ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

ESMO Preceptorship Programme

Colorectal Cancer – Valencia – May 2017

State-of-the-art: Standard(s) of local treatment (radio/chemotherapy) for rectal cancer

Rob Glynne-Jones
Mount Vernon Cancer Centre

My Disclosures: last 5 years

- **Speaker:** Roche, Merck Serono, Sanofi Aventis, Pfizer, AIS
- **Advisory Boards:** Roche, Merck Serono, Sanofi Aventis, Astra Zeneca
- **Funding to attend meetings**: Roche, Merck Serono, Sanofi Aventis,
- **Research funding**: Roche, Merck Serono, Sanofi Aventis

My Inherent Bias

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Rectal Cancer

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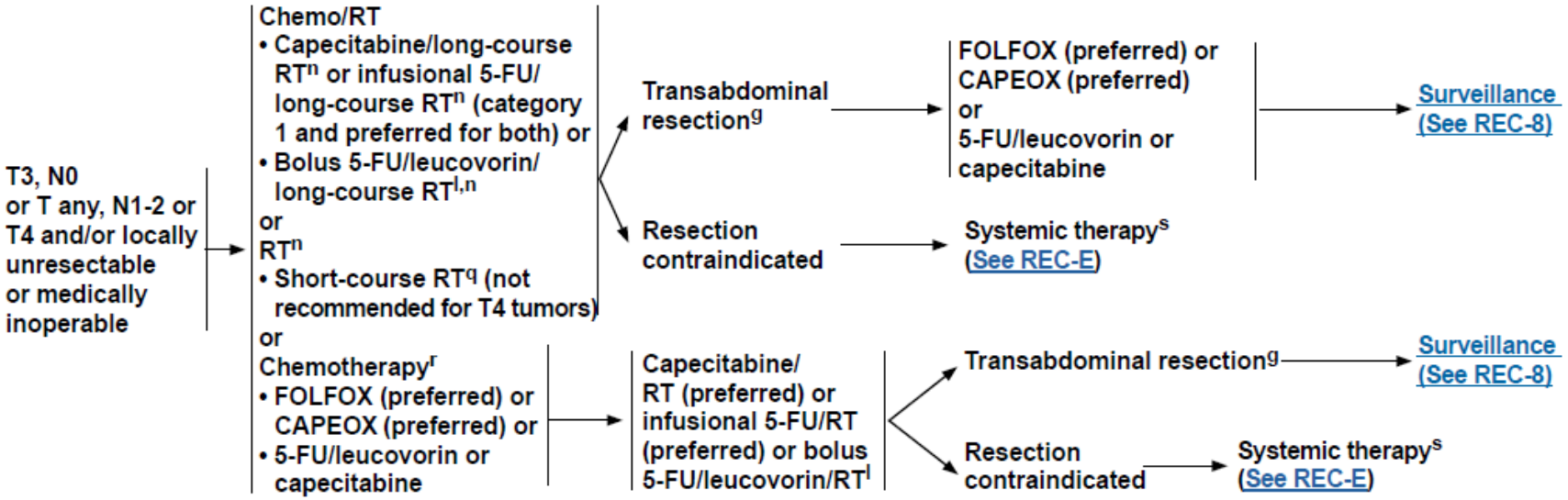
Discussion



[g] See Principles of Surgery (REC-B).
[l] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[m] See Principles of Adjuvant Therapy (REC-C).
[n] See Principles of Radiation Therapy (REC-D).
[o] Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.
[q] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.
[r] Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.
[s] FOLFOXIRI is not recommended in this setting.

⊙De Ruysschers Principle of SER

(the interval between the start of treatment and the end of radiotherapy should be as short as possible)

De Ruysscher D, et al., Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer.
J Clin Oncol 2006;24(7):1053-63

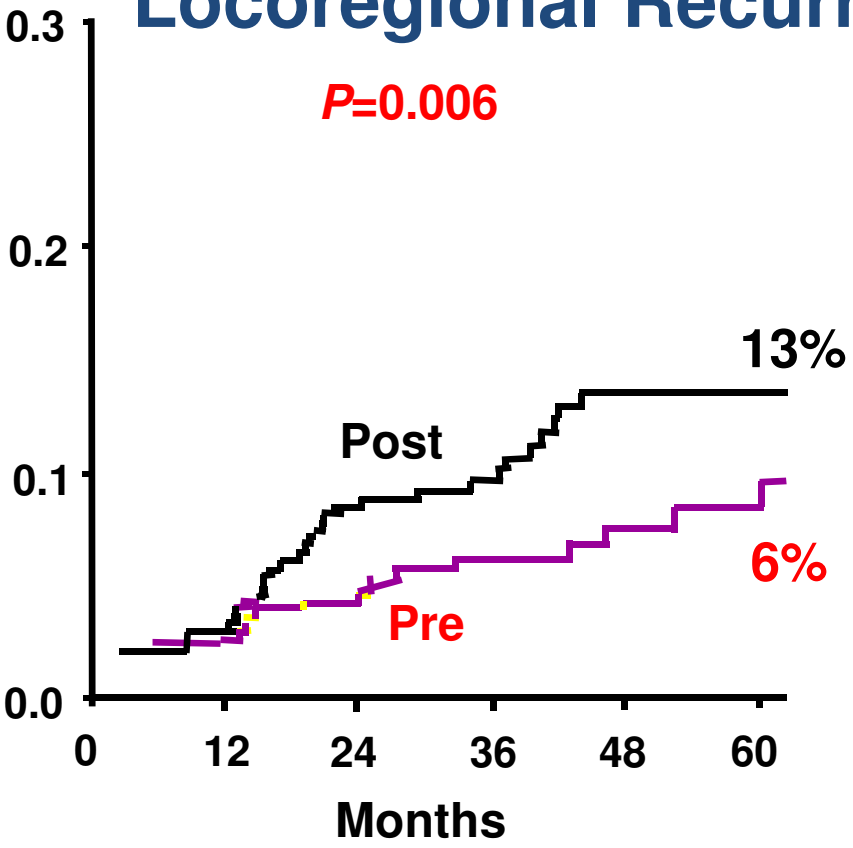
Preoperative Options to influence outcomes in rectal cancer

- Radiotherapy (5 x 5Gy)
- Chemoradiation (with fluoropyrimidine)
- Neoadjuvant chemotherapy +/- Biologicals
- (Immunotherapy)

- Different combinations and sequences of the above (4 x 3 x 2 x 1= 24)

Pre- vs post-operative chemoradiation CAO/ARO/AIO-94

Locoregional Recurrences



Acute G3/4 adverse events
27% vs 40% (p=0.001)

Long-term G3/4 adverse events
14% vs 24% (p=0.01)

There is a standard for chemoradiation

Sauer R. et al., N Engl J Med 2004;351: 1731-39

Different standards

- In different countries

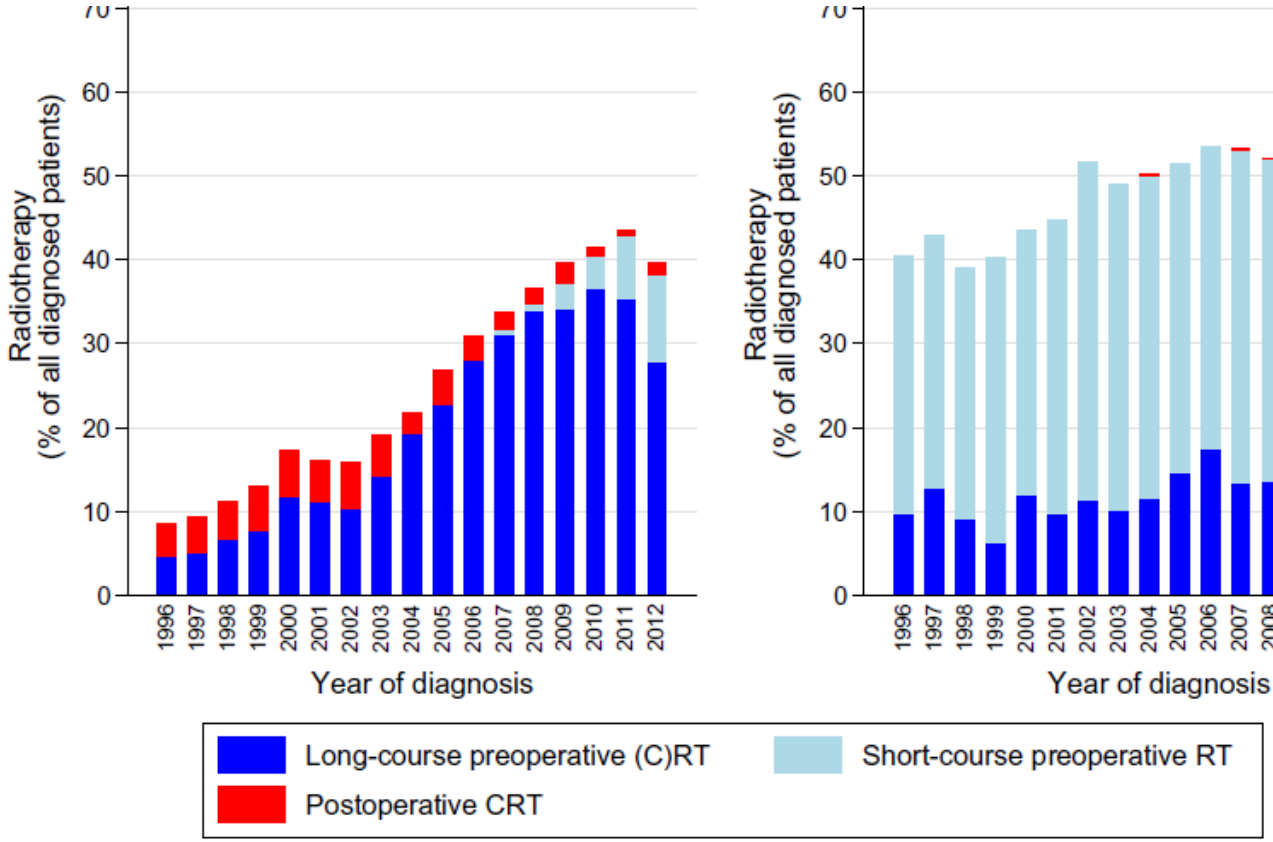
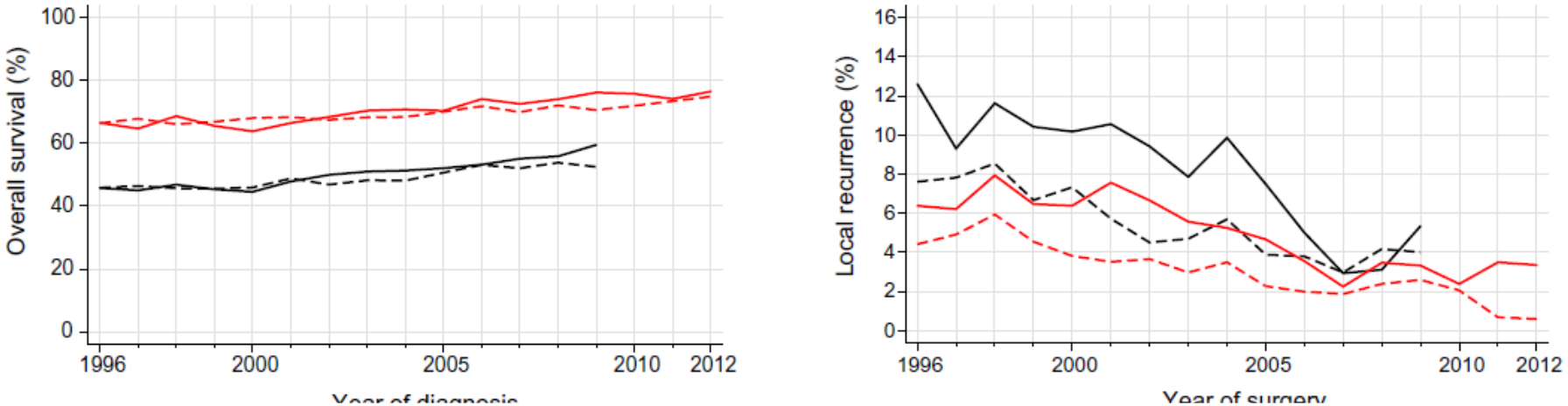
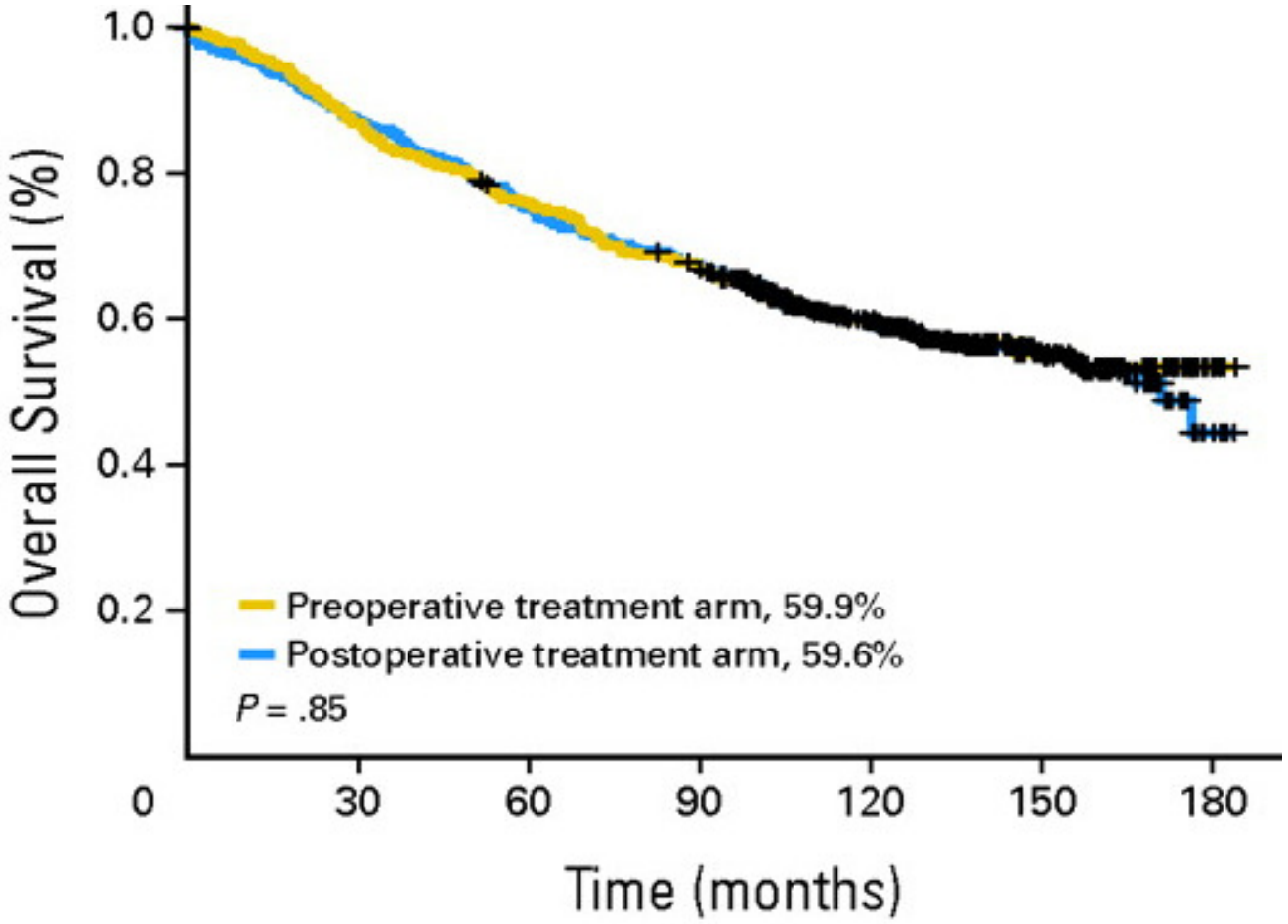


Fig. 2. Radiotherapy (RT) for all patients diagnosed with rectal cancer in Sweden and Norway from 1996 to 2012.

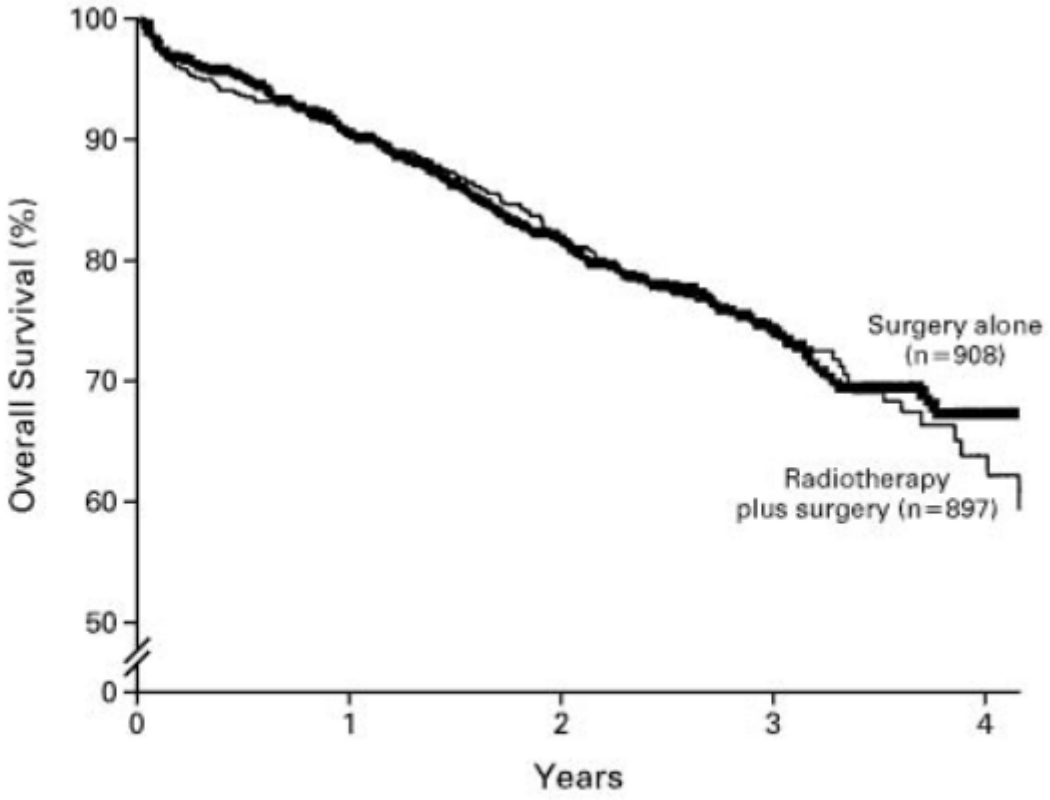


Pre- vs post-operative chemoradiation CAO/ARO/AIO-94



No. at risk							
Preop. CRT	404	351	305	268	174	67	6
Postop. CRT	395	342	295	262	172	70	6

Dutch TME trial Kapiteijn NEJM 2001



No. at Risk					
Radiotherapy plus surgery	897	741	435	192	41
Surgery alone	908	744	454	207	42

At two years, overall survival was 82.0 percent in the group assigned to radiotherapy and surgery and 81.8 percent in the group assigned to surgery alone (P=0.84).

4 Options for radiotherapy in locally advanced rectal cancer

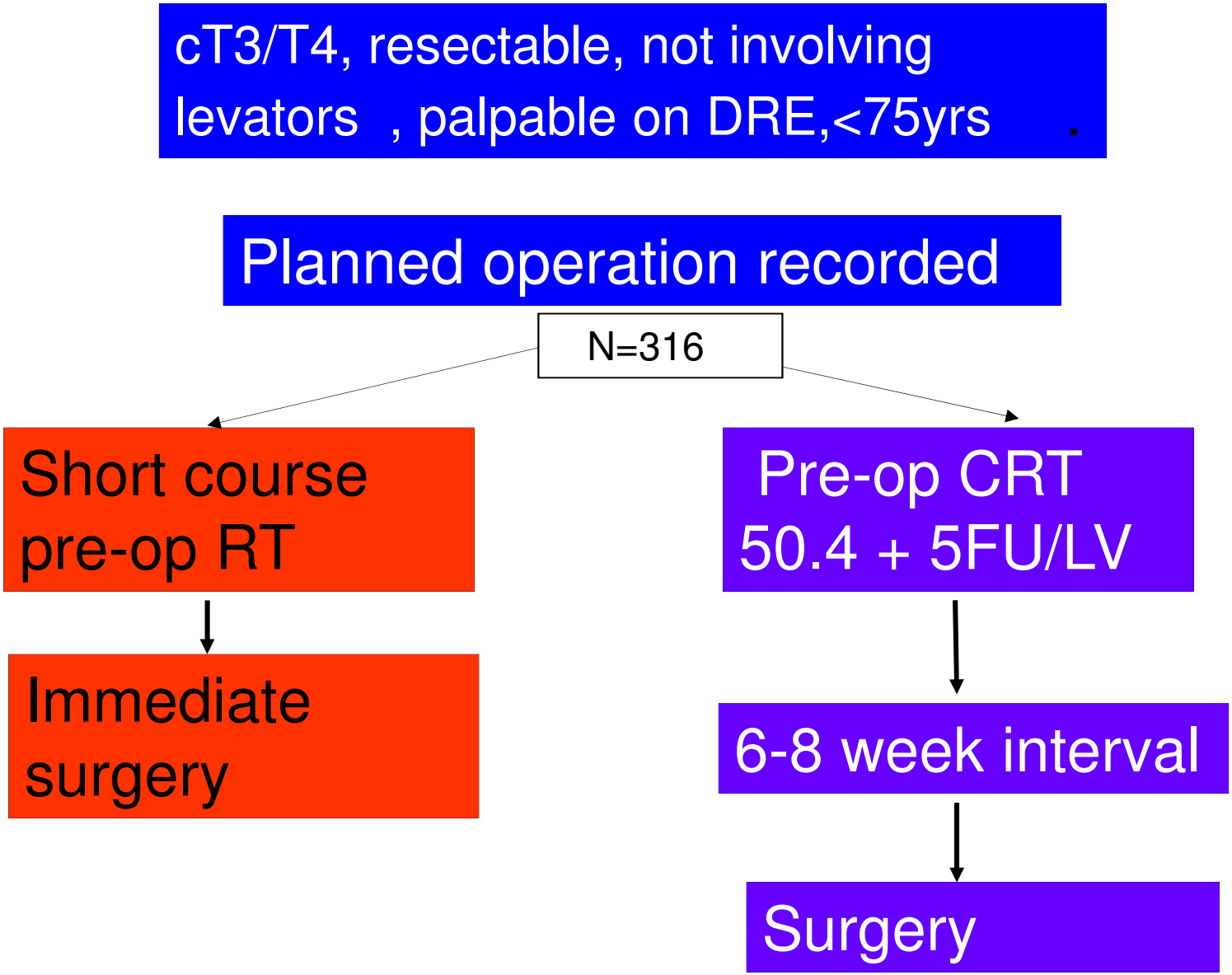
- **Preoperative short course radiotherapy SCPRT (5 X 5 Gy) immediate surgery**
- **Preoperative short course radiotherapy SCPRT (5 X 5 Gy) delayed surgery**
- **Preoperative long course chemoradiotherapy CRT (25-28 X 1.8Gy Gy)**

- **(Post-op CRT as adjuvant)**

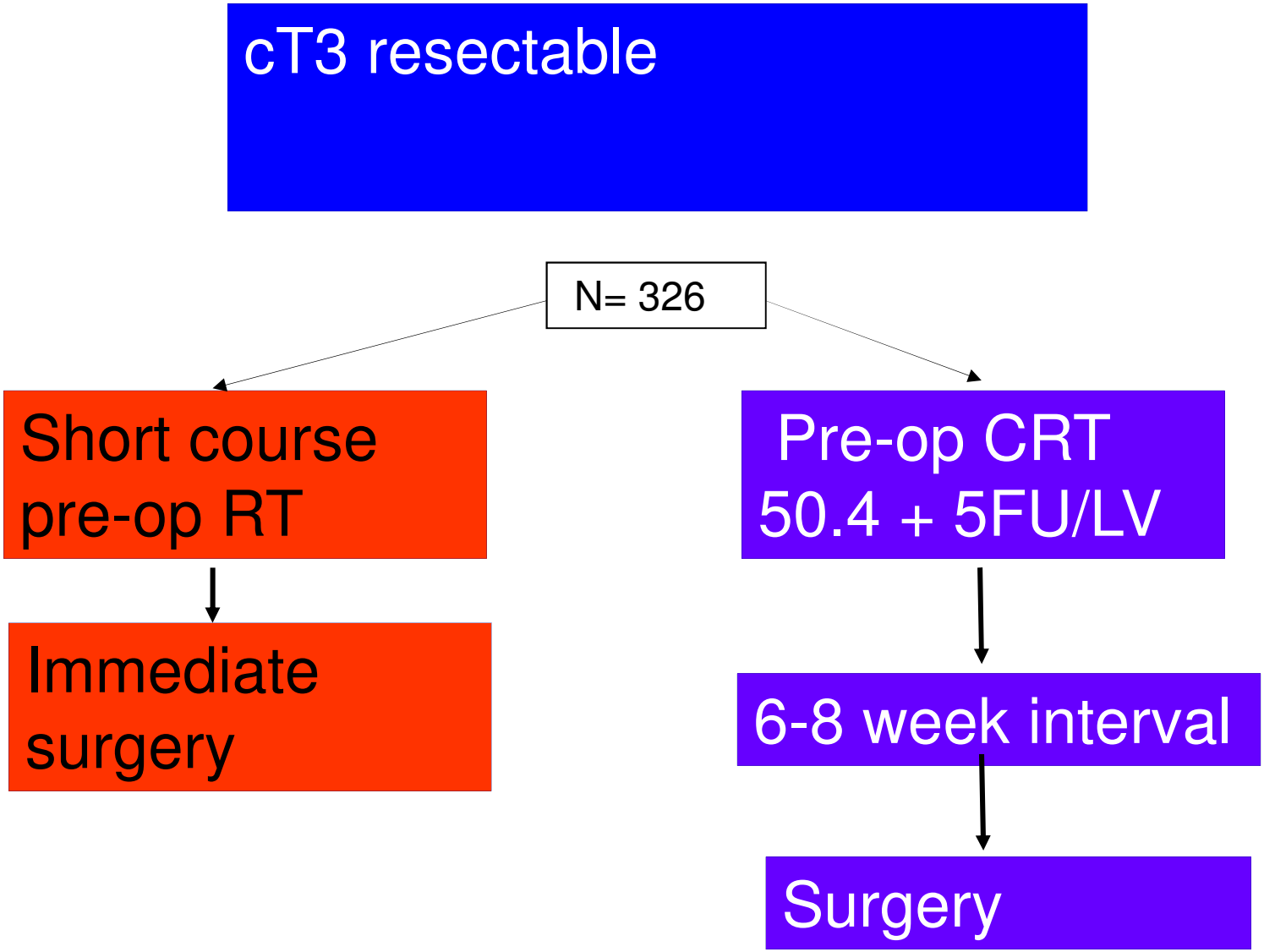
Current Wisdom

- Preoperative chemoradiation (CRT) better than postop
- Short course SCPRT=CRT for resectable cancers
- SCPRT/CRT improves local recurrence but not DFS or OS
- If circumferential resection margin (CRM) threatened on MRI needs response so CRT
- Low rectal cancers (below the levators) often have threat to CRM and may have LPLN

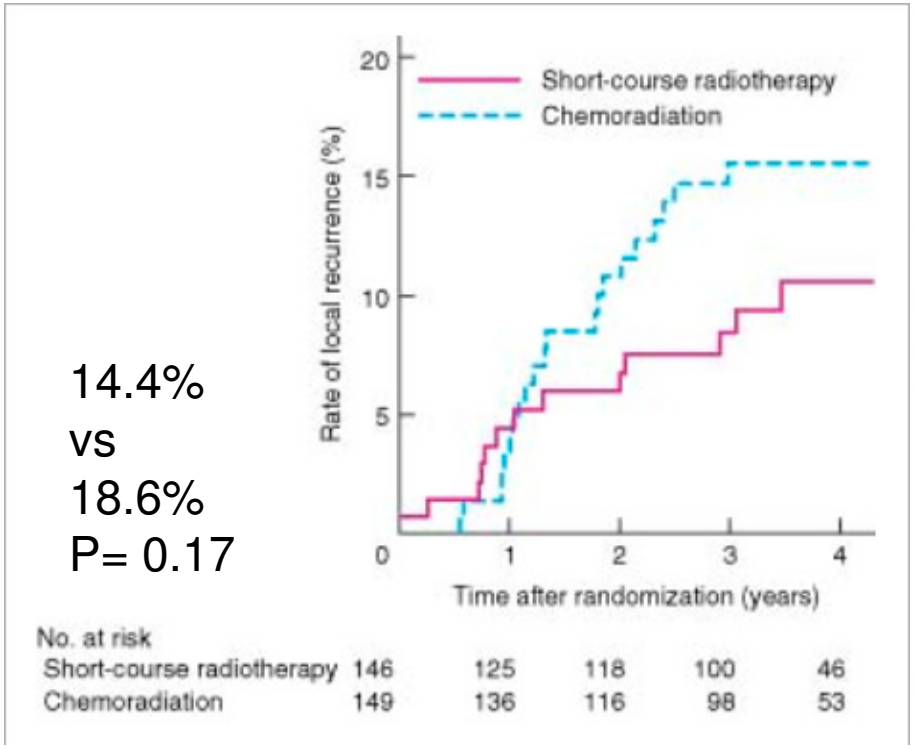
Polish trial Bujko et al Radiotherapy and Oncology 2004



TROG AGIT LSSANZ RACS trial Ngan JCO 2012

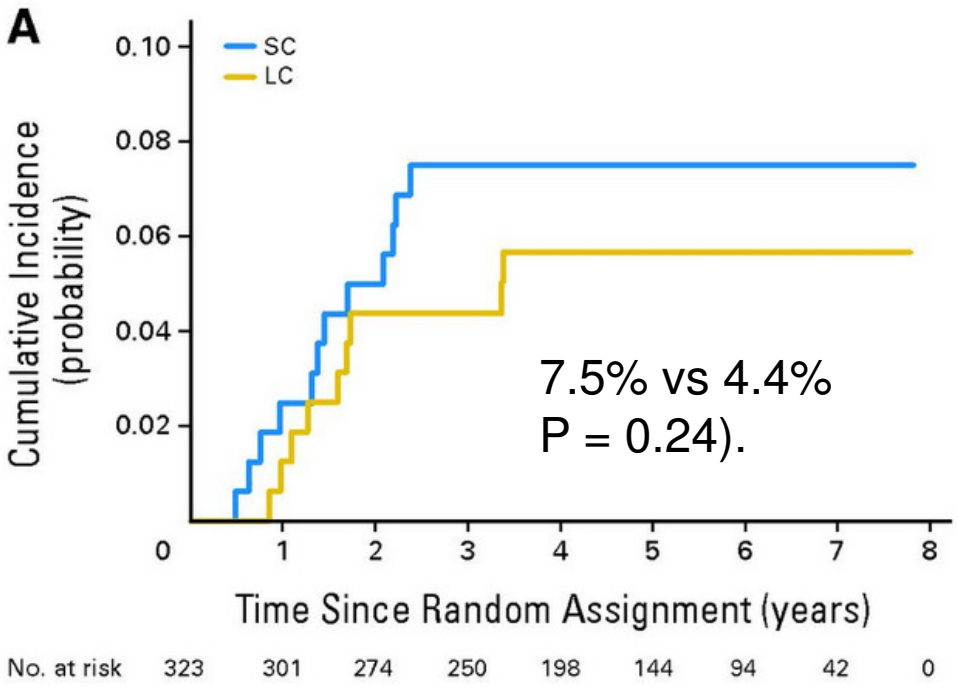


SCPRT versus CRT : no difference in local control



14.4%
vs
18.6%
P= 0.17

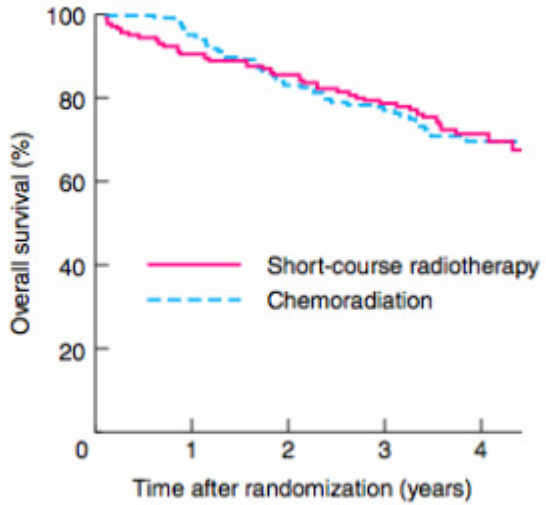
Polish Trial (Bujko 2006)



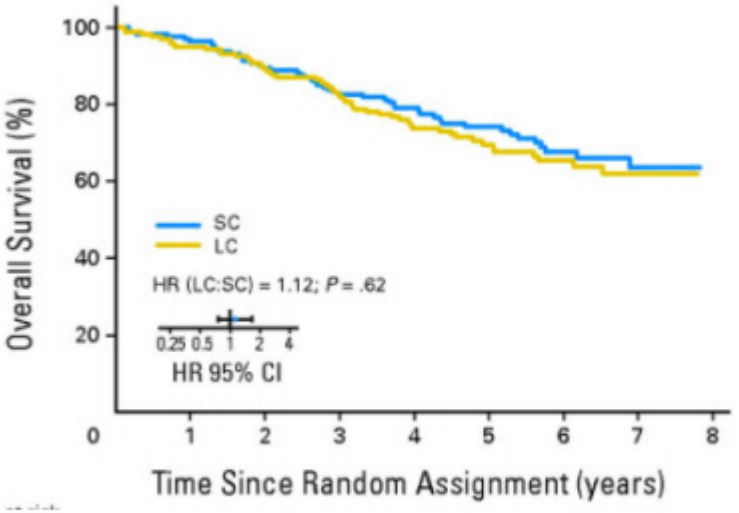
7.5% vs 4.4%
P = 0.24).

TROG-01 Trial (Ngan 2012)

SCPRT versus CRT : Equivalence in overall survival



Polish trial (Bujko 2006)

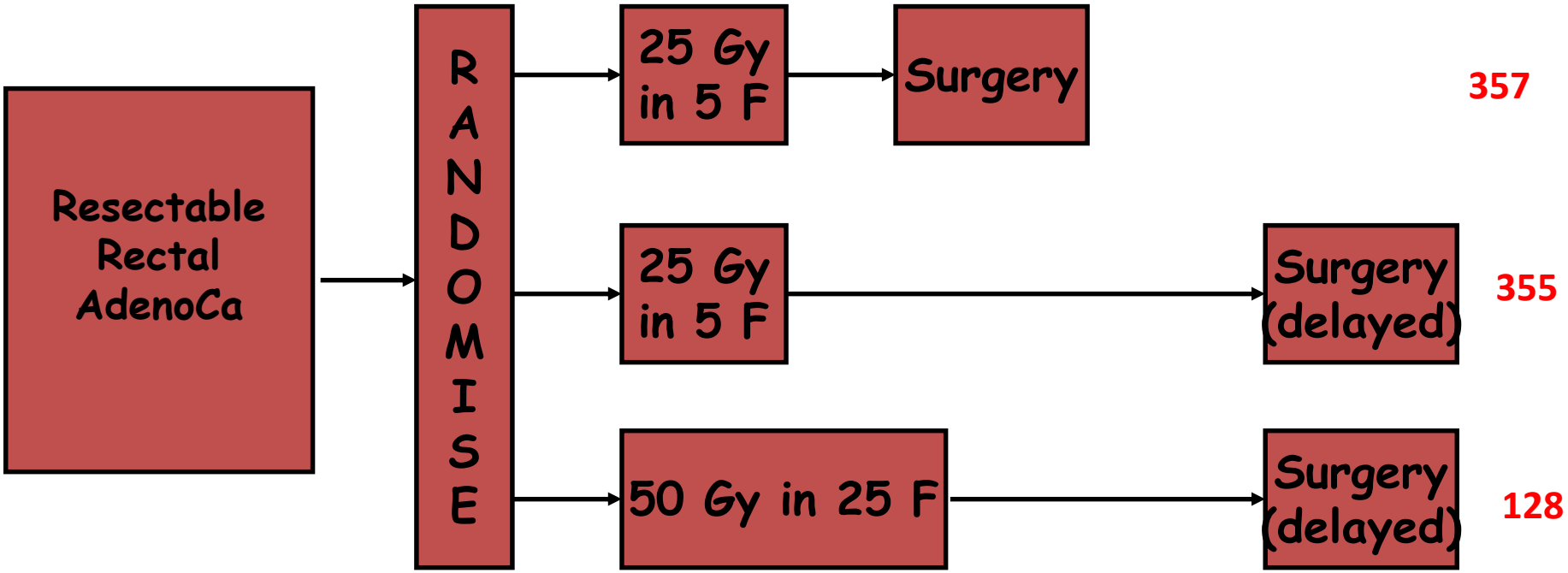


Trans-Tasman trial (Ngan 2012)

- Short course (5x5 Gy) and immediate Surgery

- Short course (5x5 Gy) and wait 6-8 weeks

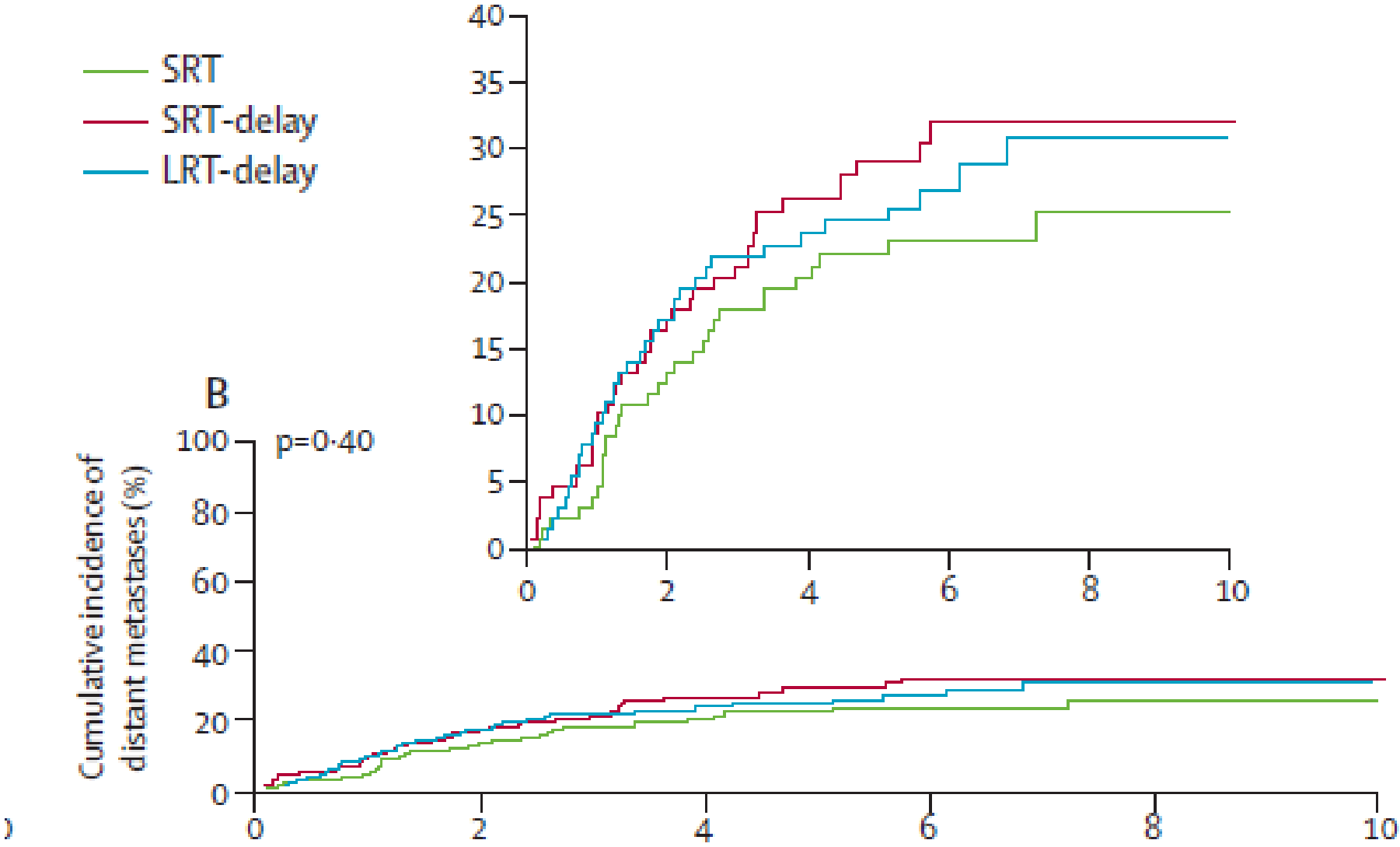
STOCKHOLM III



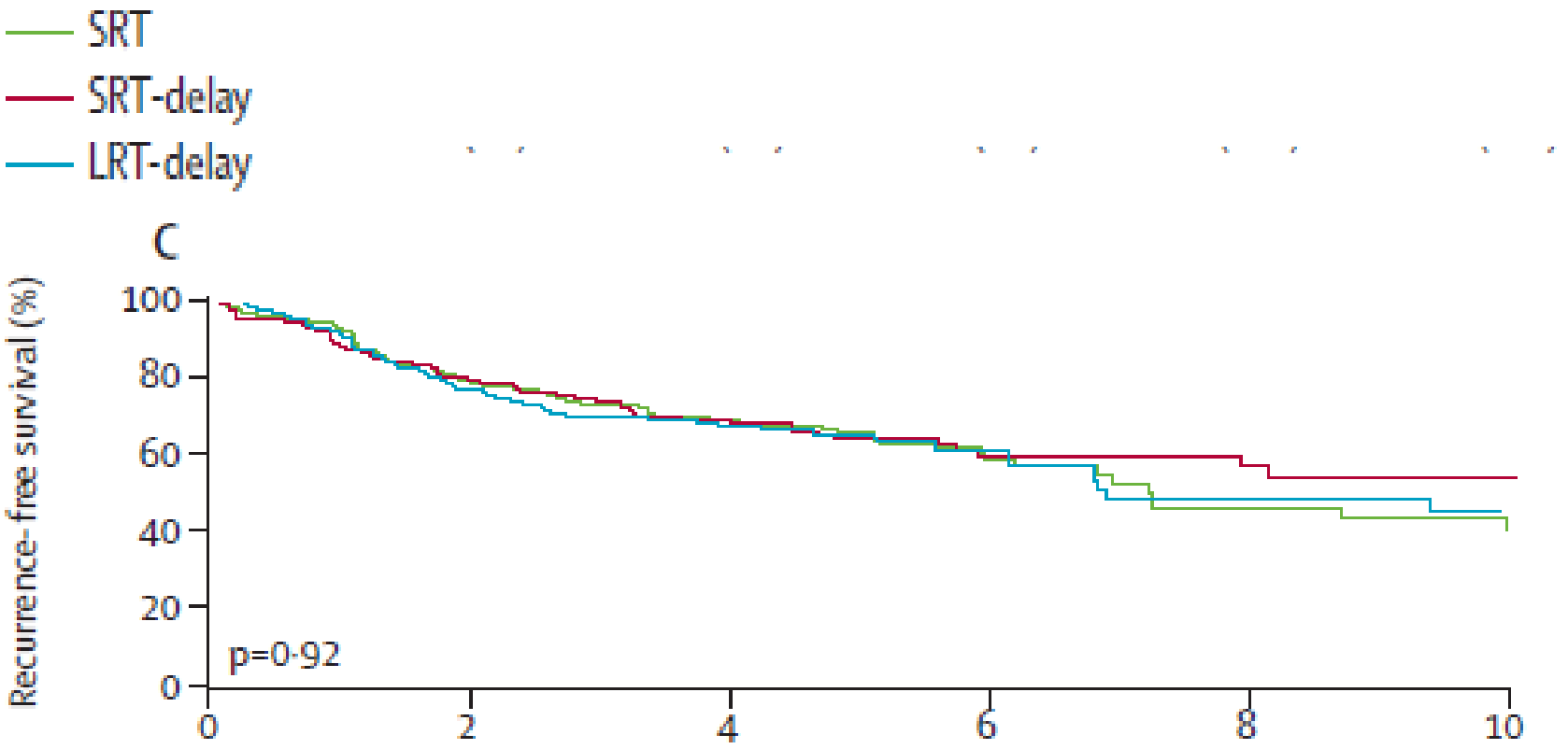
Primary endpoint: sphincter preservation rate

Pettersson et al BJS 2010/ Erlandsson 2017

Stockholm III trial : incidence of metastases

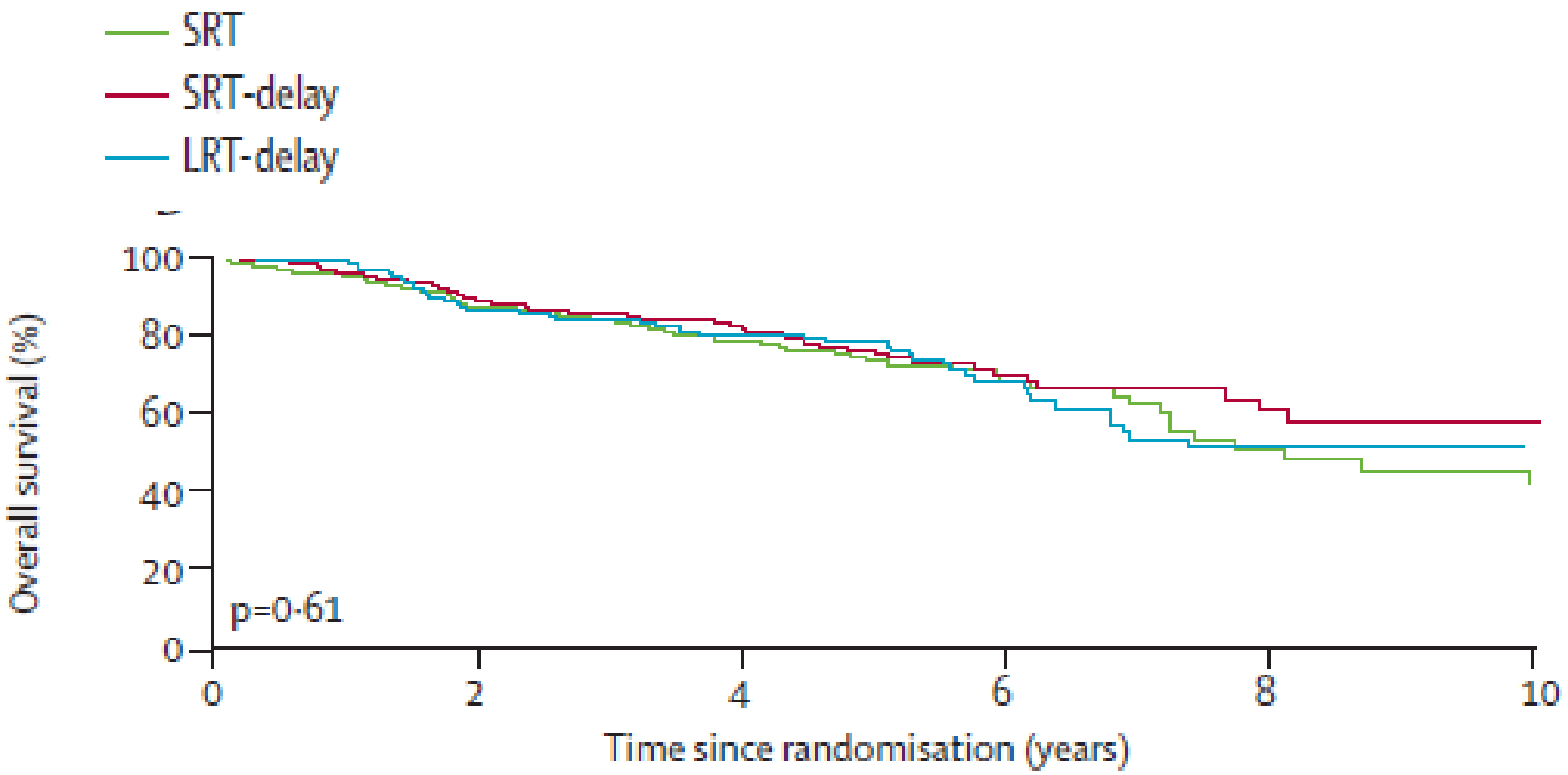


Stockholm III trial :Recurrence Free Survival



Number at risk (censored)						
SRT	129 (0)	101 (0)	82 (8)	36 (44)	18 (56)	12 (60)
SRT-delay	128 (0)	101 (0)	77 (11)	36 (45)	20 (59)	17 (62)
LRT-delay	128 (0)	97 (1)	74 (13)	34 (47)	20 (55)	9 (65)

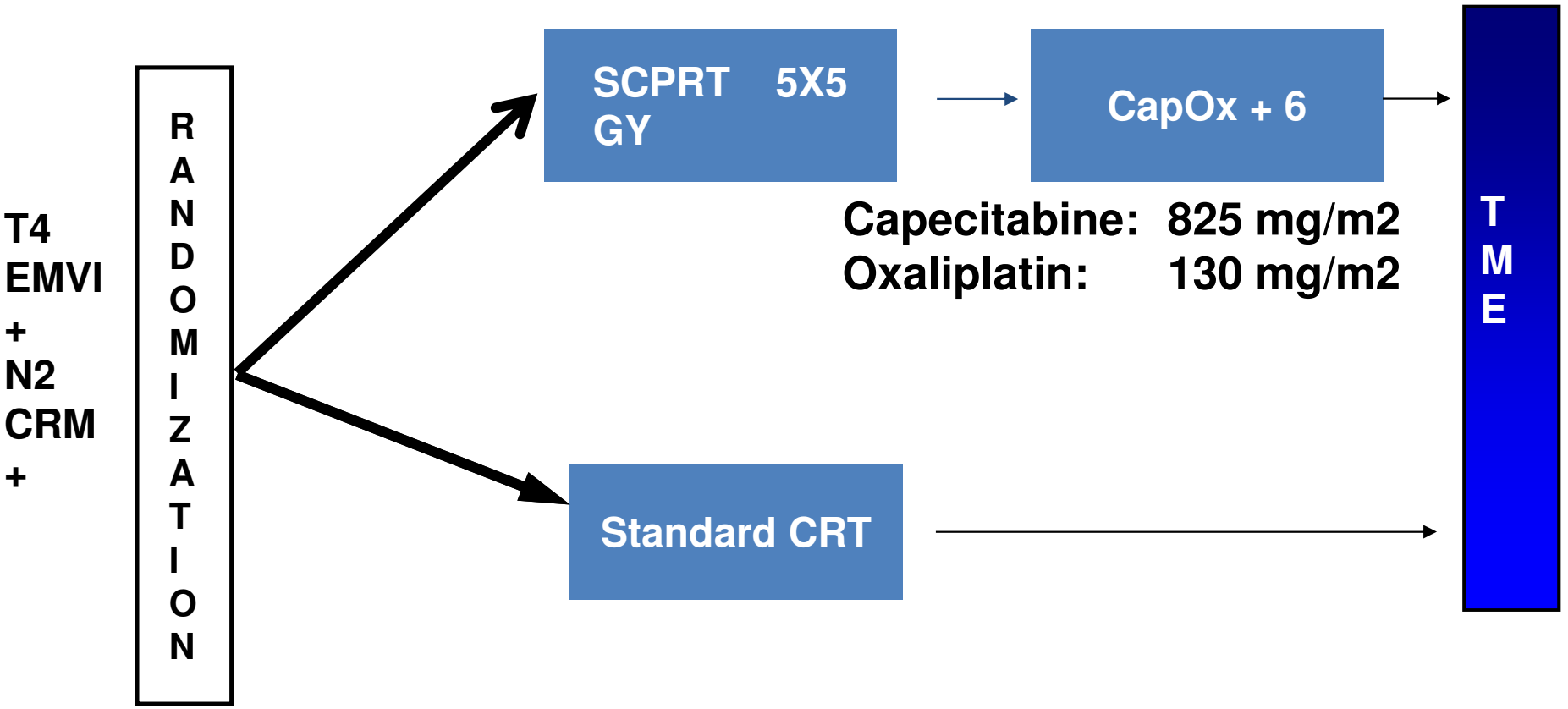
Stockholm III trial :Overall Survival



129 (0)	112 (0)	92 (11)	42 (51)	19 (65)	12 (70)
128 (0)	114 (0)	92 (14)	43 (52)	22 (68)	18 (72)
128 (0)	110 (2)	89 (15)	41 (53)	23 (62)	11 (74)

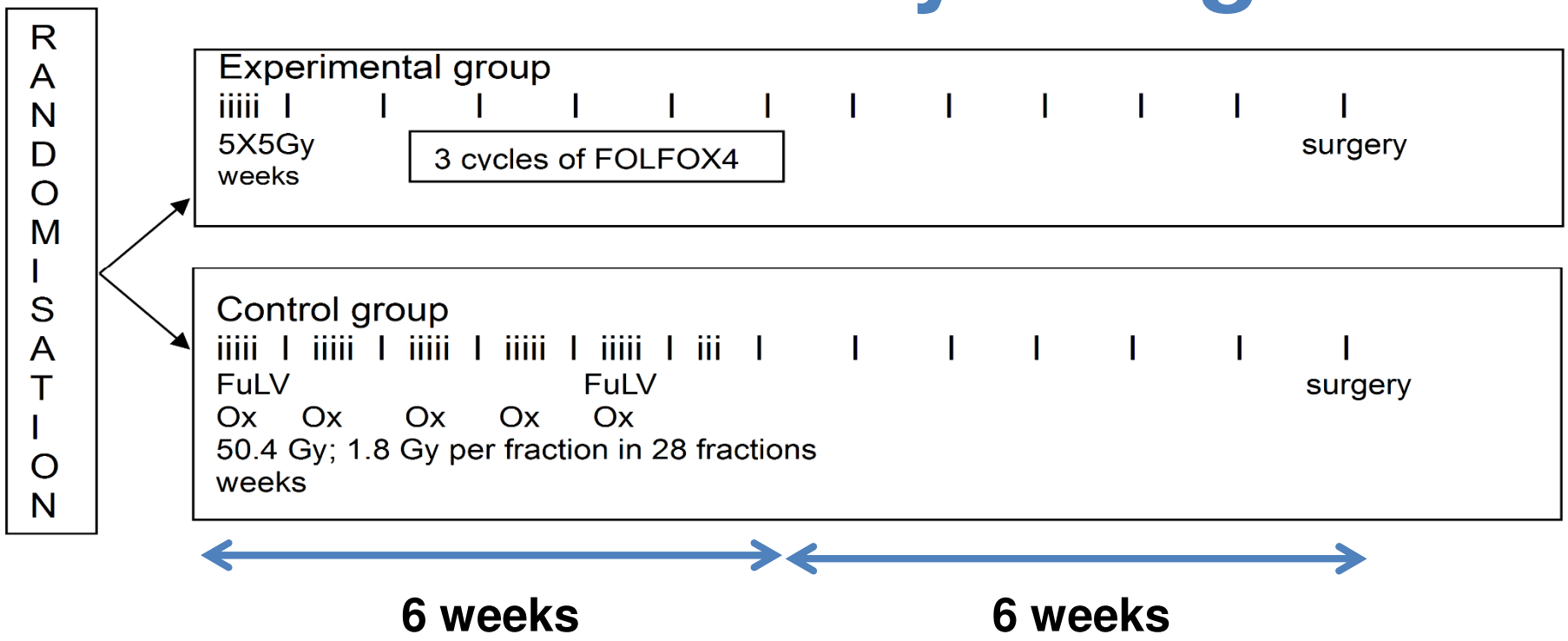
RAPIDO Trial

N = 885 patients



Primary endpoint 3 year DFS

Polish-2: study design



N = 540, randomized 1:1

cT4 or fixed at DRE cT3

M0

ECOG 0-2

Treatment length and total oxaliplatin dose were balanced.

Primary end-point [n=515]

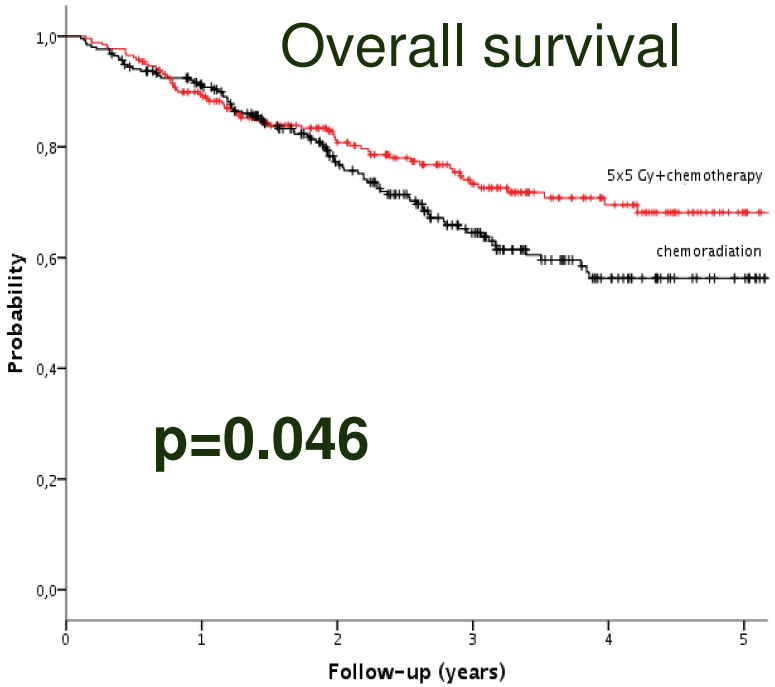
R0 resection rates (surgery performed & pathologic R0 status):

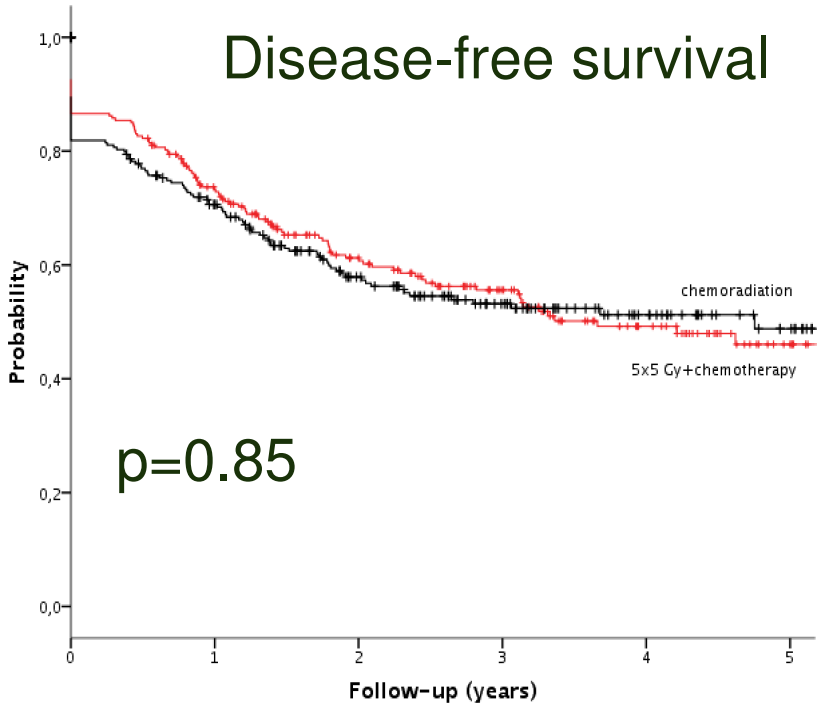
- 77% for SCPRT with 3 cycles of chemotherapy
- 71% for CRT (control arm)
- (p=0.081)

Secondary end-points

	SCRTx + FOLFOX4	CRTx	P value
Overall acute toxicity	**75%**	**83%**	**p= 0.006**
Grade III/IV toxicities	23%	21%	NS
pCR rate	16%	12%	p= 0.17

Polish-2: Secondary end-points





chemoradiation

short-course radiotherapy with consolidating chemotherapy

[median follow-up: 36 months]

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5 Options for chemotherapy in locally advanced rectal cancer

- **Induction** - pre RT (Short-course(SCPRT) or chemoradiation (CRT)
- **Concurrent** - With RT (CRT)
- **Consolidation** - post CRT or SCPRT if waiting 6 12 weeks before surgery
- **Neoadjuvant alone without RT**

- **Post-op adjuvant**

Currently - Different Philosophies

- Medical Oncology trials EXPERT, EXPERT C, SPANISH (Fernandez-Martos)/ RAPIDO /GRECCAR 4) use systemically active chemotherapy outside chemoradiation/SCPRT

- Radiation Oncology trials ACCORD 12, STAR-01, CAO/ARO/AIO-04, NSABP R04 use oxaliplatin as radiosensitizer (non systemic doses) with long course

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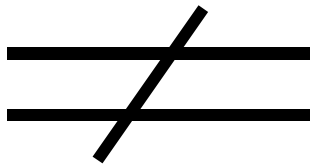
Chemotherapy Conventional wisdom

- Same rules apply as adjuvant for colon cancer (TNM EMVI etc)
- Compliance postop is worse in rectal cancer
- Many don’t even start because of healing
- So trials don’t show same benefit

Reported clinical and pathological parameteers

- Clinically imaged parameters
- cNodal
- cEMVI



- Pathological parameters
- pN
- pEMVI

In the real world in my MDT

Except maybe extracapsular nodal extension

MRI FINDINGS				
T2, T3a, T3b <4mm CRM not threatened (predicted margin ≥2mm) N0 EMVI: Negative	T3b >4mm CRM not threatened (predicted margin ≥2mm) N1 EMVI: Negative	T3b >4mm T3c CRM not threatened (predicted margin ≥2mm) N2 EMVI: Positive	T3d >15mm, T4a (resectable) CRM not threatened (predicted margin ≥2mm) N: Any EMVI: Any	T3c,T3d, T4b CRM breached or threatened (predicted margin <1mm) N:Any EMVI: Any
MRI RISK STRATIFICATION				
LOW RISK		**INTERMEDIATE RISK**		**HIGH RISK**
Low risk local recurrence	Low risk local recurrence	Moderate risk of local recurrence	High risk of local recurrence	High risk local recurrence
Low risk of metastases	Moderate risk of metastases	High risk of metastases	High risk of metastases	High risk of metastases
MRI DIRECTED CLINICAL MANAGEMENT				
Surgery alone	If able to perform good quality R0 resection, RT may be omitted	SCPRT or CRT depending on whether shrinkage of tumour required	SCPRT or CRT depending on whether shrinkage of tumour required	CRT required or SCPRT + chemo

3 Questions

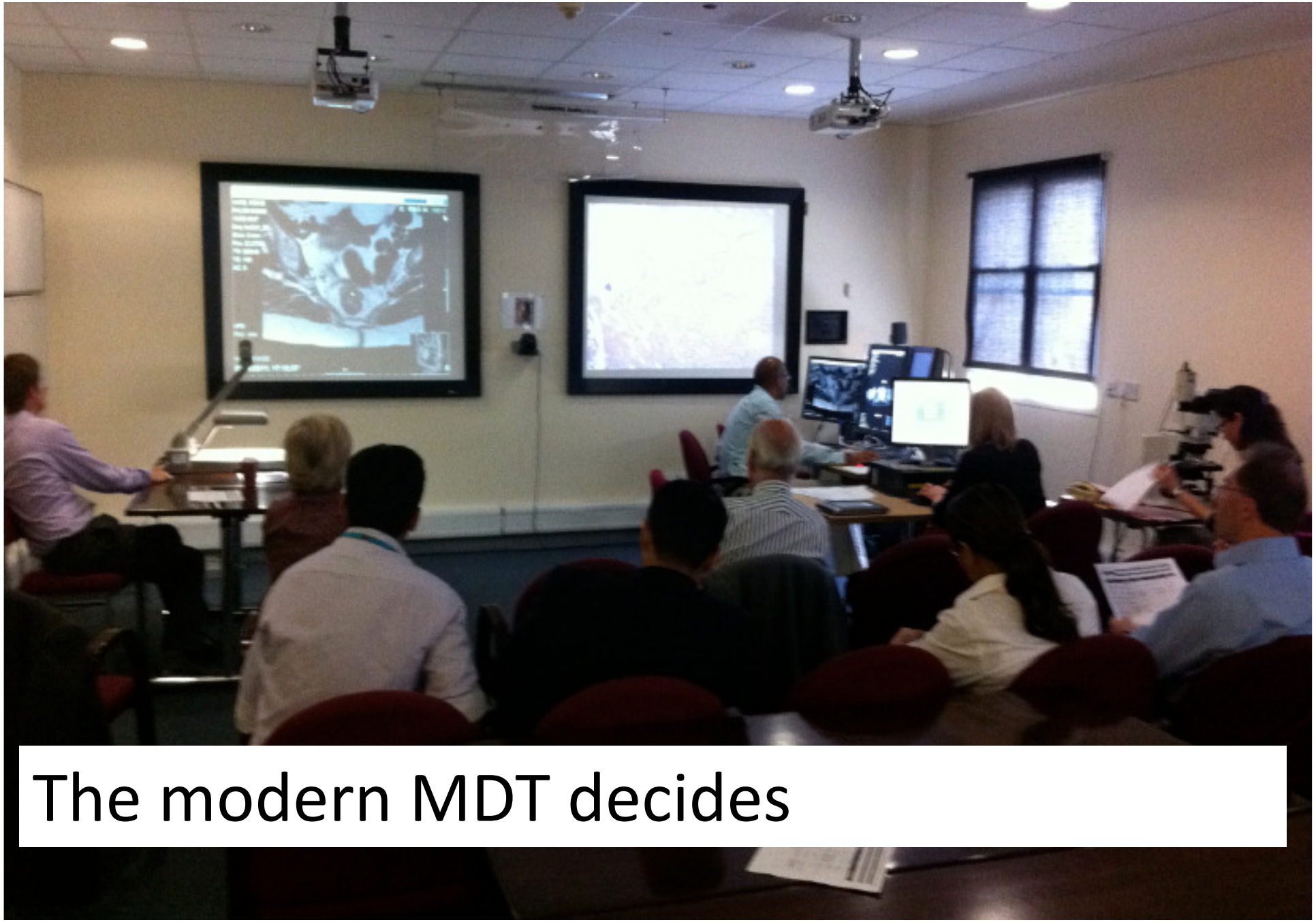
- Do you simply want to reduce the risk of local recurrence (SCPRT or CRT needed)

- Do you need to shrink the cancer to ensure an R0 resection?

(you can ignore data re irinotecan and biologicals on postop adjuvant)

- Or do you want to reduce micro-metastases?

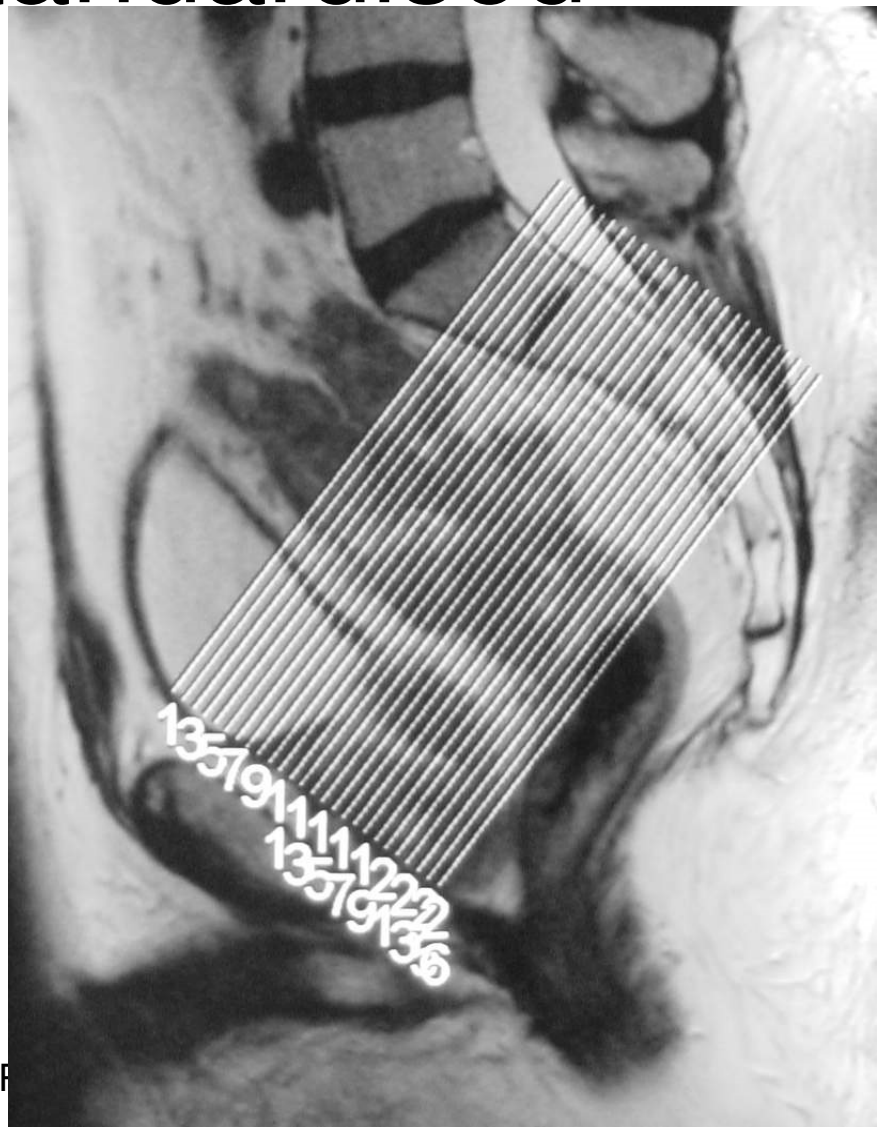
(you cant ignore data on postop adjuvant)



The modern MDT decides

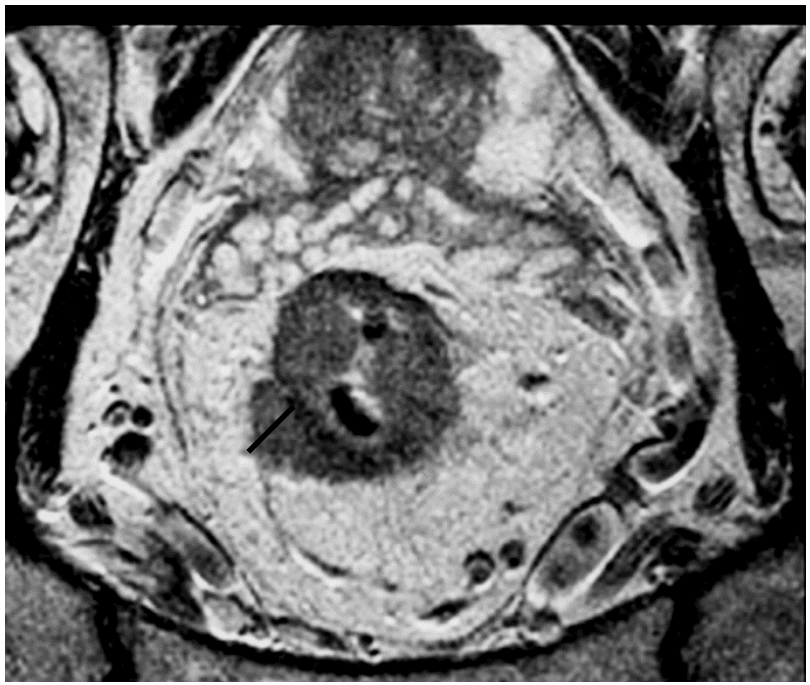
MRI is now Standardised

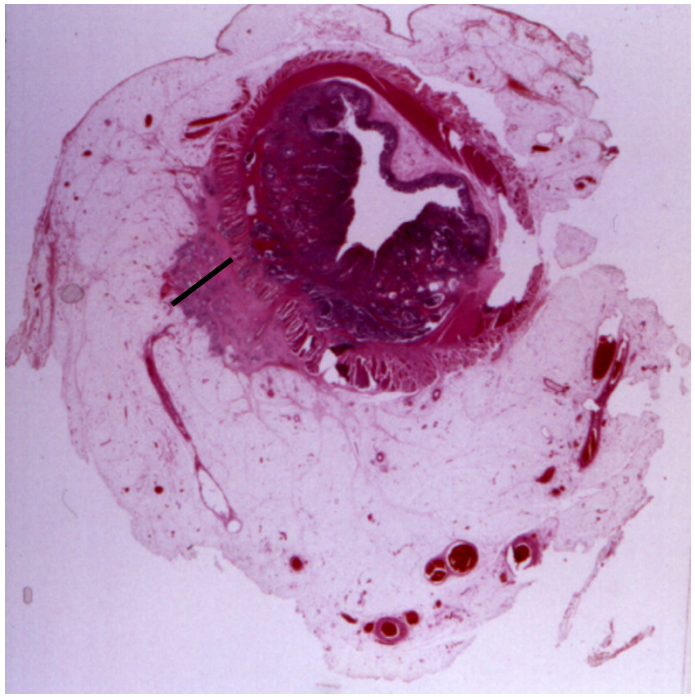
- 3mm, 16cm-18cm FOV, 4-6 NSA, 256x256 matrix, TR >3,000, TE 80-100, ETL 16
- In plane resolution 0.6mm x 0.6mm
- Brown G, Daniels IR, Richardson C et al Br J Radiol 2005; 78:245-251.



Measuring depth of extramural spread

MERCURY Radiology 2007, 243: 132-9



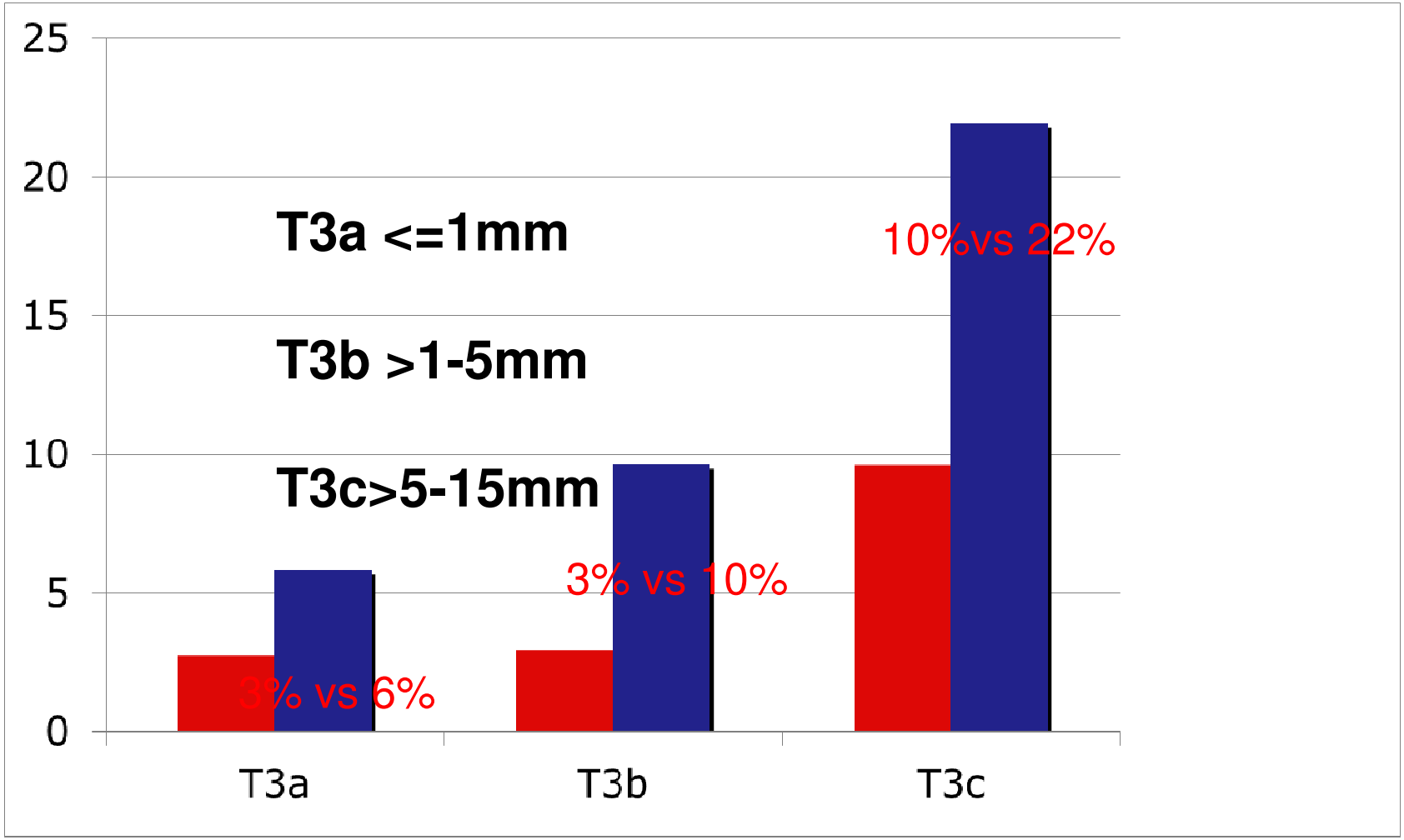


295/311 (95 %) patients who underwent primary surgery.
The mean difference between MRI and histopathology assessment of tumor EMD was -0.046 mm, SD = 3.85 mm, the 95 % CI was -0.487 to 0.395 mm.
MRI and histopathology assessment of tumor spread are considered equivalent to within 0.5 mm (≤ R).

Conventional high risk features for local recurrence

- Rectal tumour extends within 1mm or beyond mesorectal fascia
- cT3 tumours at level of levators / involving levators especially anterior tumours
- Tumour >5mm beyond muscul propria (T3c)
- T4a/T4b tumours
- Extramural vascular invasion (EMVI)
- cN2 cancers ?? Unless extracapsular

CR07: Local recurrence by T3 substage



- Quality of surgery is the biggest factor in Local recurrence –not whether or not you have radiotherapy

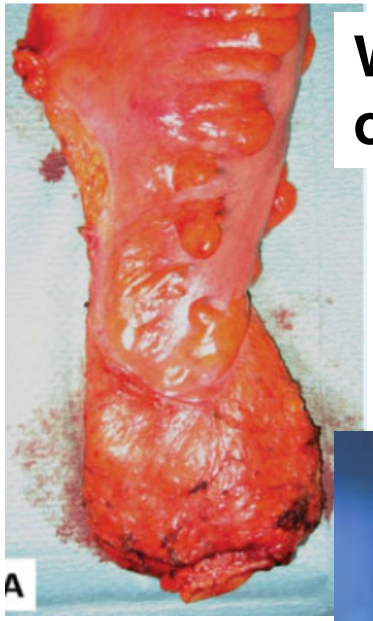
- Quality of surgery can be viewed and scored

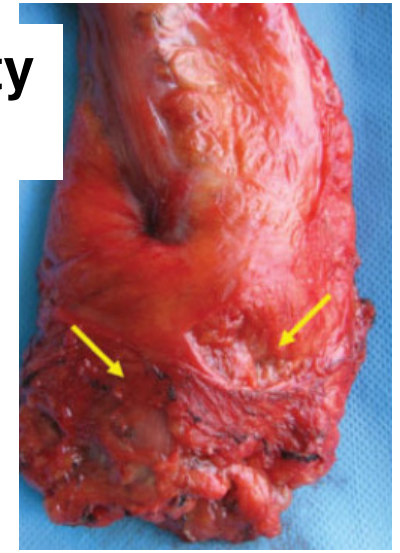
Scoring the Quality of the mesorectum

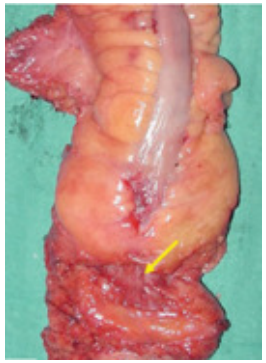
	Mesorectum	Defects	Coning	MRF
Complete	Intact, smooth	Not deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk	Down to muscularis propria	Moderate–marked	Irregular

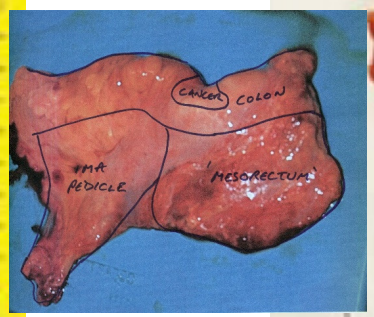
Both the specimen as a whole (fresh) and cross-sectional slices (fixed) are examined in order to make an adequate interpretation

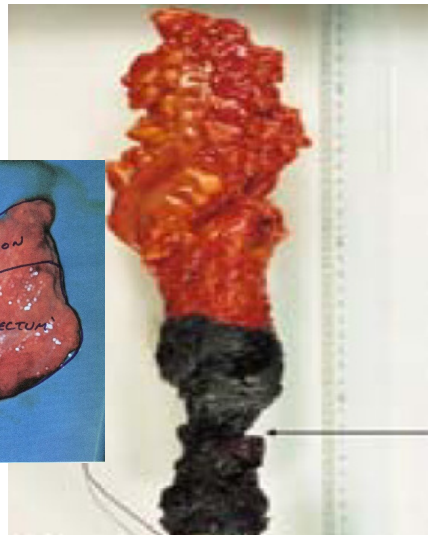
We can judge the quality of the Surgery







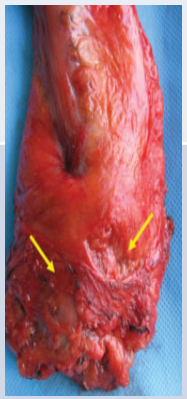




Local Recurrence rates in CRO7 according the plane of surgery

Quirke P et al Lancet. 2009 Mar 7; 373(9666): 821–828

	Plane of Surgery		
TNM stage	**Muscularis propria**	**Intra-mesorectal**	**Mesorectal**
I	**8%**	**2%**	**0%**
II	**6%**	**2%**	**5%**
III	**20%**	**14%**	**6%**



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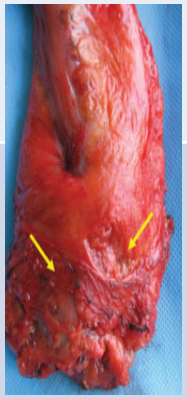

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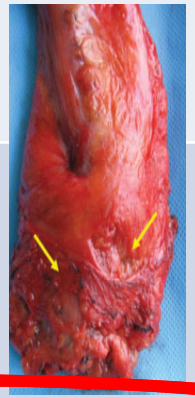
	Plane of Surgery		
TNM stage	**Muscularis propria**	**Intra-mesorectal**	**Mesorectal**
I	**8%**	**2%**	**0%**
II	**6%**	**2%**	**5%**
III	**20%**	**14%**	**6%**



- Pathologically defined Lymph nodes only affect your local recurrence rate if you leave them inside the patient!

Fokas 2014 Updated Results of the CAO/ARO/AIO-94 Trial for CRT

Preop N category	No at risk	10-Year Cumulative Incidence of Local Recurrence (%)	No at risk	10-Year Cumulative Incidence of Distant Mets (%)	No at risk	10-Year DFS (%)
Overall	391	6.9	406	30.2	361	73
cN0	161	**7.7**	169	**31.2**	152	**71.6**
cN+	213	**6.9**	220	**28.9**	193	**74.7**

In German trial defining LN status on MRI did not predict DFS or OS or LR!

Table 1.

Patient Demographics and Survival Outcomes in 111 Patients Undergoing Preoperative Therapy in the MERCURY Study

Variable	No.	OS			DFS			LR		
		Rate	95% CI	*P*	Rate	95% CI	*P*	Rate	95% CI	*P*
MRI node stage										
N0	68	52	36 to 69		56	38 to 73		22	7 to 38	
N1-2	41	54	42 to 66		54	42 to 66		17	7 to 27	

Even Gina Brown did not find that defining LN status on MRI predicted DFS or OS or LR!

Integration of oxaliplatin into CRT

Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%
Node + (stage III)	29% vs 26%	30% vs 26%	27% vs 26%	Not stated	27% vs 26%

Oxaliplatin Phase III trials: Control arm in red

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Phase III Chemoradiotherapy trials with or without Oxaliplatin

Trial	No of patients	Regimens	DFS	Difference
CAO/ARO/AIO-04 Rodel Lancet Oncology 2015	1236	CRT + Ox 60mg Plus OX adjuvant	71.2% vs 75.9%	**+4.7%** (HR 0.79)
NSABP R-04 JNCI 2016	1606	CRT + Ox 60mg	64.2% vs 69.2%	**+5%**
ACCORD 12 updated 2016 GI ASCO	598	CRT + Ox 60mg + RT 50Gy	67.9% v 72.7%	**+4.3%**
STAR-01 WGICC 2016	747	CRT + Ox 60mg	5 year 66.3% vs 69.2 %	**+2.9%** (HR 0.89)
PETTAC-6	1090	CRT + Ox 60mg Plus OX adjuvant	75% vs 74% (lowest pCR)	**-0.6% outlier**
Chinese Trial Jiao 2015	208	CRT + Ox 60mg All received adjuvant FOLFOX 6–8 cycles	3-year DFS 69.9% vs 80.6% (P>0.05)	**+10.6%**

Adjuvant trials in colon cancer using oxaliplatin in the novel arm.

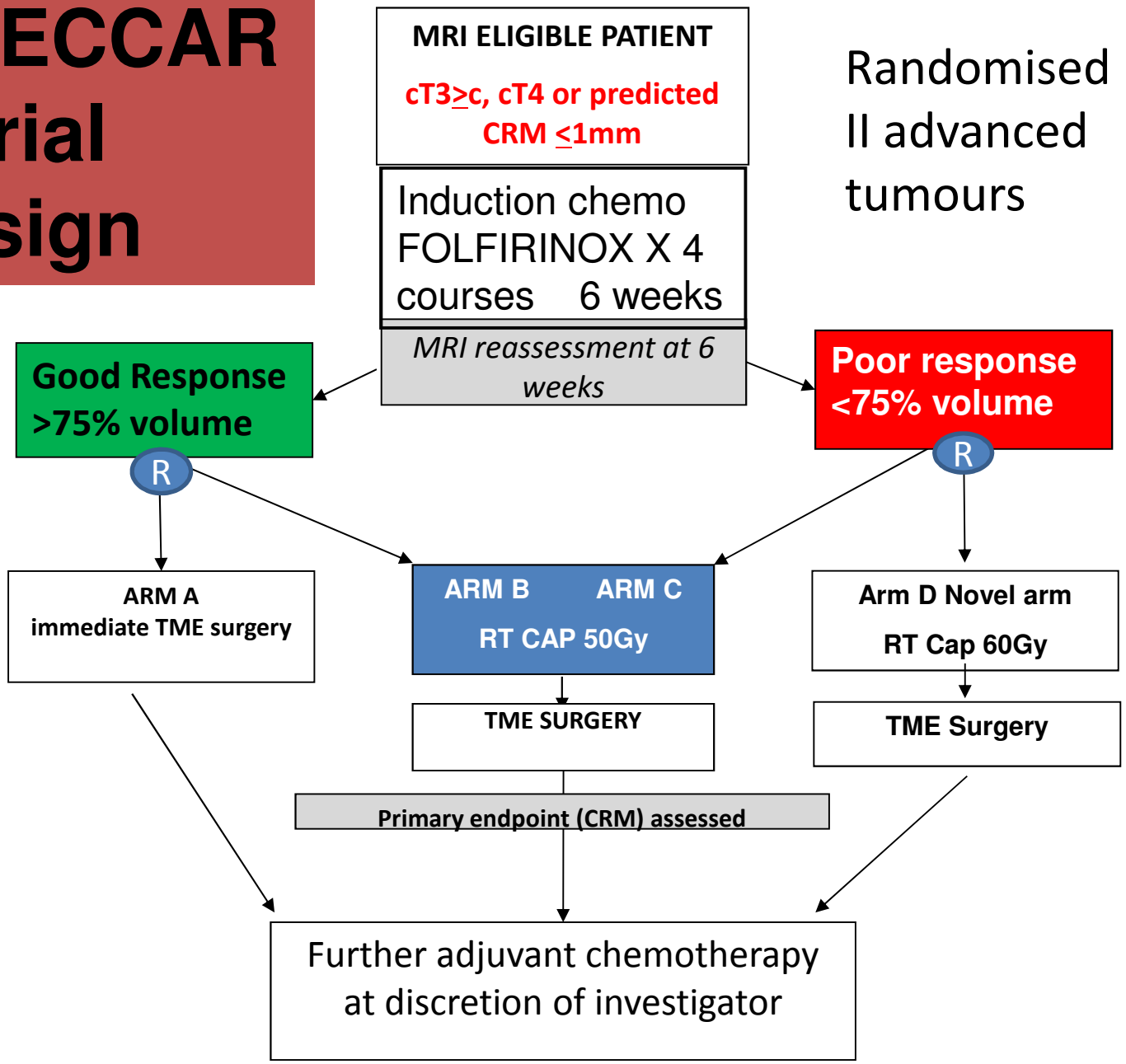
Trial	Patient No	Path Stage	Treatment arms	Median Age	Compliance to planned cycles	5 year DFS
MOSAIC (Andre 2004 updated 2015	2246	II, III	LV5FU2 FOLFOX4	60 61	86.5% 74.7%	67.5% vs 73.2% **+5.7%**
NSABP C07 (Kuebler 2007) updated 2011	2407	II, III	FULV FLOX	59 59	Not stated Not stated	64.2% vs 69.4% **+5.2%**
NO16968 (Haller 2011)	1886	III	FULV XELOX	61 62	83% 69%	3-year DFS 70.9% vs 66.5% **+4.4%**

Phase III trials – Investigating Oxaliplatin

Trial	**Eligibility**	Fluoropyrimidine Platform
CAO/ARO/AIO-04	<12cm from anal verge T3/T4 cN0/N+ TRUS, CT and/or MRI	5FU 1000mg/2 X 5 days 1-5 + 29-33
NSABP R04 N=1606	<12cm; resectable stage II, III TRUS or MRI – CT if T4/ N1-2	PVI 5FU vs Capecitabine
FFCD N=598	Palpable; resectable; T3/4 N0-2; T2 distal anterior	Capecitabine in both arms
STAR – 01 N=747	Resectable stage II, III (c stage) <12cm from anal verge	PVI 5FU in both arms
PETTAC 6 N=1090	Stage II or III resectable or expected to become resectable <12cm from anal verge	Capecitabine in both arms

GRECCAR 4 Trial Design

Randomised Phase II advanced tumours



	Good Respose		Poor Respose	
	Group A 16	Group B 14	Group C 113	Group D 51
Analysed	FOLFIRINOX **alone no CRT** **11**	FOLFIRINOX + standard CRT **19**	 **52**	FOLFIRINOX + **high dose RT** **51**
Ro Resection	90%	100%	83%	88%
CRM ≤1mm	11%	0%	14%	7%
No residual tumour	1/10 (10%)	11/19 (58%)	7/52 (13.5%)	9/46 (20%)

Phase III trials – also adjuvant Oxaliplatin

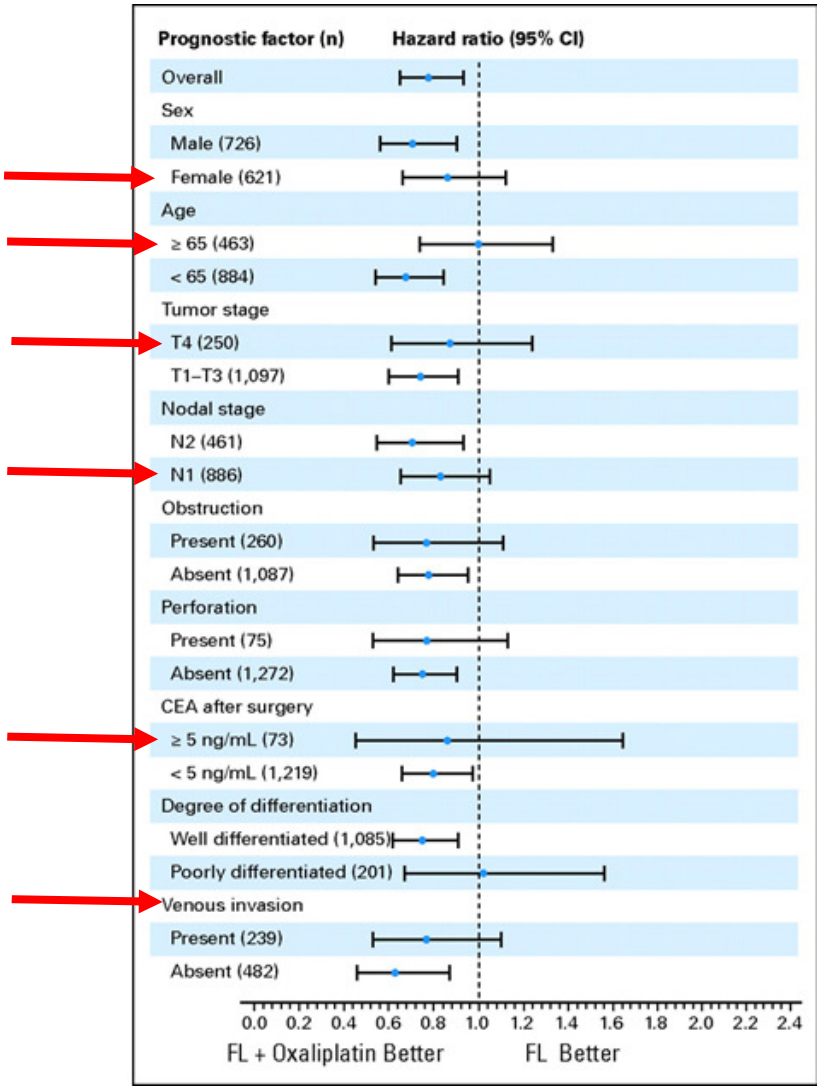
Trial	**Eligibility**	Fluoropyrimidine Platform
CAO/ARO/AIO-04	<12cm from anal verge T3/T4 cN0/N+ TRUS, CT and/or MRI	5FU 1000mg/2 X 5 days 1-5 + 29-33
NSABP R04 N=1606	<12cm; resectable stage II, III TRUS or MRI – CT if T4/ N1-2	PVI 5FU vs Capecitabine
FFCD N=598	Palpable; resectable; T3/4 N0-2; T2 distal anterior	Capecitabine in both arms
STAR – 01 N=747	Resectable stage II, III (c stage) <12cm from anal verge	PVI 5FU in both arms
PETTAC 6 N=1090	Stage II or III resectable or expected to become resectable <12cm from anal verge	Capecitabine in both arms

- Unknown whether these benefits relate to the addition of preoperative or postoperative oxaliplatin, or both.

NSABP R04 (5FU vs Capecitabine- +/- oxaliplatin)

1608 patients	**PVI 5FU** 225 mg/m², 5 days per week	**Capecitabine** 825 mg/m² BID 7 days per week
pCR	138/777 (17.8%)	161/779 (20.7%)
G3-5 diarrhoea	11.7%	11.7%
3 three-year local-regional event rates	11.2%	11.8%
5 Year DFS	66.4%	67.7%
5 year OS	79.9%	80.8%

MOSAIC Trial Benefit of Oxaliplatin

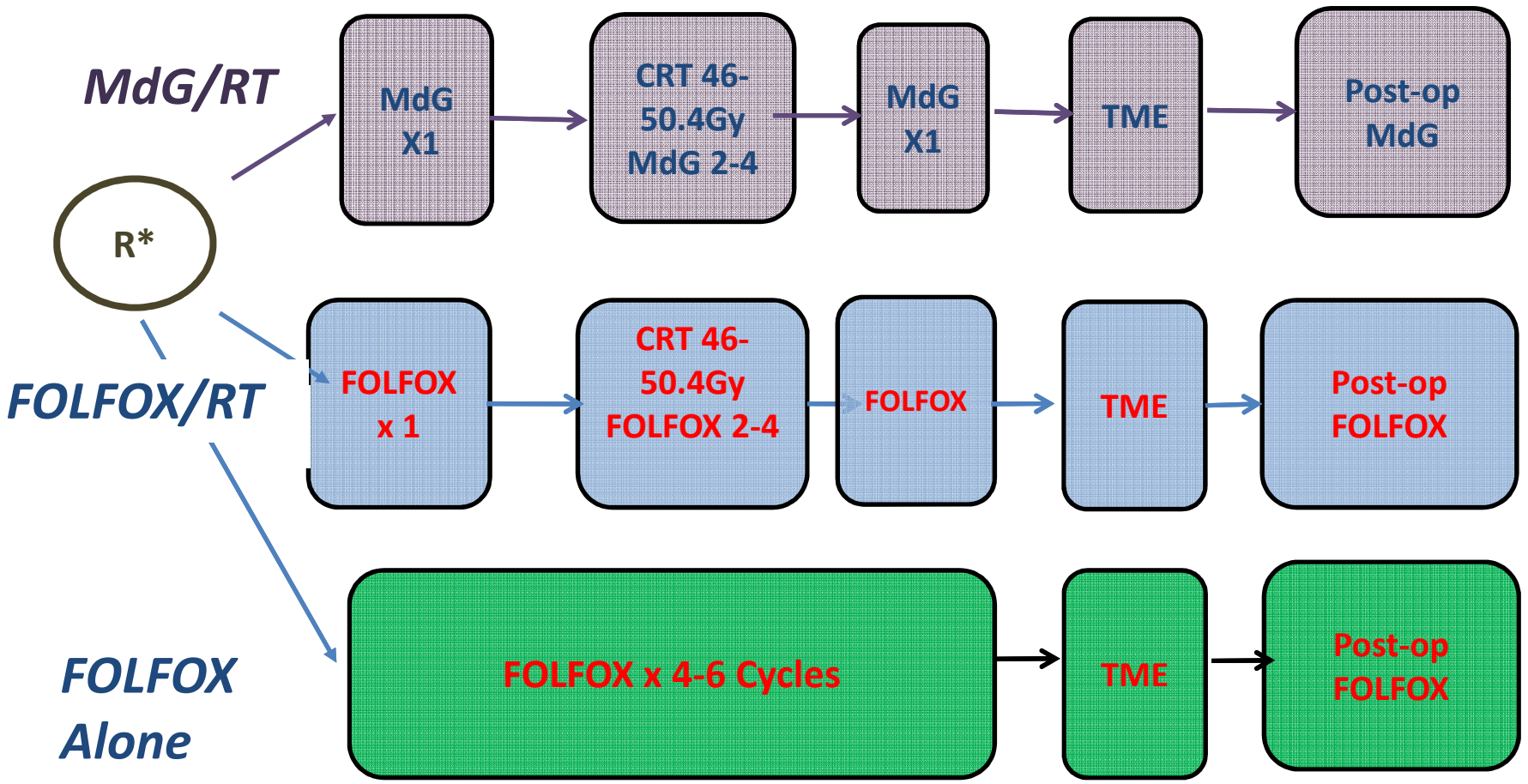


Female
Age > 65
T4
N1
CEA
EMVI

All cross unity!
So benefit if any will be small

Andre T et al N Engl J Med 2004;350:2343-51.

The FOWARC trial – Design



Endpoints

Primary endpoint: 3 yr DFS

Deng, J Clin Oncol 2016

**Patients recruited from 15 Chinese Centres 2010-2015*

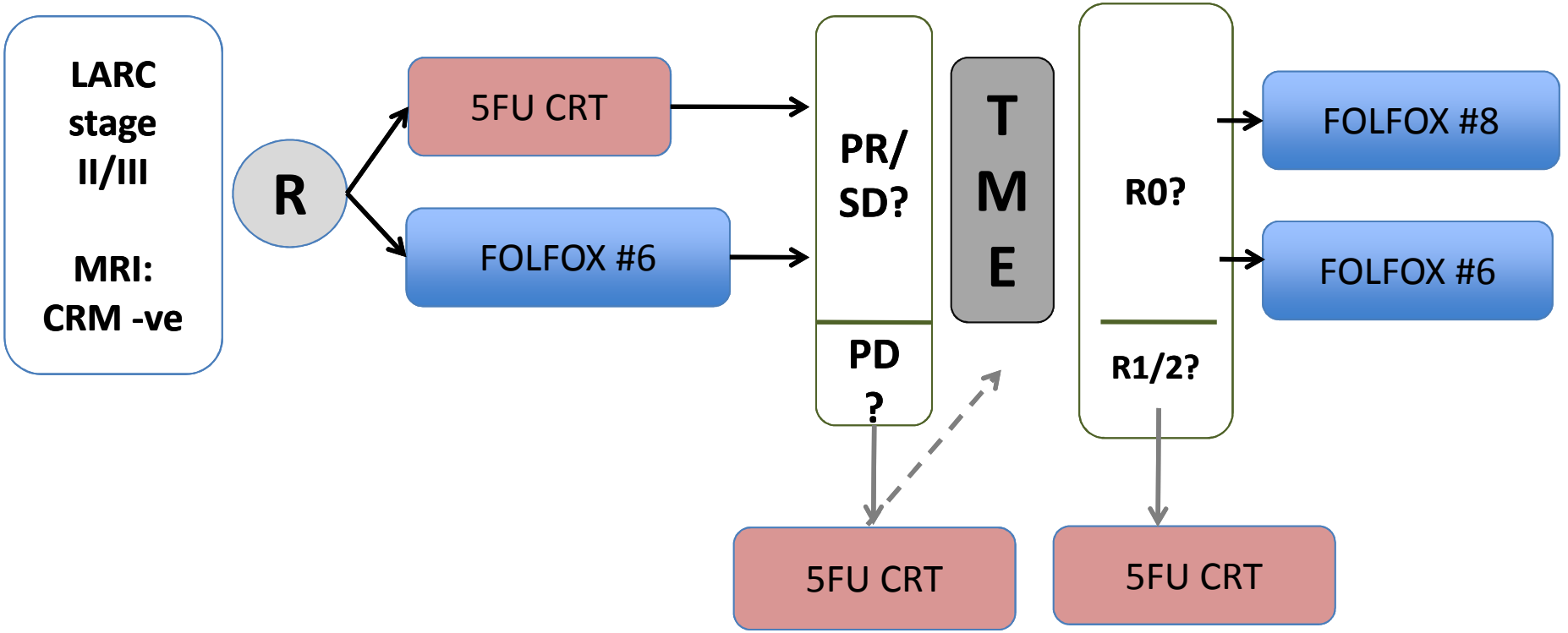
Regimens	Number of patients	G3/G4 toxicity Diarrhea	Interval to surgery (median ir days)	ypN+	pCR	TRG0-1
De Gramont RT 46-50.4Gy	165	7.7%	53	19.9%	14%	49%
FOLFOX RT 46-50.4Gy	165	14.5%	52	12.6%	27.5%	68.5%
FOLFOX alone	165	7.3%	Not stated	26.5%	6.6%	32.9%

Endpoint	STAR-01	ACCORD 12/0405	CAO/ARO/ AIO-04	NSABP R-04	PETACC-6	FOWARC
PCR	16% both arms	14% vs 19%	12.8% vs 16.5% (p=0.038)	19% vs 21%	11.5% vs 13%	14% vs 27.5%
CRM	4% vs 7%	8% vs 13%	5% vs 6%	No data	2% vs 2%	9.2% vs 10% R1/R2
yp Node + (stage III)	29% vs 26%	30% vs 26%	27% vs 26%	Not stated	27% vs 26%	19.9% vs 12.6%

Oxaliplatin Phase III trials: Control arm in red

US Intergroup phase III trial

ACOSOG, Z9062, CALGB, E81001



N planned: > 800
1° endpoint: 3y DFS
2° toxicity, local failures, OS,

Prospect

- Selective use of chemoradiation in patients with
- cT2N1 and cT3N0-1 rectal cancer undergoing sphincter-sparing low anterior resection.

Prospect

- Selective use of chemoradiation in patients with
- cT2N1 and cT3N0-1 rectal cancer undergoing sphincter-sparing low anterior resection.

- The 3-year DFS and freedom from LR for PROSPECT-eligible patients were 79.1% and 97.4%

BOSSE D et al. Clin Colorectal cancer 2016 Sep;15(3):243-9

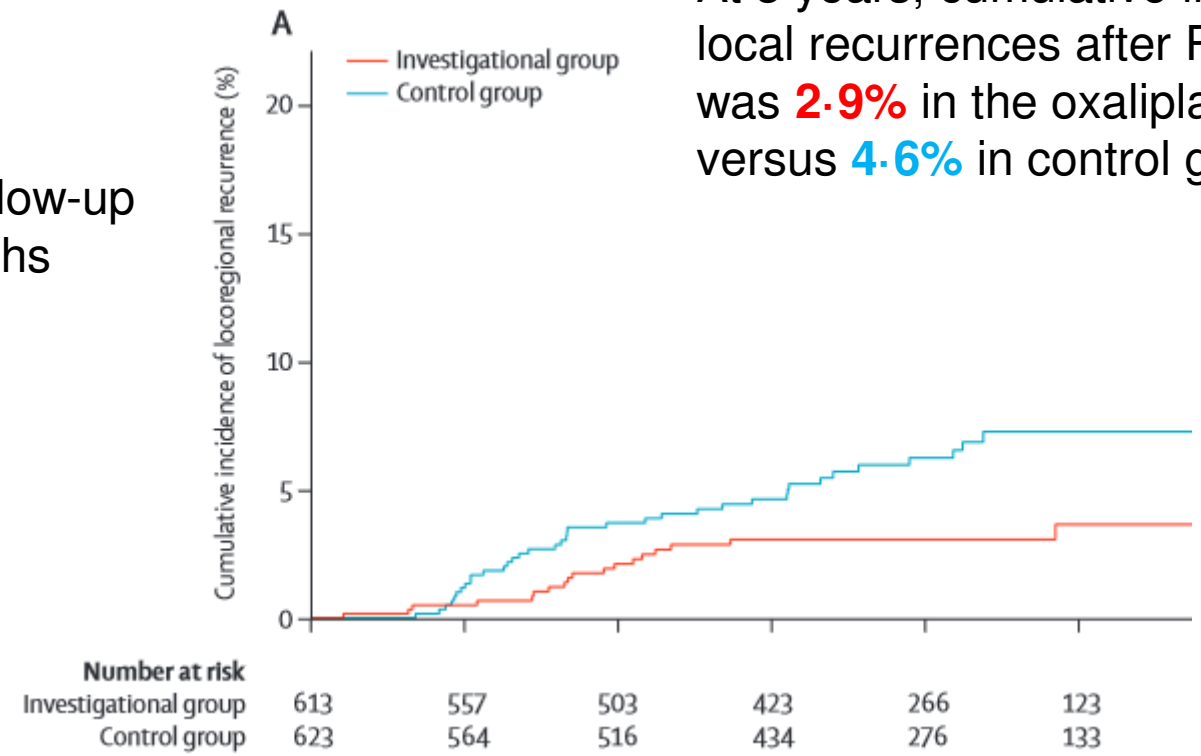
Conclusions

1. 5FU-based CRT standard for downsizing rather than SCPRT but no improvement in SpS, DFS or OS
2. SCPRT = CRT in resectable cancer
3. Radio-sensitizing 5FU-based CRT with sub therapeutic oxaliplatin ?
4. ?Need more active treatment to improve survival if CRM threatened

Thank you

The German CAO/ARO/AIO-04 Trial

median follow-up
of 50 months

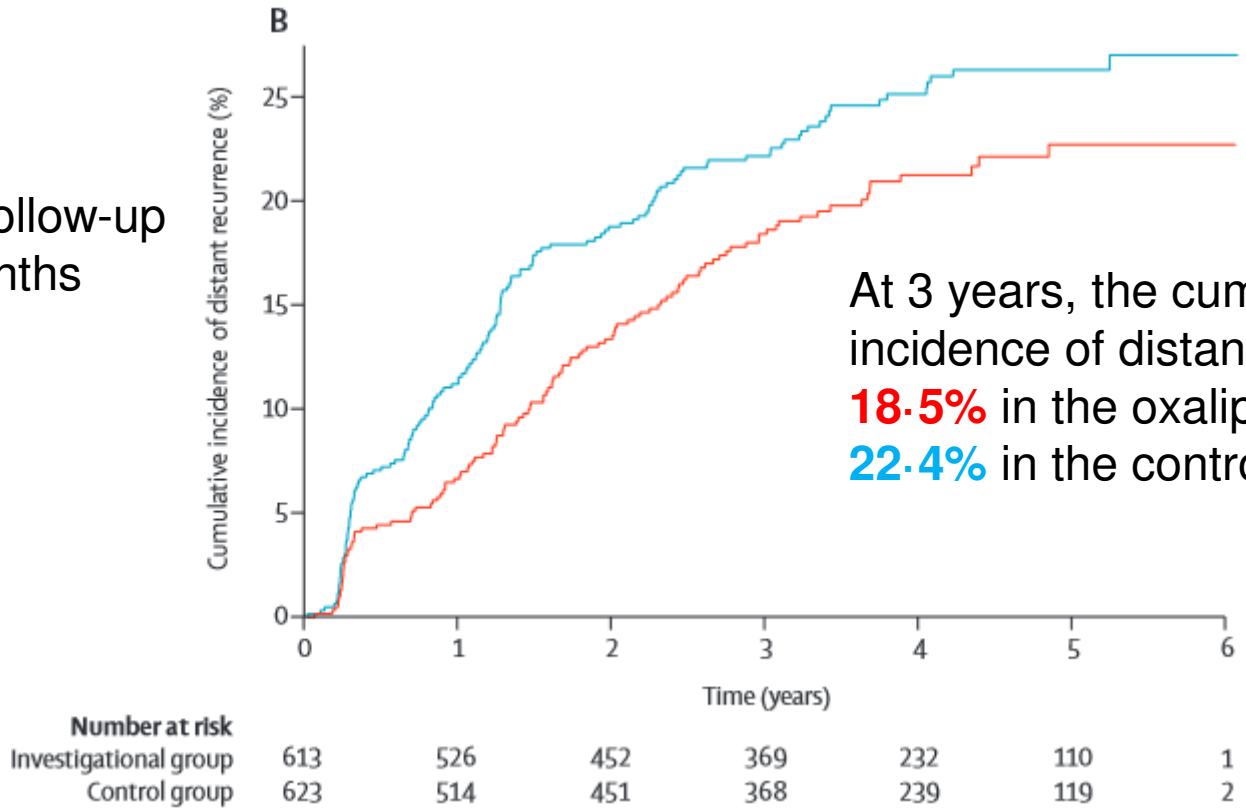


At 3 years, cumulative incidence of local recurrences after R0/1 resection was **2·9%** in the oxaliplatin group versus **4·6%** in control group

Rödel C, et al. Lancet Oncol. 2015;16(8):979-89.

The German CAO/ARO/AIO-04 Trial

median follow-up
of 50 months

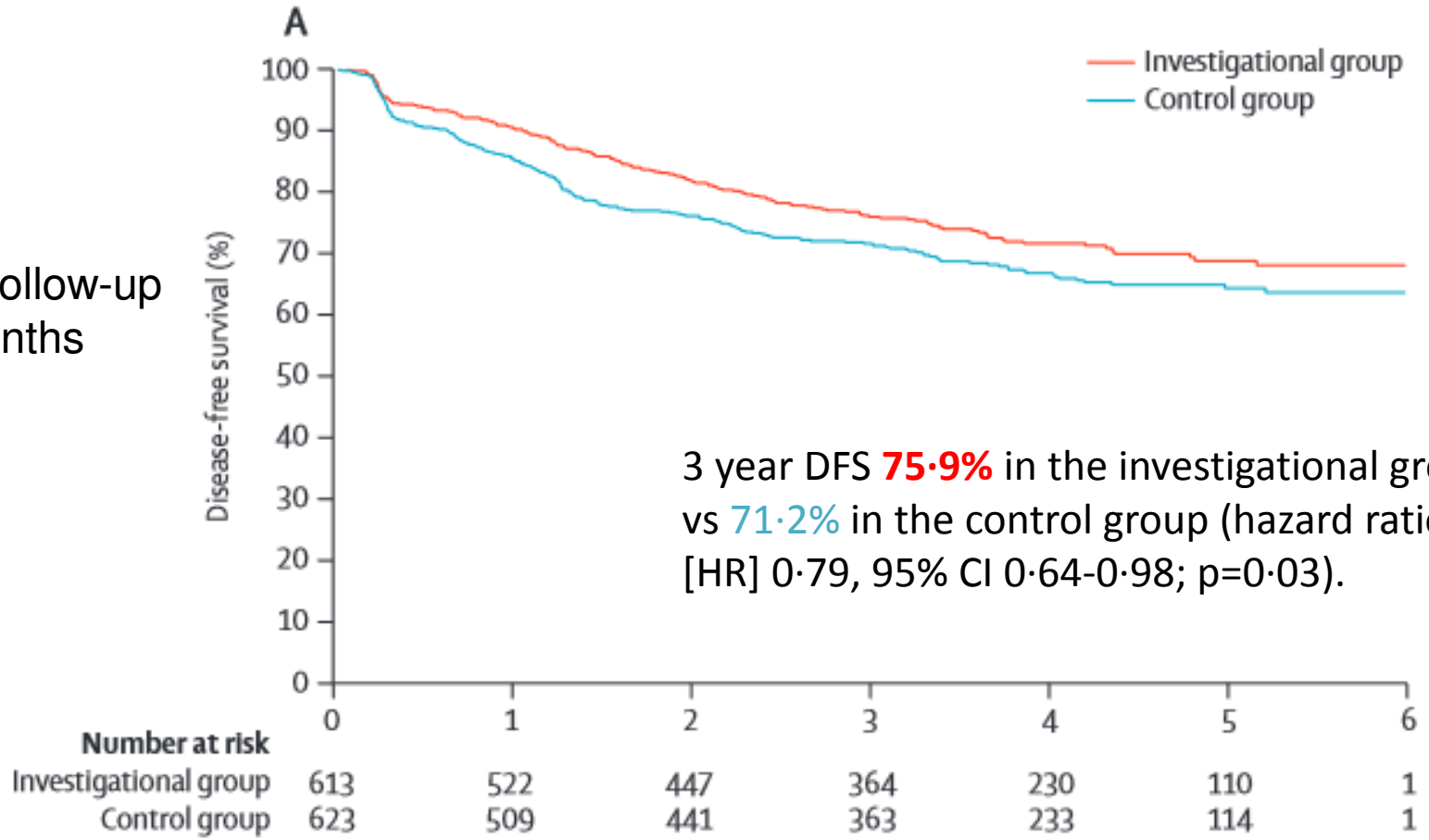


At 3 years, the cumulative incidence of distant recurrences
18·5% in the oxaliplatin group
22·4% in the control group.

Rödel C, et al. Lancet Oncol. 2015;16(8):979-89.

The German CAO/ARO/AIO-04 Trial

median follow-up of 50 months

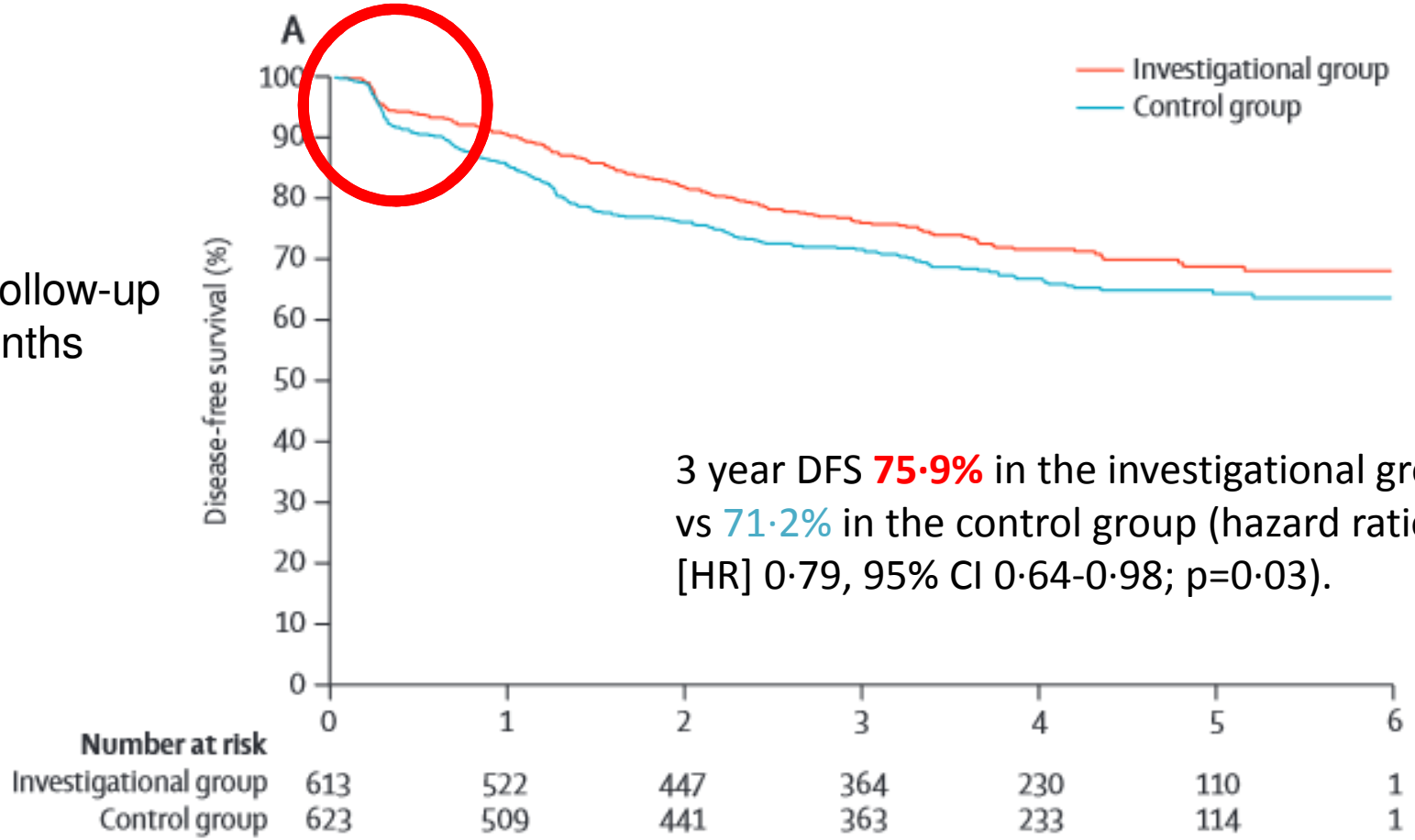


3 year DFS **75·9%** in the investigational group vs 71·2% in the control group (hazard ratio [HR] 0·79, 95% CI 0·64-0·98; p=0·03).

Rödel C, et al. Lancet Oncol. 2015;16(8):979-89.

The German CAO/ARO/AIO-04 Trial

median follow-up of 50 months



3 year DFS **75·9%** in the investigational group vs 71·2% in the control group (hazard ratio [HR] 0·79, 95% CI 0·64-0·98; p=0·03).

Rödel C, et al. Lancet Oncol. 2015;16(8):979-89.

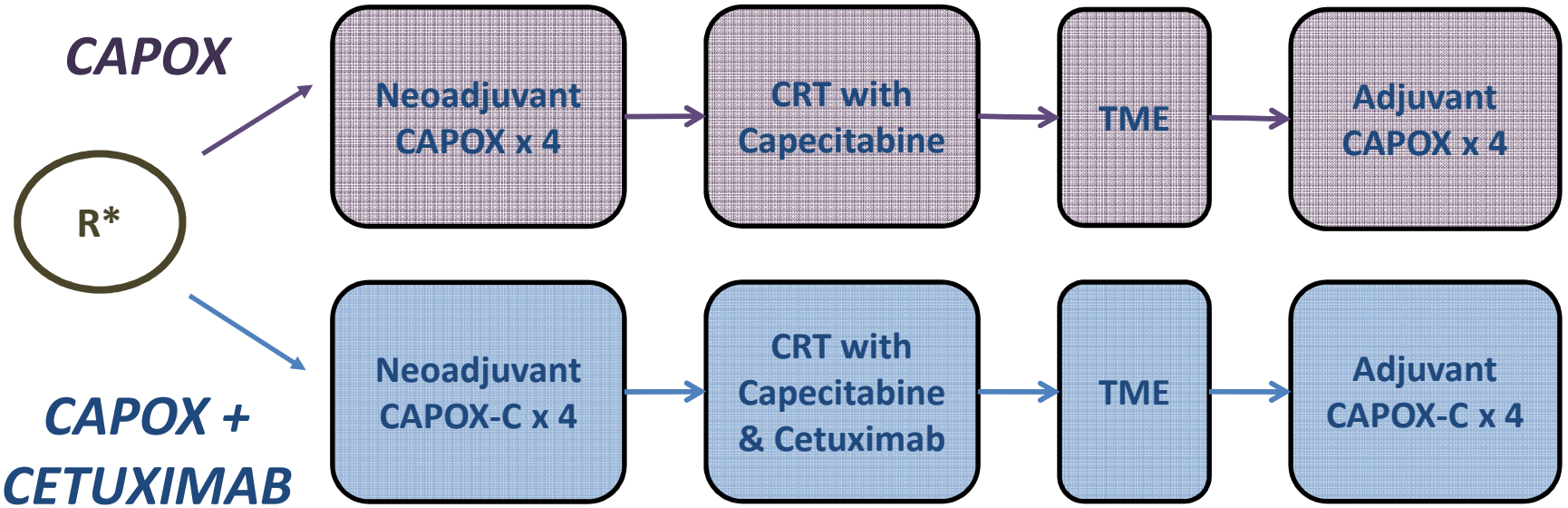
The main problem is a Confusion

between predicting a high risk of local and distant recurrence (which is reasonably robust from either preoperative MRI or postoperative histopathology)

and……

predicting the benefit from neoadjuvant/ adjuvant chemotherapy and radiotherapy if given - which is not.

The EXPERT-C trial – Design



**Patients recruited from 15 European Centres 2005-2008*

Key inclusion criteria:

- Tumours within 1mm of mesorectal fascia
- Tumours extending ≥5mm into peri-rectal fat
- T4 tumours
- Presence of extramural vascular invasion
- T3 tumours at/below levators

Endpoints

- Primary endpoint:
  CR in *KRAS/BRAF* WT patients
- Secondary endpoints:
  RR, PFS, OS, safety and QoL

Dewdney, J Clin Oncol 2012

- small tumours (T3a/b) in mid rectum and MRI defined EMVI had 3 year DFS 0%
- but larger T3c/d 3 year DFS 40% **(Patel Ann Oncol 2017)**

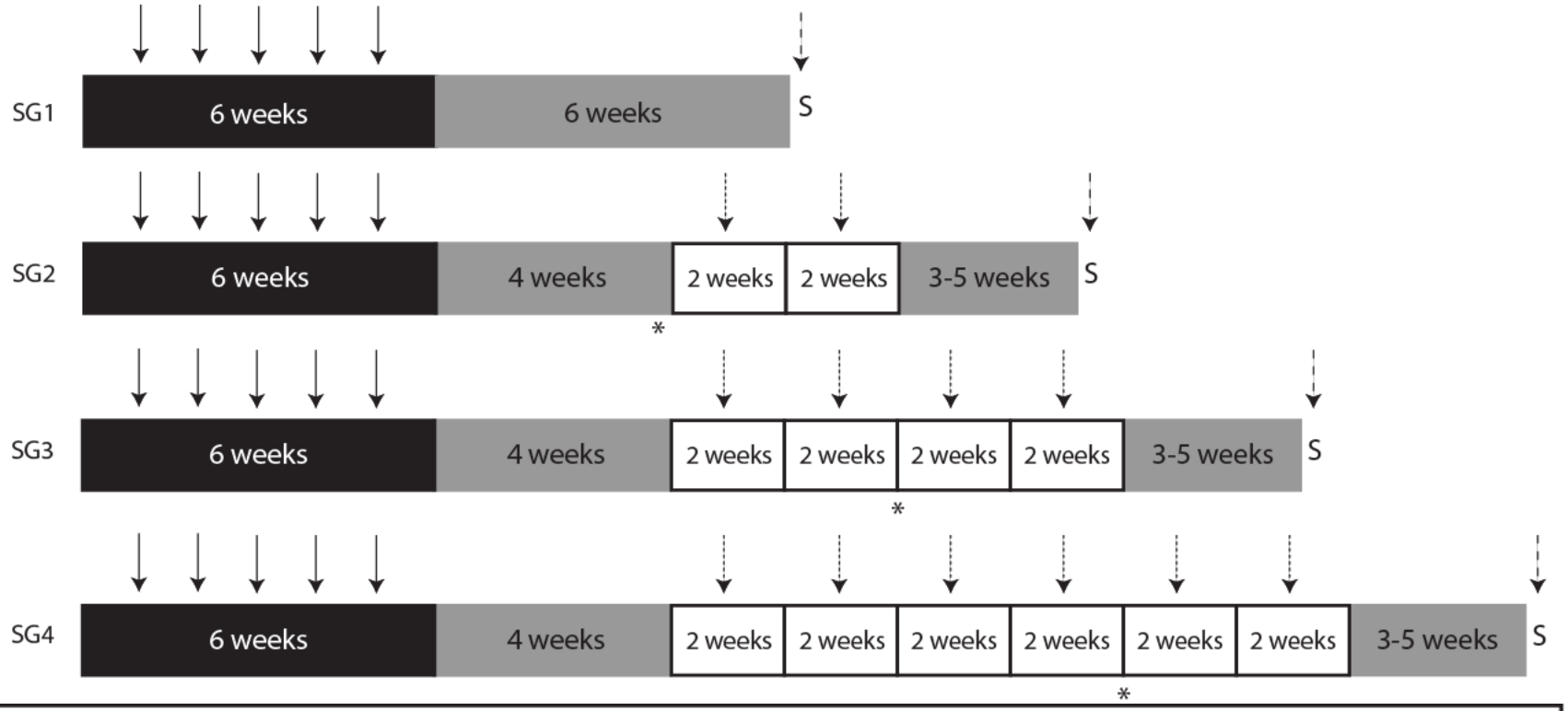
- response to radiotherapy depends strongly on tumour size (as measured from the diameter and length on the pre-treatment MRI scan) **(Jakobsen 2012, Appelt 2013).** Tumours <3.5cm respond better

What is needed is a bioscore

- Immunoscore (pre and post)
- cTNM
- Mri TRG
- ypTNM

Timing of Rectal Cancer Response to CRT

Single-arm Simon's two-stage minimax design



Radiotherapy - radiation 5 days/week, total 45 Gy (min. boost of 54 Gy, max. boost +36 Gy).

Chemotherapy - 5-FU 225 mg/m²/day as 7-day continuous infusion.

Resting Period

* **Assessment of tumor response** - by proctoscopic exam; TME if indicated by stable disease.

mFOLFOX-6 - 2-week cycles of LV 200 mg/m² or 400 mg/m² (2h infusion), oxaliplatin 85 mg/m² (2h infusion), 5-FU 400 mg/m² (bolus) and a 5-FU 2,400 mg/m² (46h infusion) (modified FOLFOX-6).

S **Surgery** - Total Mesorectal Excision (TME).

Tumour response – PCR

	Cohort 1 (60) SG1	Cohort 2 (67) SG2	Cohort 3 (67) SG3	Cohort 4 (65) SG3
pCR	11 (18%)	17 (25%)	20 (30%)	25 (38%)
Post CRT Chemo	none	2 cycles FOLFOX	4 cycles FOLFOX	6 cycles FOLFOX
Interval to surgery	8 weeks	11 weeks	15 weeks	19 weeks
N0/N+	75%/25%	75%/25%	?	?

Garcia-Aguilar, J Lancet Oncology 2015

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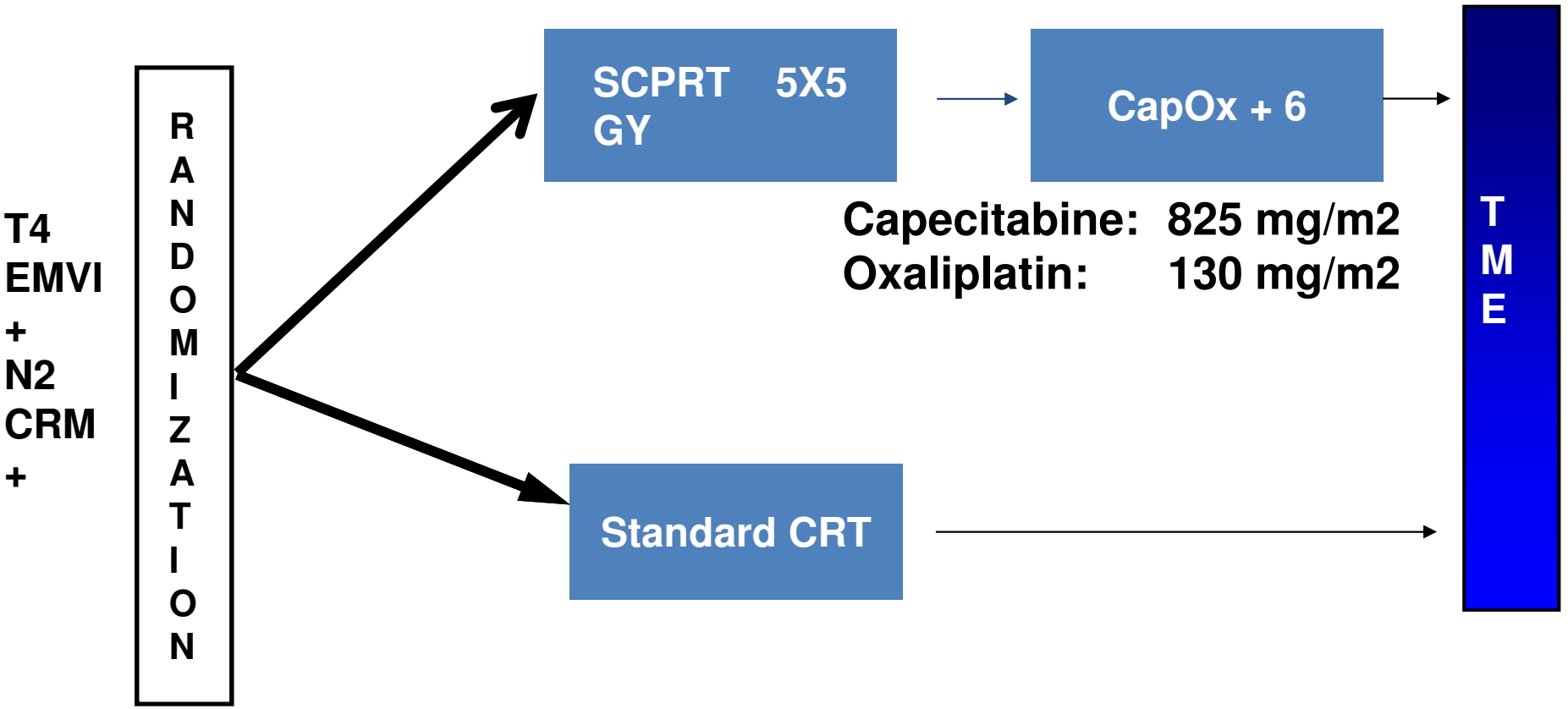
RAPIDO Trial

N = 885 patients



Primary endpoint 3 year DFS

Toxicity/Compliance

	Cohort 1 (60) SG1	Cohort 2 (67) SG2	Cohort 3 (67) SG3	Cohort 4 (65) SG3
Post CRT Chemo	none	2 cycles FOLFOX	4 cycles FOLFOX	6 cycles FOLFOX
Interval to surgery	8 weeks	11 weeks	15 weeks	19 weeks
Treatment interruptions		7%	35%	40%
Dose reductions		2%	13%	35%

Garcia-Aguilar J Lancet Oncology 2015

Toxicity/Compliance

	Cohort 1 (60) SG1	Cohort 2 (67) SG2	Cohort 3 (67) SG3	Cohort 4 (65) SG3
Post CRT Chemo	none	2 cycles FOLFOX	4 cycles FOLFOX	6 cycles FOLFOX
Interval to surgery	8 weeks	11 weeks	15 weeks	19 weeks
Pelvic Fibrosis (1-10)	2.4	3.4	4.4	3.9 p=0.0001
Technical difficulty (1-10)	4.6	4.9	5.1	4.8 (p=0.8)

Garcia-Aguilar J Lancet Oncology 2015

FOWARC Trial

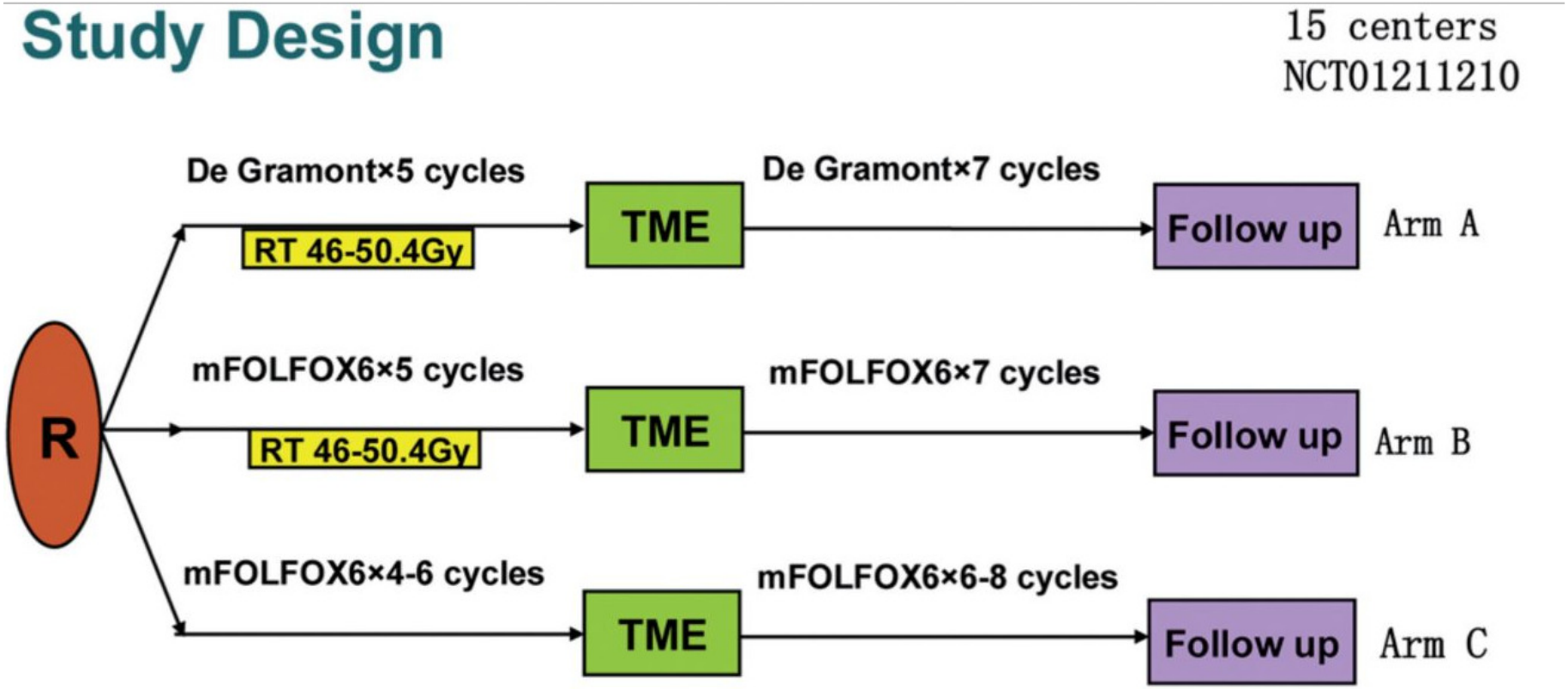


Table 3. Postsurgery Pathologic Response

Characteristic	Treatment Group, No. (%)		
	Fluorouracil- Radiotherapy	mFOLFOX6-Radiotherapy	mFOLFOX6
No. of patients	143*	149	152
pCR†	20 (14.0)	41 (27.5)	10 (6.6)
OR (95% CI)‡	1	0.428 (0.237 to 0.776)	2.309 (1.041 to 5.121)
ypStage			
0-I	53 (37.1)	84 (56.4)	54 (35.5)
OR (95% CI)‡	1	0.453 (0.283 to 0.726)	1.093 (0.679 to 1.759)
II-IV	90 (62.9)	65 (43.6)	98 (64.5)
OR (95% CI)‡	1	2.201 (1.376 to 3.520)	0.964 (0.599 to 1.552)
TRG§			
0-1	70 (49.0)	102 (68.5)	50 (32.9)
OR (95% CI)‡	1	0.431 (0.266 to 0.697)	2.032 (1.264 to 3.267)
2-3	71 (49.7)	46 (30.9)	102 (67.1)
OR (95% CI)‡	1	2.335 (1.448 to 3.765)	0.511 (0.319 to 0.819)

Abbreviations: mFOLFOX6, modified infusional fluorouracil, leucovorin, and oxaliplatin; OR, odds ratio; pCR, pathologic complete response; TRG, tumor regression grading.

*Includes two patients with progressive disease who did not undergo surgery.

†pCR was evaluated independently by two pathologists blinded to treatment groups.

‡ORs were calculated compared with the fluorouracil-radiotherapy group by using logistical regression.

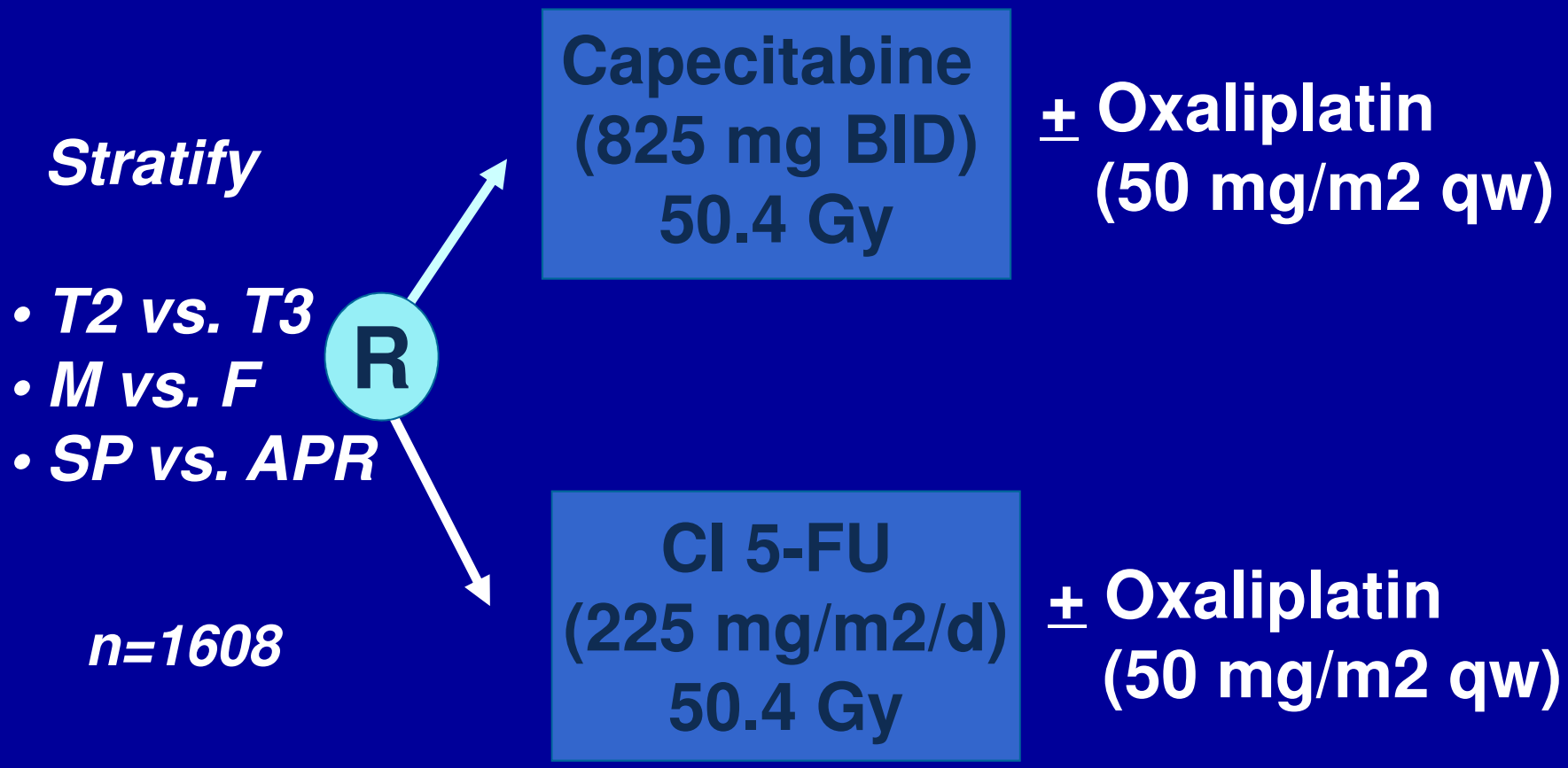
§TRG was evaluated semiquantitatively on a scale of 0 to 3 (complete to poor response, respectively).

Regimens	Number of patients	G3/G4 toxicity Diarrhea	Interval to surgery (median in days)	ypN+	pCR	TRG0-1
De Gramont RT 46-50.4Gy	165	7.7%	53	19.1%	14%	49%
FOLFOX RT 46-50.4Gy	165	14.5%	52	12.6%	27.5%	68.5%
FOLFOX alone	165	7.3%	Not stated	Not stated	6.6%	32.9%

FOWARC

Regimens	Number of patients	MRI staging	Good quality TME	G3/G4 toxicity diarrhea	Interval to surgery (median in days)	pCR	TRG0-1
De Gramont RT 46-50.4Gy	165	95%	80%	7.7%	53	14%	49%
FOLFOX RT 46-50.4Gy	165			14.5%	52	27.5%	68.5%
FOLFOX alone	165			7.3%	Not stated	6.6%	32.9%

5-FU = Cape in Pre-op Rectal Cancer: NSABP R-04



NSABP R-04, Allegra et al; ASCO GI 2014

Hypothesis

Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

Julio Garcia-Aguilar, Oliver S Chow, David D Smith, Jorge E Marcet, Peter A Cataldo, Madhulika G Varma, Anjali S Kumar, Samuel Oommen, Theodore Coutsoftides, Steven R Hunt, Michael J Stamos, Charles A Ternent, Daniel O Herzig, Alessandro Fichera, Blase N Polite, David W Dietz, Sujata Patil, Karin Avila, for the Timing of Rectal Cancer Response to Chemoradiation Consortium

Summary

Background Patients with locally advanced rectal cancer who achieve a pathological complete response to neoadjuvant chemoradiation have an improved prognosis. The need for surgery in these patients has been questioned, but the proportion of patients achieving a pathological complete response is small. We aimed to assess whether adding cycles of mFOLFOX6 between chemoradiation and surgery increased the proportion of patients achieving a pathological complete response.

Methods We did a phase 2, non-randomised trial consisting of four sequential study groups of patients with stage II–III locally advanced rectal cancer at 17 institutions in the USA and Canada. All patients received chemoradiation (fluorouracil 225 mg/m² per day by continuous infusion throughout radiotherapy, and 45·0 Gy in 25 fractions, 5 days per week for 5 weeks, followed by a minimum boost of 5·4 Gy). Patients in group 1 had total mesorectal excision 6–8 weeks after chemoradiation. Patients in groups 2–4 received two, four, or six cycles of mFOLFOX6, respectively, between chemoradiation and total mesorectal excision. Each cycle of mFOLFOX6 consisted of racemic leucovorin 200 mg/m² or 400 mg/m², according to the discretion of the treating investigator, oxaliplatin 85 mg/m² in a 2-h infusion, bolus fluorouracil 400 mg/m² on day 1, and a 46-h infusion of fluorouracil 2400 mg/m². The primary endpoint was the proportion of patients who achieved a pathological complete response, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00335816.

Lancet Oncol 2015; 16: 957–66

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http://dx.doi.org/10.1016/S1470-2045(15)00004-2

See Comment page 880

Department of Surgery (Prof J Garcia-Aguilar MD, O S Chow MD, K Avila MSc) **and Division of Biostatistics** (S Patil PhD), **Memorial Sloan Kettering Cancer Center, New York, NY, USA; Division of Biostatistics, City of Hope, Duarte, CA, USA** (Prof D D Smith PhD); **Department of Surgery, University of South Florida, Tampa, FL, USA**

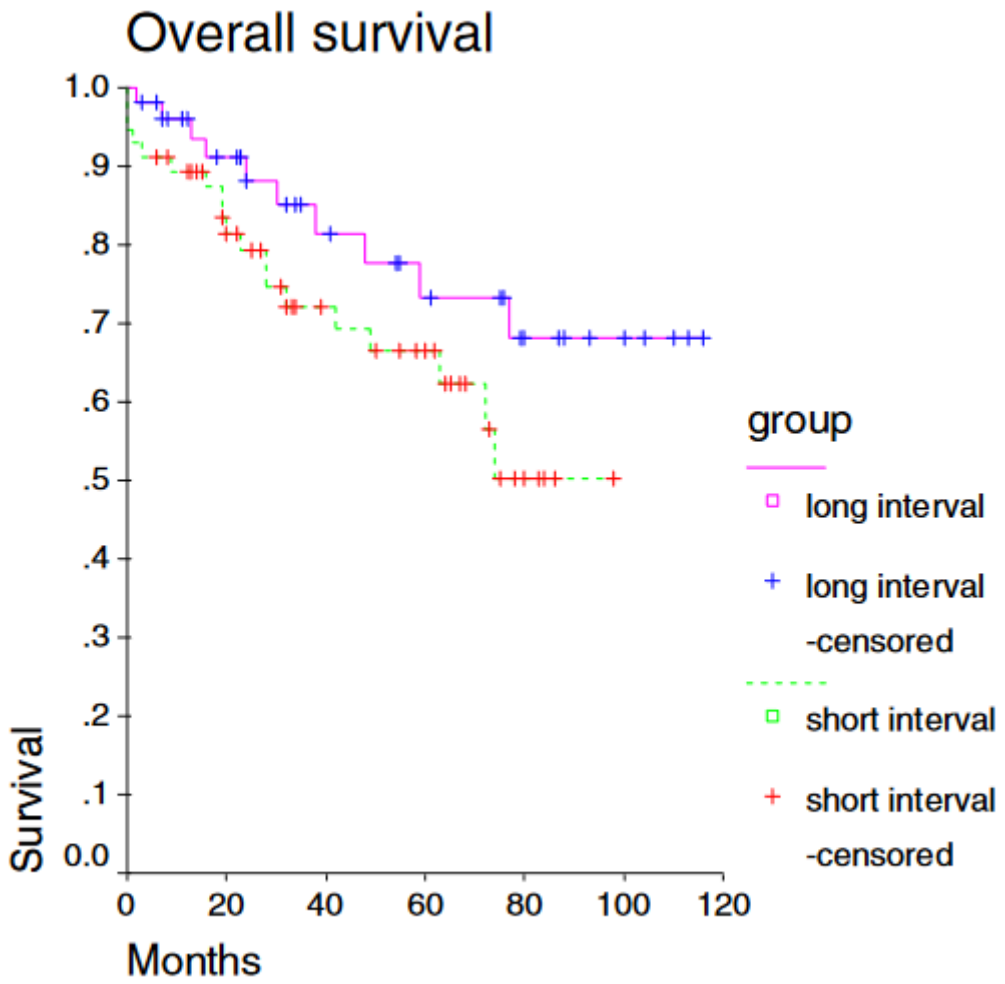


Fig. 1 No statistical difference for overall survival (p=0.12)

Veenhof AA et al Int J Colorectal Dis 2007 22(5) :507-13

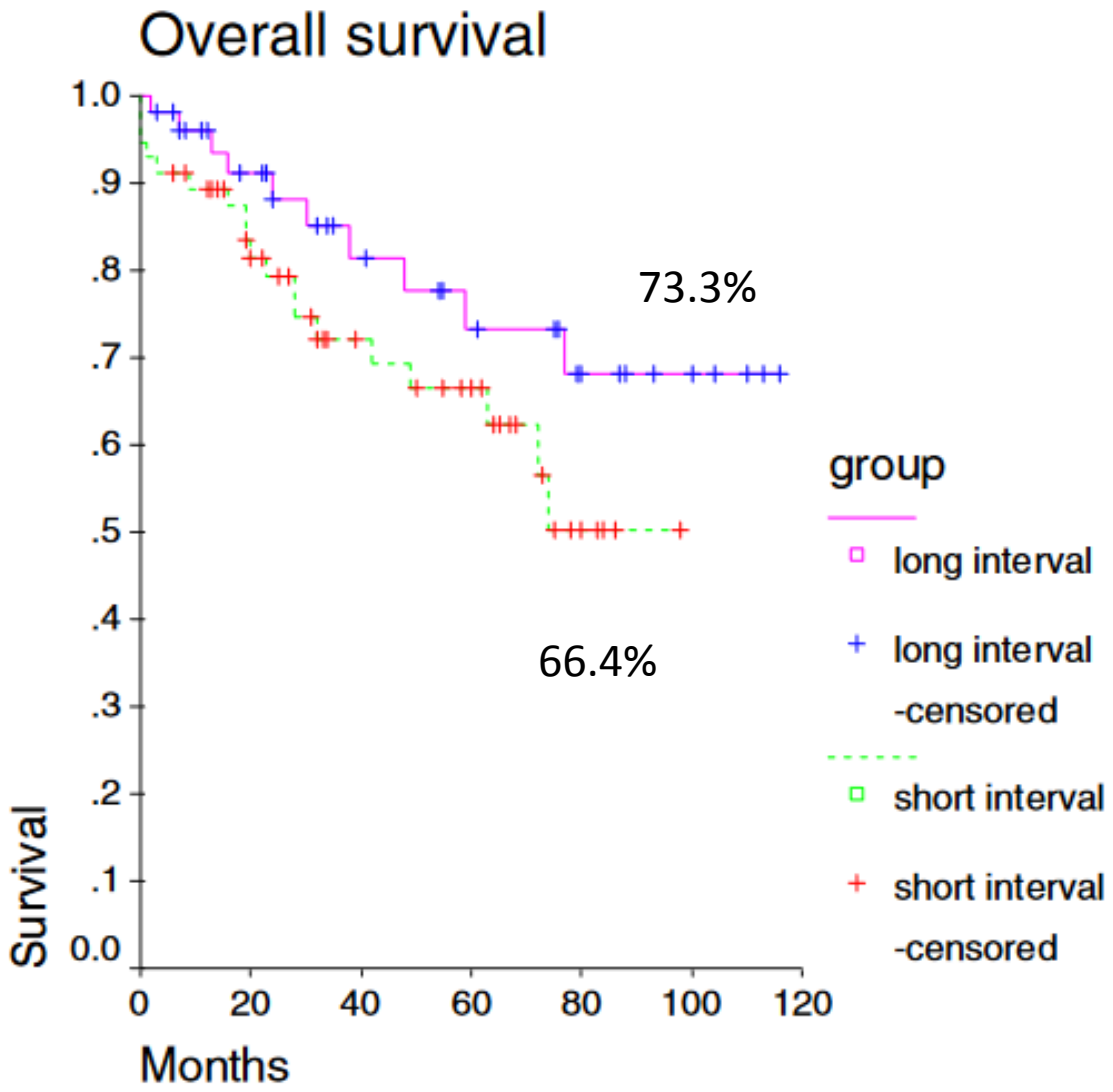


Fig. 1 No statistical difference for overall survival (p=0.12)

5 x 5Gy over 5-7 days and interval 4 versus 45 days
P=0.12

Veenhof AA et al Int J Colorectal Dis 2007 22(5) :507-13

CD3 infiltration - immunoscore

The ypTNM downstaging and TRG were used as endpoints to evaluate response to pCRT

- 72% of the biopsies with high infiltration of $CD3^+$ cells responders to CRT (complete or partial response)
- 63% of the biopsies with a low infiltration of $CD3^+$ cells were non-responders to CRT

($P = 0.015$).

Anitei M-G Clin Cancer Res 2014;20:1891

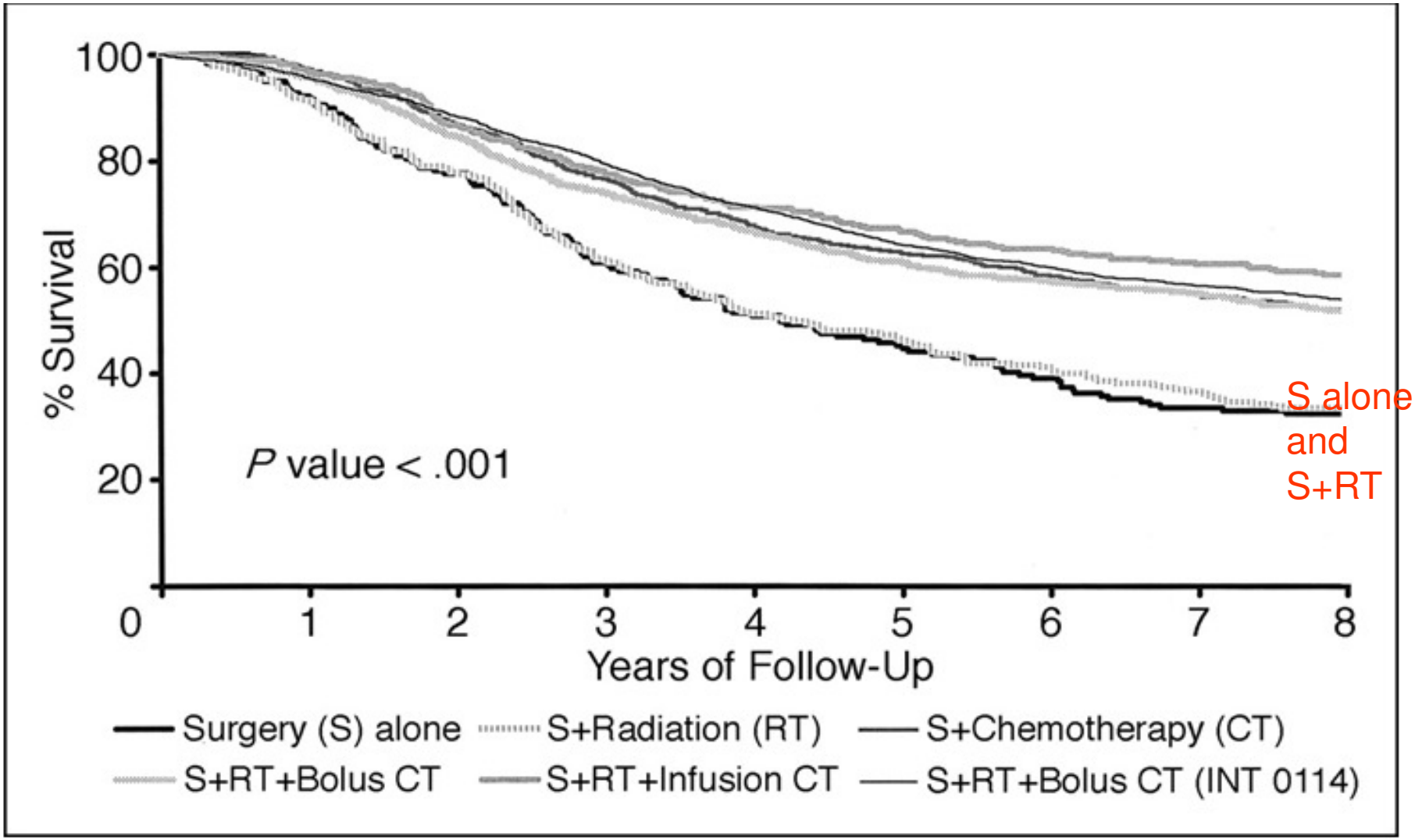
Transcriptomic classification of four consensus molecular subtypes

- **CMS1**, called MSI-like, contains most microsatellite instable (MSI) tumors and enriched for tumors with a CpG-island methylator phenotype (CIMP) and mutations in the BRAF oncogene **(14%).**
- **CMS2**, called canonical, with high chromosomal instability (CIN) and activation of the Wnt and MYC pathways **(37%).**
- **CMS3**, called metabolic - enriched in *KRAS* mutations and shows a disruption of metabolic pathways **(13%).**
- **CMS4**, called mesenchymal, has a mesenchymal phenotype and frequent CIMP phenotype **(23%)**

stratifies CRC into intrinsic subtypes with different prognosis

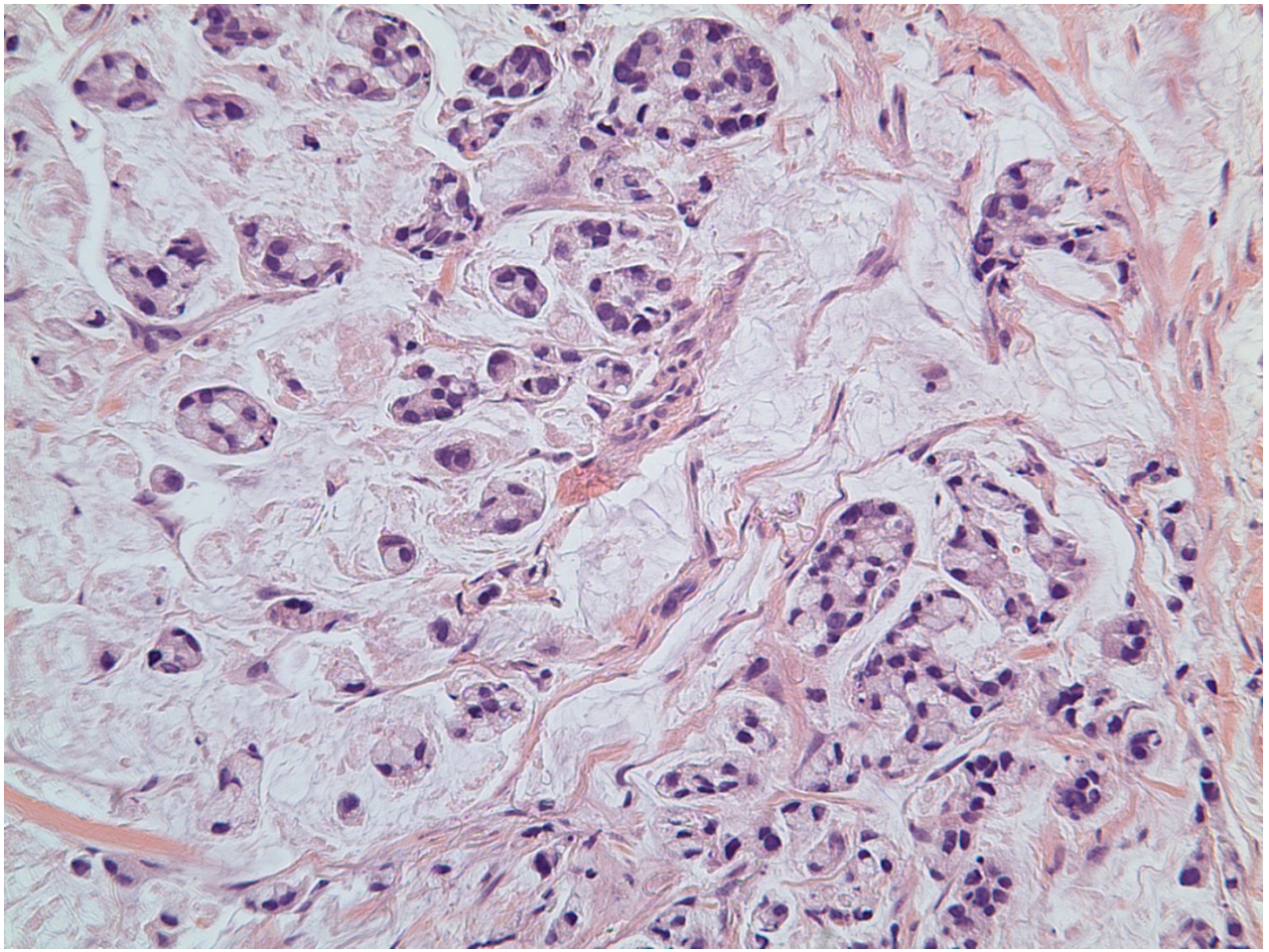
Guinney J et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350–1356.

Impact on overall survival of 6 methods of treatment in rectal cancer pooled analysis



Gunderson, L. L. et al. J Clin Oncol; 22:1785-1796 2004

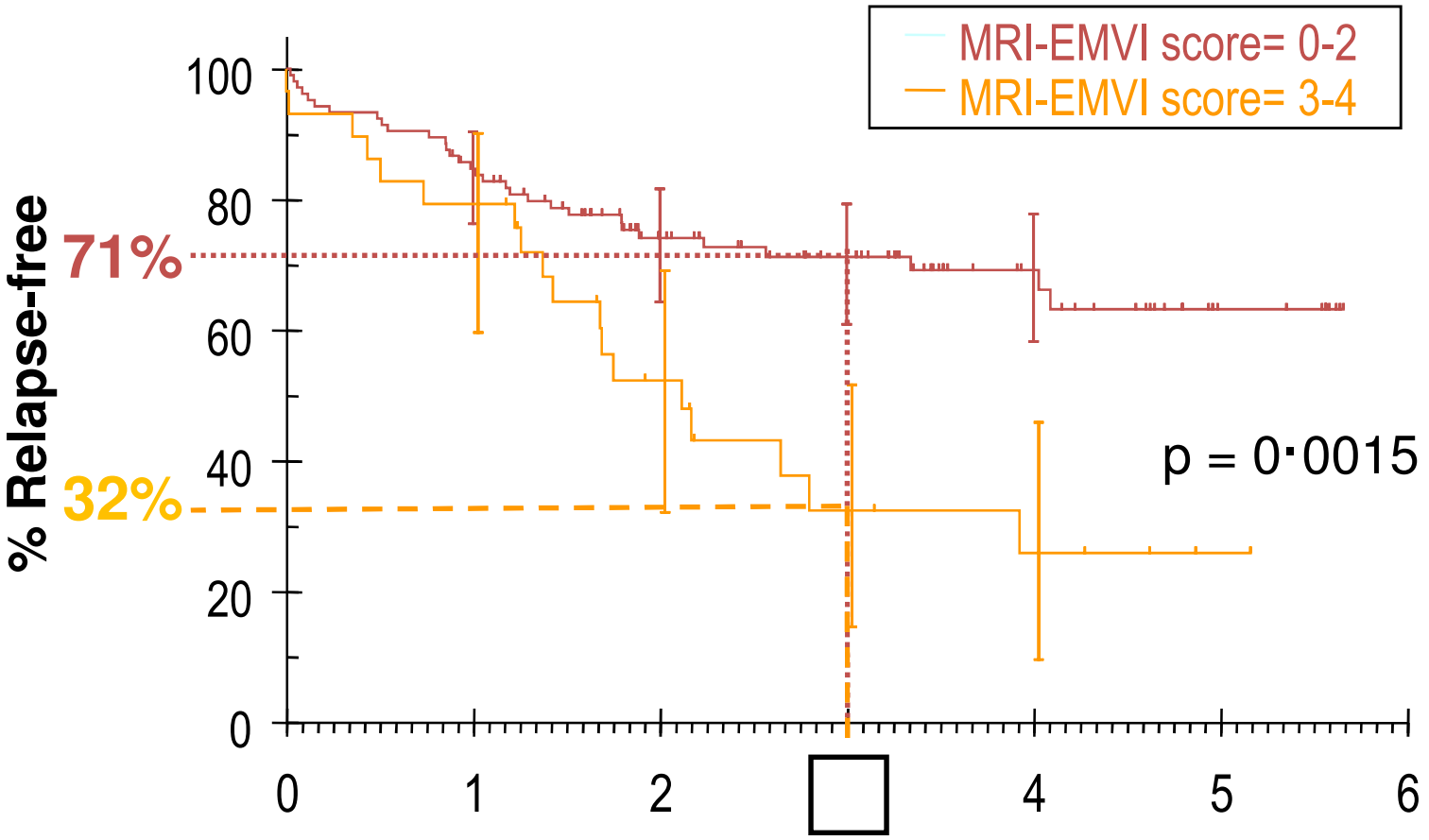
Mucinous Adenocarcinoma of the Rectum



5 % – 10 % of all rectal adenocarcinomas

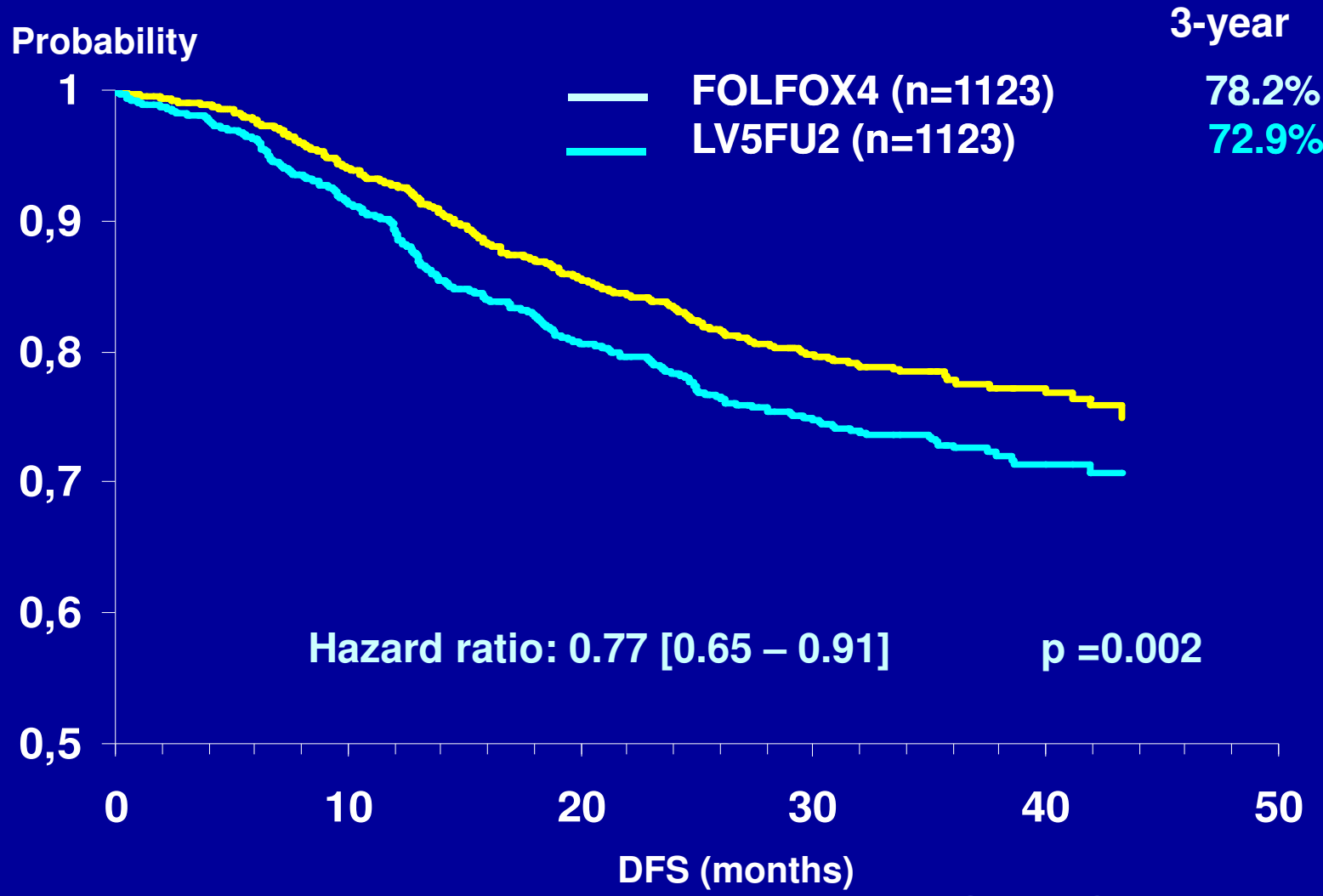
MRI-EMVI score & Outcome

n=135. Median follow-up=3·12 (0·9-5·7) years.



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

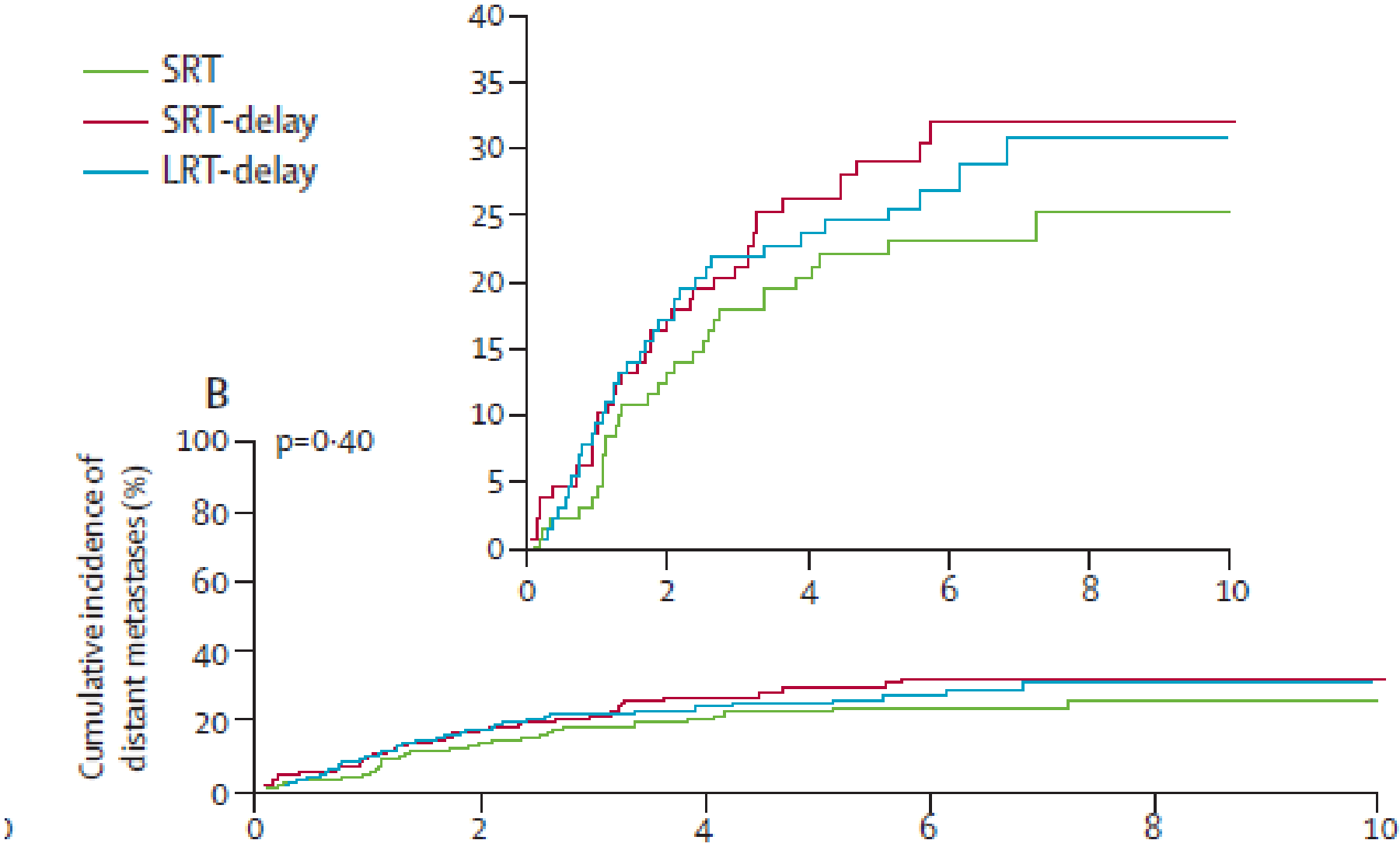
MOSAIC DFS by treatment arm (ITT)



23% risk reduction in the FOLFOX4 arm

- Simply shrinking the tumour does nothing if the CRM is clear

Stockholm III trial : incidence of metastases



ESMO Guidelines

Risk group	TN substage	Therapeutic options
Very early	cT1 sm1 (-2?) N0	Local excision (TEM). If poor prognostic signs (sm ≥ 2, high grade, V1), resection (TME) (or possibly CRT)
Early (good)	cT1-2; cT3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI	Surgery (TME) alone. If poor prognostic signs (crm+, N2) add postop CRT or CT[a]. (CRT with evaluation, if cCR, wait-and-see, organ preservation)
Intermediate (bad)	cT2 very low, cT3mrf- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI+, limited cT4aN0	Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high risk patients for surgery)
Advanced (ugly)	cT3mrf+, cT4a,b, lateral node+	Preop CRT followed by surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 × 5 Gy with a delay to surgery in elderly or in patients with severe comorbidity who cannot tolerate CRT

Case 1

- 71 years old female
- Rectal bleeding –mid/upper rectal mass
- MRI shows LARC cT4a (peritoneal) cN1(3 nodes +)
- CRM predicted 3mm – so clear
- extensive extramural vascular invasion (EMVI)
- Poorly diff adenocarcinoma

- CT no metastases
- CEA 12

Questions

- What are the risk factors here - local or distant?

- Radiotherapy or not?
- Chemotherapy up front preop or not?
- Sequence?

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- Radiotherapy or not?
- Chemotherapy up front or not?
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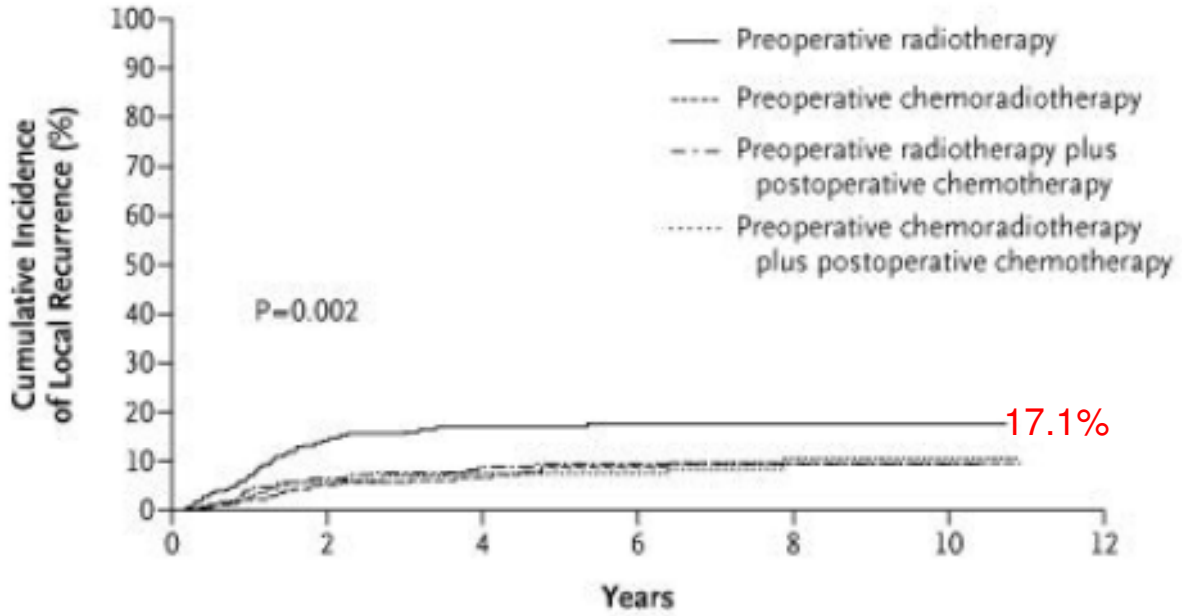
EORTC 22921 Trial

Local recurrence as a first event at 5 years was **17.1%** in the preoperative-radiotherapy group vs 8.7%, 9.6% and 7.6% in the group receiving preoperative chemoradiotherapy and postoperative chemotherapy.



No. at Risk						
Preoperative radiotherapy	252	147	87	60	24	6
Preoperative chemoradiotherapy	253	165	99	52	22	5
Preoperative radiotherapy plus postoperative chemotherapy	253	156	103	65	29	6
Preoperative chemoradiotherapy plus postoperative chemotherapy	253	159	113	59	20	3

- Pathologically defined Lymph nodes only affect your local recurrence rate if you leave them inside the patient!

- Lymph nodes on MRI (unless extracapsular spread – ie irregular borders) mean you are simply seeing LN enlarged

- – it may actually say the host immune system is working

- Either we cannot accurately stage LN preoperatively

OR

- They don’t matter

Major Questions for LARC

1. Can we enhance the activity of CRT? - SAFELY
2. How do we best integrate systemic chemotherapy in the neoadjuvant setting?
3. Which is the best partner for systemic chemotherapy

SCPRT or Chemoradiotherapy or NACT alone and no RT/CRT?