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Chemo-radiotherapy in locally advanced rectal cancer: What is the optimal strategy?

Antonio Avallone[a,*], *Paolo Delrio*[b], *Secondo Lastoria*[c], *Pasquale Comella*[a]

[a]*Gastrointestinal Medical Oncology, National Tumour Institute, Via M Semmola, Naples 80131, Italy*
[b]*Entero-proctological Surgical Oncology, National Tumour Institute, Via M Semmola, Naples 80131, Italy*
[c]*Nuclear Medicine, National Tumour Institute, Via M Semmola, Naples 80131, Italy*

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ABSTRACT

The management of locally advanced rectal cancers, although has remarkably improved in the last years, still remains a challenge. The results of recent European randomised trias have marked a paradigm shift from the postoperative to preoperative CRT approach. However, this approach do not impact on the occurrence of distant metastases, disease-free survival and overall survival, underlining the need for a more intensified approach. Moreover, the data of retrospective analysis have evidenced that an other critical point is the selection of patients for whom a risk-adapted pre and postoperative treatment should be delivered, considering that locally advanced rectal tumours are a widely heterogeneous group of tumours. Therefore, a refinements of a multimodality therapy by an integrated approach of a highly skilled multidisciplinary team is needed for a further improvement of clinical management.

1. Introduction

During the last 20 years, the treatment of rectal cancer has dramatically changed. The recognition that the involvement of the circumferential resection margin (CRM) is the strongest negative prognostic factor for local recurrence, and the consequent wide adoption in the surgical technique of the total mesorectal excision (TME) has resulted in a significant decline of the local recurrence rate. Moreover, randomised controlled trials in clinically resectable rectal cancer have supported the role of preoperative short-course radiotherapy (SRT), and of preoperative 5-fluorouracil (5-FU)-based chemo-radiotherapy (CRT) in further reducing the risk of local recurrence, even in the setting of an optimal surgery, but neither strategy has demonstrated to positively impact on the occurrence of distant metastases, disease-free survival and overall survival, underlining the need for a more intensified approach.

However, locally advanced rectal cancers are a widely heterogeneous group of tumours that may have quite different prognostic implications. Therefore, the careful identification of patients at high-risk of recurrence is a critical issue, because it is likely that not all patients need a primary and/or intensified approach. Moreover, considering that not all tumours respond uniformly to a preoperative treatment, and the poor adherence of patients to a postoperative chemotherapy, a risk-adapted strategy should be pursued also in the postoperative setting. Hence, the management of locally advanced rectal cancers, although has remarkably improved in the last years, still remains a challenge.

* *Corresponding author:* Tel.: +39 081 5903629; fax: +39 081 5903821.
E-mail address: avalloneantonio@libero.it (A. Avallone).
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2. Selection of patients for the preoperative approach

The results of recent European randomised trials on patients with locally advanced rectal cancer have highlighted the lower risk of local recurrence when preoperative 5-FU-based CRT was compared with preoperative long-course RT alone,[1,2] or postoperative CRT.[3] Moreover, there were additional benefits in favor of preoperative CRT, such as a greater sphincter preservation surgery, a better compliance with the planned treatment and a lower incidence of acute and late toxicity. These findings have marked a paradigm shift from the postoperative to preoperative CRT approach.

SRT has also demonstrated to be an effective preoperative treatment in resectable rectal cancer. The results of Dutch CKVO 95-04[4] and MRC CR07[5] trials have clearly shown a statistically significant reduction in the rate of local recurrence, and a 5% improvement in 3-year disease-free survival in the MRC CR07 trial, when SRT was combined with TME. However, SRT has the drawback of not producing a tumour shrinkage, and therefore it is unable to allow for a sphincter preservation in patients who are initially the candidate to an abdominoperineal resection (APR); moreover, due to its short duration, it is not suitable for combination with an effective cytotoxic treatment. In addition, there is a strong concern that SRT may cause more late complications, such as sexual dysfunctions and fecal incontinence, and an increased risk of second tumours.[6,7]

On the other hand, SRT compared to preoperative CRT did not result in an inferior rate of sphincter preservation, and appeared equally effective in preventing local recurrence in the Polish trial.[8] However, it should be noted that a postoperative adjuvant chemotherapy was more frequently delivered in the SRT arm (47% versus 31%, $P = 0.006$), as a consequence of the greater downstaging effect of the preoperative CRT, and this difference represents a confounding factor. Anyway, the benefit observed in these preoperative strategies did not translate in a significant reduction of the occurrence of distant metastases, and in an improvement of overall survival.

The data of retrospective analyses in patients with resectable rectal cancer have reported widely different recurrence-free and overall survival rates according to both the T and N extensions, raising the need of refining the selection of patients for different treatment strategies .[9] Moreover, in addition to the T and N stages, the key role of the CRM involvement in identifying patients with a poorer outcome, not only in terms of local and distant recurrence, but also as regards the overall survival, has clearly emerged in the last few years.[10] The worse prognosis of patients with low (less than 5 cm from the anal verge) rectal cancer has also been ascribed to the higher frequency of a CRM involvement, occurring for the natural 'coning-in' of the mesorectum in this anatomic site.[11] Interestingly, the data of the Dutch CKVO 95-04 and MRC CR07 trials have also demonstrated that a postoperative RT or CRT cannot sufficiently compensate for a positive CRM, supporting the need to achieve an R0 resection.[5,12] In the light of these findings, the prediction of a CRM involvement by a high resolution magnetic resonance imaging (MRI) plays an important role, leading to a better definition of the patient's prognosis, and avoiding unnecessary and potentially harmful treatment.[13] In this regard, it has been demonstrated that an MRI-based strategy, intensifying the preoperative treatment in the patients with a potential involvement of CRM, resulted in a significant reduction of pathologically positive CRM .[14] Moreover, the recent introduction of new MRI contrast agents (like the ultra small super paramagnetic iron oxide (USPIO) has shown that this technique may be very promising also for the detection of lymph node metastases.[15] Therefore, in the era of a preoperative approach, a staging with MRI should be mandatory for all patients with rectal cancer before any treatment decision is taken, because it may reduce the risk of overtreatment for patients with an early-stage tumour, whilst improving the identification of patients with a high-risk of recurrence.

A variety of phase II trials have shown that an intensified approach, combining different cytotoxic agents during preoperative pelvic radiotherapy in high-risk patients, led to a consistent increase of the pathological response rate, and of complete responses (pCR).[16–20] Yet, a high downstaging and pCR rate has also been achieved with a short intense regimen of chemotherapy before preoperative CRT, but an unpredictable rate of toxic deaths (5%) was reported, indicating that this approach should be used with caution, and restricted to clinical trials.[21]

However, the flaw of most of these studies is due to the heterogeneity of locally advanced rectal cancer patients included in these series, and to the lack of a standardised clinical and pathological assessment, which might have contributed to the reported high pCR rates. Moreover, the pCRs obtained after preoperative chemo-radiotherapy is not yet a validated surrogate end-point for the long-term outcome, whilst it remains to be defined whether an excellent pathological response has a true impact on the natural history of the disease, or it is merely associated with more favourable pretreatment characteristics of the patient and/or of the tumour. Furthermore, few studies have reported the long-term outcomes and the late toxicity of the combined treatment. Therefore, we still need prospective data to confirm that an intensified treatment of chemo-radiotherapy, achieving a higher rate of pCR, will also positively affect the overall survival of patients. Ongoing clinical trials will provide some insight into this important issue.

3. Selection of patients for the postoperative treatment

An other critical point, in the era of the preoperative approach, is the selection of patients for whom a risk-adapted postoperative chemotherapy should be delivered, considering that not all tumours respond uniformly to the preoperative treatment, and taking also into account the poor patient's compliance to a postoperative chemotherapy. Indeed, recent results of the EORTC 22921 trial failed to demonstrate a significant impact of postoperative chemotherapy on survival, although a late difference seemed to emerge at approximately 2 years for disease-free survival and at 4 years for overall survival.[1] This trend suggested that certain subgroups of patients may benefit from postoperative chemotherapy. A recently

published analysis of the EORTC trial reported that only patients showing a pathological downstaging after the preoperative treatment also benefited from the postoperative 5-FU-based chemotherapy.[22] However, this conclusion was drawn from an unplanned and underpowered subset analysis. Furthermore, the EORTC trial provided the intriguing finding that postoperative chemotherapy compensated for the lack of preoperative chemotherapy on local recurrence. Indeed, the 5-year local recurrence was 17.1% for patients who did not receive any chemotherapy, whilst it was about 8% for those who received some chemotherapy at any time.

A prognostic significance of the tumour regression grade (TRG) has been reported in a cohort of 406 rectal cancer patients treated with preoperative chemo-radiotherapy in the CAO/ARO/AIO 94 trial.[23] On the other hand, although the TRG was proven in this series to be prognostically valuable at the univariate analysis, a ypN+ resulted the strongest prognostic factor in the multivariate model.

The analysis of outcomes in the Polish trial has suggested that the persistence of nodal involvement after CRT could be due to chemo-radioresistance, resulting in the association with a greater potential for developing local recurrence and distant metastases.[24] The relevance of ypN has also been reported in a series of 95 patients treated with preoperative 5-FU-based chemo-radiotherapy followed by an R0 resection (and postoperative 5-FU-chemotherapy in 65 patients), in which only the ypN status resulted a significant prognostic parameter.[25] Interestingly, these investigators found that the 3-year disease-free survival for patients with ypN0 was excellent, regardless of whether they had received or not the postoperative chemotherapy (87.5% versus 87.7%), whereas patients with ypN2 status had a poor 3-year disease-free survival (30%) despite the postoperative chemotherapy. In conclusion, one might speculate that some patients likely do not require a postoperative treatment at all, whilst other patients actually need a more effective approach. Moreover, a recent study suggested that, after preoperative CRT, the proximal lymph node involvement was associated with a high incidence of metastatic disease at the time of surgery, indicating the prognostic importance of the distribution as well as of the number of lymph nodes involved.[26]

The major prognostic role of the pathological CRM involvement was also recently confirmed after a preoperative CRT. In that study, patients with borderline resectable or unresectable locally advanced rectal cancer were treated with preoperative long-course pelvic radiotherapy plus 5-FU-based chemotherapy: a significant difference was found both in 3-year disease-free survival (52% versus 9%, $P < 0.001$) and overall survival (64% versus 25%, $P < 0.0001$) between patients showing a pathologically negative CRM and those who did not.[27]

A careful histological assessment of the surgical specimens has been demonstrated to be a crucial point to obtain a correct prognostic information. Several studies have underlined that an accurate lymph node retrievement and assessment is mandatory, particularly when the tumour is staged as T3N0.[28] Moreover, a careful pathologic evaluation allows to assess the quality of surgery,[29] may be helpful in planning the post-surgical treatment, and may facilitate interstudy comparisons.

Finally, the possibility of a 'waiting and see' policy should be remembered, with surgery omission when a complete clinical response is obtained after preoperative CRT. However, there are a number of criticisms about this approach, which is based on incomplete and unclear data, also considering the difficulties of identifying patients that could avoid the surgical resection on the basis of a clinical and pathological (biopsy) assessment.[30]

However, an organ-sparing approach remains intriguing. In this regard, an interesting role in early predicting the tumour response has recently been advocated for the ^{18}F-FDG PET.[31] This imaging technique, performed 12 days after the beginning of CRT, has been demonstrated to predict the pathological response. These results are provocative, because an early identification of non-responder patients might prompt alternative treatment strategies, whilst allowing to plan a conservative surgical approach in patients with a prediction of a good pathological response. However, these new approaches require to be validated in large prospective studies.

4. Conclusion

In the last few years the common use of TME, and the shift from a postoperative to a preoperative chemo-radiotherapy approach, have substantially reduced the risk of local recurrence in locally advanced rectal cancer. Chemotherapy has been shown to play a relevant role in the management of this disease, but the integration of novel cytotoxic drugs and biologic agents in combined approaches should be widely explored, in an attempt to improve the disease downstaging and to control the distant spread. However, the key for a further improvement of the clinical management will be the accurate assessment of the disease, based not only on the clinical and pathological features but also on molecular and genetic markers,[32] for a 'risk-adapted' strategy of treatment. Moreover, early prediction of pathological tumour response by genomic approaches and imaging modalities could lead to further tailoring the rectal cancer management. Refinements of a multimodality therapy, in order to maximise the potential for cure and minimize the impact on the patients quality of life, will only derive from an integrated approach of a highly skilled multidisciplinary team.

Conflict of interest statement

None declared.

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