Non-operative Management (NOM) of Rectal Cancer: Literature Review and Translation of Evidence into Practice

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Abstract

Purpose of Review Despite mounting interest in the non-operative management (NOM, also known as watchful waiting) of rectal adenocarcinoma, limited guidance exists regarding appropriate patient selection and procedures. In this literature review targeting patients with operable adenocarcinoma of the rectum, we sought to evaluate NOM in terms of patient selection, management approaches, and outcomes with regard to both quality of life (QoL) and oncologic outcomes.

Recent Findings Despite a lack of randomized evidence comparing NOM (performed via active surveillance following neoadjuvant chemotherapy and radiation) to neoadjuvant therapy followed by planned surgery, given that the vast majority of local, regional, and distant recurrences occur early in follow-up, the available evidence points to similar oncologic outcomes and possible QoL improvement. Due to the high chance of surgical salvage in the case of locoregional recurrence, close multidisciplinary follow-up is essential.

Conclusions Under the care of an experienced multidisciplinary lower gastrointestinal team, NOM is feasible, is safe, and has the potential for improved QoL. A potential algorithm for clinically implementing NOM is described within this review.

Keywords Rectal cancer · Non-operative management · Watch and wait · Chemoradiation · Quality of life · Oncologic outcomes

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Introduction

Decades of research have led to improvements in rectal cancer outcomes, with the German phase III CAO/ARO/AIO-94 trial setting a new standard management approach since its publication. Although it established the superiority of neoadjuvant long-course concurrent chemoradiation (LCRT) followed by surgery and then adjuvant chemotherapy over adjuvant LCRT [1], this treatment paradigm has been associated with significant long-term sequelae. With local recurrence rates occurring in only 0–8% of patients, evidence is increasing to support the hypothesis that only one local therapy is required for many patients to achieve optimal balance between treatment efficacy and quality of life (QoL) [1, 2••]. Although one strategy has been to eliminate radiation therapy (RT) for early stage rectal cancer patients [3, 4], another option gaining momentum is non-operative management (NOM, also known as "watch and wait") following RT and chemotherapy. Although

avoidance of a permanent stoma is a top priority for rectal cancer patients [5, 6], historically low pathologic complete response (pCR) rates on the order of 8–10% in rectal cancer likely delayed interest in such an approach [1, 7]. Habr-Gama and colleagues were the first to report long-term outcomes noting complete clinical response (cCR) rates exceeding historic pCR rates, with the majority of cCRs maintained and nearly all patients having successful surgical salvage in the setting of locoregional recurrence [8]. Data from randomized controlled trials (RCTs) confirming equivalent outcomes of NOM vs. neoadjuvant LCRT and surgery are not available, tempering the endorsement of NOM by many national guidelines [9]. The most recent version of the National Comprehensive Cancer Network (NCCN) guidelines currently does not include NOM as part of the main treatment algorithm, although the option is described in a footnote for cT3-4 N-any patients with or without a clear circumferential resection margin (CRM), appropriately suggesting this approach only being pursued by experienced multidisciplinary teams given the rigor and nuance of treatment and follow-up [10].

The purpose of this review is to increase physician familiarity with NOM as well as its potential benefits and risks. Survey data has indicated that knowledge of the literature has been correlated with physician comfort discussing and offering NOM with their patients [11]. Survey data also reveals increasing interest in NOM by both rectal cancer patients and their physicians, with one study indicating NOM as the option most patients preferred [6]. Patients have been found to be more comfortable than physicians with accepting higher risks of regrowth (defined as primary tumor recurrence following treatment in the setting of NOM), with patients willing to pursue the approach even if it was assumed this resulted in on average up to a 20% shorter overall survival (OS) [12]. Fortunately, although RCTs are lacking available data thus far, that does not suggest outcomes are compromised with NOM [2••, 13••, 14]. A survey of Asia-Pacific colorectal surgeons determined that over 80% support the option of NOM, with about 2/3 comfortable enough to offer it to their own patients [15]. However, in order to better inform patients of the risks and benefits of their various options, physicians must have a clear understanding of the rationale behind the various facets of NOM, as well as expected outcomes. The evidence contained within this review was assessed using the Population, Intervention, Comparator, Outcome, and Study design (PICOS) framework. For the population of operable patients with adenocarcinoma of the rectum, we sought to evaluate NOM in terms of patient selection, procedures, and outcomes with regard to QoL as well as disease control and survival metrics.

Methodology

Study types within this literature review consisted of RCTs, meta-analyses, and observational studies. With librarian assistance, we developed a literature search strategy using subject headings and combinations of keyword search terms (Appendix 1). To yield a comprehensive set of relevant articles, peer-reviewed journals indexed in Ovid Medline were searched covering the timeframe from 1/1/2015–9/7/2020. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Literature Search Extension (PRISMA-S) guidelines were used to guide the identification of journal articles for this literature review [16]. Two authors (CA and PC) independently screened the literature search results and full-text articles to determine the final studies included in this review as detailed in Appendix 2. Any discrepancies between the reviewers were resolved by consensus. We reviewed the bibliographies of full articles for a comprehensive survey, and 8 additional studies were included meeting all inclusion criteria except publication date (6 published before 2015). Forward citation chaining via Web of Science was then performed on the selected documents to determine if any eligible articles published no later than 9/7/2020 had been missed by the initial search strategy, and 3 were discovered resulting in a final count of 80 references [1, 2••, 3–9, 11, 12, 13••, 14, 15, 17••, 18–25, 26•, 27–45, 46•, 47•, 48, 49•, 50–57, 58•, 59, 60, 61•, 62–69, 70•, 71–76, 77•, 78–81]. The remaining 6 references contained in this paper involve 3 guideline documents for context [10, 82, 83], PRISMA-S instructions [16], a key conference abstract [84], and the associated protocol design [85] to address important advances in NOM research. The PRISMA-S checklist is contained in Appendix 3, Table 4.

Patient Selection and Outcomes with Non-operative Management

To investigate factors predictive of tumor regrowth following cCR post-neoadjuvant LCRT, Chadi et al. performed a rigorous individual patient data meta-analysis assessing 20 core variables in 11 data sets across 10 centers for non-metastatic cT-any cN-any patients [17••]. The authors were careful to include studies with a definition of a cCR that was equivalent to São Paulo benchmarks pioneered by Dr. Habr-Gama (i.e., absence of residual ulceration, stenosis, or mass within the rectum using digital rectal exam (DRE) and endoscopic exam; of note, cross-sectional imaging was not required), with the initial cCR rate after ranging from 12 to 78%. To increase patient population homogeneity, patients receiving 5 Gy × 5 fraction (fx) short course radiation (SCRT), local excision (LE), or contact brachytherapy were excluded. The majority of series involved LCRT without induction (pre-

LCRT) or consolidation (post-LCRT) chemotherapy. With a 3-year median follow-up, the 2- and 5-year local regrowth rates were 21.4% (95% confidence interval [CI], 15.3–27.6) and 28.0% (95% CI, 20.3–35.8). Of importance is that 93.4% of regrowths occurred within 3 years. Only T-stage was associated with regrowth, with rates of 19% (95% CI, 13–28), 31% (95% CI, 26–37), and 37% (95% CI, 21–60) for T1/2 ($n = 125$), T3 ($n = 282$), and T4 ($n = 22$) disease, respectively. Clinical variables such as nodal stage, carcinogenic embryonic antigen (CEA) level, and distance to the verge did not correlate with regrowth, indicating that these variables should not be used to exclude patients from NOM.

A major concern with NOM is missing the opportunity to cure a patient. Although one retrospective series showed an increased rate of distant metastases associated with regrowth [18], this has not been described in other studies [20–23, 39]. Table 1 describes the characteristics of key NOM studies, while Table 2 summarizes their outcomes. Available data including meta-analyses have revealed that NOM does not appear associated with any detriment to distant-metastases-free survival (DMFS), non-regrowth recurrence, or disease-specific survival (DSS) [2••, 13••, 14, 19–23]. In the meta-analysis by Dossa et al., it was found this holds true even when comparing NOM patients to those found to have a cCR preoperatively or pCR at the time of surgery, a strong predictor of improved outcomes [2••]. DMFS rates were not significantly different and were ≤20% for all groups. Following local regrowth the pooled proportion of patients who had salvage therapy was 95.4% (95% CI, 89.6–99.3). Another pooled analysis noted an 88% salvage rate for all pelvic recurrences, of which 93% were R0 and 45% were sphincter-sparing [13••]. Retrospective analyses have not found any increased morbidity associated with delayed salvage surgery [24, 25]. Over 90% of locoregional and almost 80% of distant recurrences occurred within first 3 years [2••, 13••, 17, 23]. Despite shorter duration of follow-up compared to surgical series, most recurrences appear captured, and thus, NOM appears promising and on par with standard treatment with regard to oncologic outcomes.

Treatment Regimens

Radiation

In the aforementioned individual patient data meta-analysis, LCRT radiation doses ranged from 45 to 65 Gy and RT dose was not correlated with regrowth rate [17••]. In fact, the lowest rate involved a 50.4 Gy cohort. However, the question remains whether increasing the RT dose leads to an improved

initial cCR rate. In the randomized, phase II RECTAL-BOOST study, increasing the dose from 50 to 65 Gy via a 5 × 3 Gy boost increased the initial near cCR or cCR rate from 45 to 69%, but the pCR rate or 2-year sustained cCR rate was not improved (38% vs. 36%, respectively) [26•]. In the setting of NOM, data from investigators out of São Paulo, Brazil, showed that for cT3 patients, the cCR rate was between 54 and 55% regardless of whether the regimen 50.4 Gy/28 fx ("standard" LCRT) or 54 Gy/30 fx with consolidation chemotherapy ("extended" LCRT, preferred by the group since 2006) was employed [27]. Surgery-free survival at 1 and 5 years was numerically but not significantly improved with extended LCRT (42% vs. 37.9% and 33.4% vs. 27.1%, respectively). In a separate retrospective analysis of 81 patients from the same group, they found that cT2 N0 patients were significantly more likely to have a cCR with extended LCRT vs. standard LCRT (85.7% vs. 56.6%, $p < 0.001$) [28]. However, consistent with the data in the individual patient data meta-analysis by Chadi et al. [17••], once a cCR has been attained, the surgery-free survival was similar between groups [28]. Because of the improved initial cCR rate, the 5-year organ preservation rate was higher with extended vs. standard LCRT (67% vs. 30%, $p = 0.001$). These two analyses offer insight as to why cross-trial comparisons regarding cCR rates should be approached with caution due to potential biases. While tempting to note that the prospective extended LCRT-only approach published in 2013 resulted in higher cCR rates (68%) than the standard LCRT approach (49%) assessed retrospectively in 2014 (see Table 1), multiple differences including patient population, study design, and methods of cCR assessment make such comparisons challenging [21, 22]. With regard to local excision, in the ACOSOG Z6041 trial, high toxicity was noted with 54 Gy, which was decreased to 50.4 Gy, resulting in improved tolerability. However, based on other trials that investigated the effects of concurrent oxaliplatin, radiosensitizing oxaliplatin was the more likely culprit for toxicity in ACOSOG as other prospective series have not reported increased toxicity with 54 Gy. Of note, data from a meta-analysis on patterns of failure note that the superior border of RT fields could be dropped to S2/3 to limit toxicity for cT1-2 patients [29]. In a study investigating the late dose-volume effects of RT specifically on the anorectal function in rectal cancer patients, the investigators assessed the frequency of low anterior rectal syndrome (LARS), one of the most common and challenging side effects occurring from the treatment of rectal cancer. It is defined as a constellation of symptoms defined by problems with fecal frequency, incontinence/seepage, and incomplete evacuation. One-third had major LARS in this series, and the most frequent reported complaints were clustering and fecal urgency. Trends towards worse long-term anorectal function were noted with a higher anal sphincter complex radiotherapy dose [30]. Since patients choosing NOM are clearly concerned about QoL, these data

Table 1 Characteristics of key non-operative management (NOM) studies

Author (year)	NOM (n)	Study design/ recruitment period	Mean age (years)	cT and N status	RT schedule (dose to gross disease in Gy/# fx)	Chemo regimen	Definition of cCR	Proportion with cCR	Follow-up regimen (timing)
Van der Valk (2018)	880	Multi Retro (Pre-2010–2017)	63.6	T1: 2% T2: 26% T3: 51% T4: 3% N/S: 18% N+: 50%	LCRT (45–60/25–30): 91.4% RT (N/S): 7.2% BT‡ (N/S): 9.4% No RT: 3% N/A: 0.8%	With LCRT: 91.4% Cape: 49% 5-FU: 23% Induc: 0% Consol: 1%	N/S, variable	N/A (only cCR pts. included)	Initial: (N/S) DRE, Endo, imaging[a] Surveillance: wide variety with Endo: 89%, MRI pelvis: 71%, CT pelvis: 30%, EUS: 8%, PET: 4%, CEA: 22%, diagnostic LE: 5% (89% showed pCR)
Renehan (2015)	129	Multi Pro/Retro (2011–2015)	66.9[d]	T2: 24% T3: 70% T4: 6% N+: 65%	LCRT (45/25)	With LCRT: 91% Cape: 90% 5-FU: 4% Induc/Consol: 0%	DRE and Endo: no ulceration/stenosis/-mass MRI: normal	N/S overall, but 31/259 (12%) from primary institution	Initial: (≥8 weeks) DRE, Endo, MRI Surveillance: 1st 2 years MRI q4–6 months, CEA at least annually, and DRE, endo, and CT C/A/P
Martens (2016)	85 (additional 15 had LE)	Multi Pro/Retro (2004–2014)	63.2	T1–2:25% T3: 67% T4: 8% N+: 74%	LCRT (50.4/28): 95% SCRT (25/5): 5%	With LCRT: 100% Cape: 95% Induc: 0% Consol: 34% (including CAPOX for 2% SCRT pts)	DRE: normal Endo: scar only MRI: normal	N/S overall, but 24 of 141 pts. (17%) treated at primary institution were included in the 100 pts. of the series	Initial[b]: (≥8 weeks) DRE, MRI, endo Surveillance: Endo and MRI q3mos × 1 year, then q6mos, also CEA and chest/liver imaging per SOC
Habr-Gama (2014)	90	Retro (1991–2011)	58.9	T2: 19% T3: 77% T4: 4% N+: 21%	LCRT (50.4/28)	With LCRT: 100% 5-FU/LV Induc/Consol: 0%	DRE and Endo: no ulceration, mass or mucosal abnormality and normal extrarectal imaging	49% (90 of 183)	Initial: (≥8 weeks) DRE, Endo, and extrarectal imaging (via CT, ERUS, and/or MRI) Surveillance: DRE and Endo q1–2mos year 1, q3mos years 2–3, q6mos afterwards. Imaging after 6 months, then annually (modality usage: CT 100%, 21% ERUS, 11% MRI).
Habr-Gama (2013)	47	Phase 2 (2006–10)	60.2	T2: 29% T3: 67% T4: 4% N+: 39%	LCRT (54/30)	With LCRT: 100% 5-FU/LV Induc: 0% Consol: 100%	DRE and Endo: no ulceration, mass or mucosal abnormality and normal imaging (via T2W&DWI-MRI and/or PET)	68% (47 of 70 enrolled)	Initial: (10 weeks) DRE, Endo, MRI/ERUS and/or PET, full thickness bx if subtle irregularity and TME if gross tumor Surveillance: DRE and Endo q2mos year 1, q3–4mos year 2, q6mos years 3–5. MRI or PET/CT q6mos years 1–2, then annually.
Smith (2019)	113	Retro (2006–15)	67.2[d]	T2: 20% T3: 80%			DRE and Endo: scar +/- telangiectasias without	11% (113 of 1070)	Initial: (N/S) DRE and Endo, MRI inconsistent

Table 1 (continued)

Author (year)	NOM (n)	Study design/ recruitment period	Mean age (years)	cT and N status	RT schedule (dose to gross disease in Gy/# fx)	Chemo regimen	Definition of cCR	Proportion with cCR	Follow-up regimen (timing)
				T4: 0% N+:66%	LCRT (45–54/25–28 fx)	With LCRT: Cape or 5-FU: 98% LCRT alone: 27% Induc: 42% Consol: 29% Chemo alone: 1.7%	ulceration or nodularity. MRI use inconsistent pre-2013		Surveillance: DRE and Endo q3mos year 1, q4mos year 2, q6mos years 3–5
Appelt (2015)/Dizdare-vic (2020)	40	Phase 2 (2009–13)	67.0[d]	T2: 53% T3: 47% T4: 0% N+: 45%	LCRT (60/30) + BT (5/1)	Oral Tegafur-ur-acil Induc/Consol: 0%	Endo/DRE: small, white scar or superficial erosion or erosion without palpable tumor, negative bx	78% (40 of 51 enrolled)	Initial: (6 weeks) DRE, Endo + bx, pelvic MRI done to evaluate nodes, not primary Surveillance: DRE/Endo q2mos year 1, q3mos year 2, q6mos year 3, q12mos years 4–5, PET/CT q4mos year 1, q6mos year 2, q1yr years 3–5

number, *Multi* multi-institution, *cT* clinical T stage, *cN* clinical N stage, *N+* node positive, *Pro/Retro* retrospective analysis of prospectively gathered data, *Retro* retrospective study, *RT* external bean radiation therapy alone, *N/S* not specified. *NOM* non-operative management, *LE* local excision, *R0* margin negative, *Consol* consolidation chemotherapy, *Induc* induction chemotherapy, *cCR* complete clinical response, *pCR* pathologic complete response, *Cape* capecitabine, *5-FU* fluorouracil, *LV* Leucovorin, *PET/CT* positron emission tomography/computed tomography, *MRI* magnetic resonance imaging, *T2W/DWI* T2-weighted and *DWI* diffusion-weighted imaging MRI scans, *DRE* digital rectal exam, *Endo* endoscopy, *ERUS* endorectal ultrasound, *SOC* institutional standard of care, *BT* brachytherapy, *bx* biopsy, *mos* months, *wks* weeks, *Bx* biopsy; *SCRT* short course radiation therapy, *LCRT* long-course concurrent chemo radiation therapy

[a] Imaging done as per institutional preference. Only 45% received DRE, endoscopy, and MRI at initial assessment

[b] 61% cCR at initial assessment, and at 2nd assessment 3 mos. later 24% cCR and continued NOM while other 15% had LE (60% pCR, 40% ypT1–2)

[c] BT was done alone, with LCRT, or with SCRT, so due to patients being counted twice the modality percentages in this section add up to >100%

[d] Median instead of mean

Table 2 Outcomes for patients undergoing organ preservation for key non-operative management (NOM) studies

Author (year)	# Organ Presrv (n)	Median F/U (range, yrs)	Local only regrowth (%)	Regional recurrence (%)	Regional recurrence alone (%)	LRR (%)	Timing of LRR	DMFS (%)	Salvage rate and modality for isolated LRR	Salvage outcomes	CFS	OS	DSS
Van der Valk (2018)	NOM: 880	3.3 (95% CI: 3.1–3.6)	N/S	Crude: 2%	Crude: 0.8%	2-yr: 25.2%[a]	88% in 2.0 yrs	3-yr: 93%	Total: 100%[b] (n=148) Surgery: 69% LE alone: 13% LE→TME: 9% TME: 78%	TME: 88% R0, otherwise N/S	N/S	5-yr: 85%	5-yr: 94%
Martens (2016)	NOM: 129	3.4 (1–10)	Crude: 12% (of which 3% were ypT2 at LE)	Crude: 3% (All MRI detected)	Crude: 3% (all MRI detected)	3-yr: 16%	100% in 2.1 yrs.	3-yr: 97%	Total: 100% (n=13) TME: 92% Exent: 8%	92% NED (1 died from post-op TME complications)	3-yr: 95%	3-yr: 97%	N/S
Renehan (2016)	NOM: 85 LE: 15	2.8 (IQR: 1.6–3.6)	Crude: 32%	Crude: 1.6% (submucosal/ mesorectal)	N/S	3-yr: 38%	N/S	Crude: 95%	Total: 88% (n=41) Surgery: 86% BT: 14%	97% R0, otherwise N/S	3-yr: 74%	3-yr: 96%	N/S
Habr-Gama (2014)	NOM: 90	NS (0.9–67)	N/S	N/S	N/S	Crude: 31%	17 pts. ≤12 mos, 11 pts. >12 mos	Crude: 86%	Total: 93% (n=26) TME: 96% BT: 4%	Crude "94% unresectable local recurrence-free survival"	N/S (5-yr DFS 68%)	N/S	5-yr: 91%
Habr-Gama (2013)	NOM: 47	5 (1–19)	Crude: 27%	0%	0%	Crude: 27%	≤12 mos: 2/3 pts.; >12 mos: 1/3 pts.	Crude: 85%	Total: 91% (n=12) TME: 27%	Regrowth ≤12 mos: 4 of 8 NED Regrowth >12 mos: 4 of 4 NED	N/S	3-yr: 90%	N/S
Smith (2019)	NOM: 113	2.8	Crude: 12% (of which 86% had endoluminal component)	N/S (3 of 22 TME ypN+)	0%	Crude: 19%	≤12 mos: 2/3 pts.; >12 mos: 1/3 pts.	Crude: 93%	Total[c]: 100% (n=22) TME: 82% LE: 9% LE→TME: 9%	91% NED in pelvis 36% developed DM, and only 1 of 8 of these pts. is NED.	5-yr: 79%	5-yr: 73%	5-yr: 90%
Appelt (2015)/ Dizdarevic (2020)	NOM: 40	5 (IQR: 3.5–6)	Crude: 30%	0%	0%	3-yr: 25% 5-yr: 31%	N/S	Crude: 82%	Total 100% TME (n=12)	Initial report: all 9 salvage TME pts. NED	N/S	3-yr: 95% 5-yr: 85%	N/S

OPM Organ Preservation Method, *N/S* not specified, *NED* no evidence of disease, *CI* confidence interval, *IQR* interquartile range, *LRR* locoregional relapse, *CFS* colostomy-free survival, *OS* overall survival, *DSS* disease-specific survival, *DFS* disease-free survival, *NED* no evidence of disease, *mos* months, *yr* year, *LE* local excision, *NOM* non-operative management, *BT* brachytherapy, *Exent* exenteration, *DM* distant metastases, *DMFS* distant metastases-free survival, *F/U* follow-up, *MRI* magnetic resonance imaging, *pts.* patients, *TME* total mesorectal excision

[a] 97% LRR involved local regrowth

[b] All of the 69% patients with data available following local regrowth had salvage; 31% had no information following recurrence mainly because received treatment elsewhere

and patient concerns should be considered when deciding on RT dose.

There are less data when it comes to SCRT in the setting of organ preservation. A large, retrospective analysis of Dutch patients treated with either LCRT ($n = 5070$) or SCRT ($n = 764$) without further chemotherapy following an interval of 5–15 weeks revealed that significantly more patients had a pCR following LCRT (17.5%) as compared to SCRT (9.3%) [31]. An international retrospective series found that significantly more ypN+ disease was found with SCRT without neoadjuvant chemotherapy compared to LCRT, indicating SCRT alone may be inadequate to sterilize pelvic disease [32]. In a small retrospective series of patients who underwent SCRT followed by LE 8–10 weeks later, only 17% (5 of 29) of cT2 patients had a pCR as compared to 48% of cT1 patients (13 of 27) [33], with acute RT-related complications occurring in about 1/3 of patients. Other data noting QoL decreases with neoadjuvant RT +/- chemotherapy indicates LE alone is preferred whenever RT may be avoided [34]. Overall, these data indicate that SCRT alone is not an optimal strategy when NOM is the goal [31]. However, there are data noting similar outcomes between neoadjuvant SCRT and consolidation chemotherapy vs. LCRT +/- consolidation chemotherapy when treatment involves planned total mesorectal excision (TME) [35–37]. Given the current lack of data, NOM via SCRT with consolidation chemotherapy appears most appropriate in an investigative setting such as the phase 2 Non-Operative Management and Early Response Assessment in Rectal Cancer (NOM-ERA) study investigating this approach (NCT03904043). In summary, prescribing doses of 50–54 Gy in 25 fractions of 1.8–2 Gy appears most appropriate in the NOM setting. Further data, ideally gathered prospectively via RCT, is needed to allow improved personalization of the most appropriate RT dose.

Brachytherapy

To date, the highest reported cCR rate following neoadjuvant therapy was 78% in the series involving 65 Gy delivered via a 5 Gy high dose rate (HDR) brachytherapy boost after 60 Gy to the gross tumor. Fifty Gy was given to elective nodes via a simultaneous-integrated boost [38] (Table 2). Long-term follow-up revealed the 5-year regrowth at 31%, similar to series with standard RT dosing [17••, 39]. Although the majority of QoL patient-reported outcome (PRO) metrics did not vary between baseline and subsequent assessments, rectal bleeding deteriorated from baseline which was attributed to the brachytherapy boost. Outcomes with an alternative method to HDR have been described by small series of patients receiving 45–50 Gy RT + 90 Gy contact brachytherapy (CXB). These have shown initial cCR rates ranging from 64 to 98% with regrowth

rates ranging from 11 to 12% and toxicity limited to the rectum [40, 41]. Although promising, the small size of the series, non-uniform technique and outcome reporting, and short follow-up limit the definitive conclusions about the effectiveness and safety of brachytherapy. However, these early results do indicate that integration of brachytherapy into the NOM regimen is worthy of further study. The Organ Preservation in Early Rectal Adeno (OPERA) (NCT 02505750) is a phase III study comparing 45 Gy + either 9 Gy/5 fx of RT or 90 Gy/3 fx of CXB. Although brachytherapy is not standard in NOM at present, to enable future comparisons and improvements, standardizing the reporting of endorectal brachytherapy RT dose, treatment volume specifications, and toxicity are necessary.

Chemotherapy

Although there are no published RCTs investigating the optimal treatment sequence and chemotherapy regimen for NOM, there are increasing relevant data to help guide practice. While there may be certain subsets of patients who may benefit from adjuvant chemotherapy following neoadjuvant LCRT and surgery [42], various meta-analyses have shown little to no benefit thus resulting in a shift to the development of total neoadjuvant therapy (TNT). Delivering all chemotherapy neoadjuvantly increases the chance of completing all treatment [43], and this theoretically may help combat distant and other patterns of recurrence. Pathologic complete response rates have been found to improve with increasing number of cycles of induction chemotherapy [44], with the TIMING study showing a pCR rate of 18% with LCRT alone, increasing to 25%, 30%, and 38% with 2, 4, and 6 q2week cycles of FOLFOX, respectively. However, toxicity increased as well, with the Grade 3+ side effects rate at just 5% with 1 month (2 cycles) of chemotherapy vs. 35% with 3 months (6 cycles). Further data are needed to determine the ideal balance between benefit and toxicity.

For cT1 or T2 patients, retrospective data from Habr-Gama et al. revealed that patients getting 50.4 Gy with 2 q3week concurrent cycles of 5-FU (standard LCRT) were less likely than those getting 54 Gy with 6 q3wk cycles of concurrent and consolidation chemotherapy (extended LCRT) to achieve a cCR (56% vs. 86%) and avoid definitive surgical resection at 5 years (30% vs. 67%) [28]. Similar to the findings of Chadi et al. [17••], for those who achieved a cCR regardless of dose group, surgery-free survival was similar [28]. No NOM patient required medical or surgical procedures for bleeding, strictures, or pain. This indicates that treatment up to 54 Gy with consolidation chemotherapy is a reasonable, safe approach for cT2 N0 patients. Emergent data includes that from the phase 2R Organ Preservation in Rectal Adenocarcinoma

(OPRA) study (NCT02008656), where patients with MRI stage II or III disease were randomized to 4 months of induction or consolidation chemotherapy added to LCRT to 50–56 Gy [84, 85]. At a median follow-up of 2 years, there was equivalent chemotherapy compliance between the TNT approaches, with a median RT dose of 54 Gy. Three-year disease-free survival (DFS) (77–78%) and DMFS (81–83%) rates were equivalent, but there was significantly improved 3-year organ preservation with the consolidation chemotherapy as opposed to induction (58% vs. 43%, respectively ($p = 0.01$)). In the operative setting, improved ypCR findings with consolidation vs. induction chemotherapy of the phase 2R CAO/ARO/AIO-12 study lend further support to this treatment sequence [46•]. In summary, although there is no proven benefit to NOM with induction or consolidation chemotherapy, numerically, the best reported outcomes to date involve LCRT followed by consolidation chemotherapy with either FOLFOX or CAPOX. Often 4 months of consolidation therapy is considered reasonable, as this was used in OPRA and it formed the standard-of-care arm in NRG-GI002: A phase II clinical trial platform for total neoadjuvant therapy (TNT) in rectal cancer (NCT02921256). Concurrent 5-FU or capecitabine should accompany LCRT.

Integrating Local Excision into NOM

Following radiation and chemotherapy, options for organ preservation could include local excision (LE) rather than TME if there is an incomplete response. However, appropriate considerations include concerns for incompletely addressed nodal disease and/or local recurrence. In order to better understand how LE may be integrated into organ preservation strategies including NOM, it is important to review the 4 major trials that address LE following LCRT, including (1) the phase 3 GRECCAR-2 trial that involved neoadjuvant LCRT with good responders (defined as primary ≤ 3 cm post-LCRT) randomized to TME vs. local excision, (2) the phase 3 study by Lezoche et al. that randomized 100 cT2 N0 patients to either TME or LE following LCRT, (3) the single-arm phase 2 CARTS trial that involved LCRT followed by transanal endoscopic microsurgery (TEM), and (4) the phase 2 single-arm ACOSOG Z6041 trial that also involved LCRT followed by TEM [47•, 48, 49•, 50, 79]. The ACOSOG and Lezoche et al. trials only included cT2 N0 patients whereas the other two included cT3, with GRECCAR-2 also allowing node-positive patients. Despite the ACOSOG and Lezoche et al. trials not requiring a completion TME for concerning pathologic findings such as ypT2+ disease, there were no nodal
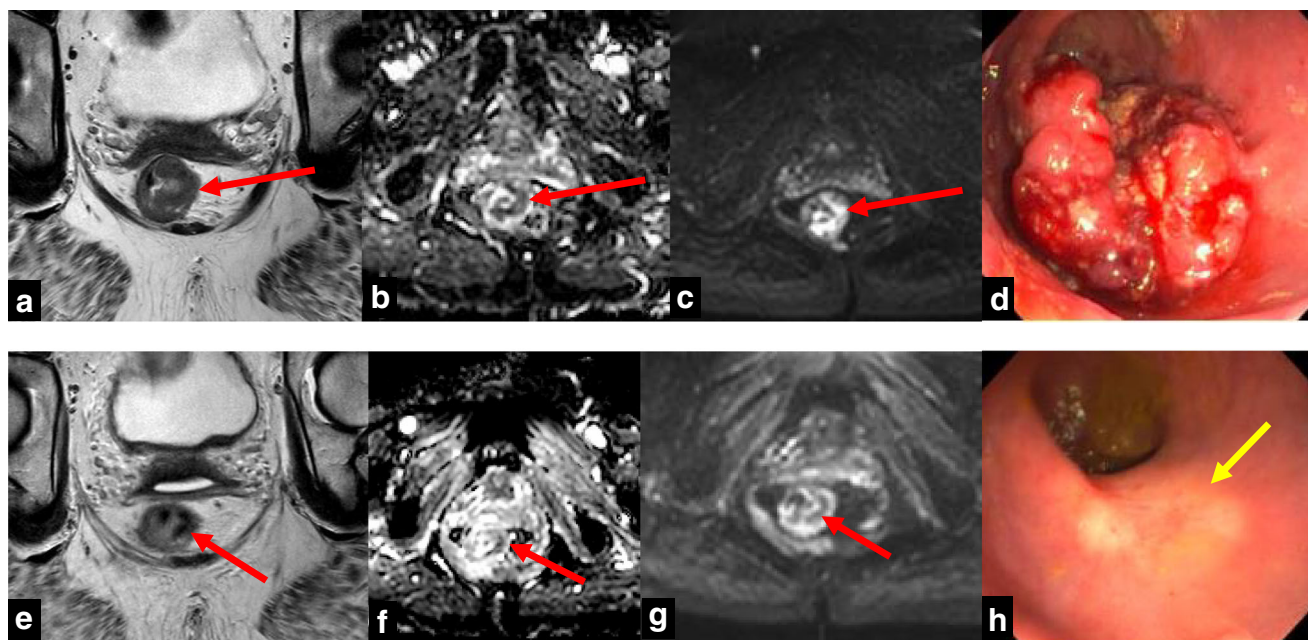

Fig. 1 66-year-old female with Stage IIIB, T3b N1b M0 adenocarcinoma of the rectum. Initial staging MRI demonstrated a centrally ulcerated left lateral wall mass (red arrows) which had intermediate intensity on T2W MRI (**a**), was hypointense on ADC map (**b**), and was hyperintense on DWI (**c**). Two mesorectal nodes were noted, and the extramural depth of invasion extended 4 mm. DRE and endoscopy (**d**) revealed a 2 cm mass 3 cm from the dentate line. Treatment involved LCRT to a prescription dose of 5400 cGy concurrent with capecitabine, followed 1 month later by 8 cycles of consolidation FOLFOX q2wks. After treatment, the lesion (red arrows) was decreased in size and was markedly hypointense on T2W (**e**), hypointense on ADC (**f**), and hypointense on DWI (**g**) consistent with cCR. The mesorectal nodes had resolved. DRE revealed a 1-cm firmness in the left lateral position with a smooth mucosal coating, and endoscopy (**h**) showed a flat white scar with telangiectasias (yellow arrow). Key: *cCR* complete clinical response, *MRI* magnetic resonance imaging, *DRE* digital rectal exam, *T2W* T2-weighted imaging, *DWI* diffusion-weighted imaging, *ADC* apparent diffusion coefficient, *FOLFOX* folinic acid, 5-FU, oxaliplatin

failures. For Lezoche et al., although TME patients may have been overtreated, oncologic outcomes were equivalent between arms. In ACOSOG, the local failure rate was only 4%. Of significant interest is that the pCR rate at the time of LE in all trials was noted to be 40–44%, supporting NOM as a potential initial strategy rather than planned LE. In GRECCAR-2, only 8% of all TME specimens and 8% of those with ypT2 disease were ypN+ at TME, lower than expected based on prior other data that ypT2 disease in initially cT3-4 or cN+ patients was associated with a node-positivity rate up to 30% [51]. As might be expected, in GRECCAR-2 ypT3 disease was associated with a 40% nodal positivity rate at TME [49•]. Another series of patients with initial cT3-4 N0-1 disease noted nodal positivity of > 10% despite ypT0 at TME suggesting a pCR of the primary does not guarantee clearance of nodal disease [52]. In a retrospective series of cT3 or cN+ patients, 50 of 362 patients received LE due to an objective clinical response that was not quite a cCR due to the presence of a residual ulcer measuring ≤ 3 cm. However, of these 50 patients, 30% underwent a completion TME for adverse pathologic findings (≥ ypT2 or R1), and 27% had positive lymph nodes on final pathology [53]. In summary, given the lack of

node positivity seen in ACOSOG and Lezoche et al., it may be surmised that the nodal positivity for ≥ ypT2 patients is driven by those with ≥ cT3 staging at diagnosis.

Because of the high rate of completion TME, in GRECCAR-2, QoL was not found to be improved compared to the LE group in the intention to treat analysis [49•]. Of importance is that patients who underwent neo-adjuvant LCRT followed by LE who then required completion TME had a 78% chance of encountering major surgical morbidity (Grades III–IV of Dindo's classification [54]) or severe side effects (definitive colostomy, anal incontinence, or impotence), as compared with only 38% who had a TME post-LCRT. As expected, the lowest rate of major toxicity (29%) was reported by patients whose treatment ended at LE following LCRT. Oncologic control did not differ between the 2 randomized groups. In the ACOSOG trial, completion TME was not required and QoL was preserved following LE [55]. In a study by Habr-Gama, it was noted that QoL and rectal function scores were improved with a NOM approach as compared to LE following LCRT [56].
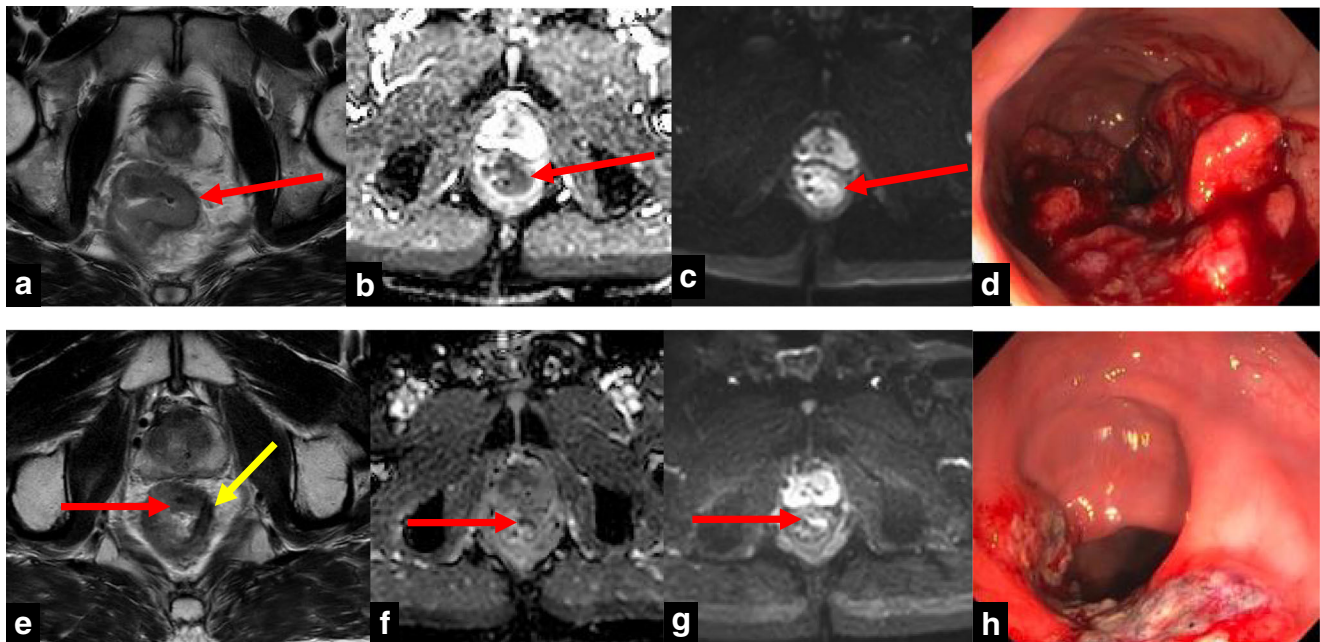

Fig. 2 57-year-old male with Stage IIA, T3b N0 M0 adenocarcinoma of the rectum. Initial staging MRI demonstrated a left lateral wall mass (red arrows) which had intermediate intensity on T2W imaging (**a**), was hypointense on ADC map (**b**), and was hyperintense on DWI (**c**). The extramural depth of invasion extended 3 mm. DRE and endoscopy (**d**) revealed a nearly circumferential mass 3 cm from the dentate line. Treatment involved 5 cycles of induction CAPOX q3wks followed 2 months later by LCRT to max dose of 5400 cGy concurrent with capecitabine. Ten weeks following LCRT, MRI showed the tumor (red arrows) had decreased in size but there was residual disease (red arrows) which had intermediate intensity on T2W (**e**), was hypointense on ADC (**f**), and was hyperintense on DWI (**g**). There was a rim of marked T2W hypointensity (yellow arrow) (**a**) representing fibrosis in area of treated tumor. **h** Endoscopy revealed regression and necrosis but still clear residual disease. He proceeded to APR and was found to have ypT2 N0 disease. Key: *MRI* magnetic resonance imaging, *DRE* digital rectal exam, *DWI* diffusion-weighted imaging, *T2W* T2-weighted imaging, *ADC* apparent diffusion coefficient, *LCRT* long-course concurrent chemoradiation, *CAPOX* capecitabine and oxaliplatin

In summary, these various data suggest very limited support for a LCRT and LE approach for patients with cT3+/cN+ disease at presentation. Given the risk of completion TME which is found to significantly increase the risk for poor QoL following LCRT, cT3+/N+ patients may be better advised to attempt organ preservation through NOM, with a plan for salvage with TME rather than LE for an incomplete response. The finding of ypT2 disease at LE for initial stage cT3+/N+ patients confers a higher risk of node positivity than ypT2 disease for patients who are cT2 N0 at diagnosis. For cT2 N0 patients who do not respond completely to LCRT during NOM and are found to have ≤ ypT2 disease at LE, favorable oncologic and QoL outcomes may be possible despite avoidance of a completion TME. This approach is not mentioned as an option in the current NCCN rectal guidelines [10], but it is a favored approach by the gastrointestinal expert American Radium Society™ Appropriate Use Committee [83].

Quality of Life

QoL benefits may be seen with NOM regardless of tumor location and the expected surgery. Of note, cancer patients' participation in social, recreational, and civic activities has been found to be strongly associated with QoL, but these activities are not well integrated into cancer survivorship research or interventions [57]. Several matched controlled studies have shown major LARS occurs in about 2/3 of patients undergoing RT and surgery, but definitive LCRT is not without problems with 1/3 of patients suffering these symptoms [58•, 59]. Beyond fecal symptoms, additional benefits noted with NOM vs. planned surgery following neoadjuvant treatment include improved physical and cognitive function, improved physical and emotional roles, better global health status, and fewer problems with sexual/urinary tract function [58•, 60]. In the absence of randomized data comparing NOM with standard surgical therapy following LCRT, Markov Decision Analyses have been performed to compare outcomes [61•, 62]. These assessments have found similar DSS, but with the benefit of superior quality adjusted survival and decreased costs. Upfront TME was preferred only when the assumed expected rates of successful surgical salvage were lower than those actually reported in the literature, with the authors concluding that NOM is a reasonable option if patients undergo close monitoring for recurrence.

Table 3 Summary of the University of Vermont Rectal Cancer Non-operative Management Algorithm

Patient selection
• cT1[a]-4b cN-any M0
• +/- EMVI or threatened circumferential radial margin
• Any location

RT dose/volumes
• 50–54 Gy in 25–30 fractions of 1.8–2 Gy (CTV 45 Gy to elective pelvic nodes, 50–50.4 Gy to mesorectum circumferentially ≤2 cm longitudinally from GTV, and 54 Gy to GTV + ≤2 cm; PTV = 0.5 cm & with daily IGRT with CBCT to confirm set-up and assess bladder filling
• (If small bowel toxicity is a concern (e.g., if small bowel $V_{50\ Gy}$>10 cc), reducing the boost size or withholding it altogether is advised. Simulation with oral contrast encouraged to help identify small bowel.)

Chemotherapy
• Concurrent with LCRT: 5-FU or Capecitabine
• Consolidation FOLFOX × 8 or CAPOX × 5 cycles starting ~ 1–2 months following CRT (endoscopy before chemotherapy encouraged (2–6 weeks after LCRT) to exclude interim progression of disease)

Initial assessment (2–3 months post-TNT completion)
• DRE
• Endoscopy (e.g., via flexible sigmoidoscopy)
• CEA
• MRI rectal protocol
• CT chest/abdomen/pelvis with contrast

Follow-up following cCR[c]
• DRE: q3mos × 2 years, then q6 months × 3 years, then prn
• Endoscopy (via flexible sigmoidoscopy preferred): q3mos × 2 years, then q6mos × 3 years, then annually
• CEA: q3mos × 2 years, then q6 months × 3 years, then prn
• MRI rectal protocol: q6–12 months×2–3 years, then annually until 5 years, then prn
• CT chest/abdomen/pelvis with contrast: q6 months × 2–3 years, then annually until 5 years, then prn

Locoregional salvage therapy
• If incomplete response or local only regrowth without metastases for initial cT1-2 N0 patients: LE or TME offered. Observation is preferred over completion TME following LE if pathology shows ≤ypT2 disease
• If incomplete response or local only regrowth without metastases for initial cT3+ patients: TME preferred
• If non-metastatic regional recurrence: TME preferred.

NOM non-operative management, *LE* local excision, *DRE* digital rectal exam, *CEA* carcinogenic embryonic antigen, *MRI* magnetic resonance imaging, *CT* computed tomography, *CBCT* cone beam computed tomography, *EMVI* extramural vascular invasion, *CRT* chemoradiation, *GTV* gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume, *FOLFOX* folinic acid, 5-FU, oxaliplatin, *CAPOX* capecitabine and oxaliplatin

[a] LE alone without neoadjuvant therapy preferred for T1 patients who are eligible [10]

[b] Consider simultaneous integrated boost intensity-modulated radiation therapy technique especially if T4b (45 Gy to elective nodes including external iliacs/50 Gy to primary all in 25 fractions), followed by 4 Gy boost

[c] q2–3-month DRE and endoscopy +/- MRI may be appropriate until cCR is achieved

Assessment of Treatment Response

Much effort has also been put into correlating pCR with tumor response assessments following LCRT [63]. Typically, a cCR has been defined as follows: (1) DRE: no palpable tumor when initially palpable; (2) endoscopy: no residual tumor, with flat, white scar and/or telangiectasia acceptable but no ulcer or nodularity; (3) T2-weighted MRI (MRI-T2W): only dark and no intermediate T2 signal with no visible nodes; and (4) diffusion-weighted MRI (MRI-DW): no diffusion restriction (Table 1) [23, 85]. However, there are limitations to all methods of assessment, with uncertainty further compounded by heterogeneity in the timing and techniques of the various assessments thus limiting definitive conclusions. For example, pCRs have been noted despite mucosal abnormalities on endoscopy, mixed signal or tumor site irregularities on MRI-T2W, restriction on MRI-DW, and suspicious nodes indicating the possibility of false positives [64, 65]. Typically, MRI rarely alters the determination of whether a cCR is present based on endoscopic assessment [70•, 71]. Fortunately, advances are being made to further gastrointestinal radiologists' ability to recognize a rectal cCR, including certain patterns of intermediate and low signal that indicate a cCR with high specificity rather than persistent disease (i.e., split scar sign) [81]. Biopsy should not be relied on as a means to rule out disease presence, with a negative predictive value (NPV) reported as low as 11% due to tumor scatter or submucosal persistence of disease [66]. The greatest value of MRI as well as CT at present lies in evaluating extraluminal recurrences. In a retrospective series involving 3 independent reviewers assessing the likelihood of a pCR based on endoscopic images following LCRT or SCRT, the ranges for sensitivity, specificity, positive predictive value (PPV), and NPV were 72–94%, 61–85%, 63–78%, and 80–89%, respectively [64]. A flat white scar was most predictive of a ypCR, with the PPV of small (< 1 cm) flat, large flat, and irregular ulcers at 40–50%, 29–33%, and 4–15%, respectively. In the setting of these ulcers, MRI often shows ambiguous findings such as heterogeneous T2 signal or small focal diffusion restriction and thus does not provide additional clarity [67]. In a prospective series of 124 patients evaluated pre-operatively 6–7 weeks post-LCRT by MRI and EUS, 75% of pCR patients had a mass in the rectal lumen or suspicious lymph nodes [68]. Therefore, for those with a near cCR, a repeat assessment 2–3 months later may be pursued. Figure 1 shows an example of a patient experiencing a cCR with resolution of all concerning clinical findings, whereas Fig. 2 illustrates MRI and endoscopic findings consistent with an incomplete response. Following LE, despite anatomic defects that may be introduced from the surgical procedure, MRI has shown utility with high T2W signal intensity and thickening of the rectal wall in recurrent disease, with DWI abnormalities also useful but slightly less sensitive [69].

Initial Assessment and Surveillance

There is an increasing amount of data noting the importance of allowing patients undergoing NOM with a near cCR to continue close follow-up, as excellent oncologic outcomes have been achieved with this approach [19]. Hupkens et al. found that > 90% of patients with a near cCR 8–10 weeks after LCRT (none received induction or consolidation chemotherapy) will achieve a cCR 6–12 weeks later [70•]. Although those achieving a cCR at the 2nd time point had a non-significant numerically higher chancer of regrowth (27% vs. 16%), 2-year OS was equivalent (98% vs. 99%). In a retrospective review of 49 consecutive patients who received the São Paulo "extended" LCRT NOM approach of 54 Gy followed by consolidation chemotherapy, Habr-Gama et al. found that only 38% of patients achieved a cCR within 10–16 weeks of neoadjuvant LCRT. The median time to a strict cCR was 18.7 weeks, with earlier T-stage patients (cT2-T3a) achieving a cCR significantly earlier than more advanced disease (cTb-d/4) [71]. Therefore, the authors of these studies offer the logical conclusion that the cCR observation period should be extended rather than proceeding directly to surgery.

It is important to note that if recurrences are identified promptly, the vast majority may be salvaged underlining the importance of close surveillance (Table 2). As noted previously, the majority of recurrences occur during the first 3 years, so closer follow-up is required initially via DRE, endoscopy, rectal protocol MRI, and CT of the chest/abdomen/pelvis with contrast [72]. Close surveillance has been found acceptable to patients and their providers [73], and even with the frequent assessments, NOM still remains more cost effective than planned surgical approaches [74]. Worse outcomes have been found in series where patient compliance with surveillance and salvage surgery is compromised [75, 76]. The location of the recurrences is almost always entirely in the bowel wall and is thus identifiable via DRE and/or endoscopy [19]. Imaging is required to identify nodal recurrences, although fortunately the risk has been found to be low with crude rates at 0–3% [19–21, 23] (Table 2). In a retrospective series of 90 patients, every patient without DWI nodal abnormalities was found to be ypN0, with the presence of DWI abnormalities noted to have a sensitivity, NPV, specificity, and PPV of 100%, 100%, 14%, and 24%, respectively [80]. Based on prospectively gathered data, the positive posttest probability for detecting a true

cCR has been reported to be as high as 98% when DRE, endoscopy, T2W, and DWI MRI all indicate a cCR [77•]. Combining modalities was also found to improve the negative posttest probability to 15% from 20% and 26% with endoscopy or MRI (T2W and DWI) alone, respectively. This signified that when all tests indicated residual disease was still present the chance of a complete response still actually being present dropped to 15%.

Follow-up should continue for a minimum of 5 years, but follow-up beyond this time is not thought necessary for cT1-2 N0 patients undergoing LE following neoadjuvant therapy given the very low risk of recurrence beyond that time. However, long-term outcomes for patients treated with NOM are still evolving. Conditional survival estimates have been calculated for a São Paulo patient population as a function of time, showing that the chance of recurrence decreases the further from treatment completion with no patients expected to recur past 8 years [78]. Patients were found to have a significantly lower risk (≤ 10%) of developing recurrences 2 years after achieving a cCR following LCRT, with no regrowths expected past 3 years for patients treated with LCRT to 54 Gy with consolidation chemotherapy (extended LCRT). While the authors recognize follow-up past 5 years might detect a small number of late recurrences, it is unclear if prolonged surveillance will have an impact on OS. The authors did note that after 2 years of follow-up, the known risk factor for relapse involving T-stage becomes less relevant, and RT dose escalation to 54 Gy combined with consolidation chemotherapy may significantly decrease recurrence at later time points.

Conclusions

Although there are no RCT data indicating the long-term safety of NOM, outcome data from Phase 1–2 studies have indicated that there are a number of patients who may be able to successfully achieve organ preservation. Based on the literature, approximately 1/3 to 2/3 of patients undergoing NOM achieve a cCR, with regrowth occurring in about 1/5 to 1/3 of patients and overall organ preservation successful in about 1/5 to 1/2 of patients (Table 2). It is understandable that before widespread acceptance of this approach, further prospective data with more universally standardized definitions of treatment response and a follow-up regimen are required (e.g., Magnetic Resonance Tumour Regression Grade as Biomarker for Stratified Management of Rectal Cancer Patients (TRIGGER, NCT02704520) and Can the Rectum be Saved by Watchful Waiting or TransAnal Surgery Following (Chemo)Radiotherapy Versus Total Mesorectal Excision for Early REctal Cancer? (STAR-TREC, NCT02945566)). For those institutions with strong

multidisciplinary groups employing high-quality rectal MRIs with skilled radiologist oversight and expertise in assessing for response and recurrence, NOM may be offered to patients of any stage with significant QoL concerns particularly if they have a distal rectal cancer. As always, shared patient-provider decision making is essential, and prospective series must emphasize PROs. With regard to the treatment regimen, more is not always better, and biology may surpass brute force through treatment escalation [26]. At present, LCRT to 50–54 Gy with strong consideration for up to 4 months of consolidation chemotherapy is in line with favorable outcomes noted by the studies found within this literature review as well as the initial results of the OPRA trial (Table 2). Table 3 describes the approach taken at the University of Vermont Cancer Center based on our experience and review of the literature. Our approach agrees well with the ASTRO Clinical Practice Guidelines for rectal cancer [82], and while our follow-up intervals are on the longer side they still fit within previously described surveillance schedules that resulted in successful outcomes (Table 1). It is important to remember that most recurrences occur within the first 3 years, and with close follow-up, the salvage rate is excellent, with the data thus far not suggesting any added surgical complications or worse oncologic outcomes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations 5-FU, Fluorouracil; ADC, Apparent diffusion coefficient; CAPOX, Capecitabine and oxaliplatin; CEA, Carcinogenic embryonic antigen; cCR, Complete clinical response; CRT, Chemoradiation; CT, Computed tomography; CTV, Clinical target volume; CXB, Contact brachytherapy; DRE, Digital rectal exam; DWI, Diffusion-weighted imaging; EMVI, Extramural vascular invasion; FOLFOX, Folinic acid, 5-FU, oxaliplatin; GTV, Gross tumor volume; HDR, High-dose rate; LE, Local excision; LCRT, Long-course chemoradiation; MRI, Magnetic resonance imaging; NOM, Non-operative management; pCR, Pathologic complete response; PICOS, Population, Intervention, Comparator, Outcome, and Study design; PRISMA-S, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Literature Search Extension; PRO, Patient-reported outcome; PTV, Planning target volume; QoL, Quality of life; RT, Radiation therapy; RCT, Randomized controlled trial; TEM, Transanal endoscopic microsurgery; TME, Total mesorectal excision; TNT, Total neoadjuvant therapy

Appendix 1. Literature search strategy for non-operative management (NOM) of rectal adenocarcinoma
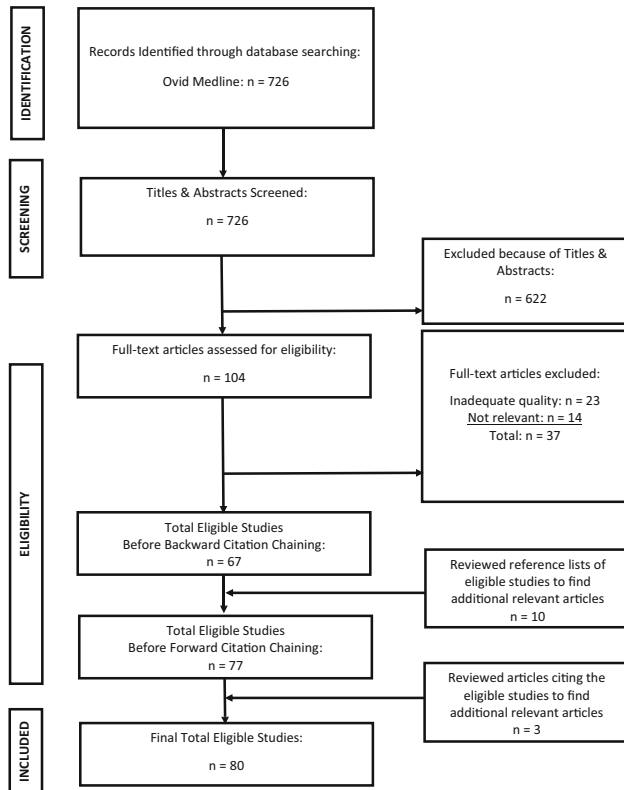
Literature Search Date Range: 1/1/2015 – 9/7/2020

Database: Ovid MEDLINE(R) without Revisions

Set Number	Search Text	Number of References Retrieved
1	*Rectal Neoplasms/	36,082
2	*Colorectal Neoplasms/	77,841
3	*Rectum/	21,685
4	*Neoplasms/	351,449
5	3 and 4	1,067
6	(rectum* or rectal* or colorectal*).ti,ab,kf.	253,449
7	(cancer* or carcinoma* or neoplas* or adenocarcinoma* or malignan* or tumor* or tumour*).ti,ab,kf.	3,404,088
8	6 and 7	185,578
9	1 or 2 or 5 or 8	198,669
10	exp Radiotherapy/	186,086
11	rt.fs.	191,660
12	exp Chemoradiotherapy/	14,896
13	Radioimmunotherapy/	3,211
14	Radiotherapy, Adjuvant/	22,427
15	(radiotherap* or radiat* or radio-chemo* or radiochemo* or irradiat* or EBRT or neoadjuvant*).ti,ab,kf.	718,520
16	(brachytherap* or intracavitar* or interstitial* or implant*).ti,ab,kf.	520,480
17	(chemo-radi* or chemoradi*).ti,ab,kf.	32,055
18	(radio-immun* or radioimmun* or immunoradio*).ti,ab,kf.	70,202
19	(CRT or RT or IGRT or nCRT or nCR or aRT or aCT or aCRT or dCRT or iCT).ti,ab,kf.	60,8242
20	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	1,914,589
21	9 and 20	31,317
22	Watchful Waiting/	3,851
23	("watchful wait*" or "watch and wait" or "active surveillance" or "expectant management" or observation* or regrowth or "rect* preserv*" or "organ* preserv*").ti,ab,kf.	892,010
24	(NOM or "non-operative manage*" or "nonoperative manage*" or "nonsurgical manage" or "non-surgical manage*").ti,ab,kf.	8,877
25	(inoperable or "wait and see" or nonoperative or "non-operative").ti,ab,kf.	30,209
26	22 or 23 or 24 or 25	925,555
27	21 and 26	1,832
28	limit 27 to yr="2015-2020"	797
29	limit 28 to English language	726

KEY: Sets 1-9: Rectal adenocarcinoma (Concept 1), Sets 10-20: Treatment addresses chemotherapy or radiation therapy (Concept 2), Set 21: (Concept 1 & 2 combined), Sets 22-26: Treatment addresses organ preservation (Concept 3), Set 27: Concept 3 combined with Concepts 1&2, Sets 28-29: Additional limits on search including date range and English language.

Appendix 2. Study selection flowsheet
for the non-operative treatment (NOM)
of rectal adenocarcinoma

IDENTIFICATION

Records Identified through database searching:

Ovid Medline: n = 726

SCREENING

Titles & Abstracts Screened:

n = 726

Excluded because of Titles & Abstracts:

n = 622

Full-text articles assessed for eligibility:

n = 104

Full-text articles excluded:

Inadequate quality: n = 23
Not relevant: n = 14
Total: n = 37

ELIGIBILITY

Total Eligible Studies
Before Backward Citation Chaining:
n = 67

Reviewed reference lists of eligible studies to find additional relevant articles
n = 10

Total Eligible Studies
Before Forward Citation Chaining:
n = 77

Reviewed articles citing the eligible studies to find additional relevant articles
n = 3

INCLUDED

Final Total Eligible Studies:

n = 80

Appendix 3

Table 4 PRISMA-S Checklist

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	2nd page
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	N/A
Study registries	3	List any study registries searched.	N/A
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	N/A
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	2nd page
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	N/A
Other methods	7	Describe any additional information sources or search methods used.	N/A
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Appendix 1
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	Appendix 1
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	N/A
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	N/A
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	N/A
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	2nd page
PEER REVIEW			
Peer review	14	Describe any search peer review process.	2nd page
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	Appendix 2
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	N/A

KEY: PRISMA-S = Preferred Reporting Items for Systematic Reviews and Meta-Analyses Literature Search Extension; N/A = not applicable

PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB, PRISMA-S Group

Last updated February 27, 2020

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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