Chapter 19
Clinical Complete Response after Neoadjuvant Chemoradiotherapy in Rectal Cancer: Operative or Non-Operative Management?

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PICO table

Patient population	Intervention	Comparator	Outcomes
Patients with complete response after neoadjuvant treatment of rectal cancer	Non-operative management	Surgery (TME)	Cancer recurrence, morbidity, disease-free survival, overall survival

Introduction

Surgical excision of the rectum and its mesorectal envelope has been the mainstay of rectal cancer treatment for over a century [1]. Despite advances in surgical technique and perioperative care, total mesorectal excision (TME) remains an operation associated with some mortality, significant morbidity, and sequelae that permanently impair quality of life [2].

Some patients with locally advanced rectal cancer (LARC) have a pathologic complete response (pCR) to neoadjuvant chemoradiotherapy (nCRT). Patients with pCR have lower local recurrence (LR) and improved survival rates compared to non-pCR patients, raising the question of whether they truly need surgery [3]. As most of the mortality, morbidity, and long-term sequelae from multimodality therapy are related to excision of the rectum, avoiding TME selectively in patients who obtain a sustained response to nCRT will improve the quality of life, with the added benefit of avoiding overtreatment.

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While the evidence suggesting that some rectal cancers can be treated with radiation alone is almost a century old, it is Angelita Habr-Gama from Sao Paulo who should be credited with suggesting that rectal cancer patients with clinically complete responses (cCR) to neoadjuvant chemoradiation could achieve long-term local tumor control without surgery [4].

These ideas were initially received with disbelief, but reports from other institutions have confirmed that surgery can be avoided in select rectal cancer patients treated with nCRT. However, the evidence supporting this treatment approach is based on small institutional series of heterogenous groups of patients who were staged using different imaging modalities, treated according to diverse radiation and chemotherapy regimens, evaluated at different times after completion of the neoadjuvant therapy, selected for observation using different criteria, and followed for relatively short periods of time. In spite of these limitations, clinicians are starting to accept a paradigm shift for this select group of rectal cancer patients, often pushed by patients motivated to avoid the consequences of a low colorectal anastomosis or a permanent colostomy. The treatment plan after neoadjuvant therapy that consists of close active surveillance, rather than surgery, is called watch-and-wait or non-operative management (NOM).

Uncertainties about Tumor Response to Neoadjuvant Therapy

While the above-mentioned studies all suggest that most patients with cCR after neoadjuvant chemotherapy can achieve prolonged local tumor control without surgery, a number of questions must be answered before NOM can be considered a standard option for patients with LARC.

The proportion of patients responding completely to neaodjuvant chemoradiation seems small and the optimal time to assess clinical response unknown. Tumor response depends on radiation dose, but doses beyond 54 Gy are rarely used in LARC patients. Adding other drugs effective in colon cancer as radiosensitizers beyond fluorpyrimidines has been found to be ineffective or prohibitively toxic [5–8]. Tumor response to chemoradiation is closely associated with time, and in patients undergoing TME after nCRT, the proportion of tumors with pCR increases with the time interval between chemoradiation and surgery [9]. As prolonging the interval to surgery and postoperative systemic chemotherapy may be unsafe in patients at risk of LR, attempts have been made to deliver systemic chemotherapy immediately before or after chemoradiation [10]. Delivering systemic chemotherapy before rather than after surgery has been shown to increase tumor response without delaying the treatment of potential micrometastatic disease. In these patients, the assessment of the clinical response, with the potential recommendation of NOM or surgery, is performed at the completion of both chemoradiation and systemic chemotherapy [10, 11]. This approach has resulted in pCR rates as high as 38 % in patients with clinical stage II and III disease and has the added advantage of increasing compliance with adjuvant systemic chemotherapy as well as shortening ileostomy time for patients after low anterior resection [10].

The lack of a reliable and uniform method of distinguishing post-treatment scar from residual tumor in the bowel wall or regional lymph nodes is the main obstacle to NOM in patients treated with neoadjuvant therapy. Most authors agree that digital rectal examination, endoscopy, and imaging studies should be used (Table 19.1). A flat white scar with or without telangiectasia and a normal digital exam are good predictors of pCR, while the presence of superficial ulceration or a palpable modularity on digital rectal exam considered an indicator of incomplete response [12, 13]. While clinical assessment tends to underestimate tumor response, there is always a possibility that tumors are concealed in or behind an apparently normal scar in the rectal wall [14]. Endorectal ultrasound, computed tomography (CT), and positron emission tomography with [^{18}F]fludeoxyglucose provide a rough estimate of tumor regression but are not sensitive enough to identify pCR [15]. Conventional MRI morphological sequences (e.g. T2- and T1-weighted images) cannot differentiate residual tumor from surrounding fibrosis, but diffusion-weighted (DW) MRI sequences may improve the diagnostic performance of morphological MRI sequences in differentiating pCR from residual tumor [16]. The criteria used to grade response undoubtedly influence the observed clinical outcomes: a strict definition reduces the proportion eligible but increases the chance of NOM success, while looser criteria increase the number of eligible patients but also risk of local tumor regrowth and distant metastasis. Currently, there are no validated criteria defining clinical and radiological tumor response, but a new set of criteria categorizing response in a 3-tier system is currently being tested in a prospective clinical trial [17].

Table 19.1 Criteria of complete response, near-complete response, and incomplete response [13]

	Complete response	Near-complete response	Incomplete response
Endoscopy	Flat, white scar Telangiectasia No ulcer No nodularity	Irregular mucosa Small mucosal nodules or minor mucosal abnormality Superficial ulceration Mild persisting erythema of the scar	Visible tumor
Digital rectal exam	Normal	Smooth induration or minor mucosal abnormalities	Palpable tumor nodules
MRI-T2W	Only dark T2 signal, no intermediate T2 signal AND No visible lymph nodes	Mostly dark T2 signal, some remaining intermediate signal AND/OR Partial regression of lymph nodes	More intermediate than dark T2 signal, no T2 scar AND/OR No regression of lymph nodes
MRI-DW	No visible tumor on B800-B1000 signal AND/OR Lack of or low signal on ADC[a] map Uniform, linear signal in wall above tumor is ok	Significant regression of signal on B800-B1000 AND/OR Minimal or low residual signal on ADC map	Insignificant regression of signal on B800-B1000 AND/OR Obvious low signal on ADC map

[a]ADC, apparent diffusion coefficient

A number of patients with apparent cCR develop tumor regrowth during follow-up. As most regrowth occurs in the bowel wall, repeated endoscopic exams are essential. Any suspicious changes in the scar should be biopsied. MRI should also be performed regularly to detect nodal disease. Changes in the size, contour, heterogeneity, or restriction of diffusion should raise the possibility of relapse. Repeated exams and continuous monitoring are often necessary to confirm recurrence.

Ultimately, finding reliable predictors of response to neoadjuvant therapy would help identify patients most likely to benefit from NOM and reduce toxicity for those who will likely have poor response. Tumor size and stage seem to predict response, with smaller, early-stage tumors being more likely to yield pCR. The search for molecular predictors of tumor response has not yielded any breakthrough findings so far. We have previously shown that rectal tumors with a KRAS mutation are less likely to respond to nCRT [18]. However, these findings await validation by studies of large independent cohorts.

Treatment Options for Patients with a cCR after Neoadjuvant Therapy: Observation or Surgery?

Unfortunately, there is no level 1 evidence regarding the oncological and functional outcomes of NOM versus standard TME after a cCR. Ideally, a randomized study should be performed, with a non-inferiority design for the non-operative arm. However, there are 2 reasons why this kind of study is difficult to perform. First, a non-inferiority study requires investigators to demonstrate that survival will not be compromised in NOM. Such a study requires a large sample size that will be difficult to achieve. Second, it is unlikely that patients who are told that NOM is an alternative option potentially offering similar oncological results would opt for randomization with a chance of undergoing surgery anyway.

Meta-analyses are also not available. Thus, the only types of studies we can analyze are retrospective series or prospectively followed patient series. Our search terms on PubMed were “complete response,” “rectal cancer,” “non-operative management,” “watch and wait,” and “wait and see.” We will discuss the oncological and functional results in the next chapters.

Evidence Supporting NOM

In this overview, we included studies in which patients with a cCR as established by digital rectal examination, endoscopy, and MRI were compared to a cohort of patients who had a resection and demonstrated pCR on pathologic examination. There is also one study in which patients were managed by NOM after cCR diagnosis established by MRI alone. In our opinion this is not the standard of care, so we did not include this study [19]. Table 19.2 shows the oncological outcomes of the 5 comparative studies in order of publication.

Table 19.2 Studies in which oncological outcomes for NOM in patients with cCR were compared to those for OM in patients with pCR

Reference	No of cCRs (NOM)	No of pCRs (OM)	Difference in T-stage[a]	Difference in distance of tumor[a]	Difference in adj. chemo[a]	Overall survival		p-value	Disease-free survival		p-value	Evidence level
						NOM	OM		NOM	OM		
Habr-Gama et al. [20]	71	22	Equal	Equal	Equal	5-year 100 %	5-year 88 %	0.01	5-year 92 %	5-year 83 %	0.09	3b
Maas et al. [4]	21	20	nm	nm	nm	2-year 100 %	2-year 93 %	0.23	2-year 89 %	2-year 91 %	0.77	3b
Smith et al. [21]	32	57	NOM	OM	OM	2-year 96 %	2-year 100 %	0.56	2-year 88 %	2-year 98 %	0.27	3b
Araujo et al. [22]	42	69	NOM	OM	Equal	5-year 72 %	5-year 90 %	0.32	5-year 61 %	5-year 83 %	0.04	4
Li et al. [23]	30	92[b]	Equal	Equal	nm	5-year 100 %	5-year 96 %	0.26	5-year 90 %	5-year 94 %	0.51	4

nm not mentioned

[a]In favor of NOM (non-operative management) or OM (operative management), meaning less advanced T-stage, higher location of the tumor or more adjuvant chemotherapy (adj. chemo)

[b]cCR patients who underwent surgery

The first comparison between 71 NOM patients with a cCR and 22 OM patients with a pCR was reported by Habr-Gama [20]. Patients were well-informed about the risks and benefits of NOM. In a retrospective series of 194 patients with near-complete response, NOM was considered too risky and surgery was performed; 22 (8.3 %) of these patients ended up having a pCR. Regarding clinical parameters and postoperative treatment, there was no significant difference between the NOM and OM patients, although it seemed that there were slightly more T3/T4 tumors in the OM group. The NOM group's disease-free survival (DFS) was similar to that of the OM group; 1-year survival (OS) was significantly better. The authors do not explain this; the question remains whether the deaths were related to the surgery, although no perioperative deaths were reported.

In a small but very carefully selected series of prospectively followed patients by Maas et al., 21 well-informed NOM patients were compared to 20 retrospectively selected OM patients with pCR. Of the 20 OM patients, 5 had cCRs and were treated before the wait-and-see policy was introduced, and 15 had a near-complete clinical response [4]. Although the study's data tables show no differences between the patient groups, no statistics were presented. There was no difference in OS and DFS between the groups.

The third study, by Smith et al., describes 32 NOM patients and 57 OM patients with a pCR [3]. NOM was described to the patients as a non-standard treatment which might compromise oncological outcomes, but the majority opted for this management because of high medical comorbidity or because they did not want to undergo surgery. The OM patients had slightly more proximal tumors and received adjuvant treatment more often but had more advanced tumors compared to the OM-patients. Even so, DFS and OS were not significantly different.

Araujo et al. conducted a retrospective analysis of 42 patients treated with NOM and compared them to 69 patients who had a pCR after resection [22]. NOM was not the standard of care in this institution, so most patients in this group were patients who refused surgery or wanted to postpone it as long as possible. DFS was significantly worse in the NOM group, but the authors also mentioned that this might be due to the fact that there were more distal cancers in this group. DFS was not significantly different if only patients with low rectal cancers were included. The most striking element of this paper is the inclusion of 20 patients in the NOM group (54 %) with residual tumor or ulceration. Although statistically this did not influence DFS, this weakens the study considerably, as in our opinion patients should be referred for surgery in the case of residual disease.

Li et al. published the only series in which patients with cCR who underwent NOM were compared to patients with cCR who underwent surgical management [23]. There seemed to be no difference clinically between the two groups. However, the reasons for treatment selection were not explained by the authors. It is unclear whether there is a time bias due to NOM's introduction at a certain time point or whether there was informed consent for this strategy. For these reasons, we consider it a weak study.

A group from the United Kingdom has recently reported a multi-institutional experience with a NOM approach versus surgical resection in rectal cancer patients treated with chemoradiation [24]. In contrast to the previously discussed series, this

study compared the outcomes of 129 patients with cCR and 228 rectal cancer patients who had surgical resection after neoadjuvant chemoradiation independent of the pathological stage. The neoadjuvant therapy regimens in the two groups were similar. After a median follow-up of 33 months from start of chemoradiation, 44 (34 %) patients with cCR had local regrowths, corresponding to an actuarial 3-year local regrowth rate of 38 %. Similar to previous findings, most local regrowths were in the bowel wall, and most underwent successful salvage treatment. The authors developed one-to-one paired cohorts (109 patients in each group) using propensity-score matching for the key confounders. The 3-year non-regrowth DFS rate (time until death, local recurrence, or distant metastasis, not including local regrowths) was 88 % for the NOM group and 78 % for the surgical group (log rank $P = 0.22$). The colostomy-free survival rates were 74 % and 47 %, respectively. The authors concluded that NOM is oncologically safe in a multi-institutional setting, supporting the standard adoption of NOM. However, the results of this study should be interpreted with caution, as tumors in NOM patients had earlier pretreatment tumor stage, were less likely to have nodal involvement, rarely had unfavorable histological features, and were more likely to have normal carcinoembryonic antigen levels. In addition, comparing patients with and without cCR, independent of the pathological stage, introduces significant bias, as tumor response is associated with improved outcome compared to non-responders.

On the basis of the first 3 studies, although they are based on only level 3b evidence, we can carefully conclude that NOM results in similar oncological outcomes associated with recurrence-free survival and overall survival compared to OM. A prerequisite for NOM is a cCR, *not* a near-complete response. Since about 70 % of patients with cCR would have a pCR after resection, you might expect less favorable oncological outcomes compared to the patients who had a resection and 100 % pCR. Instead, the similar outcomes suggest even more strongly that NOM is oncologically safe.

Local Regrowth and Salvage Therapy vs. Stoma Rates and Operative Mortality

Table 19.3 summarizes local-regrowth, stoma, and mortality rates in the 5 retrospective studies. Overall, the mean time to local regrowth in NOM patients with cCR was 31 months. Local regrowth appeared in an average of 8 % of all patients, although this also includes the Araujo study, which included near-complete responders. Ninety-four percent of all local regrowths could be salvaged, and 4 % of all cCR patients ended up with a permanent stoma. By contrast, 35 % of patients receiving OM had a permanent colostomy. The mean mortality rate after OM was 2 %. Local recurrence after this management was still present in 2 % of the cases, despite the pCR after primary surgery.

As mentioned earlier, the timing and definition of cCR can greatly influence the proportion of patients considered as having a cCR as well as associated local recurrence rates. One should bear in mind that the above-mentioned 8 % local regrowth

Table 19.3 Comparison of the rates of local failure, stoma, and operative mortality after NOM in patients with cCR and after OM in patients with pCR

Reference	Mean interval to LR in NOM (months)	No. of LR cases in NOM (%)	No. of salvage-able LR cases in NOM (%)[a]	NOM patients undergoing salvage therapy		OM		No. of LR cases in OM (%)	No. of peri-operative mortality cases (%)
				No/temporary stoma (% of all NOM patients)	Permanent stoma (% of all NOM patients)	No/temporary stoma (%)	Permanent stoma (%)		
Habr-Gama et al. [20]	60	2 (3)	2 (100)	1 local excision 1 brachytherapy	0 (0)	13 (59)	9 (41)	0 (0)	0 (0)
Maas et al. [4]	22	1 (5)	1 (100)	1 local excision	0 (0)	11 (55)	9 (45)	0 (0)	1 (5)
Smith et al. [21]	11	6 (19)	6 (100)	3 (9)	3 (9)	nm	nm	0 (0)	nm
Araujo et al. [22]	48	5 (12)	4 (80)	1 (2)	3 (7)	56 (81)	13 (19)	4 (6)	3 (4)
Li et al. [23]	22	2 (7)	2 (100)	1 local excision 1 nm	nm	52 (57)	40 (43)	2 (2)	0 (0)
Mean[a]	31	16 (8)	15 (94)		6 (4)		71 (35)	6 (2)	4 (2)

[a]Mean excludes studies in which there were 'nm' (not mentioned) data

rate is for a strongly sub-selected patient cohort. For example, in Maas et al. this cohort represented 21 patients, which was 11 % of the patients treated with chemoradiotherapy. Also, in the later Habr-Gama series, local regrowth numbers varied depending on the group of patients considered. When 68 % of the patients treated with chemoradiotherapy were managed with NOM, long-term sustained response could be achieved in 57 % [25]. These numbers are consistent with the first published prospective trial (NCT00952926) by Appelt et al. [26] This study showed 58 % local tumor control after 2 years in patients with primary low T2/T3 rectal cancers treated with chemoradiotherapy resulting in a cCR. The patients in this study had their assessment at 6 weeks after treatment completion, which is early (resulting in a 78 % cCR rate), also explaining the high local regrowth rate. All local recurrences (9 of 9) after NOM underwent resection with clear resection margins.

Functional Outcomes and Toxicity Associated with NOM

It is generally believed that functional outcomes are better in patients who have undergone NOM than in patients who have undergone a resection, owing to the risk for nerve damage and low-anterior resection syndrome. The only study comparing functional outcomes after NOM versus resection with a pCR is by Maas et al., which confirmed that functional outcomes are better after NOM [4]. Bowel function in patients in the OM group was significantly more affected by food intake, and these patients used pads and colonic irrigation more frequently, had less control over flatus, and reported more changes in their post-diagnosis/treatment bowel habits. Also, patients who had NOM had a lower mean Wexner incontinence score (0.8 versus 3.5) and a lower mean defecation frequency (1.8/day versus 2.8/day) than patients who had a resection. Appelt et al. also described good functional outcomes; there was no self-reported fecal incontinence in 72 % of patients after 1 year and in 69 % at 2 years after NOM. The median Wexner incontinence score was 0 at all time-points [26].

Regarding NOM toxicity, only one study measured it accurately: the prospective study of Appelt et al. [26]. However, in this study brachytherapy was given as a boost to 60 Gy chemoradiotherapy. Rectal bleeding was the most common symptom, reported by 78 % of the patients after 1 year, although this was mild in most patients; 6 % had grade 3 rectal bleeding, which needed transfusion or intervention, at 2 years. The authors hypothesized that this unexpected high toxicity rate might be due to the combination of chemoradiotherapy with a brachytherapy boost, which could be replaced by a boost of external beam radiotherapy. This study describes the short-term toxicity of NOM, but follow-up was too short to determine long-term radiation effects. There are reports of long-term toxicity of the rectum after irradiation of the reproductive organs in patients receiving treatment with old radiation techniques. Still, it is very difficult to weigh long-term toxicity against the morbidity prevented by avoiding an operation.

Non-Operative Management in the Elderly

Most surgery studies focus on young and healthy patients. There is strong evidence however, that in elderly patients and patients with comorbidities, surgery is associated with not only increased in-hospital mortality and 30-day mortality but also above-baseline death rates up to 1 year postoperatively [27–29].

A very thorough analytic decision model study from Smith et al. took into account the 90-day mortality rate and used a probabilistic Markov simulation to model outcomes in patients with a cCR after nCRT for rectal cancer treated with either empiric surgery or a NOM strategy [30]. Several NOM studies and the outcomes in the UK National Health Registries empiric surgery database were used in the model. The primary endpoint was overall survival; secondary outcomes were DFS and quality-adjusted life years. The model was run for 3 categories: 60-year old cohort with mild comorbidities, 80-year-old fit patient cohort with mild comorbidities (Charlson score <3), and 80-year-old cohort with significant comorbidities (Charlson score ≥ 3). The results of the study showed that, because of the increased operative risk associated with elderly and comorbidity patients, conservative management options result in superior survival at 1 year after treatment. Further, equivalent DFS and quality of life can be achieved compared with surgery in patients with a cCR. Even though the potential improvement in survival after 1 year is marginal in younger patients treated with NOM, surgery did not improve DFS and quality of life.

Future Prospective Studies

There are currently several open prospective studies and registries concerned with the question of NOM vs. OM. Many can be found on www.clinicaltrials.gov.

The only one comparing NOM versus resection in cCR is being conducted at the Cancer Institute Hospital in Sao Paulo (NCT02052921), but that trial is suffering from low accrual, which was to be expected due to previously discussed reasons. A prospective study sponsored by Royal Marsden (NCT01047969) seeks to prove the safety of NOM. It has 2 primary outcome measures at 2 years after the end of nCRT: estimation of the percentage of patients for whom surgery can be omitted and the percentage of patients with local failure, defined as positive margin status of the resected tumor or surgically unsalvageable disease.

Further, Memorial Sloan Kettering Cancer Center in New York is currently coordinating a prospective randomized trial that incorporates NOM (NCT02008656) [17]. The primary purpose is to evaluate 3-year DFS in patients with locally advanced rectal cancer randomized between induction chemotherapy with nCRT versus nCRT with consolidation chemotherapy. Patients with a cCR according to clearly defined criteria will undergo NOM. Also, quality of life and functional outcomes will be evaluated and validated. Further, molecular markers will be studied in all patients to see whether there are profiles that can predict a complete response.

Another initiative is the International Watch and Wait Database (www.iwwd.org), a prospective registry in which all patients with a near complete or clinically complete response can be entered in a secure Internet database. Dozens of centers cooperate in this project, and the actual entered patient-number is regularly updated on the website. There are frequent teleconferences between the participating centers to exchange ideas and to coordinate and optimize data analyses. The purpose is to evaluate long-term outcomes of NOM in large numbers of patients, although the differences between the centers will make this statistically challenging.

Expert Opinion

- In patients with cCR, there is more and more evidence that NOM does not compromise DFS.
- Patients with cCR should be referred to specialized surgeons who have considerable experience with cCR in LARC. Experience is essential.
- There is not enough evidence to guide decision-making in patients with near-complete clinical responses.

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