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Review article

Total neoadjuvant therapy for rectal cancer

Thérapie néoadjuvante totale pour le cancer rectal

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ABSTRACT

While outcomes for patients with locally advanced disease have improved considerably with combined modality therapy, there is now an emphasis on developing risk-adapted treatment strategies. Moreover, the primary cause of death from locally advanced rectal cancer is related to distant progression, which now exceeds the rate of local failure. Thus, the necessity to optimally address micrometastatic disease has led to increasing interest in delivering chemotherapy in the neoadjuvant setting rather than in the post-operative setting. This review critically appraises the emerging literature on the options for sequencing of therapy, focusing on the total neoadjuvant therapy paradigm as well as emerging options for omitting components of multimodality therapy.

Mots clés :
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RÉSUMÉ

Alors que les résultats obtenus chez les patients atteints d'une maladie localement évoluée se sont considérablement améliorés avec les associations thérapeutiques, l'accent est maintenant mis sur le développement de stratégies de traitement adaptées au risque. En outre, la cause principale de décès due à ce cancer rectal est liée à la progression à distance, dont le taux dépasse maintenant celui d'échec local. Ainsi, la nécessité d'aborder de manière optimale la maladie micrométastatique a conduit à un intérêt croissant pour la délivrance de la chimiothérapie dans le cadre néoadjuvant plutôt que dans celui postopératoire. Cette revue évalue de manière critique la littérature émergente sur les options pour le séquençage du traitement, en se concentrant sur le paradigme de la thérapie néoadjuvante totale ainsi que des options émergentes pour omettre des composants de la thérapie multimodale.

1. Introduction

The therapeutic approach for locally advanced (stage II or III) rectal cancer has evolved over the last three decades from upfront surgical resection to multimodality therapy incorporating chemotherapy, radiation therapy and high-quality surgery using the total mesorectal excision technique. While outcomes for patients with locally advanced disease have improved considerably with combined modality therapy with 5-year survival upwards of 75% [1], there is now an emphasis on developing risk-adapted treatment strategies. Moreover, the primary cause of death from this rectal cancer is related to distant progression, which now exceeds the rate of local failure. Although there is controversy about the impact of adjuvant chemotherapy on outcomes in rectal cancer [2,3], the necessity to better address microscopic metastatic disease has led to a growing interest in moving systemic therapy earlier in the sequencing of treatment. This review summarizes the progress in the management of locally advanced rectal cancer based on clinical trials and critically appraises the emerging literature on the options for sequencing of therapy and even omitting components of multimodality therapy. With the expanding management options, a number of important questions remain regarding how to better

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individualize use of multimodality therapy for patients with stage II or III rectal cancer, in particular with regard to predicting response to therapy and identifying the appropriate timing and sequencing of therapies.

2. Standard neoadjuvant chemoradiation

Since 1990, when the National Institutes of Health (NIH) issued a consensus statement [4], the standard management approach for patients with stage II or III rectal cancer (T3/T4 or node positive) has been a radical rectal resection, either a low anterior resection or abdominoperineal resection, combined with (neo)adjuvant chemoradiation and adjuvant chemotherapy. This paradigm was established after multiple prospective randomized trials in the 1970's and 1980's demonstrated a benefit to 5-fluorouracil-based adjuvant chemoradiation in reducing local recurrence rates over surgery alone, from 30 to 60% for locally advanced rectal cancer to 10 to 12% with adjuvant 5-fluorouracil-based chemoradiation [5,6]. The sequencing of therapy was further refined by The German Rectal Cancer Study, which established the superiority of preoperative versus postoperative administration of chemoradiation in terms of improved local control and greater chances of sphincter-preservation [1,7]. Thus, since the publication of the German Rectal Study in 2004, the standard of care in most countries has been preoperative chemoradiation followed by surgery using a total mesorectal excision and adjuvant chemotherapy. Nonetheless, the 10-year cumulative incidence of distant metastases was 30% and the 10-year disease-free survival was 68% for patients on both arms of trial [7]. The risk of distant failure now greatly exceeded the risk of local failure (10-year cumulative incidence of 7% on the preoperative arm). Thus, in order to truly impact on disease-free survival, there was a clear need to achieve better control of systemic disease.

3. Role of systemic therapy in rectal cancer

Adjuvant chemotherapy has been a standard part of the multimodality approach for patients with locally advanced rectal cancer and has been included in the United States National Comprehensive Cancer Network (NCCN) guidelines. However, this recommendation is an extrapolation from the data for adjuvant therapy for colon cancer that showed a survival benefit of 6 months of 5-fluorouracil-based chemotherapy [8,9]. The data for adjuvant chemotherapy for rectal cancer have been less conclusive. The four-arm phase III randomized EORTC 22921 trial evaluated the addition of 5-fluorouracil chemotherapy to preoperative radiotherapy as well as the benefit of adjuvant 5-fluorouracil chemotherapy. With over 1000 patients, this study failed to show a benefit in cumulative incidence of distant metastases, progression-free survival or overall survival [10]. Three more recent randomized trials have also been performed to evaluate this question, unfortunately, two were closed early due to poor accrual, but none of the studies demonstrated an improvement in survival with adjuvant therapy. The Chronicle trial randomized 113 of a planned 800 patients from the United Kingdom (UK) following 5-fluorouracil-based chemoradiation and curative resection to observation or six cycles of capecitabine and oxaliplatin (XELOX) [11]. The 3-year disease-free survival was 78% with XELOX and 71% with observation ($P = 0.56$) and the 3-year overall survival for XELOX and observation were 89% and 88%, respectively [11]. Similarly, the Dutch PROCTOR-SCRIPT phase III trial randomized pathologic (yp) stage II or III rectal cancer patients after preoperative chemoradiation or short-course radiotherapy followed by total mesorectal excision to observation or adjuvant 5-fluorouracil or capecitabine [12]. The study was powered to detect an improvement in 5-year overall survival of 10%. Unfortunately, the study was closed early due to poor accrual and with 437 of a planned 840 patients, there was no significant difference in 5-year overall survival (79.2% in the observation group and 80.4% in the chemotherapy group). Furthermore, no significant differences were demonstrated in disease-free survival, local or distant recurrence rates [12]. Italian investigators completed a phase III randomized study in 655 patient locally advanced cancer of the rectum (clinically T3–4, any N) treated with chemoradiation and surgery, who were randomized to observation or six cycles of adjuvant 5-fluorouracil and folinic acid [13]. This study was powered to detect an improvement of 10% in 5-year overall survival. However, with a median follow-up of 64 months, there was no difference in the 5-year overall survival rate, 70% in the observation arm and 69% in the adjuvant chemotherapy arm ($P = 0.77$). There was also no difference in 5-year disease-free survival (63% v. 65% for adjuvant chemotherapy; $P = 0.88$) or in the occurrence of distant metastases (21% v. 20% in the adjuvant chemotherapy arm) [13].

Two meta-analyses were performed to address the concern regarding poor accrual on two of the randomized trials have also failed to demonstrate a survival advantage for adjuvant chemotherapy for patients with rectal cancer [2,3]. In one meta-analysis, individual patient data were obtained and analysed [2]. This study demonstrated in a subgroup analyses that patients with tumors 10 to 15 cm from the anal verge, there was improved disease-free survival and fewer distant metastases with adjuvant therapy. A third meta-analysis of over 3000 patients suggested that a more individualized approach based on histologic response may be more appropriate since patients with a pathologic complete response after chemoradiotherapy may not benefit from adjuvant chemotherapy, whereas patients with residual tumour had superior outcomes when adjuvant chemotherapy was administered [14].

As might be expected, in the postoperative setting after neoadjuvant chemoradiation and radical rectal resection, the adherence with adjuvant chemotherapy is low, ranging from 43% to 74% of patients on the randomized trials completing all cycles of chemotherapy. This may have impacted on the benefit of the therapy in these intent-to-treat trials.

4. Intensifying neoadjuvant therapy

Given the limitations of administering adjuvant chemotherapy for patients with locally advanced rectal cancer, there have been attempts to intensify neoadjuvant chemoradiation with the addition of oxaliplatin to concurrent 5-fluorouracil or capecitabine and pelvic radiotherapy with the intent of both delivering more effective systemic therapy during chemoradiation and enhancing radiosensitization of the tumor cells to maximize pathologic complete response [15–18]. The addition of oxaliplatin to 5-fluorouracil-based adjuvant chemotherapy had been shown to improve disease-free survival in stage II and III colon cancer in the landmark MOSAIC trial and NSABP C-07 trial [19–21]; thus, there was rationale for evaluating the addition of oxaliplatin to multimodality therapy for locally advanced rectal cancer to improve both treatment response and disease-free survival. The incorporation of oxaliplatin with preoperative chemoradiation was investigated in five randomized controlled trials: STAR-01, ACCORD 12, NSABP R-04, the German CAO/ARO/AIO-04, and the PETACC 6 study. Disappointingly, the addition of oxaliplatin to 5-fluorouracil or capecitabine during radiotherapy increased toxicity without improving tumor response in four of the five studies [15–18,22]. The studies had conflicting results in terms of the long-term oncologic outcomes with the addition of oxaliplatin, with no significant improvement in 5-year disease-free survival or overall survival in the ACCORD 12 trial [23], while there was a significant benefit in

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