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Non-operative management of rectal cancer☆

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ABSTRACT

Despite advances in technique, surgical resection of rectal cancer remains a morbid procedure that can lead to a profound decrease in a patient's quality of life. A novel method of management, termed "Non-operative management" (NOM), mirrors the management of anal carcinoma. Patients undergo definitive treatment with only chemotherapy and radiation, with resection reserved only for salvage. Current data is encouraging-both in reduction in morbidity and similar, if not superior oncologic results. However, there are a number of barriers to the wide adoption of this practice. This manuscript seeks to describe the rationale and execution of NOM as well as present the current data and pitfalls of the approach.

Introduction

Treatment of rectal cancer has evolved substantially over the last hundred years.[1] Despite these advances, management remains challenging, particularly in regards to tumors of the distal third of the rectum.[2] Traditional management of cT3-4, N$^+$tumors, or tumors with threatened circumferential radial margin has involved neoadjuvant chemoradiotherapy (CRT), followed by definitive surgical resection. Some patients then undergo further adjuvant chemotherapy. Surgical resection remains morbid, with post-operative complications and sexual and bowel dysfunction contributing to decreased quality of life (QoL).[3–7] Furthermore, radical resection of low rectal cancer often requires a diverting ostomy, either temporary or permanent, that can impact quality of life[8,9] Early success with non-operative management (NOM) in Brazilian patients who had a complete clinical response (cCR) introduced the concept of managing rectal cancer with the anal squamous cell carcinoma paradigm, i.e. curative-intent CRT with surgery used for salvage only in the setting of recurrent or persistent disease.[10] Since that time, NOM in cCR has been increasingly studied.[11] The addition of systemic chemotherapy following CRT, so-called Total Neoadjuvant Therapy (TNT), has driven the pathologic complete response rates even higher, leading to increased interest in NOM.[12] We review here the concept, technique, evidence, and pitfalls of NOM for rectal cancer.

Concept

Non-operative management is predicated on three concepts: (1) A total mesorectal excision (TME) resection is morbid and has real implications for QoL; (2) Endoscopic and radiographic assessment of tumor response to neoadjuvant CRT can correlate with pathologic tumor response; (3) Rectal cancer can be treated in a manner parallel to anal squamous cell carcinoma, which utilizes surgical intervention only as a salvage maneuver without impacting cancer-specific survival.

Resection of the rectum remains a challenging operation despite advances in surgical technique. A recent randomized controlled trial of laparoscopic vs. open rectal cancer resections found morbidity in greater than 50% of cases, severe complications in greater than 20%, and a 30 day mortality of just under 1%. Nearly all patients in the study received neoadjuvant therapy in some form.[13] Complications affect mortality as well, particularly in the elderly, where 50% of patients older than 75 years are dead at 6 months following an anastomotic leak as opposed to 7.1% of patients younger than 75.[14] Beyond short term technical complications, rectal resection is associated with long term morbidity. The Dutch TME trial reported 38% of patients with urinary dysfunction at 5 years. Additionally, 62% of women and 76% of men reported sexual dysfunction.[15,16] Bowel dysfunction is prevalent, with 85% of patients undergoing rectal resection experiencing some dysfunction and 40% experiencing severe dysfunction.[17] Quality of life was significantly worse between those patients that experienced "some" dysfunction versus "none". For low rectal cancers, most patients receive a stoma, either temporary or permanent. This is associated with a diminished quality of life.[5] These data reveal the morbidity associated with a complex operation and suggests a rationale for NOM, provided that it is done in an oncologically sound manner.

The second principle of NOM is the reliability of clinical assessment to determine complete pathologic response. Pathologic complete response, or pCR, is defined as no viable tumor present in the resection specimen at the time of definitive operation secondary to

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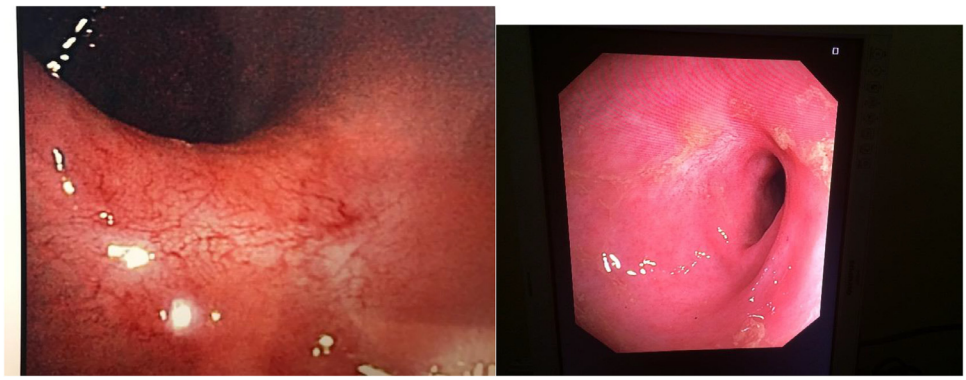

Fig. 1. Post CRT photos of rectal cancer demonstrating a complete clinical response on endoscopy. Photos courtesy of David S. Medich, MD.

preoperative treatment.[18,19] Patients who undergo CRT that results in pCR have a better overall prognosis.[20] Clinical complete response, or cCR, are those patients who have no evidence of disease on physical examination, endoscopy, and radiographic evaluation.[10,21,22] This definition of cCR excludes endoscopic findings such as an ulcer, nodule, or stenosis.[21] (Fig. 1) Various studies have shown that the sensitivity and specificity of magnetic resonance imaging (MRI) to detect complete response is 76.9–78.3 and 89.3–97.6%, respectively.[23,24] A small study examined the protocol of MRI plus clinical and endoscopic examination and found 75% accuracy in predicting pathologic complete response.[25] A comparison of pooled accuracy between MRI, endorectal ultrasound (ERUS), and CT showed accuracy of 75%, 82%, and 83% respectively.[25] Nonetheless, further experience with assessment of cCR will likely lead to greater accuracy in determining an actual complete response. Furthermore, the timing of response assessment has shifted over time, particularly with the adoption of TNT in some centers. While the rates of cCR in a recent series was 21.8% from TNT, complete response rates (cCR plus pCR after incomplete clinical response) rates was 35.7%.[26]

The final concept utilized in NOM is one of surgery only as a salvage therapy, similar to anal squamous cell carcinoma. In the original series reported by Dr. Nigro in 1974, 2 of 3 patients that underwent the eponymous protocol- of 3000 rads of external beam radiotherapy (EBRT), 5 days of 5-fluorouracil (5-FU), and a bolus of mitomycin C (MMC)- had complete pathologic responses on abdominoperineal resection. The third patient refused surgery and was NED at 14 months of follow up.[27] More modern series show complete response rates of 90% at 26 weeks[28] using 54–59 Gy of EBRT, 5-FU, and MMC.[29]

Technique

NOM is applied principally to non-metastatic patients with ≥T2 rectal cancers and/or those with nodal disease on preoperative imaging. (Fig. 2) These tumors tend to be distal, with an average distance from the anal verge of 3.9 cm.[11] The patients must be willing to comply with frequent clinic visits, physical examinations, and radiographic studies. Individual protocols vary, but CRT has tended to follow the German long-course protocol, with either 5-FU or

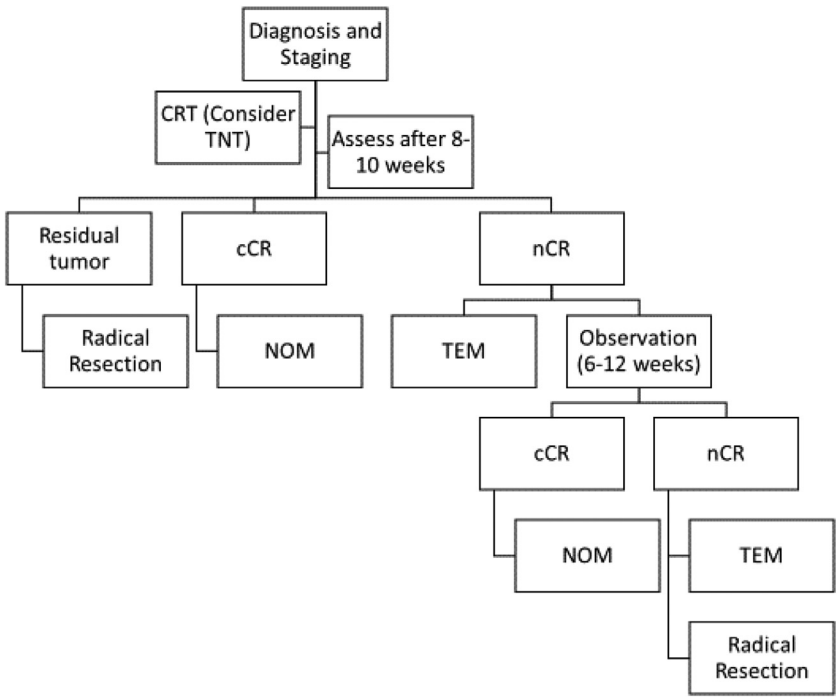

Fig. 2. Flow chart for potential NOM management of patients with low rectal cancer.
Legend: CRT—chemoradiation therapy; TNT—total neoadjuvant therapy; cCR—clinical complete response; nCR—near complete response; NOM—non-operative management; TEM—transanal endoscopic microsurgery.

capecitabine chemotherapy given concurrently with 50.4 Gy external beam radiotherapy over 5 weeks.[30] Additional chemotherapy given beyond this, as in TNT, tends to be 5-FU plus oxaliplatin (FOLFOX),[26] but this is done in a minority of the studies in the International Registry.[11]

Clinical complete response is assessed by digital rectal examination, endoscopy, and radiographic studies, most often MRI.[11,31]Reassessment occurs at anywhere from 4–24 weeks. Only one study mandated biopsy of the primary tumor at the completion of CRT to diagnose cCR.[32] Similar to anal cancer practice, there is some data to suggest that waiting longer will increase the yield of cCR.[33] In this study, the 68 patients who achieved a near cCR were offered radical resection or reassessment in 6–12 weeks. Interestingly, in the group that elected for further observation, 90% progressed to a cCR 6–12 weeks later with equivalent two-year overall survival as the original cCR group.[33] A certain percentage of patients will continue with near cCR on endoscopy and physical exam. These can include findings of a <3 cm residual flat ulcer, or irregular wall thickening on endoscopy and palpation of a superficial soft irregularity on digital rectal exam. Biopsy may reveal dysplasia or carcinoma in situ. Management of these lesions first requires restaging to ensure there is no distant or nodal disease. Then, the decision needs to be made whether to continue to observe or excise with transanal endoscopic microsurgery (TEM). We can extrapolate from the study by Hupkens et al. that further observation may further increase the cCR rate. However after three months of observation, the authors believe it is most appropriate to proceed to TEM, despite potential morbidity. Immediate radical resection should be considered for patients with unfavorable pathological features after TEM.[34] However, in this setting TEM can be associated with significant morbidity such as difficulty with wound healing that can lead to pelvic pain, tenesmus and bleeding so appropriate patient counseling is necessary.

When a patient demonstrates a cCR following CRT, NOM can be employed and the patient will enter surveillance mode. This involves a scheduled program of radiographic and endoscopic examinations as well as measurement of CEA.[35] These should take place every 3 months for two years, every 6 months for 3 years, then yearly thereafter. Regrowth is most common by year three.[11,35,36]

Salvage surgical therapy is necessary when CRT fails to produce a cCR or evaluation demonstrates local regrowth. Planned surgical intervention typically mirrors that of the original approach. Numerous studies describe TEM as a first salvage option for localized regrowth.[31,34] Evidence of locally advanced disease or nodal disease should prompt a TME resection, either by low anterior resection or abdominal perineal resection. 93% of patients can have an R0 resection with sphincter preservation rate of 45.3%.[11] However, management with TEM alone in the face of unfavorable pathological features should be avoided as salvage resection for local recurrence following CRT and TEM is associated with high rates of R1 resection (CRM+) and local re-recurrence.[34] The principles of TME still apply to any radical resection in order to decrease the risk of local recurrence.

Evidence

A number of manuscripts inform our understanding of the efficacy of a non-operative strategy. (Table 1) The earliest and most vocal advocates for NOM of rectal cancer have been Dr. Habr-Gama and the investigators from the Angelita and Joaquim Gama Institute in Brazil. They first published data on 265 patients with potentially resectable distal rectal cancer treated with neoadjuvant 5-FU, leucovorin, and 50.4 Gy radiation in 2004. 27% of patients achieved cCR and then entered an observation program including monthly physical/digital examinations, proctoscopy, biopsy, and serum CEA measurements with abdominal pelvis CT scans every 6 months for the first year. In 57.3 months of mean follow-up, 3 patients (4%) developed distant disease and 2 (3%) patients developed local recurrence. The local recurrences were salvaged with brachytherapy or transanal resection. Strengths of this study include both the systematic description of cCR and strict follow-up.[10]

This group has gone on to advocate widely for NOM and has offered extensive follow up data. They described their experience with local recurrence after cCR in 2014. In 90 patients who experienced cCR, 31% experienced recurrence, with more than half of these developing within the first year of follow-up. Salvage therapy was successful in >90% of these patients with an overall rate of organ preservation of 78%.[37]

Another recent manuscript published in 2014 described their experience with extended neoadjuvant therapy. They examined 70 patients who were treated with 54 Gy of radiation followed by 5-fluorouracil/leucovorin delivered in 6 cycles every 21 days. 68% patients experienced cCR at 10 weeks after completion of radiation. Of these, 17% developed local regrowth within the first year of follow-up. An additional 10% of patients with cCR developed late local recurrences (> one year of follow-up). Overall, 50% sustained complete clinical response over a median follow-up of 56 months and never required surgery.[38]

In 2017, the group published data that continues to reinforce the role that clinical T staging plays in NOM of rectal cancer. They studied 91 consecutive patients undergoing CRT. 67% had a cCR. While cCR rates were similar between cT2 and cT3/4 patients, early tumor regrowth were more frequent among cT3/4 when compared with cT2 patients (30% vs 3%). After Cox regression analysis, baseline T stage was an independent predictor of improved local recurrence-free survival at 1 year (OR = 0.09 (95% CI, 0.01–0.81)).[39]

A significant contributor to early NOM experience came from patients deemed unfit to undergo surgery. In 2007, Lim et al. reported 48 patients treated with CRT. cCR was seen in 56% and a partial response in 30% of patients. 18 patients had disease progression with

Table 1
Table of major studies.

Authors	Year	Patients	Stage	CCR	Distant failure	Local failure*	Salvage
Habr-Gama	2004	265	No stage IV	71 (26.8%)	3 (4%)	2 (2.8%)	2 (100%)
Lim	2007	48	No stage IV	27 (56%)	n/a	n/a	n/a
Hughes	2010	58	T3-4	10 (17%)	1 (10%)	6 (60%)	0 (0%)
Dalton	2011	49	T3-4, N1/2	6 (12%)	0 (0%)	0 (0%)	N/A
Maas	2011	192	No stage IV	21 (11%)	0 (0%)	1 (5%)	1 (100%)
Smith	2012	n/a	T2/4, N1/2	32	3 (9%)	6 (19%)	6 (100%)
Habr-Gama	2013	70	T2-4, N0-2	47 (68%)	3 (6%)	12 (25%)	11(92%)
Appelt	2015	51	T2-3, N0-N1	40 (78%)	3 (7%)	9 (22%)	9 (100%)
Araujo	2015	n/a	No stage IV	42	7 (17%)	8 (19%)	4 (50%)
Renehan	2015	n/a	No stage IV	129	7 (5%)	44 (34%)	36 (81%)
Martens	2016	100	No stage IV	61 (61%)	5 (5%)	15 (15%)	13 (87%)

* Includes any local failure.

a median follow-up of 49 months. Of the 25 deceased patients, 16 died from progressive disease and 9 from non-cancer causes.[40] In 2010, Hughes et al. described 10 patients with a cCR out of a population of 58 who did not proceed to surgery. 6 (60%) of patients suffered local recurrence with no salvage.[41] These data are important in describing the natural history of tumors after CRT, but the older and sicker cohorts make generalizability difficult.

Published in 2011, Maas et al. used a similar CRT protocol to the Habr-Gama group with the substitution of capecitabine as the radiosensitizer. They also utilized high resolution MRI to both screen and monitor patients. In their study design, they matched cCR patients with pCR patients who underwent major resection. Twenty-one patients with cCR were included in the wait-and-see policy group. Mean follow-up was 25 ± 19 months. One patient developed a local recurrence and had surgery as salvage treatment. Probabilities of 2-year disease-free survival and overall survival were comparable between cCR and pCR patients (DFS: 89% vs. 93% and OS: 100% vs. 91%, respectively).[22] This study was important as it validated the feasibility of a NOM approach in a European population.

In a manuscript published in 2012, Smith et al. also compared patients who achieved a cCR with a group that underwent resection and were found to have a pCR. Thirty-two patients were treated by NOM after a cCR and compared to 57 patients (22%) that had a pCR after neoadjuvant CRT. Factors associated with selective use of NOM included lower pretreatment stage, older age, and distal tumor location. In the cCR group, 6 (19%) recurred locally, 3 of whom also had concurrent distant recurrence. All 6 local failures were controlled by salvage rectal resection with no further local recurrence of disease. The 2-year distant disease-free survival (88% vs. 98%) and overall survival (96% vs. 100%) were similar for NOM and pCR groups.[42] Smith et al.'s study helped to establish the relationship between pCR and cCR & NOM long term outcomes.

In a well-designed, prospective study, Appelt et al. administered high dose CRT (60 Gy in 30 fractions to tumor, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy endorectal brachytherapy boost, and oral tegafur-uracil 300 mg/m(2)) every weekday for 6 weeks. They then assigned patients with cCR, negative tumor site biopsies, and no nodal or distant metastases on CT and MRI 6 weeks after treatment to a NOM group. Out of 51 patients, 40 (78%) had a cCR. Local recurrence at 1 year for patients treated with NOM was 15.5%. All were salvaged with an APR. There were three distant recurrences. The higher dose of radiation was reported as well tolerated. Critiques of the study query whether the high rate of cCR may be attributed to smaller tumors (half were cT2).[32]

Araujo et al. compared 42 NOM patients to 69 pCR patients operated after a median interval of 35 weeks after CRT. There were notable differences between the two groups as the NOM tumors were distal (83.3% vs. 59.4) and less obstructive (26.2% vs. 54.4%). Isolated LR occurred in five (11%) NOM patients and one (1.4%) in the surgical group. Four (80%) LR were salvaged in NOM group via surgery. No difference in OS was observed (71.6% vs. 89.9%) but there was a higher DFS in the surgical group (60.9% vs. 82.8%).[43] This study adds further data, but conclusions are limited by significant differences between the two cohorts.

In 2015, Renehan et al. published a propensity-score matched cohort analysis that included 129 patients who had a cCR after CRT. Of the 129 patients managed by NOM, 44 (34%) had local recurrence. Thirty-six (88%) of 41 patients with non-metastatic local recurrence were salvaged. In the matched analyses, no differences in 3-year disease-free survival were noted between NOM (88%) and surgical resection (78%). Similarly, no difference in 3-year overall survival was noted (NOM 96% vs. surgical resection 87%). In contrast, patients managed by NOM had significantly better 3-year colostomy-free survival than did those who had surgical resection (74% vs. 47%), with a 26% absolute difference in patients who avoided permanent colostomy at 3 years between treatment groups.[36] This study is important as propensity matching helped to adjust for known confounding and the outcome of colostomy-free survival added an important facet to the conversation.

Martens et al. added their single center experience in 2016. They analyzed 100 patients with rectal cancer and utilized TEM as the first line salvage technique. 61% had cCR at initial response assessment. 39 had near cCR, of whom 24 developed cCR at the second assessment and 15 patients underwent TEM (9 ypT0, 1 ypT1, 5 ypT2). Fifteen patients developed a local regrowth (12 luminal, 3 nodal), all salvageable and within 25 months. Three-year overall survival was 96.6% and disease-free survival was 80.6%. Colostomy-free survival was 94.8%, with good continence after watch-and-wait and moderate continence after TEM.[31] This study added weight to the concept of TEM for first line salvage.

A collection of studies have examined patient-reported outcomes in NOM of rectal cancer. Issues with defecation may be reduced with the omission of local excision after CRT. Both CRT and local excision are risk factors for bowel dysfunction.[17,44] Hupkens et al. performed a matched-control study comparing bowel function and health related quality-of-life (HRQL) in 82 patients undergoing either NOM or radical resection. While defecation issues and impaired HRQL were present in both cohorts, the NOM group reported significantly better functional outcomes and HRQL in several domains.[5]

Two systematic reviews have been published on NOM for rectal cancer. Dossa et al. looked at 23 studies including 867 patients. In patients with a CCR undergoing NOM, they found a pooled 2-year local regrowth of 15.7%. 95.4% of patients with regrowth had salvage therapy. In comparing patients managed by NOM with patients who were found to have a pCR after undergoing resection, there was no significant difference in terms of non-regrowth recurrence, cancer-specific mortality, disease-free survival, or overall survival.[45] A recent systematic review and pooled analysis by Dattani et al. synthesized much of the existing literature. Over 17 studies and 692 patients, they found a cCR rate of 22.4%. For patients managed non-operatively, there were 22% local regrowths, almost all of which occurred in the first three years. 88% of patients with regrowths underwent salvage and 93% had a successful R0 resection. Three year overall survival was 93.5%. These figures will serve as benchmarks for future trials.[11]

Knowledge gaps/pitfalls

The current state of knowledge on NOM of rectal cancer is promising. However there are a number of points to address before this practice becomes widely adopted as standard of care. These include continuing to accurately identify patients who achieve a cCR, the role of adjuvant chemotherapy, adherence to post-treatment surveillance protocols, and further data on patient reported outcomes. Finally, the addition of data from randomized controlled trials will further inform how this practice becomes integrated into the canon of care for rectal cancer.

One of the critical pieces of NOM involves accurate assessment of cCR and prediction of pCR. The link between the two is essential to ensuring cancer eradication and avoiding local recurrence that is potentially unsalvageable. Smith et al. highlighted potential issues with current cCR assessment when they observed that the majority of patients who obtain pCR do not display mucosal features of complete response.[46] Baucom et al. analyzed 4170 patients who underwent TME with ypT0 pathology. Almost 10% of these patients with presumed mucosal resolution had positive lymph nodes. Factors predictive of nodal disease in this group included increasing (pretreatment) clinical N-stage, high tumor grade (3/4), perineural invasion, and lymphovascular invasion.[47] The role of circulating biomarkers requires further investigation and needs to be integrated into both the assessment of cCR and surveillance. Finally, gene expression tools have shown potential to predict tumor response to chemotherapy and attention should be given to their use in NOM.[48]

According to current National Comprehensive Cancer Network guidelines, all Stage II and III patients that receive neoadjuvant CRT and proceed to resection are treated postoperatively with systemic chemotherapy (FOLFOX or its equivalent).[49] Many of the NOM manuscripts cited above do not include full dose systemic chemotherapy in their regimen. Although it is likely that there is a biologic difference in tumors that regress completely after CRT, they remain with the potential to metastasize to distant locations. Some papers have suggested that we may be able to forgo systemic treatment in this population, but there is no data to support this.

Thus, it stands to reason that standard chemotherapy should be a part of any NOM protocol, as pelvic CRT does little to address systemic disease. Delivery of mFOLFOX6 after CRT and before surgical resection increases the proportion of patients eligible for less invasive treatment strategies, while also allowing for systemic treatment of potential micrometastatic disease.[50] Another treatment strategy utilizes short course radiation followed by 4 cycles of FOLFOX. This regimen has been observed to result in 25% of patients achieving a pCR.[51] The concept of TNT with neoadjuvant FOLFOX/CAPEOX may have the greatest potential for the future non-operative treatment of rectal cancer. This treatment plan is theorized to both induce more complete responses, resulting in organ preservation as well as treat radiographically occult metastatic disease.[52]

Adherence to a strict post-treatment surveillance after NOM presents a greater burden on both the patient and the clinician when compared to current treatment. Most protocols require reassessment every 1–2 months for the first year, every 3 months for the second year and every 6 months thereafter. This mirrors surveillance after CRT for anal cancer. No data exists as to post-treatment adherence to anal cancer surveillance, but most clinicians who treat this disease appreciate a significant loss to follow up. This is an essential piece of NOM that will benefit from further study. Surveillance regimens are strict and require frequent follow up. This may not be appropriate for patients that live some distance away from their treatment center. Patient compliance needs to be discussed up front at the time of diagnosis and reinforced throughout the treatment process.

Further prospective and ultimately randomized controlled trails are required before NOM can be accepted as standard of care. There is significant research involved in this area. The National Institutes of Health-sponsored, multi-institutional, randomized controlled trial "Organ Preservation in Rectal Adenocarcinoma" study seeks to examine induction (before CRT) versus consolidation (post CRT) FOLFOX in the attempted NOM treatment of low rectal cancer (NCT02008656).[52] A group from the Instituto do Cancer do Estado de São Paulo is performing a prospective trial, randomizing patients achieving a cCR 12 weeks after CRT to surgical resection or NOM therapy (NCT02052921). Finally, a group from the United Kingdom is enrolling 99 patients on a NOM protocol to evaluate safety and survival (NCT01047969). These trials will offer further insight into the best use of NOM

Conclusions

NOM of rectal cancer is an exciting and novel approach that has the potential to drastically decrease the morbidity of treatment of rectal cancer. However, surgical resection (TME) remains the standard of care after neoadjuvant chemoradiotherapy, even in patients who appear to have a cCR to neoadjuvant therapy, unless they are poor candidates for surgery. Eligible patients should be enrolled on protocol in current RCTs or at the very least managed at high volume and high quality rectal cancer centers.

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