Nonoperative Management for T2 Low Rectal Cancer: A Western Approach

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Abstract

The possibility of organ preservation in early rectal cancer has gained popularity during recent years. Patients with early tumor stage and low risk for local recurrence do not usually require neoadjuvant chemoradiation for oncological reasons. However, these patients may be considered for chemoradiation exclusively for the purpose of achieving a complete clinical response and avoid total mesorectal excision. In addition, cT2 tumors may be more likely to develop complete response to neoadjuvant therapy and may constitute ideal candidates for organ-preserving strategies. In the setting where the use of chemoradiation is exclusively used to avoid major surgery, one should consider maximizing tumor response. In this article, we will focus on the rationale, indications, and outcomes of patients with early rectal cancer being treated by neoadjuvant chemoradiation to achieve organ preservation by avoiding total mesorectal excision.

Keywords

- rectal cancer
- watch and wait
- early tumor

Organ preservation is currently at center stage in contemporary management of rectal cancer patients. The observation of patients who achieve a complete clinical response (cCR) following neoadjuvant chemoradiation (nCRT) without immediate surgical resection with excellent functional and oncological outcomes has challenged the role of total mesorectal excision (TME) among these patients.^{1–4} However, most of the patients and reported series have so far included “accidental” organ preservation.^{5,6} “Accidental” organ preservation is a term currently used to suggest that most of these patients were not treated by nCRT for the specific purpose of achieving a cCR. Most of these patients harbored advanced rectal cancer at baseline and, therefore, would otherwise have required nCRT for oncological reasons. In the presence of high-risk features for a local recurrence, these patients were offered nCRT based on international guidelines for the purpose of minimizing local recurrence after TME surgery.^{7–11} In selected cases, a cCR was “accidentally” achieved as a consequence of nCRT setting up the context for opportunistic or accidental organ preservation. The possibility of avoiding a radical procedure and its

associated morbidity/functional consequences,^{12,13} often including the need for a definitive or a temporary stoma,¹⁴ led to the consideration of applying this treatment strategy for earlier stages of rectal cancer.^{15,16} In this setting, patients with rectal cancers with low-risk features for a local recurrence (cT2N0) after TME could be offered nCRT for the specific purpose of achieving a cCR.¹⁷ These patients would otherwise not require nCRT for oncological reasons, and therefore, nCRT could represent an intentional, instead of “accidental” organ-preservation strategy.

Primary Tumor Assessment and Selection Criteria

Initial tumor assessment for patients being considered for “intentional” organ preservation is of paramount relevance and is based on clinical findings (of digital rectal examination –DRE), endoscopic features, and radiological imaging. These studies should only be considered for the selection of patients for nCRT after confirmatory biopsies of adenocarcinoma have been obtained and properly documented.¹⁸

The first criterion for this approach is tumor location. Here, the entirety (or at least the central part) of tumors needs to be accessible by the DRE. Tumors that are not felt by DRE during physical examination will have two significant consequences in the clinical setting. First, an important piece of information regarding tumor response assessment is lost by the lack of tactile feedback after nCRT. Tumors beyond the reach of a finger will not be amenable to clinical assessment of tumor response. Second, tumors that are beyond the reach of a finger may provide the opportunity for anterior rectal resections without the need for intersphincteric resections, resulting in considerably better functional outcomes. In addition, mrT2 cancers beyond the reach of the finger are probably surrounded by considerably more robust amount of mesorectal fat, leading to significantly lower risk for pathological circumferential radial margin (pCRM) positivity. Finally, these patients are rarely candidates for a definitive stoma (through the performance of an abdominal perineal excision—APE). Clearly, exceptions to this rule include obese (particularly male) patients, and surgeons with considerably short index fingers. In both of these situations, tumors located at the level of the anorectal ring may still be beyond the reach of DRE and should still be considered for this treatment strategy.

Radiological imaging is also critical here. Magnetic resonance (MR) using dedicated protocols will provide important information for the selection of patients for this approach.¹⁹ MR should be able to identify patients with tumors located at the level of the anorectal ring or below. In most patients, the amount of mesorectal fat here is minimal. This means that patients will require at least a partial intersphincteric resection to allow for primary restoration of bowel continuity. In addition, the risk of achieving a positive (≤ 1 mm pCRM) is quite significant unless primary APE with a definitive stoma is performed.¹⁸

Finally, endoscopic features are definitely relevant for the selection of patients here. The ultimate goal here is to avoid the inclusion of patients with benign lesions or even rectal cancers that fulfill criteria for endoscopic resection through the performance of endoscopic submucosal dissection (ESD). Therefore, meticulous endoscopic assessment and characterization of pit pattern and submucosal vascular architecture will allow the identification of lesions that would only require ESD or transanal endoscopic microsurgery without the need of TME or nCRT.^{20,21}

In summary, primary tumor assessment should include the confirmation of invasive adenocarcinoma, a tumor that is accessible to DRE, MR showing a tumor located at the level or very close to the anorectal ring and endoscopic features consistent with invasive cancer not suitable for ESD.

Early Rectal Cancer and Response to Chemoradiation

One of the reasons for proposition of this approach (nCRT with organ preservation) to early rectal cancer was the understanding or hypothesis that smaller and more superficial cancers were more likely to exhibit better response to treatment.^{15,22,23} Retrospective studies suggested that tu-

mor extension or even tumor volumes were closely associated with response to nCRT.^{24,25} Series of patients with T2N0 did indeed show significantly high rates of complete pathological response after nCRT.¹⁵ However, there is no convincing evidence that T2N0 cancers more frequently achieve complete tumor regression when compared with more advanced disease.²³ One of the reasons for the lack of good evidence here is the fact that one of the limitations of MR T-status classification is specifically the distinction between late T2s and early T3 lesions. Therefore, it remains unclear whether response is more dependent on tumor volume or depth of tumor penetration.

Regardless of the definitive chances of achieving a cCR among cT2 cancers (compared with T3 and T4 cancers), it has been suggested that among tumors that achieve a cCR, more superficial tumors do so after shorter periods of time. In patients undergoing a unique nCRT, T2/T3a cancers on average achieved all three strict criteria of a cCR at 19 weeks. This was statistically shorter than patients with $\geq$ T3b who required an average of 26 weeks to achieve all strict criteria of a cCR.²⁶

However, the most significant difference between cT2 cancers and $\geq$ T3 cancers after nCRT is the actuarial risk of local recurrence or tumor regrowth (TR).²³ Once patients have achieved a cCR there is a substantial risk for the development of TR. Such risk has been reported to be around 25% after 3 years of follow-up without immediate surgery (Watch and Wait [WW]).^{2,5,27} The risk of regrowth is highest during the first year—nearly 60% of all regrowth are detected during the initial 12 months after the achievement of a cCR. T-status seems to be significantly associated with the risk of developing TR. T2 cancers are less likely to develop a TR once they have achieved a cCR. This was observed in single institutional series and also in systematic reviews using individual participant data of patients properly staged using contemporary staging tools.^{23,27}

Altogether, T2 rectal cancers may have higher complete response rates when compared with more advanced (potentially affected by small tumor volumes and not necessarily exact depth of tumor penetration), appear to achieve a cCR at shorter intervals from nCRT completion, and clearly seem to be at lower risk for the development of tumor regrowth once a cCR has been achieved and managed without immediate surgery.^{23,26,27}

Type of Treatment—The Paradoxical Approach

Considering the fact that early (cT2) rectal cancers are potentially more likely to completely respond, to achieve a complete response more quickly, and less likely to develop TR to nCRT, one could assume that less aggressive treatment strategies could be used in this scenario. However, one has to remember that the only purpose of nCRT here is to actually achieve a cCR. Therefore, all attempts have been used to maximize tumor response. Maximization of tumor response may be obtained by three different approaches: first, increasing the amount of RT delivered appears to directly correlate with the amount of response—data from series of patients undergoing different RT

doses exhibit a direct correlation with the percentage of patients achieving a complete response^{25,28–30}; second, the amount of chemotherapy delivered also appears to increase the chances of patients achieving a complete response³¹; finally, there is data to suggest that longer intervals are also associated with increased chances of achieving a complete response.^{32–34}

RT dose escalation may be obtained by direct increases in dose using a unique mode of delivery, such as external beam radiation (45 Gy vs. 50.4 Gy vs. 54 Gy vs. 60 Gy). Alternatively, association of different delivery modalities of radiation may be employed to increase the amount of radiation delivered while maintaining safety and toxicity profiles. Examples here include the use of external beam RT in association with contact or even endorectal brachytherapy. These latter alternatives allow for a more robust increase in total radiation delivery.^{28,35}

Intensification of chemotherapy may be achieved by offering additional agents (other than 5-fluorouracil [5FU]-based chemotherapy), additional cycles of chemotherapy before initiation of RT (induction chemotherapy),^{36,37} or additional cycles of chemotherapy during and immediately after RT (consolidation chemotherapy).^{17,38} All strategies have shown to increase response rates in patients with rectal cancer even though very few studies have been focused on early stage disease.

There is no question that rectal cancer response is a time-dependent phenomenon after nCRT completion.^{31,34,39,40} Initially thought to be a linear correlation where longer intervals inevitably led to increased rates of complete response to therapy, current knowledge suggests that¹ most of the tumor response is obtained within the first 6 to 8 weeks after nCRT completion^{2,41,42}; patients who achieve $\geq 70\%$ response at 6 to 8 weeks are more likely to achieve a complete response later on irrespective of the type of nCRT^{3,38,41}; achievement of all strict criteria of a cCR after nCRT is frequently after 16 weeks from RT completion.²⁶

In summary, when achievement of a cCR is the sole purpose of using nCRT, maximization of the chances of complete response may be considered even in the paradoxical context of early stage disease. More aggressive treatment of less advanced disease may actually result in significant positive impact on organ preservation and ultimate avoidance of radical surgery among patients with early tumors located at the level of the anorectal ring.¹⁷

Assessment of Tumor Response

Assessment of tumor response in practice should follow the same principles and studies used for initial tumor assessment. DRE, endoscopy, and radiological imaging should be thoroughly explored in these patients to safely select patients for a nonoperative approach.

The first response assessment should be performed at 6 to 8 weeks among patients undergoing regular nCRT with no additional cycles of chemotherapy or radiation dose-escalation strategies. Patients undergoing induction or consolidation chemotherapy and/or RT dose escalation may have first

response assessment to at least 10 to 12 weeks from RT completion.^{38,42} This first response assessment has two main objectives¹: identify potential, but rather rare, patients who are exhibiting tumor progression shortly after nCRT²; identify patients with $\geq 70\%$ response—these patients are more likely to achieve a cCR and therefore should be considered ideal candidates for a reassessment of tumor response in at least 6 to 8 weeks interval. Patients with disease progression or $<70\%$ tumor response are best candidates for immediate radical surgery or additional oncological strategies and should NOT be considered for organ-preservation strategies. Instead, patients with $\geq 70\%$ response during first response assessment are potential candidates for organ preservation.

Achievement of $\geq 70\%$ of tumor response should be consistent with any and all of the studies used during the assessment of tumor response: DRE, endoscopy, and radiological imaging (preferably MR—using magnetic resonance Tumor Regression Grade (mrTRG) estimation). Even though specific and well-defined criteria for a cCR have been reported, achievement of all of strict criteria is often not observed during first response assessment.²⁶ Instead, sequential assessment of tumor response should be able to characterize progressive response in each reassessment round until all strict criteria of a cCR are achieved. Even though there is no definitive deadline by which all patients should have achieved all strict criteria of a cCR, a few basic principles should be considered¹: intervals should be no longer than 8 weeks between rounds of reassessment of tumor response²; clear disease progression between rounds of reassessment of tumor response should prompt immediate radical surgical resection³; the majority of patients achieve all strict criteria within 26 weeks from nCRT completion.

Strict Criteria for a Complete Clinical Response

The strict criteria of a cCR are based on three pillars of assessment: (1) clinical evaluation with DRE should reveal a normal/regular mucosa surface, only minor in duration of the rectal wall without any significant irregularities; (2) endoscopic assessment is typically characterized by whitening of the mucosa with telangiectasias, absence of ulceration, mass, or stenosis of the rectum; (3) finally, radiological assessment should include the presence of an area of low-signal intensity at the original tumor location on T2-weighted magnetic resonance imaging (MRI) (mrTRG1); even though absence of restriction to diffusion on diffusion-weighted MRI should be present, in the authors' experience diffusion sequences are more frequently used to reassure findings suggested by T2.^{31–33}

Outcomes

Very few studies have specifically addressed the outcomes of nonoperative management (WW) for T2N0 rectal cancer. In 2006, our group has proposed a change in the nCRT regimens exclusively to increase or maximize tumor response for all patients undergoing neoadjuvant treatment. Previously, standard nCRT included 50.4 Gy of radiation and two cycles of concomitant 5FU-based chemotherapy. Changes to regimen

included¹ an increase of 54 Gy (by incrementing exclusively the boost of RT delivered to the primary tumor and mesorectum),² additional four cycles of 5FU-based chemotherapy delivered not only during RT but also during the “resting” period,³ increase in the resting period from 8 weeks to at least 10 weeks (in order to be able to incorporate all six cycles of chemotherapy).^{43,44}

The outcomes of this extended nCRT with RT dose escalation (to 54 Gy) and consolidation chemotherapy (additional cycles of chemotherapy during RT and resting period) were compared with the outcomes of standard nCRT for patients with distal rectal cancer. Among patients with cT3 rectal, there were no differences in the rates of organ preservation regardless of the type of nCRT regimen.⁴⁵ However, particularly among patients with early rectal cancer (cT2N0), patients undergoing extended nCRT were more likely to achieve a cCR. On multivariate analysis, the type of nCRT regimen was the only features associated with a higher chance of achieving organ preservation. Finally, extended nCRT resulted in significantly higher surgery-free survival in long-term follow-up.¹⁷

Curiously, once a cCR has been achieved, local recurrence rates and need for salvage surgery seem to be independent of the type of nCRT regimen used. These results suggest that there is little or even no benefit in offering patients additional (RT) treatment (once a cCR has been achieved) for the purpose of decreasing the risk of TR.¹⁷ In addition, patients with early-stage (cT2) who achieved a cCR but developed local regrowth were still more likely to undergo further organ preservation. Local regrowth among these patients with baseline cT2 was more frequently amenable to salvage resection by transanal local excision when compared with patients with baseline cT3/4. (Fernandez LM, Figueiredo NL, Habr-Gama A et al. Salvage Surgery with organ preservation for patients with local regrowth after Watch and Wait: Is it still possible? *Dis Colon Rectum* 2020, in press.)

Finally, even though baseline clinical T stage seems to be a risk factor for local recurrences after initial cCR, conditional survival estimates suggested that these differences may become irrelevant once patients achieve and sustain a cCR for at least 2 years (without recurrence). Ultimately, achieving and sustaining a cCR for 2 years appear to be more relevant than baseline staging for the risk of local regrowth.⁴⁶

In summary, cT2 patients may be more likely to develop a cCR (compared with advanced disease), may benefit the most from more aggressive nCRT regimen to maximize the chances of a cCR, and appear to be less likely to develop local regrowth after WW (particularly during the first 2 years); even in the event of a local regrowth, these patients are more frequently candidates for successful salvage with organ-preserving local excision.

Alternative Surgical Organ-Preservation Strategies

One of the potential problems with this approach is when patients fail to achieve a cCR. Patients who undergo nCRT for sole purpose of achieving a cCR and avoid TME may have to ultimately face surgery in the setting of potentially unneces-

sary nCRT and all of its detrimental effects when there is incomplete clinical response.⁴⁷ Most would consider that for these patients (who fail to achieve a cCR), nCRT was not beneficial. Instead, nCRT could have been considered detrimental here, due to the consequences of poor healing (high risk for anastomotic leaks) and worse functional outcomes.^{48,49}

However, many of these patients may still undergo an organ-preserving strategy in the presence of incomplete clinical response. At least two prospective studies have reported favorable oncological and functional outcomes among selected patients with early stage and small rectal cancers treated by nCRT. The ACOSOG trial enrolled patients with cT2N0 disease treated by nCRT (including capecitabine and oxaliplatin based chemotherapy) followed by local excision alone. Complete pathological response was considerably (nearly 50%) suggesting that small T2 rectal cancers may have higher complete response rates than more locally advanced disease.¹⁵ In addition, local recurrence rates after local excision were $\leq 5\%$. The GRECCAR study randomized patients with small T2/T3N0 (≤ 4 cm) disease treated by nCRT and exhibited good response to therapy (post-treatment tumors ≤ 2 cm) to TME or transanal local excision. Using a composite end point (oncological/functional) resulted in no statistically significant differences between both groups.¹⁶

Altogether, this data suggests that even patients with early stage disease that undergo nCRT (for the purpose of achieving a cCR) may still undergo an organ-preserving pathway in the setting of incomplete response. These patients could still avoid radical TME by transanal local excision in a significant proportion of patients.

Functional Outcomes

None of the studies have specifically assessed functional outcomes exclusively in patients with early stage disease undergoing “intentional” organ preservation through WW. However, there is retrospective data on functional outcomes among patients achieving a cCR managed nonoperatively. These studies suggest that patients managed by WW have superior functional outcomes when compared with TME or even to local excision after nCRT.⁴⁹ These differences also translate into better quality of life assessment between different treatment strategies.⁵⁰ Even though not perfect, quality of life assessment among patients under WW appears to be better than for patients undergoing TME.⁵⁰

Again, the problem arises among patients who undergo nCRT for the sole purpose of achieving a cCR but fail to do so. These patients with incomplete clinical response could potentially develop much worse functional outcomes after TME when compared with upfront TME without nCRT. Unfortunately, no study has yet approached this. Considering the fact that local excision is still an option among a subset of patients with incomplete response (but good response), the number of patients with early stage who may ultimately undergo nCRT for the purpose of organ preservation and still require TME is expected to be small. Still, future studies focused on the functional outcomes of patients with early stage managed by nCRT versus upfront TME are highly warranted.⁵¹

Perspectives

An accurate selection tool for this treatment strategy would be ideal. This would allow the selection of patients with tumors more likely to be responsive to nCRT, while identifying unresponsive tumors would result in the avoidance of unsuccessful, potentially unnecessary, and detrimental nCRT. Unfortunately, prediction of tumor response, particularly by gene expression profiles, has been largely unsuccessful.^{52,53} Significant intertumoral and intratumoral heterogeneity may have contributed to gene signatures with a very low number of overlapping genes between them and inaccurate separation between poor and good responders.⁵⁴ However, a prediction score based on DNA repair genes has been recently suggested for this particular purpose. A score based on specific DNA repair genes taking into consideration individual differential expression of these genes has resulted in considerably high negative predictive values in three independent cohorts of patients managed by nCRT. In this study, low scores have been associated with a poor response to nCRT regardless of the exact DNA expression platform used. A low score (observed in nearly 40% of all patients tested) resulted in poor response to nCRT in 70 to 90% of the cases. Using this strategy in consecutive cT2N0 patients is estimated to result in avoiding 36% of unnecessary nCRT, restricting nCRT to 60% and resulting in good response and the possibility of organ preservation in nearly 75% of the cases.⁵⁵

Conflict of Interest

None.

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