



ORGAN PRESERVATION IN RECTAL CANCER: REVIEW OF RECENT EVIDENCE TO WAIT AND WATCH

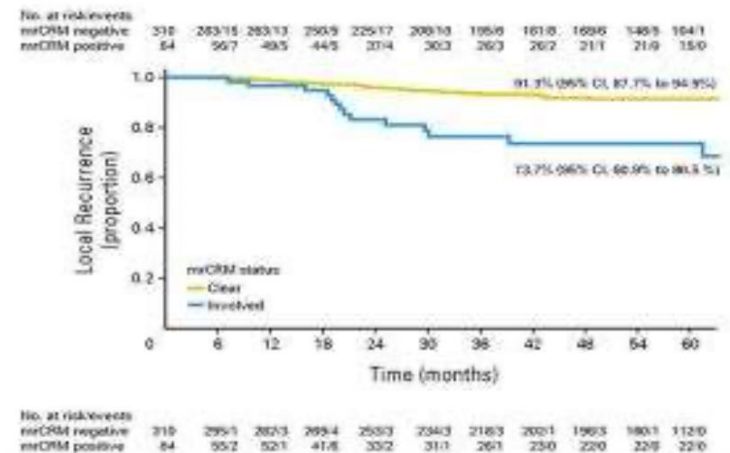
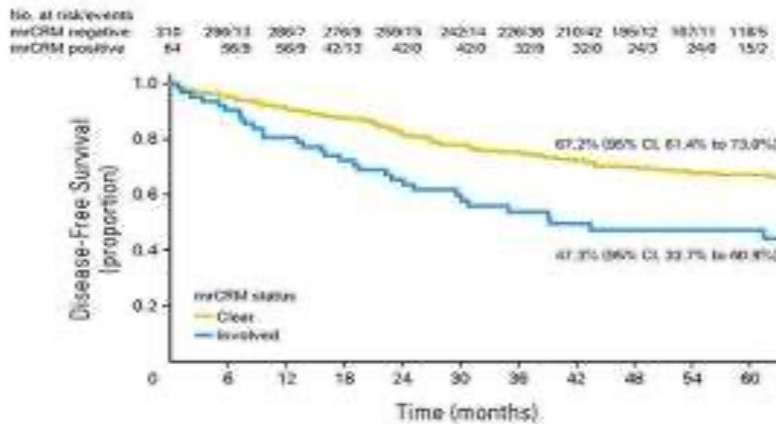
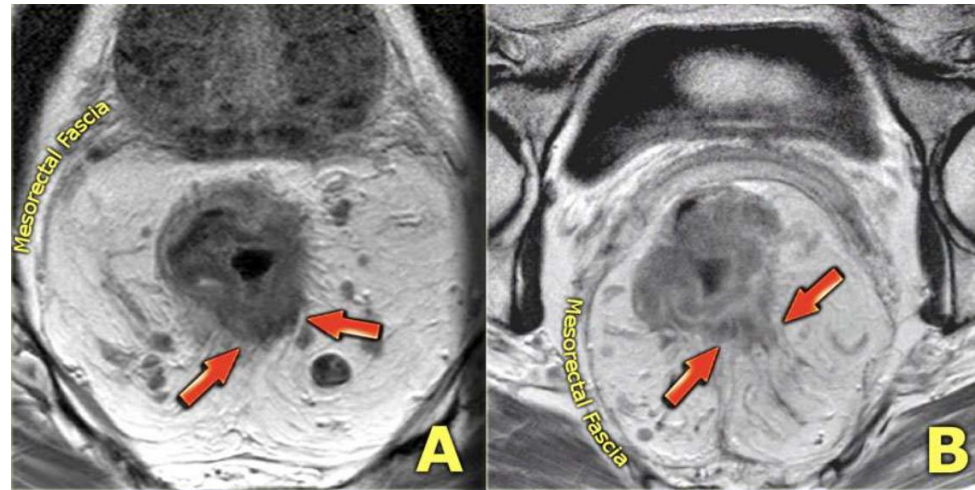


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BEYOND CONTROVERSIES: RECTAL CANCERS

- **MRI as a staging tool in rectal cancers**
 - **MERCURY Trial (JCO 2014)**
 - **Identify patients with potentially involved CRM (≤ 1 mm)**
 - **Prognostic (5-year OS 62.2% vs. 42.2%)**

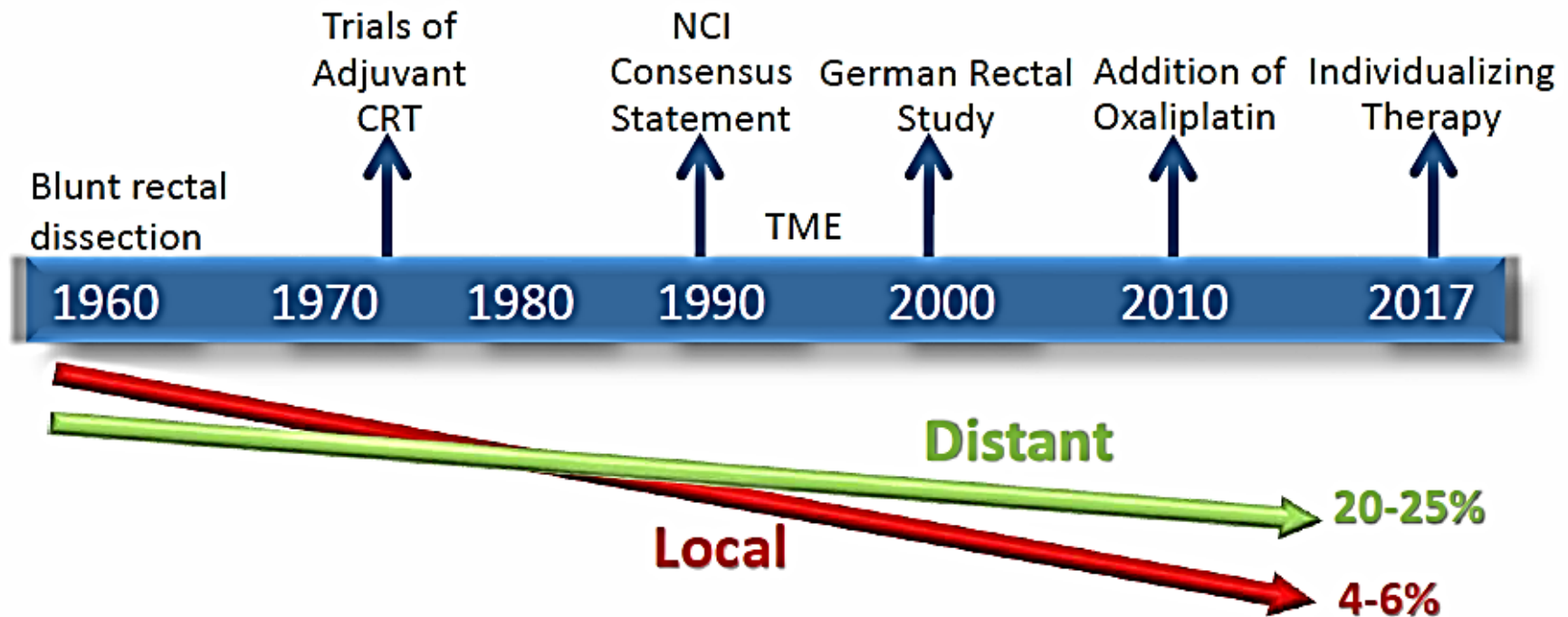


BEYOND CONTROVERSIES: RECTAL CANCERS

- Neo-adjuvant/adjuvant therapies have become engraved in the management of rectal cancers
 - T1-2N0M0: Local Failure rates <10%
 - T3N0M0, T1N1M0: LFR 15-35%
 - T3-4N1-2M0: LFR 45-65%
- 1990 NCI Consensus statement
 - “Combined postoperative chemotherapy and radiation therapy improves local control and survival in stage II/III rectal cancer patients and is recommended”
- Advances over last two decades
 - TME and improvement in surgical techniques
 - Adaptation of neo-adjuvant therapies versus post-operative therapy
 - Advances in radiation planning and delivery
 - Long term morbidities of intensified treatment approaches



EVOLUTION AND CHALLENGES: RECTAL CANCER (2019)



PARADOX

DE-ESCALATION/INTENSIFICATION/INDIVIDUALIZATION



RECTAL CANCERS: CURRENT PARADIGM

Approximately 28-29 thousand incident cases of rectal cancer in India every year [GLOBOCAN 2020]

Current treatment paradigm for patients with stage II or III rectal cancer is concurrent chemotherapy and radiation therapy (CRT) followed by total mesorectal excision.

Typical transabdominal procedures for locally advanced rectal cancer include low anterior resection for mid- and upper-rectum adenocarcinomas or abdominopelvic resection for distal rectal adenocarcinomas with anal sphincter involvement, poor presurgical anorectal function, or inability to achieve a negative distal margin with sphincter-sparing surgery

5-year overall survival (OS) rate for stage II and III rectal cancer is 76%, and the cumulative incidence rate of local and distant recurrences at 5 years is 6% and 36%, respectively



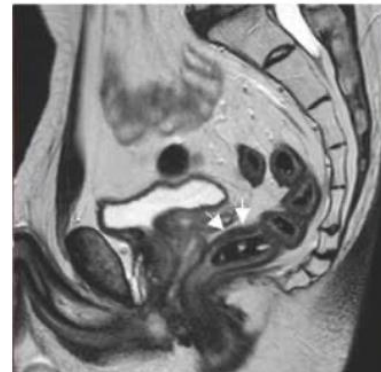
CLINICAL OUTCOME AND CHALLENGES WITH TRIMODALITY THERAPY

- The standard preoperative CRT approach yields approximately a 15% to 27% pathologic complete response (pCR) rate [N Engl J Med 351:1731-1740, 2004]
- Patients who achieve a pCR after preoperative CRT have a significantly lower local recurrence (0.7% v 2.6%) and better 5-year OS rate (92.9% v 73.4%) compared with no response or partial pathologic response [Lancet Oncol 11:835-844, 2010]
- Radical resection is associated with significant toxicity:
 - Surgical complications in ~30%
 - Per-op mortality up to 3%
 - Permanent or temporary stoma
 - Impaired bowel function
 - Late complications: Bowel obstruction, incisional hernia, Urinary incontinence, Sexual dysfunction etc.



NON-OPERATIVE MANAGEMENT OF LARC

- Can surgery be avoided in the settings of complete clinical response to pre-operative treatment in LARC?
- How often do you encounter requests of non-operative management from your patients?
- Have you treated/Do you offer this to your patients outside a clinical trial?



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

Long-term Results

(*Ann Surg* 2004;240: 309–316)

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,‡*

- 265 patients with resectable distal rectal adenocarcinoma treated with 5-FU-leucovorin and concurrent radiotherapy.
- Patients who had cCR defined as normal on digital rectal examination, no residual ulcer per proctoscopy and negative biopsy results, and no evidence of disease per radiographic imaging were considered for a nonsurgical watch-and-wait approach.
- Patients who achieved cCR (n=71 [26.8%]) underwent clinical observation, and patients without cCR (n=194 [73.2%]) were referred for radical surgical resection.
- Of note, 22 patients (8.3%) who did not achieve cCR and initially underwent surgical resection were found to have pCR in surgical specimens.
- The 5-year OS and DFS rates were 100% and 92%, respectively, for patients who underwent observation (n=71) v 88% and 83% for patients who underwent surgery and had achieved pCR (n=22).
- Overall recurrence and cancer-related mortality rates were 7.0% and 0%, respectively, in the nonsurgical group v 13.6% and 9% in the surgical group, respectively.
- Of the patients in the nonsurgical group, two of five had local-only recurrence and were able to undergo salvage resection.



Patterns of Failure and Survival for Nonoperative Treatment of Stage c0 Distal Rectal Cancer Following Neoadjuvant Chemoradiation Therapy

Angelita Habr-Gama, M.D., Ph.D., Rodrigo O. Perez, M.D., Igor Proscurschim, M.S., Fabio G. Campos, M.D., Ph.D., Wladimir Nadalin, M.D., Ph.D., Desiderio Kiss, M.D., Ph.D., Joaquim Gama-Rodrigues, M.D., Ph.D.

J Gastrointestinal Surgery; 2006

Patients with distal rectal

361 patients, 99 with clinical CR (27%)

adenocarcinoma, located 0-7 cm from the anal verge

Mean followup: 60 months

Local recurrence: 5%

4 surgical salvage

1 brachytherapy salvage

No subsequent recurrence

Mean interval to recurrence: 52 months

Patients with complete tumour regression sustained for at least 12 months were considered stage c0 and were included in the study

Pelvic recurrence: 0%

Distant metastasis: 8%

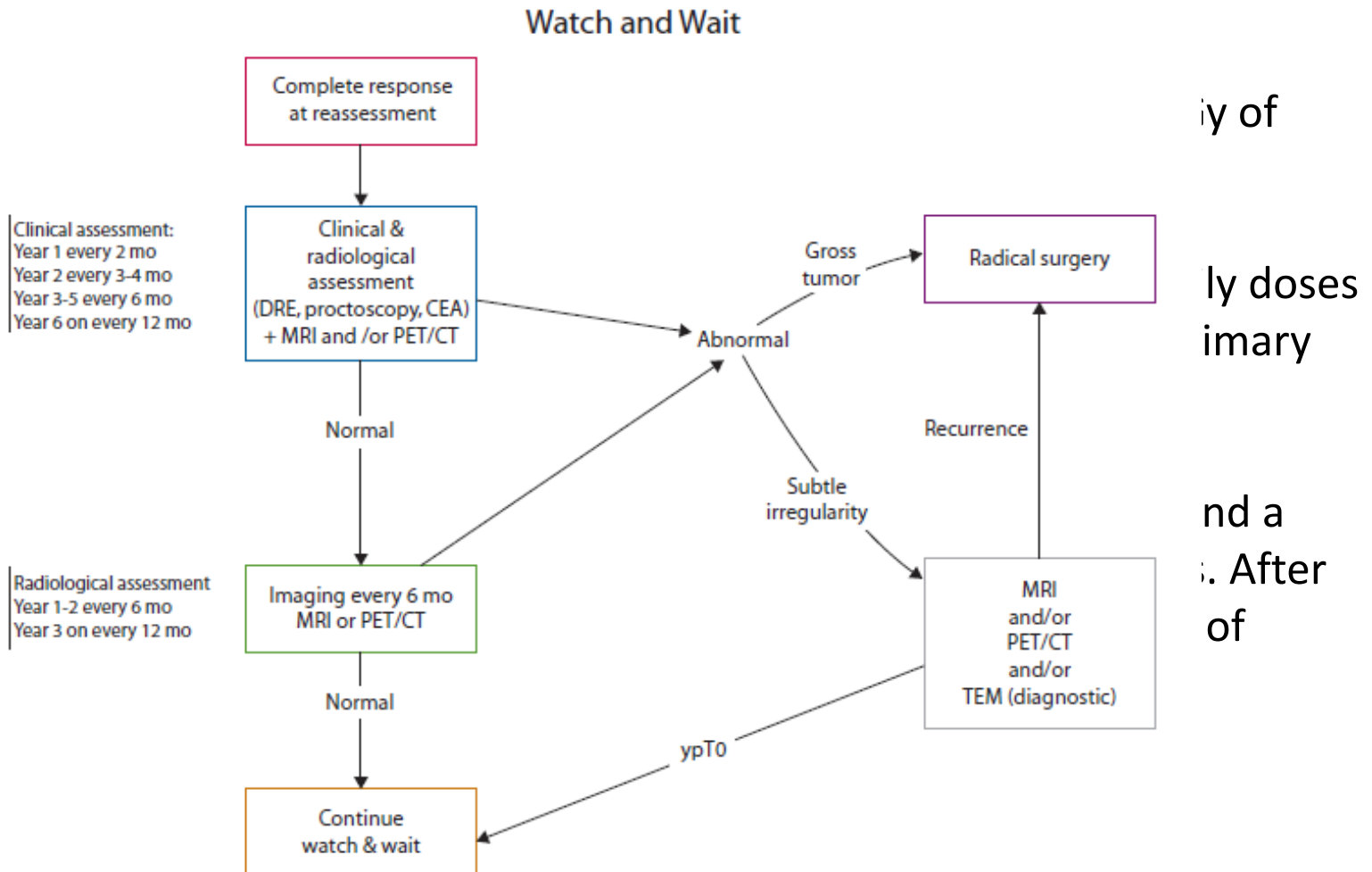
5-year OS: 93%

Watch and Wait Approach Following Extended Neoadjuvant Chemoradiation for Distal Rectal Cancer: Are We Getting Closer to Anal Cancer Management?

Dis Colon Rectum 2013; 56: 1109–1117

Angelita Habr-Gama, M.D., Ph.D.¹ • Jorge Sabbaga, M.D., Ph.D.^{1,2}

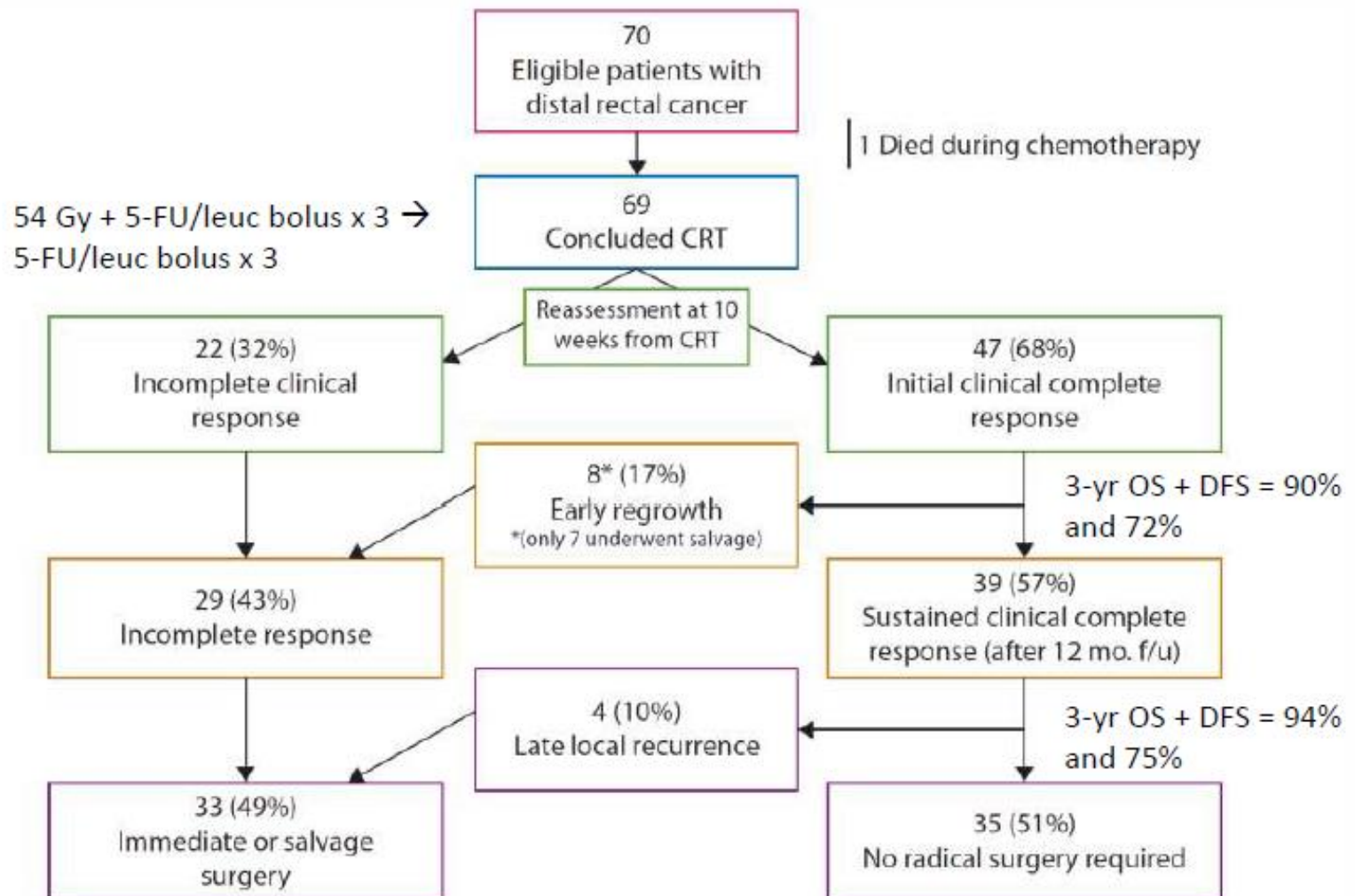
- All patients receive extended neoadjuvant chemoradiation
- In brief, patients receive 5-FU, leucovorin, and oxaliplatin (FLOX) for 1.8 months
- Concurrently with chemotherapy, patients receive 45 Gy of radiation
- Concurrently with radiation, patients receive capecitabine
- Concurrently with chemotherapy and radiation, patients receive capecitabine
- Concurrently with chemotherapy, radiation, and capecitabine, patients receive oxaliplatin
- Concurrently with chemotherapy, radiation, capecitabine, and oxaliplatin, patients receive leucovorin
- Concurrently with chemotherapy, radiation, capecitabine, oxaliplatin, and leucovorin, patients receive 5-FU
- Concurrently with chemotherapy, radiation, capecitabine, oxaliplatin, leucovorin, and 5-FU, patients receive FLOX
- Concurrently with chemotherapy, radiation, capecitabine, oxaliplatin, leucovorin, 5-FU, and FLOX, patients receive extended neoadjuvant chemoradiation
- Concurrently with chemotherapy, radiation, capecitabine, oxaliplatin, leucovorin, 5-FU, FLOX, and extended neoadjuvant chemoradiation, patients receive watch and wait



Watch and Wait Approach Following Extended Neoadjuvant Chemoradiation for Distal Rectal Cancer: Are We Getting Closer to Anal Cancer Management?

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Summary of studies: Nonsurgical vs. Surgical

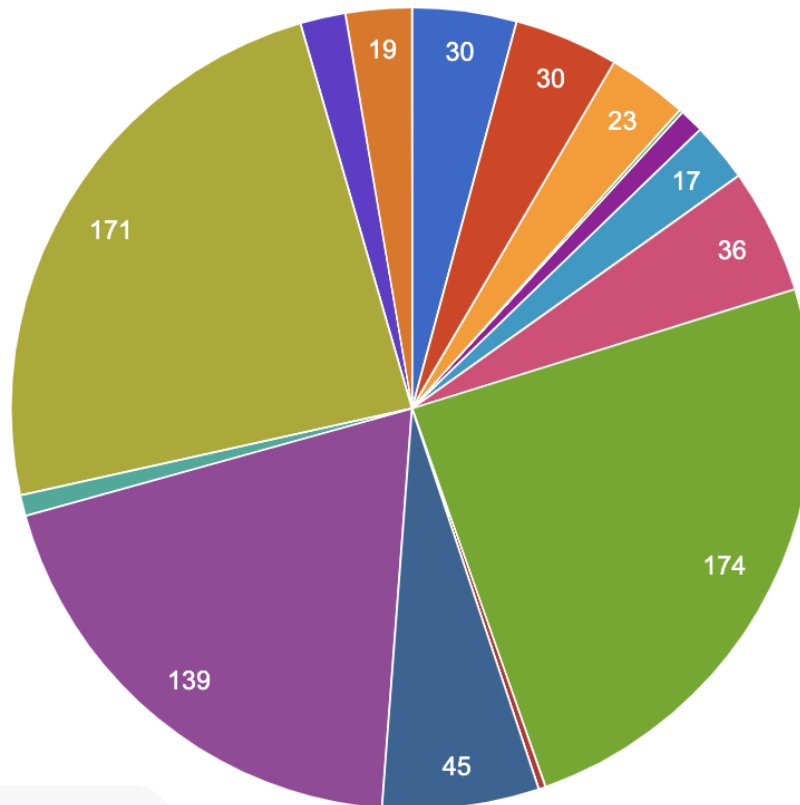
Nonsurgical v Surgical						
First Author	No. of Patients	Mean Follow-Up, months	Local Recurrence Rate, %	Distant Recurrence Rate, %	DFS Rate, %	OS Rate, %
Habr-Gama ¹³	71 v 22	57.3 v 48	2.8	4.1 v 13.6	92 v 83 (5 year)	100 v 88 (5 year)
Maas ¹⁴	21 v 20	25 v 35	4.7 v 0	0 v 5	89 v 93 (2 year)	100 v 91 (2 year)
Dalton ^{17*}	6 v 6	25.5 v NA	0 v 33.3	0 v 33.3	100 v NA	100 v NA
Smith ²⁰	32 v 57	28 v 43	18.7 v 0	9.4 v 5.2	88 v 98 (2 year)	96 v 100 (2 year)
Smith ¹⁸	18 v 30	68.4 v 46.3	5.6 v 0	5.6 v 3.3	NA	NA
Li ¹⁵	30 v 92	59 v 58	6.7 v 2.2	3.3 v 5.4	90 v 94.3	100 v 95.6
Araujo ²¹	42 v 69	47.7	11.9 v 1.4	9.5 v 10.1	60.9 v 82.8	71.6 v 89.9 (5 year)
Lai ¹⁶	18 v 26	49.9	11.1	0 v 3.8	NA	100 v 92.3
van der Valk ^{22†}	880	39	25.2	8	NA	84.7 (5 year)



International Watch & Wait database



Champalimaud
Foundation



- Amsterdam (MKI/AvL)
- Buenos aires (Hospital Italiano)
- Buenos aires (Instituto Alexander Fleming)
- Eindhoven (Catharina Ziekenhuis)
- Fortaleza (Universidade Federal)
- Leuven (UZ Gasthuisberg)
- Lisboa (Champalimaud Foundation)
- Maastricht (MUMC+)
- Moscow (N.N. Blokhin Russian Cancer Research Center)
- Nice (Centre Antoine-Lacassagne)
- OnCoRe (North West England) project
- RHYL (Glan Clwyd Hospital)
- São Paulo (Instituto A. e J. Gama)
- Stockholm (Karolinska University)
- Warszawa (MSC Memorial Cancer Center)

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study



**Lancet 2018; 391:
2537–45**

*Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Geerard L Beets, Nuno L Figueiredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium**

- 1009 patients (2015-2017)
- 880 patients (87%) with complete clinical response included
- Median follow up: 3.3 years
- 2 years local regrowth rate: 25.2% (95% CI 22.2-28.5%)
- 88% local regrowth diagnosed in first 2 years
- 97% of local regrowth were in bowel wall
- 5 Year OS 85% and DFS 94%

Age, mean (SD)	63.6 (11.7)
BMI, mean (SD)	26.7 (4.9)
Sex	
Male	603 (69%)
Female	277 (32%)
Comorbidity	
Yes	252 (29%)
No	337 (38%)
Unknown	291 (33%)
Year of decision for W&W	
Before 2010	177 (20%)
2010–14	450 (51%)
2015–17	253 (29%)
Median follow-up time, years (95% CI)	3.3 (3.1–3.6)
Clinical T stage baseline*	
cT1	14 (2%)
cT2	226 (26%)
cT3	451 (51%)
cT4	30 (3%)
Unknown	159 (18%)

Clinical N stage baseline	
cN0	309 (35%)
cN1	271 (31%)
cN2	167 (19%)
Unknown	133 (15%)
Local regrowth	
Yes	213 (24%)
No	667 (76%)
Distant metastasis	
Yes	71 (8%)
No	809 (92%)
Last study status	
In follow-up	660 (75%)
Follow-up completed	57 (7%)
Lost to follow-up	64 (7%)
Deceased	99 (11%)

RESEARCH

Open Access



A meta-analysis of the watch-and-wait strategy versus total mesorectal excision for rectal cancer exhibiting complete clinical response after neoadjuvant chemoradiotherapy

Guilin Yu^{1†}, Wenqing Lu^{2†}, Zhouguang Jiao³, Jun Qiao⁴, Shiyang Ma⁴ and Xin Liu^{4*}

Abstract

Background: Some clinical researchers have reported that patients with cCR (clinical complete response) status after neoadjuvant chemoradiotherapy (nCRT) could adopt the watch-and-wait (W&W) strategy. Compared with total mesorectal excision (TME) surgery, the W&W strategy could achieve a similar overall survival. Could the W&W strategy replace TME surgery as the main treatment option for the cCR patients? By using the meta-analysis method, we evaluated the safety and efficacy of the W&W strategy and TME surgery for rectal cancer exhibiting cCR after nCRT.

Methods: We evaluated two treatment strategies for rectal cancer with cCR after nCRT up to July 2021 by searching the Cochrane Library, PubMed, Wanfang, and China National Knowledge Infrastructure (CNKI) databases. Clinical data for primary outcomes (local recurrence, cancer-related death and distant metastasis), and secondary outcomes (disease-free survival (DFS) and overall survival (OS)) were collected to evaluate the efficacy and safety in the two groups.

Results: We included nine studies with 818 patients in the meta-analysis, and there were five moderate-quality studies and four high-quality studies. A total of 339 patients were in the W&W group and 479 patients were in the TME group. The local recurrence rate in the W&W group was greater than that in the TME group in the fixed-effects model (OR 8.54, 95% CI 3.52 to 20.71, $P < 0.001$). The results of other outcomes were similar in the two groups.

Conclusion: The local recurrence rate of the W&W group was greater than that in the TME group, but other results were similar in the two groups. With the help of physical examination and salvage therapy, the W&W strategy could achieve similar treatment effects with the TME approach.

Trial registration: Protocol registration number: [CRD42021244032](https://www.crd42021244032).

Keywords: Watch-and-wait, Complete clinical response, Total mesorectal excision, Rectal cancer, Meta-analysis

Current challenges in the NOM for rectal cancers

Standard preoperative CRT regimen

Patient selection criteria:
Unsuitable patients?

Predictors of pCR and cCR

Limitations and more challenges: NOM

- Limited duration of follow up
- Patient selection criteria not well established
- **Algorithm of surveillance**
 - Timing for residual disease detection (4-6 wks. vs. 24 wks.)
 - Interval and duration of surveillance
 - MRI and sigmoidoscopy every three months first year and every 6 months for 5 years
- Heterogeneity of studies in terms of defining and identifying CR
 - **Definition of CR:** Endoscopy, Biopsy, Endorectal USG, DRE



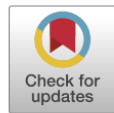
Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis

Lancet Gastroenterol Hepatol
2018

Sami A Chadi, Lee Malcomson, Joie Ensor, Richard D Riley, Carlos A Vaccaro, Gustavo L Rossi, Ian R Daniels, Neil J Smart, Melanie E Osborne,

Findings We obtained individual participant data from 11 studies, including 602 patients enrolled between March 11, 1990, and Feb 13, 2017, with a median follow-up of 37·6 months (IQR 25·0–58·7). Ten of the 11 datasets were judged to be at low risk of bias. 2-year cumulative incidence of local regrowth was 21·4% (random-effects 95% CI 15·3–27·6), with high levels of between-study heterogeneity ($I^2=61\%$). We noted wide between-centre variation in patient, tumour, and treatment characteristics. We found some evidence that increasing cT stage was associated with increased risk of local regrowth (random-effects HR per cT stage 1·40, 95% CI 1·00–1·94; $p_{\text{trend}}=0·048$). In a subgroup of 459 patients managed after 2008 (when pretreatment staging by MRI became standard), 2-year cumulative incidence of local regrowth was 19% (95% CI 13–28) for stage cT1 and cT2 tumours, 31% (26–37) for cT3, and 37% (21–60) for cT4 (random-effects HR per cT stage 1·50, random-effects 95% CI 1·03–2·17; $p_{\text{trend}}=0·0330$). We estimated that measured factors contributed 4·8–45·3% of observed between-centre heterogeneity.

Interpretation In patients with rectal cancer and clinical complete response after chemoradiotherapy managed by watch and wait, we found some evidence that increasing cT stage predicts for local regrowth. These data will inform clinician–patient decision making in this setting. Research is needed to determine other predictors of a sustained clinical complete response.



Watch-and-wait strategy in rectal cancer: Is there a tumour size limit?

Results from two pooled prospective studies

Michał Jankowski^a, Lucyna Pietrzak^b, Maciej Rupiński^c, Wojciech Michalski^d, Anna Hołdakowska^e,

Radiotherapy and Oncology 160 (2021) 229–235

Background: Frequency and predictive factors for a clinical complete response (cCR) in unselected patients are unclear.

Material and methods: Two prospective observational studies were designed and pooled to explore predictive factors for cCR. Both studies evaluated the watch-and-wait strategy in consecutive patients; the first single-institutional study in elderly with a small tumour, the second multi-institutional study in all the patients receiving standard of care preoperative radiotherapy.

Results: Four hundred and ninety patients were analysed. Short-course radiotherapy alone, or with consolidation chemotherapy or chemoradiation was given to 40.6%, 40.2% and 19.2% of the patients, respectively. The median interval from the radiation start to the first tumour response assessment was 10.2 weeks for short-course radiation and 13.2 weeks for chemoradiation. Seventy-three patients had cCR and 71 underwent w&w with the median follow-up of 24 months. The regrowth rate was 26.8%. cCR rate was 39.0% for low-risk cancer (cT1-2N0), 16.8% for intermediate-risk (cT3 with unthreatened mesorectal fascia [MRF–] or cT2N+) and 5.4% for high-risk (cT4 or MRF+). In the multivariable analysis, tumour volume (or tumour length and circumferential extent) and cN status were significant predictors for cCR. In circular cancers or with a length ≥ 7 cm ($n = 184$), cCR rate was only 2.7%, sustained cCR 1.6% and the sensitivity of cCR diagnosis 23.1%. None of 27 patients with a tumour larger than 120 cm^3 achieved cCR.

Conclusions: Considering watch-and-wait strategy is questionable in patients with circular tumours or with tumour length ≥ 7 cm.

First Author or Guideline	Proposed cCR Criteria by Select Studies
Habr-Gama ¹³	<p>Normal DRE</p> <p>No disease per CT of the abdomen and pelvis and chest x-ray</p> <p>No residual ulcer and negative biopsy finding per proctoscopy</p>
Maas ¹⁴	<p>No palpable tumor if initially palpable by DRE</p> <p>Substantial downsizing with no residual tumor or fibrosis only, residual wall thickening as a result of edema only, no suspicious lymph nodes on MRI</p> <p>No residual tumor or only a small residual erythematous ulcer or scar, negative biopsy findings from the scar, ulcer, or former tumor location by endoscopy</p>
Dalton ¹⁷	<p>No residual mucosal ulcer even if biopsy finding negative</p> <p>Normal PET scan in patients with no mucosal ulcer and negative biopsy findings</p>
Smith ²⁰	<p>No palpable tumor by DRE</p> <p>No visible pathology other than flat scar by endoscopy</p>
Li ¹⁵	<p>No palpable tumor by DRE</p> <p>No visible lesion other than flat scar by endoscopy</p> <p>No residual tumor by pelvic CT, MRI, or transrectal ultrasound</p>
Lai ¹⁶	<p>No mass, mucosal irregularity, or ulceration by DRE and endoscopic examination</p> <p>Mucosal whitening and telangiectasia</p> <p>No residual disease or extrarectal disease by CT or MRI or transrectal ultrasonography</p>
van der Valk ²²	<p>No signs of residual tumor by DRE, endoscopy, or imaging modality per participating institutional policy*</p>
ESMO ⁴	<p>No palpable tumor or irregularity by DRE</p> <p>No visible lesion by rectoscopy except flat scar, telangiectasia, or mucosal whitening</p> <p>Negative biopsy findings from the scar</p> <p>No residual tumor at primary site or lymph nodes by MRI or ERUS</p> <p>Normalized CEA level (< 5 ng/mL) after chemoradiotherapy if initially elevated</p>
NCCN ²	<p>No evidence of residual disease on DRE, rectal MRI, and direct endoscopic examination</p>

Challenges in predicting a pCR

- **Surgery:** Still the only means to reliably detect it
- **Clinical response:** discordance with path response
- **Post-RT versus residual disease**
 - DRE, Endoscopy, EUS, CT, MRI, PET
 - Only 25% of clinical CR were Pathological CR: MSKCC series
- **Biopsy after CRT difficult to interpret**
 - Positive: Unknown clinical significance of few viable cells
 - Negative: Sampling error

MOLECULAR BIOMARKERS TO PREDICT RESPONSE TO CRT

- EGFR positivity; KRAS, NRAS, and BRAF status, DNA damage response assessment, cell- free DNA, and circulating tumour cells
- KRAS mutation only, KRAS/TP53 mutation combination, and EGFR positivity associated with a lower pCR rate in patients with locally advanced rectal adenocarcinoma after CRT in retrospective studies.
- Elevated carcinoembryonic antigen (CEA) level before CRT is associated with a decreased pCR rate. Post-neoadjuvant CEA less than 5 ng/dL is associated with higher pCR rates and clinical outcomes.
- Post-CRT cell-free DNA levels were shown to be significantly lower in patients with response to CRT than in nonresponders.
- MicroRNA signatures: High serum miR-345 expression noted in CRT- resistant patients.



MONITORING PATIENTS AND CHALLENGES OF DETECTION OF TUMOR REGROWTH AND SALVAGE THERAPY


- In patients who achieve cCR and are followed by non- surgical management, the rate of intraluminal local recurrence in the first 3 years ranges between 15.7% and 34%.
 - More than 80% of local recurrences were diagnosed in the first 2 years in a study conducted by the International Watch & Wait Database.
 - Distant metastatic disease with nonsurgical management is approximately 8% to 10%.
 - In most studies, local recurrence was managed by salvage surgical resection, and up to 95.4% of patients received salvage therapy.
 - No consensus exists with regard to the frequency and duration of surveillance. The data on adherence to strict surveillance protocols are limited.
- 

TABLE 3. Surveillance Protocols and Local and Distant Recurrence Rates With Nonsurgical Management

First Author	No. of Patients in the Protocol	1st Year	2nd Year	3rd Year	4th Year	5th Year	Mean Follow-Up, months	Local and Distant Recurrence Rates, No. (%)
Habr-Gama ¹³	71	DRE once a month Proctoscopy with biopsy (when feasible) once a month CEA once a month CT AP and CXR once every 6 months	DRE once every 2 months Proctoscopy with biopsy (when feasible) once every 2 months CEA once every 2 months CT AP and CXR once every 6 months	DRE once every 6 months Proctoscopy with biopsy (when feasible) once every 6 months CEA once every 6 months CT AP and CXR every 6 months			57.3 (12-156)	2 (2.8) and 3 (4.1)
Maas ¹⁴	21	DRE once every 3 months CEA once every 3 months MRI once every 3 months CT CAP once every 6 months Endoscopy with biopsy once every 3 months	DRE once every 6 months CEA once every 3 months MRI once every 6 months CT CAP once every 12 months Endoscopy with biopsy once every 6 months	DRE once every 6 months CEA once every 3 months MRI once every 6 months CT CAP once every 12 months Endoscopy with biopsy once every 6 months	DRE once every 6 months CEA once every 6 months MRI once every 6 months CT CAP once every 12 months Endoscopy with biopsy once every 6 months	DRE once every 6 months CEA once every 6 months MRI once every 6 months CT CAP once every 12 months Endoscopy with biopsy once every 6 months	25 (5-44)	1 (4.7) and 0 (0)
Dalton ¹⁷	6	Examination under anesthesia at 3 months and 1 year CEA frequency not defined MRI once every 6 months PET/CT once every 6 months	CEA frequency not defined MRI once every 12 months PET/CT once every 12 months				25.5 (12-45)	0 (0) and 0 (0)
Smith ^{20*}	32	Flexible sigmoidoscopy once every 3 months Cross-sectional imaging† once every 6 months	Flexible sigmoidoscopy once every 4-6 months Cross-sectional imaging once every 6 months				28 (9-70)	6 (18.7) and 3 (9.4)
Smith ¹⁸	18	Proctoscopy once every 3 months CEA once every 3 months PET/CT or CT CAP once every 6 months Colonoscopy once every 6 months	Proctoscopy once every 6 months CEA once every 6 months PET/CT or CT CAP once every 12 months	Proctoscopy once every 6 months CEA once every 6 months PET/CT or CT CAP once every 12 months	Proctoscopy once every 12 months CEA once every 12 months PET/CT or CT CAP once every 12 months	Proctoscopy once every 12 months CEA once every 12 months PET/CT or CT CAP once every 12 months	68.4	1 (5.6) and 1 (5.6)

TABLE 3. Surveillance Protocols and Local and Distant Recurrence Rates With Nonsurgical Management (continued)

First Author	No. of Patients in the Protocol	1st Year	2nd Year	3rd Year	4th Year	5th Year	Mean Follow-Up, months	Local and Distant Recurrence Rates, No. (%)
Li ¹⁵	30	DRE once a month CEA once a month Endoscopy with biopsy once every 3 months TRUS once every 3 months MRI once every 6 months CT AP once every 6 months CXR once every 6 months	DRE once every 6 months CEA once every 6 months Endoscopy with biopsy once every 6 months TRUS once every 6 months MRI once every 6 months CT AP once every 6 months CXR once every 6 months	DRE once every 6 months CEA once every 6 months Endoscopy with biopsy once every 6 months TRUS once every 6 months MRI once every 6 months CT AP once every 6 months CXR once every 6 months	Annual follow-up	Annual follow-up	59 (18-100)	2 (6.7) and 1 (3.3)
Araujo ²¹	42	CEA once every 3 months Endoscopy once every 3 months	CEA once every 3 months Endoscopy once every 3 months	CEA once every 6 months Endoscopy once every 6 months	Same as 3rd year	Same as 4th year	47.7	5 (11.9) and 4 (9.5)
Lai ¹⁶	18	DRE once every 3 months Proctoscopy/colonoscopy with selective biopsy once every 3 months CEA once every 3 months CT AP, MRI, and CXR‡ once every 6 months	DRE once every 3 months Proctoscopy/colonoscopy with selective biopsy once every 3 months CEA once every 3 months CT AP and MRI once every 12 months	DRE once every 6 months Proctoscopy/colonoscopy with selective biopsy once every 6 months CEA once every 6 months CT AP, MRI, and CXR once every 12 months	Same as 3rd year	Same as 4th year	49.9	2 (11.1) and 0 (0)

Ongoing clinical trials: Wait and Watch policy

ClinicalTrials.gov Identifier	Description	Phase	Status
NCT02008656	Total neoadjuvant therapy + TEM or nonsurgical management v CRT + TEM + adjuvant chemotherapy	II	Recruiting
NCT02514278 (GRECCAR12)	FOLFIRINOX for four cycles and CRT Good responders: local excision then selective surveillance Poor responders: rectal excision v CRT Good responders: local excision then selective surveillance Poor responders: rectal excision	III	Recruiting
NCT03426397	If cCR after standard CRT, patients offered nonsurgical management protocol	Observational	Recruiting
NCT02704520 (TRIGGER)	CRT followed by surgery and adjuvant chemotherapy v CRT Good response by mrTRG: nonsurgical management and more chemotherapy Poor response by mrTRG: additional chemotherapy then surgery or defer surgery	II/III	Recruiting
NCT03125343 (WoW)	If cCR with CRT, then patients offered nonsurgical management; if patient declines, then standard surgery	National cohort study	Recruiting
NCT02945566 (STAR-TREC)	CRT then TEM v CRT cCR: may manage nonsurgically No cCR: excision biopsy with TEM v Short-course radiation cCR: may manage nonsurgically No cCR: excision biopsy with TEM	II	Recruiting

Quality of Life in Rectal Cancer Patients After Chemoradiation: Watch-and-Wait Policy Versus Standard Resection – A Matched-Controlled Study

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BACKGROUND: Fifteen to twenty percent of patients with locally advanced rectal cancer have a clinical complete response after chemoradiation therapy. These patients can be offered nonoperative organ-preserving treatment, the so-called watch-and-wait policy. The main goal of this watch-and-wait policy is an anticipated improved quality of life and functional outcome in comparison with a total mesorectal excision, while maintaining a good oncological outcome.

OBJECTIVE: The aim of this study was to compare the quality of life of watch-and-wait patients with a matched-controlled group of patients who underwent chemoradiation and surgery (total mesorectal excision group).

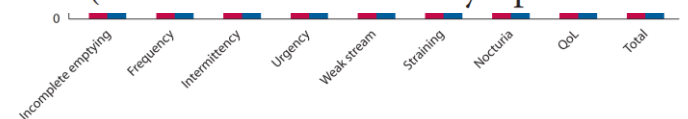
DESIGN: This was a matched controlled study.

SETTINGS: This study was conducted at multiple centers.

PATIENTS: The study population consisted of 2 groups: 41 patients after a watch-and-wait policy and 41 matched patients after chemoradiation and surgery. Patients were matched on sex, age, tumor stage, and tumor height. All patients were disease free at the moment of recruitment after a minimal follow-up of 2 years.

MAIN OUTCOME MEASURES: Quality of life was measured by validated questionnaires covering general quality of life (Short Form 36, European Organization for Research and Treatment of Cancer QLQ-C30), disease-specific total mesorectal excision (European Organization for Research and Treatment of Cancer QLQ-CR38), defecation problems (Vaizey and low anterior resection syndrome scores), sexual problems (International Index of Erectile Function and Female Sexual Function Index), and urinary dysfunction (International Prostate Symptom Score).

FIGURE 5. Defecation problems. *Significant result. LAAS = low anterior resection syndrome; TME = total mesorectal excision; W&W = watch and wait.



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Cost-Effectiveness and Quality-Adjusted Survival of Watch and Wait After Complete Response to Chemoradiotherapy for Rectal Cancer

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Abstract

Background: Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is the standard treatment for locally advanced rectal cancer. There is interest in deescalating local therapy after a clinical complete response to CRT. We hypothesized that a watch-and-wait (WW) strategy offers comparable cancer-specific survival, superior quality-adjusted survival, and reduced cost compared with upfront TME.

Methods: We developed a decision-analytic model to compare WW, low anterior resection, and abdominoperineal resection for patients achieving a clinical complete response to CRT. Rates of local regrowth, pelvic recurrence, and distant metastasis were derived from series comparing WW with TME after pathologic complete response. Lifetime incremental costs and quality-adjusted life-years (QALY) were calculated between strategies, and sensitivity analyses were performed to study model uncertainty.

Results: The base case 5-year cancer-specific survival was 93.5% (95% confidence interval [CI] = 91.5% to 94.9%) on a WW program compared with 95.9% (95% CI = 93.6% to 97.4%) after upfront TME. WW was dominant relative to low anterior resection, with cost savings of \$28 500 (95% CI = \$22 200 to \$39 000) and incremental QALY of 0.527 (95% CI = 0.138 to 1.125). WW was also dominant relative to abdominoperineal resection, with a cost savings of \$32 100 (95% CI = \$21 800 to \$49 200) and incremental QALY of 0.601 (95% CI = 0.213 to 1.208). WW remained dominant in sensitivity analysis unless the rate of surgical salvage fell to 73.0%.

> Ann Surg Oncol. 2021 Sep 16. doi: 10.1245/s10434-021-10576-z. Online ahead of print.

Cost Effectiveness of Watch and Wait Versus Resection in Rectal Cancer Patients with Complete Clinical Response to Neoadjuvant Chemoradiation

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Abstract


Background: Watch and wait (WW) protocols have gained increasing popularity for patients diagnosed with locally advanced rectal cancer and presumed complete clinical response after neoadjuvant chemoradiation. While studies have demonstrated comparable survival and recurrence rates between WW and radical surgery, the decision to undergo surgery has significant effects on patient quality of life. We sought to conduct a cost-effectiveness analysis comparing WW with abdominoperineal resection (APR) and low anterior resection (LAR) among patients with stage II/III rectal cancer.

Methods: In this comparative-effectiveness study, we built Markov microsimulation models to simulate disease progression, death, costs, and quality-adjusted life-years (QALYs) for WW or APR/LAR. We assessed cost effectiveness using the incremental cost-effectiveness ratio (ICER), with ICERs under \$100,000/QALY considered cost effective. Probabilities of disease progression, death, and health utilities were extracted from published, peer-reviewed literature. We assessed costs from the payer perspective.

Results: WW dominated both LAR and APR at a willingness to pay (WTP) threshold of \$100,000. Our model was most sensitive to rates of distant recurrence and regrowth after WW. Probabilistic sensitivity analysis demonstrated that WW was the dominant strategy over both APR and LAR over 100% of iterations across a range of WTP thresholds from \$0-250,000.

Conclusions: Our study suggests WW could reduce overall costs and increase effectiveness compared with either LAR or APR. Additional clinical research is needed to confirm the clinical efficacy and cost effectiveness of WW compared with surgery in rectal cancer.

A practical approach to nonsurgical management of rectal cancer



Locally advanced rectal adenocarcinoma diagnosis
established by multidisciplinary team

Pretreatment Staging
MRI of abdomen/pelvis
CT scan of chest
Proctoscopy

Neoadjuvant therapy (chemotherapy followed by
chemoradiotherapy or chemoradiotherapy)

Treatment Assessment
MRI of abdomen/pelvis: complete response by MRI
Proctoscopy: visual findings and negative biopsy findings
Cross-sectional chest imaging: no distant metastasis

If cCR achieved, patient and physician discuss
nonsurgical management

Surveillance by an established protocol;
more rigorous in the first 2 years at high-volume center

Thank you !!
Time to look beyond the horizon

