GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

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ESMO Preceptorship

Gastric cancer

Berlin, Germany
11-12 October 2013

The role of chemoradiotherapy in GE junction and gastric cancer

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Overview

- Postoperative chemoradiotherapy
- Preoperative chemoradiotherapy
- Palliative radiation
- Technical aspects

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- Postoperative chemoradiotherapy
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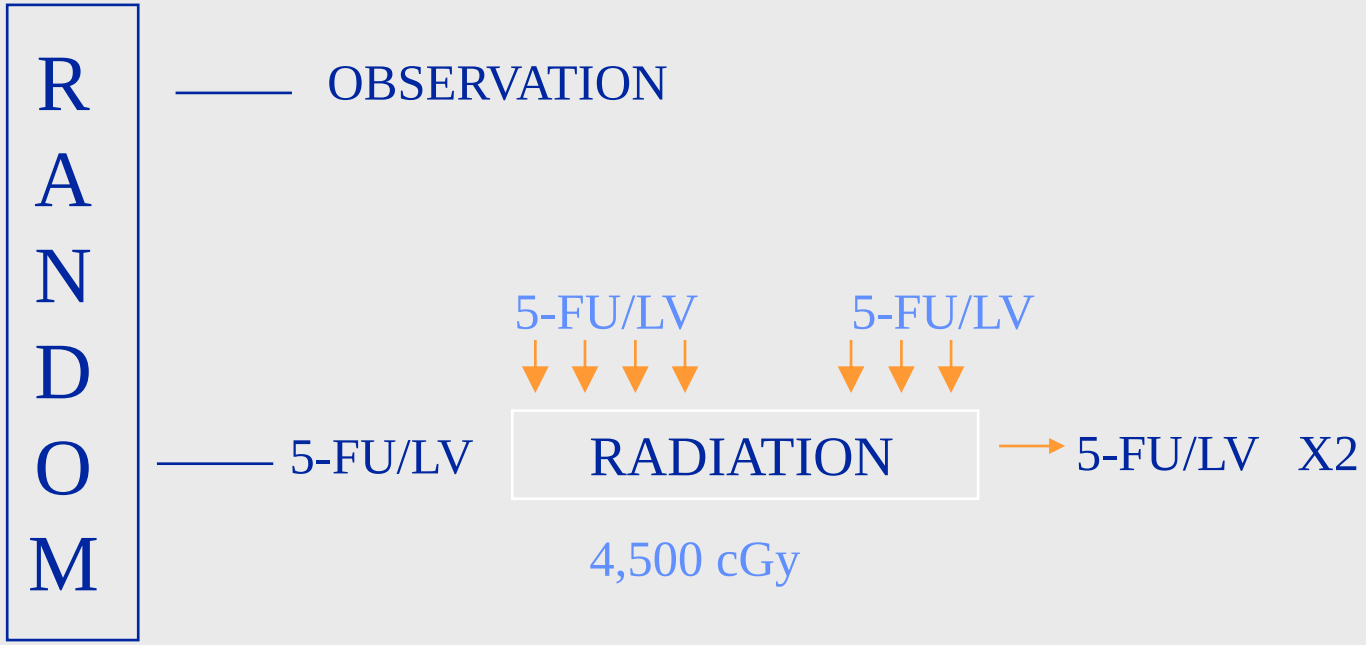
GASTRIC CANCER
SWOG 9008/INT 0116
RESECTED GASTRIC CANCER

SCHEMA

RESECTED
STAGE IB-IV (MO)
GASTRIC
ADENOCARCINOMA

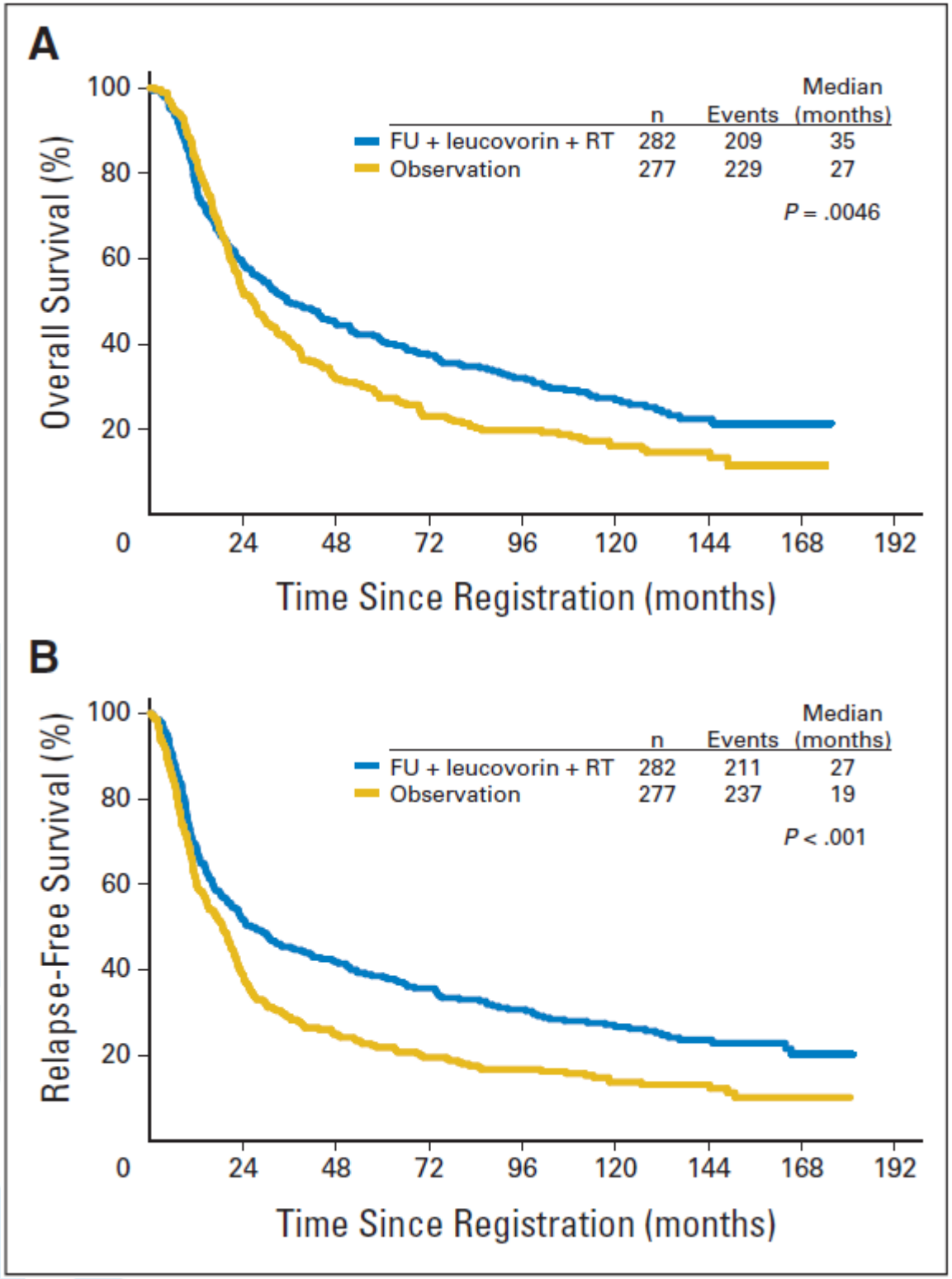


Post-operative Chemoradiotherapy

INT 0119 - SWOG 9008

	Surgery	Surgery chemo RT	p-value
Median DFS	19 months	30 months	p=0.001
3y survival Med. Survival	40% 27 months	50% 36 months	p=0.03

Macdonald J et al, NEJM 2001



Smalley et al, JCO 2012

Post-operative Chemoradiotherapy

INT 0116:

- Significant improvement in overall survival and disease free survival
- Effect mainly on local failure rate (19 vs 29%)
- Acceptable toxicity

  → New standard?

But:

- Randomization after surgery
- No optimal surgery: 54% < D1 resection
- RT: careful planning - experience!
- Chemotherapy regimen: not optimal
- Few patients in stage IB (n=39)
- Results not completely in agreement with what was expected on failure pattern

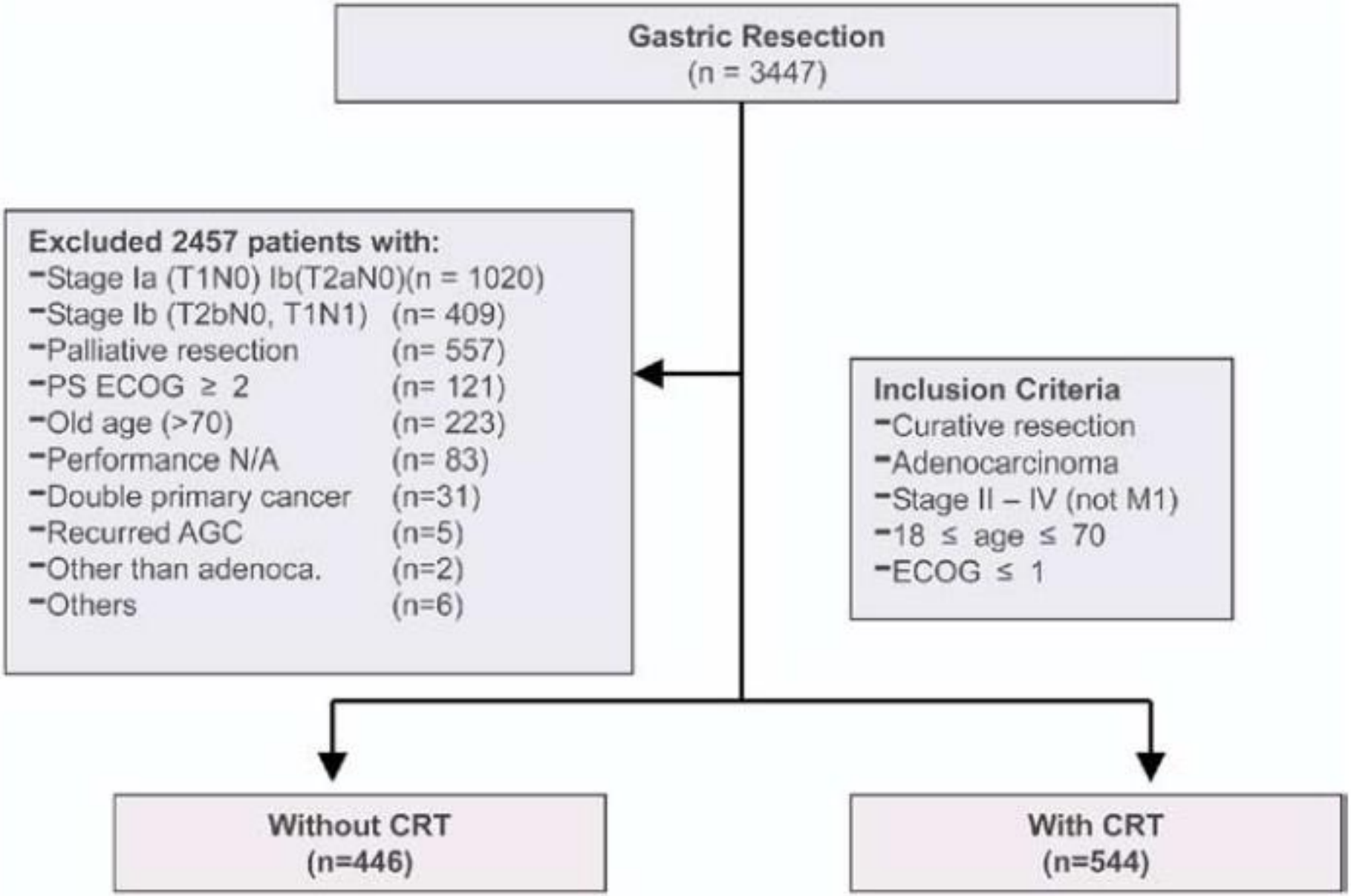
Drawbacks post-operative chemoradiation

- **35%** (!) of the RT treatment plans adjusted to avoid toxic effects on critical organs
- Still substantial major toxic effects
  - hematological: 54%
  - gastro-intestinal: 33%
- Only 64% completed postoperative treatment
- Costly treatment

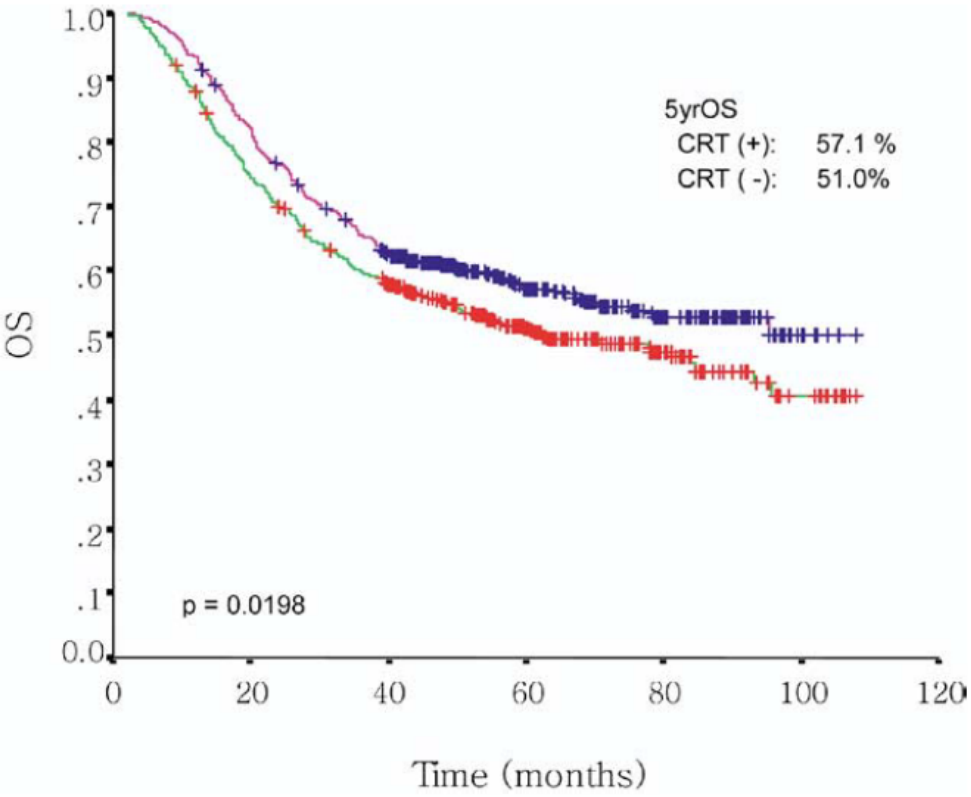
Quality Control Radiotherapy

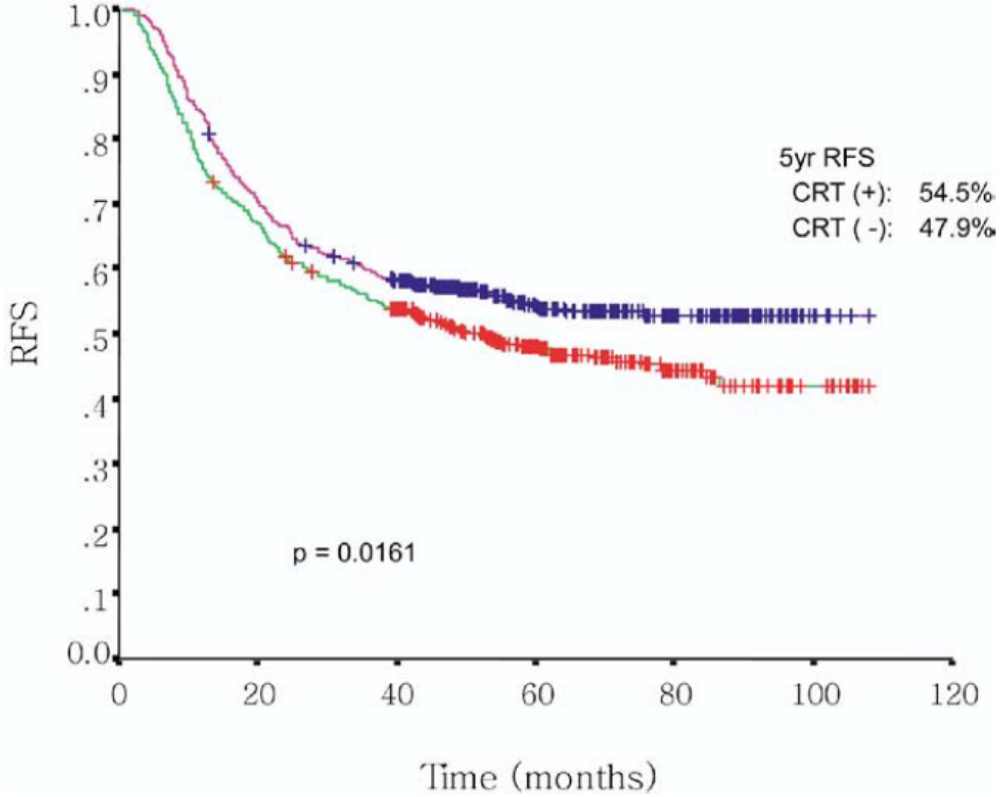
- 35% deviations from protocol
  - 10% potentially **lethal** errors
    - 9 heart in field
    - 9 both kidneys in field
    - 5 whole liver in field
- 20% excluding tumor bed
- 20% regional lymph nodes
- 10% anastomosis missed

Smalley et al, Int J Rad Onc Biol Phys, 2003

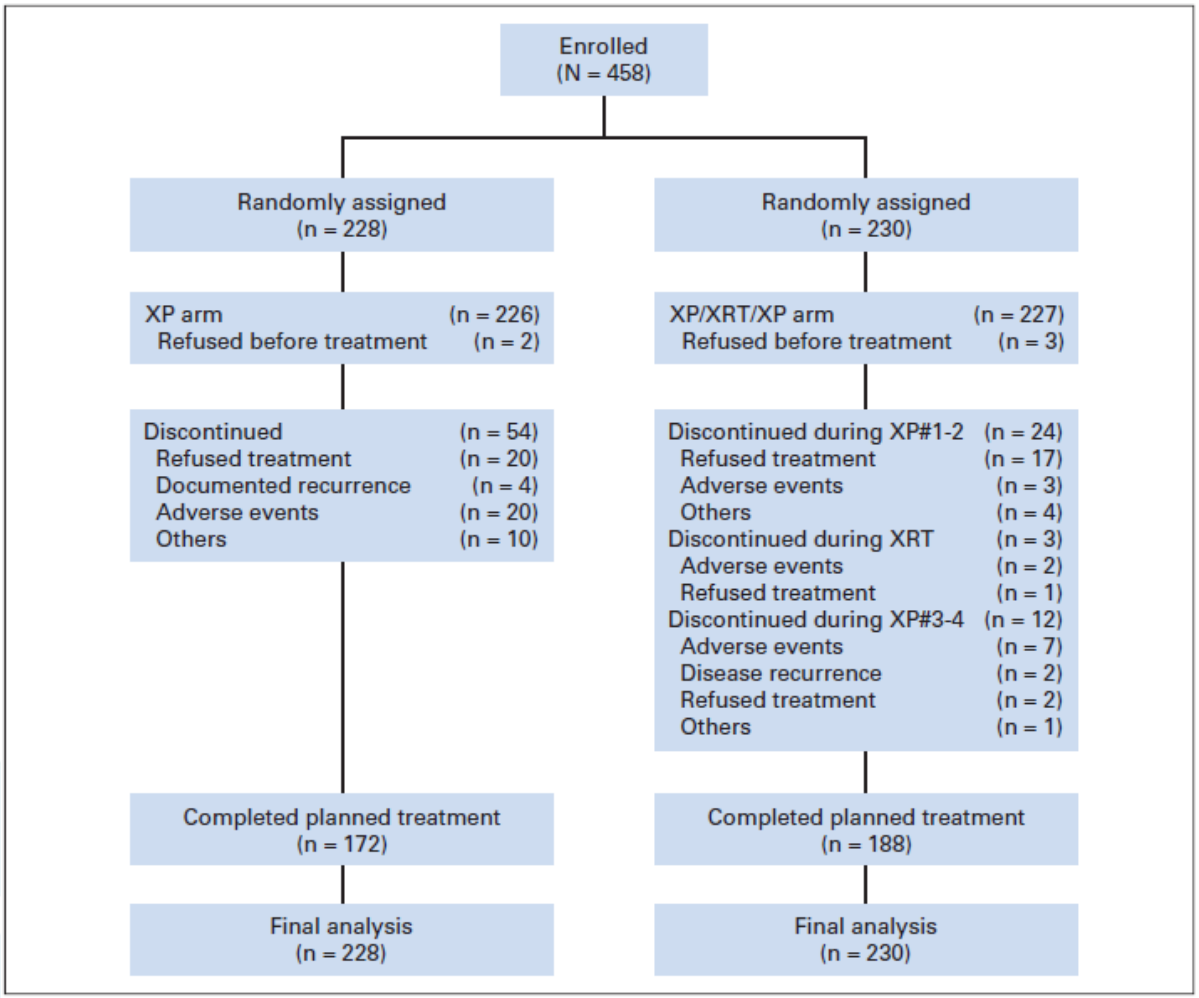


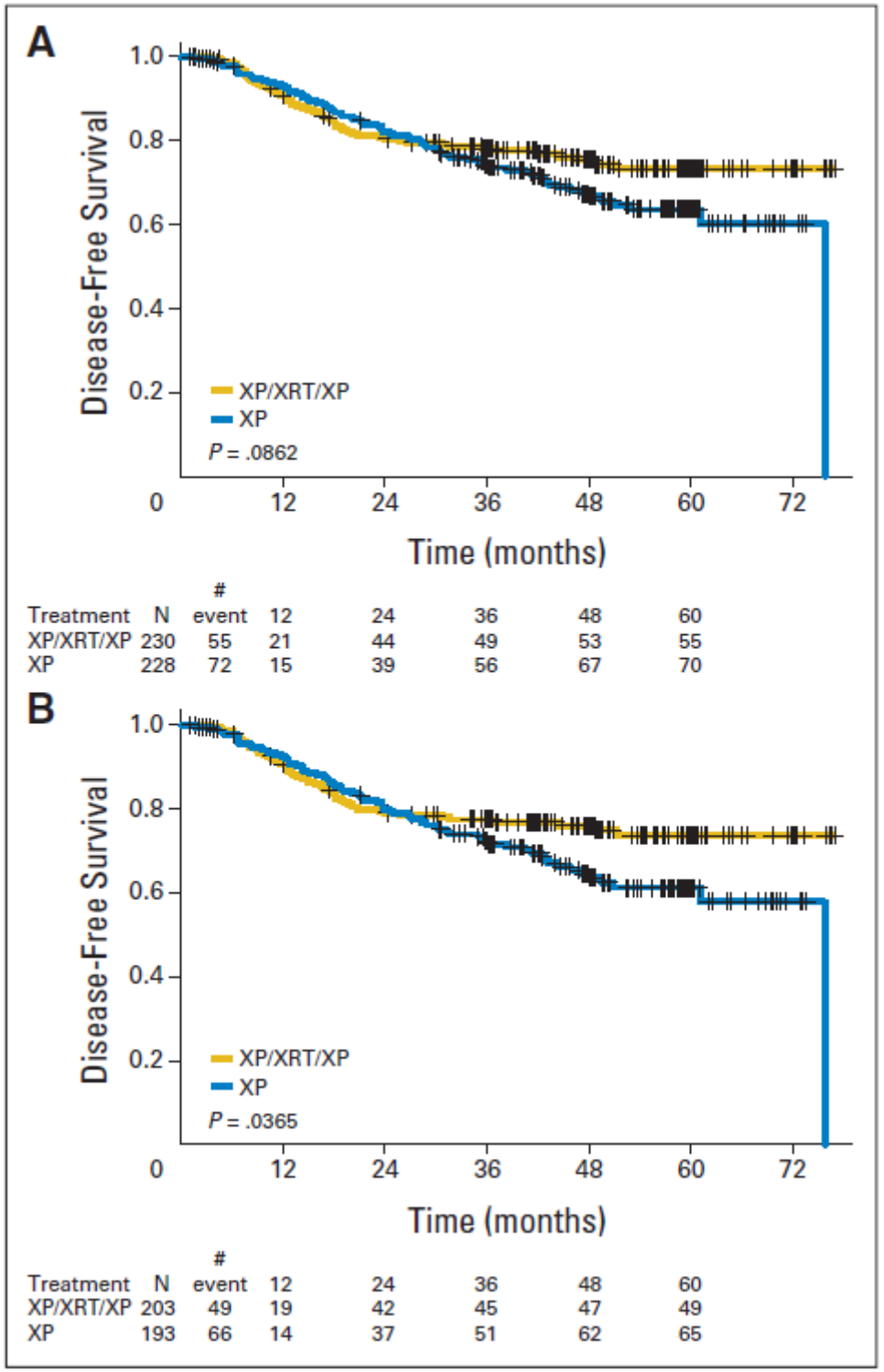
Kim et al, Int J Rad Onc Biol Phys, 2005





Kim et al, Int J Rad Onc Biol Phys, 2005

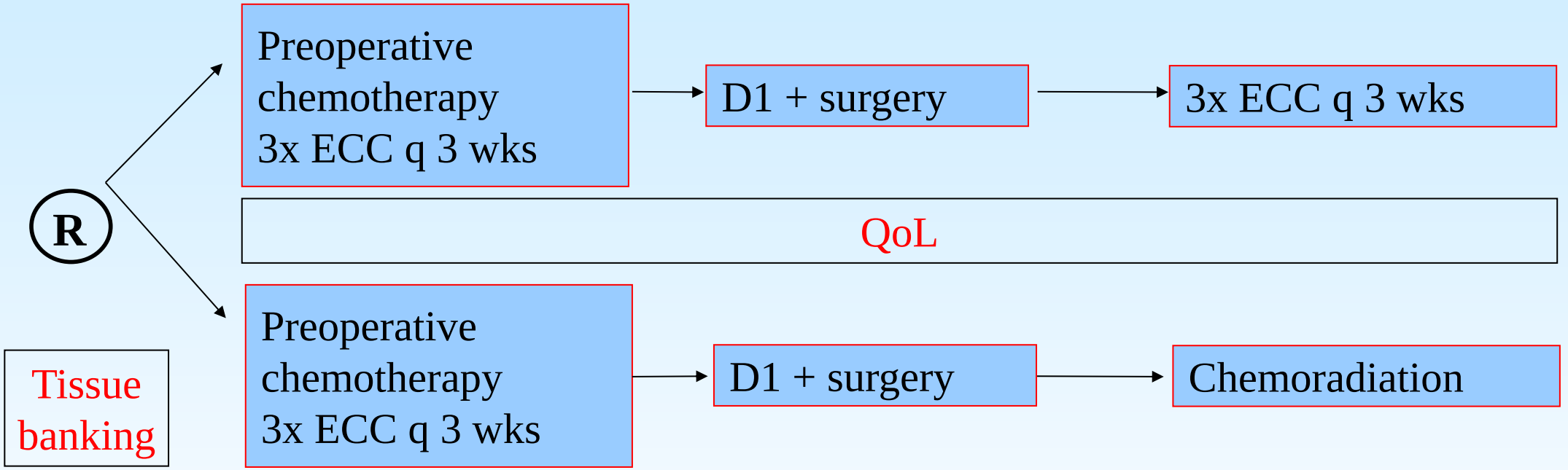




Lee et al, JCO 2012

CRITICS

Design



"MAGIC"(3xECC)

Epirubicine /Cisplatin /Capecitabine

^{3} 15 Lymph nodes
no splenectomy

45 Gy/25 fx +
capecitabine dd
cisplatin 1-5x pw

3D -CRT/IMRT

Stratified for:
- Center
- Histological type
- Localisation of tumor

Overview

- Postoperative chemoradiotherapy
- Preoperative chemoradiotherapy
- Palliative radiation
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Preoperative treatment

- Rationale/potential advantages
  - Enhance resectability
  - Assess response in primary tumour
  - Improve local control
  - Treat micrometastases early
  - Better tolerance than postoperative treatment
- Potential disadvantages
  - Staging less adequate
  - Increased postoperative morbidity
  - Disease progression

Pre-versus post-operative

UICC TNM seventh edition (2009)

- The esophagus includes the GE- junction
- A tumor of which the epicentre is within 5 cm of the GE-junction and which extends into the esophagus is classified and staged as an esophageal tumor

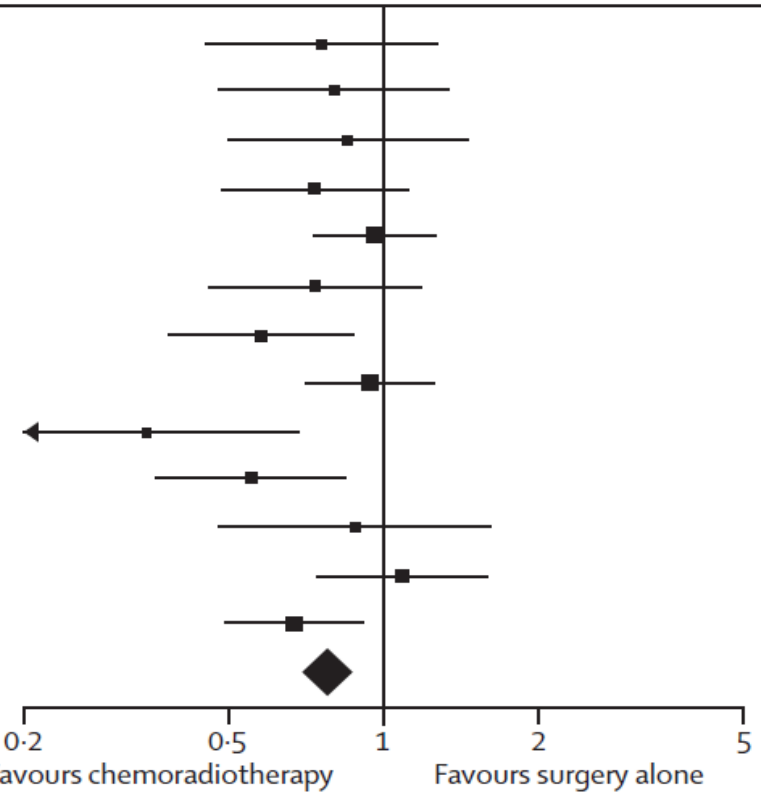
Preop CRT vs Surgery
4188 patients

A

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

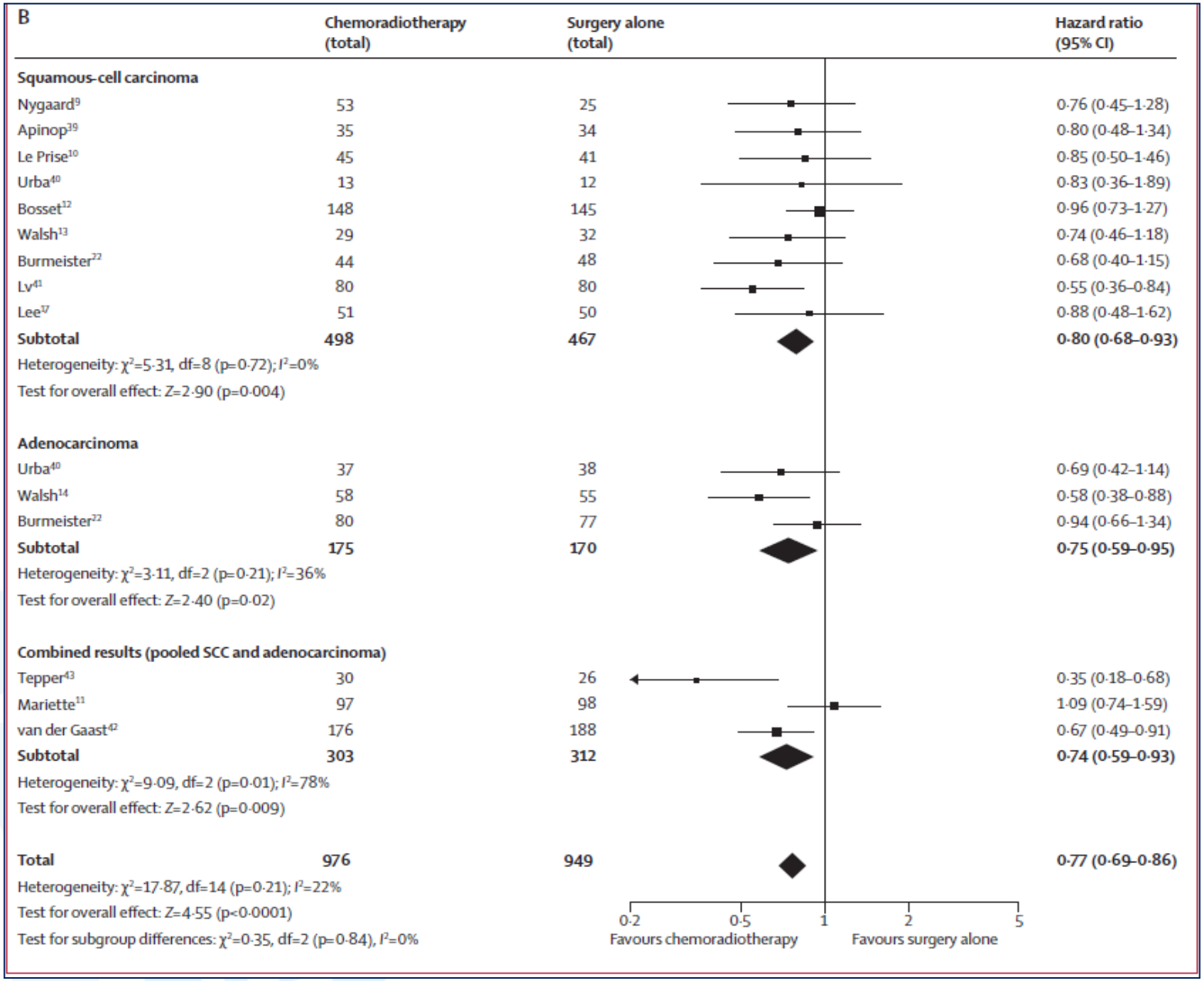
Heterogeneity: χ^2=18·04, df=12 (p=0·11); I^2=33%

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



HR: 0.78 (95% CI 0.70-0.88); p<0.0001

Sjoquist et al., Lancet Oncol 2011



HR SCC: 0.80 (95% CI 0.68-0.93); p=0.004

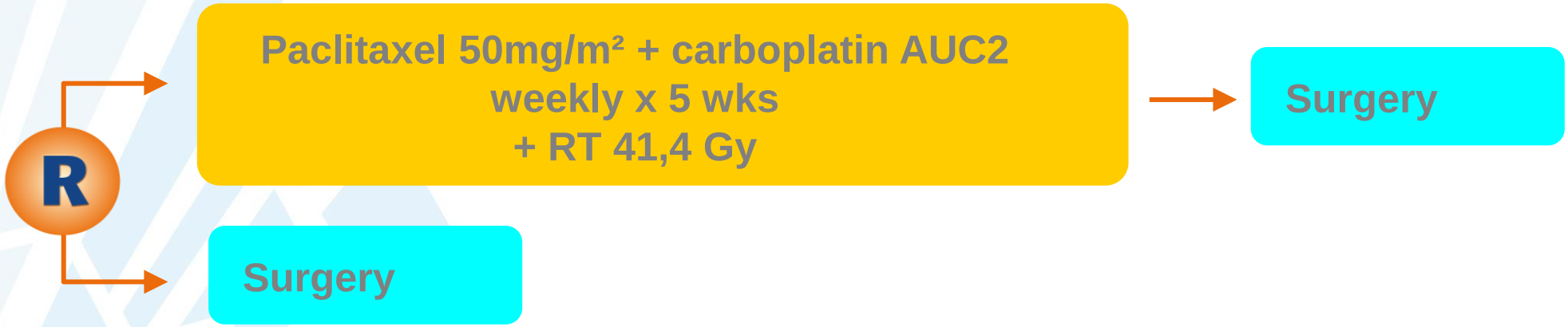
HR ADE: 0.75 (95% CI 0.59-0.95); p=0.02

Sjoquist et al., Lancet Oncol 2011

Resectable Esophageal or GE junction Cancer
CROSS Study

- Resectable esophageal adenocarcinoma or SCC
- Stage II or III : T2-3/N0-1/M0 (CT scan + EUS + PET Scan)
- WHO PS 0-1, weight loss < 10%, T length < 8 cm

- Primary objective: Overall survival + QOL



Van der Gaast et al., ASCO 2010

Resectable Oesophageal Cancer
CROSS Study

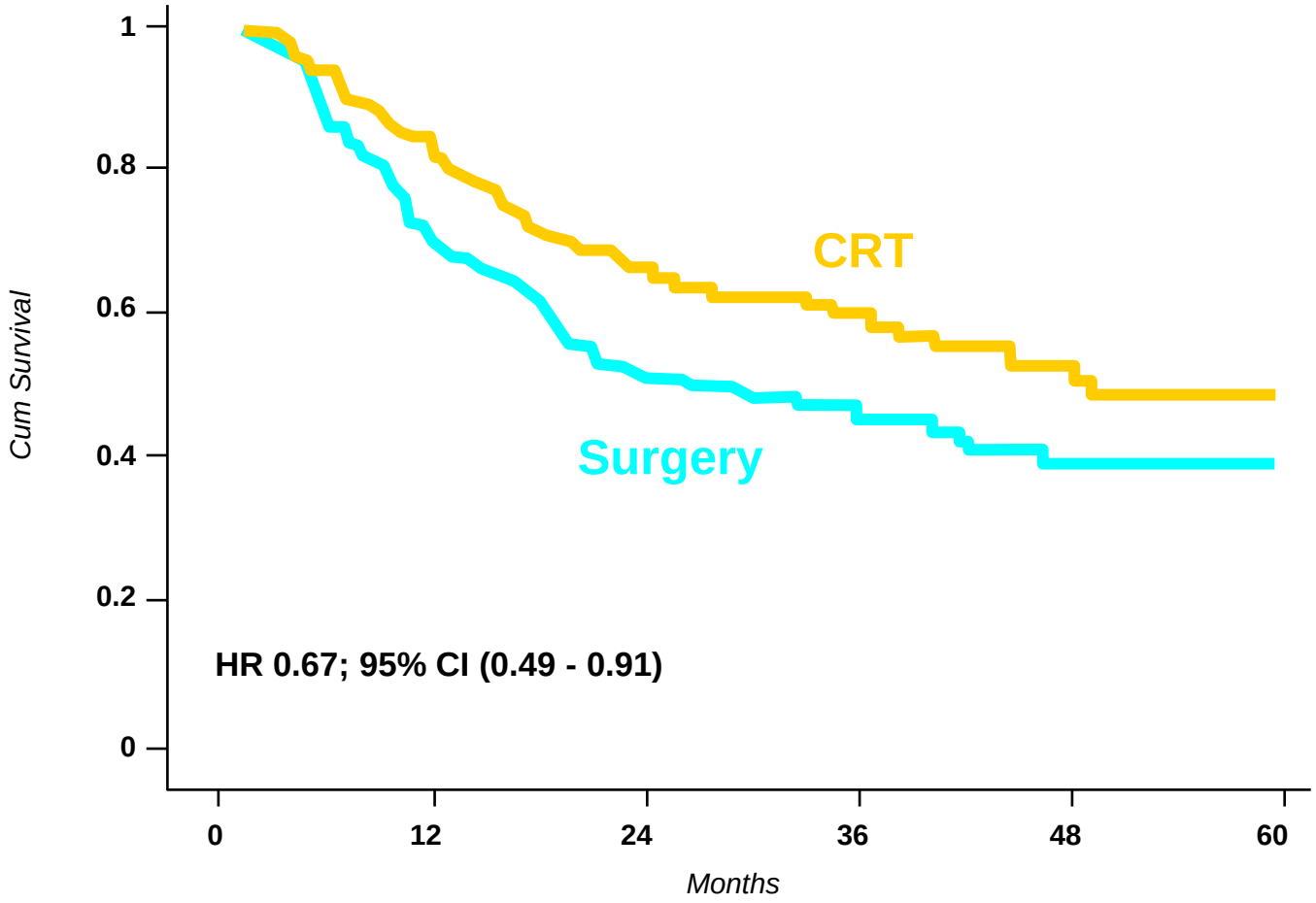
Randomized Phase III study - Netherlands

	CRT + surgery	Surgery	p
n	175	188	
Median Age	60	60	
Histology SCC/Adeno (%)	23/74	23/74	
T3 N0 or N1 (%)	79		
Surgery (resection) (%)	90	86	
Postoperative mortality (%)	3,4	3,8	
RO Resection	92,3	67	< 0,002
pCR (%)	32	-	-

Van der Gaast et al., ASCO 2010

Resectable Oesophageal Cancer
CROSS Study

Randomized Phase III study - Netherlands



Median Survival (months):

CRT + surgery: 49

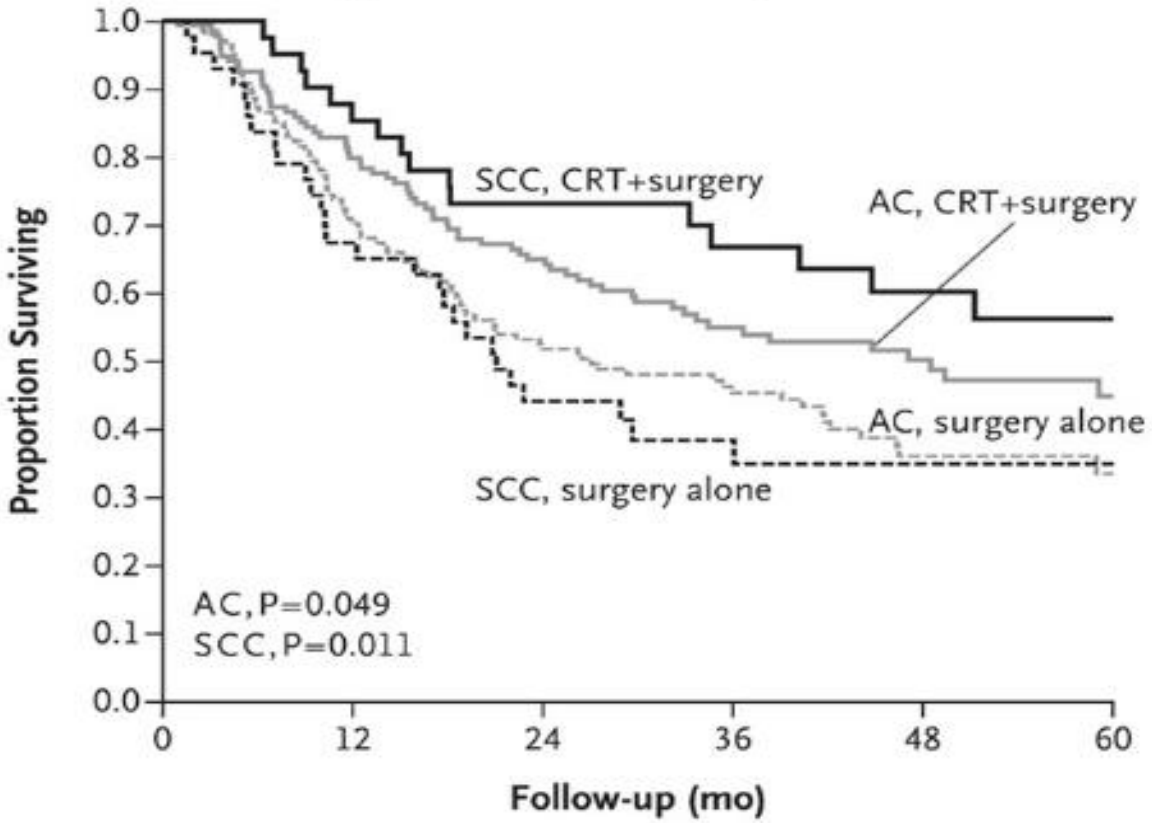
Surgery: 26

HR = 0.67; *p=0,011*

Van der Gaast et al., ASCO 2010

CROSS study

B Survival According to Tumor Type and Treatment Group

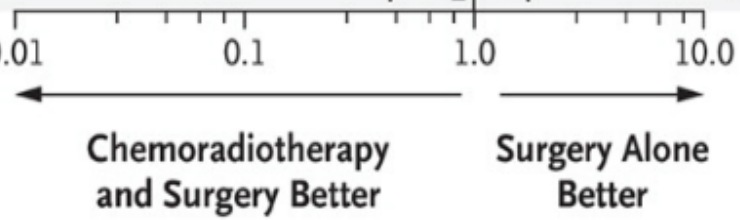


No. at Risk						
AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

van Hagen et al., NEJM 2012

CROSS study

Subgroup	Univariate Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	P Value for Adjusted Hazard Ratio
All patients	0.657 (0.495–0.871)	0.665 (0.500–0.884)	0.005
Sex			
Female	0.913 (0.482–1.729)	0.928 (0.487–1.766)	0.82
Male	0.612 (0.446–0.841)	0.614 (0.447–0.845)	0.003
Histologic type			
Other	0.627 (0.056–6.970)		
Adenocarcinoma	0.732 (0.524–0.998)	0.741 (0.536–1.024)	0.07
Squamous-cell carcinoma	0.453 (0.243–0.844)	0.422 (0.226–0.788)	0.007
Clinical N stage			
0	0.414 (0.234–0.732)	0.422 (0.239–0.747)	0.003
1	0.793 (0.567–1.108)	0.807 (0.576–1.130)	0.21
Could not be determined	0.552 (0.066–4.602)		
WHO performance score			
0	0.617 (0.452–0.844)	0.625 (0.456–0.857)	0.004
1	0.864 (0.433–1.726)	0.898 (0.753–1.631)	0.77



van Hagen et al., NEJM 2012

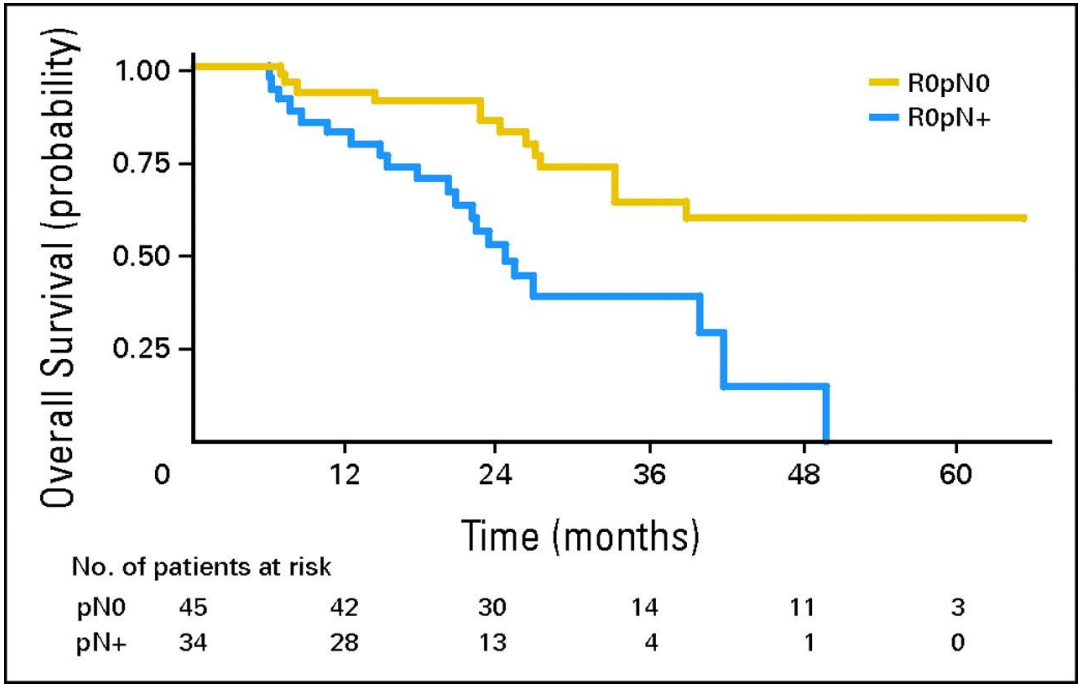
CROSS study

"Because a substantial percentage of patients in the chemoradiotherapy-surgery group in the present study (22%) had a GE-junction tumor, we favor preoperative chemoradiotherapy for such patients"

van Hagen et al., NEJM 2012

POET trial

	Arm A		Arm B		
Treatment	No.	%	No.	%	P
Patients with resection	49	100.0	45	100.0	
pT0 N0 M0	1	2.0	7	15.6	.03*
pT1-4 N0 M0	17	34.7	22	48.9	
pT0-4 N0 M0†	**18**	**36.7**	**29**	**64.4**	**.01***
pTall N M0	27	55.1	14	31.1	
pTall N M1	4	8.2	2	4.5	



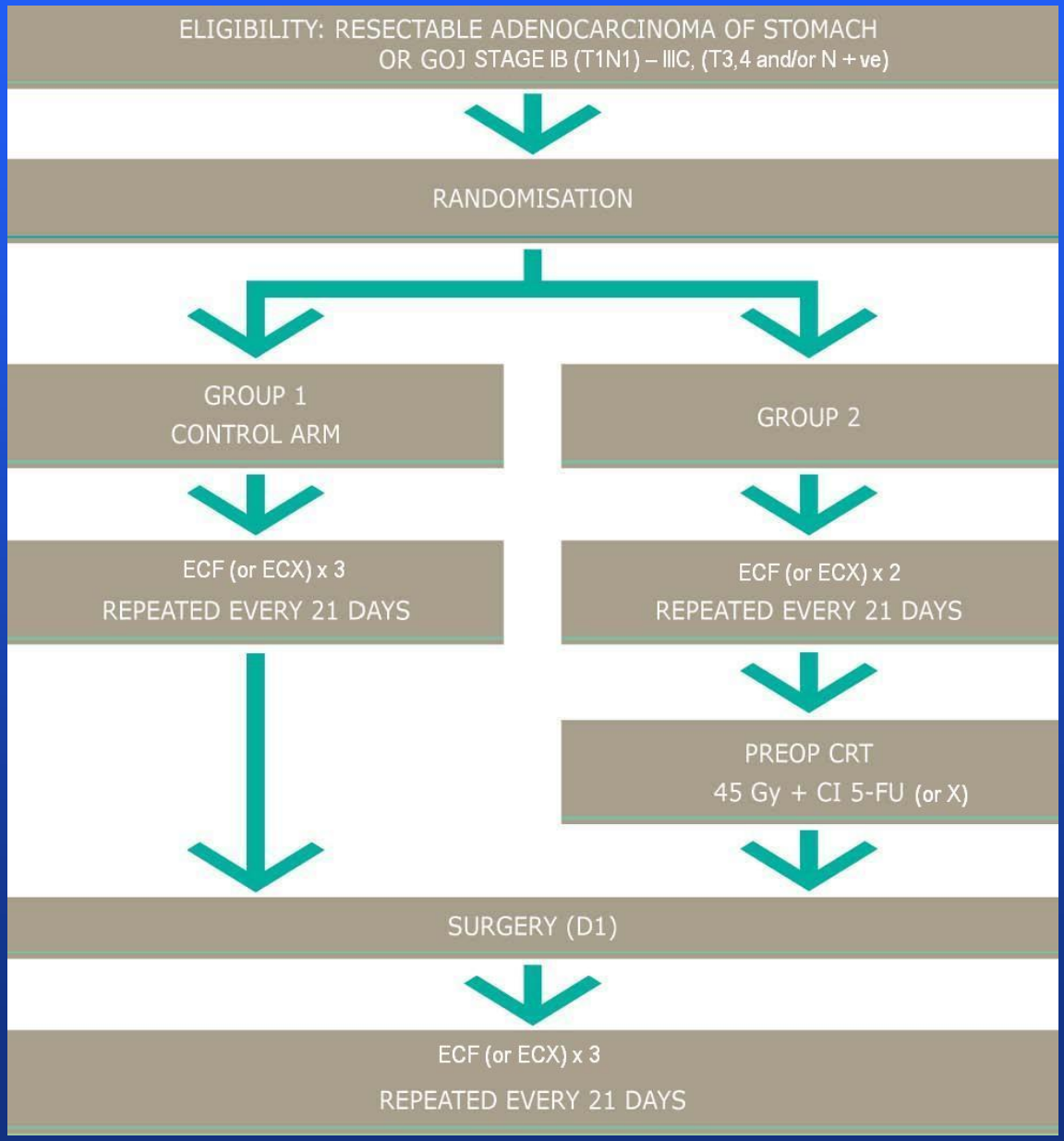
Fisher´s exact test.
†Bold text indicates data summarized from patients with pT0 N0 M0 and pT1-4 N0 M0.

Stahl et al., JCO 2009

Preoperative chemoradiotherapy

- RESPONDERS (30%-50%)
  - increased resectability rate
  - reduced locoregional recurrences
  - prolonged survival
- NON-RESPONDERS (50%-70%)
  - worse prognosis compared to surgery alone

Trial Schema



Study Design and Key Objectives

Study design:

This is a multicentre, prospective, randomised, stratified, phase II/III clinical trial

Primary objective:

To investigate whether the addition of chemoradiotherapy to chemotherapy is superior to chemotherapy alone in the neoadjuvant setting by improving pCR rates in the first instance (Part I), and subsequently overall survival (Part II), in patients undergoing adequate surgery (minimum D1 dissection) for resectable gastric and gastroesophageal junction cancer

Trial incorporates a QoL and a TR substudy

EORTC
European Organisation for Research and Treatment of Cancer

Statistical Considerations

Assumptions made for sample size calculations

- 5 y survival 40% for standard arm (chemotherapy alone)
- 5 y survival 50% for experimental arm (CRT)
- alpha=0.05 (2-sided)
- beta=0.80
- accrual rate approximately 140 patients per year

Target sample size = 752

Overview

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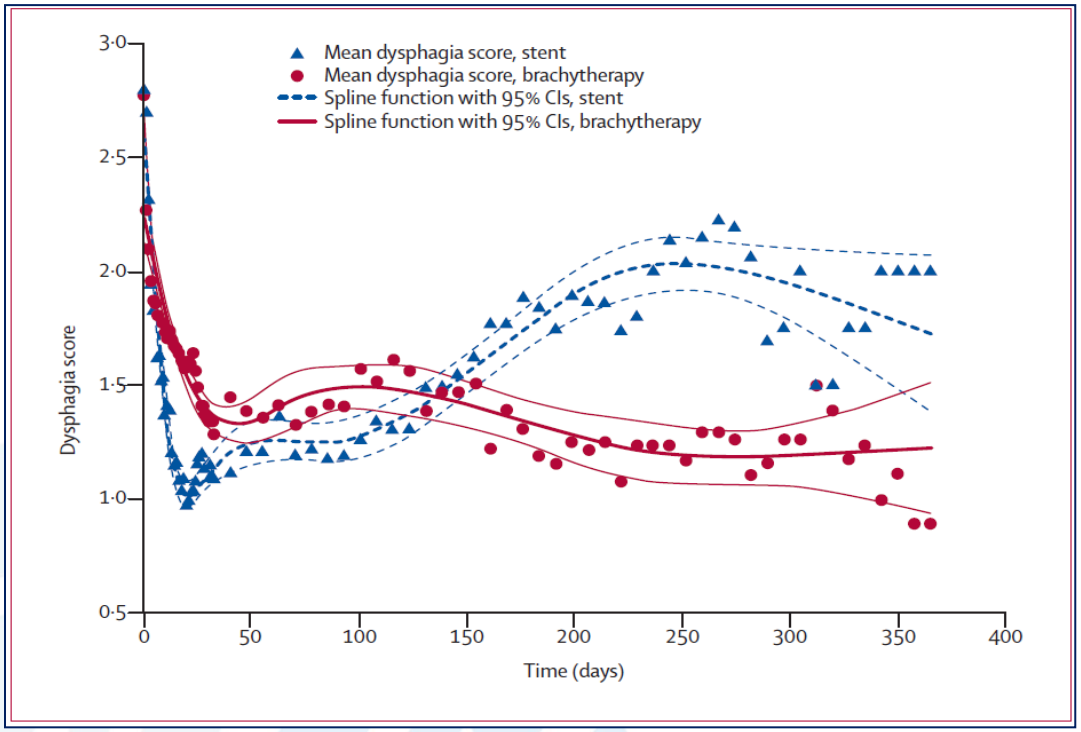
- Preoperative chemoradiotherapy
- Palliative radiation
- Technical aspects

Palliative radiation



- 209 patients
- Inoperable
- 12 Gy SD vs stent
- BT more effect on dysphagia
- BT less complications
- QoL better after BT

Homs et al, Lancet 2004

Overview

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- Palliative radiation
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Technical aspects

- Total dose
- Dose per fraction
- Total treatment time

- Targetvolume/OAR

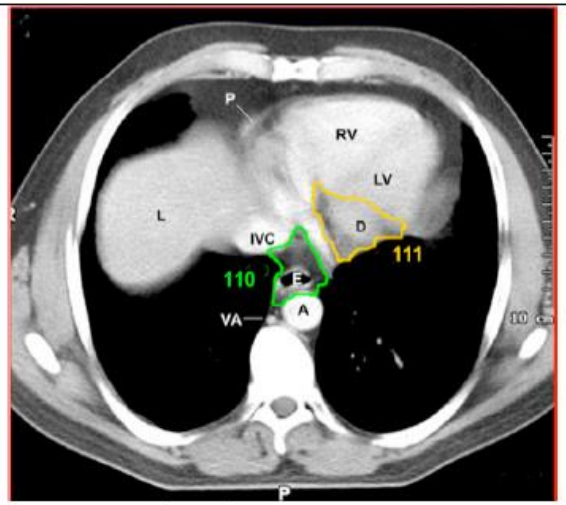
- Technique

Radiation schedules used

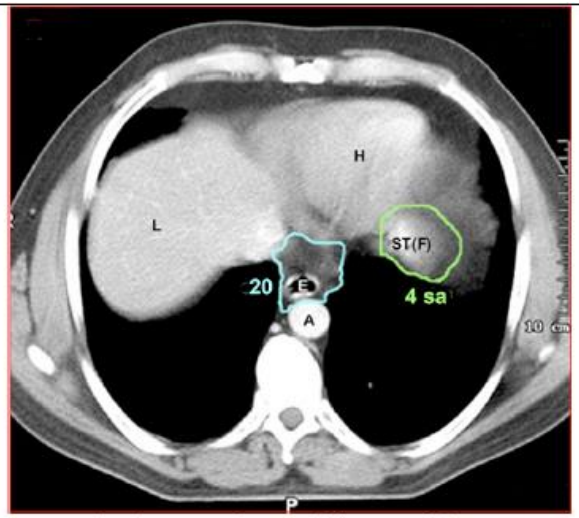
- 35 Gy in 2.3 Gy fractions over 3 weeks
- 45 Gy in 1.5 Gy fractions over 3 weeks
- 40 Gy in 2.7 Gy fractions over 3 weeks
- 41.4 Gy in 1.8 Gy fractions over 5 weeks
- …

THESE SCHEDULES CANNOT BE REGARDED AS STANDARD!

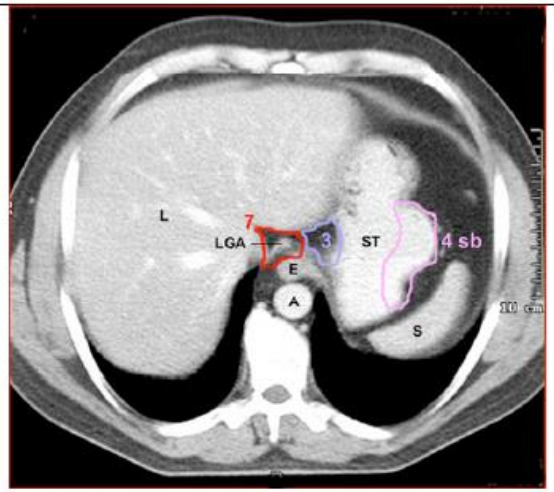
International and Japanese Gastric Cancer Association



110 - Paraoesophageal LN
111 - Supradiaphragmatic LN



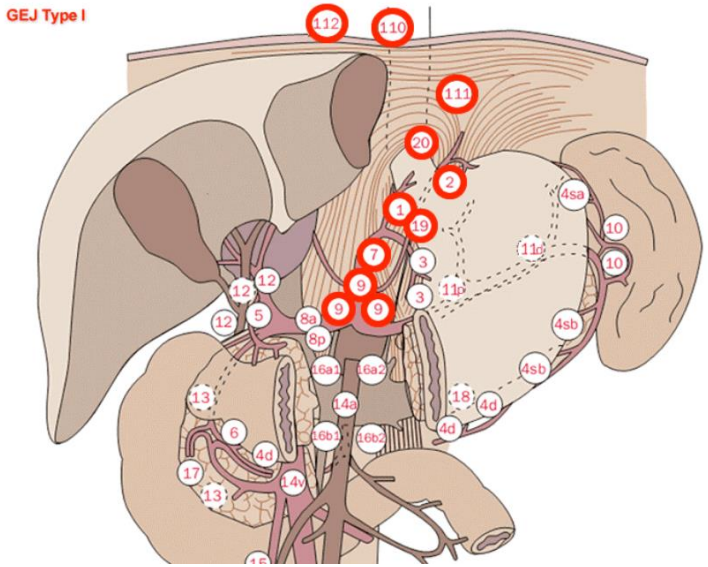
20 - LN in the oesophageal hiatus of the diaphragm
4sa - LN along the short gastric vessels



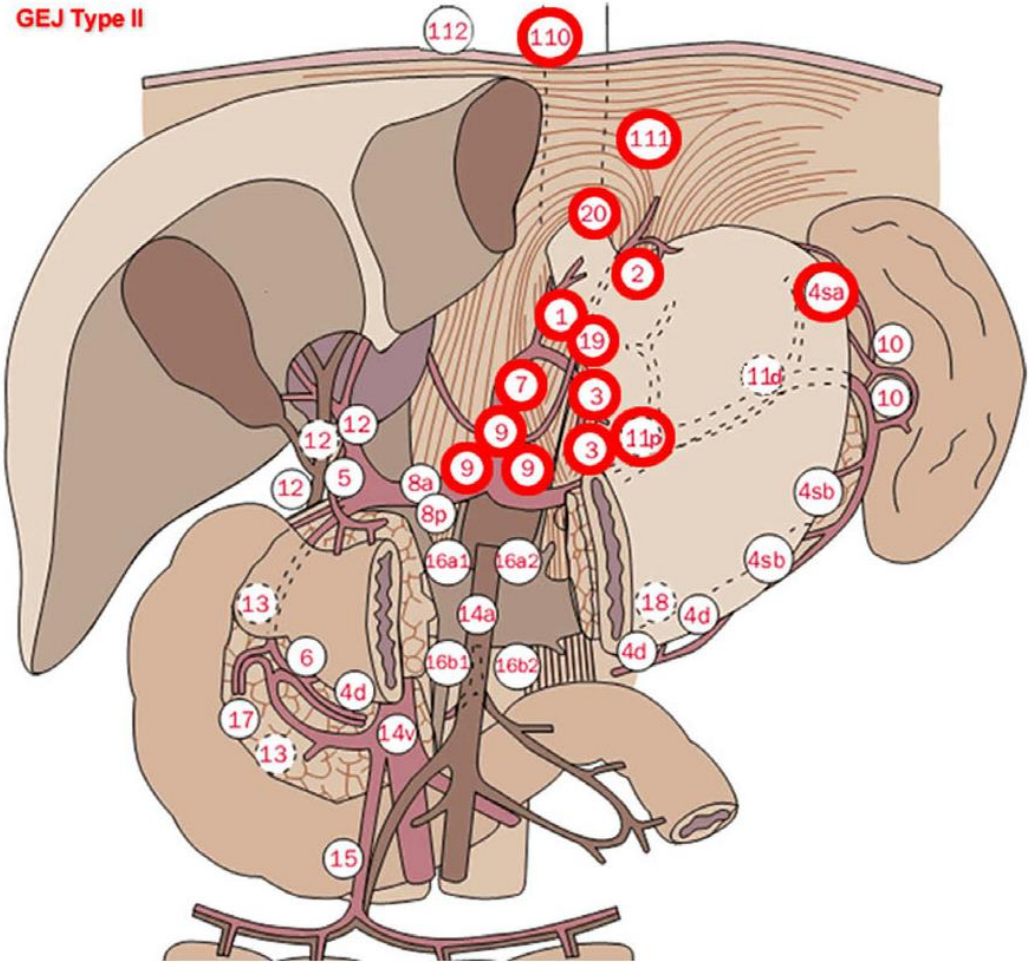
3 - LN along the lesser curvature
4sb - LN along the left gastroepiploic vessels
7 - LN along the left gastric artery

GEJ Type I

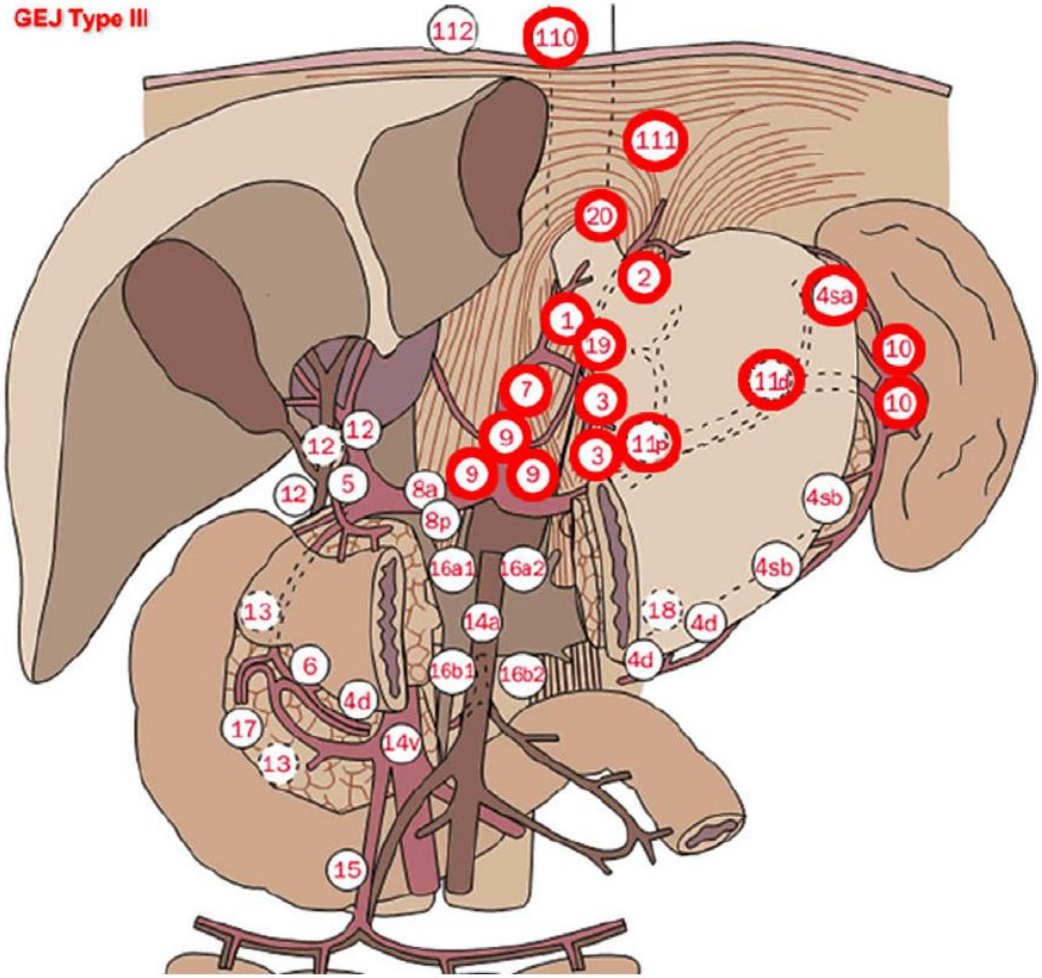
1	Right paracardial LN
2	Left paracardial LN
7	LN along the left gastric artery
9	LN around the celiac artery
19	Infradiaphragmatic LN
20	LN in the oesophageal hiatus of the diaphragm
110	Paraoesophageal LN in the lower thorax
111	Supradiaphragmatic LN
112	Posterior mediastinal LN



GEJ Type II



GEJ Type III



Radiotherapy for GE-junction tumors

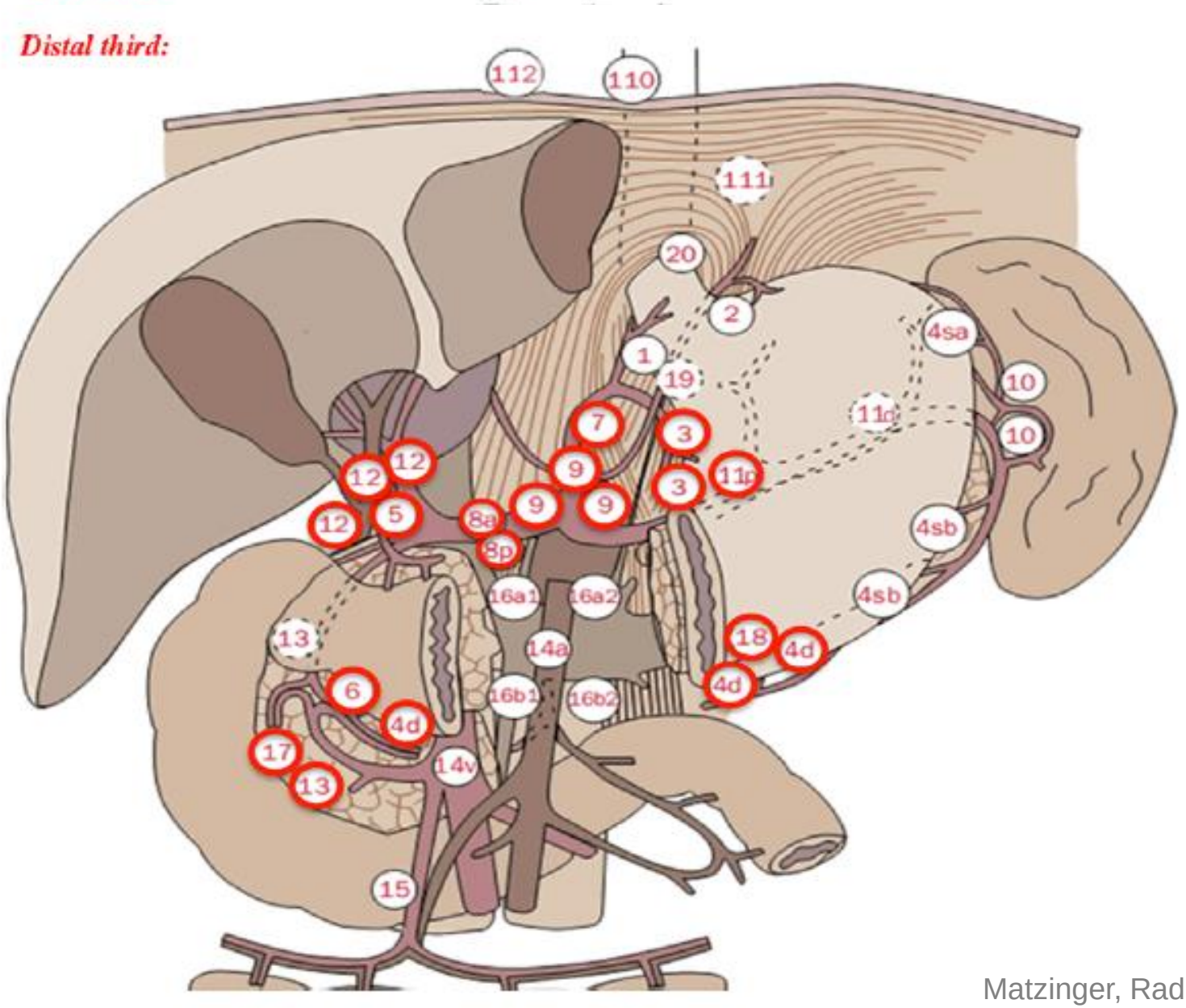
- **Dose:**
- Preoperative therapy: 40-45 Gy in 1,8-2,0 Gy/fraction in combination with chemotherapy
- Postoperative therapy: 45-50,4 Gy in fractions of 1,8 Gy combined with chemotherapy
- Maximum overall treatment time: 37 days

- **Dose limiting critical structures:**

OAR	Max. % volume to receive specified dose	Mean organ dose	Max. dose for partial organ irradiation	Maximum dose
Spinal cord				45 Gy
Liver		30 Gy	1/3 liver ≤50 Gy 2/3 liver ≤35Gy	
Kidneys		23 Gy	1/3 kidney ≤35Gy 2/3 kidney ≤20Gy	
Heart	V40 ≤30%			
Lungs	V20 ≤30%	18 Gy		

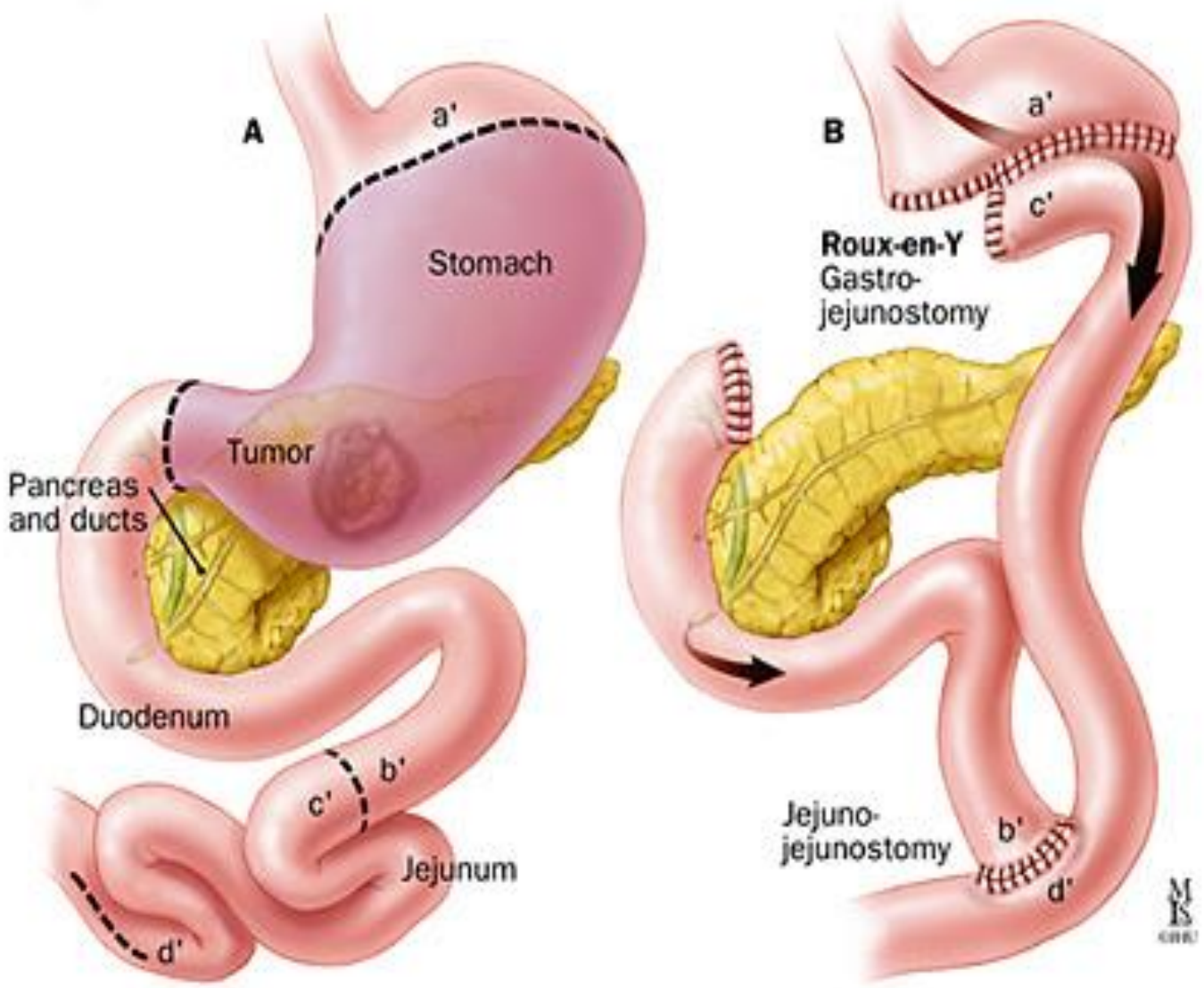
Matzinger, Radiother Oncol 2009

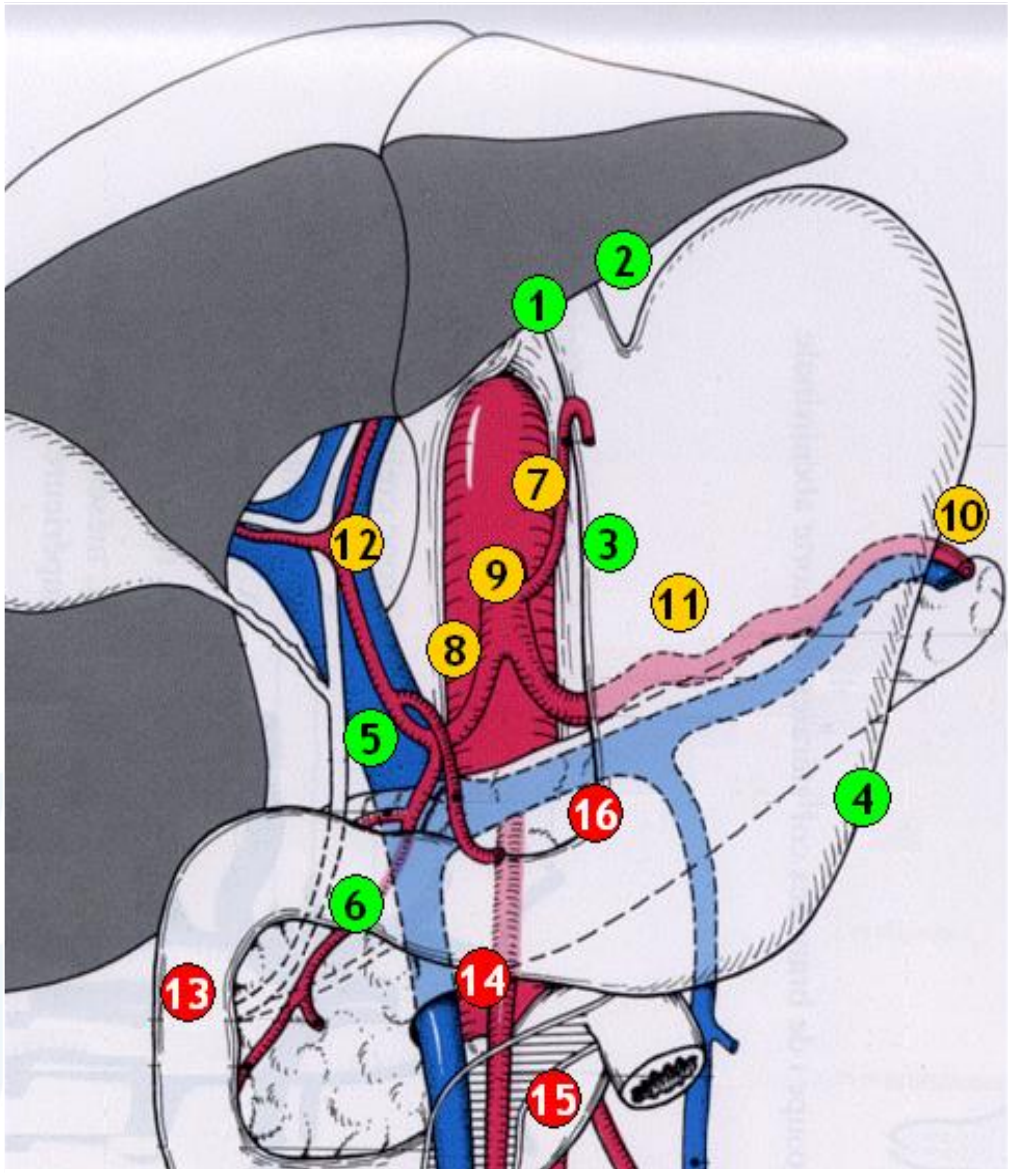
Lymph node regions at risk



Matzinger, Radiother Oncol 2009

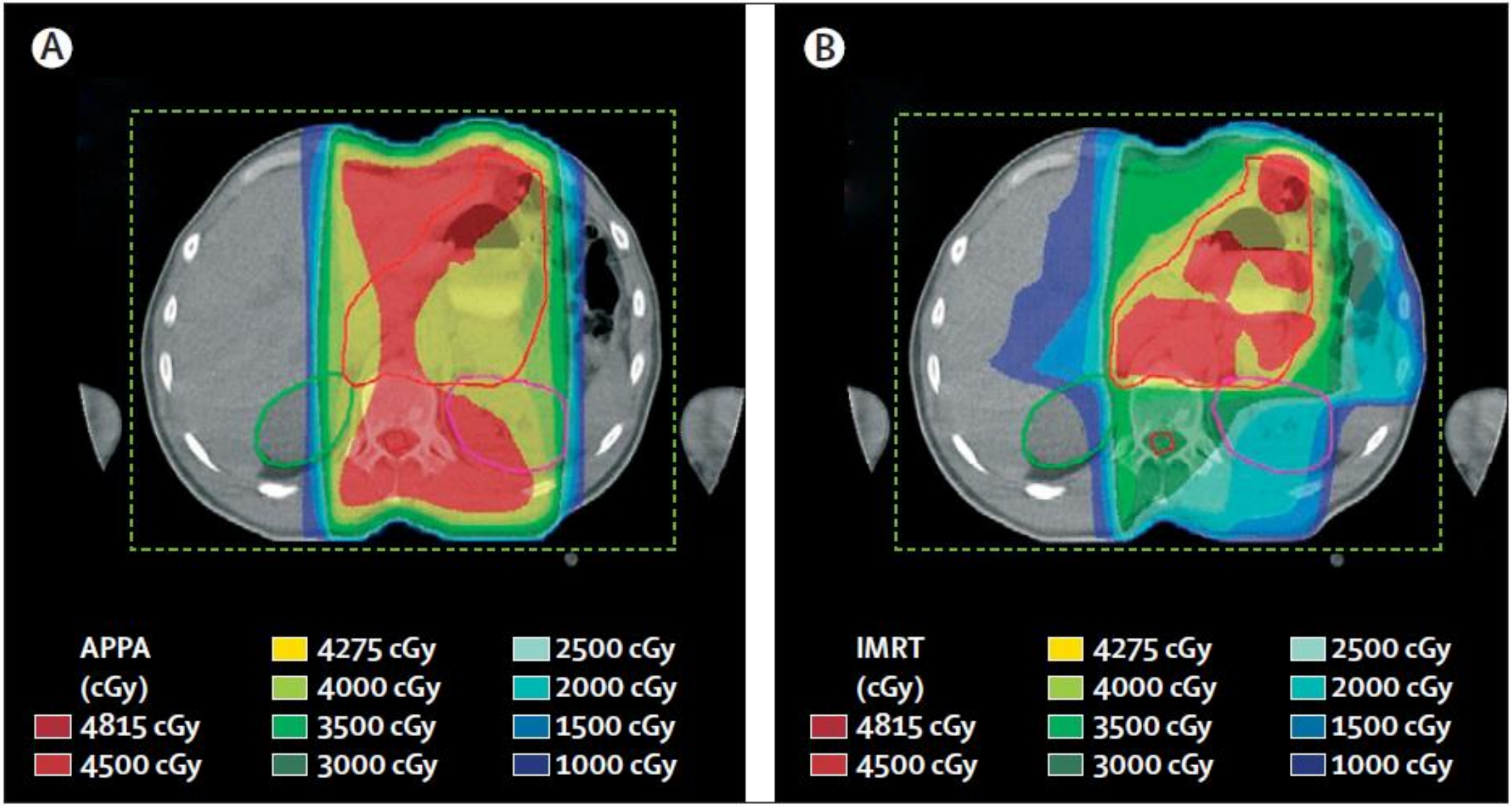
The post-operative setting





Lymph node regions at risk

1 right paracardial; 2 left paracardial; 3 lesser curvature; 4 greater curvature; 5 suprapyloric; 6 infrapyloric; 7 left gastric artery; 8 common hepatic artery; 9 celiac artery;10 splenic hilum;11 splenic artery; 12 hepatoduodenal ligament;13 posterior surface of the pancreatic head; 14 superior mesenteric vein/artery; 15 middle colic vessels;16: aorta.



Hartgrink et al, Lancet 2009

3D vs. IMRT Comparison

"In general, *V*40 and *V*50 were kept to <50 and <30%, respectively, for the heart."

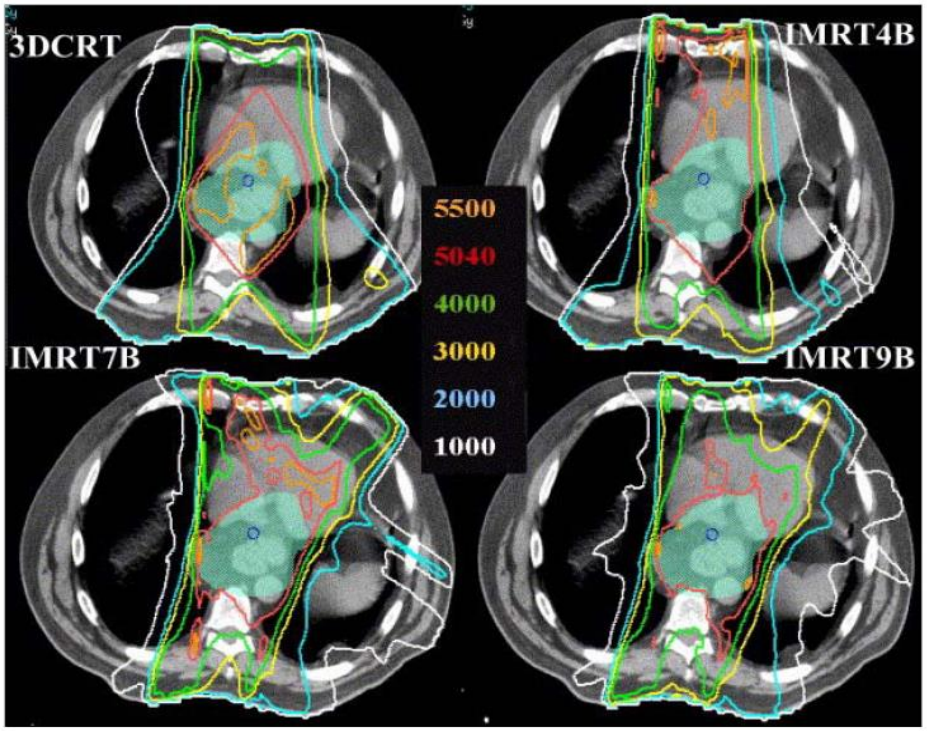


Fig. 1. Sample transverse CT images showing the isodose distributions in the middle of PTV for one of the cases studied.

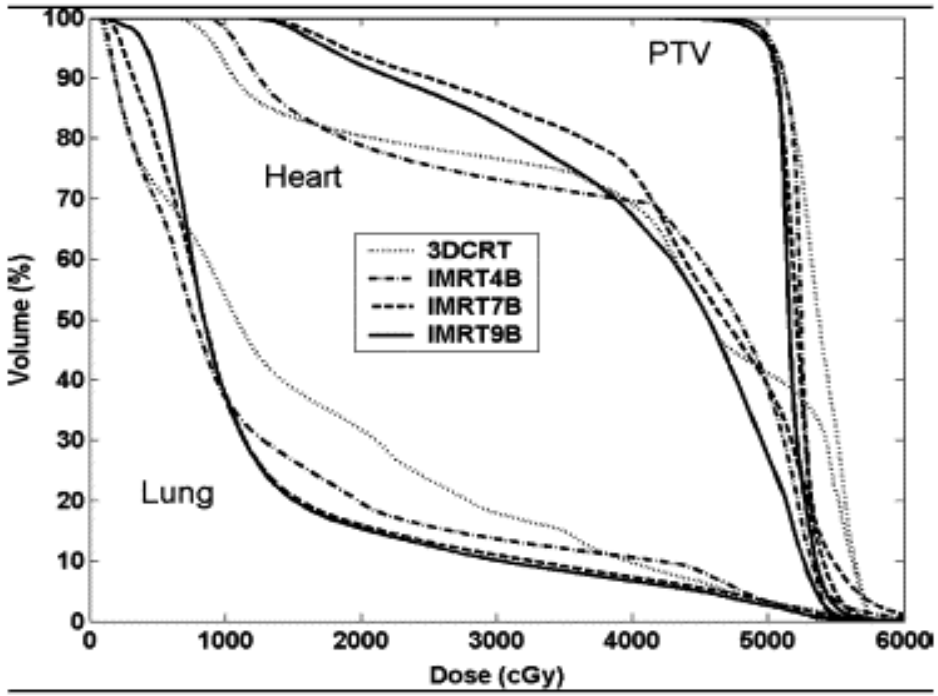


Fig. 2. DVHs from the 3DCRT and three IMRT plans for the case shown in Fig. 1.

"We gave PTV coverage and lung sparing higher priority than the other structures"

IMRT plans reduced the amount of lung treated compared to 3D-CRT

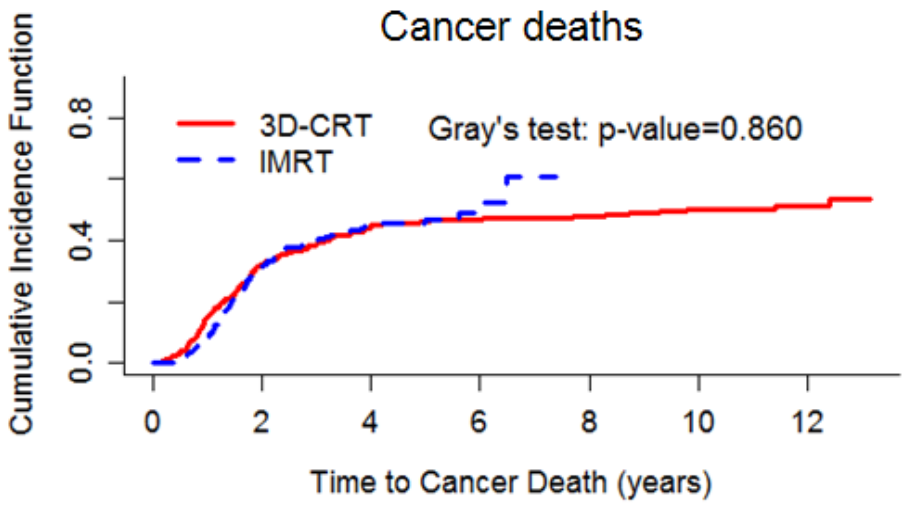
"No clinically meaningful differences were observed with respect to irradiated volumes of spinal cord, heart, liver, or total body integral doses"

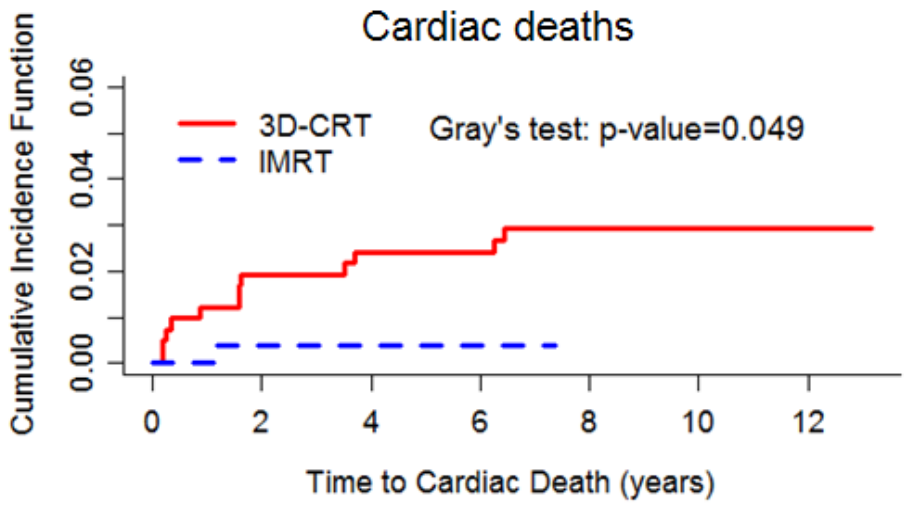
Chandra A, et. al, IJROBP 2005

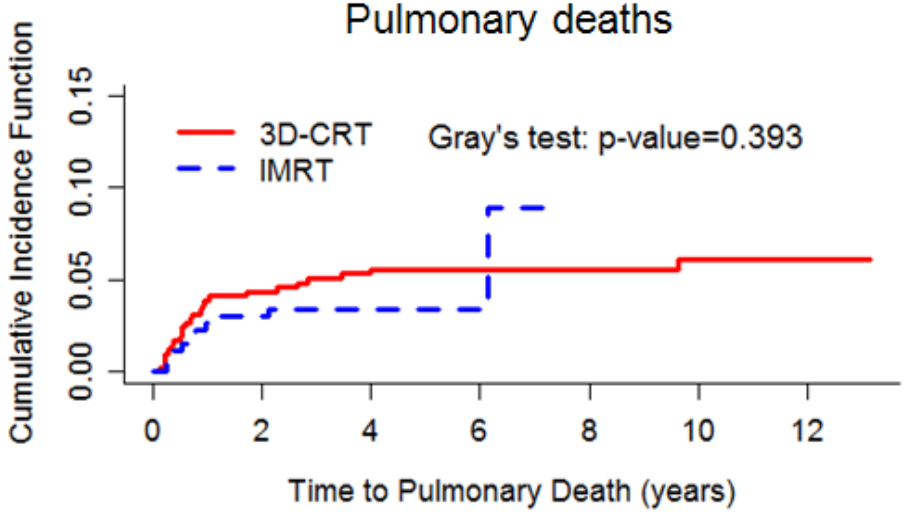
Postoperative complications related to radiation dose to organ at risk

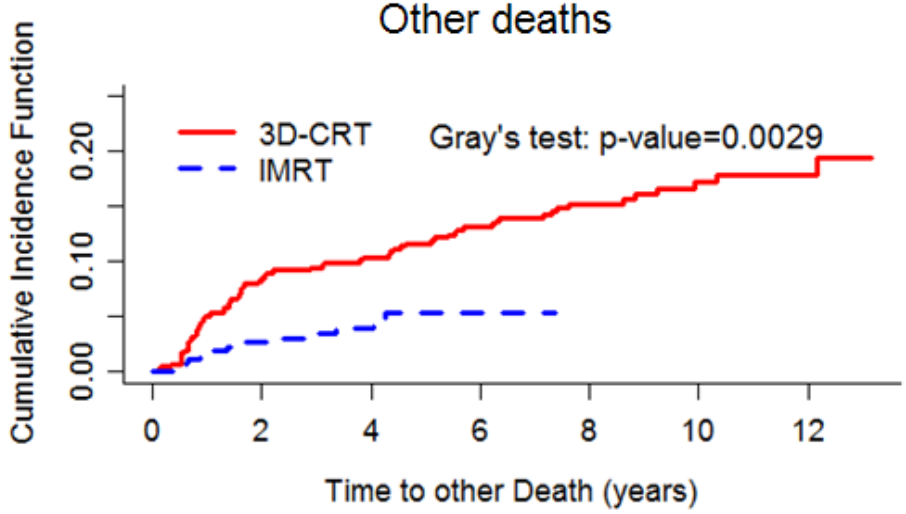
- Higher rates of postoperative pulmonary complications (ARDS, PNA) when large lung volumes receive low doses
  - Total Lung V10 ≥ 40% vs <40% : **35%** vs **8%** (p=0.014) (Lee HK et al. 2003)
  - NTCP modeling associated postoperative pulmonary complications to the amount of total lung spared from doses ≥ 5 Gy (Tucker SL et al., 2006)

IMRT has a lower incidence of cardiac and unknown related deaths

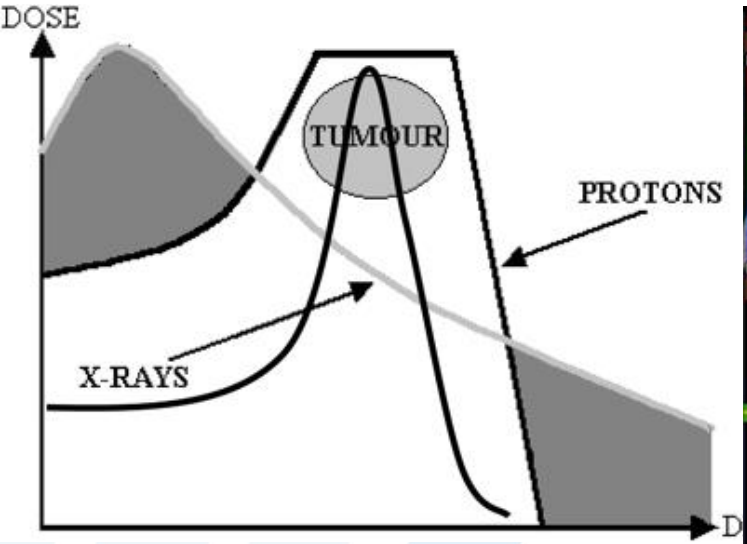




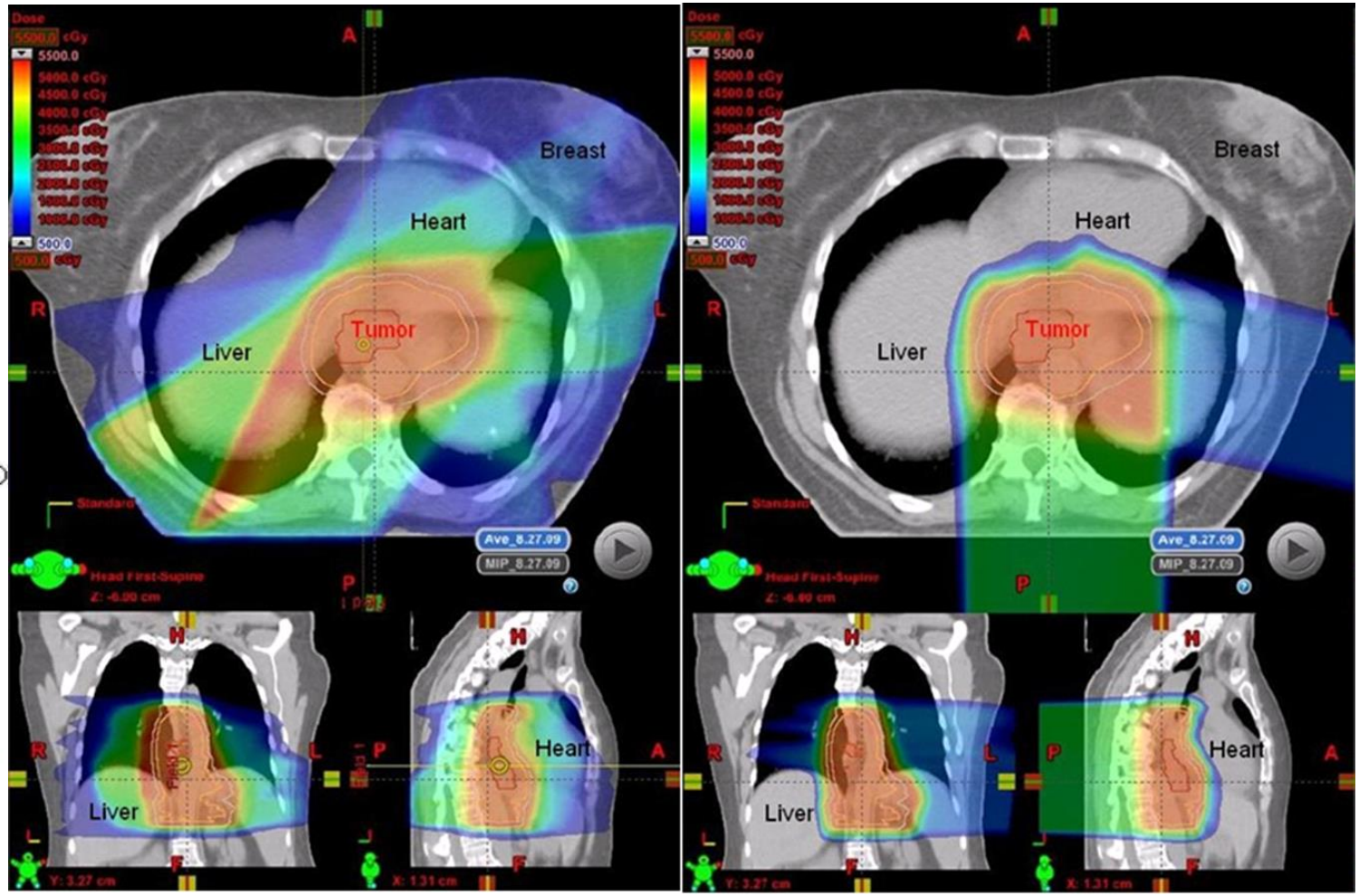




How about protons?



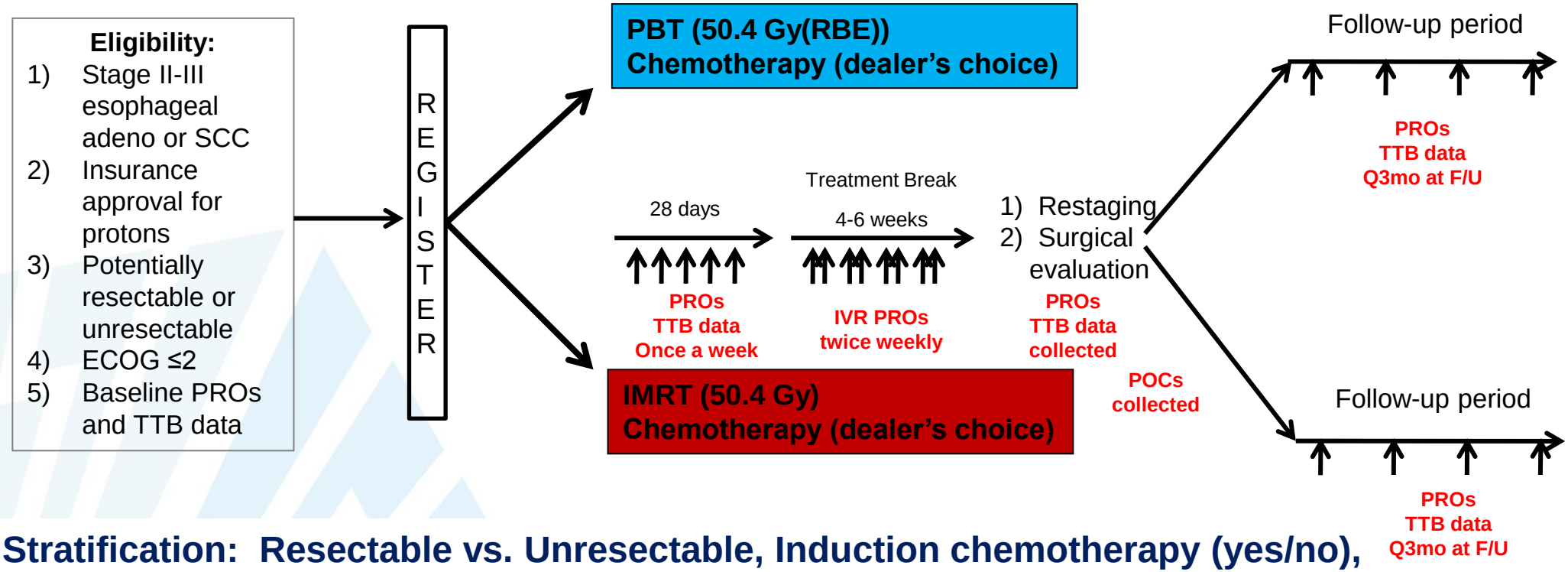
Schematic depth dose diagram of a proton beam Bragg peak, the spread out Bragg peak and a megavoltage X-ray beam The grey shaded areas indicate the extent of dose reduction



IMRT PBT

Courtesy of Matt Palmer, MD Anderson

Awaiting results from a RCT at MD Anderson



Stratification: Resectable vs. Unresectable, Induction chemotherapy (yes/no), Stage II or III, Adenocarcinoma or SCCA, Age ≥ 65 vs. < 65.

Abbrevations: PROs = Patient Reported and Physician Reported Outcomes; TTB = Total Toxicity Burden form; IVR = Interactive Voice Response system; POCs = Postoperative Complications.

Courtesy of Matt Palmer, MD Anderson.

Conclusions GEJ cancer

- Major tumor bulk in esophagus or tumors at transition (Siewert type 1 and 2):

➡ Strategy of preoperative CRT

- Major tumor bulk in stomach (Siewert type 3):

➡ Strategy of peri-operative CT awaiting results of Phase III trials

Level II evidence (CROSS/POET)

Conclusions gastric cancer

If sub-optimal surgery (<D1) or N+ disease

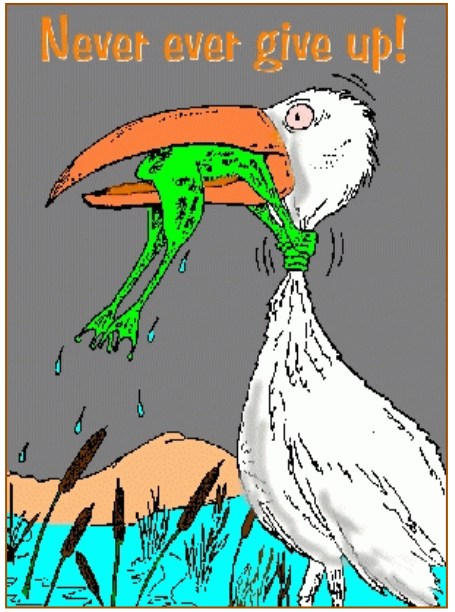
Consider (optimized) post-operative chemoradiation

Indications: (T2b), T3, T4 or N+ M0

Level II evidence (INT0116/ARTIST)

Conclusions

- A multidisciplinary approach is essential in the treatment of this disease!
  - Which type of treatment?
  - Which drugs?
  - Which total dose of radiation/fractionation?
  - Which volumes to irradiate?



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