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Rectal Cancer: Operate or wait and see?

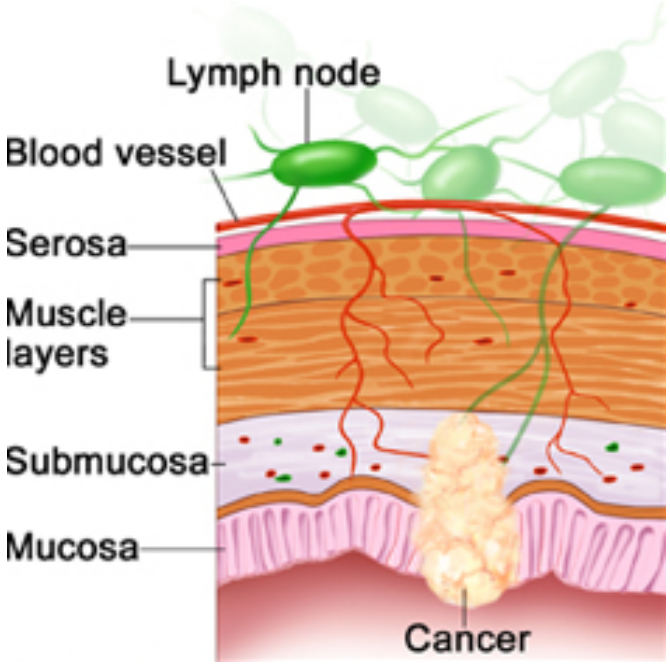
C. Coimbra Marques

Neoadjuvant chemoradiotherapy followed by radical surgery including total mesorectal excision (TME) is the standard recommended treatment for patients with locally advanced (T3-T4,N+) mid-low rectal cancers

Bujko et al. British J Surgery (2006)

Patients with ypCR have better oncological outcome

Tumour regression after neoadjuvant treatment is observed in the primary tumour but also in the mesorectal metastatic lymph nodes



Wolthuis et al Annals Surg Oncol (2011)
Hughes et al. Int J Colorectal Disease (2006)

pCR after resection

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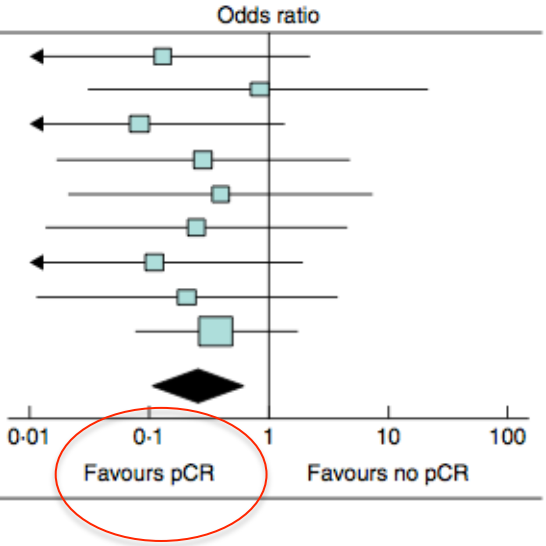
Reference	Odds ratio	*P*
Chan *et al.*[5]	0·13 (0·01, 2·23)	0·158
Hong *et al.*[17]	0·83 (0·03, 21·80)	0·909
de Campos-Lobato *et al.*[6]	0·08 (0·01, 1·39)	0·084
Rödel *et al.*[20]	0·28 (0·02, 4·82)	0·382
Ruo *et al.*[22]	0·39 (0·02, 7·50)	0·534
Shivnani *et al.*[23]	0·25 (0·01, 4·71)	0·356
Valentini *et al.*[24]	0·11 (0·01, 1·95)	0·134
Wheeler *et al.*[25]	0·21 (0·01, 3·85)	0·292
Yeo *et al.*[26]	0·37 (0·07, 1·81)	0·216
Overall	0·25 (0·10, 0·59)	0·002

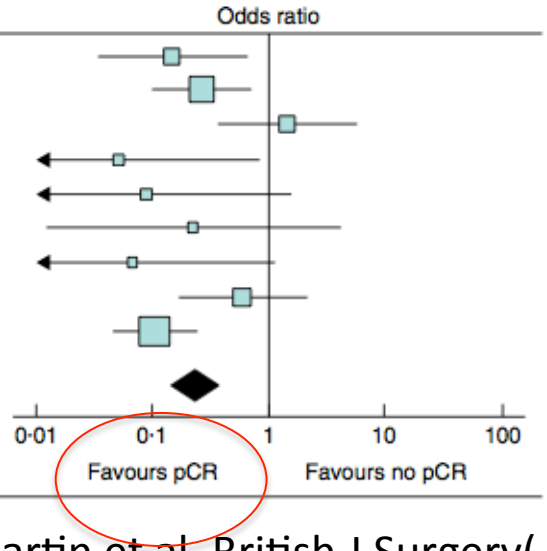
Test for heterogeneity: $Q = 1·9$, 8 d.f., $P = 0·981$, $I^2 = 0\%$



a Local recurrence

Reference	Odds ratio	*P*
Chan *et al.*[5]	0·15 (0·03, 0·65)	0·012
de Campos-Lobato *et al.*[6]	0·27 (0·10, 0·71)	0·008
Pucciarelli *et al.*[19]	1·44 (0·36, 5·84)	0·607
Rödel *et al.*[20]	0·05 (0·00, 0·84)	0·037
Roh *et al.*[21]	0·09 (0·01, 1·54)	0·097
Ruo *et al.*[22]	0·22 (0·01, 4·14)	0·315
Shivnani *et al.*[23]	0·07 (0·00, 1·13)	0·061
Valentini *et al.*[24]	0·59 (0·16, 2·16)	0·423
Yeo *et al.*[26]	0·11 (0·05, 0·25)	< 0·001
Overall	0·23 (0·11, 0·47)	< 0·001

Test for heterogeneity: $Q = 14·63$, 8 d.f., $P = 0·067$, $I^2 = 45\%$

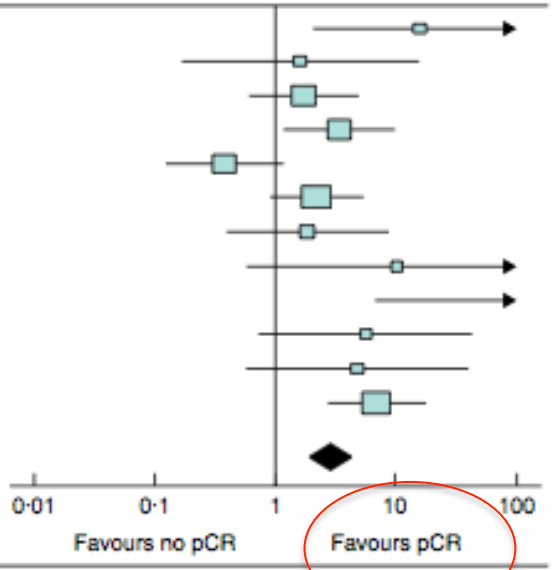


b Distant recurrence

Martin et al. British J Surgery(2012)

Reference	Odds ratio	P
Chan *et al.*[5]	15·50 (2·02, 118·73)	0·008
Ciccocioppo *et al.*[16]	1·62 (0·17, 15·72)	0·680
Kim *et al.*[18]	1·72 (0·59, 5·01)	0·317
de Campos-Lobato *et al.*[6]	3·36 (1·14, 9·88)	0·027
Pucciarelli *et al.*[19]	0·38 (0·12, 1·18)	0·095
Rödel *et al.*[20]	2·22 (0·90, 5·45)	0·083
Roh *et al.*[21]	1·85 (0·39, 8·79)	0·439
Ruo *et al.*[22]	10·11 (0·56, 181·57)	0·116
Shivnani *et al.*[23]	113·93 (6·65, 1951·68)	0·001
Valentini *et al.*[24]	5·63 (0·72, 43·90)	0·099
Wheeler *et al.*[25]	4·80 (0·56, 41·13)	0·152
Yeo *et al.*[26]	6·86 (2·63, 17·86)	< 0·001
Overall	3·28 (1·66, 6·51)	0·001

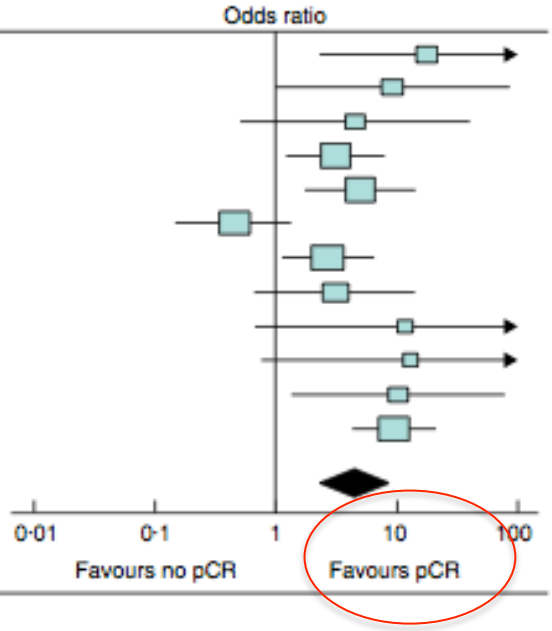
Test for heterogeneity: $Q = 27·6$, 11 d.f., $P = 0·004$, $I^2 = 60\%$



a Overall survival

Reference	Odds ratio	P
Chan *et al.*[5]	17·79 (2·33, 136·01)	0·006
Ciccocioppo *et al.*[16]	9·23 (0·99, 85·78)	0·051
Hong *et al.*[17]	4·50 (0·50, 40·65)	0·180
Kim *et al.*[18]	3·10 (1·20, 8·02)	0·019
de Campos-Lobato *et al.*[6]	5·06 (1·74, 14·70)	0·003
Pucciarelli *et al.*[19]	0·45 (0·15, 1·38)	0·162
Rödel *et al.*[20]	2·65 (1·08, 6·50)	0·033
Roh *et al.*[21]	3·09 (0·66, 14·40)	0·151
Ruo *et al.*[22]	11·73 (0·66, 210·11)	0·094
Shivnani *et al.*[23]	13·07 (0·75, 226·77)	0·078
Valentini *et al.*[24]	10·25 (1·32, 79·40)	0·026
Yeo *et al.*[26]	9·46 (4·20, 21·31)	< 0·001
Overall	4·33 (2·31, 8·09)	< 0·001

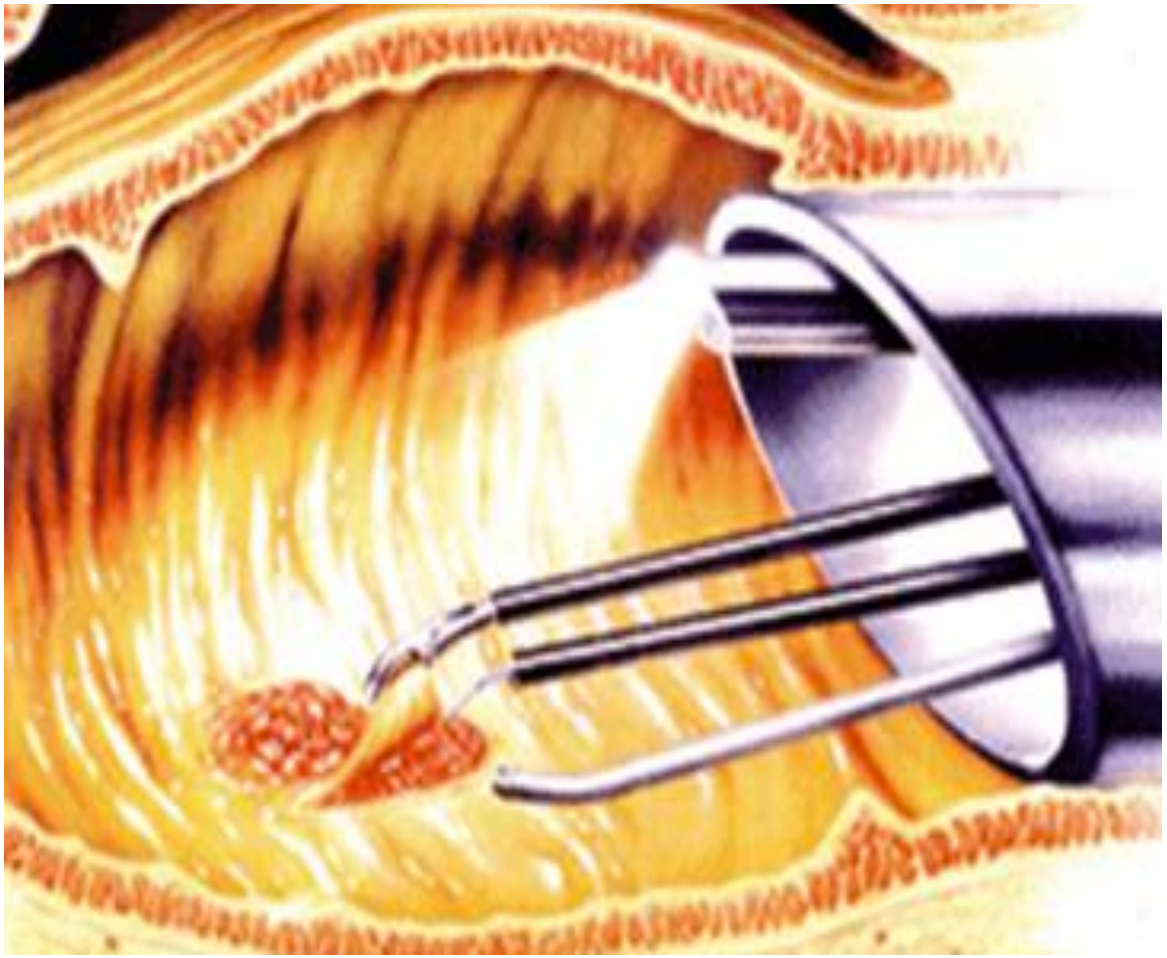
Test for heterogeneity: $Q = 25·0$, 11 d.f., $P = 0·009$, $I^2 = 56\%$



b Disease-free survival

Martin et al. British J Surgery(2012)

Organ Preservation Strategies



Guerrieri et el. Surg Endoscopy (2008)
Callender et al Ann Surg Oncol (2010)

Organ Preservation Strategies

Habr-Gama et al. Ann Surg (2004)
O'Neill et al. Lancet Oncol (2007)

Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiation Therapy

Long-term Results

Angelita Habr-Gama, MD, Rodrigo Oliva Perez, MD,* Wladimir Nadalin, MD,†*
*Jorge Sabbaga, MD,† Ulysses Ribeiro Jr, MD,‡ Afonso Henrique Silva e Sousa Jr, MD,**
Fábio Guilherme Campos, MD, Desidério Roberto Kiss, MD,* and Joaquim Gama-Rodrigues, MD‡*

Overall

Disease-free

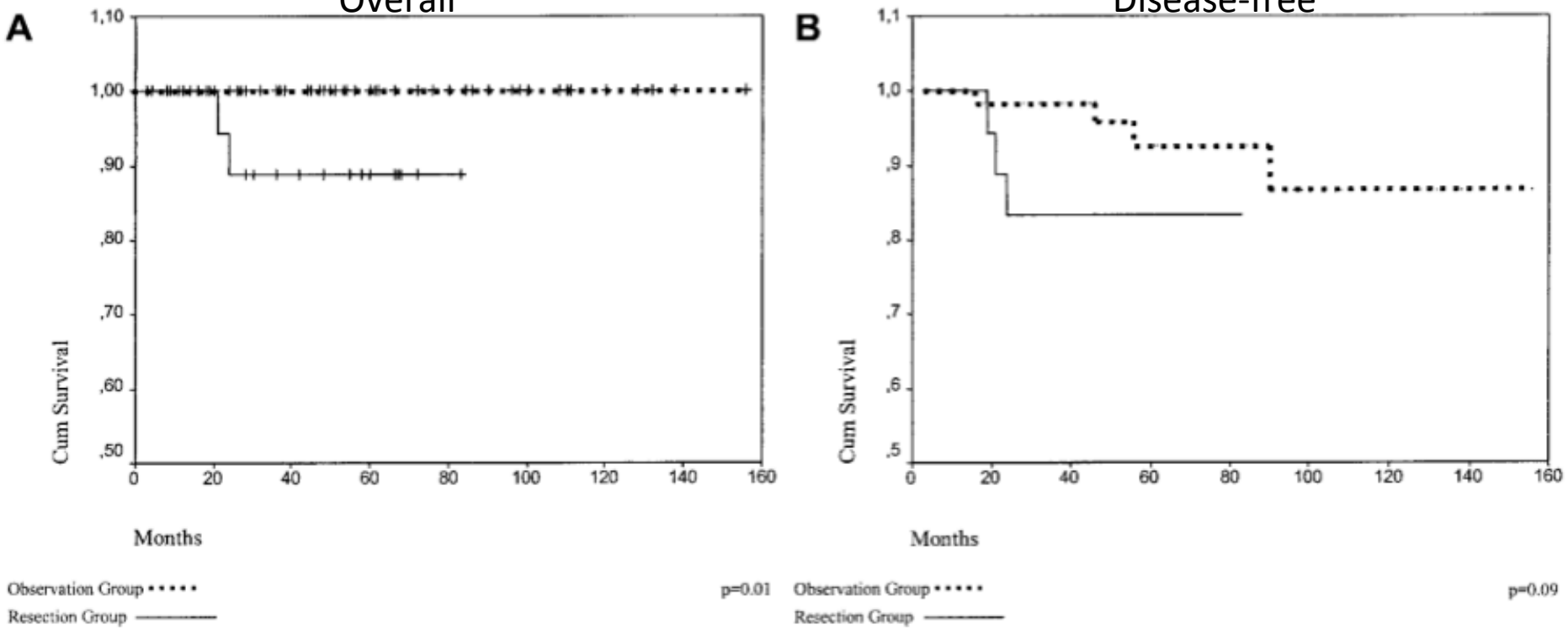


FIGURE 1. A, Overall survival. B, Disease-free survival.

Ann Surg (2004)


Morbidity
Mortality
Quality of life
Local
Distal
Recurrence
SUCCESS
FAILURE

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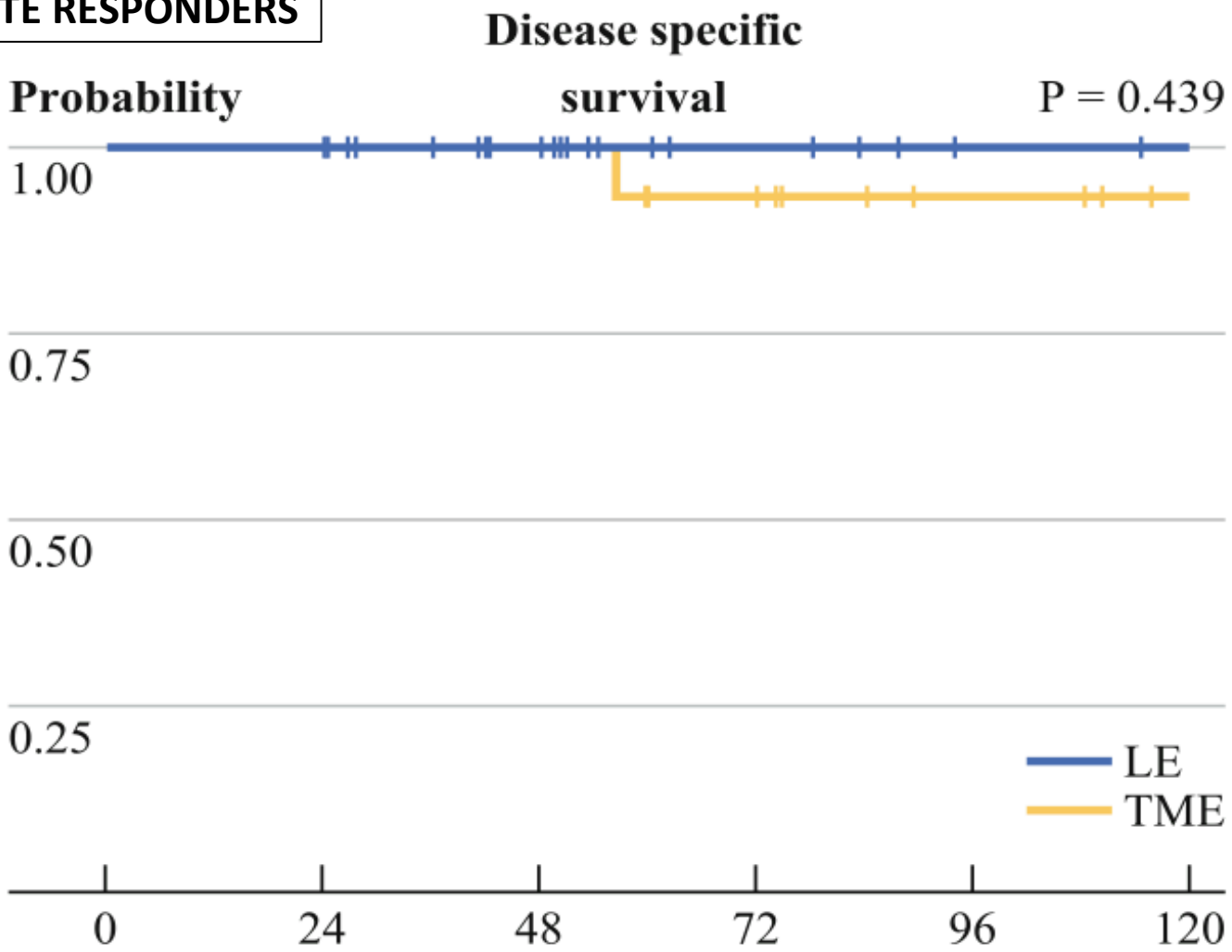
ypCR

Favorable biological tumour profile

Higher sensitivity to radiochemotherapy

Less propensity for local and distant metastases

COMPLETE RESPONDERS

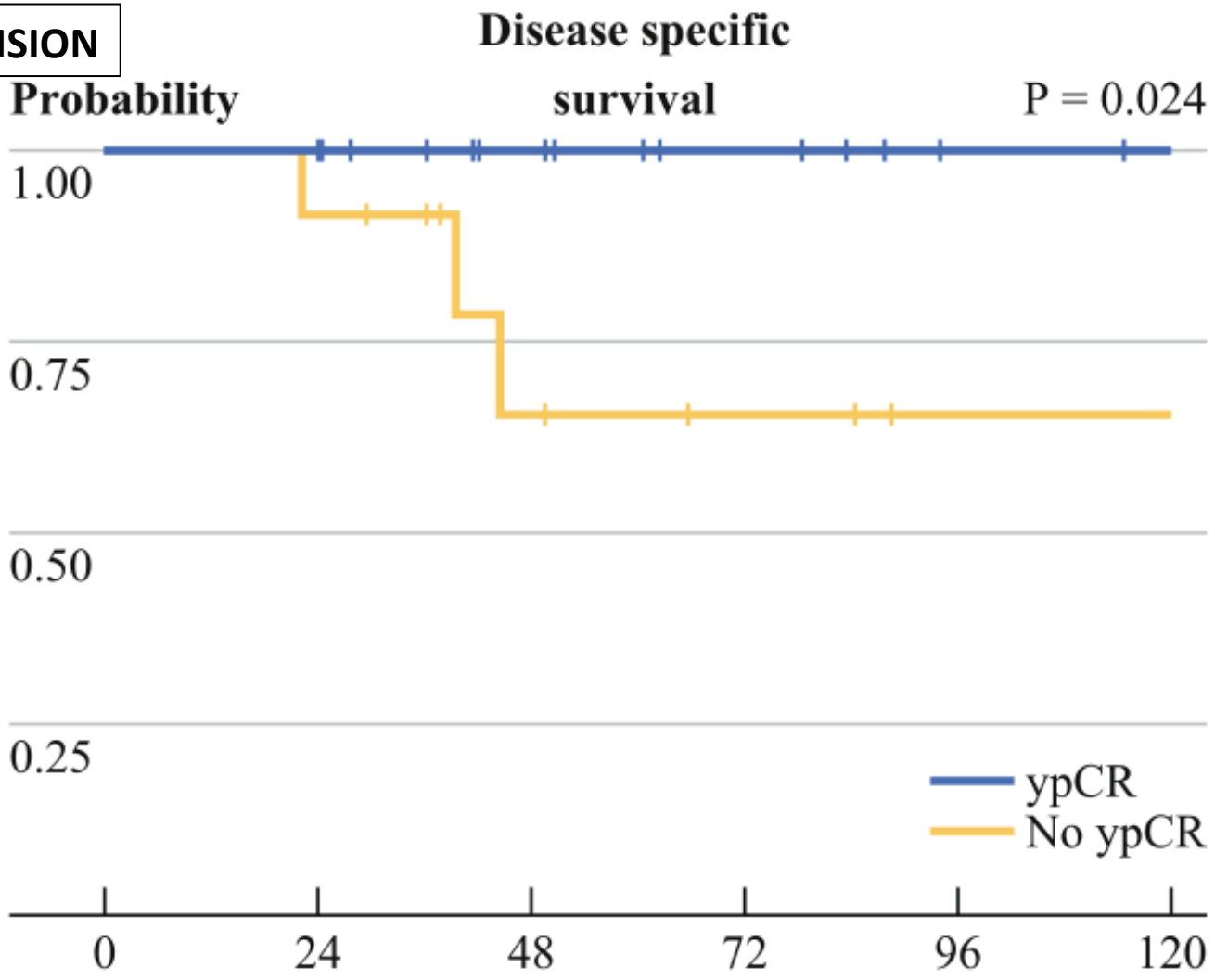


Patients at risk

LE	17	17	11	7	4	2
TME	25	24	21	12	7	3

Belluco et al. Ann Surg Oncol (2011)

LOCAL EXCISION



Patients at risk

ypCR	17	17	11	7	3	2
No ypCR	12	11	5	3	1	1

Belluco et al. Ann Surg Oncol (2011)

- Can we predict cCR?
- Is cCR true pCR?
- How do we define cCR?
- How do we assess CR?
- How should we follow up?

- Can we predict cCR?
- Is cCR true pCR?
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Table 1. PhaseII/III studies included in analysis

1st author [ref]	*n*	Radiotherapy dose (GY)/ *n* fractions	5FU drug	2nd drug	pCR *n* (%)
Bhargava P [4]	23	50.4/28	N/A(Taxane)		1 (4)
Bosset J [5]	66	45/25	BOS		9 (14)
Bosset J [3]	506	45/25	BOS		66 (13)
Boulis-Wassif S [6]	126	34.5/15	BOL		6 (5)
Bujko K [2]	157	50.4/28	BOL		22 (14)
Carau B [7]	33	50.4/28	CI		5 (15)
Carraro S [8]	22	50.4/28	BOL	Oxaliplatin	3 (14)
Carraro S [9]	37	50.4/28	BOL	Cisplatin	4 (11)
Chan A [10]	54	40/20	INTI	Mitomycin	2 (4)
Chan A [10]	27	40/20	INTI	Mitomycin	4 (15)
Chan A [10]	75	50/25	INTI	Mitomycin	19 (25)
Chang H [11]	46	50-54/25-27	INTI	Mitomycin	8 (17)
Chari R [12]	43	45/25	BOL	Cisplatin	11 (23)
Chau I [13]	36	50.4-54	CI		1 (3)
Chen E [14]	31	55.8/31	CI		3 (10)
Ciabattoni A [15]	27	45/25	BOL		6 (22)
Conzo G [16]	15	32/10	BOL		0 (0)
De La Torre A [17]	35	45/25	O		3 (9)
Feliu J [18]	41	50.4/28	O		6 (15)
Fernandez-Martos C [19]	68	45/25	O		4 (6)
Frykholm G [20]	34	40/20	INTI	Methotrexate	3 (9)
Galizia E [21]	39	50.4/28	INTI	Cisplatin	8 (21)
Gerard JP [22]	40	50/25	BOS	Oxaliplatin	6 (15)
Grann A [23]	72	50.4/28	BOL		9 (13)
Kim J [24]	45	50.4/28	CAP		12 (27)
Kim N [25]	14	50.4/28	BOL		3 (21)
Kim N [25]	14	50.4/28	O		2 (14)
Klautke G [26]	21	50.4/28	CI	Irinotecan	4 (19)
Kocakova I [27]	34	50.4/28	CAP		7 (21)
Mermershtain W [28]	23	45/25	BOL		4 (17)
Metha VK [29]	30	50.4-54/28-30	CI		10 (33)
Metha VK [30]	32	50.4/28	CI	Irinotecan	12 (38)
Mohiuddin M [31]	6	55-60/31-34	INTI		0 (0)
Mohiuddin M [31]	12	55-60/31-34	CI		8 (67)
Mohiuddin M [31]	15	45-50/25-27	INTI		2 (13)
Ngan S [32]	82	50.4/28	CI		13 (16)
Porter H [33]	36	50/25	T		5 (14)
Roh M [34]	130	50.4/28	BOL		12 (9)
Ronzoni M [35]	72	40/32	CI		13 (18)
Sauer R [1]	405	50.4/28	INTI		32 (8)
Seong J [36]	23	45/25	O		1 (4)
Tamberi S [37]	36	45/25	CI		5 (14)
Tjandra J [38]	42	45/25	BOL		6 (14)
Uzcudun A [39]	38	50.4/28	O		5 (13)
Valentini V [40]	83	37.8/20	INTI	Mitomycin	7 (8)
Valentini V [40]	80	50.4/28	INTI	Cisplatin	17 (21)
Vicario G [41]	34	50/25	CI		7 (21)
Wiltshire K [42]	47	40/20	CI		7 (15)
Wiltshire K [42]	52	46/23	CI		10 (19)
Wiltshire K [42]	36	50/25	CI		11 (31)
Wong S [43]	18	50.4/28	CAP		2 (11)
Yoon W [44]	44	50.4/28	BOL		2 (5)

N/A, Not applicable; Gy, Gray; pCR, pathological complete response; BOS, "Bosset" like schedule 5FU infused over 1 hour; BOL, Bolus 5FU; CI, Continuous infusion 5FU; INTI, Intermittent infusion 5FU *e.g.* for 96 h every 4 weeks; CAP, Capecitbine; O, Other oral 5FU drug; T, Tomudex.

Rates of pCR vary 4-30%

Hartley et al.British J Radiol (2005)

Table 2. Statistically significant factors effecting rate of pCR

Variable	Weighting (number of patients)	Adjusted pCR means with 95% confidence interval	*p*-value
Second drug			0.001
Second drug given	633	0.19 (0.12, 0.27)	
Second drug not given	2524	0.10 (0.06, 0.15)	
5-FU delivery			0.01
BOS	612	0.14 (0.08, 0.21)	
BOL	752	0.13 (0.09, 0.19)	
CAP	97	0.24 (0.12, 0.39)	
CI	554	0.23 (0.17, 0.29)	
INTI	864	0.11 (0.07, 0.16)	
T	23	0.17 (0.03, 0.38)	
O	219	0.11 (0.05, 0.19)	
N/A (Taxane)	36	0.06 (0.01, 0.27)	
Radiotherapy dose (Gy)			0.02
<45	458	0.09 (0.04, 0.14)	
45–<50	936	0.18 (0.12, 0.25)	
50–<55	1714	0.16 (0.12, 0.21)	
55+	49	0.16 (0.04, 0.34)	

N/A, Not applicable; Gy, Gray; pCR, pathological complete response; BOS, "Bosset" like schedule 5FU infused over 1 hour; BOL, Bolus 5FU; CI, Continuous infusion 5FU; INTI, Intermittent infusion 5FU; CAP, Capecitabine; O, Other oral 5FU drug; T, Tomudex.

Factors: use of a second drug
continous 5-FU and Capecitabine
radiotherapy dose > 45 Gy

Hartley et al.British J Radiol (2005)

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EORTC 22921
European Organization for Research and Treatment of Cancer

	45 Gy	45 Gy+ 5'FU
pCR	5%	14%

Bonnet et al J Clin Oncol (2005)

Reference	No. of patients*	T2†	Follow-up (months)	Chemotherapy	cCR†	Locoregional failure†	5-year survival (%)		
							Disease-free	Cancer-specific	Overall
Habr-Gama *et al.*[18] 1998	118 (1991–1996)	Yes	36	FUFA	36 of 118 (30·5)	8 of 30 (27)	NS	NS	NS
Habr-Gama *et al.*[20] 2004	265	(15)	57·3	FUFA	71 of 265 (26·8) sustained for 12 months	2 of 71 (3)	92	100	100
Habr-Gama *et al.*[21] 2005	260	(20)	57	FUFA	71 of 260 (27·3) sustained for 12 months	2 of 71 (3)	92	100	NS
Habr-Gama *et al.*[22] 2006	361 (1991–2005)	14 of 99 (14)	60	FUFA	99 of 361 (27·4) sustained for 12 months	5 of 99 (5)	85	93	93
Habr-Gama[23] 2006	360 (1991–2005)	14 of 99 (14)	NS	FUFA	99 of 360 (27·5) sustained for 12 months	6 of 99 (6)	NS	NS	NS
Habr-Gama *et al.*[25] 2011	173 (1991–2009)	(16)	65	5-FU-based	67 of 173 (38·7)	8 of 173 (4·6)	72	NS	96

Reference	No. of patients	T2*	Radiotherapy	Chemotherapy	Procedure	cCR*	Locoregional failure*
Rossi *et al.*[39] 1998	16	NS	50·4 Gy, 28 fractions, 38 days + 30 Gy brachytherapy	FUFA	No surgery	6 of 16 (38)	5 of 6 (83)
Nagakawa *et al.*[41] 2002	52	No	45–50·4 Gy, 28 fractions, 38 days	FUFA	No surgery	(19)	NS fully
Lim *et al.*[43] 2007	48	T1 and T2 (33)	Variable; mean 50 Gy, 25 fractions	PVI 5-FU 92%	No surgery	27 of 48 (56)	11 of 48 (23)
Hughes *et al.*[44] 2010	58	No (50 T4)	45 Gy, 25 fractions, 33 days	FUFA	No surgery	10 of 58 (17)	6 of 10 (60)
Seshadri[45] 2011	23	Yes	50 Gy, 25 fractions, 33 days	5-FU/MMC	No surgery	NS	10 of 23 (43)
Dalton *et al.*[26] 2012	49	No	45 Gy, 25 fractions, 33 days	Capecitabine 850 mg/m^2	No surgery	12 of 49 (24)	6 of 12 (50)
Yu *et al.*[46] 2011	22	NS	?54 Gy (minimum 50·4 Gy), 28 fractions, 38 days	Capecitabine 825 mg/m^2	No surgery; adjuvant chemotherapy in some	Did not all achieve cCR	9 of 22 (41)
Maas *et al.*[27] 2011	21	5 of 21 (24)	Minimum 50·4 Gy, 28 fractions, 38 days	Capecitabine 825 mg/m^2	No surgery; adjuvant XELOX routinely	21 of 192 (10·9)	1 of 21 (5)
Total	289						48 of 142 (33·8)

Glynne-Jones, British J Surg (2012)

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Habr-Gama[23] 2006	360 (1991–2005)	14 of 99 (14)	NS	FUFA	99 of 360 (27·5) sustained for 12 months	6 of 99 (6)	NS	NS	NS
Habr-Gama *et al.*[25] 2011	173 (1991–2009)	(16)	65	5-FU-based	67 of 173 (38·7)	8 of 173 (4·6)	72	NS	96

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Seshadri[45] 2011	23	Yes	50 Gy, 25 fractions, 33 days	5-FU/MMC	No surgery	NS	10 of 23 (43)
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Glynne-Jones, British J Surg (2012)

- Can we predict cCR?
- Is cCR true pCR?
- How do we define cCR?
- How do we assess CR?
- How should we follow up?

Table I Probability of positive mesorectal lymph nodes in good responders (ypT0-1) after radiochemotherapy for rectal cancer.

Author [references]	*n*	pT0-1	N+	%
Read *et al.* [17]	644	87	3	3
Schell *et al.* [18]	–	32	1	3
Hiotis *et al.* [19]	488	27	4*	15
Onaitis *et al.* [20]	141	34	4*	13
Busko *et al.* [21]	138	33	2	6
Zmora *et al.* [22]	109	17	2*	12
Bosset *et al.* [10]	506	65	6	9
Total	2026	295	22	7%

*For pT0.

Rullier et al. Colorectal Disease (2011)

- Can we predict cCR?
- Is cCR true pCR?
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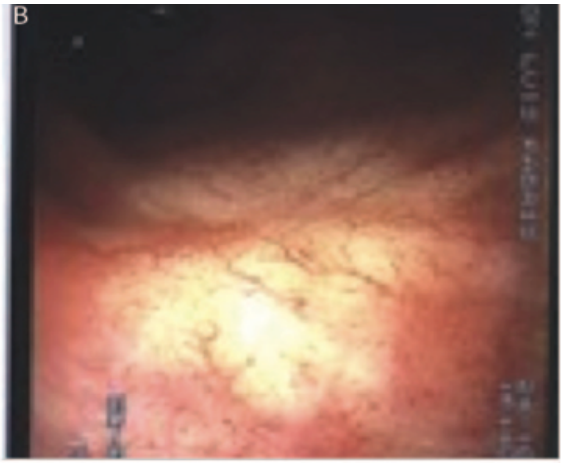
- How do we assess CR?
- How should we follow up?

Definition on cCR

- No palpable tumor on DRE
- No tumour visible on EUA
- Scar, whitening, telengiectasias
- Negative biopsies of the scar



Habr-Gama et al. Dis Colon Rectum(2010)

Definition on cCR

- No palpable tumor on DRE
- No tumour visible on EUA
- Scar, whitening, telengiectasias
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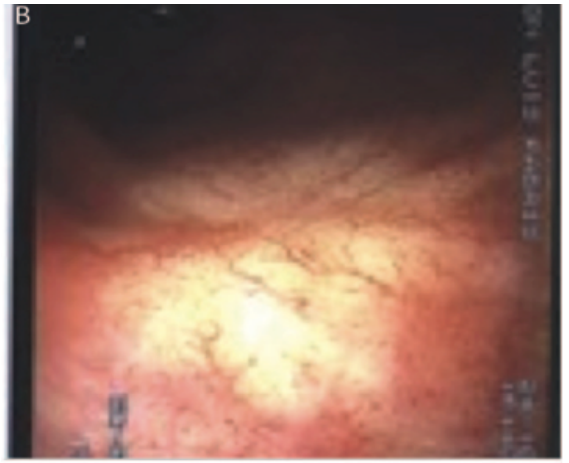
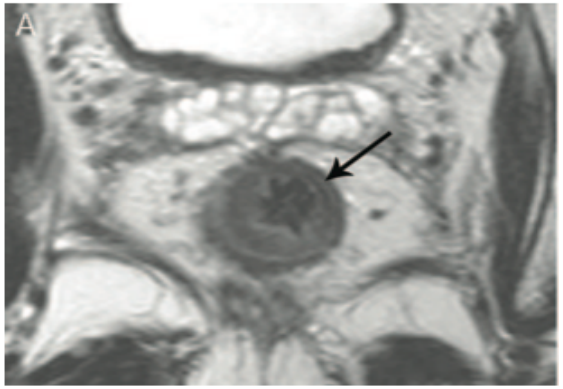
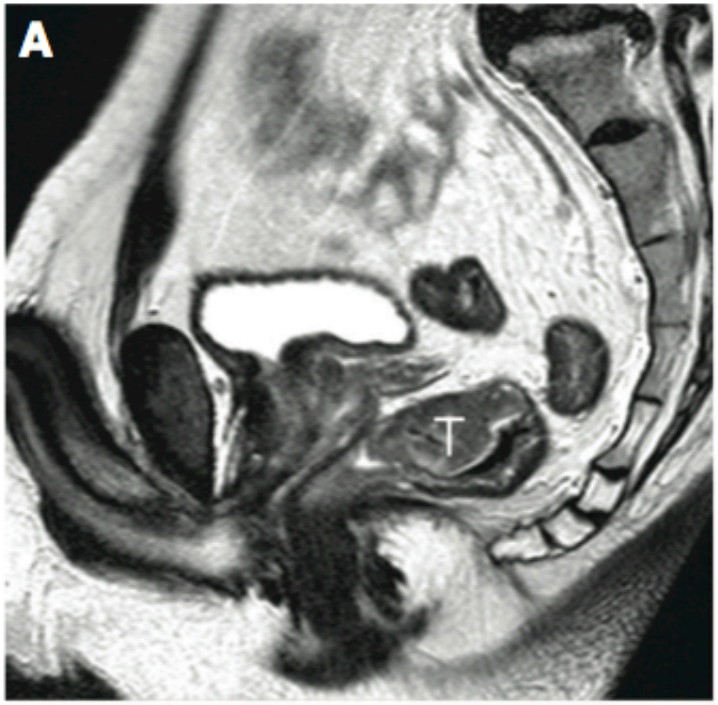


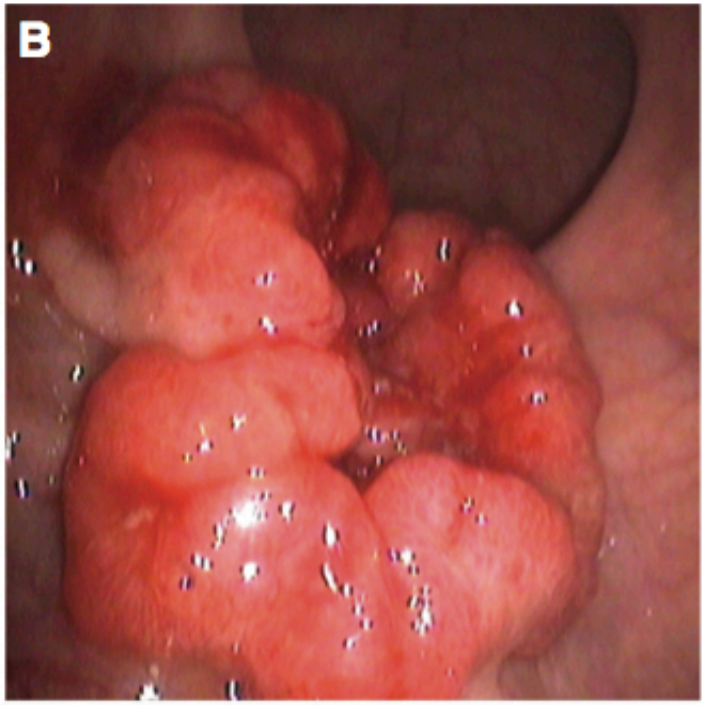
Habr-Gama et al. Dis Colon Rectum(2010)

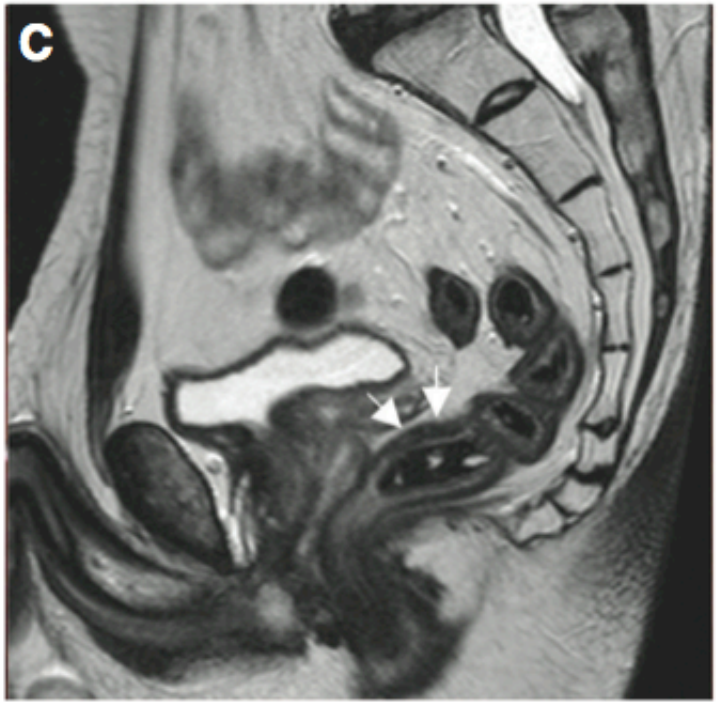
- MRI – (low signal on high b-value diffusion weighted
  fibrosis, no oedema
  no lymph nodes)
- Endorectal US
- Pet/CT scan ?

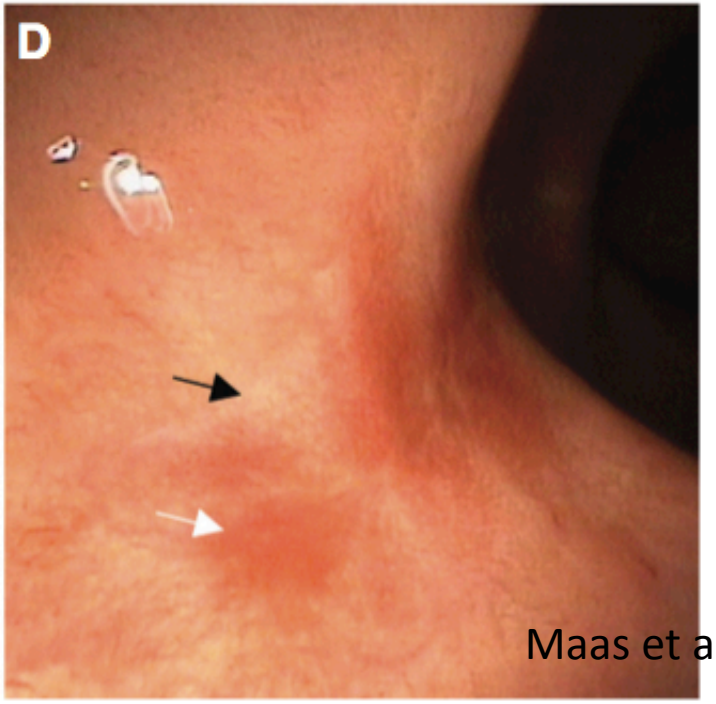


Maas et al. J Clinical Oncol(2011)



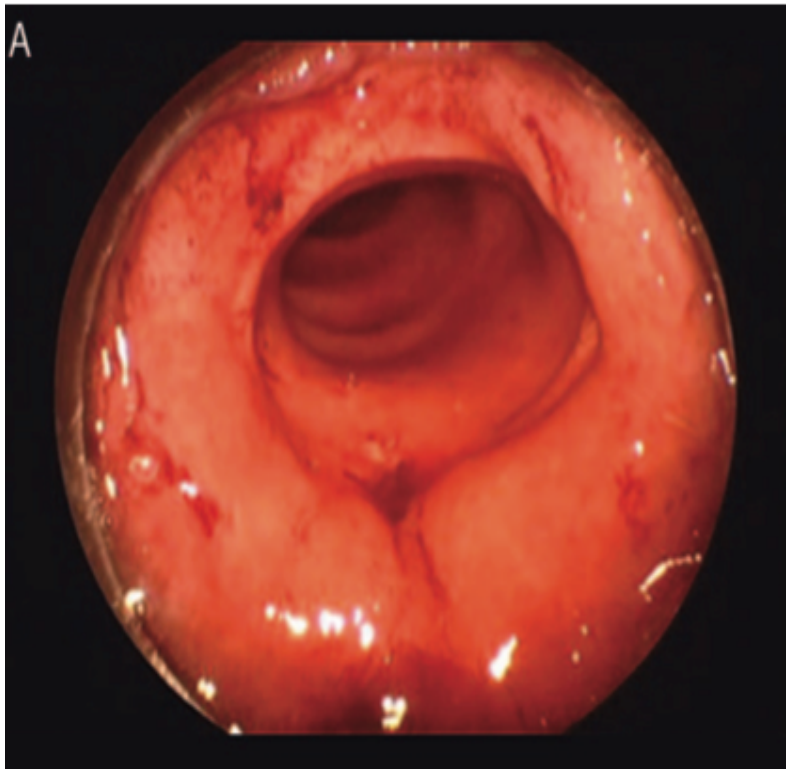






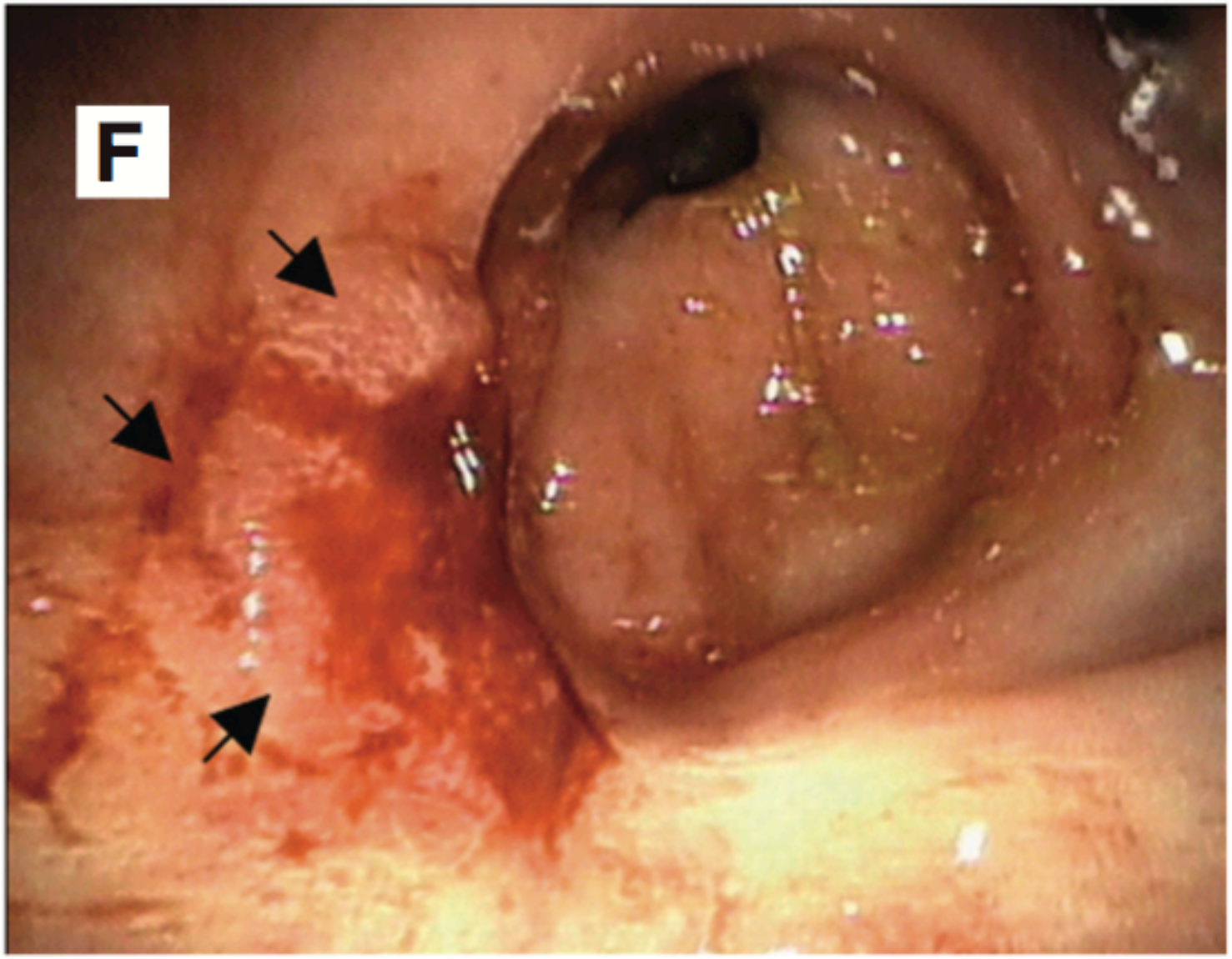
Maas et al. J Clin Oncol (2011)

- Any superficial or deep ulcer
- Any palpable nodule
- Any rectal stenosis



INCOMPLETE RESPONSE (LE vs Radical Surgery?)

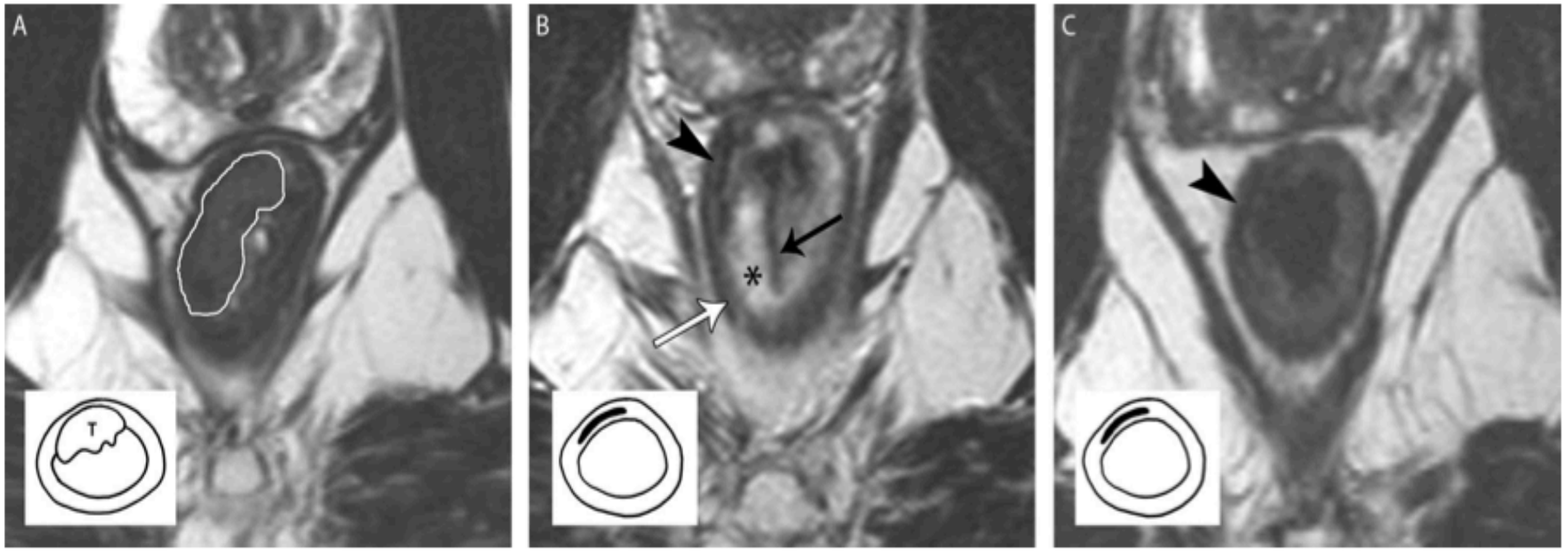
Habr-Gama et al. Dis Colon Rectum (2010)



Limits of diagnosing a cCR

- Rectoscopy shows only the mucosa, and up to 30% of the residual cancer cells are in the muscular layer or in the mesorectum
- Simple biopsies of the scar (and not LE) are insufficient to confirm CR

Changes in MRI



Lambergts et al. Dis Colon Rectum (2011)

- Can we predict cCR?
- Is cCR true pCR?
- How do we define cCR?
- How do we assess CR?
- How should we follow up?

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Follow up

Table 3 Comparison of modern studies with systematic follow-up

Reference	No. of patients	cCR*	DRE	EUA	CEA	MRI	PET/CT	Follow-up (months)	Local failure*
Dalton *et al.*[26] 2012	49	12 of 49 (24)	NS	3 and 12 months + biopsy for any suspicion of residual disease	Yes	6 weeks then every 6 months	Every 6 months	Mean 25	6 of 12 (50)
Yu *et al.*[46] 2011	22	Did not all achieve cCR	4, 8, 12, 16 weeks; 6, 9, 12, 15, 18, 21, 24 months, etc.	Endoscopy	Yes, as for DRE	4, 8, 12, 16 weeks; 6, 9, 12, 18, 24 months, etc.	8, 16 weeks + 12 months	Median 17·5	9 of 22 (41)
Maas *et al.*[27] 2011	21	21 of 192 (10·9)	4 times in year 1, twice in years 2–5	Endoscopy + biopsy	4 times in years 1–3, twice in years 4 and 5	4 times in years 1–3, twice in years 4 and 5	No	Mean 25	1 of 21 (5)
Total	92								16 of 55 (29)

*Values in parentheses are percentages. cCR, clinical complete response; DRE, digital rectal examination; EUA, examination under anaesthesia; CEA, carcinoembryonic antigen; MRI, magnetic resonance imaging; PET, positron emission tomography; CT, computed tomography; NS, not stated.

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ORIGINAL REPORT

Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer

Monique Maas, Regina G.H. Beets-Tan, Doenja M.J. Lambregts, Guido Lammering, Patty J. Nelemans, Sanne M.E. Engelen, Ronald M. van Dam, Rob L.H. Jansen, Meindert Sosef, Jeroen W.A. Leijtens, Karel W.E. Hulsewé, Jeroen Buijsen, and Geerard L. Beets

Table 1. Characteristics of Patients Following Wait-and-See Policy

Patient	Age (years)	Sex	cT Stage	cN Stage	Distance From ARJ (cm)	Adjuvant Chemotherapy	Follow-Up (months)	Planned Surgical Procedure*
1	70	Male	3	1	0	Yes	67	APR
2	62	Male	3	2	0	Yes	60	APR
3	67	Female	4	1	0	Yes	54	APR
4	75	Male	2	1	0	Yes	48	APR
5	51	Male	3	2	1	Yes	39	APR
6	52	Male	3	2	0	Yes	33	APR
7	65	Male	3	2	5	Yes	33	LAR
8	49	Female	2	2	3	Incomplete	23	LAR
9	64	Male	3	0	5.5	Yes	22	LAR
10	62	Female	3	2	6	Yes	19	LAR
11	78	Female	3	0	8	No	15	LAR
12	58	Female	4	1	0	Yes	13	APR
13	65	Male	3	2	6.5	Yes	13	LAR
14	70	Male	3	2	10	Yes	13	LAR
15	56	Male	3	1	3.5	Yes	12	LAR
16	61	Male	2	0	3	No	12	LAR
17	60	Male	1	2	4	Yes	12	LAR
18	69	Male	3	0	1.5	Yes	12	APR
19	77	Female	2	0	0	No	10	APR
20	79	Female	3	0	0	No	7	APR
21	65	Male	2	1	3	Yes	5	LAR

Abbreviations: APR, abdominoperineal resection; ARJ, anorectal junction; LAR, low anterior resection.
*Planned surgical procedure is the surgical intervention that would have been performed (on the basis of the images after chemoradiation) if patients had not followed wait-and-see policy.

Maas et al. J Clin Oncol (2011)

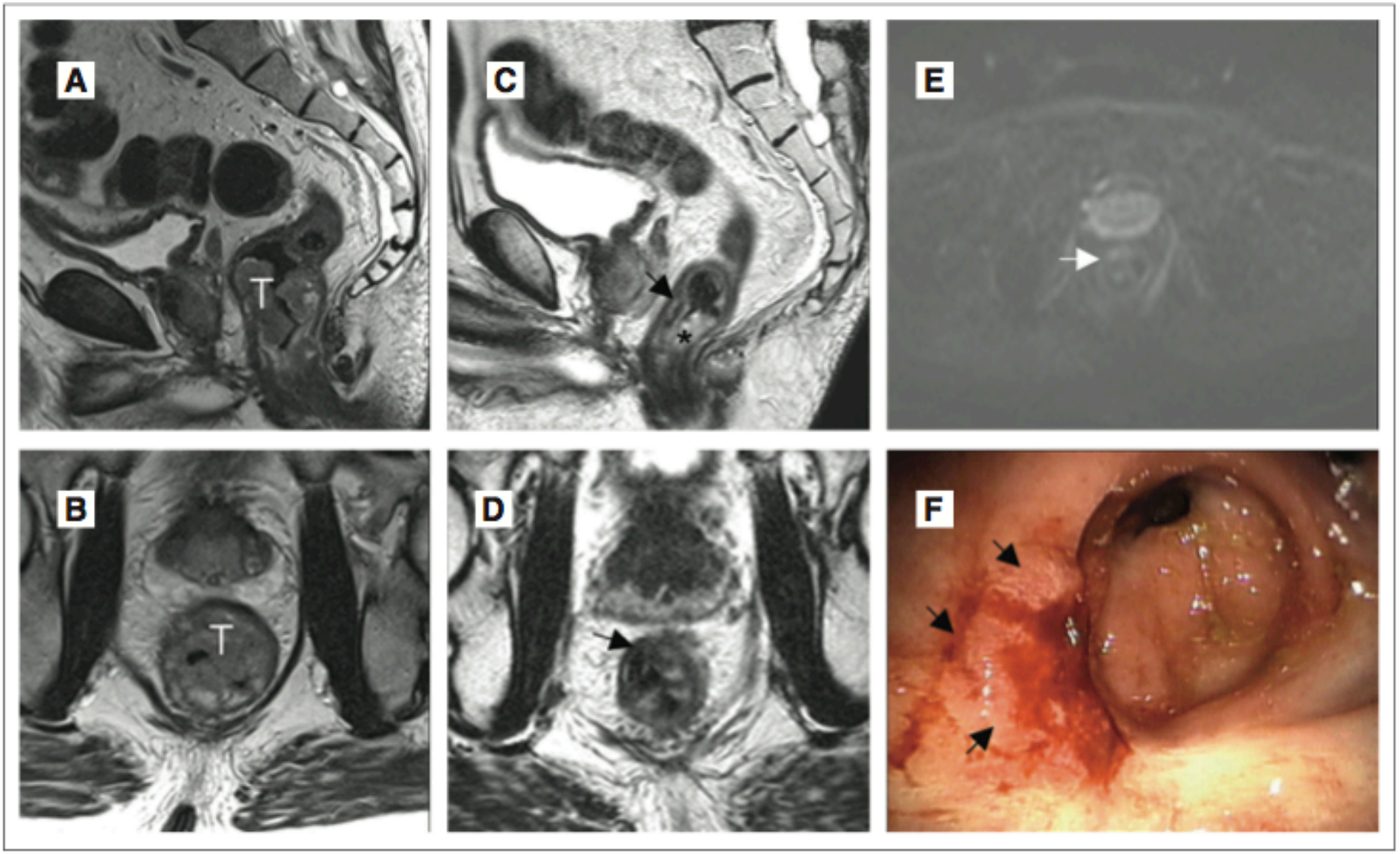
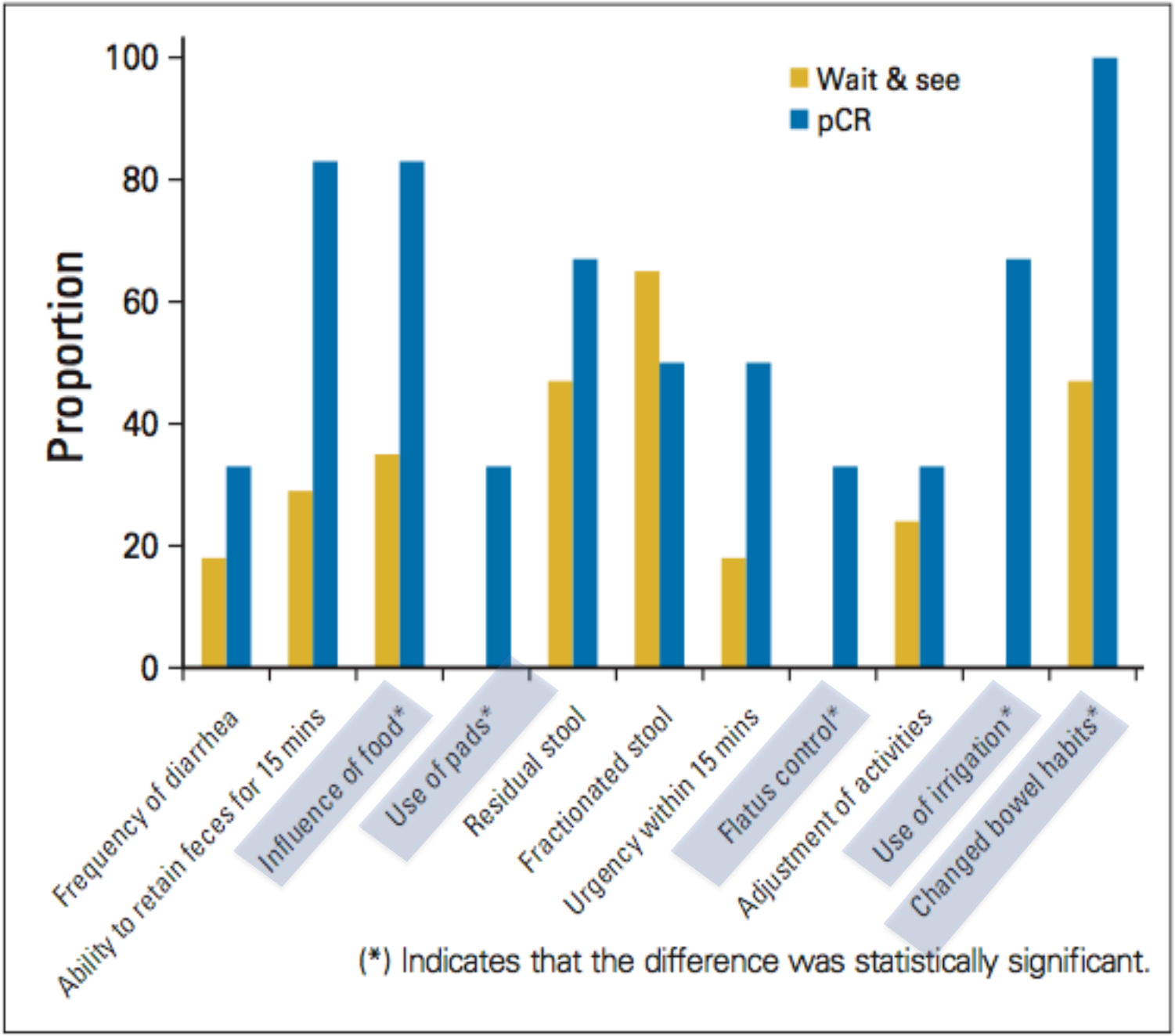


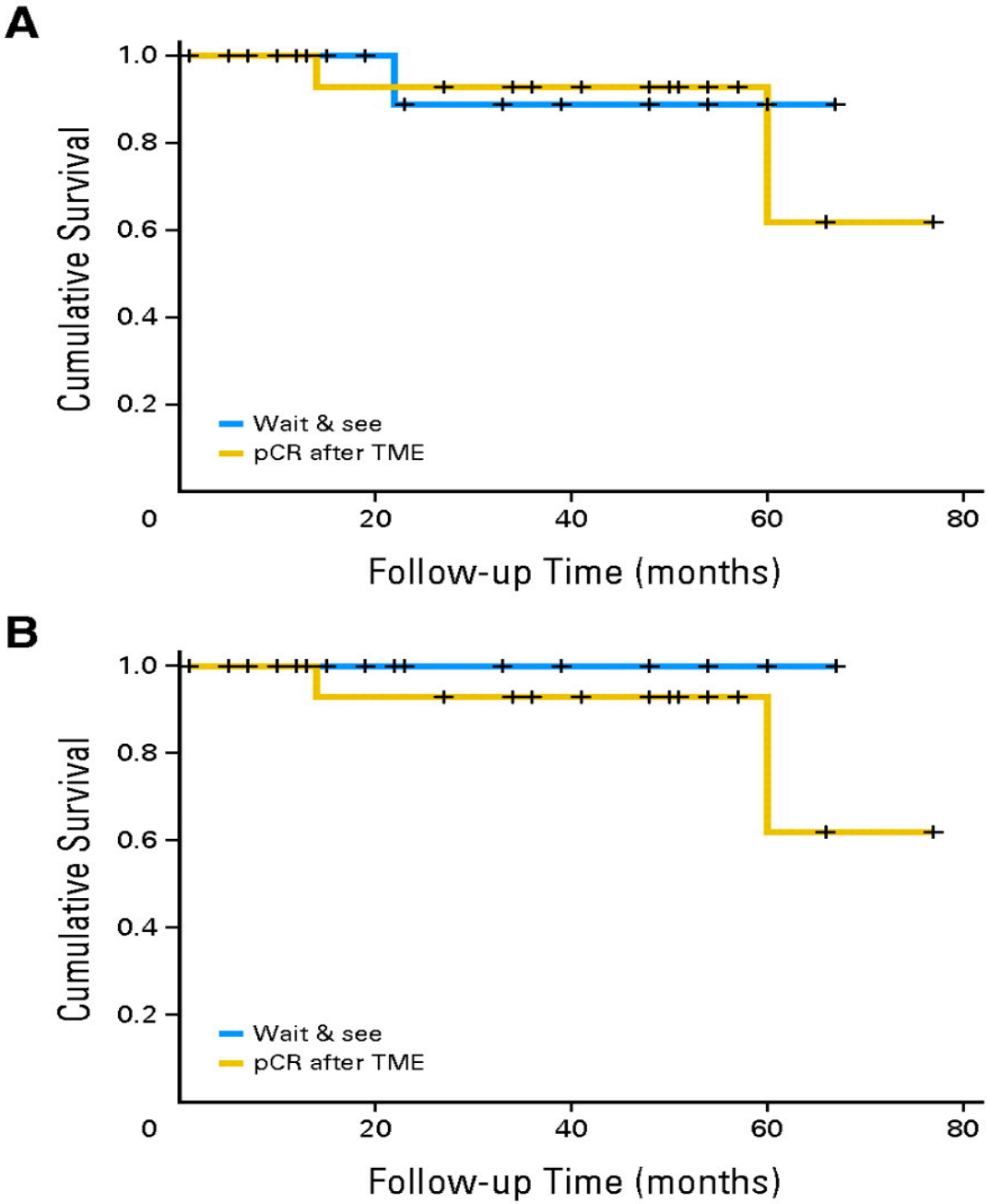
Fig 2. Images from a patient not eligible for wait-and-see policy despite remarkable response on magnetic resonance imaging. (A) T2-weighted sagittal image of a distal tumor (T) before treatment. (B) Axial T2-weighted image of the tumor (T) before treatment. (C) Image after chemoradiation showing edema (*) and a hypointense fibrotic area (black arrow) also on (D) at the former tumor location. (E) High b-value diffusion-weighted image of a small area with higher signal (white arrow), suggestive of residual tumor. (F) Obvious residual tumor (black arrows) at endoscopy after chemoradiotherapy. After total mesorectal excision, histology revealed a ypT2N0 tumor.



Maas et al. J Clin Oncol (2011)

Reference	No. of patients	T2*	Radiotherapy	Chemotherapy	Procedure	cCR*	Locoregional failure*
Rossi *et al.*[39] 1998	16	NS	50·4 Gy, 28 fractions, 38 days + 30 Gy brachytherapy	FUFA	No surgery	6 of 16 (38)	5 of 6 (83)
Nagakawa *et al.*[41] 2002	52	No	45–50·4 Gy, 28 fractions, 38 days	FUFA	No surgery	(19)	NS fully
Lim *et al.*[43] 2007	48	T1 and T2 (33)	Variable; mean 50 Gy, 25 fractions	PVI 5-FU 92%	No surgery	27 of 48 (56)	11 of 48 (23)
Hughes *et al.*[44] 2010	58	No (50 T4)	45 Gy, 25 fractions, 33 days	FUFA	No surgery	10 of 58 (17)	6 of 10 (60)
Seshadri[45] 2011	23	Yes	50 Gy, 25 fractions, 33 days	5-FU/MMC	No surgery	NS	10 of 23 (43)
Dalton *et al.*[26] 2012	49	No	45 Gy, 25 fractions, 33 days	Capecitabine 850 mg/m^2	No surgery	12 of 49 (24)	6 of 12 (50)
Yu *et al.*[46] 2011	22	NS	?54 Gy (minimum 50·4 Gy), 28 fractions, 38 days	Capecitabine 825 mg/m^2	No surgery; adjuvant chemotherapy in some	Did not all achieve cCR	9 of 22 (41)
Maas *et al.*[27] 2011	21	5 of 21 (24)	Minimum 50·4 Gy, 28 fractions, 38 days	Capecitabine 825 mg/m^2	No surgery; adjuvant XELOX routinely	21 of 192 (10·9)	1 of 21 (5)
Total	289						48 of 142 (33·8)

Maas et al. J Clin Oncol (2011)



Maas et al. J Clin Oncol (2011)

Local Failure

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Reference	No. of patients*	T2†	Follow-up (months)	Chemotherapy	cCR†	Locoregional failure†	5-year survival (%)		
							Disease-free	Cancer-specific	Overall
Habr-Gama *et al.*[18] 1998	118 (1991–1996)	Yes	36	FUFA	36 of 118 (30·5)	8 of 30 (27)	NS	NS	NS
Habr-Gama *et al.*[20] 2004	265	(15)	57·3	FUFA	71 of 265 (26·8) sustained for 12 months	2 of 71 (3)	92	100	100
Habr-Gama *et al.*[21] 2005	260	(20)	57	FUFA	71 of 260 (27·3) sustained for 12 months	2 of 71 (3)	92	100	NS
Habr-Gama *et al.*[22] 2006	361 (1991–2005)	14 of 99 (14)	60	FUFA	99 of 361 (27·4) sustained for 12 months	5 of 99 (5)	85	93	93
Habr-Gama[23] 2006	360 (1991–2005)	14 of 99 (14)	NS	FUFA	99 of 360 (27·5) sustained for 12 months	6 of 99 (6)	NS	NS	NS
Habr-Gama *et al.*[25] 2011	173 (1991–2009)	(16)	65	5-FU-based	67 of 173 (38·7)	8 of 173 (4·6)	72	NS	96

Reference	No. of patients	T2*	Radiotherapy	Chemotherapy	Procedure	cCR*	Locoregional failure*
Rossi *et al.*[39] 1998	16	NS	50·4 Gy, 28 fractions, 38 days + 30 Gy brachytherapy	FUFA	No surgery	6 of 16 (38)	5 of 6 (83)
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Maas *et al.*[27] 2011	21	5 of 21 (24)	Minimum 50·4 Gy, 28 fractions, 38 days	Capecitabine 825 mg/m^2	No surgery; adjuvant XELOX routinely	21 of 192 (10·9)	1 of 21 (5)
Total	289						48 of 142 (33·8)

Glynne-Jones, British J Surg (2012)

What happens with local recurrence?

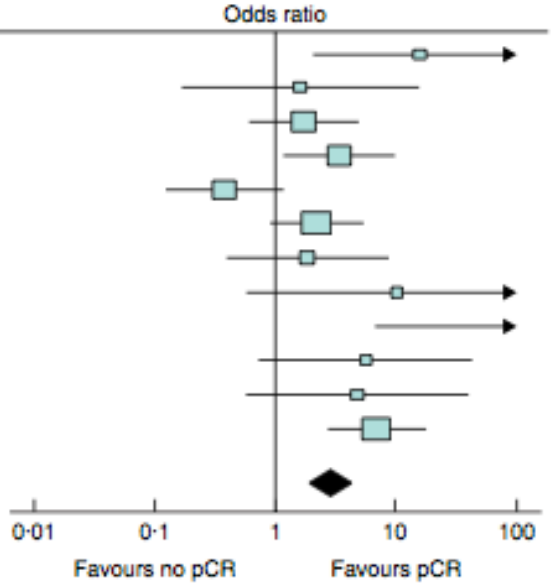
	Total no. of patients	T2	5-year survival (%)	
			Disease-free	Overall
Surgery $\leq$ 12 weeks	121	12	56	86
Surgery $>$ 12 weeks	129	9	59	82
Suspected cCR but relapsed	23	NS	52	85

cCR, clinical complete response; NS, not stated.

Habr-Gama et al. Int J Radiat Oncol Biol Phys (2008)

Reference	Odds ratio	*P*
Chan *et al.*[5]	15·50 (2·02, 118·73)	0·008
Ciccocioppo *et al.*[16]	1·62 (0·17, 15·72)	0·680
Kim *et al.*[18]	1·72 (0·59, 5·01)	0·317
de Campos-Lobato *et al.*[6]	3·36 (1·14, 9·88)	0·027
Pucciarelli *et al.*[19]	0·38 (0·12, 1·18)	0·095
Rödel *et al.*[20]	2·22 (0·90, 5·45)	0·083
Roh *et al.*[21]	1·85 (0·39, 8·79)	0·439
Ruo *et al.*[22]	10·11 (0·56, 181·57)	0·116
Shivnani *et al.*[23]	113·93 (6·65, 1951·68)	0·001
Valentini *et al.*[24]	5·63 (0·72, 43·90)	0·099
Wheeler *et al.*[25]	4·80 (0·56, 41·13)	0·152
Yeo *et al.*[26]	6·86 (2·63, 17·86)	< 0·001
Overall	3·28 (1·66, 6·51)	0·001

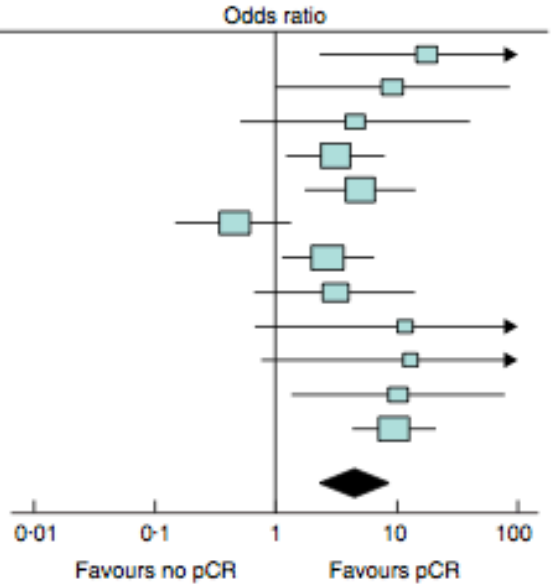
Test for heterogeneity: $Q = 27·6$, 11 d.f., $P = 0·004$, $I^2 = 60\%$



a Overall survival

Reference	Odds ratio	*P*
Chan *et al.*[5]	17·79 (2·33, 136·01)	0·006
Ciccocioppo *et al.*[16]	9·23 (0·99, 85·78)	0·051
Hong *et al.*[17]	4·50 (0·50, 40·65)	0·180
Kim *et al.*[18]	3·10 (1·20, 8·02)	0·019
de Campos-Lobato *et al.*[6]	5·06 (1·74, 14·70)	0·003
Pucciarelli *et al.*[19]	0·45 (0·15, 1·38)	0·162
Rödel *et al.*[20]	2·65 (1·08, 6·50)	0·033
Roh *et al.*[21]	3·09 (0·66, 14·40)	0·151
Ruo *et al.*[22]	11·73 (0·66, 210·11)	0·094
Shivnani *et al.*[23]	13·07 (0·75, 226·77)	0·078
Valentini *et al.*[24]	10·25 (1·32, 79·40)	0·026
Yeo *et al.*[26]	9·46 (4·20, 21·31)	< 0·001
Overall	4·33 (2·31, 8·09)	< 0·001

Test for heterogeneity: $Q = 25·0$, 11 d.f., $P = 0·009$, $I^2 = 56\%$



b Disease-free survival

Martin et al. British J Surgery(2012)

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Ongoing studies

- NCT1047969 (UK) : omission of surgery rate at 2 years and rate of salvage surgery with negative margins

- NCT00952926 (Denmark) local recurrence at 1,3 and 5 year after CRT

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Conclusion

- The « wait and see » strategy in patients with cCR after neoadjuvant treatment has obvious short-term advantages (morbidity, mortality, colostomy avoidance, function)
- Most studies are retrospective, observational with relative short follow up as recurrence may appear very late (up to 5 years) after treatment
- Accrual in an ideal setting of RCT will be difficult

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Conclusions

- It is still unclear how to select patients and how to define cCR
- Good results with low local recurrence rates have been difficult to reproduce (selection ?)
- Questions remain in regards of intensity and duration of clinical and imaging follow up
- Changes in MRI during follow-up may be very difficult to interpret

Conclusions

- To date, there are insufficient data to propose a « wait and see » strategy as a standard of treatment for patients with clinical complete response after neoadjuvant therapy for rectal cancer
- In highly selected patients, this option of treatment can be discussed
- Better knowledge of cancer biology may help in the future to select patients that could benefit from a non-operative solution