Non-operative management for Rectal Cancer
Discovering Whom, How and When by
Opera, Opra, Star-Trec, German Rectal Cancer Study Group (CAO/ARO/AIO-16).

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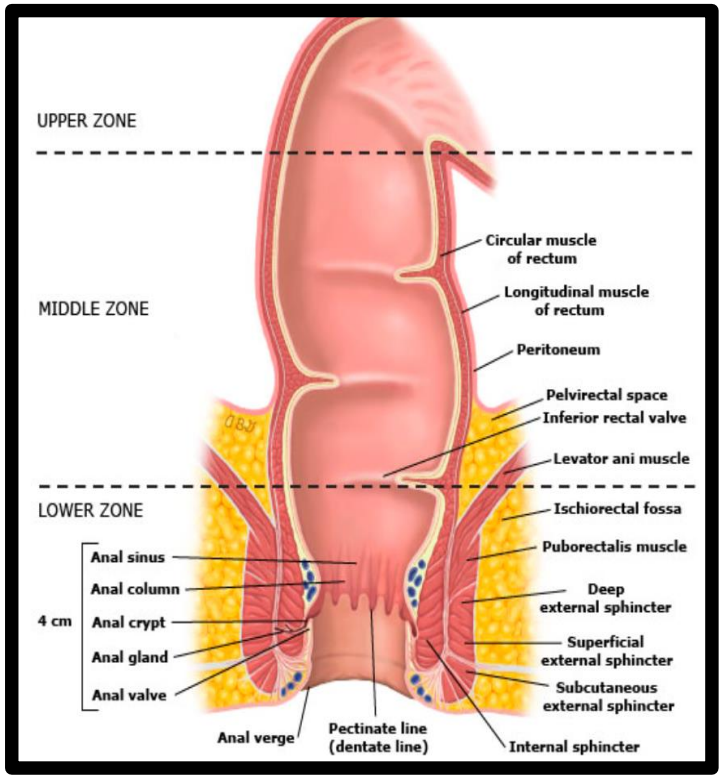
Gastro-Intestinal Disease Management Group, **Tata Memorial Centre, Mumbai**

Secretary, **GI Oncology Society**

Background

- Colo-rectal malignancies are one of the top 10 malignancies
- Worldwide trend: Increasing incidence
- Since 1990's: standard treatment was CTRT followed by TME followed by Adj CT

Lower/mid rectum: APR/TME with +/- stoma bag (permanent)



30% abandon Sx

Function:

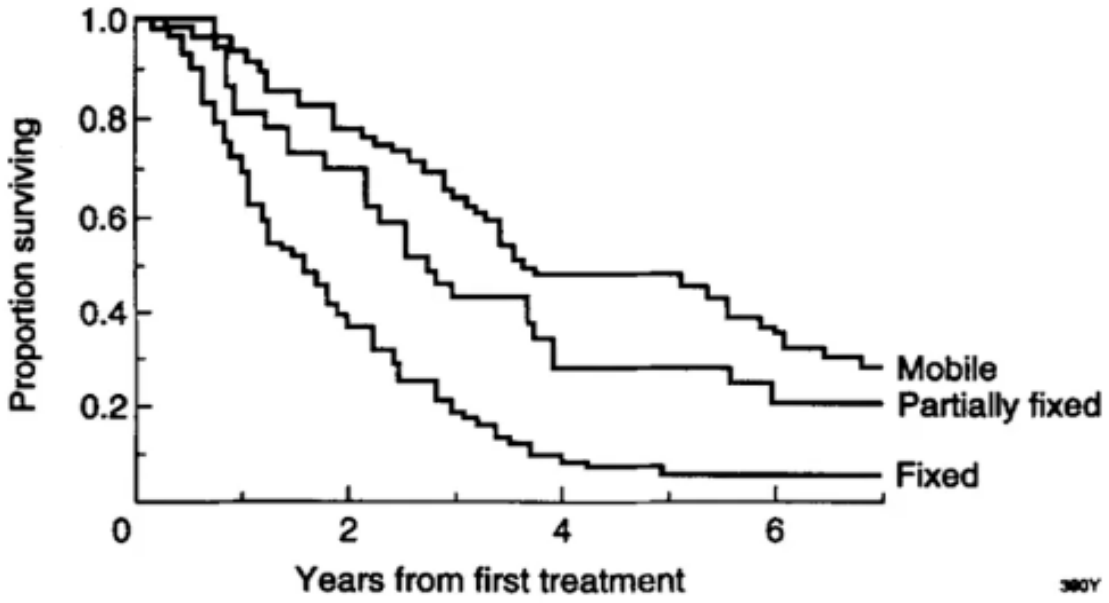
- Electrolyte (Na, K, Cl) absorption
- Anaerobic bacteria processing
- Water absorption and mixed with mucus
  - Final Stool storage & preparation

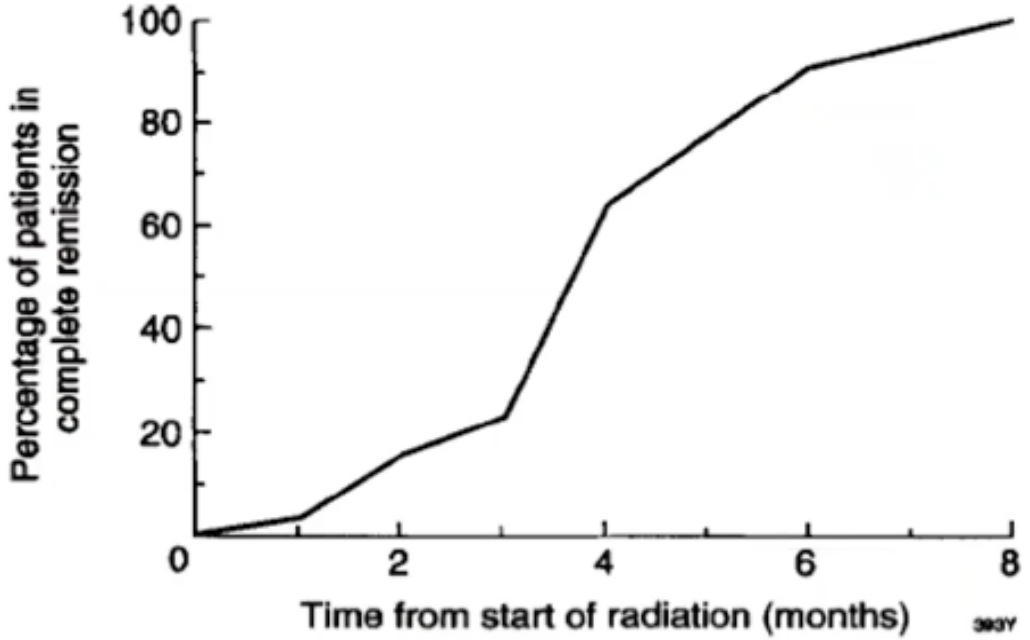
Poor QoL treatment-

Stoma dependence after APR, LARS
Social
Sexual
GU

Organ preservation is feasible
Initially patient-driven
Now the standard of care and widely adopted.

Background





Response for complete responders took up to 8 months

Brierley et al, Int J Radiation Oncol Biol Phys; 1995

The pioneering work of Jean Papillon was a challenge to the existing ortodoxy and paved the way for a new era of preserving the rectum and In the management of early rectal cancer

N Moertensen Clin Onc 2023 ; 35 : 72

Patients should be given full information

A Sun Myint Clin Onc 2023; 35: 95

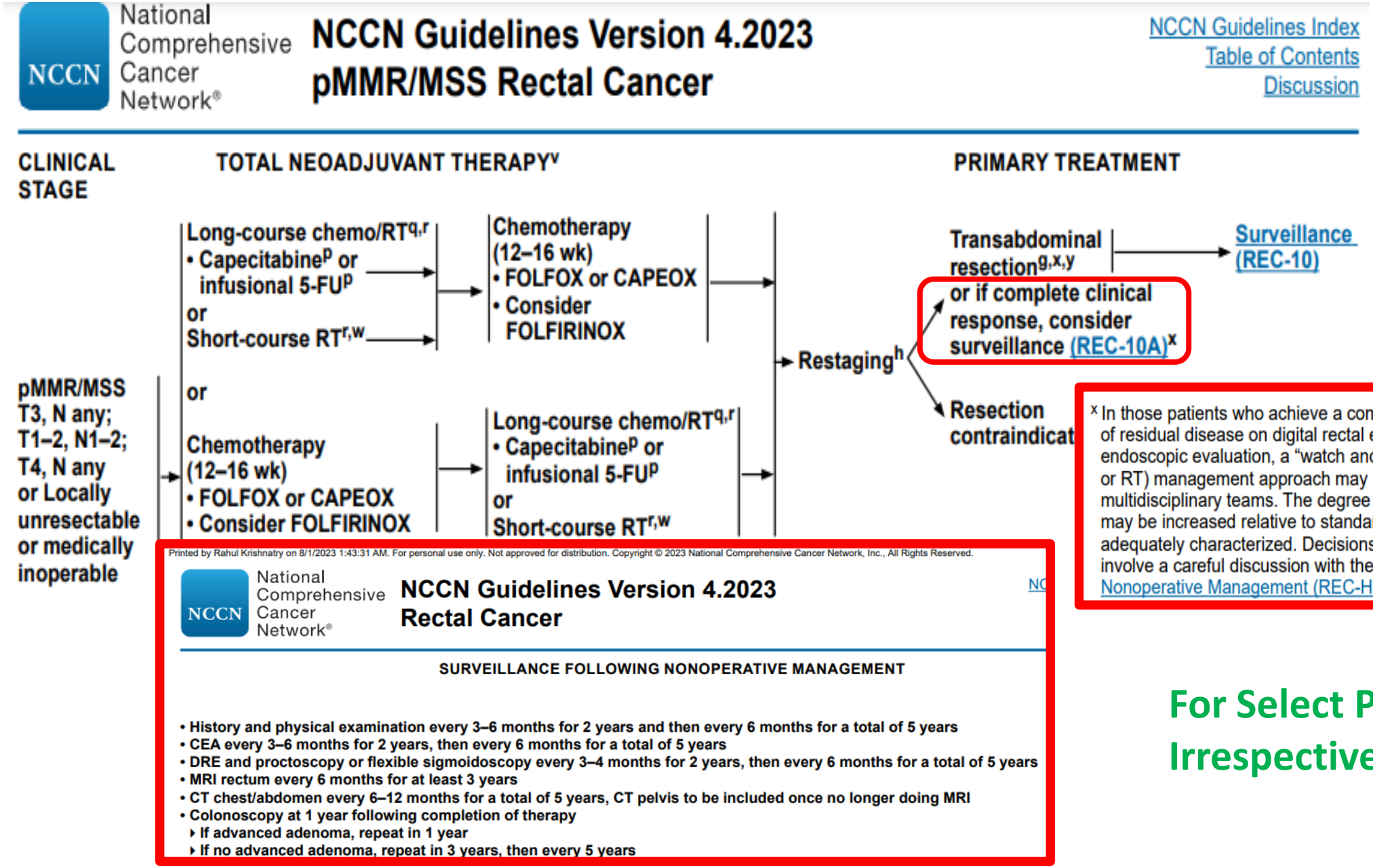
Patients preference is playing An increasingly important role

G Beets, B Grotenhuis Clin Onc 2023 ; 35 : 125

In the last two decades organ preservation Has evolved from controversy To common clinical practice

G Beets, B Grotenhuis Clin Onc 2023 ; 35 : 127

Wait and watch/Non-operative Management is a standard treatment option



[x] In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination (DRE), rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of their risk tolerance. Principles of Nonoperative Management (REC-H).

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Rectal Cancer

SURVEILLANCE FOLLOWING NONOPERATIVE MANAGEMENT

- History and physical examination every 3–6 months for 2 years and then every 6 months for a total of 5 years
- CEA every 3–6 months for 2 years, then every 6 months for a total of 5 years
- DRE and proctoscopy or flexible sigmoidoscopy every 3–4 months for 2 years, then every 6 months for a total of 5 years
- MRI rectum every 6 months for at least 3 years
- CT chest/abdomen every 6–12 months for a total of 5 years, CT pelvis to be included once no longer doing MRI
- Colonoscopy at 1 year following completion of therapy
  - If advanced adenoma, repeat in 1 year
  - If no advanced adenoma, repeat in 3 years, then every 5 years

For Select Patients
Irrespective of Sx Fitness

Patient Selection

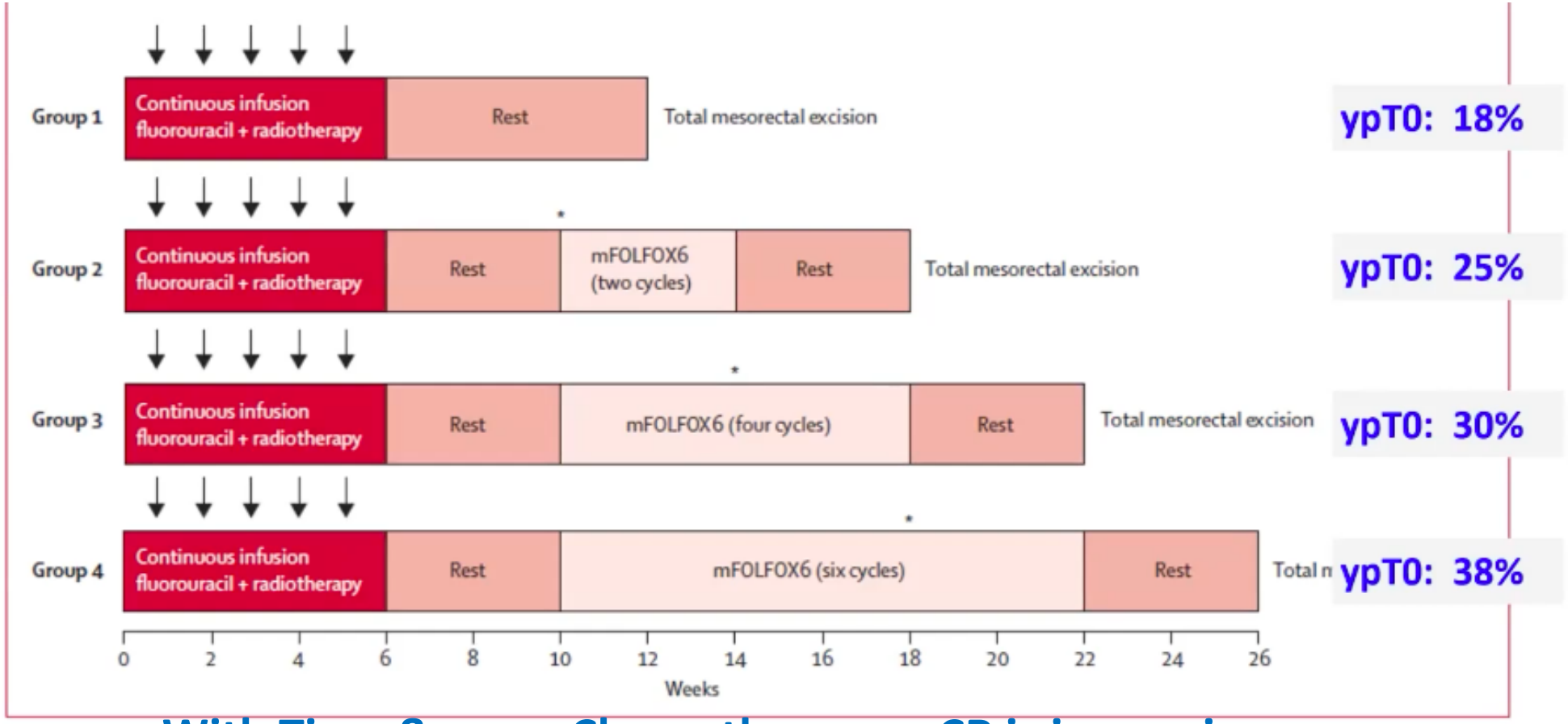
- T1-T4a
  - Non Circumferential
  - CCL<7 cm
  - Upto 10 cm from AV?
- ?N0-1/2
  - Lateral pelvic Lymph nodes
- EMVI status?
- Metastatic status

- Surveillance feasibility, patient compliance, local expertise, Teamwork
- Good Sphincter Tone

- Histology:
  - MDAC/WDAC
  - not signet or mucinous,
  - ? PDAC

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



With Time & more Chemotherapy, pCR is increasing

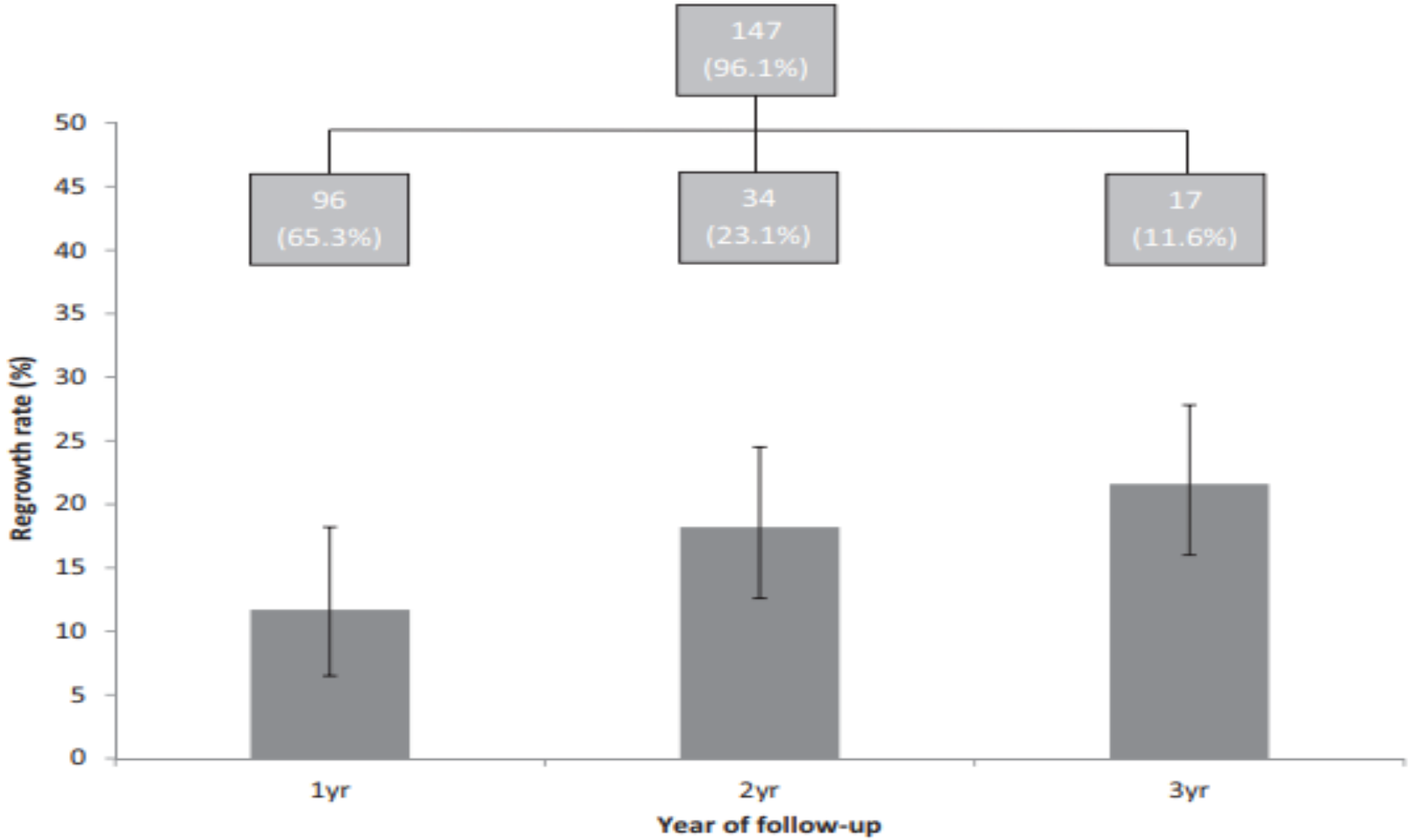
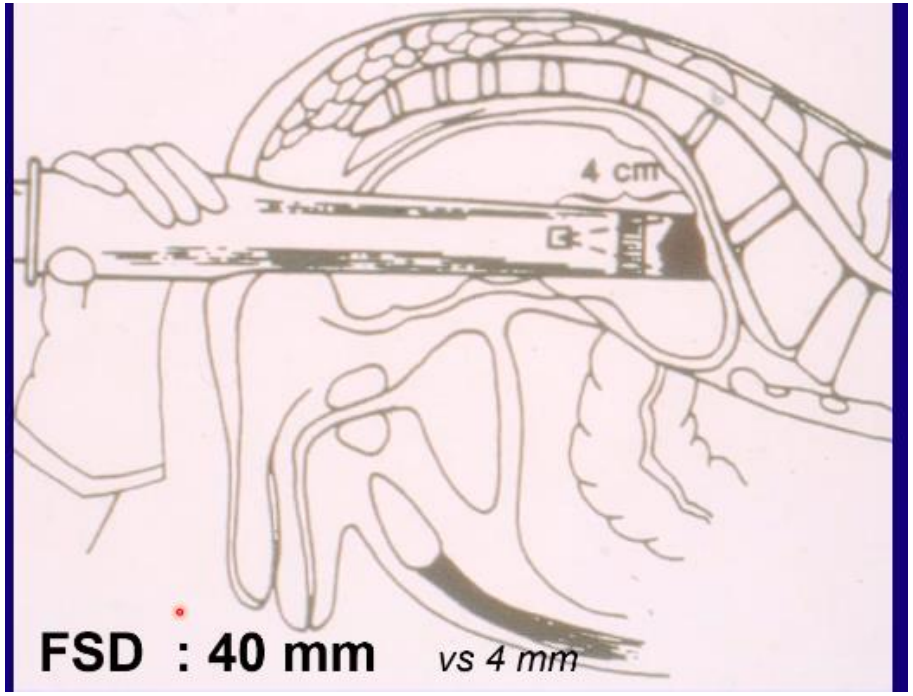
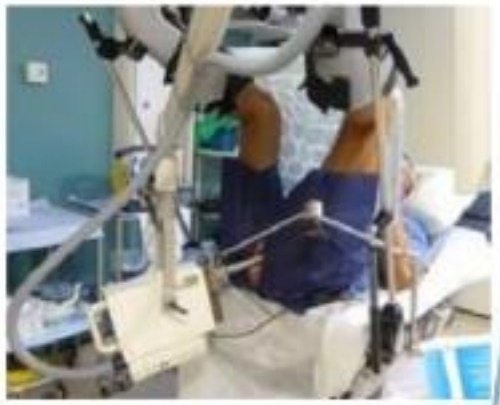


FIGURE 4. Cumulative risk of local regrowths in Watch and Wait patients. The boxes at the top of the chart represent the proportion of regrowths detected annually in the first 3 years of surveillance (Vertical lines in the box plots represent 95% CI).

Contact X Ray: Papillon technique

Treatment position





Treatment position

Malignant polyp
Mobile and exophytic
Size < 3cm
Staged as cT1 /cN0

Surface dose	**100%**	**30Gy**

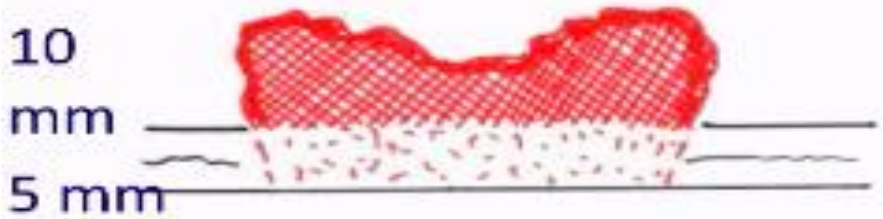
DD % depends on size of applicator for
30 mm rectal applicator FSD=38 mm

Depth dose at 5mm	**60%**	**18 Gy**

Rectal bowel wall thickness

Depth dose ay 10mm	**38%**	**11.4Gy**

« Tumor destroyed
layer by layer
and centripetaly»
J Papillon 1980



D 1
35 Gy

2,8 x 2,8 x 1,5 = 9,2 cm3

D 14
30 Gy

2.2X2.2X1.2 = 4.5 cm3

D 28
25 Gy

1.8X1.8X0.9 = 2.3 cm3

A Appelt 2021 :

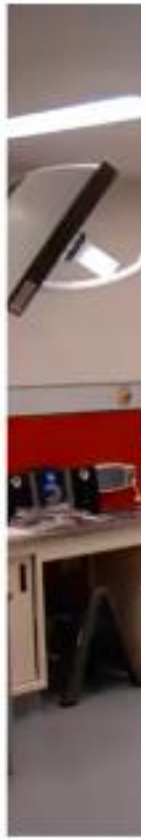
30 Gy (surface) **x 3** fr.

α/B 10 **integral dose 12 Gy**

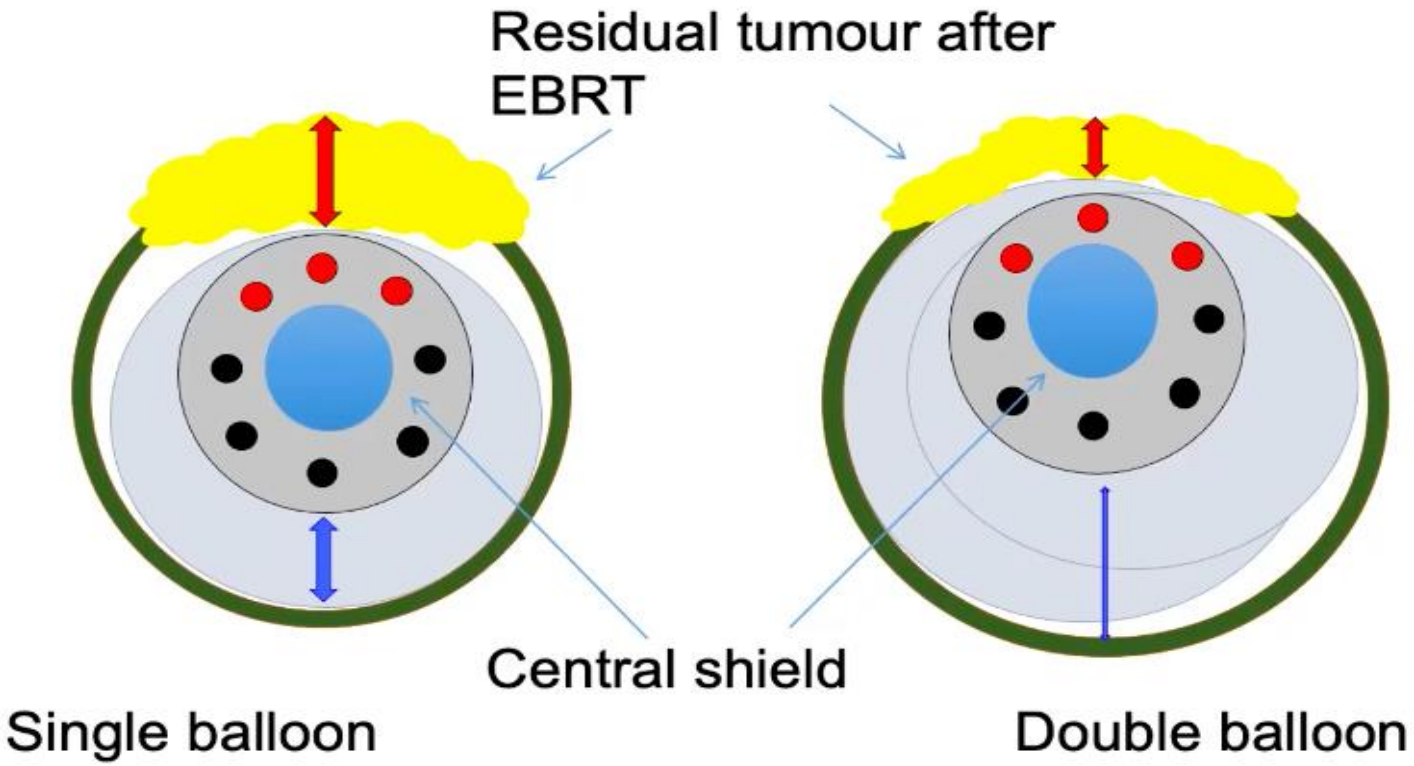
EQD2 : 92 Gy (BED)

(+ CRT 45-50 Gy)

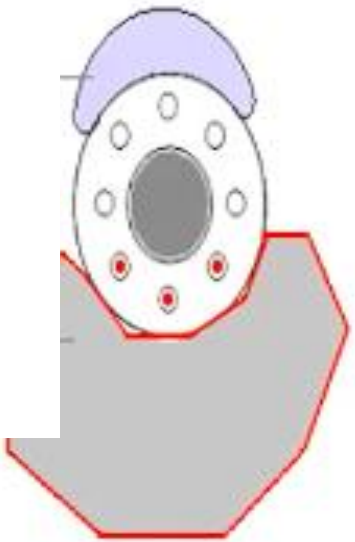
Brachytherapy suite and HDR remote after loader



Double balloon = double benefit



shield, 2 balloons



d= 8 mm

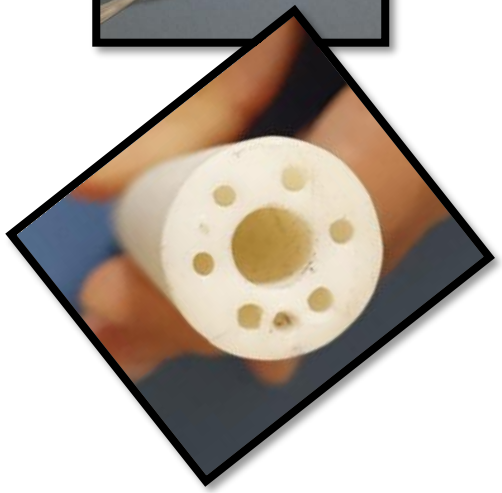
Clinical Investigation

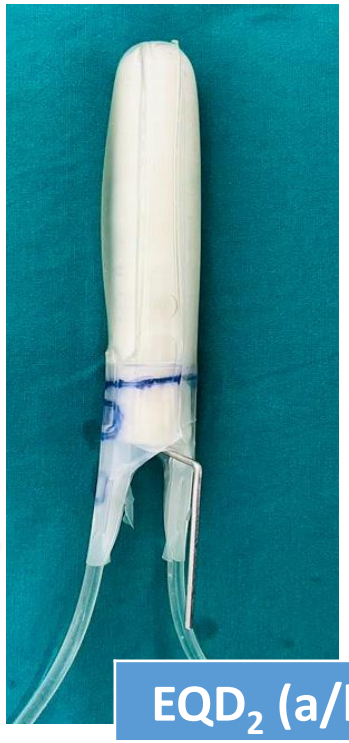
Image Guided Adaptive Endorectal Brachytherapy in the Nonoperative Management of Patients With Rectal Cancer

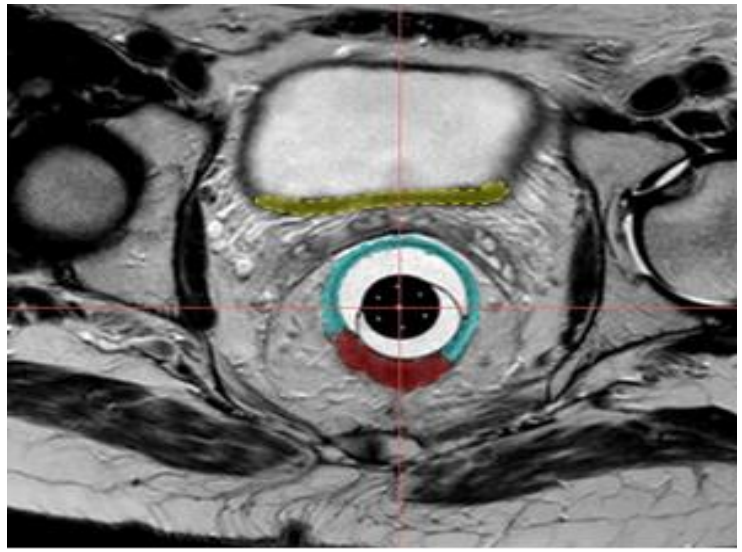
Aurelie Garant, MD,* Sindy Magnan, MD,† Slobodan Devic, PhD,‡
André-Guy Martin, MD,§ Marylise Boutros, MD,‖
Carol-Ann Vasilevsky, MD,‖ Stéphanie Ferland, MD,¶
Alexis Bujold, MD,# Sylvain DesGroseilliers, MD,**
Herawaty Sebajang, MD,†† Carole Richard, MD,†† and Té Vuong, MD*

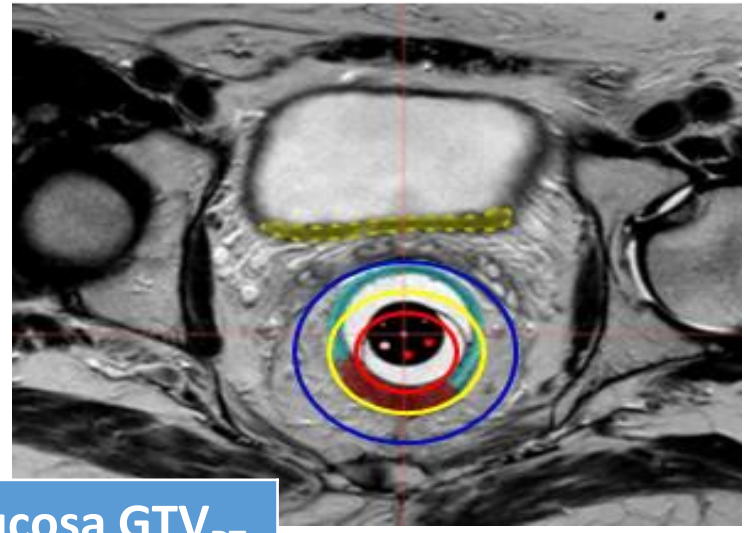
International Journal of Radiation Oncology biology • physics

MR-based Endorectal Brachytherapy









7 Gy PD to outer surface GTV_{BT}
GTV_{BT} </= 200% PD; =14 Gy/# wkly.

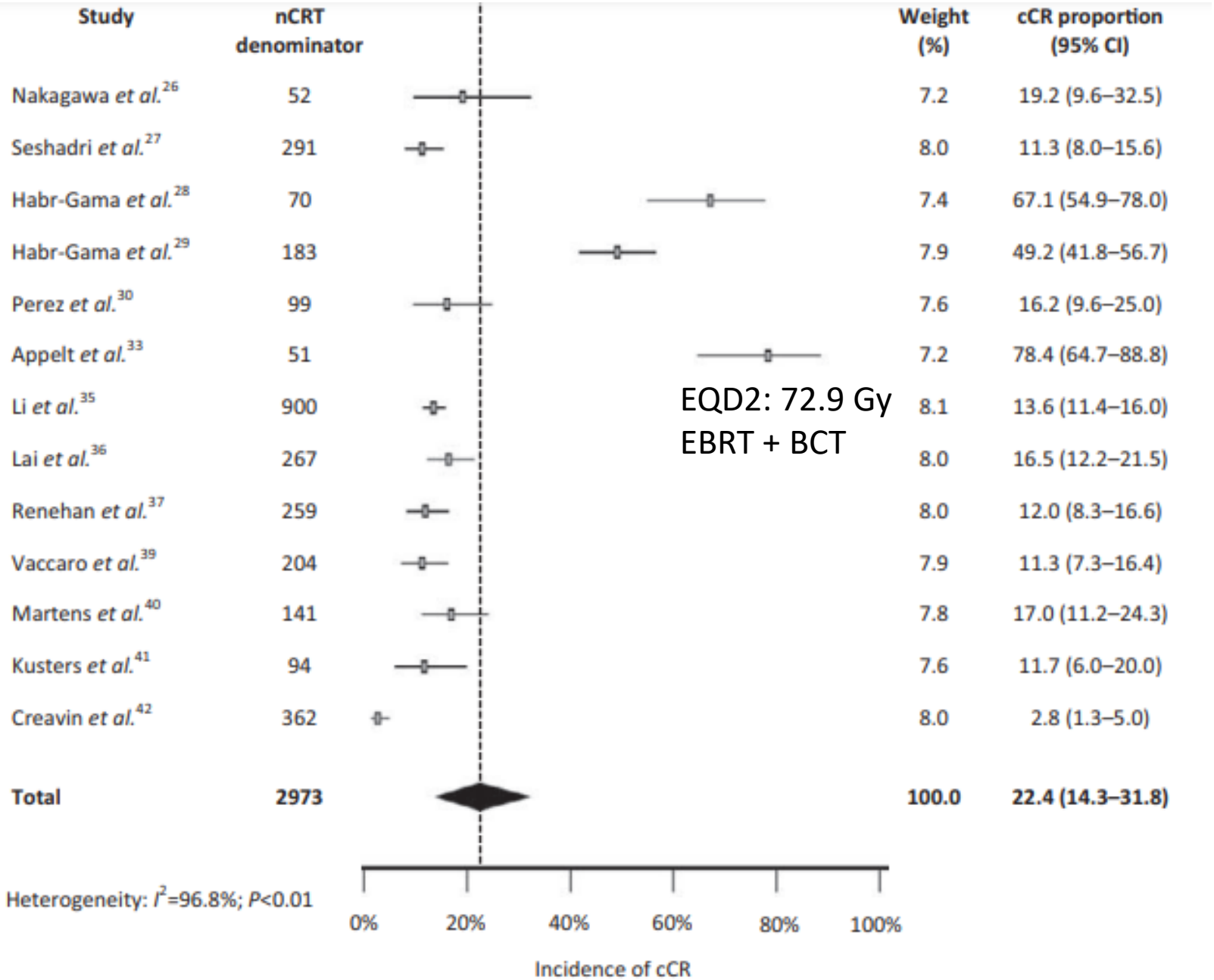
EQD_2 (a/b = 10)	Outer edge GTV_{BT}	Mucosa GTV_{BT}
LCRT - BT	79.75 Gy	134 Gy
SCRT - BT	61 Gy	115.25 Gy

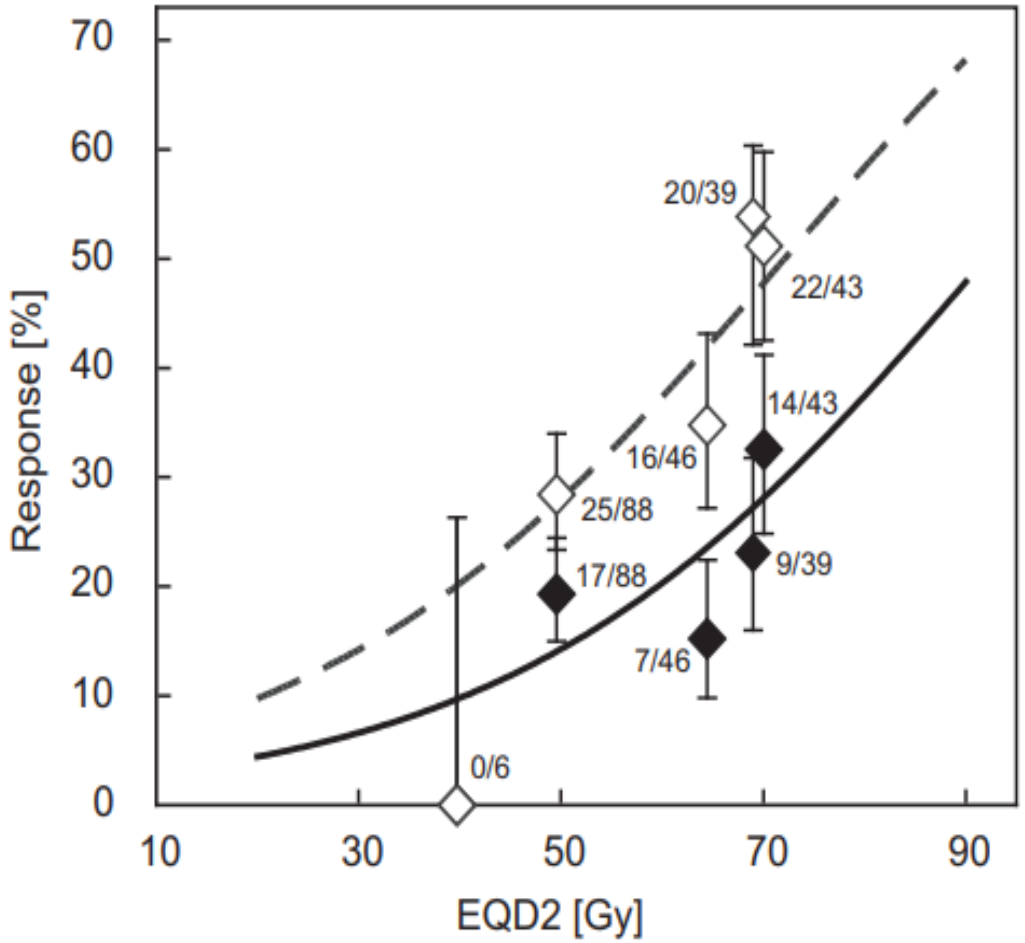
ME

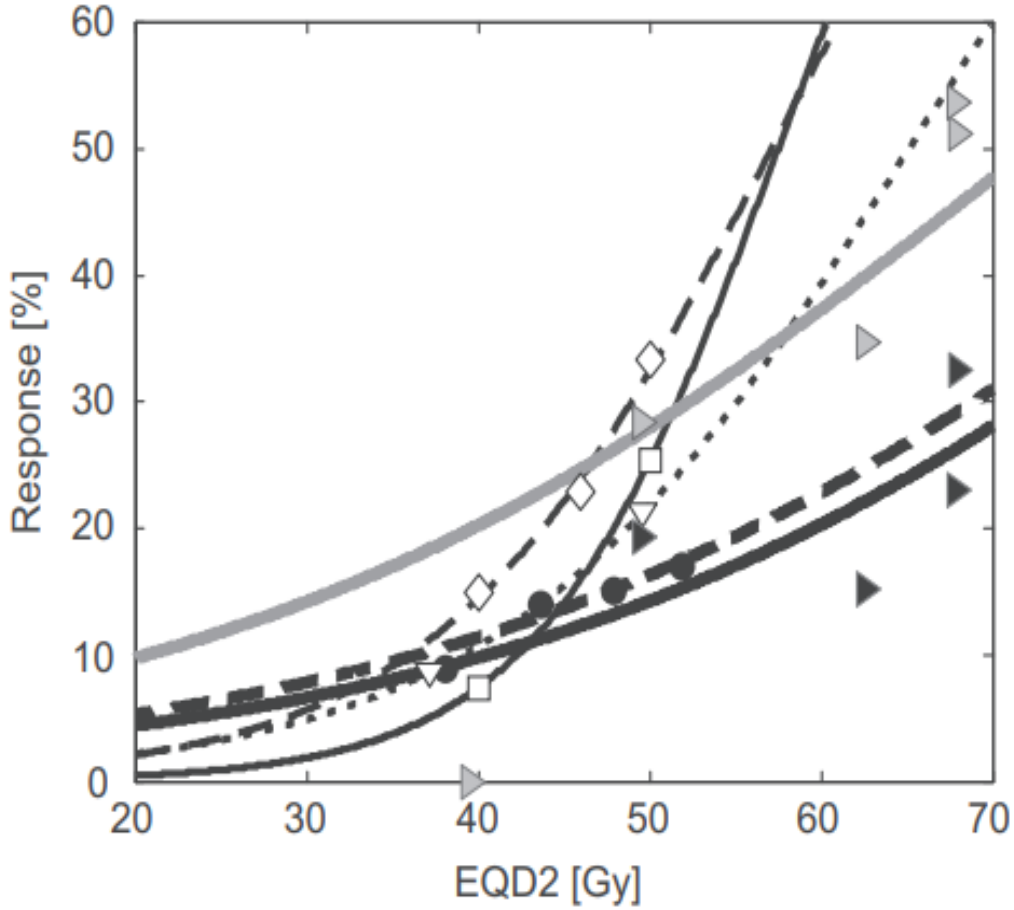
Oncological and Survival Ou
With a Clinical Complet
Chemoradiothe

A Systematic Rev

Mit Dattani, FRCS, Richard J. Heald, FRC*







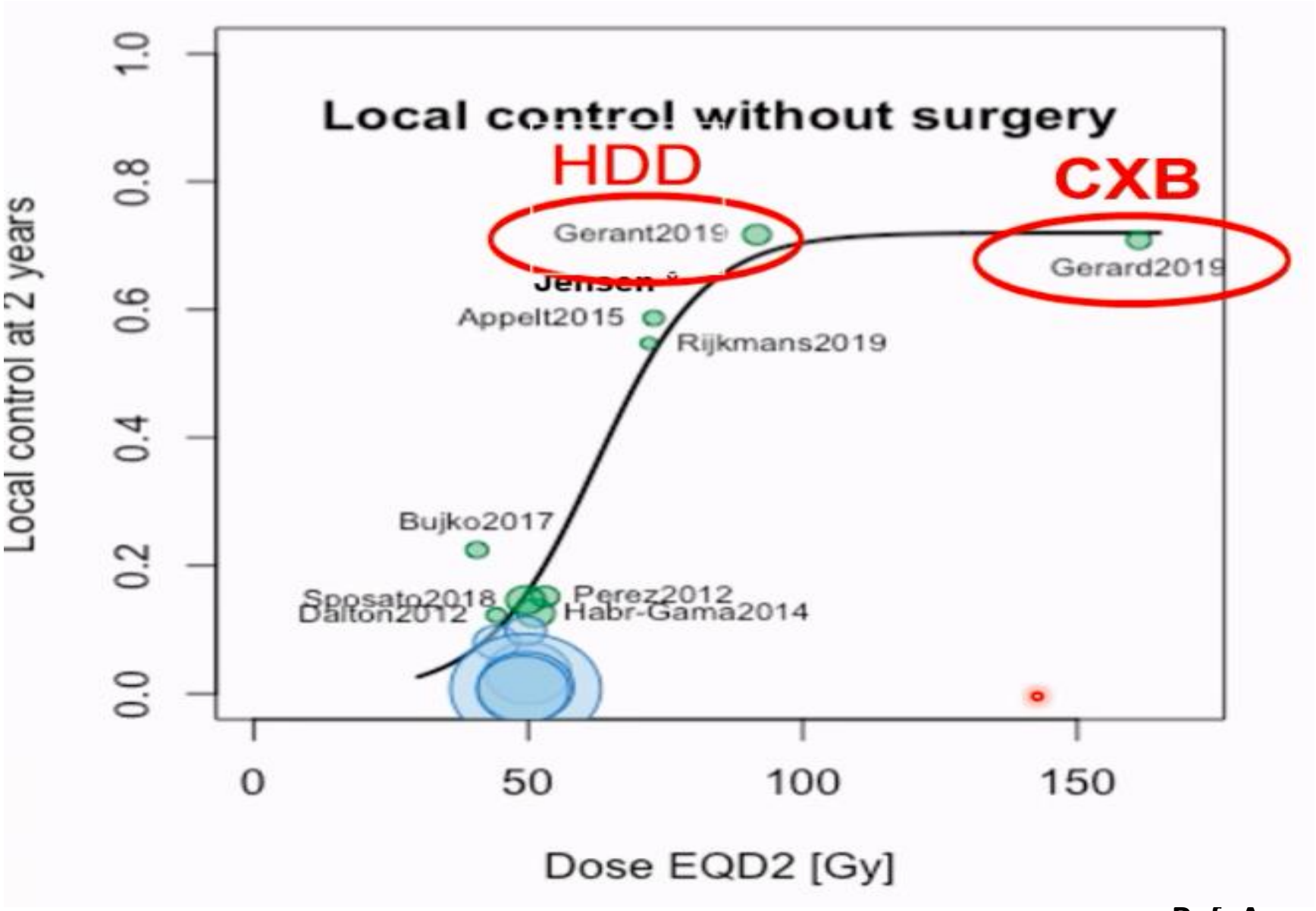
Dose-response relationships for complete response (TRG1) (solid line, filled squares) and major response (TRG1-2) (dashed line, open squares) after preoperative chemoradiation therapy (CRT) for rectal cancer.in second graph, response curves for complete response (black line/triangles) and major response (grey line/triangles).

>100 Gy10 BED needed for >80% response

Ref: Appelt et al Red 2012

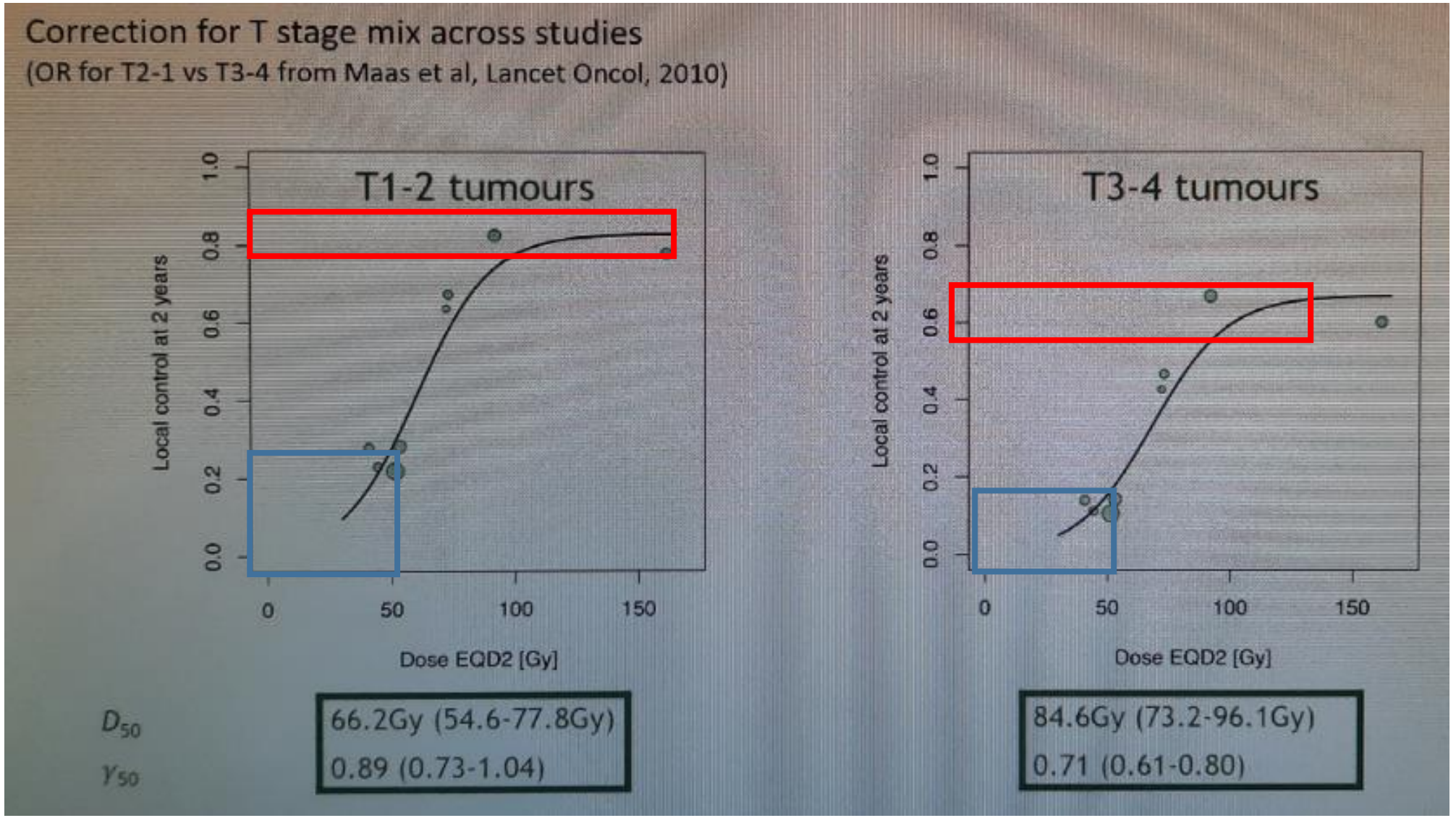
Publication	Number patients	Planned NOM	NOM at 2 years	EQD2 [Gy]	Tumour boost	T1-2 / T3-4
Dalton et al (2012)	49	Yes	12.2%	44.3	NA	8% / 92%
Perez et al (2012)	99	Yes	15.2%	53.1	EBRT	6% / 94%
Habr-Gama et al (2014)	183	Yes	12.6%	51.3	EBRT	17% / 83%
Appelt et al (2015)	51	Yes	58.7%	72.9	EBRT + brachy	53% / 47%
Li et al (2015)	900	No	3.2%	50.0	NA	NA
Renehan et al (2016)	259	No	8.0%	44.3	NA	NA
Vaccaro et al (2016)	204	No	9.8%	49.6	NA	NA
Bujko et al (2017)	59	Yes	22.4%	40.7	NA	61% / 39%
Oh et al (2018)	1063	No	0.7%	49.1	NA	12% / 88%
Sposato et al (2018)	185	Yes	14.6%	49.6	NA	NA
Garant et al (2019)	94	Yes	71.7%	91.7	Brachy	31% / 69%
Gerard et al (2019)	72	Yes	70.8%	161.3	Contact X-ray	60% / 40%
Park et al (2019)	2832	No	0.8%	49.6	NA	NA
Rijkmans et al (2019)	33	Yes	54.7%	72	Brachy	57% / 43%
Yeom et al (2019)	1140	No	1.1%	49.6	NA	NA

Dose-response curve 2-year local control with NOM



Ref: Appelt et al Red 2012

Dose-response curve 2-year local control with NOM



Ref: Appelt et al Red 2012

ACTA ONCOLOGICA
2022, VOL. 61, NO. 9, 1084–1092
https://doi.org/10.1080/0284186X.2022.2122866

Taylor & Francis
Taylor & Francis Group

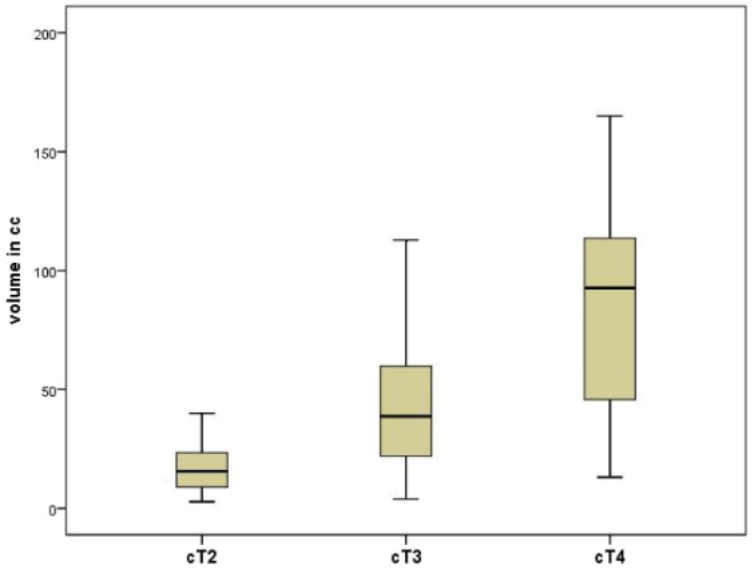
REVIEW

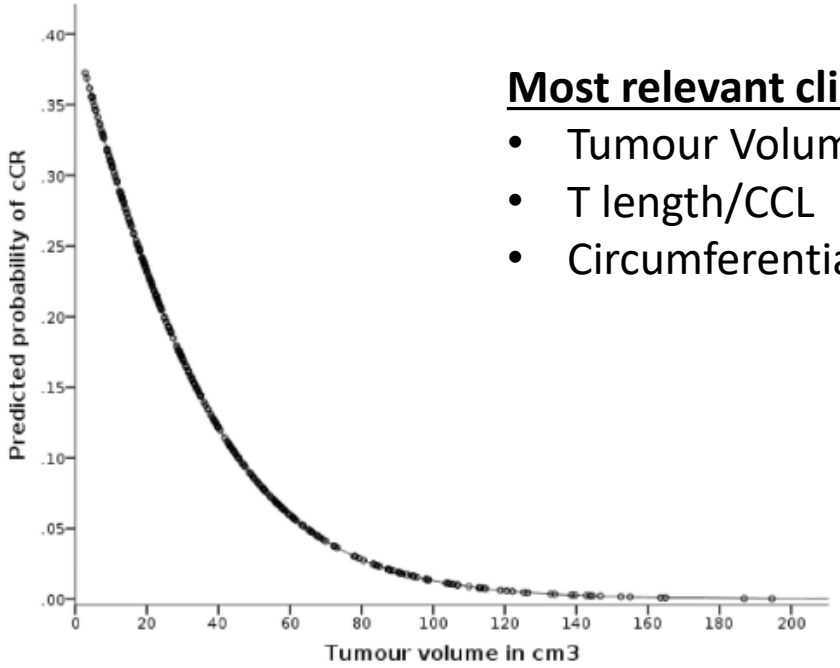
The importance of measuring baseline tumour volume (or alternatively tumour length along with its rectal circumferential extent) in the watch-and-wait strategy in rectal cancer: a review

Anna Hołdakowska[a], Jean-Pierre Gerard[b] and Krzysztof Bujko[c]

[a]Department of Radiology I, M. Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [b]Centre Antoine Lacassagne, France; [c]Department of Radiotherapy I, M. Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Size matters





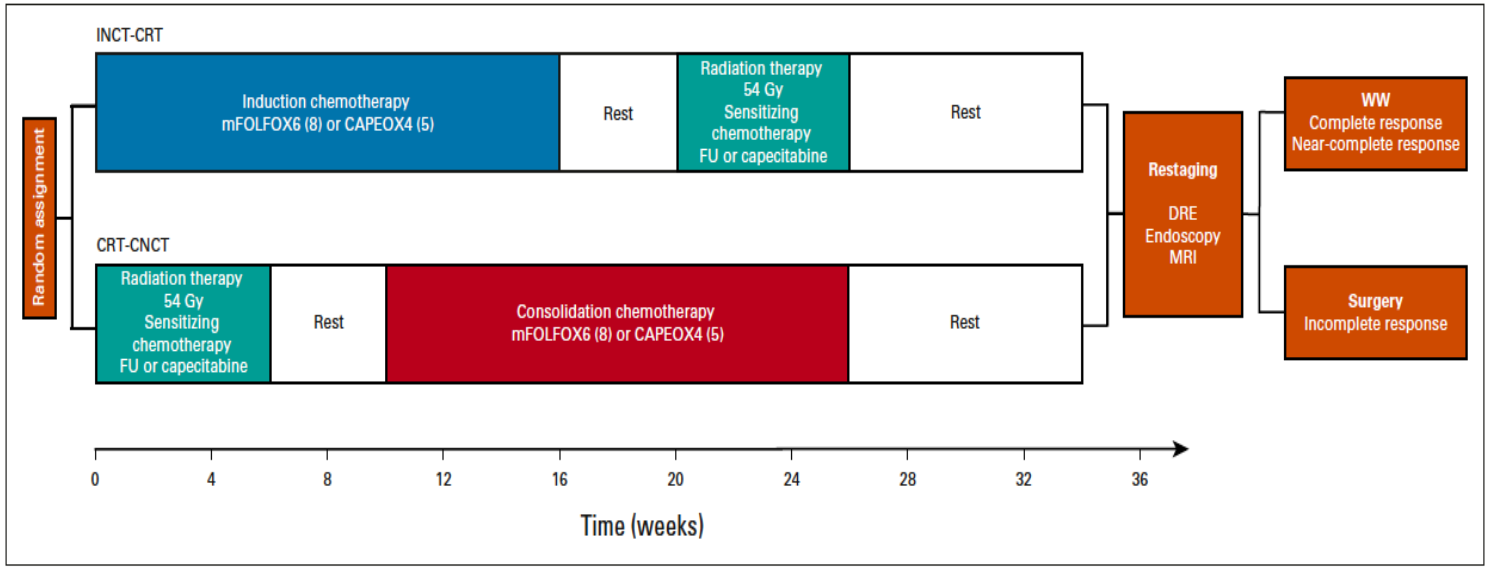
Most relevant clinical predictor of cCR at Baseline

- Tumour Volume
- T length/CCL
- Circumferential extent

original repo

Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy

Julio Garcia-Aguilar, MD, PhD[1]; Sujata Patil, PhD[2]; Marc J. Gollub, MD[3]; Jin K. Kim, MD[1]; Jonathan B. Yuval, MD[1];



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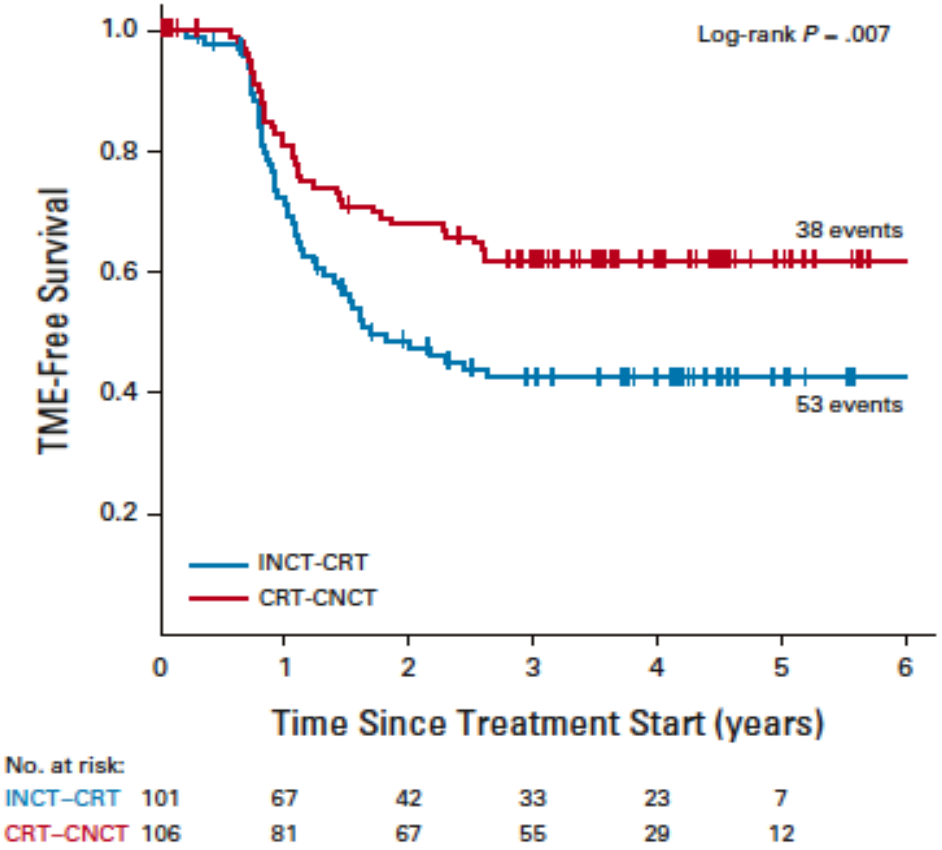


Does Chemotherapy only provides COMFORTABLE time post CTRT
OR pre CTRT Cht leads to poor Clonal Selection

Assessment Observation

- Clinical complete response (cCR): All criteria to be met:
    - Digital rectal examination (DRE) and recto-sigmoidoscopy: no palpable tumour material present, no residual tumour material or only a small residual erythematous ulcer or scar.
    - MRI: substantial downsizing with no observable residual tumour material, or residual fibrosis only (with the limited signal on diffusion weighted imaging), sometimes associated with residual wall thickening owing to edema, no suspicious lymph nodes.
    - Endoscopic biopsy: not mandatory to define cCR, biopsy should not be performed, especially if the DRE, sigmoidoscopy and MRI criteria for cCR are all fulfilled.
- Near cCR (ncCR) - DRE and recto-sigmoidoscopy: the presence of small and smooth regular irregularities including residual ulcer, small mucosal nodules or minor mucosal abnormalities, with mild persistent erythema of the scar. MRI: obvious downstaging with residual fibrosis but heterogeneous or irregular aspects and signal or regression of lymph nodes with no malignant enhancement features, but with a size of >5mm. Endoscopic biopsy: not mandatory to define ncCR, if rest is fulfilled.

IWWD consensus guidelines

IWWD Consensus for Follow-Up of NOM patients (+/- 1 month):

YEAR	SERUM CEA	DRE	ENDOSCOPY	PELVIC MRI	CECT CHEST ABDOMEN PELVIS
1st	6 months	3 months	3 months	3 months	6-12 months
2nd	6 months	3 months	3 months	3 months	Annually
3rd	3 months	6 months	6 months	6 months	Annually
4th	6 months	6 months	6 months	6 months	Annually
5th	6 months	6 months	6 months	6 months	Annually

Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2–cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial

Jean-Pierre Gerard, Nicolas Barbet, Renaud Schiappa, Nicolas Magné, Isabelle Martel, Laurent Mineur, Mélanie Deberne, Thomas Zilli, Amandeep Dhadda, Arthur Sun Myint, on behalf of the ICONE group

ORIGINAL ARTICLE

A phase III randomised trial on the addition of a contact X-ray brachytherapy boost to standard neoadjuvant chemo-radiotherapy for organ preservation in early rectal adenocarcinoma: 5 year results of the OPERA trial

D. Baron[1*], T. Pace Loscos[1], R. Schiappa[1], N. Barbet[2], E. Dost[1], S. Ben Dhia[1], S. Soltani[3], L. Mineur[4], I. Martel[5], S. Horn[6], C. Picardi[7,8], A. Stewart[9], E. Cotte[6], R. Coquard[2], G. Baudin[1], L. Evesque[1], A. Dhadda[10], A. Sun Myint[11], J. P. Gérard[1] & J. Doyen[1], on behalf of the ICONE group

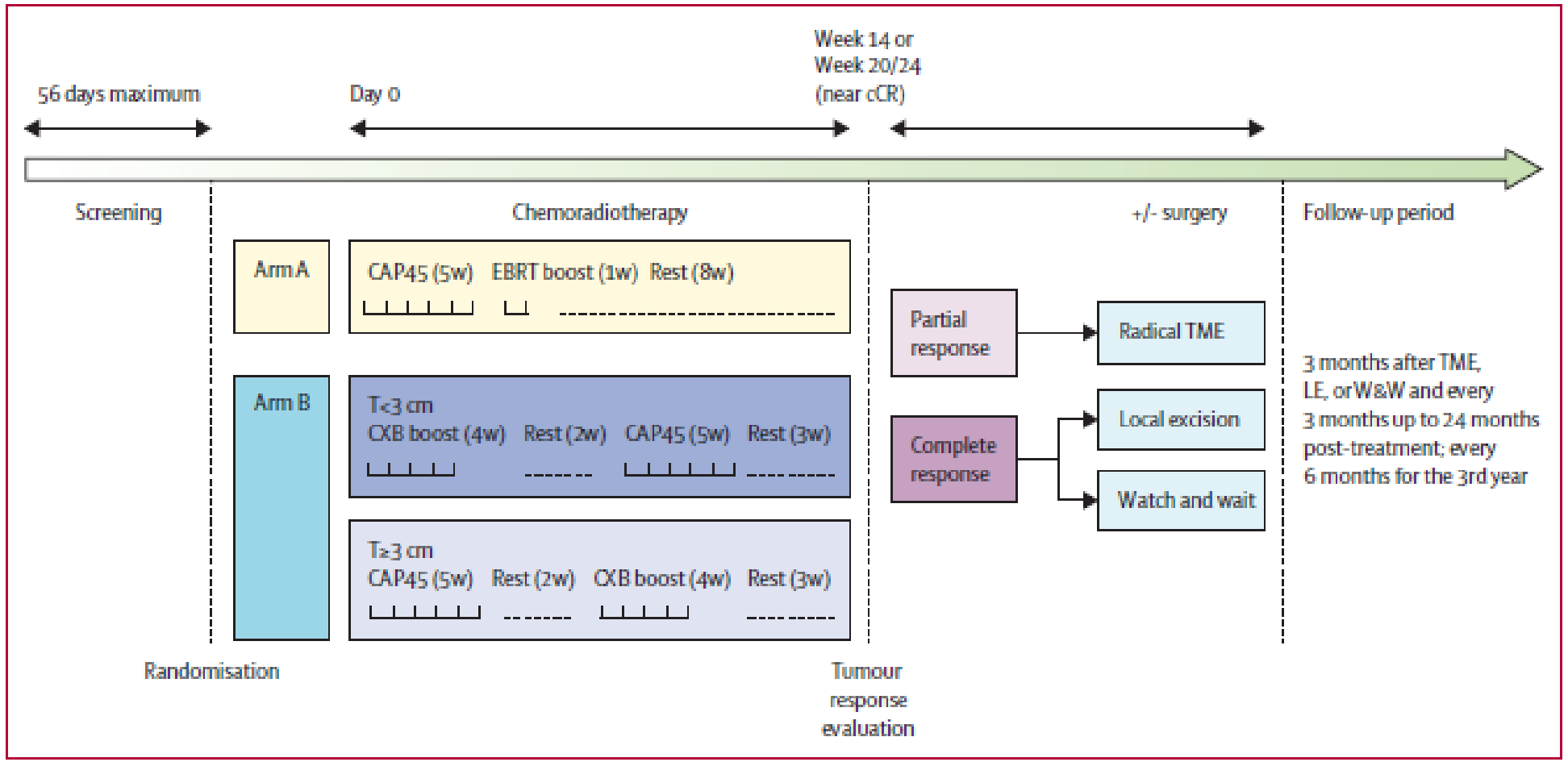
[1]Centre Antoine Lacassagne, Université Côte d'Azur, Nice; [2]Centre Oncologie Radiothérapie Bayard, Villeurbanne; [3]Institut de Cancérologie de la Loire, Saint Etienne; [4]Institut Sainte Catherine, Avignon; [5]Le Centre Régional de Lutte Contre le Cancer Léon Bérard, Lyon; [6]CHU de Lyon, Lyon, France; [7]Klinik Bethanien, Swiss Medical

Inclusion Criteria

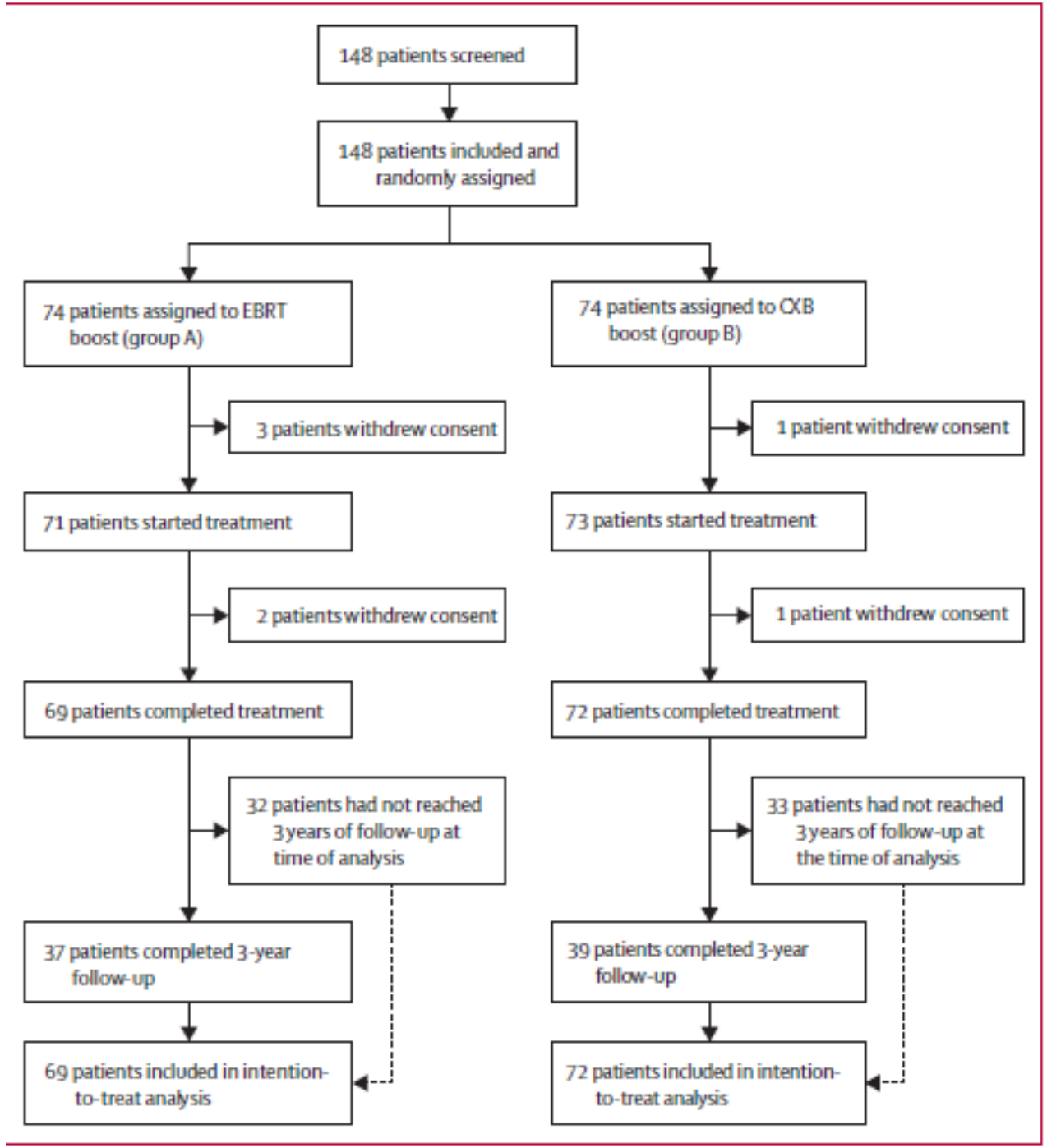
- Rectal Adenoca:
- cT2, cT3a, or T3b tumour (cN0–cN1, <8 mm)
- up to 10 cm from anal verge,
- < 5 cm in diameter,
- < half circumference.

The primary outcome was the 3-year organ preservation rate, without non-salvageable pelvic disease and without diversion stoma.

Sample size:
20% in group A versus 40% in group B, with (HR) of 0·56.
2-sided a 5%, B 7·5% (power 92·5%), 10% LTF, 236



after 146 patients had been randomly assigned. The recommendation was to stop recruitment to the trial to publish an interim report and wait until 3 years to publish results of the trial as planned in the

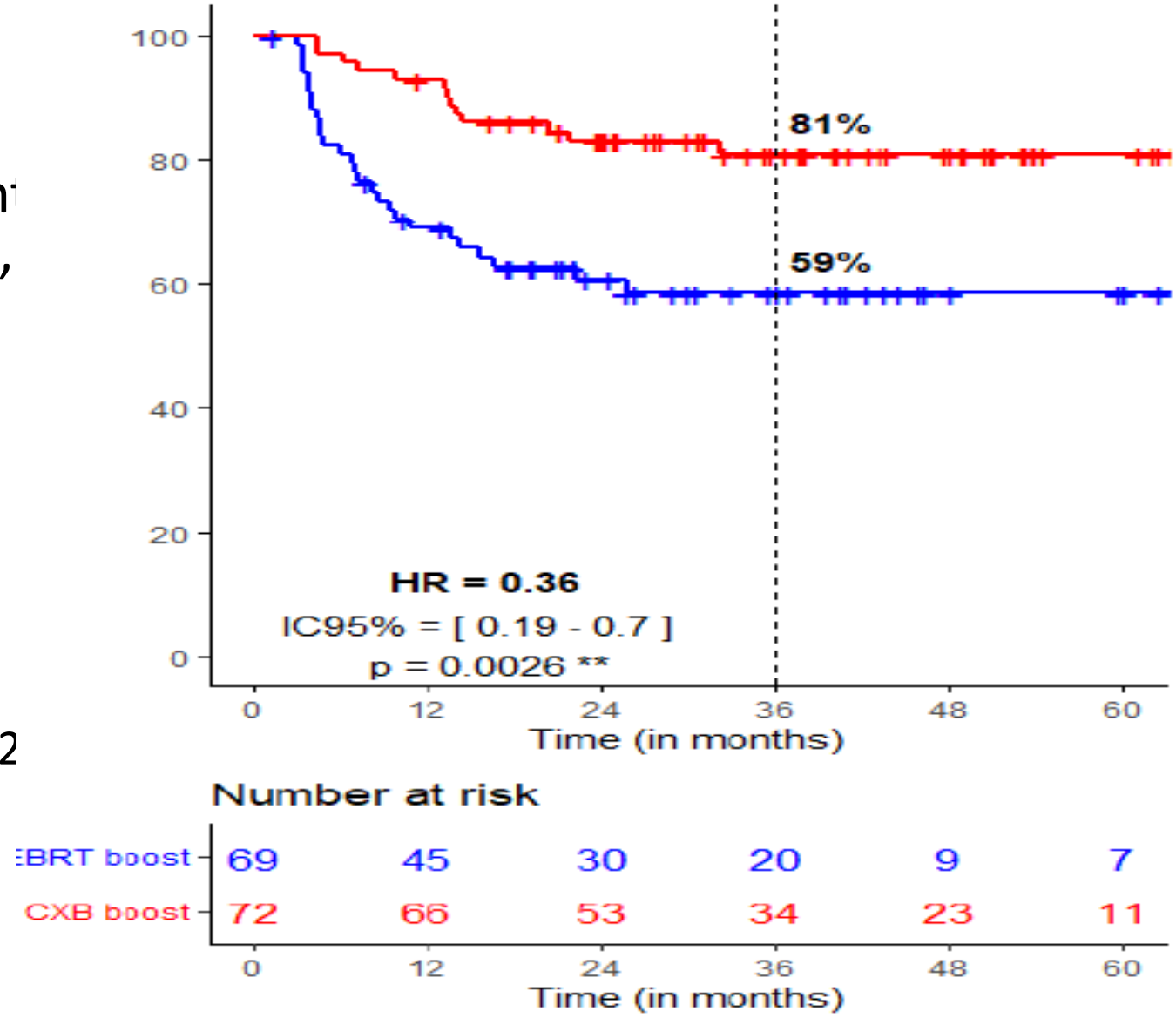

148 patients screened
148 patients included and randomly assigned
74 patients assigned to EBRT boost (group A)
74 patients assigned to CXB boost (group B)
3 patients withdrew consent
1 patient withdrew consent
71 patients started treatment
73 patients started treatment
2 patients withdrew consent
1 patient withdrew consent
69 patients completed treatment
72 patients completed treatment
32 patients had not reached 3 years of follow-up at time of analysis
33 patients had not reached 3 years of follow-up at the time of analysis
37 patients completed 3-year follow-up
39 patients completed 3-year follow-up
69 patients included in intention-to-treat analysis
72 patients included in intention-to-treat analysis

	Total			Tumours <3 cm in diameter			Tumours ≥3 cm in diameter		
	Group A (n=69)	Group B (n=72)	p value	Group A (n=29)	Group B (n=32)	p value	Group A (n=40)	Group B (n=40)	p value
Week 14									
MRI tumour regression grade			0·74			0·087			0·013
1	31 (45%)	38 (53%)	..	14 (48%)	24 (75%)	..	17 (43%)	14 (35%)	..
2	12 (17%)	18 (25%)	..	8 (28%)	3 (9%)	..	4 (10%)	15 (37%)	..
3 or 4	5 (7%)	4 (6%)	..	1 (3%)	3 (9%)	..	4 (10%)	1 (3%)	..
Unknown	21 (30%)	12 (17%)	..	6 (21%)	2 (6%)	..	15 (37%)	10 (25%)	..
MRI tumour regression grade (post-hoc analysis)			0·51			0·62			0·17
1 or 2	43 (62%)	56 (78%)	..	22 (76%)	27 (84%)	..	21 (53%)	29 (72%)	..
3 or 4	5 (7%)	4 (6%)	..	1 (3%)	3 (9%)	..	4 (10%)	1 (3%)	..
Unknown	21 (30%)	12 (17%)	..	6 (21%)	2 (6%)	..	15 (37%)	10 (25%)	..
Response			<0·0001			0·078			0·0030
Clinical complete response	27 (39%)	34 (47%)	..	16 (55%)	20 (63%)	..	11 (28%)	14 (35%)	..
Near-clinical complete response	13 (19%)	24 (33%)	..	5 (17%)	10 (31%)	..	8 (20%)	14 (35%)	..
Partial response	24 (35%)	5 (7%)	..	6 (21%)	1 (3%)	..	18 (45%)	4 (10%)	..
Stable disease	0	3 (4%)	..	0	1 (3%)	..	0	2 (5%)	..
Progressive disease	1 (1%)	0	..	0	0	..	1 (2%)	0	..
Unknown	4 (6%)	6 (8%)	..	2 (7%)	0	..	2 (5%)	6 (15%)	..
Response (post-hoc analysis)			0·0006			0·13			0·0085
Complete response (clinical or near-clinical)	40 (58%)	58 (81%)	..	21 (72%)	30 (94%)	..	19 (48%)	28 (70%)	..
Partial response, stable disease, or progressive disease	25 (36%)	8 (11%)	..	6 (21%)	2 (6%)	..	19 (48%)	6 (15%)	..
Unknown	5 (7%)	6 (8%)	..	2 (7%)	0	..	2 (5%)	6 (15%)	..

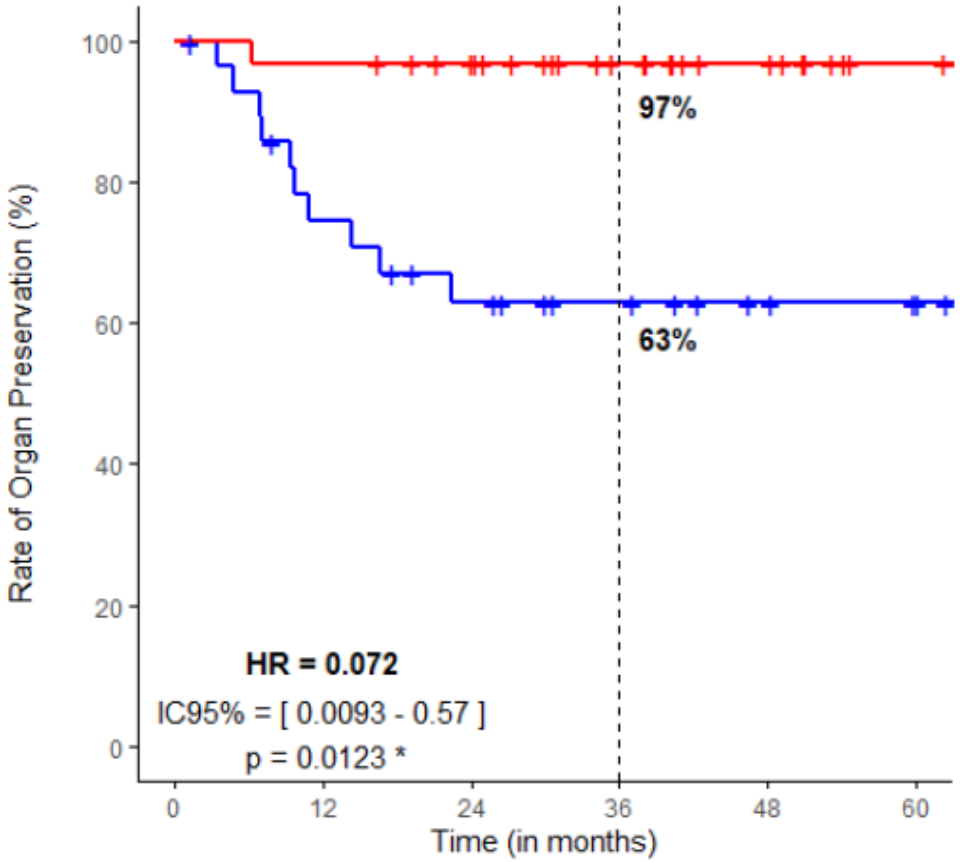
Results

- At median follow-up of 38·2 mon
  (IQR 34·2–42·5); March 15, 2022,
  - minimum follow-up of 2 years for every patient

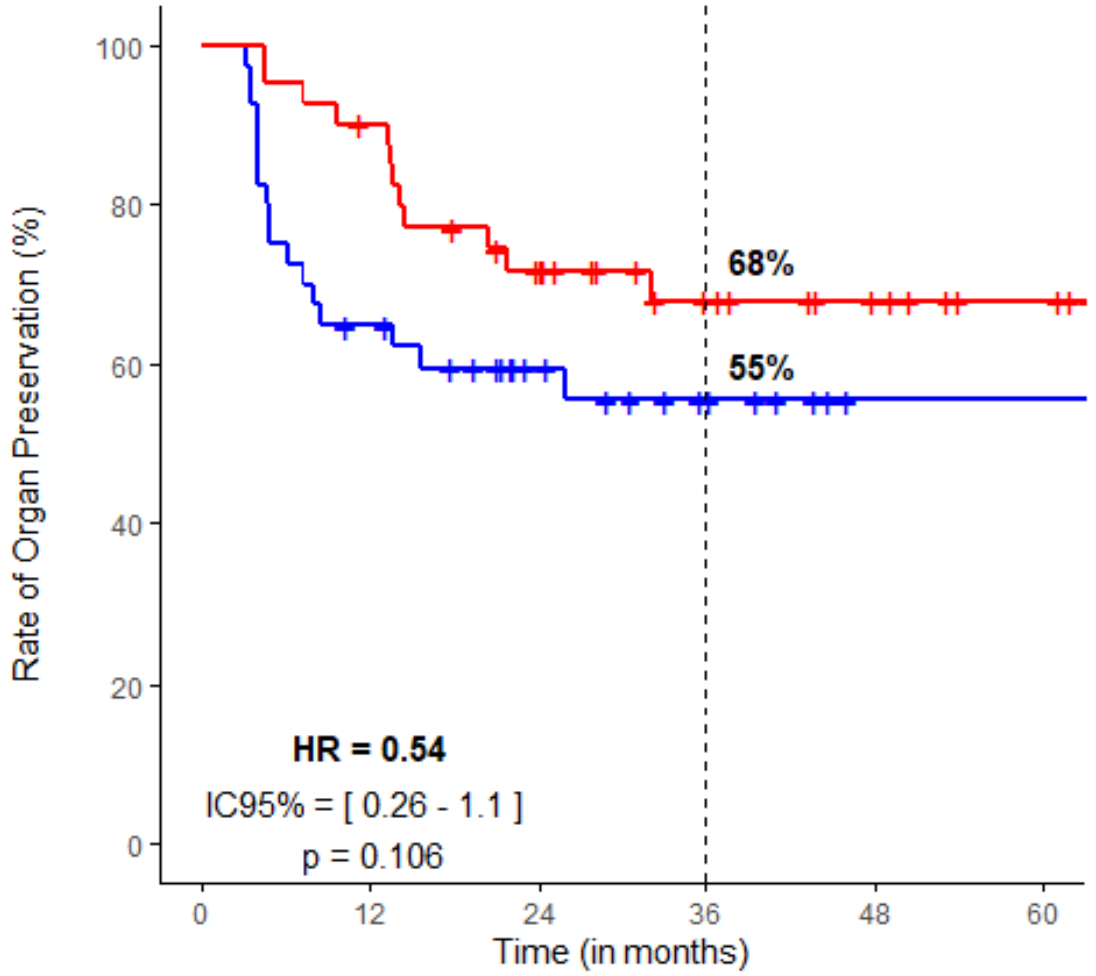
- Primary Outcome: 3-year organ preservation rate
  - 59% (95% CI 48–72) in group A
  - 81% (72–91) in group B
  - HR 0·36, 95% CI 0·19–0·70; p=0·002



Results



- In patients with tumour dia <3 cm
  - 63% (95% CI 47–84) vs. 97% (91–100)
  - HR 0·07, 95% CI 0·01–0·57; p=0·012



- In patients with tumour dia ≥3 cm
  - 55% (95% CI 41–74) vs 68% (54–85)
  - HR 0·54, 95% CI 0·26–1·10; p=0·11

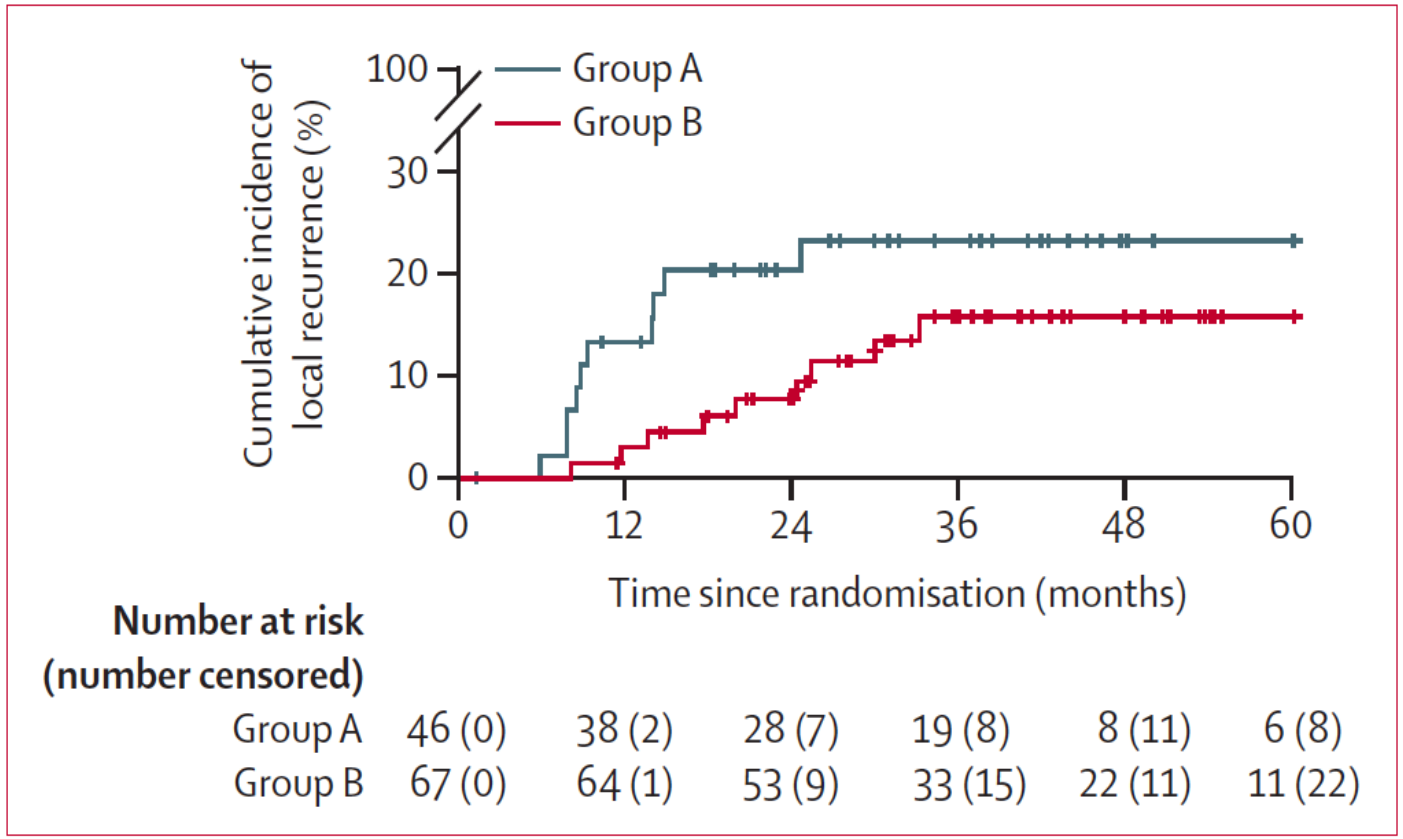


Figure 4: **Cumulative incidence of local recurrence**

No non-salvageable local recurrence

No local recurrences among patients who had total mesorectal excision

Four (21%) patients Refused surgery for their recurrences.

Factors that might predict 3-year organ preservation

2) Multivariate analysis

We constructed a multivariate model including variables with p <0.1 in univariate analysis.

A) Initial model

Variable	Hazard ratio	HR IC95% low	HR IC95% high	p-value
DIAMETERSUPERIOR_OR_EQUAL_TO_3CM	2.268668	1.125545	4.572768	0.02198255
INTERRUPTION_MORE_THAN_3_CONSECUTIVE_DAYS_45GYYES	3.279227	1.147437	9.371611	0.02664607

B) Final model after the application of the stepwise algorithm

Variable	Hazard ratio	HR IC95% low	HR IC95% high	p-value
DIAMETERSUPERIOR_OR_EQUAL_TO_3CM	2.268668	1.125545	4.572768	0.02198255
INTERRUPTION_MORE_THAN_3_CONSECUTIVE_DAYS_45GYYES	3.279227	1.147437	9.371611	0.02664607

Factors tested: cT stage (2 *vs* 3a or 3b), age, sex, differentiation (moderately *vs* well), ECOG performance status (0 *vs* 1 or 2), cN class (N0 *vs* N1), distance from anal verge (<6 cm *vs* ≥6 cm), carcinoembryogenic antigen (<2·5 ng/mL *vs* ≥2·5 ng/mL), EBRT technique (three-dimensional conformal *vs* intensity modulated radiotherapy), and contact position (knee-chest *vs* lithotomy).

	Group A (n=69)				Group B (n=72)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
Blood disorders	0	0	0	0	1 (1%)	2 (3%)	0	0
Neutropenia	0	0	0	0	0	1 (1%)	0	0
Lymphopenia	0	0	0	0	0	1 (1%)	0	0
Venous thromboembolism	0	0	0	0	1 (1%)	0	0	0
Gastrointestinal	4 (6%)	0	0	0	10 (14%)	5 (7%)	0	0
Proctitis	4 (6%)	0	0	0	7 (10%)	2 (3%)	0	0
Diarrhoea	0	0	0	0	3 (4%)	3 (4%)	0	0
General disorders and administration site conditions	0	1 (1%)	0	0	4 (6%)	0	0	0
Asthenia	0	0	0	0	2 (3%)	0	0	0
Coronary artery spams	0	1 (1%)	0	0	0	0	0	0
Anorexia	0	0	0	0	1 (1%)	0	0	0
Erectile dysfunction	0	0	0	0	1 (1%)	0	0	0
Renal and urinary disorders	2 (3%)	3 (4%)	0	0	4 (6%)	0	0	0
Urinary infection	0	2 (3%)	0	0	0	0	0	0
Dysuria	2 (3%)	1 (1%)	0	0	4 (6%)	0	0	0
Skin disorders	7 (10%)	0	0	0	2 (3%)	0	0	0
Radiation dermatitis	7 (10%)	0	0	0	2 (3%)	0	0	0
Other	4 (6%)	0	0	0	2 (3%)	0	0	0
Rectal bleeding	2 (3%)	0	0	0	0	0	0	0
Chest pain	0	0	0	0	2 (3%)	0	0	0
Oral candidiasis	1 (1%)	0	0	0	0	0	0	0
Palmar-plantar erythrodysesthesia	1 (1%)	0	0	0	0	0	0	0

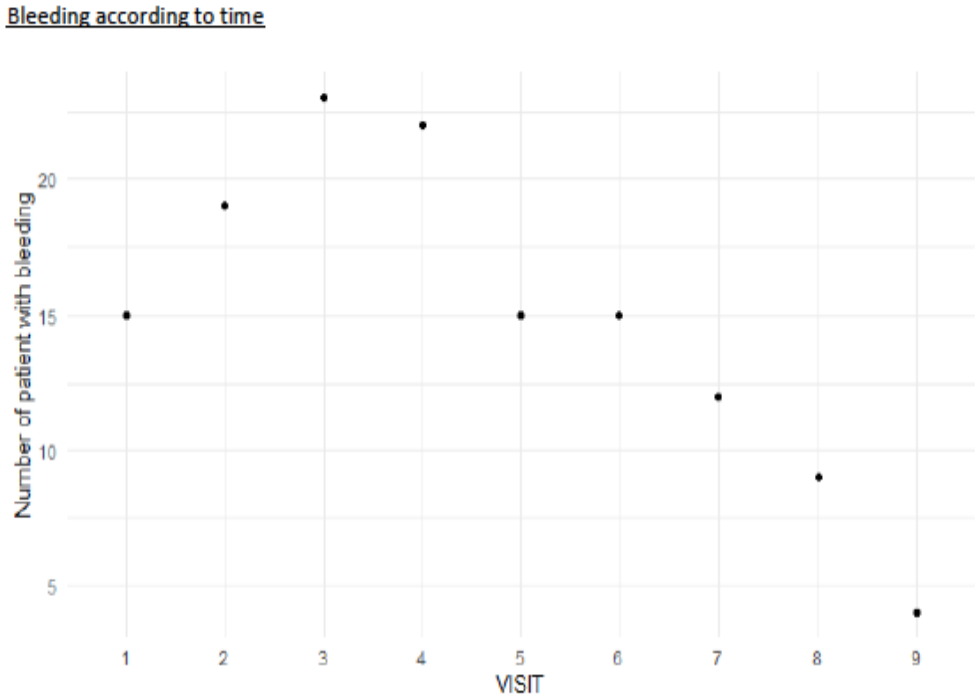
The highest-grade adverse event for each patient is reported.

Grade 2–3 early adverse event 51 patients (36%) during CTRT

Table 3: **Adverse events**

Toxicity & Functional Outcomes

- TME – 30 days
  - No deaths
  - Median hospital stay was 9 days (IQR 6–14)
  - 7/39 had second operations
- Local Excision:
  - Median hospital stay 2 days (IQR 1–3).
  - No major serious surgical complications were observed following local excision.
- No late adverse event of grade 3 or higher occurred.
- The most common late side-effect was mild rectal bleeding (grade 1–2)
  - Organ preserved: 102: Group B 63% vs 12%]; p<0·0001
  - On Average appeared 6 months after treatment, increased in incidence between 1 year and 2 years, and subsided after 3 years
- Bowel function Without TME (89)
  - LARS score $\geq$ 30
    - 21% Group A
    - 17% Group B (p=0·55)



Visit is the N° of each surveillance visit during the follow-up of the patient. The maximum of rectal bleeding is reported at visit 3 (one year after end of treatment) and the minimum at visit 9 (3 years after treatment)

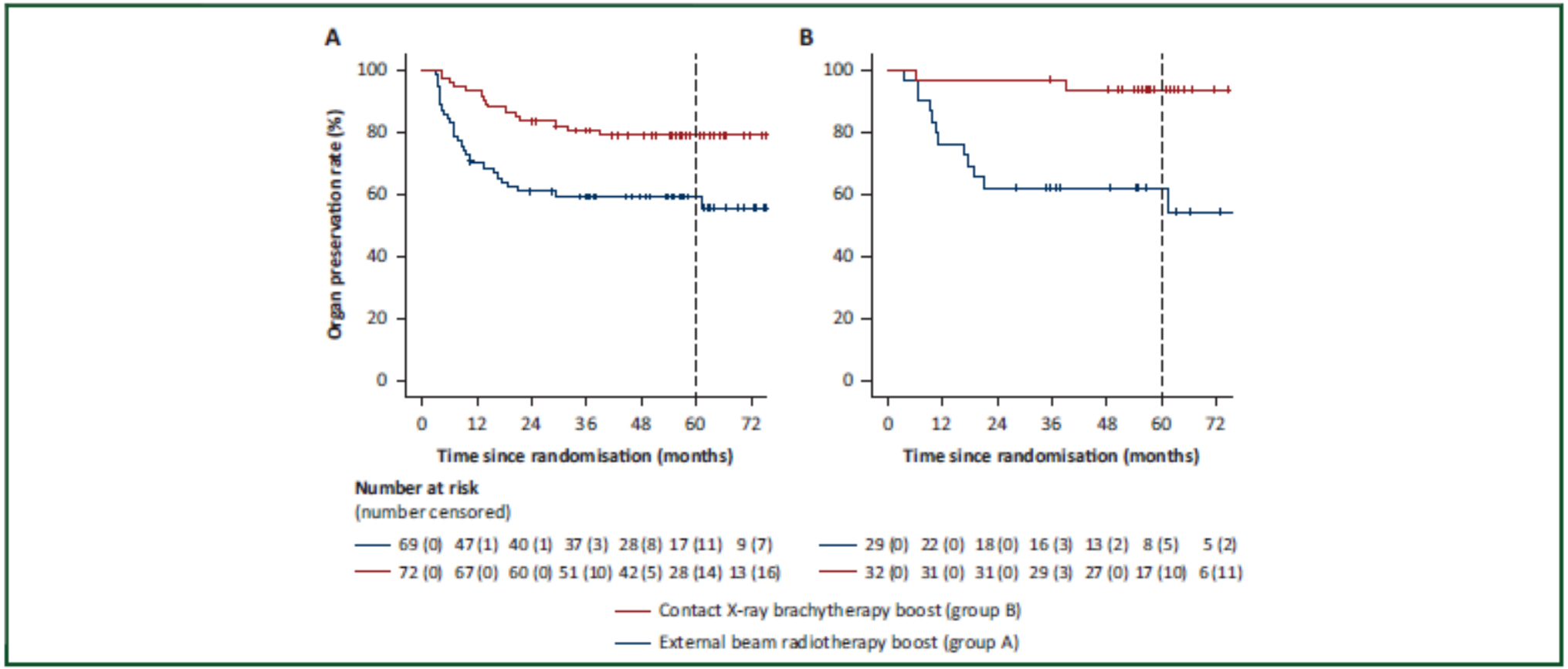


Figure 2. 5-year organ preservation rate. (A) All patients ($n = 141$). (B) Patients with tumours smaller than 3 cm ($n = 61$).

At median follow-up was 61.1 months, 5-year local regrowth was 39% vs 17% in group B (P = 0.1).
Organ preservation 56% versus B 79% (P = 0.004).
The difference was more significant if tumours <3 cm, (93%).
Rectal bleeding (grade 1-2), which was the most prevalent toxicity during follow-up, disappeared most of the time after three years. Bowel function was not worsened by the CXB boost.

Opera, Opra, Star-Trec, German Rectal Cancer Study Group (CAO/ARO/AIO-16).

original reports

Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy

Julio Garcia-Aguilar, MD, PhD[1]; Sujata Patil, PhD[2]; Marc J. Gollub, MD[3]; Jin K. Kim, MD[1]; Jonathan B. Yuval, MD[1]; Hannah M. Thompson, MD[1]; Floris S. Verheij, MD[1]; Dana M. Omer, MD[1]; Meghan Lee, BS[1]; Richard F. Dunne, MD[4]; Jorge Marcet, MD[5]; Peter Cataldo, MD[6]; Blase Polite, MD[7]; Daniel O. Herzig, MD[8]; David Liska, MD[9]; Samuel Oommen, MD[10]; Charles M. Friel, MD[11]; Charles Ternent, MD[12]; Andrew L. Coveler, MD[13]; Steven Hunt, MD[14]; Anita Gregory, MD[15]; Madhulika G. Varma, MD[16]; Brian L. Bello, MD[17]; Joseph C. Carmichael, MD[18]; John Krauss, MD[19]; Ana Gleisner, MD[20]; Philip B. Paty, MD[1]; Martin R. Weiser, MD[1];

Compliance and Toxicity of Total Neoadjuvant Therapy for Rectal Cancer: A Secondary Analysis of the OPRA Trial

Floris S. Verheij, BSc,* Dana M. Omer, MD,* Sabrina T. Lin, MS,† Jonathan B. Yuval, MD,* Hannah M. Thompson, MD,* Jin K. Kim, MD,* Sebastian C. Valdivieso, MD,‡ Li-Xuan Qin, PhD,† Abraham J. Wu, MD,§ Leonard B. Saltz, MD,‖ and Julio Garcia-Aguilar, MD, PhD*

Check for upda

Long-Term Results of Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy: The Randomized Phase II OPRA Trial

Floris S. Verheij, BSc[1]; Dana M. Omer, MD[1]; Hannah Williams, MD[1]; Sabrina T. Lin, MSc[2]; Li-Xuan Qin, PhD[2]; James T. Buckley, BSc[1]; Hannah M. Thompson, MD[1]; Jonathan B. Yuval, MD[1]; Jin K. Kim, MD[1]; Richard F. Dunne, MD[3]; Jorge Marcet, MD[4]; Peter Cataldo, MD[5]; Blase Polite, MD[6]; Daniel O. Herzig, MD[7]; David Liska, MD[8]; Samuel Oommen, MD[9]; Charles M. Friel, MD[10]; Charles Ternent, MD[11];

clinical stage II (T3-4, N0) or stage III (any T, N1-2) biopsyproven rectal adenocarcinoma

The primary end point was DFS, defined as the interval from random assignment to the first occurrence of locoregional failure, distant metastasis, a new invasive colorectal primary cancer, or death from any cause.

The trial was designed as two stand-alone phase II studies with similar hypotheses.
we used pCR rates from previous data, 20% for the INCT-CRT group and 35% for the CRT-CNCT group (Protocol)

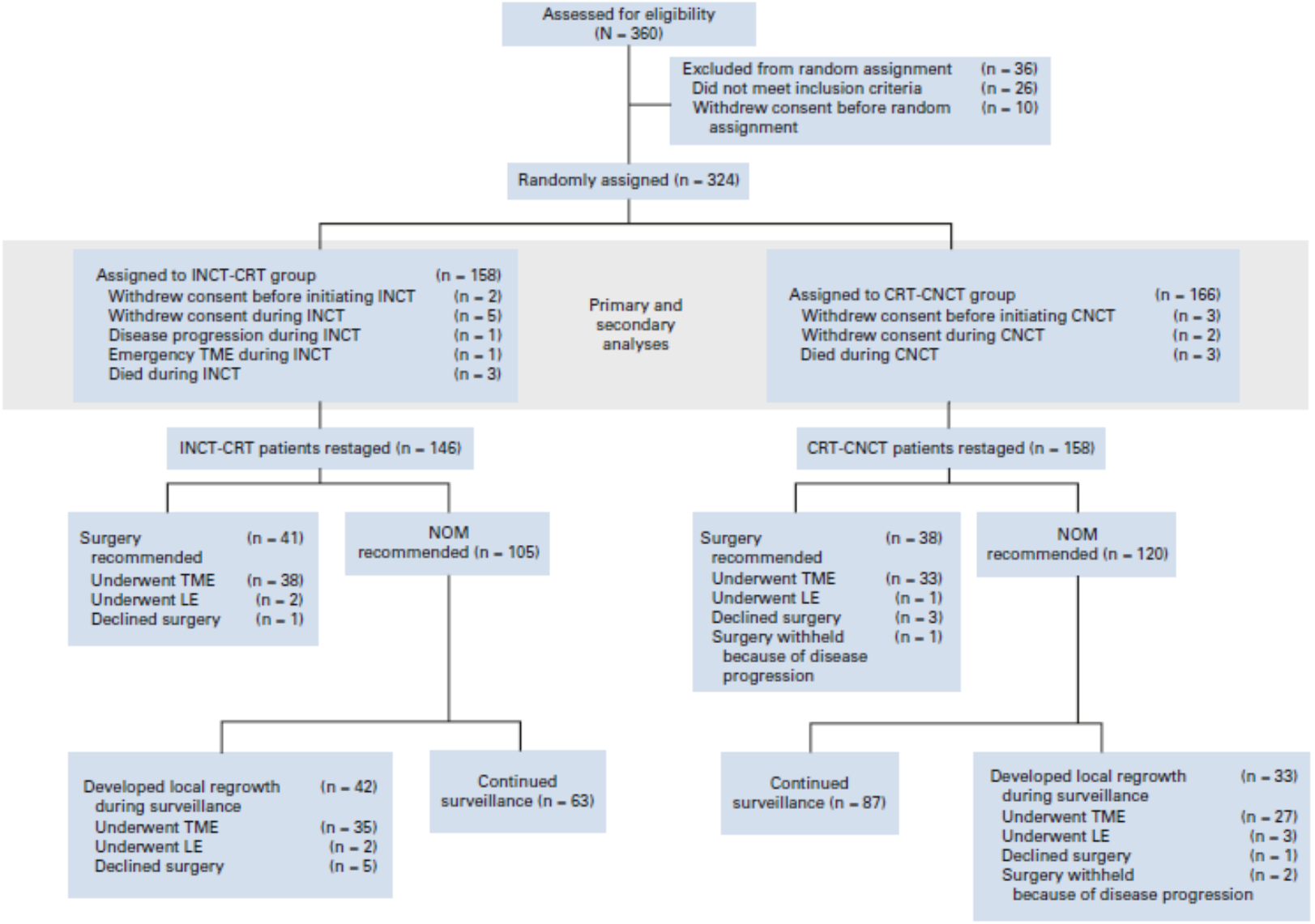


Table 1 Compliance to chemotherapy

Characteristic	INCT-CRT n = 158 (%)	CRT-CNCT n = 166 (%)	*P* value*
Started neoadjuvant chemotherapy	156 (99)	156 (94)	.04
FOLFOX	117 (74)	116 (70)	
CAPEOX	33 (21)	34 (20)	
FOLFOX and CAPEOX	6 (4)	6 (4)	
No chemotherapy	2 (1)	10 (6)	
Completed intended cycles of chemotherapy†	129 (83)	127 (77)	.28
FOLFOX‡	n = 118§	n = 117§	
Completed intended FOLFOX cycles†	101 (86)	97 (83)	.60
≥90% of planned dose fluorouracil received	81 (69)	86 (74)	.47
≥90% of planned dose oxaliplatin received	73 (62)	73 (62)	>.99
≥75% of planned dose fluorouracil received	106 (90)	109 (93)	.48
≥75% of planned dose oxaliplatin received	104 (88)	100 (85)	.57
CAPEOX‡	n = 38‖	n = 39‖	
Completed intended CAPEOX cycles†	28 (74)	30 (77)	.80
≥90% of planned dose capecitabine received	23 (61)	23 (59)	>.99
≥90% of planned dose oxaliplatin received	20 (53)	21 (54)	>.99
≥75% of planned dose capecitabine received	29 (76)	28 (72)	.80
≥75% of planned dose oxaliplatin received	26 (68)	30 (77)	.45

Abbreviations: CAPEOX = capecitabine with oxaliplatin; CRT-CNCT = chemoradiation followed by consolidation chemotherapy; FOLFOX = fluorouracil, leucovorin, and oxaliplatin; INCT-CRT = induction chemotherapy followed by chemoradiation.

Table 2 Compliance to chemoradiation

Characteristic	INCT-CRT n = 158 (%)	CRT-CNCT n = 166 (%)	*P* value*
Started radiation therapy	147 (93)	163 (98)	.03
No radiation therapy	11 (7)	3 (2)	
Median radiation dose (IQR), cGy†	5400 (5040-5400)	5400 (5040-5600)	.13
Radiation dose range, cGy†			
<4500	4 (3)	3 (2)	.93
4500-5040	45 (31)	48 (29)	
5041-5600	96 (65)	110 (67)	
>5600	2 (1)	2 (1)	
Received radiosensitizing chemotherapy†			
No	3 (2)	0	.11
Yes	144 (98)	163 (100)	
Capecitabine	122 (85)	139 (85)	.99
Fluorouracil	22 (15)	24 (15)	

Abbreviations: CRT-CNCT = chemoradiation followed by consolidation chemotherapy; INCT-CRT = induction chemotherapy followed by chemoradiation.

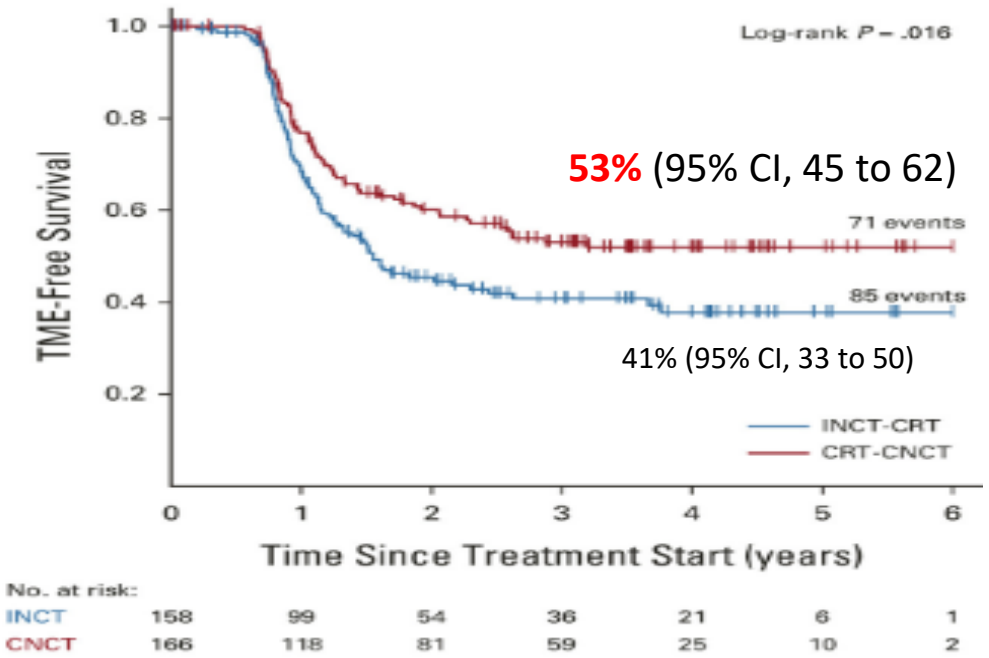
* Statistical analyses were performed using the Fisher exact test and Wilcoxon rank sum test.

† As-treated analysis (INCT-CRT n = 147, CRT-CNCT n = 163).

Table 3 Univariable and multivariable Cox proportional hazards model for TME-free survival

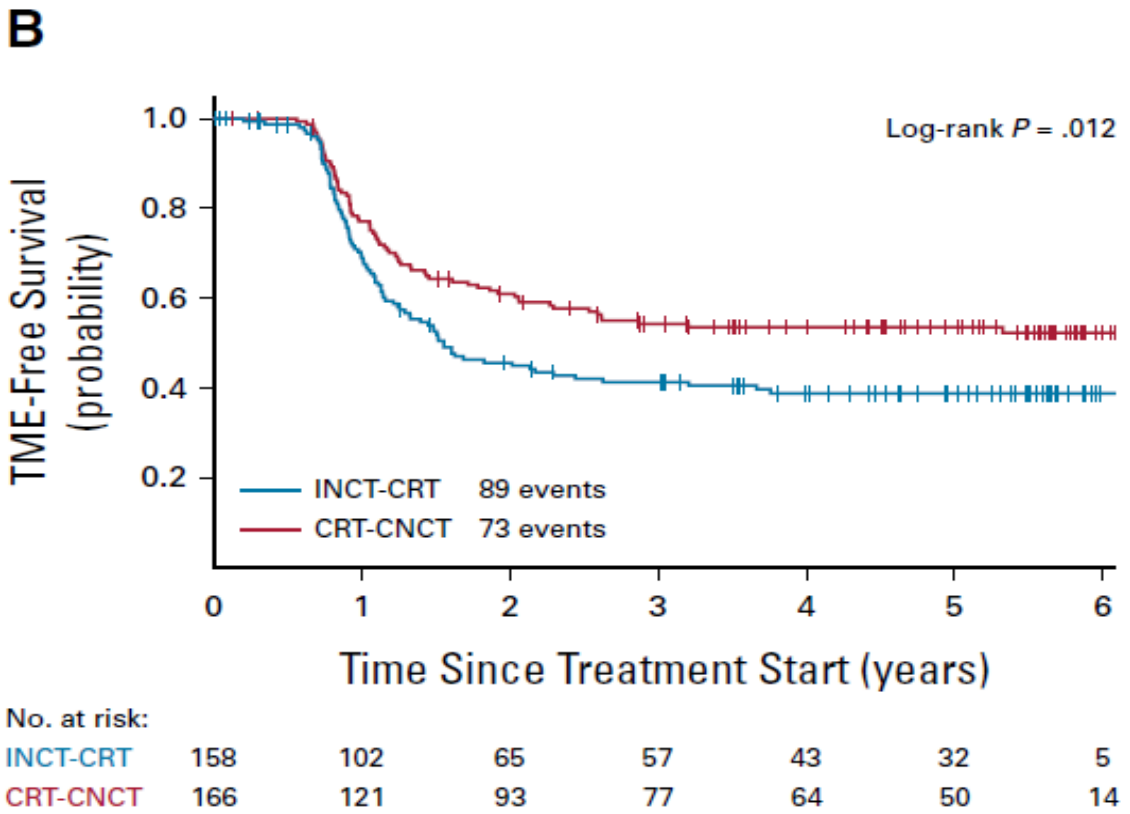
Characteristic	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Treatment group						
INCT-CRT	-	-		-	-	
CRT-CNCT	0.68	0.49-0.93	.02	0.68	0.50-0.94	.02
Age	0.99	0.97-1.00	.12			
Sex						
Female	-	-				
Male	1.04	0.75-1.45	.81			
cT classification						
1-2	-	-				
3	1.51	0.83-2.73	.18			
4	1.82	0.90-3.67	.10			
cN classification						
Negative	-	-		-	-	
Positive	1.75	1.18-2.58	.005	1.75	1.18-2.58	.005
Distance from AV, cm						
<5	-	-				
5-10	1.06	0.77-1.46	.73			
Radiation dose, cGy						

cT classification, No. (%)	
cT1-2	8 (8)
cT3	78 (77)
cT4	15 (15)
cN classification, No. (%)	
cN-negative	29 (29)
cN-positive	72 (71)
Median tumor distance from anal verge, cm (IQR)	4.3 (3.0-6.0)
High-grade tumor, No. (%)	6 (6)



3-yr TME-free survival was 41% (95% CI, 33 to 50) in the INCT-CRT group and **53%** (95% CI, 45 to 62) in the CRT-CNCT group.

5-year TME-free survival was 39% (95% CI, 32 to 48) in the INCT-CRT group and 54% (95% CI, 46 to 62) in the CRT-CNCT group (P =.012). Of 81 patients with regrowth, 94% occurred within 2 years, and 99% occurred within



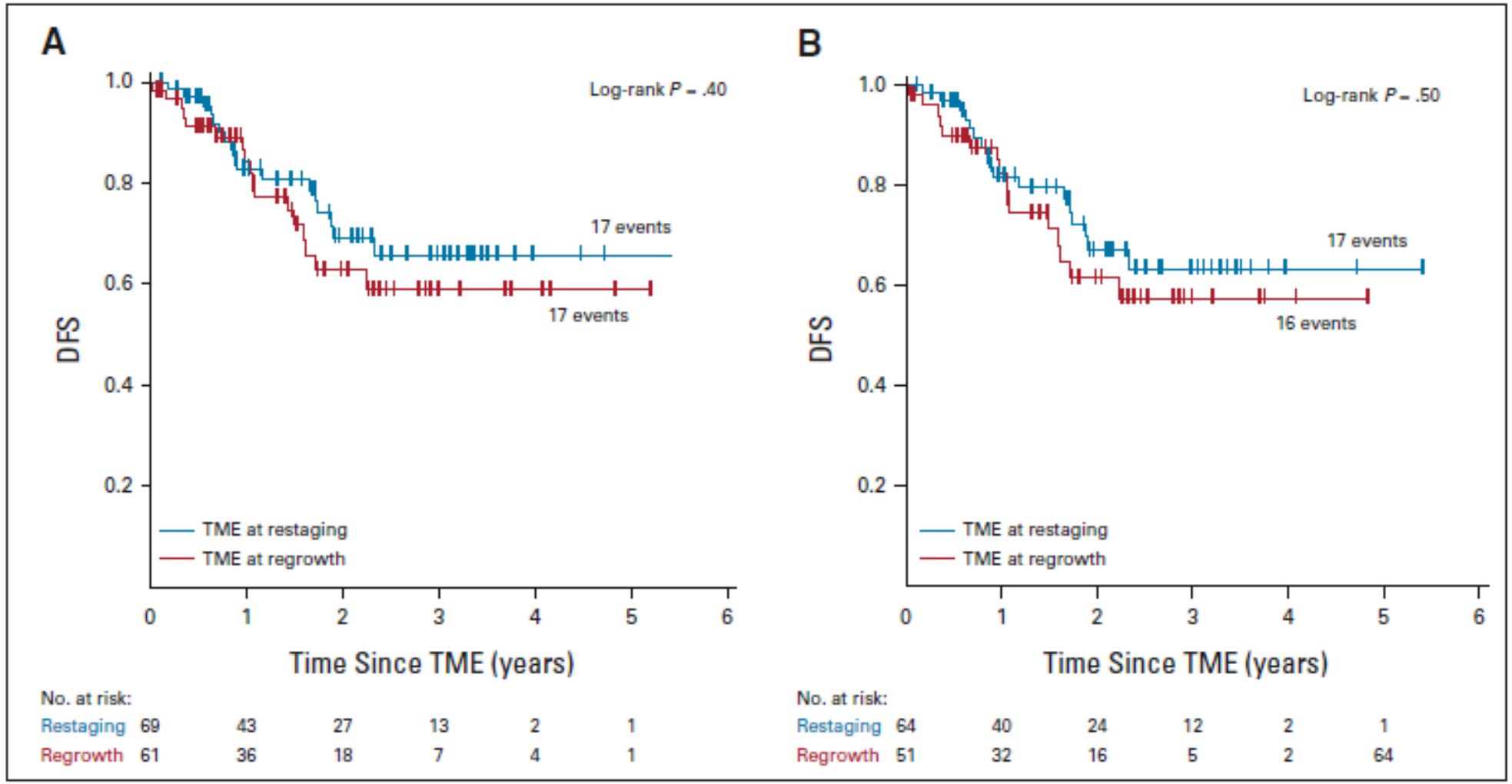


FIG 4. Kaplan-Meier estimates of DFS for (A) patients recommended TME after restaging and after tumor regrowth by intention to treat and (B) patients who actually underwent TME. Patients who developed distant metastasis before TME was recommended (three at restaging and six at regrowth) and patients in whom TME was not performed because of disease progression found at surgery (one at restaging and two at regrowth) are not included in the analysis. Six patients in each group have not reached the first follow-up clinical assessment after TME. DFS, disease-free survival; TME, total mesorectal excision.

Organ preservation after total neoadjuvant therapy for locally advanced rectal cancer (CAO/ARO/AIO-16): an open-label, multicentre, single-arm, phase 2 trial

Cihan Gani, Emmanouil Fokas, Bülent Polat, Oliver J Ott, Markus Diefenhardt, Alfred Königsrainer, Simon Böke, Andreas Kirschniak, Robert Bachmann, Dörte Wichmann, Michael Bitzer, Stephan Clasen, Ulrich Grosse, Rüdiger Hoffmann, Martin Götz, Ralf-Dieter Hofheinz, Elisabeth Germer, Christoph-Thomas Germer, Rainer Fietkau, Peter Martus, Daniel Zips, Claus Rödel

open-label, multicentre, single-arm, phase 2 trial conducted at four GRCSG centres

LCRT: 50·4Gy/28#, Concomitant
a. 5FU (250 mg/m²/day Cont. infusion D1-14 & D22-35
b. Oxaliplatin(50 mg/m²) D1,8,22,and29

Three cycles of consolidation FOLFOX

cT1–2N1–2 or cT3a–dN0/N1–2 rectal adenocarcinoma up to 12 cm from the anal verge

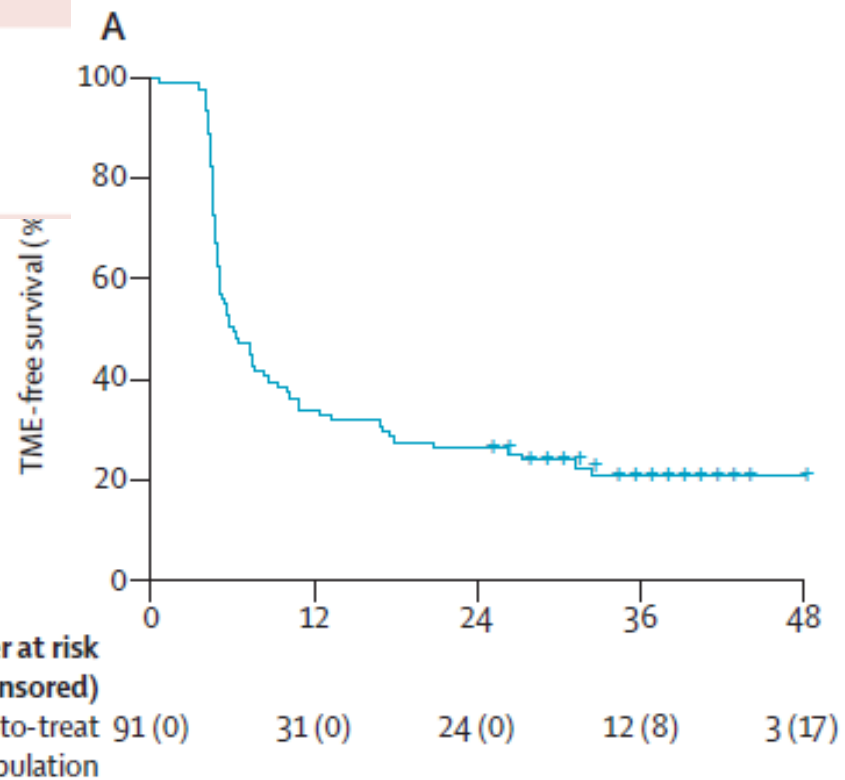
Primary endpoint: Clinical complete response rate

Simon's optimal two-stage design was used.

Non-promising if the cCR </=10% & promising if >/= 20% or higher.

First stage: 30 patients
Second stage: 89.
Type I error rate of 0·05 (one-sided), power of 80%

	Patients (n=91)
Age, years	
Mean (SD)	61 (10)
Median (IQR)	60 (52–69)
Sex	
Male	61 (67%)
Female	30 (33%)
ECOG performance status	
0	80 (88%)
1	11 (12%)
Tumour differentiation	
G1	1 (1%)
G2	83 (91%)
G3	3 (3%)
Missing data	4 (4%)
Location from anal verge	
0–6 cm	55 (60%)
>6–12 cm	36 (40%)
Clinical T category	
T2	5 (5%)
T3a	28 (31%)
T3b	27 (30%)
T3c	24 (26%)
T3d	6 (7%)
Missing data	1 (1%)
Clinical N category	
cN0	12 (13%)
cN1	34 (37%)
cN2	44 (48%)
Missing data	1 (1%)
Involvement of lateral pelvic lymph nodes on MRI imaging*	
No involvement	75 (82%)
Involvement	14 (15%)
Missing data	2 (2%)
Distance of tumour to mesorectal fascia	
≤1 mm	51 (56%)
>1 mm	38 (42%)
Missing data	2 (2%)
Extramural vascular invasion status	
Negative	62 (68%)
Minor vessels	23 (25%)
Large vessels	2 (2%)
Missing data	4 (4%)



	During chemoradiotherapy (n=91)						During consolidation chemotherapy (n=88)					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Total	21 (23%)	20 (22%)	33 (36%)	17 (19%)	0	0	0	26 (30%)	43 (49%)	17 (19%)	1 (1%)	1 (1%)
Haematological												
Leucopenia	54 (59%)	30 (33%)	7 (8%)	0	0	0	22 (25%)	37 (42%)	22 (25%)	7 (8%)	0	0
Neutropenia	79 (87%)	11 (12%)	1 (1%)	0	0	0	56 (64%)	15 (17%)	9 (10%)	7 (8%)	1 (1%)	0
Febrile neutropenia	91 (100%)	0	0	0	0	0	88 (100%)	0	0	0	0	0
Anaemia	37 (41%)	46 (51%)	7 (8%)	1 (1%)	0	0	17 (19%)	63 (72%)	8 (9%)	0	0	0
Decreased platelets	67 (74%)	23 (25%)	1 (1%)	0	0	0	38 (43%)	45 (51%)	5 (6%)	0	0	0
Gastrointestinal										0	0	0
Diarrhoea	42 (46%)	17 (19%)	23 (25%)	9 (10%)	0	0	46 (52%)	21 (24%)	18 (20%)	3 (3%)	0	0
Nausea	63 (69%)	20 (22%)	5 (5%)	2 (2%)	0	0	39 (44%)	22 (28%)	12 (15%)	2 (2%)	0	0
Vomiting	84 (92%)	6 (7%)										
Proctitis	43 (47%)	31 (34%										
Obstipation	75 (82%)	16 (18%										
Genitourinary												
Urinary frequency	59 (65%)	32 (35%										
Increased creatinine	82 (90%)	8 (9%)										
Cystitis	66 (73%)	23 (25%										
Genitourinary												
Urinary frequency	59 (65%)	32 (35%)	0	0	0	0	61 (69%)	26 (30%)	1 (1%)	0	0	0
Increased creatinine	82 (90%)	8 (9%)	1 (1%)	0	0	0	74 (84%)	14 (16%)	0	0	0	0
Cystitis	66 (73%)	23 (25%)	2 (2%)	0	0	0	70 (80%)	16 (18%)	2 (2%)	0	0	0
Other												
Pain	58 (64%)	23 (25%)	10 (11%)	0	0	0	57 (65%)	22 (25%)	8 (9%)	1 (1%)	0	0
Dyspnoea	87 (96%)	4 (4%)	0	0	0	0	77 (88%)	10 (11%)	0	1 (1%)	0	0
Infection	82 (90%)	0	3 (3%)	6 (7%)	0	0	79 (90%)	0	7 (8%)	1 (1%)	0	1 (1%)
Radiation dermatitis	66 (73%)	18 (20%)	7 (8%)	0	0	0	73 (83%)	11 (13%)	4 (5%)	0	0	0
Fatigue	50 (55%)	33 (36%)	8 (9%)	0	0	0	25 (28%)	53 (60%)	10 (11%)	0	0	0
Sensory neuropathy	62 (68%)	27 (30%)	2 (2%)	0	0	0	62 (70%)	17 (19%)	9 (10%)	0	0	0
Allergic reactions	88 (97%)	1 (1%)	1 (1%)	1 (1%)	0	0	85 (97%)	1 (1%)	2 (2%)	0	0	0

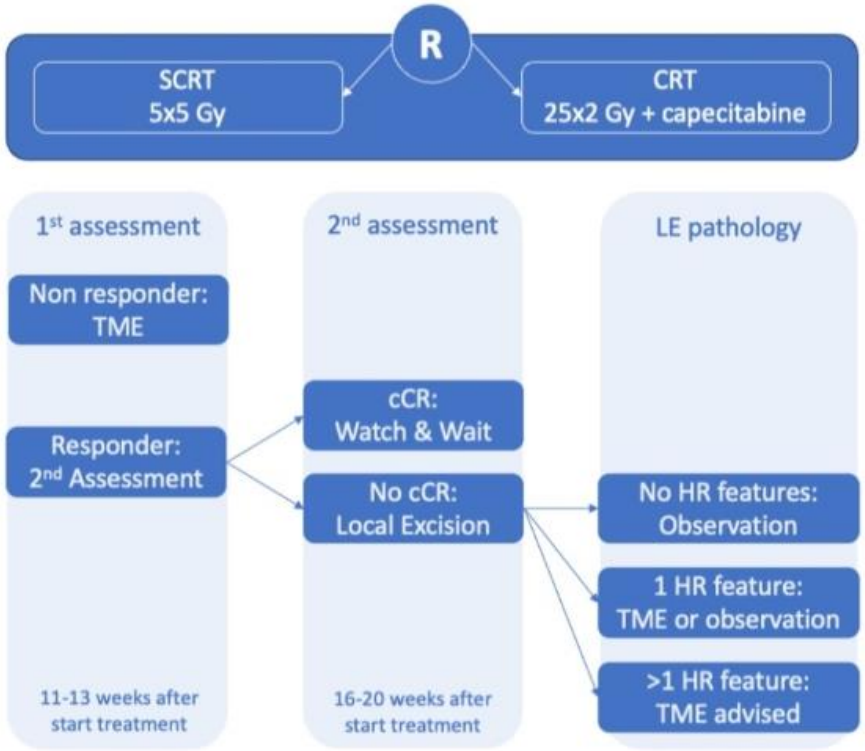
Data are n (%). The totals for each grade represent the number of patients who had that grade as their maximum grade of toxic events. Grading is by Common Terminology Criteria for Adverse Events.

ESTRO 2025

MEDIA INFORMATION

Embargoed: 00.01 hrs CEST Sunday 4 May 2025

STAR-TREC Study Shows successful Organ Preservation with Chemoradiotherapy or Short-Course Radiotherapy, Reducing the Need for Surgery in Early-Intermediate Stage Rectal Cancer Patients



To compare the effectiveness of two radiotherapy (RT) schedules in achieving organ preservation (OP)

mrT1-T3b ≤40mm in diameter N0, M0

	SCRT		CRT	
Modelled TME-Free Survival Estimate (%) at 12 months	**n=172**		**n=172**	
Phase II n=80	37.5%		81.6%	
Phase III n=264	69.0%		79.3%	
Phase II/III n=344	61.5%		79.8%	P=0.001
Treatment Status at 12 months (n | %)	**n=172**		**n=172**	
Withdrew prior to receiving treatment	3	1.7%	5	2.9%
W&W	47	27.3%	98	57.0%
LE Only	58	33.7%	36	20.9%
LE + TME	19	11.1%	6	3.5%
TME Only	45	26.2%	27	15.7%
Type of TME performed (n | %)	**n=64**		**n=33**	
Primary as part of initial treatment (without previous LE)	42	62.6%	25	75.8%
Conversion as part of initial treatment	17	26.6%	6	18.2%
Salvage for recurrence or regrowth	5	7.8%	2	6.0%
Type of resection performed (n | %)	**n=64**		**n=33**	
Low anterior resection	35	54.7%	16	48.5%
Low Hartmann's	1	1.6%	0	0%
Abdomino-perineal resection	26	40.6%	17	51.5%
Beyond TME	2	3.1%	0	0%