INCONTRO CON GLI ESPERTI XIV EDIZIONE

APPROPRIATEZZA
DELL'IMAGING
NELLA DIAGNOSTICA
E RADIOTERAPIA
DEI TUMORI
GASTROINTESTINALI

23 e 24
FEBBRAIO 2017

Fondazione Università
"G. d'Annunzio" Chieti-Pescara

Appropriatezza in Radiochemioterapia

Dott. Antonino De Paoli

UO Oncologia Radioterapica
Istituto Nazionale Tumori -CRO (Aviano)

CRO AVIANO

Treatment of Gastric Cancer
Current Issues

- **Changing epidemiology**
  (diagnosis and treatment implications)
- **Curative surgery**
  (mainstay of treatment)
- **Adjuvant chemotherapy**
  (still controversial)
- **Adjuvant chemoradiation**
  (possible benefit)
- **Perioperative chemotherapy**
  (possible benefit)

Neo-adjuvant and Adjuvant therapy for gastric cancer: different strategies

Post-operative Chemoradiotherapy (trend to preoperative CT-RT in academic centers)

Peri-operative Chemotherapy (ECF- 5FU/cisplatin)

Postoperative CT

Post-operative Chemotherapy (S-1 or combination)

Gastric Cancer
Patterns of Failure after Curative Surgery

Pattern of failure	Cumulative Incidence (%)		
	Clinical	Re-operation	Autopsy
Loco-regional	38	*69	80-93
Peritoneal	23	41	30-50
Distant mets	52	22	49

***23% as the only site of failure;**
88% as a component of failure in recurred pts.

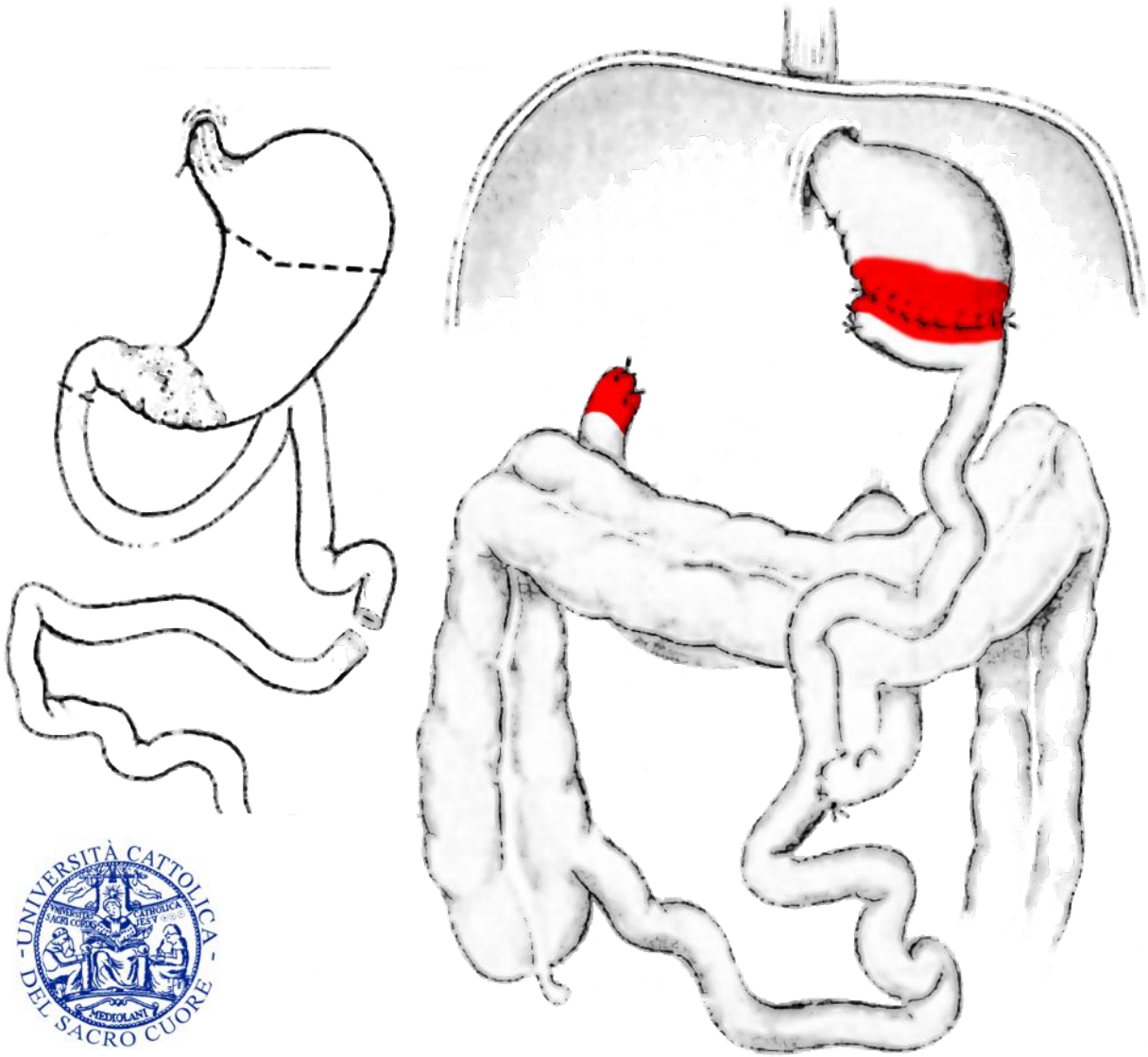
GASTRIC RT-Background

Author	Year	Pts	Relapse (%)	Locoregional Relapse (%) Remnant Stomach Duodenal Stump Regional Nodes	Sistemic Relapse (%)		
					Peritoneal	Hematogenous	Lymphatic
Yoo Median F-up 68 months	2000	2328	45.7	19.3	33.9	26.2	4.3
Maehara Median F-up 24.3 months	2000	939	62		0	44.3	4.1
Cordiano Median F-up 42 months	2002	412				30.9	-
Ohno Median F-up 17.2 months	2003	709	18.5	5.8	44.2	30.8	19.2
Wu Median F-up 76.8 months	2003	631	40.1	26.0	38.2	26.8	8.9

Median 22.3%

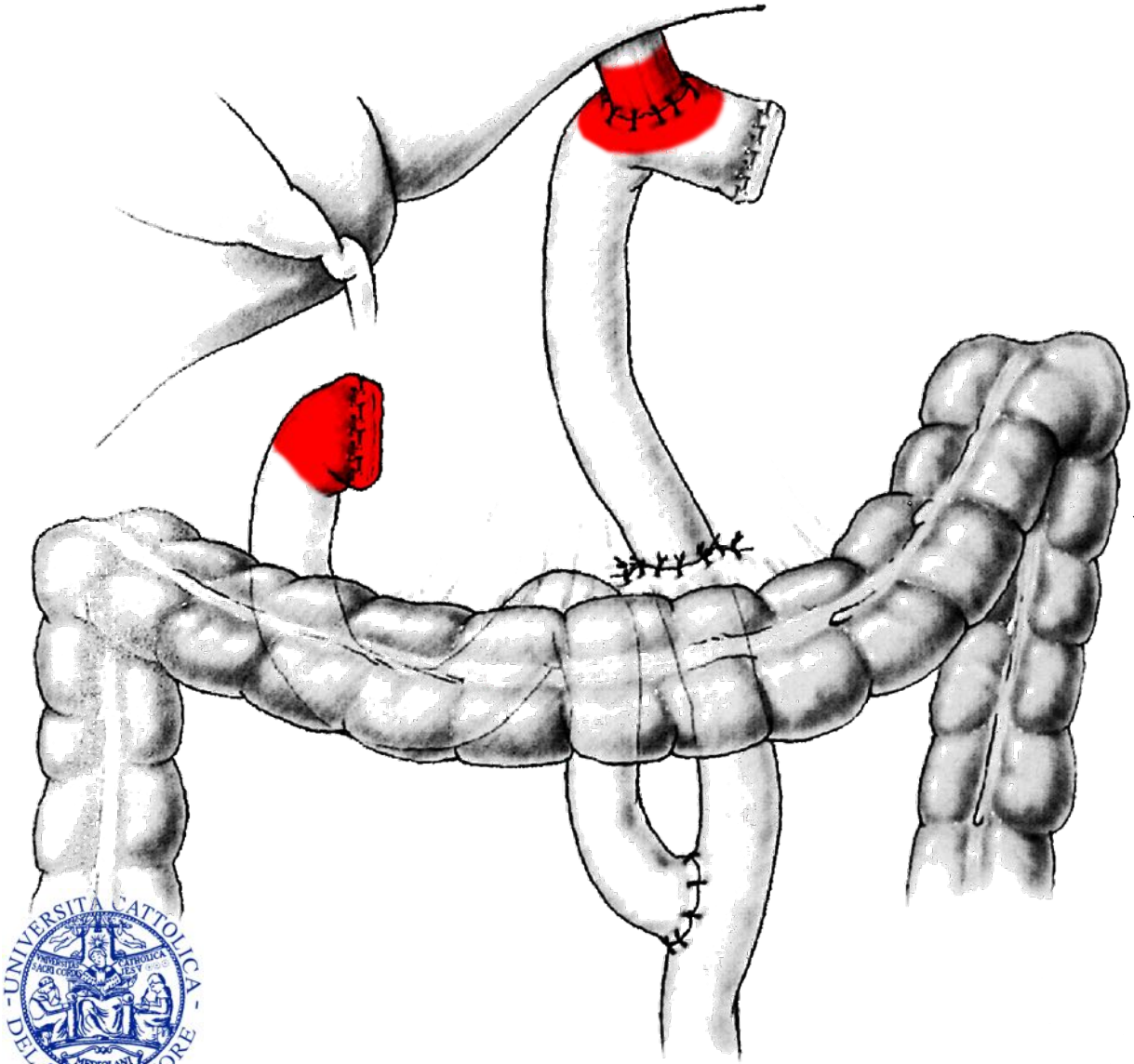
Valentini et al. Exp. Rev. 2007

Area at Risk: Anastomosis & Stump



Partial gastrectomy:
Y sec Roux
21 – 60%

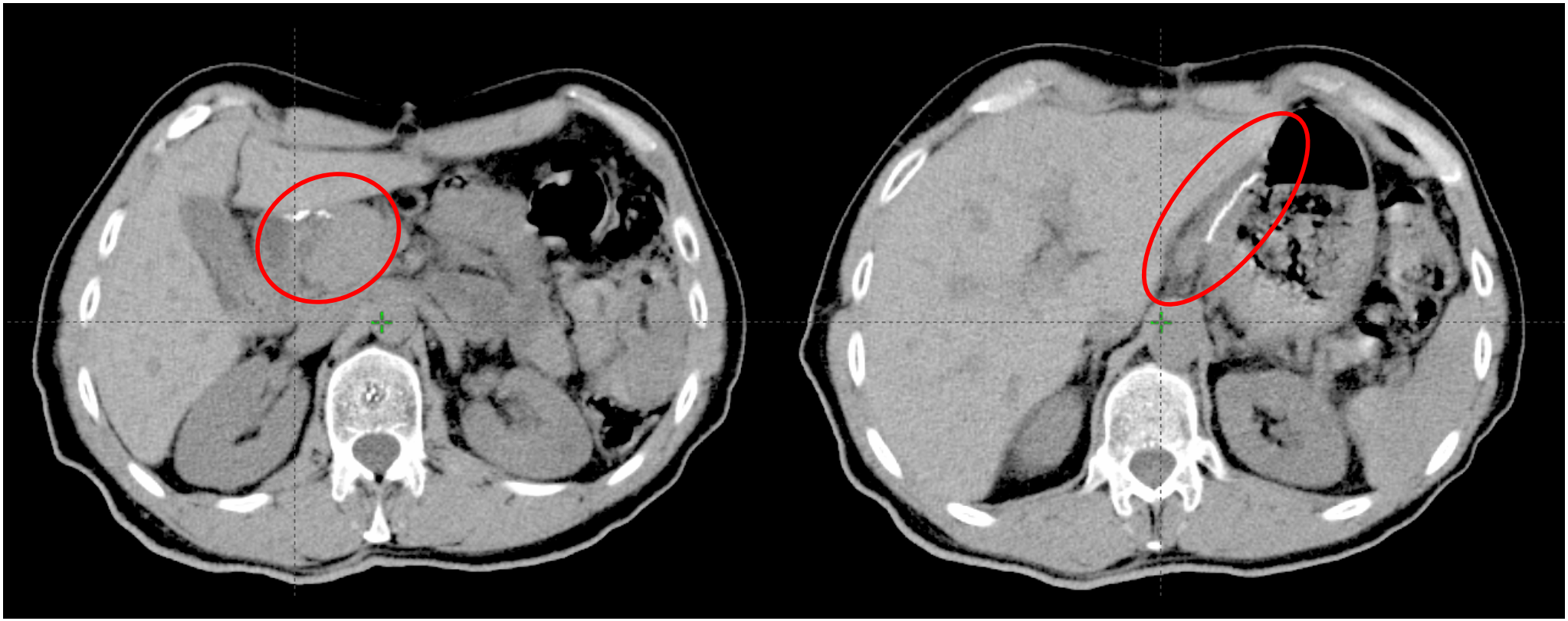
Area at Risk: Anastomosis & Stump



Total gastrectomy:
Y sec Roux
21 – 60%

Area at Risk: Anastomosis & Stump

Partial Gastrectomy

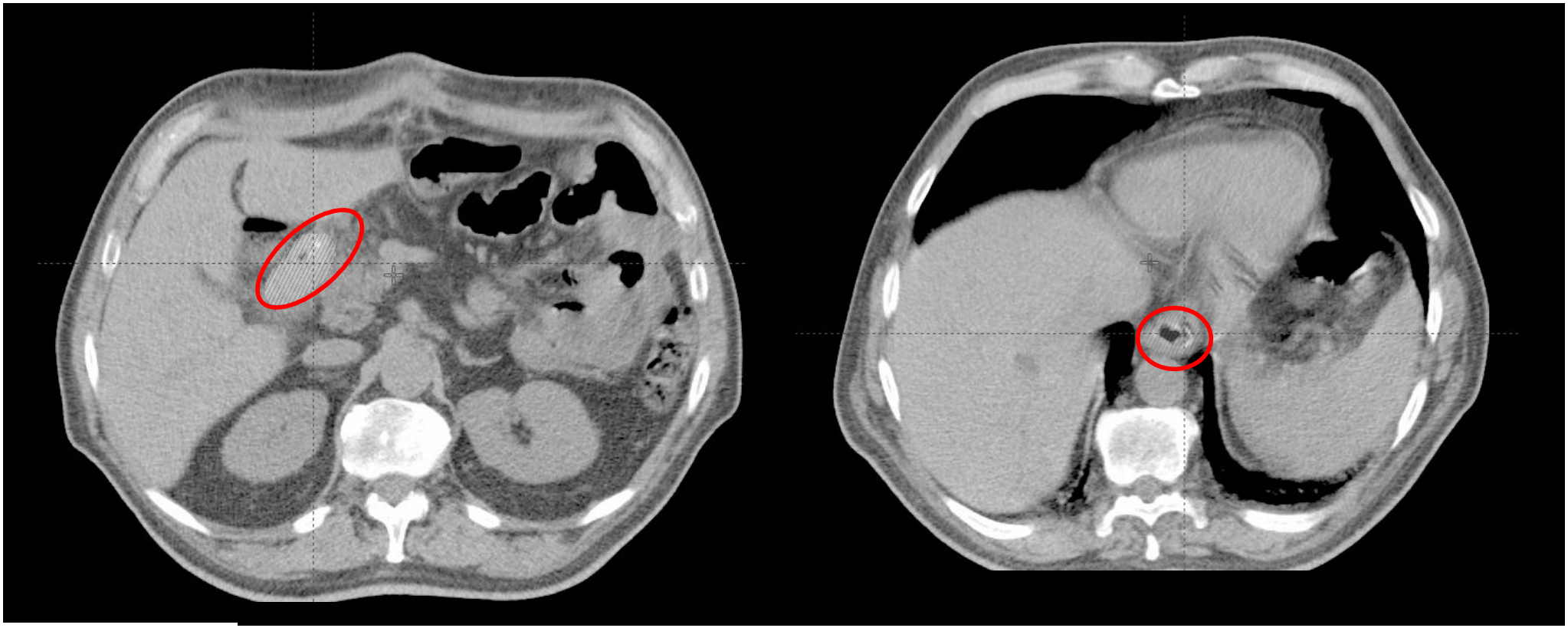


Stump

Anastomosis

Area at Risk: Anastomosis & Stump

Y sec Roux



Stump

Anastomosis

Proximal One Third

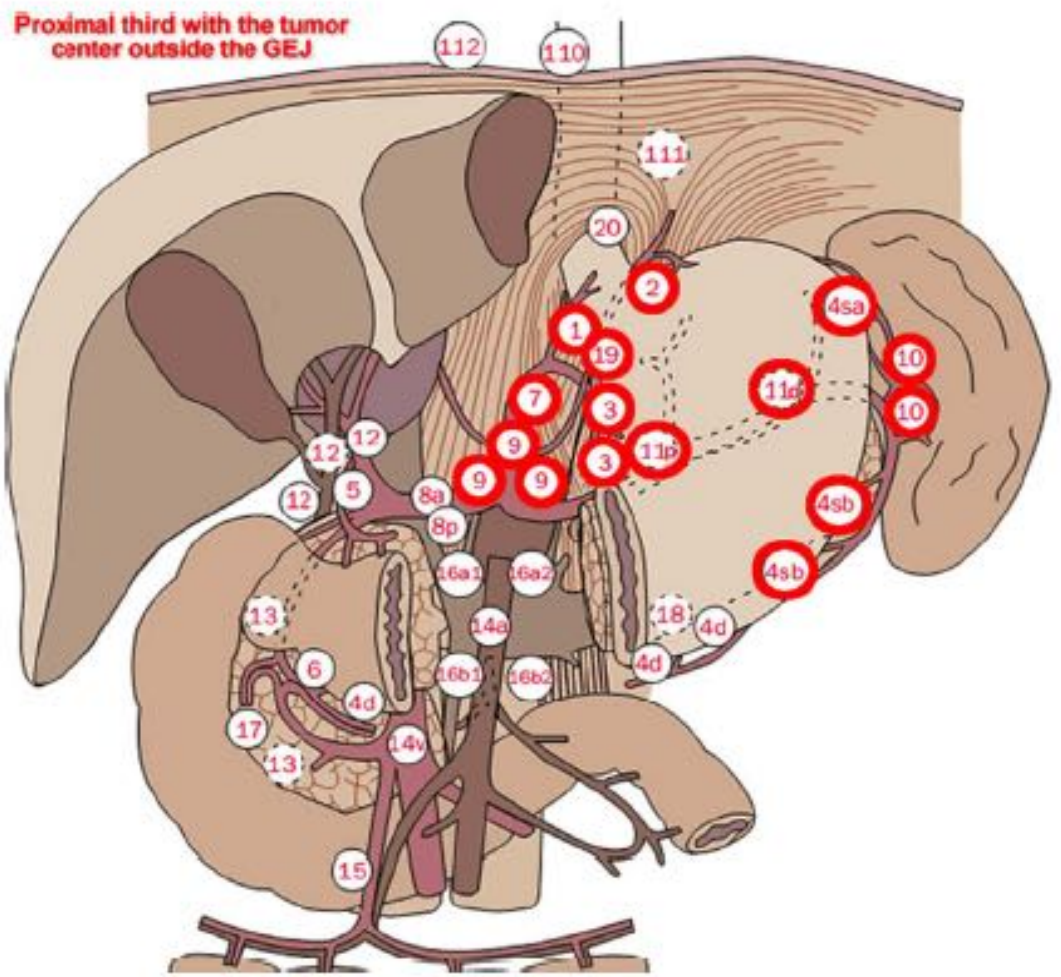


Fig. 7. Corresponding elective lymph node stations for GC tumours of the proximal third with their tumour centre outside of the gastroesophageal junction: 1, right paracardial LN; 2, left paracardial LN; 3, LN along the lesser curvature; 4sa, LN along the short gastric vessels; 4sb, LN along the left gastroepiploic vessels; 7, LN along the left gastric artery; 9, LN around the celiac artery; 10, LN at the splenic hilum; 11p, LN along the proximal splenic artery; 11d, LN along the distal splenic artery; 19, infradiaphragmatic LN.

EG JUNCTION

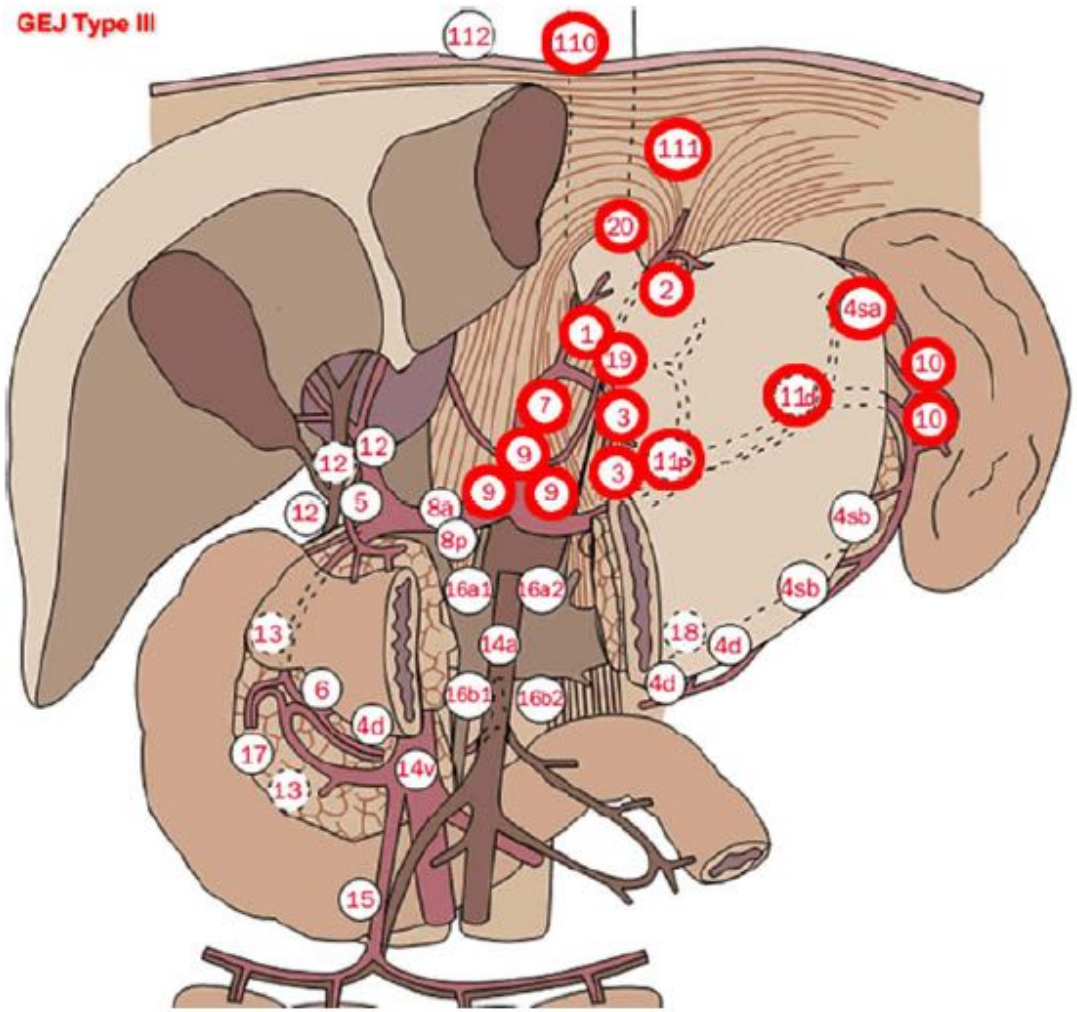


Fig. 6. Corresponding elective lymph node stations for tumours of the gastroesophageal junction. Type III: 1, right paracardial LN; 2, left paracardial LN; 3, LN along the lesser curvature 4sa LN along the short gastric vessels; 7; LN along the left gastric artery; 9, LN around the celiac artery; 10, LN at the splenic hilum; 11p, LN along the proximal splenic artery; 11d, LN along the distal splenic artery; 19, infradiaphragmatic LN; 20, LN in the oesophageal hiatus of the diaphragm; 110, paraoesophageal LN in the lower thorax; 111, supradiaphragmatic LN.

Distal One Third

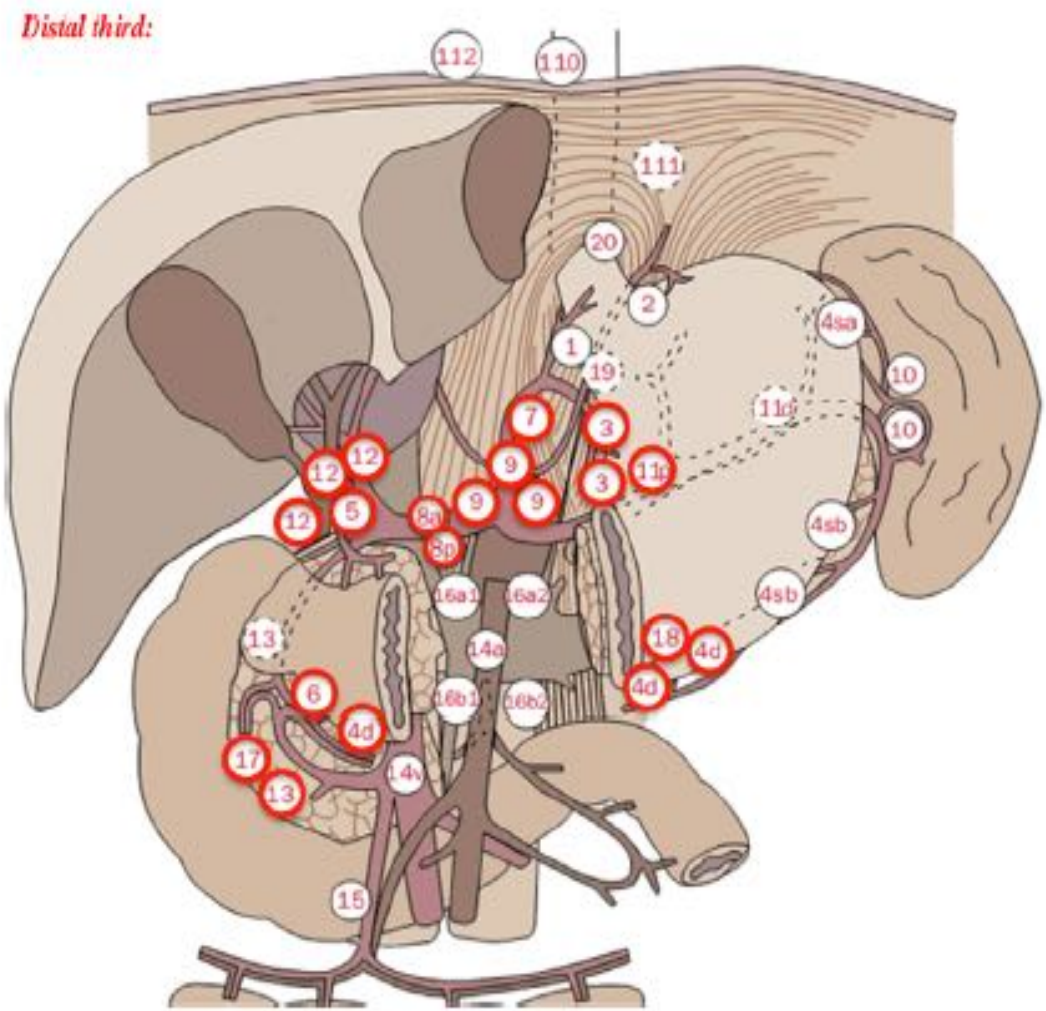
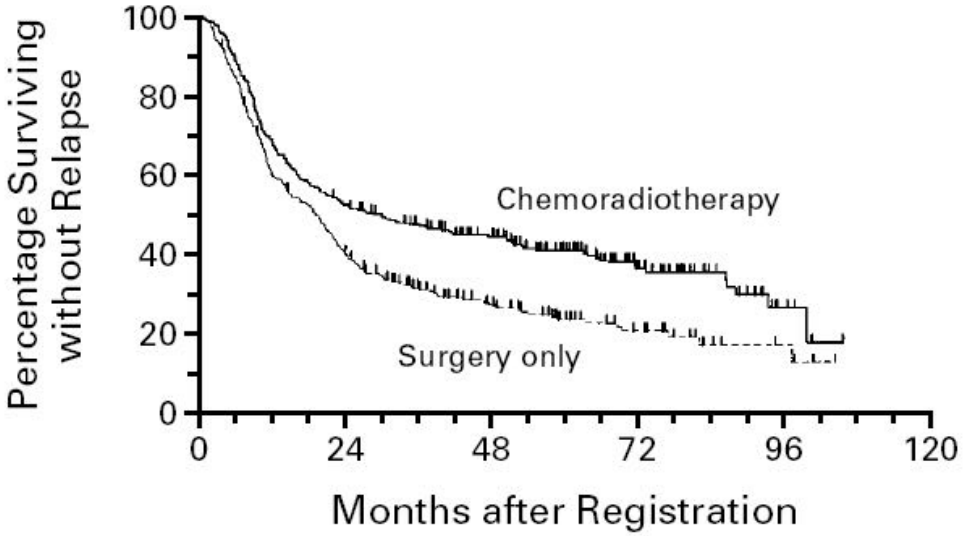


Fig. 9. Corresponding elective lymph node stations for GC tumours of the distal third: 3, LN along the lesser curvature; 4d, LN along the right gastroepiploic vessels; 5, suprapyloric LN; 6, infrapyloric LN; 7, LN along the left gastric artery; 8a, LN along the common hepatic artery (anterosuperior group); 8b, LN along the common hepatic artery (posterior group) 9, LN around the celiac artery; 11p, LN along the proximal splenic artery; 12a, LN in the hepatoduodenal ligament (along the hepatic artery); 12b, LN in the hepatoduodenal ligament (along the bile duct); 12p, LN in the hepatoduodenal ligament (behind the portal vein); 13, LN on the posterior surface of the pancreatic head; 17, LN on the anterior surface of the pancreatic head; 18, LN along the inferior margin of the pancreas.

Postop CT-RT: Possible benefit, however, limitations…

CHEMORADIOTHERAPY AFTER SURGERY COMPARED WITH SURGERY ALONE FOR ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

JOHN S. MACDONALD, M.D., STEPHEN R. SMALLEY, M.D., JACQUELINE BENEDETTI, PH.D., SCOTT A. HUNDAHL, M.D., NORMAN C. ESTES, M.D., GRANT N. STEMMERMANN, M.D., DANIEL G. HALLER, M.D., JAFFER A. AJANI, M.D., LEONARD L. GUNDERSON, M.D., J. MILBURN JESSUP, M.D., AND JAMES A. MARTENSON, M.D.



Post-op 5FU/LV x3 + RT 45Gy-5FU/LV
vs
Surgery alone

Percentage Surviving without Relapse

TABLE 4. SITES OF RELAPSE.*

SITE	PATIENTS WITH RELAPSES	
	SURGERY-ONLY GROUP (N=177)	CHEMORADIOTHERAPY GROUP (N=120)
	no. (%)	
Local	51 (29)	23 (19)
Regional	127 (72)	78 (65)
Distant	32 (18)	40 (33)

N Engl J Med, Vol. 345, No. 10 · September 6, 2001

Research Article

Does adjuvant chemoradiotherapy just compensate for poor surgery?

SEER database (n=15060) RT improves OS in all stages
Benefit improve when >25 LNs are removed

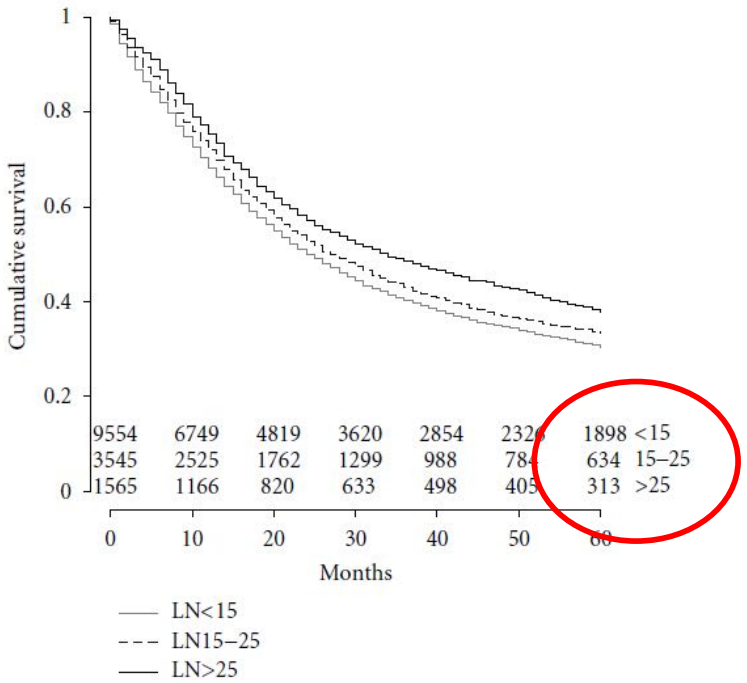


FIGURE 1: Kaplan Meier curve of overall survival by lymph node resection. Lymph node (LN).

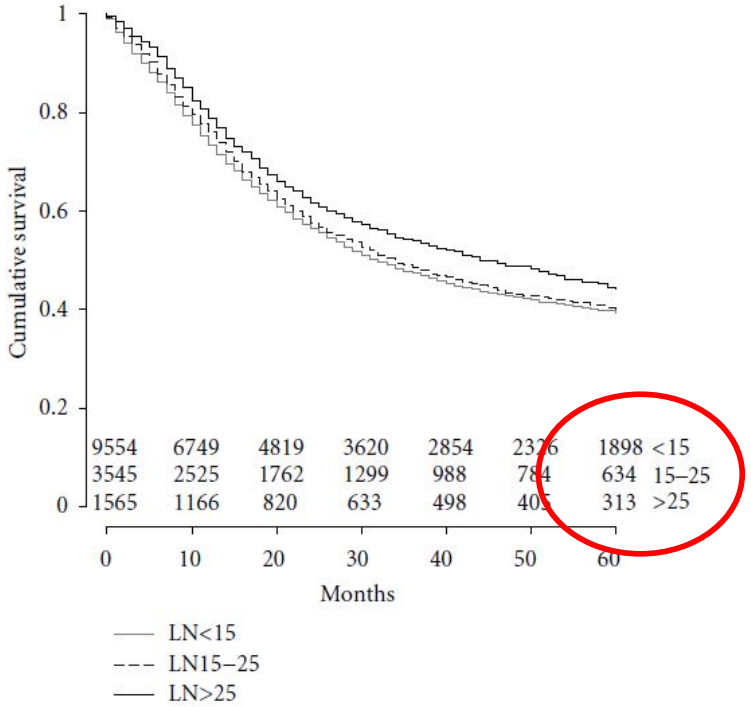


FIGURE 2: Kaplan Meier curve of disease specific survival by lymph node resection. Lymph node (LN).

International Journal of Surgical Oncology
Volume 2012, Article ID 307670, 7 pages

Postop CT-RT: Possible benefit, however, limitations…

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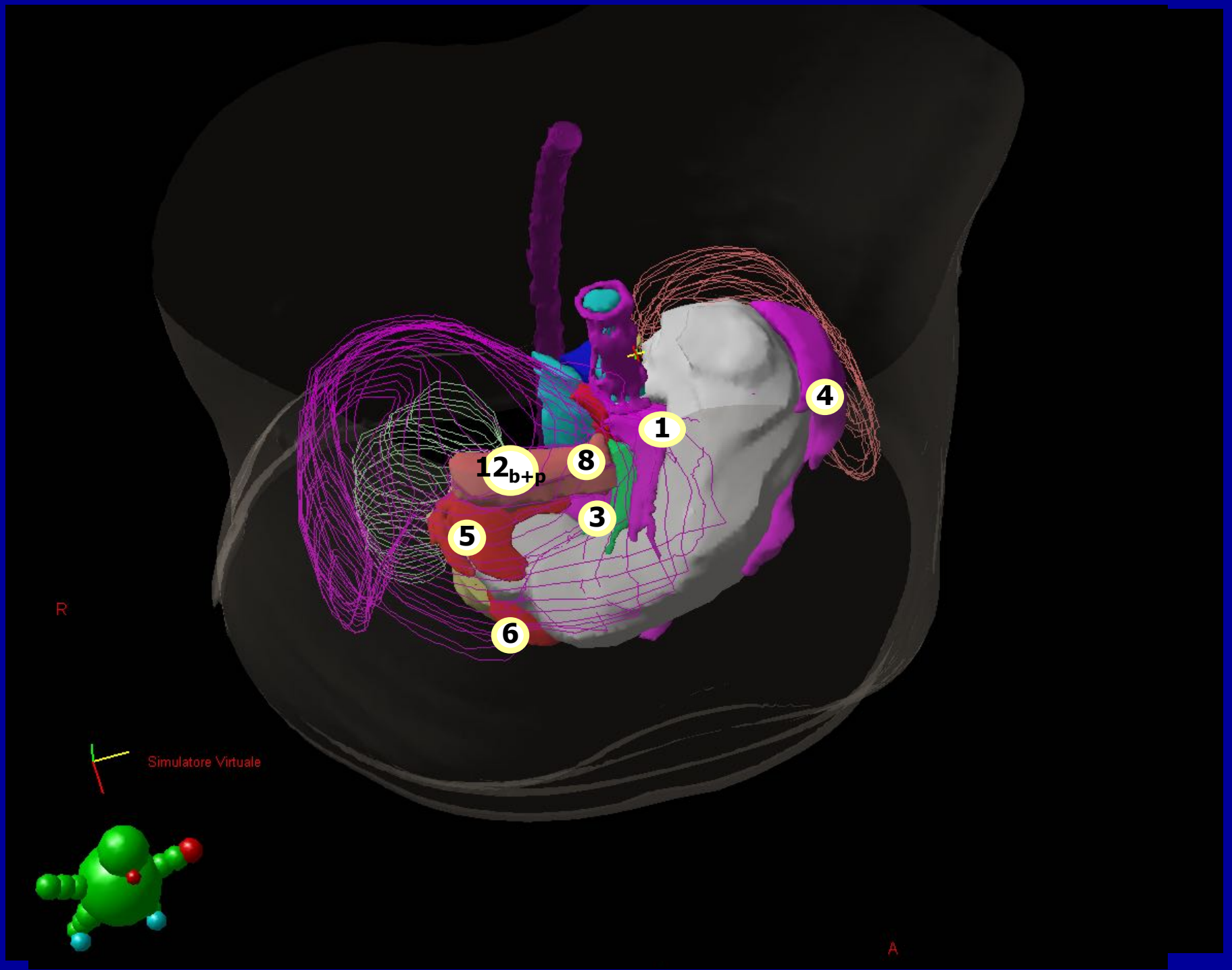
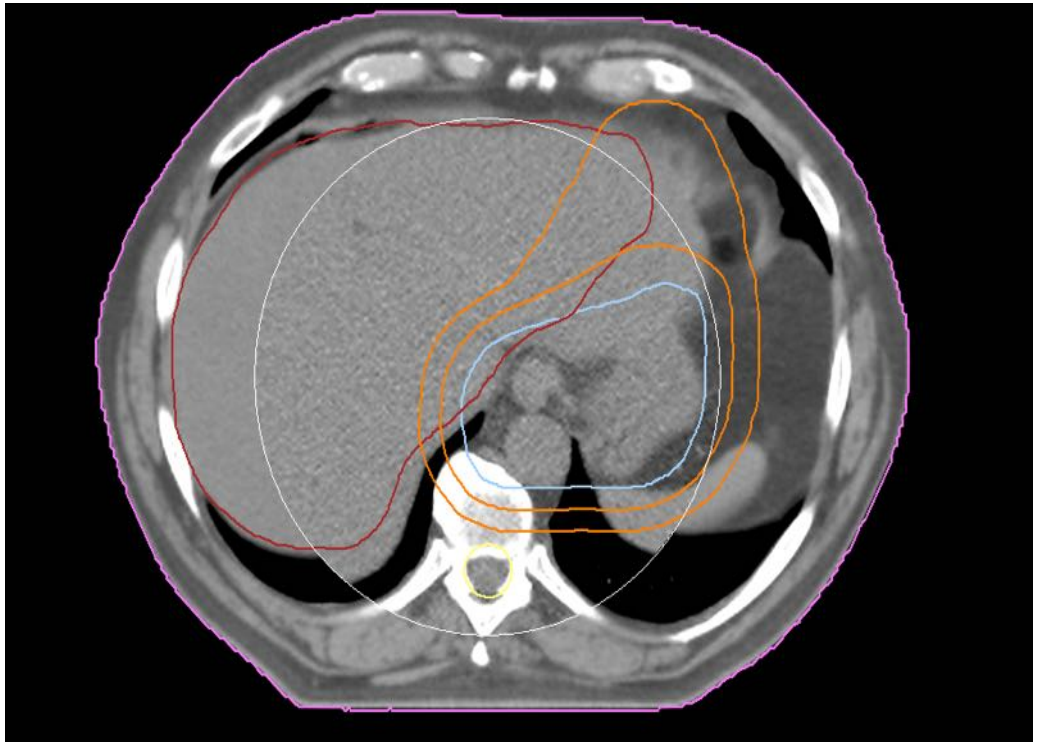
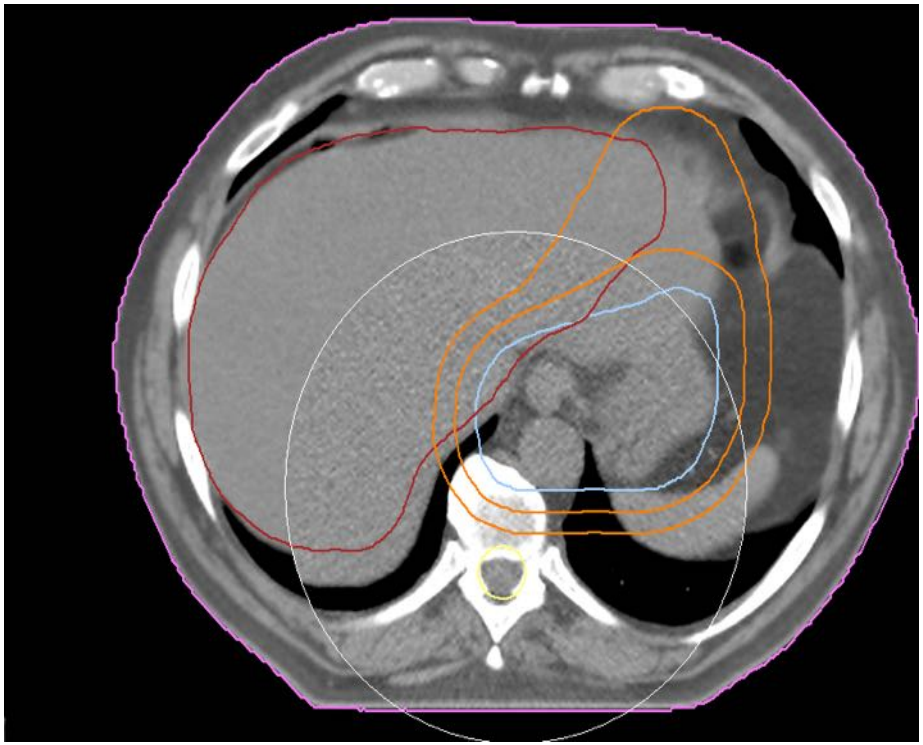

4
1
12b+p
8
3
5
6
R
A
Simulatore Virtuale

Clinical Target Volume (CTV) and Organs at Risk (OAR's) 4D-CT





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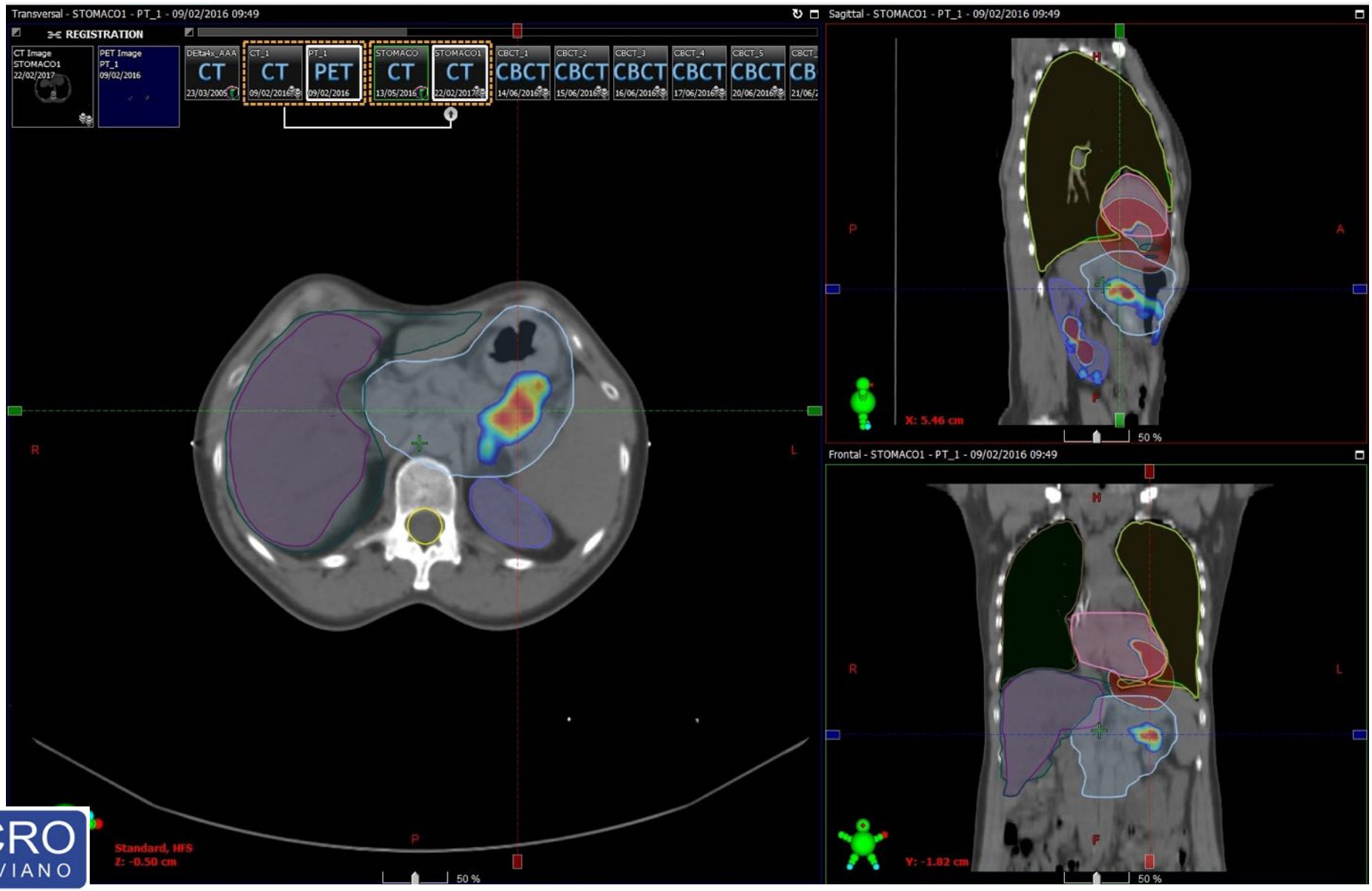
Clinical Target Volume (CTV) and Organs at Risk (OAR's) PET-CT



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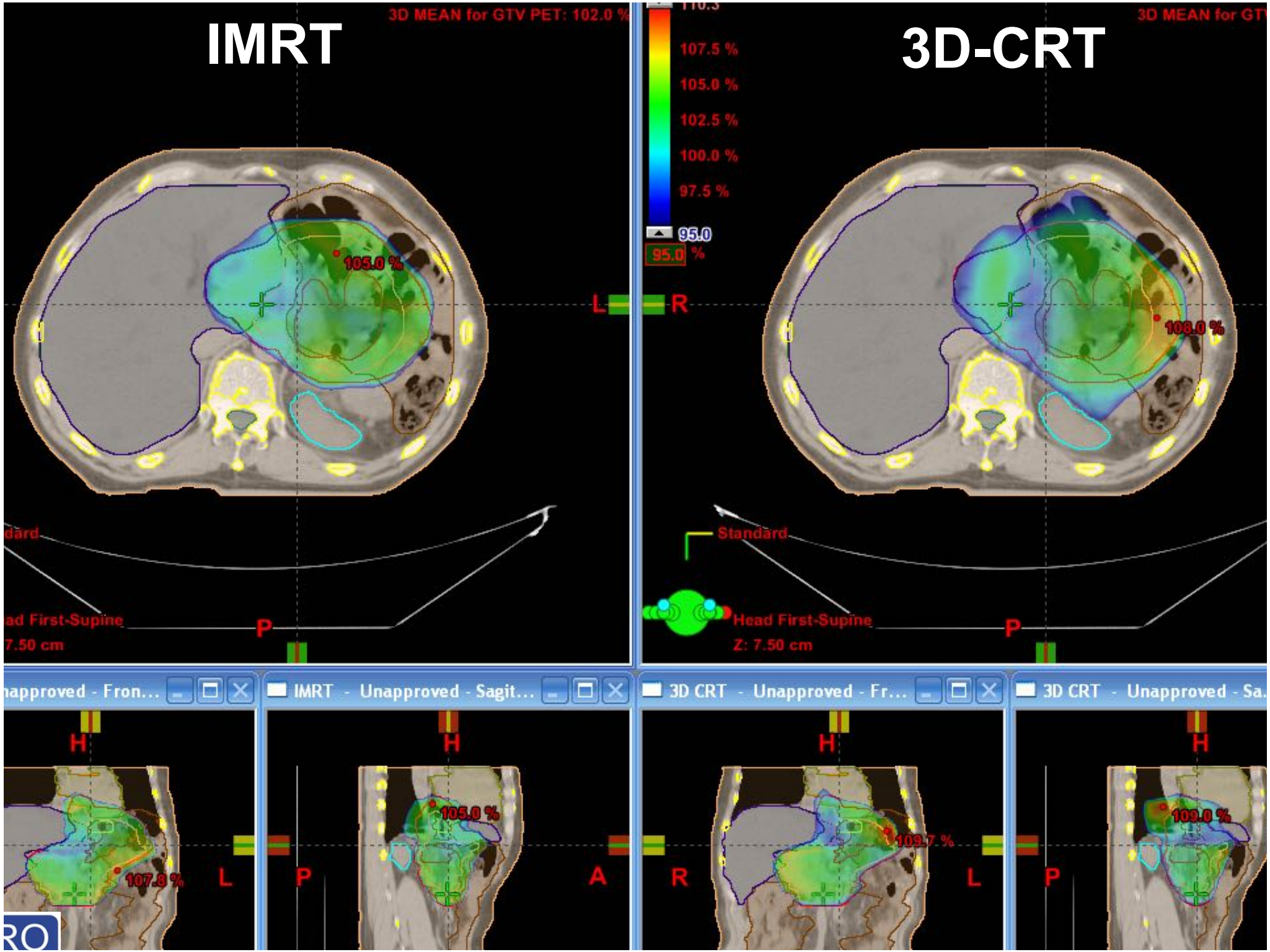
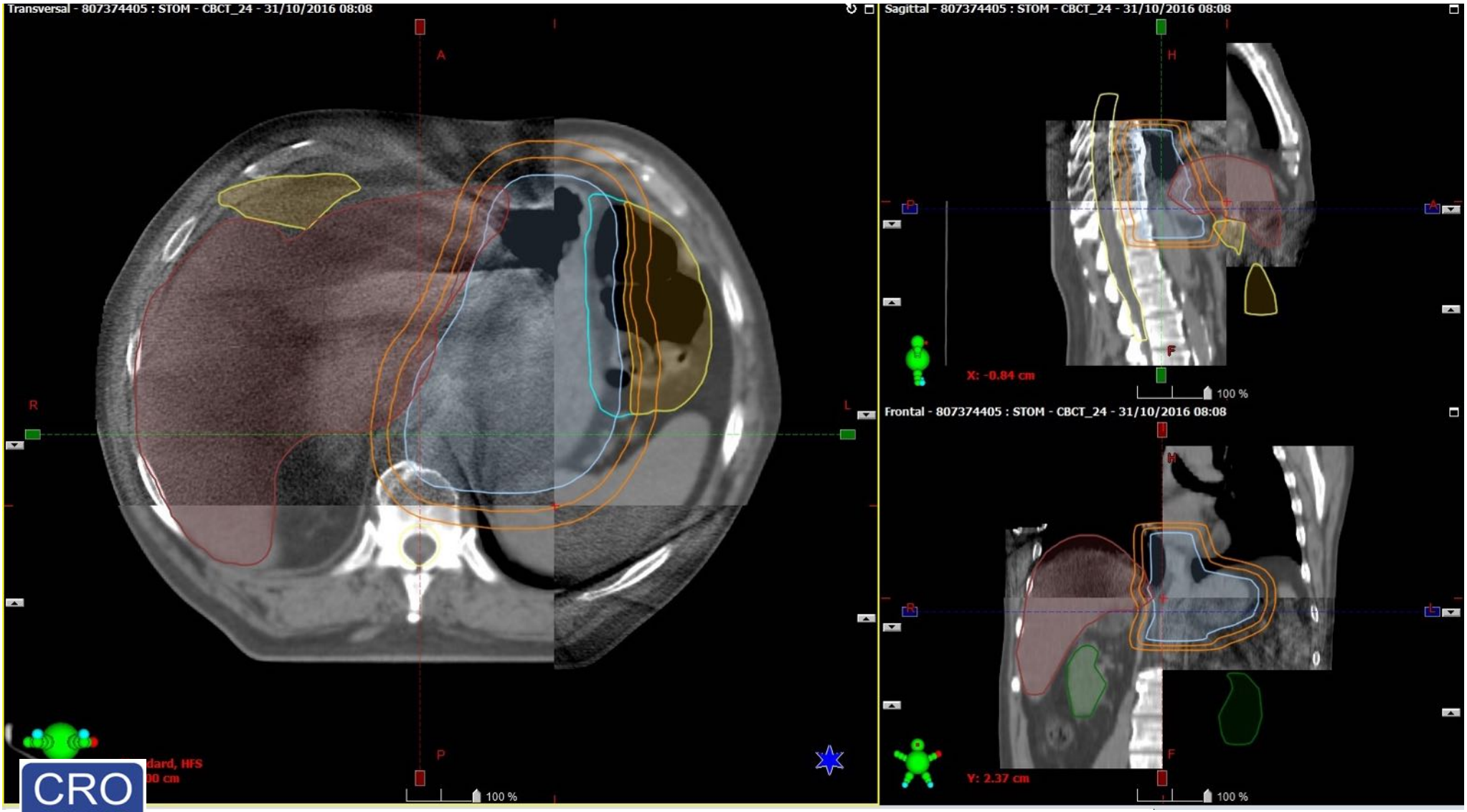

IMRT
3D-CRT
3D MEAN for GTV PET: 102.0 %
3D MEAN for GTV
107.5 %
105.0 %
102.5 %
100.0 %
97.5 %
95.0
95.0 %
105.0 %
108.0 %
L
R
P
Standard
Head First-Supine
Z: 7.50 cm
IMRT - Unapproved - Sagit...
3D CRT - Unapproved - Fr...
3D CRT - Unapproved - Sa...
H
A
107.8 %
109.7 %
109.0 %

Gastric Cancer (Cardias) IMRT-IGRT



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Ongoing Trials

US (Intergroup Trial)

Post-op 5FU/LV + RT/5FU vs ECF + RT/5FU

Does ECF improve efficacy of post-op CRT?

EU

Periop ECX vs Periop ECX-BEV (MAGIC-B)

Is there a role of biologics?

Preop ECX-Surg-postop ECX vs RT/X-DDP (CRITICS)

What is the role of post-op CRT?

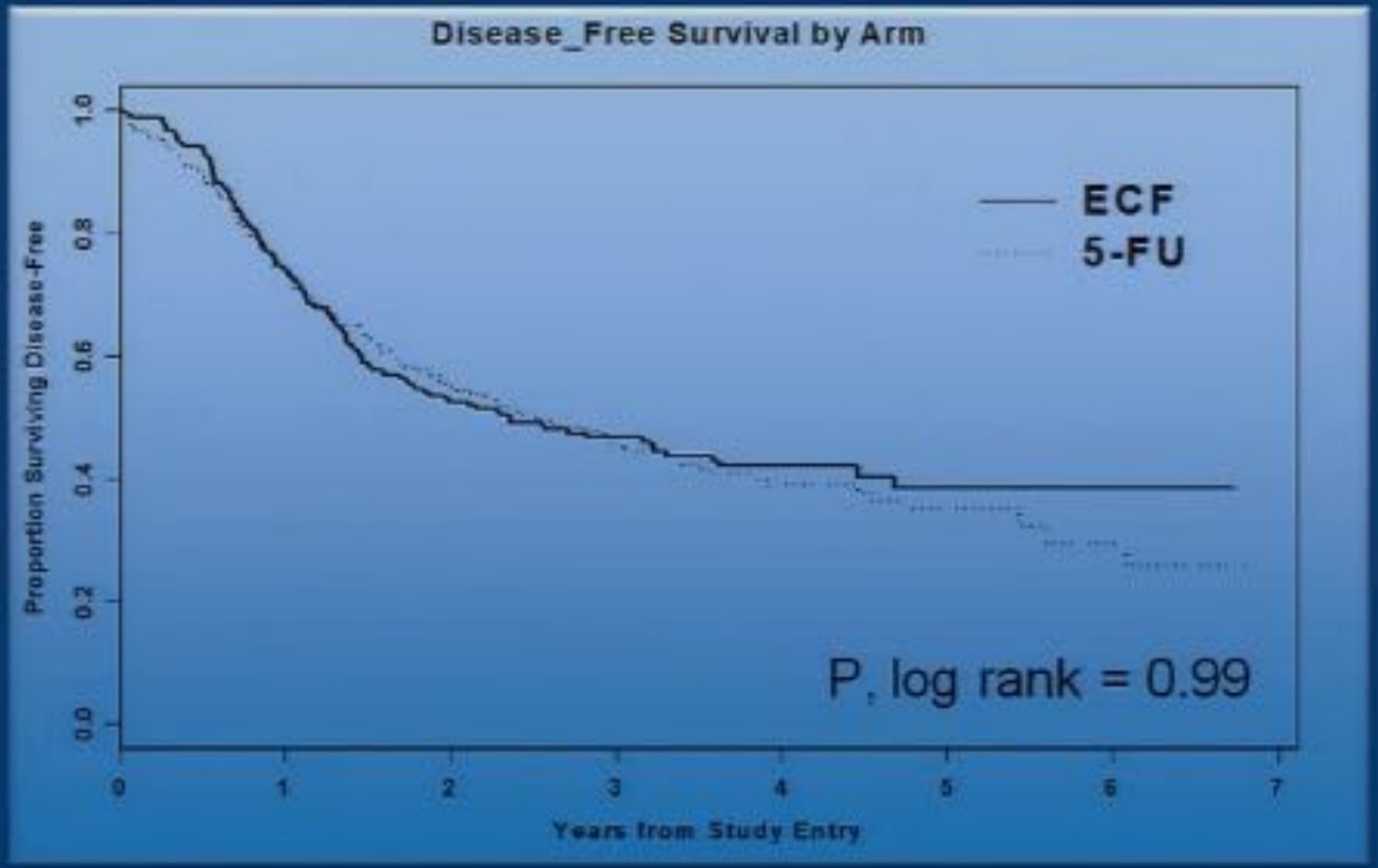
Preop ECX x3 vs ECX x2-RT/X+postop ECX (EORTC)

What is the role of pre-op CT-RT?

Japan

Adjuvant S1 vs Surgery alone

CALGB 80101 – Disease-free Survival

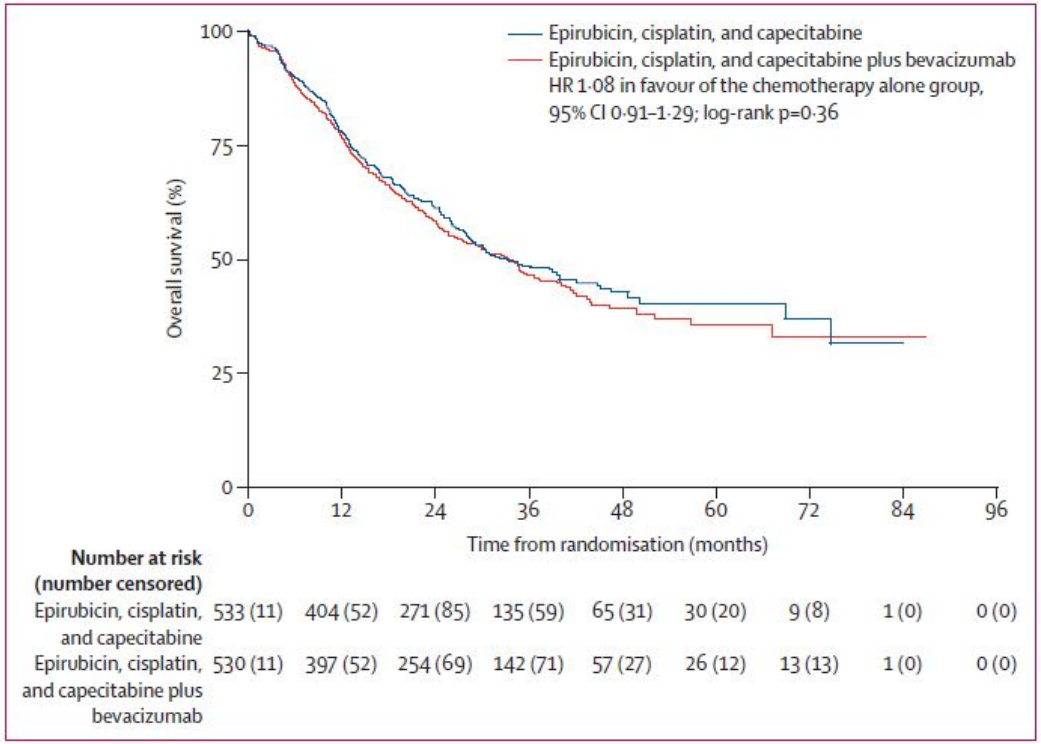


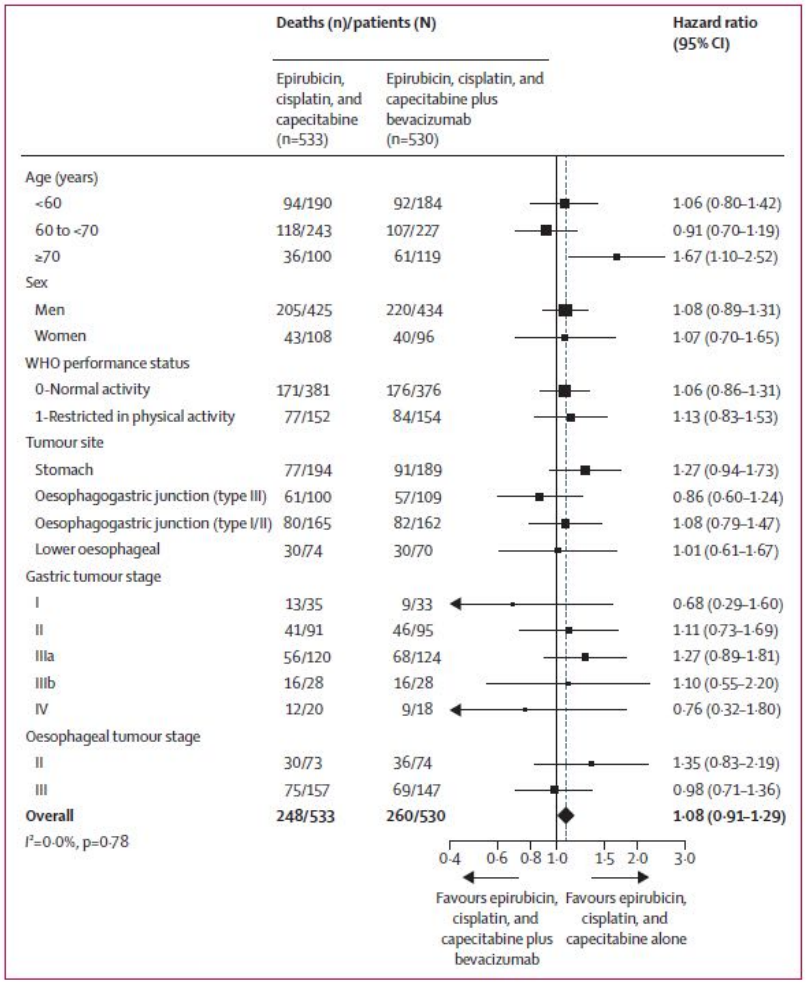
PRESENTED AT: ASCO Annual '11 Meeting

Fuchs CS et al ASCO 2011

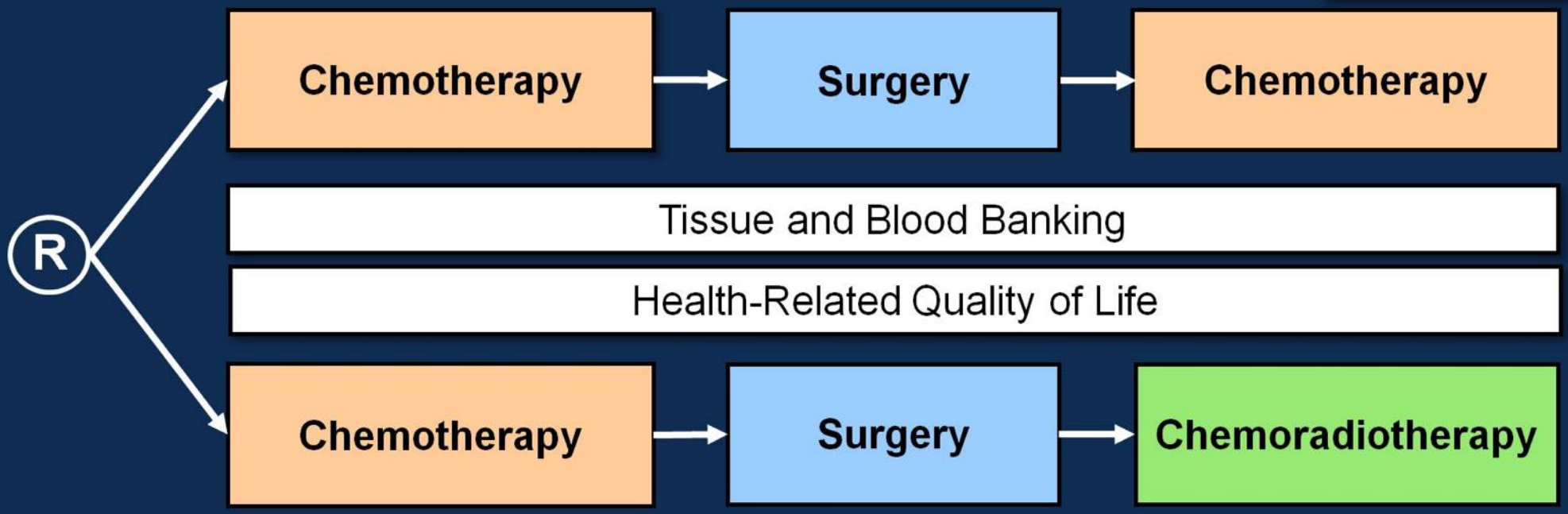
Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2–3 trial

David Cunningham, Sally P Stenning, Elizabeth C Smyth, Alicia F Okines, William H Allum, Sam Rowley, Laura Stevenson, Heike I Grabsch, Derek Alderson, Thomas Crosby, S Michael Griffin, Wasat Mansoor, Fareeda Y Coxon, Stephen J Falk, Suzanne Darby, Kate A Sumpter, Jane M Blazeby, Ruth E Langley





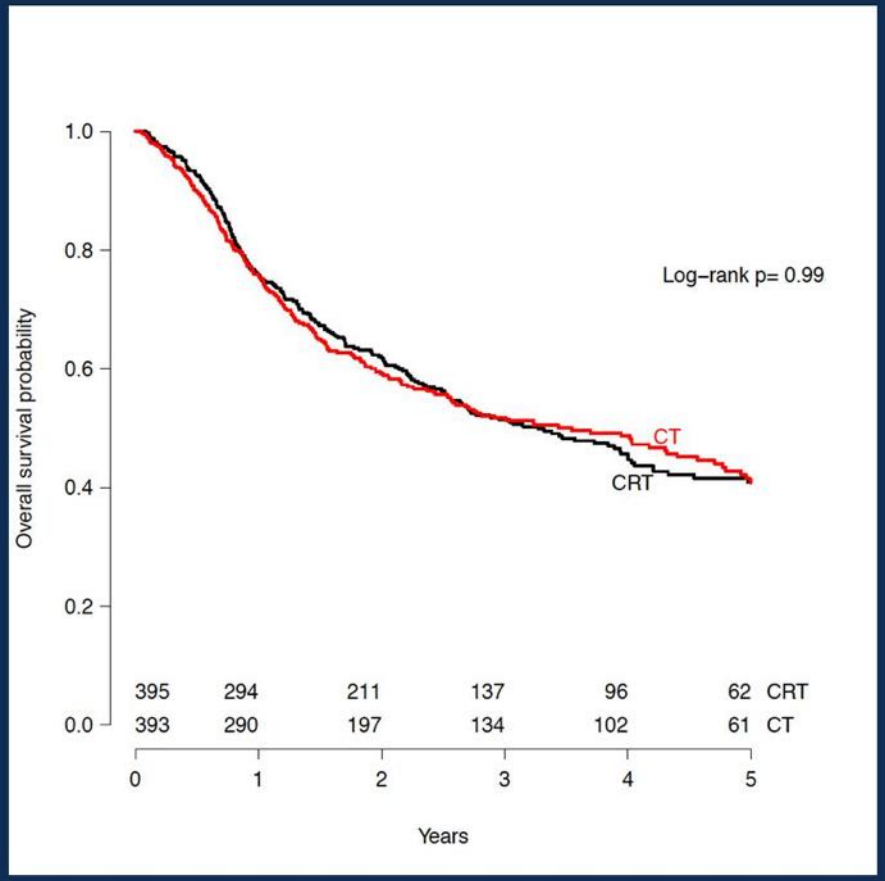
Trial design



Stratified for: Center, Histological type, Tumor localization

Presented By Marcel Verheij at 2016 ASCO Annual Meeting

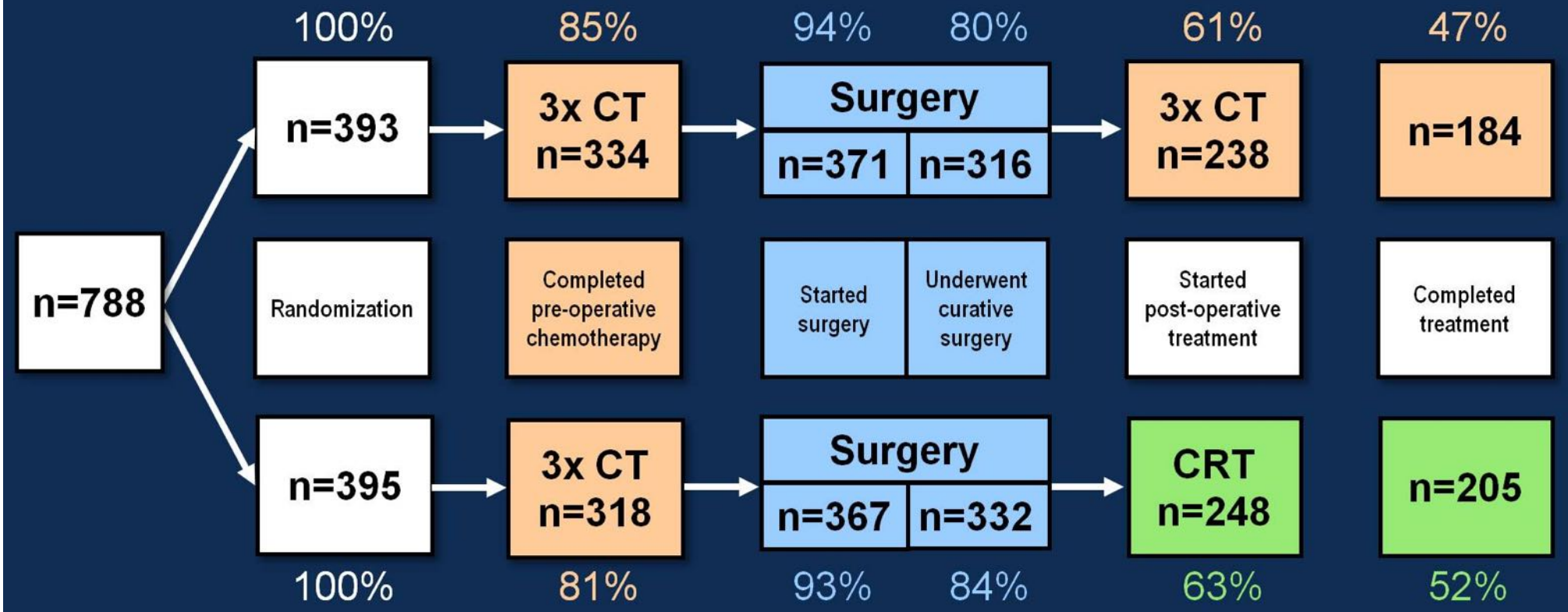
Results: Overall Survival



	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3

Presented By Marcel Verheij at 2016 ASCO Annual Meeting

Results: Study Profile



Presented By Marcel Verheij at 2016 ASCO Annual Meeting

Results: Post-operative Noncompliance

Reasons for not starting post-operative treatment after curative resection	CT n=316 (%)	CRT n=332 (%)
Refusal patient	16 (8)	19 (6)
Progressive disease	16 (8)	14 (4)
Toxicity pre-operative chemotherapy	14 (4)	13 (4)
Post-operative complications	5 (2)	18 (5)
Died	12 (4)	6 (2)
Poor condition	3 (1)	4 (1)
Other	13 (4)	7 (2)
Total	**79 (25)**	**81 (24)**

Ongoing Trials

Italy

ITACAS-2 Phase III Study

failed

Periop vs post-op EOX and assessment of benefit of post-op RT/Carbo

DOX Phase II randomised Study

Periop DOX vs Preop DOX

NEOX-RT Phase II Study

Preop EOX + RT/OX

Pre-Op CT and Post-Op RT-CT+/-IORT
A Pilot Study

N.Pts: 22; EUS Stage II-III Resectable GC

Treatment

ECF x 3 cycles
Surgery + IORT (10 Gy)
45 Gy + c.i. 5-FU 200 mg/mq/day

Downstaging	32%
R0 Response Rate	75% (85%)
G3+ toxicity	9%
RT/FU Compliance	66% (Parent. Support: 40% of pts)

Buonadonna A et al, JCO 2007

NEOX-RT Study

Patients with locally advanced uT3-4,N0 or any uT,N+M0(LPS) potentially resectable, EGJ(II-III)-Gastric Cancer

Induction chemotherapy

EOX x 3 cycles (q 3weeks)
for 9 weeks

Responding pts
CT-PET evaluation after 2 cycles EOX
Objective Response (Endoscopy/EUS) after 9 weeks

Patients with **early metabolic disease progression** (CT-PET) will undergo to immediate surgery

Chemoradiotherapy

RT 45 Gy
+ Oxaliplatin-Xeloda
for 5 weeks

Restaging
CT-PET
CT abdomen and chest
Objective Response (Endoscopy/EUS) after 4 weeks from CT-RT

Surgery
Week 22

SURGERY +/- IORT
4-6 weeks after chemoradiotherapy

Path Response Rate
R0 Resection Rate
Treat Compliance

Neoadjuvant Epirubicin, Oxaliplatin, Capecitabine and Radiation Therapy (NEOX-RT) Followed by Surgery for Locally Advanced Gastric Cancer

linterim Analysis of Multicentric Phase II Study

Antonino De Paoli , Angela Buonadonna, Elisa Turchet, Renato Cannizzaro, Salvatore Tumolo, Giancarlo Tosolini, Sara Lonardi, Vincenzo Canzonieri, Alberto Marchet, Donato Nitti, Francesco De Marchi

CRO-National Cancer Institute, Aviano; General Hospital, Pordenone; IOV-Oncologic Institute and Department of Surgical Science, University of Padova, Italy

Patient/Tumor Characteristics

Nov 2008 – Dec 2012

N. Patients	24
Age (yrs)	58 (47-73)
Male/Female	19/5
ECOG PS	
0	20
1	4
Tumor Site	
EGJ	11
Corpus	6
Antrum	7
Stage	
T3 N0	5
T2 N+	3
T3 N+	14
T4 N+	2

Treatment

	N. Pts	%
EOX x 3 cycles	^21/24	87%
⇩		
RT-Xeloda+Oxa	21/21	100%
⇩		
Surgery	21/21	100%
*IORT	12/21	57%

^2 pts had 1 cycle of CT only (1refusal and 1tumor bleeding);
1 pt with prolonged hematologic G2 toxicity after 2 cycles EOX
*IORT 10 Gy

Results: Primary Endpoint
pCR in first step of 21 ITT patients

pCR: 4/21 (19%)

Patients	uTN	pTN
1	uT3N+	pT0N0
2	uT3N+	pT0N0
3	uT3N+	pT0N0
4	uT3N+	pT0N0

Compliance to treatment

Completed Planned EOX 21/24 (87%)
Dose modification(overall cycles) 7/63 (11%)

1 pt refusal, 1 pt tumor bleeding, 1 pt prolonged G2 toxicity

Completed Planned RT (45Gy) 18/21 (86%)
Completed Xeloda (75-100%) 17/21 (81%)
Completed Oxali (4-5 cycles) 12/*20 (60%)

IMRT: mDose 45Gy (32.4-45)

*Oxali: mCycles 4 (1-5); *1 pt no Oxali for previous reaction*

Surgical Procedure Details

Complete Resection (R0)		19/21 (90%)	
Palliative resection		2	
Total Gastrectomy		13	Sutotal
Gastrectomy	6		
D2 Lymphadenectomy		19	
median excised LN (range)		19 (15-37)	
median positive LN (range)		5 (1-19)	

Median days from start CT (range): 163 (131-183)

Major postoperative complications: 1pt

INCONTRO CON GLI ESPERTI XIV EDIZIONE

Appropriatezza in Radiochemioterapia

…Summary

1. EUS – MDTC (re)Staging; TC Sim – 3D-CRT (Terapia) . **Standard**
2. DW-MRI(re)Staging; 4D-TC Sim – IMRT-IGRT (Terapia) . **Optimisation**
3. PET-CT(re)Staging; 4D-TC Sim/PET – IMRT-IGRT Gating **Investigational**

Optimal Integrated Treatment Strategy
Imaging Accuracy – Biological Markers

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