INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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REVIEW

Executive Summary of the American Radium Society on Appropriate Use Criteria for Nonoperative Management of Rectal Adenocarcinoma: Systematic Review and Guidelines

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Received Jan 24, 2024; Accepted for publication May 17, 2024

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Disclosures: C.J.A. reports personal fees from Syntactx for Data Safety Monitoring Board for Pancreatic Cancer Trial. J.E.S. reports personal fees from Arcus Biosciences and grants from MedPacto, Inc., and Clinigen, Inc. J.B. reports personal fees from AbbVie, Astellas, Atreca, Bayer, Dragonfly, I'Mab, Lilly, Incyte, EMD Serono, Pfizer, BMS, Transcenta, Tyra, Totus, Sumitomo Dainipon Pharma Oncology, 23 and me. K.R.J. is an editor for RadOncQuestions.com, LLC. P.L. reports personal fee from Viewray Inc.; grants and personal fees from AstraZeneca, Inc.; personal fees and nonfinancial support from Varian, Inc.; and personal fees from Genentech, Inc, outside the submitted work. N.S. reports personal fees and travel support from Sirtex Medical, Inc. W.S. reports personal fees from Carl Zeiss, Merck, and Varian. The remaining authors report no disclosures.

Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Acknowledgments—We thank Terence "Bear" Irwin, Patient Advocate, for providing perspective and helping the authors organize and incorporate patient priorities regarding recommendations for current and future health care options for the treatment of rectal cancer. We also thank Andrea Taylor and Ellie See, consecutive Executive Directors of the Talley Management Group, for their attention to detail and diligence in this project.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2024.05.019.

Int J Radiation Oncol Biol Phys, Vol. 120, No. 4, pp. 946–977, 2024
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2024.05.019

For patients with rectal cancer, the standard approach of chemotherapy, radiation therapy, and surgery (trimodality therapy) is associated with significant long-term toxicity and/or colostomy for most patients. Patient options focused on quality of life (QOL) have dramatically improved, but there remains limited guidance regarding comparative effectiveness. This systematic review and associated guidelines evaluate how various treatment strategies compare to each other in terms of oncologic outcomes and QOL. Cochrane and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology were used to search for prospective and retrospective trials and meta-analyses of adequate quality within the Ovid Medline database between January 1, 2012, and June 15, 2023. These studies informed the expert panel, which rated the appropriateness of various treatments in 6 clinical scenarios through a well-established consensus methodology (modified Delphi). The search process yielded 197 articles that advised voting. Increasing data have shown that nonoperative management (NOM) and primary surgery result in QOL benefits noted over trimodality therapy without detriment to oncologic outcomes. For patients with rectal cancer for whom total mesorectal excision would result in permanent colostomy or inadequate bowel continence, NOM was strongly recommended as usually appropriate. Restaging with tumor response assessment approximately 8 to 12 weeks after completion of radiation therapy/chemoradiation therapy was deemed a necessary component of NOM. The panel recommended active surveillance in the setting of a near-complete or complete response. In the setting of NOM, 54 to 56 Gy in 27 to 31 fractions concurrent with chemotherapy and followed by consolidation chemotherapy was recommended. The panel strongly recommends primary surgery as usually appropriate for a T3N0 high rectal tumor for which low anterior resection and adequate bowel function is possible, with adjuvant chemotherapy considered if N+. Recent data support NOM and primary surgery as important options that should be offered to eligible patients. Considering the complexity of multidisciplinary management, patients should be discussed in a multidisciplinary setting, and therapy should be tailored to individual patient goals/values.

Introduction/Background

Patients with rectal cancer value quality of life (QOL) to a high degree often underappreciated by physicians, with many patients even prioritizing QOL over oncologic outcomes, noting continuation of activities they enjoy as being of utmost importance[1-5] (see Appendix E1 for American Radium Society [ARS] patient advocate perspective). Fortunately, recent research has provided dramatic increases in treatment options for rectal cancer that preserve QOL without compromising overall survival (OS) or cancer control.[6] Although a trimodality treatment (TMT) approach involving long-course (LC) chemoradiation therapy (CRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy (aCT) was the standard for decades,[6] this paradigm is associated with significant long-term sequelae, especially with regard to bowel and sexual function. Despite an overall decrease in rectal cancer incidence,[7] a >50% increase for patients <50 years old since 1994 shows patients may be living longer with chronic sequelae.[8] While local recurrence (LR) occurs in <10% of patients, severe low anterior resection syndrome (LARS) occurs in approximately two-thirds receiving TMT. Thus, increasing evidence indicates that only one local therapy is typically required for most patients with rectal cancer to optimally balance treatment efficacy and QOL. In this setting, both nonoperative management (NOM, herein defined as no rectal surgery including TME or local excision [LE]) and primary surgery have emerged as treatment options.

While NOM has shown no detriment to oncologic outcomes compared to TMT,[9-12] NOM adoption has been slow due to historic data showing low pathologic complete response (pCR) rates[13,14] to chemotherapy (CT)/radiation therapy (RT). However, recent data reveal that with adequate time following completion of neoadjuvant treatment, complete clinical response (cCR) rates far exceed pCR rates, and TME-free survival (TME-FS) may exceed 50%.[9,10,15] Alternatively, QOL could be improved by eliminating RT, with neoadjuvant CT (nCT) followed by TME shown to be noninferior to a TMT approach in select patients.[16] Further, immunotherapy may be the only therapy required for certain microsatellite instability-high (MSI-H)/mismatch repair deficient (MMRd) patients,[17-20] with alternative therapies reserved for incomplete responders to immunotherapy. Thus, implementation of NOM, primary surgery, or immunotherapy when appropriate may allow treatment de-escalation and improved QOL without compromising treatment efficacy.

Although the National Comprehensive Cancer Network and American Society for Radiation Oncology guidelines endorse these options for select patients,[21,22] there is a gap in knowledge regarding the effectiveness of de-escalated treatment options compared with each other and with TMT, how to implement them, and which patients are eligible for each treatment paradigm. The present comprehensive systematic review and guidelines therefore seek to inform patient-provider shared decision making. The Population, Intervention, Comparator, and Outcome questions included (1) which patients are best suited for NOM and primary surgery; (2) what are the optimal treatment strategies regarding RT and/or systemic therapy in terms of oncologic outcomes and QOL; (3) what are the optimal modalities and their timing for assessing a cCR during NOM; and (4) what is the role of LE in the setting of salvage during NOM and organ preservation (OP) in terms of

oncologic outcomes and QOL, with the goal of providing insights and direction to practitioners based on the available evidence.

Methodology

Using the Population, Intervention, Comparator, Outcome (PICO) framework, the evidence regarding treatment outcomes was assessed using Cochrane and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 methodology.[23,24] Eligible studies included prospective phase 2 and 3 trials, meta-analyses, and retrospective analyses published between January 1, 2012, and June 15, 2023, in the Ovid Medline database. Trial size required for inclusion was ≥25 patients except for topics with limited available evidence. Nonhuman, cost analysis, and national database studies were excluded. A database search strategy was developed to address key questions. Two authors independently screened the comprehensive list of articles, and one assessed full text documents to determine the final studies included in the "Summary of Literature Review," which advised our committee recommendations. Discrepancies between reviewers were resolved by consensus. Of the 1069 unique articles identified using the search strategy, 197 were selected that satisfied all inclusion/exclusion criteria (including 1 and 14 articles identified by forward and backward citation searching, respectively; see Fig. 1 for flow diagram). Study type and quality were assessed via ARS Appropriate Use Criteria (AUC) methodology. Well-established Research and Development/University of California-Los Angeles (RAND-UCLA) consensus methodology (modified Delphi) was used by the expert panel to rate the appropriateness of the treatment options,[25] with a total of 3 voting rounds employed. Treatment option categories included (1) usually not appropriate (U, score 1-3), (2) may be appropriate (M, score 4-6), and (3) usually appropriate (A, score 7-9). Studies referenced outside the "Summary of Literature Review" are included to provide context, but unless they are also cited within the "Summary of Literature Review," they were not used by the committee to guide recommendations. The project proposal as well as this executive summary were reviewed and approved by the ARS AUC steering committee, which includes a librarian with expertise in systematic reviews. For the full search strategy (designed by CJA), see https://www.americanradiumsociety.org/page/docsbypanel#GI. For further details on ARS AUC methodology guidelines, see https://www.americanradiumsociety.org/page/aucmethodology.

Summary of Literature Review

Topic 1: Candidates for NOM

Available data including meta-analyses comparing NOM with TMT fail to show a difference in oncologic outcomes including OS, distant metastasis (DM)−free survival (DMFS), and nonregrowth recurrence.[26,27] Although a

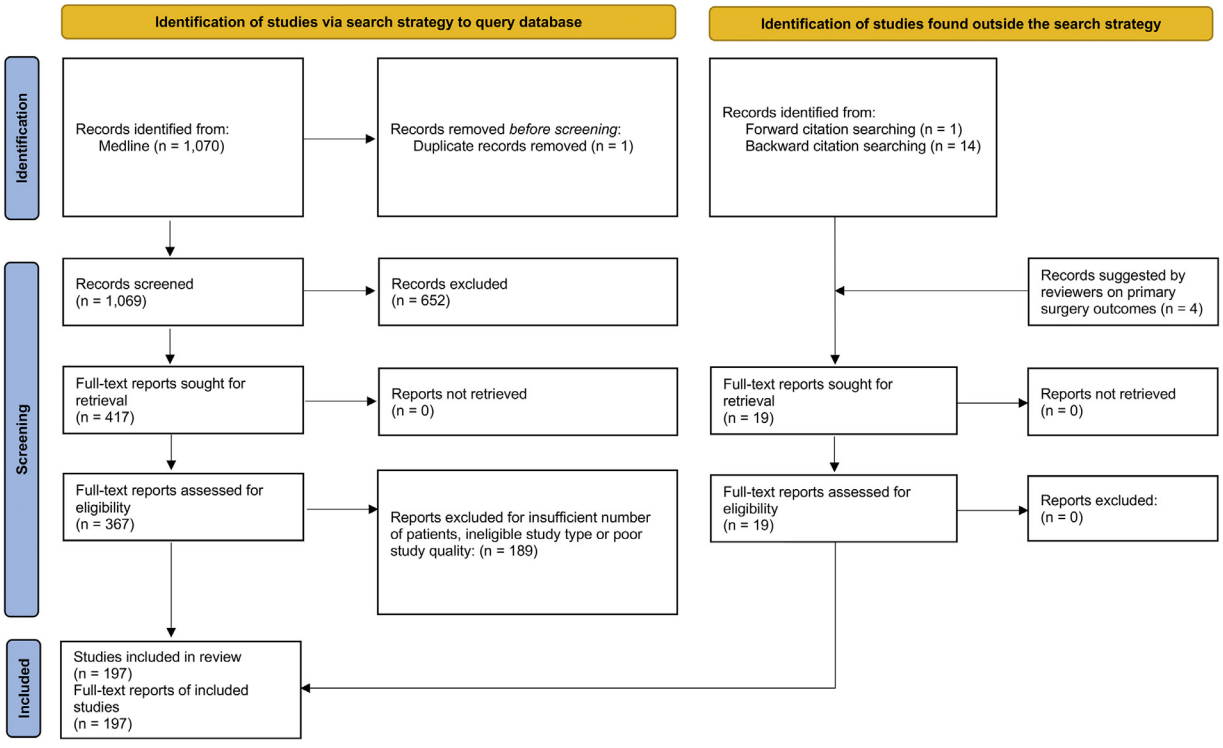

Fig. 1. Study selection PRISMA 2020 flowchart for the American Radium Society Appropriate Use Criteria for nonoperative management of rectal cancer: systematic review and guidelines.

worse DMFS has been noted in patients who experience regrowth, this has not been attributed to NOM.[27,28] Patients with tumors of all stages/locations[29]/histologies[30-32]/*KRAS* mutation status[33,34] have been found appropriate for NOM (see Appendix E2 for staging and work-up). Although TME-FS may decrease with increasing tumor size/T stage, in OPRA, the risks of regrowth were similar between patients with T3 and T4 tumors, and avoiding morbidity, especially from exenteration, may warrant attempting NOM.[35,36] QOL benefits have been found independent of tumor location and expected surgery.[37-40] Matched controlled studies indicate major bowel dysfunction including LARS occurs in about two-thirds of patients undergoing TMT, with NOM outcomes much improved but still occurring in one-fifth to one-third of respondents.[37-41] Primary surgery involves major LARS rates intermediate between that of TMT and NOM, occurring in about half of patients even without RT or CT,[42] with a meta-analysis finding a higher LARS prevalence for lower tumors.[43] Regardless of whether LC-CRT or short-course RT (SCRT) is employed, prospective data have shown surgery to have the most profound negative effect on health-related QOL. Beyond bowel toxicity, additional benefits noted with NOM versus TMT include better physical and cognitive function, improved physical and emotional roles, decreased sexual/urinary tract dysfunction, and superior global health status.[44,45] A summary of the key NOM studies is shown in Table 1.[10,15,46-49]

Topic 2: Optimal radiation dose/fractionation for NOM for rectal cancer

Subtopic 1: LC-CRT

The preponderance of NOM data involves LC-CRT, typically to 50 to 56 Gray (Gy) with associated cCR rates of 12% to 80% and 3-year regrowth rates of 16% to 38%.[9,10,15,46] The large ranges are mostly due to a lack of standardization in defining and monitoring for cCR,[28,46,50-55] as modern prospective studies have reported TME-FS >50%. Although external beam RT (EBRT) doses >54 Gy may increase pCR rates, additional toxicity has been noted and sustained cCR rates have not been improved with these doses.[56-61] Retrospective NOM data including an individual patient data meta-analysis did not find dose predictive of regrowth.[62] The strongest data in support of NOM come from the multi-institutional prospective randomized phase 2 (IIR) Organ Preservation in patients with Rectal Adenocarcinoma (OPRA) trial for patients with T3-4bN_{any} or N+ rectal cancer, which compared LC-CRT followed by consolidation CT (cCT, fluorouracil, leucovorin, oxaliplatin, FOLFOX) with induction CT (iCT, FOLFOX) followed by LC-CRT.[10] Although the NOM response rate (ie, combined cCR + near cCR [ncCR] rates) was similar between the cCT and iCT groups (74% vs 71%, respectively), cCT was associated with improved 3-year TME-FS at 53% versus 41% (P = .01) driven by a lower regrowth rate (27% vs 40%). Of note, the actual rectum OP (defined as either NOM or following LE) rate was 60% versus 47% (P = .02) in the cCT versus iCT groups, respectively, and 10% of the patients who went to surgery had a pCR. A smaller single arm phase 2 trial involving LC-CRT also recommended active surveillance for ncCR/cCR patients, with 3-year OP encouraging at 67%.[15]

Subtopic 2: SCRT

Considering patient goals that may require a more expeditious option, NOM via SCRT (5 daily fractions of RT) deserves attention. In the setting of TMT, several trials involving SCRT have shown similar oncologic outcomes when compared to LC-CRT.[63-68] Similar to LC-CRT, given that pCR rates increase with the number of cCT cycles after SCRT,[69-75] total neoadjuvant therapy (TNT) (herein defined as giving all planned RT and/or systemic therapy regardless of whether surgery is planned) is preferred with a SCRT NOM approach. Building off of the success reported in a retrospective series involving SCRT and cCT,[76] the phase 2 Non-Operative Radiation Management of Adenocarcinoma of the Lower Rectum (NORMAL-R) study (n = 19) reported a 2-year OP rate of 54%.[47] Although an optional simultaneous integrated boost beyond 25 Gy was permitted (30 Gy to primary and 35 Gy to involved lateral nodes), dose escalation was not associated with improved cCR. All 5 regrowths were salvaged with TME, and the 2-year disease-free survival (DFS) and OS were both approximately 95%. For patients with stage IV oligometastatic disease, NOM is emerging as a viable treatment approach (Table 2). Although most data exist involving SCRT because it minimizes time off CT, LC-CRT has produced encouraging TME-FS outcomes as well.[77,78]

In NORMAL-R, only involved circumferential resection margin predicted for worse cCR rates (40% vs 93%, P = .04). Regarding TMT data, although the phase 3 Polish II trial (cT4/fixed;T3N_{any}) comparing neoadjuvant LC-CRT (nLC-CRT) with SCRT + cCT did not reveal differences in oncologic or QOL outcomes,[63] in the high-risk Rectal cancer And Preoperative induction therapy followed by Dedicated Operation (RAPIDO) population (T4a/b, extramural vascular invasion positive, N2, involved lateral nodes, and/or involved mesorectal fascia [MRF]), the locoregional recurrence rate (LRR) favored the LC-CRT arm (6% for LC-CRT vs 10% for SCRT + cCT, P = .027).[65,66] Therefore, if NOM is the goal, the high-risk population noted in RAPIDO might have worse outcomes with SCRT, and LC-CRT is therefore preferred for such patients (Table 3). The ongoing phase 3 ACO/ARO/AIO-18.1 trial (NCT04246684) may provide the first prospective data for a direct comparison between the RT regimens, evaluating NOM outcomes via LC-CRT (concurrent 5-fluorouracil [5-FU] and oxaliplatin with 54 Gy in 30 fractions [fx]) versus SCRT (25 Gy in 5 fx), with both arms receiving cCT.

Acute toxicity should be followed carefully as it peaks following SCRT and was likely mitigated in trials with surgery within 1 week of RT completion[79,80] with similar QOL

Table 1 Characteristics and outcomes of key nonoperative management studies

Author (year published)	n	Study design/years	Eligibility (stage/ rectum location)	RT (Gy/no. of fx)	Chemotherapy (" × no. of cycles")	cCR (%)	Median F/U (y)	Regrowth (%)	3-y RR (%)	3-y DMFS (%)	3-y TME-FS (%)	3-y OS/DFS (%)	Toxicity
Habr-Gama et al[46] (2013)	70	Phase 2 (2006-2010)	T1-4b N_{any} (T4 4%; N+ 39%) Any location	LC-CRT (54/30)	LC-CRT: 5-FU/LV cCT only	68%	5	27%	27%	85%	NS	90%/NS	NS
Kim et al[47] (2021) "NORMAL-R"	19	Phase 2 (2016-2019)	T2-T3 N_{any} T_{any} N+ Any location	SCRT (25/5) Optional SIB Primary: (30/5) Lateral Nodes: (35/5)	cCT only: CAPOX × 5/ FOLFOX × 8	74%	2.3	26%	NS	2-y: ∼95%	2-y: ∼54%	2-y: ∼95%/ ∼90%	Gr 3/4: 53%/16% (all during chemo)
Garcia-Aguilar et al[10] (2022) "OPRA"	307	Phase 2R	T3-4b N_{any} T_{any} N+ Any location	LC-CRT (50-50.4/25-28) Optional boost: 2-6 Gy (median dose, 54)	LC-CRT: Cape/5-FU cCT/iCT: CAPOX × 5/ FOLFOX × 8	NS	2.1	NS	NS	cCT: 83% iCT: 81%	cCT: 58% iCT: 43%	cCT: NS/ 77% iCT: NS/78%	Gr 3+: 41% (INCT-CRT arm)/34% (CRT-CNCT arm)
Wang et al[15] (2023) "PKUCH-R01"	64	Phase 2 (2016-2019)	T2-T3bN_{any}M0	LC-CRT: 50.6 Gy/22 fx	cCT: CAPOX × 5	51.6%	3.3	18.4%		Rate of DMs: 2.2% in cCR/near-cCR/ 16.7% in non-cCR	67.2%	3-y DFS: 92.2%; 3-y CSS: 96.6%	Gr 3+: 6.3% during RT/ 33.9% (during cCT)
Gerard et al[48] "OPERA" (2023)	40	Phase 3 (2015-2020)	cT2-3b N0 or N1 (with LN <8 mm) <5 cm in diameter <50% rectal circumference No anal canal No EMVI No poorly differentiated	All pts. LC-CRT: 54 Gy/25 fx Arm 1: EBRT 9 Gy/5 fx Arm 2: CXB 90 Gy/3 fx	FOLFOX	A: 39% B: 47%	3.2	NS	3-y LR: 23% (A)/15% (B)	9% (same in both arms)	A: 59% B:2 81%%	98%/83% (same in both arms)	Gr 3+ early AE in A: 4% B: 5% No Gr 3+ late AEs
MORPHEUS[49] (2022)	40	Phase 2 and 3	Operable cT2-3bN0 <5 cm <50% No anal canal	All pts. EBRT: 45 Gy/25 fx Arm 1: EBRT 9 Gy/5 fx Arm 2: Weekly IGABT 30 Gy/10 fx	Concurrent: 5-FU/ Cape (225 mg/m^2/ 825 mg/m^2 twice a day)	EBRT: 50% HDR: 90%	1.3	5% (1 patient in each arm)	NS	NS	EBRT: 38.6% vs HDR 76.6%	NS	No difference

Abbreviations: 5-FU = 5-fluorouracil; AE = adverse event; Cape = capecitabine; CAPOX, capecitabine, oxaliplatin; cCR = complete clinical response; cCT = consolidation chemotherapy; CRT-CNCT, chemo-radiation followed by consolidation chemotherapy; CSS = cancer specific survival; cT = clinical T stage; CXB = contact x-ray brachytherapy; DFS = disease-free survival; DM = distant metastasis; DMFS = distant metastasis−free survival; EBRT = external beam radiation therapy; EMVI = extramural vascular invasion; F/U = follow-up; fx, fractions; Gr = grade; FOLFOX, leucovorin, fluorouracil, oxaliplatin; HDR = high-dose-rate brachytherapy; iCT = induction chemotherapy; IGABT = image-guided adaptive brachytherapy; INCT-CRT, induction chemotherapy followed by chemo-radiation; LC-CRT = long-course chemoradiation therapy; LN = lymph node; LR = local recurrence; LV = leucovorin, N+ = node positive, NORMAL-R, Non-Operative Radiation Management of Adenocarcinoma of the Lower Rectum; NS = not specified; OPERA, Organ Preservation in Early Rectal Adenocarcinoma; OPRA, Organ Preservation for Rectal Adenocarcinoma; OS = overall survival; RR = regional relapse, RT = external beam radiation therapy alone, SCRT = short-course radiation therapy; SIB = simultaneous integrated boost; TME-FS = total mesorectal excision−free survival.

Table 2 Clinical Condition: Stage IVA rectal adenocarcinoma, with synchronous oligometastatic, resectable liver disease. Variant Description: A 38-year-old man (body mass index, 22) with good performance status (Eastern Cooperative Oncology Group score, 1) and newly diagnosed T3N2aM1 nonobstructing rectal adenocarcinoma with distal edge of tumor 6 cm proximal to dentate line (microsatellite stability/proficient mismatch repair). Full colonoscopy otherwise negative and MRI is without compromised circumferential resection margin but identifies 4 abnormally enhancing enlarged mesorectal lymph nodes, maximum diameter 2 cm. Staging MRI identifies 3 synchronous liver metastases, 2 in segment VI, and 1 in segment VII; all <3 cm; normal LFTs. Liver lesions are amenable to resection and pelvic surgery would require LAR

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	SOE	SOR
Treatment options														
Planned chemotherapy alone*	U	1	4	7	3	-	-	-	-	-	3	-	EC	N
Timing of liver therapy														
LAR and synchronous resection of liver metastases followed by adjuvant chemotherapy ± pelvic RT	U	-	6	8	-	-	-	1	-	-	3	-	EC	N
iCT and pelvic RT then assessment of response† followed by LAR with synchronous resection of liver metastases (for incomplete local cCR); or NOM (for local cCR) with resection of liver metastases‡,§	M	-	-	-	3	6	2	4	-	-	5	-	Lim	N
Resection or nonsurgical local therapy of liver metastases followed by chemotherapy ± pelvic RT then assessment of response† followed by LAR (for incomplete local cCR); or NOM (for local cCR)‡,§	M	-	-	3	5	2	-	1	-	-	5	×	E C	↓
iCT and pelvic RT then assessment of response† followed by LAR with sequential local therapy of liver metastases (for incomplete local cCR); or NOM (for local cCR) and local therapy of liver metastases‡,§	M	-	-	-	7	5	1	2	-	-	5	-	Lim	N
iCT then assessment of response† followed by local therapy of liver metastases, then pelvic RT/CRT followed by LAR (for incomplete local cCR); or NOM (for local cCR)‡,§	M	-	-	-	-	1	5	5	-	-	5	×	E C	N

(*Continued*)

Table 2 (*Continued*)

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	SOE	SOR
Systemic therapy/pelvic RT sequencing														
iCT therapy followed by SCRT	A	-	-	1	1	-	-	11	2	-	7	-	EC	↑
SCRT followed by cCT	M	-	-	-	4	9	-	2	-	-	5	-	Mod	N
iCT followed by LC-CRT	M	-	-	-	-	2	6	2	-	-	6	-	Lim	N
LC-CRT followed by cCT	M	-	-	3	6	4	1	1	-	-	4	-	Lim	↓
iCT then assessment of response followed by selective use of RT prior to surgery	M	-	-	1	4	4	4	2	-	-	5	-	Lim	N
If RT; radiation dose (when considering NOM)														
SCRT 25 Gy/5 fx	A	-	-	-	-	1	-	7	2	2	7	-	M	↑
LC-CRT 45-50.4 Gy/25-28 fx	A	-	-	-	-	-	2	7	3	-	7	-	Lim	↑
LC-CRT 54-56 Gy/27-31 fx	M	-	-	-	-	2	4	3	-	-	5	×	Lim	↑
LC-CRT 60-62 Gy/28-30 fx‖	M	-	-	1	6	2	-	-	-	-	4	-	Lim	↓
If RT; radiation volumes														
Primary tumor and mesorectal, presacral, internal iliac, obturator nodes	A	-	-	-	-	-	-	2	5	4	8	-	Lim	↑
Primary tumor and mesorectal, presacral, internal iliac, obturator, and external iliac nodes	U	2	-	7	-	1	1	-	-	-	3	-	Lim	↑
If RT; radiation technique												-		
3D-CRT	A	-	-	-	-	1	-	6	3	2	7	-	Mod	↑
IMRT	A	-	-	-	-	1	1	5	3	2	7	-	Mod	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D-CRT, 3-dimensional conformal radiation therapy; A = usually appropriate; cCR = clinical complete response; cCT = consolidation chemotherapy; CRT = chemoradiation therapy; EC, expert consensus; fx, fraction; iCT = induction chemotherapy; IMRT, intensity-modulated radiation therapy; Lim, limited; LAR = low anterior resection; LC-CRT = long-course chemoradiation therapy; LFTs = liver function tests; M, may be appropriate; Mod, moderate; N = neutral; NOM = nonoperative management; RT, radiation therapy; SCRT, short-course radiation therapy; SOE, strength of evidence; SOR, strength of the recommendation; U, usually not appropriate.

* Adjuvant therapy based on final surgical pathology; postoperative chemotherapy is generally recommended for pN+ and CRT is generally recommended for pathologic tumor stage ≥ T3.

† Assessment of response when considering NOM includes digital rectal examination (DRE), proctoscopy/sigmoidoscopy, and rectal protocol magnetic resonance imaging (MRI).

‡ cCR includes no residual tumor on DRE, proctoscopy/sigmoidoscopy, and rectal protocol MRI evaluations.

§ Active surveillance includes the following:

- Proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6 to 12 months thereafter.
- Rectal protocol MRI every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter.
- Computed tomographic imaging of the chest, abdomen, and pelvis every 6 to 12 months for the first 2 years, then every 12 months thereafter.
- Consider use of circulating tumor DNA with caution and the understanding that there are false positives/negatives, and no proven benefits in outcome with treatment of early detection based on circulating tumor DNA results alone.

‖ Dose escalation using sequential or simultaneous integrated boost technique.

Table 3 Clinical Condition: Stage IIIC rectal adenocarcinoma with compromised circumferential resection margin and posterior vaginal wall invasion. Variant Description: A 48-year-old woman (body mass index, 32) with good performance status (Eastern Cooperative Oncology Group score, 1) and newly diagnosed T4bN2bM0 circumferential partially obstructing rectal adenocarcinoma with the epicenter at the dentate line (microsatellite stability/proficient mismatch repair). Unable to pass scope for colonoscopy, and chemotherapy colonography showed no other disease in the colon. Clinical examination and MRI consistent with posterior vaginal wall invasion. MRI demonstrates 7 abnormal lymph nodes, 5 in the mesorectum and 2 in the internal iliac, none larger than 2 cm in the greatest diameter. No other evidence of disease on staging imaging. Upfront surgery would require APR and vaginectomy

Treatment	Rating category	Final tabulations									Group median rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment options														
Diverting loop colostomy prior to cancer therapy	M	-	-	1	3	6	4	1	-	-	5	-	EC	N
Initial APR and vaginectomy*	U	7	1	4	1	-	1	1	-	-	2	-	Lim	↑
SCRT alone followed by surgery*	U	2	1	8	2	1	1	-	-	-	3	-	Mod	↑
LC-CRT followed by surgery*	M	-	-	2	7	5	-	1	-	-	4	-	S	↓
TNT with iCT followed by SCRT	M	1	-	2	6	1	-	-	-	-	5	×	E C	N
TNT with iCT followed by LC-CRT	M	1	-	1	5	3	3	2	-	-	5	-	S	N
TNT with SCRT followed by cCT	M	-	1	3	9	2	-	-	-	-	4	-	Mod	↓
TNT with LC-CRT followed by cCT	A	-	-	-	-	-	1	3	5	5	8	-	S	↑
iCT then assessment of response followed by selective use of RT prior to surgery	U	3	2	8	1	-	-	-	-	-	3	-	Lim	↑
Assessment of response 4-12 wk aftter completion of neoadjuvant therapy†														
-If incomplete response‡ and no evidence of progressive disease														
APR ± vaginectomy per surgeon assessment*	A	-	-	-	-	-	-	3	5	7	8	-	Mod	↑
-If nCR or cCR‡ and no evidence of progressive disease														
Active surveillance§	M	-	-	1	4	3	-	1	2	-	5	×	S	N
Proceed with planned APR and vaginectomy	A	-	-	1	-	1	2	7	3	1	7	-	S	N
If RT; radiation dose (when considering NOM)														
SCRT 25 Gy/5 fx	M	-	1	1	8	1	-	-	-	-	4	-	S	↓
LC-CRT 45-50.4 Gy/25-28 fx	A	-	-	-	-	-	-	5	5	2	8	-	S	↑
LC-CRT 54-56 Gy/27-31 fx	A	-	-	1	-	-	2	2	5	2	8	-	S	↑
LC-CRT 60-62 Gy/28-30 fx‖	M	-	-	3	4	3	1	-	-	-	4	-	Mod	N

(*Continued*)

Table 3 (*Continued*)

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	SOE	SOR
If RT; radiation volumes														
Primary tumor, vagina and mesorectal, presacral, internal iliac, obturator nodes	M	-	1	2	1	3	4	-	-	-	5	-	S	↑
Primary tumor, vagina and mesorectal, presacral, internal iliac, obturator, and external iliac nodes	A	-	-	-	-	1	-	2	6	-	7	-	Mod	N
Primary tumor, vagina and mesorectal, presacral, internal iliac, obturator, external iliac, and inguinal nodes	M	-	-	-	-	-	2	6	2	1	6	-	Mod	N
If RT; radiation technique														
3D-CRT	M	-	-	3	4	4	-	-	-	-	4	-	S	N
IMRT	A	-	-	-	-	-	-	3	5	4	8	-	Mod	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D-CRT, 3-dimensional conformal radiation therapy; A = usually appropriate; APR = abdominal perineal resection; cCR = clinical complete response; cCT = consolidation chemotherapy; EC, expert consensus; fx, fraction; iCT = induction chemotherapy; IMRT, intensity-modulated radiation therapy; Lim, limited; LC-CRT = long-course chemoradiation therapy; M = may be appropriate; Mod = moderate; N = neutral; nCR = near-complete clinical response; NOM = nonoperative management; RT, radiation therapy; S, strong; SCRT = short-course radiation therapy; SOE = strength of evidence; SOR = strength of the recommendation; TNT = total neoadjuvant therapy; U = usually not appropriate.

* Adjuvant therapy based on final surgical pathology; postoperative chemotherapy is generally recommended for pN+ and chemoradiation therapy is generally recommended for pathologic tumor stage ≥ T3.

† Assessment of response when considering NOM includes digital rectal examination (DRE), proctoscopy/sigmoidoscopy, and rectal protocol magnetic resonance imaging (MRI).

‡ cCR includes no residual tumor on DRE, proctoscopy/sigmoidoscopy, and rectal protocol MRI evaluations.

§ Active Surveillance includes the following:

- Proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6 to 12 months thereafter.
- Rectal protocol MRI every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter.
- Computed tomographic imaging of the chest, abdomen, and pelvis every 6 to 12 onths for the first 2 years, then every 12 months thereafter.
- Consider use of circulating tumor DNA with caution and the understanding that there are false positives/negatives, and no proven benefits in outcome with treatment of early detection based on circulating tumor DNA results alone.

‖ Dose escalation using sequential or simultaneous integrated boost technique.

outcomes in modern SCRT versus LC-CRT trials.[81] In NORMAL-R, all grade 3/4 adverse events occurred during cCT, and patient-reported outcome data revealed anorectal function was not different at 1 year compared with baseline.[47]

Lastly, while SCRT alone is not preferred for NOM with locoregionally advanced rectal cancer (LARC), it may be a viable treatment option for patients with stage I tumors (Table 4).[82,83] TREC randomized 55 patients with cT1-2 tumors to SCRT followed by transanal endoscopic microsurgery (TEM) or TME, with 70% of patients undergoing TEM avoiding TME. There was no difference in OS/DFS, but there were significantly less complications with SCRT/TEM versus TME (15%, mostly rectal bleeding/pain vs 39%, mostly surgical complications, respectively [P = .04]). Compared with the TME arm, OP patients had improved patient-reported bowel toxicities, QOL, and function scores.

Subtopic 3: LC-CRT versus SCRT

There are only retrospective data thus far comparing LC-CRT with SCRT for patients considering NOM. One study compared patients with stage II-III disease treated with iCT /LC-CRT versus SCRT/cCT. Although the cCR rate was ~50% in each arm, this may not be a completely fair comparison because the LC-CRT group might have performed better if given cCT based on OPRA's results.[69] Retrospective and prospective patient-reported outcomes have not found significant QOL differences between SCRT and LC-CRT patients undergoing NOM.[84,85]

In summary, either LC-CRT to 54 Gy in 27 to 30 fx or SCRT, both followed by 4 months of consolidation fluoropyridine-based CT, may result in a TME-FS rate of approximately 50%. Although there is a higher volume of data to support LC-CRT, there are low-quality data to suggest that SCRT is inferior, and both options may be offered in the shared decision-making process. Although risk factors

Table 4 Clinical Condition: Low-lying Stage I rectal adenocarcinoma. Variant Description: A 60-year-old woman (body mass index, 28) with good performance status Eastern Cooperative Oncology Group score, 1) and newly diagnosed T2N0M0, 2 cm nonobstructing adenocarcinoma with distal edge of tumor at the dentate line (microsatellite stability/proficient mismatch repair). Full colonoscopy otherwise negative and MRI shows clear circumferential resection margin and no abnormal pelvic lymph nodes. No other evidence of disease on staging imaging. Upfront surgery would require APR

Treatment	Rating category	Final tabulations									Group median rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment options														
Initial APR*	A	-	-	-	-	1	1	11	1	1	7	-	S	↑
Chemotherapy followed by LE	M	-	2	4	4	-	1	-	-	-	5	×	Mod	↓
SCRT alone followed by surgery*	U	-	2	7	2	-	-	-	-	-	3	-	S	↑
LC-CRT followed by surgery*	U	-	1	8	1	1	-	-	-	-	3	-	S	↑
LC-CRT with or without brachytherapy boost	M	-	-	1	-	3	4	3	-	-	5	×	S	N
TNT with iCT followed by SCRT	U	-	-	9	2	-	-	-	-	-	3	-	EC	↑
TNT with iCT followed by LC-CRT	M	-	-	6	3	2	-	-	-	-	5	×	Lim	N
TNT with SCRT followed by cCT	M	-	-	2	3	5	-	1	-	-	5	-	Mod	N
TNT with LC-CRT followed by cCT	M	-	-	1	1	1	1	7	-	-	5	×	Mod	N
Assessment of response 4-12 wk following completion of neoadjuvant therapy†														
-If incomplete response‡ and no evidence of progressive disease														
APR per surgeon assessment*	A	-	-	-	-	-	1	6	6	2	8	-	EC	↑
LAR as per surgeon assessment*	U	-	2	7	-	-	-	2	-	-	3	-	EC	↑
LE per surgeon assessment*	M	-	-	1	2	9	3	-	-	-	5	-	S	↑
-If nCR or cCR‡ and no evidence of progressive disease														
Active surveillance§	A	-	-	-	-	2	1	5	3	5	7.5	-	S	↑
Proceed with APR or LAR	U	2	2	7	3	-	1	-	-	-	3	-	S	↑
LE of scar followed by active surveillance§	M	-	-	2	6	6	1	-	-	-	4	-	S	↓
If RT; Radiation dose (when considering NOM)														
SCRT 25 Gy/5 fx	M	-	-	4	4	-	-	1	-	-	5	×	Mod	↓
LC-CRT 45-50.4 Gy/25-28 fx	A	-	-	-	-	-	-	8	1	4	7	-	S	↑
LC-CRT 54-56 Gy/27-31 fx	A	-	-		1	-	2	8	-	-	7	-	S	↑
LC-CRT 60-62 Gy/28-30 fx‖	M	-	-	1	5	3	-	-	-	-	4	-	Mod	↓

(*Continued*)

Table 4 (*Continued*)

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	SOE	SOR
If RT; radiation volumes														
Primary tumor and mesorectal, presacral, internal iliac, obturator nodes	A	-	-	-	-	-	-	3	4	6	8	-	S	↑
Primary tumor and mesorectal, presacral, internal iliac, obturator, and external iliac nodes	M	-	-	6	3	-	-	-	-	-	5	×	S	N
If RT; radiation technique														
3D-CRT	A	-	-	-	-	1	1	5	3	2	7	-	S	↑
IMRT	A	-	-	-	-	1	2	4	4	1	7	-	Mod	↑
EBRT and brachytherapy	M	-	-	-	7	1	2	2	-	-	4	-	Mod	↓

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D-CRT, 3-dimensional conformal radiation therapy; A, usually appropriate; APR = abdominal perineal resection; cCR = clinical complete response; cCT = consolidation chemotherapy; EBRT = external beam radiation therapy; EC = expert consensus; fx = fraction; iCT = induction chemotherapy; IMRT = intensity-modulated radiation therapy; Lim = limited; LAR = low anterior resection; LC-CRT = long-course chemoradiation therapy; LE = local excision; M = may be appropriate; Mod = moderate; N = neutral; nCR = near-complete clinical response; NOM = nonoperative management; RT = radiation therapy; S = strong; SCRT = short-course radiation therapy; SOE, strength of evidence; SOR, strength of the recommendation; TNT = total neoadjuvant therapy; U, usually not appropriate.

* Adjuvant therapy based on final surgical pathology; postoperative chemotherapy is generally recommended for pN+ and chemoradiation therapy is generally recommended for positive margin/circumferential resection margin.

† Assessment of response when considering NOM includes digital rectal examination (DRE), proctoscopy/sigmoidoscopy, and rectal protocol magnetic resonance imaging (MRI).

‡ cCR includes no residual tumor on DRE, proctoscopy/sigmoidoscopy, and rectal protocol MRI evaluations.

§ Active Surveillance includes:

- Proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6 to 12 months thereafter.
- Rectal protocol MRI every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter.
- Computed tomographic imaging of the chest, abdomen, and pelvis every 6 to 12 months for the first 2 years, then every 12 months thereafter.
- Consider use of circulating tumor DNA with caution and the understanding that there are false positives/negatives, and no proven benefits in outcome with treatment of early detection based on circulating tumor DNA results alone.

‖ Dose escalation using sequential or simultaneous integrated boost technique.

including T4a/b, extramural vascular invasion positive, N2 and/or involved lateral nodes, or involved MRF should not preclude the use of SCRT, given the worse locoregional outcomes with these characteristics noted in RAPIDO in the setting of TMT, LC-CRT might be preferred for patients harboring them when pursuing NOM.[47,65,66] If LC-CRT is not agreeable/feasible for a given patient (eg, due to psychosocial and/or financial concerns), SCRT + cCT could be more strongly considered. Given the lack of a proven benefit to a boost beyond standard SCRT, a dose of 25Gy in 5 fx is preferred.

Subtopic 4: Brachytherapy

Although dose escalation using EBRT has not proven effective, rectal brachytherapy via contact x-ray brachytherapy (CXB) using an x-ray tube positioned into the rectum or high-dose-rate brachytherapy using an iridium-192 source into the rectum via an applicator[86] have been investigated. Retrospective and prospective data report cCR rates up to 78% but with late grade 3 rectal bleeding in ~10%.[87-96] The randomized Organ Preservation in Early Rectal Adenocarcinoma (OPERA)[48] (CXB) and MORPHEUS[49] (high-dose-rate brachytherapy) trials found superior OP with a brachytherapy over an EBRT boost following LC-CRT. For OPERA, on subset analysis, only patients with tumors <3 cm benefited from CXB, with 3-year OP rates 63% versus 97% (P = .012), whereas for ≥3 cm, 3-year OP rates were 55% versus 68% (P = .11).

In both OPERA[48] and MORPHEUS,[49] eligibility was restricted to those with tumors within the mid-low rectum, cT2-3b, measuring <5 cm in size, involving <50% of the rectal circumference, and not extending into the anal canal, thereby limiting the generalizability of these data to a select cohort of patients.

In summary, brachytherapy is an emerging dose escalation option to increase cCR rates at experienced institutions.

Topic 3: Optimal systemic therapy and timing for NOM for rectal cancer

Subtopic 1: During LC-CRT

Several TMT studies have sought to improve local radiosensitization and systemic control by adding oxaliplatin to the

standard concurrent fluoropyrimidine (infusional 5-FU or capecitabine) regimens.[97-101] However, oxaliplatin was associated with increased toxicity, and all studies but one did not show any benefit to pCR rates. Thus, it is recommended that single-agent 5-FU or capecitabine should be used during LC-CRT.[102,103]

Subtopic 2: cCT versus iCT

The addition of neoadjuvant systemic CT to neoadjuvant SCRT/LC-CRT improves oncologic outcomes[73,98,104–115] and should be strongly considered as part of the NOM treatment paradigm. There are increasing data regarding the optimal sequence, duration of CT, and specific CT regimen.

Providing all (ie, TNT) or nearly all (ie, near TNT) planned CT in the neoadjuvant setting has benefits in terms of tolerability and controlling occult micrometastatic disease.[63,65,66,116-118] Retrospective and prospective TMT and NOM trials have assessed sequencing of systemic CT before (induction, iCT) or after (consolidation, cCT) RT for LARC (Table 5).[63,65,66,81,85,116,117,119-121] The multi-institutional phase 3 study CAO/ARO/AIO-12 showed significant improvement in pCR and combined pCR/cCR with cCT over iCT, with[122,123] long-term follow-up noting no significant difference in 3-year DFS, LRR, and DM.[122] These findings are consistent with retrospective analyses showing a general trend favoring cCT over iCT regarding improved response rates without consistent differences in DM.[69,124] Similarly, in OPRA, cCT significantly improved TME-FS and iCT failed to improve DFS, DMFS, or OS.[10] With no proven benefit to iCT, to optimize NOM success, cCT is recommended (Table 6).

Regarding the optimal duration of nCT, the addition of 4, 8, and 12 weeks of consolidation FOLFOX incrementally improved pCR rates to 25%, 30%, and 38%, respectively, supporting the notion increased cCT cycles could improve cCR rates as well.[116] However, grade ≥3 toxicity also increased, reaching 4%, 18%, and 36%, respectively.[116] A meta-analysis of randomized controlled trials showed no improvement in pCR rate with <12 weeks of cCT.[109] Considering these data, 12 to 16 weeks of cCT using leucovorin, fluorouracil, and oxaliplatin or capecitabine and oxaliplatin (FOLFOX/CAPOX) is recommended to optimize NOM/TMT outcomes.

Although prospective randomized data have not shown an improvement in pCR with cCT via single-agent fluoropyrimidine,[125] adding oxaliplatin to 5-FU/capecitabine has improved outcomes.[109,116] PRODIGE-23 (T3-4N_{any}M0) investigated iCT leucovorin, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) and LC-CRT followed by surgery and 3 months of aCT versus LC-CRT followed by surgery and 6 months of aCT.[119] Although LC-CRT with iCT FOLFIRINOX was associated with an improved pCR rate compared with LC-CRT alone without iCT/cCT (28% vs 12%), this pCR is similar to those in other trials involving neoadjuvant FOLFOX as noted previously (also see Table 5). Therefore, in the absence of a direct comparison between FOLFOX and FOLFIRINOX in the neoadjuvant setting, both may be considered reasonable options as cCT/iCT regimens. The ongoing Janus Rectal Cancer Trial (Alliance A022104/NRG-GI010), comparing triplet versus doublet CT with cCR as the primary endpoint, may further clarify this issue (NCT05610163).

Subtopic 3: Selective use of RT and primary surgery

While historic clinical trials showing improved locoregional control with RT have led to the widely accepted standard of neoadjuvant RT for tumors ≥T3 and/or any N+, recent data reveal select populations have a sufficiently low recurrence risk to consider avoiding RT. Three prospective LARC randomized trials have evaluated a neoadjuvant TMT approach comparing nCT alone to nLC-CRT,[16,126–128] with nCT showing noninferior oncologic outcomes and only one study finding improved pCR rates with nLC-CRT[127] (Table 7).[16,17,19,129-131] Of note, to avoid nLC-CRT, PROSPECT required a ≥20% decrease in primary size, achieved by most (94%) patients. Although overall health-related QOL was similar at all time points, at 1-year after surgery, FOLFOX-only patients noted significantly improved fatigue, neuropathy, and sexual function versus CRT.[132] In earlier-stage disease, the phase 2 CCTG CO.28 trial allowed 79% of T1-T3abN0 low/mid-rectal adenocarcinoma patients to avoid TME by receiving 3 months FOLFOX followed by TEM.[133] For upper-third tumors with clear circumferential resection margin, an individual patient data meta-analysis found no added benefit to neoadjuvant SCRT beyond surgery alone[134] (Table 8).

There are also data involving upfront TME showing RT and potentially even CT may be avoided for select patients.[129-131] The Optimierte Chirurgie Und MRT—optimized surgery and MRI-based multi- modal therapy (OCUM) treated patients (T2-4N_{any}M0; any location ≤16 cm from verge) with radiographically low-risk tumors with upfront TME and patients with high-risk tumors (MRF <1 mm to primary/nodes; cT2-3+ within 6 cm of anal verge) with nLC-CRT followed by TME and found that there were no differences in LR rates.[12] In the low-risk group with primary surgery, about 1/3 received aCT for positive nodes (FOLFOX or 5-FU/leucovorin; median number cycles, 8; IQR, 6-8; personal communication with Professor Theodor Junginger, MD via email, August 2023), with 3-year LR at 2.2%. Given that Magnetic Resonance Imaging in Rectal Cancer European Equivalence Study (MERCURY) and low-risk OCUM patients achieved excellent LRR without a size decrease requirement from nCT and with aCT only for N+ disease, it is possible that patients on PROSPECT could have avoided CRT even if the size decrease was <20% and perhaps could have avoided CT and/or RT if T3N0. However, even with LAR alone, bowel dysfunction may be significant, with major LARS occurring in approximately 20% to 60% of patients.[43] Increased chance of LARS has been noted for lower tumors defined as height of the anastomosis from the verge <4 to 5 cm.[135,136]

In summary, for select LARC patients (non-T4b; uninvolved MRF), nCT may allow avoidance of RT, and for

Table 5 Comparison of prospective trials of total/near total neoadjuvant therapy vs chemoradiation alone involving planned surgery (trimodality therapy)

Study/year	Phase/N (years)	Eligible	Med F/U (y)	Treatment	Cycles of nCT	Pre-op Gr 3+ (%)	Interval to surgery	pCR (%)	Cycles aCT	DFS	OS	LF	DMFS	Toxicity
Cisełet al[63] (Polish II) 2019	III/515 (2008-2014)	cT4; fixed T3 N_{any}	7.0	A: SCRT+CCT (6 c) B: LC-CRT	A: 6 (F) B: None	A: 23 B: 21	12.4 wk post start RT for each group	A: 16 B: 12	None	No difference 8-y DFS A: 43% B: 41%	No difference, 8-y OS 49% both groups	No difference A: 35% B: 32%	No difference A: 36% B: 34%	No difference Late Gr 3+ AEs A: 11% B: 9%
Jin et al[117] (STELLAR) 2022	III/629 (2015-2018)	Distal or middle third cT3-T4N_{any} or cT_{any}N1-2	2.9	A: SCRT + CCT (4c) B: LC-CRT	12 (C) None	20 4.7	6-8 wk post treatment	A: 21.8% B: 12.3%	A: 2c B: 6c	No difference 3-y DFS: A: 64.5% B: 62.3%	No difference 3-y OS A: 86.5% B: 75.1%	No difference 3-y LRR A: 8.4% B: 11%	No difference 3-y DMFS: A: 77.1% B: 75.3%	Acute Gr 3+ A: 15.8% B: 2.0% Late AEs: NS
Conroy et al[119] (PRODIGE) 2021	III/461 (2012-2017)	cT3-T4 N_{any}	3.9	A: FOLFIRINOX B: LC-CRT	A: 6c B: None	46*/28† 30†	6-8 wk post RT	28 12	mFOLFOX6 A: 3 mo B: 6 mo	No difference	No difference in 3-y OS: A 91% B: 88%	No difference 3-y LRR A: 4% B: 6%	No difference in 3-y DMFS: A: 79% B: 72%	No differences (toxicities listed individually for each group — neutropenia most common during chemotherapy group and lymphopenia most common in CRT group)
Van der Valk et al[85] Bahadoer et al[65,66] Dijkstra et al[81,120] (RAPIDO) 2020-2023	III/920 (2011-2016)	cT4a/b; cN2; inv. MRF; lateral N+	4.6 (initial publication) 5.6 years (5-y F/U)	A: SCRT+CCT B: LC-CRT	A: 6c B: None	48 25	22-24 wk post start RT; 2-4 wk post chemo 8 wk post RT end	A: 28 B: 14	A: None B: 8c CapeOx	Fewer 3-y disease-related treatment failure in Arm A: A: 23.7% B: 30.4%	A: 91.0% B: 88.0% OS: A: 81.7% B 80.2% P=NS	A: 8.3% B: 6.0% LRF A: 11.7% B: 8.1% P=NS	Fewer 3-y cumulative probability of DMs in Arm A A: 20 B: 26.8% Fewer 5-y cumulative probability of DMs in Arm A: A: 23.0% B: 30.4%	Acute Gr 3+ A: 48% B: 25%
Garcia-Aguilar et al[116,121] (TIMING) 2015	II/292 (2004-2012)	cT3-T4 N_{any}	NS	A: LC-CRT B: LC-CRT+2c CCT C: LC-CRT+4c CCT C: LC-CRT+6c CCT	A: 0 B: 2c C: 4c D: 6c	N/A 4‡ 18‡ 36‡	6-8 wk post RT 3-5 wk post last cycle	A: 18 B: 25 C: 30 D: 38	None	NS	NS	NS	NS	Acute Gr 3-4 AEs A: LC-CRT: 26% B: 4% C: 18% D: 36%

Abbreviations: aCT = adjuvant chemotherapy; AE = adverse event; C = CAPOX; CCT = consolidation chemotherapy; DFS = disease-free survival; DM, distant metastasis; DMFS = distant metastases free survival; F = FOLFOX; F/U = follow-up; Gr = Grade; inv. MRF= involved mesorectal fascia; LC-CRT = long-course chemoradiation therapy; LF, local failure; LRF, locoregional failure; LRR, locoregional recurrence; N+ = node positive; N/A = not applicable; nCT = neoadjuvant chemotherapy; NS = not specified; OS, overall survival; pCR, pathological complete response rate; SCRT = short-course radiation therapy; Wks = weeks of chemotherapy (1 cycle C every 3 weeks; 1 cycle FOLFOX or FOLFIRINOX every 2 weeks).

* During induction chemotherapy.

† During long-course chemoradiation therapy.

‡ During consolidation chemotherapy.

Table 6 Clinical Condition: Low- to Mid- Stage IIIB rectal adenocarcinoma. Variant Description: A 55-year-old woman (body mass index, 25) with good performance status (Eastern Cooperative Oncology Group score, 1) and newly diagnosed T3N1bM0 nonobstructing rectal adenocarcinoma 3 cm proximal to the dentate line (microsatellite stability/proficient mismatch repair). Full colonoscopy otherwise negative and MRI shows clear circumferential resection margin and 2 abnormal mesorectal lymph nodes, both 1.5 cm in greatest diameter. No other evidence of disease on staging imaging. Upfront surgery would likely be LAR with coloanal anastomosis.

Treatment	Rating category	Final tabulations									Group median rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment options														
Initial LAR with coloanal anastomosis*	M	-	-	3	6	2	-	-	-	-	4	-	Mod	N
Chemotherapy followed by surgery*	M	-	1	-	2	9	2	1	-	-	5	×	Mod	N
SCRT alone followed by surgery*	M	-	1	3	3	4	-	-	-	-	5	×	S	N
LC-CRT followed by surgery*	M	-	-	-	1	1	3	6	-	-	5	×	S	N
LC-CRT with or without brachytherapy boost	M	-	-	-	7	7	1	-	-	-	5	-	Mod	N
TNT therapy with iCT followed by SCRT	M	-	1	1	10	3	-	-	-	-	4	-	EC	N
TNT therapy with iCT followed by LC-CRT	M	-	-	1	4	5	1	3	-	-	5	-	S	N
TNT with SCRT followed by cCT	A	-	-	-	1	1	-	9	3	-	7	-	Mod	N
TNT with LC-CRT followed by cCT	A	-	-	-	-	-	1	5	7	1	8	-	S	N
Assessment of response 4-12 wk following completion of neoadjuvant therapy†														
-If incomplete response‡ and no evidence of progressive disease														
LAR with coloanal anastomosis per surgeon assessment*	A	-	-	-	-	1	-	4	5	5	8		S	↑
LE per surgeon assessment*	M	-	-	3	6	6	-	-	-	-	4		Mod	↓
-If nCR or cCR‡ and no evidence of progressive disease														
Active surveillance§	A	-	-	1	2	1	-	4	5	2	7		S	↑
Proceed with LAR with coloanal anastomosis	M	-	1	-	9	3	-	2	-	-	4		S	↓
LE of scar followed by active surveillance§	M	-	-	-	5	8	2	-	-	-	5		Mod	N
If RT; radiation dose (when considering NOM)														
SCRT 25 Gy/5 fx	A	-	-	-	-	-	3	7	2	-	7		Mod	N
LC-CRT 45-50.4 Gy/25-28 fx	A	-	-	-	-	-	-	4	7	1	8		S	↑
LC-CRT 54-56 Gy/27-31 fx	A	-	-	1	-	-	2	5	3	1	7		S	↑
LC-CRT 60-62 Gy/28-30 fx‖	M	-	-	2	5	3	1	-	-	-	4		Mod	↓

(*Continued*)

Table 6 (*Continued*)

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	SOE	SOR
If RT; radiation volumes														
Primary tumor and mesorectal, presacral, internal iliac, obturator nodes	A	-	-	-	-	-	-	2	5	4	8		S	↑
Primary tumor and mesorectal, presacral, internal iliac, obturator, and external iliac nodes	U	1	-	7	-	-	2	-	1	-	3		Mod	↑
If RT; radiation technique														
3D-CRT	A	-	-	-	-	-	1	5	3	3	7.5		S	↑
IMRT	A	-	-	-	-	1	1	3	4	2	8		Mod	↑
EBRT and brachytherapy	M	-	-	-	2	7	1	1	-	-	5		Mod	N

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D-CRT, 3-dimensional conformal radiation therapy; A = usually appropriate; cCR = complete clinical response; cCT = consolidation chemotherapy; EBRT = external beam radiation therapy; EC = expert consensus; fx = fraction; iCT = induction chemotherapy; IMRT = intensity-modulated radiation therapy; LAR = low anterior resection; LC-CRT = long-course chemoradiation; LE = local excision; M = may be appropriate; Mod = moderate; N = neutral; nCR = near-complete clinical response; NOM = nonoperative management; RT = radiation therapy; S = strong; SCRT = short-course radiation therapy; SOE = strength of evidence; SOR = strength of the recommendation; TNT = total neoadjuvant therapy; U = usually not appropriate.

* Adjuvant therapy based on final surgical pathology; postoperative chemotherapy is generally recommended for pN+ and chemoradiation therapy is generally recommended for positive margin/circumferential resection margin.

† Assessment of response when considering NOM includes digital rectal examination (DRE), proctoscopy/sigmoidoscopy, and rectal protocol MRI.

‡ cCR includes no residual tumor on DRE, proctoscopy/sigmoidoscopy, and rectal protocol MRI evaluations.

§ Active Surveillance includes:

- Proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6 to 12 months thereafter.
- Rectal protocol MRI every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter.
- Computed tomographic imaging of the chest, abdomen, and pelvis every 6 to 12 months for the first 2 years, then every 12 months thereafter.
- Consider use of circulating tumor DNA with caution and the understanding that there are false positives/negatives, and no proven benefits in outcome with treatment of early detection based on circulating tumor DNA results alone.

‖ Dose escalation using sequential or simultaneous integrated boost technique.

patients with nondistal cT1-3N0 rectal cancer, TME followed by consideration of aCT if pN+ are options that may help patients avoid RT-related toxicities without compromising oncologic outcomes. However, comparative effectiveness research is needed as it is not clear whether primary surgery, even in the absence of RT or CT, allows for better QOL (eg, bowel function) compared to NOM.

Subtopic 4: immunotherapy for high microsatellite instability/mismatch repair deficient patients

The phase 2R NRG-GI002 did not find a difference in pCR/cCR rates between TNT regimens with versus without immunotherapy concurrent with iCT but enrolled patients regardless of mismatch repair protein (MMR) expression or microsatellite instability (MSI).[137] However, for patients with deficient MMR (dMMR)/MSI-high (MSI-H) LARC, 2 prospective studies involving single-agent anti-PD-1 immunotherapy have produced cCR rates of 75% and 100%.[17,19] Other retrospective analyses of dMMR/MSI-H LARC have similarly shown promising responses to neoadjuvant immunotherapy but limited benefit to CT.[18,20,138-142] Therefore, it is reasonable to consider definitive immunotherapy for patients with dMMR/MSI-H LARC who are interested in NOM with close observation, saving RT ± CT if there is an incomplete clinical response (iCR) and then potentially surgery if CT/RT is similarly ineffective in producing an eventual cCR (Table 9).

Topic 4: Role of LE in NOM for rectal cancer

Subtopic 1: Planned LE after neoadjuvant therapy versus active surveillance for complete responders

Although the OPRA trial considered LE to be a censored failure event when assessing TME-FS,[10] there are 5 trials that investigated planned LE after LC-CRT as part of an OP strategy.[121,143-146] Two of these LE studies included only patients with stage I, cT2N0M0 tumors, and despite not requiring a completion TME for ypT2+ disease, outcomes were excellent without nodal failures.[121,143] In ACOSOG, the local failure rate was only 4%, and QOL was preserved after LE. For the GRECCAR-2, CARTS, and TAU-TEM

Table 7 Selective use of radiation therapy

Study/year	Design/N (y)	Eligibility	Treatment	Median F/U (y)	DFS	OS	pCR/R0	LR	DMFS	Toxicity
PROSPECT Schrag et al[16] 2023	Phase 2-3/1194 (2012-2018)	cT2-3N1 - Eligible for sphincter-sparing surgery	A: 6c mFOLFOX → if tumor decreased by 20% got surgery if not got CRT B: CRT (50.4Gy w/ 5-FU or capecitabine) 75% receiving median 6 cycles FOLFOX adjuvantly → Followed by TME	4.8	(5-y DS) A: 80.8% B: 78.6%	(5-y) A: 89.5% B: 90.2%	pCR: A: 23.1% B: 24.9% R0: A: 90.4% B: 91.2%	(5-y) A: 1.8% B: 1.6%	NS	G3+ A: 41% B: 22.8%
FORWARC	Phase 3/495 (2010-2015)	cT3-4N0 or cT1-4N1-2 <12 cm from verge	A: 5-FU with concurrent RT B: mFOLFOX with concurrent RT C: mFOLFOX alone. → Followed by TME	3.8	(3-y DFS): A: 72.9% B: 77.2% C: 73.5% Highest pCR with FOLFOX → CRT No OS or DFS differences	(3-y) A: 91.3% B: 89.1% C: 90.7%	NS	(3-y) A: 8.0% B: 7.0% C: 8.3%	NS	NS
CONVERT	Phase 3/663 (2014-2020)	cT2N+ or cT3-4aN_{any} No involved MRF or T4b No location requirement	A: 4cCAPOX B: CRT → Followed by TME	NS	NS	NS	pCR: A: 11.0% B: 13.8% R0: A: 99.6% B: 99.6%	NS	(Perioperative DM rate) A: 0.7% B: 3.1%	G3+ A: 12.4% B: 8.3%
CCTG CO.28	Phase 2/58 (2017-2021)	cT1-T3abN0 low/mid-rectal adenocarcinoma	6c mFOLFOX6 or 4c CAPOX followed by TES if response or TME if stable or no response	1.3	NS	NS	Reported as OPR: 57%	NS	NS	NS
OCUM 2020 Ruppert et al[129]	Prospective multicenter observational/1093 (2007-2016)	cT2-4N_{any} (16 cm verge) High risk: involved or threatened (≤1 mm) MRF, cT4 disease, or those with cT3 disease of the lower rectum (<6 cm from the anal verge). Low risk: All other pts.	Per protocol: -High risk (n=352): neoadjuvant LCRT (50.4 Gy/28 fx) → TME → adjuvant chemotherapy (in ~1/3) -Low risk (n=526): TME alone (31% Stage I)	5.1	Med F/U: 61 mos LR: 4.3% high risk vs 2.2% low risk (p=0.045) DM: 24% high risk vs 13% low risk (p<0.001)	NS	pCR: 12.2% pCRM−: 94%	(3-y) 3.1%	3-y rate DM: 17.0% (23.7% for CRT)→TME vs 12.5% for TME alone)	NS
MERCURY 2014 Taylor et al[130]	Prospective multicenter observational/374 (2002-2003)	<15 cm anal verge (84% were mid-upper rectum) T_{any} N_{any} M0	Neoadjuvant LCRT offered if mrCRM+ (defined as gross disease within 1 mm), accepted by 83% of 98 pts.	5.2	(5-y) −CRM: 67.5% +CRM: 47.3%	(5-y) −CRM: 62.2% +CRM: 42.4%	pCR: 5.7%	−CRM: 7.1% +CRM: 20.0%	NS	NS
QUICKSILVER 2019 Kennedy et al[131]	Phase 2/82 (2014-2016) N=82 T2: 20% T2/early T3: 60% T3: 21% N+: 37%	>1 MRF margin from any gross disease T2, T2/early T3, T3 with <5 mm EMD N_{any} M0 No EMVI Candidate for LAR Any location	70% TME alone 23% adjuvant chemotherapy alone for LN+ 7% adjuvant LCRT for positive CRM 88% of Stage II/III pts. did not receive RT	NS	NS	NS	−CRM: 95% +CRM: 4.9% R1: 1%	NS	NS	NS
Cercek et al[17] 2022	Phase 2/12 (NS)	cT3-4N0 (stage II) cT3$_{any}$N$_{any}$ (stage III) MMR deficient	Neoadjuvant dostarlimab IV 500mg every 3 wk	1	NS	NS	pCR: 100%	NS	NS	No Gr 3+ AEs
Chen et al[19] 2023	Phase 2/17 (2019-2022)	cT3-4 or N1-2 MMR deficient	Neoadjuvant sintilimab 200 mg IV every 3 wk, subsequent therapy depended on response to IO (either 4c IO + chemotherapy or 4c IO → surgery)	1.4	NS	NS	pCR: 75% R0: 100%	NS	NS	Only 1 patient with G3+ AE

Abbreviations: 5-FU = fluorouracil; AE = adverse event; c = cycle; CRM = circumferential resection margin; DFS = disease-free survival; DM = distant metastases; DMFS = distant metastases free survival; EMD = extramural disease; EMVI = extramural vascular invasion; F/U = follow-up; fx = fractions; LAR = low anterior resection; IO = immuno-oncology; IV = intravenous; LCRT = long-course radiation therapy; LN = lymph node; LR = local recurrence; MMR = mismatch repair; mrCRM = magnetic resonance imaging circumferential radial margin; MRF = mesorectal fascia; MERCURY = Magnetic Resonance Imaging in Rectal Cancer European Equivalence Study; NS = not specified; OPR = objective response rate; OS = overall survival; OCUM = Optimierte Chirurgie Und MRT—optimized surgery and MRI-based multi- modal therapy; pts. = patients; pCR = pathological complete response; R0 = margin-negative resection; RT = radiation therapy; TES = transanal excision surgery; TME = total mesorectal excision.

Table 8 Clinical Condition: High Stage IIA rectal adenocarcinoma. Variant Description: A 55-year-old woman (body mass index, 25) with good performance status (Eastern Cooperative Oncology Group score, 1) and newly diagnosed T3N0M0 nonobstructing rectal adenocarcinoma 10 cm proximal to the dentate line (microsatellite stability/proficient mismatch repair). Full colonoscopy otherwise negative and MRI shows clear circumferential resection margin and no abnormal lymph nodes. No other evidence of disease on staging imaging. Upfront surgery would likely be LAR.

Treatment	Rating category	Final tabulations									Group median rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment options														
Initial LAR*	A	-	-	-	-	-	1	9	1	-	7	-	S	N
Chemotherapy followed by surgery*	M	-	1	1	1	5	2	1	-	-	5	-	S	N
SCRT alone followed by surgery*	M	-	1	1	-	2	2	5	-	-	5	×	S	N
LC-CRT followed by surgery*	M	-	-	-	1	2	1	7	-	-	5	×		N
TNT with iCT followed by SCRT	M	1	-	1	8	4	1	-	-	-	4	-	EC	↓
TNT with iCT followed by LC-CRT	M	-	1	1	3	6	4	-	-	-	5	-	S	N
TNT with SCRT followed by cCT	M	-	-	1	3	7	3	1	-	-	5	-	S	N
TNT with LC-CRT followed by cCT	M	-	-	-	-	2	4	5	-	-	5	×	S	N
iCT then assessment of response followed by selective use of RT prior to surgery	A	-	1	2	-	1	-	7	3	1	7	-	S	↑
Assessment of response 4-12 wk following completion of neoadjuvant therapy†														
-If incomplete response‡ and no evidence of progressive disease														
LAR per surgeon assessment*	A	-	-	-	-	-	1	3	6	6	8	-	S	↑
LE per surgeon assessment*	M	-	1	1	4	5	-	-	-	-	4	-	Mod	↓
-If nCR or cCR‡ and no evidence of progressive disease														
Active surveillance§	A	-	-	-	-	1	3	4	6	2	7.5	-	S	↑
Proceed with planned LAR	M	-	-	1	8	2	2	2	-	-	4	-	S	N
LE of scar followed by active surveillance§	M	1	-	-	5	2	5	3	-	-	5.5	-	Mod	N
If RT; radiation dose (when considering NOM)														
SCRT 25 Gy/5 fx	A	-	-	-	-	3	-	6	4	-	7	-	Mod	↑
LC-CRT 45-50.4 Gy/25-28 fx	A	-	-	-	-	-	-	7	5	1	7	-	S	↑
LC-CRT 54-56 Gy/27-31 fx	M	-	-	-	-	2	1	6	-	-	5	×	S	N
LC-CRT 60 - 62 Gy/28-30 fx‖	M	-	-	3	4	1	1	-	-	-	5	×	Mod	N

(*Continued*)

Table 8 (*Continued*)

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	SOE	SOR
If RT; radiation volumes														
Primary tumor and mesorectal, presacral, internal iliac, obturator nodes	A	-	-	-	-	-	-	2	5	6	8	-	S	↑
Primary tumor and mesorectal, presacral, internal iliac, obturator, and external iliac nodes	U	3	1	6	1	1	-	1	-	-	3	-	S	↑
If RT; radiation technique														
3D-CRT	A	-	-	-	-	1	-	5	4	2	7.5	-	S	↑
IMRT	A	-	-	-	-	1	2	7	2	-	7	-	S	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D-CRT = 3-dimensional conformal radiation therapy; A = usually appropriate; cCR = complete clinical response; cCT = consolidation chemotherapy; EC = expert consensus; fx = fraction; iCT = induction chemotherapy; IMRT = intensity-modulated radiation therapy; LAR = low anterior resection; LC-CRT = long-course chemoradiation; LE = local excision; M = may be appropriate; Mod = moderate; N = neutral; nCR = near-complete clinical response; NOM = nonoperative management; RT = radiation therapy; S = strong; SCRT = short-course radiation therapy; SOE = strength of evidence; SOR = strength of the recommendation; TNT = total neoadjuvant therapy; U = usually not appropriate.

* Adjuvant therapy based on final surgical pathology; postoperative chemotherapy is generally recommended for pN+ and chemoradiation therapy is generally recommended for positive margin.

† Assessment of response when considering NOM includes digital rectal examination (DRE), proctoscopy/sigmoidoscopy, and rectal protocol MRI.

‡ cCR includes no residual tumor on DRE, proctoscopy/sigmoidoscopy, and rectal protocol MRI evaluations

§ Active Surveillance includes:

- Proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6 to 12 months thereafter.
- Rectal protocol MRI every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter.
- Computed tomographic imaging of the chest, abdomen, and pelvis every 6 to 12 months for the first 2 years, then every 12 months thereafter.
- Consider use of circulating tumor DNA with caution and the understanding that there are false positives/negatives, and no proven benefits in outcome with treatment of early detection based on circulating tumor DNA results alone.

‖ Dose escalation using sequential or simultaneous integrated boost technique

trials, completion TME was required for ≥ypT2-3/R1 disease.[144-146,147] Due to the high completion TME rate in GRECCAR-2 (35%), the hypothesized improvement in combined oncologic control/toxicity in the LE arm was not met with this group suffering a 78% chance of major surgical morbidity or severe side effects (anal incontinence/impotence/definitive colostomy). This high toxicity is not surprising as TME is more challenging following the anatomic changes from TEM. Significantly fewer complications were seen with LE versus TME in TAU-TEM, but in CARTS, although the 5-year LR rate was only 8%, the risk of minor and major LARS after TEM was notable at 50% and 28%, respectively.[145]

Only GRECCAR-2 reported the actual rates of nodal involvement in the TME specimen, with just 8% of all patients and 8% of the ypT2 subset being ypN+.[148] This was lower than the investigators expected, as prior retrospective data suggested node-positivity rate up to 30% for ypT2 disease but for an entirely cT3-4 and/or cN+ population.[149] Accordingly, in GRECCAR-2, ypT3 disease was associated with a higher 40% nodal positivity rate at TME.[148] Given the lack of nodal recurrences seen in ACOSOG[102] and Lezoche et al.[150] studies, it may be surmised that the 8% to 30% chance of residual nodal positivity for ≥ypT2 patients at TEM following LC-CRT is driven by ≥cT3/N+ staging at diagnosis, whereas ypN+ disease is exceptionally rare for patients cT2N0 tumors at diagnosis.[151] Of note, the pCR rate in these 5 prospective trials was 40% to 44%, suggesting LE may have been unnecessary in many, if not most, patients. A prospective observational study found NOM resulted in superior QOL to LC-CRT followed by planned LE,[152] and a meta-analysis comparing these 2 approaches showed no difference in oncologic outcomes.

LE after nCT alone without RT resulted in an overall OP rate of just <50% in the phase 2 NEO trial, which included patients with clinical T1-3bN0 low-mid rectal adenocarcinoma amenable to endoscopic resection. The 2-year LR-free survival of 90% and relatively favorable QOL/rectal function potentially support an nCT followed by LE approach in select patients with early-stage tumors.[133]

In conclusion, these data support NOM rather than planned LE for patients with cT2-3cN0-1M0 rectal cancer. Should a LE occur following LC-CRT, completion TME does not appear appropriate for patients with ypT2 rectal cancer who were cT2N0 at diagnosis given the reported 0% nodal recurrence rate, high reported pCR rates, improved

Table 9 Clinical Condition: Stage IIIB rectal adenocarcinoma, microsatellite instability-high/deficient mismatch repair. Variant Description: A 51-year-old man (body mass index, 25) with good performance status (Eastern Cooperative Oncology Group score, 1) and newly diagnosed T3N1bM0 nonobstructing rectal adenocarcinoma 5 cm proximal to dentate line (microsatellite instability-high/deficient mismatch repair). Full colonoscopy otherwise negative and MRI shows clear circumferential resection margin and 3 abnormal mesorectal lymph nodes, none greater than 2 cm in diameter. No other evidence of disease on staging imaging. Upfront surgery would likely require LAR

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	SOE	SOR
Treatment options														
Initial LAR*	M	-	2	1	12	-	-	-	-	-	4	-	Mod	↓
SCRT alone followed by surgery*	M	-	-	2	8	1	-	-	-	-	4	-	Mod	↓
LC-CRT followed by surgery*	M	-	-	2	2	7	2	2	-	-	5	-	Mod	↓
Upfront immunotherapy followed by assessment of response†/‡	A	-	-	1	3	-	-	5	3	3	7	-	Mod	↑
TNT with iCT followed by SCRT	M	1	-	-	6	1	4	2	-	-	4	-	EC	↓
TNT with iCT followed by LC-CRT	M	-	-	-	7	1	4	1	1	-	4	-	Mod	↓
TNT with SCRT followed by cCT	M	-	-	-	3	5	3	3	-	-	5	-	Mod	↓
TNT with LC-CRT followed by cCT	M	-	-	-	4	6	5	-	-	-	5	-	Mod	↓
iCT then assessment of response‡ followed by selective use of RT prior to surgery	M	-	-	2	2	6	1	-	-	-	5	-	Mod	↓
Assessment of response 4-12 wk following completion of neoadjuvant therapy‡														
-If incomplete response§ and no evidence of progressive disease														
LAR per surgeon assessment*	A	-	-	-	-	-	1	4	6	4	8	-	Mod	↑
LE per surgeon assessment*	M	-	-	1	6	7	-	1	-	-	5	-	Mod	N
-If nCR or cCR§ and no evidence of progressive disease														
Active surveillance‖	A	-	-	-	2	1	1	1	6	4	8	-	S	↑
Proceed with planned LAR	M	-	2	1	5	5	1	1	-	-	4	-	S	↓
LE of scar followed by active surveillance‖	M	-	-	3	8	3	-	1	-	-	4	-	Mod	↓
If RT; radiation dose (when considering NOM)														
SCRT 25 Gy/5 fx	A	-	-	-	-	1	2	7	2	-	7	-	Mod	N
LC-CRT 45-50.4 Gy/25-28 fx	A	-	-	-	-	-	-	5	6	1	8	-	S	↑
LC-CRT 54-56 Gy/27-33 fx	A	-	1	-	-	-	2	5	3	1	7	-	S	N
LC-CRT 60-62 Gy/28-30 fx#	M	-	-	-	7	2	-	-	-	-	4	-	Lim	↓

(*Continued*)

Table 9 (*Continued*)

Treatment	Rating category	Final tabulations 1	2	3	4	5	6	7	8	9	Group median rating	Disagree	SOE	SOR
If RT; radiation volumes														
Primary tumor and mesorectal, presacral, internal iliac, obturator nodes	A	-	-	-	-	-	-	2	6	4	8	-	S	↑
Primary tumor and mesorectal, presacral, internal iliac, obturator, and external iliac nodes	U	2	-	7	1	1	1	-	-	-	3	-	S	↑
If RT; radiation technique														
3D-CRT	A	-	-	-	-	1	1	5	4	1	7	-	S	↑
IMRT	A	-	-	-	-	-	2	6	3	1	7	-	Mod	↑

Abbreviations: ↑ = strong recommendation; ↓ = weak recommendation; 3D-CRT = 3-dimensional conformal radiation therapy; A = usually appropriate; cCR = complete clinical response; cCT = consolidation chemotherapy; EC = expert consensus; fx = fraction; IMRT = intensity-modulated radiation therapy; iCT = induction chemotherapy; Lim = limited; LAR = low anterior resection; LC-CRT = long-course chemoradiation; LE = local excision; M, may be appropriate; Mod, moderate; N = neutral; nCR = near-complete clinical response; NOM = nonoperative management; RT = radiation therapy; S = strong; SCRT = short-course radiation therapy; SOE = strength of evidence; SOR = strength of the recommendation; TNT = total neoadjuvant therapy; U = usually not appropriate.

* Adjuvant therapy based on final surgical pathology; postoperative chemotherapy is generally recommended for pN+ and chemoradiation therapy is generally recommended for positive margin/circumferential resection margin.

† Consider TNT with plan for NOM if inadequate response to immunotherapy rather than proceeding directly toward operative management.

‡ Assessment of response when considering NOM includes digital rectal examination (DRE), proctoscopy/sigmoidoscopy, and rectal protocol MRI.

§ cCR includes no residual tumor on DRE, proctoscopy/sigmoidoscopy, and rectal protocol MRI evaluations.

‖ Active Surveillance includes:

- Proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6 to 12 months thereafter.
- Rectal protocol MRI every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter.
- Computed tomographic imaging of the chest, abdomen, and pelvis every 6 to 12 months for the first 2 years, then every 12 months thereafter.
- Consider use of circulating tumor DNA with caution and the understanding that there are false positives/negatives, and no proven benefits in outcome with treatment of early detection based on circulating tumor DNA results alone.

Dose escalation using sequential or simultaneous integrated boost technique.

QOL without surgery, and nearly 80% chance of major morbidity if a TME is required after LE.[102,150] Given the high pCR rates noted with LC-CRT alone for ≤T2N0 disease, although retrospective data have shown that cCT after LC-CRT is associated with improved TME-FS,[115] it may be overtreatment. nCT without RT followed by LE is an emerging but nonstandard option at this time.[133]

Subtopic 2: LE rather than TME for incomplete responders

For patients experiencing an ncCR or iCR in the setting of NOM, retrospective data including a meta-analysis show approximately 50% to 100% avoid TME by pursuing salvage LE.[51,54,150,153,154] Therefore, if an ncCR or iCR is the best response achieved despite delaying or repeating response assessments, patients will need to weigh the potential QOL benefit from LE alone versus the risks associated with a potentially morbid salvage TME if LE is unsuccessful, and proceeding straight to TME might be preferred. If not already given, it is reasonable to consider cCT following CRT to increase the cCR rate.

Topic 5: Radiation technique and volumes for NOM for rectal cancer

Subtopic 1: Simulation

Computed tomography simulation and treatment with a full bladder (ie, urinate then drink ~16 ounces water 1 hour before procedure)/empty rectum is highly encouraged, preferably in the prone position[10,155] using a belly board to optimize bowel displacement. However, a supine position may also be suitable for safety/comfort concerns, and data suggest that patients with lower body mass index may not benefit from prone versus supine positioning in terms of bowel avoidance. Oral contrast is highly recommended to help delineate small from large bowel, and intravenous contrast is optional to help with lymph node delineation.

Subtopic 2: Appropriate radiation volumes

For all patients with rectal cancer, the entire rectal circumference should be included in the primary tumor gross tumor volume (GTV).[10] The magnetic resonance imaging (MRI) T2-weighted (T2W) ± diffusion-weighted imaging (DWI) sequences should be fused with computed tomography simulation images to assist in primary tumor GTV and GTV nodal delineation.[148]

Clinical target volume (CTV) denoting microscopic disease extension includes elective lymph nodes including at minimum, the mesorectal, obturator, internal iliac, and presacral nodes, to 45 Gy in 25 fx.[10] A 1.5 to 2 cm proximal/distal margin from the GTV along the bowel also including the adjacent mesorectum should be included in the standard boost CTV receiving 50 to 50.4 Gy.[149] In the setting of NOM, for patients receiving an optional 3.6 to 6 Gy boost beyond 50 to 50.4 Gy, a 5 to 15 mm margin around the GTV is used to create the additional boost CTV.[10] CTV nodal (CTVn) boost volumes typically involve GTV nodal + 0.5 cm margin.[156,157] The planning target volume margin may be decreased from 0.7 - 1.0 to 0.5 cm if daily image-guided RT is employed.[10,158,159]

Organs at risk (OARs) should include at minimum the bladder, small bowel, and femoral heads. Small bowel individual loop dose constraints include volume receiving 45 Gy (V45Gy) less than 100 cc,[10] volume receiving 50 Gy (V50Gy) less than 10 cc,[10] and volume receiving 55 Gy (V55Gy) less than 0.03 cc.[16] Minimizing the volume of radiated bone marrow may decrease hematological toxicity.[160,161] Dose should be minimized to the external anal sphincter (EAS) if planning target volume coverage is not compromised to potentially decrease dysfunction risk.[162] In a retrospective series of 64 patients, the EAS was located inferiorly to the inferior border of the obturator foramen in >80% of cases. While no correlation between RT dose distribution and anal-rectal dysfunction was studied, the authors suggest care should be taken when defining the inferior border of the RT field to attempt to spare the EAS.[162]

Subtopic 3: Indications for potential inclusion of elective external iliac/inguinal nodes in addition to standard elective mesorectal/internal iliac/presacral nodes

Coverage of external iliac (also known as anterior lateral lymph nodes) in T4b disease involving anterior pelvic organs is typically encouraged due to the possibility for recurrence there, even though these nodes are considered nonregional (ie, M1). In 2 retrospective series involving patients with T4 tumors, despite no elective external iliac coverage reported, recurrence rates there were only 0% to 1%.[163,164] In a third series, although 9% of patients with T4 disease experienced external iliac failure, each patient also had a concurrent distant failure. In the ACCORD 12/0405-PRODIGE 02 trial, 2 of 31 (6.5%) patients with T4 tumors (at least 1 of whom had anterior organ invasion) had a recurrence in the external iliac region, 1 in the RT field and 1 marginal recurrence.

Coverage of inguinal nodes for low-lying lesions involving the anal canal is controversial. While inguinal failure rates represent up to 10% of all LRR for rectal tumors invading the anal canal, it should be noted that that the recurrence risk despite anal canal involvement is only 0% to 6%, and inguinal failures without concurrent DMs are even rarer (0%-2%).[165-167] One series evaluating the risk of failure for tumors distal to the dentate reported a higher inguinal recurrence rate of 11.4% (n=5), but all but one patient had a concurrent distal failure.

In summary, elective radiation of external iliac nodes for T4b anterior organ invasion and inguinal/external iliac nodes for invasion beyond the dentate is reasonable, although the risk of isolated nodal failure is low.

Subtopic 4: Radiation treatment modality and technique

Intensity-modulated RT (IMRT) versus 3D conformal RT. Although a systematic review and meta-analysis found that IMRT was associated with reduced acute and late toxicity for patients treated with IMRT versus 3-dimensional (3D) conformal RT (3D-CRT), prospective studies including patients with T3-4 or N_{any} rectal cancer have not found any clear toxicity/QOL benefit based on modality.[168-170] However, the authors of the phase 2 0822 trial noted IMRT could benefit OAR avoidance within the concave target volumes created by external iliac coverage.[171] Of note, modern 3D-CRT approaches involving dynamic conformal arcs may decrease the dose to OARs including small bowel compared to traditional 3- or 4-field plans and approach the OAR sparing seen with IMRT.[172] Multiple studies have noted the 50/50.4 Gy boost may be delivered via simultaneous integrated boost.[173−177] In landmark clinical trials with either no dose escalation or moderate dose escalation, both 3D-CRT and IMRT planning were permitted.[10,48,65] It should be noted that IMRT was not associated with recurrence in the RAPIDO trial, but rather patients in the SCRT/CT experimental arm who received 3D-CRT were more likely to have LRR (P = .029).[120]

Protons. Proton therapy has also been investigated with the goal of minimizing toxicity for patients with rectal cancer. Dosimetric analyses comparing protons with photons have shown reduced treatment planning OAR doses with protons.[178-180] An analysis of the first 20 patients treated on PRORECT, the first randomized phase 2 trial comparing photons to protons for LARC, again revealed significant dosimetric advantages of proton therapy.[181] Whether dosimetric improvements translate into clinical benefits remains to be seen.

Topic 6: Assessment of treatment response and surveillance during NOM for rectal cancer

Subtopic 1: Assessment of response after neoadjuvant therapy for consideration of NOM

To optimize the chance for NOM, allowing time for cCR or ncCR is essential. In the OPRA trial, restaging was performed using digital rectal examination (DRE), endoscopic evaluation, MRI, and CT of the chest, abdomen, and pelvis within 8 (±4) weeks after TNT (median, 8 weeks), with NOM offered for cCR or ncCR responses.[10] Typically, as per OPRA, a cCR has been defined as follows: (1) DRE, no palpable tumor when initially palpable; (2) endoscopy, no residual tumor, with a flat, white scar and/or telangiectasia acceptable but no ulcer or nodularity; (3) MRI-T2W, only dark and no intermediate T2 signal with no visible nodes; and (4) diffusion-weighted MRI: no diffusion restriction. By comparison, an ncCR has the following characteristics: (1) DRE, smooth induration or minor mucosal abnormalities; (2) endoscopy, irregular mucosa, small mucosal nodules or minor mucosal abnormalities, superficial ulceration, or mild persisting erythema of the scar; (3) MRI-T2W, mostly dark T2 signal with some remaining intermediate signal and/or partial regression of lymph nodes; (4) diffusion-weighted MRI, significant regression of signal on B800-B1000. There are limitations with these definitions, as up to 15% of patients thought to have an iCR are found to have a pCR at TME[10,182]; residual endoscopic mucosal abnormalities and/or MRI intermediate T2 signal/diffusion restriction are associated with false positives[183] (see Appendix E2 for rectal cancer staging details). Of note, biopsy is only helpful to rule in disease as false negatives are common; Perez et al[184] reported a negative predictive value of 11%. The combination of clinical response assessment using DRE, endoscopy, and imaging evaluation using MRI (T2-weighted and DWI) accurately predicts a cCR in up to 98% of cases.[182,185] Although MRI assessment including changes in apparent diffusion coefficient values along with T2-weighted and DWI sequences has had a 90% accuracy for predicting pCR,[186] endoscopy is more reliable for assessing the primary tumor,[186-189] with MRI preferred for assessing nodal disease.[190]

While the accuracy of response assessment may be enhanced by artificial intelligence, radiomics, positron emission tomography (PET)−CT, and PET-MRI, data are preliminary.[191-197] Further, while circulating tumor DNA (ctDNA) presence has been associated with worse prognosis, it has not been shown to accurately predict treatment response as ctDNA absence does not necessarily indicate pCR.[191-193] Therefore, carcinoembryonic antigen (CEA) is the only currently standard recommended laboratory assessment.[10]

Regarding the optimal timing of tumor response assessment, evidence suggests delaying >6 to 8 weeks allows for a more accurate response to treatment without adversely impacting outcomes.[198-200] TMT studies have shown improved responses with delayed surgery.[201-203] Up to 90% of patients with an ncCR at 8 to 10 weeks following CRT have been found to convert to cCR 6 to 12 weeks later, and it may require >16 weeks for patients with an ncCR to convert to cCR.[188] Delaying response assessment and subsequent surgery have not been shown to increase operative time or postoperative complications or worsen any oncologic outcomes.[202,204]

In summary, in the setting of NOM, the first assessment of response should occur approximately 8 to 12 weeks after completion of CT and/or RT. If there is an ncCR, it is recommended that re-evaluation should be performed approximately 8 weeks later because many tumor responses eventually are scored as a cCR. Although there may eventually be a role for ctDNA, radiomics, and/or PET-CT or PET-MRI, they are not part of routine standard assessments at this time.[148]

Subtopic 2: Surveillance and surgical salvage after NOM for rectal cancer

Reported salvage rates after both LC-CRT and SCRT range from ~90% to 100%, with similar operative morbidity and oncologic outcomes compared with patients undergoing upfront surgery.[55,205-208] Therefore, close surveillance is critically important. Most (>90%) recurrences (local/regional/distant) occur within the first 2 years[52] and are luminal with low crude regional lymph node failure rates during NOM (≤3%).[50-52] While DMs are more common (eg, OPRA 3-year DMFS in the 82%-84% range for both study arms), no difference in DMFS or OS has been demonstrated between patients undergoing NOM with surgical salvage and those undergoing immediate surgery.[209,210]

Like response assessment, surveillance strategies typically include using endoscopy, DRE, CEA, and radiographic assessments (CT chest/abdomen/pelvis and MRI rectum). It is recommended that patients undergo endoscopy/DRE/CEA evaluations every 3 months for 2 to 3 years, then every 6 months until 5 years, and then as needed; MR rectum every 3 to 6 months for 2 to 3 years, then annually until 5 years, and then as needed; and chest/abdomen/pelvis CT every 6 months for 2 to 3 years, then annually until 5 years, and then as needed. Although ctDNA has prognostic value, there are no proven benefits with treatment of early detection based on ctDNA results alone.[191-193] Follow-up and surveillance are recommended for a minimum of 5 years with later recurrences very uncommon.[211]

In summary, most patients whose tumors recur after NOM may be surgically salvaged and typically involve local-only intralumenal disease. This approach has been associated with the same long-term oncologic outcomes as patients who undergo upfront surgery, but without the morbidity associated with TME.

Topic 7: Future Directions/Ongoing Trials

The 5-year update to OPRA published since the search strategy was performed has shown that 95% and 99% of regrowth/recurrences occur within 2 and 5 years of TNT completion, respectively, with >50% continued TME-FS and excellent oncologic outcomes comparable with those in TMT trials, thus solidifying NOM as an essential treatment option for patients with rectal cancer. Current clinical trials in colorectal cancer continue the trend for customizing treatment options to the QOL needs of the individual patient while simultaneously optimizing oncologic outcomes. General themes include (1) optimizing LC-CRT and cCT for NOM outcomes (eg, JANUS [NCT05610163]), (2) establishing role of SCRT in NOM (NOM-ERA [NCT03904043], ACO/ARO/AIO-18.1 [NCT04246684], and STAR-TREC [NCT02945566]), (3) expanding NOM/OP to earlier-stage disease including through LE (NEO-RT) and brachytherapy (ICUREC [NCT05591534]), and (4) expanding the role of immunotherapy in NOM (EA2201 [NCT04751370]).

Variant Cases and Treatment Algorithms

Variant cases were developed as examples for these guidelines to illustrate practical applications of consensus recommendations (Tables 2-4, 6, and 8-10). Figure 2 provides an algorithm to assist in selection of therapies when considering NOM treatment for adenocarcinoma of the rectum.

Summary of Recommendations

Candidates for primary surgery

- The panel recommends primary surgery as usually appropriate for a T3N0 (negative MRF) high rectal tumor for whom LAR will result in adequate bowel function. aCT should be considered if pN+. (High may be defined by measurement as 10 to 15 cm from the anal verge on proctoscopy or MRI or by anatomic landmarks roughly from the anterior peritoneal reflection to the sigmoid take-off).[212] Estimate of adequate bowel function is based on surgeon assessment, patient preoperative function, and shared decision-making discussion between surgeon and patient.

Candidates for NOM

- The panel strongly recommends NOM as usually appropriate for patients with T1-T3$N_{any}M_{any}$ rectal cancer for whom TME would result in a permanent colostomy or inadequate bowel function.
- The panel recommends that NOM may be appropriate for patients with T4b$N_{any}M_{any}$ rectal cancer for whom TME would result in a permanent colostomy or inadequate bowel function.
- The panel recommends that NOM may be appropriate for a high LARC for whom LAR is possible.

NOM regimen integration of RT and systemic therapy

- The panel recommends that NOM regimens including LC-CRT followed by cCT and LC-CRT with/without brachytherapy boost may be appropriate for the typical low-lying stage I rectal cancer if the patient declines an abdominal perineal resection.
- The panel strongly recommends upfront immunotherapy followed by assessment of response and consideration of further therapy (ie, RT, CT, and/or surgery) as usually appropriate for patients with MSI-H/dMMR rectal cancer.
- The panel recommends that iCT followed by local therapy of liver metastases and pelvic RT may be appropriate in the treatment of synchronous oligometastatic, resectable liver metastases.

NOM radiation regimens/technique

- The panel strongly recommends LC-CRT involving a radiation dose of 54 to 56 Gy in 27 to 31 fx concurrent with CT as usually appropriate for patients with T_{any}-N_{any}M0 rectal cancer pursuing NOM.
- The panel recommends that SCRT involving 25 Gy in 5 fx may be appropriate for patients with nondistal T1-3 N_{any} M0 rectal cancer pursuing NOM.
- The panel weakly recommends that SCRT involving 25 Gy in 5 fx may be appropriate for patients with distal and/or T4b N_{any} M_{any} rectal cancer pursuing NOM.
- The panel recommends that iCT followed by SCRT involving 25 Gy in 5 fx is usually appropriate for patients with oligometastatic rectal cancer pursuing NOM.
- The panel recommends that a brachytherapy boost may be appropriate to improve the cCR rate for nondistal rectal cancers.
- The panel strongly recommends either 3D-CRT or IMRT as usually appropriate in the treatment of T_{any}-$N_{any}M_{any}$ rectal cancer.
- The panel strongly recommends treating the primary tumor and mesorectal, presacral, internal iliac, and obturator nodes as usually appropriate for any patient with rectal cancer who has not received prior radiation.
- The panel recommends treating the external iliac lymph nodes as usually appropriate for any patient with rectal cancer and a tumor invading an anterior organ.
- The panel recommends that treating the inguinal and external iliac lymph nodes may be appropriate for any patient with rectal cancer and a tumor invading distal to the dentate line.

Table 10 62 year-old male (BMI = 27) with good performance status (ECOG = 1) with a prior history of prostate cancer treated with definitive hypofractionated RT (70Gy / 28 fx to the prostate and seminal vesicles) 3 years ago, now with symptomatic high-grade urethral stricture. He is evaluated by his urologist and is found to have undetectable PSA and a rectal mass is detected on clinical exam. Pelvic MRI shows a 3 cm anterior rectal mass with ill-defined planes between the mass and the prostate, suspicious for invasion, and no evidence of abnormal lymph nodes. Endoscopy identifies a fixed, ulcerated non-obstructing 3 cm mass in the anterior rectum 2 cm proximal to dentate line. Full colonoscopy otherwise negative. Biopsy identifies a rectal adenocarcinoma (MSS/pMMR). Cancer stage is T4bN0M0 (Stage IIC). The patient is deemed to require APR with prostatectomy. (Stage IIC, in the setting of prior pelvic RT)

Treatment	Rating category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	SOE	SOR
Treatment Options														
Diverting colostomy prior to cancer therapy			1	3	5	2					5	x	EC	↓
Initial APR + prostatectomy*	M			1	7	4	2	1			4		EC	↓
SCRT alone followed by surgery*	U		5	9	1						3		EC	↑
LC CRT followed by surgery*	M			1	4	9	1				5		EC	-
TNT with iCT followed by SCRT	U		3	6	2						3		EC	↑
TNT with iCT followed by LC CRT	M	1		1	2	5	3	2			5		EC	-
TNT with SCRT followed by cCT	U		2	8			1				3		EC	↑
TNT with LC-CRT followed by cCT	M			1	3	6	3	1	1		5		EC	-
iCT then assessment of response† followed by selective use of RT prior to surgery	M					2	3	6			5	x	EC	↑
Assessment of Response 4-12 weeks following completion of neoadjuvant therapy†														
-If incomplete response‡ and no evidence of progressive disease														
• APR + prostatectomy per surgeon assessment*	A	1				1		4	7	2	8		EC	↑
• Additional systemic therapy (assuming RT was given)	M				3	10	1	1			5		EC	-
-If nCR or cCR‡ and no evidence of progressive disease														
• Active surveillance§	A				1	3		5	3	3	7		EC	↑
• Proceed with planned APR +/- prostatectomy	M	1	1		5	6	2				5		EC	-
If RT; Radiation Dose														
• SCRT 25 Gy / 5 Fx	U	2	2	5	1						3		EC	↑
• LC CRT 45−50.4 Gy / 25−28 Fx	M			1	2	3	4				5		EC	-
• LC CRT 36−45 Gy / 1.5 Gy BID¶	A					1	1	7			7		EC	-

(*Continued*)

Table 10 (*Continued*)

Treatment	Rating category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	SOE	SOR
If RT; Radiation Volumes														
• Primary tumor with margin	A							4	4		7.5		EC	↑
• Primary tumor and mesorectal, presacral, internal iliac, obturator nodes	M			4	3	1			1		5	x	L	↓
• Primary tumor and mesorectal, presacral, internal iliac, obturator, and external iliac nodes	U		1	6	2						3		L	↑
If RT; Radiation Technique														
• 3D-CRT	U	1	2	4	1	1					3		Mod	↑
• IMRT	A							4	4	4	8		Mod	↑

Abbreviations: - indicates neutral; ↑, strong recommendation; ↓, weak recommendation; A, usually Appropriate; CRT, chemo-radiation; CT, chemotherapy; EC, expert consensus; EO, expert opinion; fx, fraction; L, limited; M, May be appropriate; Mod, moderate; MBO, malignant biliary obstruction; NA, not applicable; RT, radiation therapy; S, strong; SMA, superior mesenteric artery; SOE, strength of evidence; SOR, strength of the recommendation; SQ, refers to the study quality (1, 2, 3, or 4) of the references listed; U, Usually not appropriate.

[*] Adjuvant therapy based on final surgical pathology; post-op chemotherapy is generally recommended for pN+ and CRT is generally recommended for positive margin/CRM

[†] Consider TNT with plan for NOM if inadequate response to immunotherapy rather than proceeding directly toward operative management

[‡] Assessment of response when considering NOM includes DRE, proctoscopy/sigmoidoscopy, and rectal protocol MRI

****cCR includes no residual tumor on DRE, proctoscopy/sigmoidoscopy, and rectal protocol MRI evaluations

[§] Active Surveillance includes:

- proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6-12 months thereafter,
- rectal protocol MRI every 3-6 months for the first 2 years, then every 6-12 months thereafter,
- CT imaging of the chest, abdomen and pelvis every 6-12 months for the first 2 years, then every 12 months thereafter
- consider use of ctDNA with caution and the understanding that there are false positives/negatives, and no proven benefits in outcome with treatment of early detection based on ctDNA results alone

[¶] Dose escalation using sequential or SIB technique

Surveillance after a NOM treatment plan

- The panel strongly recommends the first treatment response assessment at approximately 8 to 12 weeks after completion of a NOM treatment plan.
- The panel strongly recommends active surveillance as part of a NOM/OP approach as usually appropriate for patients with an ncCR or cCR.
- The panel strongly recommends repeat assessment 8 to 12 weeks following an ncCR to assess for conversion to cCR as usually appropriate.

Role of LE

- The panel recommends that LE may be appropriate after an ncCR or cCR for patients with stage I rectal cancer.
- The panel recommends LE as usually not appropriate following an ncCR or cCR for T3-4, N+, or M+ rectal cancer.
- The panel weakly recommends that salvage LE may be appropriate for any stage rectal cancer that has an incomplete response of the primary tumor to NOM.

Selective use of RT

- The panel strongly recommends iCT followed by selective use of RT (for poor responders) prior to TME as usually appropriate for patients with high rectal tumor for whom LAR and adequate bowel function is possible.
- The panel strongly recommends iCT followed by selective use of RT (for poor responders) prior to TME as usually not appropriate for patients with T4b rectal tumors requiring an abdominal perineal resection.

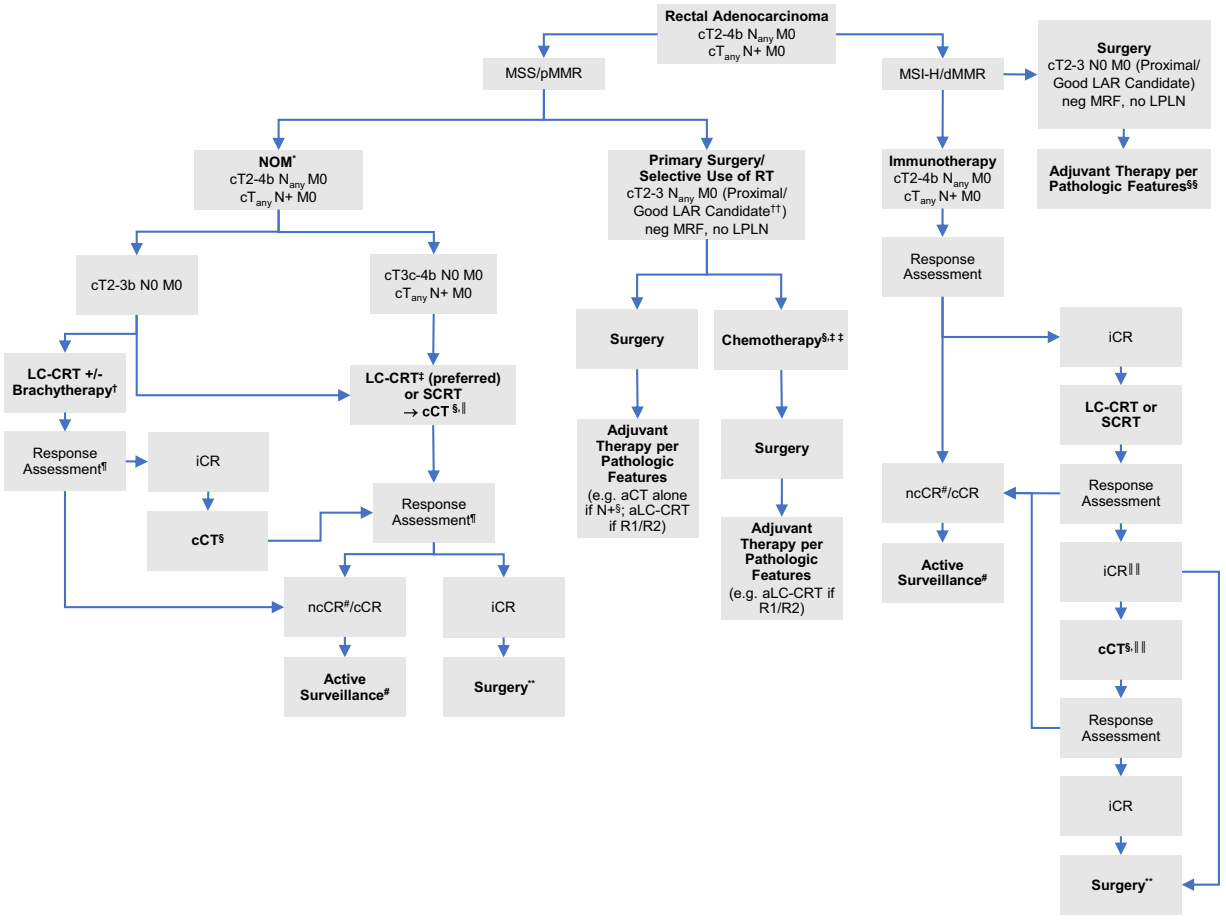

Fig. 2. Algorithm by the American Radium Society Appropriate Use Criteria Gastrointestinal Committee for integrating Non-Operative Management (NOM) into the Treatment of Rectal Adenocarcinoma *Abbreviations:* aCT = adjuvant chemotherapy; aLC-CRT = adjuvant long-course chemoradiation therapy; cCR = complete clinical response; cCT = consolidation chemotherapy; iCR = incomplete clinical response; LAR = low anterior resection; LC-CRT = long-course chemoradiation therapy; LPLN = lateral pelvic lymph nodes; MMRd = mismatch repair deficient; MSI-H = microsatellite instability-high; MSS = microsatellite stability; ncCR = near-complete clinical response; neg MRF = negative mesorectal fascia (>1 mm); pMMR = proficient mismatch repair; RT = radiation therapy; SCRT = short-course radiation therapy.

*NOM usually appropriate if total mesorectal excision (TME) would result in permanent colostomy or inadequate bowel function. No definite contraindications to NOM. Although surgical management often favored for T4b patients, NOM may be appropriate because of significant morbidity of potential pelvic exenteration and similar rates of regrowth to T3 patients if cCR is achieved.

†Brachytherapy may be appropriate if there is no extramural vascular invasion and primary tumor has following characteristics: no anal canal involvement, <50% rectal circumference, and <5 cm diameter.

‡Although there is a higher volume of data to support NOM via long-course chemoradiation (LC-CRT, preferred dose 54 Gy/27-30 fractions) leading to it being preferred versus SCRT (25 Gy/5 fractions suggested), both treatment regimens may be offered in the shared decision-making process.

§Chemotherapy: 12 to 16 weeks of FOLFOX/CAPEOX preferred, and FOLFIRINOX may be considered.

‖cCT is strongly preferred over induction chemotherapy (iCT) to optimize TME-free survival, because no oncologic outcome favors iCT over cCT. However, when considering patient preferences iCT may be appropriate.

¶First assessment 8 to 12 weeks after completion of therapy is strongly recommended.

#If ncCR, repeat assessment in 8 to 12 weeks is strongly recommended, with surgery if iCR is found to be the ultimate best response.

**TME preferred; in selected cases local excision may be appropriate for salvage with understanding TME carries significant morbidity if required after local excision.

††Proximal/good LAR candidates are defined as patients with adequate distance to dentate/sphincter complex for good expected bowel function after LAR.

Note: Figure legend is continued on the next page.

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Fig. 2: Legend continued

[‡‡]Following initial chemotherapy, response assessment may involve sigmoidoscopy +/- MRI. Patients with ≥20% response may proceed to TME; patients with <20% response may receive neoadjuvant LC-CRT (50-50.4 Gy/25-28 fx).

[§§]Due to poor responses to chemotherapy for MSI-H/dMMR tumors, adjuvant immunotherapy alone preferred if adverse path features (e.g. N+).

[‖‖]Due to poor responses to chemotherapy for MSI-H/dMMR tumors, proceeding to surgery if iCR following LC-CRT or SCRT is preferred

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