XXI Congresso Nazionale AIRO

Genova, 19-22 Novembre 2011

La Ricerca Clinica nei Trattamenti Integrati del Carcinoma Gastrico

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Gastric Cancer
Current Treatment Strategies

Post-operative Chemotherapy

Post-operative Chemoradiotherapy

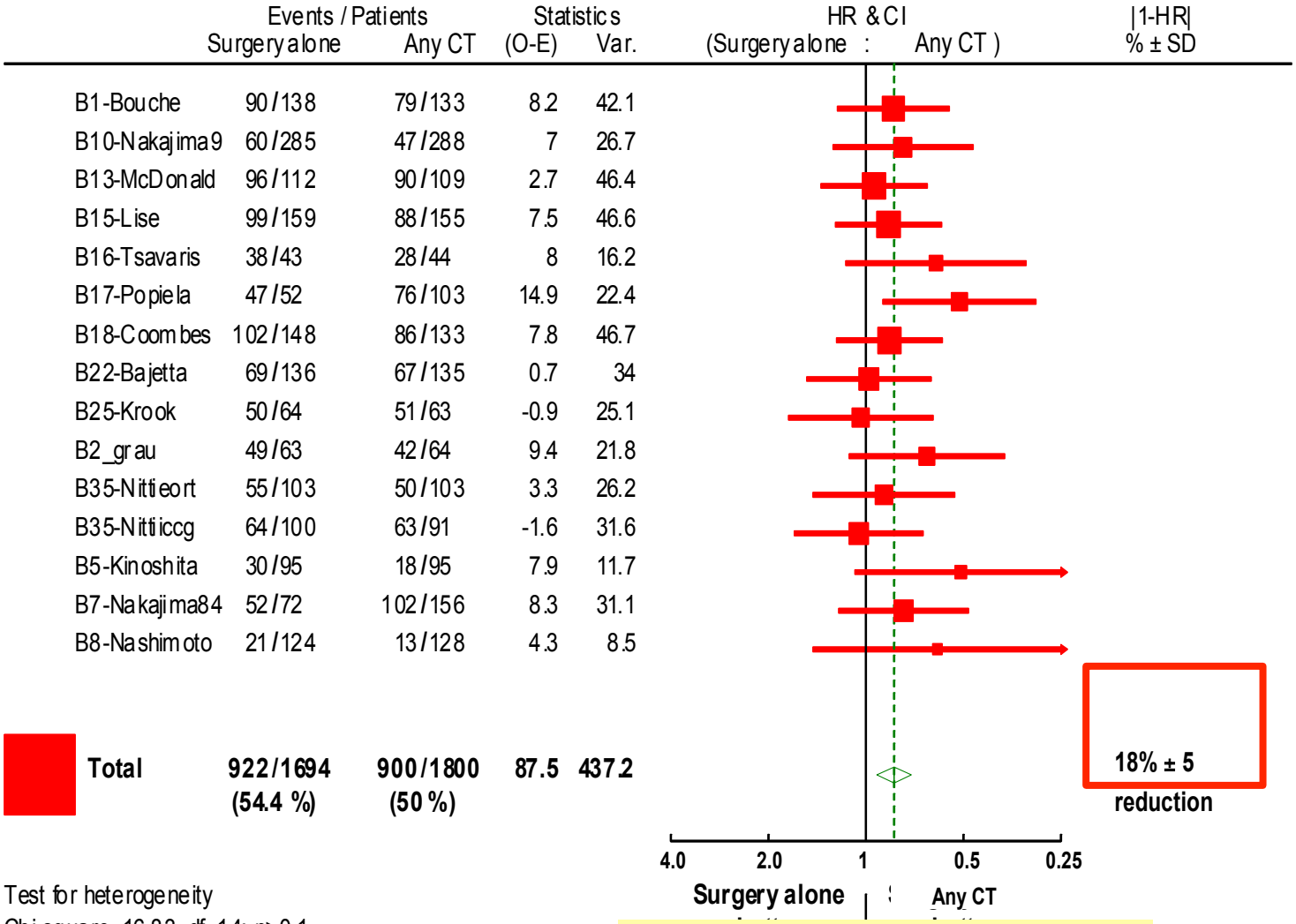
Peri-operative Chemotherapy

Pre-operative Chemoradiotherapy

Survival in Italian and EU RCTs

Author	*N*	*Arms*	*5yr-OS*
Bajetta *Ann Oncol '02*	274	EAP→FUFA **Surgery alone**	**52%** **48%**
Di Costanzo *JNCI 2008*	258	PELF **Surgery alone**	**48%** **45%**
De Vita *Ann Oncol 2007*	228	ELFE **Surgery alone**	**48%** **43.5%**
Nitti *Ann Oncol 2006*	397	FAMTX **Surgery alone**	**43%** **44%**

Overall survival: CT vs surgery alone



Paoletti X et al, JAMA,2010

Adjuvant chemotherapy
Italian Intergroup ITACA-S1 Trial

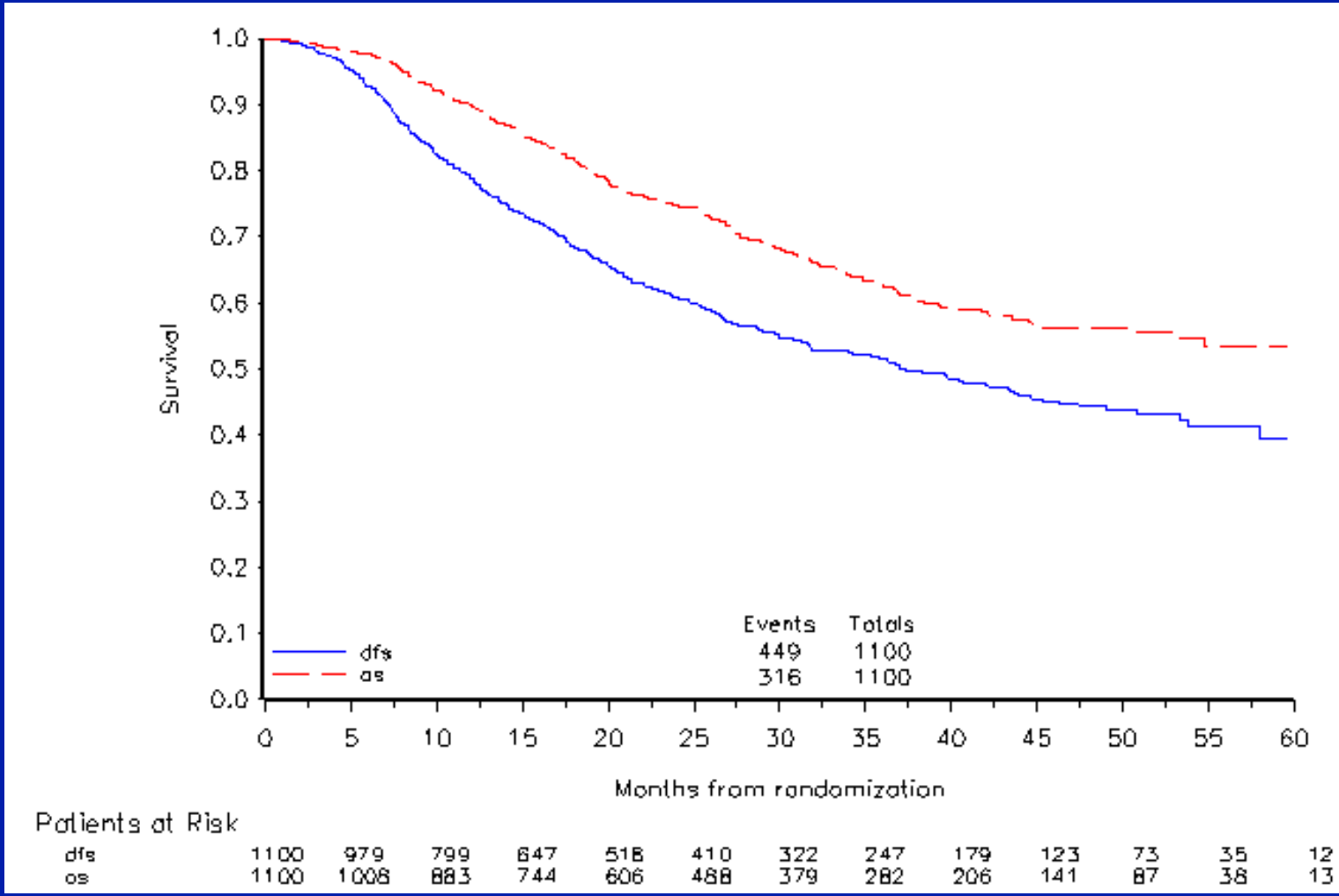
pT2b-4 N0 and/or N+; at least D1 and 15 LN; 1100 pts

Participants:
123 Italian Centers from 11 Multicenter groups

Patients recruited :
1106: 562 exp arm, 538 control arm (Febr 2005 – Aug 2009)

ITACA-S1 Study: Results

Events on global population



Median Fup: 2.5 year ; 408 pts relapsed and 316 deathed; 449 events (71% of target)

Di Bartolomeo M, Corso AIRO-GI, 2011

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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.

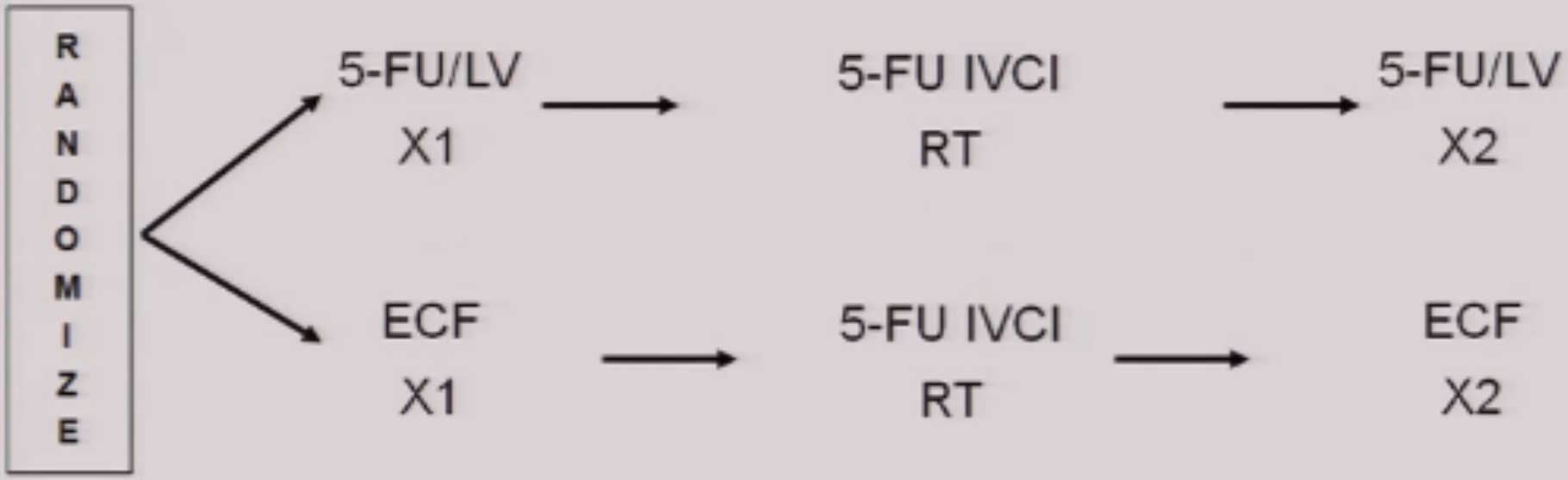
TABLE 2. REASONS FOR THE CESSATION OF CHEMORADIOTHERAPY AMONG THE 281 PATIENTS IN THE CHEMORADIOTHERAPY GROUP.

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 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)

CALGB 80101: Study Schema



5-FU/LV: 5-FU 425 mg/m^2 d1-5, LV 20 mg/m^2 d1-5

RT: 45 Gy (1.8 Gy X 25 fractions) with 5-FU 200 mg/m^2/d CI

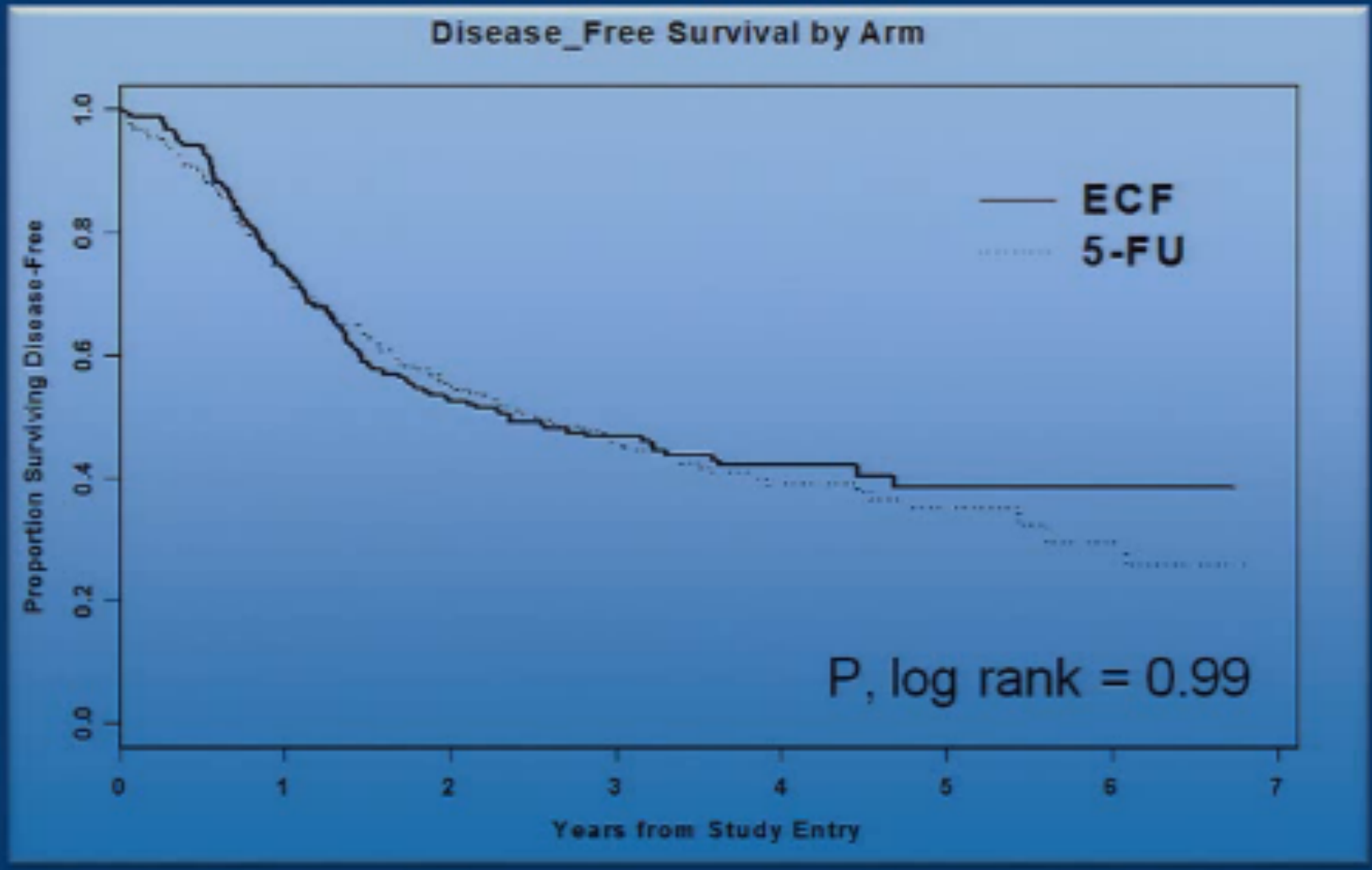
ECF (pre-RT): Epirubicin 50 mg/m^2 d1, Cisplatin 60 mg/m^2 d1, & 5-FU 200 mg/m^2/d CI d1-21

ECF (post-RT): Epirubicin 40 mg/m^2 d1, Cisplatin 50 mg/m^2 d1, & 5-FU 200 mg/m^2/d CI d1-21

Postoperative adjuvant chemoradiation for gastric or GE junction adenocarcinoma using ECF before and after 5-FU/radiotherapy compared to bolus 5-FU/LV before and after 5-FU/radiotherapy: Intergroup trial CALGB 80101

CS Fuchs, JE Tepper, D Niedzwiecki, D Hollis, HJ Mamon, RS Swanson, DG Haller, T Dragovich, SR Alberts, G Bjarnson, CG Willett, PC Enzinger, RM Goldberg, AP Venook, RJ Mayer

CALGB 80101 – Disease-free Survival



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

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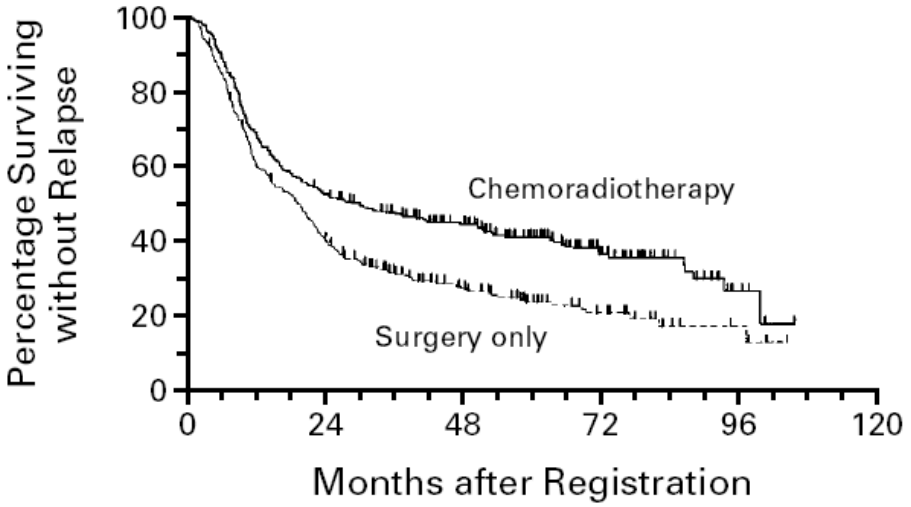

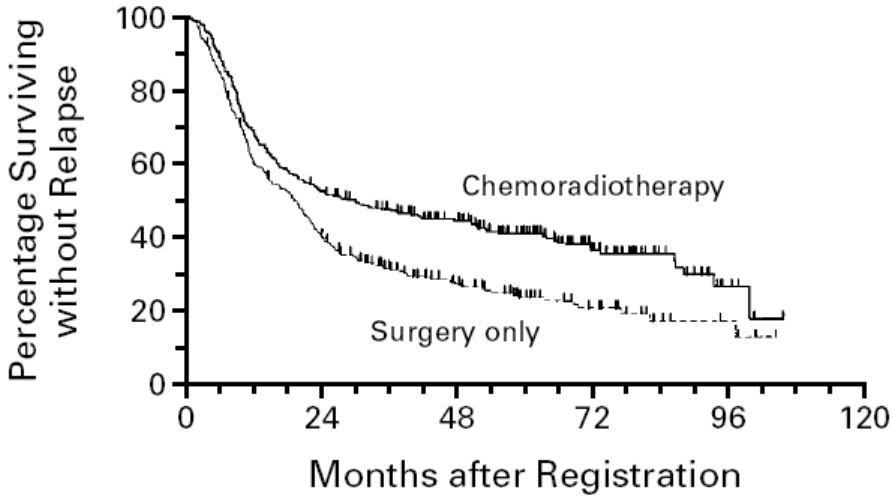

CALGB 80101- Discussion

What could we make better?

Radiation quality assurance

CALGB 80101 (Fuchs et al. 2011)
15% of the treatment plans were found to contain major deviations

INT 0116 (Macdonald et al. 2001)
6.5% major deviations

CALGB 80101- Discussion

What could we make better?

Surgical quality assurance

CALGB 80101 (Fuchs et al. 2011)
D2 LN dissection not mandated
33% pts had <15 lymph nodes examined!

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Perioperative CT - Ongoing Trials

MAGIC-B TRIAL

Stage II-IV(M0) Gastric/EG Adenocarcinoma

R
A
N
D
O
M

- ECX x 3 -- **Surgery – ECX x 3**
- **ECX x 3 + BEV – Surgery – ECX x 3+ BEV**
  BEV x 6

Randomised Phase II Study of pre or peri-operative Docetaxel, Oxaliplatin, Capecitabine (DOX) regimen in locally advanced resectable Gastric Cancer

Study Design

Multicenter, randomized, open label phase II study

DOX 2 cycles →Surgery → DOX 2 cycles → F-up

Random

DOX 4 cycles → Surgery → F-up

Study Coordinators: D Amadori, S Cascinu, G De Manzoni, F Roviello

Preop CT and Postop CT or CT-RT
Ongoing CRITICS Trial

pT2b-4 N0 and/or N+; Primary end-point: OS; Pts 788

R → **ECX x 3 – D1+ Surgery – ECX x 3**

R → **ECX x 3 – D1+ Surgery – CX/RT**

E: Epirubicyn, C: Cisplatin, X: Capecitabine

RT: 3D-CRT/IMRT 45Gy/25 fe

SURGERY week 12

Neaderlands Cancer Institue

ITACA-S 2

(*Intergroup Trial in Adjuvant Chemotherapy for Adenocarcinoma of the Stomach 2*):

Comparison of the efficacy of a peri-operative versus a post-operative chemotherapy treatment in patients with operable gastric cancer and assessment of the benefit of a post-operative chemo-radiotherapy

Sponsor: Istituto di Ricerche Farmacologiche "Mario Negri"

Supported by: AIFA

Medical Oncology: Francesco Di Costanzo *(P.Investigator)*

Radiation Oncology: Vincenzo Valentini

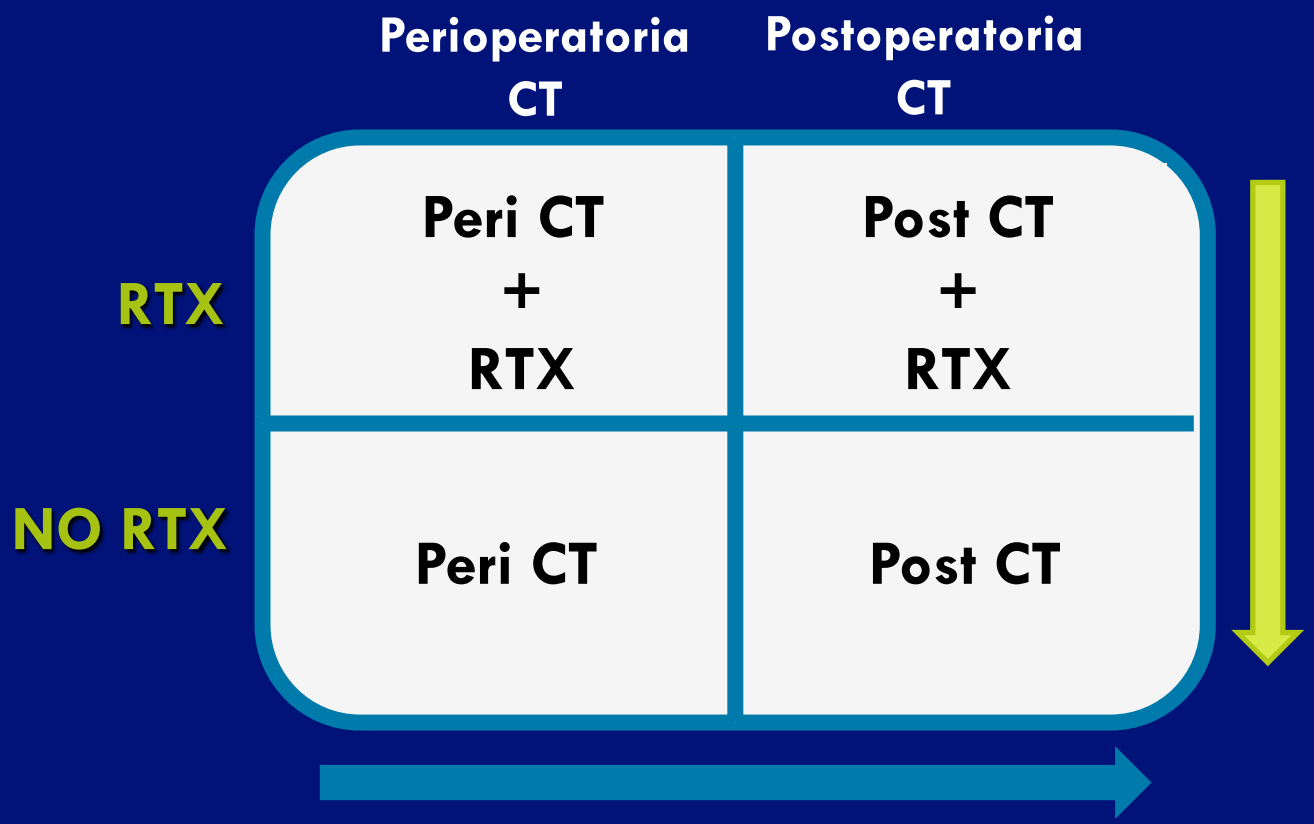
Surgery: Donato Nitti

STUDIO ITACA-S 2

adenocarcinoma dello stomaco considerato operabile

I pazienti saranno stratificati per centro, stadio di malattia, perfomance status

RANDOM INDIPENDENTI
2a RANDOM NON OBBLIGATORIA



DISEGNO DELLO STUDIO

ITACA-S 2

Arm A: peri-operative CT

Arm B: post-operative CT

Arm C: peri-operative CT +

post-operative CT- RT

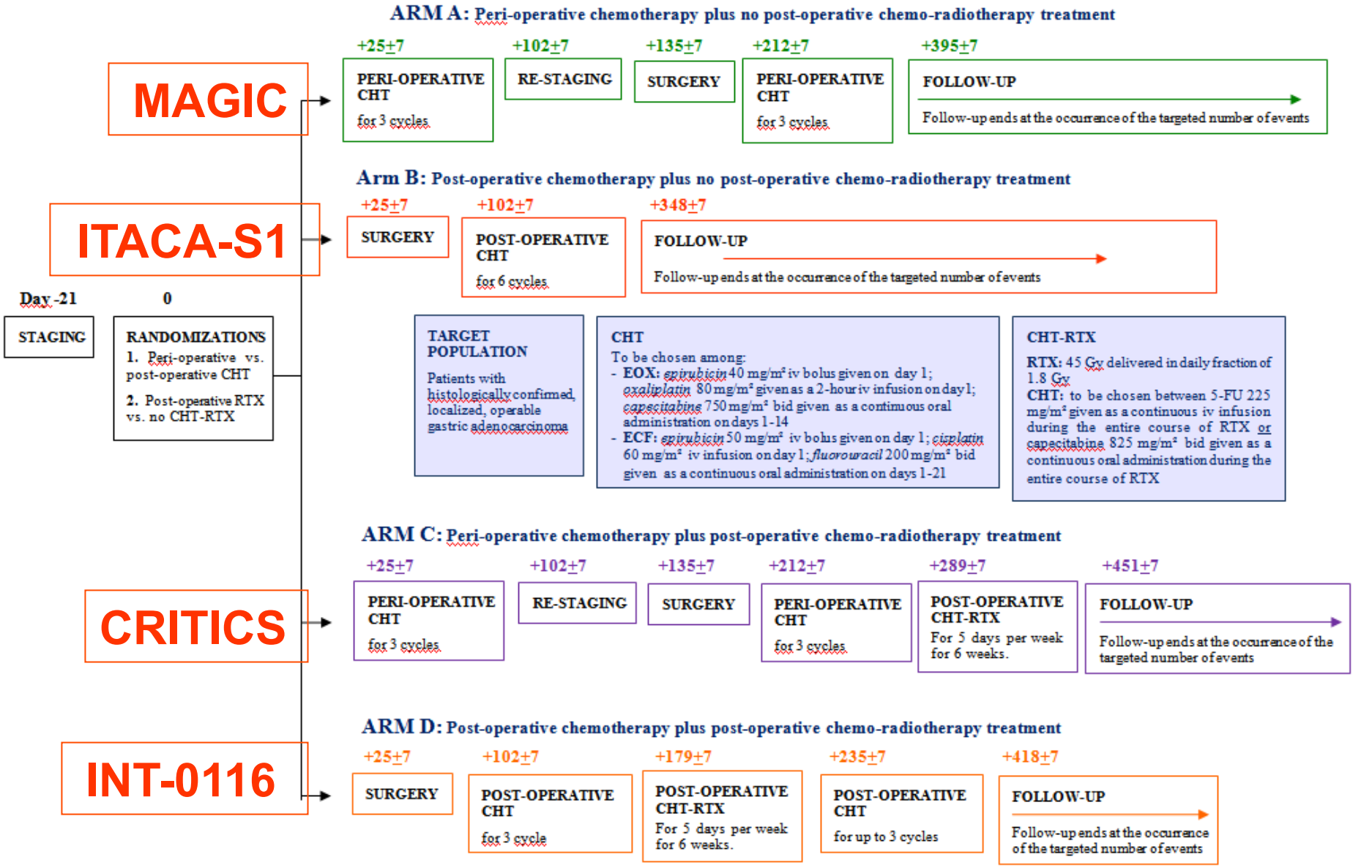
Arm D: post-operative CT+

post-operative CT- RT

CT: EOX / ECF

RT: 3D-CRT 45 Gy + Cape/FU

Annex 1 – Study flow-chart



Disegno dello Studio

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Preoperative Chemoradiotherapy in Castric Cancer- The MD Anderson

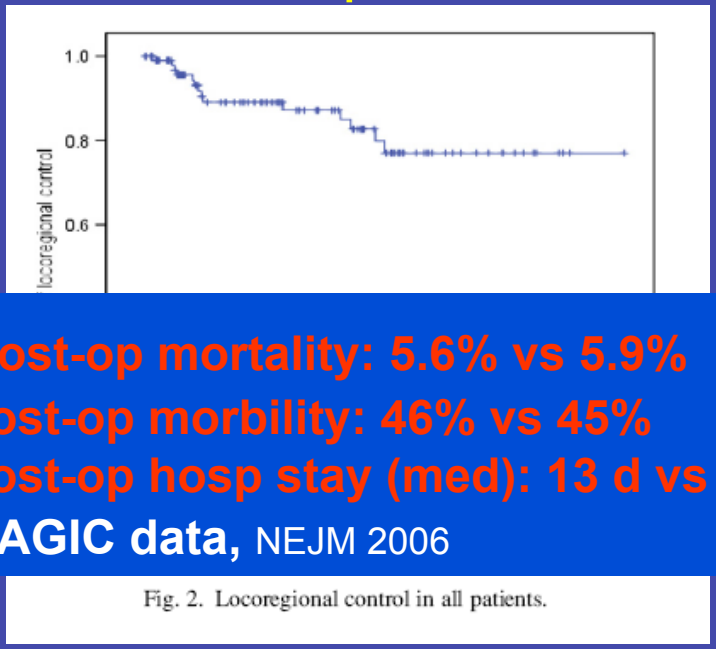


Fig. 2. Locoregional control in all patients.

Post-op mortality: 5.6% vs 5.9%
Post-op morbility: 46% vs 45%
Post-op hosp stay (med): 13 d vs 13 d
MAGIC data, NEJM 2006

pCR: 23% - R0 Rate: 95%

Post Op Compl: 38%

Post Op Death: 2.8%

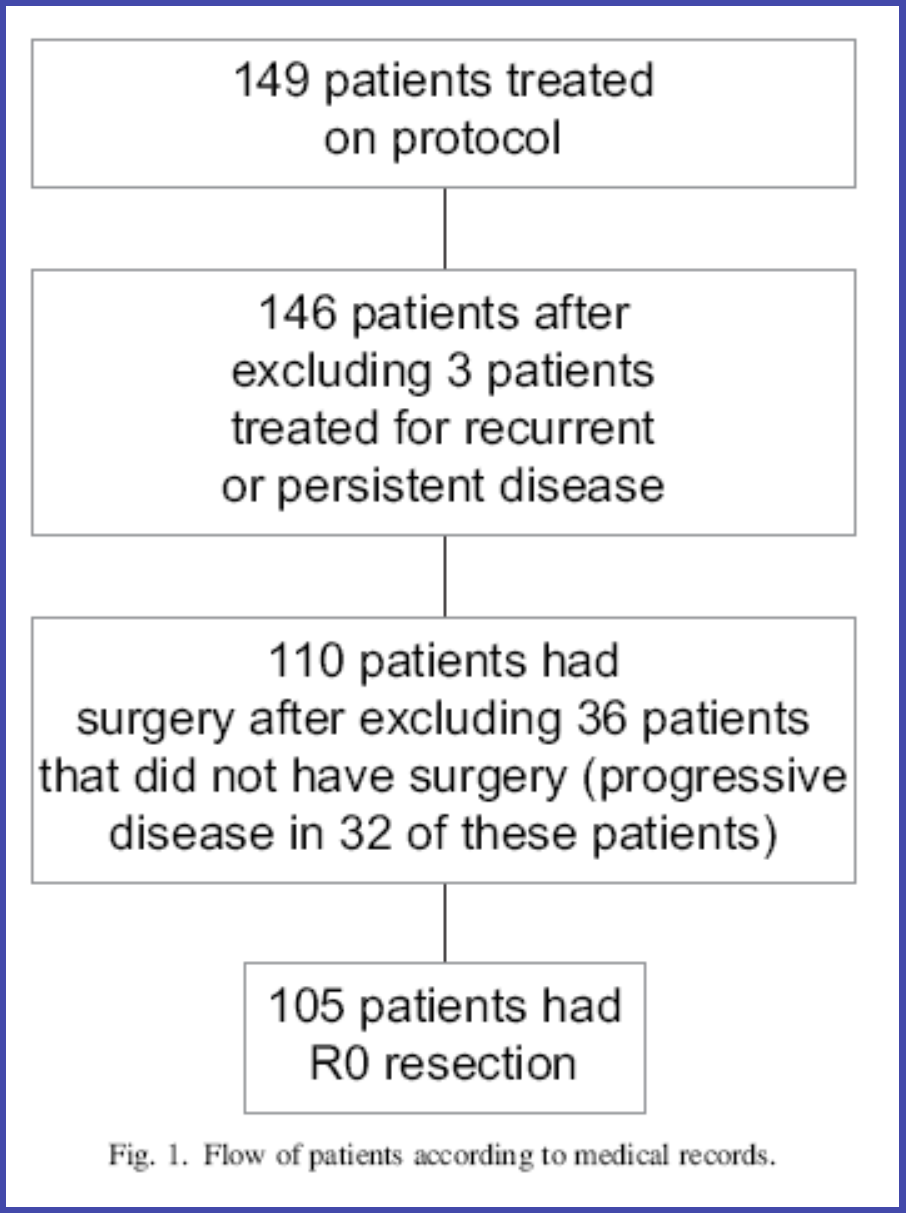


Fig. 1. Flow of patients according to medical records.

Fujitani K et al Ann Surg Oncol 2007
Reed VK et al IJROBP 2008

NEOX-RT Study

Patients with locally advanced uT3-4,N0 or any uT,N+M0(LPS) potentially resectable, locally advanced gastric cancer

Induction chemotherapy

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

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

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

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

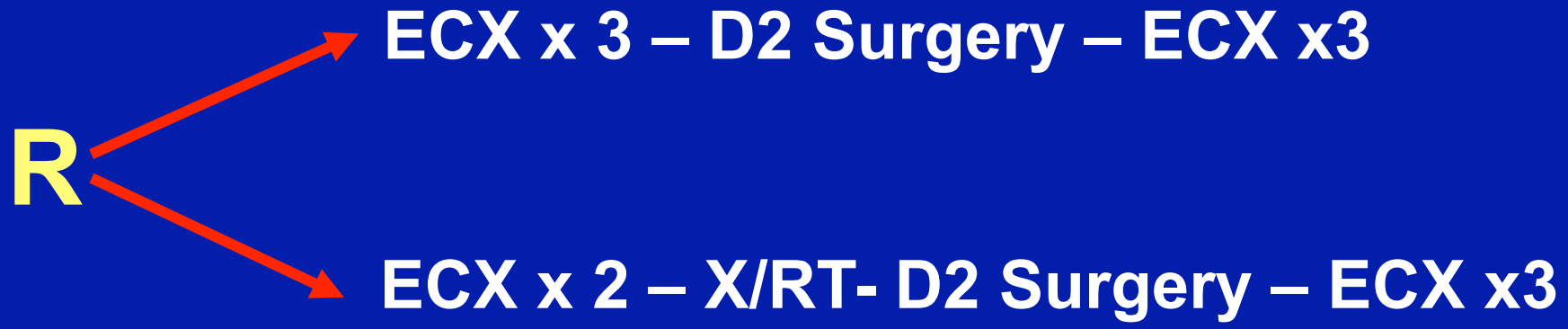
Surgery
Week 22

SURGERY +/- IORT
4-6 weeks after chemoradiotherapy

Path Response Rate
R0 Resection Rate
Treat Compliance

Preop CT vs Preop CT-RT
Ongoing EORTC Phase II Trial

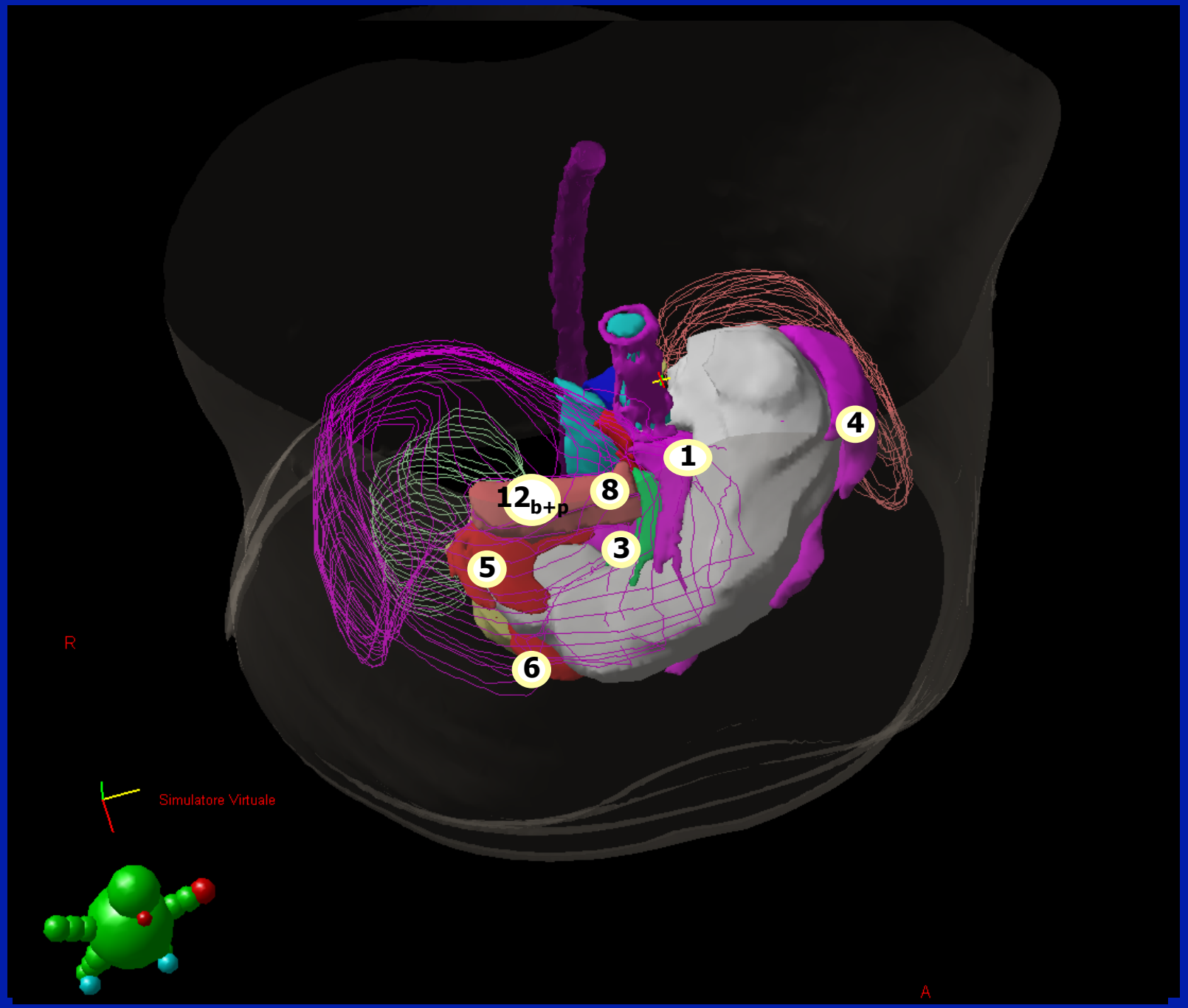
uT3-4 N0 and/or N+; Primary end-point: pCR,R0 rate



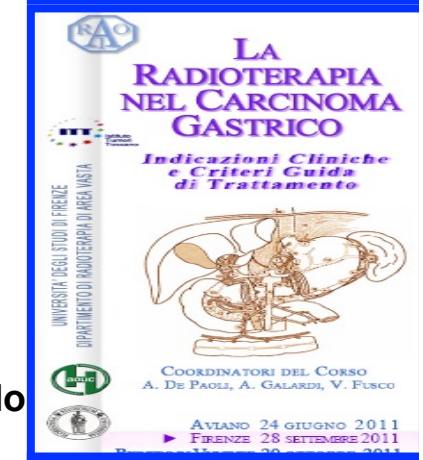
E: Epirubicyn, C: Cisplatin, X: Capecitabine

RT: 3D-CRT/IMRT 45Gy/25 fr

SURGERY week 12 -18


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

CENTRI PARTECIPANTI



Clinical Research in Gastric Cancer

Summary

- Post-op CT-RT in new CMT programs
  (US-INT, CRITICS Trial, ITACA-S2)
- Pre-op CT-RT new emerging approach
  (RTOG, EORTC, Italian Study)
- Optimal surgery is crucial
  (D2 LN dissection)
- Evolving role of RT is a major interest
  (New Drug-RT modalities;….Guidelines, QA programs !!)