WELCOME AND INTRODUCTION

NEW

UPPER GI: TECHNICAL AND CLINICAL CHALLENGES FOR RADIATION ONCOLOGISTS

28 - 31 May 2016

Brussels, Belgium

ESTRO School

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.

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)
Philippe Maingon (FR)

- Physicist,
Dirk Verellen (BE)

- RTT
Lisa Wiersema (NL)

- Delineation Administrator
Francesco CELLINI, RO (I)

- Surgeon,
William Allum (UK)

- Medical oncologist
Florian Lordick (DE)
Alain Hendlisz (BE)

- Radiologist
Angela Riddell (UK)

- 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

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	A.Hendlisz
	14.50-15.30	**Prescription interactive exercise**	All teachers

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COURSE CONTENT

30 May (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.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
	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**	Tutors: M.Verhej, F.Cellini, L.Wiersema
		Hands-on: Group 2 video on surgical procedure (highlight of key surgical steps)	W.Allum
	16.45 – 17.30	**Hands-on: Group 2 delineation Middle Third**	Tutors: M.Verhej, F.Cellini, L.Wiersema
		Hands-on: Group 2 video on surgical procedure (highlight of key surgical steps)	W.Allum

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COURSE CONTENT

Anticipation Session 4	17.30-17.50	**Lecture (20'): Chemotherapy toxicity constraints**	A.Hendlisz

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 3: Delineation	8.30 – 10.30	**Lecture (15'): Primary tumor extension pathology evaluation**	A.Quaas
		Lecture (15'): Nodal subsite involvement for stage and tumor position	A.Quaas
		Lecture (30'): Imaging of primary and nodal subsite boundaries?	A.Riddell
		Lecture (20'): recommendation for subsite delineation by stage and tumor position	P.Maingon
		Discussion on delineation exercises (40')	All teachers

Session 9: Delineation	14.00 – 16.05	**Lecture (20'): Primary tumor extension and nodal subsite involvement**	A.Quaas
		Lecture (20'): Imaging of primary and nodal subsite boundaries?	A.Riddell
		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 – 12.40	**Lecture (20'): Dose issues in esophageal tumor control**	M. Verheij
		Lecture (20'): Dose constrains for organ at risk	P.Maingon
		Interactive lecture (60'): choice among competitive plans for early and locally advanced esophageal cancer	D.Verellen
Session 10: Planning	16.30 – 18.00	**Lecture (20'): Dose issues in gastric tumor control**	M. Verheij
		Lecture (20'): Dose constrains for organ at risk	P. Maingon
		Lecture (20'): Chemotherapy toxicity constraints	F.Lordick
		Interactive lecture (60'): choice among competitive plans for gastric cancer	D.Verellen

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

Session 5: In room imaging guided radiotherapy	14.00 – 14.45	**Hands-on: Group 1 How to determine PTV margin**	D.Verellen
		Hands-on: Group 2 Tips and tricks on in room IGRT	M. Verheij, F.Cellini, L.Wiersema
	14.45 – 15.30	**Hands-on: Group 2 How to determine PTV margin**	D.Verellen
		Hands-on: Group 1 Tips and tricks on in room IGRT	P. Maingon, 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

Session 6: what we learn by failure analysis and future perspective	15.50 – 17.00	**Lecture (15'): how to distinguish primary recurrence vs nodal recurrence by imaging**	A.Riddell
		Lecture (15'): incidence and location of local recurrences after only surgery	W.Allum
		Lecture (15'): incidence and location of local recurrences after only radiotherapy	M. Verheij
		Discussion (10')	All teachers
		Lecture (15'): new perspectives in esophageal cancers	P. Maingon

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COURSE CONTENT

Session 12 : what we learn by failure analysis and future perspective	10.30 – 11.30	**Lecture (20'): how to distinguish recurrence by imaging**	A.Riddell
		Lecture (20'): new perspectives in gastric cancers	M. Verheij
		Discussion (20')	
Session 13 : end of the course	11.30 – 12.00	**Take home messages**	V. Valentini

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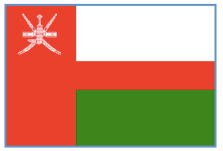
41 participants

6 

Australia

1 

Giordania

1 

Oman

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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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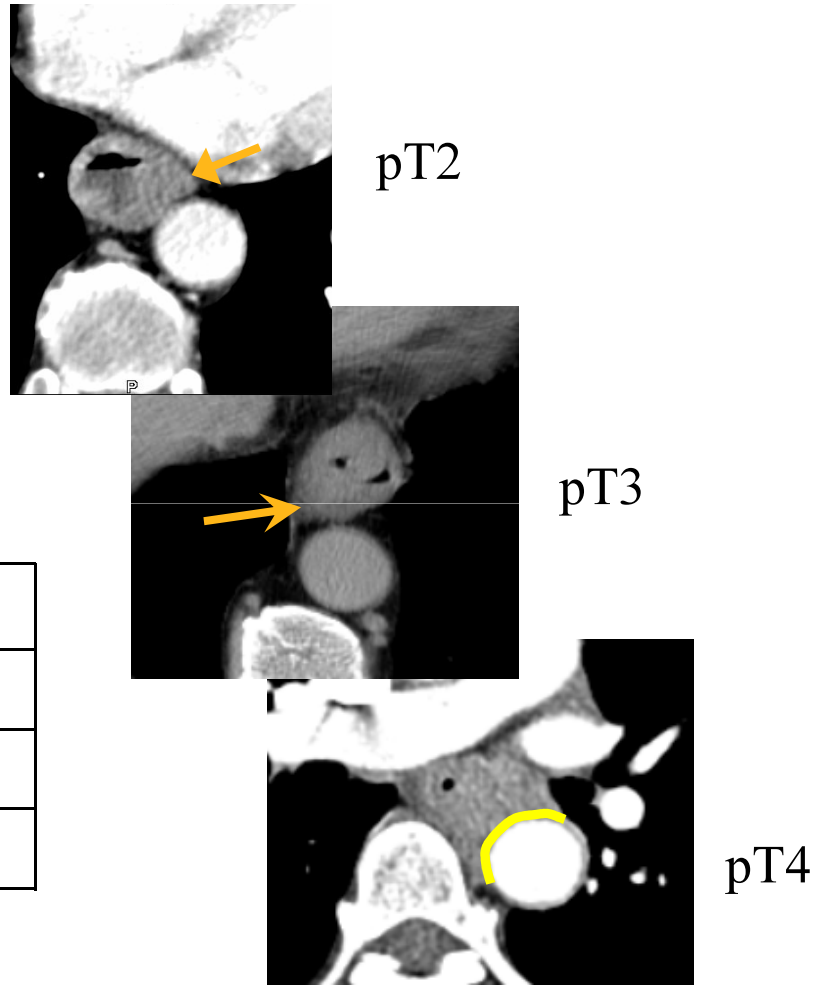
Esophageal Cancer - Current Staging Strategy

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

T staging - MDCT

Initial Staging

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



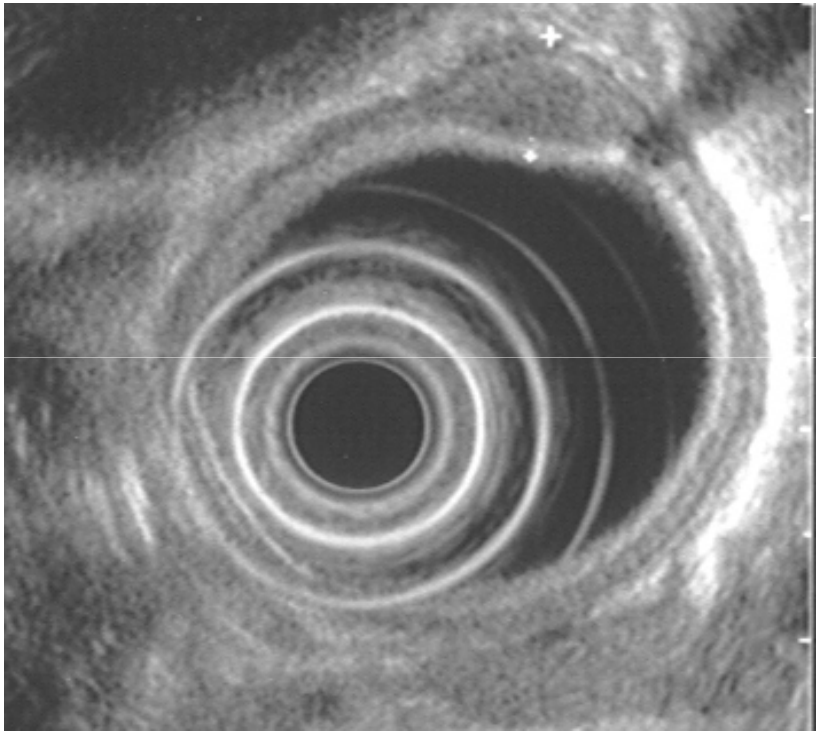
T Stage	Wall thickness	Wall Contour
T2	>3mm, <5mm	Smooth
T3	5-15mm	Irregular
T4	>15mm	Contact with adjacent structure

T Staging Accuracy - 74%*

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

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

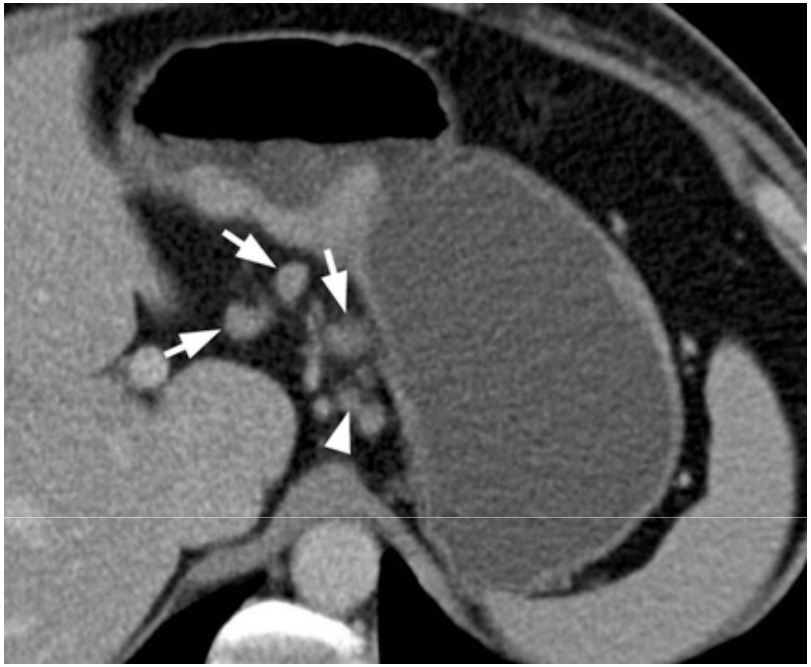
T Staging - EUS

- 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.

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.

N Staging - MDCT

Tumour volume related to nodal burden*

Figure 1

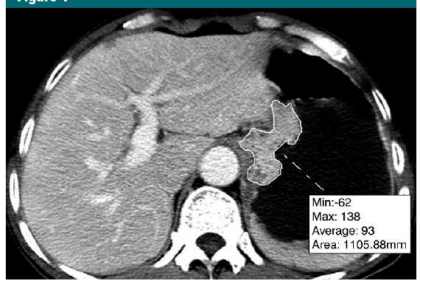


Figure 1: Transverse contrast-enhanced CT scan in 56-year-old man with AEG. Tumor area is manually drawn along margin of tumor, and value of this area (1105.88 mm) is automatically derived by software together with minimal, maximal, and average CT attenuation (in Hounsfield units).

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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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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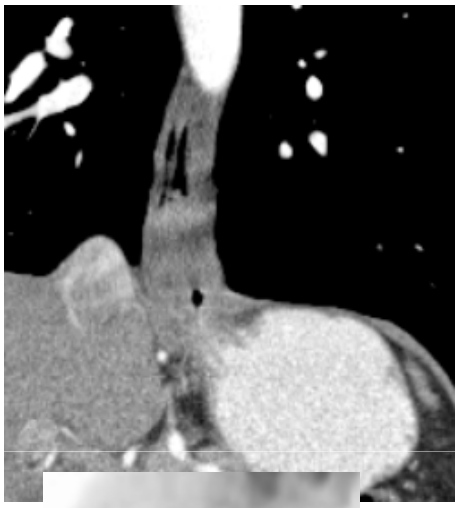
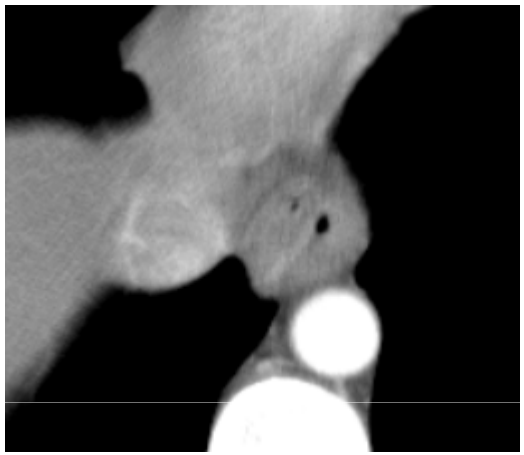
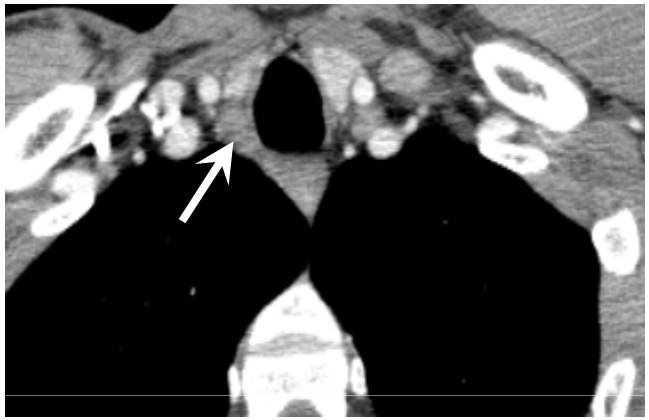
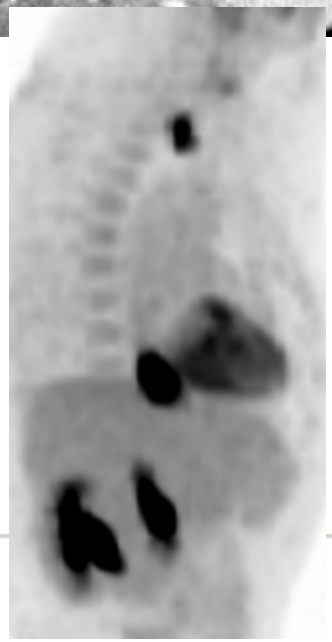
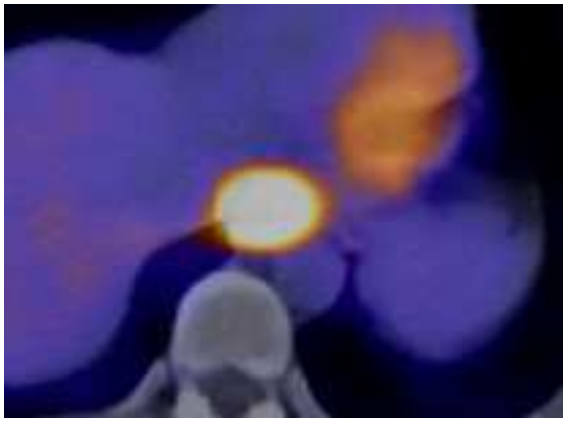
^{18}FDG-PET/CT – Staging

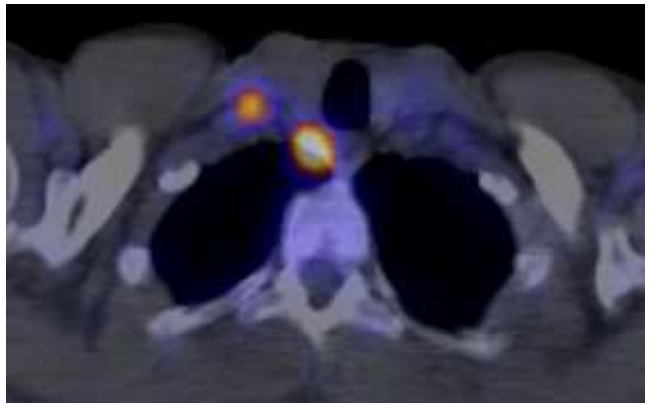






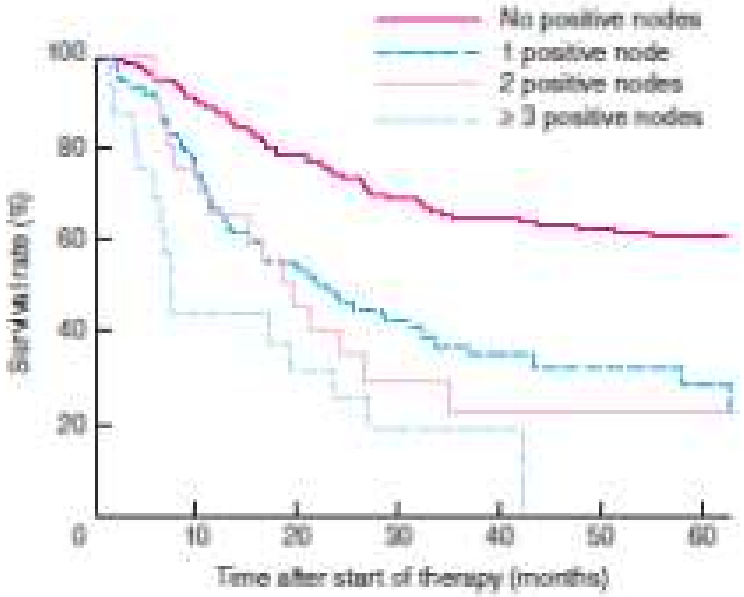






Importance of the number of nodes in prognosis

- 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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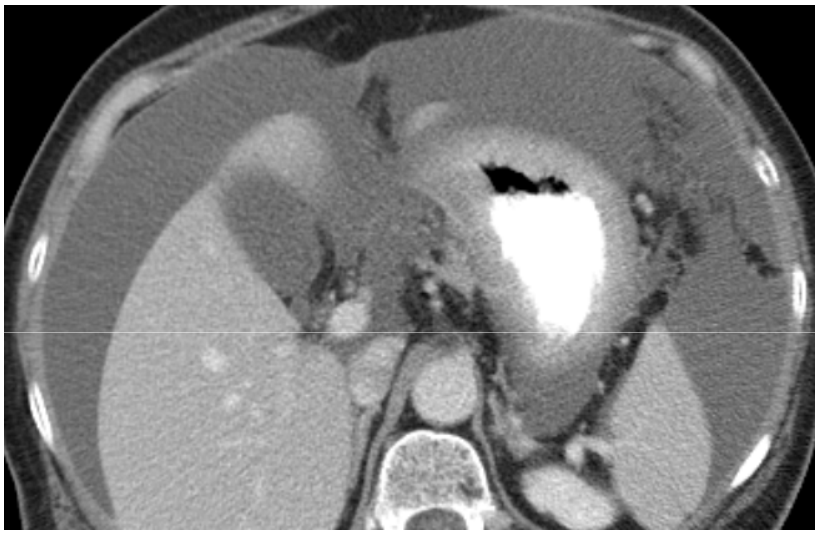
MDCT – M staging

- 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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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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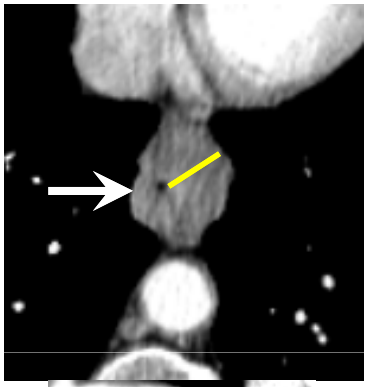
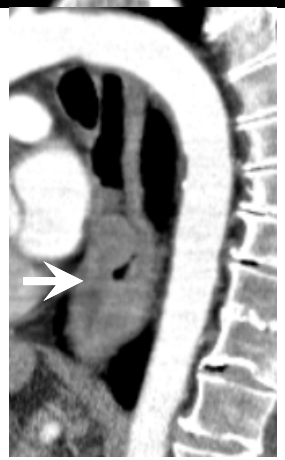
Response to chemotherapy / CRT

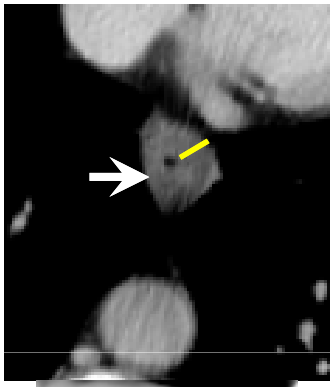
Multidetector Computed Tomography (MDCT)

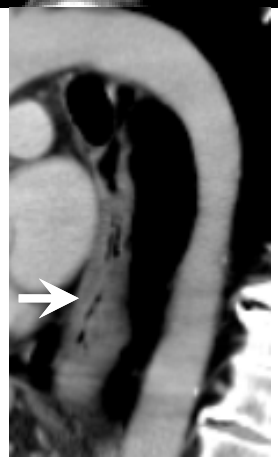




Sept 2012

3 cycles chemo





Dec 2012

Response by RECIST

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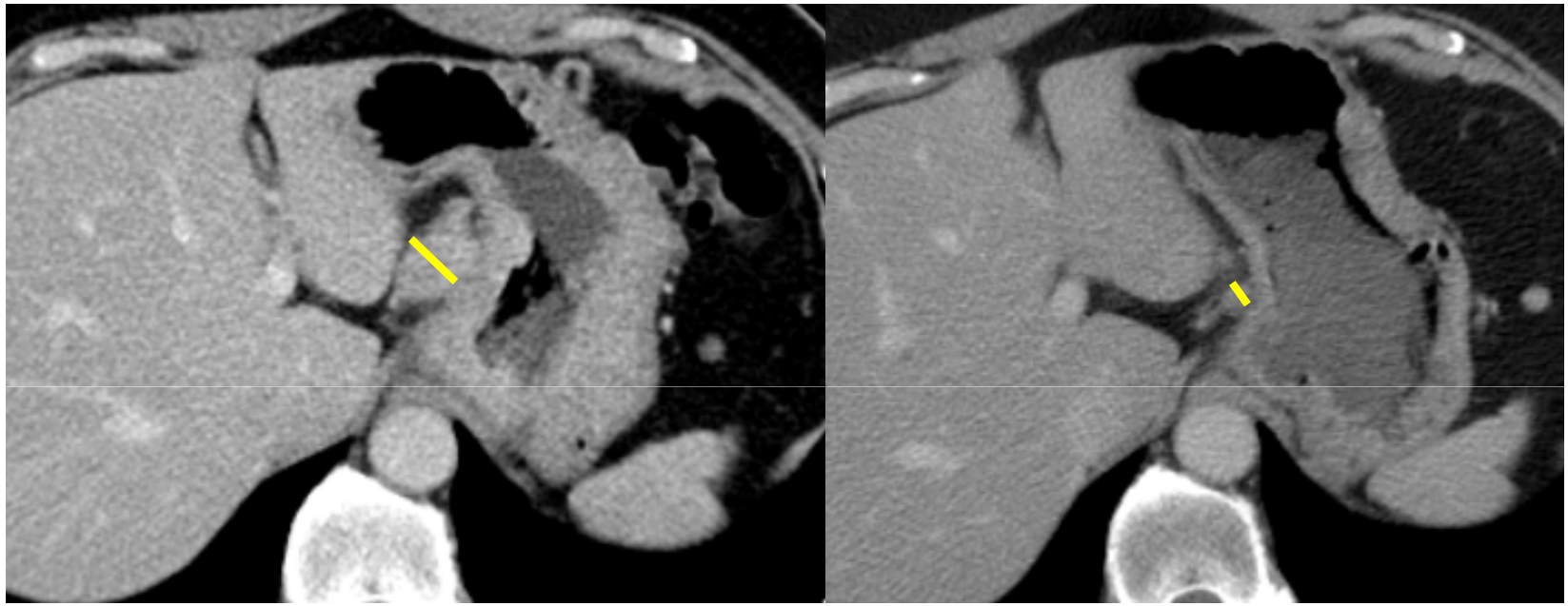
Response to chemotherapy / CRT



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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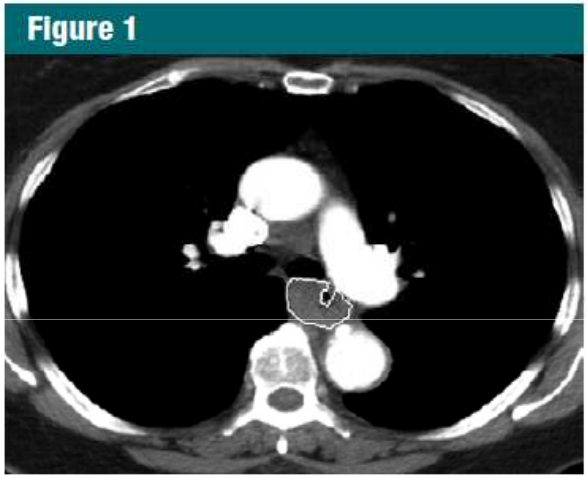
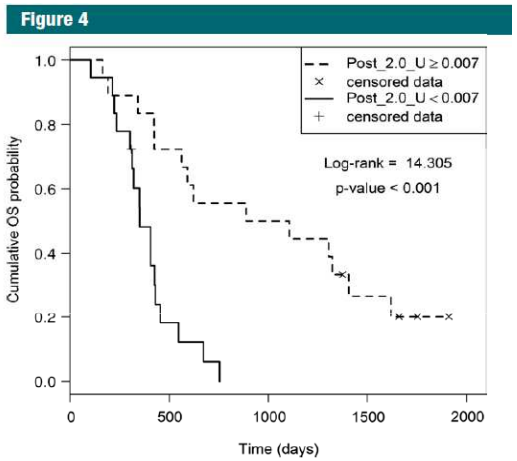
Response to chemotherapy / CRT

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

ESTRO School

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

ESTRO School

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.

ESTRO School

^{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

ESTRO School

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

^{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

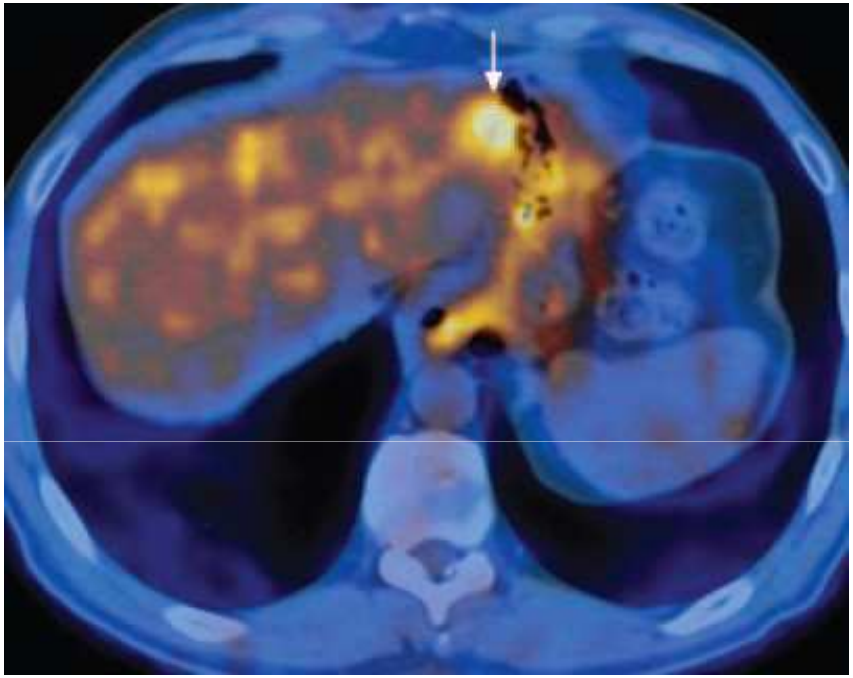
ESTRO School

Response to chemotherapy / CRT

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

ESTRO School

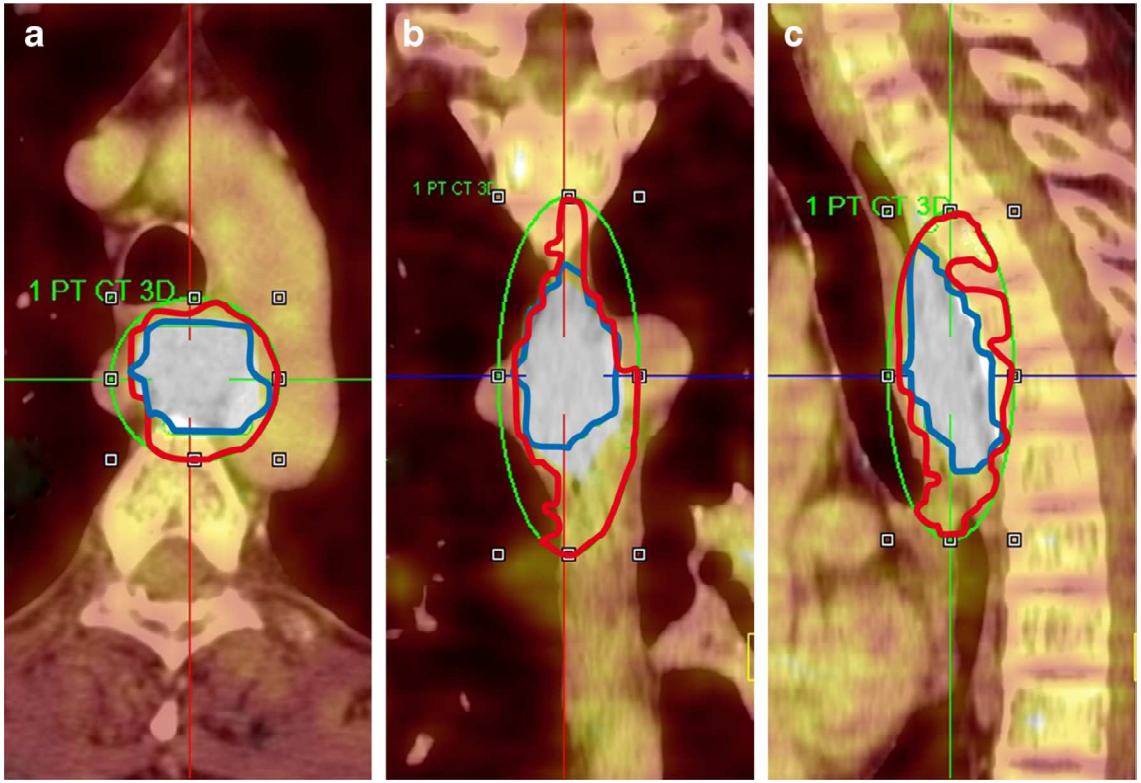
Response to chemotherapy / CRT

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]

ESTRO School

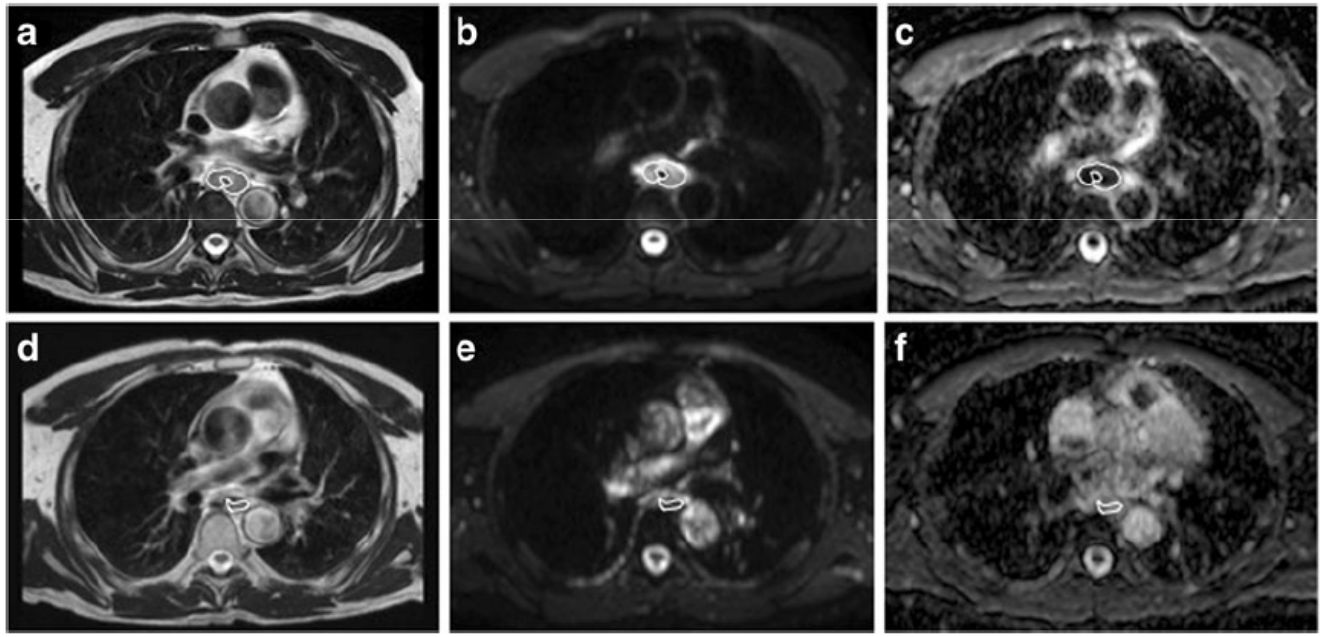
Response to chemotherapy / CRT

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

ESTRO School

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

ESTRO School

Summary

Initial Staging

- MDCT
- EUS
- ^{18}FDG-PET/CT

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

ESTRO School

Thank you

The ROYAL MARSDEN
NHS Foundation Trust

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

William Allum

NHS

EGJ tumor (TNM 7th ed.)

Oesophagus
(ICD-O C15)

Includes Oesophagogastric junction (C16.0)

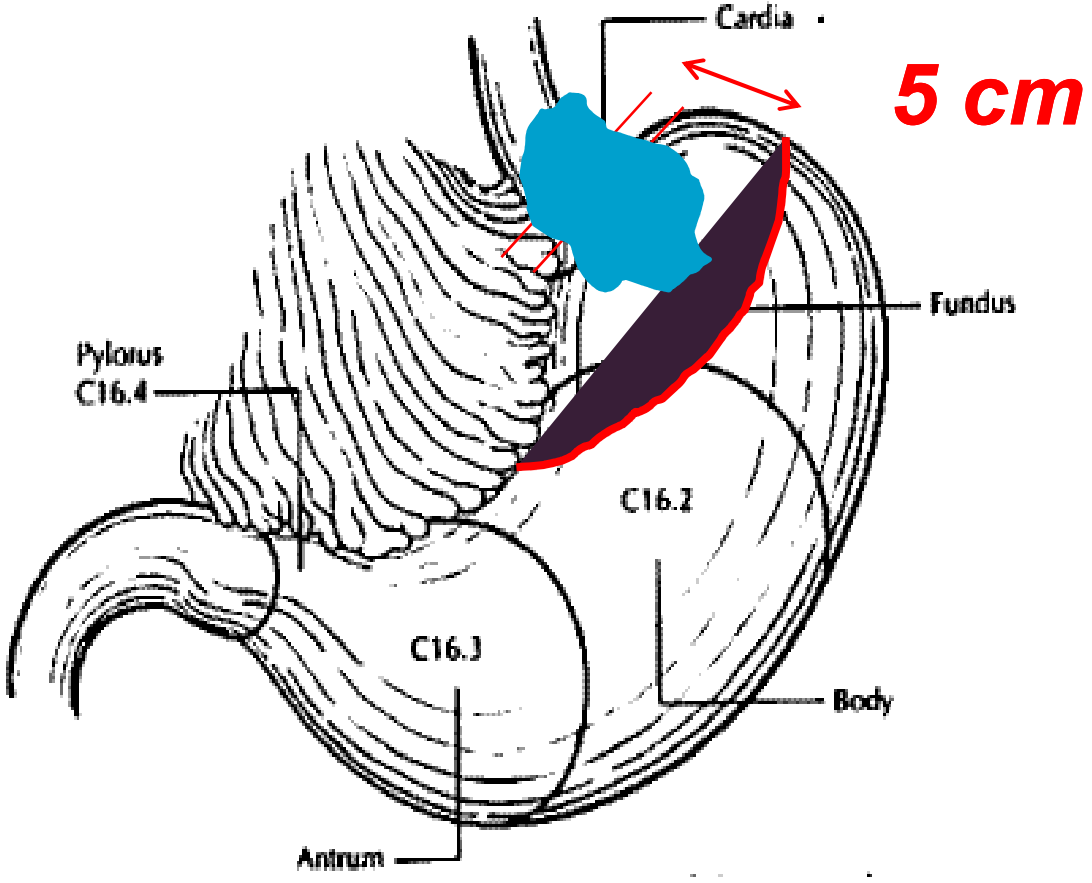
Rules for Classification

- *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.*

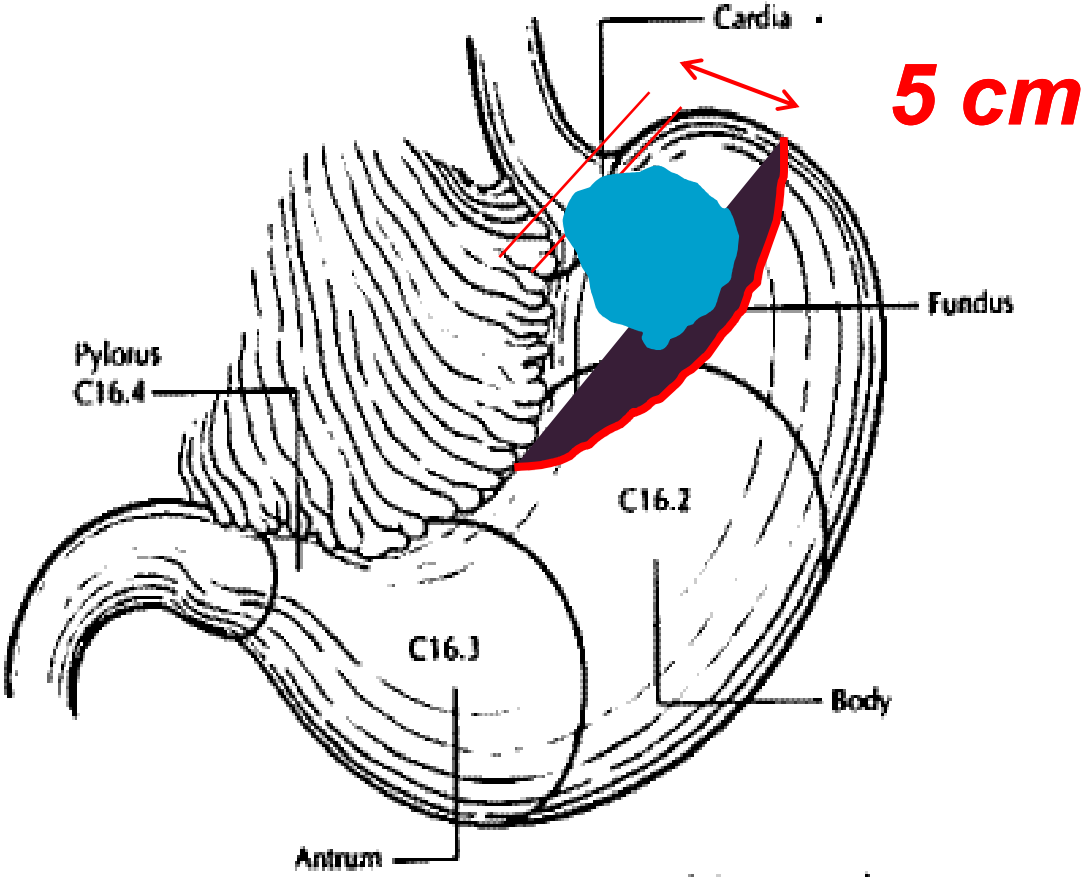
Is classified as tumour

of the oesopahgus

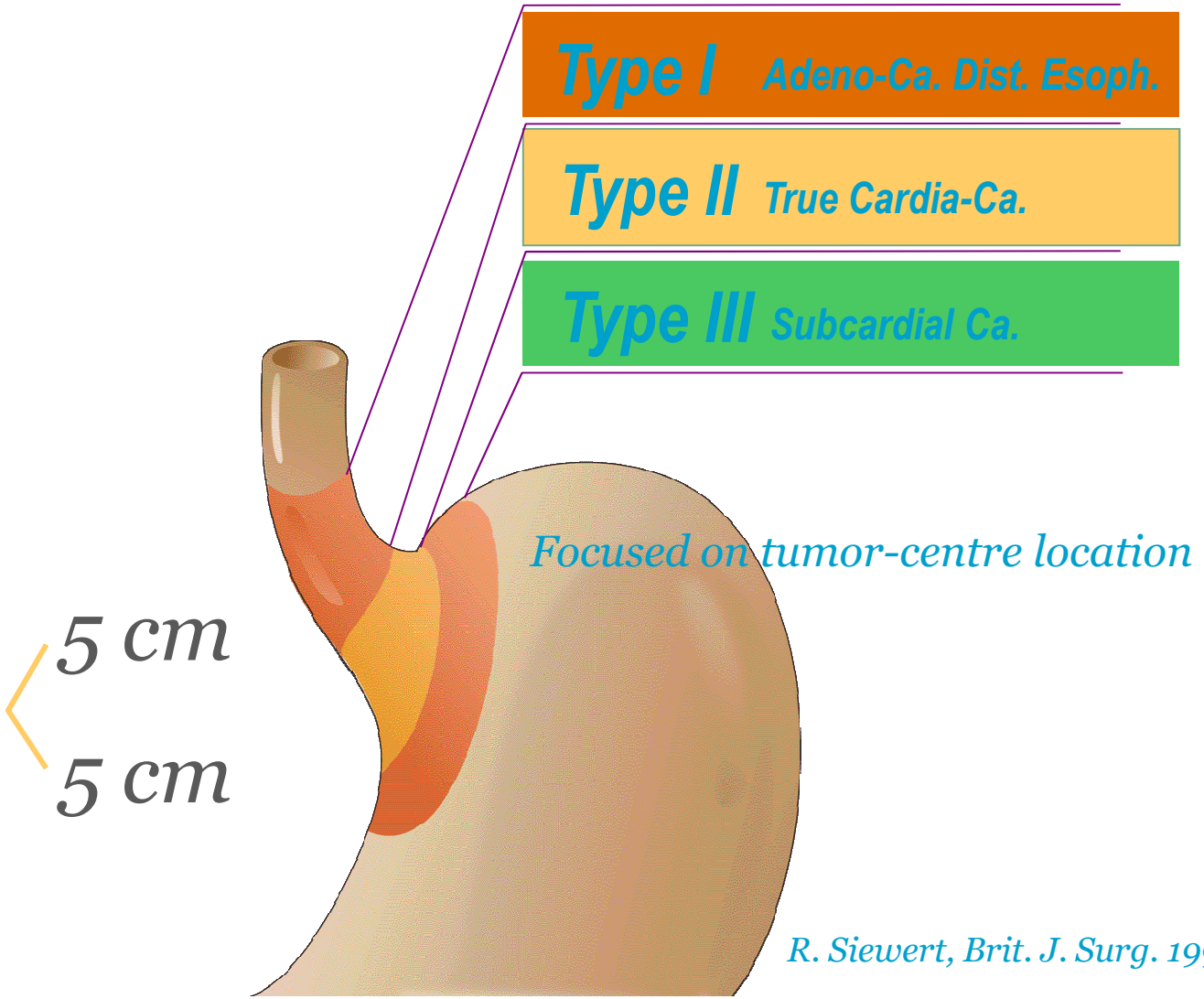


is classified as tumour

of the oesophagus

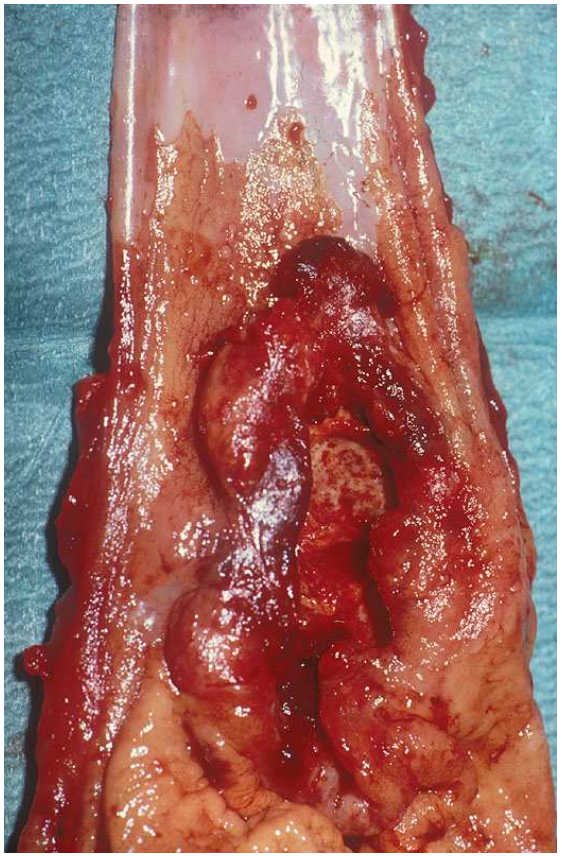


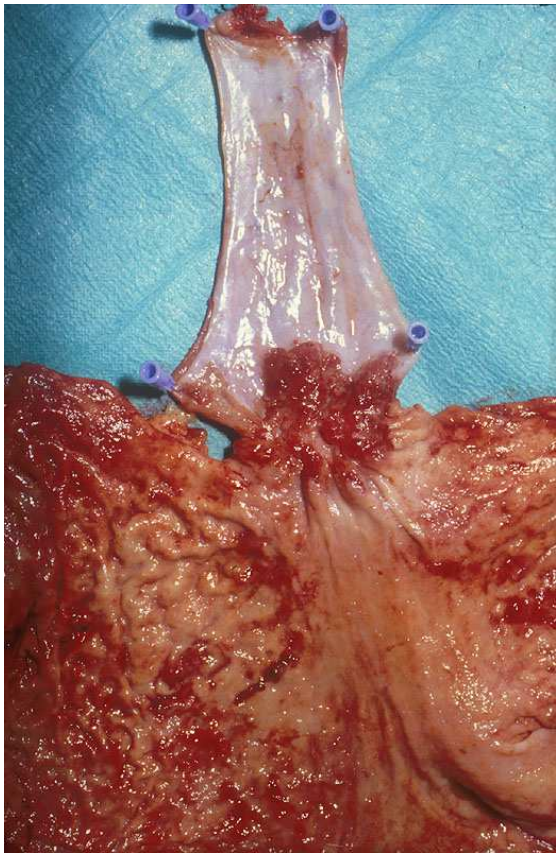
SIEWERT
AEG-Classification

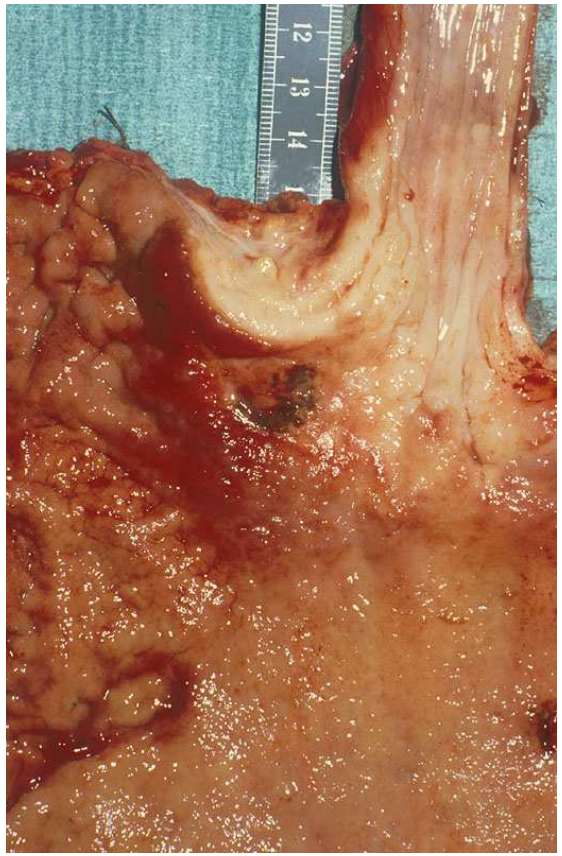


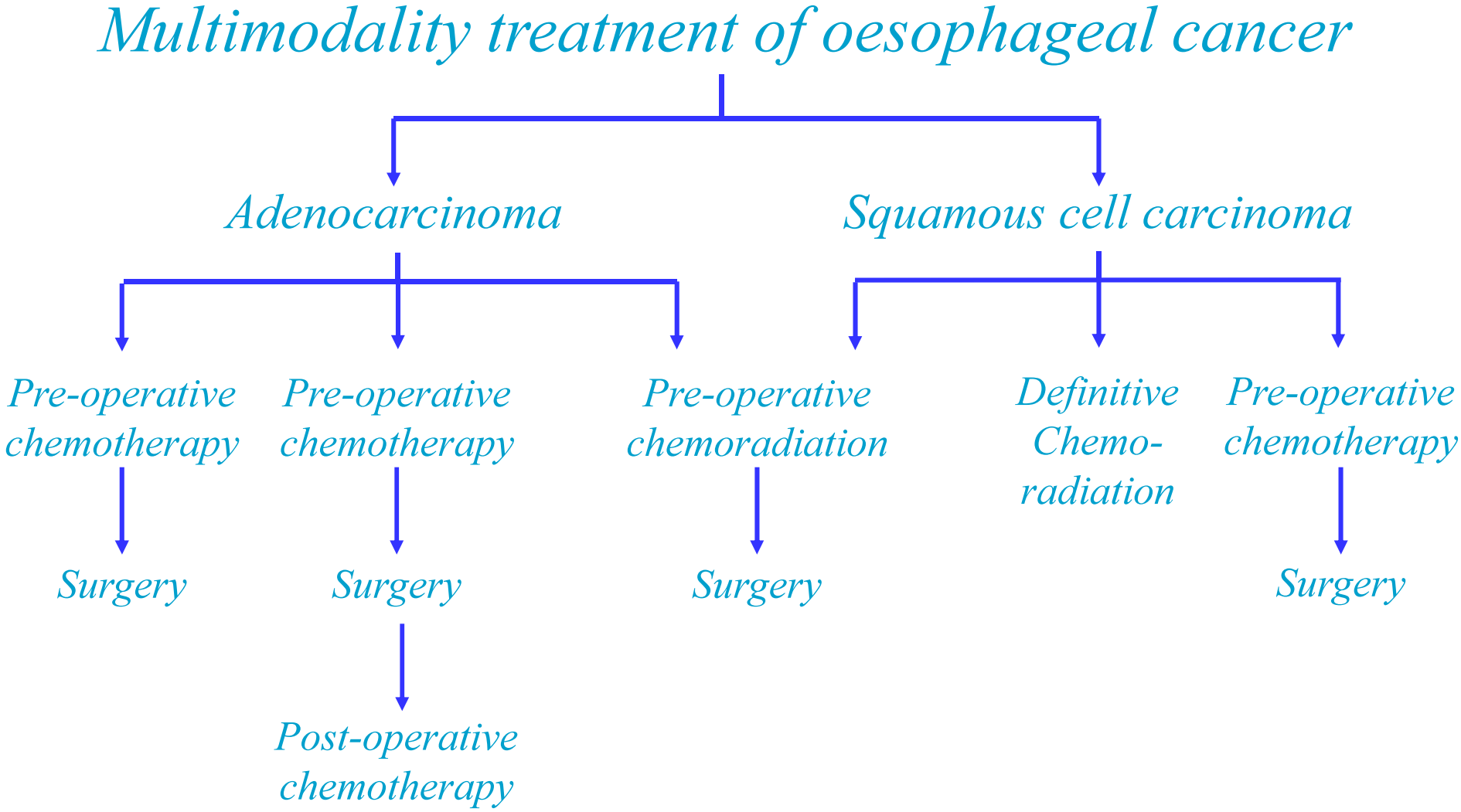
R. Siewert, Brit. J. Surg. 1998

OESOPHAGO-GASTRIC JUNCTIONAL ADENOCARCINOMA








Multimodality treatment of oesophageal cancer
Adenocarcinoma
Squamous cell carcinoma
Pre-operative chemotherapy
Pre-operative chemotherapy
Pre-operative chemoradiation
Definitive Chemo-radiation
Pre-operative chemotherapy
Surgery
Surgery
Surgery
Surgery
Post-operative chemotherapy

Aim of Surgery for Junctional Cancer

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

Operation Selection

Surgical Approach

Margins

Lymphadenectomy

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*

Dutch Trial
Trans Hiatal Oesophagectomy vs Trans Thoracic Oesophagectomy

220 patients with mid and lower oesophageal ACA

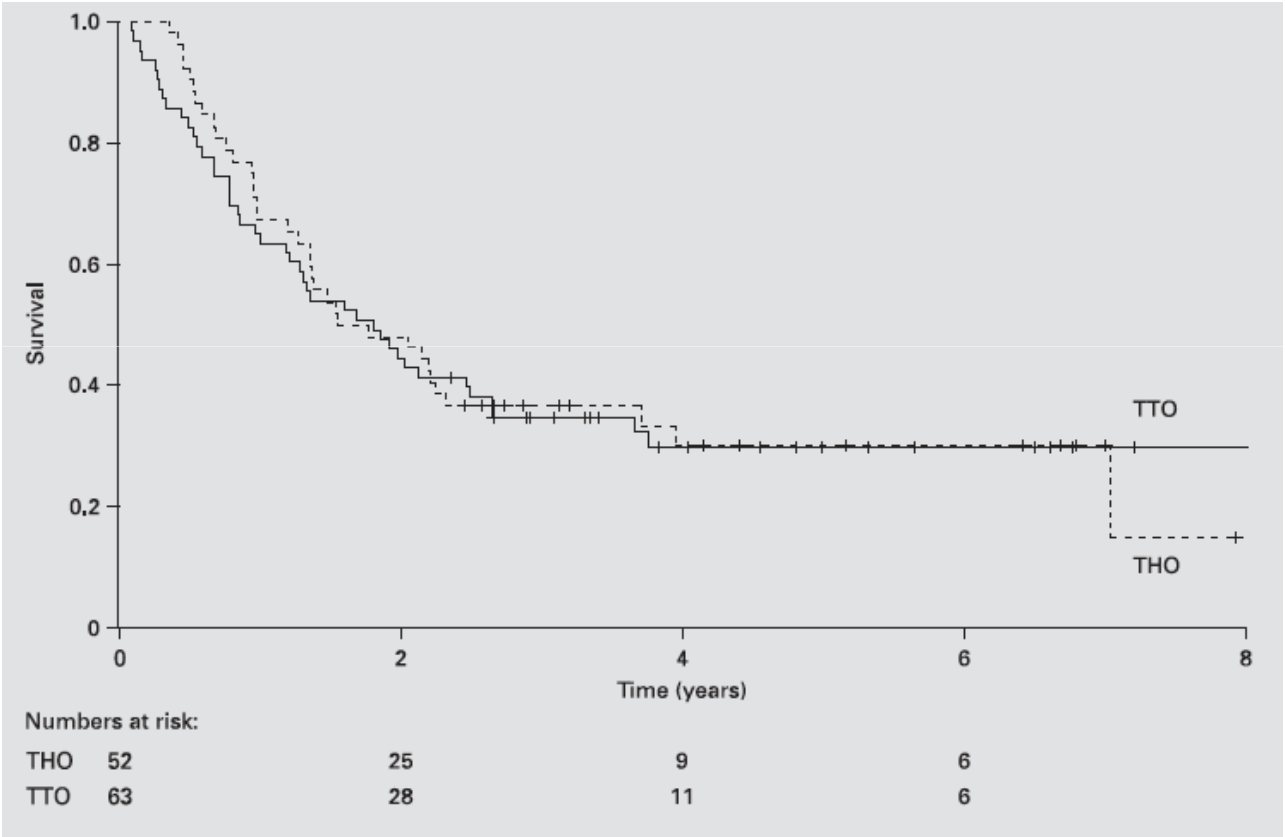
THO
- Lower morbidity

TTO
- More nodes
- More respiratory complications

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

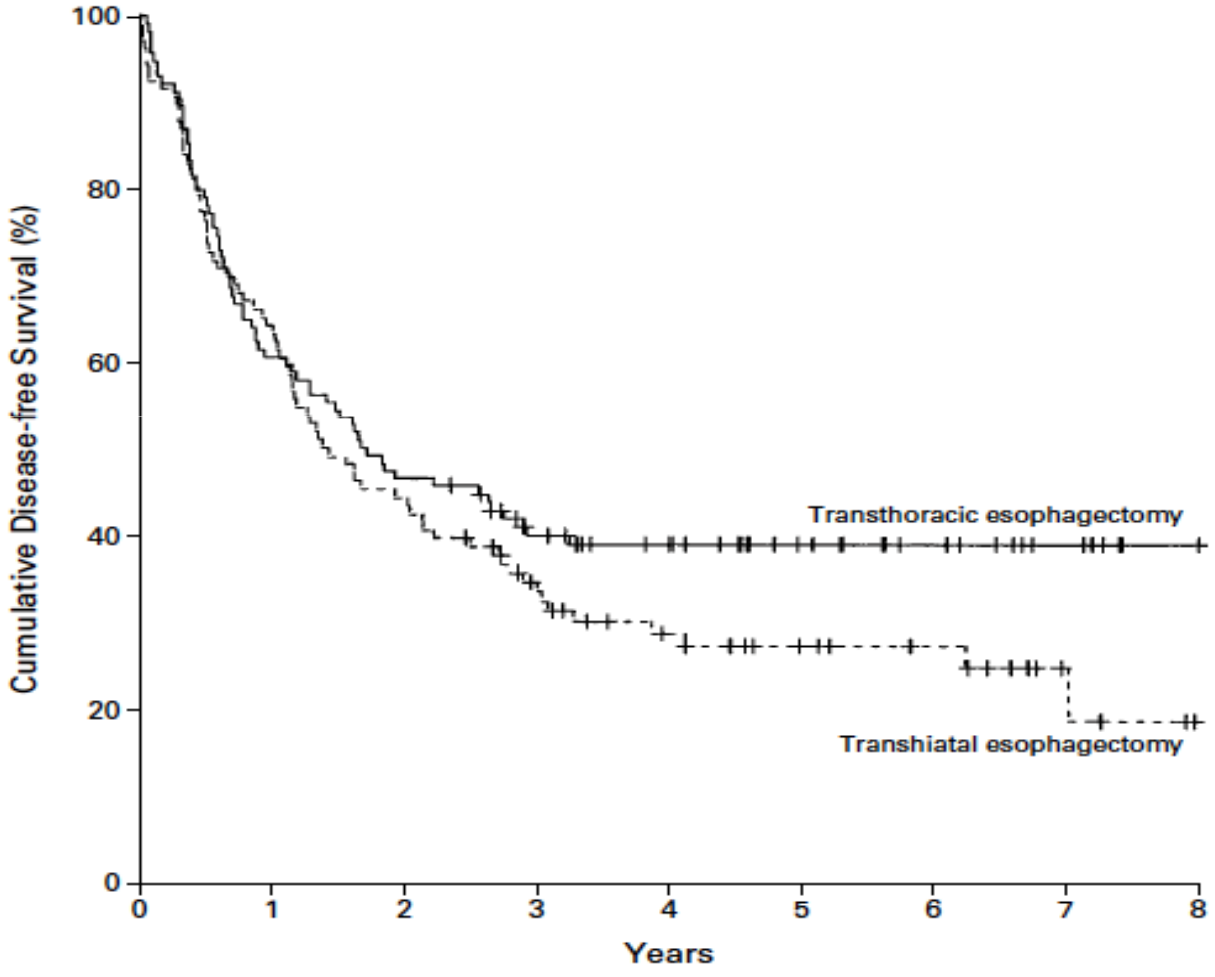
Dutch Trial

THO vs TTO



Dutch Trial

THO vs TTO



No. at Risk								
Transhiatal esophagectomy	106	68	47	32	20	15	11	4
Transthoracic esophagectomy	114	69	53	39	31	20	13	7

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

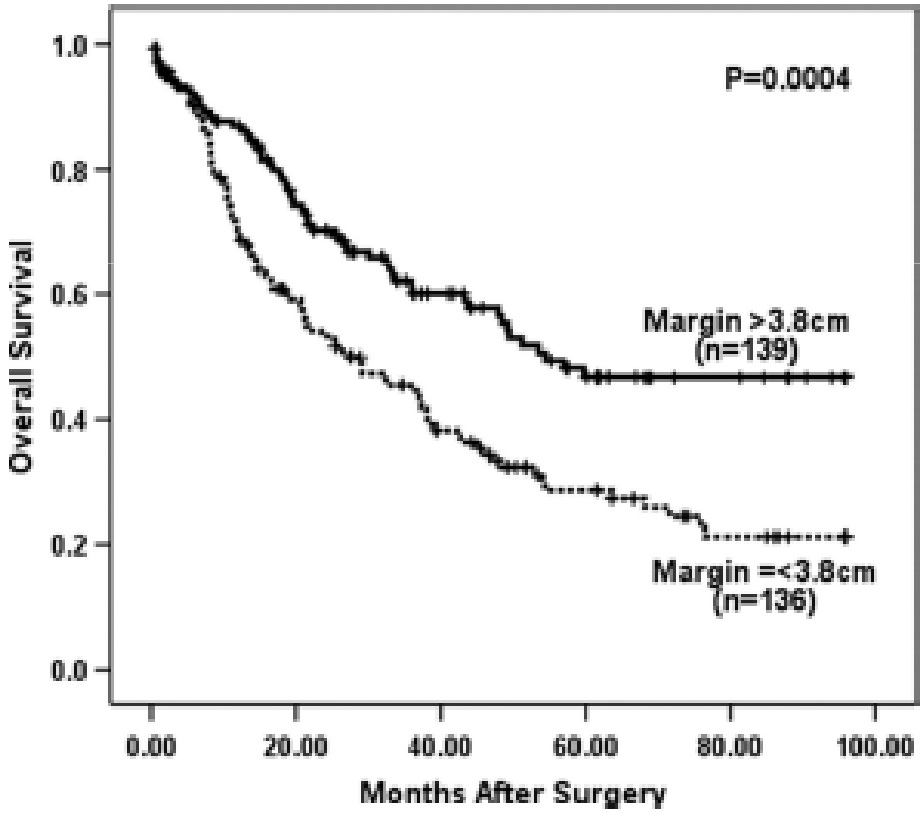
Operation Selection

Surgical Approach

Margins

Lymphadenectomy

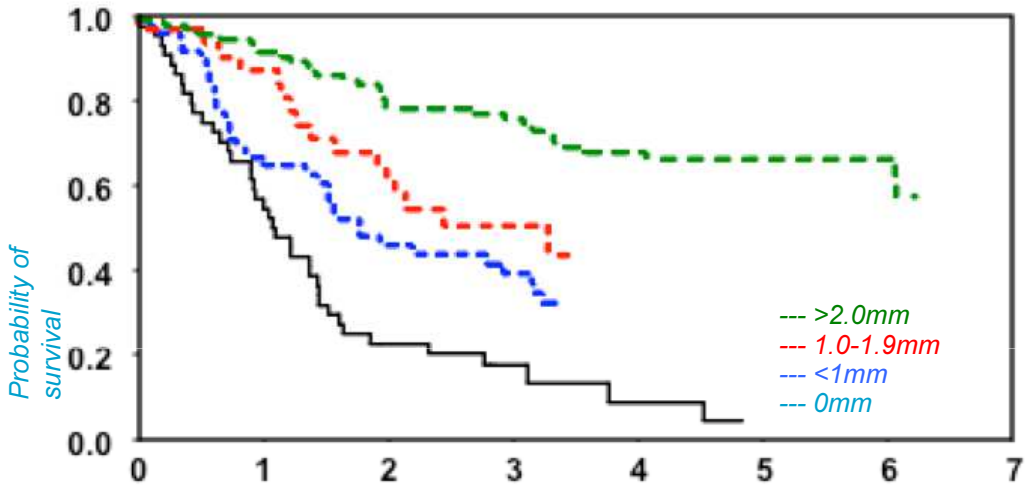
Resection Margin and Survival



Barbour et al. Ann Surg 246: 1-8

Circumferential resection margin (CRM) size correlates with overall survival

Prospective database, single institution study, N = 229

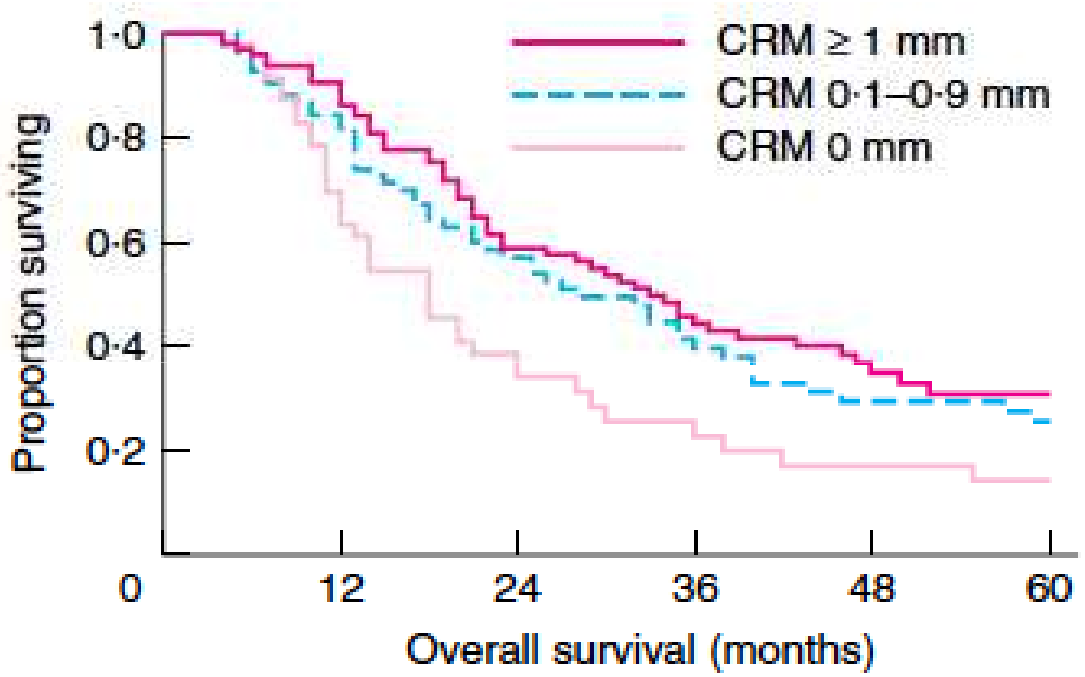


CRM	n	Median Survival (95% CI)
Positive	**45**	**1.2 yrs** (0.9-1.4)
<1mm	**48**	**1.9 yrs** (1.4-3.2)
1.0-1.9mm	**31**	**3.5 yrs** (2.0–no upper CI)
≥ 2.0mm	**105**	**Not reached**

- *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)

Survival by CRM



No. at risk			
CRM ≥ 1 mm	96	42	13
CRM 0·1–0·9 mm	83	32	13

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

OE02 update

Trial Design

Resectable carcinoma of the oesophagus

CS
Chemotherapy
and then surgery

S
Surgery alone

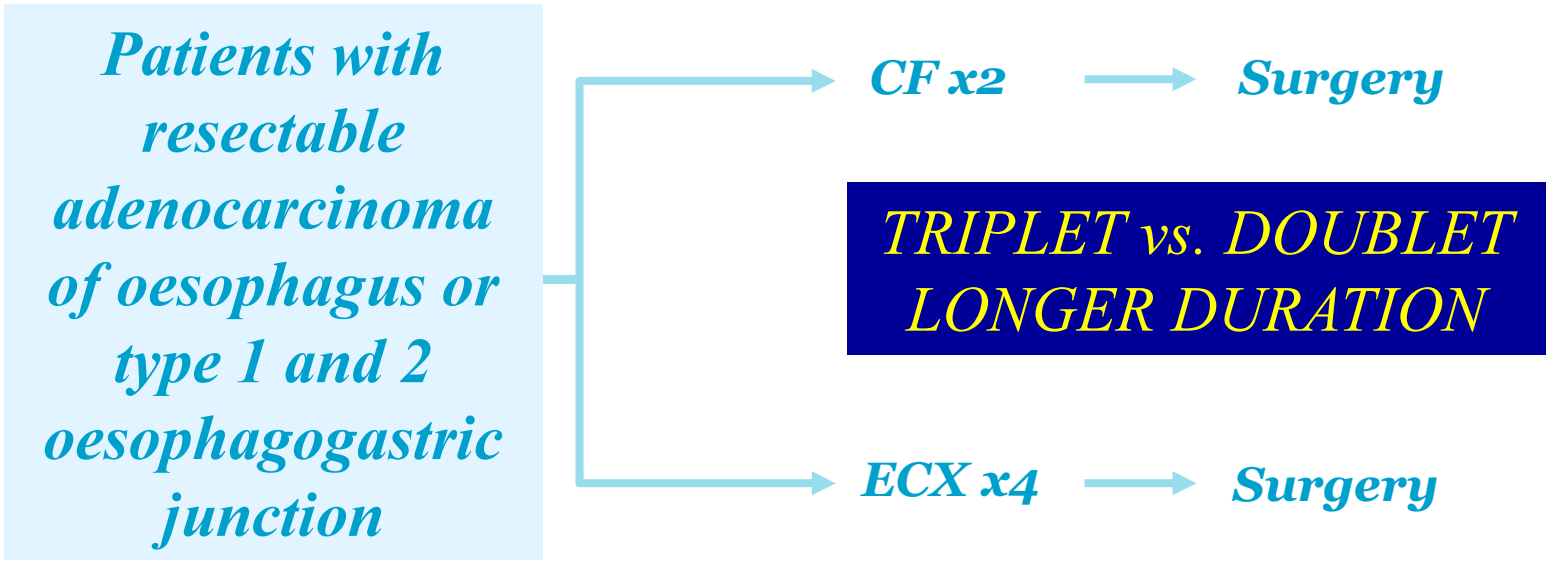
OEO2 update

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*

MRC OEO 5 trial design



- *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

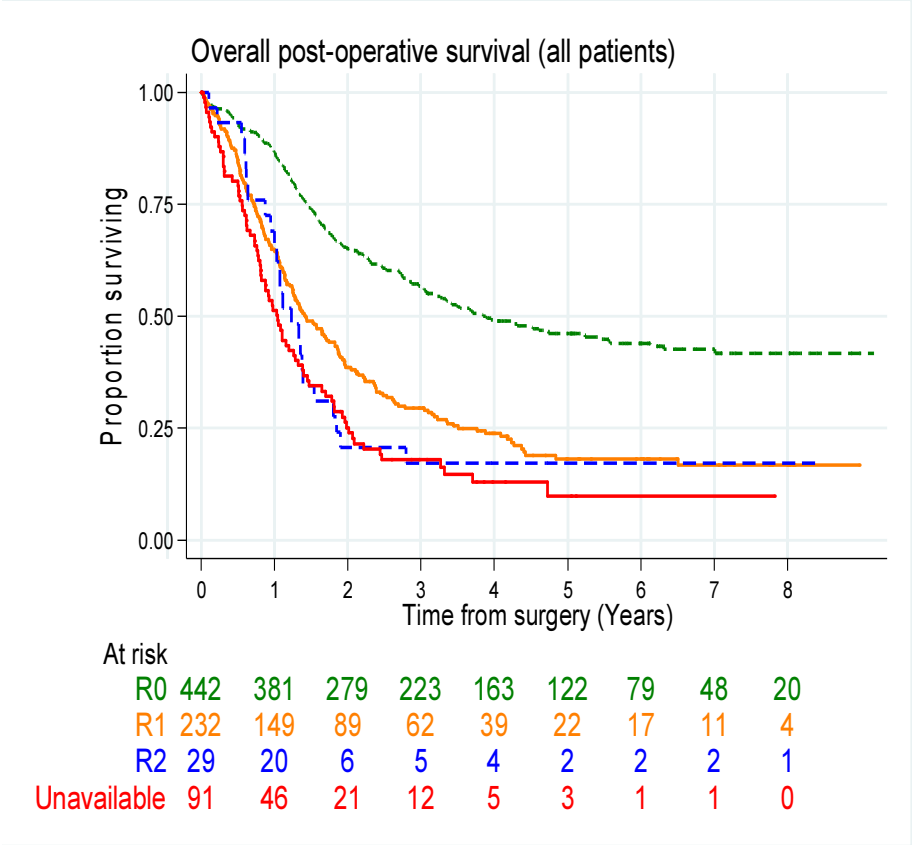
Pathology

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

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

CROSS Trial

Trial Design

Resectable carcinoma of the oesophagus

CRT
Chemo radiotherapy (Carboplatin, paclitaxel, 41.4 Gy) and surgery

S
Surgery alone

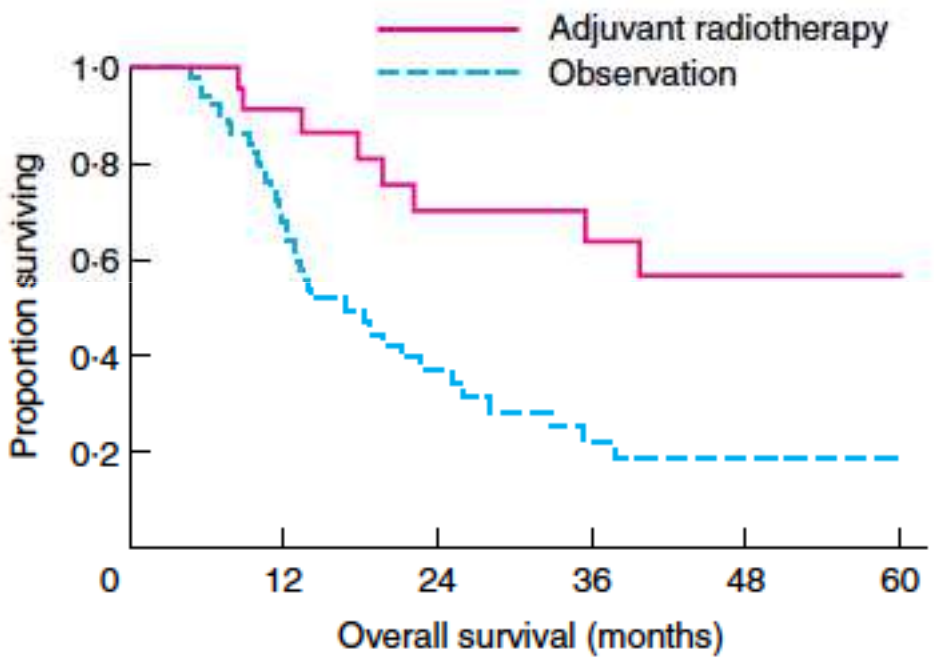
Van Hagen et al NEJM 2012;366:2074-84

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[&])				
pT-stage[§]					<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[§]					<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[#]					<0.001
R0 resection	148	(92%)	111	(69%)	
R1 resection	13	(8%)	49	(30%)	
Not available	0	(0%)	1	(1%)	

Survival after Treatment for CRM+



No. at risk			
Adjuvant radiotherapy	23	12	7
Observation	52	9	5

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

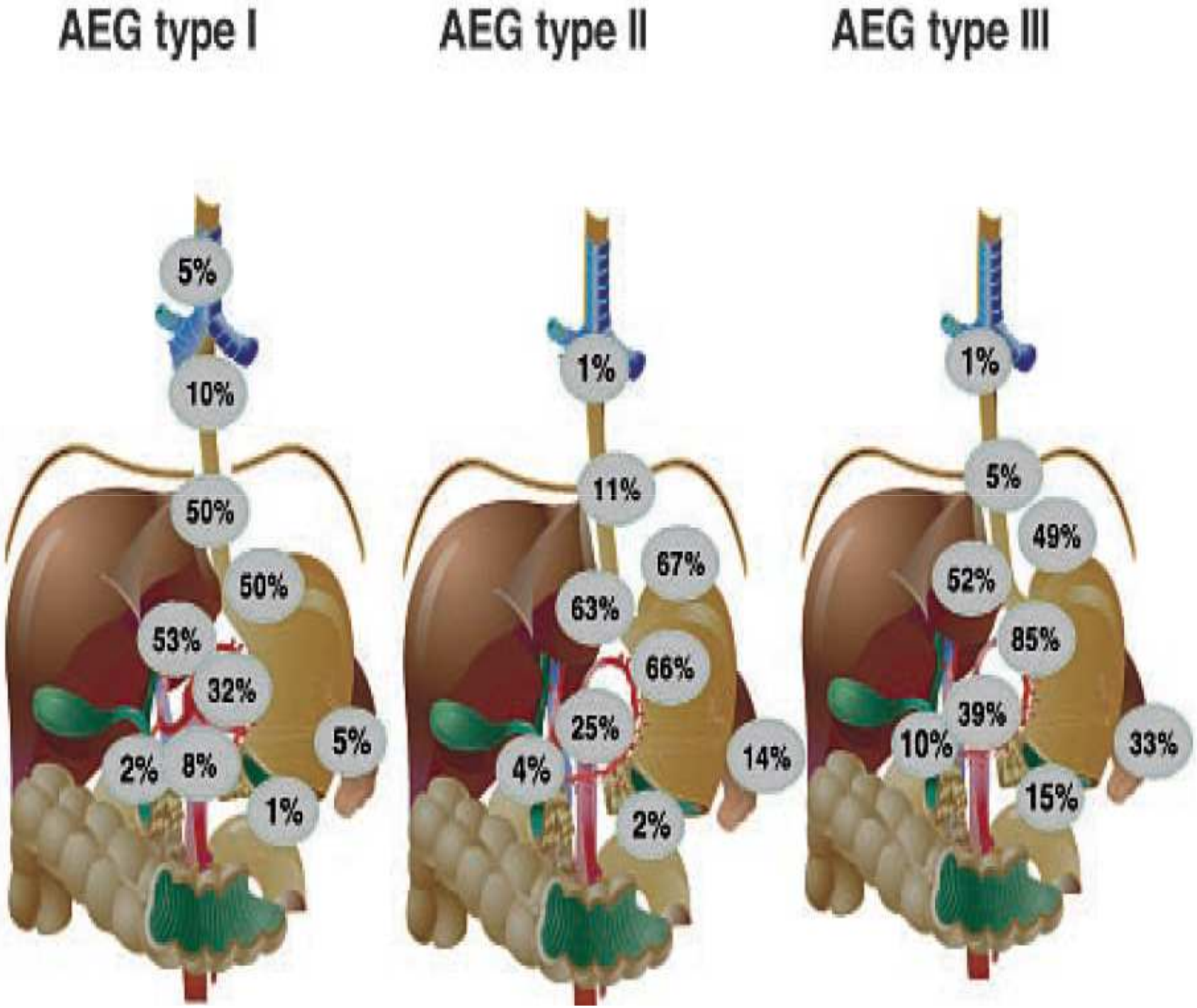
The Royal Marsden

Operation Selection

Surgical Approach

Margins

Lymphadenectomy


AEG type I
5%
10%
50%
50%
53%
32%
2%
8%
5%
1%
AEG type II
1%
11%
67%
63%
66%
25%
4%
14%
2%
AEG type III
1%
5%
49%
52%
85%
39%
10%
33%
15%

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

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

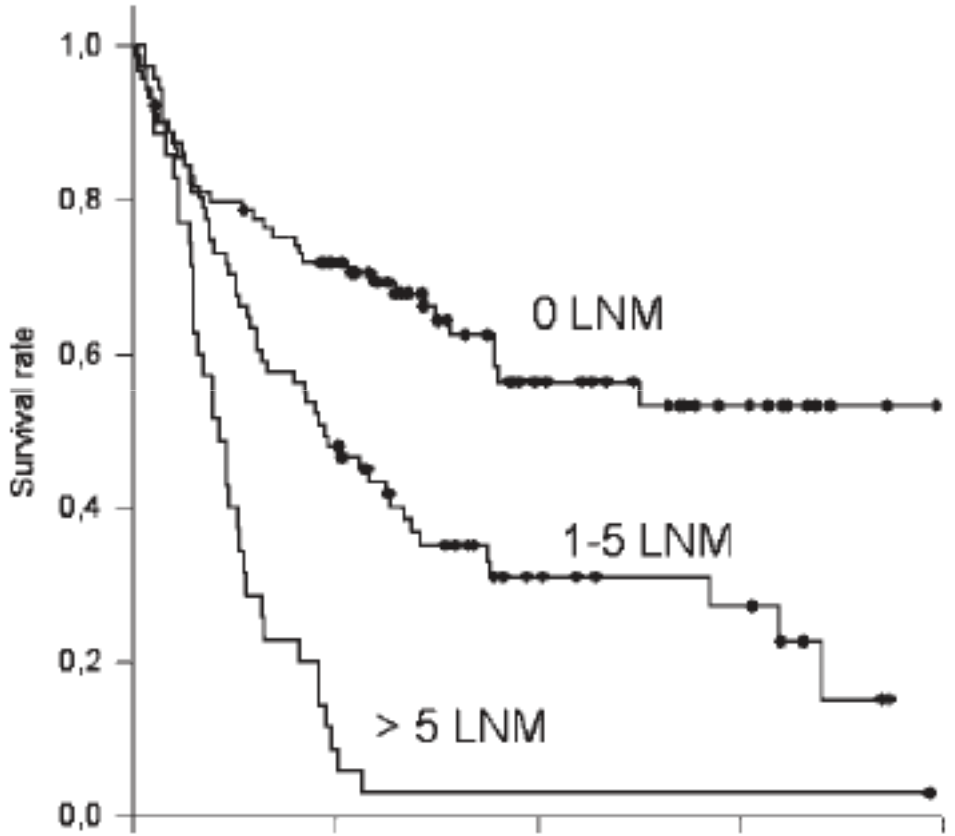
3 Field Lymphadenectomy

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	16/62	25.8	4/25	16.0
GEJ	6/36	16.7	6/34	17.6	0/2	0.0

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

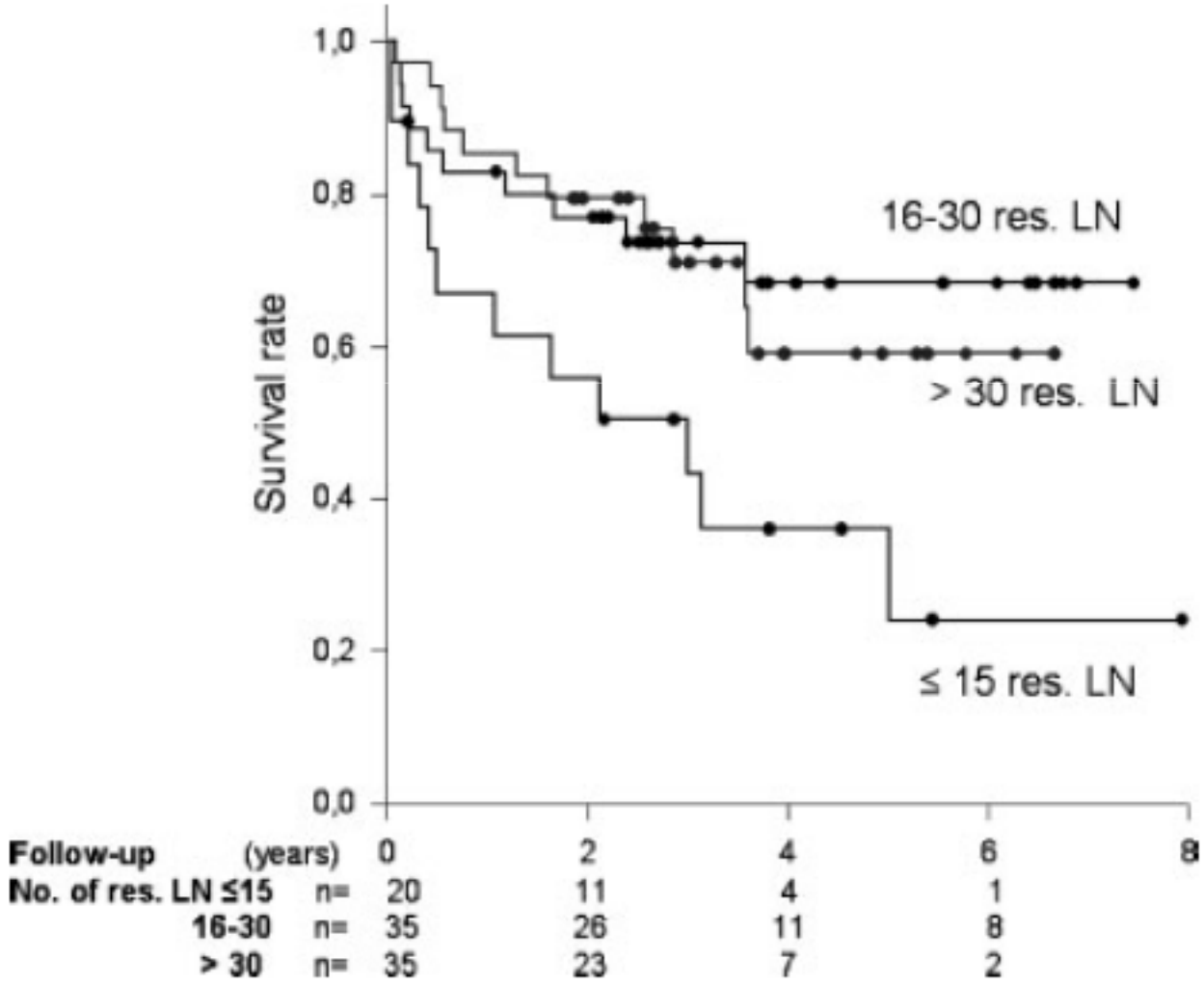
Survival by Nodal Volume



Follow-up	(years)	0	2	4	6	8
No. of LNM = 0	n=	90	64	29	17	
=1-5	n=	71	33	16	8	
> 5	n=	35	4	1	1	

Bollschweiler et al 2006

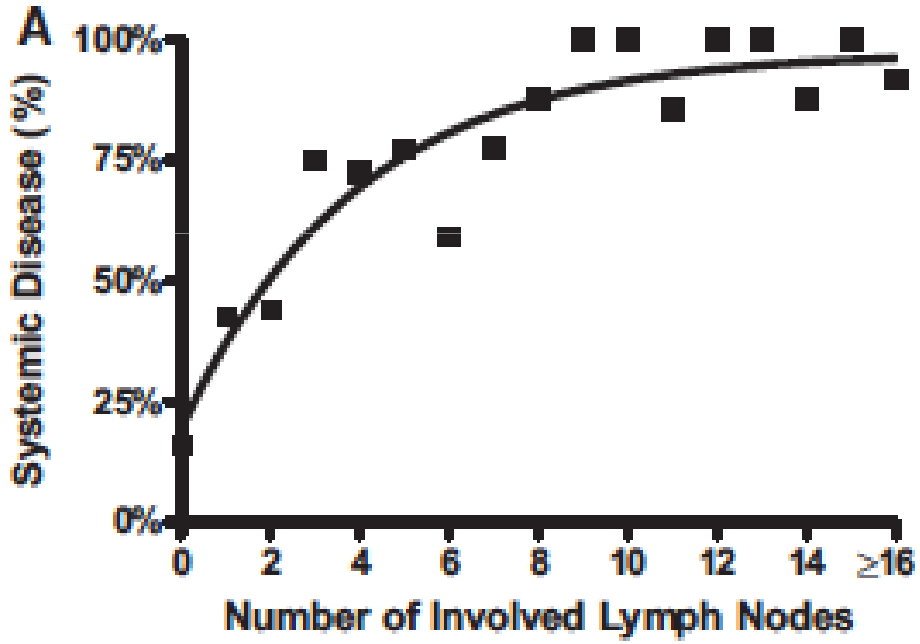
Survival by Number examined in N0 Disease



Bollschweiler et al 2006 J Surg Oncol 94:355-363

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

Health Related Quality of Life after Surgery for Junctional Cancer

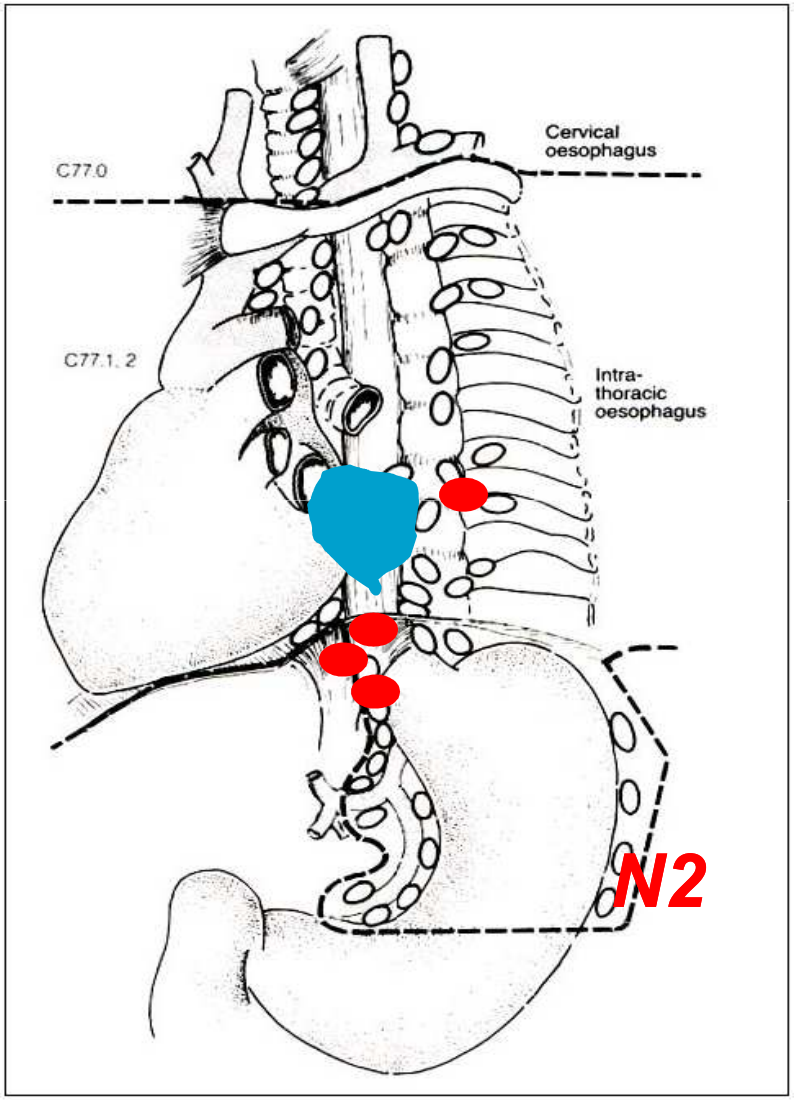
63 patients
- 20 Ext TG
- 43 TTO

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


Thank you for your attention
FULHAM ROAD


Cervical oesophagus
C77.0
C77.1, 2
Intra-thoracic oesophagus
N2

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.*

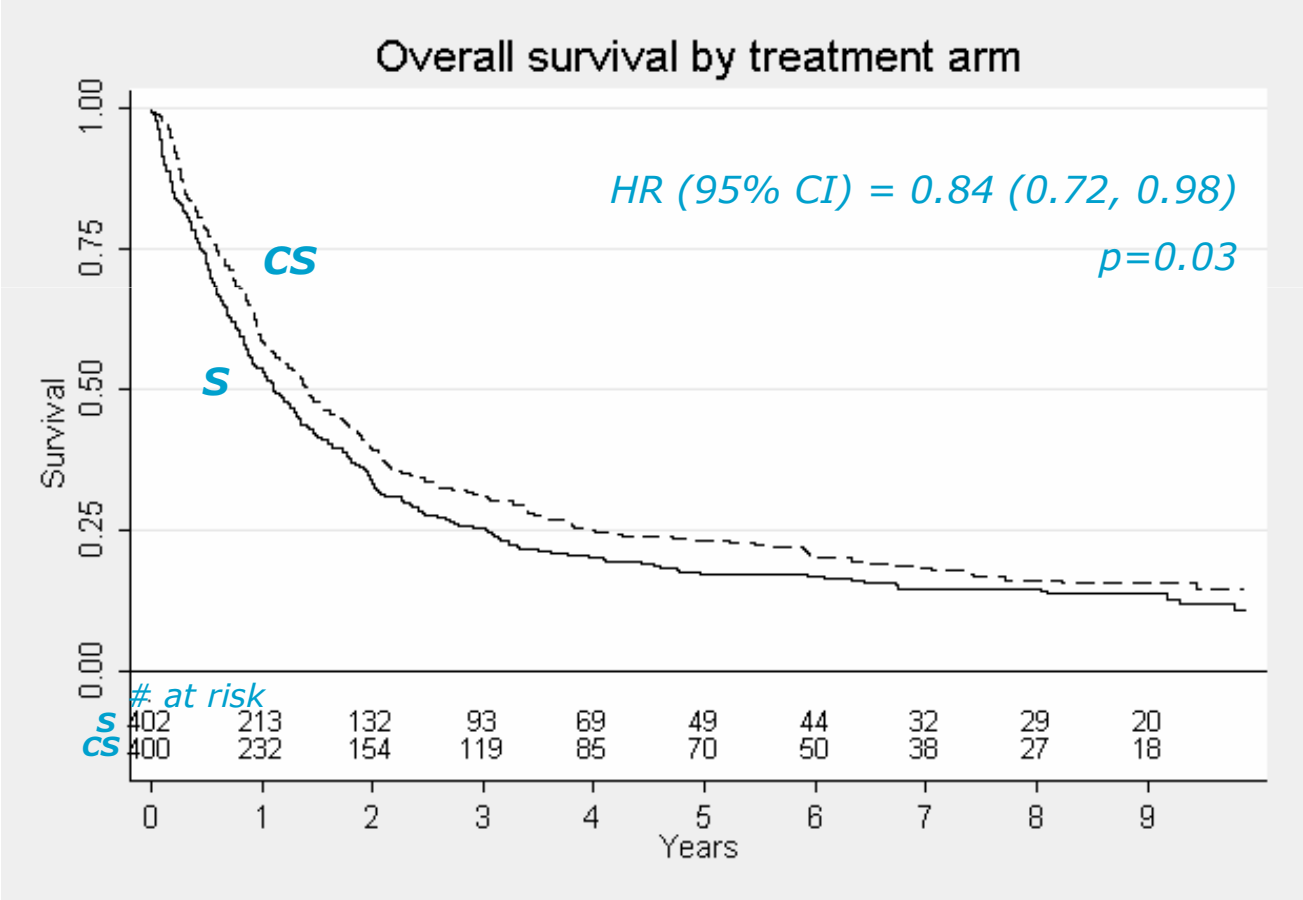
OEO2 update

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%

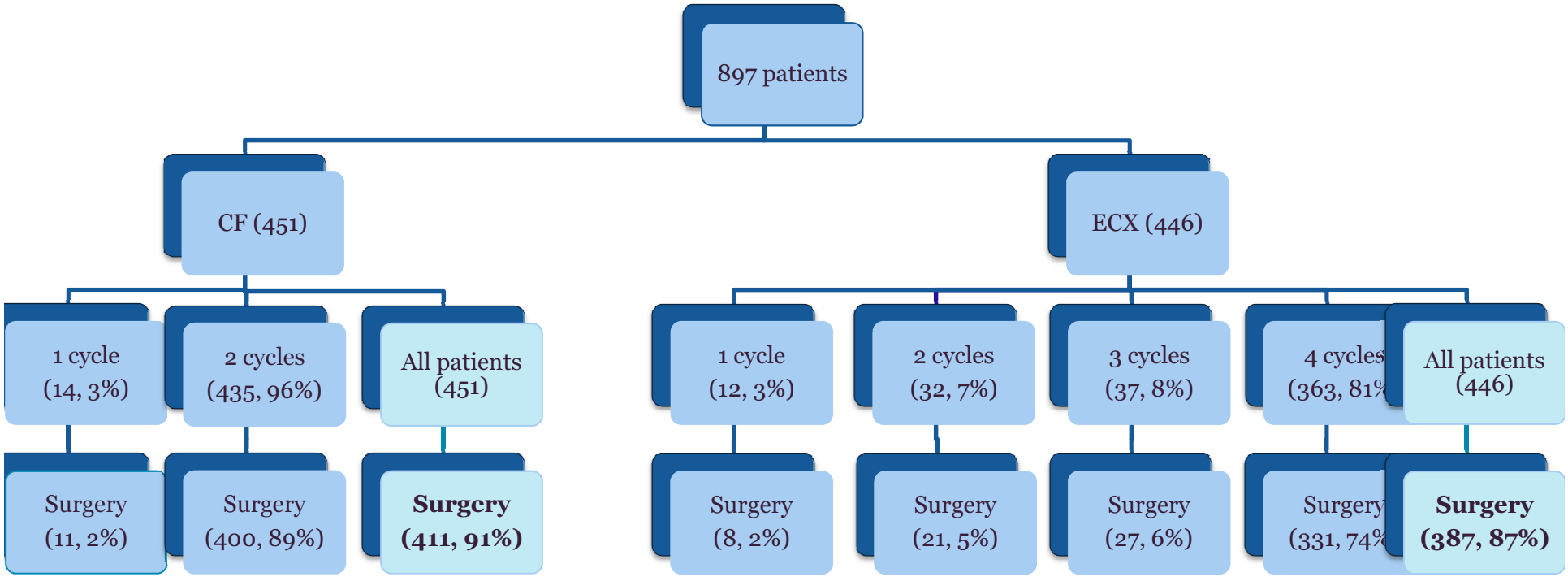
OE02 update

- 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%	

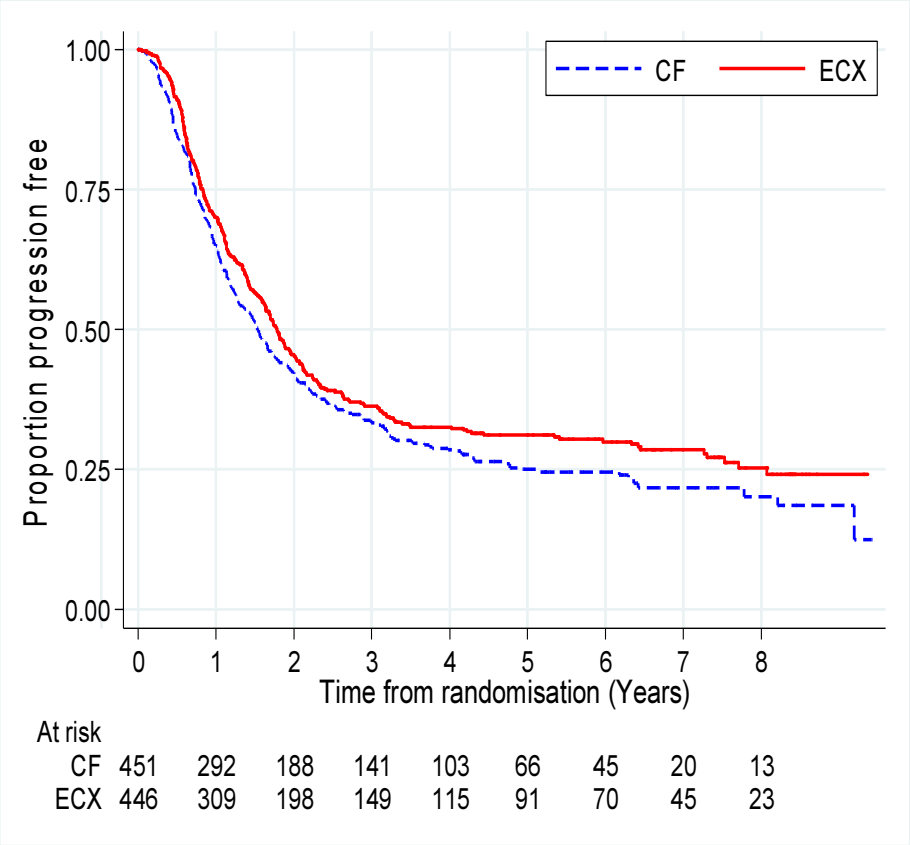
Alderson, Cunningham et al ASCO 2015

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

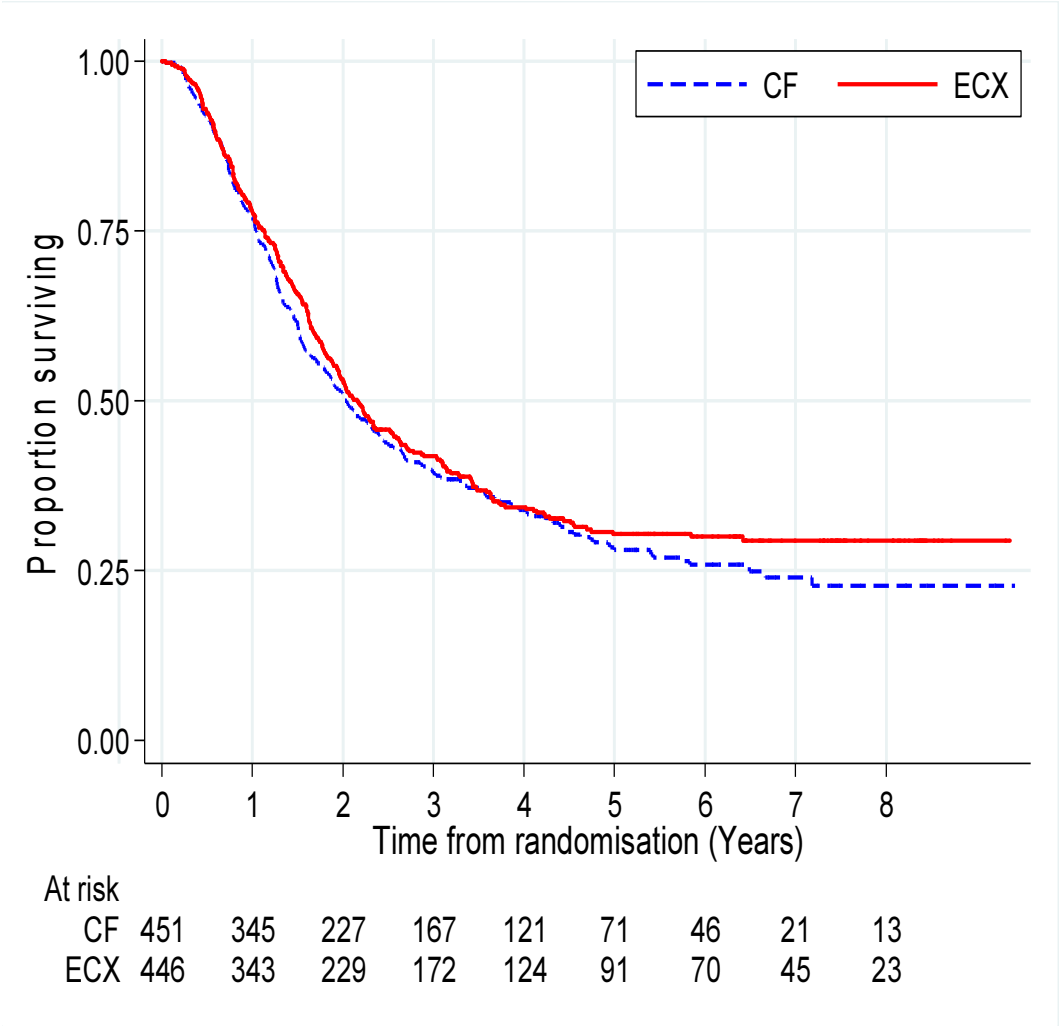
Progression free survival



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

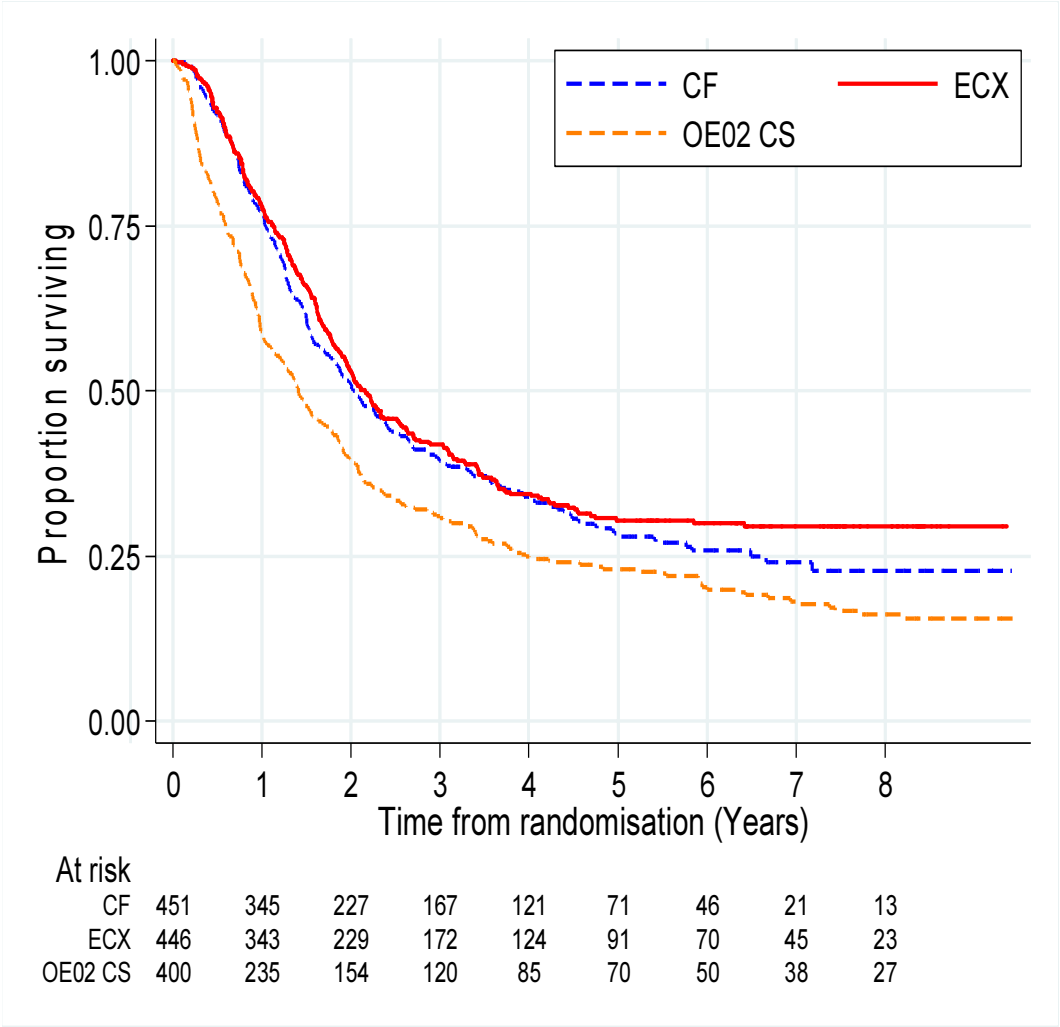
Overall survival



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%)

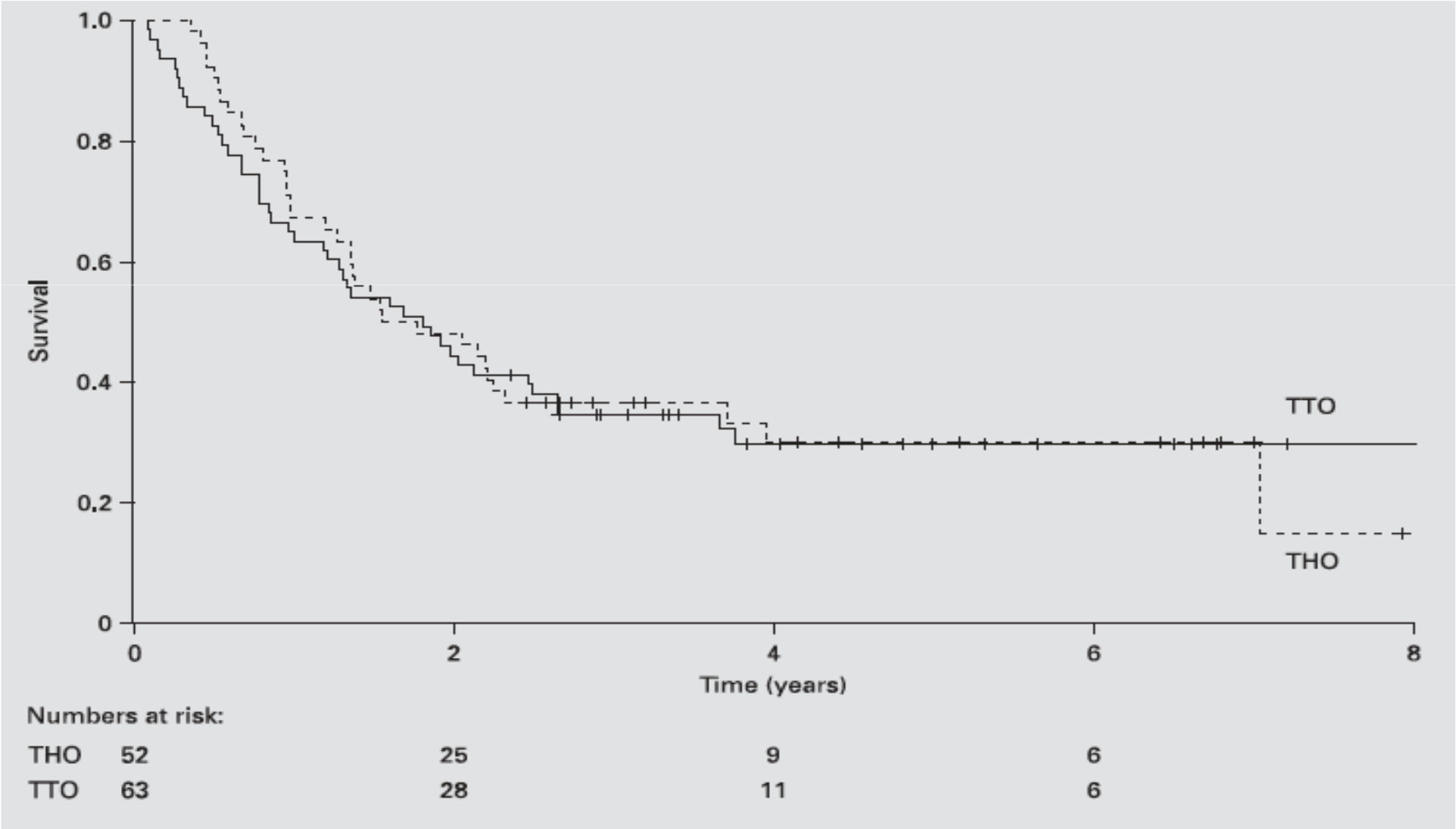
Alderson, Cunningham et al ASCO 2015

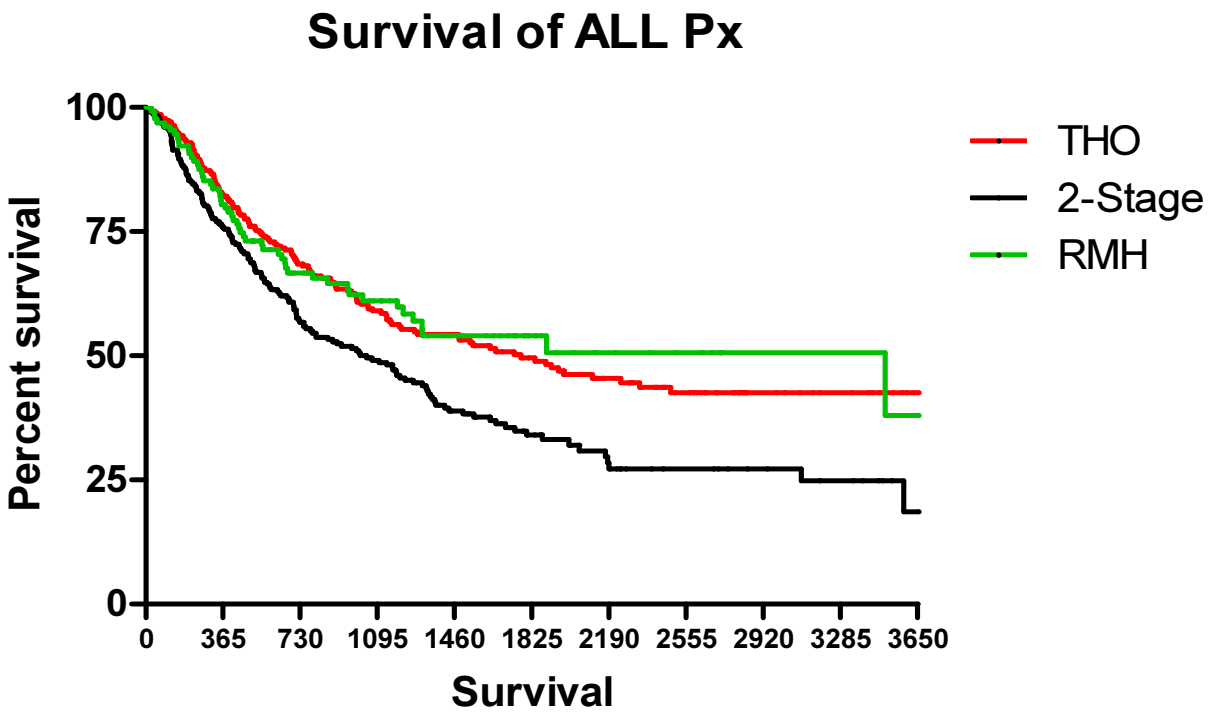
Dutch Trial

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



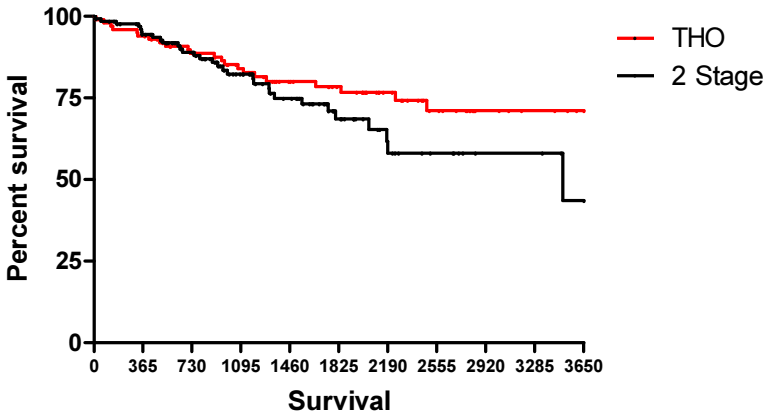


Median Survival

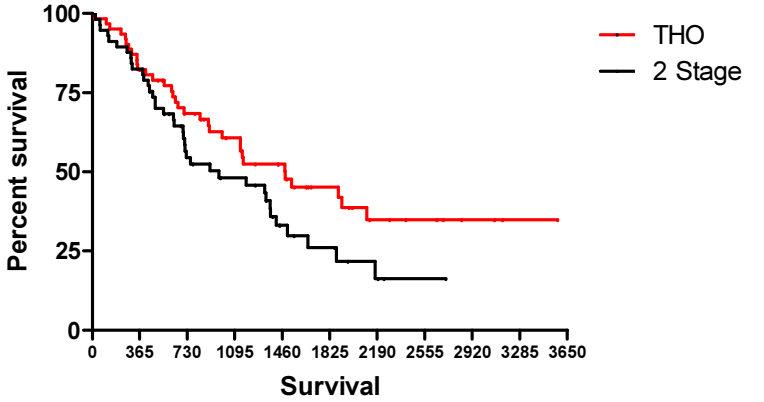
RMH	*54 months*
THO	*49 months*
2 ST	*34 months*

P < 0.0005

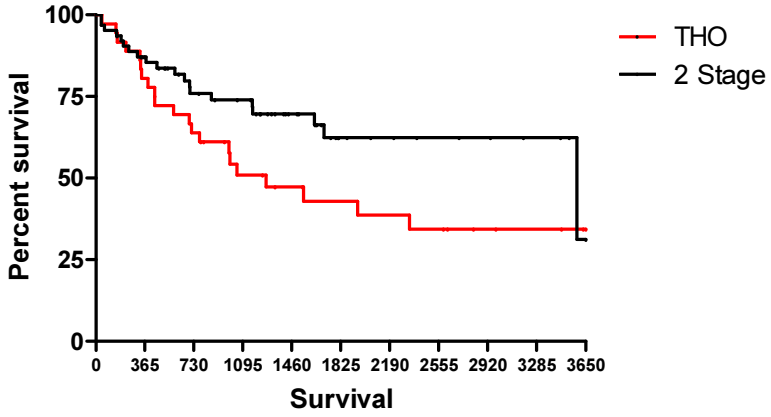
Survival of THO vs 2-ST ALL T1-2 N0:Survival proportions



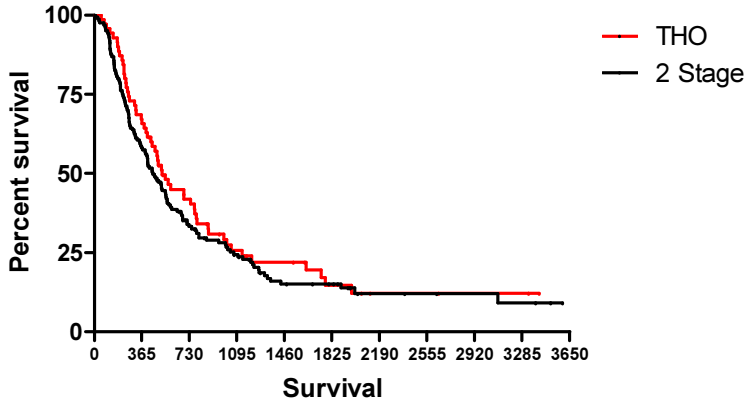
Survival of THO vs 2-ST ALL T1-2 N+:Survival proportions



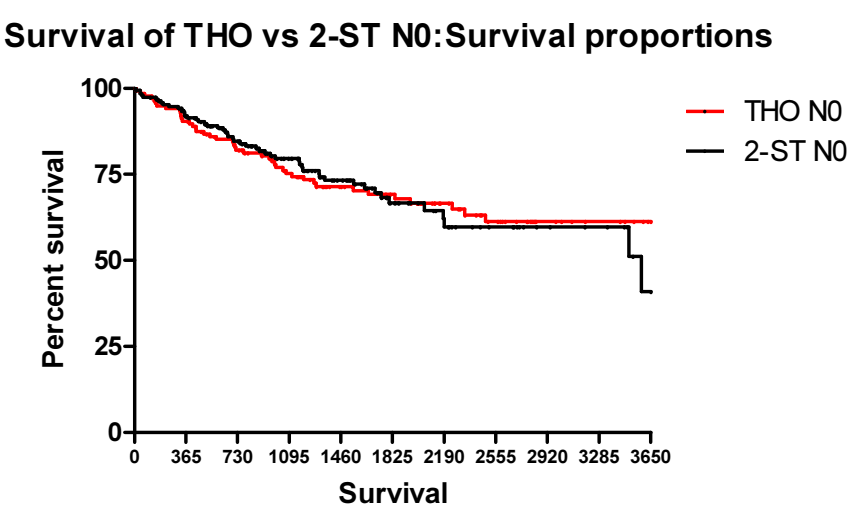
Survival of THO vs 2-ST ALL T3-4 N0:Survival proportions

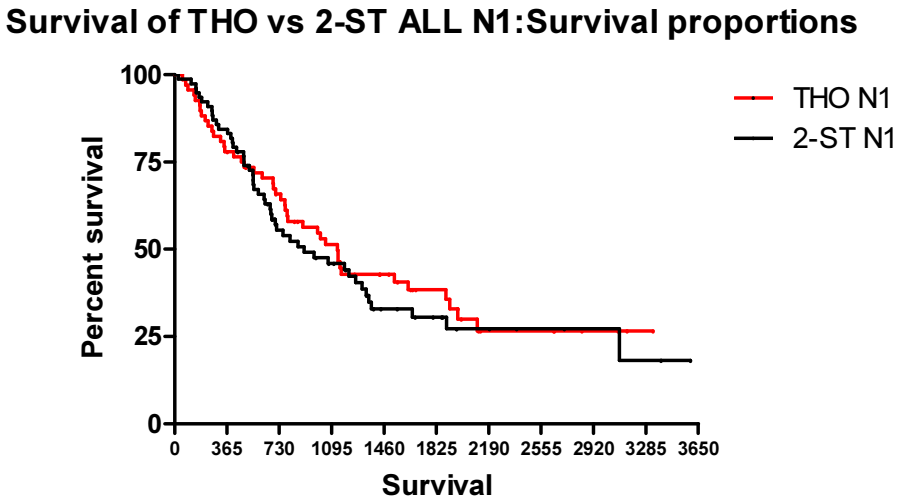


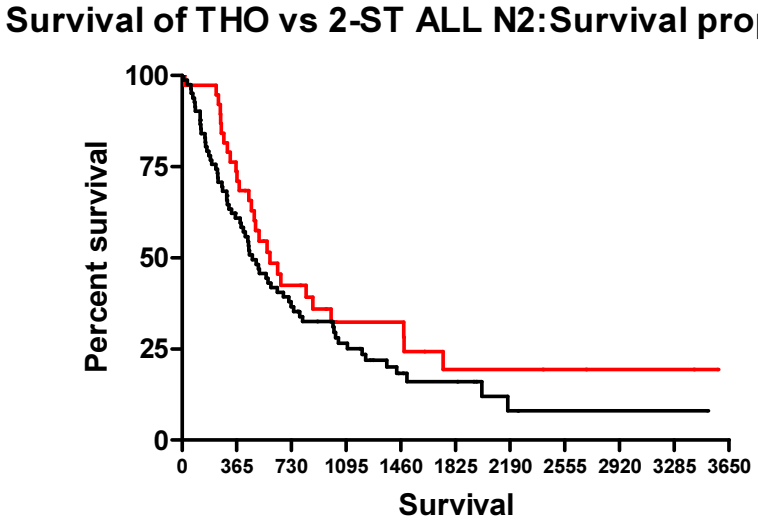
Survival of THO vs 2-ST ALL T3-4 N+:Survival proportions

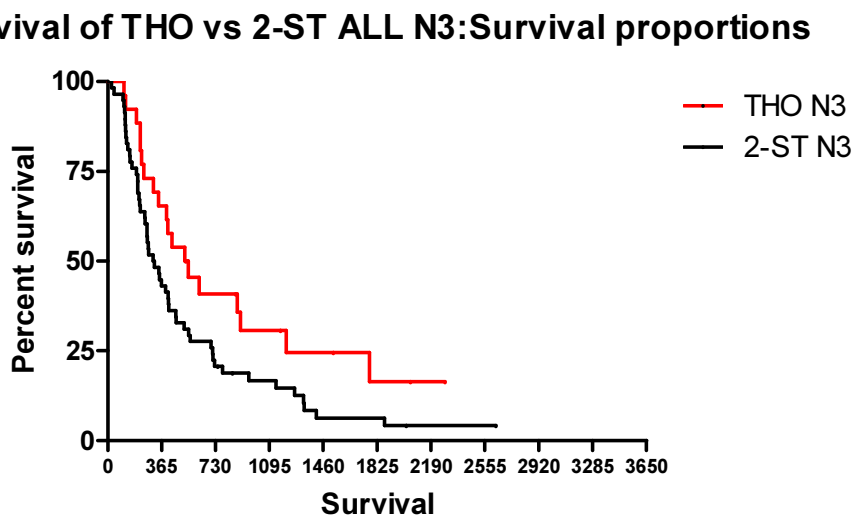


$P = ns$


Survival of THO vs 2-ST N0:Survival proportions
Percent survival
100
75
50
25
0
0 365 730 1095 1460 1825 2190 2555 2920 3285 3650
Survival
THO N0
2-ST N0

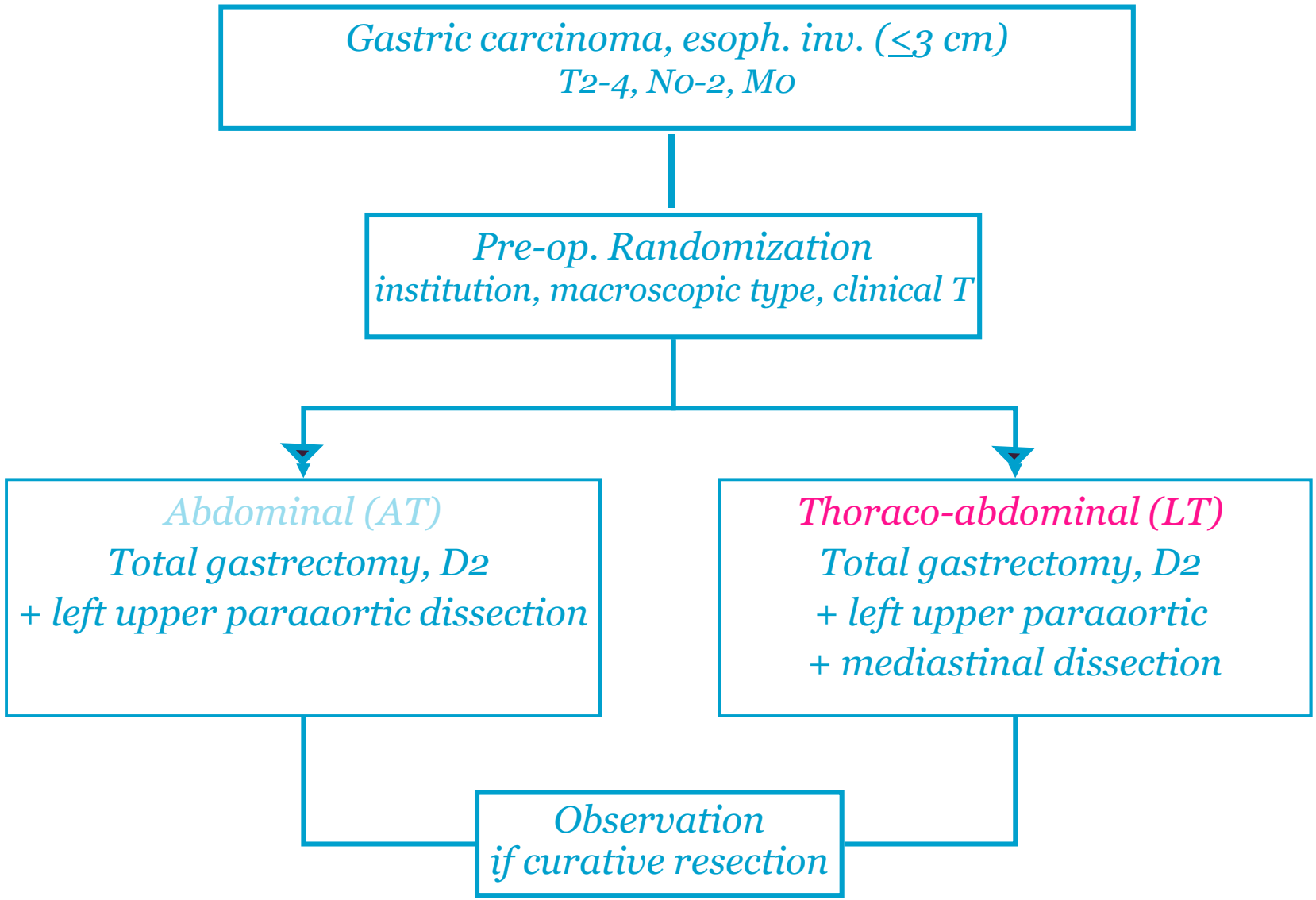

Survival of THO vs 2-ST ALL N1:Survival proportions
Percent survival
100
75
50
25
0
0 365 730 1095 1460 1825 2190 2555 2920 3285 3650
Survival
THO N1
2-ST N1


Survival of THO vs 2-ST ALL N2:Survival proportions
Percent survival
100
75
50
25
0
0 365 730 1095 1460 1825 2190 2555 2920 3285 3650
Survival
THO N2
2-ST N2

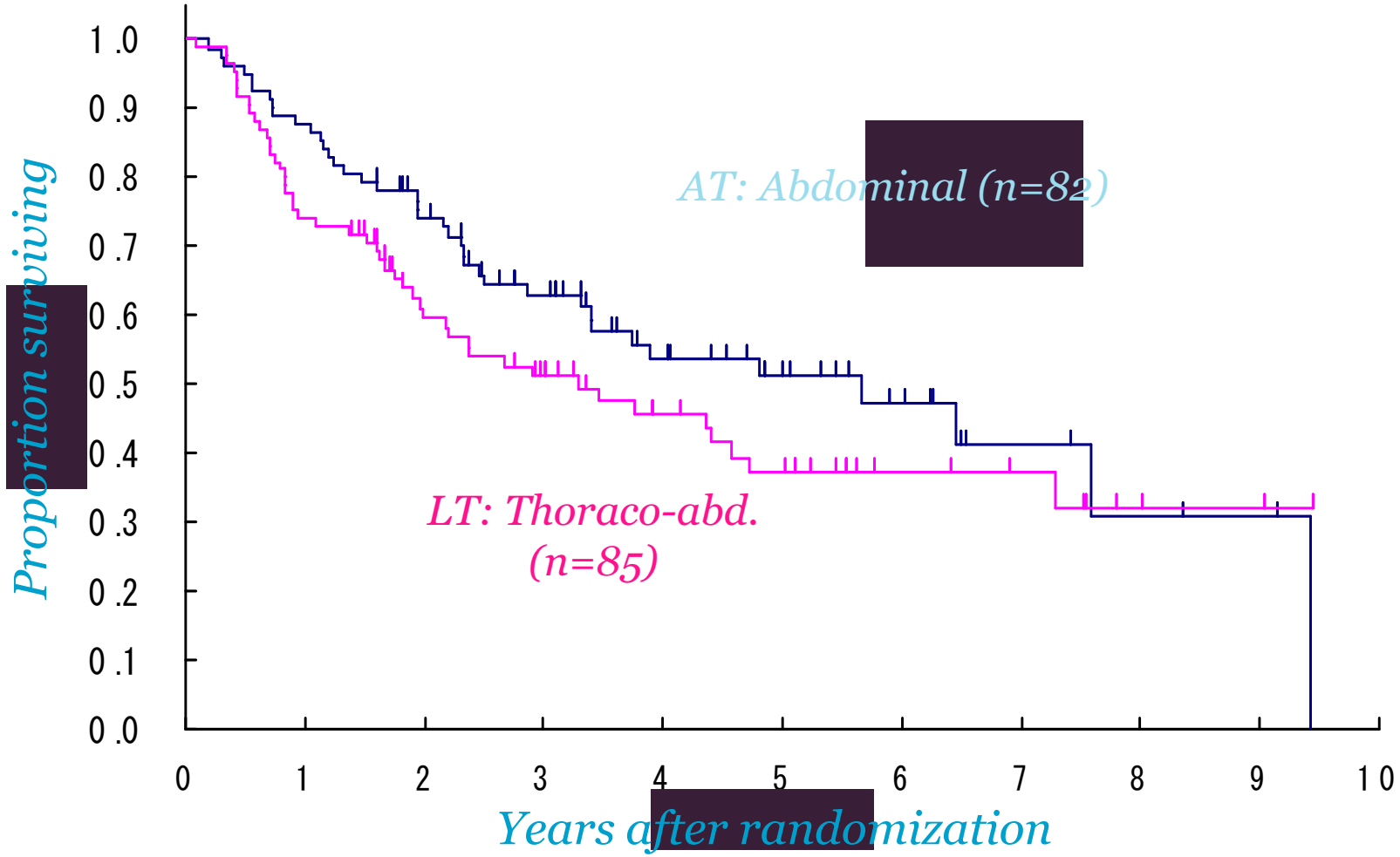

Survival of THO vs 2-ST ALL N3:Survival proportions
Percent survival
100
75
50
25
0
0 365 730 1095 1460 1825 2190 2555 2920 3285 3650
Survival
THO N3
2-ST N3

$P = ns$

JCOG 9502: Scheme



Overall Survival



Sasako M. Lancet Oncol 2006

Conclusions of JCOG 9502

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

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

Aim of Surgery for Junctional Cancer

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

Surgical Options According to Type

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

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%

Upper GI: technical and clinical challenges for RO

State of art of radiation therapy

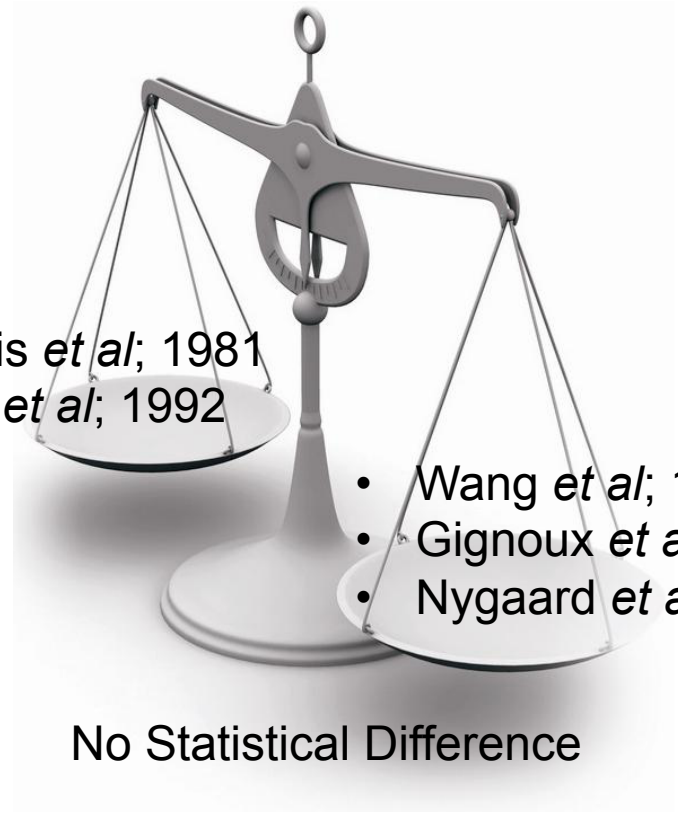
in a combined treatment perspective

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

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

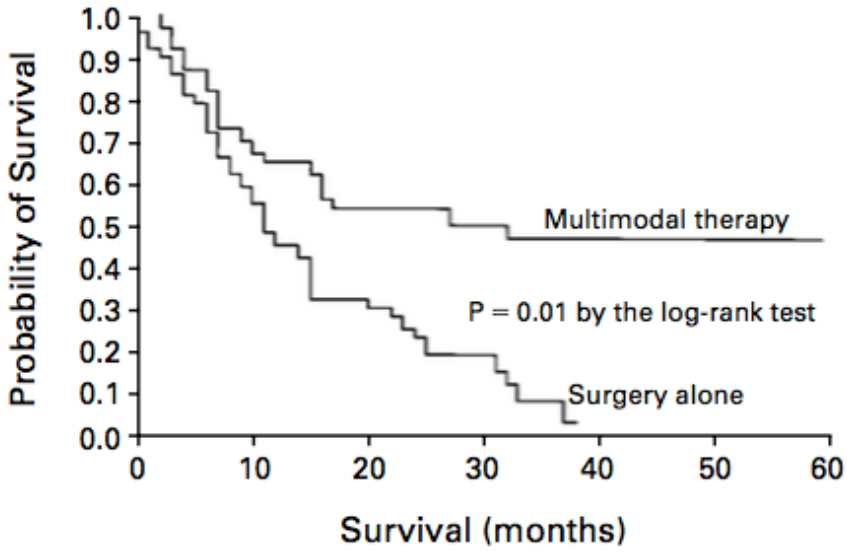
✓ **Preoperative** Chemoradiation → **Planned Esophagectomy**

✓ **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%
- Walsh et al – 1996 (Trimodality) 113 pts Adeno 100%
- Walsh et al – 1996 (Trimodality) **SVV Benefit**



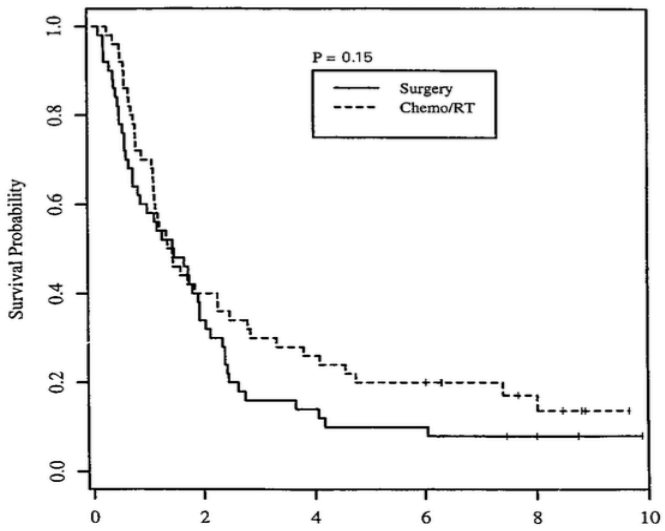
RTCT (3DCRT): 40 Gy (2.7 Gy fx) + 5Fu/CDDP

Walsh *et al*; N Engl J Med 1996

ESTRO School

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

- Urba et al – 2001 (Trimodality) Stage: n.a. Mid-Distal= 92%
- Urba et al – 2001 (Trimodality) 100 pts Adeno 75%
- Urba et al – 2001 (Trimodality) **NO SVV Benefit**

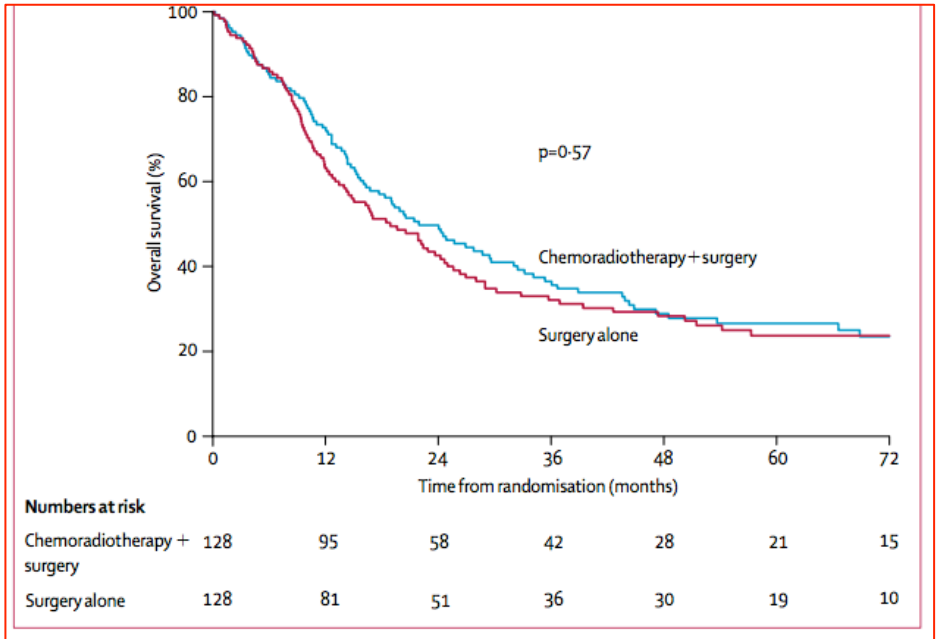


RTCT (3DCRT): 45 Gy (1.5 Gy fx x 2/day) + 5Fu/CDDP/Vimblastine

Urba *et al*; JCO 2001

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

- Burmeister et al – 2005 (Trimodality) Stage: n.a. Mid-Distal= 79%
- Burmeisteret al – 2005 (Trimodality) 256 pts Adeno 62%
- Burmeister et al – 2005 (Trimodality) **NO SVV Benefit**



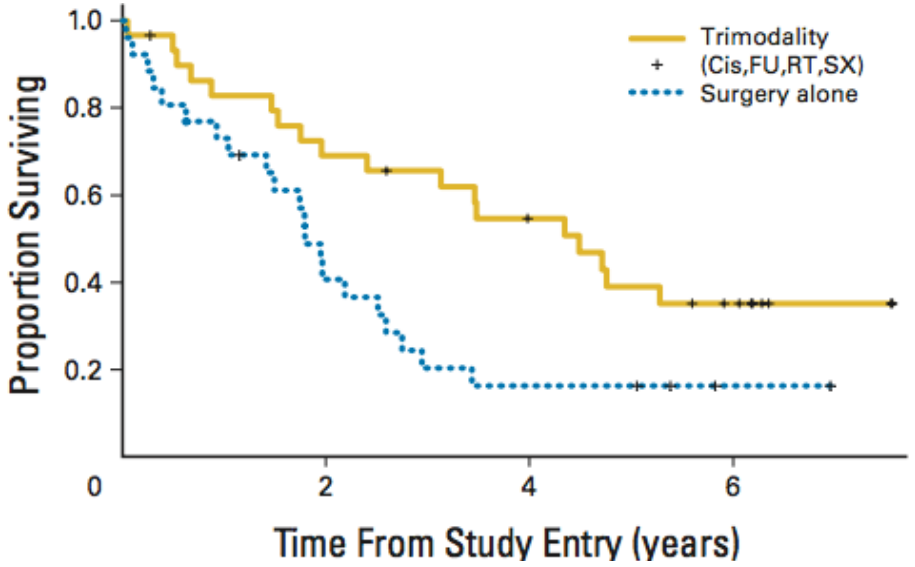
RTCT (Simulator): 35 Gy (2.4 Gy fx) + 5Fu/CDDP

Burmeister *et al*; Lancet Oncol 2005

ESTRO School

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

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



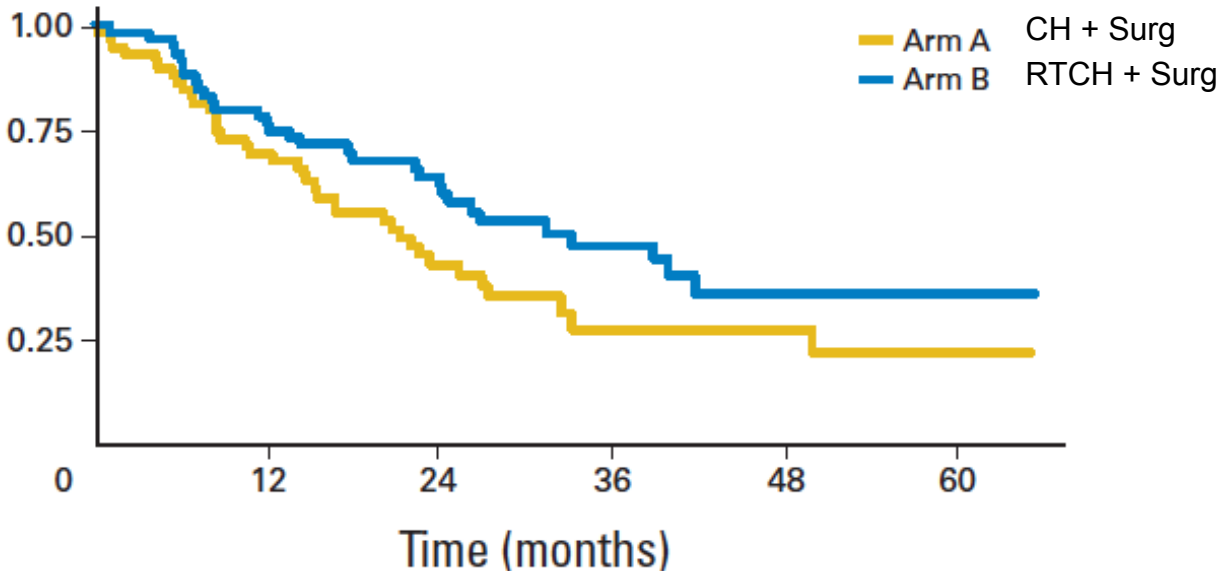
RTCT: 50.4 Gy (1.8 Gy fx) + 5Fu/CDDP

Tepper *et al*; JCO 2008

ESTRO School

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

- POET - 2009 (Trimodality) uT3-4NXM0 Siewert I-III= 100%
- POET - 2009 (Trimodality) 126 pts **(326 planned)** Adeno 100%
- POET - 2009 (Trimodality) **NO SVV Benefit**



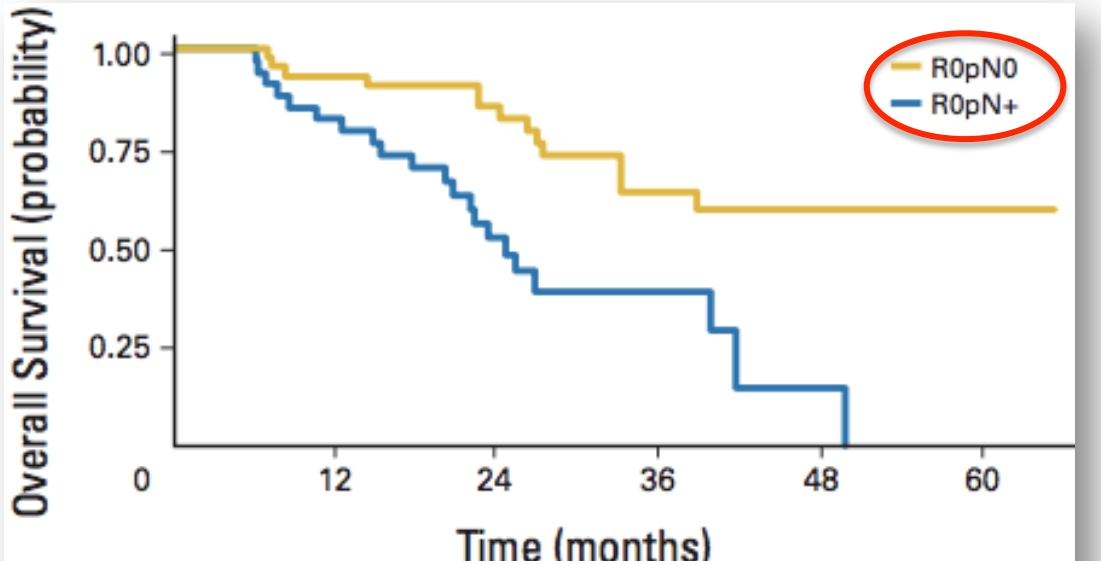
RTCT (Simulator): 2PLF + 30 Gy (2 Gy fx) + CDDP/Etoposide

Stahl *et al*; JCO - 2009

ESTRO School

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

- POET - 2009 (Trimodality) uT3-4NXM0 Siewert I-III= 100%
- POET - 2009 (Trimodality) 126 pts **(326 planned)** Adeno 100%
- POET - 2009 (Trimodality) **NO SVV Benefit**



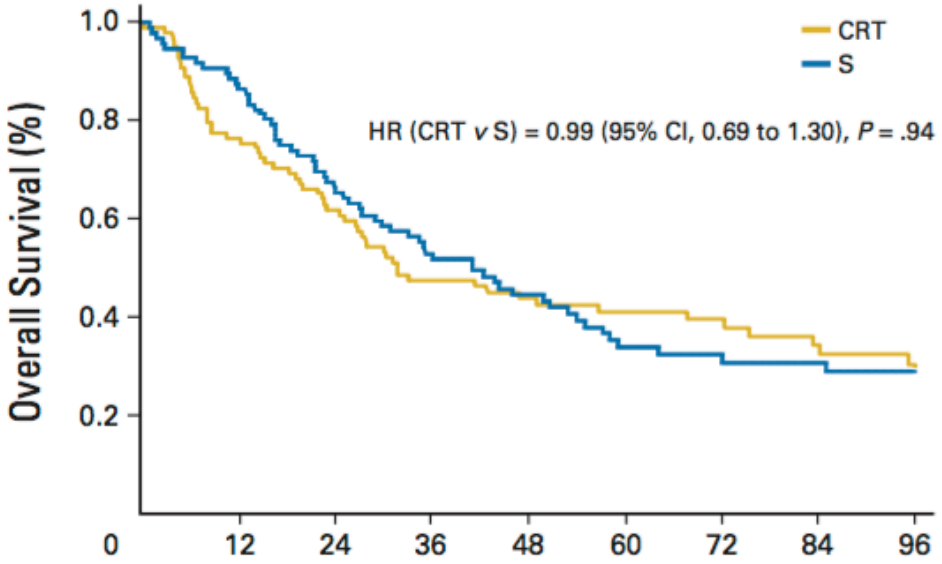
- Significant improvement of pCR (2 vs 15.6%; p=0.03) favoring RTCT
- Significant improvement of pN0 (36.7 vs 64.4%; p=0.03) favoring RTCT

Stahl *et al*; JCO - 2009

ESTRO School

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

- FFCD 9901 - 2014 (Trimodality) Stage I-II Below carina= 91%
- FFCD 9901 - 2014 (Trimodality) 194 pts Adeno 29%
- FFCD 9901 - 2014 (Trimodality) **NO SVV Benefit**



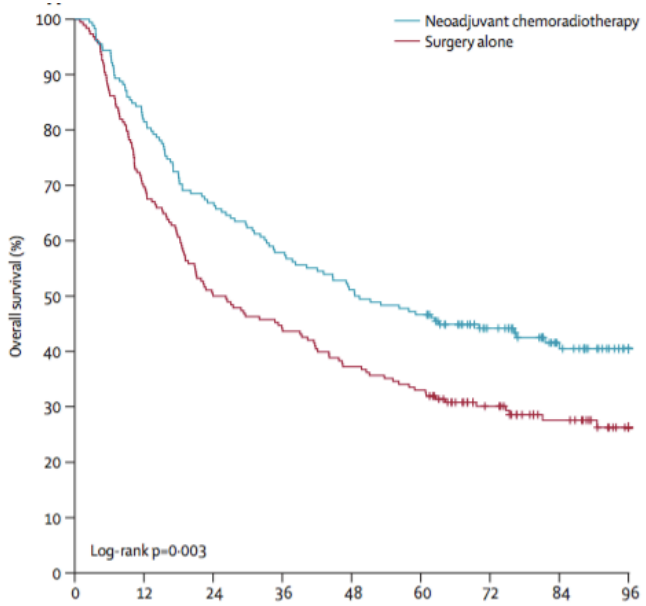
RTCT: 45 Gy (1.8 Gy fx) + 5FU + Platinum

Mariette *et al*; JCO - 2014

ESTRO School

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

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



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

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

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

	N° Pts	Accrual	Rate adeno	Tumor site	Dose/Fx (Gy)	Concurrent CT	3 yy OS % [RTCT+ surg vs. surg alone]	5 yy OS % [RTCT+ surg vs surg alone]	Median SVV (mth) [RTCT+ surg vs surg alone]	Median fup (mth)
Walsh [43]	113	1990-1995	100%	Middle+ Lower Esophagus + Cardias	40/2.7	CDDP + 5Fu	32 vs. 6 (p=0.01)	-	16 vs 11	10 (0.1-59)
Urba [46]	100	1989-1994	75%	Proximal+ Middle + Lower Esophagus + GEJ	45/1.5 (twice daily)	CDDP+ 5Fu+ Vimblastine	30 vs. 16 (p=0.15)	-	16.9 vs 17.6	98.4 (72-118.8)
Burmeister [48]	256	1994-2000	62%	Proximal +Middle+ Lower Esophagus	35/2.4	CDDP + 5Fu	42 vs. 36 (p=0.57)	21 vs. 19	22.2 vs. 19.3	65 (0.4-120)
Tepper [49]	56	1997-2000	75%	Toracic Esophagus (below 20 cm)+ GEJ <2cm distal spread in cardia	50.4/1.8	CDDP + 5Fu	-	39 vs. 16 (p=0.002)	53.8 vs. 21.5	72 (NR)
Van Hagen [50]	366	2004-2008	75%	Proximal +Middle+ Lower Esophagus + GEJ	41.2/1.8	Carboplatin + Paclitaxel	58 vs. 44 (p=0.003)	47 vs. 34	49.4 vs. 24	45.4 (25.5-80.9)

Cellini *et al*; Radiat Oncol 2014

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

Meta-analyses

Author	Trials	Period	pts	SVV Benefit for TMT	Notes
Urschel 2003 [Am J Surg]	9	1992-2002	1116	1-2-3 yy SVV	3 yy SVV benefit higher for concomitant vs sequential RTCT
Fiorica 2004 [GUT]	6	1992-2001	764	3 yy SVV	↑ postoperative mortality
Arnott 2005 [IJROBP]	5	1981-1992	1147	Non significant trend at 2 and 5 yy	SCC 86%
Greer 2005 [Surgery]	6	1992-2001	738	Small non significant trend	Same trial selection Fiorica
Gebski 2007* [Lancet Oncol]	10 (18)	1982-2006	1209 (2933 Tot)	2 yy SVV	Smaller significant benefit also for NACT
Jin 2009 [World J Gastr]	11	1992-2008	1308	1-3-5 yy SVV	
Sjoquist 2011* [Lancet Oncol]	14 (24)	1983-2004	2048 (4188 Tot)	2 yy SVV	CROSS reported as Abstract
Wang 2012 [Dig Dis Sci]	12	1992-2009	1529	1-3-5 yy SVV	- SVV benefit only for concomitant RTCT - SVV benefit only for SCC
Deng 2014 [Diagn Pathol]	13	2001-2013	1930	Significant: ↓ Postop ✚ ↓ Loc Recs ↓ M+ Rates	- "postoperative efficacy" - Potential bias - CROSS Included
Fan 2016 [Thoracic Cancer]	5 (RTCT vs CT)	2007-2011	678	- Svv benefit of RTCT vs CT	- RTCT perioperative mortality and complication rates higher than CT

State of art of radiation therapy in Esophageal Cancer

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

- Walsh et al – 1996 (Trimodality) — Phase III Trial Chir ± Preop RTCT
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- 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**

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- INT 0123 - 2002 — Phase III Trial RTCT (50Gy) vs RTCT (65Gy)

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

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✓ **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

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✓Chemoradiation → or Selective Esophagectomy

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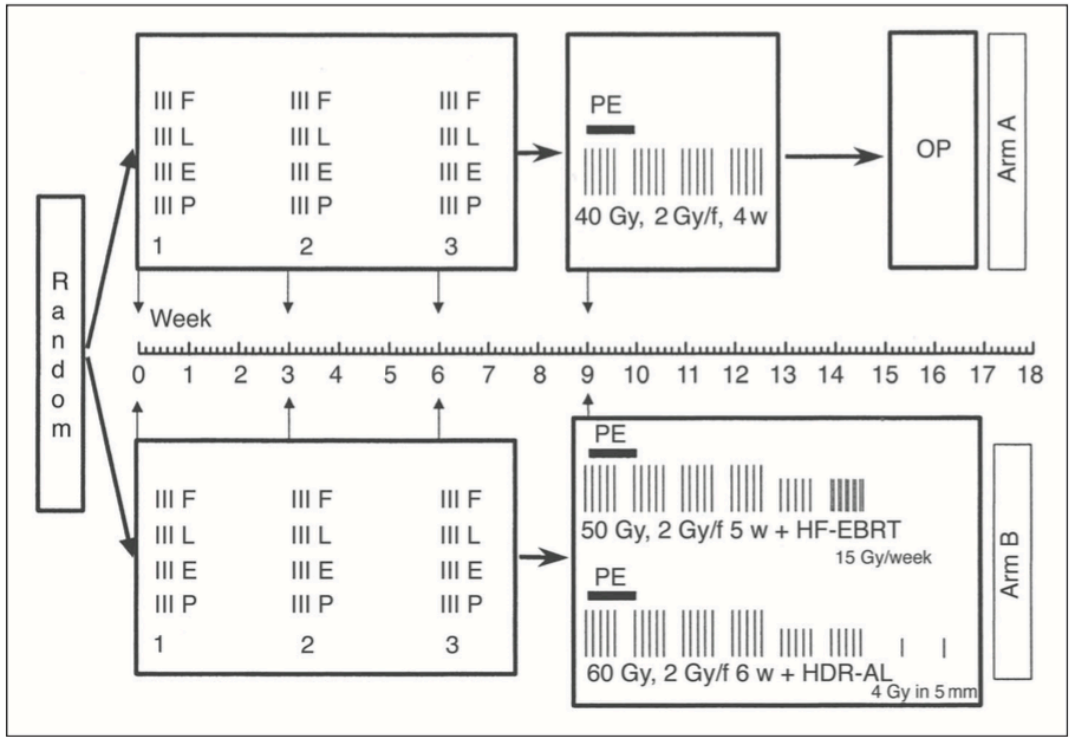

Stahl *et al*; JCO 2005

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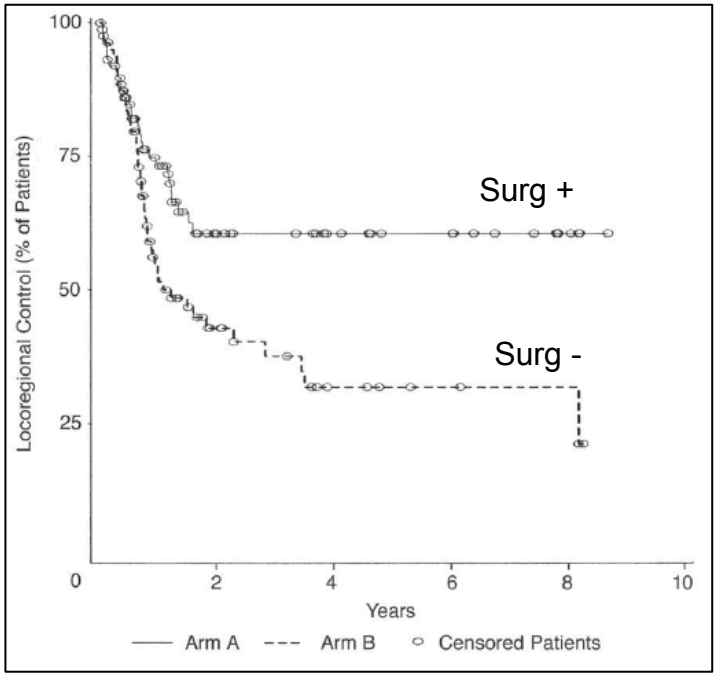
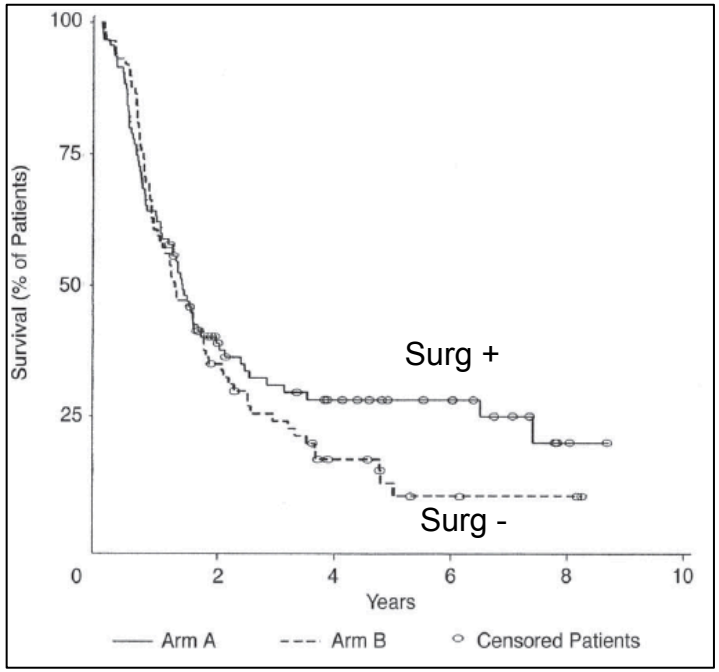
Local control



Survival



Stahl *et al*; JCO 2005

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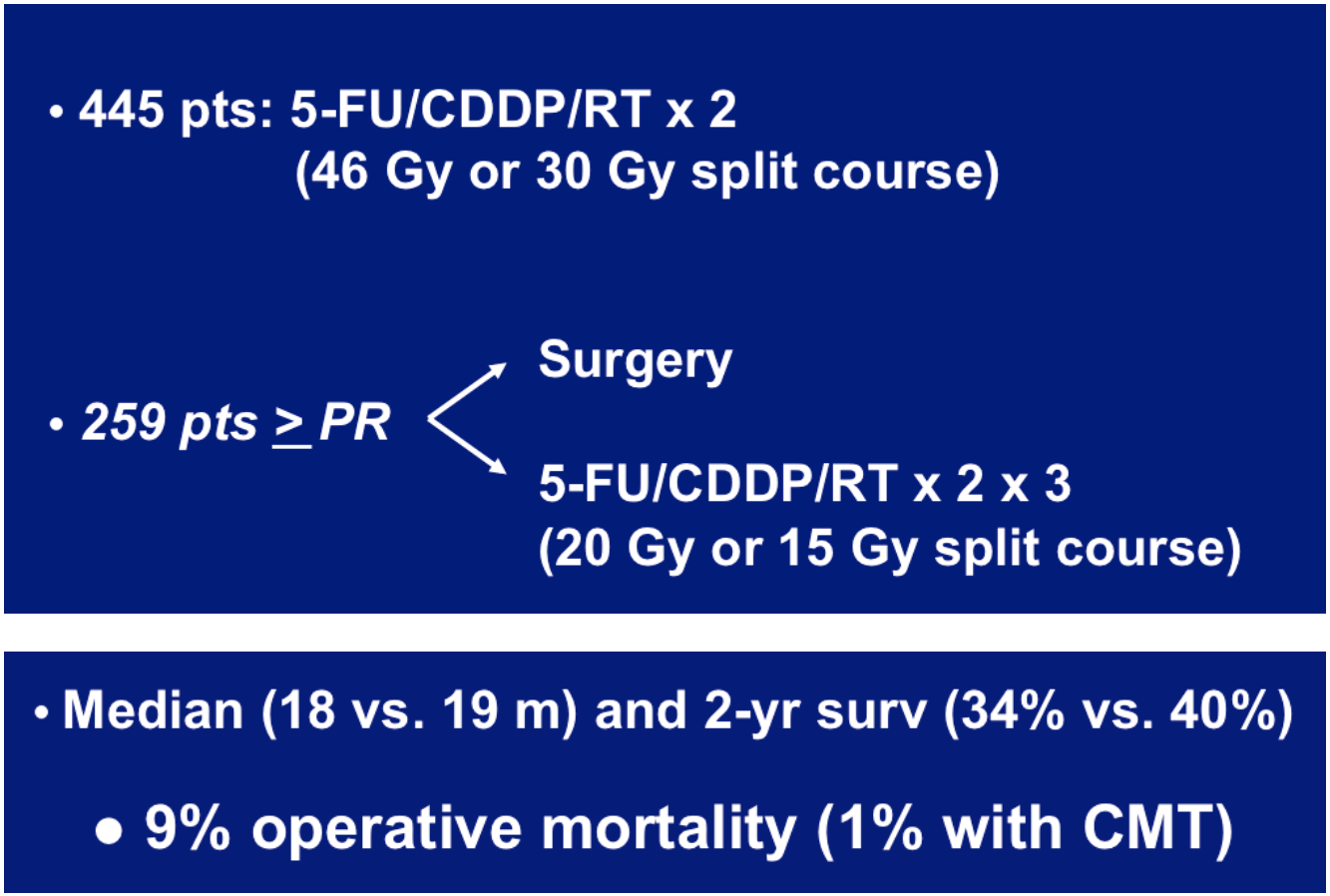
- FFCD 9102 – 2015 T3-N0/N1-M0 thoracic esophageal cancer



Mariette *et al*; - EJC - 2015

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✓Chemoradiation → or Selective Esophagectomy

- FFCD 9102 – 2015 T3-N0/N1-M0 thoracic esophageal cancer

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)

In non-responders, median OS was longer for those who underwent surgery compared to non-operated : **17.0** versus **5.5** months (p<0.0001),

Mariette *et al*; - EJC - 2015

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State of art of radiation therapy in Esophageal Cancer

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

- Walsh et al – 1996 (Trimodality) — **SVV Benefit**
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State of art of radiation therapy in Esophageal Cancer

- ✓ Is Preoperative Chemorad. **detrimental for surgery?**

✓ Is Preoperative Chemoradiation **detrimental for surgery?**

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EJSO 41 (2015) 282–294

EJSO
the Journal of Cancer Surgery

www.ejso.com

Review

Survival benefit and additional value of preoperative chemoradiotherapy in resectable gastric and gastro-oesophageal junction cancer: A direct and adjusted indirect comparison meta-analysis

K. Kumagai [a,*], I. Rouvelas [a], J.A. Tsai [a], D. Mariosa [b], P.A. Lind [c,d], M. Lindblad [a], W. Ye [b], L. Lundell [a], C. Schuhmacher [e], M. Mauer [f], B.H. Burmeister [g], J.M. Thomas [g], M. Stahl [h], M. Nilsson [a]

Kumagai *et al*; EJSO 2015

✓ Is Preoperative Chemoradiation **detrimental for surgery?**

neoadjuvant CT plus S vs S alone

no evidence to suggest that neoadjuvantCT increased the risk of any type of postoperative complication.

neoadjuvant CRT plus S vs S alone

no evidence to suggest that neoadjuvant CRT increased the risk of any type of postoperative complication.

SCC higher risk of total postoperative mortality and treatment-related mortality compared with surgery alone. No difference with ADK

Kumagai *et al*; EJSO 2015

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State of art of radiation therapy in Esophageal Cancer

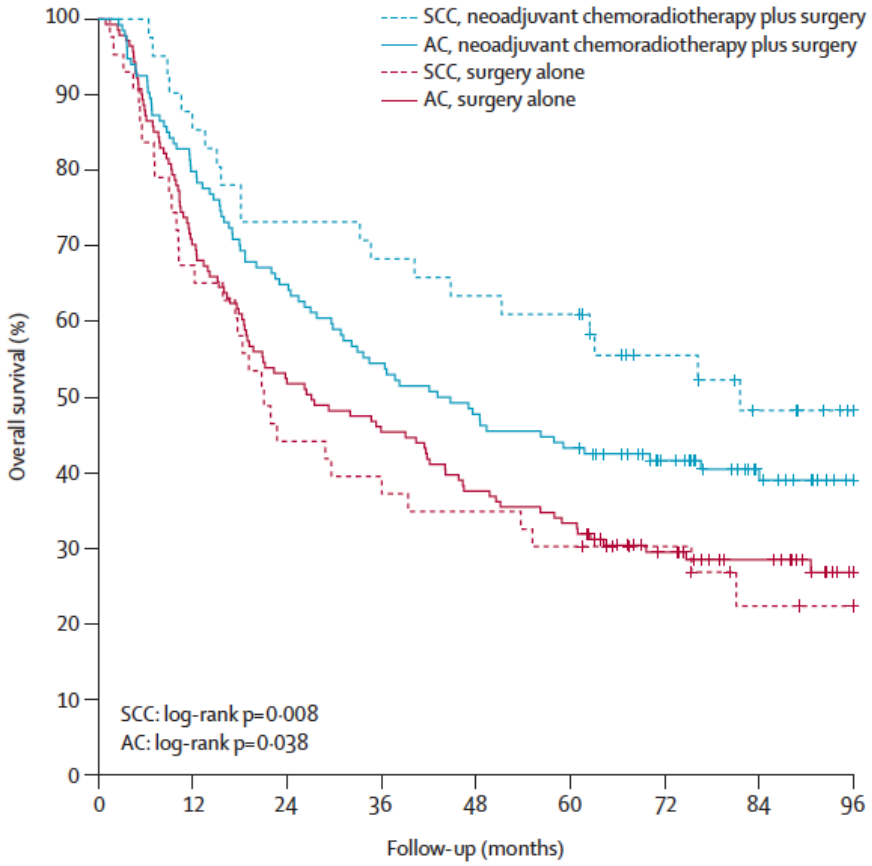
- ✓ Is Preoperative Chemorad. **detrimental for surgery?** **NO**

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

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

CROSS - 2015 (Trimodality)

Phase III Trial Chir ± Preop RTCT



Shapiro *et al*; Lancet Oncol 2015

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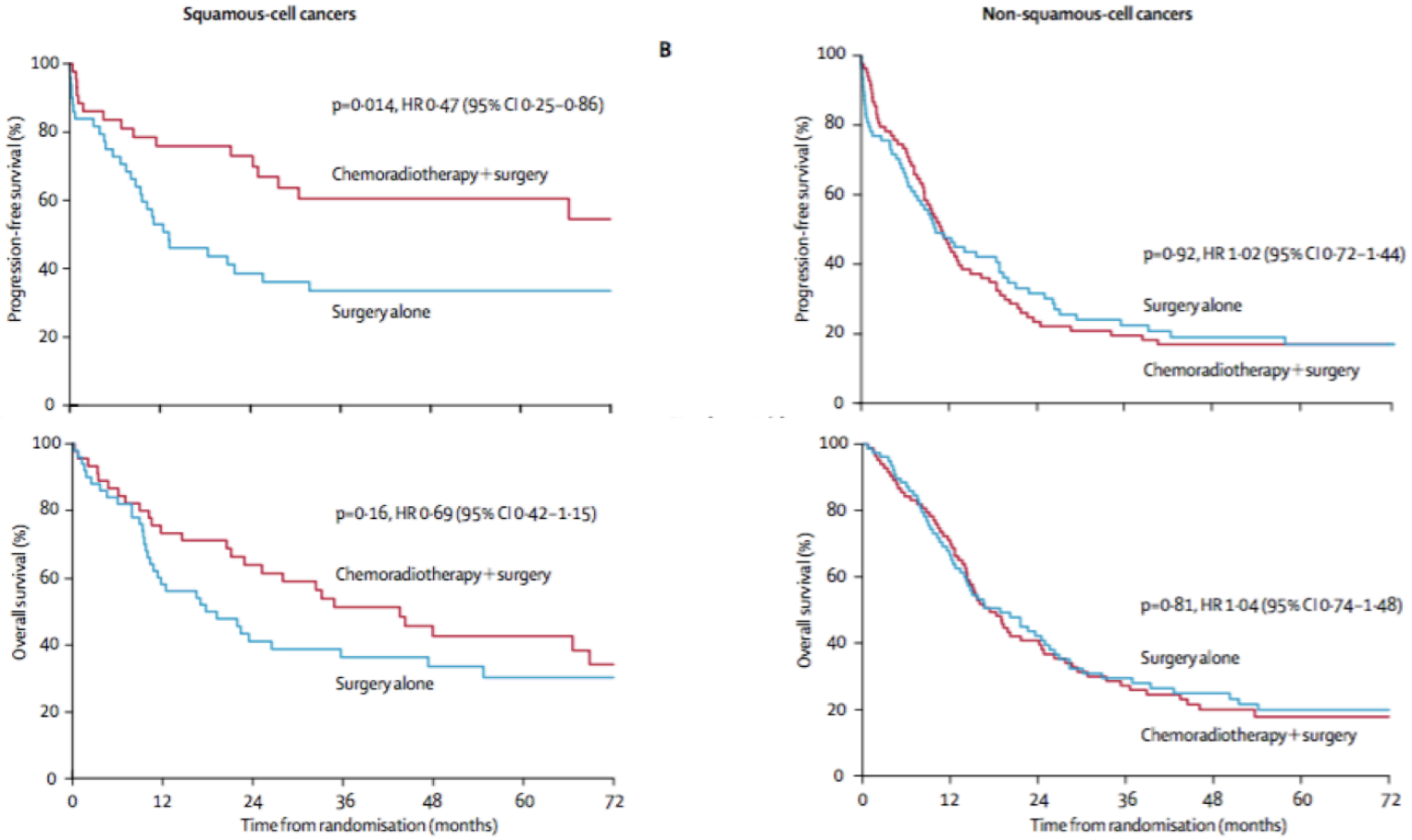
✓Does **histology** affect radiotherapy **response?**

Burmeister et al – 2005 (Trimodality)

Burmeisteret al – 2005 (Trimodality)

Phase III Trial Chir ± Preop RTCT

256 pts Adeno 62%



Burmeister *et al*; Lancet Oncol 2005

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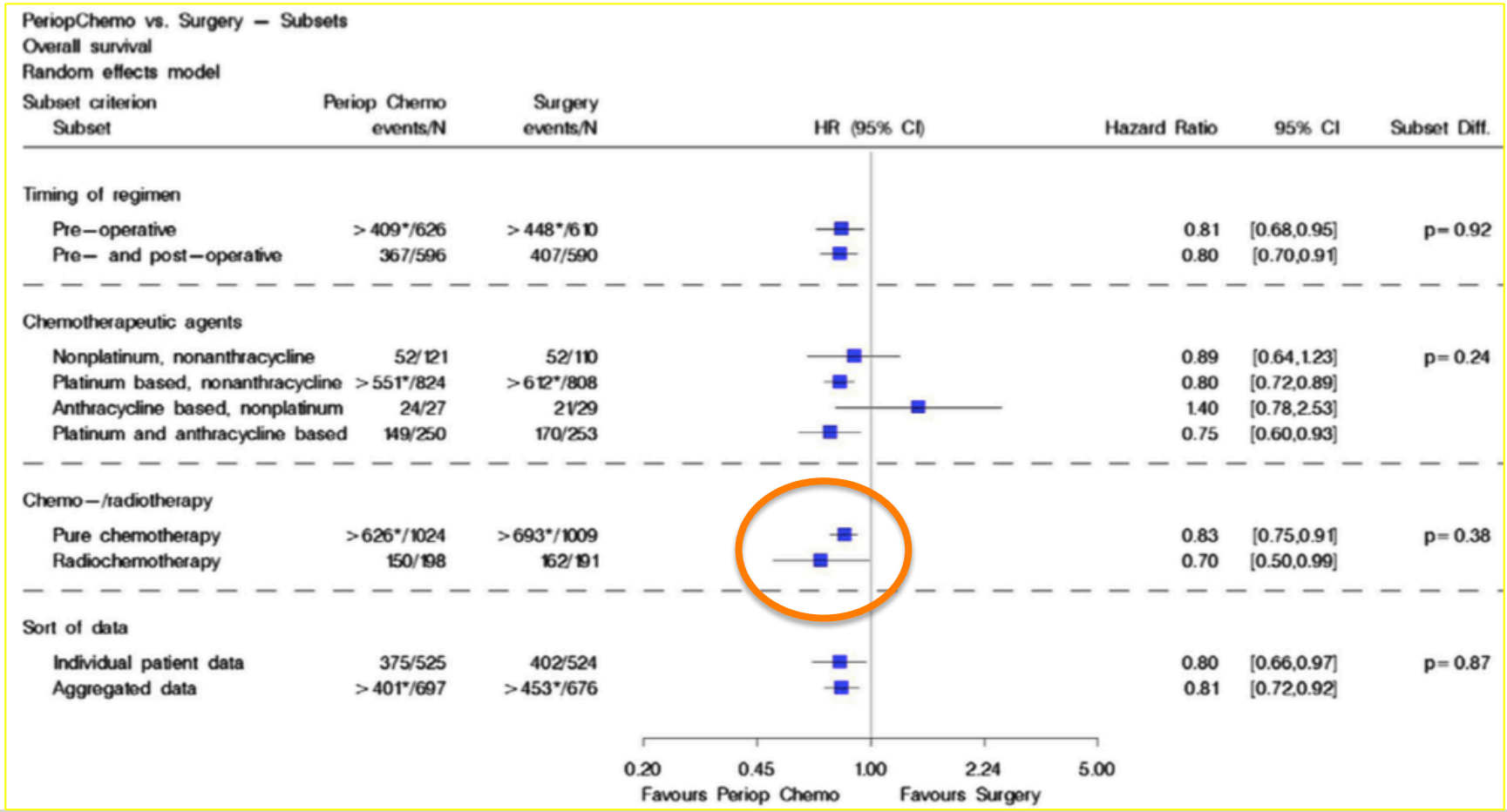
✓Does **histology** affect radiotherapy **response?**

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



Ronellenfitsch *et al*; Eur J Cancer - 2013

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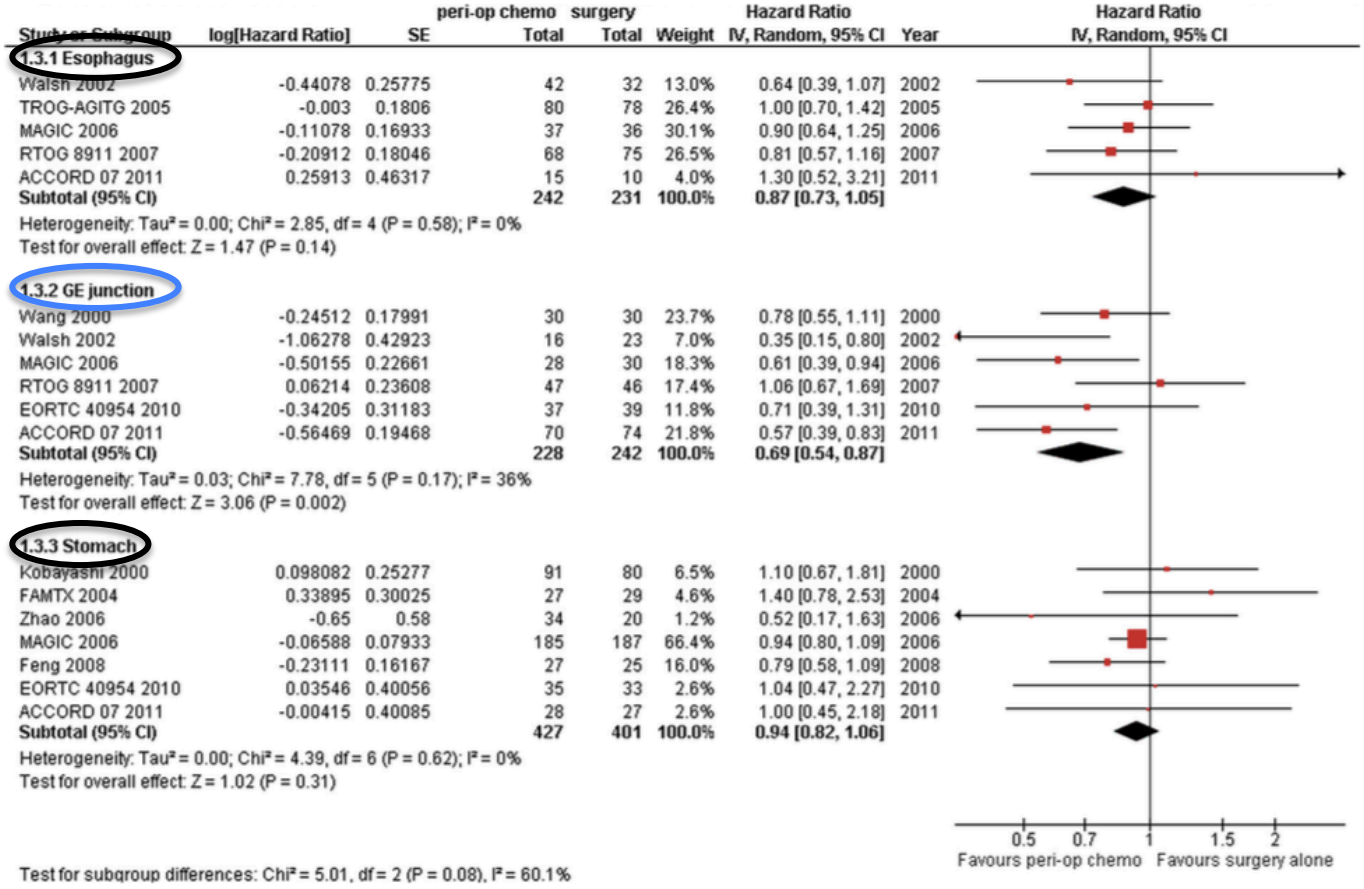

Study or Subgroup	log[Hazard Ratio]	SE	peri-op chemo Total	surgery Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
1.3.1 Esophagus							
Walsh 2002	-0.44078	0.25775	42	32	13.0%	0.64 [0.39, 1.07]	2002
TROG-AGITG 2005	-0.003	0.1806	80	78	26.4%	1.00 [0.70, 1.42]	2005
MAGIC 2006	-0.11078	0.16933	37	36	30.1%	0.90 [0.64, 1.25]	2006
RTOG 8911 2007	-0.20912	0.18046	68	75	26.5%	0.81 [0.57, 1.16]	2007
ACCORD 07 2011	0.25913	0.46317	15	10	4.0%	1.30 [0.52, 3.21]	2011
Subtotal (95% CI)			**242**	**231**	**100.0%**	**0.87 [0.73, 1.05]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 4 (P = 0.58); I² = 0%							
Test for overall effect: Z = 1.47 (P = 0.14)							
1.3.2 GE junction							
Wang 2000	-0.24512	0.17991	30	30	23.7%	0.78 [0.55, 1.11]	2000
Walsh 2002	-1.06278	0.42923	16	23	7.0%	0.35 [0.15, 0.80]	2002
MAGIC 2006	-0.50155	0.22661	28	30	18.3%	0.61 [0.39, 0.94]	2006
RTOG 8911 2007	0.06214	0.23608	47	46	17.4%	1.06 [0.67, 1.69]	2007
EORTC 40954 2010	-0.34205	0.31183	37	39	11.8%	0.71 [0.39, 1.31]	2010
ACCORD 07 2011	-0.56469	0.19468	70	74	21.8%	0.57 [0.39, 0.83]	2011
Subtotal (95% CI)			**228**	**242**	**100.0%**	**0.69 [0.54, 0.87]**	
Heterogeneity: Tau² = 0.03; Chi² = 7.78, df = 5 (P = 0.17); I² = 36%							
Test for overall effect: Z = 3.06 (P = 0.002)							
1.3.3 Stomach							
Kobayashi 2000	0.098082	0.25277	91	80	6.5%	1.10 [0.67, 1.81]	2000
FAMTX 2004	0.33895	0.30025	27	29	4.6%	1.40 [0.78, 2.53]	2004
Zhao 2006	-0.65	0.58	34	20	1.2%	0.52 [0.17, 1.63]	2006
MAGIC 2006	-0.06588	0.07933	185	187	66.4%	0.94 [0.80, 1.09]	2006
Feng 2008	-0.23111	0.16167	27	25	16.0%	0.79 [0.58, 1.09]	2008
EORTC 40954 2010	0.03546	0.40056	35	33	2.6%	1.04 [0.47, 2.27]	2010
ACCORD 07 2011	-0.00415	0.40085	28	27	2.6%	1.00 [0.45, 2.18]	2011
Subtotal (95% CI)			**427**	**401**	**100.0%**	**0.94 [0.82, 1.06]**	
Heterogeneity: Tau² = 0.00; Chi² = 4.39, df = 6 (P = 0.62); I² = 0%							
Test for overall effect: Z = 1.02 (P = 0.31)							
Test for subgroup differences: Chi² = 5.01, df = 2 (P = 0.08), I² = 60.1%							

Hazard Ratio IV, Random, 95% CI

0.5 0.7 1 1.5 2

Favours peri-op chemo Favours surgery alone

Ronellenfitsch *et al*; Eur J Cancer - 2013

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- ✓ Does **histology** affect radiotherapy **response?** **YES/NO**
- ✓ Does dose **impact long term outcome?**

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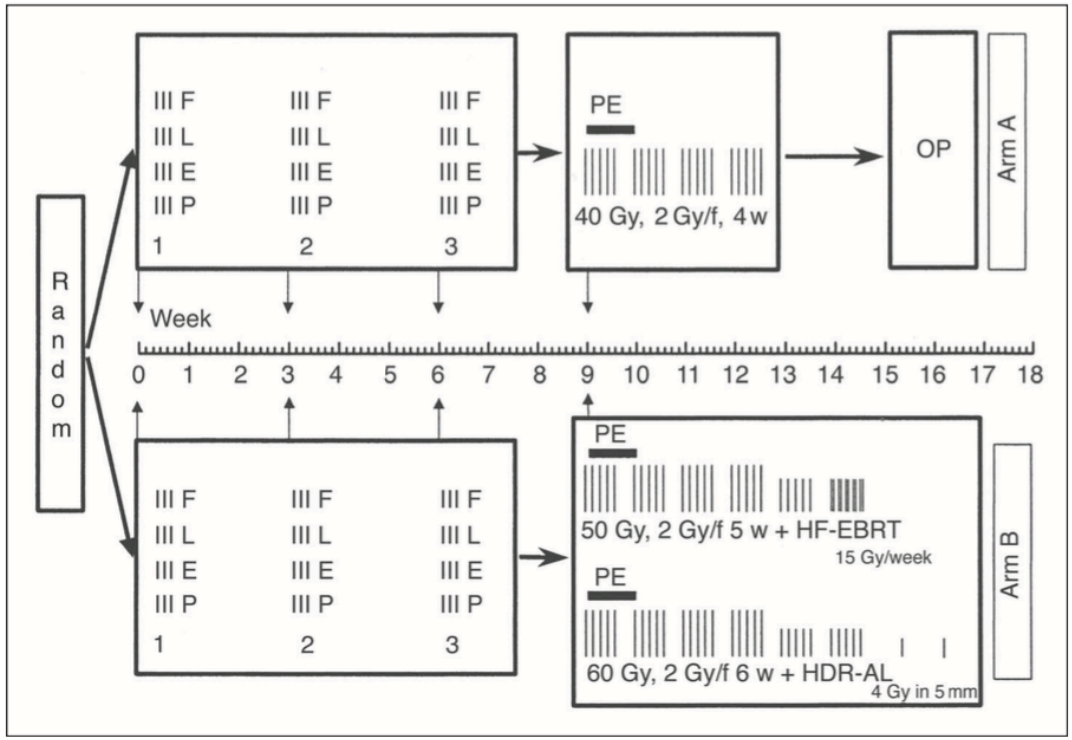

Stahl *et al*; JCO 2005

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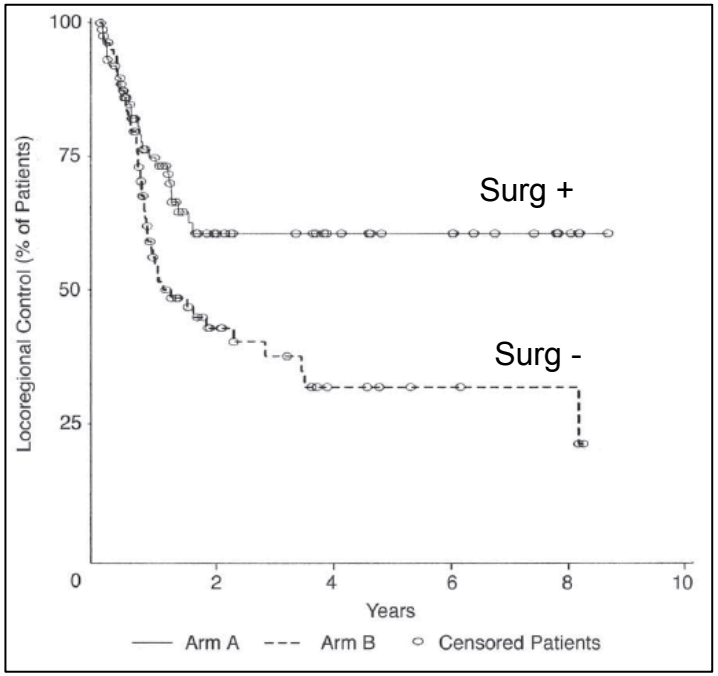
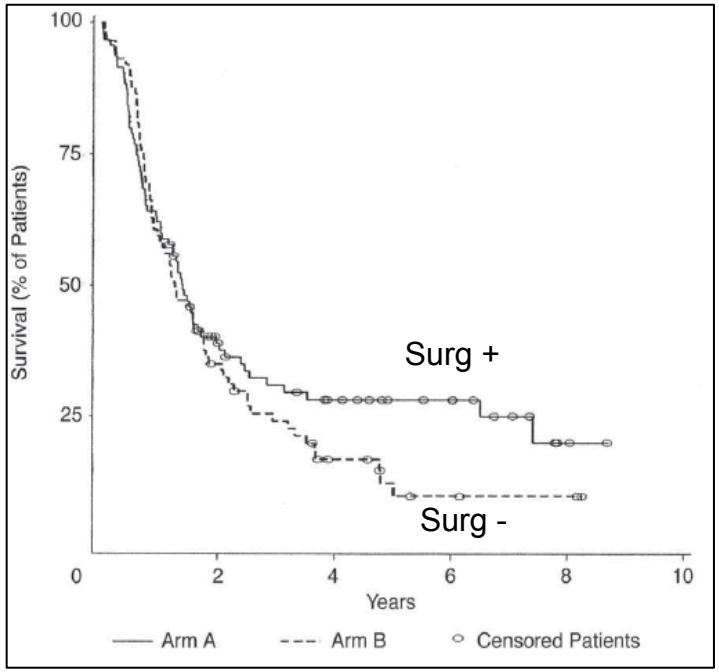


Survival



Stahl *et al*; JCO 2005

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

	N° Pts	Accrual	Rate adeno	Tumor site	Dose/Fx (Gy)	Concurrent CT	% pCR (N° pts RTCT arm)
Walsh [43]	113	1990-1995	100%	Middle+ Lower Esophagus + Cardias	40/2.7	CDDP + 5Fu	25% (13/52)
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Van Hagen [50]	366	2004-2008	75%	Proximal +Middle+ Lower Esophagus + GEJ	41.2/1.8	Carboplatin + Paclitaxel	29% (47/161)

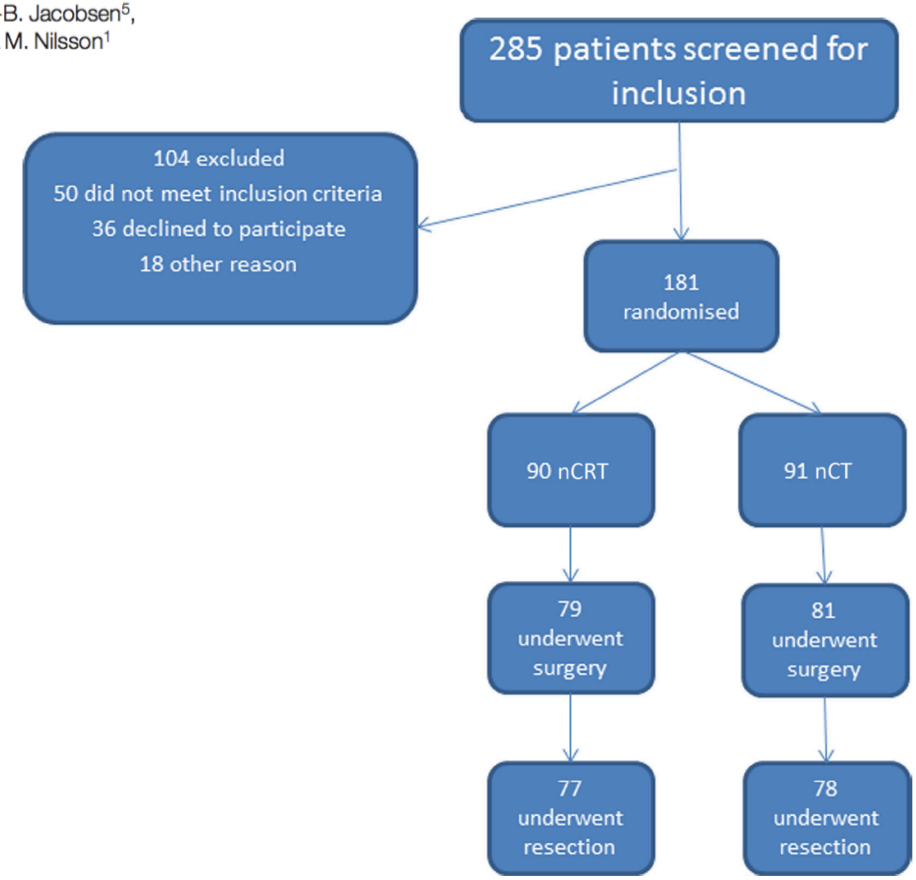
Cellini *et al*; Radiat Oncol 2014

ESTRO School

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

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]



Kelvebro *et al*; Ann Oncol 2016

ESTRO School

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

pCR & RO

(%)	nCT	nCRT	*P*-value
Tumour regression grade[a,b]			<0.001
1: Histological complete response	7 (9)	22 (28)	0.002
2: 1%–10% tumour cells	5 (6)	19 (24)	
3: >10%–50% tumour cells	5 (6)	14 (18)	
4: >50% tumour cells	61 (78)	23 (29)	
Surgical resection[c]	78 (86)	78 (87)	0.85
R0 resection[b,d]	58 (74)	68 (87)	0.042

Toxicity

(%)	nCT	nCRT	*P*-value
40 Gy neoadjuvant radiotherapy	–	74 (85)	–
3 cycles of neoadjuvant chemotherapy	78 (86)	67 (74)	0.06
Severe adverse events			
Infection	5	5	
Nausea and vomiting	2	6	
Nutritional deficiency	13	13	
Gastrointestinal symptoms	1	5	
Cardiovascular event	7	14	
Renal failure	7	4	
Infection	5	5	
Neutropaenia/thrombocytopaenia	2	5	
Other	3	3	
Death[a]	1	2	
Total number of SAE	41	57	0.14
Postoperative outcome			
30-day mortality	0 (0)	1 (1)	1.0
90-day mortality	2 (3)	6 (8)	0.28
Surgical complication[b]	27 (35)	29 (38)	0.69

Kelvebro *et al*; Ann Oncol 2016

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State of art of radiation therapy in Esophageal Cancer

- ✓ Is Preoperative Chemorad. **detrimental for surgery?** **NO**
- ✓ 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

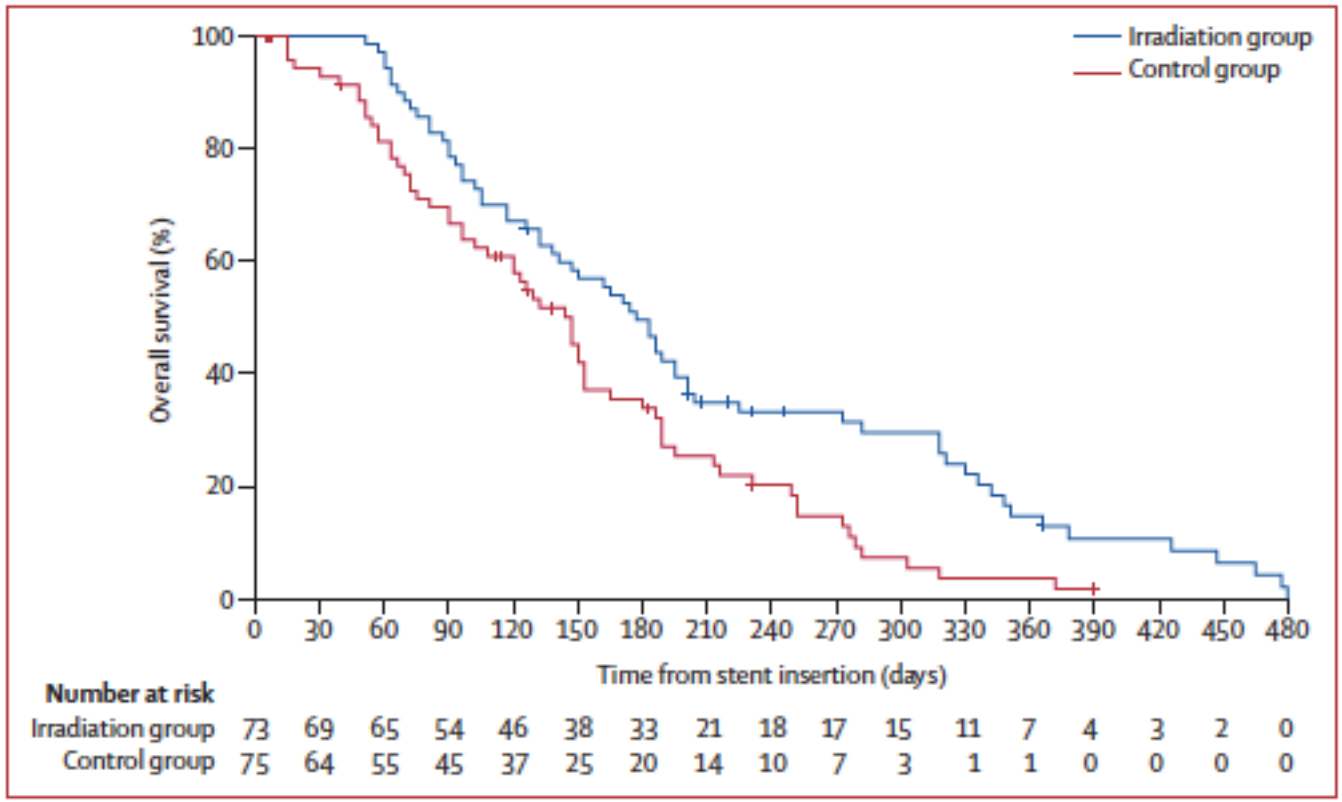
Hai-Dong Zhu, Jin-He Guo*, Ai-Wu Mao*, Wei-Fu Lv*, Jian-Song Ji*, Wen-Hui Wang, Bin Lv, Rui-Min Yang, Wei Wu, Cai-Fang Ni, Jie Min, Guang-Yu Zhu, Li Chen, Mei-Ling Zhu, Zhen-Yu Dai, Peng-Fei Liu, Jian-Ping Gu, Wei-Xin Ren, Rui-Hua Shi, Gao-Feng Xu, Shi-Cheng He, Gang Deng, Gao-Jun Teng*

Zhu *et al*; Lancet Oncol 2014

ESTRO School

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

Survival



Zhu *et al*; Lancet Oncol 2014

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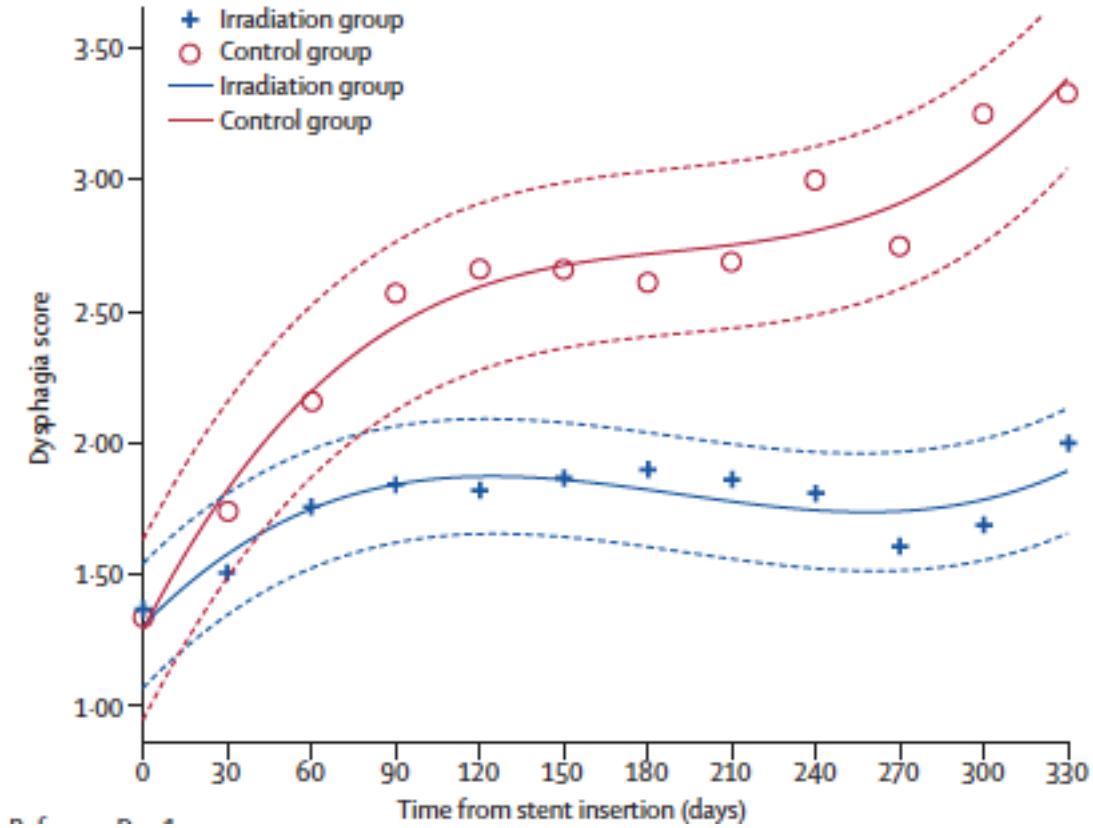
✓Is there any role for **Brachytherapy in palliation**?



Zhu *et al*; Lancet Oncol 2014

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State of art of radiation therapy in Esophageal Cancer

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

State of art of Chemotherapy in a combined treatment perspective

Upper GI: technical and clinical challenges for radiation oncologists

INSTITUT JULES BORDET INSTITUUT

Alain Hendlisz
Institut Jules Bordet

28th may 2016

ESTRO School

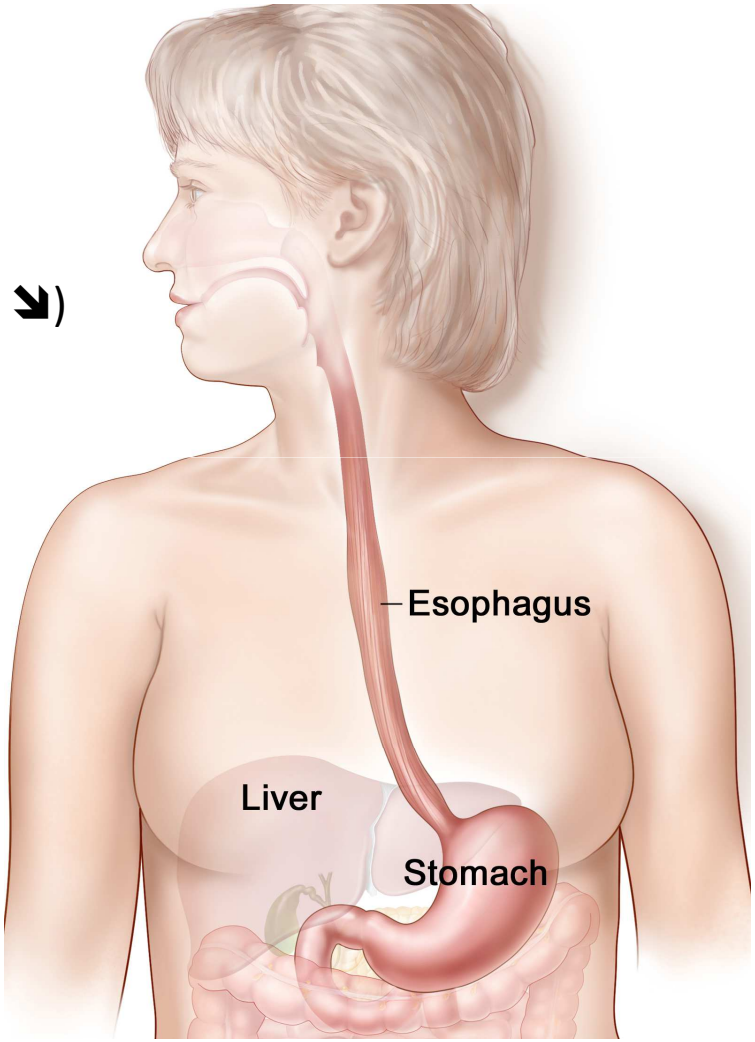
Esophageal & Eso-Gastric Cancer

43700/year Western Europe

2 histologies:

- **a**denocarcinoma (< GORD & obesity, ↗)
- **s**quamous cell carcinoma(< alcohol & tobacco, ↘)

40% metastatic at diagnosis



Etzinger et al. NEJM; Pennarthur et al. Lancet 2013; Rustgi et al. NEJM 2014

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2 histologies:

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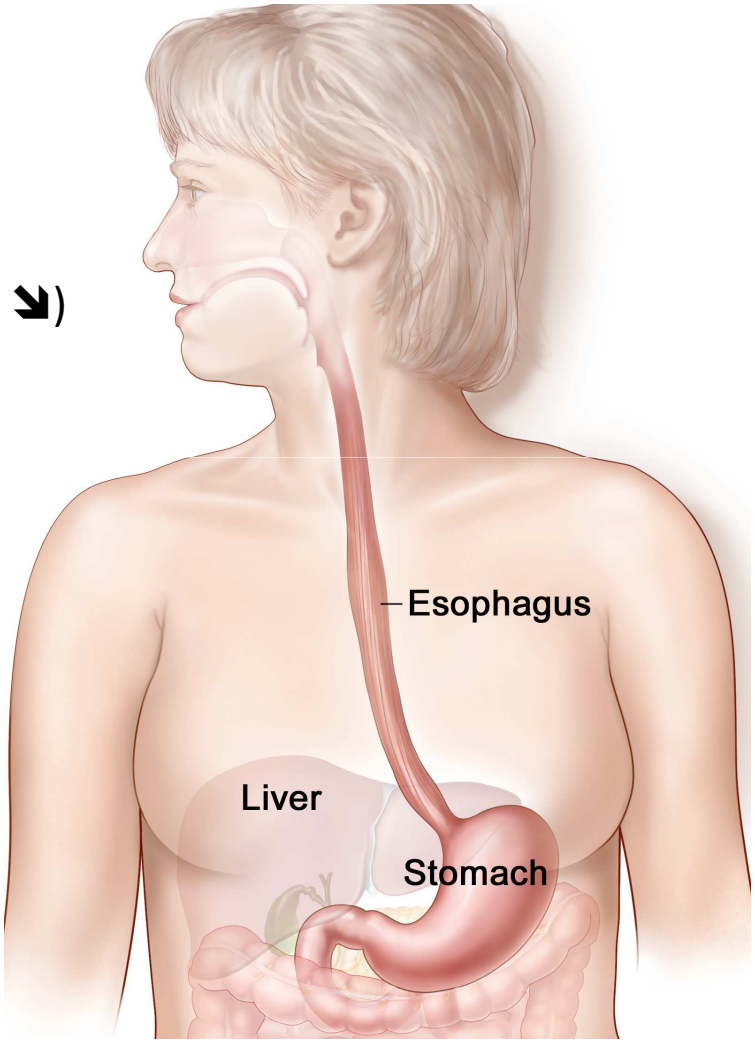
40% metastatic at diagnosis

Stage	Tumor	Nodes	Metastasis	5-yr OS %
0	Tis	N0	M0	>95
I	T1	N0	M0	50–80
IIA	T2-3	N0	M0	30–40
IIB	T1-2	N1	M0	10–30
III	T3 T4	N1 Any N	M0 M0	10–15
IVA	Any T	Any N	M1a	<5
IVB	Any T	Any N	M1b	<1



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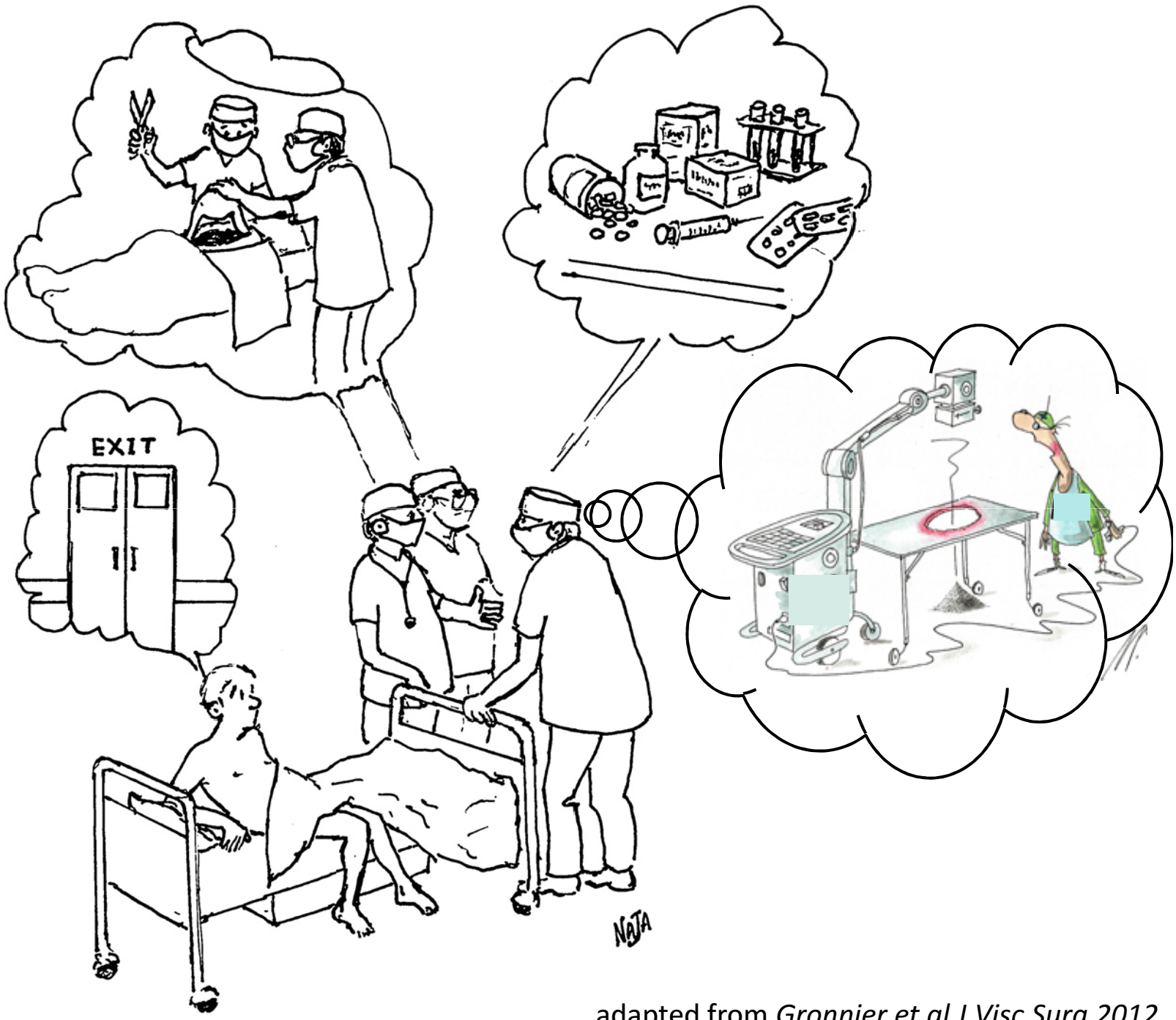

adapted from *Gronnier et al J Visc Surg 2012*

POST-OPERATIVE treatments fail to improve OS

	N	population	experimental	mOS (months)	3-year Survival (%)	
Zieren, 1995	68	100% SCC	Surg +/- RT	NR	20 vs 22	O
Fok, 1993	130	80% SCC 20% ADC	Surg +/- RT	15.2 vs 8.7	NR	O
Teniere, 1991	221	100% SCC	Surg +/- RT	18 vs 18	17.6 vs 18.6 (5yrs)	O
Xiao, 2003	495	100% SCC	Surg +/- RT	NR	31.7 vs 41.3 (5yrs)	O
Ando, 2003	242	100% SCC	Surg +/- CT	NR	52 vs 61 (5yrs)	O
MacDonald, 2005	556	80% adc gastr 20% adc oeso	Surg +/- RTCT	27 vs 36	41 vs 50	✔

PRE-OPERATIVE treatments improve OS

	N	population	Type	mOS (months)	3-year Survival (%)	
Kelsen, 1998	440	46% SCC 54% ADC	Surg +/- CT	14.9 vs 16.1	26 vs 23	○
MRC, 2002 Allumet, 2009	802	31% SCC 69% adc	Surg +/- CT	13.3 vs 16.8	17 vs 23 (5 yrs)	✔
Cunningham, 2006	503	74%adc gastr 26%adc oeso	Surg +/- CT périopératoire	NR	23 vs 36 (5 yrs)	✔

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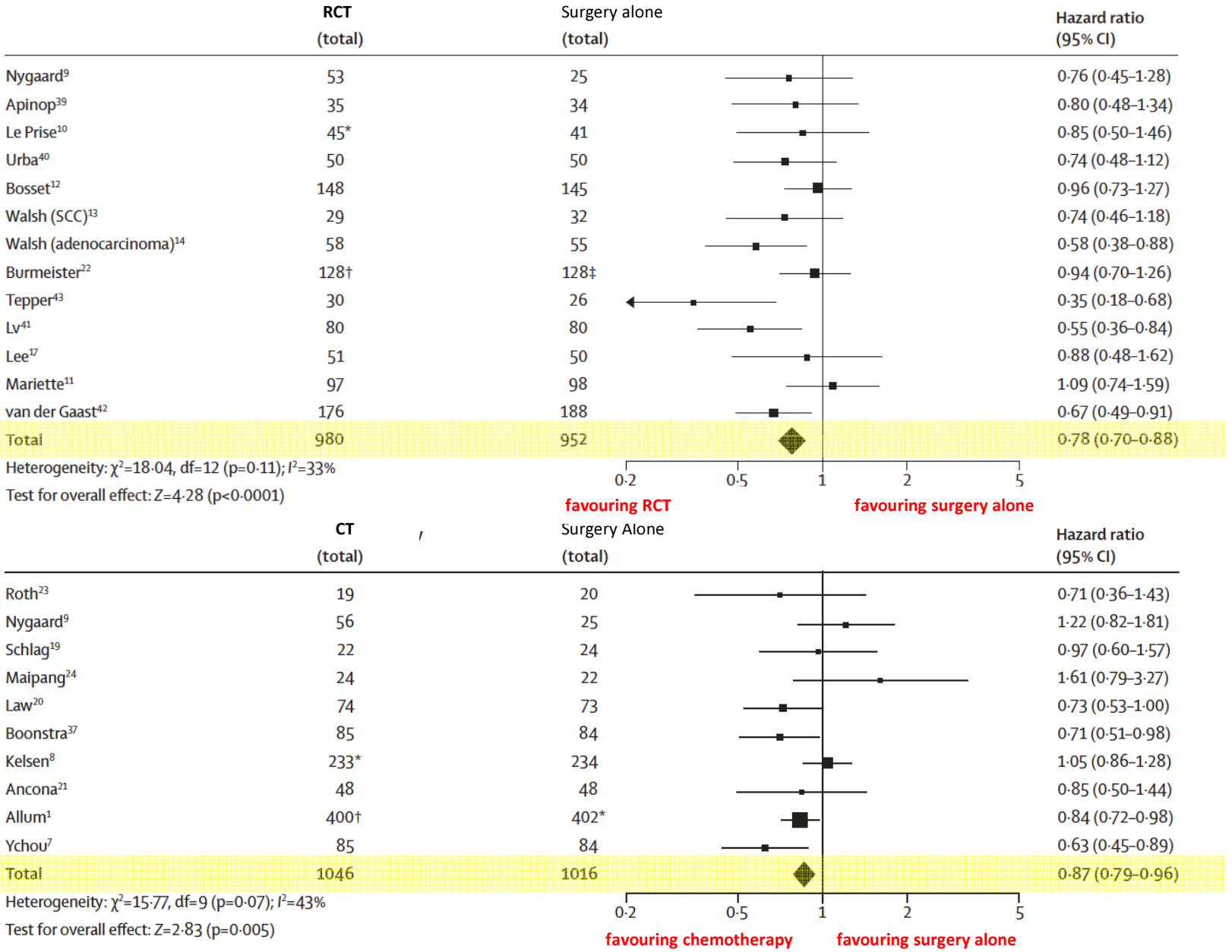
Le Prise, 1994	86	100% SCC	Surg +/- RTCT	10.0 vs 10.0	47 vs 47 (1 yr)	○
Walsh, 1996	103	100% ADC	Surg +/- RTCT	11.0 vs 16.0	6 vs 32	✔
Bosset, 1997	282	100% SCC	Surg +/- RTCT	18.6 vs 18.6	34 vs 36	○
Urba, 2001	100	25% SCC 75% ADC	Surg +/- RTCT	17.6 vs 16.9	16 vs 30	○
Burmeister, 2005	256	37% SCC 63% ADC	Surg +/- RTCT	22.2 vs 19.3	NR	○
Tepper, 2008	56	25% SCC 75% ADC	Surg +/- RTCT	21.5 vs 53.8	16 vs 39 (5 yrs)	✔

Meta-Analysis (24 studies 4188 patients)



Sjoquist et al. Lancet Oncol 2011

Meta-Analysis (24 studies 4188 patients)

Preop RCT : ↗ **22%** patients survival [HR 0.78 (95%CI 0.70-0.88) p<0.0001]

25-30% pCR

Preop CT: ↗ **13%** patients survival [HR 0.87 (95%CI 0.79-0.96) p=0.005]

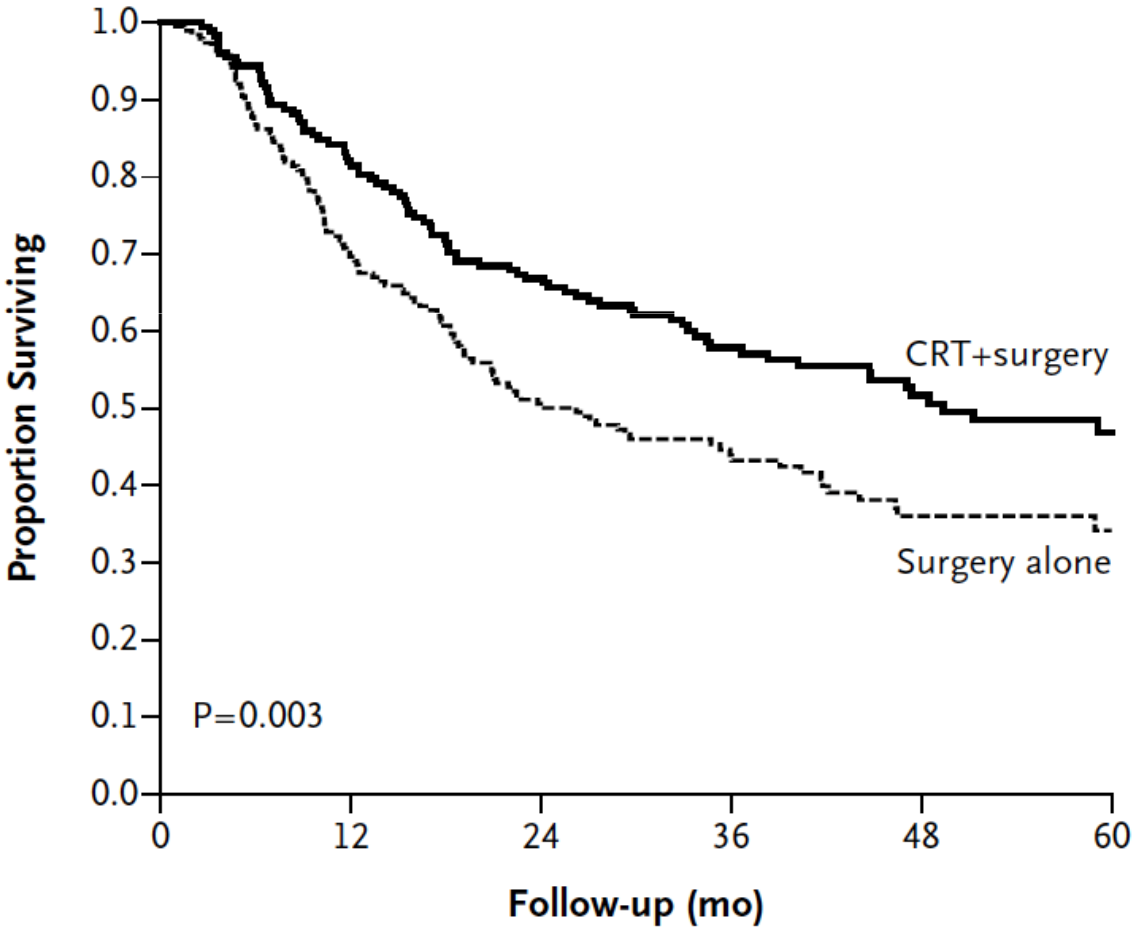
10-13.5% pCR

→ **Clear benefit of preop CT or RTCT**

→ **Unproven «feeling» that RTCT > CT**

Sjoquist et al. Lancet Oncol 2011

CROSS trial



368 patients

75% adenocarcinoma

25% squamous cell C.

RTCT ↗ mOS **34%**

[HR 0.657; 95% CI 0.495-0.871; P=0.003]

Van Hagen et al. NEJM 2012

Adjuvant Treatment: Esophageal cancer

Provisional Conclusions

Surgery alone is not anymore the standard treatment

Preop RTCT ↗ mOS

Preop CT ↗ mOS (a little bit less?)

Remaining Questions

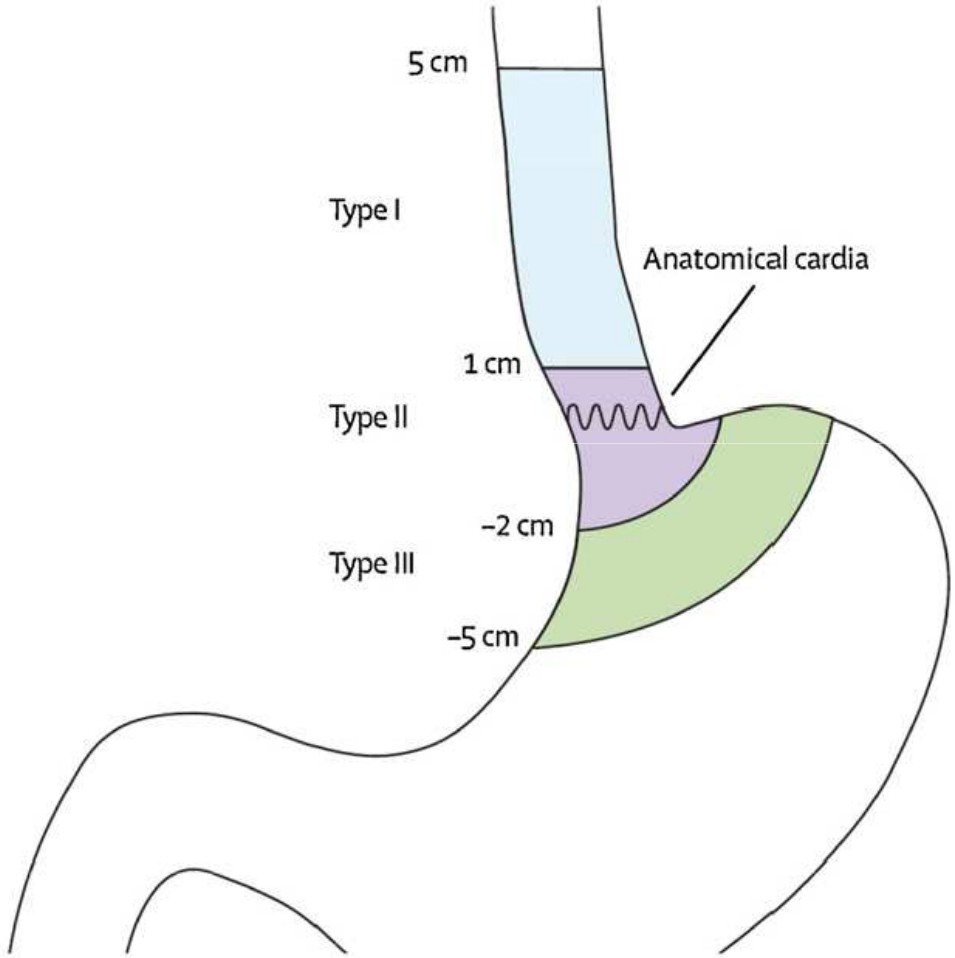
Preop CT or RCT?

Who should not receive preop treatment?

Backbone CT different?

Preop CT or RCT?

Eso-Gastric Junction: SIEVERT classification



Mariette et al Lancet Oncol 2011

Surgery according to location

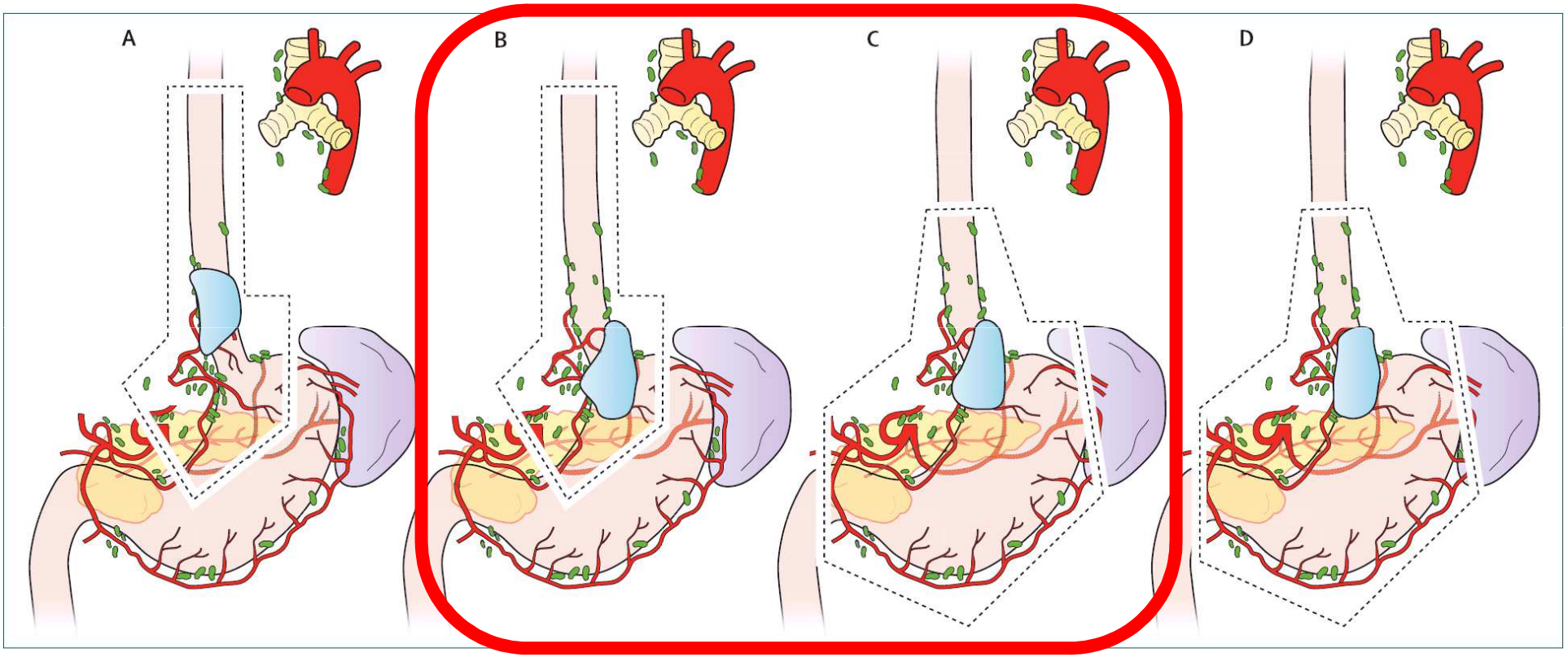
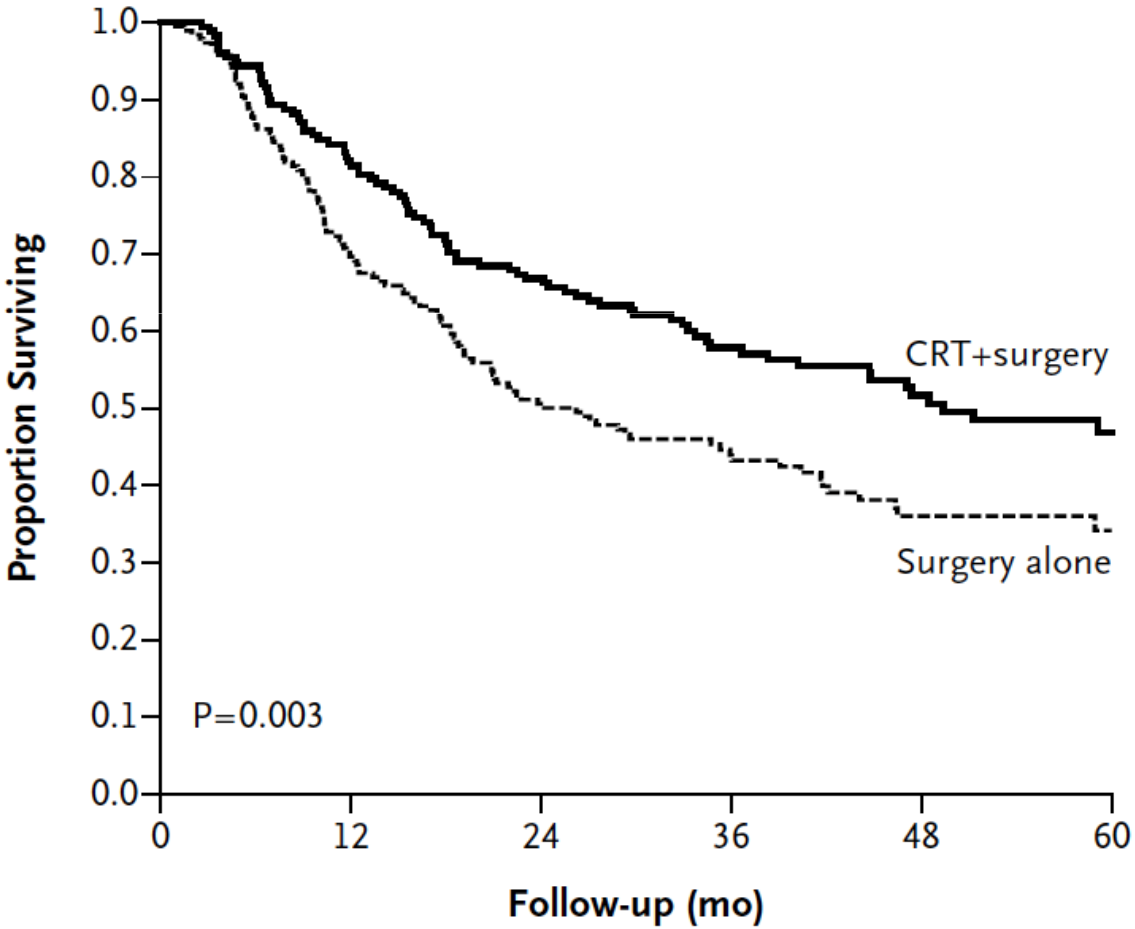


Figure 4: **Schematic representation of recommended extent of surgical resection for oesophagogastric junction adenocarcinomas**
Type I (A; subtotal oesophagectomy with superior polar gastrectomy), type II (subtotal oesophagectomy with superior polar gastrectomy [B] or total gastrectomy with inferior oesophagectomy [C]), and type III (D; total gastrectomy). Blue region is tumour site.

Mariette et al Lancet Oncol 2011

Who should not receive preop treatment?

CROSS trial



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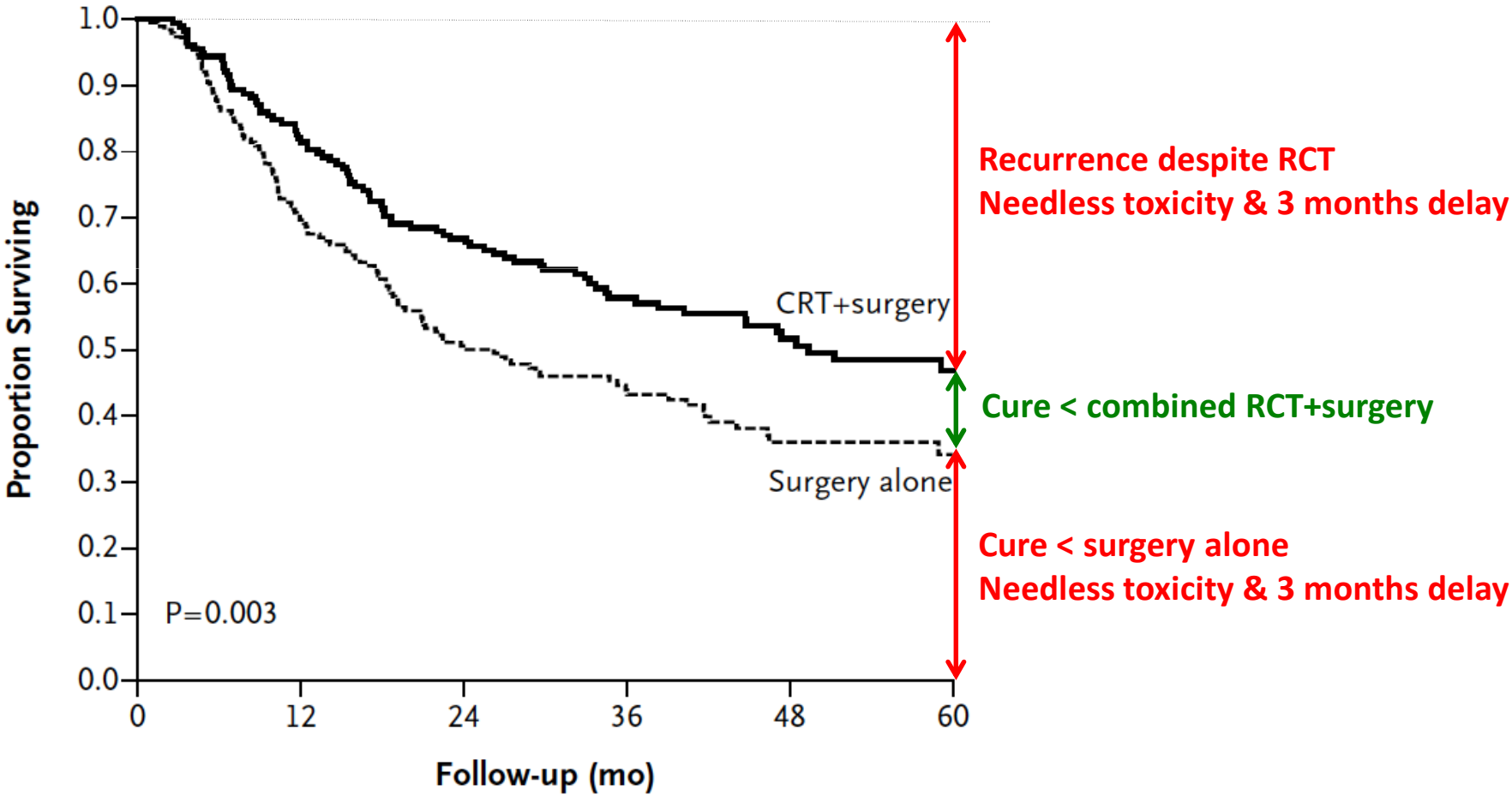
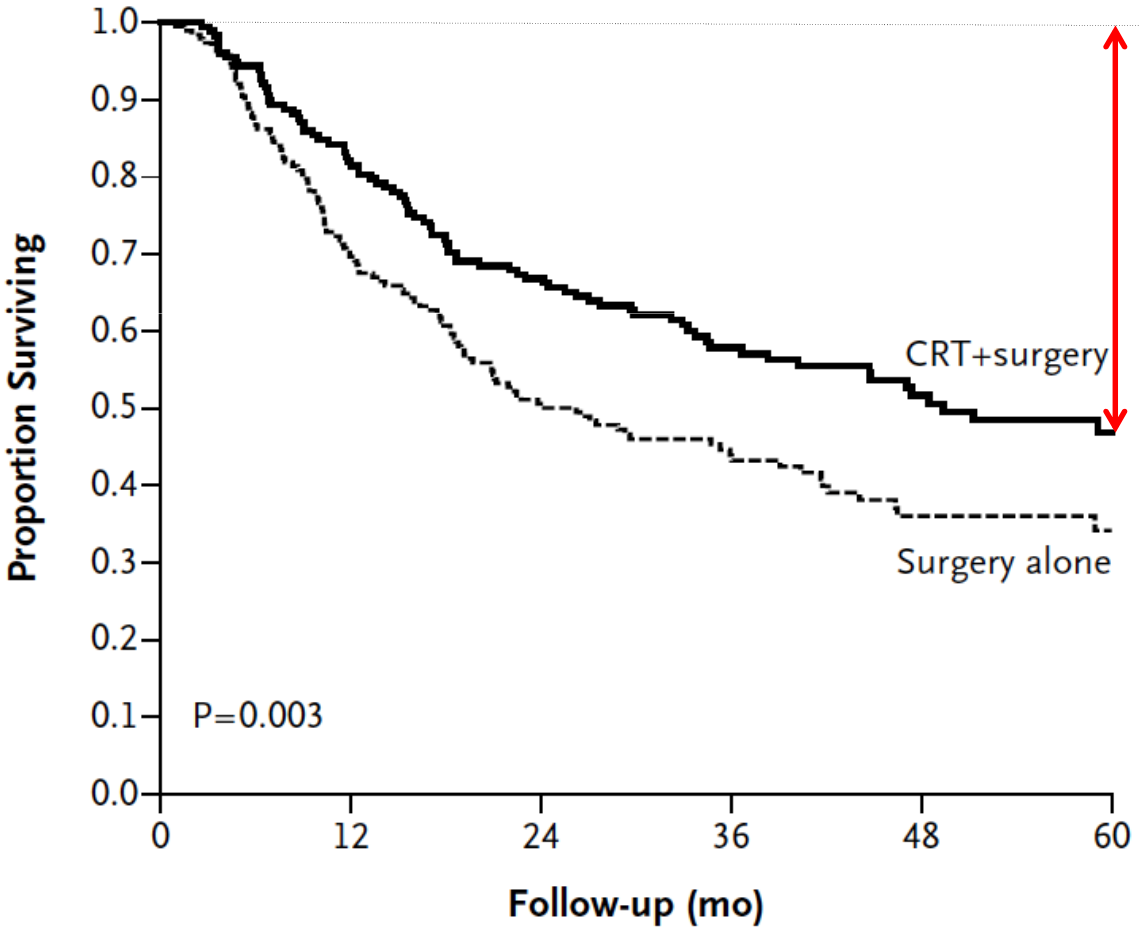
Van Hagen et al. NEJM 2012

The extent of benefit from preop treatment



Van Hagen et al. NEJM 2012

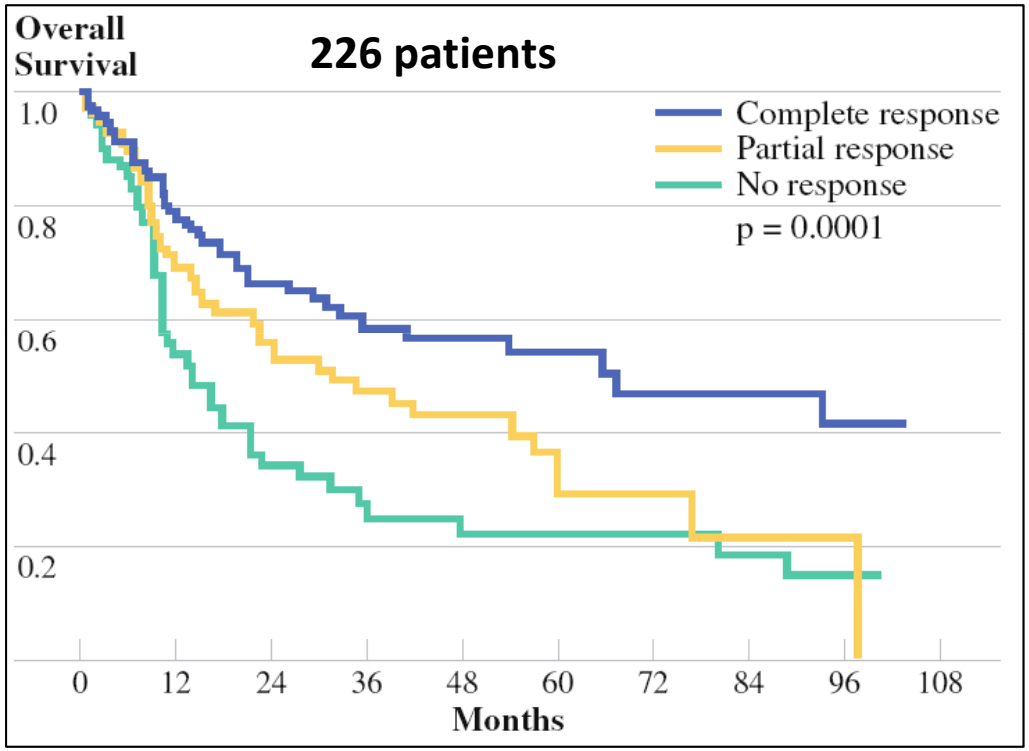
The extent of benefit from preop treatment



Recurrence despite RCT
Needless toxicity & 3 months delay

Van Hagen et al. NEJM 2012

Predictive biomarker for preop RCT: pCR

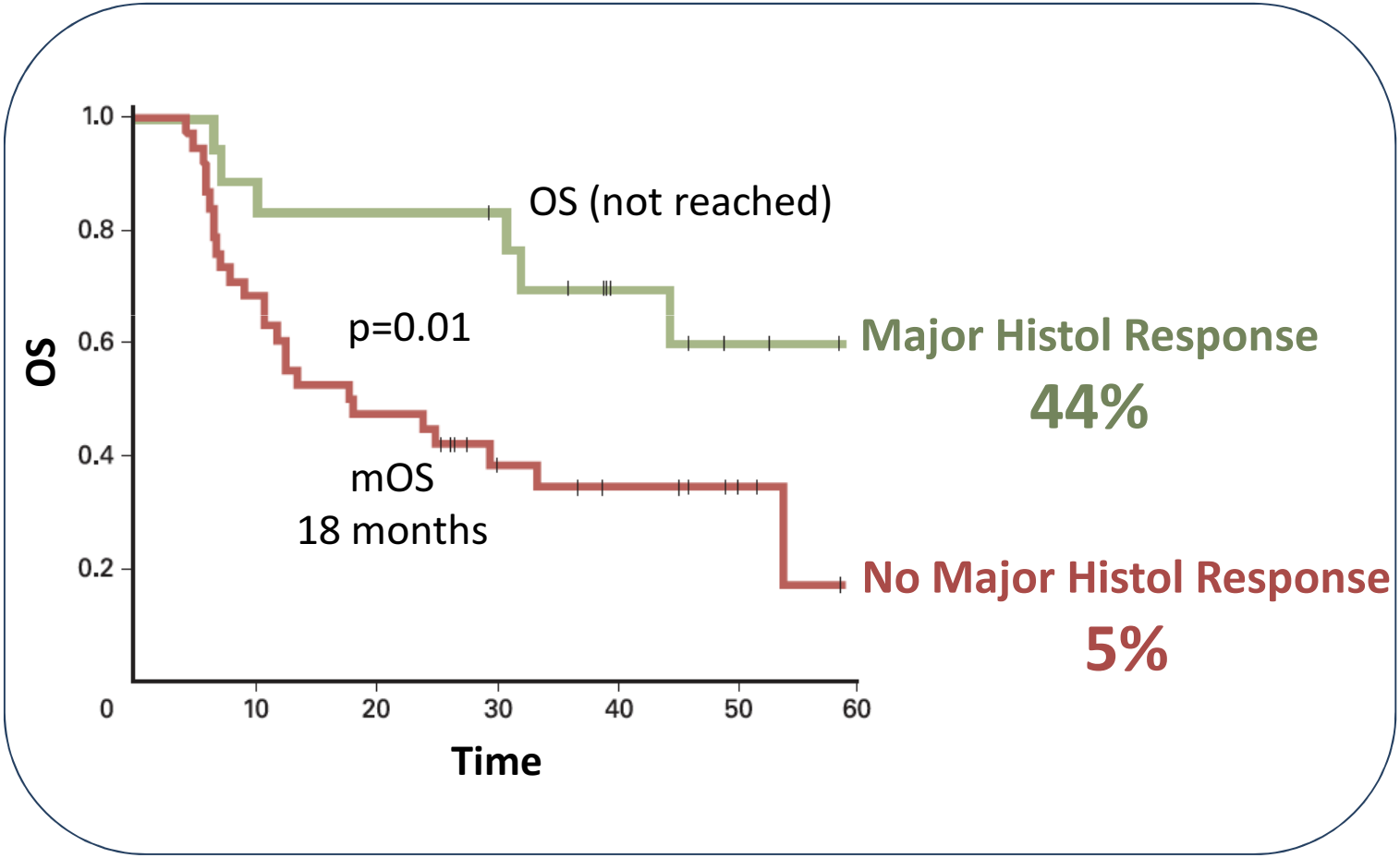


<u>Residual Question</u>: Is complete pathological response **predictive** or **prognostic**?

Meredith et al. Ann Surg Oncol 2010

Predictive biomarker for preop RCT: Metabolic Imaging

Metabolic Response after 1 course CT



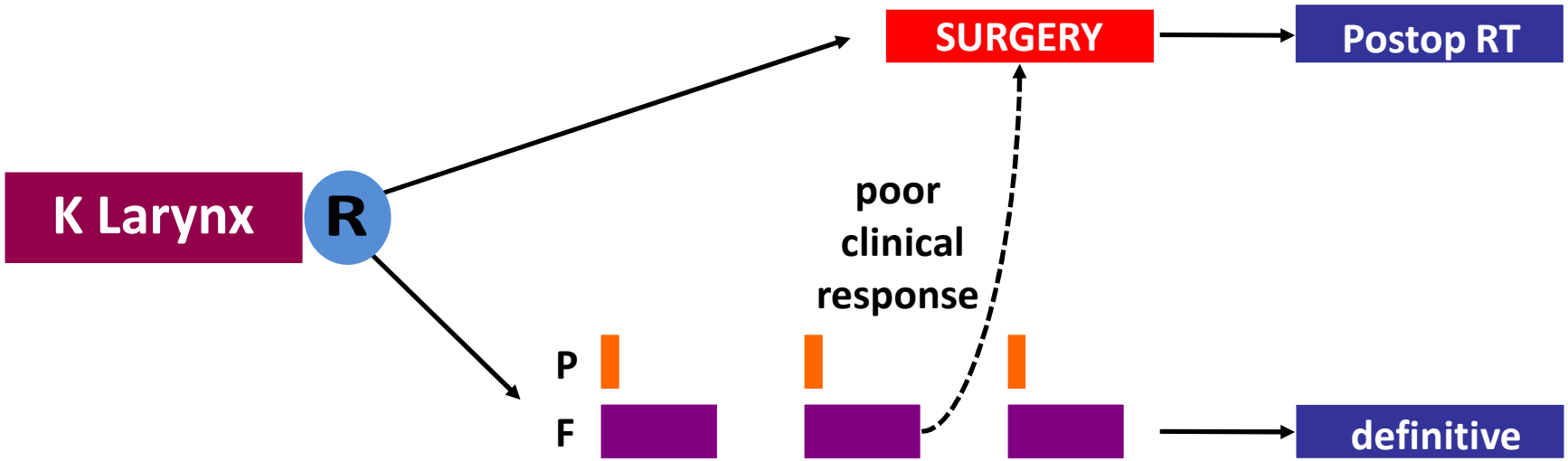
<u>Residual Question</u>: is Metabolic Response **predictive** or **pronostic**?

Ott et al. J Clin Oncol 2006

Pitfalls in Metabolic Assessment of Response

- Poorly studied **during** RCT (pro-inflammatory effect?)
- Poorly correlated with pathological response **after** RCT
- Needless **after** RCT (treatment already given)

Non-response to CT predict non-benefit RCT (H&N)



conservatrice approach (definitive RCT) less mutilating

Lefebvre et al. JNCI 1996

Department of Veterans Affairs Laryngeal Cancer Study Group NEJM 1991

MR CT biomarker for RTCT benefit?

SCC

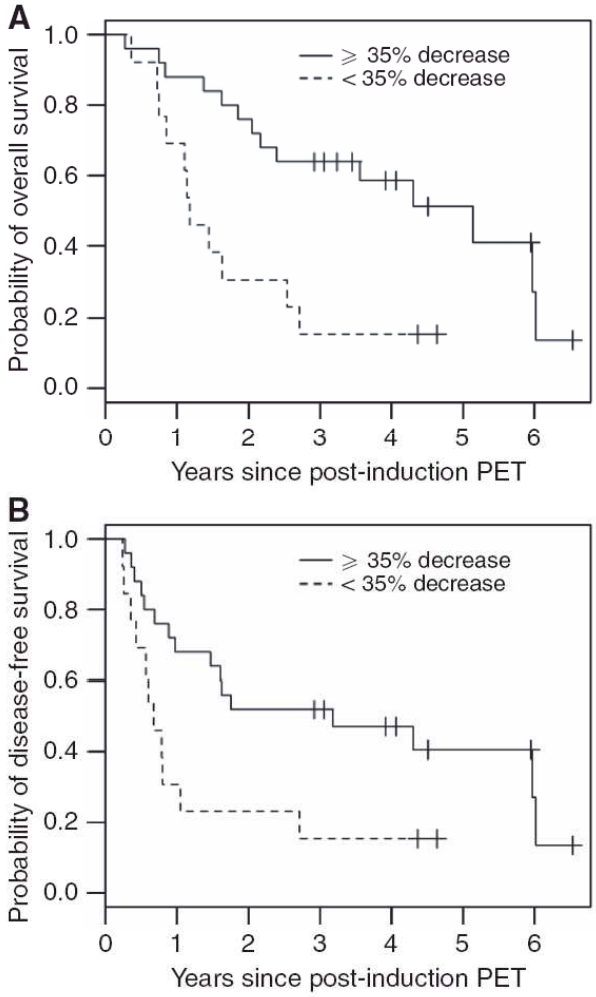
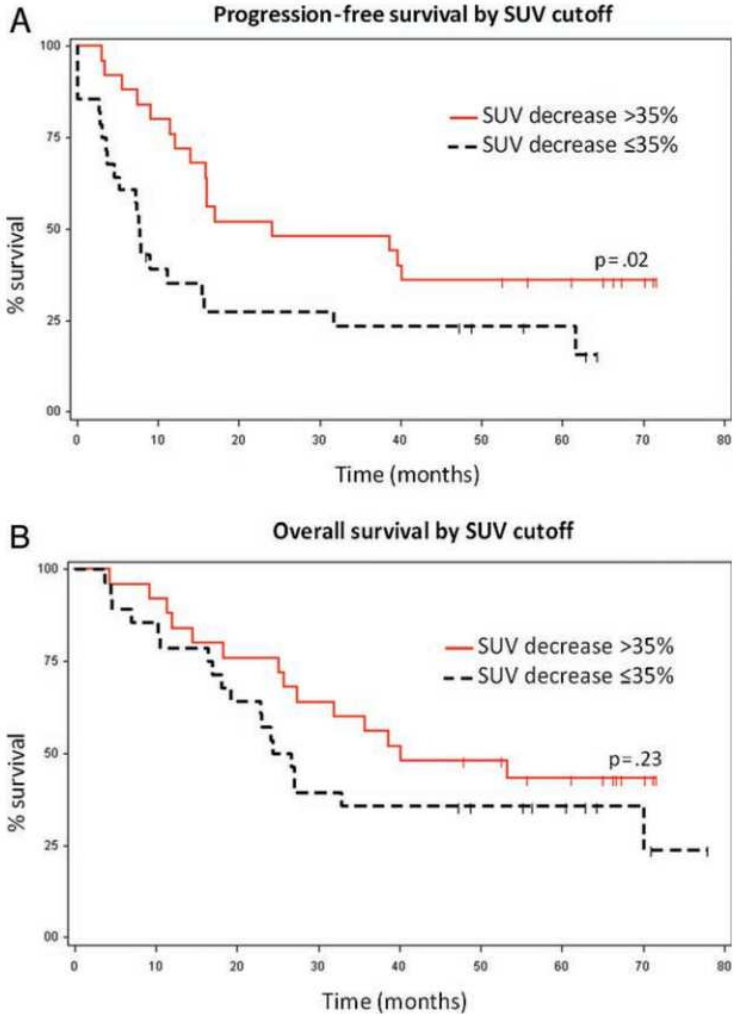


Figure 3. (**A**) OS by metabolic response status ($P = 0.004$). (**B**) DFS by metabolic response status ($P = 0.02$).

Chhabra et al, Br J Cancer 2015

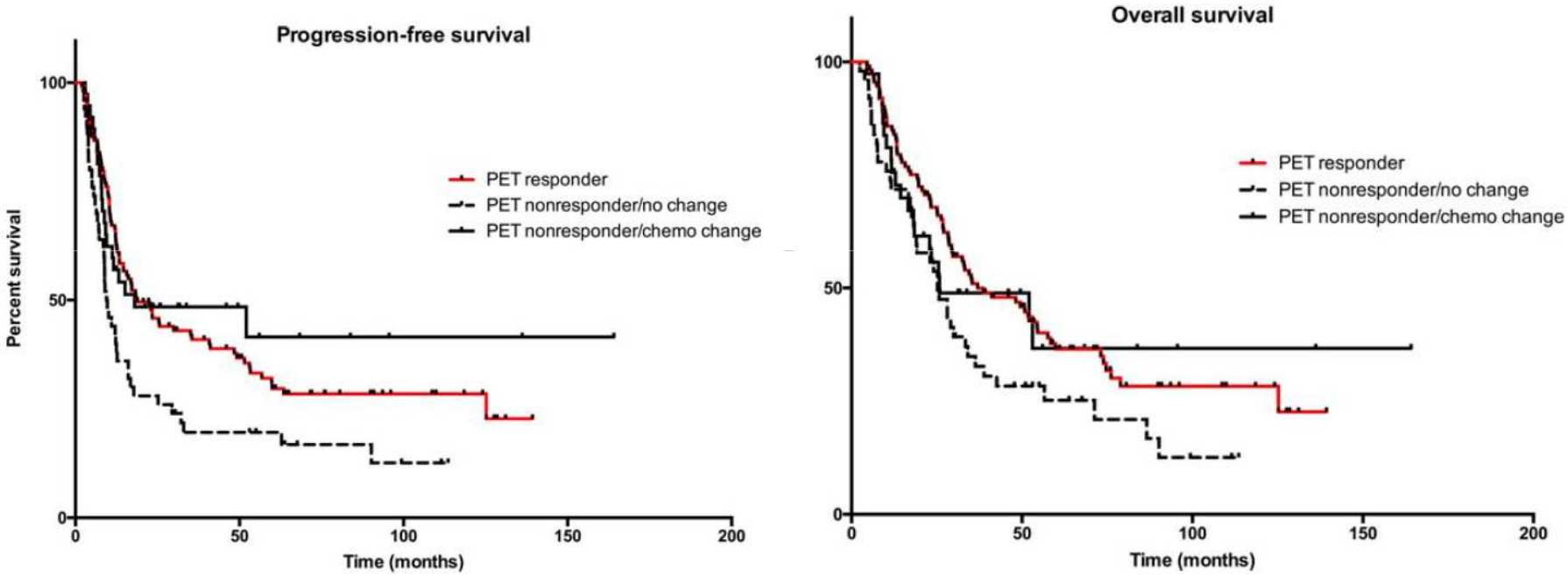
ADC



Ilson et al, Cancer 2012

MR induction CT biomarker for RTCT?

ADC



Ku et al, Cancer 2016

Are there differences between CT backbones?

Are there differences between CT backbones?

Study	Histol	Intent	Arms	Drugs	N	pCR	mOS (months)	2-yr OS
Herskovic 1992	20%SCC 80%ADC	definitive	RCT (50Gy)	5FU/DDP	129	NA	8.9	38%
			RT (64Gy)	-		NA	12.5	50% (p<0.001)
Bosset 1996	SCC	preop	RCT (18.5Gy split dose preop	DDP	143	26%	18.6	-
			surg alone	-	139	-	18.6	-
Walsh 1996	ADC	preop	RCT (40Gy) preop	5FU/DDP	58	25%	16	37
			surg alone	-	55	-	11 (p=0.001)	26 (p=0.01)
Ajani 2013	97%ADC 3%SCC	preop	inductionCT-RCT-Surgery	5FU/oxaliplatin	55	26%	46	-
			RCT-surgery	5FU/oxaliplatin	54	13% (NS)	43	-
Crosby 2013	26%ADC 71%SCC	definitive	RCT	cape/DDP	129	-	25.4	-
			RCT+cetuximab	cape/DDP + cetux	129	-	22.1 (p=0.035)	-
Conroy 2014	85%ADC 15%SCC	definitive	RCT	FOLFOX	134	-	20.2	-
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Van Hagen 2012	75%ADC 25%SCC	preop	RCTpreop	CBDCA/taxol	178	29%	49.4	-
			surgery	-	188	-	24.0 (p=0.003)	-

Perspectives in RCT

- **PReoperative Chemoradiation (Paclitaxel-carboplatin or FOLFOX) for Resectable Esophageal and Junctional Cancer (PROTECT)**

  Preop RCT CBDCA/Taxol vs RCT FOLFOX

- **NCT01333033**

  Preop FOLFOX vs CBDCA then RCT (backbone CT according to early FDGPET response)

CONCLUSIONS

Surgery alone no longer standard of care

Adjuvant CT or RCT not efficient

Preop CT or RCT valuable options (RCT > CT?)

No obvious difference between drugs in terms on efficacy

Obvious differences between drugs in terms of safety

High medical need for predictive tools

Thanks for the attention

Chemotherapy toxicity constraints

Upper GI: technical and clinical challenges for radiation oncologists

Alain Hendlisz
Institut Jules Bordet
28th may 2016

INSTITUT JULES BORDET INSTITUUT

ESTRO School

Toxicity from Combined Modality is complex

Exclusion criteria for CT

5FU: DPD deficiency
Allergy to the compound
Recent ischemic cardiac event (<6months)

DDP: Renal insufficiency
Allergy to the compound
Recent ischemic cardiac event (<6months)
Polyneuropathy

Oxaliplatin: Allergy to the compound
Recent ischemic cardiac event (<6months)
Polyneuropathy

Paclitaxel: Liver tests alteration
Major fluid effusion (pleural, ascitis, …)
Allergy to the compound
Recent ischemic cardiac event (<6months)
Polyneuropathy

Irinotecan: Gilbert syndrom
Direct bilirubin increase
Intestinal events (obstruction, chronic/acute inflammation)
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PLATINUM SALTS

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Toxicities associated with monthly 5FU/DDP

Study	Arms	RT	N	histol	severe GI toxicity	severe hematol tox	life-threatening
Herscovic 1992	RT alone	64Gy (2Gy/f)	60	20%SCC 80%ADC	18%	3%	3%
	RCT (monthly DDP/5FU)	50Gy (2Gy/f)	61		41% (incl 33% stomatitis)	48%	20%
Walsh 1995	Surg alone	-	58	100%ADC			
	preopRCT (monthly DDP/5FU)	40Gy (2.6Gy/f)	55		5%	4%	5%

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Walsh 1995	Surg alone	-	58	100%ADC	-	-	-
	preopRCT (monthly DDP/5FU)	40Gy (2.6Gy/f)	55		5%	4%	5%
VanCutsem 2006	monthly DDP/5FU	-	224	100%ADC	47% (incl 27% stomatitis)	57%	12%

Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial

DDP 60 mg/m² (D1) & **capecitabine** 625 mg/m² 2*(D1-21)
cycles 3 and 4 with RT (50 Gy/25 fractions) +/- weekly **cetuximab**

Arm	mOS (months)	grade III-IV non-hematol tox (%)	
RCT	25.4	63	
RCT+cetux	22.1 (p=0.035)	79* (p=0.004)	* including 3 treatment-related deaths

19% no RT in cetux arm (vs 8%)

Crosby et al Lancet Oncol 2013

	CRT plus cetuximab (n=129)	CRT only (n=129)
Haematological	27 (21%)	36 (28%)
Haemoglobin	3 (2%)	3 (2%)
WBC	14 (11%)	21 (16%)
ANC	15 (12%)	24 (19%)
Platelets	11 (9%)	6 (5%)
Lymphocytes	5 (4%)	3 (2%)
Non-haematological	102 (79%)	81 (63%)
Cardiac disorders	8 (6%)	2 (2%)
Cardiac ischaemia/infarction	3 (2%)	1 (<1%)
Other	5 (4%)	1 (<1%)
Dermatological	28 (22%)	5 (4%)
Acne	9 (7%)	0
Hand-foot syndrome	7 (5%)	4 (3%)
Rash	14 (11%)	0
Other	9 (7%)	1 (<1%)
Metabolic/laboratory	31 (24%)	14 (11%)
Hypomagnesia	9 (7%)	2 (2%)
Hypokalaemia	9 (7%)	7 (5%)
Hypophosphataemia	6 (5%)	1 (<1%)
Hyponatraemia	2 (2%)	1 (<1%)
Bilirubin	2 (2%)	0
Hyperuricaemia	2 (2%)	0
Other	13 (10%)	6 (5%)
Pulmonary	8 (6%)	4 (3%)
Dyspnoea	8 (6%)	3 (2%)
Other	2 (2%)	1 (<1%)
Constitutional symptoms	27 (21%)	26 (20%)
Fatigue	26 (20%)	25 (19%)
Weight loss	3 (2%)	3 (2%)
Gastrointestinal	55 (43%)	57 (44%)
Diarrhoea	12 (9%)	8 (6%)
Dysphagia	35 (27%)	37 (29%)
Stomatitis	4 (3%)	2 (2%)
Nausea	6 (5%)	11 (9%)
Oesophagitis	3 (2%)	7 (5%)
Vomiting	7 (5%)	11 (9%)
Anorexia	12 (9%)	13 (10%)
Other	7 (5%)	9 (7%)
Infection	8 (6%)	9 (7%)
Febrile neutropenia	3 (2%)	3 (2%)
Infection with normal ANC	5 (4%)	6 (5%)
Neurological	5 (4%)	5 (4%)
Vascular	14 (11%)	13 (10%)
Thrombosis/thrombus/embolism	14 (11%)	12 (9%)
Other	2 (2%)	1 (<1%)
Other	12 (9%)	10 (8%)

All randomly assigned patients received at least one dose of treatment. CRT=chemoradiotherapy. WBC=white blood cell. ANC=absolute neutrophil count. CTCAE=Common Terminology Criteria for Adverse Events.

Table 3: CTCAE grade 3 or 4 toxicity in patients during treatment (weeks 1 to 12)

Toxicities associated with Oxaliplatin

Study	Arms	RT	N	histol	severe GI toxicity	severe hematol tox
Ajani 2013	induct 5FU IVC/ weekly oxali ° +RCT 5FU IVC/weekly oxali	50.4Gy (2Gy/f)	55	97%ADC 3%SCC	<5%	<5%
	RCT 5FU IVC/weekly oxali		54		<5%	<5%

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	RCT 5FU IVC/weekly oxali		54		<5%	<5%
Conroy 2014	FOLFOX-RCT	50Gy (2Gy/f)	134	85%ADC 15%SCC	≈30%	29%
	monthly 5FU/DDP-RCT	50Gy (2Gy/f)	133		≈30%	29%

Different schedules of CT – Different irradiation fields… Different toxicities

Study	Histol	Intent	Arms	Drugs	N	pCR	mOS (months)	2-yr OS
Herskovic 1992	20%SCC 80%ADC	definitive	RCT (50Gy)	5FU/DDP	129	NA	8.9	38%
			RT (64Gy)	-		NA	12.5	50% (p<0.001)
Bosset 1996	SCC	preop	RCT (18.5Gy split dose preop	DDP	143	26%	18.6	-
			surg alone	-	139	-	18.6	-
Walsh 1996	ADC	preop	RCT (40Gy) preop	5FU/DDP	58	25%	16	37
			surg alone	-	55	-	11 (p=0.001)	26 (p=0.01)
Ajani 2013	97%ADC 3%SCC	preop	inductionCT-RCT-Surgery	5FU/oxaliplatin	55	26%	46	-
			RCT-surgery	5FU/oxaliplatin	54	13% (NS)	43	-
Ilson 2012	75%ADC 25%SCC	preop	inductionCT-RCT-surg	DDP/CPT11	55	16%	32	-
Crosby 2013	26%ADC 71%SCC	definitive	RCT	cape/DDP	129	-	25.4	-
			RCT+cetuximab	cape/DDP +cetux	129	-	22.1 (p=0.035)	-
Conroy 2014	85%ADC 15%SCC	definitive	RCT	FOLFOX	134	-	20.2	-
			RCT	5FU/DDP	133	-	17.5 (p=0.7)	-
Van Hagen 2012	75%ADC 25%SCC	preop	RCTpreop	CBDCA/taxol	178	29%	49.4	-
			surgery	-	188	-	24.0 (p=0.003)	-

IRINOTECAN

Toxicities associated with Irinotecan

Study	Arms	RT	N	histol	severe GI toxicity	severe hematol tox
Ilson 2012	preop weekly **Irino** 65mg/m^2/**DDP** 30mg/m^2 x 4 then idem+RT	50.4Gy (2Gy/f)	55	75%ADC 25%SCC	13%	31%* *5% neutropenic fever

12% ThromboEmbolic Events
8% no RT
5% post-operative mortality

Study	Histol	Intent	Arms	Drugs	N	pCR	mOS (months)	2-yr OS
Herskovic 1992	20%SCC 80%ADC	definitive	RCT (50Gy)	5FU/DDP	129	NA	8.9	38%
			RT (64Gy)	-		NA	12.5	50% (p<0.001)
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			surg alone	-	139	-	18.6	-
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			RCT-cetuximab	cape/DDP + cetux	129	-	22.1 (p=0.035)	-
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			RCT	5FU/DDP	133	-	17.5 (p=0.7)	-
Van Hagen 2012	75%ADC 25%SCC	preop	RCTpreop	CBDCA/taxol	178	29%	49.4	-
			surgery	-	188	-	24.0 (p=0.003)	-

PACLITAXEL

Toxicities associated with CBDCA/paclitaxel

Study	Arms	RT	N	histol	severe GI toxicity	severe hematol tox
Van Hagen 2012	preop CBDCA/paclitaxel-RCT	41.4Gy (1.8Gy/f)	178	75%ADC 23%SCC	6%	2%
	surgery	-	188		-	-

R0 resection 92% RCT–surgery versus 69% surgery (P<0.001)
4% postoperative mortality (both groups)
8% no RT in RCT group

Combined Modality Toxicity is complex

depends on:

the patients' particular medical condition

the pattern of RT (dose,fraction, length, fields, dosimetry, …)

the drugs and schedule

the intent of treatment

But the whole team should take responsibility

CONCLUSIONS

Toxicity from combined RCT variable and difficult to assess

< **H**uge heterogeneity of CT and RT variables

Highly dependant on treatment modalities

Tailoring therapy allowed

RCT work in progress needing cross-talks between specialties

THANK YOU

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ESTRO:
Upper GI: technical and clinical challenges for Radiation Oncologists

Oesophagus: Primary tumor extension pathology evaluation

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 7th edition (since 2010)
- Importance of lymph nodes metastasis
- Patho-anatomical basics, reportings and technical workflow

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Facts

- Germany 2016: 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% SCC
- 40% Adenocarcinoma

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

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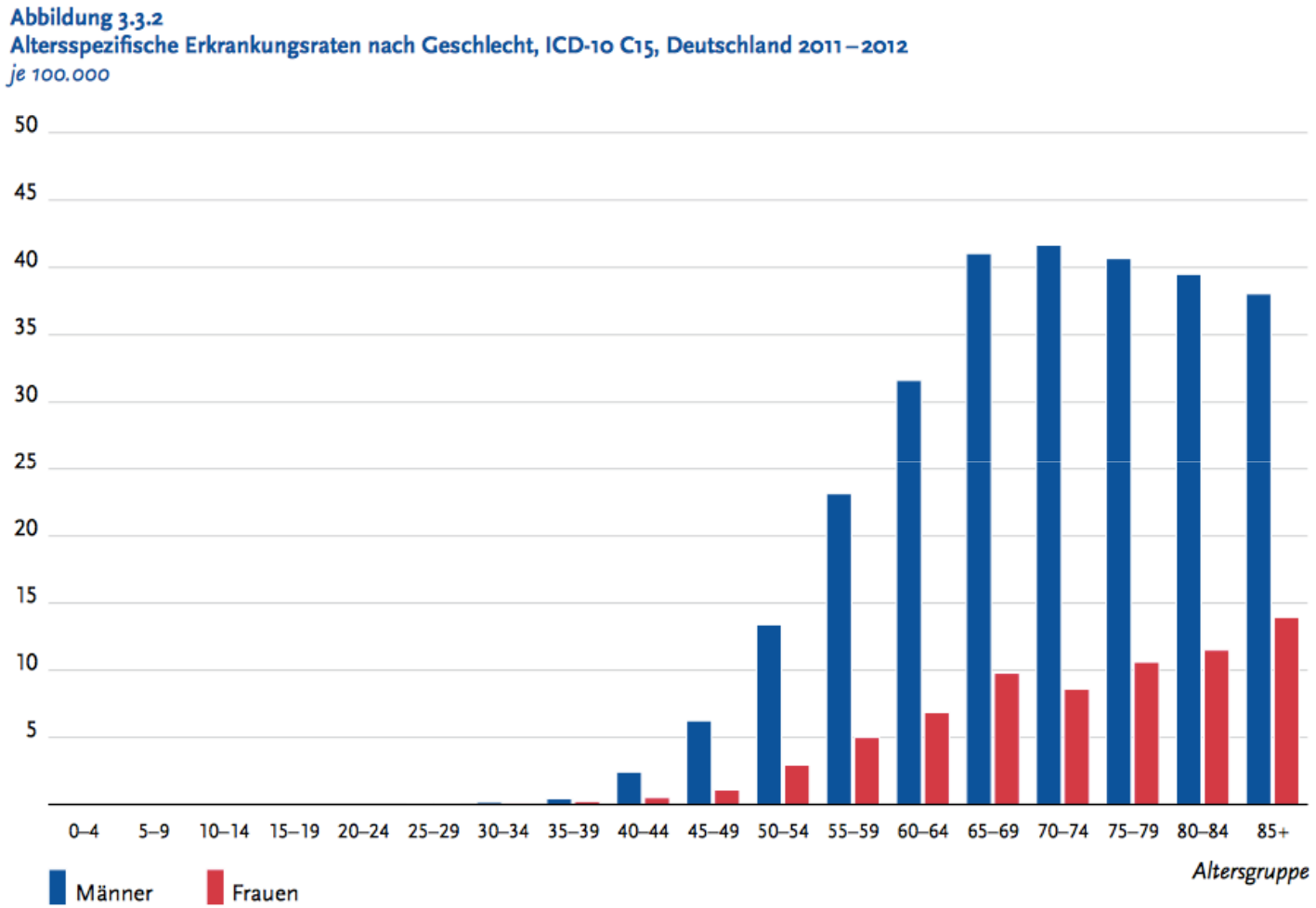
Facts – age distribution



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

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Usually: SCC or Adeno-Ca

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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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

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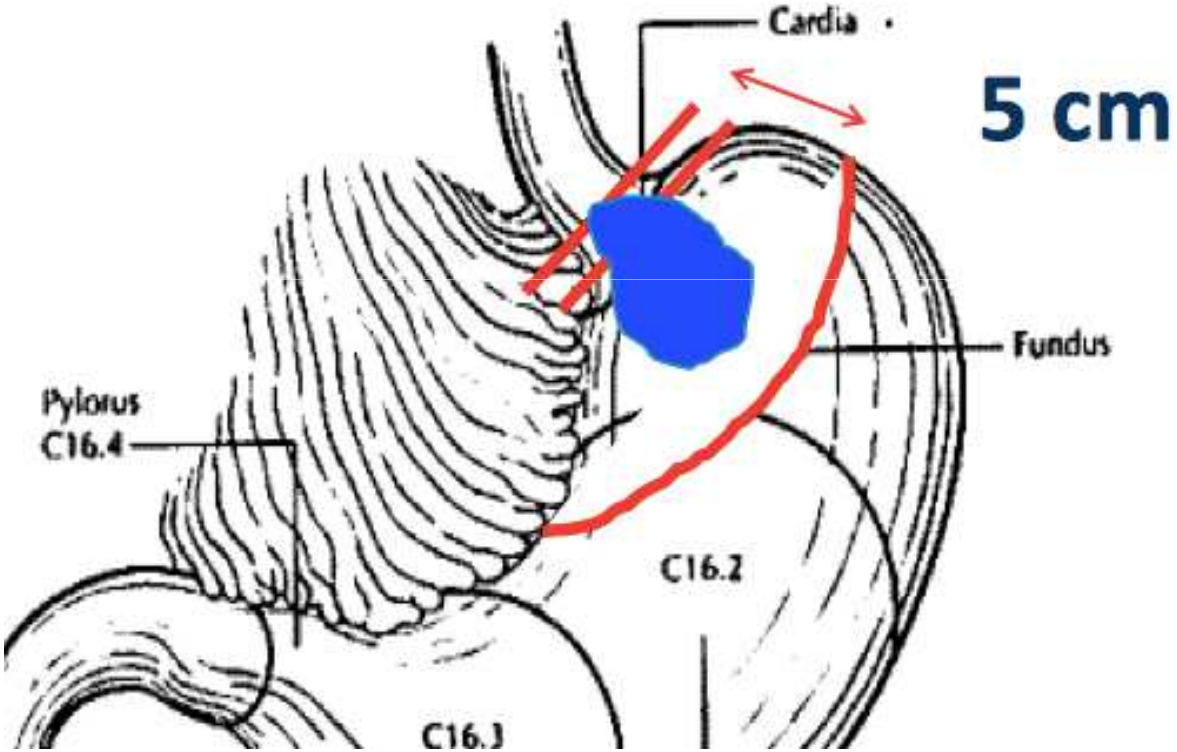
Definition oesophageal/gastric adenocarcinoma Definition changed 2010



A tumour of epicentre 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 epicentre 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

Modified from: Wittekind and Schmiegel

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Staging: UICC

Oesophagus 7th edition

TNM definitions: AJCC = UICC

Tis	Carcinoma in situ /High-grade dysplasia
T1	lamina propria or submucosa
	T1a lamina propria or muscularis mucosae
	T1b submucosa
T2	muscularis propria
T3	adventitia
T4	adjacent structures
	T4a pleura, pericardium, diaphragm, or adjacent peritoneum
	T4b other adjacent structures, e.g. aorta, vertebral body, trachea

N0	No regional lymph node metastasis
N1	1 to 2 regional lymph nodes
N2	3 to 6
N3	>6

[N1 was site dependent]

M - Distant Metastasis

M1 Distant metastasis

[M1a,b were site dependent]

Changes from 6th edition

Union for International Cancer Control www.uicc.org

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

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Staging: UICC

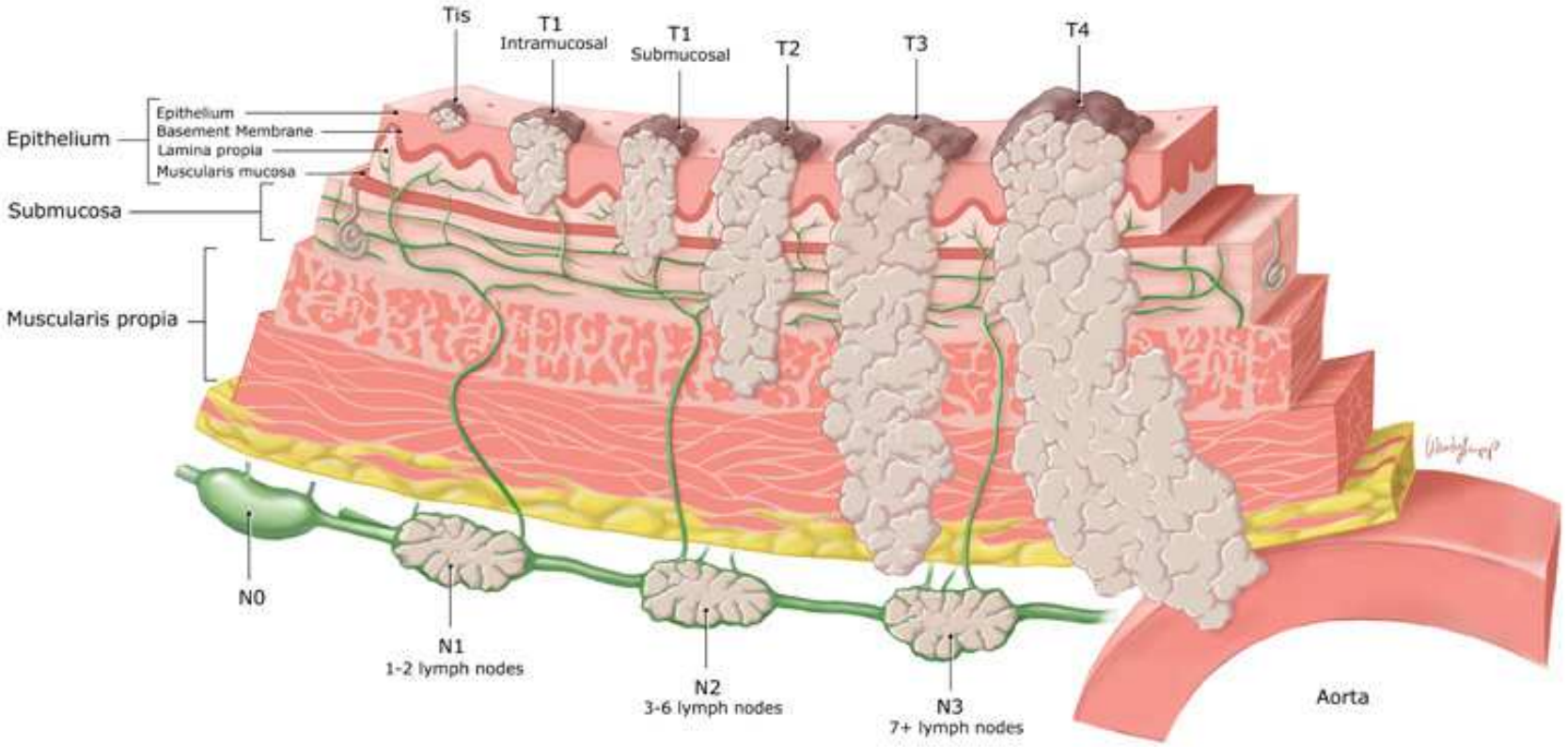
pT1a is sub-divided

- 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

Esophageal Cancer Staging



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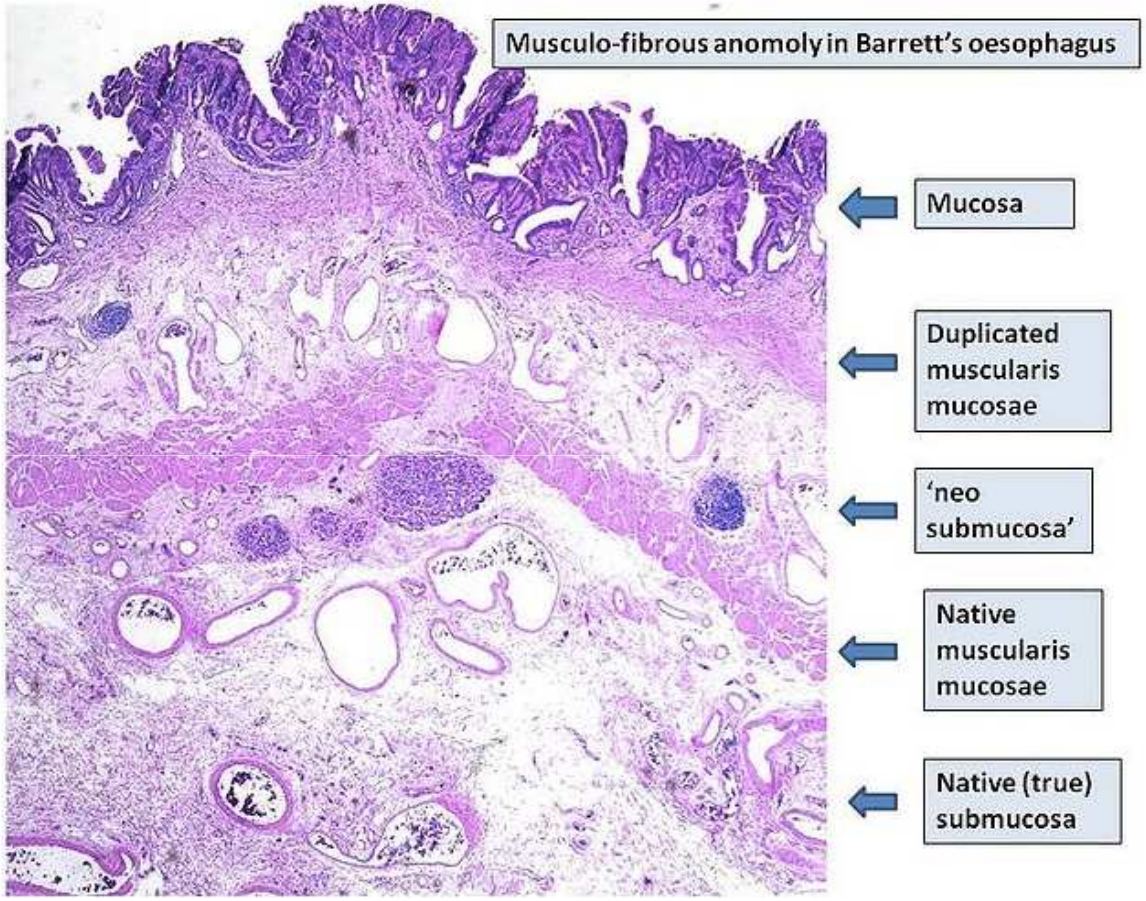
double layer of muscularis mucosae in Barrett (pT1a; m1-m4)



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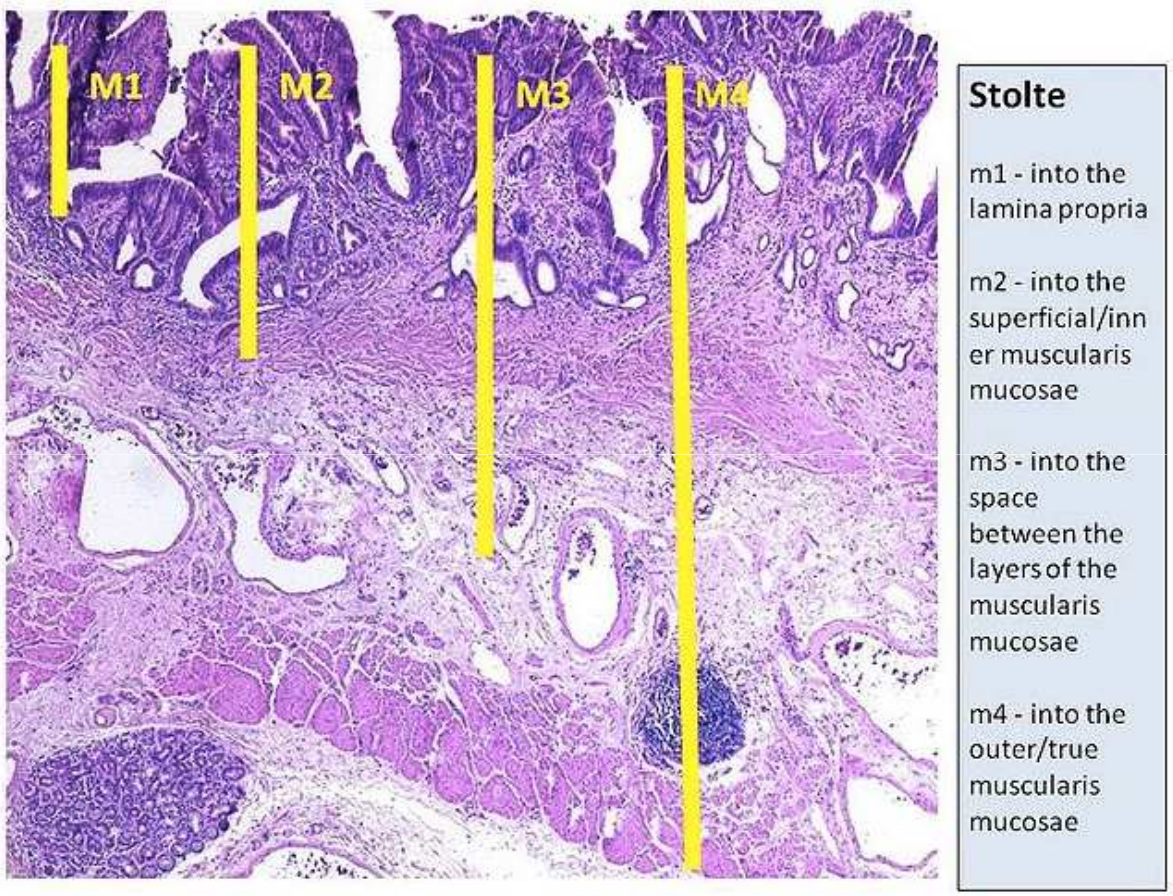
double layer of muscularis mucosae in Barrett (pT1a; m1-m4)

Stolte staging system (mucosa)



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:

1) Depth of invasion (primary tumor extension)
2) Lymph node involvement
3) Stage/prognostic groupings

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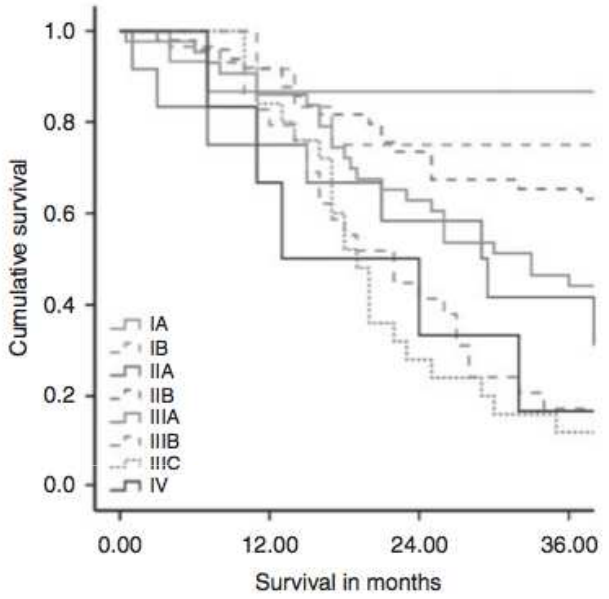
Prognostic grouping

Prognostic grouping: Squamous cell carcinoma

	T	N	M	Grade	Location*
Group 0	Tis	0	0	1	Any
Group IA	1	0	0	1, X	Any
Group IB	1	0	0	2, 3	Any
	2, 3	0	0	1, X	Lower, X
Group IIA	2, 3	0	0	1, X	Upper, middle
	2, 3	0	0	2, 3	Lower, X
Group IIB	2, 3	0	0	2, 3	Upper, middle
	1, 2	1	0	Any	Any
Group IIIA	1, 2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
Group IIIB	3	2	0	Any	Any
Group IIIC	4a	1, 2	0	Any	Any
	4b	Any	0	Any	Any
	Any	3	0	Any	Any
Group IV	Any	Any	1	Any	Any

Biggest problem in oesophageal carcinoma:

- Lymph nodes metastasis indicate poor prognosis
- Metastasizes early
- Often: locally advanced tumors



No. at risk	0 months	12 months	24 months	36 months
Stage IA	15	13	13	13
Stage IB	12	11	9	9
Stage IIA	12	9	7	4
Stage IIB	49	45	36	30
Stage IIIA	43	37	27	19
Stage IIIB	29	23	12	4
Stage IIIC	25	21	7	3
Stage IV	6	4	2	1

Figure 3 Oesophageal cancer survival related to TNM7 prognostic groups.

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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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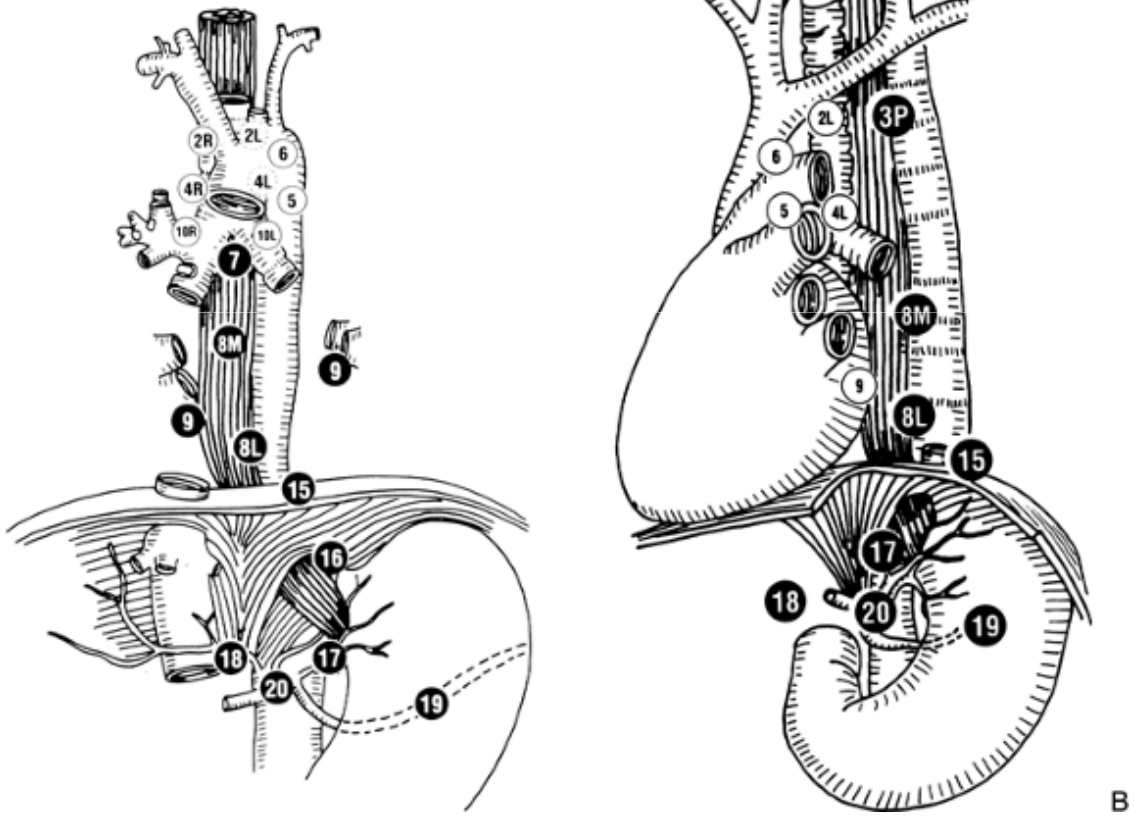
Regional Lymph Nodes

Localisation using TNM 7th edition:

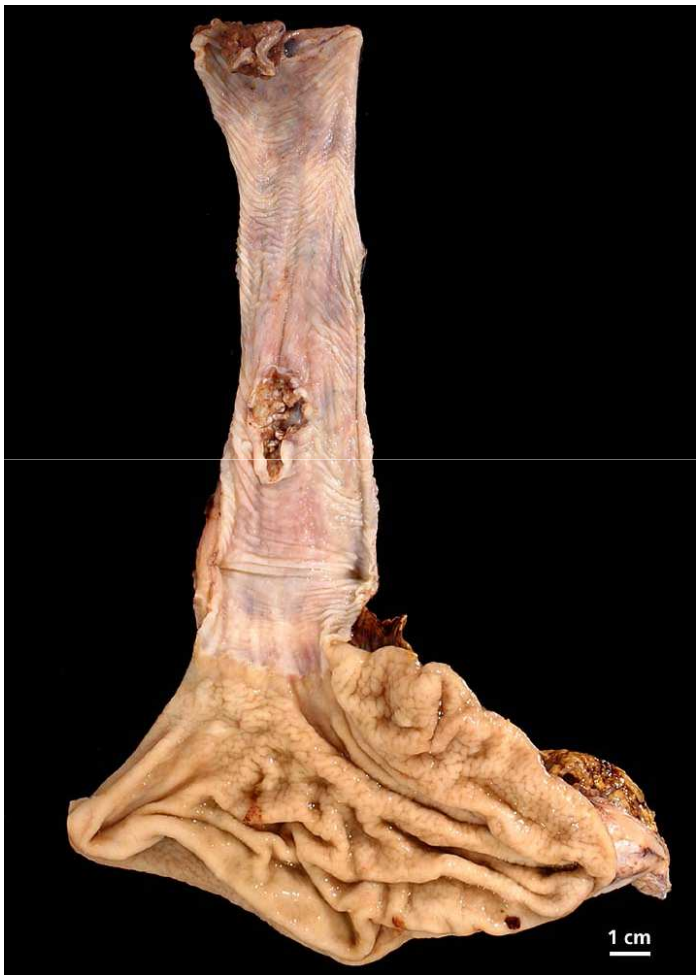
- Regional lymph nodes, irrespective of the site of the primary those in the oesophageal drainage – including:

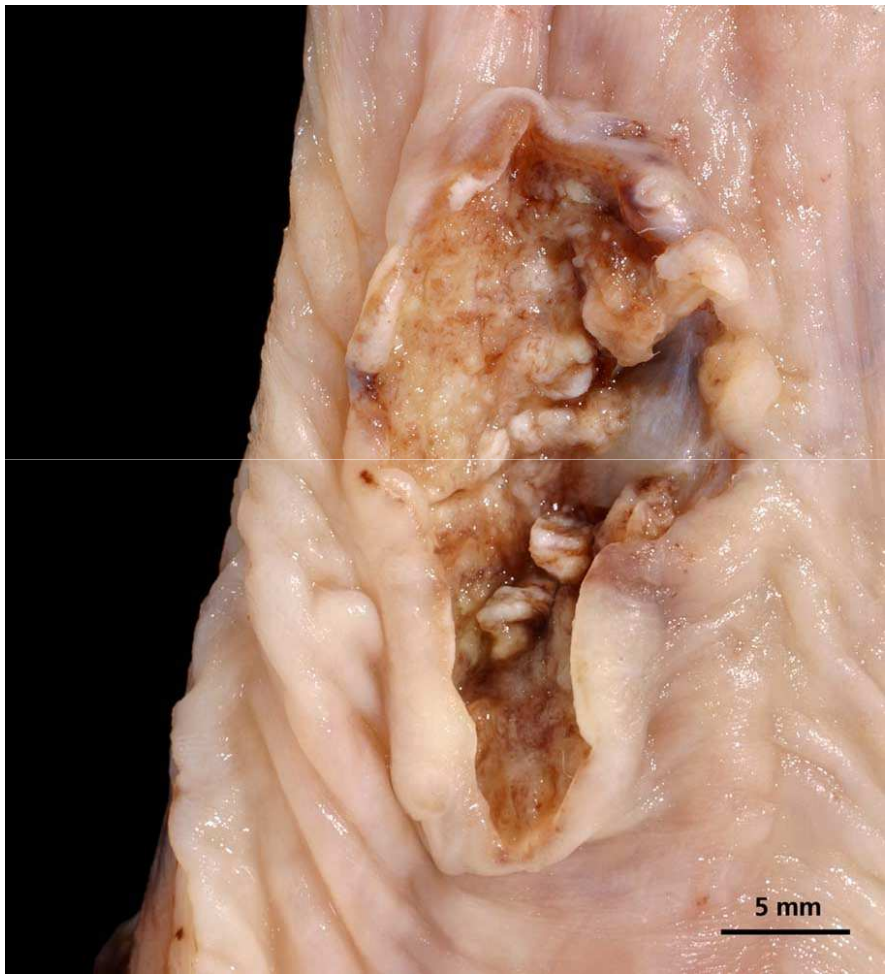
paraoesophageal, paratraechael,
dorsal medistinum, lung hilum,
inferior thyroid artery,
left gastric artery (celiac axis)
paraesophageal in the neck.



How many we need:

- >15 lymph nodes





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

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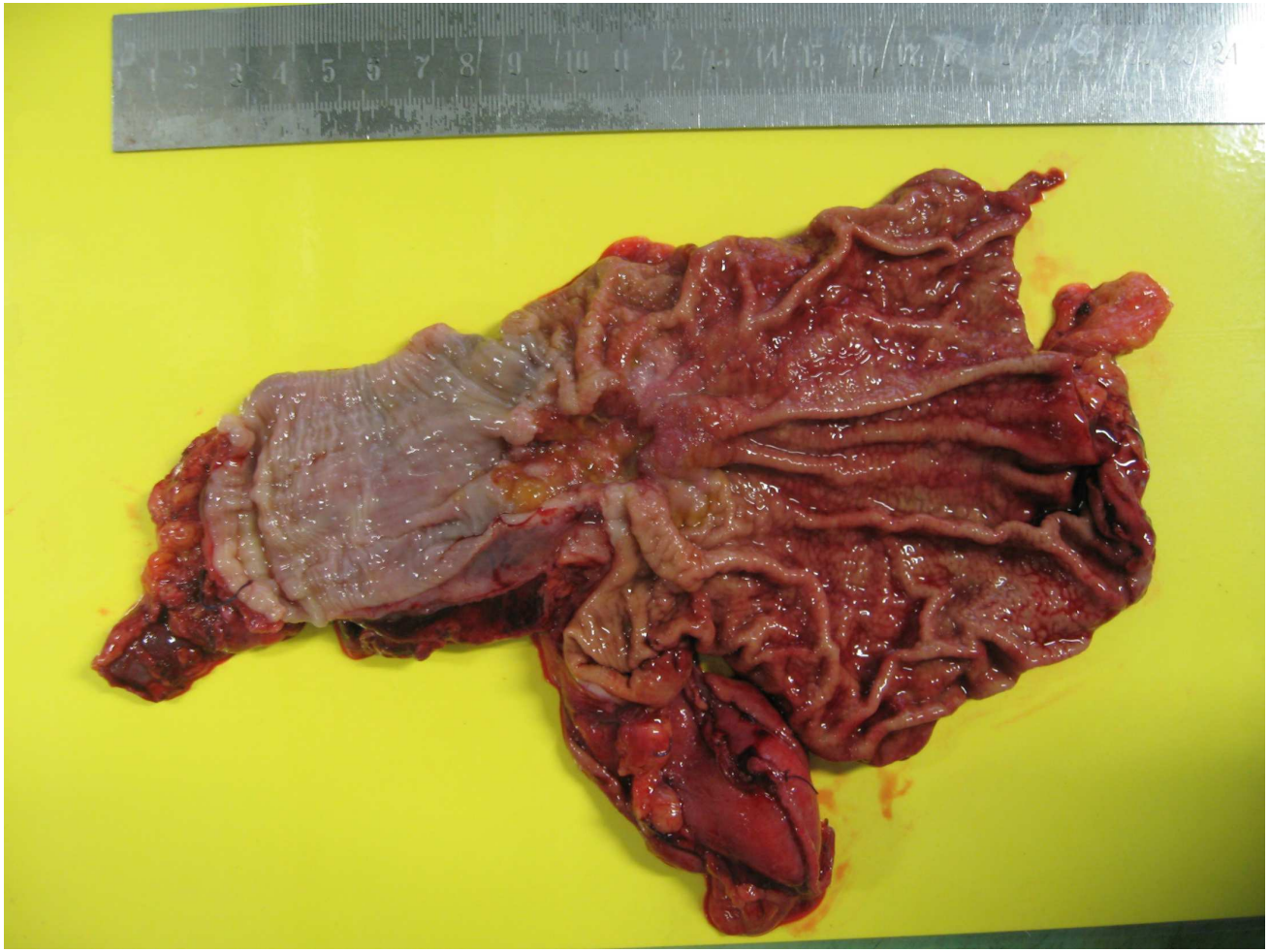
Adenocarcinoma



Localisation: distal parts of oesophagus/oesophgeal-gastric junction

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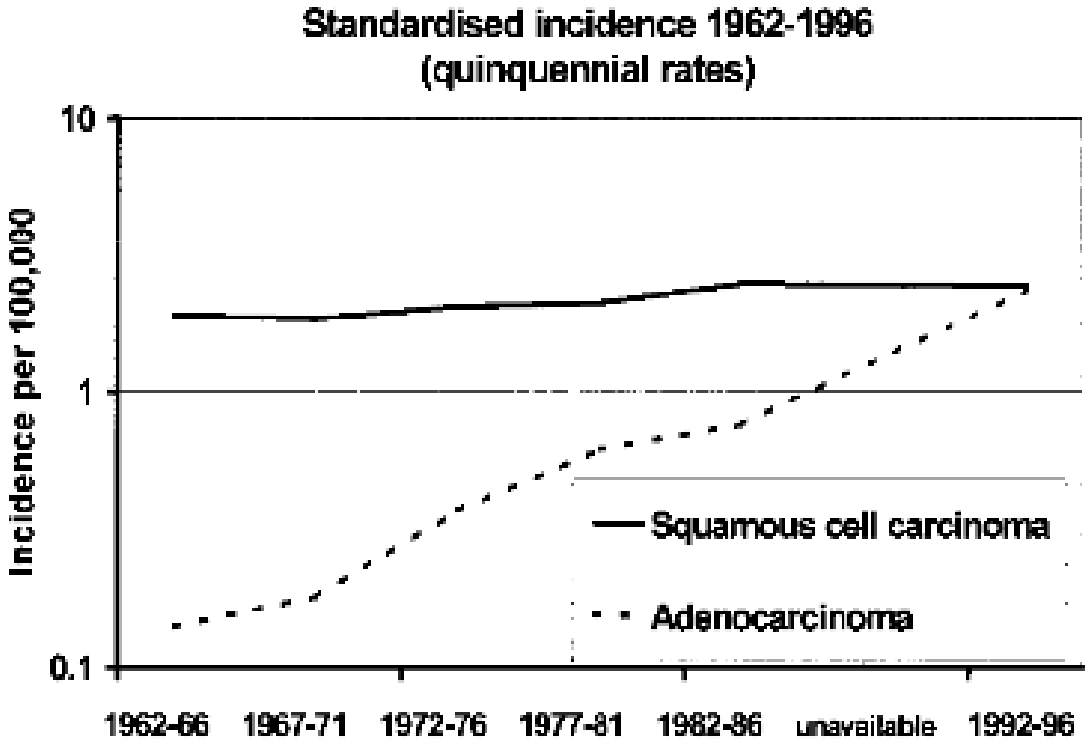
Adenocarcinoma of eosophagus: Incidence continues to increase



From: Powell et al. Int J Cancer 2003

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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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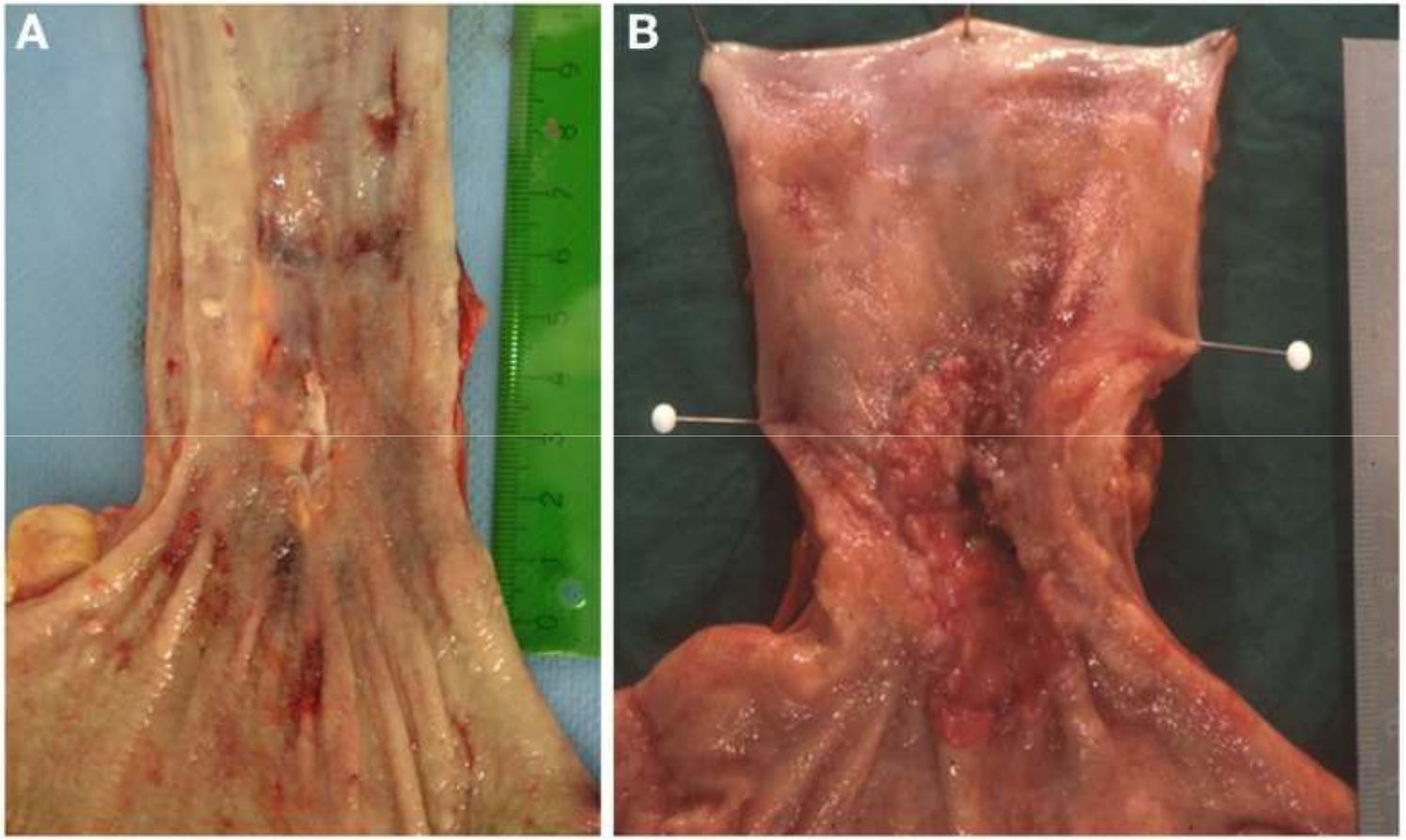
Photographic documentation Adenocarcinoma



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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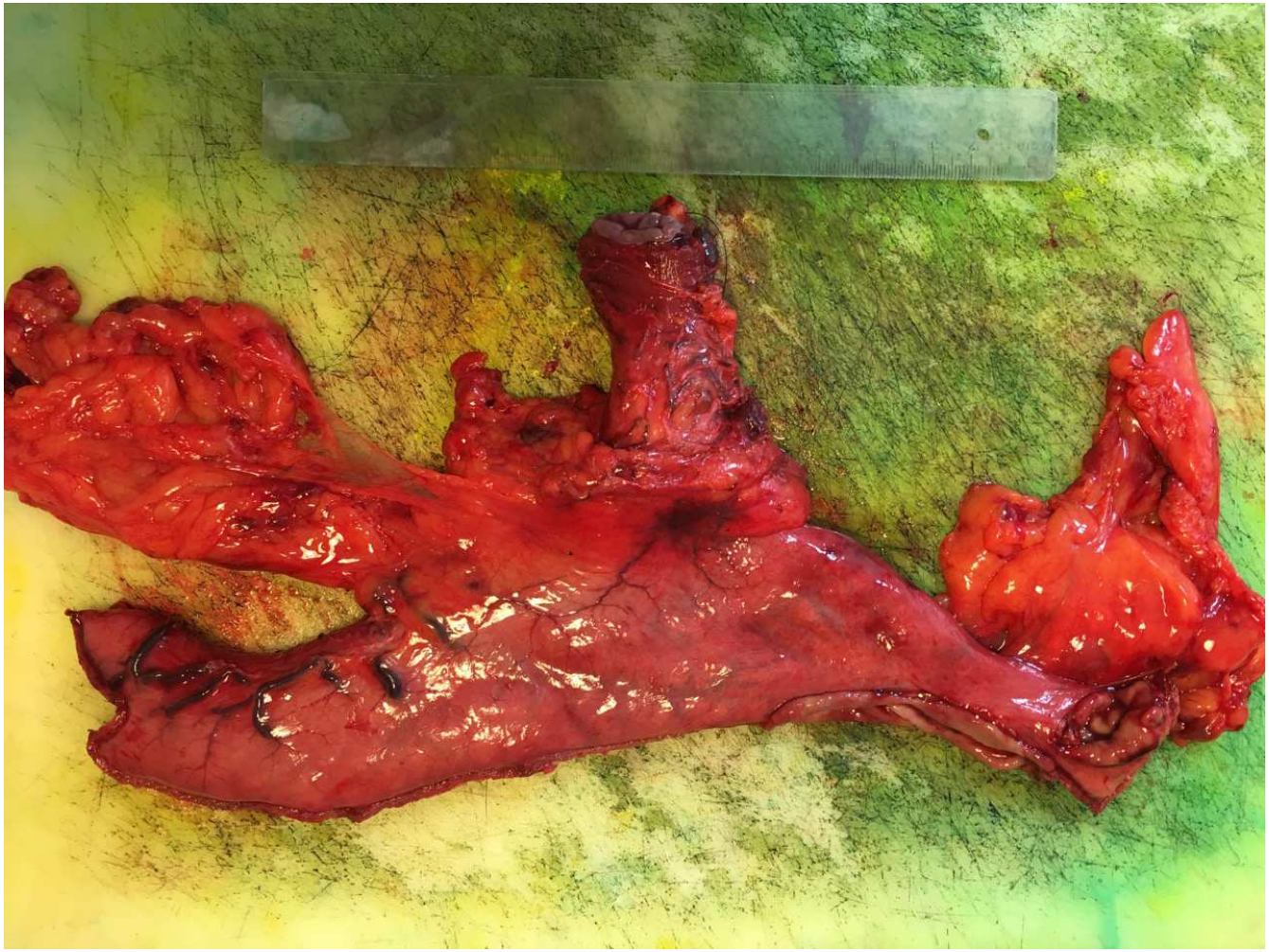
Surgical specimens



Adenocarcinoma of GEJ

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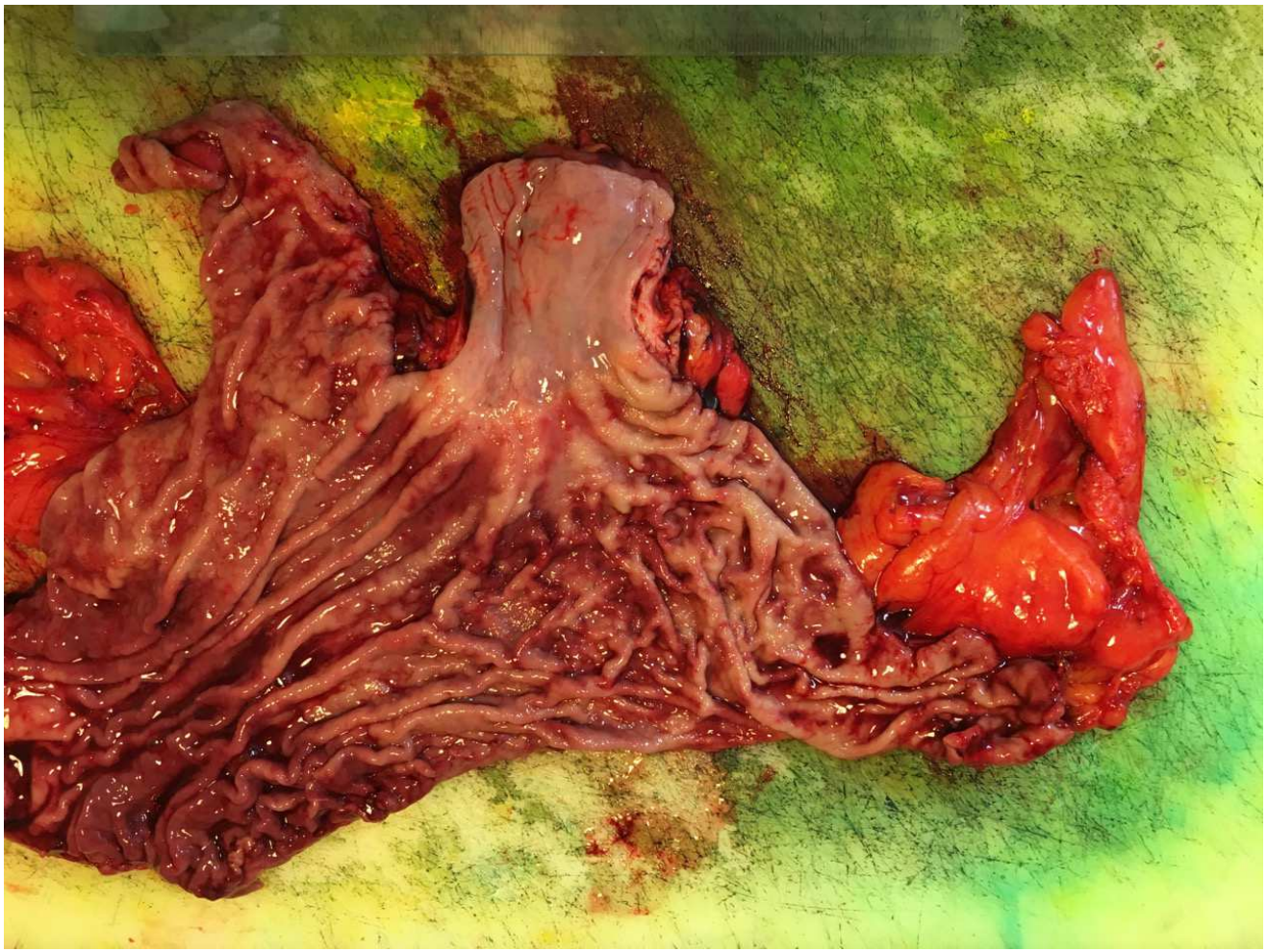
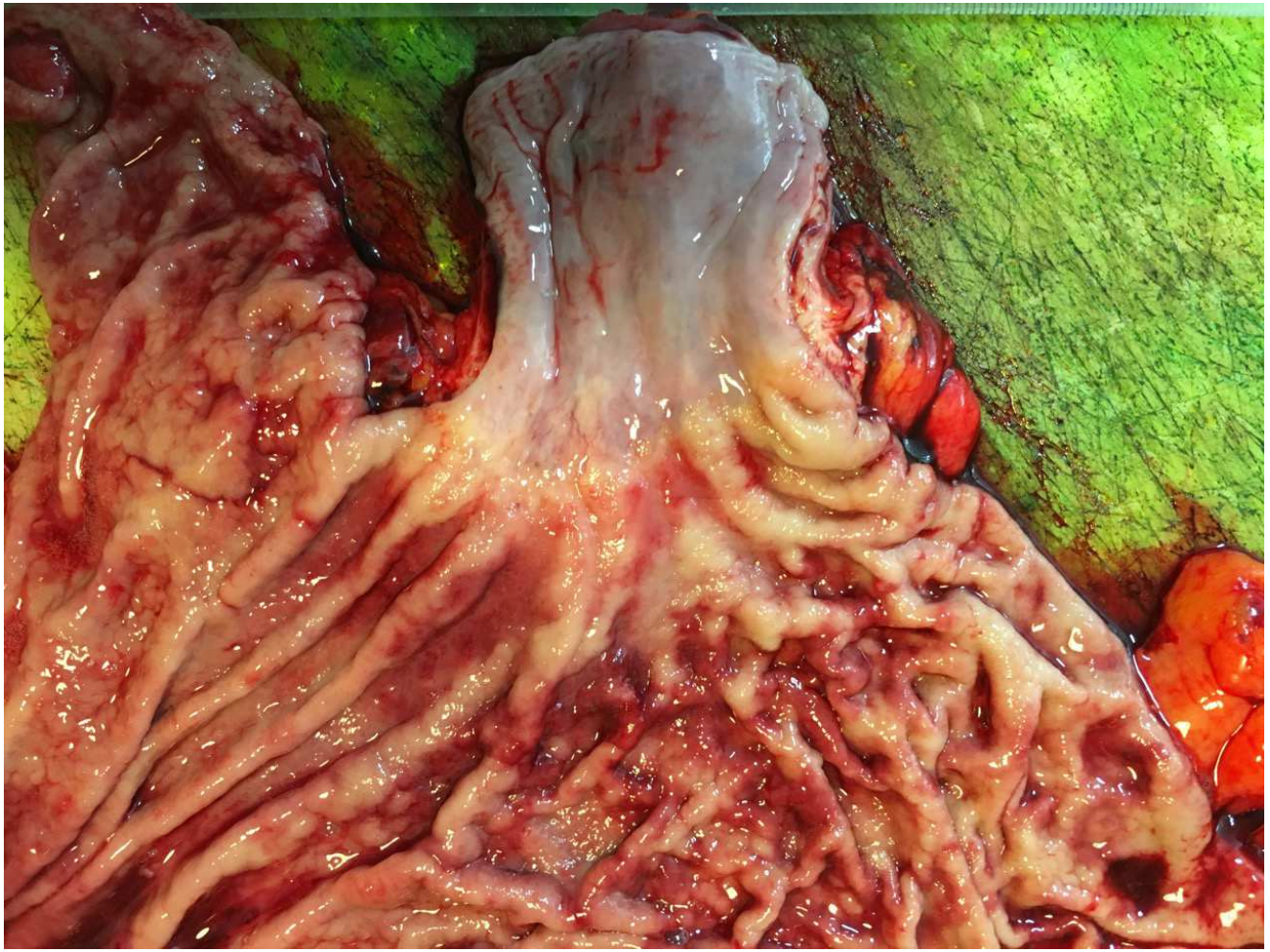
Surgical specimens



Adenocarcinoma of GEJ

UNIKLINIK KÖLN

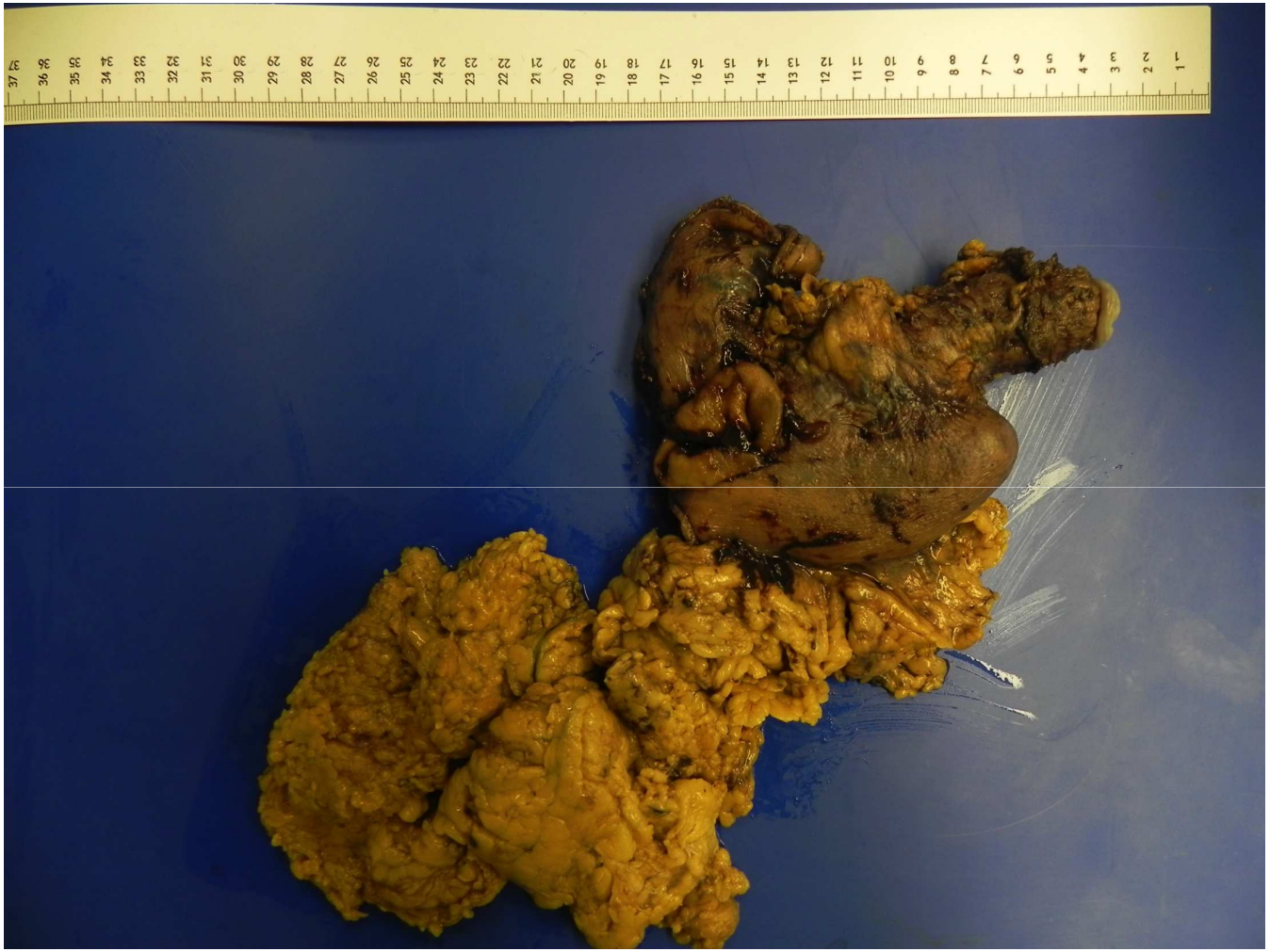
Surgical specimens



Adenocarcinoma of GEJ

UNIKLINIK KÖLN

Surgical specimens



Adenocarcinoma of GEJ – distal oesophagus/proximal stomach incl. omentus majus
After neodjuvant treatment

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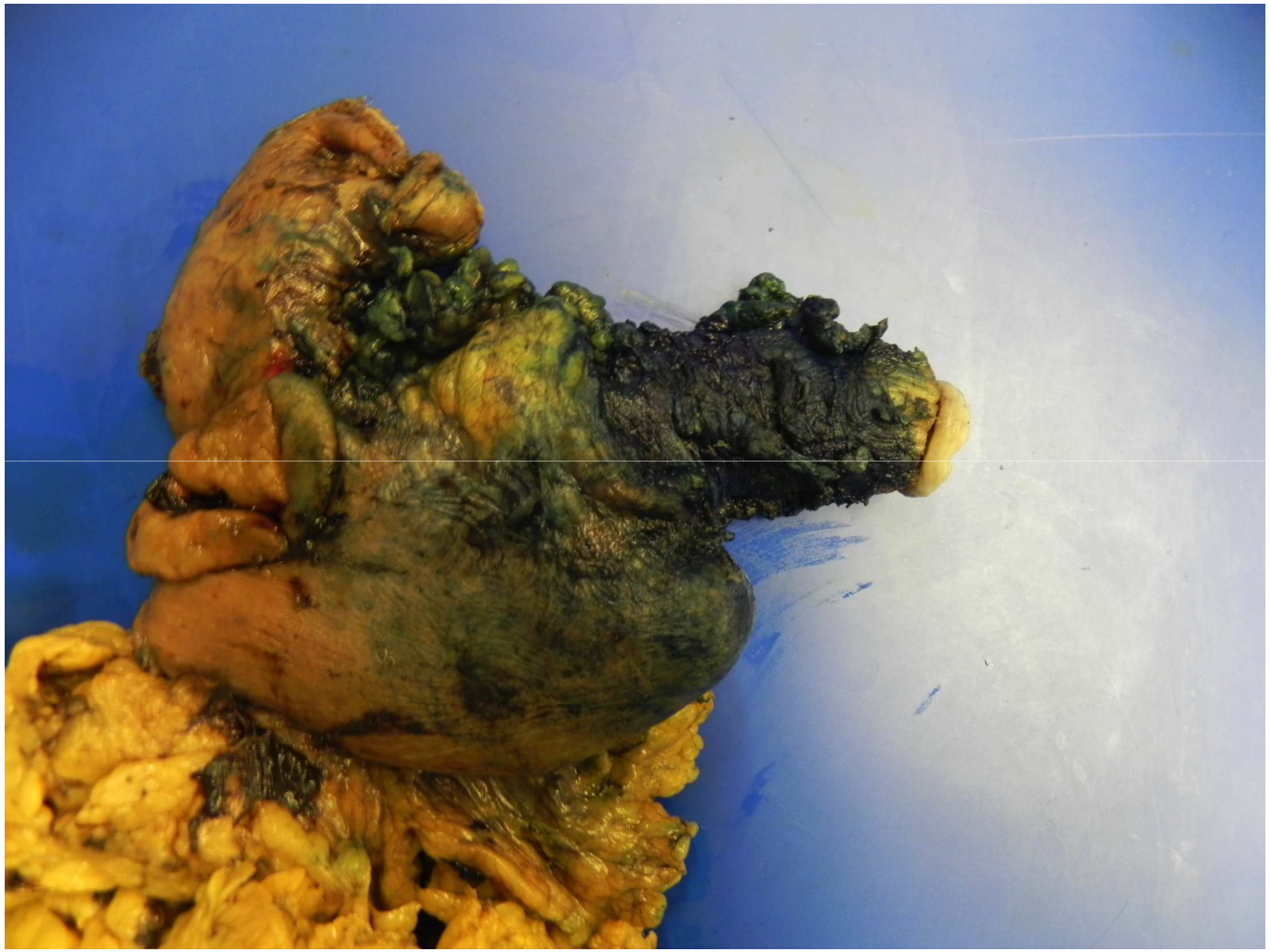
Surgical specimens



Colour-marked circumferential margin

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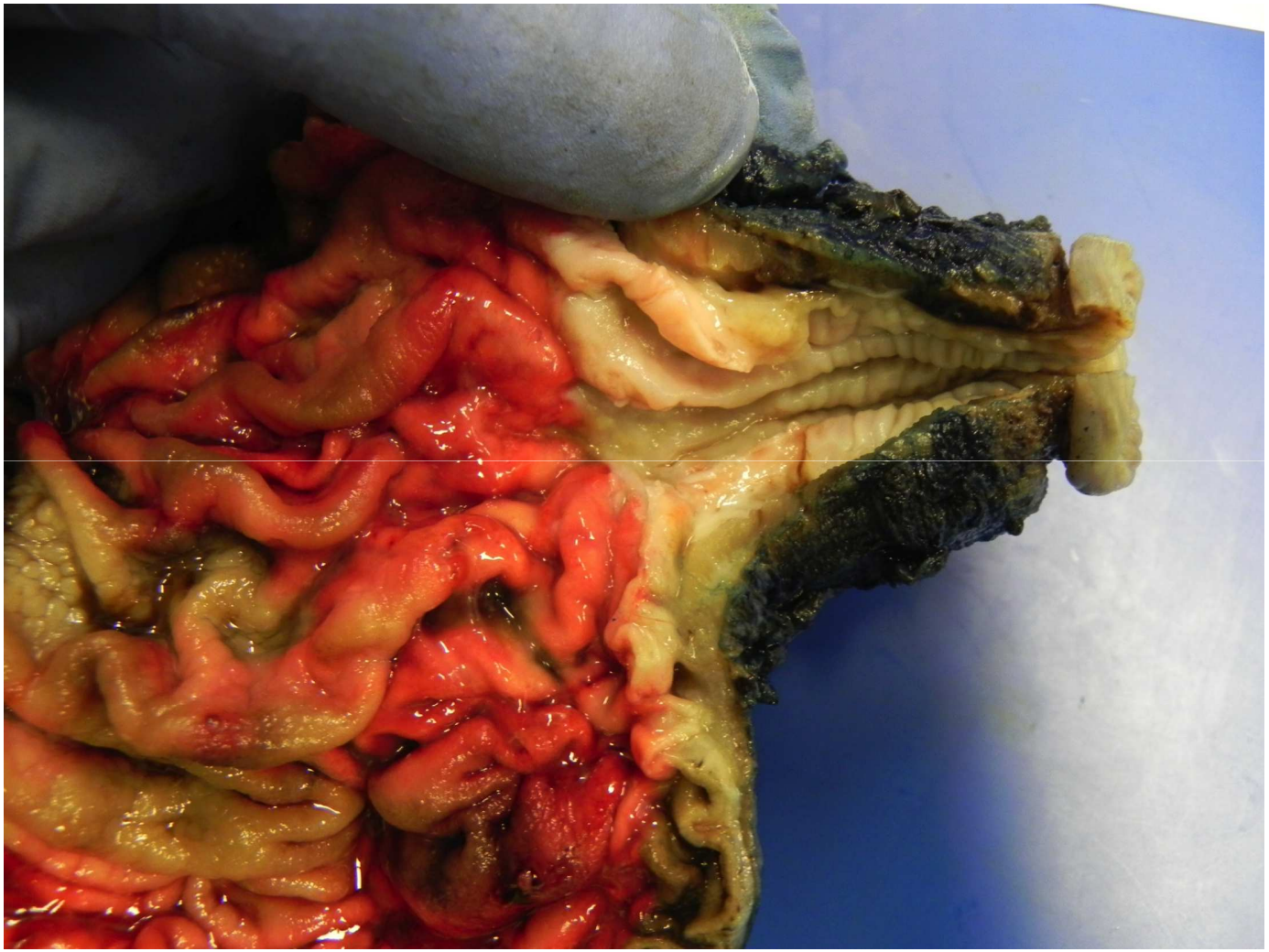
Surgical specimens



Macroscopically just small residual tumor.

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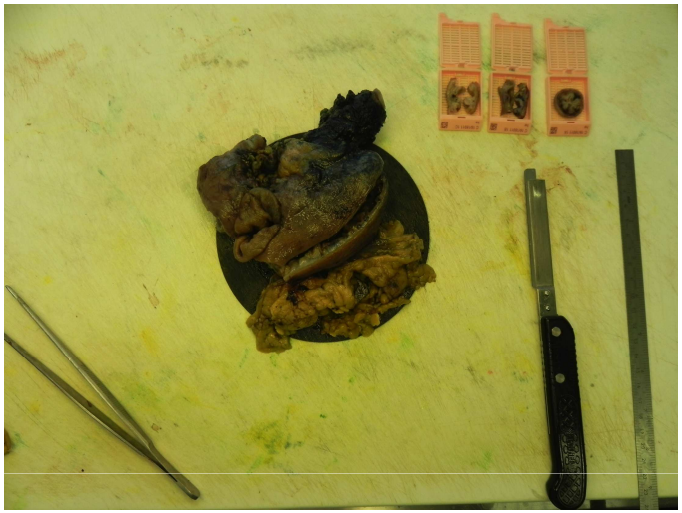
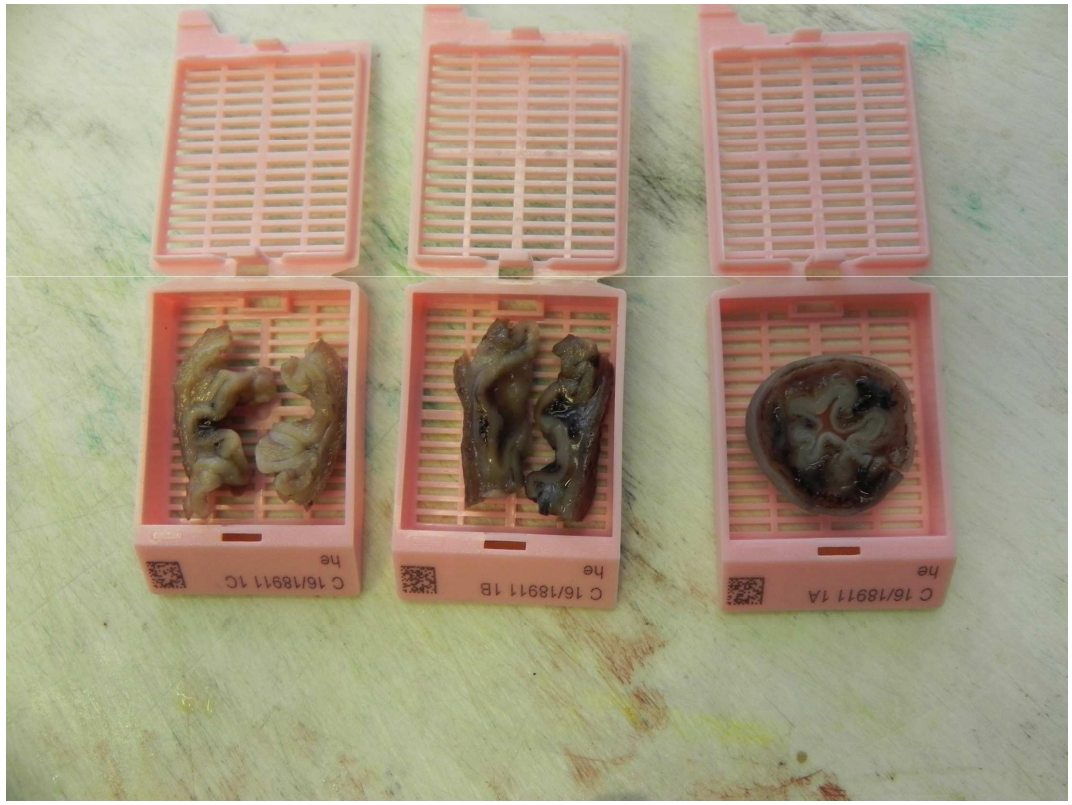
Surgical specimens





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 4-5 mm thick

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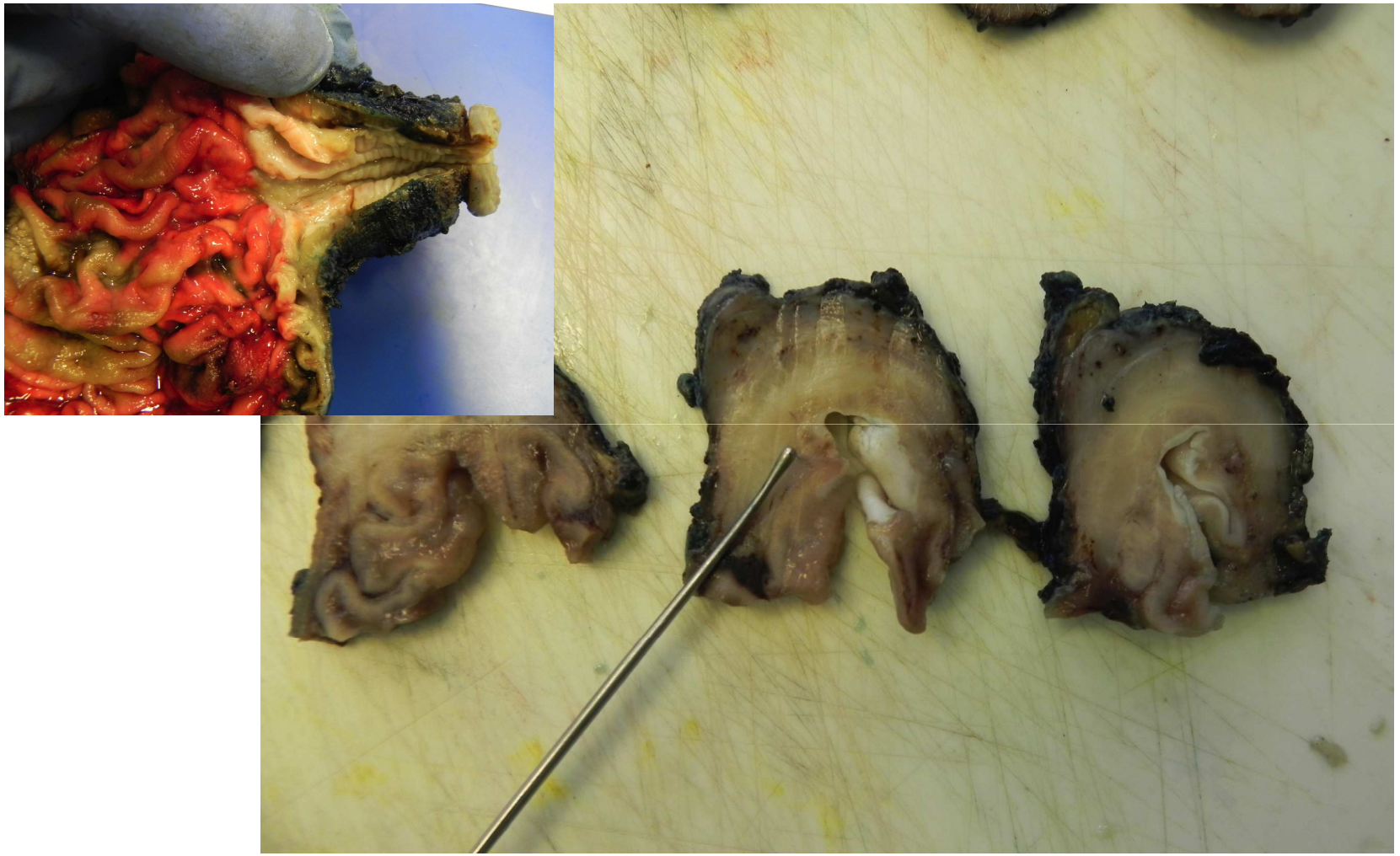
Surgical specimens



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

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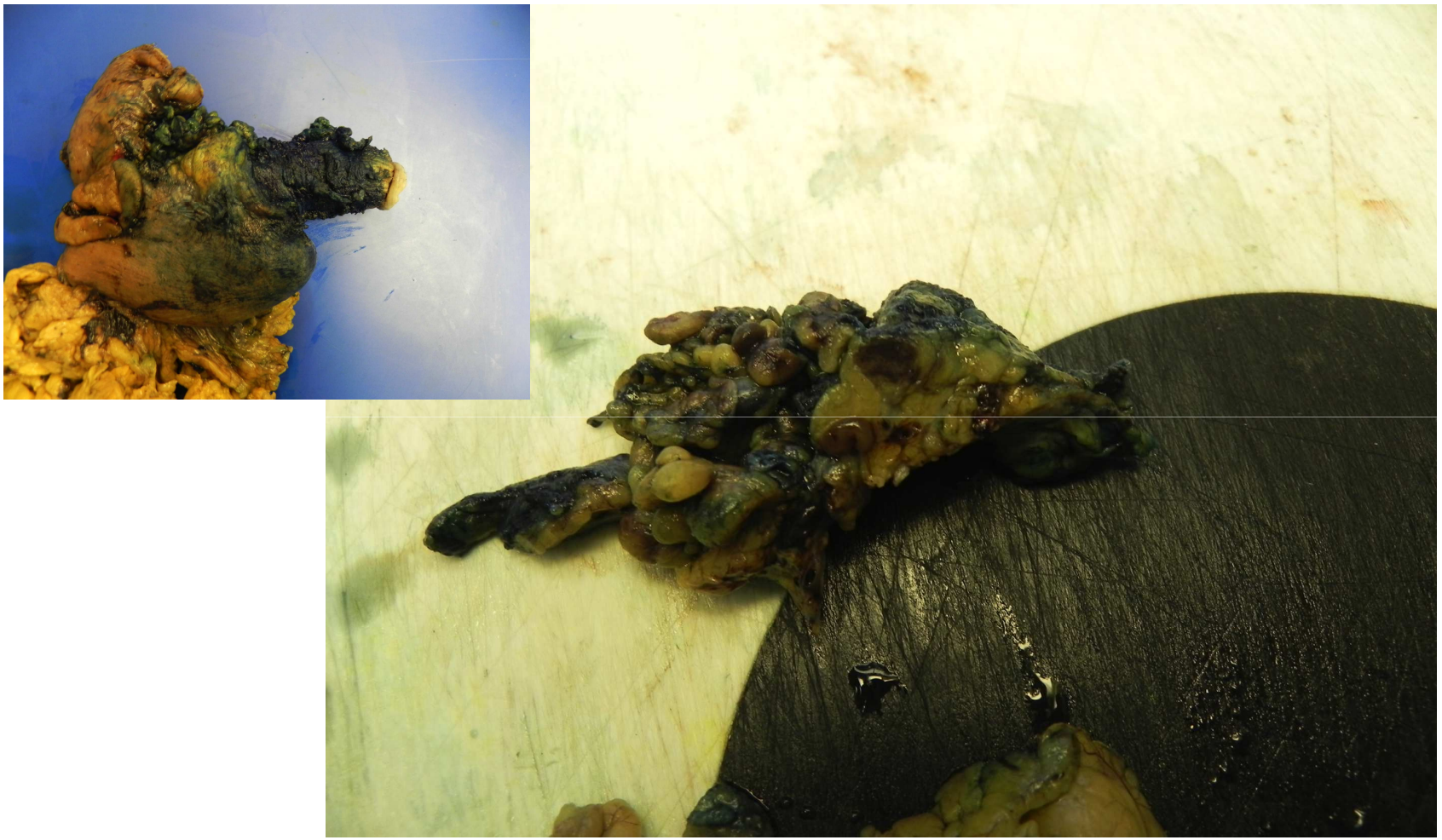
Surgical specimens



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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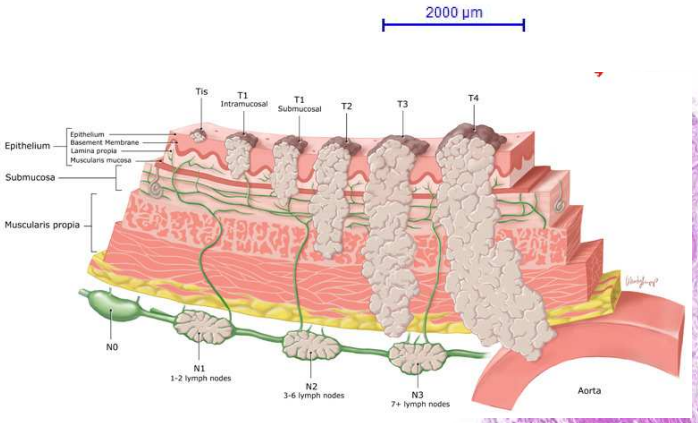
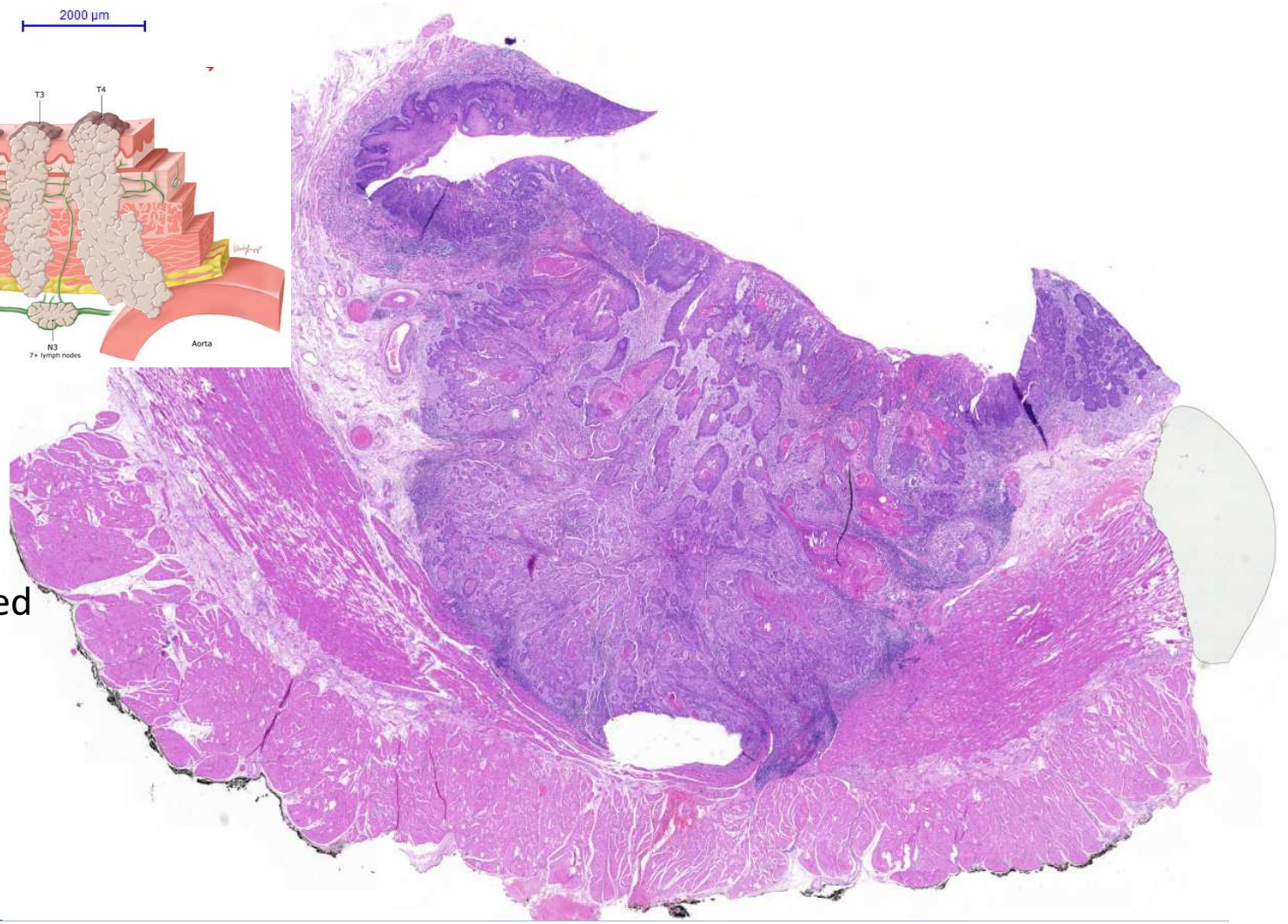
SCC – pT?





Coloured margin

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Summary

1: incidence of adenocarcinoma is increasing (SCC to Adeno-Ca: 60/40)

2: 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)

3: >15 regional lymph nodes

4: standardized work flow in pathology
embedding of whole tumor bed

5: regression scores after neoadjuvant treatment

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Questions

1: why do we have differences in responding to treatment (major and minor responder)?

2: can we find tumor sub-types (like in adenocarcinoma of lung or stomach)?

3: can liquid biopsies be helpful in detection recurrences?

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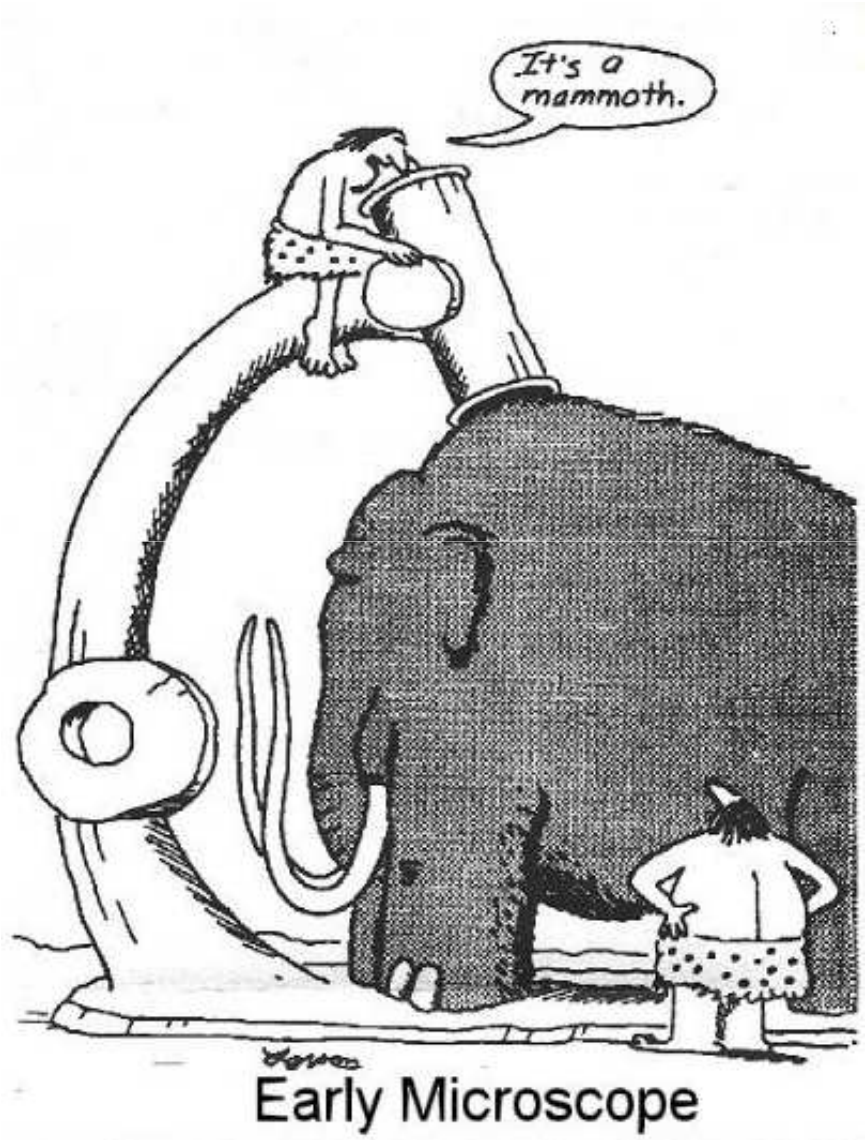
Thank you for your attention



Early Microscope

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Gastric tumors: Primary tumor extension pathology evaluation

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
- Tumor extension evaluation – using UICC- TNM 7th edition (since 2010)
- Lymph nodes stations (D1-D4)
- Patho-anatomical basics and reportings

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Facts

- Germany 2016: 9.200 men /6.400 women
- 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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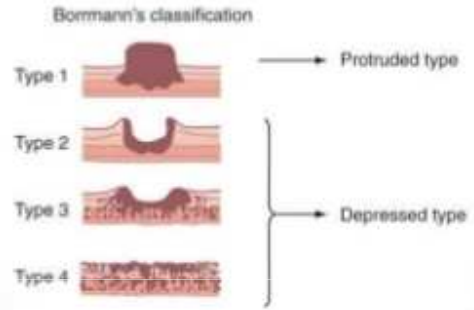
Traditional morphology based diagnostics

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

Lauren's

INTESTINAL	DIFFUSE
Environmental	Familial
Gastric atrophy, intestinal metaplasia	Blood type A
Men >women	Women >men
Increasing incidence with age	Younger age group
Gland formation	Poorly differentiated, signet ring cells
Hematogenous spread	Transmural/lymphatic spread
Microsatellite instability *APC* gene mutations	Decreased E-cadherin
p53, p16 inactivation	*p53, p16* inactivation

- Differentiated — Undifferentiated

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	

From: Bing Hu, Gastric cancer: Classification, histology and application of molecular pathology, J Gastrointest Oncol 2012;3(3):251-261

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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

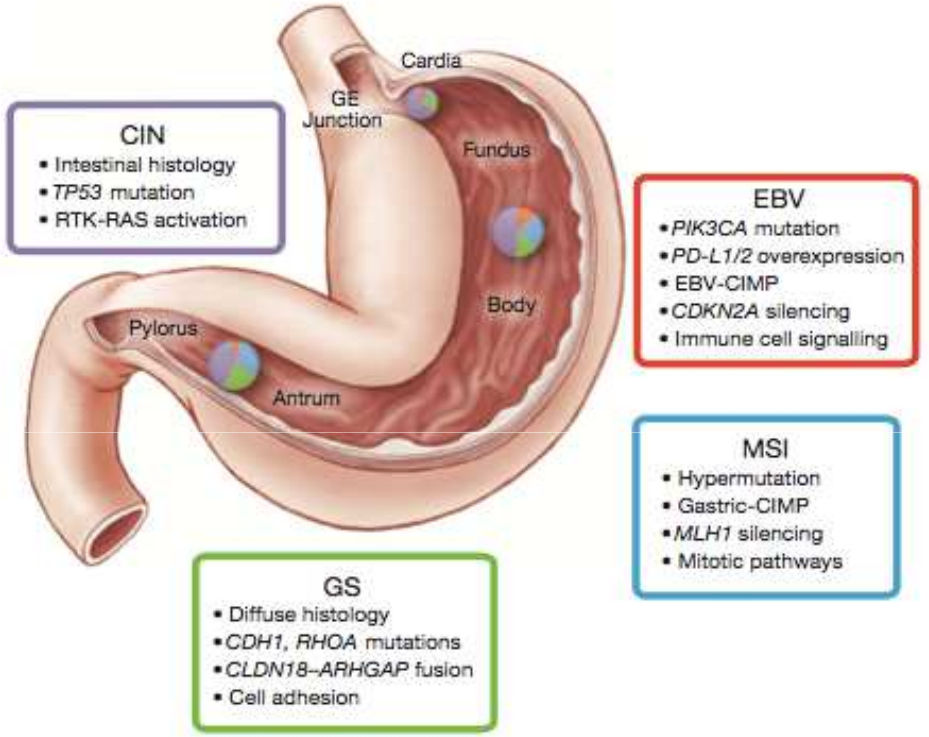

Figure 6 | Key features of gastric cancer subtypes. This schematic lists some of the salient features associated with each of the four molecular subtypes of gastric cancer. Distribution of molecular subtypes in tumours obtained from distinct regions of the stomach is represented by inset charts.

From: CancerGenomeAtlasResearchNetwork, „comprehensive molecular characterization of gastric adenocarcinoma“ Nature 2014

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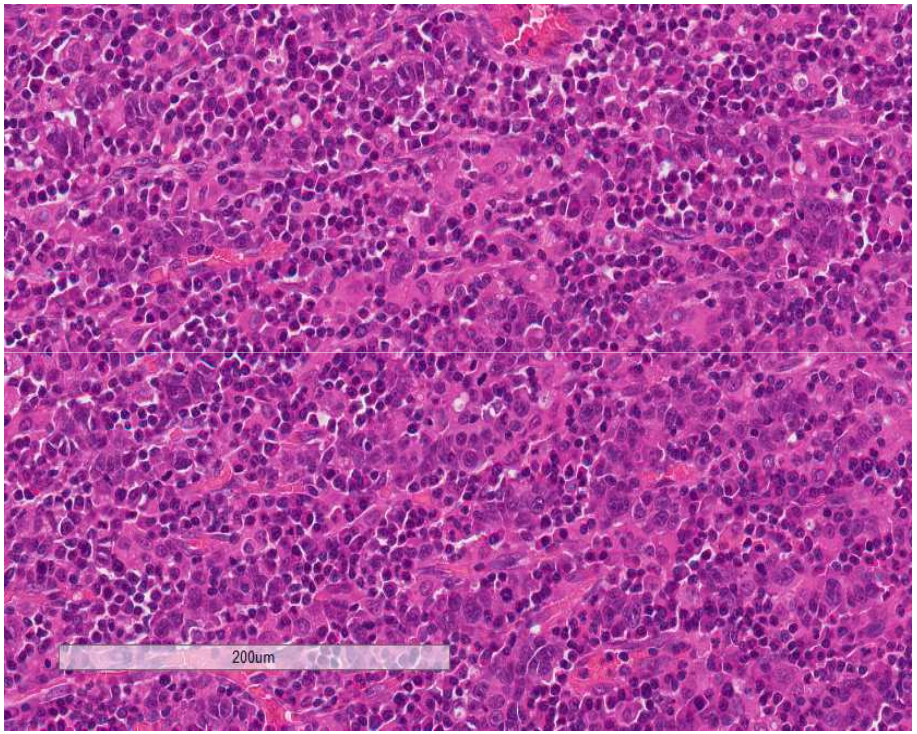
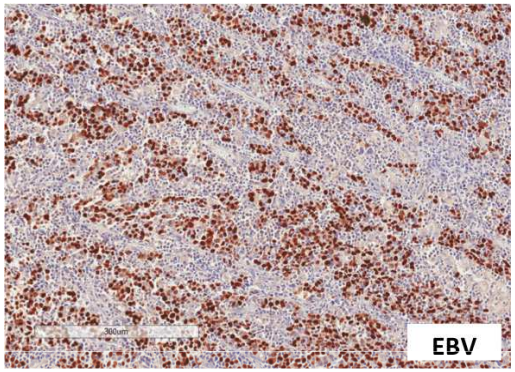
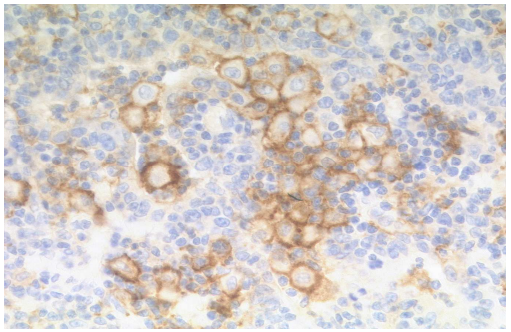
EBV+ gastric carcinoma



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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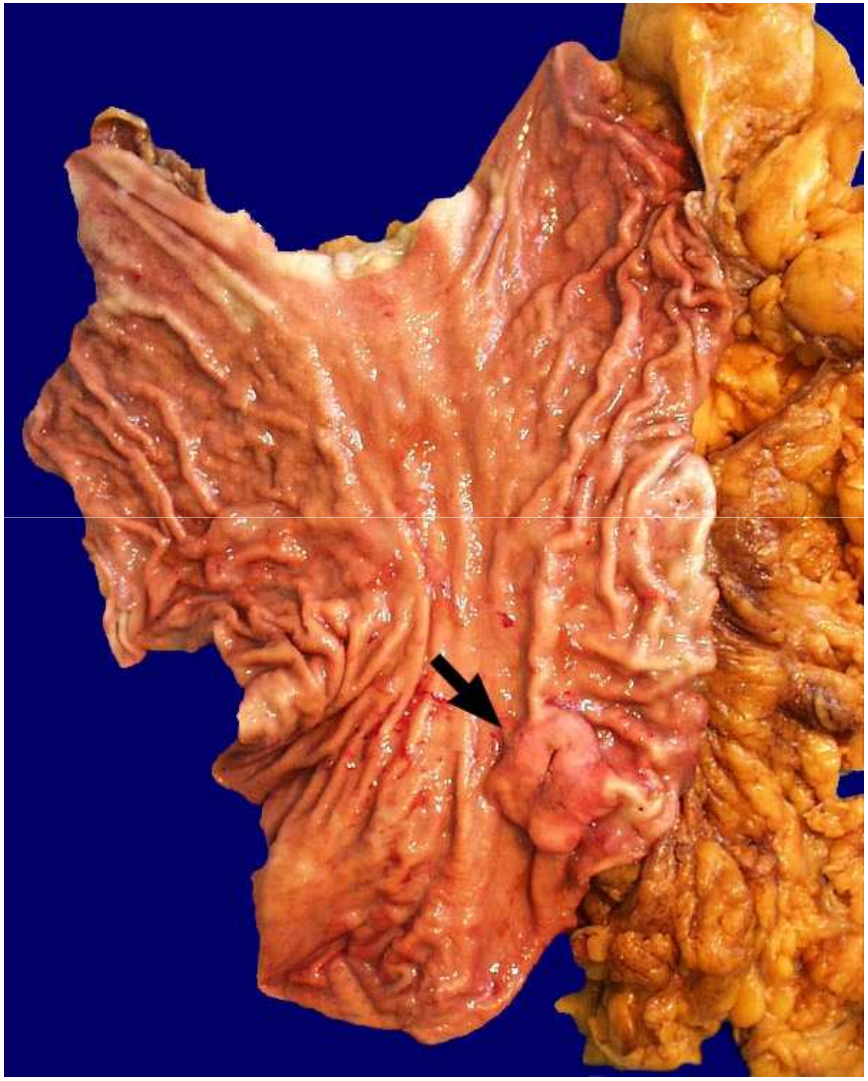
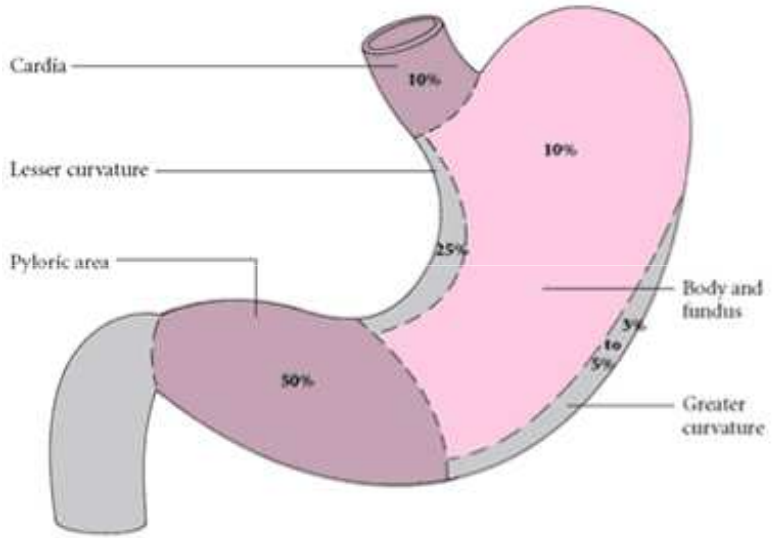
Distribution





But: increased incidence of cardia carcinoma/GEJ carcinoma. More „intestinal type“ carcinoma, more often Her2/neu positive

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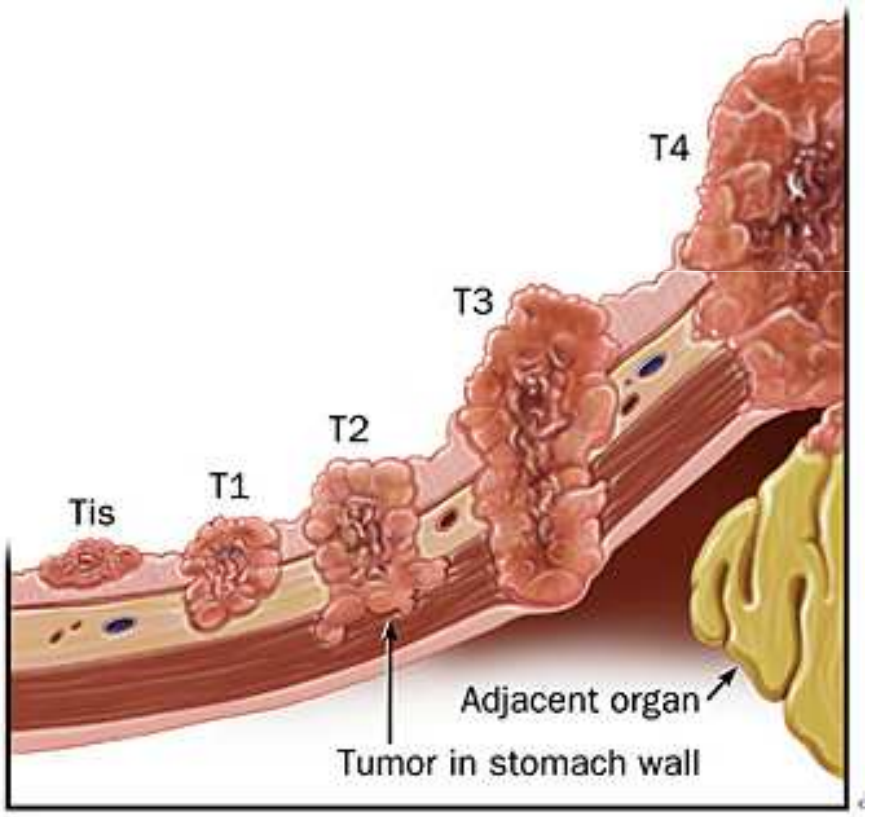
TNM

Stage	Description
T Stage	
Tis	Carcinoma in situ; intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosa, or submucosa.
T1a	Tumor invades lamina propria or muscularis mucosa.
T1b	Tumor invades submucosa.
T2	Tumor invades the muscularis propria.
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures.
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures.
T4a	Tumor invades serosa (visceral peritoneum).
T4b	Tumor invades adjacent structures.*
N Stage	
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 6 regional nodes
N2	Metastasis in 7 to 15 regional nodes
N3	Metastasis in more than 15 regional nodes
M Stage	
M0	No distant metastasis
M1	Distant metastasis



From: neoadjuvant.wikidot.com staging

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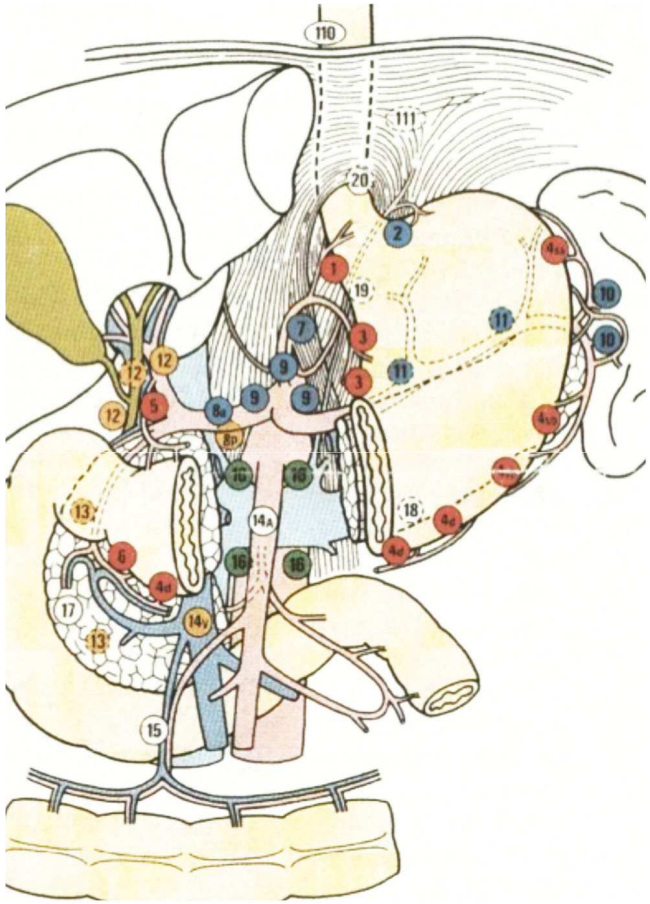
Lymphnodes stations

16 different LN stations surround the stomach (D1-D4)



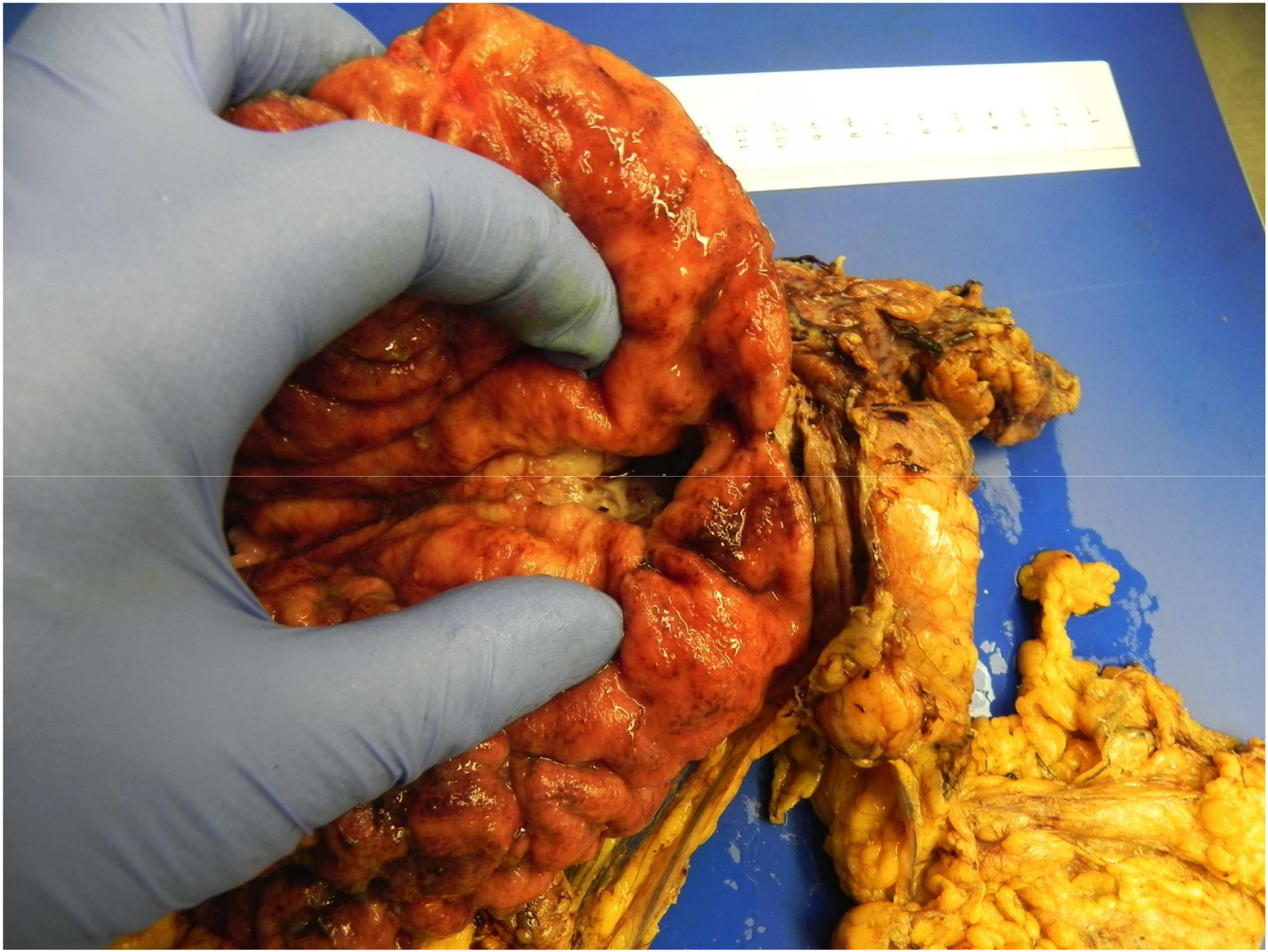
D1 dissections:
LN stations 1-6; N1 level
1 Right cardia
2 Left cardia
3 along lesser curvatur
4 along right curvatur
5 suprapyloric
6 infrapyloric

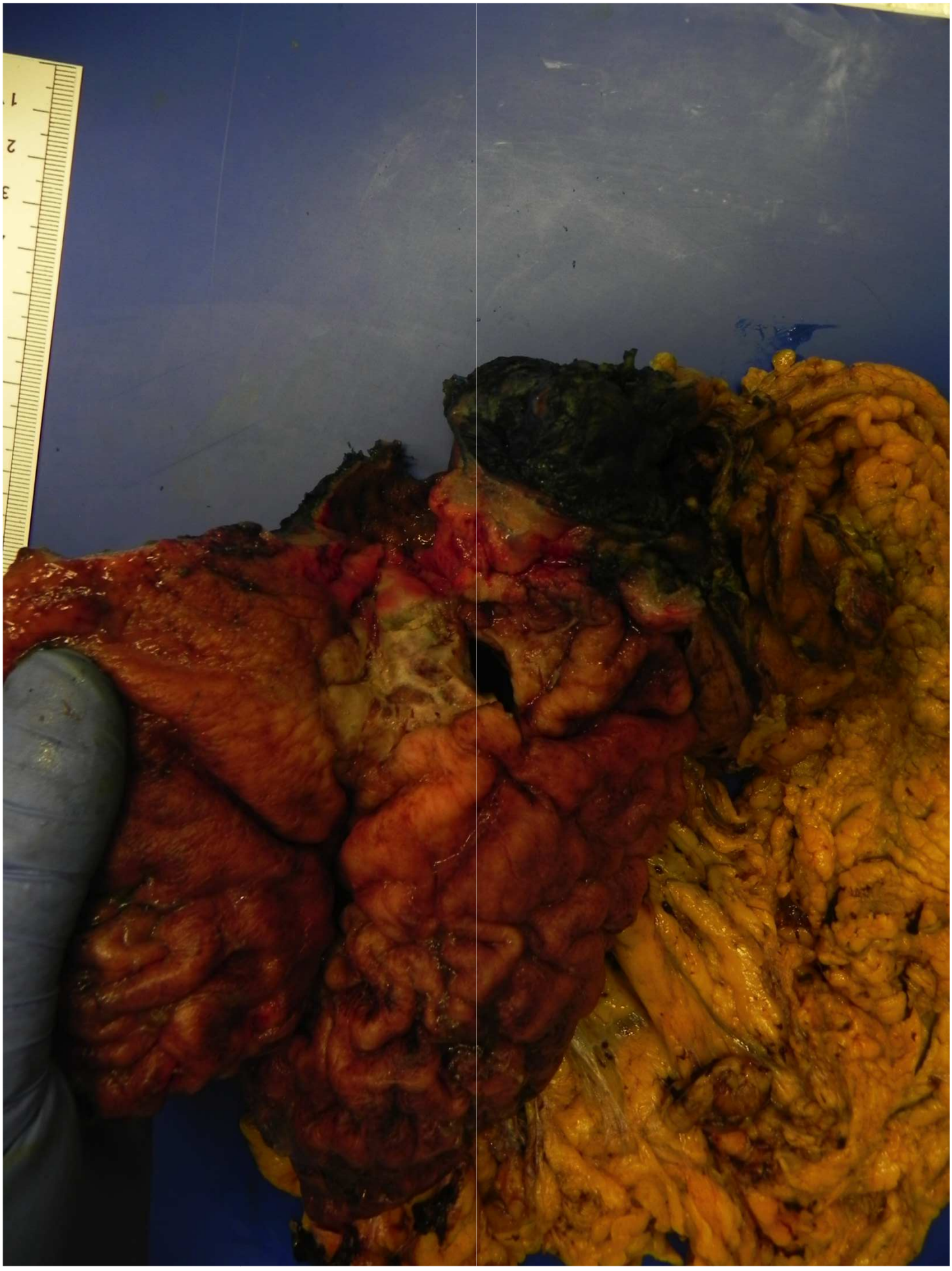
D2 dissections:
LN stations 7-11; N2 level
7 left gastric artery
8 common hepatic artery
9 celiac trunk
10 splenic hilus
11 splenic artery

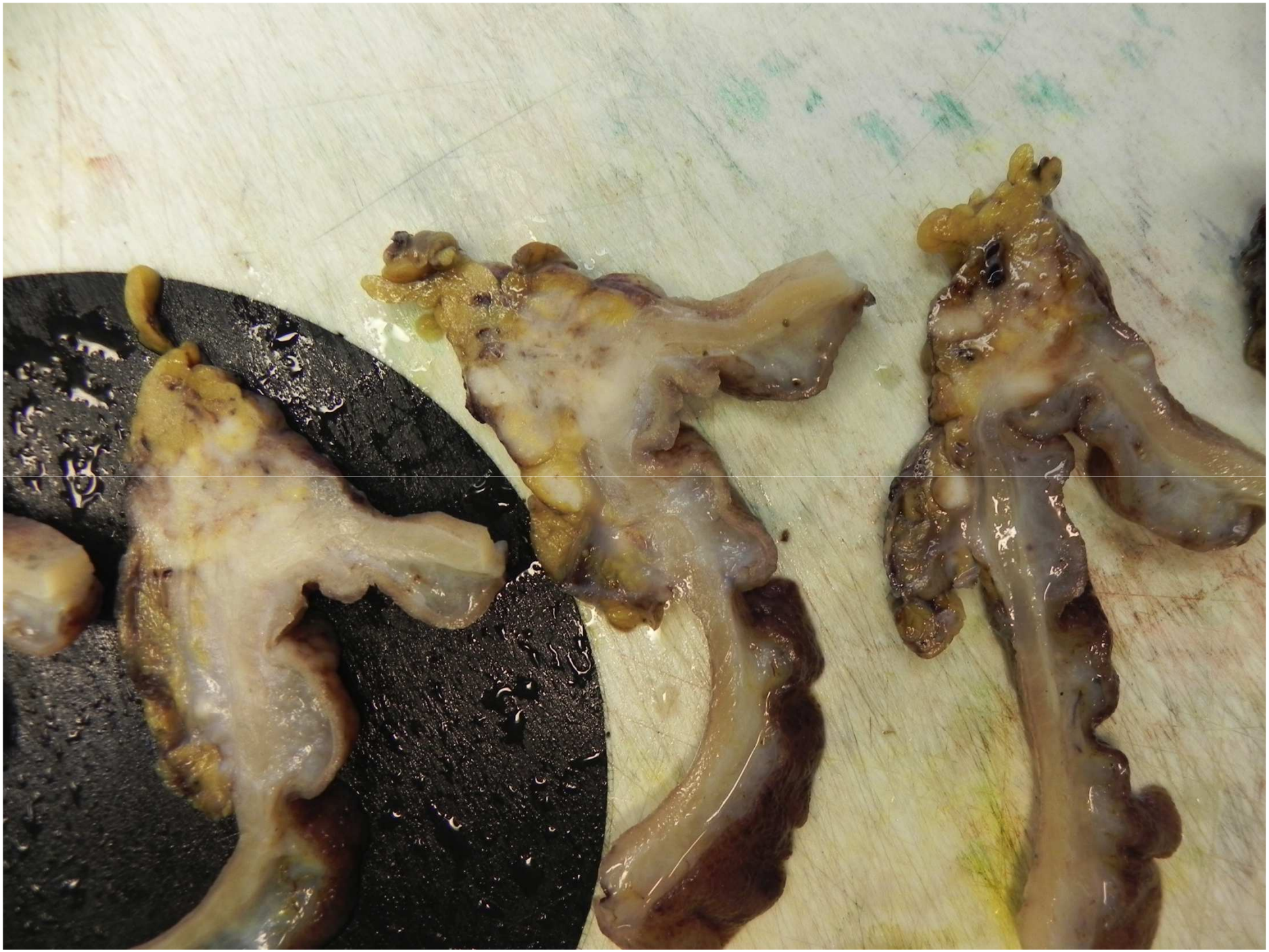
D3 dissections:
LN stations 12-14; N3 level
12 hepatoduodenal ligament
13 posterior surface of pancreas head
14 root of the mesentery/ artery/vein

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.








C 16/18815 2A
he
C 16/18815 2B
he
C 16/18815 2C
he

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Summary

1) two main types: intestinal and diffuse adenocarcinoma (according to Lauren)
2) some advances in molecular subtyping (MSI and EBV related: checkpoint inhibition?)
3) >15 regional lymph nodes (D1 and D2)
4) regression scores after neoadjuvant treatment

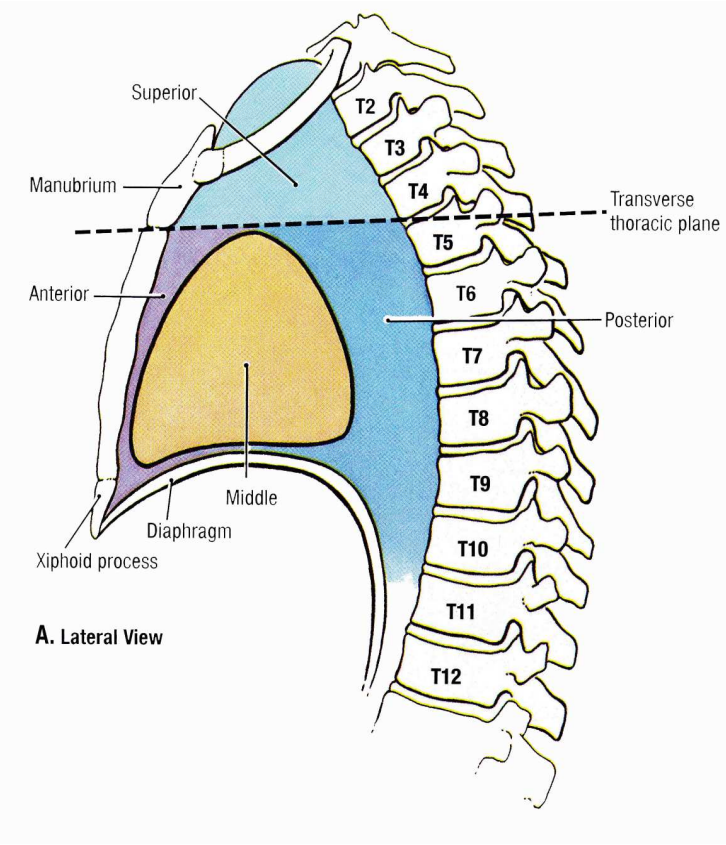
Imaging of primary and nodal subsite boundaries in Esophageal Cancer

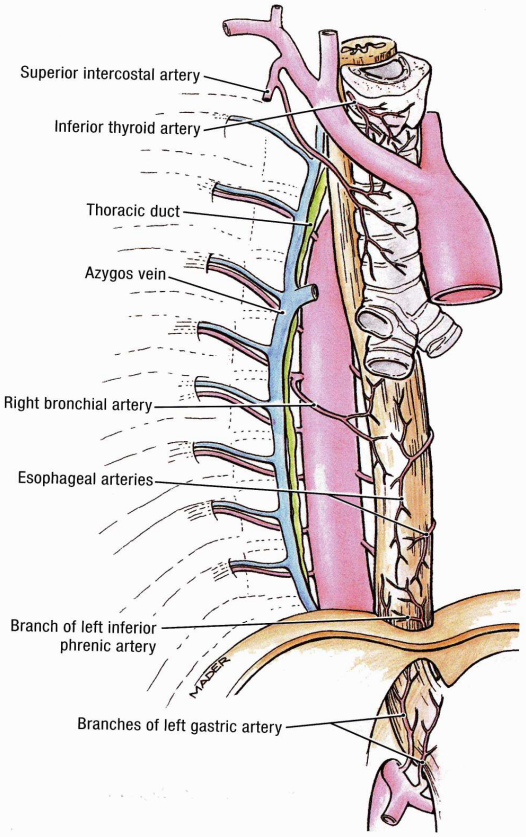
Dr Angela M Riddell

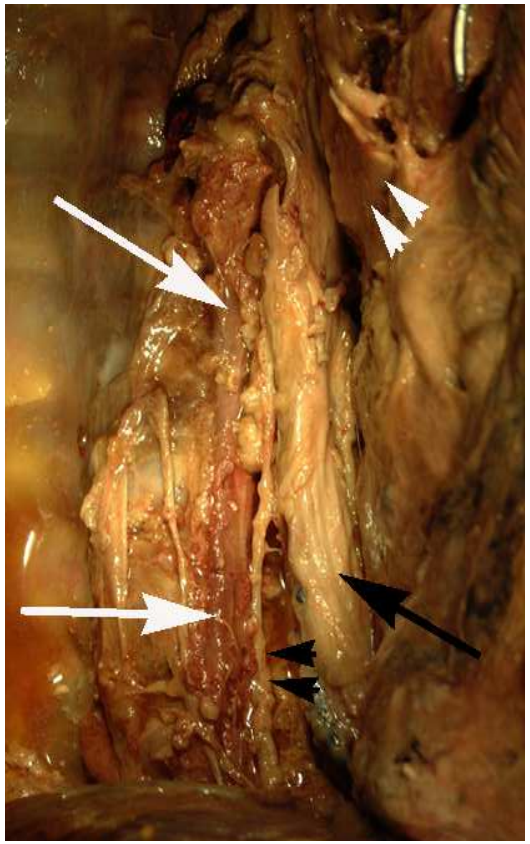
Royal Marsden, London. UK

ESTRO School

Anatomy







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

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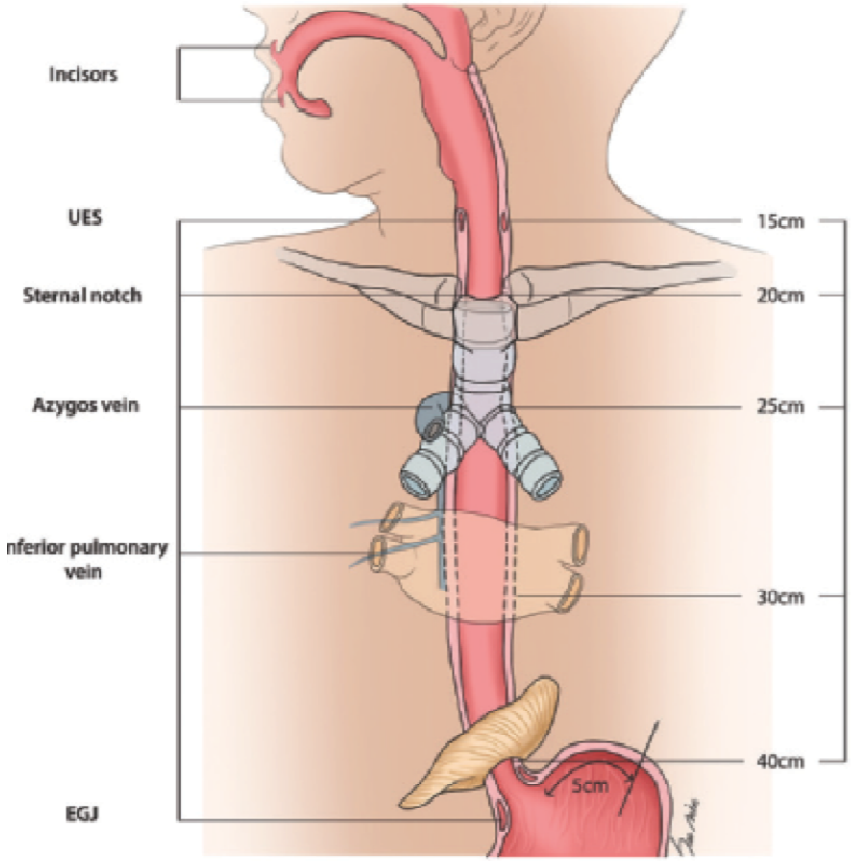
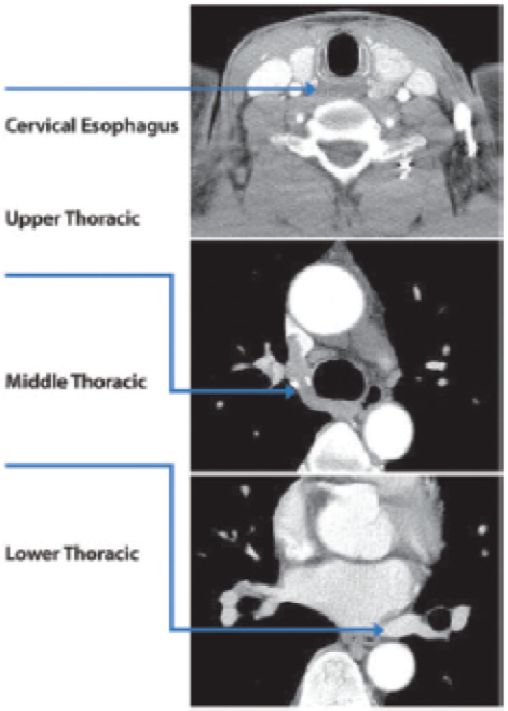
Anatomy: Oesophagus





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

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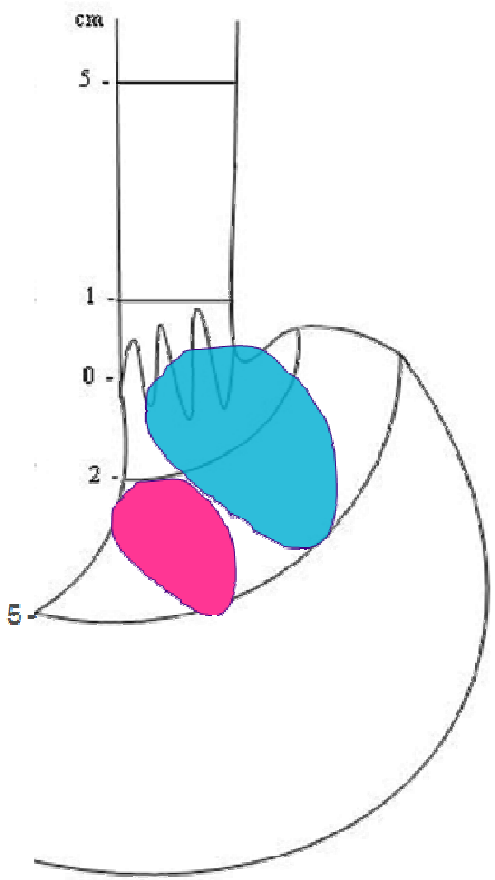
Anatomy: Gastro-oesophageal junction (GOJ)

- 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]
- ***Note: Definitions are new for 7th Edition***



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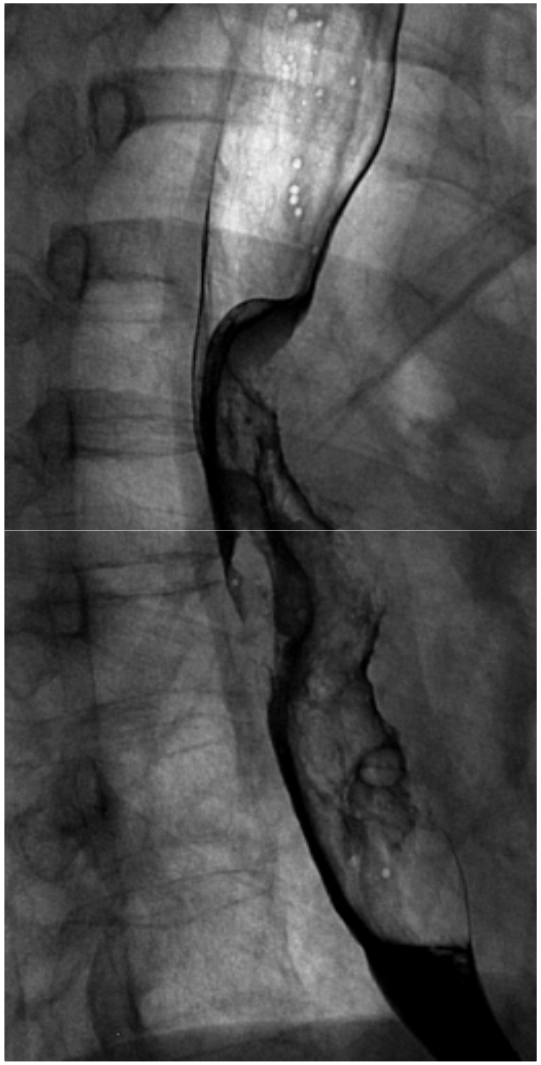
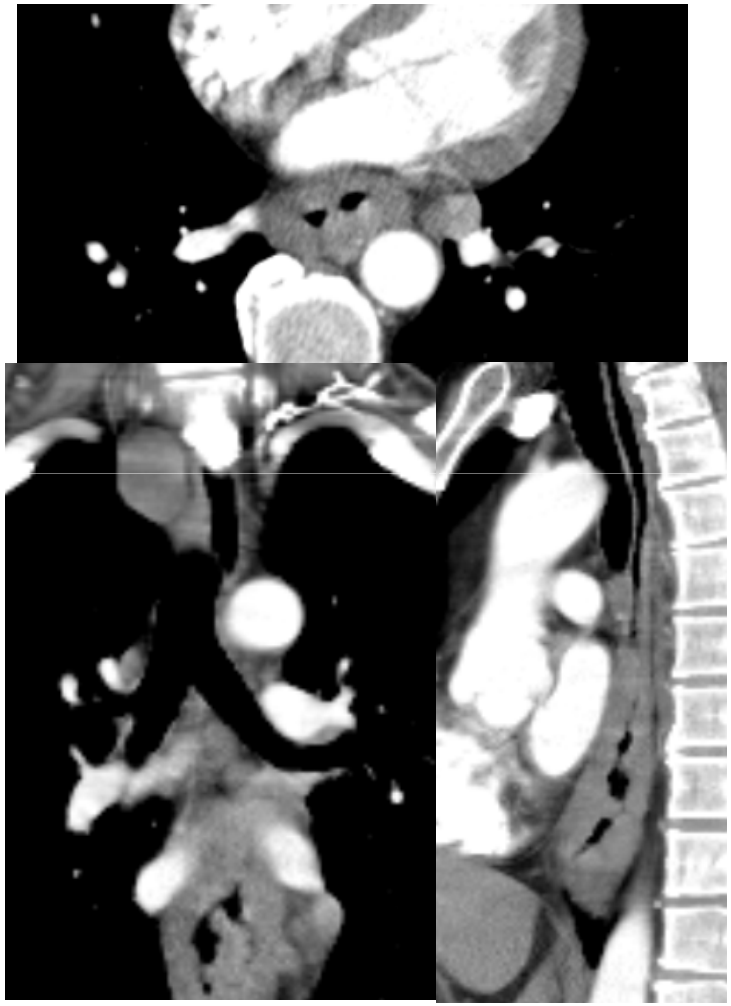
Imaging the primary



Double contrast barium swallow

- tumour length & location

Imaging the primary



Double contrast barium swallow

- tumour length & location

MDCT

- relationship to surrounding structures

MDCT Technique

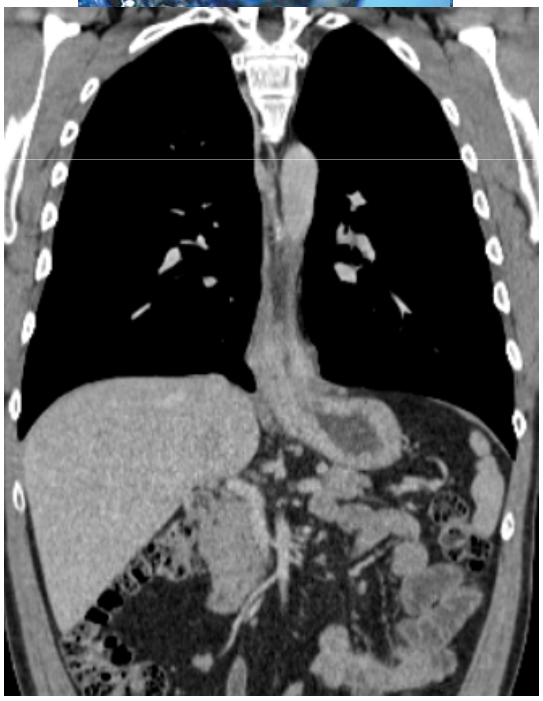
Oral contrast – 500mls

+/- carbon dioxide granules

+/- hyoscine butylbromide (Buscopan)

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

Chest & abdomen (pelvis)



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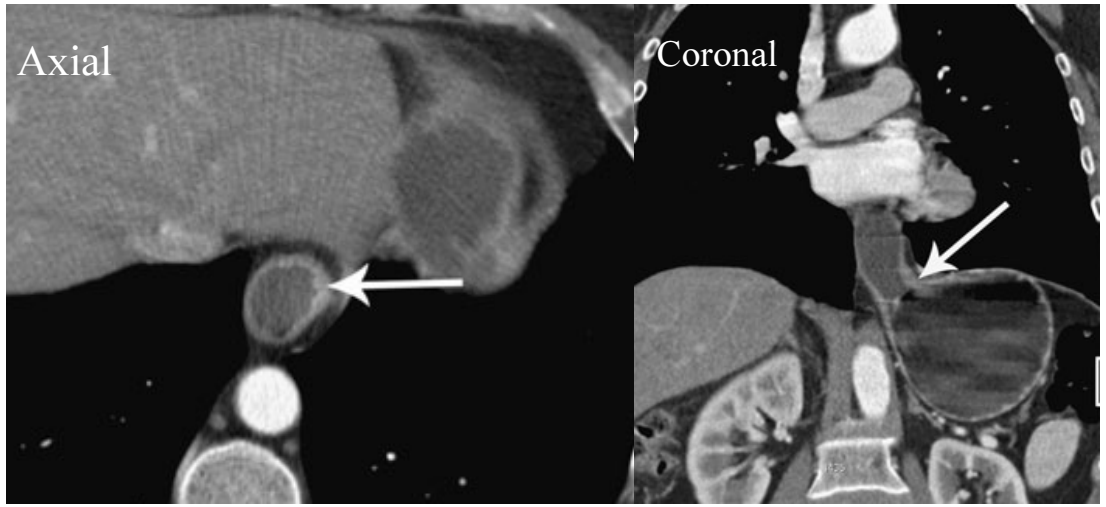
Staging the primary: Hydro-MDCT

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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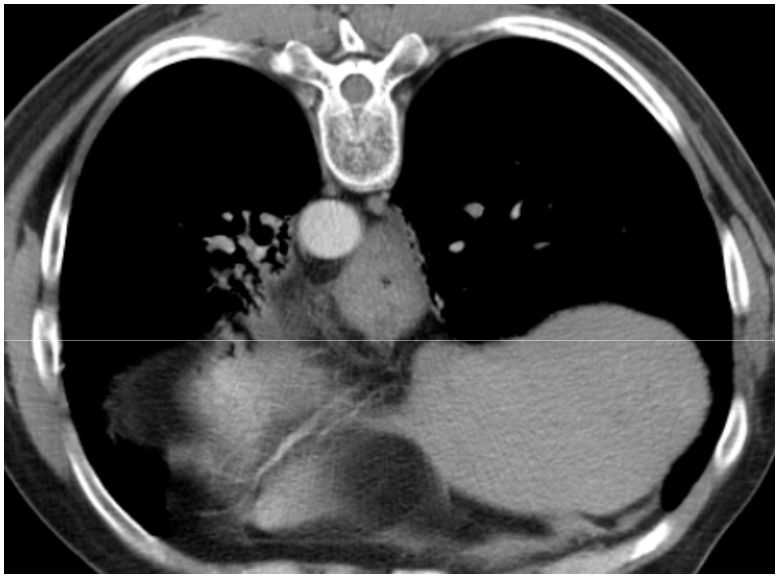
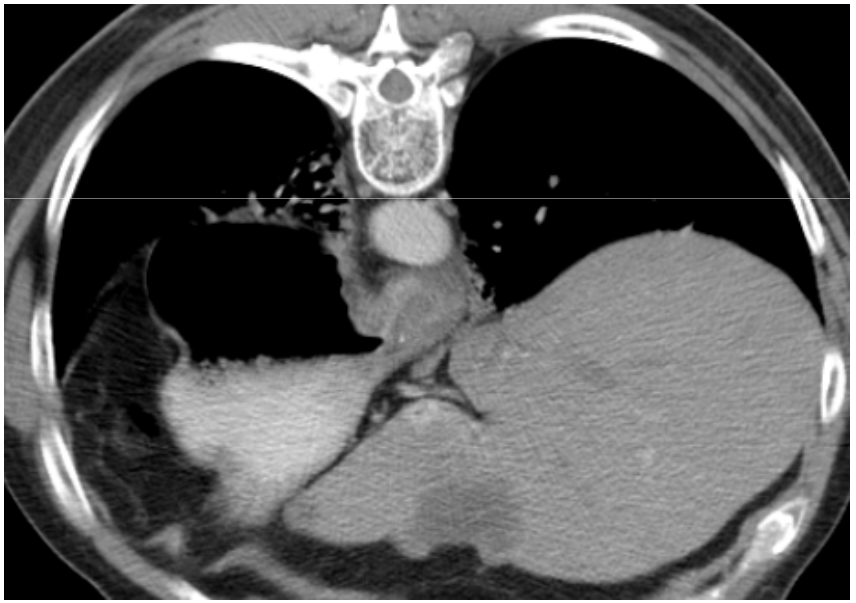
Prone imaging



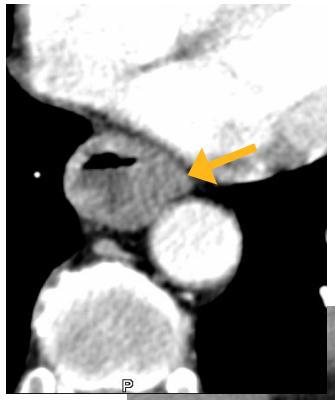


Contact versus invasion of aorta

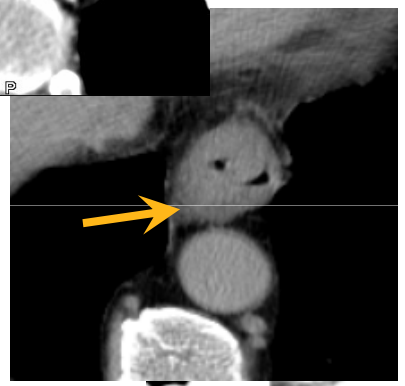
Staging the primary

Initial Staging

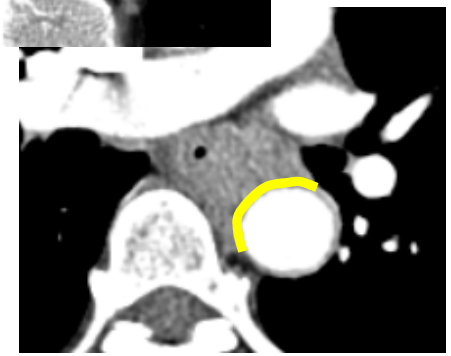
- T stage - based on wall thickness and outline
- Limited soft tissue contrast
- Poor for early tumours



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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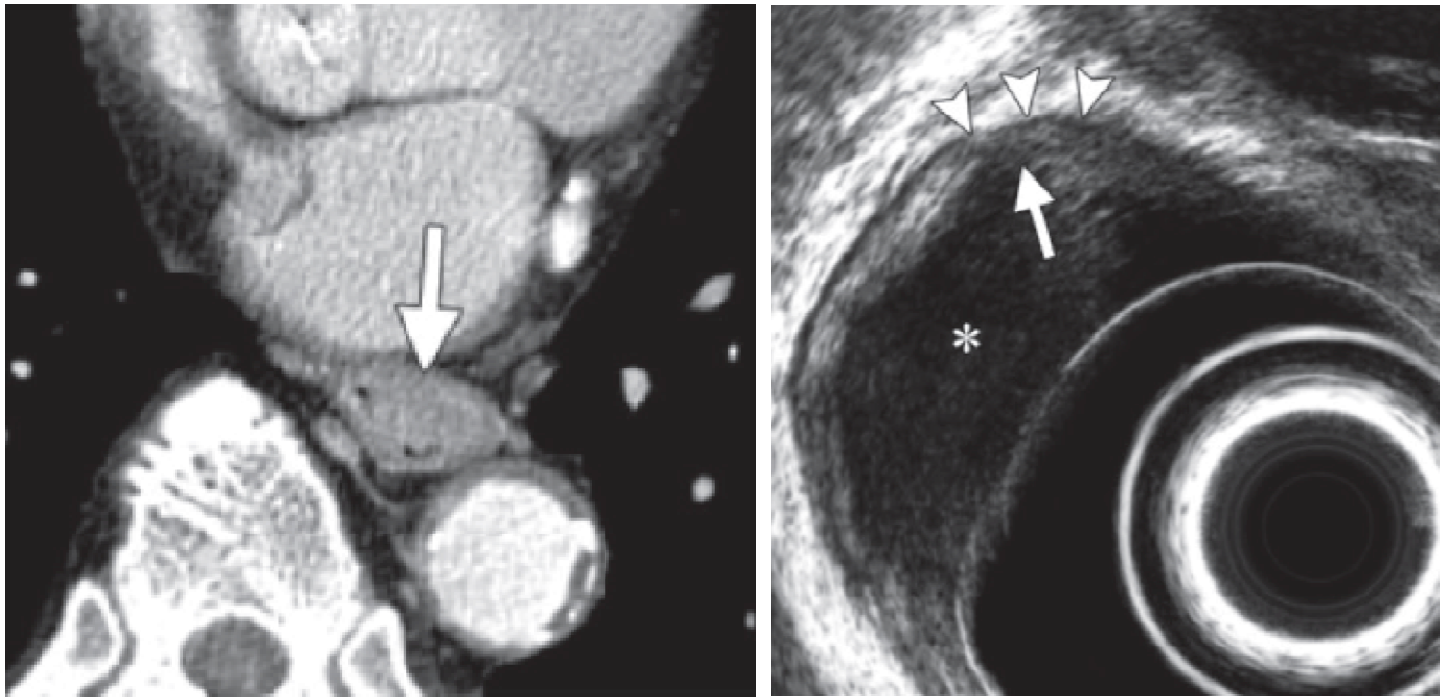
Imaging the primary

- 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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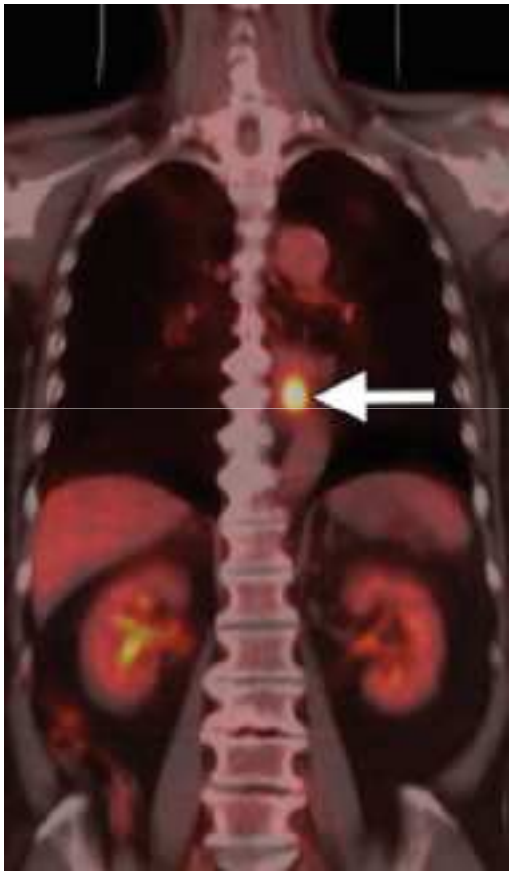
Imaging the primary – PET-CT

- 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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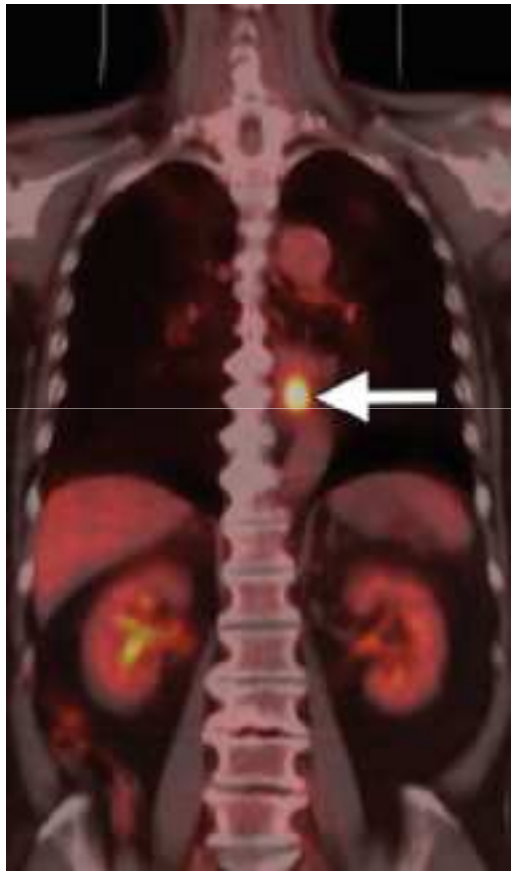
Imaging the primary – PET-CT

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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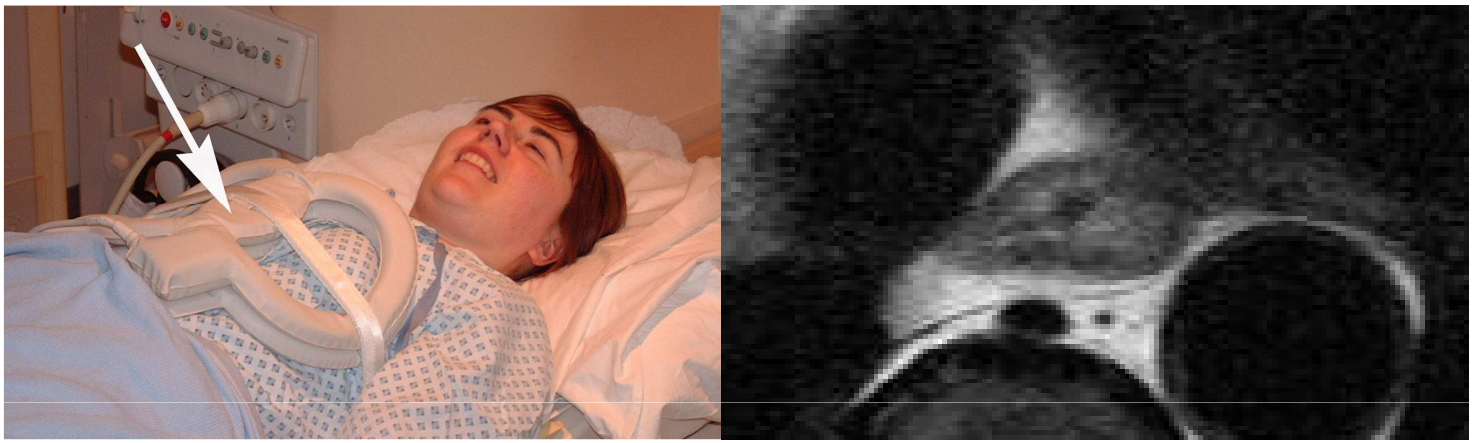
Imaging the primary: High Resolution MRI

- 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

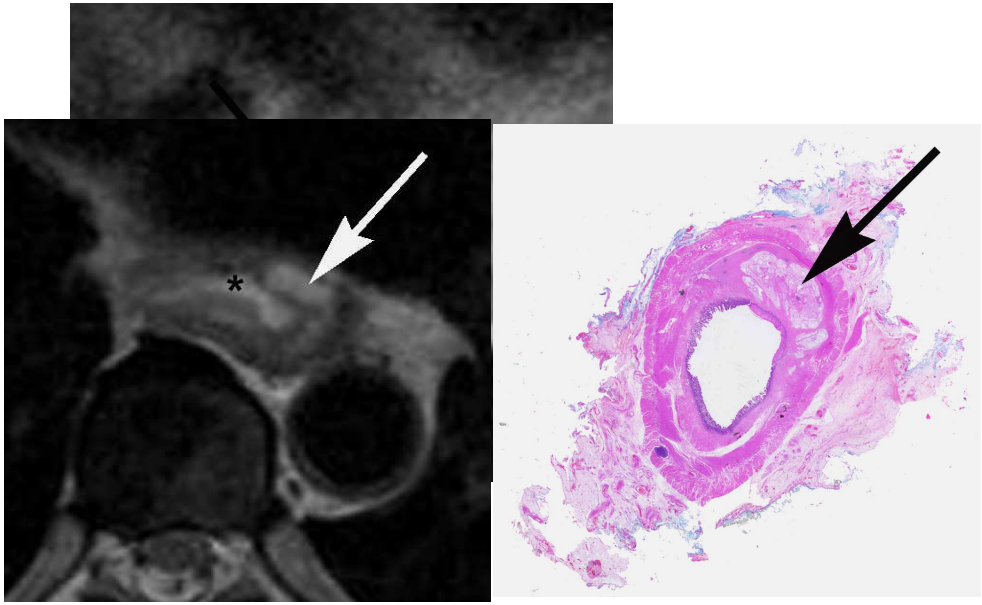
Antispasmodic

400mls water prior to scan

No requirement for IV contrast

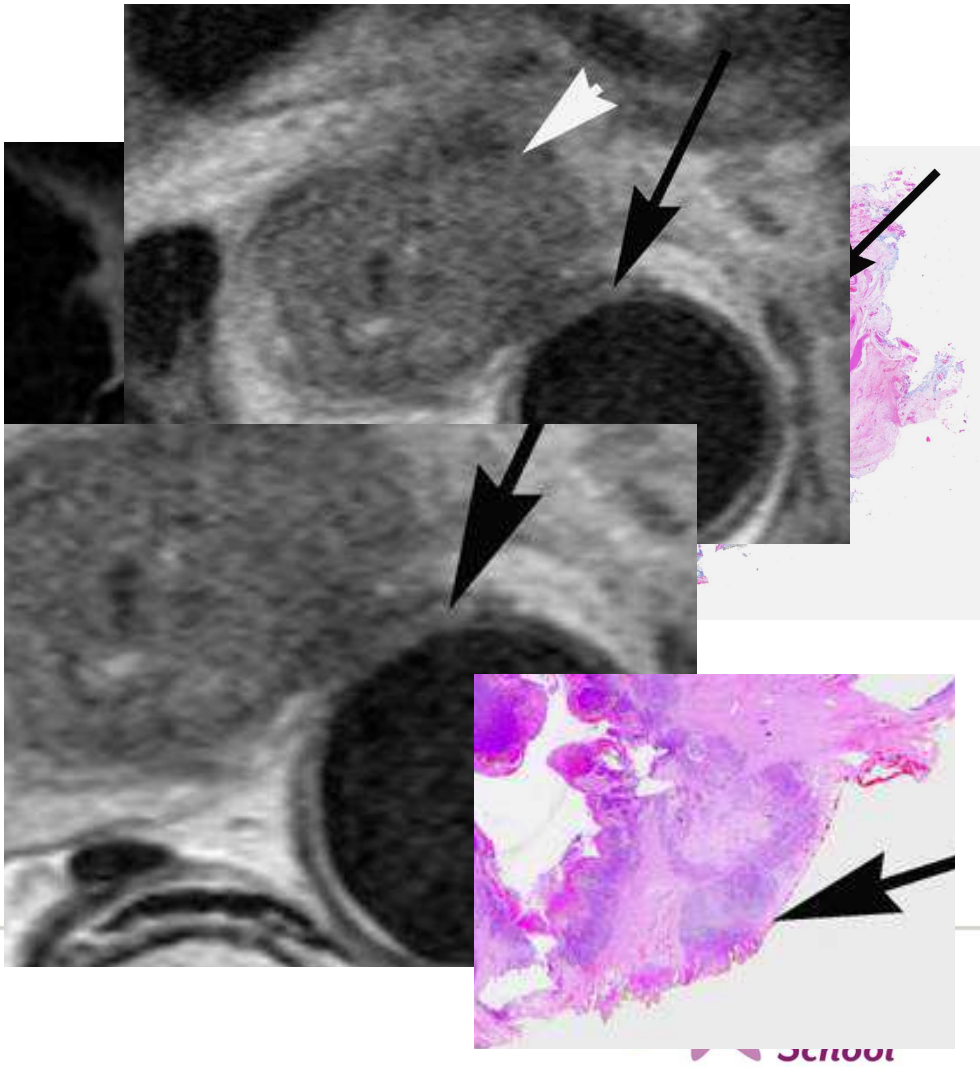
Potential advantages of MRI over MDCT

- Superior soft tissue contrast
  - Local staging
  - Tumour characterisation



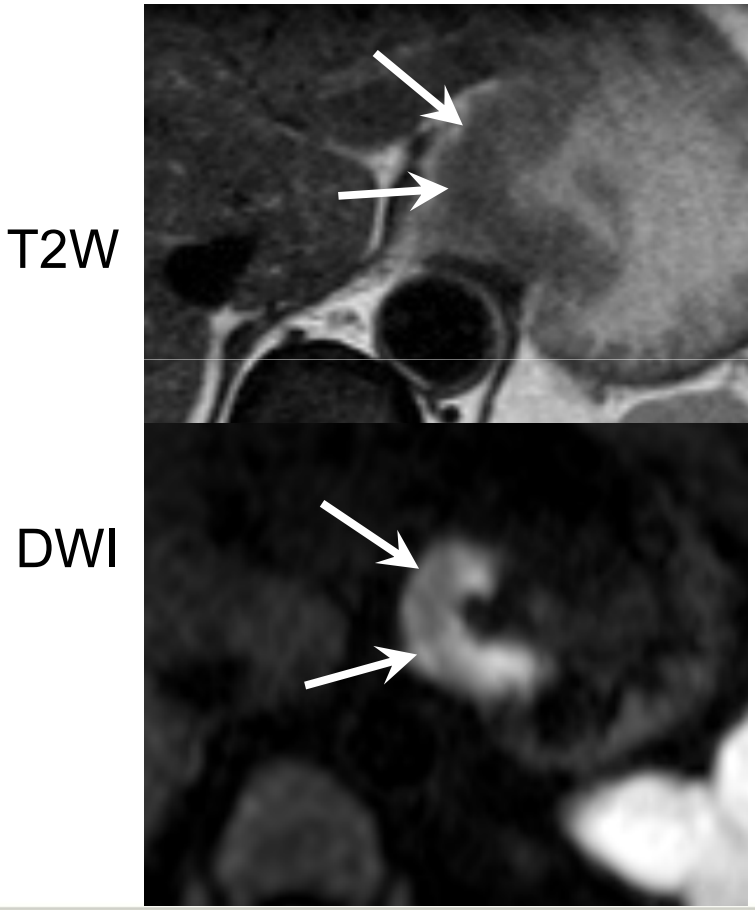
Potential advantages of MRI over MDCT

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

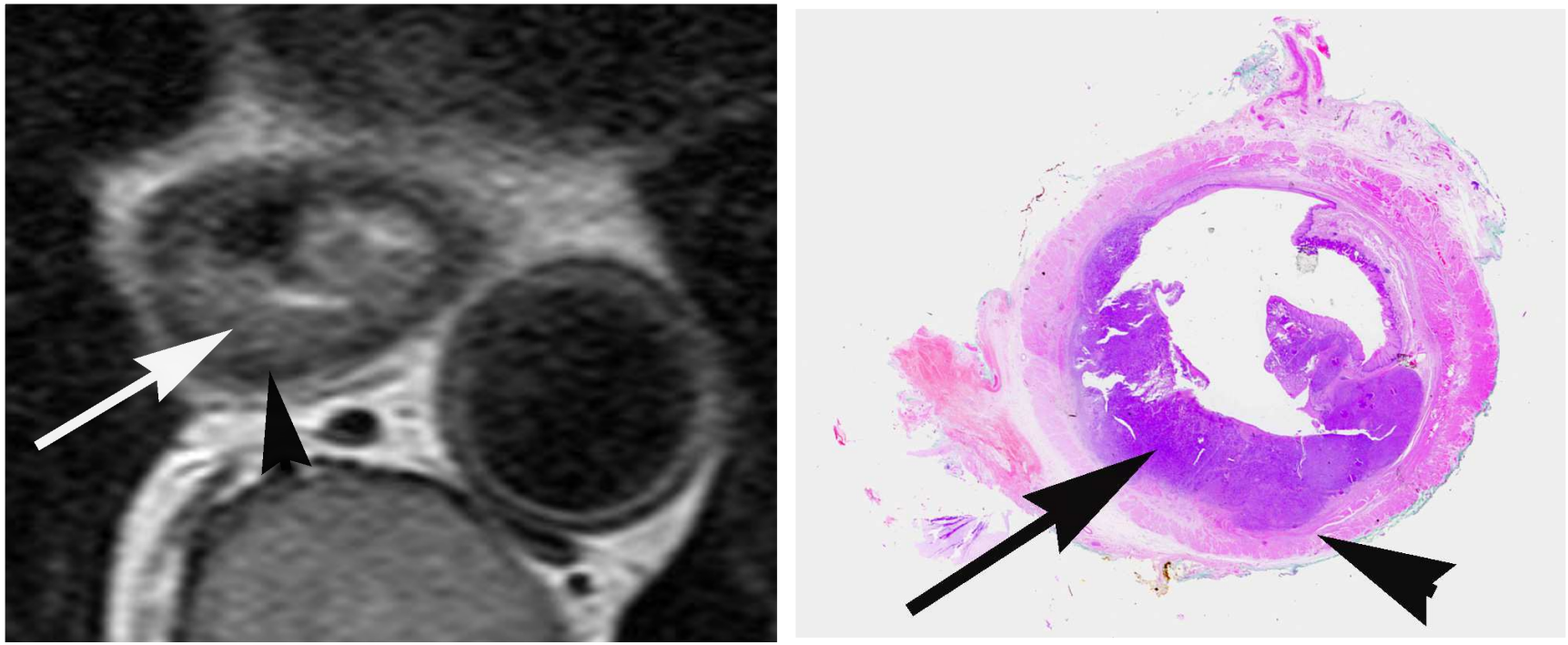


Potential advantages of MRI over MDCT

- 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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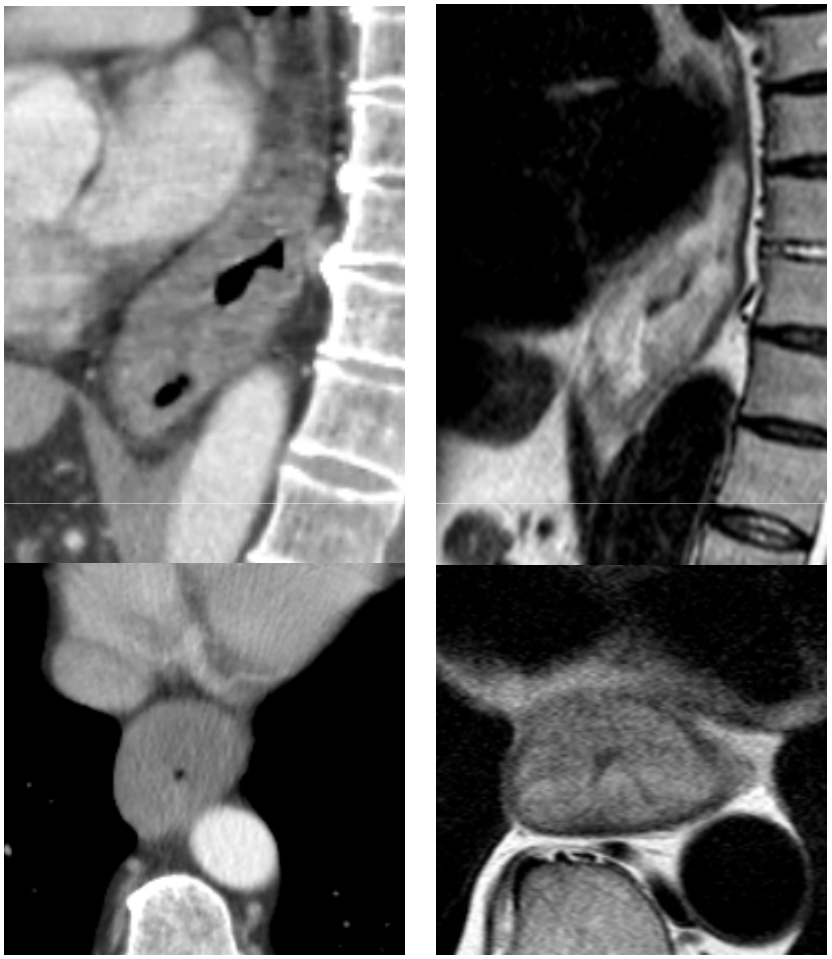
Imaging the primary

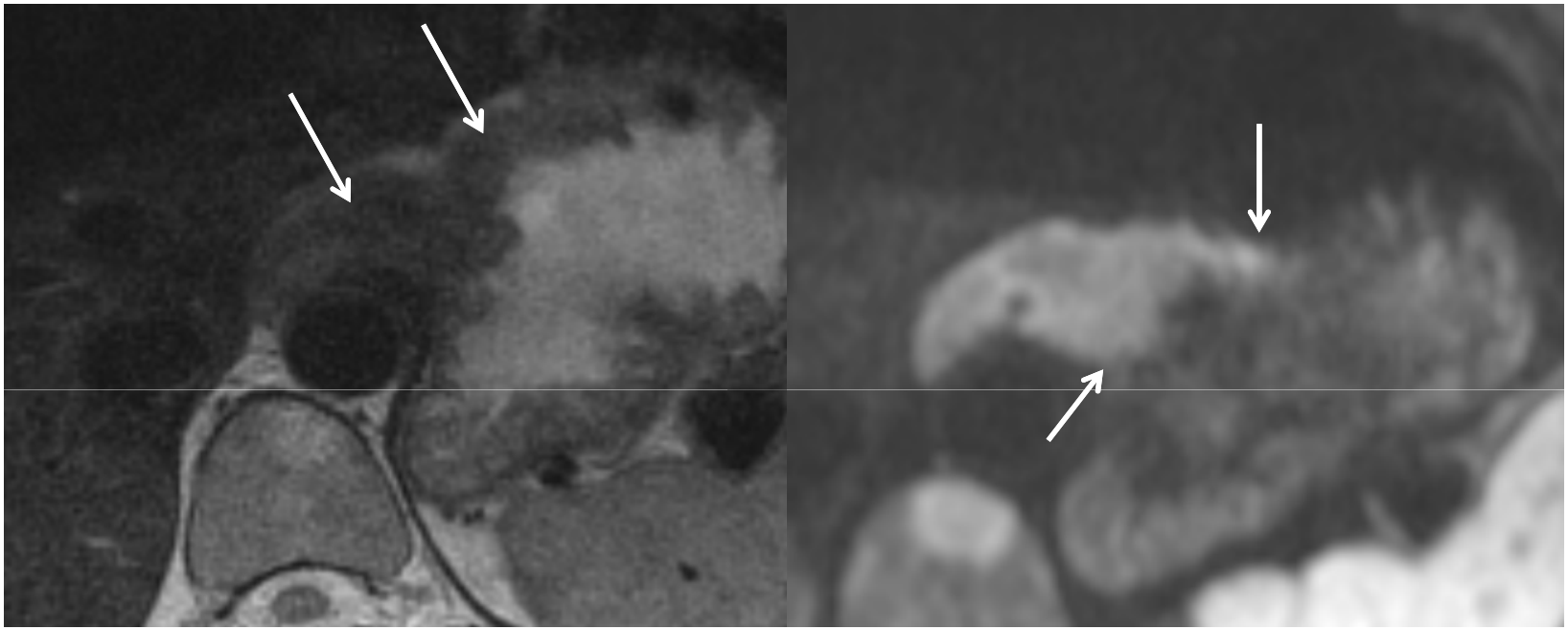
Tumour delineation

- Radiotherapy & Surgical planning



CT T2W MRI

Tumour delineation – DWI MRI

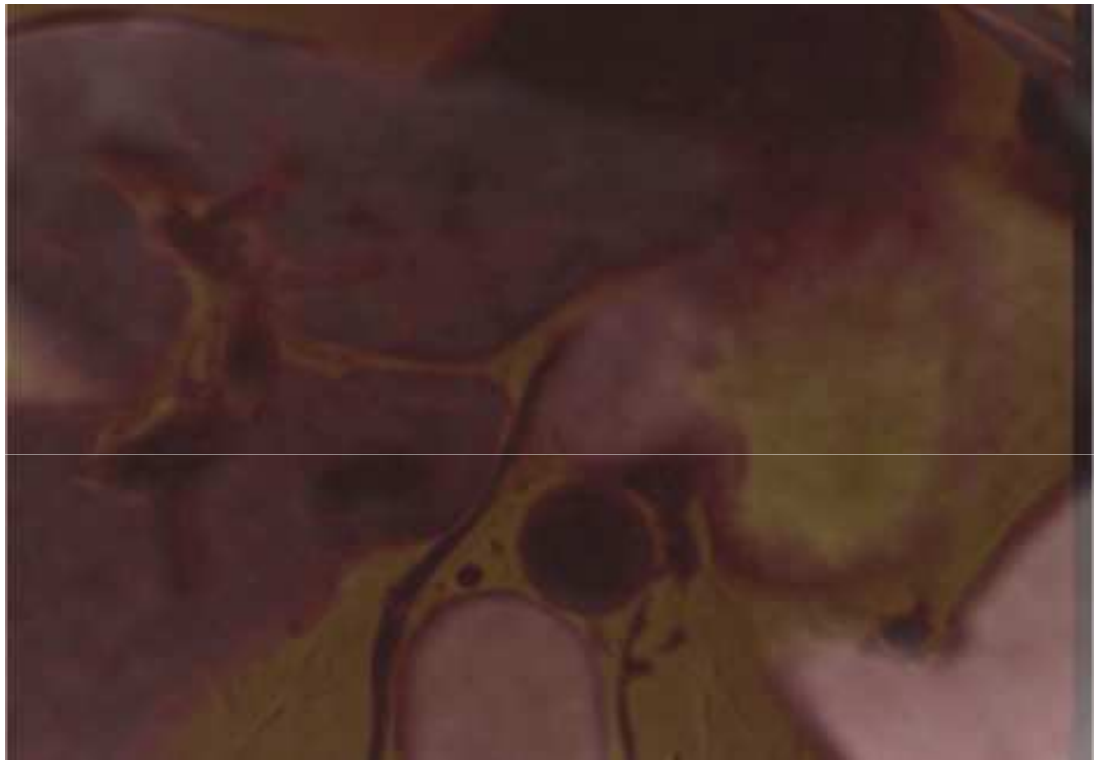


T2W

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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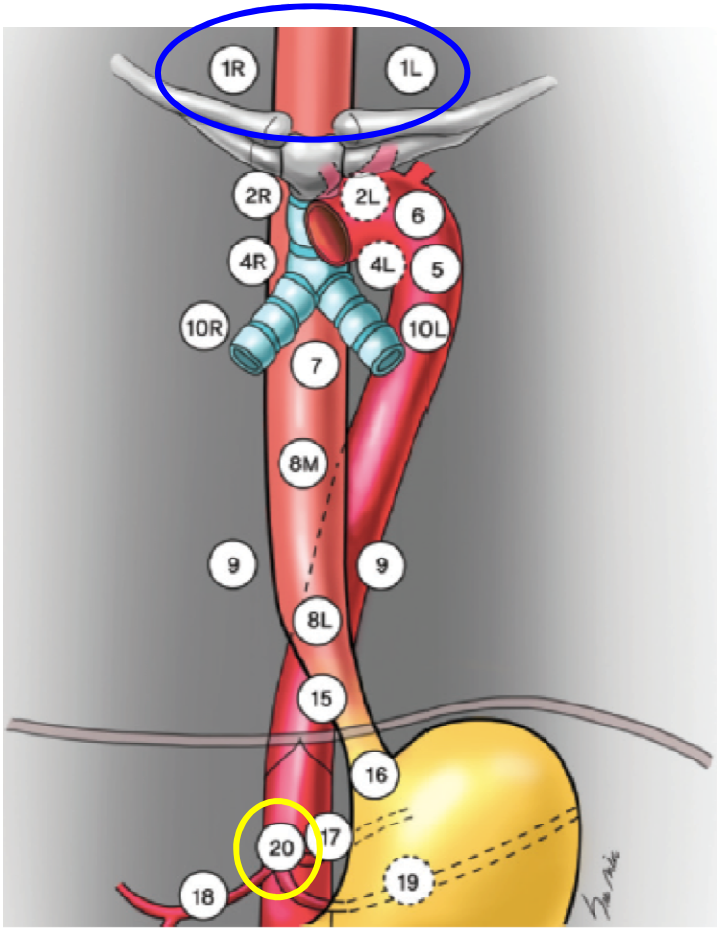
Anatomy: regional nodal stations



- 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
- TNM7 – includes coeliac axis nodes as regional (TNM6=M1a)

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

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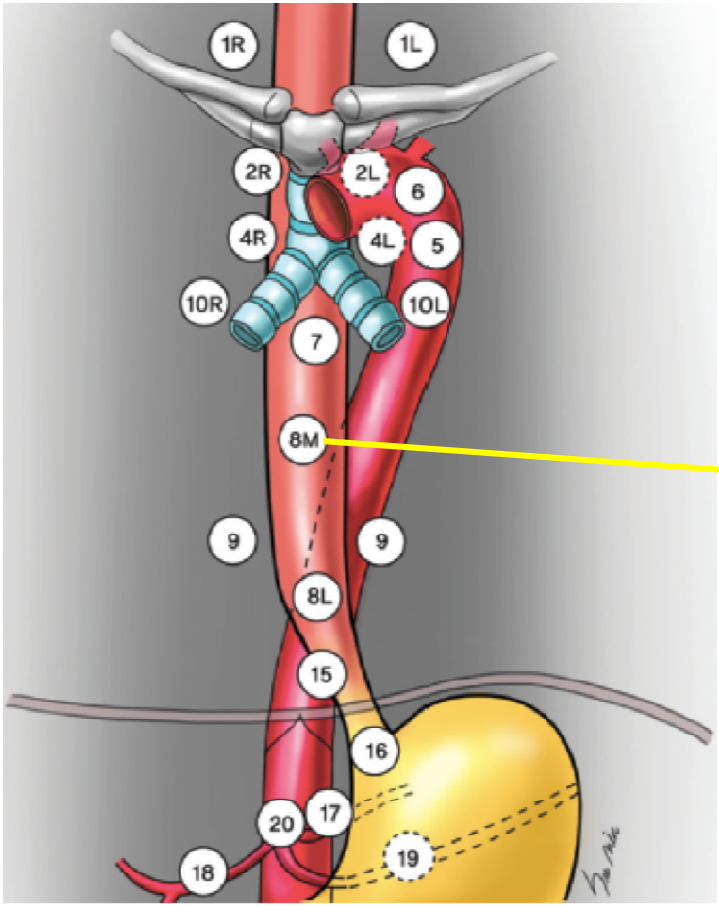
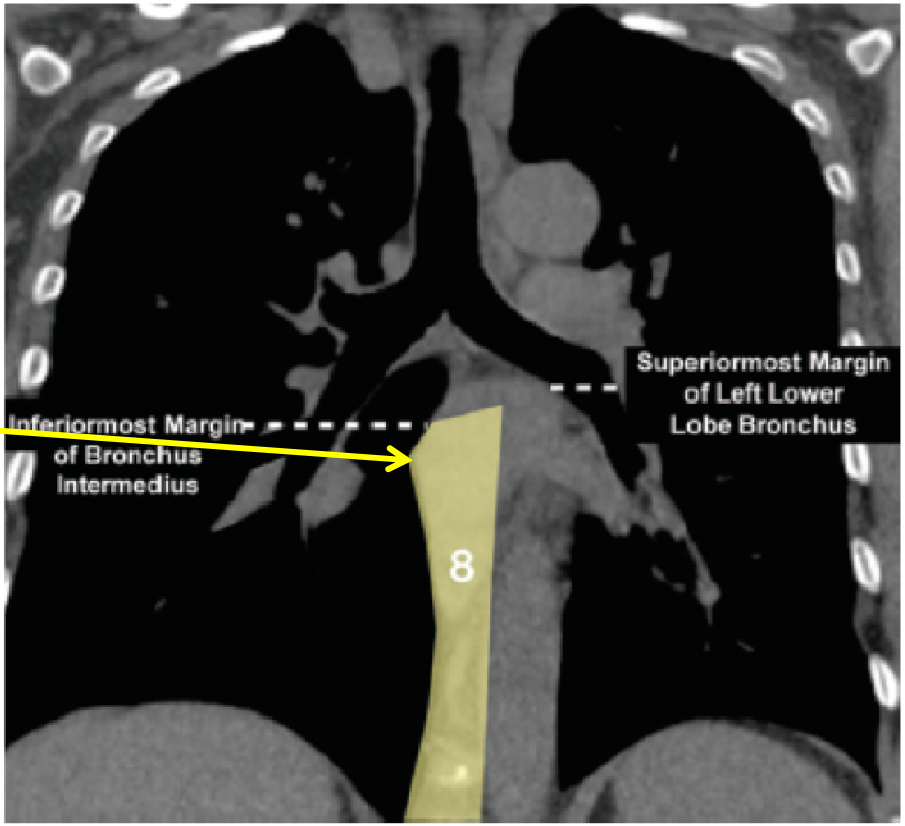
Anatomy: regional nodes





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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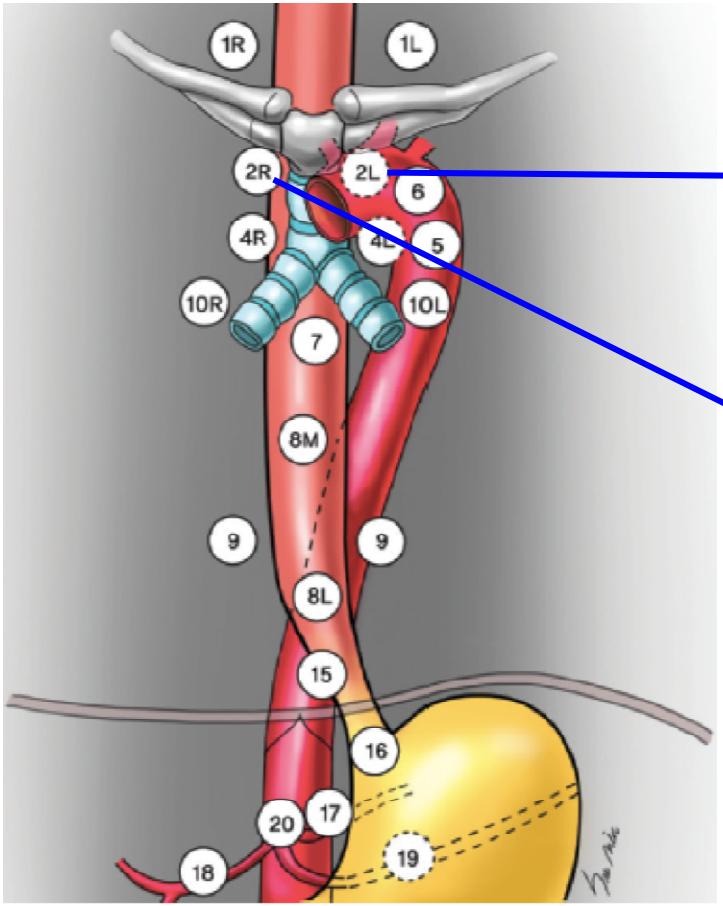
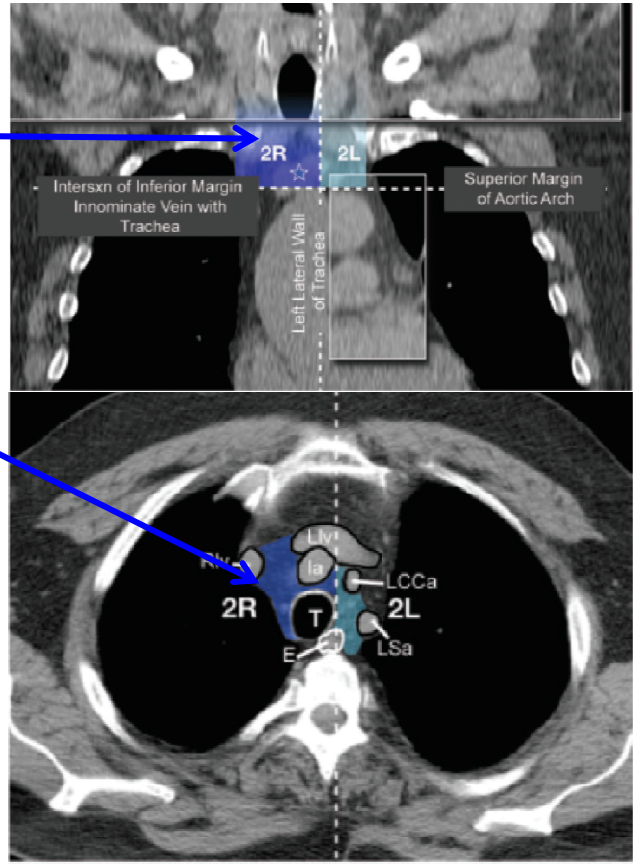
Anatomy: regional nodes





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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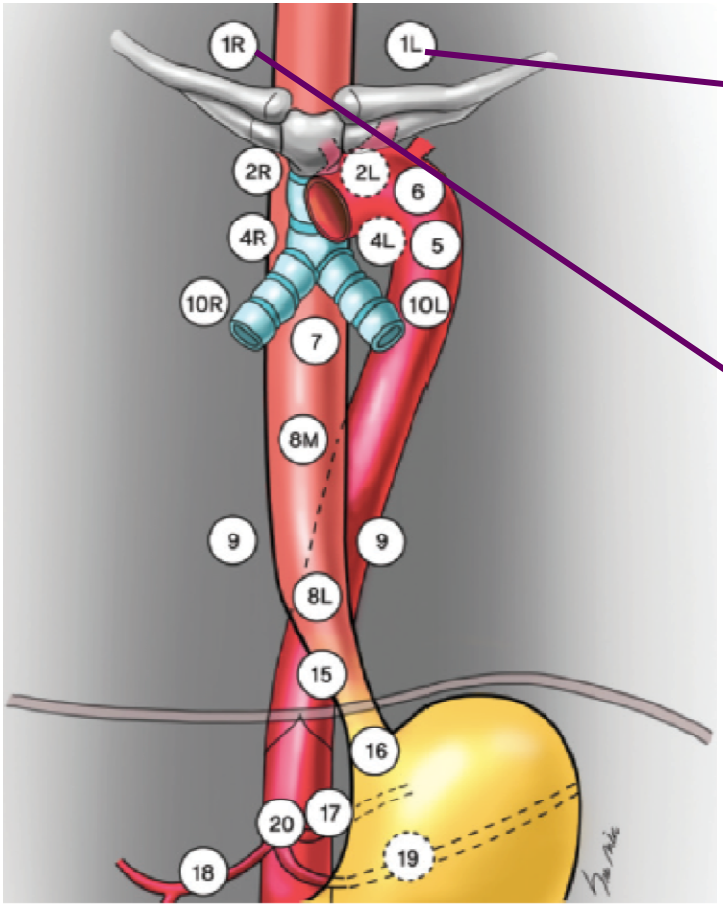
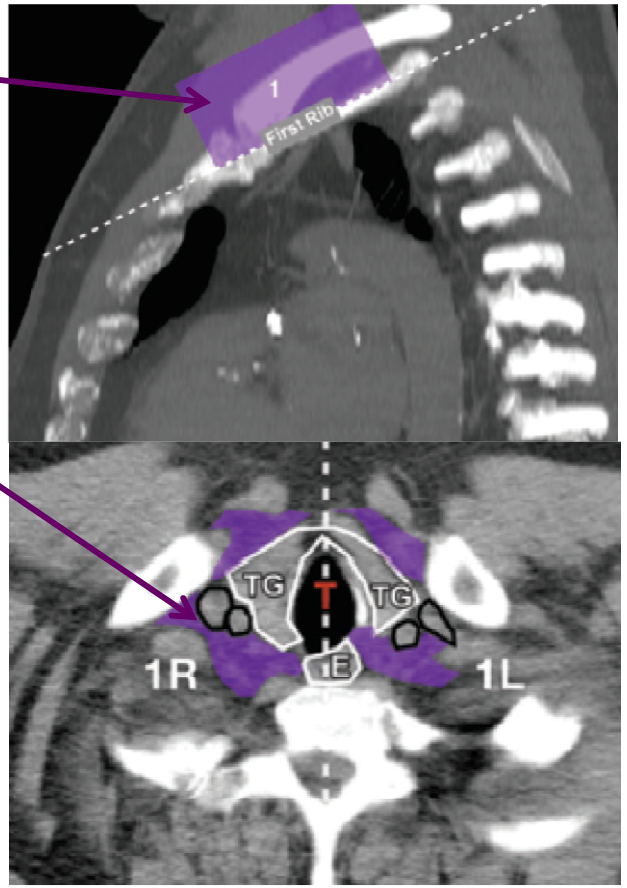
Anatomy: regional nodes





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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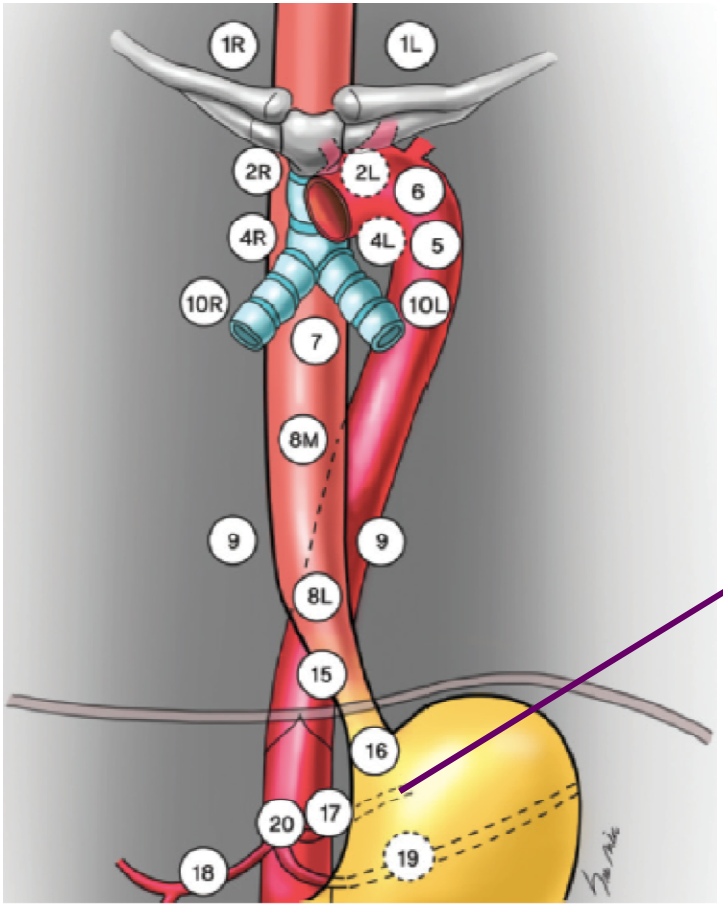
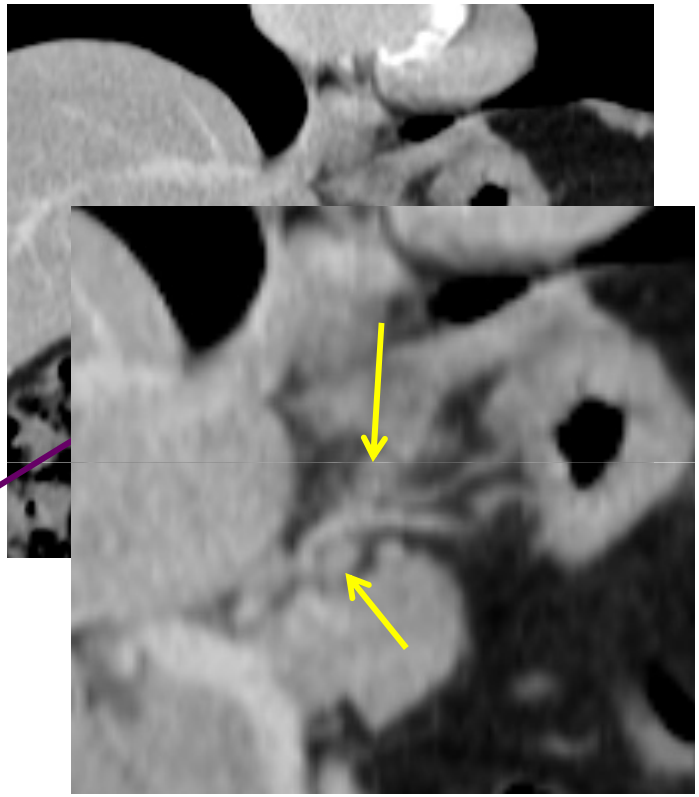
Anatomy: regional nodes





Left gastric artery node

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

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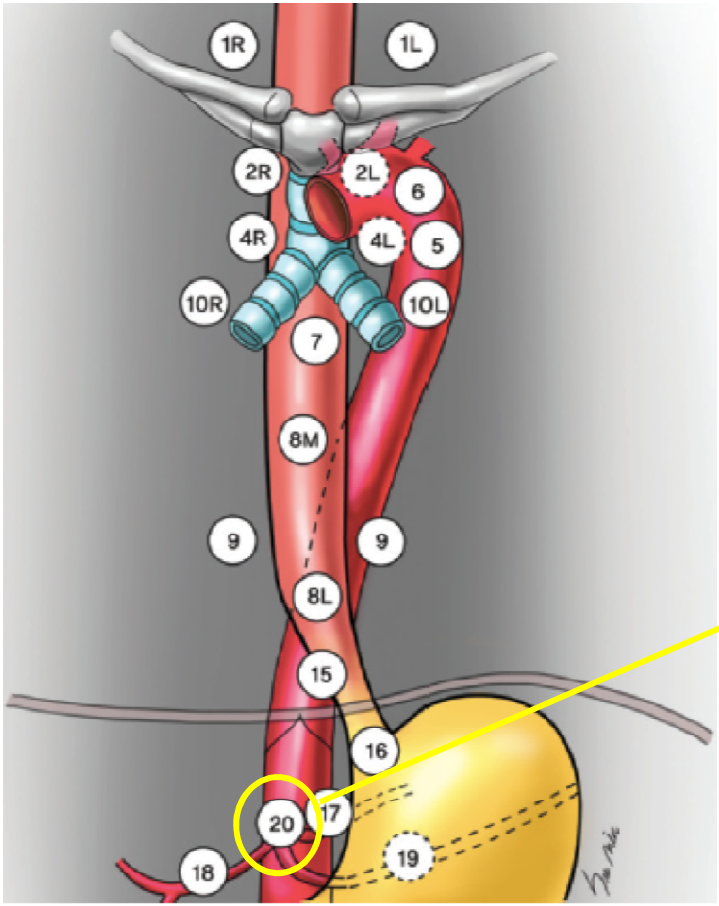
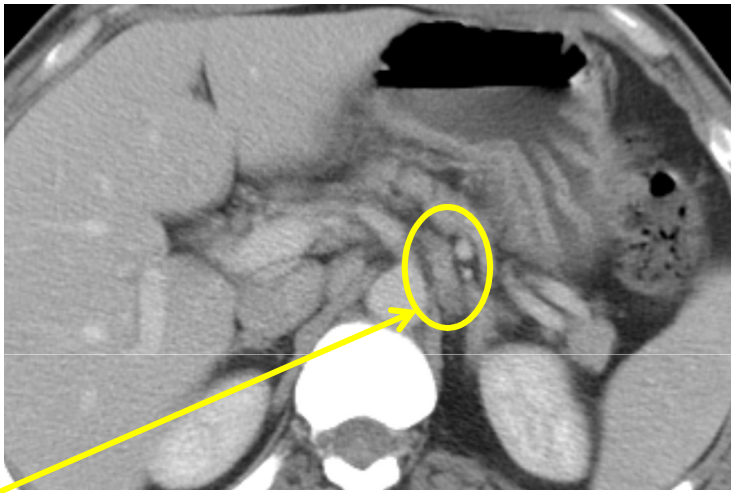
Anatomy: regional nodal stations





Coeliac axis lymph node

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

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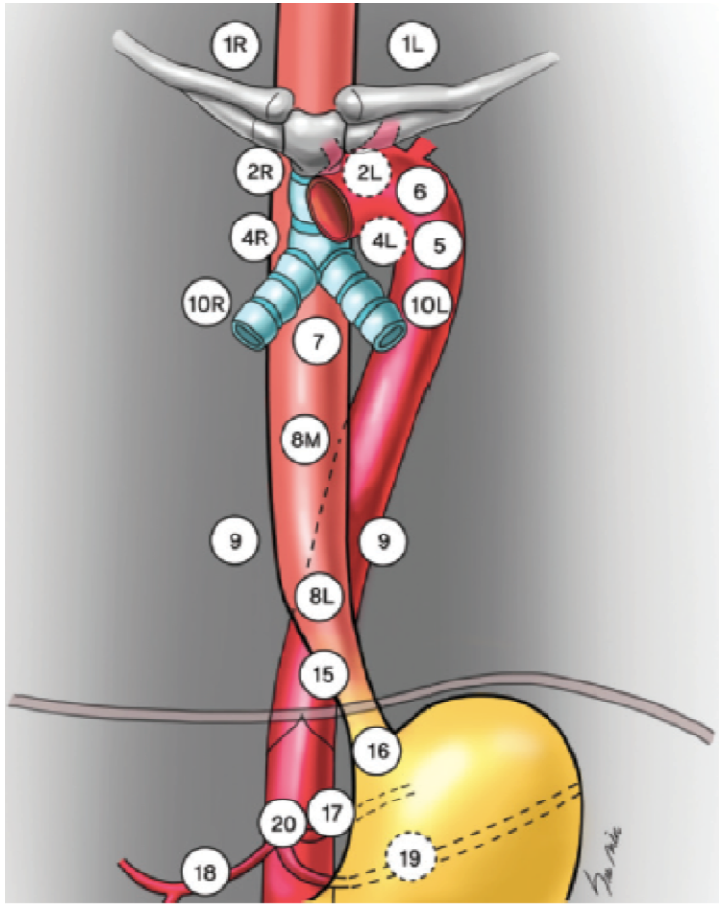
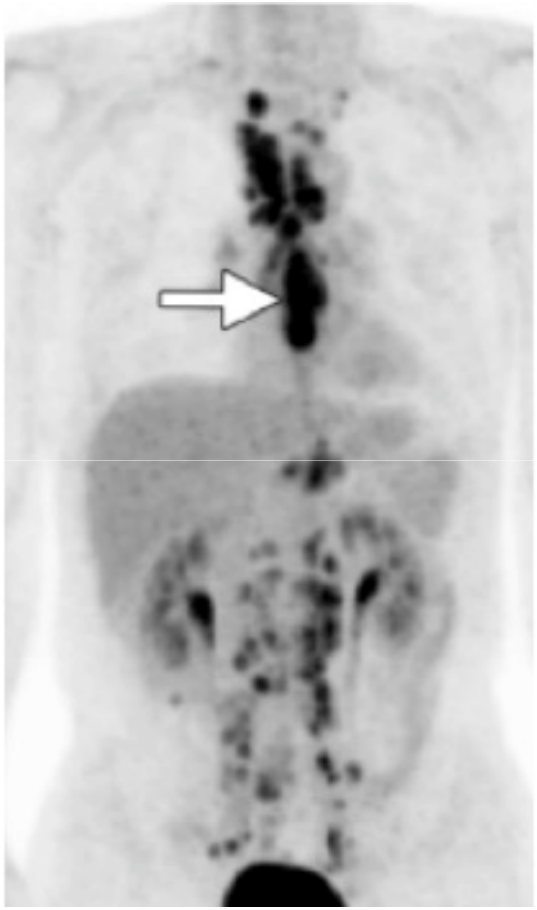
Anatomy: regional nodal stations – PET-CT





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

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Regional Lymph nodes

Determining nodal involvement

Modality	Criteria	Comment	Sensitivity	Specificity
CT	Size	Intrathoracic & intra abdominal nodes >10mm & supraclavicular nodes >5mm are considered involved	63-87%	14-43%
EUS	Morphology	Malignant nodes: round; hypoechoic. Capability for FNA	85%	85%
PET-CT	SUV	Lower sensitivity due to reduced ability to detect nodes near the primary in some instances	51%	84%

Summary

Identification of anatomical landmarks

- Enables accurate location of primary & involved nodal stations

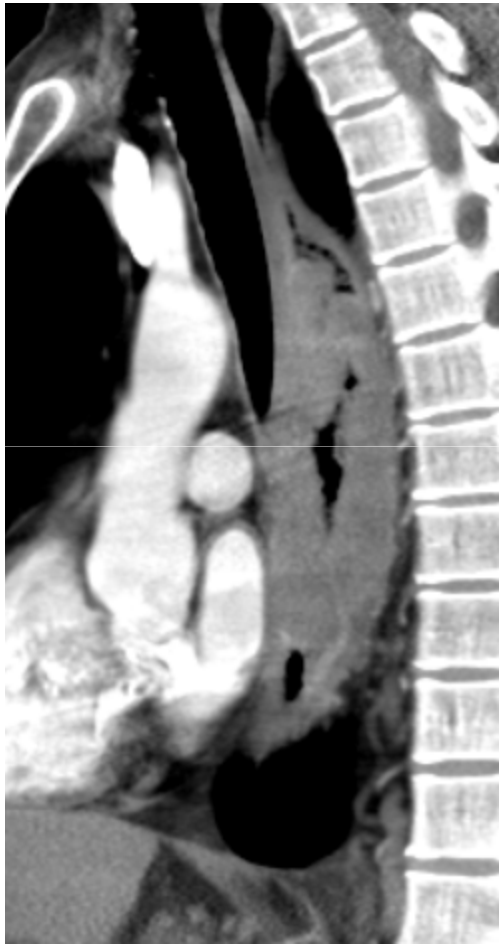
Multimodality approach to imaging

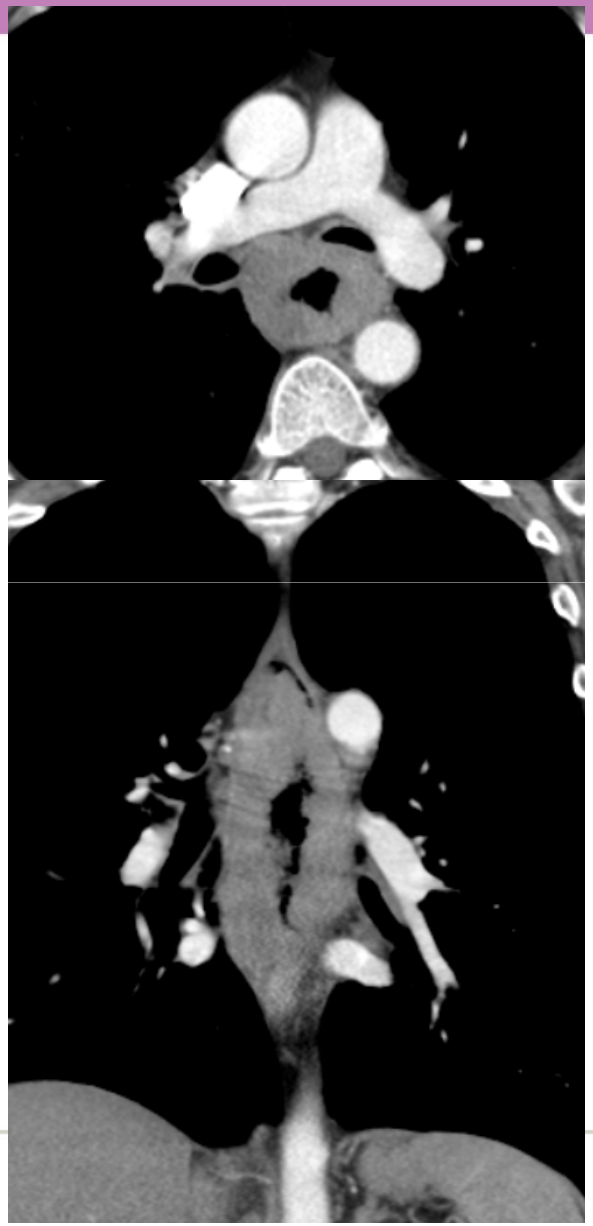
- MDCT
- EUS & PET-CT can refine identification and staging
- MRI likely to be used increasingly in the future

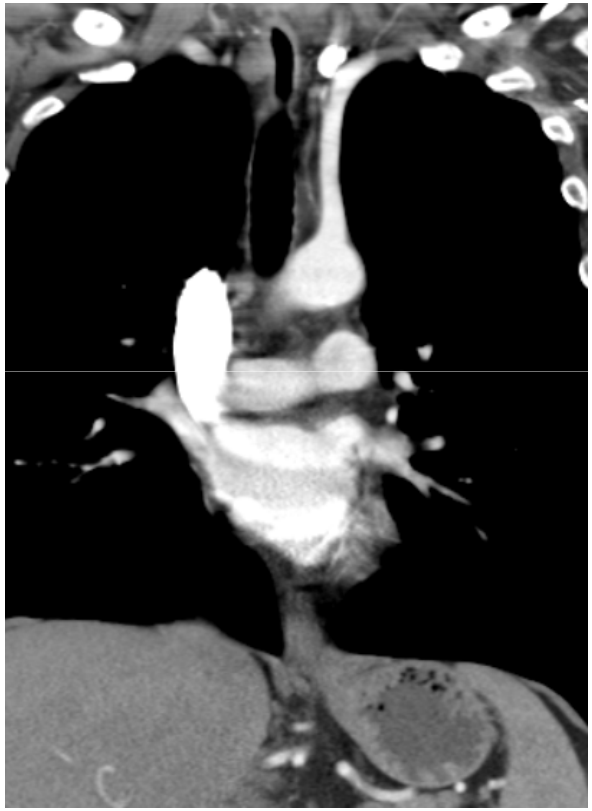
Quiz

Male patient presenting with dysphagia

Quiz







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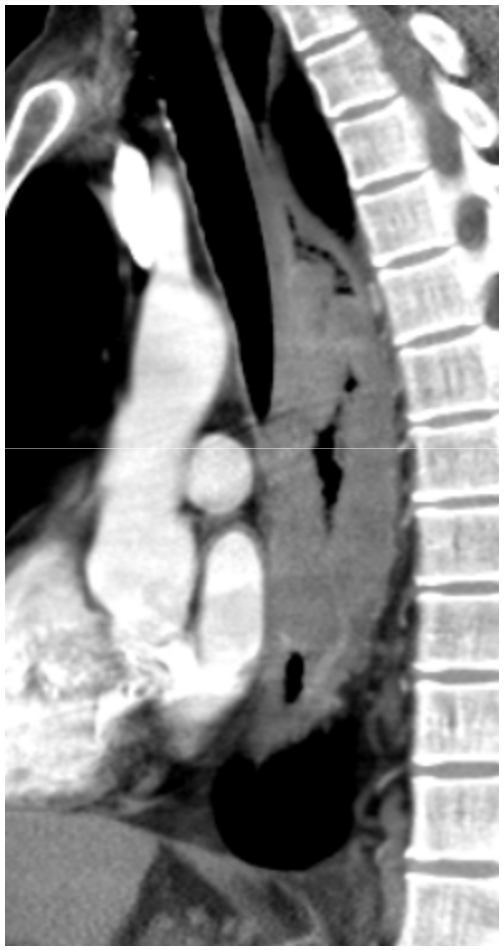
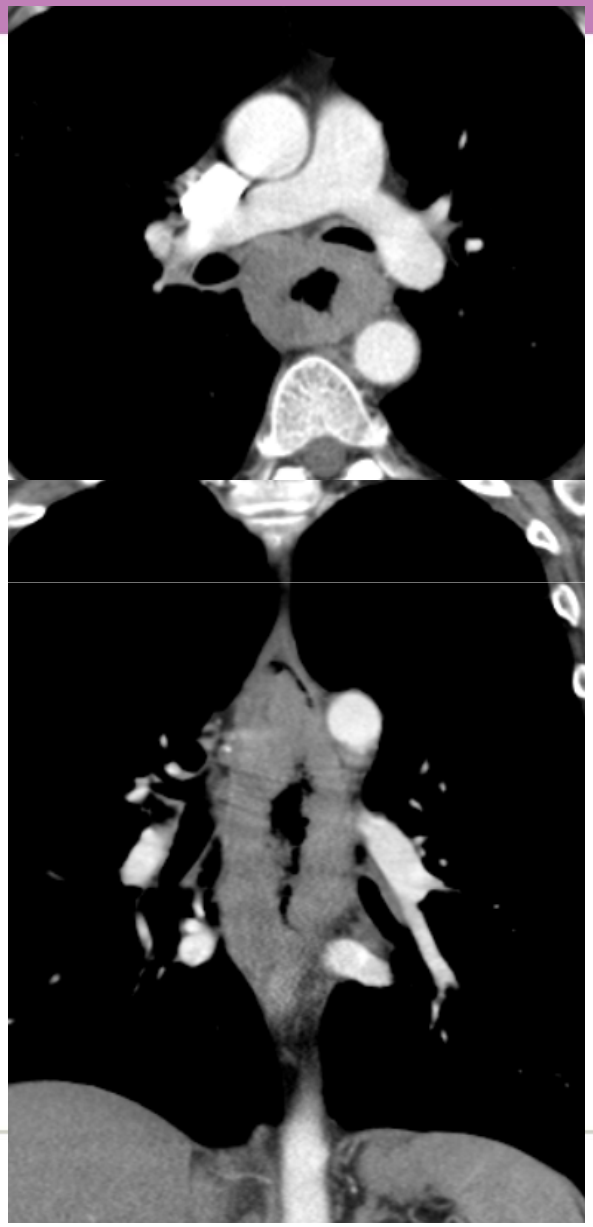
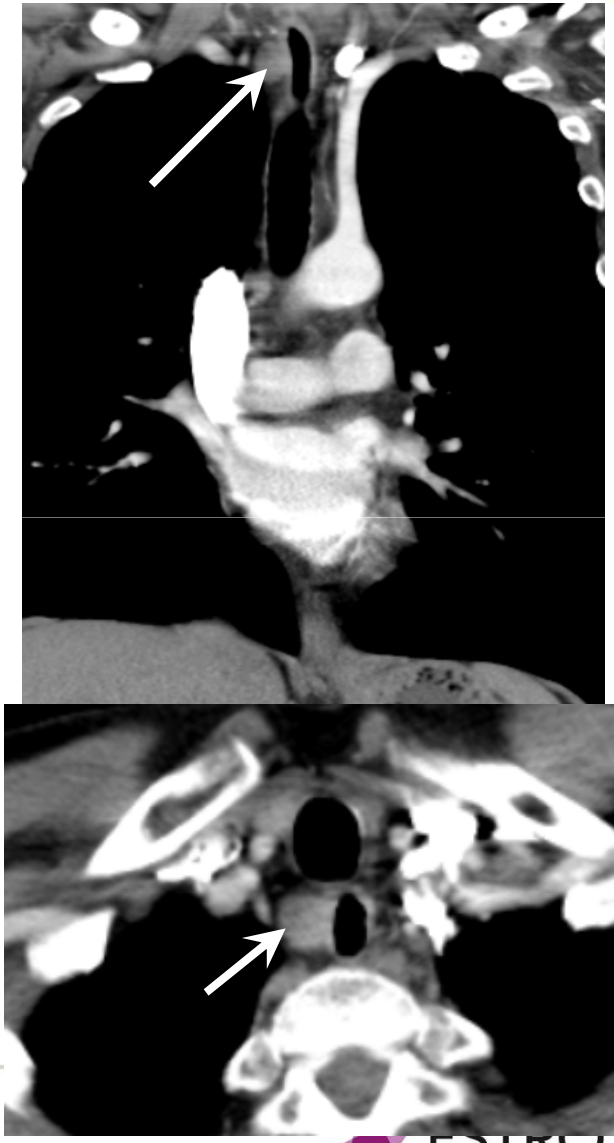
Quiz

- Describe the location of the tumour
- Stage the tumour

Quiz







Quiz

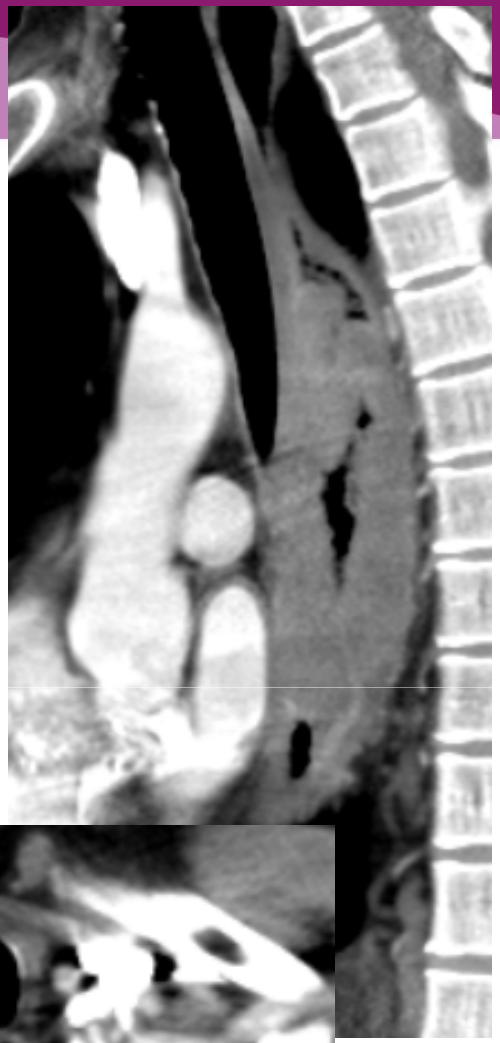
Location

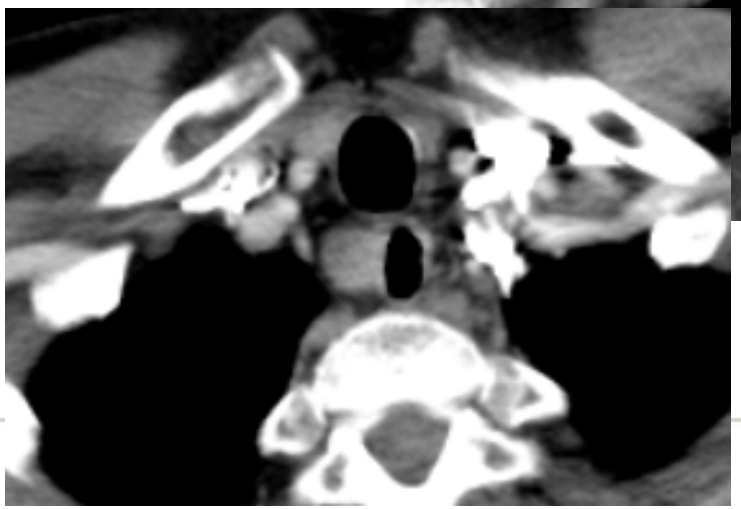
mid & lower oesophagus

Tumour Stage

Bulky T3 N1

Node at station 1





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Thank You

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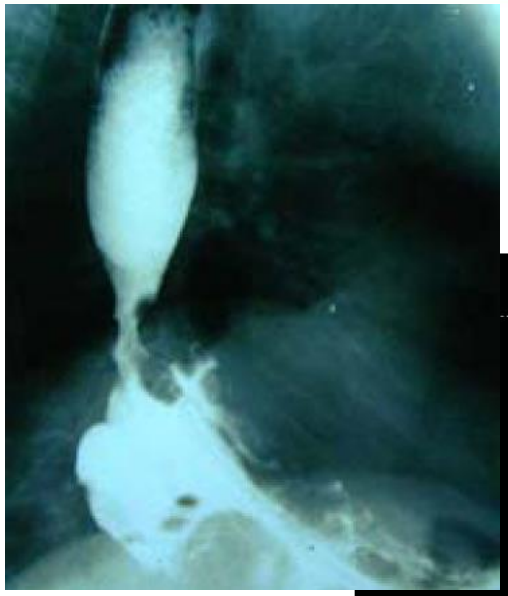
Recommendation for sub-site delineation by stage and tumor position

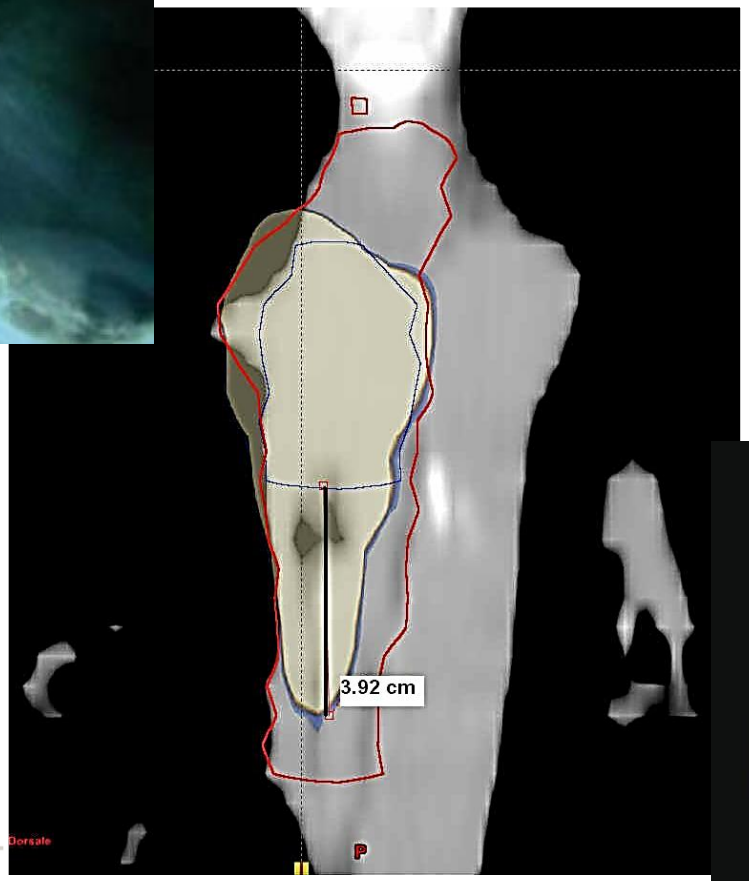
Prof. Philippe MAINGON

Radiation Oncology Department, CGFL, Dijon

Radiation Oncology Department, GHU La Pitié Salpêtrière Charles Foix, Paris

GTV

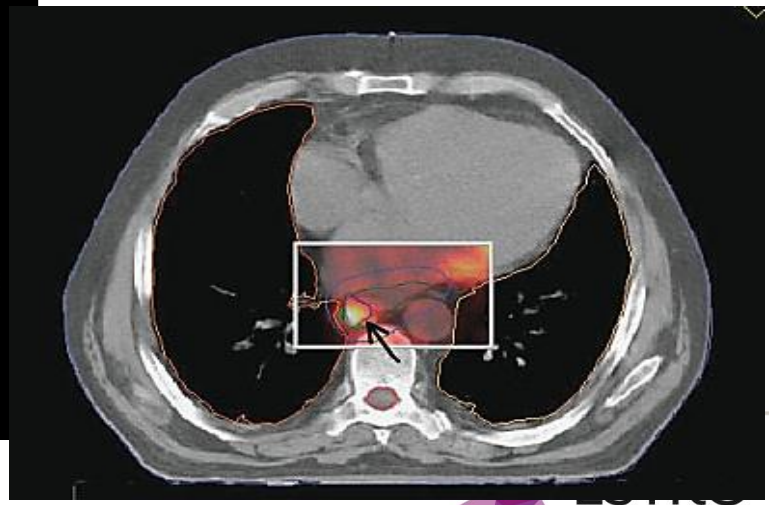




30% endoscopy not feasible

CRITERIAS:

- N+ scan >6.5mm,
- EUS+
- PET+



Resection versus PET scan

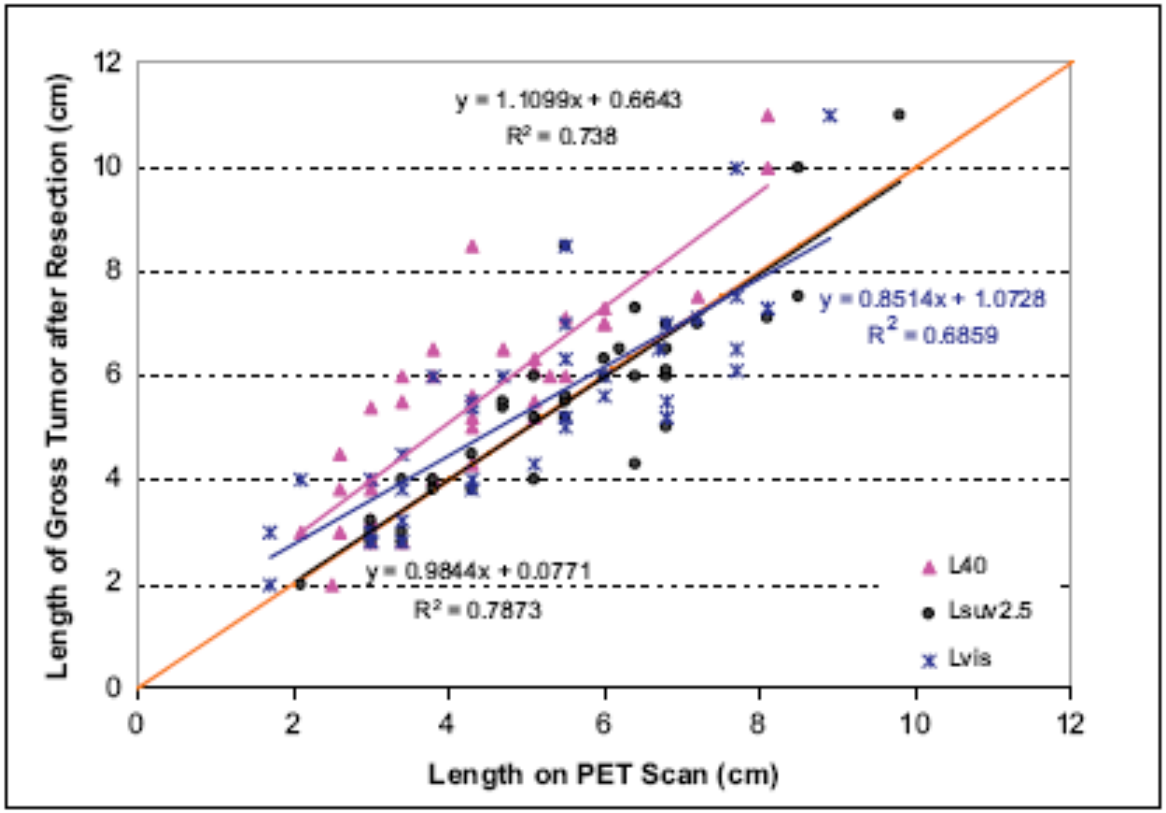


Fig. 2. Image–pathology correlations.

Xiaojun Zhong IJROBP 2009;73:136-141

Integrated PET - CT

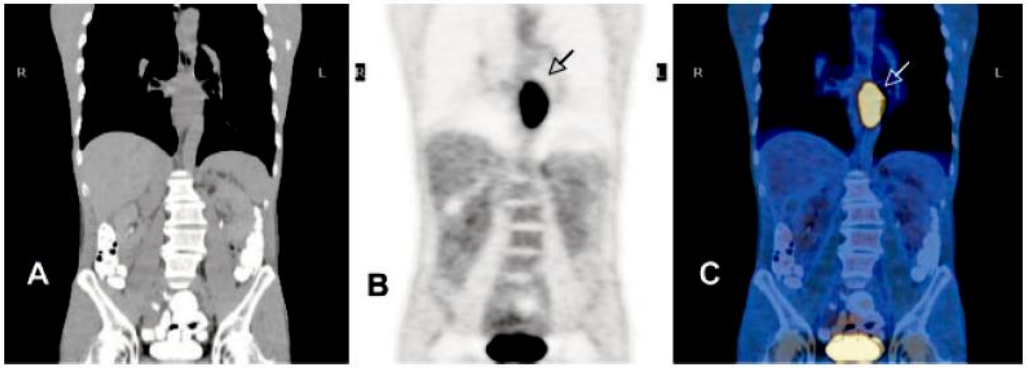


FIGURE 1. Integrated PET/CT of a patient showing NPA = 1 in the primary (arrow). (A) CT scan; (B) PET scan; (C) integrated image.

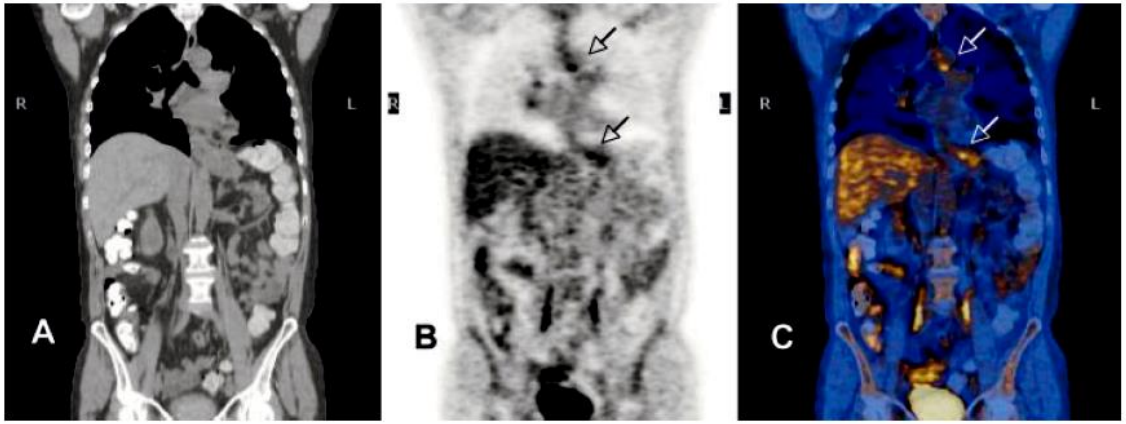


FIGURE 2. Integrated PET/CT of a patient showing NPA = 2 in the primary and mediastinum (arrows). (A) CT scan; (B) PET scan; (C) integrated image.

Hong D. Cancer 2005;104:1620-6

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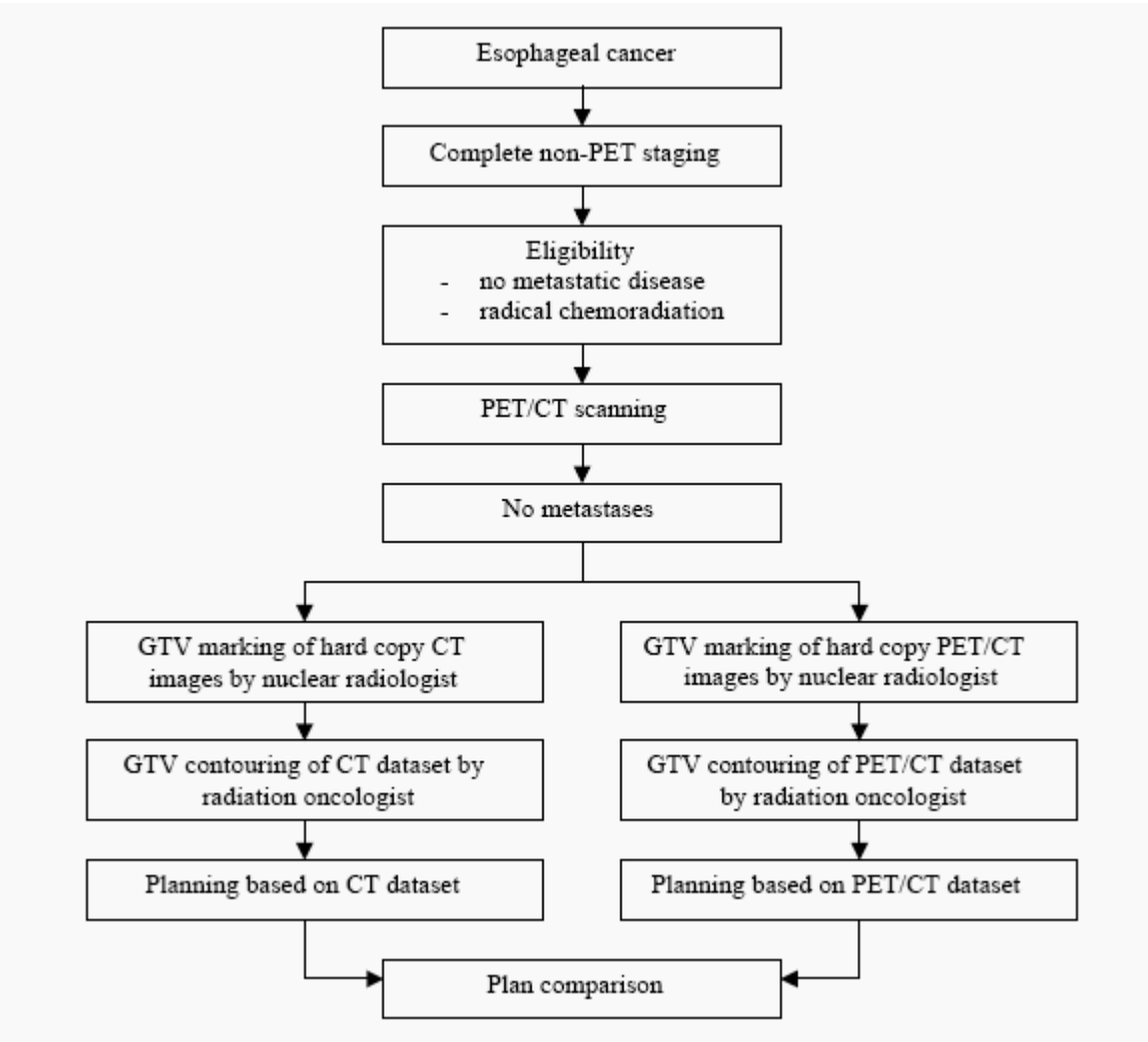
Impact of PET-CT on RT planning



Leong T. Radiother Oncol 2006;78:254-61

Impact of PET-CT on RT planning

- PET-avid disease was excluded from GTV in 68% if CT alone were used.
- Median percentage of volume of GTV-CT not included in GTV-PET was 38%.
- The median percentage of GTV-PET not included in the PTV-CT was 6% ….

Leong T. Radiother Oncol 2006;78:254-61

Esophageal cancers

- PET can improve the RT planning

  Duong Eur J Nucl Med Imaging 2006
- PET is more accurate for nodal assessment
- Distant lymph nodes and distant metastasis

  Van Westreneen JCO 2004
- PET shows the longitudinal extent better than CT
- PET may be the only way to visualize the lower border of the tumor

CTV DEFINITION

- On surgical specimens: n= 34 SCC/32ADK
- Microscopiques extensions

- **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

- **Supero-inferior (mean value) =**
  - 50mm = 100% in field
  - 30mm = 94% in field

Gao S et al., IJROBP 2007

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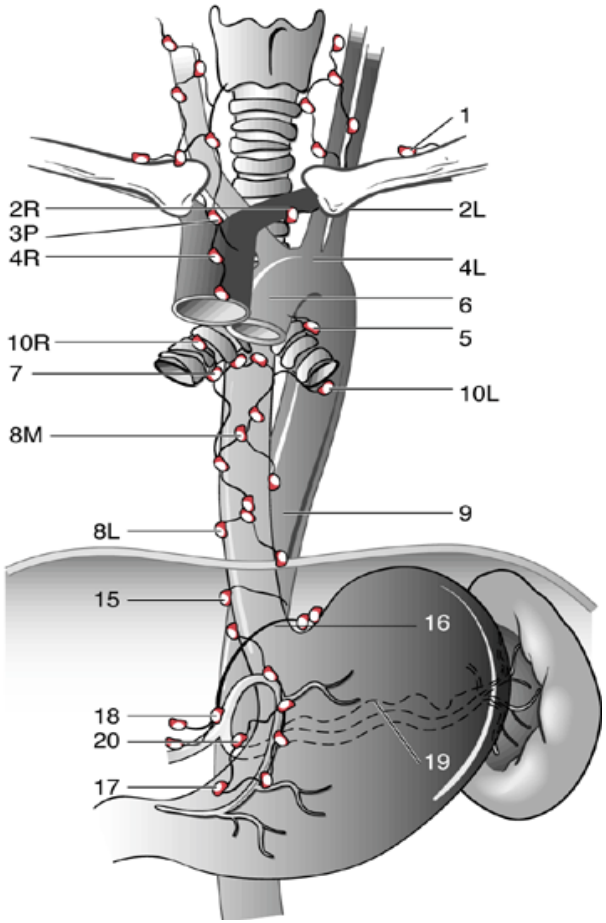
RTOG Staging system



	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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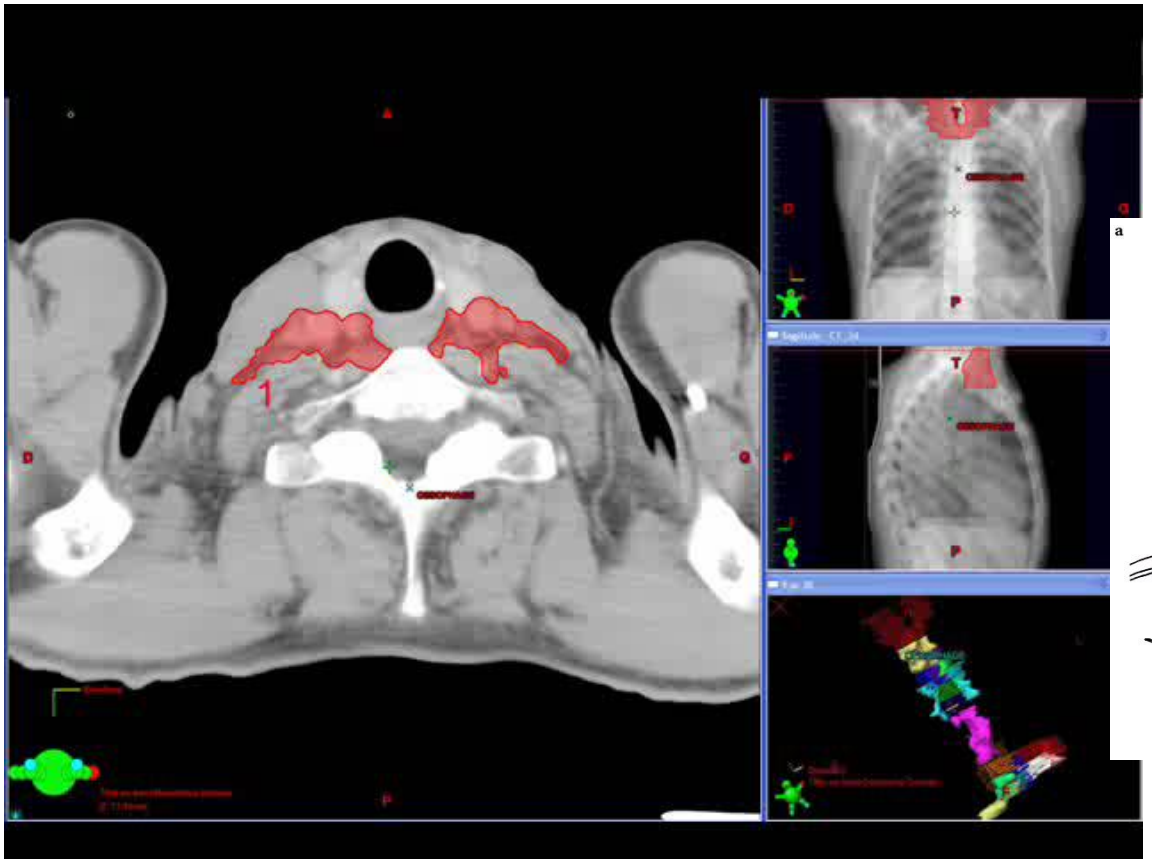
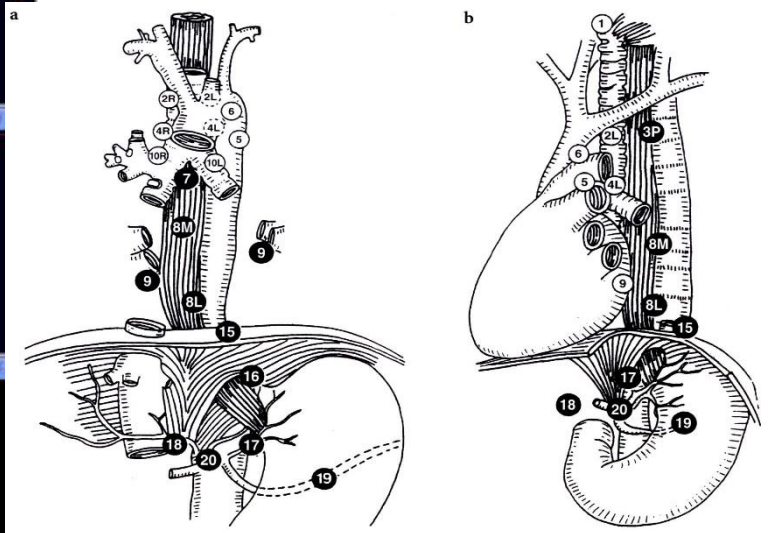
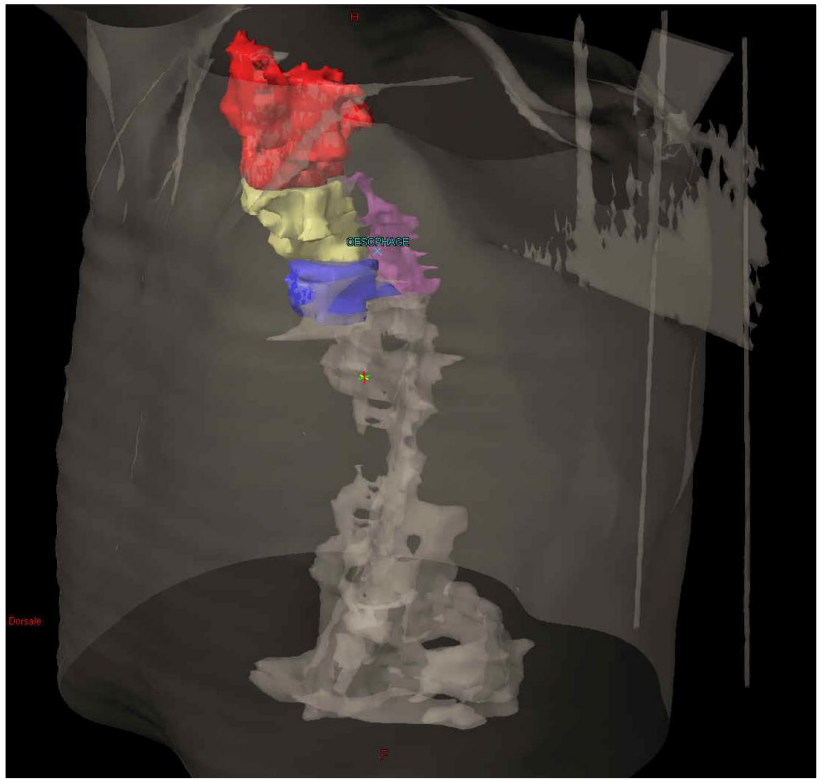
ATLAS





Volumes – Cervical Esophagus



T + 5cm

Positive nodes

- **If ENI :**

Niveau 1

Niveau 2R/2L

Niveau 3P

Niveau 4

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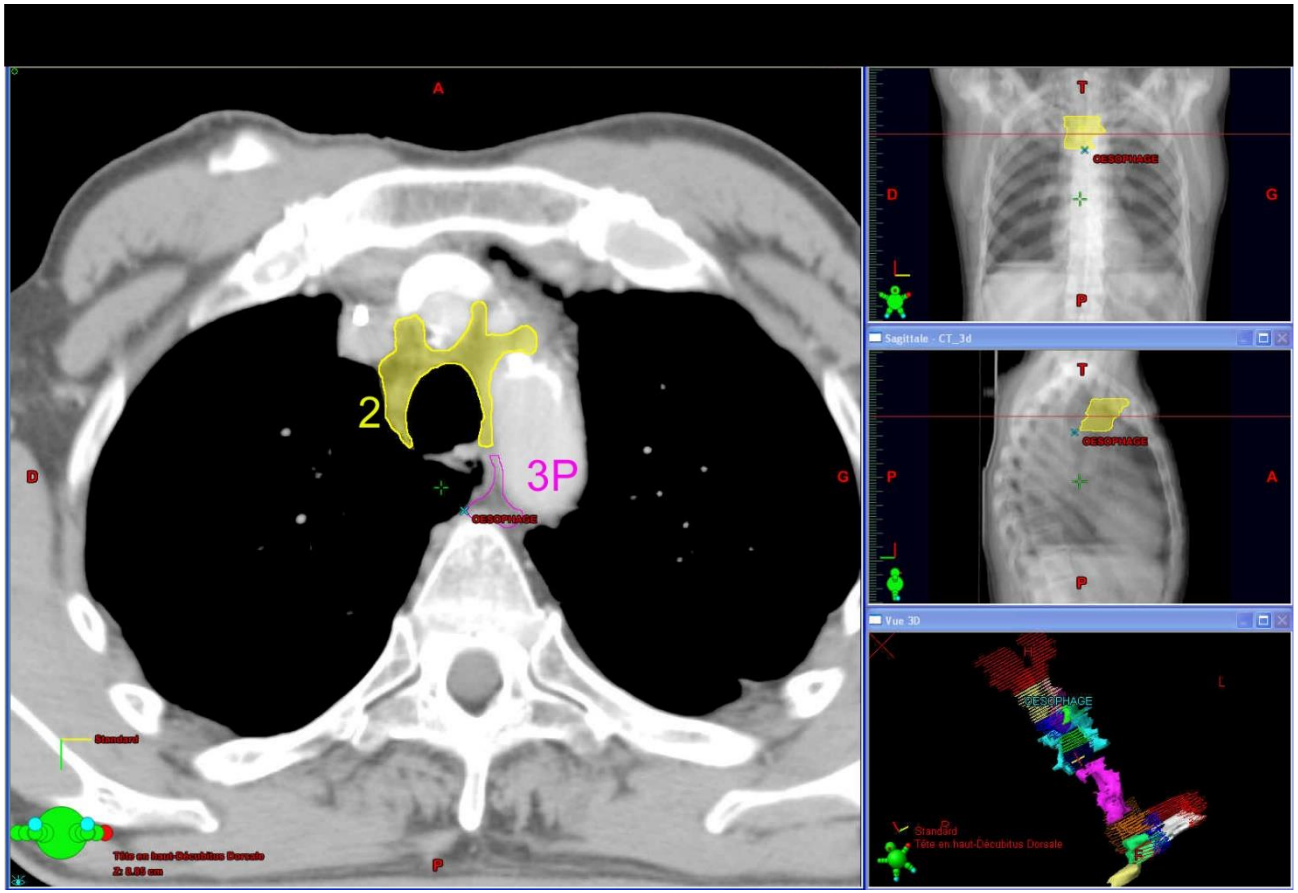
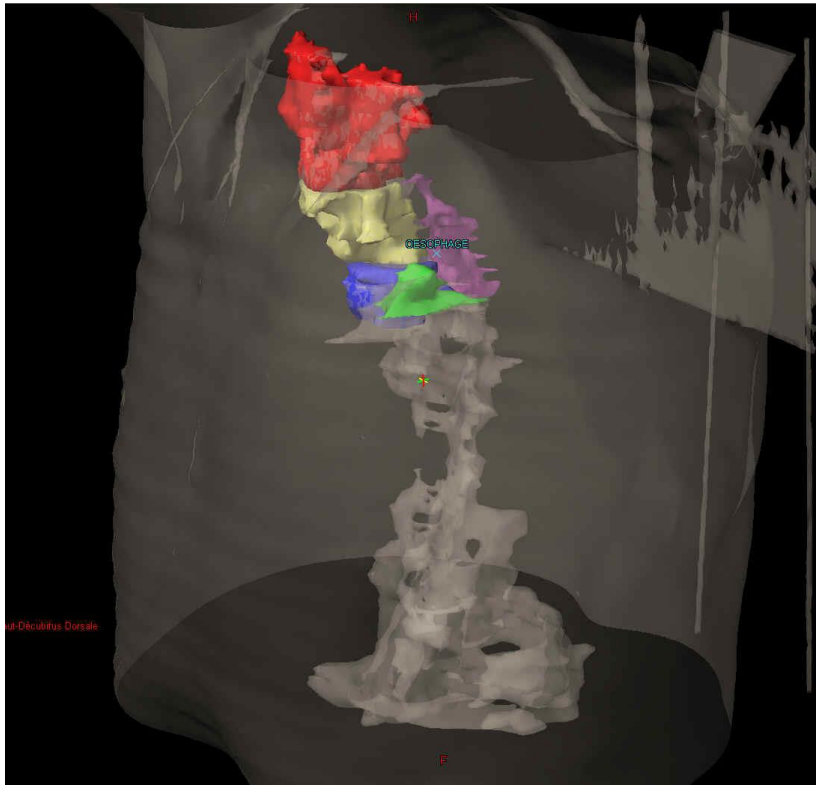
Cervical esophagus



Volumes – Upper third



Positive nodes

- **If ENI :**

Niveau 1

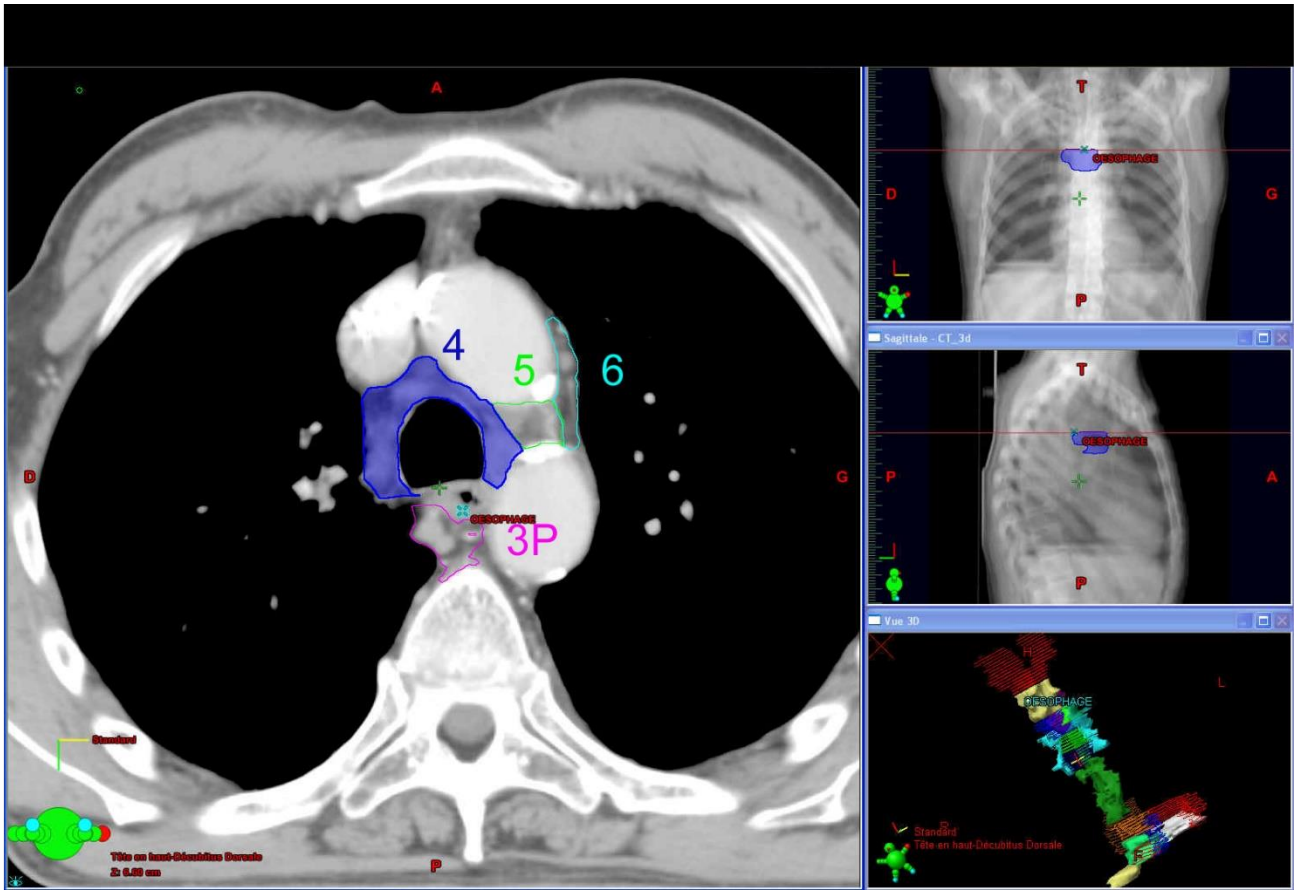
Niveau 2R/2L

Niveau 3P

Niveau 4

Niveau 5

Upper third



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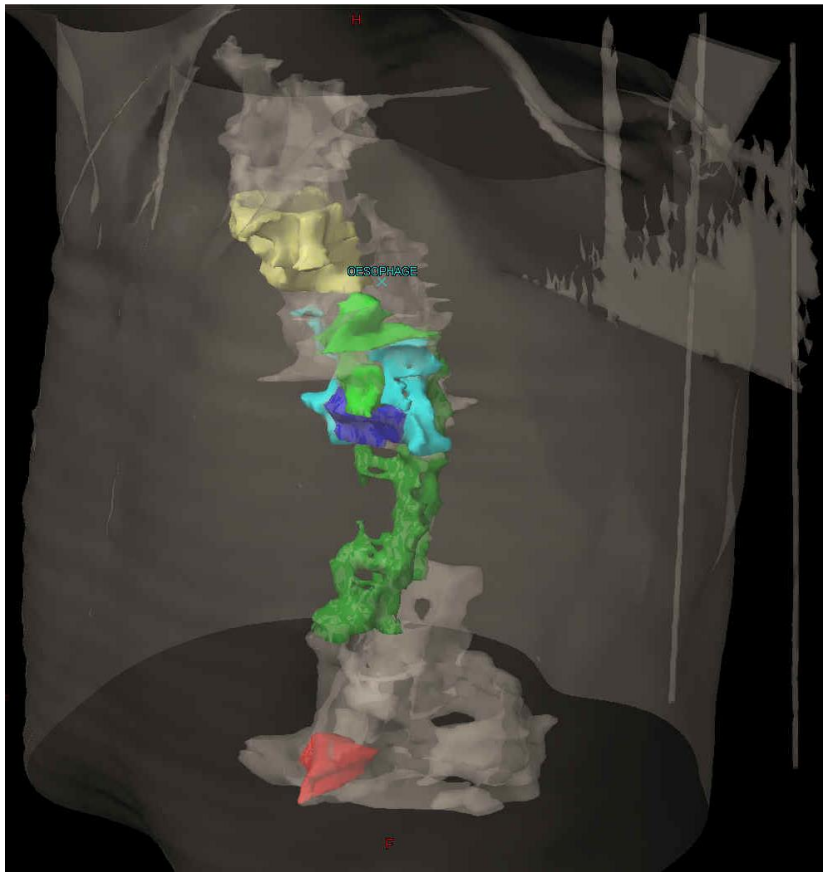
Volumes – Middle third



Positive nodes

- If ENI :

Niveau 2R/2L

Niveau 5

Niveau 7

Niveau 8M/8L

Niveau 9

Niveau 10

Niveau 17

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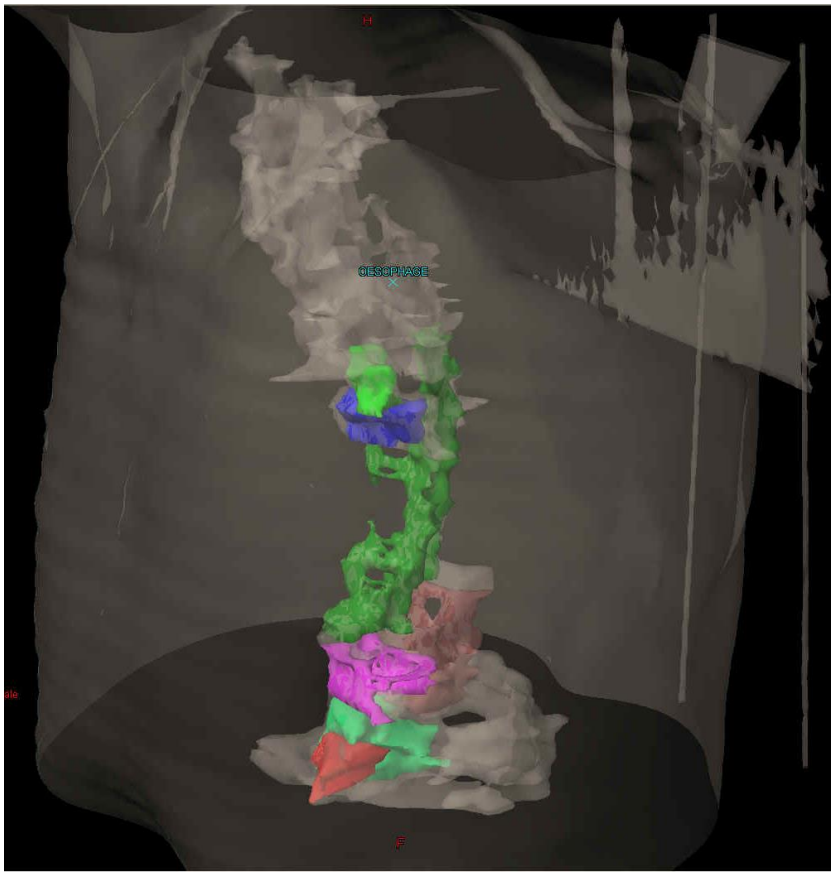
Volumes – Lower third



Positive nodes

- **If ENI :**

Niveau 7

Niveau 8L

Niveau 9

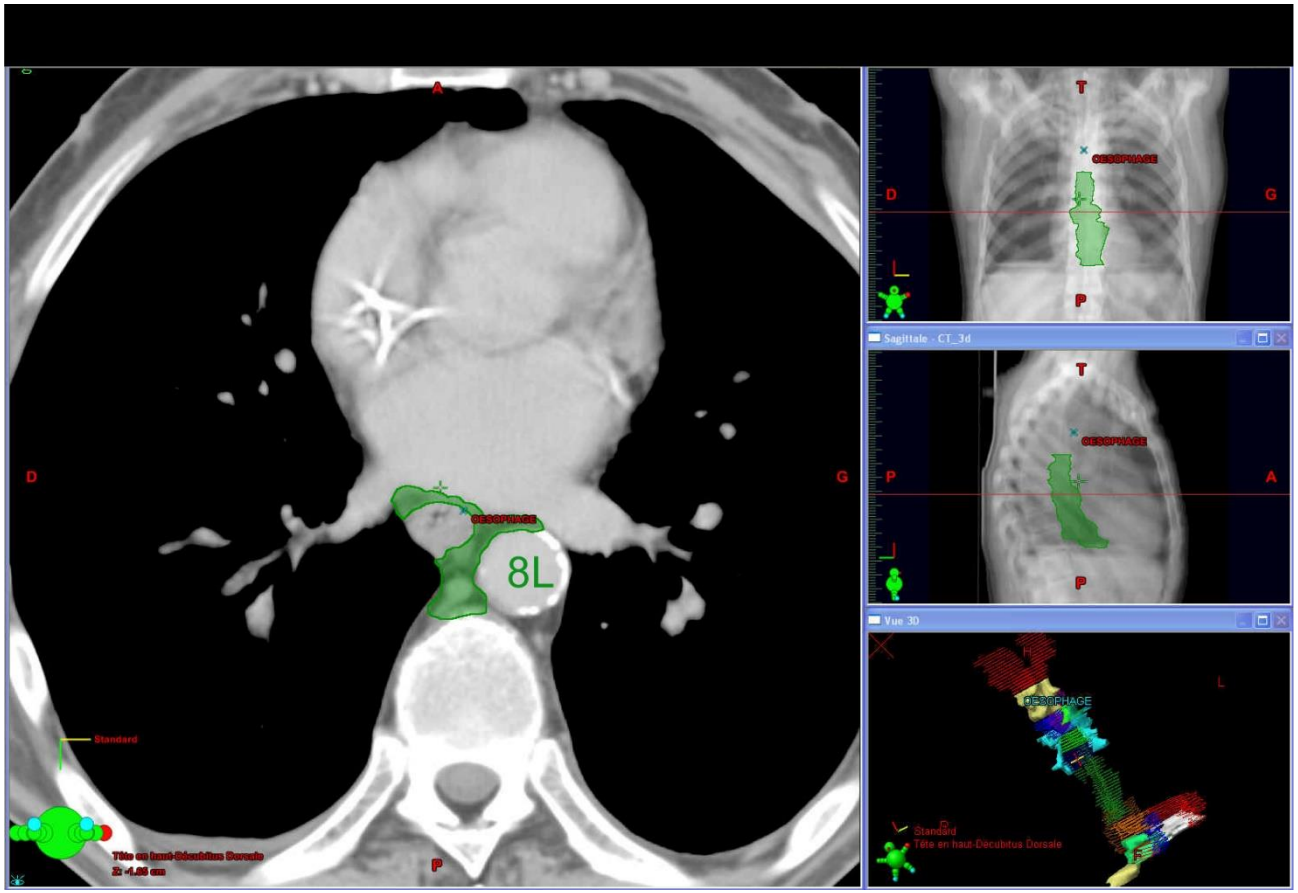
Niveau 15

Niveau 16

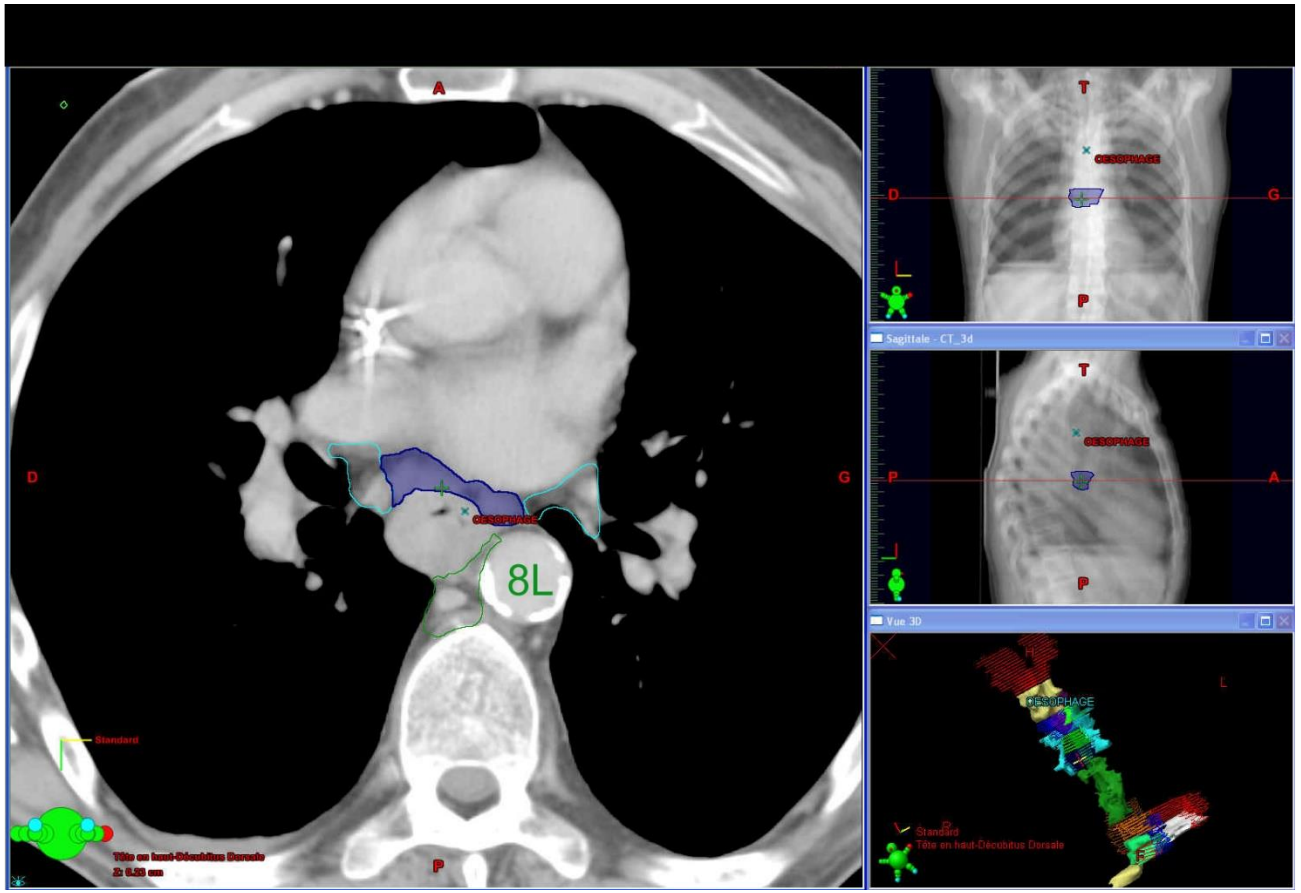
Niveau 17

Niveau 20

Para esophageal lymph nodes



Pulmonary ligament = 9



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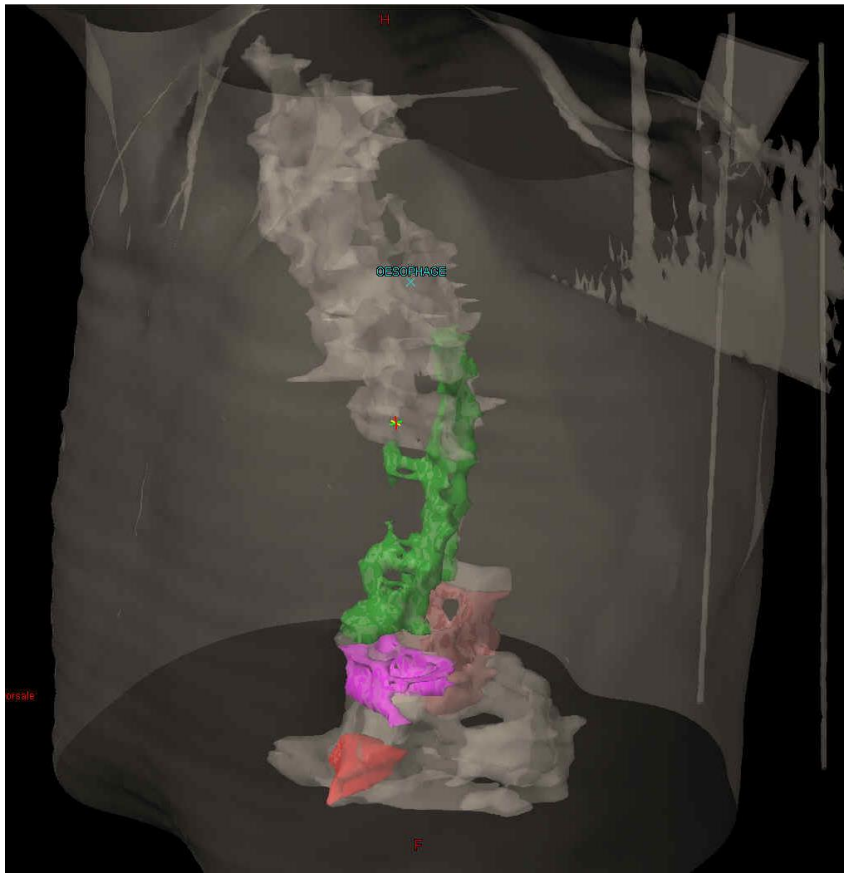
Volumes – Abdominal



Positive nodes

- **If ENI :**

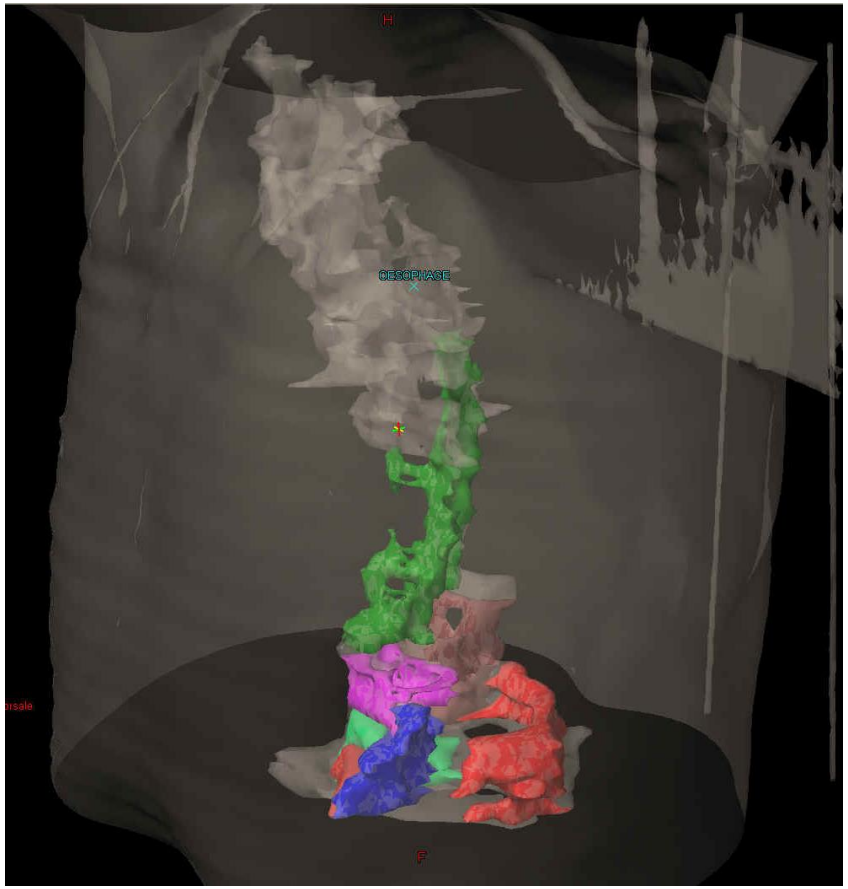
Niveau 8

Niveau 15

Niveau 16

Niveau 17

Volumes – Siewert type I



Positive nodes

- If ENI :

Niveau 8

Niveau 15

Niveau 16

Niveau 17

Niveau 20

Gastric network

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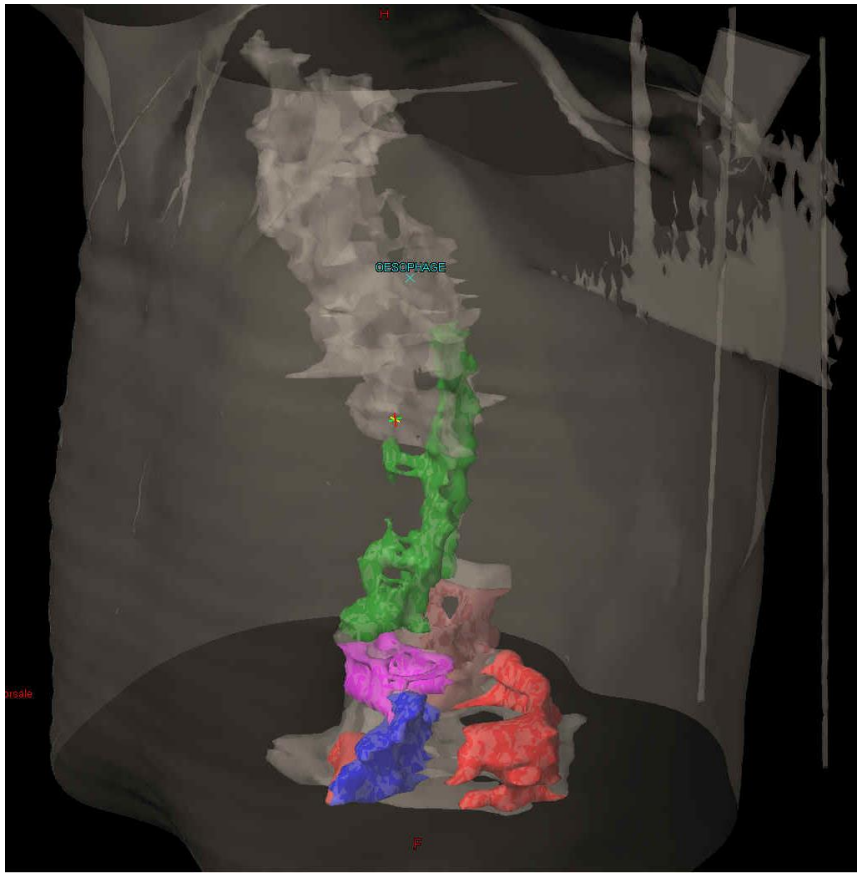
Volumes – Siewert type II



Positive nodes

- **If ENI :**

Niveau 8

Niveau 15

Niveau 16

Niveau 17

Gastric network

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			×	×	×	×	×

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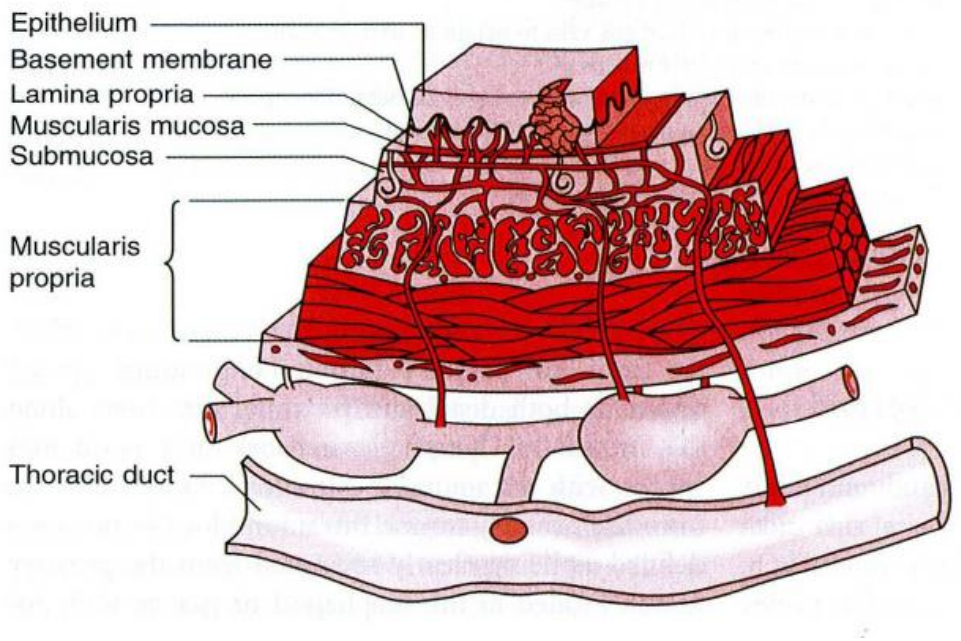
ENI versus IFRT ? Regional lymph node involvement and CTV

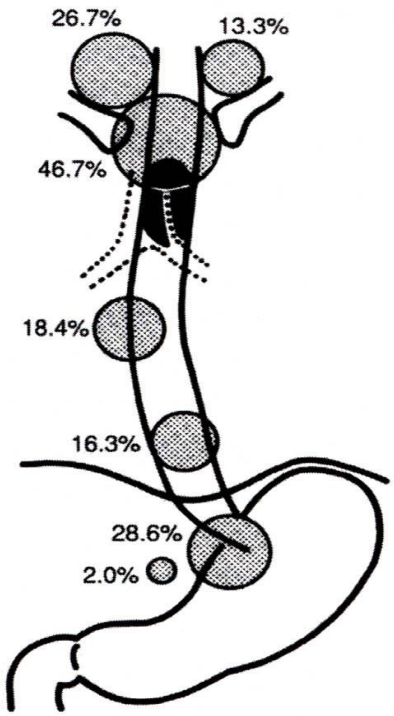
Tis	0%
T1b	31-56%
T2	58-78%
T3	83-100%



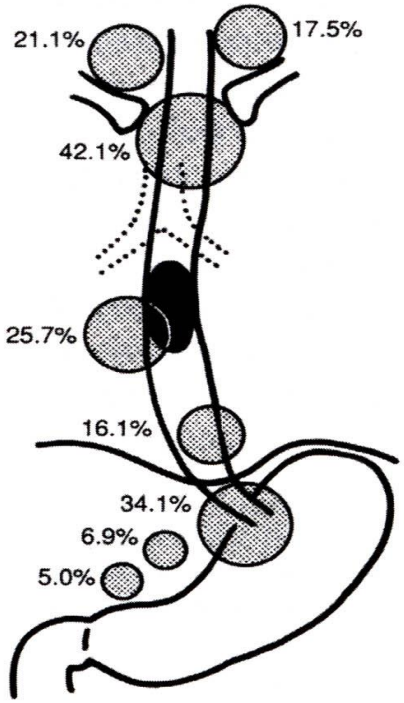
Distant lymph node metastasis

'Skip metastasis'

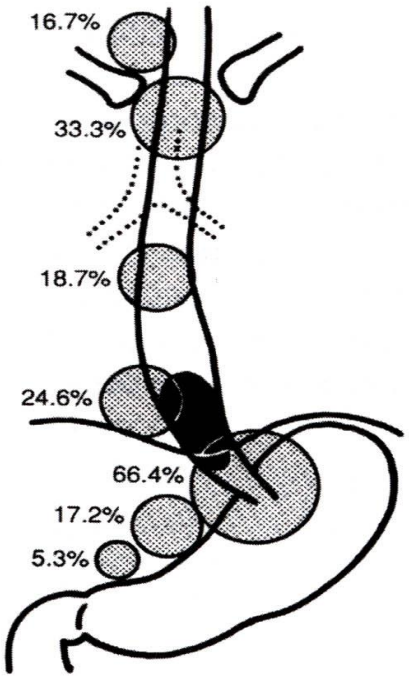
A COMPLEX LYMPHATIC NETWORK



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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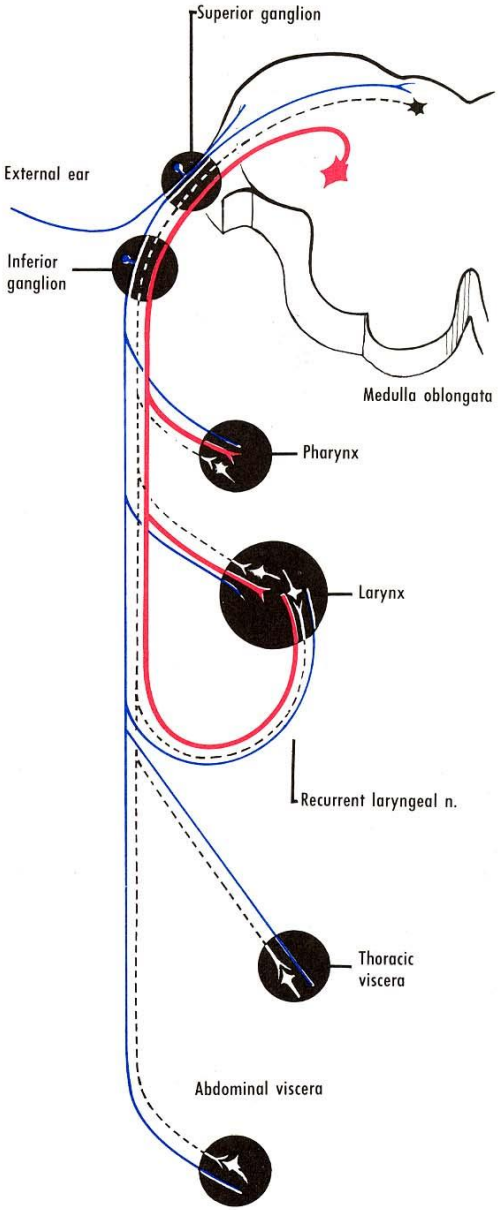
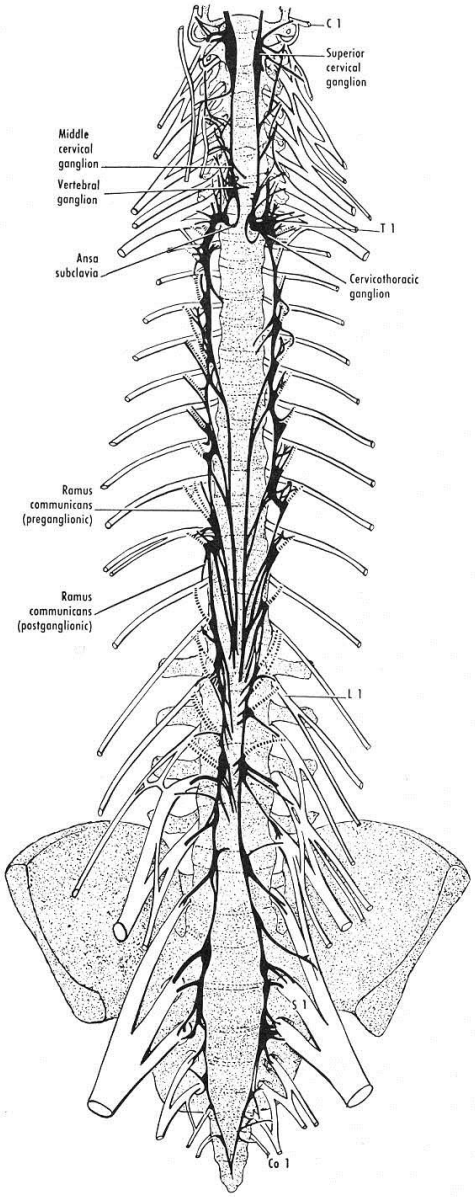
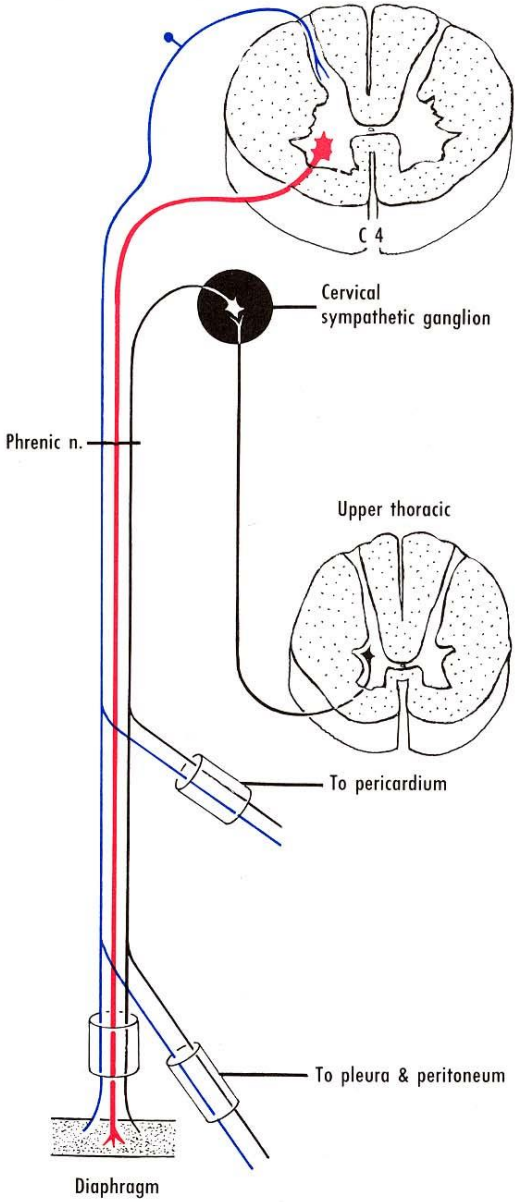


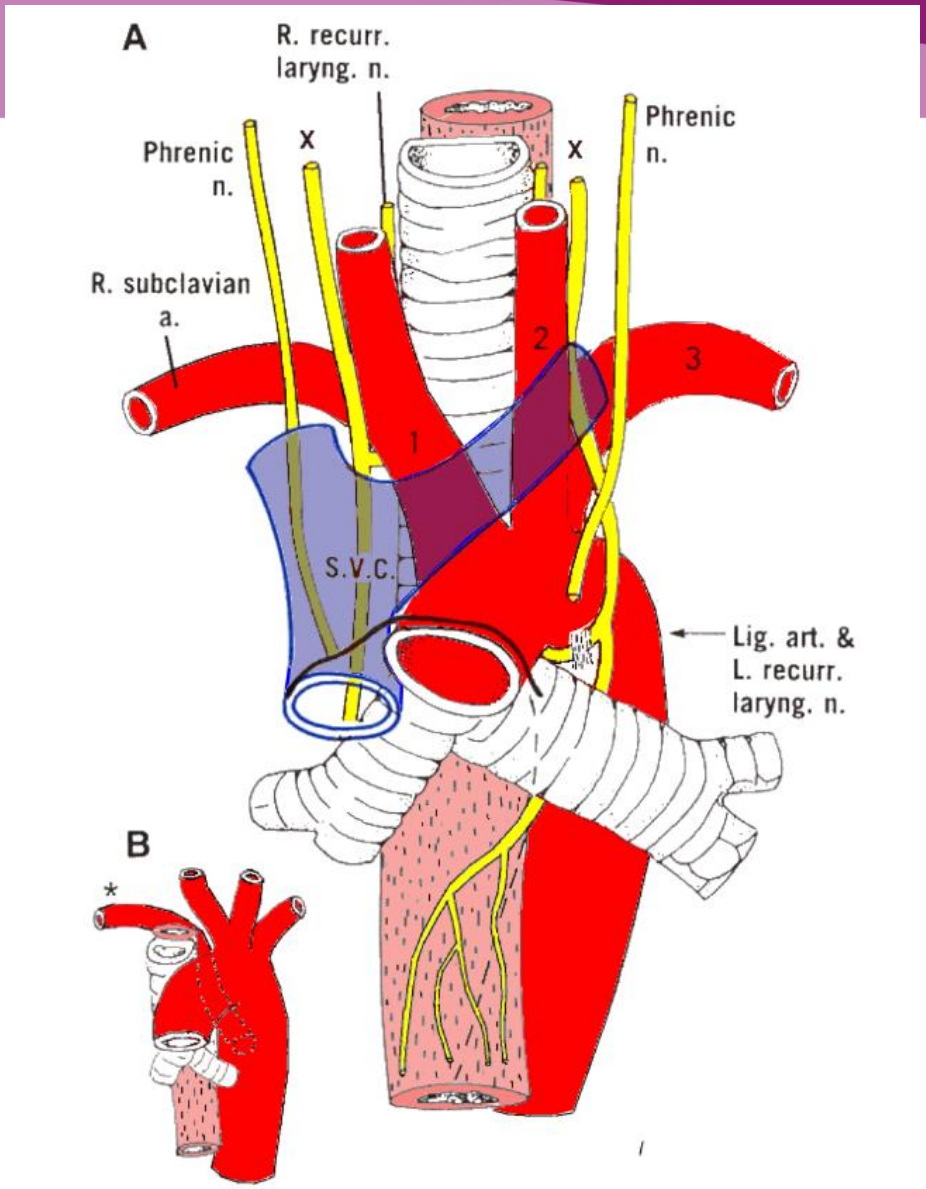




Vagus or X nerve

Sympathic trunk

Phrenic nerve


A
R. recurr.
laryng. n.
Phrenic
n.
X
X
Phrenic
n.
R. subclavian
a.
2
3
1
S.V.C.
Lig. art. &
L. recurr.
laryng. n.
B
*

ENI versus IFRT ? Regional lymph node involvement and CTV

	Cervical	Upper third	Middle third	Lower third	Lower abdomen
Upper	30.7	42	12.9	2.6	9
Middle	16.8	21.1	28.1	7.8	21.4
Lower	11	10.5	19.6	23	39.9

Ding Br J Radiol 2012

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ENI versus IFRT ? Lymph node metastasis and micrometastases

	Sensitivity		Specificity	
CT scan	0.50	*0.41-0.60*	0.83	*0.77-0.89*
EUS	0.80	*0.75-0.84*	0.70	*0.65-0.75*
FDG-PET	0.57	*0.43-0.70*	0.85	*0.76-0.95*

Van Viet Br J Cancer 2008

- Micrometastases do not influence the survival of pN0 patients
- Micrometastases is totally unpredictable
- Better OS after 3 field lymphadenectomy may suggest the benefit of ENI
- The number of positive lymph nodes is related to prognosis

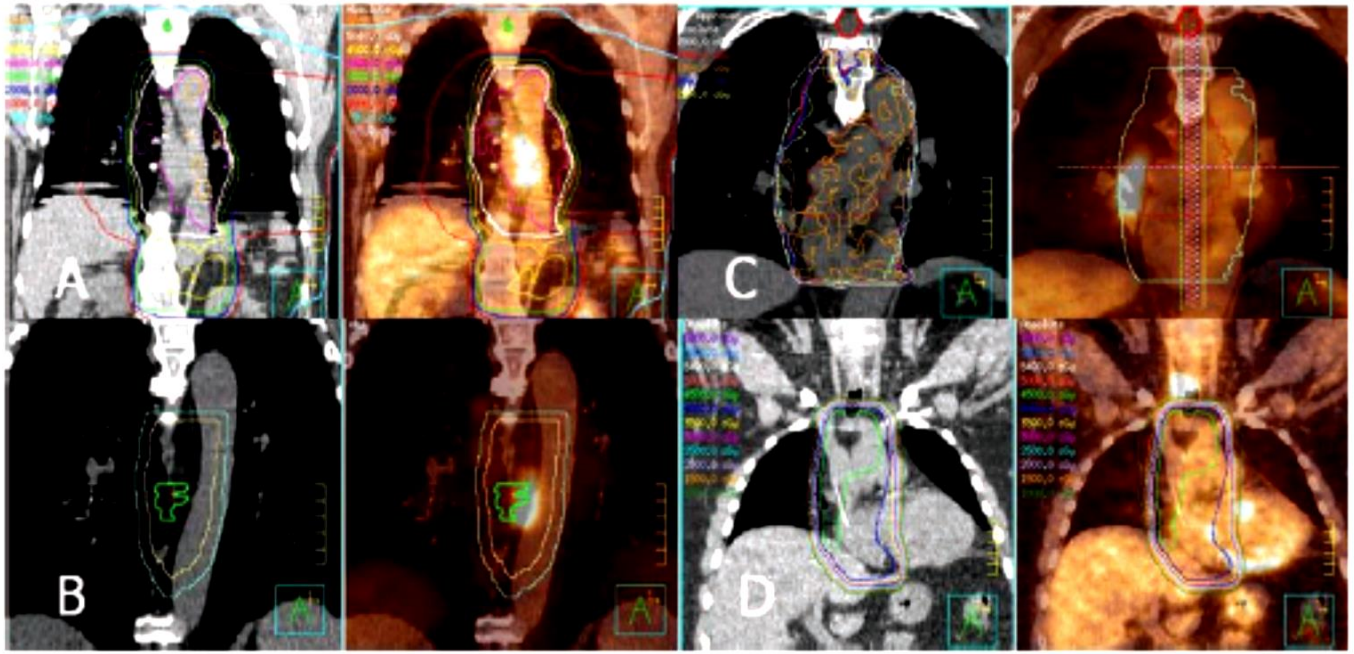
ENI versus IFRT ? Chemoradiotherapy and the incidence of regional failure

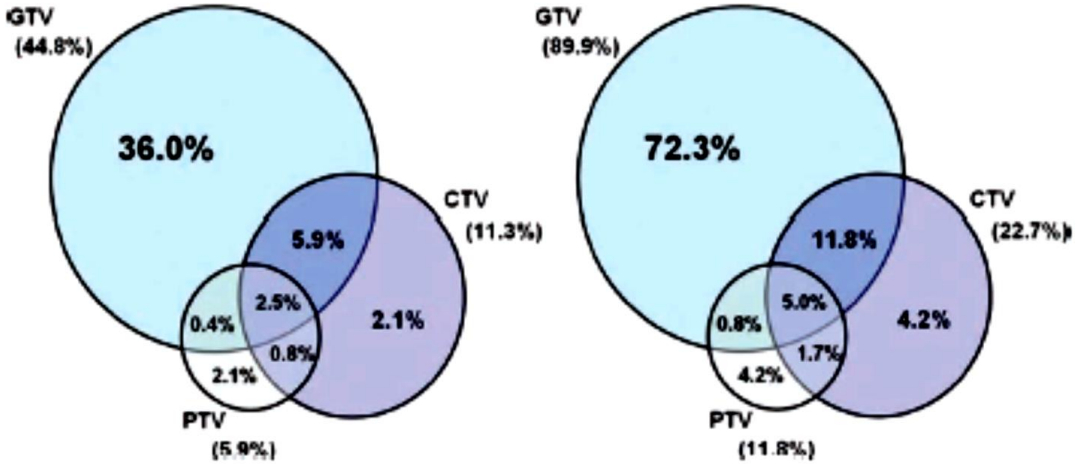
- Chemotherapy or CRT is able to reduce nodal metastases
- If tumor shows a major response, micromet are significantly reduced (nbre of nodes and nbre of positive nodes).
- The clinical relevance of micromets depend of tumor aggressiveness, the host immune status and the response to treatment
- Incidental irradiation is considerable using 3DCRT

ENI versus IFRT? Patterns of failure

	T1	T2-T3	T4
RR	90%	60-90%	57-88%
CR	88-97%	50-60%	17-39%

- The incidence of regional lymph node failure is low with or without ENI (1-6%)
- IFRT should be feasible for T1 stage EC
- Most of the failure occur in the GTV (85%)





Welsh J. Cancer 2012;118:2632-40

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ENI versus IFRT? Patterns of failure

- **Preoperative setting** Oppedijk JCO 2014

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.

- Even for CR after CRT, the primary and the distant organ rather than the regional lymph node were the prominent sites of recurrence.
- For early and advanced EC, the majority of the failures occurs in the GTV (the primary). Only few patients experienced solitary regional node failure.
- No clear recommendation regarding differenciation

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RTOG 85-01

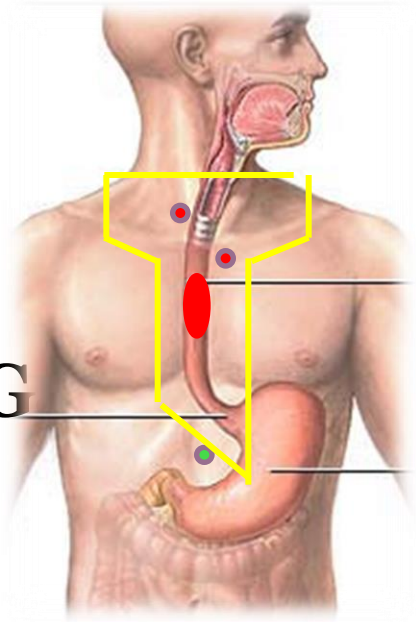
RT 2D

ENI

AP-PA

30 Gy

Susclav – EG



Boost 2D

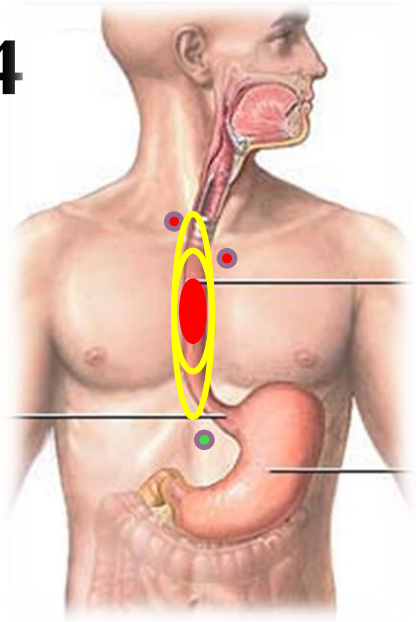
T + 5cm : 20Gy

Int. 0123

RT 2D

T + 5cm : 50.4

IFRT



Boost

T + 2cm : 14.4Gy

ENI or IFRT ?

- To date, no universally accepted opinion regarding the extent of the RT field has been established, especially for the CTV.

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

- For the CTV T cranial and caudal margins of 3-5 cm and radial margin of 1-1.5 cm are used considering the submucosal spread.

Oesophageal cancer

Dose issues in esophageal tumor control

Marcel Verheij MD PhD
Department of Radiation Oncology
NKI, Amsterdam

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Contents

Introduction

Treatment options

Radiotherapy: OAR, dose-constraints

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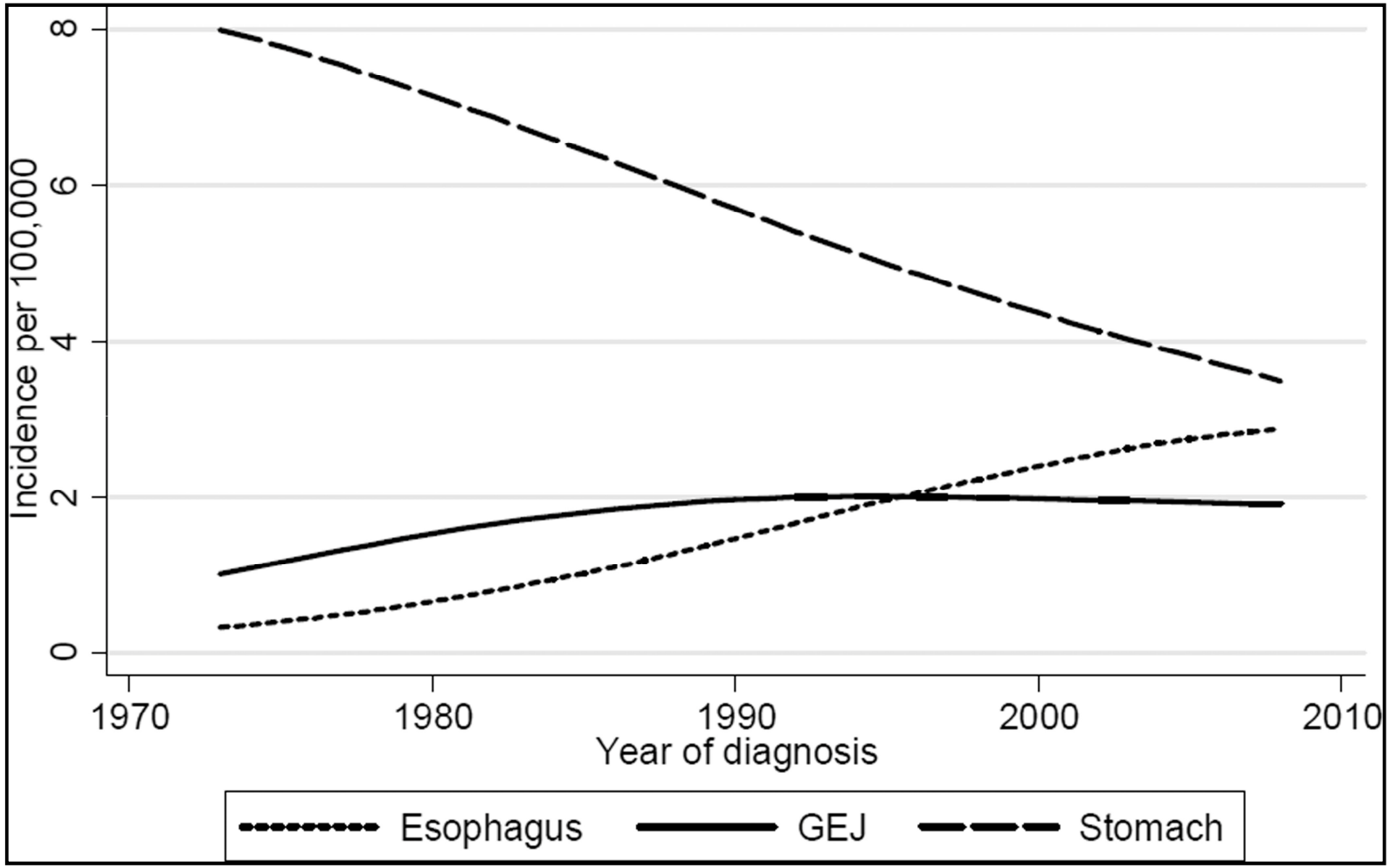
Incidence of adenocarcinoma of the esophagus, GEJ, and stomach 1973-2008, United States



Buas et al, Semin Radiat Oncol 2013

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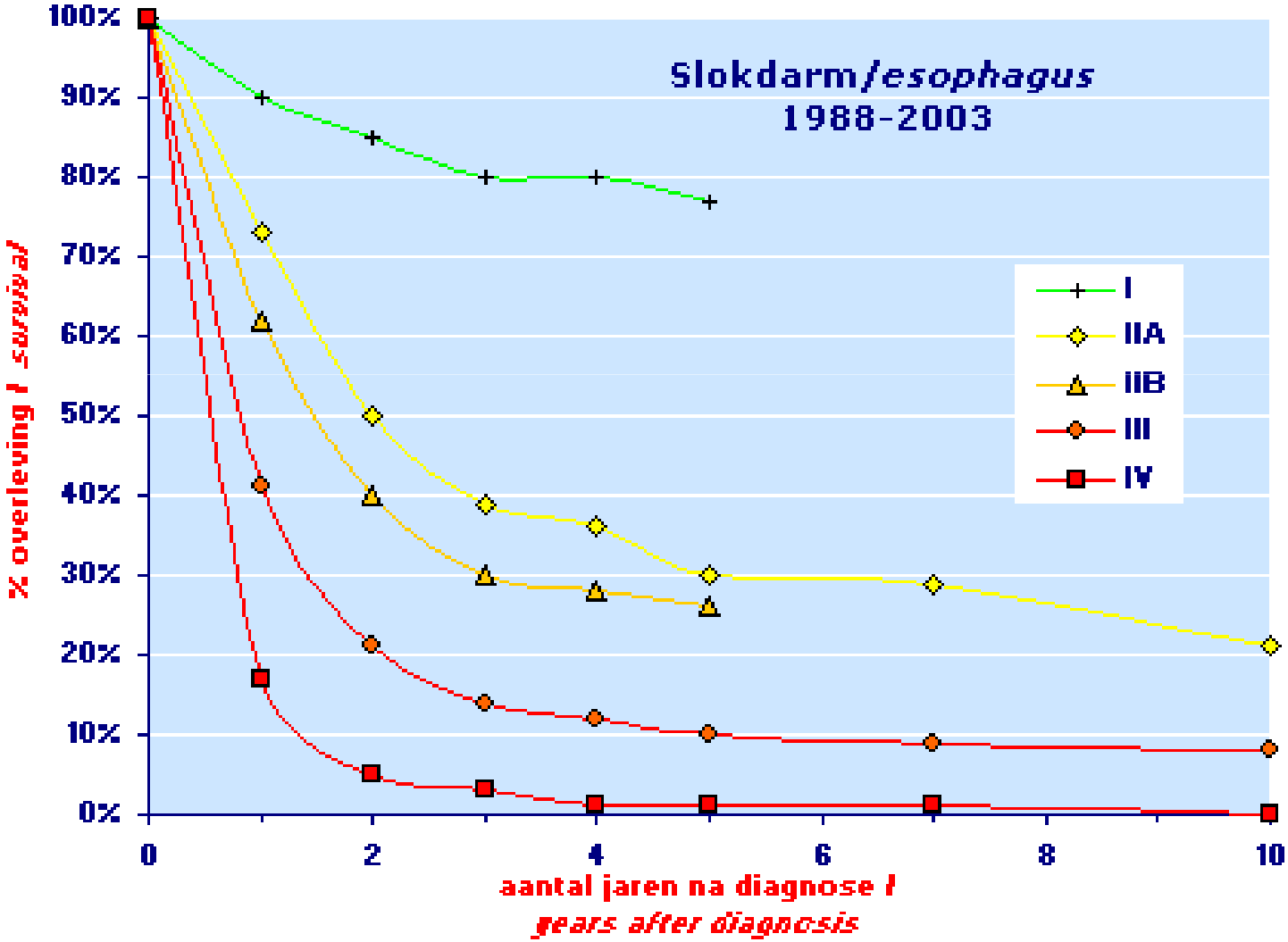
I K a

Relatieve overleving naar stadium
relative survival according to stage



ESTRO School

Esophageal cancer: risk factors

Oesophageal SCC

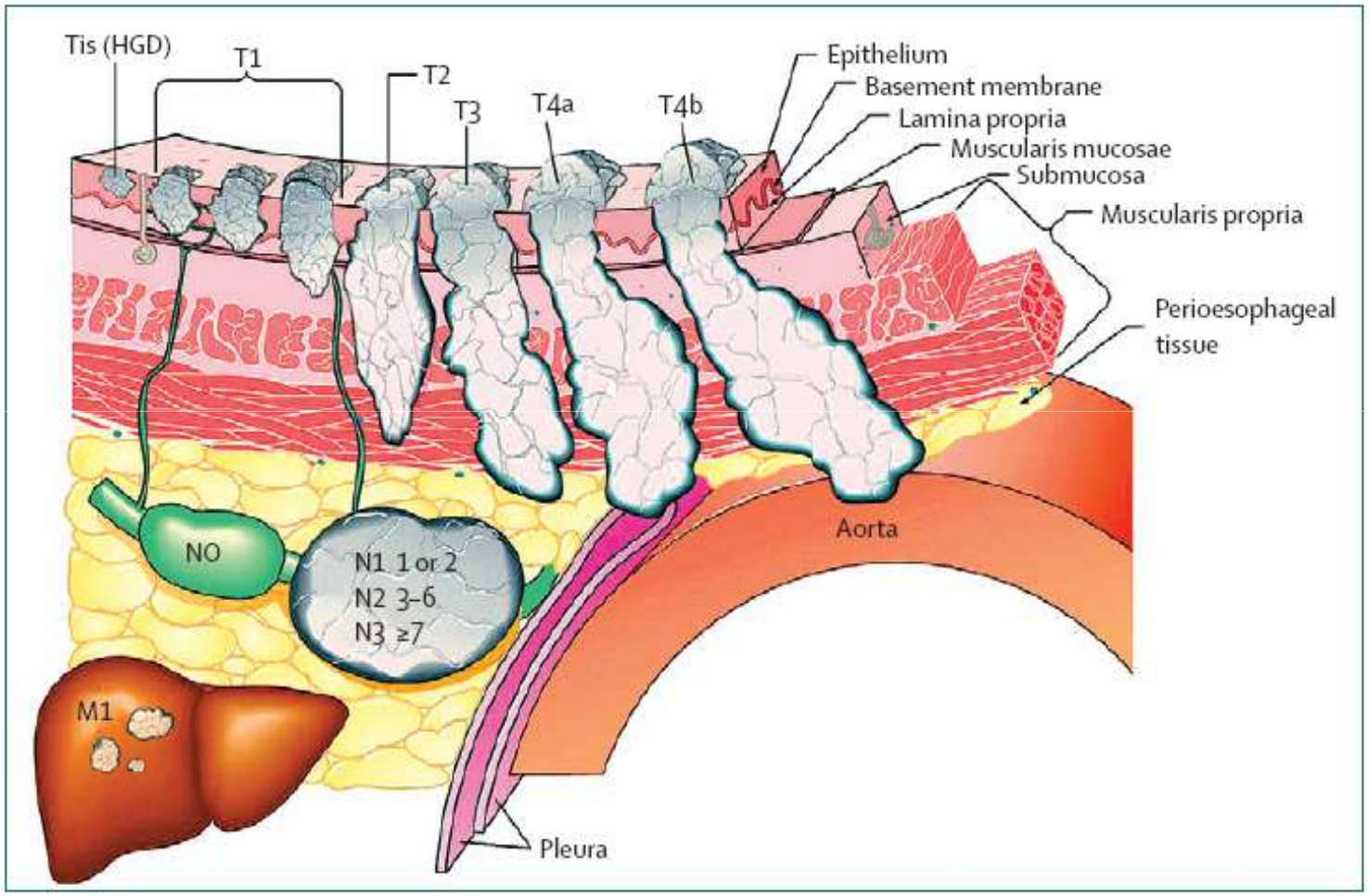
- Tobacco use
- Alcohol consumption
- Mutations of enzymes that metabolise alcohol
- Achalasia
- Caustic injury
- History of thoracic radiation
- Low socioeconomic status
- Poor oral hygiene
- Nutritional deficiencies
- Non-epidermolytic palmoplantar keratoderma

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**

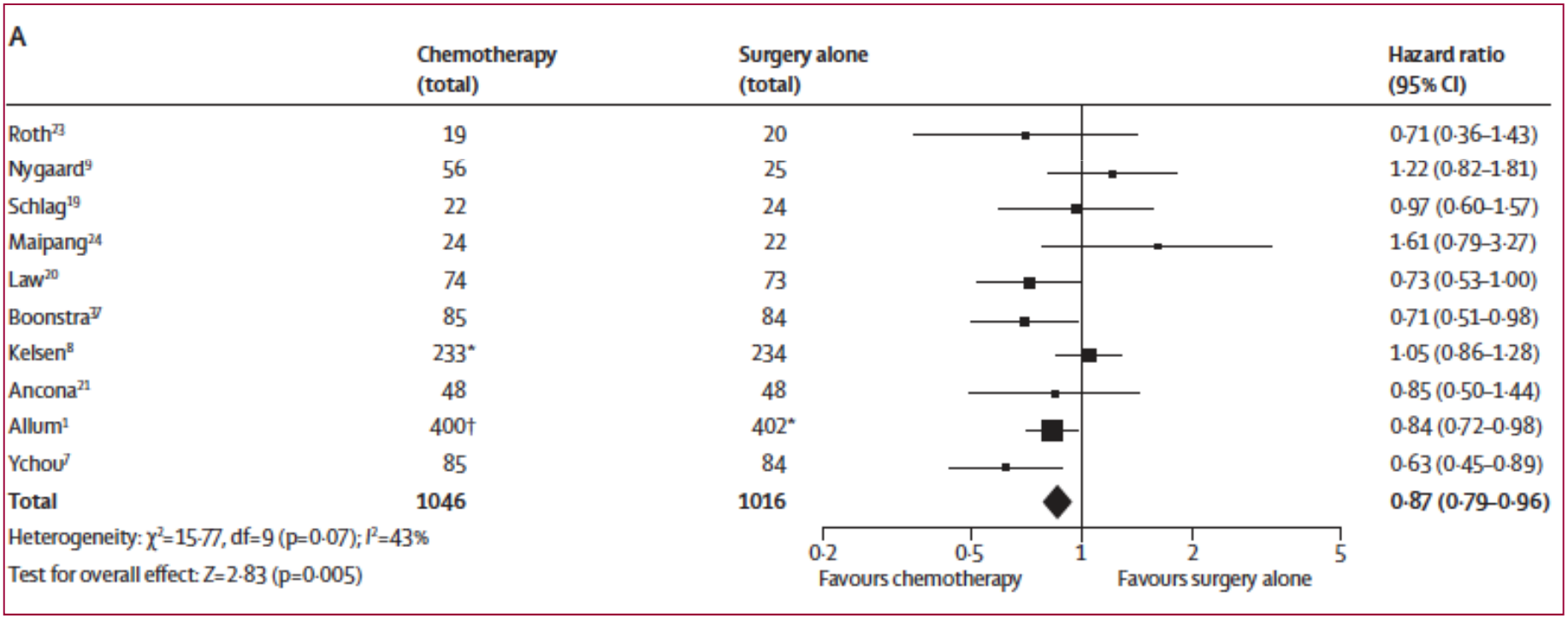
- Rationale: control early spread of systemic disease
- Conflicting results
- MAGIC study (Cunningham) may not be generalisable to all esophageal adenocarcinoma (26% EGJ/adeno oes)

Pennathur et al, Lancet 2013

ESTRO School

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



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
- Conflicting results
- CROSS study and meta-analysis show benefit for preoperative CRT

Pennathur et al, Lancet 2013

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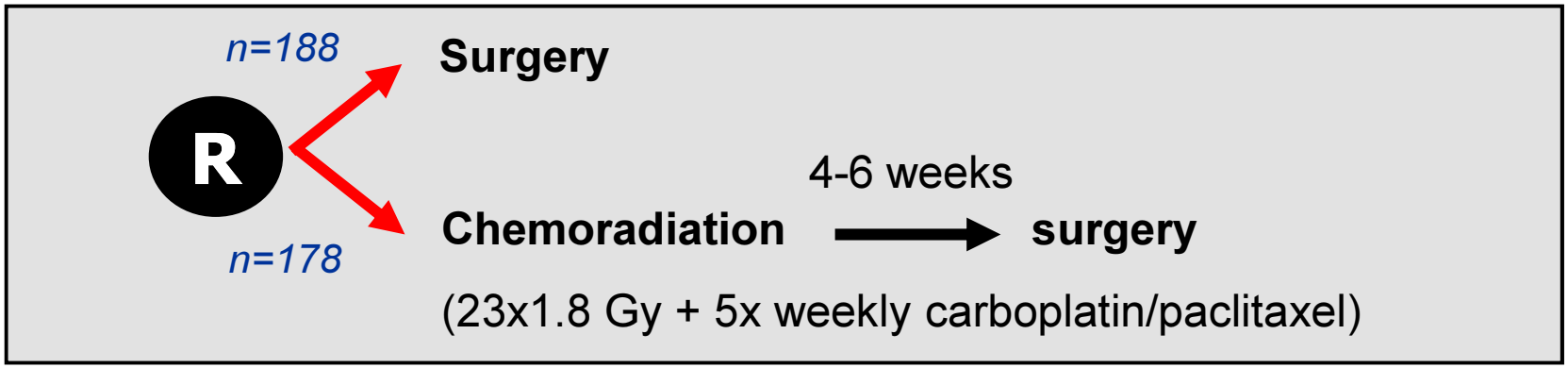
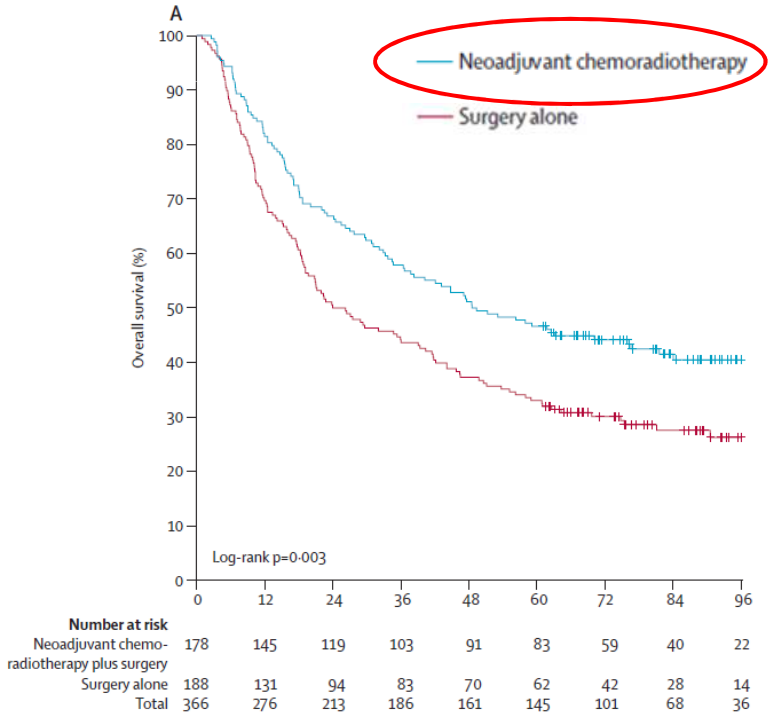
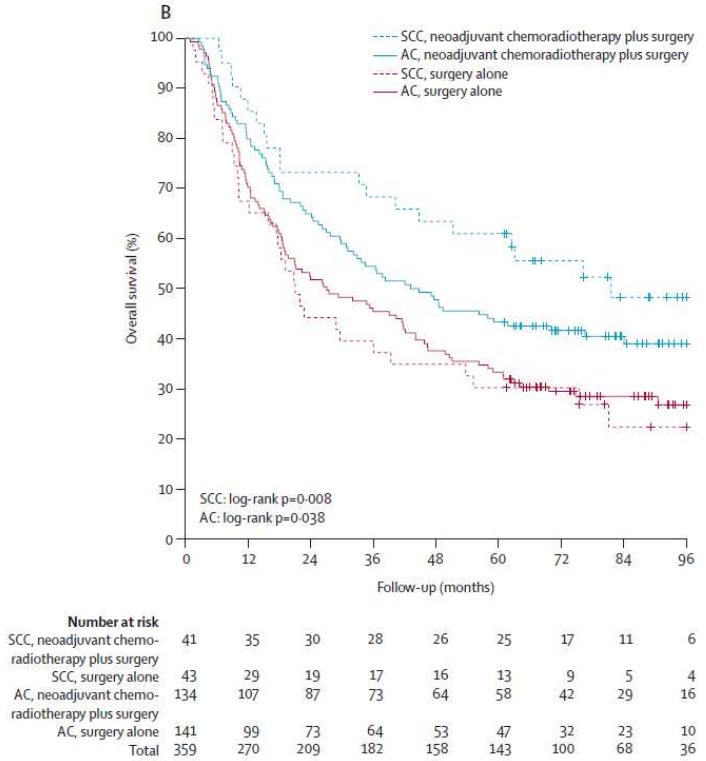
Pre-operative chemoradiation improves outcome in esophageal and junctional cancer: the CROSS trial







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

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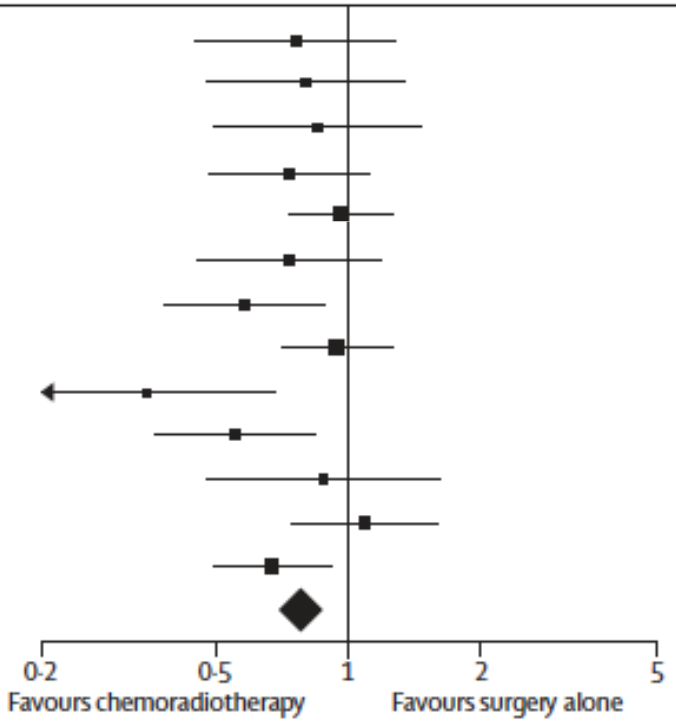
	Chemoradiotherapy (total)	Surgery alone (total)	Hazard ratio (95% CI)
Nygaard[9]	53	25	0·76 (0·45–1·28)
Apinop[39]	35	34	0·80 (0·48–1·34)
Le Prise[10]	45*	41	0·85 (0·50–1·46)
Urba[40]	50	50	0·74 (0·48–1·12)
Bosset[12]	148	145	0·96 (0·73–1·27)
Walsh (SCC)[13]	29	32	0·74 (0·46–1·18)
Walsh (adenocarcinoma)[14]	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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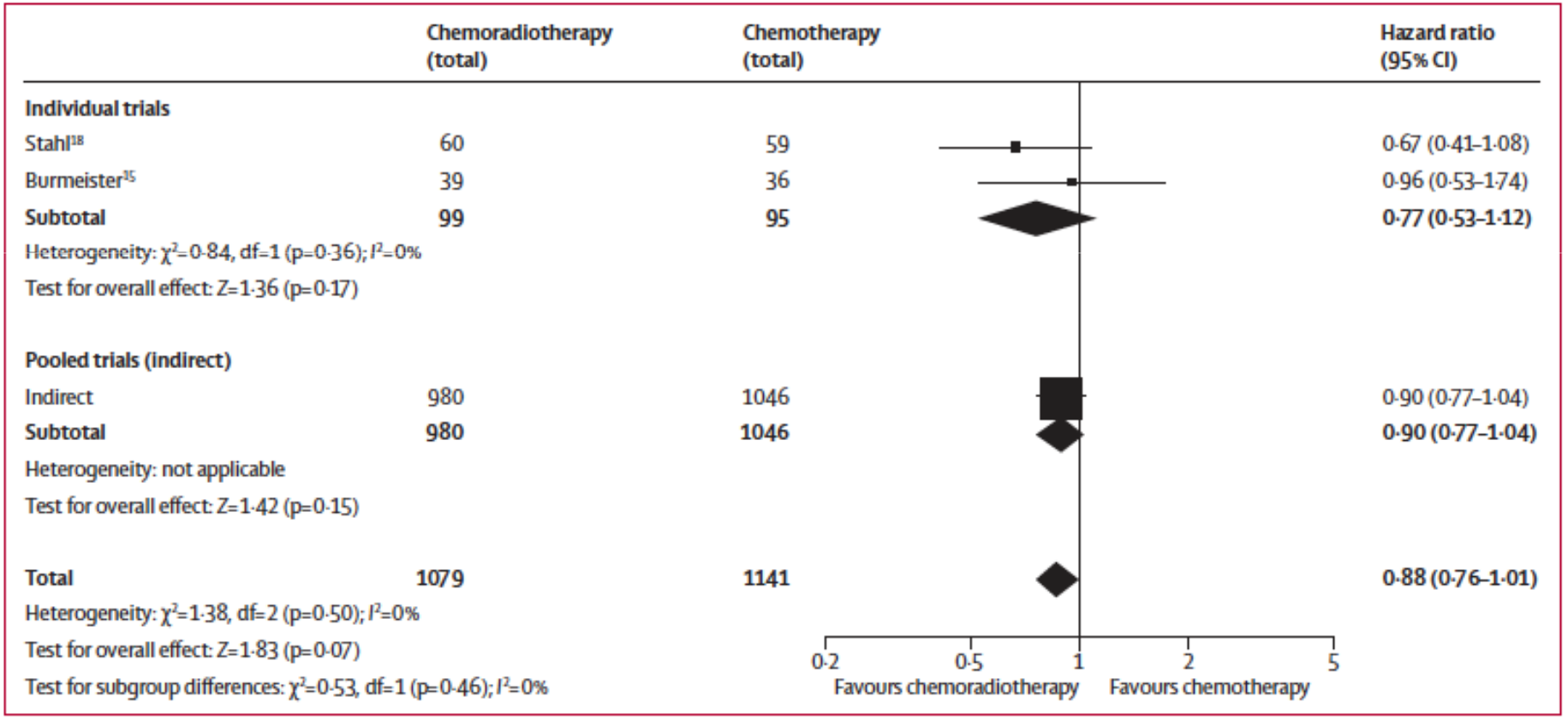

Sjoquist et al. Lancet Oncol 2011

ESTRO School

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†
Mariette[41]‖	2000	45 Gy in 25 fractions over 5 weeks	Two cycles: cisplatin 75 mg/m² day 1 or 2; fluorouracil 800 mg/m² days 1–4	Concurrent	SCC and adenocarcinoma	195	68
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

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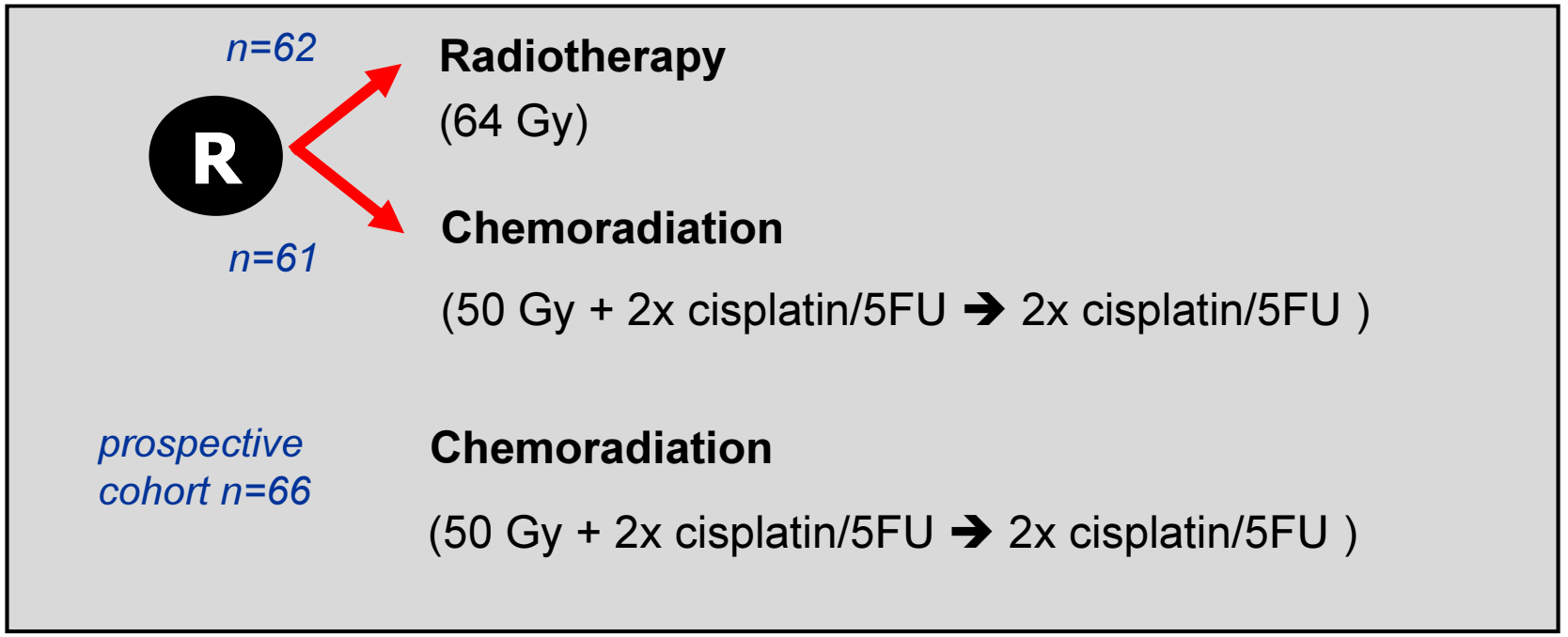
Definitive chemoradiotherapy vs. radiotherapy in locally advanced esophageal cancer: RTOG 85-01



Al-Sarraf et al. J Clin Oncol 1997

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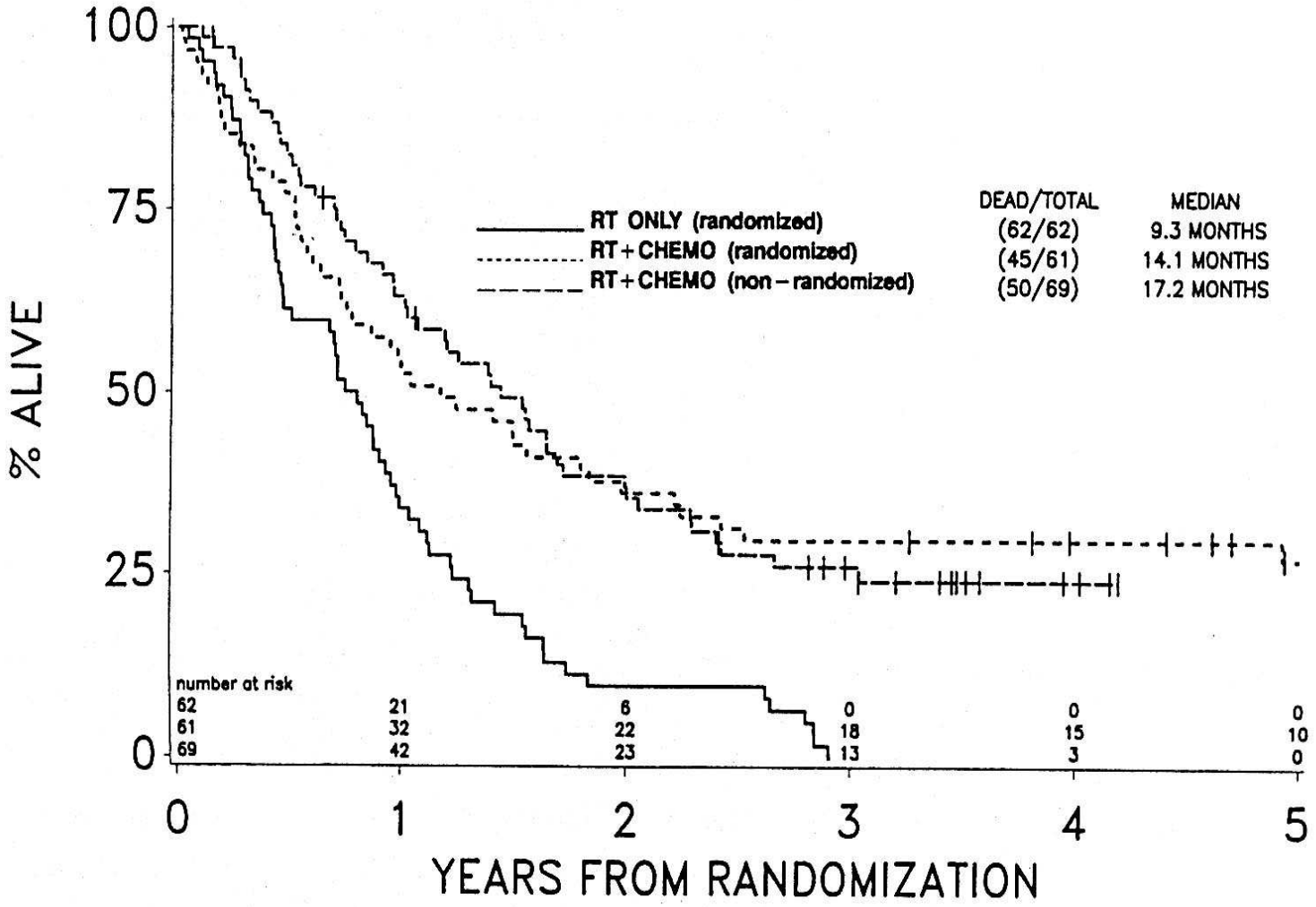
Definitive chemoradiotherapy is superior to radiotherapy in locally advanced esophageal cancer: RTOG 85-01



Al-Sarraf et al. J Clin Oncol 1997

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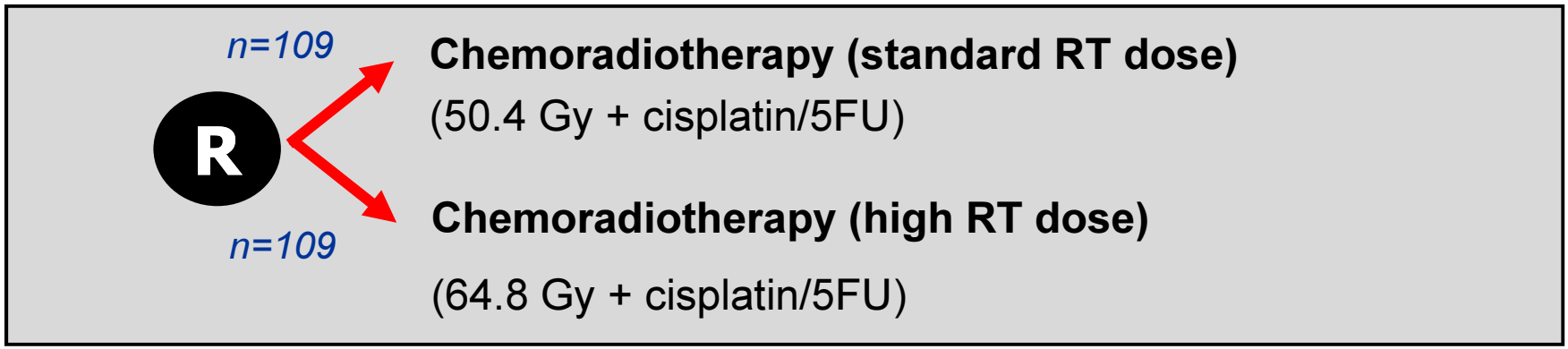
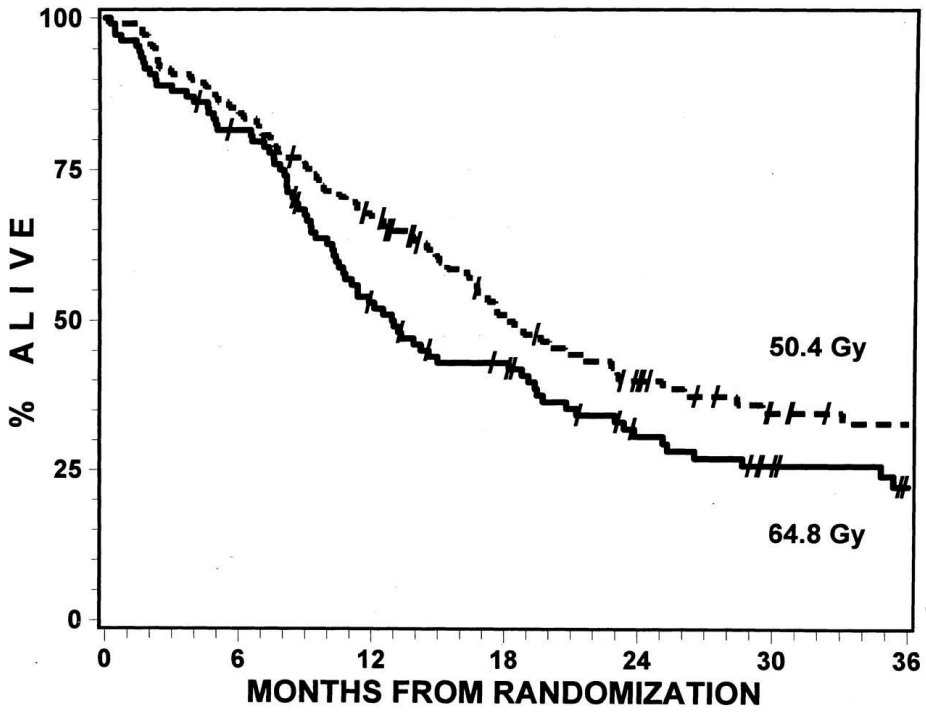
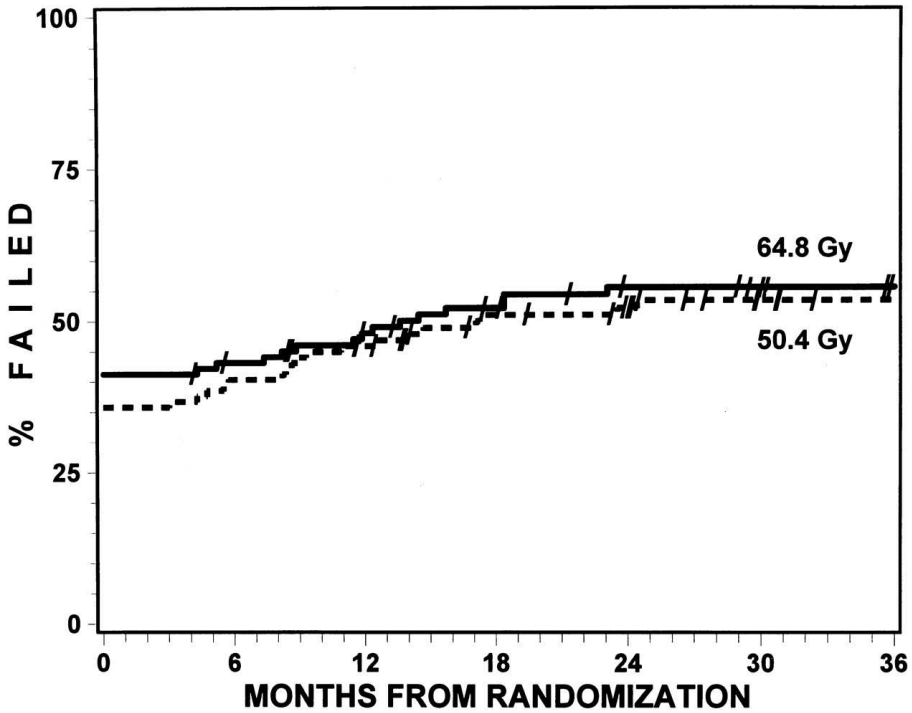
Definitive chemoradiotherapy in esophageal cancer: higher radiation dose does not improve outcome: RTOG 94-05







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

ESTRO School

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

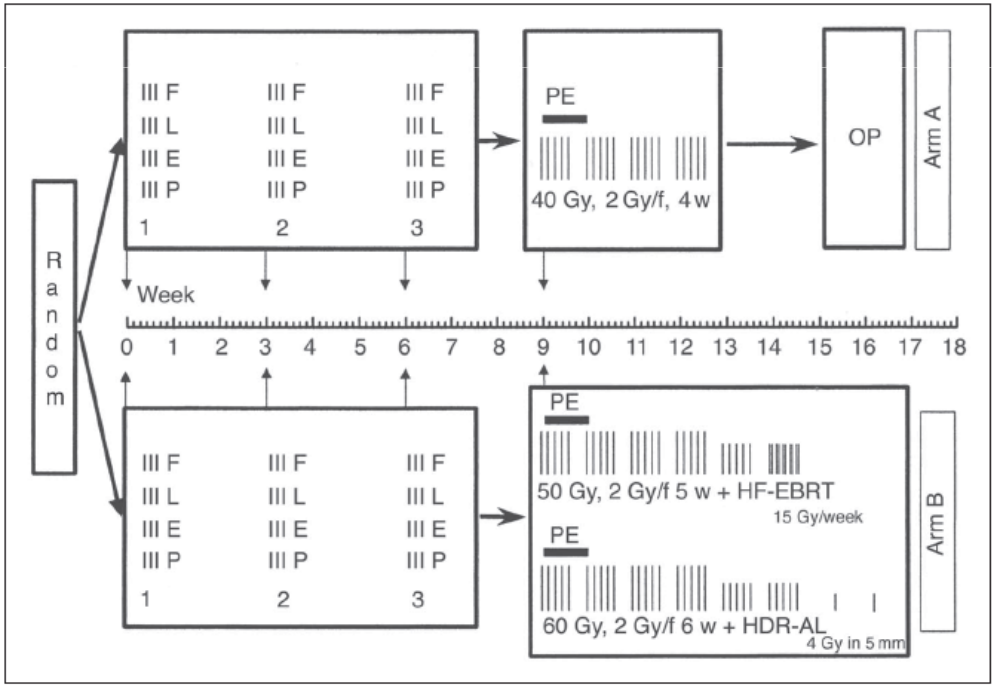
n=86

R

n=86

Chemotherapy ➔ chemoradiotherapy (40 Gy) ➔ surgery

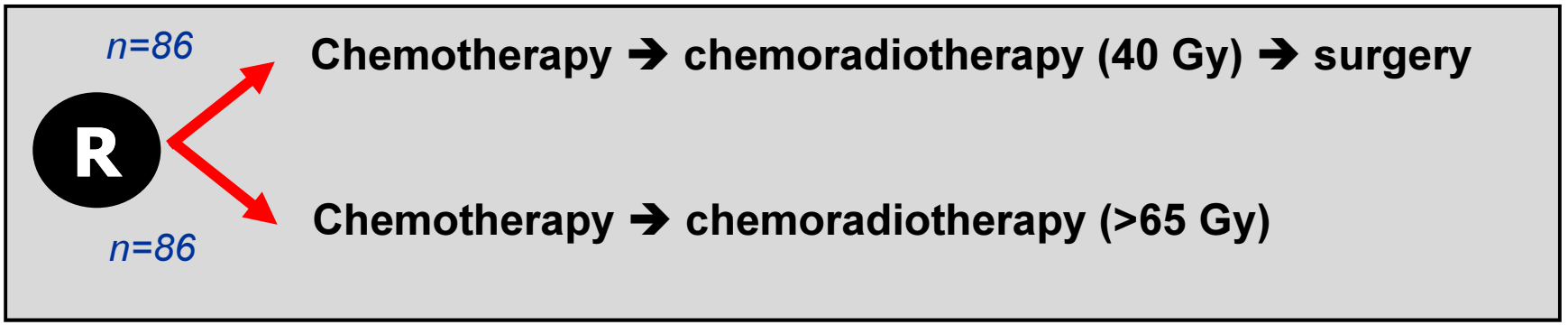
Chemotherapy ➔ chemoradiotherapy (>65 Gy)

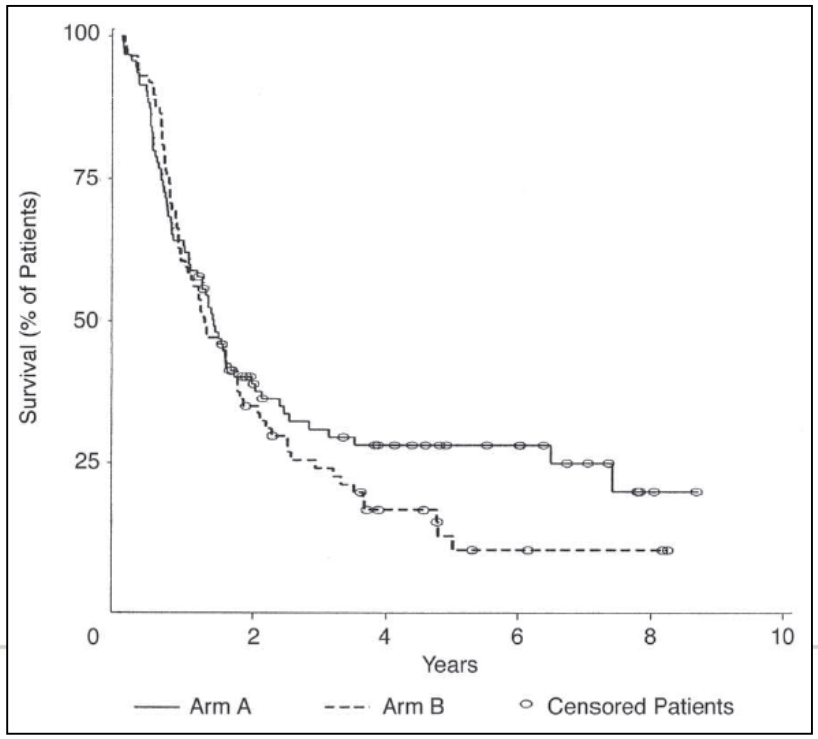


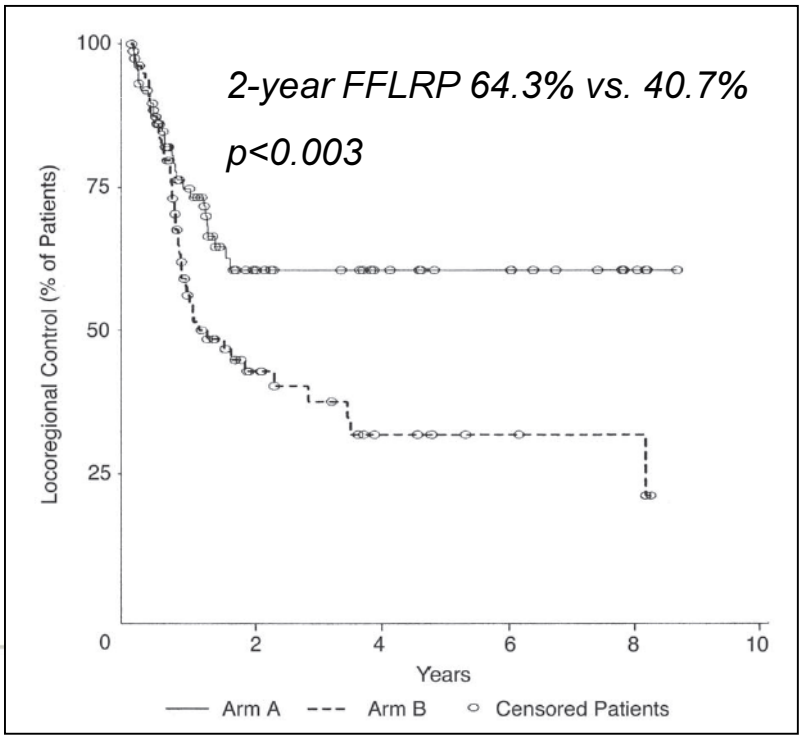
Stahl et al. J Clin Oncol 2005

ESTRO School

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







Stahl et al. J Clin Oncol 2005

A Randomized Trial of Dose Escalation in definitive Chemoradiotherapy for patients with Oesophageal cancer

Primary objective

To improve the local tumor control rate by escalating the RT dose in definitive CRT for patients with locally irresectable or medically inoperable carcinoma of the esophagus or gastric junction

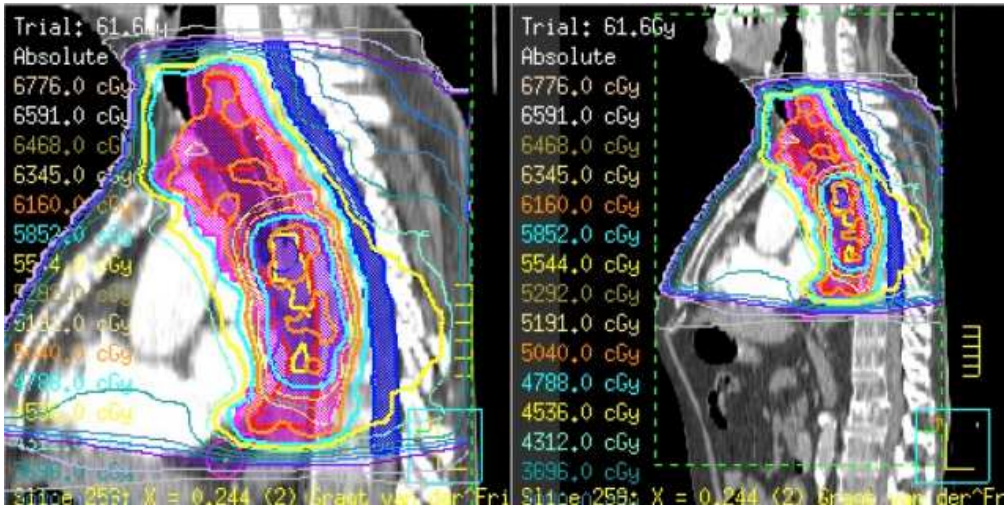
Dutch dose escalation trial definitive CRT

ART-DECO

R

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

Experimental: 61.6 Gy/28 fr (SIB boost GTVoes) + C/P



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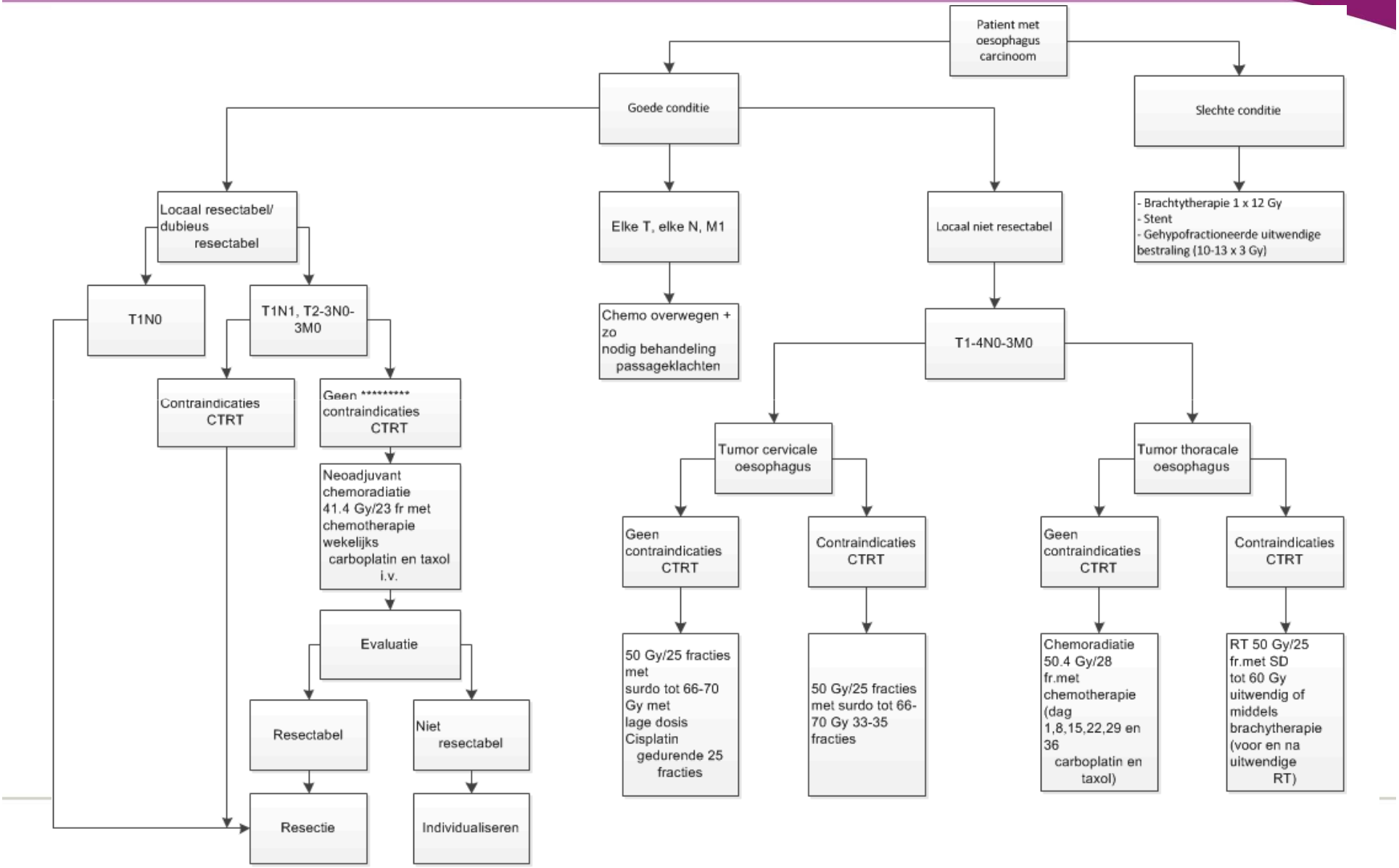
Critical structures and dose constraints

- Lungs: EQD2 $D_{mean} \leq 16$ Gy ($\alpha/\beta=3$)
- Heart: 3/3 <40 Gy; 2/3 <50 Gy; 1/3 < 66 Gy
  (<30% cardiac silhouette may receive 40 Gy)
- Spinal cord: EQD2 $D_{max} \leq 50$ Gy ($\alpha/\beta=2$)

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?)*

Flow diagram



NB. TNM classificatie 7e editie

ESOPHAGUS: Dose constraints for Organs at Risk

Prof. Philippe MAINGON

Organs at Risk …

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

- Vessels, pericarde, coronary arteries
- Esophagus

- Patient at risk

Organs at Risk …

- **Heart**
- **Lungs**
- **Spinal cord**
- **Vertebrae**
- **Thyroïd**
- **Stomach**
- **Liver**
- Biliary tract
- Pancreas
- Spleen
- Kidneys
- **Vessels, pericarde, coronary arteries**
- **Esophagus**
- **Patient at risk**

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

OAR

National Comprehensive Cancer Network (NCCN) Guidelines

- Liver V60%<30Gy
- Kidney 2/3 ≤ 20Gy
- Spinal cord Dmax=45Gy
- Heart 1/3<50Gy
- Lungs ALARA

National Comprehensive Cancer Network guidelines, Clinical practice guidelines in oncology, Esophageal cancer, 2009.

http:// www.nccn.org. Accessed 07 January 2009

Normal tissue tolerance dose

Esophagus

Volume	0	20	40	60	70
0-20%	<1%	5-10%	<10%	<20%	
20-40%					
40-60%			>30%	>50%	
60-80%					
80-100%					

Dose (Gy)

- Dose limit = 50 Gy Mean dose > 34 Gy *Sing IJROBP 2003*
- Entire circumference
- Lenght of esophagus receiving more than 55 Gy *Maguire IJROBP 1999*

- Acute esophageal toxicity is the greatest predictor of late toxicity

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

Normal tissue tolerance dose

Dose (Gy)	0	20	40	60	70

Spinal Cord

Volume	0	20	40	60	70
0-20%	<1%		<5%	10-50%	
20-40%					
40-60%					
60-80%					
80-100%					

Lung

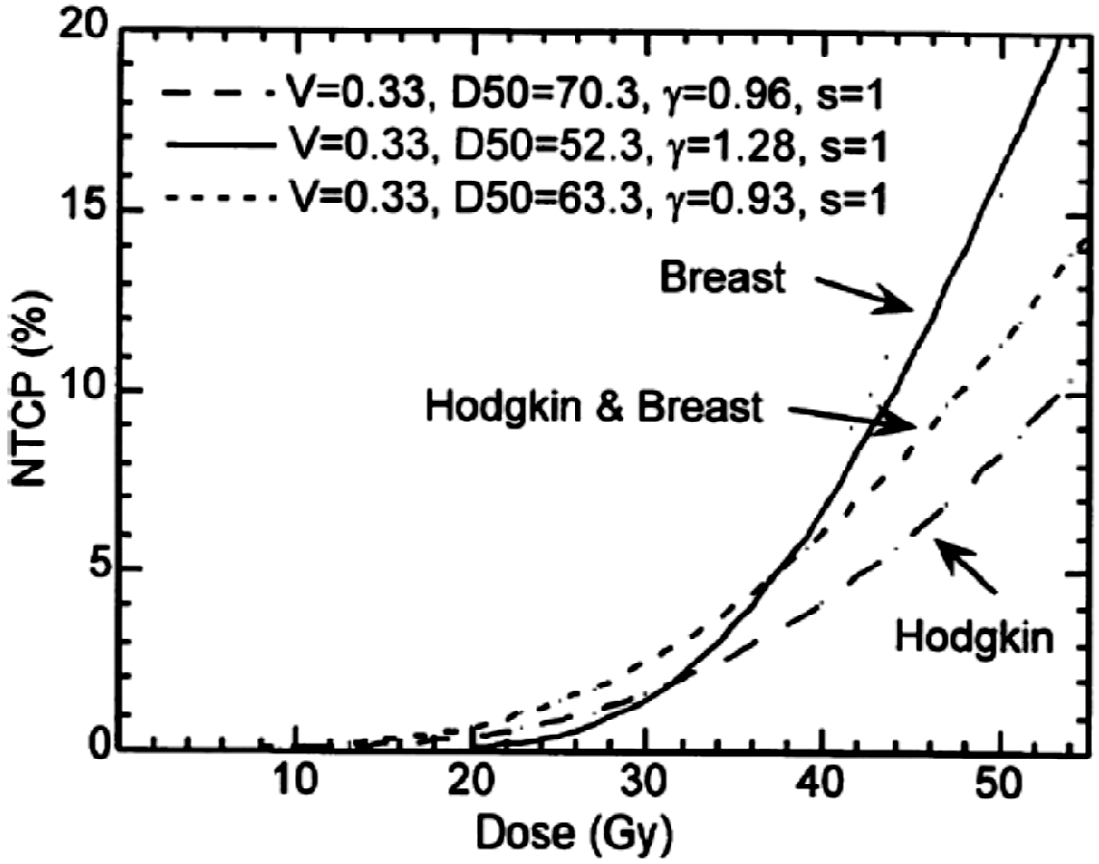
Volume	0	20	40	60	70
0-20%	<5%	<5%	<10%	<20%	>20%
20-40%					
40-60%		10-20%	30-50%		>75%
60-80%		>50%			
80-100%					

Heart

Volume	0	20	40	60	70
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%					

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

QUANTEC: Dose volume effect in the heart



Gagliardi G. IJROBP 2010

QUANTEC: Dose volume effect in the heart

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 $V_{30} < 46\%$	

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QUANTEC: Dose volume effect in the heart

Table 4. Cardiac perfusion defects: Dose–volume predictors and NTCP parameteters

Authors, Year, Reference	Diagnosis, No. of patients, Years of treatment	OAR	Fractionation schedule, Dose data	Predictive parameters	NTCP parameters
Das *et al.* 2005 (28)	Breast 73 Patients, 1998 (started)	Left ventricle contoured on SPECT	45–60 Gy/ 1.8–2.0 Gy/fr Individual 3D data	Left ventricular volume V_{23}, V_{33}	RS (95% CI) *D50* = 12 Gy (8;24) γ = 0.6 (0.4;4.6) s = 1 (0.6;1) LKB* (95% CI): TD50 = 29 Gy (18;44) σ (dose var) = 12 Gy (8;35) a = 6.3 (2.5;9.8)

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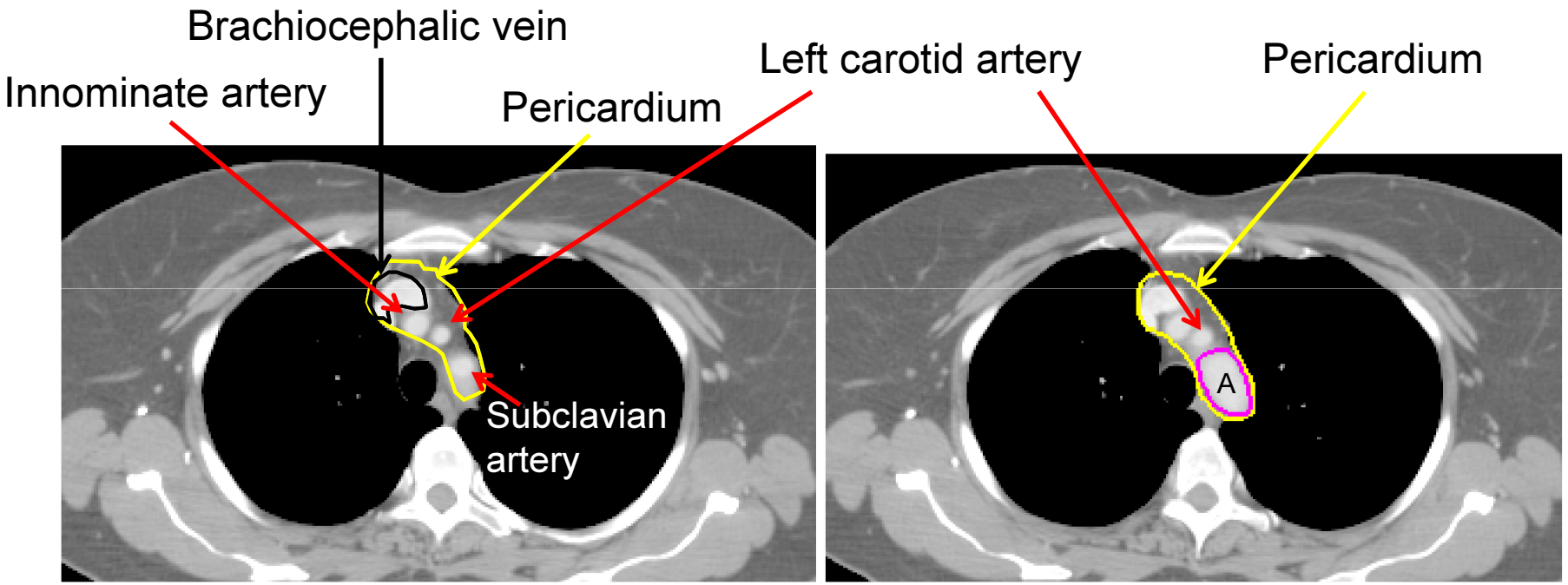
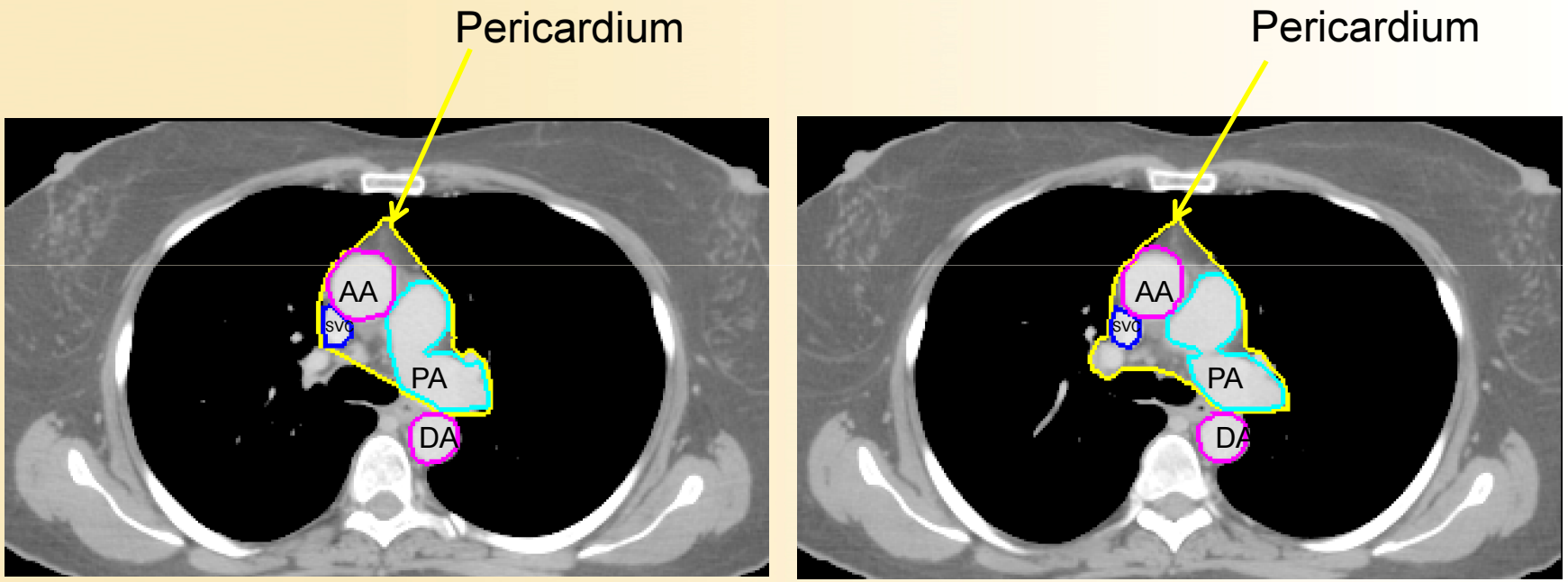
Pericardium starts …



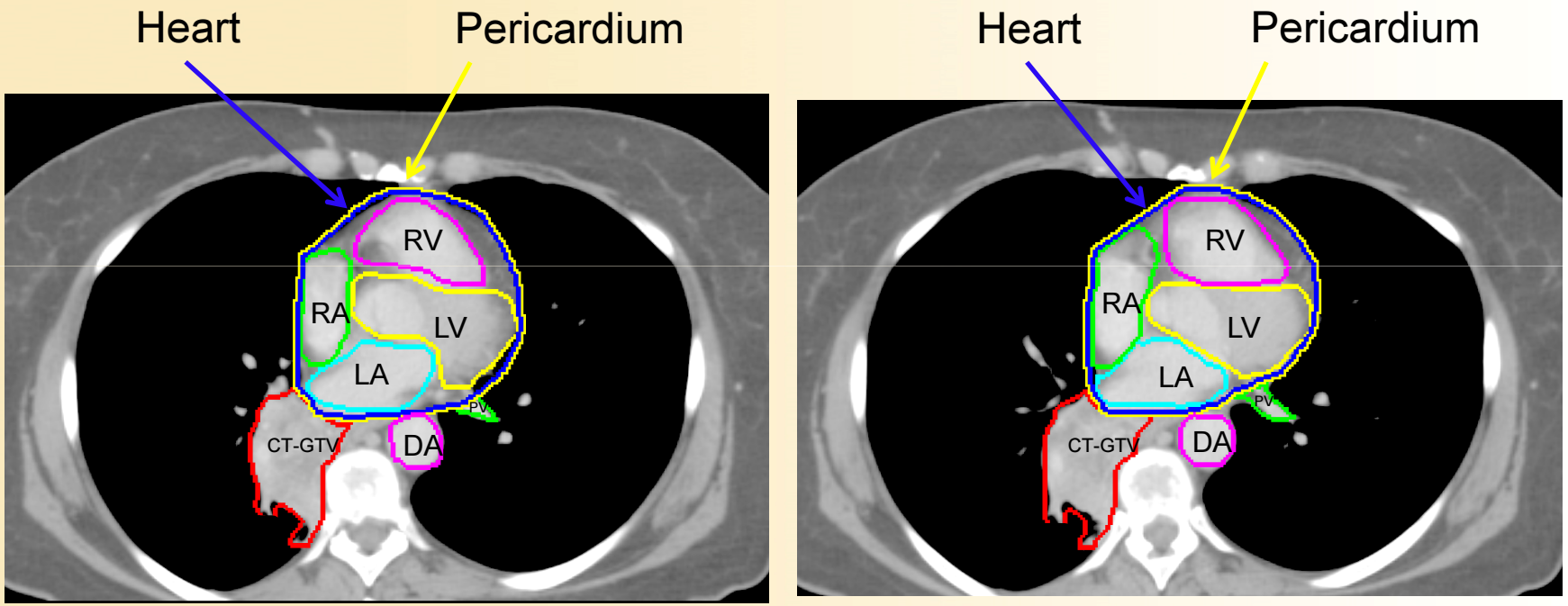
Pericardium starts at 1-2 slices (5-6 mm) above the superior end of the aortic arch

Pericardium Continues…



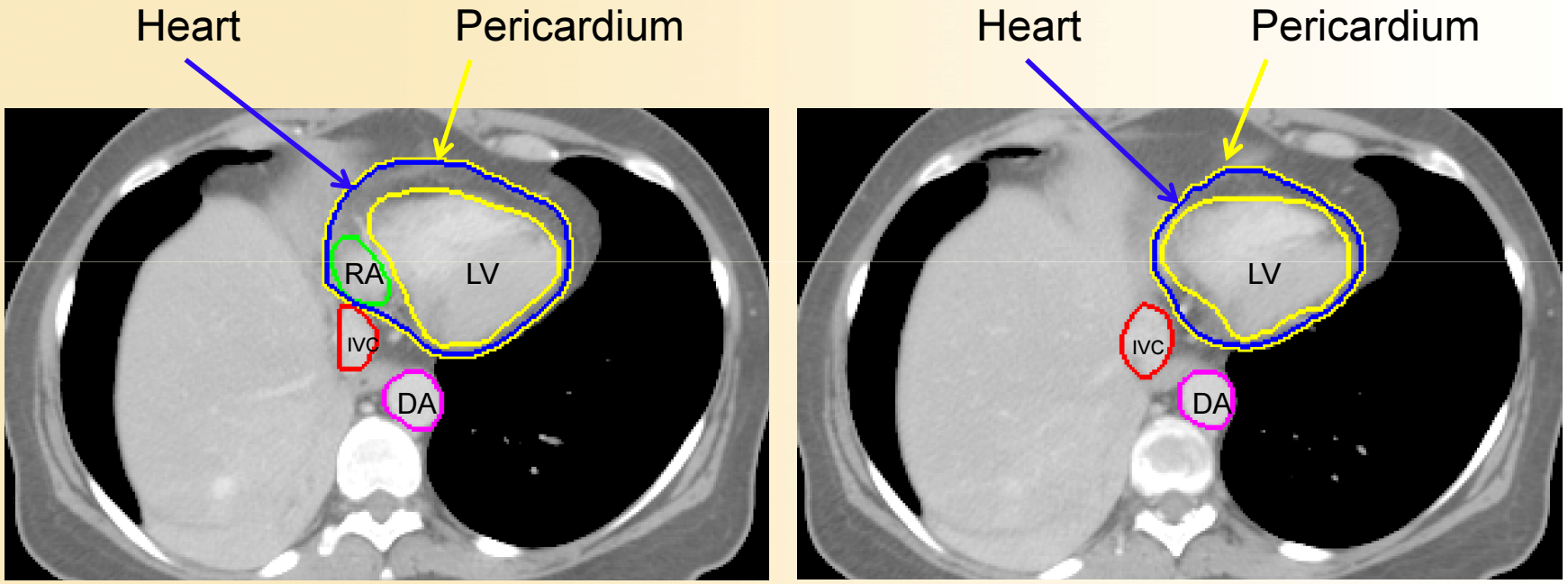
SVC=Superior vena cava
PA=Pulmonary artery
AA=Ascending aorta
DA=Descending aorta

Heart and pericardium continue…



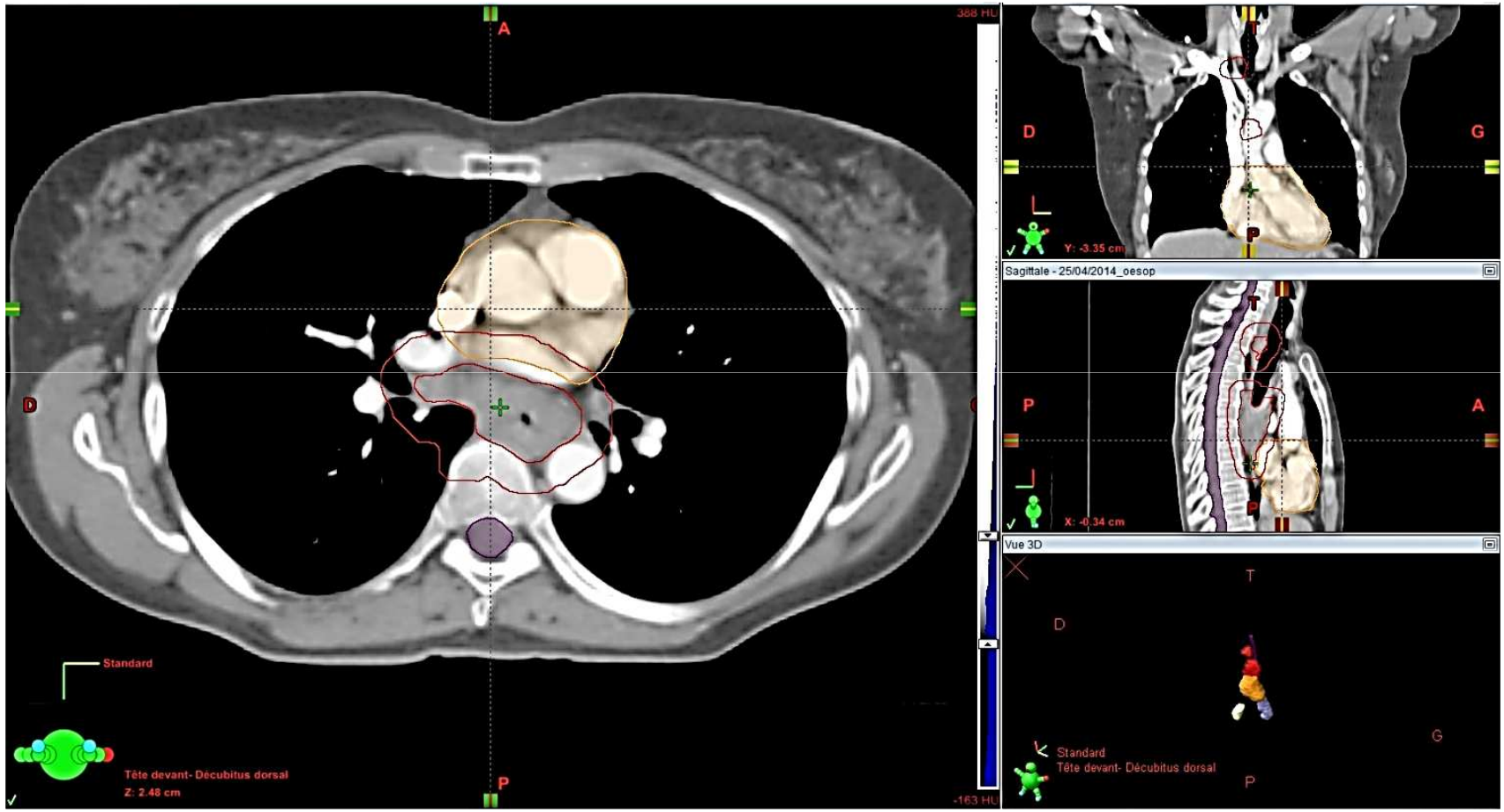
RA=right atrium, RV=right ventricle
LV=left ventricle, LA=Left atrium
DA=descending aorta

Heart and pericardium continue…



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

Pericardium …



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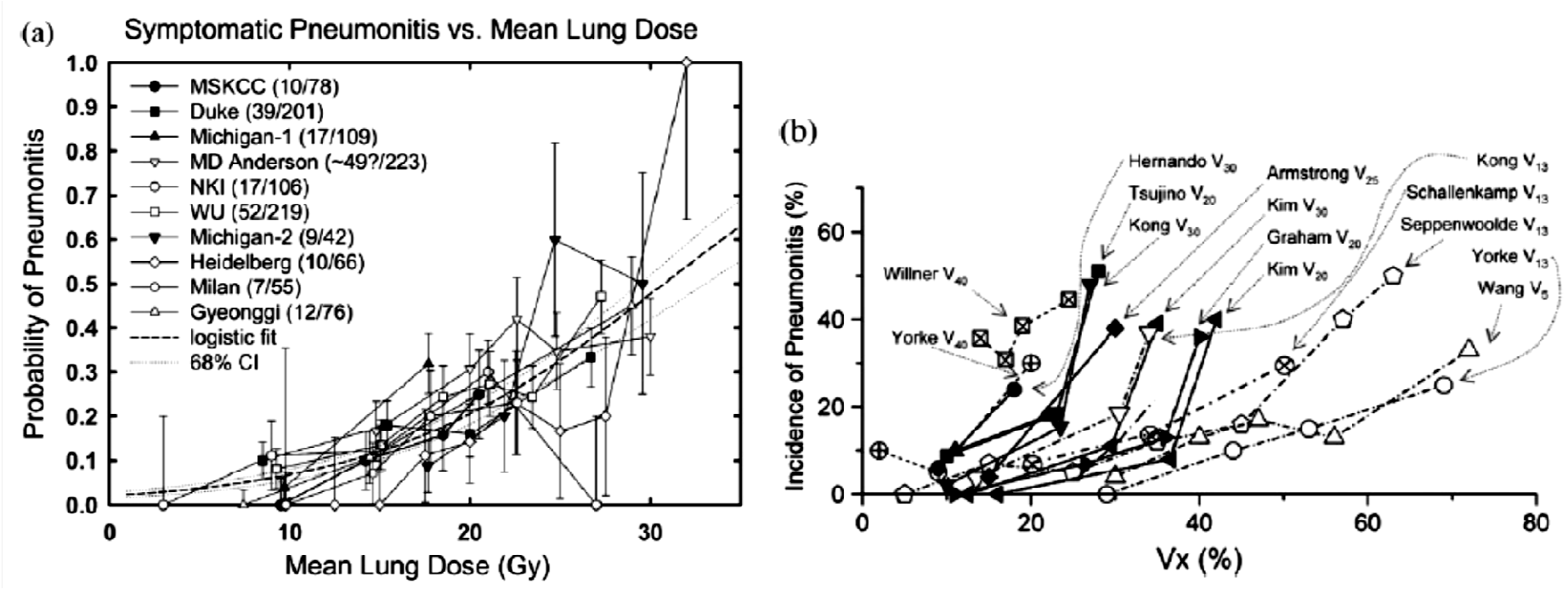
Radiation Dose-Volume effect in the lung



Marks L. IJROBP 2010

OAR

Heart

Coronary artery stenosis …

Pericarditis 27.7% (5.3 m FU)

- V30 < 46% = 13%
- V 30 > 46% = 73%

VEF : 59% before vs 54% after (p<0.01)

Carr ZA et al., IJROBP 2005
Wei X et al., IJROBP 2008
Tripp P et al., Dis esophagus 2005

Lungs

Lungs V20

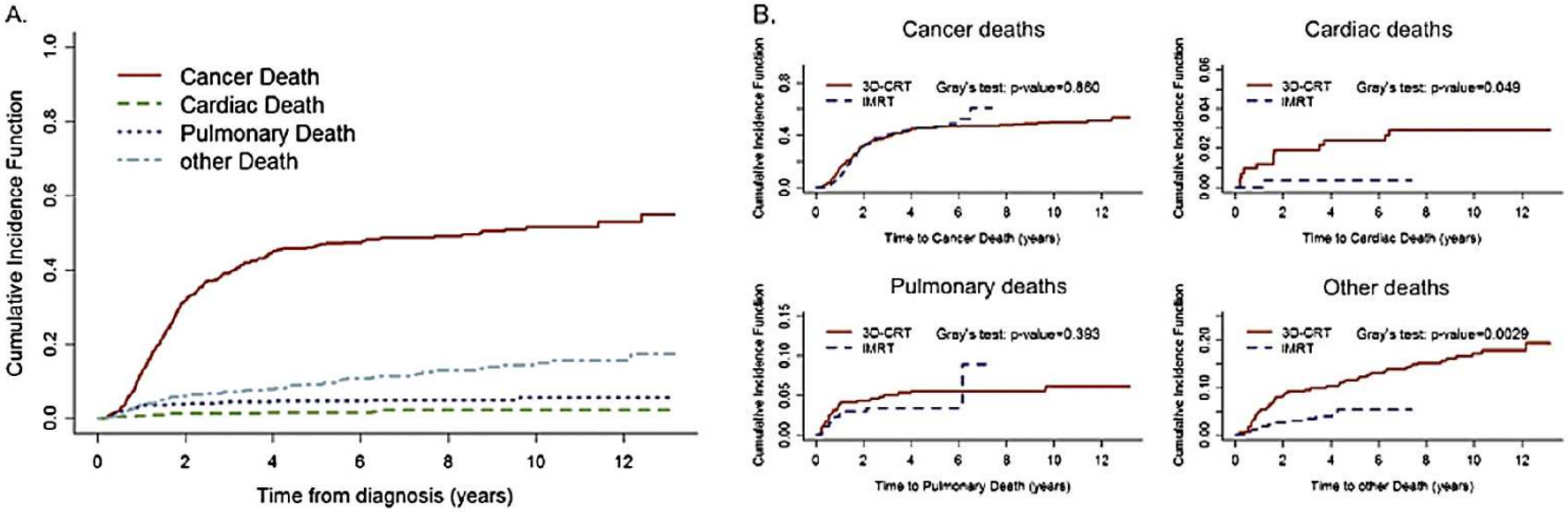
- <22% : 100% G0
- 22-31% : 8% G2
- >32% : G3

- >40% : 23% de G3-5

V5, V10 (<40%+++), V13, V15 = associated with radiation pneumonitis

Graham MV et al., IJROBP 1999
Tsujino K et al., IJROBP 2003
Schallenkamp JM et al., IJROBP 2007
Lee HK et al., IJROBP 2003

IMRT : Evolution or Revolution?



Lin, S.H. et al., IJROBP (2012)

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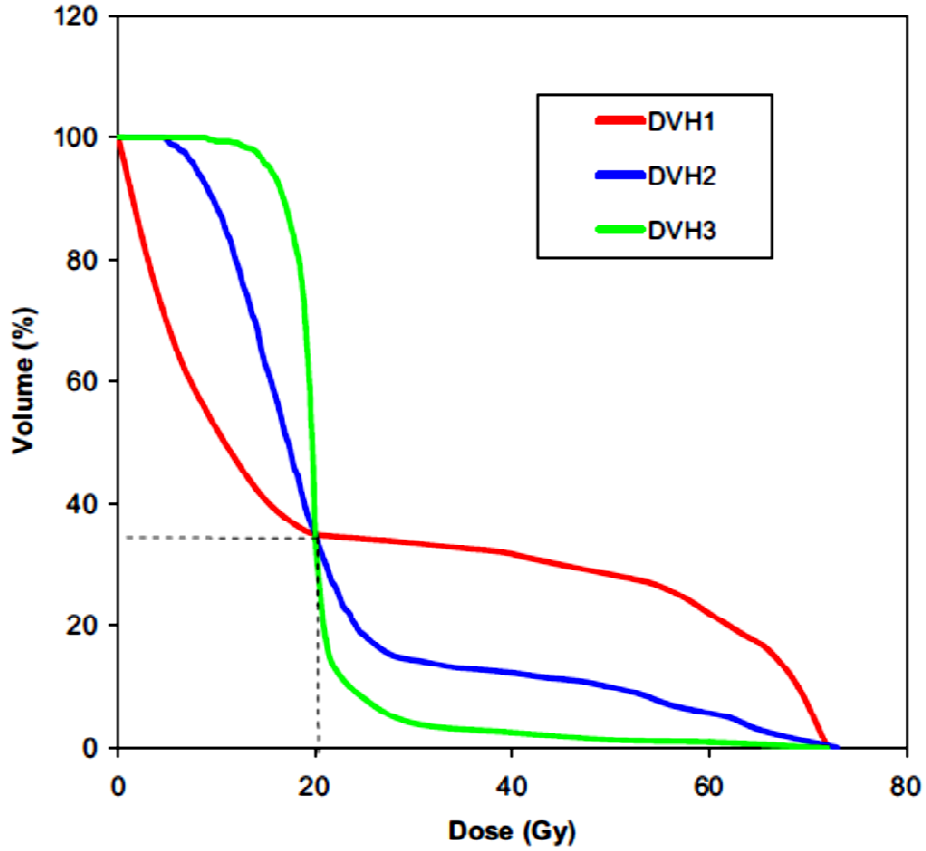
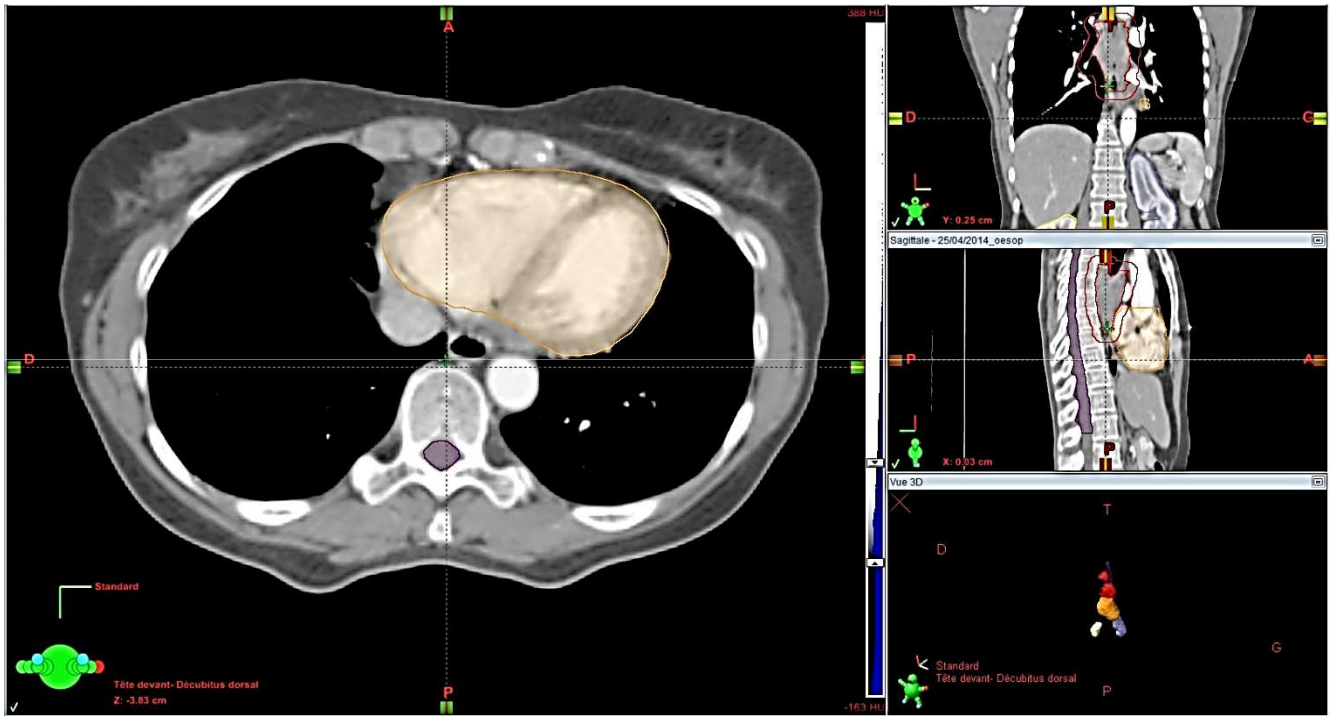
The problem of a point dosimetric descriptor …



Kong FM Semin Radiat Oncol 2007;17:109-120

Spinal cord and Pericardium …



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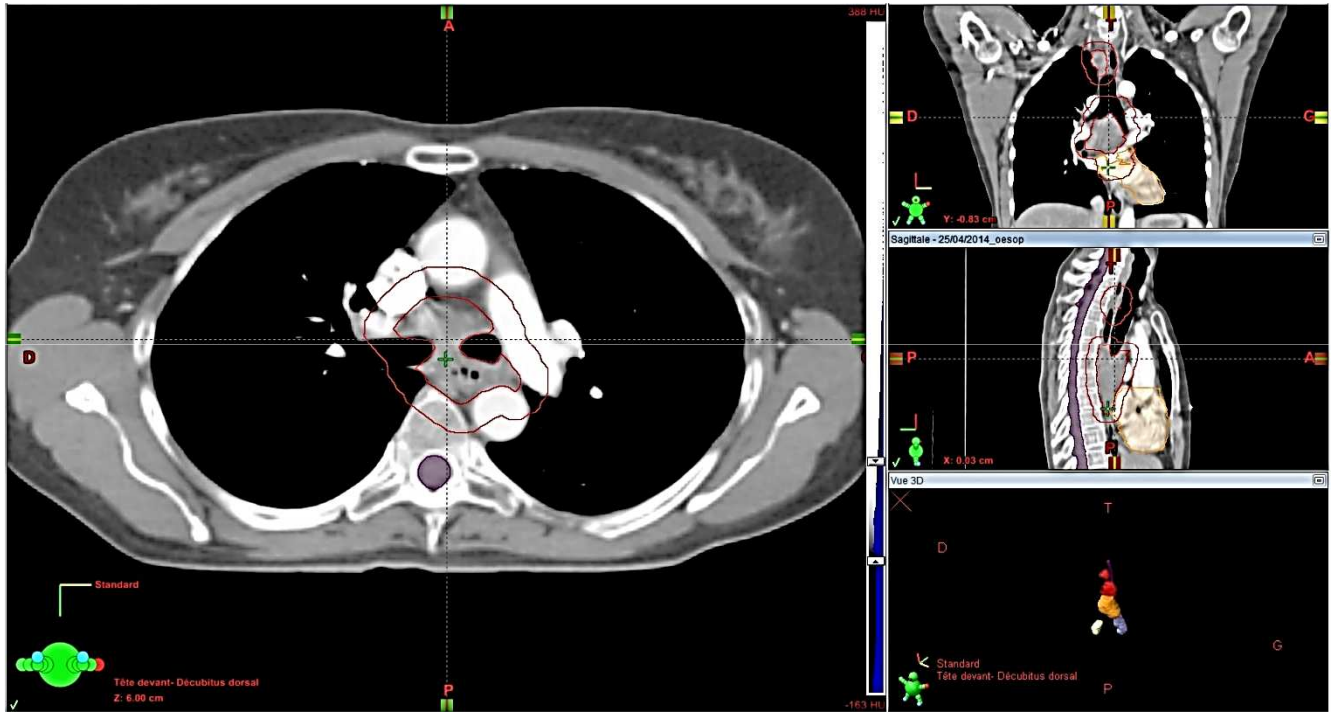
Spinal cord continues …



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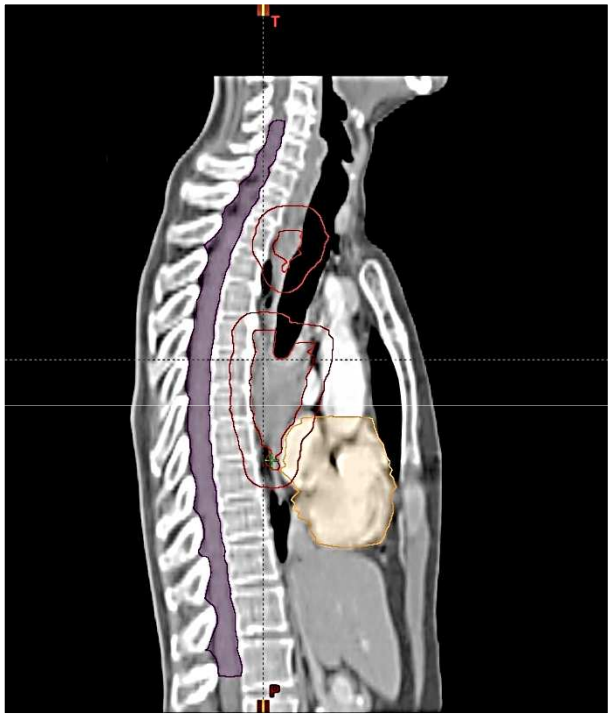
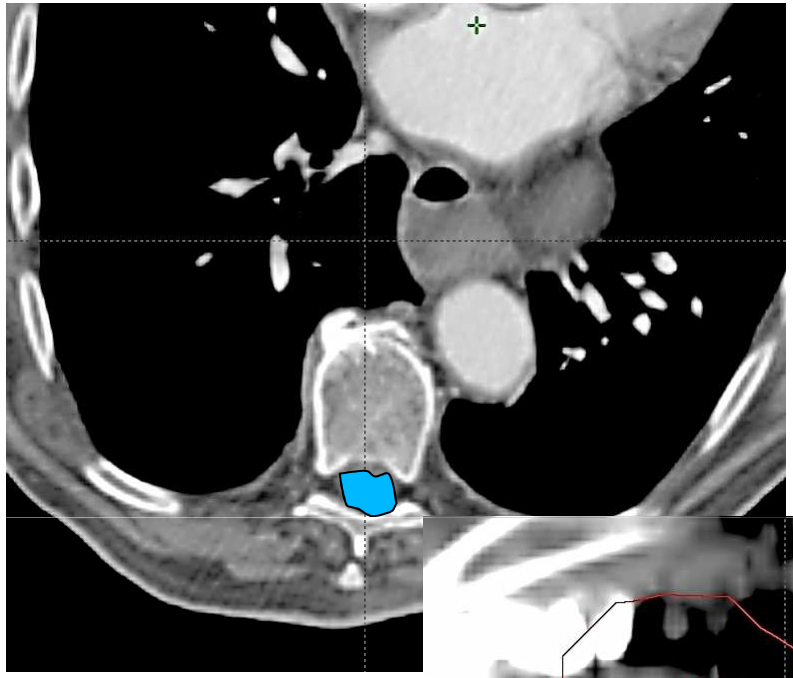
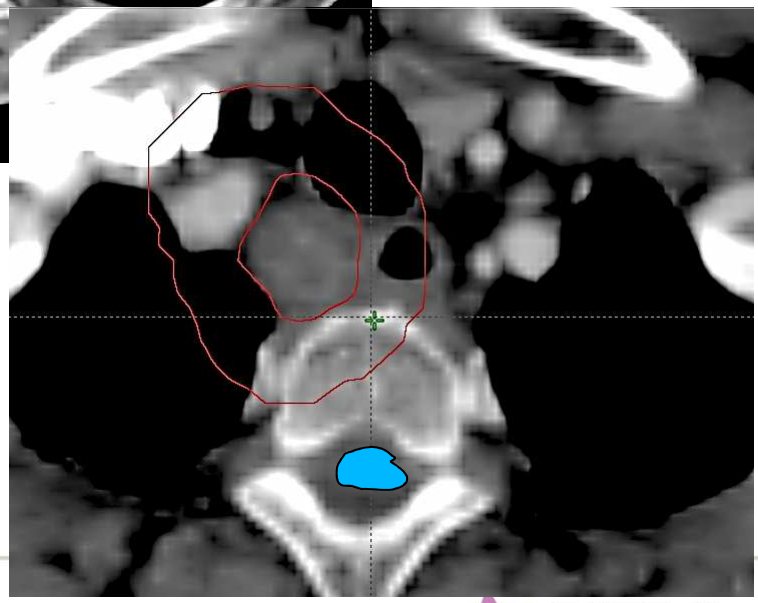
Spinal cord … Which one ?







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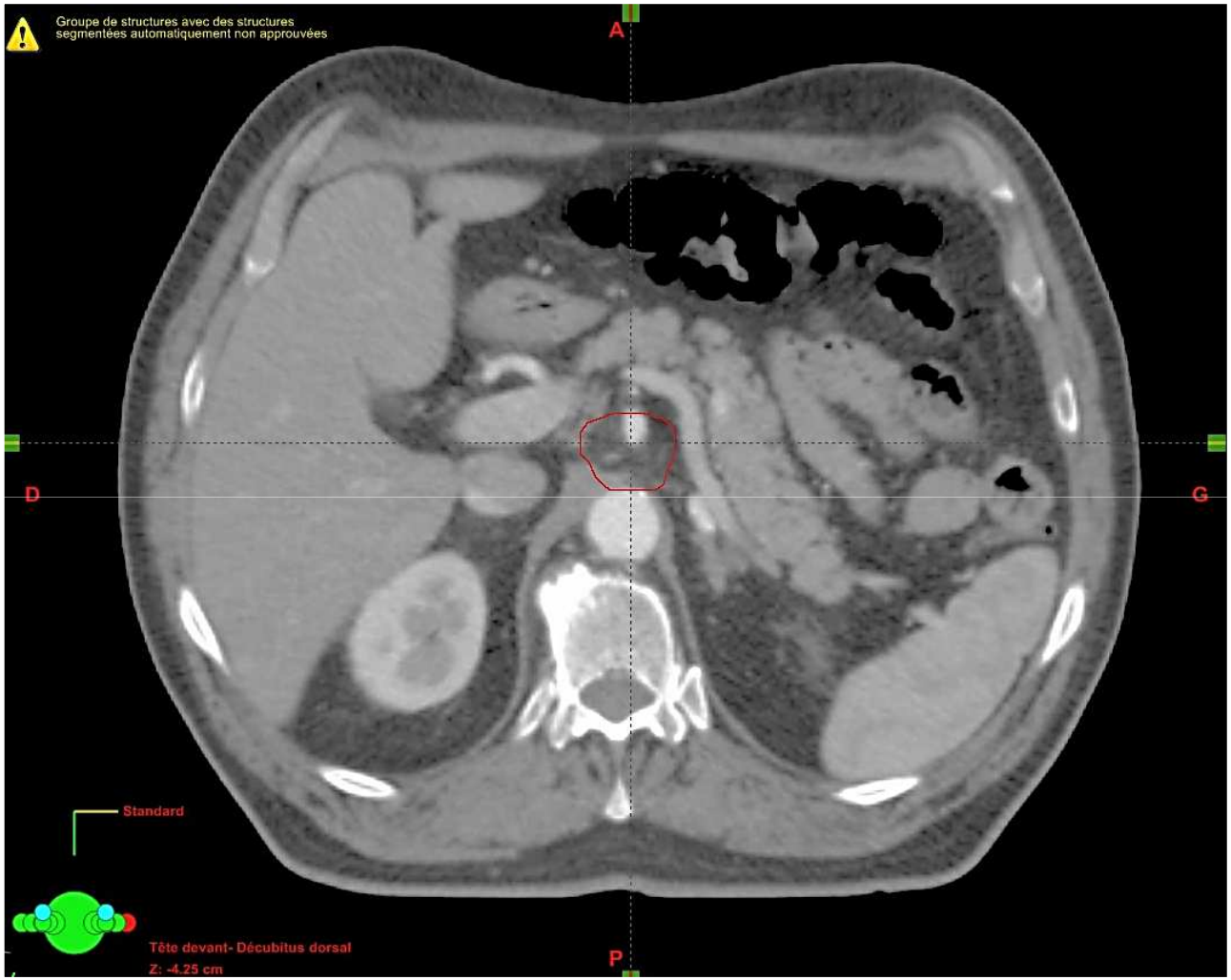
Bottom of the PTV …



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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

Universitair Ziekenhuis Brussel

Vrije Universiteit Brussel

Dirk Verellen

DV is involved in an on-going scientific collaboration with BrainLAB AG, RaySearch, MIM software Inc.

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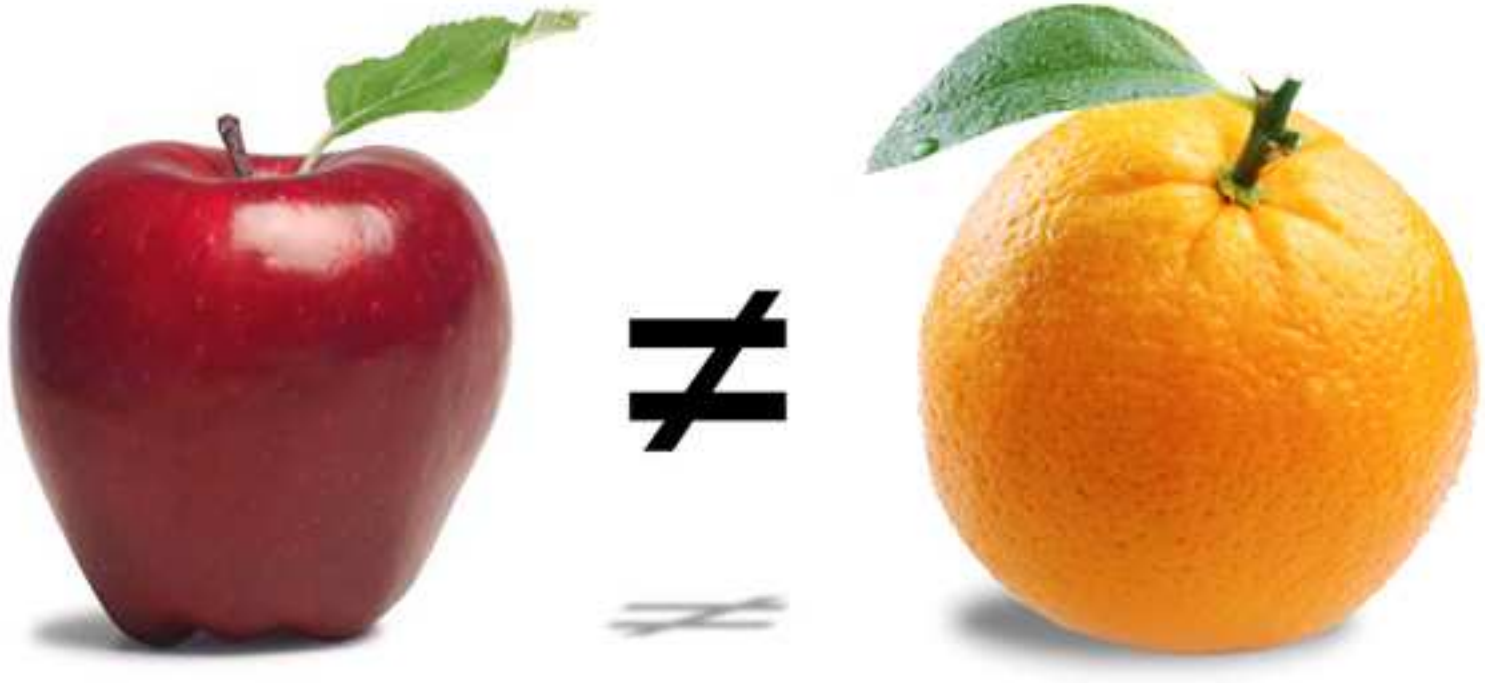
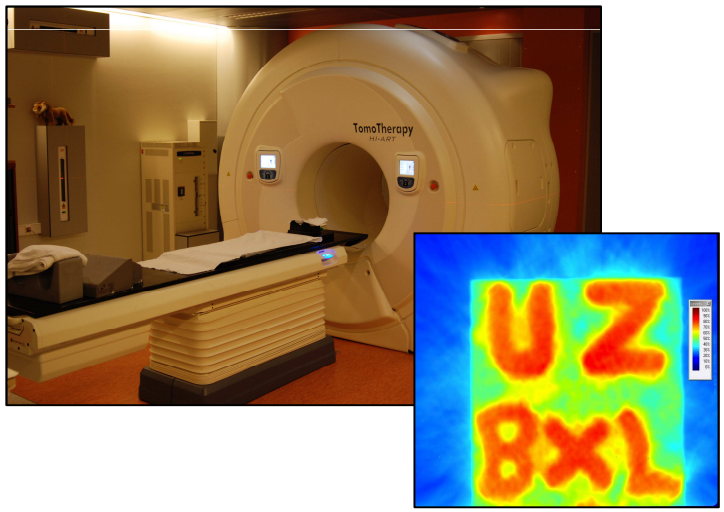
Outline

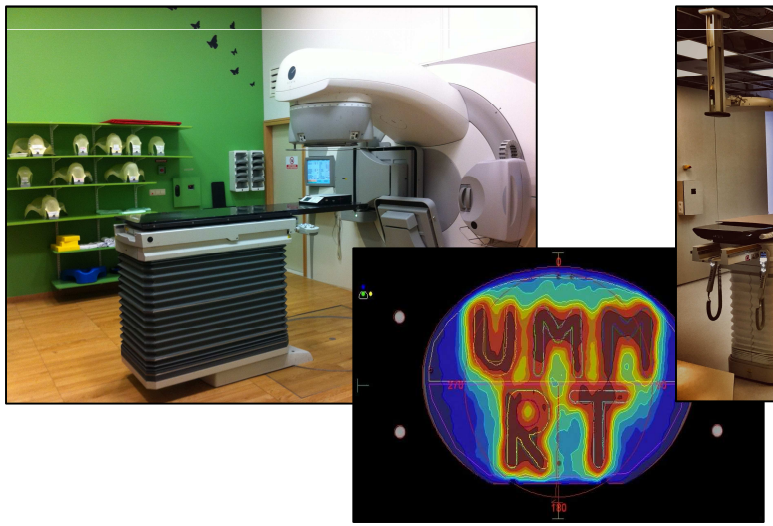
- How to compare plans?
- Oesophagus: 3D-CRT versus VMAT
- Oesophagus: 3D-CRT versus Helical TomoTherapy
- Partial gastrectomy: 3D-CRT versus Helical TomoTherapy

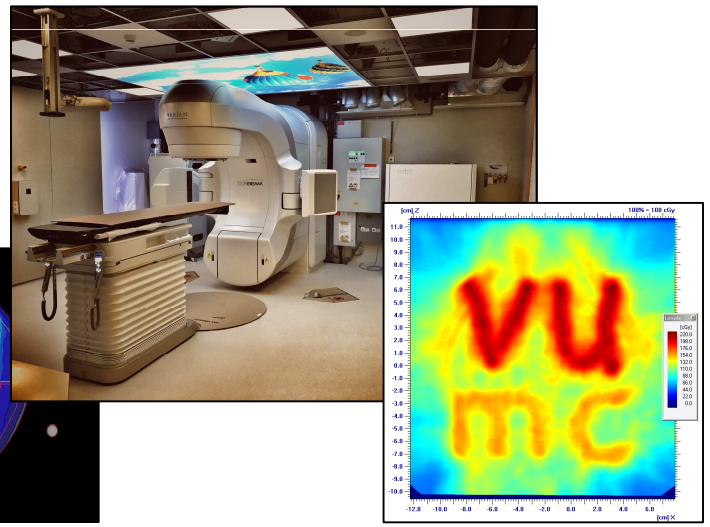


A few disclaimers

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







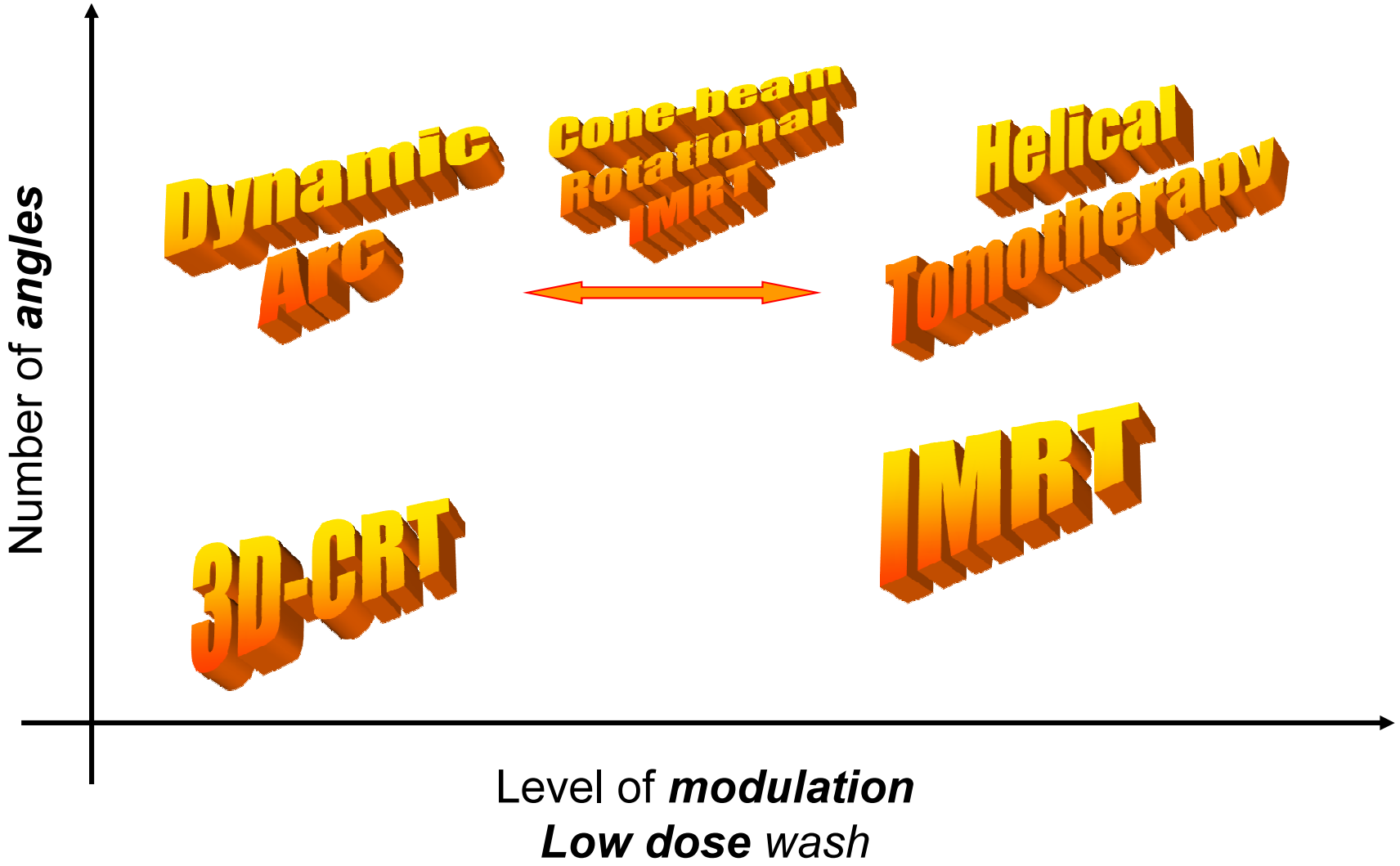
- The plans shown in this presentation are typical plans as they would be performed in clinic, generated by a dosimetrist.
  - eg focus on a certain constraint in the optimizer could drive the IMRT plan to outperform another on that particular variable … bias, selectivity ….
  - The acceptance criteria,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

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

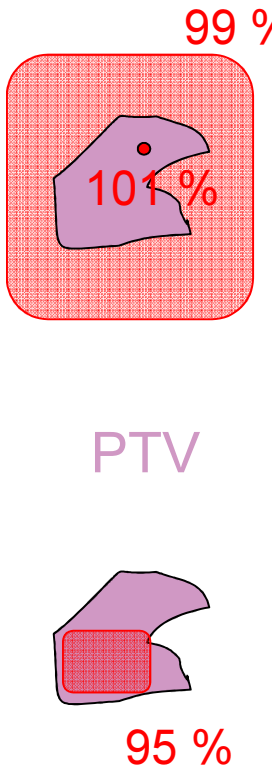


Dose homogeneity & Conformity

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.

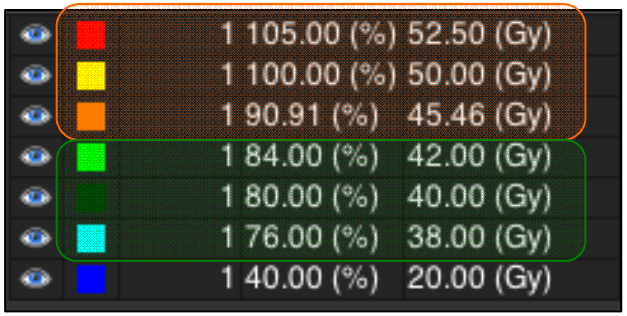
- **Treatment objectives**:
  - PTV: 95% of PTV to receive 95% of D_p
  - Lung: MLD: 19Gy, $V_{20} \leq 20\%$, $V_5 \leq 70\%$
  - Heart: $V_{30} \leq 46\ \%$
  - Myelum: $D_{2\%}$: 30Gy

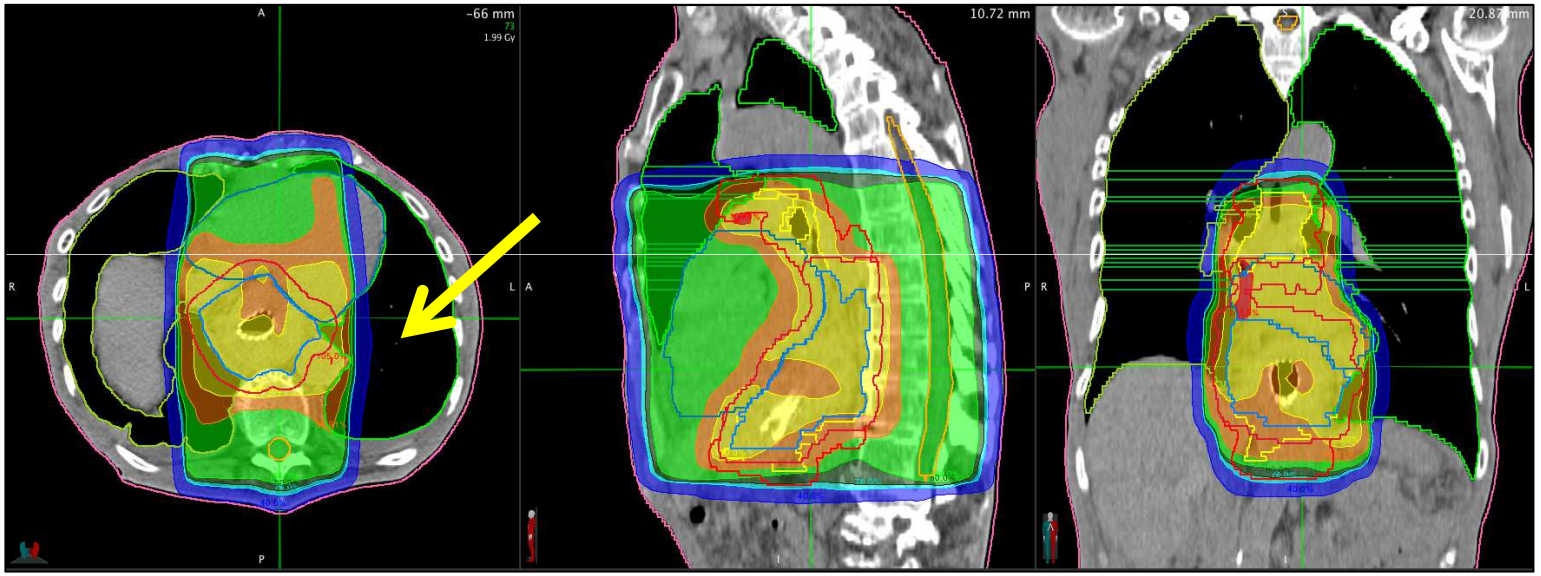
Oesophagus, a case study (1)

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

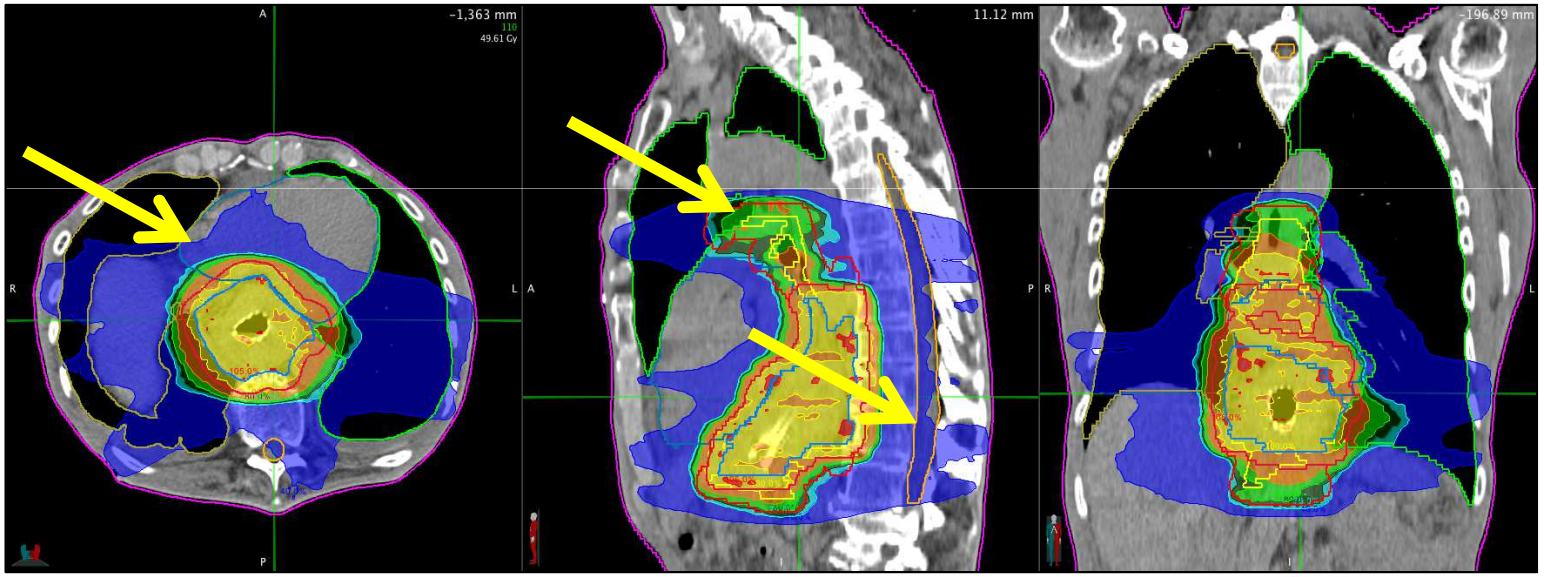
Oesophagus, a case study (1)

- 3D-CRT



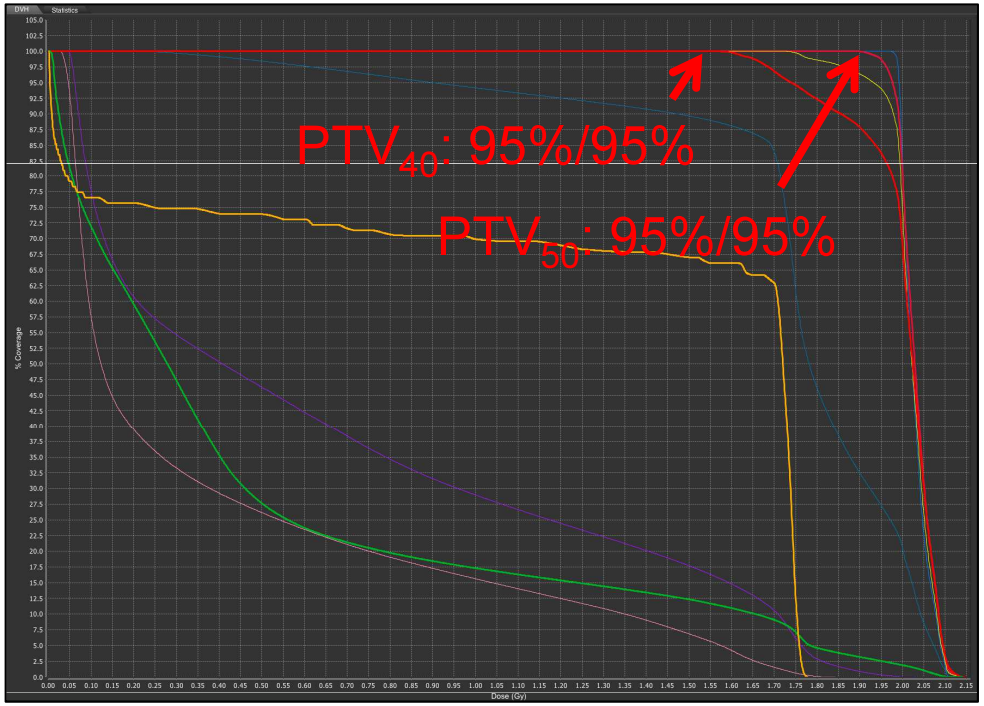


- VMAT

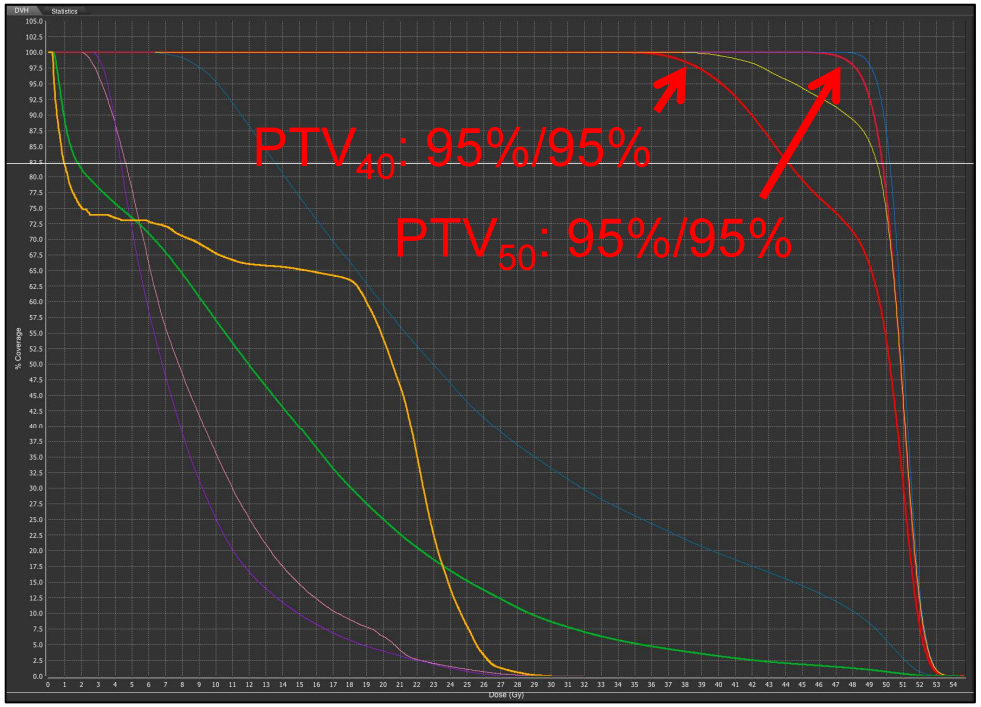


Oesophagus, a case study (1)

3D-CRT



VMAT



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

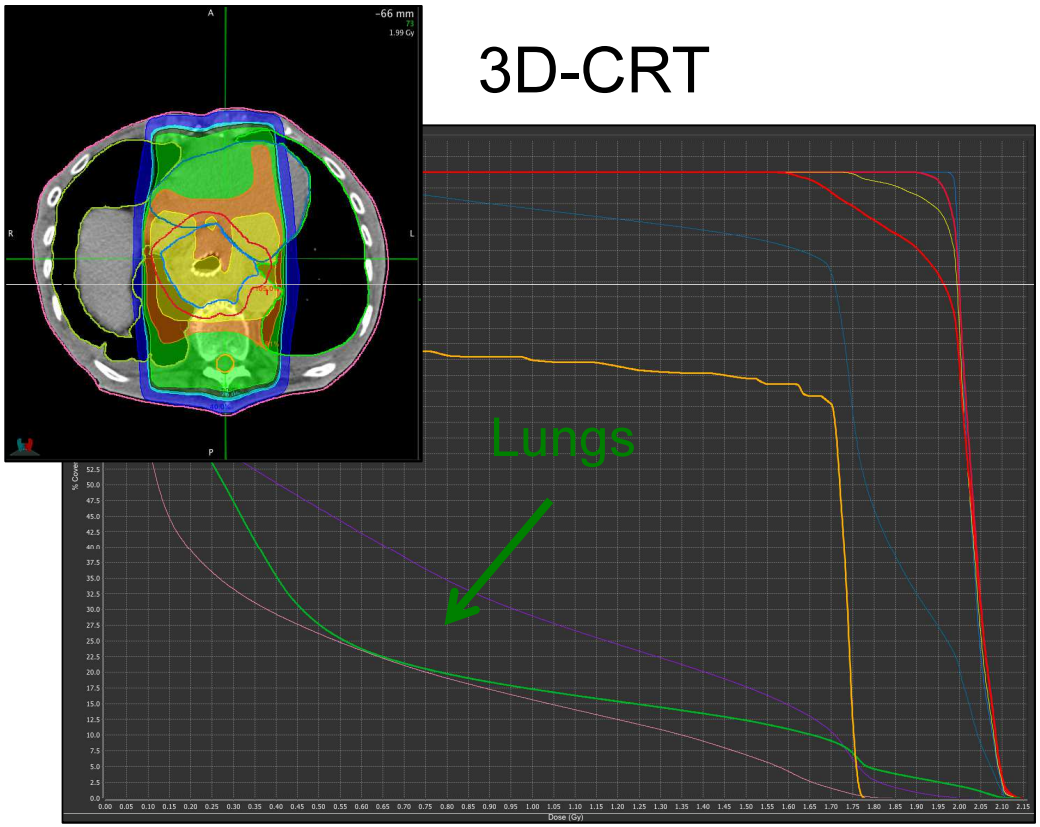
more homogenous

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

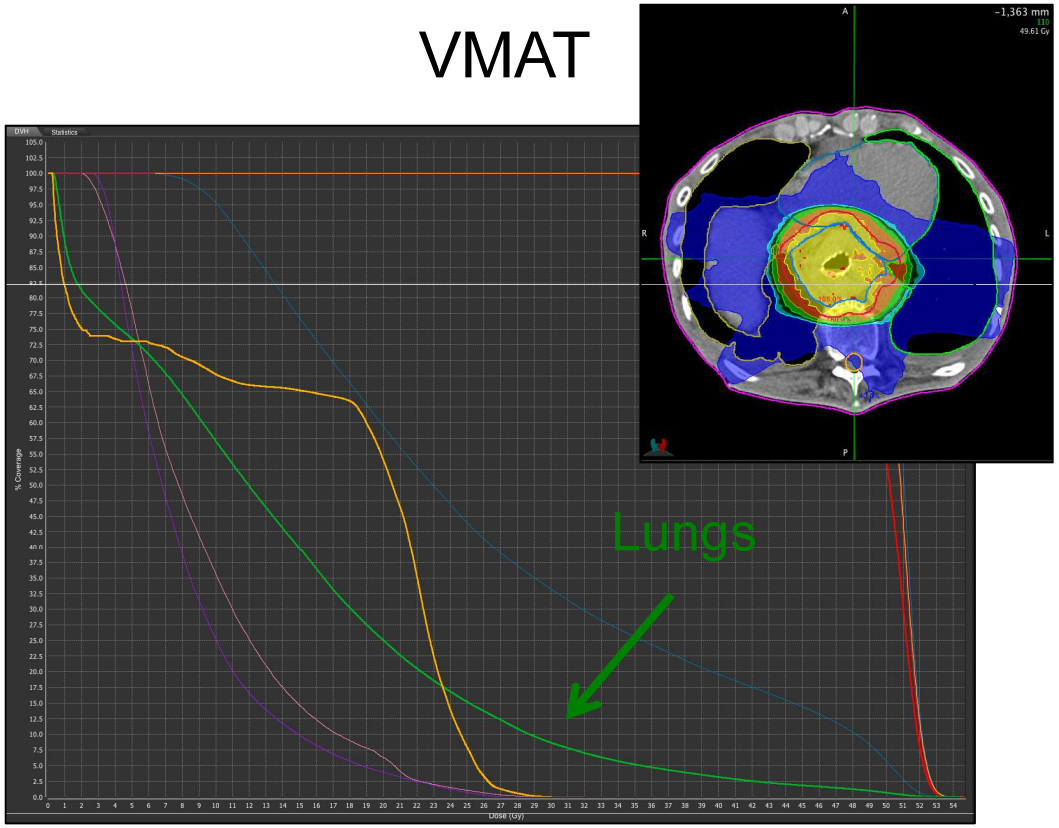
low dose wash

Oesophagus, a case study (1)

3D-CRT



VMAT

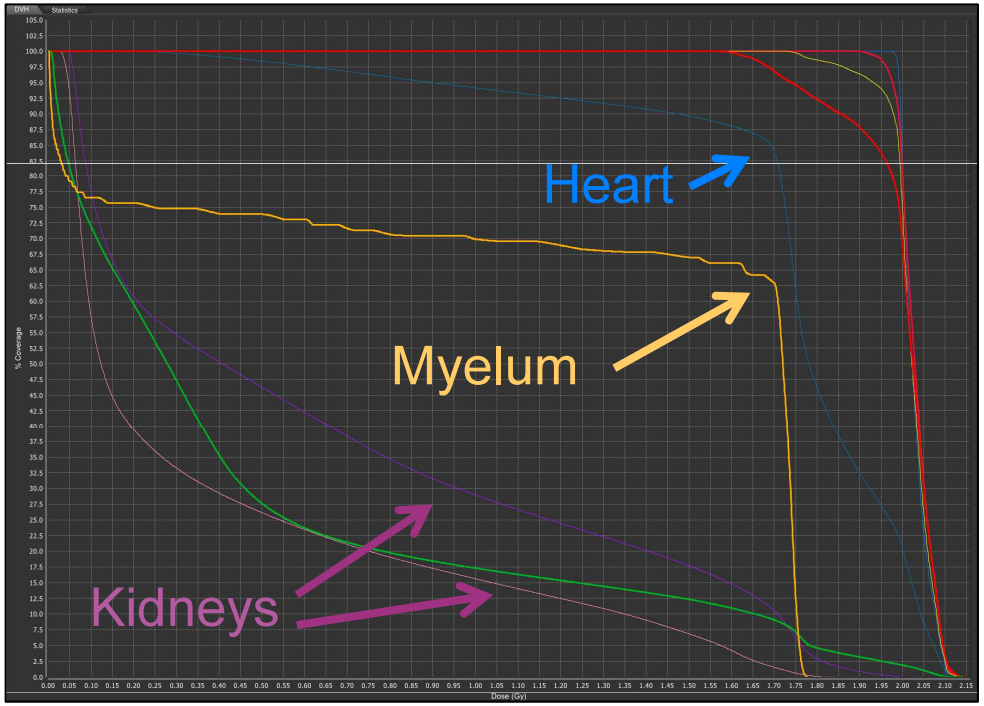


Lungs		
	objective	3D-CRT
V_{20}	< 20%	20
V_5	< 70%	60
MLD	< 19Gy	12

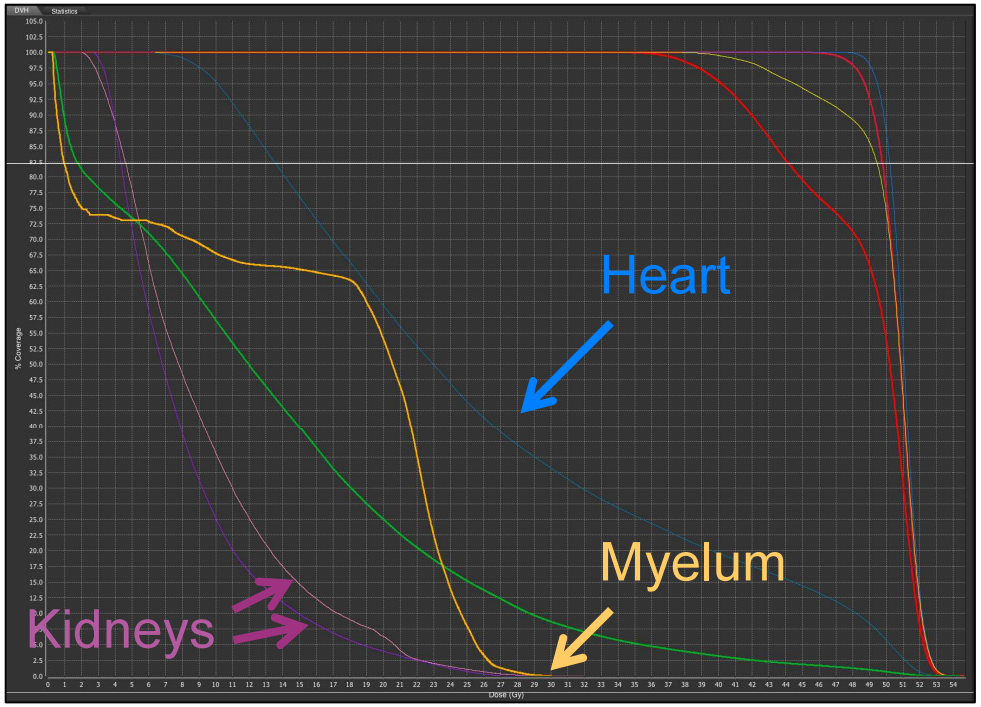
Lungs		
	objective	VMAT
V_{20}	< 20%	25
V_5	< 70%	73
MLD	< 19Gy	14

Oesophagus, a case study (1)

3D-CRT



VMAT

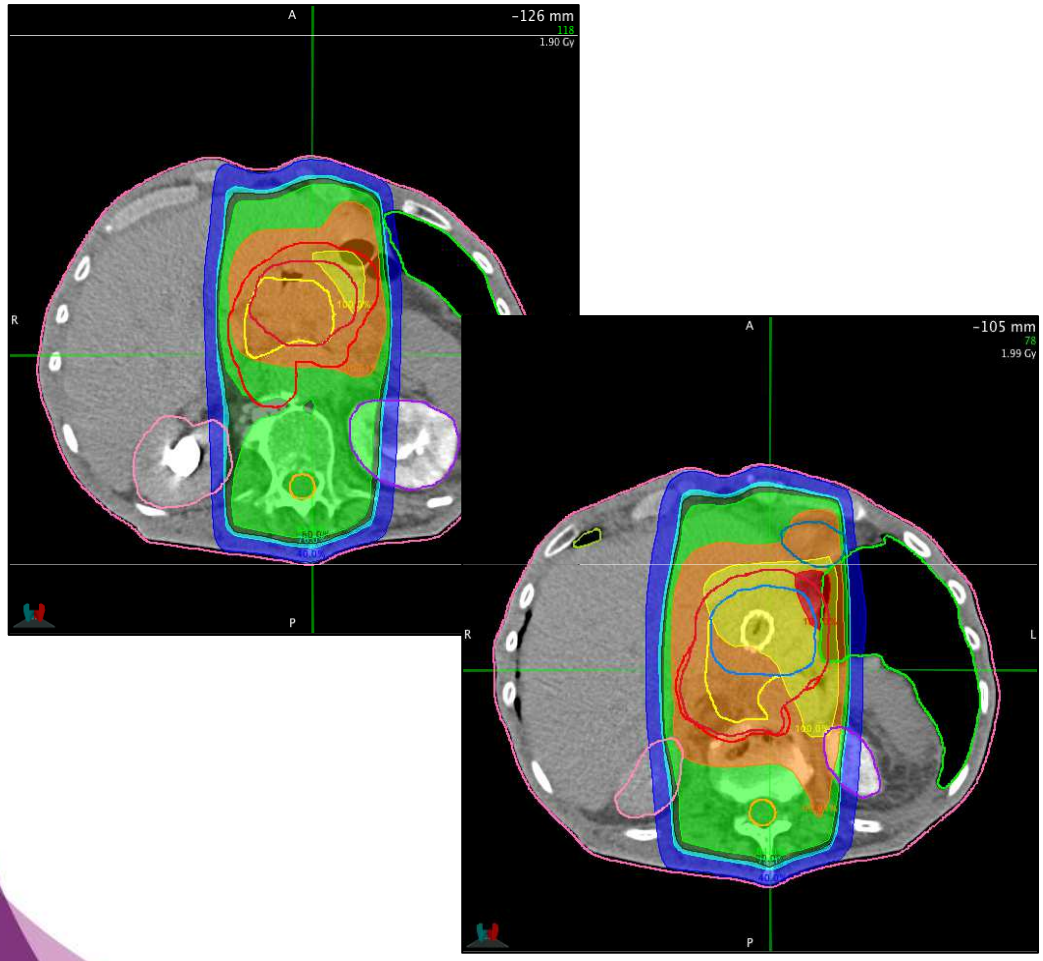


	objective	3D-CRT
Heart	$V_{30} < 46\%$	**93%**
Myelum	$D_{2\%} < 30Gy$	**45%**
Kidney L	Mean dose	**10Gy**
Kidney R	Mean dose	**17Gy**

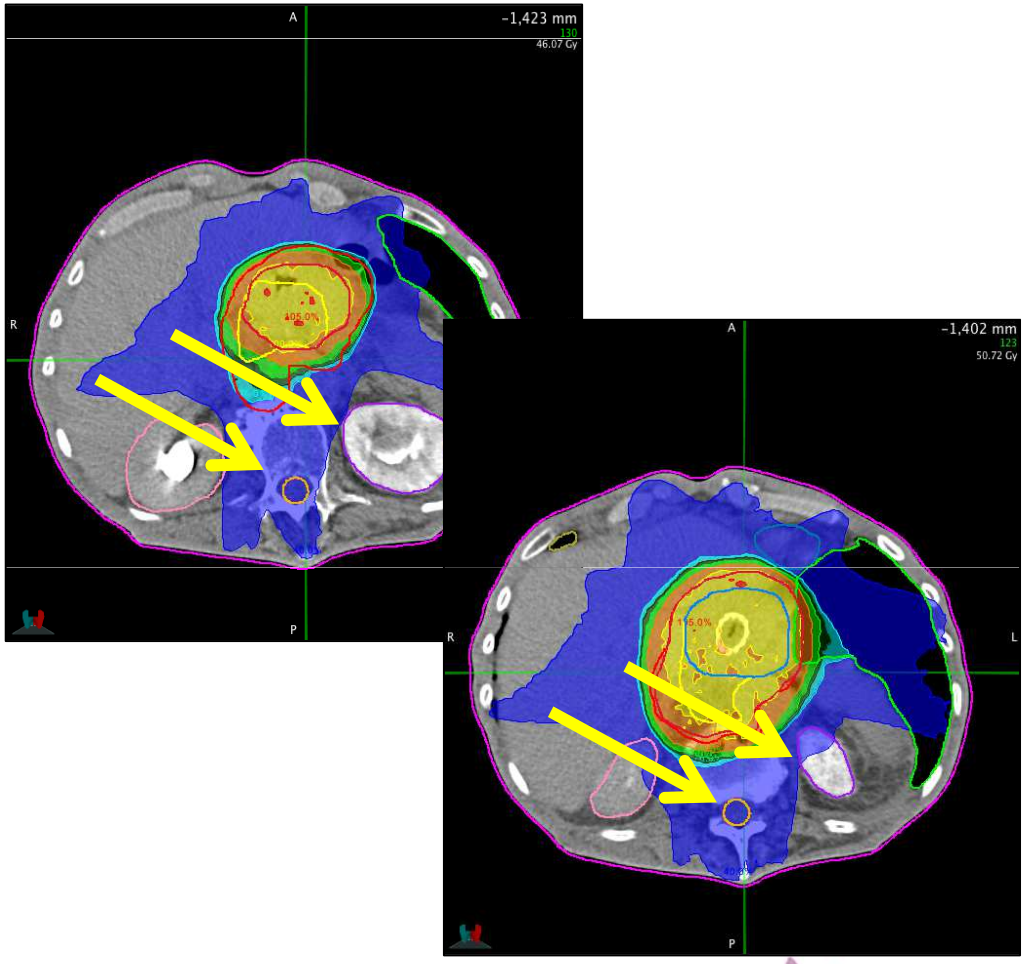
	objective	VMAT
Heart	$V_{30} < 46\%$	**33%**
Myelum	$D_{2\%} < 30Gy$	**30%**
Kidney L	Mean dose	**8gy**
Kidney R	Mean dose	**9Gy**

Oesophagus, a case study (1)

3D-CRT



VMAT



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

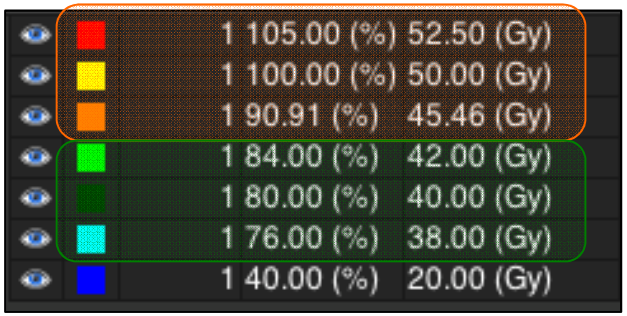
Oesophagus, a case study (2)

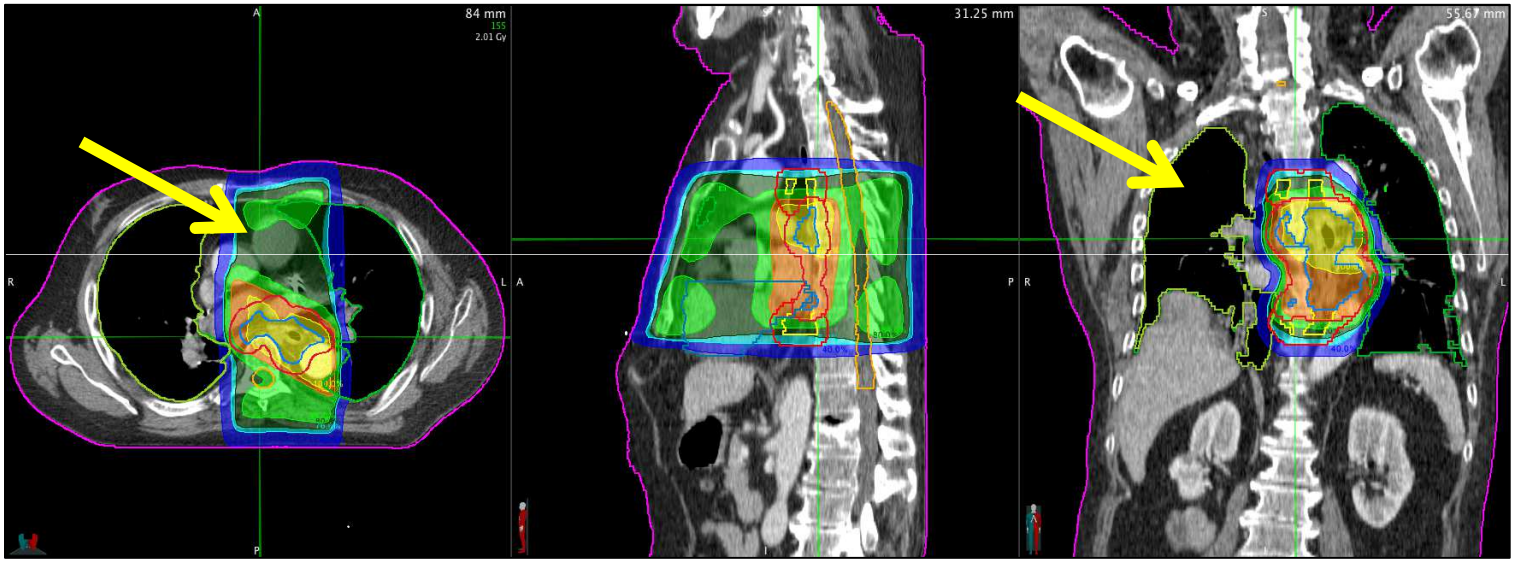
- 3D-CRT:
  - Elekta Infinity
  - 4 beams, box technique (6 and 15MV)
  - TPS: XiO CMS

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

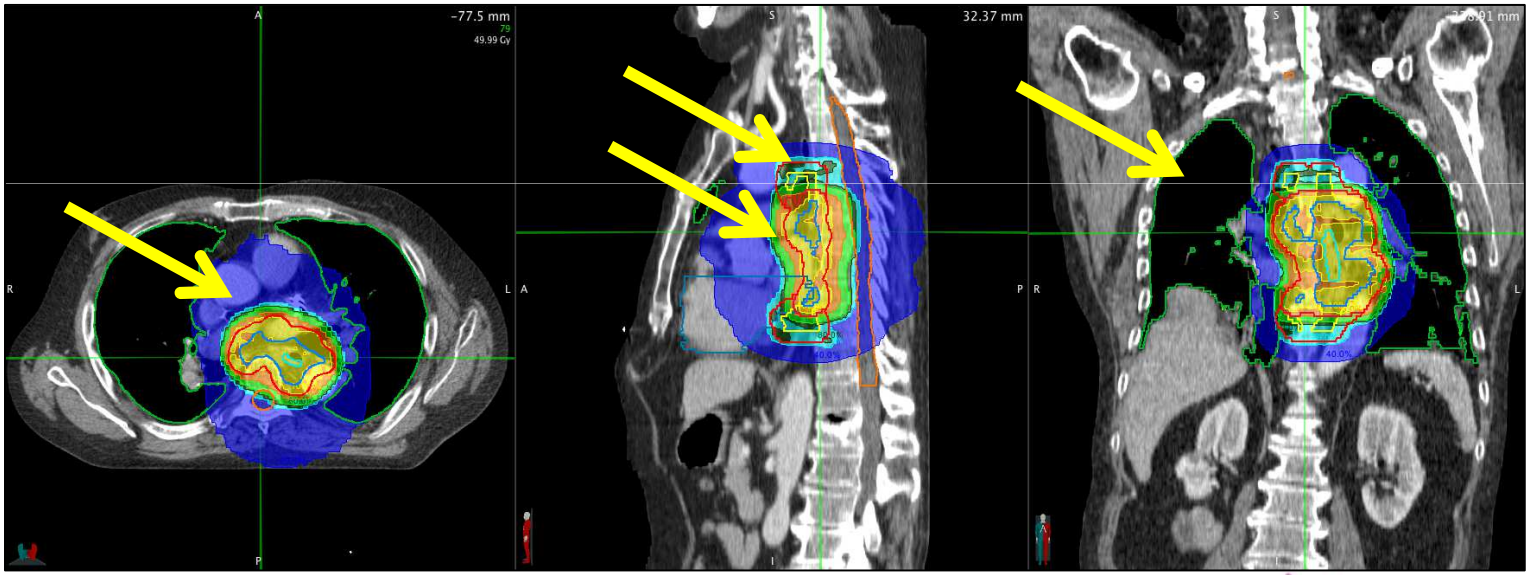
Oesophagus, a case study (2)

- 3D-CRT



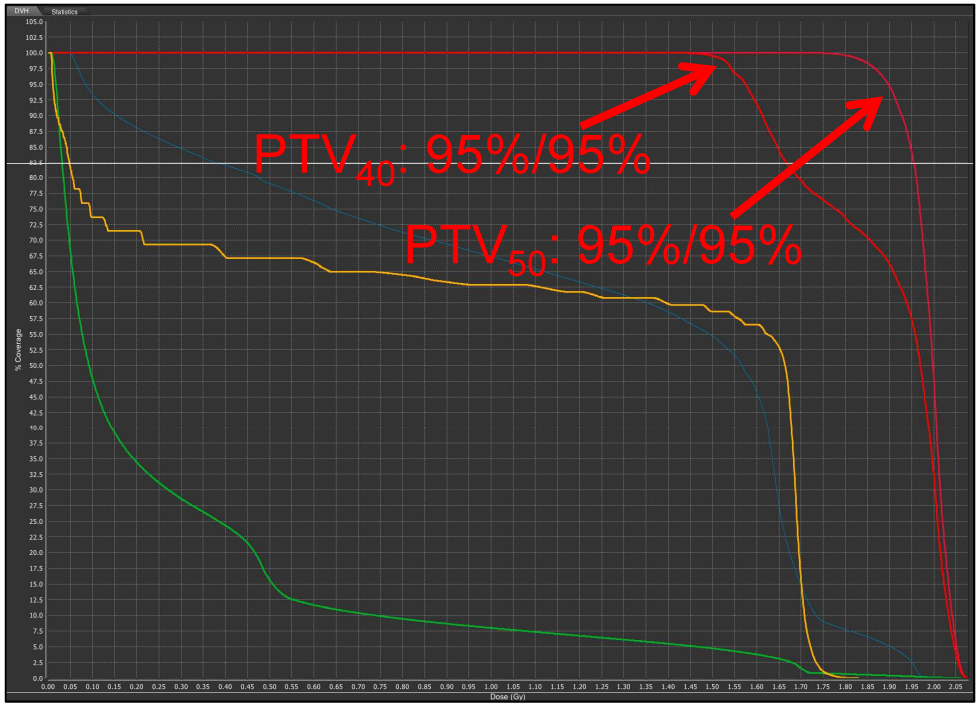


- Tomo

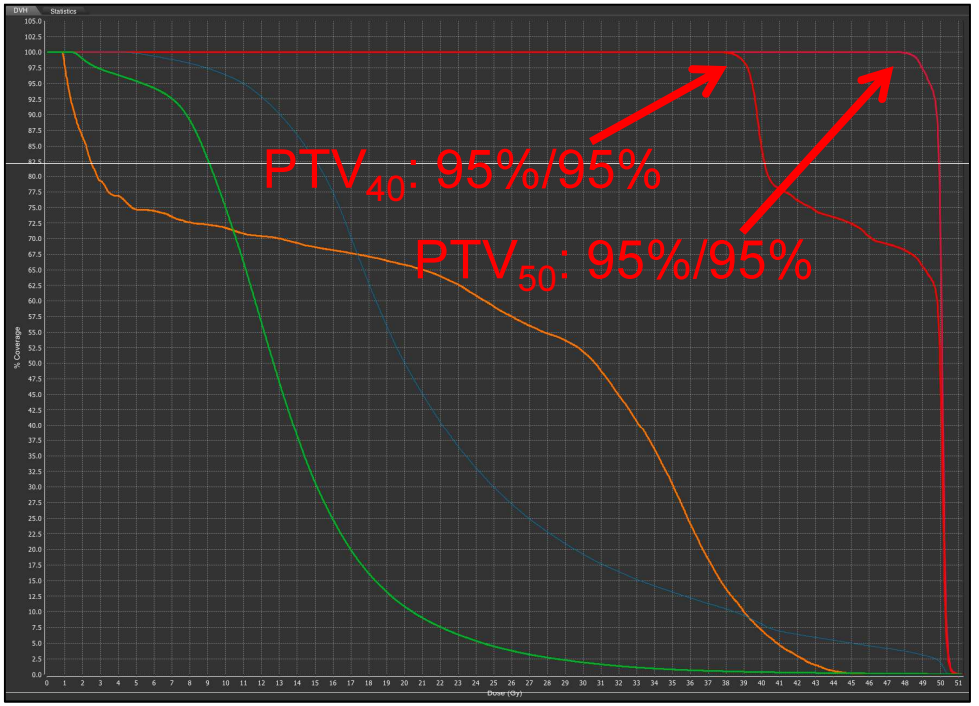


Oesophagus, a case study (2)

3D-CRT



Tomo

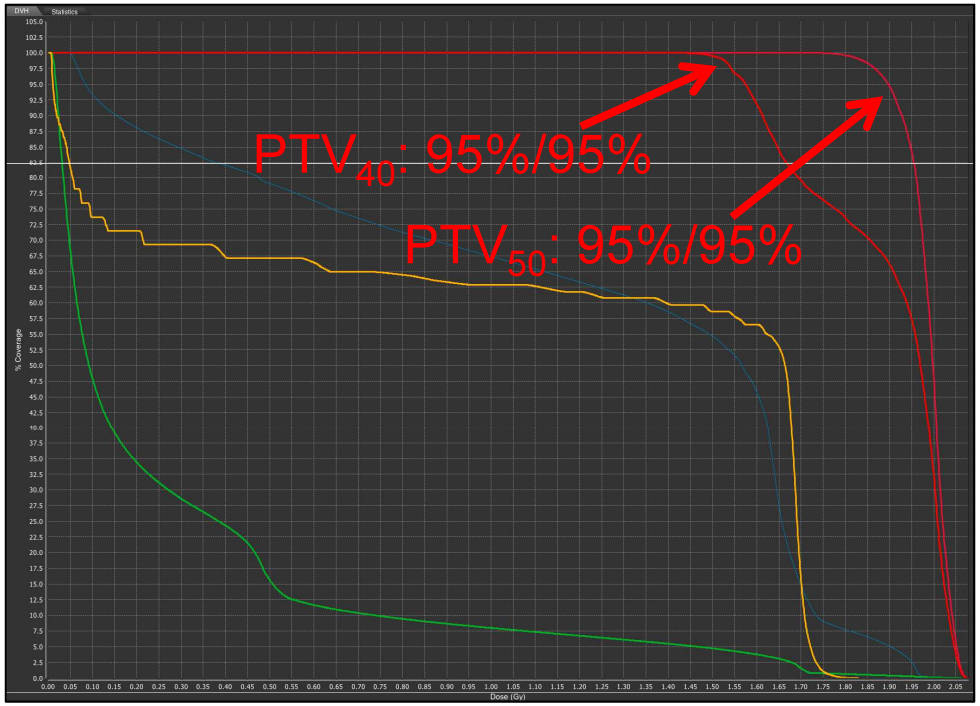


3D-CRT		
	40 Gy	**50 Gy**
PI	0.20	1.78
HI	**0.42**	**0.19**
GI	**1.71**	17.83

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

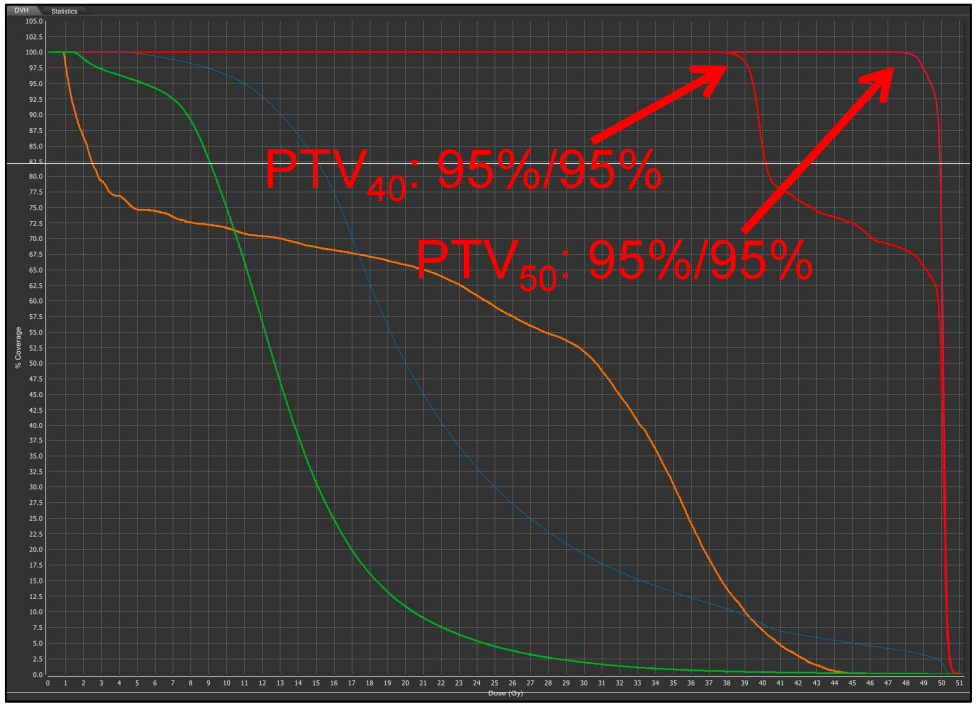
Oesophagus, a case study (2)

3D-CRT



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

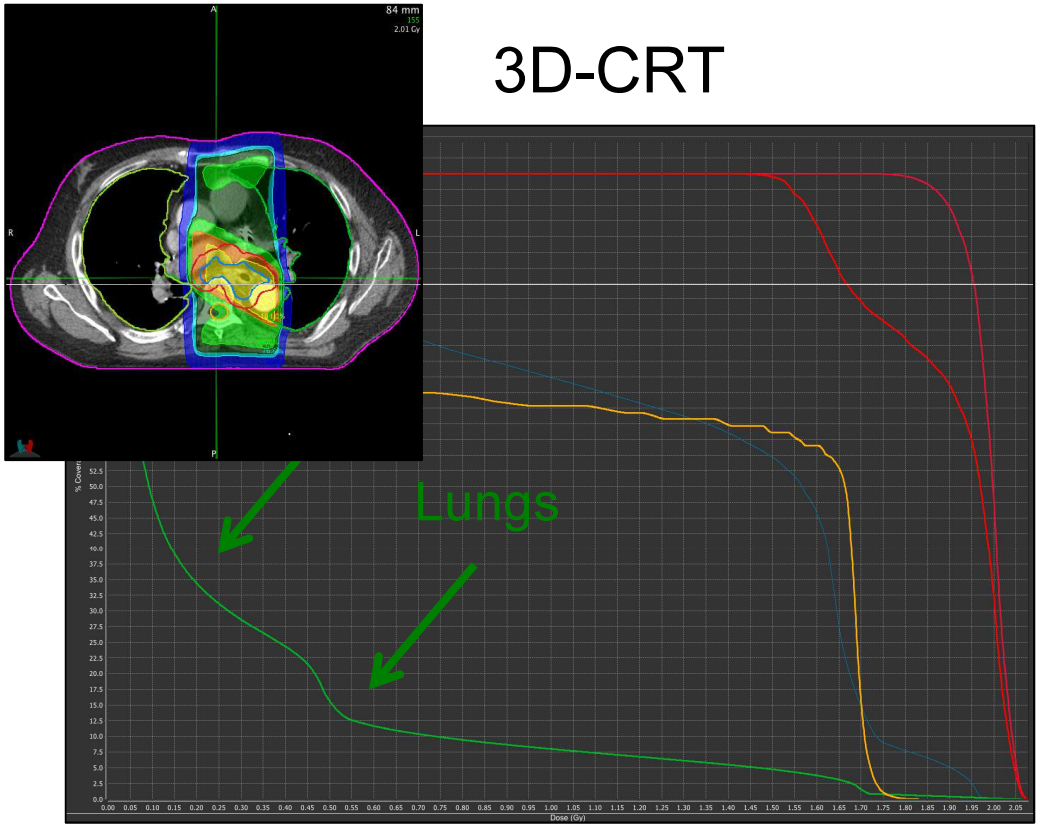
Tomo



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

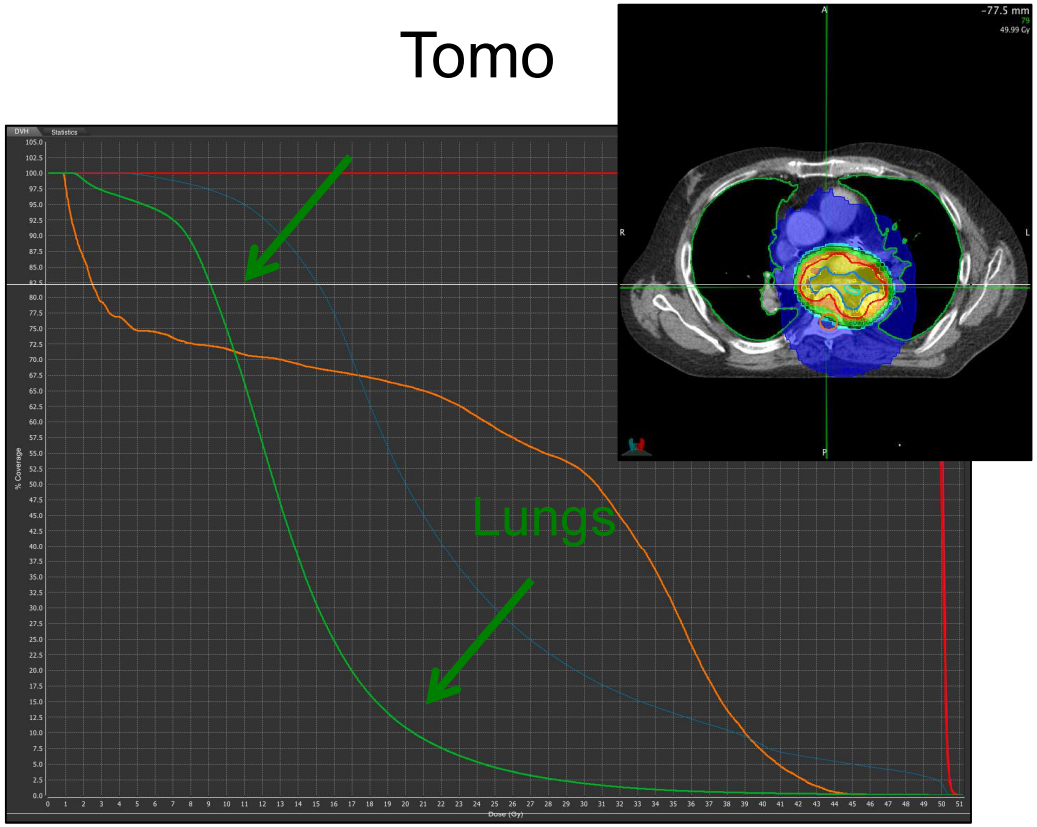
Oesophagus, a case study (2)

3D-CRT



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

Tomo

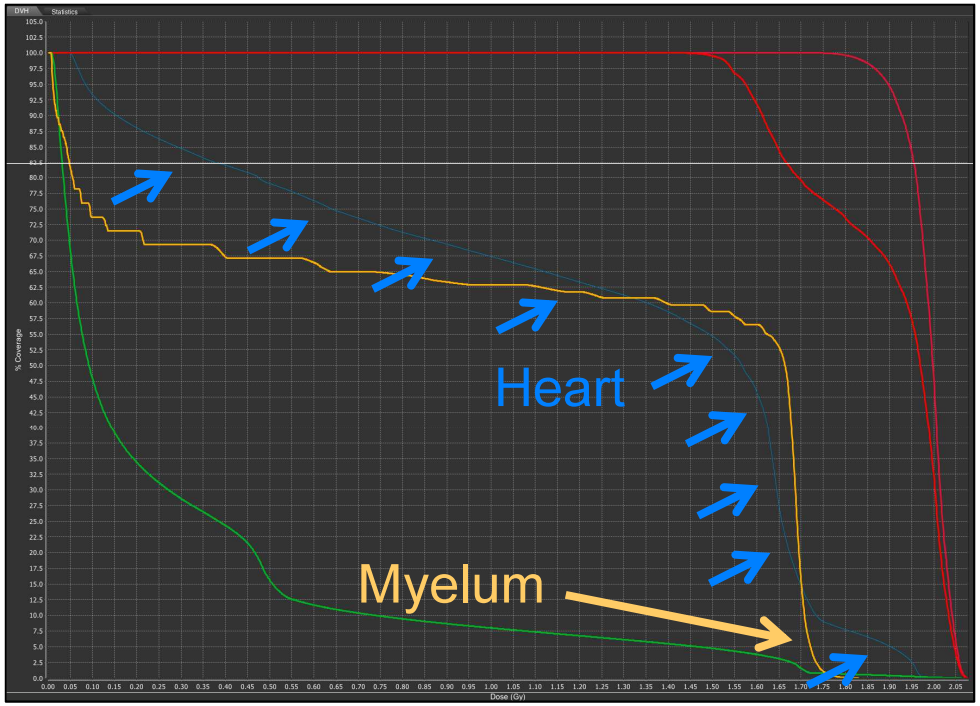


Lungs		
	objective	Tomo
V_{20}	< 20%	11
V_5	< 70%	95
MLD	< 19Gy	14

low dose wash

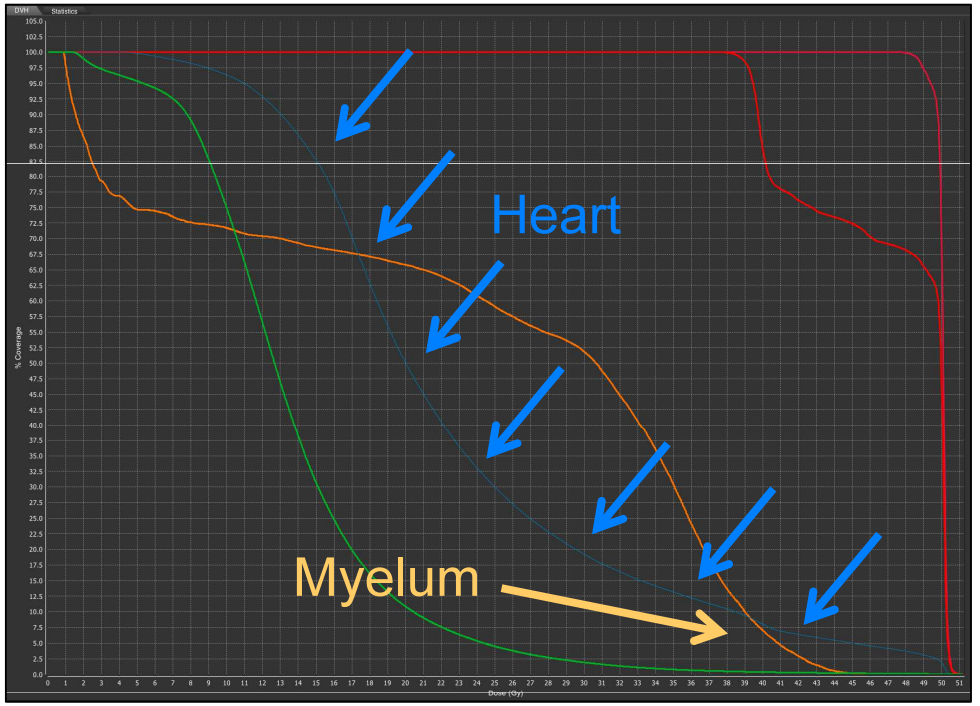
Oesophagus, a case study (2)

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

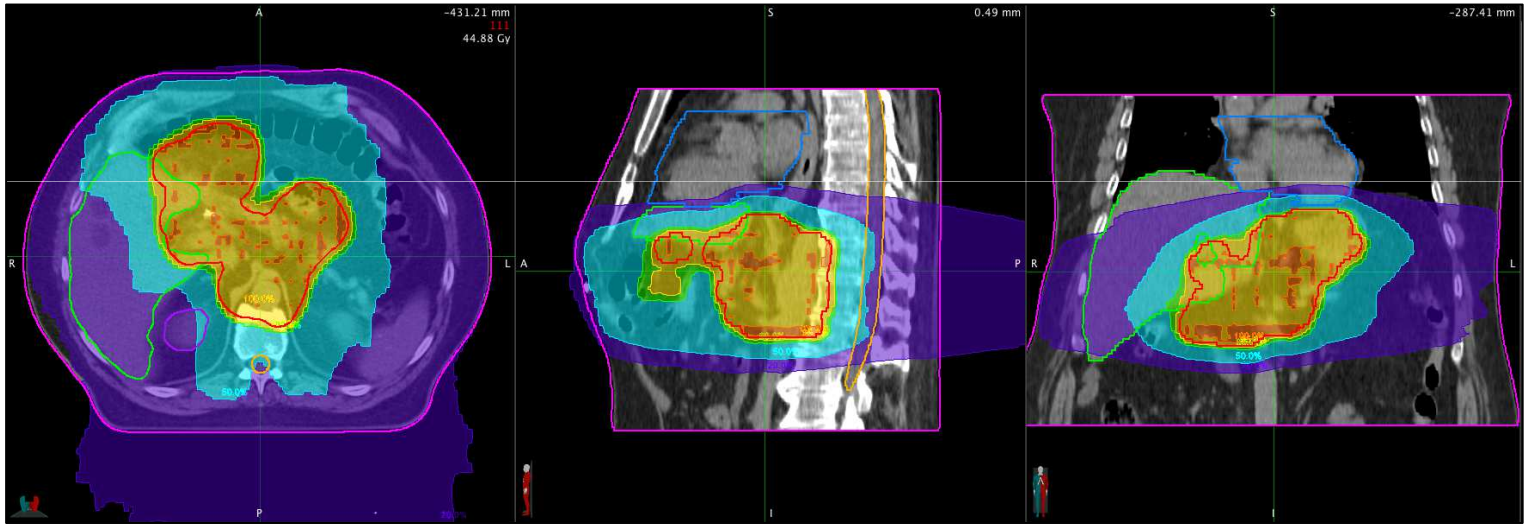
- Tomo:
  - TomoTherapy
  - Helical tomotherapy
  - TPS: Hi-Art

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)

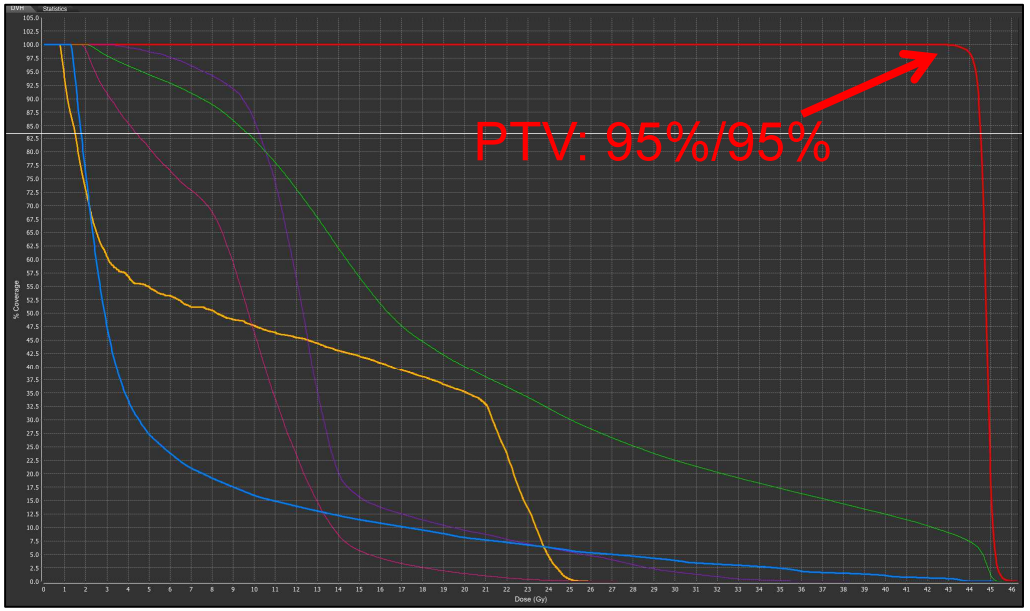
- Tomo



Stomach, a case study (3)

3D-CRT

Tomo



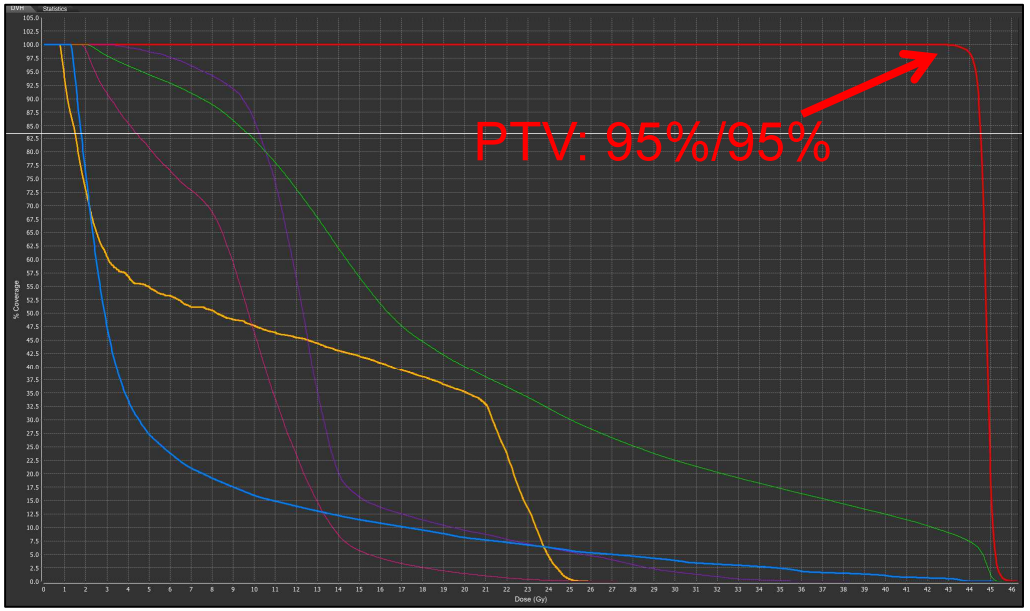
3D-CRT	
PI	0.57
HI	**0.11**
GI	**2.78**

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

Stomach, a case study (3)

3D-CRT

Tomo

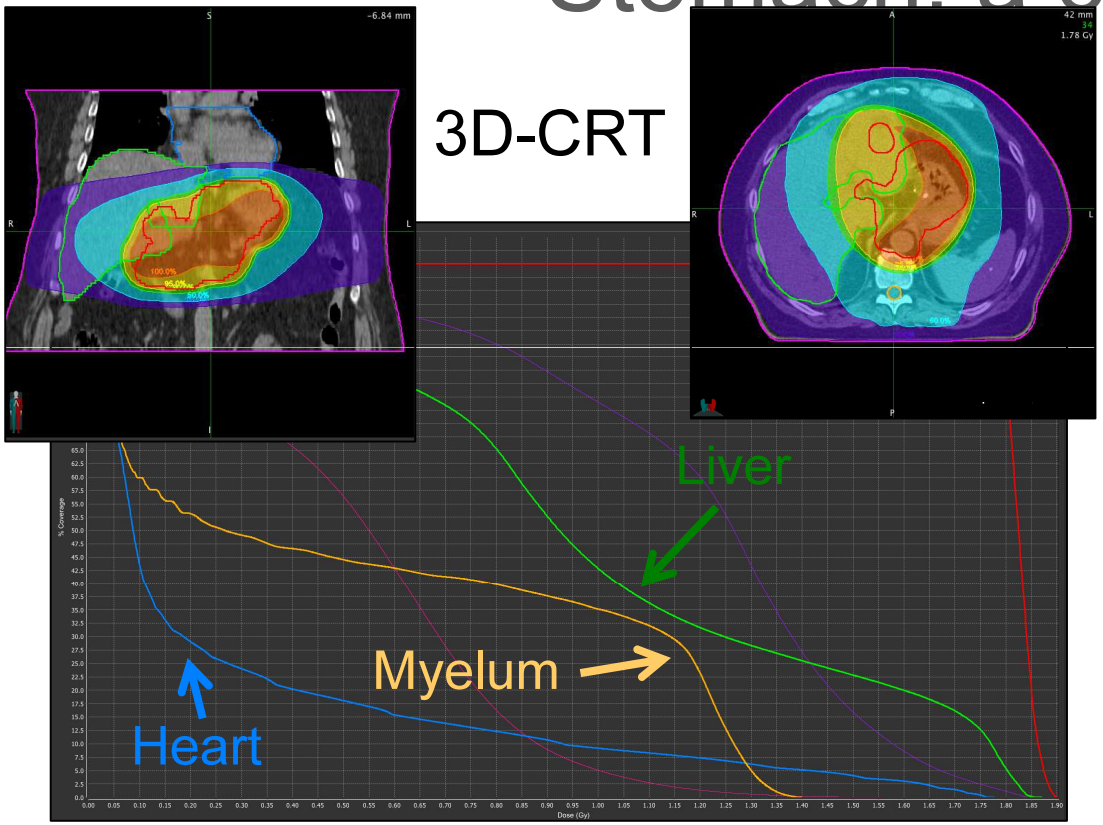


3D-CRT	
PI	**0.57**
HI	0.11
GI	2.78

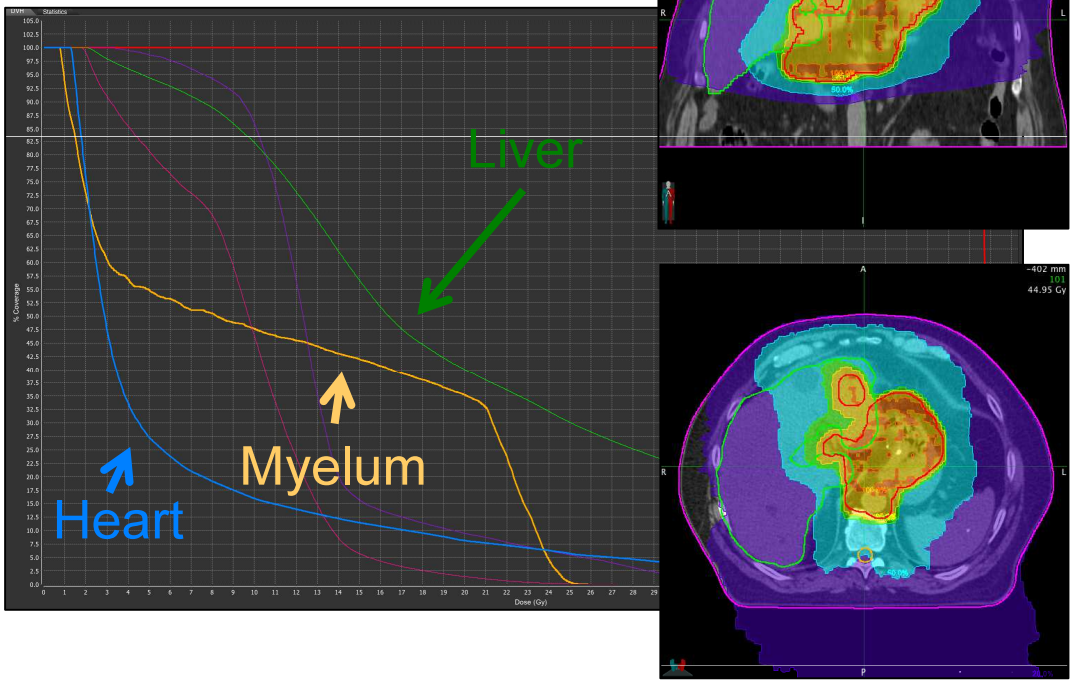
Tomo	
PI	**0.84**
HI	0.10
GI	3.29

Stomach, a case study (3)

3D-CRT



Tomo

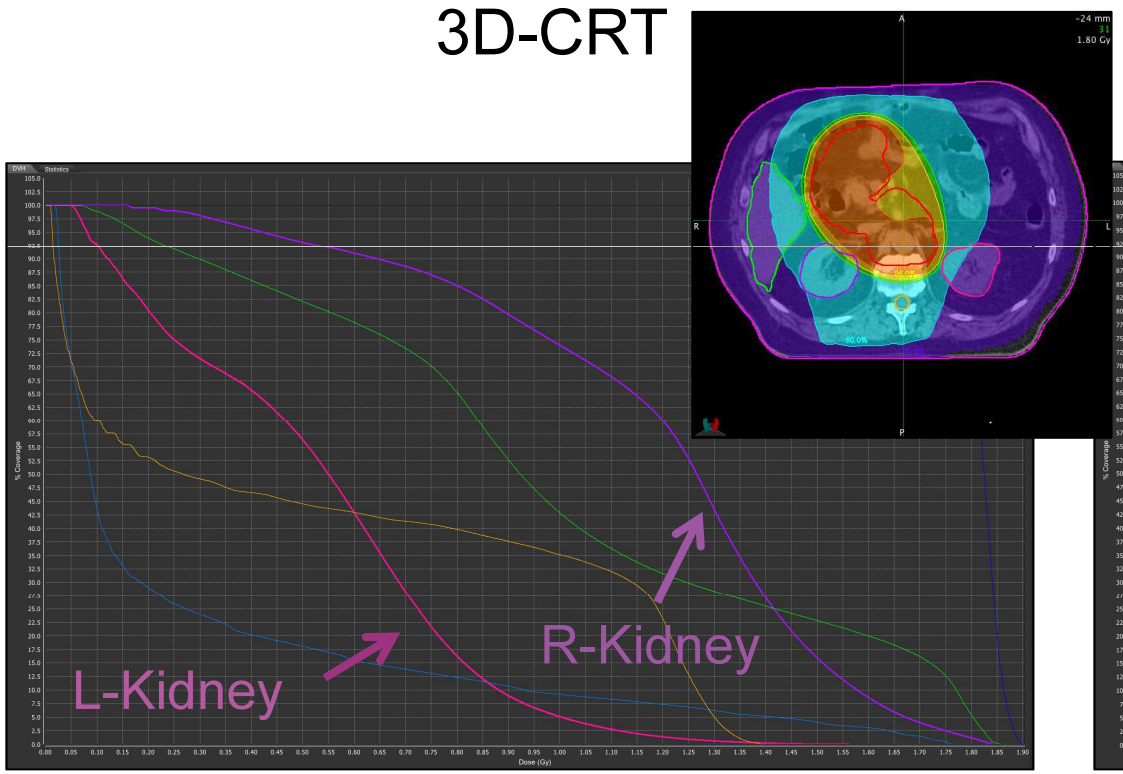


3D-CRT		
	objective	
Liver	V_{30}	31.7%
Heart	V_{30}	7.3%
Myelum	$D_{2\%}$	35.0Gy

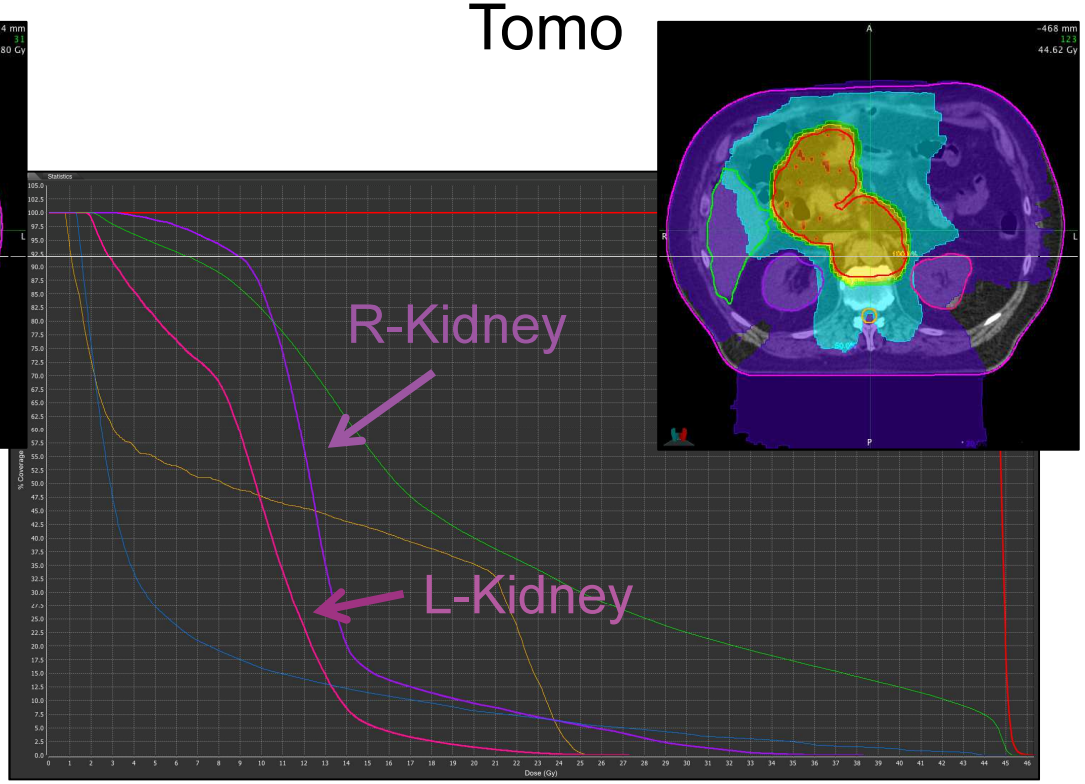
Tomo		
	objective	
Liver	V_{30}	**22.5%**
Heart	V_{30}	**3.9%**
Myelum	$D_{2\%}$	**25.8Gy**

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

ESTRO School

WWW.ESTRO.ORG/SCHOOL

PTV margins

Universitair Ziekenhuis Brussel

Vrije Universiteit Brussel

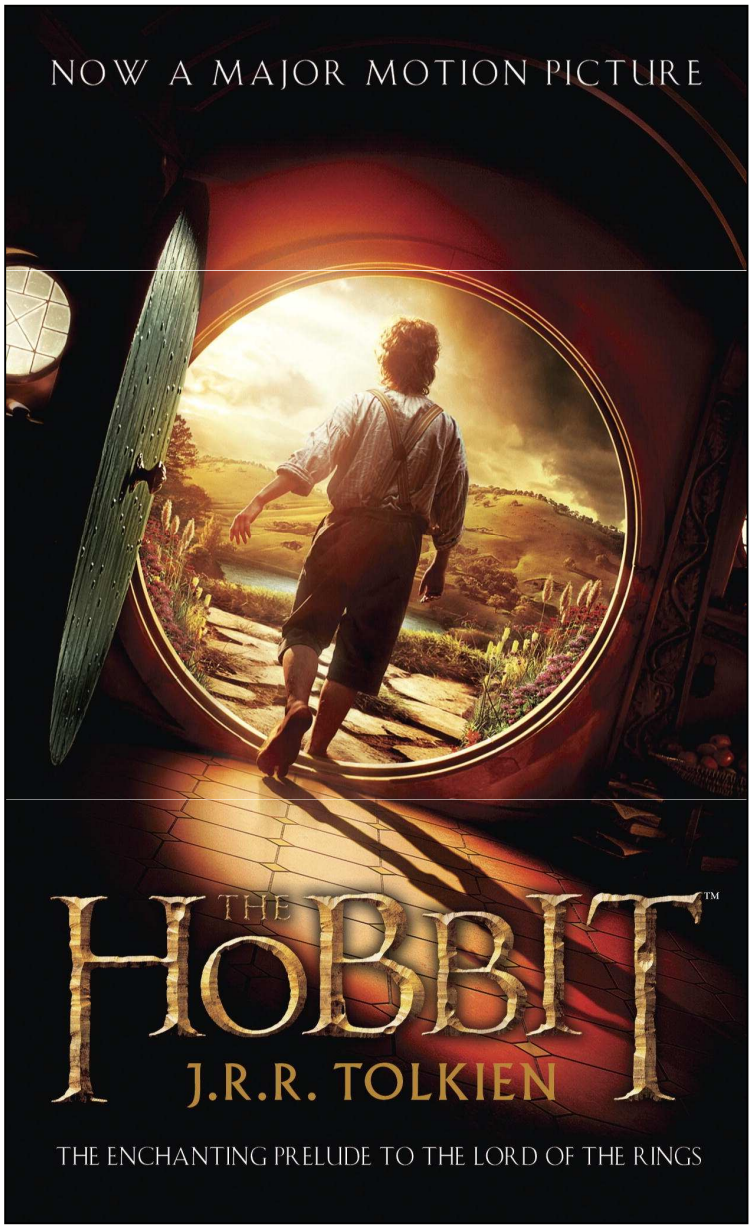
Dirk Verellen

DV is involved in an on-going scientific collaboration with BrainLAB AG, RaySearch, MIM software Inc.

ESTRO School

The PTV

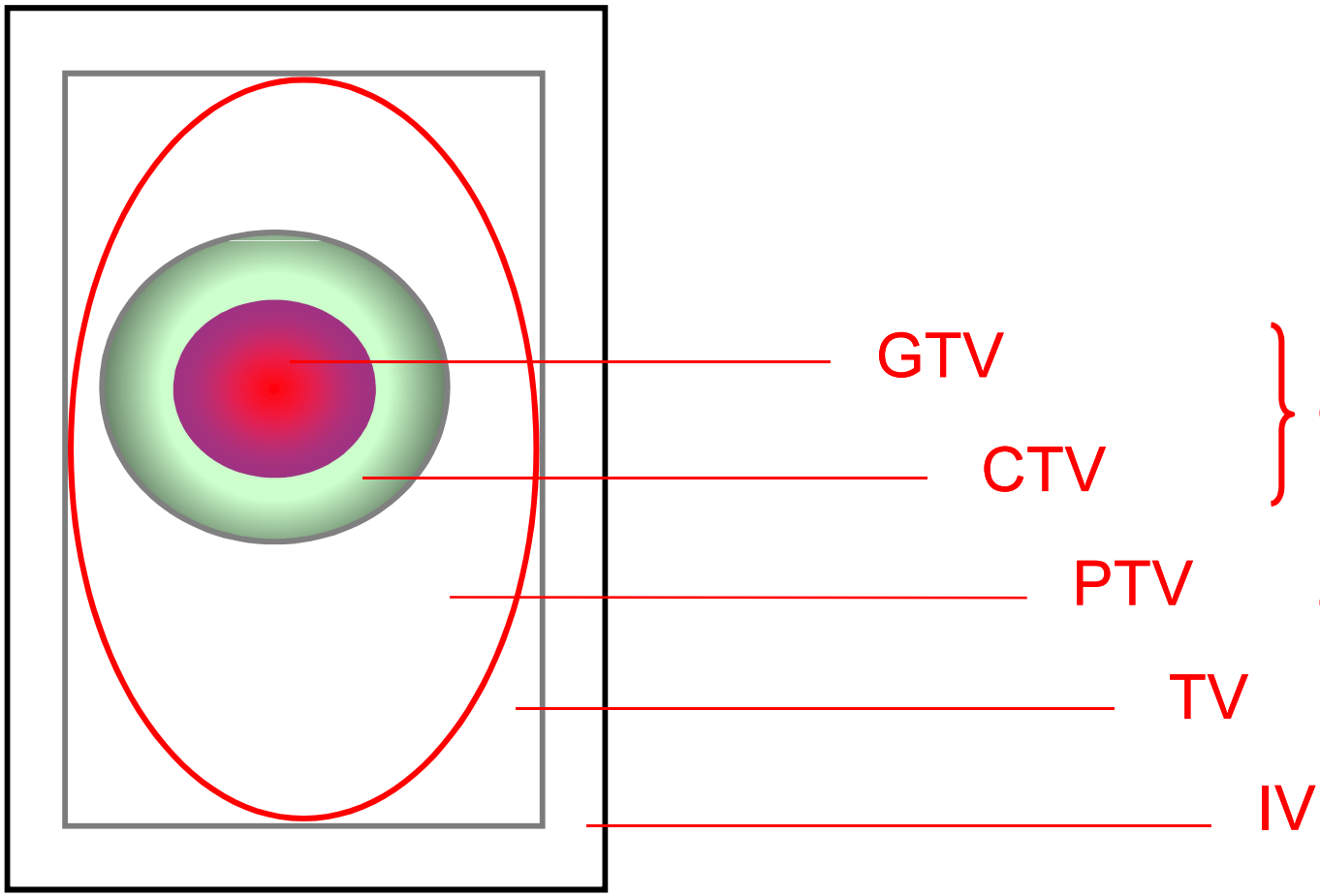
- There and back again



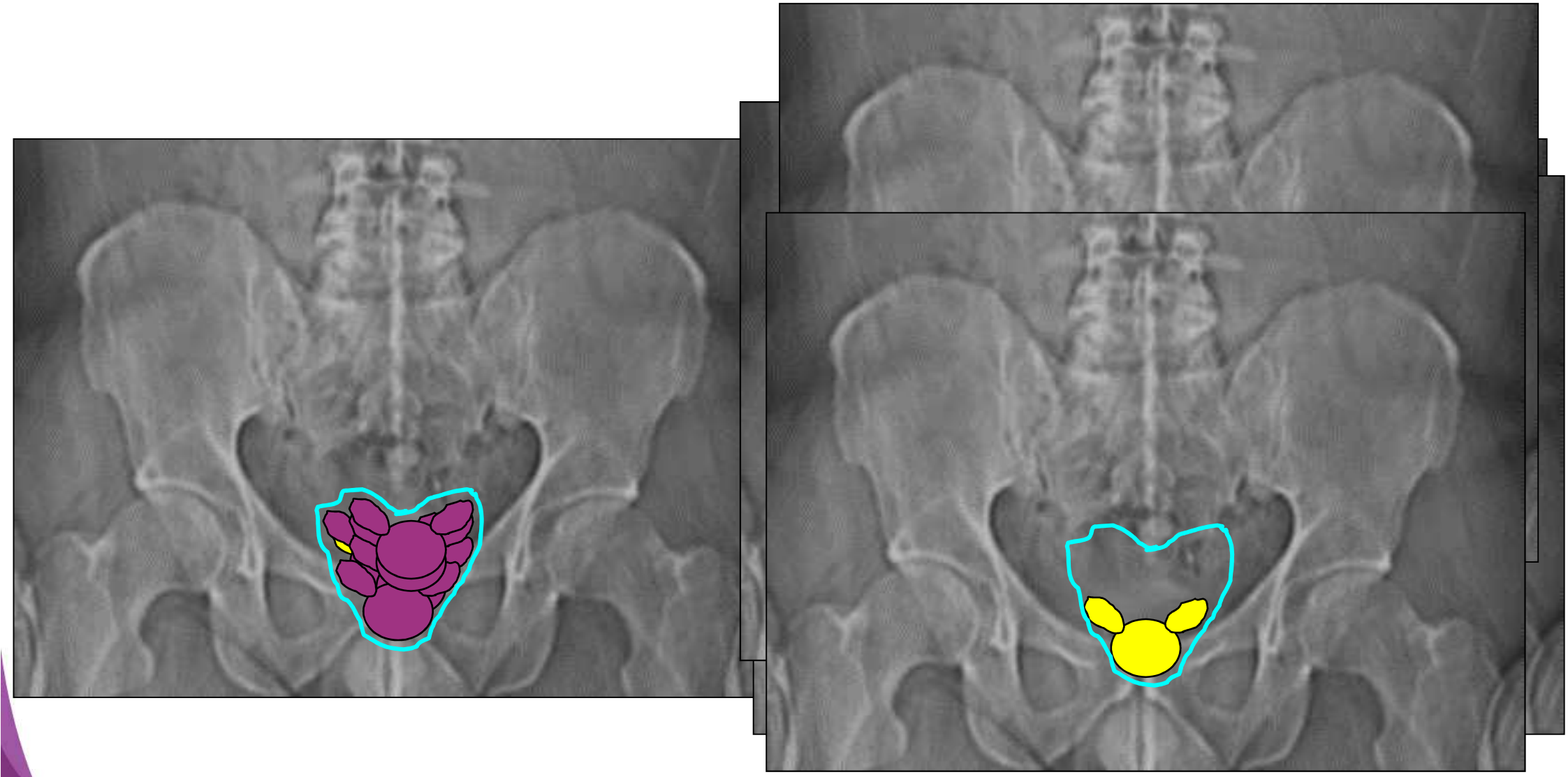
Outline

- 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

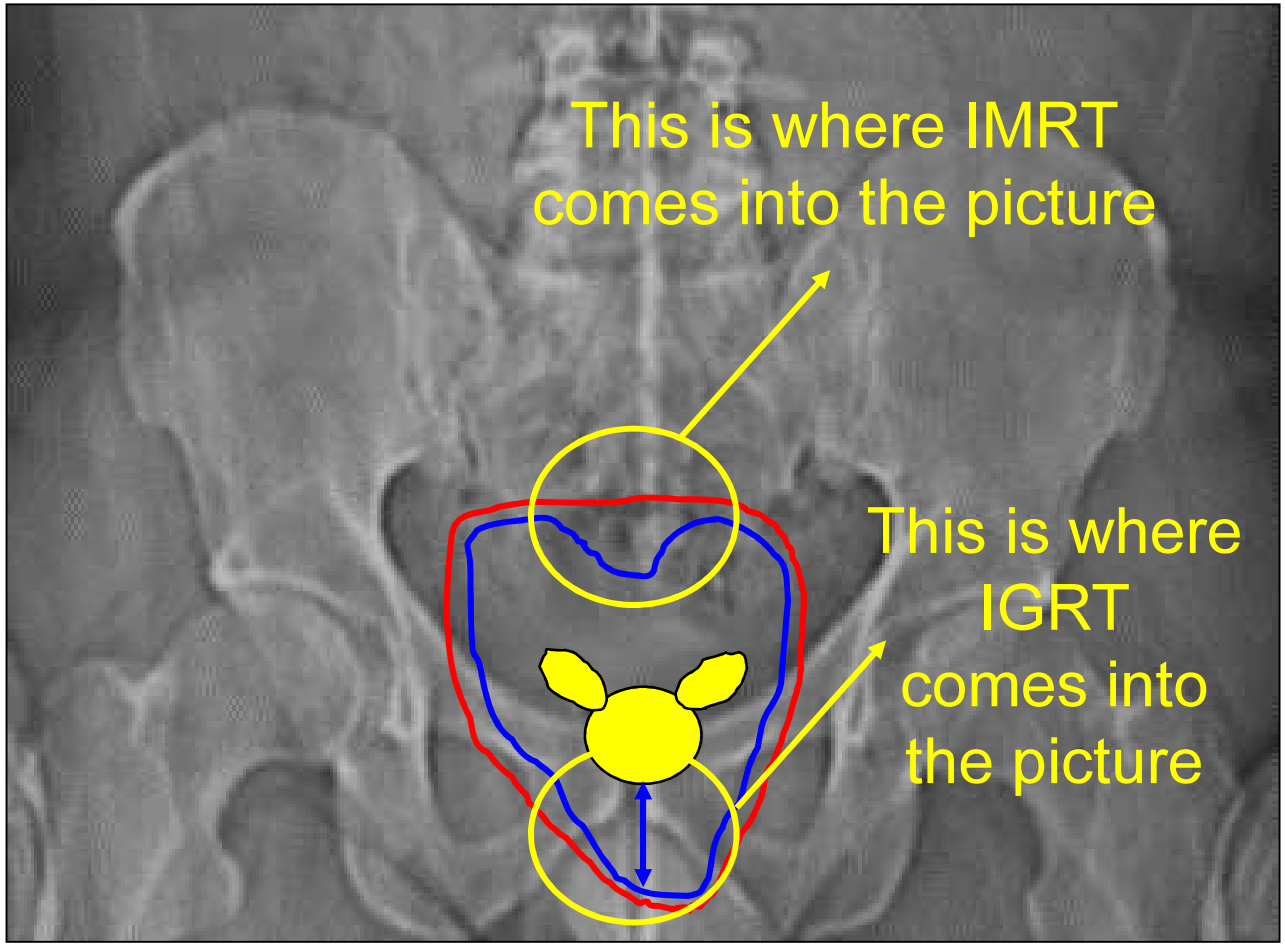


Let's start with the definition



"The dancing prostate"

Let's start with the definition



Set up Margin

+

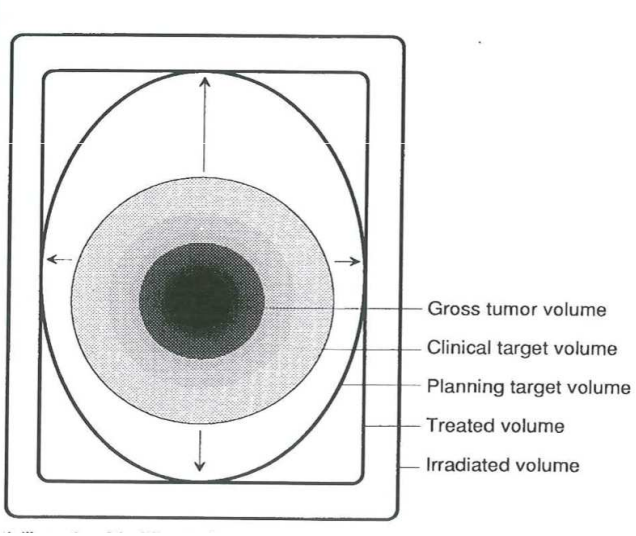
Internal Margin

Irradiated Volume

"The dancing prostate"

Let's start with the definition

- ICRU 50



- ICRU 62

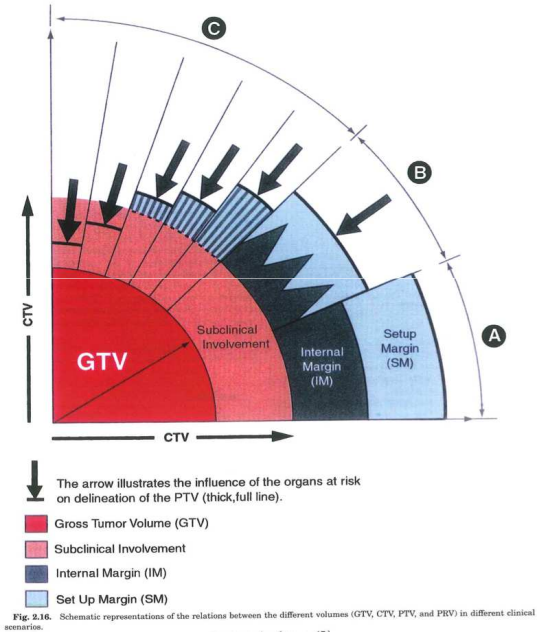


Fig. 2.16. Schematic representations of the relations between the different volumes (GTV, CTV, PTV, and PRV) in different clinical scenarios.

- … ICRU 83 …

Let's start with the definition

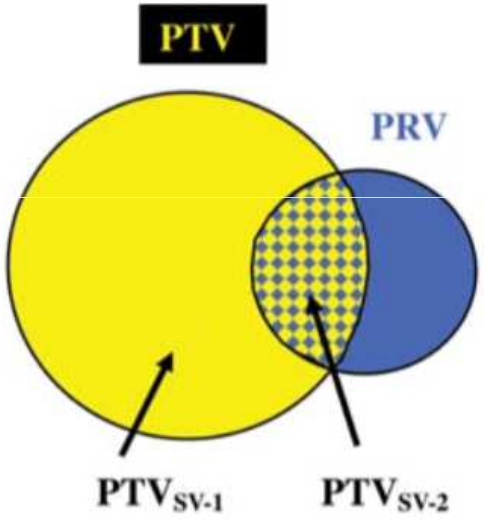
- **ICRU 83**:
  - The PTV is **A GEOMETRICAL CONCEPT** introduced for treatment planning and evaluation. **It is the recommended tool to shape absorbed-dose distributions to ensure that the prescribed absorbed dose will actually be delivered to all parts of the CTV with a clinically acceptable probability**, 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

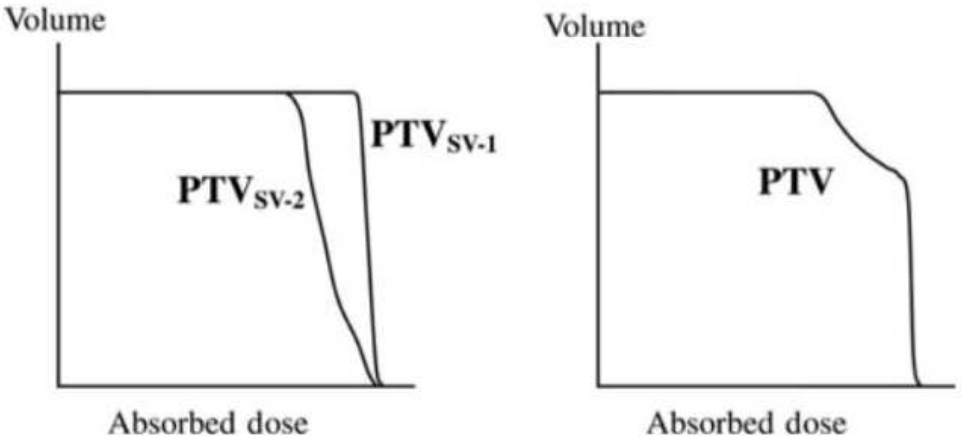
- **ICRU 83**:
  - In earlier ICRU documents, the possibility of **compromising** the margins of the PTV if they encroached on **OAR** was suggested (ICRU, 1999; 2004; 2007), but is **no longer recommended**. To reduce the CTV-to-PTV margin has always been a temptation. As an example, the CTV-to-PTV 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**:

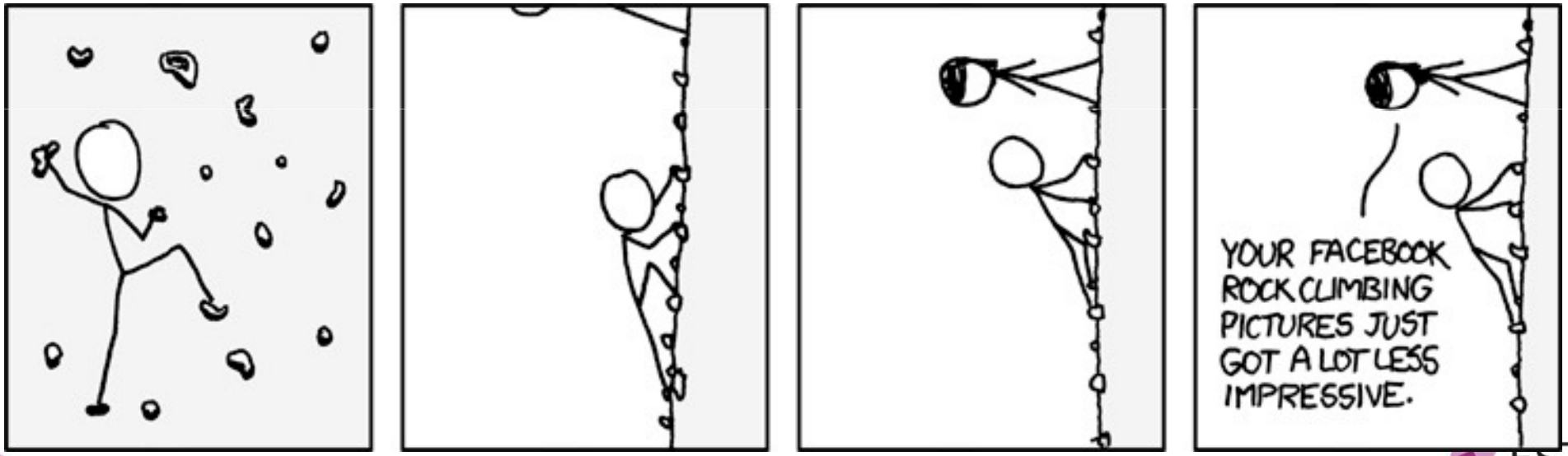


$$PTV = PTV_{SV-1} + PTV_{SV-2}$$



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**??????



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

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

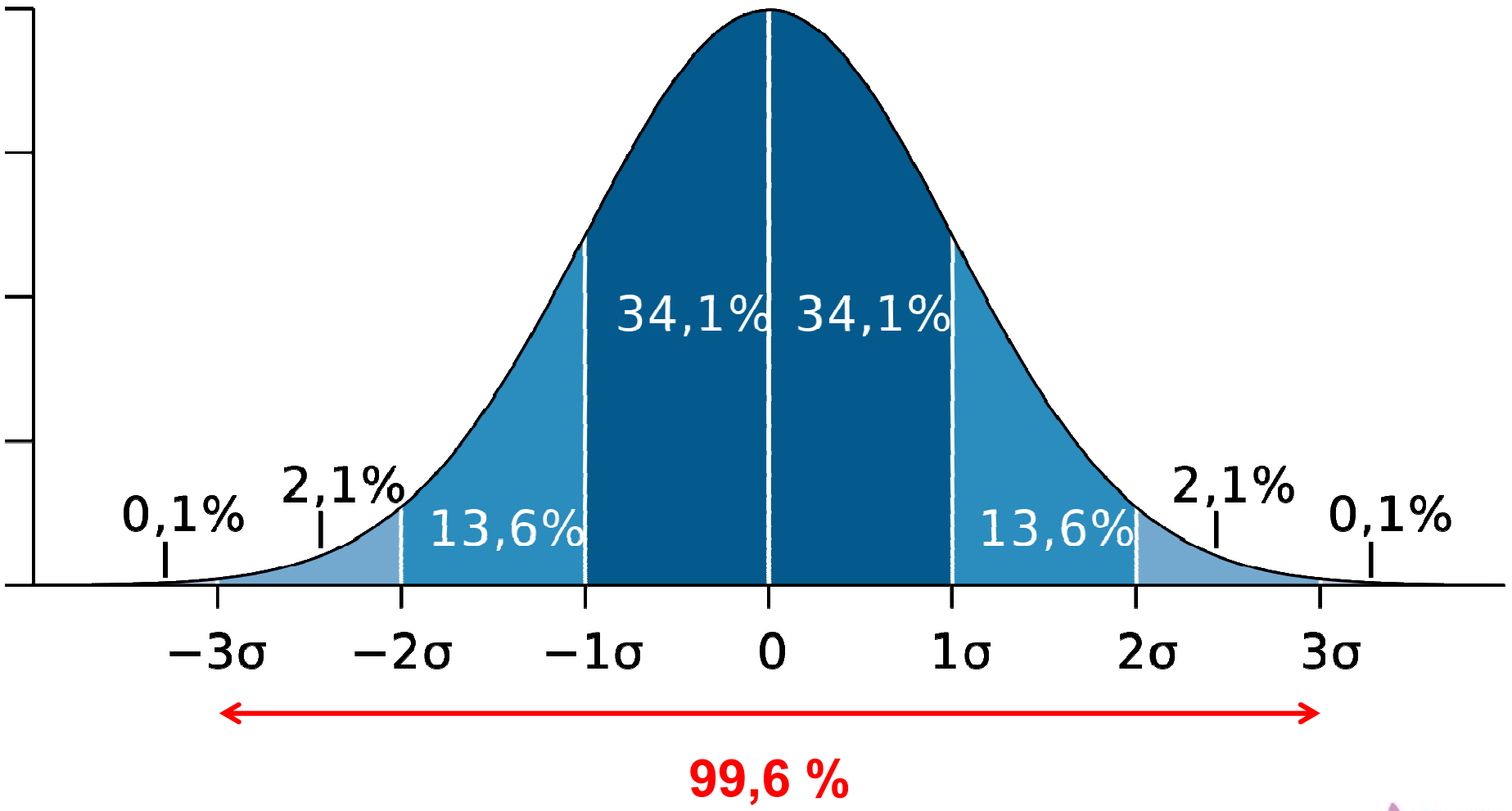
(van Herk et al, IJROBP 47: 1121-1135, 2000)

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

- Without knowing what it’s about

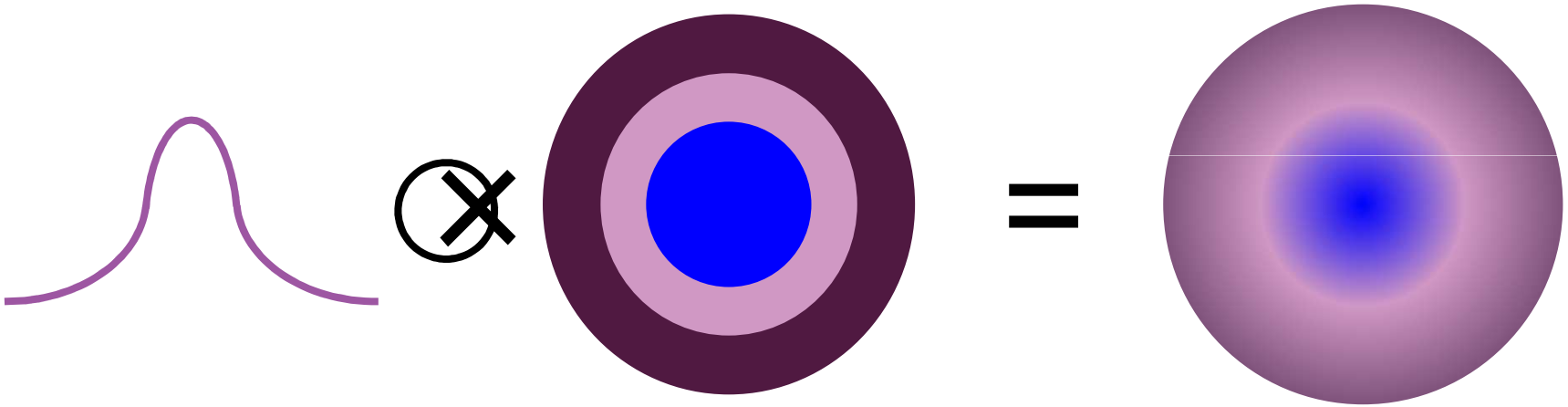
It's all about probabilities

- This idea assumes Normal Distributions!

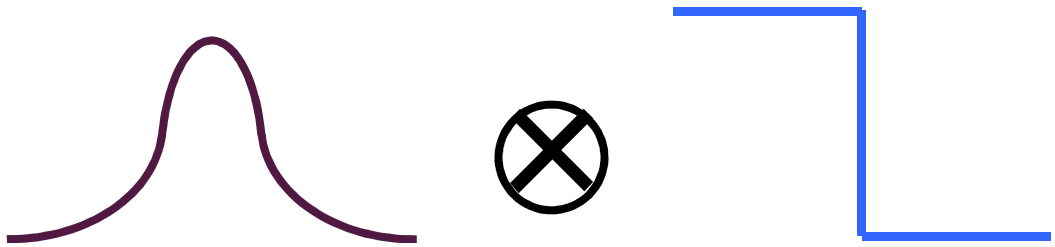


The “blurring” part: random

- “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



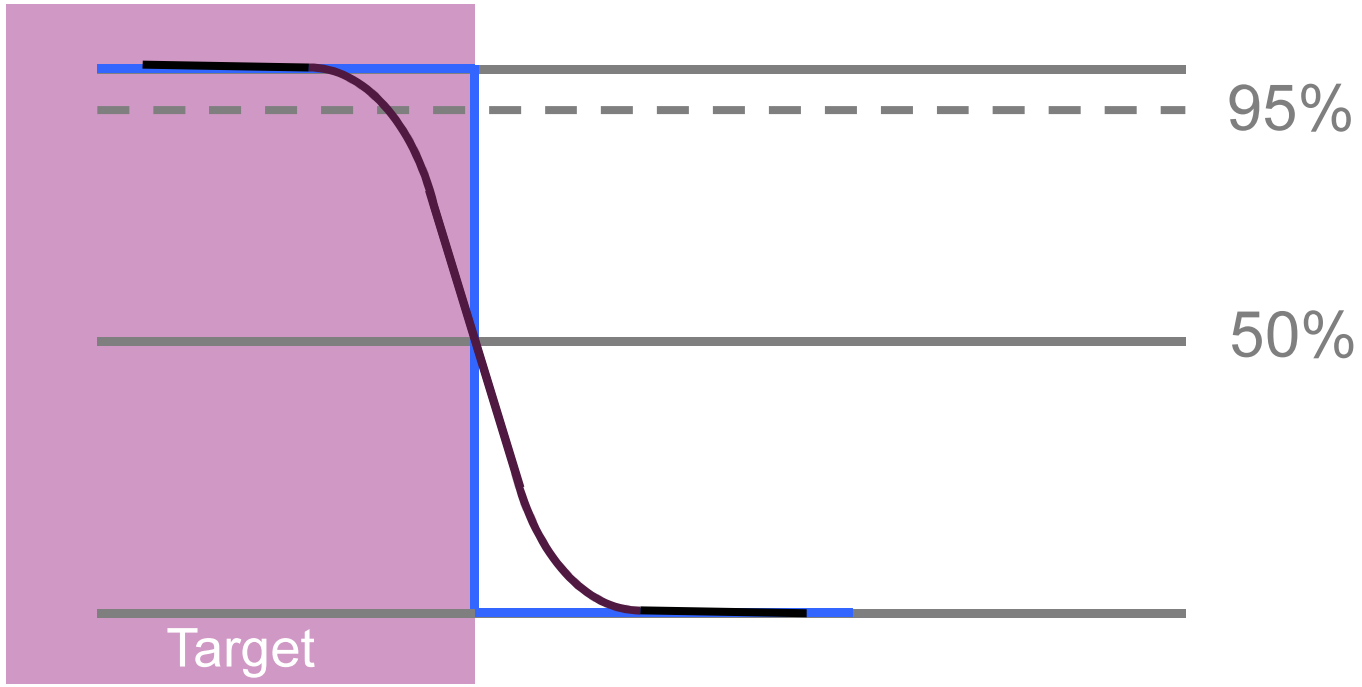
The “blurring” part: random



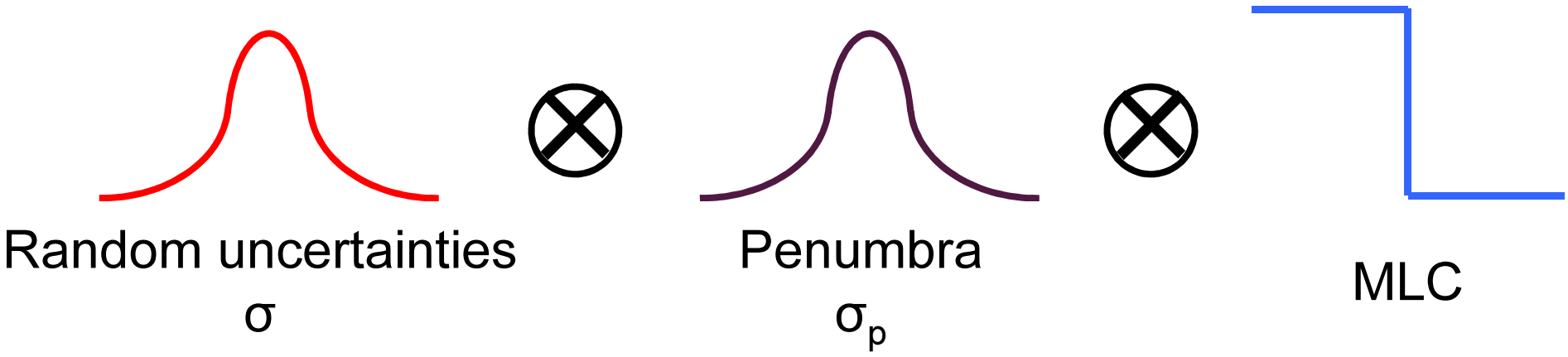
Penumbra

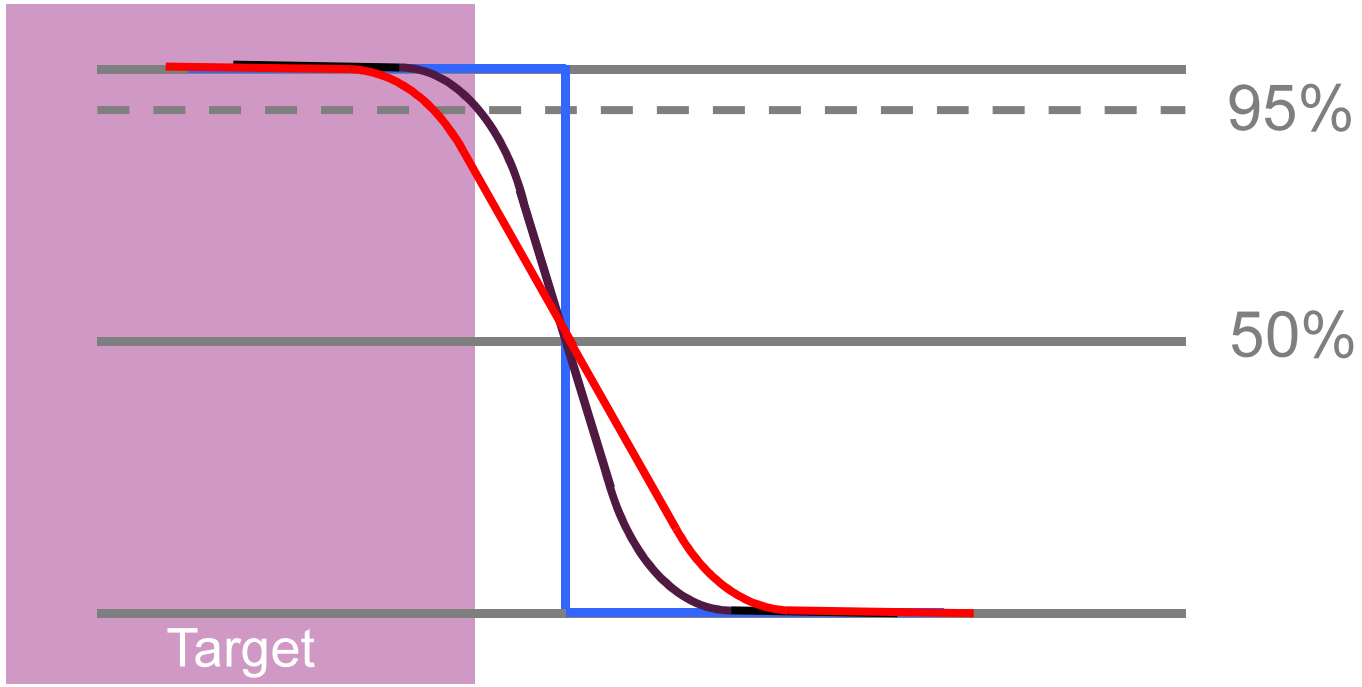
σ_p

MLC



The “blurring” part: random



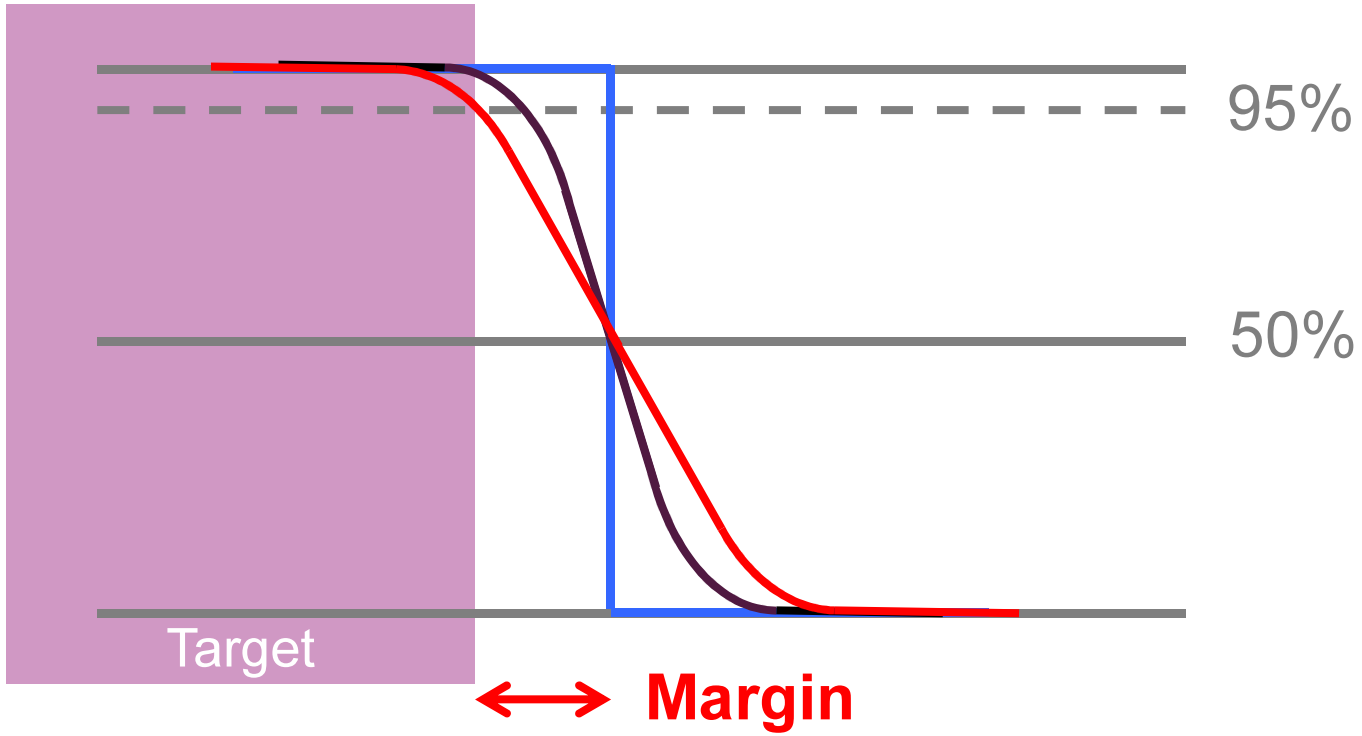


The “blurring” part: random

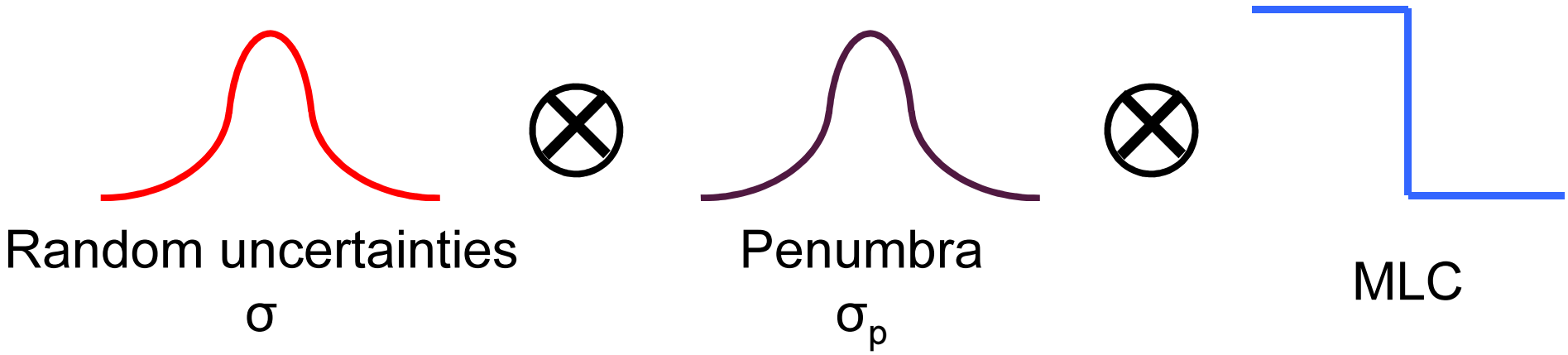
Random uncertainties
σ

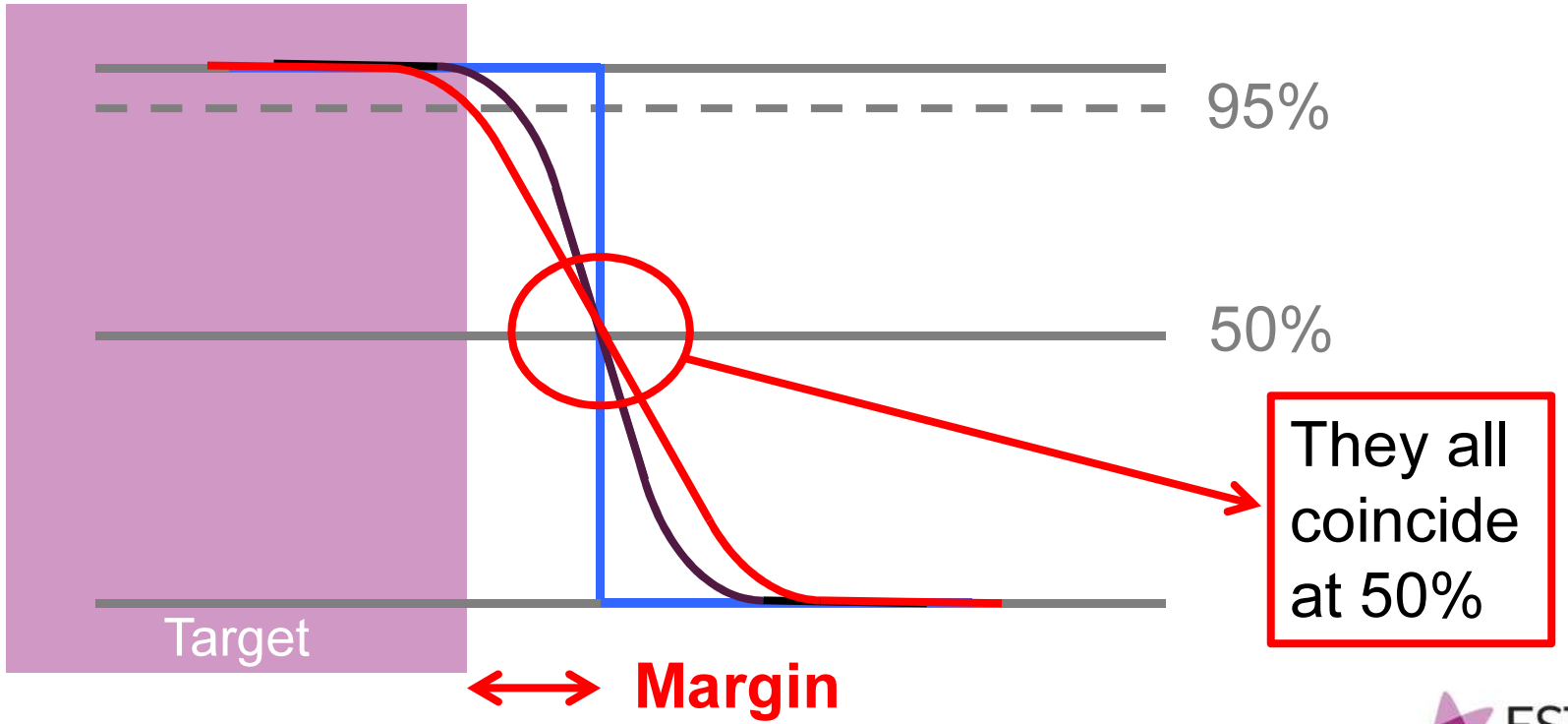
Penumbra
σ_p

MLC



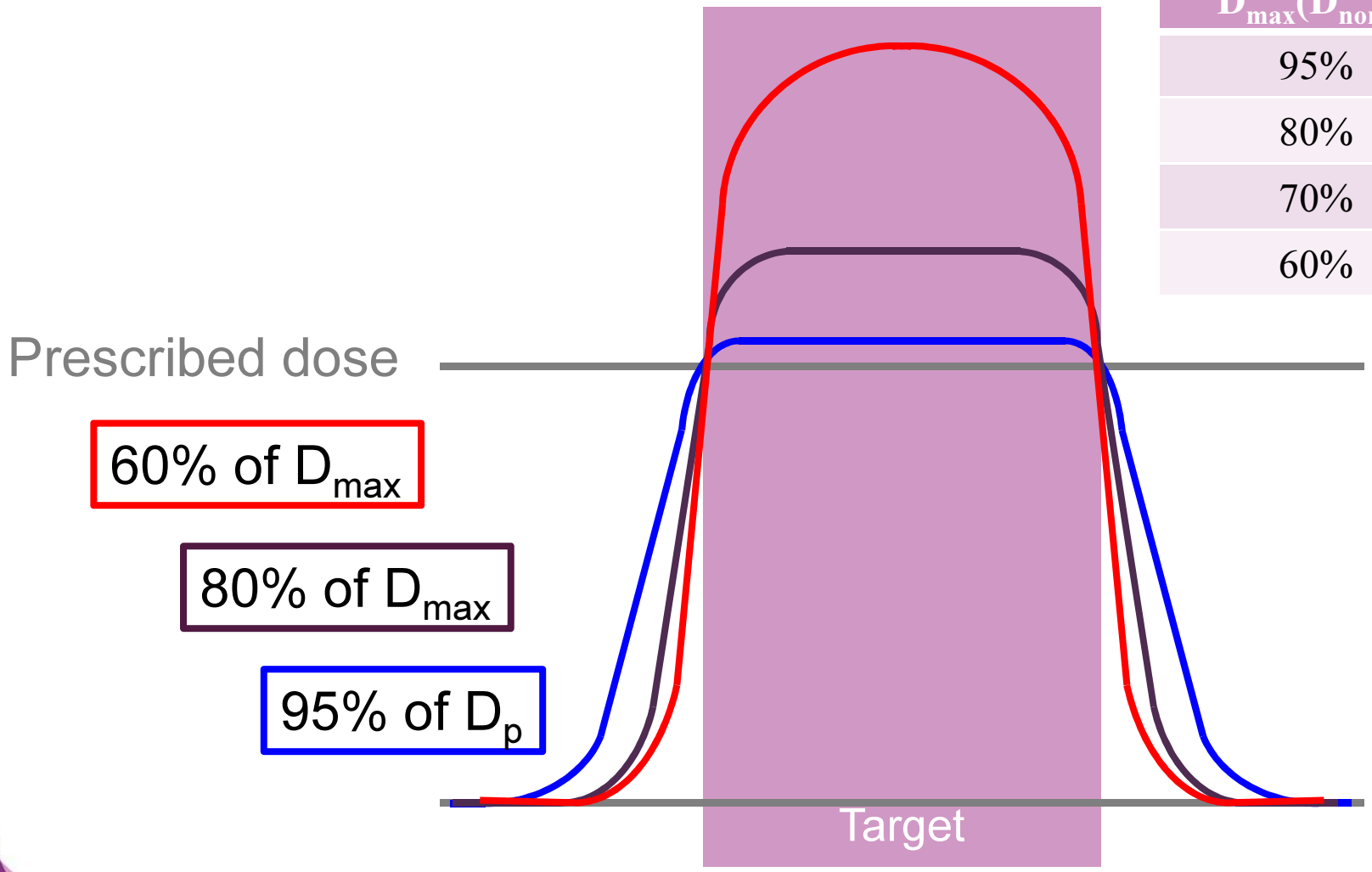
Dose prescription and margins





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

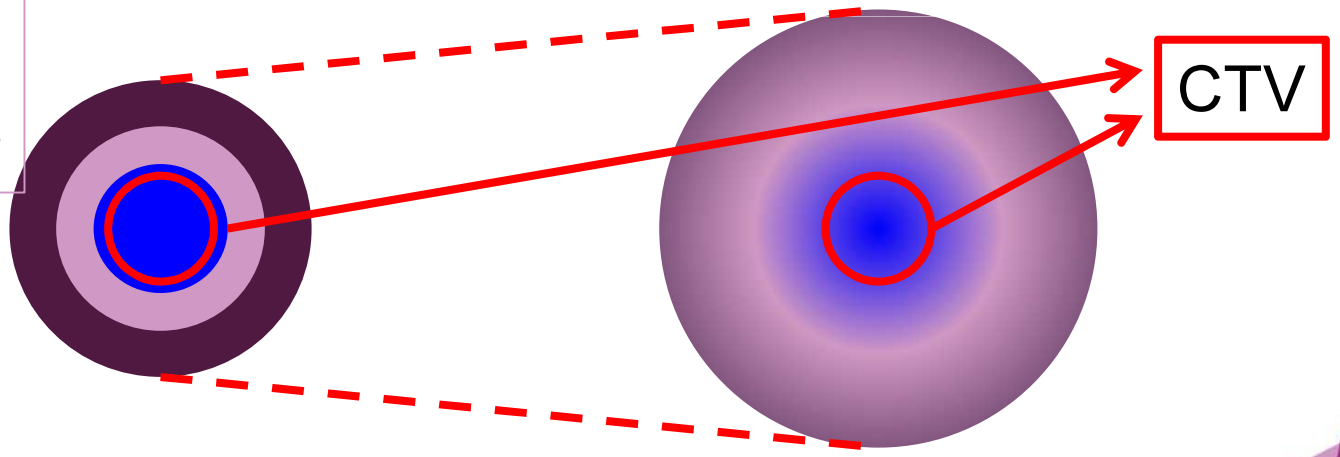
- Cumulative minimum dose to CTV ≥ 95% of prescription dose

	σ_p
Water	3.2
Lung	6.4

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

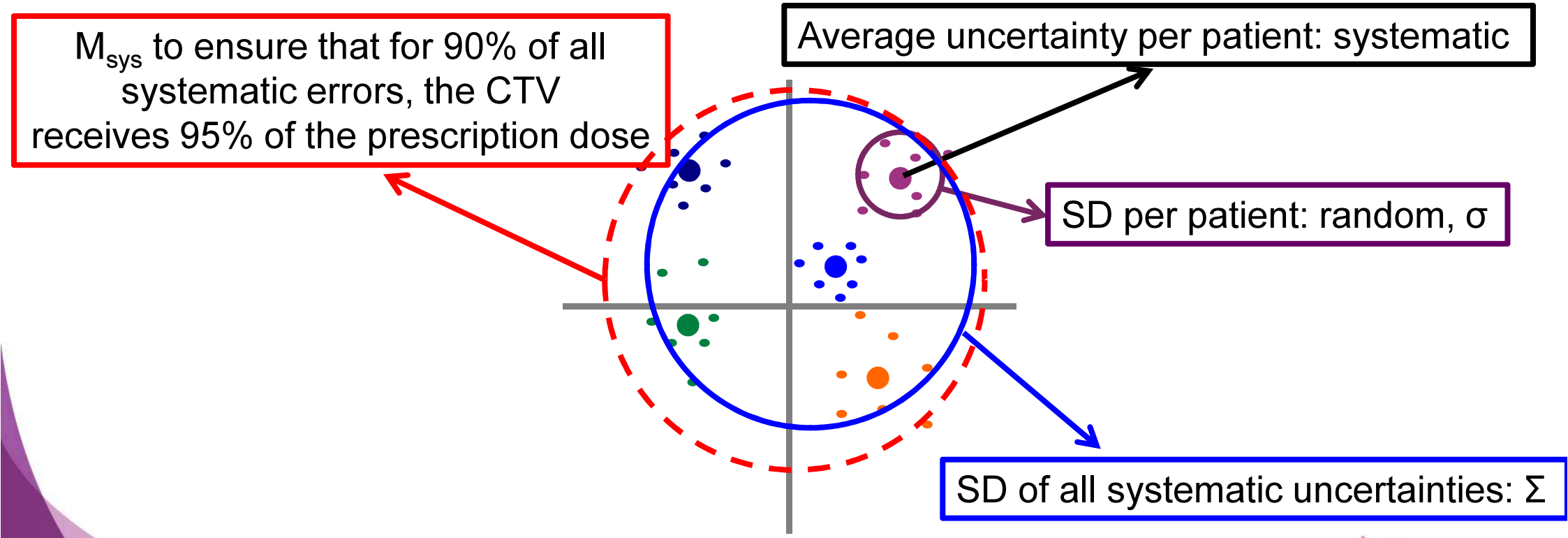
% of D_{norm}	β
95%	1.64
80%	0.84
70%	0.52
60%	0.25

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

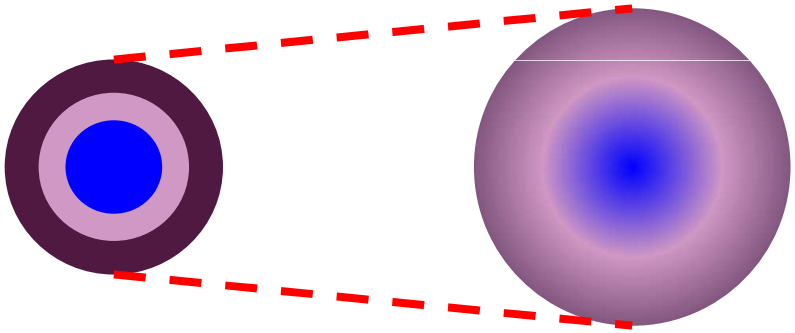
- Assuming a “spherical” target

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

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

Margins and the “van Herk recipe”

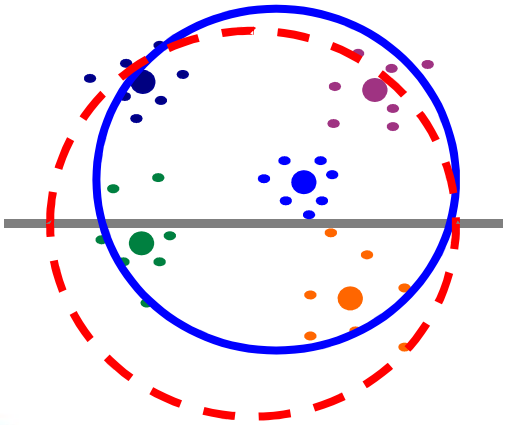
- “Blurring” part: cumulative minimum dose ≥ 95% of D_p



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

$$\beta = 1.64$$

- “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:

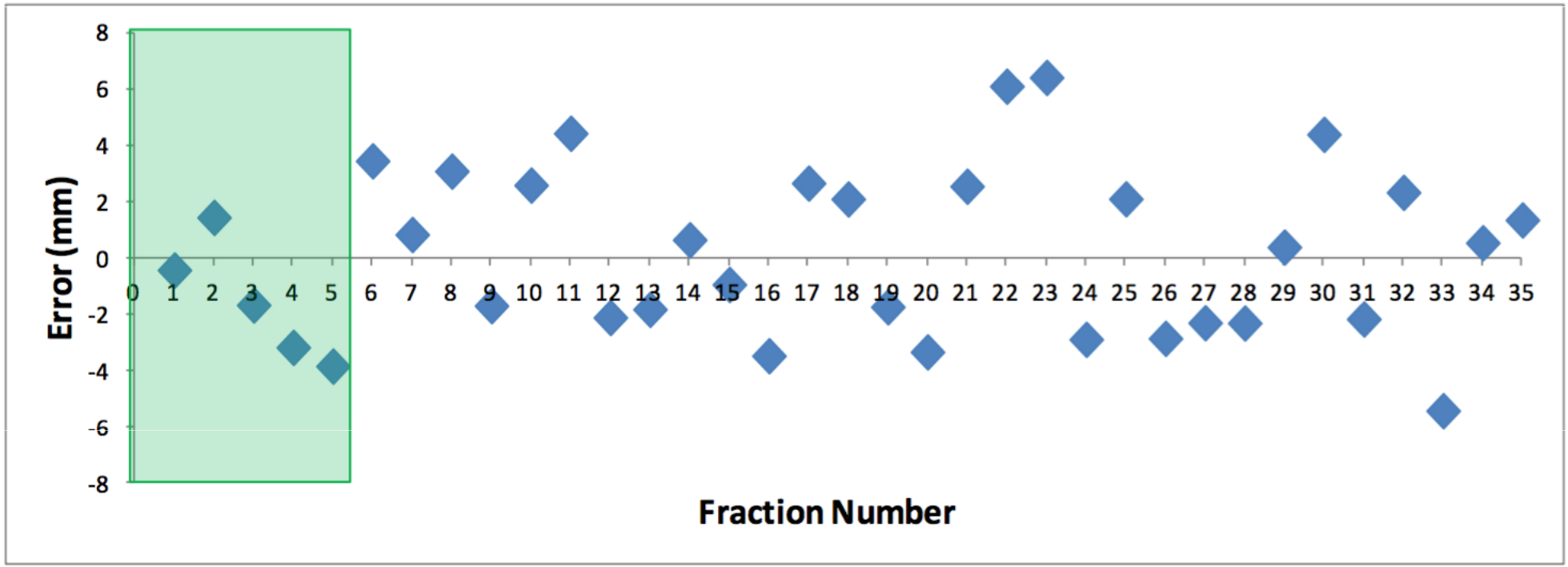
$$\Sigma = \sqrt{\Sigma_a^2 + \Sigma_b^2 + \Sigma_c^2}$$

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

  - **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)

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

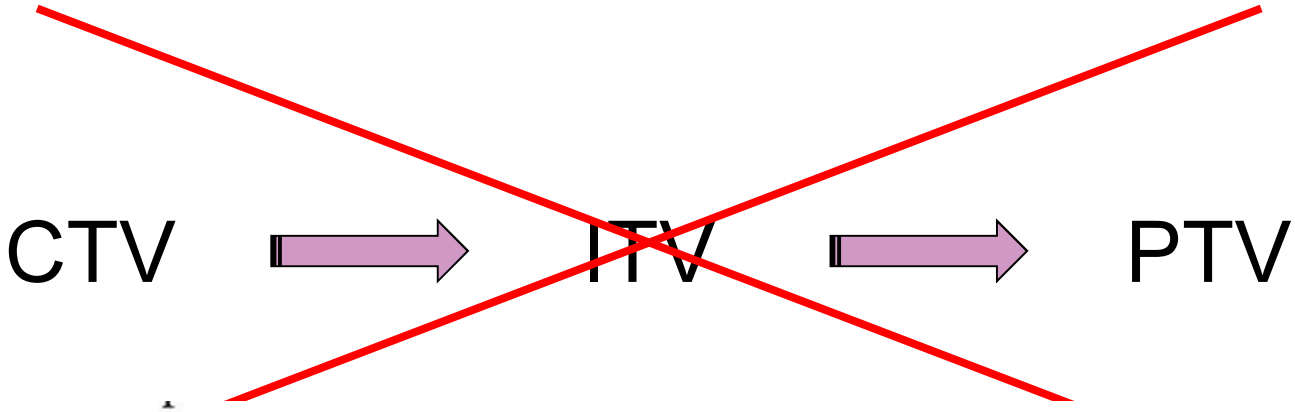
- Effective random uncertainty (blur)

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

$N \to 1$

… and motion management

- Based on the previous, it is obvious that



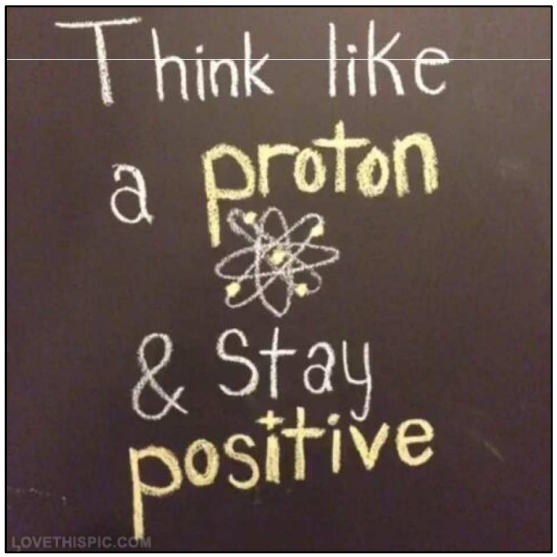
$$\mathbf{M}_{ptv} = \alpha\sqrt{(\boldsymbol{\Sigma}^2{}_i + \boldsymbol{\Sigma}^2{}_e)} + \beta\sqrt{(\boldsymbol{\sigma}^2{}_i + \boldsymbol{\sigma}^2{}_e + \boldsymbol{\sigma}^2{}_p)} - \beta\boldsymbol{\sigma}_p, \quad (13)$$

- 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):

	Pat 1	Pat 2	…	Pat 10
Fraction 1				
Fraction 2				
…				
Fraction 3				
Average				
SD				

SD (averages) = $\Sigma_{intrafr}$ = -0.52mm

average (SD) = $\sigma_{intrafr}$ = 1.99mm

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	

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

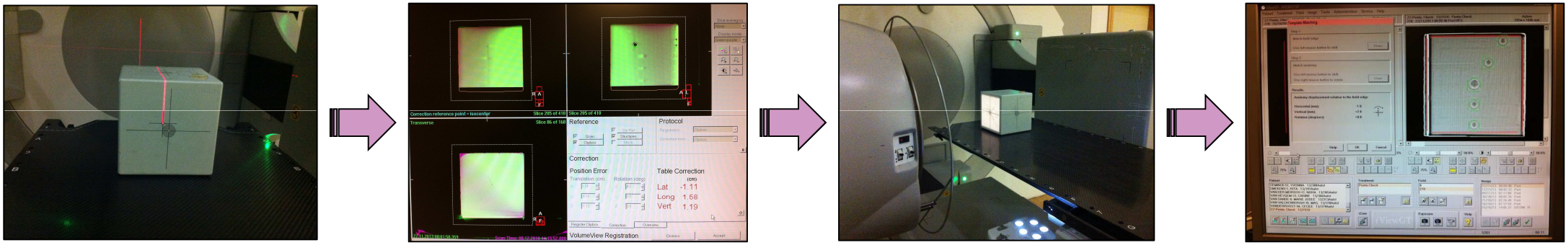
α=2.5
β=1.64

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)

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.

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

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)

Margin reduction …

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

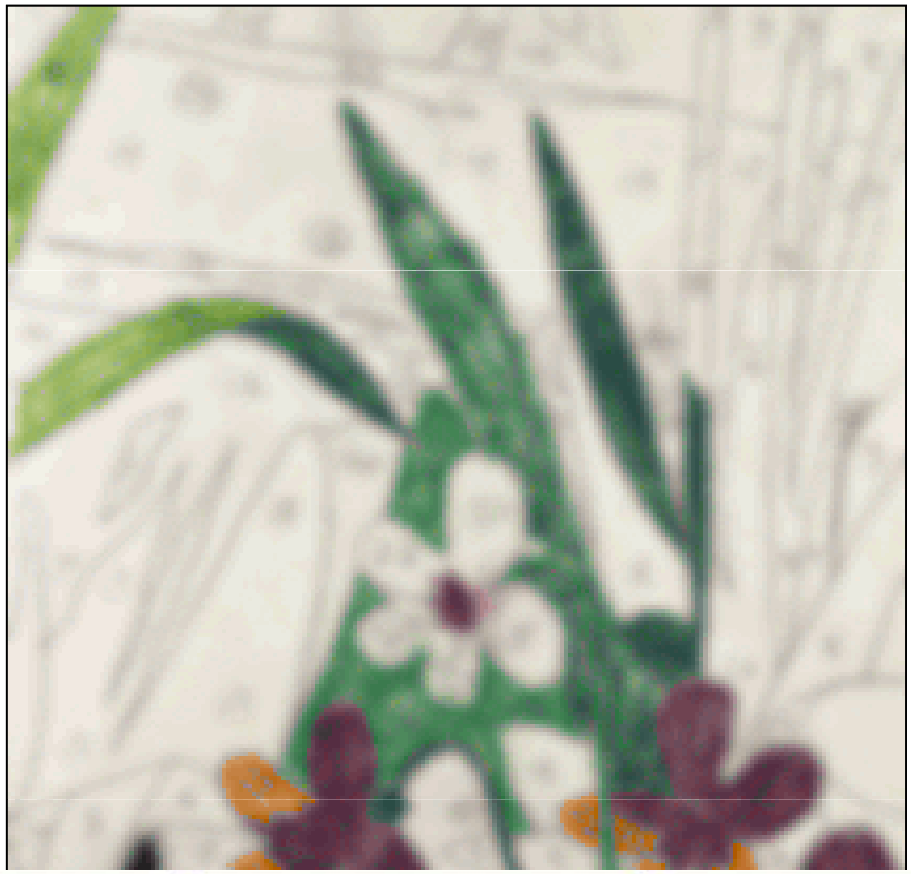
margin recipes are still a necessity,
especially to cope with uncertainty in CTV

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

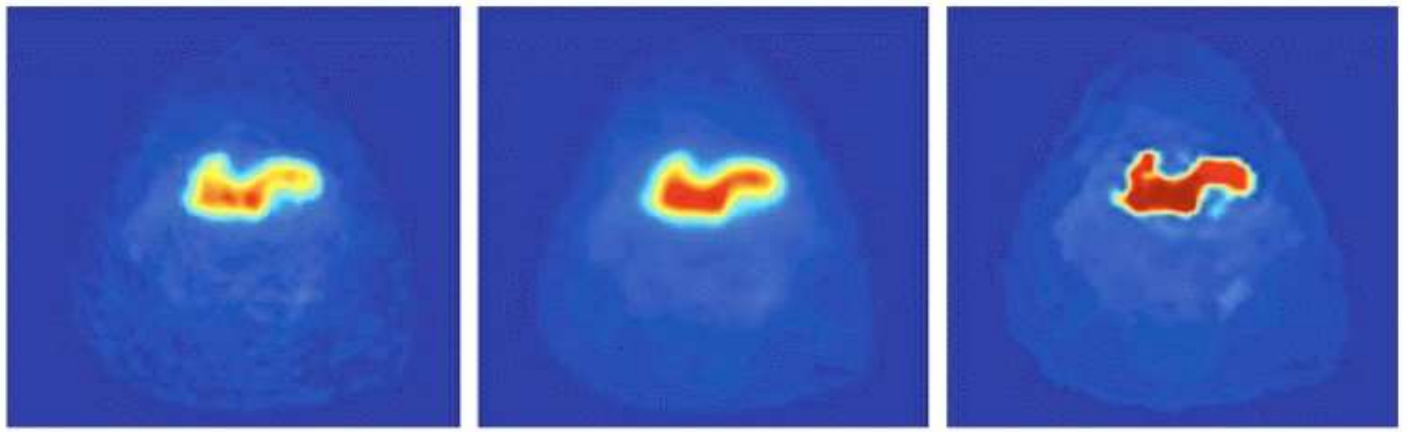
Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distened rectum on the planning CT in spite of image guidance by implanted markers.

Int J Radiat Oncol Biol Phys 2009

Dose painting by numbers …

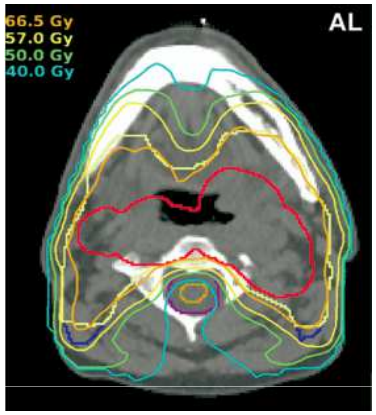


Courtesy
X. Geets

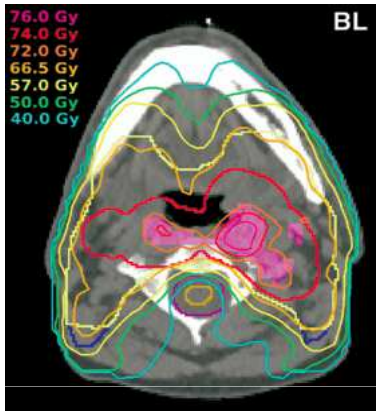


Dose painting by numbers …

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



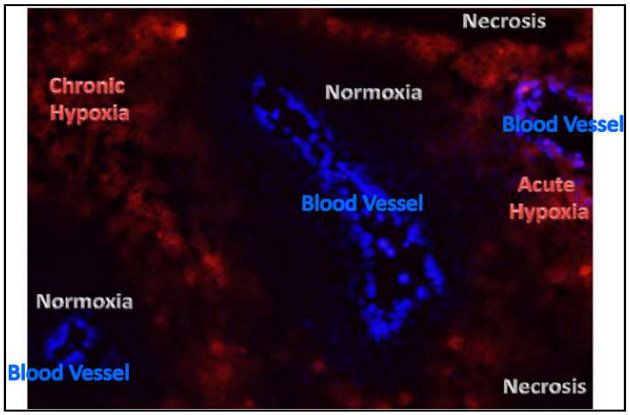
"conventional IMRT"
or
dose sculpting

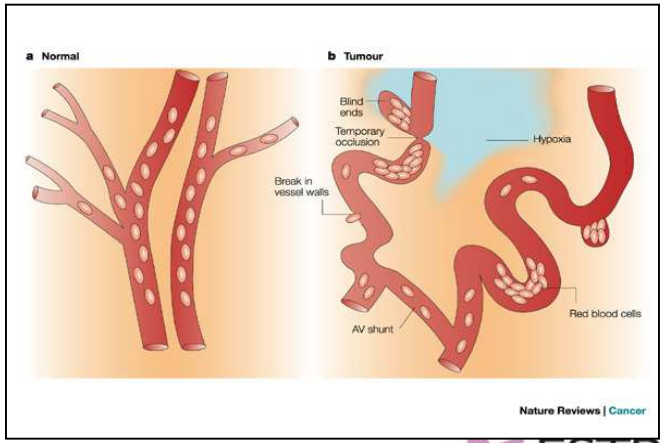


Dose escalation
based on
FDG-PET

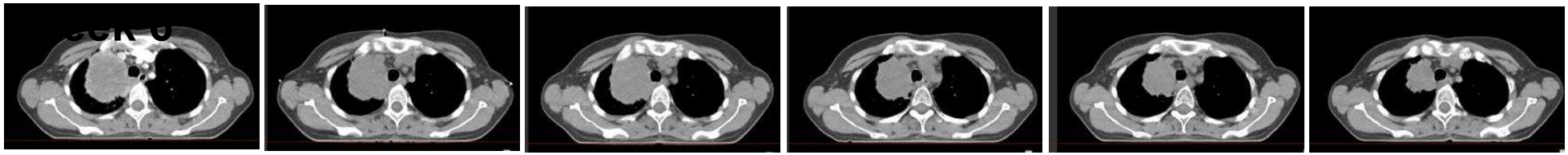
Dose-painting
Based on
Dynamic F-MISO

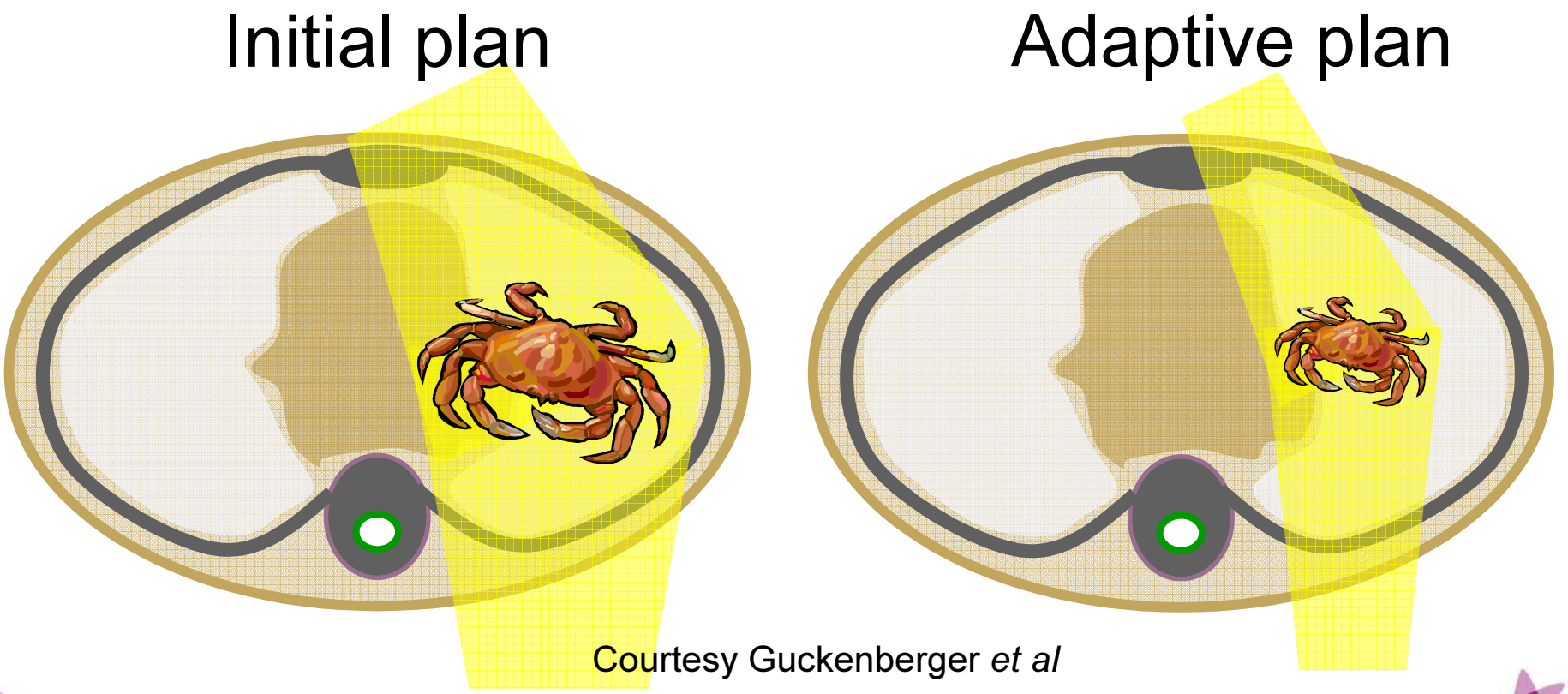
Courtesy Thorwarth *et al.*





Adaptive radiotherapy …



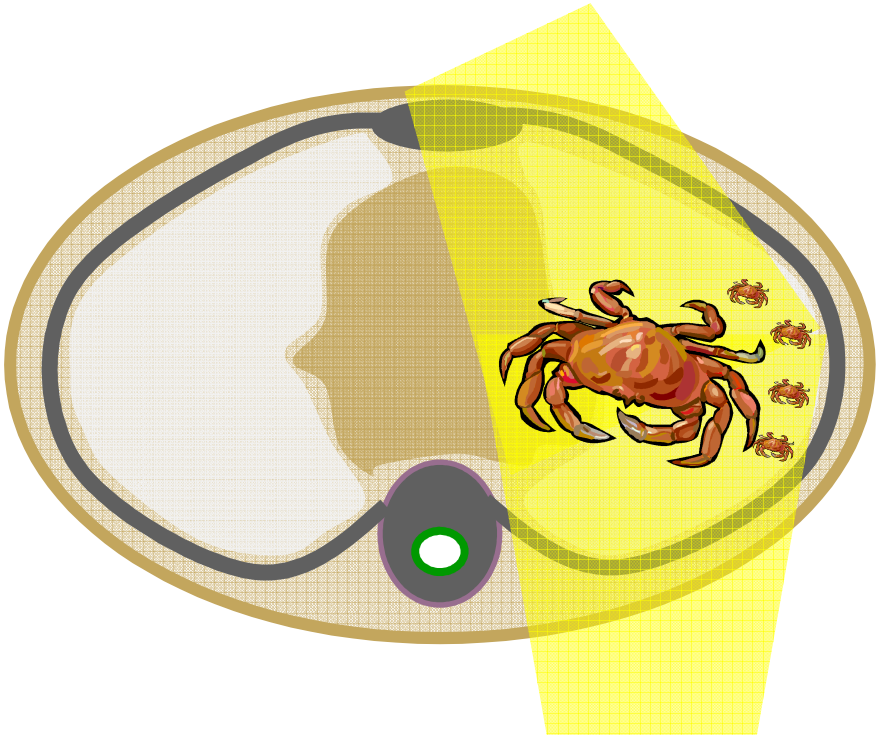


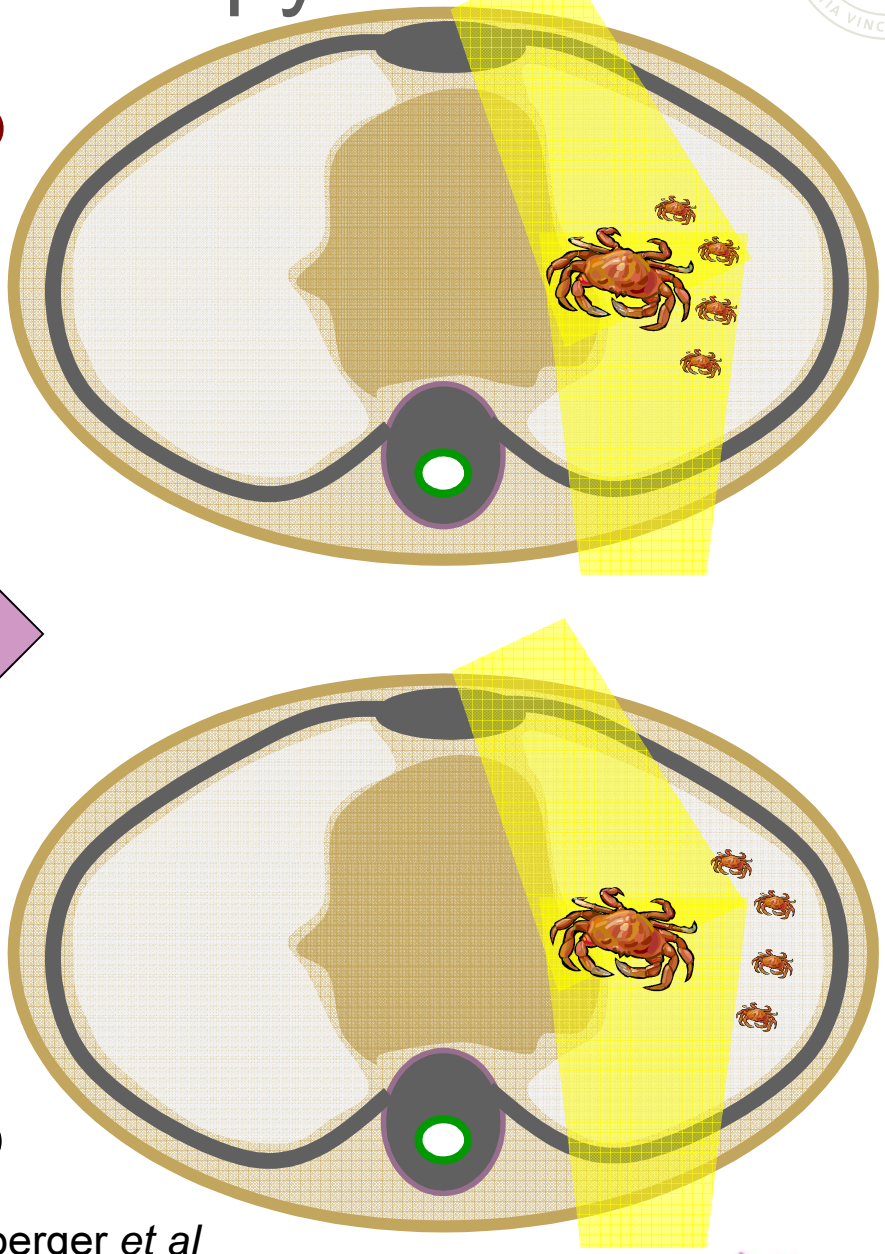
Courtesy Guckenberger *et al*

Adaptive radiotherapy …

Best case scenario

Initial plan



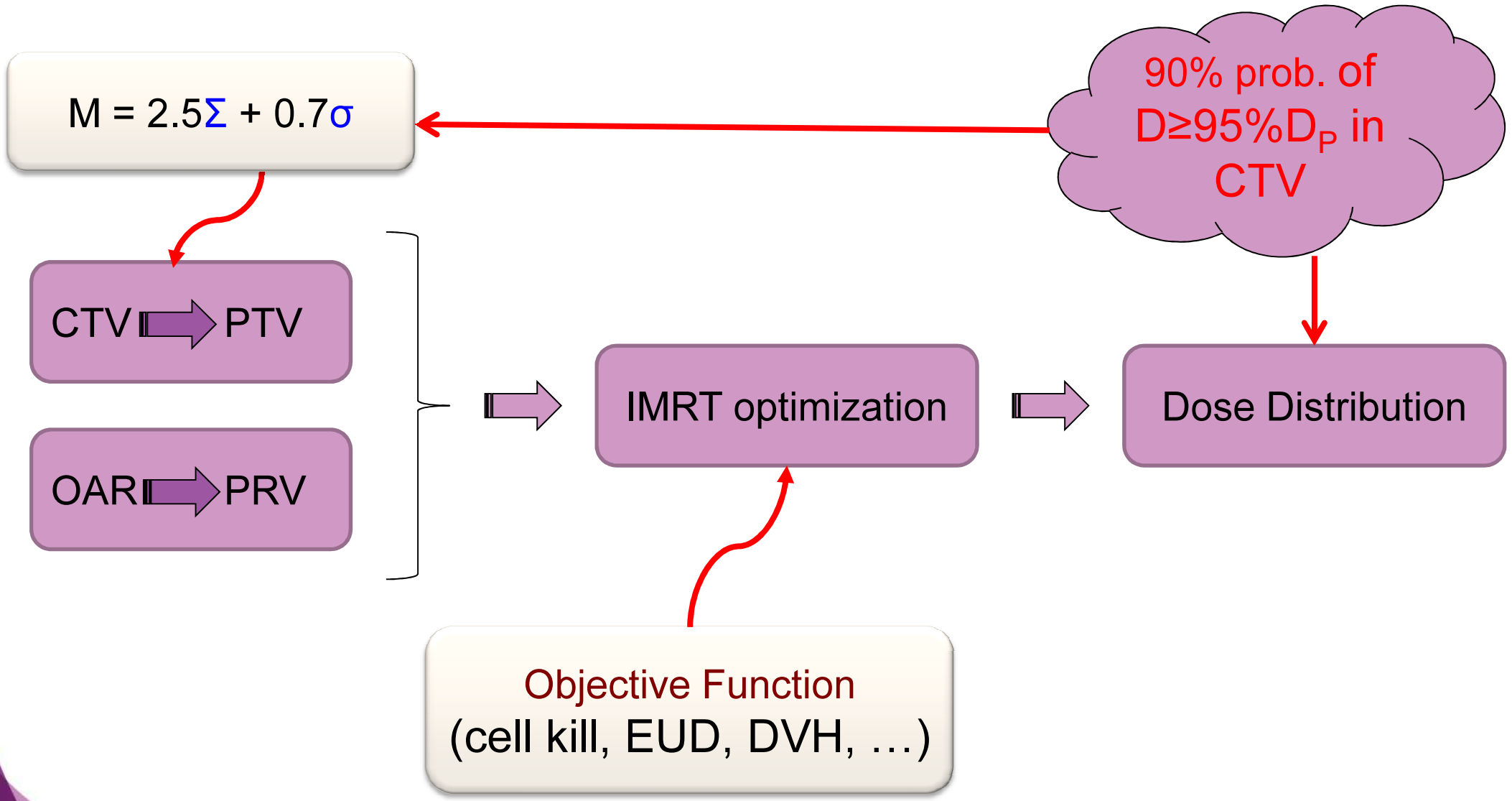


ART

Worst case scenario

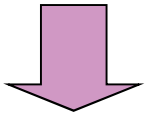
Courtesy Guckenberger *et al*

“Conventional” IMRT planning

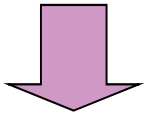


Motion compensation techniques

Knowledge on organ motion
(clinical studies, multiple CT scans, 4D CT)

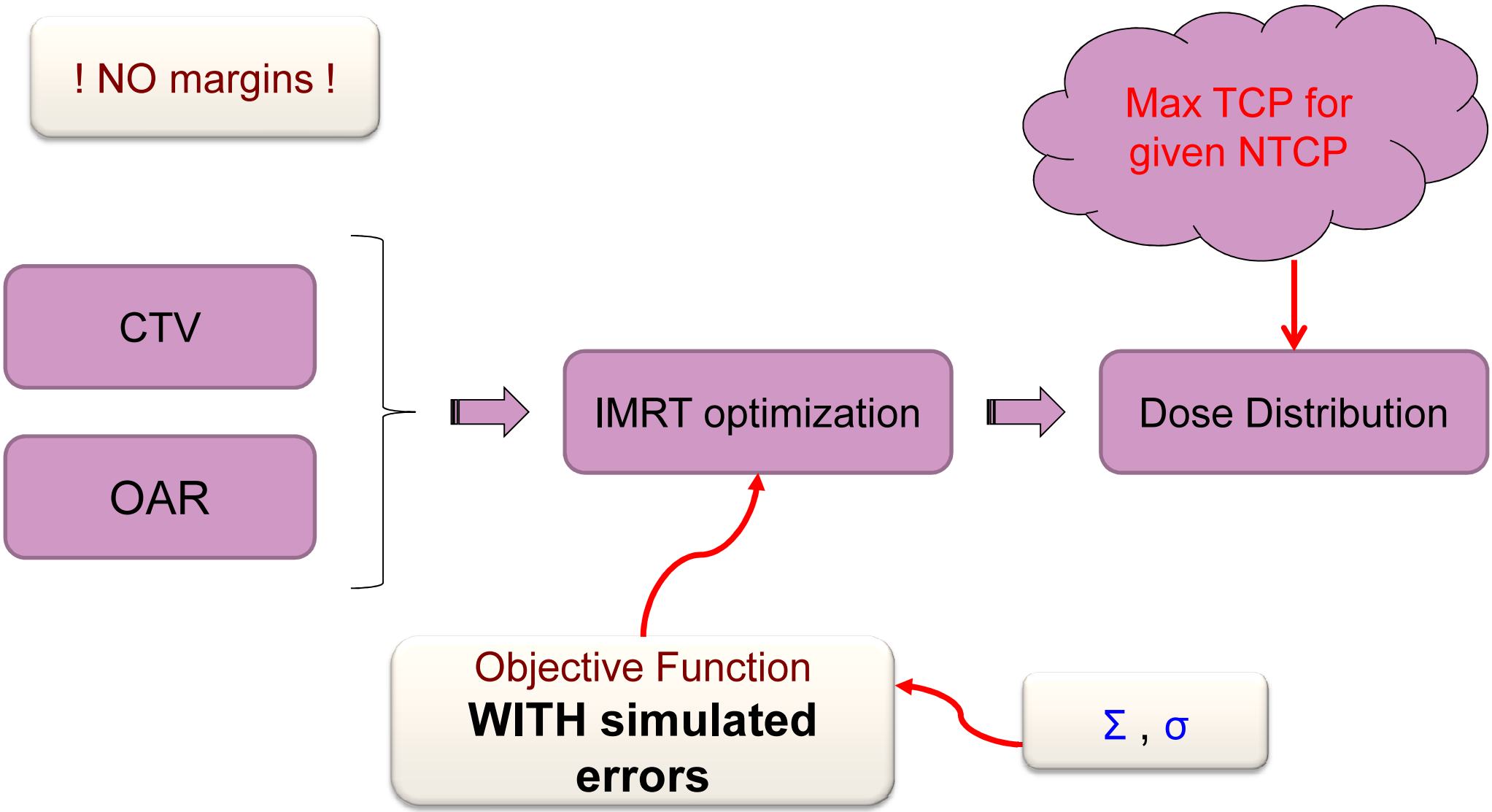


Mathematical model to describe organ motion induced geometric changes
Probability distribution of patient geometries



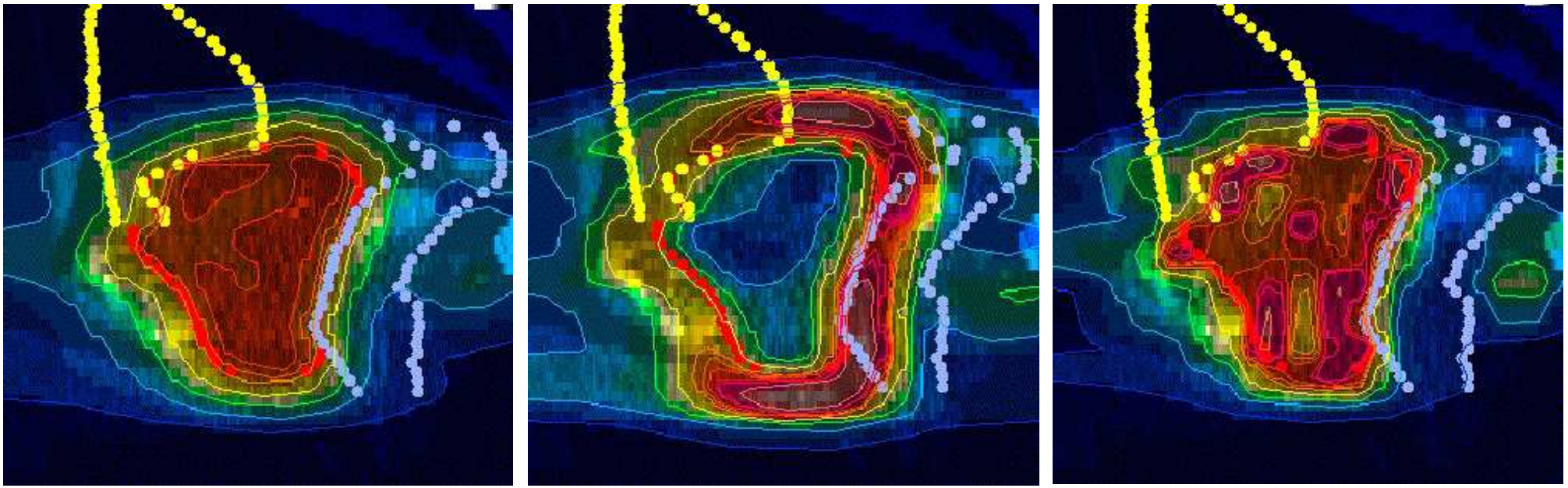
Probabilistic IMRT optimization

“Probabilistic” IMRT planning



“Probabilistic” IMRT planning

Expectation value | Dose variance per voxel | Risk, ‘static’ dose



Courtesy U. Oelfke

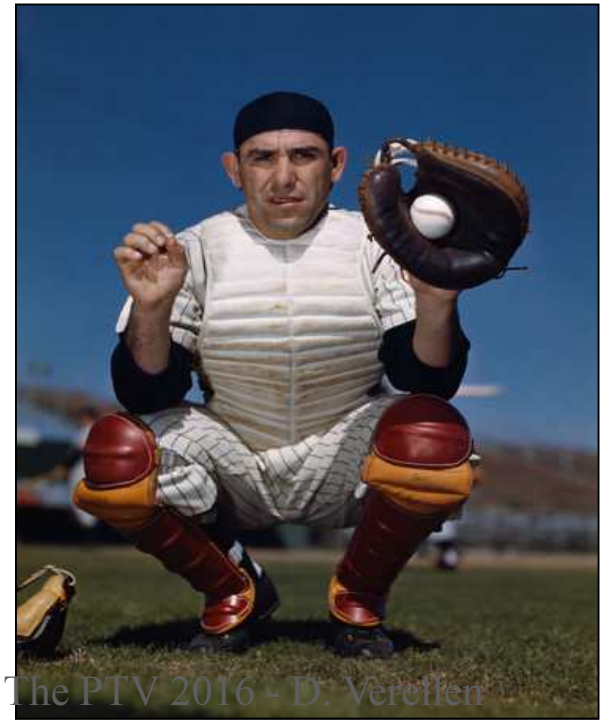
- These probabilistic approaches, require some prior knowledge of patient motion and tumor mobility, and assume a ‘reasonable’ reproducible, predictive breathing pattern

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.**"



Esophageal Cancer: How to distinguish primary from nodal recurrence by imaging

Dr Angela M Riddell

Royal Marsden, London. UK

ESTRO School

Patterns of relapse in Esophageal Cancer

- 47-58% patients treated with neoadjuvant/peroperative chemotherapy & surgery develop recurrence
- Recurrence occurs within 2-3 years of surgery
- Distant failure is more common than locoregional recurrence

Oppedijk V, van der Gaast A, van Lanschot J et al. 2014 JCO doi:10.1200/JCO.2013.51.2186
Moorcraft S, Fontana E, Cunningham D et al 2016 BMC Cancer 16:112

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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

Predictors for locoregional relapse

Multivariant analysis

- Surgery alone
- Pathological nodal stage N1
- Squamous cell carcinoma sub type

pCR (59 patients)

- 17% (10 patients) developed recurrence; 1 had isolated LRR

R1 resection

- No significant difference in LRR with R1 resection, although trend shown (36% surgery alone vs 29% CRT+S)

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)

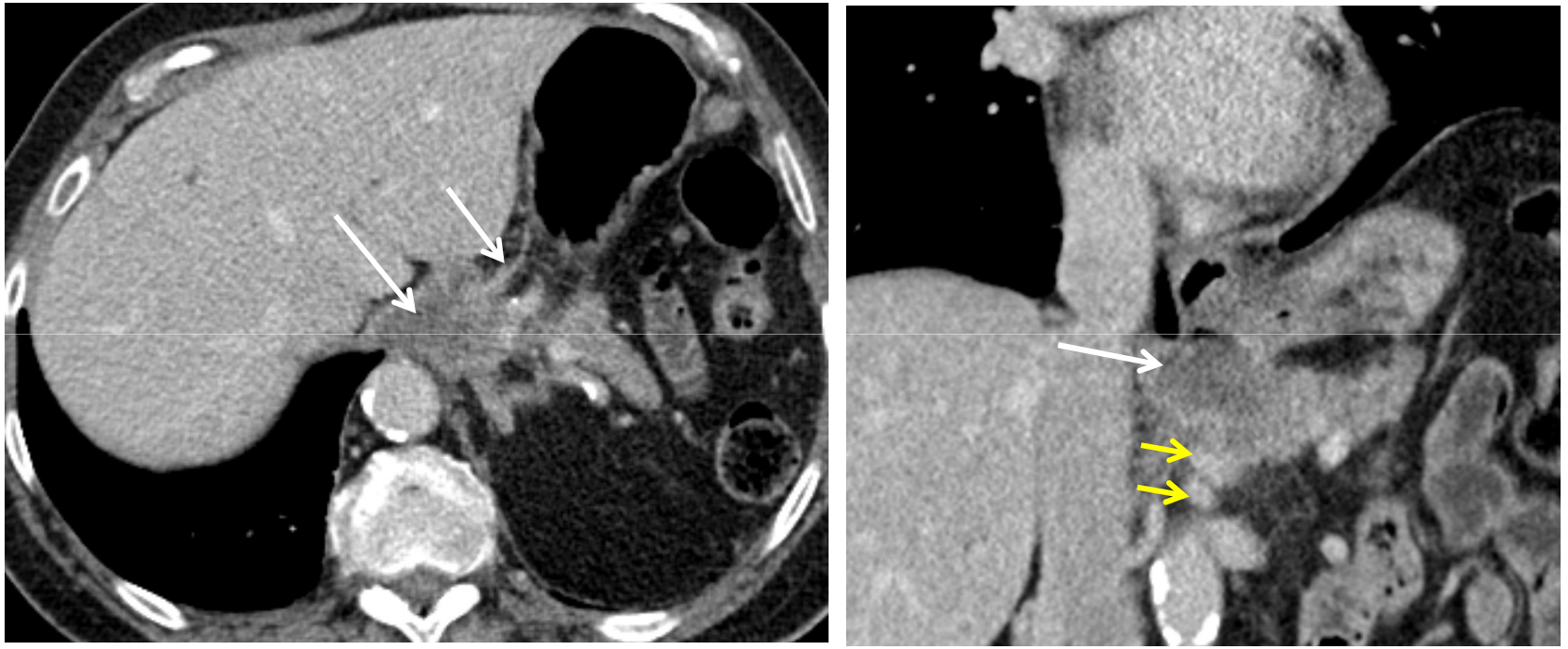
Recurrence	Infield	Outfield	Borderline	Unknown	Total
LRR only	2	2	2	1	7
Distant only	0	43	0	1	44
LRR plus distant	9	11	3	0	23
Total	11	56	5	2	74

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

Primary versus nodal relapse

81 female. Previous CRT for SCC at 31cm

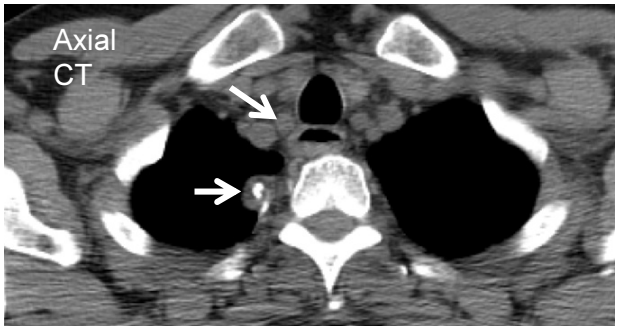


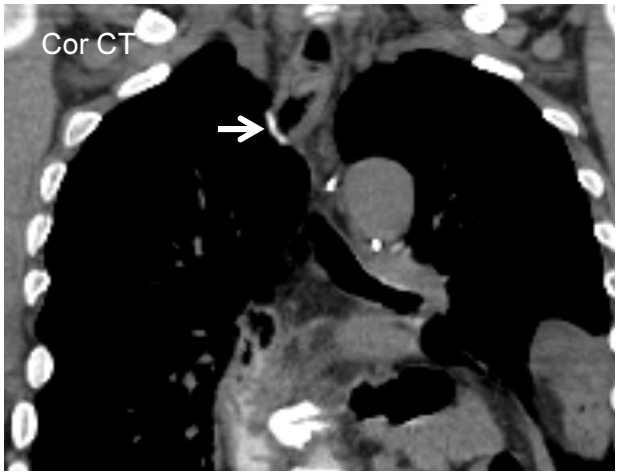
Nodal relapse centred on left gastric territory extending to coeliac (Stations 7 & 9)

Primary versus nodal relapse

69 year old male diagnosed with adenocarcinoma in 2008. Underwent perioperative chemotherapy & surgery (Ivor Lewis)

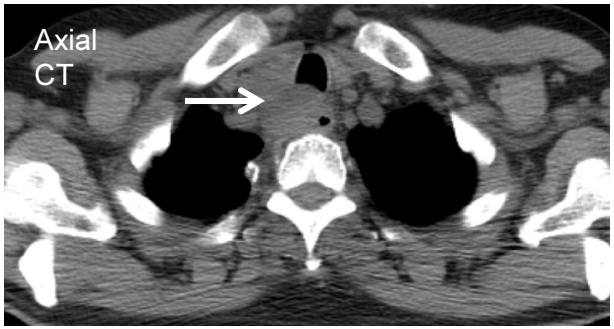
25.02.2010

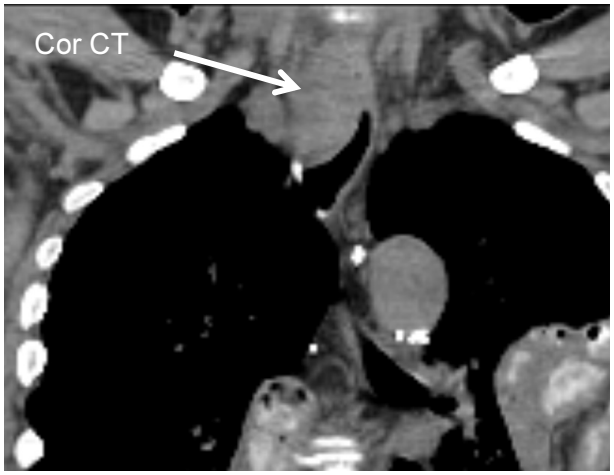




Baseline post op

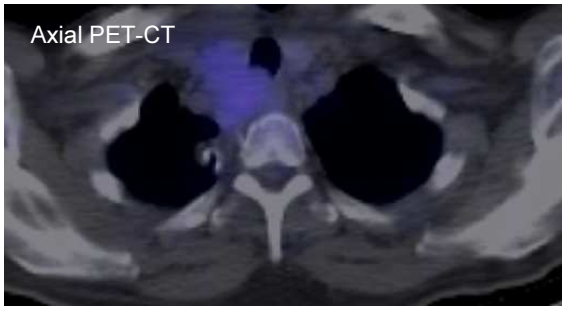
11.07.2011



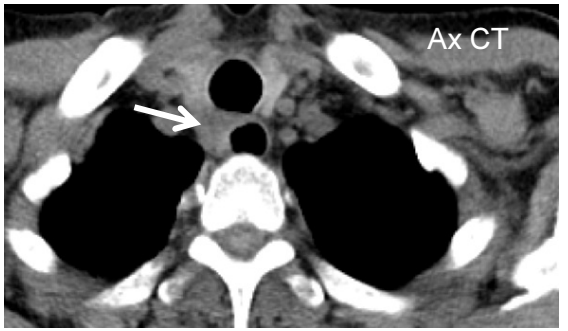


Recurrence eccentric to oesophageal anastomosis

01.07.2011



12.04.2012



Response post 8♯ chemotherapy

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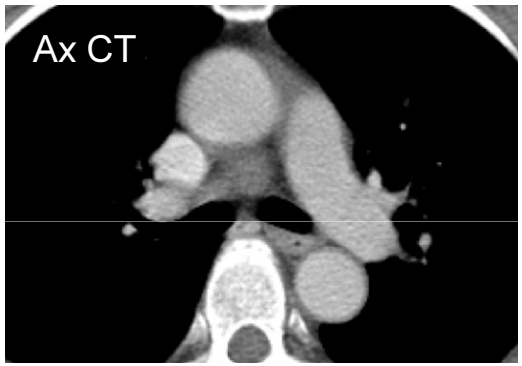
Primary versus nodal relapse

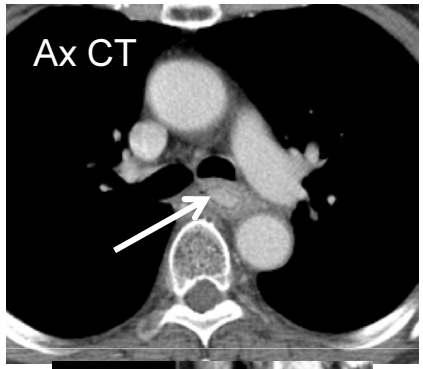
69 year old female with SCC mid oesophagus. Diagnosed March 2015 and underwent ECX & CRT; completed in August 2015

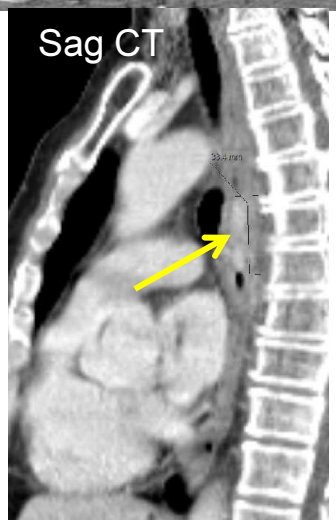
18.06.2015



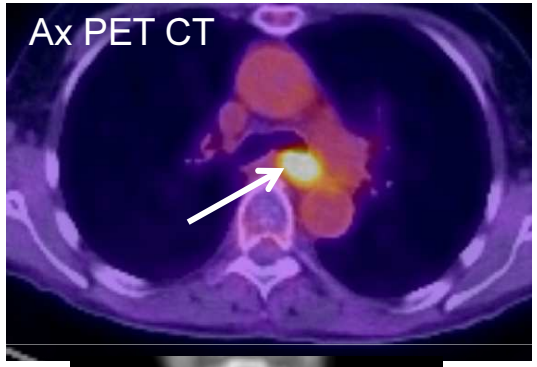
Baseline

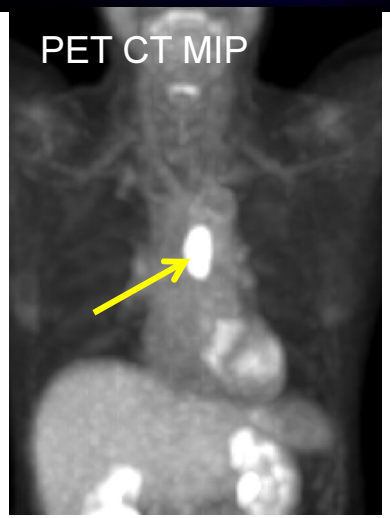
17.02.2016





18.02.2016





Relapse: epicentre in oesophageal wall.
Endoscopy biopsy positive

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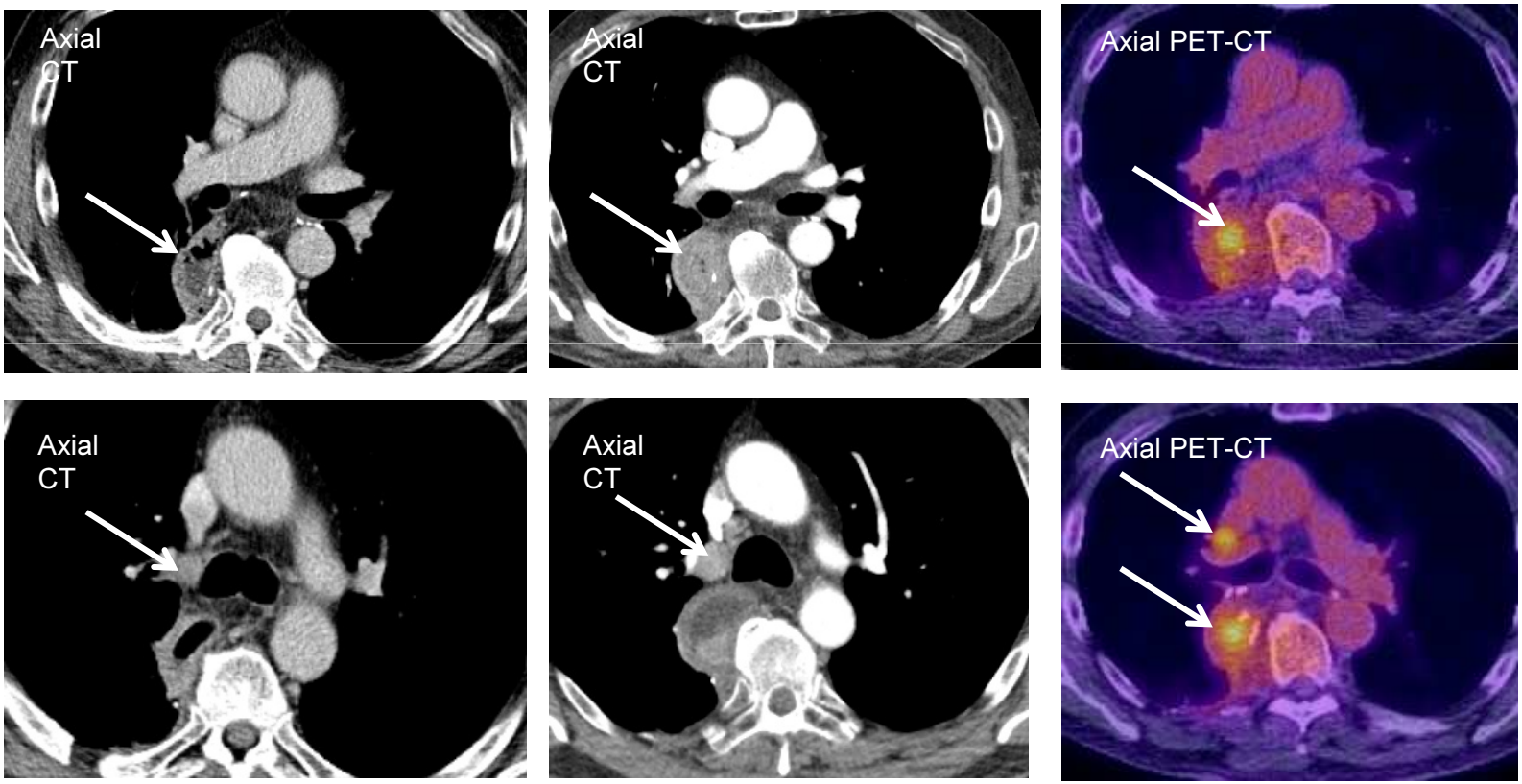
Primary versus nodal relapse

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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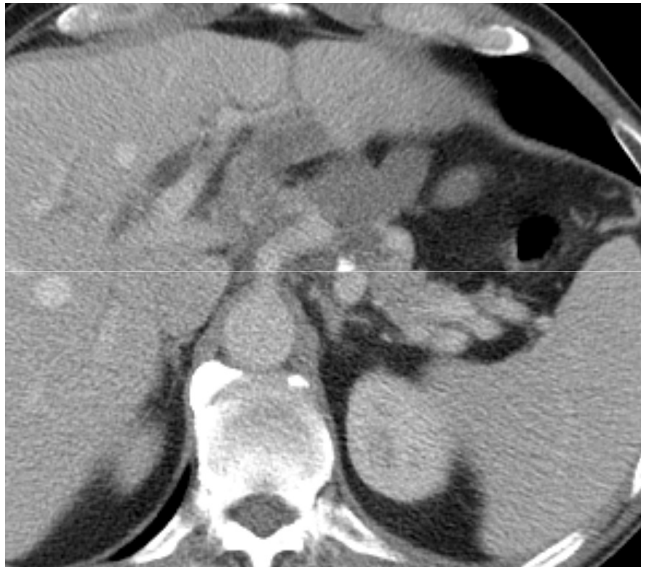
Primary versus nodal relapse

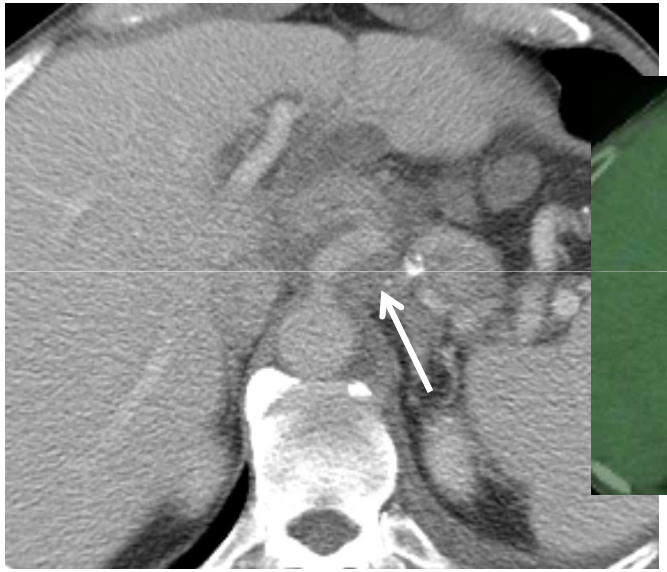
52 year old male patient T3N1 ACA of GOJ – Type II.

04.03.2009



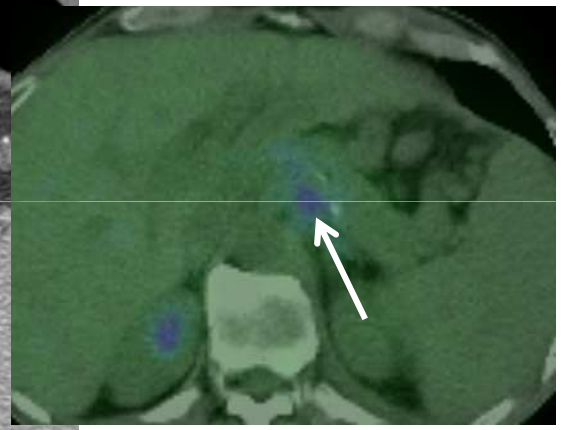
Baseline post op

17.07.2009



Increase in soft tissue adjacent to coeliac axis

28.07.2009



Area FDG avid on PET-CT

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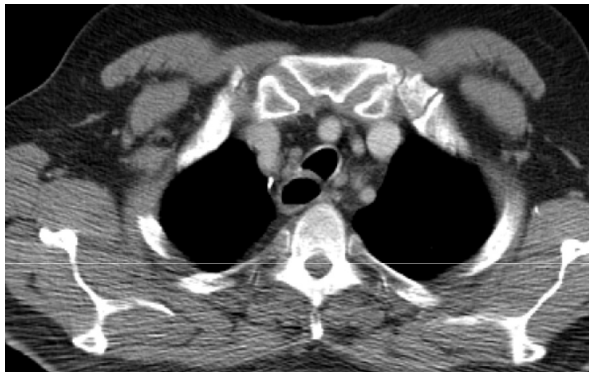
Primary versus nodal relapse

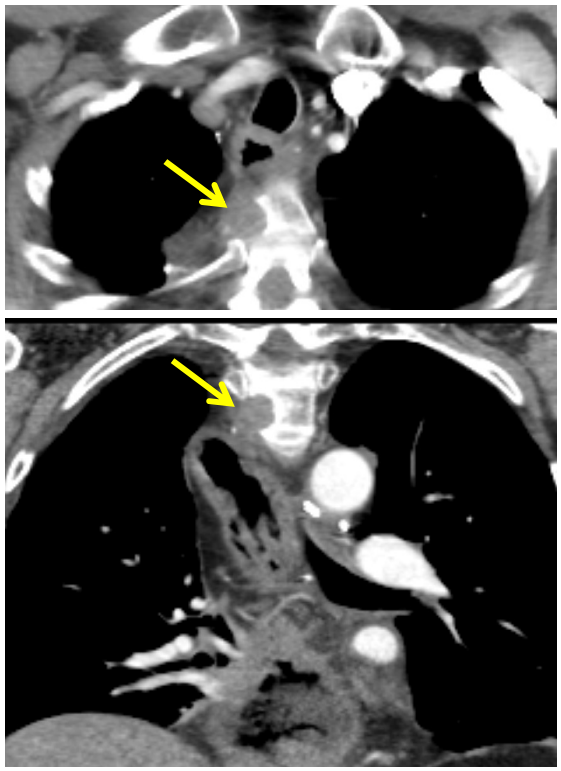
74 year old male patient underwent Ivor Lewis oesophagectomy following perioperative chemotherapy. 1 year post op he developed back pain.

30.05.2014



Baseline

08.10.2014



Bone involvement due to direct extension from LRR, not haematogenous spread

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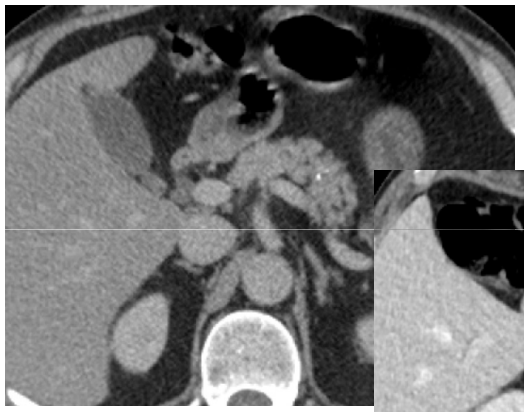
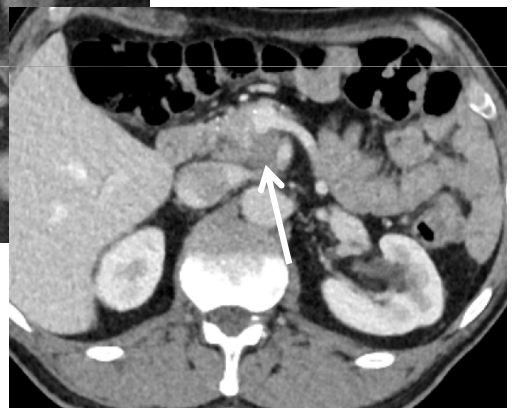
60 year old male patient. Underwent preoperative ECX x4 followed by surgery for pT3N2M0 R0 TRG4 GOJ tumour. Post op he had 54Gy in 30♯ completed Feb 2015. Presented with rectal bleeding

10.02.2014



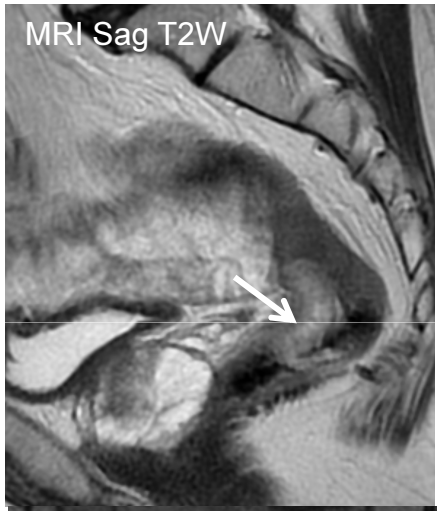
Baseline

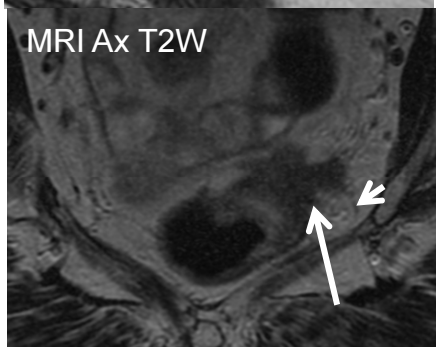
13.04.2016



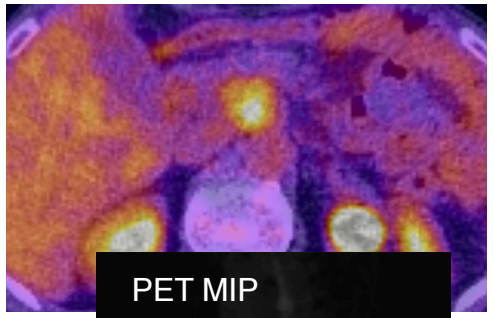
SMA Nodal relapse

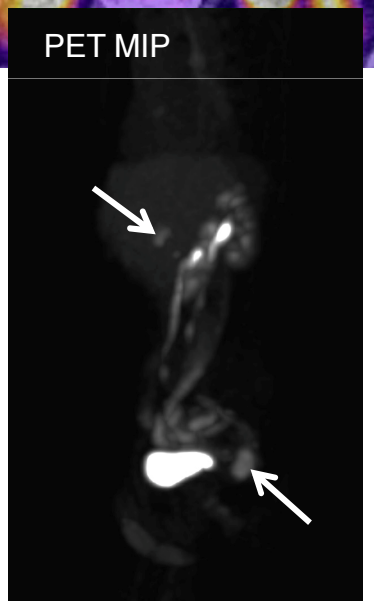
13.04.2016





24.05.2016





Biopsy showed adenocarcinoma with immunohistochemistry profile consistent with an oesophageal primary similar to original primary

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Primary versus nodal relapse

Summary

- Nodal relapse may be adjacent to the anastomosis or separate
- When separate from primary, can readily confirm nodal relapse.
- Multiple imaging investigations can identify regional lymph node involvement.
- When relapse is adjacent to the anastomosis determine the epicentre of the soft tissue
- Local relapse centred on the wall
- Nodal relapse often eccentric
- It may not be possible to differentiate primary from nodal relapse
- The two may co-exist

Thank you

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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			

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

Histological Subtype

Histology	Local	Regional	Distant
Adenocarcinoma	23%	23%	55%
Squamous Cell Carcinoma	23%	43%	34%

Predication 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 Relapse MSKCC

Symptomatic – 50%

CT – 45%

27 / 100 person years in year 1

4/100 person years in year 6

Treatment of Relapse RMH

Further treatment for recurrent disease **Yes**	**72 (72%)**
Type of treatment for recurrent disease Chemotherapy Radiotherapy Chemoradiotherapy Surgery	 63 (88%) 21 (29%) 1 (1%) 5 (7%)

Survival (Mariette)

Median survival after relapse

7 months

Oesophageal cancer

Incidence and location of local recurrences after radiotherapy

Marcel Verheij MD PhD
Department of Radiation Oncology
NKI, Amsterdam

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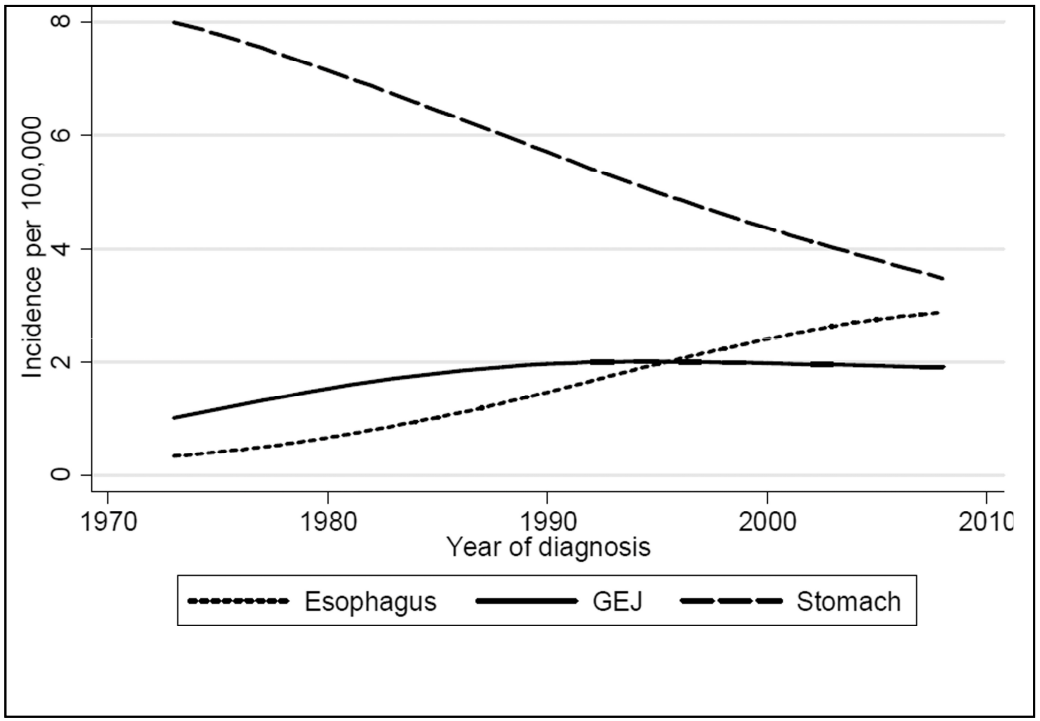
Contents

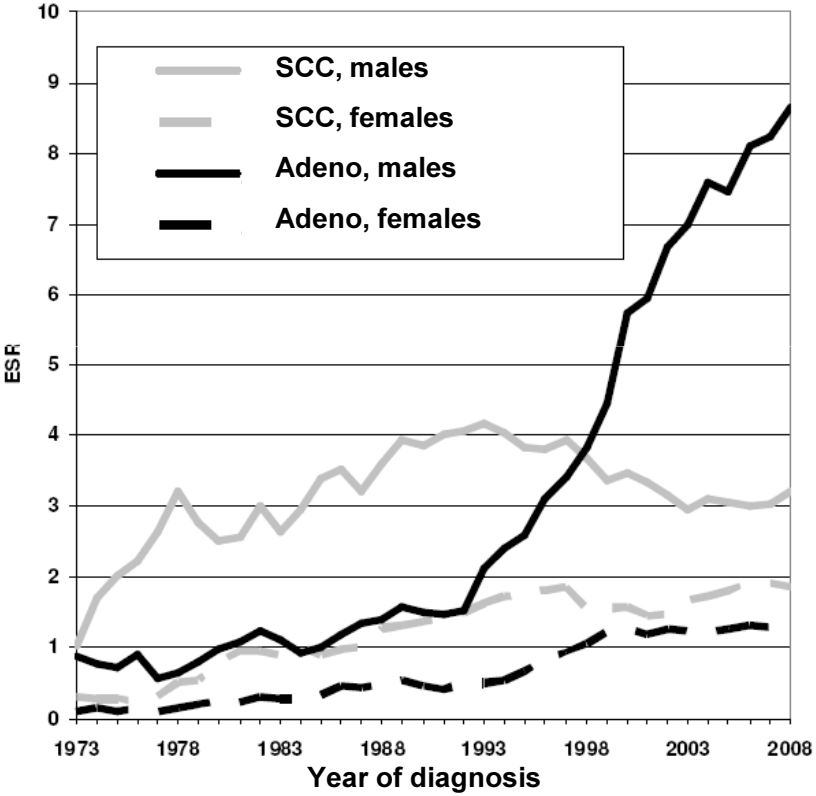
- Introduction
- Lymphatic drainage
- Patterns of failure

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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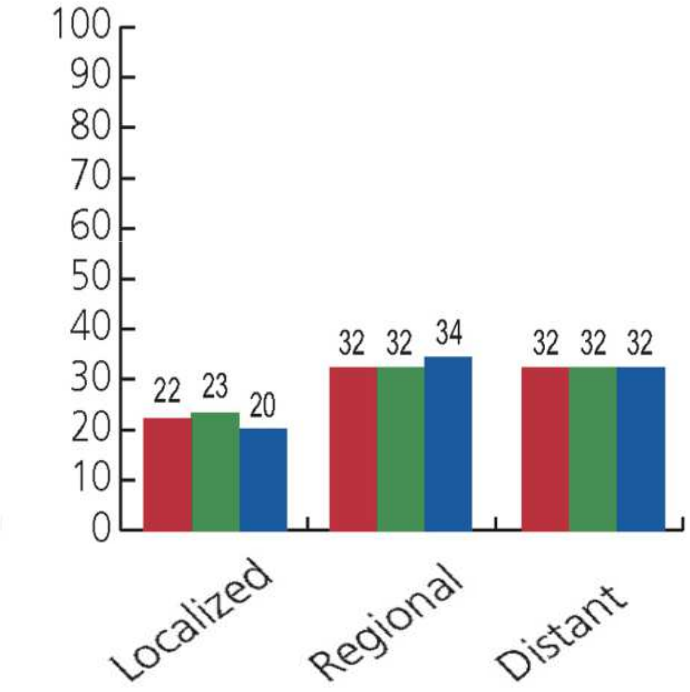
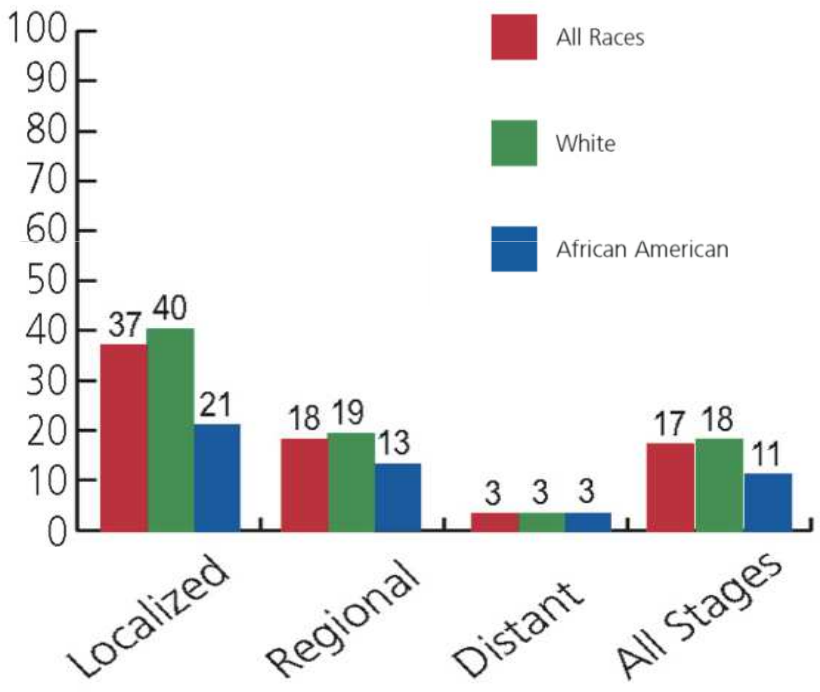
Distribution by stage at diagnosis



5-year survival by stage



Cancer Statistics 2012, CA Cancer J Clin, Jan 2012

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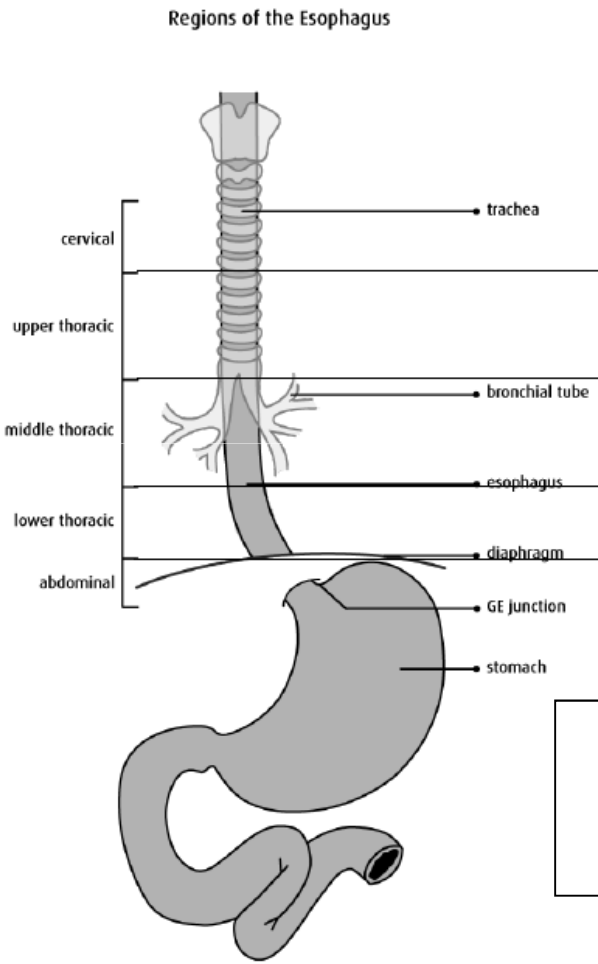
Tumor localization and histology

Cervical

Thoracic

Junction, type I ; II ; III



Endoscopy:

Thorax inlet to 25 cm from SDA

25 to 32 cm

32 to 42 cm

SCC: 50%	mid 1/3
30%	distaal 1/3
AC: >90%	distal 1/3

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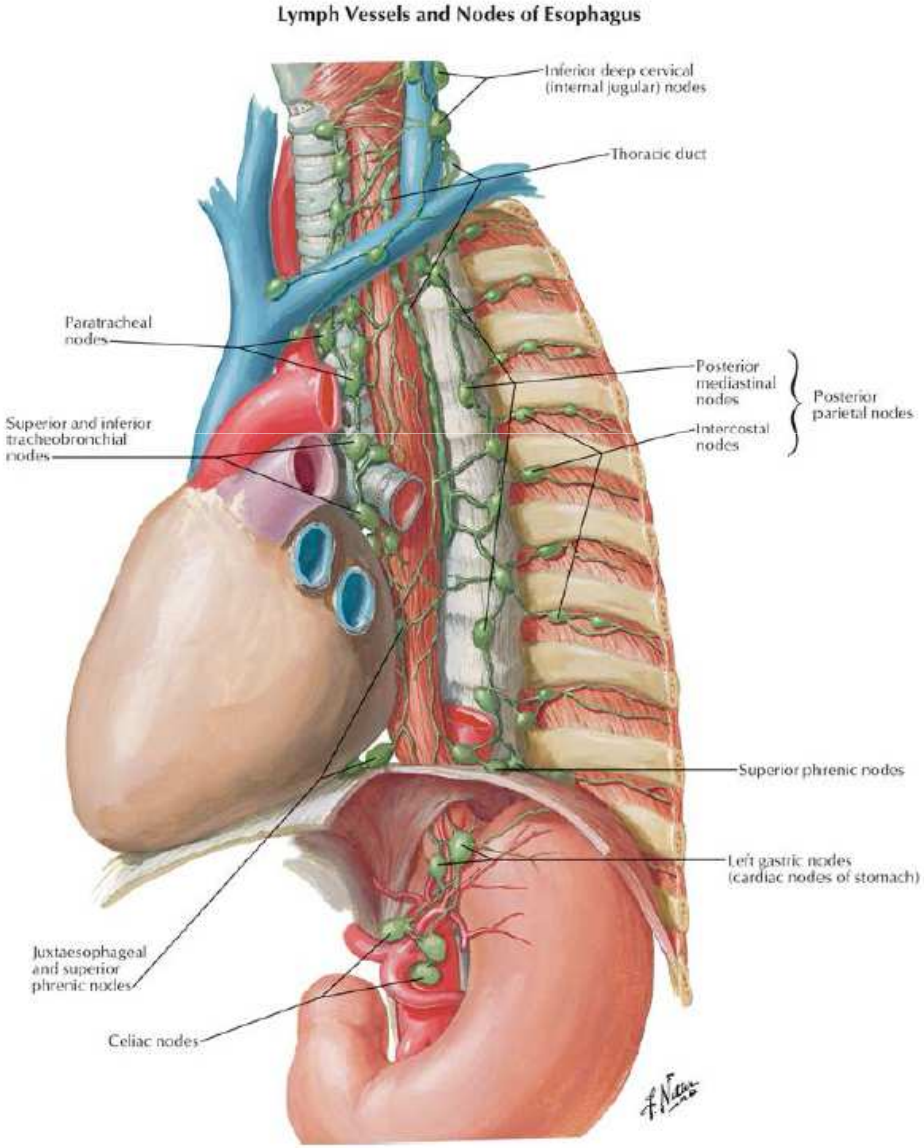
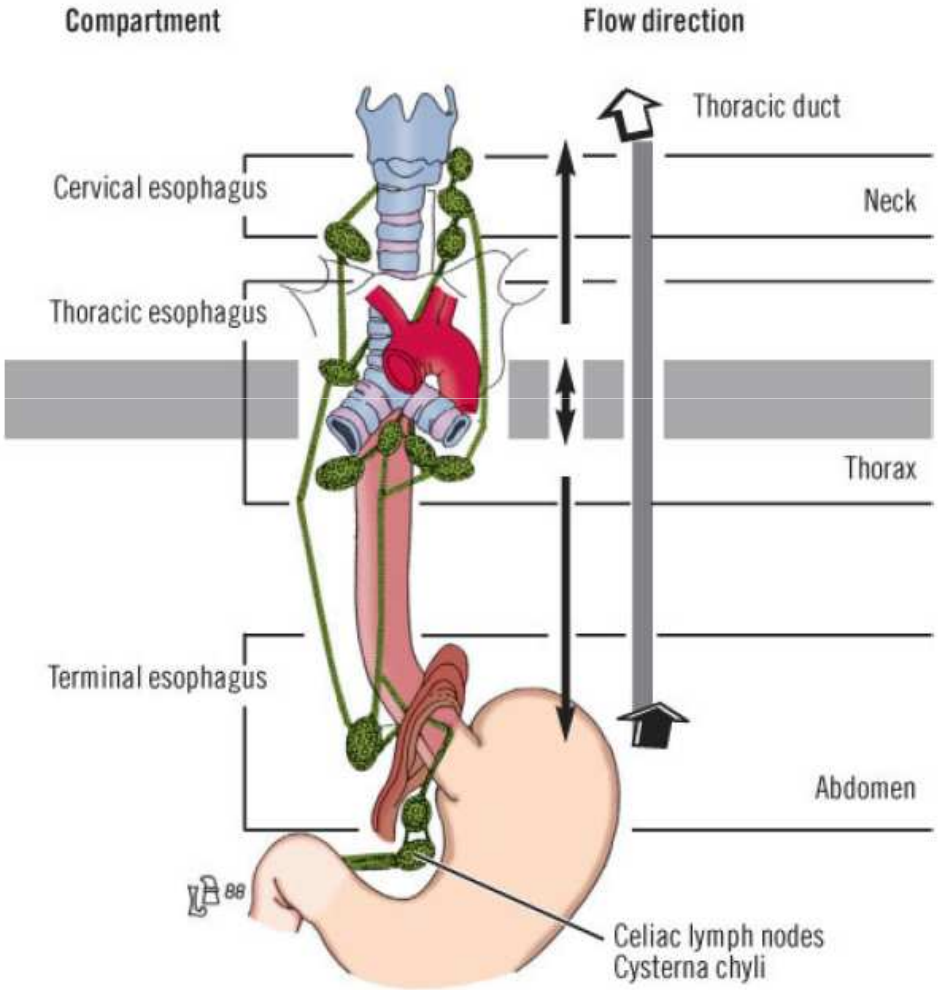
Lymphatic drainage



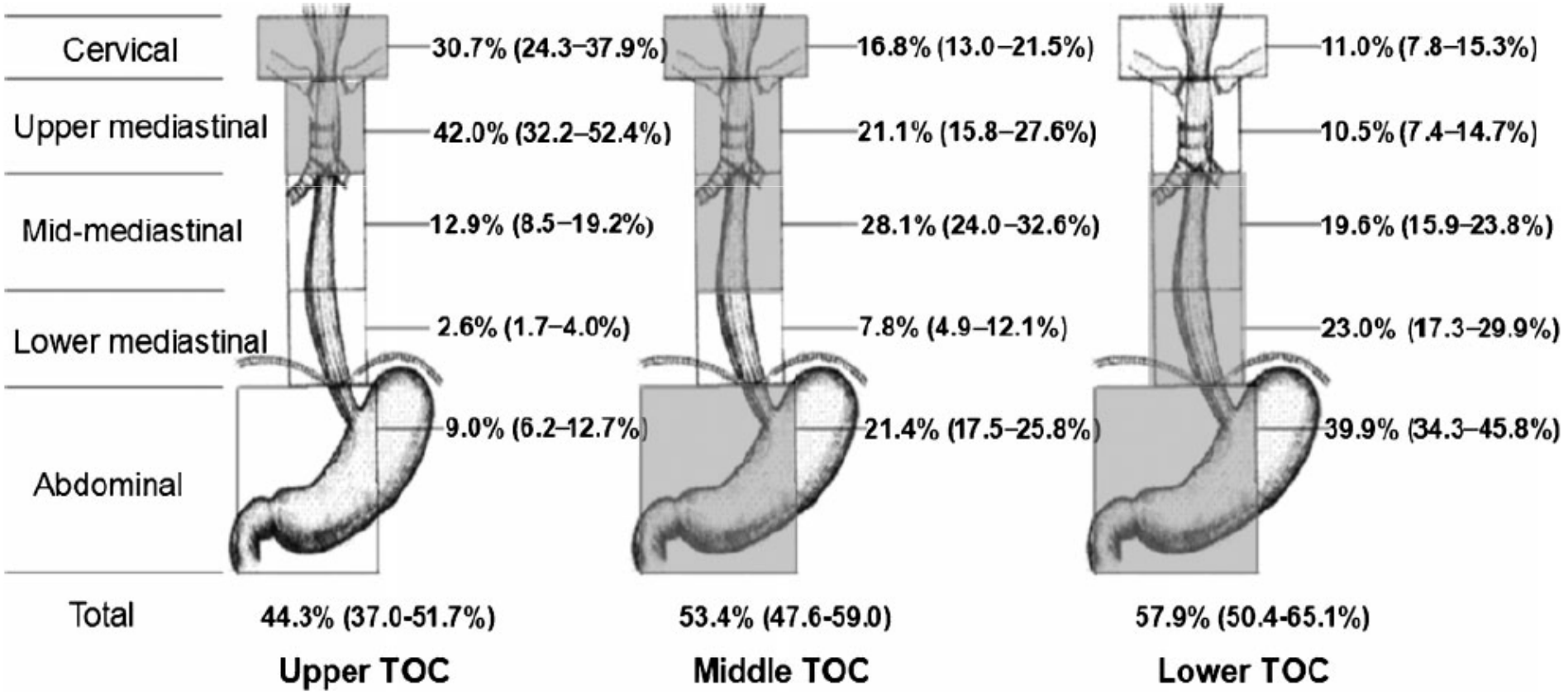


The British Journal of Radiology, 85 (2012), e1110–e1119

A meta-analysis of lymph node metastasis rate for patients with thoracic oesophageal cancer and its implication in delineation of clinical target volume for radiation therapy

[1,2†]X DING, MD, [1,2,3†]J ZHANG, PhD, [1,2*]B LI, MD, PhD, [1,2]Z WANG, MD, [1,2]W HUANG, MD, [1,2]T ZHOU, MD, [1,2]Y WEI, MD and [1,2]H LI, MD

Predominantly SCC



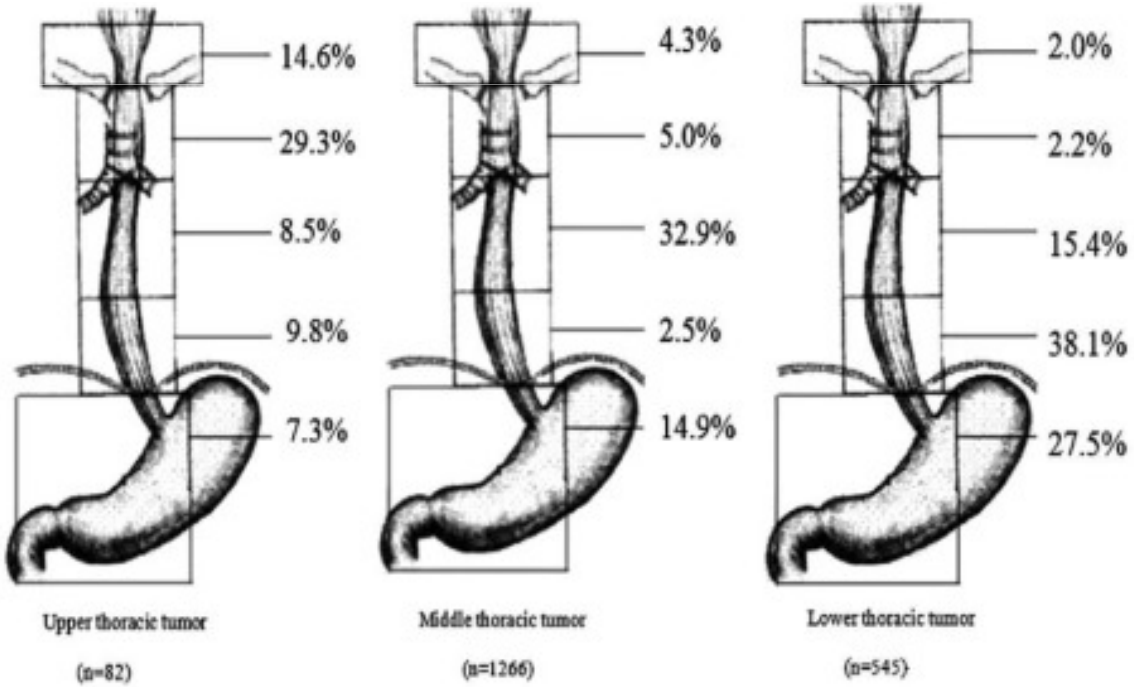
Lnn regions LNMR >15% considered as high risk ➔ included in target volume

Rate of LNM in different regions according to the location of the primary tumor

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.



Cheng et al. Explore the Radiotherapeutic Clinical Target Volume Delineation for Thoracic Esophageal Squamous Cell Carcinoma from the Pattern of Lymphatic Metastases. Journal of Thoracic Oncology, Volume 8, Issue 3, 2013, 359–365

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Rate of LNM in different regions according to the location of the primary tumor

TABLE 5. Multivariate Analysis of Risk Factors Associated with Lymph Node Metastasis in Esophageal Squamous Cell Carcinoma

Parameters	B	S.E.	Wald	Sig.	OR	95%CI for OR
Age	−0.012	0.005	5.437	0.020	0.988	0.978–0.998
Path	0.044	0.065	0.456	0.500	1.045	0.920–1.188
Depth	0.561	0.068	68.929	<0.001	1.753	1.536–2.002
Length	0.144	0.027	28.131	<0.001	1.155	1.095–1.218
Diff	0.683	0.076	80.139	<0.001	1.980	1.705–2.299

Depth, the depth of tumor invasion; Length, the length of tumor; Diff, the histologic differentiation; Path, pathological morphology type; OR, odds ratios; CI, confidence interval.

Journal of Medical Imaging and Radiation Oncology •• (2016) ••–••

MEDICAL IMAGING—RADIATION ONCOLOGY—ORIGINAL ARTICLE

Distribution of lymph node metastases on FDG-PET/CT in inoperable or unresectable oesophageal cancer patients and the impact on target volume definition in radiation therapy

Melanie Machiels,[1] Sanne J Wouterse,[2] Elisabeth D Geijsen,[1] Rob M van Os,[1] Roel J Bennink,[3] Hanneke WM van Laarhoven[4] and Maarten CCM Hulshof[1]

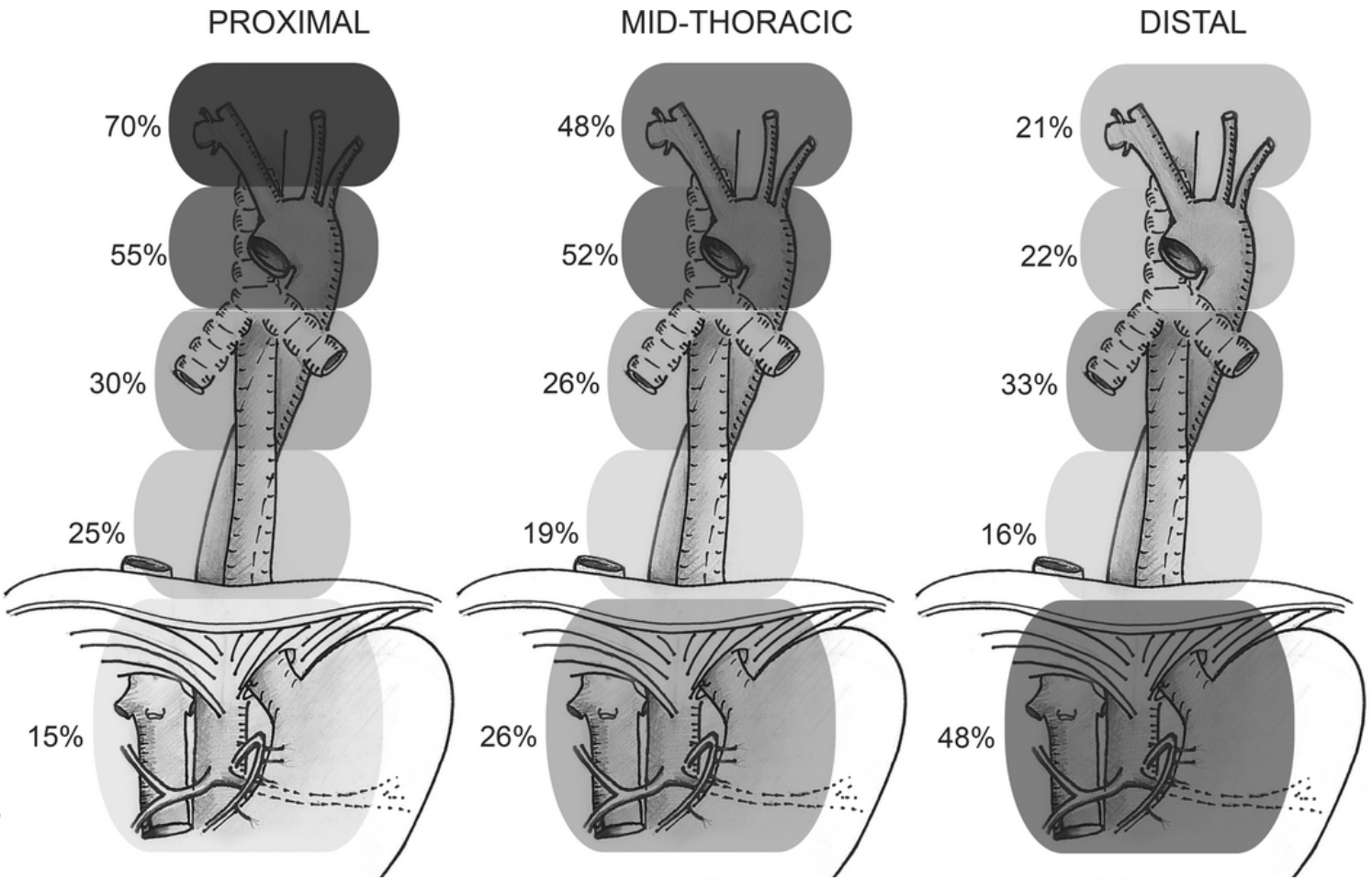

Fig. 1. Percentages of lymph node metastasis on FDG-PET/CT per lymph node region and tumour location. Lymph node regions *(from top to bottom)*; cervical, upper mediastinal, mid-mediastinal, lower mediastinal and abdominal. Grey scale correlates with risk of lymph node metastasis.

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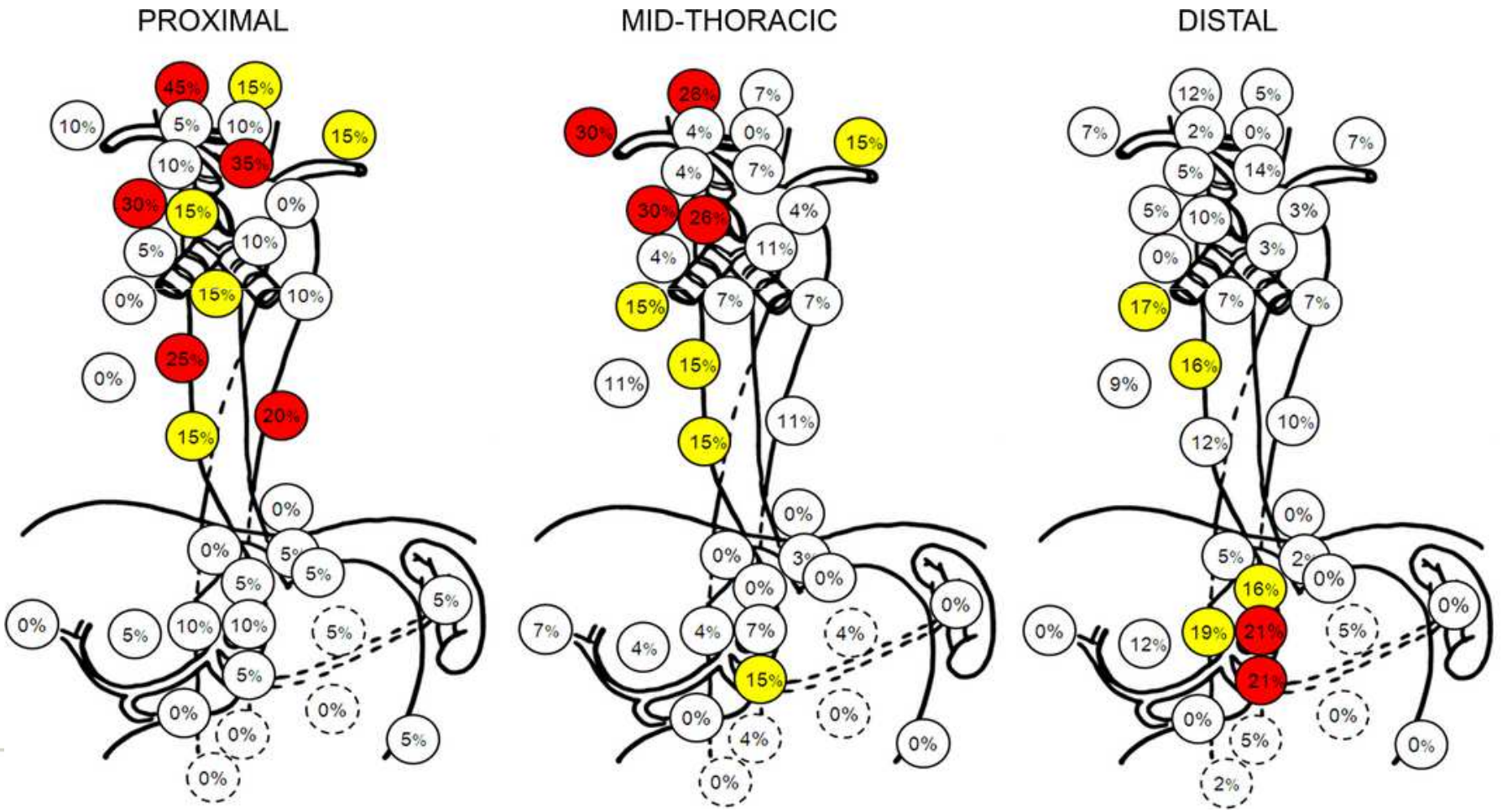
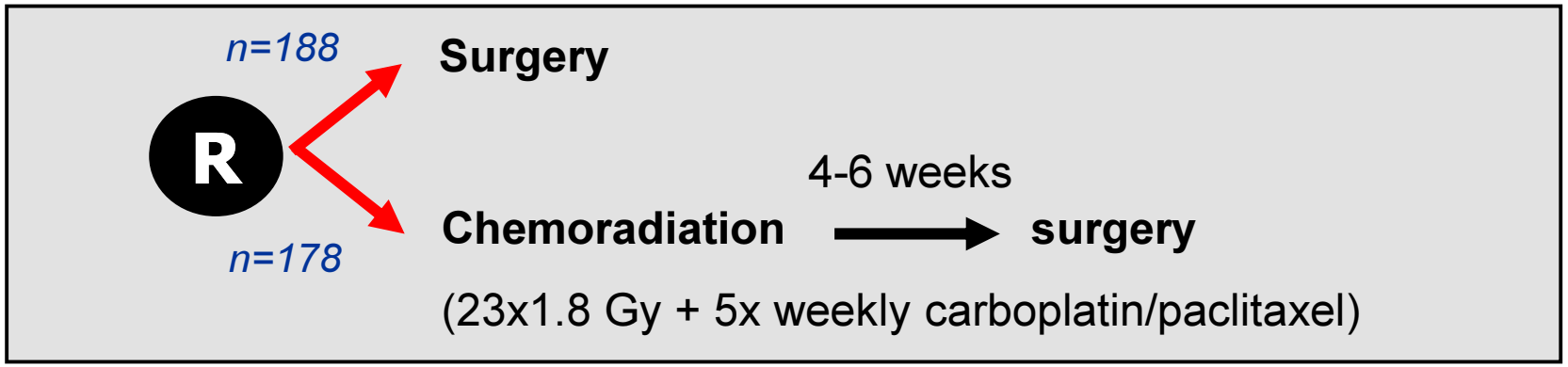
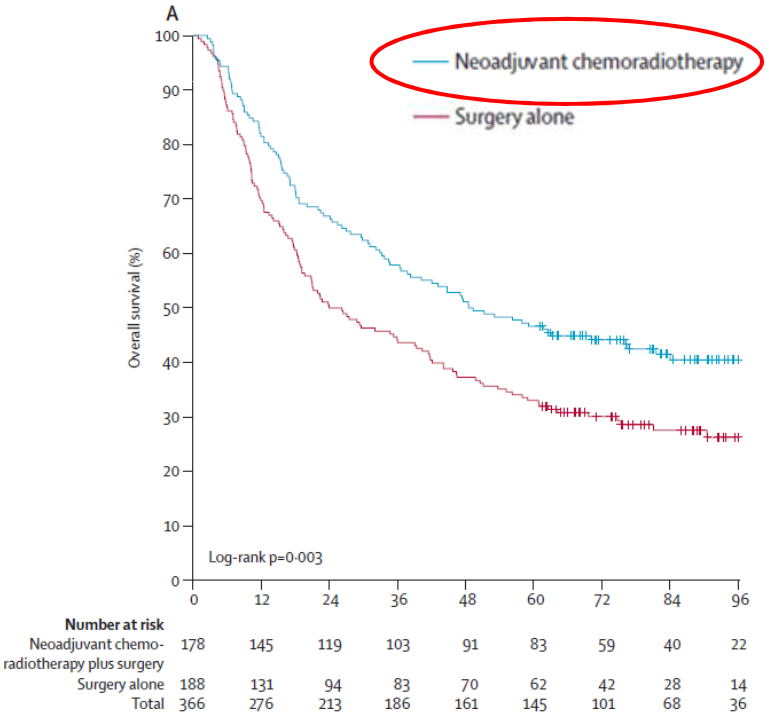
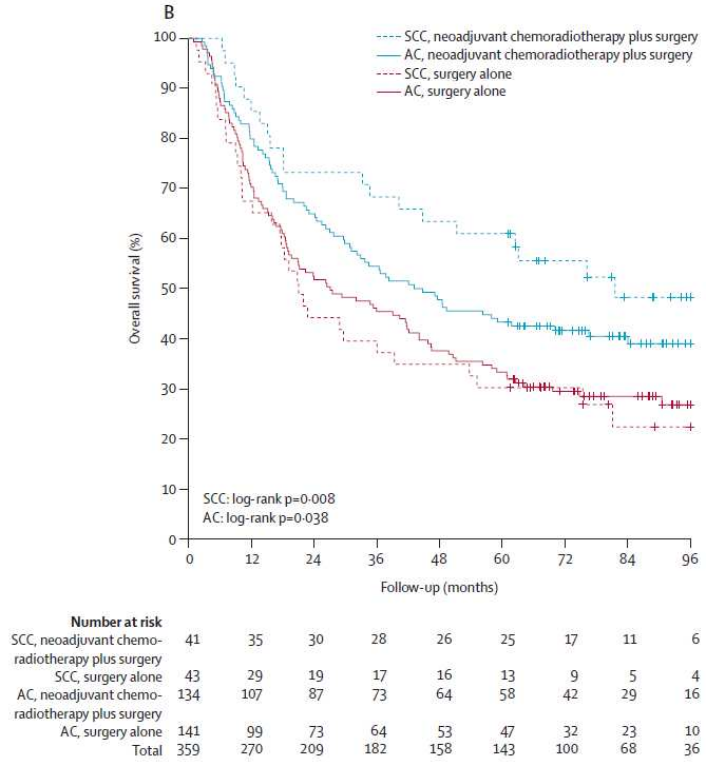


Fig. 2. Lymph node metastasis rates (LNMR) on FDG-PET/CT per individual lymph node site (defined by the Japanese Society of Oesophageal Diseases and the Japanese Gastric Cancer Association) for each tumour location. High-risk regions (≥ 20% LNMR) are indicated in red and intermediate-risk regions (≥ 15% LNMR) in yellow

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

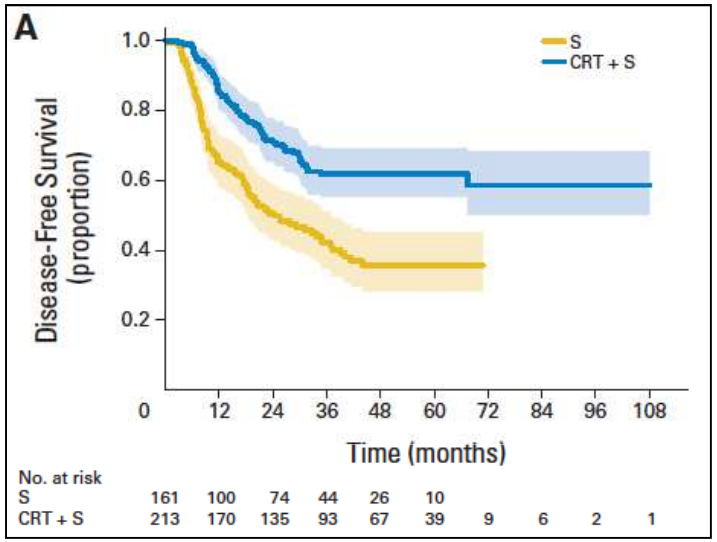


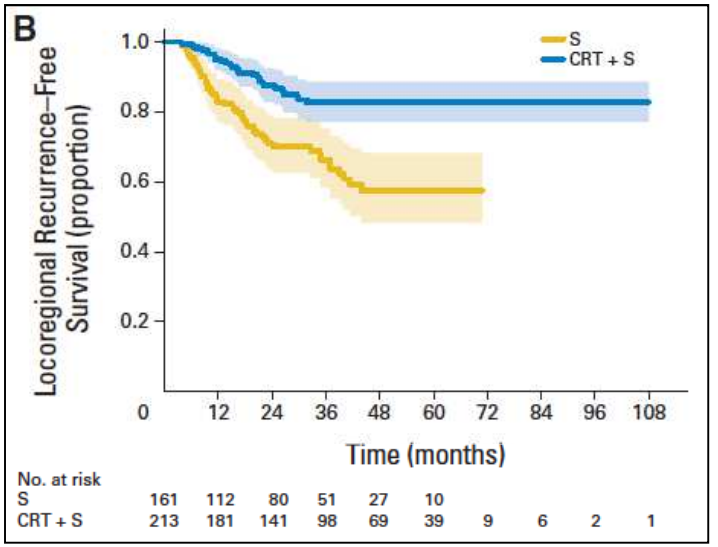


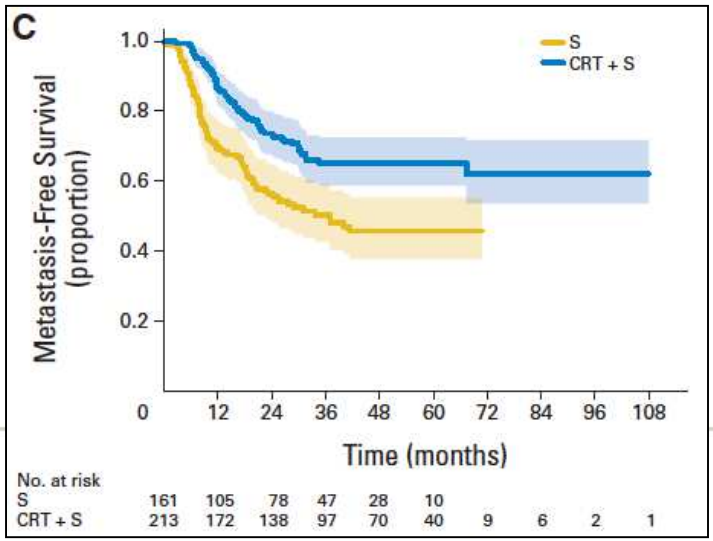


Shapiro et al. Lancet Oncol 2015 (median FU 84.1 months)

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







	S	CRT + S
All recurrences	58%	35%
Distant recurrences	36%	29%
Locoregional recurrences	**36%**	**13% 3% isolated LRR**

Oppedijk et al. J Clin Oncol 2014

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

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.

5%

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Table 4. Univariable and Multivariable Cox Regression Analyses for LRRs in Patients Undergoing Resection (n = 374)

	LRR Incidence (%)		Univariable		Multivariable	
Factor	S Arm	CRT + S Arm	HR	95% CI	HR	95% CI
Method of resection (TTE *v* THE)	20 *v* 17	6 *v* 8	0.83	0.54 to 1.29	NA	
Tumor length (≤ 5.0 *v* > 5.0 cm)	23 *v* 39	16 *v* 11	0.89	0.54 to 1.46	NA	
Clinical T stage (T1-2 *v* T3-4)	31 *v* 35	5 *v* 17	1.32	0.76 to 2.29	NA	
Clinical nodal stage (N0 *v* N1)	31 *v* 35	10 *v* 18	1.50	0.93 to 2.41	NA	
Pathologic nodal stage (N0 *v* N1)	22 *v* 38	10 *v* 23	**3.66**	**2.2 to 5.85**	**2.85**	**1.59 to 5.11**
Involved margins (R0 *v* R1)	34 *v* 36	13 *v* 29	**2.29**	**1.38 to 3.76**	NA	
Histology (SCC *v* AC)	47 *v* 30	15 *v* 14	0.70	0.44 to 1.12	**0.49**	**0.29 to 0.82**
Sex (male *v* female)	33 *v* 34	12 *v* 20	1.12	0.67 to 1.87	NA	
Treatment arm (S *v* CRT + S)	27	14	**0.37**	**0.23 to 0.59**	**0.50**	**0.29 to 0.86**
pCR after CRT (no *v* yes)*	NA	7 *v* 17	0.36	0.13 to 1.05	NA	

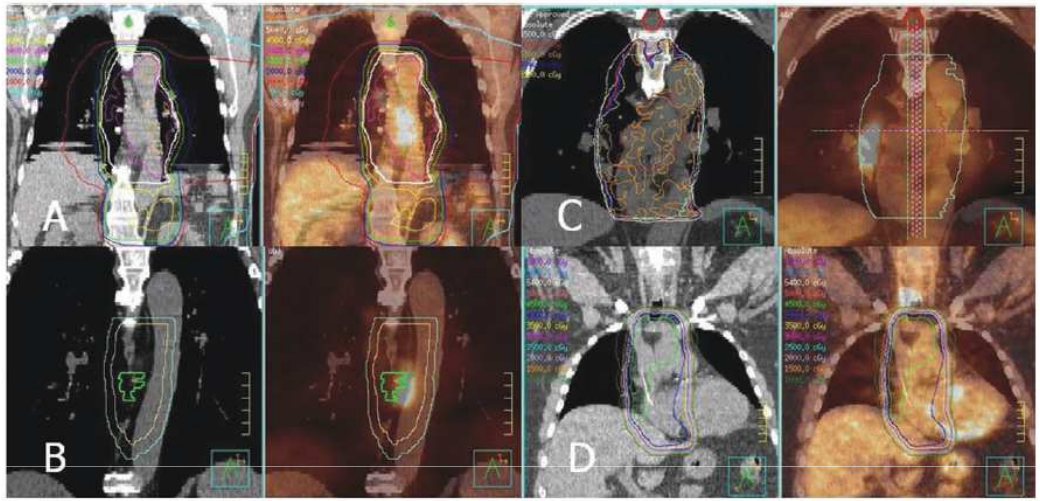
NOTE. Bold font indicates significance.

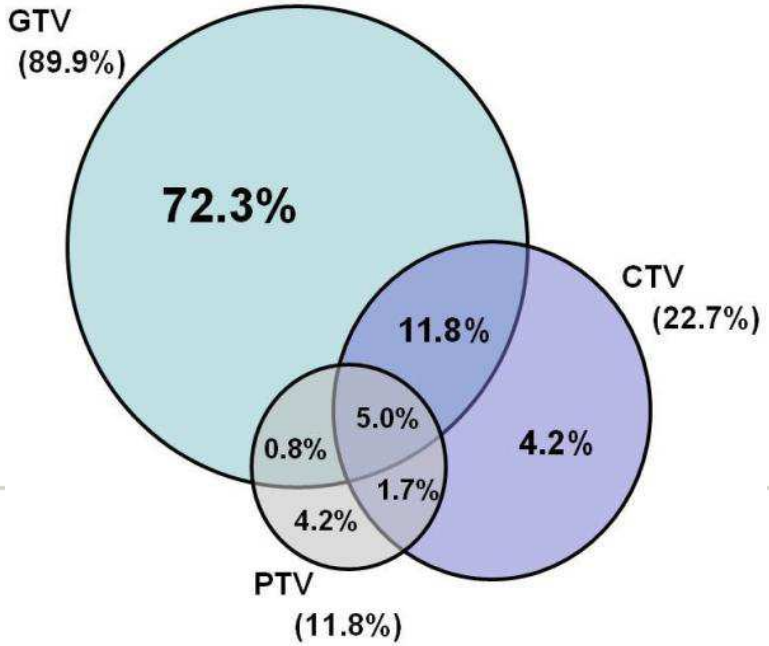
Abbreviations: AC, adenocarcinoma; CRT, chemoradiotherapy; HR, hazard ratio; LRR, locoregional recurrence; NA, not applicable; pCR, pathologic complete response; S, surgery; SCC, squamous cell carcinoma; THE, transhiatal esophagectomy; TTE, transthoracic esophagectomy.

*Factor only available in the CRT + S arm and therefore not suitable for multivariable analysis.

Failure patterns in patients with esophageal cancer treated with definitive chemoradiation

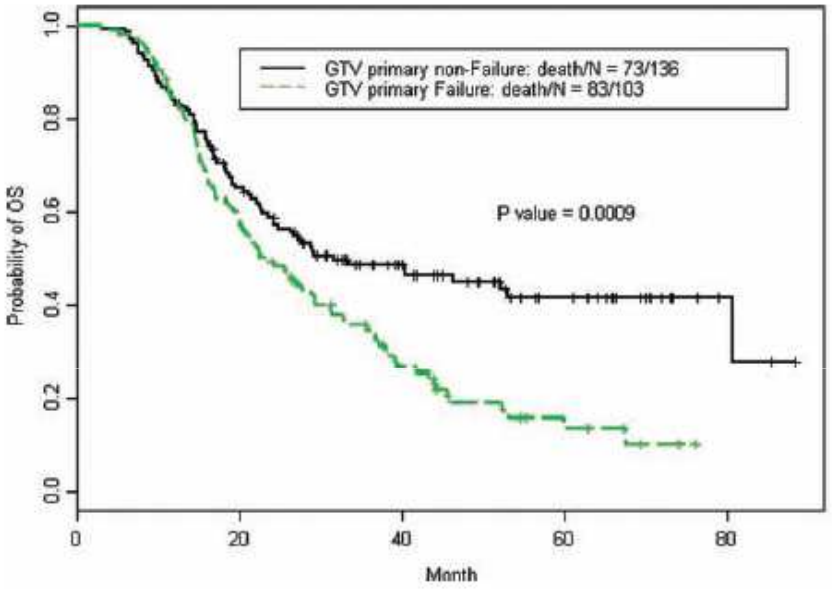
- 239 patients dCRT
  - 87% T3/T4
  - 50.4Gy/28 fr + 5FU
- median FU 52.6 months
  - 50% (n=119) local failure
  - 48% (n=114) distant failure
  - 31% (n= 74) NED
  - Local failure (n=119)
    - 90% GTV failure(107/119)
    - 23% CTV failure (27/119)
    - 12% PTV failure (14/119)

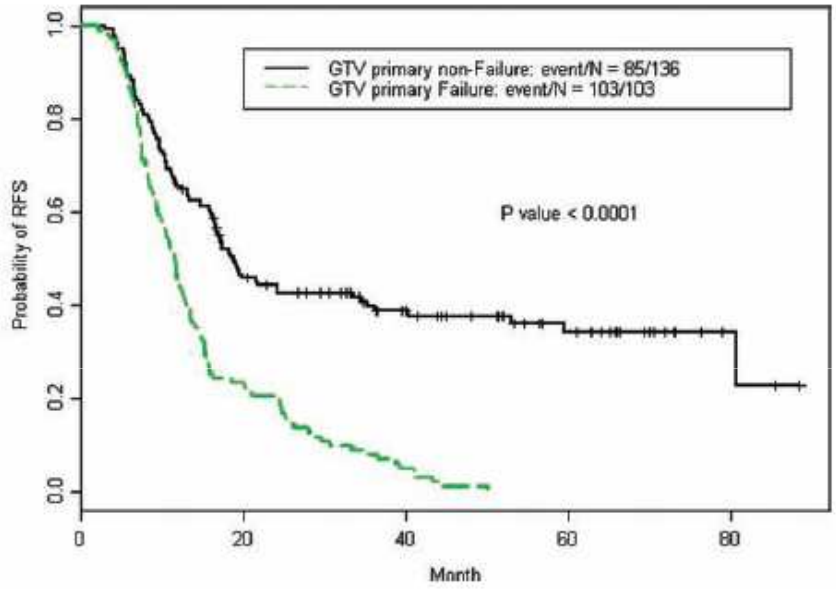




Welsh, Cancer 2012

Failure patterns in patients with esophageal cancer treated with definitive chemoradiation





Welsh, Cancer 2012

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Summary

- Patters of failure after nCRT:
- Distant metastases: 36% ➔ 29%
- Locoregional failure: 36% ➔ 13%
- Recurrence within the radiation target volume occurred in only 5%, mostly combined with outfield failures.

- Patterns of failure after dCRT:
- Distant metastases: 50%
- Locoregional failure: 50%
- Most failures at site of macroscopic tumor

New perspectives in esophageal cancers

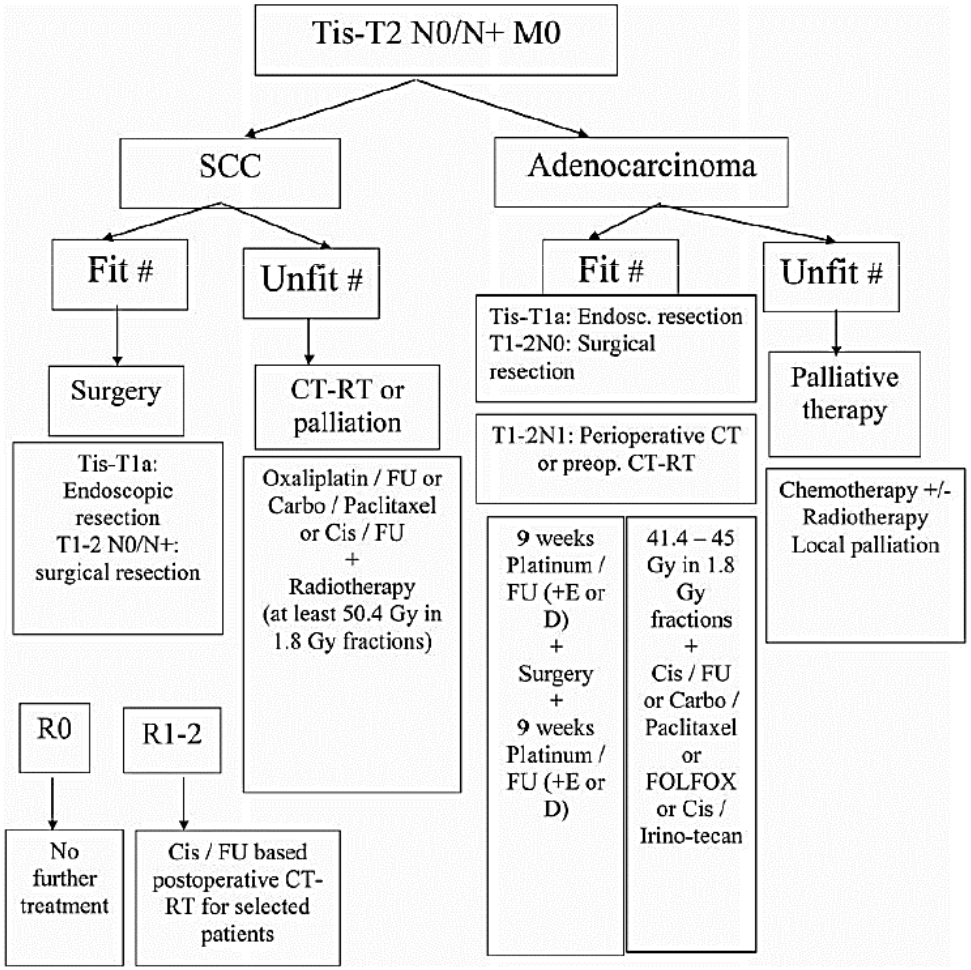
Prof. Philippe MAINGON

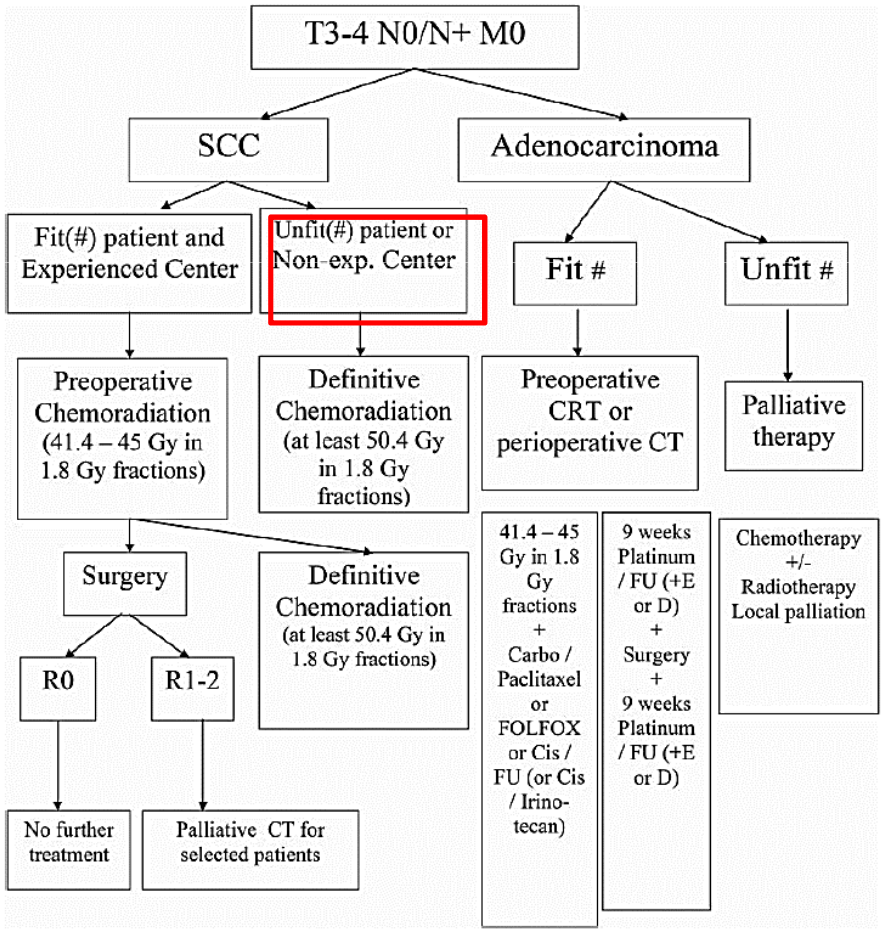
ESTRO School

Annals of Oncology 24 (Supplement 6): vi51–vi56, 2013
doi:10.1093/annonc/mdt342

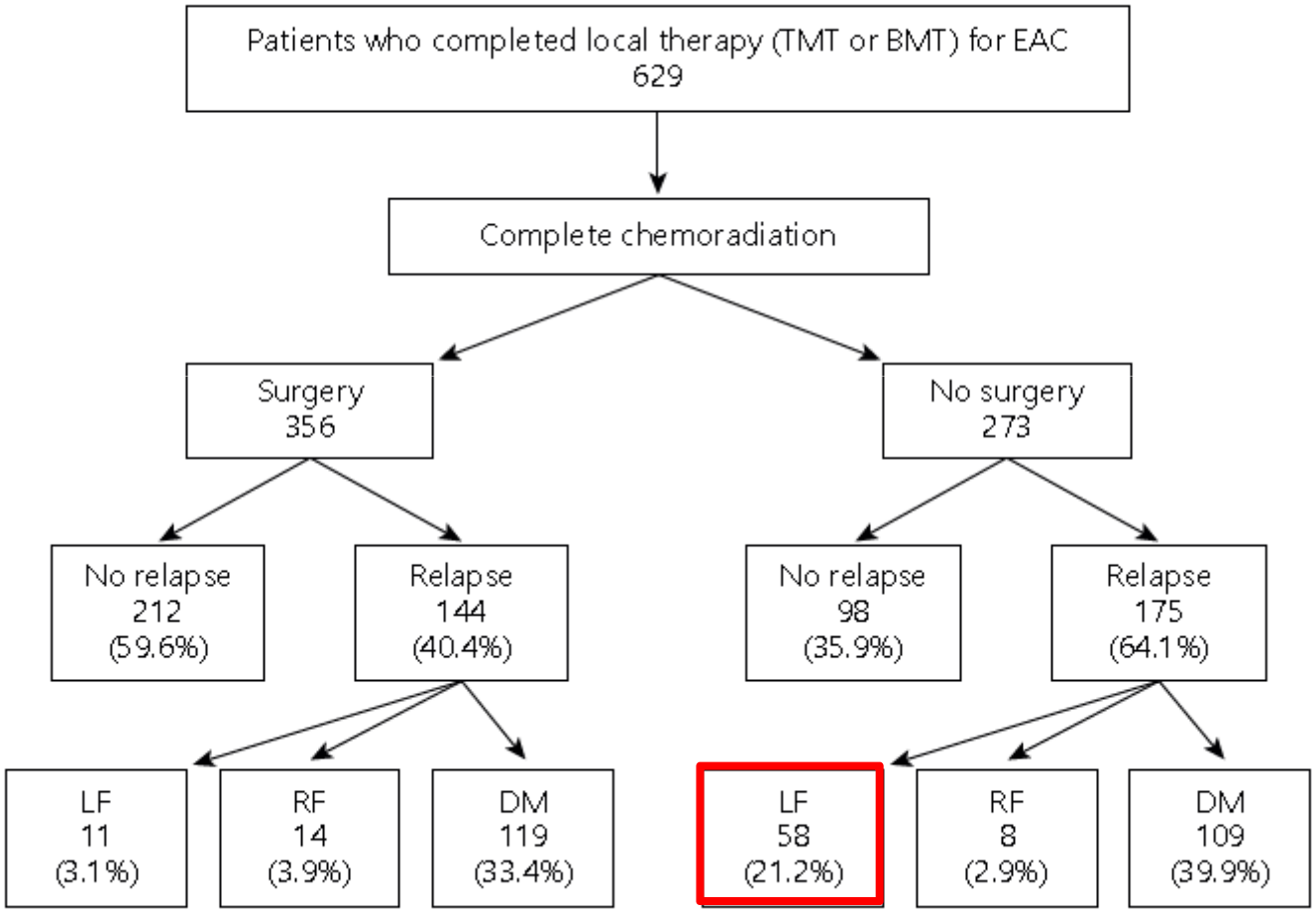
Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Stahl[1], C. Mariette[2], K. Haustermans[3,4], A. Cervantes[5] & D. Arnold[6], on behalf of the ESMO Guidelines Working Group*





Sites of failure



Shiozaki H et al., Oncology 2014

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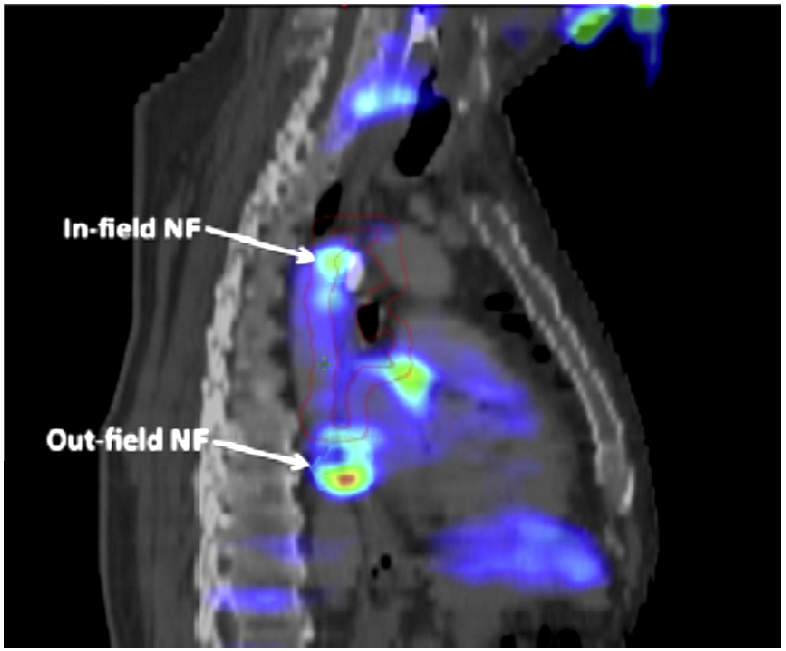
Mapping of failures after radiochemotherapy

Patients' characteristics and treatment.

Characteristics	$n = 34$
Sex	
Men	26 (76.5%)
Women	8 (23.5%)
Age	
Median [range]	60.9 years [45–80.8 years]
Histology	
Squamous cell carcinoma	29 (85.3%)
Adenocarcinoma	5 (14.7%)
Tumor sites	
Cervical esophagus	3 (8.8%)
Upper third	5 (14.7%)
Middle third	13 (38.2%)
Lower third	11 (32.3%)
Cardia	2 (5.9%)

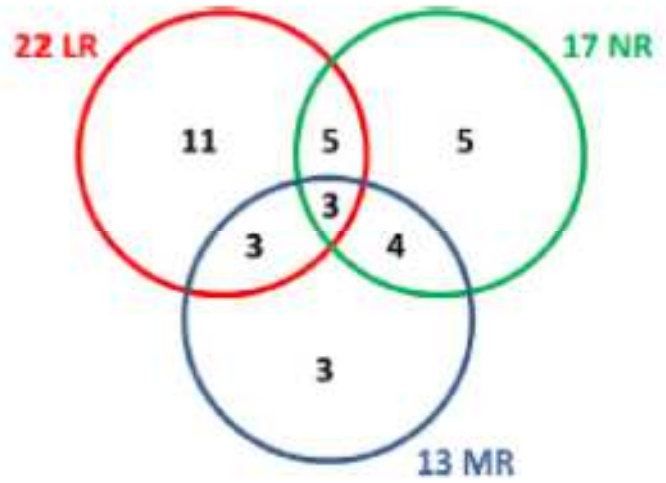


Bednarek C. Radiother Oncol 2015;116:252-56

Mapping of failures after radiochemotherapy

Topography of failures by involved/non-involved nodal stations at baseline.

Topography of failures by involved/non-involved nodal stations at baseline	$n = 34$
Uninvolved	24 (70.6%)
Involved	3 (8.8%)
Involved + 1 uninvolved	5 (14.7%)
Involved + > 2 uninvolved	2 (5.8%)



Bednarek C. Radiother Oncol 2015;116:252-56

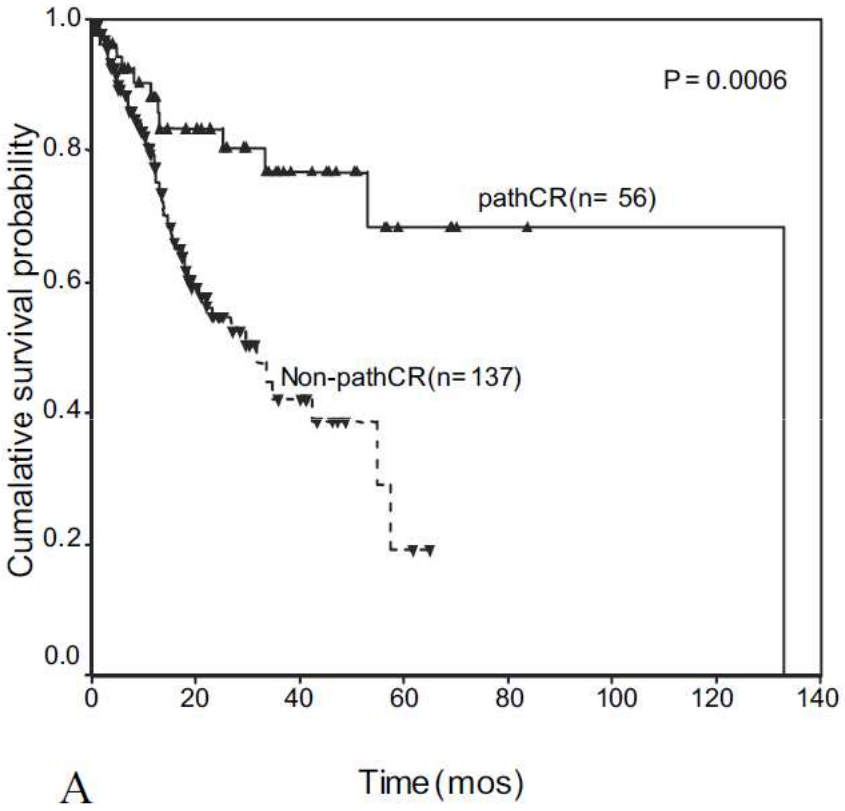
Which way ?

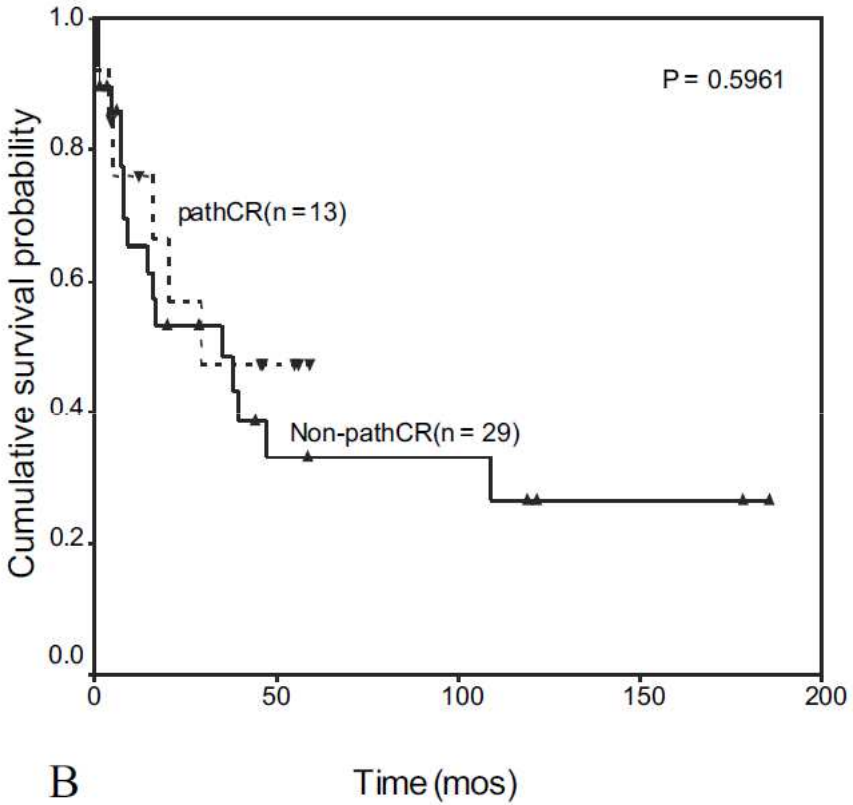
- **Radiotherapy**
  - Technique
  - Dose and fractionation
- **Chemotherapy**
  - New agents
  - Targeted agents
- **Surgery**
  - Selection of patients
  - Selection of centers
  - Techniques
- **Multidisciplinary tumor board**
  - Expertise
  - Clinical research

Which way ?

- **Radiotherapy**
  - Technique
  - Dose and fractionation
- Chemotherapy
  - New agents
  - Targeted agents
- Surgery
  - Selection of patients
  - Selection of centers
  - Techniques
- Multidisciplinary tumor board
  - Expertise
  - Clinical research

Adenocarcinoma vs. SCC: response





ADK

SCC

Rohatgi et al., Cancer 2006

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RTOG 9405 (INT 0123)

STRATIFY

Weight loss
≥ or < 10%

Tumor size
≤ or > 5 cm

Histology
Adeno
Squamous (87%)

RANDOMIZE

5-FU/CDDP X 4
+
64.8 Gy

5-FU/CDDP X 4
+
50.4 Gy

Minsky B et al., JCO 2002

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Which way for CRT ?

patient selection. The 2012 annual report of the UK National Oesophago-gastric Cancer Audit[38] has showed an improvement in outcomes for patients undergoing surgery, with 45% of patients surviving for 3 years. Both of these areas have scope for further development, namely the incorporation of CT-PET more directly into radiotherapy planning and assessment of caseload, with outcomes in specialist non-surgical services.

We believe, however, that by using newer radiotherapy techniques, such as intensity-modulated and image-guided radiotherapy, we can now safely deliver a higher

Crosby T et al., Lancet Oncol

colleagues' trial.[1] As Crosby and
radiation doses of 60 Gy or higher
safe to deliver to patients with thes
cause significant morbidity. A succe
radiotherapy and a targeted therapy
advance against this disease and wel

1.8 Gy are regarded as standard treatment of definitive radiotherapy in the United States. Increased radiation doses up to 60 Gy in fractions of 1.8–2.0 Gy are recommended in parts of Europe and Japan for definitive chemoradiotherapy. This is due to an obvious dose–response correlation of radiotherapy in oesophageal cancer and the positive experience with these radiation doses in prospective multi-centre trials [16, 17] (Figure 1).

Stahl M et al., Ann Oncol 2013

School

CONCORDE (PRODIGE 26)

STRATA

Centre

Weight loss
≥ vs < 10%

Stade
I – II vs. III

Pathology
Adeno vs.
Squamous cell

RANDOM

FOLFOX-4 X 6
+
40 Gy (ENI : N ≥ 20%)
• Boost 10 Gy

FOLFOX-4 X 6
+
40 Gy (ENI : N ≥ 20%)
• Boost 26 Gy

Main Objective: 2 years DFS

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Which way ?

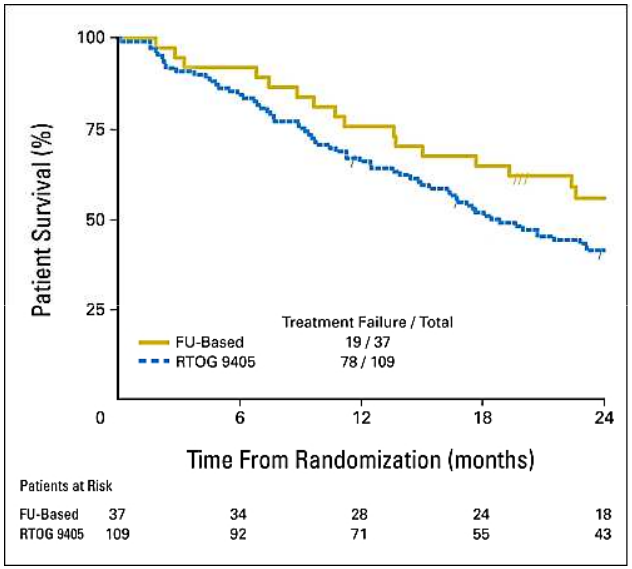
- Radiotherapy
  - Technique
  - Dose and fractionation
- **Chemotherapy**
  - New agents
  - Targeted agents
- Surgery
  - Selection of patients
  - Selection of centers
  - Techniques

- Multidisciplinary tumor board
  - Expertise
  - Clinical research

RTOG 0113 : Taxanes in CRT

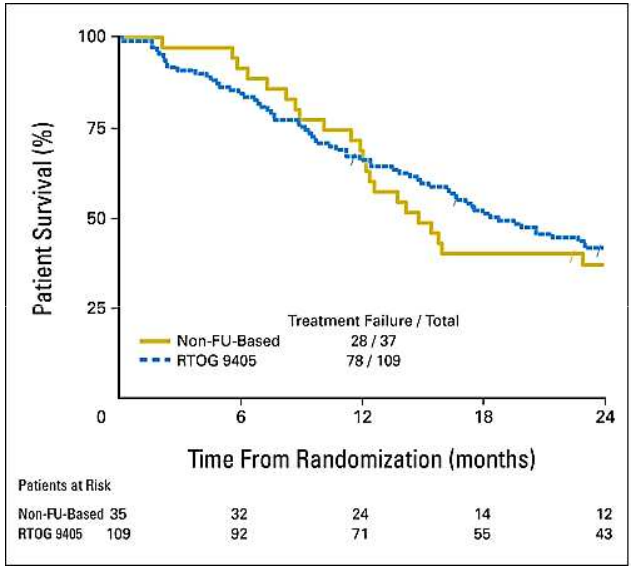
Induction CT: CDDP-5FU-Taxol

XRT 50.4Gy + 5-FU/Taxol



	G3	G4	G5
Acute	54%	27%	3%
Late	5%	3%	-

XRT 50.4Gy + CDDP/Taxol



	G3	G4	G5
Acute	43%	40%	3%
Late	9%	3%	3%

Ajani JA et al., JCO 2008

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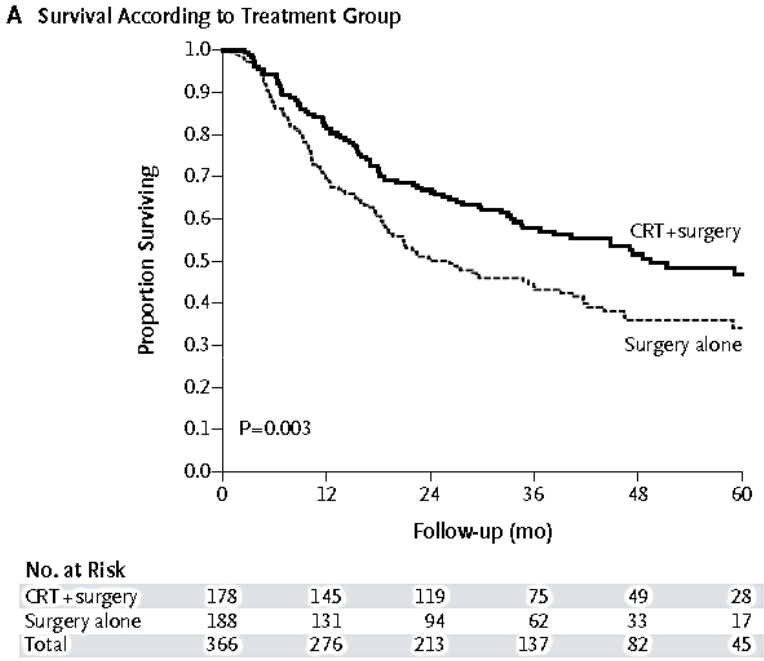
CROSS Trial

273 ADK/ 86 SCC

RTC-3D : 41.4Gy

Carbo AUC 2

Taxol 50 mg/m²/ Weekly



OS = 49 months vs. 26 months

Van Hagen P. et al., NEJM 2012

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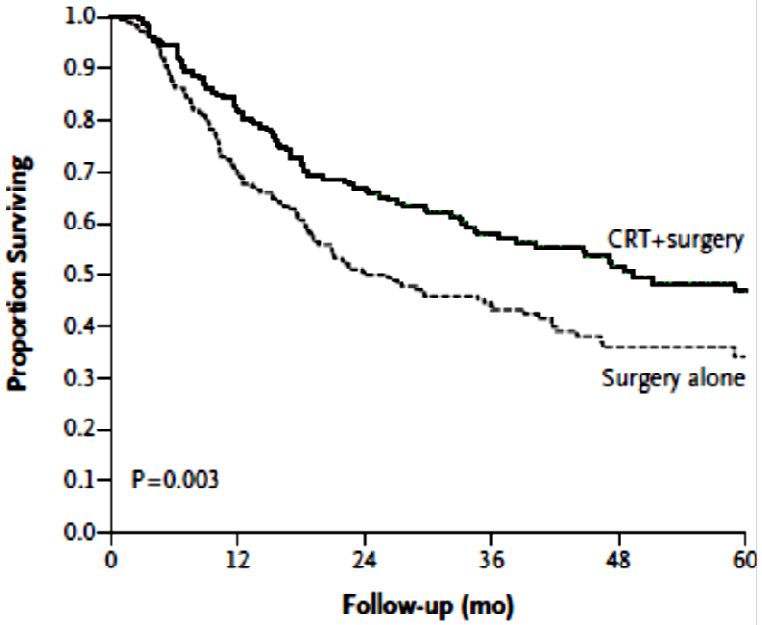
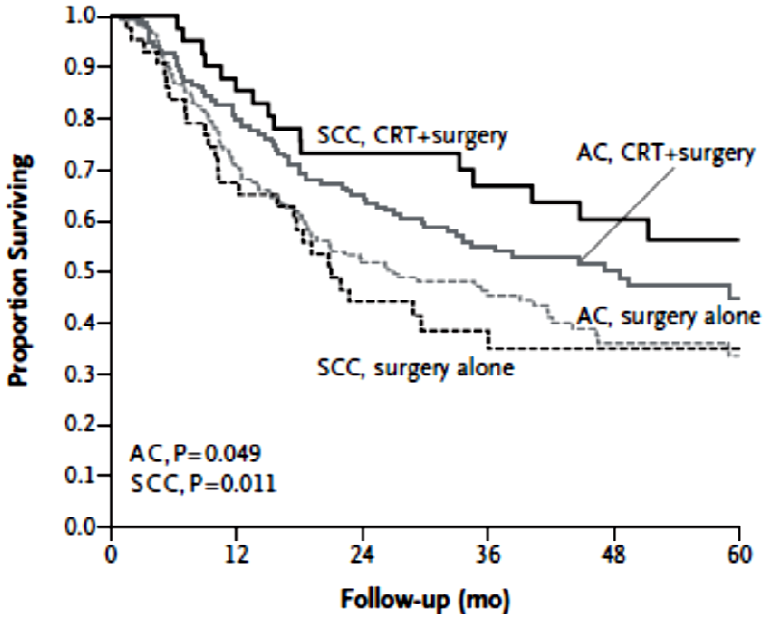
Preoperative chemoradiotherapy

A Survival According to Treatment Group



No. at Risk						
CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45

B Survival According to Tumor Type and Treatment Group



No. at Risk						
AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

Van Hagen P. N Eng J Med 2012:366:2074-84

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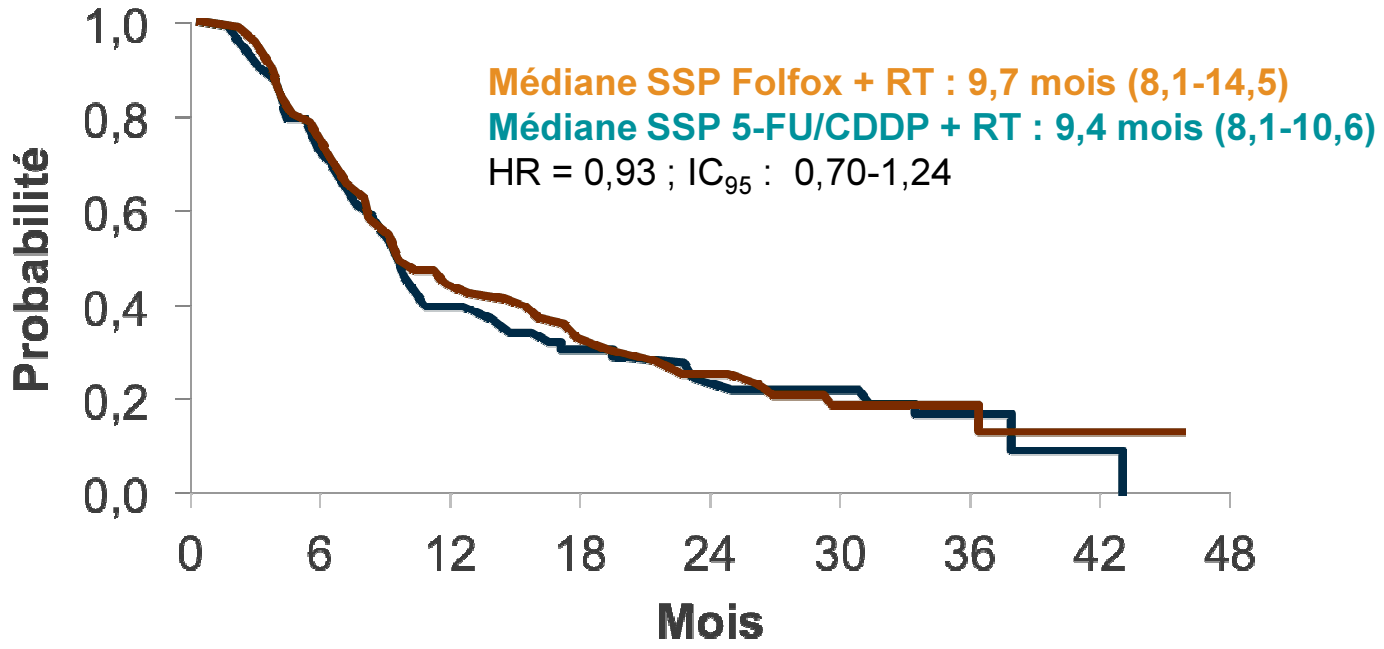
PRODIGE 5 / ACCORD 17

CDDP/5-FU vs. FOLFOX-4



5-FU/CDDP + RP	133	89	44	29	18	11	5	1	0
FOLFOX + RT	134	90	50	29	17	8	4	3	2

ASCO® 2012 - D'après Conroy T et al., LBA4003

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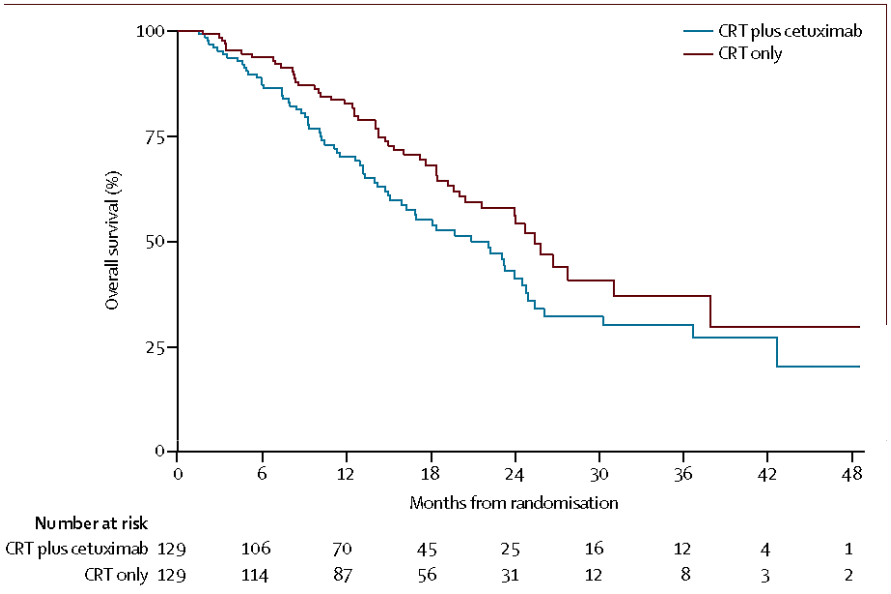
PRODIGE 5 / ACCORD 17

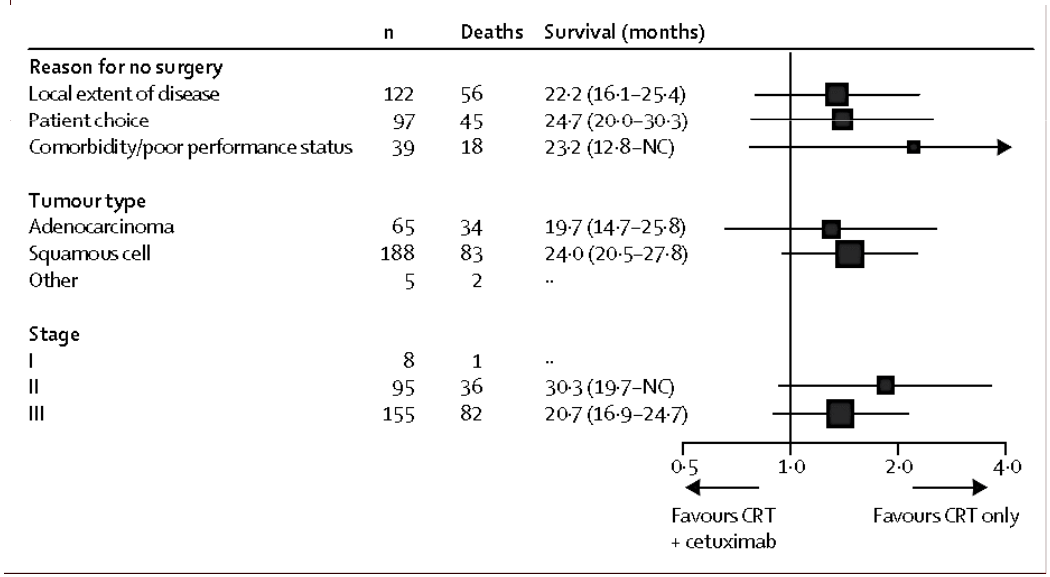
CDDP/5-FU vs. FOLFOX-4

Toxicities (all grades)	**RTX + 5-FU - CDDP**	**RTX + FOLFOX 4**
Mucositis (%)	32	26,7
Alopecia (%)	9,4	1,5
Renal failures(%)	11,7	3
Neuropathy(%)	0,8	18,3
Toxic deaths (%)	6,4	1,1

Scope 1



OS : 25.4 mos vs. 22.1 mos,
HR= 1.53 [1.03-2.27], p= 0.035



Crosby T. et al., Lancet Oncol 2013

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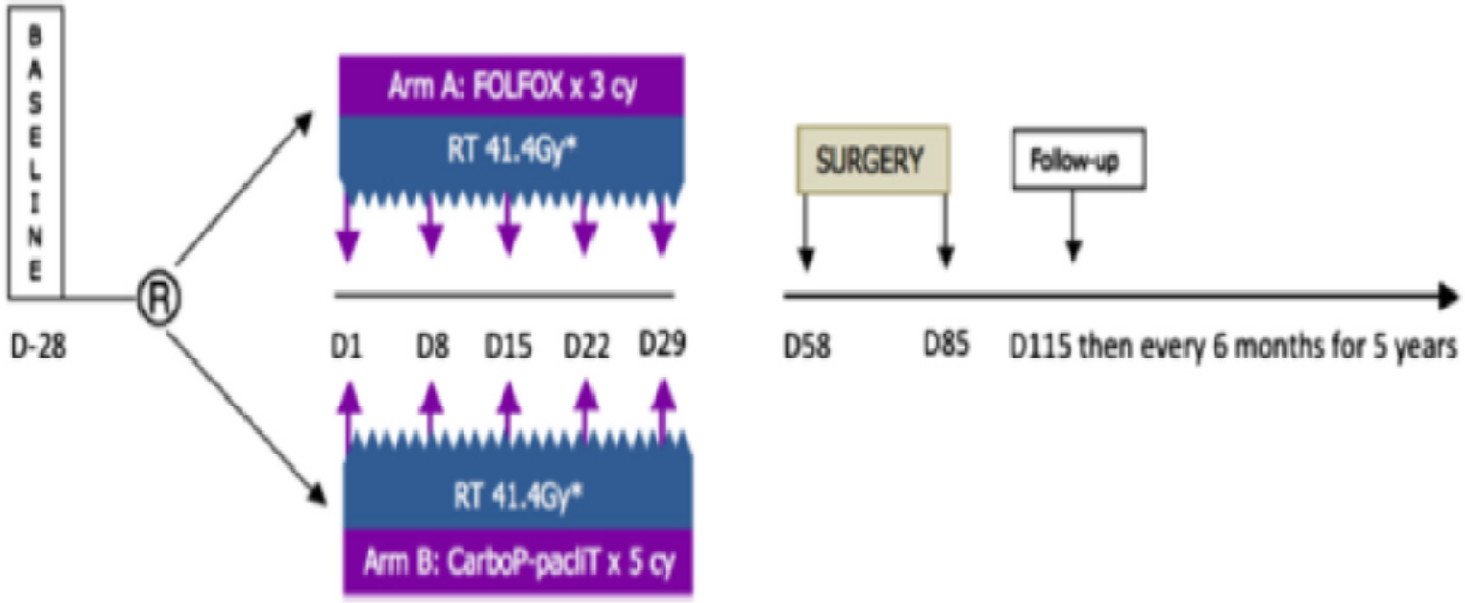
PROTECT 14-02

- Randomized phase II trial, 106 Patients
- Preoperative chemoradiation comparing Paclitaxel-Carboplatin versus FOLFOX



Messager M. BMC Cancer 2016

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PDQ National Cancer institute

- **Esophageal cancer**
- **Treatment**
- **Phase III**

  1- Proton beam radiation therapy or IMRT

  2- Pembrolizumab versus investigator's choice standard therapy (progression after first line therapy)

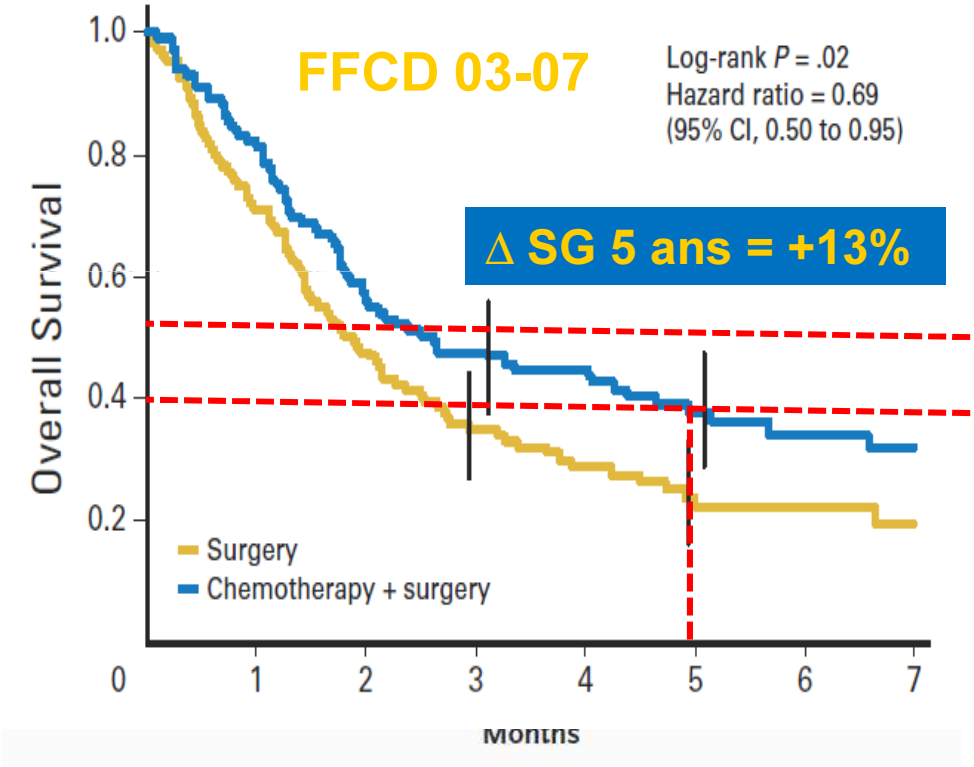
- **Phase II / Phase I**
  - Probiotic (1), Receptor antagonist LY294068 (1), Margetuximab and Pembrolizumab (1), Afatinib and traztuzumab (1), Regorafenib (2), Nintedanib (1)
  - DCF in metastatic setting (1)

Which way ?

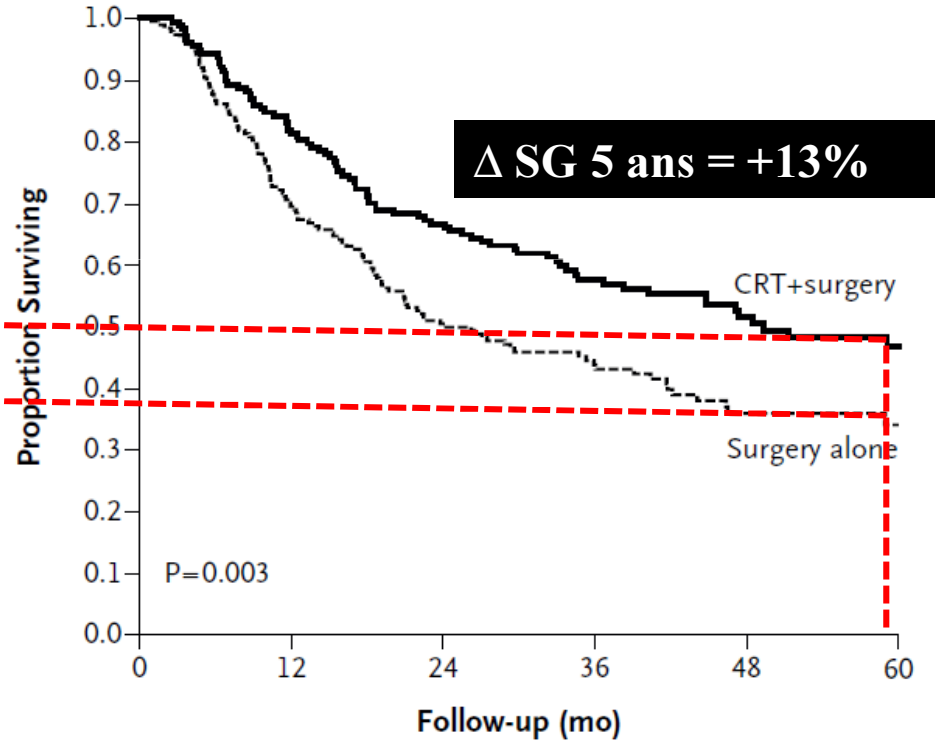
- Radiotherapy
  - Technique
  - Dose and fractionation
- Chemotherapy
  - New agents
  - Targeted agents
- **Surgery**
  - Selection of patients
  - Selection of centers
  - Techniques
- Multidisciplinary tumor board
  - Expertise
  - Clinical research

CT or CRT in the preoperative setting ?

Cunningham D. et al., NEJM 2006
Ychou M. et al., JCO 2011



van Hagen P. et al., NEJM 2012



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22114-40111 TOP GEAR
TRIAL OF PREOPERATIVE THERAPY FOR GASTRIC AND ESOPHAGOGASTRIC JUNCTION ADENOCARCINOMA

A randomised phase III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer

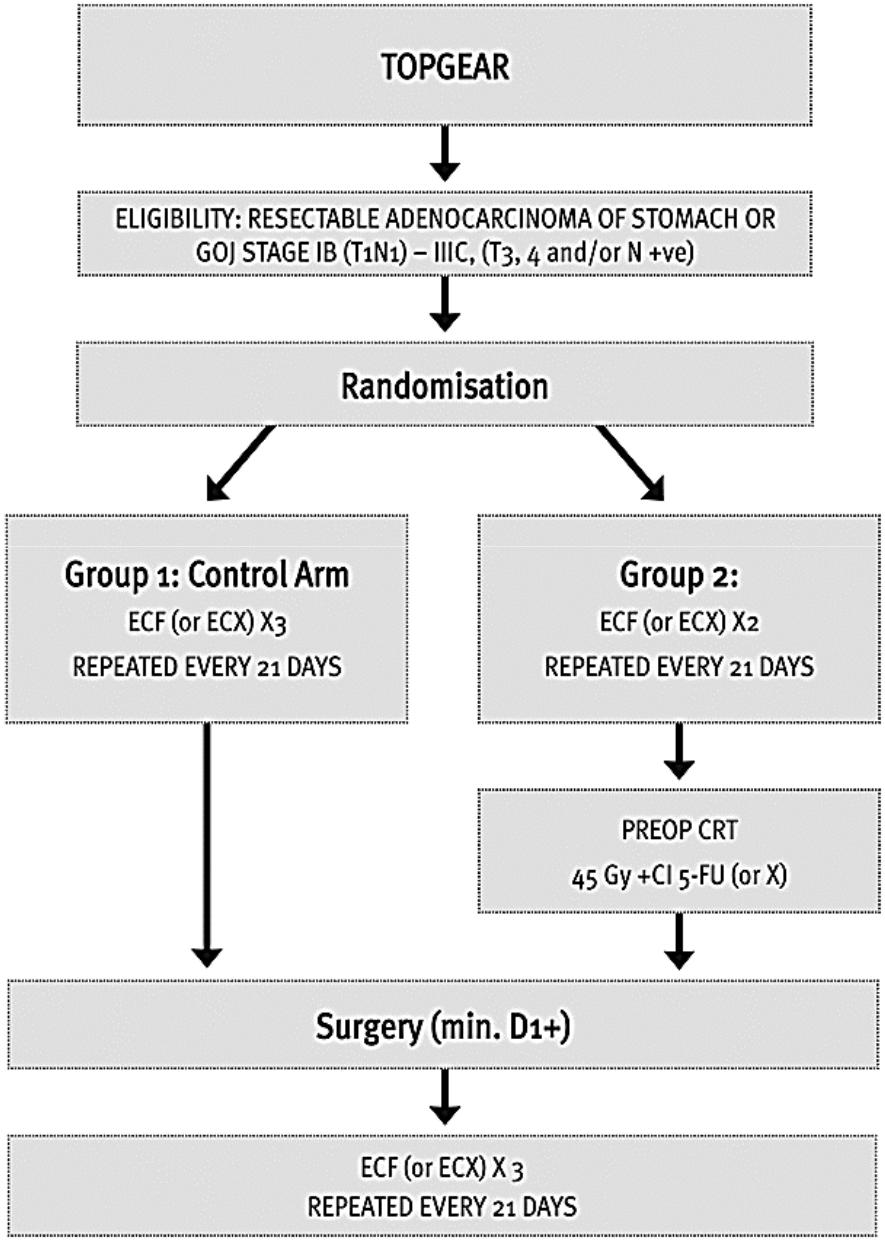
Study Coordinator: Karin Haustermans (ROG)

Study co-coordinator: Florian Lordick (GI)

Leading group: AGITG

Study coordinator AGITG: Trevor Long

22114 - 40111: Study schema



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22114 - 40111: Study endpoints

- **Part 1 (Phase II component)**
  - Primary: Pathological complete response rate
  - Secondary:
    - Toxicity (including surgical morbidity and mortality)
    - Feasibility of preoperative chemoradiation (compliance)
    - Accrual

- **Part 2 (Phase III component)**
  - Primary: Overall survival
  - Secondary:
    - Disease free survival
    - Toxicity
    - Pathological response rate
    - Surgical R0 resection rate

Traveling to a High-volume Center …

- Traveling to a high-volume center is associated with improved survival for patients with esophageal cancer.
- 4679 patients with T1-3 N1 M0 in the National Cancer Data Base from 2006-211
  - Travel patients were more likely to undergo esophagectomy (68% vs 43%) and had significantly better 5-year survival (40% vs 21%)
- Strategy that support patient travel for treatment at high-volume centers may improve esophageal cancer outcomes.

Speicher PJ, Ann Surg 2016

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Surgery after high-dose CRT ?

	S (n= 35)	XRT-CT (66Gy) + S (n= 30)	P-value
IC Unit hospitalization Mediane (min-max)	3 (0-148)	4.5 (0-85)	0.96
Hospitalisation Mediane (min-max)	18 (11-187)	16 (9-177)	0.61
Lung complications	21 (60%)	19 (63.3%)	0.80
Acute lung toxicity	18 (51.4%)	15 (50.0%)	1.0
Pneumonia	15 (42.9%)	14 (46.7%)	0.81
Chylothorax	0	1 (3.3%)	0,46
Postoperative death	3 (8.6%)	5 (16.7%)	0.45

Hurmuzlu M; Radiother Oncol 2010

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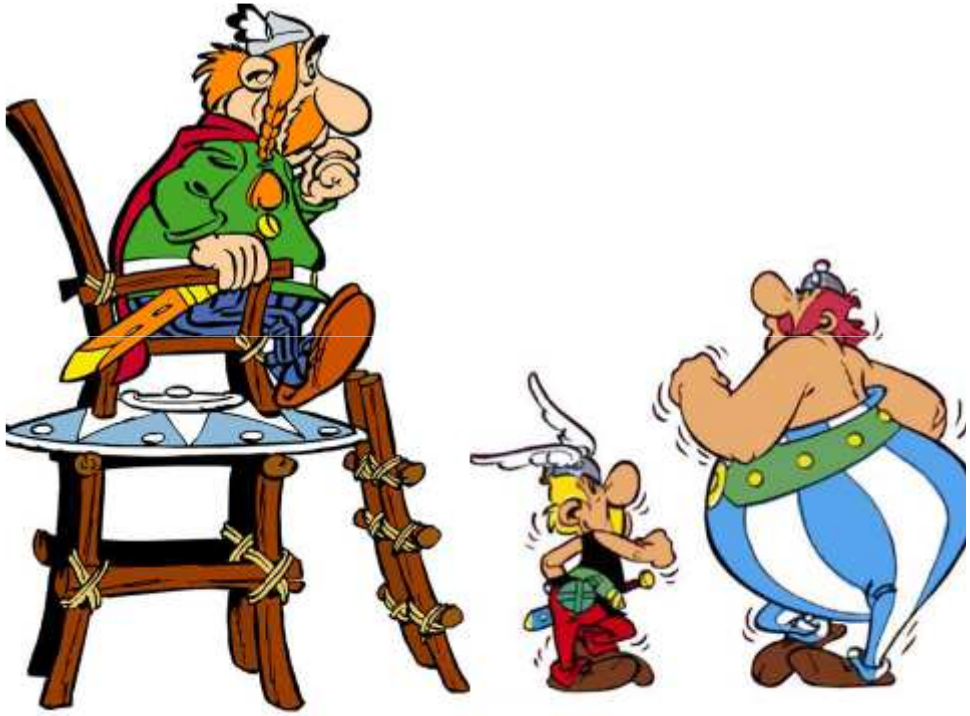
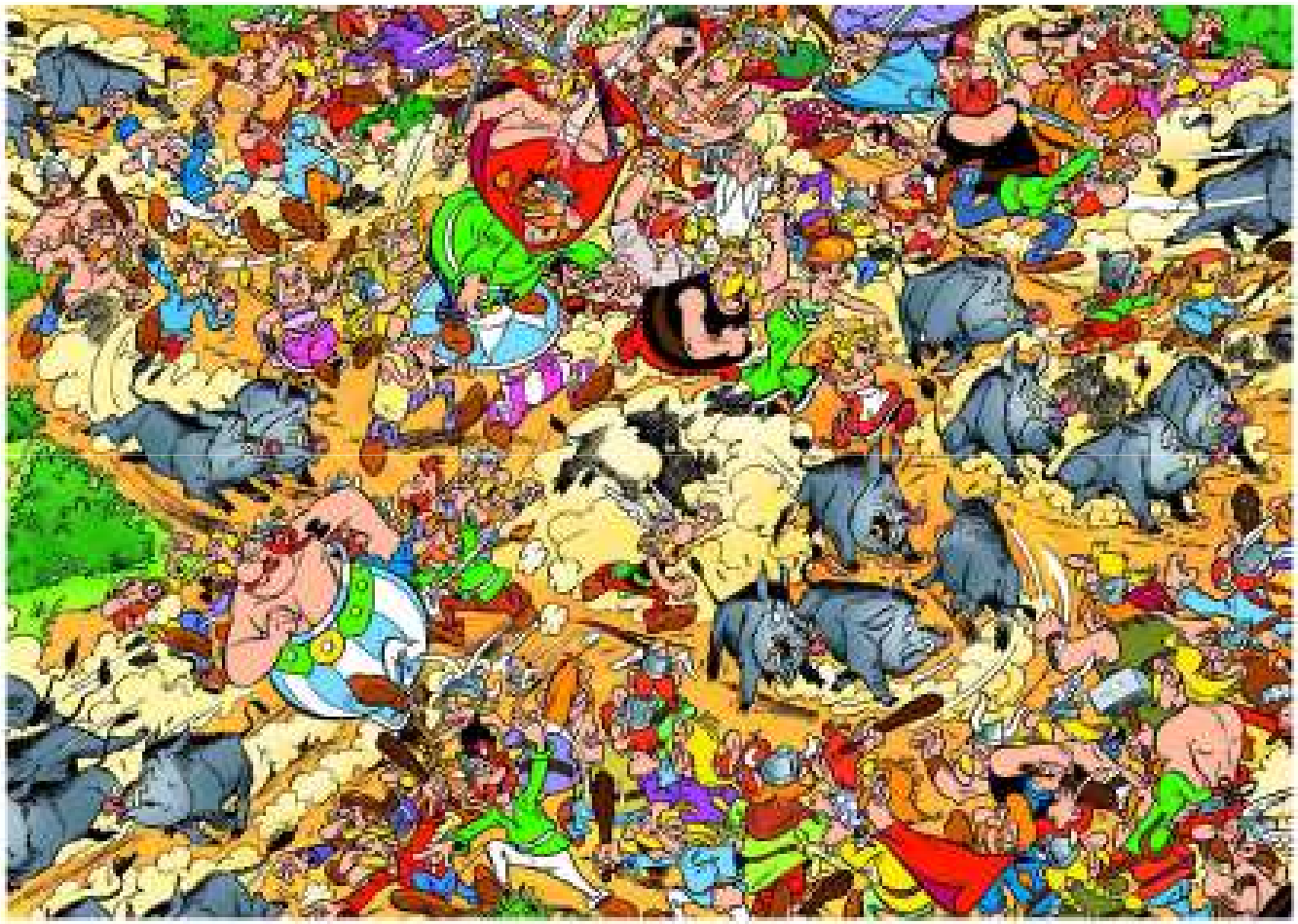
Which way ?

- Radiotherapy
  - Technique
  - Dose and fractionation
- Chemotherapy
  - New agents
  - Targeted agents
- Surgery
  - Selection of patients
  - Selection of centers
  - Techniques

- **Multidisciplinary tumor board**
  - Expertise
  - Clinical research





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Science versus Conscience versus EBM

	Surgery	CRT	CRT-S
Local Control	↗↗	↘↘	↗↗↗
Regional Control	↗	↗↗	↗↗
Distant Control	-	↗	↗
Late complications	↘↘	↘	↘↘↘
Overall survival	=	=	=
Quality of life	?	?	?

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CRAZY-FRANKENSTEIN.COM

Gastric Cancer – Staging & Imaging of primary & nodal subsite boundaries

Dr Angela M Riddell
Royal Marsden, London. UK

30/05/2016

STOMACH 7TH EDITION - AJCC

Primary Tumor		Regional Lymph Nodes	
TX	Primary tumour cannot be assessed	NX	Lymph nodes cannot be assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis
Tis	Carcinoma in situ	N1	1 to 2 regional lymph nodes
T1	Lamina propria or submucosa	N2	3 to 6 nodes (was N1)
– T1a	Lamina propria or muscularis mucosae	N3	≥ 7 nodes
– T1b	Submucosa	– N3a	7 to 15 nodes (was N2)
T2	Muscularis propria *(was T2a)*	– N3b	≥16 nodes (was N3)
T3	Subserosa *(was T2b)*	**Distant Metastasis**	
T4	Adjacent structures	M0	No distant metastasis
– T4a	Perforates serosa *(was T3)*	M1	Distant metastasis
– T4b	Other adjacent structures *(was T4)*		

Staging of Gastric Cancer

Two main categories:

Early gastric cancer

Malignant invasion confined to the mucosa & submucosa

Advanced gastric cancer

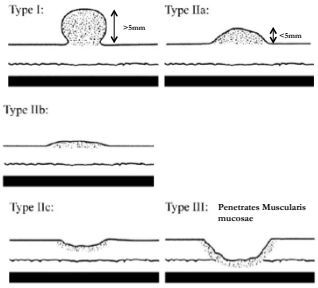
Malignant invasion into the muscularis propria

Early Gastric cancer

Elevated

Flat

Depressed



Adapted from: Ba-Ssalamah A, Prokop M et al. Radiographics 2003; 23:625-644

Gastric Cancer Staging

Diagnosis – Endoscopic biopsy

Initial Imaging:

MDCT

Potentially operable disease:

PET/CT – exclude distant spread

Laparoscopy

EUS – Early disease, Proximal/ Distal Extent

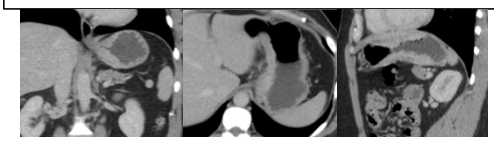
MRI

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

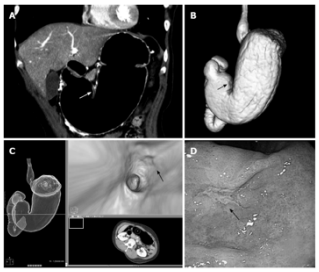
Portal venous phase imaging (70 second delay)
Thorax, abdomen & pelvis



Scan parameters aim to achieve resolution that can enable MPR postprocessing using isotropic voxels

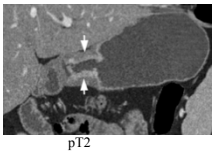
MDCT - Scan Technique

Virtual gastroscopy

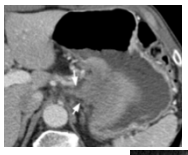


03/01/13

MDCT - T Staging



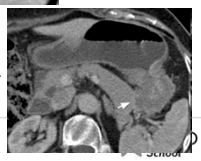
pT2
Smooth outer wall



pT3
Irregular outer wall due to infiltration into perigastric fat.

Parameter	Percentage range
Accuracy	77 - 89%
Sensitivity	83-100%
Specificity	80 -97%

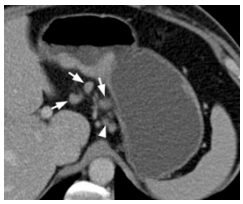
pT4
Direct infiltration of the pancreas



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



Parameter	Percentage range
Sensitivity	62.5 - 91.9%
Specificity	50 - 87.9%

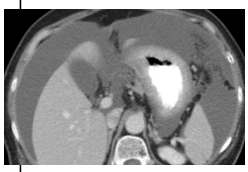
Stage	No of Regional Nodes
N1	≤2
N2	3-6
N3	≥7

Kwee RM, Kwee TC. 2009 Gastric cancer; 12: 6-22

MDCT – M staging

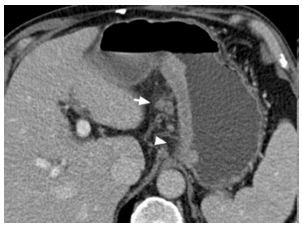
- Detection of hepatic mets: sens 88%, spec 99%*.
- Detection of peritoneal disease
  No ascites: sens 30%†
  In presence of ascites:
  Sens 51%, Spec 97%*

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.

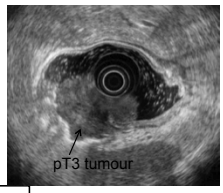
Gastric Cancer staging



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

EUS - N Staging

Provides morpholgical information
- Malignant nodes: round, hypoechoic, lose echogenic hilum
- Fine needle aspiration (FNA) possible

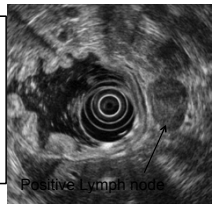
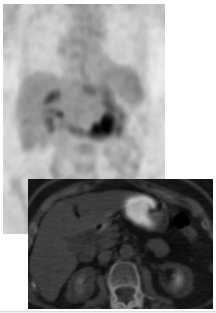


Image from: Bohle W et al. 2011 J Gastrointestin Liver Dis; Vol. 20 No 2, 135-139

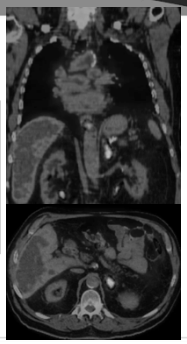
^{18}FDG-PET/CT

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
- ^{18}FDG-PET/CT not currently advocated for gastric cancer staging



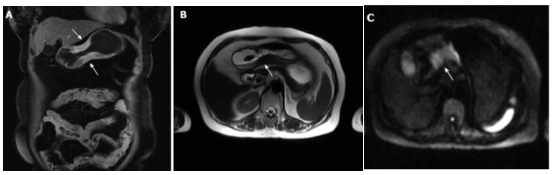
^{18}FDG-PET/CT

Main advantage
Identification of occult metastatic disease*



*Kinkel K, Ying L et al (2002) Radiology 224:748–756

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

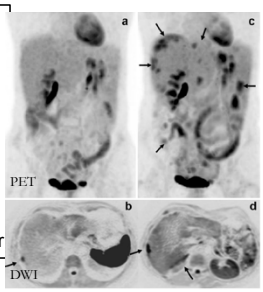
M Staging – Peritoneal disease

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

Summary

Staging
- MDCT – exclude metastatic disease
- PET-CT – refine staging & localise tumour

- EUS – defining prox / distal extent
- MRI – research

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Primary & Nodal subsite boundaries

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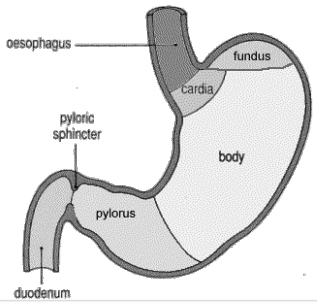
Anatomical regions of the stomach



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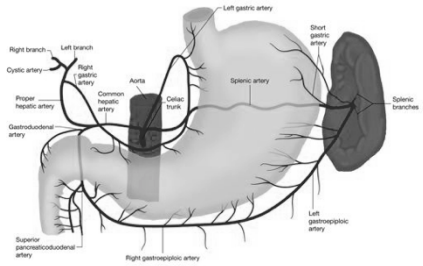
Anatomy – stomach arterial supply



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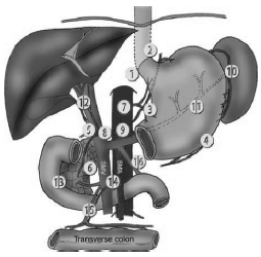
Upper Abdominal Lymph nodes groups



Station Number	Name
1	right cardia
2	left cardia
3	lesser curvature
4	greater curvature
4sa; 4sb; 4d	short gastric; left gastroepiploic; right gastroepiploic
5	Suprapyloric
6	Infrapyloric
7	left gastric artery
8	common hepatic artery
9	celiac trunk
10	Splenic hilus
11	Splenic artery
12	hepatoduodenal ligament
13	posterior surface of the head of the pancreas
14	root of the small bowel mesentery
15	Paracolic
16	Para-aortic

Lim J S, Yun M J, Kim M J et al 2006. Radiographics; 26: 143-156

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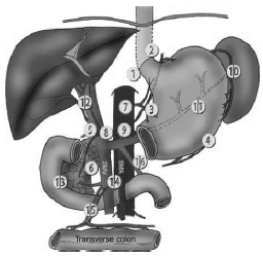
Upper Abdominal Lymph nodes groups



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15	Paracolic
16	Para-aortic

D1

Lim J S, Yun M J, Kim M J et al 2006. Radiographics; 26: 143-156

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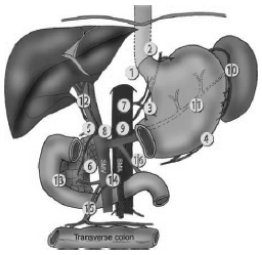
Upper Abdominal Lymph nodes groups



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15	Paracolic
16	Para-aortic

D2

Lim J S, Yun M J, Kim M J et al 2006. Radiographics; 26: 143-156

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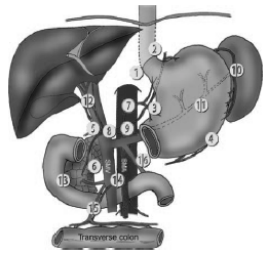
Upper Abdominal Lymph nodes groups



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D3

Lim J S, Yun M J, Kim M J et al 2006. Radiographics; 26: 143-156

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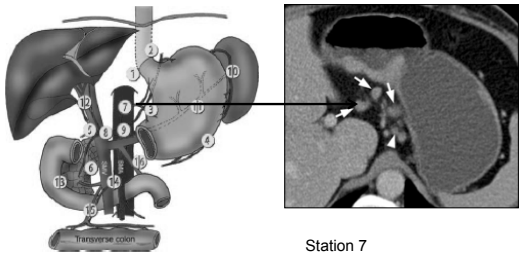
Upper Abdominal Lymph nodes groups



Station 7
Left gastric artery territory

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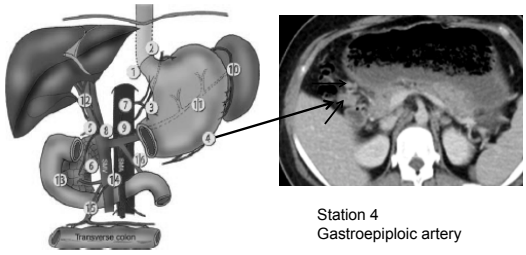
Upper Abdominal Lymph nodes groups



Station 4
Gastroepiploic artery

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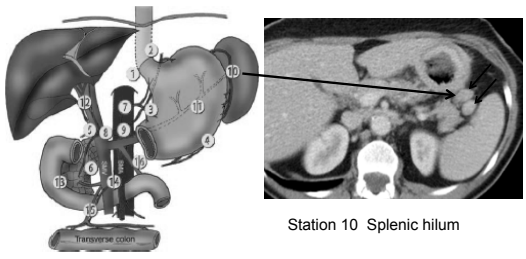
Upper Abdominal Lymph nodes groups



Station 10 Splenic hilum

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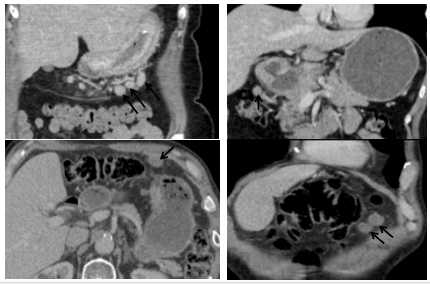
Upper Abdominal Lymph nodes groups

Difficulty distinguishing Gastroepiploic nodes from peritoneal disease



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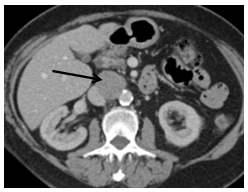
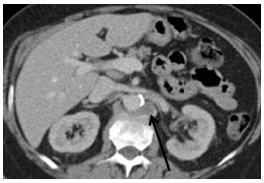
Upper Abdominal Lymph nodes groups



Station 16 Para aortic



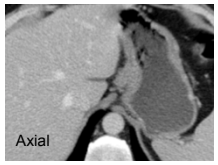
Metastatic nodes

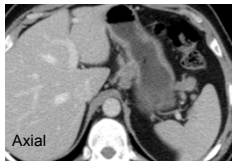
Case 1

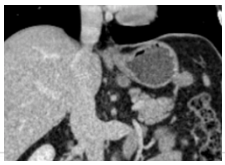
Case 1

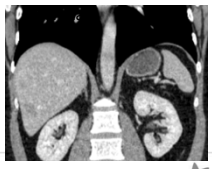
- 65yr old male presented with abdominal pain and weight loss

Case 1





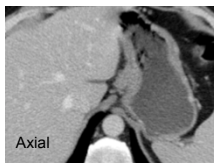


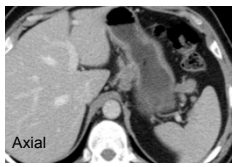


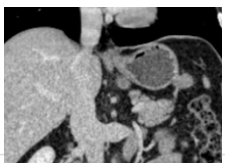
Case 1

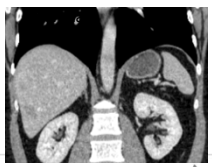
- Stage the tumour
- If there are nodes involved; state which nodal stations

Case 1









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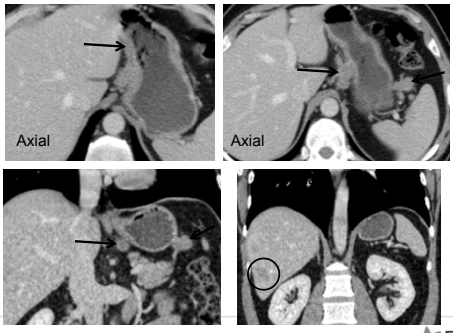


Case 1

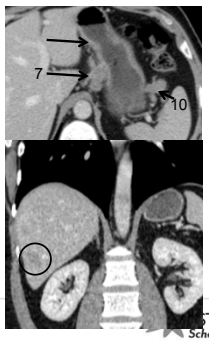
Tumour stage:

T3N2M1

Nodal Stations

Left gastric artery – 7

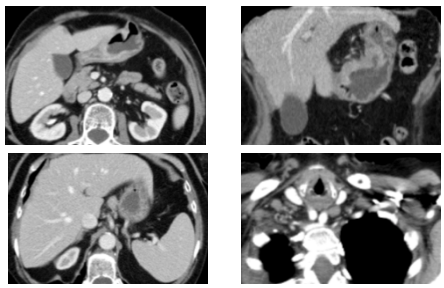
Splenic hilum - 10



Case 2

72 year old female with weight loss and anaemia

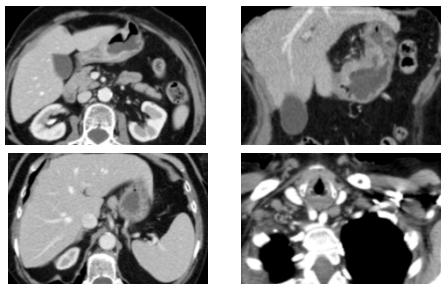
Case 2



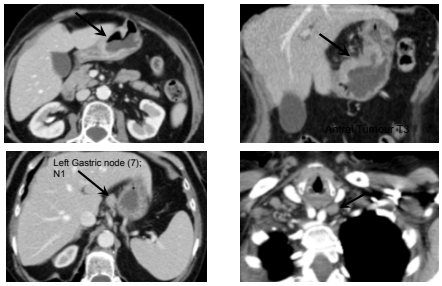
Case 2

- Describe the location of the tumour
- Stage the tumour
- Identify any nodal stations involved

Case 2



Case 2



T3N1 ?? M1 – Supraclavicular node…

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Case 2

What to do next?

- Consider supraclavicular node positive based on size (9mm)?
- Arrange a PET-CT scan
- Arrange an U/S +/- FNA

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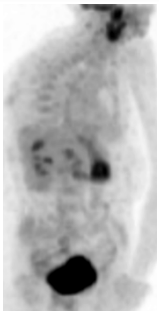
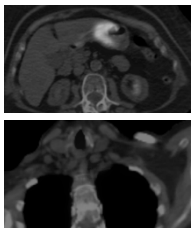
Case 2

Moderate FDG avidity in node 'equivocal' on PET-CT

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Case 2

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

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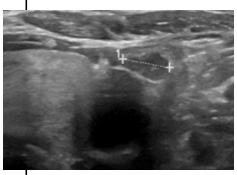
Case 2

- An U/S with FNA was arranged
- Sonographic appearance in keeping with a reactive node.
- Cytology – C1



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Case 2

The patient was given neoadjuvant therapy

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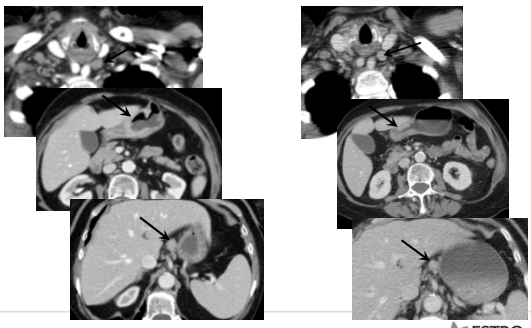
Case 2



Post x2 Chemo cycles - PR

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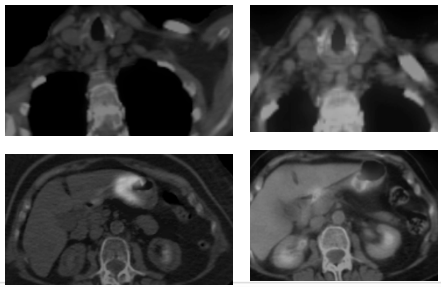
Case 2



Post x2 Chemo cycles - PR

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Case 2

- 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.

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Thank you

03/01/13

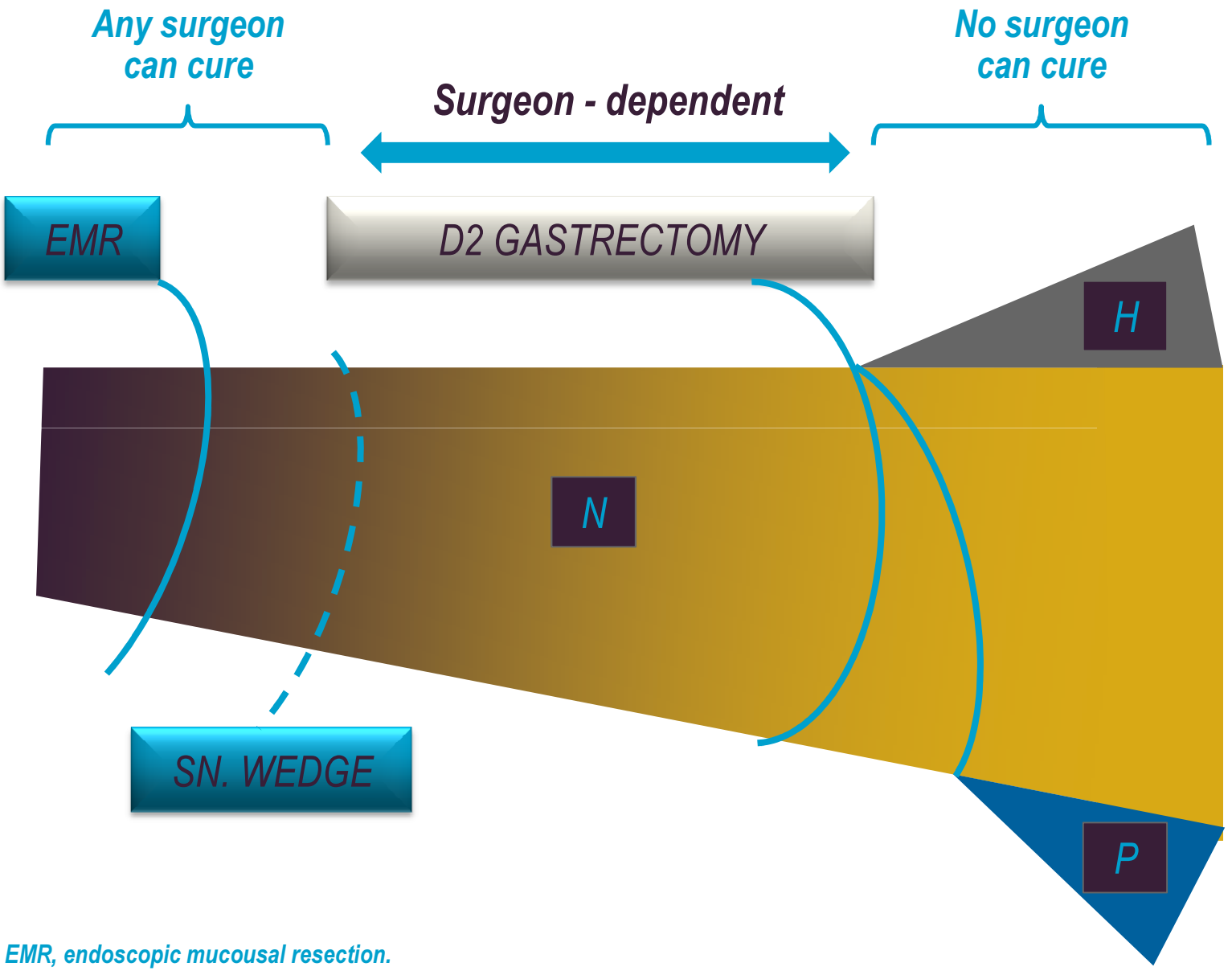
ESTRO School

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

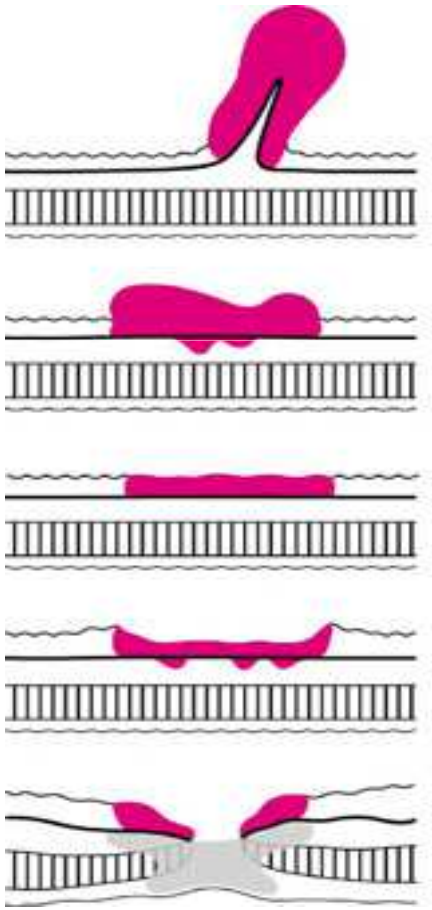
NHS



EMR, endoscopic mucousal resection.

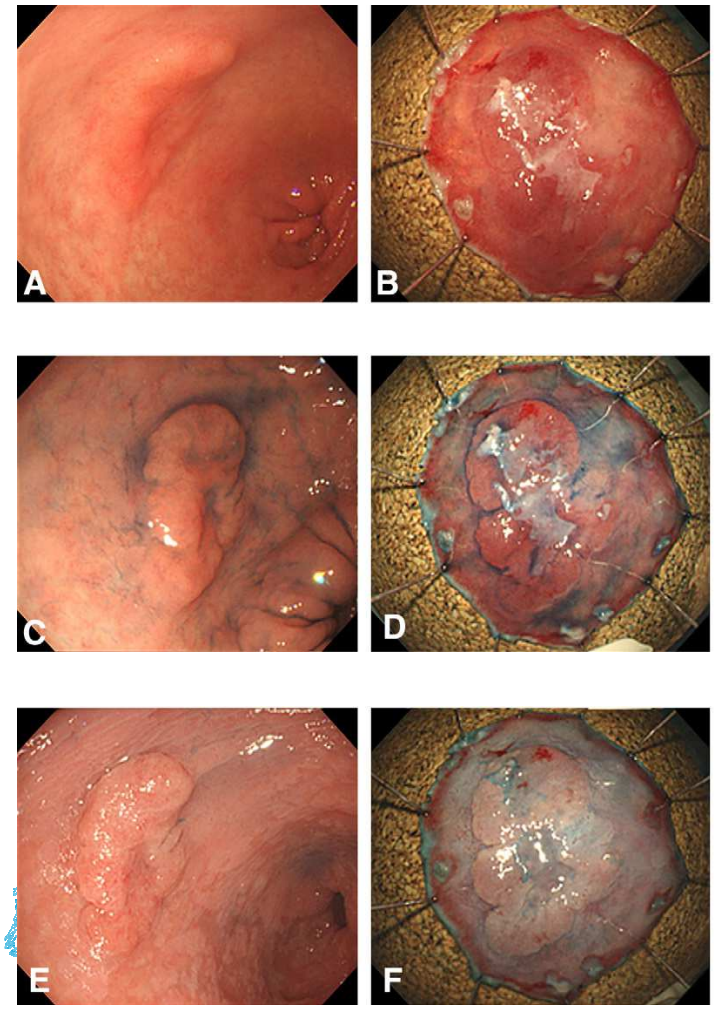
Multipurpose device

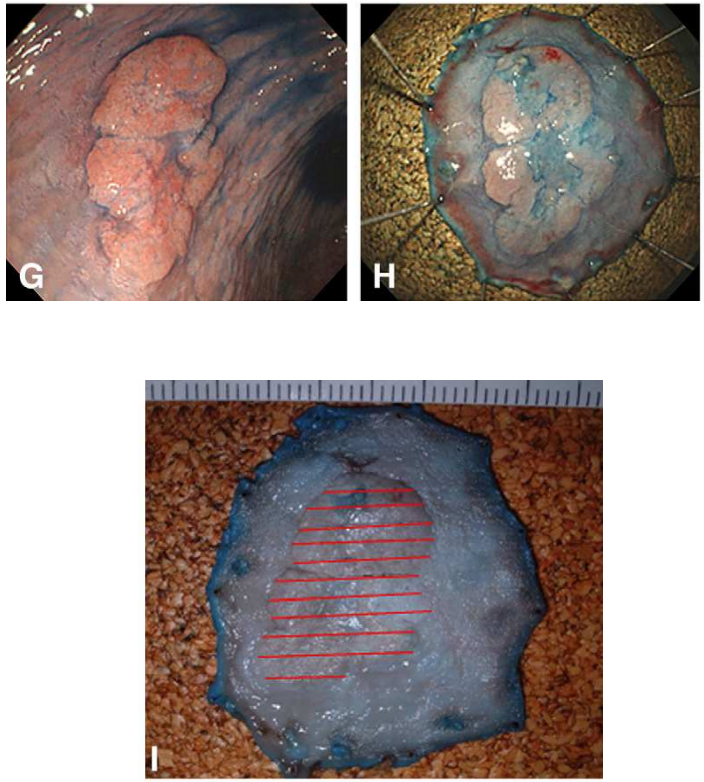
T1 TUMOURS



- 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

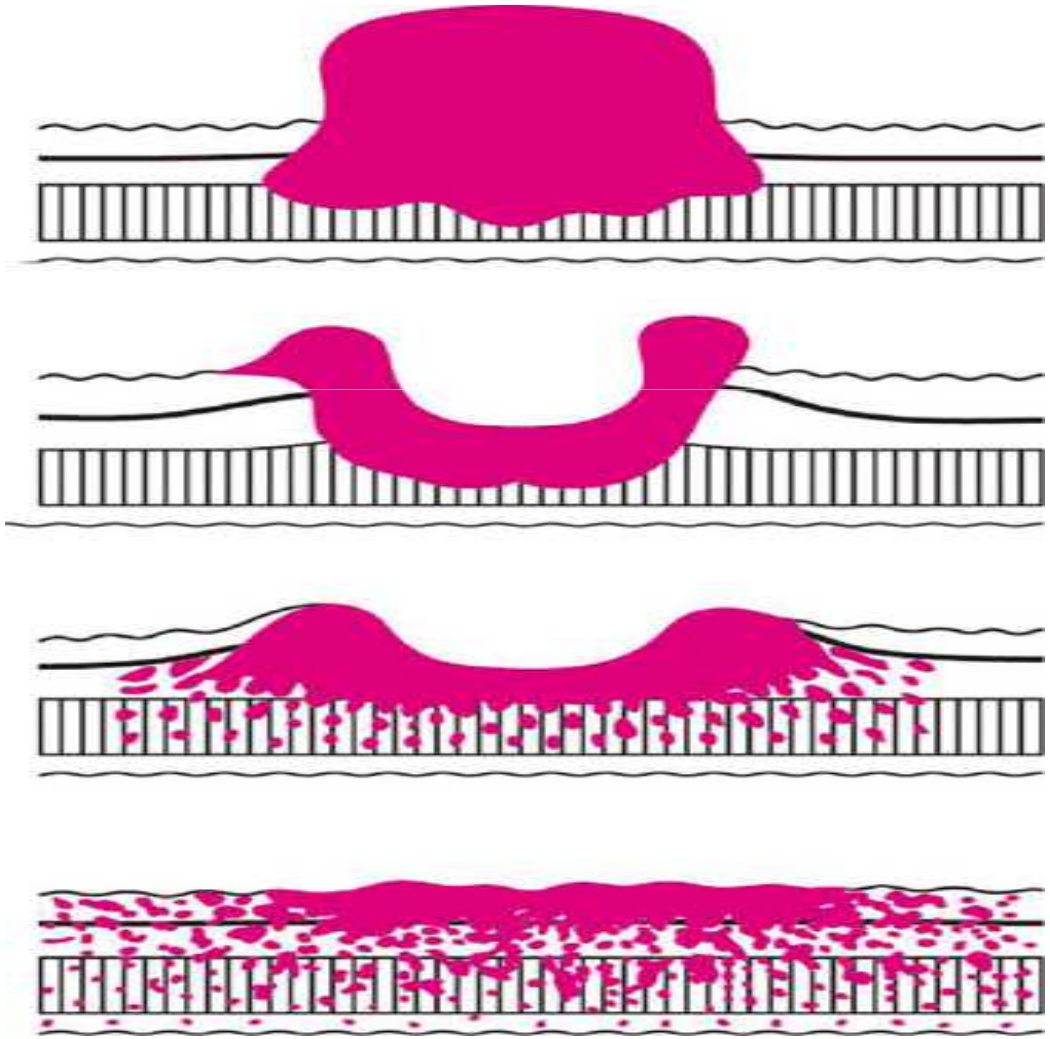
Multiple sections of LN detects metastasis

SURGERY FOR EARLY GASTRIC CANCER

T1 m	D1 alpha (Stations 7 & 8)
T1 sm	D1 beta (D1 alpha + station 9 & 11p)

Function preserving gastrectomy

LOCALLY ADVANCED GASTRIC CANCER



Mass

Ulcerative

Infiltrative, ulcerative

Infiltrative, diffuse

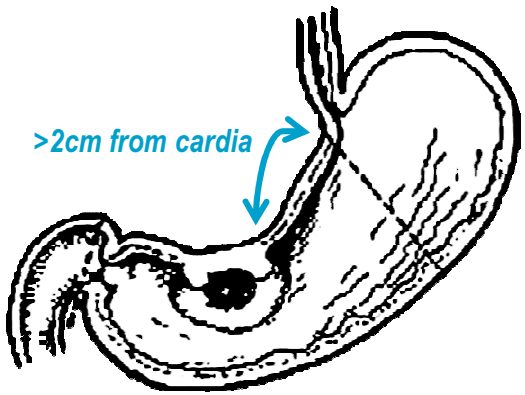
R0 Resection

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

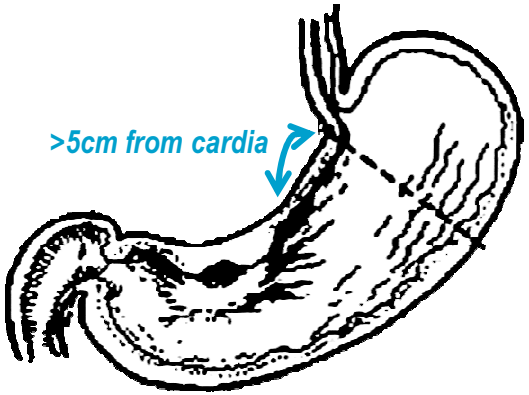
Hermanek P, Wittekind C. Pathol Res Pract. 1994;190(2):115-123.

Indication and Division Lines for Distal Subtotal and Total Gastrectomy

Distal subtotal gastrectomy

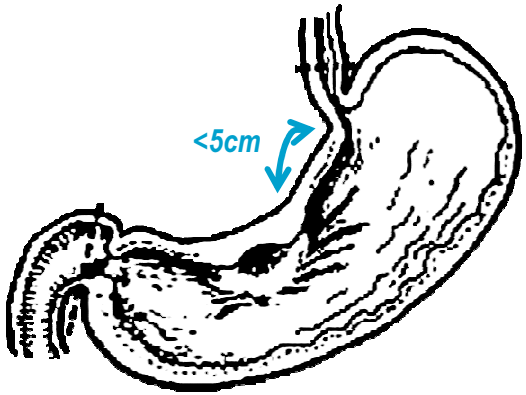


Early cancer or well-circumscribed advanced cancer

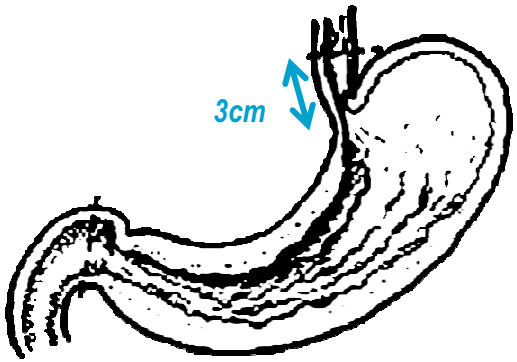


Infiltrative advanced cancer

Total gastrectomy

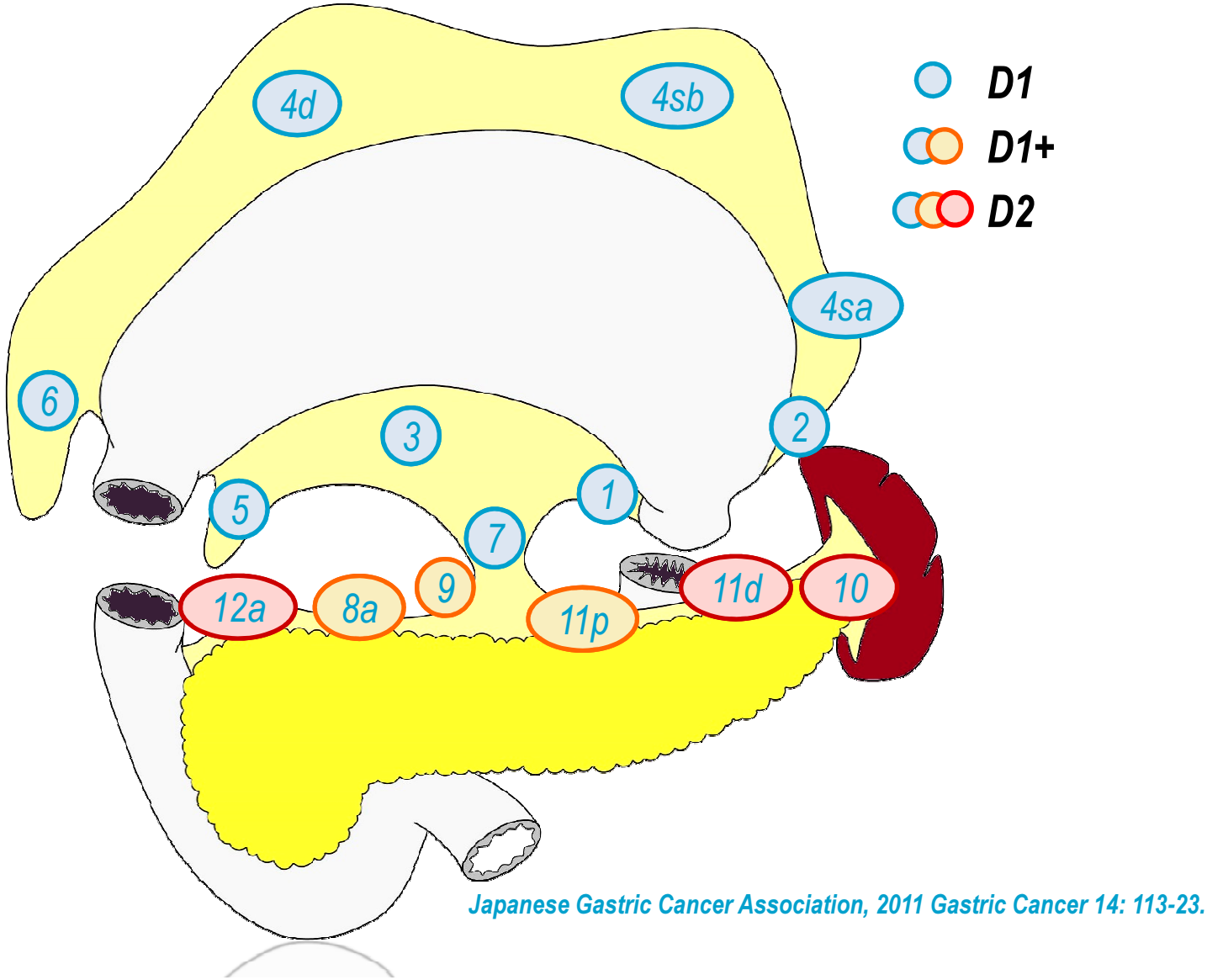


When the proximal distance from the cardia is less than the required length, total gastrectomy is indicated



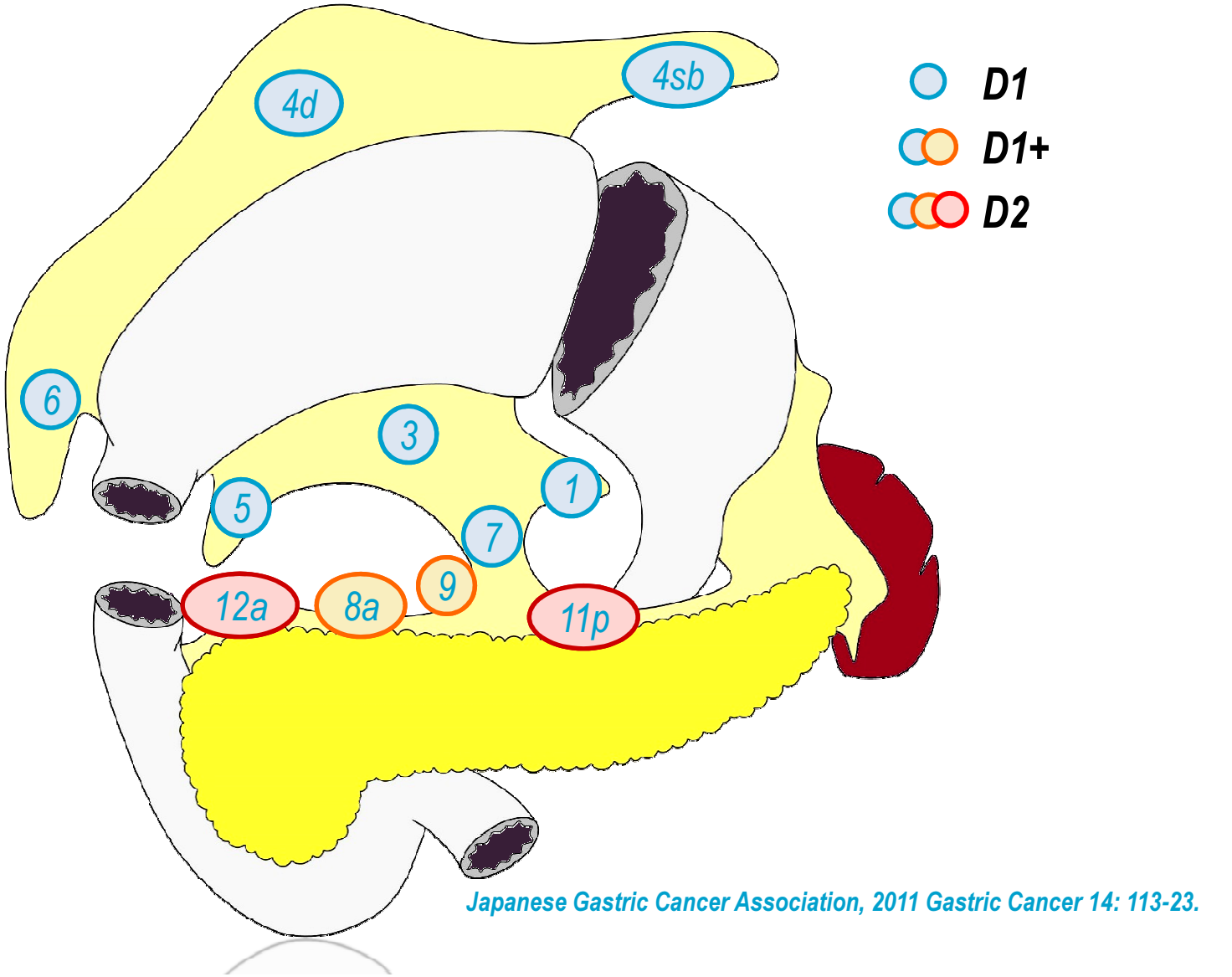
Total gastrectomy is always indicated in diffuse carcinoma (Borrmann type 4) regardless of its size

Total Gastrectomy and Lymph Node Dissection



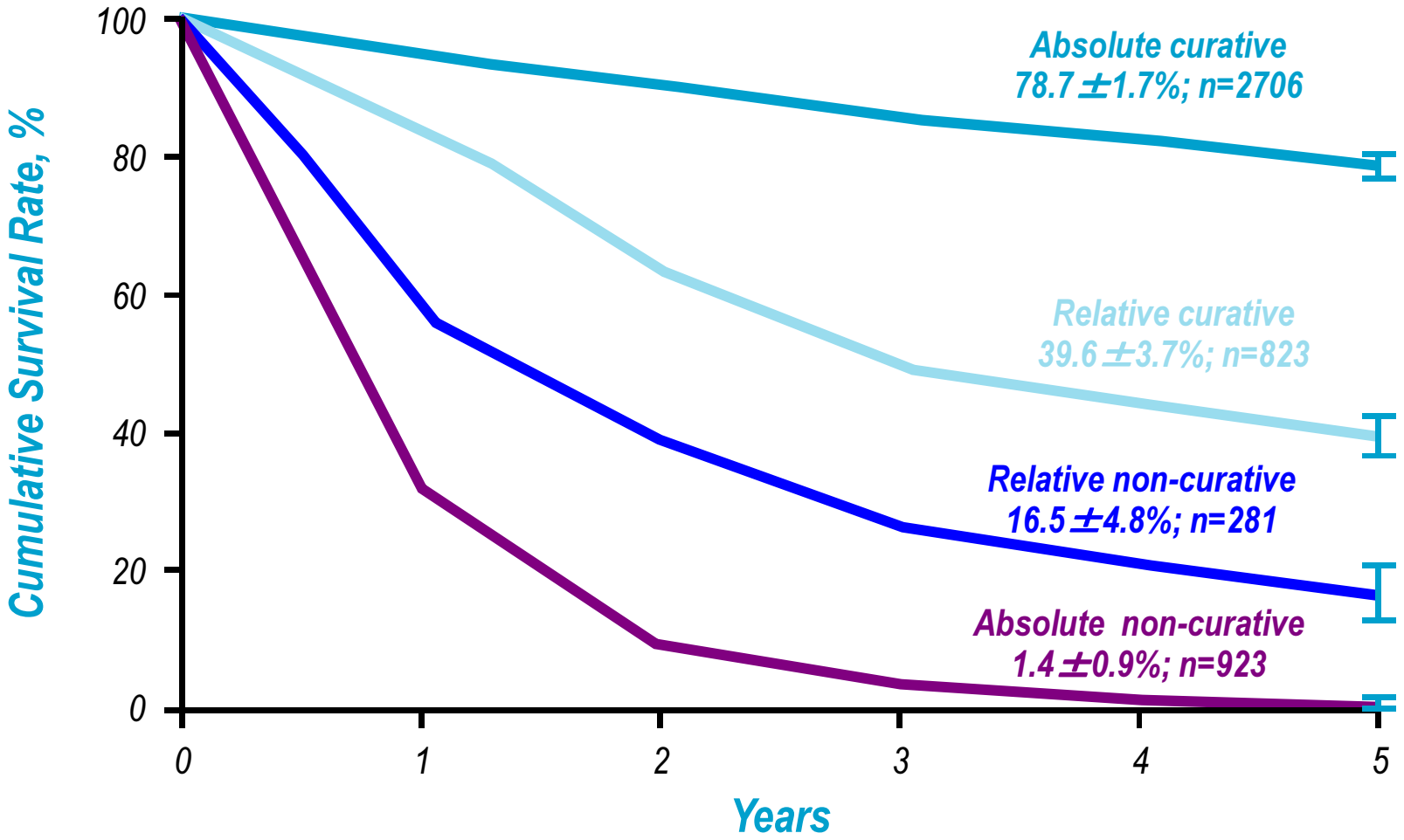
Japanese Gastric Cancer Association, 2011 Gastric Cancer 14: 113-23.

Distal Gastrectomy and Lymph Node Dissection



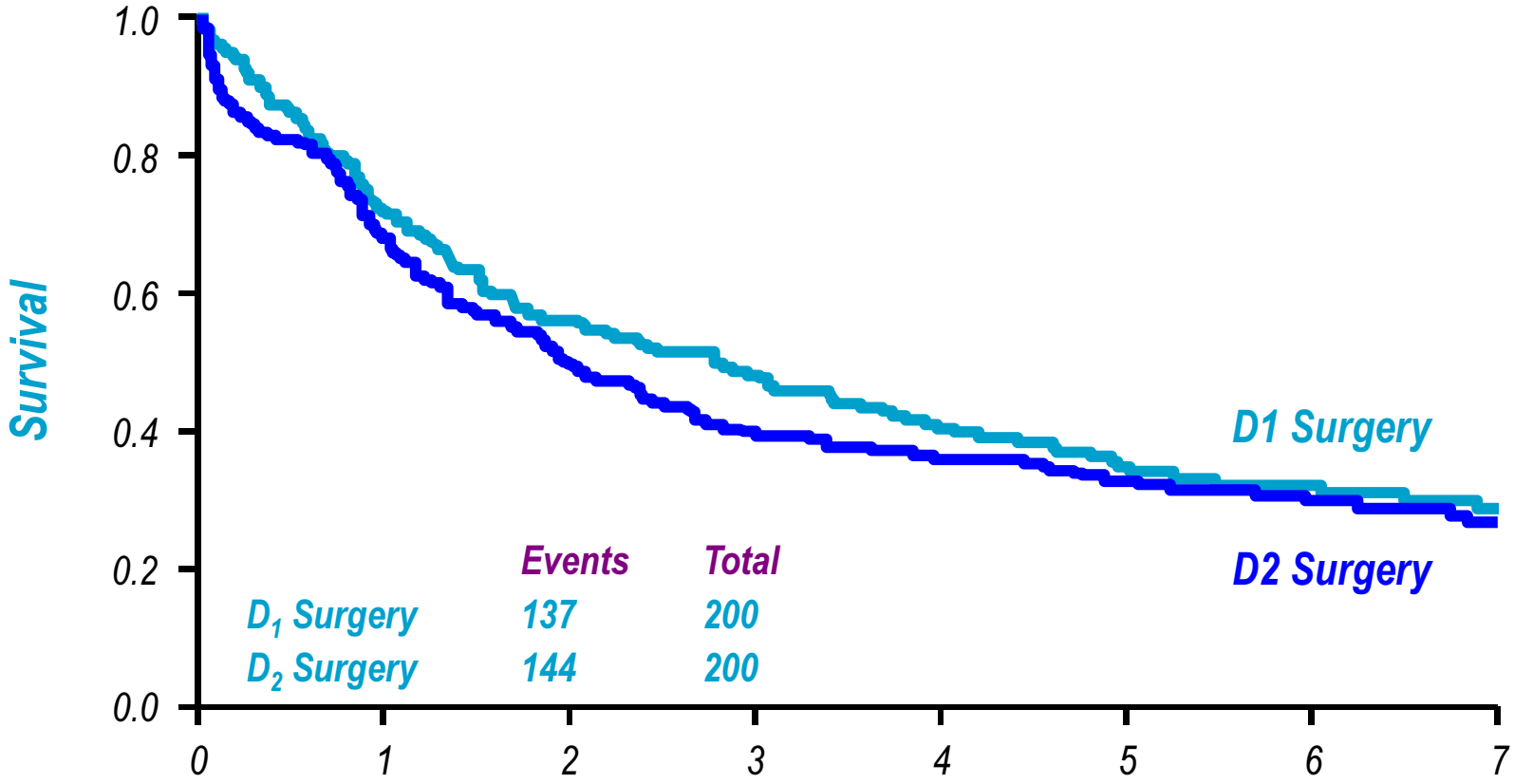
Japanese Gastric Cancer Association, 2011 Gastric Cancer 14: 113-23.

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%

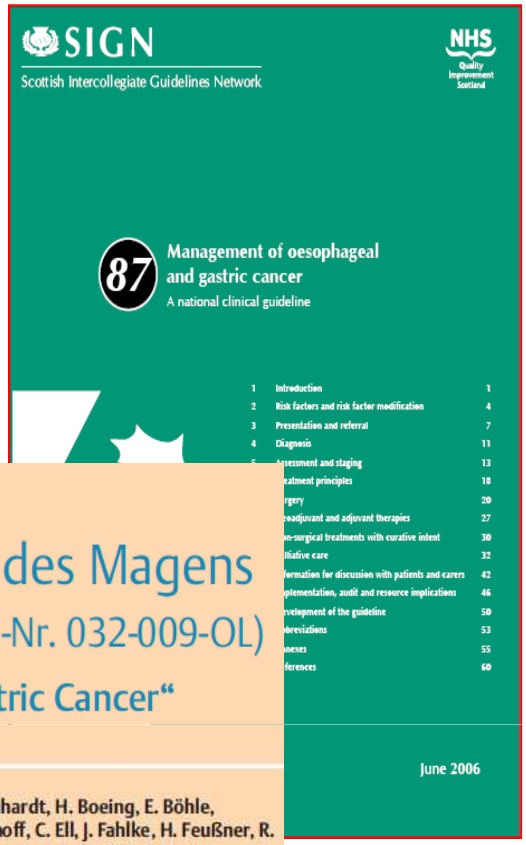
Degiuli M, et al. Br J Surg. 2014; 101:23-31

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	D2 – without pancreatectomy or splenectomy
	R0	

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.

The Royal Marsden

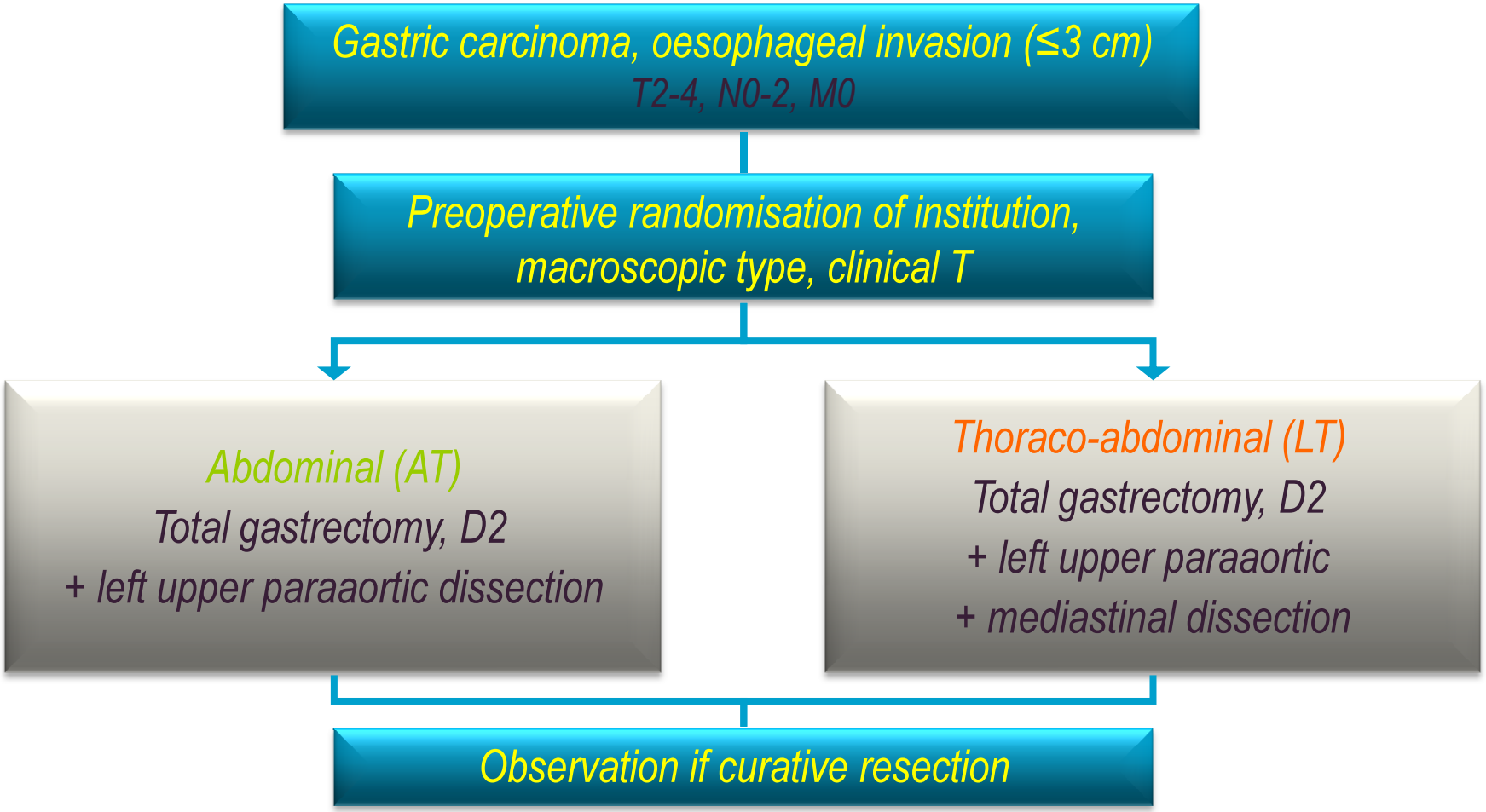
JCOG 9502

Randomized trial in Siewert type II and III cancers

Left thoraco-abdominal approach versus abdominal transhiatal approach

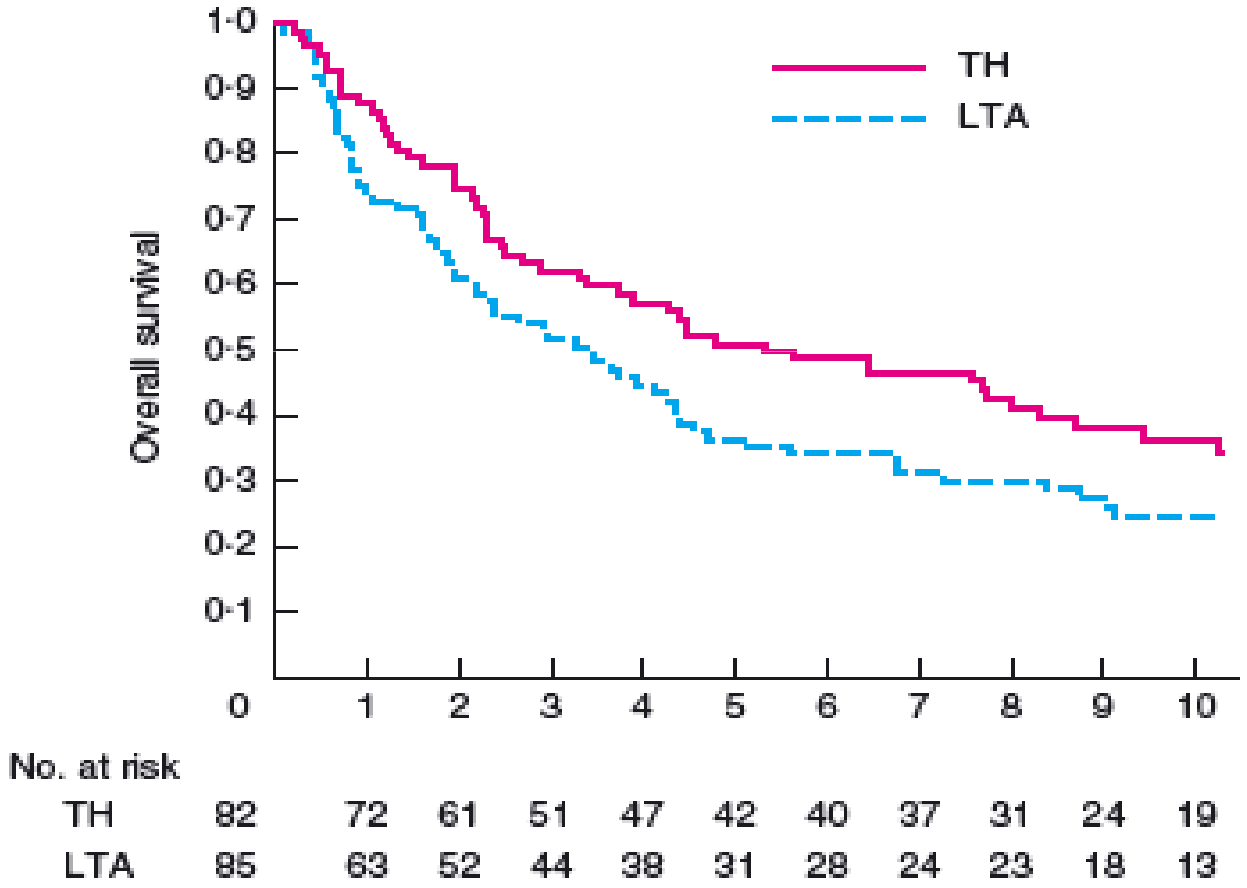
JCOG, Japan Clinical Oncology Group.
Sasako et al. Lancet Oncol. 2006;7(8):644-651; BJS 2015; 102:341-8.

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.

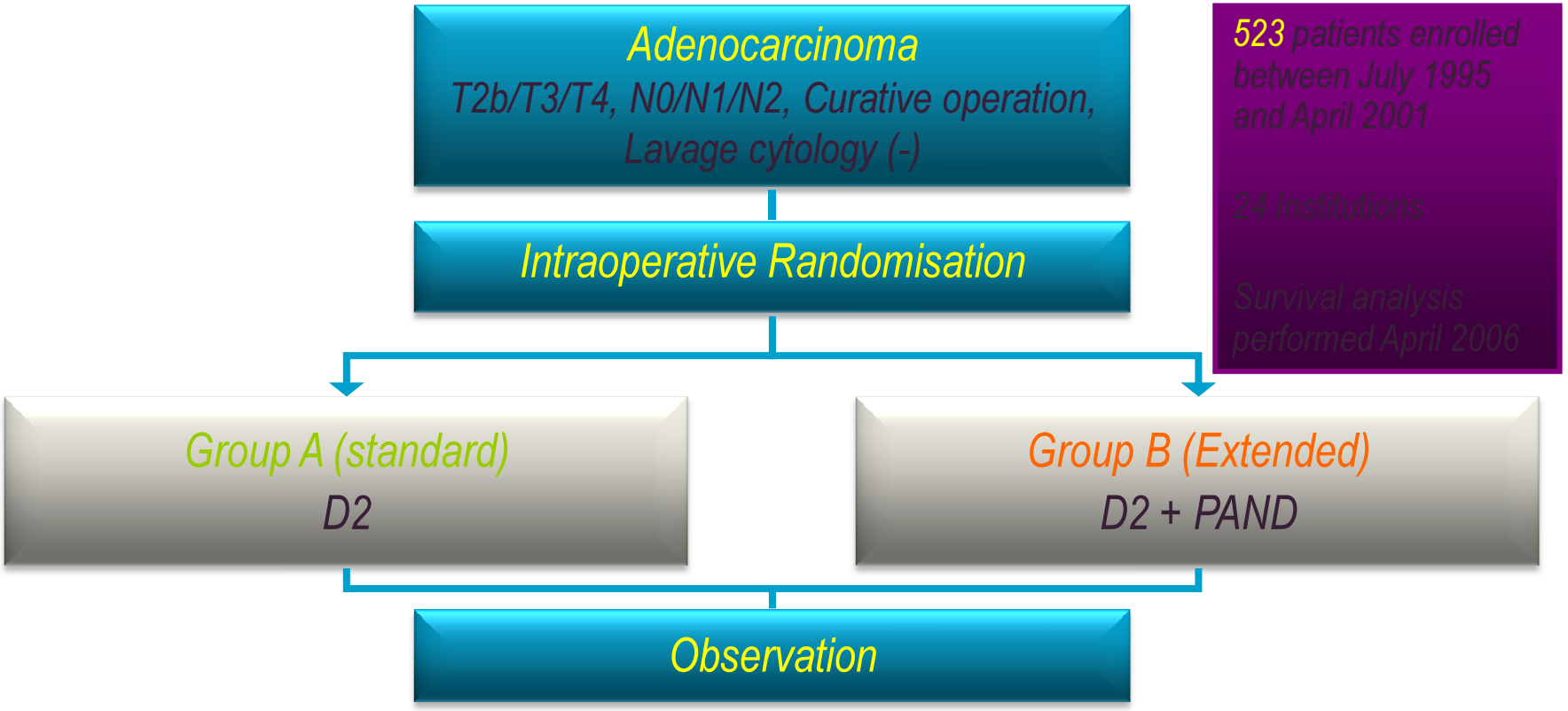
The Royal Marsden

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

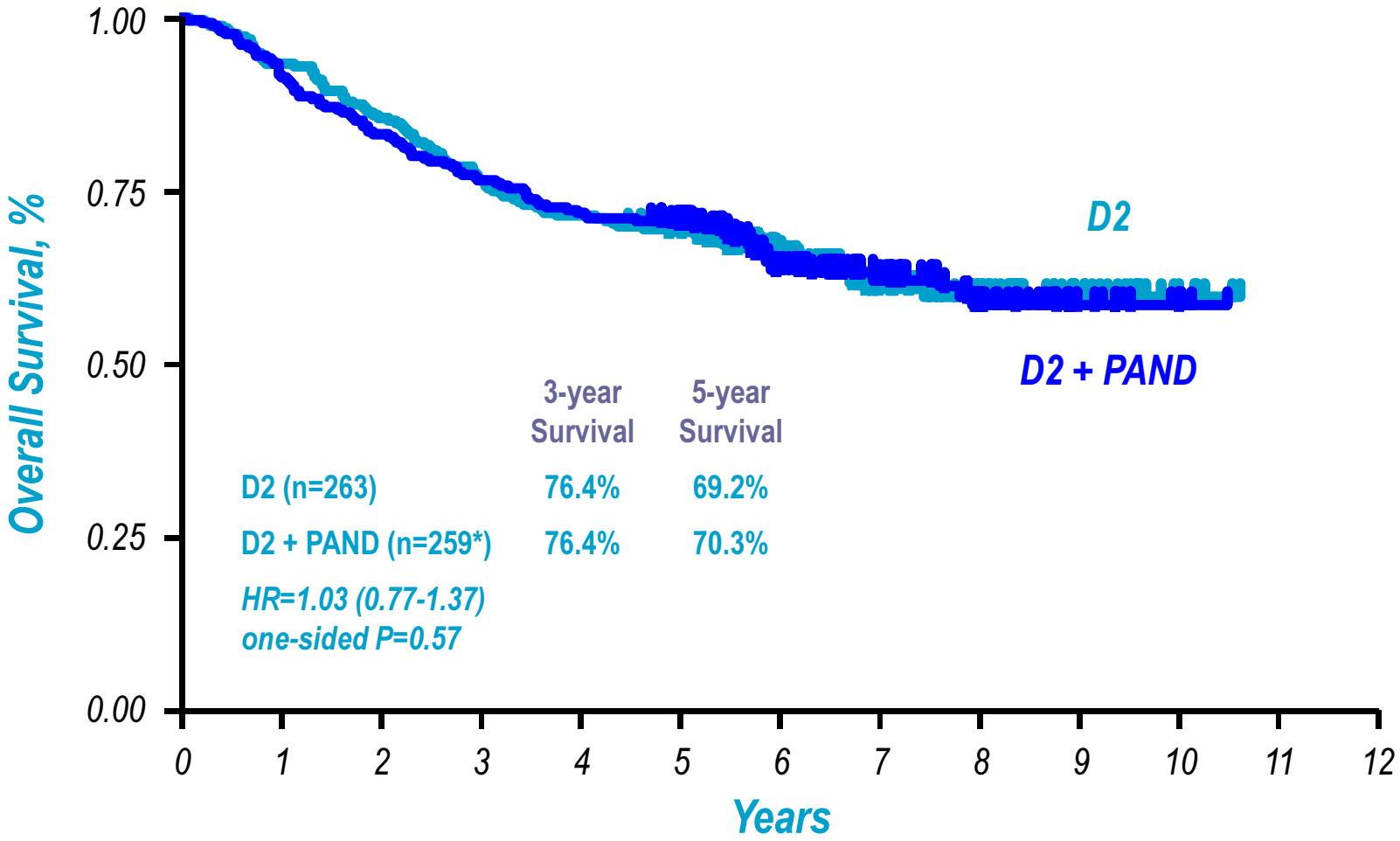
Endpoints

1. Overall survival
2. Recurrence-free survival, morbidity/mortality

PAND, para-aortic nodal dissection.

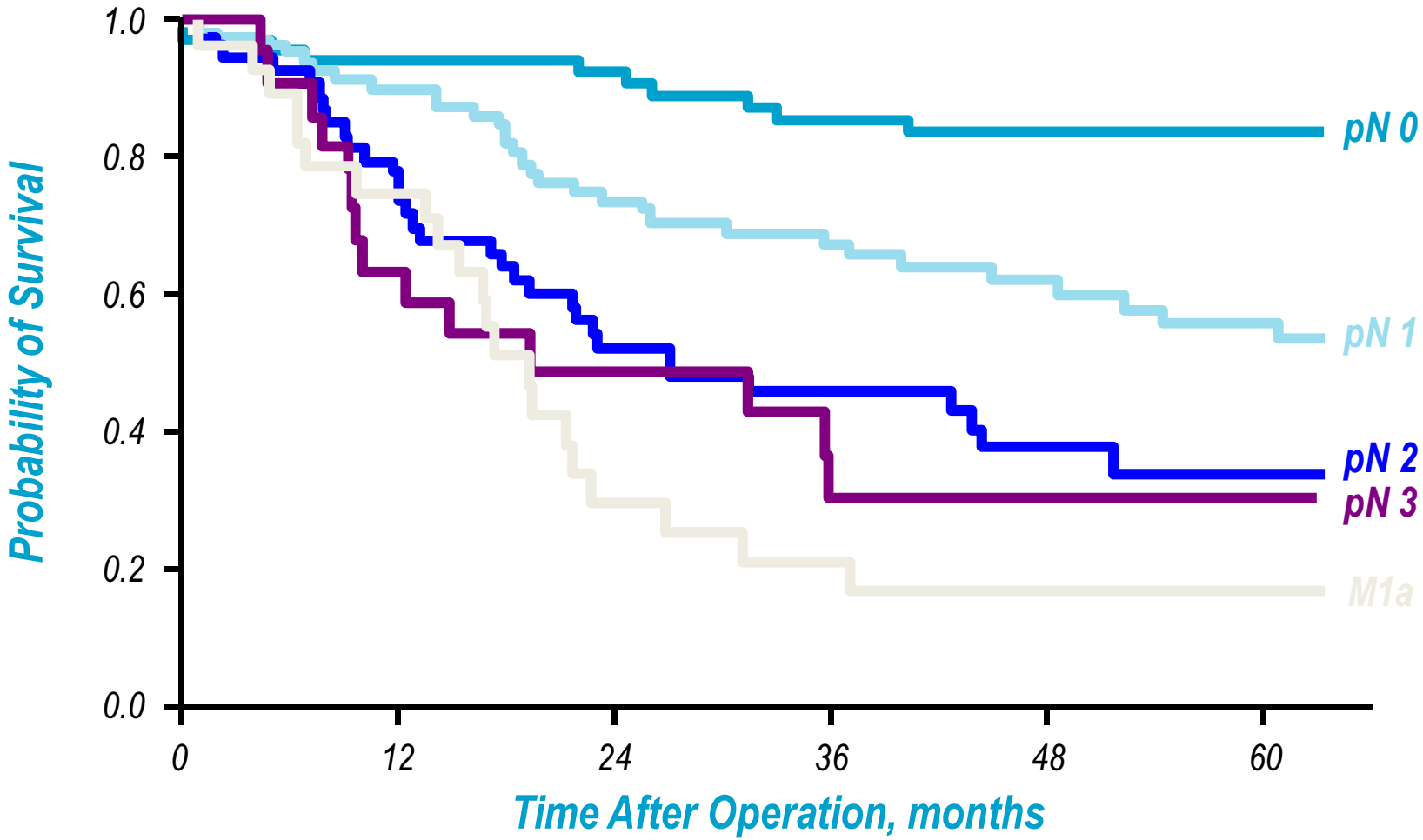
Sasako M, et al. N Eng J Med. 2008;359(5):453-462.

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

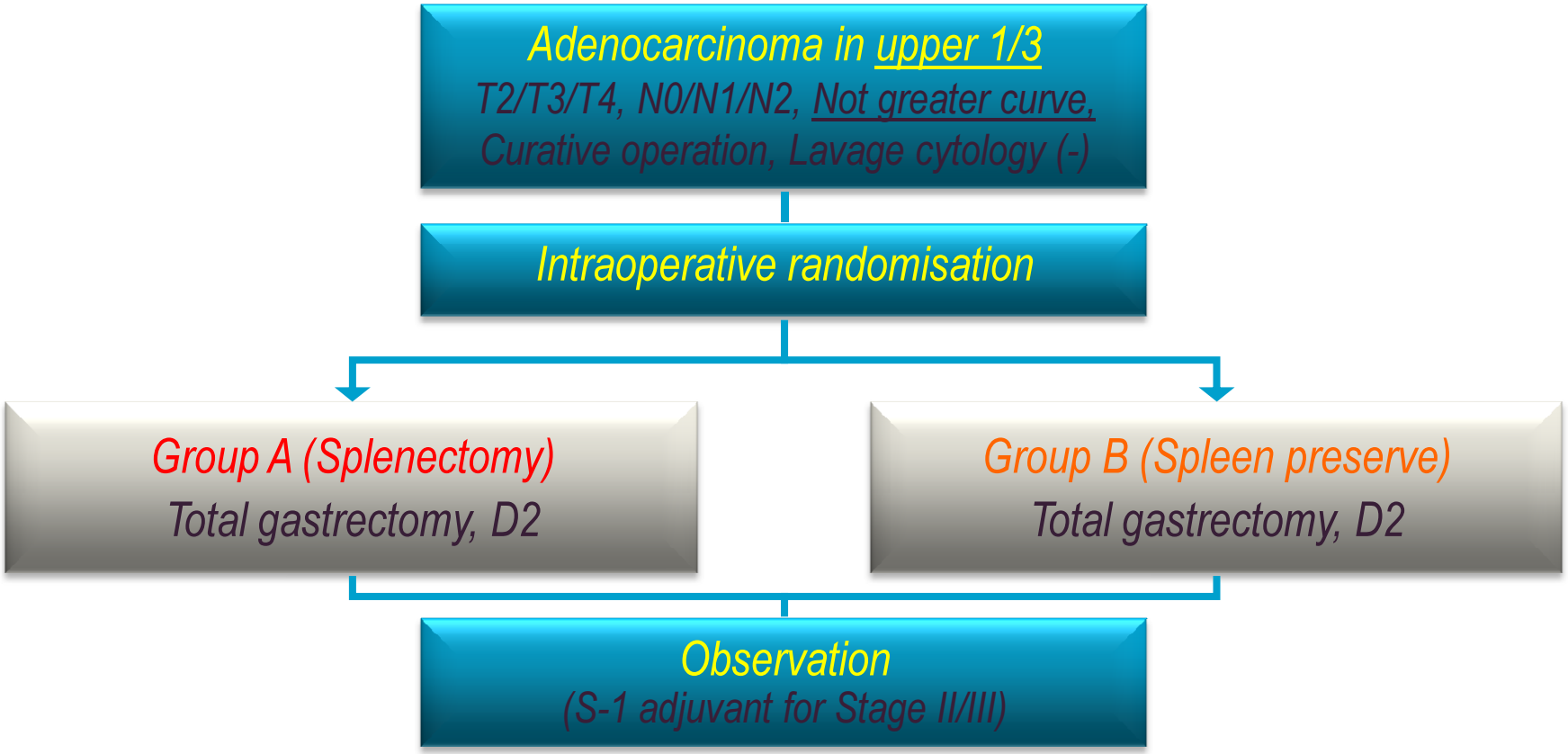
T3/4 cancers

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

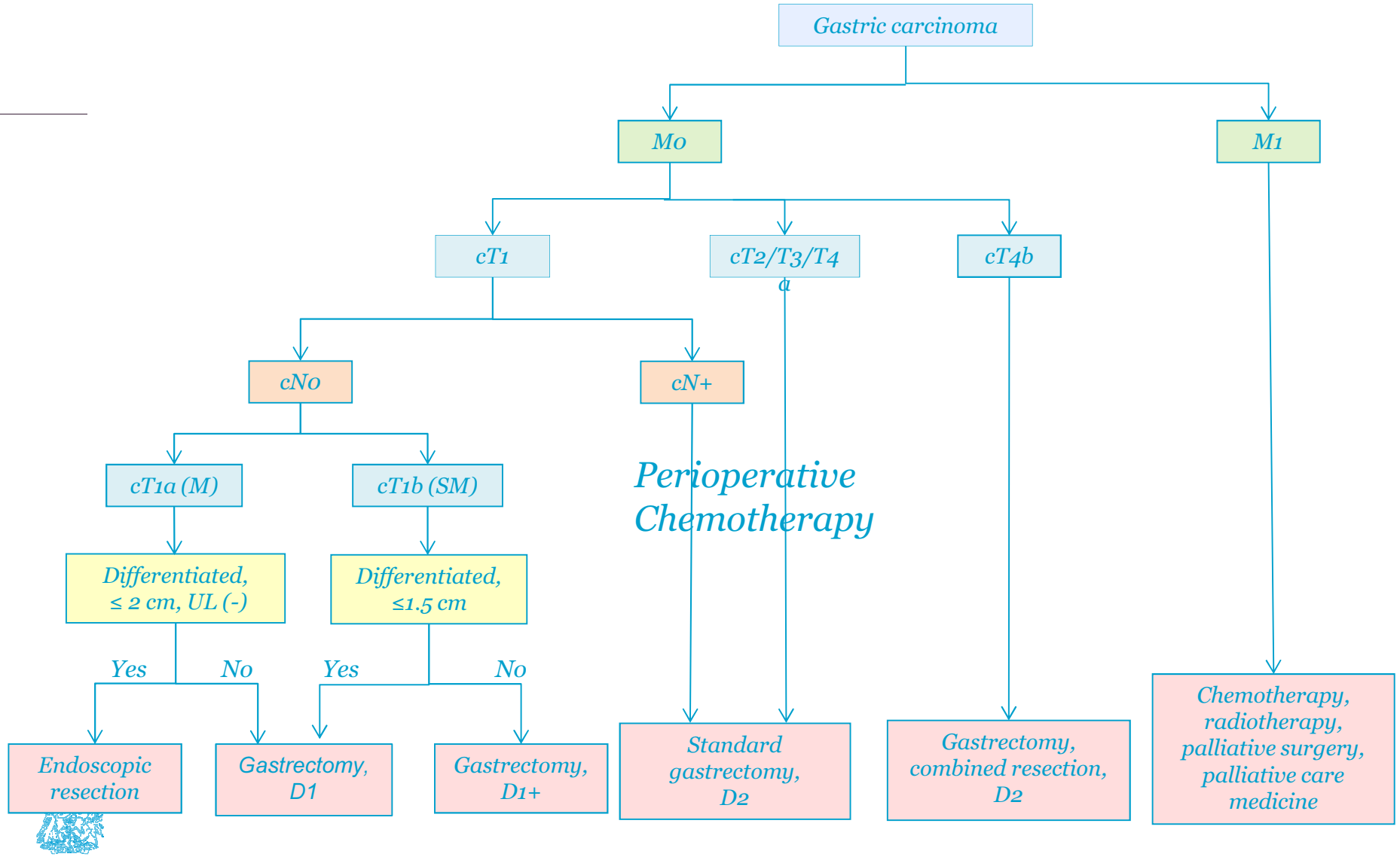
JCOG 0912

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.

The Royal Marsden

Algorithm of Standard Treatment



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%


Thank you for your attention
FULHAM ROAD

The Royal Marsden

The Royal Marsden

Upper GI: technical and clinical challenges for RO

State of art of radiation therapy

in a combined treatment perspective

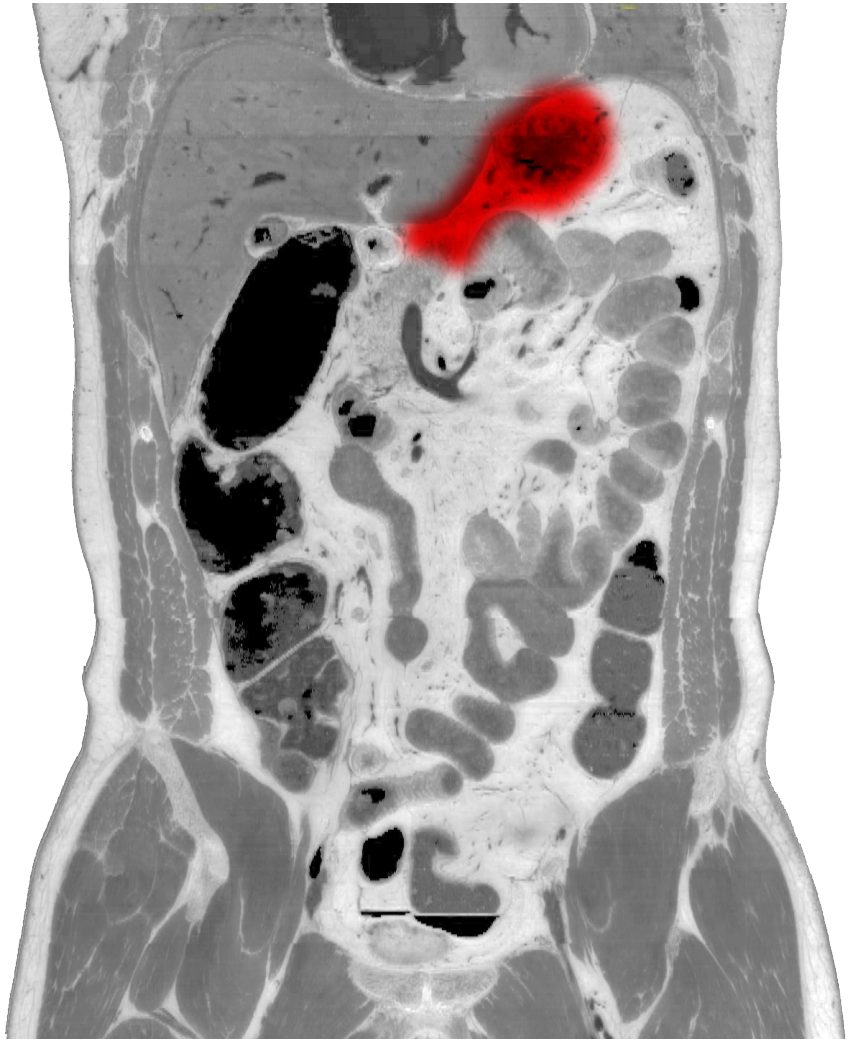
State of art of radiation therapy in Gastric Cancer

- ✓ **Background** and **assumptions**
- ✓ **Post-operative** Chemoradiation
- ✓ **Pre-operative Chemoradiation**
- ✓ **Intra-operative RT**

✓Background and assumptions: the challenge

Sites of Recurrence

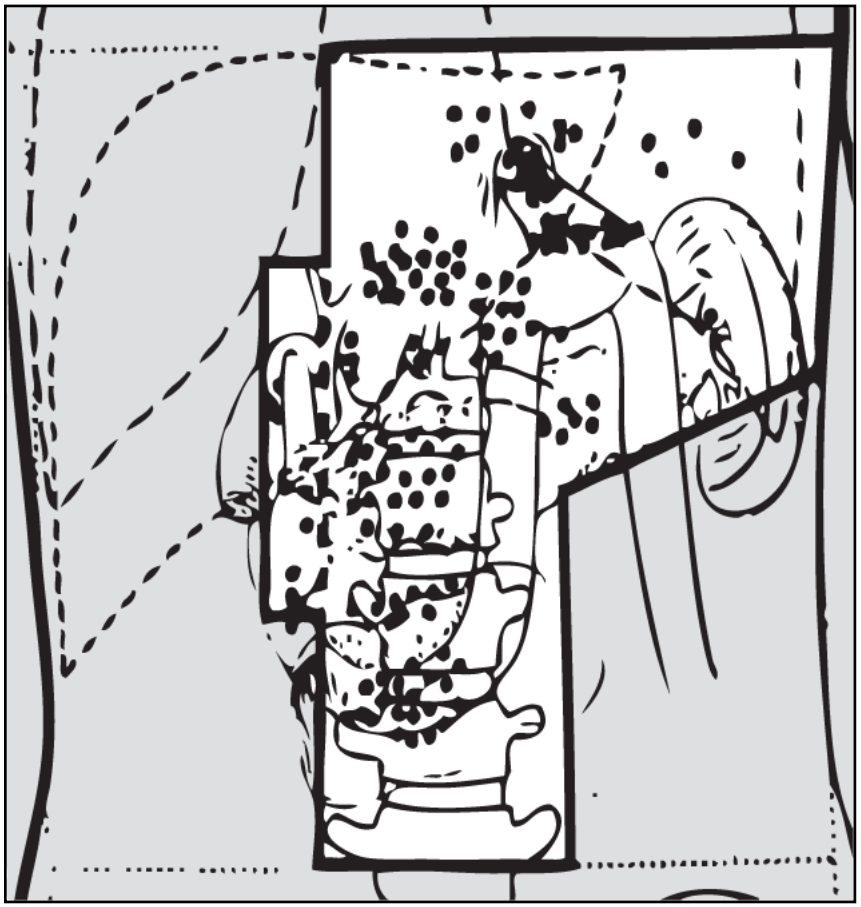
Only Failure	Any Component
23%	69%
21%	42%
5%	23%



Gunderson LL Sosin H – IJROBP - 1982

ESTRO School

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	28.5	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

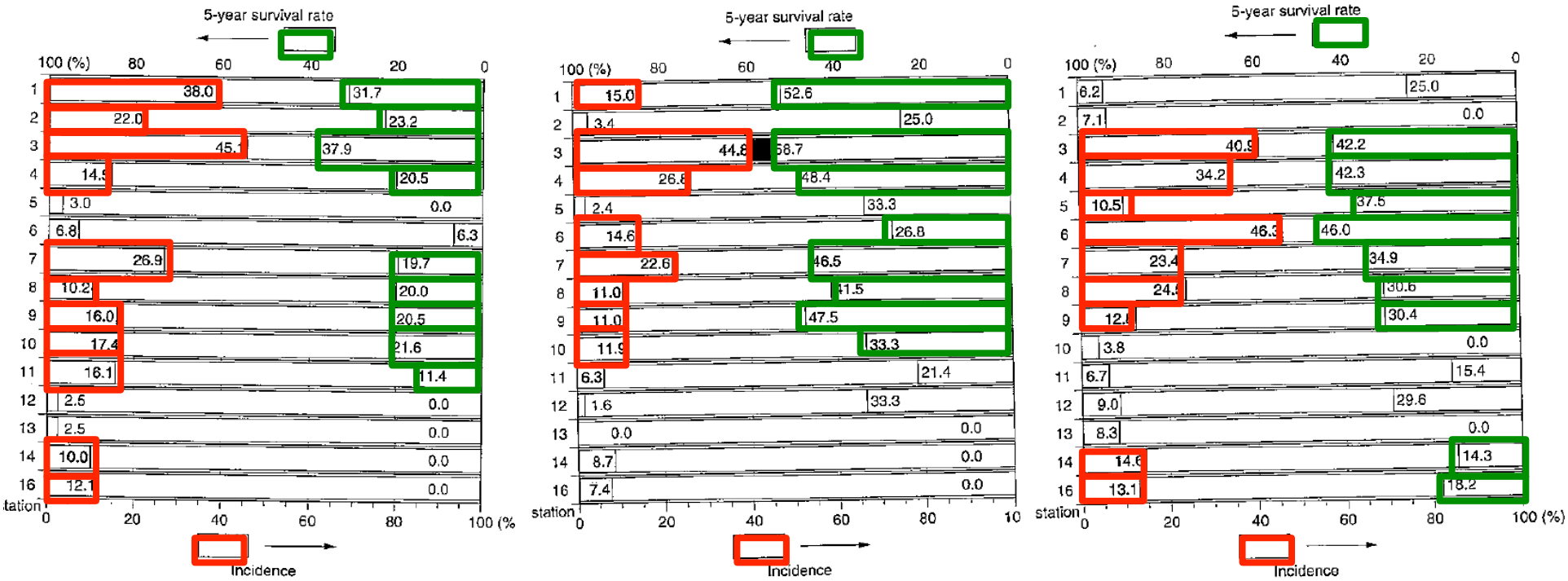
22.3%

Valentini V et Al – Exp Rev – 2007

ESTRO School

✓Background and assumptions: the challenge

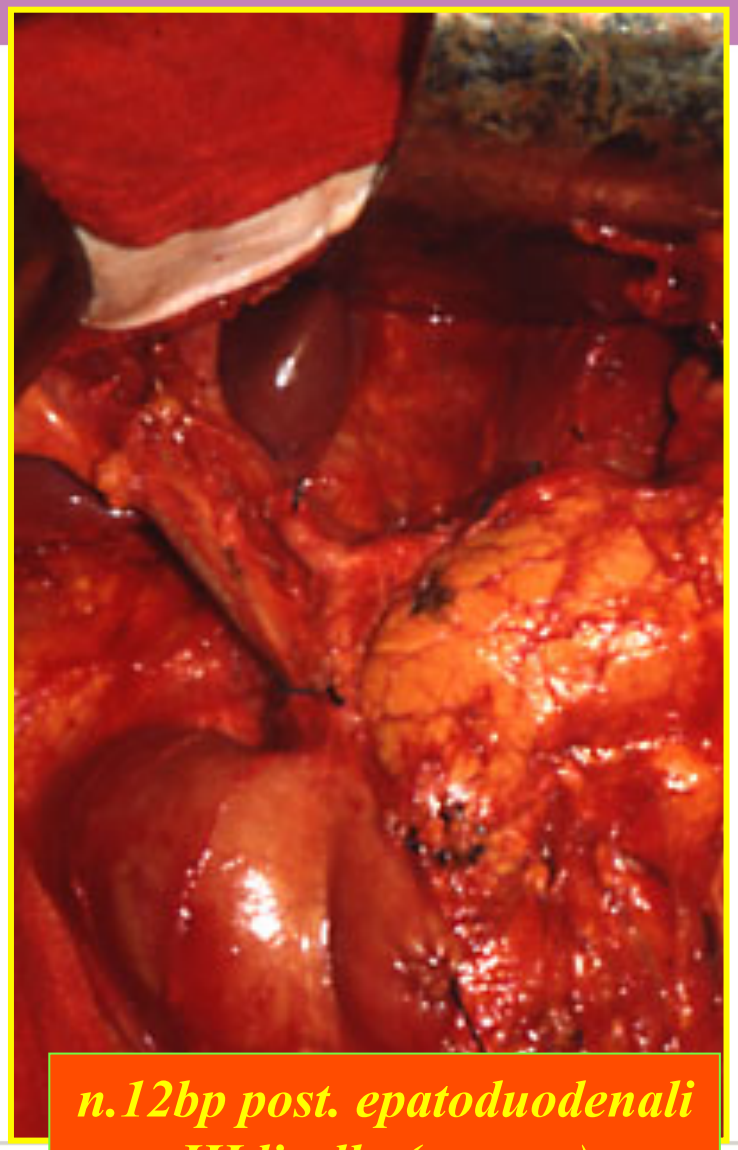
4683 patients



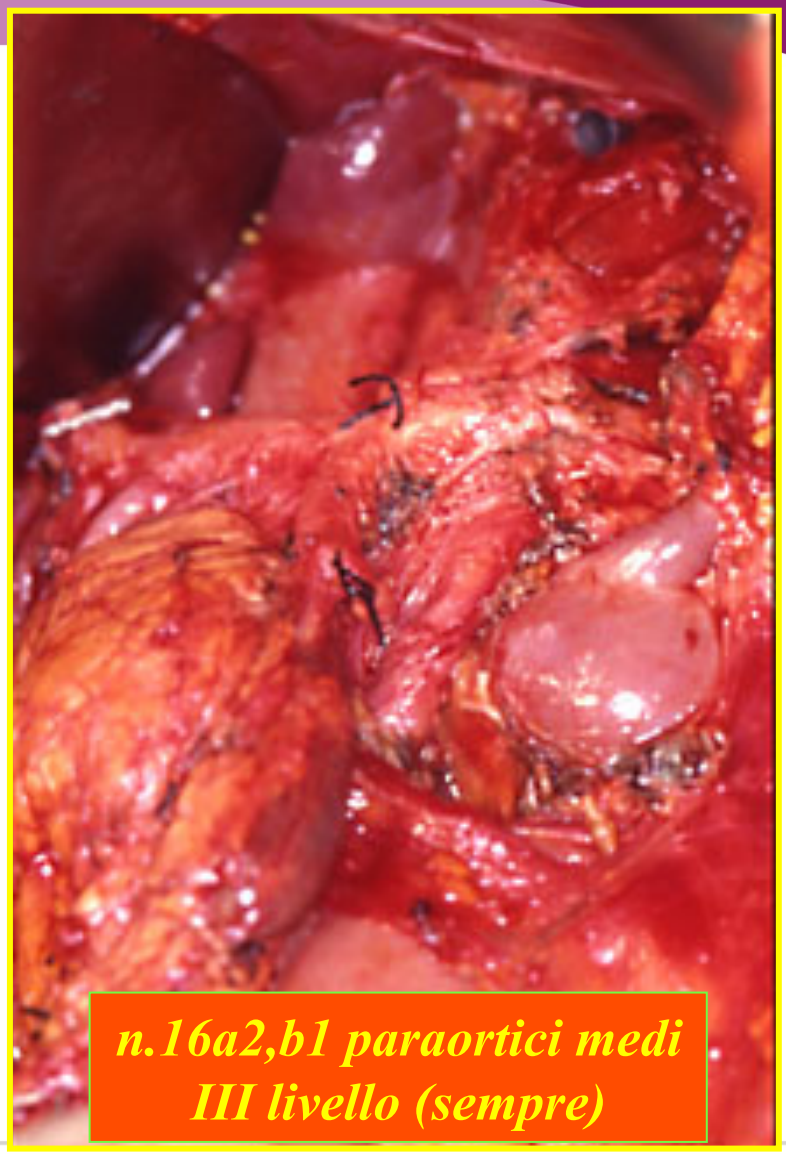
proximal **middle** **distal**

Sasako M – Gastric Cancer - 1999

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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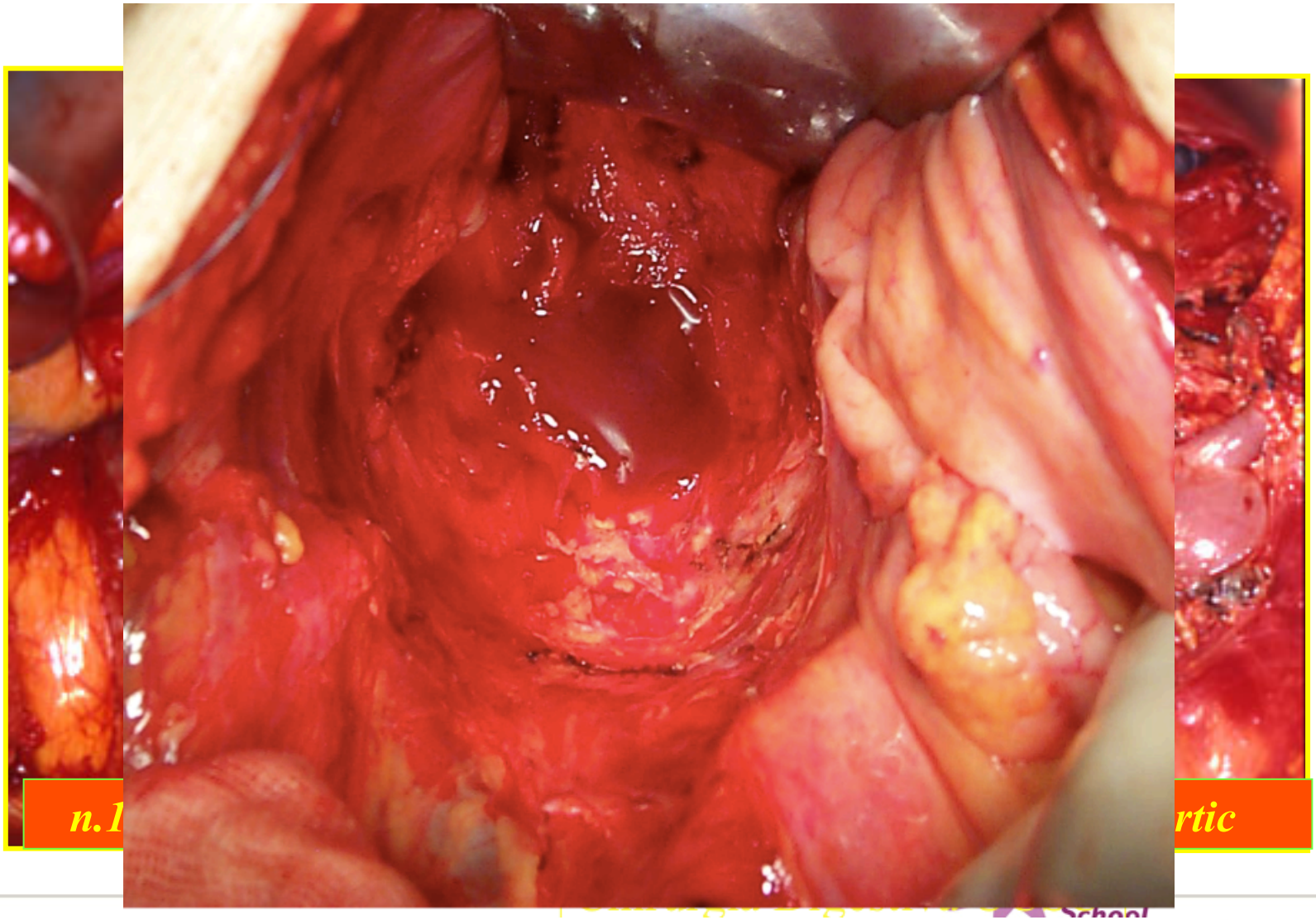
✓Background and assumptions: the challenge



By the courtesy of F.Pacelli, UCSC, Rome

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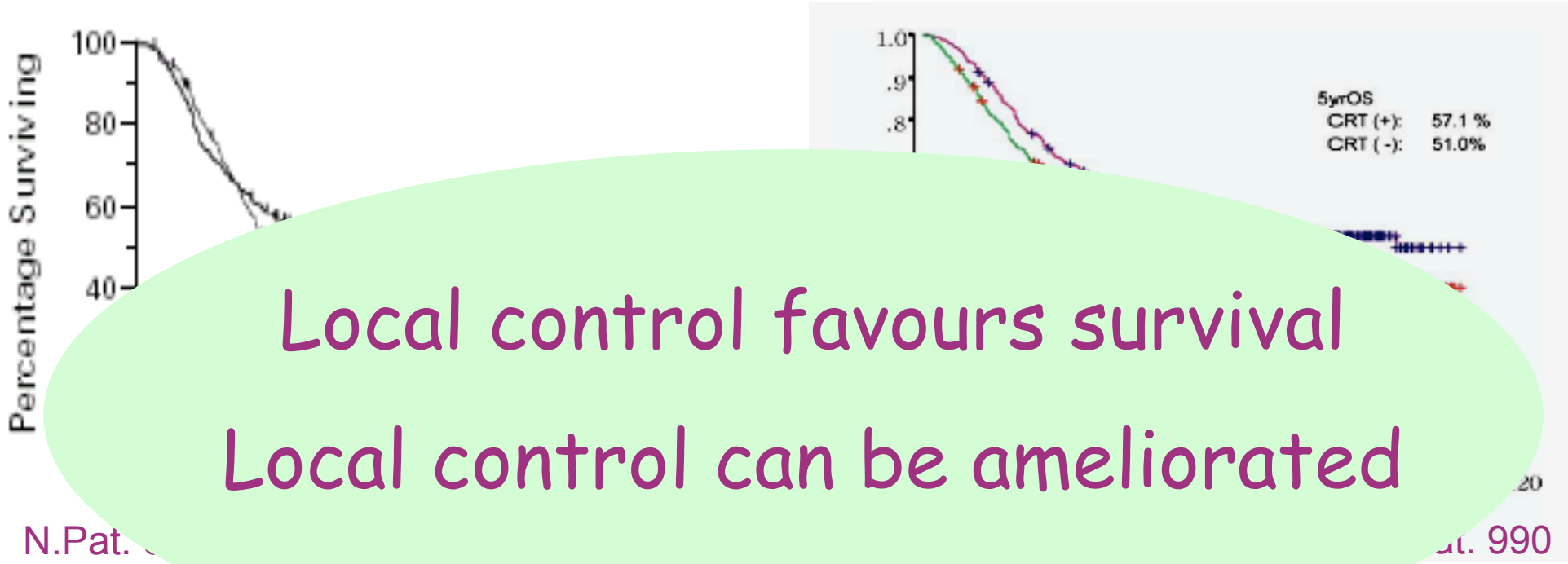
✓Background and assumptions: the challenge



N.Pat. … gt. 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

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)

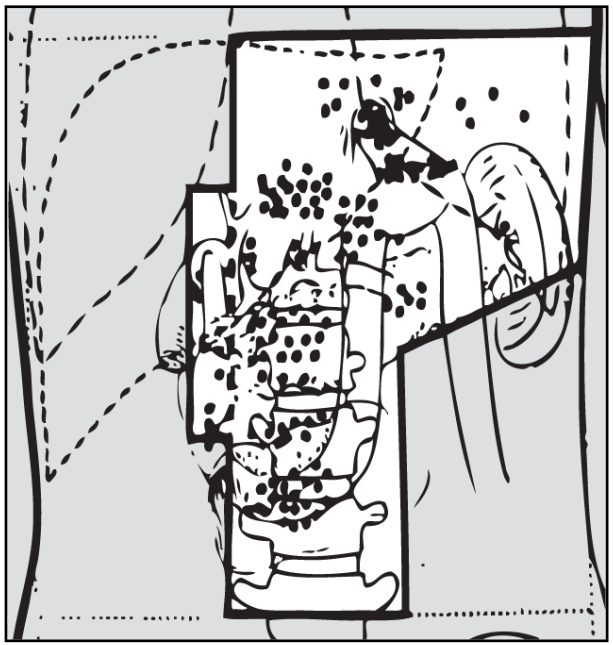
TABLE 3. MAJOR TOXIC EFFECTS OF CHEMORADIOTHERAPY.*

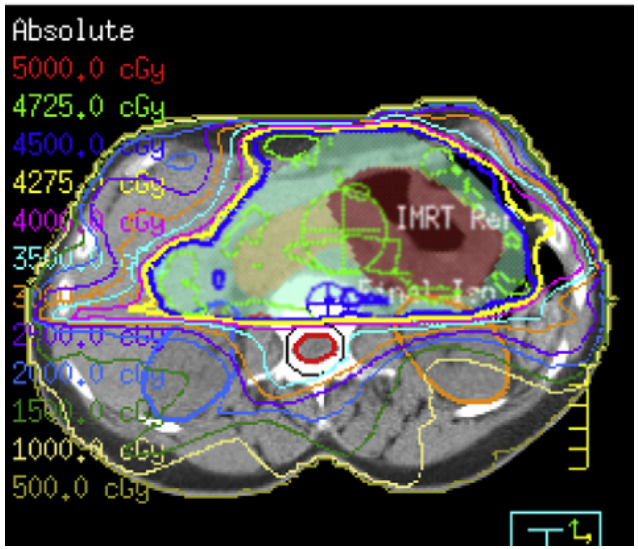
TYPE OF TOXIC EFFECT†	NO. OF PATIENTS (%)
Hematologic	148 (54)
Gastrointestinal	89 (33)
Influenza-like	25 (9)
Infection	16 (6)
Neurologic	12 (4)
Cardiovascular	11 (4)
Pain	9 (3)
Metabolic	5 (2)
Hepatic	4 (1)
Lung-related	3 (1)
Death†	3 (1)

Macdonald JS et Al – NEJM -2001

ESTRO School

✓Background and assumptions: the challenge





2D 3D IMRT

ESTRO School

✓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

Treatment arms:

- CT-RTCT (IMRT)-CT-CT
- CT arm = same regimen

Zhu W-g el al – *Radiother and Oncol*– 2012

Zhu W-g el al – *Radiother and Oncol*– 2012

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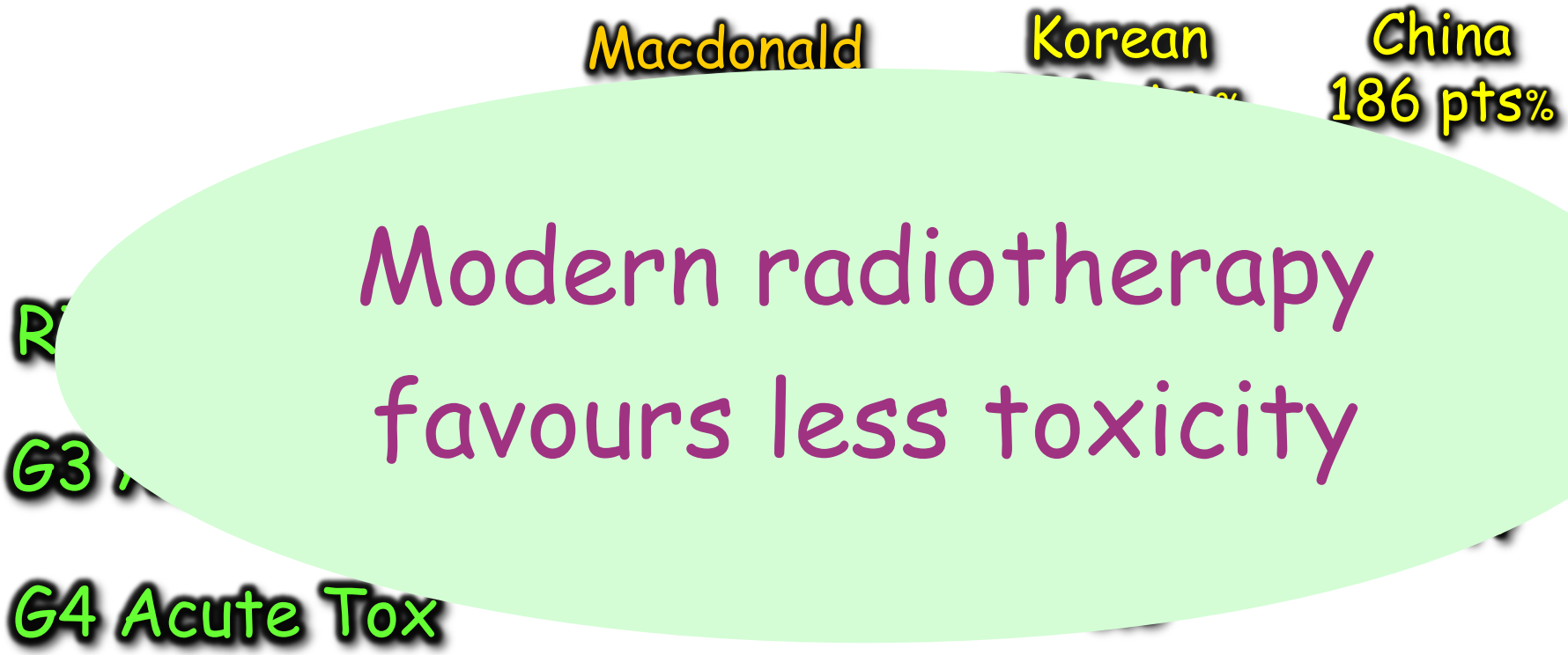
✓Background and assumptions: the challenge



Macdonald JS et Al – NEJM -2001
Kim S, Macdonald JS et Al – IJROBP – 2005
Zhu W et Al – Radioth Oncol - 2012

ESTRO School

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

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✓Post-operative Chemoradiation

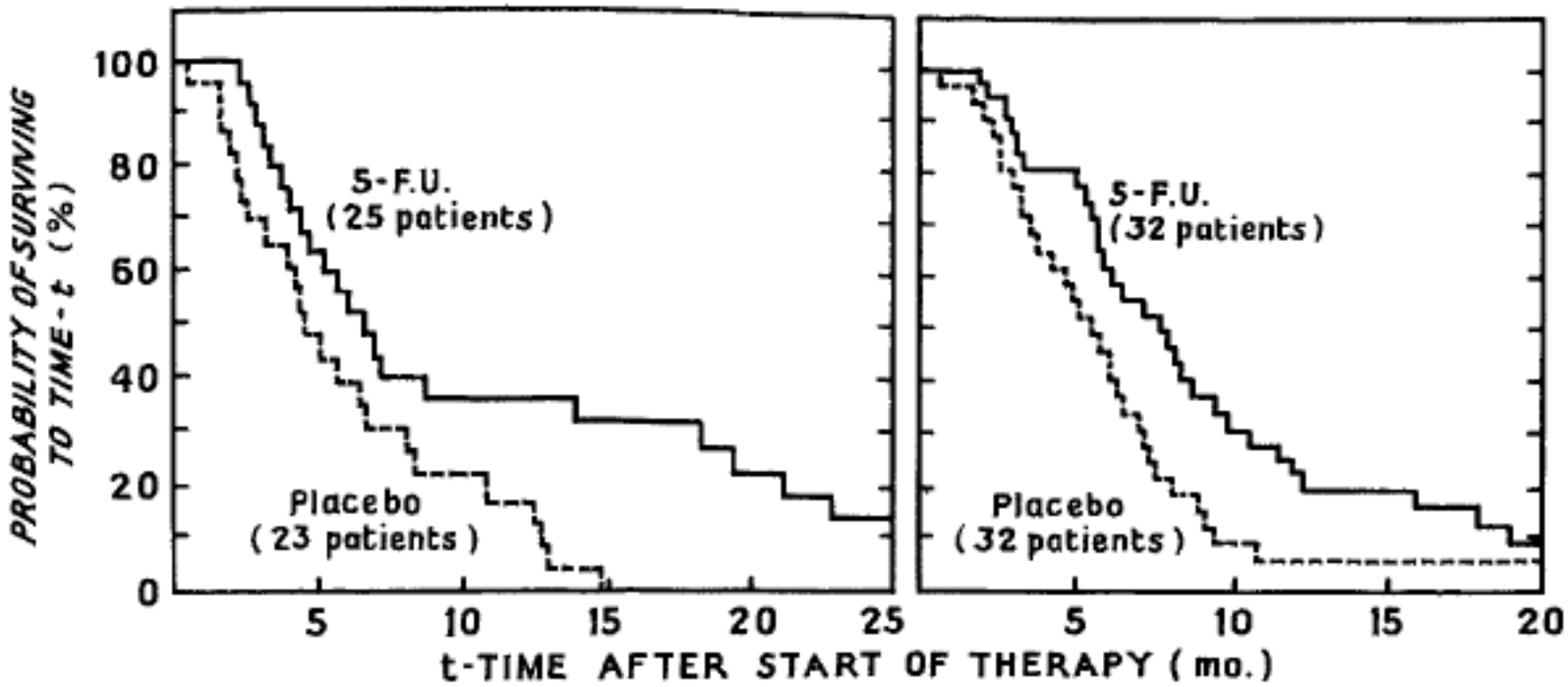

Fig. 1—Survival curves for patients with unresectable adenocarcinoma of stomach.

Fig. 2—Survival curves for patients with unresectable adenocarcinoma of pancreas.

RTCT (2D): 35-40 Gy (1.8-2.2 Gy fx) + 5Fu

Moertel *et al*; Lancet Oncol 1969

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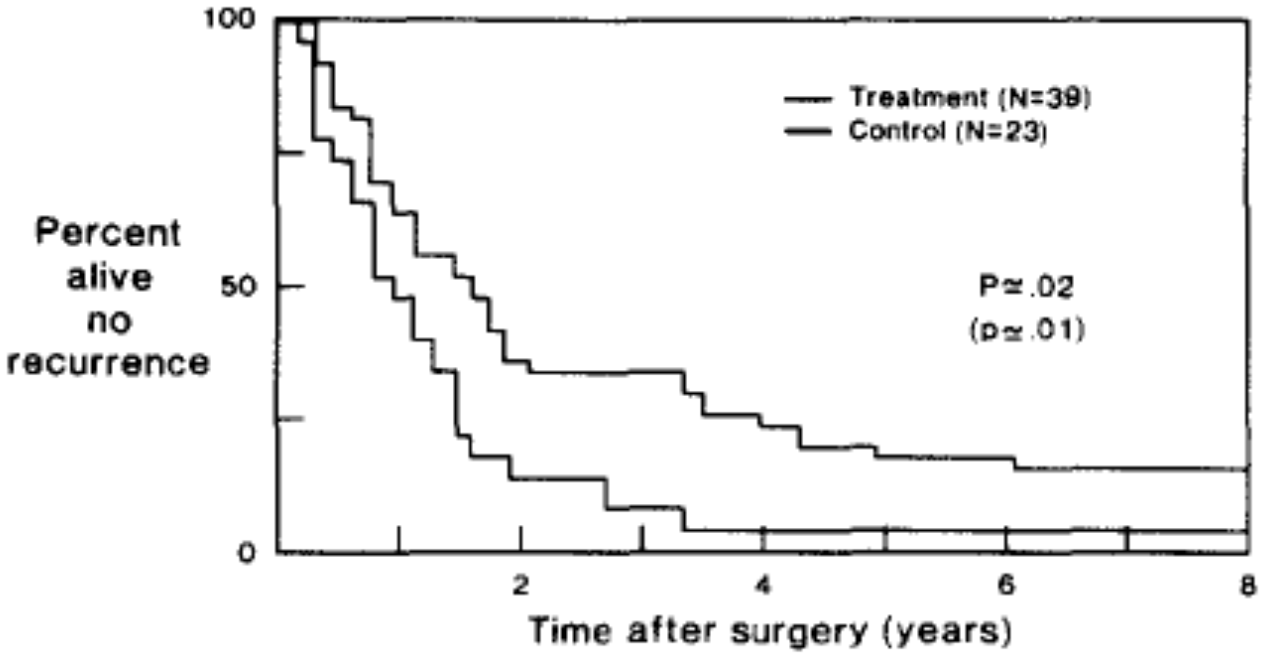
✓Post-operative Chemoradiation

- Moertel et al – 1984 Stage Resectable 39 pts
- Moertel et al – 1984 **SVV Benefit**



RTCT (2D): 37.5 Gy (1.5 Gy fx) + 5Fu

Moertel *et al*; JCO 1984

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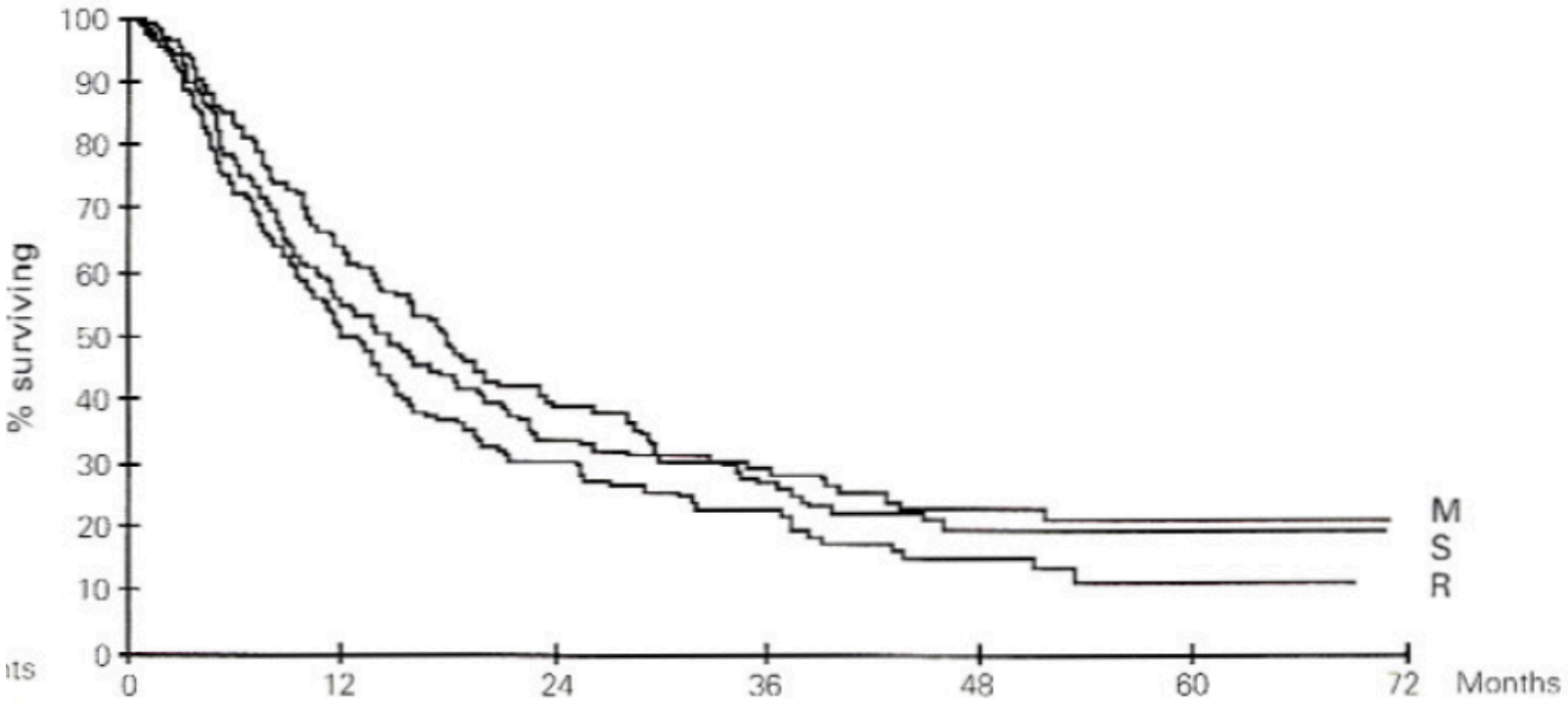
✓Post-operative Chemoradiation

- Allum et al – 1989 Stage Resectable 436 pts
- Allum et al – 1989 Surgery vs MAF vs RT
- Allum et al – 1989 **NO SVV Benefit**



RT (2D): 45 + 5 Gy (2 Gy fx)

Allum *et al*; JCO 1989

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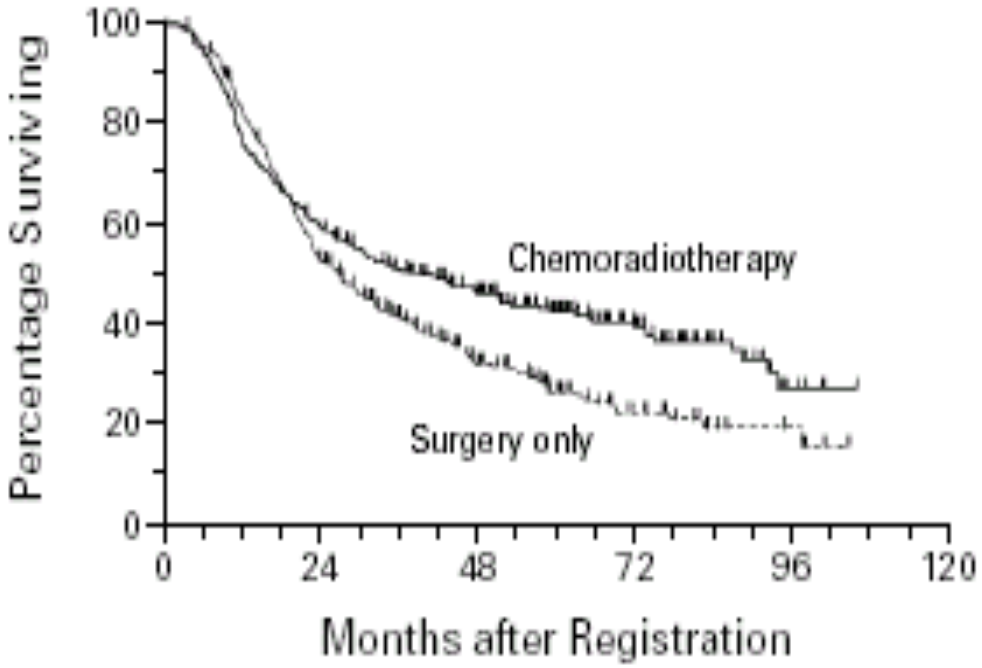
✓Post-operative Chemoradiation

- Macdonald et al – 2001 Stage IB through IVM0, R0 556 pts
- Macdonald et al – 2001 Surg vs Surg + Ch / RTCH / 2Ch
- Macdonald et al – 2001 **SVV Benefit**



RT (2D): 45 Gy (1.8 Gy fx)

Macdonald *et al*; NEJM 2001
Smalley *et al*: JCO 2011

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✓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
B. Minsky – personal communication – 2005

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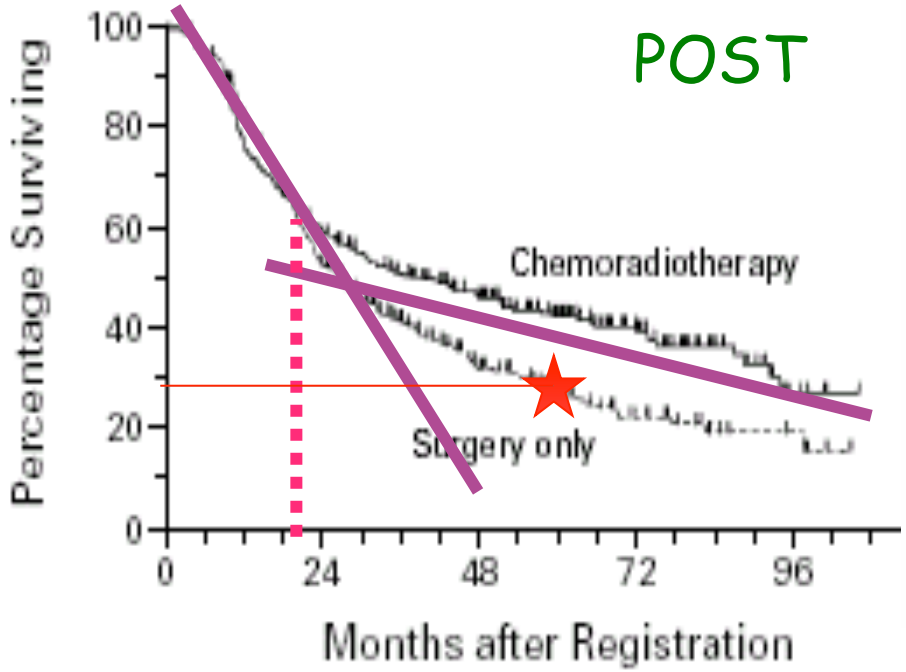
✓Post-operative Chemoradiation

INT-0116

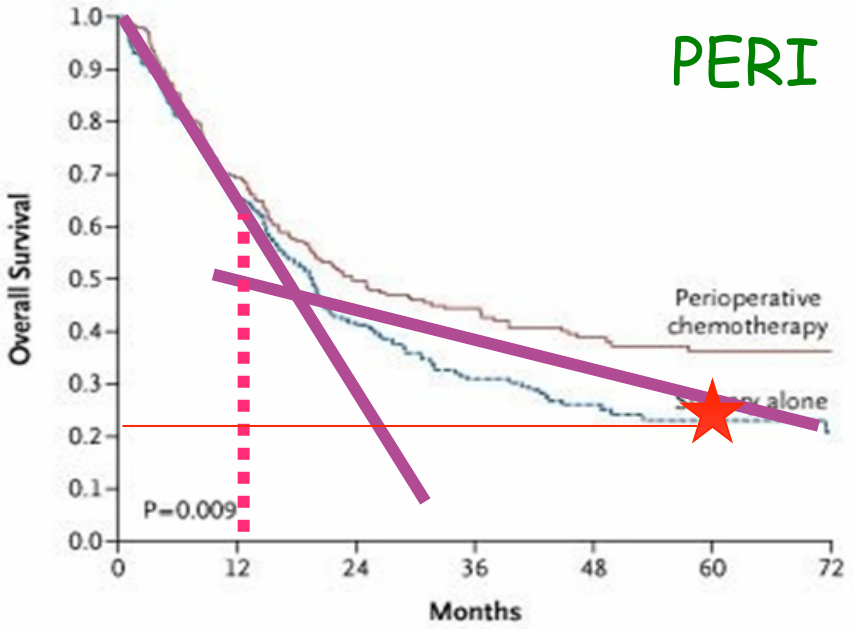
POST



D2 = 10%

Magic

PERI



D2 = 41%

Macdonald JS et Al – NEJM -2001
Cunningham D et Al – NEJM - 2006

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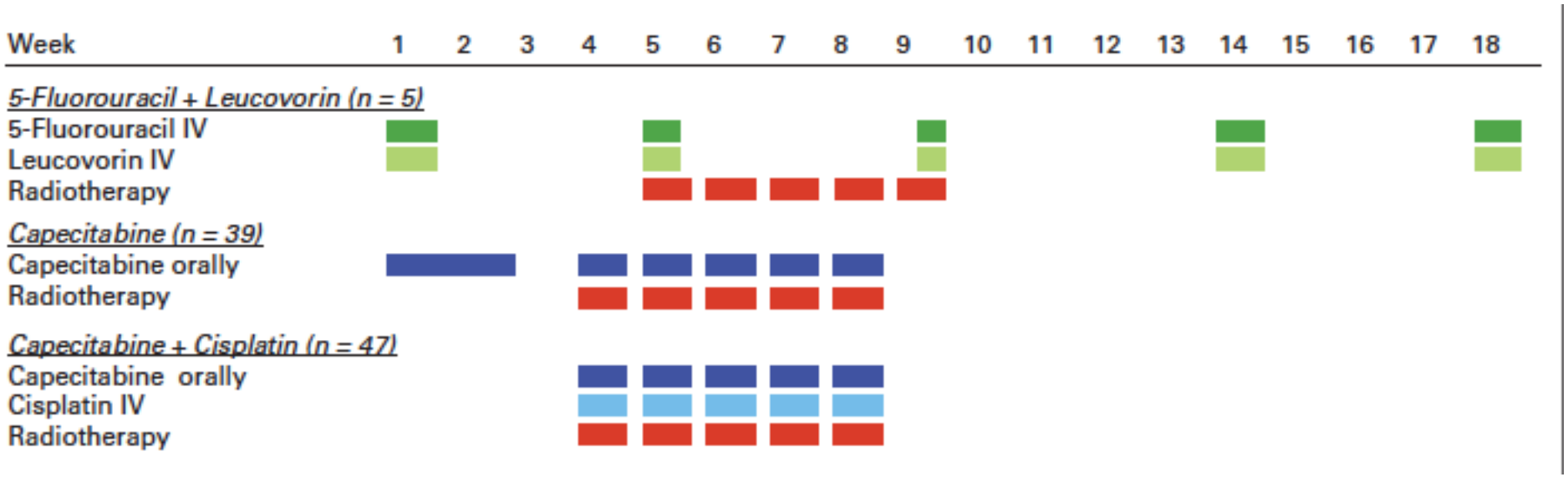
✓Post-operative Chemoradiation

- 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)

Dikken *et al*: JCO 2010
Bonenkamp JJ et al: NEJM 1999

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✓Post-operative Chemoradiation

- Dikken et al – 2010 Stage IB to IV 113 pts
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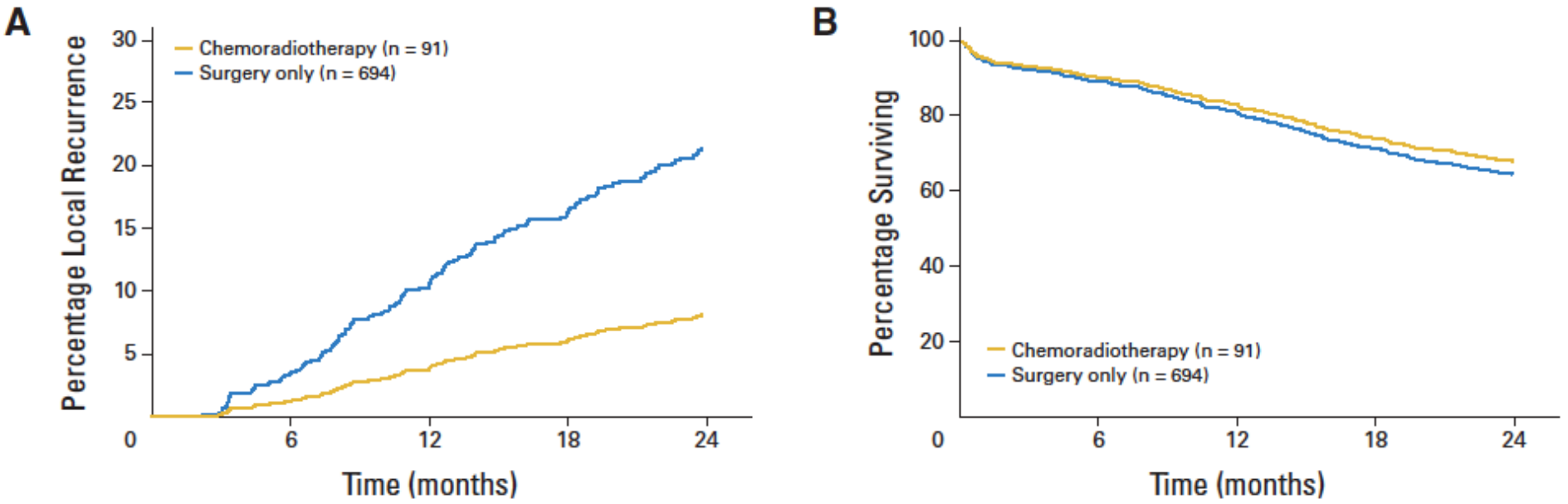


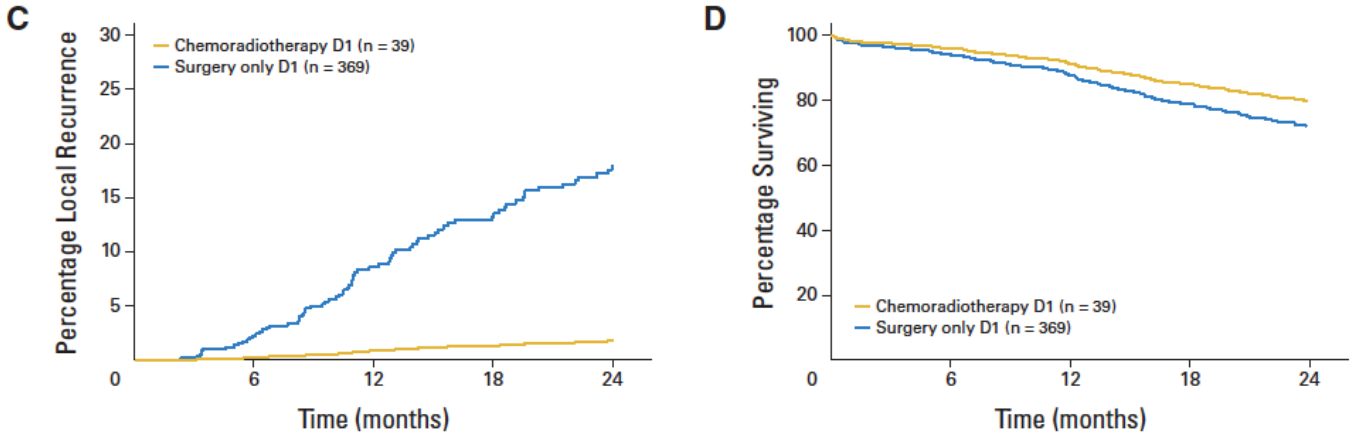
Dikken *et al*: JCO 2010
Bonenkamp JJ et al: NEJM 1999

ESTRO School

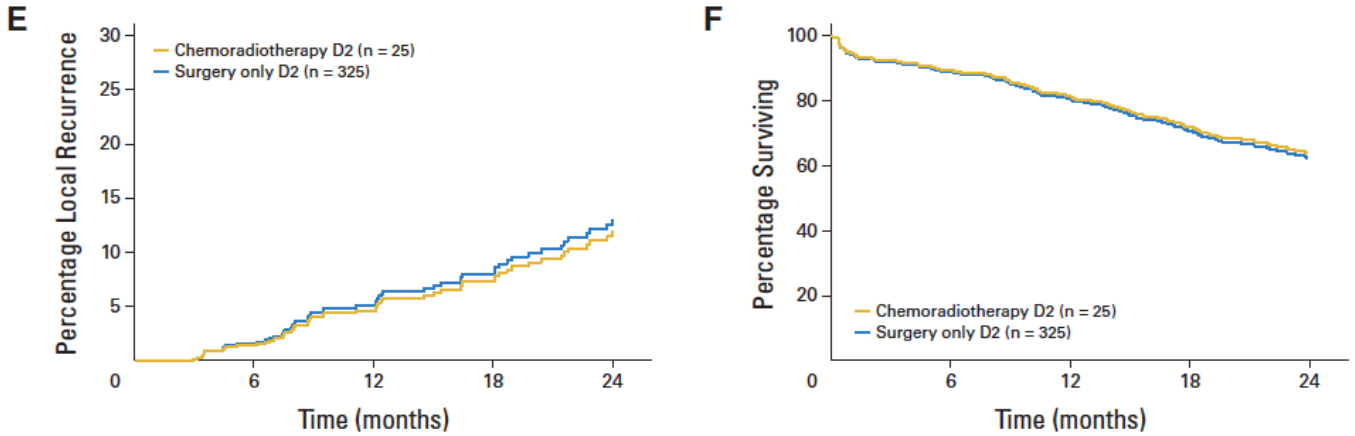
✓Post-operative Chemoradiation

- 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

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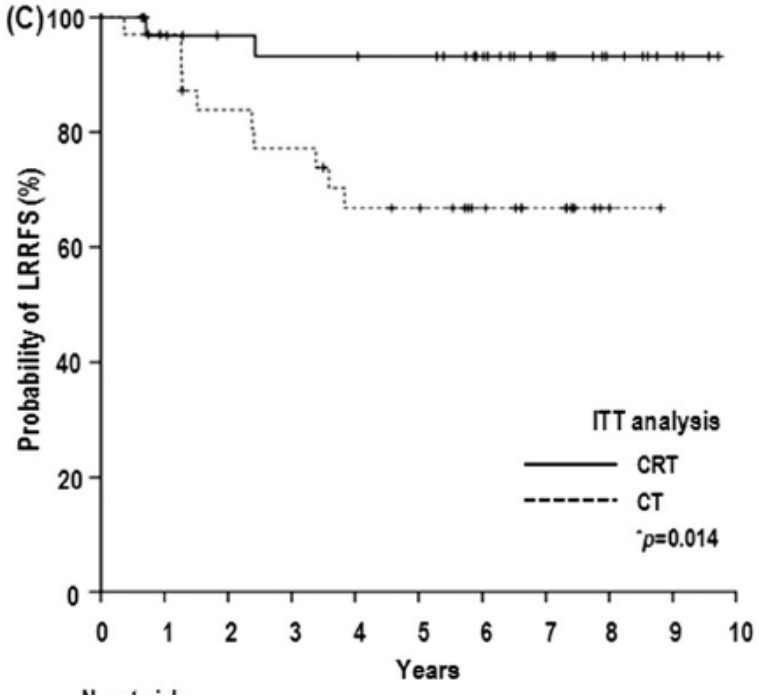
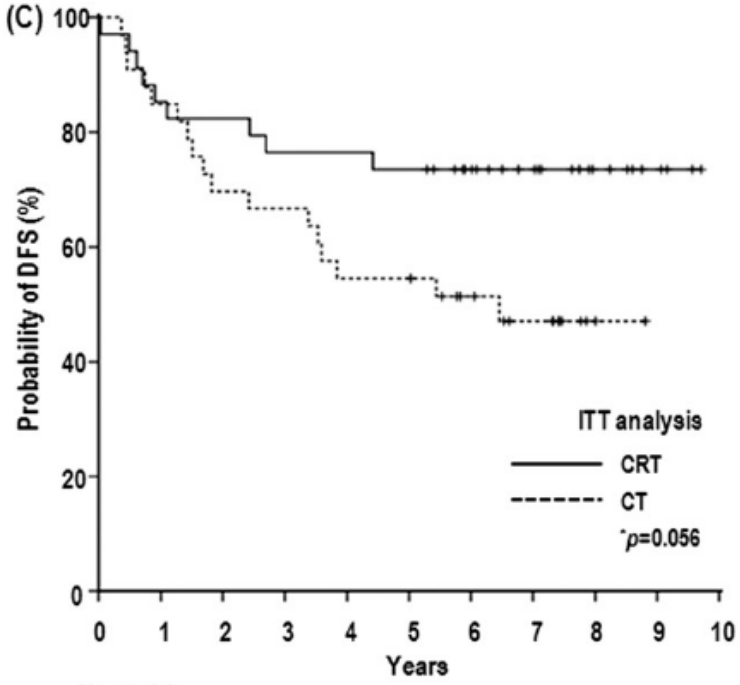
✓Post-operative Chemoradiation

- Kim et al – 2012 Stage III and IV(M0) 90 pts
- Kim et al – 2012 D2 5 folowed by FUL vs FUL RT+FU 2FUL

Stage III





RT (3D) : 45 Gy (1.8 Gy fx)

Kim *et al*: IJROBP 2012

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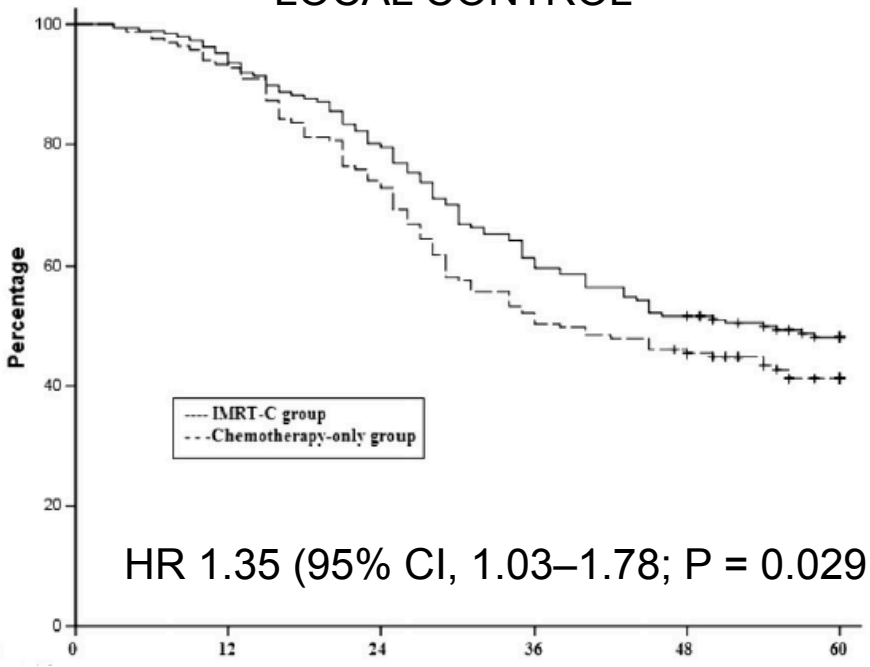
✓Post-operative Chemoradiation

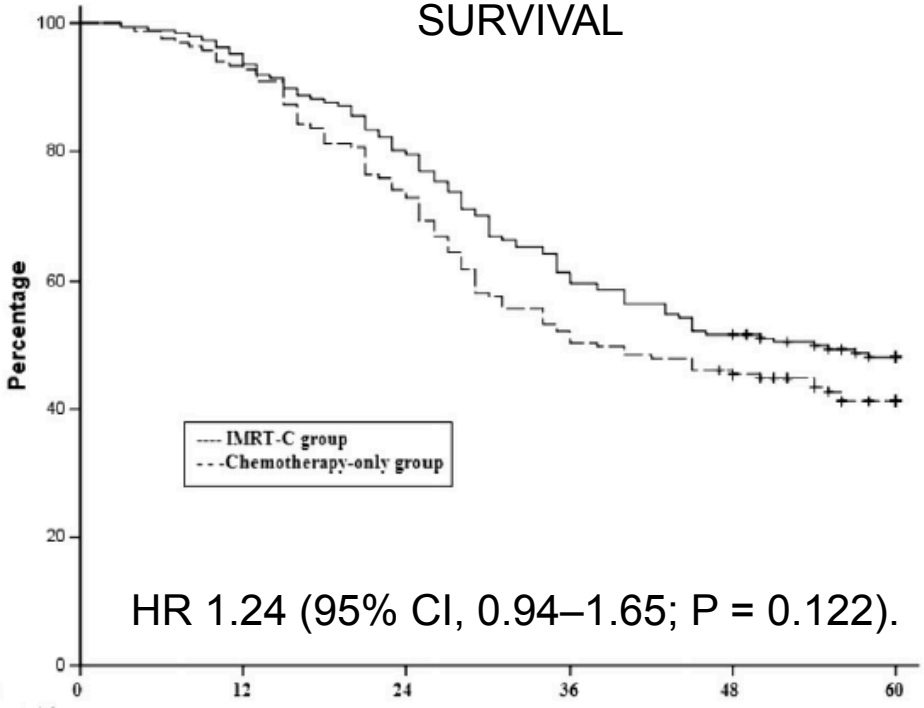
- Zhu et al – 2012 Stage T3 or T4 and (or) N positive(M0) 404 pts
- Zhu et al – 2012 D2 5 folowed by FUL vs FUL RT+FU 2FUL

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)

Zhu *et all*: Radiot Oncol 2012

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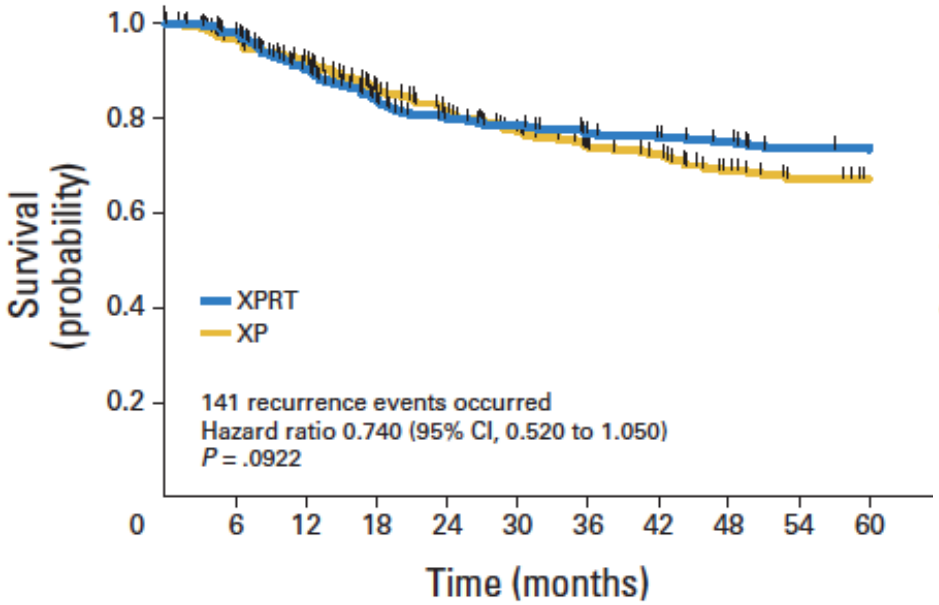
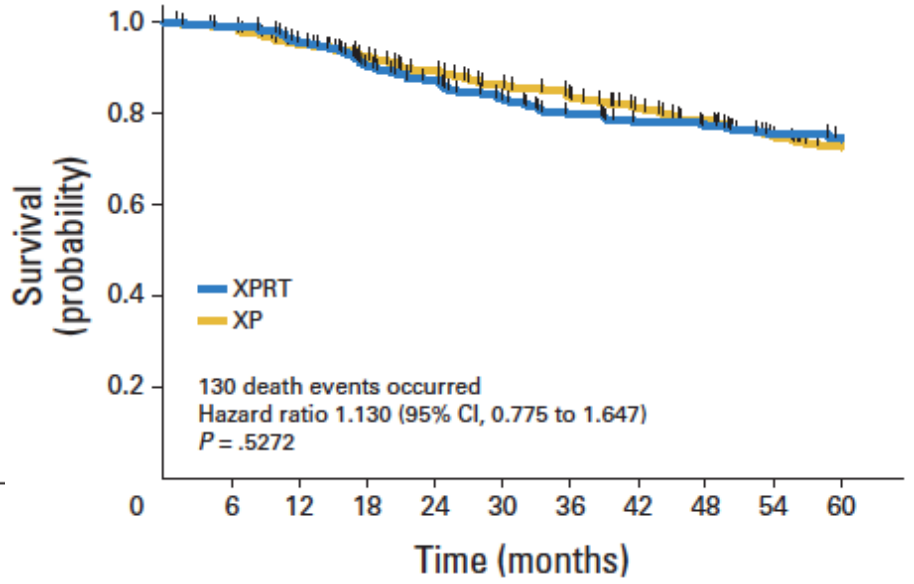
✓Post-operative Chemoradiation

- Park et al – 2015 Stage IB to IV (M0, R0) 458 pts
- Park et al – 2012 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 all*: JCO 2015

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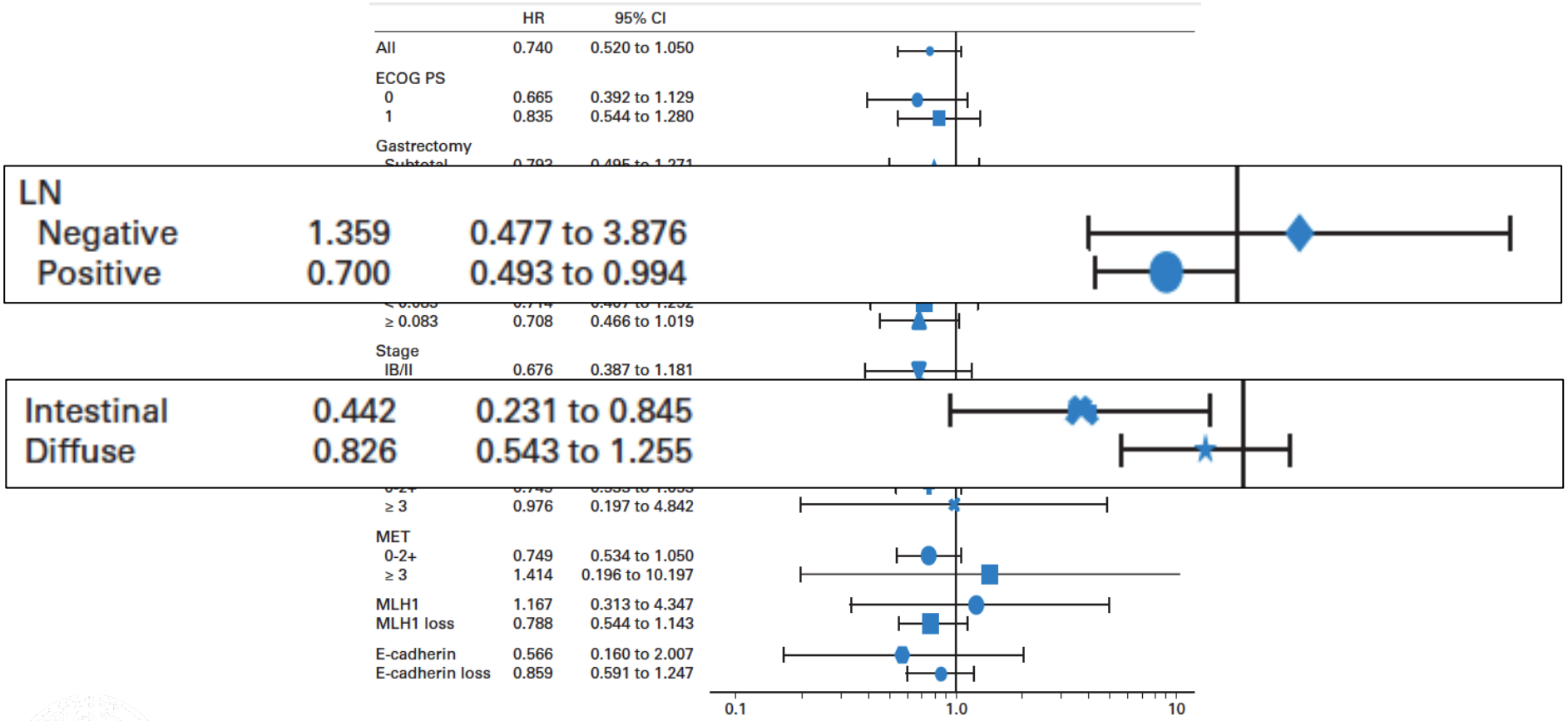

Lee *et al*. JCO 2012
Park *et all*: JCO 2015

ESTRO School

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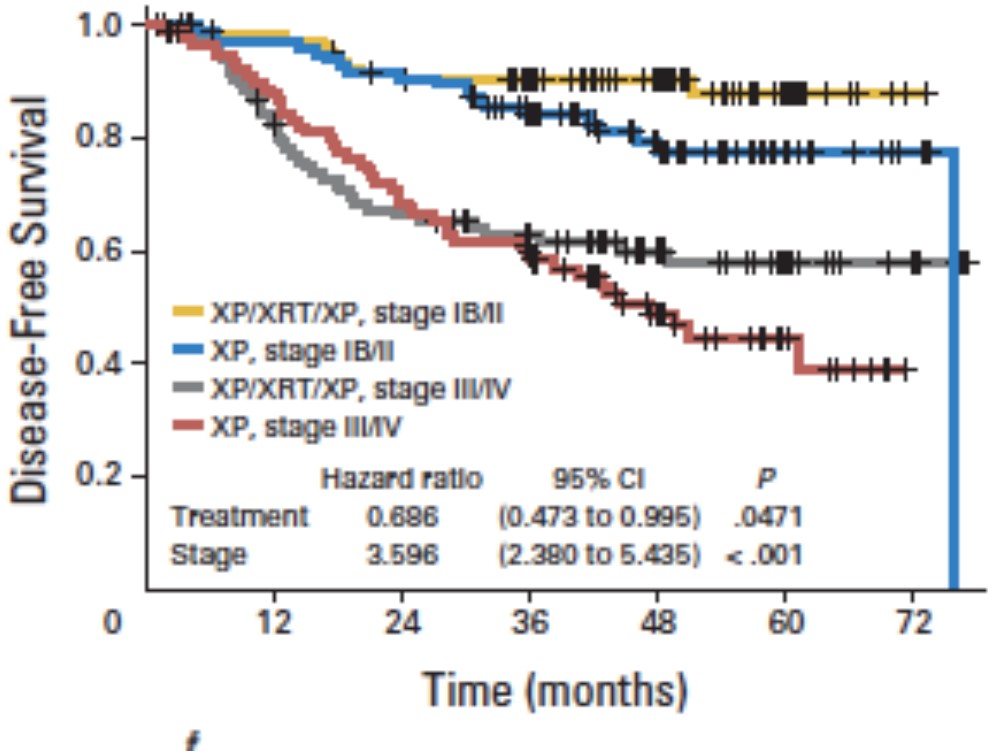

RT (3D) : 45 Gy (1.8 Gy fx)

Lee *et al*. JCO 2012
Park *et al*: JCO 2015

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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

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

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✓Post-operative Chemoradiation

CRITICS trial

(ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach).

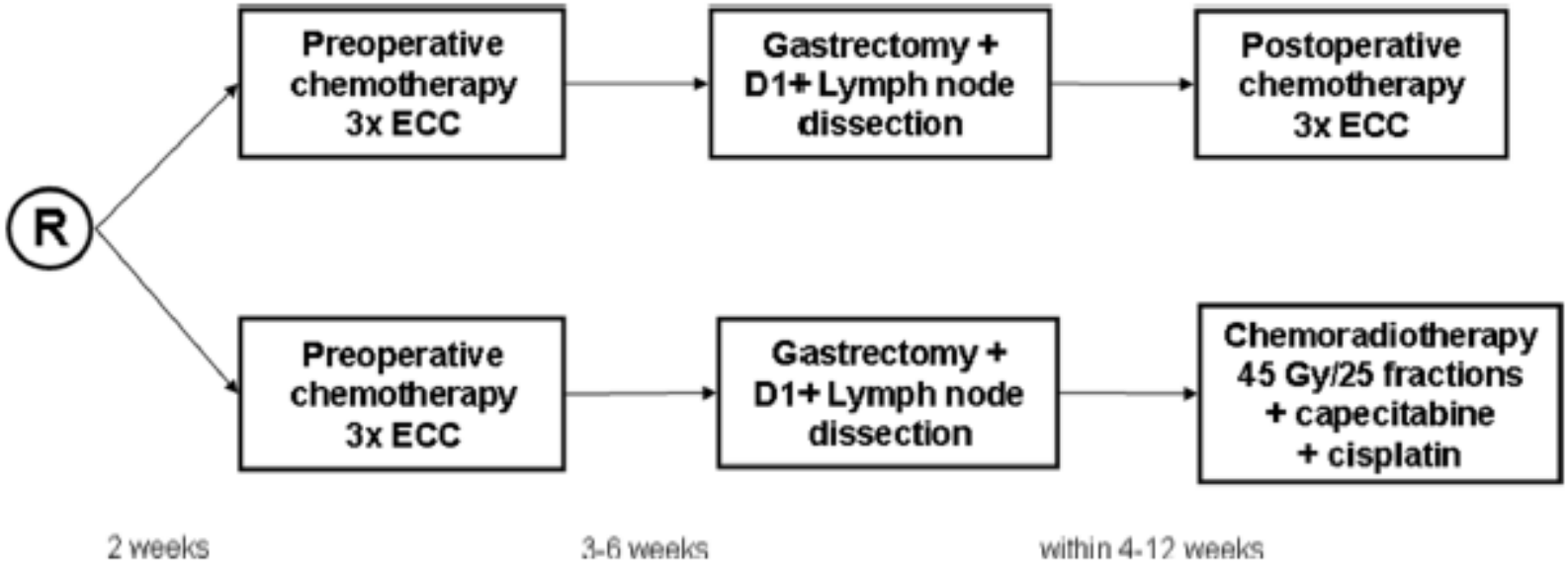

Figure 1 Randomization scheme. R: randomization. ECC: epirubicin, cisplatin, capecitabine.

Dikken *et al*: BMC 2011

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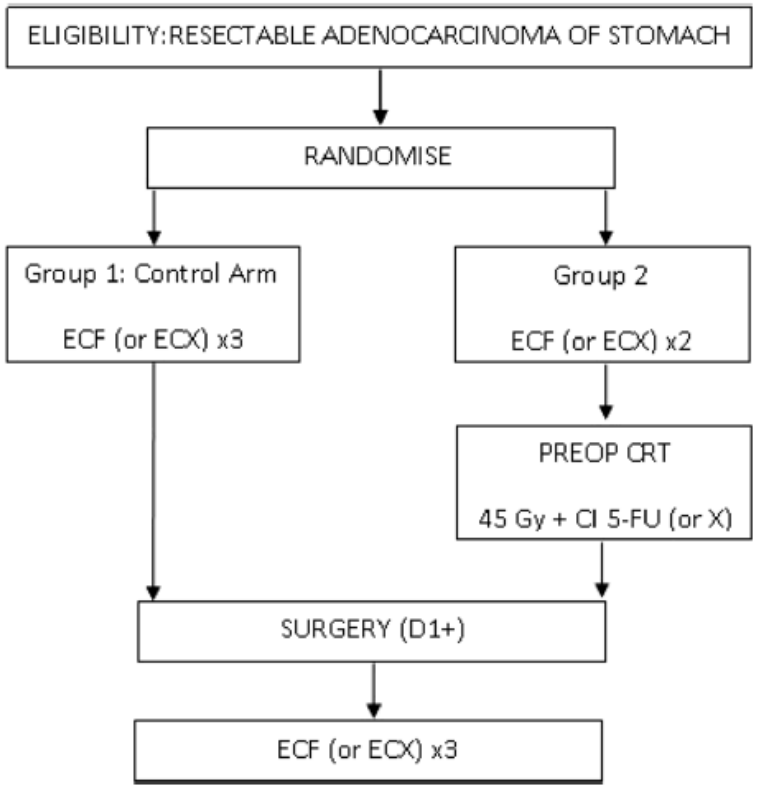
✓Post-operative Chemoradiation

TOPGEAR

(Trial Of Preoperative therapy for Gastric and Esophagogastric junction AdenocaRcinoma)



Leong *et al*: BMC 2015

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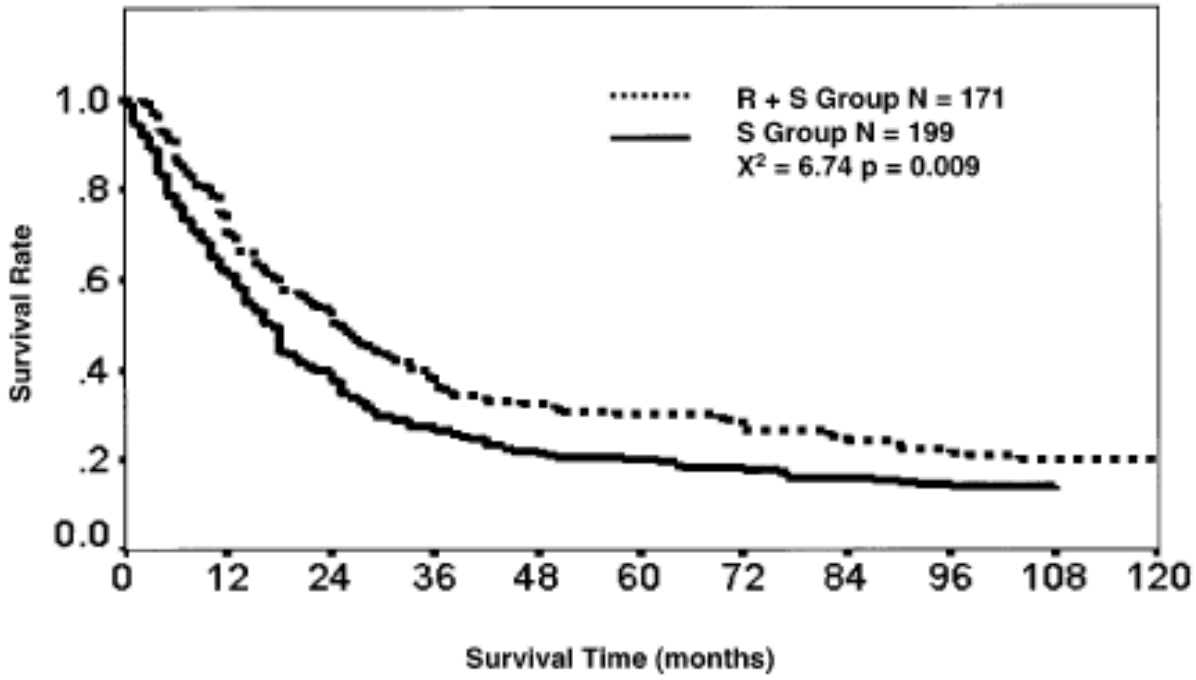
✓Pre-operative Chemoradiation

- Zhang et al – 1998 Stage not contraindicated for surgery (M0) 370 pts
- Zhang et al – 1998 RT + Surg vs Surg



RT (2D) : 40 Gy (2.0 Gy fx)

Zhang *et al*. IJROBP 1998

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✓Pre-operative Chemoradiation

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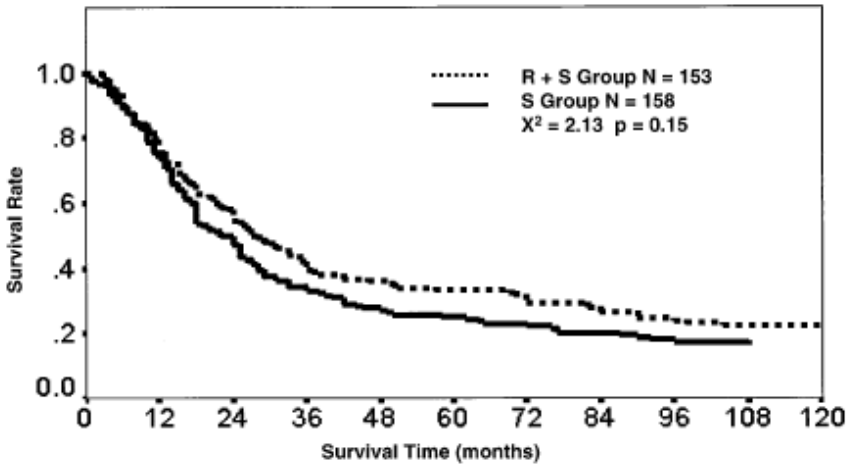
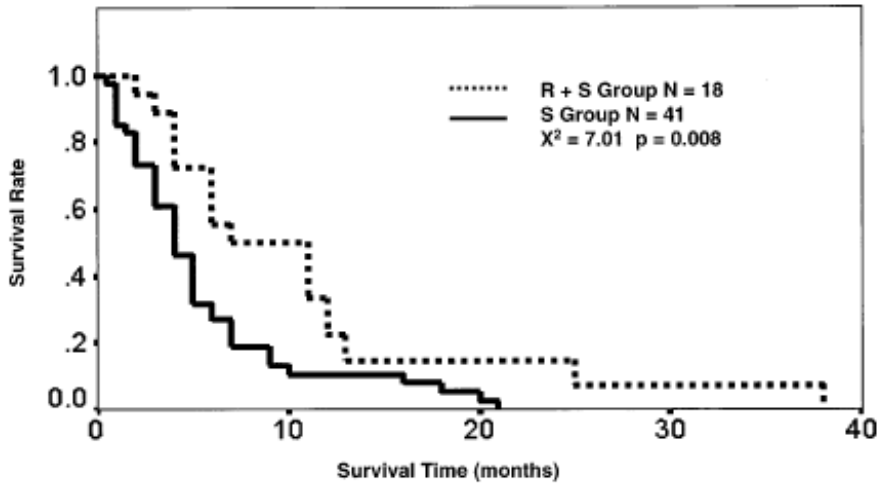
- Zhang et al – 1998 RT + Surg vs Surg

Radical Surgery



Palliative Surgery



RT (2D) : 40 Gy (2.0 Gy fx)

Zhang *et al*. IJROBP 1998

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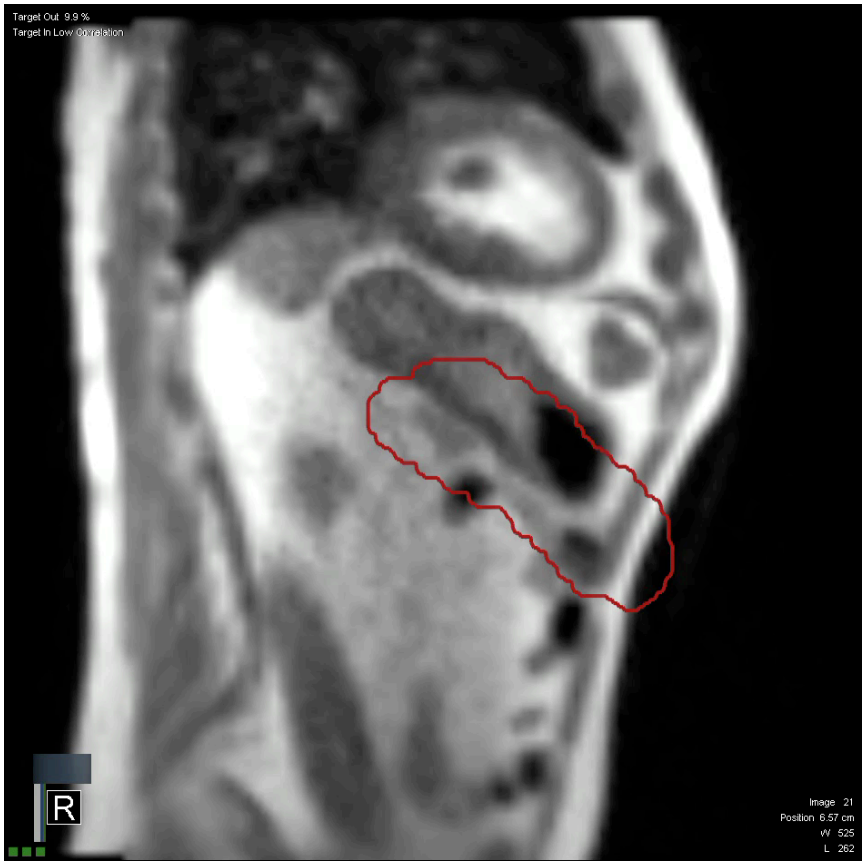
✓Pre-operative Chemoradiation

MRI based IGRT



Gemelli ART Advanced Radiation Therapy

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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

Kim 2012	Trend RTCHEM vs Chem
Zhu 2012	Trend RTCHEM vs Chem
Park 2015	No benefit RTCHEM but

✓ **Pre-operative Chemoradiation**

Zhang 1998	Seeding perspective

✓ **Intra-operative RT**

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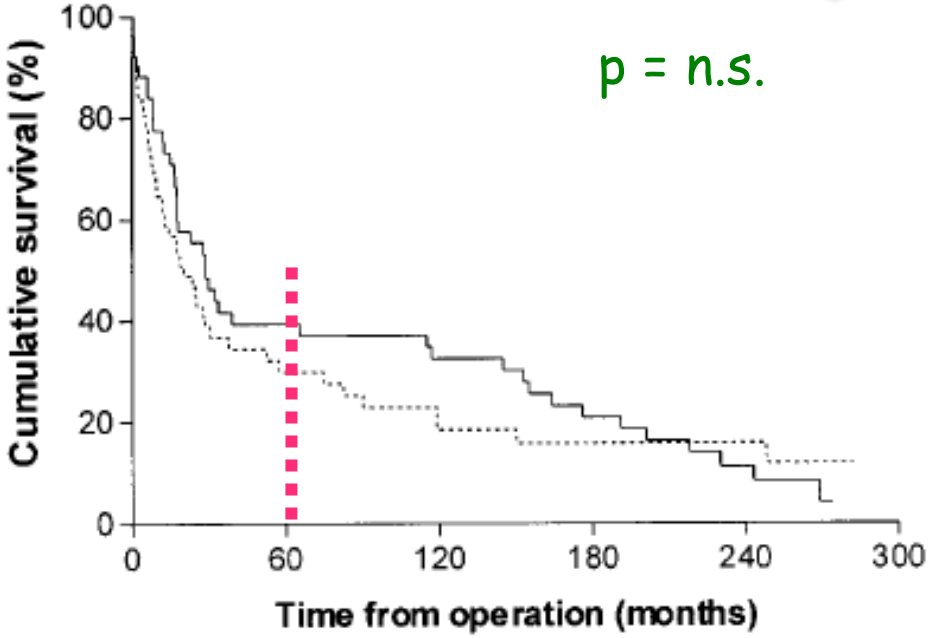
✓Intra-operative Radiotherapy

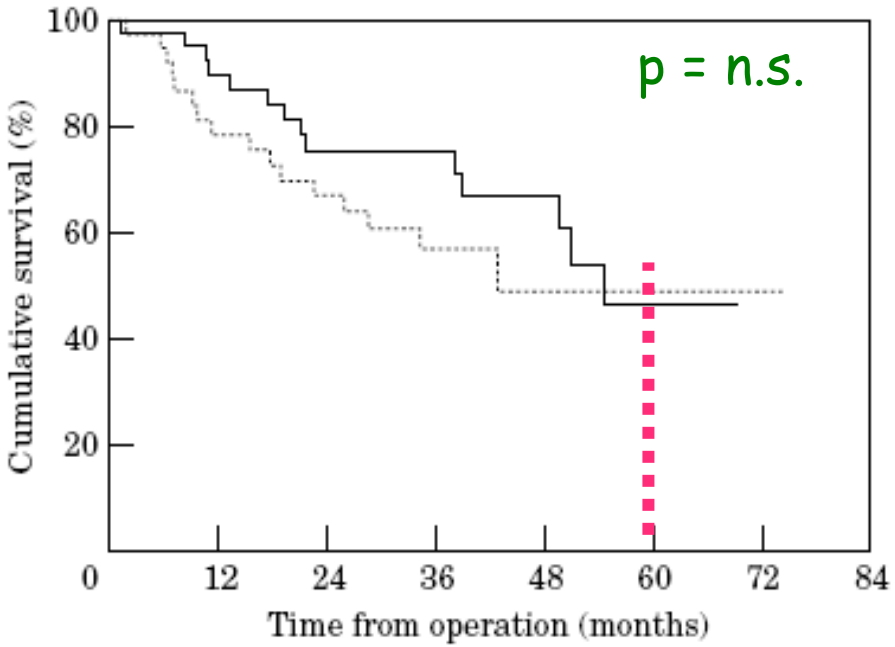
112 patients

p = n.s.



PreopRT vs Surg

p = n.s.



PreopRT vs Surg + IORT

RT (2D) : 20 Gy 4.00 Gy fx) + IORT 20

Skoropad VJ et Al – EJSO - 2000
Skoropad VJ et Al – JSO – 2002

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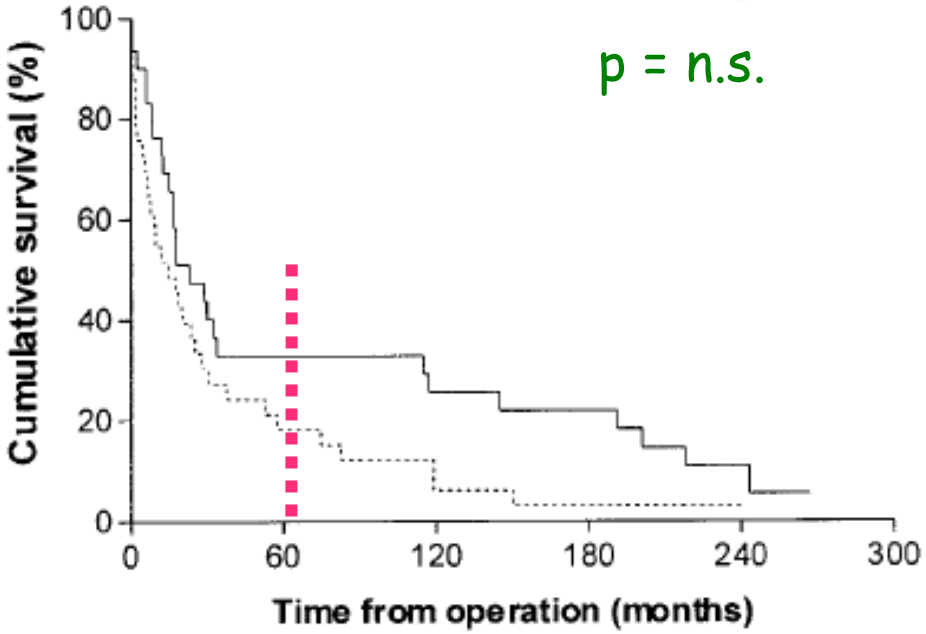
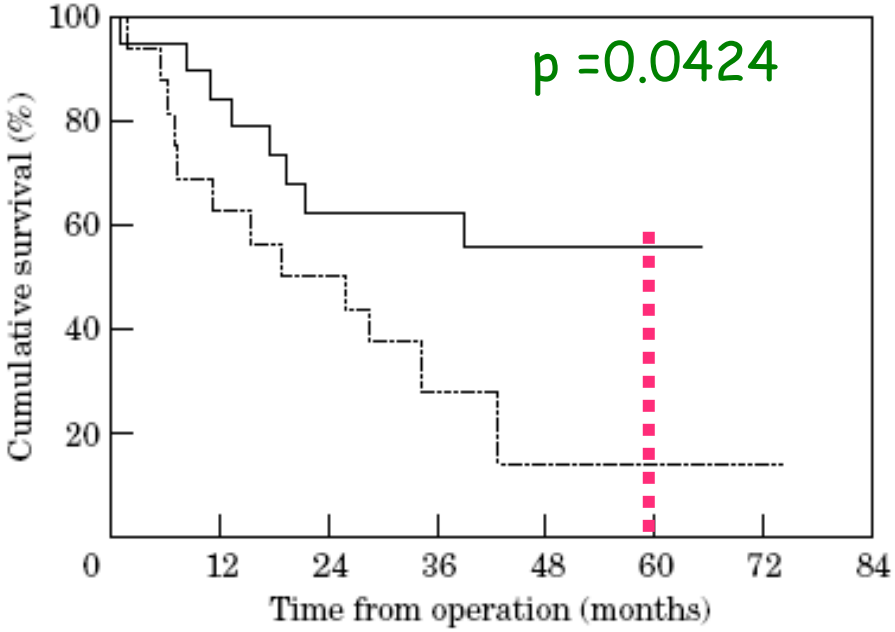
✓Intra-operative Radiotherapy

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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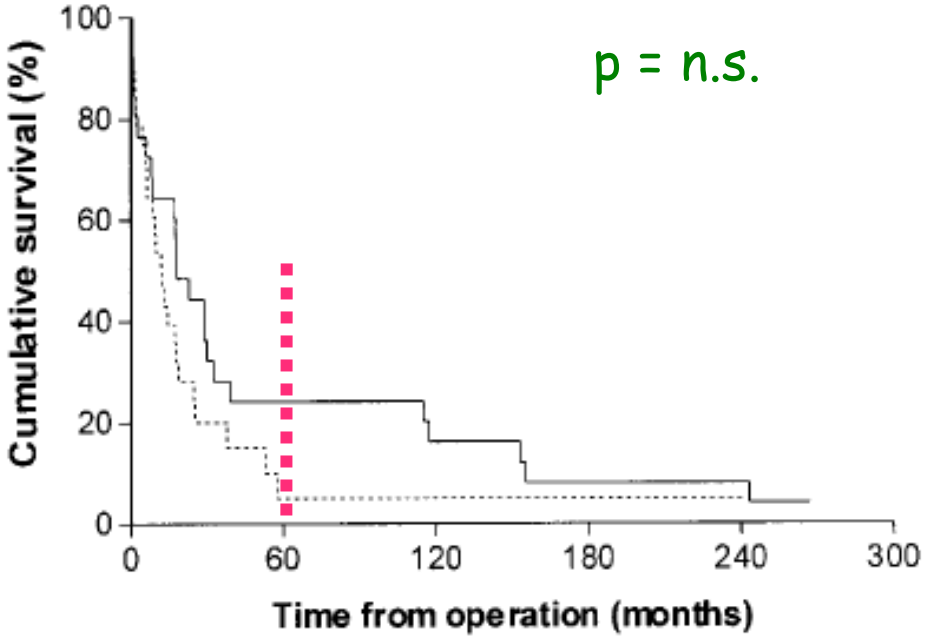
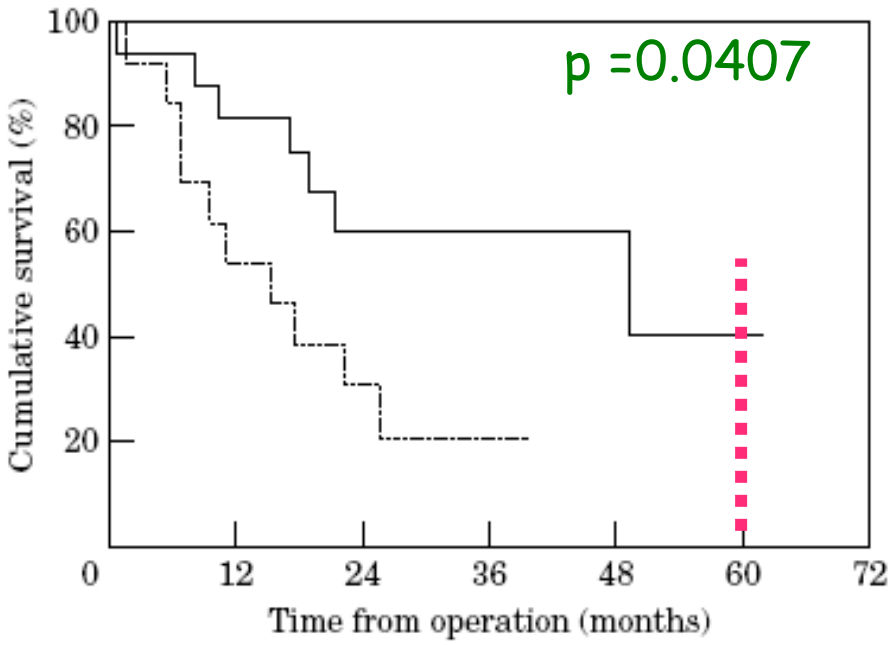
✓Intra-operative Radiotherapy

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**

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

✓ **Pre-operative Chemoradiation**

Zhang 1998	Seeding perspective

✓ **Intra-operative RT**

Skoropad 200	Seeding perspective

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Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

UCCL UNIVERSITÄRES KREBSZENTRUM

State of Art of Chemotherapy in a Combined Treatment Perspective

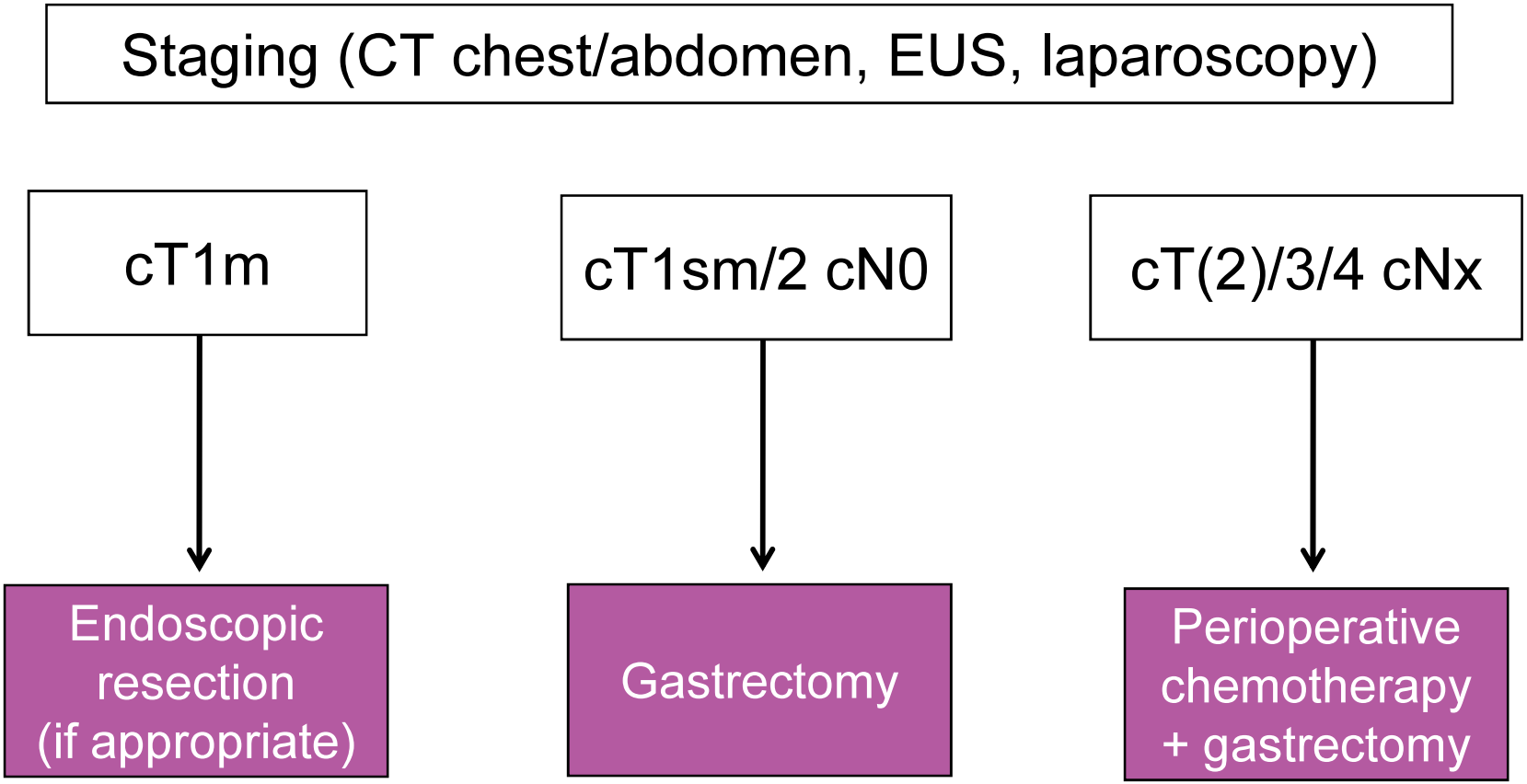
Prof. Florian Lordick, MD

Director University Cancer Center Leipzig

UCCL

Curative Treatment of Gastric Cancer – Europe

EORTC recommendations



CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; EUS, endoscopic ultrasound scan.

Lutz MP, et al. *Eur J Cancer* 2012;48:2941–53

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Curative Treatment of Gastric Cancer – World

N America

Adjuvant R-CTx

45 Gy + 5FU/LV

Asia

Adjuvant CTx

S-1 or Capox

Europe

Perioperative CTx

(Epirubicin)-Platin-5FU

5FU, fluorouracil; CTx, chemotherapy; R-CTx; radiochemotherapy; S-1, tegafur/gimeracil/oteracil.

Lordick F. *ASCO* 2011

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Peri-/Preoperative Therapy

3 randomized phase-III-studies

- UK: **MAGIC** (n=503)

Cunningham D et al. *N Engl J Med* 2006;355:11-20

- France: **FNCLCC** (n=224)

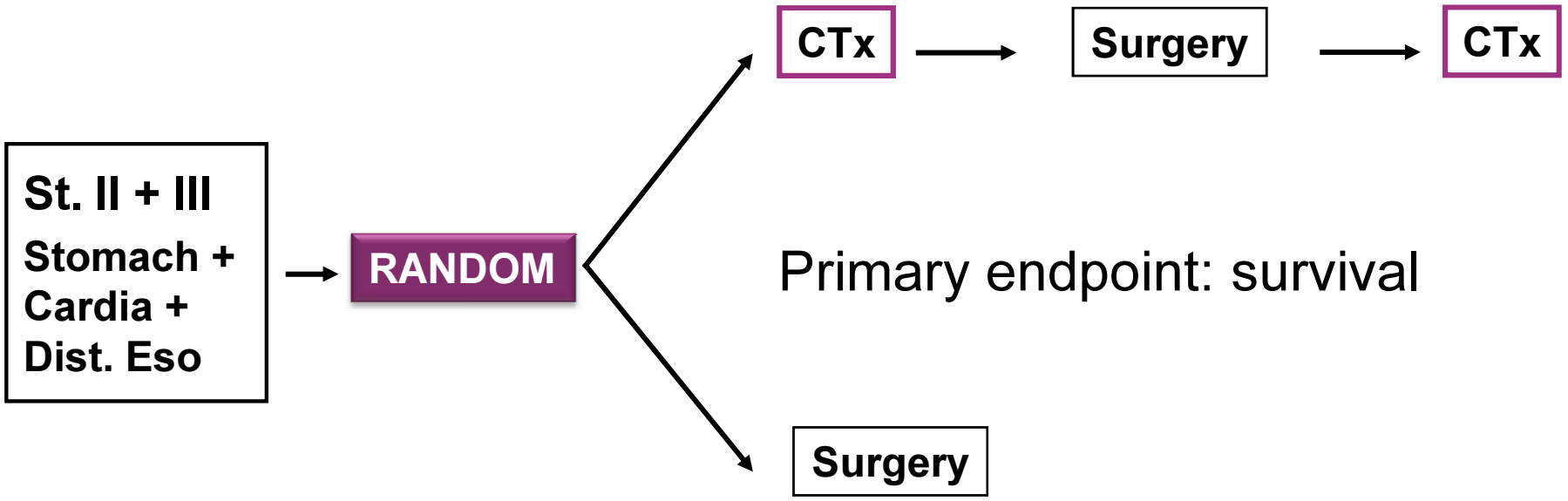
Ychou M. et al. *JCO* 2011; 29: 1715-21

- Germany: **EORTC 40954** (n=144)

Schuhmacher C. et al. *JCO* 2010; 28: 5210-5218

Peri-/Preoperative Therapy

MAGIC + FNCLCC



*Chemotherapy regimen: MAGIC, ECF (Epirubicin, Cisplatin, Fluorouracil)
FNCLCC, CF (Cisplatin, Fluorouracil)

Cunningham D et al. *N Engl J Med* 2006;355:11-20
Ychou et al. *J Clin Oncol* 2011; 29: 1715-21

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Feasibility of chemotherapy

	MAGIC (9 wks ECF)	**FNCLCC** (8 wks CF)
Pre-op. CTX completely given	86%	89%
Post-op. CTX given	55%	51%

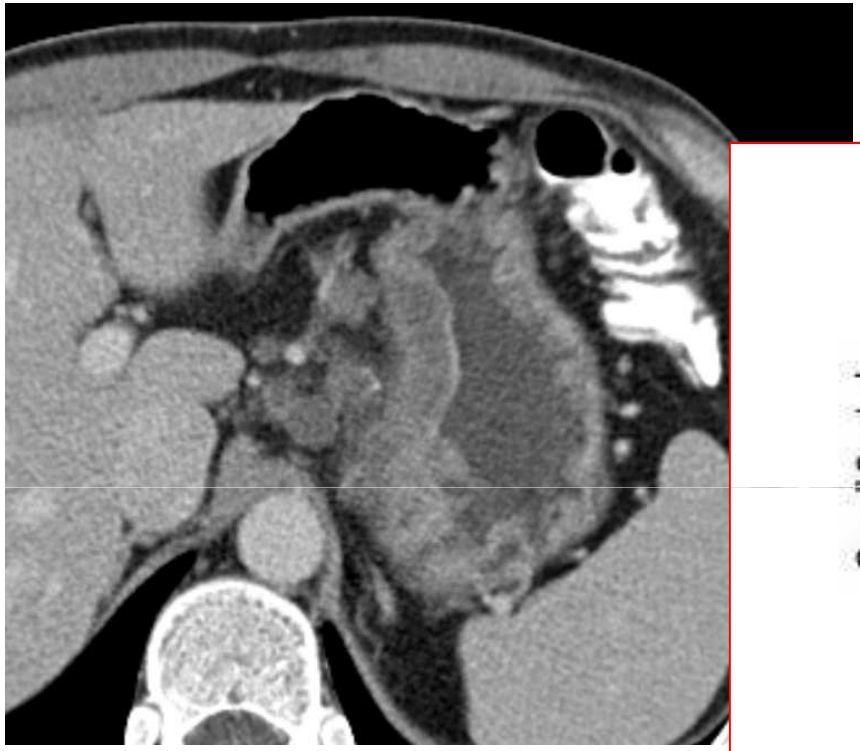
Cunningham D et al. *N Engl J Med* 2006;355:11-20
Ychou et al. *J Clin Oncol* 2011; 29: 1715-21

Postoperative mortality

MAGIC (n=503)		FNCLCC (n=224)	
CTX	SURG	CTX	SURG
6%	6%	5%	4%

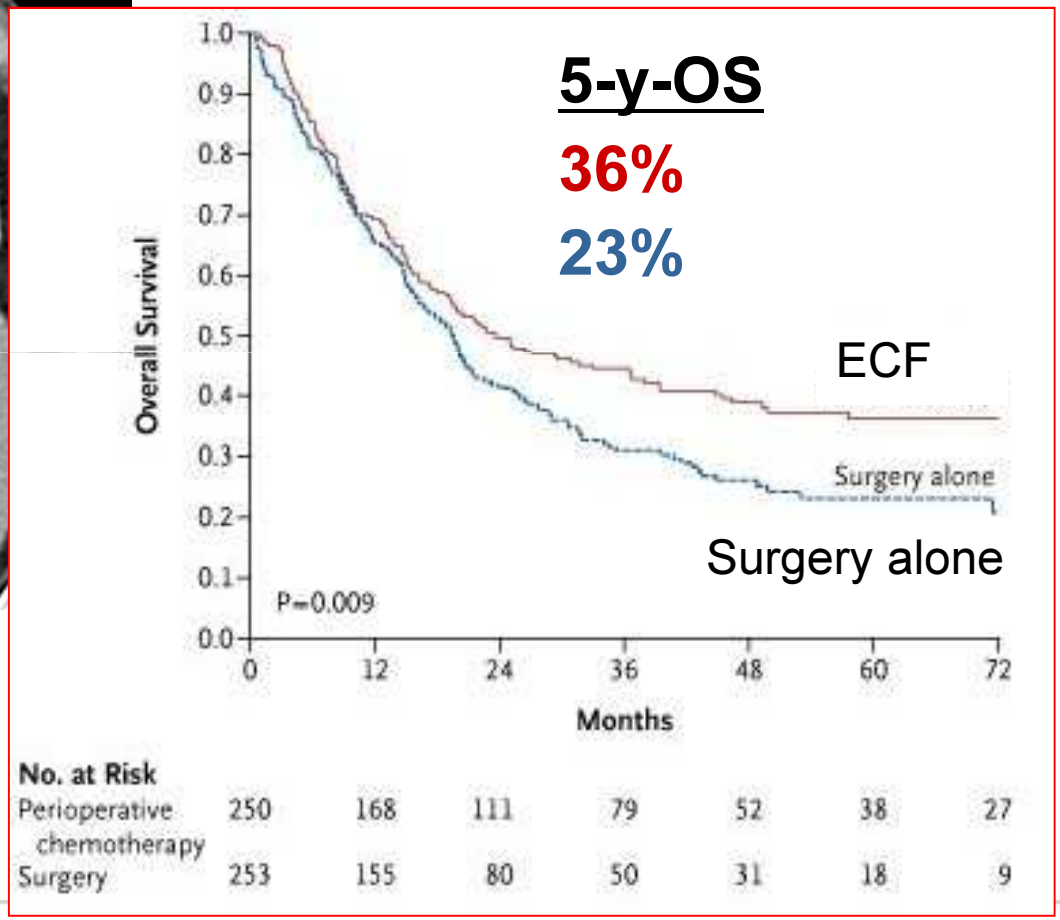
Cunningham D et al. *N Engl J Med* 2006;355:11-20
Ychou et al. *J Clin Oncol* 2011; 29: 1715-21

Peri-/Preoperative Therapy



Gastric Cancer 74%
AEG 26%

UK MAGIC 2006



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Cunningham D et al. *N Engl J Med* 2006;355:11-20

Current Studies Integrating Radiotherapy

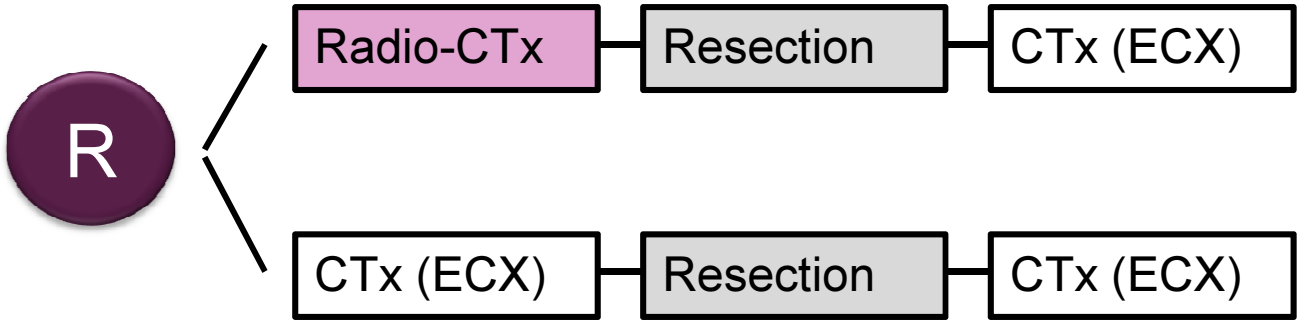
AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

TROG CANCER RESEARCH

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

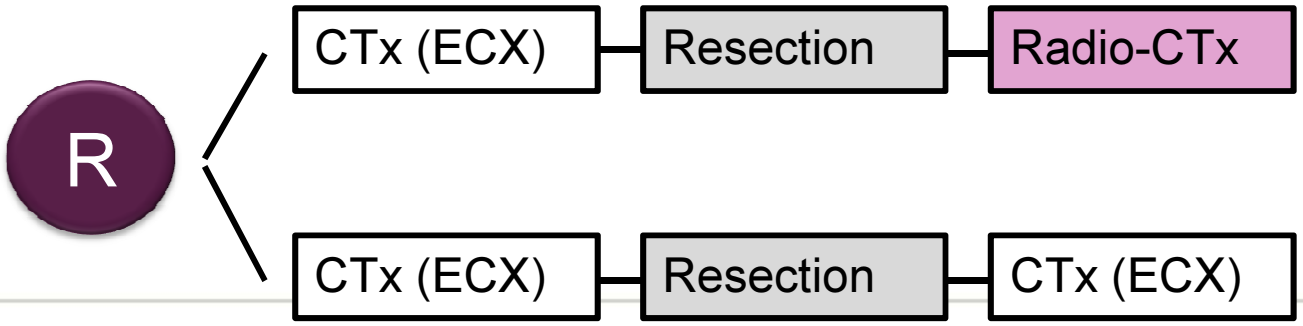
EORTC European Organisation for Research and Treatment of Cancer

TOPGEAR
(AUS, CAN, EU)
Stage Ib-IVa



DUCG Dutch Upper GI Cancer Group

CRITICS
(NL, Sweden)
Stage Ib-IVa



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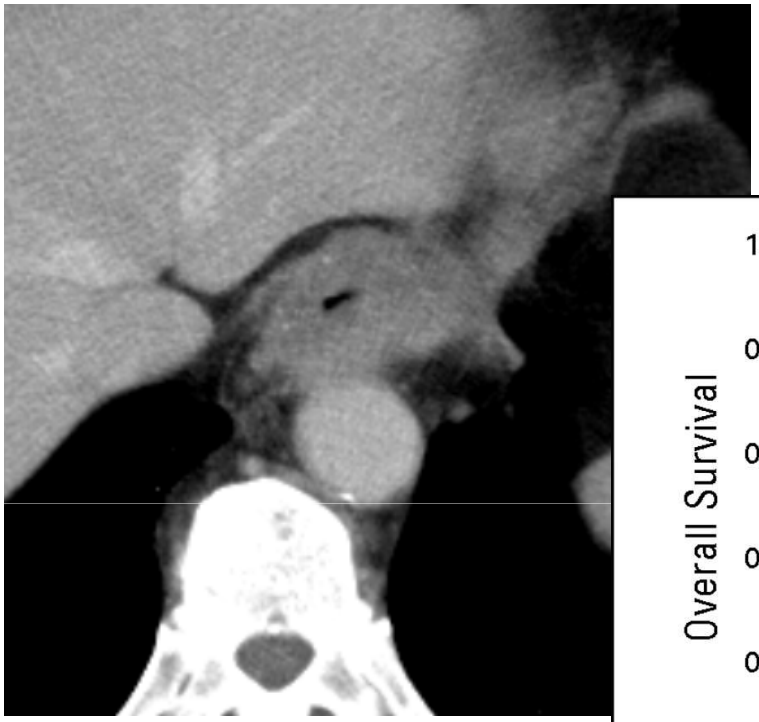
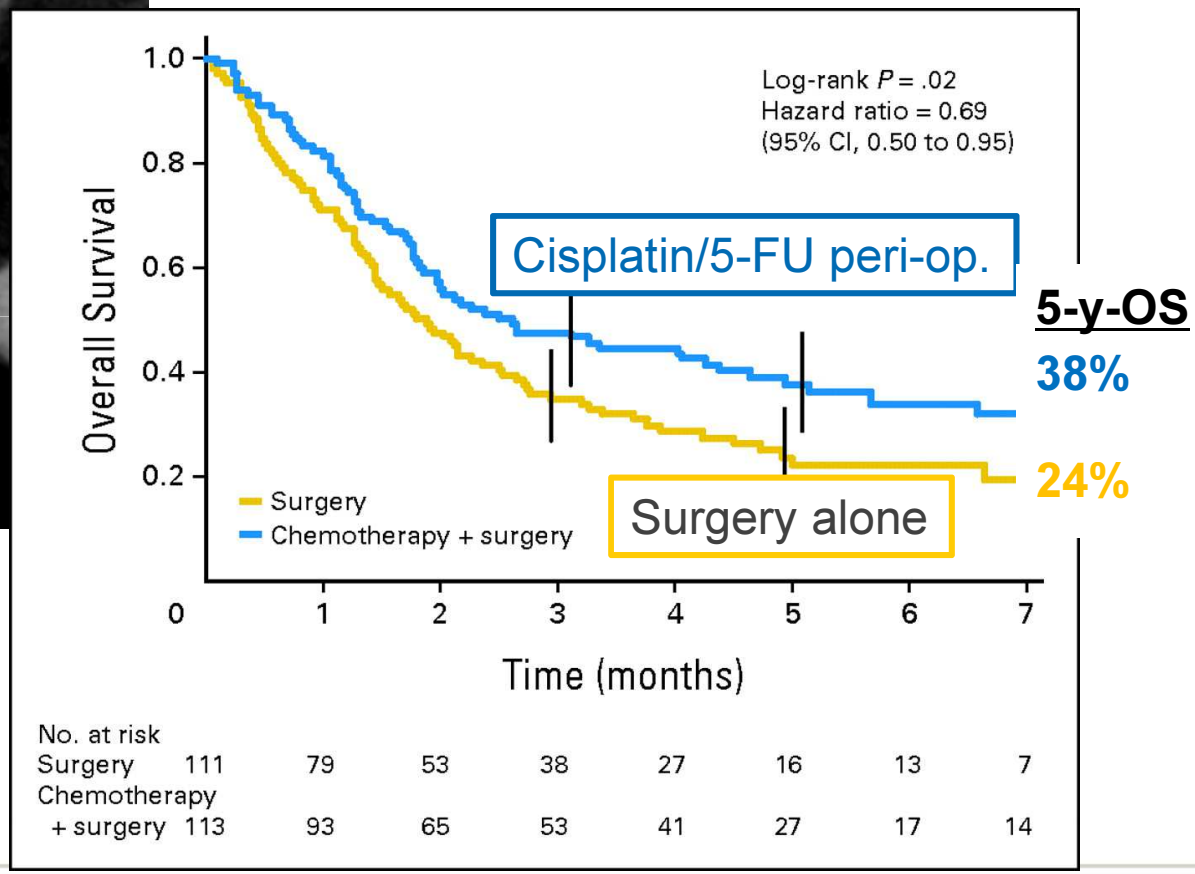
Peri-/Preoperative Therapy



France FNCLCC 2011



5-y-OS

38%

24%

Gastric Cancer	**25%**
AEG	**75%**

Ychou et al. *J Clin Oncol* 2011; 29: 1715-21

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Tumor Response

Ann Surg Oncol
DOI 10.1245/s10434-011-2147-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Adenocarcinomas of the Esophagogastric Junction Are More Likely to Respond to Preoperative Chemotherapy than Distal Gastric Cancer

Daniel Reim, MD[1], Ralf Gertler, MD[1], Alexander Novotny, MD[1], Karen Becker, MD[2], Christian Meyer zum Büschenfelde, MD[3], Matthias Ebert, MD[4], Martin Dobritz, MD[5], Rupert Langer, MD[2], Heinz Hoefler, MD[2], Helmut Friess, MD[1], and Christoph Schumacher[1]

TABLE 1 continued

Characteristic	All ($n = 551$) n	%	AEG ($n = 394$) n	%	GC ($n = 157$) n	%	P value, AEG vs. GC
Lauren type							0.0001
Nonintestinal	300	54.4	184	46.7	116	73.9	
Intestinal	251	45.6	210	53.3	41	26.1	
HPR							0.008
Becker 1	130	23.6	105	26.6	25	15.9	
Becker 2	152	27.6	110	27.9	42	26.8	
Becker 3	269	48.8	179	45.4	90	57.3	

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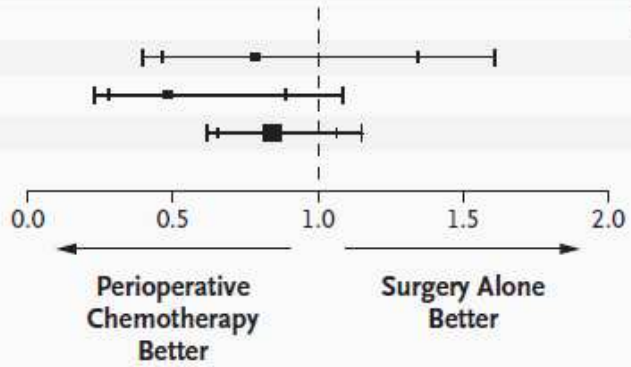
Reim D et al. *Ann Surg Oncol* 2011; DOI 10.1245/s10434-011-2147-8

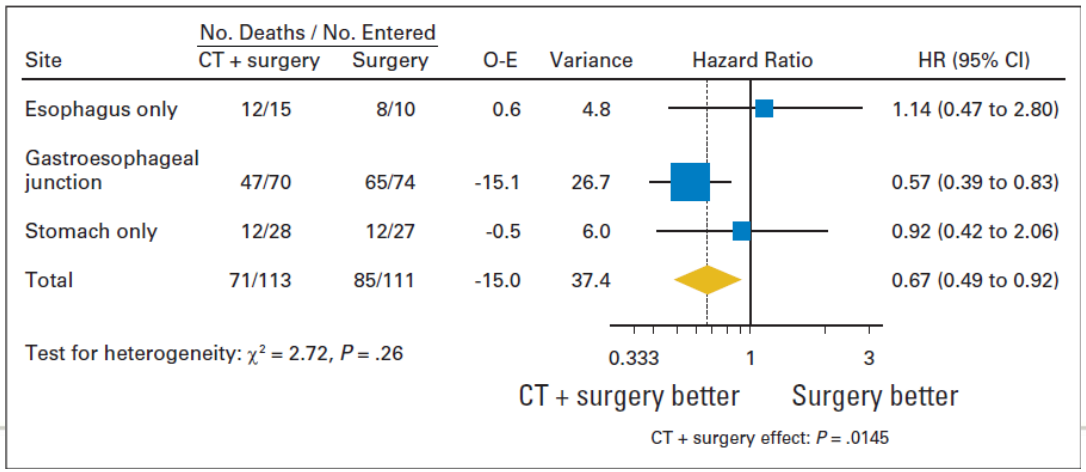
Tumor Response

UK MAGIC 2006

Site of primary tumor			P for interaction=0.25
Lower esophagus	23/37	25/36	
Esophagogastric junction	13/28	23/30	
Stomach	113/185	122/187	
Total	149/250	170/253	



FNCLCC 2011



Site	No. Deaths / No. Entered CT + surgery	Surgery	O-E	Variance	Hazard Ratio	HR (95% CI)
Esophagus only	12/15	8/10	0.6	4.8		1.14 (0.47 to 2.80)
Gastroesophageal junction	47/70	65/74	-15.1	26.7		0.57 (0.39 to 0.83)
Stomach only	12/28	12/27	-0.5	6.0		0.92 (0.42 to 2.06)
Total	71/113	85/111	-15.0	37.4		0.67 (0.49 to 0.92)

Test for heterogeneity: $\chi^2 = 2.72$, $P = .26$

Cunningham D et al. *N Engl J Med* 2006;355:11-20
Ychou et al. *J Clin Oncol* 2011; 29: 1715-21

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Novel Drugs

Chemotherapy	**Taxanes**	**AIO-FLOT-4** FLOT vs. ECF Phase II presented
Anti-Angiogenesis	**Bevacizumab**	**STO-3 (MAGIC-B)** ECX+/-Bevacizumab Phase III negative
Anti-Her2	**Trastuzumab/ Pertuzumab**	**EORTC-INNOVATION** CX +/- anti-HER2 Phase II/III now starting

Docetaxel – First Data

original articles

Annals of Oncology

Annals of Oncology 24: 2068–2073, 2013
doi:10.1093/annonc/mdt141
Published online 16 April 2013

Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy

S. Lorenzen[1,†], P. Thuss-Patience[2,†], S. E. Al-Batran[3], F. Lordick[4], B. Haller[5], T. Schuster[5], C. Pauligk[3], K. Luley[6], D. Bichev[2], G. Schumacher[7] & N. Homann[8]

[1]3rd Department of Internal Medicine, Hematology/Medical Oncology, Klinikum rechts der Isar, Technische Universität München, Munich; [2]Department of Haematology, Oncology and Tumorimmunology, Campus Virchow- Klinikum, Charite-University Medicine Berlin, Berlin; [3]Krankenhaus Nordwest, UCT University Cancer Center, Frankfurt am Main; [4]University Cancer Center Leipzig (UCCL), University Clinic Leipzig, University of Leipzig, Leipzig; [5]Institute for Medical Statistics and Epidemiology,

Pooled analysis (n=120 neoadjuvant treated patients)
Gastro-Tax (Munich), DCX (Berlin), FLOT (Frankfurt)

pCR-rate 18/120 patients (15%)

Lorenzen S. et al. *Ann Oncol* 2013; 24: 2068-34

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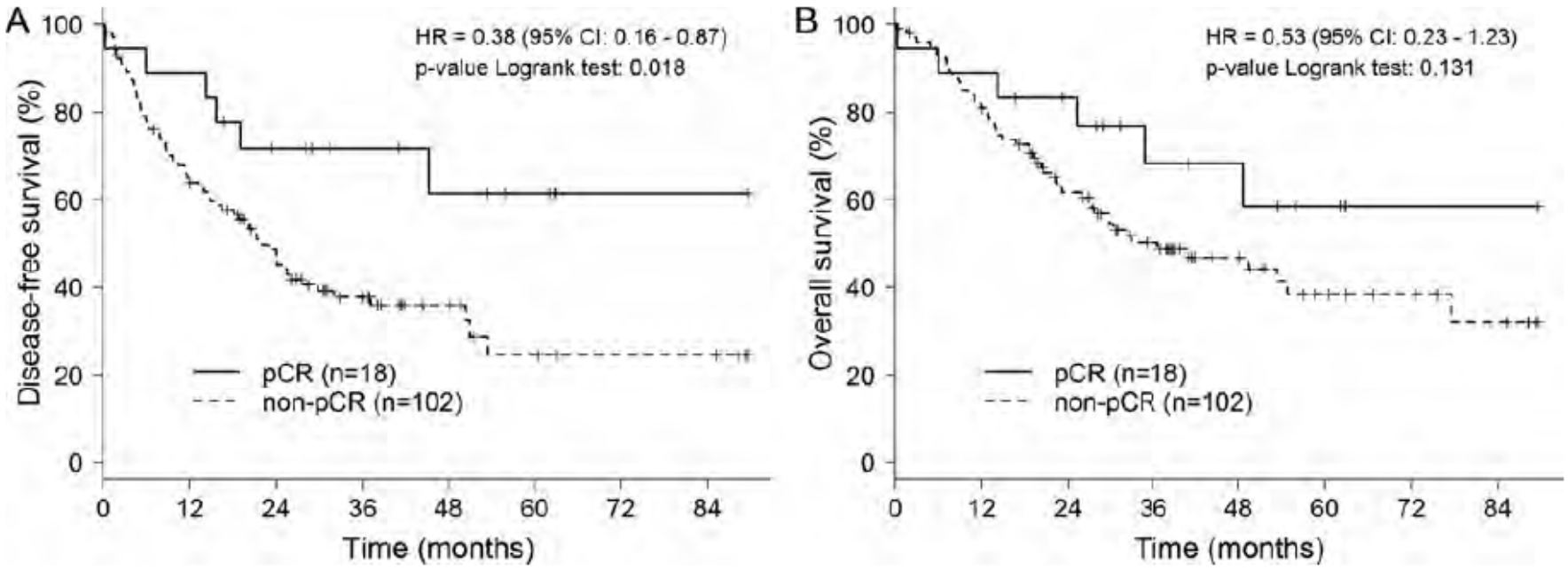
Docetaxel – First Data



pCR associated with better DFS and OS

Lorenzen S. et al. *Ann Oncol* 2013; 24: 2068-34

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FLOT-4 Study

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable stages
- T2-4, every N, M0 or every T, N+, M0

STRATIFICATION

R

n=714

4xFLOT - OP - 4xFLOT

FLOT: docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, qd14

3xECF(X) - OP - 3xECF(X)

ECF(X): Epirubicin 50 mg/m2, d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), qd21

AIO

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Primary endpoint Phase II (n=300): rate of complete pathological remission (pCR)
Primary endpoint for phase III (n=714): OS, HR 0.76, power 80%, p<0.05

Pauligk et al. *ASCO* 2015; #4016

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FLOT-4 Study

ITT Population:

FLOT n=128
ECF(X) n=137

Pathological Remission	ECF/ECX		FLOT		P value
	no.	%	no.	%	(2-sided)
CR	**8**	**5,8**	**20**	**15,6**	**.015**
SR	23	16,8	27	21,1	
CR+SR	31	22,6	47	36,7	.015
PR	28	20,4	23	18,0	
MR	44	32,1	45	35,2	
NR	8	5,8	4	3,1	
Not resectable	26	19,0	9	7,0	

Pauligk et al. *ASCO* 2015; #4016

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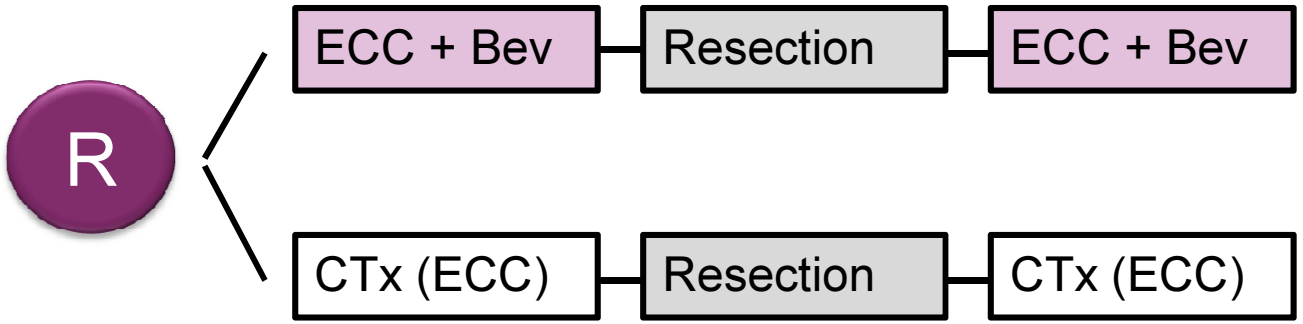
Anti-Angiogenesis (Bevacizumab)

CANCER RESEARCH UK

STO-3/MAGIC-B
(UK)
Stage Ib-IVa



*Chemotherapy: ECC (epirubicine, cisplatin, capecitabine)
Bev (bevacizumab)

Okines et al. *Annals of Oncology* 2013; 24: 702–709

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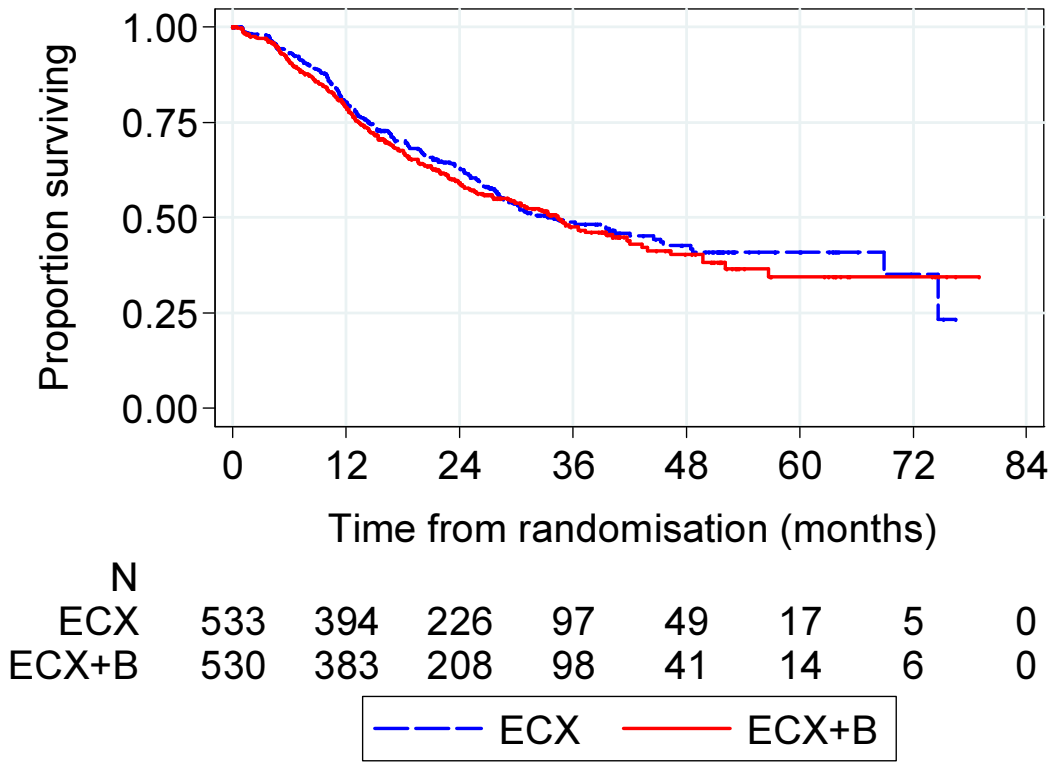
Anti-Angiogenesis (Bevacizumab)

- **472 deaths** (233 ECX, 239 ECX+B) have been observed
  - Median follow-up is 33 months in both arms



Overall survival		
Median OS	ECX	33.97 months
	ECX+B	34.46 months
Hazard Ratio		**1.067**
(95% CI)		**(0.8911 to 1.279)**
Log-rank p-value		**0.4784**

3-year overall survival (95% CI)	
ECX	48.9% (43.6% to 53.8%)
ECX+B	47.6% (42.3% to 52.7%)

Secondary outcomes	
PFS	HR=1.026 p=0.7683
DFS	HR=1.006 p=0.9425

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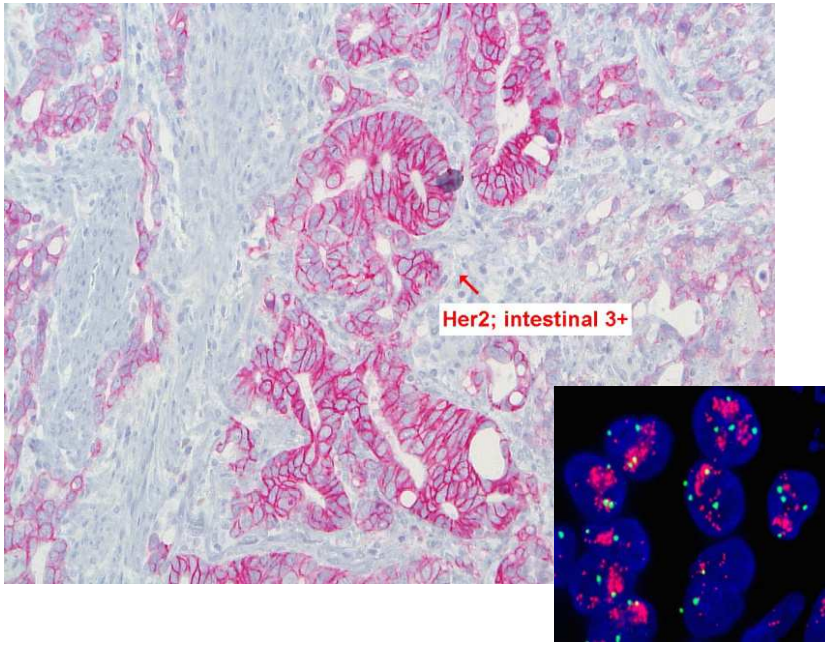
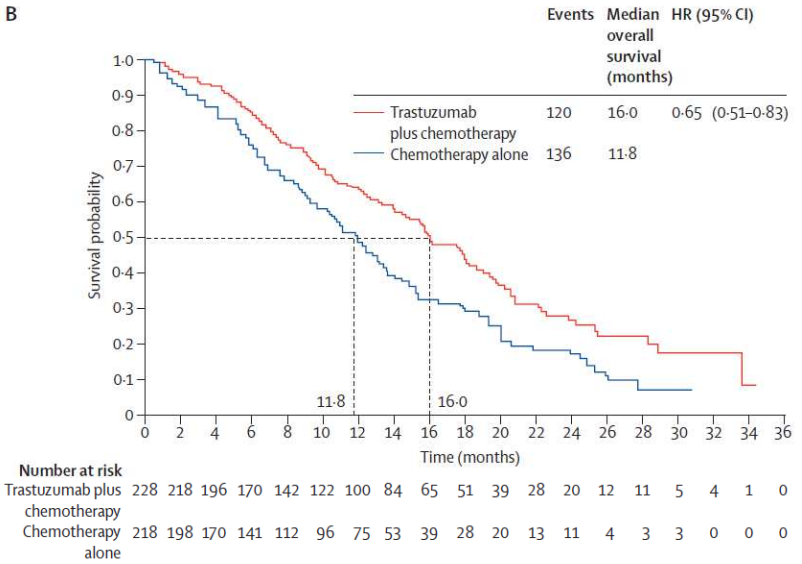
Cunningham et al. *ECCO Meeting* 2015

HER2-positive Gastric Cancer





Survival gain with Trastuzumab in HER2-pos. Gastric cancer in Stage Stage IV (ToGA study)

- 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)

Bang Y et al. *Lancet* 2010; 376: 687-697

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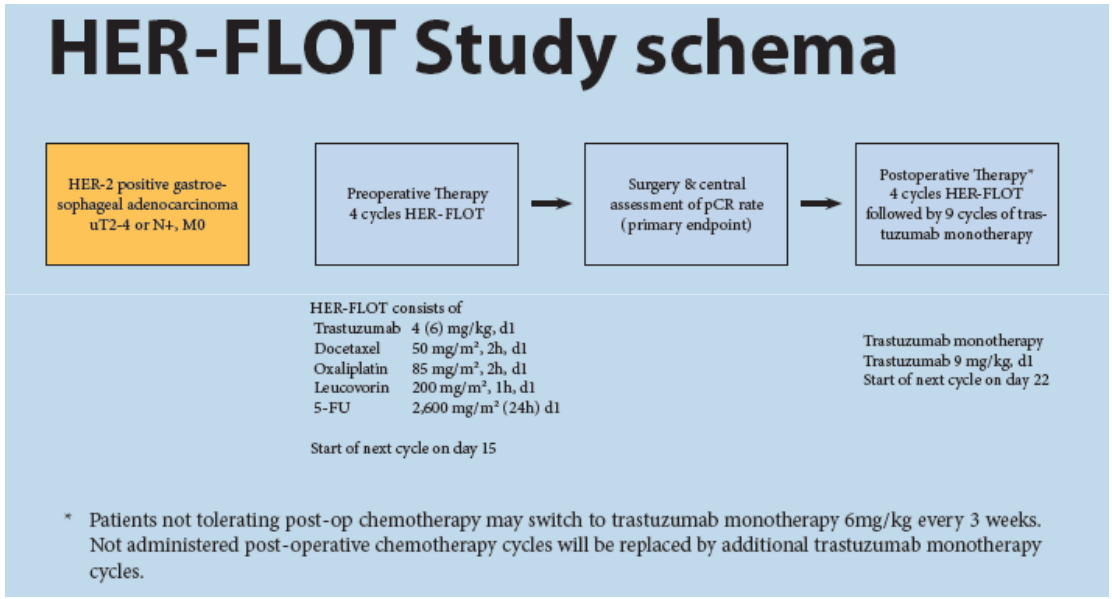
Anti-HER2 – Trastuzumab Neoadjuvant



AIO

pCR-rate: 12/57 (21%)

R0 resection 93%

Hofheinz R et al. *ASCO* 2014 (abstract #4073)

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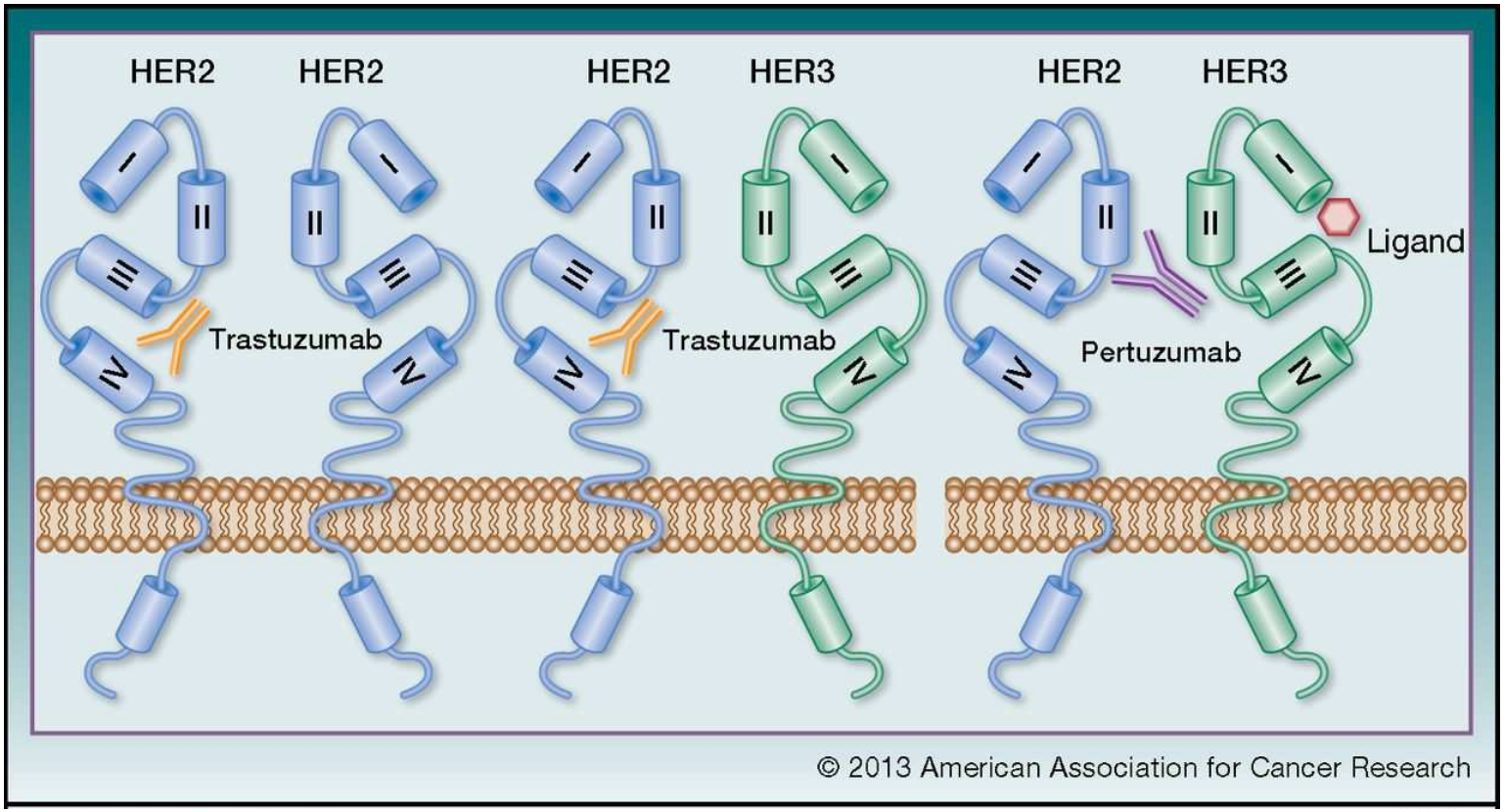
Anti-HER2 – Trastuzumab and Pertuzumab



The mechanism of action of pertuzumab and trastuzumab. Trastuzumab binds to the ECD IV of the HER2 receptor, preventing the spontaneous formation of homodimers (HER2–HER2) and ligand-independent heterodimers (HER2–HER3 and also HER2–HER1 and HER2–HER4). Pertuzumab binds to the dimerization domain of the HER2 receptor (ECD II), preventing the formation of ligand-induced HER2 heterodimers.

from: **Metzger-Filho O, et al**. Clin Cancer Res 2013; 19: 5552-5556

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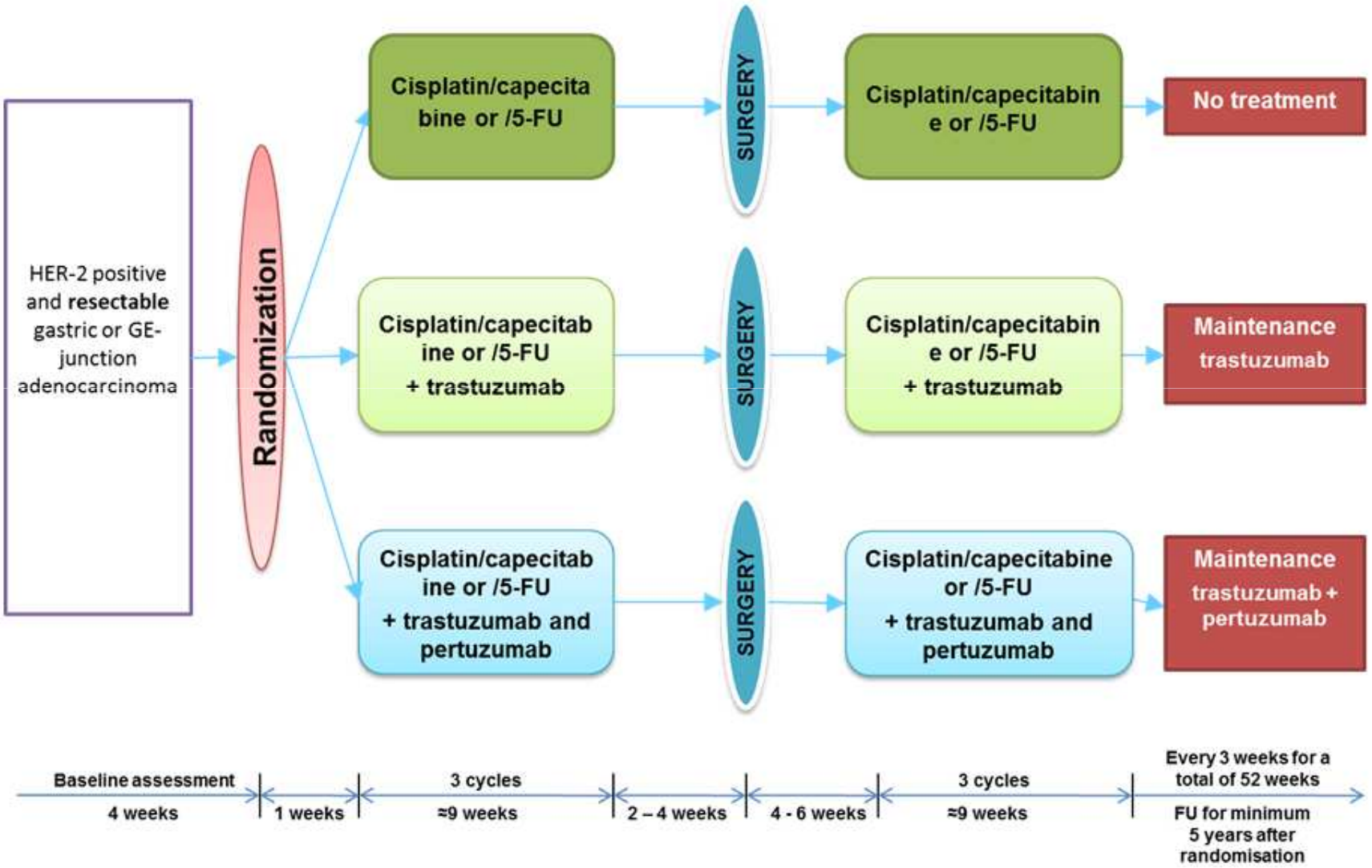
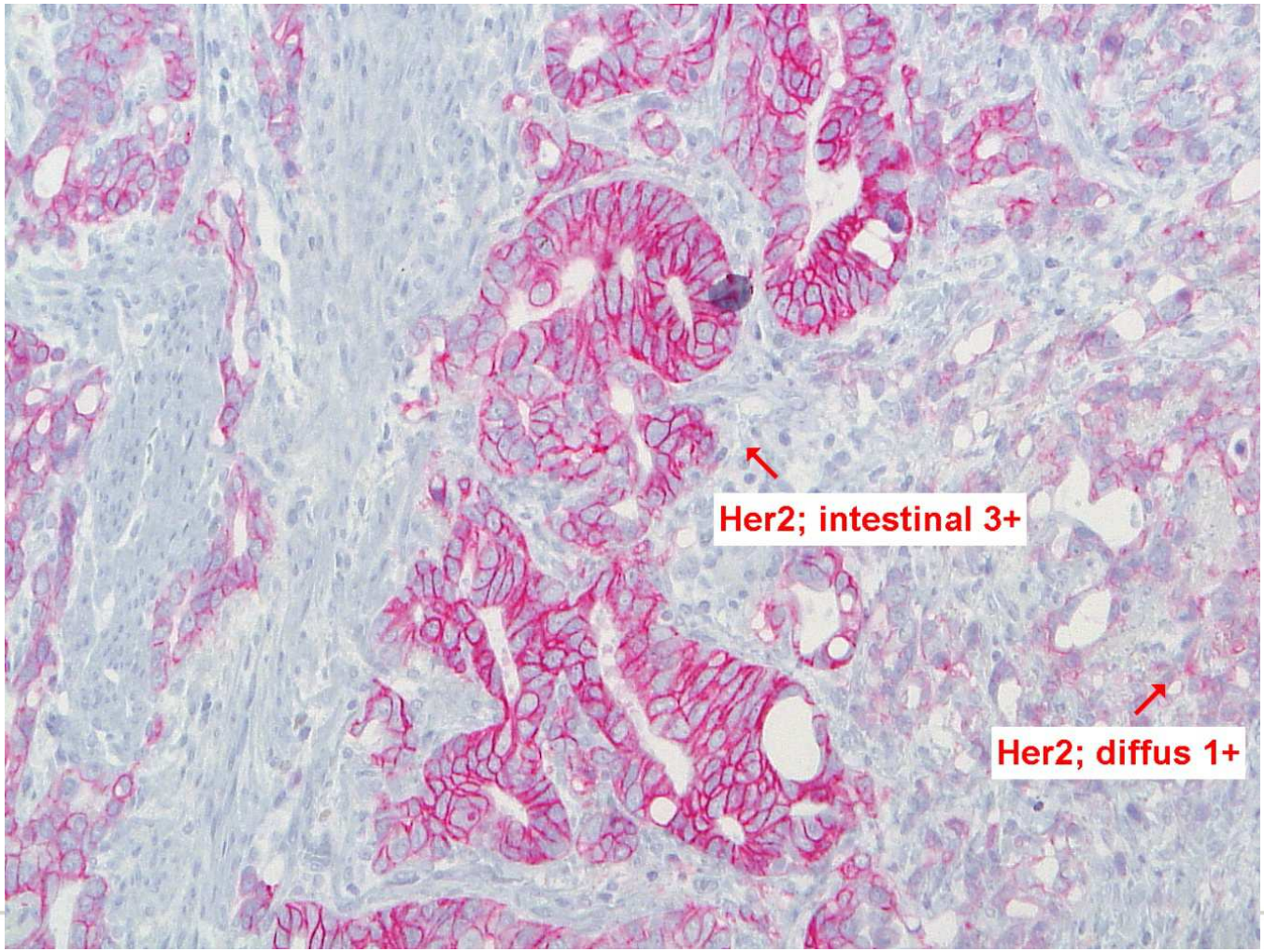
Anti-HER2 – INNOVATION Neoadjuvant



Anti-HER2 – Challenges

Focal staining for HER2 in 33% of gastric cancers



HER2, human epidermal growth factor receptor 2.

Lordick F, Janjigian YY. *Nat Rev Clin Oncol* 2016 [Epub]

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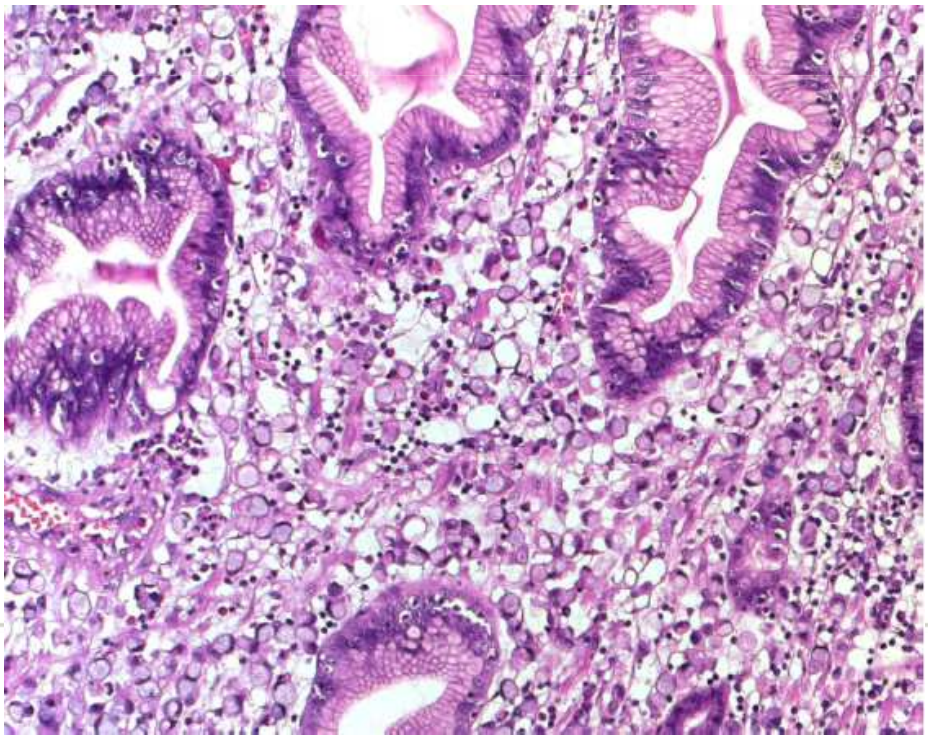
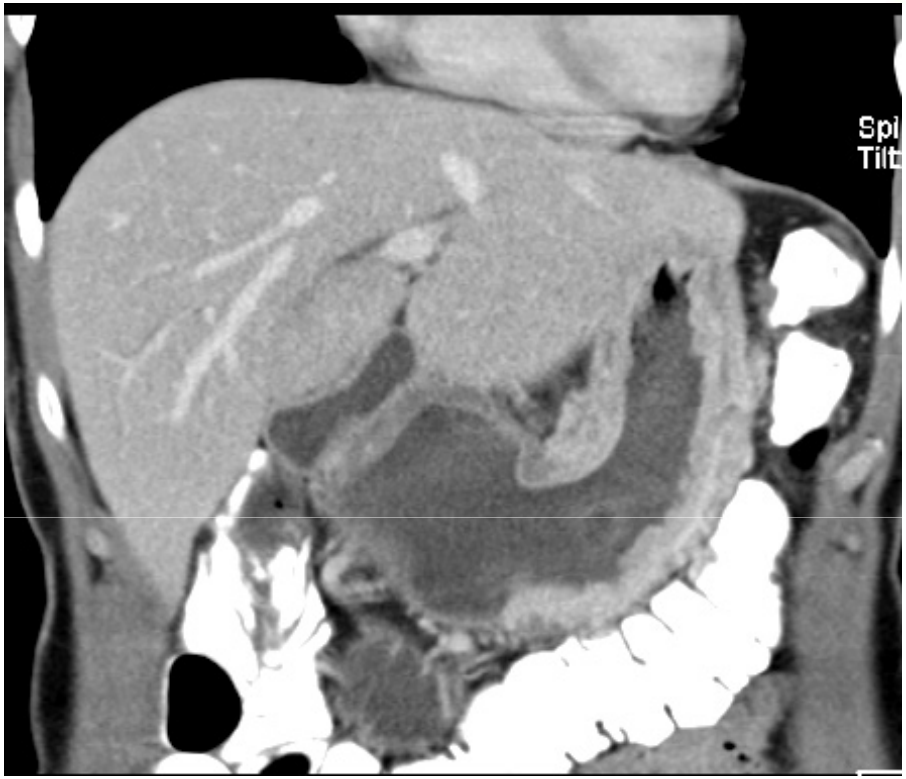
Diffuse Type – Signet Ring Cell - Challenges





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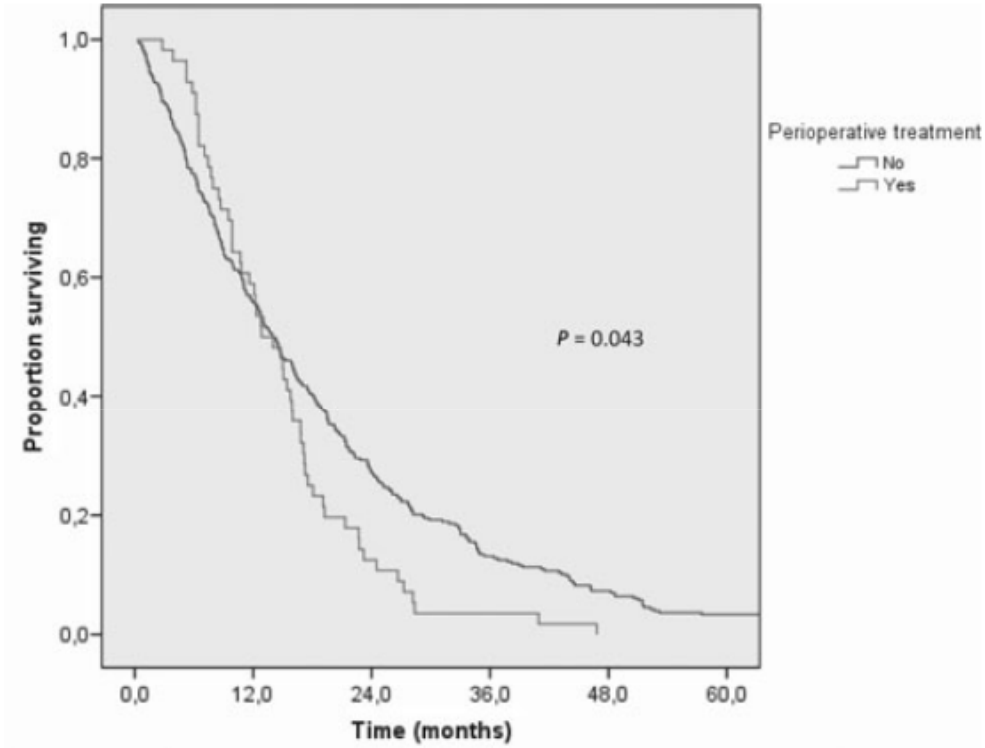
Diffuse Type – Signet Ring Cell - Challenges

Retrospective analysis from a national French register: periop. chemo



S group	753	420	204	99	55	26
PCT group	171	101	21	6	0	0

Caveat:

- retrospective
- No central pathologic assessment

Hypothesis: signet ring cell cancers do not benefit from neoadjuvant chemoTx

Messager et al. *Ann Surg* 2011; 254:684–6939

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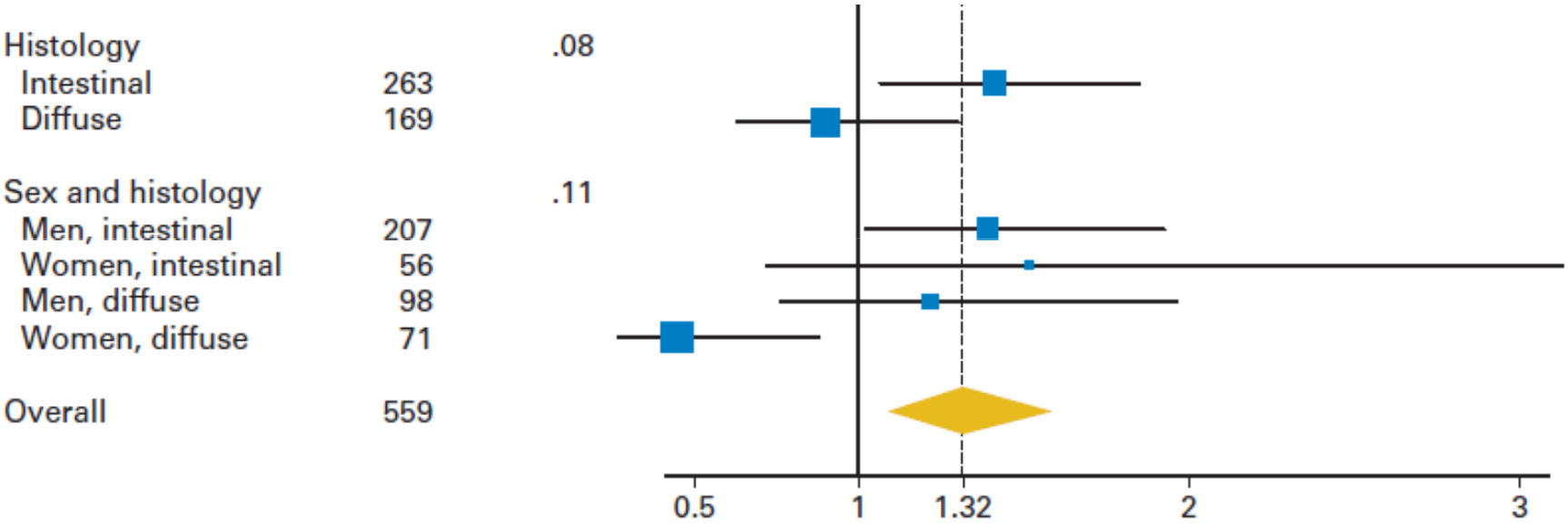
Diffuse Type – Signet Ring Cell - Challenges

Post-hoc analysis from SWOG/INT-0116 (USA): adjuvant radio-CTx



Hypothesis: diffuse type tumors do not benefit from adjuvant radio-CTx

Smalley et al. *J Clin Oncol* 2012;30:2327-2333

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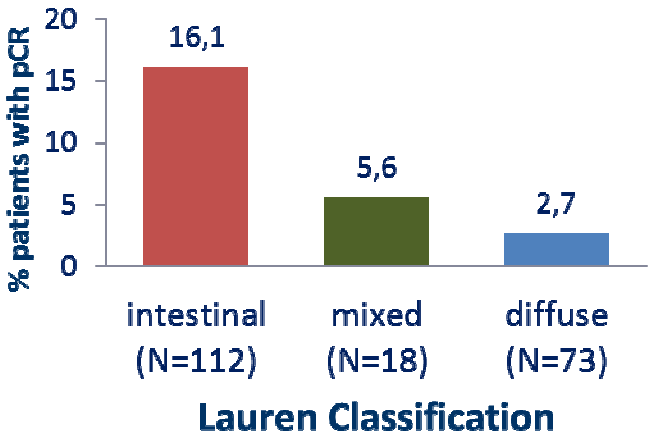
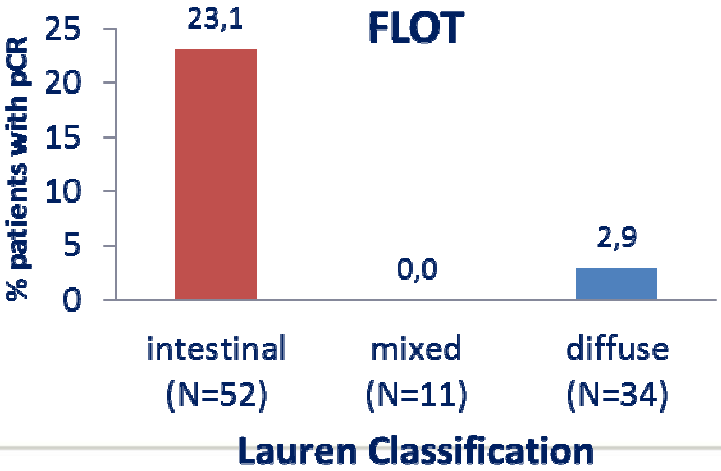
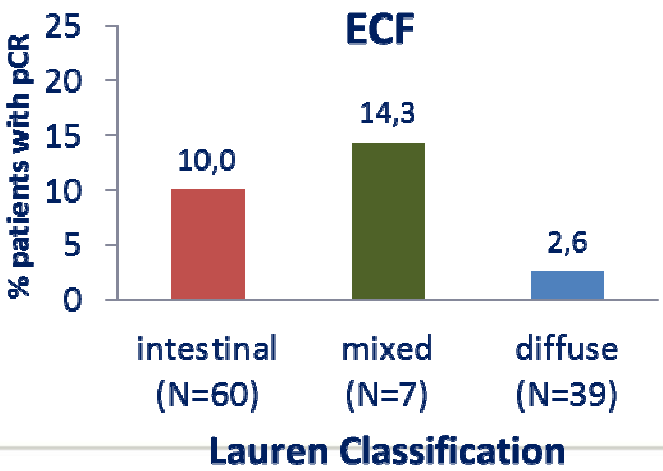
Diffuse Type – Signet Ring Cell - Challenges

Even "FLOT" does not work







Pauligk et al. *ASCO* 2015; #4016

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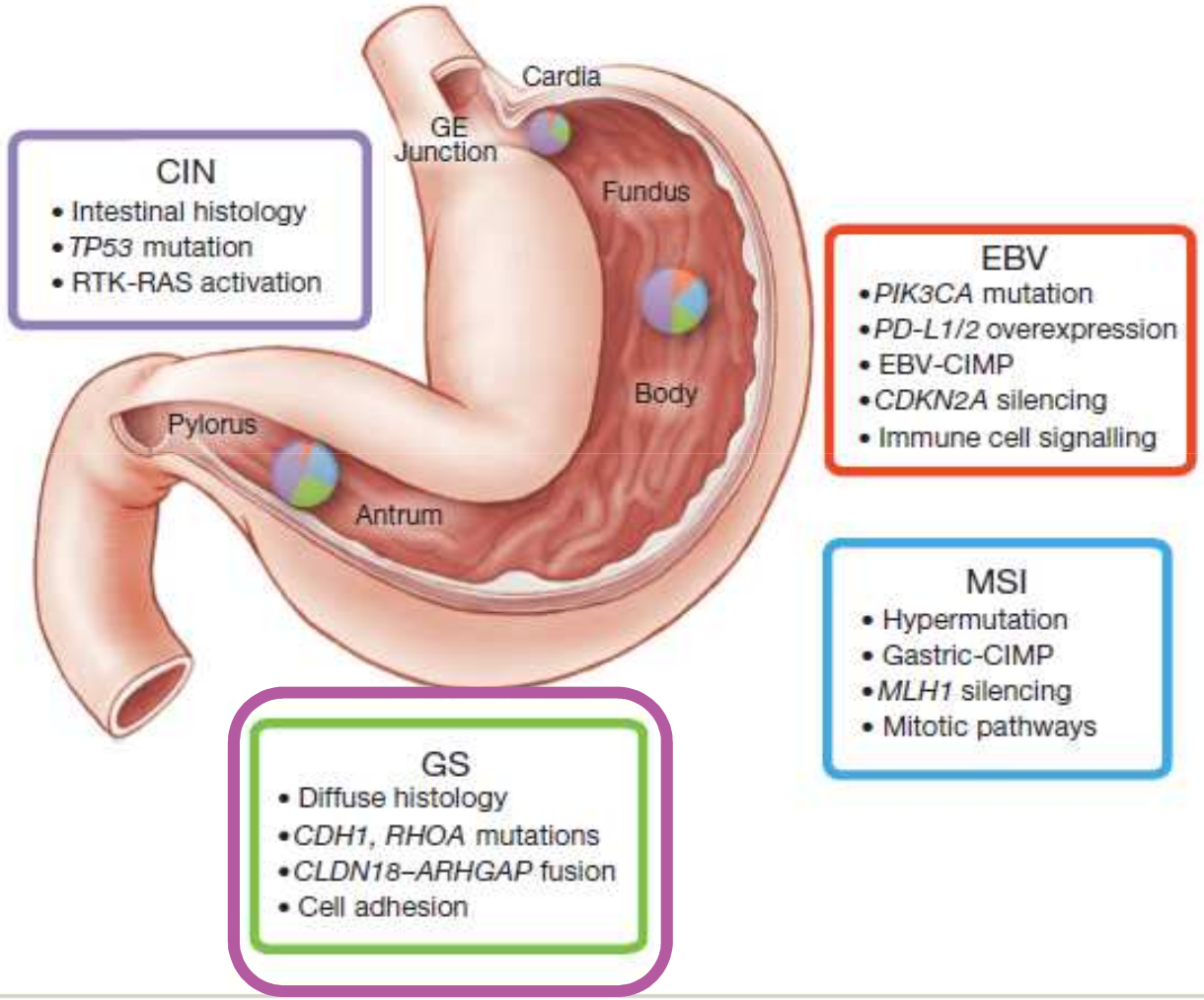
The Future – New Molecular Targets?



CIMP, CpG island methylator phenotype; CIN, chromosomal instability; EBV, Epstein–Barr virus; GE, gastroesophageal; GS, genomically stable; MSI, microsatellite instability.

The Cancer Genome Atlas Research Network. *Nature* 2014;513:202–9

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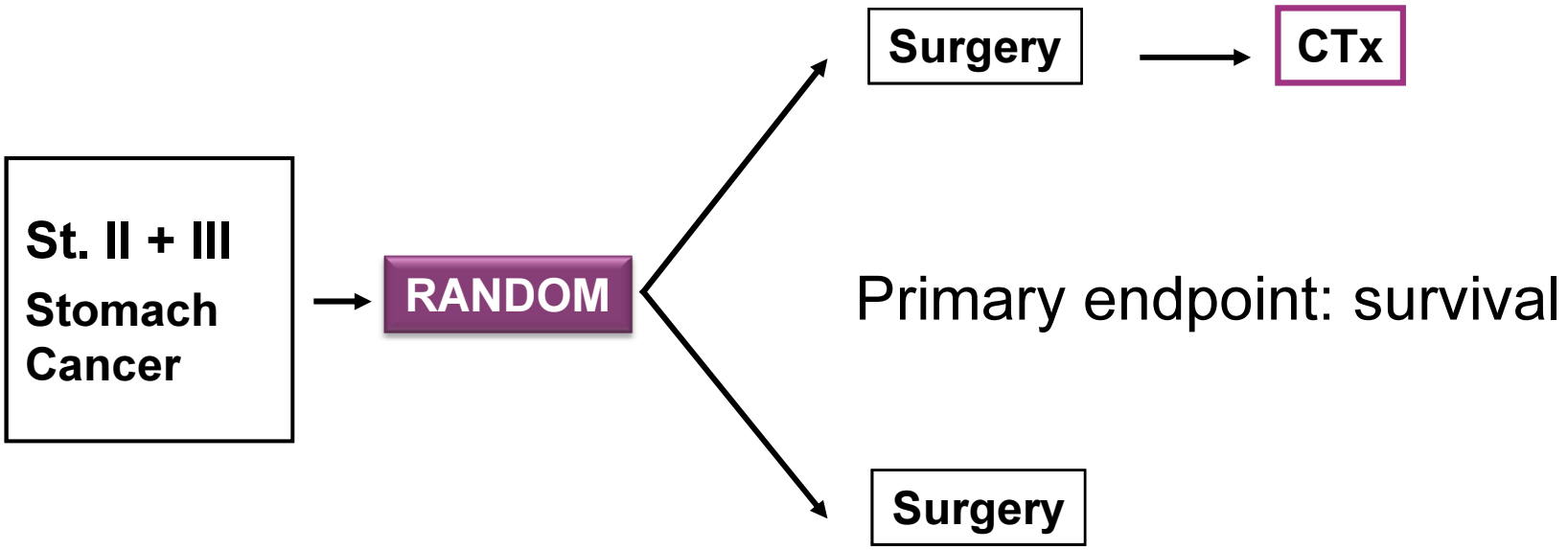
Multiple Adjuvant Studies



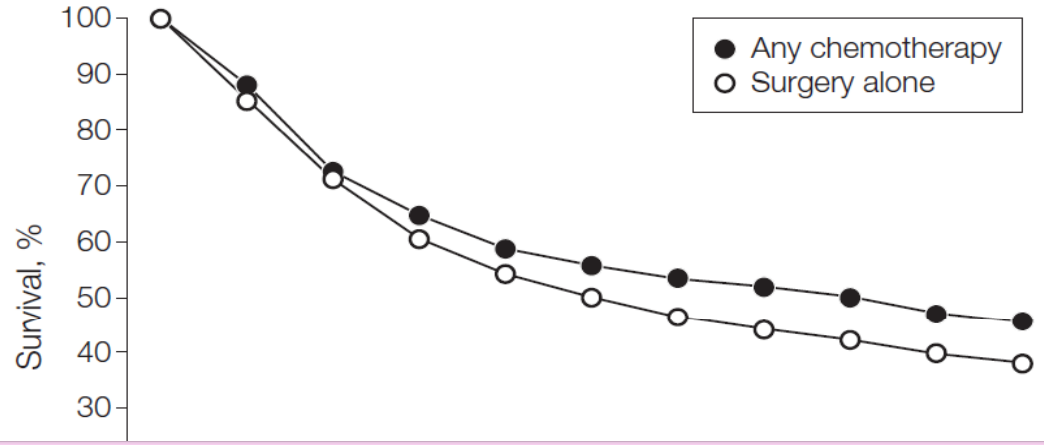
Adjuvant Approach

Metaanalysis	Studies (n)	Patients (n)	Odds ratio (CI)
Hermans 1993	11	2096	0.88 (0.78-1.08)
Earle 1999	13	1990	**0.80 (0.66-0.97)**
Mari 2000	21	3658	**0.82 (0.75-0.89)**
Janunger 2002	21	3962	**0.84 (0.74-0.96)**
GASTRIC 2010	17	3838	**0.82 (0.75-0.90)**

- **5-year survival benefit ~ 5% (GASTRIC 2010)**
- **Some more benefit in node positive tumors (Janunger 2002)**

Adjuvant Approach

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years



5- year survival

Surgery alone	**49.6 %**
Adjuvant chemotherapy	**55.3 %**

HR = 0.82; p < 0.001

GASTRIC Group *JAMA* 2010; 303:1729-37

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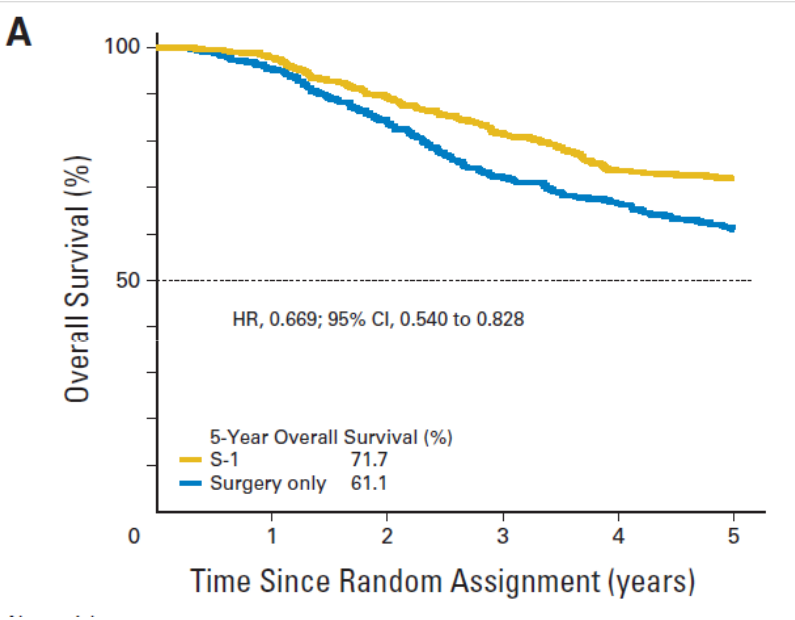
Adjuvant Approach

Japan ACTS-GC 2007 (1 year S-1)



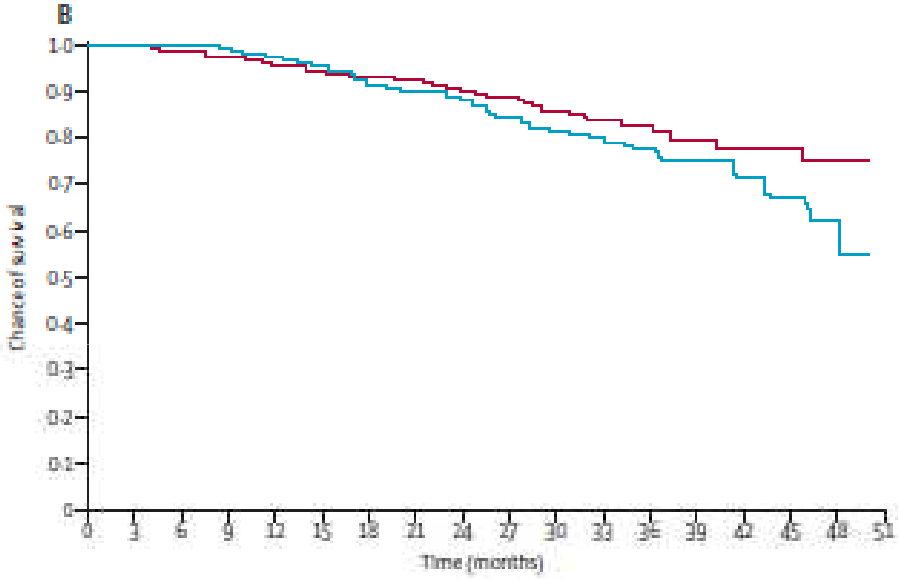
Overall Survival

HR = 0,669 (95% CI, 0.540 to 0.828)

P = 0,003

Sakuramoto S et al. *N Engl J Med* 2007;357:1810-1820
Sasako et al. J Clin Oncol 2011; 29: 4387-4393

Korea/China/Taiwan Classic 2012 (6 mon Cape-Ox.)



Overall Survival (preliminary)

HR = 0,72 (95% CI, 0.52 to 1.00)

P < 0,0493

BangYJ et al. *Lancet* 2012; 379: 315-21

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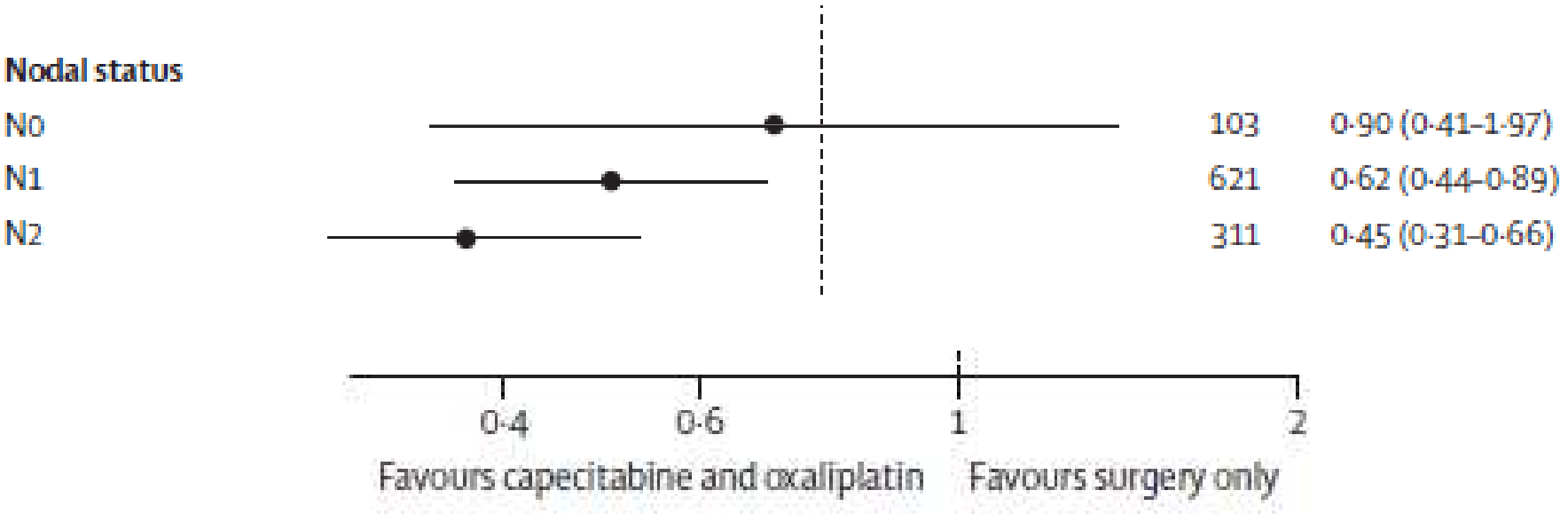
Adjuvant Approach

Korea/China/Taiwan
Classic 2012



BangYJ et al. *Lancet* 2012; 379: 315-21

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Adjuvant Approach

- Adjuvant chemotherapy is moderately effective
- Gain in overall survival ~ 5 %
- Combination more effective in N+ disease

- Is it worth intensifying adjuvant chemotherapy?

Adjuvant Approach

GISCAD

5-FU (375mg/m² bolus) / LV (20mg/m²) d1-5; q4w x 6

N = 400

wPELF (weekly cisplatin, epirubucine, LV, 5-FU) x 8

Cascinu et al., *J Nat Canc Inst* 2007; 99: 601-607

ITACA-S

5-FU (400-600mg/m²) / LV (100mg/m²) d1-2; q2w x 9

N = 1106

FOLFIRI x 4 → Docetaxel/Cisplatin x 3

Bajetta et al., *Ann Oncol.* 2014; 25: 1373-8

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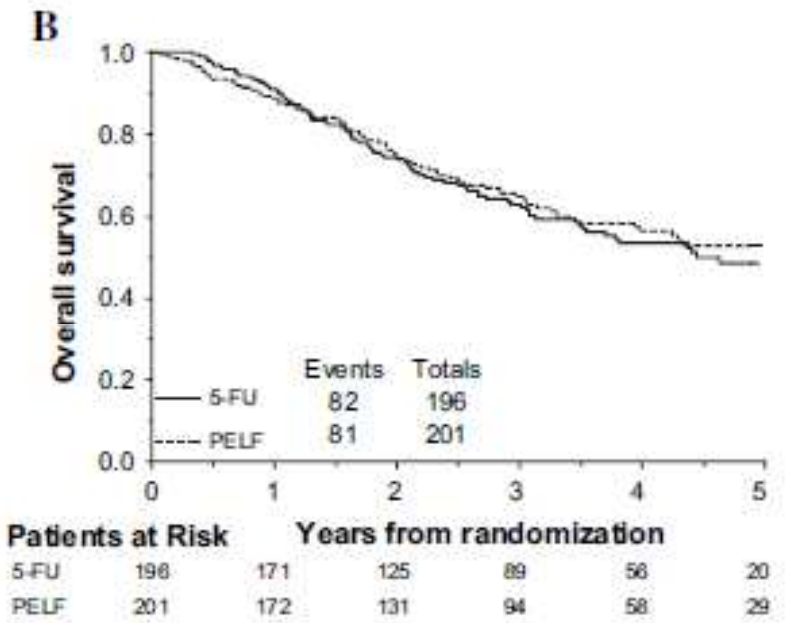
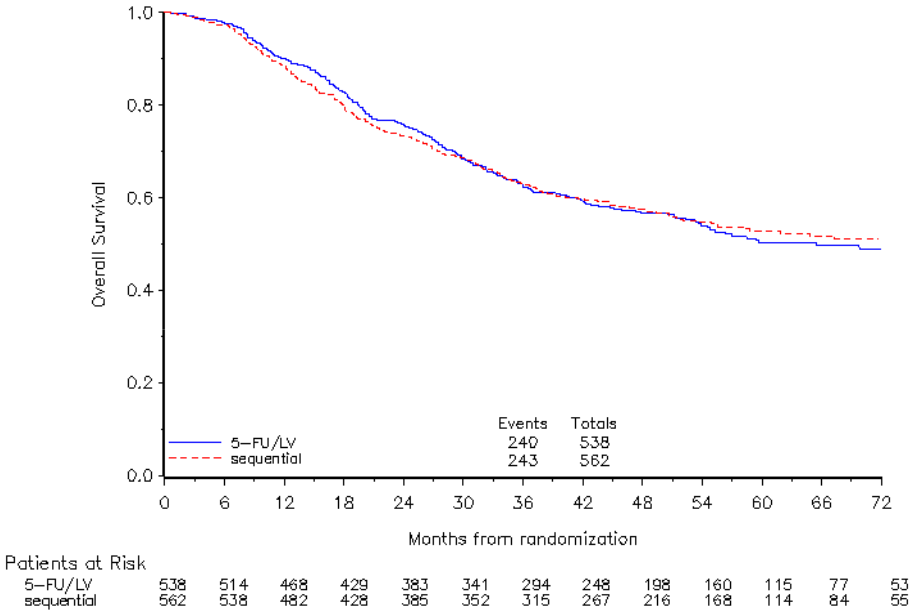
Adjuvant Approach

GISCAD Study



Cascinu et al., *J Nat Canc Inst* 2007; 99: 601-607

ITACA-S Study



Bajetta et al., *Ann Oncol.* 2014; 25: 1373-8

Postoperative CTx intensification did not improve outcomes in EU

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Summary

- Perioperative chemotherapy is the EU standard of care fo T3-4 and/or N+
- Perioperative CTx is based on platinum and a fluoropyrimidine
- Studies on integration of RTx and comparative studies areeongoing
- Taxanes may improve chemotherapy response and survival
- Anti-angiogenic treatment is not effective
- Anti-HER2-directed treatment: under investigation
- Adjuvant chemotherapy marginally effective
- Intensification of adjuvant / postoperative chemotherapy has thus far not improved survival outcomes

8 – 11 May 2019, Prague (CZ)

Universitätsklinikum Leipzig
Anstalt öffentlichen Rechts

13th INTERNATIONAL
GASTRIC CANCER CONGRESS IGCC 2019

INTERNATIONAL GASTRIC CANCER CONGRESS PRAGUE 2019

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- Venue
- Prague
- Czech Republic
- 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.

Gastric tumors: Pathology evaluation

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
- Tumor extension evaluation – using UICC- TNM 7th edition (since 2010)
- Lymph nodes stations (D1-D4)
- Patho-anatomical basics and reportings

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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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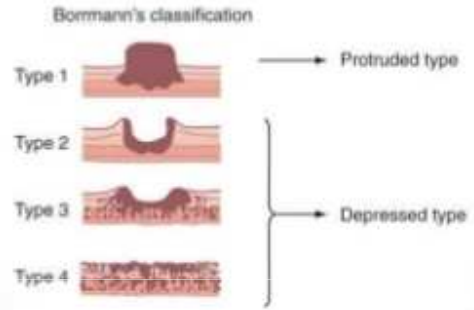
Traditional morphology based diagnostics

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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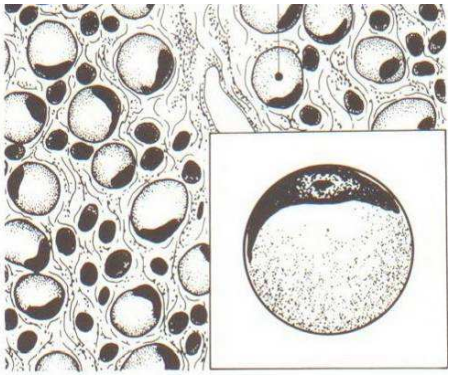
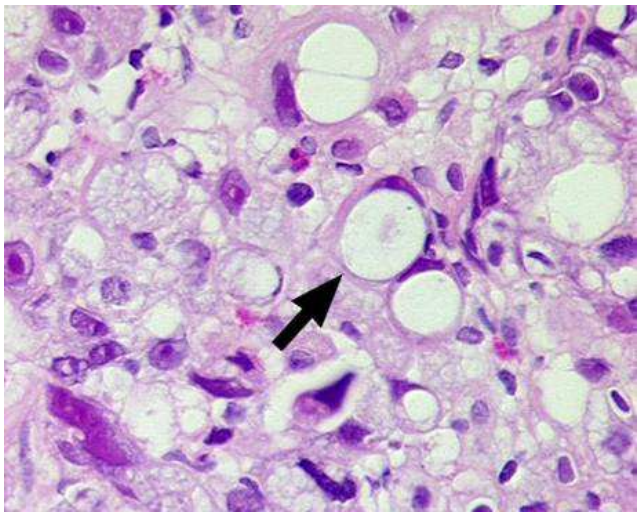
Traditional morphology based diagnostics

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

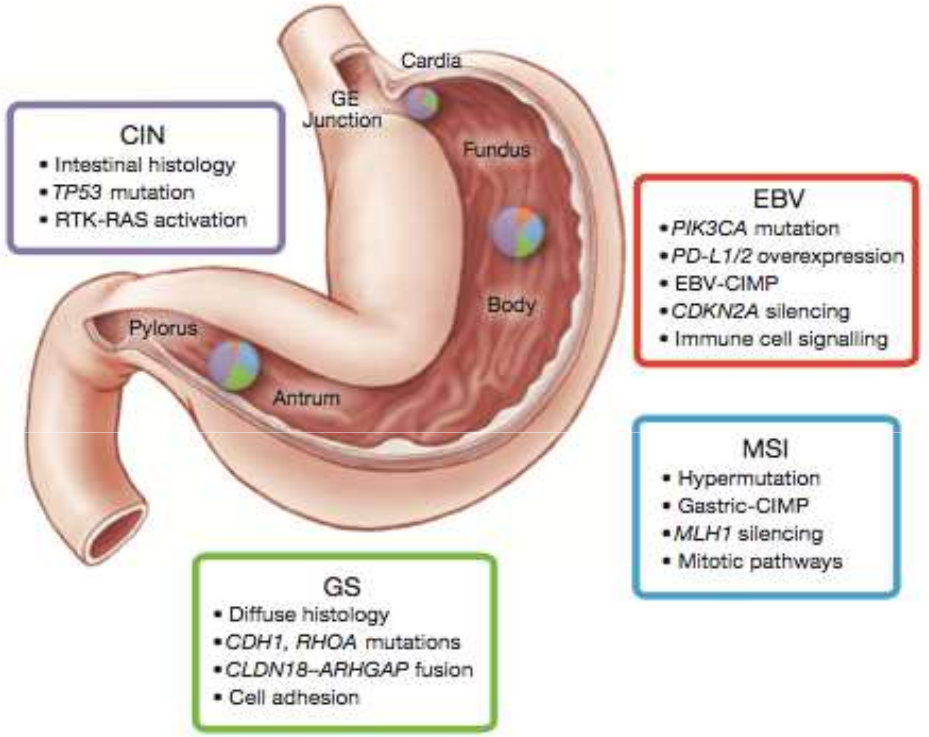

Figure 6 | Key features of gastric cancer subtypes. This schematic lists some of the salient features associated with each of the four molecular subtypes of gastric cancer. Distribution of molecular subtypes in tumours obtained from distinct regions of the stomach is represented by inset charts.

From: CancerGenomeAtlasResearchNetwork, „comprehensive molecular characterization of gastric adenocarcinoma“ Nature 2014

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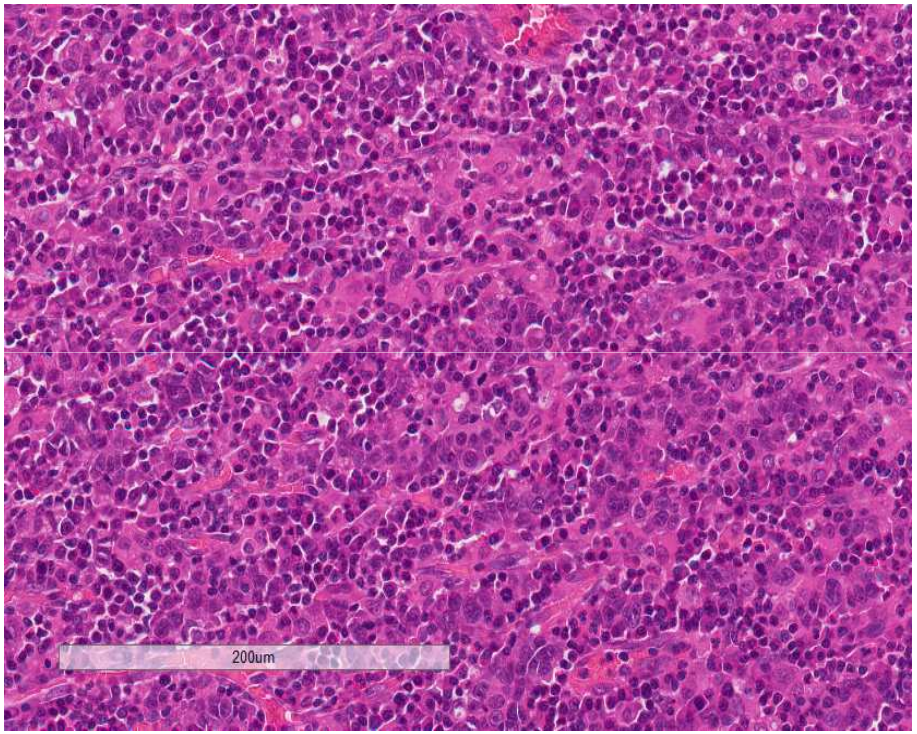
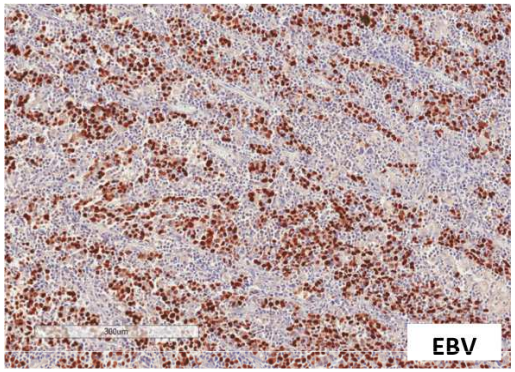
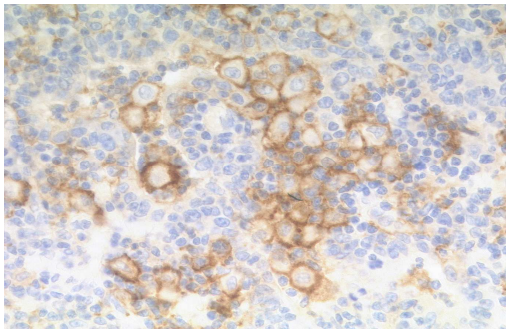
EBV+ gastric carcinoma



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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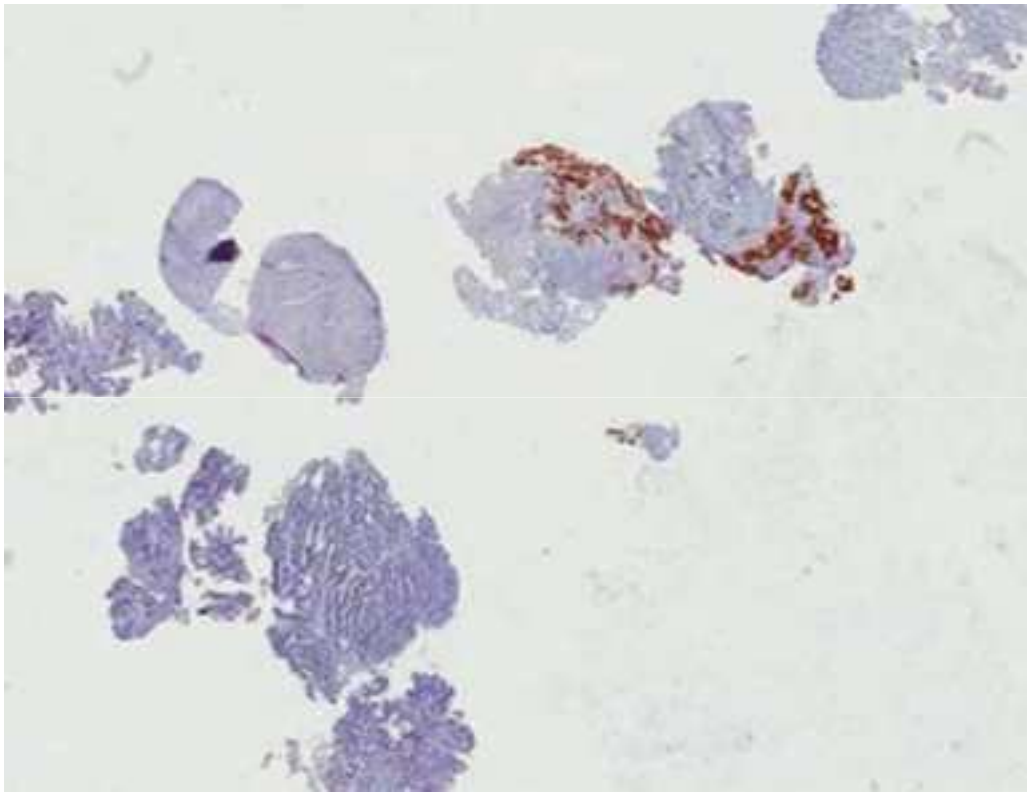
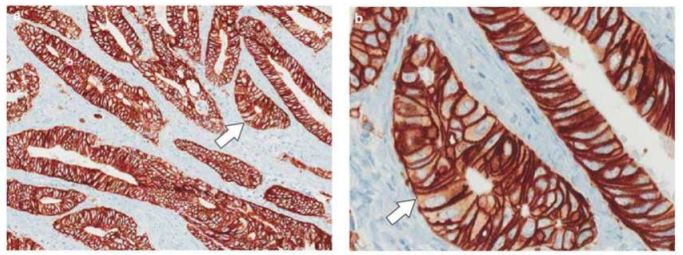
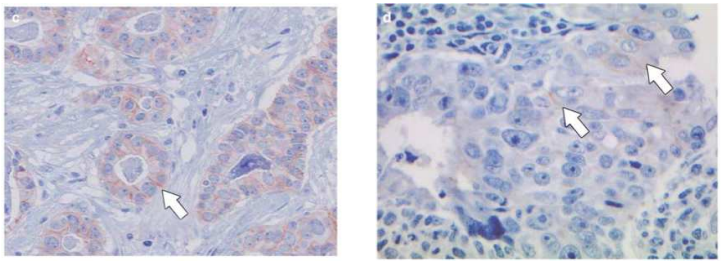
Her2+ gastric carcinoma





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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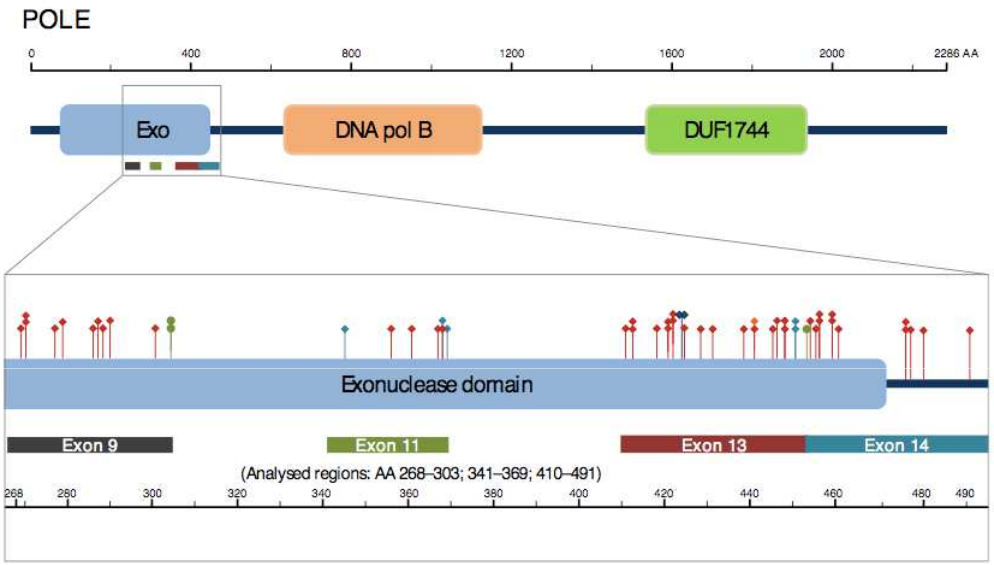
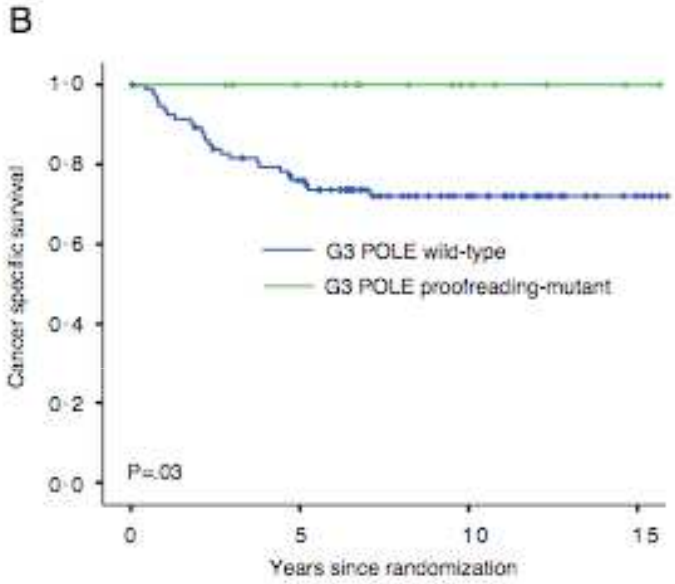
POLE-mutated gastric carcinoma?





- 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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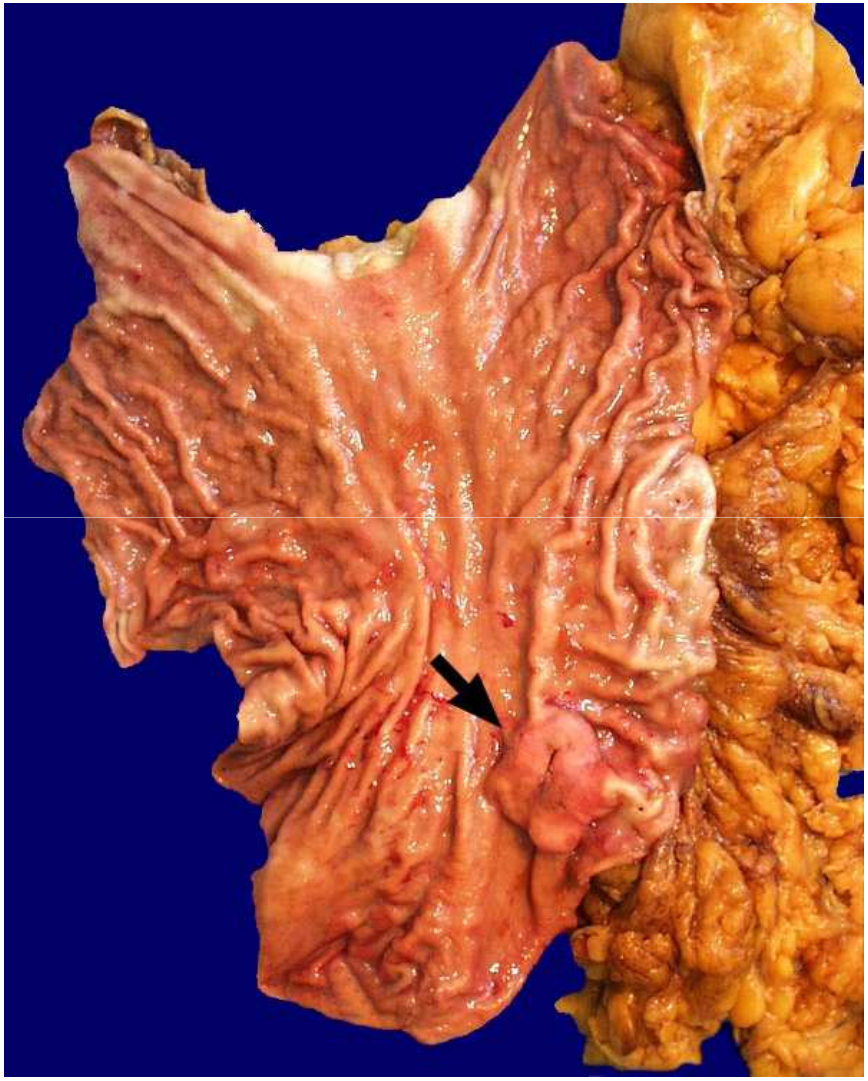
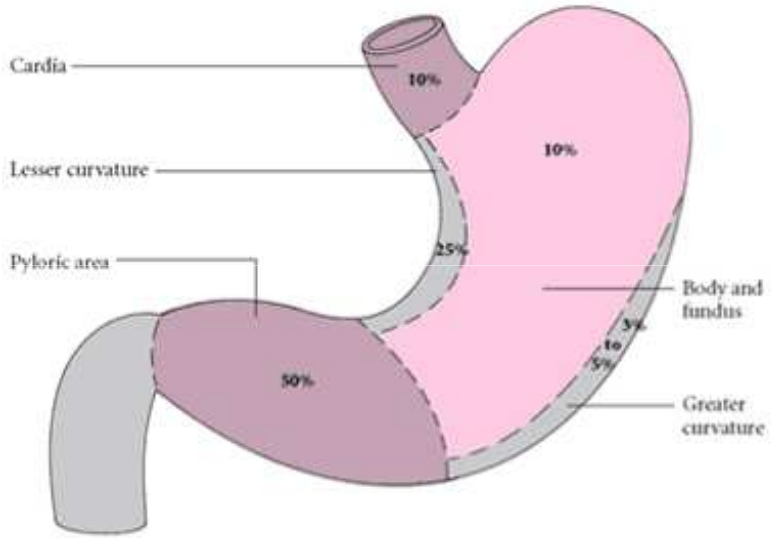
Distribution





But: increased incidence of cardia carcinoma/GEJ Carcinoma. „Intestinal type“ carcinoma, more often Her2/neu positive

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TNM

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor invades lamina propria or submucosa
T1a	Tumor invades lamina propria
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades subserosa (was T2b)
T4a	Tumor perforates serosa (was T3)
T4b	Tumor invades adjacent structure
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes (was N1)
N3a	Metastasis in 7 to 15 regional lymph nodes (was N2)
N3b	Metastasis in more than 16 regional lymph nodes (was N3)
Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

From: Hye Seung Han and Gregory Y. Lauwers, Connection 2010

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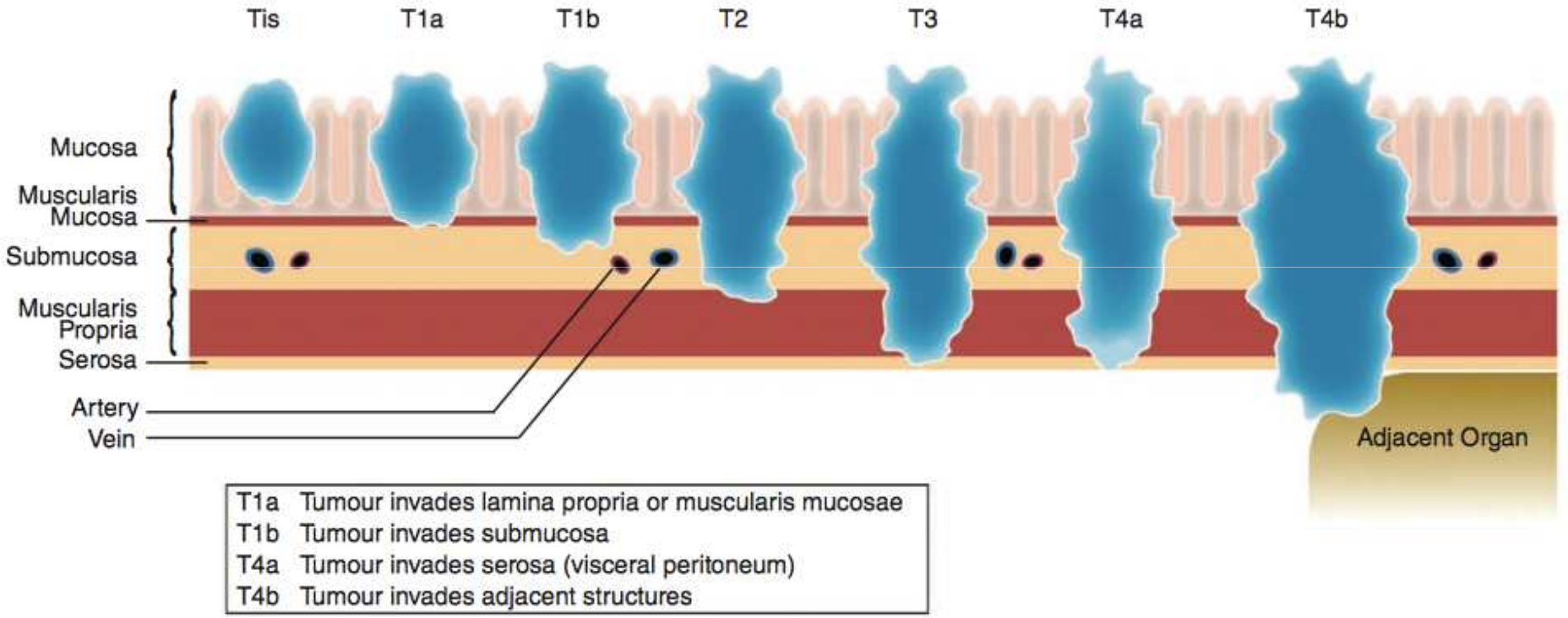
TNM



From: Hye Seung Han and Gregory Y. Lauwers, Connection 2010

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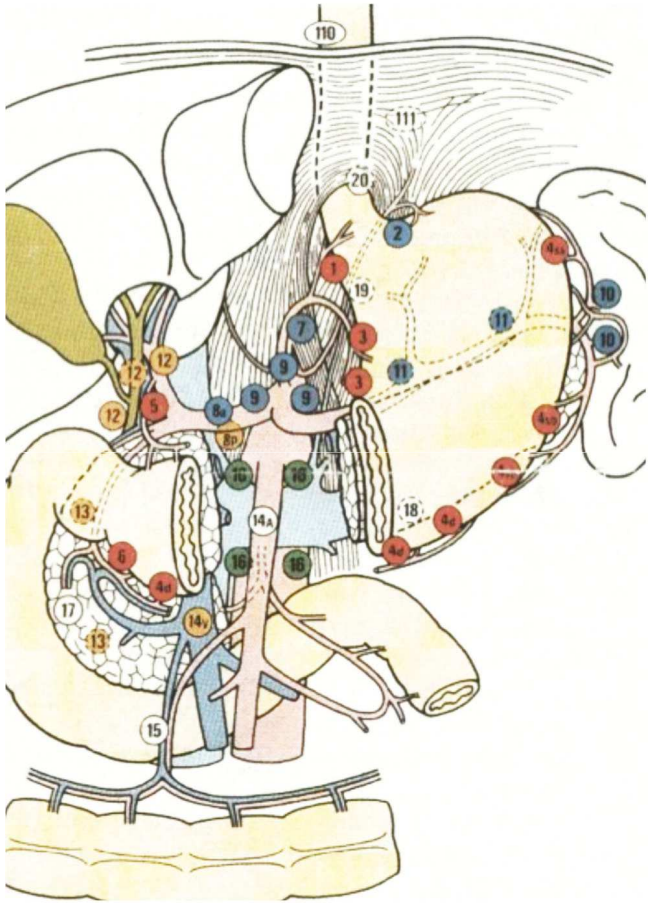
Lymphnodes stations

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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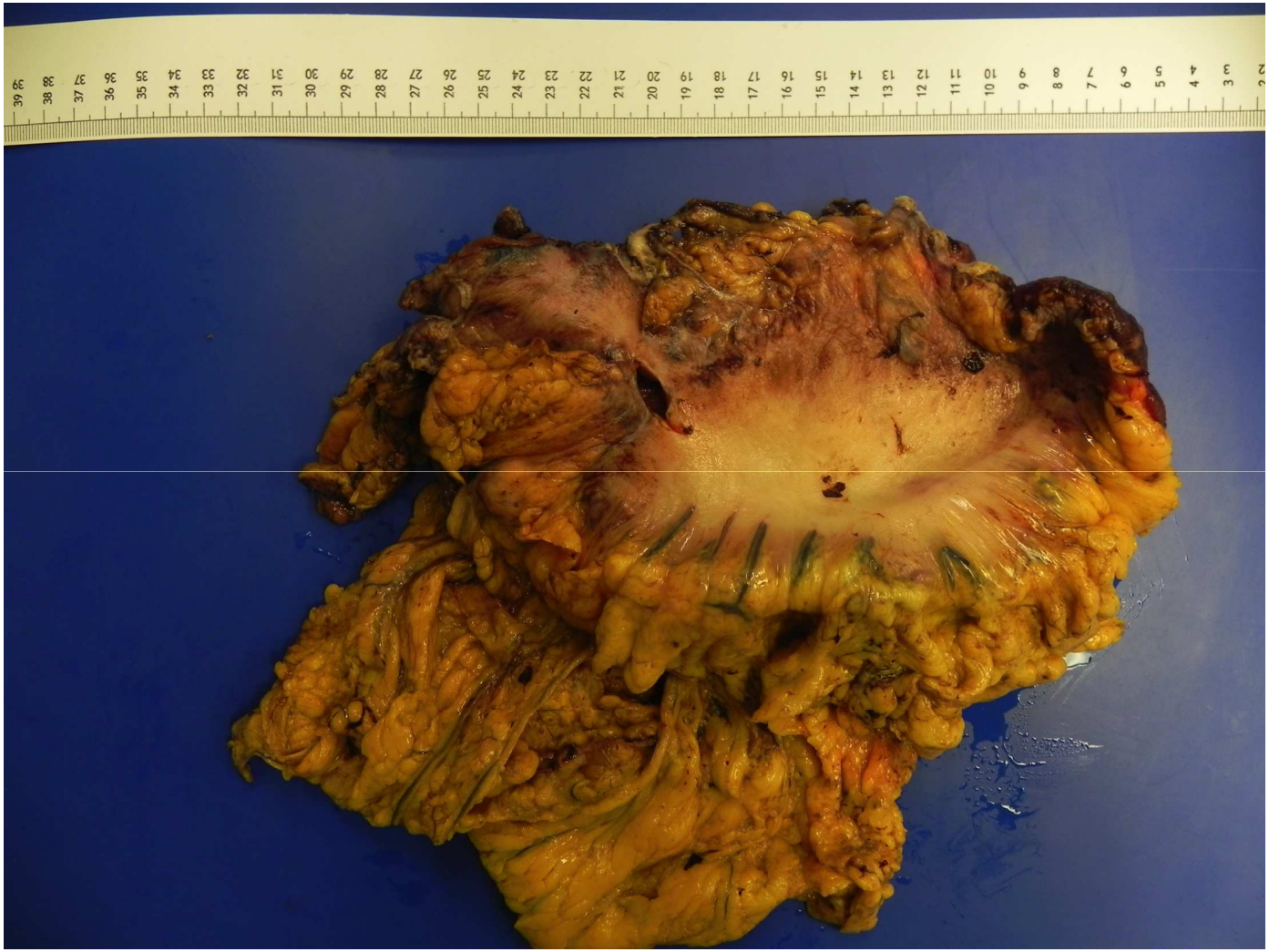
Surgical specimens



Gastrectomy

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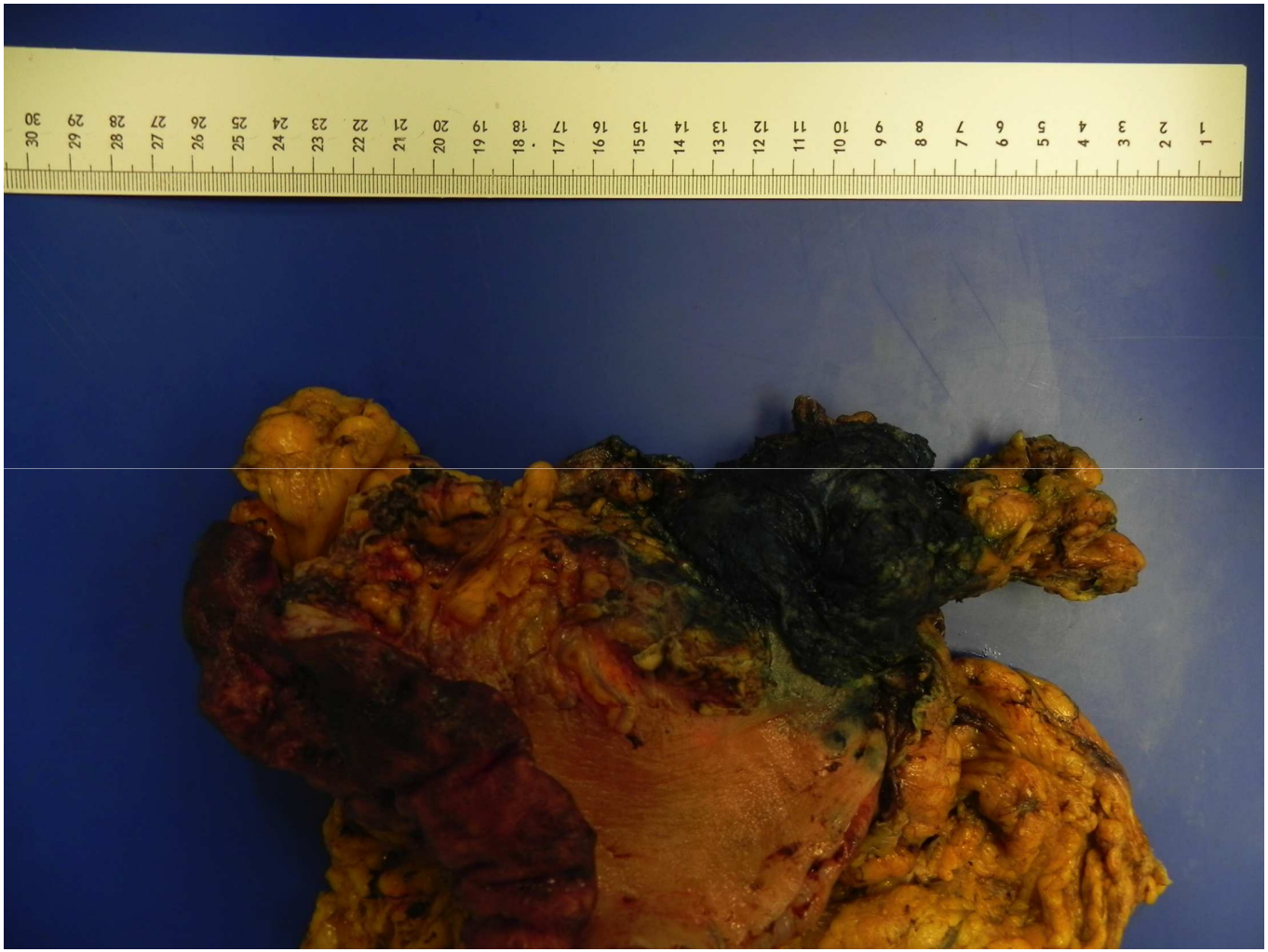
Surgical specimens



Colour-marked serosa

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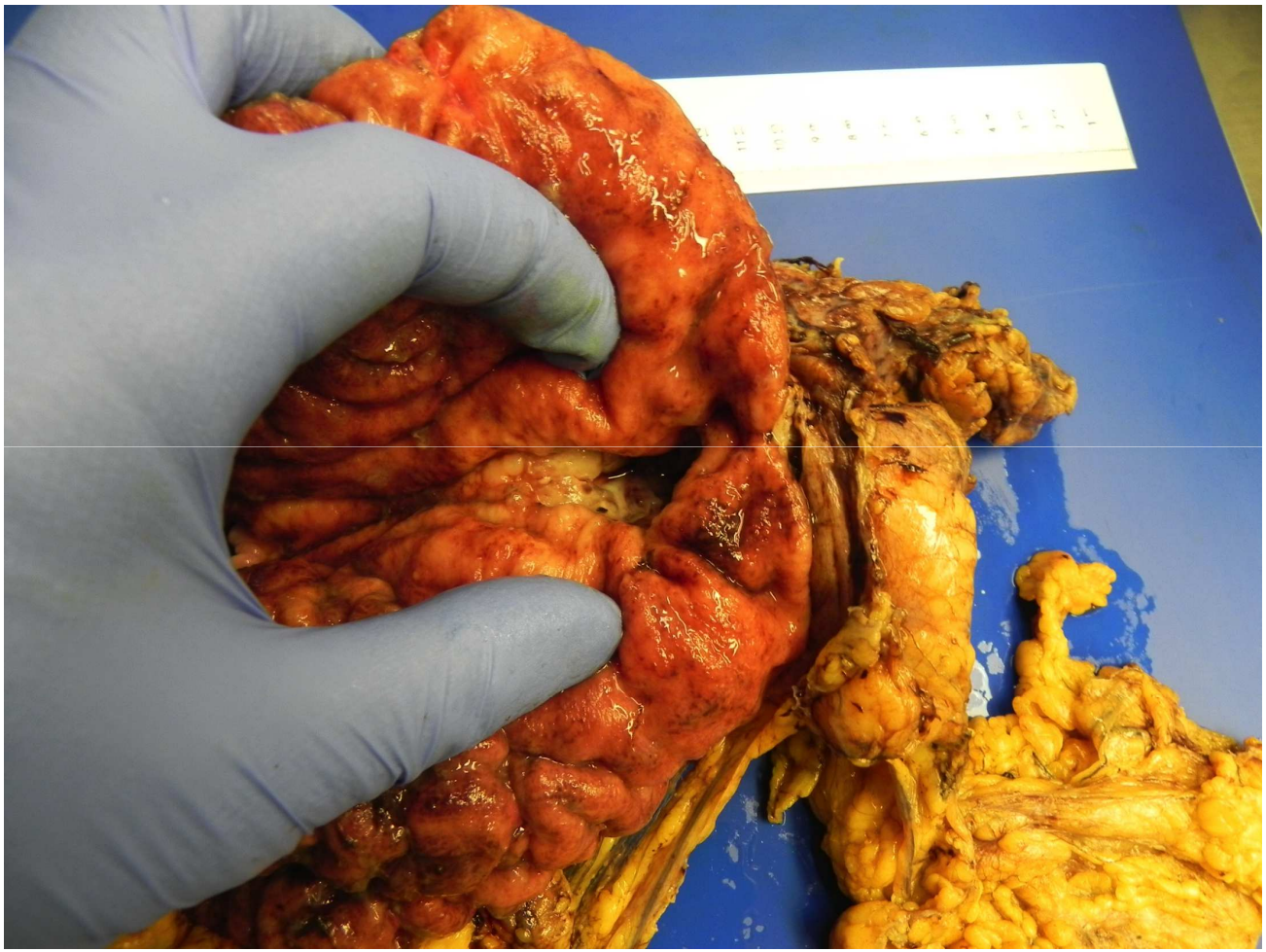
Surgical specimens



Ulcerated tumor

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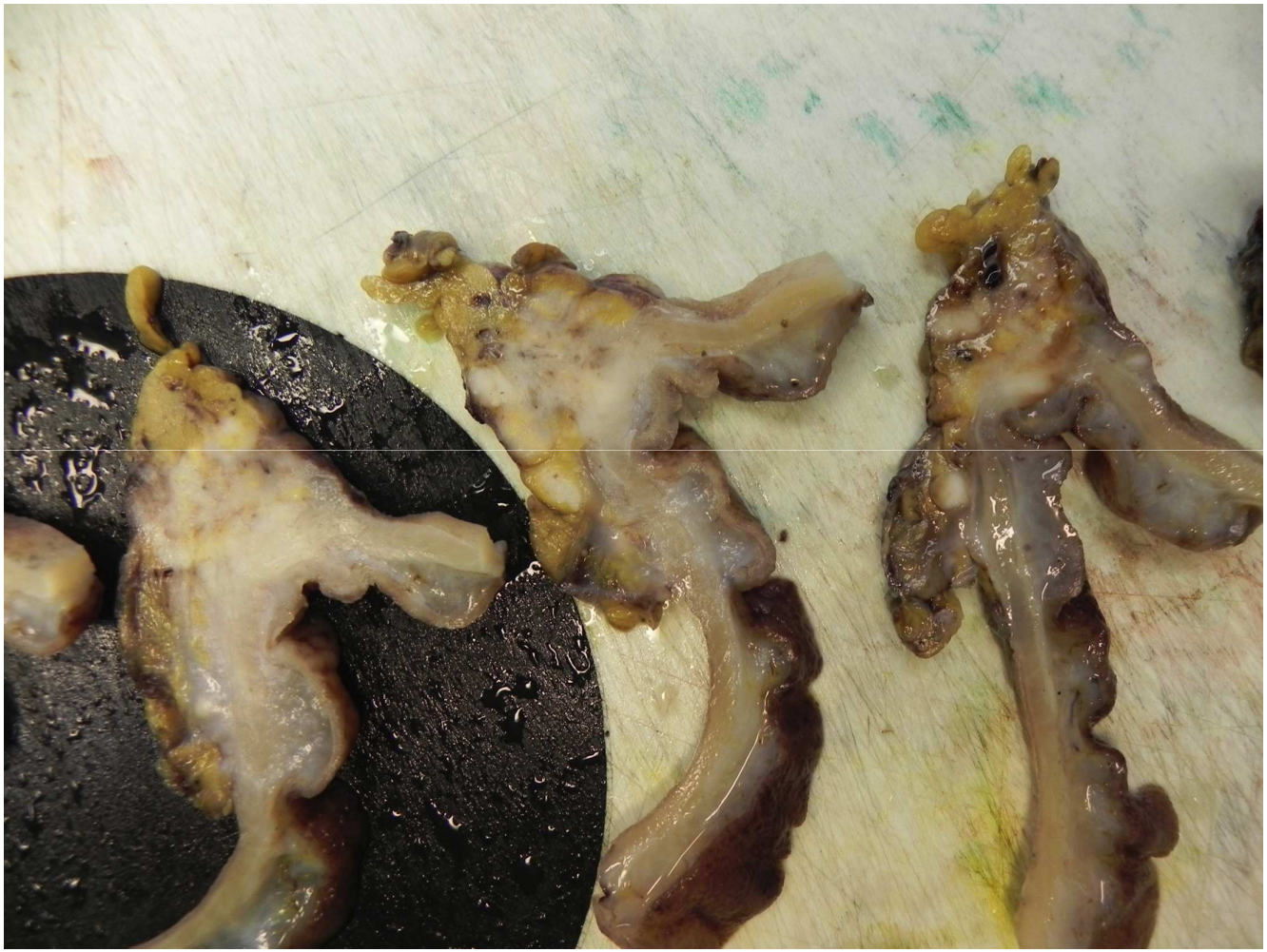
Surgical specimens



Probably already lymph nodes metastasis

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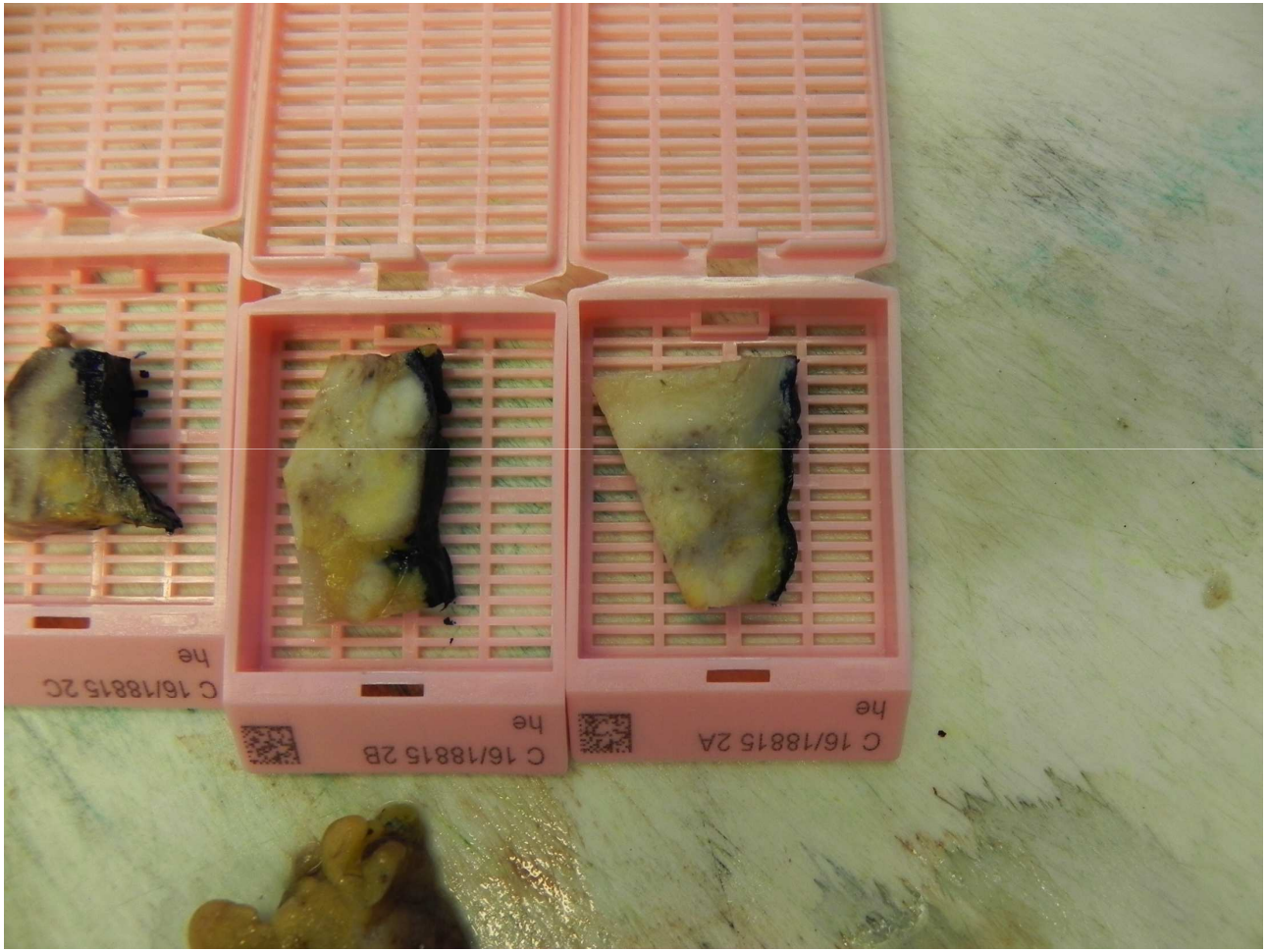
Surgical specimens



Tumor in close contact to serosa – probably pT4a

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Summary

1) two main types: intestinal and diffuse adenocarcinoma (according to Lauren)

1) Many (and rare) special types according to WHO

3) some progress in molecular subtyping
(MSI and EBV related: checkpoint inhibition effective?)
(Which tumor-subgroup/patients are particulary therapy sensitively?)

4) >16 regional lymph nodes

5) regression scores after neoadjuvant treatment (e.g. Becker et.al)

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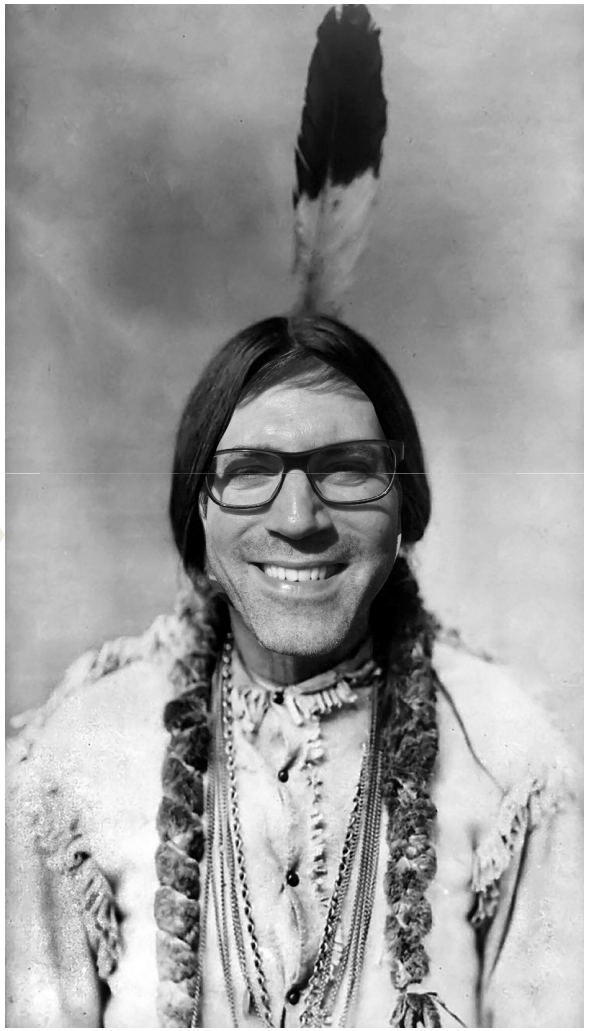
„the new pathologist“

1997: deliverer of diagnosis



2020: „Chief Treating Bull“

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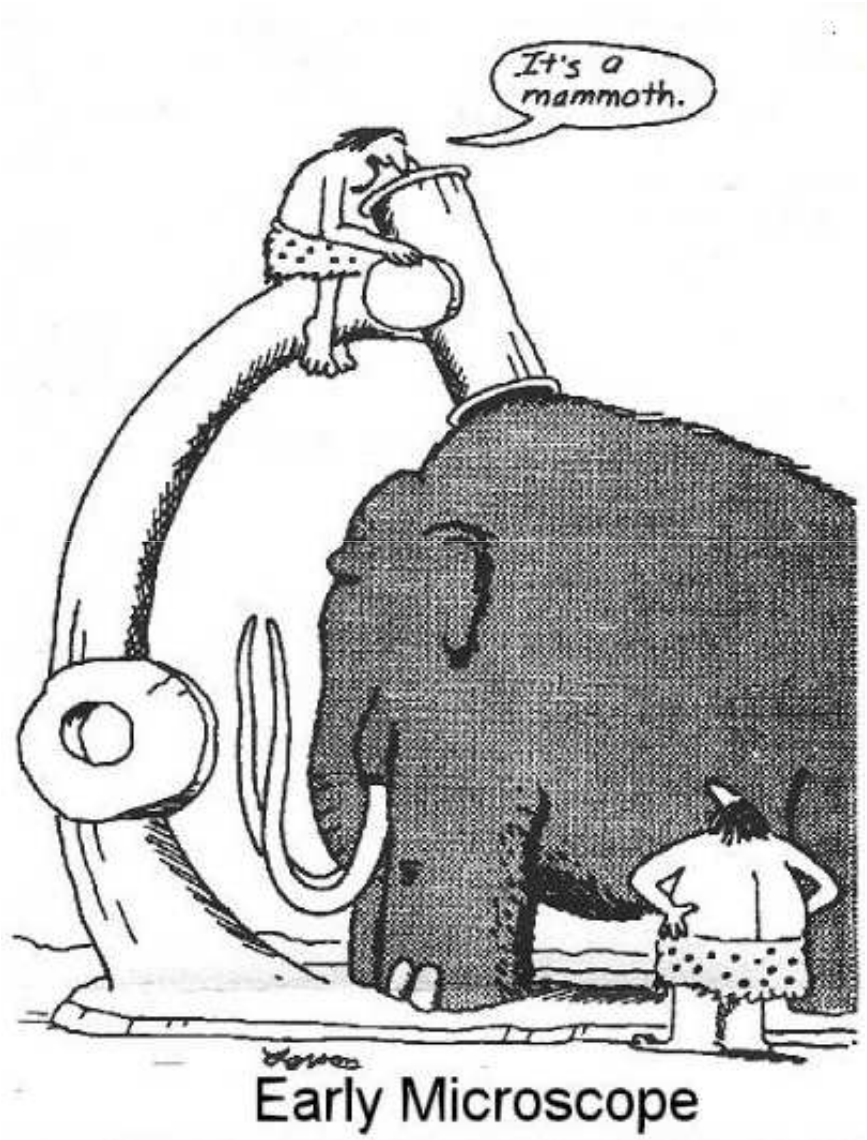
Thank you for your attention



Early Microscope

Gastric Cancer – Staging & Imaging of primary & nodal subsite boundaries

Dr Angela M Riddell

Royal Marsden, London. UK

ESTRO School

STOMACH 7TH 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 *(was T2a)*
- T3 Subserosa *(was T2b)*
- T4 Adjacent structures
  - T4a Perforates serosa *(was T3)*
  - T4b Other adjacent structures *(was T4)*

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 (was N1)
- N3 ≥ 7 nodes
  - N3a 7 to 15 nodes (was N2)
  - N3b ≥16 nodes (was N3)

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

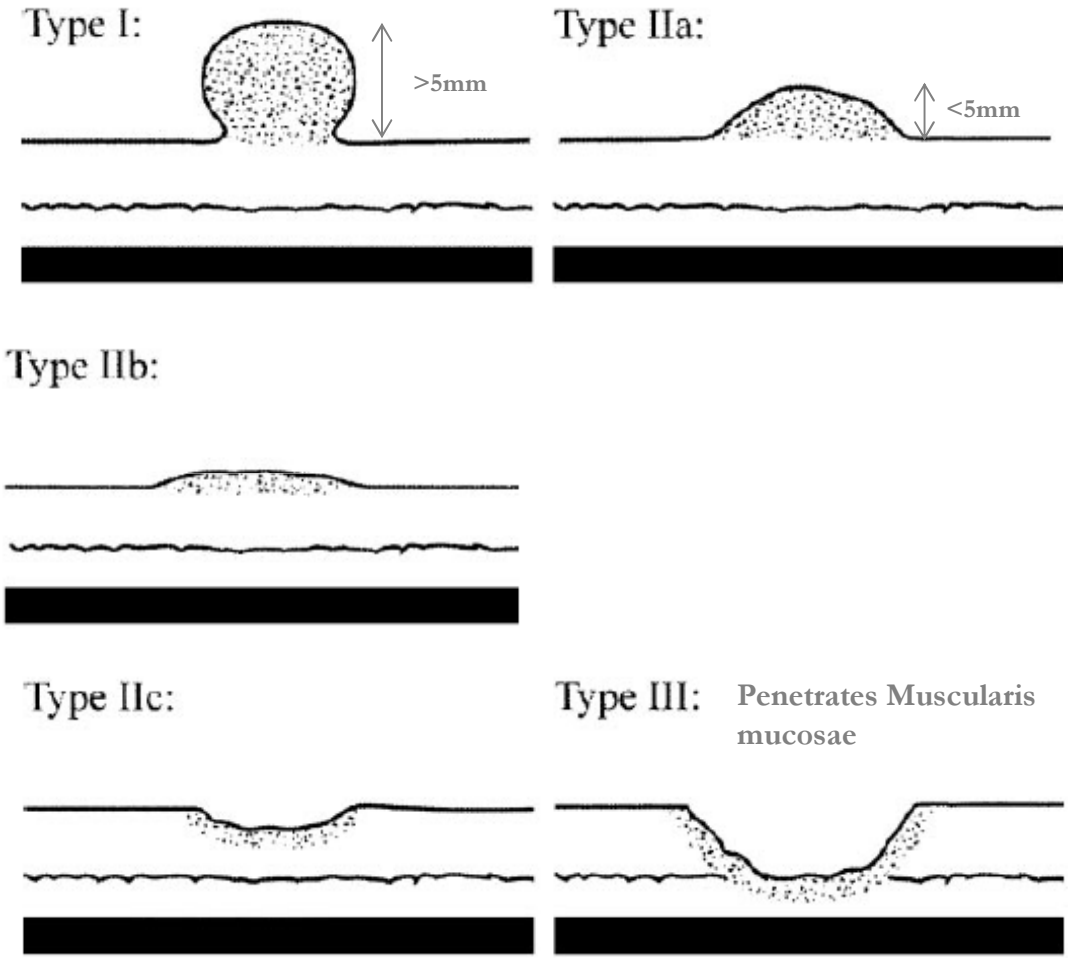
Malignant invasion into the muscularis propria

Early Gastric cancer

Elevated

Flat

Depressed



Adapted from: Ba-Ssalamah A, Prokop M et al. Radiographics 2003; 23:625-644

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Gastric Cancer Staging

Diagnosis – Endoscopic biopsy

Initial Imaging:

- MDCT

Potentially operable disease:

- PET/CT – exclude distant spread
- Laparoscopy

- EUS – Early disease, Proximal/ Distal Extent
- MRI

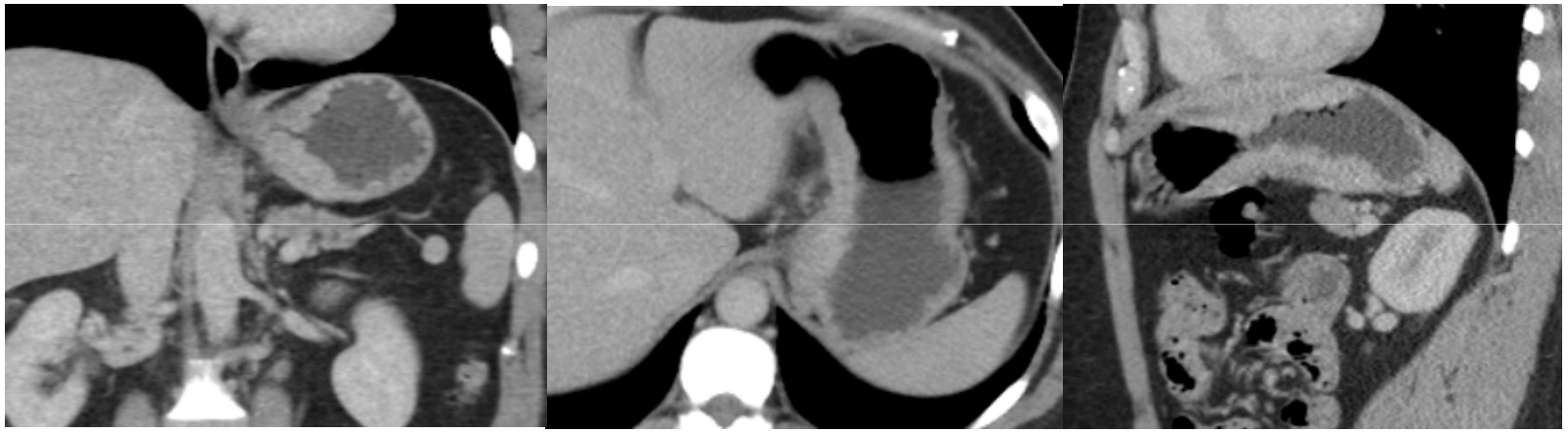
MDCT - Patient preparation

- Fasted for 6hrs
- Gastric distension
  - Anti spasmodic –Buscopan®
  - Oral contrast – water
- Position
  - Supine
  - Prone
  - Oblique angle to improve regional gastric distension

MDCT - Scan Technique

Portal venous phase imaging (70 second delay)

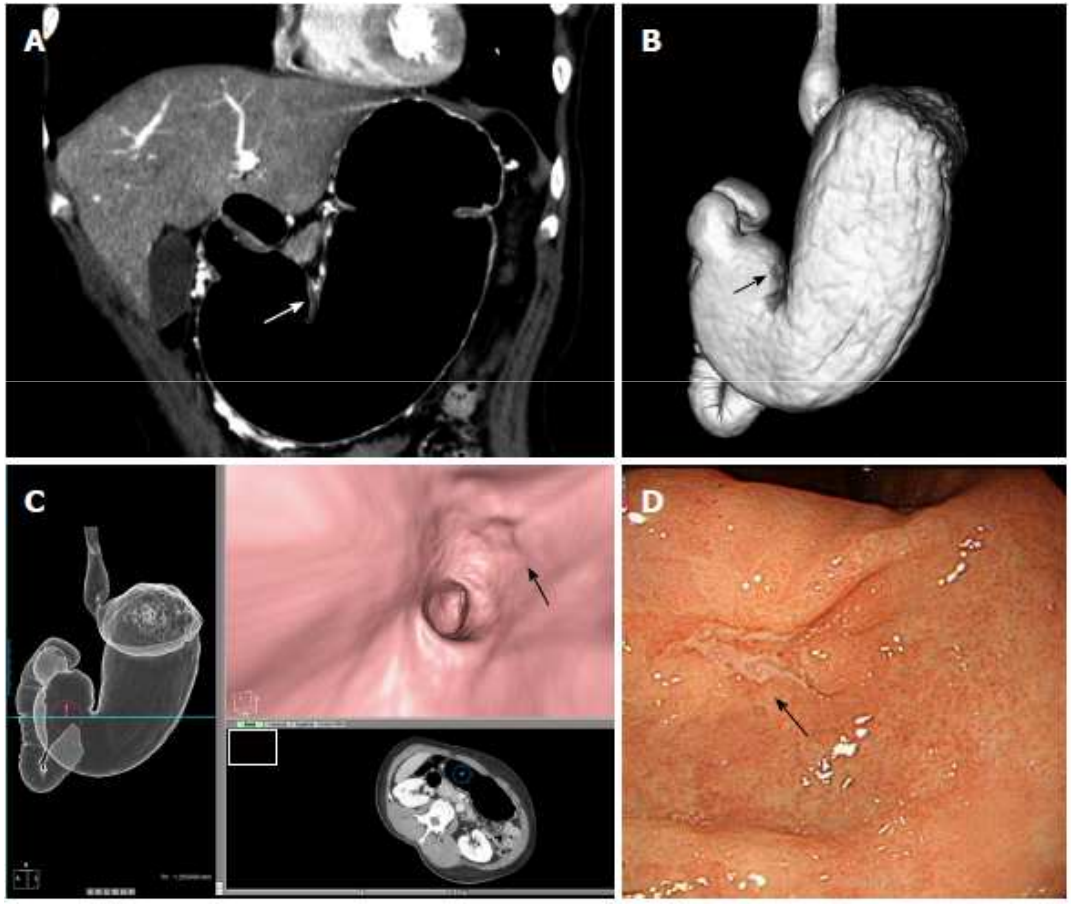
Thorax, abdomen & pelvis



Scan parameters aim to achieve resolution that can enable MPR postprocessing using isotropic voxels

MDCT - Scan Technique

Virtual gastroscopy



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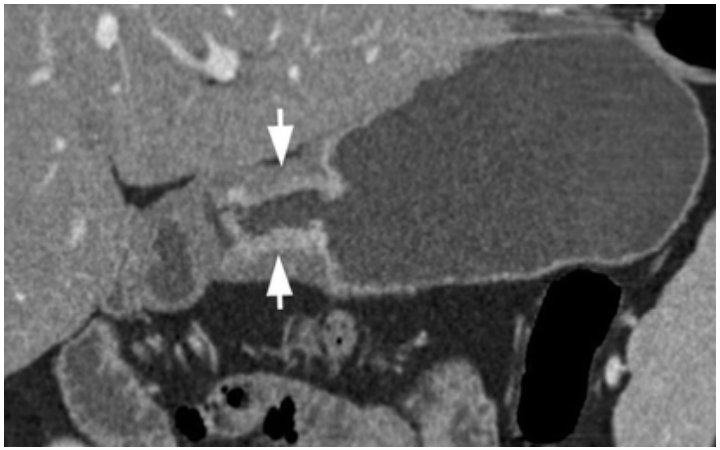
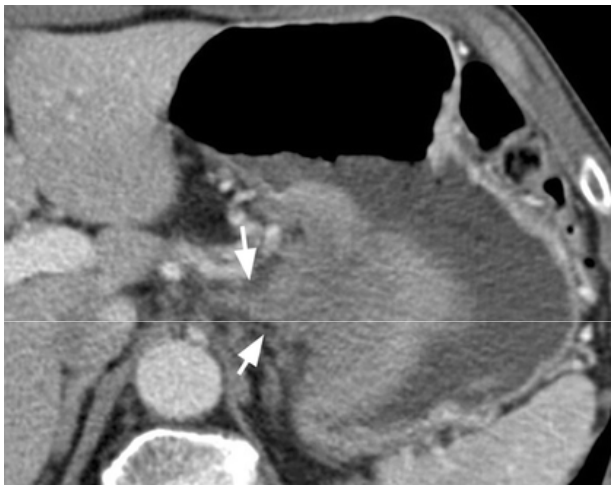
MDCT - T Staging



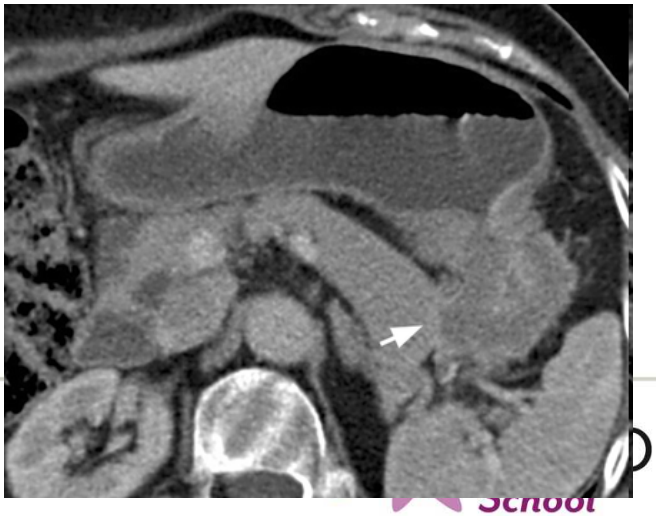
pT2



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

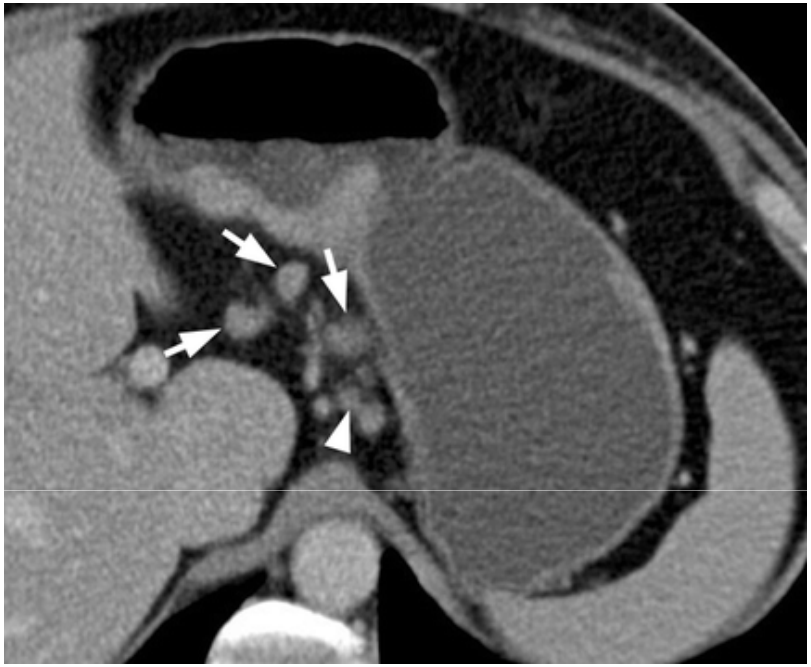
N staging depends on the number of lymph nodes involved

CT - high specificity, but low sensitivity

Based on size criteria (short axis):

≥6mm perigastric

≥ 8mm extra perigastric



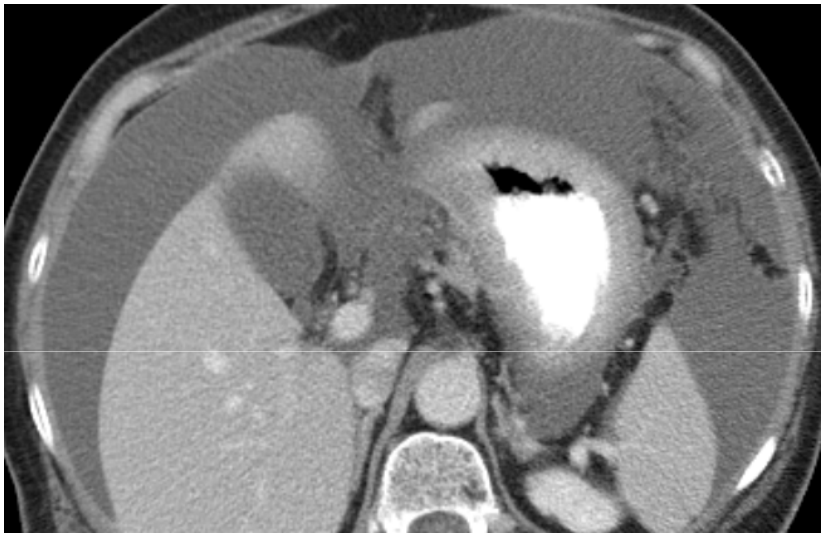
Parameter	Percentage range
Sensitivity	62.5 - 91.9%
Specificity	50 - 87.9%

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

Kwee RM, Kwee TC. 2009 Gastric cancer; 12: 6-22

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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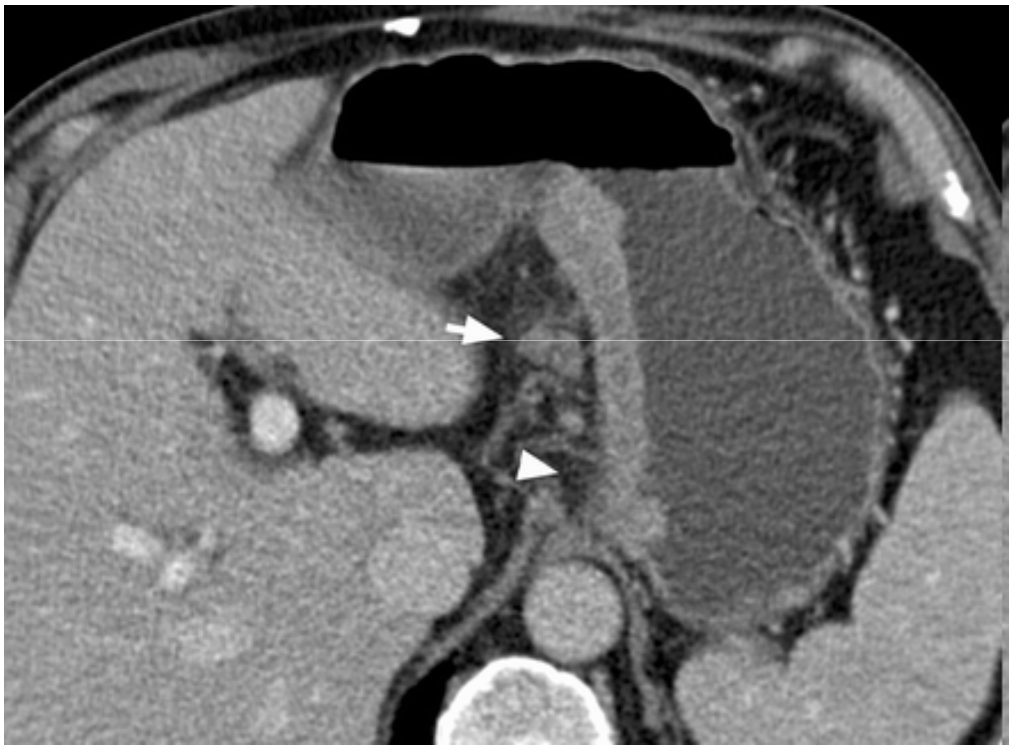
Gastric Cancer staging



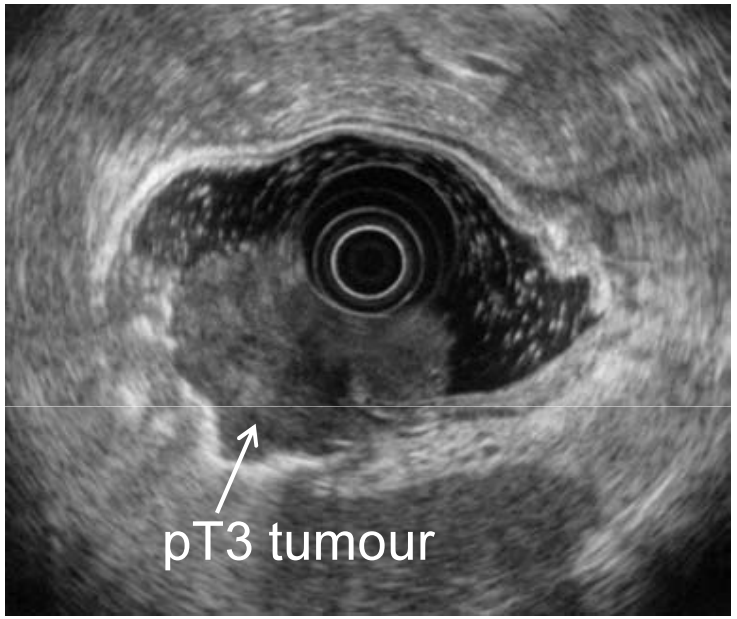
CT Report:

- 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

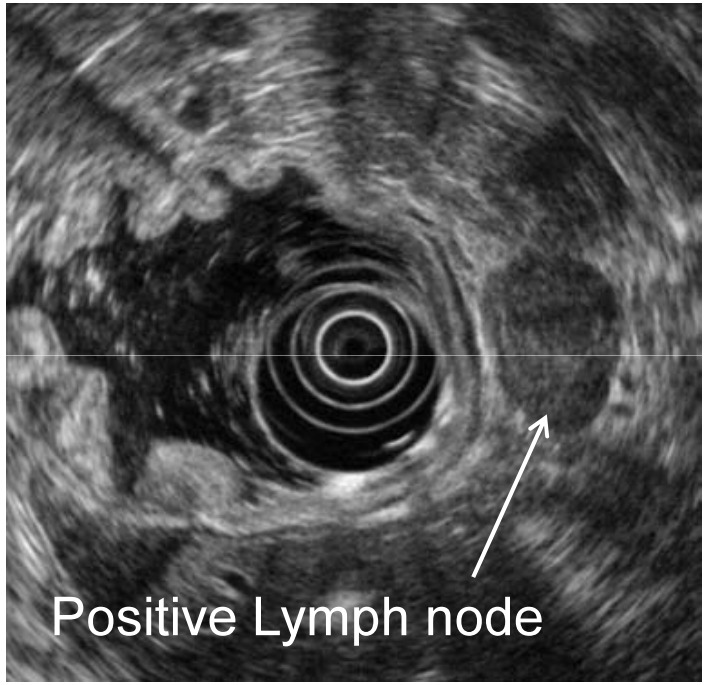


Image from: Bohle W et al. 2011 J Gastrointestin Liver Dis; Vol. 20 No 2, 135-139

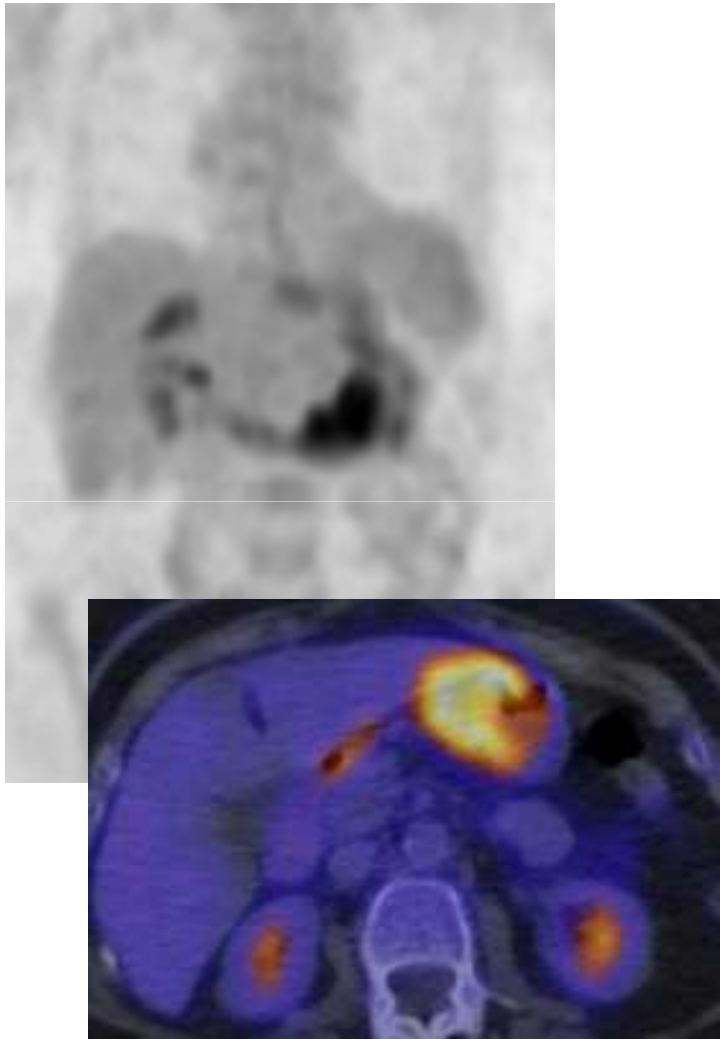
^{18}FDG-PET/CT

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

- ^{18}FDG-PET/CT not currently advocated for gastric cancer staging



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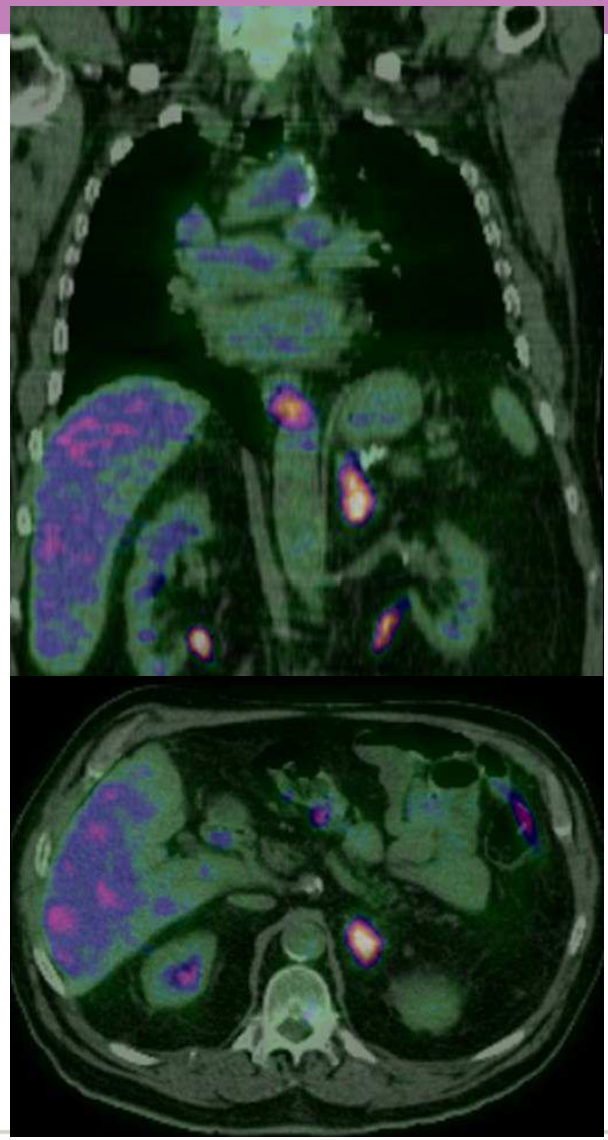
^{18}FDG-PET/CT

Main advantage

Identification of occult metastatic disease*



*Kinkel K, Ying L et al (2002) Radiology 224:748–756

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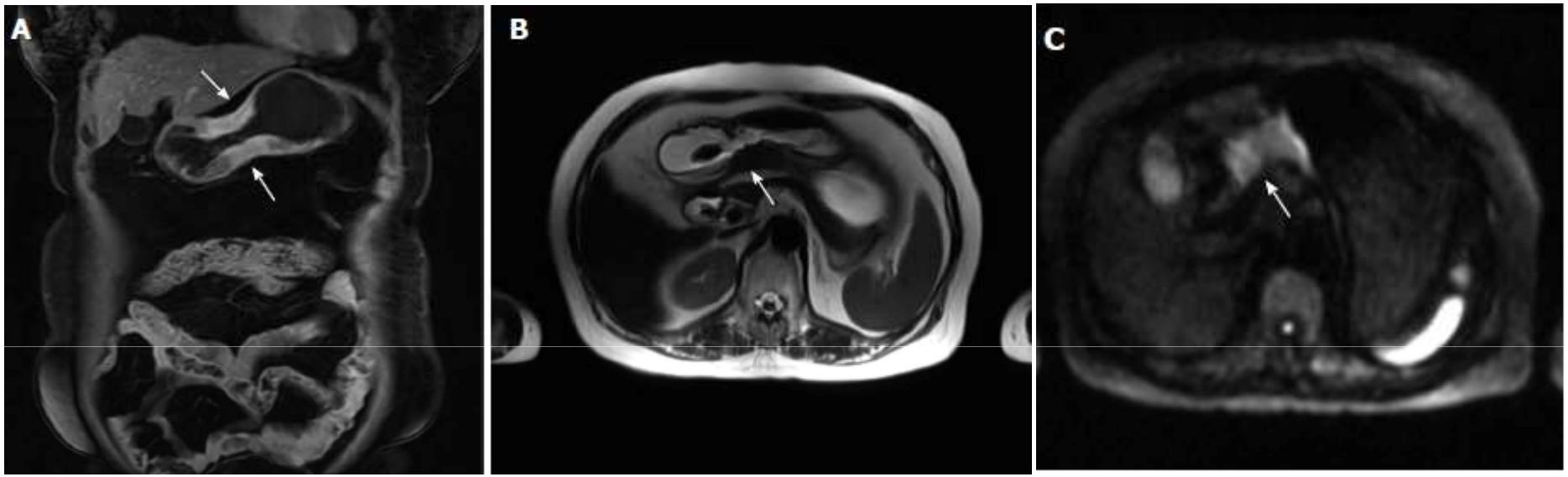
Gastric Cancer Staging - MRI



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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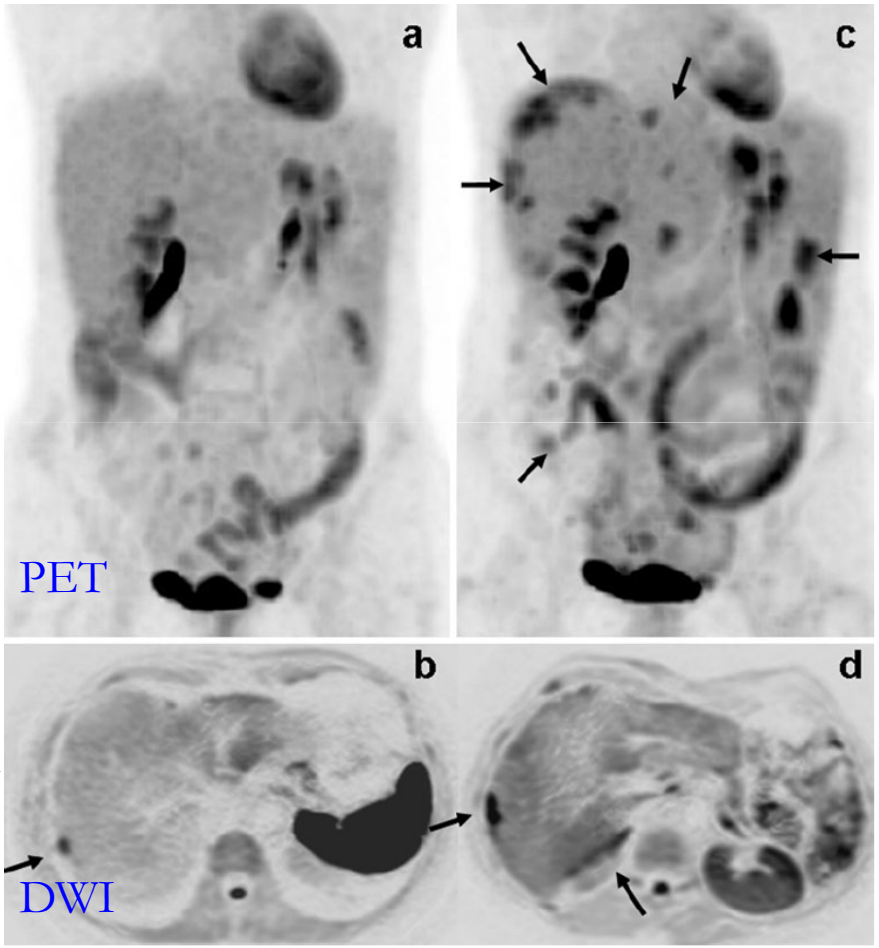
M Staging – Peritoneal disease

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

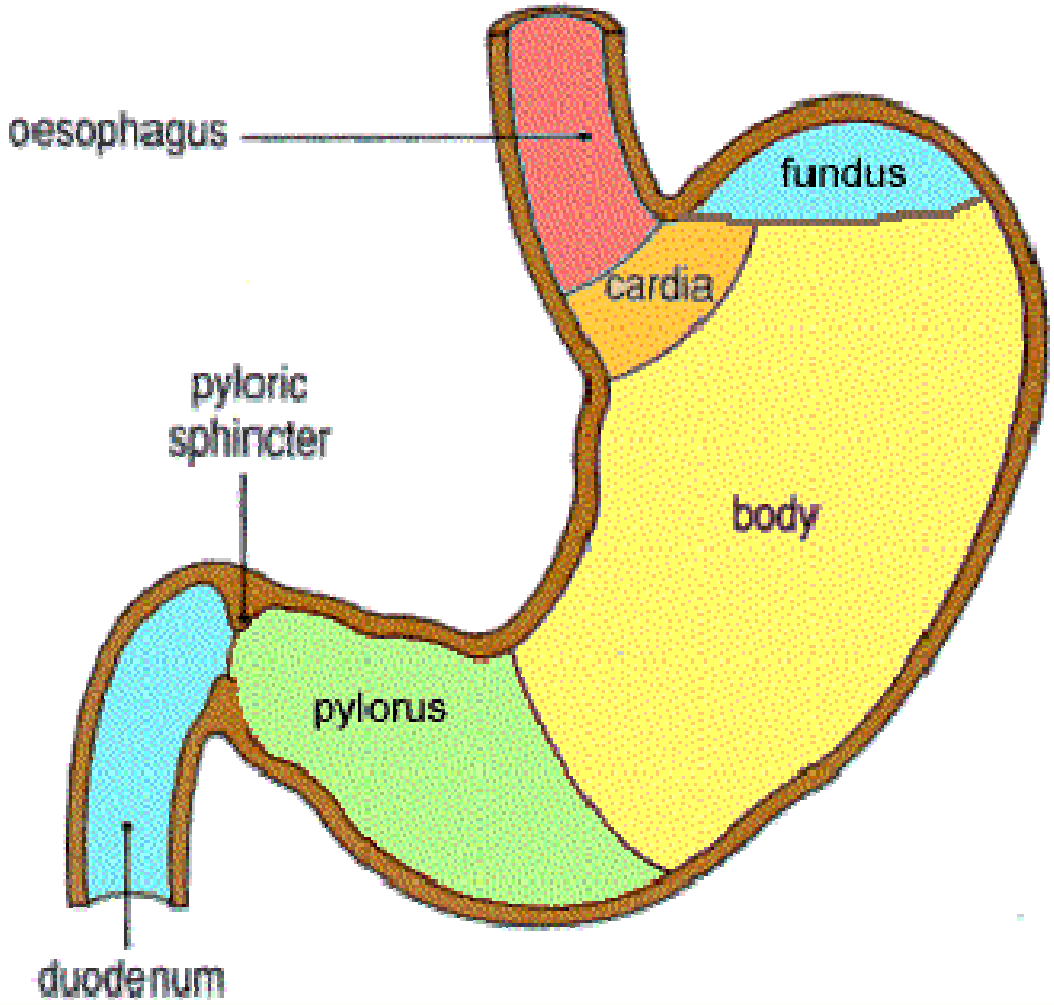
Staging

- MDCT – exclude metastatic disease
- PET-CT – refine staging & localise tumour

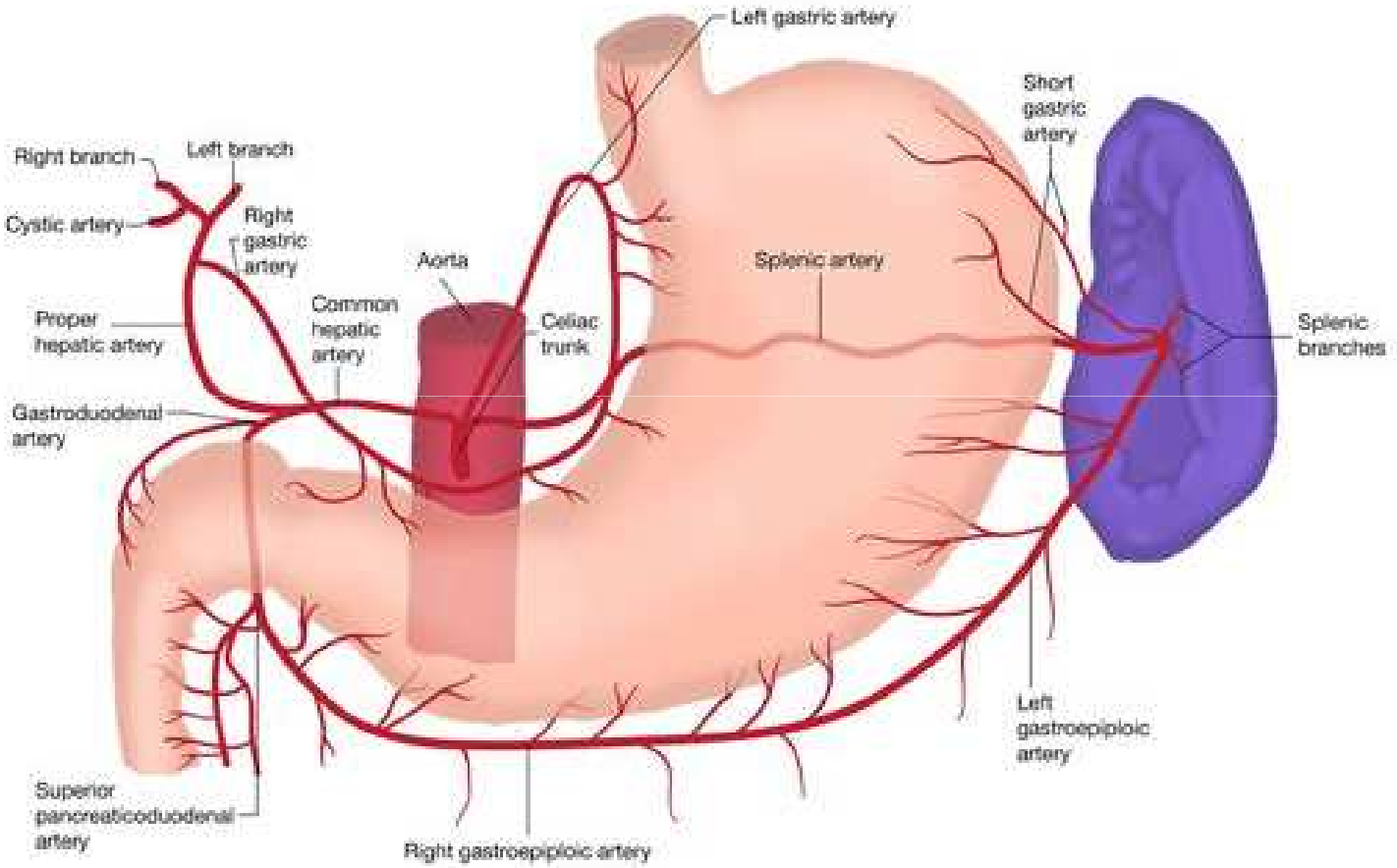
- EUS – defining prox / distal extent
- MRI – research

Primary & Nodal subsite boundaries

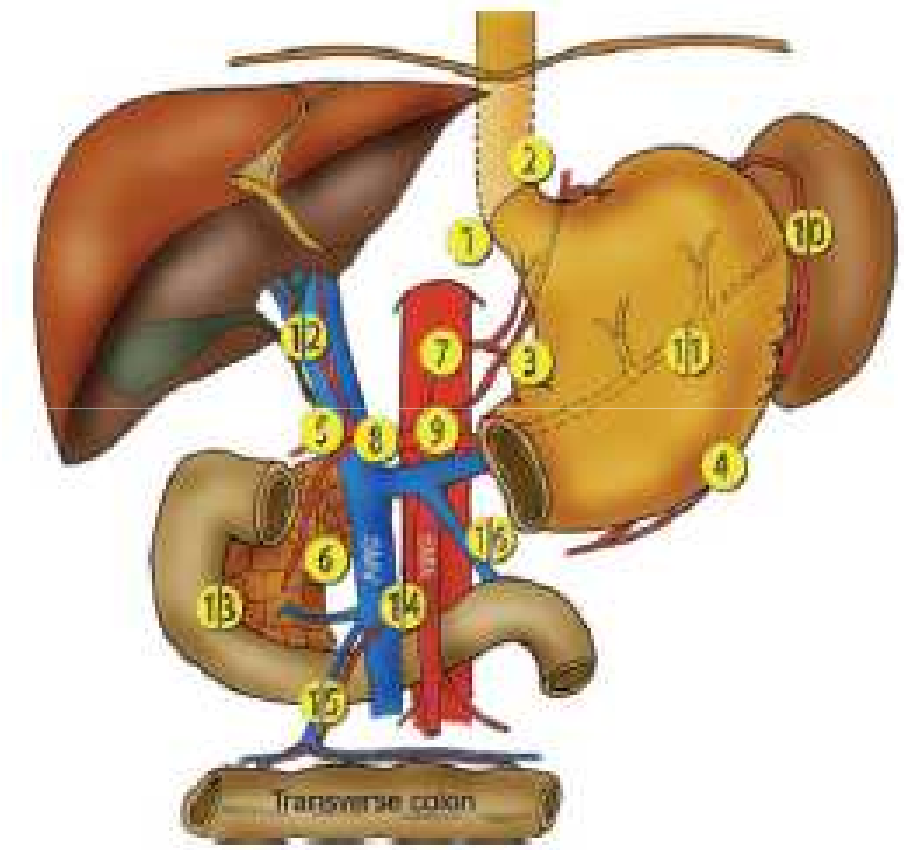
Anatomical regions of the stomach



Anatomy – stomach arterial supply



Upper Abdominal Lymph nodes groups



Station Number	Name
1	right cardia
2	left cardia
3	lesser curvature
4	greater curvature
4sa; 4sb; 4d	short gastric; left gastroepiploic; right gastroepiploic
5	Suprapyloric
6	Infrapyloric
7	left gastric artery
8	common hepatic artery
9	celiac trunk
10	Splenic hilus
11	Splenic artery
12	hepatoduodenal ligament
13	posterior surface of the head of the pancreas
14	root of the small bowel mesentery
15	Paracolic
16	Para-aortic

Lim J S, Yun M J, Kim M J et al 2006. Radiographics; 26: 143-156

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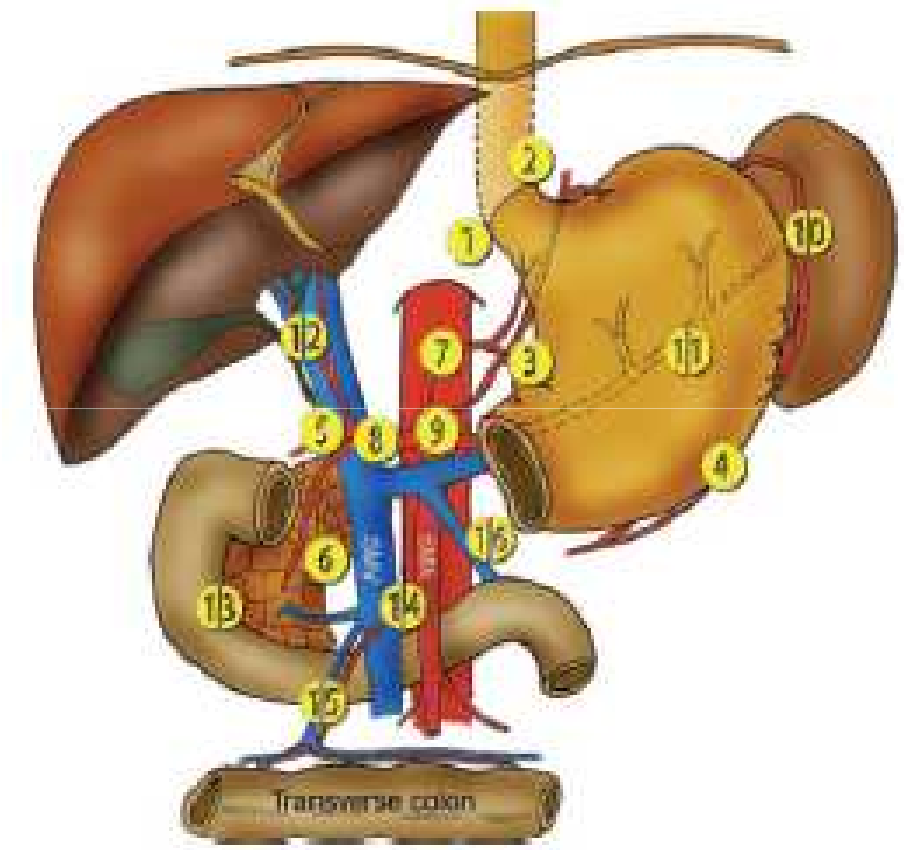
Upper Abdominal Lymph nodes groups



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D1

Lim J S, Yun M J, Kim M J et al 2006. Radiographics; 26: 143-156

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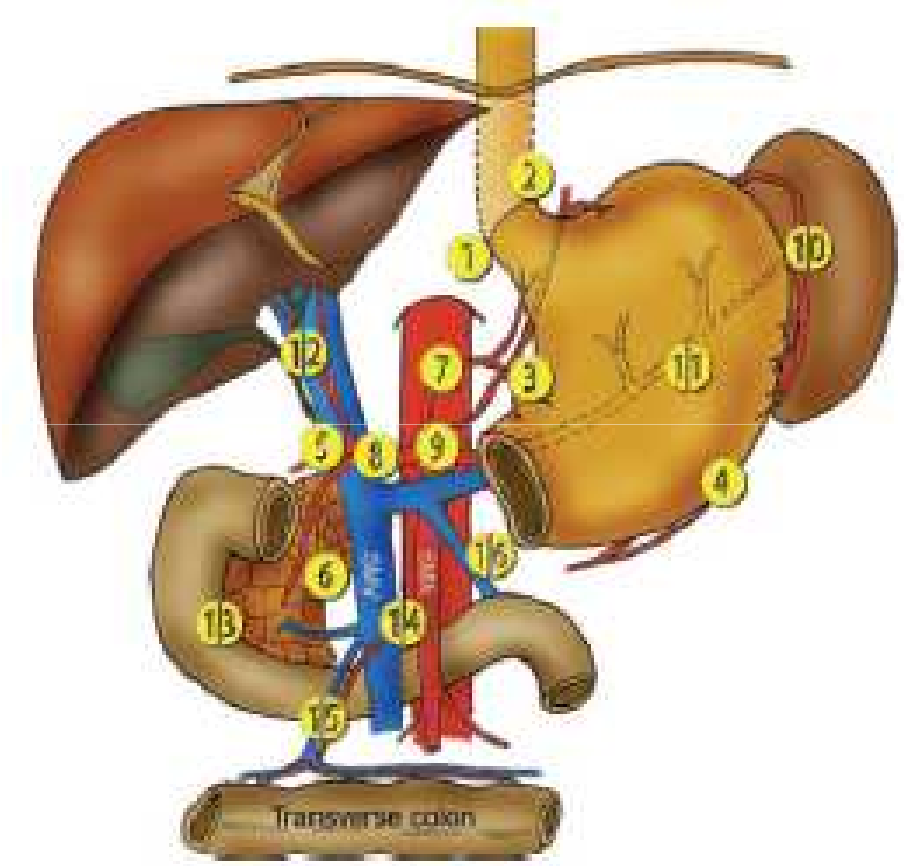
Upper Abdominal Lymph nodes groups



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16	Para-aortic

D2

Lim J S, Yun M J, Kim M J et al 2006. Radiographics; 26: 143-156

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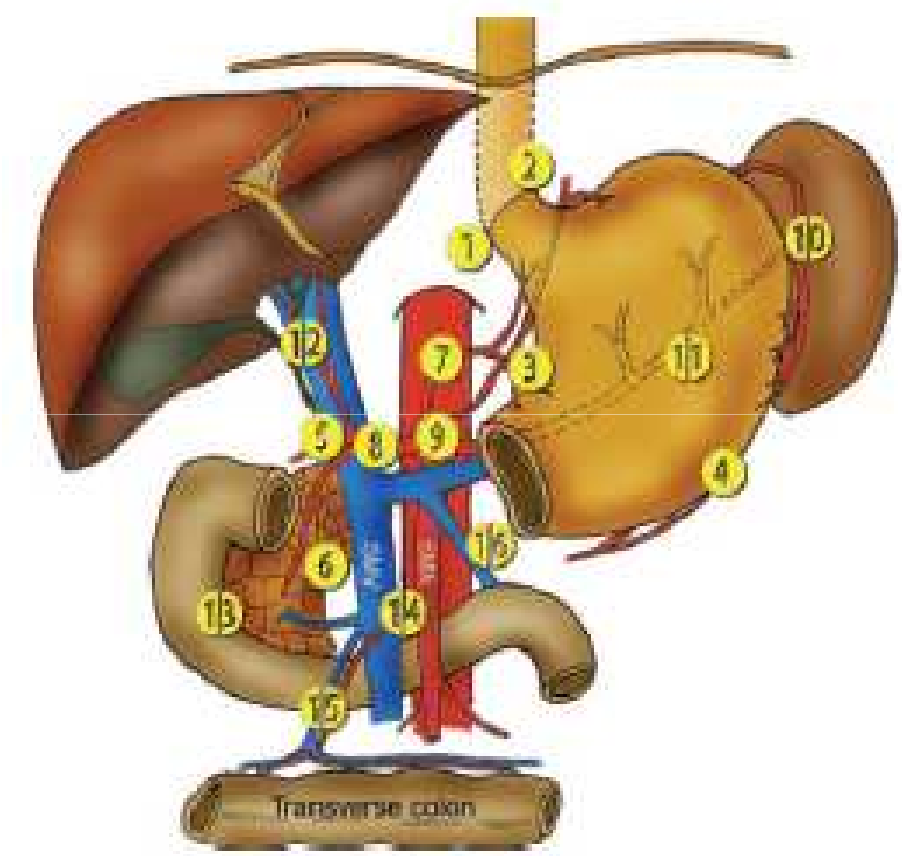
Upper Abdominal Lymph nodes groups



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13	posterior surface of the head of the pancreas
14	root of the small bowel mesentery
15	Paracolic
16	Para-aortic

D3

Lim J S, Yun M J, Kim M J et al 2006. Radiographics; 26: 143-156

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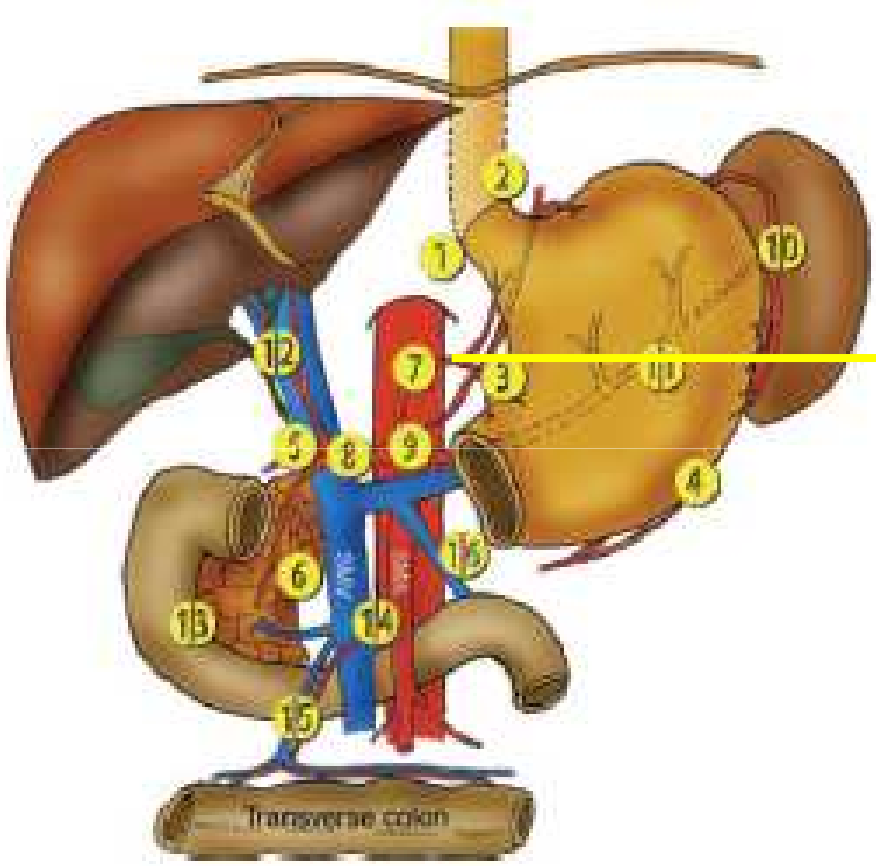
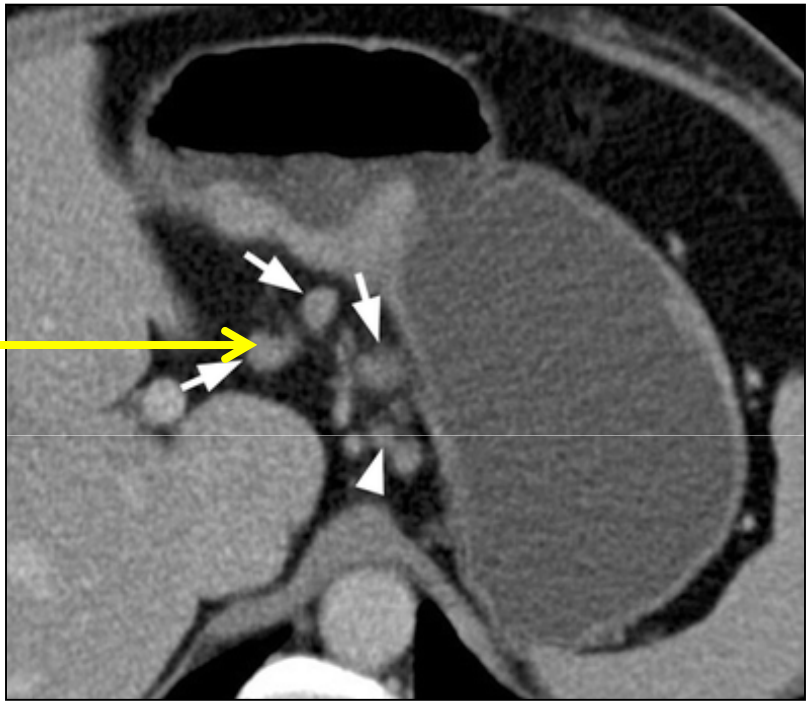
Upper Abdominal Lymph nodes groups





Station 7
Left gastric artery territory

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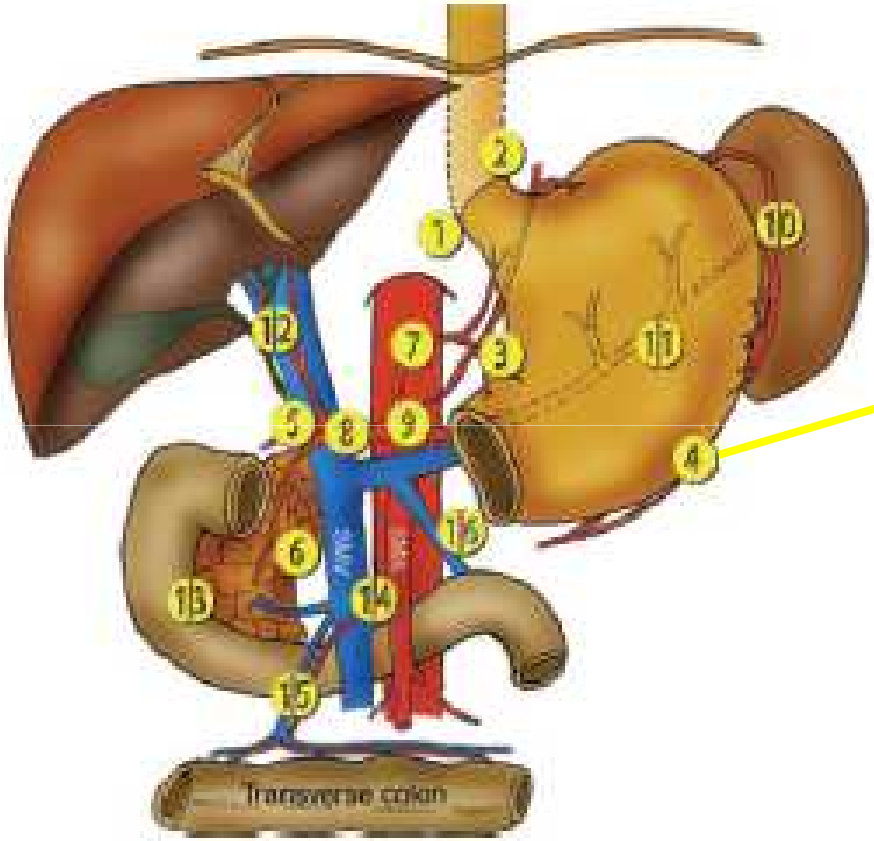
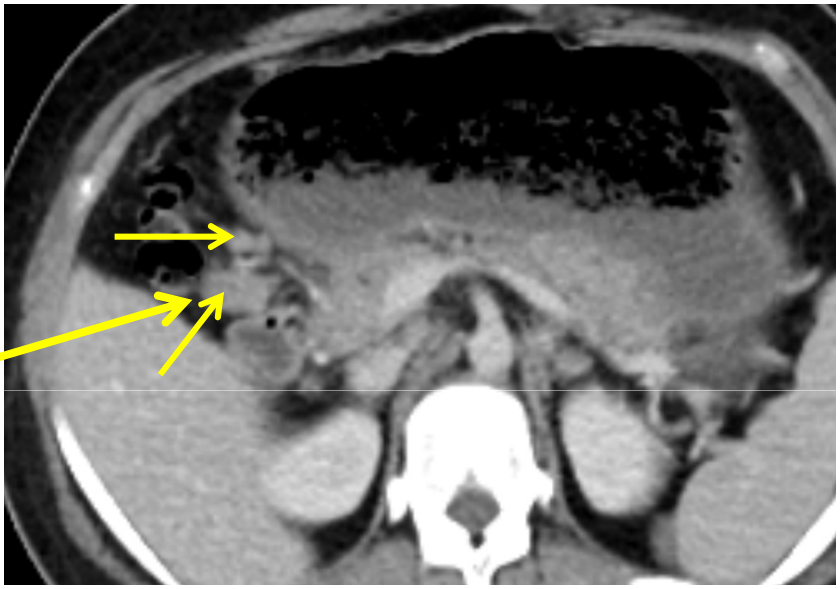
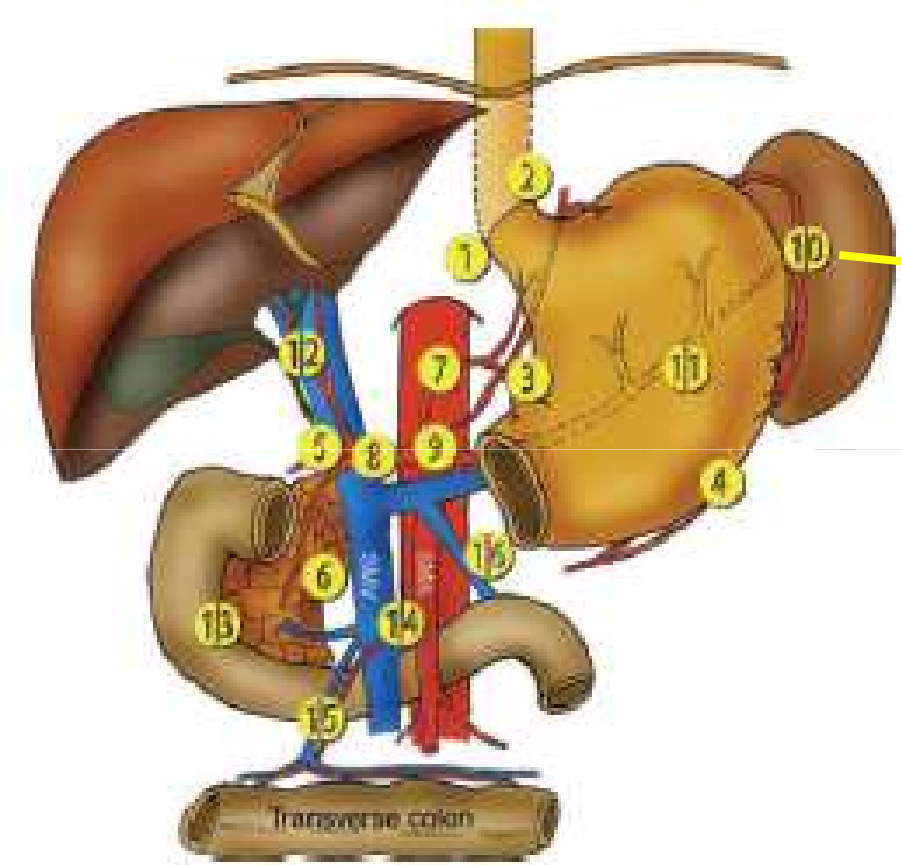
Upper Abdominal Lymph nodes groups

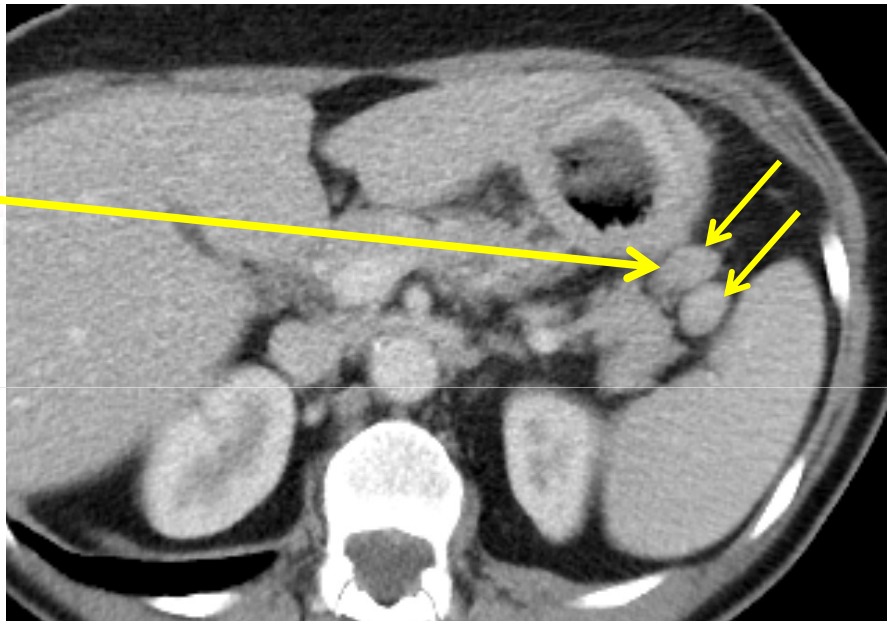




Station 4
Gastroepiploic artery

Upper Abdominal Lymph nodes groups

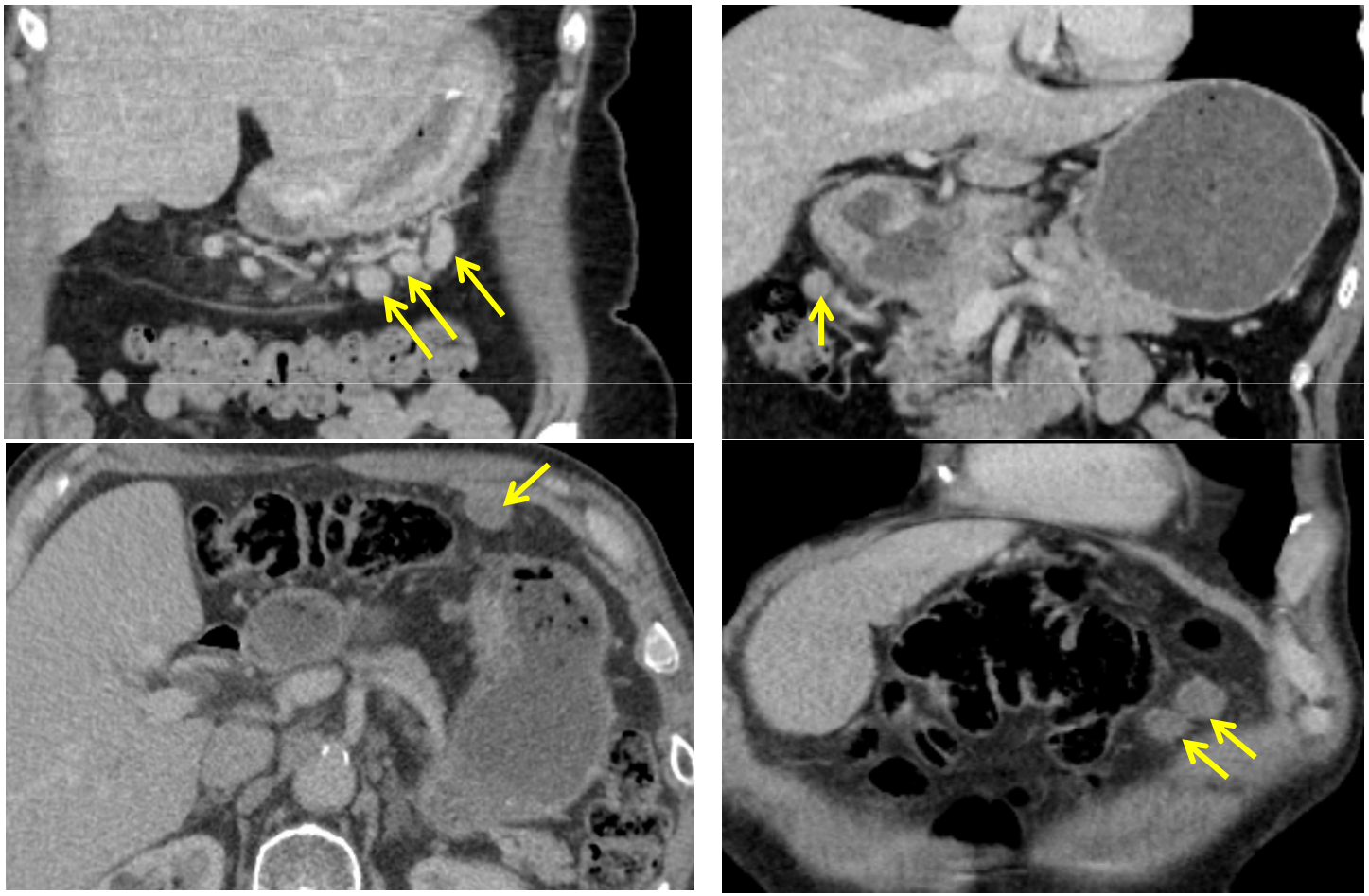




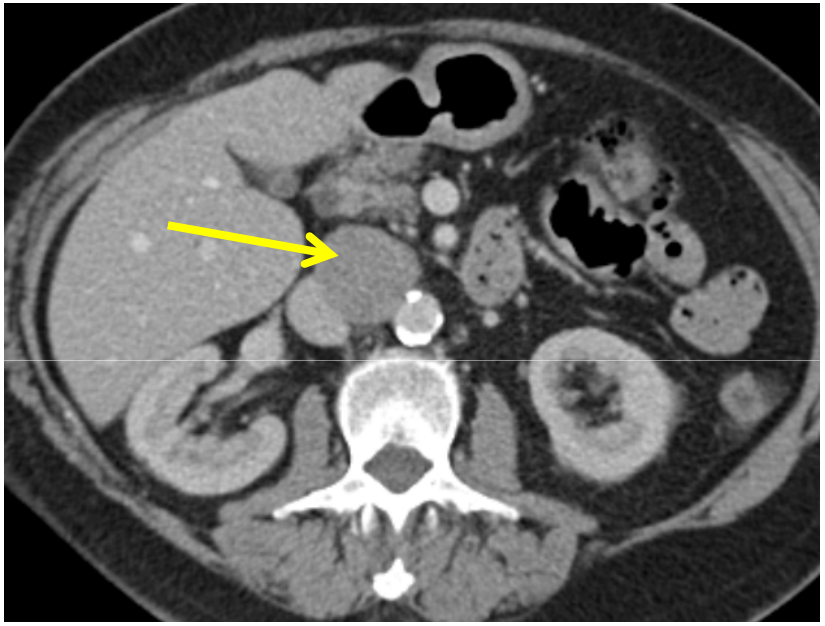
Station 10 Splenic hilum

Upper Abdominal Lymph nodes groups

Difficulty distinguishing Gastroepiploic nodes from peritoneal disease

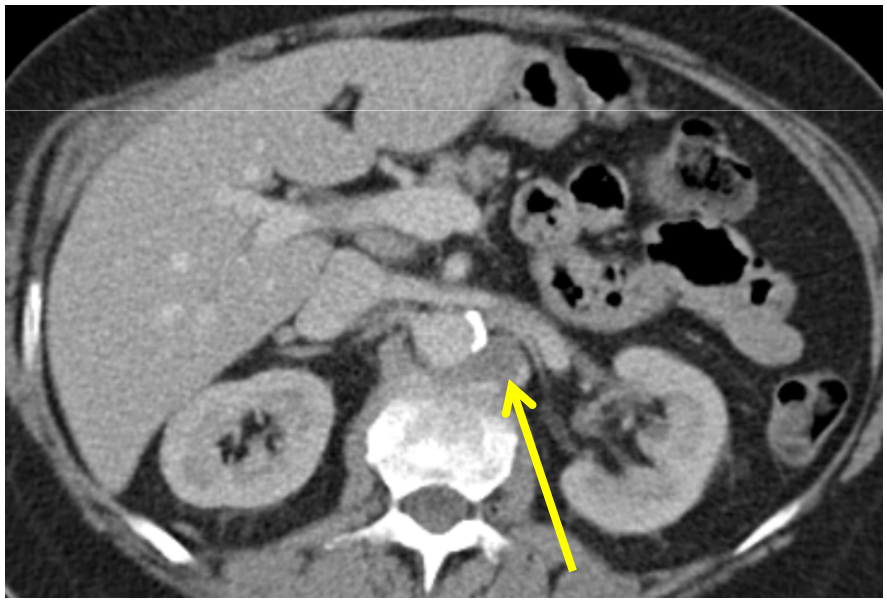


Upper Abdominal Lymph nodes groups



Metastatic nodes

Station 16 Para aortic

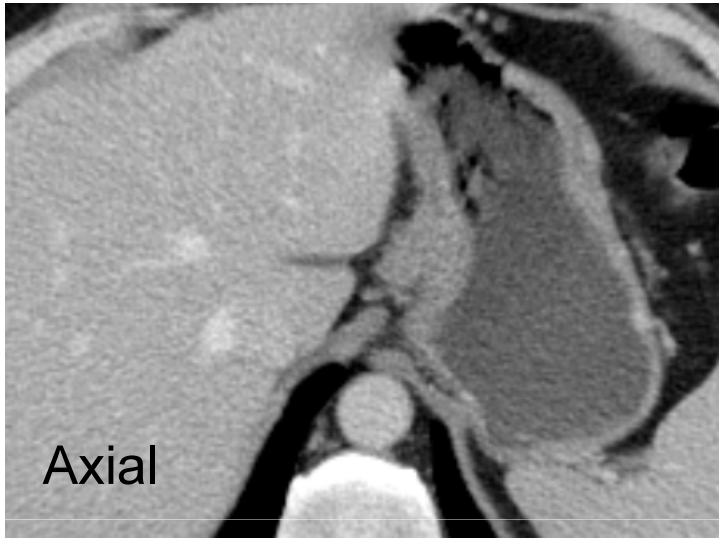


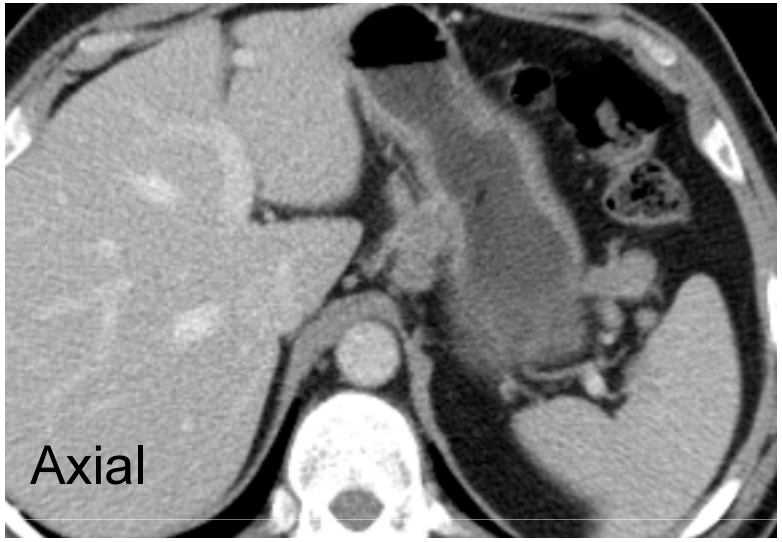
Case 1

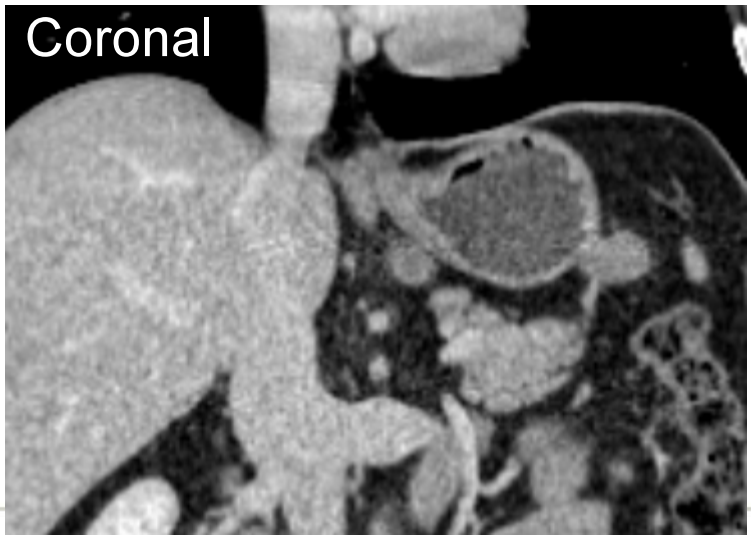
Case 1

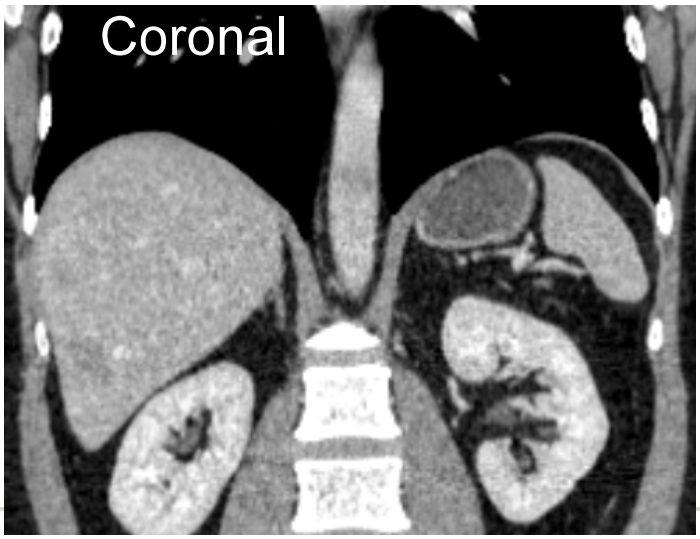
- 65yr old male presented with abdominal pain and weight loss

Case 1









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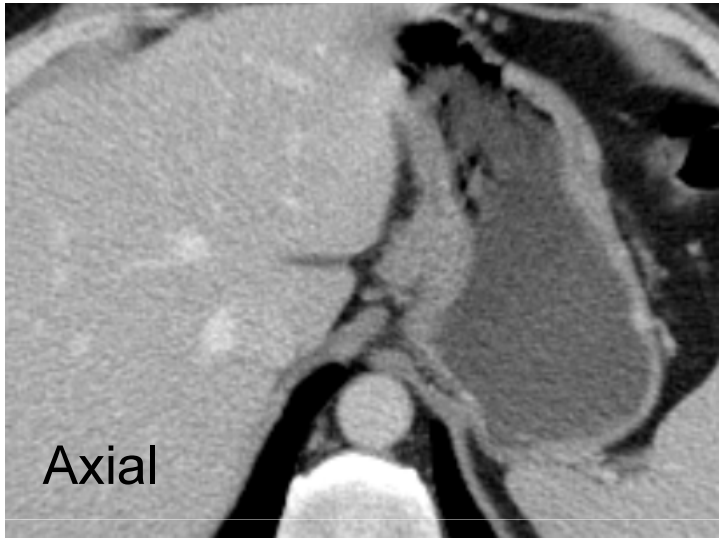
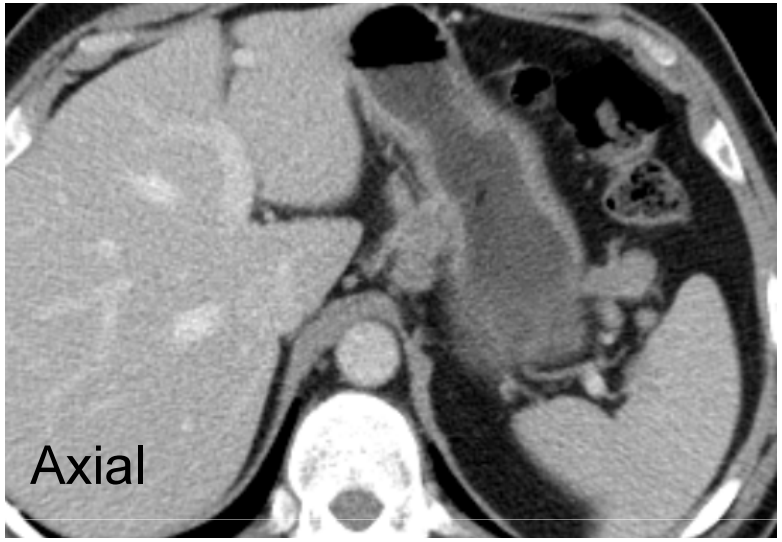
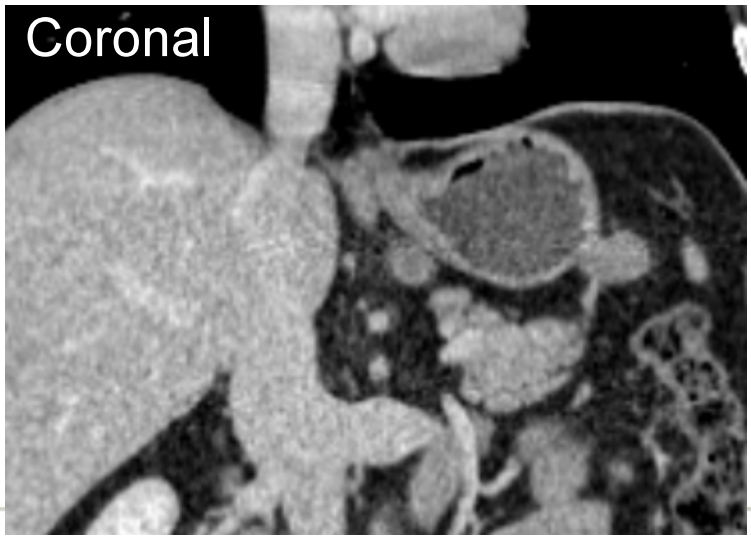
Case 1

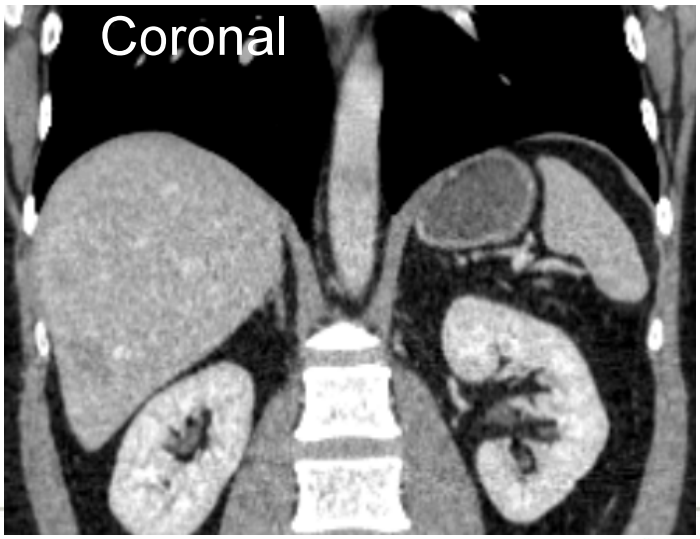
- Stage the tumour
- If there are nodes involved; state which nodal stations

Case 1









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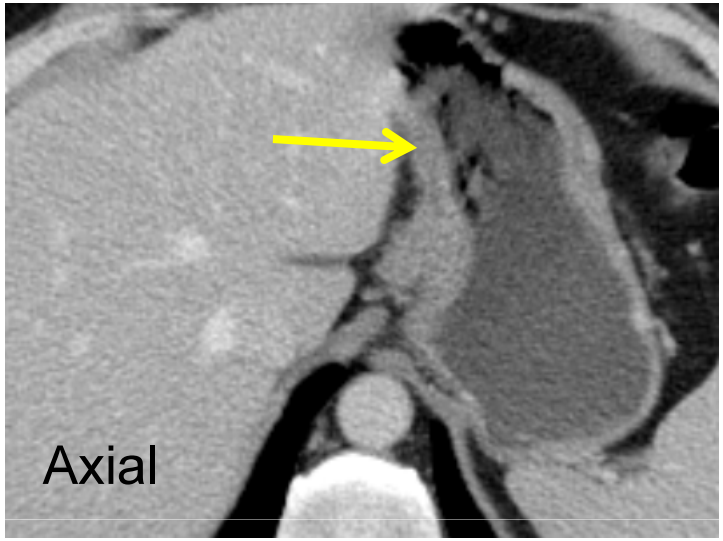
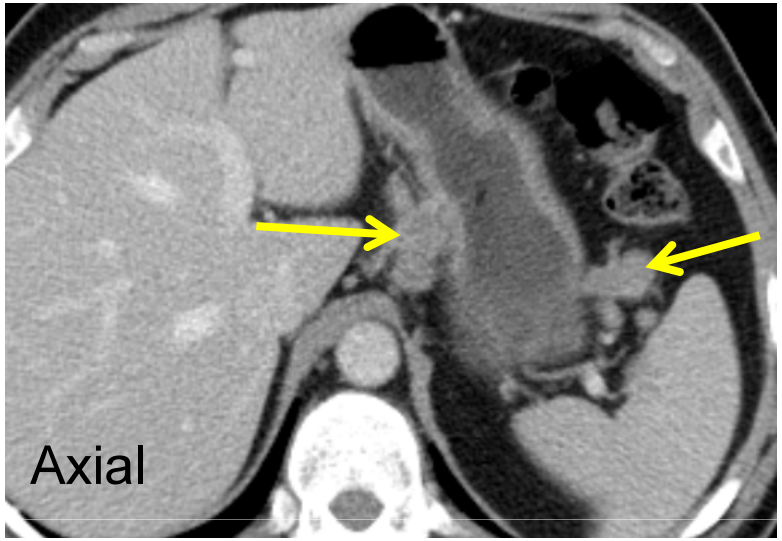
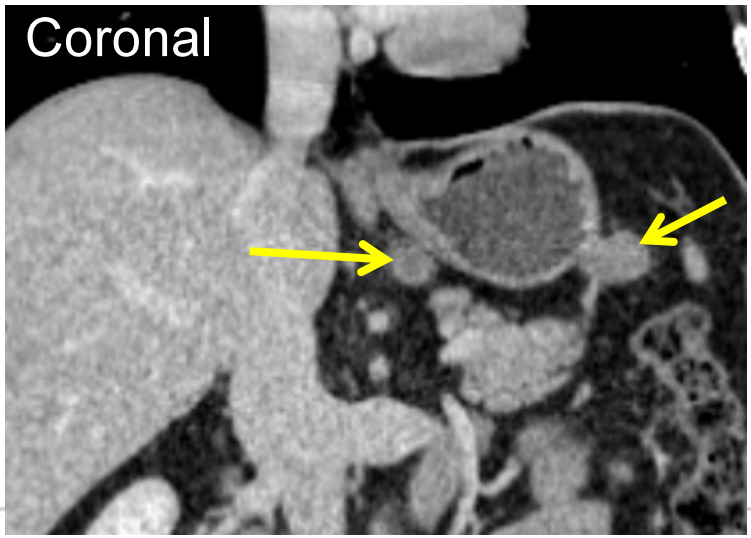
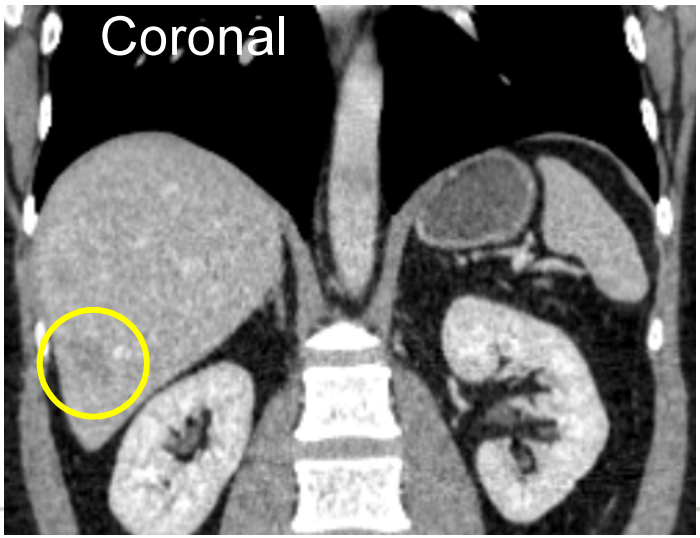
Case 1









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Case 1

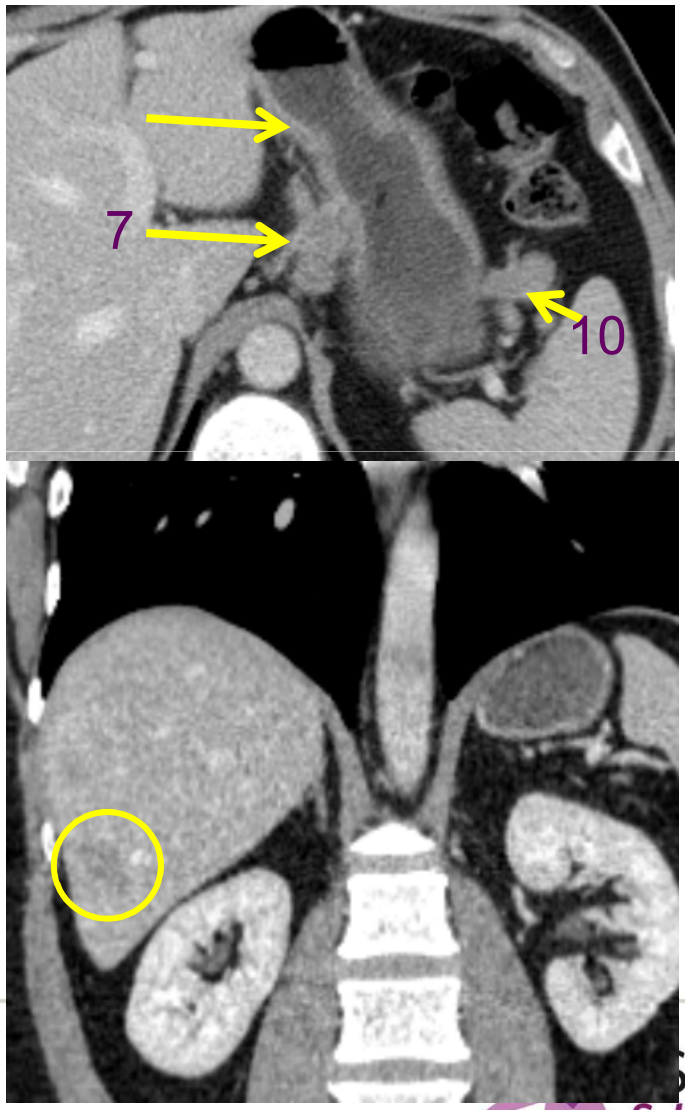
Tumour stage:

T3N2M1

Nodal Stations

Left gastric artery – 7

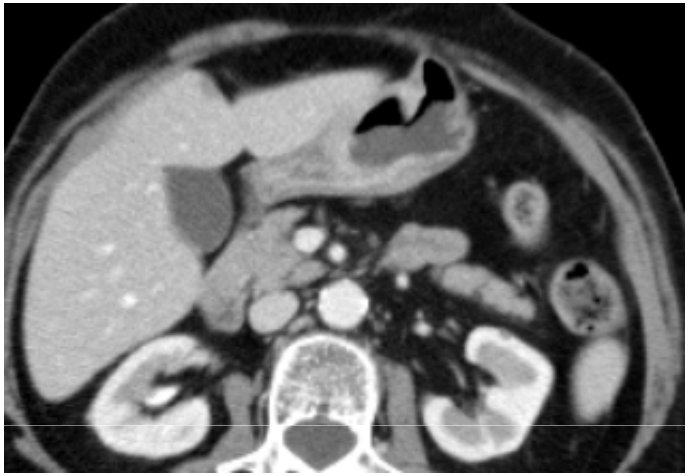
Splenic hilum - 10

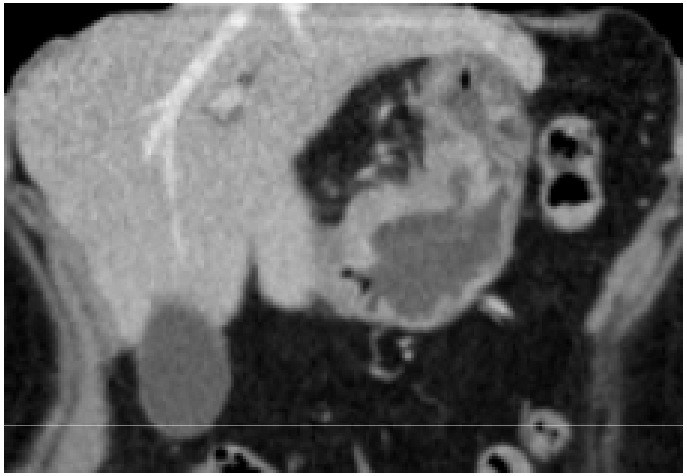


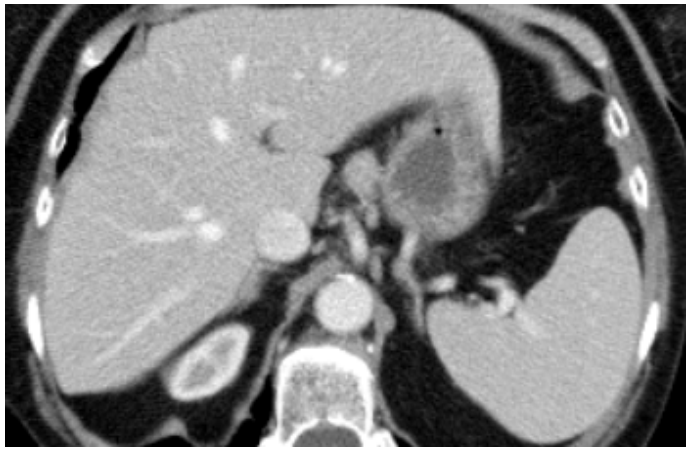
Case 2

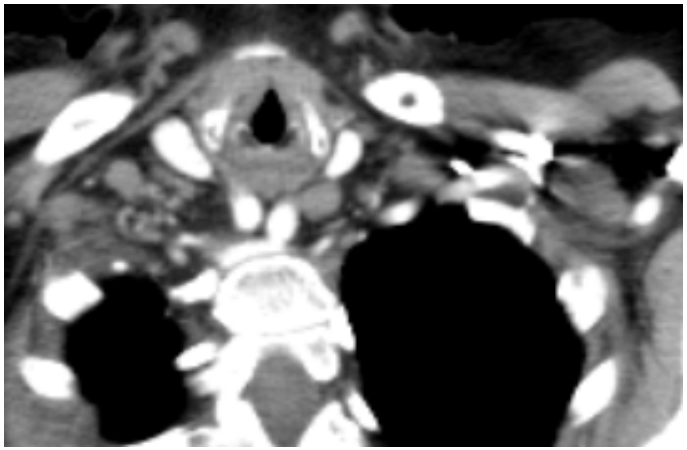
72 year old female with weight loss and anaemia

Case 2









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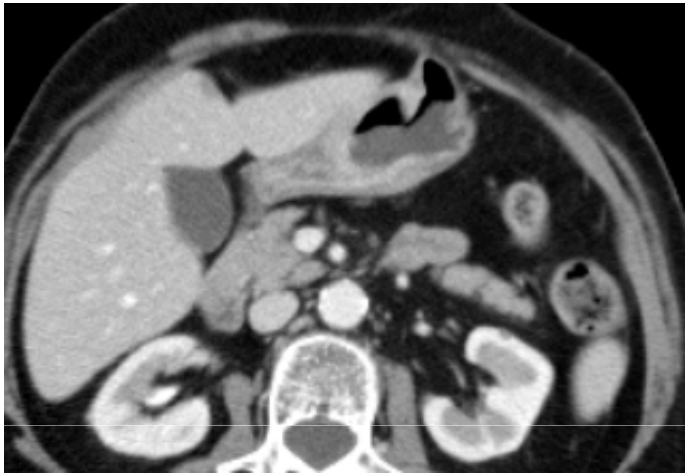
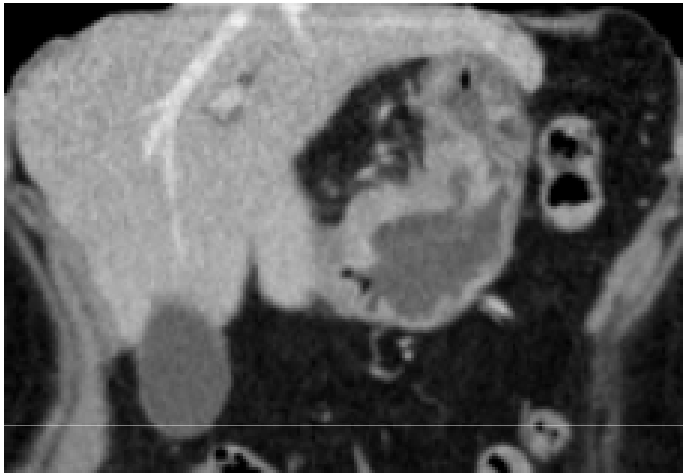
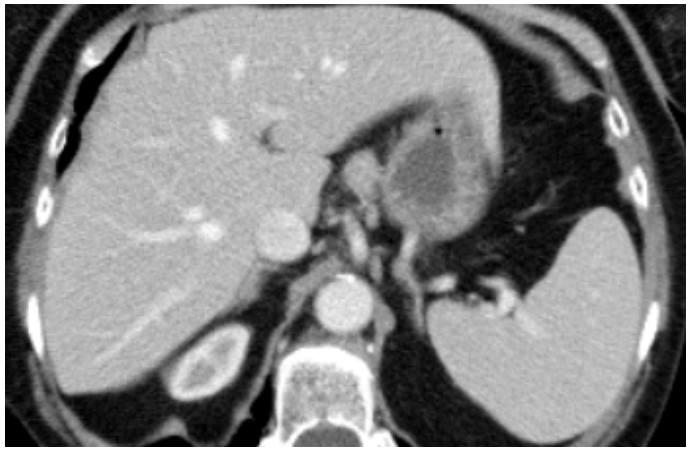
Case 2

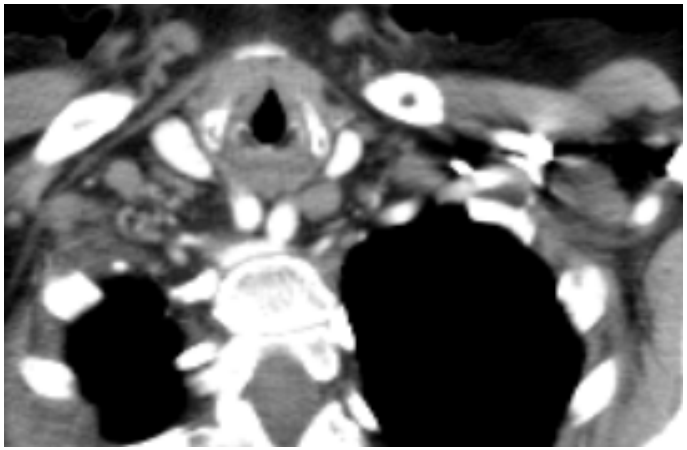
- Describe the location of the tumour
- Stage the tumour
- Identify any nodal stations involved

Case 2









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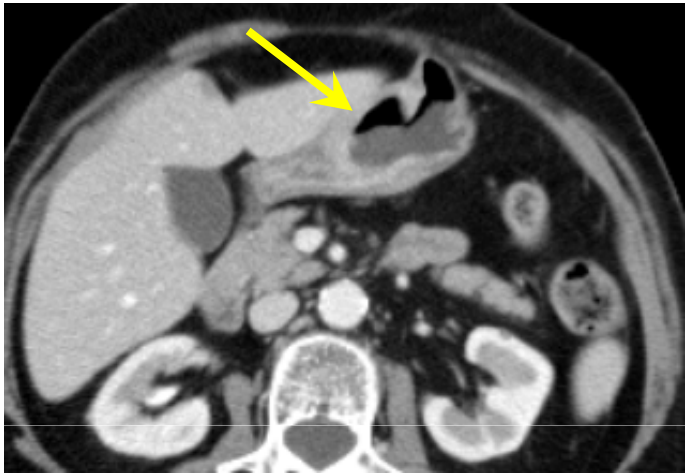
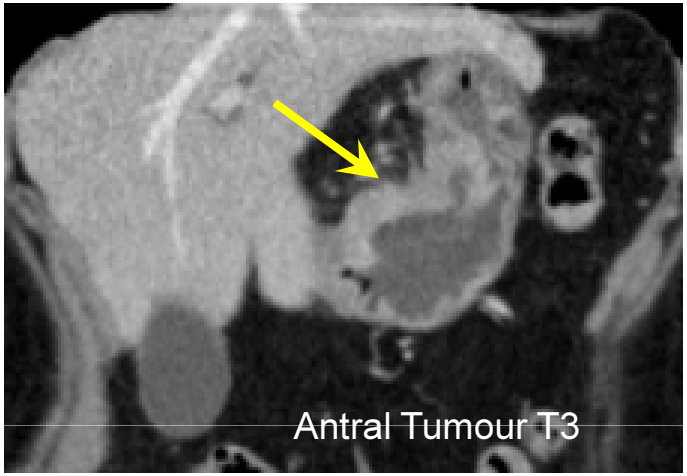
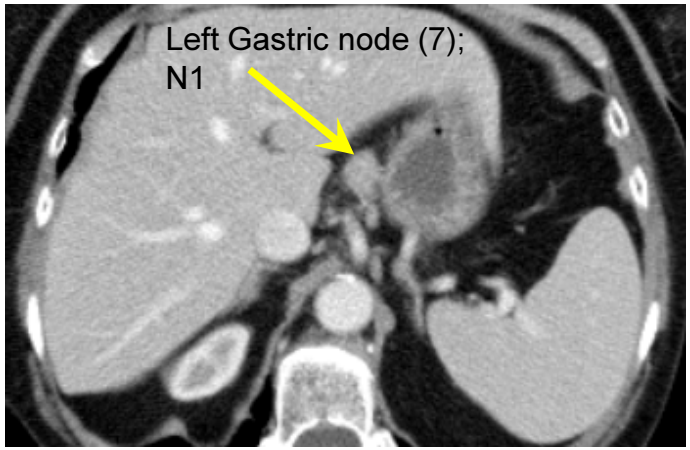
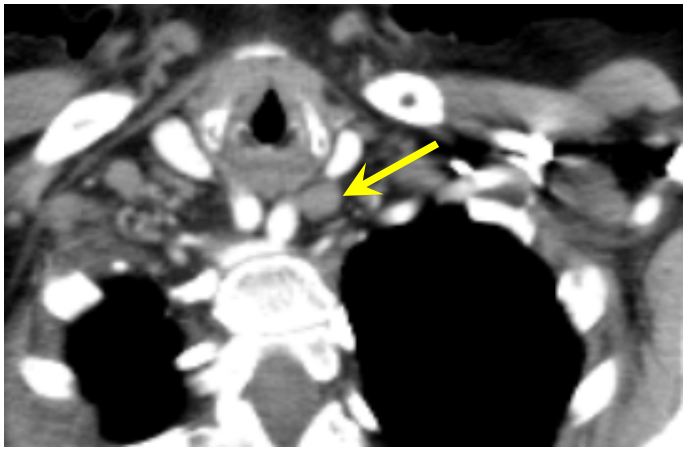
Case 2









T3N1 ?? M1 – Supraclavicular node…

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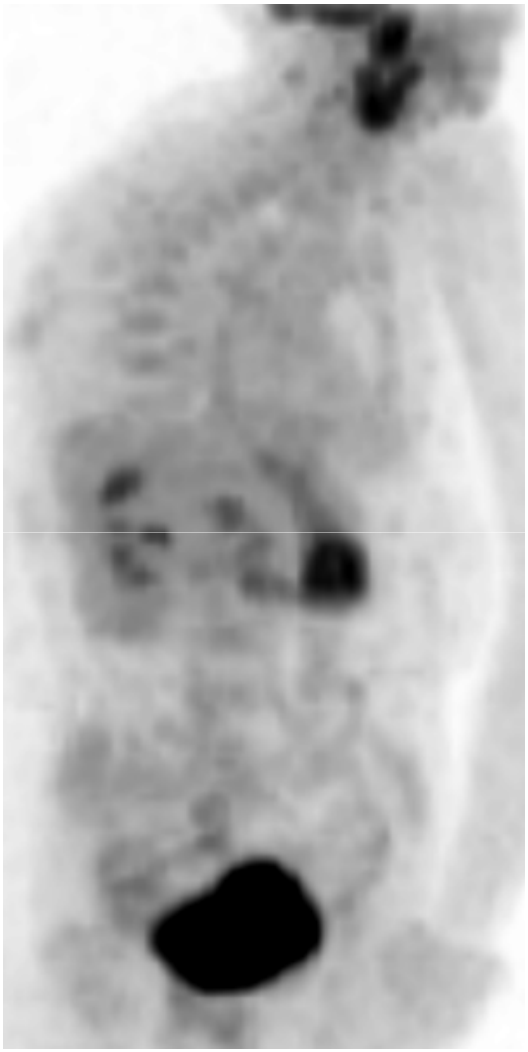
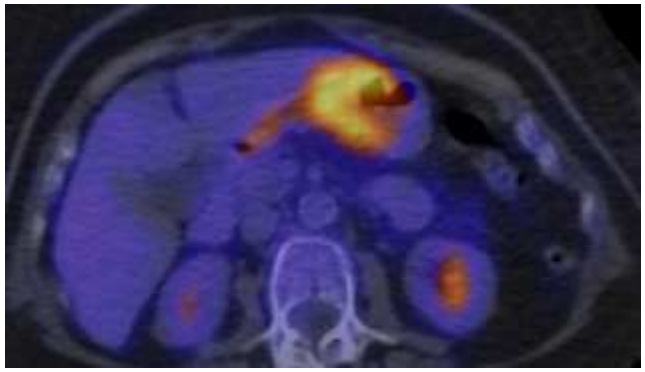
Case 2

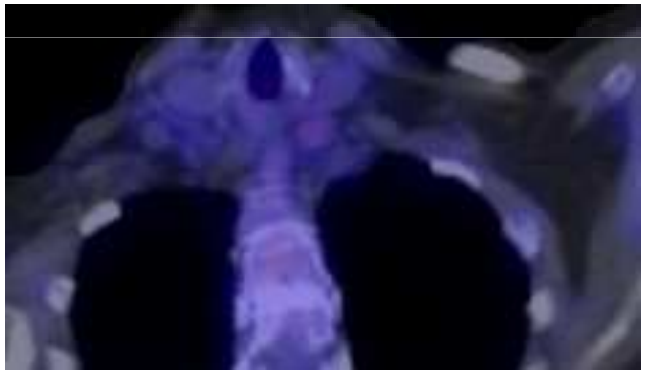
What to do next?

- Consider supraclavicular node positive based on size (9mm)?
- Arrange a PET-CT scan
- Arrange an U/S +/- FNA

Case 2







Moderate FDG avidity in node ‘equivocal’ on PET-CT

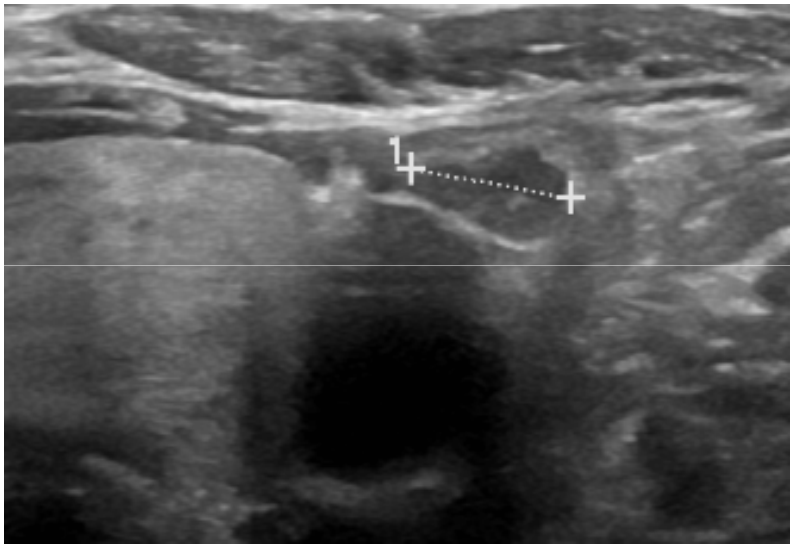
Case 2

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 2

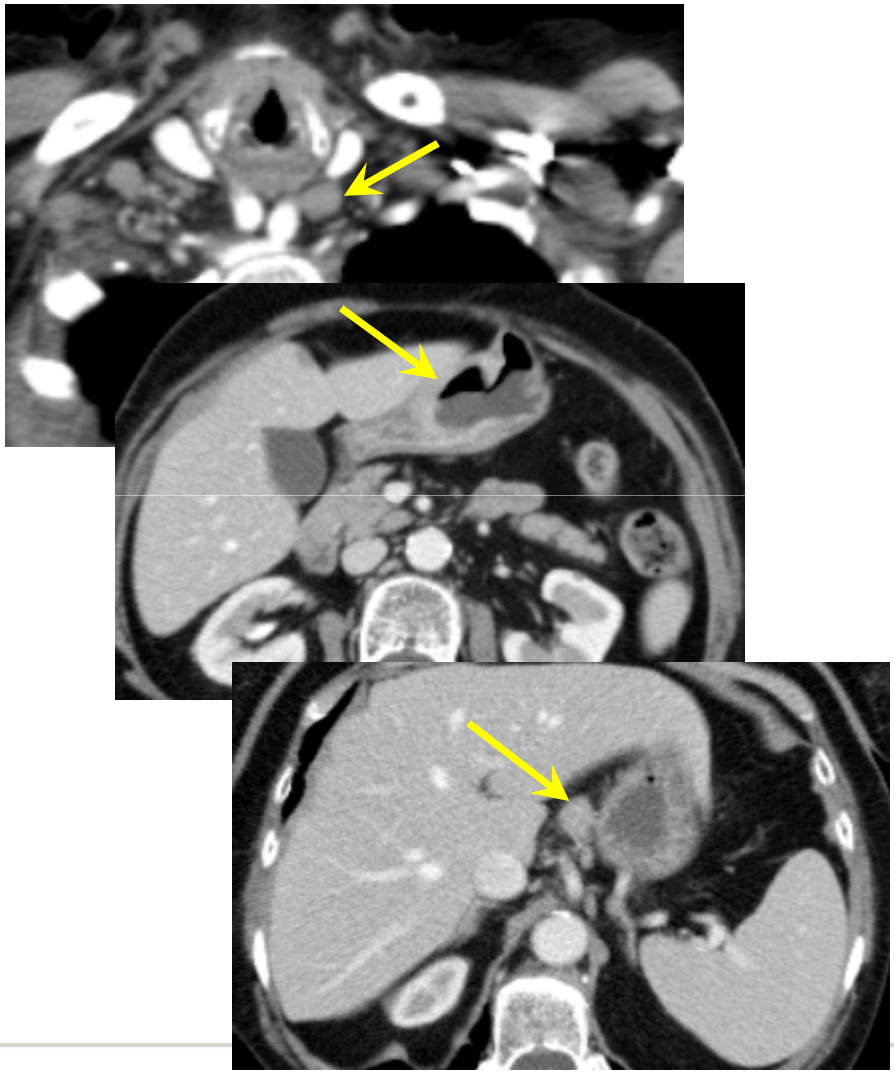
- An U/S with FNA was arranged
- Sonographic appearance in keeping with a reactive node.
- Cytology – C1

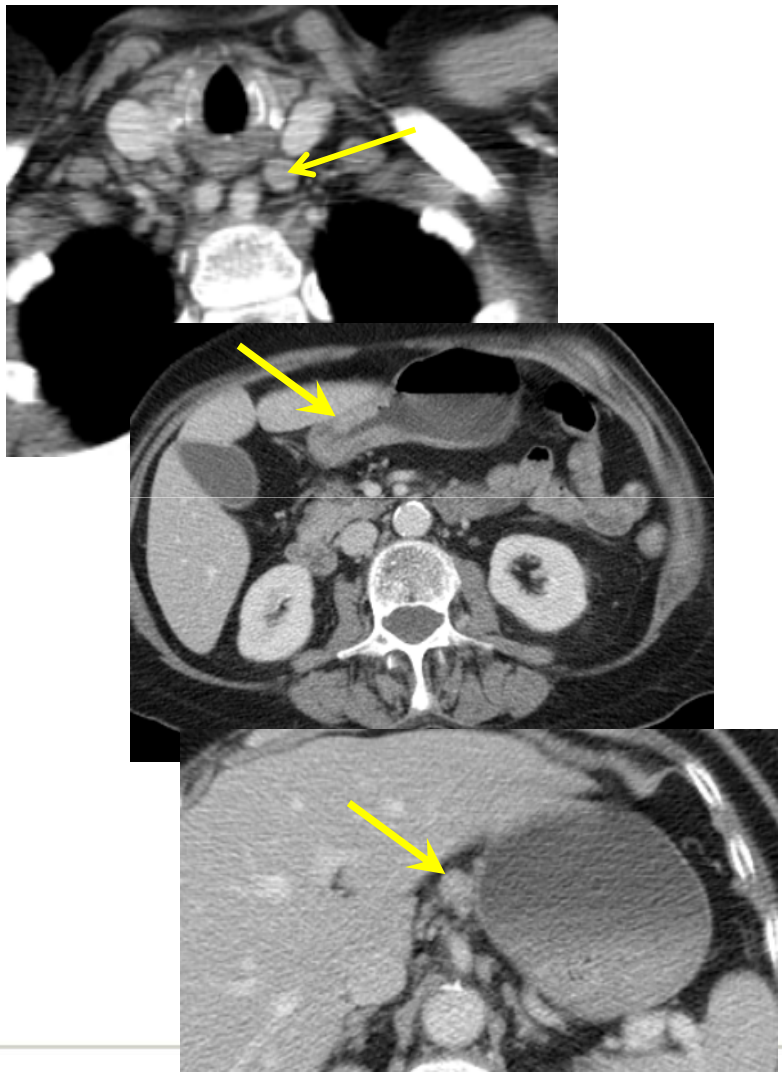


Case 2

The patient was given neoadjuvant therapy

Case 2





Post x2 Chemo cycles - PR

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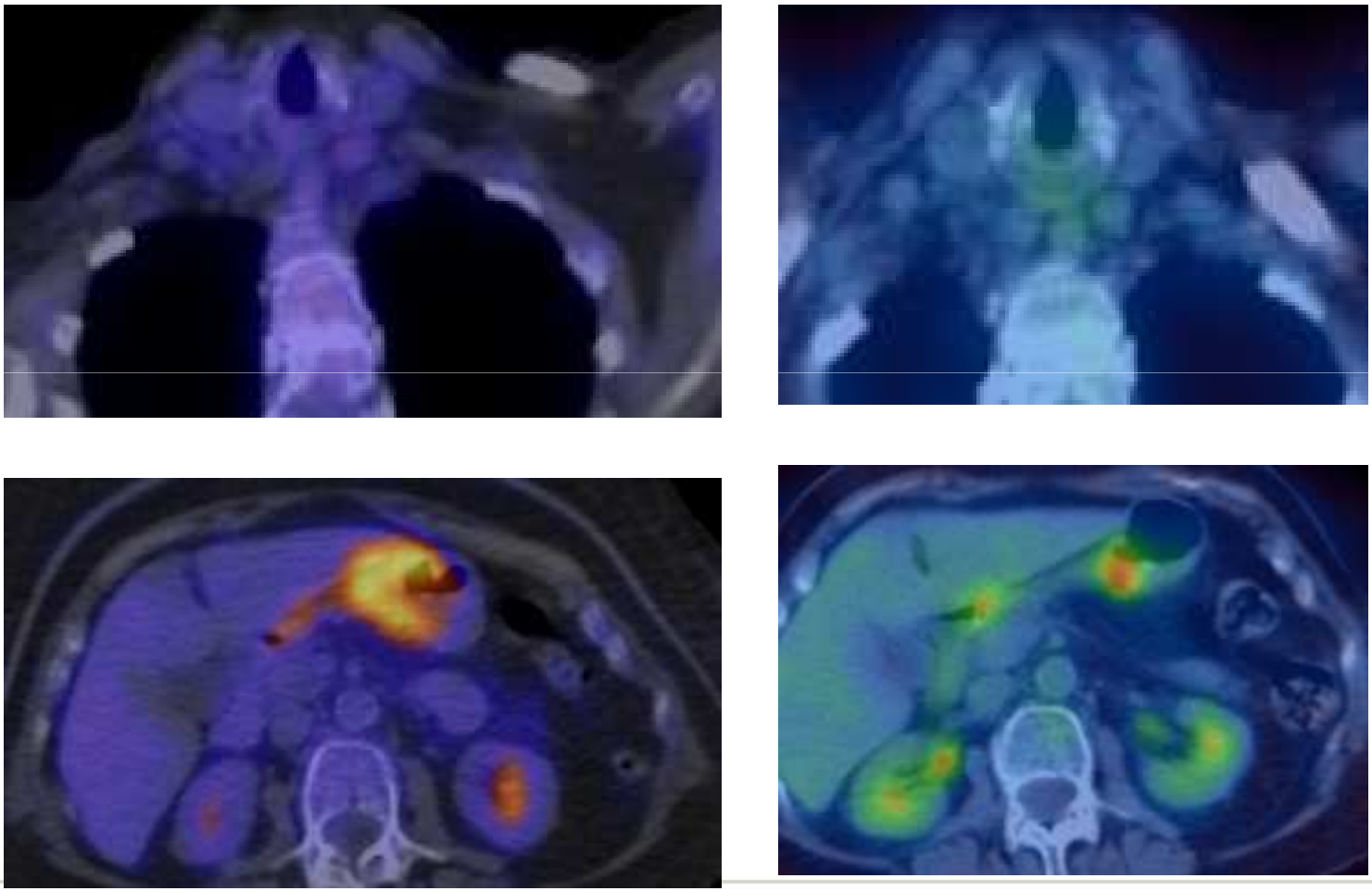
Case 2



Post x2 Chemo cycles - PR

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Case 2

- 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.

Thank you

Gastric Cancer: How to distinguish recurrence 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

Primary versus nodal relapse

- Challenging!
- Extremely difficult sometimes to identify relapse
- Much more difficult to determine nodal from anatomotic recurrence
- Mobile tissues, follow up difficult
- No specific rules….

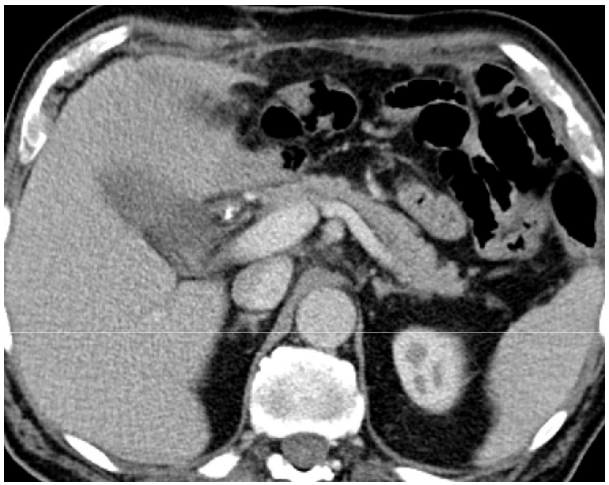
Gastric cancer patterns of disease relapse

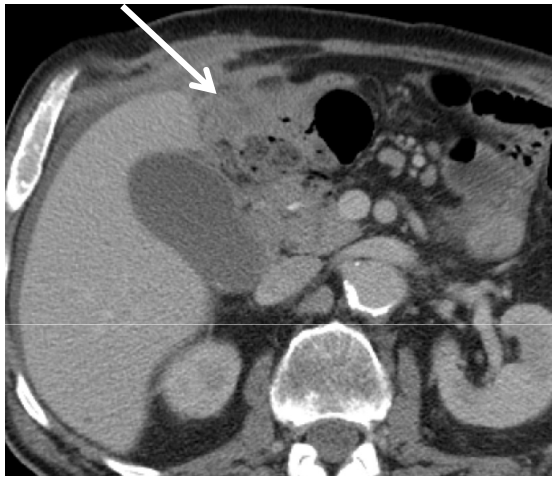
Male patient underwent a total gastrectomy on 09.09.2014 post neoadjuvant chemotherapy. The path staging was pT3bN1 R0 (3/40 nodes positive).

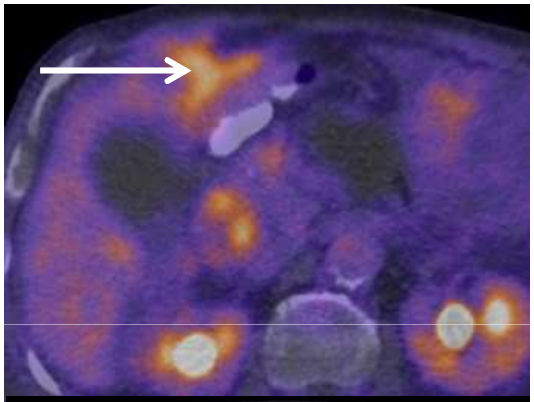
29.10.2014

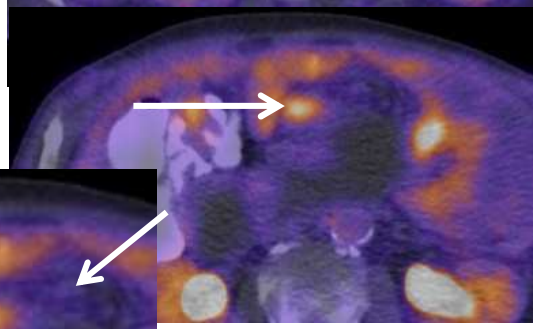
12.02.2015

06.03.2015

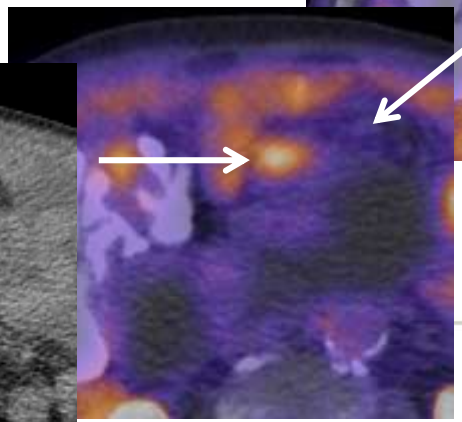


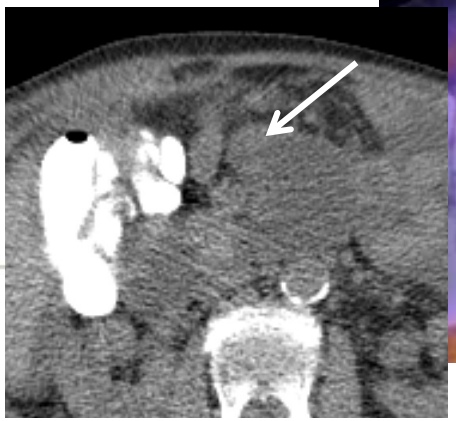






Baseline





Serosal disease causing small bowel obstruction

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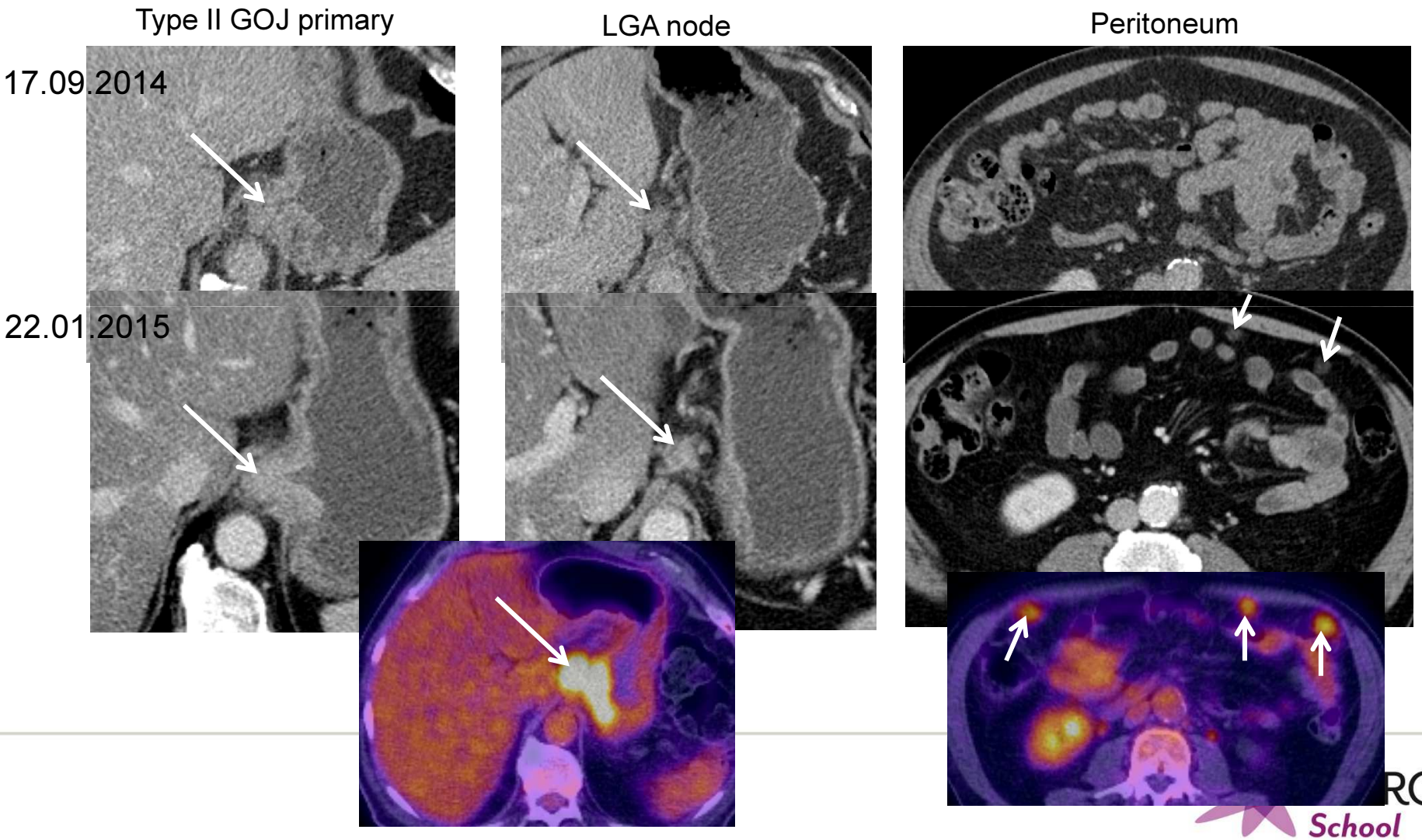
Primary versus nodal relapse

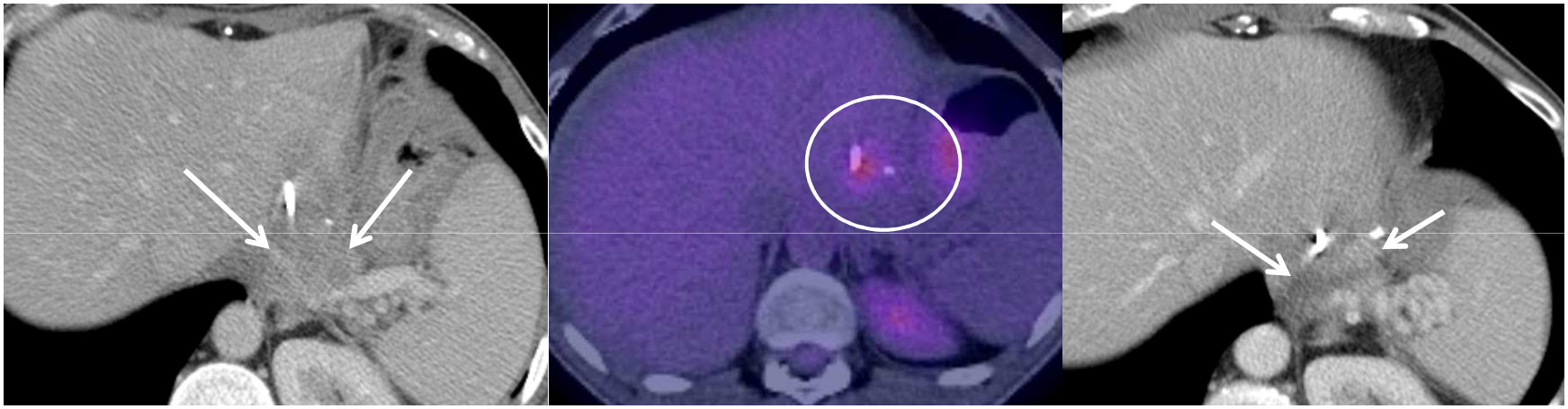
Type II GOJ tumour staged as T3N2. Commenced chemo. Progressive symptoms of dysphagia.



Primary versus nodal relapse

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



Loco-regional relapse ?nodal?primary…….

Partial response post chemotherapy

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

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

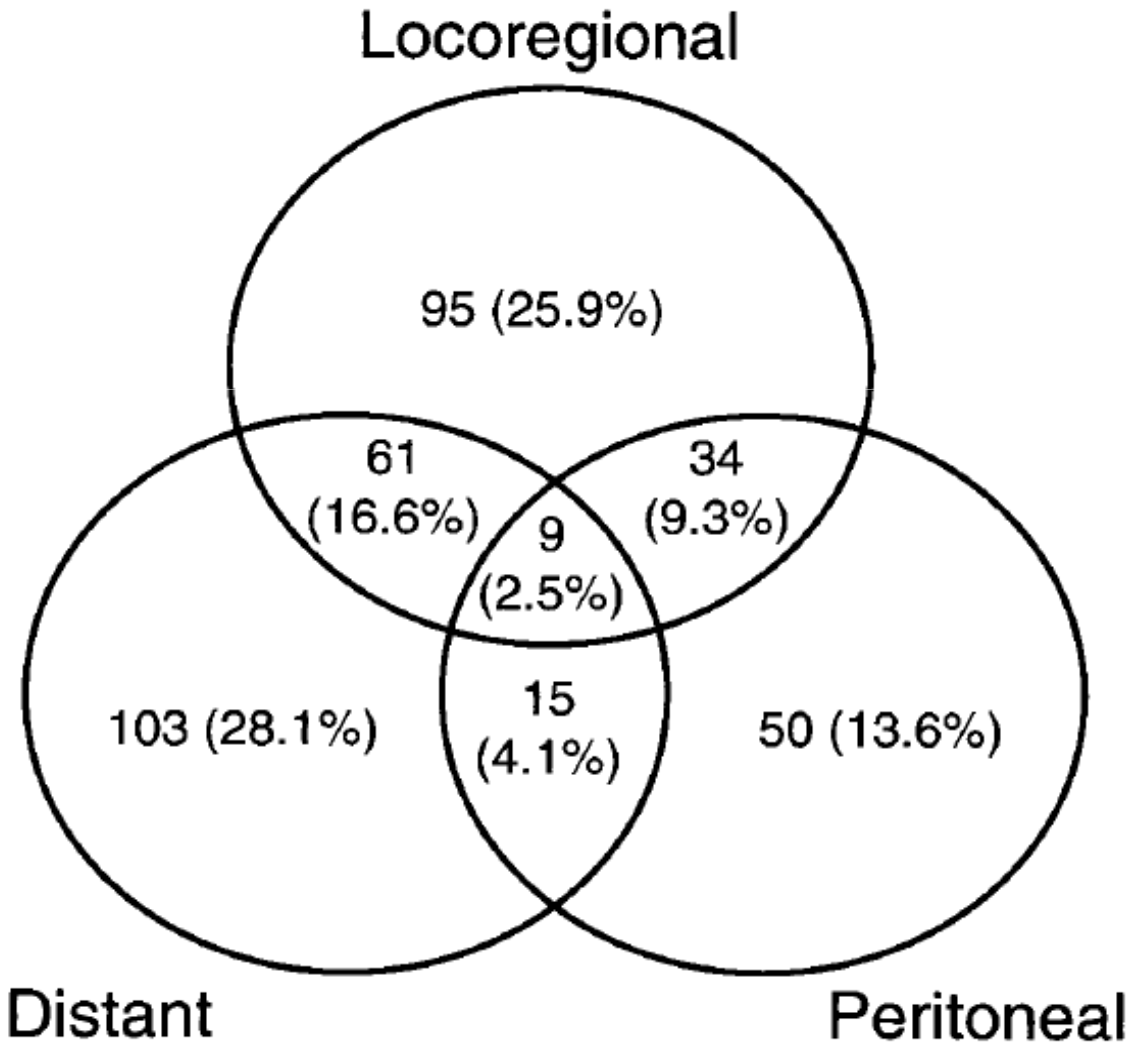
Pattern of Recurrence

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%

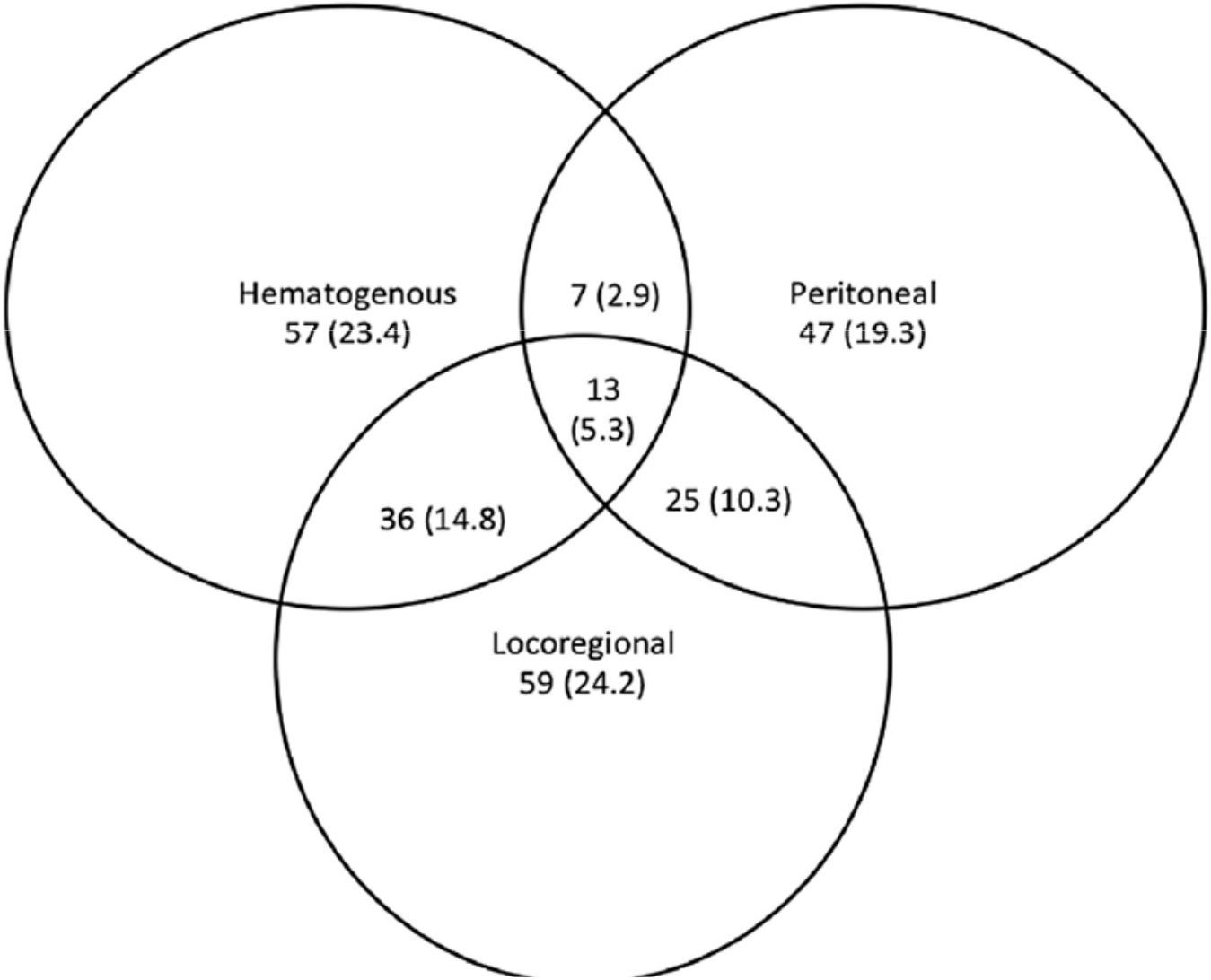
Site of Relapse

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%)**

Pattern of Recurrence
MSK series



Pattern of Recurrence
US Gastric Cancer Collaborative Group



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.

Sites of Recurrence

Site of recurrence	No. of patients	Sole site	Associated with other sites
Peritoneal	77	61	16
Locoregional	96	68	28 (13)
Lymph node	49	36	13 (4)
Gastric stump	13	8	5 (2)
Gastric bed or adjacent organs	34	24	10 (7)
Haematogenous	75*	56	21*(3)
Liver	57	41	16 (2)
Lungs	9	7	2
Bone	5	4	1
Skin	5	3	2 (1)
Brain	1	1	0

Predication 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** **No** **Unknown**	 **24 (51%)** **16 (34%)** **7 (15%)**
Symptoms at time of relapse Yes	 34 (72%)
How relapse was first detected in asymptomatic patients Routine tumour markers Routine CT Concurrent routine CT/ markers Endoscopy Other	(n = 12) 4 (33%) 4 (33%) 3 (25%) 1 (8%) 0 (0%)

Treatment of Relapse

Further treatment for recurrent disease	
Type of treatment for recurrent disease	
	19 (86%)
Chemotherapy	3 (14%)
Radiotherapy	0 (0%)
Chemoradiotherapy	1 (5%)
Surgery	

Survival

Median survival after relapse

5 months (US GC Collaborative)

6 months (MSKCC)

Recommendation for subsite delineation by stage and tumor position

Francesco Cellini MD, EF

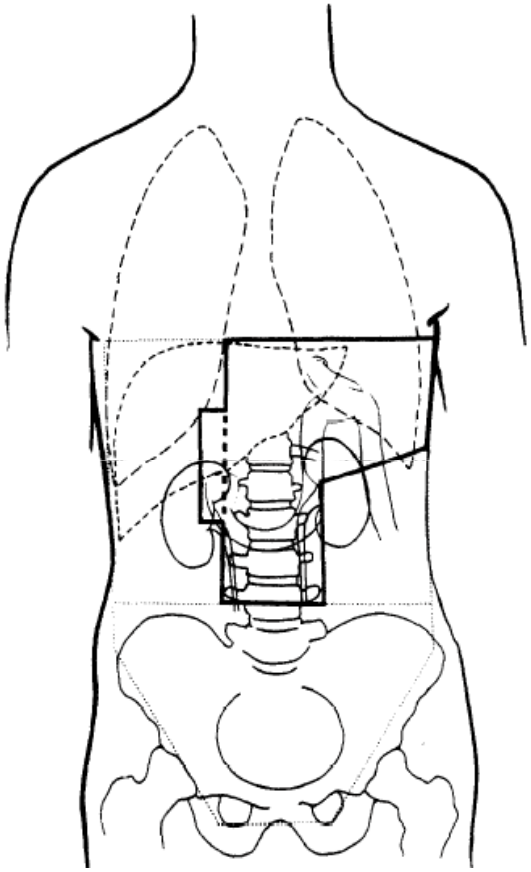
Gemelli ART
Radiotherapy Department
Fondazione Policlinico A. Gemelli
Università Cattolica S. Cuore
Roma

Outline

- CTV Definition: Background and Issues
- CTV Selection
- CTV Identification

} Preoperative Setting
} Postperative Setting

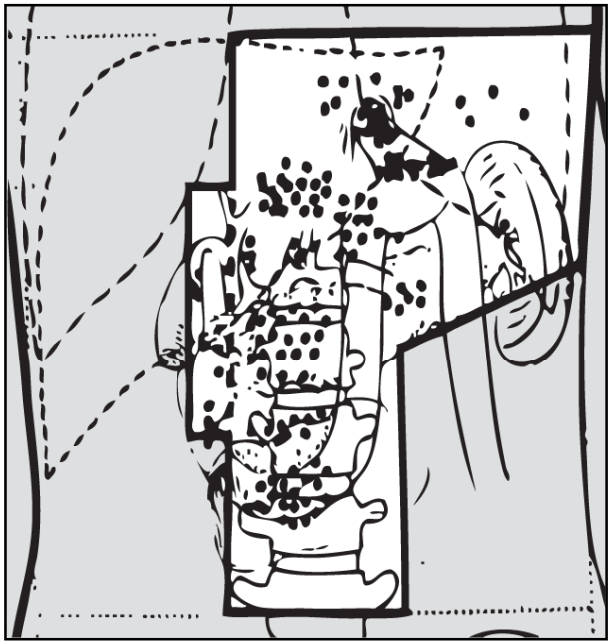
CTV Definition: Background

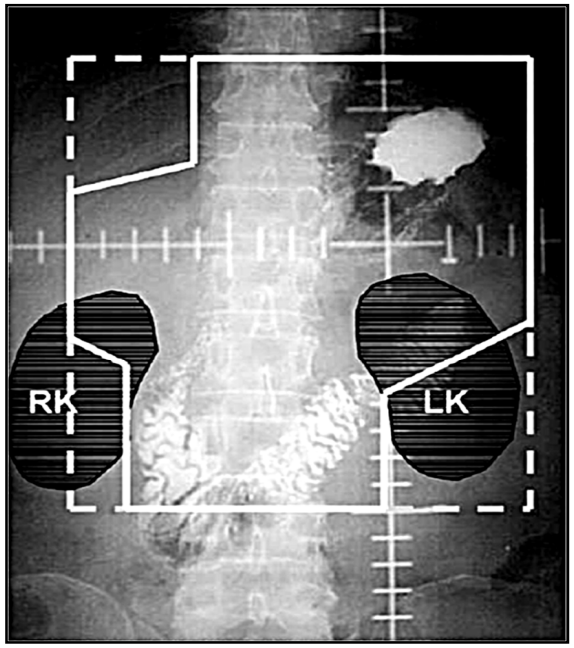


Gunderson *et al.; IJROBP* -1981

CTV Definition: Background

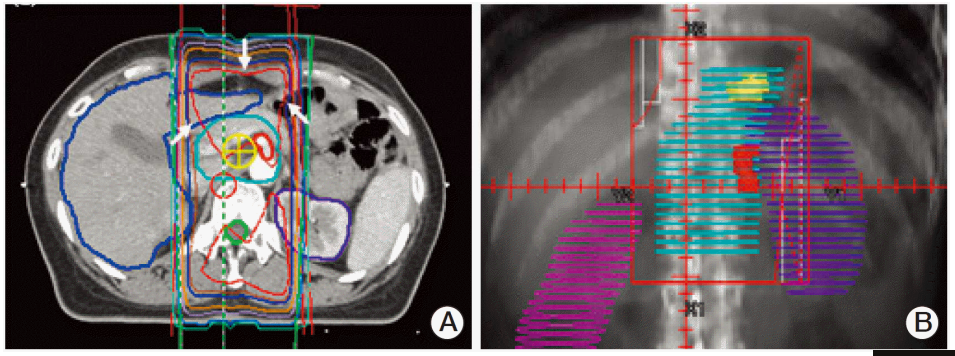
Radiotherapy Targeting

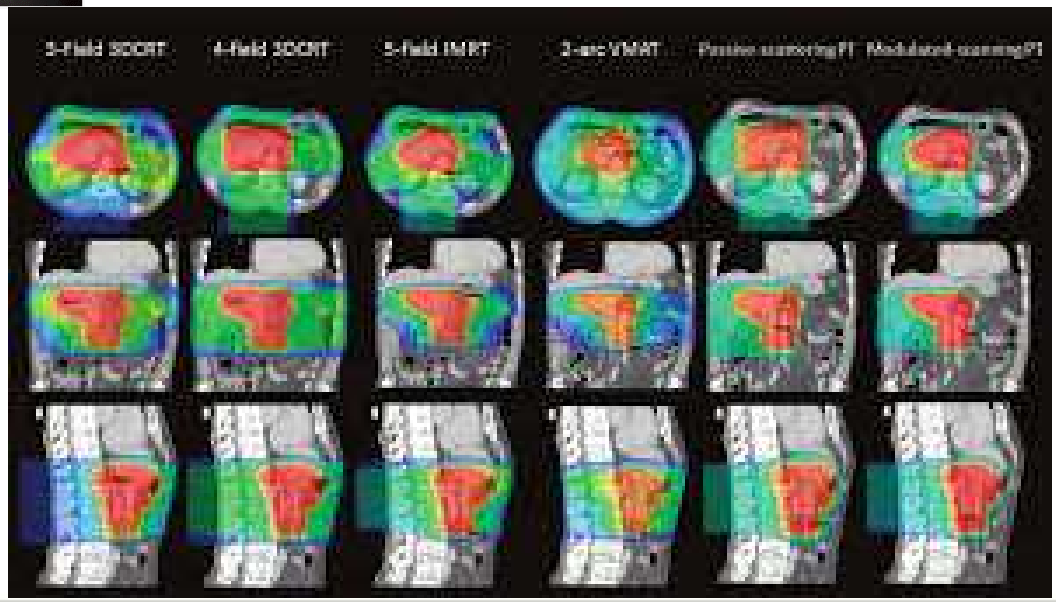




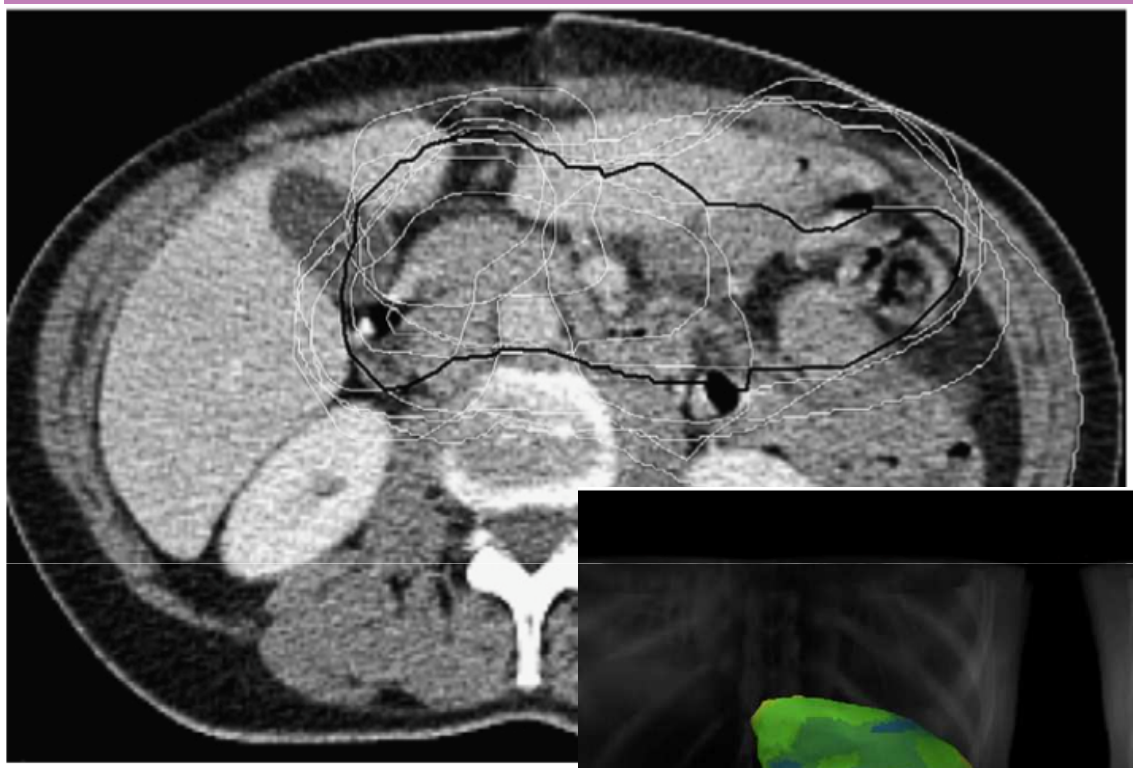
CTV Definition: Background

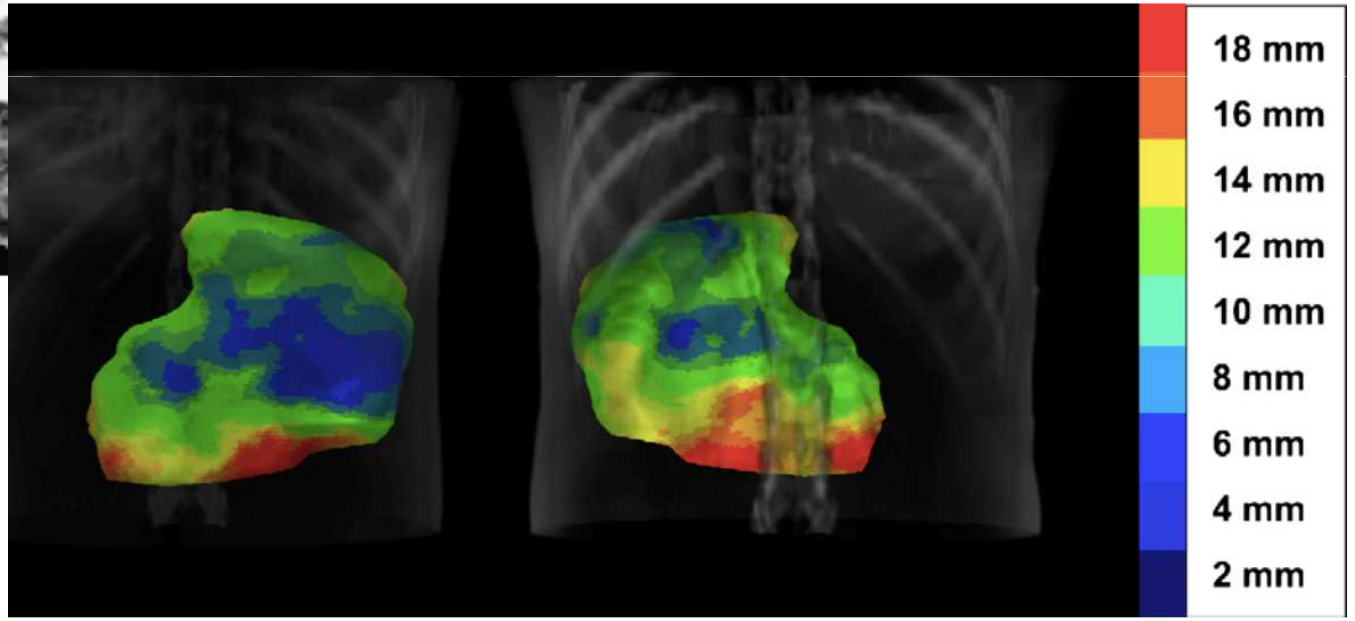
Radiotherapy Targeting





CTV Definition: Issues





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Jansen *et al.; IJROBP* -2010

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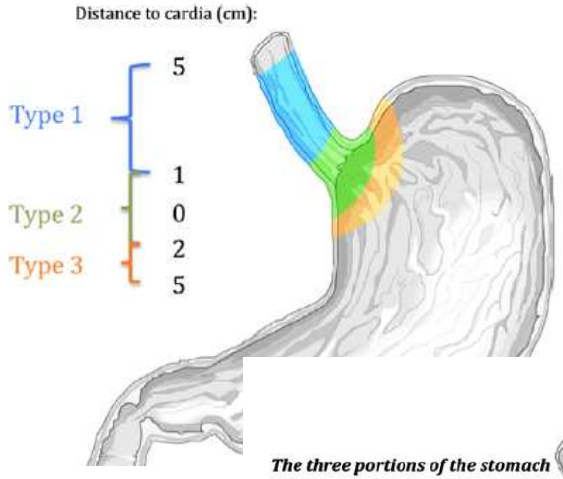
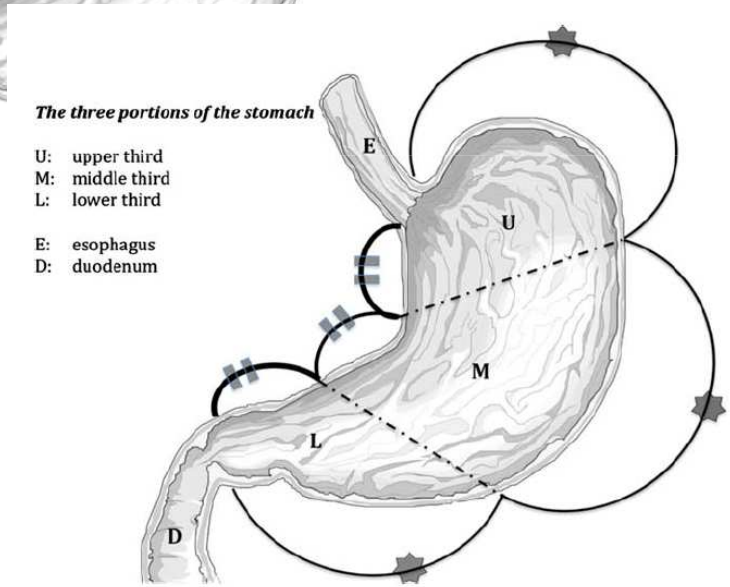
CTV DEFINITION: Issues

CTV Selection

CTV Identification

CTV DELINEATION: Preoperative Setting





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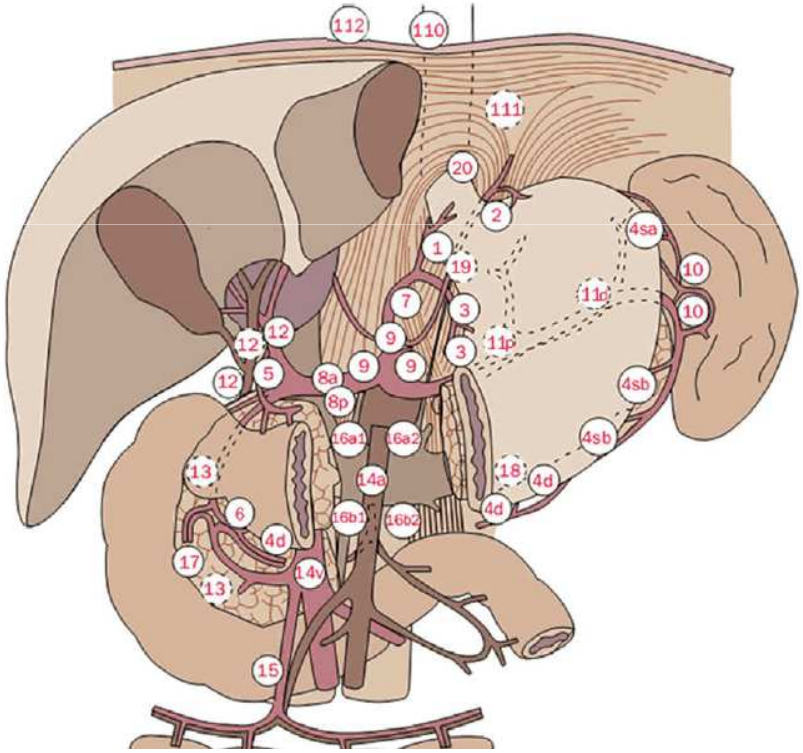
ELSEVIER

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]



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Matzinger *et al.; Radiother Oncol* -2009

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CTV DELINEATION: Preoperative Setting

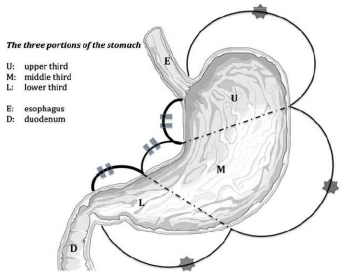
GTV tumor + GTV nodal

↓ ↓

+ 1.5 cm= CTV tumor + 0.5 cm= CTV nodal

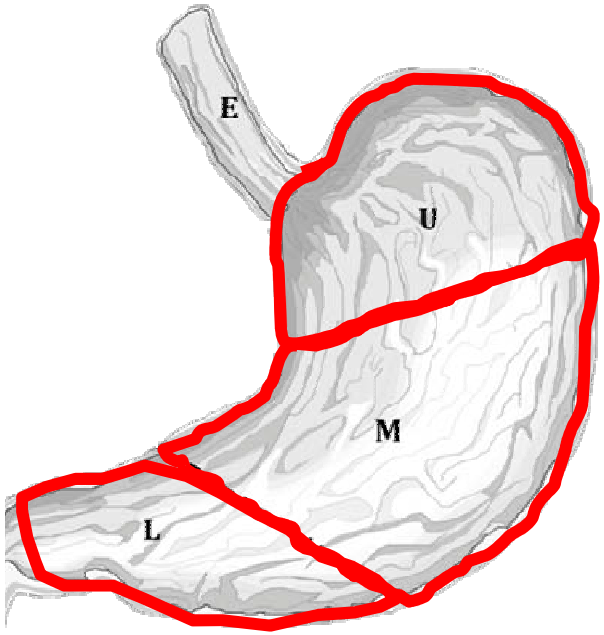
+

CTV Gastric



Matzinger *et al.; Radiother Oncol* -2009

CTV DELINEATION: Preoperative Setting



UP ⅓ = Stomach wo Pylorus + Antrum
(CTV= GTV + 5 mm minimum)

MID ⅓ = Whole Stomach

LOW ⅓ = Stomach wo Cardias + Fundus
(If Pylorus or Duodenum "+" Include 3 cm Duodenum:)

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Matzinger *et al.; Radiother Oncol* -2009

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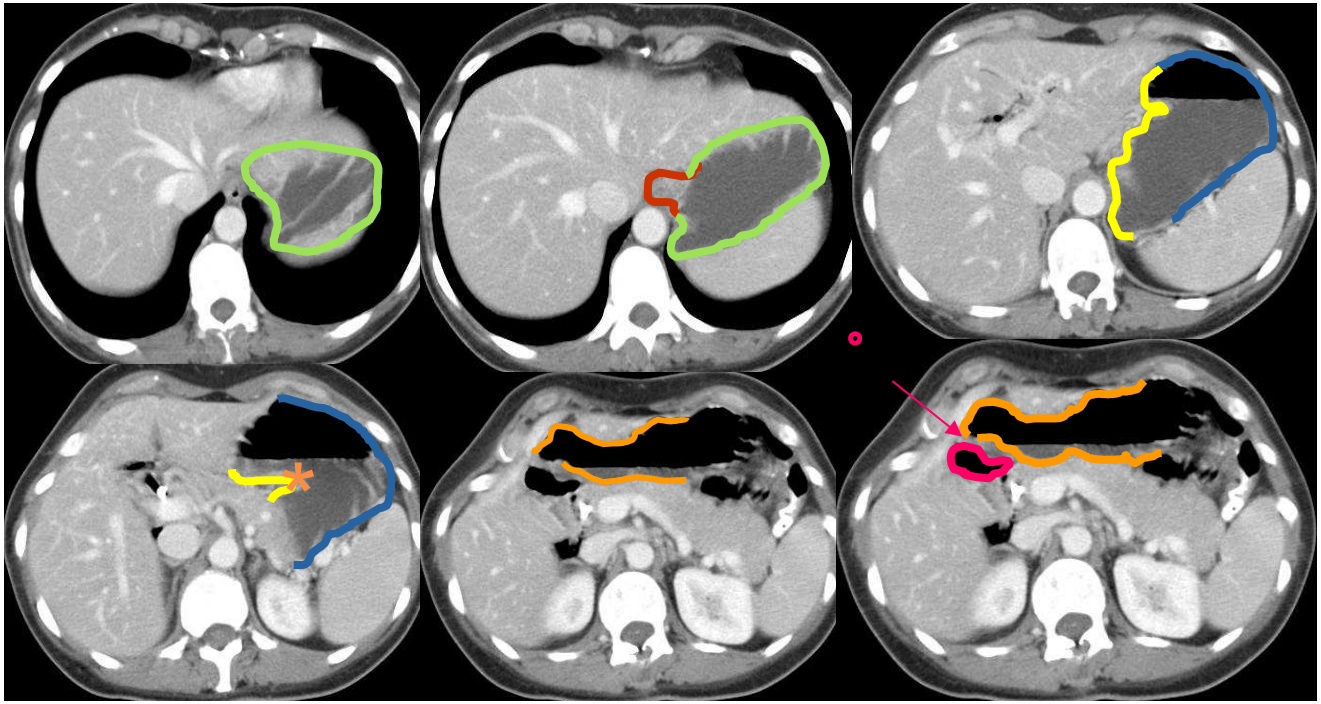
CTV DELINEATION: Preoperative Setting

Stomach CT Anatomy



FUNDUS
CARDIAS
GREATER CURVATURE
* ANGULUS
LESSERE CURVATURE
ANTRUM
BULB
° PYLORUS

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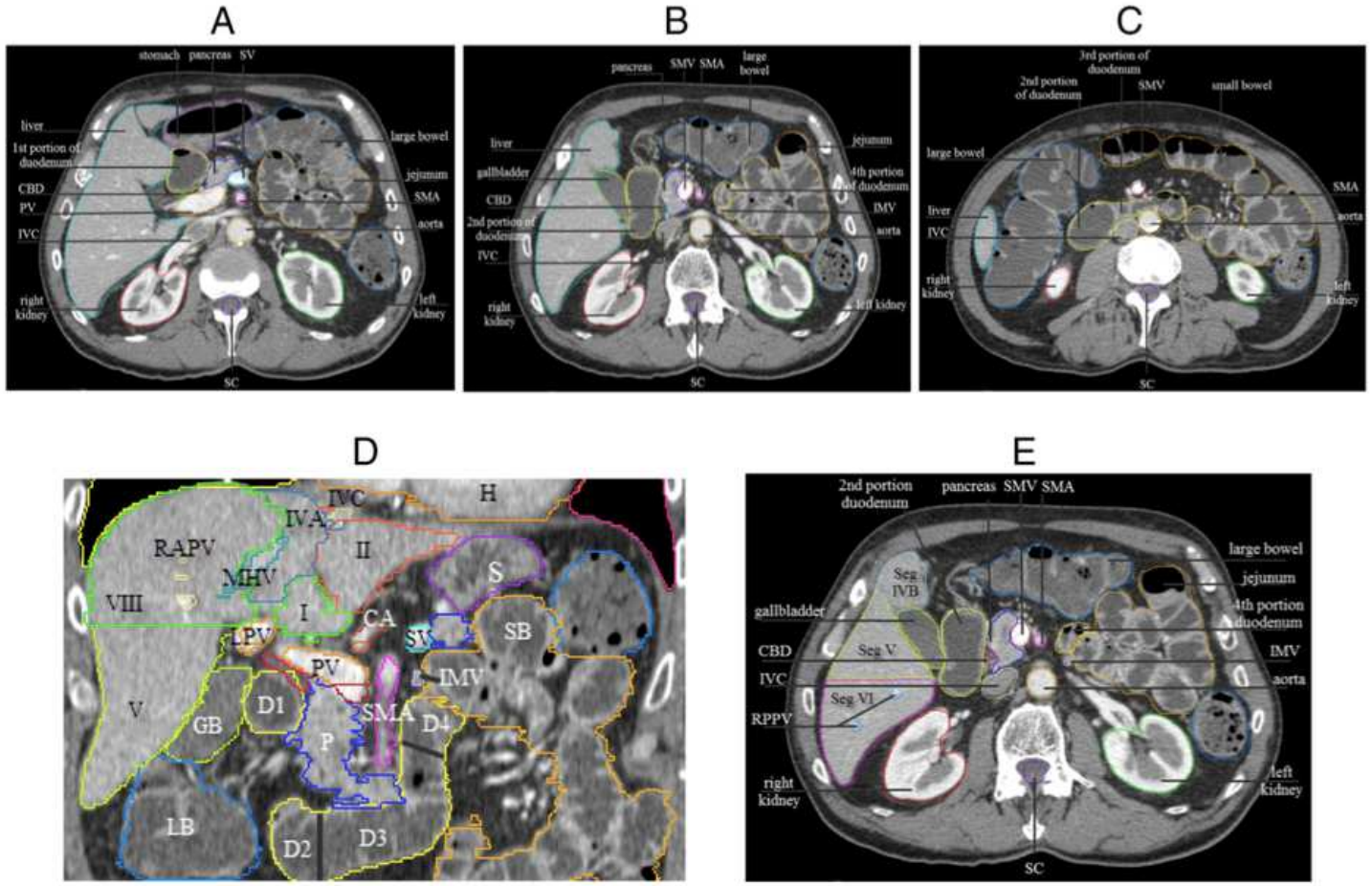
CTV DELINEATION: Preoperative Setting

Organs Anatomy



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Jabbour *et al.; PRO* -2014

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CTV DELINEATION: Preoperative Setting

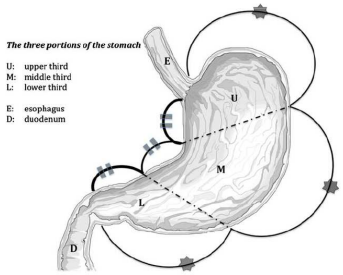
GTV tumor + GTV nodal

+ 1.5 cm= CTV tumor

+ 0.5 cm= CTV nodal

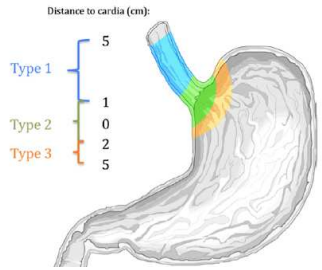
+

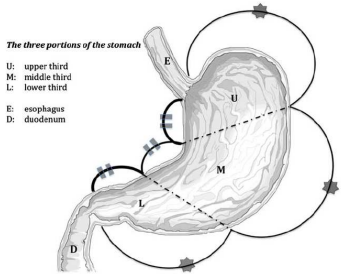
CTV Gastric



+

CTV Elective





Matzinger *et al.; Radiother Oncol* -2009

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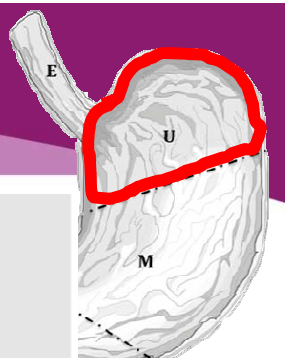
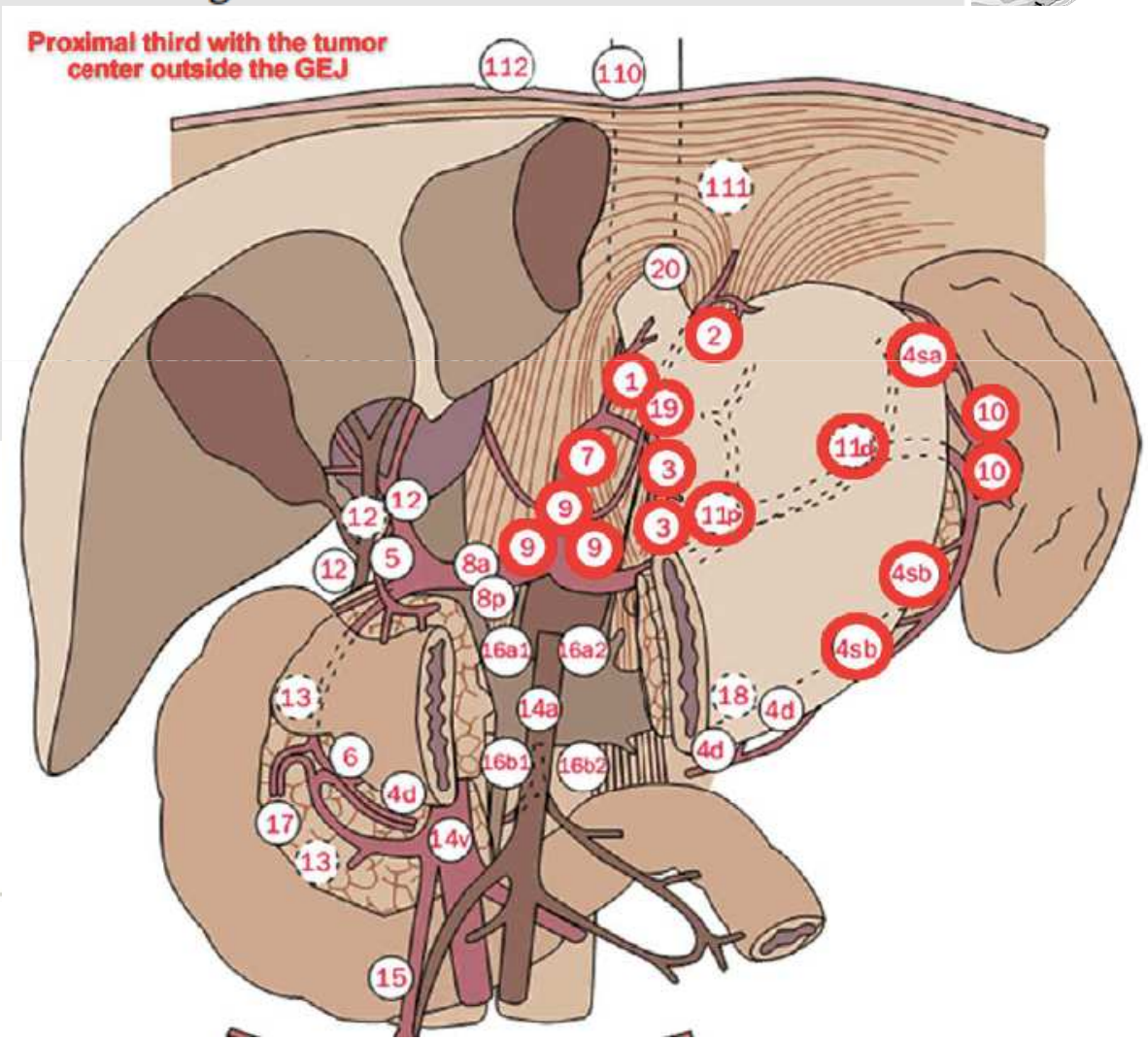
CTV DELINEATION: Preoperative Setting



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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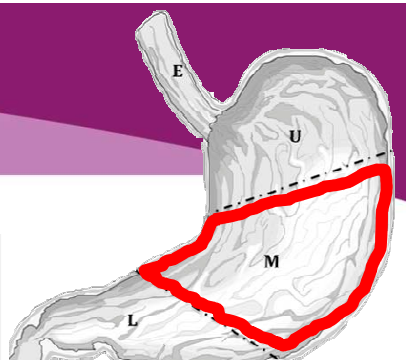
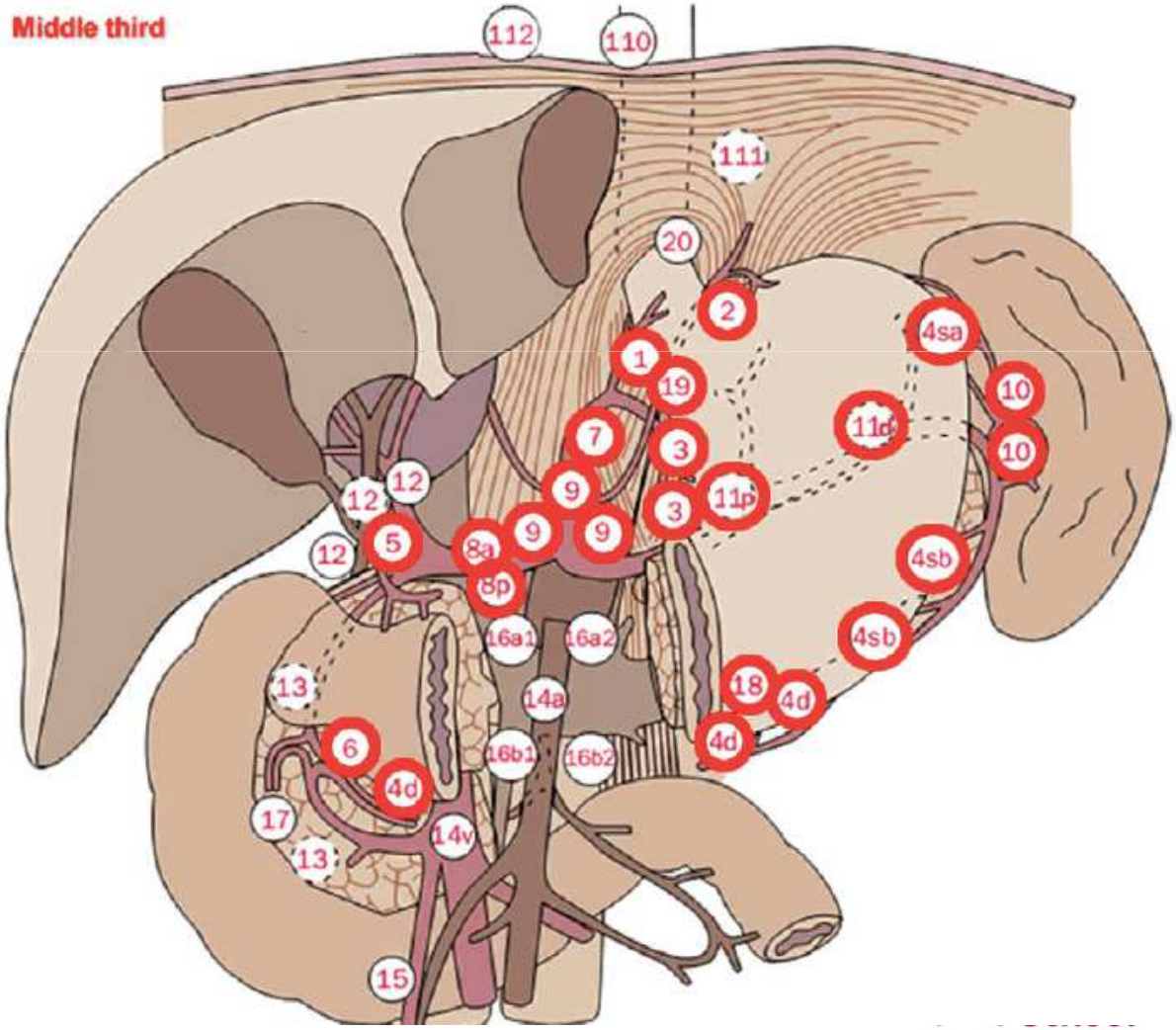
CTV DELINEATION: Preoperative Setting



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
		(
	8b	L
		g
	9	L
	10	L
	11p	L
	11d	L
	18	L
	19	in



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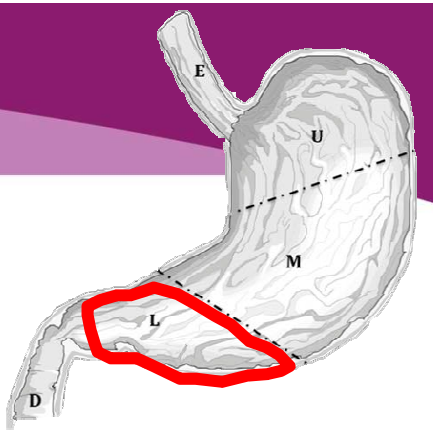
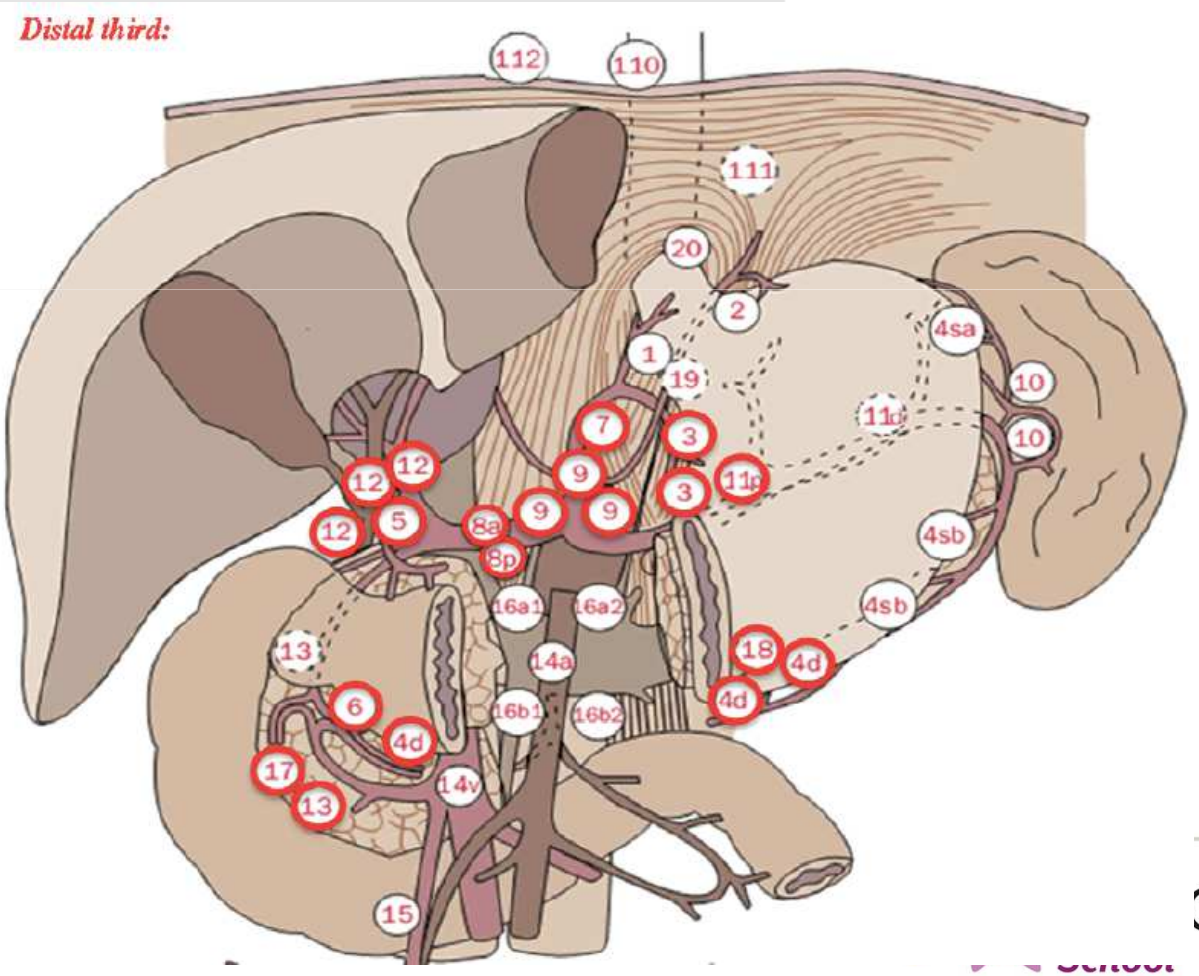
CTV DELINEATION: Preoperative Setting

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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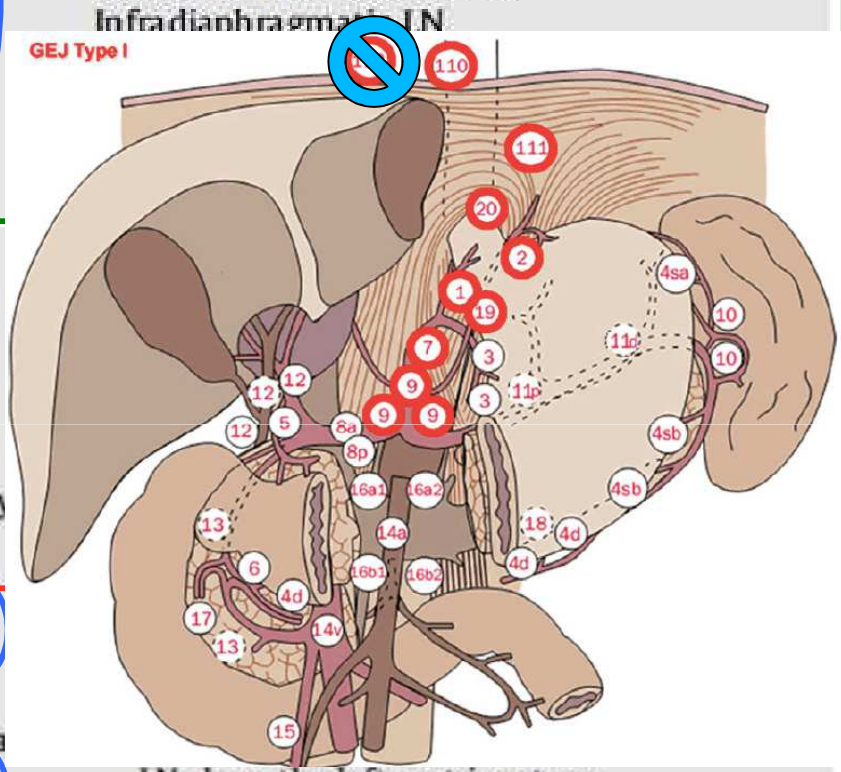
CTV DELINEATION: Preoperative Setting

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	LN in the oesophageal hiatus of the diaphragm
	110	Paraoesophageal LN in the lower thorax
	111	Supradiaphragmatic LN
	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 diaphragm
	110	Paraoesophageal LN in the lower thorax
	111	Supradiaphragmatic LN

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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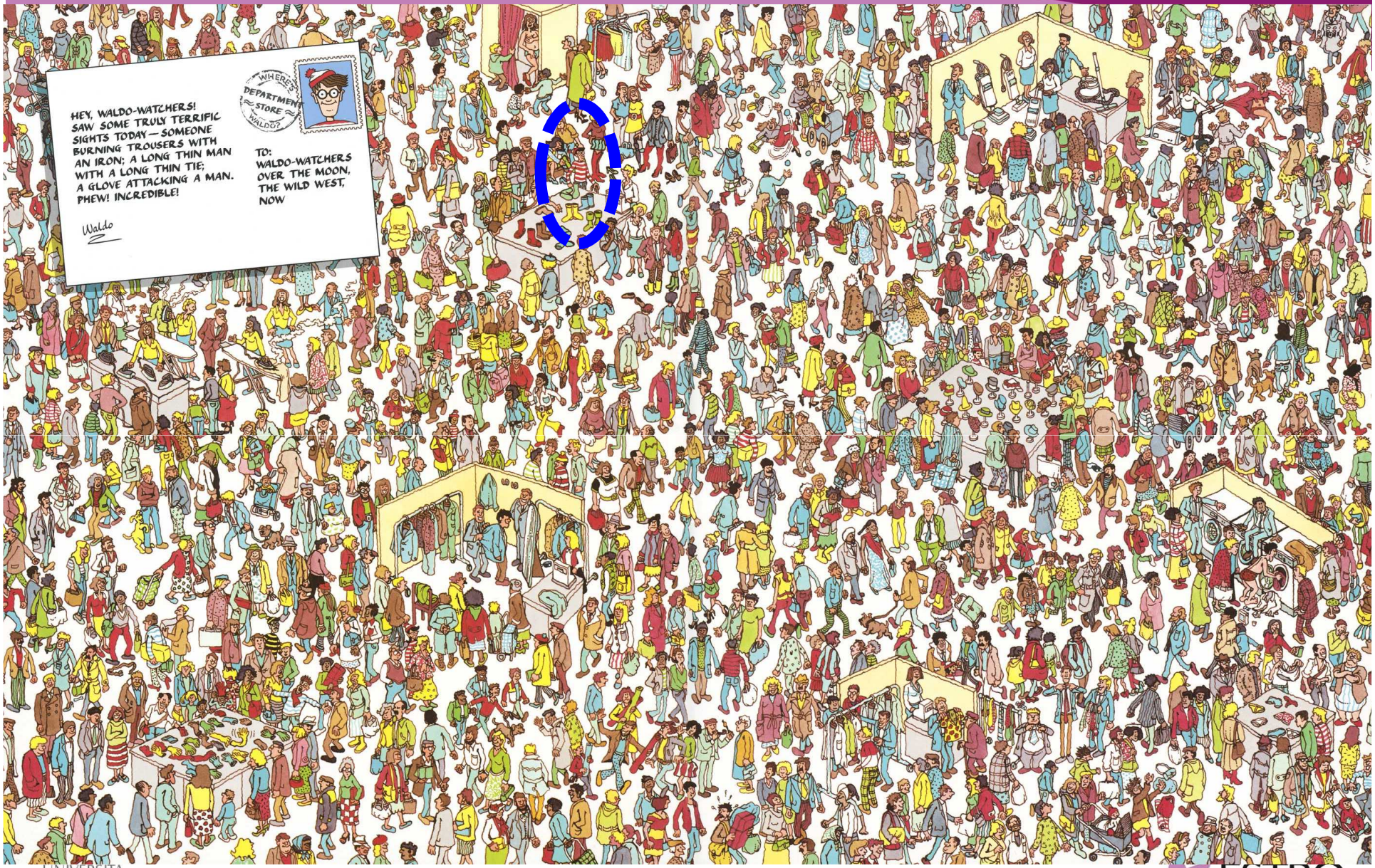
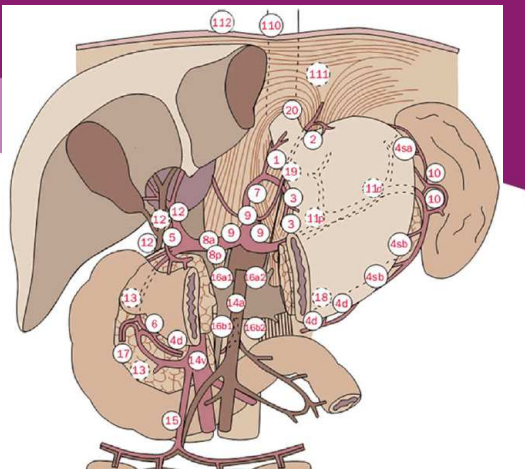
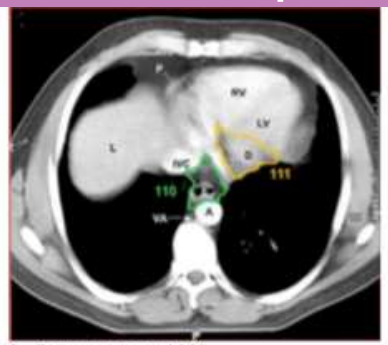
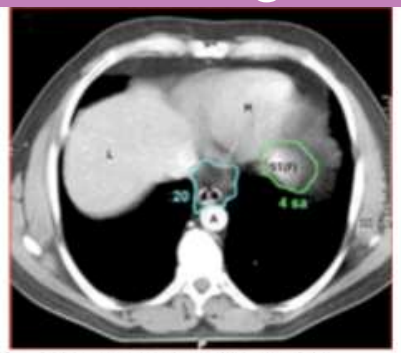

HEY, WALDO-WATCHERS!
SAW SOME TRULY TERRIFIC
SIGHTS TODAY—SOMEONE
BURNING TROUSERS WITH
AN IRON; A LONG THIN MAN
WITH A LONG THIN TIE;
A GLOVE ATTACKING A MAN.
PHEW! INCREDIBLE!
Waldo
WHERE'S
DEPARTMENT
STORE
WALDO?
TO:
WALDO-WATCHERS
OVER THE MOON,
THE WILD WEST,
NOW

CTV DELINEATION: Preoperative Setting

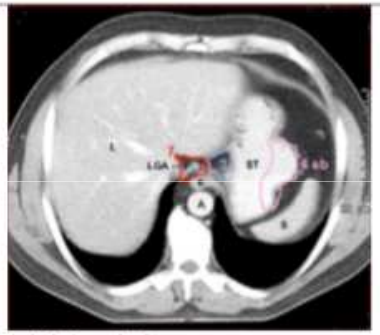




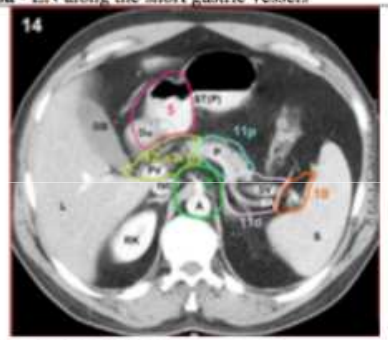
110 - Paraoesophageal LN
111 - Supradiaphragmatic LN



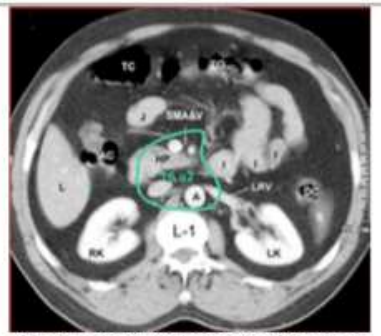
20 - LN in the oesophageal hiatus of the diaphragm
4sa - LN along the short gastric vessels



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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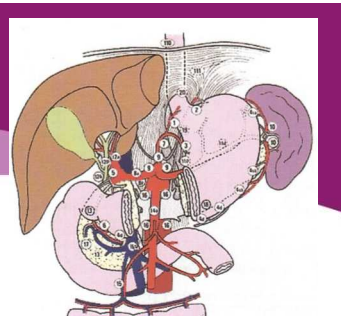
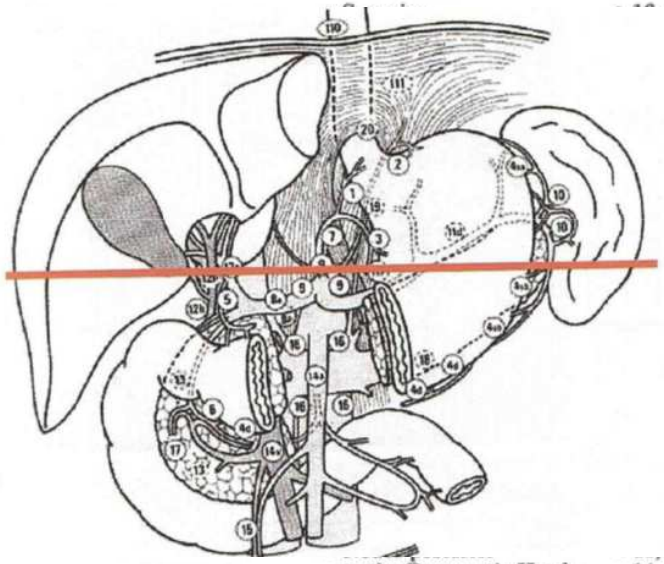
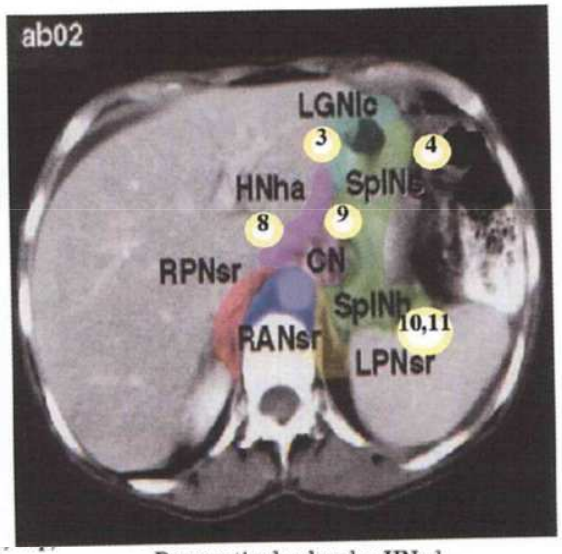
CTV DELINEATION: Preoperative Setting



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





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Cellini *et al.; Rays* -2003

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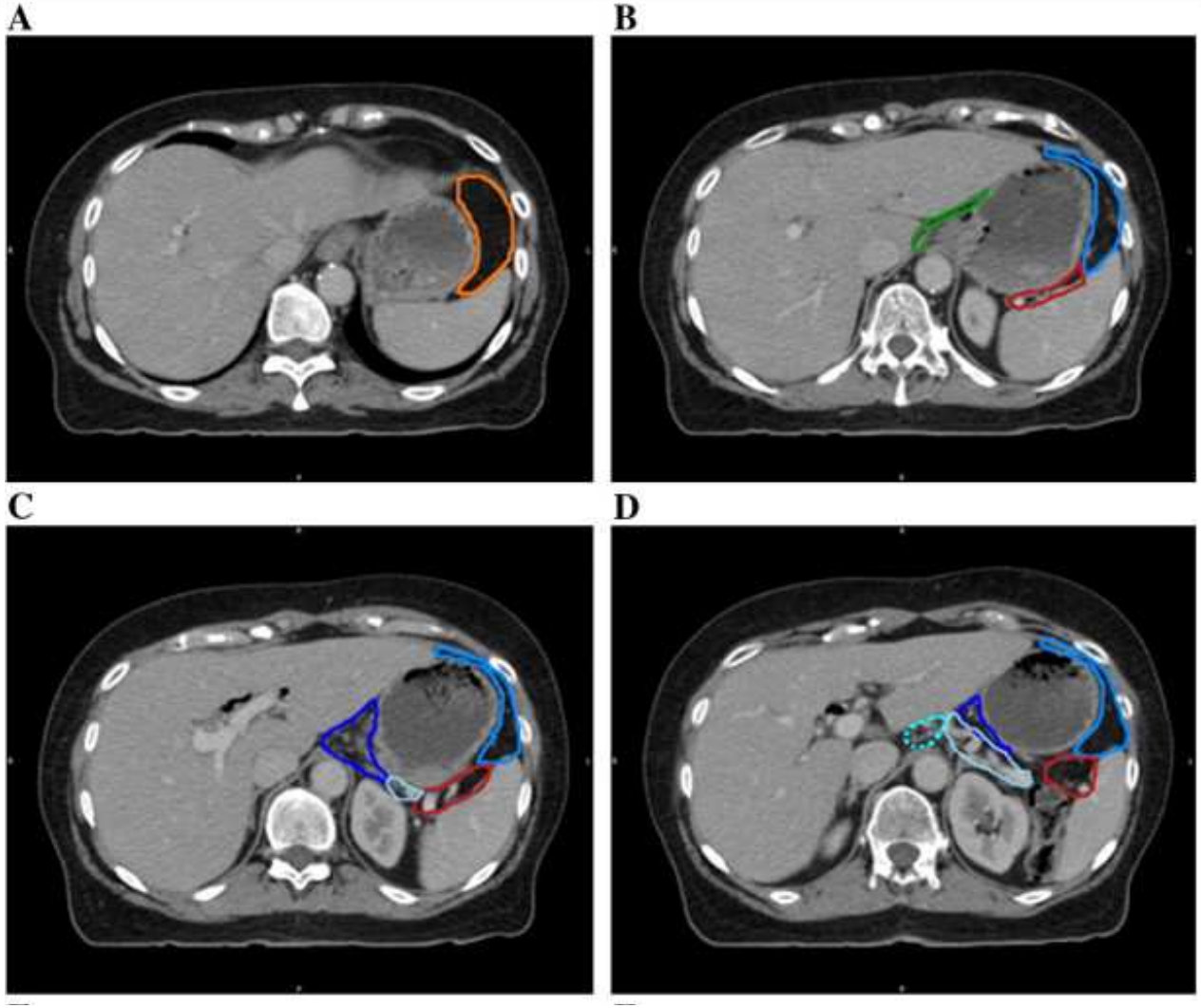
CTV DELINEATION: Preoperative Setting



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Wo *et al.; PRO* - 2013

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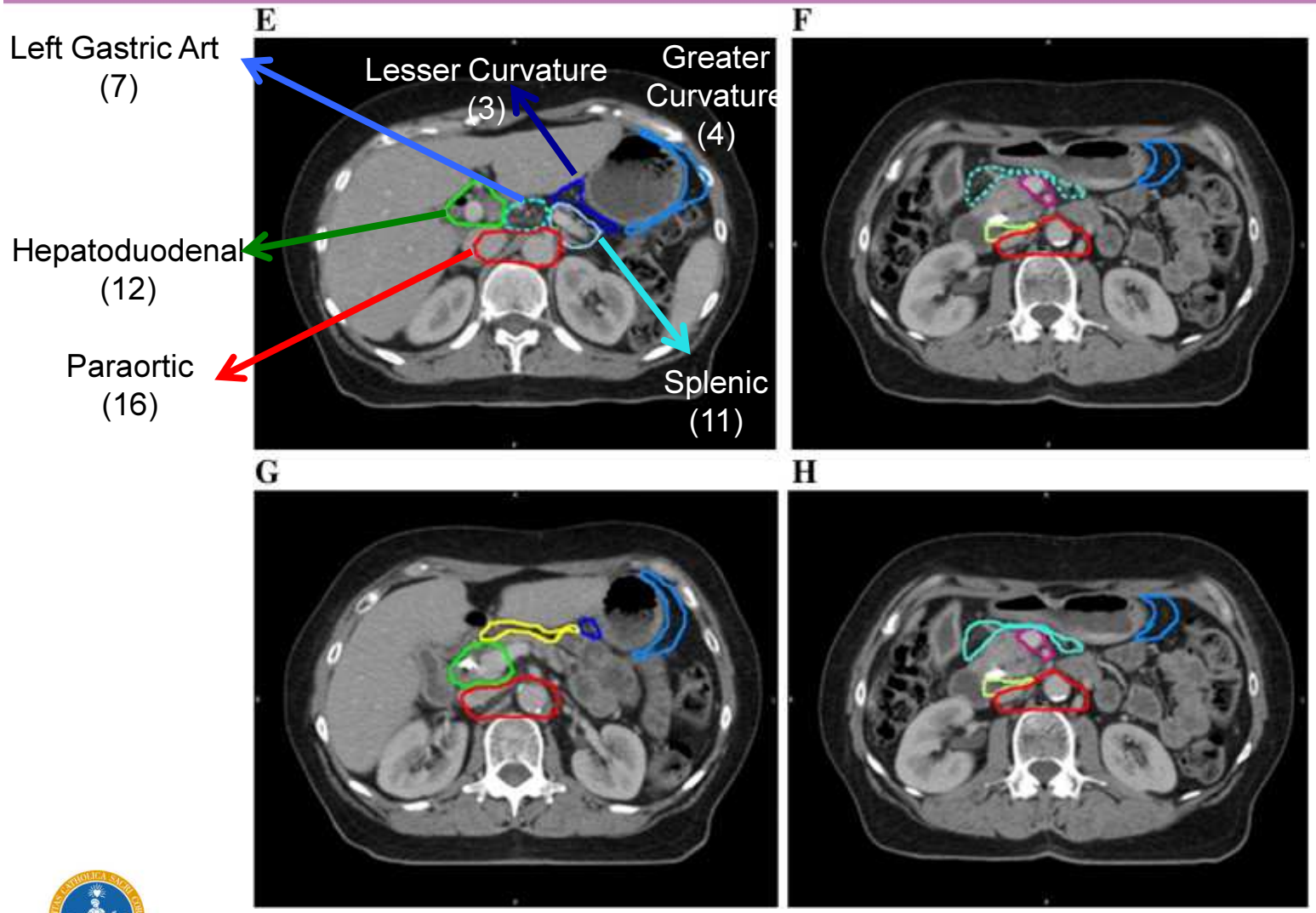

Splenic LN (11)

"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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Wo *et al.; PRO* - 2013

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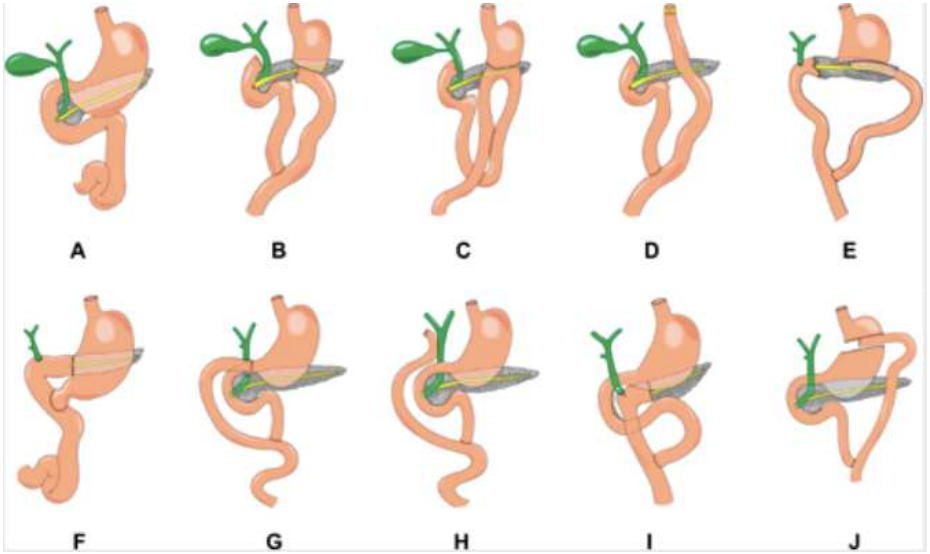
CTV DELINEATION: Postoperative Setting



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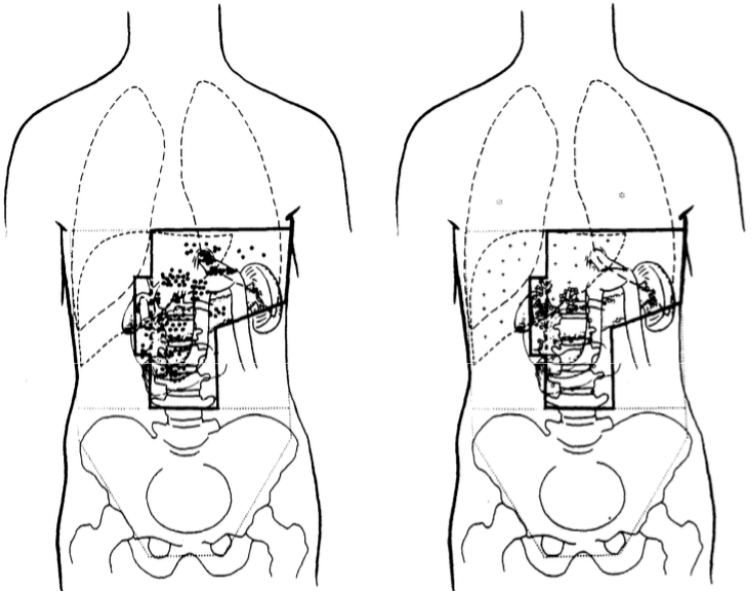
CTV DELINEATION: Postoperative Setting



CTV Definition:

- Post-surgical gastric remnant;
- Gastric bed structure;
- Anastomoses;
- Duodenal stump;
- Primary and Secondary areas of LN drainage;

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Gunderson *et al.; IJROBP* -1981

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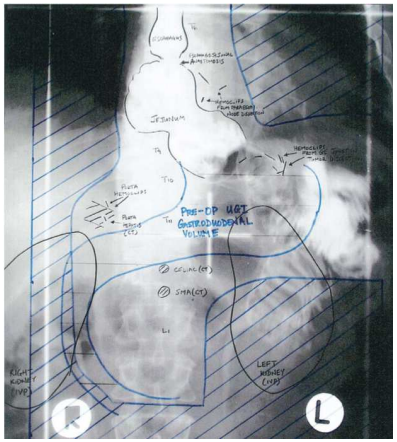
CTV DELINEATION: Postoperative Setting

CTV Definition: Tumor bed and longitudinal surgical margins

GEJ- UP ⅓



UP ⅓ :

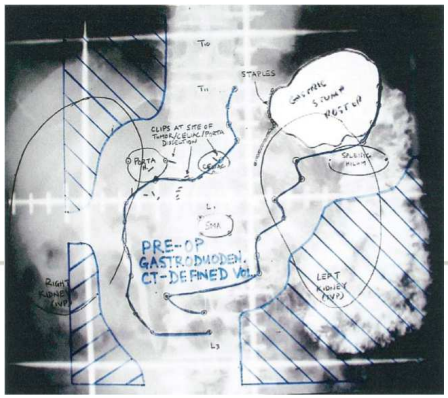
- Paraesophageal;
- Perigastric nodes (if subtotal surg)
- Subpyloric is optional

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



LOW ⅓

- Subpyloric;
- Pancreaticoduodenal;
- Splenic hilar is optional

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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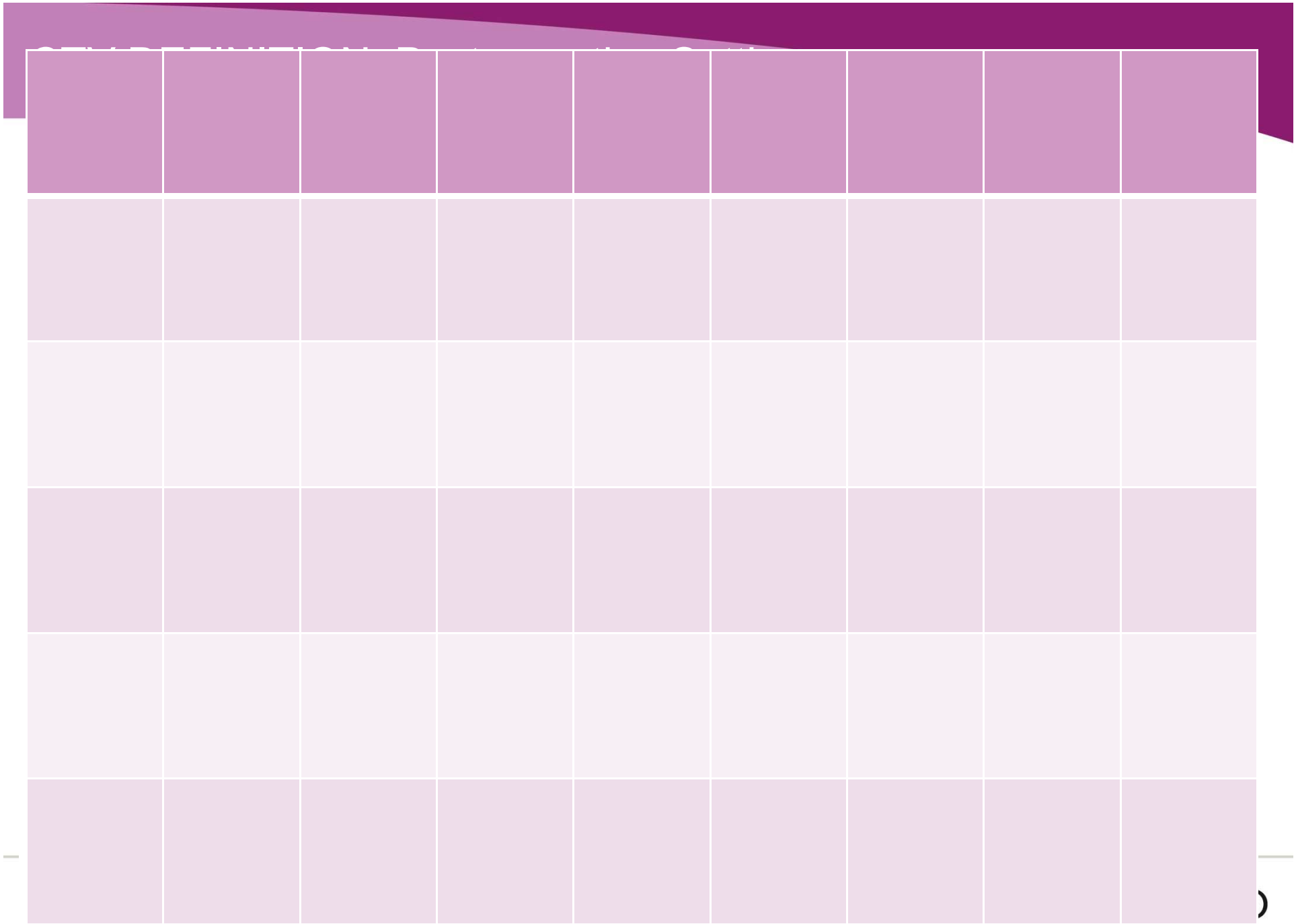
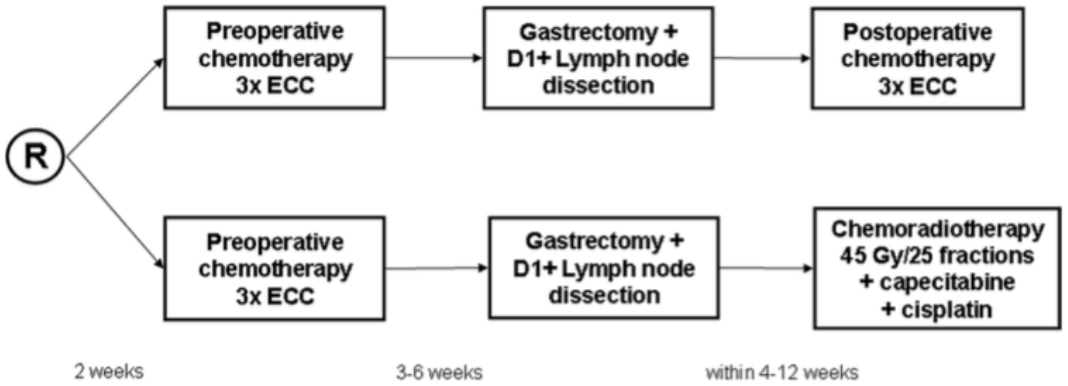


CTV DELINEATION: Postoperative Setting

CTV consists of 3 parts:

1. Anastomoses
2. Gastric Bed/Remnant
3. Lymphnodes



CTV DELINEATION: Postoperative Setting

1. Anastomoses

- duodenal stump has to be treated in tumors of the distal stomach

- for tumors of the proximal stomach or GE- junction, the oesophagojejunal anastomosis has to be treated

- for GE-junction tumors a margin of 4cm of oesophagus (paraoesophageal nodes) has to be included in the CTV

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]**

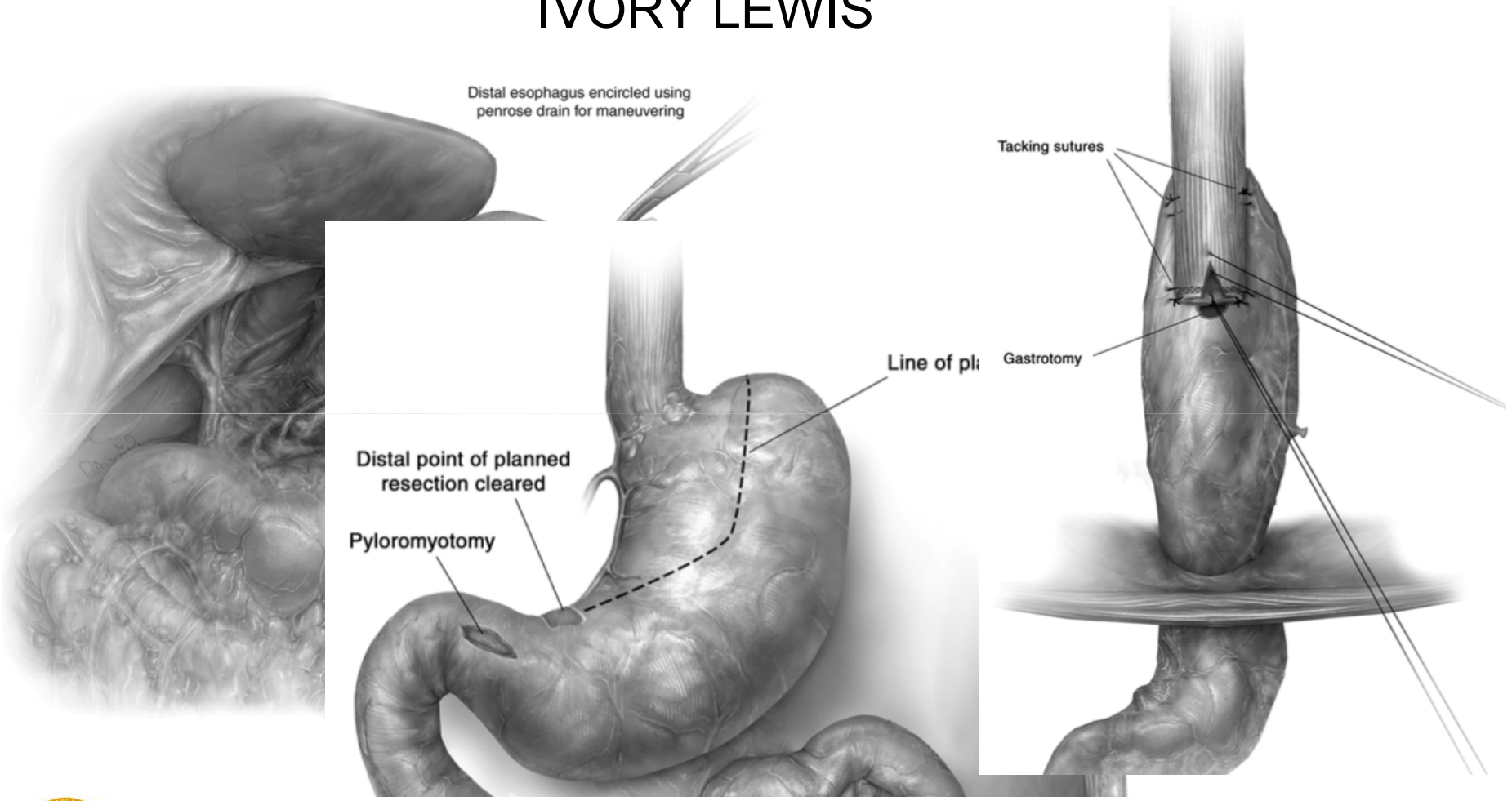
+ all combinations when tumor invaded more than one part of the stomach before start of treatment

- **Corpus/m**eliac (left gastric art ic hilum, suprapancreatic, porta hepatis, pancreaticoduodenal **[Stations 3-13]**

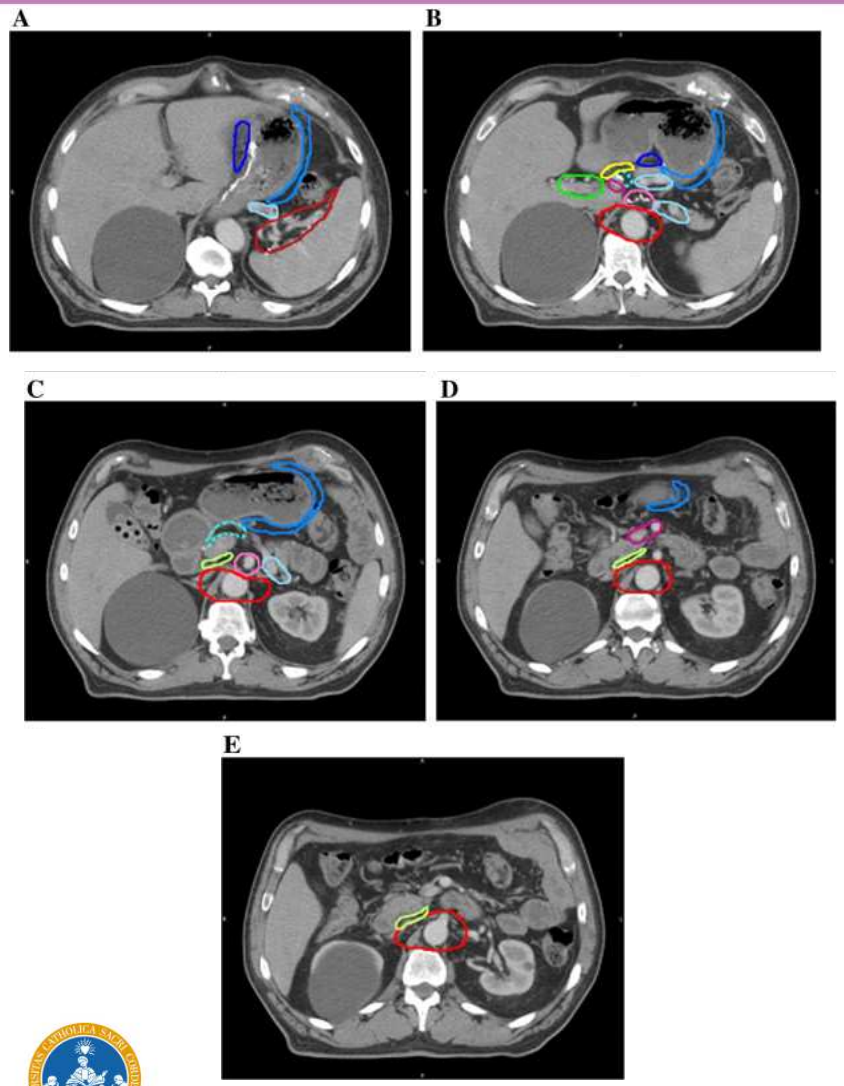
- **Antrum/distal 1/3:** perigastric, suprapyloric, infrapyloric, splenic artery, pancreaticoduodenal, porta hepatis, celiac (left gastric artery, common hepatic artery and celiac axis), suprapancreatic **[Stations 3-9;11-13]**

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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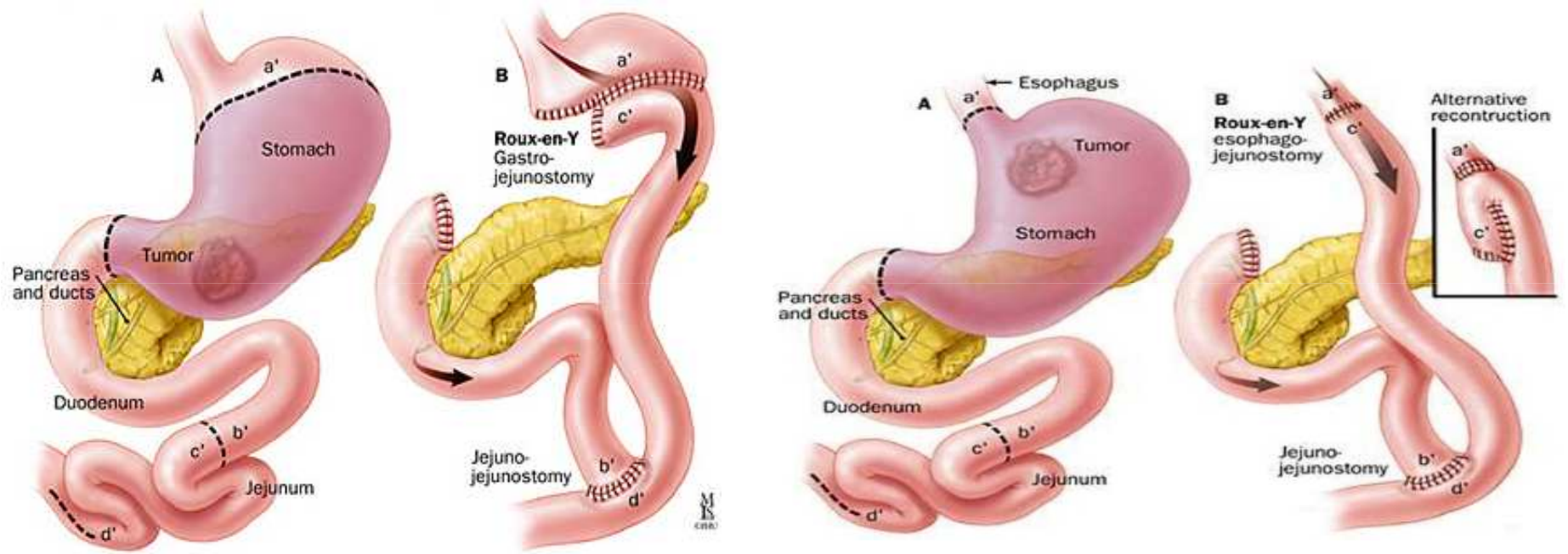
CTV DELINEATION: Postoperative Setting – Surgical Approach

Roux-En-Y



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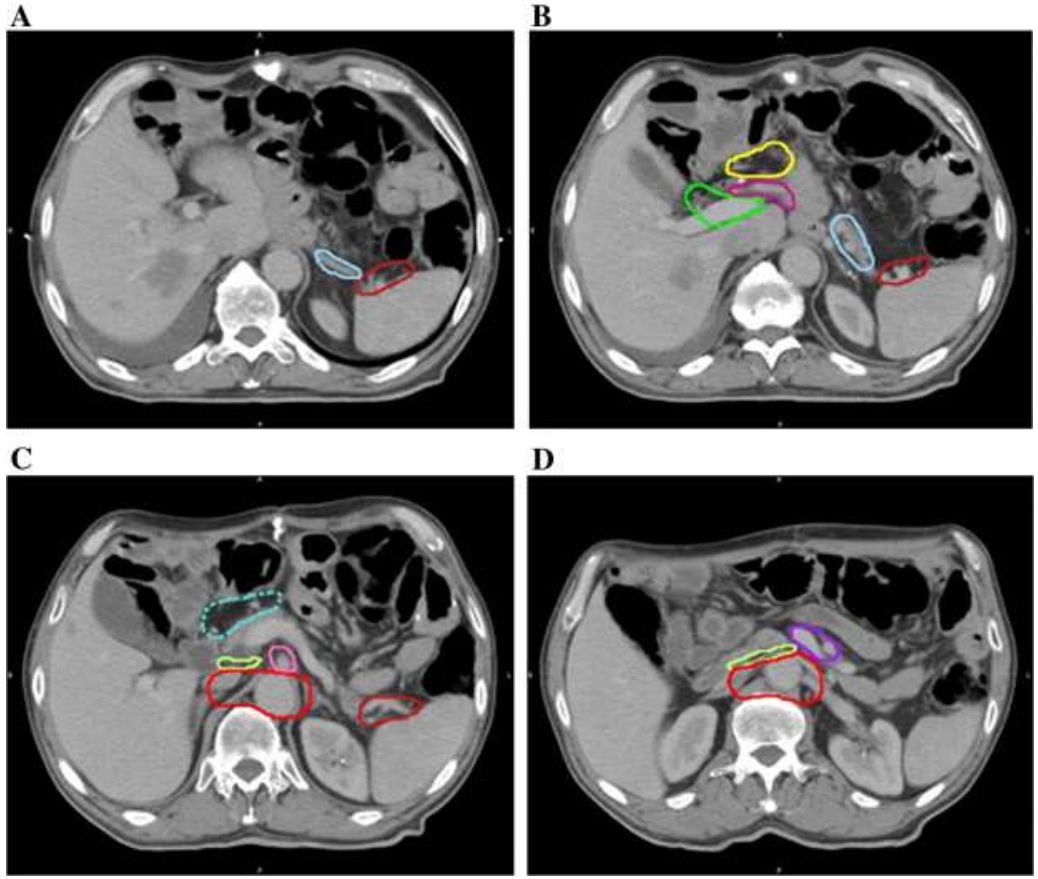
CTV DELINEATION: Postoperative Setting – Surgical Approach

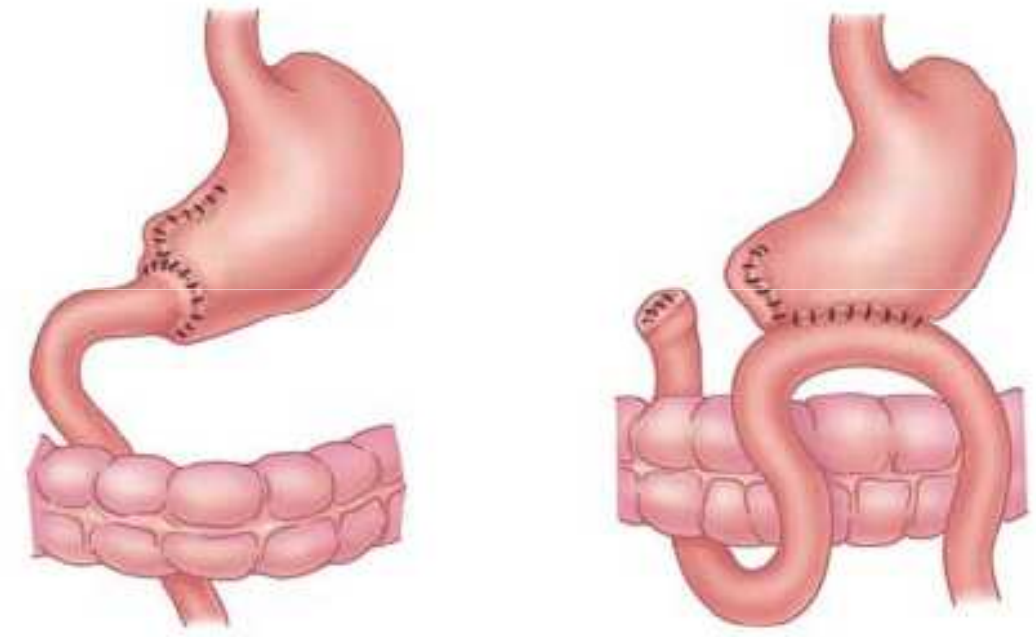


Roux-En-Y

- 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



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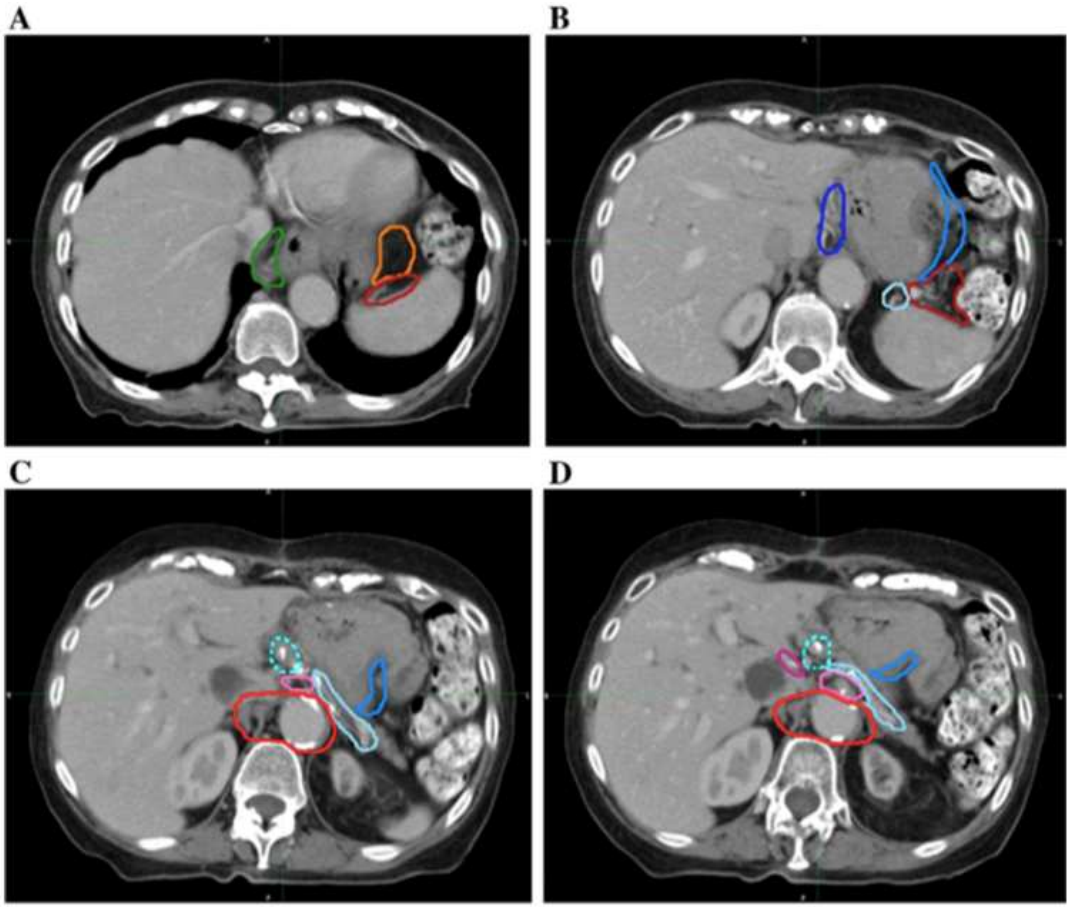
CTV DELINEATION: Postoperative Setting – Surgical Approach



Subtotal Gastrectomy

- Paracardial and portions of the lesser and greater nodes not dissected
- Infrapyloric and suprapyloric ideally removed

CTV DELINEATION: Guidelines

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

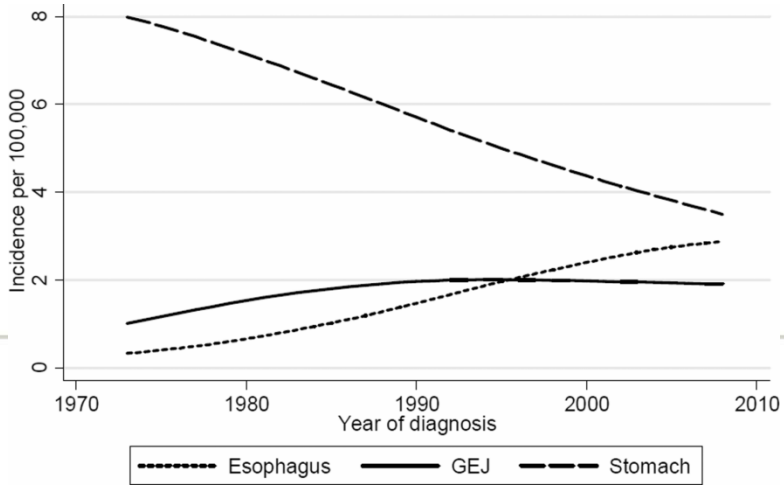
Marcel Verheij MD PhD
Department of Radiation Oncology
NKI, Amsterdam

Contents

- Introduction
- Current evidence-based treatment strategies
- Radiotherapy: OAR, dose-constraints and delivery techniques

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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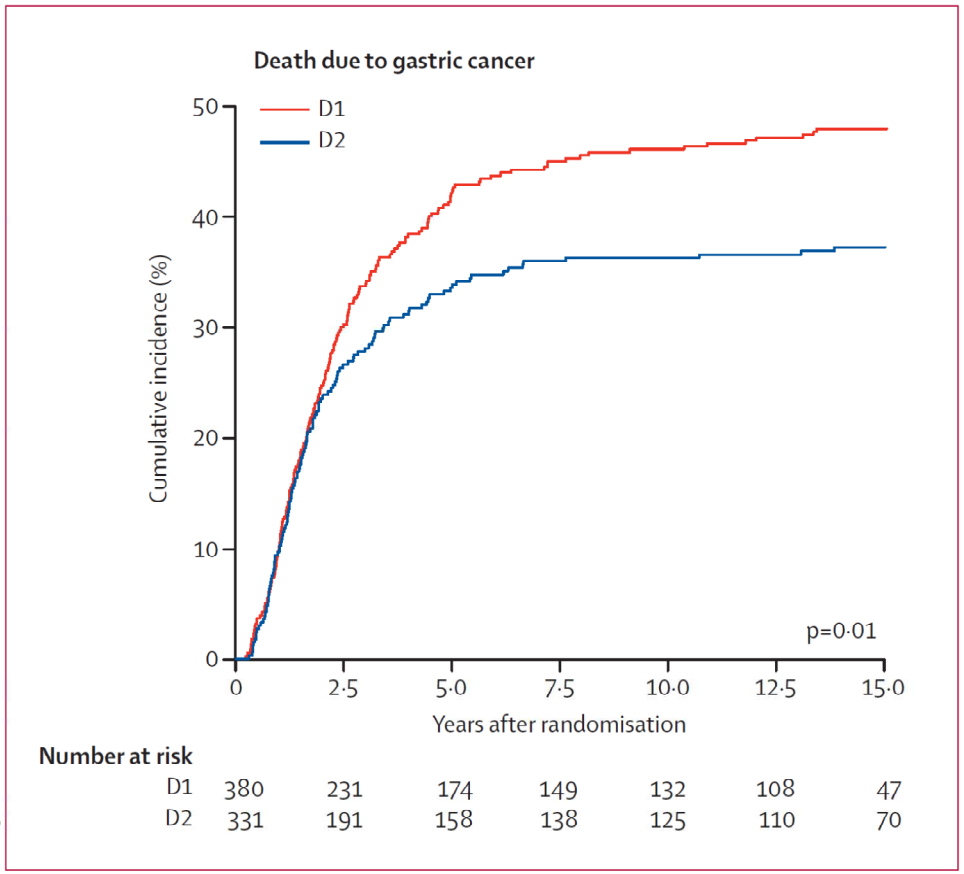
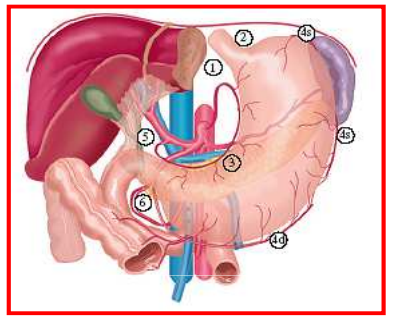
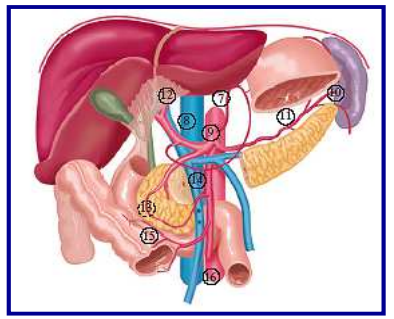
Surgical treatment of gastric cancer

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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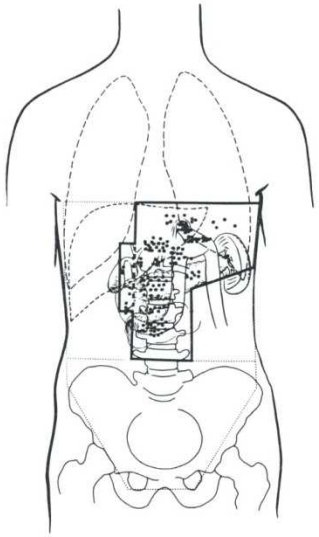
High locoregional failure rates after curative resection

Recurrences	Mean	Range
Locoregional - only	54%	(29-72%)
Locoregional - total	88%	(38-94%)
Distant - only	25%	(18-35%)



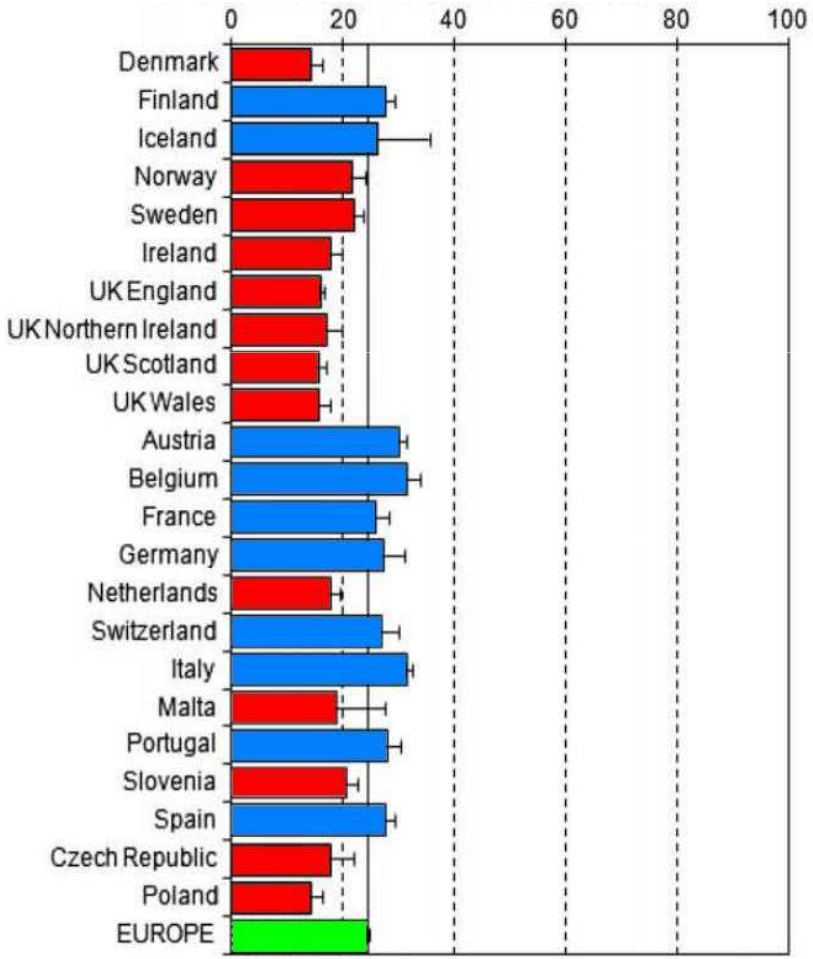
Gunderson et al. 1982; Smalley et al. IJROBP 2002; Lim et al. Br J Cancer 2004

ESTRO School

Survival of gastric cancer patients in Europe

Age-standardized 5-year relative survival (%)

1995–1999: EUROCARE-4



Sant et al. Eur J Cancer 2009

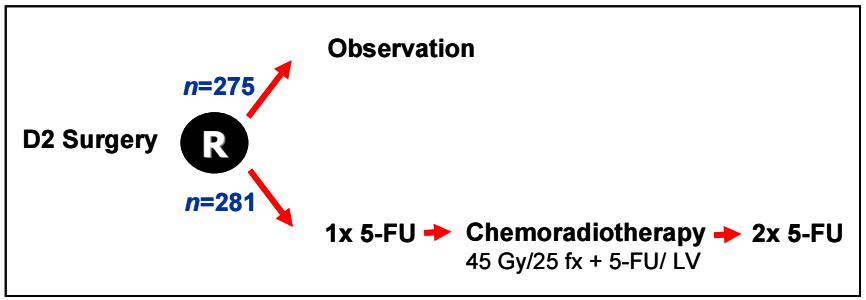
1999–2007: EUROCARE-5

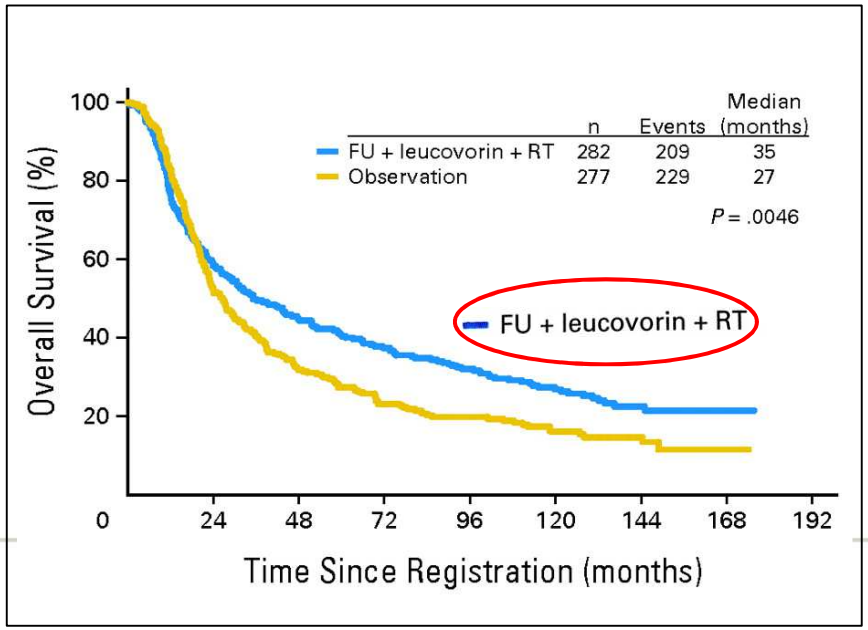
	Stomach cancer
European mean	25·1 (24·8–25·4)
Central Europe	28·1 (27·6–28·5)
Austria	31·0 (29·9–32·2)
Belgium*	30·5 (29·1–32·0)
France*	26·3 (24·9–27·6)
Germany*	31·3 (30·6–32·0)
Switzerland*	31·6 (29·2–34·1)
Netherlands	20·4 (19·7–21·2)

De Angelis et al. Lancet Oncol 2014

Evidence-based (neo-)adjuvant strategies (1)

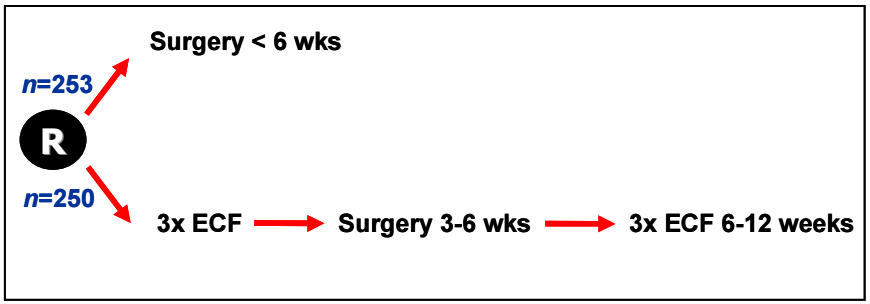
SWOG-Intergroup 0116 Trial

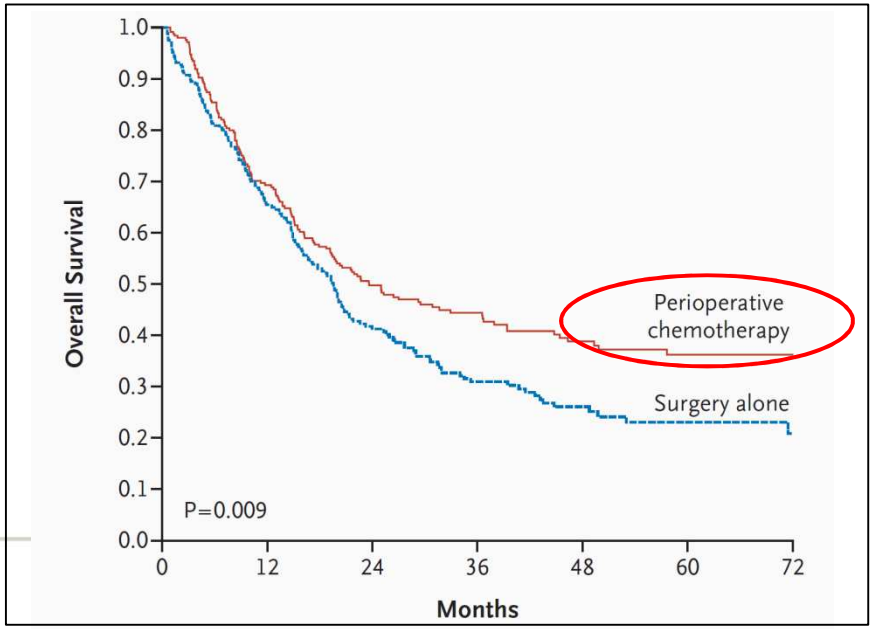




Macdonald et al. NEJM 2001; Smalley et al. JCO 2012

MAGIC Trial

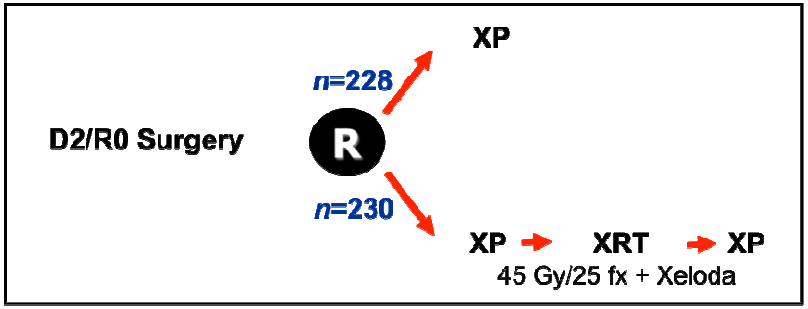


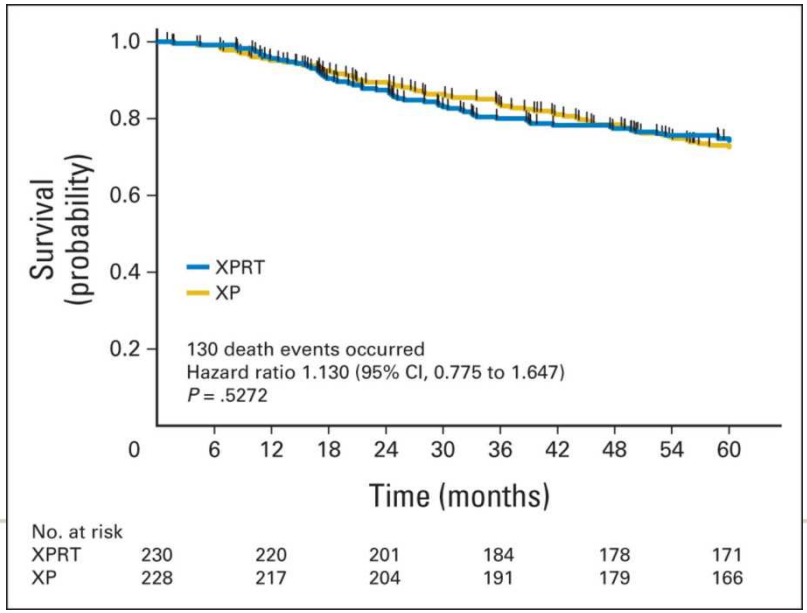


Cunningham et al. NEJM 2006

Evidence-based (neo-)adjuvant strategies (2)

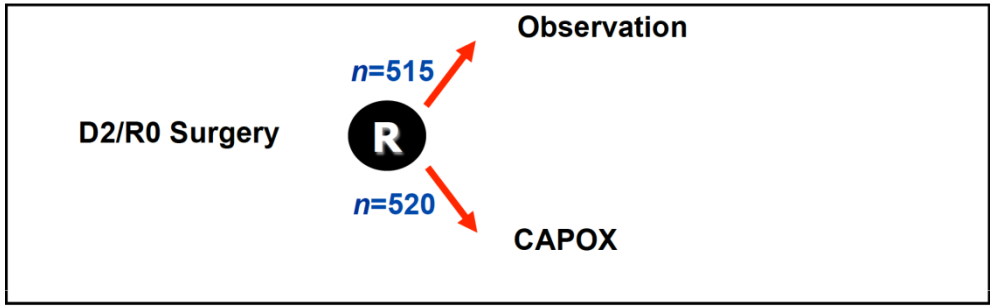
ARTIST Trial

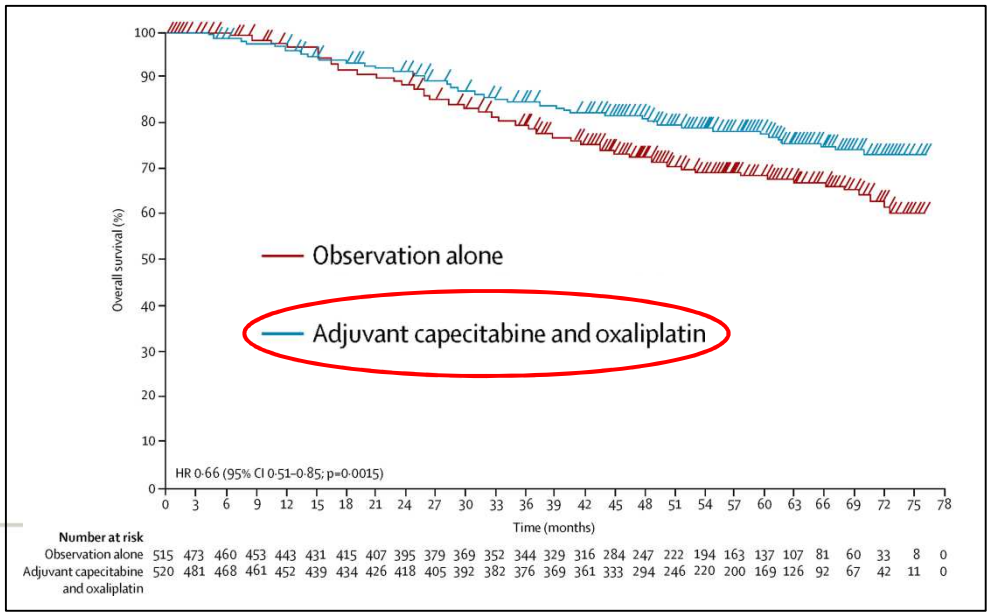




Lee et al. J Clin Oncol 2012; Park et al. J Clin Oncol 2015

CLASSIC Trial





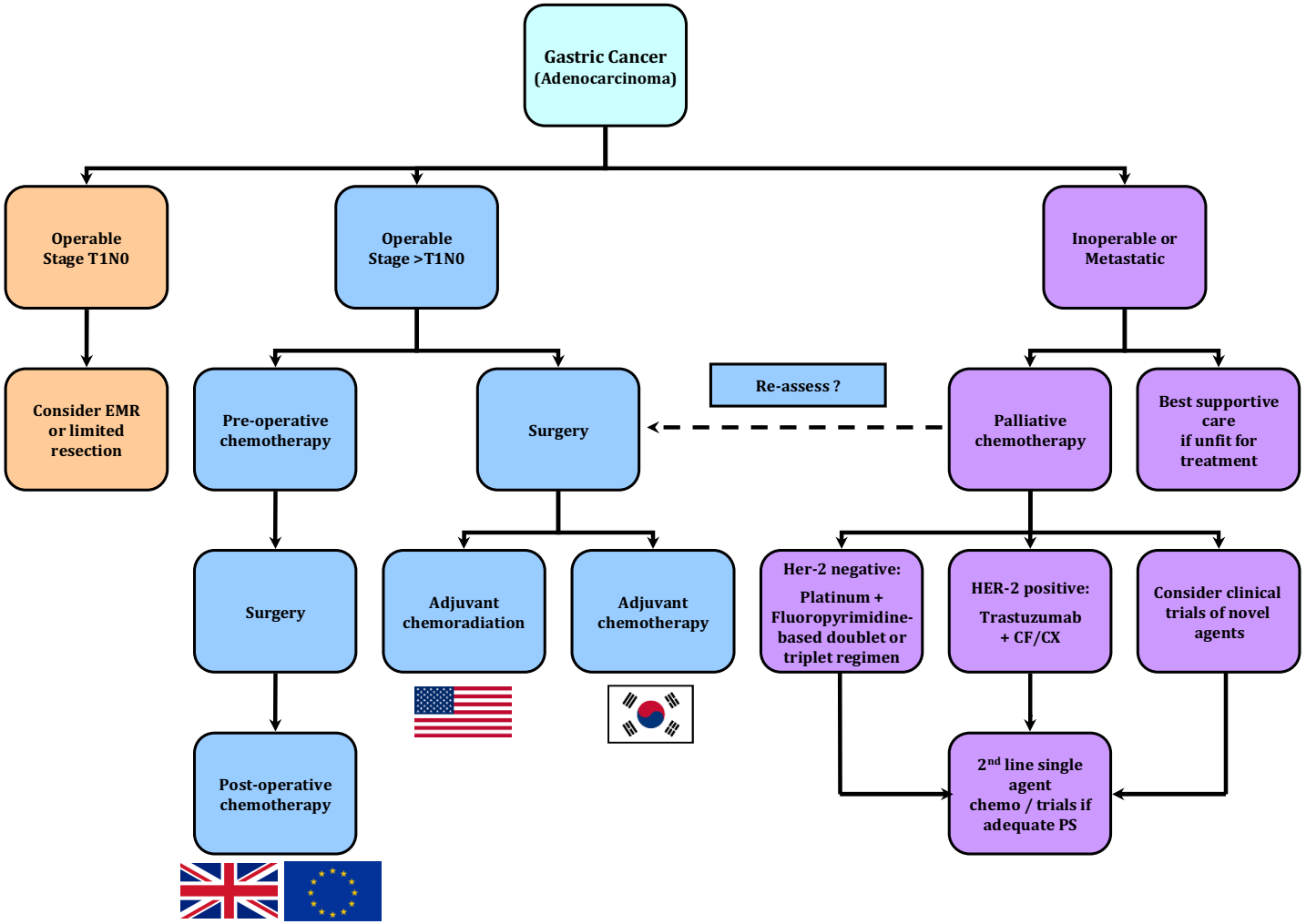
Bang et al. Lancet 2012; Noh et al. Lancet Oncol 2014

clinical practice guidelines

Ann Oncol 2013, Radiother Oncol 2014, Eur J Surg Oncol 2014

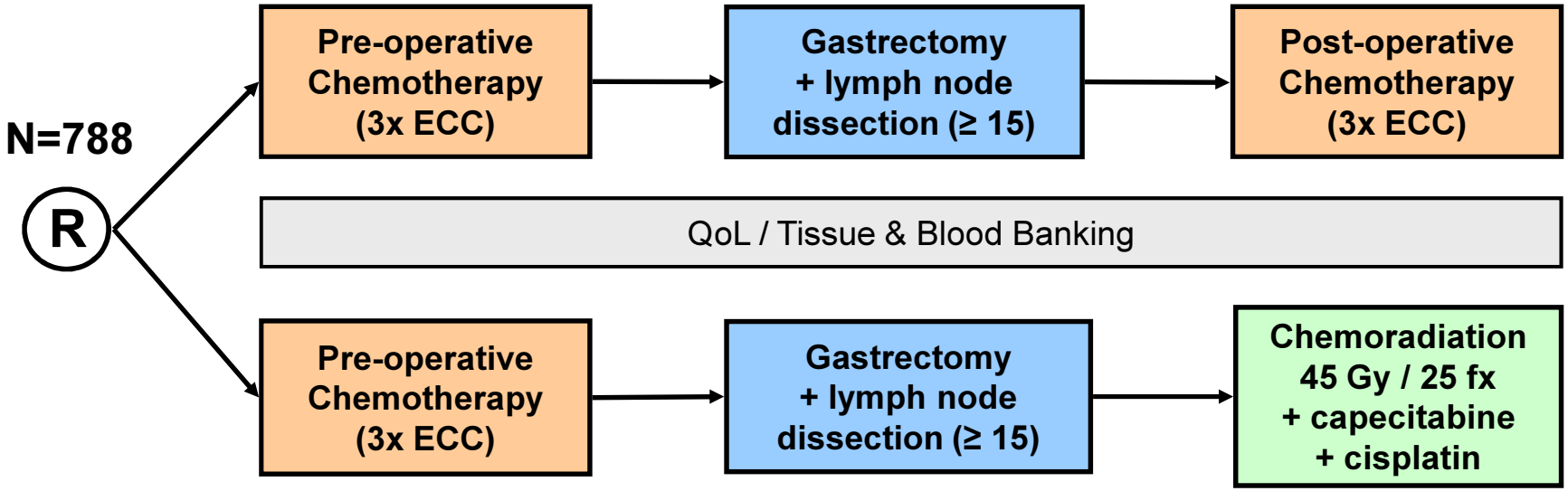
Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

T. Waddell[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6*]



CRITICS trial

- Study design -



www.CRITICS.nl; Dikken et al. BMC Cancer 2011

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Summary (1)

- *Gastric cancer has a poor outcome*

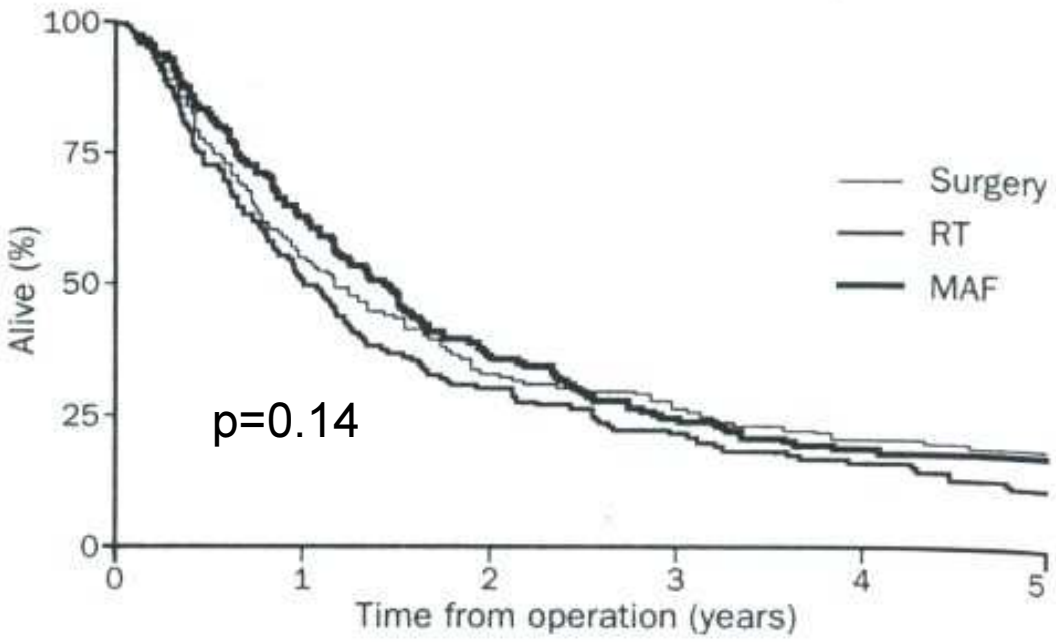
- *Despite adequate surgery (D2; ≥15 ln), local-regional recurrence rates remain high*

- *Evidence-based strategies to improve surgical results are:*

  - *post-operative chemoradiation (SWOG/US)*
  - *peri-operative chemotherapy (MAGIC/EU)*
  - *adjuvant chemotherapy (ARTIST, CLASSIC/Asia)*

- *CRITICS compares peri-operative chemotherapy with pre-operative chemotherapy and post-operative chemoradiation after adequate surgery*

Post-operative radiotherapy: British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer



No survival benefit

Treatment	No at risk					
S	145	81	49	40	31	29
RT	153	79	47	34	26	18
MAF	138	88	50	35	27	26

Hallissey et al, Lancet 1994

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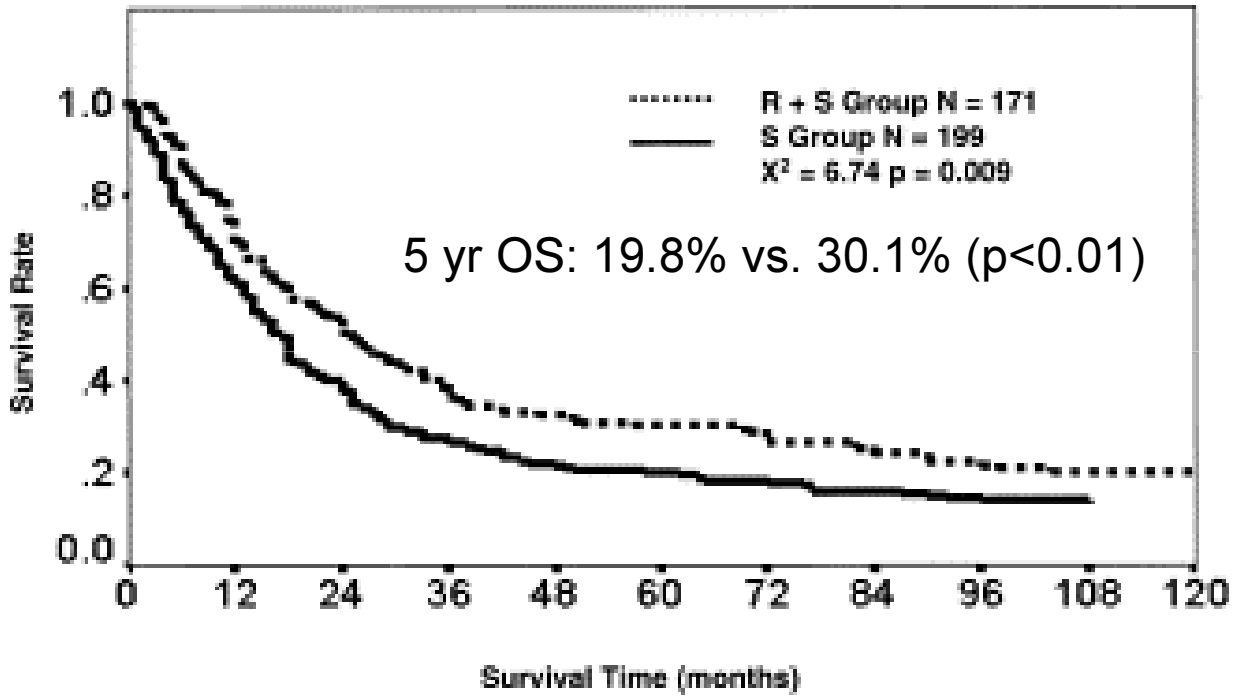
Pre-operative Radiotherapy

40 Gy + surgery vs. surgery alone (n=370)



Zhang et al. IJROBP 1998

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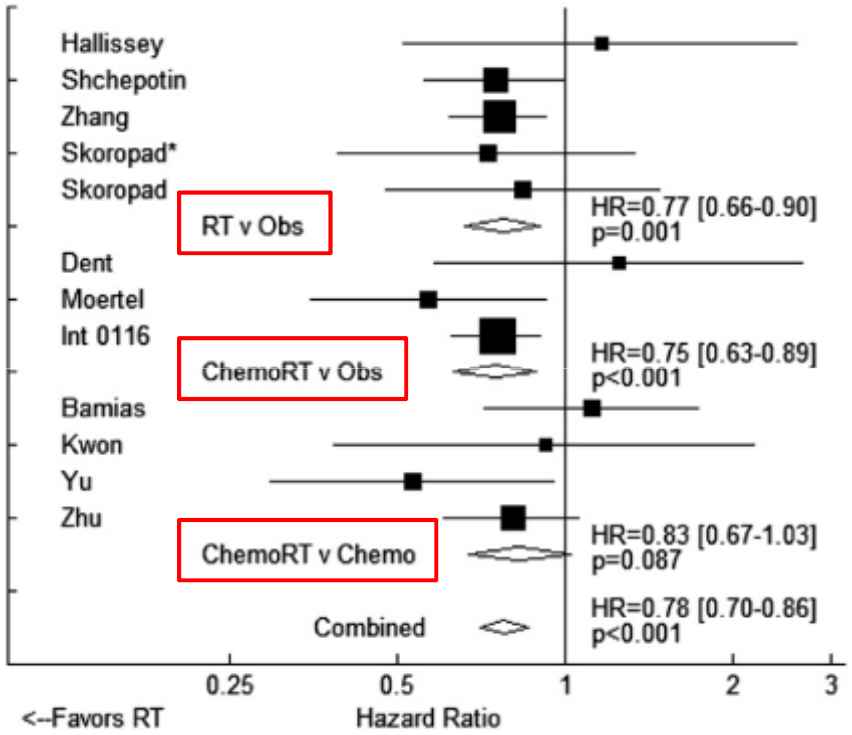
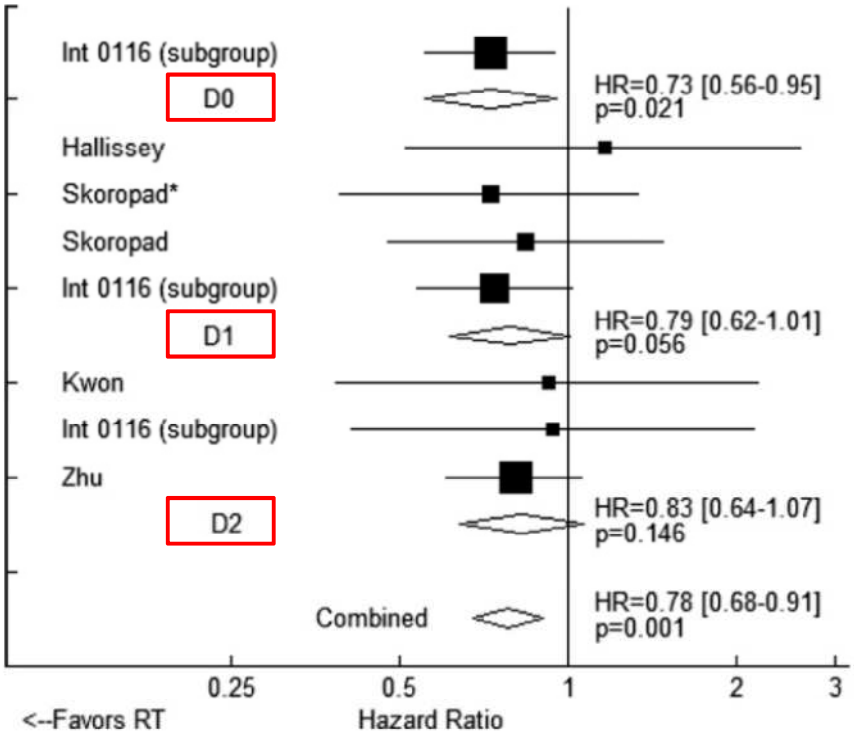
Who benefit from adjuvant (chemo-)radiation for gastric cancer? A meta-analysis (n=2811)





Ohri et al. IJROBP 2013

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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:

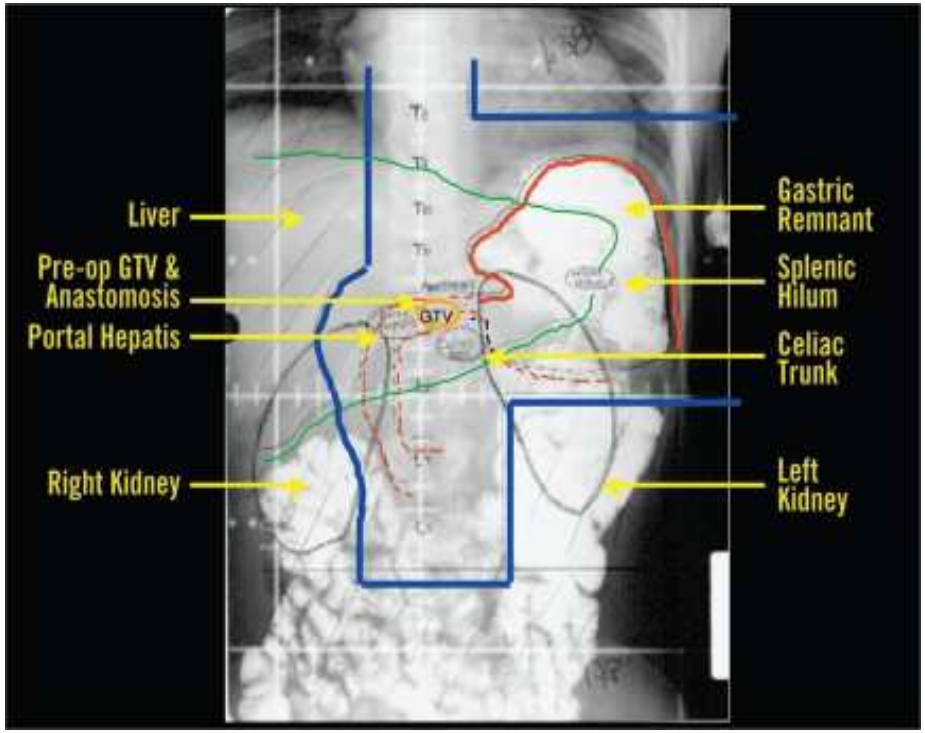
- 34% had major radiation treatment plan deviation
- outdated radiation techniques; no data on late toxicity (kidney)

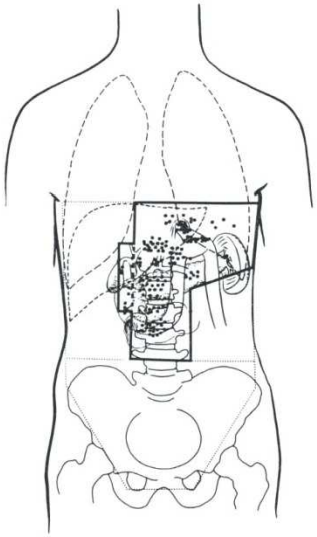
Suboptimal chemotherapy:

- according to present standard, chemotherapy was suboptimal and the interaction with radiation limited

Radiotherapy-technique according to the SWOG protocol (2001)

2D AP-PA





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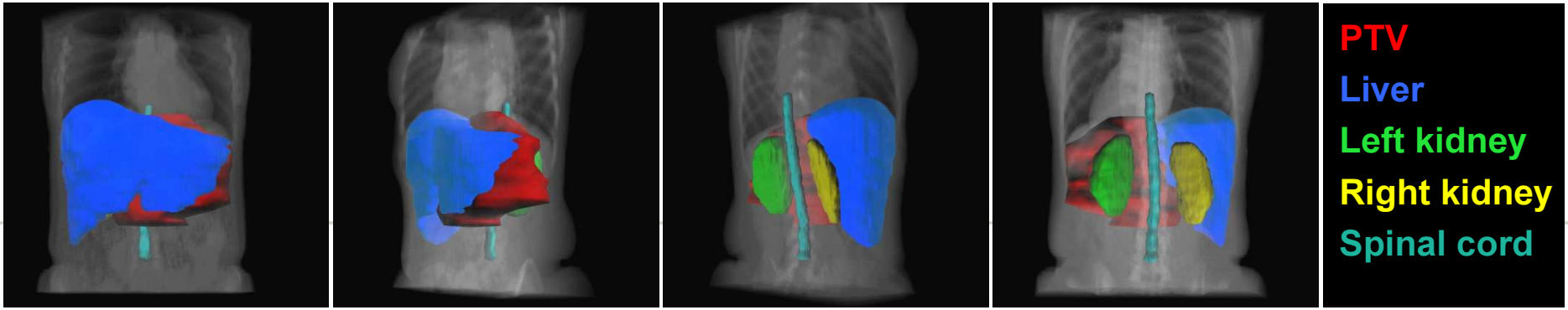
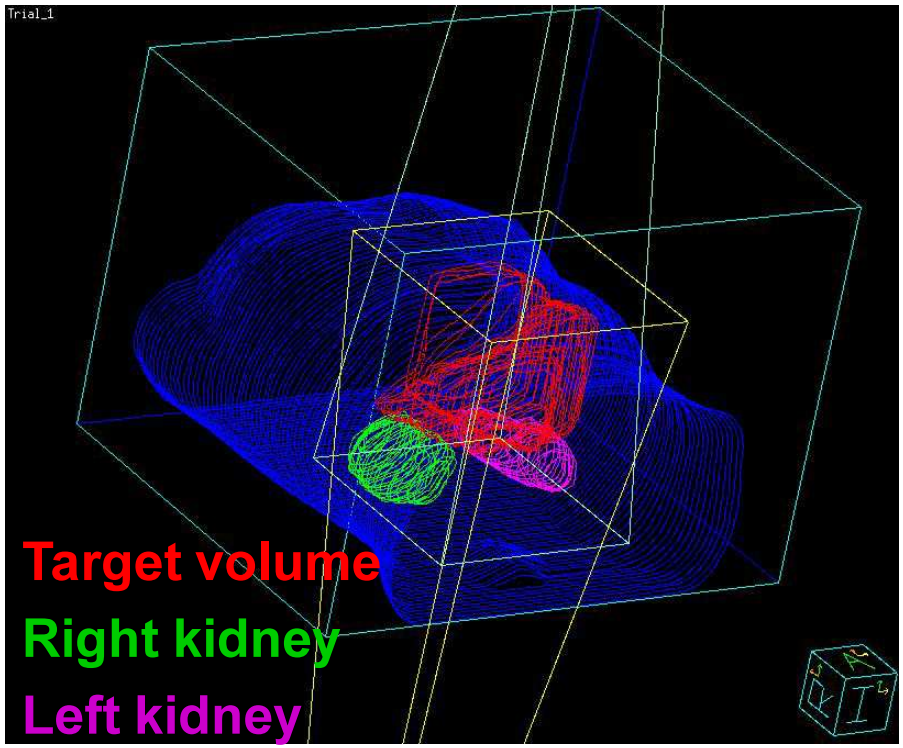
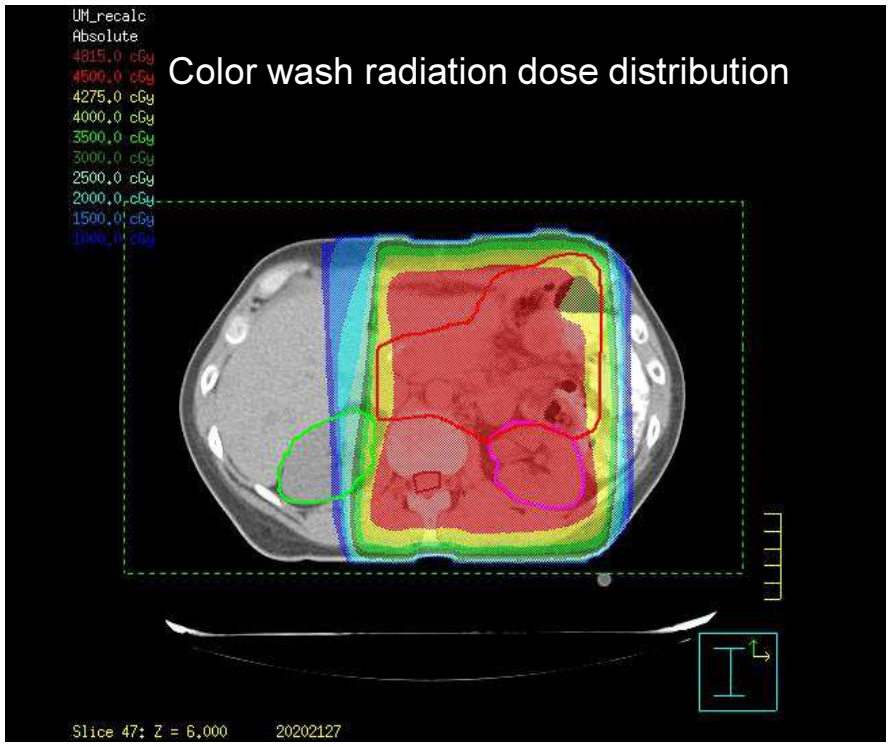
Critical structures and dose constraints

- 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

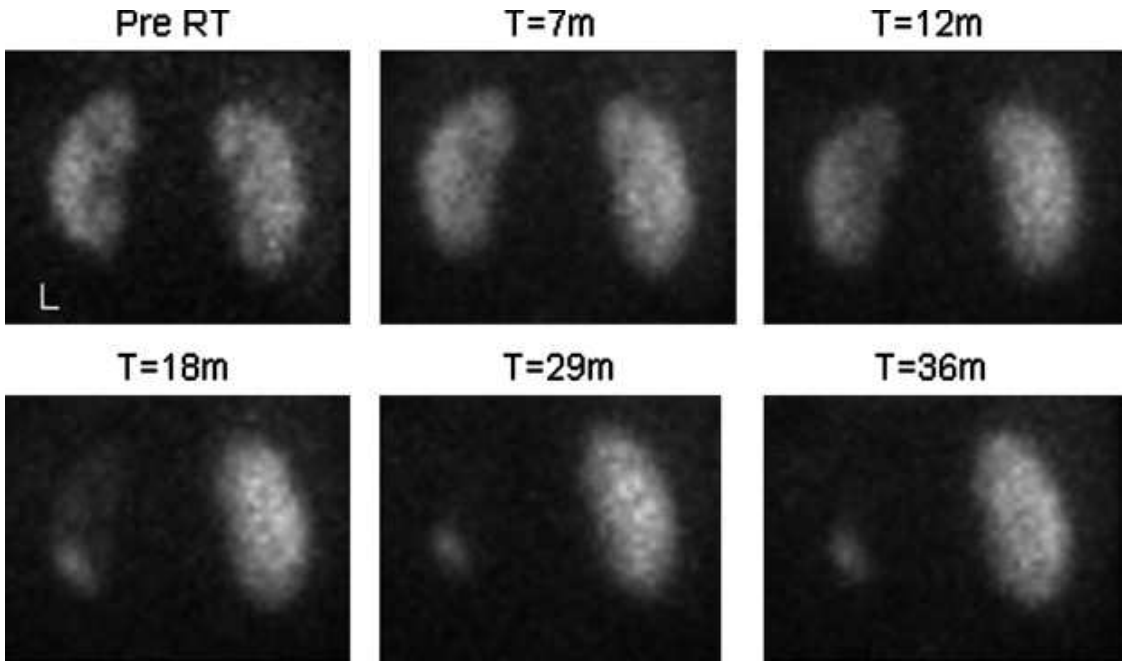


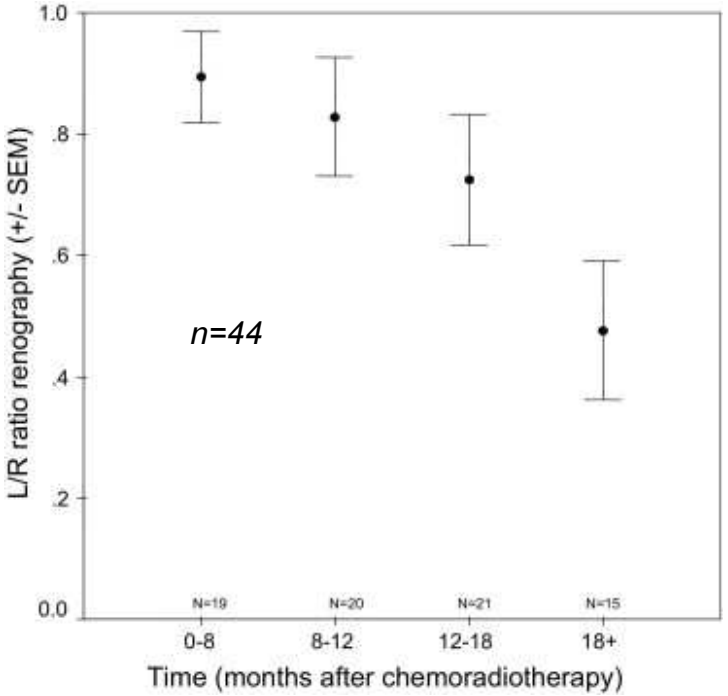


Jansen et al. IJROBP 2007

ESTRO School

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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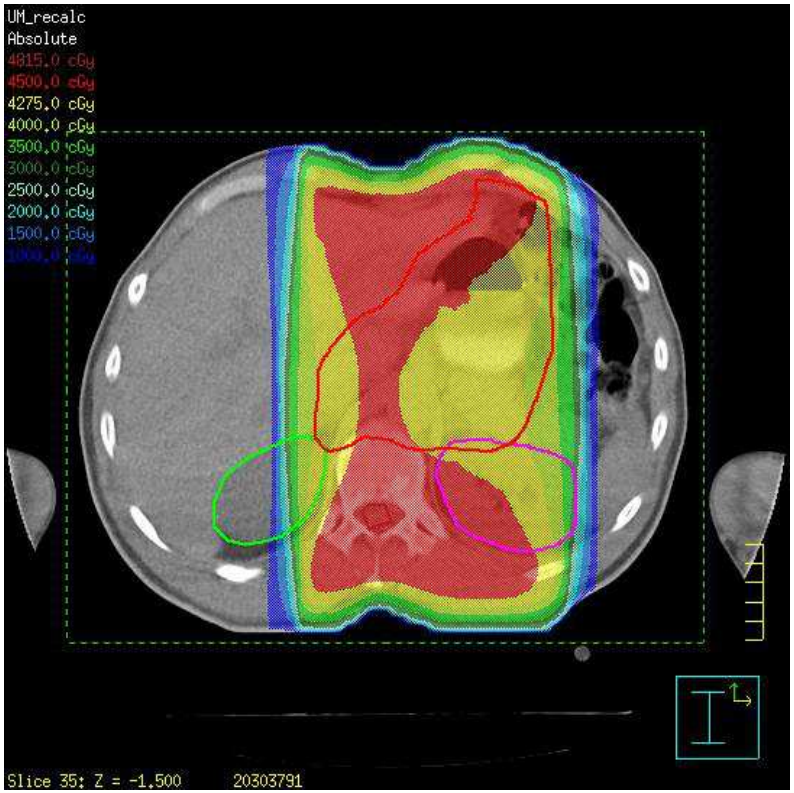
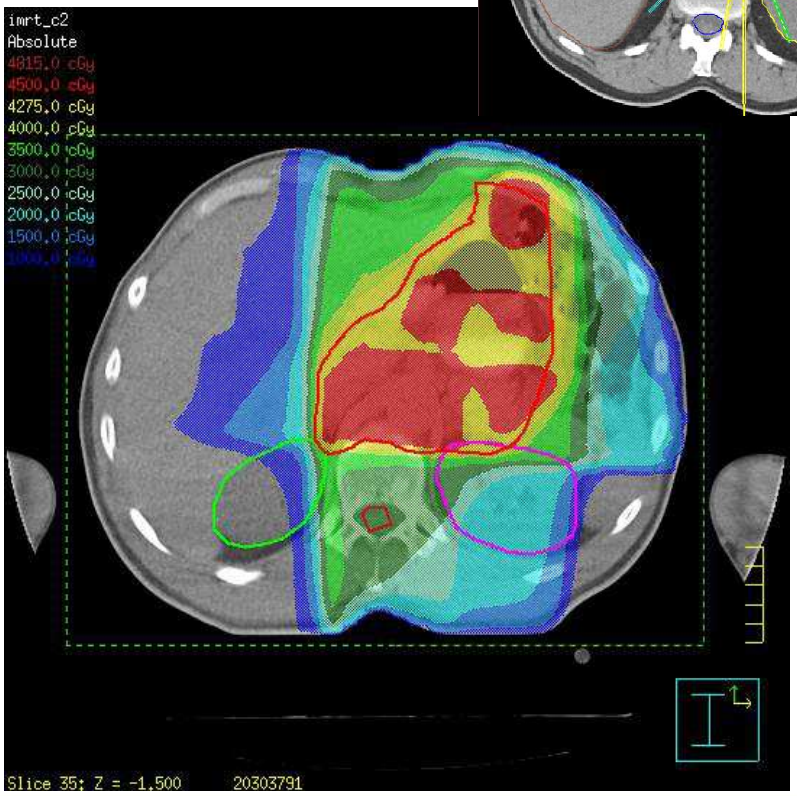
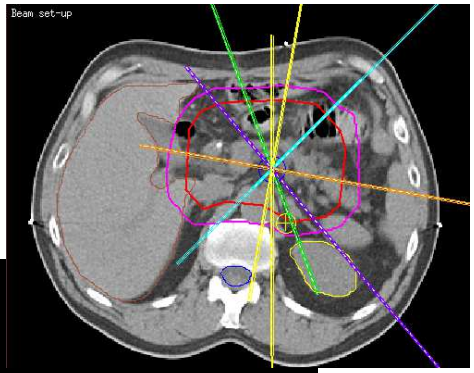
Advanced radiation techniques reduce the dose to both kidneys







Conventional AP-PA

IMRT

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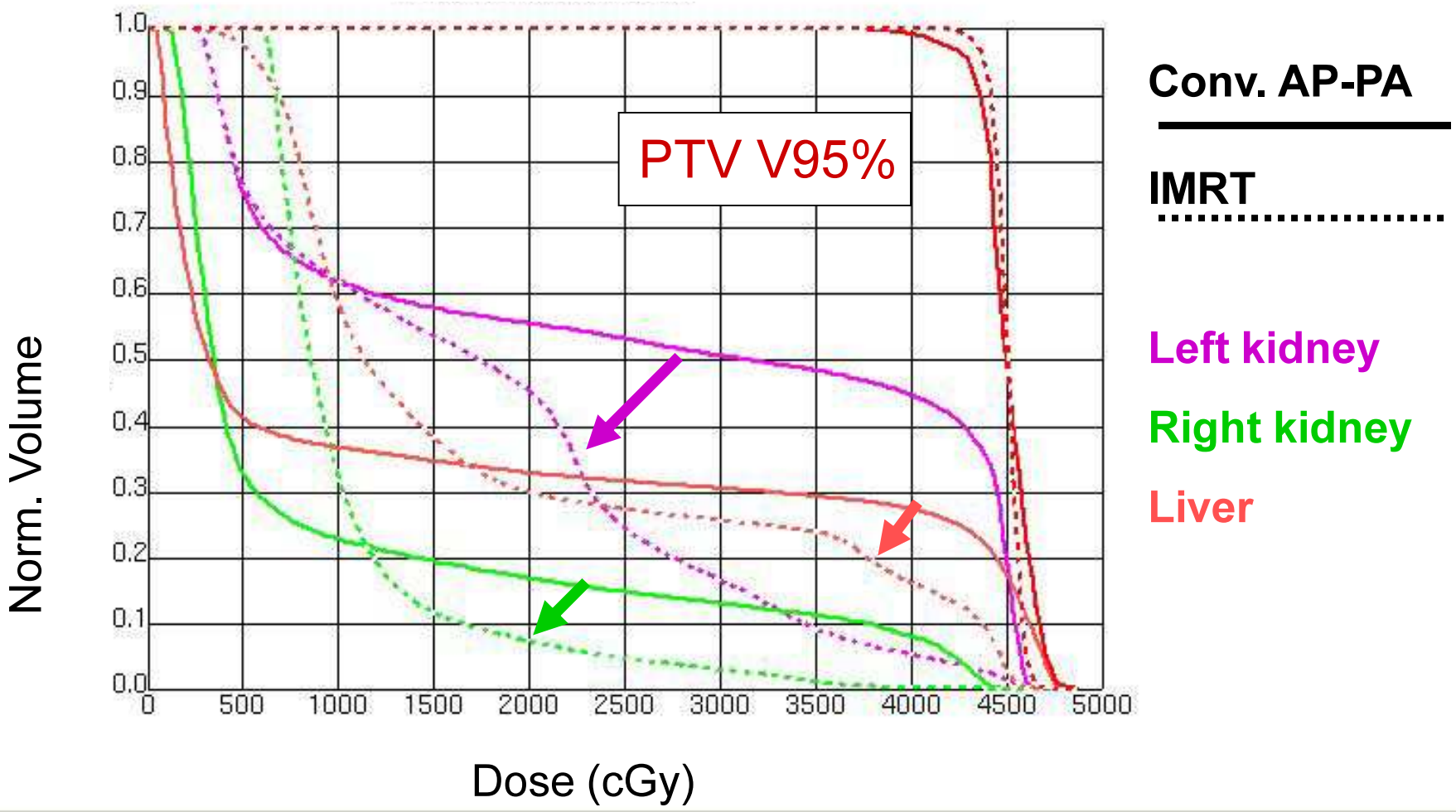
Advanced radiation techniques reduce the dose to both kidneys



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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 %

ESTRO School

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ESTRO School

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Right kidney V20Gy (± SD)	17 ± 11 %	9 ± 5 %
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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PTV V95% (± SD)	95 ± 3	98 ± 2

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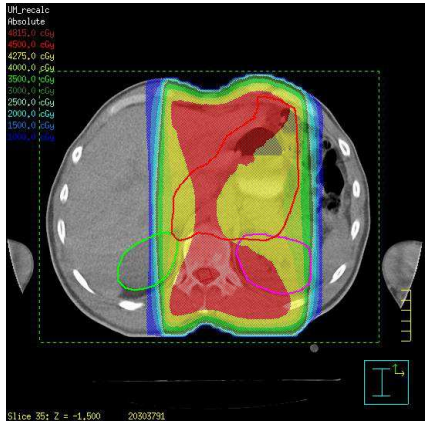
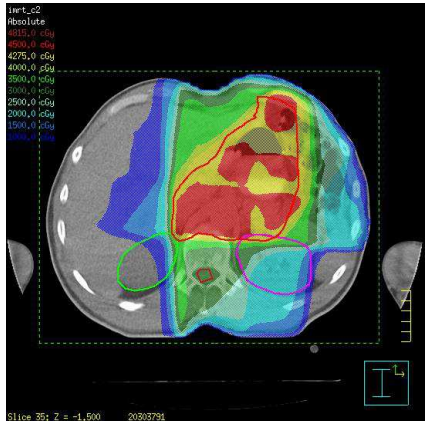
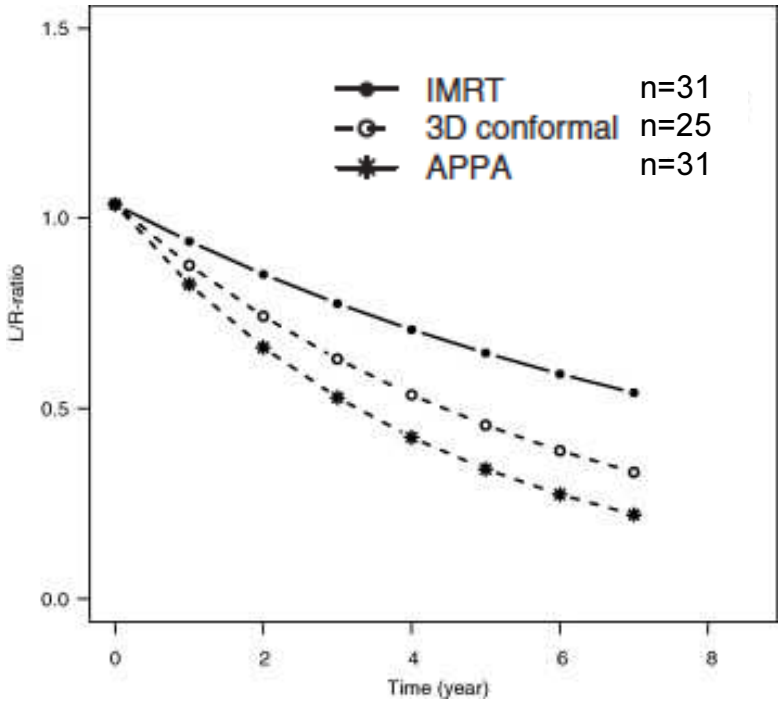
IMRT limits nephrotoxicity after chemoradiotherapy for gastric cancer



AP-PA



IMRT



Trip et al. Radiother Oncol 2014

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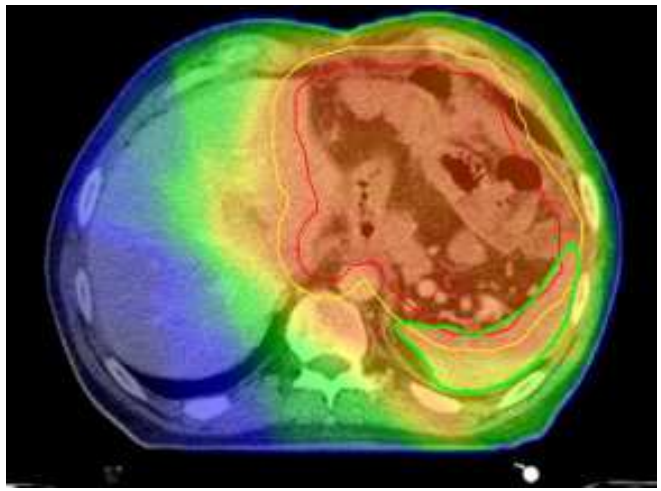
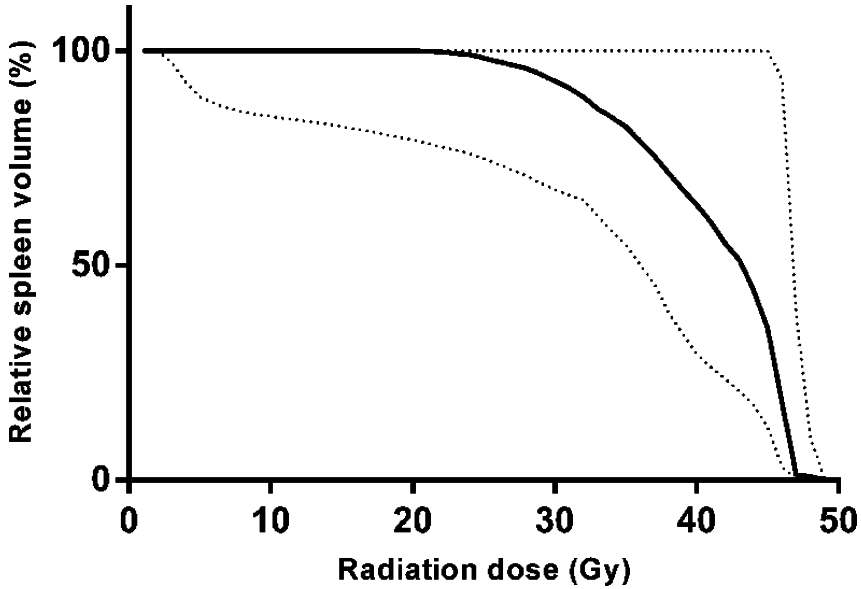
Late splenic toxicity following postoperative chemoradiotherapy in gastric cancer





Trip et al. Radiother Oncol 2015

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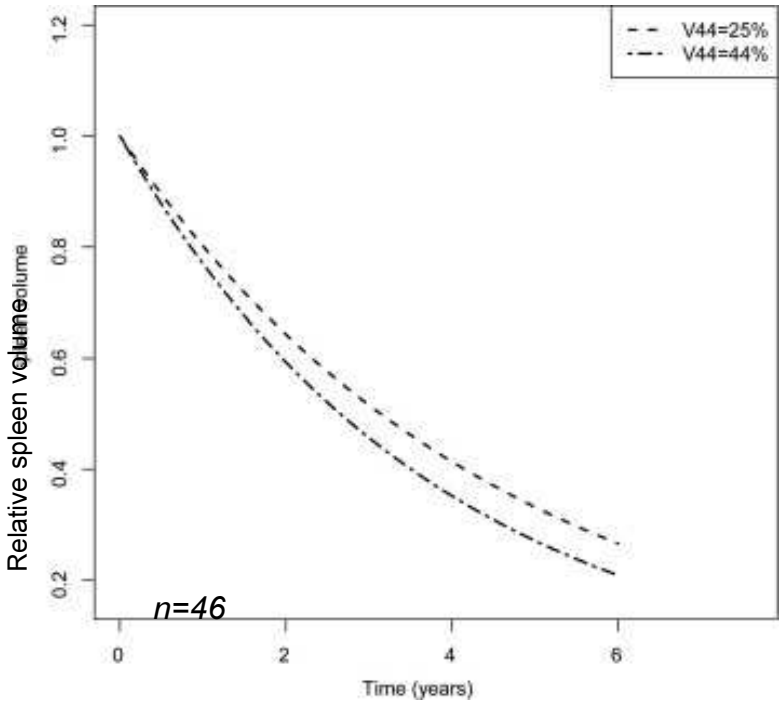

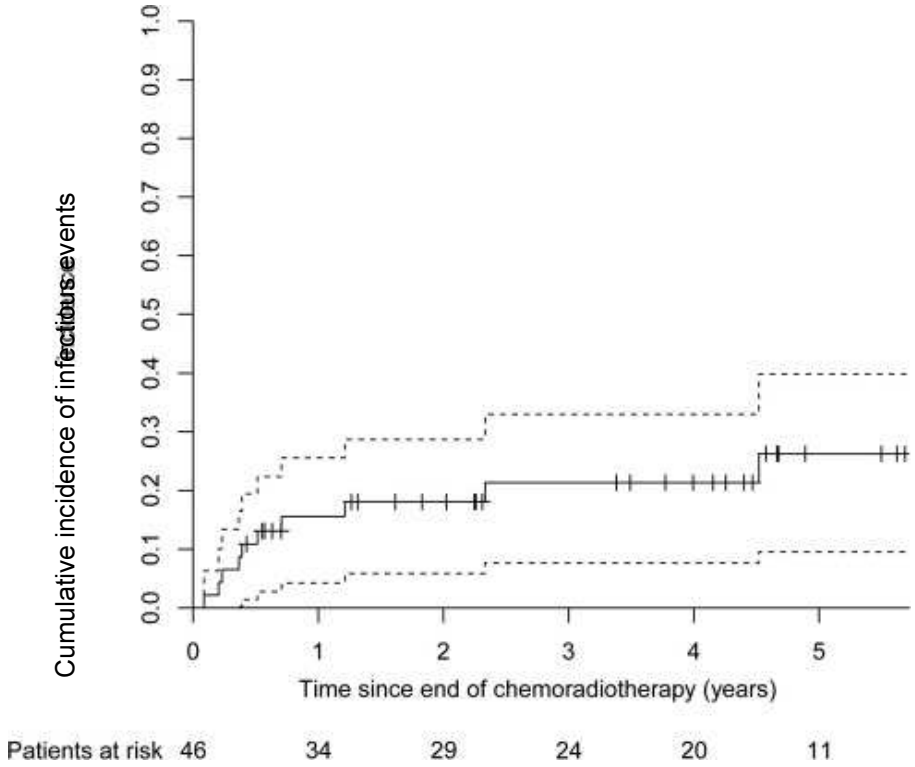

Trip et al. Radiother Oncol 2015

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Summary (2)

- *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*

CRITICS delineation atlas:

https://90354444eae87e1325758f006fb0199c07bb65e2.googledrive.com/host/0B-hpenFdfLiNTjNyRHV1dnYxVkE/ABDOMEN/CTV Gastric CA in CRITICS trial.pdf

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GASTRIC TUMORS: Dose constraints for Organs at Risk

Prof. Philippe MAINGON

- The patient should be instructed to avoid intake of a heavy meal for 3 hours before simulation and treatment. When clinically appropriate, use of IV and/or oral contrast for CT simulation may be used to aid in target localization.
- Use of an immobilization device is strongly recommended for reproducibility of daily set-up.
- All patients should be simulated and treated in the supine position.
- The uncertainties arising from variations in stomach filling and respiratory motion should also be taken into consideration.

Int. J. Radiation Oncology Biol. Phys., Vol. 52, No. 2, pp. 283–293, 2002

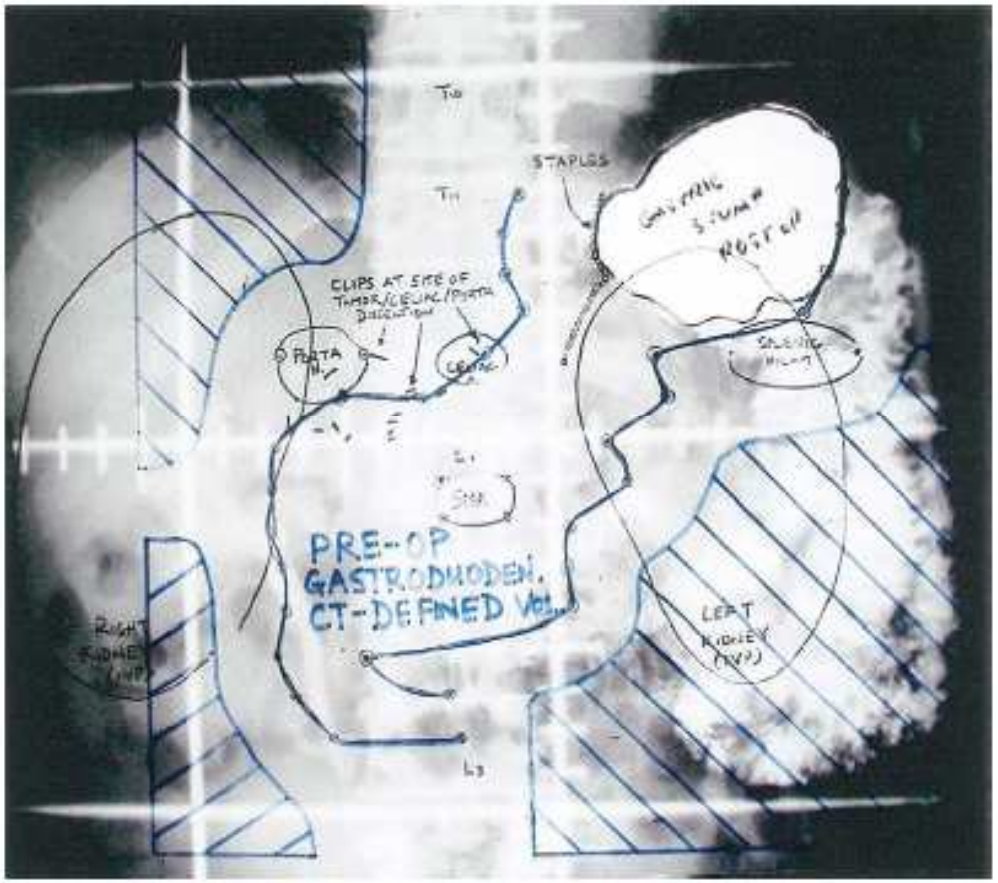
0360-3016/02/$–see front matter

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.¶



Smalley SR IJROBP 2002;52:283-93

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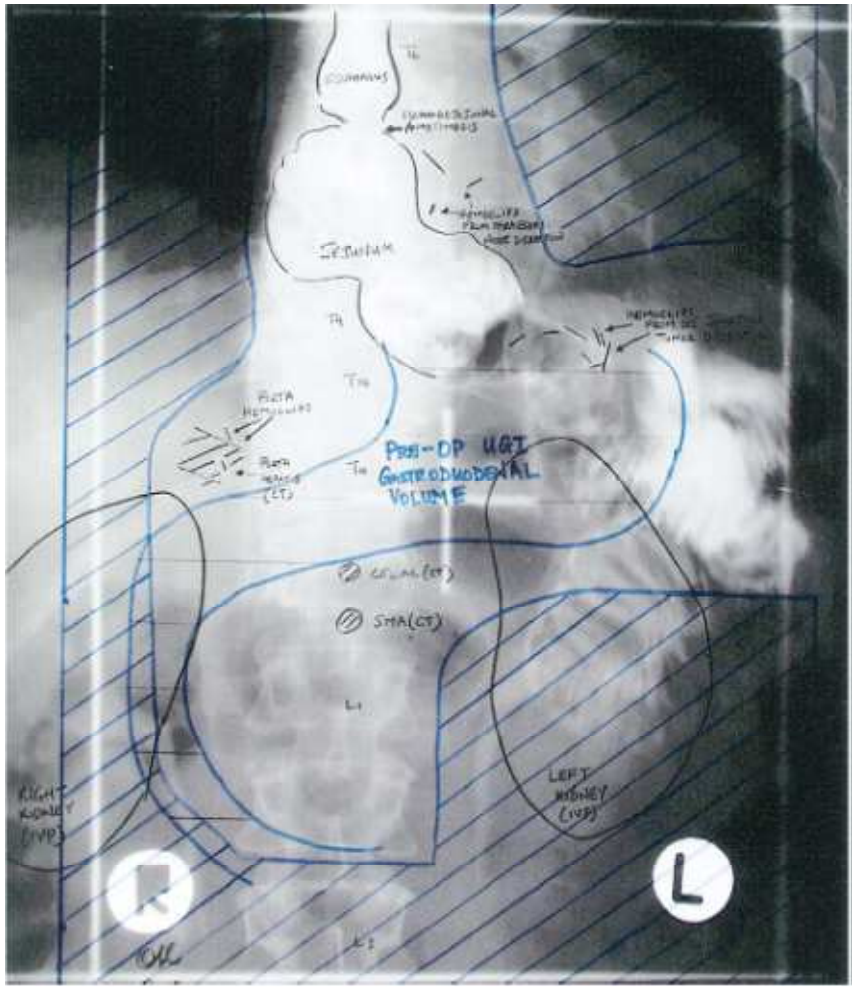

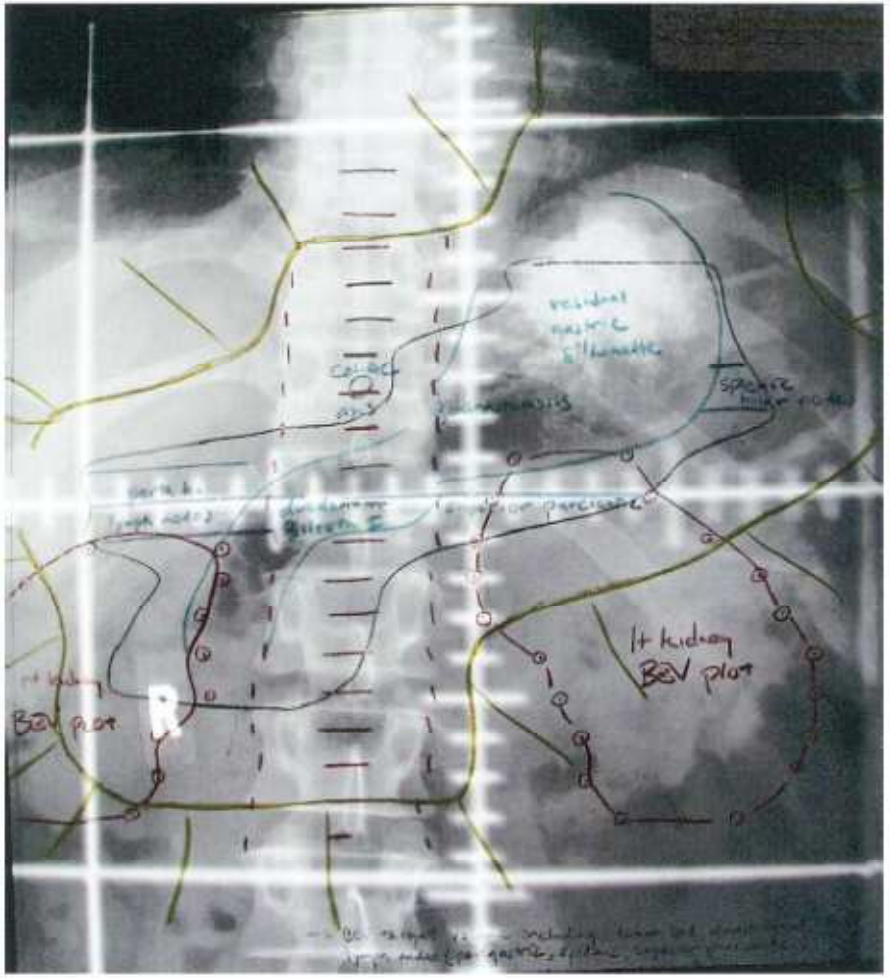

Smalley SR IJROBP 2002;52:283-93

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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- Heart
- Lungs
- **Spinal cord**
- Vertebrae
- Thyroïd

- **Stomach**
- **Liver**
- **Biliary tract**
- **Pancreas**
- **Spleen**
- **Kidneys**

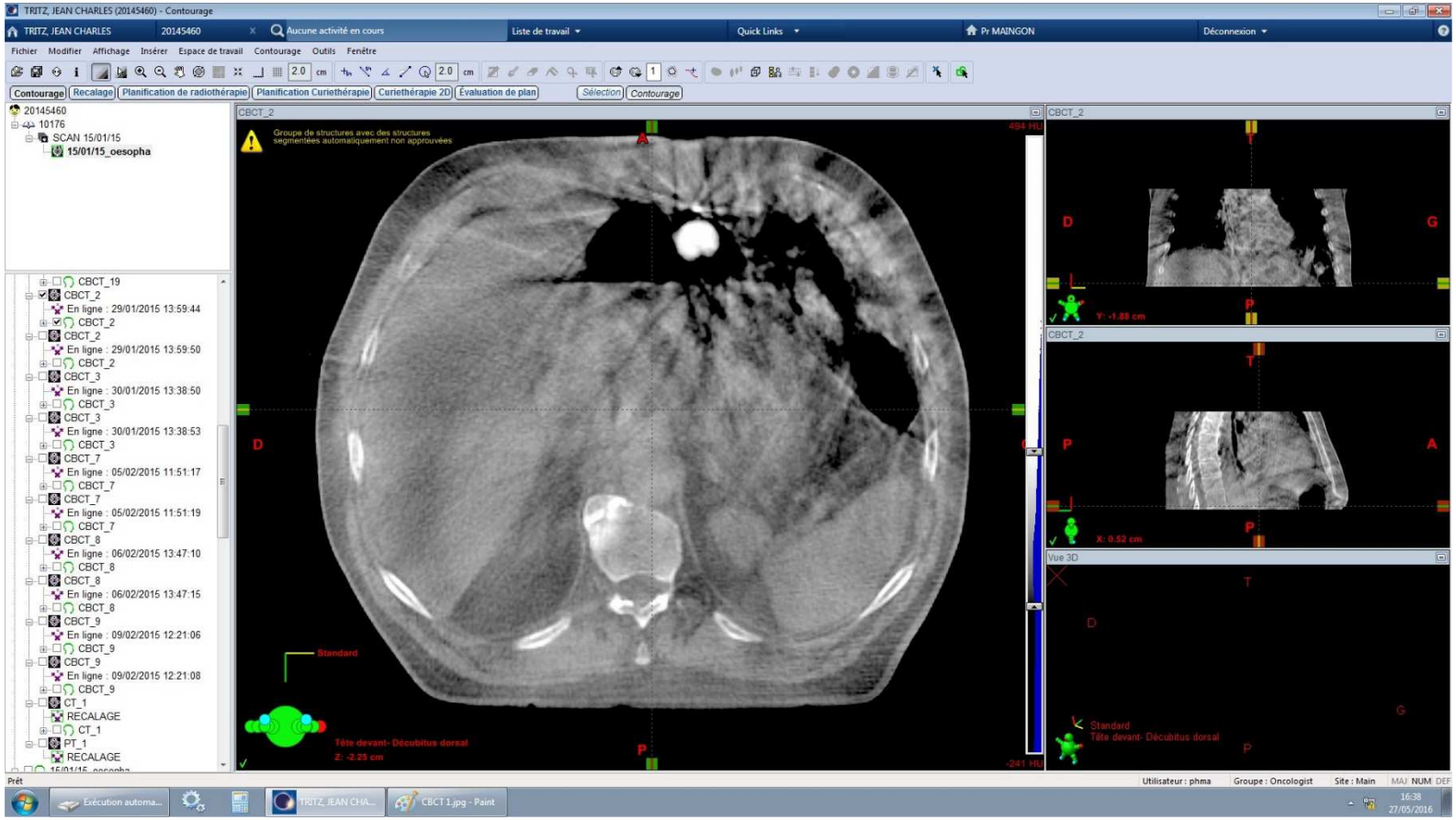
- Vessels, pericarde, coronary arteries
- Esophagus
- Patient at risk

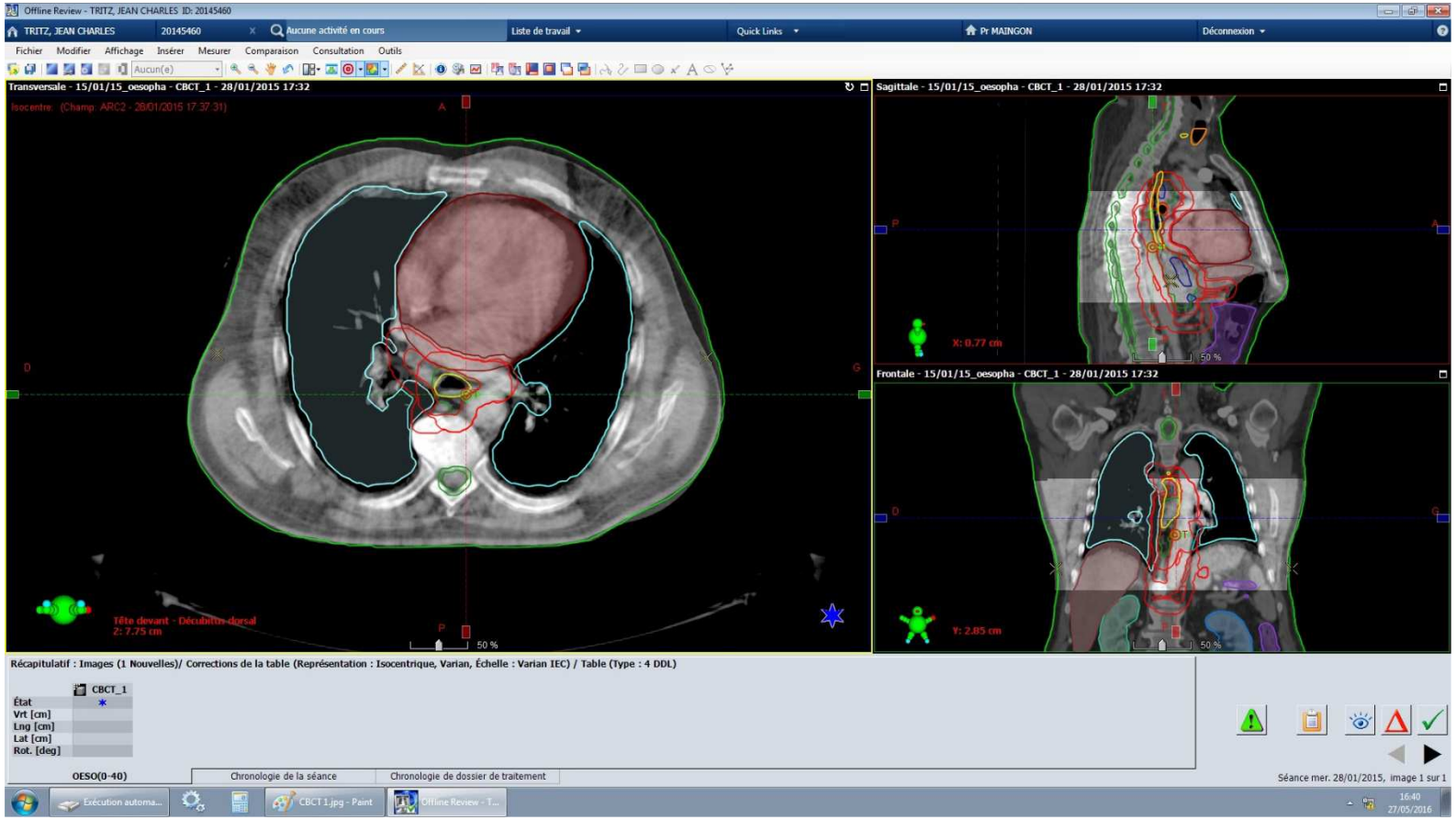
Normal tissue tolerance dose

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


TRITZ, JEAN CHARLES (20145460) - Contourage
Contourage
Recalage
Planification de radiothérapie
Planification Curiethérapie
Curiethérapie 2D
Évaluation de plan
Sélection
Contourage
20145460
10176
SCAN 15/01/15
15/01/15_oesopha
CBCT_2
Groupe de structures avec des structures segmentées automatiquement non approuvées
Standard
Tête devant- Décubitus dorsal
Vue 3D



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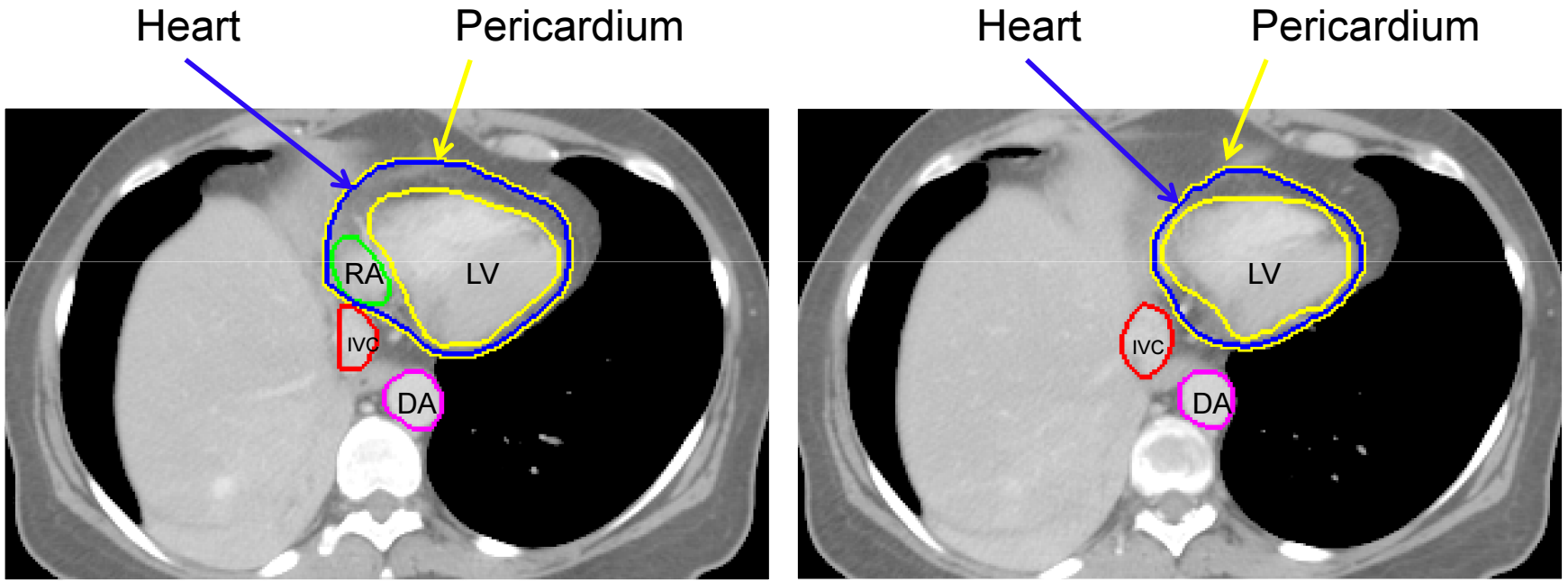
Heart, pericardium or left ventricule ?



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

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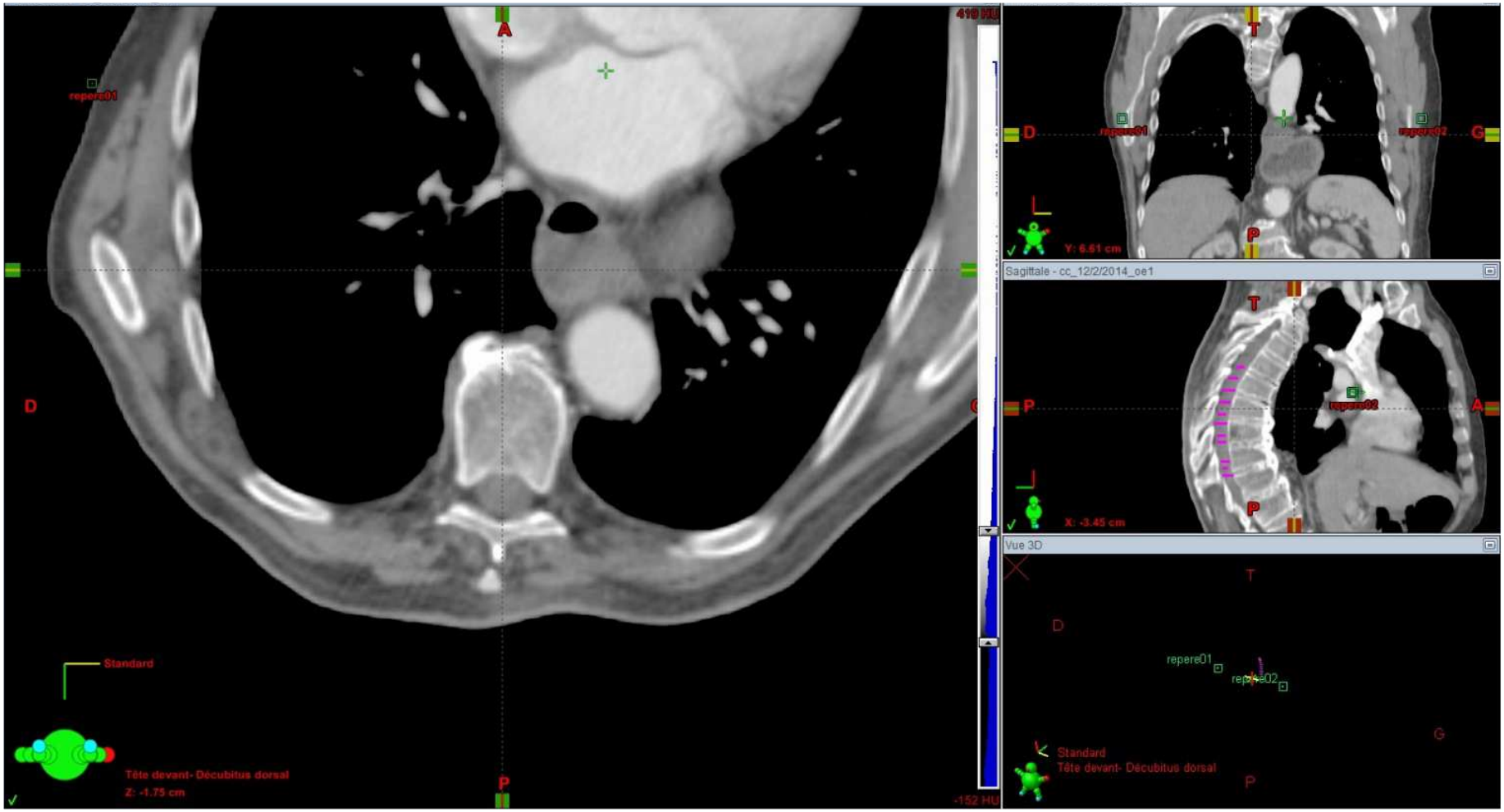

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QUANTEC: dose-volume effects in the stomach and small bowel

- **Testicular cancer irradiation:**
  - Ulceration rate = Dose < 50 Gy : 4% Dose > 50 Gy : 16%
  - Perforation rate = 2% versus 14%

  Brich Arch Int Med 1955
- No evidence that adding chemotherapy adds some toxicity

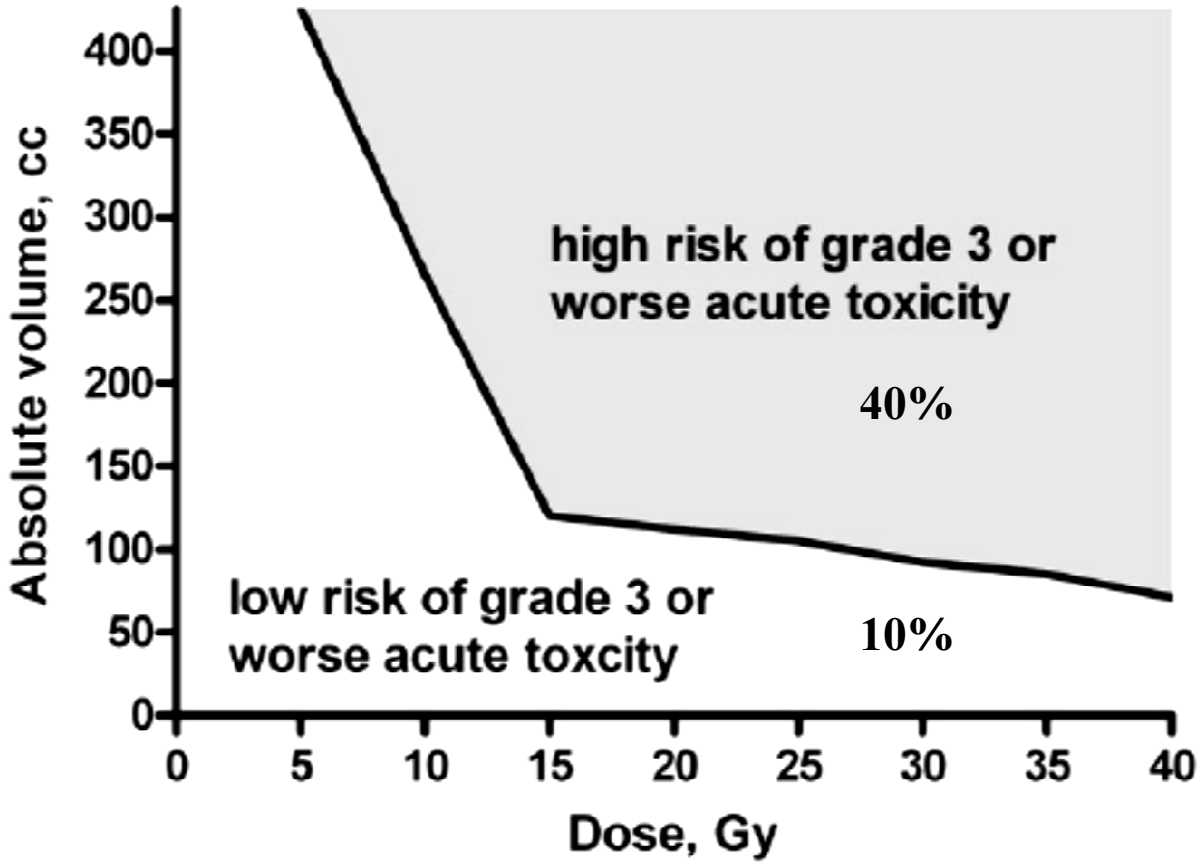
- **Hodgkin disease**:
  - Cosset; 516 patients receiving close to 40 Gy
    - Ulcer = 25 4.8%
    - Severe gastritis = 9 1.7%
    - Obstruction = 2 0.4%
    - Dose per fraction dependant

  Cosset JM, Radiother Oncol 1988

Kavanagh B. IJROBP 2010

QUANTEC: dose-volume effects in the stomach and small bowel

Volume of individual bowel loops NOT the peritoneal space …



Baglan – Robertson Threshold model

Kavanagh B. IJROBP 2010

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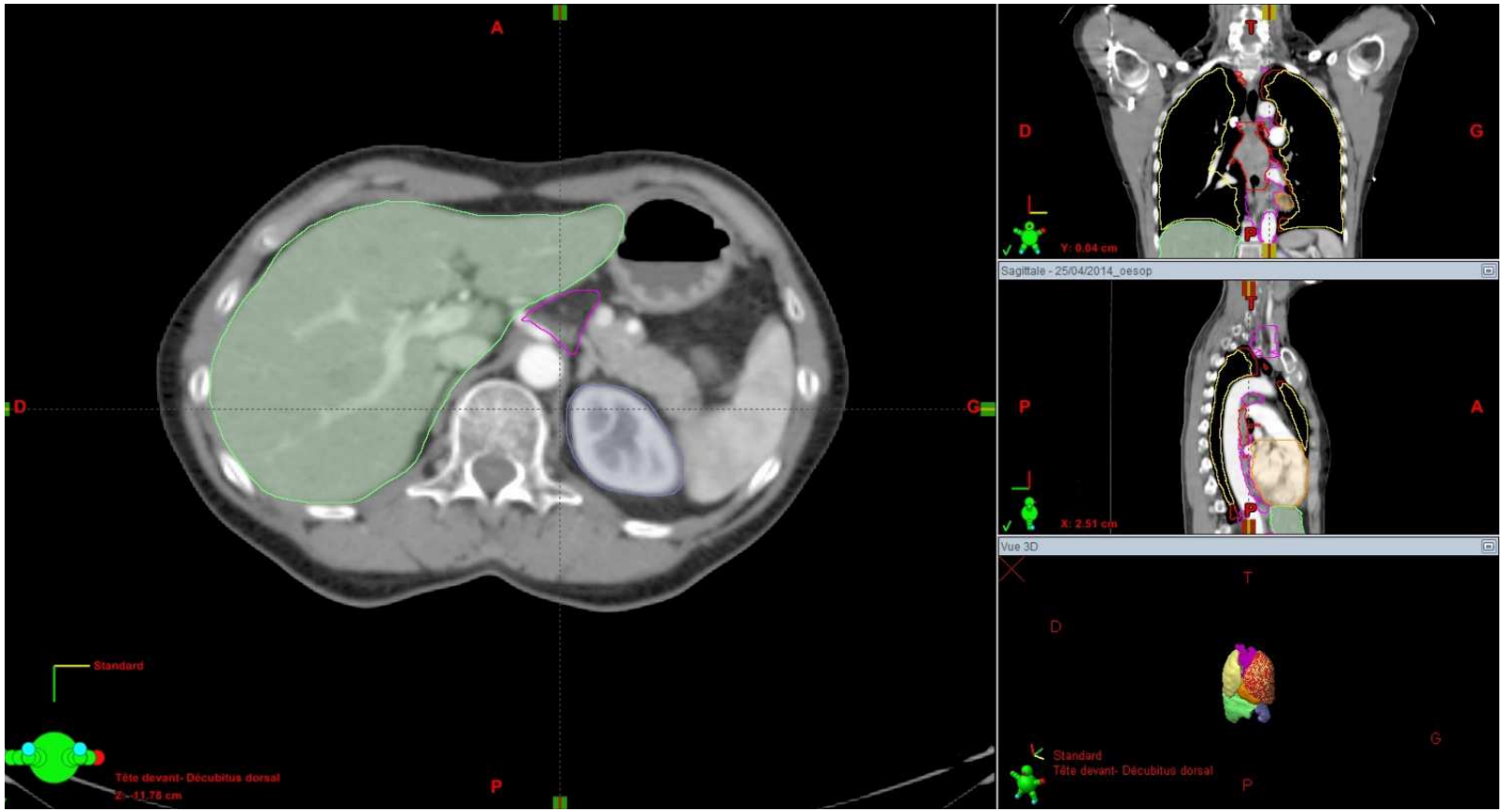
LIVER



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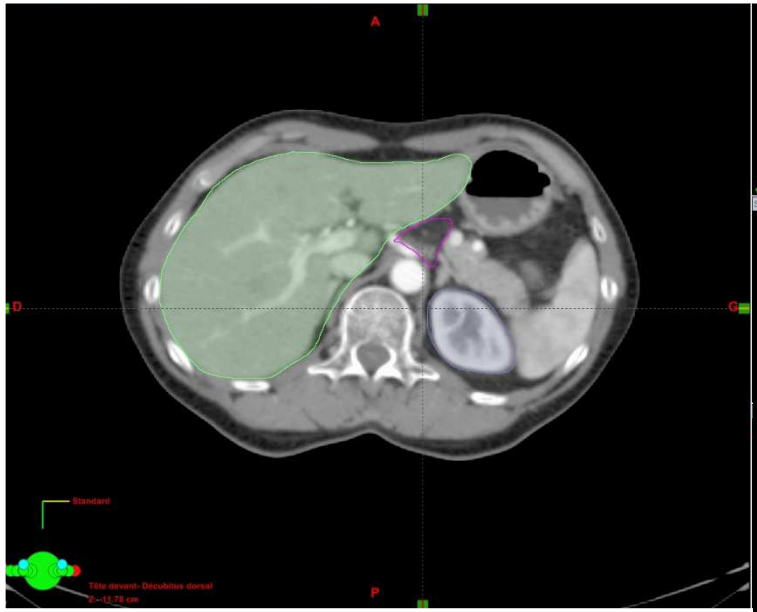
QUANTEC: Radiation-induced liver toxicity

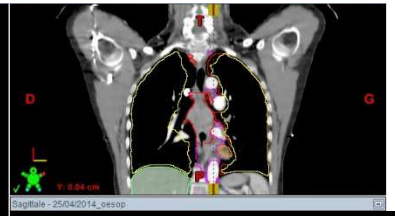
Table 2. Series of fractionated partial liver irradiation and rates of RILD

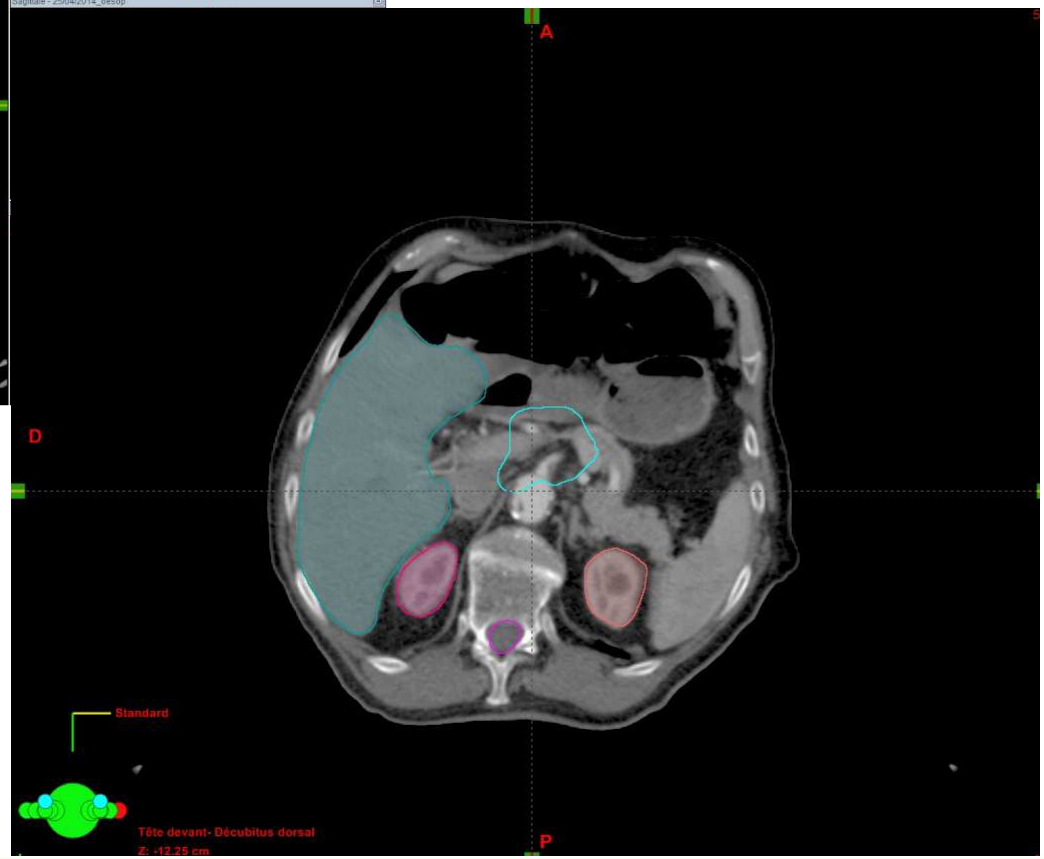
Study group	*n*	Diagnosis	Baseline Child-Pugh score	Prescription dose fractionation	Crude percent RILD	Mean normal liver dose in patients with vs. without RILD	Factors associated with RILD
Michigan (8, 23)	203*	PLC + LMC	203 A	1.5 Gy twice daily	9.4% (19/203)	37 Gy vs. 31.3 Gy	PLC vs. LMC mean liver 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

Kidneys







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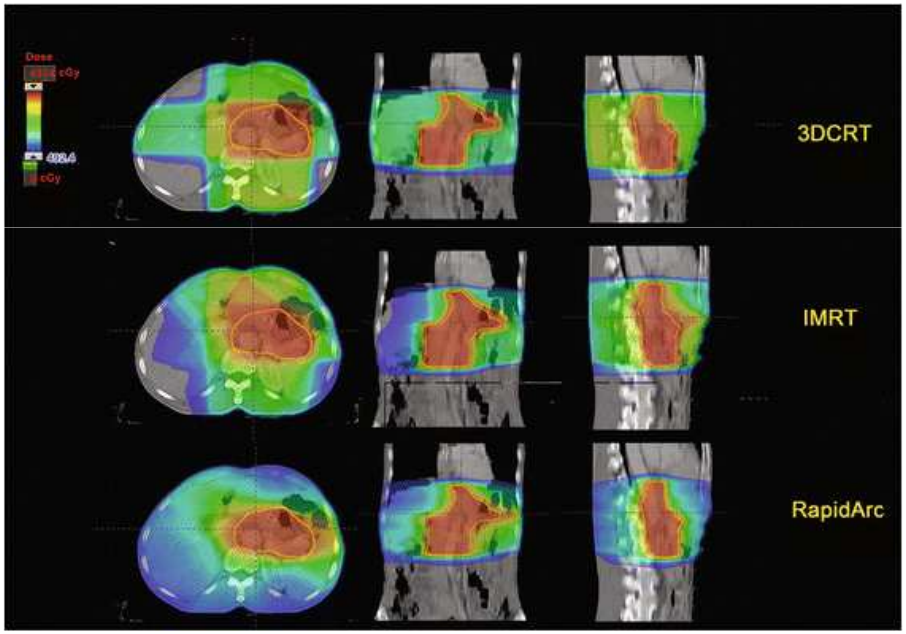
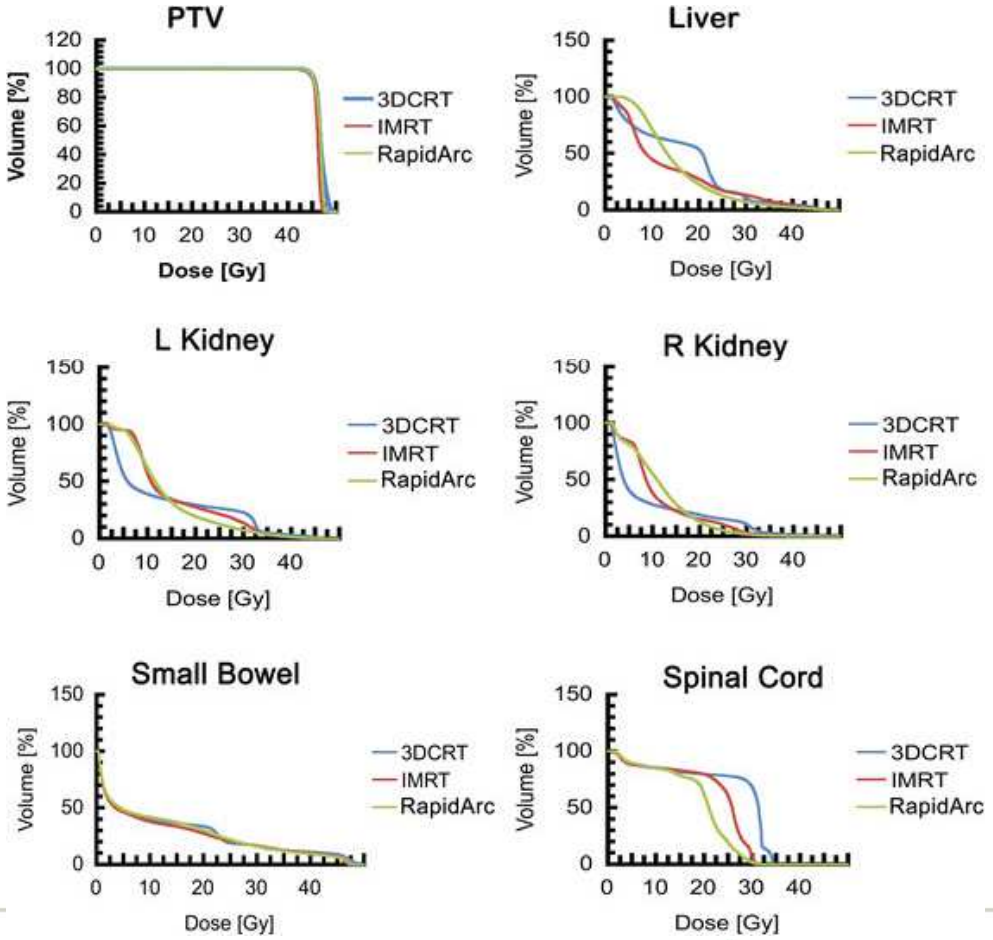
Double-arc volumetric modulated therapy improves dose distribution compared to static gantry IMRT and 3D conformal radiotherapy for adjuvant therapy of gastric cancer





Zhang Radiat Oncol 2015;10:114

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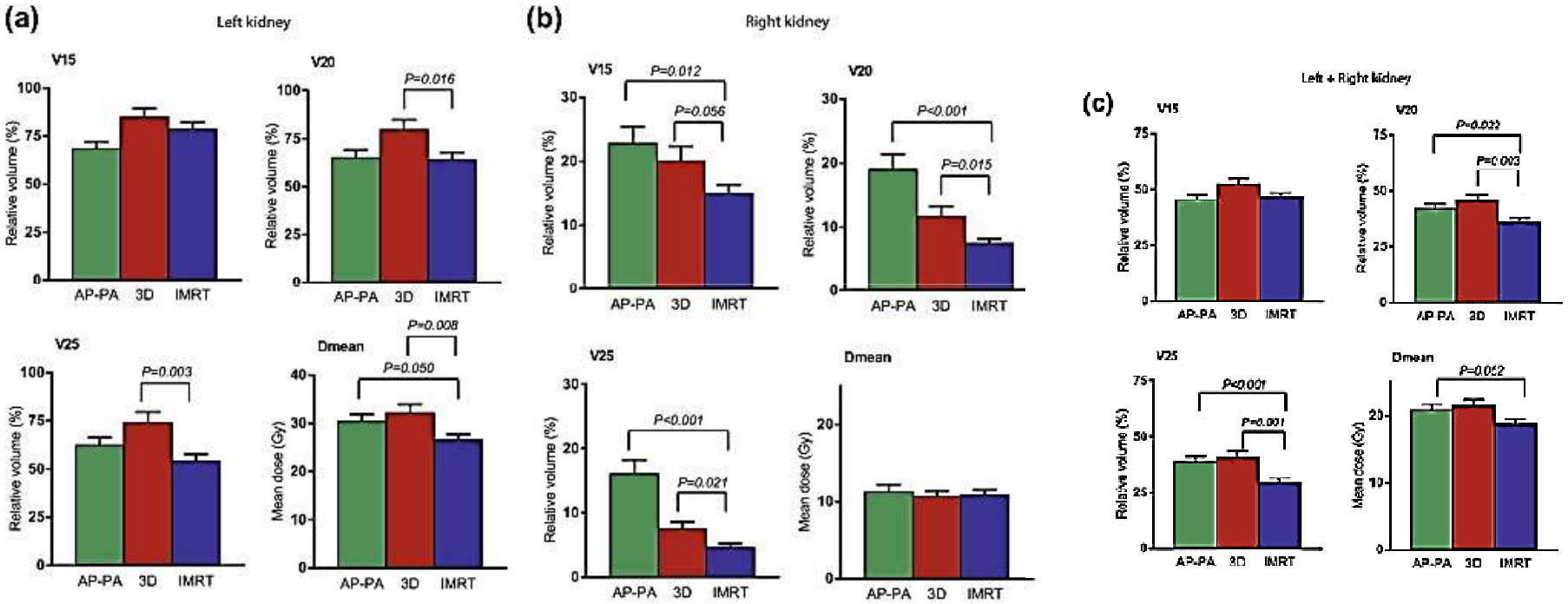
IMRT limits nephrotoxicity after chemoradiation for gastric cancer



Trip A. Radiother Oncol 2015;114:421-426

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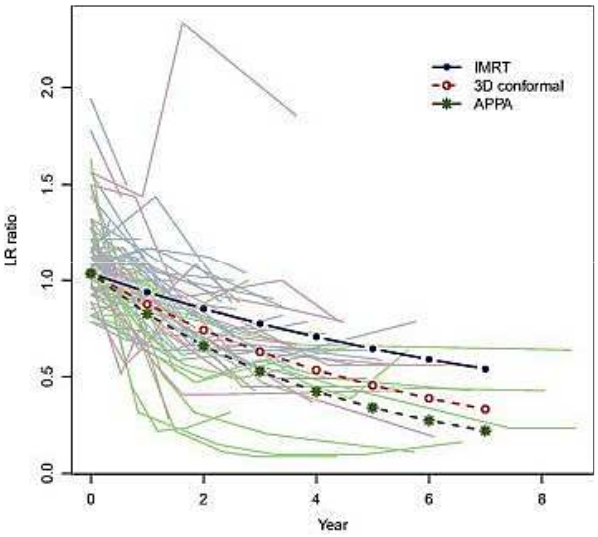
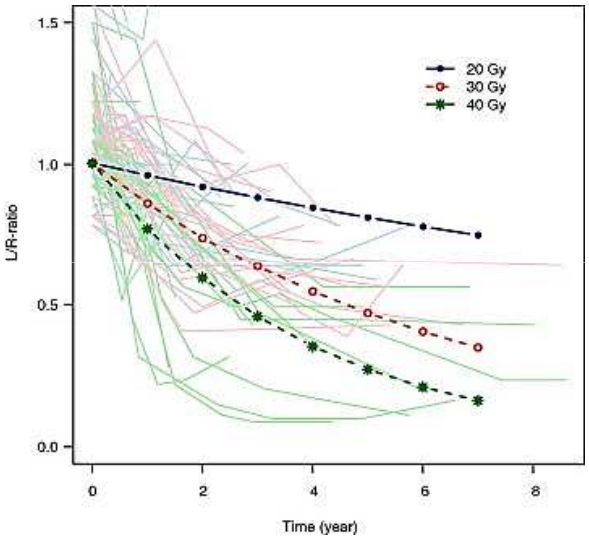
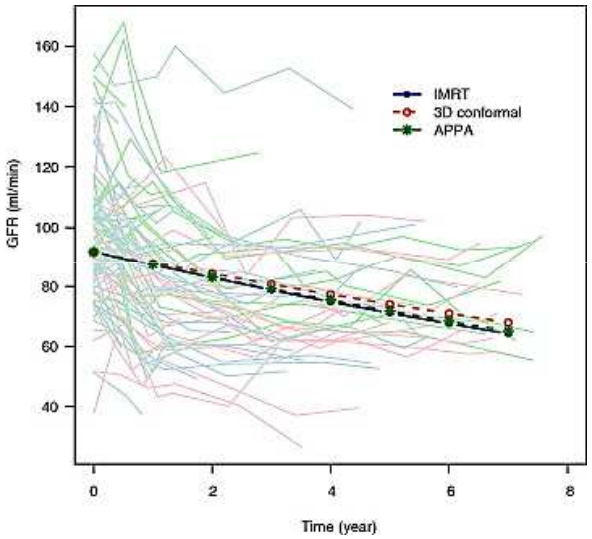


Left renal function
Mixt effect model



Dose effect relationship
D mean
Tc99m-mAG3-renography



GFR
Cockcroft-Gauss formula

Trip A. Radiother Oncol 2015:114:421-426

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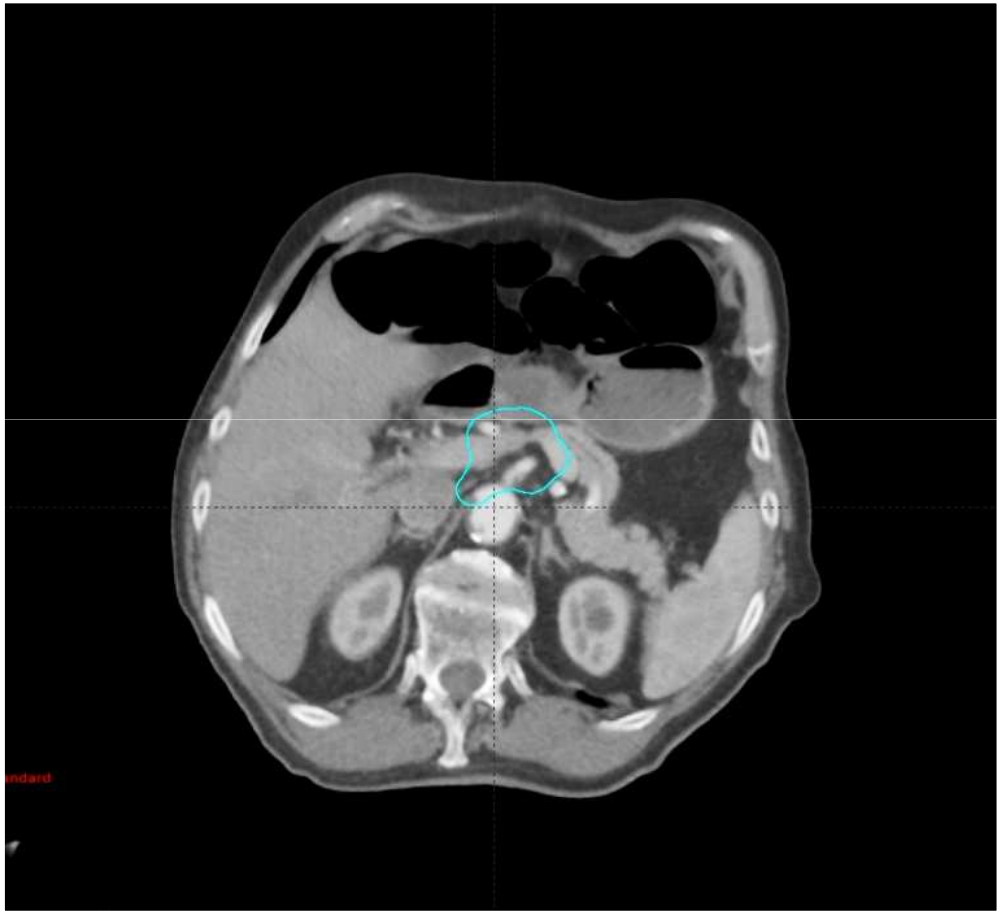
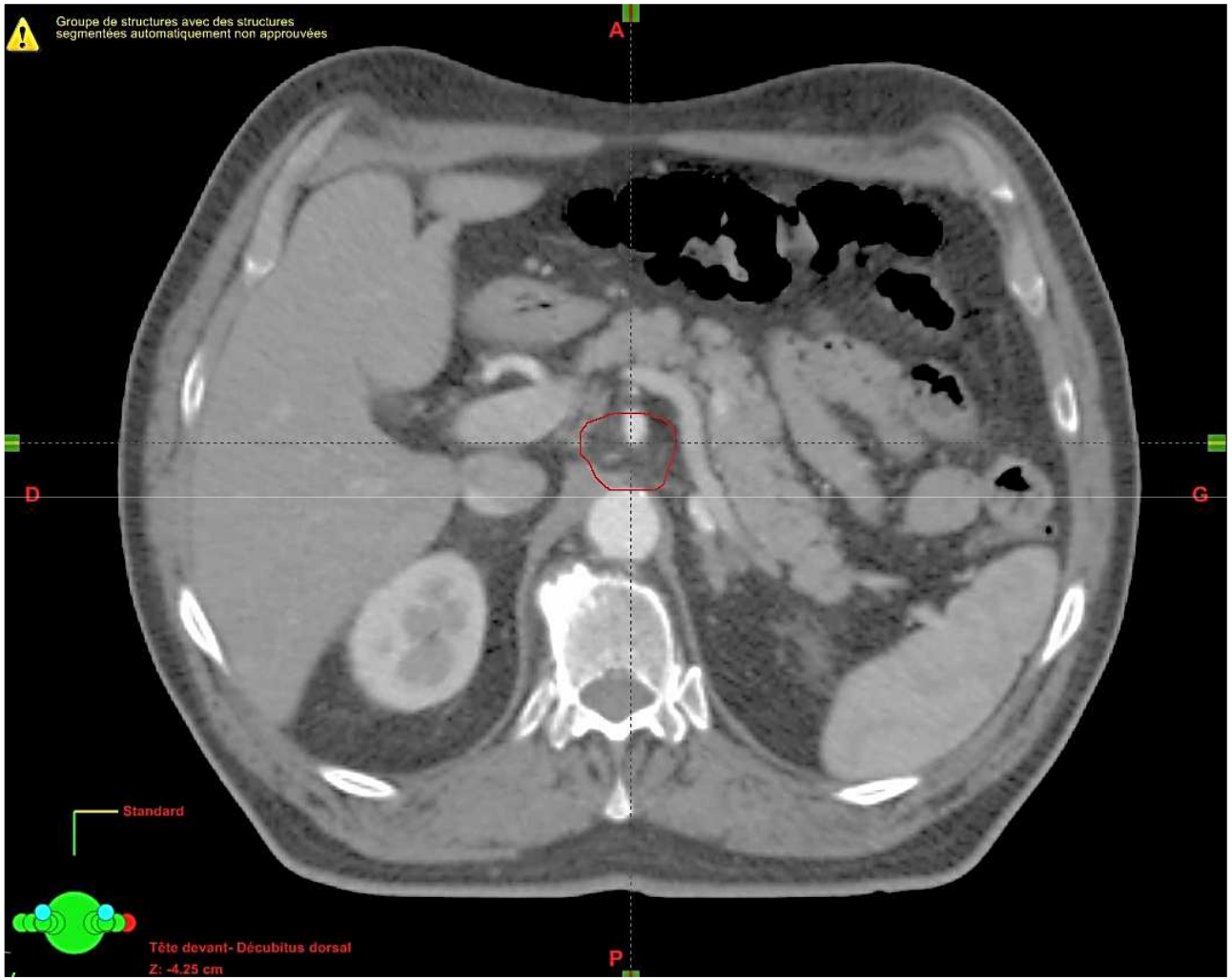
Others … ?





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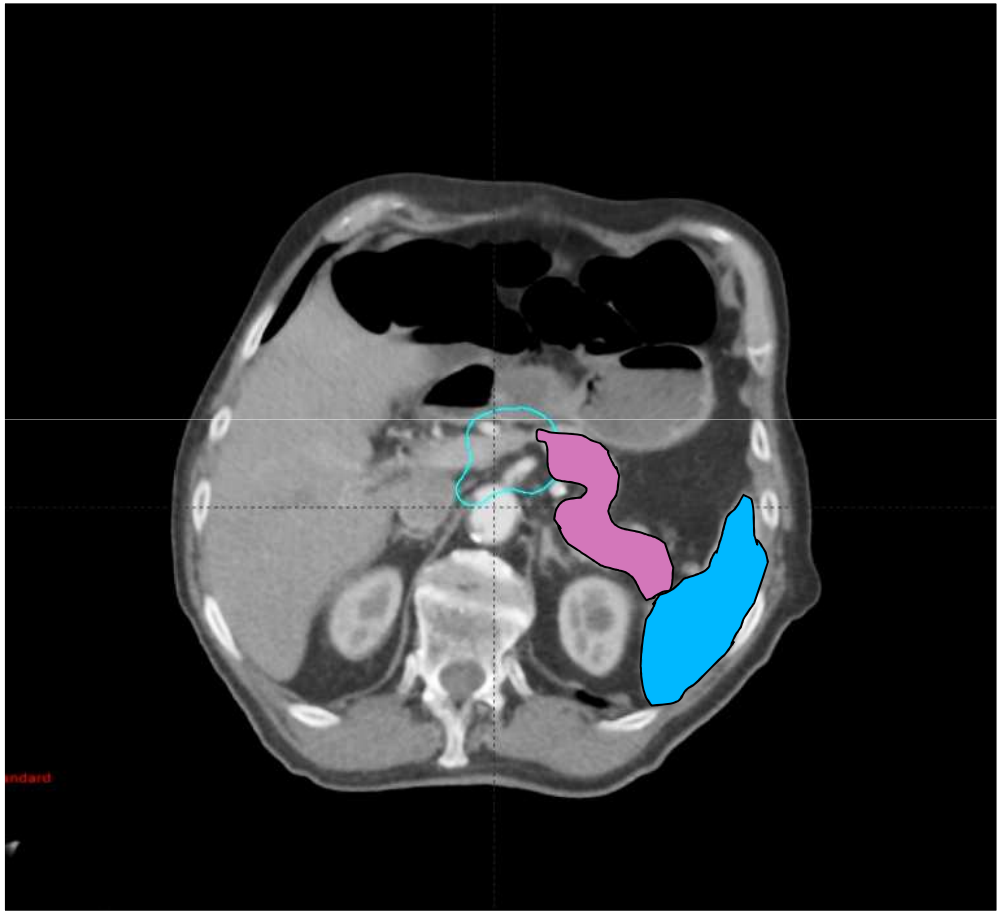
Others …



QUANTEC: Small bowel

Table 1. Quantitative analyses of acute small bowel toxicity

Authors, Reference, No. of patients	Primary cancer	Prescription dose (Gy)	Observed predictor of toxicity
Baglan *et al.* (18) (*N* = 40)	Rectal	45–50	Threshold volume at given doses
Roeske *et al.* (19) (*N* = 50)	Cervix	45	Absolute small bowel volume (peritoneal space) receiving 45 Gy
Tho *et al.* (20) (*N* = 41)	Rectal	45	Absolute small bowel volume receiving 5–40 Gy
Huang *et al.* (21) (*N* = 80)*	Cervix, endometrial	39.6–45	Absolute small bowel volume: > 16 Gy (prior surgery) >40 Gy (no prior surgery)
Robertson *et al.* (22) (*N* = 96)	Rectal	45–50	Baglan threshold model doses (see Fig. 1)
Gunnlaugsson *et al.* (23) (*N* = 28)	Rectal	50	Absolute small bowel volume >15 Gy

Kavanagh B. IJROBP 2010

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Kavanagh B. IJROBP 2010

Chamotherapy Toxicity Constraints

Prof. Florian Lordick, MD

Director University Cancer Center Leipzig

UCCL

Drugs used for Gastric Cancer (I)

Drugs	Main Toxicity	Prevention	Contraindication
Cisplatin	Nausea-Emesis +++	Antiemetics	
	Nephrotoxicity +++	Hydration	GFR < 60ml/min kg
	Ototoxicity +++	none	Hardness of hearing
	Neurotoxicity +++	none	Pre-existing neuropathy
Oxaliplatin	Neurotoxicity +++	none	Pre-existing neuropathy
	Nausea-Emesis ++	Antiemetics	
Epirubicine	Hematological +++	Selected cases: GCSF	Myelodysplasia
	Nausea-Emesis ++	Antiemetics	
	Cardiac ++	Close monitoring	LVEF≤ 50%
	Secondary leukemias	none	
	Hair loss	none	

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Drugs used for Gastric Cancer (II)

Drugs	Main Toxicity	Prevention	Contraindication
5-Fluorouracil	Diarrhea	none	CED (relative)
	Mucositis	Oral rinses	none
	Cardiac	Close monitoring	Angina pectoris
Capecitabin	Hand-foot-syndrome	Urea 10%	
Docetaxel	Neurotoxicity +++	none	Pre-existing neuropathy
	Hematological +++	Selected cases: GCSF	Myelodysplasia
Trastuzumab	Cardiac ++	Close monitoring	LVEF≤ 50%
Irinotecan	Diarrhea	Anticholinergics	CED (relative)
	Nausea-Emesis ++	Antiemetics	

Nausea and Emesis

MASCC/ESMO ANTIEMETIC GUIDELINE 2016

MASCC™ Multinational Association of Supportive Care in Cancer WWW.MASCC.ORG

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Multinational Association of Supportive Care in Cancer

Organizing and Overall Meeting Chairs:
Matti Aapro, MD
Richard J. Gralla, MD
Jørn Herrstedt, MD, DMSci
Alex Molassiotis, RN, PhD
Fausto Roila, MD

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Nausea and Emesis

Committee I (1/5): The Four Emetic Risk Groups

HIGH	Risk in nearly all patients (> 90%)
MODERATE	Risk in 30% to 90% of patients
LOW	Risk in 10% to 30% of patients
MINIMAL	Fewer than 10% at risk

Nausea and Emesis

Committee I (2/5): Emetic Risk Groups – Adults – Single IV Agents

HIGH	Anthracycline/cyclophosphamide combination* Carmustine Cisplatin Cyclophosphamide ≥ 1500 mg/m² Dacarbazine Mechlorethamine Streptozocin		
MODERATE	Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide < 1500 mg/m² Cytarabine > 1000 mg/m²	Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan	Oxaliplatin Romidepsin Temozolomide** Thiotepa Trabectedin

* The combination of an anthracycline and cyclophosphamide in patients with breast cancer should be considered highly emetogenic.
** No direct evidence found for temozolomide IV. Classification is based on oral temozolomide, since all sources indicate a similar safety profile.

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Nausea and Emesis

Committee I (3/5): Emetic Risk Groups – Adults – Single IV Agents

LOW	Aflibercept	Eribulin	Panitumumab
	Belinostat	Etoposide	Pemetrexed
	Blinatumomab	5-Fluorouracil	Pegylated liposomal doxorubicin
	Bortezomib	Gemcitabine	Pertuzumab
	Brentuximab	Ipilimumab	Temsirolimus
	Cabazitaxel	Ixabepilone	Topotecan
	Carfilzomib	Methotrexate	Trastuzumab-emtansine
	Catumaxumab	Mitomycin	Vinflunine
	Cetuximab	Mitoxantrone	
	Cytarabine ≤ 1000 mg/m²	Nab- paclitaxel	
	Docetaxel	Paclitaxel	

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Nausea and Emesis

Committee I (4/5): Emetic Risk Groups – Adults – Single IV Agents

MINIMAL	Bevacizumab	Pembrolizumab
	Bleomycin	Pixantrone
	Busulfan	Pralatrexate
	2-Chlorodeoxyadenosine	Rituximab
	Cladribine	Trastuzumab
	Fludarabine	Vinblastine
	Nivolumab	Vincristine
	Ofatumumab	Vinorelbine

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Nausea and Emesis

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	5-HT_3 + DEX + NK_1
High AC	5-HT_3 + DEX + NK_1
Carboplatin	5-HT_3 + DEX + NK_1
Moderate (other than carboplatin)	5-HT_3 + DEX
Low	5-HT_3 or DEX or DOP
Minimal	No routine prophylaxis

5-HT_3 = serotonin$_3$ receptor antagonist	DEX = DEXAMETHASONE	NK_1 = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)	DOP = dopamine receptor antagonist

NOTE: If the NK_1 receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist.

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Nausea and Emesis

DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	**DEX** or (if APR 125mg for acute: (**MCP** + **DEX**) or **APR**)
High AC	None or (if APR 125mg for acute: **DEX** or **APR**)
Carboplatin	None or (if APR 125mg for acute: **APR**)
Oxaliplatin, or anthracycline, or cyclophosphamide	**DEX** can be considered
Moderate (other)	No routine prophylaxis
Low and Minimal	No routine prophylaxis

DEX = DEXAMETHASONE | MCP = METOCLOPRAMIDE | **APR** = APREPITANT

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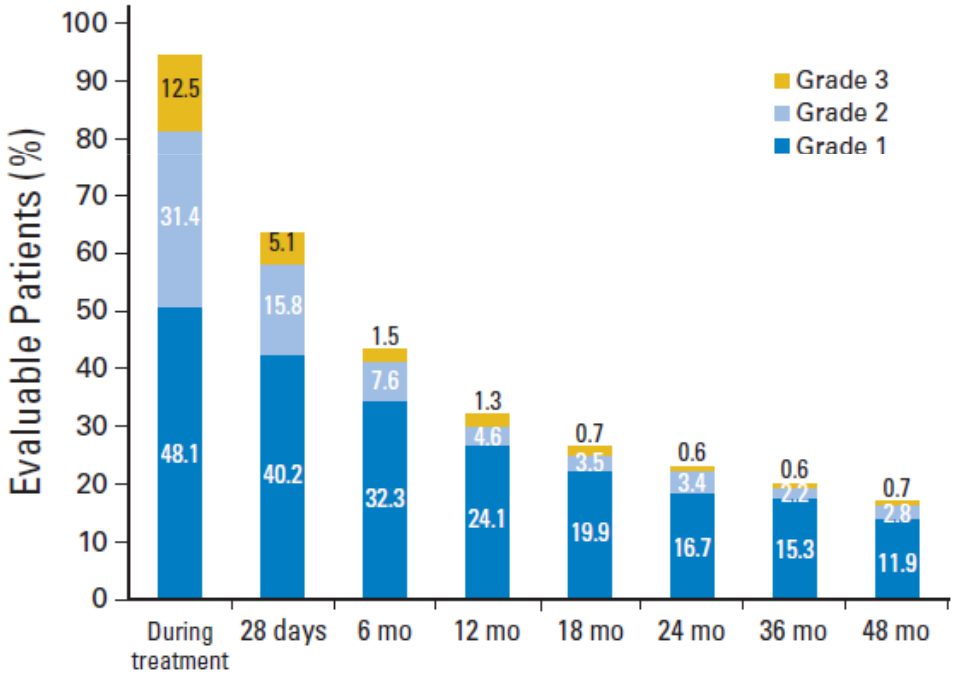
Neurotoxicity

Oxaliplatin

Standard for colon cancer. Very frequently used for gastric cancer



Frequency of neuropathy in the MOSAIC-study (colon st. 3)

André et al. *J Clin Oncol* 2012; 27: 3109-16

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Neurotoxicity

VOLUME 32 · NUMBER 10 · APRIL 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium and Magnesium to Prevent Oxaliplatin-Induced Sensory Neurotoxicity (N08CB/Alliance)

Charles L. Loprinzi, Rui Qin, Shaker R. Dakhil, Louis Fehrenbacher, Kathleen A. Flynn, Pamela Atherton, Drew Seisler, Rubina Qamar, Grant C. Lewis, and Axel Grothey

Processed as a Rapid Communication manuscript. See accompanying articles on pages 991 and 1006

Charles L. Loprinzi, Rui Qin, Pamela Atherton, Drew Seisler, and Axel Grothey, Alliance Statistics and Data

ABSTRACT

Loprinzi CL et al., *J Clin Oncol* 2014, 32: 997-1005

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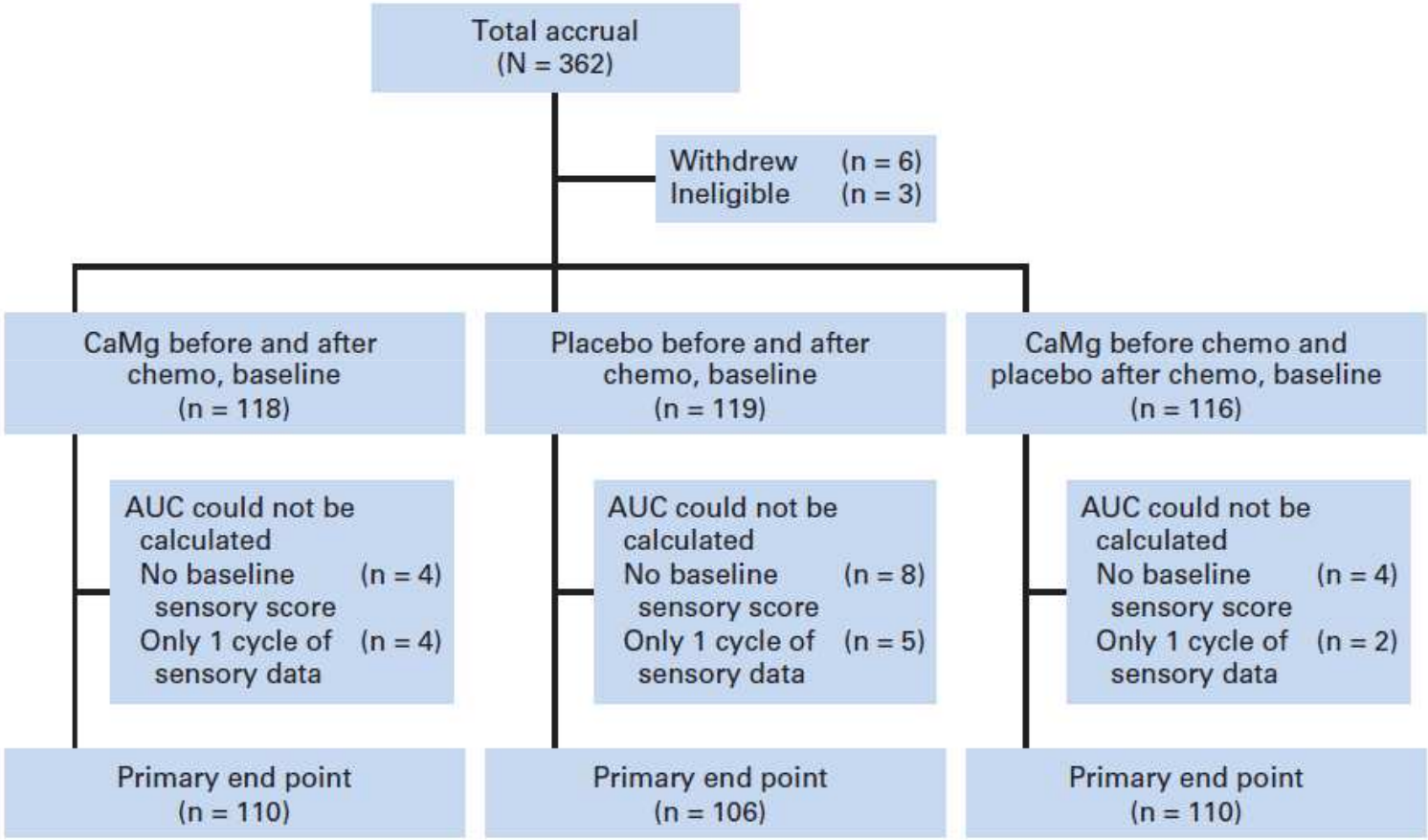
Neurotoxicity



Loprinzi CL et al., *J Clin Oncol* 2014, 32: 997-1005

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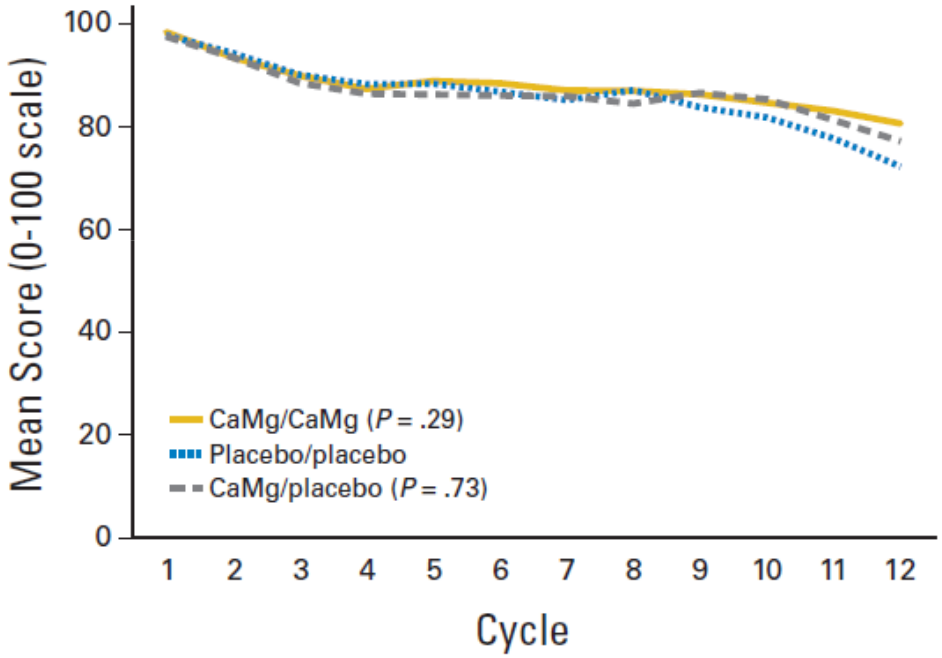
Neurotoxicity

Peripheral sensory neuropathy: mean score

(EORTC Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 instrument)



No. at risk												
CaMg/CaMg	114	108	103	103	97	88	89	84	76	73	58	46
Placebo/placebo	111	105	104	104	95	92	82	81	71	66	52	40
CaMg/placebo	112	105	109	105	95	99	94	85	80	71	59	51

Loprinzi CL et al., *J Clin Oncol* 2014, 32: 997-1005

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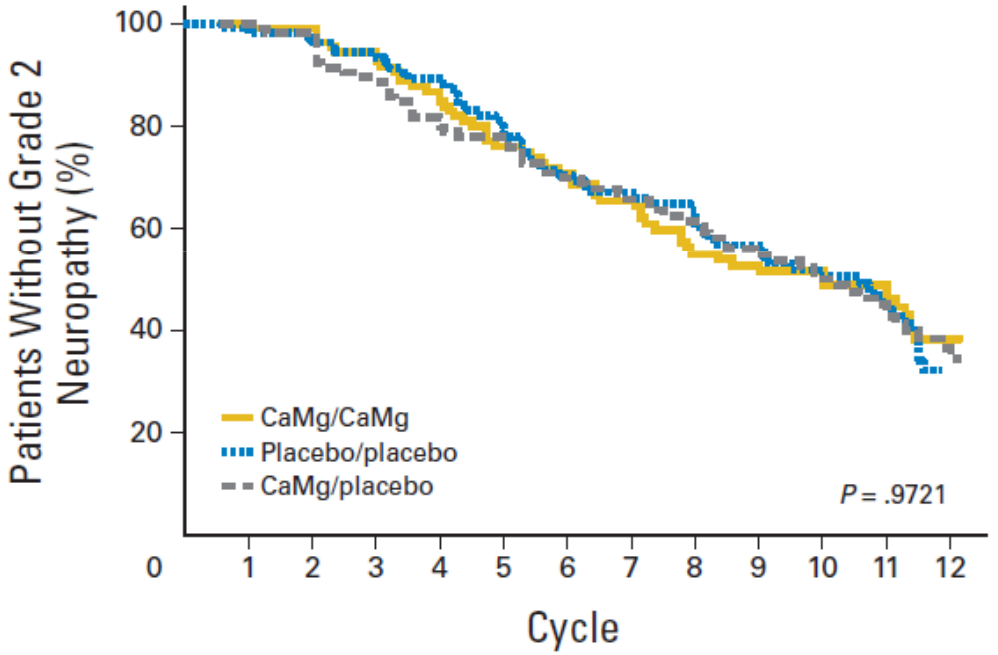
Neurotoxicity

Patients without grade 2 neuropathy

(EORTC Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 instrument)



No. at risk													
CaMg/CaMg	110	110	107	99	90	76	67	58	47	43	39	35	19
Placebo/placebo	107	106	103	93	84	78	70	63	56	48	41	37	18
CaMg/placebo	111	108	101	94	89	77	65	61	55	46	40	36	13

Loprinzi CL et al., *J Clin Oncol* 2014, 32: 997-1005

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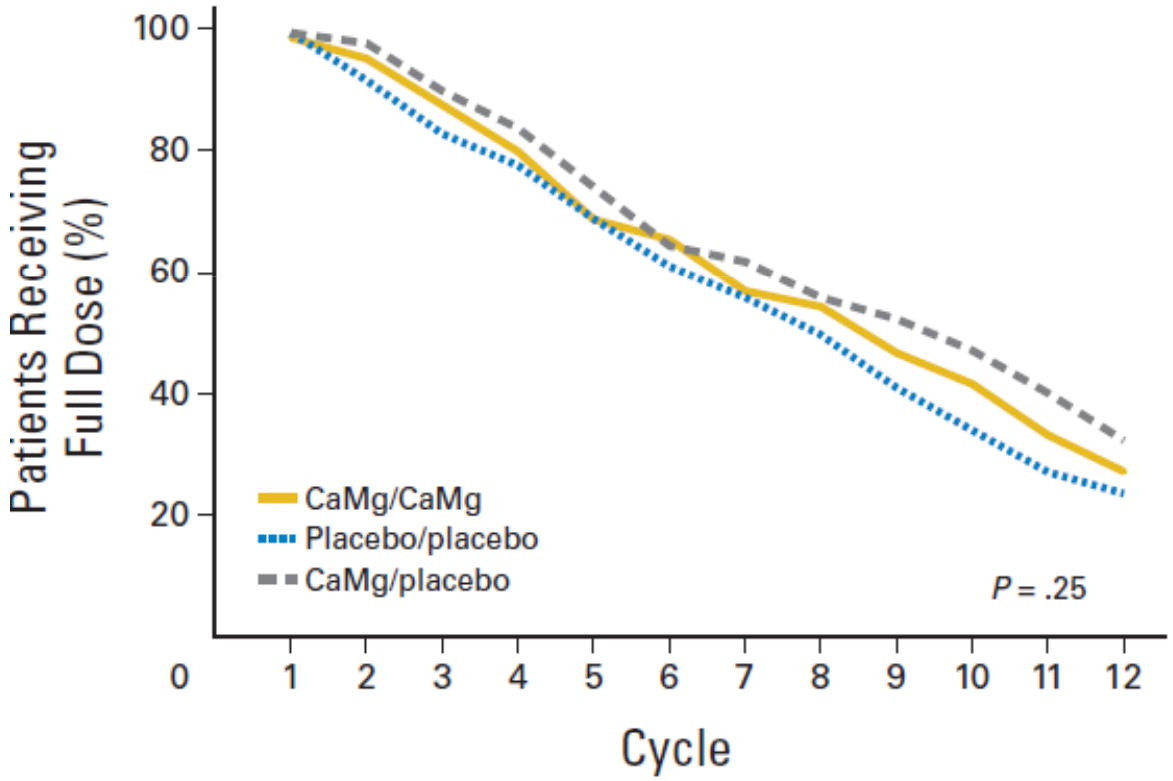
Neurotoxicity

Patients with full oxaliplatin doses



Loprinzi CL et al., *J Clin Oncol* 2014, 32: 997-1005

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Neuropathic pain

N=231

<u>Patients with neuropathic pain > grade 1</u>
- previous platin or taxane

Instruments:
Brief Pain Inventory

R A N D O M

Duloxetin* 5 weeks → Placebo
first week 30mg, then 60mg

Primary endpoint: neuropathic pain

Placebo 5 weeks → Duloxetin*
first week 30mg, then 60mg

*__Duloxetin__ (Cymbalta): Serotin-Noradrenalin Re-Uptake Inhibitor (SNRI)

Smith EML et al., *JAMA* 2013, 309: 1359–1367

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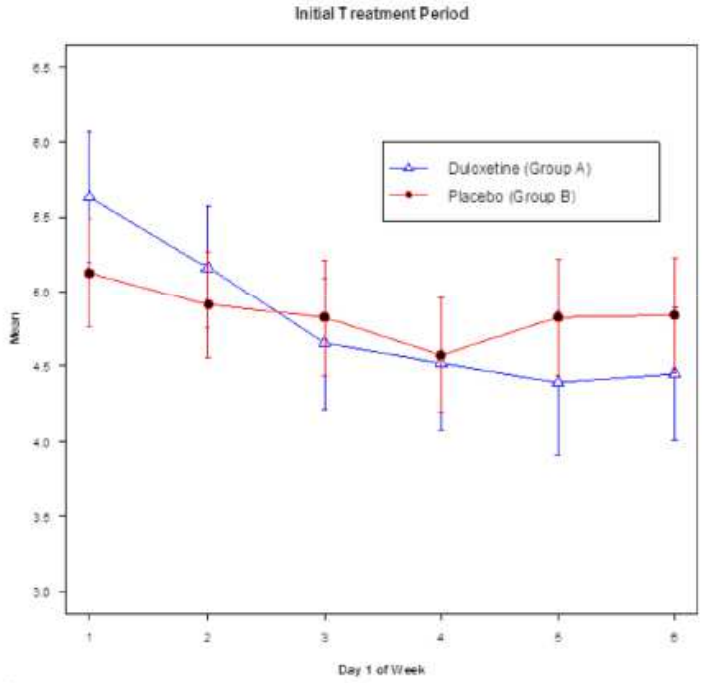
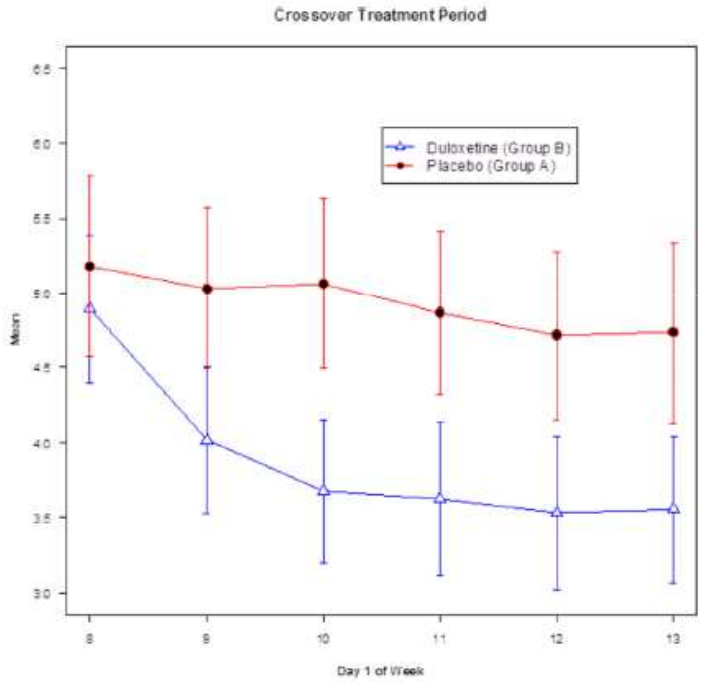
Neurotoxicity

Brief Pain Inventory - Score





# Patients												
Group A	87	86	86	87	85	87	67	65	65	66	63	67
Group B	94	92	91	91	91	94	74	68	71	69	66	74

Smith EML et al., *JAMA* 2013, 309: 1359–1367

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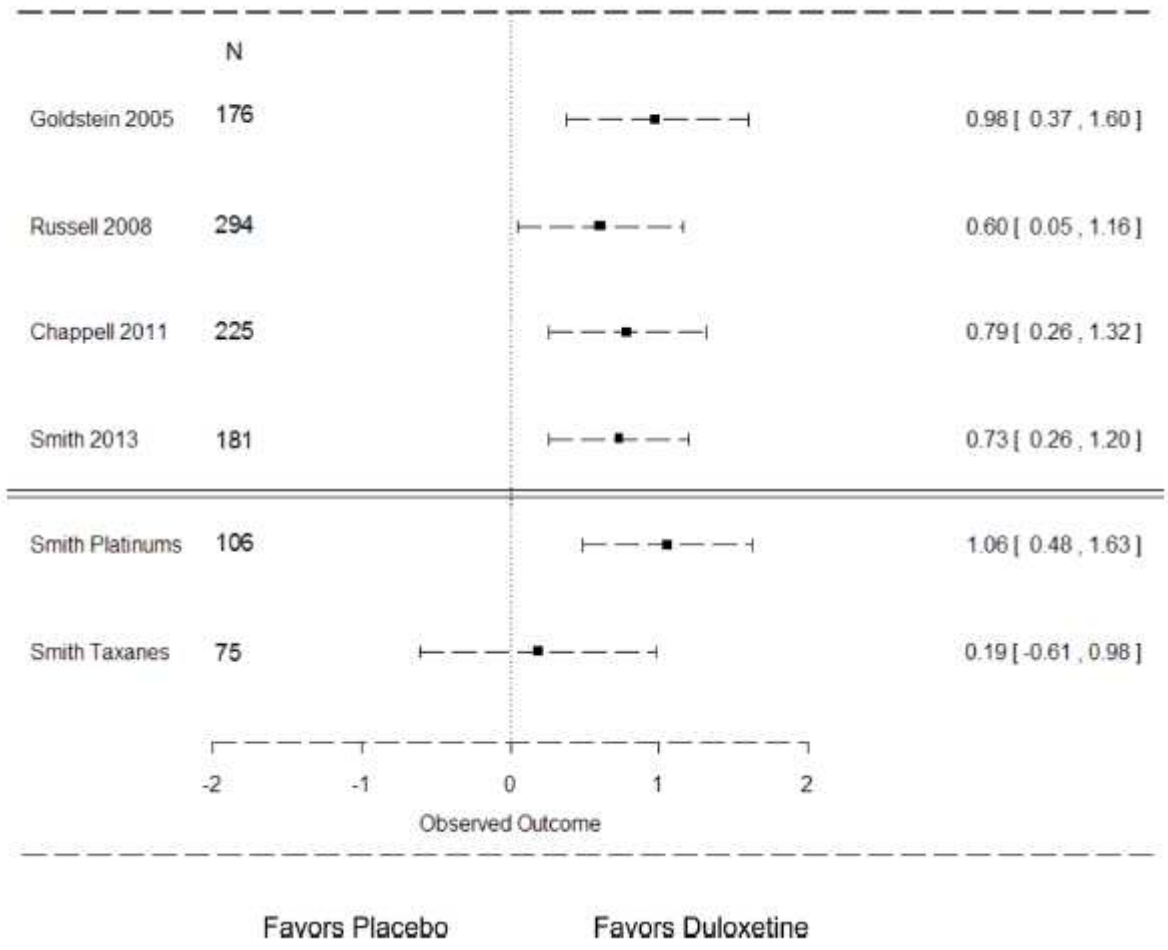
Neurotoxicity

Diabetic neuropathy

Fibromyalgia

Osteoarthritis

Chemo-neuropathy



Smith EML et al., *JAMA* 2013, 309: 1359–1367

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Neurotoxicity - Summary

- There is no effective **prophylaxis** for **Platin-induced neuropathy**.

  Calcium-Magnesium is not effective!

- **Duloxetin** ist **moderately effective for treatment** of chemotherapy-induced **neuropathic pain**

Smith EML et al., *JAMA* 2013, 309: 1359–1367

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Hematotoxicity

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update

Thomas J. Smith, Kari Bohlke, Gary H. Lyman, Kenneth R. Carson, Jeffrey Crawford, Scott J. Cross, John M. Goldberg, James L. Khatcheressian, Natasha B. Leighl, Cheryl L. Perkins, George Somlo, James L. Wade, Antoinette J. Wozniak, and James O. Armitage

Thomas J. Smith, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Kari Bohlke, American Society of Clinical Oncology, Alexandria; Scott J. Cross, Virginia Oncology Associates, Norfolk; James L. Khatcheressian, Virginia Cancer Institute, Richmond, VA; Gary H. Lyman, Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA; Kenneth R. Carson, Washington University, St Louis, MO; Jeffrey Crawford

A B S T R A C T

Purpose

To update the 2006 American Society of Clinical Oncology guideline on the use of hematopoietic colony-stimulating factors (CSFs).

Smith TJ et al., *J Clin Oncol* 2015, 33:3199-212

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Hematotoxicity

Key Points

- Primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia based on patient-, disease- and treatment-related factors. Primary CSF prophylaxis should also be administered in patients receiving dose-dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSF support when available. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

- Secondary prophylaxis with a CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

- CSFs should not be routinely used for patients with neutropenia who are afebrile. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

- CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors predictive of poor clinical outcomes. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Smith TJ et al., *J Clin Oncol* 2015, 33:3199-212

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Hematotoxicity

Table 1. Patient Risk Factors for Febrile Neutropenia

Risk Factor
In addition to chemotherapy regimen and type of malignancy, consider the following factors when estimating patient's overall risk of febrile neutropenia[23-25]:
Age ≥ 65 years
Advanced disease
Previous chemotherapy or radiation therapy
Preexisting neutropenia or bone marrow involvement with tumor
Infection
Open wounds or recent surgery
Poor performance status or poor nutritional status
Poor renal function
Liver dysfunction, most notably elevated bilirubin
Cardiovascular disease
Multiple comorbid conditions
HIV infection

Smith TJ et al., *J Clin Oncol* 2015, 33:3199-212

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Hematotoxicity

Table 2. Patient Risk Factors for Poor Clinical Outcomes Resulting From Febrile Neutropenia or Infection[28]

Risk Factor
Sepsis syndrome
Age $>$ 65 years
Profound neutropenia (absolute neutrophil count $< 0.1 \times 10^9$/L)
Neutropenia expected to last $>$ 10 days
Pneumonia
Invasive fungal infection
Other clinically documented infections
Hospitalization at time of fever
Prior episode of febrile neutropenia

Smith TJ et al., *J Clin Oncol* 2015, 33:3199-212

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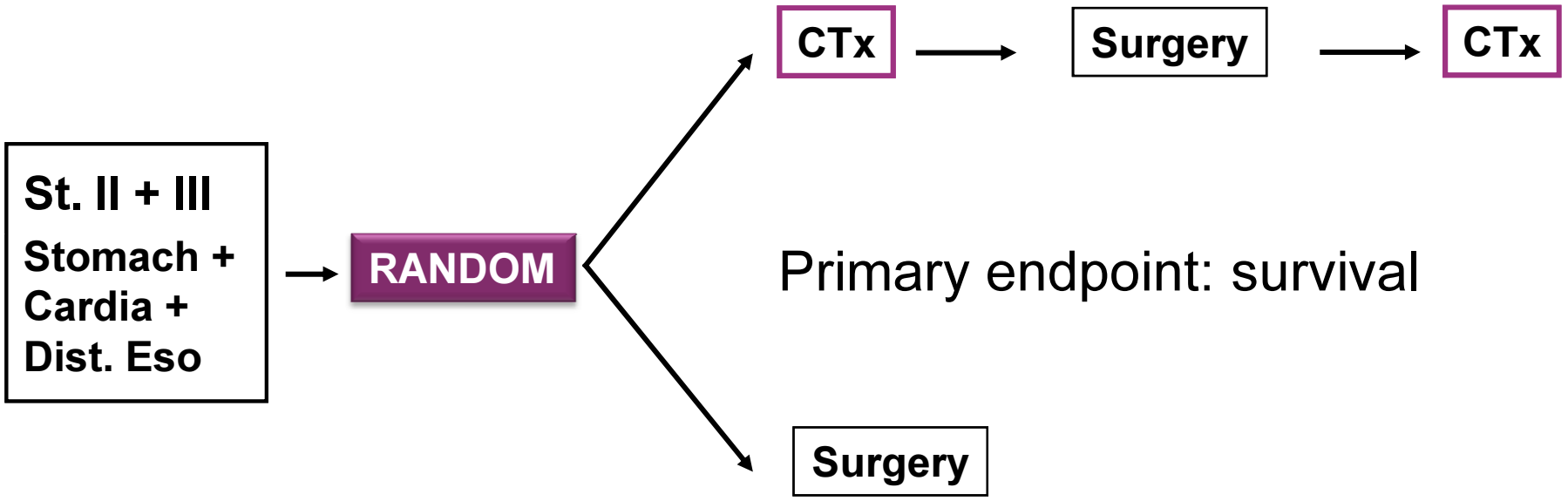
Peri-/Preoperative Therapy

MAGIC + FNCLCC



*Chemotherapy regimen: MAGIC, ECF (Epirubicin, Cisplatin, Fluorouracil)
FNCLCC, CF (Cisplatin, Fluorouracil)

Cunningham D et al. *N Engl J Med* 2006;355:11-20
Ychou et al. *J Clin Oncol* 2011; 29: 1715-21

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Feasibility of chemotherapy

	MAGIC (9 wks ECF)	**FNCLCC** (8 wks CF)
Pre-op. CTX completely given	86%	89%
Post-op. CTX given	55%	51%

Cunningham D et al. *N Engl J Med* 2006;355:11-20
Ychou et al. *J Clin Oncol* 2011; 29: 1715-21

Current Studies Integrating Radiotherapy

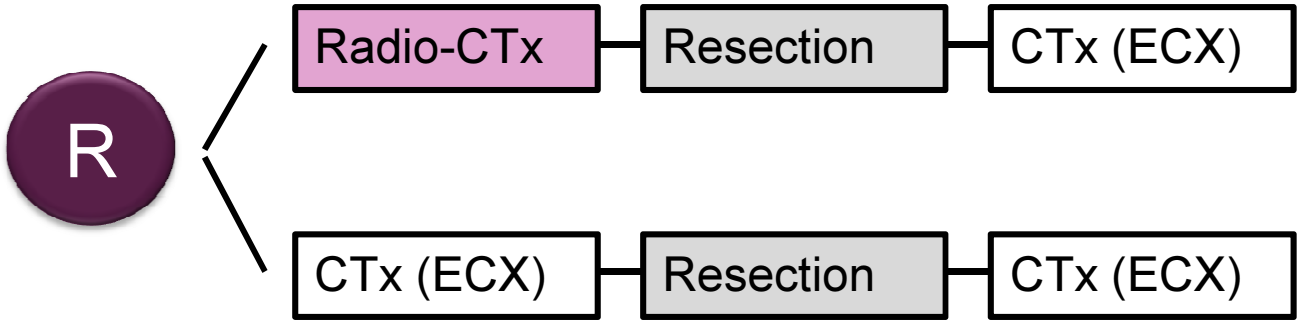
AUSTRALASIAN GASTRO-INTESTINAL AGITG TRIALS GROUP

TROG CANCER RESEARCH

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

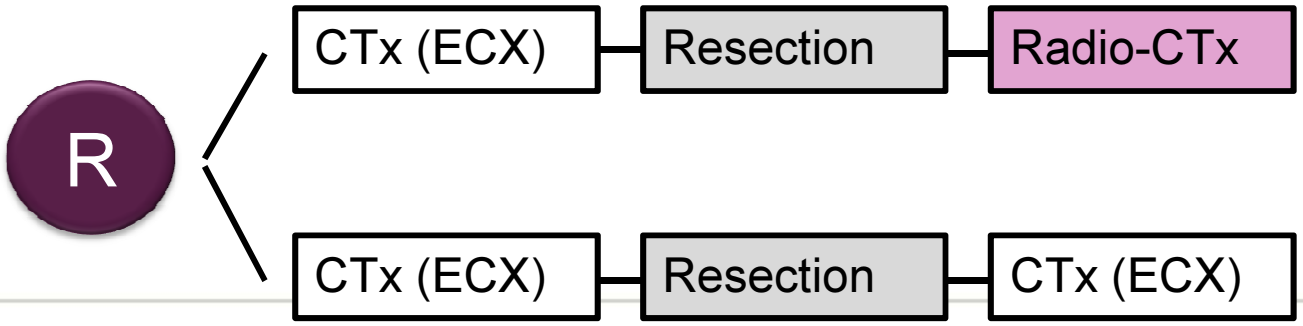
EORTC European Organisation for Research and Treatment of Cancer

TOPGEAR
(AUS, CAN, EU)
Stage Ib-IVa



DUCG Dutch Upper GI Cancer Group

CRITICS
(NL, Sweden)
Stage Ib-IVa



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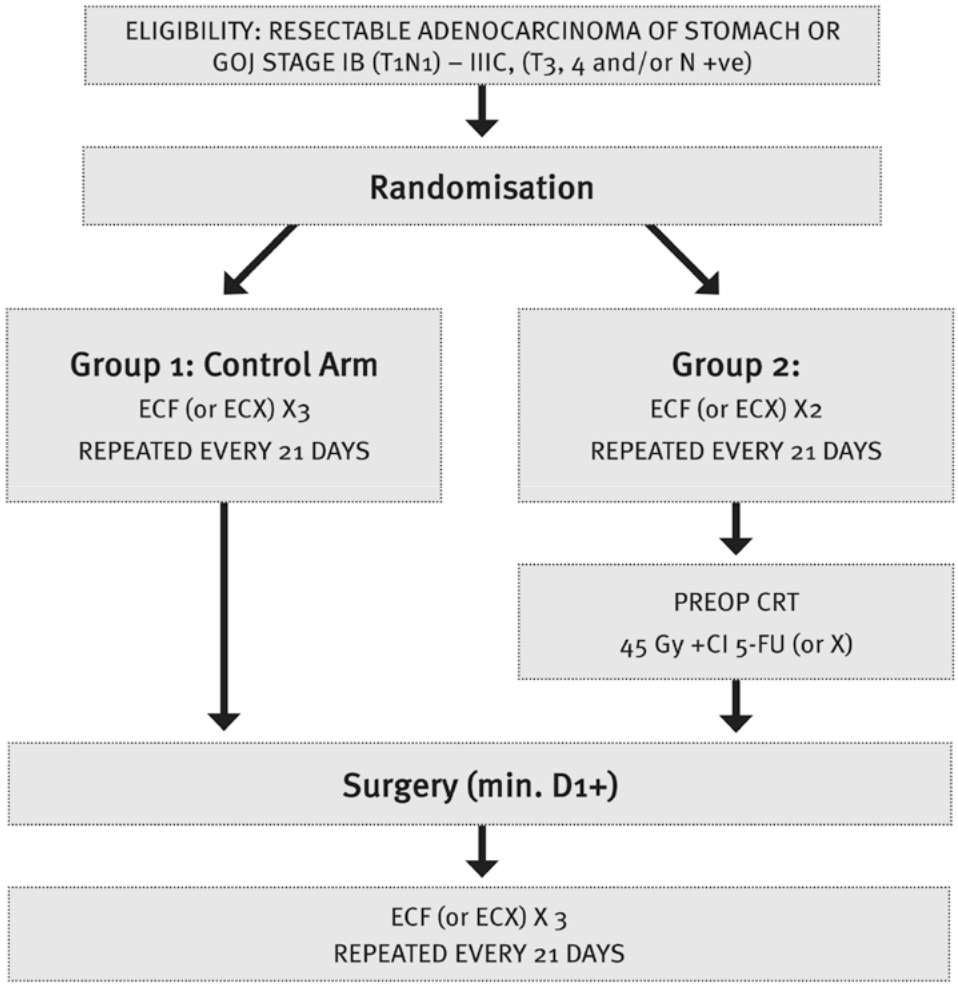
TOPGEAR Study



Leong T et al., *submitted* 2016

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TOPGEAR Study

Table 2. Treatment compliance

Perioperative ECF	CRT group	ECF group
Preoperative ECF	(N=60)	(N=60)
- received all cycles	59 (98.3%)	56 (93.3%)
Postoperative ECF	(N=48)	(N=53)
- received all cycles	24 (50%)	34 (64%)
Chemoradiation	(N=60)	-
- received CRT	55 (92%)	-
- received 45 Gy (of 56 RT patients)	55 (98%)	-
Surgery	(N=60)	(N=60)
- received surgery	51 (85%)	54 (90%)
- median time to surgery	5.7 weeks	4.9 weeks

(no significant differences)

Leong T et al., *submitted* 2016

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TOPGEAR Study

Table 3. Gastrointestinal toxicity

Toxicity: grade ≥3	CRT group (N=60) no. (%)	ECF group (N=60) no. (%)
Nausea	8 (13.3)	4 (6.7)
Vomiting	5 (8.3)	4 (6.7)
Dysphagia	6 (10)	5 (8.3)
Esophagitis	3 (5)	1 (1.7)
Anorexia	6 (10)	7 (11.7)
Diarrhoea	10 (16.7)	7 (11.7)
Overall gastrointestinal	18 (30)	19 (31.7)

(no significant differences)

Leong T et al., *submitted* 2016

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TOPGEAR Study

Table 4. Hematologic toxicity

Toxicity: grade ≥3	CRT group (N=60) no. (%)	ECF group (N=60) no. (%)
Neutropenia	27 (45)	24 (40)
Febrile neutropenia	6 (10)	5 (8.3)
Leukocytes	6 (10)	7 (11.7)
Anaemia	3 (5)	4 (6.7)
Thrombocytopenia	1 (1.7)	2 (3.3)
Overall hematologic	31 (51.7)	30 (50)

(no significant differences)

Leong T et al., *submitted* 2016

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TOPGEAR Study

Table 5. Surgical complications

Toxicity: grade ≥3	CRT group (N=51) no. (%)	ECF group (N=54) no. (%)
Anastomotic leak	4 (7.8)	3 (5.6)
Intra-abdominal sepsis	3 (5.9)	4 (7.4)
Wound infection	1 (2)	2 (3.7)
Chest infection	5 (9.8)	5 (9.3)
Respiratory failure	1 (2)	0
Cardiac ischemia	0	1 (1.9)
Overall surgical	11 (21.6)	12 (22.2)

(no significant differences)

Leong T et al., *submitted* 2016

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Summary

- Main toxicities are
  - Nausea and Emesis
    (MASCC guidelines for prophylaxis)
  - Neurotoxicity (no prophylaxis available)
  - Hematological (ASCO guidelines)
  - GI toxicity (diarrhea and mucositis)

8 – 11 May 2019, Prague (CZ)

Universitätsklinikum Leipzig
Anstalt öffentlichen Rechts

13th INTERNATIONAL
GASTRIC CANCER CONGRESS IGCC 2019

INTERNATIONAL GASTRIC CANCER CONGRESS PRAGUE 2019

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- Venue
- Prague
- Czech Republic
- 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.

New perspectives in gastric cancer

Marcel Verheij MD PhD
Department of Radiation Oncology
NKI, Amsterdam

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Strategies to improve outcome

- Treatment-related
- Patient-related
- Tumor-related

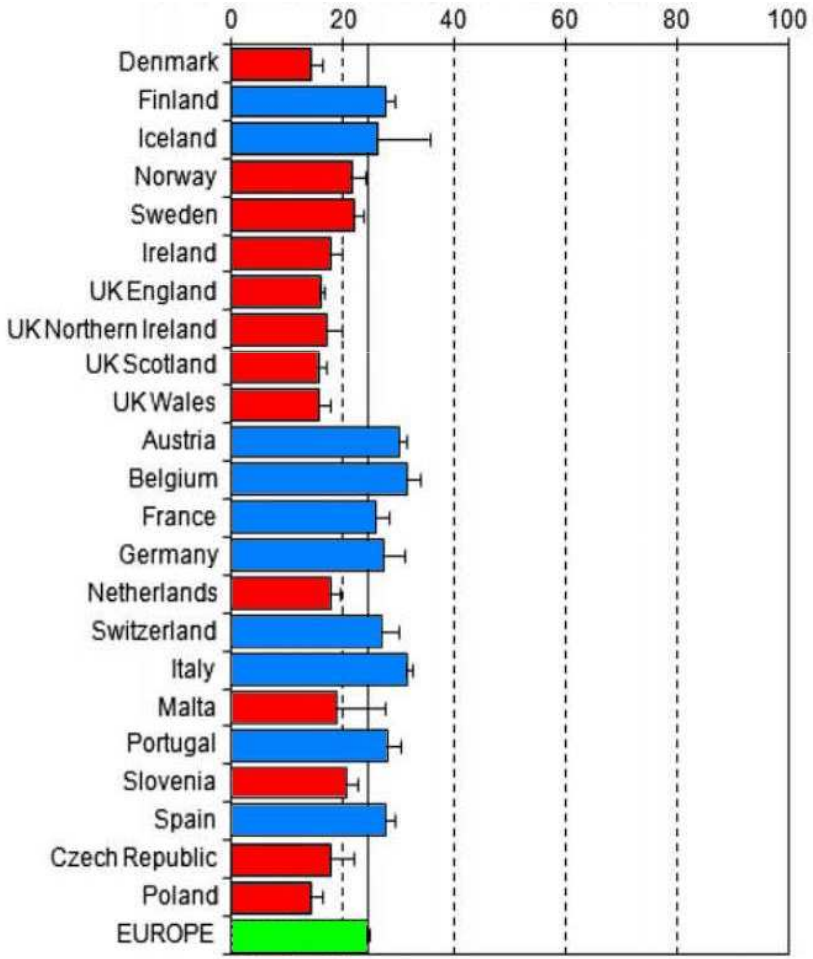
Strategies to improve outcome

- 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

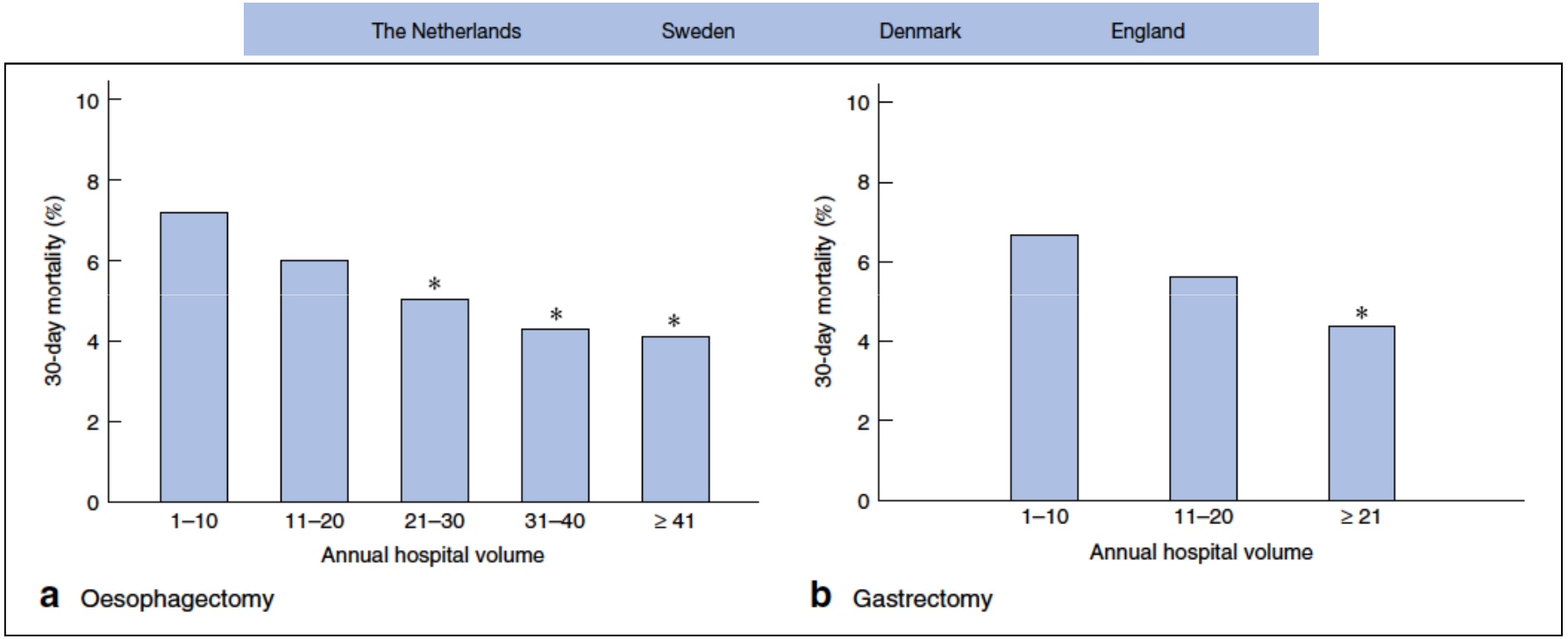

Fig. 4 Postoperative 30-day mortality after a oesophagectomy and b gastrectomy, adjusted for sex, age, and histology, by annual hospital volume (procedures per year). *$P < 0{\cdot}050$ *versus* 1–10 (generalized estimated equations)

Dikken et al. Eur J Surg Oncol 2012

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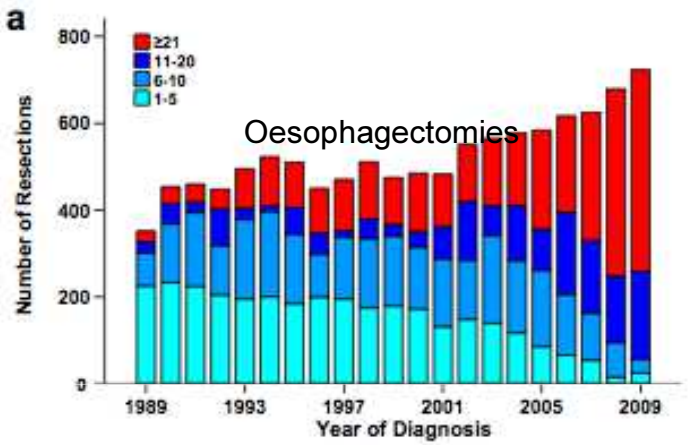
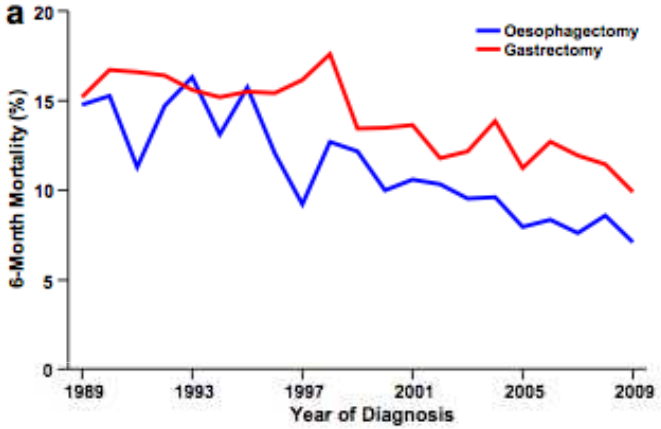
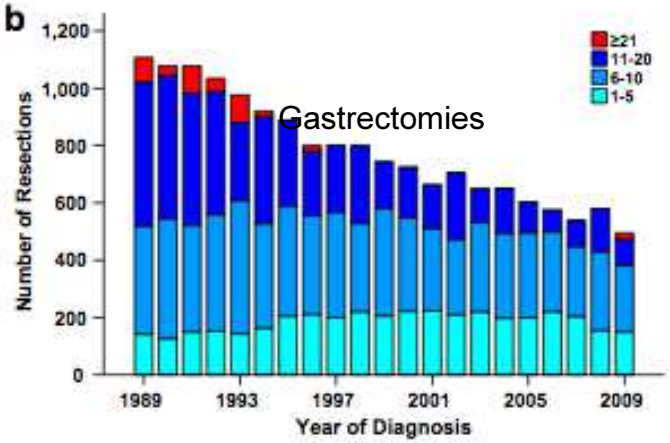
Improving surgical quality

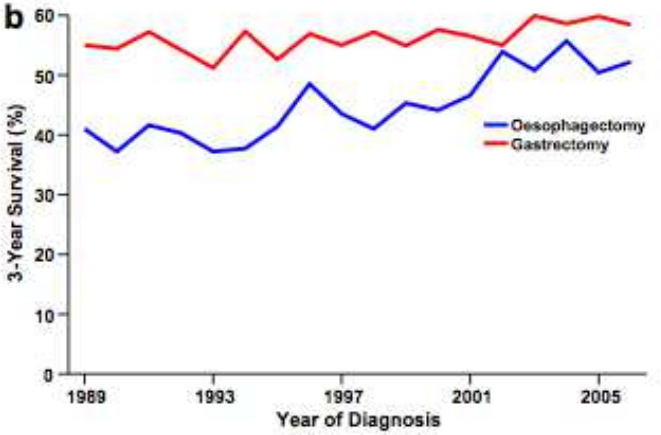
The effect of centralization

Number of resections per hospital volume category and surgical outcome in The Netherlands









Dikken et al. Eur J Cancer 2012

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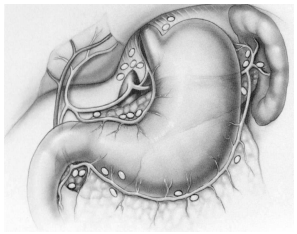
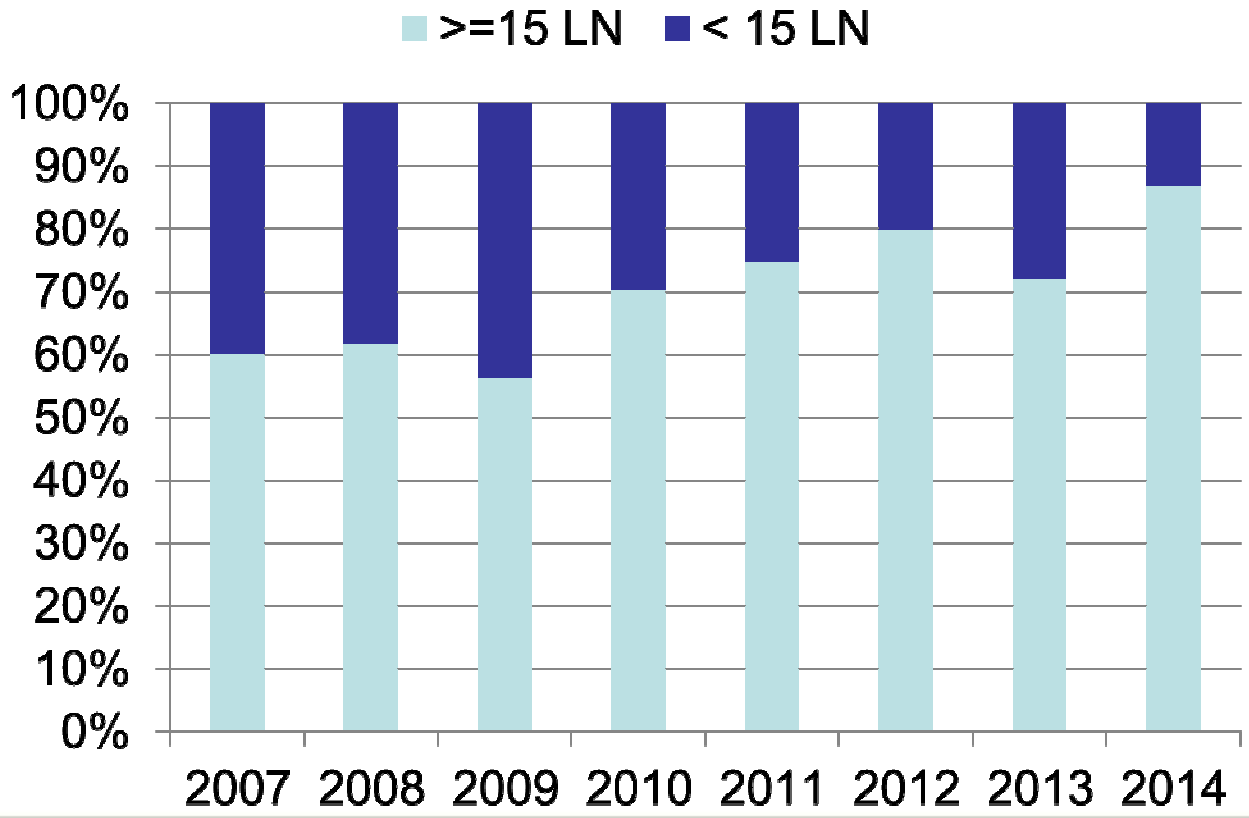
CRITICS trial

- Number of examined lymph nodes -



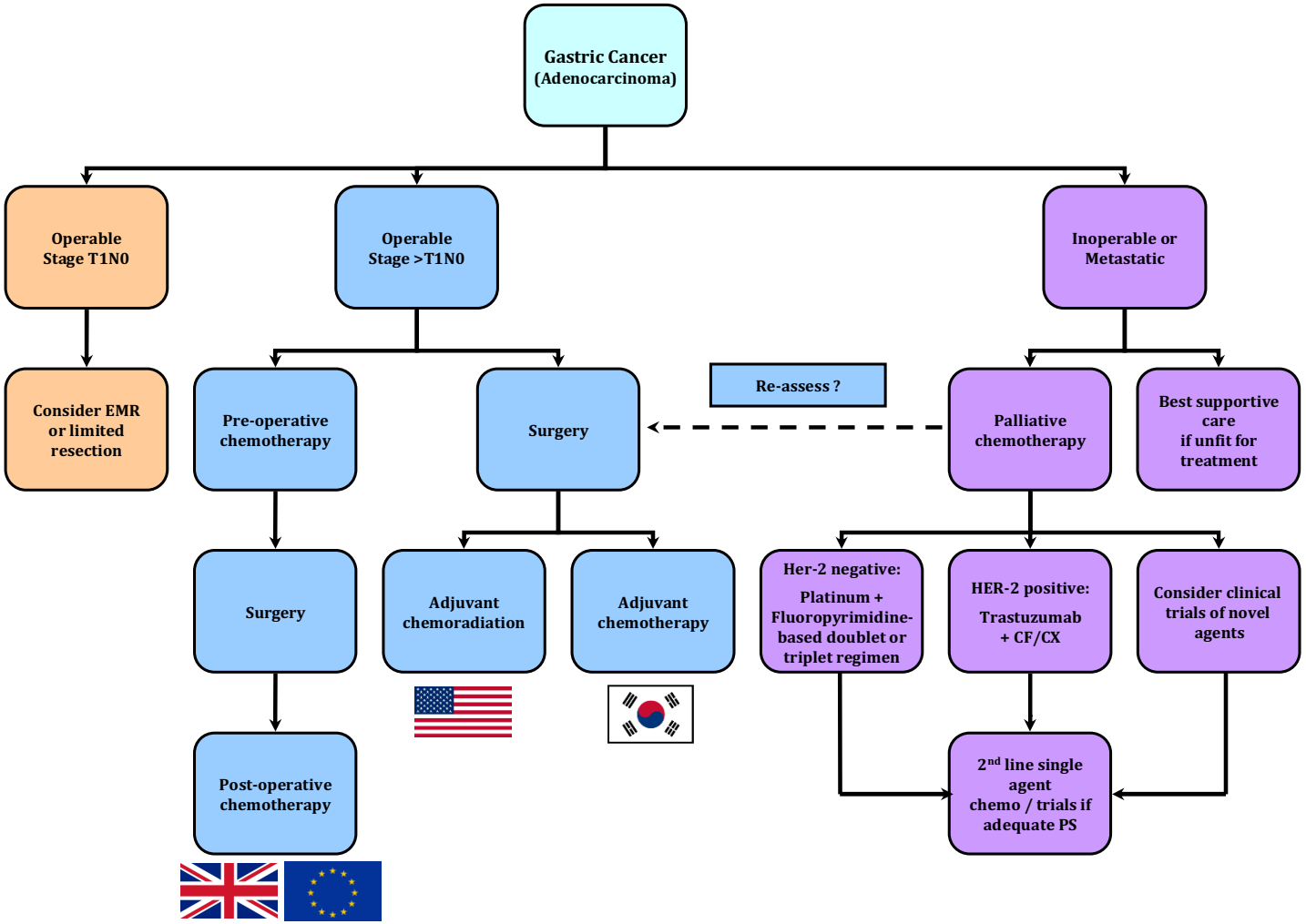


clinical practice guidelines

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%
ARTIST	**S** ➔ CT	75%
ARTIST	**S** ➔ CRT	82%
CLASSIC	**S** ➔ CT	67%
TOPGEAR part 1	CT ➔ **S** ➔ CT	60%
TOPGEAR part 1	CT ➔ CRT ➔ **S** ➔ CT	46%
CRITICS	CT ➔ **S** ➔ CT CT ➔ **S** ➔ CRT	49%

S=Surgery; CT=ChemoTherapy; CRT=ChemoRadioTherapy

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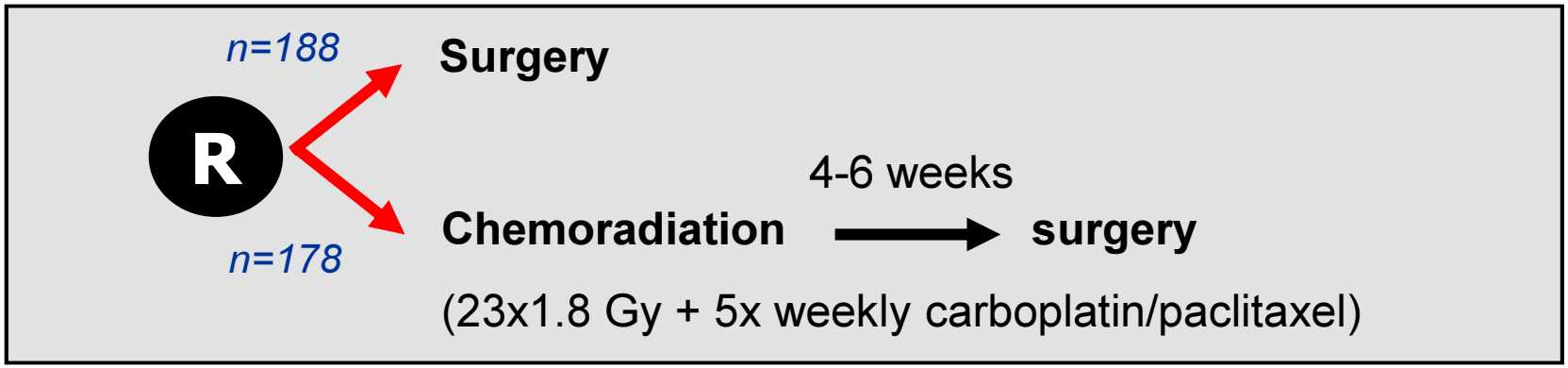
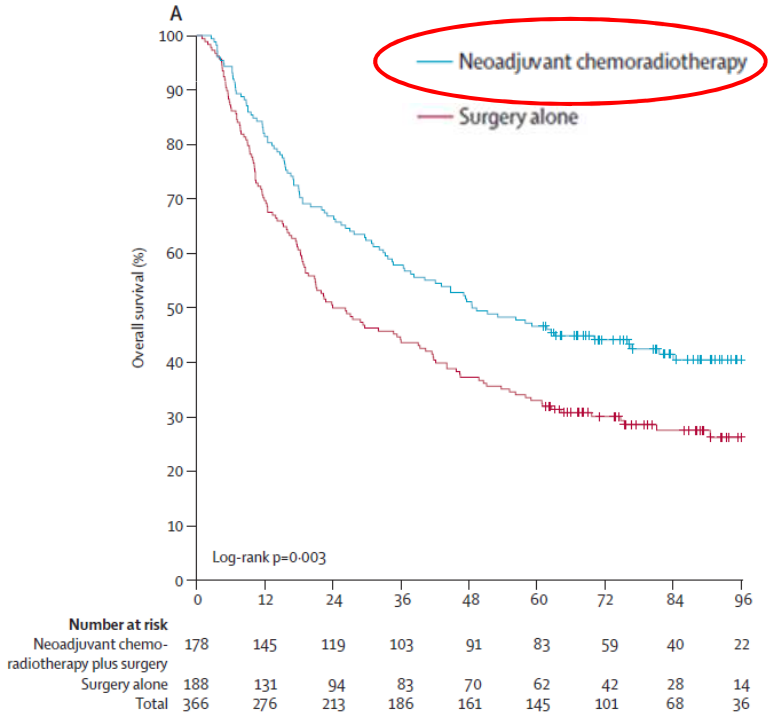
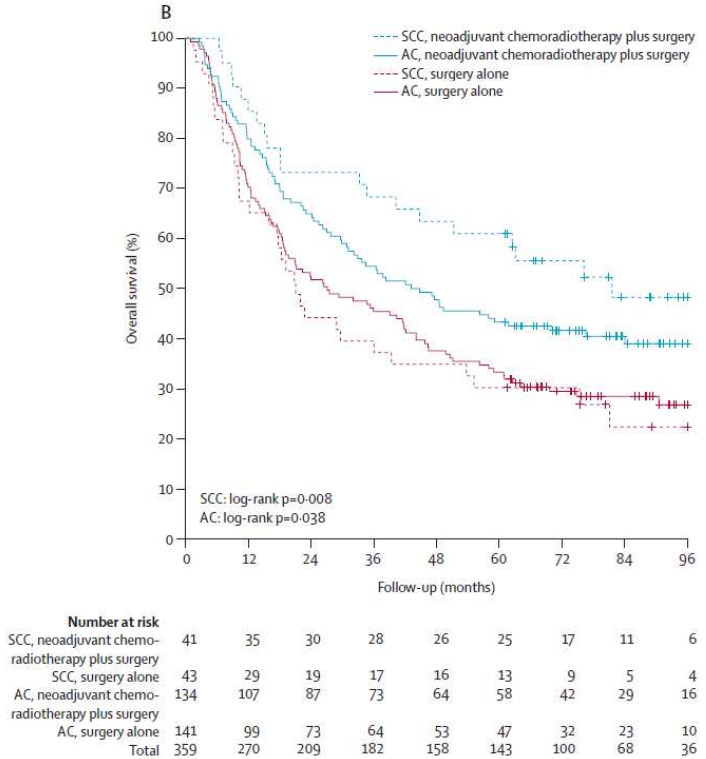
Pre-operative chemoradiation improves outcome in esophageal and junctional cancer: the CROSS trial

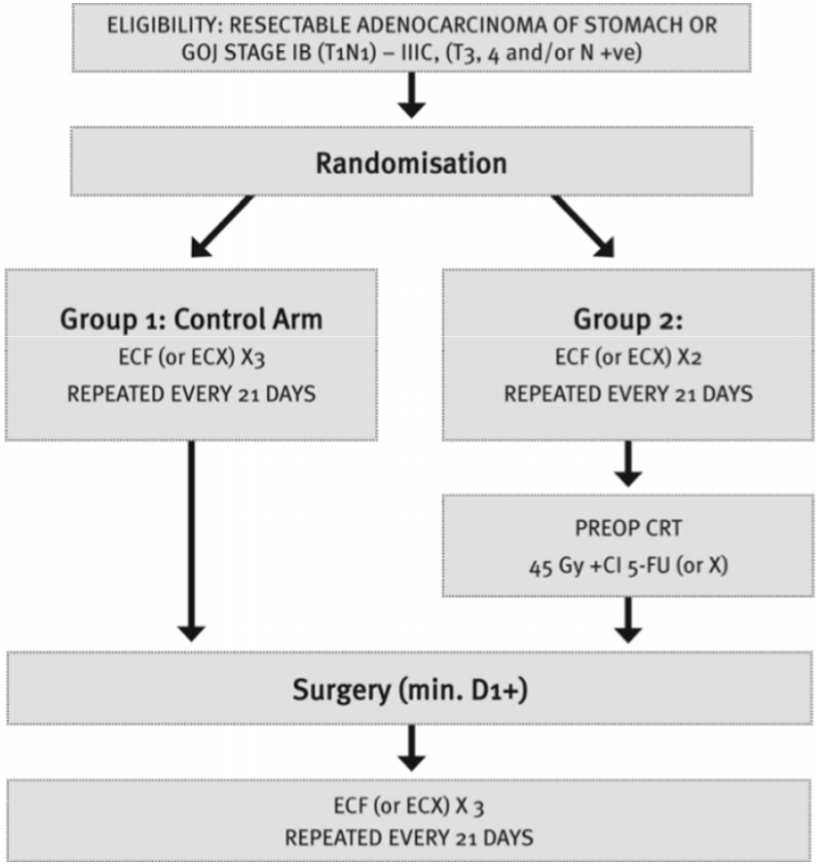






Shapiro et al. Lancet Oncol 2015 (median FU 84.1 months)

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

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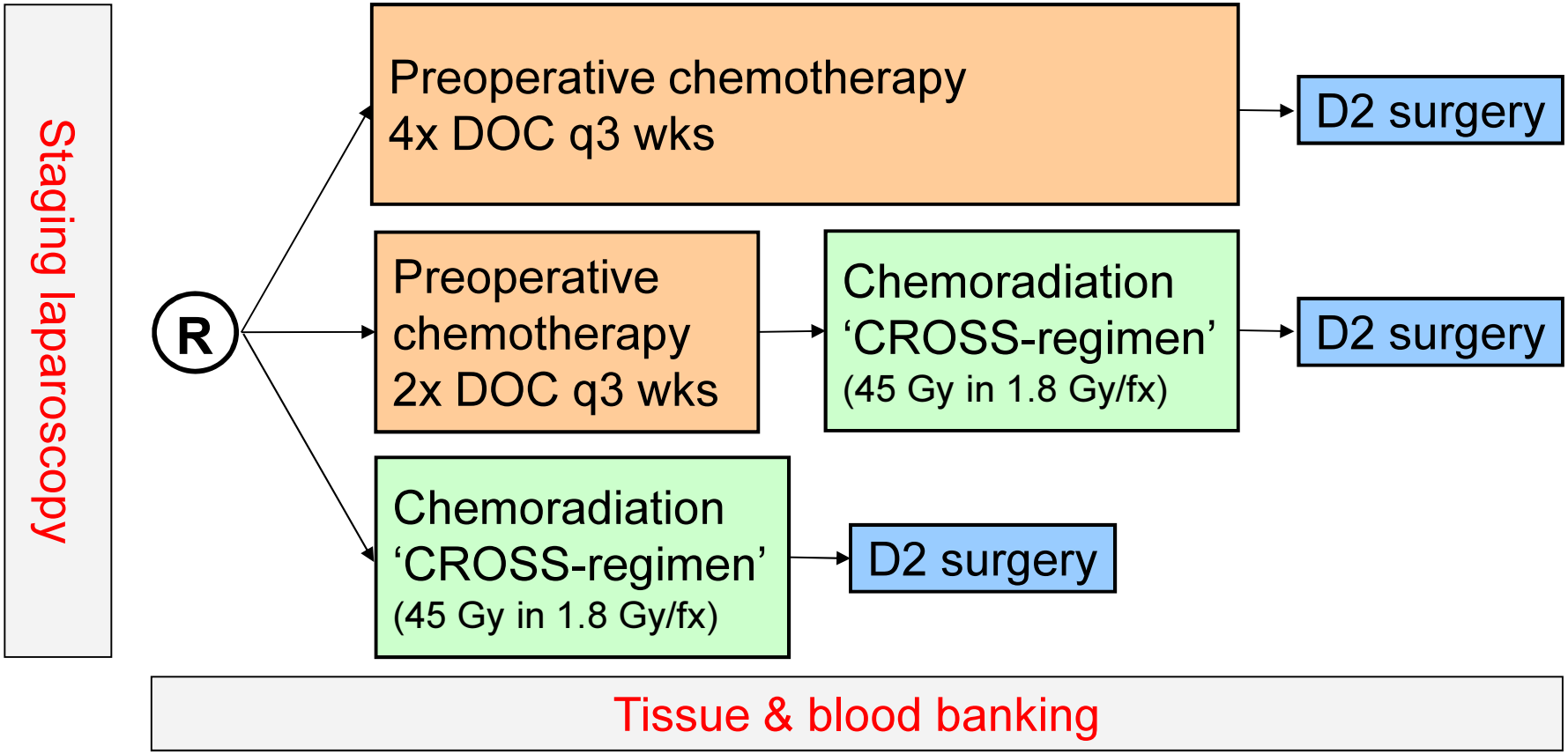
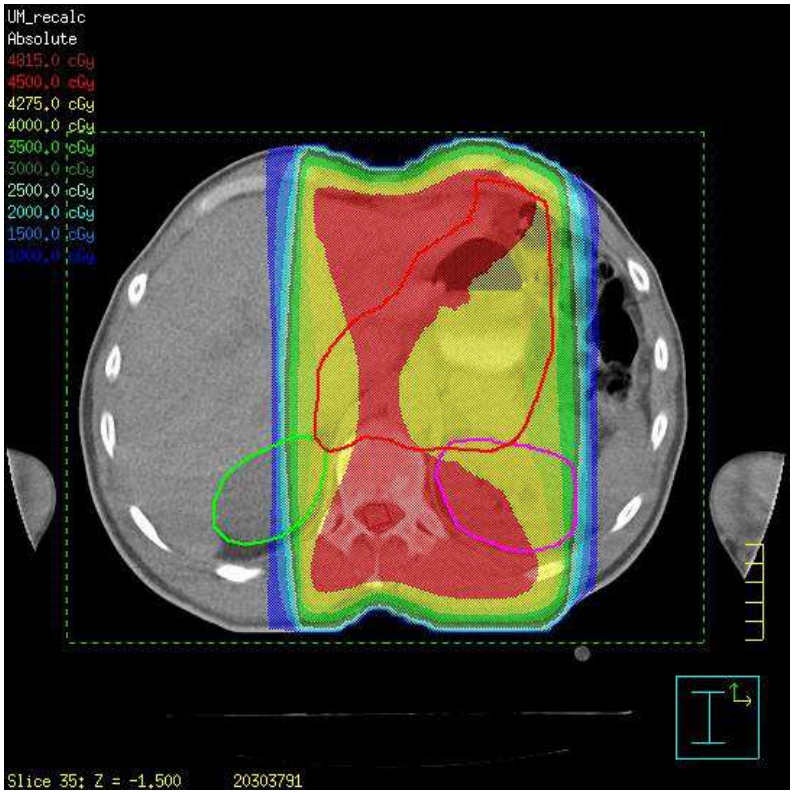
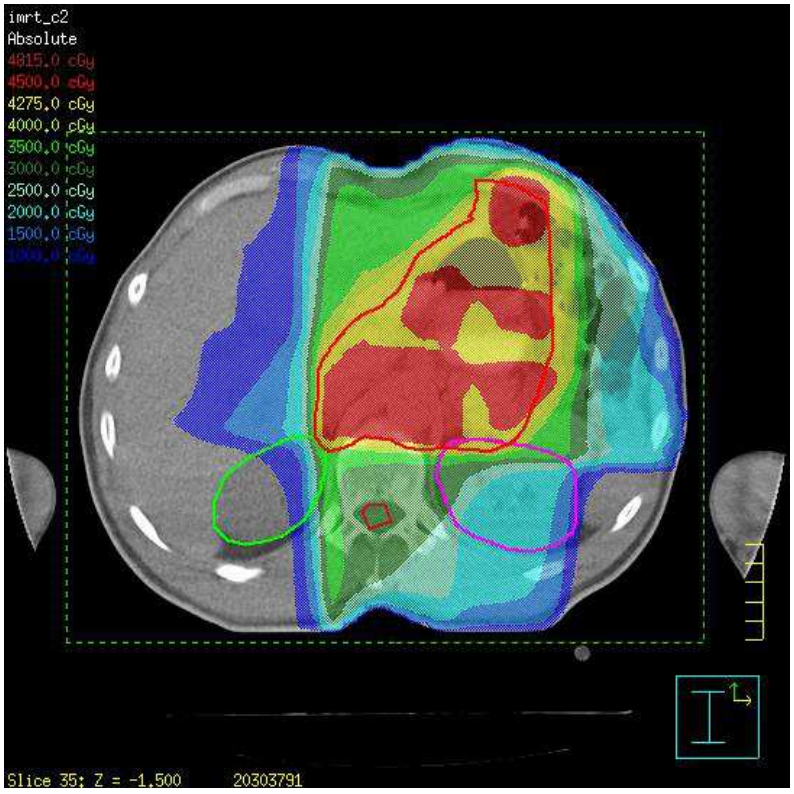
Design CRITICS-II



Advanced radiation techniques reduce the dose to both kidneys



Conventional AP-PA



IMRT

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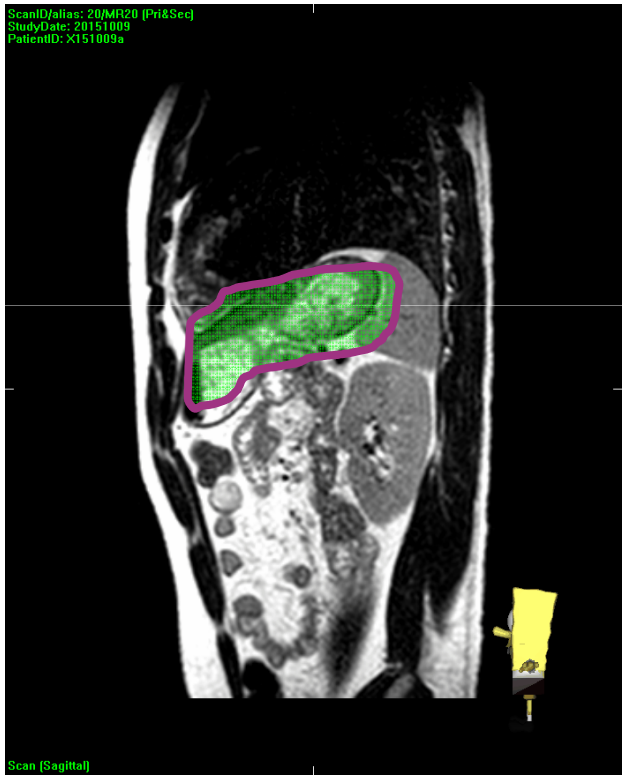
Optimal image-guided radiotherapy in gastric cancer: MR-guided radiotherapy

- 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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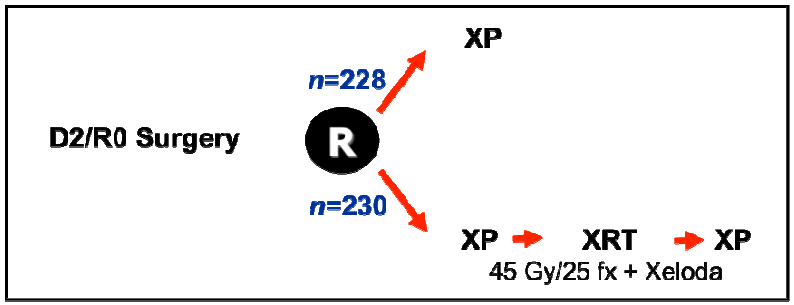
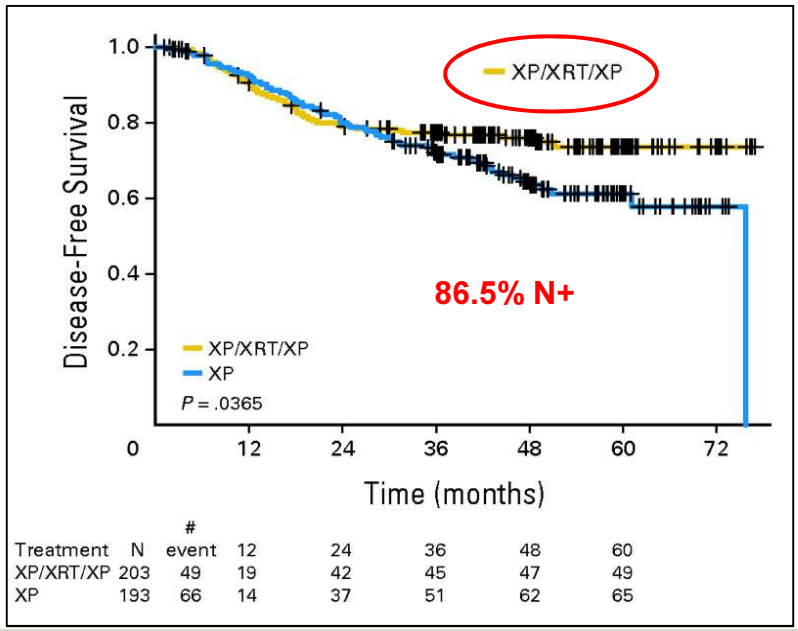
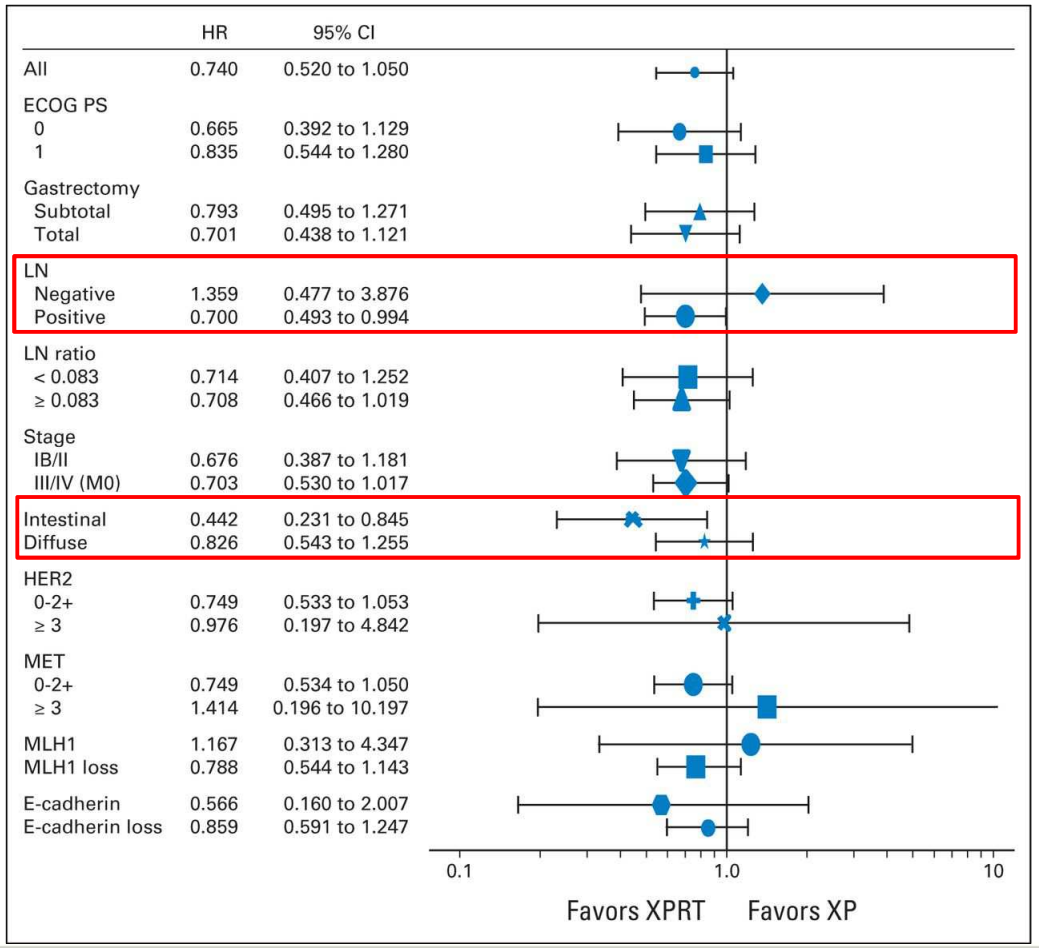
ARTIST Trial: Post-operative chemoradiotherapy improves DFS in lymph node-positive patients







Lee et al. JCO 2012

Park et al. JCO 2015

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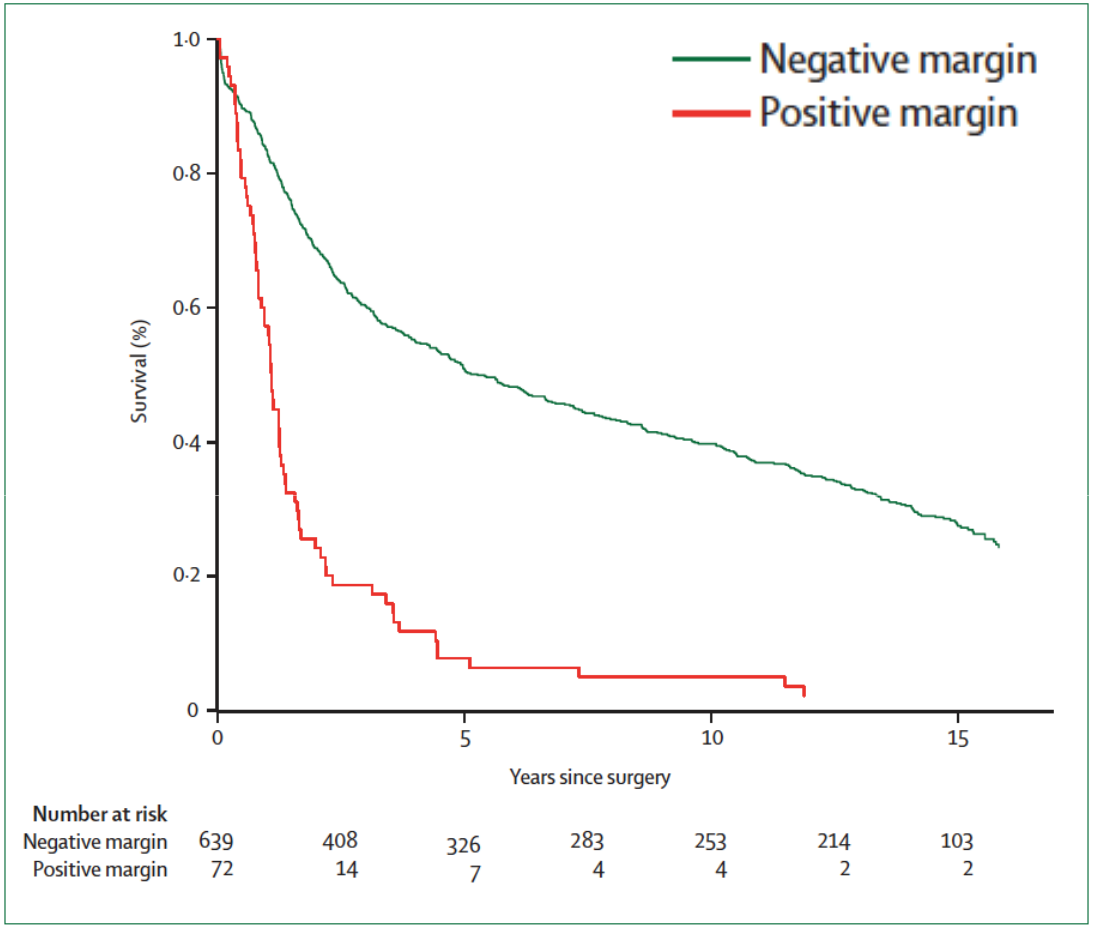
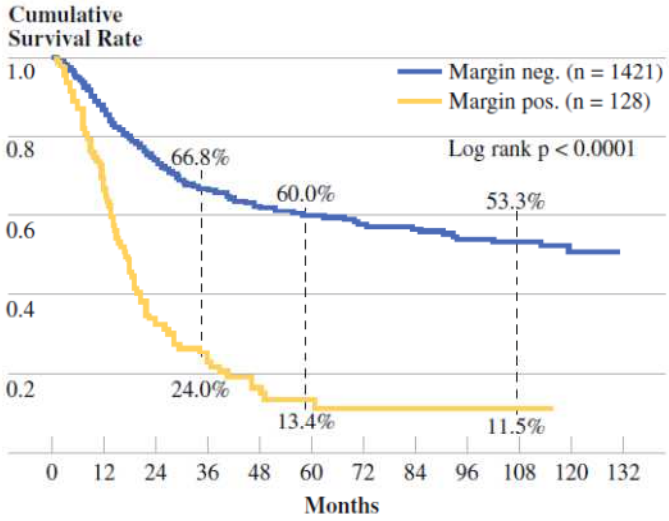
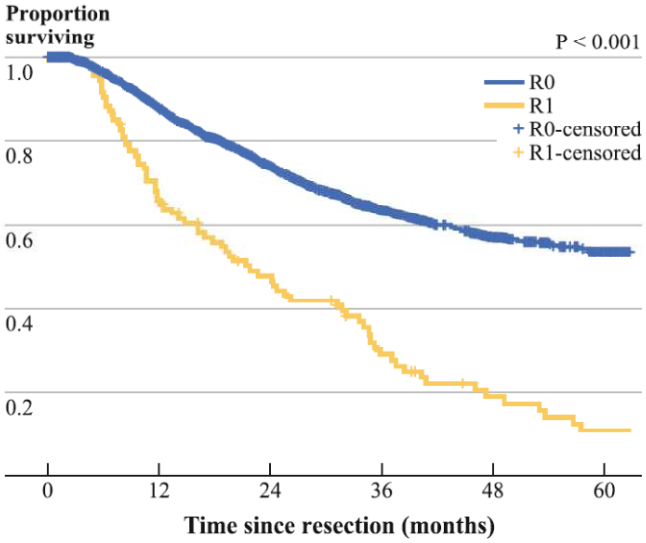
Impact radicality resection margin on survival



Hartgrink et al. Lancet 2009

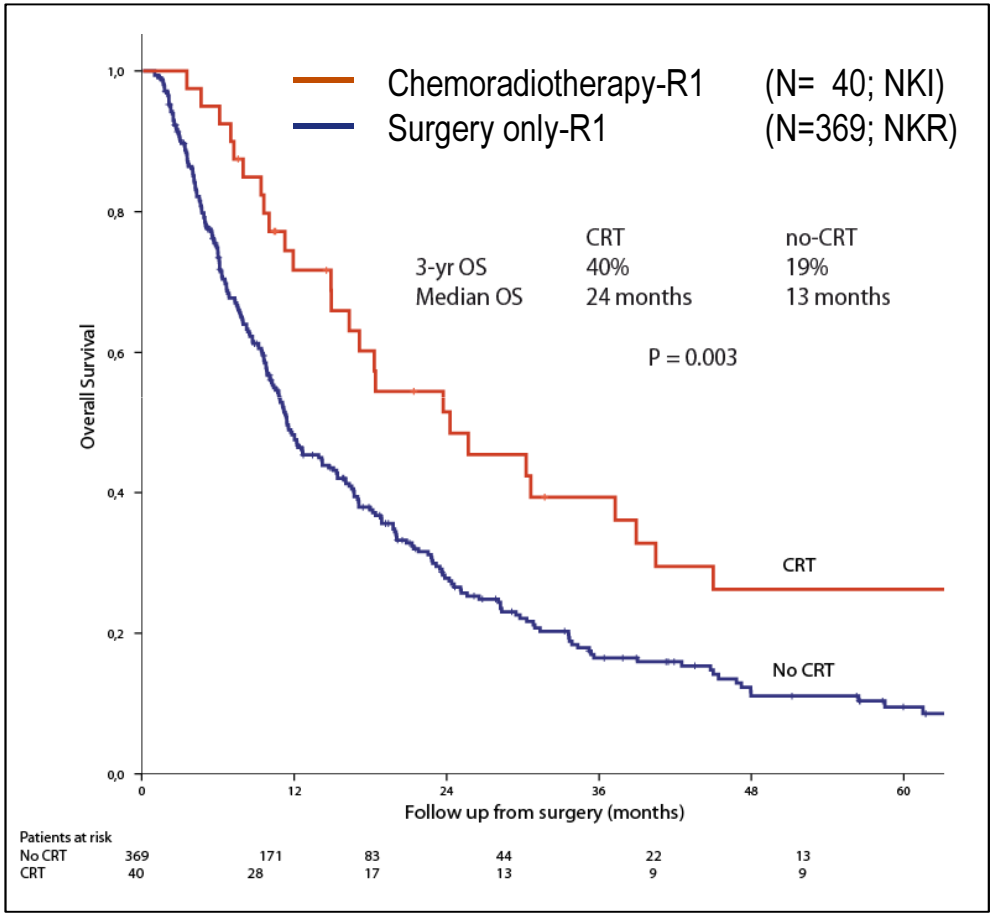


Wang et al. ASO 2009



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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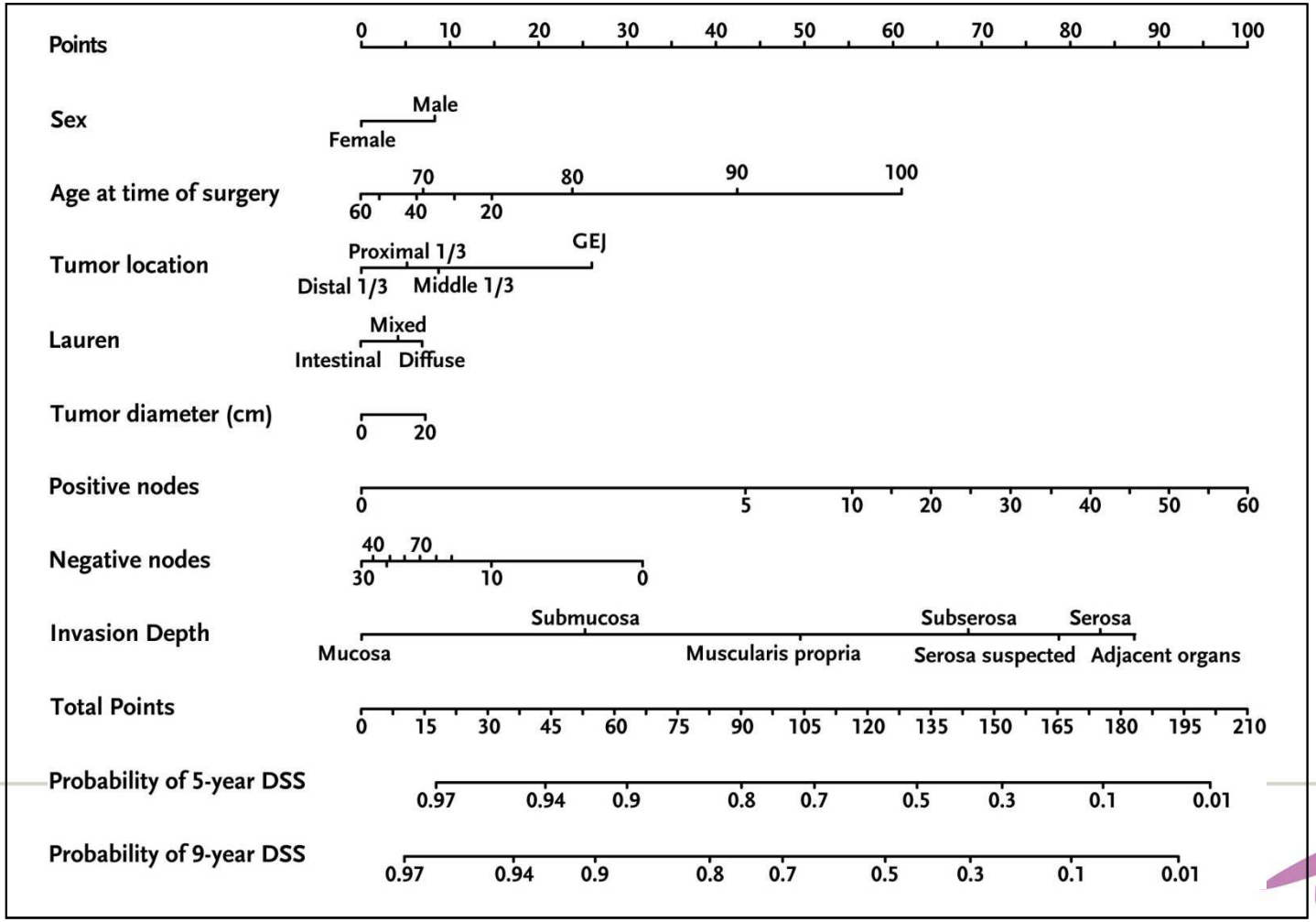
Performance of a Nomogram Predicting Disease-Specific Survival After an R0 Resection for Gastric Cancer in Patients Receiving Postoperative Chemoradiation Therapy

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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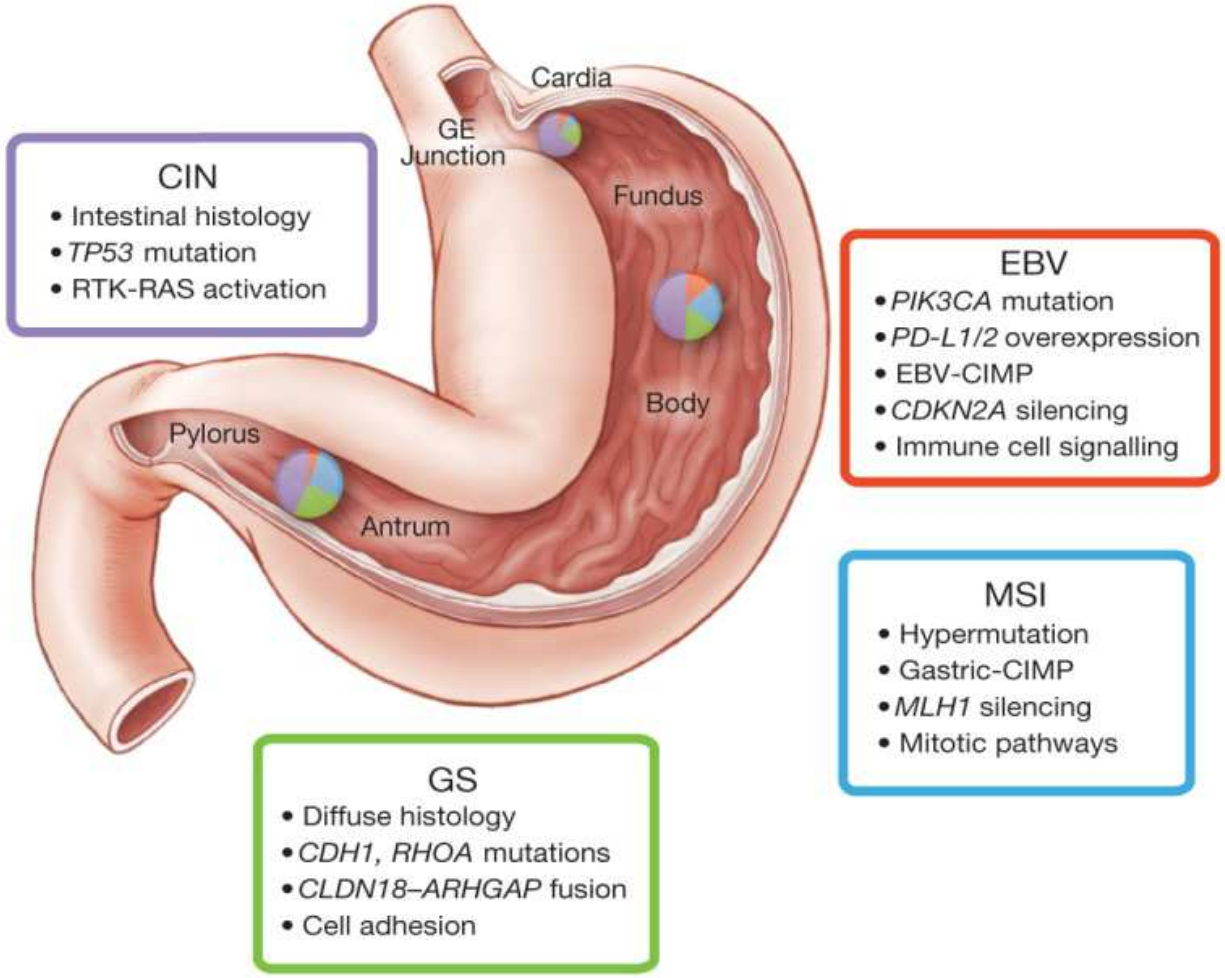
Strategies to improve outcome

Treatment-related: where, when and how?

Patient-related: who?

Tumor-related: which?

Key features of gastric cancer subtypes



Bass et al. Nature 2014

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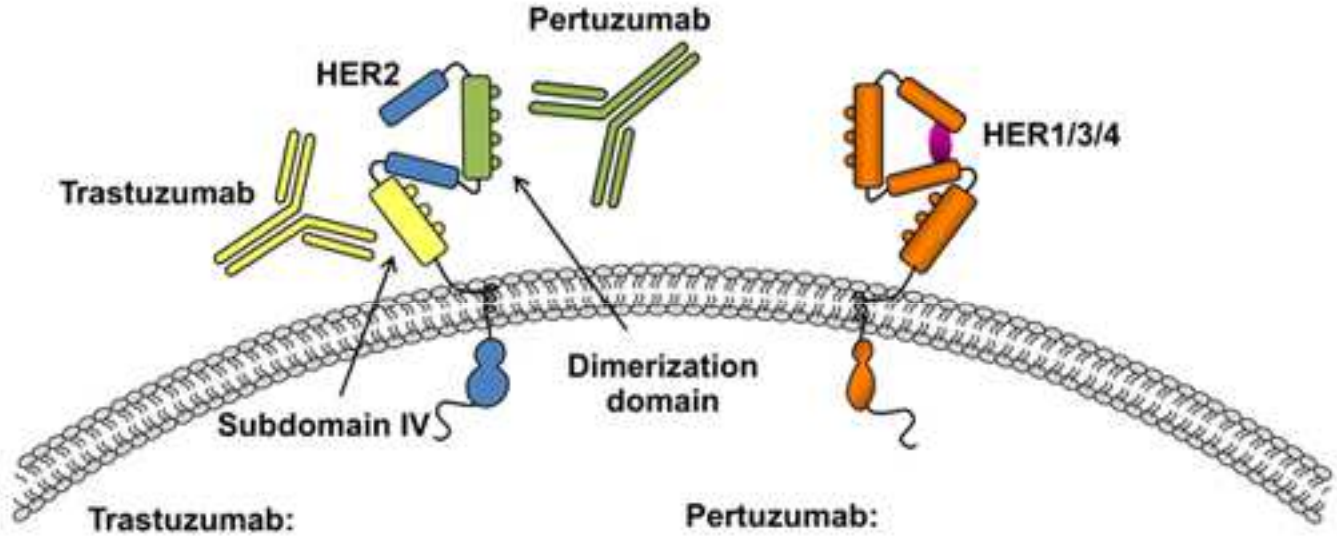
HER2 positive primary GC:

Pertuzumab and Trastuzumab
Complementary Mechanisms of Action



Trastuzumab:

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Pertuzumab:

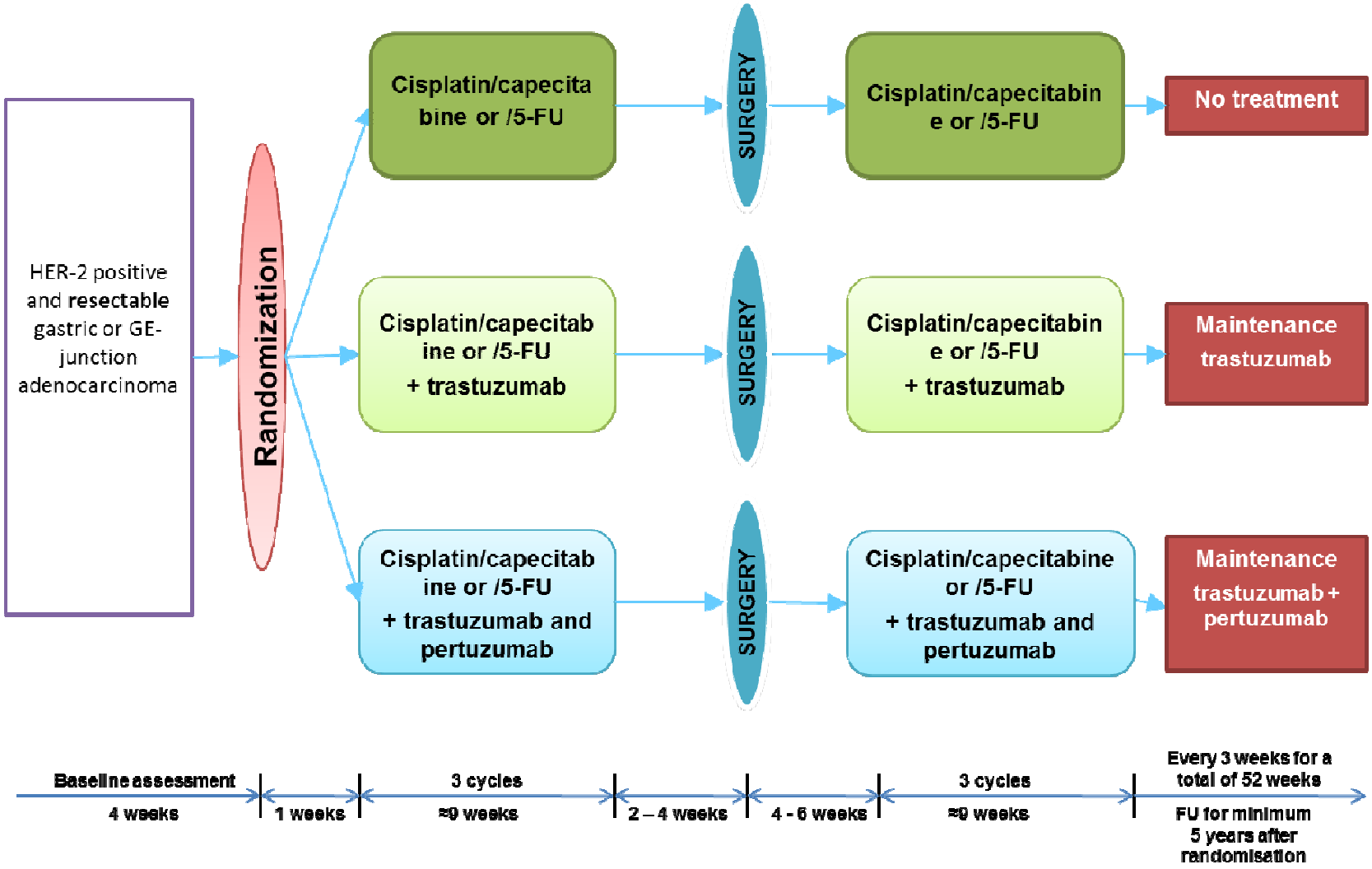
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

Baselga J, et al.[5]

DUCG
Dutch Upper GI Cancer Group

EORTC
The future of cancer therapy

Design INNOVATION trial



EORTC
The future of cancer therapy

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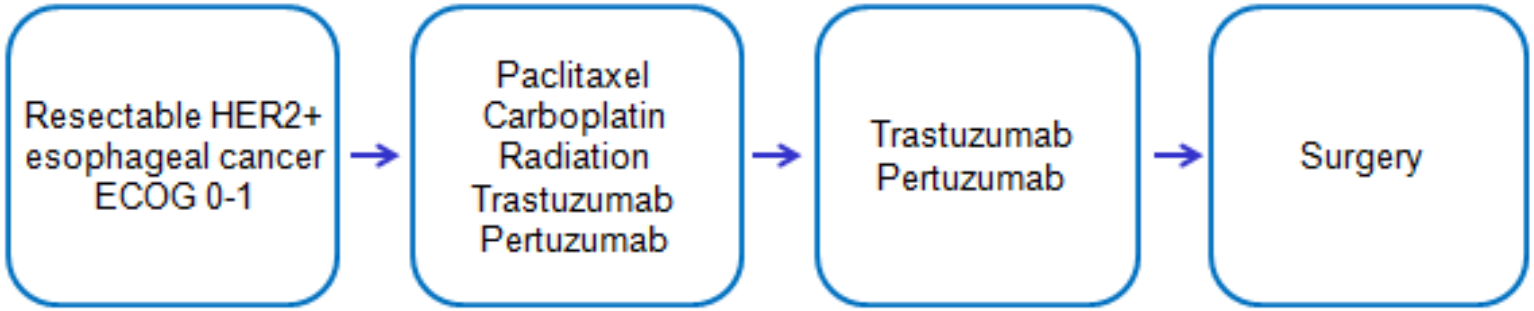
Design TRAP trial



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*