

Reviewer Assessment

Alanna Ebigbo*, Andreas Probst and Helmut Messmann

Endoscopic treatment of early colorectal cancer – just a competition with surgery?

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***Corresponding author: Alanna Ebigbo**, Department of Gastroenterology, Klinikum Augsburg, Stenglinstr. 2, Augsburg 86156, Germany, E-mail: alanna.ebigbo@klinikum-augsburg.de

Reviewers' Comments to Original Submission

Reviewer 1: anonymous

Sep 24, 2017

Reviewer Recommendation Term:	Revise with Major Modification
Overall Reviewer Manuscript Rating:	60
Custom Review Questions	Response
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	3
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	3
How comprehensive and up-to-date is the subject matter presented?	3
How adequate is the data presentation?	3
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?	4
Does the reader get new insights from the article?	2
Please rate the practical significance.	2
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.	3
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

Endoscopic treatment of early colorectal cancer - just a competition with surgery?

This manuscript highlights various aspects of the endoscopic treatment of colorectal cancer when compared to full resectional surgery.

I have the following comments and suggestions that the authors may wish to consider:

Major comments:

- 1) Low risk pT1 cancers include both well and moderately differentiated adenocarcinomas. Most are moderately differentiated rather than well differentiated, Poor differentiation or undifferentiated cancers are usually considered high risk, although poor differentiation in the context of mismatch repair deficiency/microsatellite instability is considered low risk. TNM version 8 now recommends routine testing of MMR status in all colorectal cancers so molecular biological information should now be routinely available in addition to traditional morphological classifiers of risk. This should be acknowledged.
- 2) Features of high and low risk pT1s are presented as either one or the other, but unfortunately even what appear to be objective measurements e.g. depth of submucosal invasion, are subjective and are not proven to be reproducible between pathologists. This subjectivity when assessing risk should be acknowledged.
- 3) Budding is presented as a high risk feature, yet there are several systems which are subjective and confusing. There is now a recently accepted international consensus system for analysing budding. This should be referenced.
- 4) The authors state "However, other studies have shown that the quality of evidence regarding these pathologic predictive factors is poor and in select patients endoscopic resection alone may be adequate even in the presence of submucosal invasion (3)." It is not clear how this statement relates to the previous sentence, which highlights high risk features predicting nodal metastases. Submucosal invasion alone is not a high risk feature, it is the definition of a cancer rather than a pre-cancerous adenoma with high grade dysplasia.
- 5) Please clarify whether EFTR includes locally excised specimens such as TEMS or TAMIS? If not please clarify for the reader how these procedures differ in terms of the specimen produced.
- 6) Similar to the quality of mesorectal surgery predicting outcomes, it is likely that the quality of local excision surgery is also related to the risk of recurrence. Positive margins can be seen if the tumour is understaged, or if there is a failure to stick to the intended tissue planes, especially at the lateral edges of the local excision where there is a tendency to 'cone in', A comment on the importance of the quality of local excision surgery would be helpful.
- 7) Br J Surg. 2009; 96: 280-90 describes the risk of recurrence according to various high risk features. It is surprising that this important study is not referenced in the review.
- 8) The review suggests that early cancers should now be resected using local excision. The review does not really expand on the issue raised in the title i.e. how the use of local excision vs. surgery is being used for these lesions around the world. How many lesions are inappropriately being offered surgery at the current time in different healthcare systems? How do we change this to ensure that more are locally resected, if appropriate? A summary flow chart of the questions that should be asked when deciding between local excision and full surgery would be helpful.
- 9) Other points of interest are not sufficiently addressed. The relative morbidity and mortality of local techniques and full resectional surgery should be presented. How intensively should patients be followed up following local excision of an early cancer? How does full resection after local recurrence following local excision affect long term outcomes compared to primary resectional surgery? What are patient attitudes to local excision vs. full resectional surgery?

Minor comments:

- 1) "proper muscle layer" is better clarified as the muscularis propria.
- 2) I am not sure how much the endoscopic images used as figures help the reader to make a decision about the use of an endoscopic procedure vs. surgery.

Reviewer 2: Eloy Espi

Sep 17, 2017

Reviewer Recommendation Term:

Revise with Major Modification

Overall Reviewer Manuscript Rating:

N/A

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?

4

Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
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Does the reader get new insights from the article?	2
Please rate the practical significance.	2
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.	4
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.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

I had the privilege of reviewing this paper, a review of the evidence on endoscopic treatment of early colorectal cancer. I think is a good review in terms of easy reading and good figures.

I have some advices:

- 1.- In abstract change: "... the methods of choice for the treatment of early colorectal cancer..." for "the methods of choice for the treatment of most early colon cancer and some rectal cancer..."
- 2.- In introduction...change "should be the method of choice in the care of patients with early colorectal cancer?" to "should be the method of choice in the care of selected patients with early colorectal cancer?"
- 3.- In the section of endoscopy vs surgery... It should be a better explanation of the cases where surgery should be preferred to endoscopy.
- 4.- In rectal cancer there has been a good experience with TEM and TAMIS surgery (not even mentioned). There are good results with these approach. In the same section I think that is important to mark the importance of the complete study of all malignant lesions BEFORE the resection, in order to a good clinical decision of resection vs other kind of treatment (studying the patient after the resection is linked to conflicts in the decision making process).
- 5.- I think is important to give some words to the importance of tattooing the lesions to a better control after the resection (re-endoscopy, surgery, etc).

Authors' Response to Reviewer Comments

Oct 04, 2017

Dear Editors and reviewers,

Please find attached, a point-by-point revision of our manuscript "Endoscopic treatment of early colorectal cancer – just a competition with surgery?"

The authors wish to thank the reviewers for their detailed comments and hope the revised manuscript now qualifies for publication.

Best regards

Reviewers' comments:

Reviewer #1: Endoscopic treatment of early colorectal cancer - just a competition with surgery?

This manuscript highlights various aspects of the endoscopic treatment of colorectal cancer when compared to full resectional surgery.

I have the following comments and suggestions that the authors may wish to consider:

Major comments:

1) Low risk pT1 cancers include both well and moderately differentiated adenocarcinomas. Most are moderately differentiated rather than well differentiated, Poor differentiation or undifferentiated cancers are usually considered high risk, although poor differentiation in the context of mismatch repair deficiency/microsatellite instability is considered low risk. TNM version 8 now recommends routine testing of MMR status in all colorectal cancers so molecular biological information should now be routinely available in addition to traditional morphological classifiers of risk. This should be acknowledged.

>> Acknowledged

2) Features of high and low risk pT1s are presented as either one or the other, but unfortunately even what appear to be objective measurements e.g. depth of submucosal invasion, are subjective and are not proven to be reproducible between pathologists. This subjectivity when assessing risk should be acknowledged.

>> Acknowledged

3) Budding is presented as a high risk feature, yet there are several systems which are subjective and confusing. There is now a recently accepted international consensus system for analysing budding. This should be referenced.

>> Referenced

4) The authors state “However, other studies have shown that the quality of evidence regarding these pathologic predictive factors is poor and in select patients endoscopic resection alone may be adequate even in the presence of submucosal invasion (3).” It is not clear how this statement relates to the previous sentence, which highlights high risk features predicting nodal metastases.

>> The statement tries to justify the endoscopic resection of early rectal cancer even in the presence of high risk features bearing in mind that the quality of evidence regarding these features is poor.

Submucosal invasion alone is not a high risk feature, it is the definition of a cancer rather than a pre-cancerous adenoma with high grade dysplasia.

>> We meant “deep” sm-invasion, we have changed this in the text.

5) Please clarify whether EFTR includes locally excised surgical specimens such as TEMS or TAMIS? If not please clarify for the reader how these procedures differ in terms of the specimen produced.

>> Clarified

6) Similar to the quality of mesorectal surgery predicting outcomes, it is likely that the quality of local excision surgery is also related to the risk of recurrence. Positive margins can be seen if the tumour is understaged, or if there is a failure to stick to the intended tissue planes, especially at the lateral edges of the local excision where there is a tendency to ‘cone in’, A comment on the importance of the quality of local excision surgery would be helpful.

>> A comment has been included.

7) Br J Surg. 2009; 96: 280-90 describes the risk of recurrence according to various high risk features. It is surprising that this important study is not referenced in the review.

>> Referenced

8) The review suggests that early cancers should now be resected using local excision. The review does not really expand on the issue raised in the title i.e. how the use of local excision vs. surgery is being used for these lesions around the world. How many lesions are inappropriately being offered surgery at the current time in different healthcare systems? How do we change this to ensure that more are locally resected, if appropriate? A summary flow chart of the questions that should be asked when deciding between local excision and full surgery would be helpful.

>> Due to the heterogeneity of the lesions and their localisations involved in this topic and the different levels of expertise in various parts of the world, the authors do not think that a simple summary flow chart can render sufficient justice to the question of therapeutic approach. However, we have stated that lesions should generally be evaluated extensively by an expert experienced in the endoscopic evaluation and treatment of colorectal lesions, and in many situations, a multidisciplinary discussion between endoscopist and rectal surgeon becomes necessary to ensure appropriate treatment.

9) Other points of interest are not sufficiently addressed. The relative morbidity and mortality of local techniques and full resectional surgery should be presented. How intensively should patients be followed up following local excision of an early cancer? How does full resection after local recurrence following local excision affect long term outcomes compared to primary resectional surgery? What are patient attitudes to local excision vs. full resectional surgery?

>> The authors have included these aspects.

Minor comments:

1) “proper muscle layer” is better clarified as the muscularis propria.

>> Clarified

2) I am not sure how much the endoscopic images used as figures help the reader to make a decision about the use of an endoscopic procedure vs. surgery.

>> The authors included the images to illustrate the endoscopic treatment options available for the treatment of early colorectal cancer. Also reviewer 2 has commented these images as “good figures”.

Reviewer #2: I have had the privilege of reviewing this paper, a review of the evidence on endoscopic treatment of early colorectal cancer. I think is a good review in terms of easy reading and good figures.

I have some advices:

1.- In abstract change: “.... the methods of choice for the treatment of early colorectal cancer....” for “the methods of choice for the treatment of most early colon cancer and some rectal cancer...”

>> Changed

2.- In introduction...change “should be the method of choice in the care of patients with early colorectal cancer?” to “should be the method of choice in the care of selected patients with early colorectal cancer?”

>> Changed

3.- In the section of endoscopy vs surgery... It should be a better explanation of the cases where surgery should be preferred to endoscopy.

>> The authors have now included this.

4.- In rectal cancer there has been a good experience with TEM and TAMIS surgery (not even mentioned). There are good results with these approach. In the same section I think that is important to mark the importance of the complete study of all malignant lesions BEFORE the resection, in order to a good clinical decision of resection vs other kind of treatment (studying the patient after the resection is linked to conflicts in the decision making process).

>> Included with detailed emphasis on TAMIS.

5.- I think is important to give some words to the importance of tattooing the lesions to a better control after the resection (re-endoscopy, surgery, etc).

>> Done

Reviewers' Comments to Revision

Reviewer 1: anonymous

Oct 09, 2017

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	75
Custom Review Questions	Response
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	N/A
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?	4
Does the reader get new insights from the article?	4

Please rate the practical significance.	4
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.	5 - High/Yes
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

The authors have addressed all of my comments satisfactorily. I have no further issues to raise.

Reviewer 2: Eloy Espi

Oct 07, 2017

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	70

Custom Review Questions

	Response
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
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?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	3
Please rate the practical significance.	3
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	4
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.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

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