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OPINION REVIEW

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, and works to avoid both poor oncological outcome and overtreatment. Digital rectal examination, endoscopy, and pelvic magnetic resonance imaging are the recommended modalities for local tumour restaging, while chest and abdominal computed tomography are 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, especially for patients receiving prolonged total neoadjuvant therapy. The timely identification of patients who are radioresistant and at risk of disease progression remains challenging.

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

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 avoidance of both poor oncological outcomes and overtreatment. 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.

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INTRODUCTION

Treatment of locally advanced rectal cancer (LARC) 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 investigating 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, many patients with LARC respond very well to the treatment; indeed, pathological complete response (pCR), defined as the absence of residual tumour cells at the primary tumour site and the mesorectal lymph nodes, is achieved in approximately 20% of patients. This rate may be as high as 28%-38% with the implementation of TNT regimens; as a result, an even larger proportion may have a near-complete response[5-7]. Patients with 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 attributable 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 that of the average LARC patient[10,11]. In these patients, the possibility of disease progression during neoadjuvant treatment or the waiting period should be taken into account. Its correct identification allows for modification of the treatment plan, intensifying the systemic treatment, or optimising surgical management by extending 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 to avoid poor oncological outcomes or overtreatment. The aim of this review is 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 with respect to tumour response assessment criteria. Originally, Habr-Gama *et al*[12] dichotomised the categorisation into complete and incomplete. They considered patients to have cCR if there was an absence of any residual ulcer, mass, or stenosis of the rectum by 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 cCR. They did not routinely perform endoscopic biopsies and considered radiological imaging consistent with cCR in the absence of suspicious mesorectal enlarged, irregularly bordered, and heterogeneous nodes, and in the presence of fibrotic changes within the rectum (*i.e.* low signal intensity areas with or without submucosal hypertrophy)[13]. The guidelines suggested the same criteria for the definition of 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 based on the findings of DRE, endoscopy, and magnetic resonance imaging (MRI) [T2-weighted and diffusion-weighted imaging (DWI) sequences][16]. They classified ncCR as tumours that showed a marked response to neoadjuvant therapy but did not fulfil all the criteria of 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 cCR, they were regarded as incomplete responders. This 3-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 by a panel of experts for use in the definition of tumour response (Table 1; Figures 1-4)[20].

Table 1 Recommended tumour response schema for rectal cancer after neoadjuvant chemoradiotherapy

	cCR	ncCR	Poor response
DRE	No palpable tumour material present	Minor mucosal abnormalities	Palpable tumour mass; Cases who do not fulfill the criteria for either a cCR or ncCR
Endoscopy	No residual tumour material or only a small residual erythematous ulcer or scar; Endoscopic biopsy not mandatory to define a cCR, biopsy should not be performed, especially if the DRE, rectoscopy and MRI criteria for a cCR are all fulfilled	Small and smooth regular irregularities including residual ulcer, or small mucosal nodules or minor mucosal abnormalities, with mild persisting erythema of the scar; Endoscopic biopsy not mandatory	Visible macroscopic tumour; Cases who do not fulfill the criteria for either a cCR or ncCR
MRI	Substantial downsizing with no observable residual tumour material, or residual fibrosis only (with limited signal on diffusion weighted imaging), sometimes associated with residual wall thickening owing to oedema, no suspicious lymph nodes	Obvious downstaging with residual fibrosis but heterogeneous or irregular aspects and signal or regression of lymph nodes with no malignant enhancement features, but with a size > 5 mm	Visible macroscopic tumour and/or lack of regression of involved lymph nodes; Cases who do not fulfill the criteria for either a cCR or ncCR

DRE: Digital rectal exam; cCR: Clinical complete response; ncCR: Near clinical complete response; MRI: Magnetic resonance imaging.

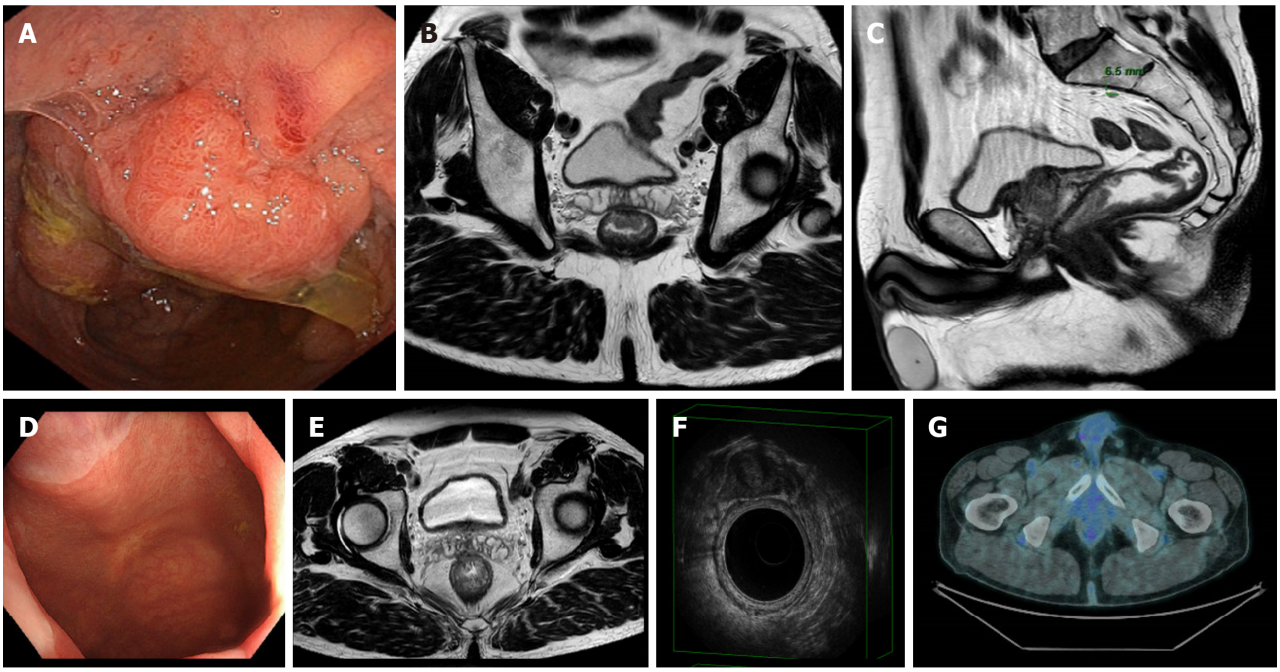

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Figure 1 A case of clinical complete response confirmed at pathology. A-C: A 61-year-old male patient with rectal cancer. Endoscopy (A) and magnetic resonance imaging (MRI) (B and C) findings staged a tumour of the low rectum (cT3aN1, mesorectal fascia negative, extramural venous invasion negative, pelvic nodes negative). The patient underwent neoadjuvant chemoradiotherapy; D-G: Restaging at 15 wk after the beginning of the neoadjuvant chemoradiotherapy showed a clinical complete response at endoscopy (D), MRI (E), endorectal ultrasound (F), and 18-fluorodeoxyglucose-computed tomography/positron emission tomography (G).

WHEN TO CARRY OUT RESTAGING

Evidence regarding the optimal timing of restaging is not yet available. The ideal interval should allow for 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 (*e.g.*, 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 leads 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 number of patients having a major pathological response (pCR or few residual cells)[22]. In

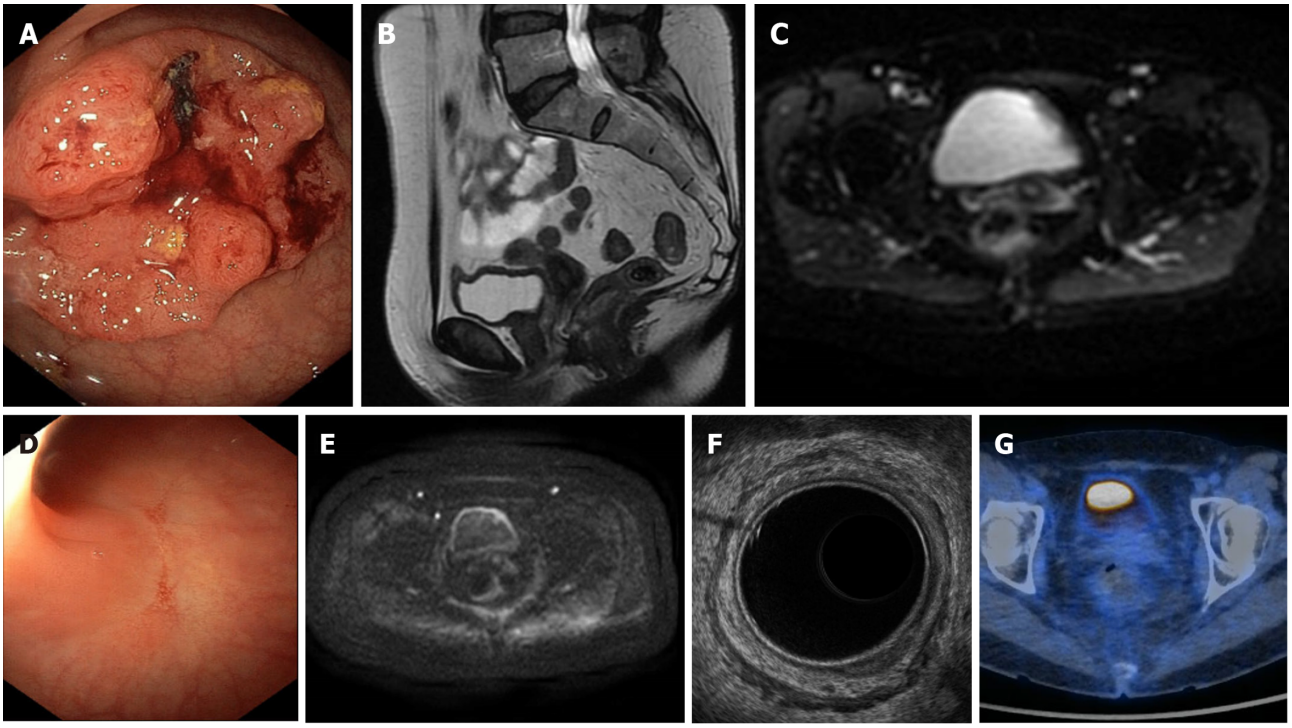

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Figure 2 A case of clinical complete response confirmed at pathology. A-C: A 57-year-old female patient with rectal cancer. Endoscopy (A) and magnetic resonance imaging (MRI) (B and C) findings staged a tumour of the low of rectum (cT3aN0 mesorectal fascia negative, extramural vascular invasion negative, pelvic nodes negative). The patient underwent neoadjuvant chemoradiotherapy; D-G: Restaging at 15 wk after the beginning of therapy showed a clinical complete response at endoscopy (D), MRI (E), endorectal ultrasound (F), and 18-fluorodeoxyglucose-computed tomography/positron emission tomography (G).

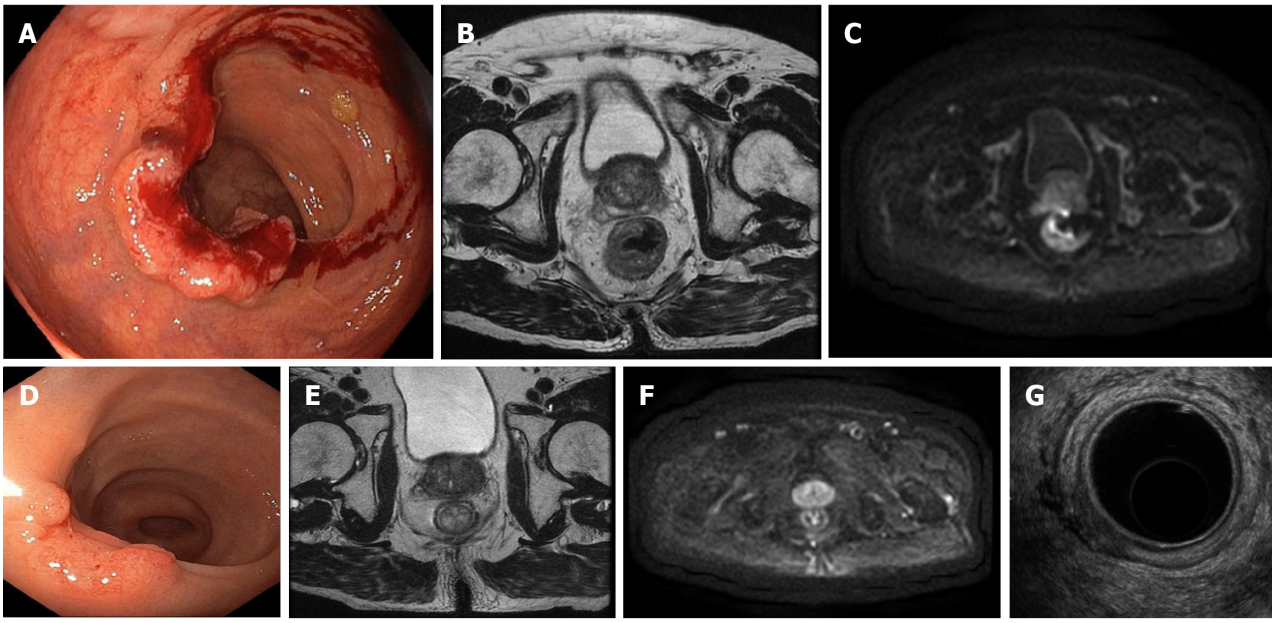

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Figure 3 A case of near clinical complete response confirmed at pathology (ypT1N0). A-C: An 84-year-old male patient with rectal cancer. Endoscopy (A) and magnetic resonance imaging (MRI) (B and C) staged a tumour of the low rectum (cT3aN0M0, mesorectal fascia negative, extramural vascular invasion negative, pelvic nodes negative). The patient underwent short-course radiotherapy; D-G: The restaging at 15 wk after the beginning of neoadjuvant radiotherapy showed a near clinical complete response at endoscopy (D), MRI (E and F), and endorectal ultrasound (G).

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%, as compared to 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

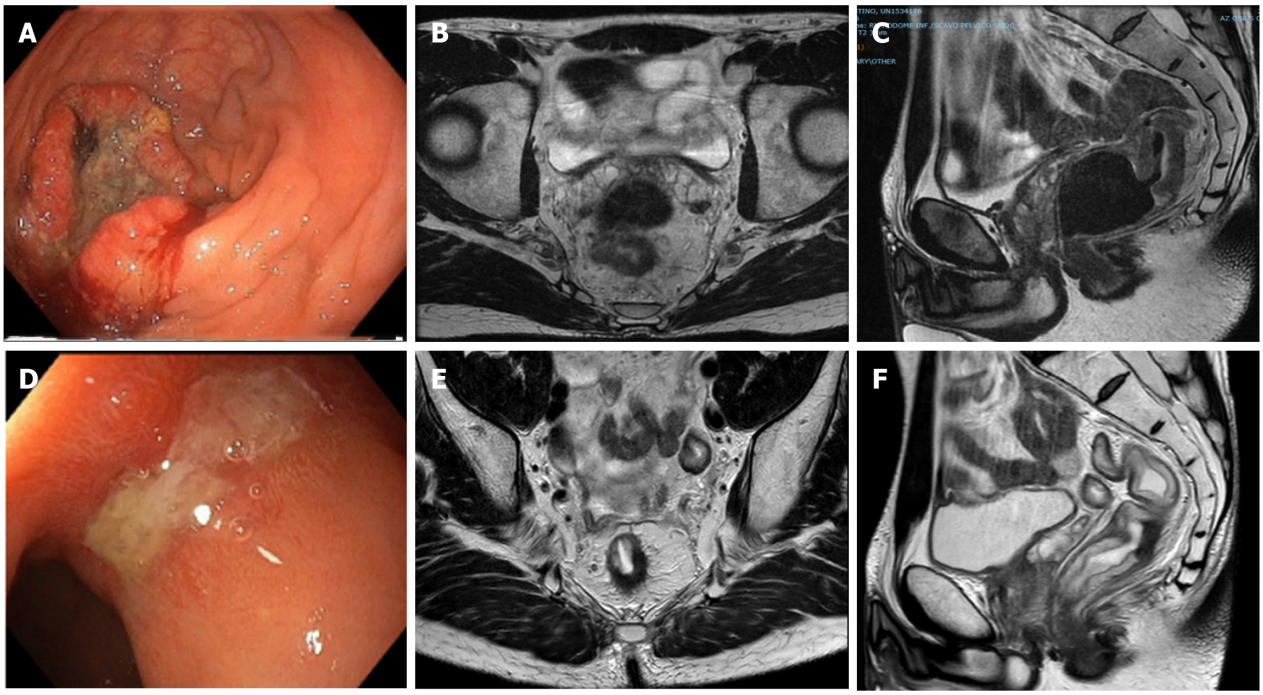

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Figure 4 A case of poor response confirmed at pathology (ypT2N0). A-C: A 42-year-old male with rectal cancer. Endoscopy (A) and MRI (B and C) staged a tumour of the middle rectum (cT3bN2, mesorectal fascia negative, extramural vascular invasion positive, pelvic nodes negative). The patient underwent total neoadjuvant therapy; D-F: Restaging at 20 wk after the beginning of neoadjuvant radiotherapy showed a poor response at endoscopy (D) and MRI (E and F).

rate (15% *vs* 17.4%; $P = 0.59$)[24]. In contrast, a British trial (6 wk *vs* 12 wk) found a significant increase in the pCR rate (9% *vs* 20%, $P < 0.05$)[25]. Similarly, an increased pCR rate (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 with respect to 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 timing of 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 2 to 6 cycles of FOLFOX during the waiting period before surgery. In any case, 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 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; this 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 outcome and DFS at 5 y and 10 y (reaching almost a 20% difference at 10 y for the overall survival)[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 a < 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 (*e.g.*, advanced clinical T stage)[20]. Moreover, owing to variations in preoperative treatment design and duration across the different trials, they agreed that defining a specific time point for assessing cCR was impossible, and 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 a 2-step approach comprising a 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 (*i.e.* 20-38 wk after commencing treatment)[20]. In the end, if restaging after preoperative treatment reveals 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, each of these tools has limitations in predicting pathological findings after a surgical resection. These limitations stem from the inability of these imaging methods to differentiate residual tumour from radiation-induced fibrosis; this leads to erring on the safe side, overestimating the amount of tumour. Nevertheless, the current aim of local response assessment is not to correct T-staging but to differentiate between "good responders" (who are ypT0N0 or ypT1N0) and "poor responders." In the latter, the risk of incomplete resection [*e.g.*, 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 both 77%[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 diffusion-weighted (DWI) MRI improved the results, increasing the sensitivity and specificity for T-stage 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: First, after CRT, approximately 40% of lymph nodes decrease in size and approximately 44% disappear on 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 increased accuracy of nodal staging after CRT[46]. However, in cases of ypT0, the sensitivity, specificity, positive predictive value, and negative predictive value for predicting remaining lymph node metastasis with MRI were quite low (37%, 84%, 70%, and 57%, respectively)[47]; this may be attributable 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 prior tumour invasion are challenging to differentiate from residual tumour tissue, unless an intact fat plane becomes visible between the tumour and the MRF or 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 7 mm on a primary MRI to a short axis measurement of 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 3-dimensional EUS (3D-EUS) parameters to improve accuracy in tumour response assessment. They found that a value of 3.55 mm for adjusted thickness (*i.e.* 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 for 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 response and anal sphincter infiltration[59-61]. Therefore, EUS is simple and inexpensive tool which, together with MRI and other diagnostic methods, can be useful for restaging rectal cancer. However, this modality is highly operator-dependent and limited to proximal and stenotic rectal tumours and close visual fields that only allow for the evaluation of perirectal lymph nodes.

Endoscopy

Endoscopy only allows for the proper evaluation of the mucosa. Although the healing of the mucosa is generally considered to be a sign of 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 that 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 MRI together predict CR, this is correct in 98% of cases; when all 3 modalities indicate residual tumour, there still a 15% chance of 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 biopsy as mandatory for diagnosing a complete or a near complete CR[20].

Contrast-enhanced thoraco-abdominal computed tomography

Although the value of CT in assessing local response is relatively low, this tool plays a role in determining the presence of distant metastases and current guidelines recommend its use in restaging [15]. A recent systematic review showed 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 that were not apparent on initial clinical staging, but that become detectable in the few months of the restaging. In any case, its identification requires modifying the therapeutic programme. Singhal and colleagues 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 factors that 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 a tool to determine tumour response[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 higher accuracy in detecting extra-hepatic and hepatic colorectal metastatic disease than CT alone[71].

Table 2 Take-home message

Re-staging	
Why	It allows for the development of a tailored surgical treatment with the goal of avoiding poor oncological outcomes and overtreatment
When	It remains unclear. Experts recommend: (1) For patients receiving neoadjuvant chemoradiotherapy or short-course radiotherapy, the 2-step approach, at 12 wk and 16-20 wk after starting treatment if organ preservation is a priority; (2) For patients receiving total neoadjuvant therapy, assessment at 20-38 wk after commencing treatment according to the duration of the treatment; and (3) In case of ncCR, a second assessment 3 mo later taking into account initial tumour stage and treatment approach, if organ preservation is a priority. 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 cT stage)
How	Digital rectal examination, endoscopy and pelvic MRI for local tumour restaging; Chest and abdominal CT for distant disease. The current aim of local response assessment is not correct T-staging but the accurate differentiation between "good responders" (who are ypT0N0 or ypT1N0) and "poor responders." In the latter, the risk of incomplete resection, such as MRF positivity, adjacent organ or anal sphincter infiltration, and residual lateral pelvic node involvement should also be identified

CT: Computed tomography; ncCR: Near clinical complete response; MRI: Magnetic resonance imaging.

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- and N-staging as compared to 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 the 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 still need large-scale prospective validation.

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

CONCLUSION

The ultimate goal of restaging is to determine the possibility of changing the planned treatment strategy. DRE, endoscopy, and pelvic MRI are the recommended modalities for local tumour restaging, while chest and abdominal CT are used for assessing distant disease. Nevertheless, the most practical and cost-efficient strategy for assessing tumour response also depends on local logistics and expertise. The optimal length of time between commencing treatment and restaging, in terms of both oncological safety and clinical effectiveness of treatment, remains unclear, especially in patients receiving prolonged TNT. The timely identification of patients who are radioresistant and at risk of disease progression is challenging. Table 2 summarizes the key points discussed in this review.

FOOTNOTES

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