Which Neoadjuvant Treament in GEJ ?

Pro Chemotherapy

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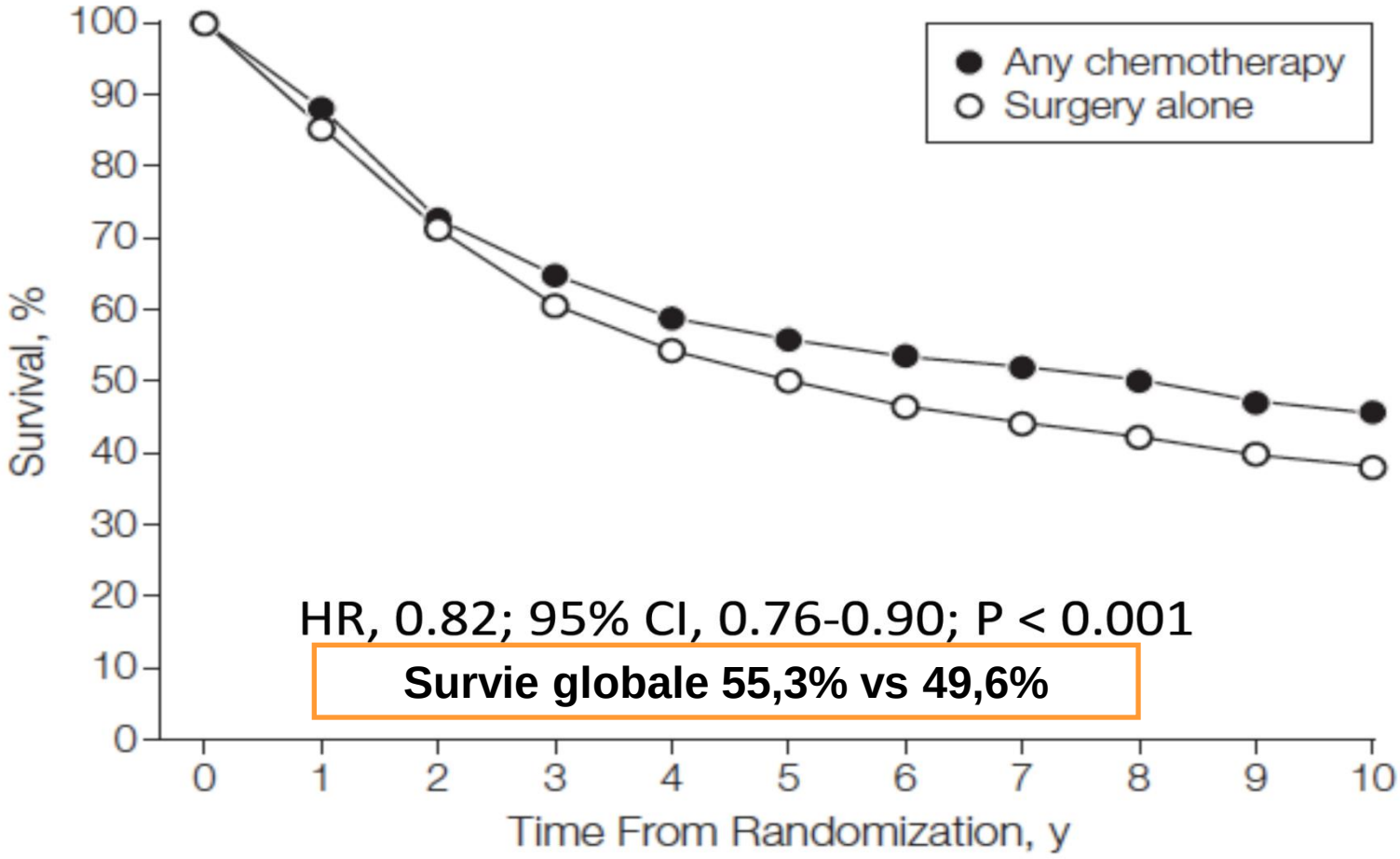
Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer

A Meta-analysis

JAMA, May 5, 2010—Vol 303, No. 17

R0 CT

GASTRIC Group
(Global Advanced/Adjuvant Stomach Tumor Research International Collaboration)



HR, 0.82; 95% CI, 0.76-0.90; P < 0.001

Survie globale 55,3% vs 49,6%

- 17 trials
- n=3838

No. at risk

Any chemotherapy	1924	1688	1385	1217	1080	929	709	526	390	297	243
Surgery alone	1857	1568	1300	1092	952	782	583	407	267	172	138

NEOADJUVANT CHEMOTHERAPY : ADVANTAGES

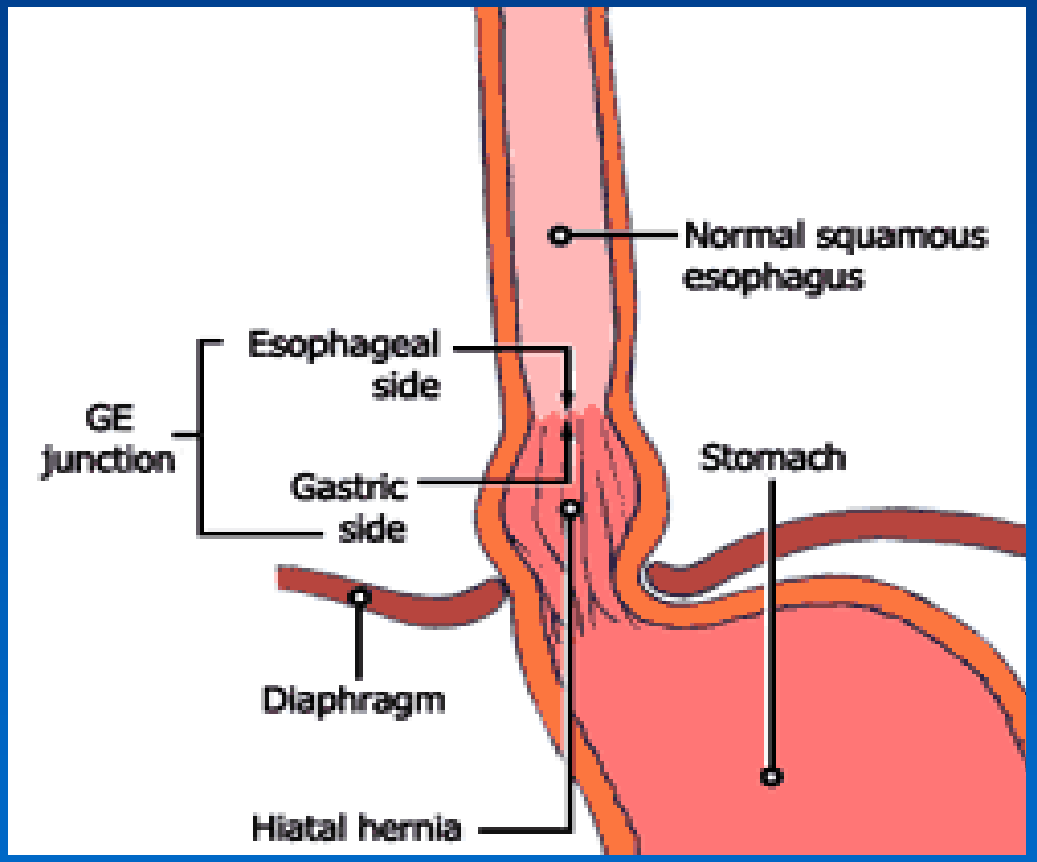
- Downstaging / Downsizing and improving of R0 resection
- To treat micrometastatic disease before surgery
- To evaluate chemosensitivity
- Better safety of chemotherapy before post-op morbidity

NEO-ADJUVANT CHEMOTHERAPY : RISKS

- Disease progression before Surgery
- To increase post-operative morbidity (and mortality ?)
- Difficulty of Response assessment on primary tumor

Gastroesophageal Junction Tumors: Classification and Treatment

- **Siewert Classification[1]**
  - Type I: lesions with center 1-5 cm proximal to the GE junction
  - Type II: lesions with center 1 cm proximal to and 2 cm distal to the GE junction
  - Type III: lesions with center 2-5 cm distal to the GE junction
    - Treated like gastric cancer



1. Siewert et al. *Ann Surg*. 2000.232:353.

Preoperative chemotherapy

Study	# Patients	Pathology	Chemotherapy	Tumor Location	5-year survival
MRC OEO-2, 2002	Chemo: 400 Surgery: 402	SCC, Adeno	Cisplatin/5-FU	G: 10% LE: 65%	Chemo: 23% Surgery: 17% P = 0.03
Cunningham *et al*, 2006	Chemo: 250 Surgery: 253	Adeno	ECF	G: 74% GE/LE: 26%	Chemo: 36% Surgery: 23% P = 0.001
Kelsen *et al*, 2007	Chemo: 233 Surgery: 234	SCC, Adeno	Cisplatin/5-FU	Esophagus	Chemo: 26% Surgery: 23% 3 y P = 0.53
Schumacher *et al*, 2010	Chemo: 72 Surgery: 72	Adeno	Cisplatin/5-FU	G: 49% GE: 51%	Chemo: 73% Surgery: 70% 2 y P = 0.46
Ychou *et al*, 2011	Chemo: 113 Surgery: 111	Adeno	Cisplatin/5-FU	G: 25% GE/LE: 75%	Chemo: 38% Surgery: 24% P = 0.001

MAGIC : Design

MAGIC
(Medical Research Council Adjuvant Gastric Infusional Chemotherapy)

N = 250

R

N = 253

ECF X 3 → 219 (88%) **Surgery** → **ECF X 3**

240 (95%) **Surgery**


The NEW ENGLAND JOURNAL of MEDICINE

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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. Lofts, 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 et al. NEJM 2006

FNCLCC -FFCD 9703: Design

N = 113

R

N = 111

FP* x 2 → 109 (96%) **Surgery** → **FP* x 4**

110 (99%) **Surgery**


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JOURNAL OF CLINICAL ONCOLOGY

Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial

Marc Ychou, Valérie Boige, Jean-Pierre Pignon, Thierry Conroy, Olivier Bouché, Gilles Lebreton, Muriel Ducourtieux, Laurent Bedenne, Jean-Michel Fabre, Bernard Saint-Aubert, Jean Genève, Philippe Lasser, and Philippe Rougier

Ychou et al. J Clin Oncol 2011

* FP = 5FU : 800 mg/m² CI x 5 Days -CDDP : 100 mg/m² D1 or D2 1 h

Characteristics of patients

	MAGIC		FNCLCC-FFCD	
	ECF n=250	S n=253	FP n=113	S n=111
Median Age (y) (range)	62 (29-85)	62 (23-81)	63 (36-75)	63 (38-75)
Sex: M (%)	82 %	76 %	85 %	82 %
WHO status 0/1	68/32	68/32	74/26	75/25
Stomach	74 %	74 %	25 %	24 %
LOG / Junction	26 %	26 %	75 %	76 %
Tumor size (cm)	5	5	4	4

Downstaging

	MAGIC			FNCLCC-FFCD		
pT, N (%)	**ECF**	S	p	FP	S	p
T1/T2	**52**	38	0.009	42	32	0.16
T3/T4	**48**	62		58	68	
N0/N1	**84**	76	0.01	(N0) 33	20	0.54
N2/N3	**16**	29		(N+) 67	80	

Resection rate R0

	MAGIC			FNCLCC-FFCD		
	ECF	S	p	FP	S	p
Resection R0 (%)	79%	70%	0.03	84%	73%	0.04

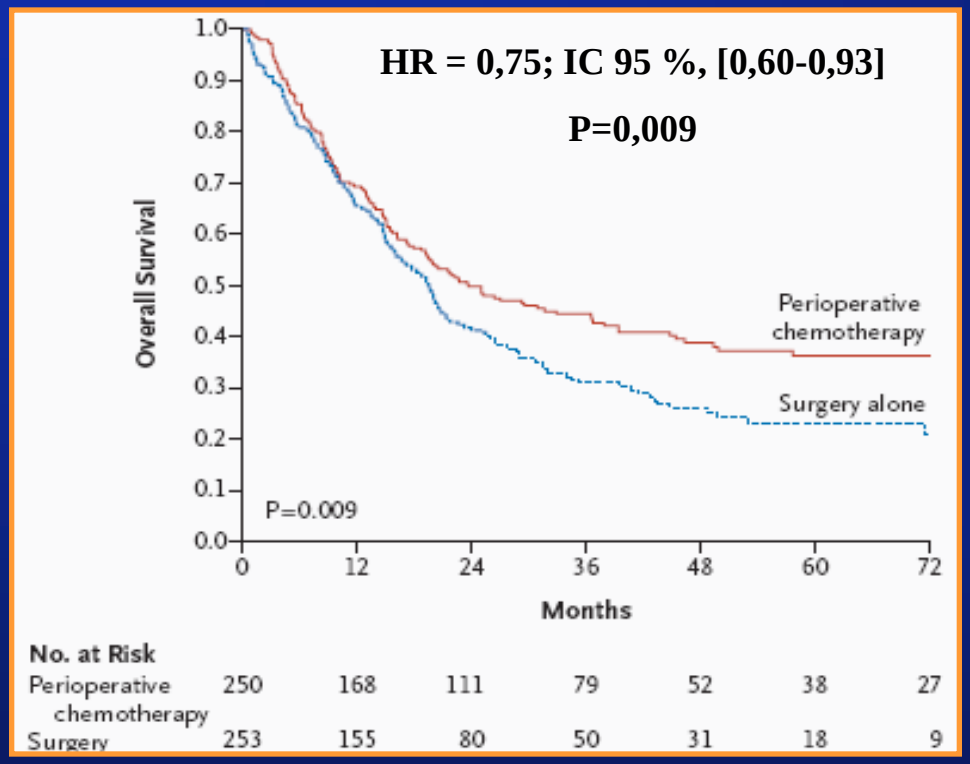
Haematologic toxicity

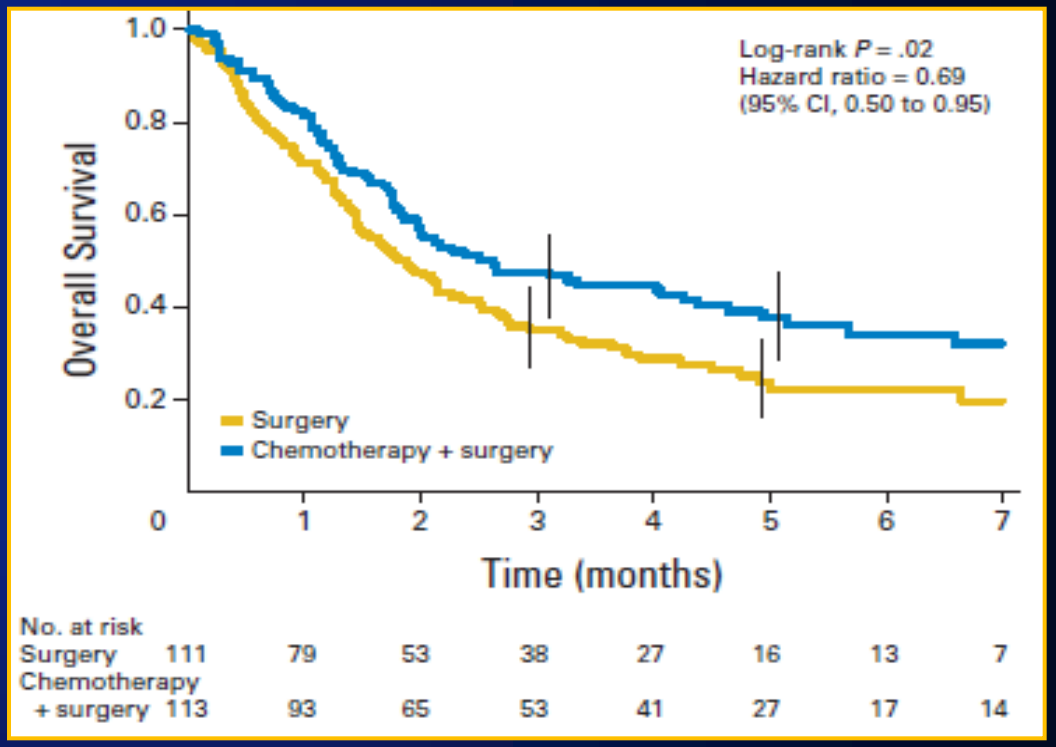
Grade ¾ (%)	ECF pre-op (MAGIC)	FP pre-op (FNCLCC-FFCD)
Complete pre-op CT	215 (86%)	109 (96%)
Neutropenia	24	20
Anemia	5	
Thrombopenia	< 1	5
Post-op CT	137 (55%)	54 (48%)

Recurrences

	MAGIC		FNCLCC-FFCD	
	ECF	S	FP	S
Local	**36 (14,5%)**	52 (20,6%)	14 (12%)	9 (8%)
Distant	**61 (24,4%)**	93 (36,8%)	49 (42%)	62 (56%)
Total	**39 %**	57 %	55 %	64 %

Overall survival





	MAGIC		FNCLCC-FFCD	
OS	**ECF**	**Surgery**	**FP**	**Surgery**
5-years	**36%**	**23%**	**38 %**	**24 %**
HR (p)	0,75 (p=0,009)		0,69 (p=0,002)	

Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: Systematic review with meta-analysis combining individual patient and aggregate data

U. Ronellenfitsch et al., EJC 2013

- 14 trials, 2422 pts
- 8 trials (1049 pts, 43.3%) with individual data
- Preop chemo associated with longer OS:
  - HR = 0.81, 95% CI 0.73-0.89, P<0.0001
  - 5y OS: 23% versus 32%
- Larger benefit for GE jonction and for ChemoRadiotherapy but NS
- Longer DFS, Higher R0 resection, downstaging
- No more post operative complications

PENDING QUESTIONS

- Can we combine perioperative chemotherapy and radiotherapy ?
  - *Pre-operative Radiochemotherapy for Gastroesophageal jonction adenocarcinomas ?*
  - Pre-operative Chemo combined with post-operative Radiochemotherapy

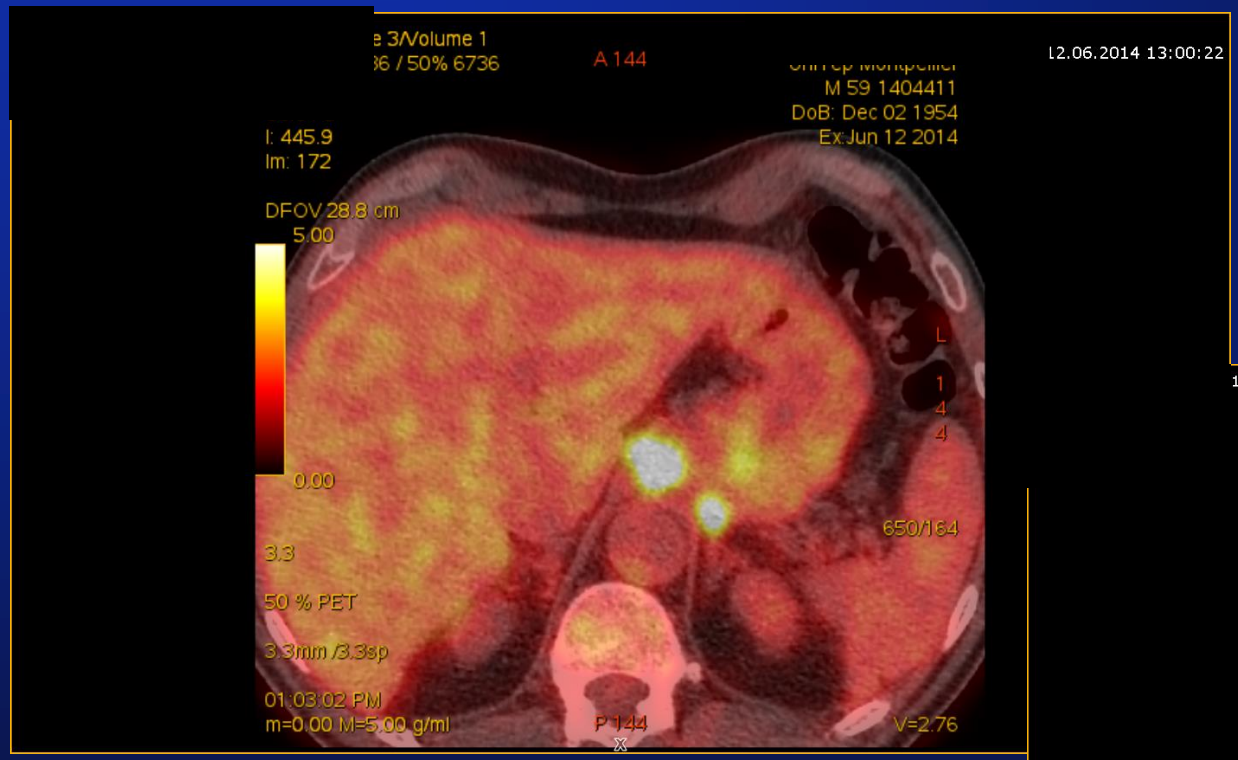
- Can we improve peri-operative chemotherapy ?
  - FOLFOX better tolerated than cisplatin based chemo
  - Intensification using Taxanes (FLOT regimen)

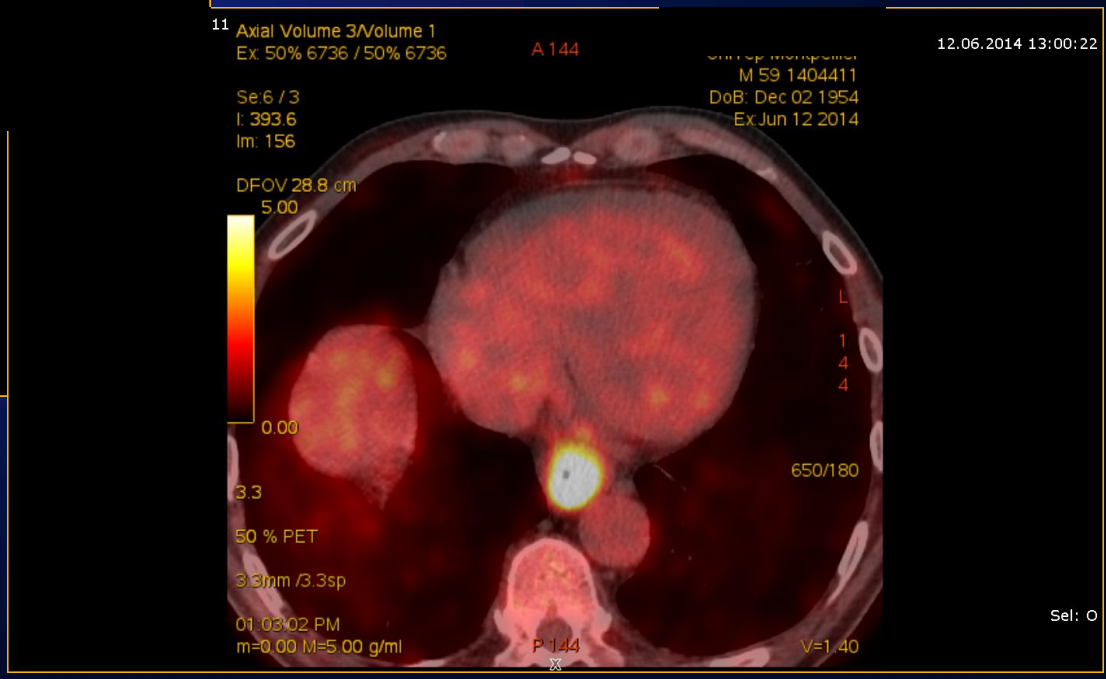
PENDING QUESTIONS

- Can we use Targeted Therapies ?
  - Trastuzumab for HER2 tumors
  - Disappointing results with Cetuximab and Bevacizumab in advanced desease
  - Hope with anti-cmet therapies

- Can we find early predictive markers of efficacy ?
  - Early assessment of response on Pet-scan
  - Biomarkers or molecular signatures on pre therapeutic biopsies

GEJ Adenocarcinoma, 10 cm, 65 years, no comorbidities: Peri-op CT or Pre-op RT-Ct ?





CONCLUSION : PRE-OPERATIVE MULTIDISCIPLINARY DECISION