

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

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Review

Alanna Ebigbo*, Andreas Probst and Helmut Messmann

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

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Abstract: The endoscopic treatment of cancerous and precancerous lesions in the gastrointestinal (GI) tract has experienced major breakthroughs in the past years. Endoscopic mucosal resection (EMR) is a simple and efficient method for the treatment of most benign lesions in the GI tract. However, with the introduction of endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (EFTR), the scope of lesions eligible for endoscopic treatment has been widened significantly even in the colon. These methods are now being used routinely not just for the treatment of benign lesions but also in the curative en bloc resection of early colorectal cancers. The quick, efficient, and noninvasive character of these endoscopic procedures make them not just an alternative to surgery but, in many cases, the methods of choice for the treatment of most early colon cancers and some rectal cancers.

Keywords: early colorectal cancer; EMR; ESD; full-thickness resection; TEMS.

Introduction

The endoscopic treatment of precancerous and early cancerous lesions in the gastrointestinal (GI) tract has experienced major breakthroughs in the last decades especially with the introduction of resection methods such as endoscopic submucosal dissection (ESD) and the full-thickness resection device (FTRD) technique. In any comparison between endoscopic treatment and surgery, the advantages of the former, including lower cost and shorter hospital stay, are obvious. Additionally, endoscopic resection most often leads to curative en bloc resection, which is mandatory and must be specifically considered as a quality measure.

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Andreas Probst and Helmut Messmann: Department of Gastroenterology, Klinikum Augsburg, Augsburg, Germany

The question that needs to be answered is whether endoscopic treatment offers an equal or higher quality of oncologic therapy for early colorectal cancer than surgery. Considering the fact that endoscopic treatment is usually less invasive than surgery and bearing in mind the aforementioned advantages, can we then rightfully imply that endoscopic treatment is not just a competitor or an alternative to surgery but should be the method of choice in the care of selected patients with early colorectal cancer?

In this paper, various aspects of endoscopic treatment of early colorectal cancer will be highlighted and the progress that has been made in the past decade will be demonstrated. The pros and cons of endoscopic therapy as opposed to surgery will be discussed. At the end of this argumentative paper, it should become evident that, in certain situations, endoscopic therapy is the method of choice and not just a competition with surgery.

Early colorectal cancer

Early colorectal cancer with a submucosal invasion depth of ≤ 1000 μm and without lymphovascular/vascular invasion or tumor budding is traditionally considered as a low-risk cancer with a risk of lymph node (LN) metastasis of $<1\%$ [1]. In a systematic review and meta-analysis of histopathologic factors influencing the risk of LN metastasis in early colorectal cancer, Beaton et al. [2] analyzed 23 cohort studies including >4000 patients and could demonstrate that in early colorectal cancer a depth of submucosal invasion by the tumor of >1 mm, lymphovascular invasion, poor differentiation, and tumor budding are significantly associated with LN metastasis. Various studies have shown that the quality of evidence regarding pathologic predictive factors is poor, and in select patients, endoscopic resection alone may be adequate even in the presence of deep submucosal invasion of >1000 μm [3]. However, the depth of submucosal invasion may often be subjective and not always reproducible between pathologists.

For tumor budding, there is now a recently accepted international consensus system for the reporting, scoring, and assessment of tumor budding in colorectal cancer

[4]. Tumor budding is an independent predictor of LN metastasis in pT1 colorectal cancer [5, 6], and this scoring system should be part of the pathologic workup of early colorectal cancers.

In addition to these traditional predictive markers of clinical outcome in colorectal cancer, the routine testing for molecular biomarkers, including mismatch repair (MMR) deficiency and microsatellite instability (MSI), is now recommended because it offers additional molecular biological information for the risk stratification of colorectal cancers [7]. Poor differentiation or undifferentiated cancers, for example, are usually considered high risk, although poor differentiation in the context of MMR deficiency/MSI is considered low risk. Abundant evidence suggests that MMR status is a valuable prognostic and predictive biomarker for nonmetastatic colorectal cancer and so should be performed routinely [8].

Guidelines

The European Society of Gastrointestinal Endoscopy (ESGE) recommends ESD for the en bloc resection of colorectal lesions with a high suspicion of limited submucosal invasion, especially for lesions larger than 20 mm. In these guidelines, the endoscopic suspicion of submucosal invasion is based on two main features: (1) an irregular surface pattern or a nongranular laterally spreading tumor (LST) type and (2) a depressed or pseudodepressed morphology (Figure 1) [9]. LST nongranular-type lesions have been shown to have a relatively high risk for submucosal

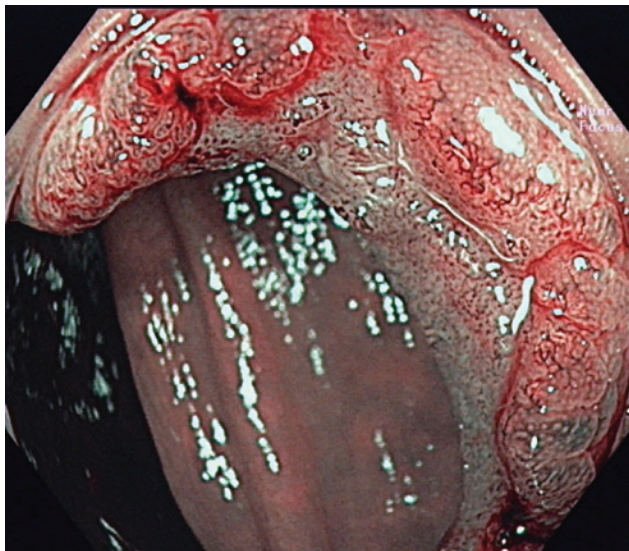


Figure 1: LST nongranular type with a depressed surface.

invasive cancer of up to 69%, and in lesions with a pseudodepressed morphology, this risk rises even up to 73.5% [10]. Other data show a risk of multifocal submucosal invasion in approximately 30–56% of all nongranular colorectal lesions [11]. As such, great emphasis must be laid on the en bloc resection of such lesions to make a reliable histopathologic analysis of tumor margins possible.

Endoscopic resection techniques

Endoscopic mucosal resection (EMR)

EMR is performed using a snare and usually after the submucosal lifting of the lesion by fluid injection. Snares of different sizes and braiding can be used depending on the size and morphology of the lesion. EMR is usually indicated for benign adenomas and smaller lesions (<20 mm). In these lesions, an en bloc resection rate of up to 80% can be achieved [12, 13]. However, with flat lesions exceeding a particular size, EMR often results in a “piecemeal” strategy that has a relatively high risk of recurrence [14]. In one study on 479 patients, the risk of recurrence after EMR was up to 41% in lesions >40 mm in size [15]. In another study on 252 large nonpedunculated adenomas (>20 mm), evident residual neoplasia was seen in 31.69% of lesions followed up after 3–6 months [16].

For large colorectal polyps, underwater EMR (UEMR) was recently directly compared to conventional EMR with regard to efficacy and safety [17]. UEMR was associated with fewer recurrences and earlier curative resections compared to conventional EMR with no significant difference in adverse events rate.

LST with a uniformly granular surface morphology have a low risk of submucosal invasive cancer, so piecemeal EMR is considered sufficient as an endoscopic treatment modality (Figure 2A–C) [18]. Colorectal lesions with a Paris type Ip morphology are also excellently well suited for snare resection, and even large pedunculated polyps with cancerous differentiation can be resected in toto, provided the snare is positioned correctly at the base of the stalk (Figure 3A and B).

In early colorectal cancer, an R0 resection of the lesion is paramount. As the histopathologic analysis of the resection margins is not possible after piecemeal resection, all lesions with a high suspicion of invasive cancer, as described above, must undergo a treatment modality with a good chance of en bloc resection. In this situation, EMR has its limitations and other methods such as the ESD are preferable [19].

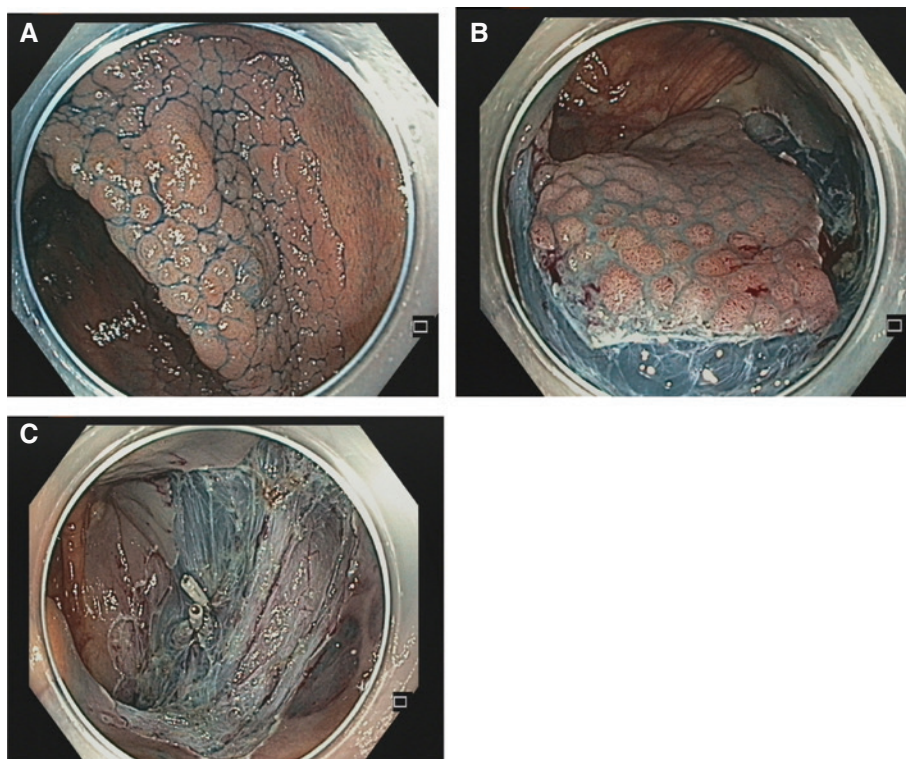


Figure 2: (A–C) Piecemeal EMR of an LST granular type in the cecum.

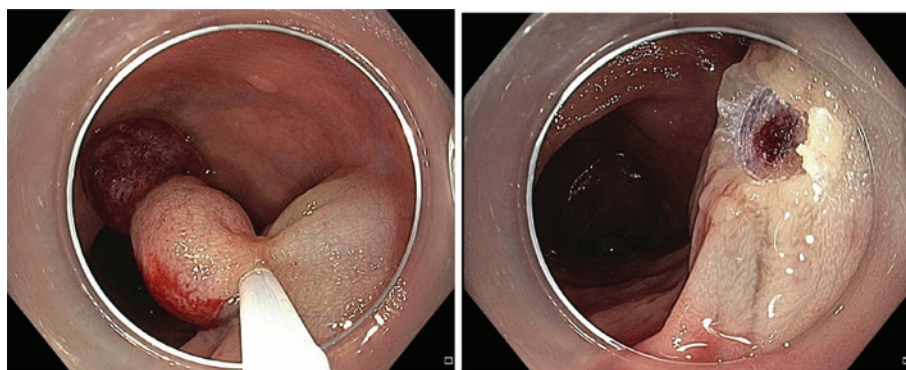


Figure 3: (A and B) Snare EMR of a small pedunculated carcinoma.

ESD

ESD has significantly better clinical outcomes than EMR with low recurrence rates of about 1.2% [20]. In a current meta-analysis by Fuccio et al. [21], ESD for colorectal neoplasia was reported to have excellent en bloc resection rates of 86% in non-Asian countries and up to 93% in Asia. Although the curative R0 resection rates differed significantly between Asian (86%) and non-Asian (73%) countries, further progress is constantly being made even in European countries. For example, Probst et al. [10] recently

demonstrated an R0 resection rate of up to 84% for benign colorectal neoplasias and a low recurrence rate of <5%.

ESD involves the circumferential mucosal incision around the lesion or tumor and subsequently the step-wise dissection of the submucosa underneath the tumor and just above the proper muscle layer (Figure 4A–D). Special knives are used depending on the preference of the endoscopist. Recently, ESD knives with the ability of both injection and dissection have been developed, enabling easy and quick manipulation without the change of instruments.

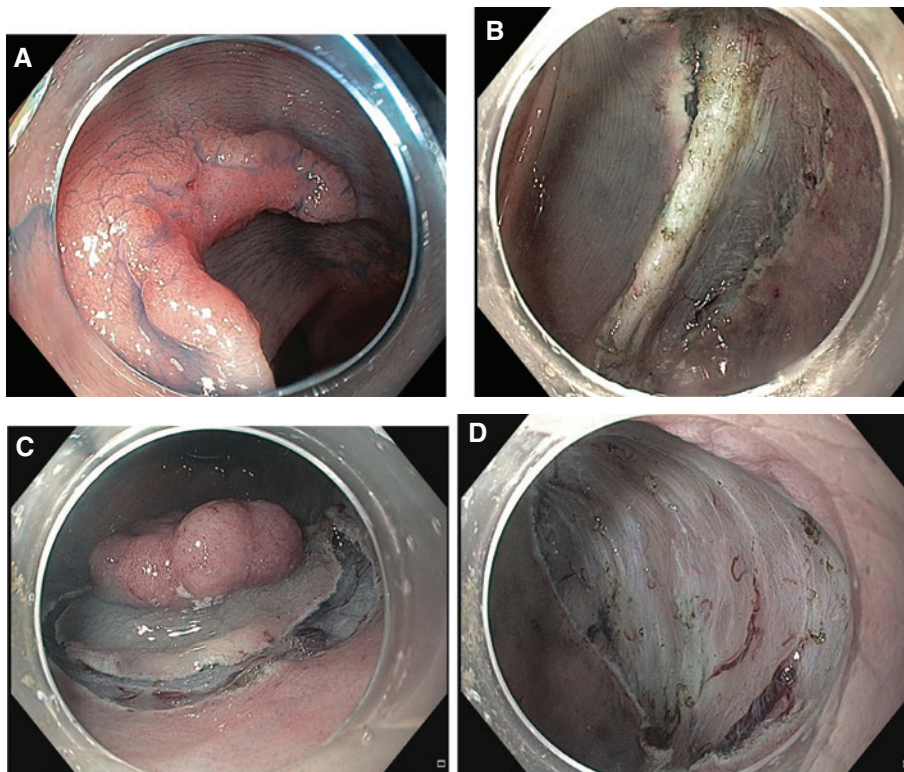


Figure 4: (A and B) ESD resection of an early carcinoma in the transverse colon and (C and D) ESD resection of a rectum adenoma with high-grade intraepithelial neoplasia (HGIEN).

ESD in general is a “difficult to learn” procedure and requires a high level of practice and dedication to achieve a satisfactory level of proficiency [22]. ESD in the right hemicolon probably belongs to the most difficult and tedious endoscopic resection procedures. In a prospective single-center series on 182 cases localized mostly proximal to the rectum, en bloc and R0 resection rates of 88.4% and 62.6%, respectively, were reported [23]. Furthermore, the efficacy of ESD for lesions up to 50 mm was shown to be satisfactory, whereas larger lesions were associated with low R0 resection rates and long procedure times. For lesions between 20 and 50 mm, a mean procedure time of 92.7 min was recorded. This single-center report underlines the fact that ESD is feasible and efficient even in the right hemicolon. However, it also shows that large colonic lesions proximal to the rectum still pose a major challenge to western endoscopists, and for large colonic lesions with suspected submucosal invasion, an alternative approach is warranted. It is obvious that ESD in the colon is technically challenging and time-consuming; however, in the hands of an expert, it becomes an important “first-choice option” for the treatment of early colorectal cancer. Although the colon ESD perforation rate in the study of Sauer et al. [23] was about 9%–10%, the

rate of perforations leading up to emergency surgery was low (just about 1%) and most perforations were treated endoscopically.

Endoscopic full-thickness resection (EFTR)

The endoscopic treatment of neoplasms in the GI tract experienced a major breakthrough with the introduction of the EFTR technique. In their review paper, Schmidt et al. [24] described classical indications for EFTR and include the “re-resection” of T1 carcinomas, the curative treatment of early colorectal lesions, and the resection of polyps in difficult anatomic localizations. When an early colorectal cancer is wrongly diagnosed as a benign adenoma and then resected classically using piecemeal EMR, it may become impossible to determine the R-status or the depth of submucosal invasion. In this situation, EFTR becomes a valuable instrument to obtain a full-thickness specimen of the resection site, broadening the diagnostic repertoire.

In the case of a correctly diagnosed early colorectal cancer, EFTR leads to a complete (R0) resection of the neoplasm including the underlying muscularis propria

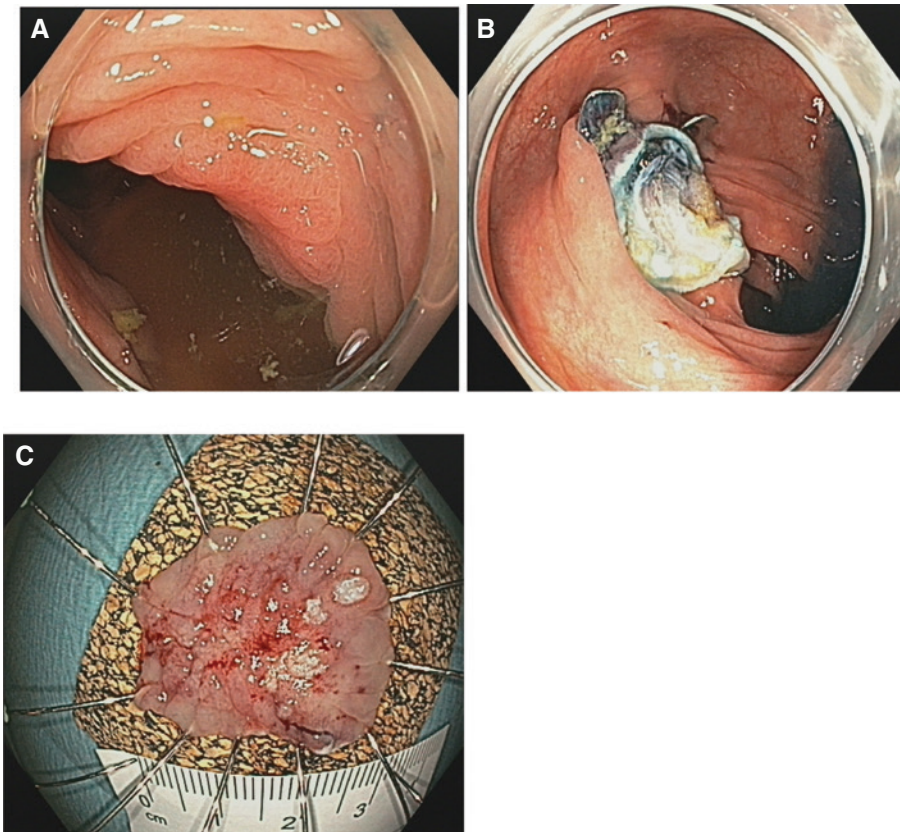


Figure 5: (A–C) EFTR of a T1 carcinoma in the descending colon.

as well as the immediate closure of the resulting defect (Figure 5A–C). An accurate histologic diagnosis of the depth of submucosal invasion is possible.

The FTRD® (“Full Thickness Resection Device”; Ovesco, Tuebingen, Germany) is the over-the-scope device that has been approved for EFTR in the lower GI tract in Europe since September 2014.

The minimally invasive surgical methods for a full-thickness resection of an early rectal cancer include transanal endoscopic microsurgery (TEMs) and transanal minimally invasive surgery (TAMIS), and like the EFTR, they usually lead to full-thickness resection specimens of rectal lesions. Whereas these transanal surgical methods are limited to the rectum, the EFTR using the FTRD® can be implemented in all sections of the colorectum, including the cecum.

Furthermore, EFTR using the FTRD® offers an important option for the endoscopic treatment of difficult lesions that when treated with EMR or ESD may result in the perforation of the colon. Such lesions include polyps with the “nonlifting sign” due to scarring, recurrent lesions, or lesions with submucosal infiltration. Neoplasms arising in the appendiceal orifice or in close proximity to diverticula have also been shown to be resectable with EFTR.

In a recently published prospective multicenter study on 181 patients in nine centers, EFTR using the FTRD® was technically successful in 89.5% with an R0 resection rate of 76.9%, and in cases with cancer, R0 resection was achieved in 72.4%. EFTR was shown to be safe with a 2.2% rate of emergency surgery due to complications [25].

Endoscopy or surgery?

The endoscopic treatment of early colorectal cancer is effective and minimally invasive and has a low recurrence rate, and it can be rightfully postulated that endoscopy has overtaken surgery in many cases of early colorectal cancer.

Although direct comparative studies between ESD and surgery are lacking, a retrospective comparison of both methods for early colorectal cancer indicated a better quality of life for patients after ESD [26]. Even the resection of rectal cancers that have encroached into the upper anal canal as well as tumors in the colon can be successfully resected endoscopically using ESD or EFTR, respectively.

TEMS and TAMIS are excellent surgical treatment options for early rectal cancer. These procedures remain more invasive than ESD or EFTR, and some studies have even shown significantly higher recurrence rates [27, 28]. However, as the case in most complex resection procedures, the quality of local endoscopic resection surgery and the steep learning curve plays an important role in the risk of recurrence [29].

Bach et al. [30] described a predictive model for local recurrence after TEMS for rectal cancer and found that three histopathologic variables were independent predictors of local recurrence: the depth of tumor invasion, the presence of lymphovascular invasion, and the maximum tumor diameter.

The management of unfavorable histopathologic findings after the local excision of colorectal cancers often includes a radical surgical resection. Several studies have reported that the oncologic outcomes in patients treated by immediate radical surgery after local excision for unfavorable histologic findings are comparable to that of radical surgery performed as a primary treatment [31]. However, a careful endoscopic assessment of colorectal lesion using various endoscopic classifications, chromoendoscopy, as well as magnification endoscopy should be done before the choice of treatment is made. The correct pretherapeutic evaluation of such lesions may help to distinguish between precancerous adenomas and deeply invasive cancer and as such improves the choice of therapeutic approach. It may be helpful to mark lesions not eligible for endoscopic resection with a submucosal tattoo to facilitate the localization of the resection site during surgery, especially when a laparoscopic-assisted resection is performed subsequently.

Complications after the TAMIS procedure are infrequent with an overall rate of 7.4%, and in TEMS, the most common complications include hemorrhage (27%), urinary tract infection (21%), and suture line dehiscence (14%) [31]. The adverse effects of full resectional surgery are well documented with a total mortality rate of 3.3%, clinical leak rates of 16% if a diverting stoma was not used, interruption of autonomic innervation to the bladder and sexual organs, urinary incontinence in 34%, and fecal incontinence in up to 60% of patients [31]. The early detection of rectal cancers through screening programs should increase the chances of treating more colorectal cancers in an early stage using local resection techniques with much lower morbidity and mortality rates [30].

As a result of these significant differences in the adverse effect rates between full resectional surgery and local resection, patients' attitudes will tend toward local

resections techniques, especially if explained carefully by an expert with experience in the procedure.

The indications for TAMIS are similar to TEMS and include benign rectal neoplasms or well-selected T1 cancers with histologically favorable features where the risk of nodal metastasis is low [32]. In unclear situations, with questionable T1 versus T2 morphology with no evidence of nodal metastasis, a TAMIS resection can serve as an "excisional biopsy," guiding further treatment with the final pathology report [32]. A more radical oncologic resection may then be implemented if the pathology returns as a T2 lesion [32]. Finally, patients with more advanced lesion (T3) who are medically unfit to have a more radical surgery can be considered for TAMIS resection [32].

In the management of early colorectal cancer, a multidisciplinary discussion between the endoscopist and the rectal surgeon is often necessary to ensure the optimal choice of treatment for the patient.

After the curative local resection of early colorectal cancer, endoscopic follow-up is necessary with a colonoscopy at 1 year and thereafter depending on the findings. For rectal cancer, a proctoscopy every 6 months for 5 years is generally recommended [31].

Conclusion

We can rightfully conclude that the endoscopic treatment of early colorectal cancer is not just a competition with surgery but should be, with some exceptions, the treatment of choice for low-risk colorectal lesions. A surgical approach is warranted in certain situations especially where endoscopic treatment fails or in the presence of high-risk features. The management of early colorectal cancers using local excision methods such as ESD or EFTR and TEMS or TAMIS in the rectum has significantly improved morbidity and mortality associated with cancer resection while at the same time maintaining excellent clinical and oncologic outcomes. Finally, as colorectal cancer screening programs have led to an increase in the detection of early-stage colorectal cancer, physicians, health-care providers, surgeons, and gastroenterologists must be educated on the possibilities, strengths, and pitfalls of these methods and ensure that their patients are informed and guided adequately.

Author Statement

Research funding: Authors state no funding involved. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent is not applicable.

Ethical approval: The conducted research is not related to either human or animals use.

Author Contributions

Alanna Ebigbo: conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. Andreas Probst: data curation; formal analysis; project administration; supervision; writing – review and editing. Helmut Messmann: conceptualization; data curation; formal analysis; methodology; project administration; supervision; visualization; writing – review and editing.

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- Supplemental Material:** The article (<https://doi.org/10.1515/iss-2017-0037>) offers reviewer assessments as supplementary material.

Reviewer Assessment

Alanna Ebigbo*, Andreas Probst and Helmut Messmann

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

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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:
Overall Reviewer Manuscript Rating:

Revise with Major Modification
 N/A

Custom Review Questions

Is the subject area appropriate for you?
 Does the title clearly reflect the paper's content?
 Does the abstract clearly reflect the paper's content?

Response

4
 5 - High/Yes
 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?	5 - High/Yes
Are units and terminology used correctly?	4
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.	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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