	Iveson et al[22]
MET	METGastric	Phase III	MET IHC	Onartuzumab/FOLFOX vs. FOLFOX	Negative (OS)	Shah et al[23]
FGFR2	SHINE	R-Phase II/second	FGFR2 amplification	AZD4547/paditaxel vs. paclitaxel	Negative (PFS)	Bang et al (2015)[24]
mTOR	GRANITE	Phase III/second or third	All comer	Everolimus vs. placebo	Negative (OS)	Ohtsu et al[25]
AKT	MK2206	Phase II/second	All comer	MK-2206	Response rate, 1%	Ramanathan et al[26]
ATM	Olaparib	R-Phase II/second	ATM IHC	Paclitaxel/olaparib vs. paclitaxel/placebo	Negative (PFS)	Bang et al (2015)[27]
VEGF	MEGA	R-Phase II/first	All comer	FOLFOX/aflibercept vs. FOLFOX	Negative (6-mo PFS)	Enzinger et al[28]
HER2	GATSBY	Phase II/III/ second	HER2 IHC	TDM1 vs. paclitaxel or docetaxel	Negative (OS)	Kang et al[29]
VEGFR-2	RAINBOW	Phase III/second	All comer	Paclitaxel/ramucirumab vs. paclitaxel/placebo	Positive (OS)	Wilke et al[30]
VEGFR-2	REGARD	Phase III/third	All comer	Ramucirumab vs. placebo	Positive (OS)	Fuchs et al[31]

Negative trials with targeted agents have ***substantially out numbered the positive trials*** (the ToGA, REGARD, and RAINBOW trials) in GAC in the past decade

Major factors accounting for this negative outcome may be

(1) ***many trials did not select the patient population based on specific target***,

(2) ***inaccurate biomarker for patient selection*** (i.e., HER2, FISH vs. HER2 IHC)

Molecular classification of gastric cancer

ANNALS OF ONCOLOGY
Annals of Oncology 27: 763–769, 2016

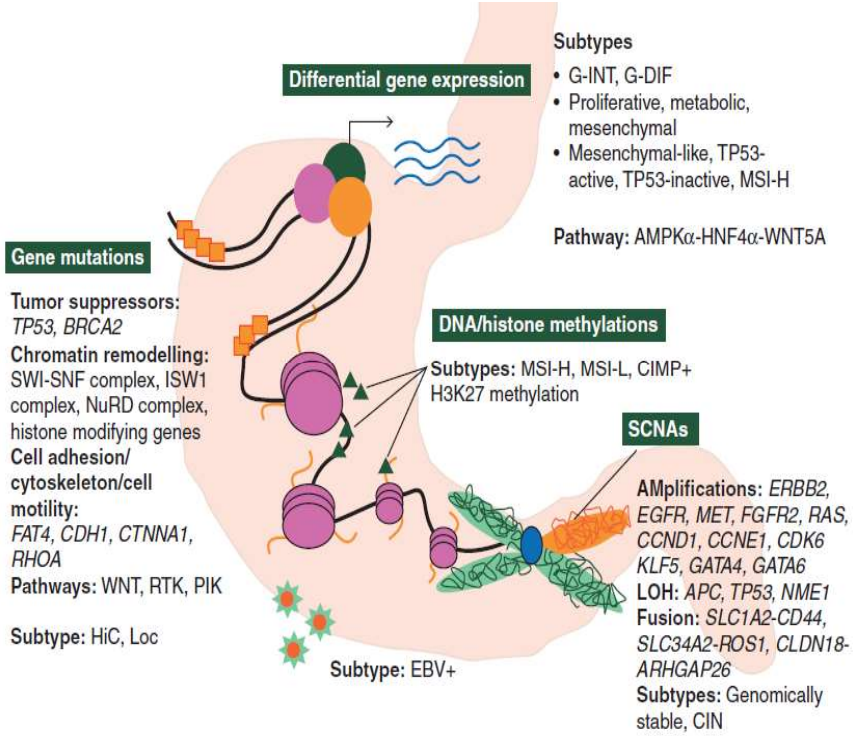


Figure 1. Genetic and epigenetic modification of gastric cancer (GC). The genetic alteration that contributes to GC involves gene mutations, differential gene expression as well as somatic copy number alterations (SCNAs). The epigenetic modifications involve DNA as well as histone methylation.

- Recent ***advancements in genomic technology have now allowed*** GCs to be studied at high resolution and at the molecular level
- Such ***molecular profiling data*** have greatly facilitated ***identification of candidate driver alterations in GC***
- Achieving an understanding of potential driver alterations involved in GC pathogenesis can lead to the ***identification of*** clinically important biomarkers and ***potential treatment targets***

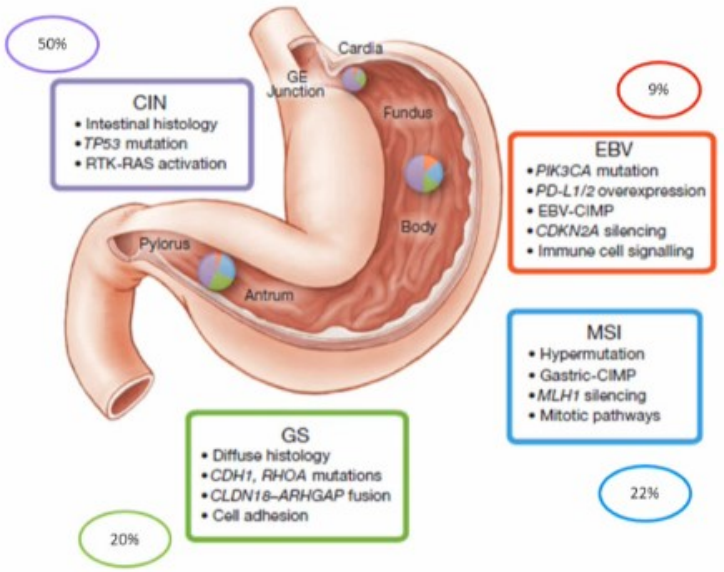
Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network*

nature

VOL 513 | 11 SEPTEMBER 2014

Comprehensive molecular characterization of GC - TCGA



The landmark Cancer Genome Atlas (TCGA) study performed sequencing of 295 gastric cancer samples on 6 different molecular platforms

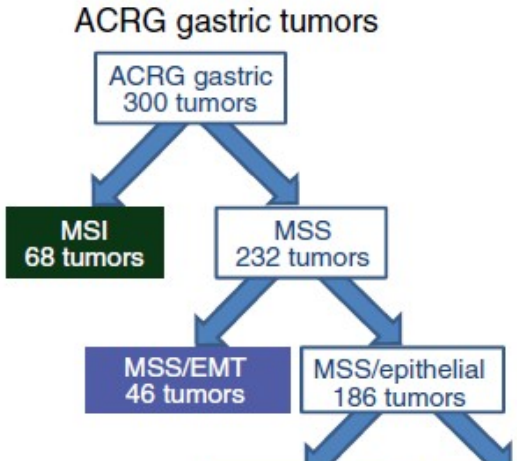
Based on this, ***gastric cancer was clustered into 4 groups***:

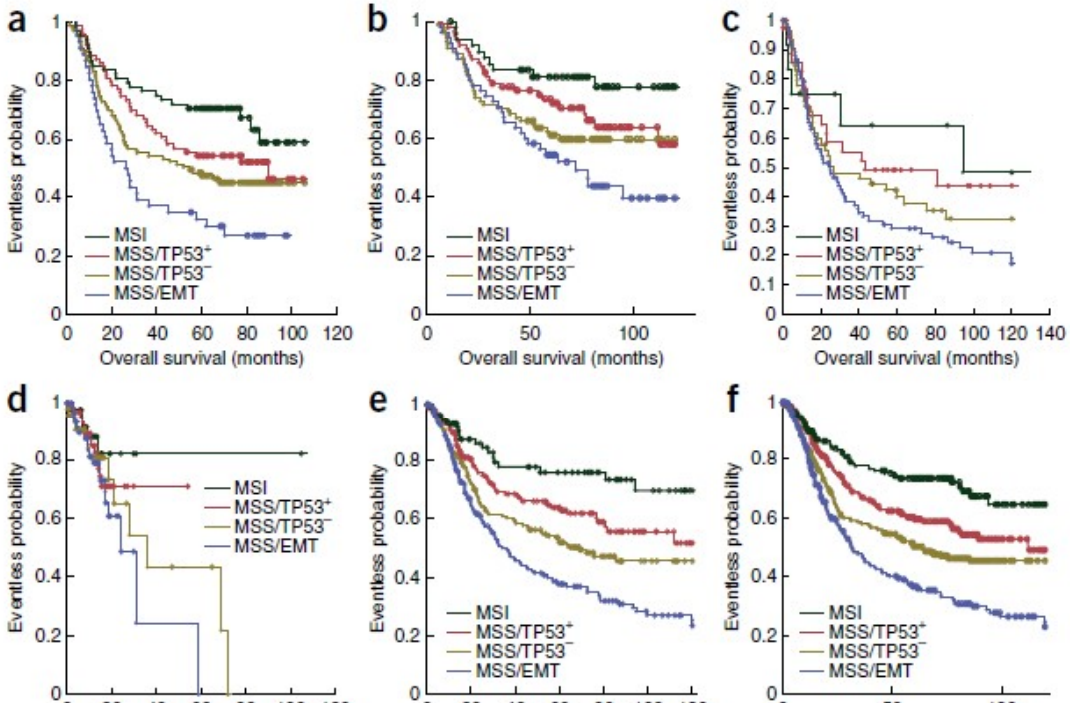
- ✓ ***Ebstein-Barr virus(EBV) positive*** (9%),
- ✓ ***tumours with microsatellite instability (MSI)*** (22%),
- ✓ ***genomically stable tumours*** (20%)
- ✓ and those with ***chromosomal instability*** (50%)

Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes

nature medicine
VOLUME 21 | NUMBER 5 | MAY 2015

The ***Asian Cancer Research Group (ACRG)*** used gene expression data to ***describe four molecular subtypes linked to distinct patterns of molecular alterations, disease progression and prognosis***





Do we have distinct treatment choices for these different molecular pathways?

Figure 1 The four distinct subtypes in GC

Figure 2 Molecular subtype and survival association.

ESTRO School

Mismatch Repair Deficiency, Microsatellite Instability, and Survival

An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial

JAMA Oncology

JAMA Oncol. doi:10.1001/jamaoncol.2016.6762

IMPORTANCE Mismatch repair (MMR) deficiency (MMRD) and microsatellite instability (MSI) are prognostic for survival in many cancers and for resistance to fluoropyrimidines in early colon cancer. However, the effect of MMRD and MSI in curatively resected gastric cancer treated with perioperative chemotherapy is unknown.

Figure 1. Overall Survival by Microsatellite Instability (MSI) Status and Treatment Arm in the Study Patients

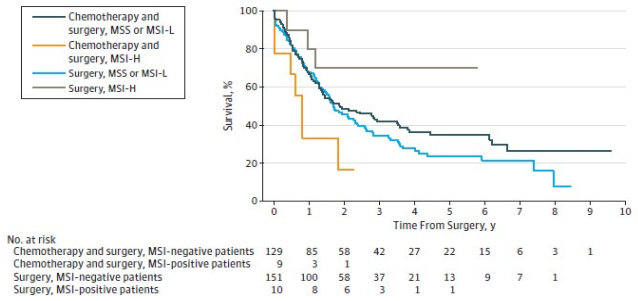
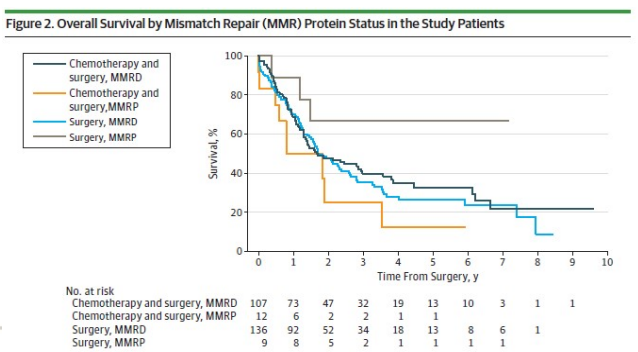


Figure 2. Overall Survival by Mismatch Repair (MMR) Protein Status in the Study Patients



We found that patients with MSI-H or MMRD tumors have superior survival compared with patients with MSS/MSI-L or MMRP tumors when treated with surgery alone and conversely have inferior survival to patients with MSS/MSI-L or MMRP tumors when treated with perioperative chemotherapy plus surgery. These findings are significant, because if validated, they suggest that patients with MSI-H or MMRD may not benefit (or may experience a detrimental effect) from perioperative chemotherapy and may be better served by a surgery-only approach. Because MSI or MMRD tumors comprise up to 10% to 20% of stomach cancers in some series, this finding has the potential to affect large numbers of patients.[15]

Molecular classification of gastric cancer

EXPERT REVIEW OF MOLECULAR DIAGNOSTICS
EXPERT REVIEW OF MOLECULAR DIAGNOSTICS, 2017
VOL. 17, NO. 3, 293–301

The accurate classification of MSI-GC may become clinically relevant for two reasons:

- (1) MSI-GCs may not require ***any standard adjuvant (radio-)chemotherapy*** in a curative setting;
- (2) MSI-GCs express the immune checkpoint molecules PD-L1 and PD-1 and ***may be considered suitable for the treatment with immune checkpoint inhibitors*** in the palliative setting

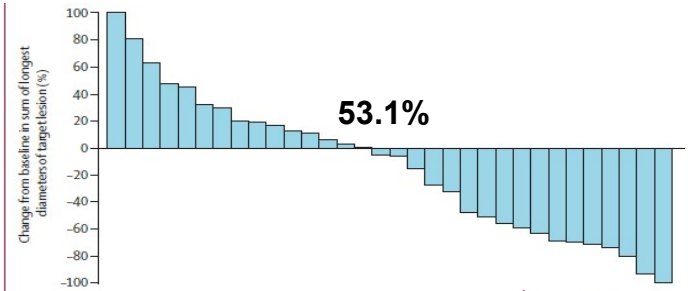
Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial

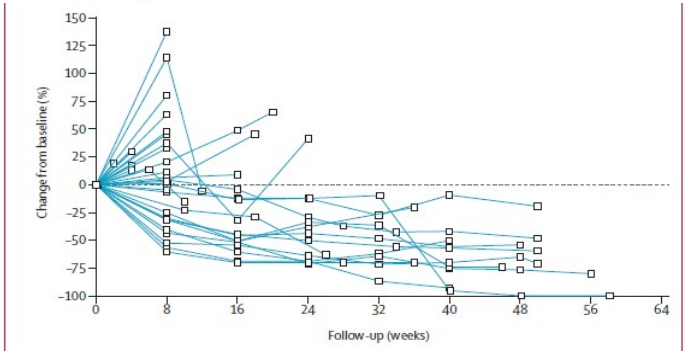
THE LANCET Oncology

Lancet Oncol 2016; 17: 717–26

Background Expression of PD-L1 has been shown to be upregulated in some patients with gastric cancer. As part of the phase 1b KEYNOTE-012 study, we aimed to assess the safety and activity of the anti-PD-1 antibody pembrolizumab in patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

	Central review*		Investigator review	
	Asia (n=17)	Rest of the world (n=19)	Asia (n=19)	Rest of the world (n=20)
Objective response (%, 95% CI†)	4 (24%, 7–50)	4 (21%, 6–46)	7 (37%, 16–62)	6 (30%, 12–54)
Best overall response				
Complete response‡	0	0	0	0
Partial response‡	4 (24%)	4 (21%)	7 (37%)	6 (30%)
Stable disease	3 (18%)	2 (11%)	2 (11%)	1 (5%)
Progressive disease	7 (41%)	12 (63%)	10 (53%)	13 (65%)
No assessment§	0	1 (5%)	0	0
Not determined¶	3 (18%)	0	0	0
Time to response (weeks)	8 (7–8)	8 (8–12)	8 (7–16)	8 (8–16)
Duration of response (weeks)	40 (32–NR)	NR (22–NR)	40 (30–NR)	42 (40–NR)
Median progression-free survival (95% CI; months)	1·9 (1·8–5·7)	1·8 (1·6–5·8)	1·9 (1·4–10·6)	1·8 (1·6–7·1)
Median overall survival (95% CI; months)	11·4 (3·1–NR)	NR (3·5–NR)	11·4 (3·1–NR)	NR (3·5–NR)





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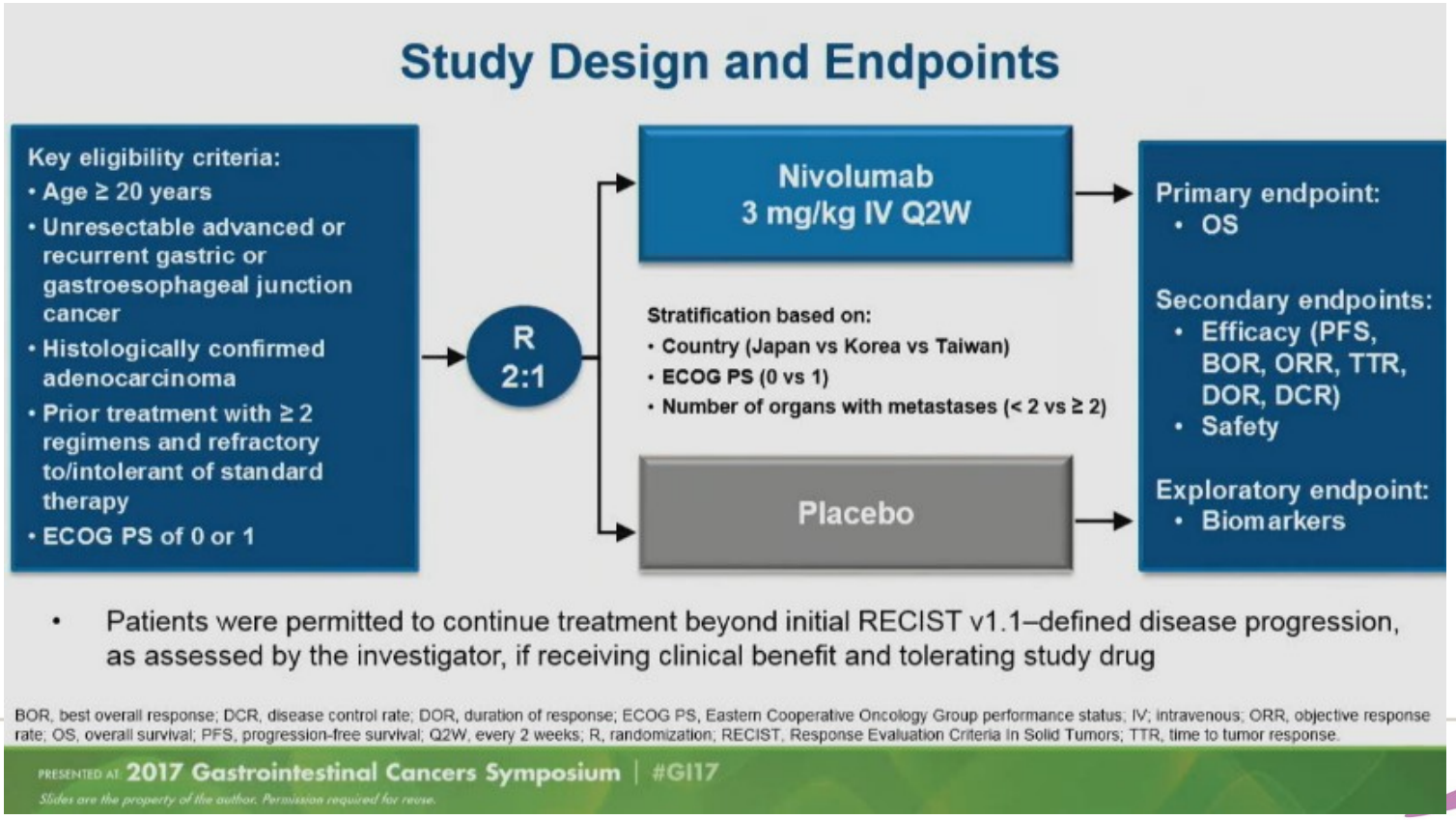
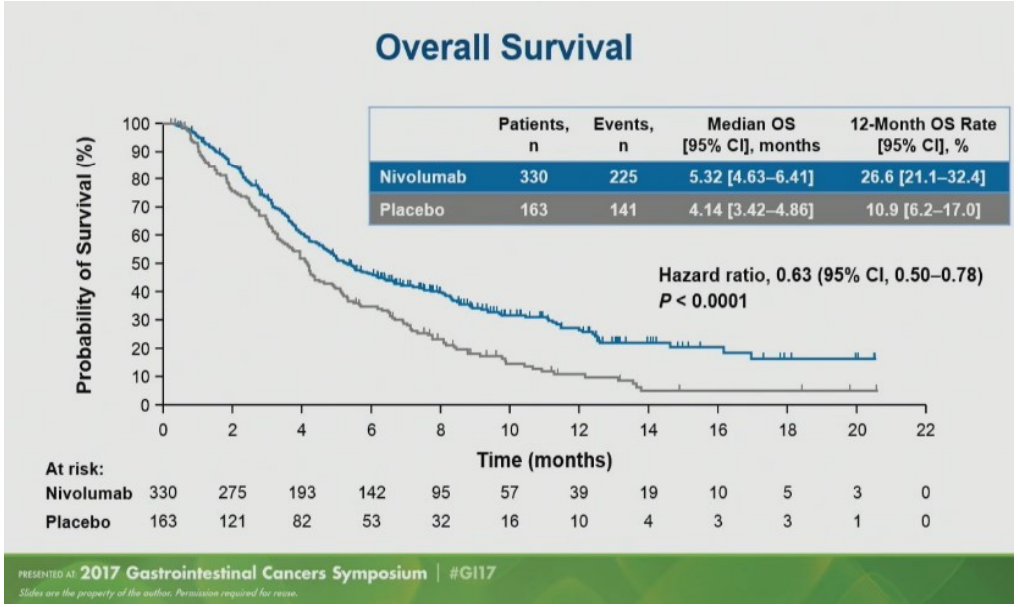
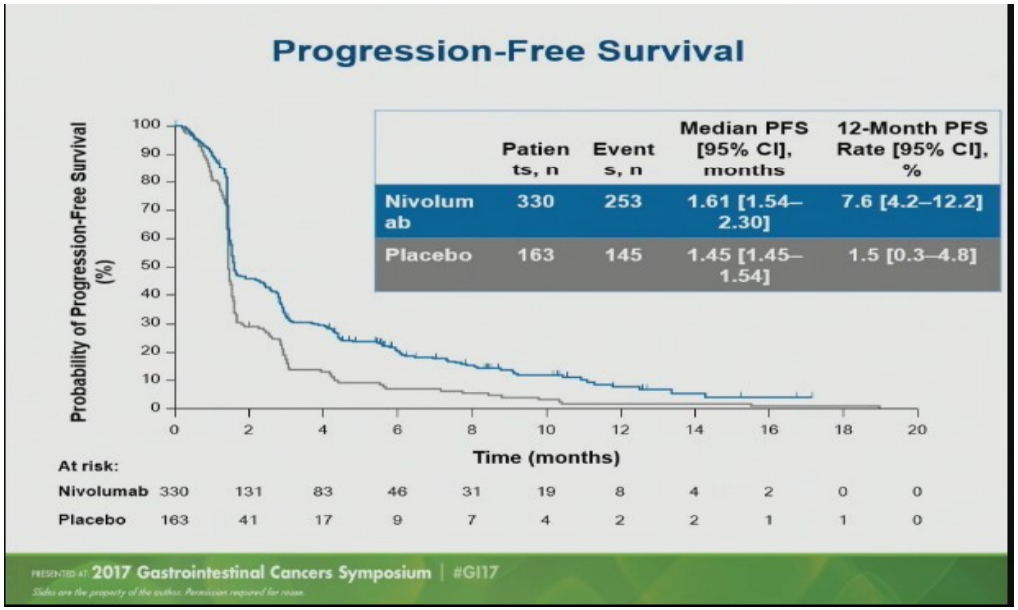
Nivolumab (ONO-4538/BMS-936558) as Salvage Treatment After Second- or Later-Line Chemotherapy for Advanced Gastric or Gastroesophageal Junction Cancer (AGC): A Double-Blinded, Randomized, Phase 3 Trial



Nivolumab (ONO-4538/BMS-936558) as Salvage Treatment After Second- or Later-Line Chemotherapy for Advanced Gastric or Gastroesophageal Junction Cancer (AGC): A Double-Blinded, Randomized, Phase 3 Trial



	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]



	Patients, n	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], %
Nivolumab	330	253	1.61 [1.54–2.30]	7.6 [4.2–12.2]
Placebo	163	145	1.45 [1.45–1.54]	1.5 [0.3–4.8]

ESTRO School

Lecture (15'): Palliative chemotherapy

First line

- ✓ *Doublets or triplets?*
  - *Triplets only in patients with high symptom burden*
  - *Stop using epirubicin*

Second line

- ✓ *What should be a standard?*
  - *Ramucirumab-paclitaxel*
- ✓ *Are all patients candidated to a second line therapy?*
  - *PS 0-1; PFS > 3-6 months*

Molecular classification

- ✓ *Do we have distinct treatment choices for these different molecular pathways?*
  - *Work in progress*
- ✓ *How can we address tumor heterogenity when we design GC clinical trials?*

How can we address tumor heterogeneity when designing GC clinical trials?

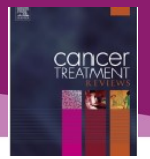
- **Learn everything you need to know for the targeted agents from early on! (Do not wait until phase III)**
- Crucial to address this early on because..

The Case for Biomarker Driven Trials

- Oncology drug trials 2009-2014- comparison between 42 drugs that failed Phase III versus 37 drugs gaining FDA approval
- Failed drugs were studied using biomarker-driven approaches in 16% of cases versus 57% of approved drugs (P<0.001)
- 28% of failed drugs versus 87% (P<0.001) passed proof of concept in Phase II before moving on.
- No correlation to study sites, trial design or funding characteristics emerged from the failed drug analysis.

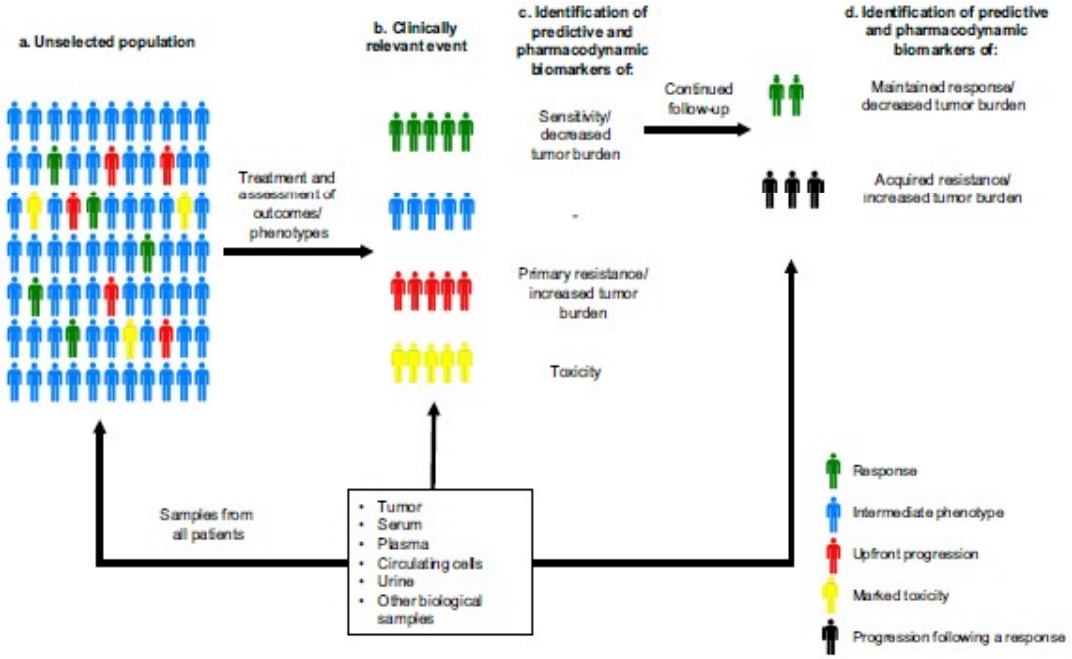
Jardim DL et al. Cancer Treat Rev. 2017 Jan;52:12-21.

Strategies to design clinical studies to identify predictive biomarkers in cancer research



Cancer Treatment Reviews 53 (2017) 79–97

In this manuscript, a multidisciplinary panel proposes a ***methodological framework—the DESIGN guidelines***—to standardize the clinical design of biomarker identification studies and to develop future research in this pivotal field

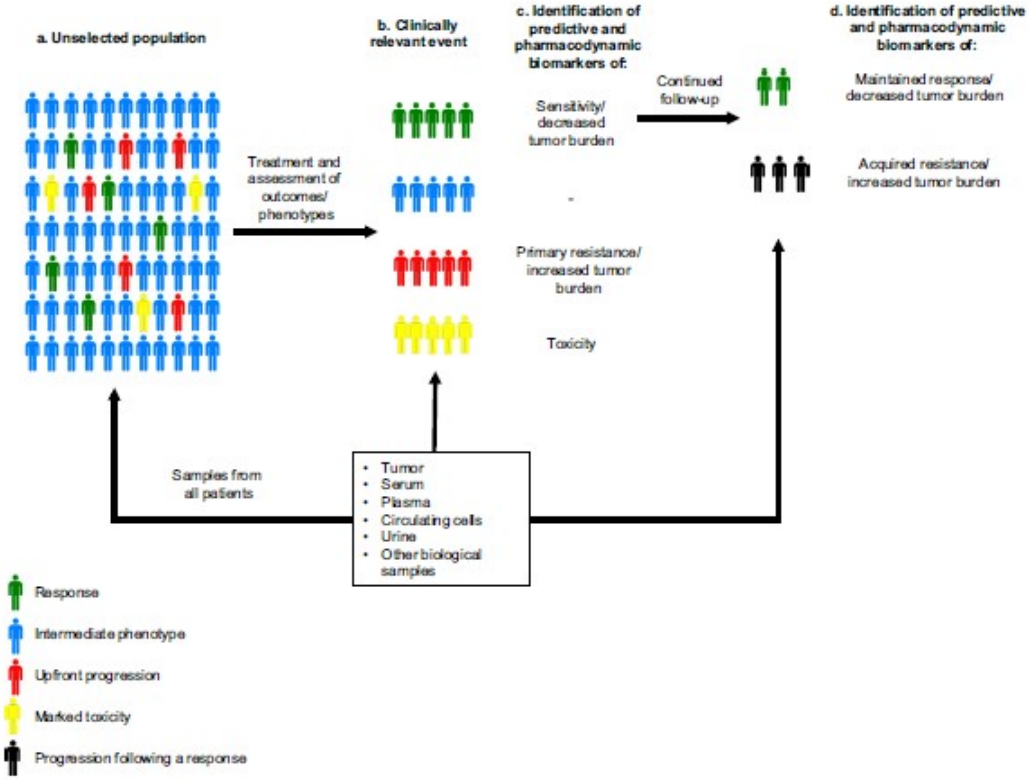


Design of biomarker identification studies using ***sequential samples from patients treated with systemic therapies***:

a. ***Baseline samples*** are obtained from all patients treated with a particular drug

b. ***Sequential samples*** are obtained whenever a clinically relevant event (i.e., response, progression or marked toxicity) is observed

Strategies to design clinical studies to identify predictive biomarkers in cancer research



Cancer Treatment Reviews 53 (2017) 79–97

c. ***Baseline and sequential samples from patients presenting clinically relevant events may be interrogated*** to identify predictive or pharmacodynamic associated biomarkers

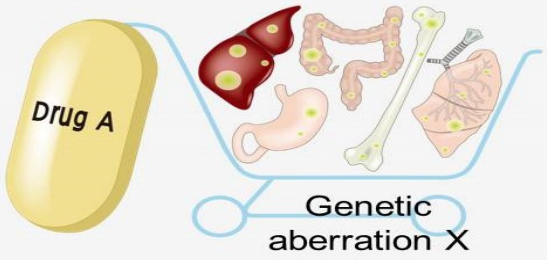
d. ***Sequential samples of patients presenting initial responses may be used to identify biomarkers associated with sustained response and/ or decreased tumor burden***; or with development of acquired resistance and/ or increased tumor burden

Upfront biomarker driven trials in GC

Innovative Clinical Trial Designs: Basket Trials vs Umbrella Trials

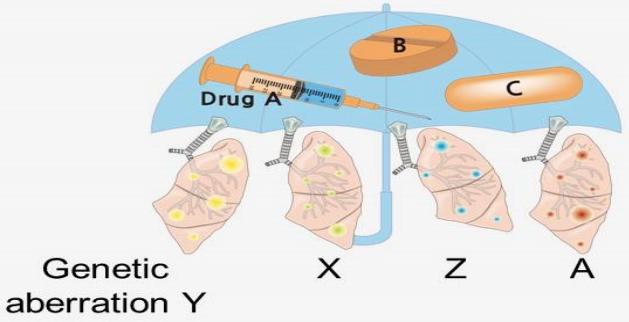
Basket/Bucket trial

Test the **single** drug targeting a same genomic alteration across a **variety** of cancer types.



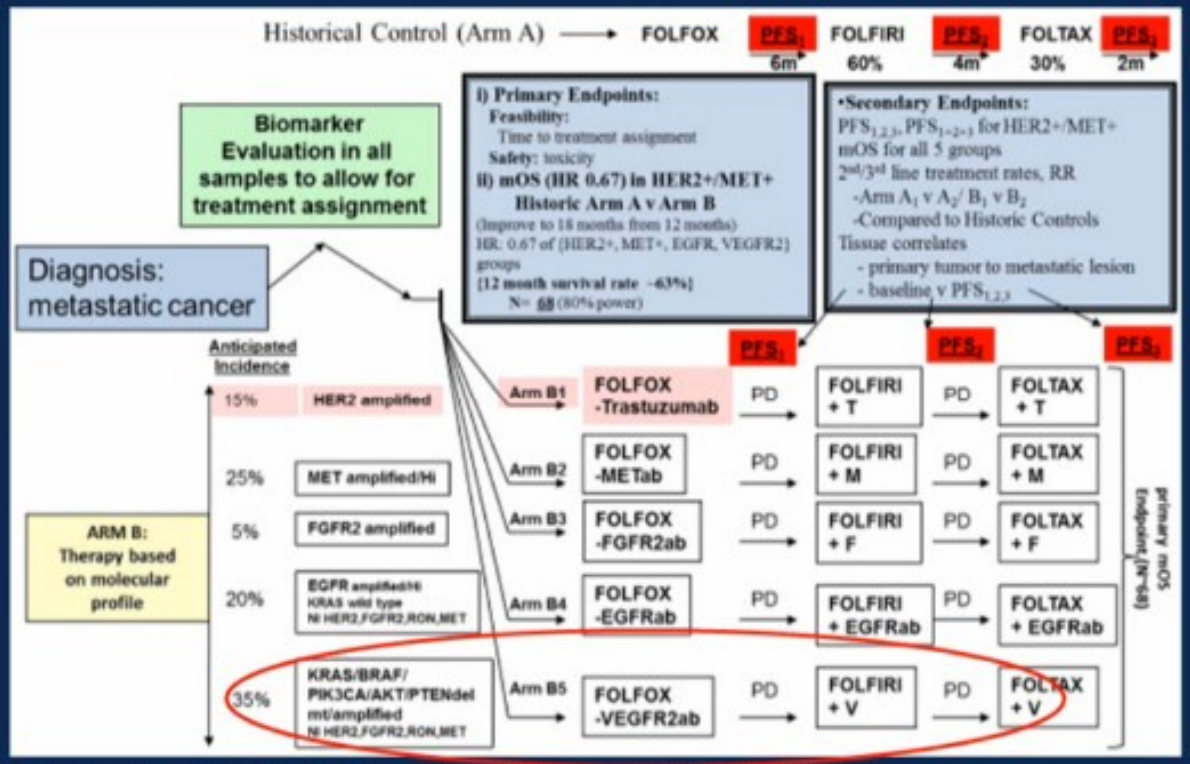
Umbrella trial

Test the **multiple** drugs targeting multiple different genomic alterations in a **single cancer** subtype.



Kummar S, JNCI 2015

Next-Generation Trials: PANGEA



Catenacci. Expansion Platform Type II: Testing a Treatment Strategy. *Lancet Oncol* 2015.

Catenacci *et al.* Toward personalized treatment for gastroesophageal adenocarcinoma (GEC): Strategies to address tumor heterogeneity—PANGEA.
ASCO GI 2014. NCT02213289

PRESENTED AT: 2016 Gastrointestinal Cancers Symposium

ESTRO School

28 March (Tuesday)

Lecture (15'): Palliative chemotherapy

First line

- ✓ *Doublets or triplets?*
  - *Triplets only in patients with high symptom burden*
  - *Stop using epirubicin*

Second line

- ✓ *What should be a standard?*
  - *Ramucirumab-paclitaxel*
- ✓ *Are all patients candidated to a second line therapy?*
  - *PS 0-1; PFS > 3-6 months*

Molecular classification

- ✓ *Do we have distinct treatment choices for these different molecular pathways?*
  - *Work in progress*
- ✓ *How can we address tumor heterogenity when we design GC clinical trials?*
  - *Methodological framework*
  - *Innovative clinical trial designs*

Thanks!

n.silvestris@oncologico.bari.it

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New perspectives in gastric cancer

Marcel Verheij MD PhD
Department of Radiation Oncology
NKI, Amsterdam

Strategies to improve outcome

- Treatment-related
- Patient-related
- Tumor-related

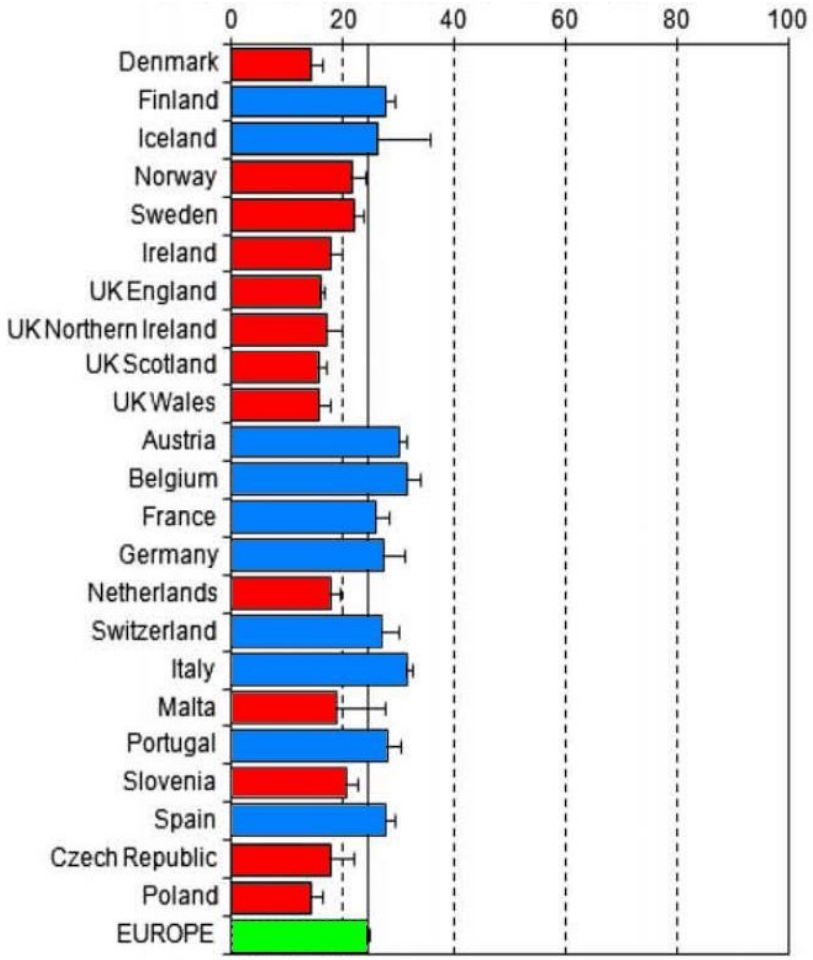
Strategies to improve outcome

- Treatment-related: where, when and how?
- Patient-related
- Tumor-related

Survival of gastric cancer patients in Europe

Age-standardized 5-year relative survival (%)

1995-1999: EUROCARE-4



Sant et al. Eur J Cancer 2009

1999-2007: EUROCARE-5

	Stomach cancer
European mean	25·1 (24·8–25·4)
Central Europe	28·1 (27·6–28·5)
Austria	31·0 (29·9–32·2)
Belgium*	30·5 (29·1–32·0)
France*	26·3 (24·9–27·6)
Germany*	31·3 (30·6–32·0)
Switzerland*	31·6 (29·2–34·1)
Netherlands	20·4 (19·7–21·2)

De Angelis et al. Lancet Oncol 2014

Improving surgical quality

The effect of centralization

Comparison of gastric cancer surgery in Denmark: 1999-2003 versus 2003-2008

	1999-2003	2003-2008
No. of departments	37	5
No. of operations	537	417
Anastomotic leakages (%)	6.1	5.0
Hospital mortality (%)	8.2	2.4*
Patients with ≥15 lymph nodes removed (%)	19	76*

Jensen et al. Eur J Surg Oncol 2010

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Improving surgical quality

The effect of centralization

National data obtained from cancer registries or clinical audits in the Netherlands, Sweden, Denmark and England. Between 2004 and 2009, 10 854 oesophagectomies and 9010 gastrectomies were registered

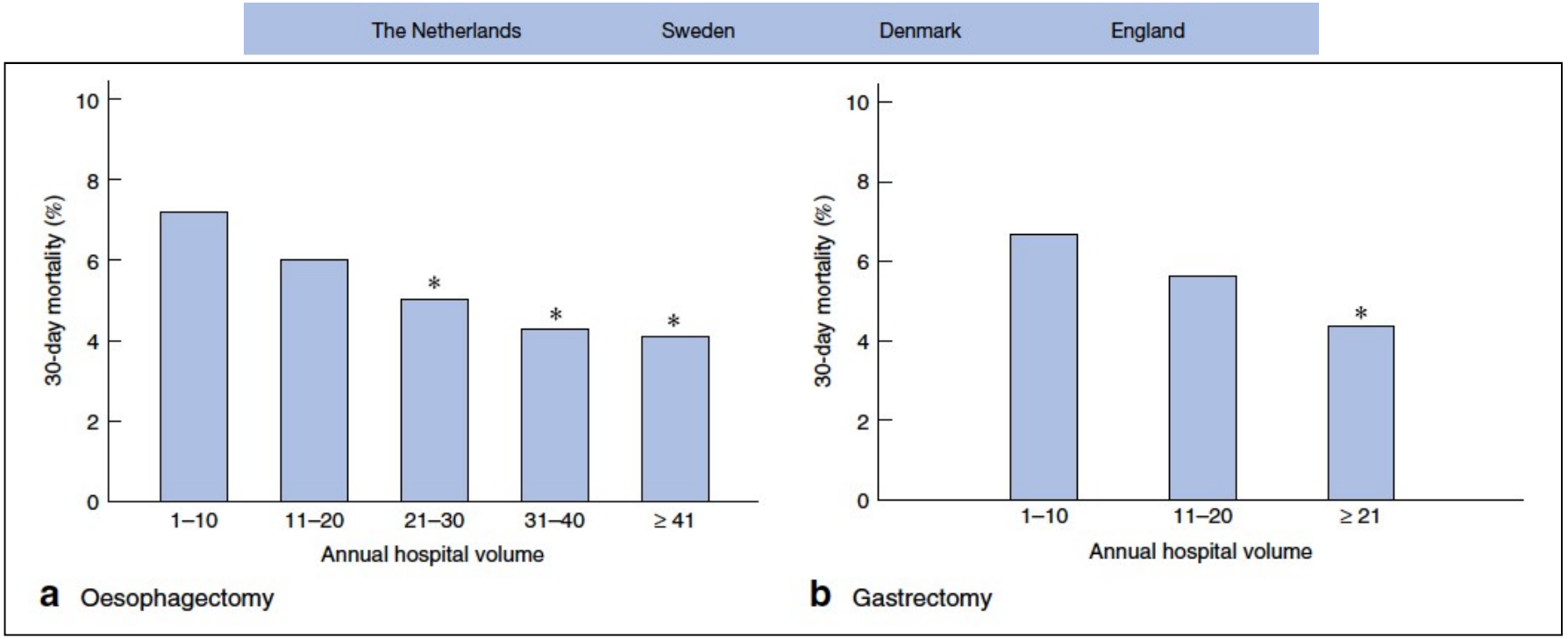

Fig. 4 Postoperative 30-day mortality after a oesophagectomy and b gastrectomy, adjusted for sex, age, and histology, by annual hospital volume (procedures per year). *$P < 0{\cdot}050$ *versus* 1–10 (generalized estimated equations)

Dikken et al. Eur J Surg Oncol 2012

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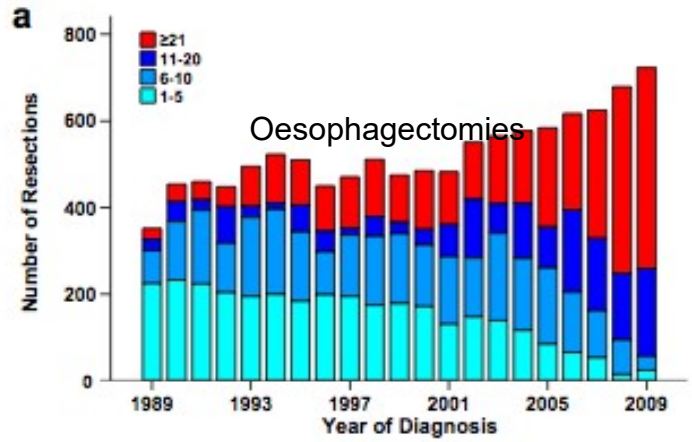
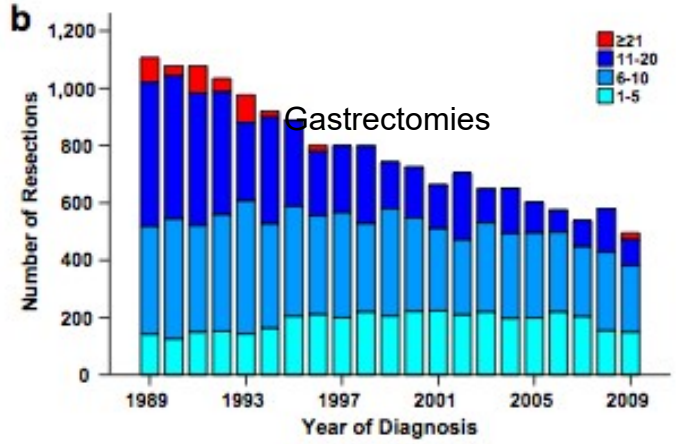
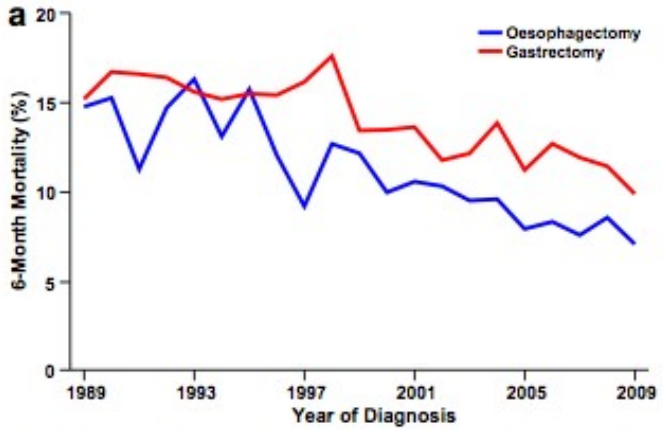
Improving surgical quality

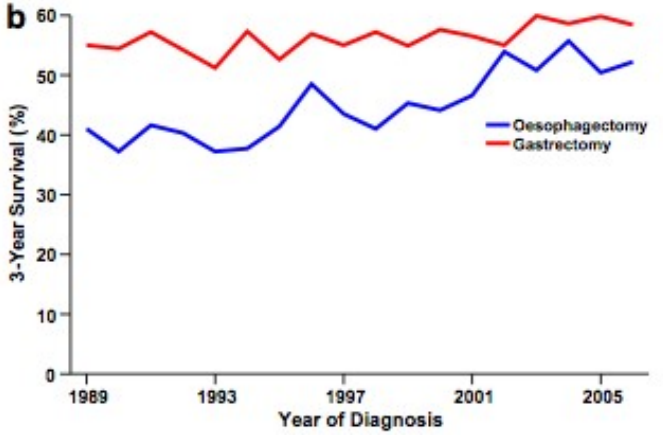
The effect of centralization

Number of resections per hospital volume category and surgical outcome in The Netherlands









Dikken et al. Eur J Cancer 2012

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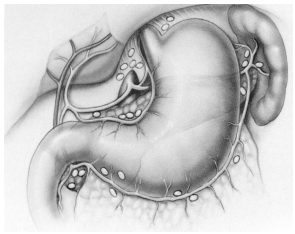
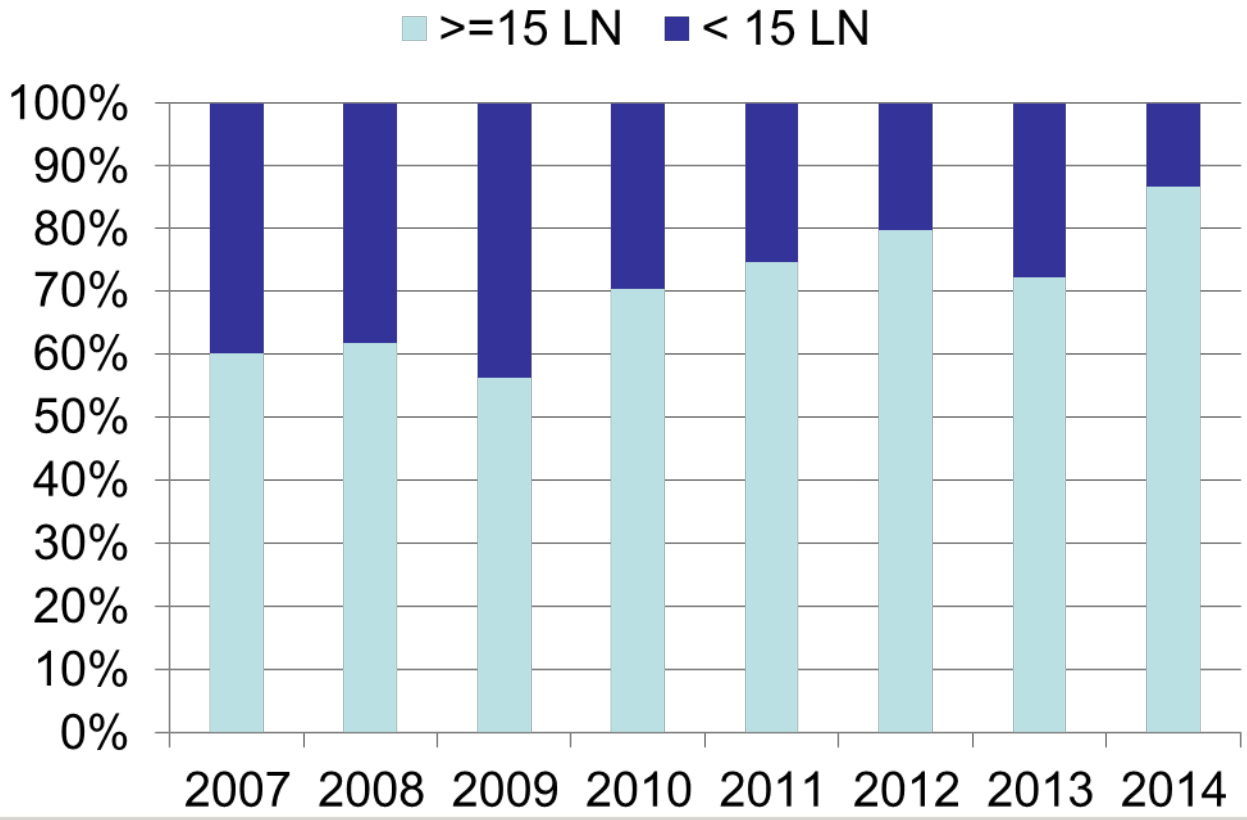
CRITICS trial
- Number of examined lymph nodes -



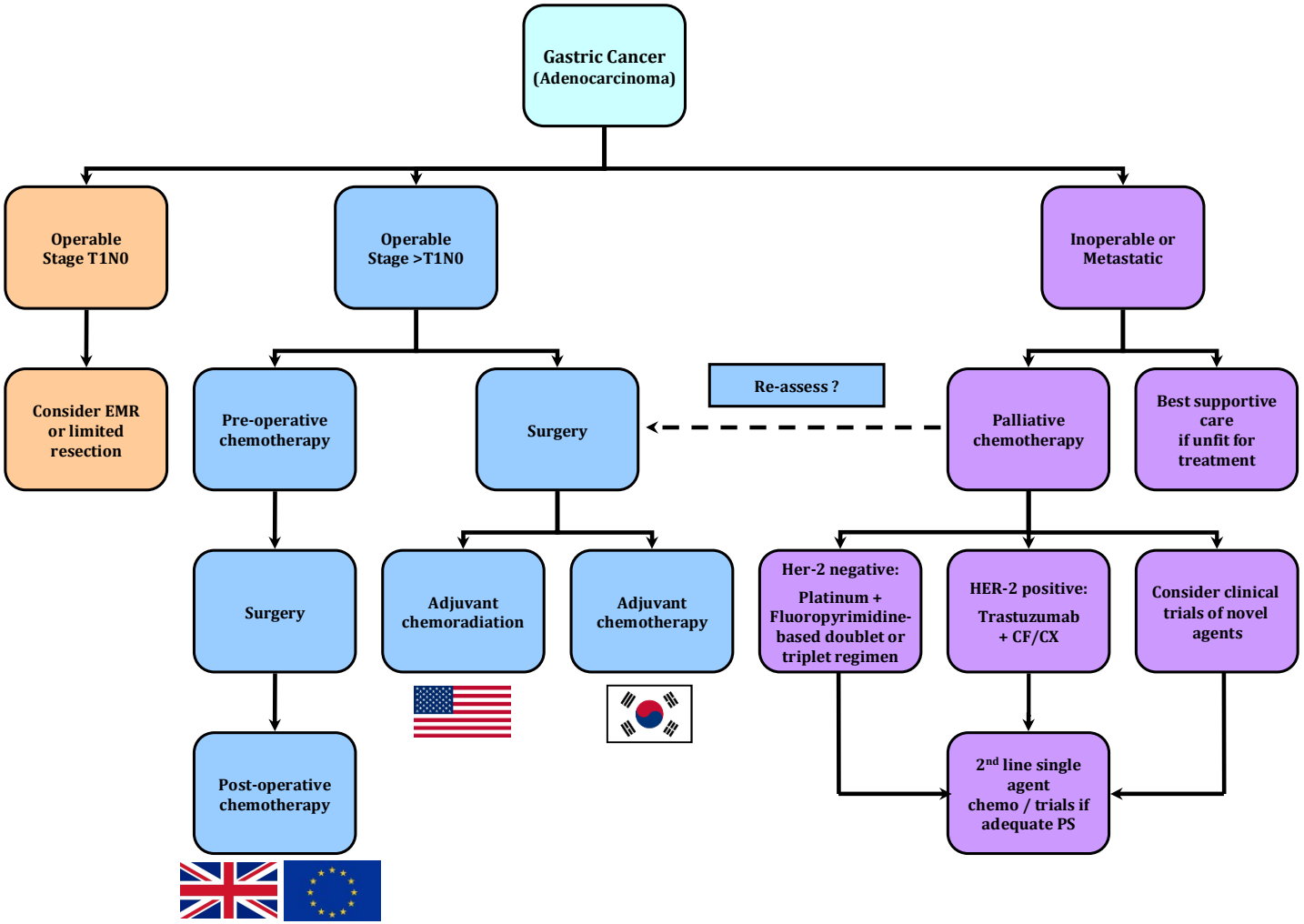


clinical practice guidelines

Ann Oncol 2013, Radiother Oncol 2014, Eur J Surg Oncol 2014

Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

T. Waddell[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6*]



Poor patient compliance in post-operative phase

Study	Treatment arm	% Completed
SWOG	**S** → CRT	64%
MAGIC	CT → **S** → CT	42%
MAGIC-B (MRC ST03) MAGIC-B (MRC ST03)	CT → **S** → CT CT+B → **S** → CT+B	40% 37%
ARTIST ARTIST	**S** → CT **S** → CRT	75% 82%
CLASSIC	**S** → CT	67%
TOPGEAR part 1 TOPGEAR part 1	CT → **S** → CT CT → CRT → **S** → CT	60% 46%
CRITICS	CT → **S** → CT CT → **S** → CRT	47% 52%

S=Surgery; CT=ChemoTherapy; B=Bevacizumab; CRT=ChemoRadioTherapy

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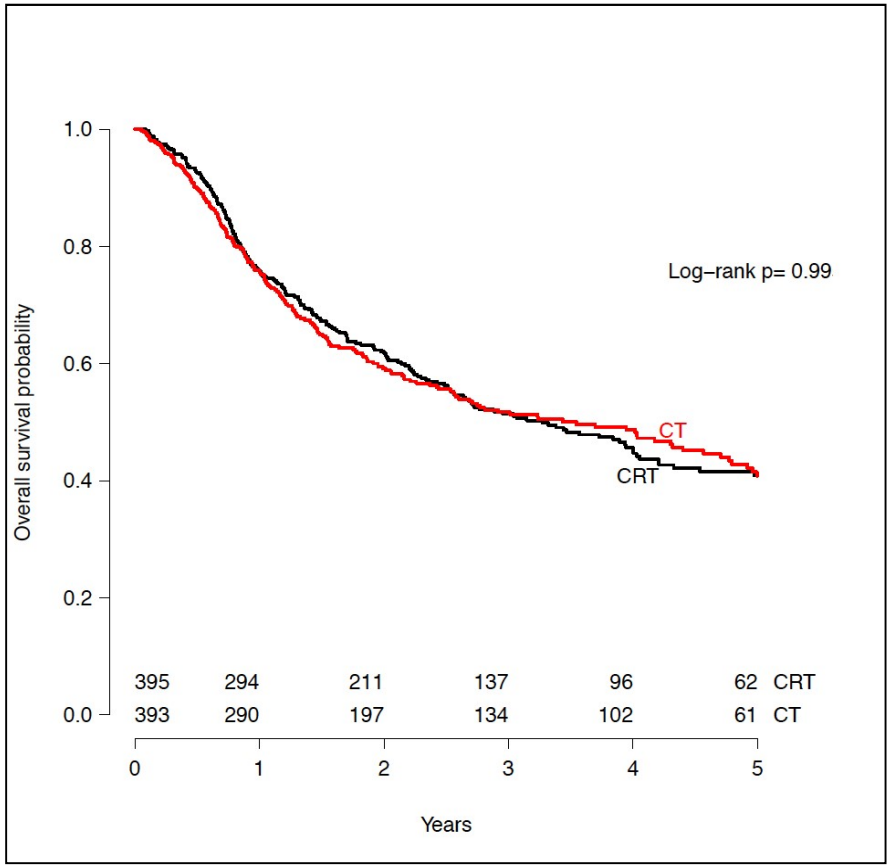
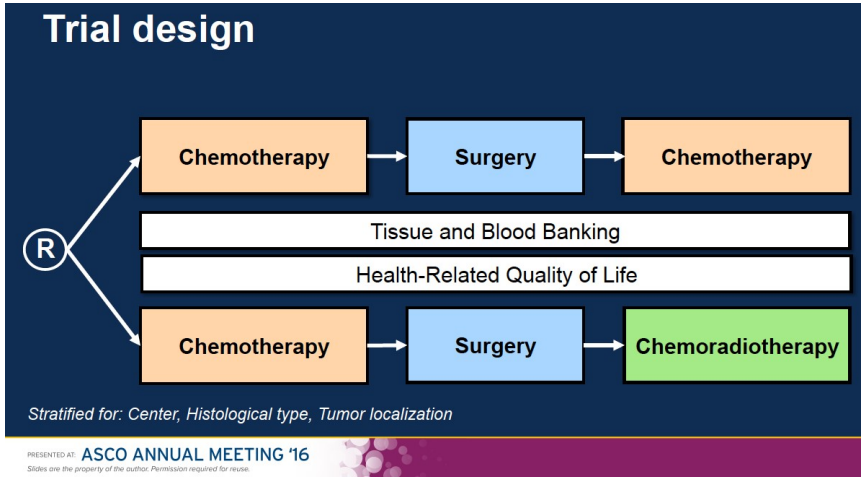
CRITICS trial
- Overall survival -





	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3

Verheij et al. ASCO 2016

Pre-operative chemoradiotherapy is an attractive approach

Advantages

- Smaller treatment volume by more accurate target definition
- Downstaging/-sizing; higher chance of radical R0 surgery
- Good compliance (CROSS)
- Early indication of treatment sensitivity

Disadvantages

- No information on histology, lymph node status
- Toxicity may delay definitive surgery

Pre-operative chemoradiotherapy: phase I-II studies

Authors	Patients	RT	Chemotherapy	Surgery	Outcome
Allal et al. IJROBP 2005; Ann Oncol 2003	N=19 T3-4 or N+	Median dose 38.4 Gy (hyperfx)	2 cycles of Cisplatin (100 mg/m^2) d1; 5FU (800 mg/m^2) d1-4; leucovorin (60 mg bid) d1-4 Second cycle during RT	D2 with (sub) total gastric resection	R0 resection 100% pCR+pPR 47% 2yr OS 71%
Ajani et al. JCO 2004	N=34 T2-3, Nany or T1N1	45 Gy/25 fx	2 cycles of Cisplatin (20 mg/m^2) d 1-5; 5FU (200 mg/m^2) 21 days; leucovorin (20 mg^2) d1, 8, 15 During RT: 5FU (300 mg/m^2) dd conti. iv	D2 Median number lymph nodes examined: 16	R0 resection 70% pCR+pPR 54% 2yr OS 54%
Lowy et al. Ann Surg Oncol 2001	N=24 ≥T2 and/or N+	45 Gy/25 fx 10 Gy intra-operative	5FU c.i. (300 mg/m^2)	83% D2 Rest PD	11% pCR 63% sign treatment effect
Ajani et al. JCO 2005	N=41 T2-3N0-1 T1N1	45 Gy/25 fx	2 induction courses of fluorouracil, paclitaxel and cisplatin; 5FU and paclitaxel concurrent with RT	98% S 78% R0	pCR 20% pPR 15%
Ajani et al. JCO 2006	N=43 assessable [20 institutions] T2-3N0-1 or T1N1	45 Gy/25 fx	2 induction courses with 5FU, leucovorin and cisplatin; fluorouracil and paclitaxel concurrent with RT	50% D2	pCR 26% R0 77% Med surv 23.2 m 1yr surv 72%
Wydmanski et al. R&O 2007	N=40 TNM??	45 Gy/25 fx	4 5FU and LV based schedules (1st and last week of RT)	80% S (D2)	R0 94% pCR 17.5% pPR 20% 2yr surv 63%
Saikawa et al. IJROBP 2008	N=29 evaluable	40 Gy/20 fx	S1 (60 mg/m2/d) and Cisplatin (6 mg/m^2/d)	33% S D2; > 10 months	R0: 100% pCR: 4/30 (13.3%) Med surv 25 m
Trip et al. R&O 2014	N=25 II-IV (M0)	45 Gy/25 fx	weekly carboplatin and paclitaxel concurrent with RT	84% D1+	R0: 72% pCR: 16%
Combined	***19 - 43 pts***	***40 - 45 Gy***	***5FU/cis-/carboplatin/ paclitaxel***	***D2***	***R0: 70 - 100%*** ***pCR: 11 - 26%***

From: Trip et al. Transl Gastrointest Cancer 2015

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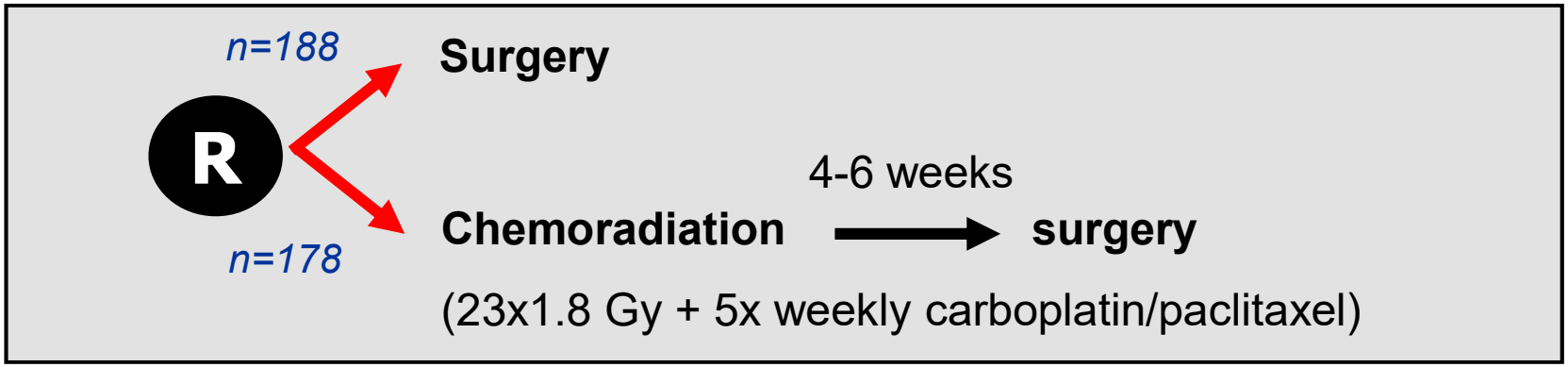
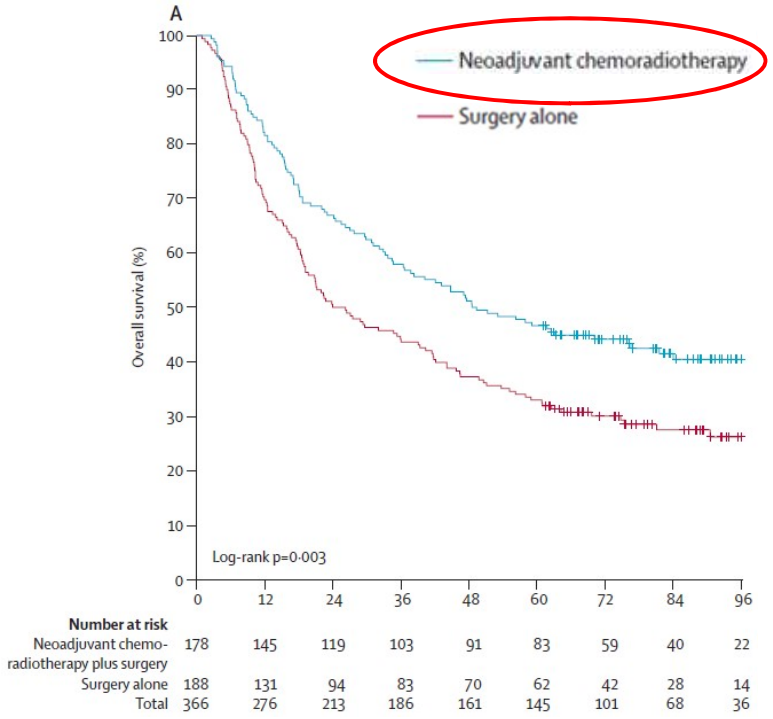
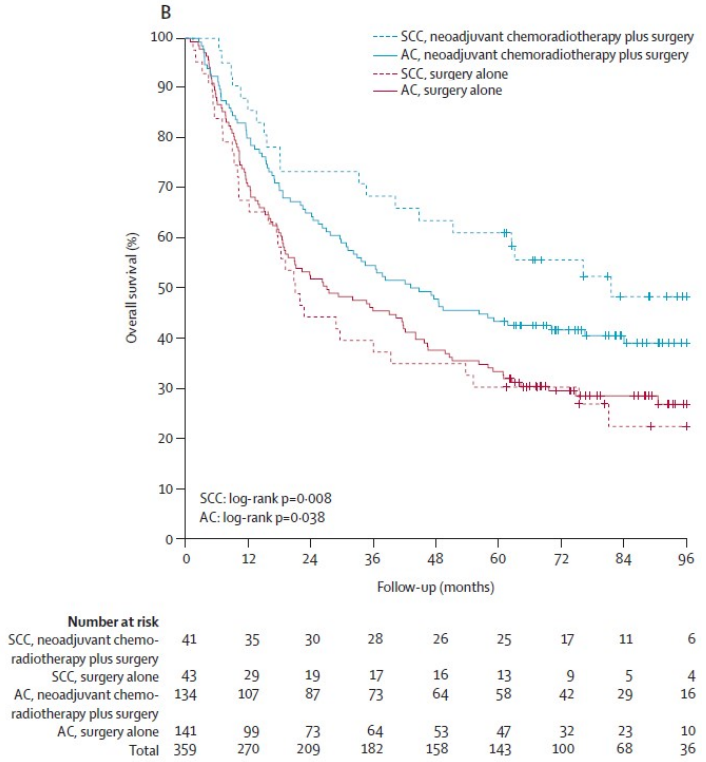
Pre-operative chemoradiation improves outcome in esophageal and junctional cancer: the CROSS trial

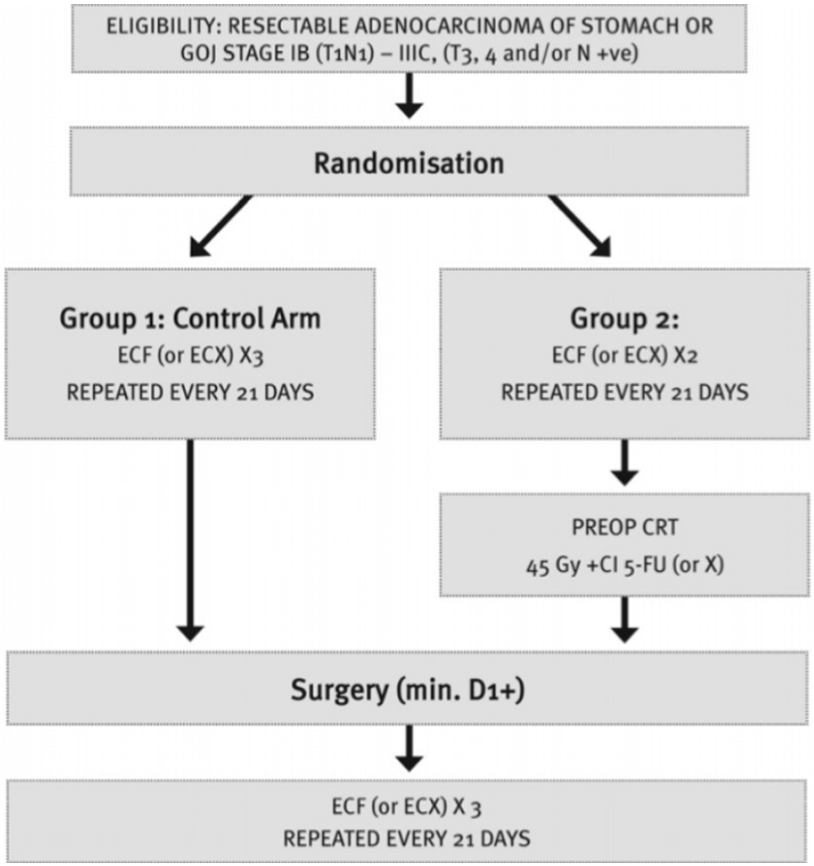






Shapiro et al. Lancet Oncol 2015 (median FU 84.1 months)

Pre-operative chemoradiotherapy is feasible and safe: early results from the TOPGEAR study

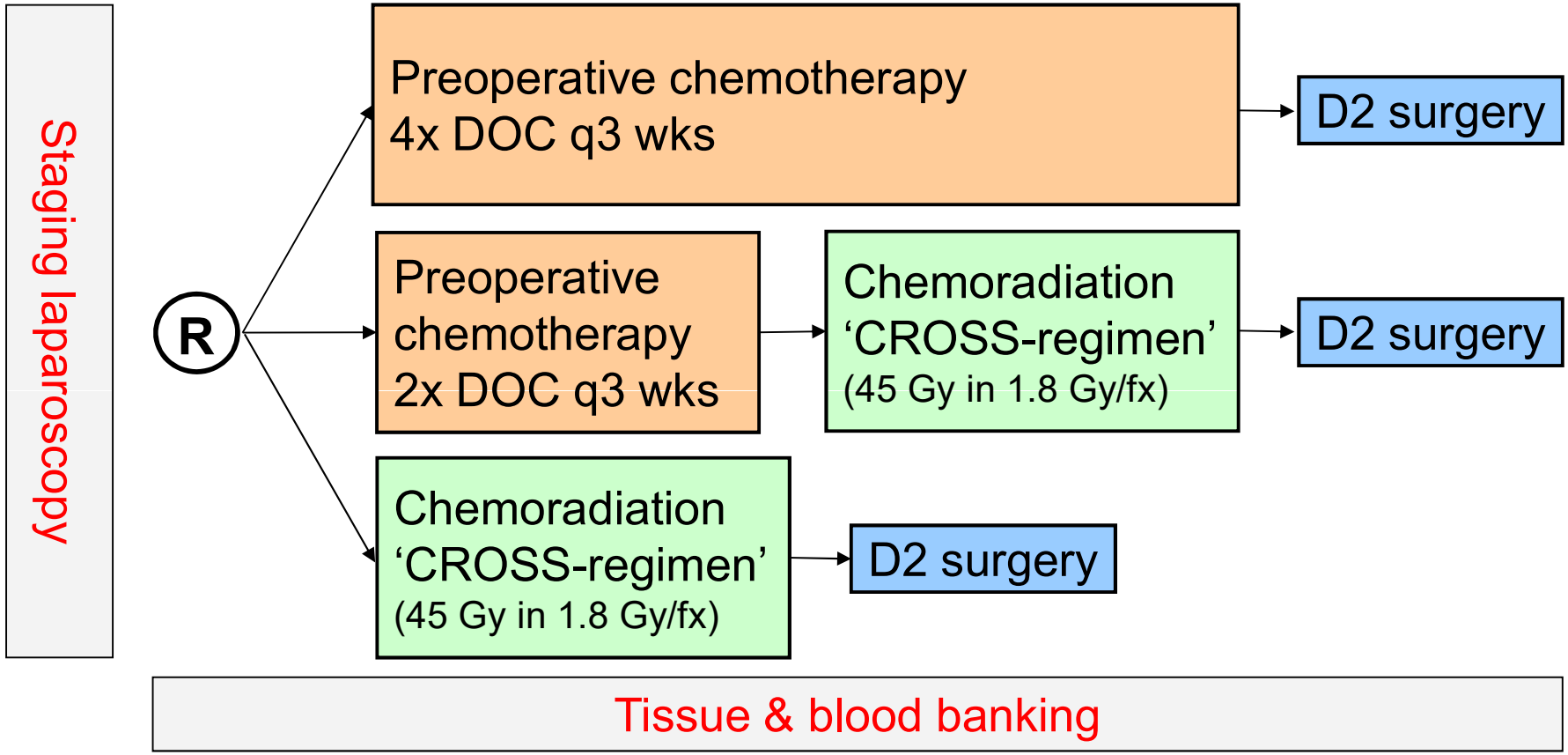


PART 1 (n=120):

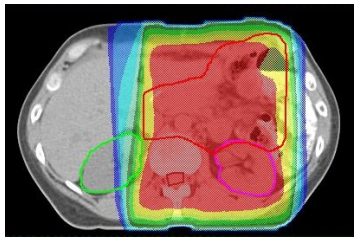
- Grade ≥3 anastomotic leakage: 5.6% vs. 7.8%
- Grade ≥3 intra-abdominal sepsis: 7.4% vs. 5.9%

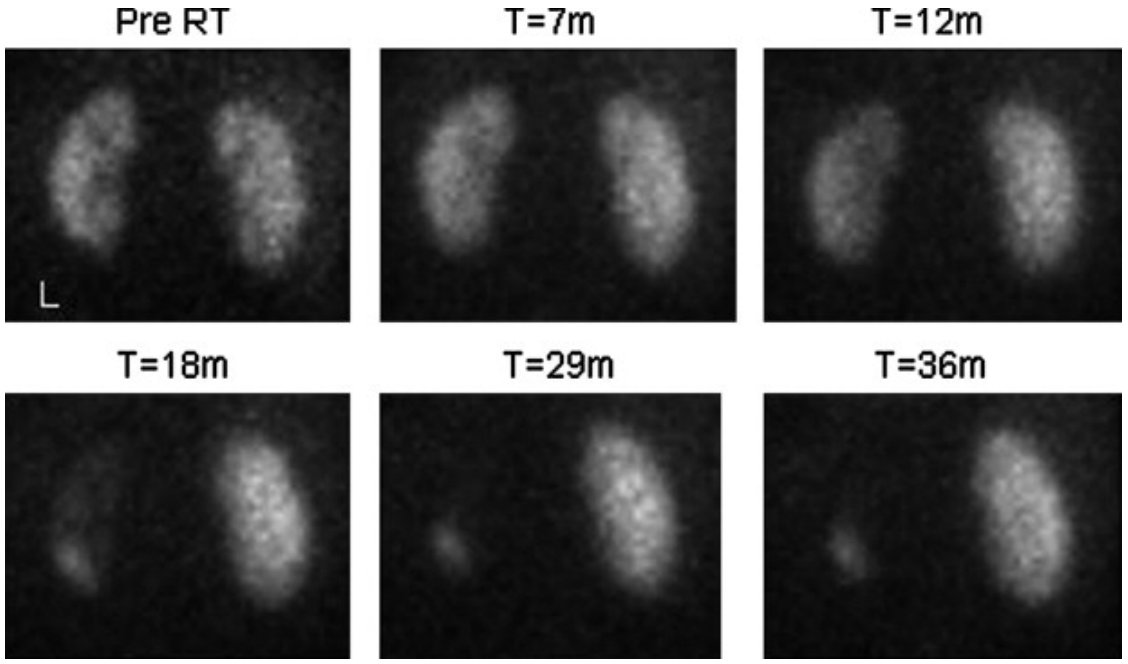
Leong et al. BMC Cancer 2015, ECC Vienna 2015

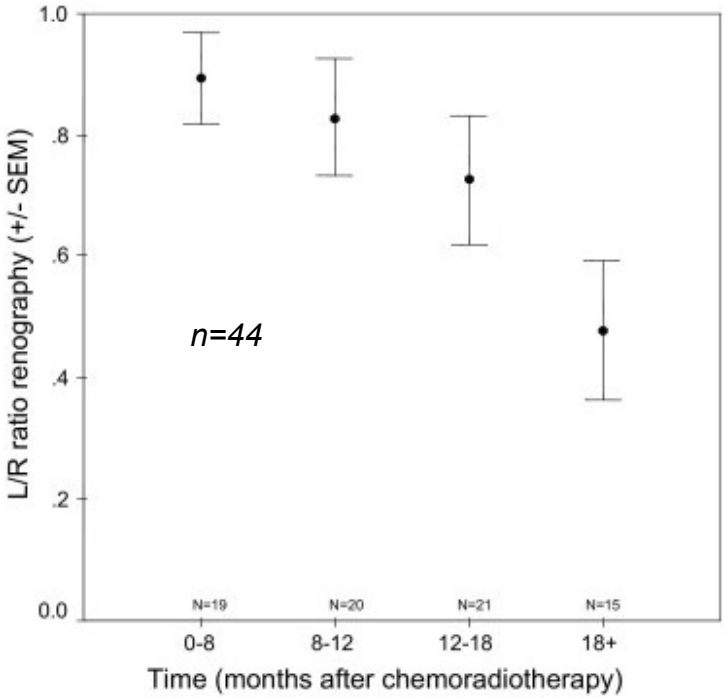
Design CRITICS-II



Late renal toxicity following postoperative chemoradiotherapy in gastric cancer







Jansen et al. IJROBP 2007

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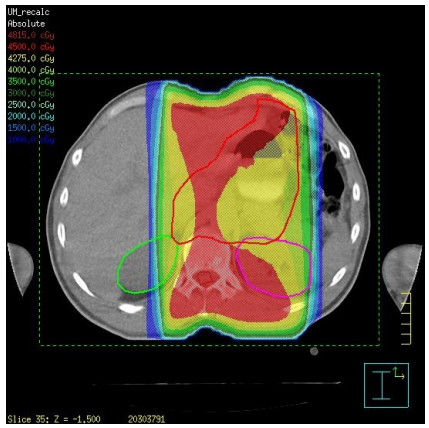
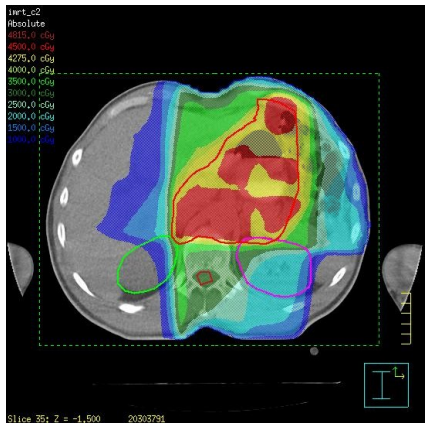
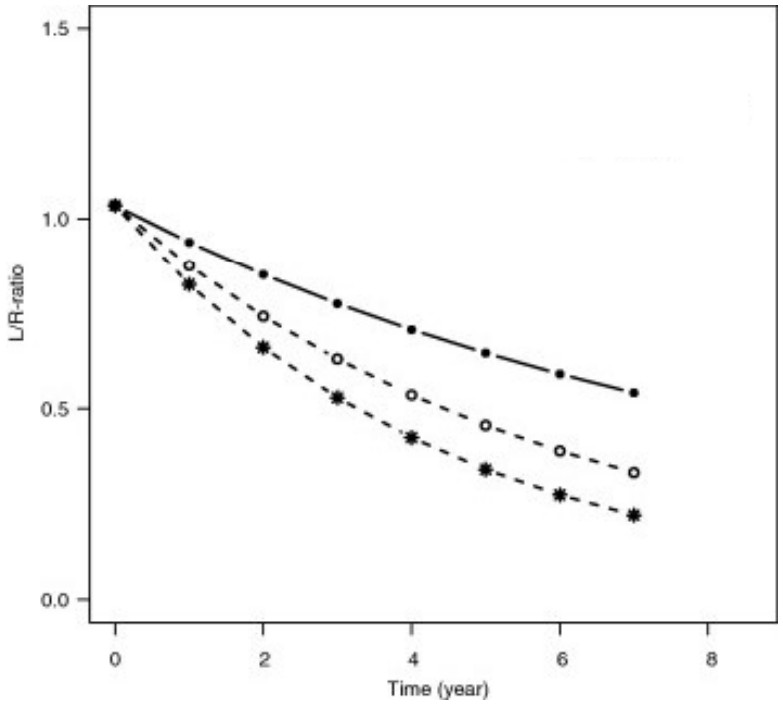
Advanced radiation techniques reduce the dose to both kidneys



AP-PA



IMRT



Trip et al. Radiother Oncol 2014

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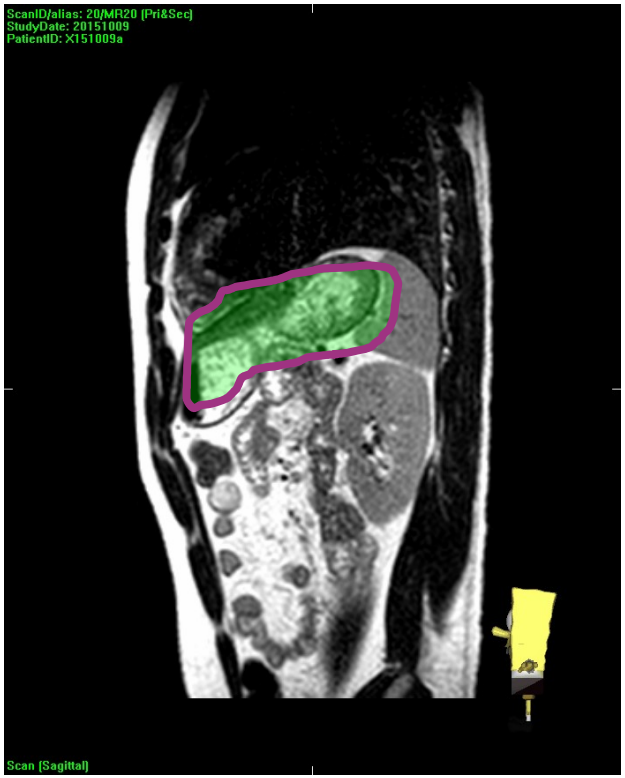
Optimal image-guided radiotherapy in gastric cancer: MR-guided radiotherapy

- Intrafraction
  - respiration
  - heart pulsation
  - peristalsis
- Interfraction
  - stomach filling



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Strategies to improve outcome

Treatment-related: where, when and how?

Patient-related: who?

Tumor-related

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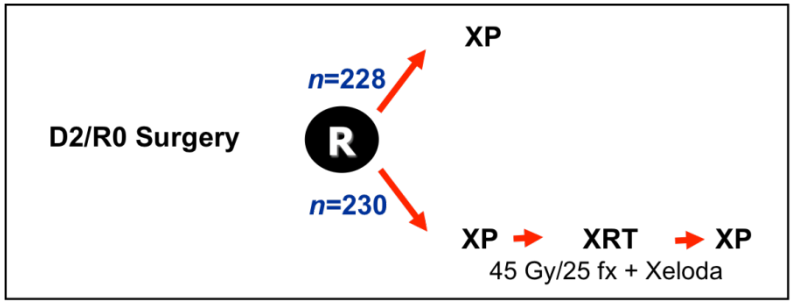
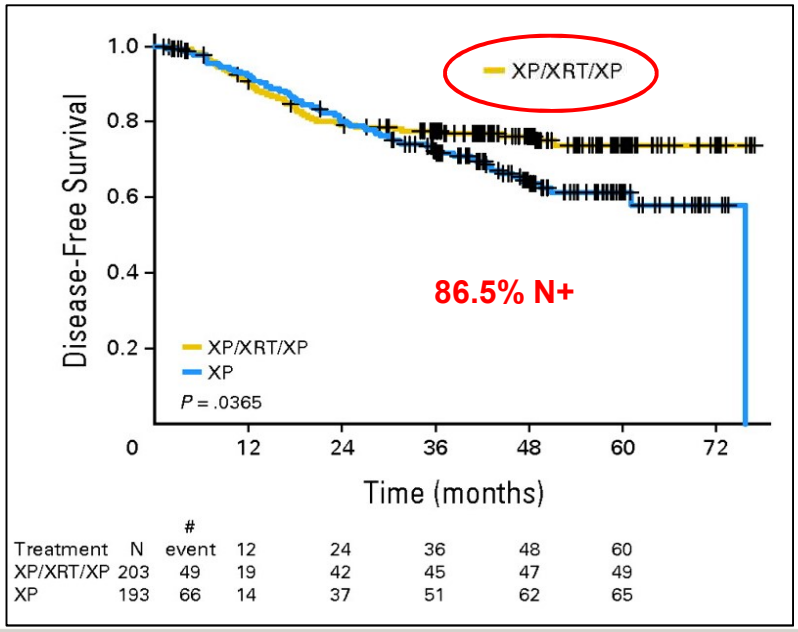
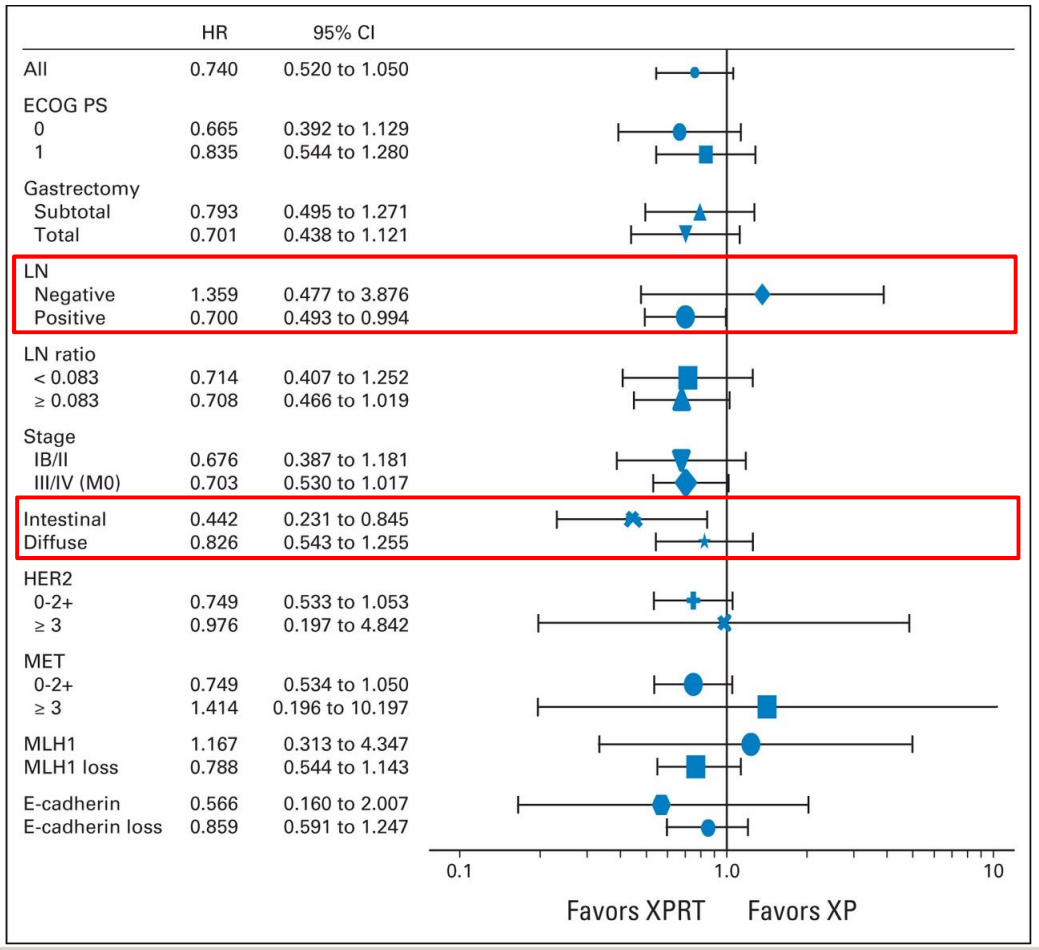
ARTIST Trial: Post-operative chemoradiotherapy improves DFS in lymph node-positive patients







Lee et al. JCO 2012

Park et al. JCO 2015

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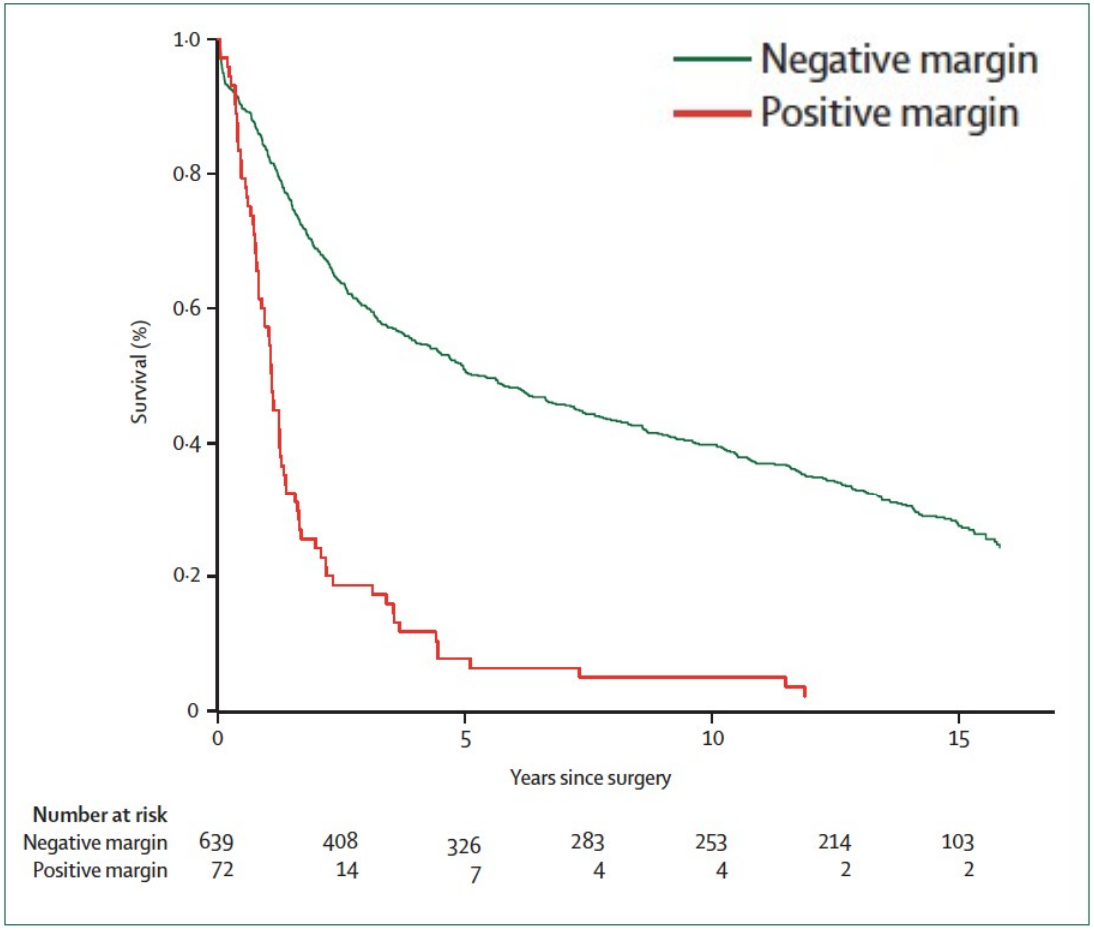
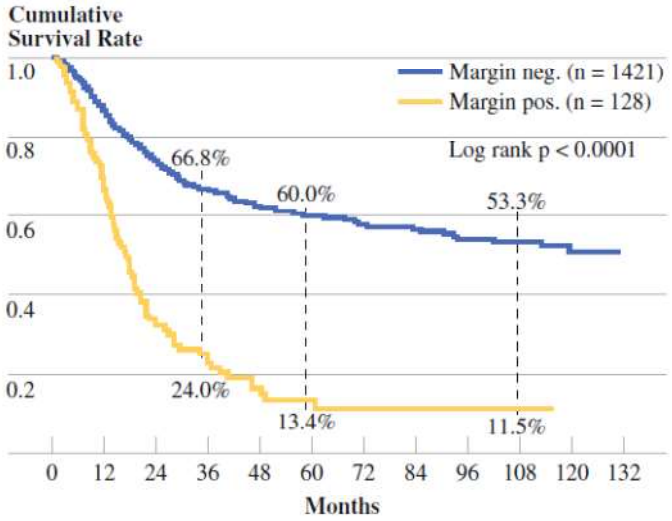
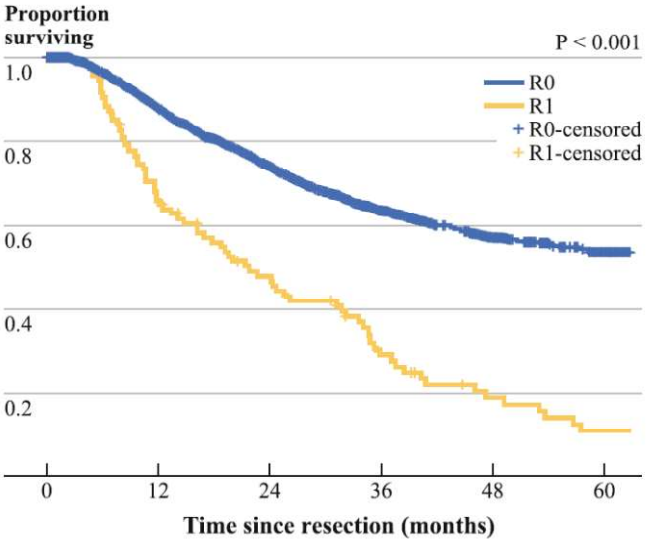
Impact radicality resection margin on survival



Hartgrink et al. Lancet 2009

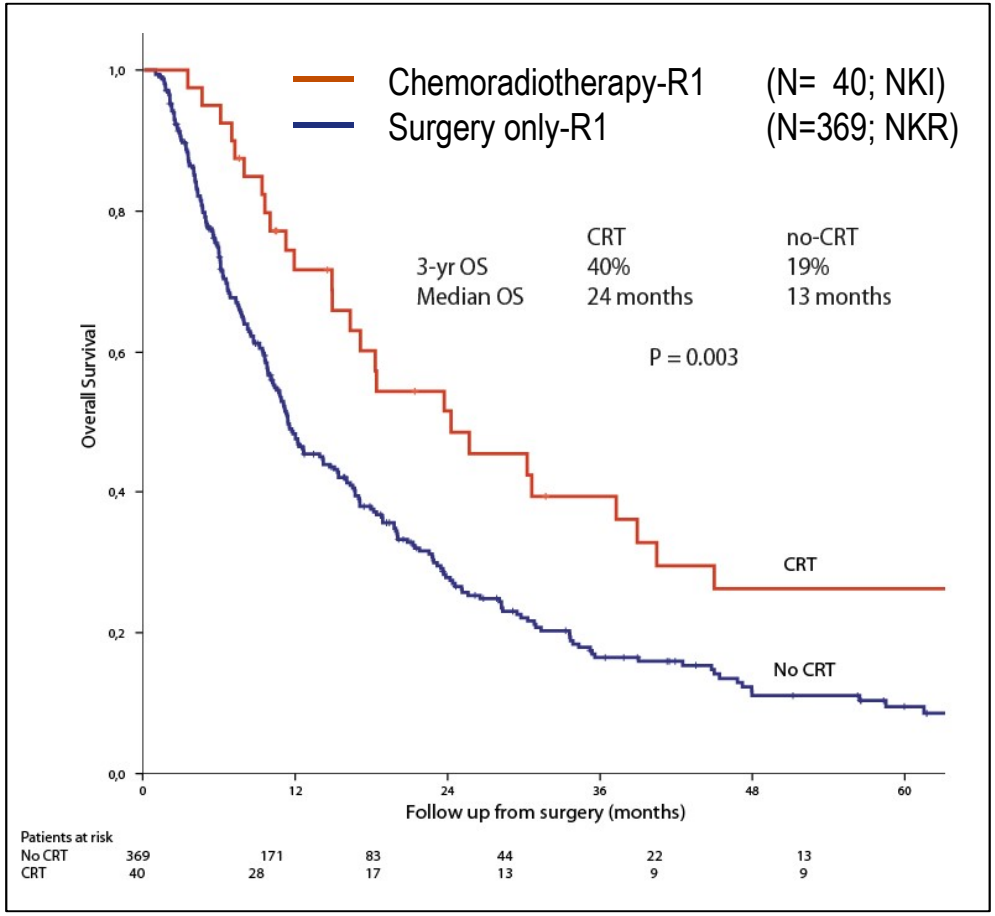


Wang et al. ASO 2009



Bickenbach et al. Ann Surg Oncol 2013

Post-operative chemoradiotherapy improves overall survival as compared to surgery only following R1 resection



Stiekema et al. Ann Surg Oncol 2015

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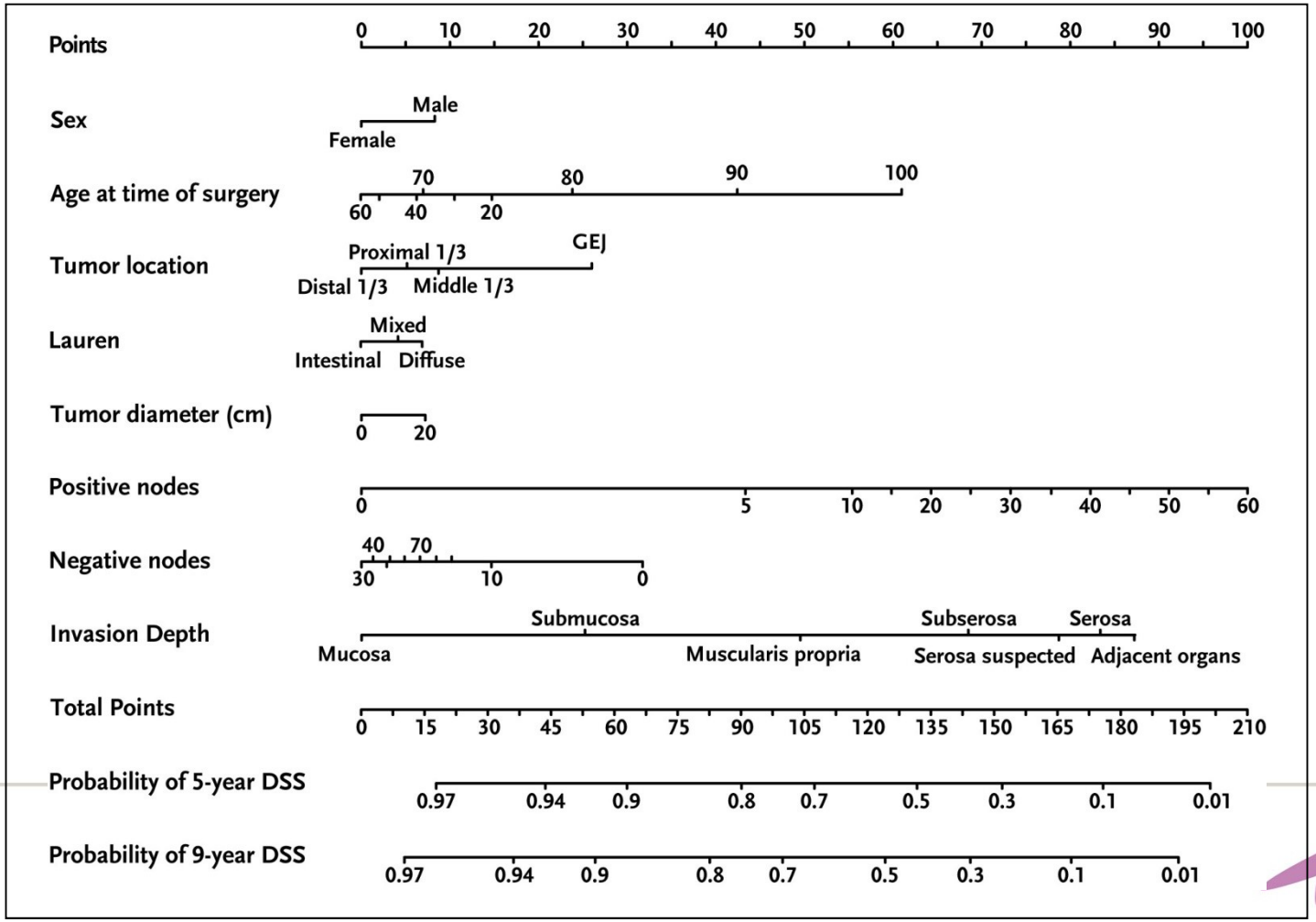
Performance of a Nomogram Predicting Disease-Specific Survival After an R0 Resection for Gastric Cancer in Patients Receiving Postoperative Chemoradiation Therapy

Johan L. Dikken, MD, PhD,[*,§] Daniel G. Coit, MD,[*] Raymond E. Baser, MS,[†] Mithat Gönen, PhD,[†] Karyn A. Goodman, MD,[‡] Murray F. Brennan, MD,[*] Edwin P.M. Jansen, MD, PhD,[‖] Henk Boot, MD, PhD,[¶] Cornelis J.H. van de Velde, MD, PhD,[§] Annemieke Cats, MD, PhD,[¶] and Marcel Verheij, MD, PhD[‖]

International Journal of Radiation Oncology biology • physics



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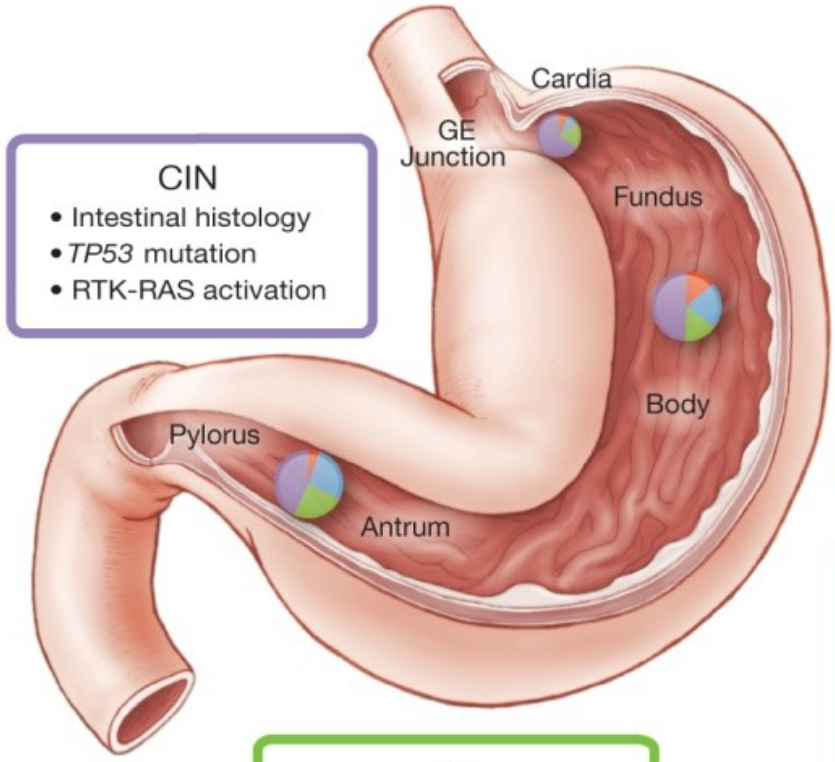
Strategies to improve outcome

Treatment-related: where, when and how?

Patient-related: who?

Tumor-related: which?

Key features of gastric cancer subtypes



CIN
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

EBV
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

GS
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

High MSI: no chemotherapy?
Smyth et al. JAMA Oncol 2017

Bass et al. Nature 2014

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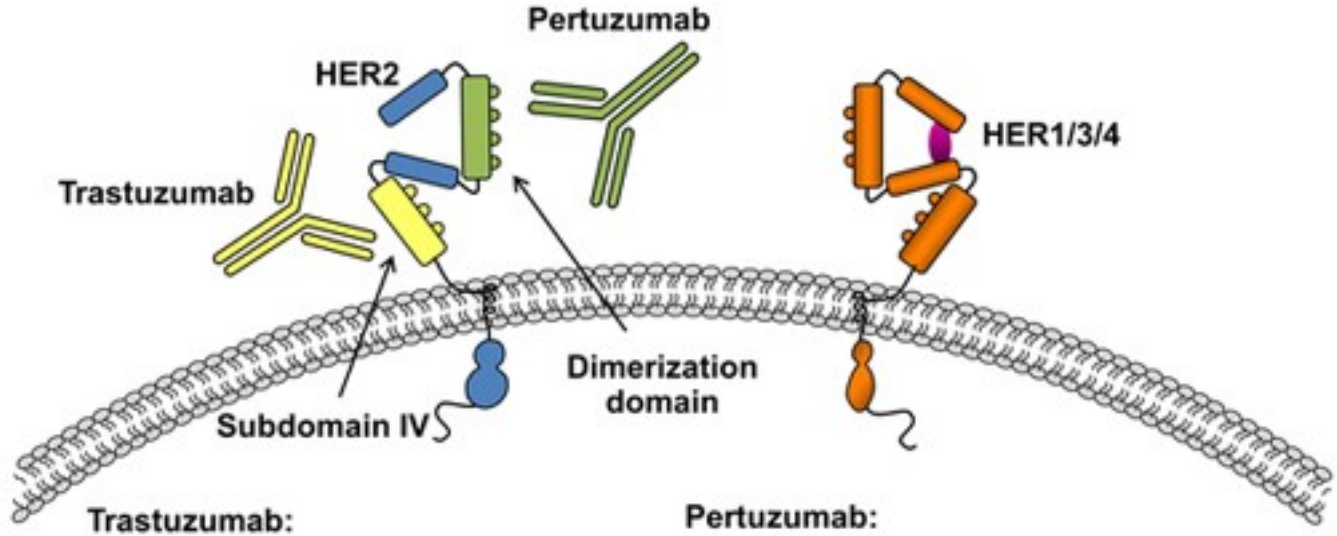
HER2 positive primary GC:

Pertuzumab and Trastuzumab
Complementary Mechanisms of Action



Trastuzumab:

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Pertuzumab:

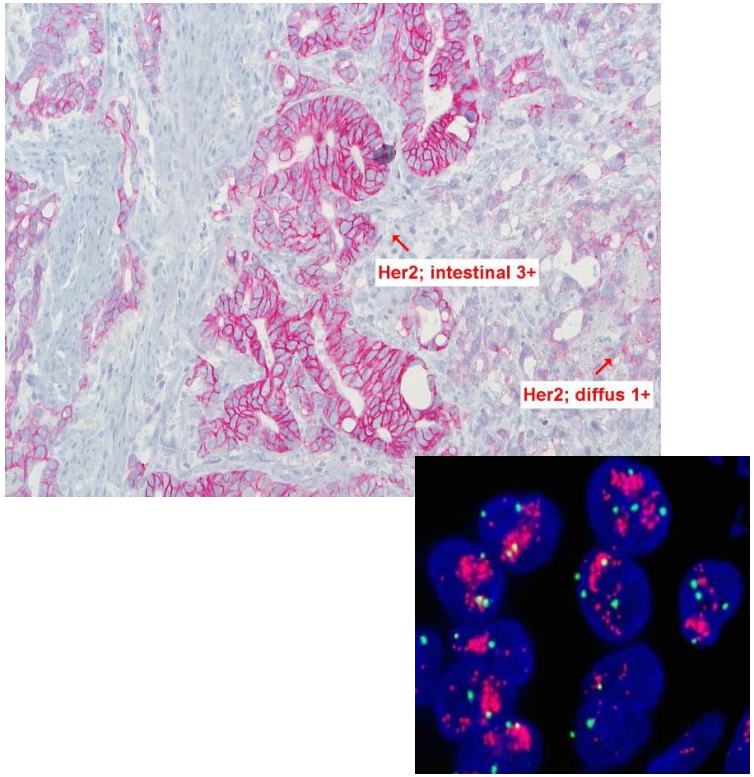
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

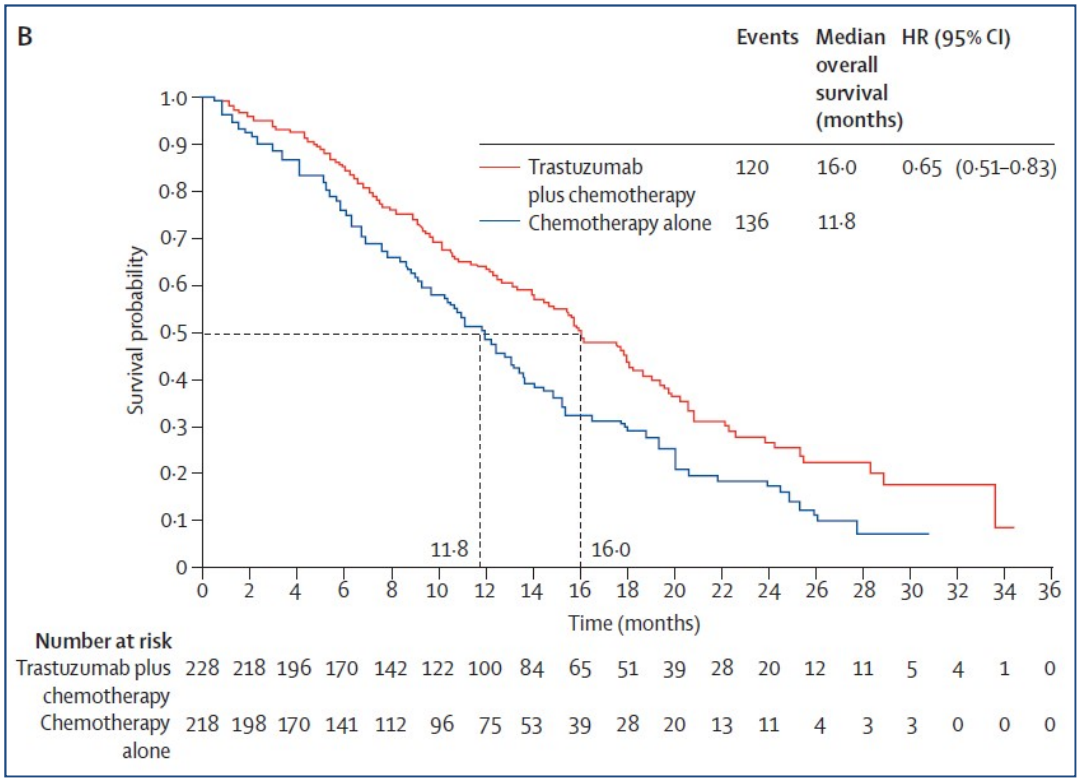
Baselga J, et al.[5]

DUCG
Dutch Upper GI Cancer Group

EORTC
The future of cancer therapy

Survival gain by Trastuzumab in HER2-positive stage IV gastric cancer: the ToGA trial





Bang et al. Lancet 2010

- *Therapeutically relevant HER2 positivity: ~ 16%*
- *Trastuzumab in HER2-positive stage IV gastric cancer: Survival 16.0 vs. 11.8 months (HR=0.65; 95% CI 0.51-0.83)*

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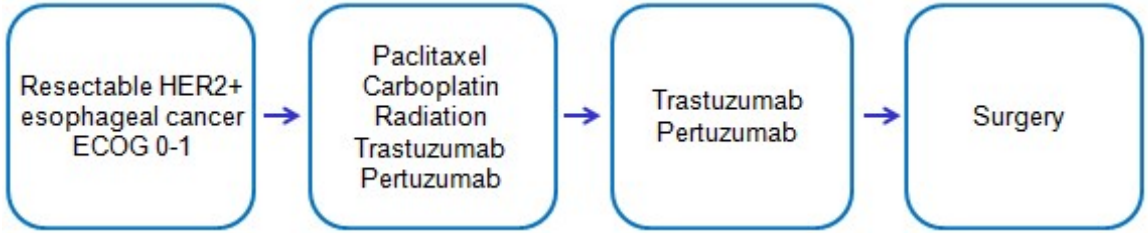
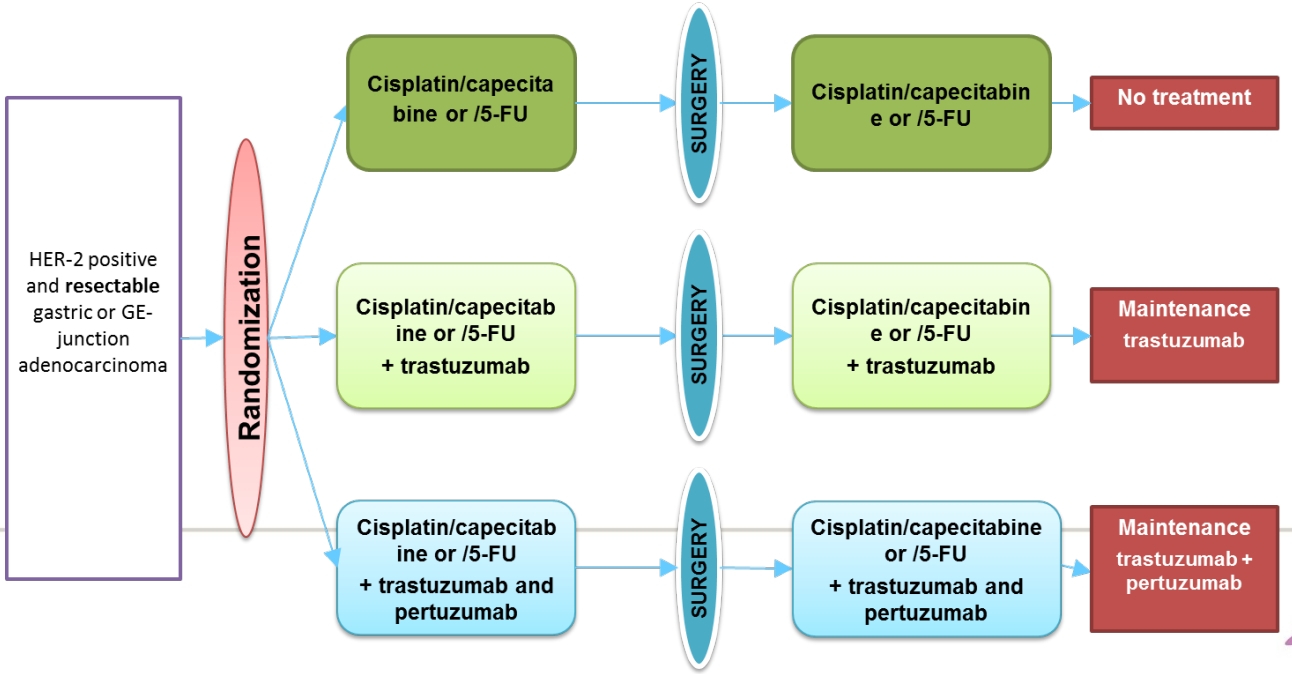
Targeting Her2/neu

HER2+ esophageal cancer: TRAP trial



HER2+ gastric cancer: INNOVATION trial



EORTC The future of cancer therapy

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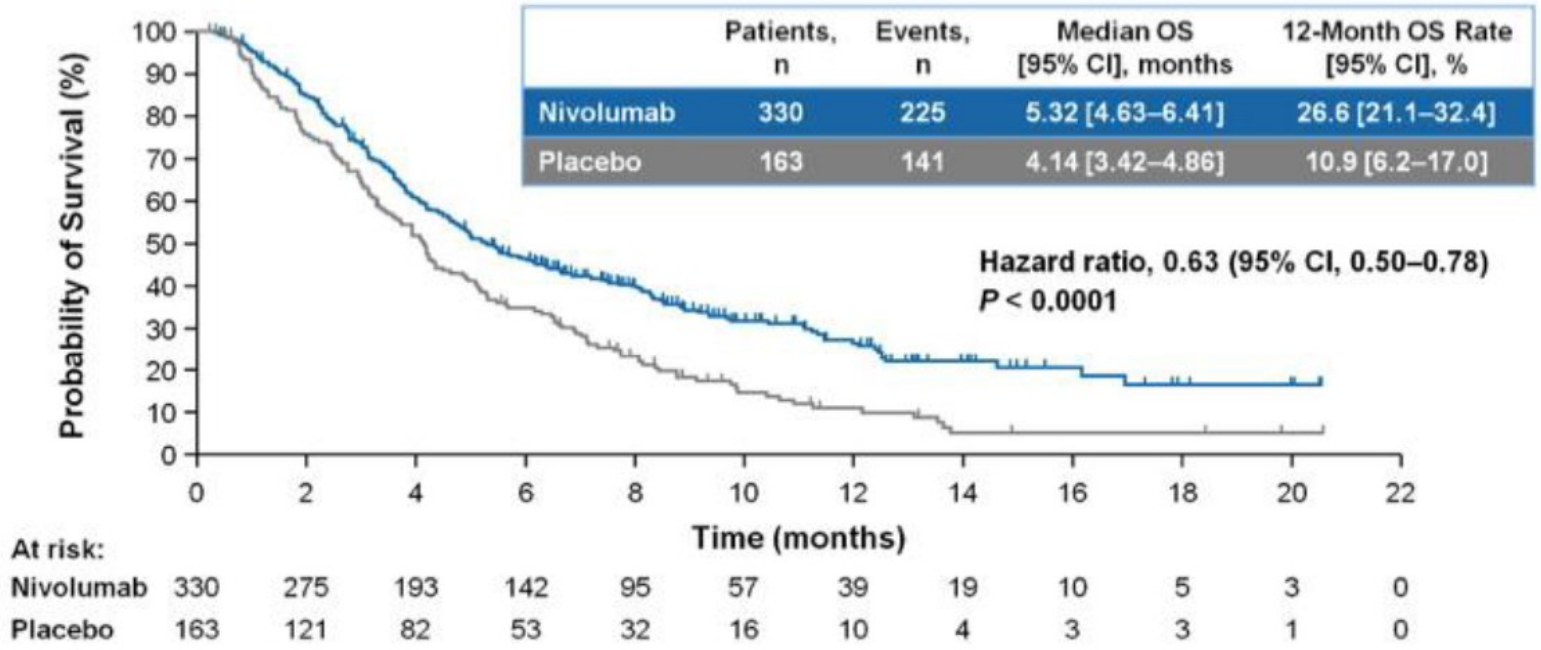
Immunotherapy: Nivolumab as salvage treatment



	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]

Presented by Kang YK et al. ASCO GI 2017

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New perspectives: summary

- Treatment-related: where, when and how?
  - *in specialized high-volume centers*
  - *in pre-operative setting*
  - *by state-of-the-art and innovative techniques*
- Patient-related: who?
  - *specific subgroups*
- Tumor-related: which?
  - *specific subtypes*

Lymph node imaging

Riccardo MANFREDI, MD, MBA, FESGAR
Department of Radiology
University of Rome “A. Gemelli”
Rome – Italy

Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Outline

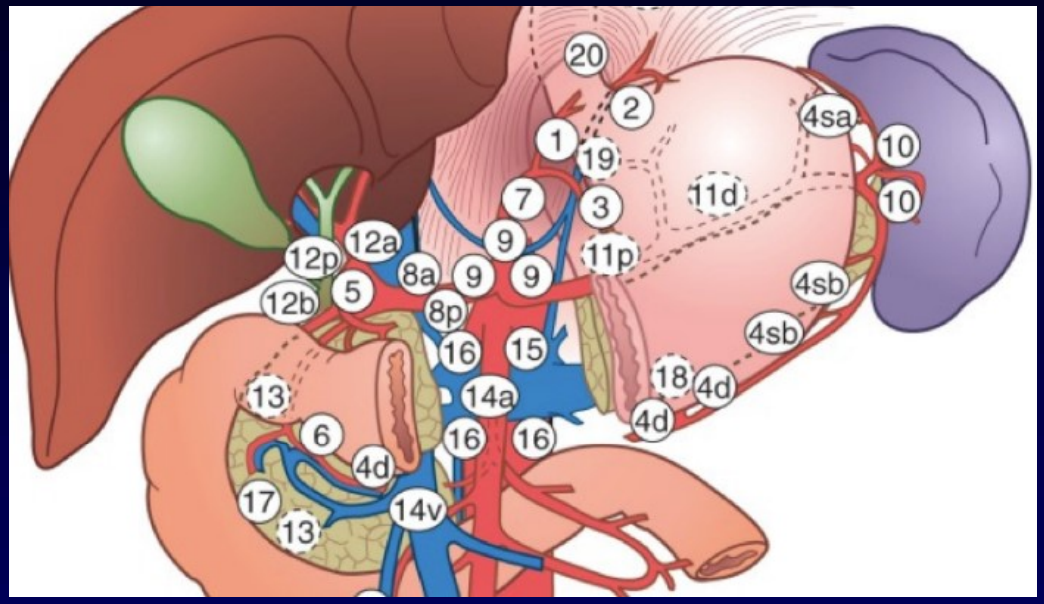
- Prognosis
- Management
- Pelvic Lymph Node sites
- Diagnostic imaging
  - MRI morphology
  - DCE MRI
  - Diffusion-weighted MRI
  - MR lymphography with USPIOs
  - PET/CT
  - Sentinel node techniques

Rationale

- Dissemination to lymph nodes is one of the principle routes of metastatic disease
- Lymph node assessment is a mandatory part of tumour staging

Prognosis

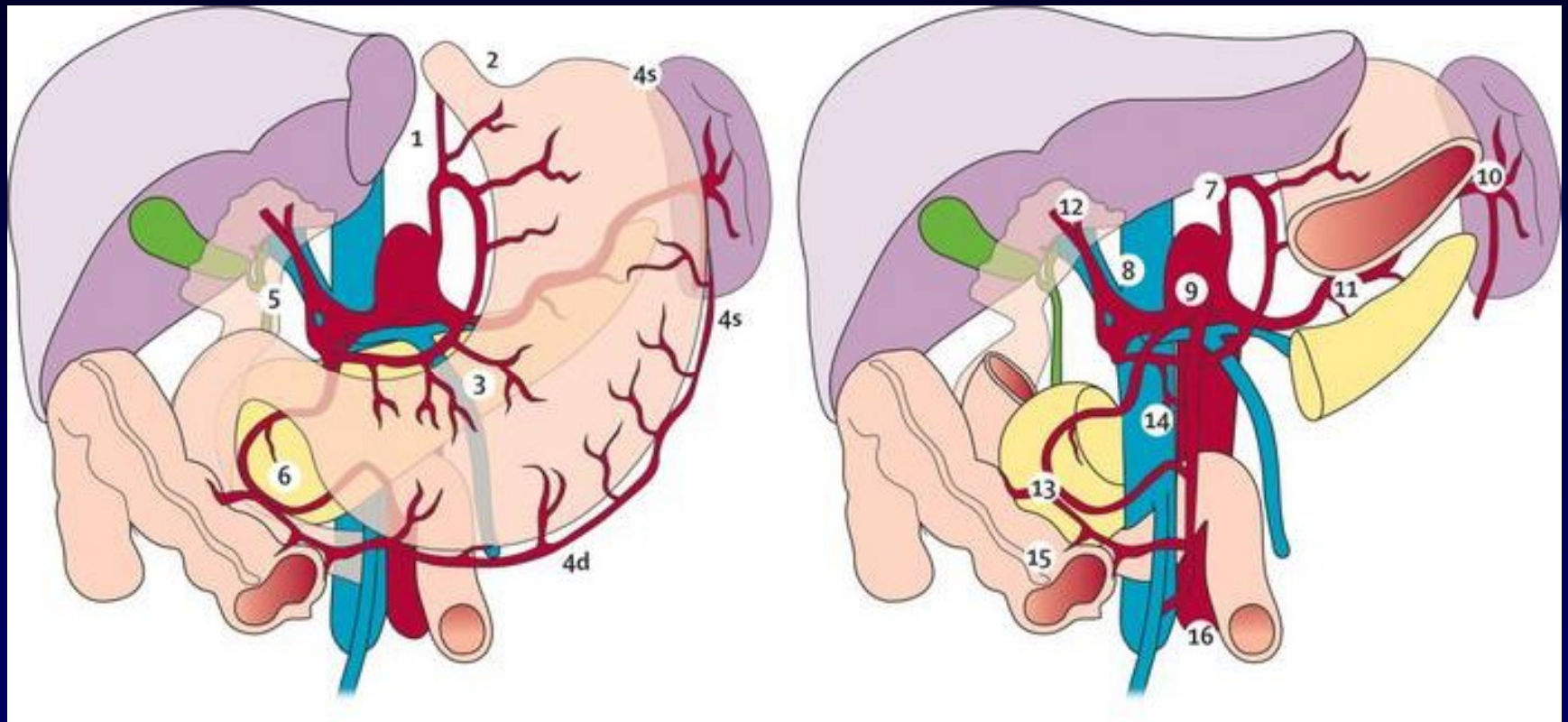
Pancreatic Lymph nodes



- I stations: Posterior and anterior surface of the head, mesenteric artery
- II stations: Common hepatic artery, hepatic hilum and abdominal aorta

Ishikawa Surgery 1997; Napai J Jpn Surg 1987; Kayara Surgery 1995 and Cancer 1999

Gastric lymph nodes



N1 Lymph nodes (perigastric)

1 Right cardiac nodes
2 Left cardiac nodes
3 Nodes along the lesser curvature
4d Lymph nodes along the short gastric and the left gastroepiploic vessels
4s Lymph nodes along the right gastroepiploic vessels
5 Suprapyloric nodes
6 Infrapyloric nodes

N2 Lymph nodes (branches coeliac axis)

7 Nodes along root left gastric artery
8 Nodes along common hepatic artery
9 Nodes around coeliac axis
10 Nodes at splenic hilum
11 Nodes along splenic artery

N3 Lymph nodes

12 Nodes at the hepatoduodenal ligament
13 Retropancreatic (periduodenal) nodes
14 Nodes at the root of the mesentery

N4 Lymph nodes

15 Nodes along the middle colic vein
16 Para-aortic nodes

Diagnostic Imaging

Criteria for LN involvement

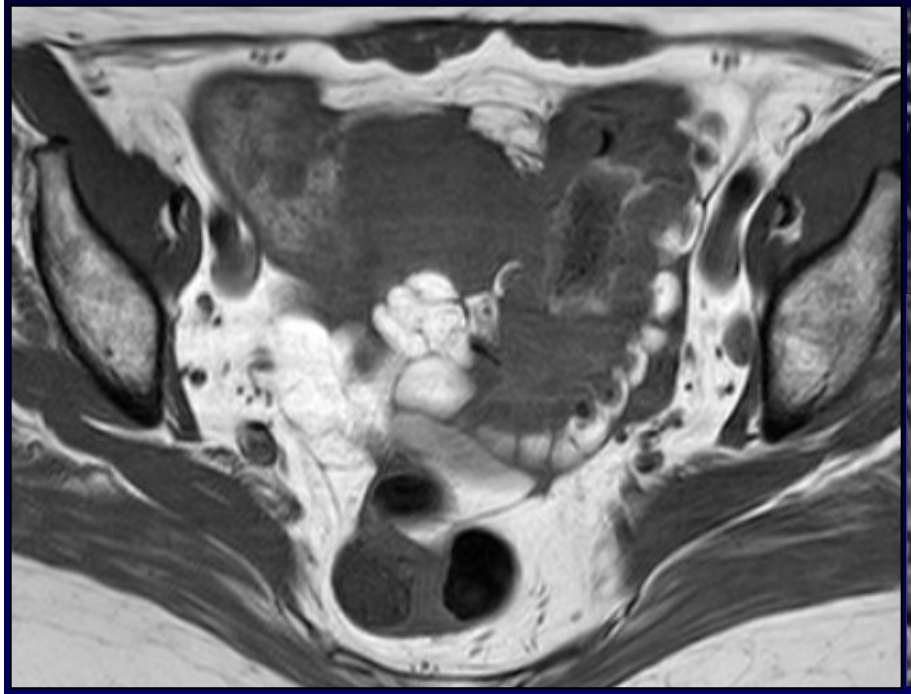
- Ultrasound
  - superficial nodes only
  - FNA
- CT and MRI
  - Morphology
  - Number and site
  - Nodal size

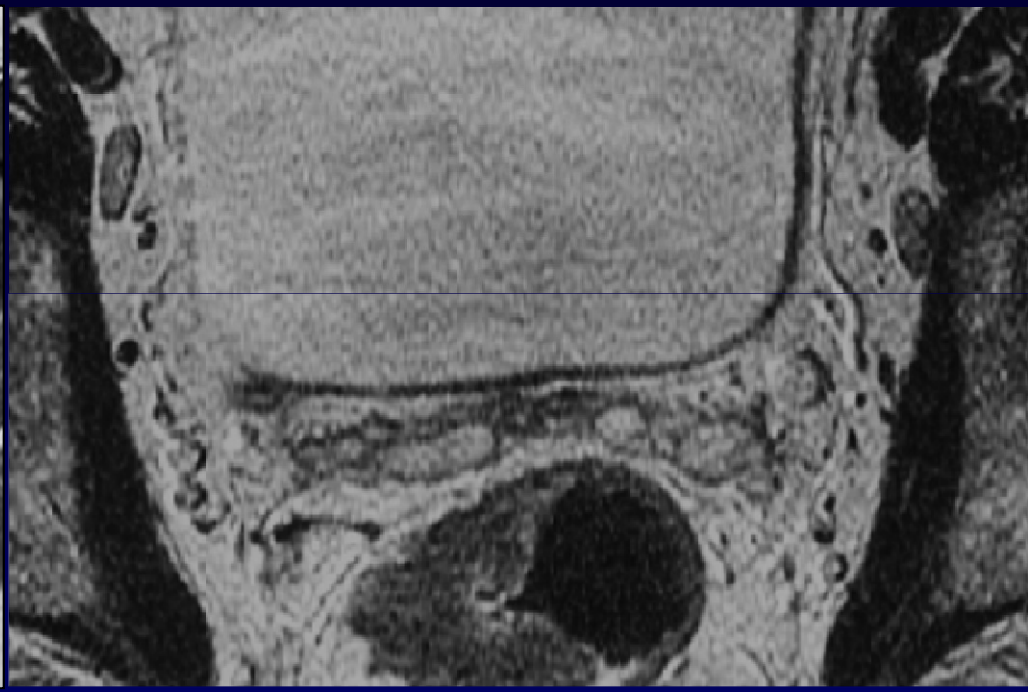
Methods for LN diagnosis

- MRI morphology
- DCE MRI
- Diffusion-weighted MRI
- MR lymphography with USPIOs
- PET/CT
- Sentinel node techniques

- Fatty Hilum
- Shape
- SI ≈ primary tumour
- Necrosis
- Extra-capsular extension
- Size

Morphology: Benign LNs





Fatty hilum
Small size

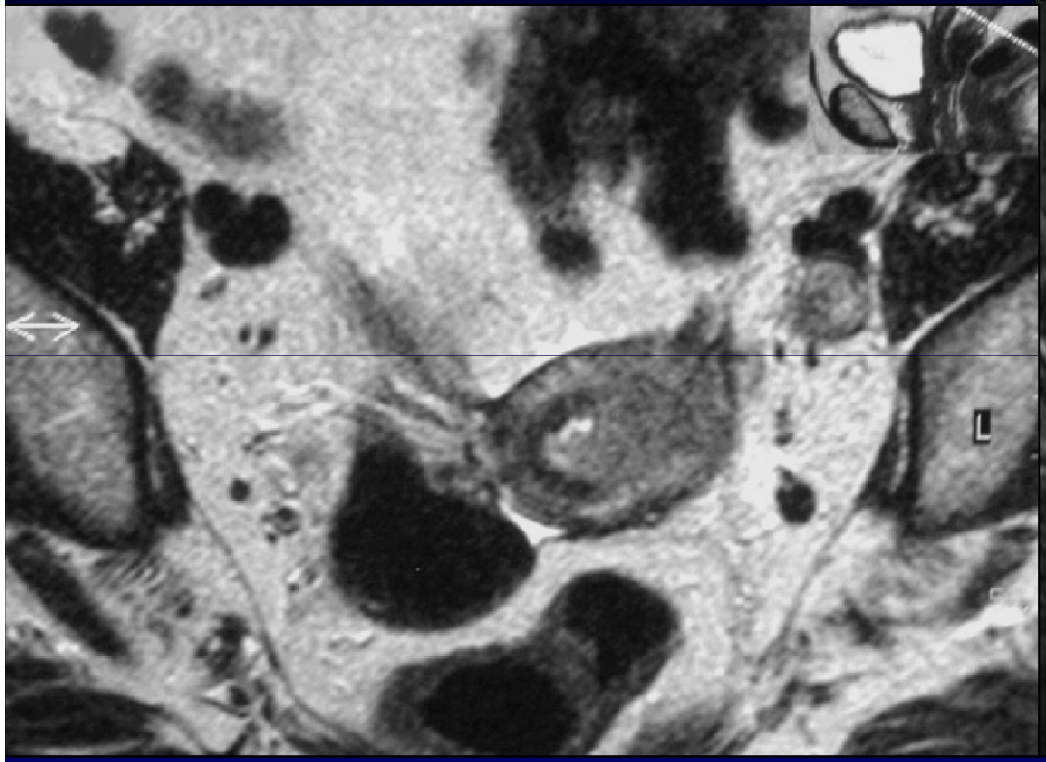
Long thin ovoid shape

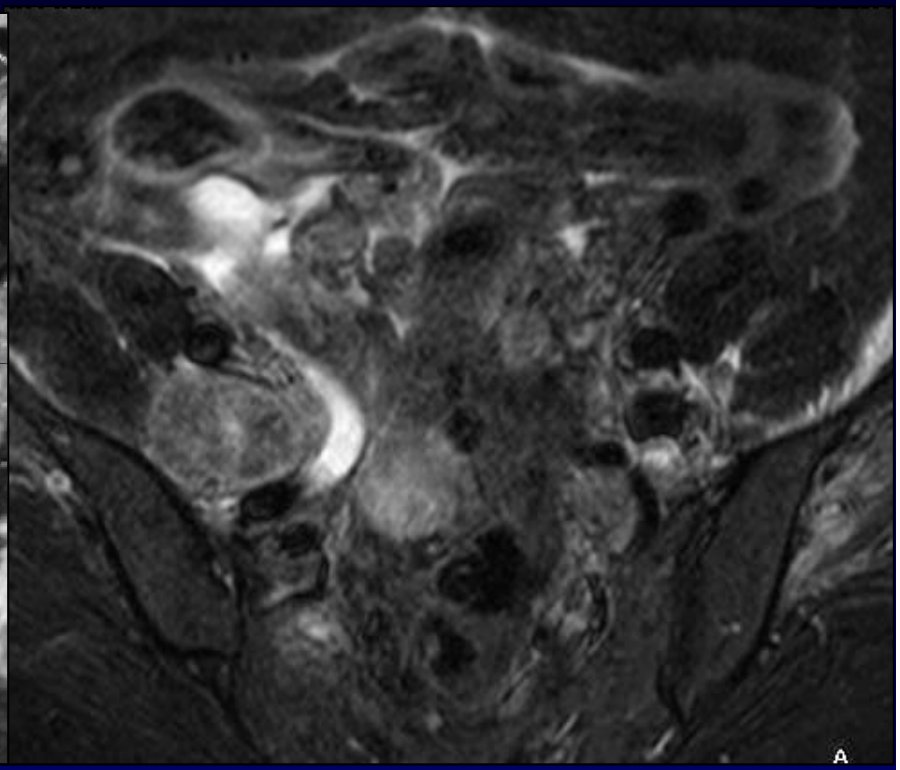
Morphology: Malignant LNs

- Malignant characteristics
  - Round shape
  - Necrosis
  - Signal intensity similar to primary tumour*
  - Extracapsular tumour extension
  - Speckled calcification (e.g. in mucinous adenocarcinoma of colon or ovary)

*Barentsz J et al, Radiology 1996; 201:185-193

Morphology
Nodal Shape





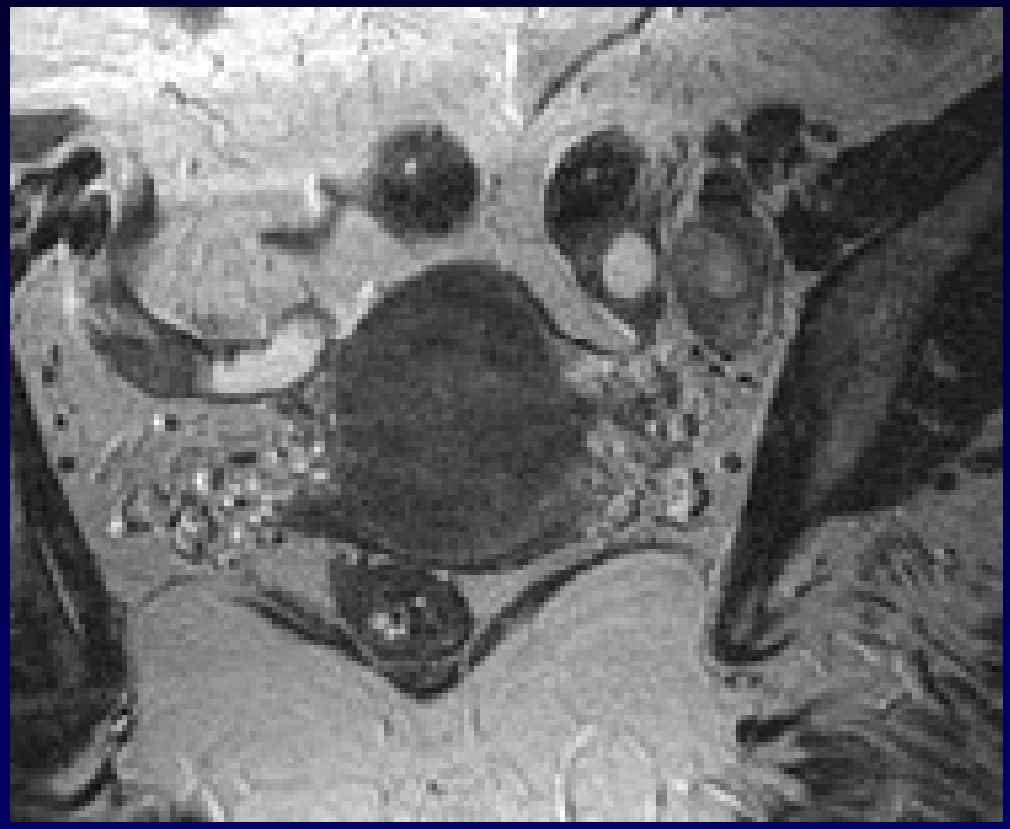
Round node 8 – 10 mm SA

Ovoid node > 10 mm SA

Jager et al, AJR, 1996

Morphology: Malignant LNs

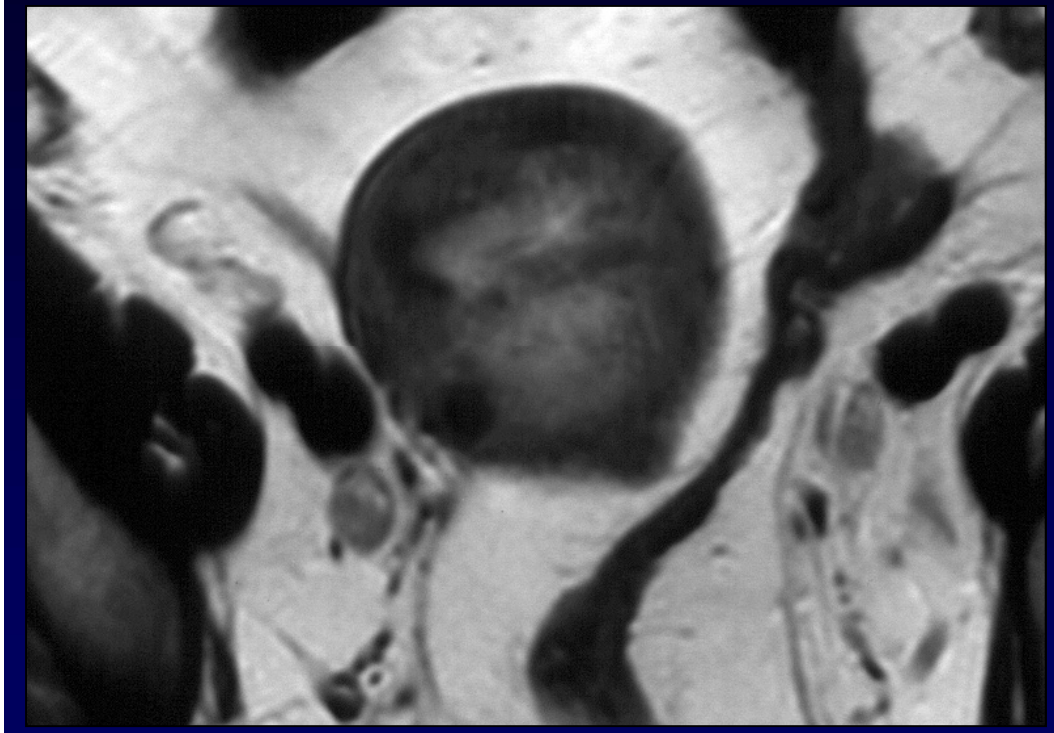
Necrosis



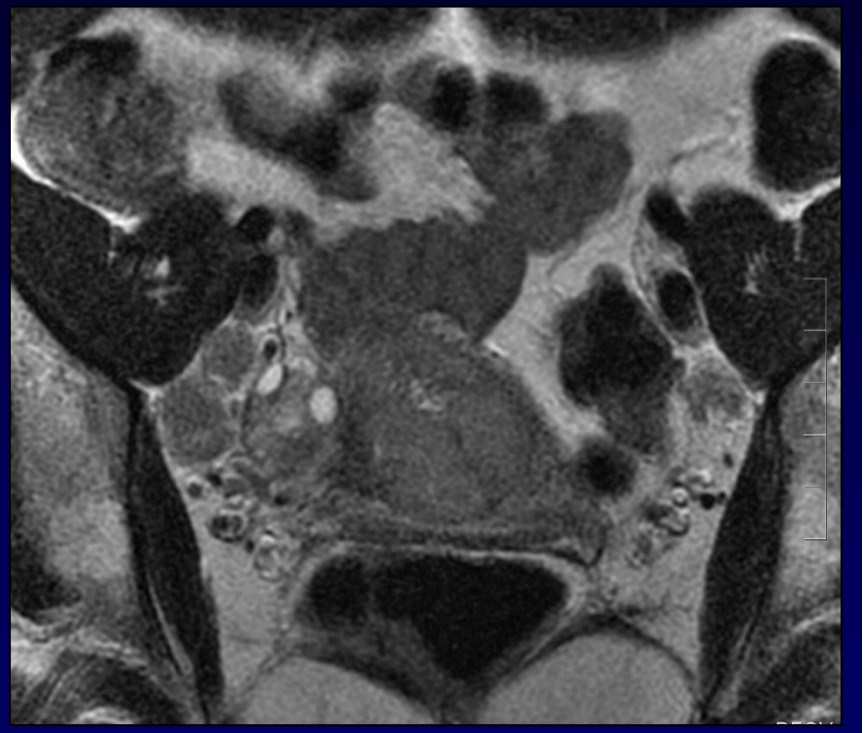
PPV of Necrosis: 100%

Kim SH, et al, AJR 1994

Morphology: Malignant LNs



Similar SI to primary tumour



Irregular contour or

Extra-capsular tumour

Yang et al, AJR 2000

Barentsz J et al, Radiology 1996; 201:185-193

Morphology: Malignant LNs

Rectal Cancer

Benign	Malignant
Smooth border	Irregular border
Uniform signal intensity	Mixed signal intensity

High resolution MRI

Sensitivity 85%; Specificity 97%

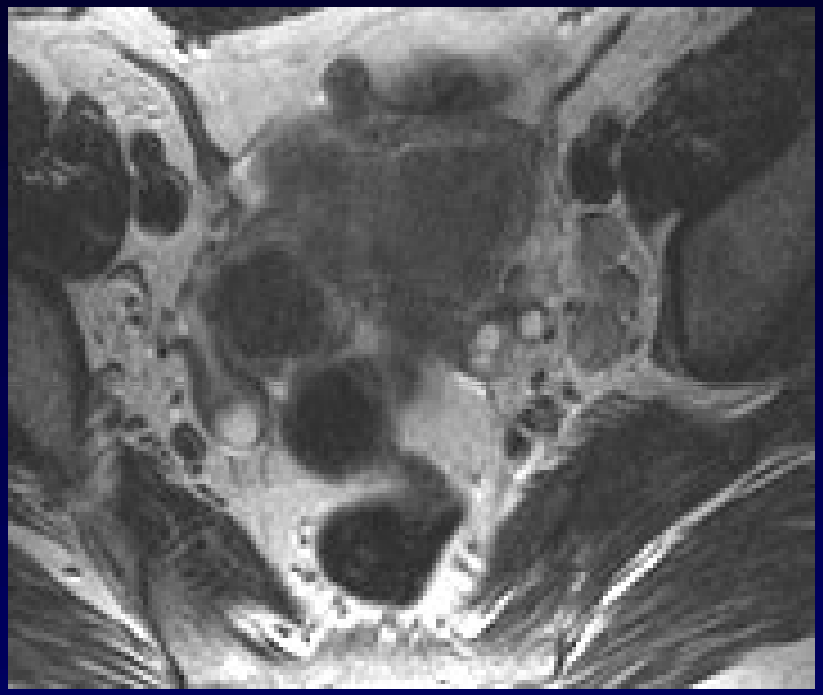
Brown et al, Radiology, 2003;227;371-377

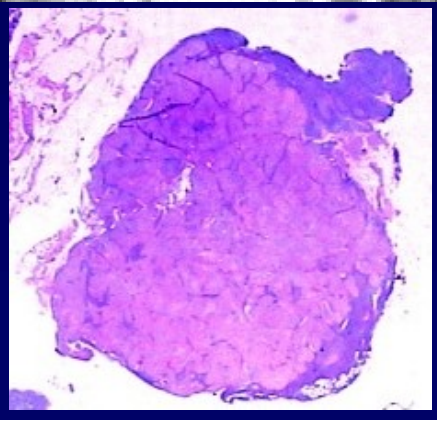
Nodal Site

- Recognized drainage routes
- Suspicious nodes:
  - Borderline node at expected site of drainage
  - Asymmetric obturator nodes in cervical or endometrial cancer
  - Unusual site for visible node
    - e.g. para-cervical, pre-sacral or para-vescical

Nodal site and Number

- Cluster of normal or borderline sized nodes within the drainage route may cause concern
- Very little specific data is available





Lymph Node Size

- Measurement of **maximum short axis diameter** is relatively constant, regardless of the orientation of the node
- Normal nodal size varies depending on the anatomical site

Glazer G et al, AJR, 1985;144;261-265

Lymph Node Size: Upper limits of normal

- Short axis
  - Lower para-aortic 11 mm
  - Common iliac 9 mm
  - Internal iliac 7 mm
  - Obturator 8 mm
  - External iliac 10 mm
- 'Size Ratio'
  - <8 mm benign (minimal SA)
  - >10 mm malignant
  - 8 – 10mm – malignant if round (SA/LA > 0.8)

Carrington B, Imaging in Oncology, 2nd Ed, p1007
Jager et al, AJR, 1996;167:1503-1507

Size criteria are unreliable

Prostate cancer

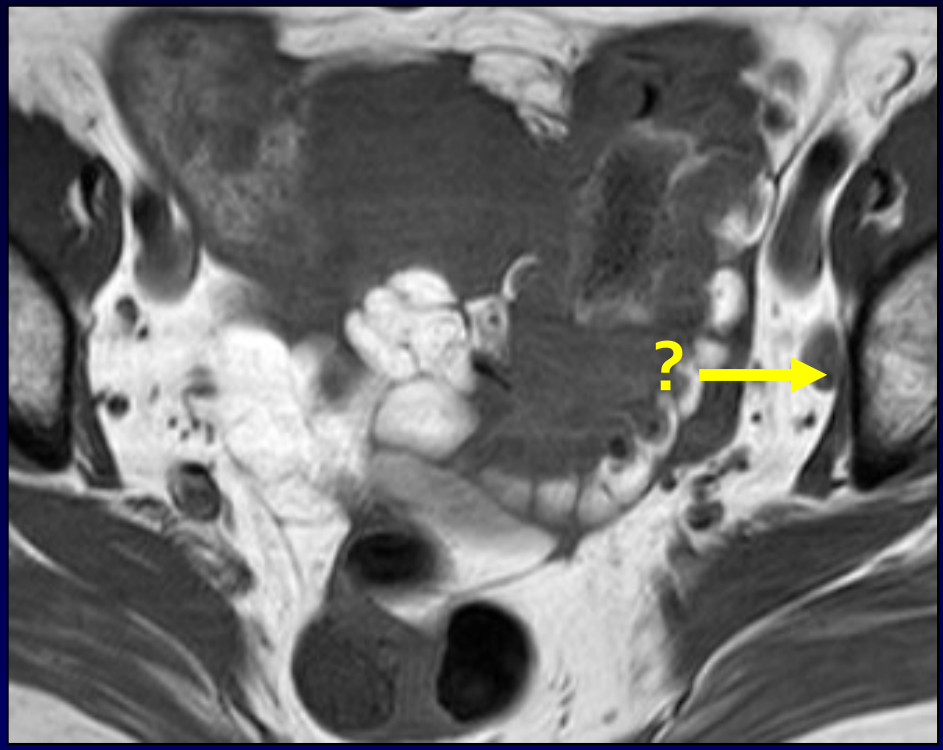
- 71% of nodal mets did not fulfil size criteria

Cervix cancer

- 80% of nodal mets < 10mm

Rectal cancer

- RDOG study – 322 patients
- sensitivity 38%



Normal sized node may contain a metastasis

Harisinghani et al, NEJM, 2003
Benedetti, 1996
Zerhouni EA, Radiology, 1996

MR diagnosis of nodal metastases in cervical cancer:

Size criteria

• Sensitivity	35 – 68%
• Specificity	67 - 93%
• PPV	50 - 67%
• NPV	77 – 96%

Beyersdorff et al 1995, Eur J Gyn Oncol: 16; 274
Reinhardt et al, 2001, Radiology: 218;776
Narayan et al, Int J Gynecol Cancer 2001: 11;263
Yu et al, AJR: 171,707

Methods for LN diagnosis

- MRI morphology
- Dynamic CE MRI
- Diffusion-weighted MRI
- MR lymphography with USPIOs
- PET/CT
- Sentinel node techniques

Dynamic CE-MRI

LNs in bladder cancer

- Malignant nodes demonstrated early enhancement
  - Sensitivity increased from 71 to 86%
  - Specificity remained high 98 vs 95%
- Wash out rate of contrast in the primary tumour was faster in node positive patients – but this could not predict nodal status

Barentsz J et al, Radiology 1996; 201:185-193
Bahri S et al Ann Oncol, 2008
Tuncbilek et al, Eur J Radiol, 2005

Dynamic CE-MRI

LNs in breast cancer

- Nodal enhancement index of >21% and nodal area of > 0.4 cm^2 indicated nodal involvement
- Enhancement index of <21% and nodal area of < 0.4 cm^2 carried very high negative predictive value for nodal involvement

Murray AD et al, BJR, 2002

Methods for LN diagnosis

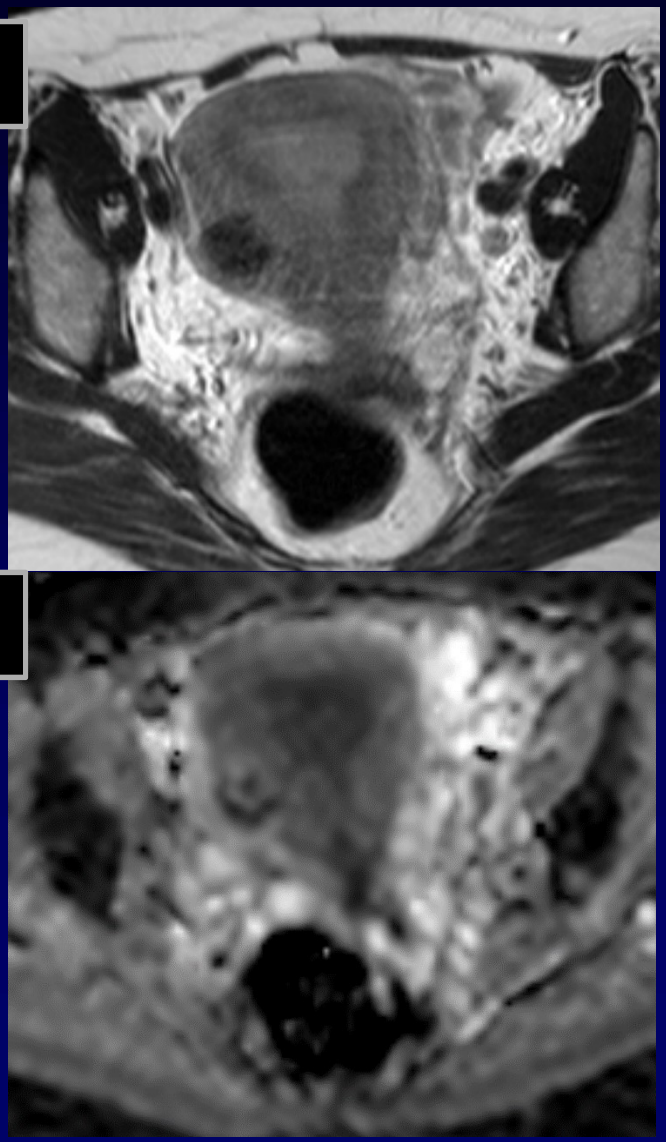
- MRI morphology
- DCE MRI
- Diffusion-weighted MRI
- MR lymphography with USPIOs
- PET/CT
- Sentinel node techniques

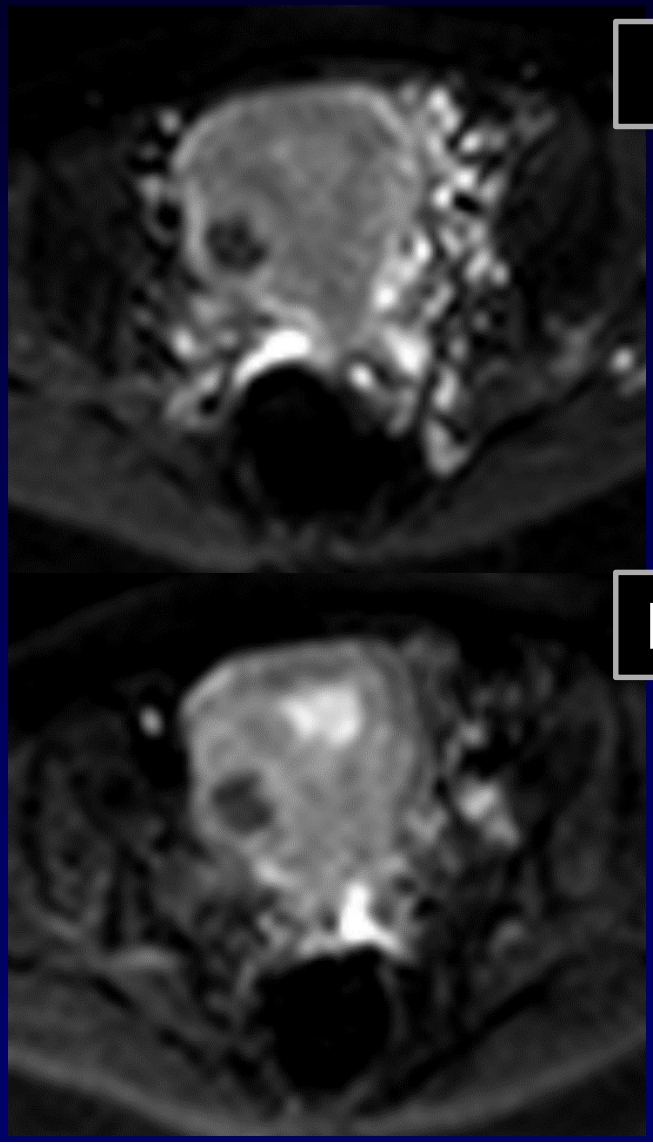
DW-MRI

- Diffusivity of water molecules within tissue
  - Does not require injection of contrast medium
  - High cellular density = ⬇⬇ diffusivity
  - Reduced diffusivity is seen as low ADC
- Proven in detecting malignant disease in endometrium and cervix
- Evaluating response to radiotherapy

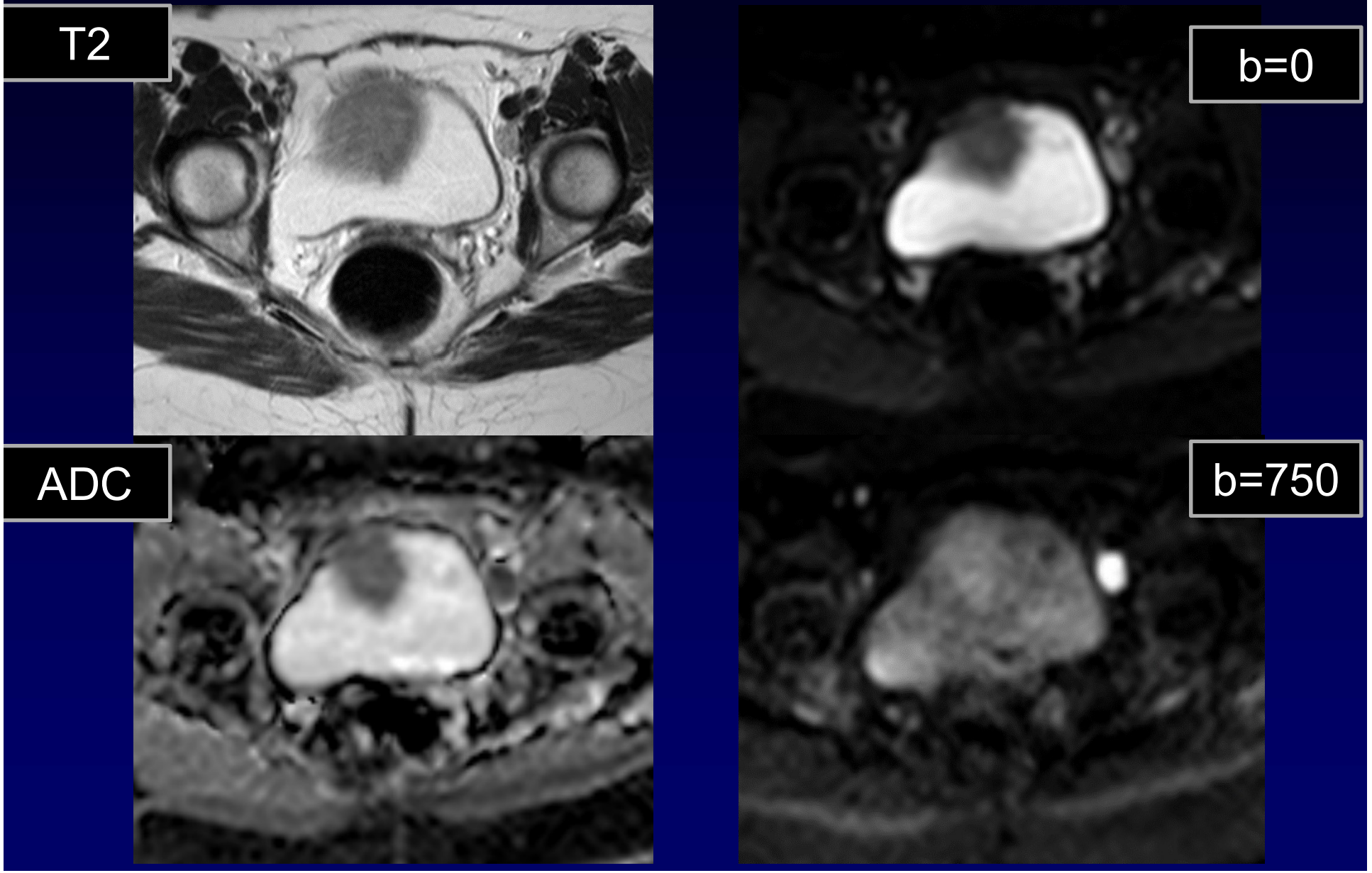
Tamai K et al, JMRI, 2007
McVeigh P et al, Eur Radiol 2008
Harry et al, Gyn Oncol 2008

DWI: Endometrial ca.

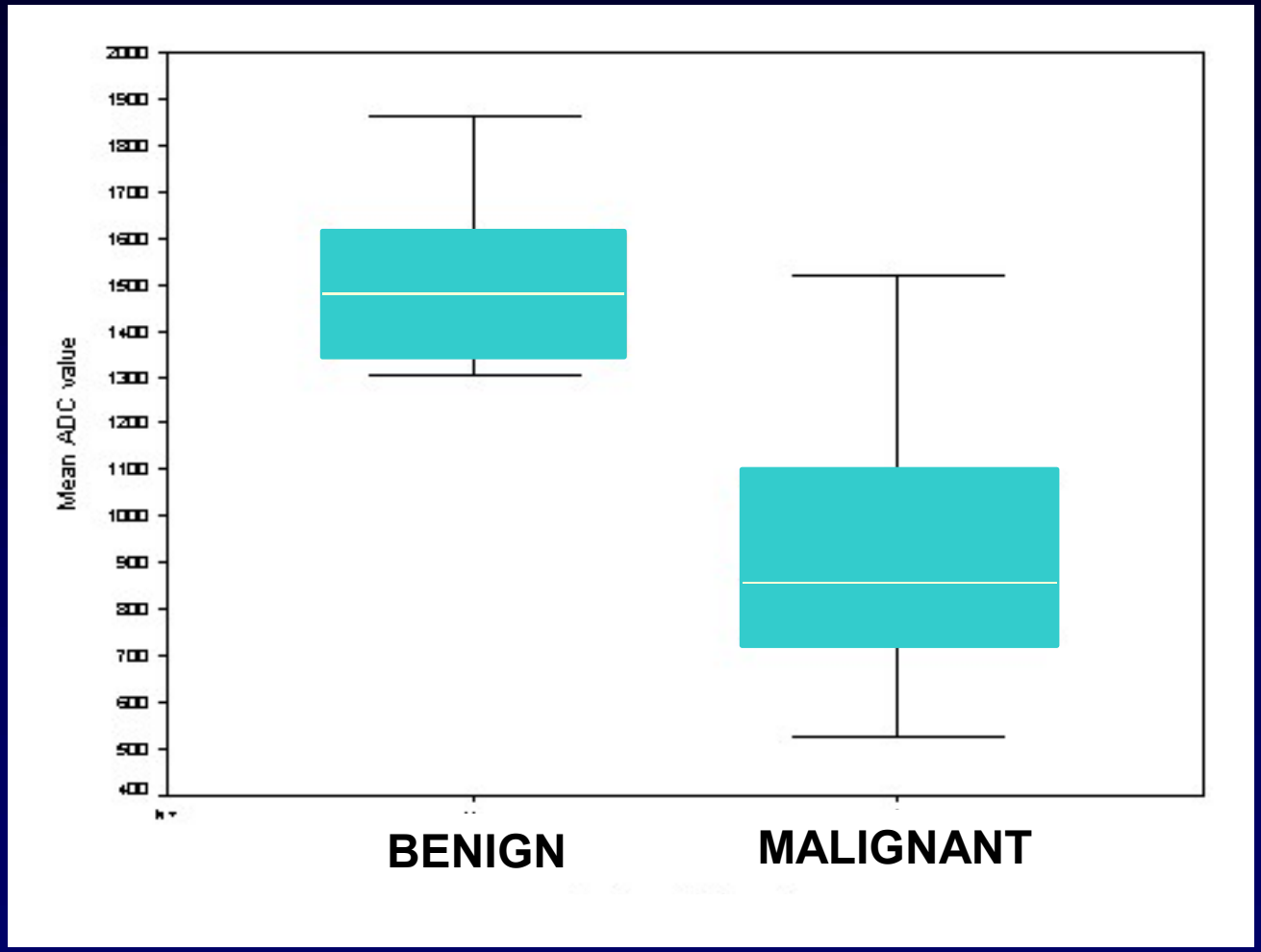




DWI Lymph Nodes

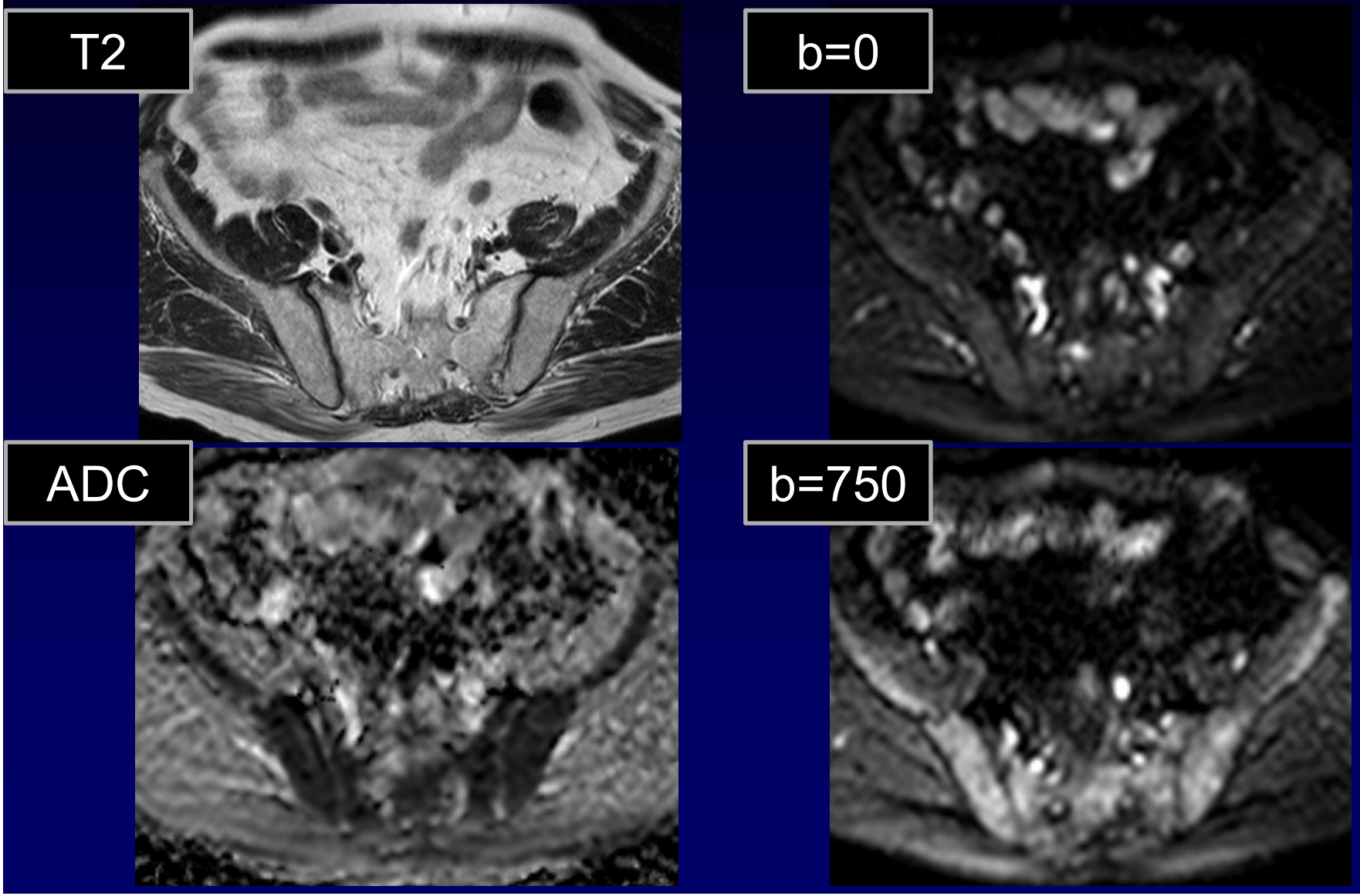


Normal endometrium vs. malignant



Bharwani N et al, ICIS 2009

DWI Lymph Nodes



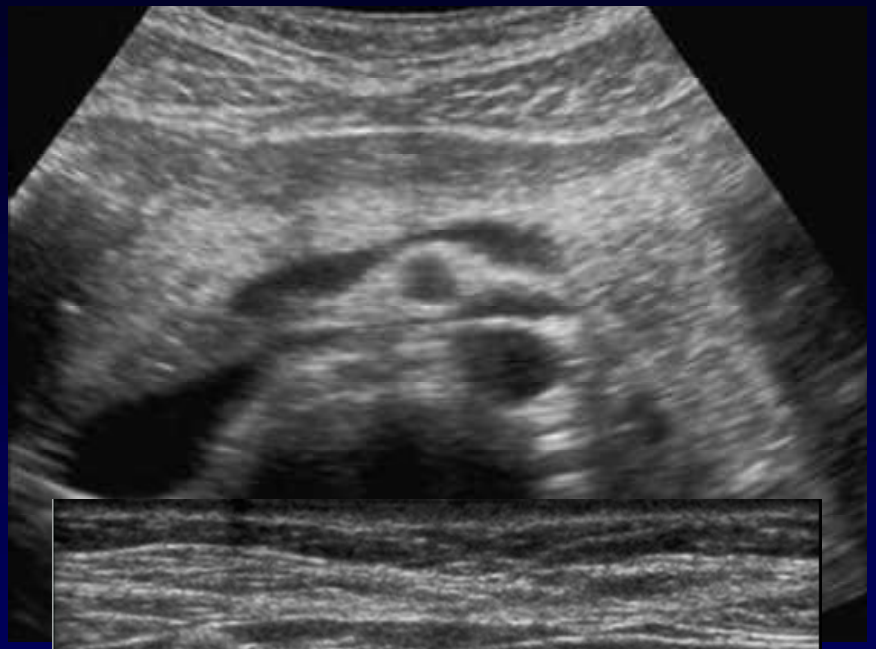
DWI in pelvic cancer

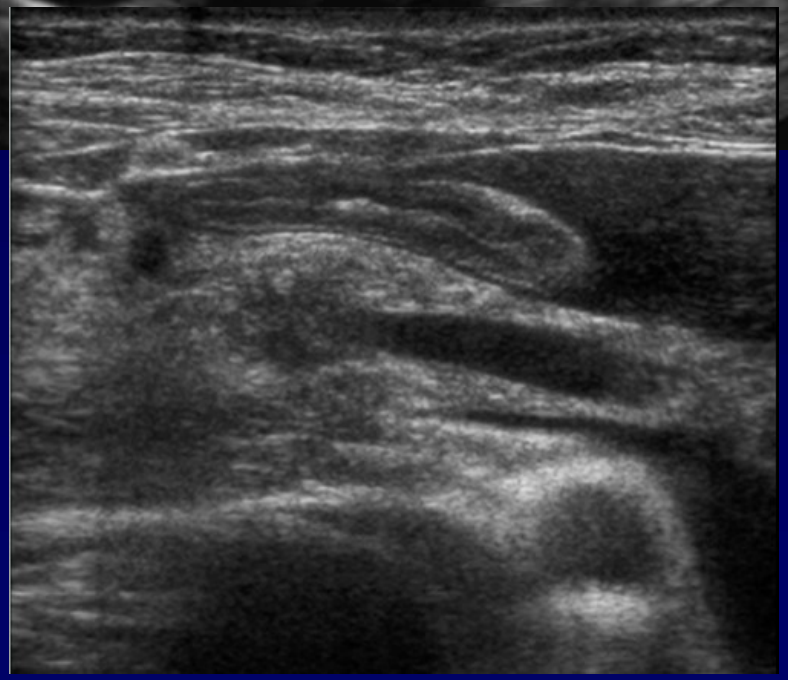
Author	N pts	Tumour	Comment	sens	spec
Lin		EC/CC	Used cut-off ADC value Identified 5mm positive node	0.83	0.98
Kim	125	CC		0.87	0.80
Chen	61			0.83	0.75
Thoeny		Prostate	Combined DWI and USPIO	Signif increase	
Choi	163	CC	Minimum ADC correlated best with FDG avidity	0.86	
Nakai	18	Gynae	No difference in size or ADC between benign and mal LN		
Roy	259	Pelvic	No difference in ADC btw benign and malignant LN		
Thoeny Radiol 14	120	Bladder/prostate	Prospective, 3T. All had normal size nodes (per patient & per side)	0.64-0.79 0.43-0.64	0.79-0.85

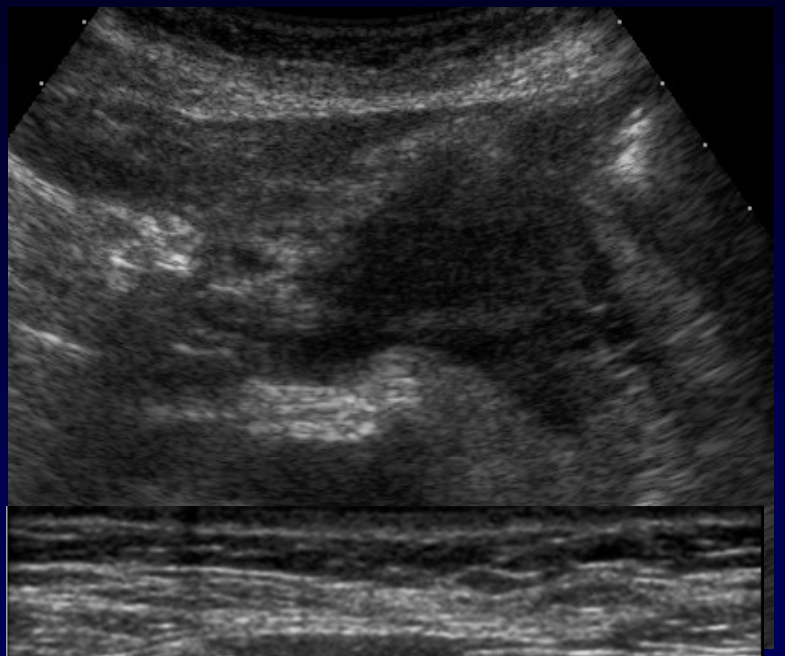
OUTLINE

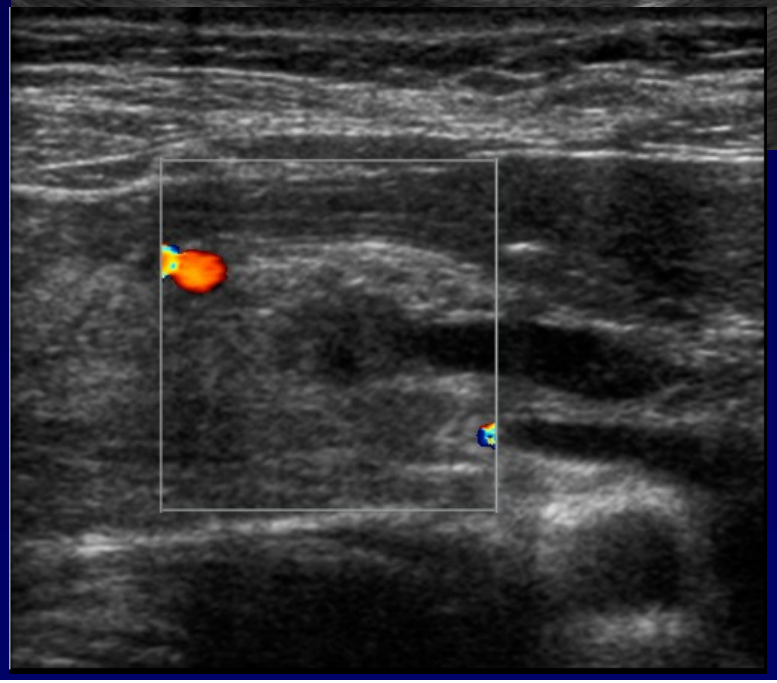
- Solid pancreatic neoplasms:
  - Adenocarcinoma
  - Neuroendocrine neoplasms
- Cystic pancreatic neoplasms
  - intraductal mucinous neoplasms (IPMNs)
  - Serous cystadenoma
  - Mucinous cystadenoma

Detection: US

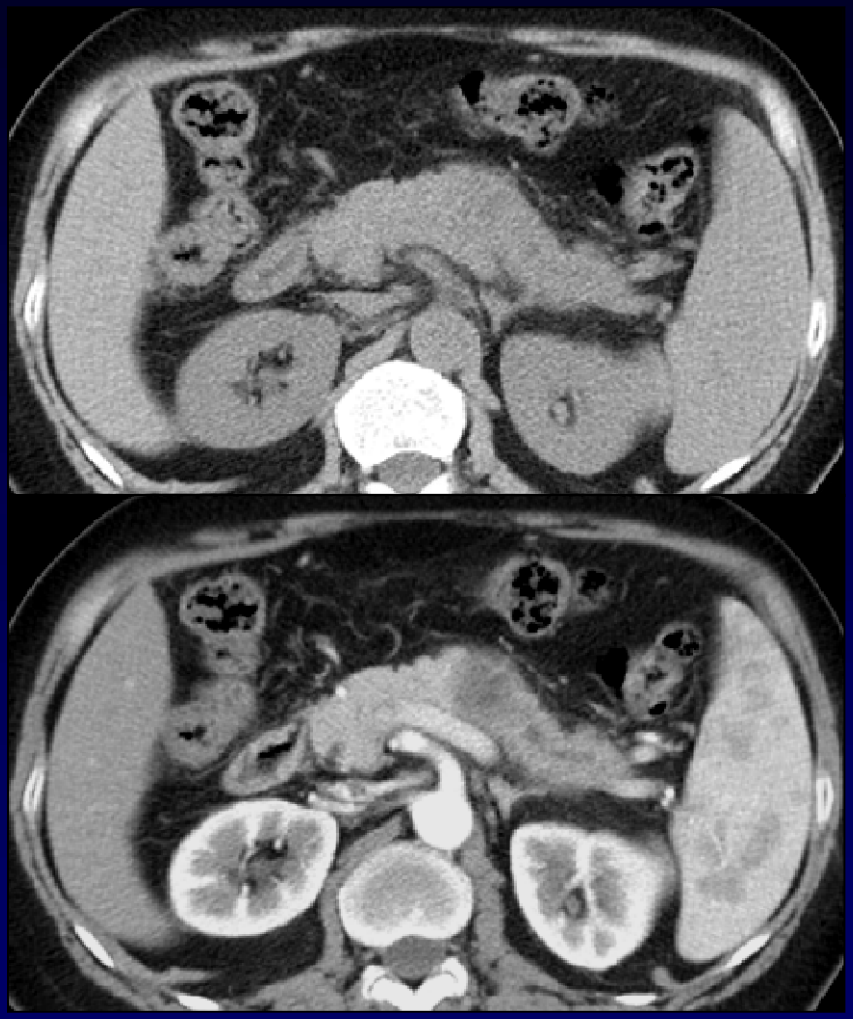




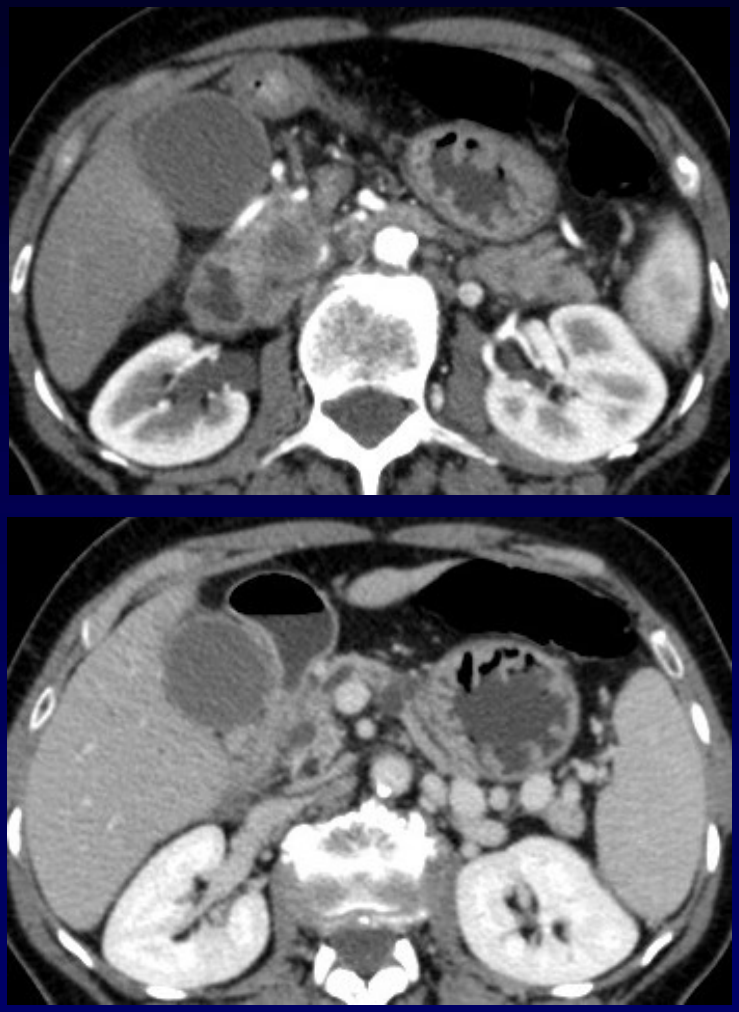




Detection: CT



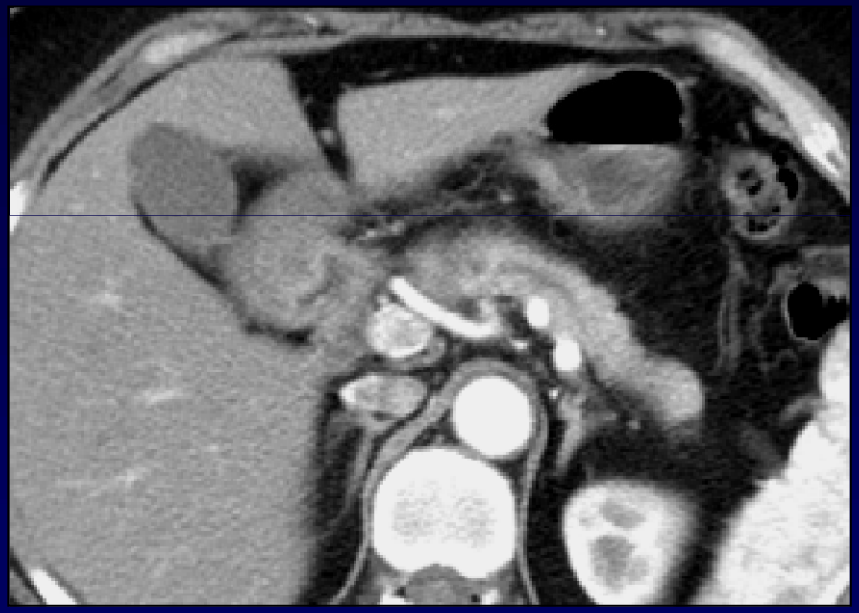
Hypo-density/-vascularity

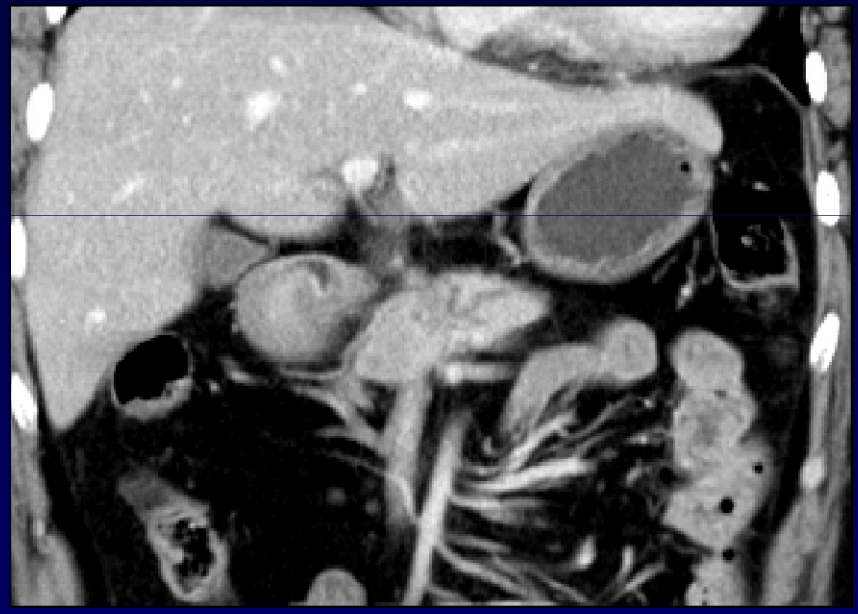


Upstream atrophy

McNulty NJ et al Radiology 2001

Detection
Ductal stenosis





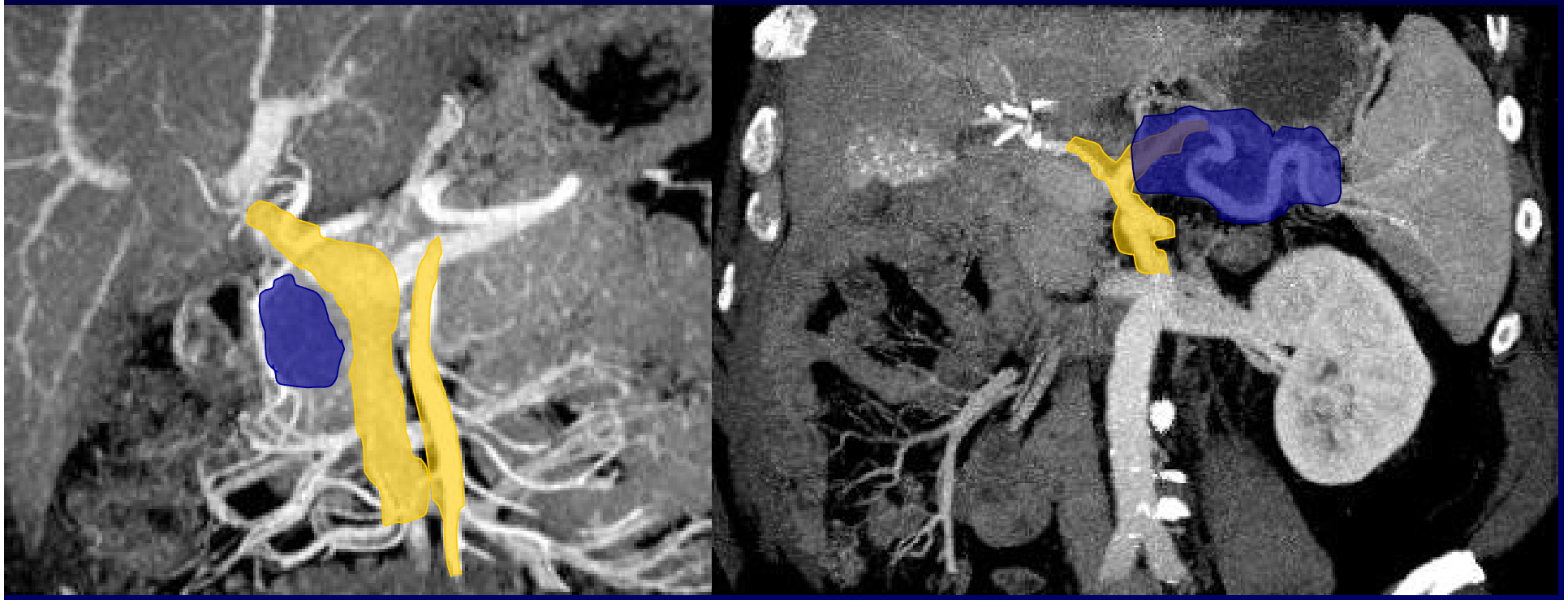
Isodense in 11%

Prokesch RW, et al Radiology 2002

Treatment planning

Vessel invasion

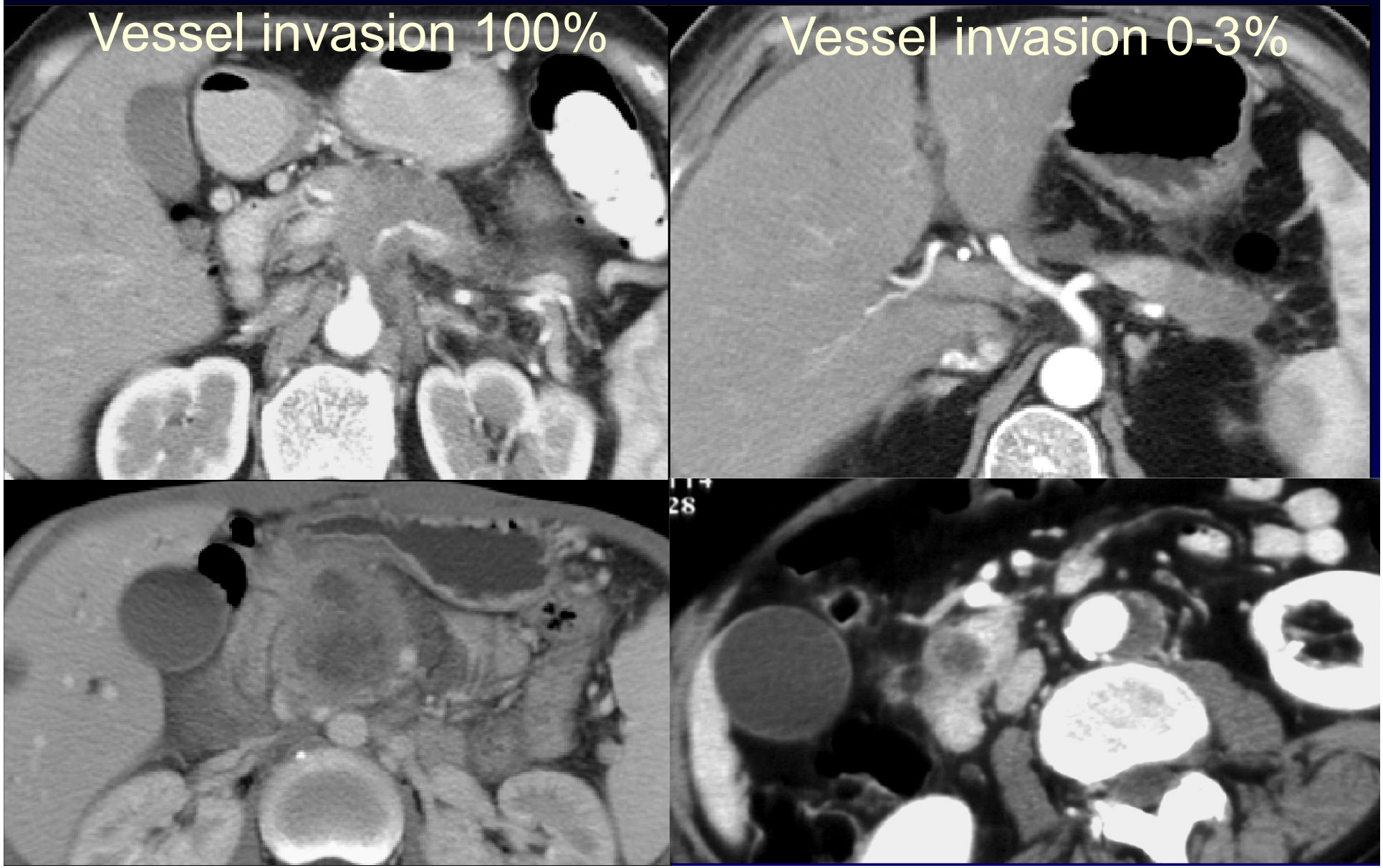
- Venous involvement function of:
  - +++ tumor location
  - tumor biology



SMV SMA

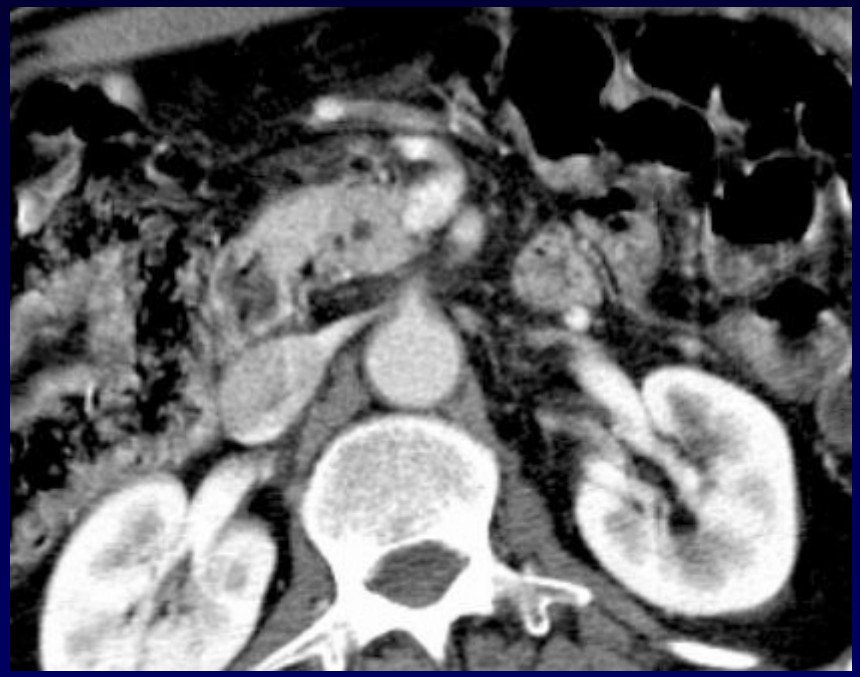
Fuhrman, Ann Surg 1996

Vessel invasion



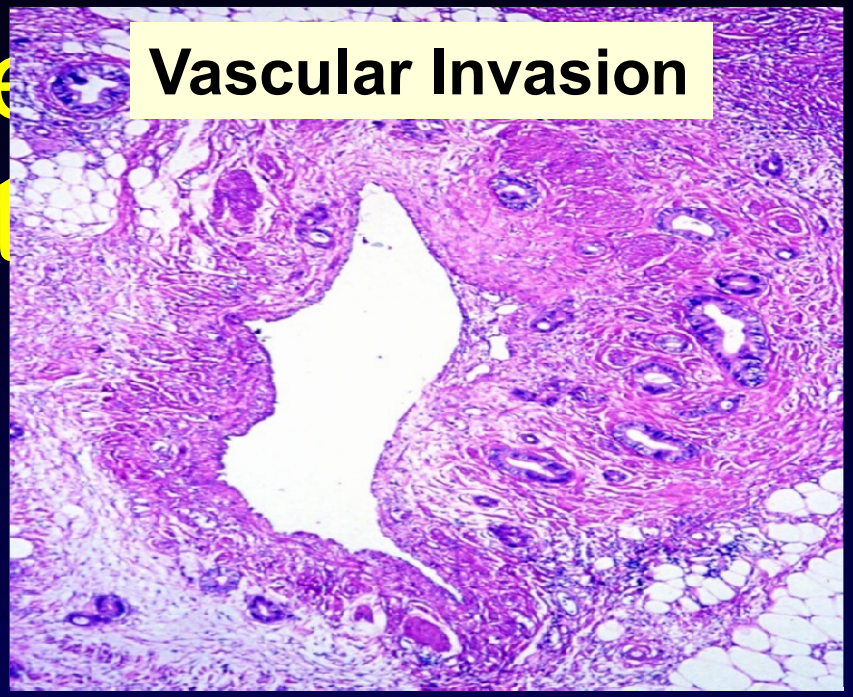
Borderline re
Vessel contact

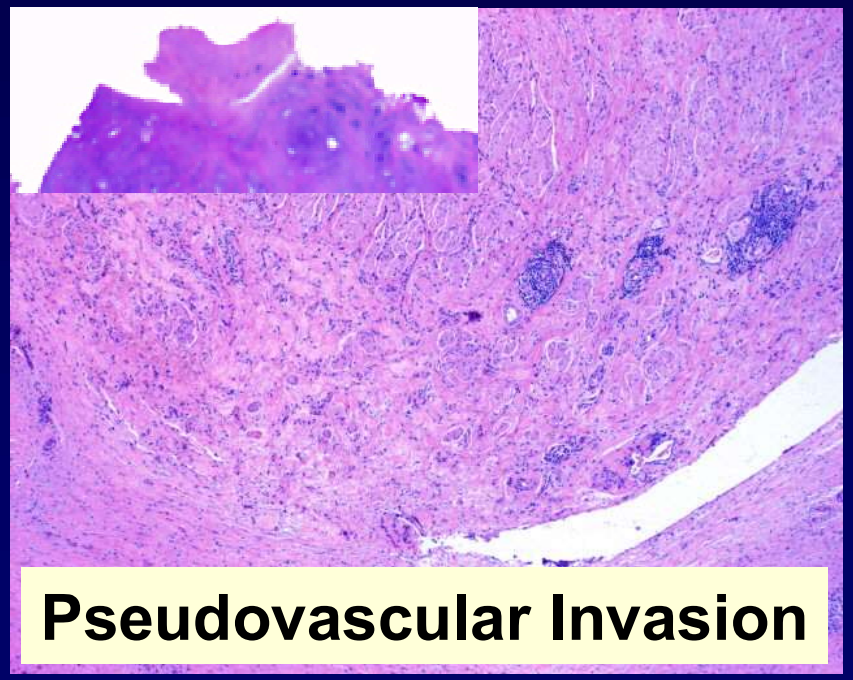
Vessel invasion 50-88%



Particularly after CH/RT

Lu, AJR 1997, O´Malley AJR 1999





WELCOME AND INTRODUCTION

UPPER GI: TECHNICAL AND CLINICAL CHALLENGES FOR RADIATION ONCOLOGISTS - FULLY BOOKED

25-28 March, 2017
Rome, Italy

ESTRO School

TAKE HOME MESSAGE

COURSE AIM

The aim of the course is to support an interactive educational environment by peer review of each step of radiation therapy practice (indication, prescription, delineation, planning, IGRT, outcome evaluation) according to the modern available technologies and knowledge and taking care of the clinician, physicist and RTT perspectives.

TAKE HOME MESSAGE

COURSE AIM

Specialists of different disciplines will support the radiation oncology audience in understanding the clinical needs, anatomic and pathologic details, and the therapeutic achievements needed to exploit the radiation technology at the best.

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LEARNING OUTCOMES

By the end of this course, for each upper GI tumour site, participants should be able to practice:

- Proper indication for radiation therapy in a multidisciplinary perspective
- Prescription
- Tailored delineation according to tumour location and stage
- Dose distribution optimisation and comparison
- Optimal use of available IGRT technologies
- Proper monitoring of tumour response an control.

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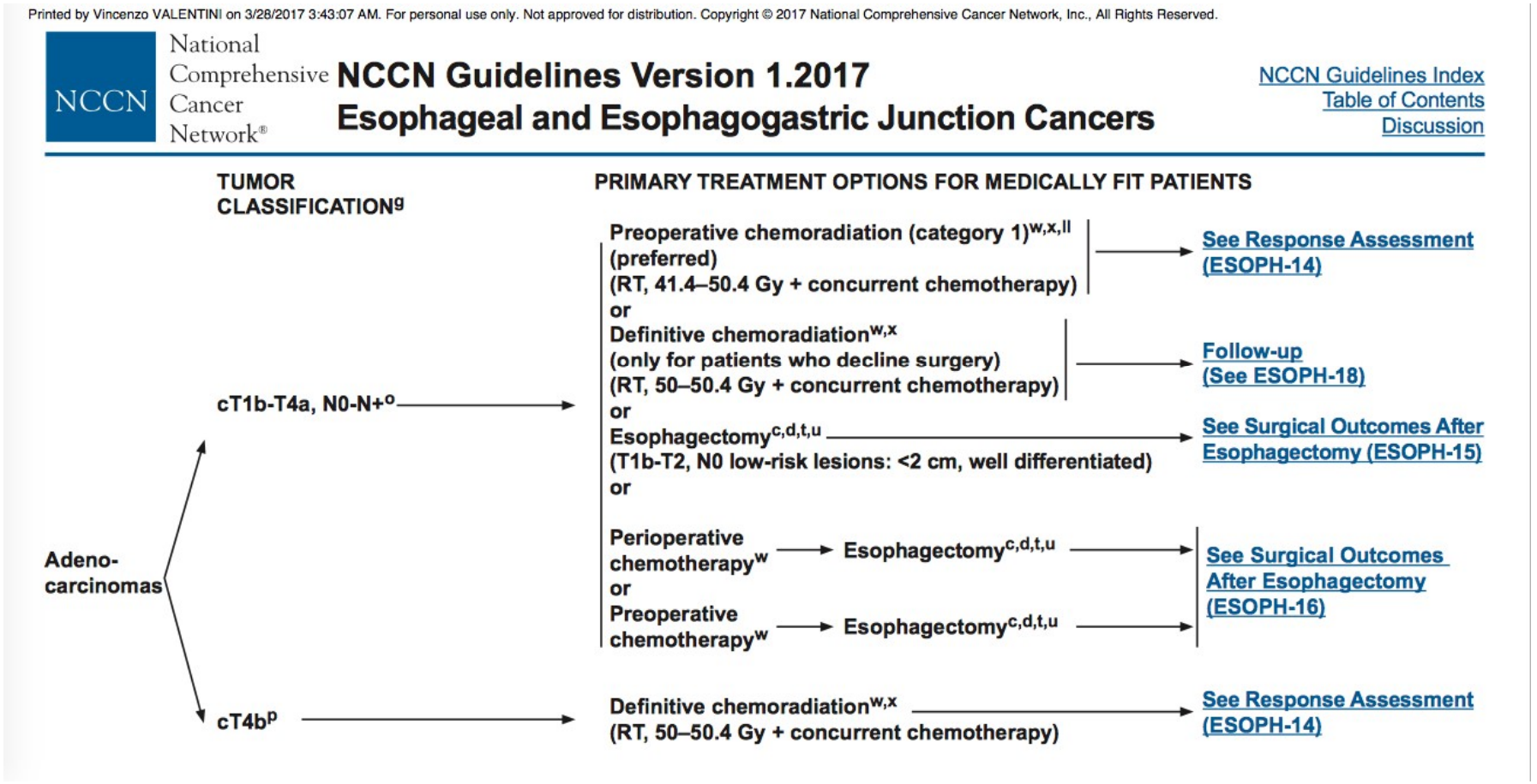

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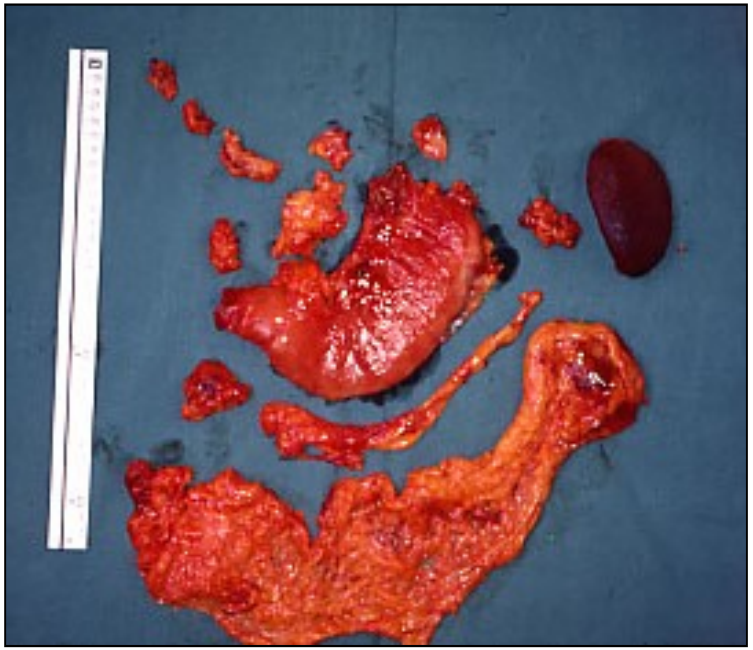

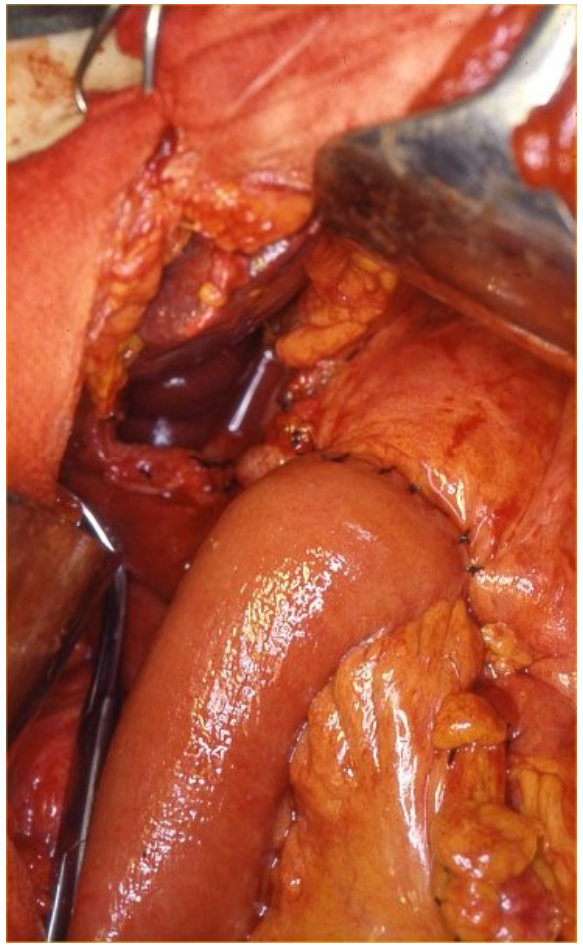

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- Radiation Oncologists
Vincenzo Valentini (IT)
Marcel Verheij (NL)
Oscar Matzinger (CH)

- Physicist,
Dirk Verellen (BE)

- RTT
Lisa Wiersema (NL)

- Delineation Administrator
Francesco Cellini, RO (IT)

- Surgeon,
William Allum (UK)

- Medical oncologist
Florian Lordick (DE)
Nicola Silvestris (IT)

- Radiologist
Angela Riddell (UK)
Riccardo Manfredi (IT)

- Pathologist
Alexander Quaas (DE)

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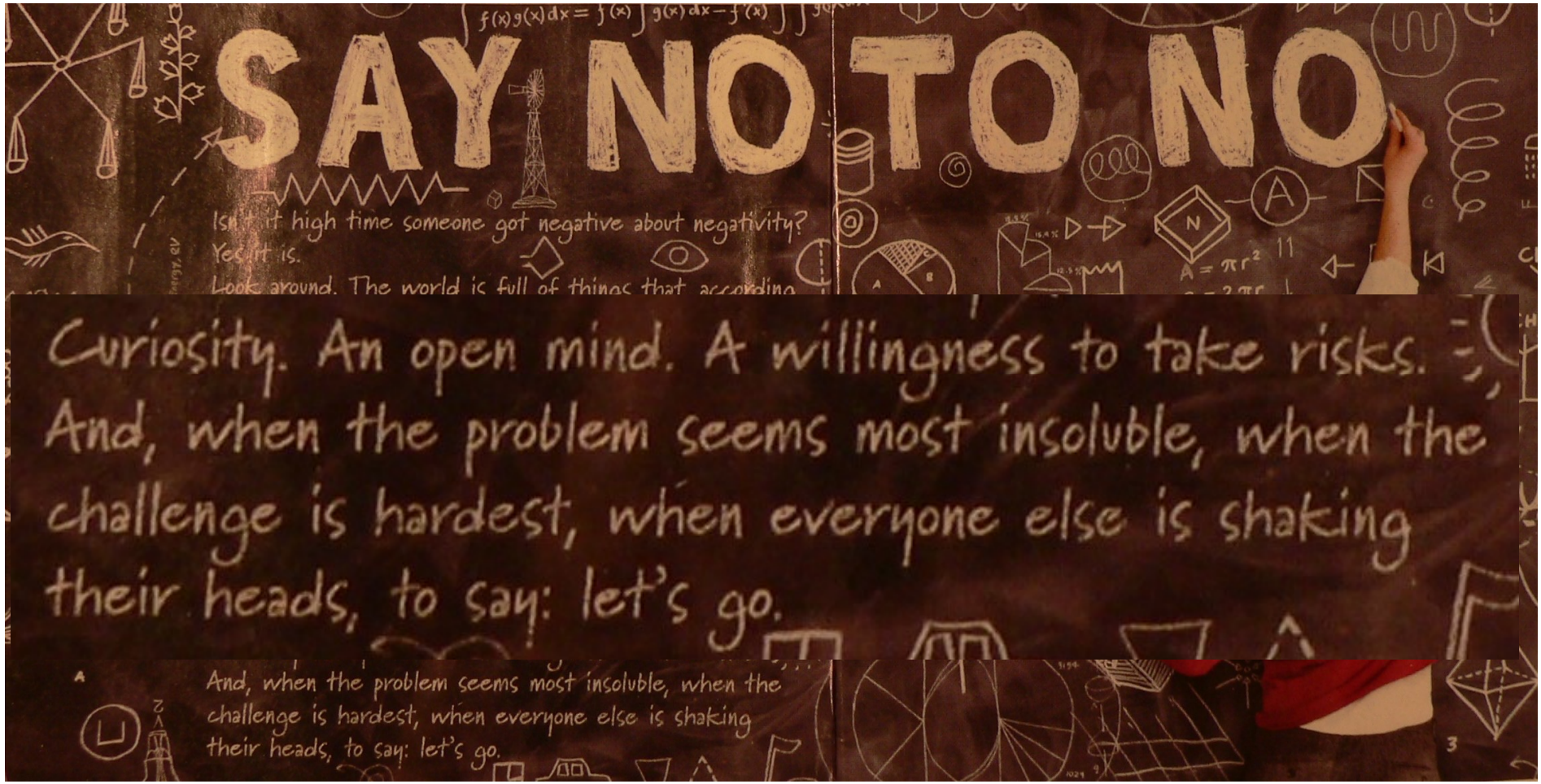

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