

Colorectal Cancer

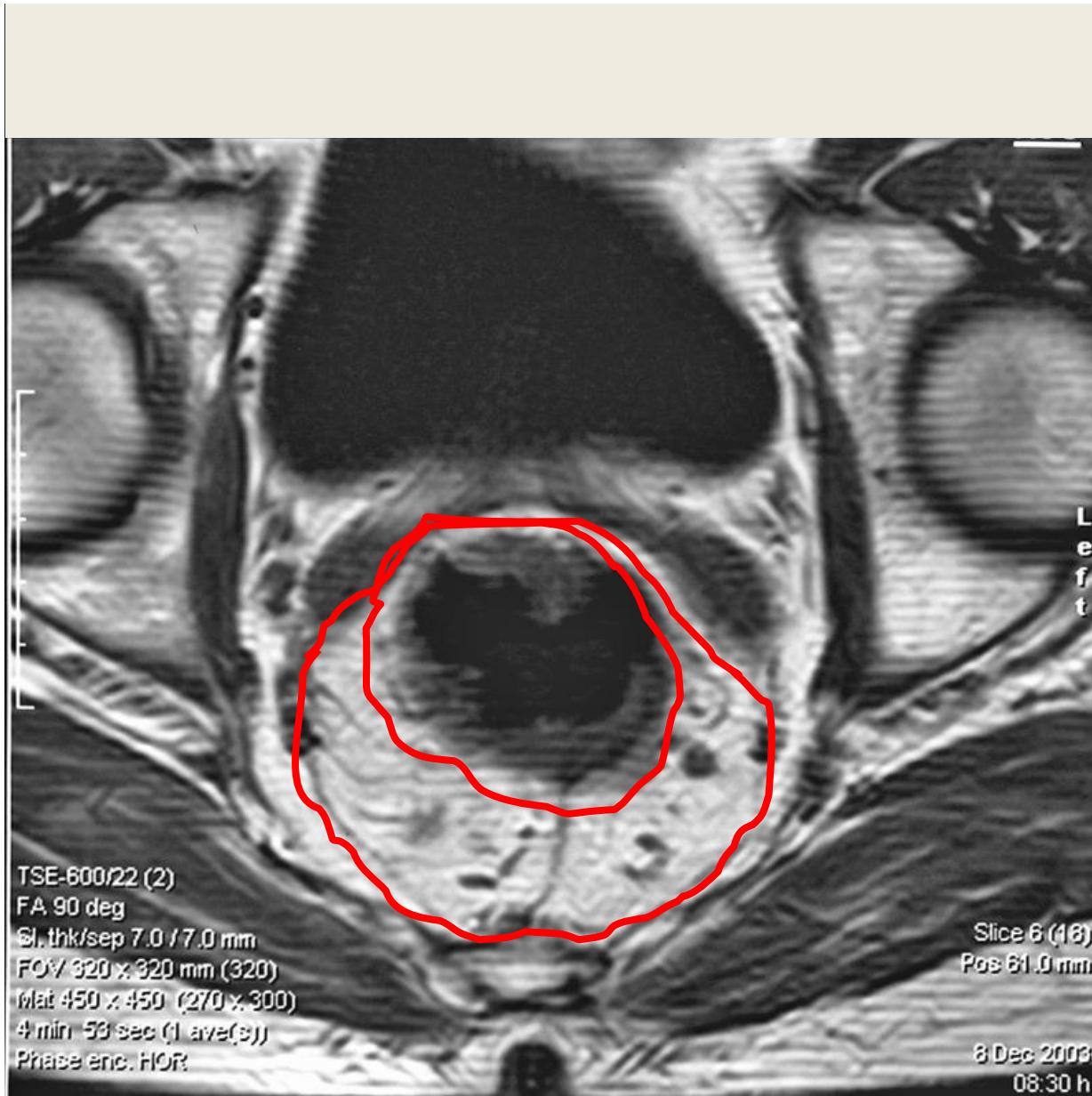
Dirk Arnold

CUF Hospitals Cancer Centre
Lisbon, Portugal

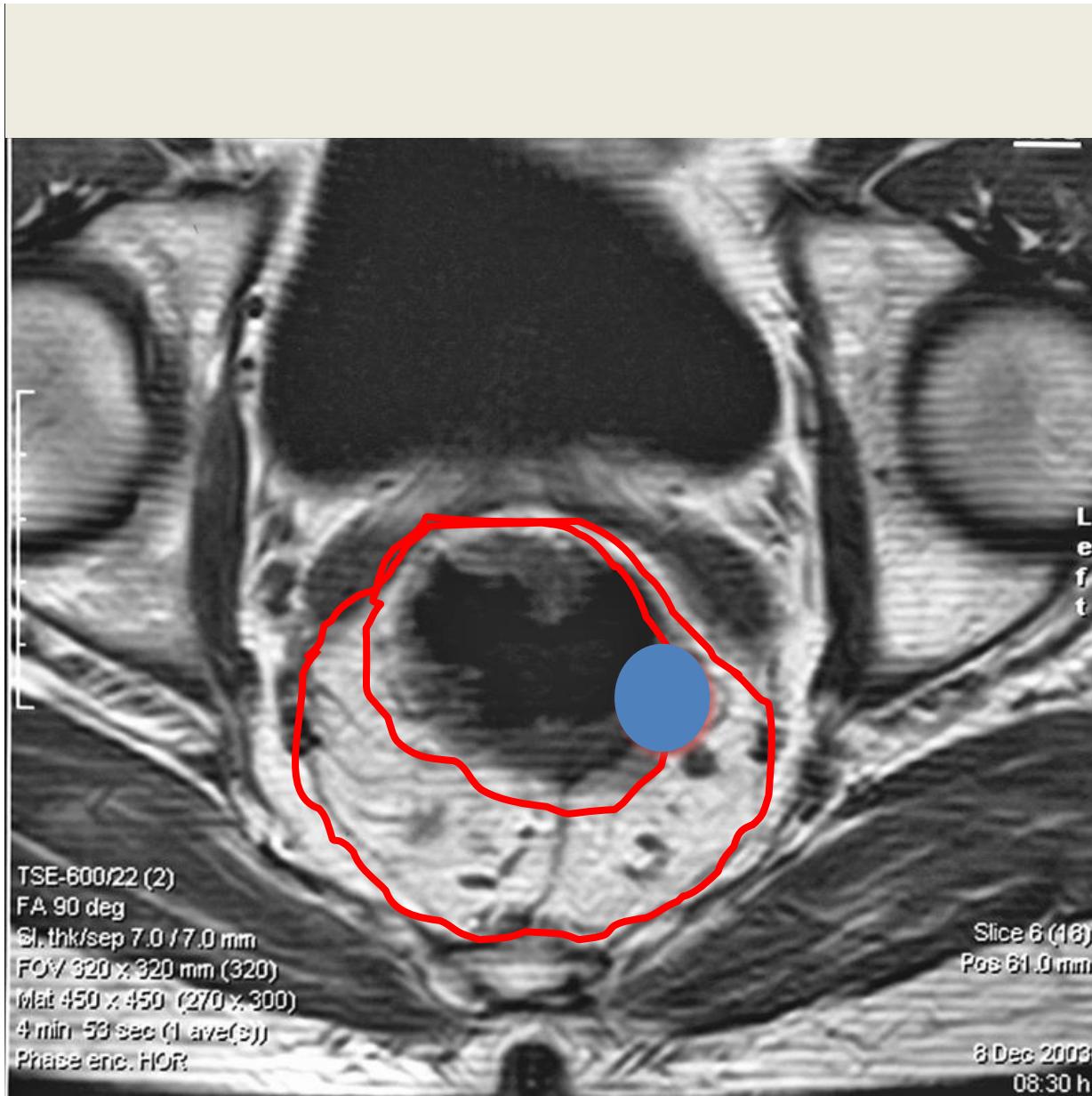
Disclosure slide

- Research Support
Roche, sanofi
- Honoraria (Presentations)
Roche, Merck Serono, Bayer, Servier
- Consultancy fee
Roche, Merck Serono, Bayer, Terumo, Servier

64j, T3, N?



64j, T3b, N?



64 y/o male patient: More information

- MRI: T3b, N?
- EUS: likely N+ / suspect (single Ln., < 12mm)
- Rigid proctoscopy: 8-11.5 cm ab ano
- CT: no clear distant mets., 2 small pulmonary lesions
- Biopsy: Adenocarcinoma
- Molecular Pathology: RAS wild type
- History: smoker for > 20 yrs (20 py), cessation for 5 yrs
- No significant comorbidities

Questions to the Board

- More diagnostics? (→ PET) ?
 - Peripheral lung lesions without clear hypermetabolism

Questions to the Board

- More diagnostics? (→ PET) ?
 - Peripheral lung lesions without clear hypermetabolism
- Which treatment goal exists?
- Which strategy as the initial step?
 - Pre-operative chemoradiation with 5FU or Capecitabine?
 - Pre-operative chemoradiation with FP + Oxaliplatin?
 - 5x5 Gy RT?
 - Chemotherapy only (→ Surgery)
 - No pretreatment, upfront Surgery?

64 y/o male patient: More information

- preoperative CRT with Capecitabine/45 Gy
- underwent LAR / TME
- yCRM negative / R0
- ypT3b N1, minimal pathohistologic regression

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Questions to the Board

- Which adjuvant treatment?
 - None
 - Cape / FU
 - FU or Cape plus oxaliplatin

64 y/o male patient: More information

- preoperative CRT with Capecitabine/45 Gy
- underwent LAR / TME
- yCRM negative / R0
- ypT3b N1, minimal pathohistologic regression
- CT: Lung lesions: slightly increased in size

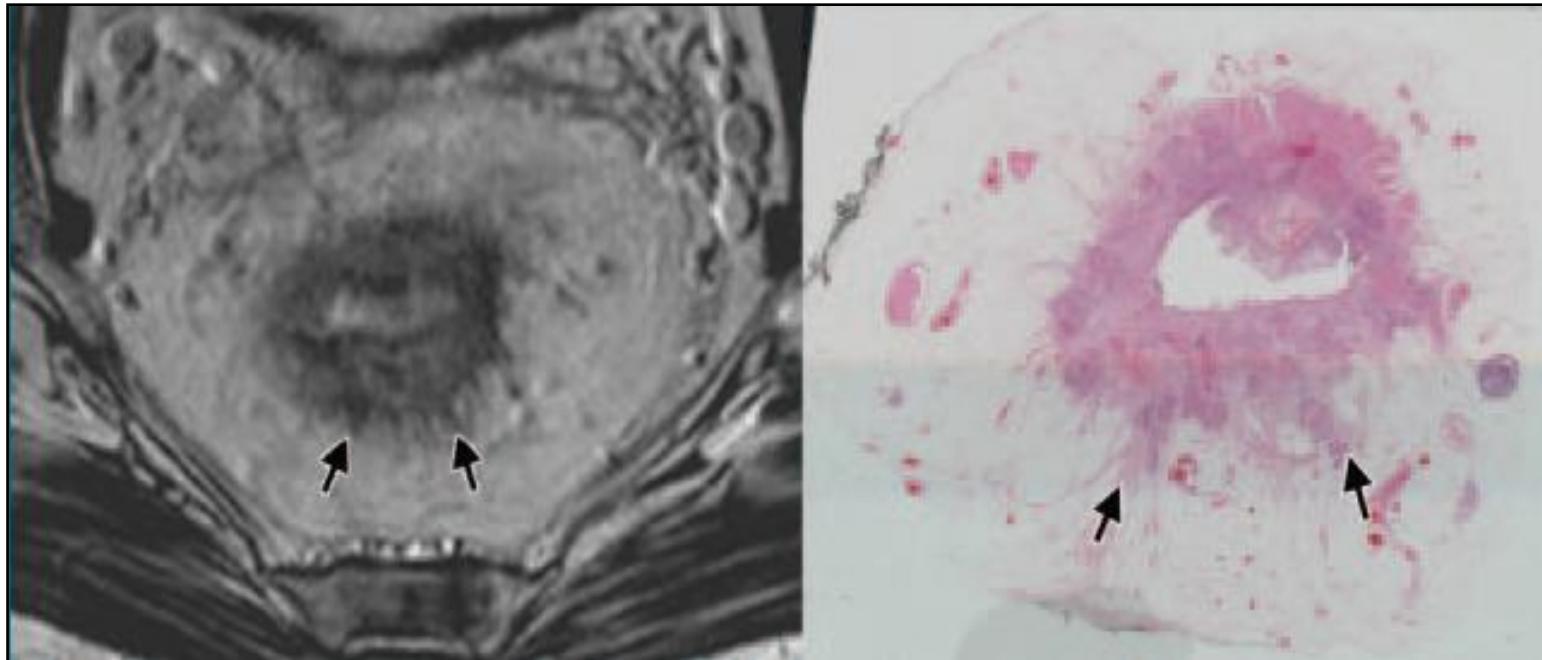
Questions to the Board

- Which adjuvant treatment? (if adjuvant)
 - None
 - Cape / FU
 - FU or Cape plus oxaliplatin
- Which further treatment? (if suspected M+)
 - upfront surgery of lung lesions
 - „inductive“ chemotherapy only (e.g. FOLFOX)
 - „inductive“ therapy with chemotherapy plus bevacizumab
 - „inductive“ chemotherapy plus anti-EGFR?

Back-up slides

Mercury Study

e.g. T3 Tumor: Correlation Pathology and MRI



„In 273 (92.5%) of the 295 patients, the depth of tumor spread depicted on [...] MR images was **within 5 mm of the histopathologic measurement.**“

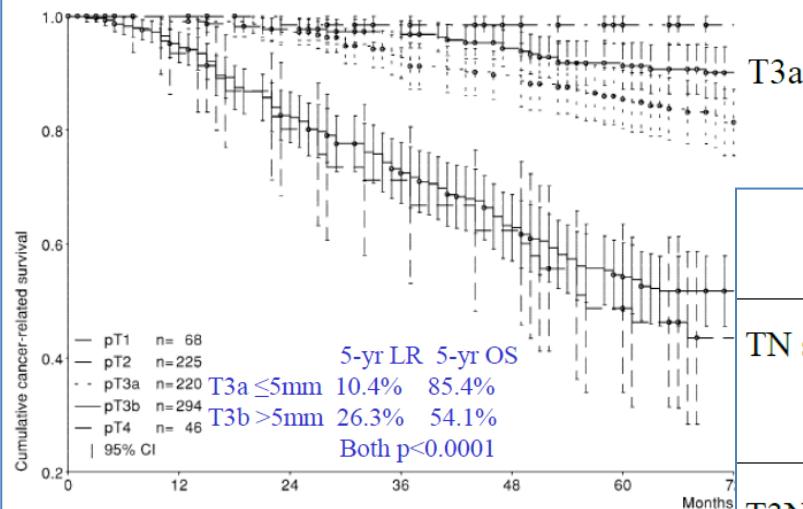
Local Control with RT and CRT

	Local failure
FFCD (%)	8%
EORTC (%)	9%
AIO/CAO/ARO (%)	6%
Polish trial (%) 5x5	9%
MRC CR 07 (%) 5x5	5%
Dutch TME (%) 5x5	6%

Bosset 2006; Gerard 2006; Sauer 2004; Bujko 2006; Sebag-Montefiore 2006; Peeters 2007

e.g. T3 tumors

Extramural spread ($\leq 5\text{mm}$ vs. $>5\text{mm}$)



N0 vs. N1 vs. N2

TN staging	Pooled analysis 1 ¹		Pooled analysis 2 ²		SEER analysis ³	
	n	5-yr OS	n	5-yr OS	n	5-yr OS
T3N0	668	74%	1,060	75%	10,615	64%
T3N1	554	61%	887	60%	5,787	52.4%
	663	48%	935	44%	3,755	37.5%

Merkel et al, Int J Colorectal Dis 2001

Extramural venous invasion (EMVI)

Ouchi et al	Synchronous liver metastases	Metachronous liver metastases	Absence of liver metastases
Presence of EMVI	17/19 (89.5%)	12/16 (75%)	4/26 (15.4%)
p<0.001			

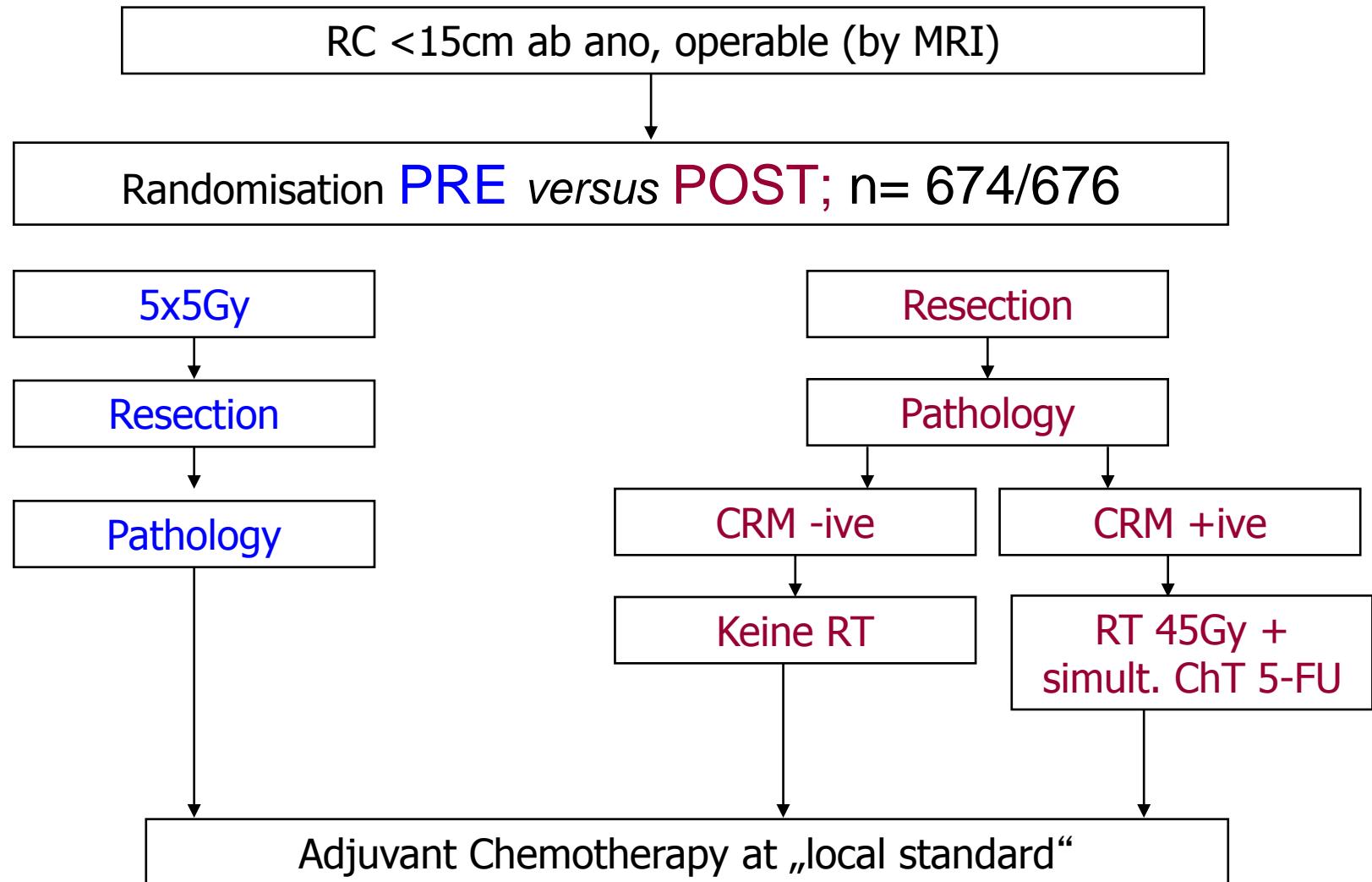
Gunderson et al, J Clin Oncol 2010

Dressen et al	Local recurrent rectal cancer	Control with no local recurrent rectal cancer
Presence of EMVI	38/92 (41%)	24/185 (13%)
Odds Ratio: 4.79; 95% CI: 2.20-10.5; p<0.001		

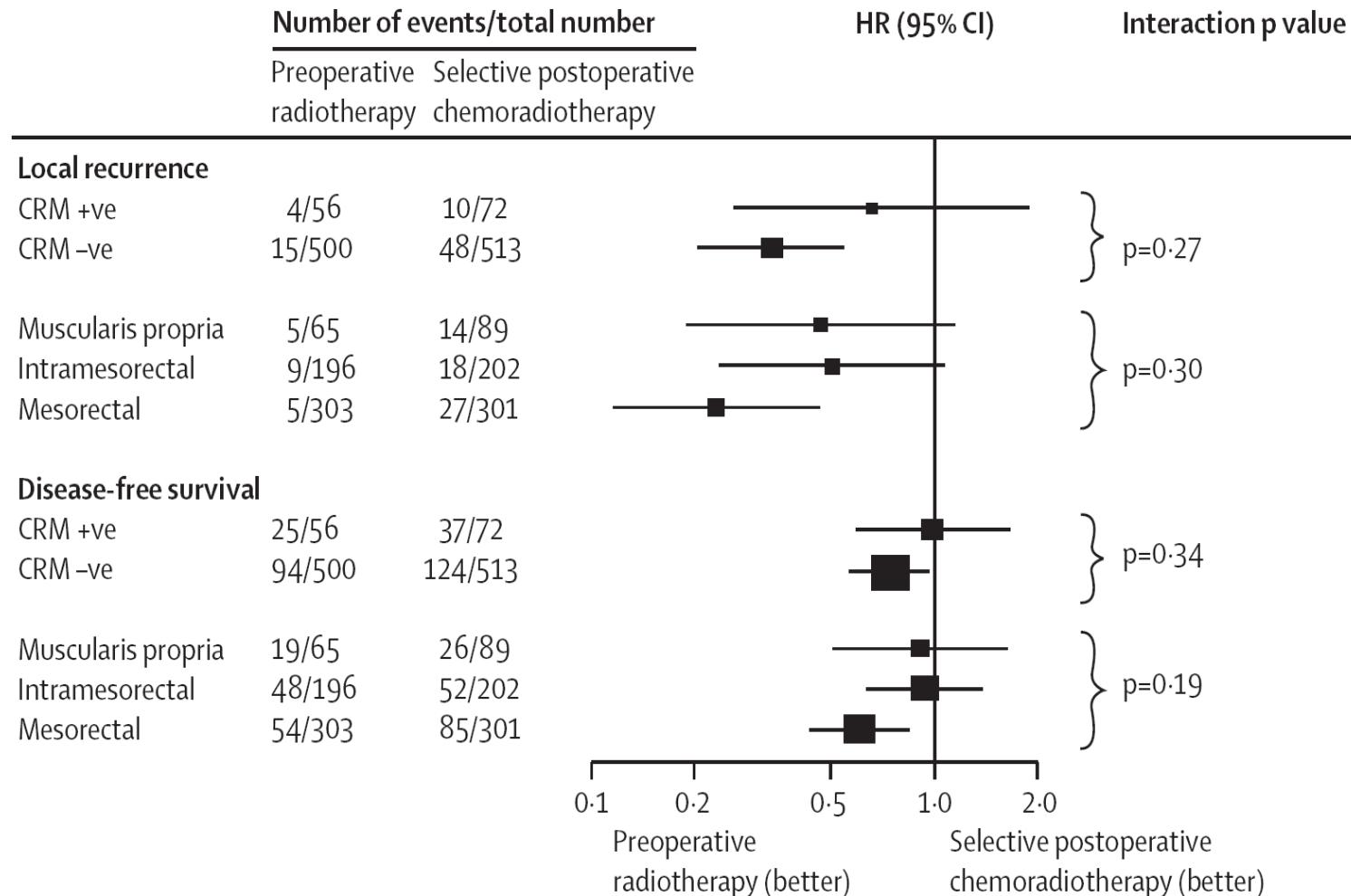
Ouchi et al, Cancer 1996

Dressen et al., Eur J Cancer 2009

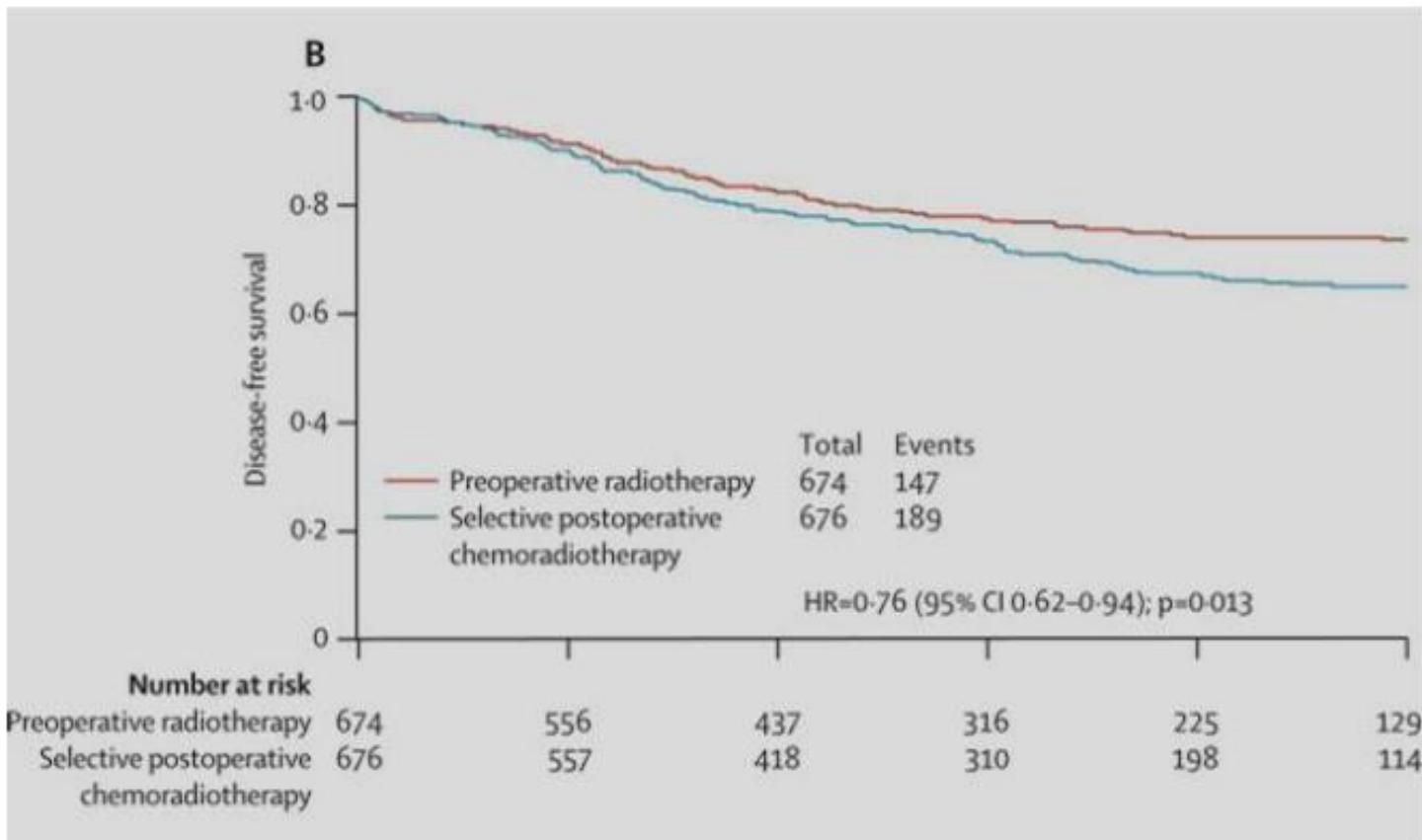
MRC CR 07 Trial: 5x5 Gy „for all“ or selective adjuvant RChT ?



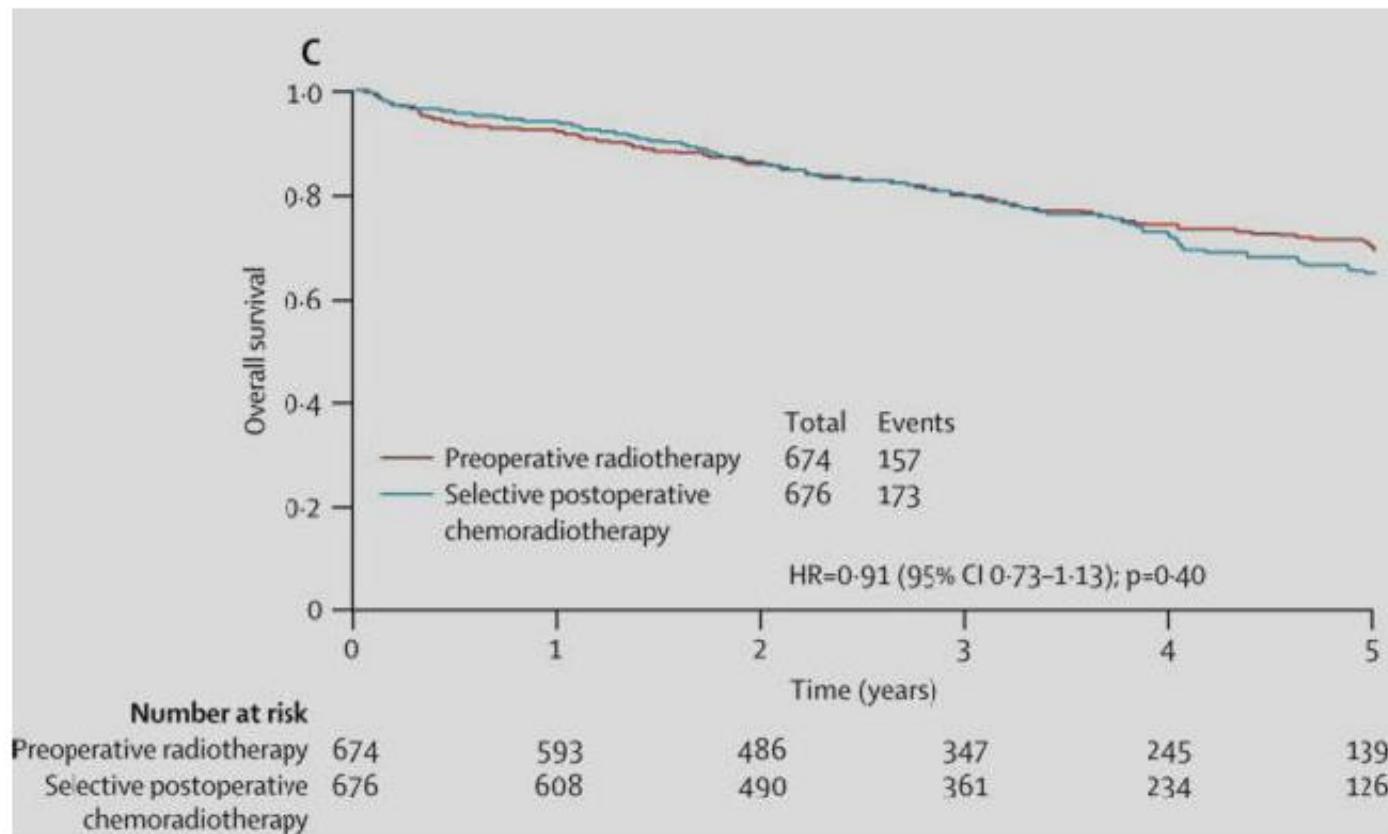
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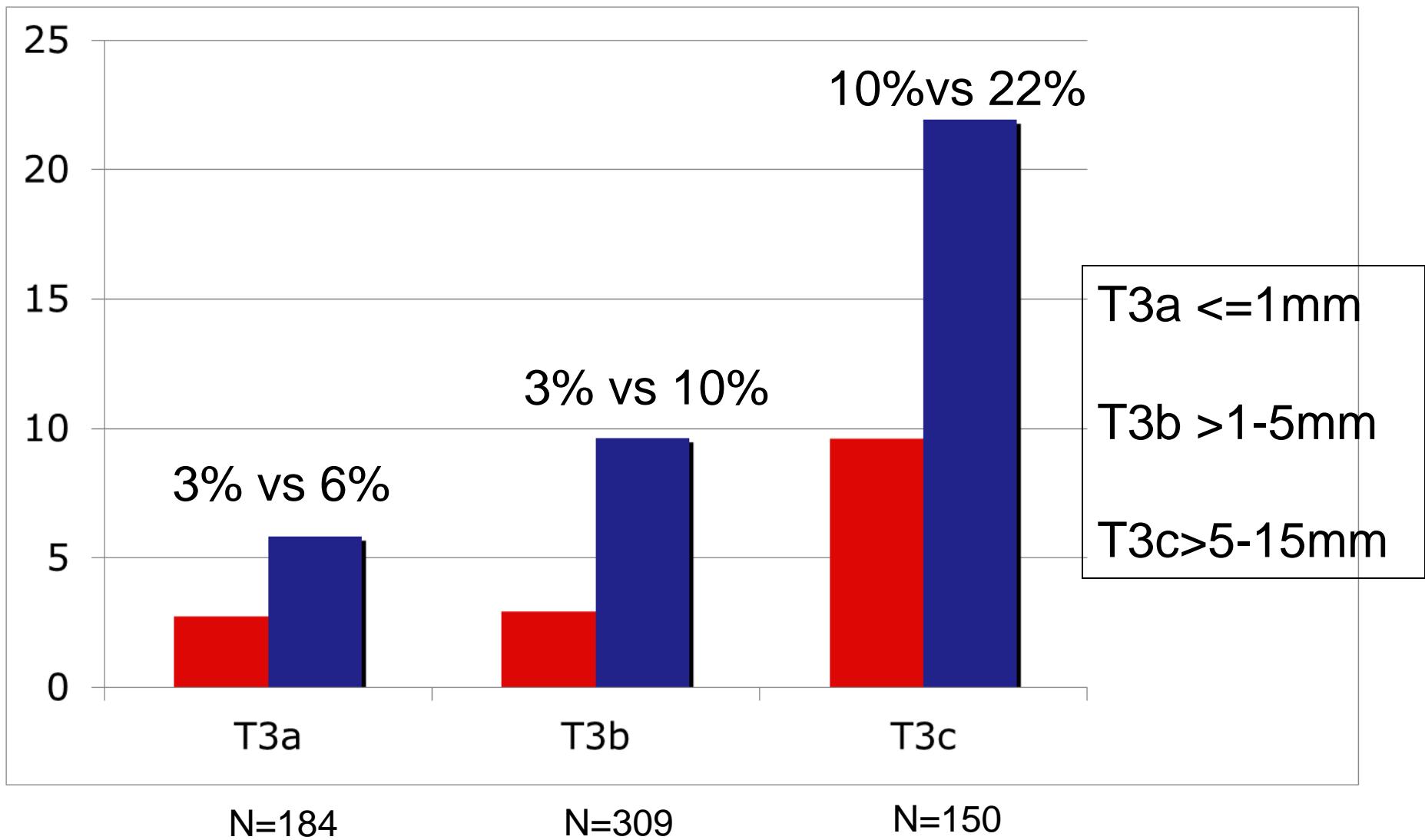
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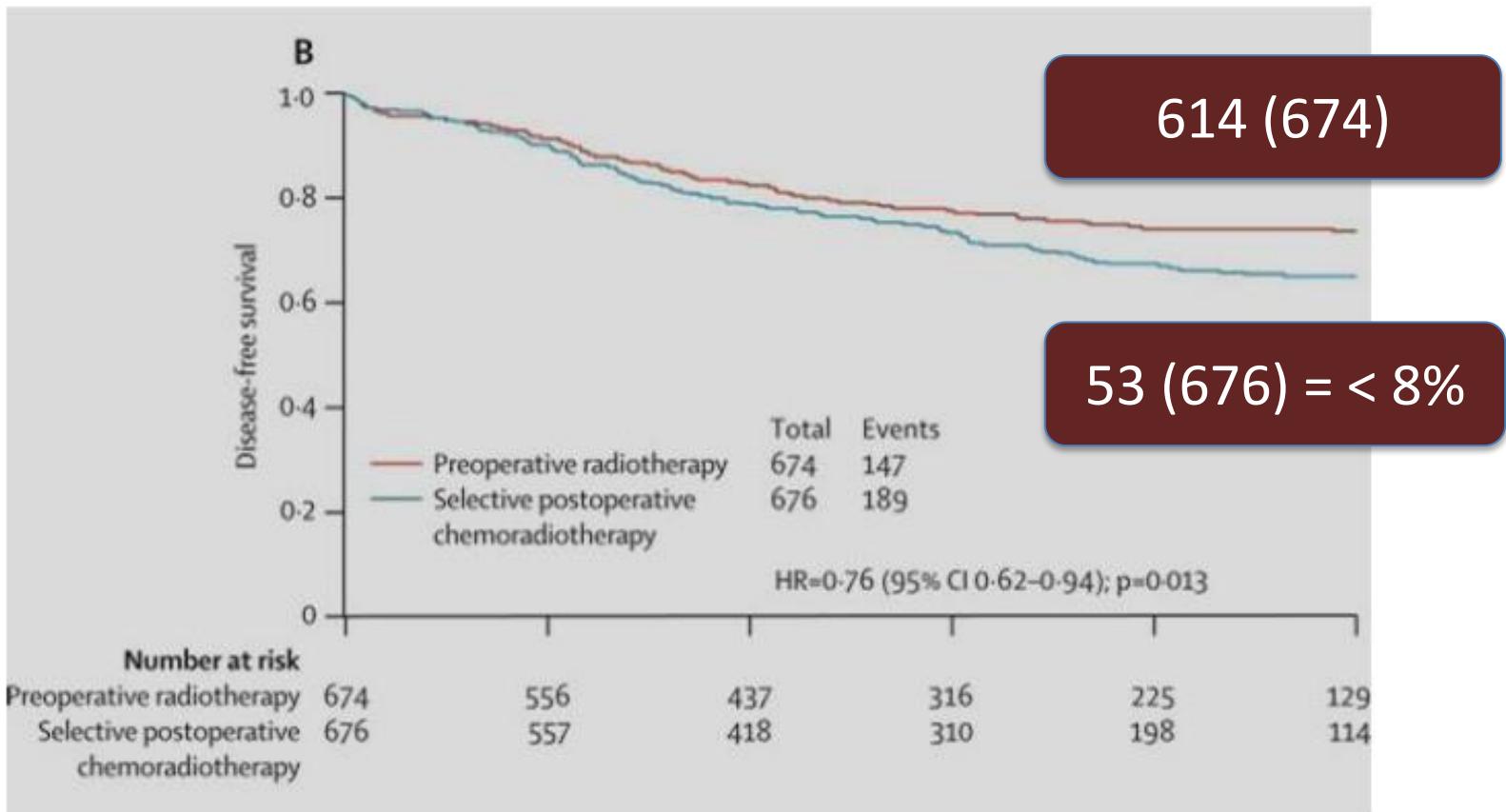
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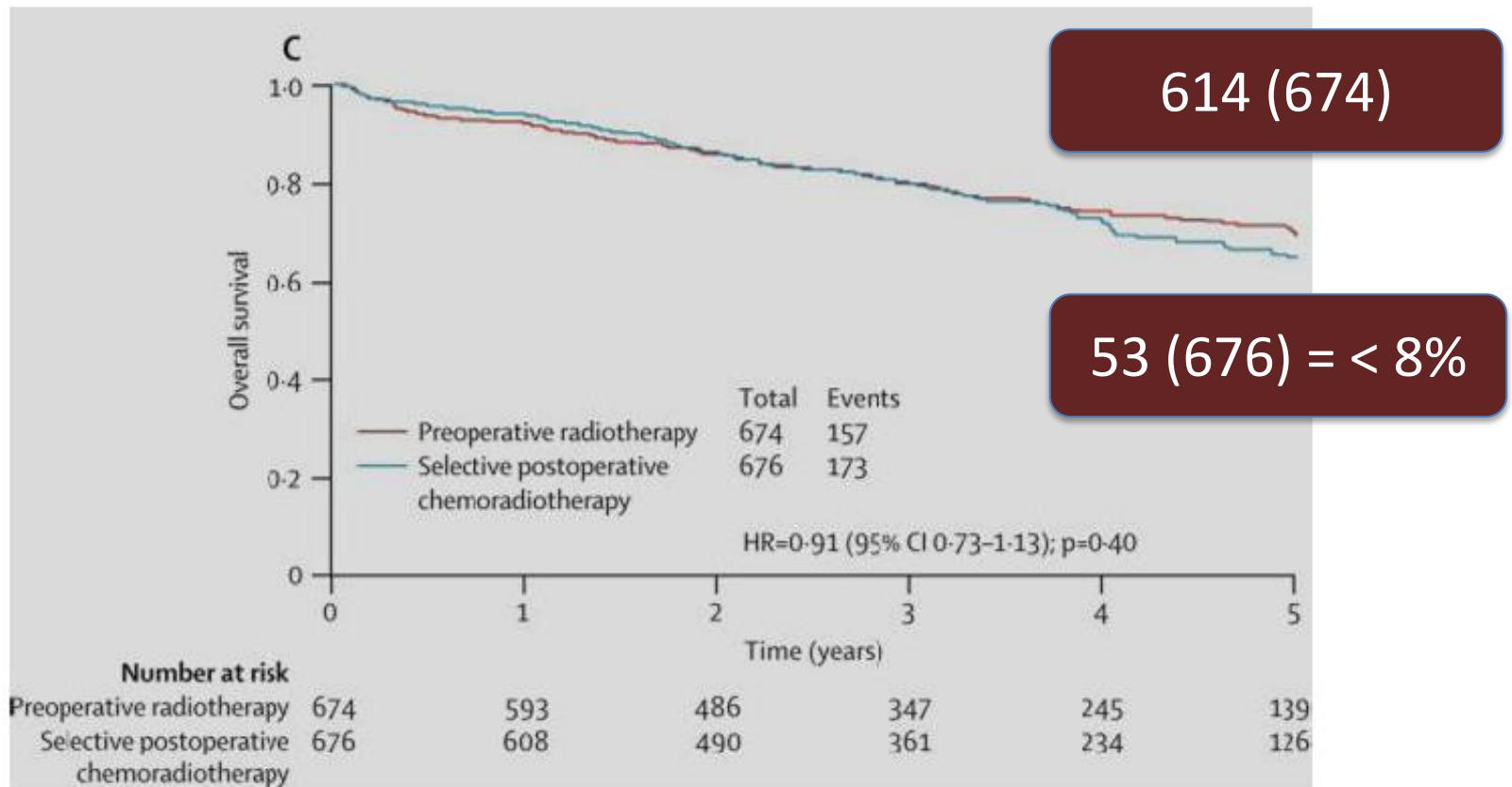
CR07 : Local recurrence by T3 substages



MRC CR 07 Trial: 5x5 Gy „for all“ or selective adjuvant RChT ?



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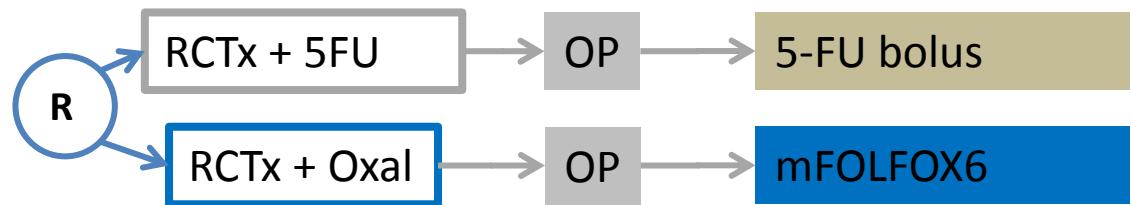
Does Oxaliplatin improve results of RCT?

	ACCORD 12/0405-Prodigie 2	STAR-01	NSAPB R-04	CAO/ARO/AIO-04
Number of patients	598	747	1608	1236
Main inclusion criteria	cT3-4 adenocarcinoma, accessible to digital rectal examination, ≤80 years	cT3-4 or cN+adenocarcinoma, within 12 cm from anal verge, ≤75 years	cT3-4 or cN+adenocarcinoma, within 12 cm from anal verge, no upper age limit	cT3-4 or cN+adenocarcinoma, within 12 cm from anal verge, no upper age limit
Primary endpoint	pCR	Overall survival, pCR as protocol-planned comparative analysis	Locoregional relapse pCR, sphincter-saving surgery	Disease-free survival
Preoperative chemoradiotherapy regimen	50 Gy+capecitabine 1600 mg/m ² daily 5 days a week+oxaliplatin 50 mg/m ² once a week during radiotherapy vs 45 Gy+capecitabine 1600 mg/m ² daily 5 days a week during radiotherapy	50.4 Gy+fluorouracil 225 mg/m ² daily+oxaliplatin 60 mg/m ² once a week during radiotherapy vs 50.4 Gy+fluorouracil 225 mg/m ² daily during radiotherapy	50.4 Gy+capecitabine 1600 mg/m ² daily 5 days a week with or without oxaliplatin 50 mg/m ² once a week during radiotherapy vs 50.4 Gy+fluorouracil 225 mg/m ² daily with or without oxaliplatin 50 mg/m ² once a week during radiotherapy	50.4 Gy+fluorouracil 250 mg/m ² daily plus oxaliplatin 50 mg/m ² once in weeks 1, 2, 4, 5 of radiotherapy vs 50.4 Gy+fluorouracil 1000 mg/m ² weeks 1 and 5 of radiotherapy
Cumulative dose of preoperative concurrent chemotherapy (planned)	Capecitabine 40 000 mg/m ² with or without oxaliplatin 250 mg/m ²	Fluorouracil 8550 mg/m ² with or without oxaliplatin 360 mg/m ²	Fluorouracil 8550 mg/m ² , capecitabine 40 000 mg/m ² , with or without oxaliplatin 250 mg/m ²	Fluorouracil 7000 mg/m ² plus oxaliplatin 200 mg/m ² vs fluorouracil 10 000 mg/m ²
Compliance with preoperative chemoradiotherapy in oxaliplatin groups	Radiotherapy: 87% received full dose Oxaliplatin: 41% received full dose	Radiotherapy: 84% received full dose Oxaliplatin: 66% received all six infusions (with or without dose reduction)	Not reported	Radiotherapy: 94% received full dose Oxaliplatin: 85% received full dose
Grade 3-4 toxicity: preoperative chemoradiotherapy with oxaliplatin vs without	25% vs 11% (p<0.001)	24% vs 8% (p<0.001)	15% vs 7% (p<0.001) (only grade 3-4 diarrhoea)	23% vs 20%
pCR rate: with oxaliplatin vs without	19% vs 14% (p=0.09)	16% both groups (p=0.90)	21% vs 19% (p=0.46)	17% vs 13% (p=0.04)
Distant metastasis at surgery: with oxaliplatin vs without	2.8% vs 4.2% (abdominal)	0.5% vs 2.9% (abdominal)	Not reported	4% vs 6% (all sites)
Adjuvant chemotherapy	No specific recommendation	Fluorouracil-based	No specific recommendation	Fluorouracil, leucovorin, and oxaliplatin vs fluorouracil

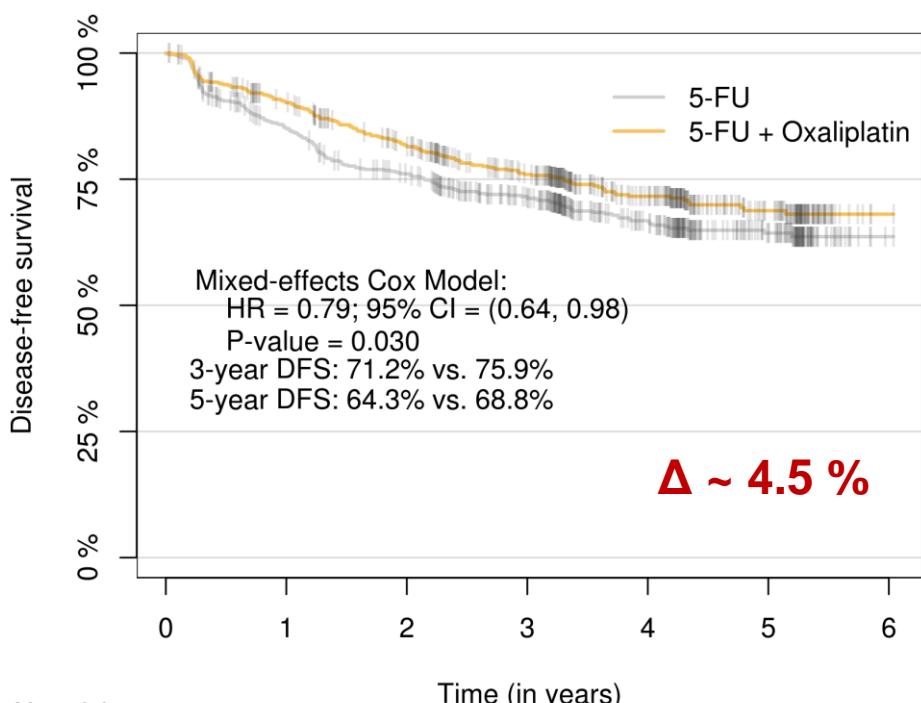
ACCORD=Actions Concertées dans les Cancers Colorectaux et Digestifs. Prodigie=Partenariat de Recherche en Oncologie Digestive. STAR=Studio Terapia Adjuvante Retto. NSAPB=National Surgical Adjuvant Breast and Bowel Project. CAO/ARO/AIO=Chirurgische Arbeitsgemeinschaft für Onkologie/Arbeitsgemeinschaft Radiologische Onkologie/Arbeitsgemeinschaft Internistische Onkologie. pCR=pathological complete response.

Table 6: Phase 3 trials adding oxaliplatin to preoperative fluorouracil-based chemoradiotherapy in stage 2-3 rectal cancer

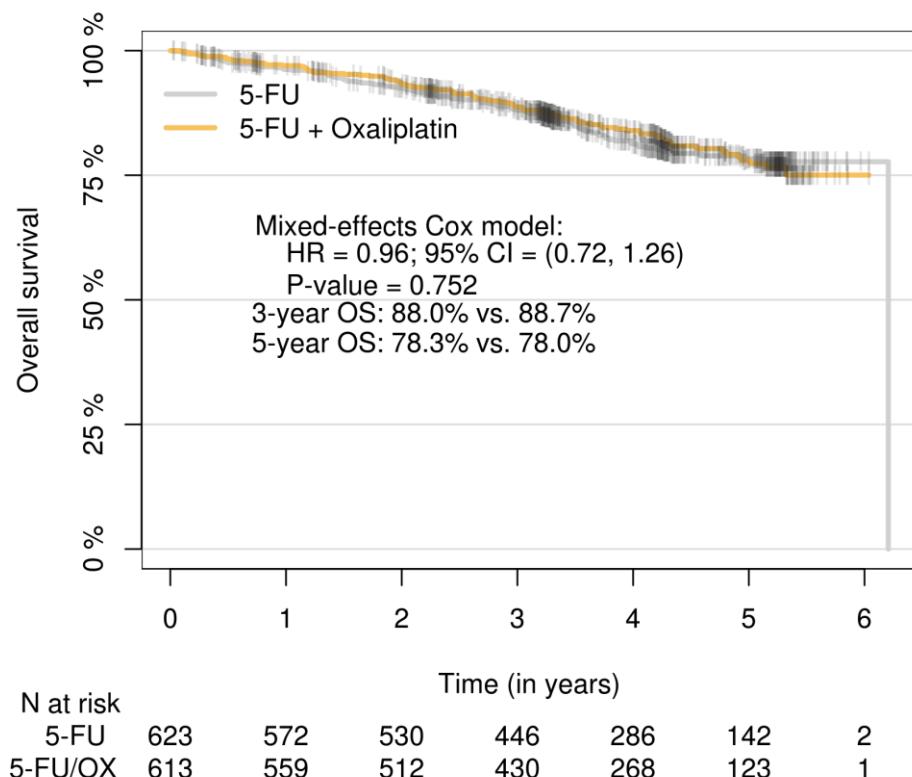
AIO/AROCAO-04



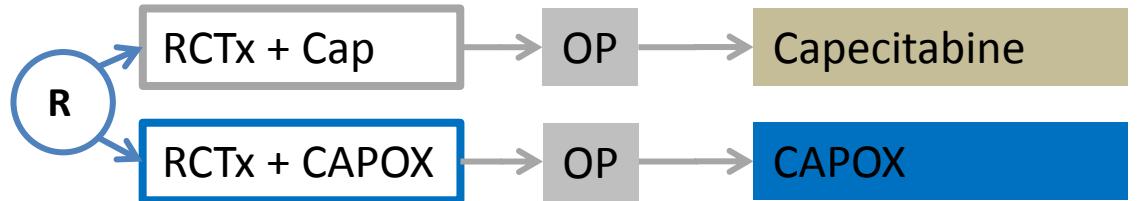
Disease free survival



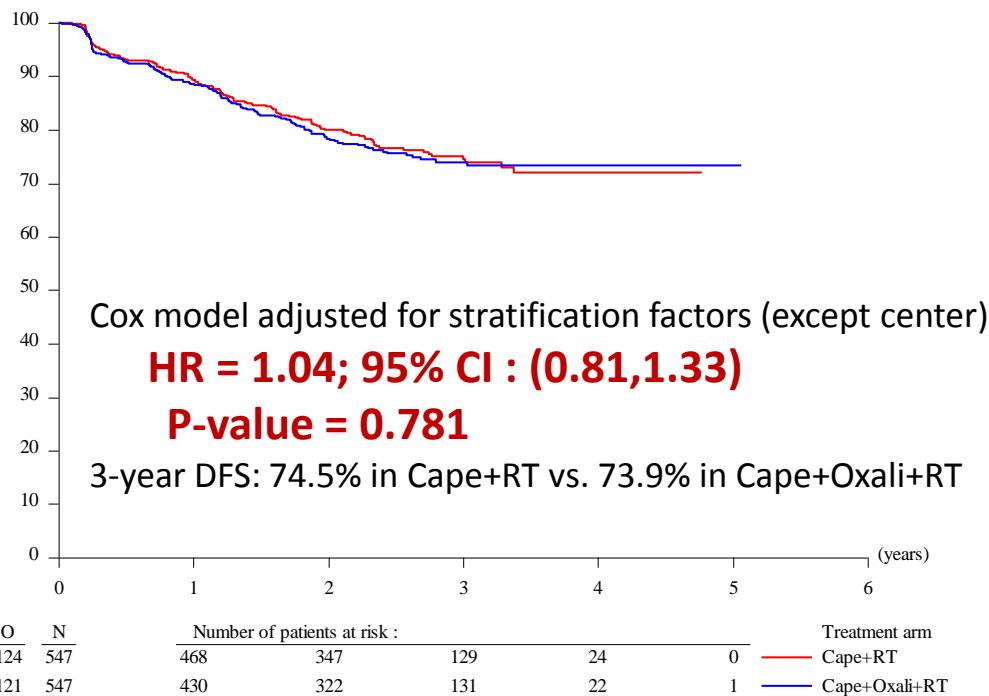
Overall survival



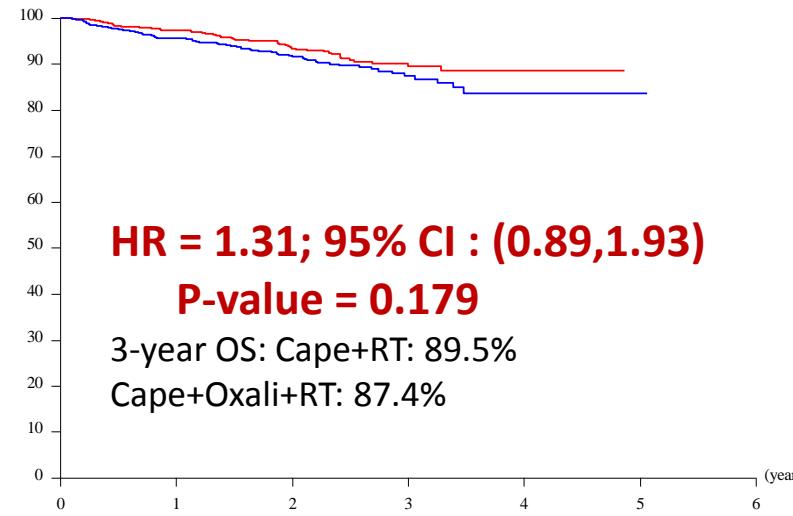
PETACC6:
EORTC GITCG, AIO,
AGITG, EORTC ROG,
BGDO and FFCD



Disease free survival

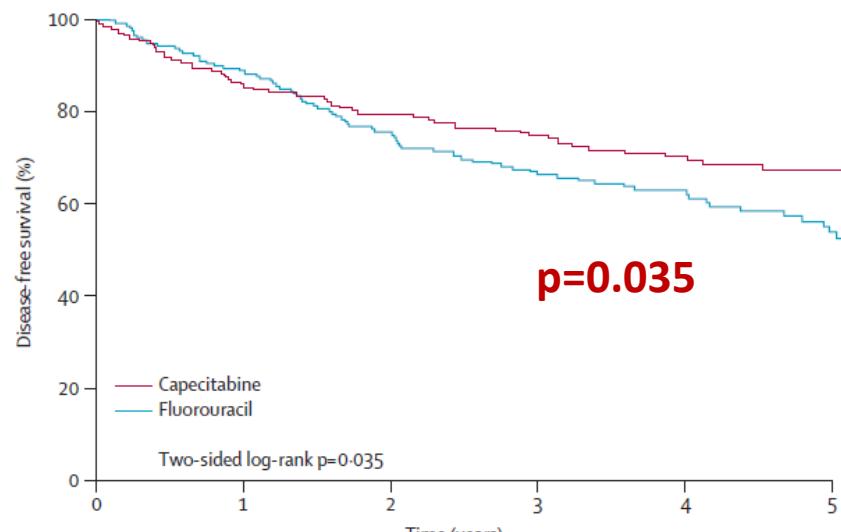


Overall survival



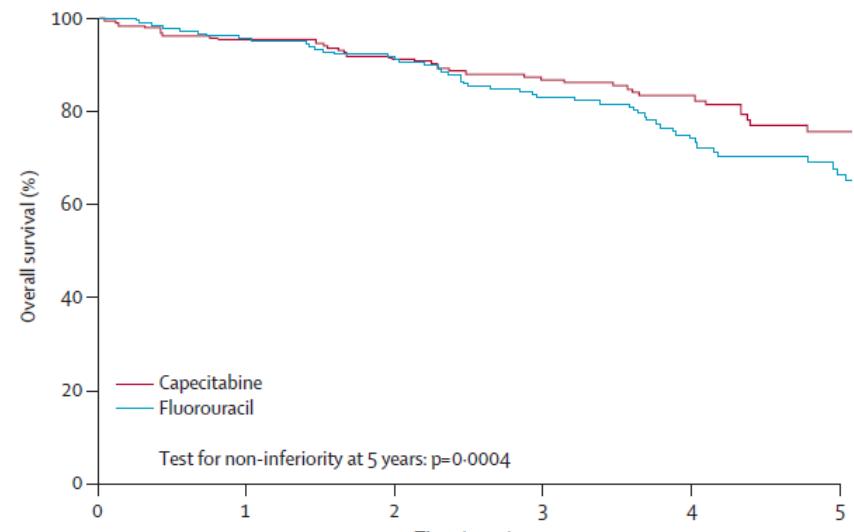
Capecitabine vs. 5-FU bolus perioperative treatment of rectal cancer

Disease free survival



Number at risk	
Fluorouracil	195
Capecitabine	197

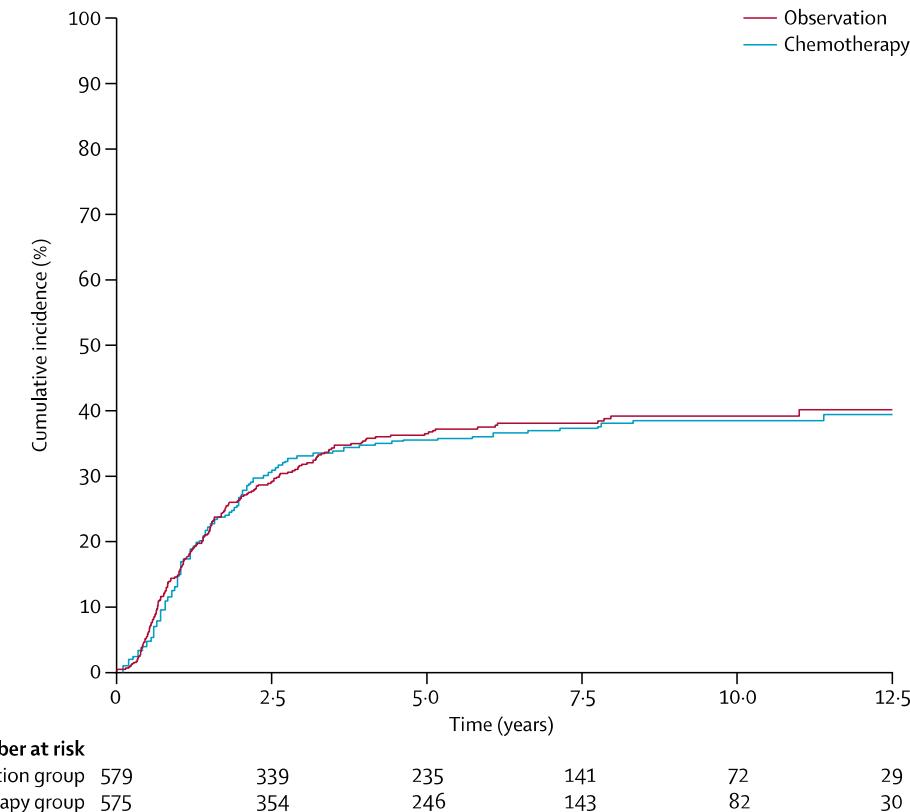
Overall survival



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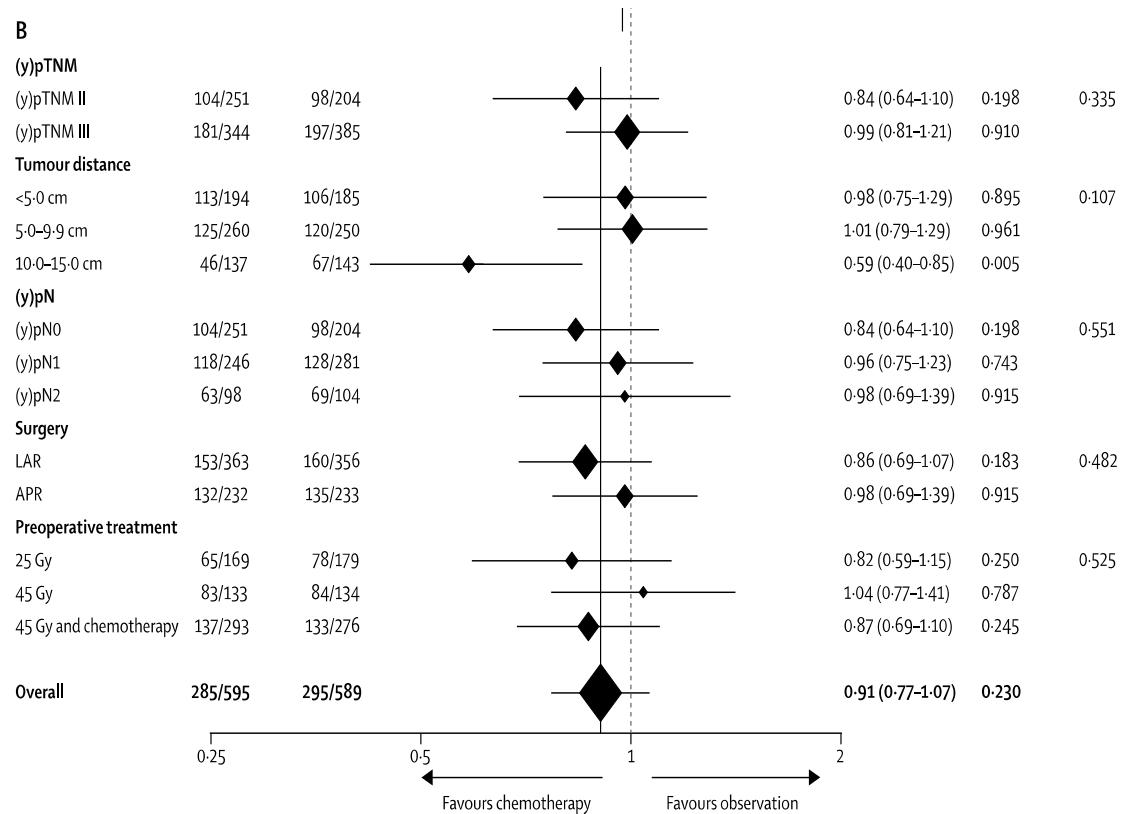
Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data

Anne J Breugom*, Marloes Swets*, Jean-François Bosset, Laurence Collette, Aldo Sainato, Luca Cionini, Rob Glynne-Jones, Nicholas Counsell, Esther Bastiaannet, Colette B M van den Broek, Gerrit-Jan Liefers, Hein Putter, Cornelis J H van de Velde



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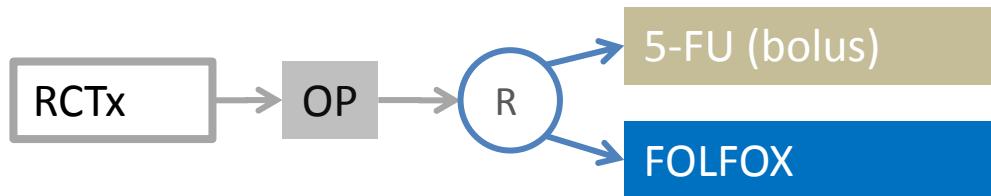
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Metaanalysis on chemotherapy in LARC: Discussions

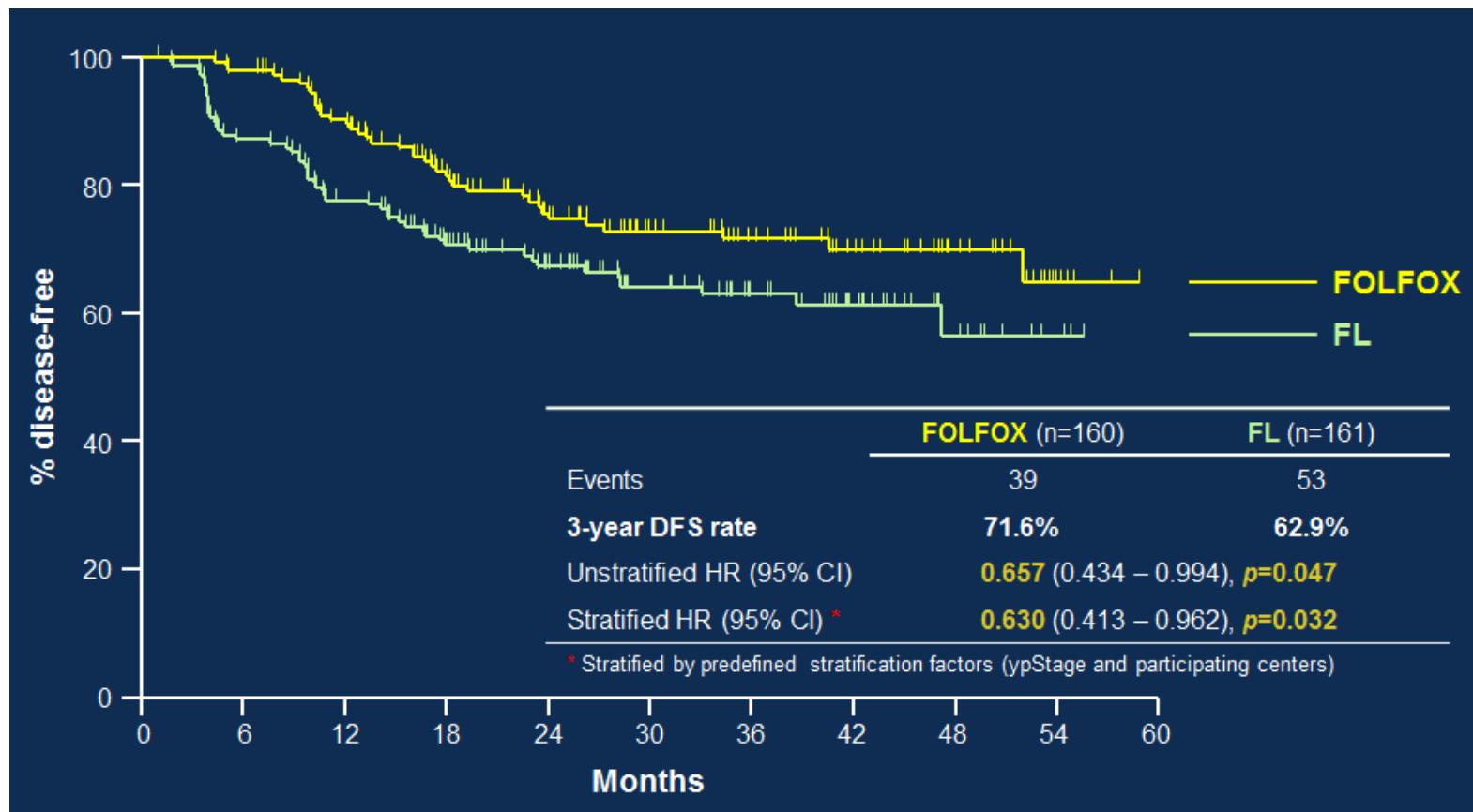
- After which radiotherapy / chemorad?
- „high risk“ population? (stage III, different staging systems,...)
- Individual trials underpowered
- Chemotherapy suboptimal
-

Breugorn et al., Lancet Oncol, 2015
Cervantes et al., Lancet Oncol, 2015



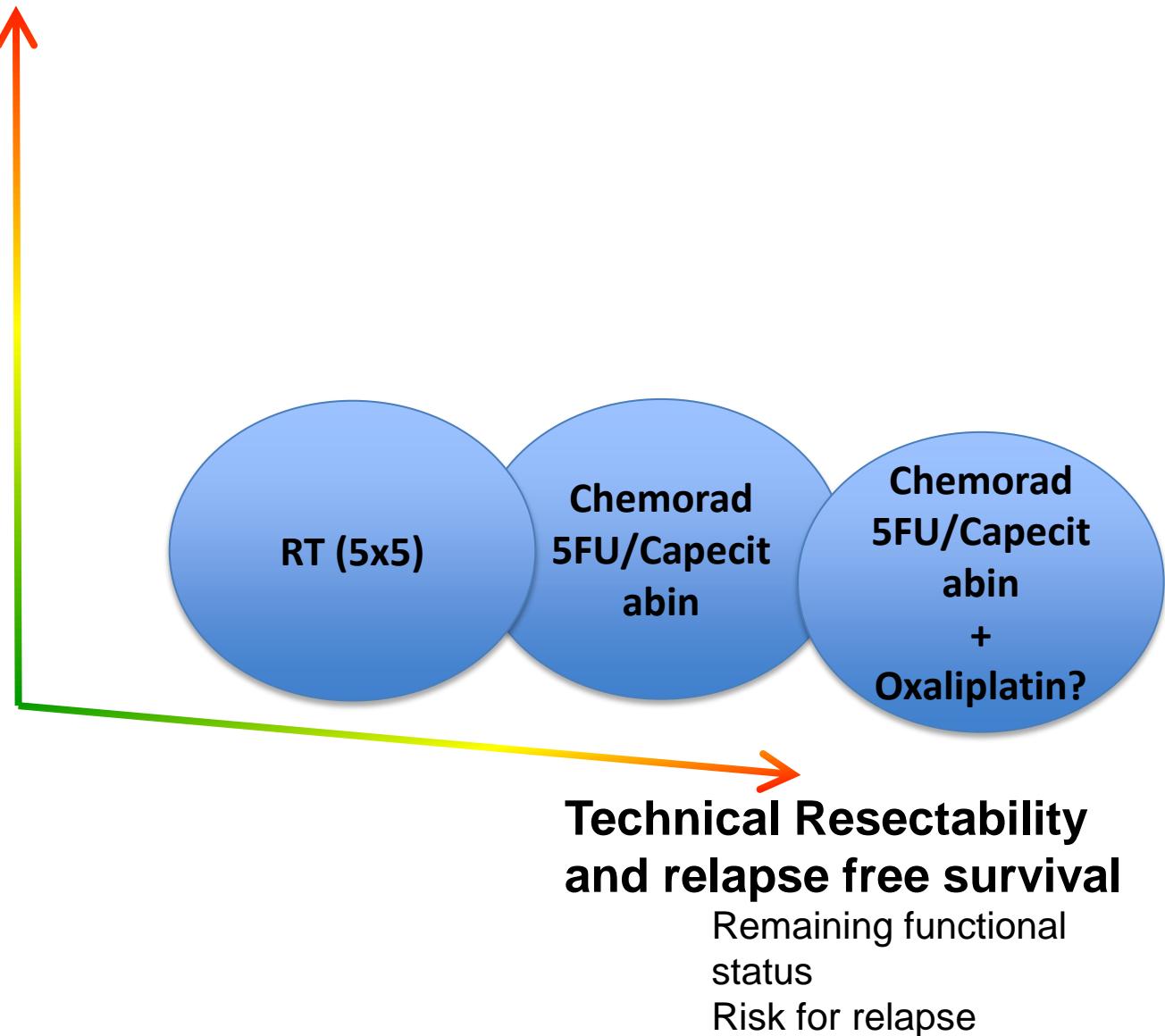
5-FU ADORE

Disease free survival; (ITT)



(Prognostic) factors for distant failure

- Size?
- Nodal status?
- Tumour markers?
- (response to) CRT?



(Prognostic) factors for distant failure

- Size?
- Nodal status?
- Tumour markers?
- (response to) CRT?



adjuvant
5FU/Oxali?

adjuvant
5FU?

no
adjuvant?
5FU/Capecit
abin



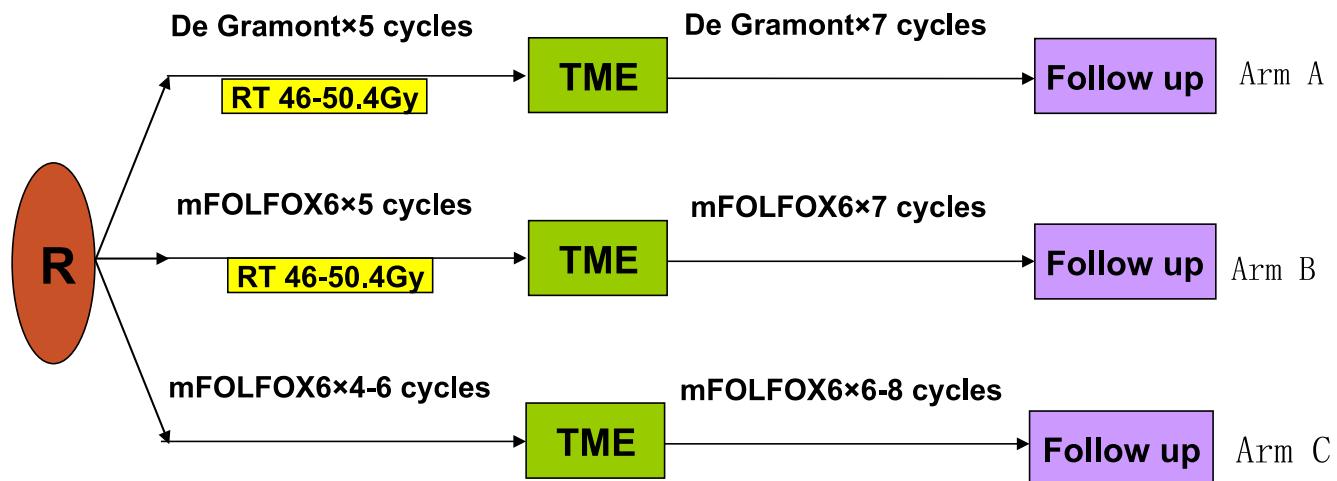
**Technical Resectability
and relapse free survival**

Remaining functional
status
Risk for relapse

FOWARC: Design

Study Design

15 centers
NCT01211210



Radiation begin from day1 of cycle 2 chemotherapy

Radiation was conducted as long course in 23-25 fractions according to the principles of radiation therapy in NCCN guideline

De Gramont regimen constitutes of leucovorin 0.4/m² d1, followed by 5-FU 0.4/m² bolus iv, followed by 2.4/m² CIV 48 hours. With oxaliplatin 85mg/m² 2 hours IV infusion prior to leucovorin constitutes FOLFOX regimen.

Radiation is added to Arm C according to the physician's decision.

1° Endpoint: 3y DFS (60 → 75%)

Deng et al., ASCO 2015; #3500

FOWARC: Results

Consort Diagram

Patient-characteristics (intention-to-treat)

Age median, yrs
Gender, Male (%)
cT4b (%)
cT4a (%)
cT3 (%)
cT2 (%)
cN2a (%)
cN2b (%)
cN1 (%)
Clinical staging
Tumor length (cm)
Distance from a (cm, mean±SD)

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Preoperative CRT/CT: safety and compliance

	Arm A N=155	Arm B N=158	Arm C N=163
Grade 3/4 leucopenia (%)	19 (12.9)	29 (19.0)	9 (5.7)
Grade 3/4 nausea/vomiting (%)	4 (2.6)	9 (5.7)	4 (2.5)
Grade 3/4 diarrhea (%)	12 (7.7)	23 (14.5)	12 (7.3)
Grade 3/4 radiodermatitis (%)	22 (14.1)	32 (20.3)	—
Radiation proctitis	15 (9.7)	20 (12.6)	—
Full dose chemo (%)	137 (88.4)	150 (94.9)	154 (94.5)
Full dose RT (%)	134 (86.4)	143 (90.5)	—

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FOWARC: Results

Surgery

Pathology of resection

Subgroup of patients with low rectal cancer (tumor located within 5 cm from the anal verge)

	Arm A N=77	Arm B N=72	Arm C N=61
cT4b (%)	6 (7.8)	9 (12.5)	3 (4.9)
cN2a (%)	17 (22.1)	6 (8.3)	8 (13.1)
cN2b (%)	4 (5.2)	5 (6.9)	3 (4.9)
pCR (%)	12 (15.6)	21 (29.2)	4 (6.6)
ypT1-2N (0%)	30 (39.0)	43 (59.8)	24 (39.4)
TRG 0-1 (%)	35 (45.5)	45 (62.5)	20 (32.8)
Sphincter reservation (%)	57 (74.0)	56 (77.8)	48 (78.7)
Anastomotic leakage (%)	11 (14.2)	10 (13.9)	2 (3.3)

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Deng et al., ASCO 2015; #3500

Thank you for your attention!



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