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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Road to organ preservation in locally advanced rectal cancer

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SUMMARY

Introduction In the past 20 years there has been significant change in the treatment of rectal cancer, especially in terms of multimodal approach. Surgery is, at least for now, the mainstay treatment for resectable rectal cancer. Preoperative chemoradiotherapy is, regardless of its modality, short or long course, different chemotherapeutic regiments, widely recommended for locally advanced rectal cancer. After neoadjuvant treatment, 15–27% of patients experience pathological complete response (pCR). These patients could benefit from non-operative management, thus avoiding potential surgical complications and possible reduction in the quality of life. Unfortunately, one cannot precisely define, while omitting surgery, which patients have pCR. For this reason Habr-Gama, a pioneer in the "watch-and-wait" strategy, developed a new endpoint for non-operative management – clinical complete response. To measure the response, in the absence of pathological examination, same diagnostic tools are used as in initial staging, but none is reliable enough to be used alone.

This article is focusing on critical points in the reassessment of response to preoperative chemoradiotherapy for advanced rectal cancer, which is mandatory for appropriate selection of patients who might benefit from non-operative management.

Keywords: rectal cancer; organ preservation; non-operative management; chemoradiation therapy; total neoadjuvant therapy, clinical complete response; pathologic complete response

INTRODUCTION

Surgery is, at least for now, the mainstay treatment for resectable rectal cancer. Anatomic description of total mesorectal excision emphasizing mesorectum, mesorectal fascia, and circumferential resection margin introduced by Heald et al. [1] in 1982 and the implementation of this technique, managed to reduce the incidence of local recurrence. In cases of locally advanced rectal cancer radiotherapy combined with surgery results improved in terms of local recurrence, and according to a Swedish trial even overall survival improved [2, 3]. Fluorouracil based chemotherapy was added for radiosensitising. According to a meta-analysis which included five studies, preoperative administration of combined chemo and radiotherapy offers better results than preoperative radiotherapy alone at five years in terms of local recurrence ($p < 0.001$), but without statistically significant difference in disease-free survival ($p = 0.27$) or overall survival ($p = 0.58$) [4]. A German rectal cancer study demonstrated superiority of preoperative administration of radiotherapy with concurrent chemotherapy, in comparison to the same regiment applied in the postoperative setting in terms of five-year local recurrence ($p = 0.006$), but also without statistical difference in overall survival (OS), disease free survival (DFS) and distant recurrence [5]. Fluorouracil-based chemotherapy is most widely used in a neoadjuvant setting, although in search of an ideal radiosensitizing agent, other drugs, such as oxaliplatin, capecitabine, and irinotecan, are being tested [6].

According to published data there seem to be no benefits from postoperative administration of fluorouracil-based chemotherapy in patients who already received preoperative chemoradiotherapy, since it doesn't offer better results in terms of local recurrence, OS, and DFS [7, 8]. The long-term results from of the EORTC 22921 study, after a median follow-up of 10.4 years, confirmed these results [9].

In order to clear the dilemma regarding short-course and long-course radiotherapy, a systematic review of 16 trials (12 in meta-analysis) was conducted in 2014. The authors concluded that there is no difference in local recurrence, DFS, and OS between patients treated with short-course preoperative radiotherapy with immediate surgery and long-course preoperative chemoradiotherapy, suggesting that short-course radiotherapy could be more convenient in centers with longer waiting lists or lack of medical resources [10].

Given these oncological results, regardless of its modality, short or long course, or different chemotherapeutic regiments, preoperative chemoradiotherapy is widely recommended for locally advanced rectal cancer.

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RESPONSE TO PREOPERATIVE CHEMORADIOTHERAPY

After preoperative chemoradiotherapy, 15–27% of patients have pathological complete response (pCR). According to Quah et al. [11], pCR is absence of any viable tumor cells in the resected specimen, irrespective of the proportions of necrosis and fibrosis. It can also be measured as tumor response grade (TRG) from 0 to 4 [12]. Some studies use the Mandard grading, which is adopted from the measurement of response in oesophageal cancer (grades from I to V). According to long-term results from CAO/ARO/AIO-94 trial, 10-year DFS for patients with TRG 4 is 89.5%, while for those with TRG 0 it is 1–63%. According to multivariable analysis, residual lymph node metastasis (ypN+) and TRG are independent prognostic factors for cumulative incidence of distant metastasis and DFS ($p = 0.039$) [13]. Similar results were published in 2008 on 119 patients treated with preoperative chemoradiotherapy for locally advanced rectal cancer, showing pCR of 14.2% [14]. In this study, response grades I or II according to Mandard are good indicators of DFS and are better prognostic factors than down-staging. The data from pooled analysis on 3,105 patients corroborated these results, showing five-year DFS of 83.3% for patients with pCR, and 65.6% for those without pCR ($p < 0.0001$), which could be the result of biological characteristics of the tumor [15].

Patients with pCR might be overtreated with surgery and there is a trend for strict surveillance and organ preserving in these cases. Unfortunately, we cannot precisely define while omitting surgery which patients have pCR. For this reason, Habr-Gama et al. [16] developed a new endpoint for non-operative management – clinical complete response (cCR), which is absence of clinically detectable residual primary tumor.

In a study from UK on 129 patients from two centers, only one third of patients who were deemed with cCR actually had pCR according to the Mandard classification [17]. The authors explain their reported rate of pCR (10.1%) with a different chemoradiotherapy protocol and with the interval to surgery, which was within four to eight weeks, since it is recognized that waiting beyond this point could result in better response [17]. Escalating radiation doses may also have influence on tumor response but at the same tame could compromise functional outcome [18]. The role of other radiotherapy techniques in improving response is beyond the scope of this paper.

In 2016, two meta-analyses were published on the subject of interval to surgery, with pCR as the primary endpoint, while DFS, OS, and sphincter preservation were secondary endpoints. A meta-analysis from Italian authors included 13 prospective and retrospective studies with 3,587 patients [19]. According to their results, pCR improved by 5.8% when the interval to surgery was longer than six to eight weeks, without compromising OS and DFS and with similar complication rates and sphincter preservation. A systematic review and meta-analysis by Wang et al. [20] included 15 retrospective studies with 4,431 patients and pCR ranging from 8.3% to 28%. The highest pCR rates were recorded in patients operated on beyond eight weeks after the end of chemoradiotherapy, which was associated with an approximately 49% higher chance for pCR compared to patients who were operated on earlier. Prolonging the interval beyond 10 or 12 weeks did not offer further advantages and also didn't affect survival or rate of sphincter spearing procedures [20].

PREDICTORS OF RESPONSE

A number of retrospective studies were undertaken in an attempt to identify predictive factors of response to neoadjuvant treatment using simple blood tests (hemoglobin, Ne/Ly ratio, albumin, and fibrinogen), biomarkers (Ki67 and thymidylate synthase and EGFR expression, wild-type p53 status, microRNA, etc), morphological characteristics of the tumor, and the distance from the anal verge or certain imaging features [21–28]. Few of them are reproducible. Results from several studies showed that the N stage is a predictor of response to preoperative chemoradiotherapy [23, 29]. According to Russo et al. [30], the absence of mutation of commonly mutated cancer genes may be associated with a higher likelihood of having a pCR. In the same study, the level of CEA ≤ 2.5 and smaller tumor size were predictive factors of pCR. Other studies have also found decreasing tumor size to predict response, thus suggesting it should be considered as a valid parameter for selecting patients for organ preserving [29]. The level of CEA either at diagnosis or post-chemoradiotherapy is also an independent risk factor for response according to several retrospective studies [28, 29, 31]. A recently published study by Probst et al. [32], which included data on 18,113 patients retrieved from the National Cancer Database, showed that high CEA at diagnosis was independently associated with decreased pCR response ($p < 0.001$), pathological tumor regression ($p < 0.001$), tumor downstaging ($p < 0.001$), and OS ($p < 0.001$). According to these results, patients with increased pretreatment levels of CEA are not good candidates for organ preservation.

CRITICAL POINTS IN REASSESSMENT

In an ideal scenario, one could be able to identify patients with complete response in the restaging process and select patients for non-operative management, thus avoiding operation and possible early or late morbidity, reduction in the quality of life, especially in cases where permanent colostomy is needed. For reassessment, in the absence of pathological examination, the same diagnostic tools are used which were available for initial staging [digito-rectal examination (DRE), proctoscopy, and imaging techniques]. Concordance between DRE and pathologically based assessment of response to preoperative chemotherapy was investigated in a prospective study by Guillem et al. [33] in 94 patients with locally advanced rectal cancer. After a median interval of 48 days from the completion of therapy, the patients were referred to surgery and under anesthetics the same surgeon who performed the initial

assessment performed comprehensive DRE. DRE underestimated the response in 73 patients (78%), overestimated it in none, and was able to identify only 21% of patients with pCR. The overall concordance of DRE and pathologic response was only 22%. The specificity of clinical examination in determining complete or near-complete pathologic response (≥ 90% tumor regression) was 56%, the sensitivity was 24%, and positive and negative predictive value was 19% and 61%, respectively, while the accuracy was 49%.

Proctoscopy further allows visual confirmation of digital findings. Habr-Gama et al. [34] provided a comprehensive overview of clinical and endoscopic features in cCR and proposed further standardizations. According to this overview, any residual finding needs surgical attention, from excision to more radical surgery, while biopsies are not recommended. Patients with cCR should have no more than whitening of the mucosa, telangiectasia with mucosal integrity to be considered for the organ preserving approach [34]. However, data from a retrospective study conducted by Smith et al. [35] showed that only 16 out of 61 patients with pCR had mucosal irregularity and by that fulfilled the criteria for cCR. On the other hand, six out of 22 (27%) patients with mucosal cCR still had the residual disease. Han et al. [36] also tried to determine the correlation between endoscopic findings and ypT in a retrospective study which included 481 patients. Pathological good response was defined as ypT ≤ 1. Patients were randomized either into the testing or the validation group. The validation was done using endoscopic findings determined in the testing group. Endoscopic features that correlated with good pathological response were scaring, telangiectasia, and erythema, while nodule, ulcer, stricture, and remnant tumor were signs of minimal or no response. The kappa statistic for interobserver model was 0.965. This classification system showed high specificity and negative predictive value but low sensitivity and positive predictive value, implying that it can strongly predict patients with minimal or no response but is less able to identify good response. They further suggest that these criteria could be helpful in selecting candidates for local excision (LE) [36].

Whether or not local excision is necessary is still debatable. Issa et al. [37] reviewed results from 31 patients with cCR who underwent LE (transanal excision or transanal endoscopic microsurgery) after neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Twenty-three patients had ypT0 while in eight patients the residual disease was found. After median follow up of 87 months, three patients died from other causes. No distant or local recurrences were observed in remaining patients [37]. Accurate selection of patients for LE is still lacking, while salvage radical surgery can be challenging [38]. A recent systematic review and meta-analysis compared the outcome of patients after preoperative chemoradiotherapy followed by LE, with patients who had radical surgery after neoadjuvant treatment [39]. Local recurrence rate was higher with LE, although it didn't reach statistical significance (p = 0.40). There was no difference in 10-year OS (p = 0.93). The same results were obtained for the subgroup with T3 / any N stage tumors. After LE, the status of the mesorectal lymph nodes remains unknown. The reported median rate of lymph node metastases in patients with pCR is 7%; thus, mucosal response should not be the single factor for patient selection. Patients with understaged nodal involvement and LE have poorer outcome, since lymph node status is the most important prognostic factor in rectal cancer. The biggest challenge is to adequately evaluate lymph node status after preoperative chemoradiotherapy and this is the basis for criticism in organ preserving [40].

Reassessment is further performed using imaging techniques like computed tomography (CT), endorectal ultrasound or magnetic resonance imaging (MRI). Conventional MRI is less accurate for reassessment than initial staging, mostly due to the difficulty in distinguishing fibrosis, oedema, and normal mucosa from small foci of a residual tumor [41]. According to a meta-analysis, conventional ultrasound and MRI are unreliable for both T and N stage. In T2-weighted imaging, fibrous tissue as a result of chemoradiotherapy may be indistinguishable from the tumor [42]. Diffusion-weighted imaging MRI (DWI-MRI) is helpful in distinguishing residual viable tumor from treatment-related changes and can depict microstructural and metabolic treatment-induced changes of the tumor before morphological changes become apparent. It allows performing quantitative measures such as apparent diffusion coefficient (ADC), which may be useful as an imaging biomarker of tumor characteristics [43]. In order to investigate the added value of qualitative DWI-MRI evaluation in assessment and to evaluate the diagnostic performance of ADC measurements, Foti et al. [44] conducted a single-institution study including 31 patients with locally advanced rectal cancer. The pCR rate was 16.1%. According to their results, diagnostic performance of added DWI-MRI to conventional MRI was better than MRI alone. Sensitivity improved from 20% to 80%, negative predictive value from 87.5% to 96.6%, and accuracy from 87.9% to 99.6%. In three cases the interpretation of additional DWI-MRI allowed corrections of diagnostic errors made on the basis of conventional MRI interpretation alone, differentiating viable tumor from fibrosis. Additionally, according to their results, pretreatment examination ADC value has a potential to predict treatment response, suggesting that the change in ADC values has the potential to provide a surrogate biomarker of treatment response in rectal cancer [44]. Guillem et al. [45] in a prospective study compared the ability of fluorodeoxyglucose positron emission tomography (FDG-PET) and CT in detecting pCR, whose rate was 21%. These procedures failed to adequately distinguish a pCR from an incomplete response; also none of the PET parameters like mean or standard uptake value, total lesion glycolysis, are accurate for distinguishing pCR from incomplete response [45]. In a paper by Joye et al. [46], 14 relevant studies on the role of DWI and FDG-PET/CT in the assessment of pCR after chemoradiotherapy were systematically reviewed. Pooled analysis showed that qualitative DWI assessment had a higher accuracy in predicting pCR than quantitative analysis (87% vs. 74–78%), but sensitivity of ADC measurements are higher than qualitative DWI assessment (78–80% vs. 53%).

Quantitative and qualitative FDG-PET/CT has a similar predicting response. The ability of functional imaging to predict pCR is affected by the interval between the end of chemoradiotherapy, reassessment, and surgery. Generally, a low pretreatment ADC, an increase in ADC, and a decrease in standardized uptake value are associated with better response to radiochemotherapy. Pooled analysis shows that qualitative DWI assessment 5–10 weeks after the end of radiochemotherapy outperforms ADC-based DWI parameters. They conclude that DWI and FDG PET/CT are not accurate enough to safely select patients for organ preservation [46].

ROAD TO ORGAN PRESERVATION

Several studies published their results with watch-and-wait policy, including the pioneering work of Habr-Gama, with promising results in terms of oncological safety, although most are retrospective in nature [47–51]. Conclusions are similar: larger number of patients included in prospective analysis is required, longer follow-up is needed, and selection criteria must be strict, as well as the protocol of surveillance. In the largest study published so far, 229 patients with surgical resection after preoperative chemoradiotherapy and 129 patients with cCR who were managed with watch-and-wait were matched for the T stage, age, and performance status (109 patients in each group) [52]. More than 60% of patients in the watch-and-wait group avoided major surgery without compromising oncological safety, compared to the group with surgical resection. Patients managed by the watch-and-wait strategy had a significantly better three-year colostomy-free survival rate than those who had surgical resection. Reassessment after preoperative chemoradiotherapy and selection of patients who might benefit from the watch-and-wait strategy still remains a critical issue.

Although advantages of the watch-and-wait strategy are reduced stoma requirements, improved functional results, and avoidance of major surgery, this approach has its weakness. Disadvantages over surgery are the following: difficulties in determining clinical stage 0, follow-up is imperative, as is surgeon–patient confidence [53]. It's rather difficult to conduct randomized trial in a situation where informed patients would have their own preferences.

In lack of randomized control trials and in order to provide solid evidence on organ preservation in rectal cancer, in 2014, a group of experts following their meeting in Lisbon created the International Watch & Wait Database (IWWD), which should provide more information on individualized risk with this approach. This is especially important for motivated patients who are willing to trade unknown oncological risk for a good quality of life. The decision making process is less complicated for high-risk elderly patients than for the young and fit [54]. The results are awaited.

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Пут ка презервацији органа код узнапредовалог карцинома ректума

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САЖЕТАК

У последњих двадесетак година дошло је до значајних промена у лечењу карцинома ректума. Хирургија представља методу избора у лечењу ресектабилног карцинома ректума. Преоперативна хемиорадиотерапија је широко прихваћена у лечењу локално узнапредовалих тумора ректума. Након неоадјувантне терапије код 15–27% болесника долази до комплетног патолошког одговора. Ови болесници могу имати користи од неоперативног лечења, избегавајући потенцијалне хируршке компликације и могуће смањење квалитета живота. Нажалост, не може се прецизно, без операције, дефинисати комплетан патолошки одговор. Из овог разлога је Хабр-Гама развила нови циљ неоперативног лечења – комплетан клинички одговор. За процену одговора, у одсуству патохистолошког налаза, користе се исти дијагностички поступци као и при иницијалном стадирању, али ниједан није довољно поуздан да би се користио самостално. Овај рад се фокусира на критичне моменте у процени одговора на преоперативну хемиорадиотерапију код узнапредовалих карцинома ректума, која је неопходна у правилном одабиру болесника који могу имати користи од неоперативног лечења.

Кључне речи: карцином ректума; презервација органа; нехируршко лечење; хемиорадијација; тотално неоадјувантно лечење, клинички комплетни одговор; патолошки комплетни одговор