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NON-SURGICAL MANAGEMENT OF EARLY STAGE RECTAL CANCER

Joleen Hubbard, MD

Associate Professor Medical Oncology

GI Medical Oncology, Mayo Clinic Rochester, MN

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WHAT IS NON-SURGICAL MANAGEMENT OF RECTAL CANCER?

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- Accurately identifying patients who have had a complete clinical response to neoadjuvant therapy
- Following a surveillance protocol to identify recurrences early so that survival is not compromised
- Other names:
  - Non-operative management
  - Watch-and-Wait strategy

DEFINITION OF COMPLETE CLINICAL RESPONSE (cCR)

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- No evidence of disease after neoadjuvant therapy
  - **Digital rectal exam (DRE)**
    - Flat mucosa without mass or nodularity
  - **Endoscopy**
    - Flat white scar with or without telangiectasias and lack of ulceration or nodularity
  - **MRI**
    - No detectable tumour or lymph node

cCR, complete clinical response; MRI, magnetic resonance imaging
Smith JJ et al. BMC Cancer 2015;15:767

THE HISTORY OF THE ‘WATCH-AND-WAIT’ STRATEGY

PIVOTAL STUDY: HABR-GAMA 2004

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- Published a study reporting a 'watch-and-wait' (W&W) approach
  - Retrospective study of from 1991-2002: 93 patients (71 with cCR and 22 with pCR at surgery)
    - 80% with T3/T4 lesions
    - 22.5% with node + disease
  - 27% cCR to neoadjuvant therapy
  - 3% local recurrence rate
  - 4% distal recurrence rate
  - 92% DFS at 5 years
  - 100% OS at 5 years
- Suggested W&W may be a feasible approach for patients
- **Since then, there have been multiple W&W strategy studies published**
- **A review of several prospective studies follows…**

cCR, clinical complete response; DFS, disease-free survival; Gy, gray; OS, overall survival; pCR, pathologic complete response; T, tumour; W&W, watch-and-wait

Habr-Gama A et al. Ann Surg 2004;240(4):711-7

MAASTRICHT UNIVERSITY STUDY

- **100 patients with cCR or near cCR**
  - 85 patients → NOM
  - 15 patients underwent TEM
- Median follow-up = 3.4 years
- **3-year OS = 97%**
- **3-year DMFS = 97%**

cCR, clinical complete response; DMFS, distant metastases-free survival; NOM, non-operative management; OS, overall survival; TEM, transanal endoscopic microsurgery

Martens MH et al. JNCI 2016;108(12):1-10

DANISH PROSPECTIVE STUDY: HIGH-DOSE CRT

- **55 patients with distal rectal cancer, cT2-3, N0-1**
- IMRT 60 Gy/30 fx to tumour, 50 Gy/30 fx to pelvis + concurrent oral tegafur-uracil
- Endorectal brachytherapy boost: 5 Gy
- 6 weeks post-CRT: endoscopy + MRI
- **78% cCR observed**
  - 2-year LR = 26%
  - All salvaged with R0 surgery
  - No increase in surgical complications
- **Low rate (<10%) G3+ acute/late toxicity**

cCR, complete clinical response; CRT, chemoradiation; cT, clinical tumour stage; fx, fractions; G, grade; Gy, gray; IMRT, intensity-modulated radiotherapy; LR, local recurrence; MRI, magnetic resonance imaging; N, node; R, residual tumour

Appelt AL et al. Lancet Oncol 2015;16:919-27

HABR-GAMA PROSPECTIVE STUDY

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- **70 patients with T2-4 N0-2M0 distal rectal cancer**
- Neoadjuvant chemoradiotherapy included 54 Gy and 5FU/LV delivered in 6 cycles every 21 days
- **47 (68%) patients had initial cCR**
  - 27% local recurrence
  - most (17%) within first 12 months
  - 4 patients (10%) >12 months of follow-up
- **35 patients (50%) avoided surgery**
- **3-year OS = 90%**

5FU, fluorouracil; cCR, complete clinical response; Gy, gray; M, metastasis; LV, leucovorin; N, node; OS, overall survival; T, tumour
Habr-Gama A et al. Dis Colon Rectum 2013;56(10):1109-17

NOM SYSTEMATIC REVIEW

- **Pooled data from 23 studies, 867 patients with rectal adenocarcinoma managed by W&W after cCR to neoadjuvant chemoradiation**
- **2-year local recurrence rate: 15.7%**
  - 95% had salvage surgeries
- **NOM vs. surgery with cCR or pCR**
  - No difference in OS or cancer-specific mortality

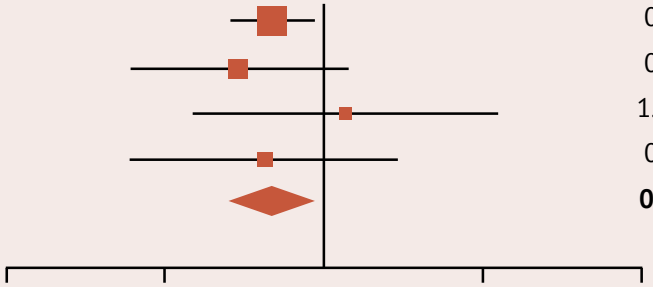
cCR, complete clinical response; NOM, non-operative management; OS, overall survival; pCR, pathologic complete response; W&W, watch-and-wait
Dossa F et al. Lancet Gastroenterol Hepatol 2017;2:501-13

SURGERY WITH PCR VS CCR MANAGED BY W&W

A. Disease-free survival for patients treated by surgery with pCR vs W&W

	W&W		Surgery with pCR		Weight (%)	HR IV, random (95% CI)
	Events	Total	Events	Total		
Araujo et al (2015)	23	42	22	69	77.4	0.47 (0.26-0.84)
Smith et al (2012)	N/A	32	N/A	57	10.1	0.29 (0.06-1.43)
Maas et al (2011)	1	21	4	20	5.5	1.39 (0.15-12.41)
Smith et al (2015)	2	18	2	30	6.9	0.42 (0.06-2.98)
Total		**113**		**176**	**100**	**0.47 (0.28-0.78)**

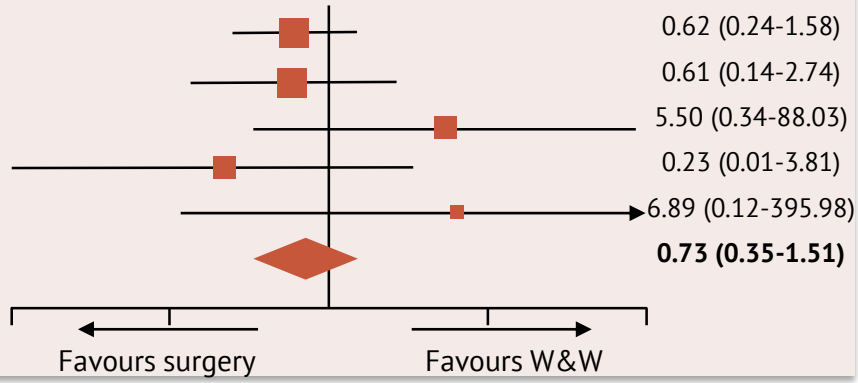
Heterogeneity: τ^2=0.00; X^2=1.31, DF=3 (p=0.73);I^2=0%
Test for overall effect: Z=2.89, p=0.004



B. Overall survival for patients treated by surgery with pCR vs W&W

	W&W		Surgery with pCR		Weight (%)	HR IV, random (95% CI)
	Events	Total	Events	Total		
Araujo et al (2015)	8	42	10	69	59.6	0.62 (0.24-1.58)
Smith et al (2012)	N/A	32	N/A	57	23.5	0.61 (0.14-2.74)
Maas et al (2011)	0	21	2	20	6.9	5.50 (0.34-88.03)
Gossedge et al (2012)	1	15	1	13	6.8	0.23 (0.01-3.81)
Smith et al (2015)	0	18	1	30	3.3	6.89 (0.12-395.98)
Total		**128**		**189**	**100**	**0.73 (0.35-1.51)**

Heterogeneity: τ^2=0.01; X^2=4.03, DF=4 (p=0.40);I^2=1%
Test for overall effect: Z=0.85, p=0.40



cCR, complete clinical response; CI, confidence interval; DF, degrees of freedom; HR, hazard ratio; IV, inverse variance; pCR, pathologic complete response; W&W, watch-and-wait.

Dossa F et al. Lancet Gastroenterol Hepatol 2017;2:501-13

AMONG THOSE WITH cCR, SURGERY VS W&W

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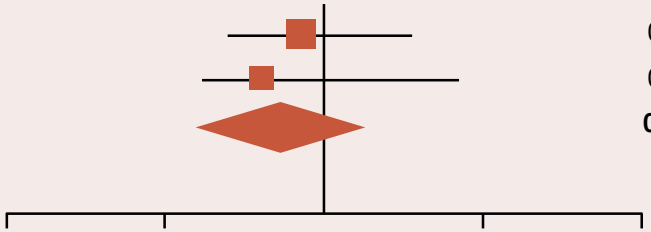
A. Disease-free survival for patients treated by surgery with cCR vs W&W

	W&W		Surgery with cCR		Weight (%)	HR IV, random (95% CI)
	Events	Total	Events	Total		
Li et al (2015)	3	30	10	92	65.6	0.65 (0.18-2.36)
Lai et al (2016)	2	18	3	26	34.4	0.43 (0.07-2.56)
Total	**5**	**48**	**13**	**118**	**100**	**0.56 (0.20-1.60)**

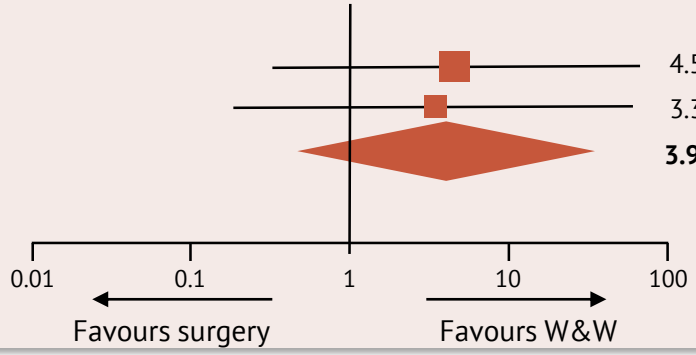
Heterogeneity: τ^2=0.00; X^2=0.13, DF=1 (p=0.71);I^2=0%
Test for overall effect: Z=1.08, p=0.28



B. Overall survival for patients treated by surgery with cCR vs W&W

	W&W		Surgery with cCR		Weight (%)	HR IV, random (95% CI)
	Events	Total	Events	Total		
Li et al (2015)	0	30	3	92	53.5	4.50 (0.33-62.28)
Lai et al (2016)	2	18	3	26	46.5	3.33 (0.20-55.69)
Total	**2**	**48**	**6**	**118**	**100**	**3.91 (0.57-26.72)**

Heterogeneity: τ^2=0.00; X^2=0.02, DF=1 (p=0.88);I^2=0%
Test for overall effect: Z=1.39, p=0.16



cCR, complete clinical response; CI, confidence interval; DF, degrees of freedom; HR, hazard ratio; IV, inverse variance; W&W, watch-and-wait.
Dossa F et al. Lancet Gastroenterol Hepatol 2017;2:501-13

SUMMARY OF NOM RECTAL CANCER STUDIES

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Study	No.	cT3-4 (%)	cN+ (%)	CRT	cCR (%)	F/u (y)	LR (%)	OS (%)
Prospective studies								
Maastricht, Netherlands	21	71	71	50.4 Gy + cape	11	2.1	5	100 (2y)
	100	75	74	50.4 Gy + cape	---	3.4	15	97 (3y)
Sao Paulo, Brazil	70	71	39	54 Gy + 5FU/LV → 5FU/LV	68	4.7	27	90 (3y)
Denmark	40	47	45	60 Gy + 5 Gy brachy + tegafur-uracil	78	2.0	26 (2y)	100 (2y)
Retrospective studies								
Sao Paulo, Brazil	99	82	28	50.4 Gy + 5FU	27	5.0	6	93 (5y)
MSKCC, USA	113	80	66	45–54 Gy + FP +/- FOLFOX	11	3.6	21 (5y)	73% (5y) 90% DSS
Manchester, UK	129	76	65	45 Gy + cape	---	2.8	38 (3y)	96 (3y)
IWWD	880	54	50	---	---	3.3	25 (2y)	85 (5y)

5FU, fluororouracil; brachy, brachytherapy; cape, capecitabine; cCR, complete clinical response; cN, clinical lymph node stage; CRT, chemoradiation therapy; cT, clinical tumour stage; DSS, disease-specific survival; FOLFOX, folinic acid, fluorouracil and oxaliplatin; F/u, follow-up; Gy, gray; IWWD, International Watch and Wait Database; LR, local recurrence; LV, leucovorin; MSKCC, Memorial Sloan Kettering Cancer Center; NOM, non-operative management; OS, overall survival; y, year

Habr-Gama A et al. J Gastrointest Surg 2006 Dec;10(10):1319-28; Smith JJ et al. JAMA Oncology 2019;5(4):e185896; Maas M et al. J Clin Oncol 2011;29:4633-40; Martens MH et al. JNCI 2016;108(12):1-10; Habr-Gama A et al. Dis Colon Rectum 2013;56(10):1109-17; Appelt AL et al. Lancet Oncol 2015;16:919-27; Renehan AG et al. Lancet Oncol 2016;17:174-83; van der Valk M et al. Lancet 2018;391(10139):2537-45

MSKCC STUDY LONG-TERM FOLLOW-UP

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- Rectal cancer patients (N=1070) who underwent neoadjuvant therapy (diagnosed from 1/1/06 to 1/31/15)

	cCR → W&W	TME with pCR
n	113 (11%)	136 (13%)
Median age	67	57
Median distance from anal verge	5.5 cm	7.0 cm
5-year DFS	75%	92%
5-year OS	73%	94%
DSS	90%	98%
Distant metastases	8%	4%

cCR, complete clinical response; DFS, disease-free survival; DSS, disease-specific survival; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; pCR, pathologic complete response; TME, total mesorectal excision; W&W, watch-and-wait
Smith JJ et al. JAMA Oncology 2019;5(4):e185896

MSKCC STUDY LONG-TERM FOLLOW-UP

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- **22 patients (20%) in the W&W group had local regrowth**
  - Median time to regrowth 11.2 months
  - All had salvage surgery
  - 20 (91%) of patients remained free of pelvic disease
- 5-year rectal preservation rate with W&W was 79%
- **Among W&W patients who experienced local regrowth, distant metastases 36% vs. 1% who did not**
  - Difference in disease biology?

MSKCC, Memorial Sloan Kettering Cancer Center; W&W, watch-and-wait
Smith JJ et al. JAMA Oncology 2019;5(4):e185896

WHAT IS THE APPROPRIATE FOLLOW-UP FOR PATIENTS WITH A cCR?

	Years
Every 3 months	1
Every 4 months	2
Every 6 months	3-5
Every 12 months	5+

cCR, complete clinical response
Smith JJ et al. ASCO GI 2015 (Abstract 509)

IMPORTANT POINTS ON cCR

- Does NOT equal pCR
- As pCR improves, it is likely more patients will be identified with a cCR
- The trend toward moving more therapy upfront (as in the TNT approach) may lead to more patients with a cCR

cCR, complete clinical response; pCR, pathologic complete response; TNT, total neoadjuvant therapy

SURVIVAL FOR RECTAL CANCER WITH STANDARD OF CARE

	5 years (N=421)	10 years (N=404)
OS	76%	59.6%
Local relapse	6%	7.1%
Distant metastases	36%	29.8%

- Total TNT approach has also become an option:

Chemo, chemotherapy; OS, overall survival; rads, radiotherapy; TNT, total neoadjuvant therapy

Cercek A et al. JAMA Oncology 2018;4(6):e180071; Sauer R et al. NEJM 2004; 351:1731-40; Sauer R et al. JCO 2012;30(16):1926-33

TNT APPROACH

- A single-institution retrospective analysis
  - T3/4 or node-positive rectal cancer

	Traditional CRT (n= 320)	TNT (n = 308)
CR	21%	36%

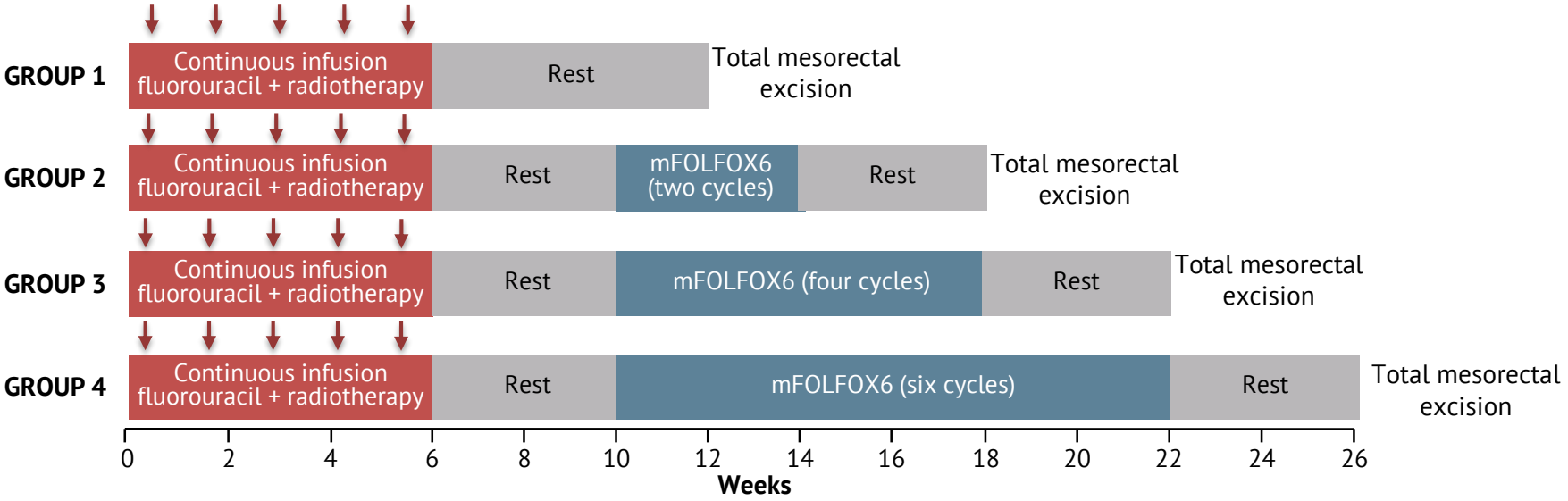
- CR = pCR or cCR for 12+ months
- Patients in the TNT group received a greater percentage of the planned chemotherapy dose vs. the CRT with adjuvant chemotherapy group

CR, complete response; cCR, complete clinical response; CRT, chemoradiotherapy; pCR, pathologic complete response; T, tumour; TNT, total neoadjuvant therapy

Cercek A et al. JAMA Oncology 2018;4(6):e180071

SURGERY TIMING STUDY

- Non-randomised Phase 2 Trial, Stage 2 and 3 rectal cancer



Outcome	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)
Sphincter-sparing surgery	77%	75%	75%	68%
pCR	18%	25%	30%	38%

mFOLFOX6, folinic acid, fluorouracil and oxaliplatin; pCR, pathological complete response

Garcia-Aguilar J et al. Lancet Oncol 2015;16:957-66

NOM FOR RECTAL CANCER: SUMMARY

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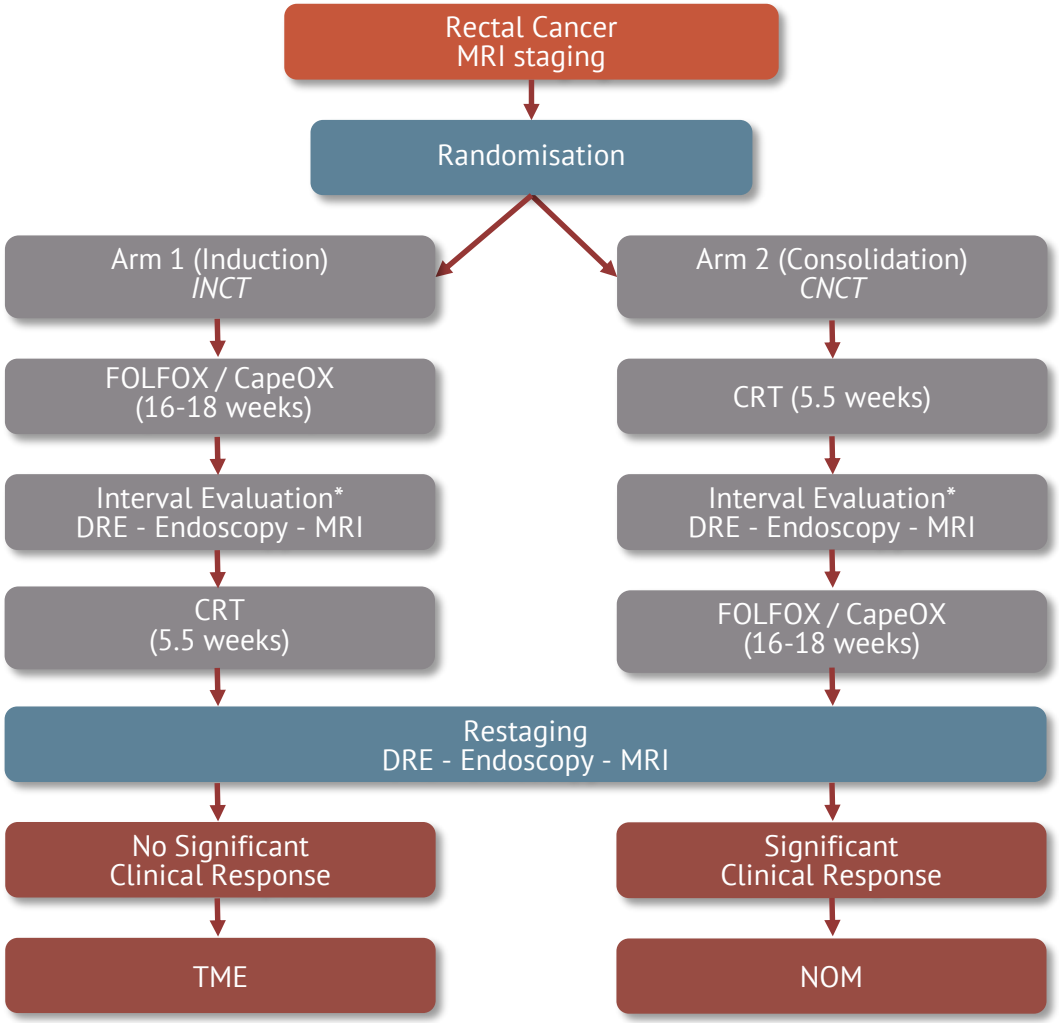
- **cCR rates: vary depending on approach**
  - Traditional NAT, 21%
  - Possibly higher with TNT approach
- **With NOM: approximate 25% local recurrence**
- **95% can be salvaged with TME**
- **Short-term survival does not appear to be compromised**
  - More data on long-term survival needed

cCR, complete clinical response; NAT, neoadjuvant therapy; NOM, non-operative management; TME, total mesorectal excision; TNT, total neoadjuvant therapy

Cercek A et al. JAMA Oncology 2018;4(6):e180071

ONGOING STUDIES

US NOM MULTI-CENTER PHASE II TRIAL



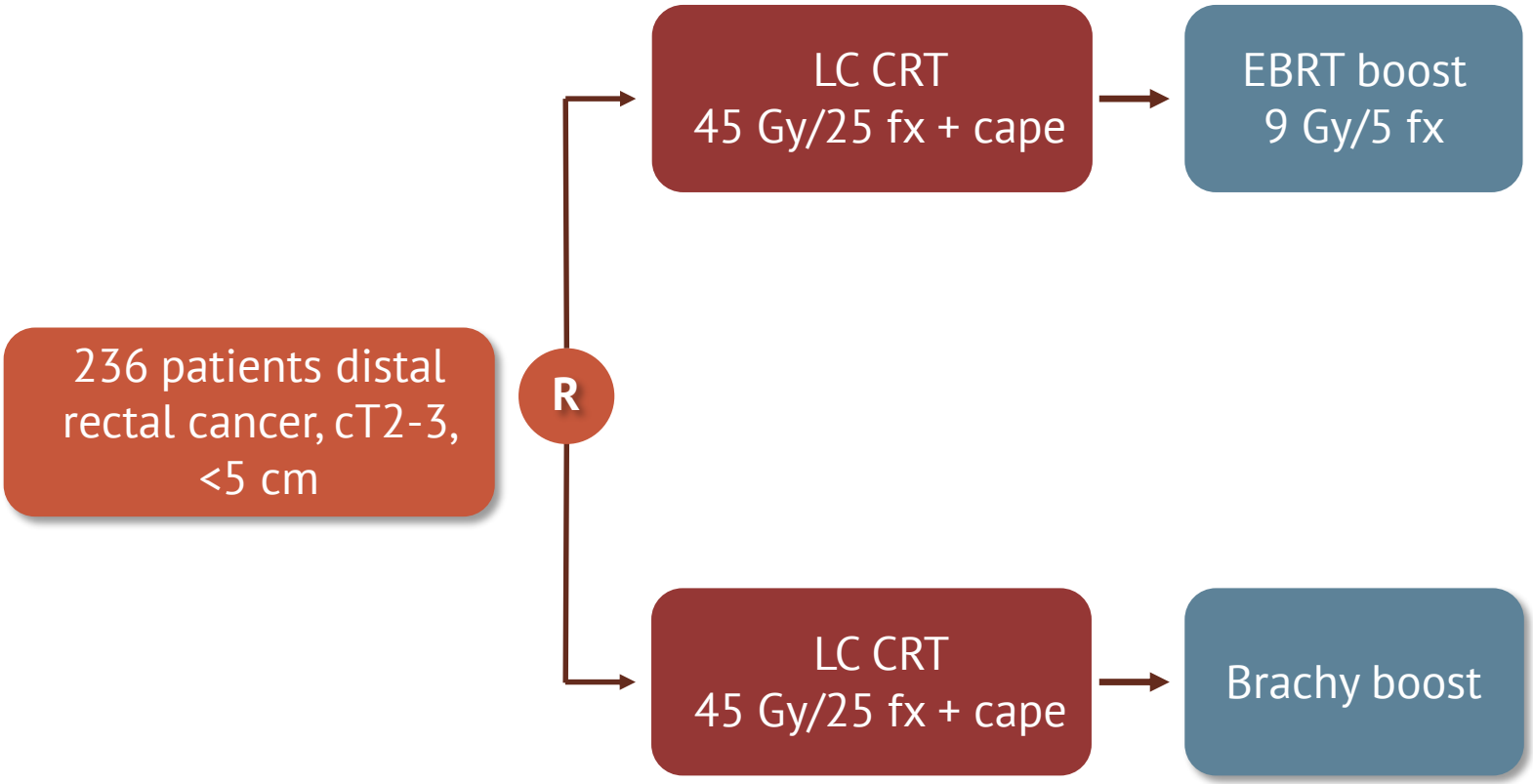
- Stage II-III rectal cancer
- N=202
- EBRT: 56 Gy/28 fx
- Primary endpoint: 3 years DFS
- Arm considered promising if 3-year DFS ≥ 85%

*Patients with tumour progression at the interval evaluation will be treated according to standard of care

CapeOX, oxaliplatin and capecitabine; CNCT, consolidation neoadjuvant chemotherapy; CRT, chemoradiation therapy; DFS, disease-free survival; DRE, digital rectal examination; EBRT, external beam radiotherapy; FOLFOX, folinic acid, fluorouracil and oxaliplatin; fx, fractions; Gy, gray; INCT, induction neoadjuvant chemotherapy; MRI, magnetic resonance imaging; NOM, non-operative management; TME, total mesorectal excision

Smith JJ et al. BMC Cancer 2015;15:767

TRIGGER: EUROPEAN NOM MULTI-CENTER PHASE III TRIAL



Phase III Study objectives:

- Primary objective is to compare 3-year DFS in the control arm vs the mrTRG-directed management arm
- OS, CFS, DR and LR in the control arm vs the mrTRG-directed management arm, and tumour regrowth rates in patients treated with deferral of surgery

Brachy, brachytherapy; cape, capecitabine; CFS, colostomy-free survival; cT, clinical tumour stage; DFS, disease-free survival; DR, distant recurrence; EBRT, external beam radiotherapy; fx, fractions; Gy, gray; LC CRT, long-course chemoradiation therapy; LR, local recurrence; mrTRG, magnetic resonance tumour regression grade; NOM, non-operative management; R, randomisation; OS, overall survival

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576102/

https://clinicaltrials.gov/ct2/show/NCT02704520

IS NON-OPERATIVE MANAGEMENT OR WATCH-AND-WAIT STRATEGY APPROPRIATE FOR OUR PATIENTS?

There are varying opinions!

NCCN GUIDELINES V2 2019

- For patients who achieve a cCR
  - **DRE, rectal MRI, and endoscopic evaluation**
- A watch-and-wait, non-operative management approach may be considered **in centres 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 characterised
- Decisions for non-operative management should involve **a careful discussion with the patient of his/her risk tolerance**

cCR, complete clinical response; DRE, digital rectal examination; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network
https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

WHAT PATIENTS WOULD BE APPROPRIATE FOR NOM STRATEGY?

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- **cCR – determined at a tertiary care centre**
  - DRE, MRI, endoscopy
- Patients who are **not candidates for a sphincter preserving operation**
  - For those who will not end up with a permanent ostomy, not worth the risk
- Patients at **high risk for morbidity/mortality from any surgical resection**
- Patients who **will be compliant with a strict surveillance schedule**
- Patients who are **well informed, willing to accept unknown risks**

cCR, complete clinical response; DRE, digital rectal examination; MRI, magnetic resonance imaging; NOM, non-operative management

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antoine.lacombe@cor2ed.com

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GI CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com