Review

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Complete response after chemoradiotherapy for rectal cancer: what is the reasonable approach?

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Abstract: With the increasing use of preoperative treatment rather than upfront surgery, it has become evident that the response of rectal carcinoma to standard chemoradiotherapy (CRT) shows a great variety that includes histopathologiocally confirmed complete tumor regression in 10–30% of cases. Adaptive strategies to avoid radical surgery, either by local excision or non-operative management, have been proposed in these highly responsive tumors. A growing number of prospective clinical trials and experiences from large databases, such as the European Registration of Cancer Care (EURECCA) watch-and-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 appropriate inclusion criteria and optimize CRT regimens in order to maximize the number of patients achieving complete response. Standardized re-staging procedures have to be investigated to improve the prediction of a sustained 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.

Keywords: chemoradiotherapy; complete response; local excision; non-operative management; rectal cancer; wait-and-see strategies.

Introduction

Radiotherapy (RT), chemotherapy, and surgical resection are important elements of the multimodal treatment for patients with rectal cancer. Preoperative 5-fluorouracil-(5-FU)-based chemoradiotherapy (CRT) followed by total mesorectal excision (TME) approximately 6 weeks thereafter, or short-course RT followed by immediate TME, have substantially reduced local recurrences in patients with locally advanced disease [1, 2]. However, long-term follow-up for these trials failed to demonstrate an improvement in either disease-free (DFS) or overall survival (OS). More recent developments in multimodal rectal cancer treatment have incorporated combination chemotherapy beyond 5-FU, and/or molecularly targeted agents, given before, during, or following preoperative or definitive CRT/RT to potentially increase both the systemic efficacy and local response [3].

With the increasing use of preoperative treatment rather than upfront surgery, it has become evident that the response of rectal carcinoma to standard CRT shows a great variety that includes histopathologiocally confirmed complete tumor regression (pCR, ypT0N0) in 10–30% of cases [4]. Thus, adaptive strategies to avoid radical surgery – by local excision or non-operative management – in these highly responsive tumors have been proposed and are currently tested in prospective clinical trials and validated in large prospective databases and registries. This review aims to provide an overview of chances and challenges of this approach.

Radiotherapy or chemoradiotherapy followed by limited surgery

Local excision (LE) after CRT or short-course RT has been tested in low-lying clinical T2 and early T3 tumors in an attempt to avoid radical surgery with a permanent colostoma. In an earlier meta-analysis, Borschitz et al. [5] reported on seven (mostly retrospective) studies, conducted between 1990 and 2007, comprising 237 patients

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with cT2-3 rectal cancer treated with LE 4–6 weeks after standard 5-FU-CRT. Median follow-up times ranged from 24 to 55 months, and local failure rates were 0%, 2% (range, 0–6%), 7% (range, 6–20%) in patients with ypT0, ypT1, and ypT2, respectively.

A prospective, multicenter Polish trial tested neoadjuvant short-course 5×5 Gy plus a 4-Gy boost or 5-FU-CRT (55.8 Gy) followed by LE 6–8 weeks thereafter in 89 patients with unfavorable cT1-2N0 or small cT3N0 tumors [6]. If the LE confirmed ypT0 or ypT1 with clear margins, no further treatment was applied, whereas radical surgery was recommended for all other patients. The 2-year local recurrence rate was 10% after LE, and no recurrences were reported for patients treated by radical surgery. Interestingly, multivariable analysis indicated better local control after CRT + LE compared to 5×5 Gy + LE (5.3% vs. 21.5% at 2 years, p = 0.04), however, event numbers for local recurrence were low (13 of 81 patients), limiting any firm conclusions regarding the efficacy of both regimen. The Dutch CARTS study used transanal endoscopic microsurgery (TEM) after preoperative CRT in patients with cT1-3 distal rectal cancer and achieved organ preservation in 50% of patients [7]. The American College of Surgeons Oncology group has recently completed the ACOSOG Z6041 phase II trial for patients with clinical T2N0 rectal cancer who received preoperative CRT (total dose 50.4–54 Gy) with capecitabine and oxaliplatin followed by transanal LE 6 weeks after completion of CRT [8]. Among the 76 patients who underwent LE, 38 patients (49%) had ypT0 or ypTis tumors, 11 (14%) had ypT1 tumors, 24 (31%), and 3 (4%) had ypT2 and ypT3 tumors, respectively. All but one had negative margins. With a median follow-up of 56 months, the local recurrence rate was 4%, and 6% had distant metastases.

An Italian study randomized 100 patients with distal cT2N0 tumors (diameter <3 cm) after standard neoadjuvant 5-FU-CRT to TME or TEM. After more than 8 years of follow-up, local recurrences were not significantly different (6% and 8% after TME and TEM, respectively). (Table 1) [9].

The most recent French multicenter GRECCAR 2 randomized trial compared LE versus TME in patients with initially staged T2/T3 lower rectal cancer (maximum initial size 4 cm) who achieved a good clinical response (residual tumor 6–8 weeks after CRT: ≤2 cm) to preoperative CRT (50 Gy with concurrent capecitabine and oxaliplatin) (Table 2) [10]. The primary endpoint was a composite outcome of death, total recurrences, morbidity, and side effects at 2 years after surgery. This trial failed to show superiority of LE over TME for the intention-to-treat population, mainly because many patients in the LE group (26 of 74) received a completion TME for ypT2/3 status after

Table 1: Italian randomized trial of TEM versus TME after 5-FU-CRT in early, low-lying rectal cancer.

Inclusion criteria: cT2N0 G1-2; 6 cm from anal verge; tumor diameter <3 cm	5-FU-CRT + TEM	5-FU-CRT + TME	p-Value
Number of patients	50	50	
ypT0/1/2 (%)	28/24/48 (all R0)	26/24/50 (all R0)	n.s.
Blood loss (mL, median)	45	200	<0.001
Duration of surgery (min, median)	90	174	<0.001
Major postop complications	2%	6%	0.25
Stoma (definitive)	0%	24%	<0.001
Local failure (median F/U: >8 years)	8%	6%	n.s.
Distant failure (median F/U: >8 years)	4%	4%	n.s.

Table 2: French GRECCAR 2 randomized trial of LE versus TME after good response to capecitabine/oxaliplatin-CRT in early, low-lying rectal cancer.

Inclusion criteria: cT2/3N0-1, ≤8 cm from anal verge; initial tumor diameter ≤4 cm; good response to CRT (residual tumor ≤2 cm)	CRT + LE	CRT + TME	p-Value
Patients randomized and analyzed	74[a]	71	
Primary outcome: composite of death, recurrence, morbidity, side effects at 2 years	56%[a]	48%	0.43
Death	5%[a]	6%	0.98
Tumor recurrence	16%[a]	20%	0.63
Major morbidity, total (LE/TME completion)	24%[a] (12%/78%)	22%	0.68
Side effects, total (LE/TME completion)	35%[a] (19%/59%)	29%	0.54

[a]Includes 26 patients with LE + completion TME due to ypT2-3 status after LE.

LE. Completion TME after LE was associated with markedly increased morbidity and side effects, and compromised the potential advantages of LE. This trial strongly suggests that better patient selection to avoid unnecessary completion TME is required to improve the LE strategy.

Definitive chemoradiotherapy – the non-operative management (NOM) approach

Investigators from the University of Sao Paulo were the first to pioneer the selective non-operative management (NOM) approach for patients with potentially resectable rectal cancer who experience a clinically complete response (cCR) to CRT. In early reports, Habr-Gama et al. [11] described the outcomes of 361 patients with cT2-4 and or cN+ rectal cancer treated with standard neoadjuvant CRT (50.4 Gy plus 5-FU/folinic acid) and assessed for response 8 weeks after completion of CRT with clinical, endoscopic, and radiologic studies. Patients with initial cCR (n = 122, 34%) underwent a strict watch-and-wait strategy with monthly examinations for the first year; 23 of these 112 patients (19%) developed local tumor regrowth within 12 months. Only patients without any local regrowth within the first year of follow-up were considered to have a sustained cCR. A total of 99 of 361 (27.4%) patients met the criteria for sustained cCR at 1 year and had a mean follow-up of 60 months, during which five patients developed endoluminal (all salvaged), seven distant, and one combined recurrences. In a more recent report, this group used a more intense CRT regimen of 54 Gy in 32 fractions with three concurrent cycles of 5-FU/folinic acid every 21 days, followed by three further cycles of consolidation chemotherapy before response assessment 9 weeks after completion of CRT: initial cCR in 70 patients with T2-3 distal rectal cancer was 68% and sustained cCR at 1 year of follow-up was 57% [12].

Maas et al. [13] aimed to replicate the results from Sao Paulo with modern MRI techniques. Re-staging was performed 6–8 weeks after completion of standard CRT (50.4 Gy, concurrent capecitabine) for clinically T3-4 and/or N+ rectal cancer patients using digital rectal examination, high-resolution MRI, and endoscopy plus biopsies. If these examinations indicated no residual tumor or residual fibrosis only, patients were eligible for a non-operative approach combined with intensive follow-up: 21 of the 192 (11%) patients had evidence of cCR. With a median follow-up of 25 months, only one patient developed a local recurrence (successfully treated with salvage surgery), 20 patients are alive without disease. Patients with cCR included in a wait-and-see policy did at least as good as a control group of 20 patients with a pCR after radical surgery, but had less toxicity and better short-term bowel function. In a more recent update of this strategy, including 100 patients with cCR and a median follow-up of 41 months, local regrowth occurred in 15 patients (12 luminal, three nodal), all salvageable, with a 3-year local regrowth-free survival of 85% and a 3-year overall survival of 97%. Continence after watch-and-wait based on the Vaizey incontinence score was excellent [14]. These data are in contrast to older retrospective series of unselected patients treated with CRT and non-operative management because of medical inoperability or patient refusal, where disease progression finally occurred in up to 50% of patients [15], indicating that selection of CRT-responding patients for organ preservation is a key element.

Another prospective watch-and-wait approach from Denmark evaluated patients with low-lying (<6 cm from anal verge) cT2-3, cN0-1 rectal cancer [16]. Patients were treated with an increased radiation dose (60 Gy in 30 fractions with an additional 5-Gy endorectal brachytherapy boost) and concurrent oral tegafur-uracil. Response was assessed 6 weeks after CRT by endoscopy/biopsy and MRI, and complete responders were prospectively observed (every 2 months for 1 year, every 3 and 6 months for years 2 and 3, respectively, and then annually). A total of 40 out of 51 eligible patients (78%) met the criteria of clinical complete response. With a median follow-up of 24 months, the 1- and 2-year cumulative incidence of local tumor regrowth for these 40 patients were 15% and 26%, respectively. All these patients were successfully salvaged without additional recurrences. The most common late toxicity was bleeding from the rectal mucosa (any grade 78%, grade 3 in 7% at 1 year of follow-up), indicating that the cumulative dose of RT (60-Gy external beam + 5-Gy brachytherapy boost) resulted in significant mucosal RT-induced damage.

Although substantially more follow-up and larger numbers of patients are needed to validate the NOM approach, the growing number of clinical trials and experiences from large databases, such as the European Registration of Cancer Care (EURECCA) watch-and-wait database [17], or the recent Oncological Outcome after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) project [18], will provide more information on its safety and efficacy, and help to select appropriate patients. The latter reported on 129 patients, with clinical complete response after CRT, who were managed by watch and wait. With a median follow-up

of 33 months, 44 (34%) had local regrowths, and 36 of 41 patients (88%) with non-metastatic local regrowths were salvaged successfully [18].

Can the NOM approach be further optimized?

The most commonly used time interval between completion of preoperative CRT and surgical resection has traditionally been 4–6 weeks. An emerging body of data suggests that – reminiscent to anal cancer treatment – the response to CRT in patients with rectal cancer is time dependent, and maximal local tumor regression may well take longer than the standard 6 weeks to surgery. Several retrospective studies have addressed the time interval as predictor of tumor response, surgical morbidity, and long-term outcome. In a series of 132 patients with locally advanced rectal cancer, Tulchinsky et al. [19] found that patients operated on more than 7 weeks after CRT had similar rates of perioperative complications compared to patients operated in 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 disease-free survival ($p = 0.05$). 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 after preoperative 5-FU-CRT. The study failed to show an impact of a longer waiting period on the pCR rate (15% in the 7-week arm versus 17.4% in the 11-week arm). To some extent, this unexpected result might be caused by the high 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 [20].

Several groups have used a prolonged interval between CRT and surgery for adding consolidation chemotherapy. With this approach, effective CRT is administered early to prevent local disease progression, and tumor response might be increased by allowing the tumor more time to regress before surgery while also providing effective systemic treatment early to reduce the risk of developing systemic disease. In that context, the Timing of Rectal Cancer Response to Chemoradiation Consortium in the US conducted a prospective phase 2 trial of preoperative CRT (50.4–54 Gy with 225 mg/m^2/day continuous infusion of 5-FU during RT) and delayed the time point of surgery (Figure 1). Study group 1 underwent surgery 6 weeks after completion of CRT. Patients in study groups 2, 3, and 4 received two, four, or six cycles of FOLFOX during the waiting period before surgery (performed 11, 15, and 19 weeks, respectively, after completion of CRT). The pCR rate of patients treated in study group 1 was 18% compared with 25%, 30%, and 38%, respectively, for study groups 2–4 without an apparent increase in surgical complications [21].

The Memorial Sloan Kettering Cancer Center randomized phase 2 trial (Figure 2) is currently underway to test the feasibility of incorporating a NOM approach to the multimodality treatment. This study will evaluate the 3-year DFS in MRI-staged T2-3, N0, or Tany N1-2 rectal cancer patients treated with CRT and either induction or consolidation chemotherapy and TME or NOM [22]. Another prospective phase 2 trial from Sao Paulo

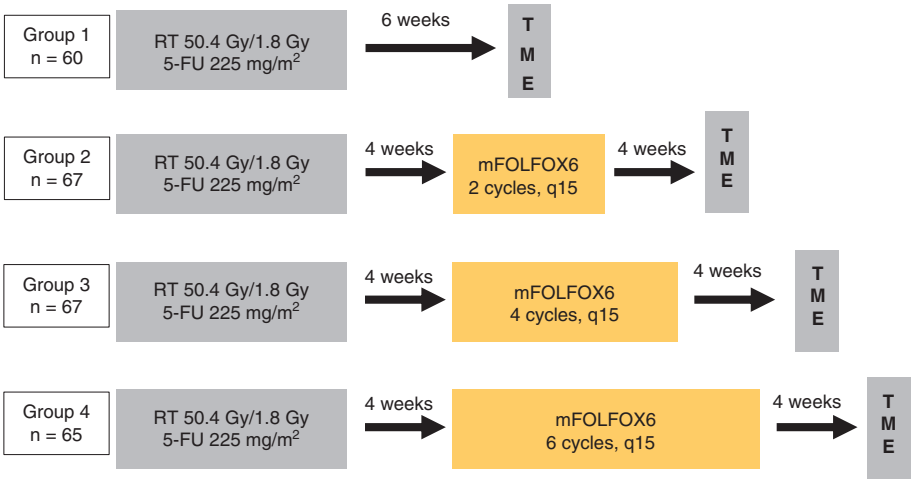

Figure 1: The TIMING Trial (Timing of Rectal Cancer Response to Chemoradiotherapy Trial) in locally advanced T3/4 and or N+ rectal cancer patients.

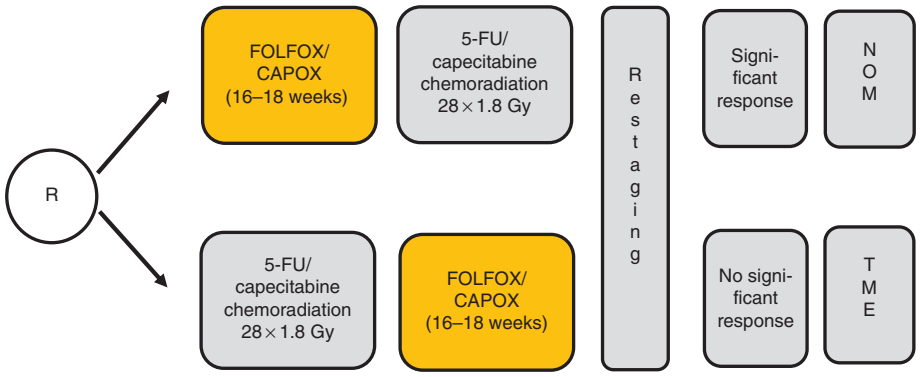

Figure 2: Trial schema of the MSKCC-based multicenter randomized phase II trial of induction chemotherapy versus consolidation chemotherapy with 5-FU/capecitabine and oxaliplatin before or after chemoradiotherapy in MRI-staged T2-3, N0, or Tany N1-2 rectal cancer (NOM, non operative management; TME, total mesorectal excision).

randomizes patients with a cCR 12 weeks after CRT to TME or close observation (NCT02052921).

Can we reliably predict (pathological) complete response?

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 the endoscopic criteria for the definition of a cCR. Based on these criteria, any deep ulceration, superficial ulcer, palpable nodule, or stenosis should prompt surgical resection [23]. Maas et al. [24] prospectively evaluated a five-tier scale for endoscopic re-evaluation of patients after preoperative CRT. By defining a "white scar with telangiectasia" 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% [25].

Several groups have investigated the accuracy of magnet resonance imaging (MRI) with or without diffusion-weighted imaging or positron emission tomography (PET) for the prediction of pCR. In a meta-analysis of 20 studies using MRI, the sensitivity to predict a ypT0 status was only 19.1%; the specificity was 94.6% [26]. A standardized MRI-based tumor regression grading (mrTRG) has been investigated by the investigators of the MERCURY studies. By defining three of the five grades of the mrTRG scale as compatible with a pCR, the authors reported a sensitivity of 94% for the prediction of a pCR. On the other hand, 85% of the patients with mrTRG1-3 had residual tumor in the surgical specimen resulting in a specificity of only 25% [27]. The poor accuracy is mainly caused by the limited ability of MRI to distinguish between residual tumor and non-malignant RT-induced findings in the rectal wall. The sensitivity can be increased by incorporating functional MRI sequences. For instance, Joye et al. [28] reported a pooled sensitivity of 78% using the post-treatment apparent diffusion coefficient (ADC). Data on restaging with PET-CT after preoperative CRT have been disappointing with a pooled accuracy in a meta-analysis of only 65% [28]. Van Stiphout et al. developed a predictive model for pCR 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, it decreased to 67% in the validation cohort [29]. In summary, currently, neither MRI nor PET-CT provides sufficient sensitivity with an acceptable positive predictive value for the prediction of a pCR.

Caveats of the NOM approach after CRT

The ultimate test to prove that the non-inferiority of a novel treatment compared the current standard of care is a randomized trial. However, it is unlikely that for a 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 as a considerable number of patients with a cCR might not give consent for major surgery. Well-designed prospective trials with strict inclusion and restaging criteria that address the challenges mentioned before are needed. 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 2 years to ensure timely diagnosis of local regrowth. Considering the excellent salvage rates reported in recent 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 cCR. First, patients with initially resectable tumors might develop irresectable regrowth or lesions that require abdominoperineal resection, while low anterior resection would have been sufficient in the first place. The second concern is the development of local failures leading to *de novo* distant metastases that no longer allow curative treatment. While patients need to be informed about the still experimental character of the non-operative approach, the current literature suggests the safety of this approach.

Conclusion

Pioneering data from Brazil and subsequent studies have shown that selected patients with rectal cancer can safely be treated with CRT alone. Although substantially more 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 EURECCA watch-and-wait database, or the recent OnCoRe project, will provide more information on its safety and efficacy, and help to select appropriate patients. Evidently, those with low-lying early tumors (cT2, small cT3), who would otherwise require abdominoperineal resection with a permanent stoma, would benefit most from NOM. Future studies will have to establish CRT regimens that will maximize the number of patients that can be managed non-operatively [30]. In these studies, novel innovative restaging procedures have to be investigated in order to improve the prediction of a pCR, 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.

Author Statement

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Author Contributions

Claus Rödel: conceptualization; data curation; formal analysis; investigation; methodology; visualization; writing – original draft; writing – review and editing. Emmanouil Fokas: conceptualization; data curation; formal analysis; investigation; methodology; visualization; writing – original draft; writing – review and editing. Cihan Gani: conceptualization; data curation; formal analysis; investigation; methodology; visualization; writing – original draft; writing – review and editing.

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Supplemental Material: The article (https://doi.org/10.1515/iss-2017-0041) offers reviewer assessments as supplementary material.

Reviewer Assessment

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Reviewers' Comments to Original Submission

Reviewer 1: Bruce Minsky

Nov 02, 2017

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Overall Reviewer Manuscript Rating:	85

Custom Review Questions	**Response**
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	5 - High/Yes
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	4
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	5 - High/Yes
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:
none

Reviewer 2: anonymous

Nov 27, 2017

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	90

Custom Review Questions	**Response**
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	4
Are units and terminology used correctly?	N/A
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	4
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	5 - High/Yes
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

This is a very interesting and excellent written review of the different approaches to omit surgery following chemoradiation of rectal surgery. Most of the recently published trials are mentioned.. There are only a few remarks which may be considered by the authors:

- The Polish trial (Bujko et al. 2013 ref. 6) compared also the efficacy of 5+5 Gy versus CRT in a multivariate analysis and found that following CRT the local recurrence rate was significantly low in th CRT arm (6,2% versus 11,8%; P=0.04)
- There are some older reports on omission of surgery following CRt with higher rates of local recurrences (Dalton et al. 2012; Lim et al. 2007) These publications should be commented critically.
- Appelt et al. reported a high rate of bleeding CTC grade 3 in aboiut 5%; CTC grade 2 10- 15%; which should be discussed critically.(perhaps to their high dose of RT?)
- I am missing the report of Renehan et al. 2016 (Lancet Oncology) comparing the results of omission of surgery and surgery following CRT in a register study and found a local regrowth in about 30 %; but nevertheless a better colostomy free survival (47% versus 74%)
- To my knowledge Habr-Gama defined local recurrences based of the patients one year following CRT. This difference compared to other studies should be mentioned because it explains the relatively low rate of local recurrences in their collectives.
- It should perhaps be mentioned that the chance of getting a higher rate of cCR in earlier tumours (cT2/3) than in cT3/$ tumours

Authors' Response to Reviewer Comments

Nov 30, 2017

Point-by-point response to the reviewers comments

Reviewer #2: This is a very interesting and excellent written review of the different approaches to omit surgery following chemoradiation of rectal surgery. Most of the recently published trials are mentioned.
Thank you

There are only a few remarks which may be considered by the authors:

1. The Polish trial (Bujko et al. 2013 ref. 6) compared also the efficacy of 5+5 Gy versus CRT in a multivariate analysis and found that following CRT the local recurrence rate was significantly low in th CRT arm (6,2% versus 11,8%; P=0.04)
Thank you. This information has now been added, page 4, 2. para:
"Interestingly, multivariable analysis indicated better local control after CRT + LE compared to 5 x 5 Gy + LE (5.3% versus 21.5% at 2 years, p=0.04), however, event numbers for local recurrence were low (13 of 81 patients), limiting any firm conclusions regarding the efficacy of both regimen."

2. There are some older reports on omission of surgery following CRt with higher rates of local recurrences (Dalton et al. 2012; Lim et al. 2007) These publications should be commented critically.
Thank you. These data are now commented on page 7, 1. para:
"These data are in contrast to older retrospective series of unselected patients treated with CRT and nonoperative management because of medical inoperability or patient refusal, where disease progression finally occurred in up to 50% of patients [15], indicating that selection of CRT-responding patients for organ preservation is a key element."

3. Appelt et al. reported a high rate of bleeding CTC grade 3 in aboiut 5%; CTC grade 2 10- 15%; which should be discussed critically. (perhaps to their high dose of RT?)
Thank you. This information is now given page 7, 2. para.:
"The most common late toxicity was bleeding from the rectal mucosa (any grade 78%, grade 3 in 7% at 1 year of follow-up), indicating that the cumulative dose of RT (60 Gy external beam + 5 Gy brachytherapy boost) resulted in significant mucosal RT-induced damage."

4. I am missing the report of Renehan et al. 2016 (Lancet Oncology) comparing the results of omission of surgery and surgery following CRT in a register study and found a local regrowth in about 30 %; but nevertheless a better colostomy free survival (47% versus 74%)
Thank you. The Renehan study is reported on page 7 last para. and page 8 1. para:
"...or the recent Oncological Outcome after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) project [18], will provide more information on its safety and efficacy, and help to select appropriate patients. The latter reported on 129 patients with clinical complete response after CRT who were managed by watch and wait. With a median follow-up 33 months, 44 (34%) had local regrowths and 36 of 41 patients (88%) with non-metastatic local regrowths were salvaged successfully [18]."

5. To my knowledge Habr-Gama defined local recurrences based of the patients one year following CRT. This difference compared to other studies should be mentioned because it explains the relatively low rate of local recurrences in their collectives.
This information is given on page 6, 1. para
"Only patients without any local regrowth within the first year of follow-up were considered to have a sustained cCR. A total of 99 of 361 (27.4%) patients met the criteria for sustained cCR at 1 year"...

6.It should perhaps be mentioned that the chance of getting a higher rate of cCR in earlier tumours (cT2/3) than in cT3/$ tumours
Thank you. This is now included page 12, last para.
"Evidently, those with low-lying early tumors (cT2, small cT3) who would otherwise require abdominoperineal resection with a permanent stoma would benefit most from NOM."

Reviewers' Comments to Revision

Reviewer 2: anonymous

Dec 04, 2017

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	90

Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	5 - High/Yes
Are units and terminology used correctly?	N/A
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	N/A
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	5 - High/Yes
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

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