

Reviewer Assessment

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

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Reviewers' Comments to Original Submission

Reviewer 1: Bruce Minsky

Nov 02, 2017

Reviewer Recommendation Term:	Accept
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
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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 about 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
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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 the 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 regimens.”

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 about 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 cT3/4 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
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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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