Which Neoadjuvant Tx in GE Junction Ca?

Pro Chemo Radiotherapy

ESMO: 16th World Congress on Gastrointestinal Cancer

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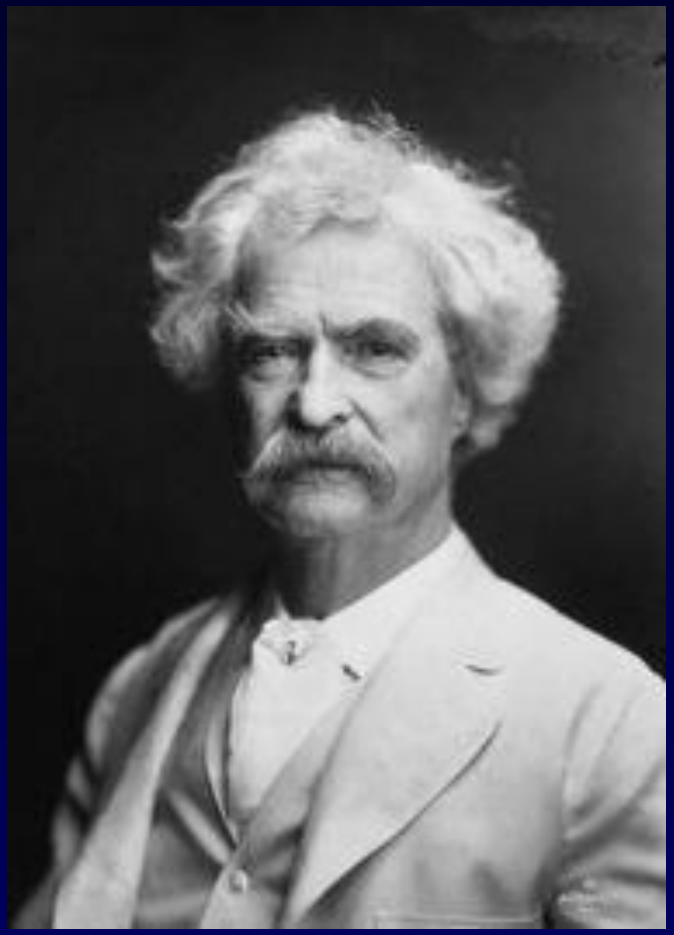
Disclosures: Section/Senior Editor: Up to Date, Cancer, Comprehensive Course in Radiation Oncology



I am not one of those who in expressing opinions confine themselves to facts

Mark Twain

Operable GEJ Cancer

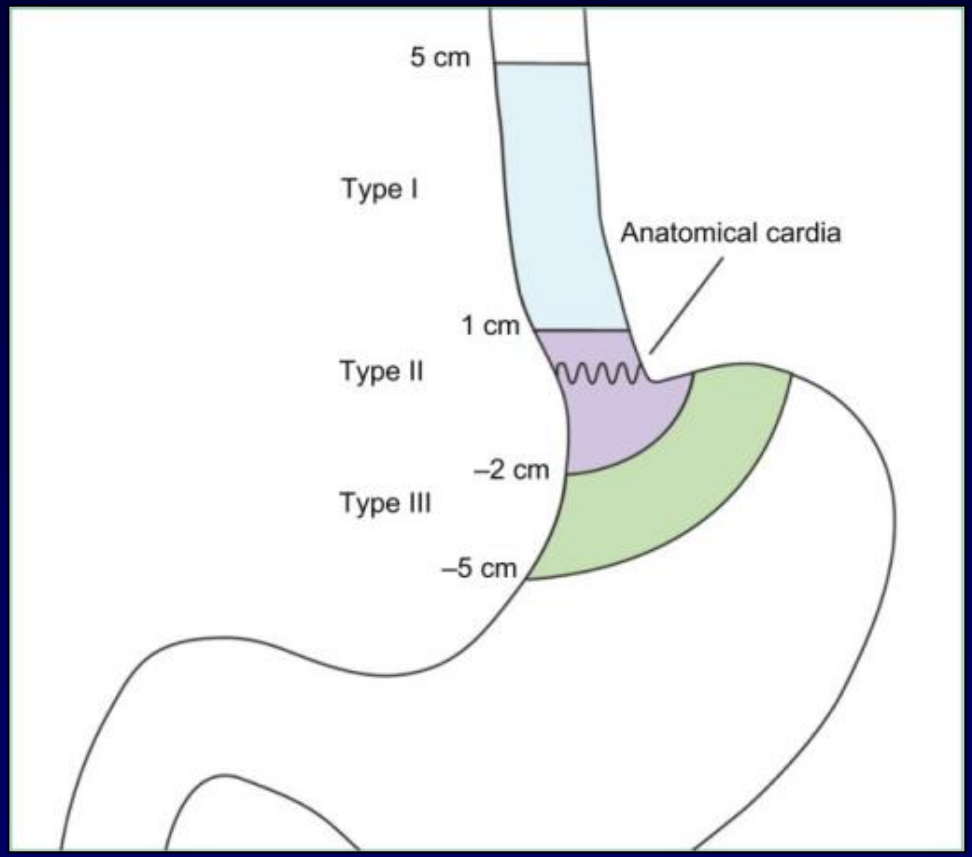
- Neoadjuvant ChT
- Perioperative ChT
- Neoadjuvant EBRT + ChT

Important Caveats

- Histology (SCC / Adenoca)
- Staging (Non-Uniform)
- Location (Distal Esophagus, GEJ, Stomach)
- GEJ: Siewart Classification

Siewart Classification: GEJ Carcinoma

- Type I: lesions with center 1-5 cm proximal to the GEJ
- Type II: lesions with center 1 cm proximal to and 2 cm distal to the GEJ
- Type III: lesions with center 2-5 cm distal to the GEJ



Operable Esophageal Ca: Neoadjuvant ChT

MRC (802 pts):

2 cycles of 5-FU/CDDP + S vs S alone

Intergroup 113 (440 pts):

3 cycles of 5-FU/CDDP + S vs S alone

MRC (OEO2)

	Pre-op CT	Surgery
R0 resection	**60%**	**54%**
Margin +	**29%**	**32%**
Post-op death	**9%**	**10%**
Median survival	**17 m**	**13 m**
2-year survival	**43%**	**34%**
5-year survival	**23%**	**17%**

Allum: JCO 2009

Intergroup 113

	Pre-op CT	Surgery
R0 resection	62%	59%
Margin +	14%	30%
Post-op death	6%	6%
LRF (R0 only)	32%	31%
Median survival	15 m	16 m
5-year survival	20%	20%

Kelsen JCO 2007

Periop Chemo: Distal Esophagus/GEJ/Gastric

Study	Pt #	R0 (%)	Med OS	OS5 (%)
MAGIC	503			
ECF→S→ECF		69	24 mo	36
S		66	20 mo	23
FNCLCC/ FFCD	224			
CF→S→CF		84	-	38
S		73	-	24

Perioperative ChT

- ± R0
- Improved PFS
- Improved OS

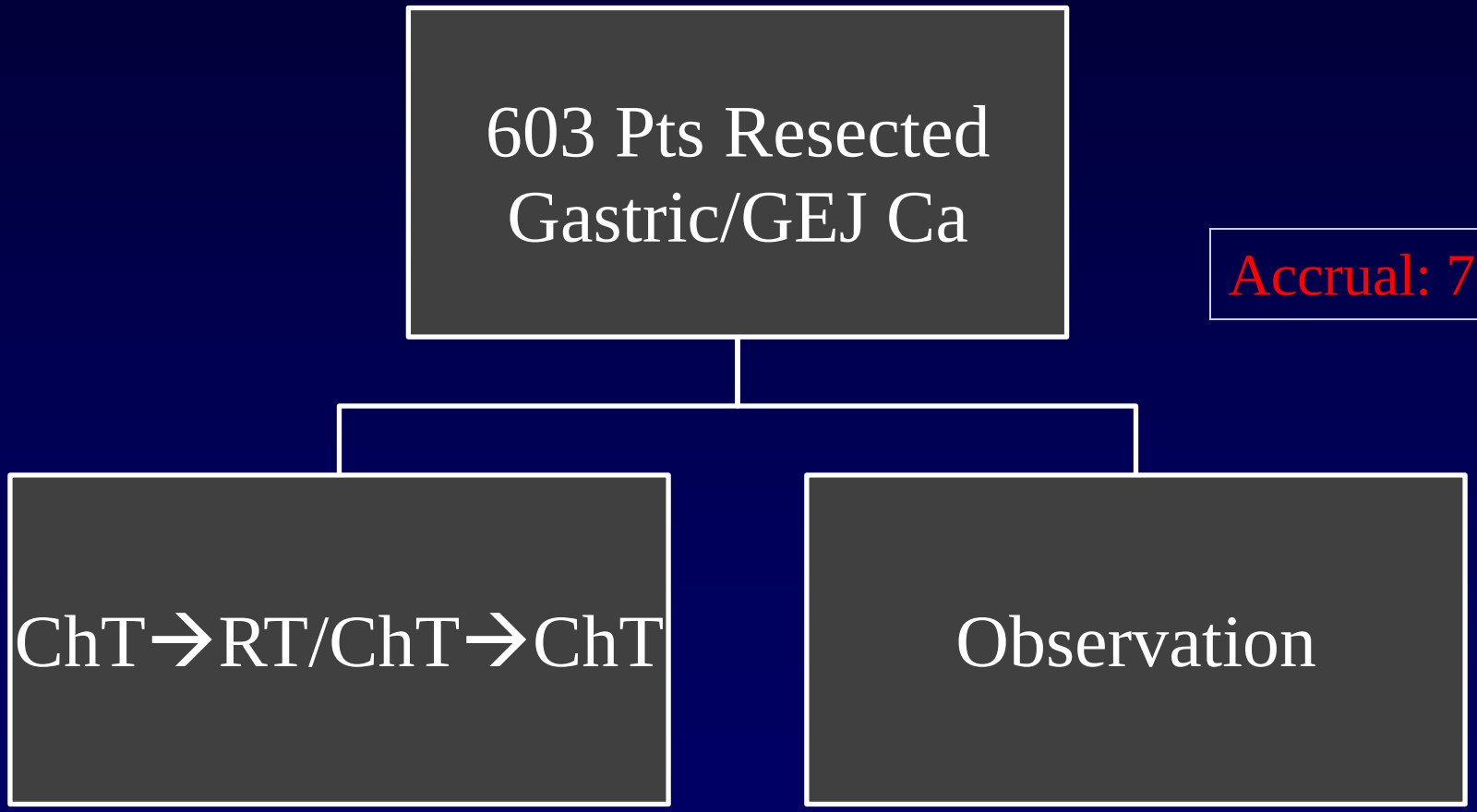
ChT Trials: Pattern of Failure Analysis

Study	TX	Pt #	Extent of Resection (%)	DM (%)	LF/RF (%)
Intergroup 113	ChT + S S	129 (R0) 126 (R0)	63 (R0) 59	41 43	27 29
MRC	ChT+S S	400 402	60 (R0) 54	24.2 19.4	18.7 16.7
MAGIC	ChT + S S	250 253	69.3 (Curative) 66.4	- -	- -
FNCLCC/ FFCD	ChT + S S	113 111	87 (R0) 74	42 56	24 26

Operable Esophageal Ca: Neoadjuvant/Perioperative ChT

- ChT: Modest impact
- ± Improvements in Extent of Resection and DM Rates
- No impact on LF/RF

Gastric/GEJ Ca: Postoperative ChT/EBRT (Intergroup 0116)



NEJM 2001 / J Surg Onc 2005

Gastric/GEJ Cancer: Postoperative ChT/EBRT (Intergroup 0116)

- ***20% GE Junction***
- Statistically ↑DFS (Tx): 49% vs 32%
- Statistically ↑OS (Tx): 52% vs 41%
- G3/4 Toxicity: 41% / 32%

Intergroup 0116: Patterns of Failure

	# Pts	Relapse (%)	LF/RF (%)	DM (%)
Adjuvant ChT/RT	281	52	24	16
Control	275	76	47	18

Smalley JCO 2012

Intergroup 0114: Conclusions

Adjuvant RT/ChT:

- Decreased LF/RF
- Decreased Overall Relapse Rates
- Improved OS

Esophageal Ca: Preop CMT Phase III Trials

Study	Median f/u (y)	3-yr Surv	Surv Difference
Urba (Mich)	5.6	CMT/S: 32% S alone: 15%	p=.07
Bosset EORTC	4.6	CMT/S: 33% S alone: 36%	NS
Walsh (Ire)	1.5	CMT/S: 32% S alone: 6%	p=.01
Burmeister (Aus)	5.4	CMT/S: 35% S alone: 31%	NS

Esophageal Ca: Preop CMT Phase III Trials

Study	Median f/u (y)	3-yr Surv	Surv Difference
Tepper CALGB	6.0	CMT/S: 39%* S alone: 16%	P=.002

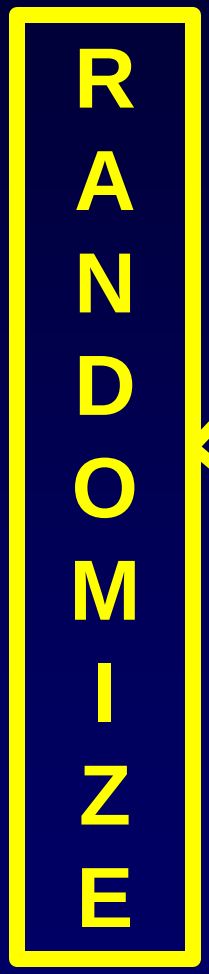
*5 yr data

CROSS Study

368 pts

Resectable esophageal/GE jxn cancer

T1N1, T2-3N0-1
(EUS Mandated)



CRT->Surgery
Carboplatin/Paclitaxel
41.4 Gy
N=178

Surgery alone
N=188

Primary endpoint: OS

Van Hagen et al NEJM 2012;366:2074

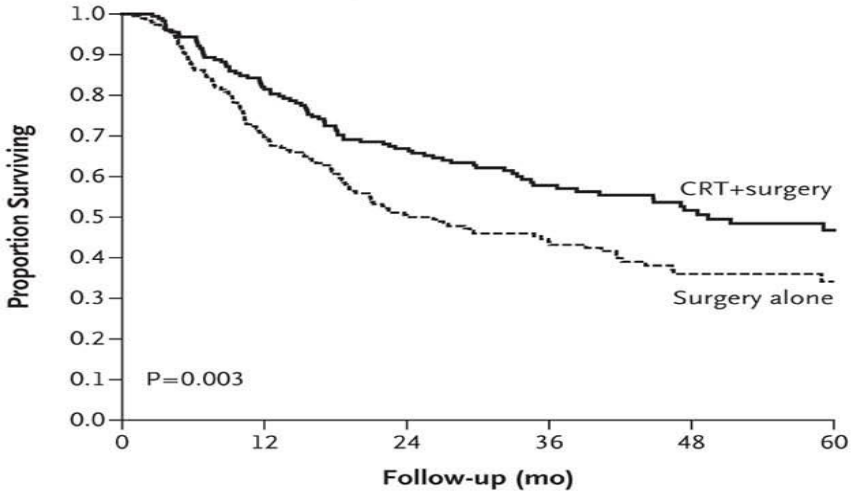
CROSS Study

	R0	Hosp Deaths	Anas Leak	pN+	Med OS
ChT/RT-Surg	92%*	4%	22%	31%*	49 mo*
Surg	69%	4%	30%	75%	24 mo

pCR: 29% CMT group (23% adeno, 49% SCC)

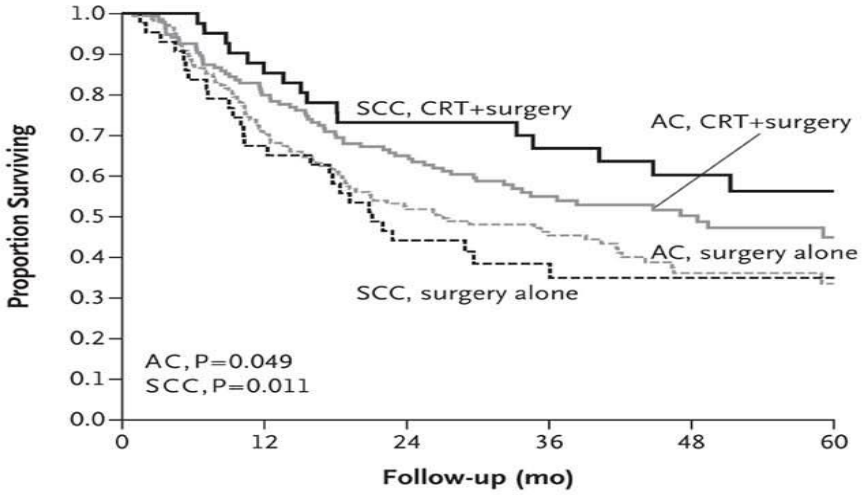
Van Hagen et al NEJM 2012;366:2074

A Survival According to 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

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

Cross Trial: Patterns of Failure

	# Pts.	LF/RF (%)	P.C. (%)	DM (%)
Neoadjuvant ChT/RT	213	14	4	29
Control	161	34	14	35

Oppedijk: JCO 2014

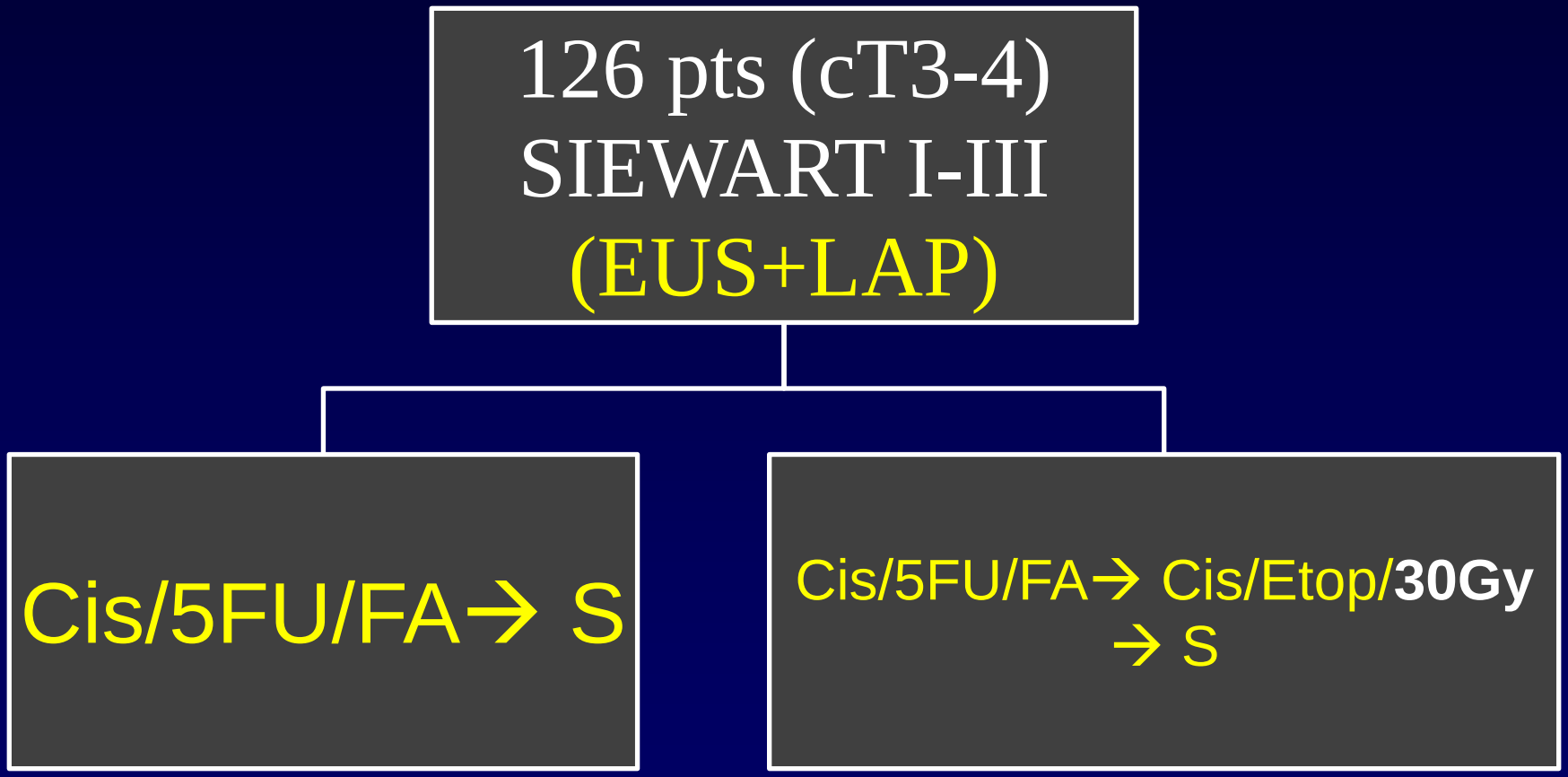
CROSS

Largest Randomized CMT+S vs S trial

CMT improves:

- R0 resection rates
- OS vs S alone
- W/O ↑ mortality
- LC/RF –> Enhanced OS

Operable Esophageal Ca: Neoadjuvant ChT vs Neoadjuvant CMT



Stahl: JCO 2009

Results: Neoadjuvant ChT vs Neoadjuvant CMT

Arm	Pts	R0	pCR	N0	Median Survival	3 yr OS	Local Control
Chemo	59	70%	2%	37%	21 mos	28%	59%
Chemo RT	60	72%	16%	64%	33 mos	47% P = 0.07	77% P = 0.06

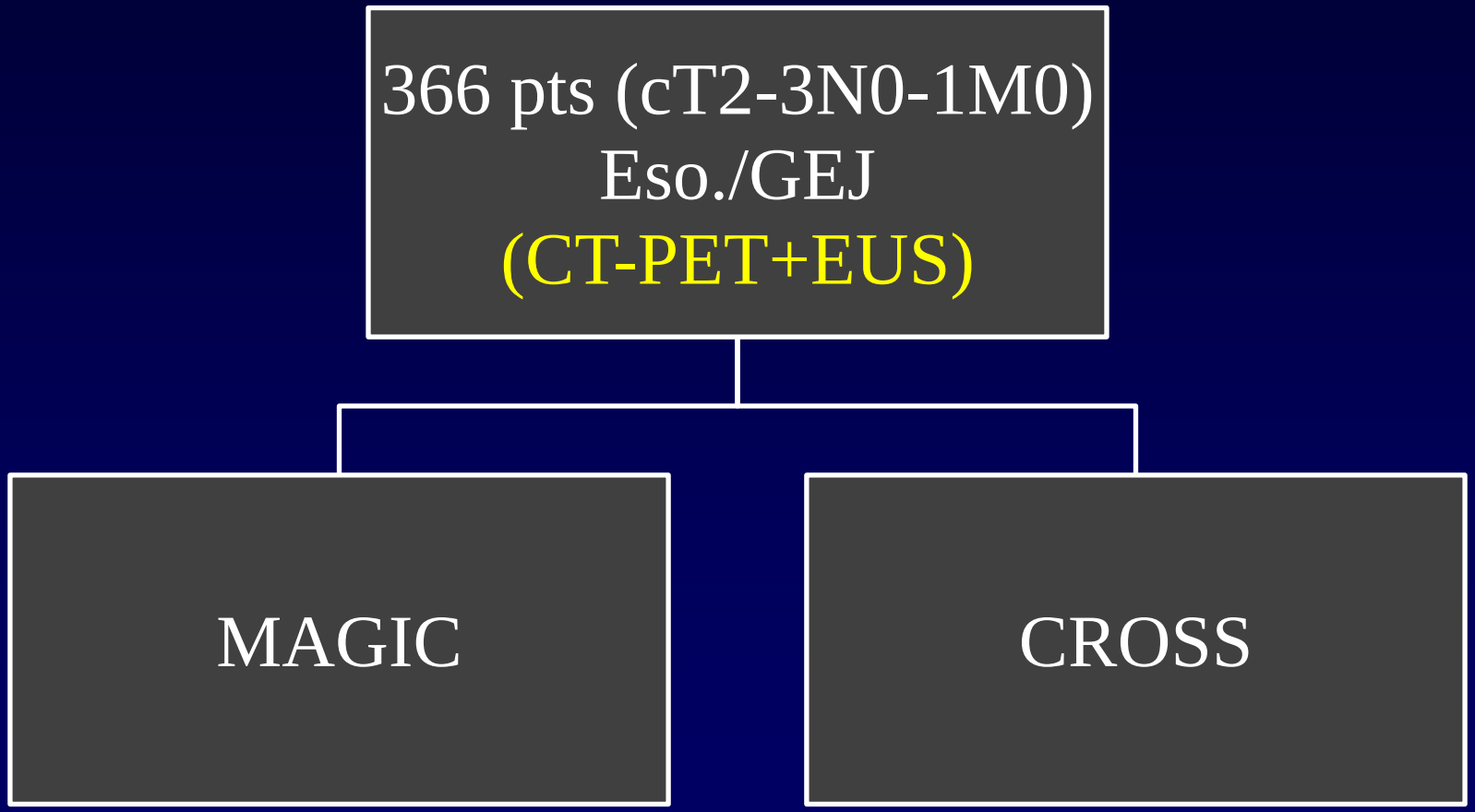
Stahl: JCO 2009

Operable Esophageal Ca: Neoadjuvant ChT vs CMT

Conclusions: Preop CMT improves OS vs chemo only in locally advanced esophagogastric adenoca

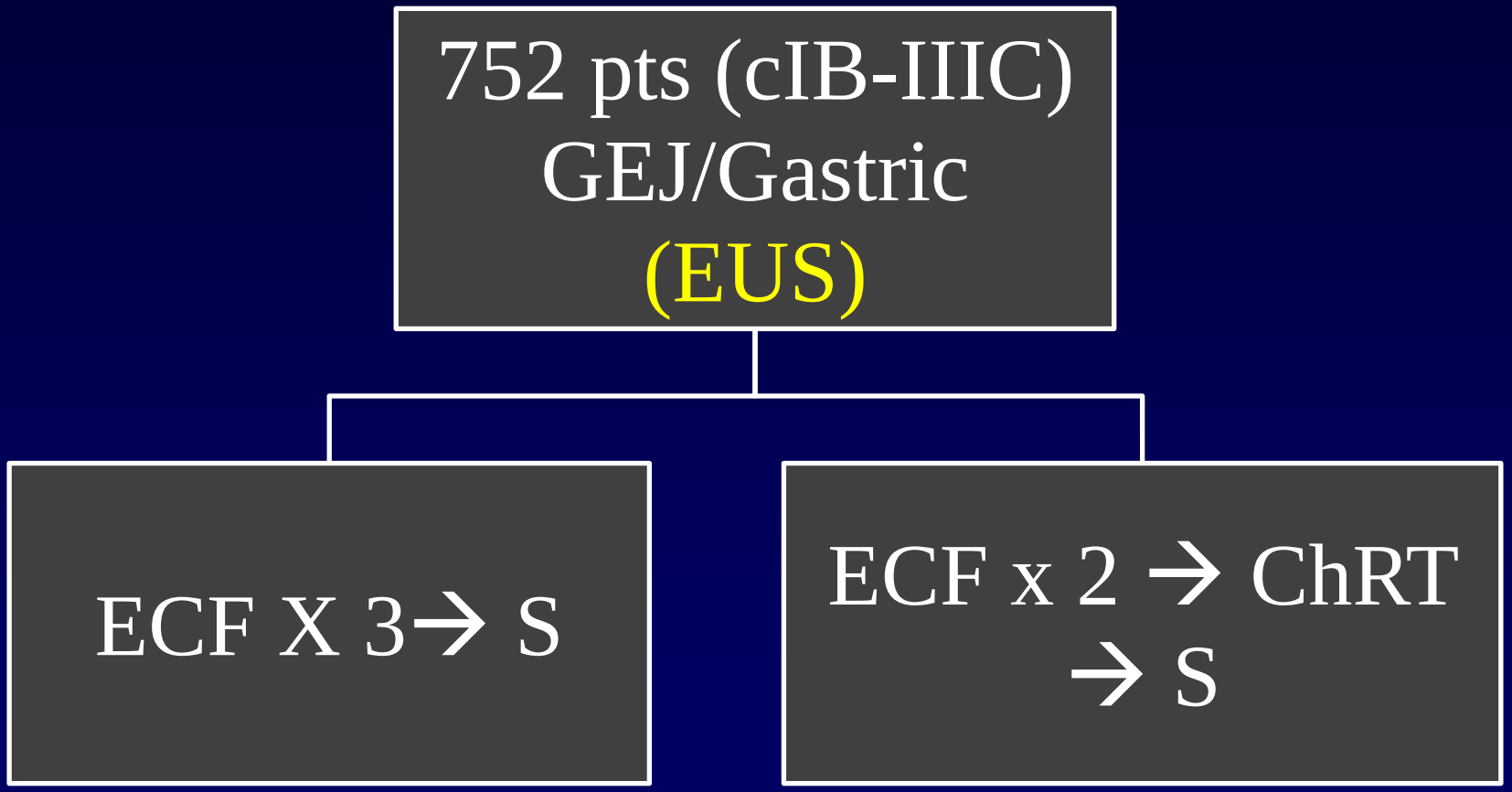
Stahl JCO 2009

ICORG: Esophageal/GEJ Adenocarcinoma



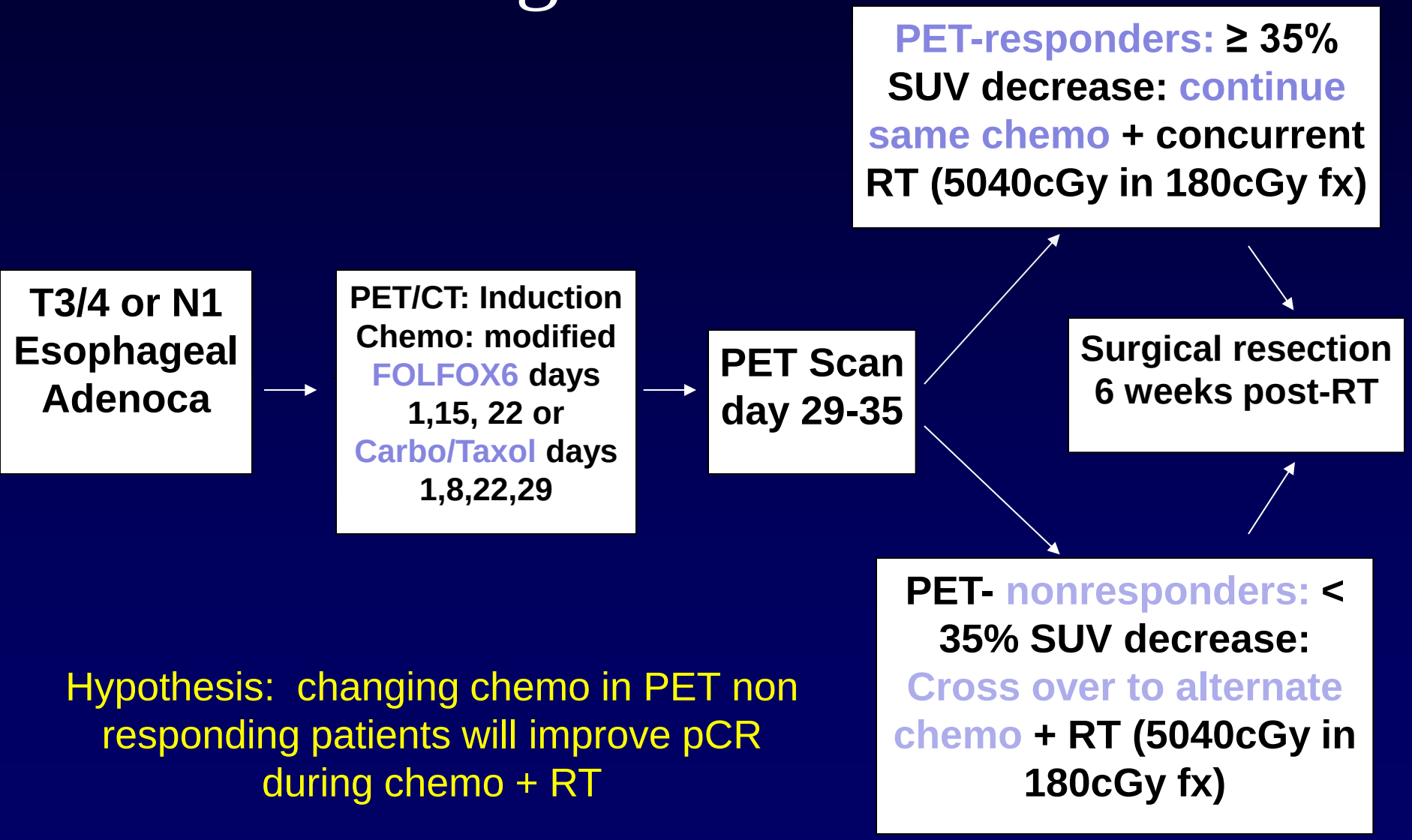
Clinical Trials.gov (2012)

TOPGEAR: Siewart's II/III GEJ and Gastric Adenocarcinoma



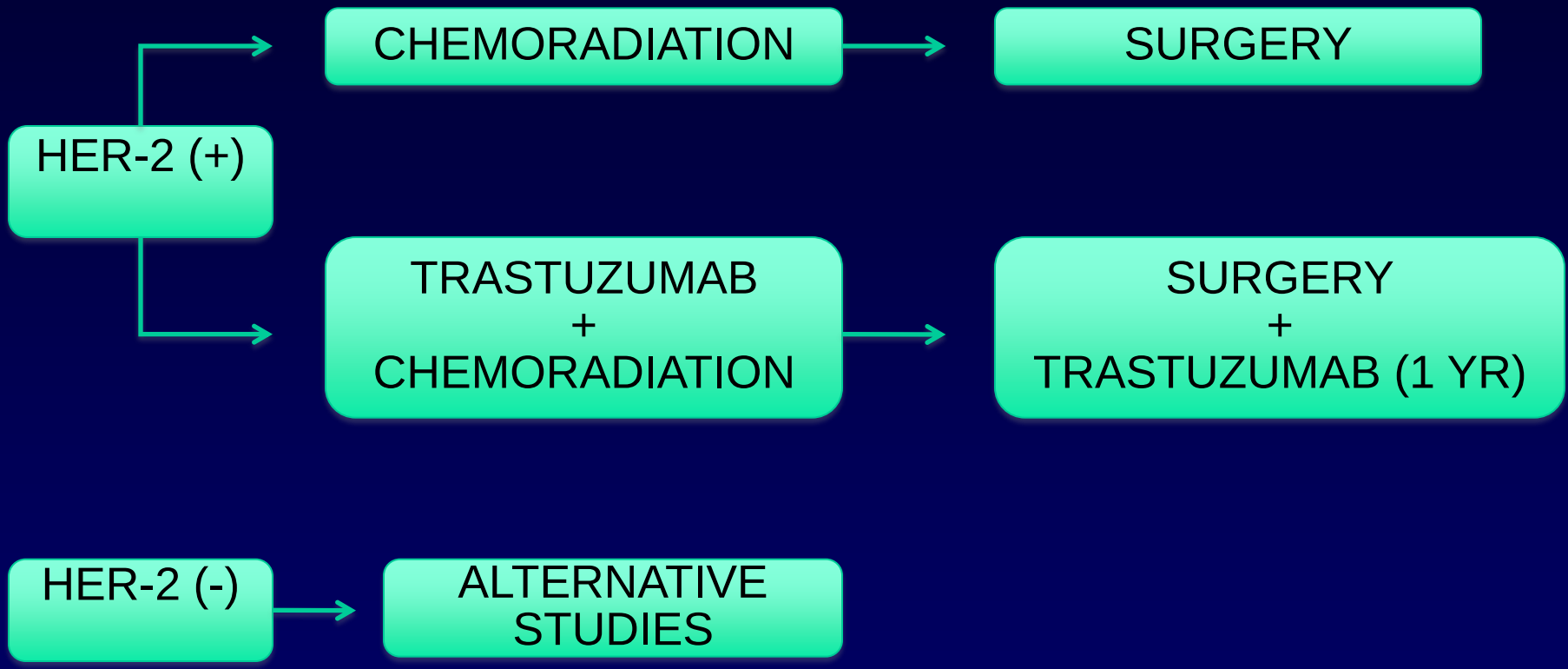
Clinical Trials.gov (2009)

PET Scan Directed Therapy Trial Design: CALGB 80803



Hypothesis: changing chemo in PET non responding patients will improve pCR during chemo + RT

RTOG 1010: Phase III Study of Neoadjuvant Trastuzumab and Chemoradiation for Esophageal Adenocarcinoma



H. Safran – P.I.

Conclusions

- Neoadjuvant RT/ChT improves LC/RF and enhances Survival
- Neoadjuvant/Perioperative ChT: Improves Survival by ↑ Extent of Resection and ↓ DM
- The Reality: Both are required and efficacious