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Organ-preservation strategies in rectal cancer: advances and challenges

Laura Melina Fernandez¹ & Rodrigo Oliva Perez^{*,1,2,3,4}

¹Department of Colorectal Surgery, Angelita & Joaquim Gama Institute, São Paulo 04001, Brazil

²Department of Gastroenterology, University of São Paulo School of Medicine, São Paulo 04001, Brazil

³Department of Molecular Oncology, Ludwig Institute for Cancer Research, São Paulo Branch, São Paulo 01308, Brazil

⁴Department of Surgical Oncology, Digestive Surgical Oncology Division, BP- A Beneficência Portuguesa de São Paulo, São Paulo 01323-900, Brazil

* Author for correspondence: Tel.: +55 11 3884 8845; rodrigo.operez@gmail.com

“Organ-preserving strategies have gained popularity in the recent years in order to avoid the morbidity, mortality and even functional consequences of major surgery with proctectomy and total mesorectal excision.”

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Neoadjuvant chemoradiation (nCRT) may lead to tumor regression in a significant proportion of patients with distal rectal cancer [1]. Organ-preserving strategies have gained popularity in the recent years in order to avoid the morbidity, mortality and even functional consequences of major surgery with proctectomy and total mesorectal excision. Selected patients with clinical and radiological evidence of significant tumor regression after nCRT could be the ideal candidates to these alternatives, including transanal local excision of near-complete responses and even no immediate surgery with strict surveillance (watch and wait protocol) if there is evidence of complete clinical response (cCR) [2–7].

One of the basic principles of organ preservation after neoadjuvant therapies is assessment of tumor response during the decision-making process and prior to final surgical or even nonsurgical strategy.

Clinical and endoscopic findings have been described to standardize features associated with a cCR [8]. However, a significant proportion of patients without cCR may still harbor complete pathological response [9]. Therefore, clinical and endoscopic assessment may significantly underestimate complete tumor regression to neoadjuvant treatment [9]. Significant improvements in imaging modalities and interpretation placed radiology as an essential tool for this purpose. In this setting, radiological studies are now standard for the assessment of response not only to assess primary tumor response but also for the assessment of the mesorectal compartment [10–12]. High-resolution magnetic resonance (MR) is currently widely used for the assessment of response. Signal intensity of the primary tumor may help differentiate fibrosis from residual disease and contribute to the diagnosis of a cCR [11]. PET/CT imaging may provide additional information for the prediction of response to CRT [13,14]. Although not routinely performed, the combination of metabolic activity and tumor metabolic volume could be used to predict and identify complete responders in such patients [15].

One of critical challenges here is how to predict or identify patients that are more likely to completely respond to nCRT? This information is crucial for optimal selection of patients to organ-preserving strategies.

Several features seem to be associated with the likelihood of developing complete response to nCRT including patient/tumor and treatment-related characteristics. Tumor extension has been associated with complete response rates, suggesting that larger tumors are less likely to develop complete response [7,16–19]. However, T-category at baseline staging may also be relevant in the identification of patients more likely to avoid definitive surgery. Even though initial cCR may be similar after nCRT completion between cT3 and cT2 patients, cT2 develop significantly less local recurrences in long-term follow-up after nonoperative management [20]. Treatment-related features may also be quite significant in the chances of developing a cCR [1]. Higher doses of radiation therapy may be useful for this particular purpose. Several studies have suggested this dose-escalation effect in response to

treatment, particularly associated with the amount of boost delivered to the primary tumor [7,21–23]. Concomitant chemotherapy or even consolidation chemotherapy (given prior to radiotherapy [RT] or even after RT completion during the resting period) has been shown to affect cCR/pathologic complete response (pCR) rates [24]. The addition of mFOLFOX after standard CRT led to a significant increase in pCR rates and the number of chemotherapy cycles was an independent predictor of pCR among these patients [25]. Finally, the interval between neoadjuvant therapy and assessment of response may play a role [26]. Longer interval periods have been associated with higher rates of pCR/cCR even though one recent randomized study has failed to demonstrate such benefits when comparing 7–11 weeks [27–30].

Altogether, if nCRT with RT dose-escalation and consolidation chemotherapy is offered to a cT2N0 rectal cancer, a cCR is likely to be achieved and sustained long-term in nearly 70% of patients [31]. Considering the possibility of organ preservation to these patients with low-lying tumors otherwise candidates for coloanal or even definitive colostomies, these alternative regimens become increasingly attractive to patients and physicians, despite of the challenges in assessment of response and follow-up.

Several series reported so far using this strategy with no immediate surgery after a cCR have reported excellent salvage rates after a local recurrence and acceptable oncological outcomes [32–34]. However, it appears these patients need to be followed for life with a rather intensive follow-up, particularly in the early periods following nCRT completion.

Ultimately, nCRT is only required for local disease control after total mesorectal excision in selected patients with high-risk features (circumferential resection margin ≤ 1 mm, cN2, extramural venous invasion-positive [EMVI+]) [35]. In this setting, the only benefits of offering nCRT to early cancers, such as cT2N0 and low-risk cT3, would be the chances of offering organ preservation [36]. On the other hand, those patients with low-risk tumors that eventually do NOT develop cCR, still need to face radical surgery, now in the setting of preoperative radiation leading to significantly worse functional outcomes and postoperative morbidity [37–39]. Therefore, the current dilemma in distal low-risk rectal cancer is the following: Should we offer nCRT for the chances of developing a cCR (nearly 70%) and assume the risk of having to deal surgically with the (nearly 30%) nonresponders (now in the setting of preoperative RT)? Or should we avoid nCRT to all (100%) of these patients going straight to radical to surgery with much better functional outcomes (compared with surgery with preoperative RT) but take away from them the chances of avoiding surgery after all?

The solution for this puzzle would be the development of an accurate predictor of tumor response such as a molecular biology test. Several studies have attempted to establish a clinically useful gene signature capable of predicting response to nCRT [40–43]. Even though more than 17 signatures have been reported with nearly 1000 genes, there is minimal overlap between genes in all of these signatures. One of the potential reasons for these findings is the presence of significant intratumoral heterogeneity within these tumors [44]. This means that gene signatures derived from single biopsy specimens may not work simply because these fragments are not representative of the entirety of the tumors they were taken from.

Until accurate predictors remain unavailable in this setting, this dilemma will haunt patients and their colorectal surgeons, medical and radiation oncologists.

What the future holds in this area

Organ-preserving strategies have gained popularity in patients with rectal cancer undergoing neoadjuvant treatment. Patients with complete clinical and radiological response could be ideal candidates to no immediate surgery. Although patients with high-risk tumor features for local recurrence are the traditional candidates to nCRT for local disease control, recent studies have suggested that low-risk early-stage rectal cancers may be more likely to achieve complete response and ultimately avoid definitive surgery. In this setting, modern management of rectal cancer will have to include the possibility of use neoadjuvant treatment for the sole purpose of organ preservation to low-risk rectal cancers with the inherent risk of offering unnecessary (and potentially detrimental) radiation to a number of patients that never achieve a complete response and still need to face radical surgery.

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