

Challenges in determining the benefits of restaging after chemoradiotherapy for locally advanced rectal cancer

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Colorectal cancer, April 2014, Vol. 3, No. 2, Pages 121-125

Primary staging

Primary staging in rectal cancer is essential for determining the optimal treatment strategy and consists of local staging and screening for distant metastases. Local staging is important to determine the surgical approach and to identify individual risk factors for recurrence, such as depth of extramural spread, lymph node involvement, mesorectal fascia (MRF) involvement and extramural vascular invasion.¹⁻⁴ Patients with low risk for recurrence can be treated by surgery alone, whereas patients with a high risk for recurrence must be treated with neoadjuvant (chemo-)radiotherapy to decrease the chance of local recurrence.^{5,6}

Screening for distant metastases is important to identify metastasized patients who require a different treatment approach. Patients with resectable synchronous distant metastases should be treated with curative intent by resection of the distant metastases and primary tumor. Patients with unresectable distant metastases can be safely spared rectal surgery and treated with systemic chemotherapy with a low chance of emergency surgery.⁷

For primary local staging, magnetic resonance (MR) imaging is superior compared to other imaging modalities currently available. Accuracies of tumor staging, nodal staging and MRF-involvement by MR imaging are higher compared to the accuracies of Computed Tomographic (CT) scans and endoscopic ultrasound sonography (EUS).⁸⁻¹⁰ Moreover, the multicenter Mercury study with 12 colorectal units in 4 European countries showed MR imaging to be highly accurate and reproducible.¹¹ Therefore, MR imaging is recommended in all guidelines as preferred imaging modality in the preoperative assessment of rectal cancer.¹²⁻¹⁴ For screening for distant metastases, most guidelines advise a thoraco-abdominal CT-scan.^{12,14}

Chemoradiotherapy and potential benefits of restaging

Neoadjuvant chemoradiotherapy (CTxRTx) is administered to reduce local recurrence rates, to facilitate tumor downstaging and additionally leads to a pathological complete response (pCR) in 11-19%.^{3,6,15-17} The identification of good versus poor responders before definitive surgery is important, because patients may be offered less radical or rather more radical surgery. Therefore, patients are increasingly being restaged after administering CTxRTx and many advocate to perform restaging routinely.¹⁸ Restaging could have implications for surgical management. For example, tumor shrinkage may lead to sphincter sparing surgery instead of an abdominoperineal resections with a permanent stoma. Furthermore, there is a growing interest in selecting those patients who are likely to have achieved a pCR, because these patients could be offered a 'wait and see policy' and spared rectal surgery at all.

Does restaging alters treatment strategy and is it safe?

The most important problem of restaging is that generally the accuracy of predicting tumor stage is poor. This is mainly caused by the difficulty differentiating between vital tumor and radiation induced fibrosis. Other radiation-induced changes, such as edema, inflammation and necrosis also contribute to a poor accuracy. Especially, the sensitivity of tumor staging in patients after CTxRTx is concerning. A recent meta-analysis reported a poor mean sensitivity of 50% and a mean specificity of 91%, while only discriminating between T0-2 vs. T3-4.¹⁹ Accuracies predicting exact tumor stage are even poorer.^{20,21} On the other hand, the accuracy of predicting lymph node involvement in restaging is higher compared to primary staging, but still the specificity nodal restaging is concerning. The same meta-analysis reported a mean specificity of 60% and a mean sensitivity of 76%.¹⁹

One of the most important questions regarding the clinical use of restaging remains unanswered: Does restaging indeed alter surgical treatment? Theoretically, tumor downstaging caused by CTxRTx may result in more sphincter saving procedures, which could explain the increase of the sphincter sparing procedures in the last decades from 17% in the early 80s²² to 79% in 2011.²³ However, none of the randomized controlled trials evaluating the effect of CTxRTx was able to demonstrate a significant increase in the rate of sphincter saving surgery. This suggests that the increase is more likely to be caused by advances in the surgical practice than by administering CTxRTx.²⁴ Moreover, it remains unclear whether performing less radical procedures in downstaged patients is safe, keeping in mind that imaging is insufficient to detect possible vital tumor remnants in the radiation induced fibrosis.²⁵ Another problem is the considerable change of under- and overstaging. Obviously, the risk of overstaging is higher due to the replacement of vital tumor into fibrosis, but understaging of tumor status occurs in 7-22% of the patients.^{20,21,26} Surgeons should be cautious performing less radical resections based on restaging imaging, because understaging may lead to incomplete resections and these are disastrous for oncologic outcome.²

A potential interesting aspect of restaging is that in case of complete tumor disappearance treatment plan could be altered into a wait and see policy. Although the results of studies with a wait and see policy are promising,^{27,28} it is important to realize that omitting surgery is no standard practice. The results of a wait and see policy are based on few studies and the majority of the studies originates from one single center with limited long term follow up. Based on these data, a wait and see policy is not proven to be safe. Therefore, restaging with the idea to alter treatment plan into a wait and see policy should only be performed in clinical trials. Moreover, due to the very poor sensitivity of predicting a pCR of 19%, restaging in a wait and see policy should only be performed as an integrated part of several examinations, including endoscopy and digital examination.¹⁹ The diagnostic accuracy of predicting a pCR may be increased by performing local excisions by transanal endoscopic microsurgery (TEM). In the

near future, the CARTS trial will provide the answer whether this approach is safe and feasible.²⁹ However, not only accurate determination of tumor stage is important to safely alter treatment into a wait and see policy. Accurate assessment of possible malignant lymph nodes is at least even important. Unfortunately, the specificity of 60% of nodal restaging shows there is a considerable chance of missing malignant lymph nodes.

Benefits of local restaging

A potential involved circumferential resection margin (CRM) or the relationship of the tumor to the MRF has emerged as one of the most powerful predictors of outcome. Surgical dissection outside of this fascia has become central in the efforts to achieve CRM negativity and is possible in many cases. This is the concept behind the beyond total mesorectal excision (TME) approach.³⁰ The accuracies of predicting MRF-involvement after CTxRTx are acceptable with a sensitivity of 76% and a specificity of 86%.¹⁹ This makes restaging is useful for determining MRF-involvement in patients and to assess the need for resections beyond the TME plane. However, surgeons should keep in mind that there is a considerable change of overtreatment by performing unnecessary multivisceral resections or undertreatment by performing incomplete resections.

Another interesting and potentially useful aspect of restaging is that radiologically determined tumor response can be used as early prognostic factor. The mercury study group has demonstrated that radiologically determined poor tumor response was associated with poorer overall survival and disease free survival.³¹ In these patients, post-operative follow up could be intensified to detect distant metastases in an early stage or could be offered more aggressive (neo)adjuvant therapy.

Improvements in accuracy of local restaging

Although accuracies of restaging are generally poor, there have been gains in restaging accuracies in the hands of dedicated and experienced radiologists. Recent studies have reported accuracies up to 80%.^{25,32,33} This is caused by the use of high resolution MRI techniques, the use of validated reporting criteria and by diffusion weighted (DW) imaging. DWI-MRI significantly improves accuracies in tumor staging and also seems to improve the sensitivity of predicting a pCR.^{19,34}

Restaging for distant metastases

Generally, rectal surgery is scheduled after an interval of 6 weeks after ending CTxRTx. However, rectal surgery is now often postponed to 9 or even 12 weeks as longer intervals may enhance tumor downstaging, increase pCR rates and reduce complication rates.^{35,36} Currently, the interval between initial staging and surgery may take up to 4-5 months. Due to this long interval, restaging by a thoraco-abdominal CT-scan could detect distant metastases, which developed during CTxRTx. Also considering that only the advanced

stages of rectal cancer with subsequently the highest risk of developing of distant metastases are treated with CTxRTx. Two recently published studies have demonstrated the development of distant metastases in 7-12% of the patients being restaged by a thoraco-abdominal CT-scan.^{21,37} This is essential information, because the development of distant metastases alters the optimal surgical strategy. Patients with resectable metastases can undergo resections of both rectal tumor and distant metastases, while patients with unresectable metastases can be spared rectal surgery.

Conclusions

Currently, the actual benefits of local restaging for clinical practice are limited. Accuracies of tumor and nodal staging after administering CTxRTx are too low to safely alter definitive surgical procedure or to apply a wait and see policy. However, restaging is useful to evaluate MRF-involvement in locally advanced rectal cancer and to assess whether resections beyond the TME plane are necessary. Furthermore, restaging can evaluate tumor response, which can be used as early prognostic factor. Restaging by thoraco-abdominal CT-scan is valuable to detect distant metastases developing during CTxRTx. A considerable proportion develops distant metastases during CTxRTx and these patients require a different surgical strategy. Moreover, some patients develops unresectable distant metastases and these patients can even be spared rectal surgery. Future research should focus on improvement of restaging accuracies and on evaluating the safety of performing less radical surgery in downstaged patients.

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