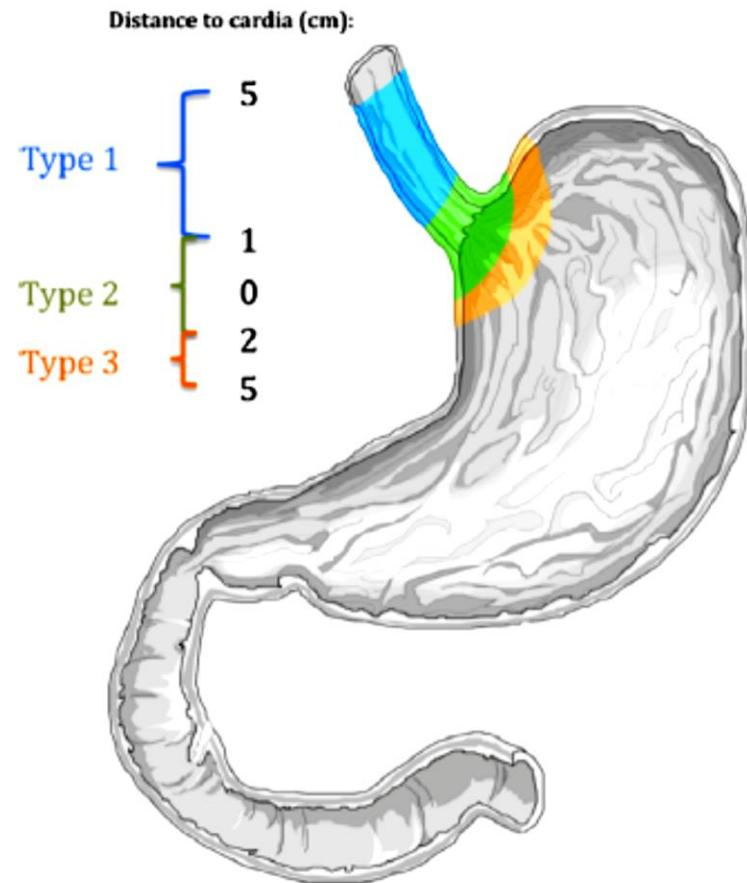


Radiothérapie des cancers de l'estomac

Bénéfices, simulation, volumes cibles, doses et fractionnement, validation du plan de traitement,
association radio-chimiothérapie

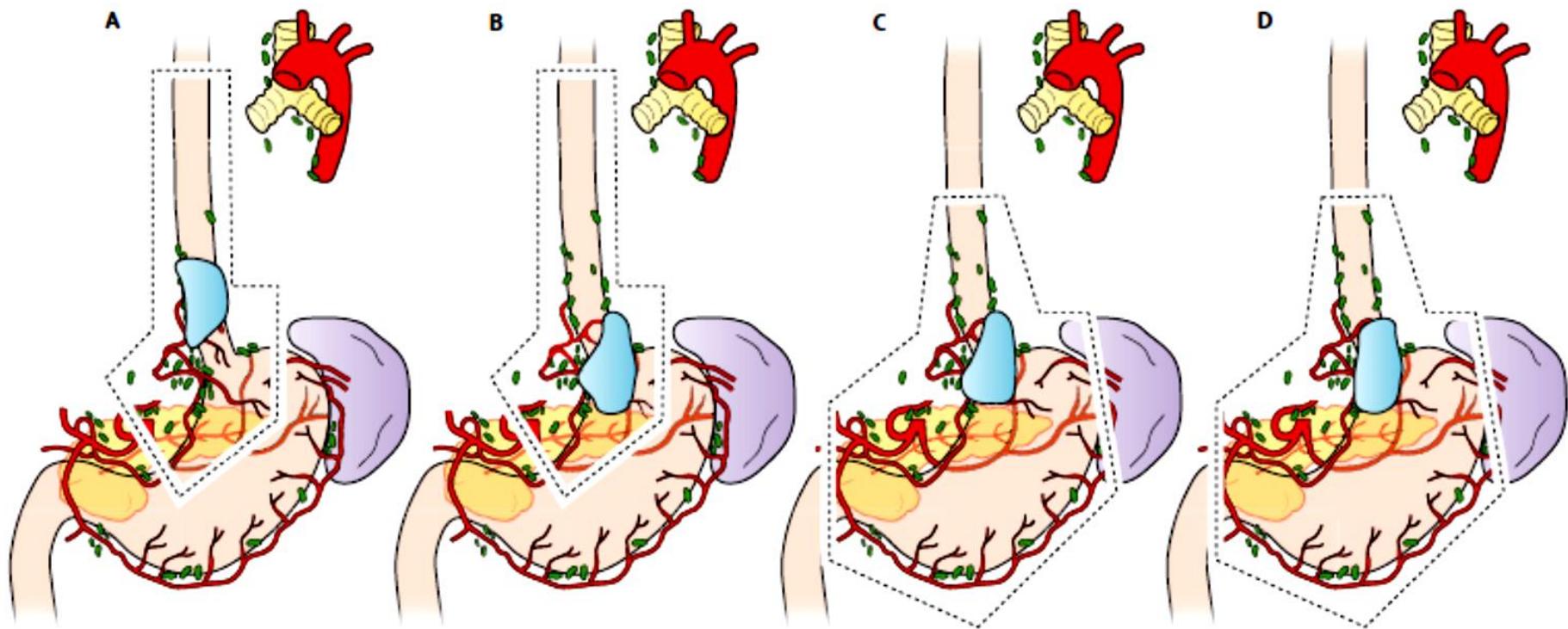
Prof. Philippe MAINGON
Radiation Oncology Department
Centre Georges-François Leclerc, Dijon

Siewert staging system



Siewert JR Ann Surg 2000;232:353-61

Oesogastric junction adenocarcinoma : Which therapeutic approach ?



Mariette C. Lancet Oncol 2011;12:285-93



Un Oncologue Radiothérapeute en Gastro-entérologie ...

1. INDICATION

2. VOLUMES

3. DOSES

4. TECHNIQUE

Un Oncologue Radiothérapeute en Gastro-entérologie ...

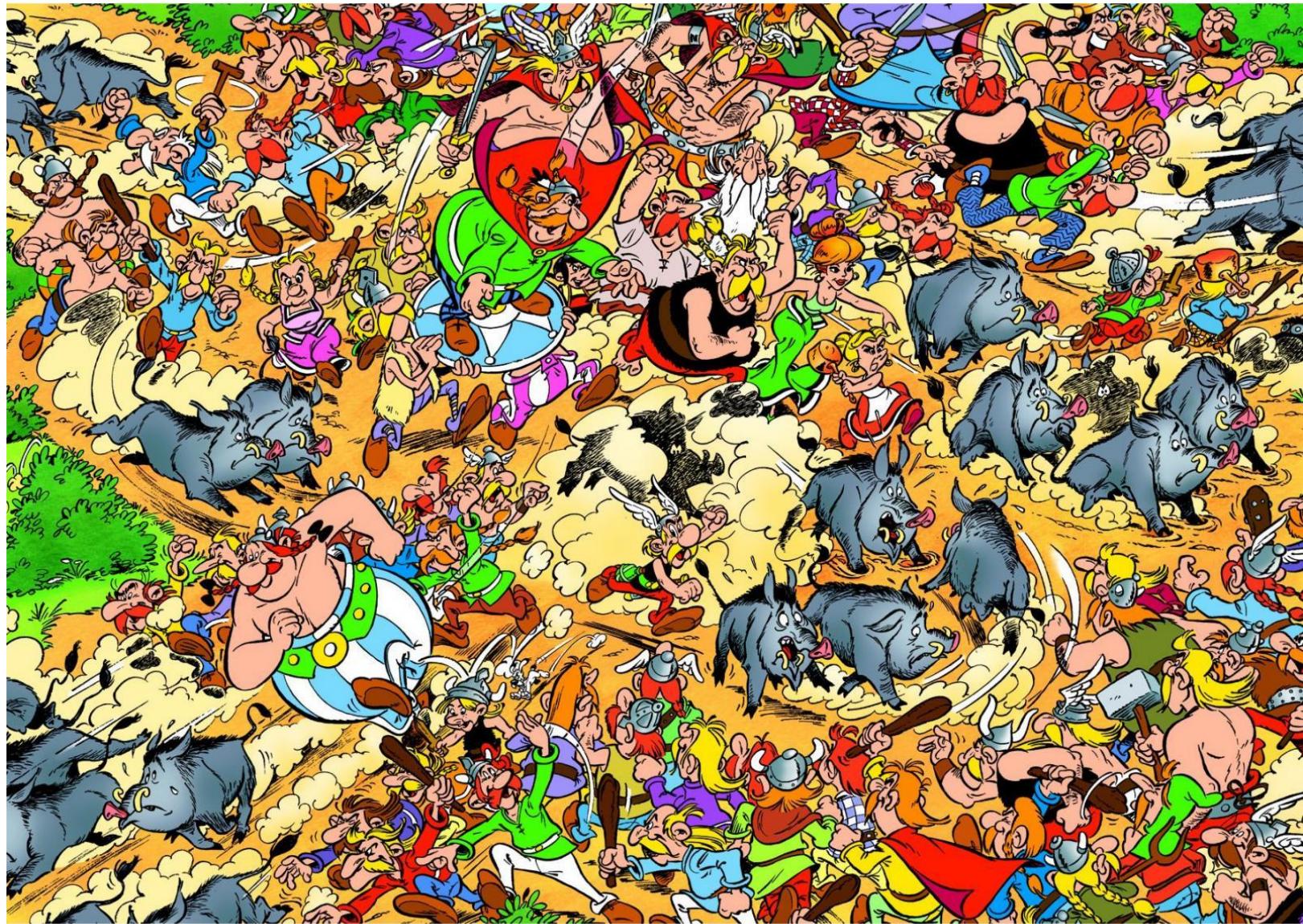
1. INDICATION

- Stratégie en RCP
 - ✓ Radiothérapie
 - ✓ Radio-chimiothérapie

Un Oncologue Radiothérapeute en Gastro-entérologie ...

1. INDICATION

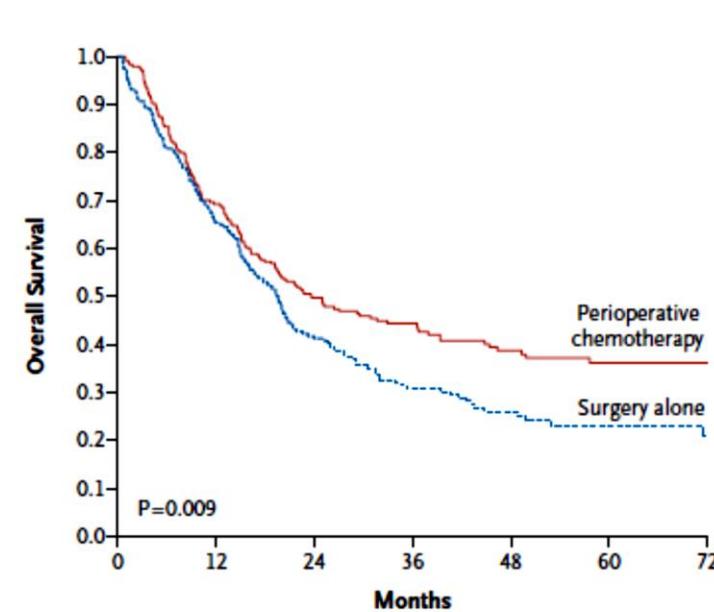
- Stratégie en RCP
 - Chirurgie
 - Place des traitements associés ?



Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Loftus, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

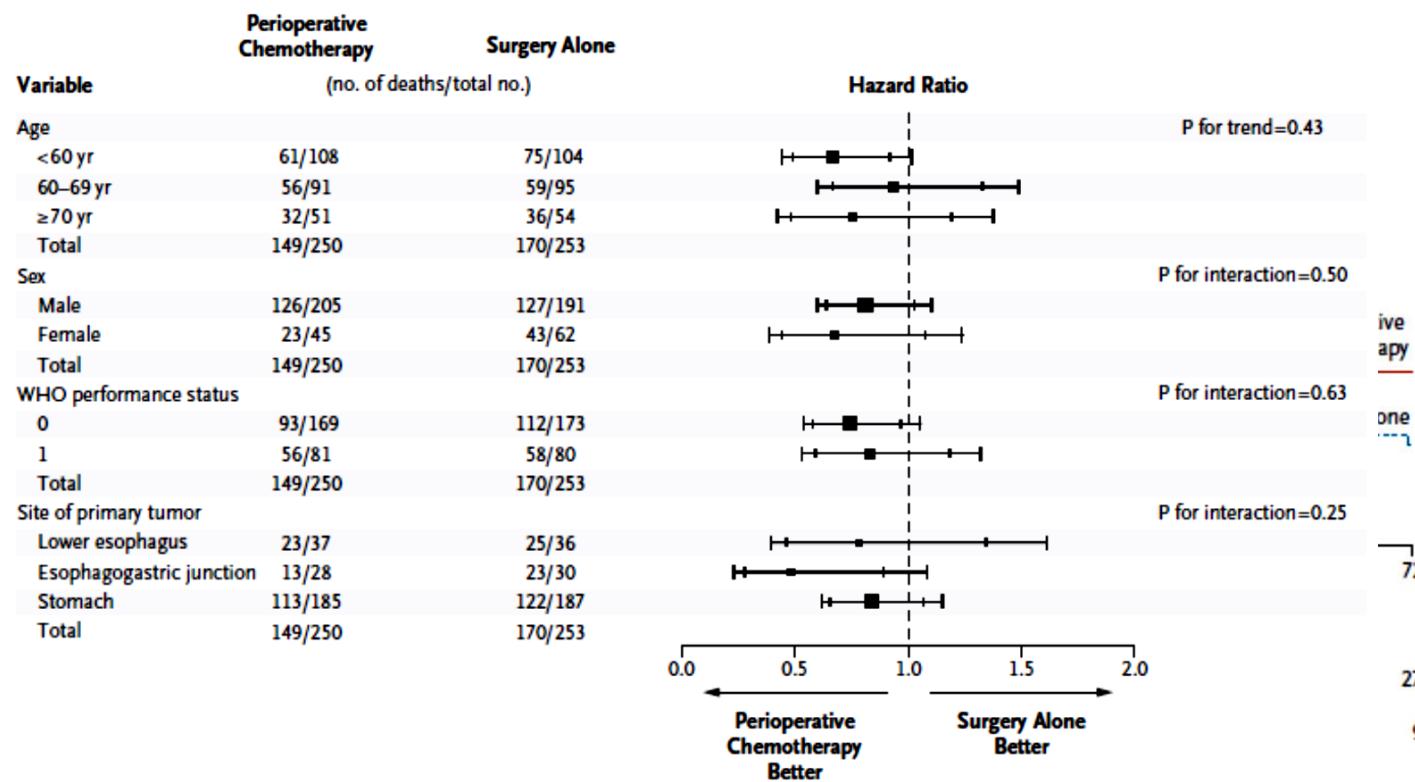
Site of tumor — no. (%)		
Stomach	185 (74.0)	187 (73.9)
Lower esophagus	37 (14.8)	36 (14.2)
Esophagogastric junction	28 (11.2)	30 (11.9)
Maximum tumor diameter		
0.0–3.9 cm — no. (%)‡	50 (30.9)	61 (33.3)
4.0–7.9 cm — no. (%)‡	79 (48.8)	87 (47.5)
8.0–11.9 cm — no. (%)‡	29 (17.9)	24 (13.1)
12.0–15.9 cm — no. (%)‡	2 (1.2)	8 (4.4)
>16.0 cm — no. (%)‡	2 (1.2)	3 (1.6)



No. at Risk	Perioperative chemotherapy	250	168	111	79	52	38	27
Surgery		253	155	80	50	31	18	9

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Loftus, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*



Cunningham D. New Eng J Med 2006;355:11-20

Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction

Macdonald JS et al NEJM 2001, 345;10:725-730

- 556 patients
- Résection chirurgicale complète
- Stades IB à IVM0, PS 2
- 45Gy, 25f : lit tumoral, marges = 2 cm
 ganglions régionaux
- Assurance de qualité AVANT (35%) et après (6,5%)

Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.

Macdonald et al NEJM 2001;345:725-730

- PROTOCOLE:

- 1- **Chimiothérapie** 1 cycle
 - 5Fu (425 mg/m²) AF (20mg/m²) J1 à J5
- 2- **Radio-chimiothérapie** J28
 - 45 Gy, 1,8 Gy/f, 5 semaines
 - 5Fu (425 mg/m²) AF (20mg/m²) J1-J4 et J28-J30
- 3- **Chimiothérapie** 2 cycles
 - 5Fu (425 mg/m²) AF (20mg/m²) J1 à J5

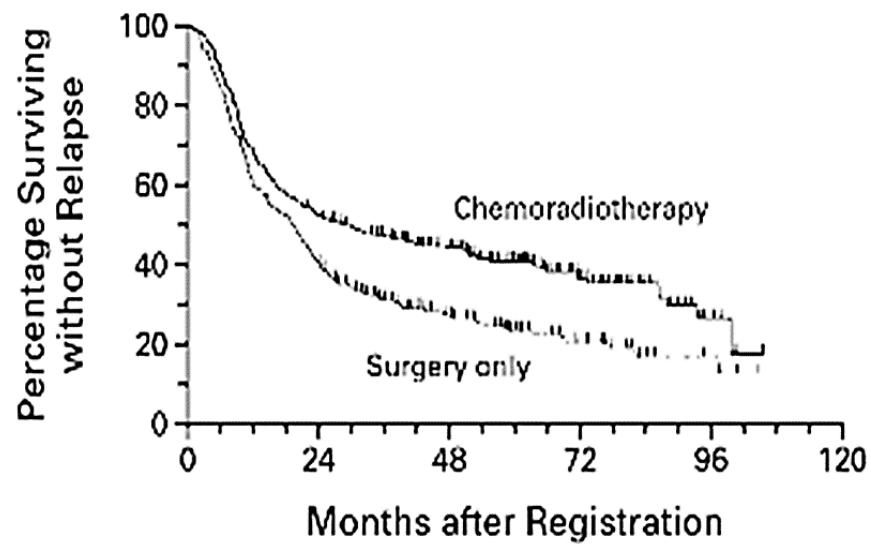
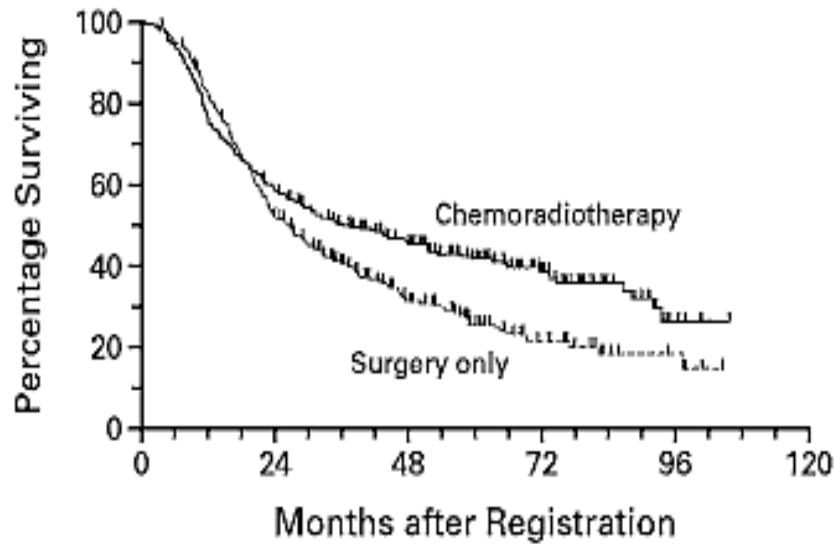
Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.

Macdonald et al NEJM 2001,10;345:725-730

- CHIRURGIE :

- Gastrectomie totale avec curage D2
 - Ganglions péri-gastriques, coeliaques, spléniques, cardia et hépatique selon la localisation
- D2: 10%
- D1: N+ = 36%
- D0: 54%
- Facteur non significatif dans l'essai

Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.
Macdonald et al NEJM 2001;10;345:725-730



Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.
Macdonald et al NEJM 2001;10;345:725-730

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)

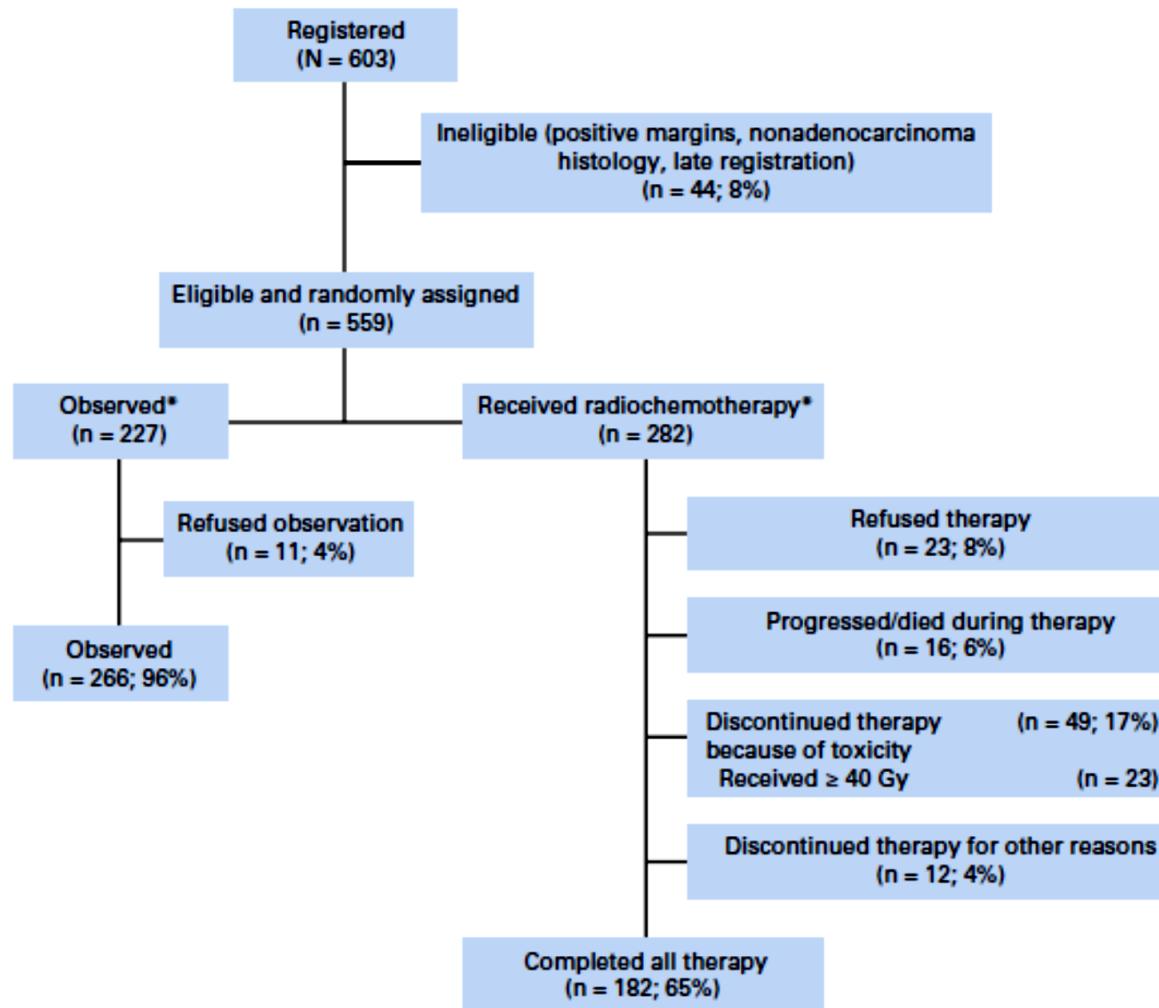
TABLE 3. MAJOR TOXIC EFFECTS OF CHEMORADIOTHERAPY.*

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)

* Major toxic effects were defined as those of grade 3 or higher. Data are for the 273 patients who received chemoradiotherapy.

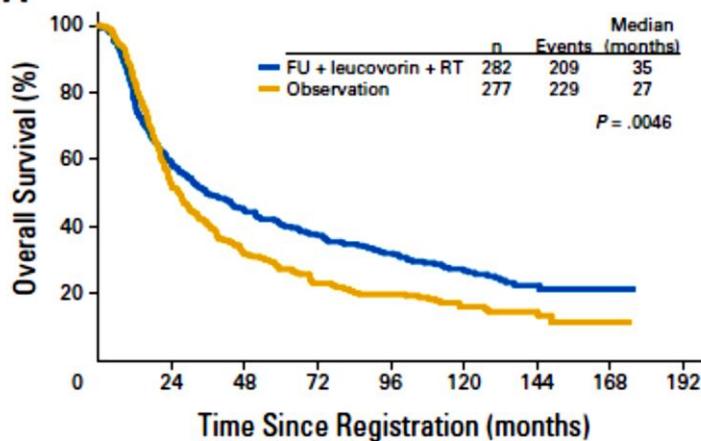
† One patient died from a cardiac event, one from sepsis complicating myelosuppression, and one from pulmonary fibrosis.

INT 0116: updated analysis



INT 0116: updated analysis

A



B

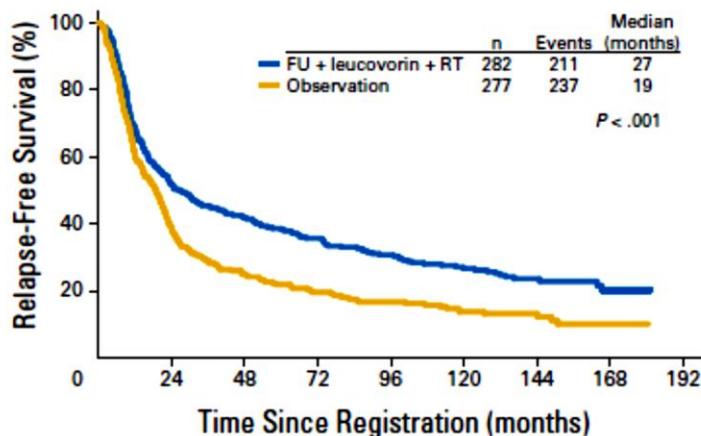
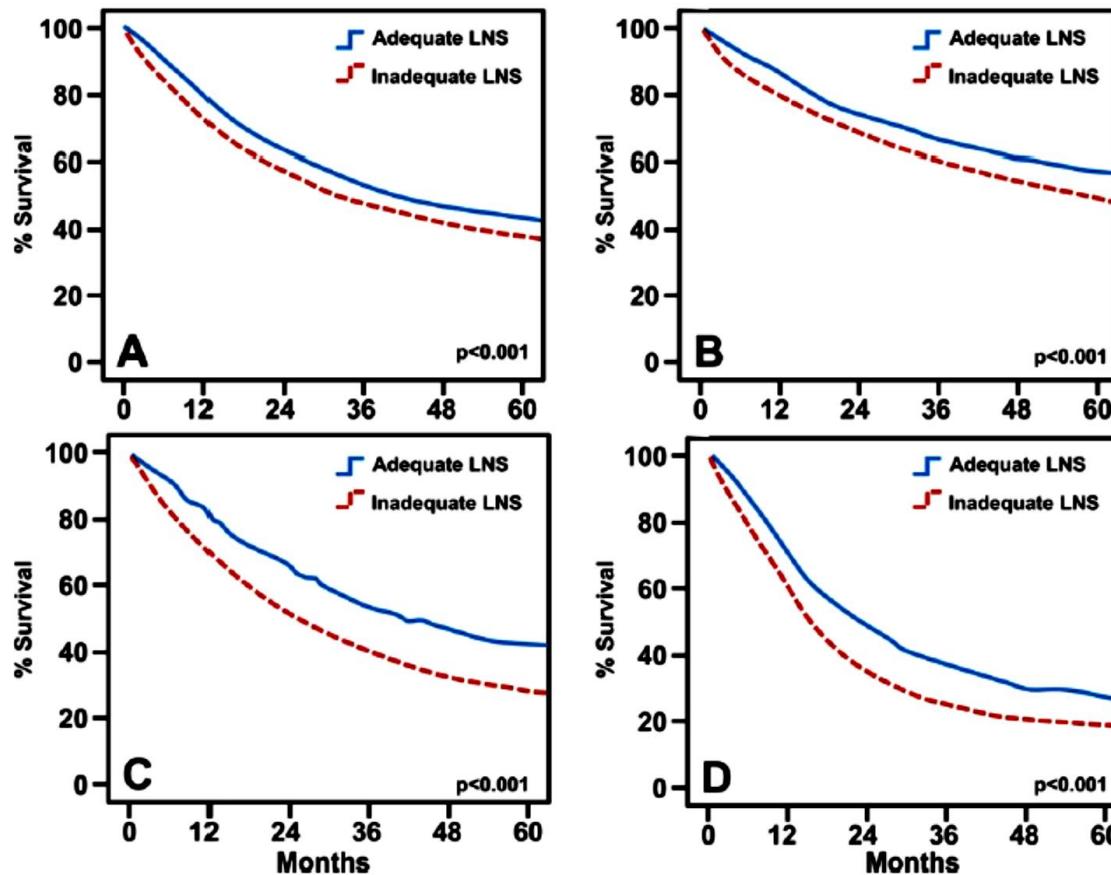


Table 2. Patterns of Failure by Arm

Relapse Status	Radiochemotherapy		Control (surgery alone)		Total	
	No.	%	No.	%	No.	%
No relapse*	135	48	67	24	202	36
Relapse*	147	52	210	76	357	64
Sites of relapse (% of those randomly assigned)*						
Local	7	2	21	8	28	5
Regional	62	22	109	39	171	31
Distant	46	16	49	18	95	17
Unknown site	32	11	31	11	63	11
Total	282		277		559	

Impact of inadequate LNS on OS in resectable gastric cancer



Datta J. Cancer 2014

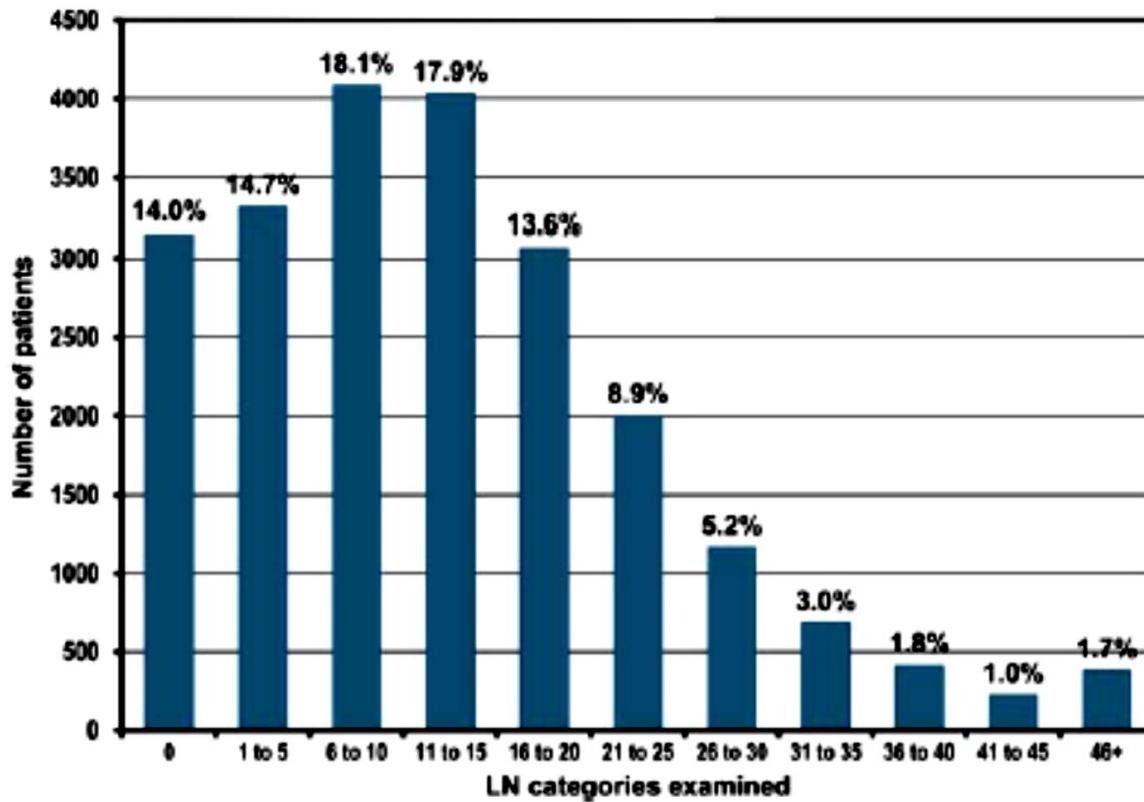
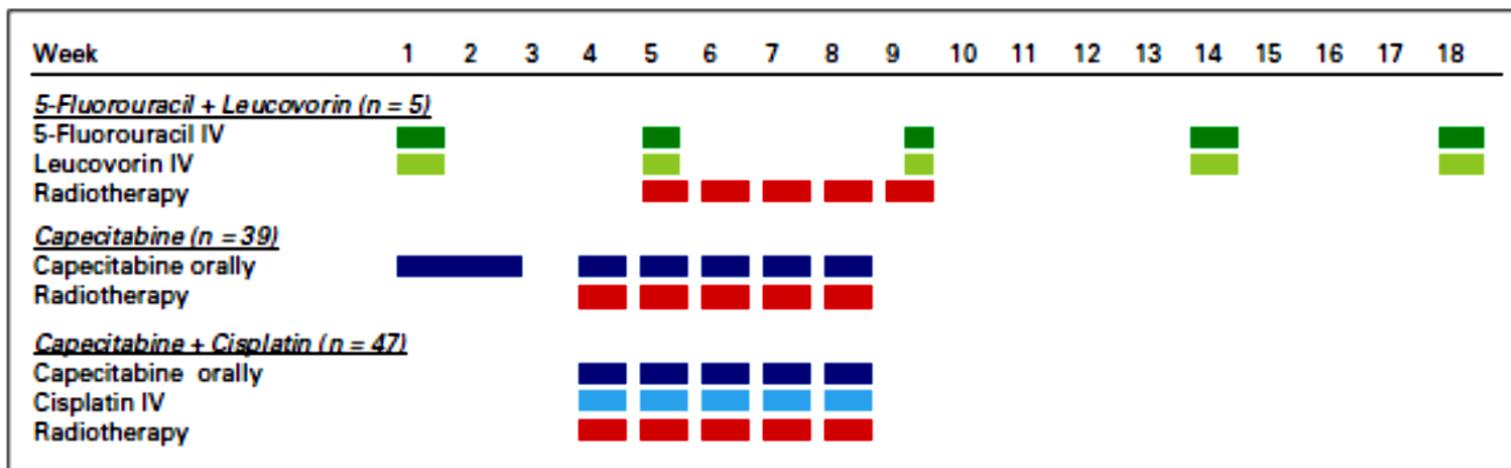


Figure 1. Absolute and relative frequency of patients within lymph node (LN) examination categories for the overall cohort ($n = 22,409$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Impact of the Extent of Surgery and Postoperative Chemoradiotherapy on Recurrence Patterns in Gastric Cancer

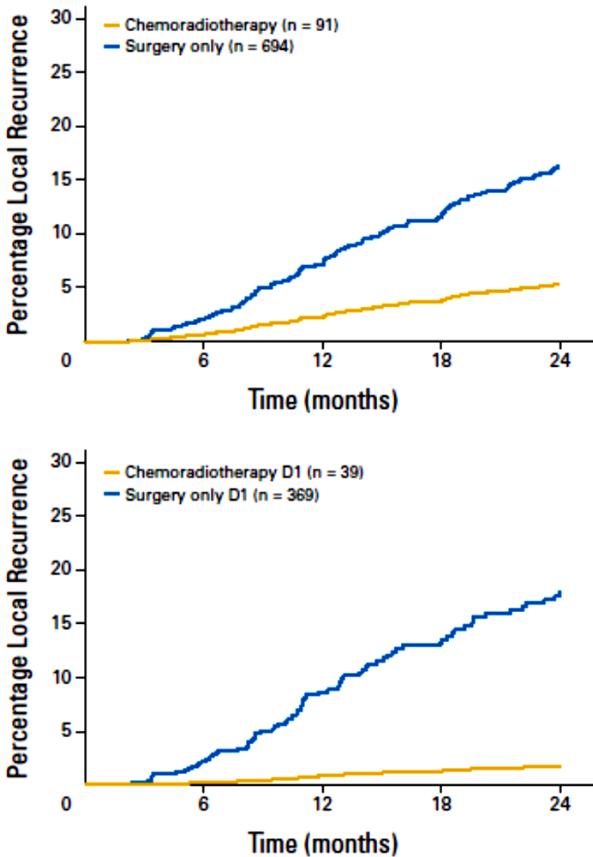
Johan L. Dikken, Edwin P.M. Jansen, Annemieke Cats, Berdine Bakker, Henk H. Hartgrink,
Elma Meershoek-Klein Kranenbarg, Henk Boot, Hein Putter, Koen C.M.J. Peeters, Cornelis J.H. van de Velde,
and Marcel Verheij

- 91 patients versus 694 DGCT D1= 369 D2= 325

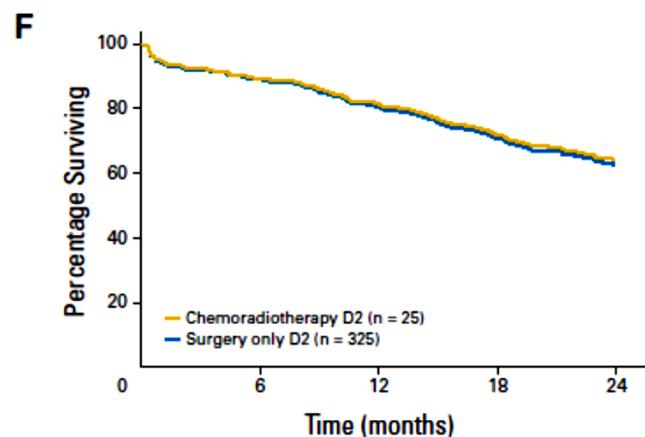
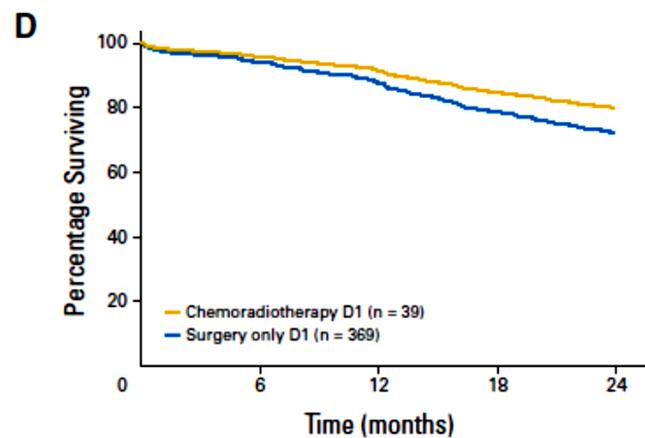
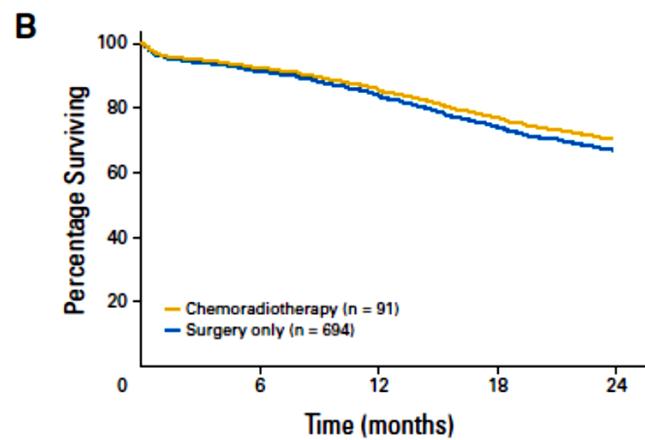
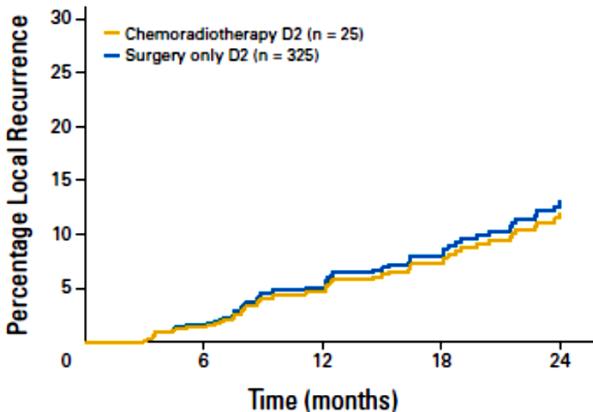


- Maruyama Index for unresected Disease M1

CRT – D1



CRT – D2



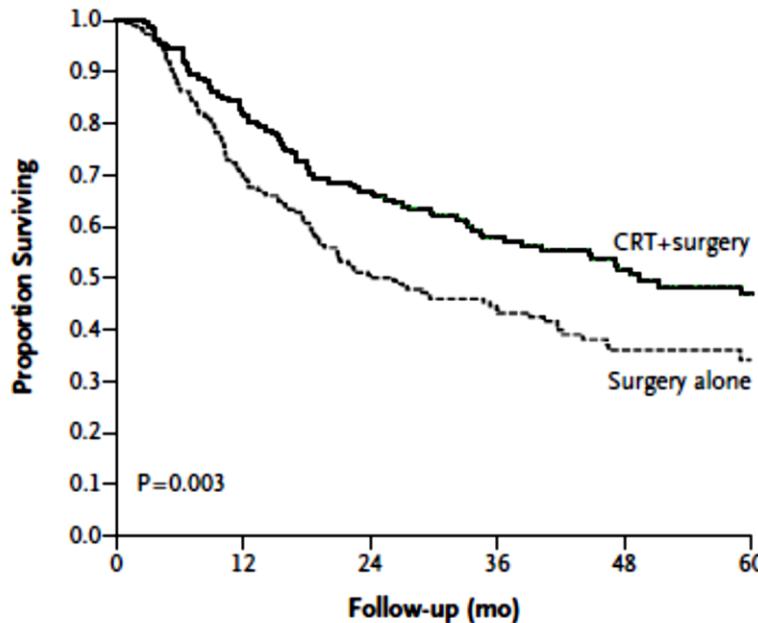
Preoperative chemoradiotherapy for esophageal or junctional carcinoma: CROSS

- Carboplatin 2mg/ml/mn + Paclitaxel 50 mg/m²
 - Days 1,8,15,22,29
- Radiotherapy: 41.4 Gy / 23f /1.8 Gy GTV + 1.5cm + 4 cm
- 837 patients (437 excluded) 368 randomized
- NCI CTC AE V 3.0: RTCT : Grade 3 or higher = 13% 1 toxic death

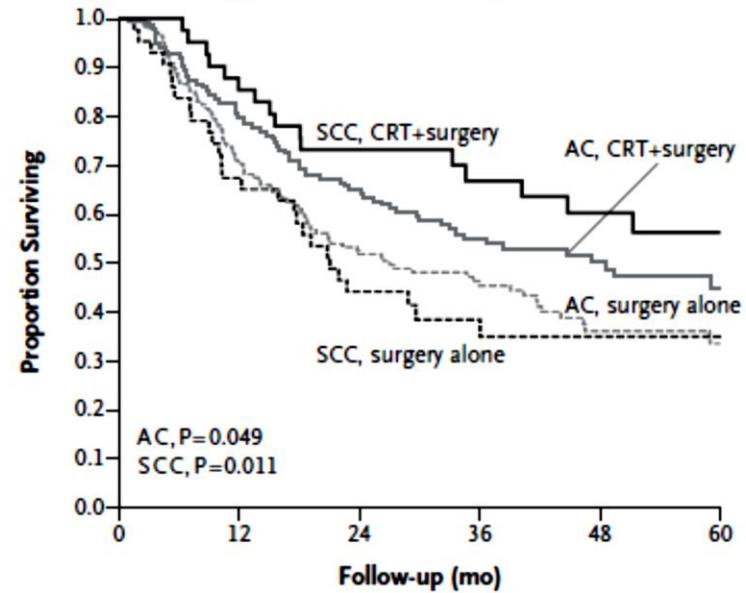
	S	RTCT – S	
• Resection rate	13%	4%	p<0.002
• Postop death	3%	2%	p=0.85
• R0 resection	69%	92%	p<0.001
• Resected LN	18	15	p=0.17
• N+	75%	31%	p<0.001

Preoperative chemoradiotherapy for esophageal or junctional carcinoma: CROSS

A Survival According to Treatment Group

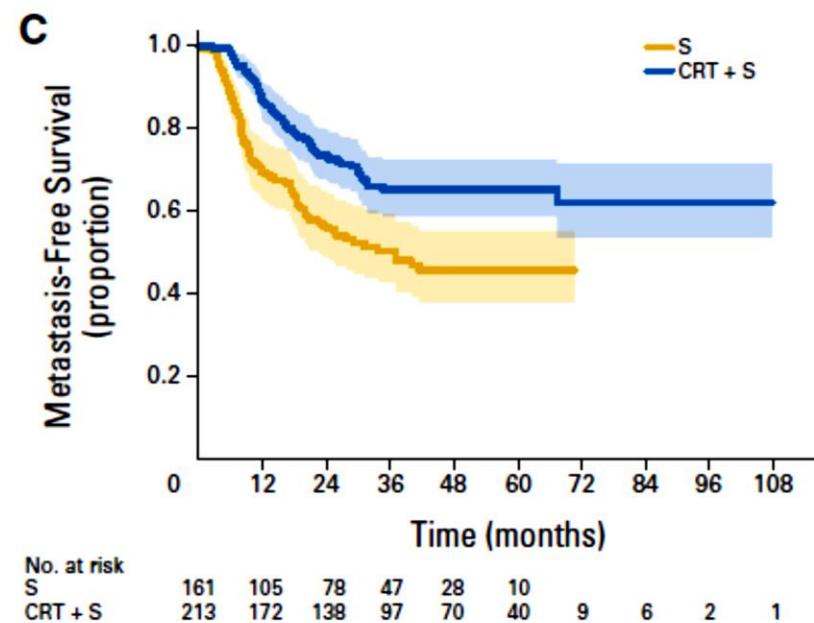
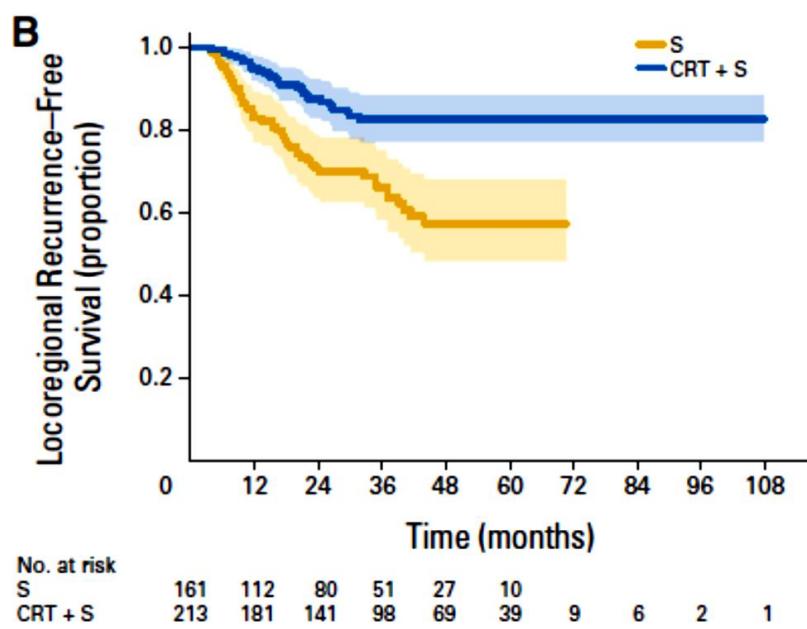
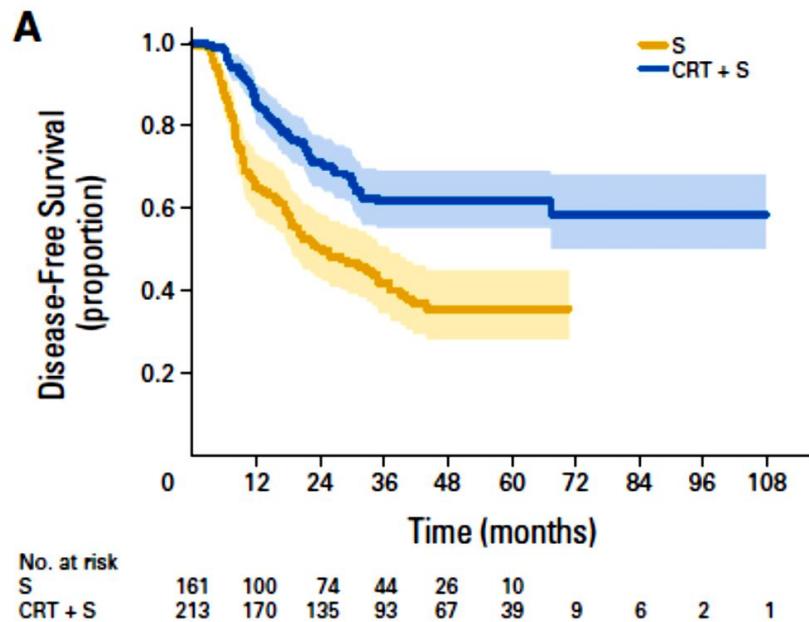


B Survival According to Tumor Type and Treatment Group

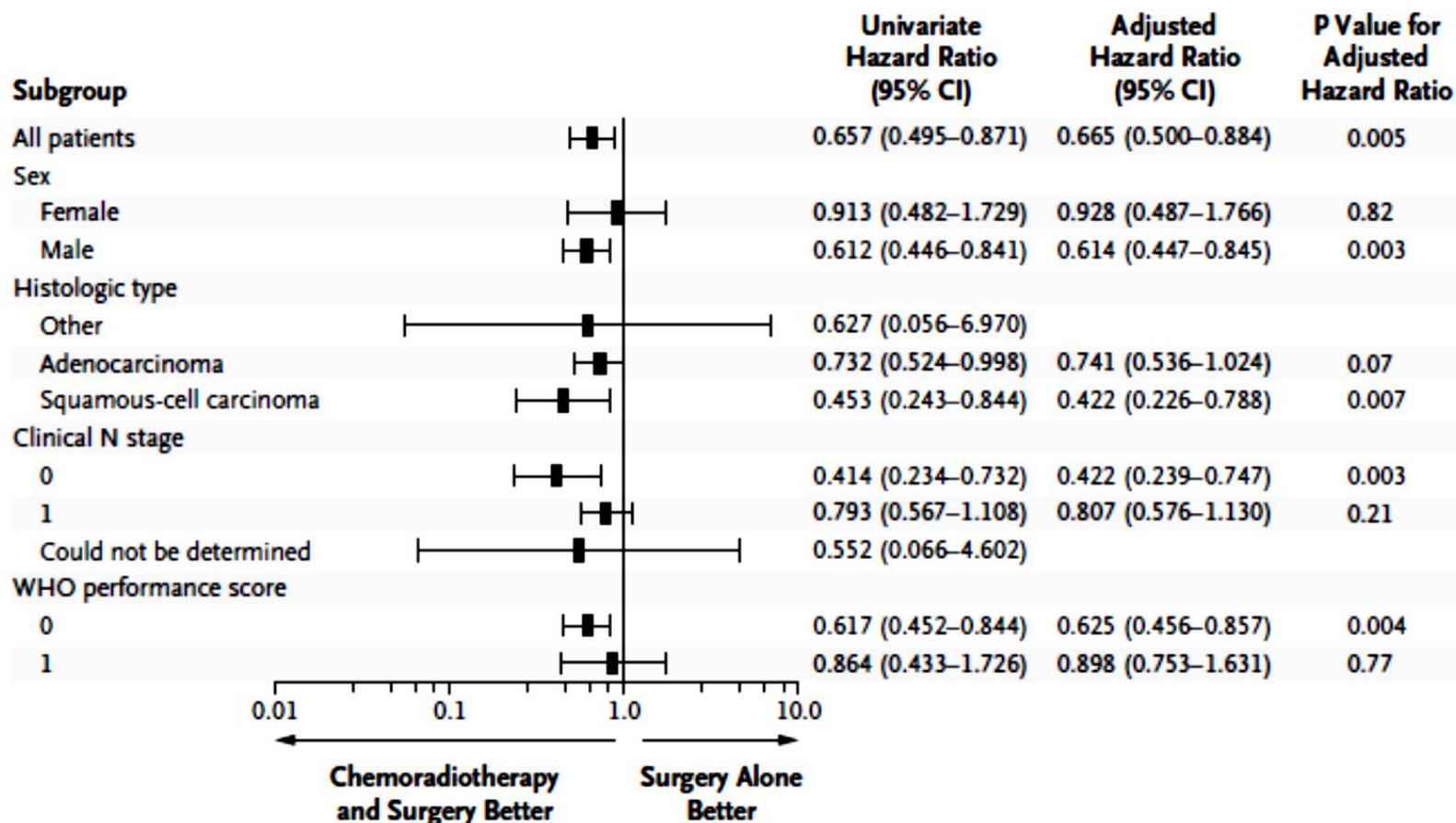


No. at Risk						
CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45

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

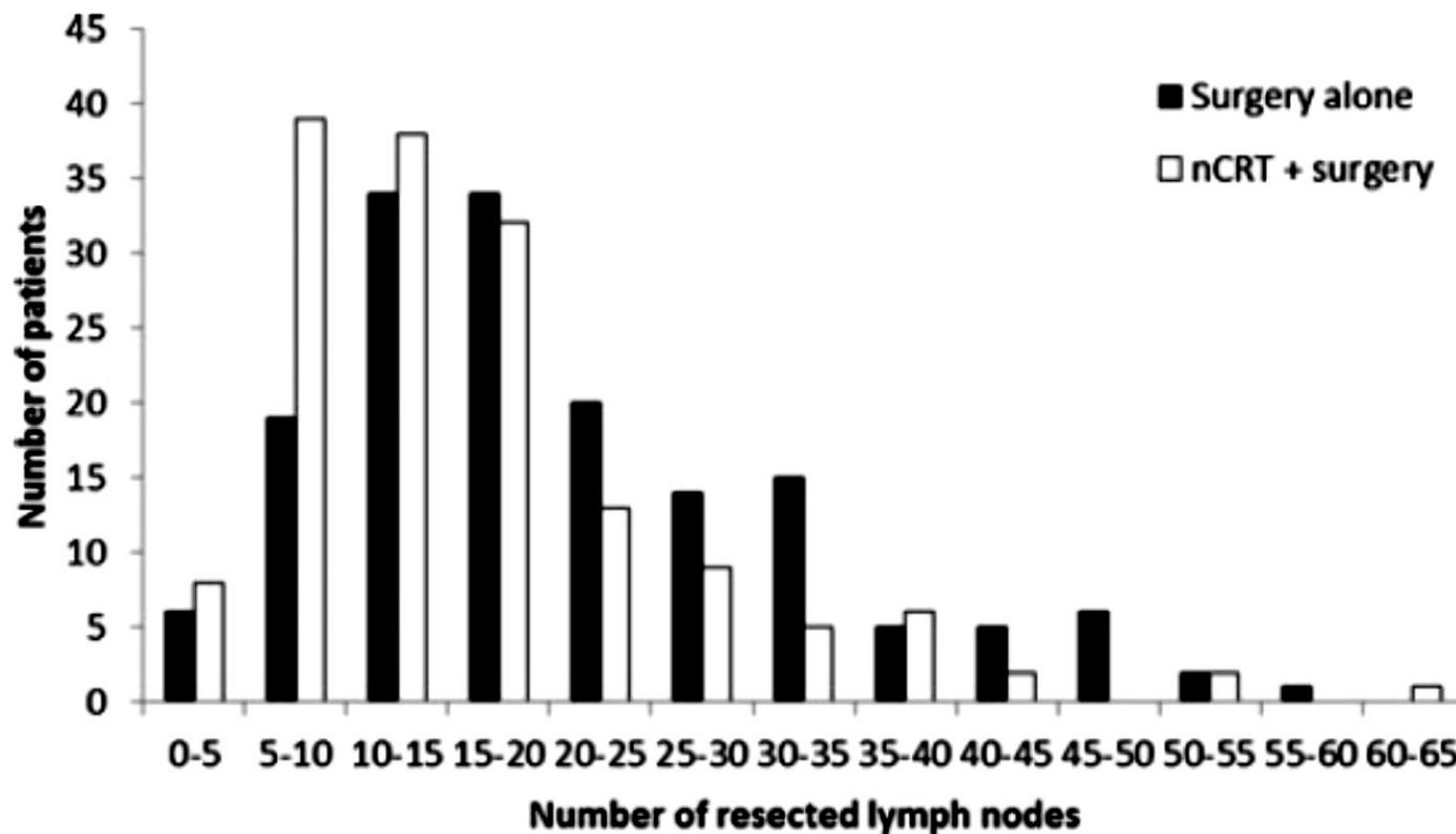


Oppedijk V. JCO 2014;32:385-91



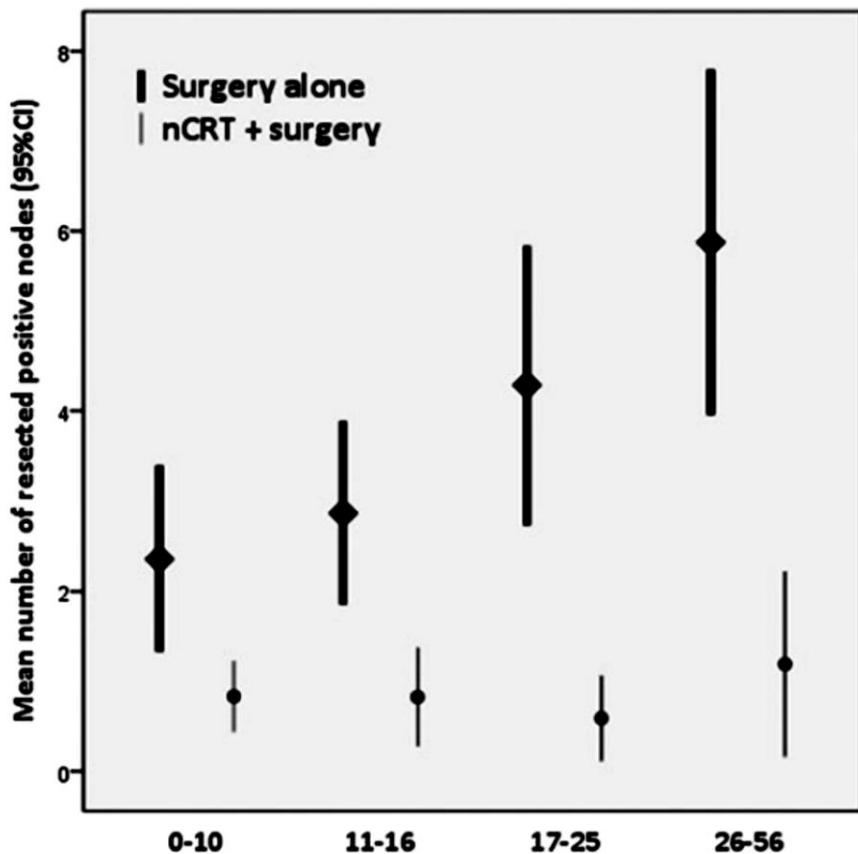
Van Hagen P. N Eng J Med 2012;366:2074-84

Lymph Node Retrieval During Esophagectomy With and Without Neoadjuvant Chemoradiotherapy



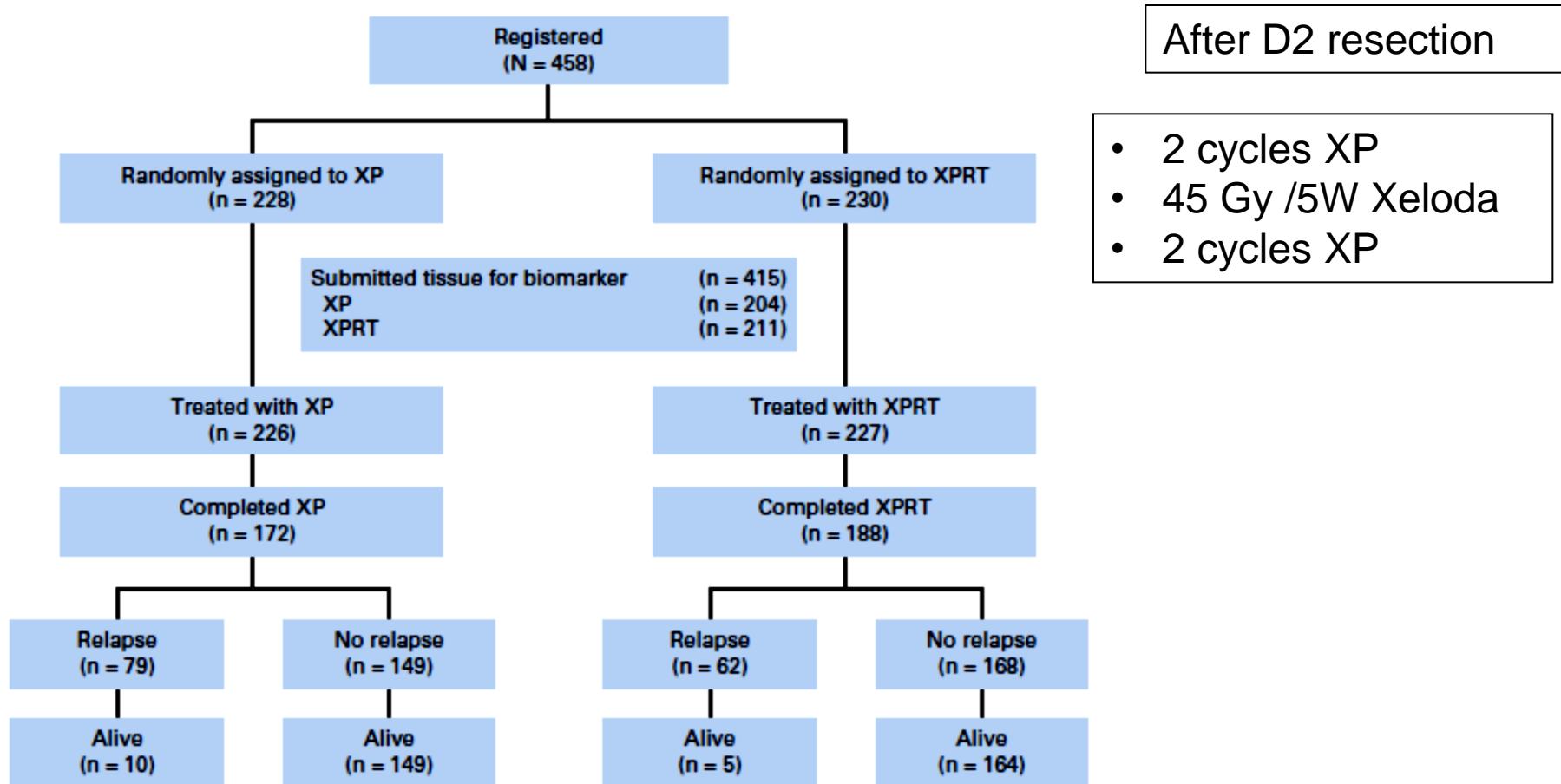
Talsma A.K. Ann Surg 2014;260:786-93

Lymph Node Retrieval During Esophagectomy With and Without Neoadjuvant Chemoradiotherapy

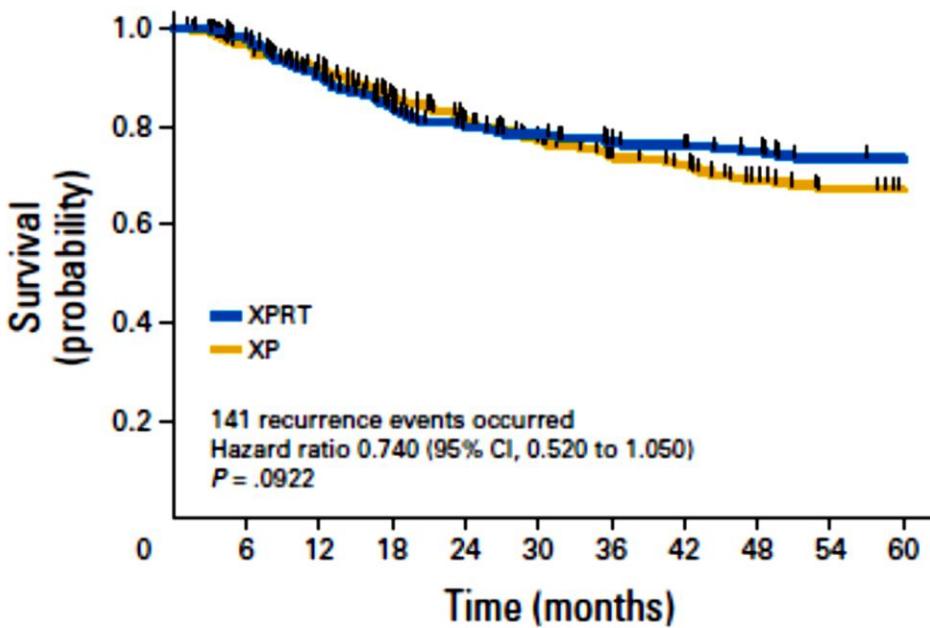


The total number of resected lymph nodes was significantly associated with survival in the surgery arm but not in the multi-modality arm.

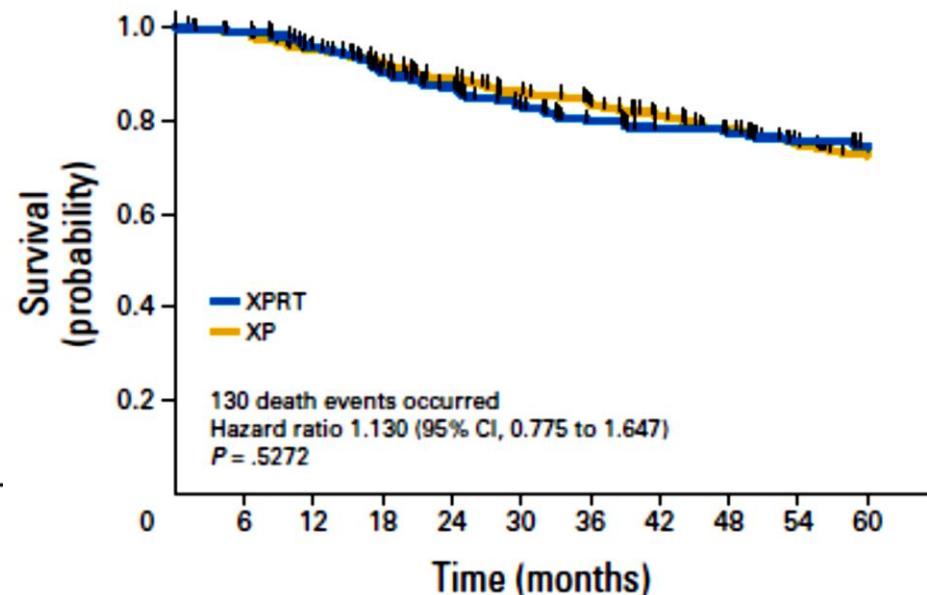
ARTIST trial: Adjuvant chemotherapy versus chemoradiation in gastric cancer



ARTIST trial: Adjuvant chemotherapy versus chemoradiation in gastric cancer



No. at risk	
XPRT	230
XP	228



No. at risk	
XPRT	230
XP	228

La ‘TRI-THERAPIE’

- 1- Chimiothérapie d'induction
- 2- Radio-chimiothérapie
- 3- Chirurgie
 - 38 patients, uT3: 90%, uN1: 66%
 - Résection RO : 95%
 - Réponse complète histo-pathologique: 30%
 - Recul médian: 20 mois, médiane non atteinte.

Ajani JA, Cancer, 2001;92:279-86

La ‘TRI-THERAPIE’

- The use of trimodality therapy for the treatment of operable esophageal carcinoma in the veteran population Billingsley KG et al Cancer 2001,92;5:1272-1280
 - 695 patients
 - 77% chirurgie seule
 - 23% : radio-chimiothérapie d’induction puis chirurgie
 - Survie médiane = 15 mois
 - Pas d’impact de la ‘tri-thérapie’ sur la survie

INDICATIONS

• OESOGASTRIC JUNCTION

- T1-2 N0 : Surgery
- T1-4 N1-3:

TYPES I – II – III

TYPES I et II preoperative or perioperative chemotherapy + Surgery
but chemoradiation should be discussed

TYPE III : perioperative chemotherapy or postoperative chemoradiation

• GASTRIC ADENOCARCINOMA

- T1 – 2 N0 : Surgery
- Others : perioperative chemotherapy or postoperative chemoradiation

Adjuvant postoperative chemoradiation in gastric cancer during the 2004 – 2008 period

		CHEMORADIATION		
	N	No	Yes	p
Overall		79 %	21 %	
Sexe	Female	87 %	13%	0.047
	Male	74 %	26%	
Age	< 65	52 %	48%	0.001
	65 – 74	77 %	23%	
	> 75	97.5 %	2.5%	
Charlson score	0	67 %	33 %	0.001
	1	83 %	17 %	
	2+	100 %	-	
Multidisciplinary M.	Yes	72 %	28 %	0.007
	No	89 %	11 %	

Adjuvant postoperative chemoradiation in gastric cancer during the 2004 – 2008 period

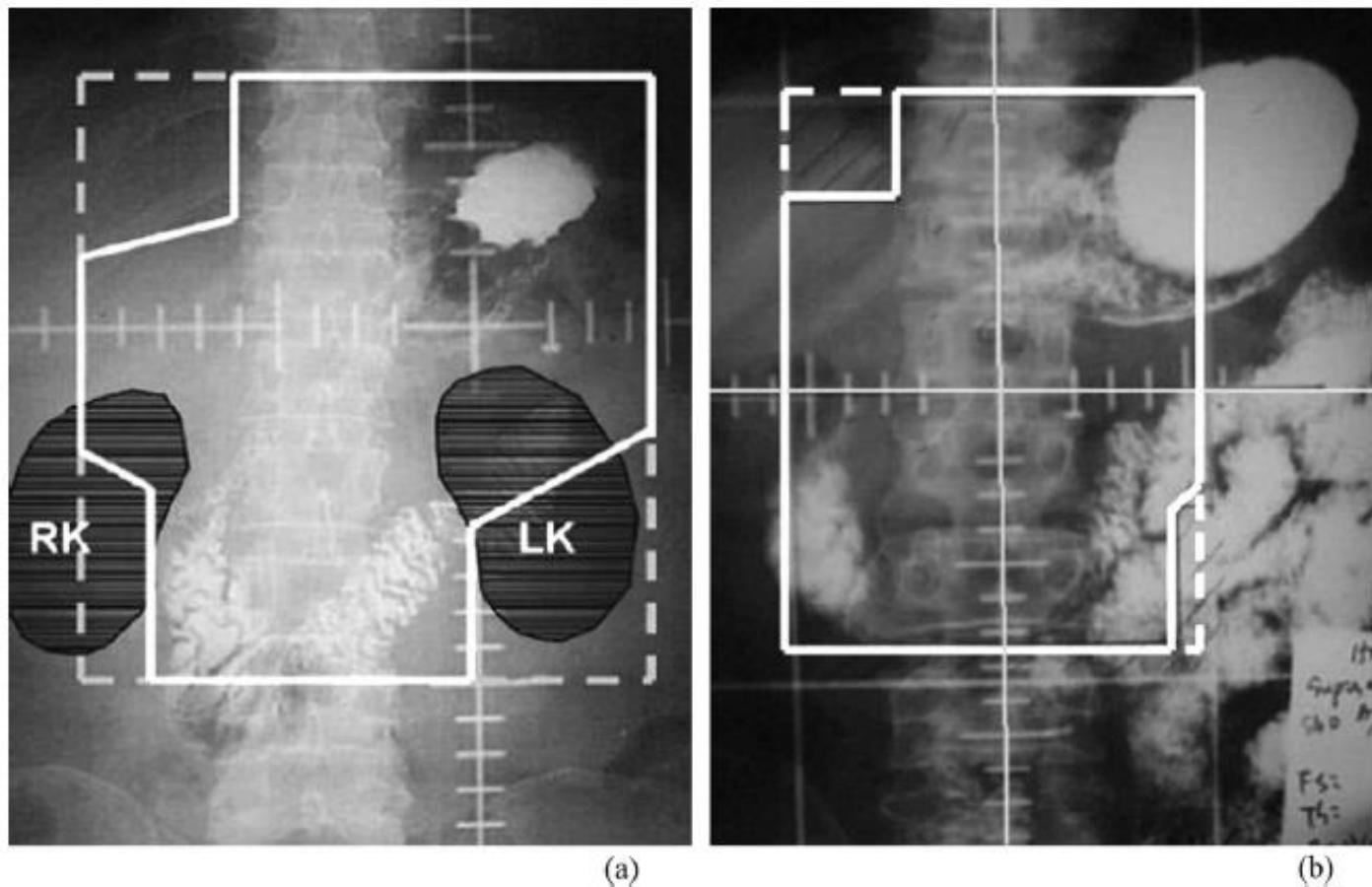
		CHEMORADIATION		
		Odds Ratio	CI	p
Sexe	Female	1		
	Male	1.11	[0.39 – 3.15]	0.846
Age	< 65	1		
	65 – 74	0.41	[0.16 – 1.05]	
	> 75	0.03	[0.01 – 0.15]	0.00000
Charlson score	0	1		
	> 1	0.26	[0.09 – 0.72]	0.009
Multidisciplinary M.	Yes	1		
	No	0.22	[0.08 – 0.64]	0.005

Un Oncologue Radiothérapeute en Gastro-entérologie ...

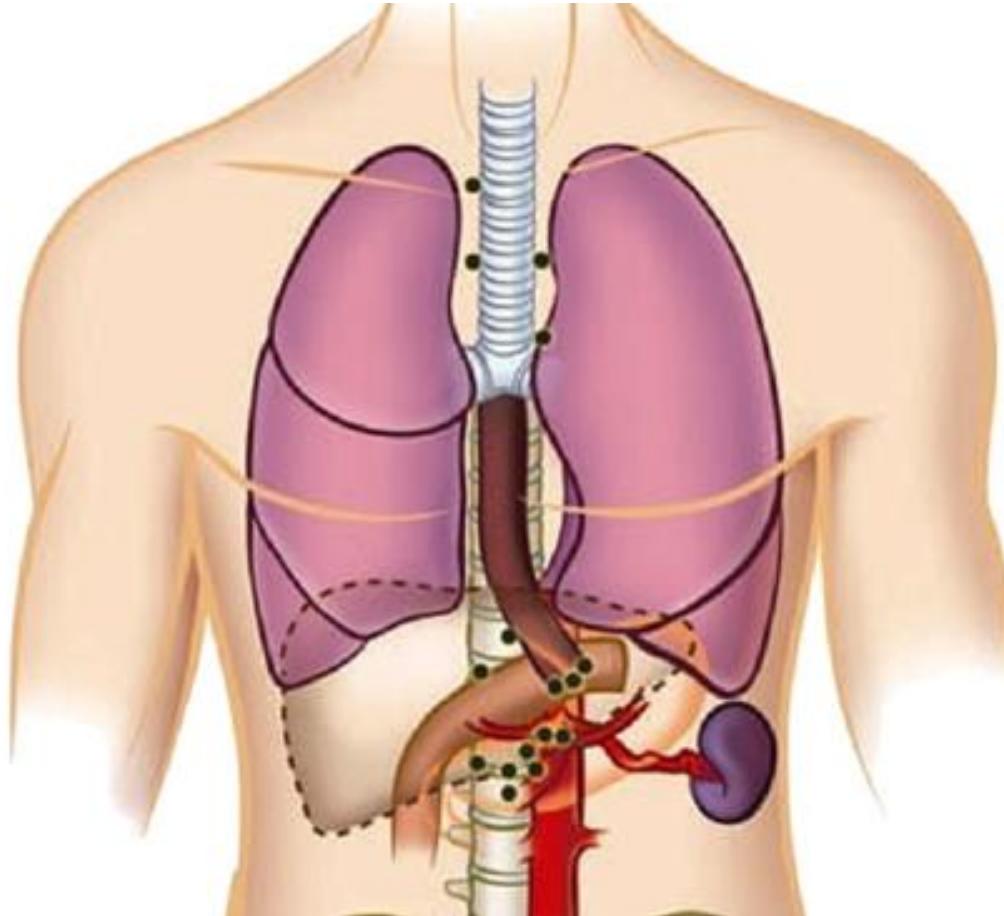
2. Volumes

- Primitif
- Ganglions

A new suggestion for the radiation target volume after subtotal gastrectomy in patients with stomach cancer



Pattern of LR recurrence in gastric cancer patients treated with preoperative chemoradiotherapy



Reed V. IJROBP 2008;71:741-747

Anatomy

The three portions of the stomach

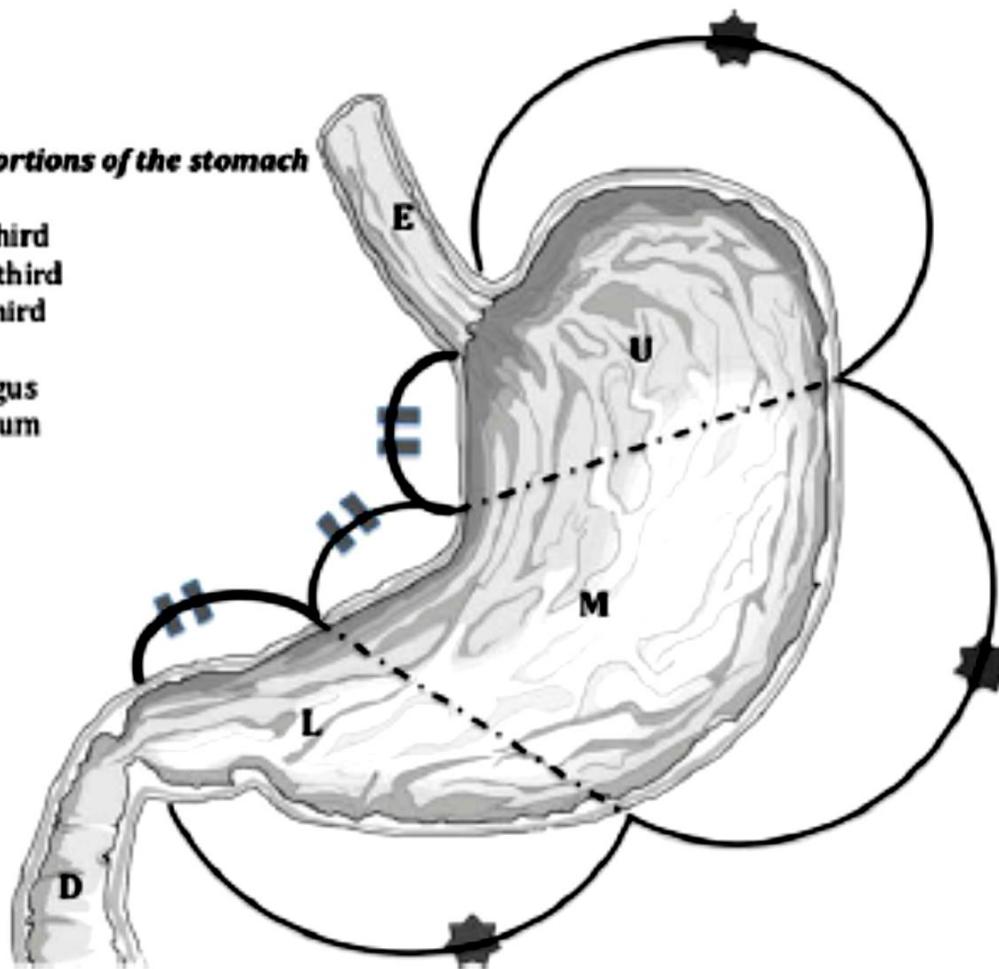
U: upper third

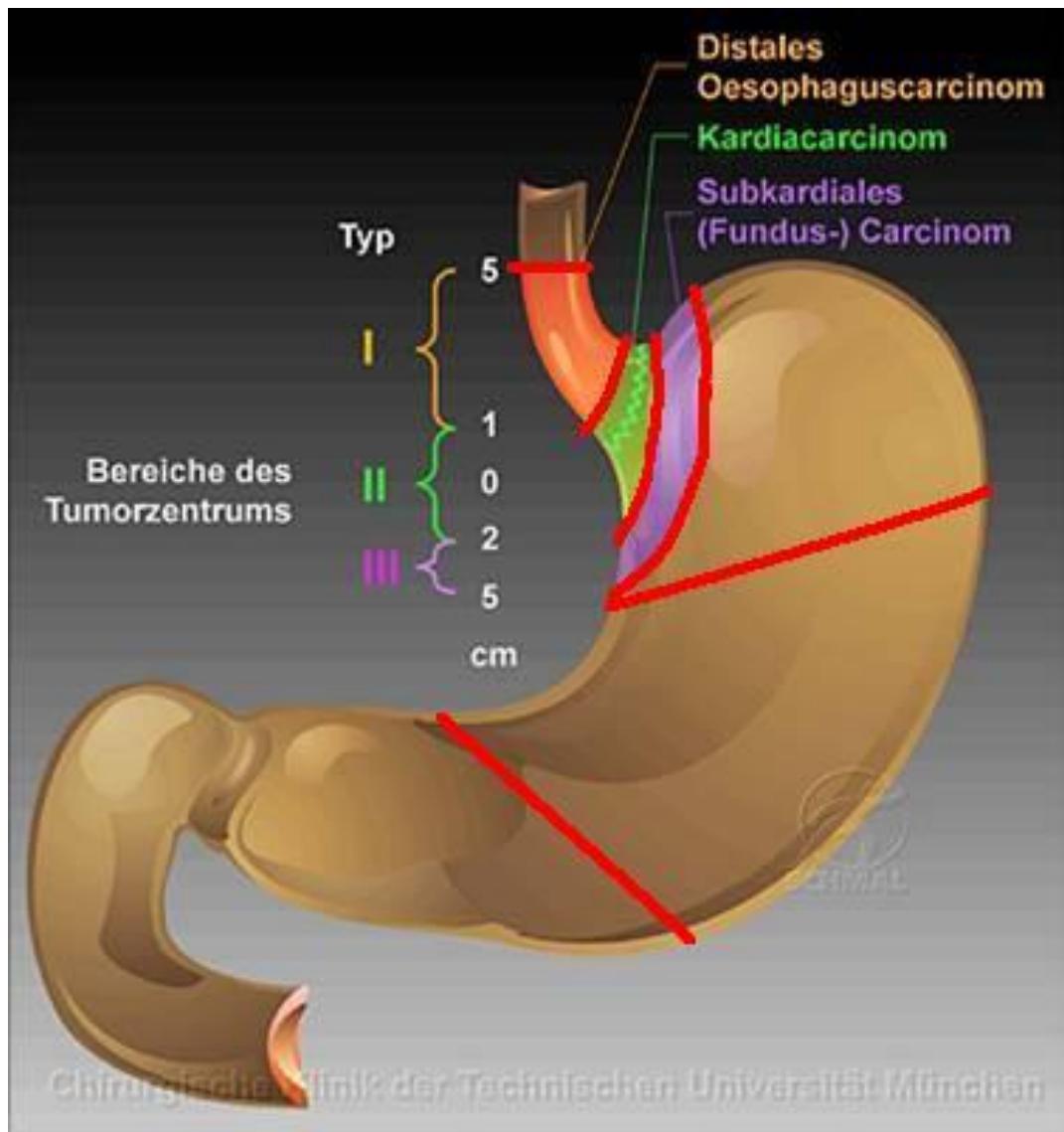
M: middle third

L: lower third

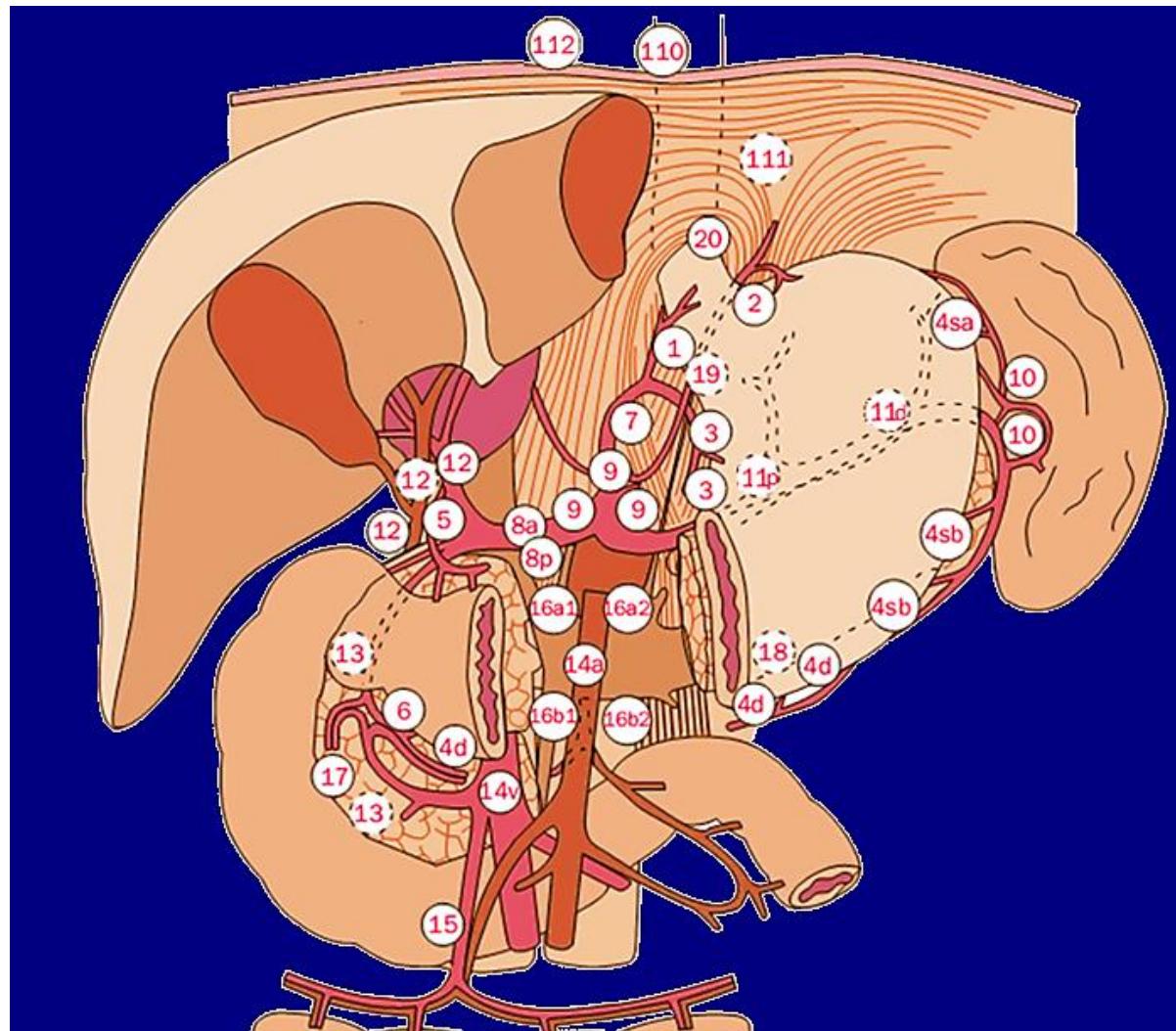
E: esophagus

D: duodenum





Japanese Classification of Gastric cancer Lymph node stations JGCA 1998



Japanese lymph node compartments

5 Y - OS

N0 n=2155 45% **82%**

N1 n= 907 19% **50%**

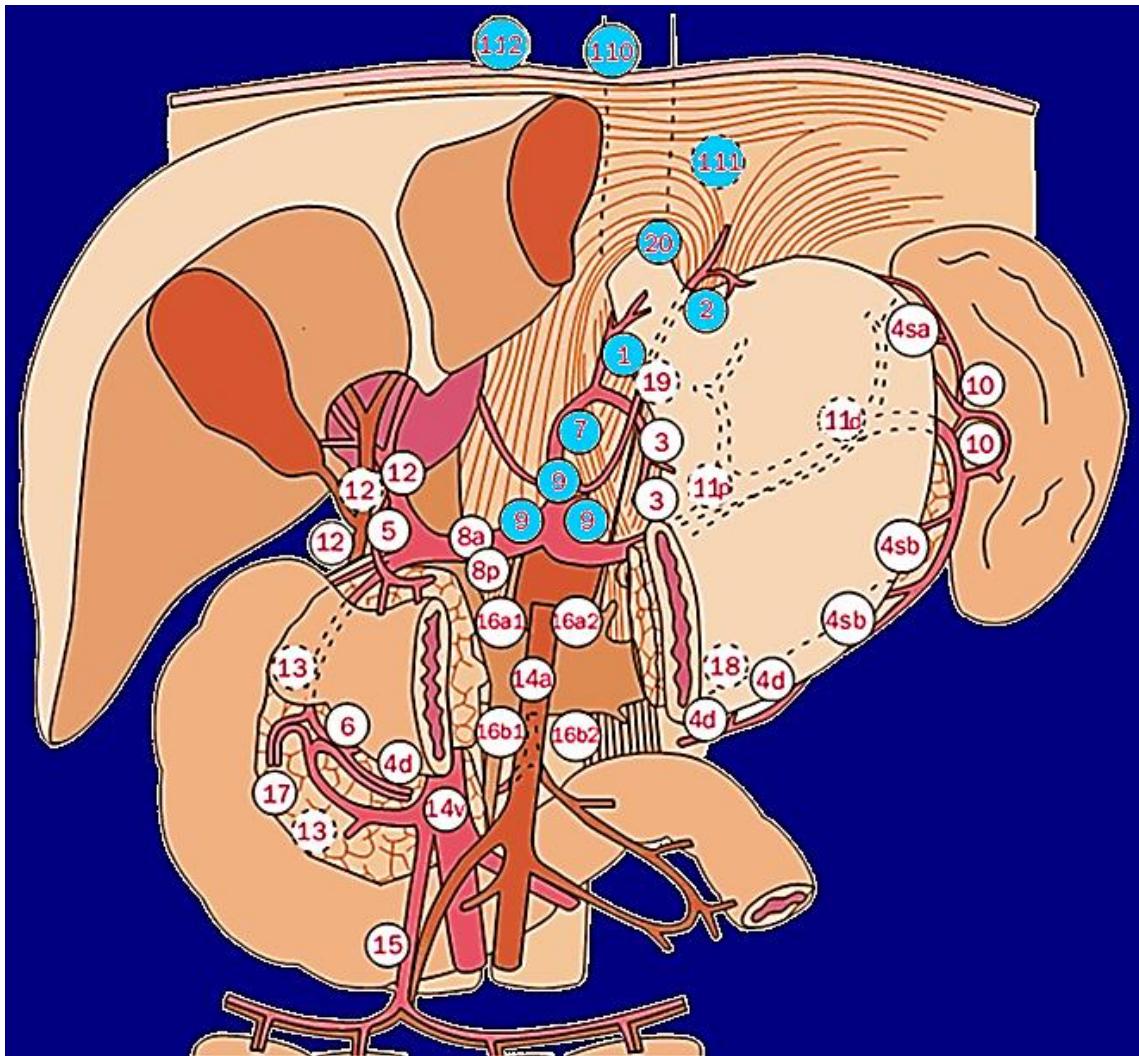
N2 n=1211 25% **24%**

N3 n= 295 6% **6%**

N4 n=159 3% **2%**

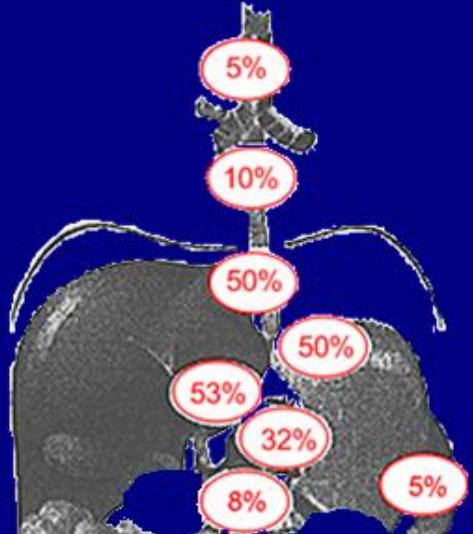
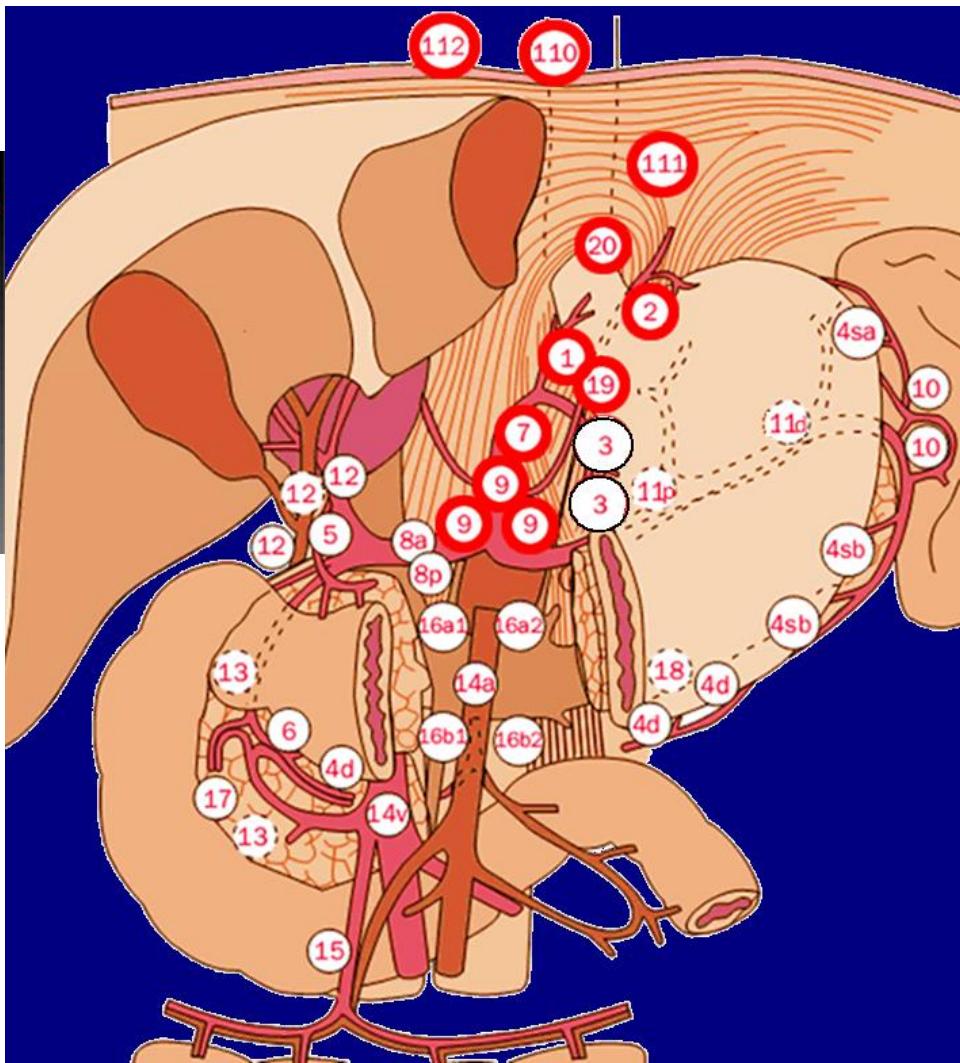
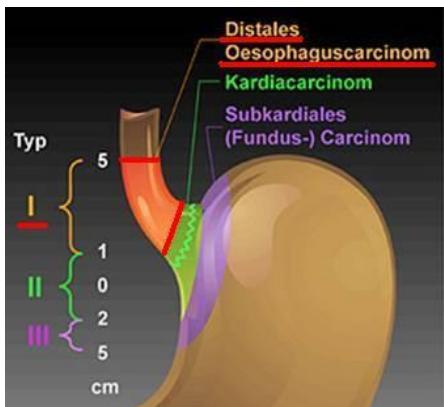
Adenocarcinomas of the GEJ

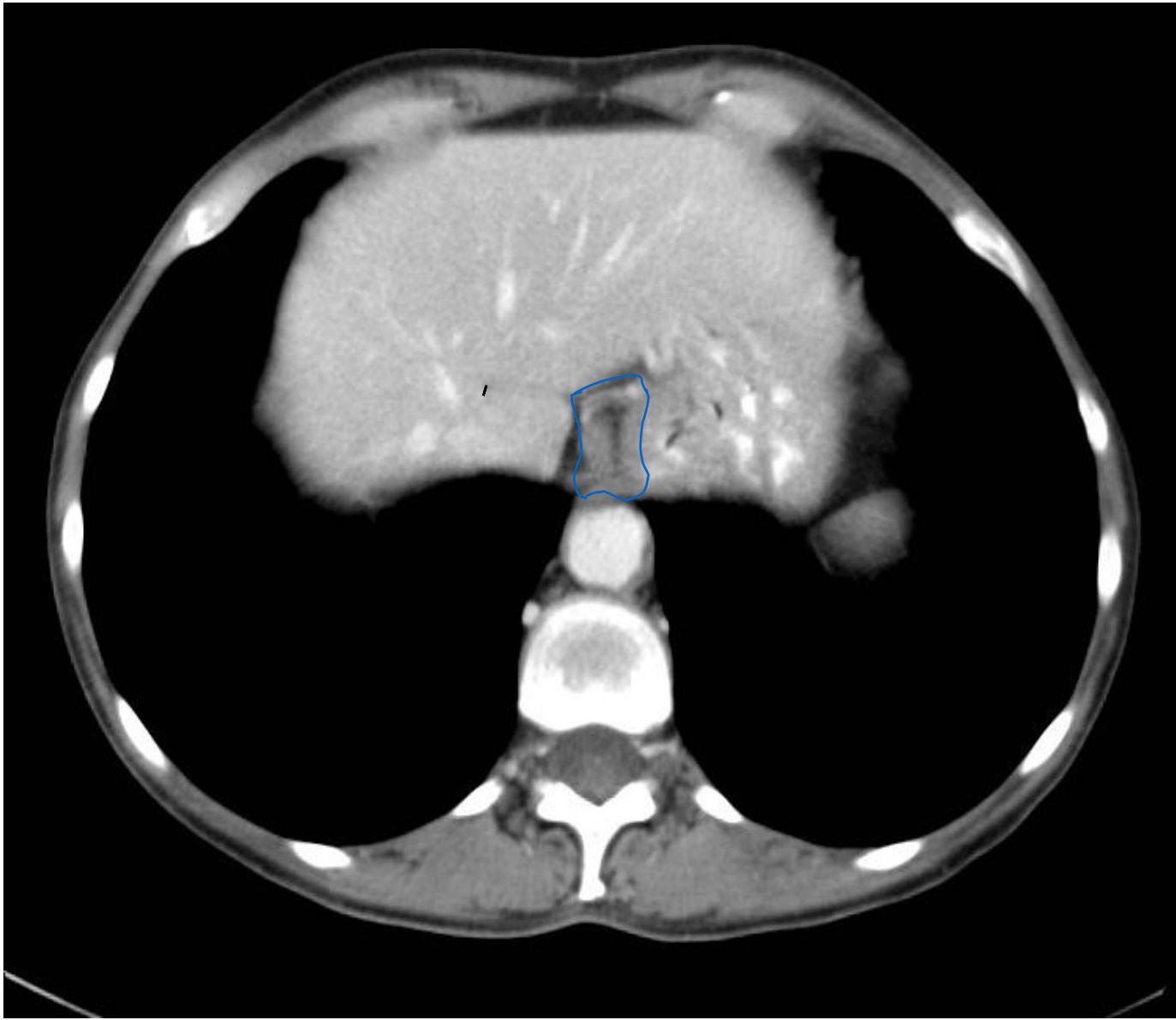
Regional lymph nodes UICC TNM 2002



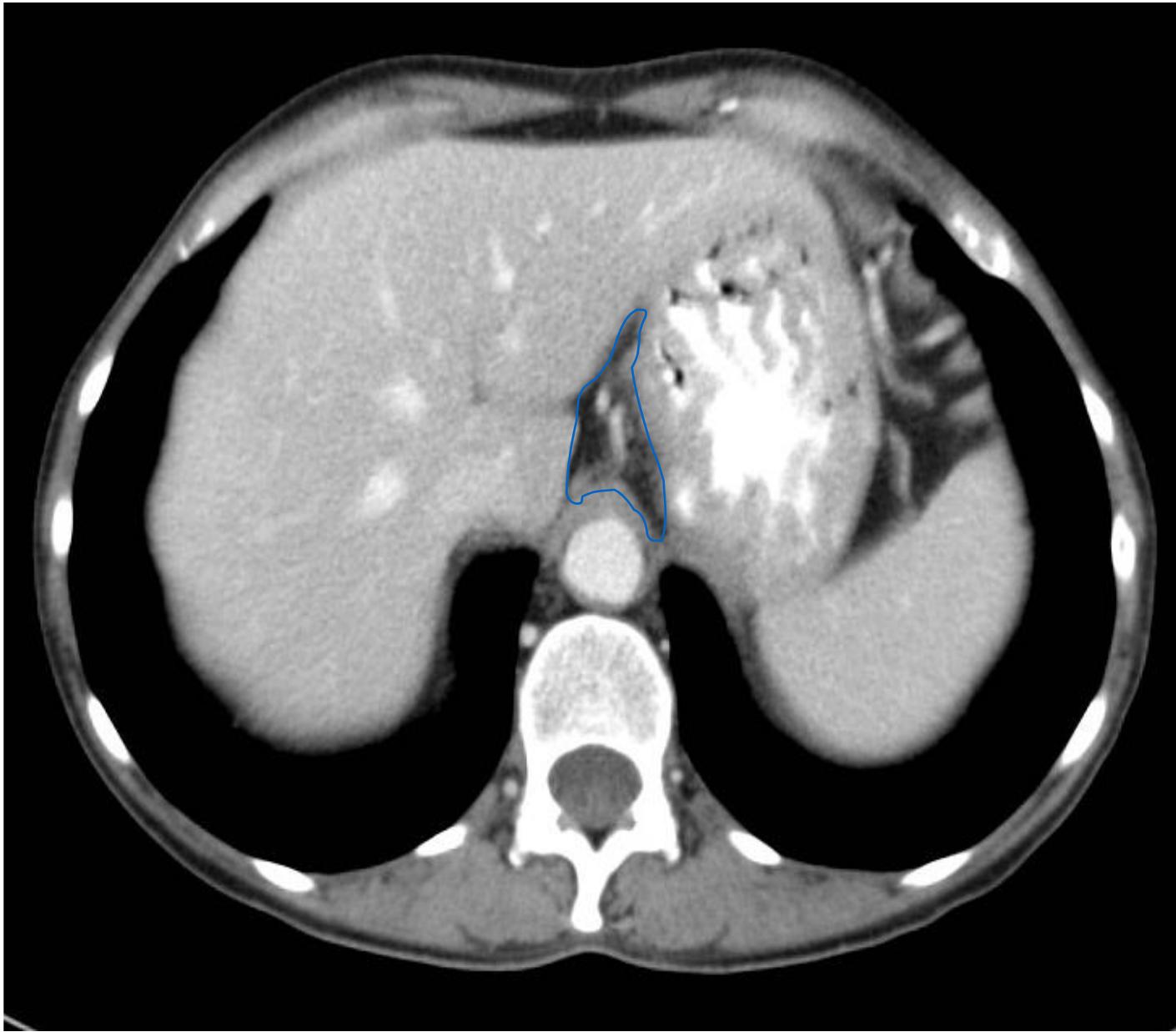
Target volume definition

GEJ I





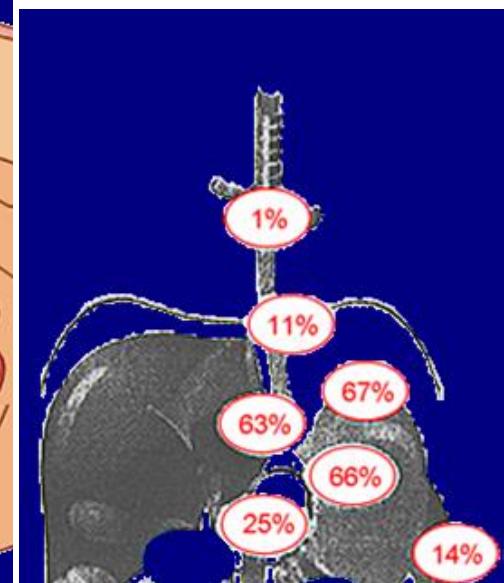
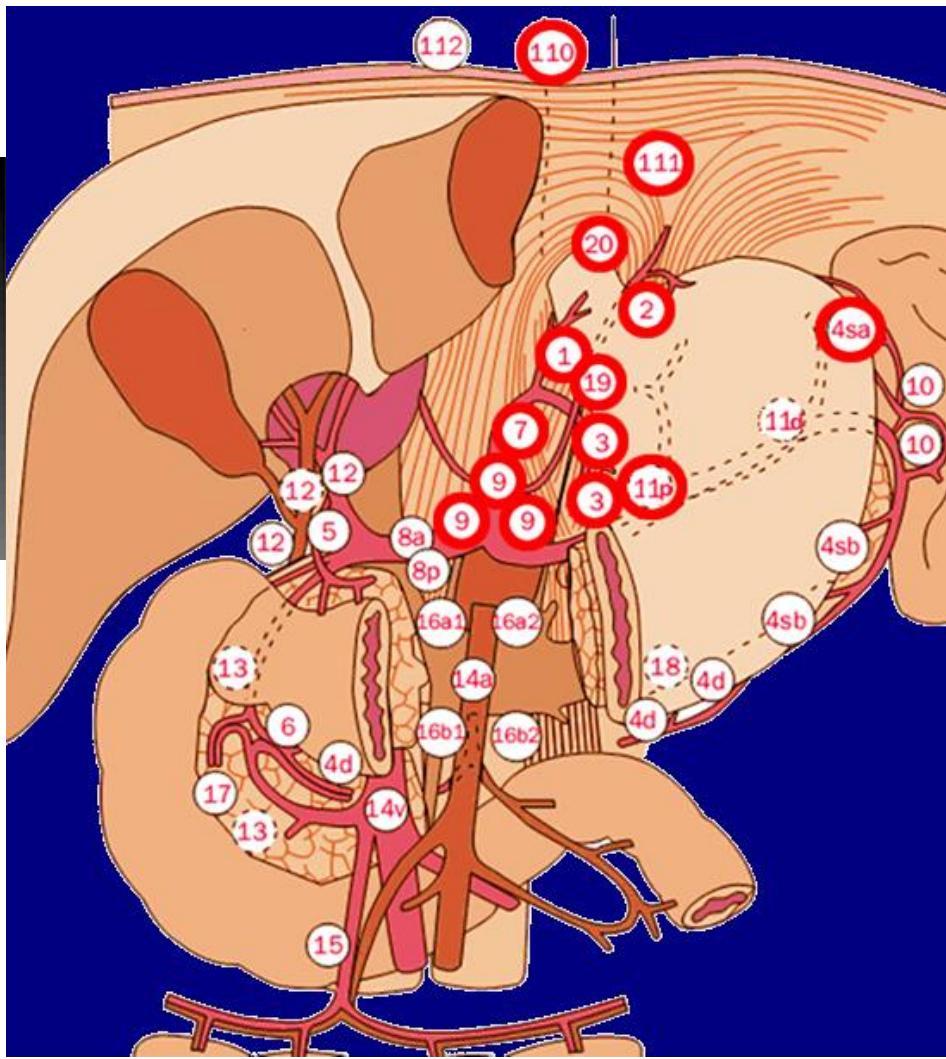
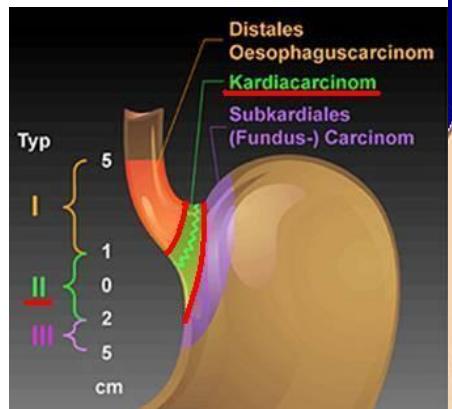
1 and 2: paracardial nodes left and right

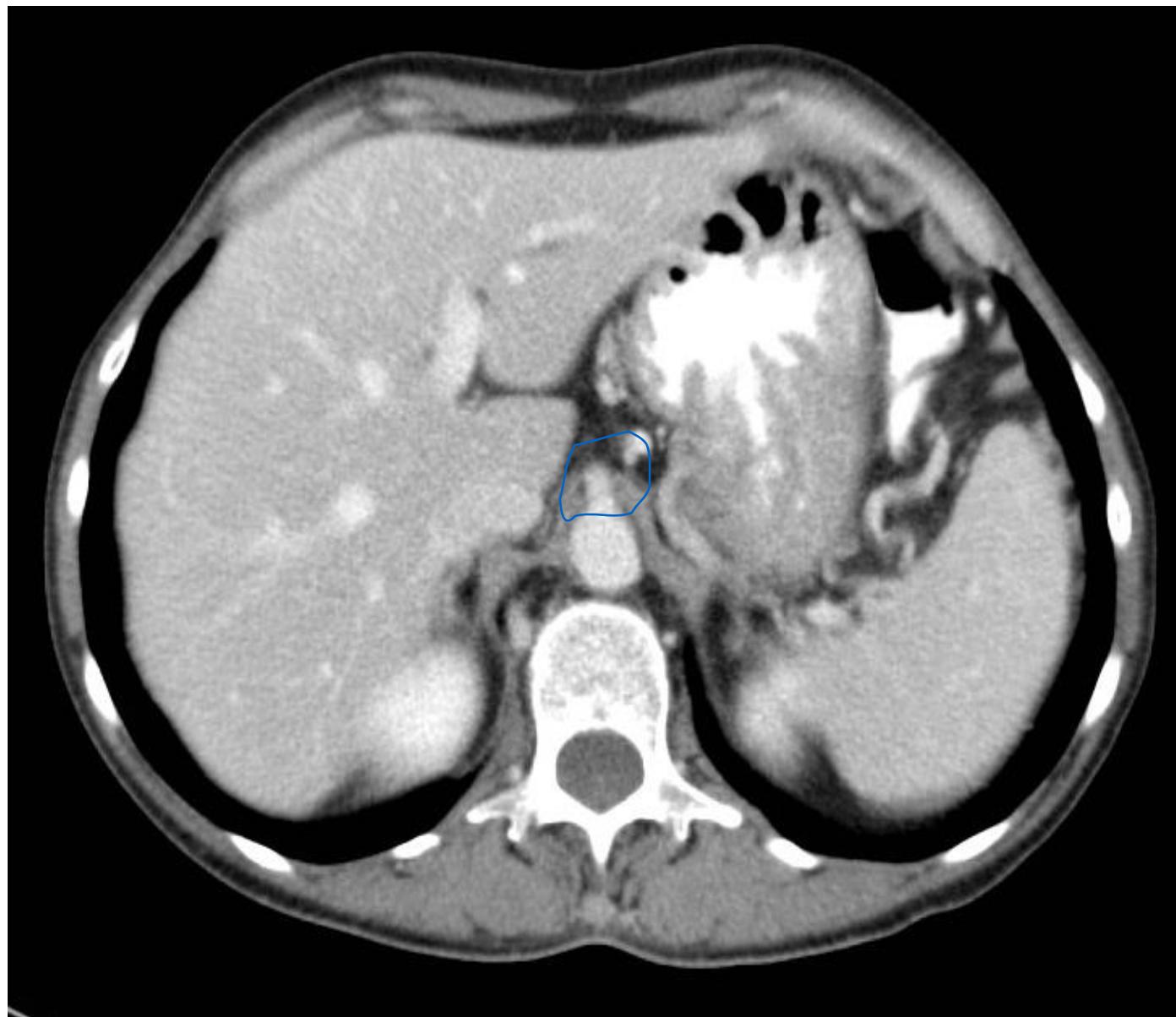


7: left gastric artery

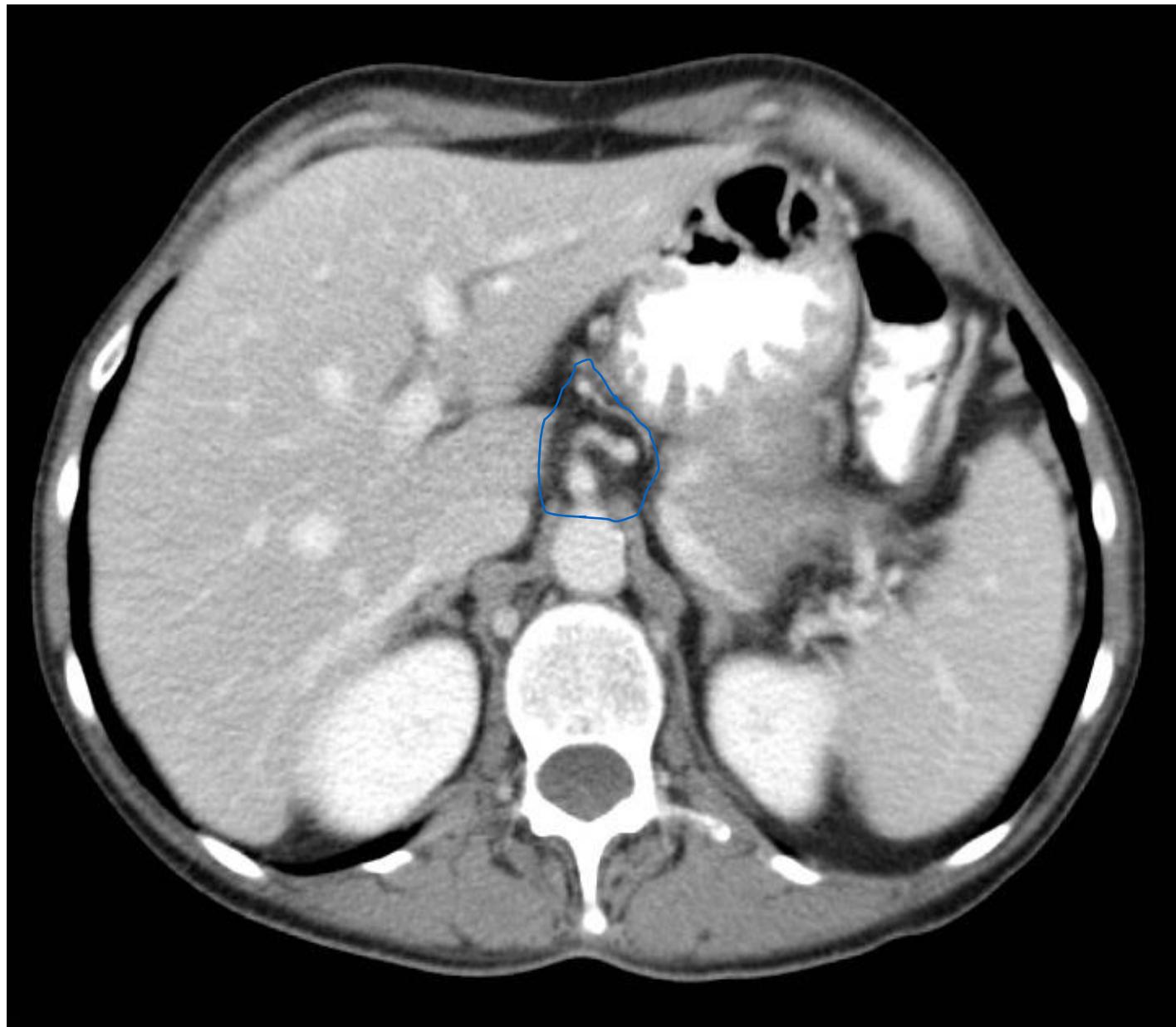
Target volume definition

GEJ II





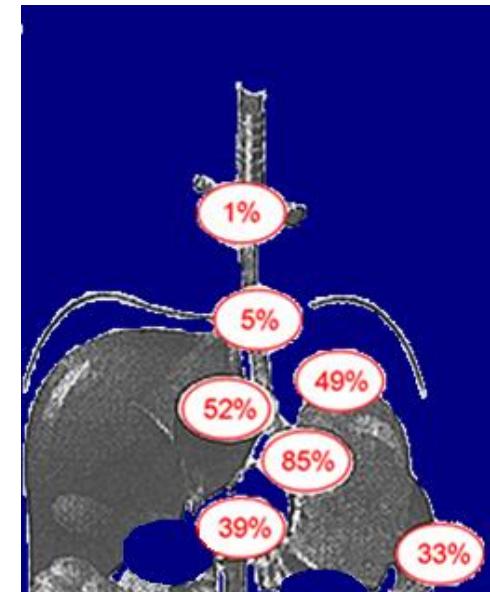
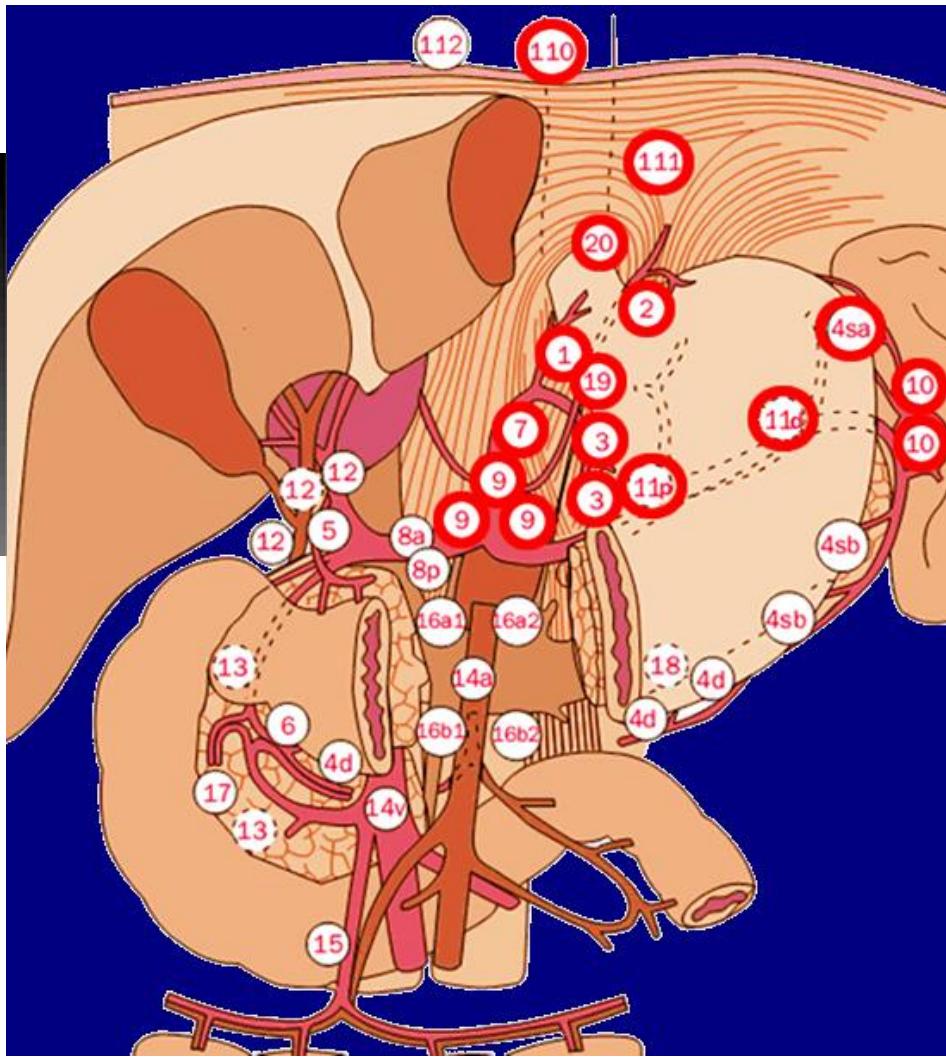
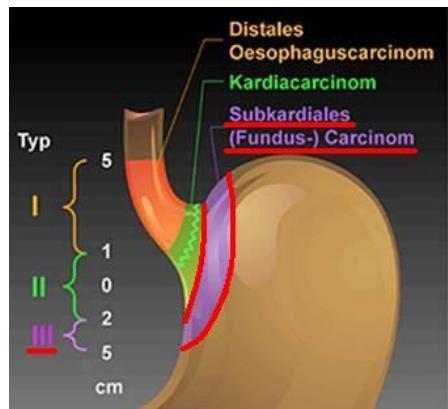
9: celiac artery

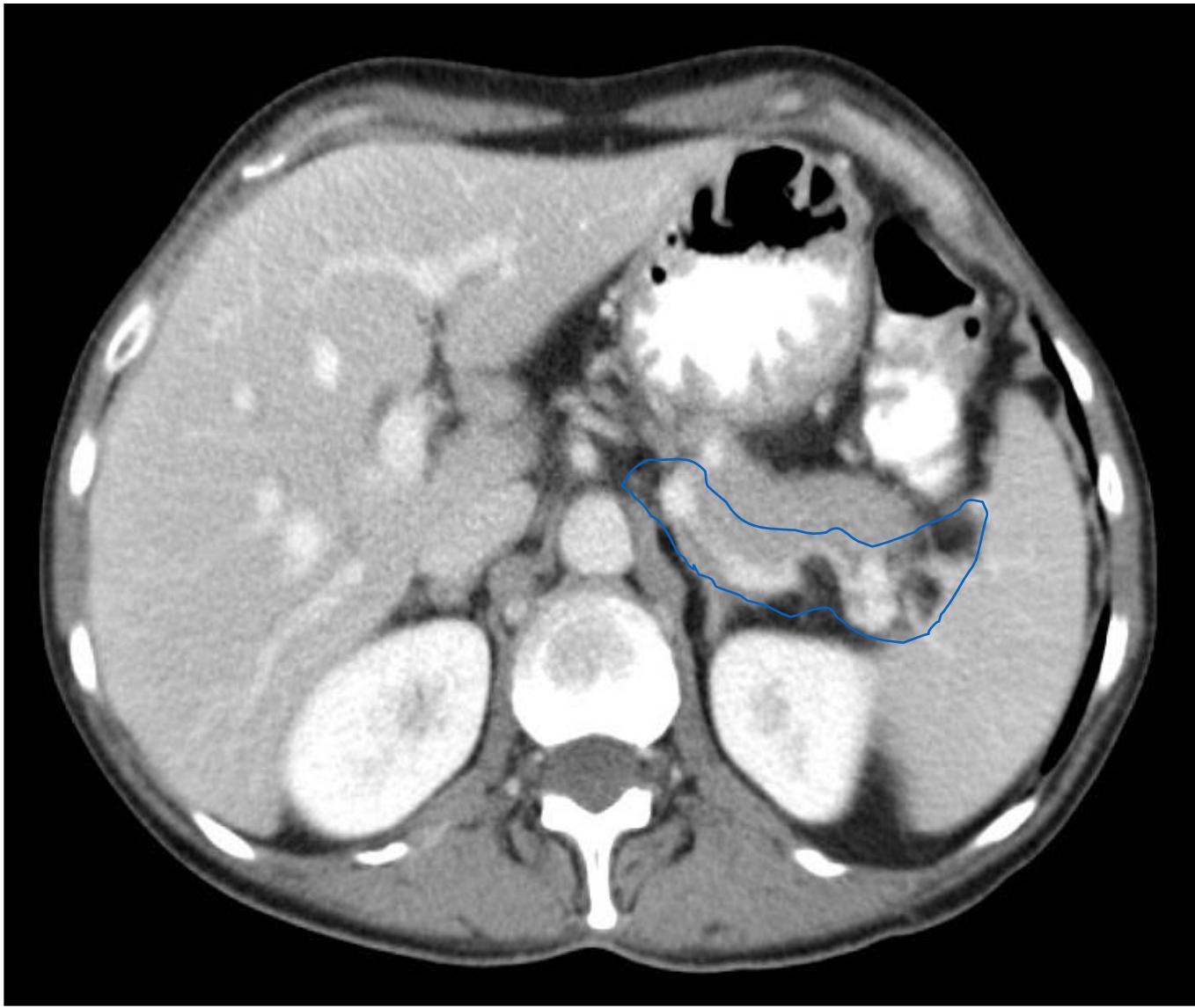


9: celiac trunc

Target volume definition

GEJ III

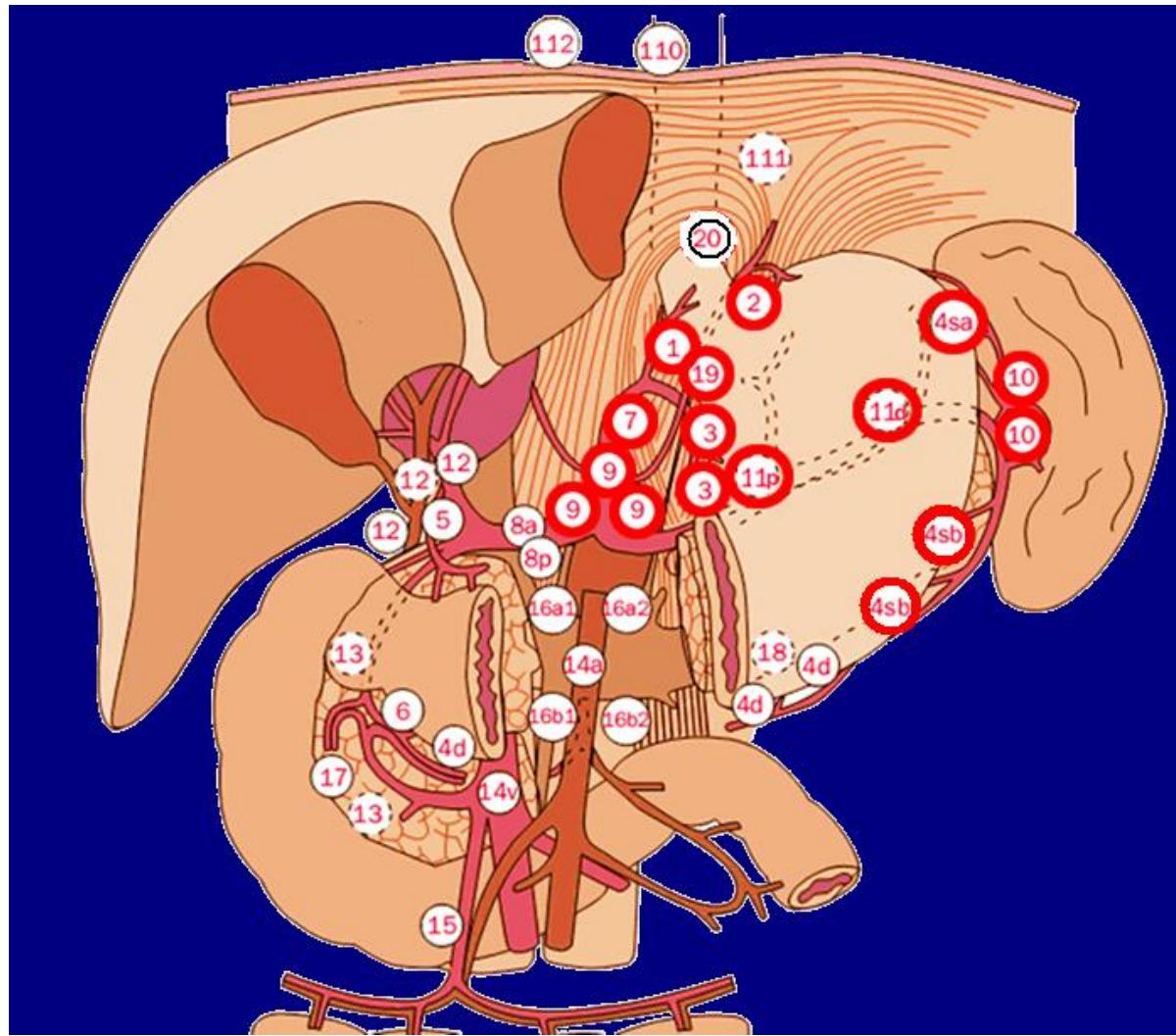




10: splenic hilum
11: splenic artery

Target volume definition

Proximal third

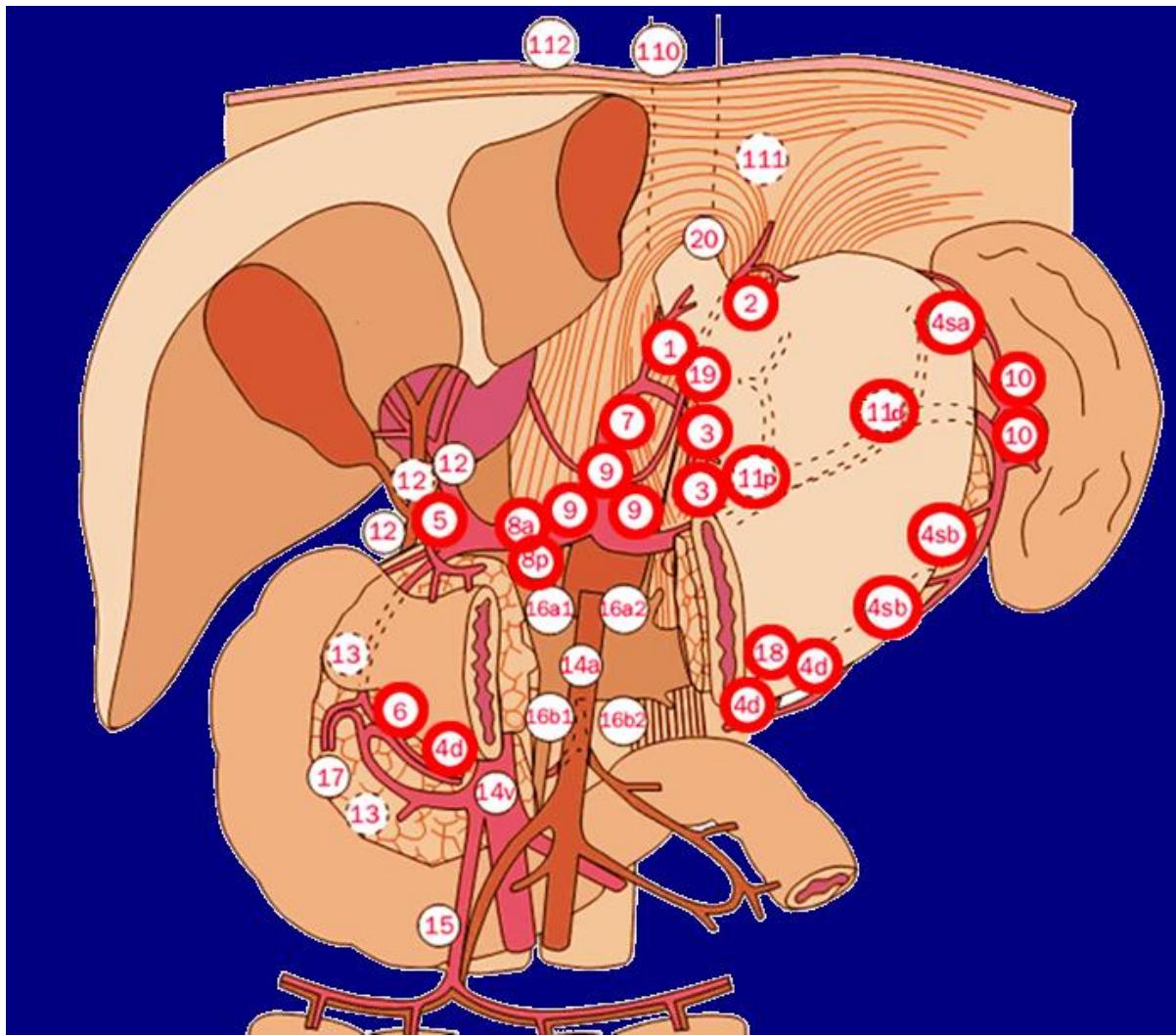


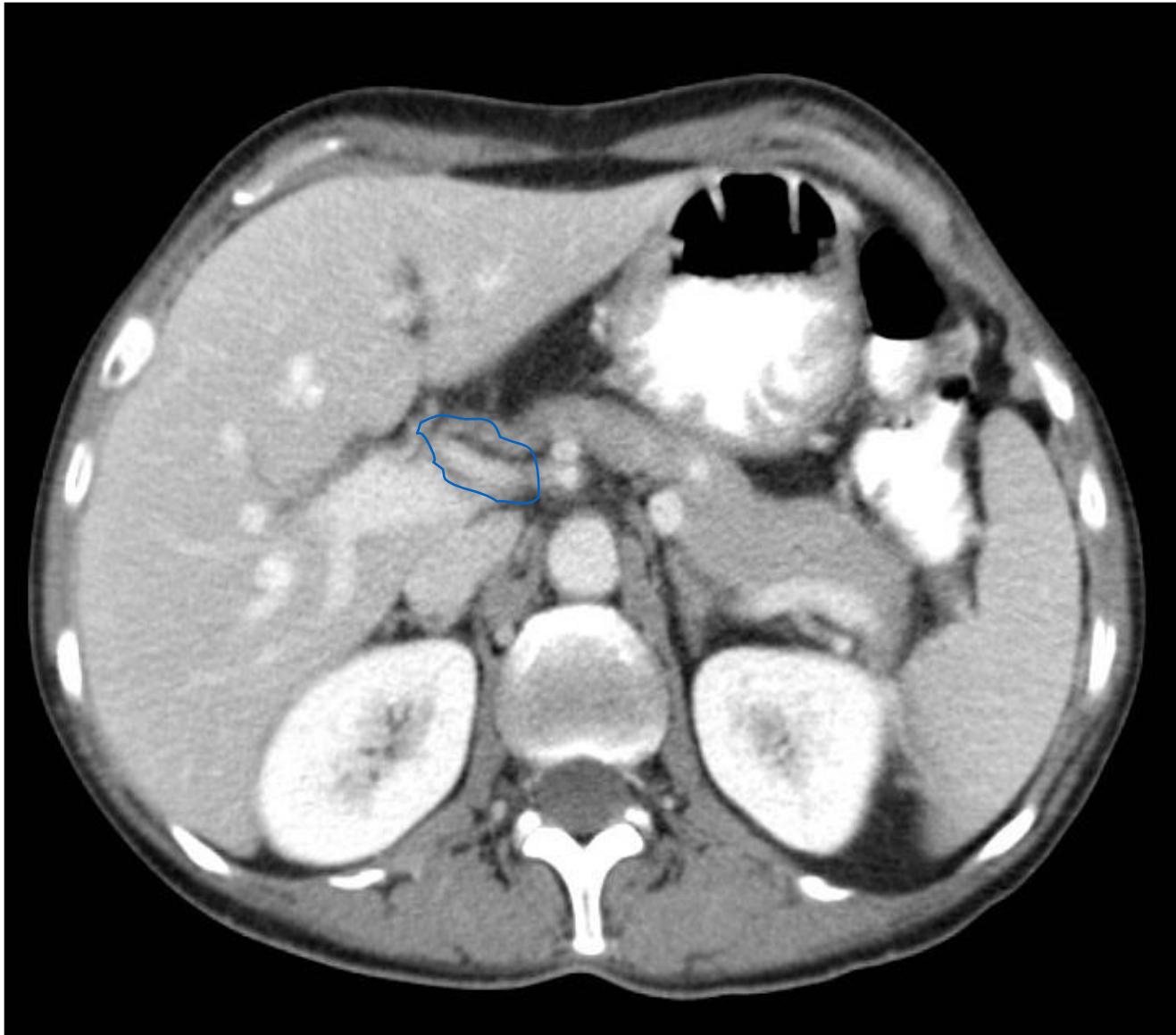


3: lesser curvature
4: greater curvature

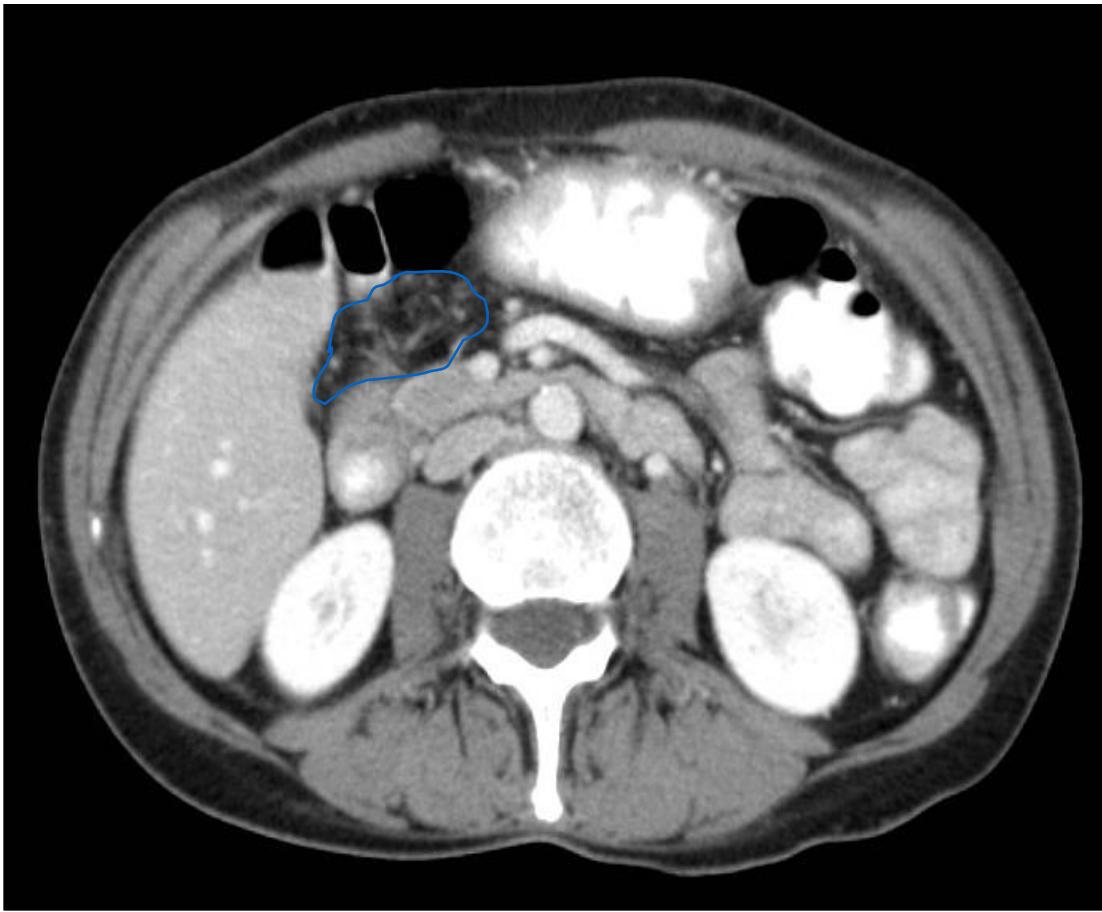
Target volume definition

Middle third





8: common hepatic artery



12: hepatoduodenal ligament

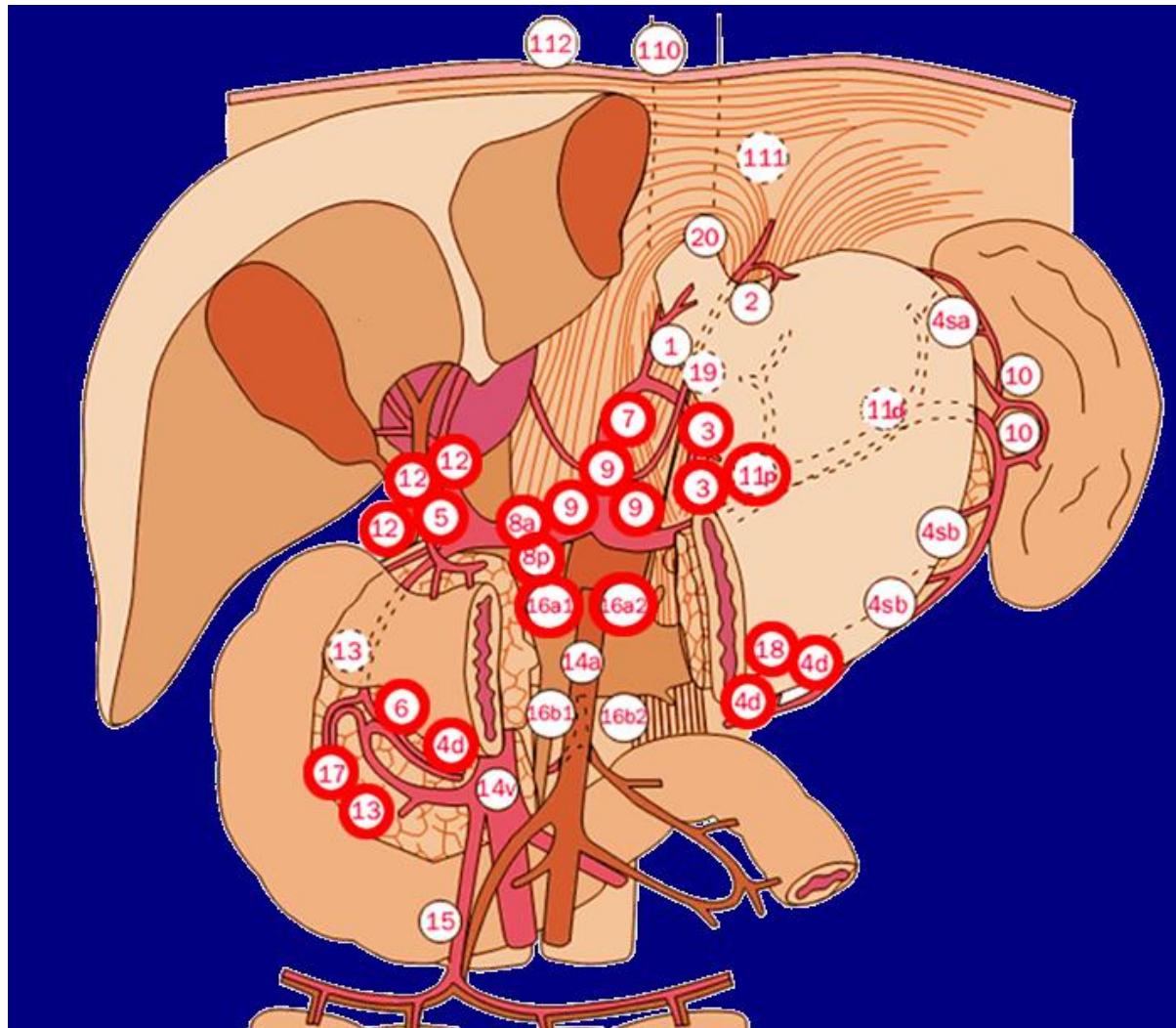


5: suprapyloric

12: hepatoduodenal ligament

Target volume definition

Distal third

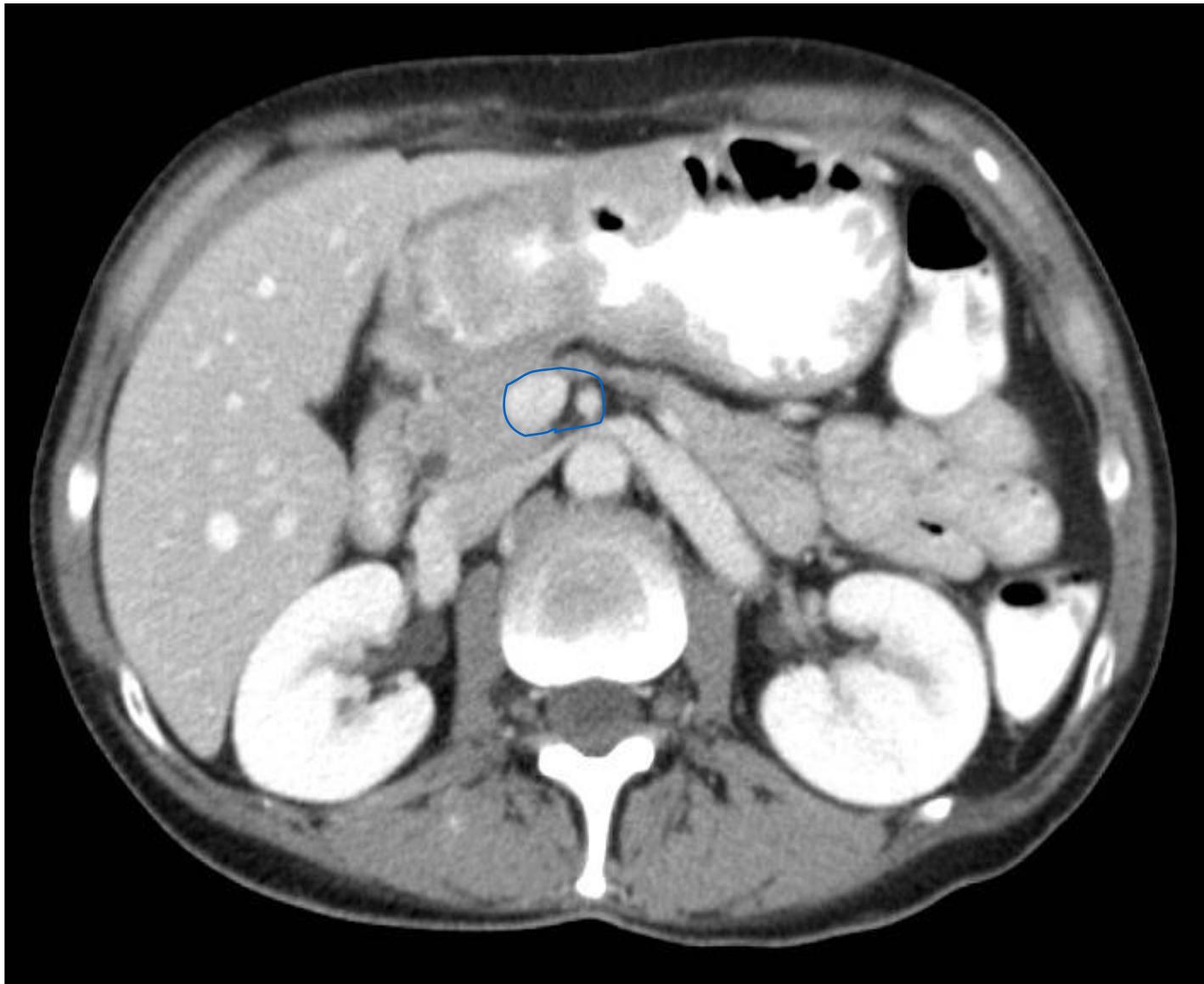




6: infrapyloric



13: posterior surface of the pancreatic head



14: superior mesenteric vein/artery

ATLAS and GUIDELINES

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

Matzinger O¹, Gerber E, Bernstein Z, Maingon P, Haustermans K,
Bosset JF, Gulyban A, Poortmans P, Collette L, Kuten A.

Radiother Oncol. 2009;92:164-75

- Upper abdominal normal organ contouring guidelines and atlas: a Radiation Therapy Oncology Group consensus.

Jabbour SK¹, Hashem SA², Bosch W³, Kim TK⁴, Finkelstein SE⁵, Anderson BM⁶, Ben-Josef E⁷, Crane CH⁸, Goodman KA⁹, Haddock MG¹⁰, Herman JM¹¹, Hong TS¹², Kachnic LA¹³, Mamon HJ¹⁴, Pantarotto JR¹⁵, Dawson LA¹⁶.

Pract Radiat Oncol. 2014;4:82-9

Un Oncologue Radiothérapeute en Gastro-entérologie ...

3. Dose

- Marges
- Contraintes aux OARs

Target volume delineation

GEJ and stomach

- location of the primary tumour
- corresponding regional lymph nodes
- CTV = corresponding lymph node stations
- PTV = CTV + 1 cm

Target volume delineation

Organs at risk

spinal cord

V45

0%

lungs

V20

20%

heart

V40

30%

liver

V30

60%

kidneys

V20

70% + 30%

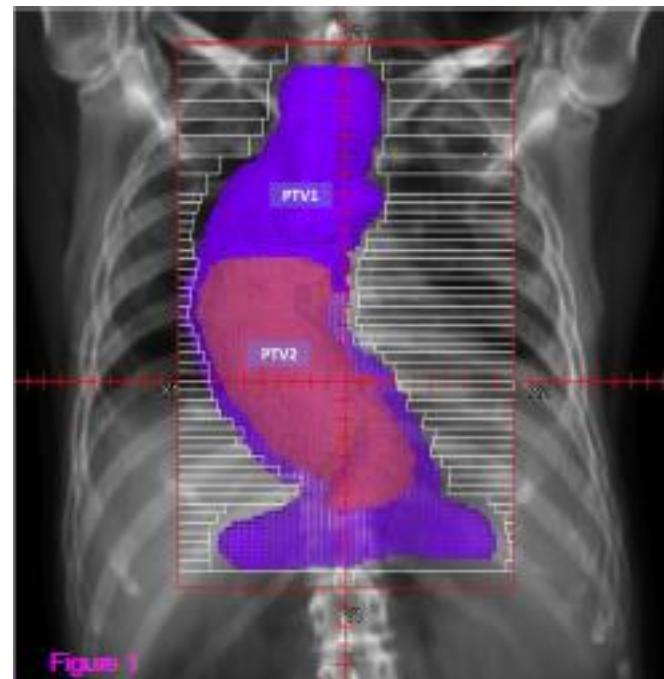
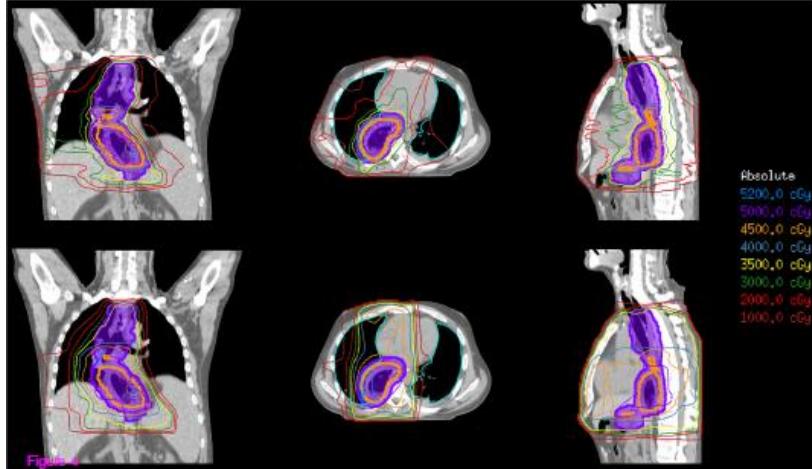
Un Oncologue Radiothérapeute en Gastro-entérologie ...

4. Technique

- 3D CRT
- IMRT
- Static / Dynamic / Rotational
- Procedures of IGRT

Adjuvant concurrent chemoradiation using intensity-modulated radiotherapy and simultaneous integrated boost for resected high-risk adenocarcinoma of the distal esophagus and gastro-esophageal junction

- 18 patients
- 2 ECF and 2 CF concurrently
 - CDDP 60 mg/m²
- PTV 1 = 39 Gy / 28 F
- PTV 2 = 50.4 Gy / 28 F



Yaremko B.P. RO 2013;8:33

CAN ALL CENTERS PLAN INTENSITY-MODULATED RADIOTHERAPY (IMRT) EFFECTIVELY? AN EXTERNAL AUDIT OF DOSIMETRIC COMPARISONS BETWEEN THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY AND IMRT FOR ADJUVANT CHEMORADIATION FOR GASTRIC CANCER

HANS T. CHUNG, M.D., F.R.C.P.C.,* BRIAN LEE, M.D., Ph.D.,[†] EILEEN PARK, B.Sc.(HONS),*
JIADE J. LU, M.D., M.B.A.,* AND PING XIA, PH.D.[†]

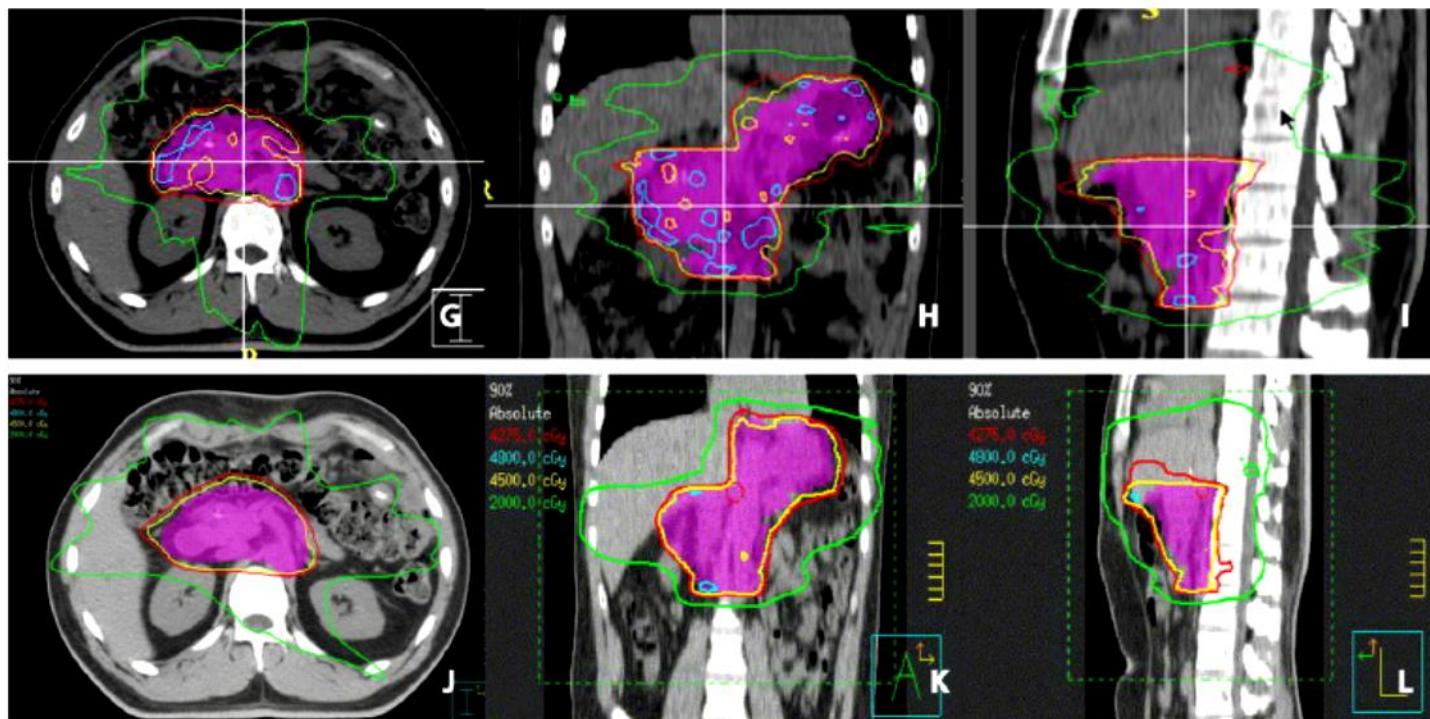


Fig. 1. Sample three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) treatment plans from the National University Hospital, Singapore, with CMS Xio (3D-CRT: [A] axial; [B] coronal; [C] sagittal; IMRT: [D] axial; [E] coronal; [F] sagittal), and the University of California-San Francisco with Nomos Corvus ([G] axial; [H] coronal; [I] sagittal) and ADAC Pinnacle ([J] axial; [K] coronal; [L] sagittal). Isodose lines: blue 48 Gy; yellow 45 Gy; red 42.75 Gy; green 20 Gy. Planning target volume in magenta.

CAN ALL CENTERS PLAN INTENSITY-MODULATED RADIOTHERAPY (IMRT) EFFECTIVELY? AN EXTERNAL AUDIT OF DOSIMETRIC COMPARISONS BETWEEN THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY AND IMRT FOR ADJUVANT CHEMORADIATION FOR GASTRIC CANCER

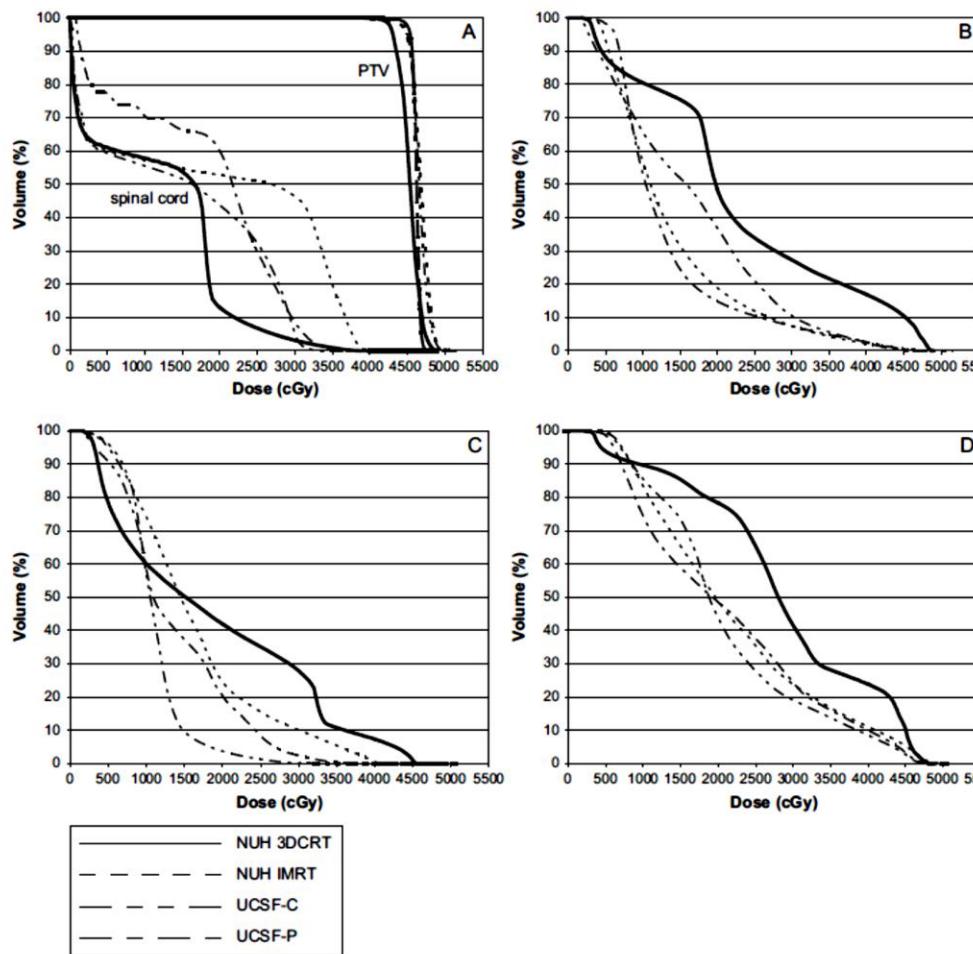


Fig. 2. Dose–volume histograms from a representative patient for National University Hospital, Singapore three-dimensional conformal radiotherapy (NUH 3DCRT), NUH intensity-modulated radiotherapy (NUH IMRT), University of California-San Francisco IMRT Corvus (UCSF-C), and UCSF IMRT Pinnacle (UCSF-P) for (A) the spinal cord and planning target volume (PTV), (B) right kidney, (C) left kidney, and (D) liver.

Table 2. Comparison of dose coverage of the planning target volume and radiation to organs at risk by 3D-CRT and IMRT (NUH)

Variable	3D-CRT NUH	IMRT NUH	p
Planning target volume			
V45 (%)	72.0 ± 10.8	95.0 ± 0*	<0.001
D2cm ³ (Gy)	48.5 ± 1.0	49.8 ± 1.4	0.016
Right kidney			
V20 (%)	21.2 ± 11.1	20.7 ± 3.6	0.89
Mean dose (Gy)	13.1 ± 4.4	16.9 ± 11.3	0.17
Left kidney			
V20 (%)	28.9 ± 13.1	25.1 ± 3.3	0.31
Mean dose (Gy)	15.4 ± 4.2	16.7 ± 1.0	0.29
Liver			
V30 (%)	40.2 ± 6.4	24.5 ± 1.9	<0.001
V40 (%)	20.0 ± 4.3	12.9 ± 2.1	<0.001
Mean dose (Gy)	26.3 ± 1.8	22.7 ± 1.4	<0.001
Spinal cord			
Maximum dose (Gy)	29.5 ± 9.8	39.4 ± 2.5	0.005

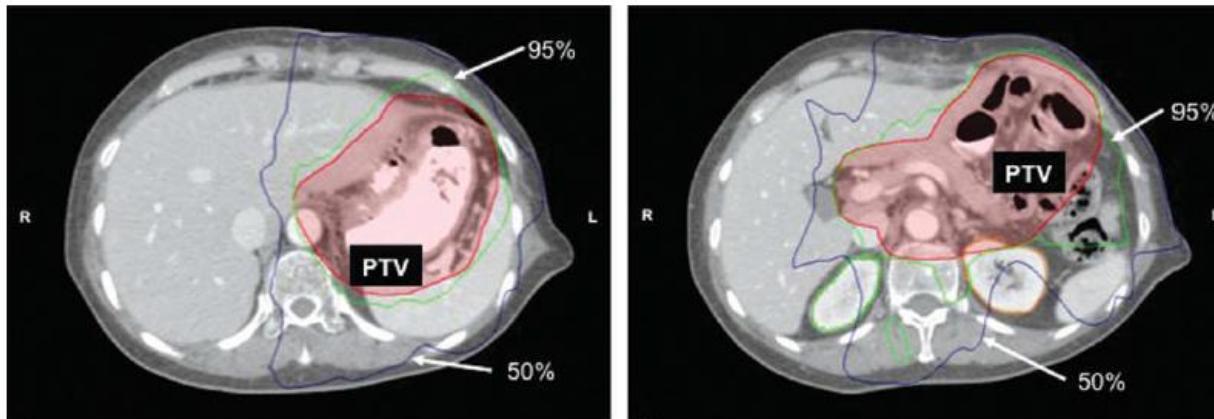
Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; NUH = National University Hospital, Singapore.

Values are mean ± SD.

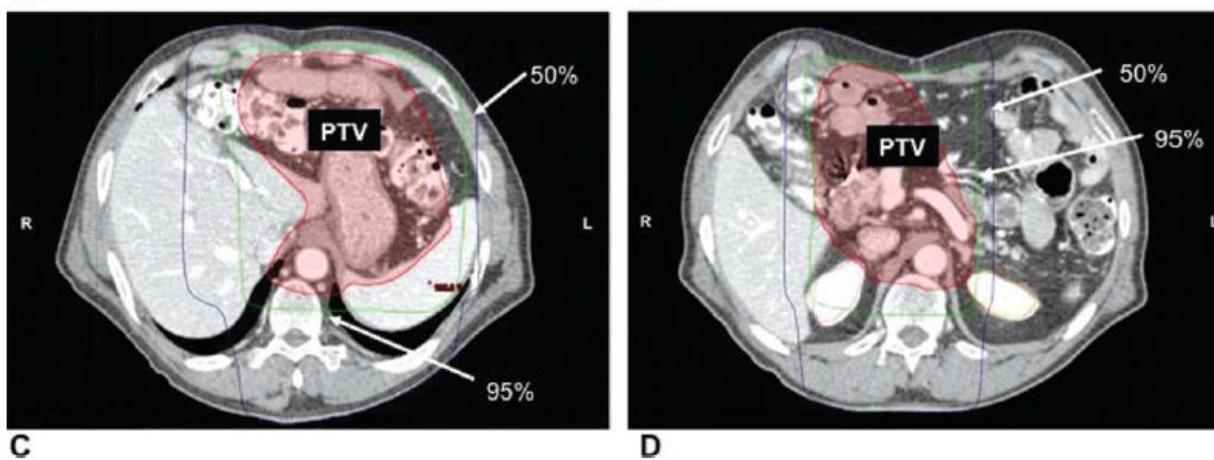
* All IMRT plans were renormalized such that D95% = 45 Gy.

Comparison of Intensity-Modulated Radiotherapy and 3-Dimensional Conformal Radiotherapy as Adjuvant Therapy for Gastric Cancer

IMRT

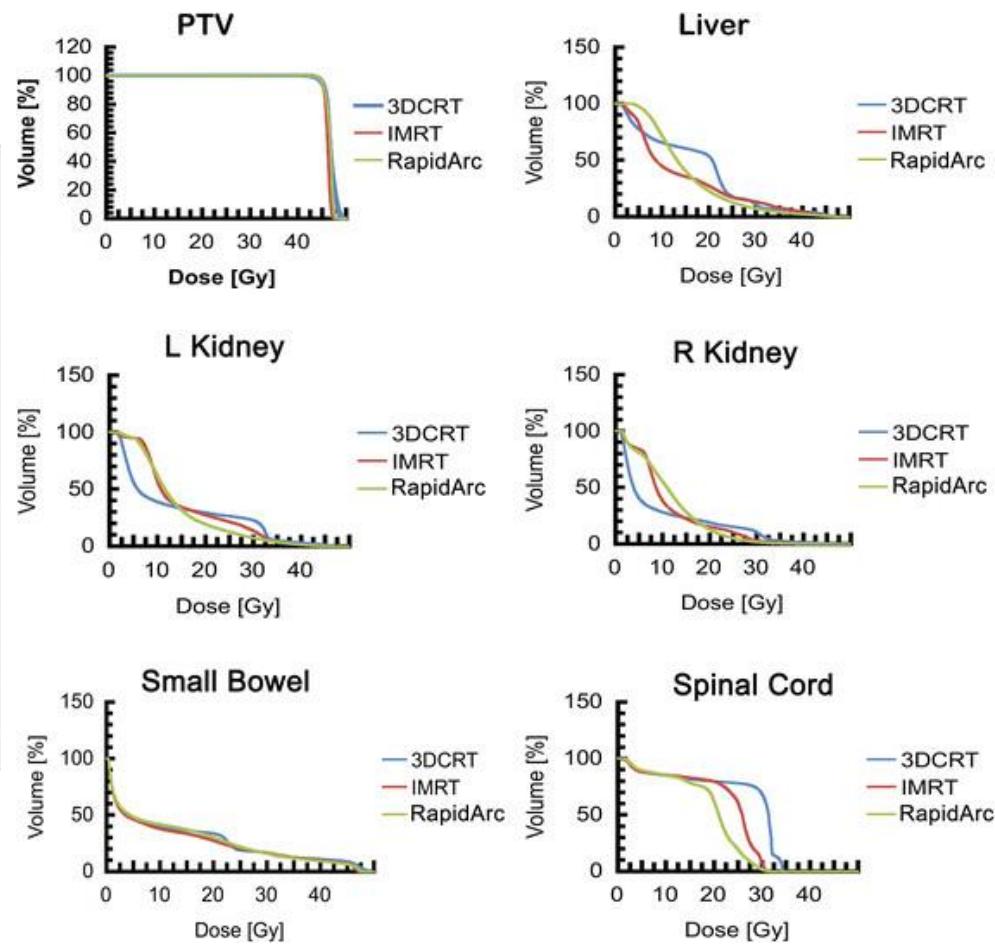
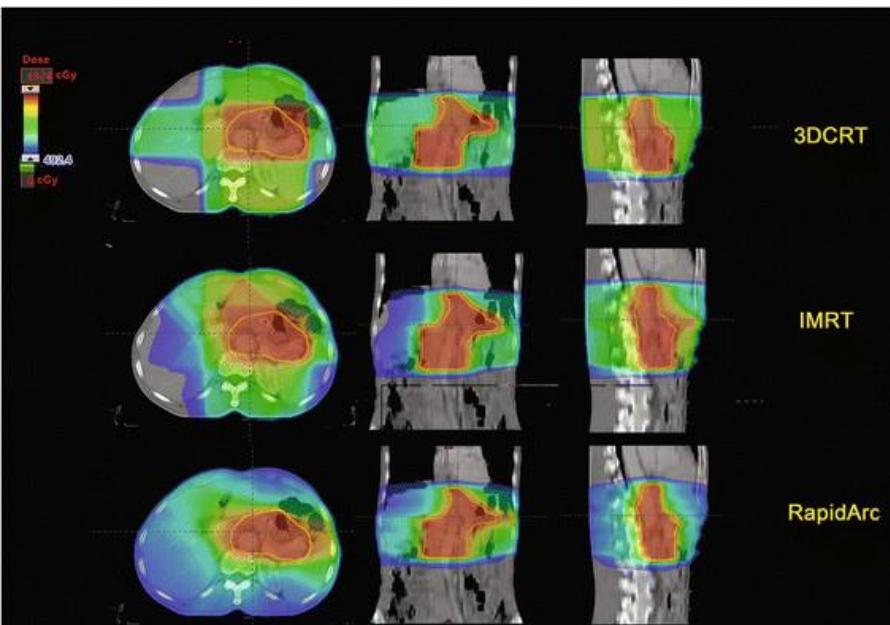


3DCRT

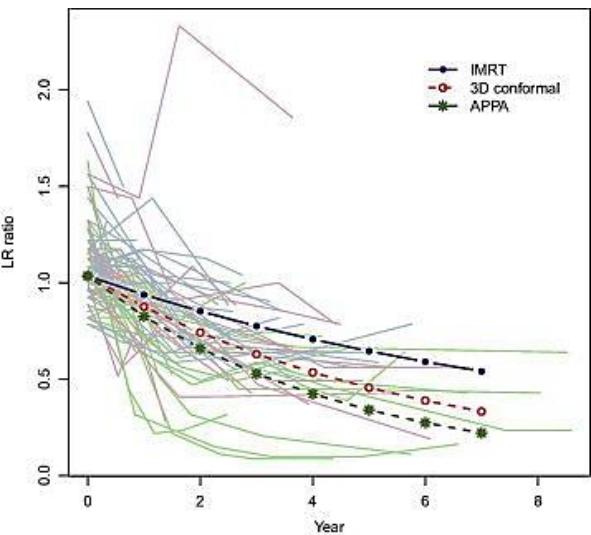


Min A.Y. Cancer 2010;

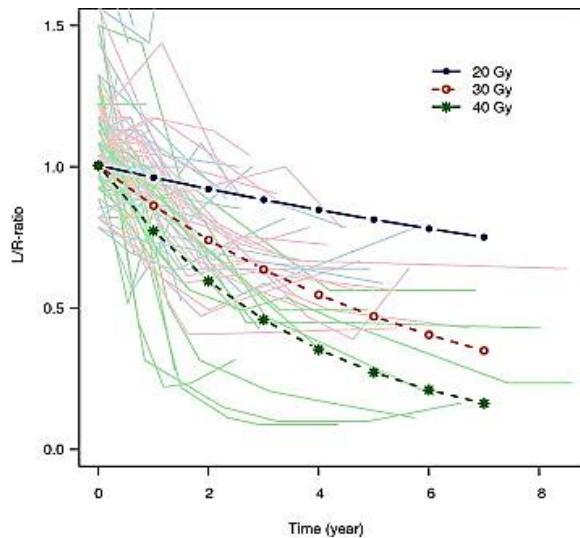
Double-arc volumetric modulated therapy improves dose distribution compared to static gantry IMRT and 3D conformal radiotherapy for adjuvant therapy of gastric cancer



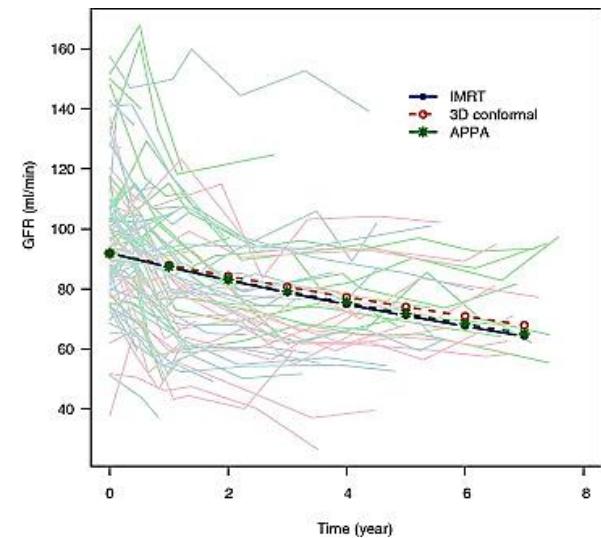
Double-arc volumetric modulated therapy improves dose distribution compared to static gantry IMRT and 3D conformal radiotherapy for adjuvant therapy of gastric cancer



Left renal function
Mixt effect model

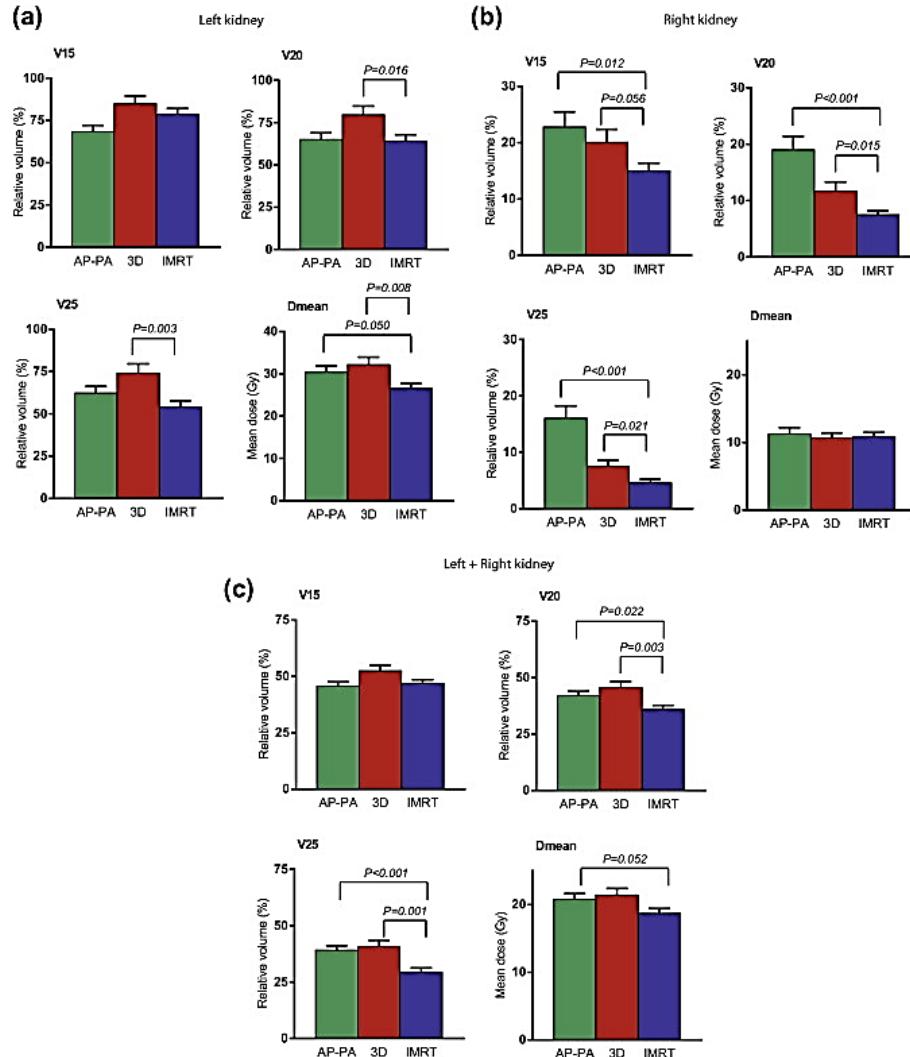


Dose effect relationship
D mean
Tc99m-mAG3-
renography



GFR
Cockcroft-
Gauss formula

IMRT limits nephrotoxicity after chemoradiation for gastric cancer



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

Un Oncologue Radiothérapeute en Gastro-entérologie ...

4. Technique

- 3D CRT
- IMRT
- Static / Dynamic / Rotational
- Procedures of IGRT

Un Oncologue Radiothérapeute en Gastro-entérologie ...

5. Protocoles ouverts

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

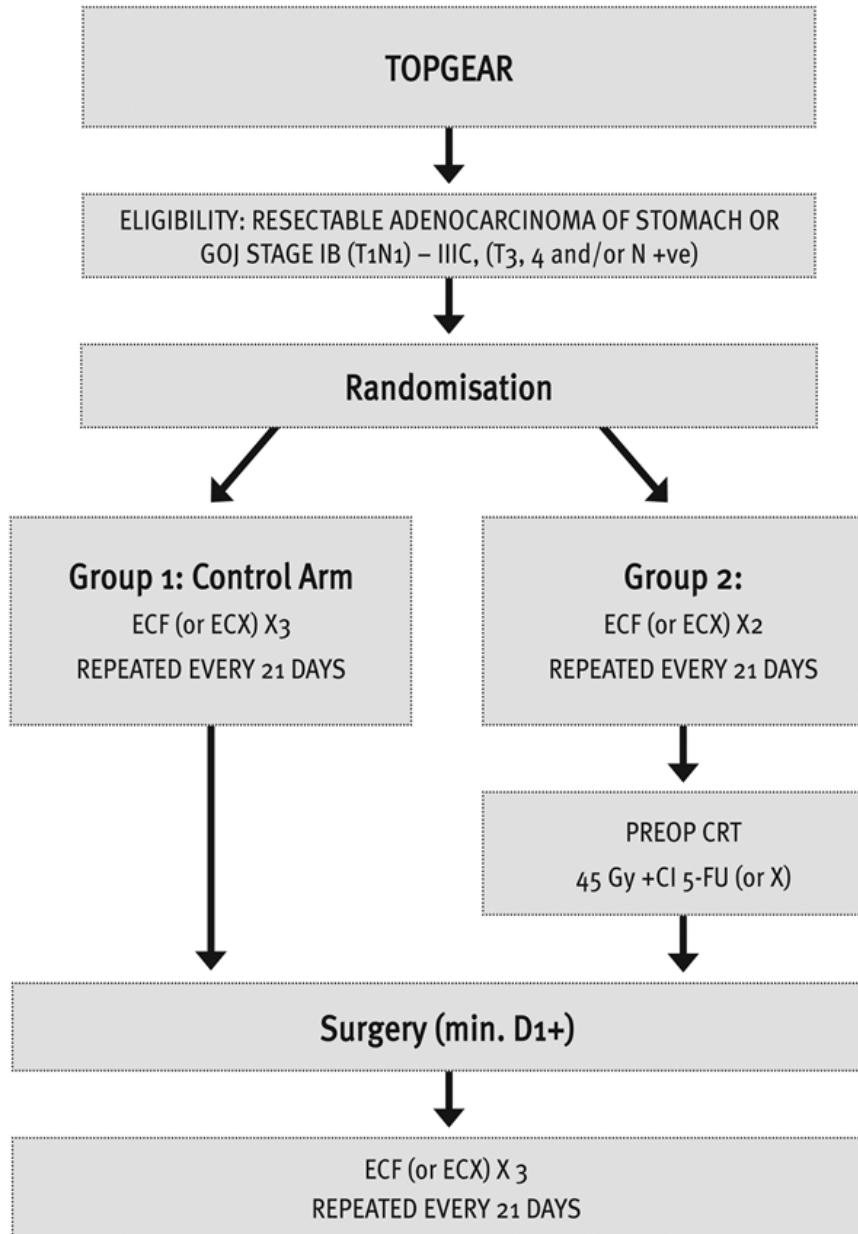
Study Coordinator: Karin Haustermans (ROG)

Study co-coordinator: Florian Lordick (GI)

Leading group: AGITG

Study coordinator AGITG: Trevor Long

22114 - 40111: Study schema



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

ADCI 002 Prodigie French

- Phase II/III multicentrique randomisé en plan factoriel évaluant
 - Chirurgie première versus chimiothérapie première
 - Chimiothérapie par XELOX versus ECF
- dans les adénocarcinomes gastriques à cellules indépendantes.

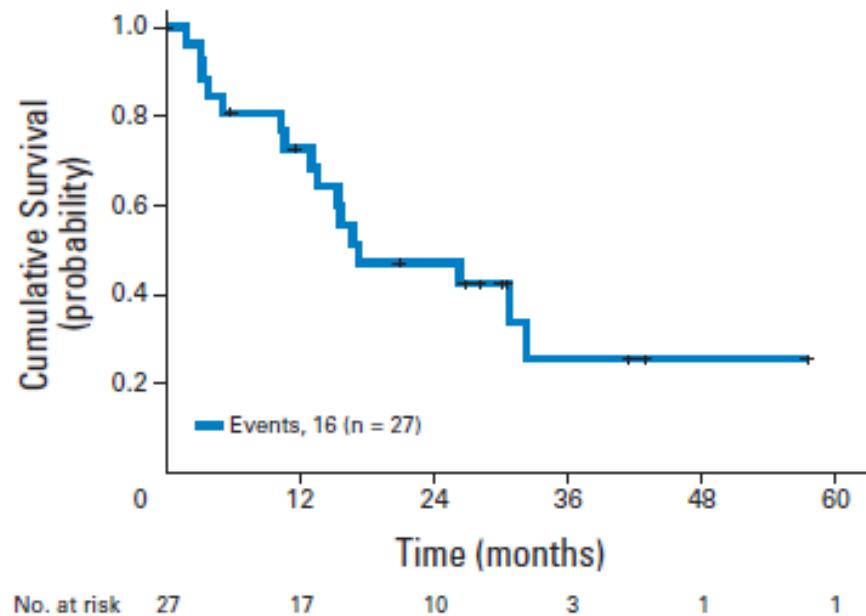
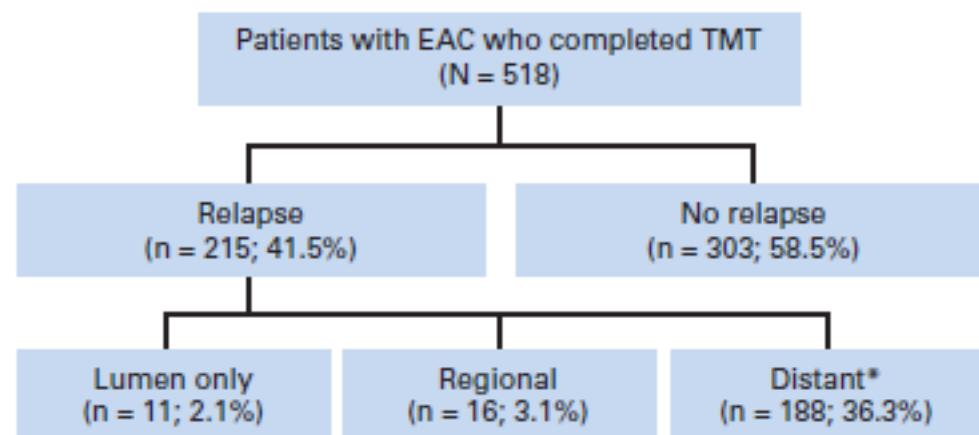
- **BRAS A:** 3 ECF - Gastrectomie totale avec curage D2 – 3 ECF
- **BRAS B:** 3 XELOX – Gastrectomie totale curage D2 – 3 XELOX
- **BRAS C:** Chirurgie – 6 ECF
- **BRAS D:** Chirurgie – 6 XELOX

Surveillance

- Thésaurus National de Cancérologie Digestive
 - Pas de surveillance hors clinique
 - Surveillance des gastrectomisés ...
 - Suivi des patients irradiés

Locoregional Failure Rate After Preoperative Chemoradiation of Esophageal Adenocarcinoma and the Outcomes of Salvage Strategies

Kazuki Sudo, Takashi Taketa, Arlene M. Correa, Maria-Claudia Campagna, Roopma Wadhwa, Mariela A. Blum, Ritsuko Komaki, Jeffrey H. Lee, Manoop S. Bhutani, Brian Weston, Heath D. Skinner, Dipen M. Maru, David C. Rice, Stephen G. Swisher, Wayne L. Hofstetter, and Jaffer A. Ajani





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