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 Paolo/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 regrowths 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-Flourouracil (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 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 I: 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].

Renehan 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-

ever this will happen at the price of higher local regrowths and patients need to be informed about the absolute necessity of follow-up investigations in short intervals.

Challenge II: strategies to maximize the pathological complete response rate

Prolonging the interval between radiochemotherapy and response assessment

The most commonly used time interval between completion of preoperative CRT and surgical resection has traditionally been 4–6 weeks. For many years the Lyon R90-01 study was the only randomized trial in which patients with locally advanced rectal cancer treated with preoperative RT (39 Gy in fractions of 3 Gy) were randomly assigned to have surgery at two different time intervals following radiotherapy: after 2 weeks or after 6–8 weeks. The longer interval resulted in a higher response rate compared to the 2-week interval (pathologic downstaging 10.3% vs. 26%, $p = 0.005$) and a trend towards a higher pCR rate (7% vs. 14%, $p = 0.166$) [16]. Several retrospective series have addressed longer interval as a predictor of tumour response, surgical morbidity, and long-term outcome. In a series of 132 patients with locally advanced rectal cancer, Tulchinsky et al. found that patients operated more than 7 weeks after CRT had similar rates of perioperative complications as compared to patients operated on less than 7 weeks after CRT, however, the longer CRT-to-surgery interval was associated with significantly improved pCR rates (35% vs. 17%, $p = 0.03$) and significantly higher disease-free survival [17]. These results were confirmed by Kalady et al. who found a 31% pCR rate in patients receiving surgery more than 8 weeks after CRT compared to 16% in patients operated on within 8 weeks of CRT [18]. In an attempt to prospectively validate this very promising data the GRECCAR-6 trial randomly assigned 265 patients to surgery after either 7 or 11 weeks from the end of preoperative radiochemotherapy. The study was designed to detect an increase of the pCR rate from 12% to 26%. However, the study failed to show an impact of a longer waiting period on the pCR rate. The pCR rate was 15% in the 7-week arm and 17.4% in the 11-week arm. To some extent this unexpected result might be caused by the higher number of protocol violations in the 7-week arm as 20.8% of the patients in the 7-week arm underwent surgery later than planned compared with 8.6% in the 11-week arm [19]. Yet a meta-analysis and registry studies published after the launch of GRECCAR-6 suggest a less relevant role of the interval between the end of radiochemotherapy and surgery below 10% [20,21]. Based on these published studies, the sole prolongation of the interval is unlikely to qualify a relevantly higher number of patients for a non-operative treatment approach of their cancer. On the other hand, this is challenged by early data from a prospective, randomized British trial showing an increase of the pCR rate from 9% to 20% in patients undergoing surgery 6 weeks after the end of radiotherapy compared to patients with surgery after 12 weeks [22]. Final and more detailed results from this trial might lead to a re-appraisal of this approach.

One of the concerns associated with postponing surgery beyond 6–8 weeks is that patients who have only poorly responded to treatment remain untreated in the interval and may progress. A strategy to circumvent this issue is to "fill" the waiting period with systemic treatment. Gao et al. report a prospective trial in which 51 patients with locally advanced rectal cancer received a neoadjuvant "sandwich treatment" consisting of one cycle of induction CAPOX prior to radiochemotherapy with 2 concomitant cycles of CAPOX and one cycle of CAPOX between the end of radiochemotherapy and surgery which took place 6 to 8 weeks after the last fraction of radiotherapy. The authors reported an impressive 42.2% pCR rate with an acceptable toxicity profile [23]. Similarly "*The Timing of Rectal Cancer Response to Chemoradiation Consortium*" in the United States designed a prospective phase II trial of preoperative CRT (50.4–54 Gy with 225 mg/m²/day continuous infusion 5-FU during RT) with additional cycles of chemotherapy (modified FOLFOX6) during the waiting period before surgery. Patients were treated in 4 different groups: the first group of patients underwent surgery 6–8 weeks after the completion of radiochemotherapy (group 1) while patients in groups 2–4 received additional 2, 4 or 6 cycles of mFOLFOX6 before undergoing surgery. The pCR rate increased continuously from 18% in group 1 to 25%, 30% and 38% in groups 2, 3 and 4, respectively. Surgeons noted an increase in pelvic fibrosis with a prolonged interval however this did not translate into a higher surgical difficulty [24]. While the advantage of this approach of consolidative chemotherapy and delayed surgery with regards to tumour downstaging is obvious, the increased degree of fibrosis at the time of surgery is a caveat. In the GRECCAR-6 trial patients in the delayed surgery group had a significantly lower rate of optimal mesorectal resection (90% in the 7 week group vs, 78.7% after 11 weeks, $p = 0.016$). Unfortunately, the quality of the mesorectal resection is not reported in the TIMING trial. Taken altogether, the approach to prolong the interval between the end of radiotherapy and surgery and filling the interval with additional chemotherapy seems highly promising and has the potential to increase the proportion of patients who may safely omit radical surgery. This concept is currently tested in two randomised trials (NCT02008656, NCT02363374).

Beyond 5-FU: alternative chemotherapy regimens

Based on the positive results from colon cancer adjuvant treatment studies [25], there was a great interest to test the efficacy of oxaliplatin in the setting of preoperative radiochemotherapy. The German CAO/ARO/AIO-04 study has been positive both in terms of increased pCR rates and 3-year disease free survival with the use of oxaliplatin both concomitantly with preoperative 5-FU-based radiotherapy and postoperatively. The addition of oxaliplatin with the doses and intensities applied in the CAO/ARO/AIO 04 was well tolerated and associated with high compliance [26]. Meta-analyses indicated that oxaliplatin added to preoperative radiochemotherapy may indeed increase pCR rates and disease-free survival in selected patients, but also enhances acute toxicity [27,28]. However, given the contradictory results and lack of a clear long-term oncological benefit in the 7 randomized trials testing this combination so far, oxaliplatin as a radiosensitizer is not currently recommended to be routinely added to 5-FU-based preoperative radiochemotherapy [26,29–36].

While 5-FU based chemotherapy is the backbone of concomitant radiochemotherapy several other agents have been tested in addition to 5-FU in order to improve both early endpoints such a pathologic response rates and as well long-term outcomes. In particular molecularly targeted agents have been extensively studied [37]. While most of the agents, particularly the EGFR inhibitors, had failed to show a relevant impact on response and survival endpoints, there have been concerns about increased postoperative morbidities with others, particularly the VEGF-inhibitors [38–41].

Heating the tumour – hyperthermia for rectal cancer

Another strategy to enhance the local effects of radiochemotherapy is deep regional hyperthermia. A meta-analysis of 5 prospective phase II or phase III studies by the Cochrane Collaboration showed a significant increase in pathological complete response rates for combined radiotherapy with deep regional hyperthermia compared with radiotherapy alone [42]. Regarding trimodal neoadju-

vant treatment with radiochemotherapy and hyperthermia interim data from a prospective phase III study showed partial and complete responses in 66% of patients treated with additional hyperthermia compared with 49% of patients treated with radiochemotherapy only [43]. Furthermore, Schroeder et al. report a pCR rate of 16.4% in patients treated with preoperative 5-FU based radiochemotherapy and deep regional hyperthermia. On subset analysis this number increased to 22.5% when only patients with at least four hyperthermia treatments were included [44]. Further long-term follow-up in these patients was promising compared with patients who had been treated with radiochemotherapy only [45]. Maluta et al. achieved a pCR rate of 23.6% with an oxaliplatin-based high dose radiochemotherapy regimen plus deep regional hyperthermia [46]. Two prospective trials aiming to reproduce this retrospective data are currently ongoing [47,48].

Dose escalation

It is intuitive to consider dose escalation an appropriate intervention to improve clinical and pathological complete response rates. Indeed, Appelt et al. showed a clear dose–response correlation by pooled analysis of data from two prospective trials with different degrees of dose escalation [49]. In a subsequent prospective organ preservation trial in patients with early low lying rectal cancer (cT2-3, cN0-1) the same group tested a dose escalated radiochemotherapy protocol with 60 Gy in 30 fractions and a subsequent 5 Gy brachytherapy boost and found a cCR of 71%. This number is highly impressive despite the fact that 35% patients had stage I and presumably smaller tumours [14]. Smaller tumour size has previously been shown to be correlated with higher complete response rates [49]. In a meta-analysis of 14 studies reporting pathological and toxicity data after dose escalated radiotherapy the pooled pCR rate was 18.1% when an $EQD2 \geq 60$ Gy was applied [50]. While there is little doubt that dose escalation will lead to higher rates of complete response rates, some questions and concerns remain: There is only limited data on rectal function and quality of life, particularly in terms of fecal incontinence after dose escalated radiotherapy without subsequent surgery. In the previously mentioned Danish trial 7% of patients suffered from grade III° rectal bleedings one year after the end of radiotherapy. Furthermore, significant inter- and intrafraction variability of the rectum has been described and the required margins to ensure sufficient boost volume coverage result in relevant rectal volumes that have be irradiated [51,52]. While a simultaneous integrated boost approach has been shown to result in higher conformality and normal tissue sparing in other entities [53], this strategy is currently difficult to realize in rectal cancer due to the poor visualization of the primary tumour with cone-beam imaging. Recent technical developments with novel MRI and LINAC hybrid devices may allow precise boost placements with acceptable margins in the future [54]. All available imaging modalities have shown limited accuracy for predicting nodal status [55] but a pathological complete remission of the primary tumour has been shown to be a good predictor for sterilization of mesorectal lymph nodes [8]. Yet it is unknown if this correlation will remain when dose escalation of the primary tumour will result in more complete remission of the primary tumour.

Challenge III: prediction of a pathological complete response

Clinical parameters

All available diagnostic tools are limited in their ability to predict a pathological complete response. Based on their extensive experience with organ preservation in rectal cancer, Habr-Gama et al. suggested endoscopic criteria for the definition of a cCR. According to these criteria any deep ulceration, superficial ulcer, palpable nodule or stenosis should prompt surgical resection [56].

Smith et al. validated these criteria in a retrospective study of 238 specimens of which 61 had a pathological complete response of the primary tumour. Using the criteria of Habr-Gama et al. resulted in a sensitivity for the prediction of a ypT0 status of only 26% with a specificity of 97%. In particular, the inclusion of a residual ulcer as a criterion not compatible with a cCR dramatically lowered the sensitivity since 40 of 61 patients with a pathological complete response had a residual ulcer. Maas et al. prospectively evaluated a five tier scale for endoscopic reevaluation of patients after preoperative radiochemotherapy. By defining a "white scar with teleangiectasia" and "a nonpalpable ulcer with regular borders and negative biopsy" as findings that could be used to select patients for a non-operative approach, they report a sensitivity of 53% and a positive predictive value of 90%. Another retrospective study using a similar threshold for the definition of a cCR including a "flat whitish or reddish scar ulcer, or a flat active/healing stage ulcer with regular edges" resulted in a comparable sensitivity of 65.2% and a positive predictive value of 78.9% [57].

Imaging

Several groups have investigated the accuracy of MRI with or without diffusion weighted imaging or PET for the prediction of a pathological complete response. In a meta-analysis of 20 studies using MR imaging the sensitivity to predict a ypT0 status was only 19.1%, the specificity was 94.6% [58]. A standardized MRI based tumour regression grading (mrTRG) resembling Dworak's regression scale for pathological downstaging has been investigated by the initiators of the MERCURY studies [59,60]. In their first report, patients with more pronounced mrTRG had significantly improved overall survival and disease-free survival rates compared with patients with poor response as assessed by mrTRG. In a more recent study mrTRG was correlated with the presence of a pCR after preoperative radiochemotherapy. By defining three of the five grades of the mrTRG scale as compatible with a pCR the authors report a sensitivity of 94% for the prediction of a pCR. On the other hand 85% of patients with mrTRG1-3 had residual tumour in the surgical specimen resulting in a specificity of only 25% [61]. The poor accuracy is mainly caused by the limited ability of MRI to distinguish between residual tumour and non-malignant radiotherapy induced findings in the rectal wall. The sensitivity can be increased by incorporating functional MRI sequences. For instance, Joye et al. report a pooled sensitivity of 78% using the post treatment apparent diffusion coefficient (ADC). However, the positive predictive value is poor with 46%. In terms of an organ-preservation study this would mean, that more than half of patients classified as complete responders by functional MRI potentially harbour residual tumour cells which is not acceptable. Data on restaging with PET-CT after preoperative radiochemotherapy has been disappointing with a pooled accuracy in a meta-analysis of only 65% [62]. Van Stiphout et al. developed a predictive model for pCR prediction based on clinical parameters and sequential PET-CT scans before and during treatment. While for a distinct subgroup with a high probability for a pCR the accuracy was 100% in the training cohort, yet it decreased to 67% in the validation cohort [63]. In summary, currently neither PET-CT nor MRI provide sufficient sensitivity with an acceptable positive predictive value for the prediction of a pCR.

Novel diagnostic tools to be further investigated

Radiomics

There is a growing interest in extracting more data from imaging studies than the sole visualization of patient and tumour anatomy or functional information using diffusion weighted imaging. "Radiomics" is the extraction and quantification of a variety of imaging features like texture, intensity and shape that can then

be correlated with different oncological parameters [64]. For instance, Leijenar et al. showed a significantly different overall survival of oropharyngeal cancer patients depending on a radiomics signature [65]. There is limited but promising data for radiomics as a tool for pCR prediction in rectal cancer. By extracting "kurtosis" as a single texture feature in T2 weighted MRI sequences of 12 rectal cancer patients, De Cecco et al. reported a sensitivity and specificity of 100% and 67% for the prediction of a pCR [66]. Ke Nie and colleagues applied artificial neuronal networks to create a prediction set of radiomics features from both anatomical and functional MRI studies of 48 rectal cancer patients. The predictive performance was measured as the area under the curve (AUC) of a receiver operating characteristic (ROC) curve. The AUC for pCR prediction was 0.84 and for the prediction of a good response of 0.89 [67]. Further studies of radiomics as predictive tool for rectal cancer with larger dataset are ongoing.

Molecular biomarkers and assessment of intrinsic radiosensitivity

A major limitation in the curative management of rectal cancer is represented by the lack of available biomarkers for clinical use. An extensive literature review on 1204 articles identified thymidylate synthase (TS) and EGFR as the most promising putative single biomarkers in locally advanced rectal cancer (LARC) [68]. A multicenter retrospective analysis showed a possible detrimental impact of EGFR positivity on attaining a pCR [69]. A prospective phase 2 study failed to demonstrate a relapse-free survival difference between two prespecified good and poor risk groups based on the thymidylate synthase gene polymorphisms in the context of neoadjuvant treatment [70]. Interestingly, a single center experience on 116 patients correlated high expression of survivin (an apoptosis-inhibitor) after neoadjuvant treatment with radioresistance and poor prognosis [71]. Extrapolating from the metastatic setting, inconclusive results are available regarding the translational implication of k-nRAS/BRAF status in locally advanced rectal cancer, thus restraining from their routine clinical implementation. Recently, a retrospective study on 229 patients showed that the presence of kras mutation before neoadjuvant treatment was independently correlated with worse pCR at multivariate analysis (OR 0.34; 95% CI 0.17–0.66, $p < 0.01$) after adjusting for clinical variables [72]. Taking all data together, definitive evidence on the biological heterogeneity and treatment resistance mechanisms of rectal cancer is critically missing. The absence of molecular predictors for pCR is relevant in the context of organ preservation approaches. The possibility to evaluate the intrinsic radiation sensitivity of individual rectal cancer patients represents a major goal in the scope of personalized treatment. In recent years, the gH2AX assay has been recognized as a very sensitive method to detect radiation-induced cell damage [73]. From a molecular perspective, it is well known that the phosphorylation of variant X of histone H2A (H2AX) is one of the earliest cellular events that occur in the process of DNA damage response (DDR) marking the chromatin region where DNA double strand breaks (DSB's) have been induced. It has been further demonstrated that there is a direct correlation between the number of gH2AX clusters and DNA DSB's [74]. If the cellular DNA repair machinery is successfully set in place, the clusters ("foci") of H2AX molecules are rapidly dephosporylated [75–78]. Several groups showed that the number of residual gH2AX foci after 24 h of irradiation or the rate of dephosporylation represent sensitive predictors of cell survival after radiotherapy [79,80]. By developing an innovative method of ex-vivo irradiation of fresh tumour tissue, Menegakis et al. applied the gH2AX assay on patient-derived material highlighting its potential to be used as a surrogate marker of intrinsic radiosensitivity in clinical practice [81]: in particular, in a heterogeneous population of 25 patients with different tumour types, expected differences of radio-responsiveness were reflected by the number of residual foci. In the 3 colorectal cancer patients included in the study, the individual slope values of the dose–response curve suggested an intermediate level of radiosensitivity. In view of the lack of predictive biomarkers for a pCR in rectal cancer, a prospective clinical assessment of gH2AX assay in this scenario would be noteworthy. The validation of its translational relevance on an individual-patient basis should be warranted in future trials of organ preservation.

"Liquid biopsy"

Recent improvements in genetic testing include cost-efficient, high-throughput sequencing techniques that allow individual analysis of tumour-specific genetic profiles and 'fingerprints'. Personalized treatment approaches might be supported by the definition of risk groups based on genetic alterations. It is anticipated that future clinical trials will identify new genetic biomarkers that will not only predict tumour responses to radiation therapy but also severity of side effects. These biomarkers will potentially help to avoid over- or undertreatment of patients. Based on these developments, liquid biopsies are a relatively new concept in oncology. Tumour desoxyribonucleic acids (DNA) can be detected in circulating tumour cells (CTCs) and cell-free tumour DNA (ctDNA). Liquid biopsies are minimally invasive blood-derived biomarkers and appear a very promising tool in precision medicine to potentially monitor cancer dynamics 'real-time', and correlate therapy response and mutation profiles accordingly [82,83]. In the context of radiotherapy and rectal cancer, data is sparse. Agostini et al. observed a difference between levels of the cell free DNA (cfDNA) integrity index after radiochemotherapy in patients achieving good tumour regression after preoperative radiochemotherapy compared with patients with poor response [84]. Levels of ctDNA determined by the detection of tumour specific rearrangement were correlated with the clinical course of four patients with locally advanced rectal cancer by Carpinetti et al. [85]. In one of the reported cases, the rise of ctDNA preceded the diagnosis of disease recurrence earlier than imaging studies or the carcinoembryonic antigen (CEA), and thus appears potentially useful in particular for the early prediction of recurrences. ctDNA could not be detected during follow-up of patients who remained disease free. If the above mentioned results can be confirmed in a larger population ctDNA might be a useful and minimally invasive tool for response prediction and follow-up in organ-preservation trials.

Challenge IV: safety

The ultimate test to prove the non-inferiority of a novel treatment compared the current standard of care is a randomized trial. However, it is unlikely that for non-operative management of rectal cancer such a randomized trial would recruit successfully. A high non-compliance rate and protocol violations have to be expected since a considerable number of patients with a cCR might not give consent for major surgery. We therefore require well designed prospective trials with sharp inclusion and restaging criteria that address the challenges mentioned before. Furthermore, a very close follow-up of patients managed non-operatively is warranted. Most studies so far have used three- or four-monthly imaging studies and endoscopic examinations for the first two years to ensure timely diagnosis of local regrowth. Considering the excellent salvage rates in these studies this follow-up regimen appears appropriate. There have been concerns that individual patients might be disadvantaged by the omission of surgery after being diagnosed with a complete clinical response. First, patients with initially resectable tumours might develop irresectable regrowth or lesions that require abdominoperineal resection while deep anterior resection would have been sufficient initially. The second concern is the development of local failures leading to de-novo distant metastases that do no longer allow curative treatment. While patients need to be informed about the experimental character of the non-operative approach the current literature suggests the safety of this approach. In the prospective Dutch organ-preservation trial a total of two of

patients developed both local and distant failures [13]. Even if in both cases the recurrences could have been avoided by immediate surgery the potential decrease in oncological safety is small and has to be weighed against the risk for postoperative mortality and the considerable number of patients that can avoid permanent colostomy. Furthermore, a recent propensity-score matched cohort study showed no loss of oncological safety with a wait & see strategy after a clinical complete remission [15].

Summary and perspective

Pioneering data from Brazil and subsequent studies have shown that selected patients with rectal cancer can safely be treated with radiochemotherapy alone. Although substantially longer follow-up and larger numbers of patients are needed to validate the organ preservation approach, the growing number of prospective clinical trials and experiences from large databases, such as the European Registration of Cancer Care (EURECCA) watch & wait database, or the recent Oncological Outcome after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) project, will provide more information on its safety and efficacy, and help to select appropriate patients. Future studies will have to establish radiochemotherapy regimens that will maximize the number of patients that can be managed non-operatively. In these studies, novel innovative restaging procedures have to be investigated in order to improve the prediction of a pathological complete response and long-term close follow-up with thorough documentation of failure patterns and salvage therapies will have to prove the oncological safety of this approach.

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