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Restaging rectal cancer following neoadjuvant chemoradiotherapy

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Abstract

Correct tumour restaging is pivotal for identifying the most personalised surgical treatment for patients with locally advanced rectal cancer undergoing neoadjuvant therapy; it allows avoiding both poor oncological outcomes or over-treatment. Digital rectal examination, endoscopy and pelvic magnetic resonance imaging are the recommended modalities for local tumour restaging while chest and abdominal computed tomography are those utilised for the assessment of distant disease. The optimal length of time between neoadjuvant treatment and restaging, in terms of both oncological safety and clinical effectiveness of treatment, remains unclear, above all in patients receiving prolonged total neoadjuvant therapy. The timely identification of patients who are radioresistant and at risk of disease progression is challenging.

Key Words: Locally advanced rectal cancer; Restaging; Pelvic magnetic resonance imaging; Endorectal ultrasound; Computed tomography scan; Colonoscopy

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Core Tip: Correct tumour restaging is pivotal for identifying the most personalised surgical treatment for patients with locally advanced rectal cancer undergoing neoadjuvant therapy; it allows avoiding both poor oncological outcomes or over-treatment. However, there are no guidelines regarding the definition, timing and diagnostic techniques to be carried out. This study provides the most up-to-date evidence on this topic and the outstanding issues worthy of future research.

INTRODUCTION

Locally advanced rectal cancer (LARC) treatment requires a multidisciplinary approach. In recent decades, the widespread use and optimisation of total mesorectal excision (TME) and the constant use of neoadjuvant chemoradiotherapy (nCRT) have sharply decreased the rate of local recurrence after surgery[1,2]. Two randomised phase 3 trials on total neoadjuvant therapy (TNT) have recently resulted in a significant improvement in disease-free survival (DFS) and disease-related treatment failure as compared with standard nCRT, setting a new standard of care[3,4]. Nevertheless, the response to neoadjuvant therapy remains highly divergent. It is well established that, after neoadjuvant therapy, a notable number of patients having LARC responds very well to the treatment; a pathological complete response (pCR), defined as the absence of residual tumour cells at the primary tumour site and the mesorectal lymph nodes, occurs in approximately 20% of patients. This rate may be as high as 28%-38% with the implementation of TNT regimens; in addition, an even larger proportion may have a near-complete response[5-7]. Patients with a pCR after TME resection demonstrate excellent survival, with fewer than 1% having local failure and 8% having systemic recurrence[8]. Therefore, the benefit of TME in patients achieving a complete response has been questioned. Organ-preservation strategies are becoming more popular to safely avoid the morbidities associated with radical surgery and to maintain anorectal function in those patients who achieved a clinical complete response (cCR) or a near-cCR (ncCR)[9]. On the other hand, approximately 40% of patients respond poorly or not at all to therapy[5]. This is likely due to more aggressive tumour biology. Poor-responders and non-responders to neoadjuvant therapy are at risk of both local and distant relapse, which may be higher than the average LARC patient[10,11]. In these patients, the possibility of disease progression during neoadjuvant treatment or a waiting period should be taken into account. Its correct identification allows for modification of the treatment plan, intensifying the systemic treatment or optimising the surgical management by extending the resection beyond the mesorectal plane or performing multiorgan resection.

Therefore, the ability to accurately assess the response to neoadjuvant therapy is the key to tailored treatment avoiding poor oncological outcomes or over-treatment. The aim of this review was to evaluate the current evidence regarding tumour response assessment in terms of definition, timing and diagnostic techniques.

DEFINITION OF TUMOUR RESPONSE TO NEOADJUVANT THERAPY

There is no standardisation in response assessment criteria. Originally, Habr-Gama *et al*[12] dichotomised the answer into complete and incomplete. They considered patients to have a cCR in the absence of any residual ulcer, mass or stenosis of the rectum using digital rectal exam (DRE) and proctoscopy; whitening of the mucosa, teleangiectasias, and subtle loss of pliability of the rectum were also considered to be consistent with a cCR. They did not routinely perform endoscopic biopsies and considered radiological imaging consistent with a cCR in the absence of suspicious mesorectal enlarged, irregularly bordered and heterogeneous nodes, and in the presence of fibrotic changes within the rectum (low signal intensity areas with or without submucosal hypertrophy)[13]. The guidelines suggested the same criteria for the definition of a cCR[14,15]. In the attempt to standardise the definition of a clinical response, Memorial Sloan Kettering graded response as complete, near-complete, or incomplete using DRE, endoscopy, and magnetic resonance imaging (MRI) [T2-weighted and diffusion-weighted imaging (DWI) sequences][16]. They classified ncCR, referring to tumours which showed a marked response to neadjuvant therapy, but did not fulfil all the criteria of a cCR at the time of response assessment, such as: (1) Smooth induration or minor mucosal abnormalities on DRE; (2) Irregular mucosa, small mucosal nodules or minor mucosal abnormalities, superficial ulceration or mild persisting erythema of the scar on endoscopy; and (3) Mostly dark T2 signal, some remaining intermediate signal and/or partial regression of the lymph nodes on MRI. If patients did not meet all these criteria and those for a cCR, they were regarded as incomplete responders. This three-tiered response/regression schema was tested prospectively in the OPRA trial[17]. Maas *et al*[18] and Martens *et al*[19] provided a pragmatic definition of cCR, ncCR and non-complete

response. This classification has recently been recommended for use in the definition of tumour response by a panel of experts (Table 1, Figures 1-4)[20].

WHEN TO CARRY OUT RESTAGING

Evidence regarding the optimal timing of restaging is not yet available. The ideal interval should allow the safe identification of responders and non-responders by balancing the time to fully express the maximal effects of the therapy and the time to avoid tumour repopulation or disease progression. In effect, tumour response is a dynamic process associated with tumour-related factors (*e.g.*, size, histology, and molecular profile) and treatment-related factors (such as radiotherapy dose and fractionation, chemotherapy, and the time interval between preoperative and/or definitive treatment and the decision to proceed to non-operative management or local excision or TME)[21]. Knowledge of the kinetics of tumour response comes primarily comes from the operative context.

Several trials have shown how lengthening the interval between radiation therapy and surgery, and adding systemic therapy led to higher rates of pCR. In the historic Lyon R90-01 randomised trial, a longer interval (6-8 wk *vs* 2 wk) between completion of the radiotherapy and surgery led to a significant increase in patients having a major pathological response (pCR or few residual cells)[22]. In the phase 3 Stockholm III trial, the rate of complete pathological response in the short course radiation-delay arm (4-8 wk) was 11.8%, higher compared with 1.7% for the short course radiation-immediate arm (within 1 wk)[23]. An additional extension beyond 8 wk was subsequently tested in the prospective trials. The GRECCAR-6 trial (7 wk *vs* 11 wk) showed that the longer interval did not increase the pCR (15% *vs* 17.4%, $P = 0.59$)[24]. Instead, a British trial (6 wk *vs* 12 wk) found a significant increase in the pCR (9% *vs* 20%, $P < 0.05$)[25]. Similarly, an increased pCR (18% *vs* 10%, $P = 0,027$) was also reported by a Turkish trial for an interval of more than 8 wk *vs* less than 8 wk after chemoradiotherapy[26]. A large retrospective series of patients revealed the highest pCR rates in patients operated on 9-13 wk from the end of CRT[27-29]. Analogously, a pooled analysis of international randomised trials (Accord12/0405, EORTC22921, FFCD9203, CAO/ARO/AIO-94, CAO-ARO-AIO-04,

INTERACT and TROG01.04) has also suggested that the best time to achieve pCR is at 10 wk, and the lengthening of the surgical interval was not detrimental concerning survival outcomes[30]. The Timing of Rectal Cancer Response to Chemoradiation Consortium trial, a prospective phase 2 cohort trial in which preoperative chemoradiotherapy and sequentially increased the time-point of the surgery were evaluated, showed an increase in pCR rates when the average time from radiotherapy to surgery was progressively increased from 6 wk to 11 wk, 15 wk and 19 wk (18%, 25%, 30% and 38%, respectively)[6].

Whether these differences can be explained by the use of intensified chemotherapy or by the prolonged interval before surgery remains uncertain as patients operated on after 11-19 wk received two to six cycles of FOLFOX during the waiting period before surgery. In any case, the consolidation chemotherapy in the TNT approach has recently emerged as the new option for optimizing tumour response; however, it made the detection of the optimal timing of restaging even more complex[31,32].

Moreover, with regard to patients who eventually did not experience a complete or a good response, the benefits related to the practice of waiting up to 11-12 wk before proceeding to surgical resection appeared less obvious. Studies evaluating the effects of the delayed time interval did not report a negative impact on long-term cancer outcomes[30,33]. However, not all the studies carried out a sub-analysis by tumour stage; therefore, the favourable long-term outcomes of the responder group may have masked or mitigated the adverse effects occurring in the non-responder group. In the RAPIDO trial, the Authors suggested that an early response assessment should be encouraged in order to identify, at an earlier point in time, poor responders and, above all, patients with disease progression during preoperative treatment[3]. A large retrospective series of patients from the population-based Dutch Surgical Colorectal Audit found that the proportion of T4 tumours and metastatic disease increased with a longer time interval to surgery, and it was particularly evident in the group resected beyond 10-11 wk from the end of CRT[27]. In a large multicentre retrospective cohort study of 1064 patients with a minor or null tumour response to neoadjuvant chemoradiotherapy, a wait time longer than 8 wk before surgery was associated with significantly worse overall and DFS at 5

and 10 years (reaching almost a 20% difference at 10 years for the OS)[10]. Unfortunately, it is not possible to identify poor responders up-front.

Patient selection based on pre-treatment characteristics is challenging, although some features, including < 1 mm circumferential margin, extramural venous invasion, and extensive mesorectal and pelvic lymph node involvement, are associated with lower cCR rates[34-36]. Currently, there is insufficient evidence to recommend proper timing for the earlier identification of patients with a poor response before the conventional time. Nevertheless, experts advise caution and selective earlier imaging in patients with tumours featuring certain high-risk characteristics (such as advanced clinical T stage)[20]. Moreover, owing to variations in preoperative treatment design and duration across the different trials, they agreed that defining one specific time point for assessing a cCR was impossible, and they recommended that the response assessment should be determined from the start of treatment[20]. Thus, for patients with early-stage tumours receiving CRT or short-course radiotherapy, they recommended the two-step approach which involves response assessment at 12 wk and 16-20 wk after starting treatment; for patients receiving TNT, they recommended that the timing of the cCR assessments should be adapted according to the duration of the treatment, that is, 20-38 wk after commencing treatment[20]. In the end, if restaging after preoperative treatment reveals an ncCR, taking into account initial tumour stage and treatment approach, the panel supported waiting longer (*e.g.*, 3 mo later as was reported in several case studies) if organ preservation was a priority[20].

HOW TO CARRY OUT RESTAGING

The standard methods of response assessment following preoperative therapy rely on clinical examination using DRE, endoscopy, MRI, endorectal ultrasound (EUS) and CT. However, all these tools have limitations in predicting pathological findings after a surgical resection. These limitations are the result of the difficulty of these imaging methods to differentiate the residual tumour from the radiation-induced fibrosis which leads to erring on the safe side, overestimating the amount of tumour. Nevertheless, the

current aim of local response assessment is not really correct T-staging; it is the accurate differentiation between "good responders" (who are ypT0N0 or ypT1N0) and "poor responders". In the latter case, the risk of incomplete resection, such as mesorectal fascia (MRF) positivity, adjacent organ or anal sphincter infiltration and residual lateral pelvic node involvement should also be identified.

Pelvic MRI

MRI is the modality of choice for local staging of LARC due to its excellent soft-tissue resolution; it also plays an essential role in the evaluation of treatment response[37,38]. In a recent meta-analysis, the reported global sensitivity and specificity for T-staging were 81% and 67%, respectively and, for N-staging, they were 77% in both cases[39]. These results confirmed those of a previous meta-analysis in which the pooled sensitivity and specificity were 50.4% and 91.2%, respectively for the T-stage, and the sensitivity for the prediction of a complete response was even lower (19%)[40]. The addition of DWI MRI improved the results, increasing the sensitivity and specificity rate for T-stage up to 83.6% and 84.8%, respectively[40,41]. Nevertheless, many complete responses were still missed. The magnetic resonance tumour regression grade (TRG) system and a pattern-based approach have been proposed to improve diagnostic performance[42,43]. In experienced hands, the sensitivity of detecting a complete response was 74% when using the former system and 94% with the latter approach[42,43]. To properly identify "good responders", accurate nodal restaging is also important. A pooled analysis showed that the incidence of positive lymph nodes in ypT0 patients was approximately 5%[44]. Although nodal restaging remains a challenge, it seems to be more accurate than primary staging[45]. According to Heijnen *et al*[46], this could be explained by the following two reasons. First, after CRT, approximately 40% of lymph nodes decrease in size and approximately 44% disappear at MRI, and second, the prevalence of pathological positive nodes is lower as compared with the initial staging, leading to a higher negative predictive value (95%) and to increased accuracy of nodal staging after CRT[46]. However, in cases of ypT0, the sensitivity, specificity, positive and negative predictive values for predicting remaining

lymph node metastasis with MRI were quite low (37%, 84%, 70% and 57%, respectively)[47]. Probably owing to the fact that residual disease occurs within very small nodes. van Heeswijk and colleagues showed that the absence of lymph nodes on restaging DWI MRI was highly predictive of ypN0 status[48]. Nevertheless, the role of DWI in this setting is still under debate[45]; MRI also plays a pivotal role in identifying the risk factors for incomplete resection. The evaluation of MRF status is less accurate than that of the pretreatment assessment (66%)[40,49,50]. In the case of residual involvement of the adjacent organs or mesorectal fascia, radiologists tend to overstage as fibrotic strands of former tumour invasion are challenging to differentiate from residual tumour tissue, unless an intact fat plane becomes visible between the tumour and the MRF or the adjacent organs. Moreover, in distal tumours, invasion of the internal sphincter, intersphincteric plane, and external sphincter/Levator ani has to be assessed to determine the feasibility of sphincter preservation. Furthermore, careful attention should be paid to identifying the lateral nodes as these nodes, when involved, have an important influence on long-term outcome. A recent large multicentre cohort study, evaluating the lateral nodes before and after CRT, showed that nodes 7 mm or greater before CRT (short axis) had a higher risk for local recurrence than smaller nodes[51]. Moreover, in the case of shrinkage of the lateral nodes from ³7 mm on a primary MRI to a short axis £4 mm, lateral lymph node dissection can be avoided[52].

EUS

Similar to MRI, the accuracy of EUS is disappointing in restaging. A number of studies on this topic have shown that the overall accuracy of EUS for ypT-stage and ypN-stage was quite variable, ranging from 38% to 75%, and from 59% to 80%, respectively[53-55]. Overstaging was more common in the majority of series, mainly due to the difficulty in differentiating fibrosis from residual cancer; EUS correctly predicted pCR in only approximately 50%-64%of cases[53-55]. These results were confirmed in a meta-analysis in which the sensitivity and specificity for T0-stage were 37% and 94%, respectively[56]. Zhang *et al*[57] have recently evaluated three-dimensional EUS parameters to improve

accuracy in tumour response assessment. They found that a value of 3.55 mm for adjusted thickness, that is the difference between the thickness of the muscularis on the residual side and the thickness of contralateral muscularis, correctly detected the TRG 0 cases with a sensitivity of 73%, a specificity of 81%, and an accuracy of 78%. Moreover, they concluded that, utilising the 3D-EUS method as a part of the criteria of a cCR would significantly improve the accuracy of the evaluation[57]. Some case-series studies have indicated that optimal accuracy of EUS could be obtained when the tumour location was within 6 cm from the anal verge, and the examination was carried out by an experienced operator[54,58,59]. Studies comparing the accuracy of MRI and EUS in the same patients at the same time have reported conflicting results regarding T- and N-staging[59-61]. Nevertheless, EUS was more accurate than MRI for predicting pathologic complete responder and anal sphincter infiltration[59-61]. Therefore, EUS is simple and inexpensive tool which, together with MRI and other diagnostic methods, in can be useful restaging rectal cancer; however, it is highly operator-dependent and limited to proximal and stenotic rectal tumours and close visual fields which only allow evaluating perirectal lymph nodes.

Endoscopy

Endoscopy makes it possible to properly evaluate only the mucosa. Although the healing of the mucosa is generally considered to be a sign of a cCR, residual tumour remains deeper in the rectal wall and mesorectum in approximately 27% of cases. On the other hand, the presence of an ulcer on endoscopy, although significantly associated with pathological incomplete response, occurs in 66% of cases with complete response on pathology[62-64]. In clinical practice, to facilitate the decision-making process, additional information can be obtained from the MRI. However, studies which have evaluated this issue have produced contradictory results. Some have shown that a combination of multiple examinations did not improve accuracy[65,66]. In contrast to these findings, in a small prospective cohort study, Maas *et al*[18] showed that when DRE, endoscopy and MR together predict a CR, this is correct in 98% of the cases; when all three modalities indicate

residual tumour, there still a 15% chance for a CR[67]. Advanced endoscopy technologies, such as narrow-spectrum technologies and autofluorescence imaging, may improve the evaluation of the rectal wall mucosa and mucosal vascularity[68]. In the setting of restaging assessment, they may help in differentiating between clinical response and residual tumour.

Biopsies have only a limited clinical value for ruling out residual cancer. They do not provide any additional diagnostic value and could lead to false-negative results as residual cancer cells are often found in the muscularis propia[69]. Therefore, experts did not recommend a biopsy as mandatory for diagnosing a complete or a near complete CR[20].

Contrast-enhanced thoraco-abdominal computed tomography

Although the value of computed tomography (CT) in assessing local response is relatively low, this tool plays a pivotal role in determining the presence of distant metastases. In effect, the current guidelines recommend its use in restaging[15]. A recent systematic review has shown that restaging identified new metastatic disease in 6% of patients[11]. Although the overall detection rate of disease progression is low, the clinical impact of identifying early disease progression prior to surgical therapy is important to consider. Newly detected distant disease in such a short period may represent a more biologically aggressive tumour or synchronous distant metastases which are not apparent on the initial clinical staging, but which become detectable in the few months of the restaging. In any case, its identification requires modifying the therapeutic programme. Singhal and colleagues have found that patients with poorly differentiated tumours had a significantly higher rate of systemic disease progression than those with well or moderately differentiated tumours (36% *vs* 7%, respectively). Nevertheless, more studies are necessary to identify the factors which may predict short-interval disease progression.

18F-fluorodeoxyglucose positron emission tomography/CT

According to the guideline, positron emission tomography (PET) should not be routinely used as response tool[15]. The pooled sensitivity and specificity reported for complete response were 71% and 76%, respectively[70]. Moreover, the metabolic grade [max standardised uptake value (SUVmax)] of the tumour at initial staging did not predict response to chemoradiotherapy; as with pretreatment SUVmax, the arithmetic difference between pre- and post-SUVmax was also not statistically significant[70]. A systematic review showed that PET/CT had a higher accuracy for detecting extra-hepatic and hepatic colorectal metastatic disease than CT alone[71].

Future directions and research

Combined 18F-fluorodeoxyglucose (18F-FDG) PET/MRI has recently been proposed as an effective imaging modality for rectal cancer patients owing to its ability to provide high-resolution anatomical and functional features. Although the role of 18F-FDG PET/MRI in rectal cancer has yet to be established, the evidence in a recent review has suggested that 18F-FDG PET/MRI could be used for rectal cancer restaging due to its better accuracy in T staging and N staging as compared with PET/CT or MRI alone; for M staging, on the other hand, it performed less well than other techniques for lung metastases[72].

Some novel MRI techniques, such as dynamic contrast-enhanced MRI, magnetisation transfer ratio and textural analysis (*e.g.*, radiomics), have been studied to overcome some limitations of MRI in the restaging of rectal cancer. These tools have been evaluated in promising small retrospective studies; however, they are not currently used in routine clinical practice as they await large-scale prospective validation.

Circulating biomarkers, such as cell-free DNA, have been tested to predict a cCR and/or tumour regrowth. They have not been incorporated into current practice due to limited data, but provide promising results for future investigation and validation.

CONCLUSION

The ultimate goal of restaging is the possibility of changing the planned treatment. Digital rectal examination, endoscopy and pelvic MRI are the recommended modalities for local tumour restaging while chest and abdominal CT are those used for assessing distant disease. Nevertheless, the most practical and cost-efficient strategy for tumour response also depends on local logistics and local expertise. The optimal length of time between commencing treatment and restaging, in terms of both oncological safety and clinical effectiveness of treatment, remains unclear, above all in patients receiving prolonged TNT. The timely identification of patients who are radioresistant and at risk of disease progression is challenging. Table 2 gives the take-home message.

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