REVIEW

Future directions in combined modality therapy for rectal cancer: reevaluating the role of total mesorectal excision after chemoradiotherapy

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Abstract: Most patients who develop rectal cancer present with locoregionally advanced (T3 or node-positive) disease. The standard management of locoregionally advanced rectal cancer is neoadjuvant concurrent chemoradiotherapy (nCRT), followed by radical resection (low-anterior resection or abdominoperineal resection with total mesorectal excision). Approximately 15% of patients can have a pathologic complete response (pCR) at the time of surgery, indicating that some patients can have no detectable residual disease after nCRT. The actual benefit of surgery in this group of patients is unclear. It is possible that omission of surgery in these patients, termed selective nonoperative management, can limit the toxicities associated with standard, multimodal combined modality therapy without compromising disease control. In this review, we discuss the clinical experiences to date using selective nonoperative management and various attempts at escalation of nCRT to improve the number of patients who have a pCR. We also explore several clinical, laboratory, imaging, histopathologic, and genetic biomarkers that have been tested as tools to predict which patients are most likely to have a pCR after nCRT.

Keywords: rectal cancer, chemoradiotherapy, total mesorectal excision, nonoperative management, organ preservation

Introduction

Up to 70% of patients with nonmetastatic rectal cancer present with locoregionally advanced disease.[1] Locally advanced rectal cancer (LARC) is generally defined as T3 or node-positive rectal cancer. The standard of care for LARC in the United States is neoadjuvant concurrent chemoradiotherapy (nCRT) given with conventional fractionation over 6 weeks, followed by radical resection with total mesorectal excision (TME) and adjuvant chemotherapy.

With TME, there can be up to a 2% mortality rate. Length of hospital admissions average 15 days.[2,3] The incidence of morbidity ranges from 6% to 35%, which includes anastomotic leak, pain, and blood loss from the procedure.[4] Between 20% and 40% of patients have severe sexual dysfunction after surgery.[5,6] There are also compelling data regarding the effect of resection on quality of life. Patients undergoing abdominoperineal resection (APR), in particular, have reported decreased quality of life.[7] According to Pachler and Wille-Jørgensen, it is unclear whether low-anterior resection minimizes this decline in quality of life compared with APR.[8]

Because many reports indicate that approximately 15% of patients with LARC have a pathologic complete response (pCR) to neoadjuvant therapy at the time of surgery,[9] it is reasonable to wonder whether the risks of TME outweigh the benefits in this select group of patients. Select series indeed show excellent long-term outcomes

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in patients who have a pCR to nCRT without subsequent TME, suggesting that it is possible to avoid planned, radical resection in some patients.[9,10] A review by O'Neill et al discussed some of the key issues that must be addressed in pursuing such an approach in patients with LARC.[11] In this review, we describe the rationale and clinical experiences using selective nonoperative management (SNOM), highlight avenues to improve the efficacy of nCRT to render more patients with a pCR, and explore potential biomarkers associated with response to nCRT that could help identify optimal candidates for SNOM.

Methods

We performed a review of the literature concerning selective nonoperative management in LARC by searching MEDLINE for English-language articles to identify studies with the following subject matter: "rectal cancer", "neoadjuvant chemoradiotherapy", "pathologic complete response", "selective nonoperative management after neoadjuvant chemoradiotherapy", "radiotherapy dose escalation", "chemotherapy escalation and novel combinations", and "clinical, imaging, and biologic biomarkers predicting for response to treatment". Retrospective cohort and case-control series, as well as prospective cohort and Phase I, II, and III clinical trials, were included in our review.

pCR as an indicator of long-term outcomes

The ideal candidates for SNOM are patients with the best responses to nCRT. pCR, or the complete eradication of macroscopic and microscopic tumor as judged by histopathologic

evaluation of the specimen from the radical resection, is the most desirable outcome after nCRT. In the German CAO/ARO/AIO-94 randomized Phase III trial of preoperative versus postoperative CRT on which the current standard of therapy of preoperative chemoradiotherapy is based, 8% of patients had a pCR after preoperative therapy.[12] Of these patients, only 2.9% developed a local recurrence at 10 years after TME. Several large series demonstrate that patients with a pCR at the time of surgery have substantially improved long-term local control, distant control, and disease-free survival (DFS; Table 1).[9,10,13] It is unclear how much radical resection contributes to the low rate of local recurrence in patients with a pCR. Unfortunately, there are no randomized data that directly compare outcomes with or without surgical excision in this group of patients, and proper identification of patients with a pCR without performing radical resection and detailed histopathologic analysis is difficult. Despite these issues, using the pCR as a surrogate for the ultimate response may help identify the patients who are most appropriate for SNOM.

Clinical experiences exploring SNOM

The most extensive clinical experience using SNOM is from Sao Paulo, Brazil. There have been multiple publications on the outcomes of patients treated at two institutions in Brazil: the University of Sao Paulo Medical School, Sao Paulo and the Angelita and Joaquim Gama Institute, Sao Paulo.[14–18] Eligibility included T3–4 disease, node-positive or T2 distal rectal tumors that would otherwise require an APR. In the initial reports, staging was performed via physical exam, digital rectal examination (DRE), rigid proctoscopy, chest

Table 1 5-year outcomes in a large series evaluating disease outcomes in patients with rectal cancer obtaining a pathologic complete response to neoadjuvant chemoradiotherapy

Group (n)	Local recurrence at 5 years	Distant metastasis at 5 years	Recurrence-free survival at 5 years	Overall survival at 5 years
Irish meta-analysis[10]				
pCR (n = 1263)	3%	11%	83%	88%
No pCR (n = 2100)	10%	25%	66%	76%
P-value	<0.001	<0.001	<0.001	<0.001
Dutch pooled analysis[9]				
pCR (n = 484)	1%	9%	87%	90%
MD Anderson[13]				
pCR (n = 131)	1%	7%	91%	93%
Intermediate response (n = 210)	2%	10%	79%	87%
Poor response (n = 384)	9%	27%	59%	77%
P-value	0.002	<0.001	<0.001	0.002

Note: Intermediate response, ypT1–2 N0; poor response, ypT3–4 or ypN1–2.
Abbreviation: pCR, pathologic complete response.

X-ray, computed tomography (CT) abdomen/pelvis, and serum carcinoembryonic antigen (CEA).[14,15] Patients were treated with 50.4 Gy and concurrent 5-fluorouracil (5-FU) and leucovorin.[14,15] Response assessment was performed by a colorectal surgeon 8 weeks after nCRT, using the same staging modalities. Patients who were felt to have a complete clinical response (cCR), which was defined as no significant residual ulcer and no positive biopsy, did not undergo surgery. Instead, they had monthly physical exam, DRE, proctoscopy, biopsy if feasible, and serum CEA assessment for the first year, which was increased to every 2 months for the second year and then 6 months for the third year. CT abdomen/pelvis and chest X-ray were repeated every 6 months for the first year.

In their largest report comparing operative with nonoperative management, Habr-Gama et al demonstrated favorable results of SNOM.[14] Of 265 patients treated with nCRT, the outcomes of 22 patients with a pCR after surgery were compared with the outcomes of 71 patients who had a cCR for at least 12 months. There was no difference in 5-year overall survival (OS) or DFS between patients. Importantly, there were no cancer-related mortalities in the nonoperative group. Two (3%) patients had endorectal recurrences, both of whom were salvaged (one with brachytherapy and one with transanal excision). A subsequent analysis of 361 patients using the same protocol provided more insight into the patterns of failure of patients treated with SNOM (Table 2).[15] Of 122 patients who had a cCR to nCRT (34% of the entire cohort), 99 (81%) maintained a cCR for 1 year. Patients with endorectal-only failures (5%) were successfully salvaged without further recurrence, and none died of rectal cancer.

Over time, the Brazilian protocol has evolved.[17,18] Patients are currently additionally staged using pelvic magnetic resonance imaging (MRI) or endorectal ultrasound (ERUS).[19] Patients are treated with 54 Gy rather than 50.4 Gy and receive three cycles of adjuvant chemotherapy and reassessment at 10 weeks. Patients with any suspicious areas undergo full-thickness local excision for diagnostic purposes. Although the definition likely evolved over the course of the published studies, a strict definition of cCR has been published by Habr-Gama et al.[20] Patients with any residual deep ulceration, any superficial ulcer or irregularity (even if only mucosal), or any palpable nodule on DRE are considered to have an incomplete clinical response, whereas those with no palpable abnormality, white discoloration of mucosal surface, telangiectasia, or subtle loss of pliability of the rectal wall could be considered as having a cCR.

There are some limitations to the Brazilian experience. The outcomes of patients who initially achieved a cCR but had a recurrence within the first year (who were excluded from analysis) have not clearly been discussed. Poor outcomes in these patients could sway one away from SNOM. In addition, stage I patients are not typically treated with nCRT and have more favorable outcomes than those with LARC, yet 11% of patients in the latter paper had stage I (T2N0) disease, potentially favorably biasing the results.[15]

Several other institutions have reported the outcomes of their patients who were treated with SNOM. Table 2 describes these outcomes.[21–24] Maas et al reported excellent outcomes in their patients treated with SNOM.[21] In this study, patients with a cCR (n = 21) were compared with 20 patients with a pCR at surgery. Nearly half (10/21) of the patients treated nonoperatively would have required an APR, and all had sphincter preservation, whereas nearly half (9/20) of those in the surgical group required permanent colostomy. One of the patients developed a local recurrence in the nonoperative group, whereas none did in the operative group. This patient with recurrence had a transanal excision with complete resection. The cumulative 2-year DFS was 89% versus 93%, and 2-year OS was 100% versus 91%, for the nonoperative and surgical groups, respectively, with differences that were not statistically significant. A series from Memorial Sloan-Kettering Cancer Center found that when comparing 32 patients treated with nonoperative management with 57 patients with pCR at surgery, patients treated without surgery had a higher risk of local recurrence (19%; n = 6).[22] However, all recurrences were successfully salvaged with surgery, and there was no difference in DFS, distant metastasis, or survival between the two groups. Two series from the United Kingdom have also evaluated SNOM as a treatment approach, but neither of these studies compared the outcomes of these patients with those of patients treated with planned surgery.[23,24]

There are several limitations to the published experiences of SNOM. The most important issue is that the bulk of the data come from small, retrospective, single-institution series with relatively short follow-up. In addition, most studies included patients with earlier-stage disease (some cT2N0 patients). The favorable outcome of these patients may have made the outcomes of the nonoperative group appear more favorable than would be expected for LARC. An important point to highlight is that the patients in these relatively small cohorts may have been carefully selected for consideration of nonoperative management based on location and size. For example, in the series by Habr-Gama et al, approximately 72% of patients had N0 disease, and mean tumor size was 3.8 cm.[15] It is difficult to translate these results to patients with

Table 2 Clinical experiences of selective nonoperative management in locally advanced rectal cancer after neoadjuvant chemoradiotherapy

	Brazil[15]	The Netherlands[21]	Memorial Sloan-Kettering[22]	Exeter[23]	Multicenter UK[24,*]
Study design	Retrospective	Retrospective/prospective	Retrospective	Retrospective	Phase II
Inclusion criteria	T3–4; node-positive; or T2 N0 requiring APR	T4 or advanced T3; and/or ≥3 involved nodes; or distal tumor with 1–3 involved nodes	≥T3 or node-positive, or T2 for sphincter preservation	Threatened or involved CRM (≤1 mm) or node-positive	≥T3 or node-positive
Concurrent chemo-radiotherapy regimen	5-FU/50.4 Gy	CAP/50.4 Gy	5-FU or CAP/50.4 Gy	CAP/45 Gy	CAP/50.4 Gy
Adjuvant chemotherapy	None	CAP-OX (81%)	FOLFOX, CAP-OX, or 5-FU/LV (53%)	NR	Per NICE criteria[121] (%NR)
Response assessment modality	Clinical, endoscopic, and radiological modalities at 8 weeks	MRI at 6–8 weeks after treatment; endoscopy only if no tumor or fibrosis only on MRI	DRE, endoscopy, selective biopsy, MRI, CT, ERUS, and/or CEA per physician discretion at 4–10 weeks	First MRI at 6–8 weeks; if little evidence of residual tumor, then EUA with biopsy of scar; if negative, then PET	CT and MRI performed at 4 weeks and discussed at multidisciplinary conference
Criteria for nonoperative management	No residual ulcer or negative biopsy	No residual tumor or suspicious lymph nodes on MRI, no residual tumor on endoscopy, negative biopsy from scar, ulcer, or former tumor location, resolution of palpable tumor on DRE	No palpable tumor and no pathologic appearing tissue on endoscopy other than a flat scar	Little evidence of tumor on MRI, no residual ulcer/tumor on EUA, negative biopsy of scar, and negative PET	Considered for deferral of surgery if good partial response or complete response
Follow-up	Clinical exam, proctoscopy, biopsy of suspicious areas, and CEA[†]	DRE, MRI, endoscopy with biopsy, CT, and CEA 4 times in first year and then less frequently	Flexible sigmoidoscopy every 3 months and then less frequently	Repeat EUA at 3 months and 1 year; PET and MRI every 6 months, then yearly	NR
Number treated with NOM	99[‡]	21	32	6	19
Initial local recurrence	6%	5%[¶]	21%[¶]	0%[§]	47%
Ultimate local recurrence[§]	1%	0%	0%	0%	NR[¶]
Distant metastasis	8%	0%[||]	8%[||]	0%[**]	NR
DFS	75%[§]	89%[||]	88%[||]	100%[||]	NR
OS	90%[§]	100%[||]	96%[||]	100%[**]	NR

Notes: *Abstract form only; †Follow-up was monthly for first year, then every other month for the second year, then every month for the second year, then every 3 months for the third year, and then every 6 months thereafter. ‡Only 99 of 122 patients maintained a complete clinical response without surgery for 1 year and were included in the analysis. §Of 9 patients with a local recurrence, 6 patients underwent salvage surgery with clear margins Ultimate local recurrence is the percentage of the cohort with local recurrence after both nonoperative management and salvage surgery. ¶Mean follow-up was 25.5 months. ||2-year outcomes reported. **2-year outcomes reported. §10-year outcomes reported.
Abbreviations: APR, abdominoperineal resection; CAP, capecitabine; CAP-OX, capecitabine and oxaliplatin; CEA, carcinoembryonic antigen; CT, computed tomography; DFS, disease-free survival; DRE, digital rectal exam; ERUS, endorectal ultrasound; EUA, exam under anesthesia; 5-FU, 5-fluorouracil; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; NOM, nonoperative management; NR, not reported; OS, overall survival; PET, positron emission tomography; FOLFOX, 5-Fluorouracil, Leucovorin, and Oxaliplatin; LV, Leucovorin.

higher and more advanced tumors with a clinical complete response. In addition, the proportion of patients who achieved a cCR after nCRT in each of these studies was relatively low (10%–34%).[15,21,23] The definition of cCR, methods of determining response, follow-up frequency, and clinical/imaging modalities to assess for recurrence differ from study to study. In the series that compares the outcomes of nonoperative with operative patients, the patients selected as controls are those with a pCR after radical surgery. As discussed later, cCR does not necessarily correlate with pCR, and thus these control groups may not be the optimal comparison group for the nonoperative cCR patients.

Before SNOM can be implemented in routine practice, more robust data are necessary. Ultimately, a randomized trial comparing the two approaches would provide the strongest evidence, but a large cohort study with structured and long-term follow-up could also be useful to better define the outcomes with SNOM. A more ideal comparison would involve patients with cCR (rather than pCR), using prospectively defined criteria, who are then either observed or resected.

Efforts to improve the efficacy of nCRT

It is likely that to be a candidate for SNOM, a patient needs to have at least a cCR to treatment. The 10–34% cCR rates in the above studies, as well as the 15% pCR rate, suggest that only a minority of patients are potential candidates for SNOM. Advances in chemotherapy and radiation therapy could improve these rates and increase the proportion of patients eligible for SNOM.

Radiation dose escalation and altered fractionation

One way to improve the pCR rate after nCRT is to intensify radiotherapy (RT). Conventional RT is typically given as 1.8–2 Gy per fraction once a day until the total dose is reached. Altered RT fractionation, which refers to changes in the daily dose and total treatment time, has been attempted to improve the response to RT. Short-course RT is unlikely to be the preferred approach for SNOM because it results in a low pCR rate. Two randomized studies compared long-course RT (50.4 Gy) with short-course RT (25 Gy) followed by radical resection.[25,26] Disease control outcomes and reported toxicity between the two regimens were similar, but the pCR rate was higher in the 50.4 Gy group than in the 25 Gy group in both studies (15–16% compared with 1%). A caveat to this is that the short time after completion of RT to resection (1 week) could have limited the number of pCRs in the

short-course RT group. If they had undergone surgery later, more pCRs may have been detected.[27] Radiation Therapy Oncology Group (RTOG) 0012 evaluated a hyperfractionated schema of 55.2–60 Gy in 1.2 Gy fractions twice daily with concurrent 5-FU compared with 50.4–54 Gy with conventional fractionation and 5-FU and irinotecan.[28] The rate of pCR was high for both groups (26%); there was no statistically significant difference.

Several attempts have been made to improve pCR and disease control outcomes using RT dose escalation (Table 3). Among patients treated with long-course RT, there appears to be a benefit in dose escalation from 40 to 50 Gy. A study of patients treated in three consecutive RT dose schedules found that with increasing dose from 40 to 50 Gy, the pCR rates, local control, cause-specific survival, and progression-free survival improved.[29] Mohiuddin et al found that patients treated with more than 55 Gy and continuous infusion 5-FU had a substantially higher pCR rate compared with those receiving less than 50 Gy (44% versus 13%; $P = 0.05$).[30] In a series by Wiltshire et al, patients treated with 46 Gy or more had improved local recurrence-free survival, DFS, and OS compared with patients treated with 40 Gy, but escalation to 50 Gy did not improve outcomes.[31] Unfortunately, most of the above series indicate that with elevated dose, there is also increased toxicity, potentially limiting the applicability of high RT doses.

Increasing the RT dose with modalities other than External Beam RT (EBRT) has also been assessed. Unlike EBRT, which is the use of X-rays to deliver radiation to tumors, brachytherapy refers to the placement of radioisotopes within or near tumor tissues, and contact X-ray RT (CXR) is the use of a narrow beam of low-energy photon radiation placed in close proximity to tumor tissues. Both of these specialized modalities have the advantage of limiting dose to surrounding normal tissues in comparison with a multifield, EBRT approach. The role of using these modalities as a boost to escalate RT dose from EBRT has not been established. A randomized trial comparing 50.4 Gy versus 50.4 Gy with 10 Gy endorectal high-dose-rate brachytherapy boost found no difference in pCR rate (18% in both groups).[32] In contrast, a randomized trial of EBRT compared with EBRT with CXR boost revealed improved pathologic response (defined as no, or few residual cells at the time of surgery) in the high-dose group.[33] Of note, CXR therapy for rectal cancer has been primarily studied for low-lying and less advanced tumors; the applicability of this treatment approach to more advanced or more proximal tumors is unclear.

Newer technologies, such as intensity-modulated radiotherapy (IMRT), may allow for safer RT dose escalation.

Table 3 Radiotherapy dose escalation studies in locally advanced rectal cancer

Study	N	Key inclusion criteria	Study design	nCRT regimen	pCR	Toxicity
Polish[25]	312	T3–4, resectable tumor, no sphincter involvement	Phase III, randomized	5-FU/50.4 Gy versus 25 Gy	16% versus 1% (P=NR)	Severe late: 7% versus 10% (P=0.36)
TROG[26]	326	cT3 tumor	Phase III, randomized	5-FU/50.4 Gy versus 25 Gy	15% versus 1% (P=0.22)	Late grade 3–4: 8% versus 6% (P=0.53)
Calgary[29]	156	Locally advanced rectal cancer	Retrospective	5-FU/40 Gy versus 5-FU + LV + MMC/40 Gy* versus 5-FU + LV/50 Gy	4% versus 15% versus 25% (P<0.002)	Increased grade 2 skin and GI morbidity with each successive schedule
Kentucky[30]	33	Fixed tumor	Retrospective	5-FU/45–50 Gy versus 5-FU/55–60 Gy	13% versus 44% (P=0.05)	Grade 3: 33% in entire cohort
Princess Margaret[31]	134	T3–4 or N1–2	3 Phase II trials, nonrandomized	5-FU/40 Gy versus 5-FU/46 Gy versus 5-FU/50 Gy	15% versus 23% versus 33% (P=0.07)	Grade 3–4: 13% versus 4% versus 14% (P=0.20)
Lyon R96-02[33]	88	T2–3 involving ≤2/3 circumference	Phase III, randomized	39 Gy† versus 39 Gy + 85 Gy CXR	7% versus 21% (P=NR)	Similar acute radiotherapy and surgical complications in both groups
Denmark[32]	248	T3–4, resectable, with MRI circumferential margin <5 mm	Phase III, randomized	UFT + LV/50.4 Gy versus UFT + LV/50.4 Gy + 10 Gy HDR brachytherapy	18% versus 18% (P=NS)	Grade ≥2 nonheme: 40% versus 50%
Colorado[38]	8	Stage II–III	Phase II, nonrandomized	CAP/55 Gy IMRT	38%	Grade 4 diarrhea = 13%, no other grade ≥3 toxicity
Fox Chase[39]	8	T3–4 or N1–2	Phase I, nonrandomized	CAP/55 Gy IMRT	0%	Grade 3 toxicity = 38%

Notes: *Received 18 Gy post-operatively. †Optional 25-Gy brachytherapy boost.
Abbreviations: CAP, capecitabine; CXR, contact X-ray therapy; 5-FU, 5-fluorouracil; GI, gastrointestinal; heme, hematologic; HDR, high dose rate; IMRT, intensity-modulated radiotherapy; LV, leucovorin; MMC, mitomycin C; MRI, magnetic resonance imaging; nCRT, neoadjuvant chemoradiotherapy; NR, not reported; NS, not significant; pCR, pathologic complete response; TROG, TransTasman Radiation Oncology Group; UFT, uftoral.

IMRT uses advanced planning and delivery techniques that can reduce the amount of high-dose radiation to normal tissues by varying the intensity of radiation delivered in each field. This normal tissue sparing has the potential to minimize toxicity because most adverse effects of radiation are a result of high doses to normal tissues. Several series show that IMRT decreases doses to critical normal organs and may thus safely allow for further dose escalation.[34,35] De Ridder et al and Engels et al performed a Phase II study of 108 patients with cT3–4 tumors treated with neoadjuvant RT alone, using an IMRT and simultaneous integrated boost (SIB) approach with helical tomotherapy.[36,37] Patients with anticipated close circumferential resection margins received 55.2 Gy, whereas the others received 46 Gy. Both groups were treated to a smaller treatment volume to allow for small bowel sparing. The pCR rate was 8%, but a favorable acute toxicity profile was noted in comparison with that seen for previously reported, standard RT techniques. A small Phase II study of eight patients treated using a simultaneous integrated boost approach to 55 Gy in 2.2 Gy/fraction to gross tumor found three of eight patients had a pCR.[38] However, a Phase I study of eight patients at Fox Chase Cancer Center (Philadelphia, PA, USA) found unacceptable toxicity (38% had grade 3 toxicity) with a similar treatment approach, albeit with larger treatment volumes.[39]

The small sample sizes of these studies limit the ability to make conclusions regarding the risk–benefit ratio of dose escalation with IMRT.

The effect of regional hyperthermia to nCRT on response has also been assessed in several series. In a retrospective review of 106 patients, Schroeder et al found that patients treated with the addition of regional hyperthermia had improved pCR rates (16.4% versus 6.7%).[40] However, two single-group Phase II studies combining hyperthermia with nCRT found similar pCR compared with nCRT alone.[41,42] Therefore, the role of hyperthermia is unclear.

Chemotherapy agent, dose, and timing modifications

The backbone of concurrent chemotherapy in the nCRT regimen has traditionally been 5-FU. Importantly, the schedule in which the drug is administered has been shown to affect its efficacy. Continuous infusional 5-FU has been shown to be more effective than bolus 5-FU in the metastatic setting and adjuvant concurrent CRT setting[43,44] and has therefore been adopted as the standard chemotherapy schedule when given as nCRT. An attractive alternative to infusional 5-FU is the oral fluoropyrimidine, capecitabine, which likely is at least equivalent to 5-FU, if not better. In a randomized

Phase III trial, capecitabine was associated with a trend toward improved pCR rate (14% versus 5%; $P = 0.09$), 3-year DFS (71% versus 63%; P = not reported), and 5-year survival (66% versus 61%; P = not reported) in patients treated with nCRT for LARC.[45]

Despite encouraging Phase II studies, Phase III studies combining other agents with capecitabine or 5-FU have mostly not improved pCR rates (Table 4). Although several trials showed no benefit for the addition of oxaliplatin,[46–48] the German CAO/ARO/AIO-04 randomized Phase 3 trial showed a modest improvement in pCR.[49] RTOG 0012 revealed no

benefit in pCR with the addition of irinotecan.[28] A single-group Phase II study of 25 patients demonstrated an encouraging pCR rate of 32% with the addition of bevacizumab to capecitabine and 50.4 Gy but must be confirmed in a larger randomized trial.[50] Adding cetuximab to nCRT does not appear to improve pCR.[51,52]

Additional chemotherapy after nCRT and before surgical resection has also been investigated. A follow-up study by Habr-Gama et al included 29 patients treated with three extra cycles of bolus 5-FU and leucovorin after nCRT.[17] cCR at 10 weeks was 76% (n = 22), and of these, 63% (n = 14) had a

Table 4 Addition of combination chemotherapy agents to 5-FU- or CAP-based nCRT

Study	N	Key inclusion criteria	Study design	nCRT regimen/ groups	pCR	Grade 3–4 toxicity
German multicenter[45]	161	Nonmetastatic rectal cancer	Phase III, randomized	5-FU/50.4 Gy	5%	Worse any-grade leucopenia (P=0.04)
				CAP/50.4 Gy	14% (P=0.09)*	Worse any-grade fatigue (P=0.002), proctitis (P<0.001), and hand-foot-skin (P<0.001)
ACCORD 12/0405-Prodige 2[46]	598	T2 anterior/lower rectum or T3 or resectable T4	Phase III, randomized	CAP/45 Gy	14%	11%
				CAP-OX/50 Gy	19% (P=0.09)	25% (P<0.001)
STAR-01[47]	747	Resectable T3–4 or N1–2, M0	Phase III, randomized	5-FU/50.4 Gy	16%	8%
				5-FU + OX/50.4 Gy	16% (P=0.90)	24% (P<0.001)
NSABP R-04[48]	1608	T3–4 or N1–2	Phase III, randomized	5-FU/50.4 Gy	All groups 19%–23%†	Diarrhea: 7% (no OX)
				CAP/50.4 Gy		
				5-FU + OX/50.4 Gy		Diarrhea: 15% (OX) (P<0.0001)
				CAP-OX/50.4 Gy		
CAO/ARO/ AIO-04[49]	401	T3–4 or N1–2	Phase III, randomized	5-FU/50.4 Gy	13%	20%
				5-FU + OX/50.4 Gy	17% (P=0.038)	23% (P=NR)
Radiation therapy Oncology Group 0012[28]	103	T3–4	Phase II, randomized	5-FU/55.2–60 Gy (twice daily)	26%	Acute: 42%; late: 4%‡
				5-FU + IRI/50.4–54 Gy (once daily)	26% (P=NR)	Acute: 51%; late 8%‡
EXPERT-C[52]	165	Tumor ≤1 mm from mesorectal fascia, T3 at or below levators, extramural extension ≥5 mm, T4, or extramural venous invasion	Phase II, randomized	CAP-OX → CAP/50.4 Gy	7%	2%¶
				CAP-OX + CETUX → CAP + CETUX/50.4 Gy	11% (P=0.714)	23% (P=NR)¶
Slovenia[51]	37	Stage II–III	Phase II, Nonrandomized	CAP + CETUX → CAP/45 Gy	8%	Diarrhea: 11%‡ Dermatitis: 16%‡
MDACC[50]	25	T3 and N0–1	Phase II, Nonrandomized	CAP + BEV/50.4 Gy	32%	None

Notes: *Capecitabine was also associated with a trend toward improved 3-year disease-free survival and 5-year overall survival in the neoadjuvant chemoradiotherapy cohort. †5-FU based: 19% versus capecitabine-based: 23% (P=0.012), oxaliplatin-based: 19% versus non-oxaliplatin-based: 21% (P=0.46). ‡Grade 3 only. ¶Grades 3–5.
Abbreviations: CAP, capecitabine; BEV, bevacizumab; CAP-OX, capecitabine + oxaliplatin; CETUX, cetuximab; 5-FU, 5-fluorouracil; IRI, irinotecan; nCRT, neoadjuvant chemoradiotherapy; NR, not reported; OX, oxaliplatin; pCR, pathologic complete response; →, followed by.

cCR for 1 year. It is important to note that in this study, 17% of patients had stage I disease. A nonrandomized multicenter Phase II trial treated patients with nCRT, followed by 2 cycles of modified FOLFOX-6 (5-fluorouracil, leucovorin, and oxaliplatin) if a cCR by imaging and proctoscopy was achieved after nCRT.[53] Patients treated with post-nCRT chemotherapy had a higher rate of pCR at the time of TME compared with patients who had standard nCRT followed by TME (25% versus 18%), but this difference was not statistically significant.

Identifying the best responders

For SNOM to be successful, it is imperative to identify patients who have a pCR after nCRT without radical resection. Various methods are used to assess those who are most likely to have an excellent response, including clinical factors, physical exam findings, and laboratory and genetic factors. Here, we discuss various modalities of assessment and their strengths and weaknesses.

Clinical parameters

Several clinical factors have been associated with improved response to nCRT. One series found higher pCR rates for less rectal wall circumference involvement and lower pCR rates for tumors involving more than 60% of the circumference and being more than 5 cm from anal verge.[54] Although some studies suggest that initial clinical T-stage and N-stage may be associated with response,[55,56] others suggest that these characteristics may not be as important as genetic factors.[57,58]

It is possible that treatment response (and factors that may influence response) are dependent on time between nCRT and surgery. A longer interval between nCRT and radical surgery may improve pCR rates, and this delay of resection may not compromise local control.[16,27,59,60] A randomized study from Lyon found that pathologic downstaging was increased when the interval between RT and surgery was increased from 2 weeks to 6–8 weeks (10% versus 26%; $P = 0.005$), although the primary endpoint of sphincter-preserving surgery was not significantly different.[61] Even patients treated with short-course RT can have a pCR rate of 8% if surgery occurs after 4 weeks (compared with 1% at 1 week).[62] However, in the Brazilian experience, using conventional nCRT followed by surgery, patients who had more than 12 weeks delay had no difference in pCR, DFS, or survival compared with those who had surgery at 12 weeks or less.[16] The current National Comprehensive Cancer Network guideline is an interval between nCRT and radical resection of 5–10 weeks.[63]

Clinical assessment is the most commonly used form of post-treatment response assessment. A review from Memorial Sloan-Kettering of patients treated with nCRT followed by resection evaluated post-treatment DRE and proctoscopy to evaluate clinical response to CRT and found that only 25% of patients with cCR actually had a pCR, which was generally 6 weeks after nCRT (with response assessment 1 week before surgery).[64] Another study found that complete response by DRE only correctly identified pCR in 21% of patients with a pCR.[65] In addition, many patients with pCR may have residual mucosal abnormality at the time of response assessment.[66] For patients who have what appears to be an incomplete clinical response, a series from Perez et al found that 21% of patients with a negative endoscopic biopsy actually had a pCR.[67] These findings make post-treatment physical exam findings even more difficult to use in decision making. For these reasons, pretreatment clinical parameters, physical exam findings after treatment, and post-treatment biopsy are not sufficient to predict pCR.

Imaging modalities

Several imaging modalities are commonly used in the initial staging and response assessment of patients with rectal cancer, including CT and ERUS. The ability of ERUS and CT to individually predict for pCR both at the primary and nodes is relatively modest.[68–70] An Italian series of 46 patients compared ERUS, CT, and MRI at 4 weeks after nCRT. In this study, radiographic staging by ERUS or CT that indicated no residual abnormality in the rectal wall was considered T0, tumor felt to be confined to the rectal wall was called T1 or T2, full-thickness involvement of the rectal wall with infiltration of the perirectal fat was T3, and invasion of surrounding organs/structures was T4. Lymph nodes 5 mm or larger were considered to be positive. The accuracy was 64% for ERUS and 74% for CT in predicting pT0 status, and 61% for ERUS and 62% for CT for predicting pN0 status.[69]

MRI is a promising imaging modality to evaluate anatomic changes after nCRT. Still, RT fibrosis can make interpretation difficult, and although MRI is effective for identifying disease that only involves the rectal wall, it cannot reliably identify patients with pCR. In the Italian series, the accuracy of MRI at 4 weeks after nCRT for pT0 was 77%, and for pN0 it was 65%.[69] The Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) study was a prospective cohort study of patients treated with nCRT followed by surgical resection.[71] In this study, an MRI tumor regression grade (mrTRG) was created based on the TRG for histopathologic response.[72] Although the mrTRG

was useful for detecting unfavorable pathologic response (ypT3–4 or TRG 0–2), it is unclear whether it can predict pCR at surgery.[73] In addition, only 44% of patients had a favorable response (ypT0–3a) in this study at the time of histopathologic evaluation, and only 11% had pCR. This highlights the minority of patients who would be applicable for SNOM with the current treatment platform and MRI response assessment.

Positron emission tomography (PET) offers insight into the metabolic activity of tissues, potentially complementing anatomic imaging. A Brazilian study found a 73% negative predictive value and 85% accuracy of PET/CT for detecting incomplete response.[74] Other studies have suggested PET may not be as accurate.[75,76] A prospective study of 80 patients treated with nCRT followed by radical resection found that PET/CT did not predict pathologic response, but a decrease in SUV (standardized uptake value) was associated with lower disease recurrence.[77] These clinical data, as well as the issue of interobserver variation and no clear standard criteria for response assessment, suggest that the use of PET or PET/CT alone to predict pCR has questionable utility.

Individually, each of these imaging modalities does not appear to be suitable to identify patients with a pCR. However, when combined, they have greater prognostic value. In the Brazilian series, the accuracy of PET/CT combined with clinical exam was 96% in predicting pCR.[74] In a Taiwanese series of 166 patients, using MRI, colonoscopy, and rebiopsy to reassess patients at 4 weeks after nCRT, the accuracy was 78% for pCR.[78] However, it is important to note that the majority of data using multimodality reassessment are retrospective in nature, are subject to selection bias, and may be influenced by expertise.

CEA and other laboratory findings

Several studies have evaluated whether clinical response assessment can be augmented by pre-and post-treatment CEA levels. One study found that pretreatment CEA levels higher than 5 ng/mL were associated with a poor response to nCRT.[57] Another study found that patients with a pCR had a lower pretreatment and post-treatment CEA level, and that no patients with an elevated post-treatment CEA (>5 ng/mL) level had a pCR.[79] In this series, post-treatment CEA levels had a stronger association with outcome than pretreatment levels. Another series found that pre-nCRT versus post-nCRT CEA changes were not associated with pCR rate, but those patients with high pretreatment CEA and poor reduction (<70%) after nCRT had a higher risk for local and distant recurrence.[80] A Brazilian series found that

patients with post-treatment CEA levels lower than 5 ng/mL had higher rates of cCR, pCR, DFS, and OS than those who did not.[81] Ultimately, a standard definition of "low" CEA or "good" response must be identified for optimal use of CEA in treatment decision making.

Other laboratory tests have also been evaluated. Kawai et al found that pre-nCRT thrombocytosis was associated with worse response by barium enema, or pathologic response.[82] Kitayama et al found that patients who had a complete response had higher lymphocyte ratios and lower neutrophil ratios, suggesting that part of the response to nCRT may be immune-mediated.[83] These series hint that other lab parameters may be of use but must be validated in other series before they may be used clinically.

Tumor histopathologic markers

Numerous histopathologic markers have been evaluated to identify patients who will have a good response to nCRT and/or good prognosis (Table 5).[84–105] None have been identified as unequivocal biomarkers of response across all studies. Most biomarkers have been found to be associated with both improved and inferior response in different studies. Most of the studies are small, single-institution series; few are validated externally; and varying nCRT regimens were used. The most extensively studied marker has involved p53 mutations.[106–108] A meta-analysis found that wild-type p53 was associated with improved rates of "good response."[109] Despite these positive findings, neither p53 nor any of the other studied biomarkers are likely to singularly predict for those destined to have a pCR. The response to treatment is likely too complex to be modeled adequately with one biomarker.

Table 5 Investigated histopathologic factors possibly associated with response to neoadjuvant chemoradiotherapy

Marker of interest	References
p53	106–109
Thymidylate synthase	84–87
Epidermal growth factor receptor	86,88–91
Bax	84,92,93
Ki-67	84,94,95,98
p21	96,97
Vascular endothelial growth factor	91,98
Remodeling and spacing factor 1	99
Matrix metallopeptidase 9	100
Insulin-like growth factor 2 mRNA-binding protein 3	101
HMG-coA synthase 2	102
PIK3CA	103
XRCC1 polymorphism	104
Cox2 overexpression	105

Abbreviations: Bax, BCl-2-associated X protein; HMG, 3-hydroxyl-3-methyl-glutaryl-CoA; PIK3CA, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha isoform; XRCC1, X-ray repair cross-complementing protein 1; Cox2, cyclooxygenase-2.

Gene and microRNA expression profiles

Several groups have identified tumor gene expression profiles that may be associated with response to nCRT.[110–112] Interestingly, the gene expression profiles in these studies do not necessarily highlight genes known to be important. Kim et al specifically identified a gene expression profile that identified pCR with 84% accuracy in a testing sample and 87% accuracy in a validation cohort.[113] This profile was composed of 95 genes involved in multiple cellular pathways, including *MMP14*, *MSX2*, *RAD23B*, *Thymidylate synthase*, *FGFR4*, and *ENO1*. Similarly, micro (mi)RNA expression profiles may be associated with response to therapy.[114,115] An Italian study found a miRNA expression profile that predicted pCR with a sensitivity and specificity of 100%.[116] This study included 38 patients with LARC treated with capecitabine and oxaliplatin with 45 Gy RT. Biopsy specimens were analyzed to identify a 13-miRNA expression profile composed of eleven miRNAs that were upregulated and two miRNAs that were downregulated in pCR patients. All of the nine patients with a pCR had upregulation of miR-630 and miR-622, whereas all patients without a pCR had downregulation of these two miRNAs. However, this profile has not been confirmed externally and may not be practical because detailed knowledge regarding individual miRNA levels of expression is required. These findings are encouraging, but further research is necessary to identify and validate the optimal profile to translate it into clinical use.

Circulating/disseminated tumor cells

Circulating tumor cells (CTCs), or tumor cells identified in the peripheral blood, and disseminated tumor cells, tumor cells identified in the bone marrow, have also been evaluated for their role in response prediction. There are no series evaluating whether the presence, concentration, or changes in concentration before or after nCRT of CTCs can identify patients who are likely to have a pCR. One of the challenges with using CTCs as a biomarker for response is that only 30–60% of patients with rectal cancer have detectable CTCs.[117,118] An Austrian study found that CTCs were more likely to be detected in patients with a good response to nCRT (ypT0–2) than in nonresponders at the time of surgery (63% versus 18%), and responders had decreased detection over the course of treatment.[117] A Norwegian study found that disseminated tumor cell detection was not associated with radiologic TNM stage or TRG score at the time of surgery after nCRT.[118]

Circulating cell-free DNA

Circulating cell-free DNA (cfDNA) is another promising biomarker. Agostini et al studied 67 patients undergoing nCRT and found that the post-treatment cfDNA integrity index and levels of Alu 247 fragments were independently associated with improved response rate.[119] Similarly, Zitt et al found that responders had lower levels of cfDNA after treatment compared to nonresponders.[120] However, these findings must be validated, and the ability of cfDNA parameters to predict pCR is unknown.

Toward the development of a SNOM protocol

A standardized approach toward SNOM of rectal cancer has yet to be defined. All of the SNOM series discussed earlier differ in the frequency of follow-up and modalities of initial staging and response assessment. It is likely that even if the merits of a SNOM approach are confirmed in further studies, the optimal protocol would be the subject of much debate. It is clear that the ideal protocol would have comprehensive staging with clinical examination, colonoscopy, and imaging such as ERUS, MRI, and PET-CT both before starting nCRT and for tumor response assessment. The optimal chemoRT regimen is unknown, but 50.4 Gy with FU is not sufficient to achieve meaningful rates of pCR. Patients must be followed frequently. On the basis of the Habr-Gama and Dutch series, it appears that the highest risk for recurrence is within the first year after treatment, when follow-up would need to be closest. In the second year, the frequency of follow-up could be decreased, with gradual relaxation up to 5 years. Long-term follow-up would be essential to establish safety, given the possibility for late recurrences[12] and potential for late toxicity in the intact rectum. Further protocols should also include biomarkers, such as CTCs or cfDNA, which may better predict for pCR and improved outcome. In addition, newer imaging modalities, such as novel PET tracers, should be incorporated, as traditional imaging modalities have limitations in predicting pCR. The ideal timing of surgery in those without a cCR is also unknown. It appears that anywhere from 8 to 12 weeks or more may be safe, but the incremental delay in surgery to potentially allow for increased appreciation of pCR must be weighed against the increased risk of recurrence. However, patients who do reach this point with a cCR could be considered appropriate for omission of surgery.

Conclusion

Several series suggest that SNOM is safe and feasible in a small proportion of patients with locally advanced

rectal cancer. However, the literature describing this approach is mostly retrospective and single-institution in nature, with small numbers and varied methodology. In addition, many of these studies lack long-term follow-up. These issues limit the ability to consider SNOM a safe alternative to the standard treatment paradigm. Larger prospective studies with long-term follow-up, ideally randomized prospective trials comparing standard combined modality therapy with SNOM, are necessary to further evaluate the safety and efficacy of this approach. Until more robust studies confirm its appropriateness, SNOM cannot be incorporated into routine practice. Even if further study supports SNOM of rectal cancer, perhaps only a minority of patients will obtain the cCR necessary to pursue SNOM using current nCRT regimens and response assessment tools. Further research is necessary to improve the efficacy of nCRT to induce a complete response. Simultaneously, oncologists must better identify patients who have had a pCR, as current assessment and detection approaches have demonstrated insufficient accuracy to alter treatment. There are biomarkers with encouraging preliminary results, however, which must be validated and confirmed in larger, multicenter cohorts. With progress in these areas, perhaps SNOM will not only be feasible and safe but also be the approach of choice in a subset of patients with LARC.

Disclosure

The authors report no conflicts of interest in this work.

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