



Review Article

Organ preservation in rectal cancer – Challenges and future strategies

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ABSTRACT

Neoadjuvant radiochemotherapy with subsequent total mesorectal excision is the standard of care for locally advanced rectal cancer. While this multimodal strategy has decreased local recurrences rates below 5%, long-term morbidities are considerable in terms of urinary, sexual or bowel functioning. At the same time approximately 10–20% of patients have no evidence of residual tumour in their surgical specimen. Pioneering studies from Brazil have suggested that surgery can safely be omitted in carefully selected patients with a clinical complete response after radiochemotherapy. Although confirmatory studies showed similar results, challenges in terms of optimizing radiochemotherapy for organ-preservation, appropriate selection of patients for non-operative management and the safety of this approach remain. The present review will summarize the current data on organ-preservation in rectal cancer and discuss the challenges that need to be addressed in future trials.

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Introduction

Over the last decades, locally advanced rectal cancer has transitioned from a disease with local failure rates of up to 40–50% [1], to one with local control rates that have been as high as 98% after three years in recent trials [2]. These impressive results have mainly been achieved through increasingly aggressive therapies in all involved treatment modalities. In surgery, the introduction of total mesorectal excision (TME) has dramatically decreased local recurrence rates [3]. For low lying tumours, extralevatoric abdominoperineal excision has been proposed as an even more radical treatment compared with “standard” abdominoperineal excision [4]. The addition of chemotherapy [5] and the shift of radiochemotherapy from the post- to the preoperative setting have been game-changers further decreasing failure rates [6]. However this excellent oncological outcome comes with a price. For patients with low lying tumours sphincter preservation is not feasible in most cases and a permanent colostomy is required. But even for patients with tumours in the middle rectum long-term morbidities after trimodal therapy are considerable [7,8]. Efforts to identify subgroups of patients who might be candidates for less aggressive treatment without compromising oncological safety are the logical consequence. For this purpose, two major approaches have emerged. One is the omission of radiotherapy based on pretherapeutic magnetic resonance imaging (MRI) defined selection criteria or the selective use of radiotherapy for patients with poor response to induction therapy [9,10]. The second strategy is the omission of surgery in patients with a clinical complete response (cCR) after radiochemotherapy. The present review will discuss the concept and data on organ-preservation with the selective use of surgery in locally advanced rectal cancer and address challenges we are faced with in order to further establish and refine this strategy in the future.

Early data on organ preservation in rectal cancer – two key studies

Data from a single institution in Sao Paulo/Brazil dominated the literature on organ-preservation in rectal cancer for years. In 2004 Habr-Gama et al. reported a retrospective analysis of 71 patients who had achieved a cCR after radiochemotherapy and did not undergo subsequent surgery. Oncological outcome in this study was excellent with only two patients developing locoregional recurrences which both could be successfully salvaged by resection or brachytherapy. Overall survival in patients who had achieved a clinical complete response was 100% after five years. By definition in this study patients were only considered as clinical complete responders if a clinical complete response was sustained for a minimum of 12 months, which made this patient cohort a highly selected subgroup [11]. However, Habr-Gama and colleagues published updated analyses with additional patients, longer follow-up and more detailed recurrence patterns in 2006 and 2014 suggesting the safety of the organ-preservation approach. In the report published in 2006, 122 out of 361 patients (34%) had an “initial cCR” at 8 weeks after completion of radiochemotherapy. Of these 122 patients, 23 developed local regrowth within the first 12 months and were excluded from further analysis after undergoing immediate surgery. The remaining 99 patients met the definition for a “sustained cCR”. After a median follow-up of 59.7 months only 5 of these 99 patients developed isolated local recurrences that were all successfully salvaged by either radical surgery, local excision or brachytherapy. A total of 7 distant and one combined recurrence (local and distant) yielded a promising five-year overall and disease-free survival of 92.7% and 85.0% respectively [12].

In 2011 the first prospective study on organ preservation in rectal cancer was published by Maas et al. In contrast to previous reports

strict criteria for a clinical complete response were defined. At restaging 6–8 weeks after 5-Fluorouracil (5-FU) based radiochemotherapy it was required that no residual tumour was visible on MRI with diffusion weighted imaging (DWI) and the only endoscopic finding that was compatible with a cCR was a “small residual erythematous ulcer or scar”. With these very strict criteria only one of 21 patients who had qualified for non-operative management developed an isolated local regrowth that could successfully be salvaged with secondary surgery. The cumulative probability for disease free survival (DFS) after a median follow-up of 23 months was 93%. Compared with patients who had not achieved a cCR and underwent surgery, scores for bowel functioning were significantly higher indicating less toxicity. However, at the same time the very careful selection process based on endoscopic and MRI findings resulted in a cCR rate of only 10.9% and 75% of the pathological complete responses after surgery were missed on restaging after radiochemotherapy [8]. Based on the low sensitivity to predict a pCR with the very strict definition of a clinical complete response, the group defined criteria for a “near-complete response” that should qualify more patients for an organ-preservation approach. Indeed, out of the total 100 patients reported in an updated publication of the study group as many as 39 patients had qualified for organ preservation after having a “near-complete response” on initial evaluation after radiotherapy. Interestingly, 24 of these 39 patients met criteria for “complete response” on re-evaluation three months after the first evaluation [13].

Challenge 1: how low can we put the threshold?

Applying a lower threshold to define a patient as a clinical complete responder will inevitably result in a higher rate of local regrowth. After introducing the “near clinical response” in the Dutch study 15 of 100 patients developed local regrowth (12 luminal, 3 nodal), while with the more conservative definition of a cCR in the earlier report only 1 of 21 patients had failed locally. A close follow-up protocol allowed the early detection and successful salvage of all isolated local recurrences except one.

Similar data has been reported by Appelt et al. In this prospective Danish trial 40 of 51 patients (78%) with distal rectal cancer achieved a cCR. The dose-escalated radiotherapy regimen consisted of 60 Gy in 30 fractions with concomitant oral tegafur-uracil and an additional 5 Gy boost delivered by brachytherapy. The definition of a cCR was exclusively based on endoscopic findings plus negative biopsies from the former tumour site. MRIs were performed however had no role in the reevaluation of the primary tumour. With this strategy 25.9% of patients classified as clinical complete responders developed local recurrences with 100% of these being resected with clear margins [14].

Renahan et al. report on 129 patients with a cCR after radiochemotherapy and non-operative management. Again the definition of a cCR was mainly driven by findings at endoscopy or digital rectal exam and the role of imaging studies was solely the evaluation of the mesorectal space and pelvis. In this study the actuarial local regrowth rate was 38% after three years. Salvage treatment was performed in 36 of 41 patients with isolated local recurrences. Three of the five patients without salvage surgery were not considered fit enough for major surgery. It is not clear whether these patients were initially considered to be suitable for surgery at all. The remaining two of five patients without salvage treatment refused salvage surgery. In a propensity-score matched analysis based on pretherapeutic parameters, patients treated with a non-operative approach had superior outcome in terms of disease-free survival, overall survival and colostomy-free survival [15].

The existing data suggests that a rather low threshold for the definition of a clinical complete response may be justified, how-

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