

ROUND 1

World Journal of Clinical Cases

Dear Editors,

We thank the Reviewers for their careful appraisal of our manuscript and their useful comments. In response to the Reviewer's comments, we have revised the manuscript in a point-by-point manner.

We hope that our manuscript, entitled "**Clinicopathological features of small T1 colorectal cancer**" is now suitable for publication in *World Journal of Clinical Cases* and look forward to hearing from you at your earliest convenience.

Yours sincerely,
Katsuro Ichimasa

Response for the Reviewer

Thank you for your careful review of our paper. We have answered each of your points below.

Reviewers' comments:

Reviewer #1

Keywords: 1) Please make sure that the keywords are found in US-NLM at:

<https://meshb.nlm.nih.gov/MeSHonDemand>

Response: Thank you for your useful comment. We have changed the keywords as follows:

"Colorectal neoplasms; lymphatic metastasis; biological phenomena; polyps"

Introduction: The authors demonstrated what is already known about the topic clearly, except for this mentioned paragraph starting with "Recently, the strategy of "resect and discard" has emerged" 2) (Resect and discard) is not always beneficial for patients' care and this issue has been argued in several literatures, so I recommend

discussing this point in the discussion section.

Response: Thank you for highlighting this issue. In accordance with your comment, we have rewritten the Introduction and have described the resect and discard strategy in the Discussion section.

(Introduction)

“Recently, the “resect and discard” strategy has emerged. In this approach, polyps smaller than 10 mm that are preoperatively diagnosed by magnifying narrow-band imaging do not need to be sent for pathological examination because of its high diagnostic performance despite the potential risk of small invasive cancer, which should be assessed to determine the additional surgical resection [16].”

(Discussion)

“The “resect and discard” strategy using optical diagnosis is an attractive approach for endoscopists, pathologists, and patients, and enables a major reduction in the cost of screening and surveillance colonoscopy. However, it has the potential risk to discard small, advanced neoplasia, which are lesions of less than 10 mm with advanced histology (high grade dysplasia, villous component, and adenocarcinoma). Notably, in T1 CRC, additional surgical resection after endoscopic resection is required according to the risk of LNM on the basis of the pathological findings of resected specimens to achieve a cure. More than 60% of T1 CRCs are misdiagnosed as adenoma by endoscopists according to a recent prospective study in the Netherlands^[1]. In our study, small lesions occupied approximately 10.1% of total T1 CRCs, which had equal potential for metastasis to lymph nodes compared with large lesions. Therefore, careful observation by endoscopy should be undertaken when adopting the “resect and discard” strategy.”

3) Line5: “cut into parallel 2- to 3-mm-thick sections” Kindly make sure that the used measurement unit is 2-3 microns NOT (millimeter) .

Response: Thank you for your comment. The specimens were cut into 2- to 3-mm (millimeter)-thick sections. Thus, it is definitely millimeters and not microns.

4)Line7: “diagnosed on the basis of the World Health Organization” should be; diagnosed on the basis of the 2019 World Health Organization.

Response: Thank you for pointing this out. Accordingly, we have changed the relevant phrase to “diagnosed on the basis of the 2019 World Health Organization classification.”

5) Cite the tables properly.

Response: Thank you for your comment. We have added all the table citations to the Results section accordingly.

6) First paragraph looks repetition, no need for this “In this study, we revealed the clinicopathological features of small T1 CRCs compared with large T1 CRCs. Small T1 CRCs were comparable to large T1 CRCs regarding the rate of LNM, followed by the rate of lymphatic and vascular invasion, tumor differentiation, and tumor budding”.

Response: Thank you for your useful comment. To address this issue, we have deleted the first sentence “In this study,...” from the Discussion.

7) What is the utility of references number 18 and 19?

Response: As per your comment, we have deleted references 18 and 19 from the manuscript.

8) Language final revision is advised

Response: Thank you for your comment. A draft of our manuscript was edited by a native English-speaking editor. We have attached the certification.

Reviewer #2: The authors have made good attempts at providing insight into what contribution tumor size could make in T1 colorectal carcinomas. The study design is adequate and the results are noteworthy. In a broad sense, the discussion section needs to be developed more to harness the important findings of this study. More in-depth discussion is required. Other specific comments are outlined below.

Response: Thank you for your encouraging comments. Accordingly, we added a paragraph emphasizing the important findings of this study to the Discussion session, as follows:

“The “resect and discard” strategy using optical diagnosis is an attractive approach for endoscopists, pathologists, and patients, and enables a major reduction in the cost of screening and surveillance colonoscopy. However, it has the potential risk to discard small, advanced neoplasia, which are lesions of less than 10 mm with advanced histology (high grade dysplasia, villous component, and adenocarcinoma). Notably, in T1 CRC, additional surgical resection after endoscopic resection is required according to the risk of LNM on the basis of the pathological findings of resected specimens to achieve a cure. More than 60% of T1 CRCs are misdiagnosed as adenoma by

endoscopists according to a recent prospective study in the Netherlands^[1]. In our study, small lesions occupied approximately 10.1% of total T1 CRCs, which had equal potential for metastasis to lymph nodes compared with large lesions. Therefore, careful observation by endoscopy should be undertaken when adopting the “resect and discard” strategy.”

Minor issues:

comment 1. please recast the statement on lines 85-87. Some words might be missing there.

Response: Thank you for your comment. We have rewritten the relevant sentences as follows:

“However, tumor size is not mentioned in these guidelines. Although tumor size was reported to be a risk factor for prognosis in advanced cancers, few reports have investigated the correlation between tumor size and clinicopathological features including the presence of LNM in T1 CRC^[2, 3].”

comment 2. The concept of tumor budding described by the authors do not seem to agree with the recent International Tumor budding consensus recommendations. Would the authors be pleased to revise their tumor budding assessment using the current guidelines?

Response: Thank you for your useful comment. We assessed the grade of tumor budding according to the current Japanese guidelines. We have rewritten the definition of tumor budding and added the relevant guidelines reference:

““Tumor budding” is defined as a cancer cell nest consisting of one or fewer than five cells that infiltrate the interstitium at the invasive margin of the cancer. On selecting the region where tumor budding is the greatest, the front of the tumor growth is observed at 200× magnification to count the number of tumor buds: BD1, 0–4; BD2, 5–9; and BD3, ≥ 10 ^[4].”

comment 3. The first sentence under the discussion section may need revision. please check that. There are few others such as lines 203 and 211.

Response: Thank you for your useful comment. Because this sentence was repetitive, as Reviewer 1 also pointed out, we have deleted it.

comment 4. The points made from line 224 to 231 would fit more in the methods and results sections. Better still, this whole paragraph can be revised to bring out clearly the

authors' intended meaning.

Response: Thank you for your useful comment. We have replaced this paragraph in the Results section as per your comment and have rewritten it as follows:

“We present a typical case of small T1 CRC with LNM positivity in Figure 2. An 8-mm lesion with depressed type morphology was identified in the sigmoid colon. According to the magnification endoscopy findings, we predicted that the depth of invasion was T1b. Therefore, we selected surgical resection with lymph node dissection as the first-line treatment for this lesion. The final pathological findings were well to moderately differentiated adenocarcinoma, positive lymphovascular invasion, positive vascular invasion, 3750- μ m depth of invasion, grade 2 tumor budding, and positive LNM. Despite the small lesion, it had risk factors for LNM and showed LNM positivity, and thus required surgical resection to achieve a cure. Of course, pre-treatment endoscopic diagnosis was important; however, if endoscopic resection was selected for this type of lesion, we should resect it with a negative margin and properly stratify the risk for LNM on the basis of the histopathological diagnosis.”

comment 5. The conclusion needs revision to make it more constructive.

Response: Thank you for your useful comment. We have revised the conclusion accordingly.

“In conclusion, we investigated the clinicopathological features of small T1 CRCs and revealed that there was no significant difference in the rate of LNM, followed by the rate of vascular invasion, lymphatic invasion, or histological grade, between the small and large tumor groups. Therefore, we should determine the requirement for additional surgical resection after endoscopic resection of T1 CRC on the basis of a careful pathological diagnosis, even if it is a small lesion.”

comment 6. Concerning gender as presented on the Tables, only data for males were presented. Is there a reason for this? What is the observation regarding the significant difference in tumor size among males ($p = .03$) on table 2?

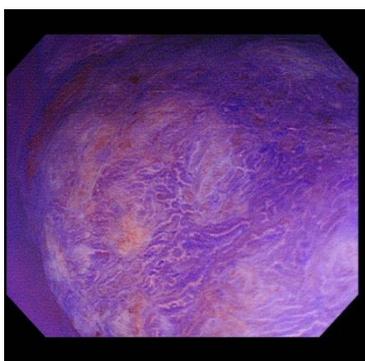
Response: Thank you for your useful questions. We have presented the data of both males and females. In addition, we have provided all data for the other factors in the tables.

comment 7. Regarding the figures, the alphabetical annotations were placed above the figures. Please look at that again.

Response: Thank you for your useful comment. The alphabetical annotations have been replaced below the figures.

comment 8. Figure 2c is a photomicrograph said to be of a well differentiated carcinoma. At this scanning power of the microscope, readers may not be able to discern this. a higher magnification photomicrograph would be appropriate please.

Response: Thank you for your useful comment. To address this issue, we have replaced Figure 2c with endoscopic images at a higher magnification, as attached.



Article Highlights

Research background:

Additional surgical resection of T1 colorectal cancer after endoscopic resection is determined according to the risk of lymph node metastasis on the basis of the histopathological findings of resected specimens.

Research motivation:

Clinicopathological features including the rate of lymph node metastasis in small (<10 mm) T1 colorectal cancer were unknown.

Research objectives:

The purpose of this study was to clarify the clinicopathological characteristics of small (<10 mm) T1 colorectal cancer compared with large (≥ 10 mm) tumors.

Research Methods:

We retrospectively analyzed clinicopathological features, including the rate of lymph node metastasis, of 1,152 T1 colorectal cancers divided into two groups: small (<10 mm) and large (≥ 10 mm) tumors.

Research results:

Small T1 colorectal cancer had a similar rate of lymph node metastasis, followed by a positive rate of histological grade and lymphovascular invasion, compared with large tumors.

Research conclusions:

Because there were no significant differences in the rate of lymph node metastasis between small and large T1 colorectal cancers, the decision on whether to undertake secondary surgical resection should be determined according to pathological findings, regardless of tumor size.

Research perspectives:

Because this was a single-center retrospective study, prospective multicenter studies are required to validate these findings.

Audio Core Tip:

This is a retrospective study to evaluate the clinicopathological features in T1 colorectal cancers. We compared clinicopathological factors including lymph node metastasis between the two groups: a small group (<10 mm) and a large group (≥10 mm). Since there was no significant difference in the rate of lymph node metastasis followed by histological grade, vascular invasion, or lymphatic invasion, between small and large T1 colorectal cancers, the requirement for additional surgical resection should be determined according to pathological findings, regardless of tumor size.

1 Vleugels JLA, Koens L, Dijkgraaf MGW, Houwen B, Hazewinkel Y, Fockens P, Dekker E, group Ds. Suboptimal endoscopic cancer recognition in colorectal lesions in a national bowel screening programme. *Gut* 2020; **69**(6): 977-980 [PMID: 31822579 PMID: PMC7282551 DOI: 10.1136/gutjnl-2018-316882]

2 Beppu K, Nagahara A, Terai T, Matsumoto K, Shibuya T, Sakamoto N, Osada T, Kawabe M, Otaka M, Ogihara T, Watanabe S. Clinicopathological characteristics of colorectal cancer less than 10 mm in diameter and invading submucosa and below. *Journal of gastroenterology and hepatology* 2010; **25 Suppl 1**: S57-61 [DOI: <https://dx.doi.org/10.1111/j.1440-1746.2010.06234.x>]

3 Park SH, Oh SO, Park SS, Roh SJ, Han KS, Kim B, Hong CW, Kim BC, Sohn DK, Chang HJ, Park SC, Oh JH. Characteristics of minute T1 colorectal cancer in relevance to pathology and treatment. *Annals of surgical treatment and research* 2020; **98**(4): 199-205 [DOI:

<https://dx.doi.org/10.4174/ast.2020.98.4.199>]

4 Japanese Society for Cancer of the C, Rectum. Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition [Secondary Publication]. *Journal of the anus, rectum and colon* 2019; **3**(4): 175-195 [PMID: 31768468 PMCID: PMC6845287 DOI: 10.23922/jarc.2019-018]

ROUND 2

Comment by the reviewer (05775699)

Your choice of Japanese tumour budding determination and grading protocol is well respected. All other responses are acceptable too. In the conclusion section, "Therefore, we should determine the requirement for additional surgical resection after endoscopic resection of T1 CRC on the basis of a careful pathological diagnosis, even if it is a small lesion." may read as "Therefore, requirements for additional surgical resection after endoscopic resection of T1 CRC should be determined on the basis of a careful pathological diagnosis, even if it is a small lesion."

Response: Thank you for your comment. As per the reviewer's comment, I rewrote the conclusion section as follows. "Therefore, requirements for additional surgical resection after endoscopic resection of T1 CRC should be determined on the basis of a careful pathological diagnosis, even if it is a small lesion."