Published in final edited form as:

Ann Surg Oncol. 2017 July ; 24(7): 1904–1915. doi:10.1245/s10434-017-5841-3.

Non-operative management or “watch and wait” for rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy – a critical appraisal.

Tarik Sammour, MBChB, PhD¹, Brandee A. Price, PhD¹, Kate J Krause, MLIS², and George J Chang, MD, MS^{1,3,*}

¹Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

²Research Medical Library, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

³Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Purpose—There is increasing interest in non-operative management (NOM) for rectal cancer with complete clinical (cCR) response after neoadjuvant chemoradiation (nCRT). The aim of this review is to summarize the available data on NOM, with the intention of formulating standardised protocols on which to base future investigation.

Methods—Systematic review following PRISMA guidelines was conducted. A highly sensitive literature search identified all relevant studies published between Jan 2004 and Dec 2016. Data extraction and quality assessment was performed independently by two authors, and resolved by consensus with a third.

Results—In total, 15 studies met inclusion criteria including 920 patients, 575 (62.5%) who underwent NOM after cCR, and the rest forming a surgical control group. The weighted mean followup was 39.4 (12.7) months in the NOM group and 39.8 (5.1) months in the surgery group. The pooled re-growth rate in the NOM group was 21.3% at a mean of 15.6 (7.0) months. Surgical salvage was possible and undertaken in 93.2% of these patients. Overall survival in the NOM group was 91.7%, and disease free survival was 82.7%. For the comparison proctectomy group, pooled rates of local recurrence, overall survival and disease free survival were 8.4%, 92.4%, and 87.5%, respectively.

Conclusion—NOM may be a feasible option for surgically eligible rectal cancer patients with cCR after nCRT. Before such a strategy can be widely implemented, further prospective data is required with standardised definitions, diagnostic criteria, and management protocols, with an emphasis on shared patient-provider decision making and patient centered outcomes.

*Corresponding author: George J. Chang, M.D., M.S., F.A.C.S., F.A.S.C.R.S., Professor, Department of Surgical Oncology, Unit 444, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Houston, TX 77230, United States of America; gchang@mdanderson.org; tel: 713-563-1875.

We declare that we have no relevant conflicts of interest.

Introduction

The standard of care in stage II and III rectal cancer treatment is total mesorectal excision with neo-adjuvant radiation or chemoradiation followed by adjuvant chemotherapy. Among those patients who undergo neoadjuvant treatment, approximately 10-20% will achieve a pathologic complete response which has been associated with excellent long term prognosis for both local and distant control.^{1,2} However, surgery for rectal cancer is associated with significant morbidity and potential adverse impact on quality of life. Because of this, there has been increasing interest in the pursuit of strategies that incorporate non-operative management after chemoradiation therapy.³

The major difficulty with this approach has been the challenge of identifying patients with pathological complete response using clinical assessment which is presently limited and inaccurate.⁴ Clinical complete response has been reportedly observed in upwards of 40% of patients of whom more than half will have residual viable tumor identified upon pathologic review of the surgical specimen. As a result, selection of patients for non-operative management based on the surrogate measure of complete clinical response remains a balance of risk proposition, the safety of which is being actively investigated.^{5,6} Even in the context of published clinical trials, there is no standardization of patient selection criteria, diagnostic methods, or management algorithms.^{7,8} This makes interpretation of the data in a clinically meaningful way very difficult for healthcare providers and patients.⁹ Thus, the decision to consider a non-operative treatment strategy requires the consideration of a complex set of tradeoffs regarding potential treatment outcomes in the setting of significant uncertainty.^{10,11}

The aim of this clinical review is to summarize the available data on non-operative management as an alternative to total mesorectal excision, with the specific intention of formulating standardised selection and diagnostic criteria, as well as management and surveillance protocols on which to base future investigation.

Methods

Research question

In patients with rectal cancer who have a complete clinical response (cCR) after neo-adjuvant chemo-radiotherapy (nCRT) and undergo non-operative management (NOM), what is rate of pelvic disease failure (recurrence or regrowth)? What is the rate of curative salvage surgery after treatment failure? Among salvaged patients, what proportion require a colostomy?

Search strategy

Relevant primary studies published between January 2004 and November 2016 were identified from Ovid MEDLINE, Cochrane, and Ovid EMBASE (including in-process and non-indexed citations). A highly sensitive search strategy was employed (Supplement 1) incorporating the following elements with no language restriction:

- Population: Patients with rectal cancer at least 18 years of age treated with nCRT eligible for curative surgical resection.
- Intervention: NOM after nCRT with assessment of cCR, but without local excision.
- Comparator: Rectal cancer patients treated with standard of care: nCRT followed by surgical resection (proctectomy).
- Outcomes:
 - Primary: Rate of local regrowth (including mesorectal nodal disease)
 - Secondary: Overall and disease free survival, curative salvage surgery rate, sphincter preservation / colostomy rate.

The references of the chosen articles were also screened for inclusion. For multiple publications reporting on the same patient population, the most recent publication was used.

Inclusion criteria were:

- Clinical controlled (RCTs, cohort) or observational studies (prospective and retrospective).
- Studies including adult human subjects aged ≥ 18 years eligible for curative resection.
- Included patients with primary rectal adenocarcinoma who underwent nCRT.
- Provide sufficient description of treatment modalities.
- Provide criteria for diagnosing a clinical complete response.

Exclusion criteria

- Systematic reviews, meta-analyses, non-human studies, editorials.
- Studies in which patients were only treated with neoadjuvant radiotherapy.
- Studies that only reported data for local excision of the primary tumor (in either study arm).
- Studies in which only comorbid, frail, and/or palliative patients were treated with NOM.
- Studies that did not report any clinical outcome data.
- Studies that did not have follow-up data.

Appraisal and data extraction

All results identified from the search were entered into a unified database, after-which duplicate results were removed. Two authors (TS, BP) independently reviewed the titles and abstracts of every record identified by the search and decided on inclusions based on the above criteria. Differences in assessment were resolved by consensus and evaluation by a third reviewer (GJC). One review author performed data extraction (BP).

Quality assessment

Two reviewers independently assessed risk of bias based on the Newcastle-Ottawa Scale for non-randomized studies. Differences in assessment were resolved by consensus and evaluation by a third reviewer (GJC).

Data synthesis

A narrative synthesis of the findings from the included studies was developed and structured around diagnostic criteria, patient selection, type of intervention, and outcome. Summary data was presented as mean (SD) for continuous variables and percentages for categorical variables. We anticipated that data summation by meta-analysis would be limited scope because of study heterogeneity, however, we planned to attempt to pool results if this was possible where studies have used the same intervention, comparator, and outcome measure.

Results

Search results

In total, 5566 citations were identified from the initial search and the titles were screened, yielding 411 abstracts for further review (Figure 1). There was a dramatic increase in the total number of publications between 2006 and 2016 (Figure 2).¹² Ultimately, 15 studies met inclusion criteria and were selected for the final assessment, all of which were all published between 2009 and 2016. Among a total of 920 patients included, 575 (62.5%) underwent NOM after a cCR.^{13–27} Eight studies reported data for an adequate control proctectomy group, but there was significant variation. Four used a post-surgical pathological complete response (pCR) group for comparison^{14,16,25,26}, 2 used cCR tumors undergoing surgery,^{19,20} 1 used both,²² and 1 used a surgical group matched for clinical stage (regardless of tumor response).²³ Outcome data for incomplete response, non-response, and local excision were excluded from comparisons as these were not regarded as adequate control group data.^{13,15,17,18,21,27} Due to this significant heterogeneity in the control arms (and follow-up duration), formal meta-analysis of results was not performed.

Study quality assessment

Quality assessment is presented in Table 1. Overall, studies generally described the selection of the NOM group and their outcomes with remarkable detail (Appendices 1 & 2); however, the description of the control group was deficient in many of the studies, which lead to fewer stars awarded to those studies. For comparability, only four studies (27%) included a comparable group of cCR patients opting for or randomized to surgery. Another four studies compared NOM patients to pCR patients; however, the remaining studies (7; 47%) did not list any comparison group. Oncologic outcomes were reported for all NOM groups.

Neo-adjuvant and adjuvant treatment

The neoadjuvant treatment regimen was outlined in all the included studies (see Table 1). Long course radiotherapy (45 – 65 Gy) was given in all studies, with 50.4 Gy being the most common treatment dose. Concurrent chemotherapy was fluoropyrimidine based in all instances. In contrast, the use of consolidation or adjuvant chemotherapy was highly

variable, ranging from frequent use,^{18,25,26} to use only if staged as node positive prior to neoadjuvant treatment,^{15,21} infrequent use,^{14,20,23} and complete omission.^{13,16,17,19,22} Consolidation or adjuvant chemotherapy, when used, was most commonly 5-FU based with the addition of Oxaliplatin in two studies.^{21,25}

Patient selection criteria for NOM

Tumor distance from the anal verge was defined in 12 studies and varied, although most only included tumors in the mid and low rectum (Appendix 1). Clinical staging inclusion criteria were reported in 13 studies, most commonly cT2-T4, N0-2, M0, with exclusion of early T stage (T0/T1) and Stage IV patients. Three studies excluded T4 patients,^{13,20,26} and only one study included patients with metastatic stage IV disease.²⁶

Clinical Complete Response Diagnosis

The clinical diagnosis of complete response required correlation of digital rectal exam (DRE), endoscopy, and MRI in most studies (Appendix 2). Uniformly, tumor had to be absent on DRE, but definitions of endoscopic and imaging findings varied. Common endoscopic criteria included “flat scar” and “absence of ulceration”, and MRI criteria were “significant regression with fibrosis and with no residual tumor”, “low signal intensity on T2 images”, and “no evidence of extra-rectal residual disease”. Negative biopsies of the residual lesion were only explicitly mandated in two studies.^{16,21}

Surveillance protocol

Clinical examination, proctoscopy, CEA level, MRI rectum, and CT chest, abdomen, and pelvis were used consistently for surveillance (Appendix 3). Although the timing of these investigations was highly variable, clinical assessment/proctoscopy was most commonly recommended every 1 to 3 months for at least one year, with reducing frequency thereafter. CEA level was commonly done every 3 – 6 months long term. CT and MRI imaging were both most commonly performed every 6 months for first year and then yearly thereafter. PET-CT was utilized in only 5 studies.^{13,16,20,26,27}

Outcomes

Follow-up duration was reported in all studies for NOM and comparison surgery groups (three studies reported overall followup duration for both groups together and this duration was assumed to be the same in each group). The weighted mean followup time was thus 39.4 (12.7) months in the NOM group and 39.8 (5.1) months in the surgery group (Table 2). The pooled re-growth rate (including mesorectal nodal disease) was 21.3% at a weighted mean of 15.6 (7.0) months. Surgical salvage was possible and undertaken in 93.2% of patients who developed a regrowth (with the rest most commonly reported as insalvagable/palliated). For patients undergoing salvage, the colostomy rate was 54.4% (the overall colostomy rate for the NOM group was 12.0% as intention to treat vs 36.1% in the surgery group). Overall survival in the NOM group (reported in 14 studies) was 91.7%, and disease free survival (reported in all studies) was 82.7%. For the comparison proctectomy group, pooled rates of local recurrence, overall survival and disease free survival were 8.4%, 92.4%, and 87.5%, respectively.

Discussion

We have performed a systematic review of published data on the NOM of rectal cancer after cCR to CRT. While there was significant heterogeneity between studies, in particular with respect to comparison groups which prevented formal meta-analysis. In addition, there was variation in inclusion criteria, treatment strategy, and follow-up duration. Furthermore, small sample sizes, short duration of follow-up, reporting bias from retrospective studies, and differences in entry criteria have likely influenced our point estimates. Despite this, some insights were gained into the efficacy and potential advantages of this procedure in selected patients. After a weighted mean followup of over 3 years, the pooled regrowth rate was 21.3%, with surgical salvage possible in a majority but not all patients (>90%), and an overall survival of >90% in the whole group. The colostomy rate was much lower than in the surgical resection group.

In the absence of level 1 evidence for the oncologic efficacy for NOM strategies, surgical resection remains the standard of care. However, based on the available data, it would be reasonable to offer NOM as a prospectively evaluated option for active surveillance to selected patients with cCR. In doing this, it is important to explain the potential benefits and harms of this management approach in detail and ensure that the patient is able to make an informed decision. While it may be difficult to conduct randomized controlled trials on this topic, it is imperative that this approach is investigated through high quality prospective and comparative data collection, with standardised definitions to enable inter-study and inter-institutional comparisons.²⁸

Based on the reported data, we propose the following guidelines for prospective management erring on the side of being conservative where possible due to the still experimental nature of the intervention and the difficulty in accurately identifying a pCR based on clinical characteristics,^{29,30} and with an emphasis on patient centered decision making and outcomes (Table 3).

Neo-adjuvant and adjuvant treatment

Patients should undergo long course combination chemoradiotherapy with fields that include the tumor, the presacral nodes, the mesorectal region and the internal iliac nodes. Generally a 3 or 4 field technique should be used delivering 45 Gy in 25 fractions to the pelvis, and a 5.4 Gy boost (3 fractions) to the tumor bed and presacral region (total dose 50.4 Gy). IMRT may be considered in selected cases to reduce toxicity. Concurrent chemotherapy includes: 5-FU 250-300mg/m²/day IV continuous infusion, Monday through Friday on days of radiation therapy, or Capecitabine 825 mg/m² PO twice daily, Monday through Friday on days of radiation therapy. Post nCRT chemotherapy should either be single agent fluoropyrimidine (5-FU or capecitabine) or combination mFOLFOX (5-FU and oxaliplatin) as per standard schedules and at physician discretion.

Patient selection criteria for NOM

All patients must undergo baseline DRE, endoscopy, complete radiographic staging evaluation including CT chest/abdomen/pelvis, and a rectal cancer pelvic MRI (Appendix

1). An MRI of the abdomen or PET/CT may be performed in lieu of the CT. The eligibility criteria, definition of a cCR, structured surveillance protocol, and prospective collection of relevant outcomes for NOM patients are summarized in Table 3. Future guidelines will be informed by well controlled prospective studies with clearly defined control groups of eligible patients who undergo surgery (and not NOM).

Limitations—A limitation to this analysis is the significant heterogeneity of the included studies. In addition, data on local excision was not included. While it has been proposed as a method of further improving patient selection by providing additional staging information, the role of local excision in the rectal cancer with cCR has yet to be clearly defined. There are also potential drawbacks such as: false negatives, false positives (particularly in terms of timing of the excision in the setting of a responding tumor), sphincter damage in very low tumors, the absence of nodal staging information, and the real risk of specimen fracture due to weakening of the rectal wall should proctectomy be required at a later date. The estimates for tumor regrowth in individual studies may be affected by the stringency of the inclusion criteria for the NOM strategy and small sample size which may be mitigated in part by evaluation of pooled data from all of the studies. Furthermore, NOM for comorbid and/or frail patients was not assessed in this review; however, published data suggests that NOM is superior to surgical resection in this patient population.¹¹ Finally, scientific meeting abstracts were not included in the search, and assessment of publication bias was not performed.

Conclusion

NOM with active surveillance may be a feasible option for surgically eligible rectal cancer patients with cCR after nCRT. However, before such a strategy can be widely implemented, further prospective data is required with standardised definitions, diagnostic criteria, and management protocols, with an emphasis on shared patient-provider decision making and patient centered outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to acknowledge MDACC Cancer Center Support Grant (CCSG; P30 CA016672), the Aman Trust for Colorectal Cancer Research and Education (GJC) and the Andrews Family Fund for Colorectal Cancer Research (GJC).

Funding

This work was supported in part by the MDACC Cancer Center Support Grant (CCSG; P30 CA016672) and the Aman Trust for Colorectal Cancer Research and Education (GJC) and the Andrews Family Fund for Colorectal Cancer Research (GJC).

Appendix

Appendix 1:

Patient Eligibility Criteria

	Criteria	Number of papers	References
Diagnosis	Rectal adenocarcinoma	15	13-15, 17-18, 21-27
Location	Low (6-8 cm)	5	13, 17-18, 23-24
	Mid (>8-10 cm)	4	14, 19, 22, 27
	High (>10 cm)	3	15, 20-21
	Not specified	3	16, 25-26
Stage	I	7	16-17, 20, 23-26
	II	13	13, 16-27
	III	13	13, 16-27
	IV	1	26
	Not specified	2	14-15
T stage	T1	2	24, 26
	T2	8	13, 16-18, 20, 23-24, 26
	T3	12	13, 16-18, 18-26
	T4	9	16-18, 20-25
	Not specified	3	14, 19, 27
N stage	N1	7	13, 16-17, 19-20, 24-25
	N2	5	16-17, 20, 24-25
	N+	5	15, 23-26
	Not specified	3	14, 19, 27
M stage	M0	12	13, 15-18, 20-25, 27
	M+	1	26
	Not specified	2	14, 19

Items in bold were most frequently used.

Appendix 2:

cCR diagnostic criteria

Assessment	Criteria	Number	References
DRE	No palpable tumor	12	13, 15-19, 21-25, 27
	Not defined	3	14, 20, 26
Endoscopy	Flat scar without ulceration	8	15, 17-19, 23-25, 27
	Superficial scar with minimal ulceration	2	13, 21
	Absence of deep ulceration	1	22
	Not defined	4	14, 16, 20, 26
Imaging	Significant regression with fibrosis and without residual tumor	2	16, 20
	Regression with no or minimal residual tumor or no extra-rectal disease	5	17-19, 21-22
	Not (well) defined	8	13-15, 23-27

Assessment	Criteria	Number	References
Biopsy	Negative biopsies	2	16, 21

Items in bold were most frequently used. DRE: Digital Rectal Exam

Appendix 3:

Surveillance protocols

	Assessment	Frequency	Duration	Number	References
Clinical Examination	DRE/Endoscopy	1-2 months	Year 1	4	13, 17, 18, 27
		3-4 months	Year 1	10	15, 17, 19-26
			Year 2	8	13, 14, 17, 19, 20, 22, 23, 24
			Year 3	1	22
		6 months	Year 2	3	23, 25, 26
			Year 3	8	13, 17, 19-21, 25-27
			Years 4+	6	14, 17, 19-22
		12 months	Years 4+	1	13
	CEA	2 months	Year 1	2	17, 18
			Year 2	1	17
		3 months	Year 1	7	17-22, 25, 26
			Year 2	5	17, 19-22
			Year 3	2	21, 22
		6 months	Year 1	1	23
			Year 2	1	26
			Year 3	2	20, 26
			Years 4+	3	20-22
		12 months	Years 1-2	1	23
	EUA	At 3 months	Year 1	1	16
		At 12 months	Year 1	2	16, 23
Imaging	MRI	3-4 months	Year 1	6	15, 21-24, 27
		6 months	Year 1	9	15-20, 23, 26, 27
			Years 2+	4	20-22, 27
		12 months	Years 2+	3	16, 17, 19
	PET/CT or CT	3-4 months	Year 1	2	13, 22
		6 months	Year 1	8	15-17, 19-21, 24, 26
			Year 2	5	13, 15, 20, 22, 24
			Year 3+	3	15, 20, 22
		12 months	Year 1	1	23
			Year 2	4	16, 17, 19, 21
			Years 3+	5	13, 16, 17, 19, 21

Items in bold were most frequently used. EUA: Examination Under Anesthesia.

References

1. Tural D, Selcukbiricik F, Ozturk MA, et al. The relation between pathological complete response and clinical outcome in patients with rectal cancer. *Hepato-gastroenterology*. 9 2013;60(126):1365–1370. [PubMed: 24298571]
2. Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 5 20 2012;30(15):1770–1776. [PubMed: 22493423]
3. Perez RO. Complete clinical response in rectal cancer: a turning tide. *The Lancet. Oncology*. 2 2016;17(2):125–126. [PubMed: 26705855]
4. Hiotis SP, Weber SM, Cohen AM, et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. *Journal of the American College of Surgeons*. 2 2002;194(2):131–135; discussion 135–136. [PubMed: 11848629]
5. Neuman HB, Elkin EB, Guillem JG, et al. Treatment for patients with rectal cancer and a clinical complete response to neoadjuvant therapy: a decision analysis. *Diseases of the colon and rectum*. 5 2009;52(5):863–871. [PubMed: 19502849]
6. Minsky BD. Rectal cancer: is ‘watch and wait’ a safe option for rectal cancer? *Nature reviews. Gastroenterology & hepatology*. 12 2013;10(12):698–700.
7. Glynn-Jones R, Wallace M, Livingstone JJ, Meyrick-Thomas J. Complete clinical response after preoperative chemoradiation in rectal cancer: is a “wait and see” policy justified? *Diseases of the colon and rectum*. 1 2008;51(1):10–19; discussion 19–20. [PubMed: 18043968]
8. Singh-Ranger G, Kumar D. Current concepts in the non-operative management of rectal cancer after neoadjuvant chemoradiation. *Anticancer research*. 5 2011;31(5):1795–1800. [PubMed: 21617242]
9. Glynn-Jones R, Hughes R. Complete Response after Chemoradiotherapy in Rectal Cancer (Watch-and-Wait): Have we Cracked the Code? *Clinical oncology*. 2 2016;28(2):152–160. [PubMed: 26625960]
10. Chang GJ. Simulating watch and wait for rectal cancer. *Diseases of the colon and rectum*. 2 2015;58(2):155–156. [PubMed: 25585071]
11. Smith FM, Rao C, Oliva Perez R, et al. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. *Diseases of the colon and rectum*. 2 2015;58(2):159–171. [PubMed: 25585073]
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*. 7 21 2009;6(7):e1000097. [PubMed: 19621072]
13. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncology*. 8 2015;16(8):919–927. [PubMed: 26156652]
14. Araujo RO, Valadao M, Borges D, et al. Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study. *European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 11 2015;41(11):1456–1463.
15. Creavin B, Ryan E, Martin ST, et al. Organ preservation with local excision or active surveillance following chemoradiotherapy for rectal cancer. *British journal of cancer*. 12 20 2016.
16. Dalton RS, Velineni R, Osborne ME, et al. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? *Colorectal Dis*. 5 2012;14(5):567–571. [PubMed: 21831177]
17. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *International journal of radiation oncology, biology, physics*. 3 15 2014;88(4):822–828.
18. Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, Sao Juliao GP, Gama-Rodrigues J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a

- prospective study using additional chemotherapy during the resting period. *Diseases of the colon and rectum*. 12 2009;52(12):1927–1934. [PubMed: 19934911]
19. Lai CL, Lai MJ, Wu CC, Jao SW, Hsiao CW. Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or “watch and wait”. *International journal of colorectal disease*. 2 2016;31(2):413–419. [PubMed: 26607907]
 20. Lee SY, Kim CH, Kim YJ, Kim HR. Oncologic Outcomes according to the Treatment Strategy in Radiologic Complete Responders after Neoadjuvant Chemoradiation for Rectal Cancer. *Oncology*. 2015;89(6):311–318. [PubMed: 26426305]
 21. Martens MH, Maas M, Heijnen LA, et al. Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. *Journal of the National Cancer Institute*. 12 2016;108(12).
 22. Nahas SC, Rizkallah Nahas CS, Sparapan Marques CF, et al. Pathologic Complete Response in Rectal Cancer: Can We Detect It? Lessons Learned From a Proposed Randomized Trial of Watch-and-Wait Treatment of Rectal Cancer. *Diseases of the colon and rectum*. 4 2016;59(4):255–263. [PubMed: 26953983]
 23. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *The Lancet. Oncology*. 2 2016;17(2):174–183. [PubMed: 26705854]
 24. Sanchez Loria F, Iseas S, O'Connor JM, et al. Non-surgical management of rectal cancer. Series of 68 cases, long follow up in two leading centres in Argentina. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 11 2016;48(11):1372–1377.
 25. Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Annals of surgery*. 12 2012;256(6):965–972. [PubMed: 23154394]
 26. Smith RK, Fry RD, Mahmoud NN, Paulson EC. Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. *International journal of colorectal disease*. 6 2015;30(6):769–774. [PubMed: 25787162]
 27. Vaccaro CA, Yazzi FJ, Ojra Quintana G, et al. Locally advanced rectal cancer: Preliminary results of rectal preservation after neoadjuvant chemoradiotherapy. *Cirugia espanola*. 5 2016;94(5):274–279. [PubMed: 26980259]
 28. Das P, Minsky BD. A watch-and-wait approach to the management of rectal cancer. *Oncology (Williston Park)*. 10 2013;27(10):962–968. [PubMed: 24367851]
 29. Smith FM, Chang KH, Sheahan K, Hyland J, O'Connell PR, Winter DC. The surgical significance of residual mucosal abnormalities in rectal cancer following neoadjuvant chemoradiotherapy. *Br J Surg*. 7 2012;99(7):993–1001. [PubMed: 22351592]
 30. Smith FM, Wiland H, Mace A, Pai RK, Kalady MF. Clinical criteria underestimate complete pathological response in rectal cancer treated with neoadjuvant chemoradiotherapy. *Diseases of the colon and rectum*. 3 2014;57(3):311–315. [PubMed: 24509452]

Synopsis

Non-operative management of rectal cancer with complete clinical response after neoadjuvant chemoradiation may be a feasible option in selected patients. Until further data is available, we recommend conservative selection criteria with an emphasis on shared patient-provider decision making.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure 1:
PRISMA diagram

Figure 2:
Published studies on Non-operative management.

Table 1:

Study Characteristics and Quality Assessment

Study	Study design *	Level of evidence	Quality Assessments ♦			Primary Endpoint or Objective	Control Group	Patients with cCR N = 920			nCT Regimen	nRT Regimen (Gy)	Reassessment (weeks)	Consolidation Chemo
			S	C	O			NOM 575	Proctectomy 345					
Appelt ¹³	PO	II	3	0	2	LR			40		UFT	60 + 5 EBRT	6	None
Araujo ¹⁴	RD	II	4	0	2	OS, DFS, LR, DM	pCR		111		5-FU/Cape	45-50.5	6	Yes, but not specified (4.8%)
Creavin ¹⁵	PD	II	4	0	3	OS, DFS			10		5-FU	50-54	6-8	If N+ at presentation (65%)
Dalton ¹⁶	RD	II	4	0	2	OS, DFS	pCR		12		Cape	45	6	None
Habr-Gama ¹⁷	PO	II	3	0	3	LR, salvage-ability			90		5-FU	50.4-54	8	None
Habr-Gama ¹⁸	PO	II	3	0	2	Toxicity			22		5-FU	54	10	5-FU (100%)
Lai ¹⁹	RD	II	4	1	3	OS, DFS, LR, DM	cCR with Surgery		44		5-FU	45-54	8-12	None
Lee ²⁰	RD	II	4	1	3	OS, DFS, LR, DM	cCR with Surgery		36		5-FU	50.4	6	Yes, but not specified (12.5%)
Martens ²¹	PO	II	3	0	3	OS, DFS, LR, DM			85		Cape	50.4	10	CapOx if N+ at initial staging (38%)
Nahas ²²	PT	II	4	1	3	OS, DFS, LR, DM	cCR with Surgery and pCR		24		5-FU	50.4	8	None
Renehan ²³	PO/RD	II	4	1	2	DFS, LR, CFS	Matched surgical patients		218		5-FU/Cape	45	8	Yes, but not specified (6%)
Sanchez Loria ²⁴	RD	II	1	0	2	OS, DFS, LR, DM			68		Cape	50.4	9	Yes, but not specified (23%)
Smith JD ²⁵	RD	II	4	0	2	OS, DFS, LR, DM	pCR		89		5-FU/Cape	45-56	4-10	FOLFOX, CapOx, 5-FU (53%)
Smith RK ²⁶	RC	II	4	0	2	OS, DFS, LR, DM	pCR		48		5-FU/Cape	Long course	7-24	5-FU (61 %)

Study	Study design *	Level of evidence	Quality Assessments			Primary Endpoint or Objective	Control Group	Patients with cCR N = 920			nCT Regimen	nRT Regimen (Gy)	Reassessment (weeks)	Consolidation Chemo
			S	C	O			NOM 575	Proctectomy 345					
								18	30					
Vaccaro ²⁷	RD	II	3	0	3	OS, DFS, LR, DM			23		5-FU	50.4	8-12	Not specified
								23	0 (7 LE)					

cCR: Complete clinical response; pCR: pathological complete response; cNR: clinical no response, or incomplete response, NOM: Non-operative Management; nCT: Neoadjuvant chemotherapy; nRT: Neoadjuvant radiotherapy; LE: Local Excision.

^{*} P-prospective; R-retrospective; O-observational; D-prospective database; C-chart; T-Randomized controlled trial;

S-Selection, C-Comparability, O-Outcome;

[†] 27 patients reported, but 5 censored from analyses due to short follow-up.

Table 2:

Regrowth, Salvage, and Survival rates

Study (Ref)	Non-operative Management							Proctectomy				
	Follow-up time (months)	Overall survival	Disease Free Survival	Local regrowth	Time to regrowth (Months)	Salvage Surgery	Colostomy	Follow-up time (months)	Overall survival	Disease Free Survival	Local recurrence	Colostomy
Appell ¹³	23.9	40 (100)	40 (100)	9 (23)	10.4	9 (100)	9 (22.5)	-	-	-	-	-
Araujo ¹⁴	47.7	30 (72)	26 (61)	5 (12)	24.2	4 (80)	3 (7)	46.7	62 (90)	57 (83)	1 (1.4)	13 (19)
Creavin ¹⁵	42	9 (90)	8 (80)	1 (10)	19	1 (100)	NS	-	-	-	-	-
Dalton ¹⁶	25.5	6 (100)	6 (100)	0	-	-	0	39.3	6 (100)	6 (100)	0	4 (67)
Habr-Gama ¹⁷	60	70 (78)	60 (67)	28 (31)	16	26 (93)	13 (14)	-	-	-	-	-
Habr-Gama ¹⁸	23	22 (100)	18 (82)	3 (14)	9.4	3 (100)	1 (5)	-	-	-	-	-
Lai ¹⁹	49.9	18 (100)	16 (89)	2 (11)	25	2 (100)	0	42.3	24 (92)	25 (96)	0	3 (12)
Lee ²⁰	41	NS	6 (75)	2 (25)	NS	1 (50)	1 (13)	41	NS	24 (86)	1 (4)	2 (7)
Martens ²¹	41.4	80 (94)	78 (92)	12 (14)	14.6	11 (92)	6 (7)	-	-	-	-	-
Nahas ²²	31.8	4 (100)	4 (100)	1 (25)	6	1 (100)	0	31.8	20 (100)	20 (100)	0	2 (10)
Renehan ²³	33	105 (96)	96 (88)	44 (34) [*]	NS	36 (88) [*]	28 (26)	33	95 (87)	85 (78)	NS	58 (53)
Sanchez Loria ²⁴	37.5	64 (93.8)	52 (76.3)	9 (13.2)	29	NS	3 (4.4)	-	-	-	-	-
Smith JD ²⁵	28	31 (97)	28 (88)	6 (19)	11	6 (100)	3 (9)	42	57 (100)	56 (98)	0	NS
Smith RK ²⁶	68.4	18 (100)	16 (89)	1 (6)	9.4	1 (100)	1 (6)	46.3	29 (97)	29 (97)	0	8 (27)
Vaccaro ²⁷	46	23 (100)	22 (95.7)	4 (17)	12	4 (100)	0	-	-	-	-	-

All results are presented as number (percentage) unless otherwise stated.

Disease free survival is non-regrowth disease free survival, measured as the number of patients without disease related to the primary rectal cancer at the end of the followup period (successful resections after local regrowth in the non-operative management group were considered disease free, if they did not recur locally or at a distant site).

NOM: Non-operative management; Ref: Reference; NA: Not Applicable; NS: Not Stated;

^{*}Data obtained from unmatched cohorts

Summary Recommendations

Table 3:

Patient Selection	Eligibility criteria		cCR	Active Surveillance	Outcomes
	Inclusion	Exclusion			
<ul style="list-style-type: none"> ■ DRE ■ Proctosigmoidoscopy ■ Radiographic staging <ul style="list-style-type: none"> ○ CT chest/abdomen/pelvis ○ rectal cancer pelvic MRI 	<ul style="list-style-type: none"> ■ Histologically confirmed diagnosis of rectal adenocarcinoma ■ Radiologically measurable disease ■ cT2-T4a, N+ ■ Nodal involvement confined to radiation field. ■ Written informed consent for treatment and follow-up 	<ul style="list-style-type: none"> ■ cT4b ■ Tumor is causing symptomatic bowel obstruction (patients who have diverting ostomy are still eligible but obstructing tumor will preclude complete examination for response assessment) ■ Any prior pelvic radiation ■ Contraindication to fluoropyrimidine-based chemotherapy (e.g. DPD deficiency) ■ Unwilling or unable to provide informed consent 	<ul style="list-style-type: none"> ■ DRE: No palpable tumor when initially palpable by DRE. ■ Endoscopy: No residual tumor AND white scar. Negative biopsies from scar are not mandatory. ■ MRI (T2): Substantial downsizing with no residual tumor <ul style="list-style-type: none"> ○ OR residual fibrosis ○ OR residual wall thickening due to edema with fibrosis ○ AND no suspicious lymph nodes 	<ul style="list-style-type: none"> ■ DRE, proctoscopy, and CEA every 3 months for the first 2 years, then every 6-12 months for a total of 5 years. Scar biopsy not required unless suspicion of regrowth ■ MRI pelvis every 6 month for 2 years and then annually ■ CT chest/abdomen every 12 months for 5 years 	<ul style="list-style-type: none"> ■ Prospective data collection ■ Total number of eligible patients for inclusion ■ Rate of cCR ■ Number of patients offered NOM ■ Number of patients who consent to NOM ■ Tumor regrowth and salvage rate ■ Overall survival and disease free survival (DFS) at 1, 3, and 5 years. ■ Colostomy-free rate ■ Patient-reported outcomes (quality of life, functional outcomes).