



Grand'angolo in radioterapia oncologica Gastro-Intestinale

Maria Antonietta Gambacorta

Università Cattolica del Sacro Cuore

Roma



RECTAL CANCER

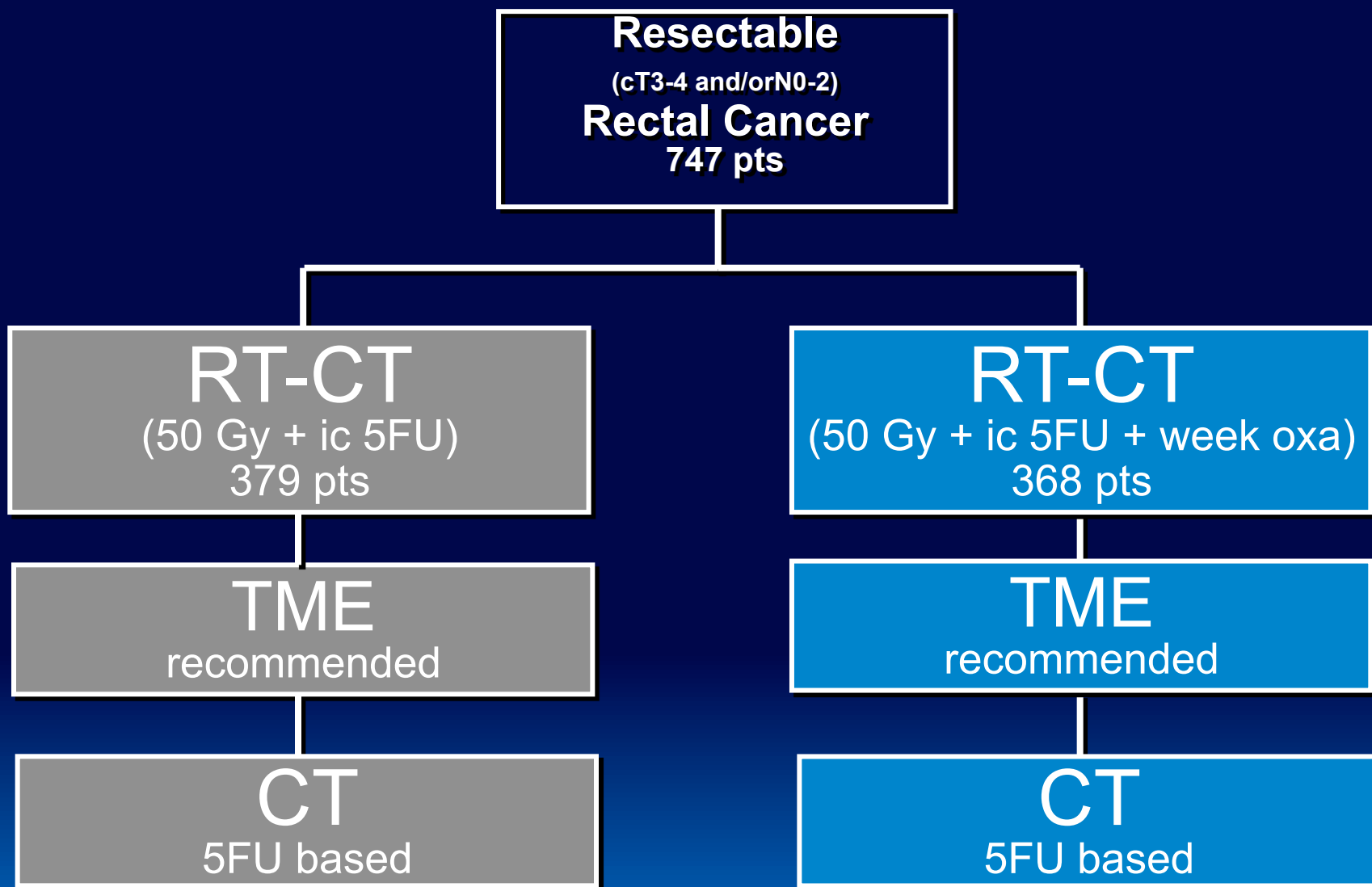
Oxaliplatin in preop RT-CT

Yes or Not?



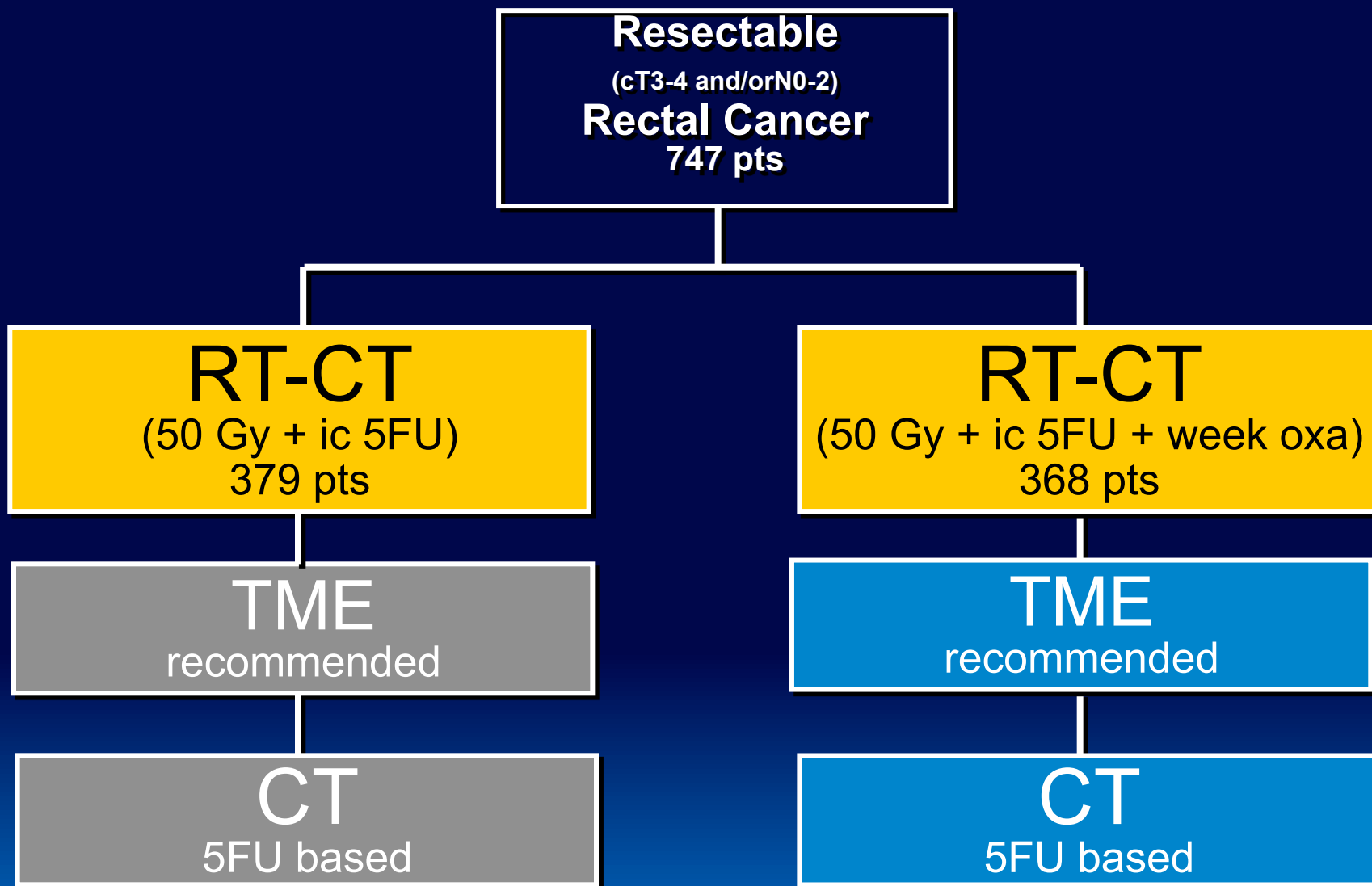
STAR Trial

Studio **A**diuvante **T**erapia **R**etto



STAR Trial

Studio **A**diuvante **T**erapia **R**etto



STAR Trial

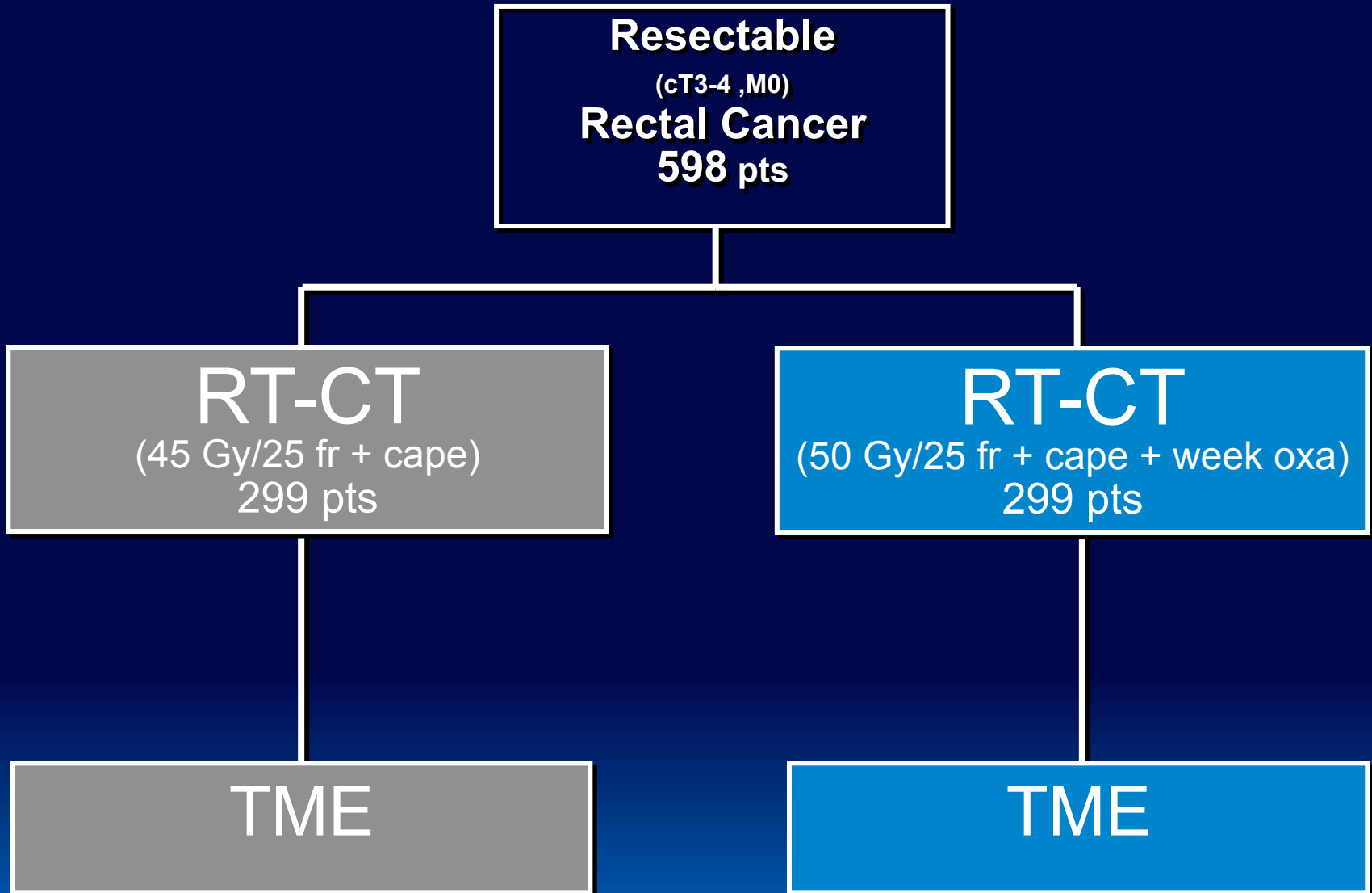
Studio **A**diuvante **T**erapia **R**etto

	RT - 5FU	RT-5FU-oxa
pCR	16 %	16 %

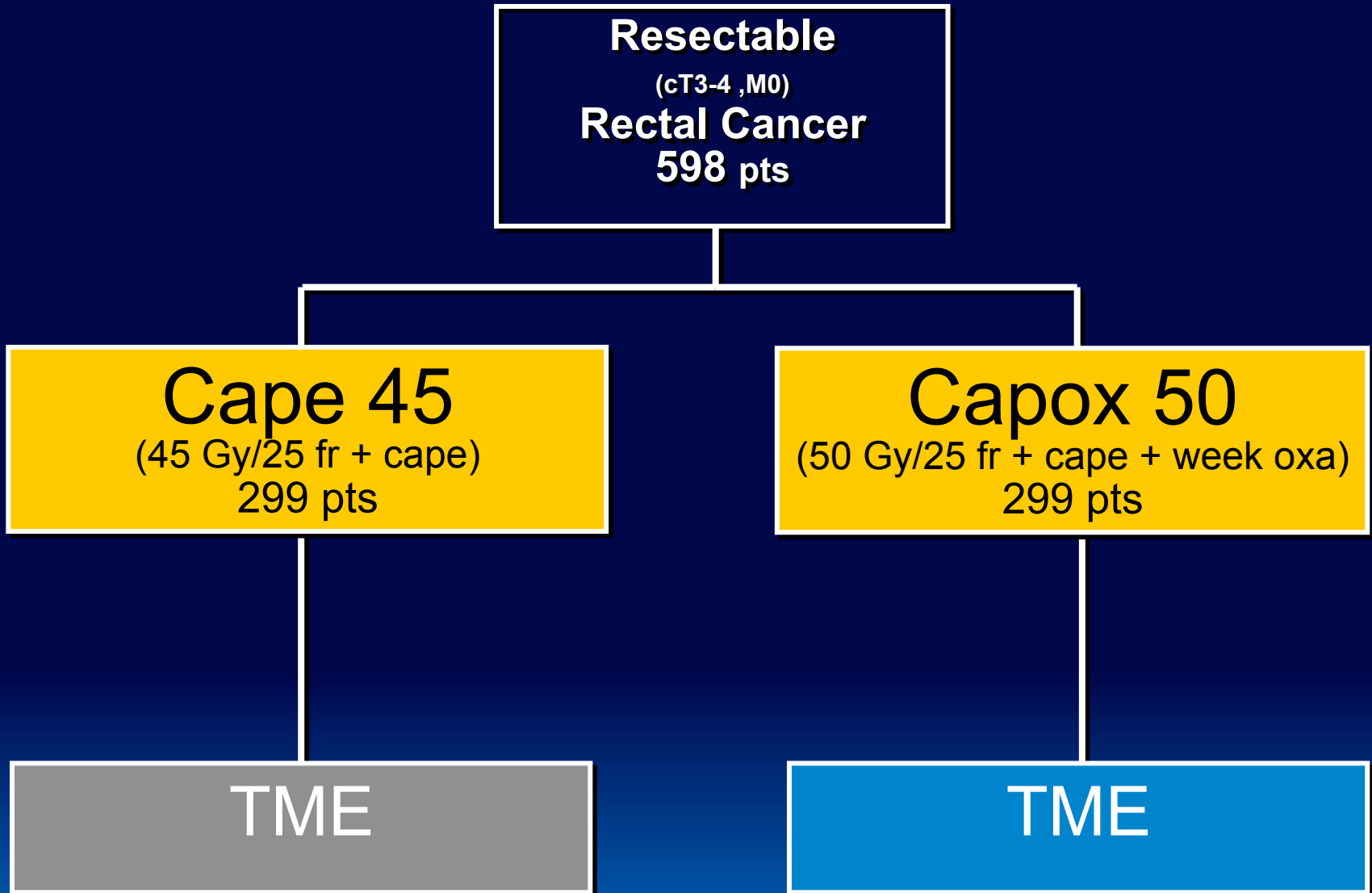
$p = 0.904$



ACCORD Trial



ACCORD Trial



ACCORD trial

	CAPE 45	CAPOX 50
pCR	13.9 %	19.2 %

$p = 0.09$



ACCORD trial

Acute toxicity	Cape 45	Capox 50	p
all	10.9	25.4	< 0.001
diarrhea	3.2	12.6	< 0.001
haematologic	3.7	4.8	ns
fatigue	0.8	5.1	0.004
dermatitis	0.4	1.4	ns
peripheal neuropaty	0.4	5.1	0.002
H & F syndrom	0.8	0	ns

ACCORD trial

Acute toxicity	Cape 45	Capox 50	p
all	10.9	25.4	< 0.001
diarrhea	3.2	12.6	< 0.001
haematologic	3.7	4.8	ns
fatigue	0.8	5.1	0.004
dermatitis	0.4	1.4	ns
peripheal neuropaty	0.4	5.1	0.002
H & F syndrom	0.8	0	ns

STAR trial: acute tox

Acute toxicity	RT-5 FU	RT – 5FUoxa	p
all	8	24	< 0.001
diarrhea	4	15	< 0.001
anemia	0.5	0	ns
fatigue	0	3	< 0.001
dermatitis	2	5	0.037
neurosensory	0	1	0.026

STAR trial: acute tox

Acute toxicity	RT-5 FU	RT – 5FUoxa	p
all	8	24	< 0.001
diarrhea	4	15	< 0.001
anemia	0.5	0	ns
fatigue	0	3	< 0.001
dermatitis	2	5	0.037
neurosensory	0	1	0.026

STAR trial: compliance

Treatment	RT-5 FU	RT – 5FUoxa	p
RT 50 Gy	92	84	< 0.001
RT 45 Gy	97	91	< 0.001
5FU 80% dose	90	80	< 0.001
Oxaliplatin 6 wks		69	

STAR trial: compliance

Treatment	RT-5 FU	RT – 5FUoxa	p
RT 50 Gy	92	84	< 0.001
RT 45 Gy	97	91	< 0.001
5FU 80% dose	90	80	< 0.001
Oxaliplatin 6 wks		69	

NSABP R04 TRIAL

Stratify:

Participating center

Clinical Tumor Staging (stage II vs III)

Surgical Intent

(sphincter-saving vs non-sphincter-saving)

RANDOMIZE

1608 pts

Arm I:

225mg/m²/d 5-FU + RT (d1-5)

RT5-FU /cape

Arm III:

825 mg/m² PO bid C + RT (d1-5)

Arm II:

225 mg/m²/d 5-FU + RT (d1-5) +
50 mg/m² Ox (d1)

RT-oxa-5FU/cape

Arm IV:

825 mg/m² PO bid C + RT (d1-5)
+ 50 mg/m² Ox (d1)

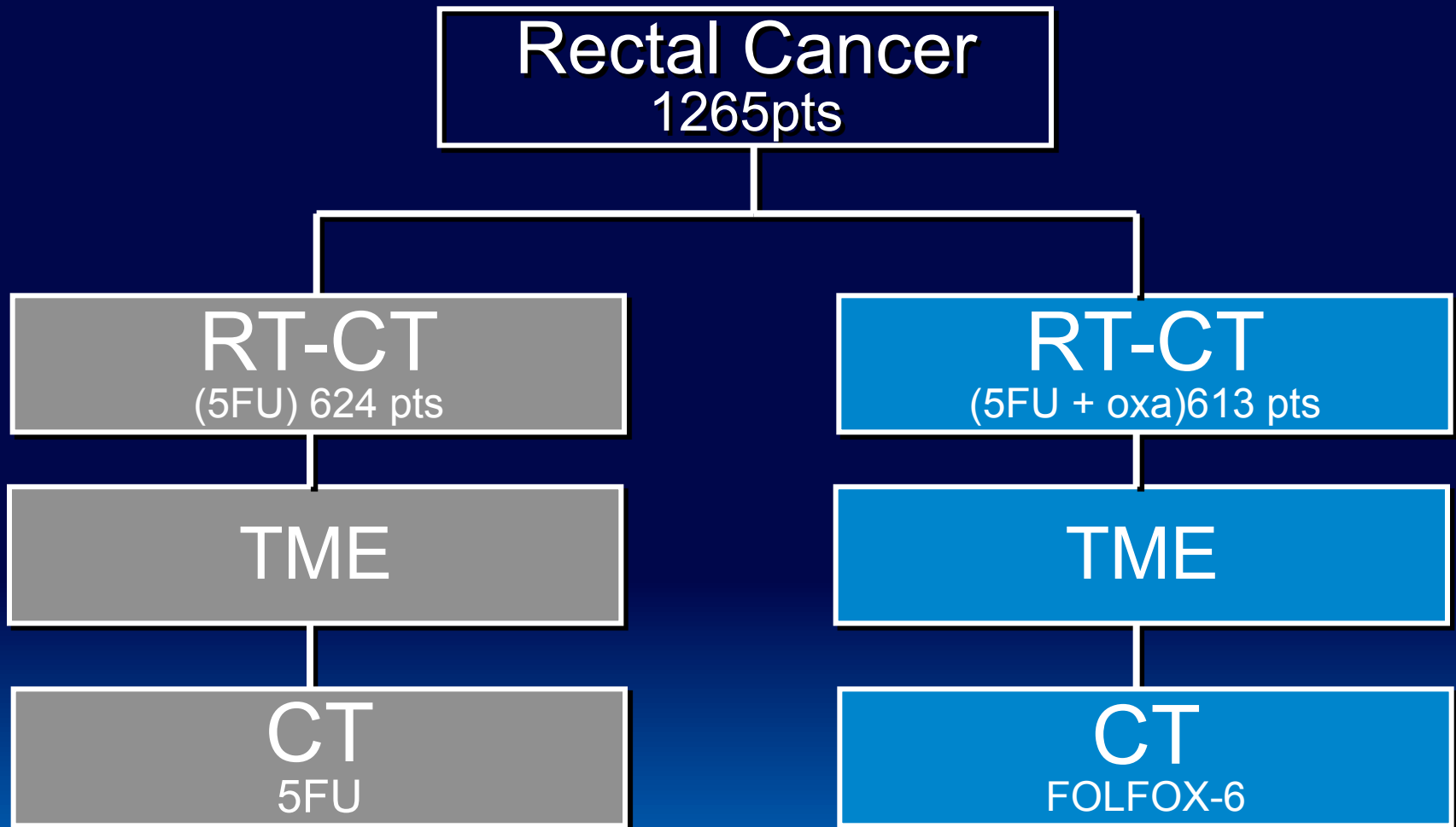
SURGERY

NSABP R04 TRIAL

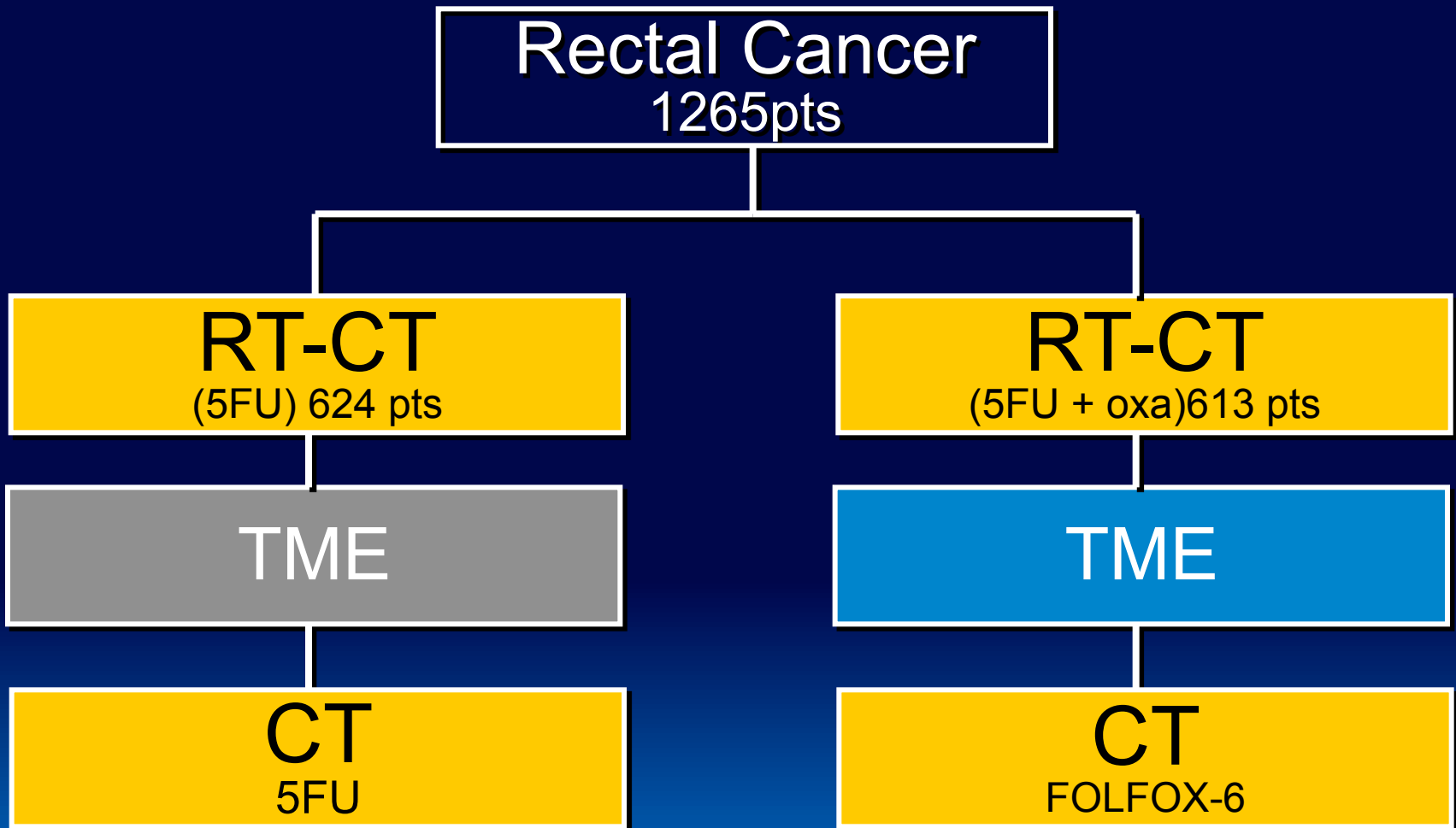
Endpoint	(FU or CAPE) No OX	(FU or CAPE) + OX	P value
pCR	111/580 = 19.1%	121/578 = 20.9%	0.46
SSS	370/582 = 63.6%	353/584 = 60.4%	0.28
SD	35/152 = 23.0%	29/151 = 19.2%	0.48
Grade 3/4 diarrhea	41/622 = 6.6%	97/631 = 15.4%	< 0.0001



German Trial (CAO-ARO-AIO-04)



German Trial (CAO-ARO-AIO-04)



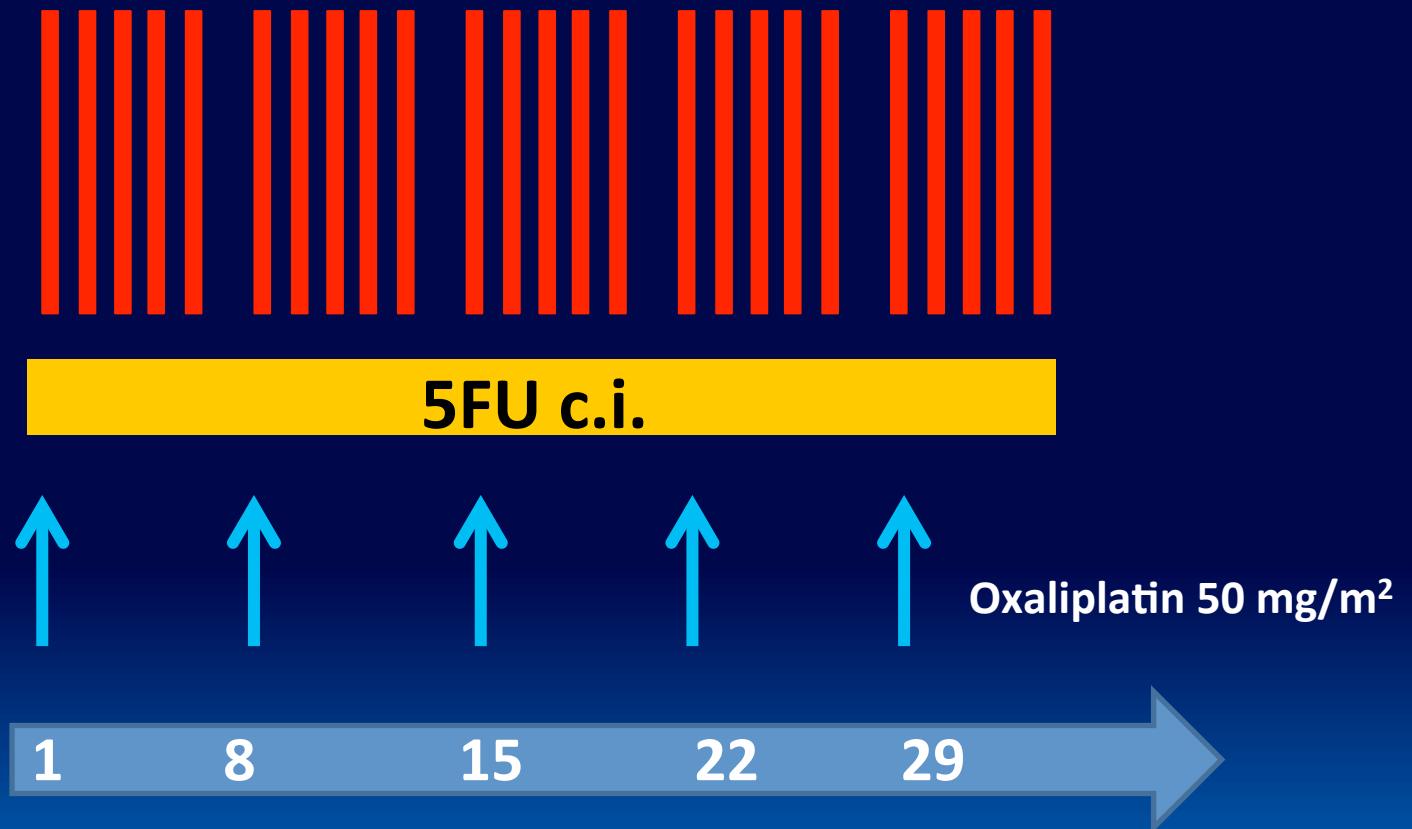
German Trial (CAO-ARO-AIO-04)

	RT-5FU	RT-5FU- oxa	p
pCR	12.8%	16.5%	0.045
Full RT dose	95%	94%	n.s.
Full CT dose	80%	85%	n.s.

German Trial (CAO-ARO-AIO-04)

	RT-5FU	RT-5FU- oxa	p
pCR	12.8%	16.5%	0.045
Full RT dose	95%	94%	n.s.
Full CT dose	80%	85%	n.s.

German Trial (CAO-ARO-AIO-04)



OXALIPLATIN ARMs

	pCR	Acute G3+ GI tox	RT compliance	5FUCT compliance
STAR	16	15	84	69
ACCORD	19.2	12.6	87	41
NASBP R04	20.9	15.4	na	na
CAO-ARO- AIO 04	16.5	na	94	85

OXALIPLATIN ARMs

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RECTAL CANCER

Oxaliplatin in preop RT-CT

increased pCR controversial

50 Gy pCR > 16%

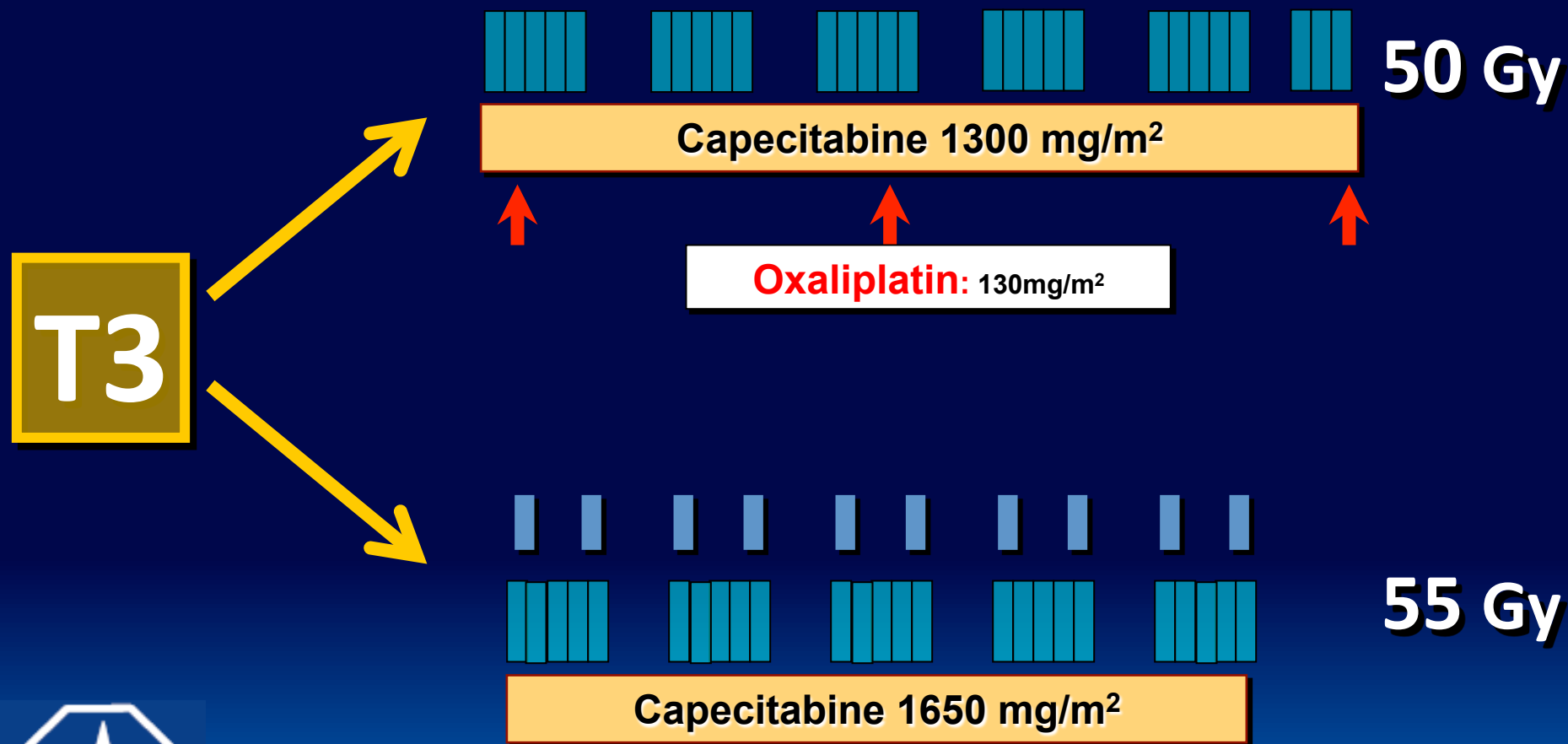
oxa: acute tox ↓ dose RT ↓ dose CT

Awaited LC, MFS, DFS, OS

pCRM -, M+ @ surgery

INTE.R.A.CT

250/616 enrolled



RECTAL CANCER

SURVIVAL



Pre-op RT alone: pre TME

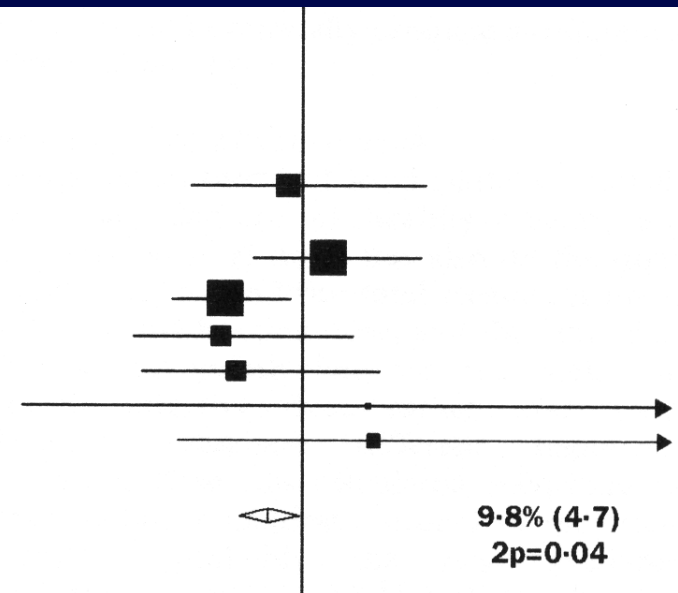
3 Meta-analysis

SBU – systematic overview

Biologically effective dose > 30 Gy

BED ≥30 Gy

1963 Yale ¹¹	46/23; 40.8	../15	../16
1972 Rotterdam A ¹²	34.5/15; 34.6	../50	../50
1973 RTOG 7203/40 ^{6*}	40–46/22; 36.2	../17	../19
1976 EORTC-40761 ¹³	34.5/15; 34.6	121/236	125/230	-2.3	53.3
1978 São Paolo ¹⁴	40/20; 36.0	../34	../34
1980 Stockholm I/II ^{15,16}	25/5; 37.5	306/502	306/517	9.5	129.1
Swedish RCT ¹⁷	25/5; 37.5	290/581	329/584	-34.2	133.8
1981 UK MRC 2 ¹⁸	40/20; 36.0	98/139	110/140	-10.7	39.4
1982 NW England ¹⁹	20/4; 30.0	100/143	97/141	-8.1	37.9
1984 PMH Toronto ²⁰	45/25; 36.9	4/9	4/12	0.3	1.8
1984 SGSTCIRC Japan ²¹	30/15; 30.6	41/90	31/76	3.0	16.1
Subtotal with data		960/ 1700 (56.5%)	1002/ 1700 (58.9%)	-42.3	411.4



Cammà C et al. *Jama* 2000

Colorectal CC Group, *Lancet* 2001

Glimelius B et al, *Acta Oncol* 2002

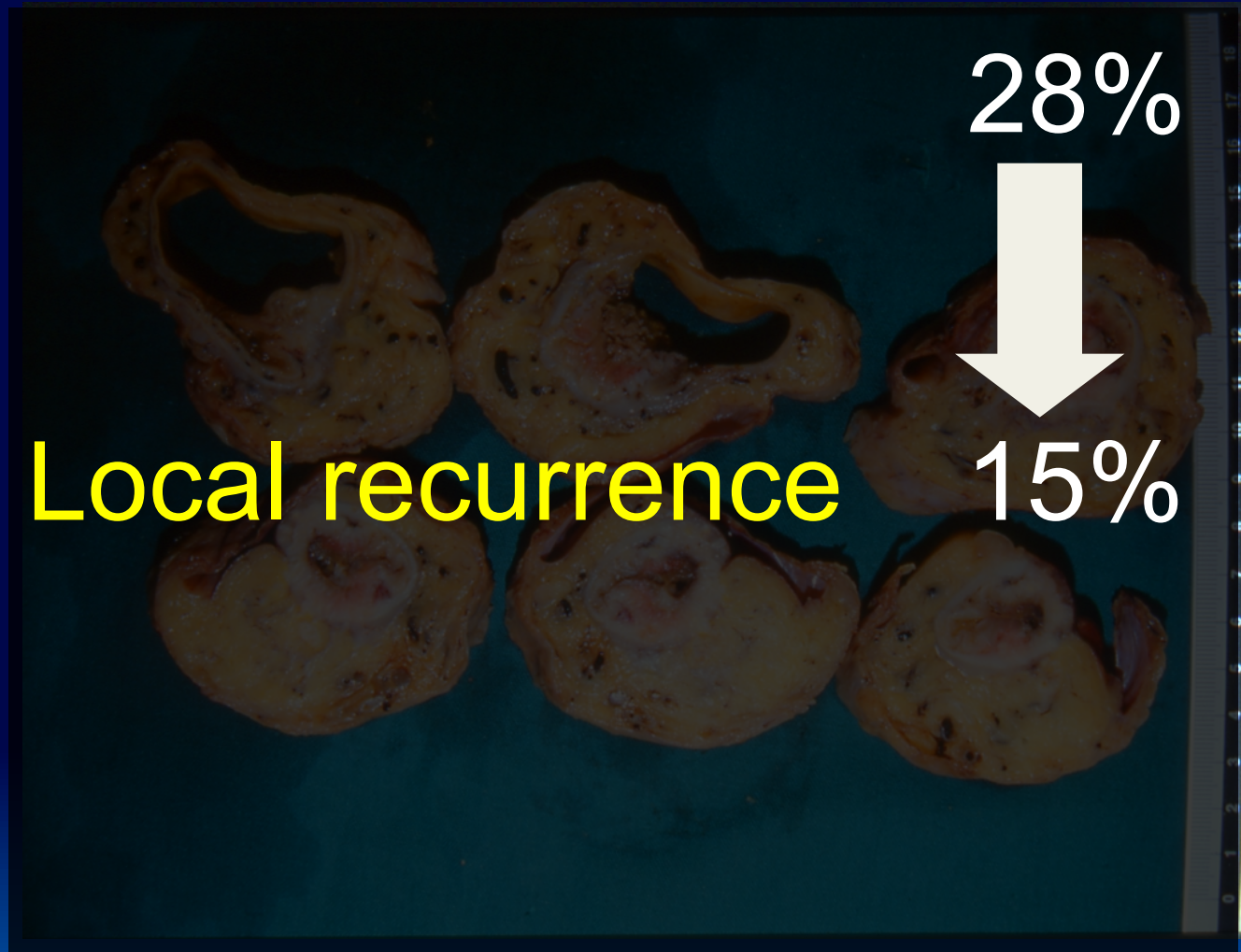
Pre-operative RT pre TME: Local Control & SURVIVAL

Sweden trial: 1168 pts

Local rel. gain	27 % → 11%	16%
Survival gain	58 % → 48%	10%

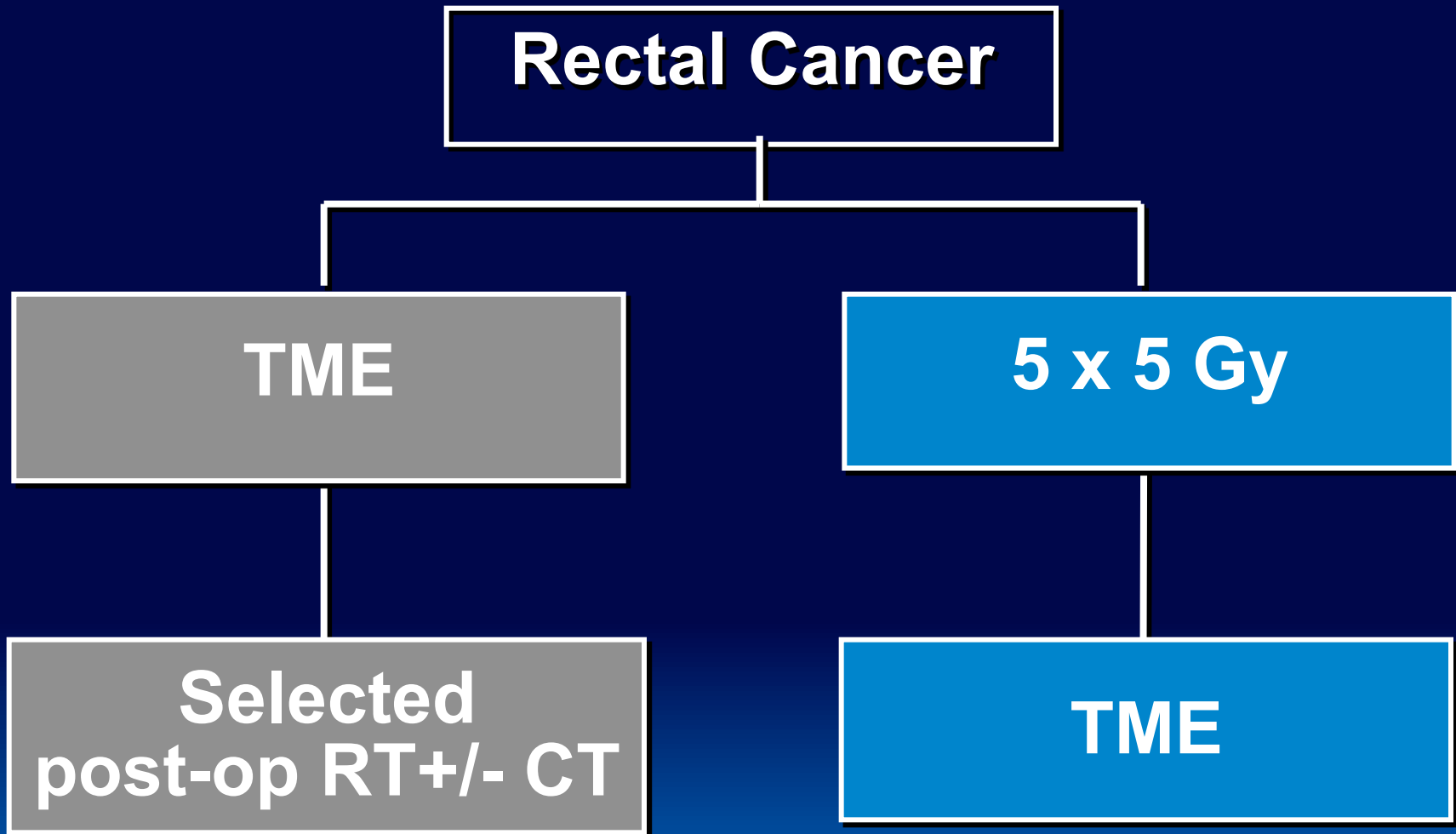


Total Mesorectum Excision



Heald RJ, *Lancet* 1986
Glimelius B, *Eur J Onc* 2005

Pre-op ERT vs TME: Dutch & MRC



Kapitejn E et al, N Engl J Med 2001
Sebag-Montefiore D et al, Lancet 2009

Pre-op RT vs TME: Dutch & MRC

Rectal Cancer

```
graph TD; A[Rectal Cancer] --> B[TME]; A --> C[5 x 5 Gy]; B --> D[Selected post-op RT +/- CT]; C --> E[TME];
```

TME

5 x 5 Gy

**Selected
post-op RT +/- CT**

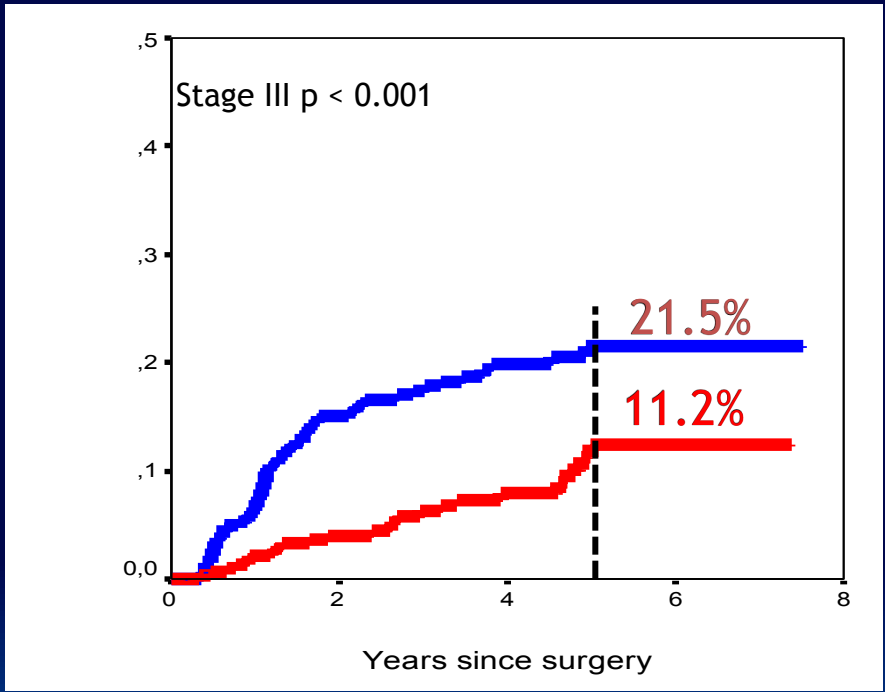
TME

Kapitejn E et al, N Engl J Med 2001
Sebag-Montefiore D et al, Lancet 2009

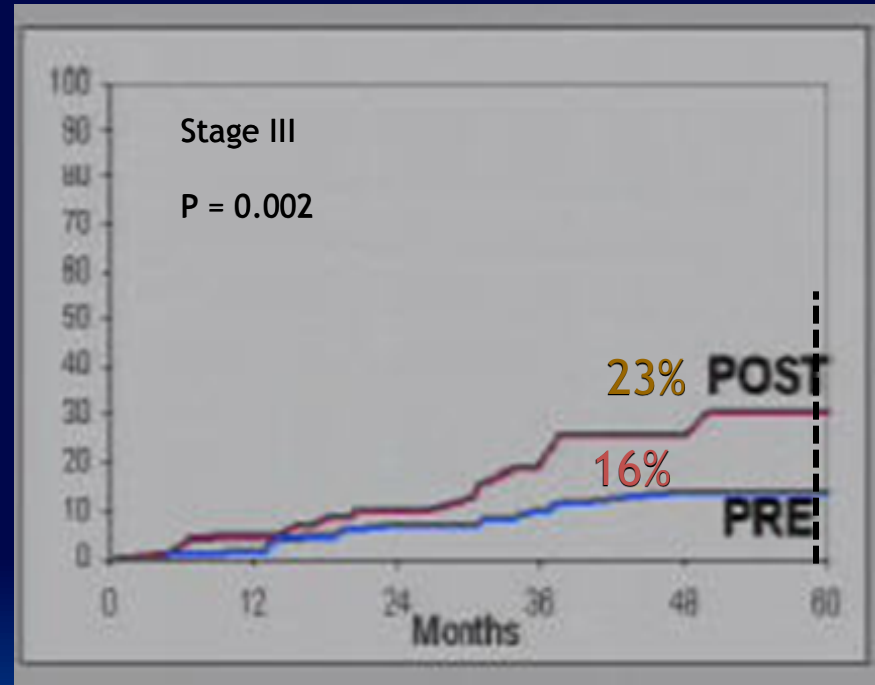
Pre-op RT alone vs TME

Local Recurrence

Short ERT



Duch Trial



MRC CR07

Preop RT vs Preop Chemo-RT

Local Recurrence

Long course RT

	RT LC-RTCh %	p
EORTC 22921	17 - 8	< 0.05
FFCD 9203	17 - 8	< 0.05



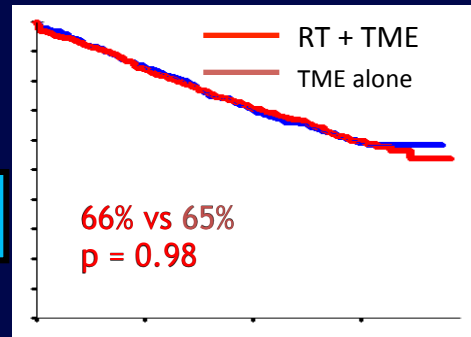
Bosset JF et al, N Engl J Med 2006

Gerard JP et al, JCO 2006

Preoperative trials

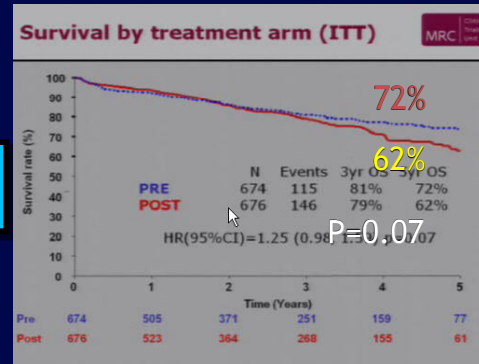
Survival

Duch Trial



Short ERT

MRC CR07



Survival

RT - RTCh

%

EORTC 22921

65 - 65 ns

FFCD 9203

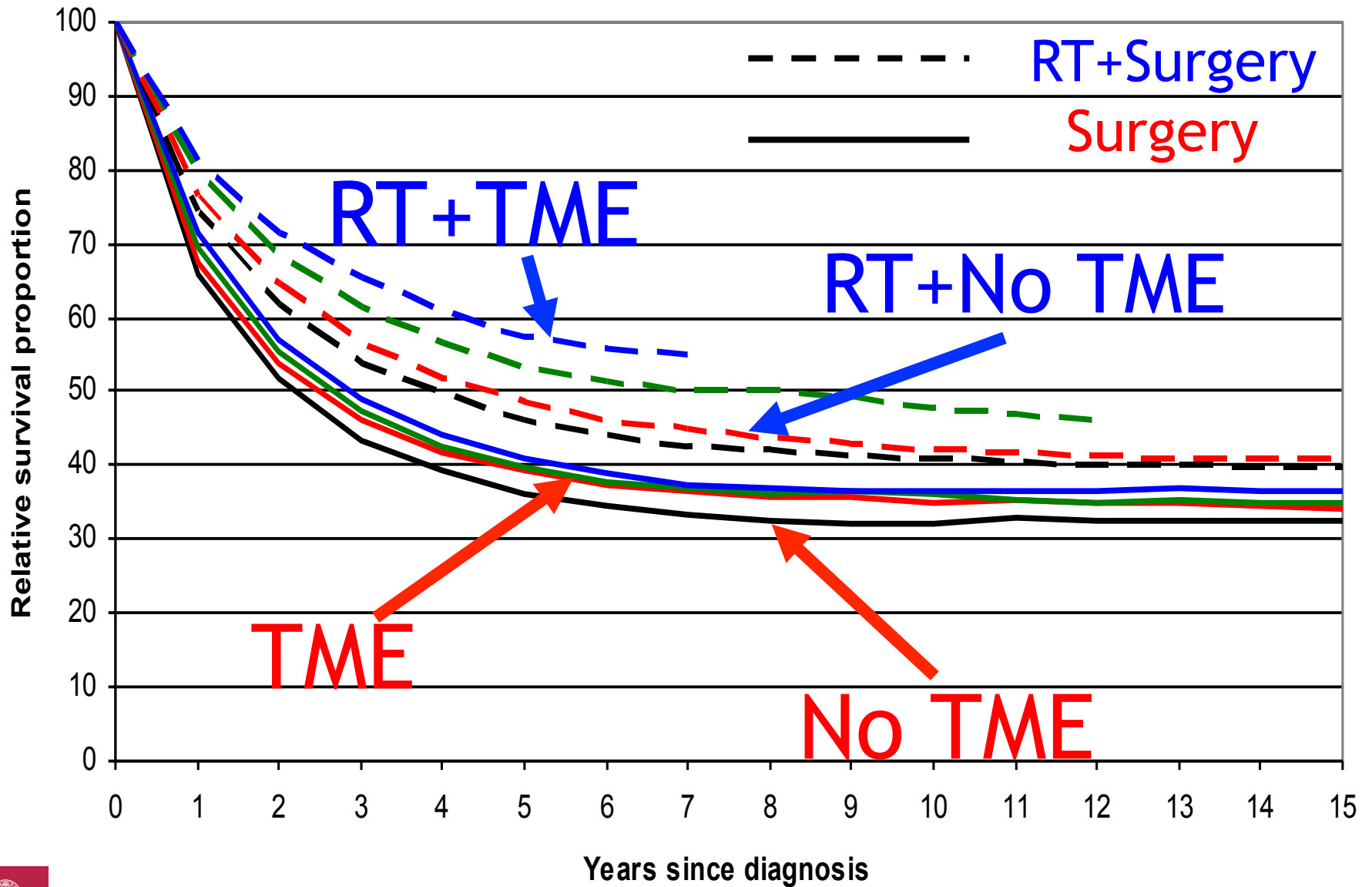
67 - 68 ns

Polish Trial

67 - 66 ns

Long ERT

Cumulativ relativ survival of Rectal cancer in Sweden

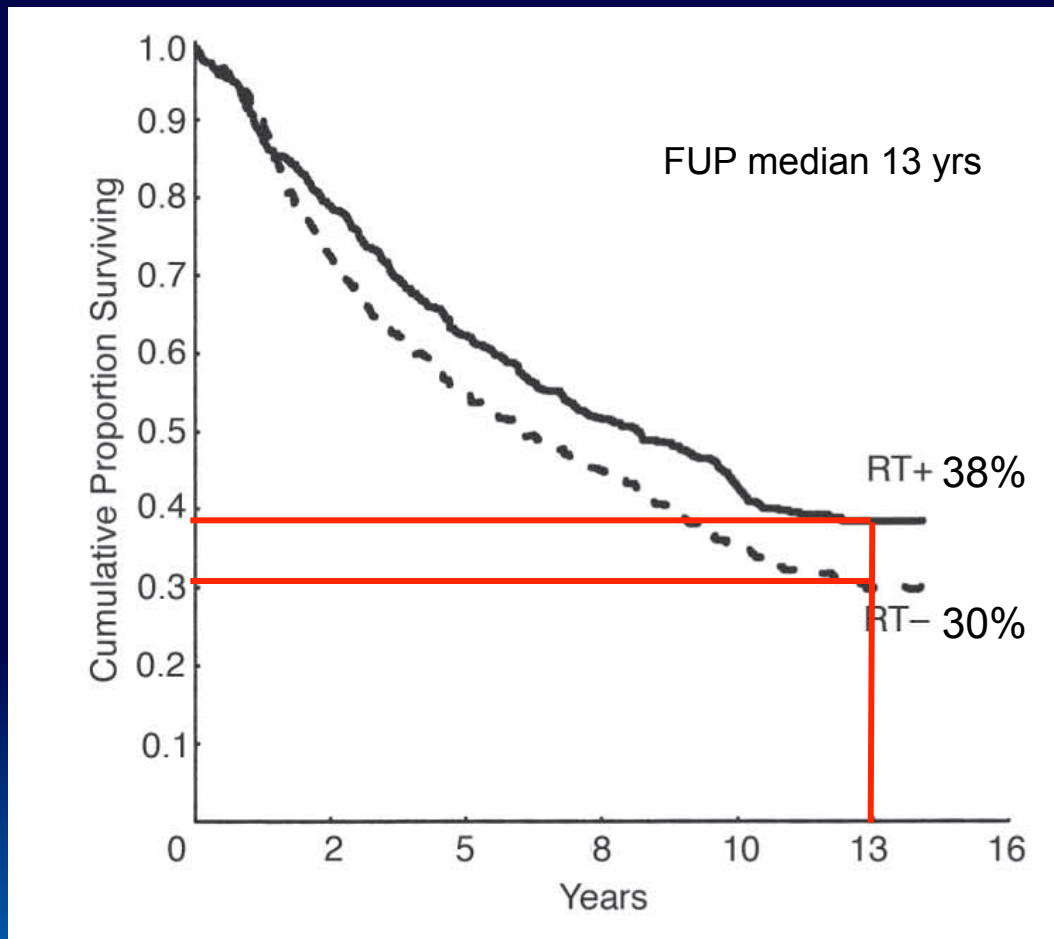


By the courtesy of L.Pahlman - ESTRO/ESSO/ESMO Course - 2009

Preoperative trials & survival

Sweden trial: 908 R0/1168 pts

Long-term updated outcomes



p = 0.008



Cause of death

Dutch Trial: **1382 R0** (pCRM-) / 1681pts

12 years Update of Dutch Trial

	RT + TME (691)	TME (691)
Rectal cancer	38%	48%
Other	2%	52%

p = 0.01



Cause of death, R0 patients

12 years Update of Dutch Trial

	RT+TME (n=315)	TME alone (n=319)
Rectal cancer	119 (38%)	152 (48%)
Radiotherapy complications	2 (<1%)	0 (0%)
Surgery complications	20 (6%)	16 (5%)
Secondary malignancy	43 (14%)	30 (9%)
Cardiovascular cause	46 (15%)	45 (14%)
Pulmonary cause	16 (5%)	15 (5%)
Infectious cause	3 (1%)	2 (<1%)
Neurological cause	4 (1%)	4 (1%)
Ileus	3 (1%)	2 (<1%)
Other	39 (12%)	32 (10%)
Unknown	20 (6%)	21 (7%)

Data are number (%). Pearson χ^2 test between all causes of death $p=0.448$.
RT=radiotherapy. TME=total mesorectal excision.



Survival in RT-Chem

5 randomized European trials

3253 patients

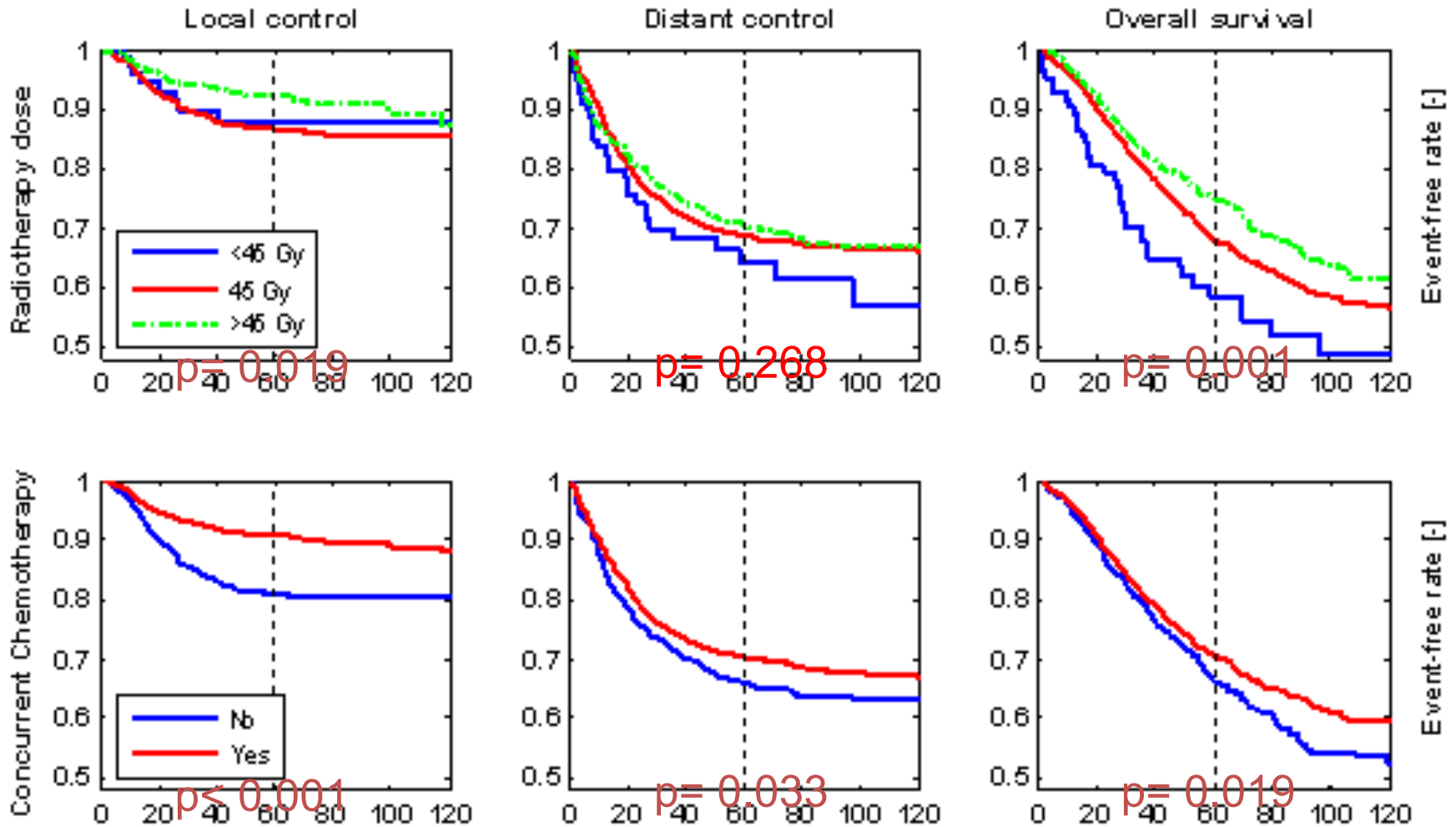
- **EORTC trial** (Bosset et al, 2006)
- **French trial** (Gerard et al. 2006)
- **German trial** (Sauer et al. 2004)
- **Polish trial** (Bujko et al. 2006)
- **Italian CNR trial** (Cionini L. et al. in press)



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del Sacro Cuore



RTCHEM monovariate analysis

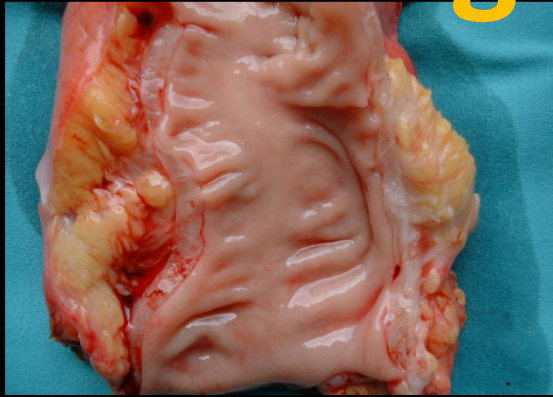
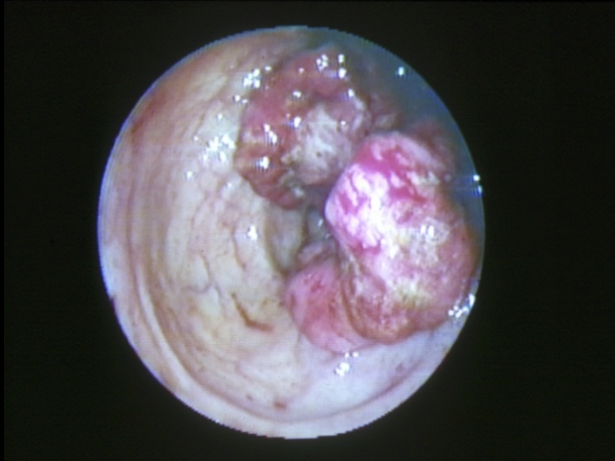


RECTAL CANCER

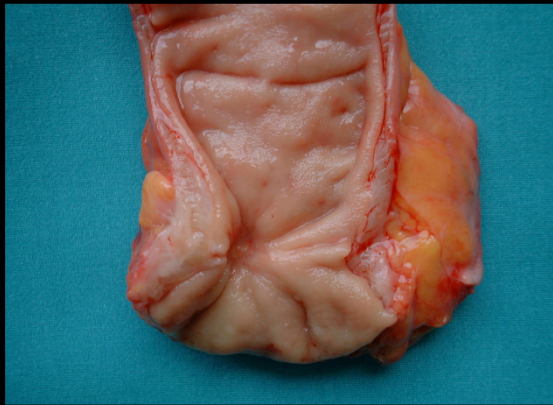
From prescription by consensus



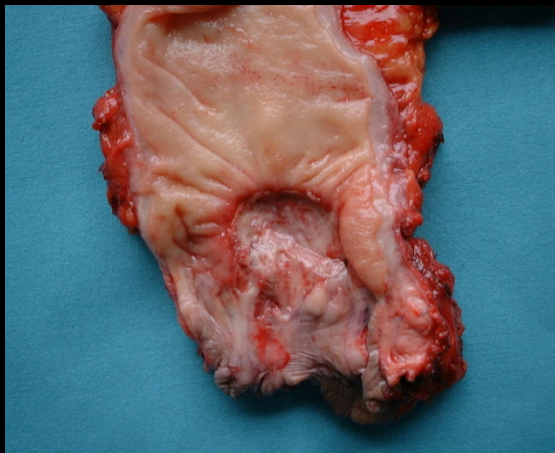
Tumor heterogeneity



GOOD
Complete



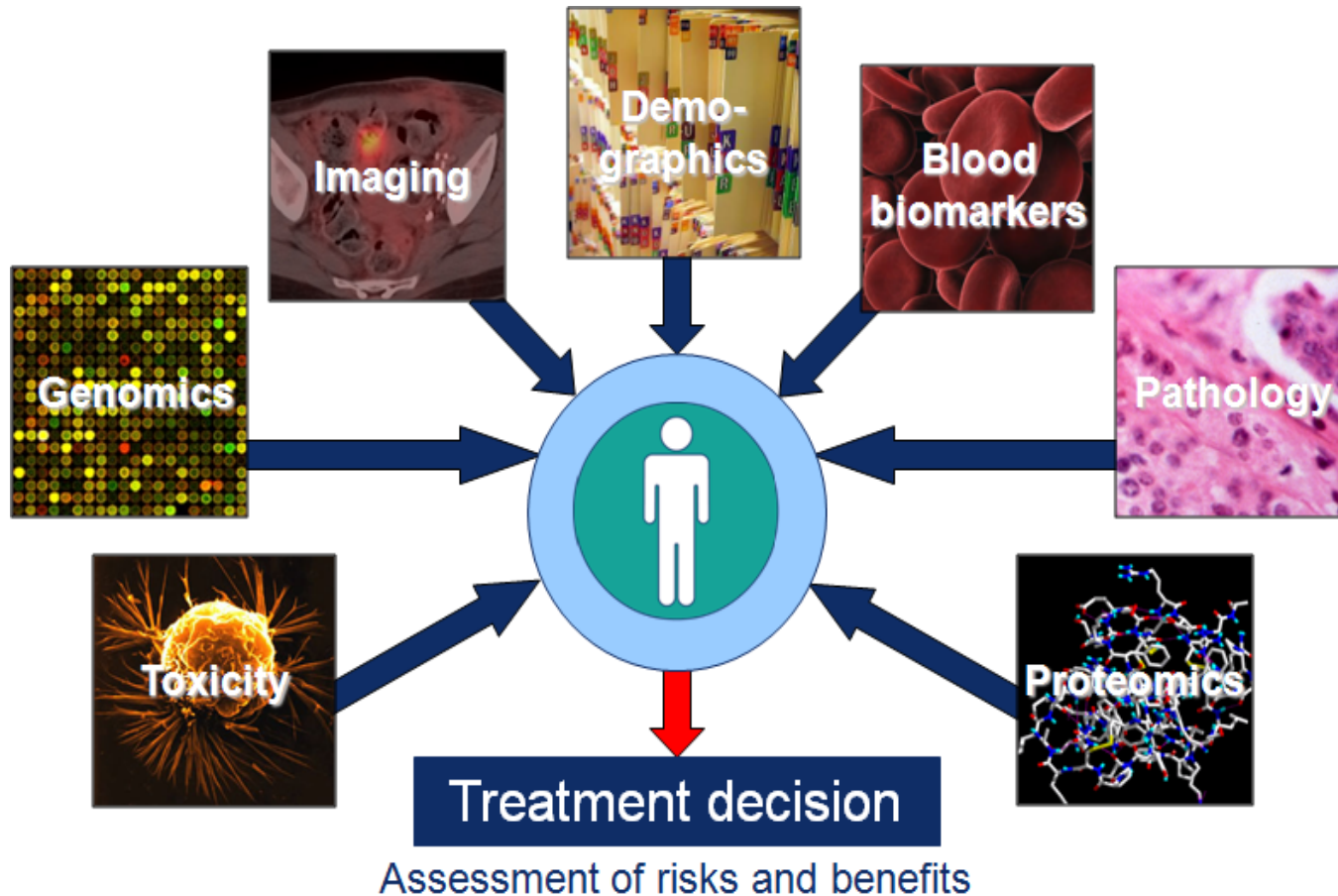
BAD
Partial



UGLY
No



How to handle heterogeneous evidences



Nomograms for Predicting Local Recurrence, Distant Metastases, and Overall Survival for Patients With Locally Advanced Rectal Cancer on the Basis of European Randomized Clinical Trials

Vincenzo Valentini, Ruud G.P.M. van Stiphout, Guido Lammering, Maria Antonietta Gambacorta, Maria Cristina Barba, Marek Bebenek, Franck Bonnetain, Jean-Francois Bosset, Krzysztof Bujko, Luca Cionini, Jean-Pierre Gerard, Claus Rödel, Aldo Sainato, Rolf Sauer, Bruce D. Minsky, Laurence Collette, and Philippe Lambin

MAASTRO CLINIC CANCER PREDICTION MODELS



Input

Gender:

Male Female

Age (years):

57

Clinical tumor stage (cT):

3

Radiotherapy dose [Gy]:

>45

Concomittant chemotherapy:

no yes

Surgery procedure:

LAR APR

Pathological tumor stage (pT):

0

Pathological nodal stage (pN):

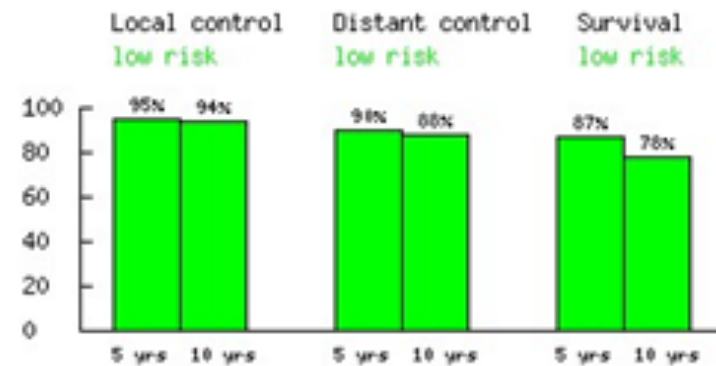
0

Adjuvant chemotherapy:

no yes

Output

The estimated probabilities for local control, distant control, overall survival for this particular rectal cancer patient are:



Interpretation: If there would be a group of 100 patients with the same characteristics as this individual patient, 95 patients would have no local recurrence, 90 patients would have no distant metastases, 87 patients would be alive 5 years after the treatment. Due to the fact that a model can never be completely the same as the "real world", these numbers could be lower or higher, but these are the most likely values. This particular patient has a low risk to develop a local recurrence, low risk to develop distant metastases, low risk to die within 5 years after treatment.

MAASTRO CLINIC CANCER PREDICTION MODELS



Input

Gender:

Male Female

Age (years):

57

Clinical tumor stage (cT):

3

Radiotherapy dose [Gy]:

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Concomittant chemotherapy:

no yes

Surgery procedure:

LAR APR

Pathological tumor stage (pT):

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Pathological nodal stage (pN):

0

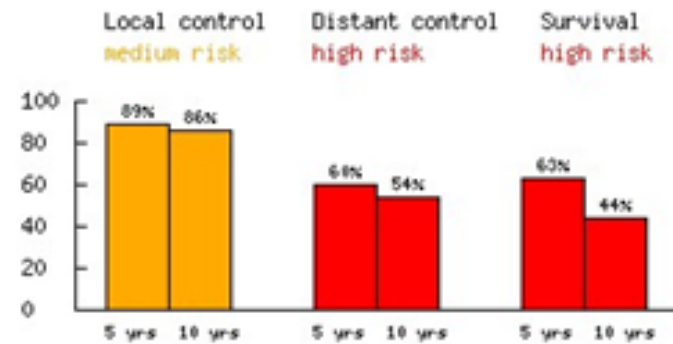
Adjuvant chemotherapy:

no yes



Output

The estimated probabilities for local control, distant control, overall survival for this particular rectal cancer patient are:



MAASTRO CLINIC CANCER PREDICTION MODELS



Input

Gender:

Male Female

Age (years):

57

Clinical tumor stage (cT):

3

Radiotherapy dose [Gy]:

>45

Concomittant chemotherapy:

no yes

Surgery procedure:

LAR APR


Pathological tumor stage (pT):

3

Pathological nodal stage (pN):

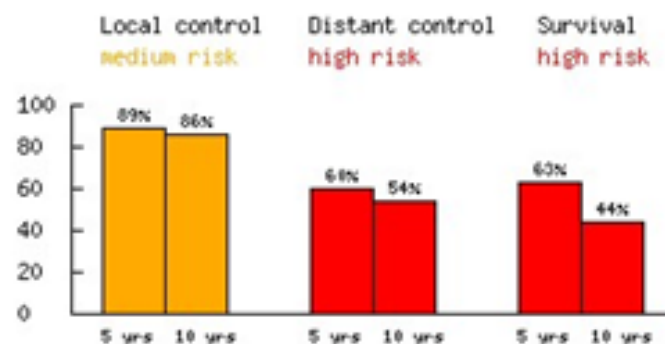
0

Adjuvant chemotherapy:

no yes 

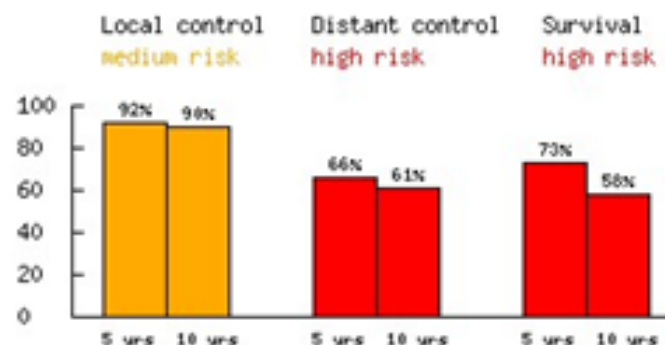
Output

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Output

The estimated probabilities for local control, distant control, overall survival for this particular rectal cancer patient are:





Welcome to the MAASTRO prediction website *Last update: 13-07-2011*

Response Model Input

Tumour length (2.0 - 15.0 cm):

SUV_{max-pre} (1.0 - 25.0):

SUV_{max-post} (1.0 - 25.0):

Output Response Model

The response index of SUV_{max} between pre- and the post-treatment scan is **72%**

The probability that the patient will have a pathological complete response after surgery is **39%**

Interpretation: If there would be a group of 100 patients with the same characteristics as this individual patient, 39 patients would have a pathological complete response after the chemoradiotherapy treatment. Due to the fact that a model can never be completely the same as the "real world", the number 39 could be lower or higher, but 39 is the most likely value.



Modulation strategies

– CONSENSUS & GUIDELINES

- multidisciplinary approach

– NOMOGRAMS

- option selection from an menu

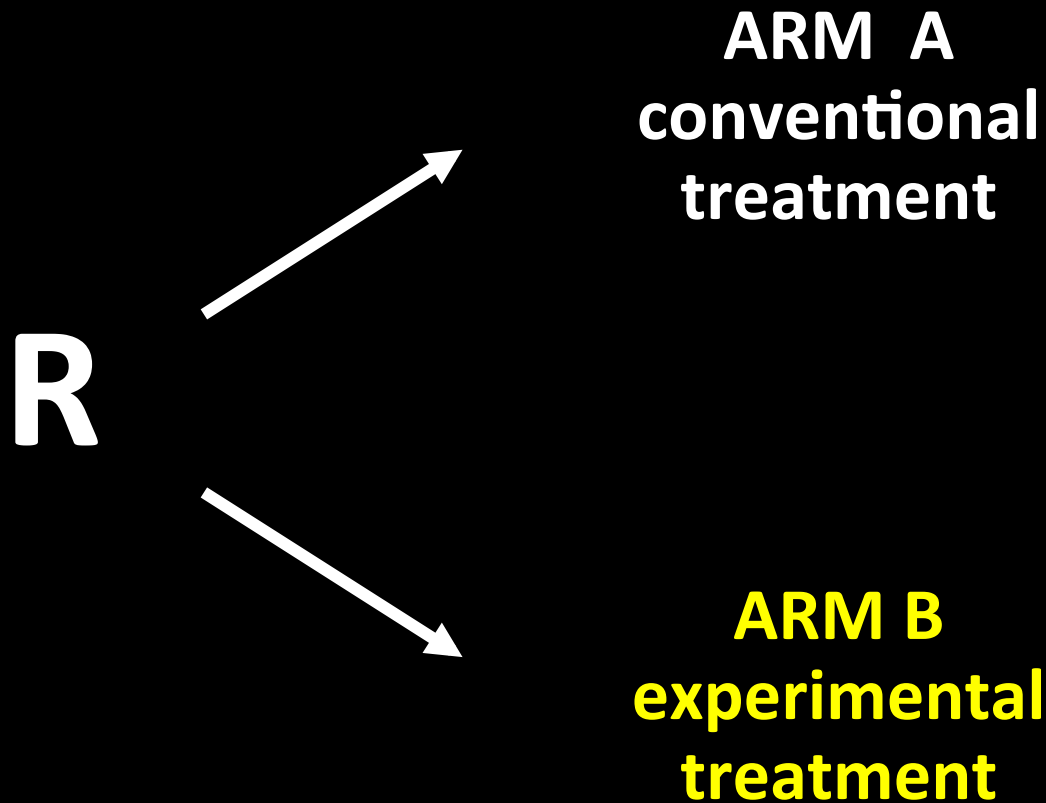
– RESOURCES SPARING

- Postoperative CHEMOTHERAPY
- Follow-up: frequencies/exams

– RESEARCH

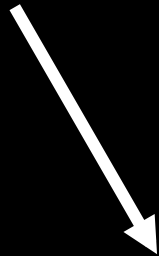


Conventional study design



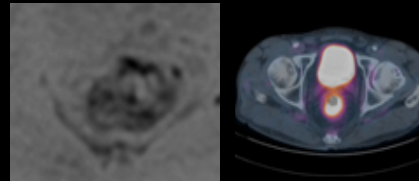
Adaptive study design

R



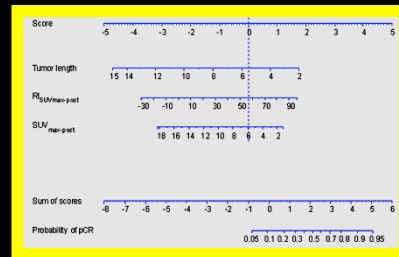
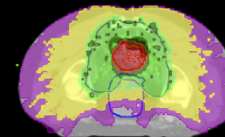
ARM A
RT + 1 drug

Surgery deescalation

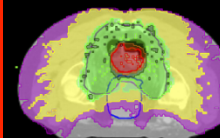


ARM B
Start with arm A

RT intensification



CT intensification



2 drugs

2 drugs

S



- Low risk
- Medium risk
- High risk

RECTAL CANCER

From prescription by consensus

to prescription by numbers





DOMENICA 20 NOVEMBRE

SALA LEVANTE PONENTE

14.00 - 15.30 WORKSHOP

Integrazioni terapeutiche nel carcinoma gastrico

Moderatori: A. Grandinetti (Verona), S. Pergolizzi (Messina)



Stato dell'arte nel trattamento adiuvante del carcinoma gastrico:
evidenze e prospettive - **A. Morganti** (Campobasso)

La ricerca clinica nei trattamenti integrati adiuvanti - **A. De Paoli** (Aviano)

Le sedi di recidiva locale dopo trattamento chirurgico - **G.B. Doglietto** (Roma)

La definizione del target nella radioterapia adiuvante - **D. Genovesi** (Chieti)

Nuove tecnologie nell'irradiazione adiuvante: quali evidenze? - **M.F. Osti** (Roma)

La tossicità del trattamento integrato - **G.C. Mattiucci** (Roma)

Discussione

Gastric Cancer

From one for all...

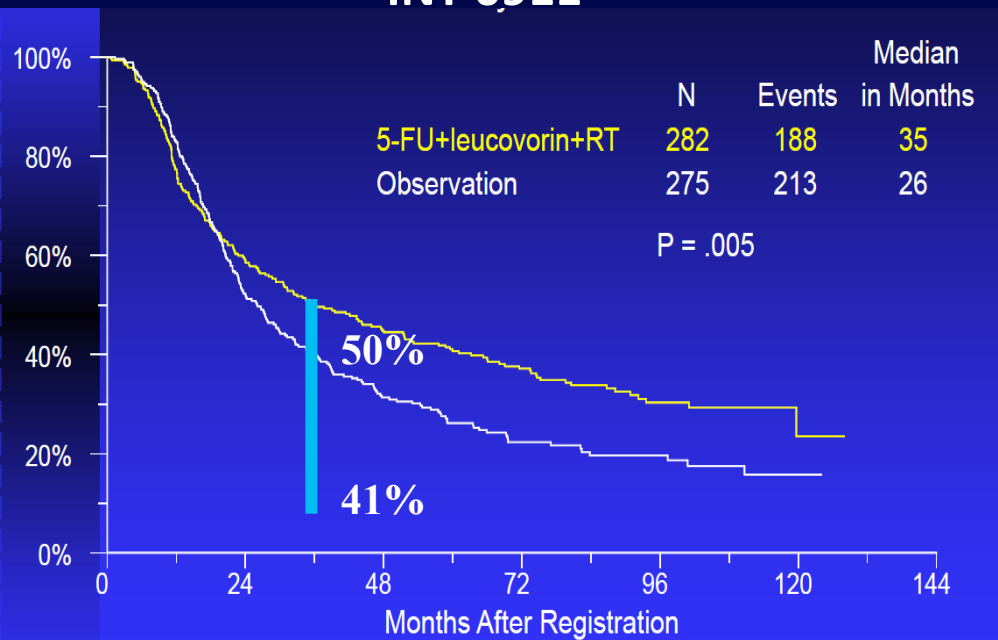


Survival

Post-op RTCT

S CT-RTCT-CT (5FU)

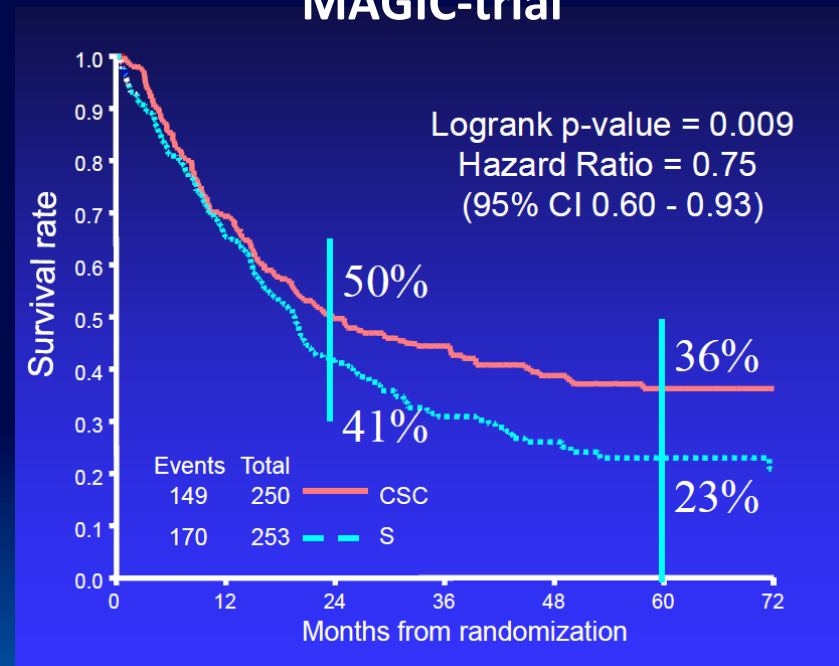
INT 0911



Peri-op RTCT

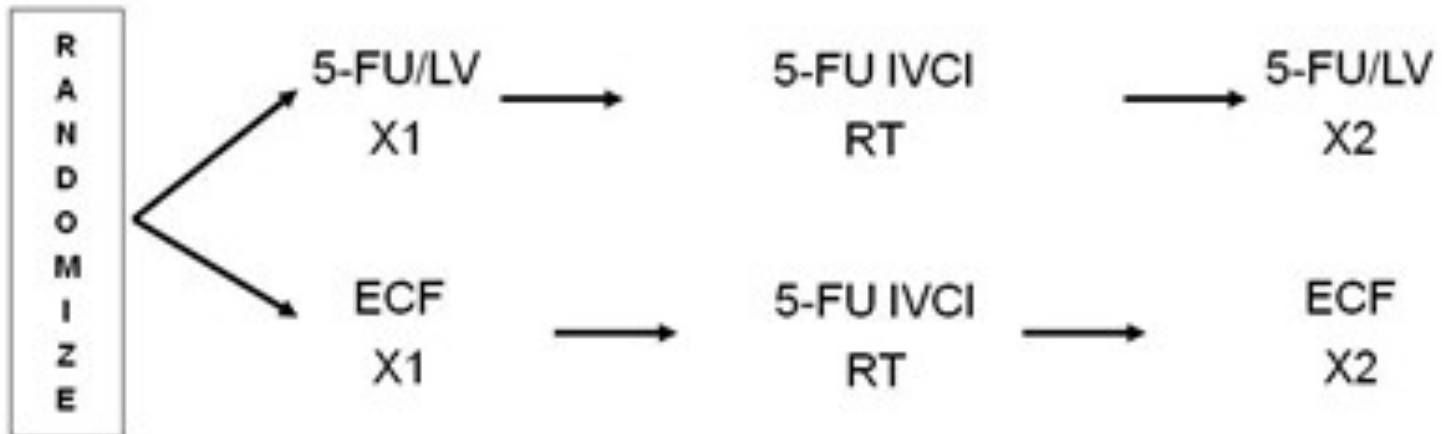
CT (ECF) - S -CT (ECF)

MAGIC-trial



INT 0116 + MAGIC: CALGB 80101

CALGB 80101: Study Schema



5-FU/LV: 5-FU 425 mg/m² d1-5, LV 20 mg/m² d1-5

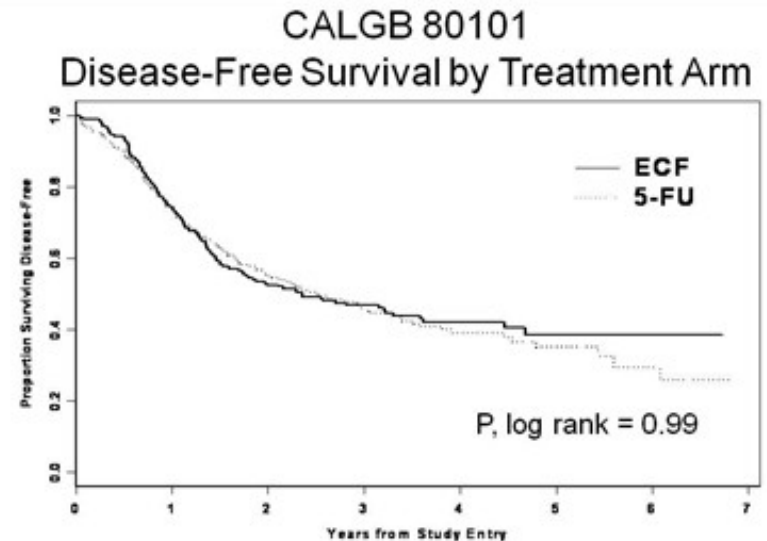
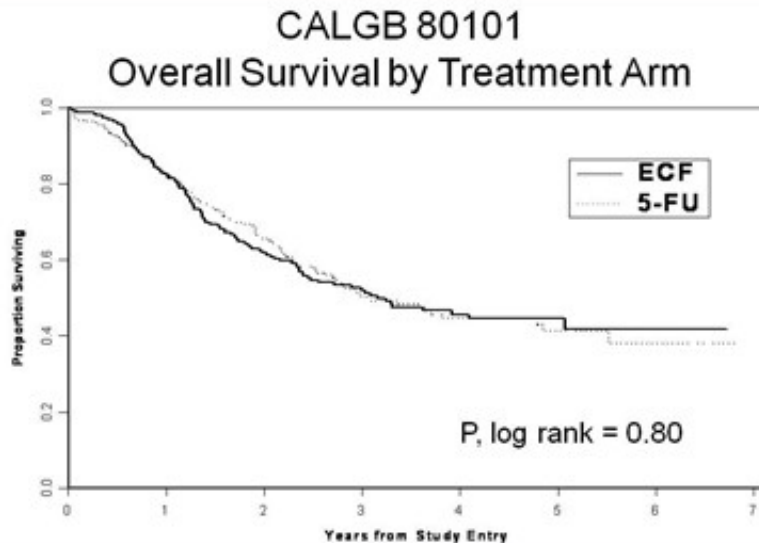
RT: 45 Gy (1.8 Gy X 25 fractions) with 5-FU 200 mg/m²/d CI

ECF (pre-RT): Epirubicin 50 mg/m² d1, Cisplatin 60 mg/m² d1, &
5-FU 200 mg/m²/d CI d1-21

ECF (post-RT): Epirubicin 40 mg/m² d1, Cisplatin 50 mg/m² d1, &
5-FU 200 mg/m²/d CI d1-21



INT 0116 + MAGIC: CALGB 80101



CALGB 80101
Overall Survival by Treatment Arm

Arm	Median OS*	3-year OS	5-year OS	Hazard Ratio (95% CI)
5-FU/LV	36.6 mos	50%	41%	
ECF	37.8 mos	52%	44%	1.03 (0.80-1.34)

*P, log rank = 0.80

CALGB 80101
Disease-Free Survival by Treatment Arm

Arm	Median DFS	3-yr DFS	5-yr DFS	Hazard Ratio (95% CI)
5-FU/LV	30.1 mos	46%	35%	
ECF	28.2 mos*	47%	38%	1.00 (0.79-1.27)

*P, log rank = 0.99

Gastric Cancer Guidelines

SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS (For Patients Who Have Received Preoperative Therapy)	TUMOR CLASSIFICATION ^a	POSTOPERATIVE TREATMENT
<u>R0 resection^m</u>	T2, N0	Observe or 5-FU ± leucovorin or capecitabine, ⁿ then fluoropyrimidine-based chemoradiation, ^{k,l,r} then 5-FU ± leucovorin or capecitabine ⁿ for selected patients ^o or ECF or its modifications if received preoperatively (category 1)
	T3, T4 or Any T, N+	5-FU ± leucovorin or capecitabine, ⁿ then fluoropyrimidine-based chemoradiation, ^{k,l,r} then 5-FU ± leucovorin or capecitabine ⁿ or ECF or its modifications if received preoperatively (category 1)

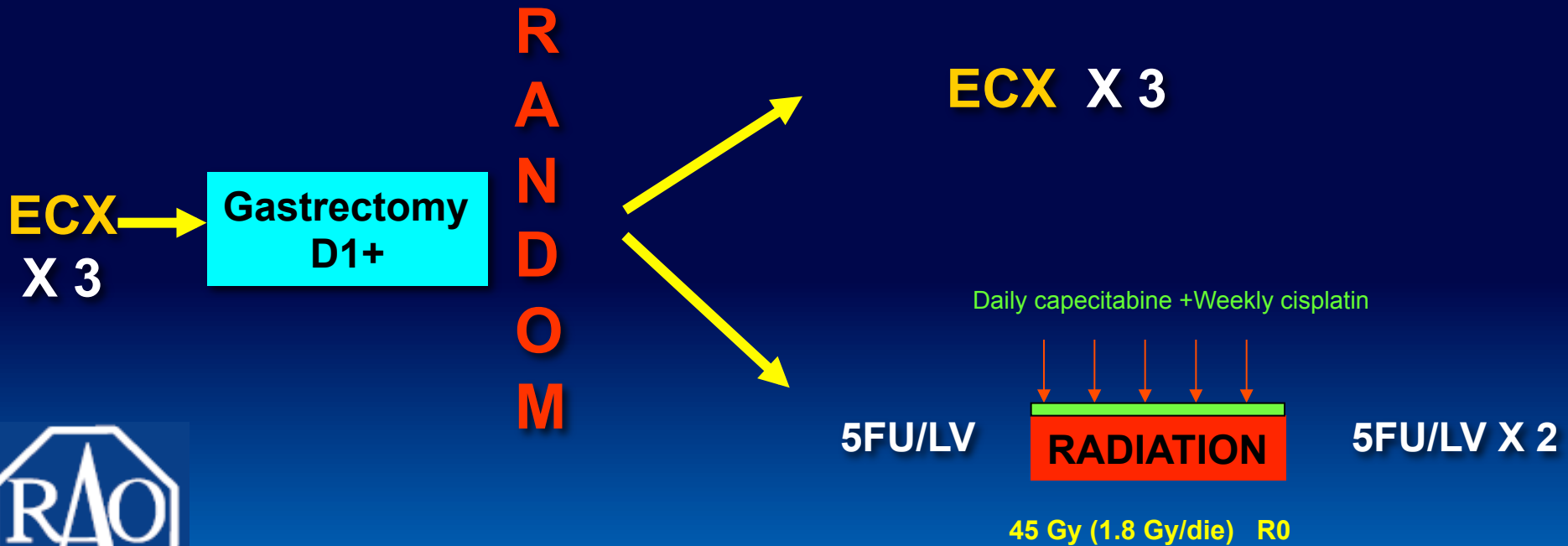
→ [Follow-up \(see GAST-6\)](#)



INT 0116 vs MAGIC : CRITICS Trial

ChemoRadiotherapy after InductionchemoTherapy In Cancer of the Stomach

788 patients;
May 2011:350 pts



Ongoing trial: ITACAS-2

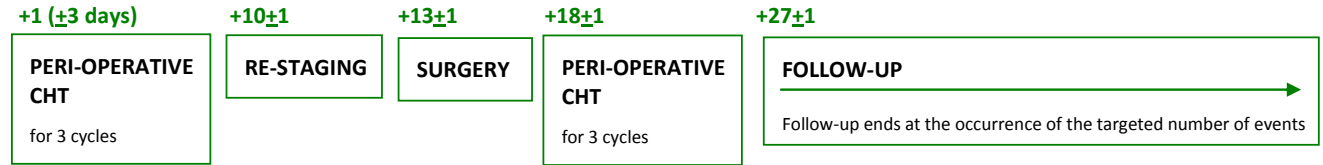
Intergroup Trial in Adjuvant Chemotherapy for Adenocarcinoma of the Stomach

PERI-CT	POST-CT
PERI-CT +RT	POST-CT +RT

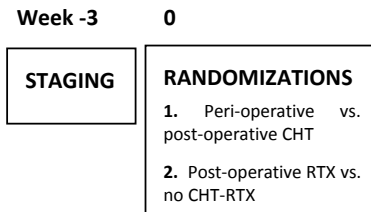


ITACAS-2 trial

ARM A: Peri-operative chemotherapy



ARM B: Post-operative chemotherapy



TARGET POPULATION

Patients with histologically confirmed, localized, operable gastric adenocarcinoma

CHT

To be chosen among:

- EOX**: epirubicin 50 mg/m² iv bolus day 1 every 3 weeks; oxaliplatin 130 mg/m² iv infusion in 2-3h day 1 every 3 weeks; capecitabine 625 mg/m² bid day 1 po continuously
- ECF**: epirubicin 50 mg/m² iv bolus day 1 every 3 weeks; cisplatin 60 mg/m² iv with standard hydration day 1 every 3 weeks; fluorouracil 200 mg/m² daily by continuous infusion via central line.

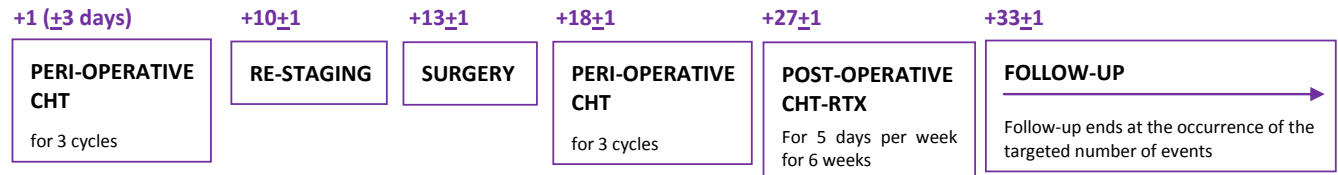
CHT-RTX

RTX: 45 Gy delivered in daily fraction of 1.8 Gy

CHT: to be chosen between

- 5-FU 225 mg/m² given as a continuous iv infusion **or**
- capecitabine 825 mg/m² bid given as a continuous oral administration during the entire course of RTX

ARM C: Peri-operative chemotherapy plus post-operative chemo-radiotherapy treatment



ARM D: Post-operative chemotherapy plus post-operative chemo-radiotherapy treatment



Magic

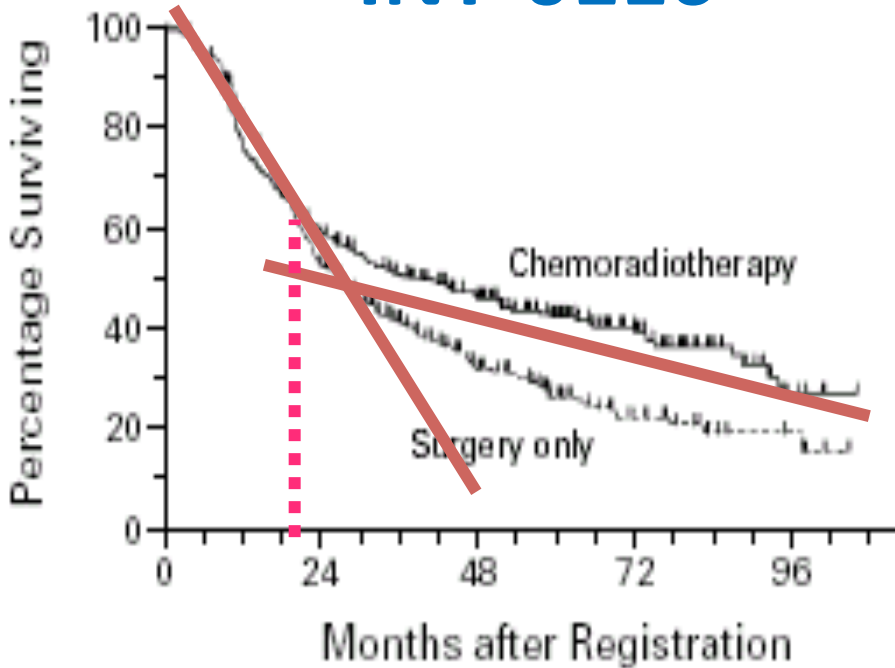
post-CT

CRITIX exp arm

INT 0116

“L-SHAPE”

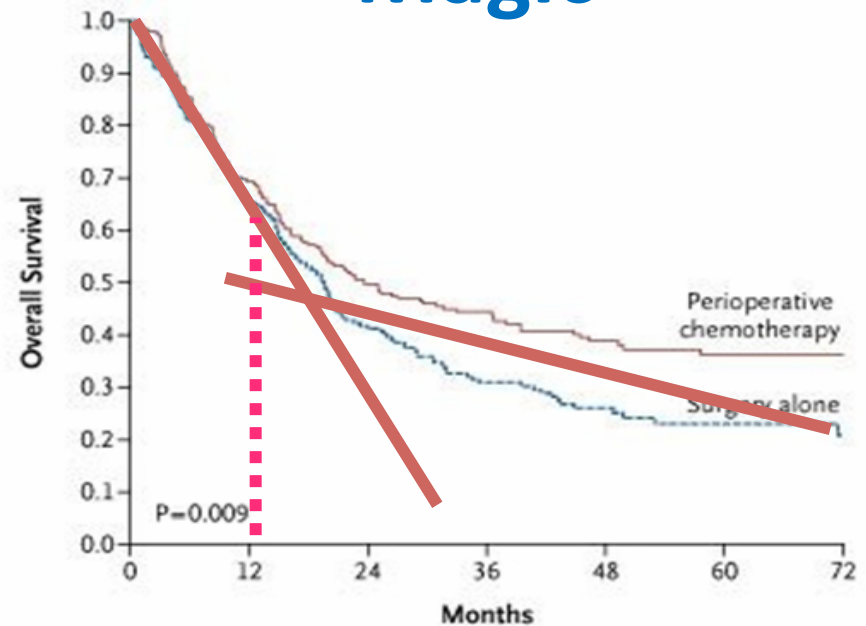
INT-0116



D2 = 10%

Macdonald et al N Engl J Med 2001

Magic



D2 = 41%

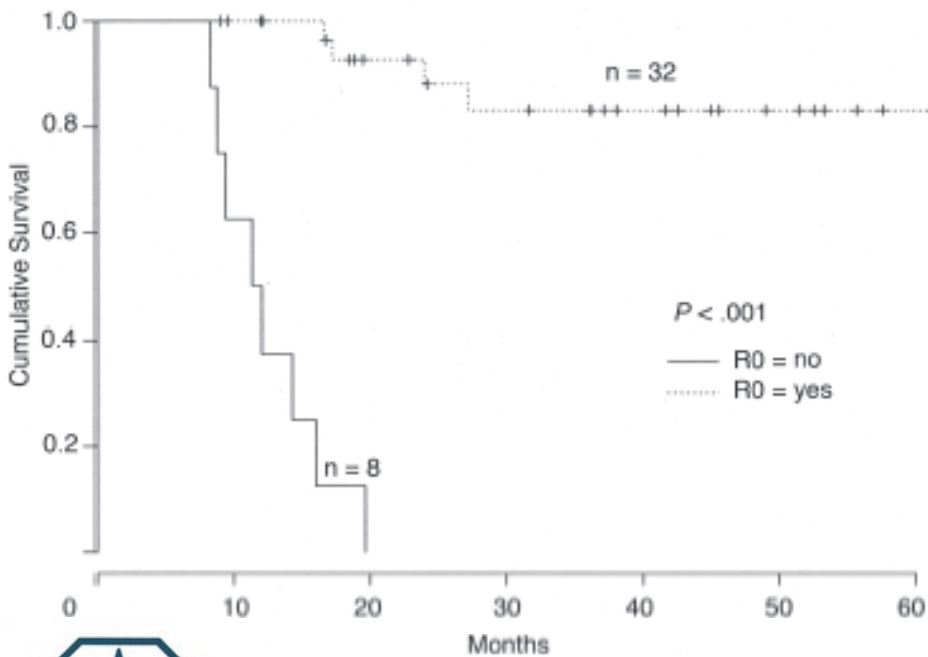
Cunningham et al N Engl J Med 2006

By courtesy of V. Valentini

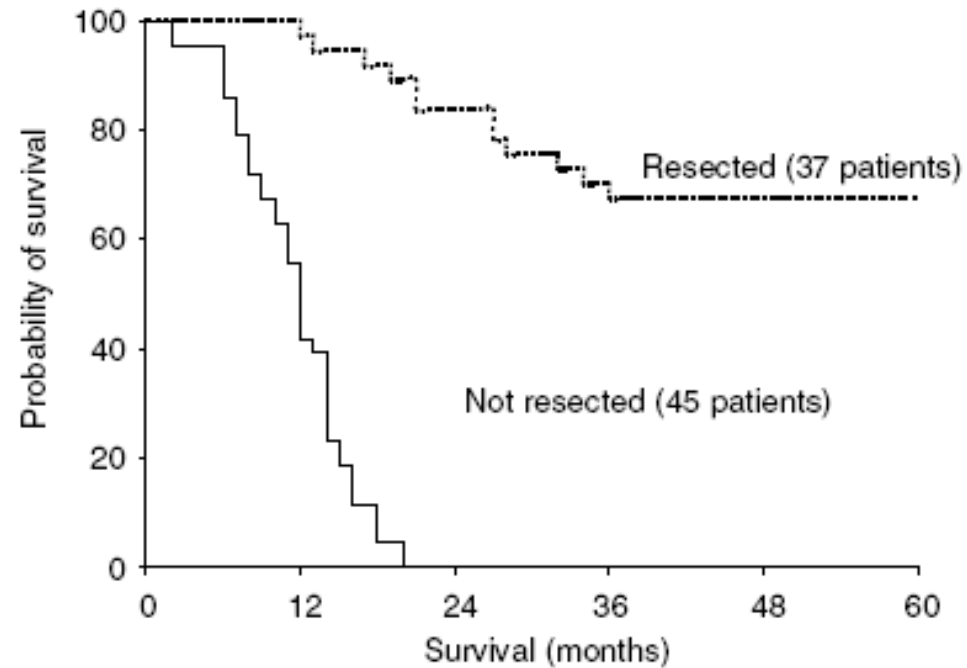
Primary Chemo+RT

Neoadjuvant

RT+Chemo



Chemo



Cascinu S et al, BJC 2004
Ajani JA et al, JCO 2005

Neoadjuv. Chemo +/-RT

The risk of tumour progressions

	MDACC	Magic trial
PD @surgery not resected	9/41 (22%)	37/209 (18%)



Adaptive therapy: NEOX-RT

uT3-4,N0 or any uT,N+M0 (LPS)

potentially resectable

Induction chemotherapy

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

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

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

Gastric Cancer

From one for all...

to one for group



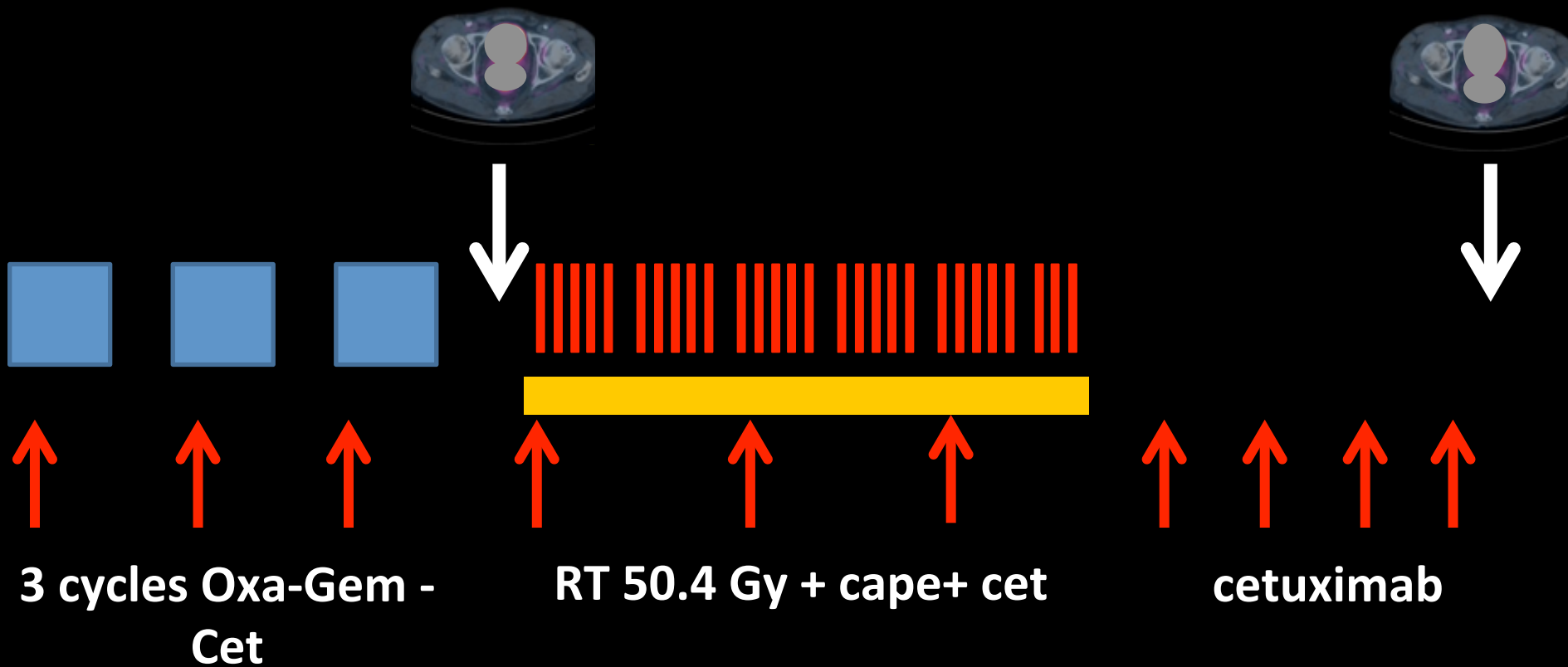
Pancreatic Cancer



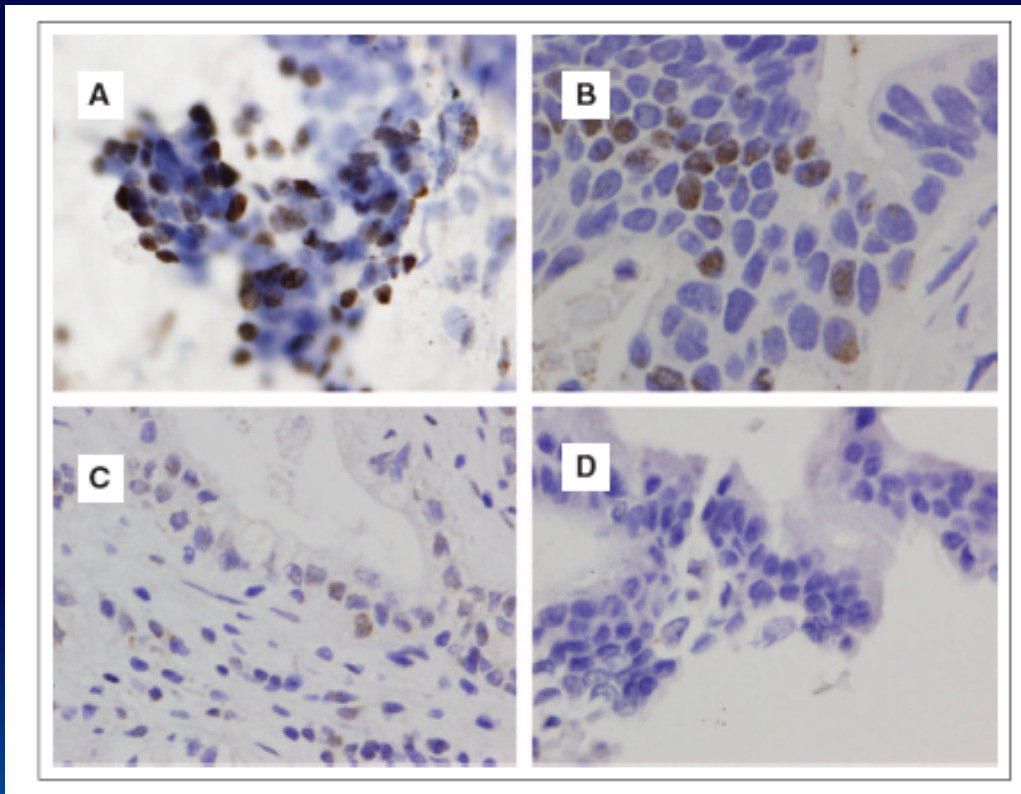
Phase II Trial of Cetuximab, Gemcitabine, and Oxaliplatin Followed by Chemoradiation With Cetuximab for Locally Advanced (T4) Pancreatic Adenocarcinoma: Correlation of Smad4(Dpc4) Immunostaining With Pattern of Disease Progression

Christopher H. Crane, Gauri R. Varadhachary, John S. Yordy, Gregg A. Staerke, Milind M. Javle, Howard Safran, Waqar Haque, Bridgett D. Hobbs, Sunil Krishnan, Jason B. Fleming, Prajnan Das, Jeffrey E. Lee, James L. Abbruzzese, and Robert A. Wolff

Unresectable pancreatic cancer



Smad4(Dpc4)



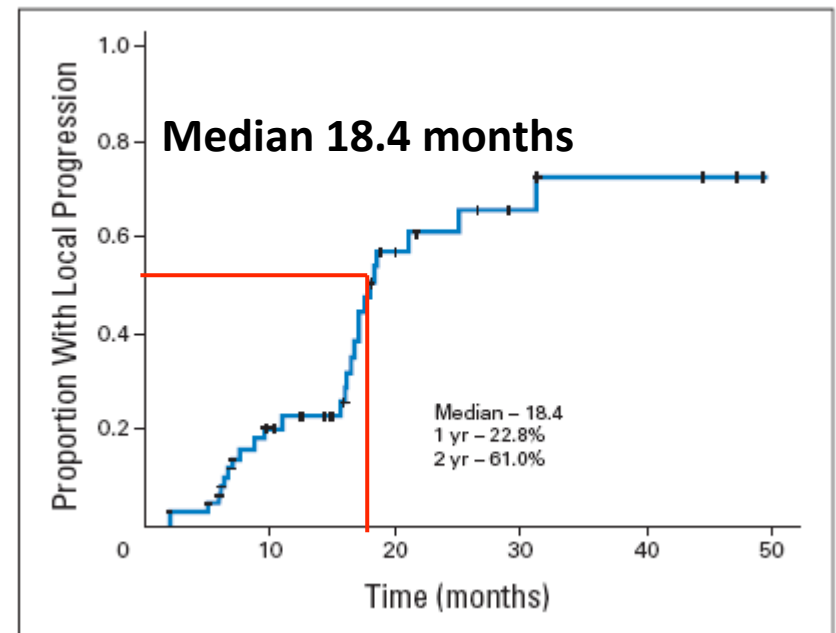
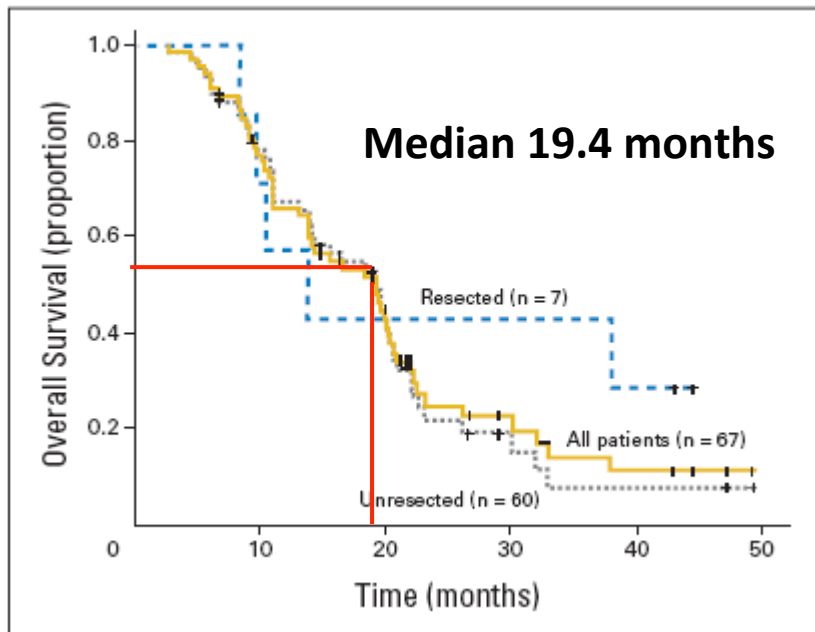
tumor suppressor gene

inactivated in 53%

prognosis

pattern of
disease spread

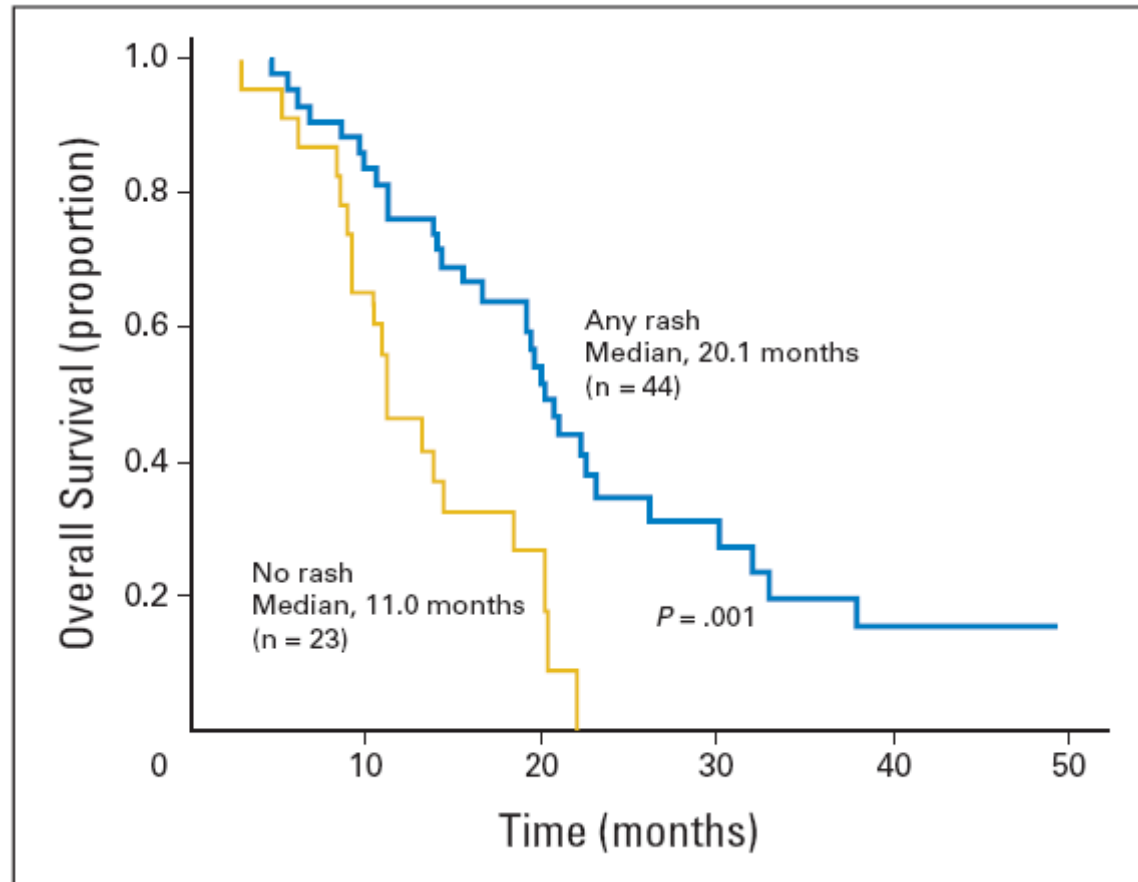
Unresectable pancreatic cancer



**Local control and improved survival
Cetuximab as radiosensitizer ?!**

Crane CH et al, JCO 2001

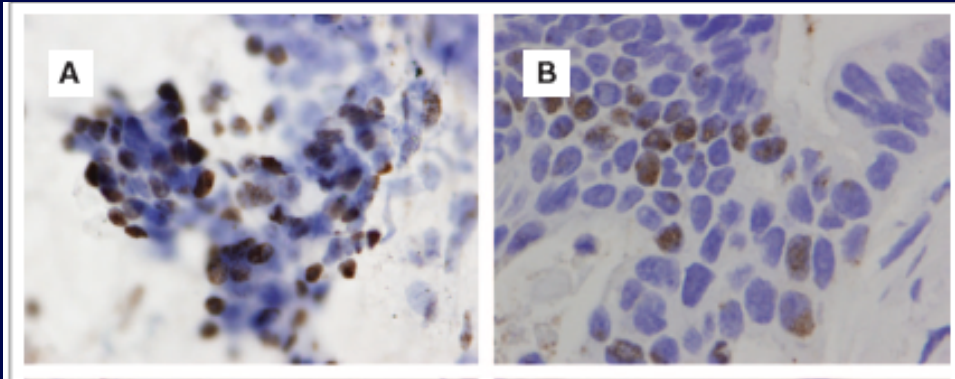
Unresectable pancreatic cancer



Smad4(Dpc4) and progression

41 pts

Active Smad4 (Dpc4)

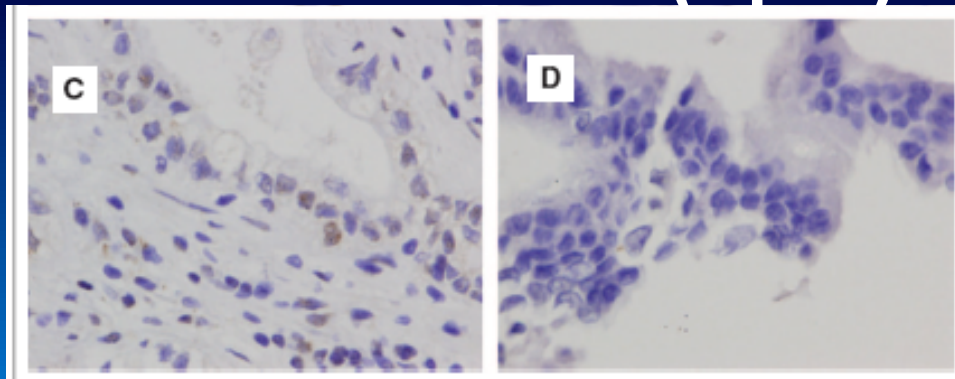


11/15 pts

73.3% LOCAL

$p = 0.016$

Inactive Smad4 (Dpc4)



10/14 pts

71.4% DISTANT

Crane CH et al, JCO 2001

Pancreatic Cancer

RADIATION

ONCOLOGIST



Pancreatic Cancer

RADIATION ONCOLOGIST



Genova, 19-22 novembre 2011
Porto Antico di Genova
Centro Congressi



Associazione
Italiana
Radioterapia
Oncologica

- **Rectal cancer:**
 - Dose and response
 - Survival
 - Prescription by number
- **Gastric cancer:**
 - ...to one for one
- **Pancreatic cancer:**
 - Room for advancement

