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Prof Ze-Mao Gong
Science Editor
Editorial Office
World Journal of Gastroenterology

Manuscript No: 38987
"Current clinical management of gastrointestinal stromal tumor"

Dear Prof Gong,

We greatly appreciate the comments from you and the peer reviewers. We have taken all comments into account in the revision of our manuscript (All changes highlighted in red in the revised manuscript). Our point-by-point responses to all comments are provided below.

Responses to editor's suggestions.

1) We uploaded a language certificate by professional English language editing companies.

2) We uploaded an audio file describing our final core tip.

3) We provided all authors abbreviation names and manuscript title in the Core tip section.

4) We found one repeated reference (Original Ref 83) and deleted it.

5) We uploaded PPT version of Fig. 1, 2, 3, 4, 5, 6, 7. However, Fig 8 was complicated. We copied the Fig 8 from the original article PDF and converted it to TIFF file. So we have no PPT version.

6) We uploaded the video in the revised files.

Responses to reviewers' comments

Responses to Reviewer #1 (00071178)

1) We agree with the reviewer's suggestion to address the usefulness of tyrosine kinase inhibitors in cases of R0 resection. We have already mentioned this merit in the Treatment section of the original version of the manuscript ("In contrast, the introduction of tyrosine kinase inhibitors has dramatically improved the management of GISTs, prolonging recurrence-free survival after surgery…."), but only briefly. Adjuvant imatinib in cases of R0 and R1 resection is currently indicated in patients with high-risk GISTs and is recommended for 3 years. For patients with intermediate-risk GISTs, the evidence is not sufficient to make such a conclusion. According to the reviewer's kind suggestion, we have revised the text relevant to this issue in the **TREATMENT** section.

We have revised the following text on page 13, line 15 in the revised manuscript (**TREATMENT** section):

"In contrast, the introduction of imatinib (first-line tyrosine kinase inhibitor) has dramatically improved the management of GISTs, prolonging recurrence-free survival after surgery [82] and extending overall survival in metastatic or unresectable cases [14]. Three years of adjuvant therapy with imatinib for patients with high-risk GISTs who have undergone macroscopic complete tumor resection (R0 and R1) is recommended because it improves overall survival and recurrence-free survival [82]."

2) We appreciate the reviewer's recommendation regarding the three valuable articles concerning symptoms of GISTs. However, the main focus of our review is **early management of asymptomatic small SELs.** Therefore, we will not use these articles at this time.

Response to Reviewer #2 (00504187)

We are happy to have obtained an A rank for publication from the reviewer.

Response to Reviewer #3 (00058401)

We are happy to have obtained an A rank for publication from the reviewer.

Response to Reviewer #4 (00504581)

1) Although the reviewer requested that we change the order of the sections (**HISTOLOGICAL FINDINGS, TUMOR TISSUE SAMPLING METHODS, DIAGNOSTIC PROCESS**), we believe that the original order facilitates maximal understanding by readers. Therefore, we did not change the section order.

2) According to the reviewer's kind suggestion, we have defined "DOG1" at its first use in both the **Abstract** and **INTRODUCTION** section:

Abstract: "Pathologically, diagnosis of a GIST relies on morphology and immunohistochemistry [KIT and/or discovered on gastrointestinal stromal tumor 1 (DOG1) is generally positive]."

INTRODUCTION: "GISTs should be diagnosed by immunohistochemical analysis including assessment of KIT, CD34, and/or discovered on gastrointestinal stromal tumor 1 (DOG1) [8,22,23]."

3) (i) Although the reviewer pointed out the lack of an important reference (Faulx Ashley L, GIE 2017), we have already quoted this reference (Ref. No. 62) in the original version of the manuscript.

(ii) Clinically malignant features on endoscopy include irregular borders, ulceration, and/or growth during endoscopic follow-up **(Ref. 36:** Nishida T, et al. Dig Endosc. 2013). According to the reviewer's kind suggestion, we have added malignant features on endoscopic examination to the **ENDOSCOPY** section (page 8, line 6 in the revised manuscript):

"Irregular borders, ulceration, and/or growth during endoscopic follow-up are considered clinically malignant features on endoscopy [36]."

(iii) SMT v.s. SEL

A submucosal tumor (SMT) is defined as an intramural tumor under the mucosa (i.e., epithelium). A subepithelial lesion (SEL) is defined as a lesion under the epithelium; thus, SELs include SMTs and other SMT-like lesions such as extramural compression. Endoscopic SMTs include true SMTs and other SMT-like lesions as mentioned above. Therefore, SEL is the better term. The term "SEL" has recently been used more frequently than "SMT" in endoscopy journals. The use of both "SEL" and "SMT" in our article has the risk of introducing confusion. We decided to use only "SEL" in

this paper. According to the reviewer's kind suggestion, we have changed all cases of "SMT" to "SEL" in this article.

4) According to the reviewer's kind suggestion, we have added some related text concerning malignant EUS features of GISTs and three new references to the **EUS** section (page 8, line 25 in the revised manuscript):

"According to previous reports, possible high-risk EUS features for GISTs are a size of >2 cm, irregular borders, heterogeneous echo patterns, anechoic spaces, echogenic foci, and growth during follow-up [44,45]. However, Kim et al. [46] reported that tumor size and EUS features cannot be used to preoperatively predict the risk of malignancy of medium-sized (2–5 cm) gastric GISTs. At present, estimation of the risk of malignancy of GISTs of <5 cm by EUS imaging alone seems to be difficult."

References

[44] **Palazzo L,** Landi B, Cellier C, et al. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. Gut. 2000;46:88–92. [PMID: 10601061 DOI: 10.1136/gut.46.1.88]

[45] **Chak A,** Canto MI, Rösch T, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. Gastrointest Endosc. 1997;45:468–73. [PMID: 9199902 DOI: 10.1016/S0016-5107(97)70175-5]

[46] **Kim MN**, Kang SJ, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Prediction of risk of malignancy of gastrointestinal stromal tumors by endoscopic ultrasonography. Gut Liver. 2013 ;7: 642-7. [PMID: 24312703 DOI: 10.5009/gnl.2013.7.6.642.]

5) (i) The tissue sample volume obtained by EUS-FNA is usually small. Therefore, assessment of mitosis by EUS-FNA is difficult. Ando et al. [Ref. 60. Gastrointest Endosc 2002] reported that the MIB-1 labeling index is accurate for diagnosis of malignant GISTs because Ki-67-positive cells can be easily recognized in the small specimens obtained by EUS-FNA. According to the reviewer's kind suggestion, we have addressed mitotic index evaluation by EUS-FNA and added a reference in the ***EUS-FNA*** section (page 10, line 17 in the revised manuscript):

"Evaluation of mitosis is important to determine the metastatic risk of GISTs. Unfortunately, the tissue sample volume obtained by EUS-FNA is usually small. Therefore, assessment of mitosis by EUS-FNA is difficult. Ando et al. [60] reported that the MIB-1 labeling index is accurate (100%) for diagnosis of malignant GISTs

because Ki-67-positive cells can be easily recognized in the small specimens obtained by EUS-FNA."

Reference

[60] Ando N, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T, Hayakawa T. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. Gastrointest Endosc. 2002;55:37-43. [PMID: 11756912 DOI: 10.1067/mge.2002.120323]

(ii) The tissue sample volume obtained by endoscopic biopsy using endoscopic submucosal dissection or endoscopic snare resection techniques is usually large. Therefore, a mitotic count is more easily obtained. However, such approaches have a risk of perforation leading to tumor cell seeding. According to the reviewer's kind suggestion, we have addressed the mitotic index evaluation by endoscopic resection techniques and added two references in the "***Endoscopic biopsy using endoscopic submucosal dissection or endoscopic snare resection techniques***" section (page 11, line 8 in the revised manuscript):

"An additional advantage of these methods is the ability to evaluate the risk classification of GISTs using the mitotic count per 50 high-power fields [65,66]."

References

[65] **Dolak W,** Beer A, Kristo I, Tribl B, Asari R, Schöniger-Hekele M, Wrba F, Schoppmann SF, Trauner M, Püspök A. A retrospective study on the safety, diagnostic yield, and therapeutic effects of endoscopic unroofing for small gastric subepithelial tumors. Gastrointest Endosc 2016;84:924-9. [PMID: 27109457 DOI: 10.1016/j.gie.2016.04.019]

[66] **Kobara H,** Mori H, Nishimoto N, Fujihara S, Nishiyama N, Ayaki M, Yachida T, Matsunaga T, Chiyo T, Kobayashi N, Fujita K, Kato K, Kamada H, Oryu M, Tsutsui K, Iwama H, Haba R, Masaki T. Comparison of submucosal tunneling biopsy versus EUS-guided FNA for gastric subepithelial lesions: a prospective study with crossover design. Endoscopy International Open 2017; 05: E695–E705. [PMID: 28782002 DOI: 10.1055/s-0043-112497]

On page 11, line 10 in the revised manuscript, we have revised a related sentence in the "***Endoscopic biopsy using endoscopic submucosal dissection or endoscopic snare resection techniques***" section:

"However, ESD and endoscopic snare resection are invasive procedures; therefore, endoscopists should pay special attention to intraoperative bleeding and perforation while performing these techniques because such complications may cause severe hypotension or tumor cell seeding."

6) According to the reviewer's kind suggestion, we have addressed the use of tyrosine kinase inhibitors and added two references in the **TREATMENT** section (page 13, line 15 in the revised manuscript):

"In contrast, the introduction of imatinib (first-line tyrosine kinase inhibitor) has dramatically improved the management of GISTs, prolonging recurrence-free survival after surgery [82] and extending overall survival in metastatic or unresectable cases [14]. Three years of adjuvant therapy with imatinib for patients with high-risk GISTs who have undergone macroscopic complete tumor resection (R0 and R1) is recommended because it improves overall survival and recurrence-free survival [82]. Sunitinib (second-line tyrosine kinase inhibitor) [83] and regorafenib (third-line multikinase inhibitor) [84] can be used in advanced GISTs after treatment failure with imatinib."

References

[83] **Demetri GD**, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006 ;**368**:1329-1338. [PMID: 17046465 DOI: 10.1016/S0140-6736(06)69446-4]

[84] **Demetri GD**, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; 381:295-302.

Response to Reviewer #5 (01047625)

Thank you for your comments.

1) According to the reviewer's kind suggestion, we have more clearly explained how these contour maps are constructed on page 14, line 12 in the revised manuscript (**PROGNOSIS AND RISK CLASSIFICATION** section):

"In addition, contour maps (Figure 8) can be created based on investigation of the prognosis of many cases worldwide. In these maps, the risk of recurrence at the 10th year after surgical treatment of a GIST is calculated using the maximum diameter of the tumor, the number of mitoses, the tumor site, and the presence or absence of tumor capsule rupture; continuous risk assessment is also possible [87]."

2) According to the reviewer's kind suggestion, we have described what the different areas of color of mean in the figure legend (page 46, line 22 in the revised manuscript):

"Areas of colors according to the recurrence rate at the 10th year after surgical treatment of GIST: Blue-black: 0%–10%, Blue: 10%–20%, Light blue: 20%–40%, Gray: 40%–60%, Pink: 60%–80%, Red: 80%–90%, Dark red: 90%–100%."

Response to Reviewer #6 (00008633)

Thank you for your comments.
1) The reviewer suggested that the review is too long and that there are many repetitions. We partially agree with the reviewer's opinion, but we believe that some similar sentences are necessary to ensure that readers gain a good understanding. According to the reviewer's kind suggestion, we have deleted one sentence and revised a related sentence as shown below.

We have deleted the following sentence from the **DIAGNOSTIC PROCESS** section on page 11, line 8 in the original manuscript:

"For some SELs, such as a lipoma, cyst, or lymphangioma, and for extraluminal compression by surrounding normal organs or lesions, the endoscopic and EUS appearances are considered diagnostic and tissue sampling is not required."

On page 12, line 8 in the revised manuscript, we have revised the following sentence in the **DIAGNOSTIC PROCESS** section:

"First, all SELs are examined by EUS, and the SELs mentioned in the EUS section (Figure 3) that are conclusively diagnosed by EUS findings only are excluded."

2) We disagree with the reviewer's opinion. We believe that Figures 3 and 5 are useful tools to ensure that readers have a good understanding of the diagnostic strategy of GISTs.

3) CT is the main focus in the "POSTOPERATIVE FOLLOW-UP" section.
According to the reviewer's kind suggestion, we have renamed this section "POSTOPERATIVE FOLLOW-UP BY CT."

4) According to the reviewer's kind suggestion, we have added new information regarding the use of tyrosine kinase inhibitors and added two references in the **TREATMENT** section (page 13, line 15 in the revised manuscript):

"In contrast, the introduction of imatinib (first-line tyrosine kinase inhibitor) has dramatically improved the management of GISTs, prolonging recurrence-free survival after surgery [82] and extending overall survival in metastatic or unresectable cases [14]. Three years of adjuvant therapy with imatinib for patients with high-risk GISTs who have undergone macroscopic complete tumor resection (R0 and R1) is recommended because it improves overall survival and recurrence-free survival [82]. Sunitinib (second-line tyrosine kinase inhibitor) [83] and regorafenib (third-line multikinase inhibitor) [84] can be used in advanced GISTs after treatment failure with imatinib."

References

[83] **Demetri GD**, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006 ;**368**:1329-1338. [PMID: 17046465 DOI: 10.1016/S0140-6736(06)69446-4]

[84] **Demetri GD**, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013; 381:295-302.

5) According to the reviewer's kind suggestion, we have moved some sentences from the "MANAGEMENT OF SMALL SELs SUSPECTED TO BE GISTs" to other sections (EUS or EUS-FNA sections).

On page 8, line 22 in the revised manuscript, we have moved the following sentence from "MANAGEMENT OF SMALL SELs SUSPECTED TO BE GISTs" to the **EUS** section:

"The typical EUS imaging feature of a GIST is a hypoechoic solid mass. EUS can accurately discriminate a SEL suspected to be a GIST (hypoechoic solid mass) from other SELs, including lipomas, cysts, varices, and extra-gastrointestinal compression."

On page 10, line 10 in the revised manuscript, we have revised and moved the underlined sentence below from "MANAGEMENT OF SMALL SELs SUSPECTED TO BE GISTs" to the "*EUS-FNA*" section:

"Unfortunately, EUS-FNA for a subepithelial hypoechoic solid mass of <1 cm is technically difficult using a standard EUS-FNA scope; thus, EUS-FNA is recommended for masses of >1 cm [56,57]. However, forward-viewing and curved linear-array echoendoscopes [58] and drill needles [59] have recently been developed and are expected to improve the diagnostic rate of small SELs. The rate of adverse events associated with EUS-FNA using a 22-gauge needle is reportedly close to 0% [54-56]."

On page 16, line 17 in the revised manuscript, we have deleted the two underlined sentences below and added related sentences to the "**MANAGEMENT OF SMALL SELs SUSPECTED TO BE GISTs"** section:

The typical EUS imaging feature of a malignant SEL, including a GIST, is a hypoechoic solid mass. EUS can accurately discriminate a SEL suspected to be a GIST (hypoechoic solid mass) from other SELs, including lipomas, cysts, varices, and extra-gastrointestinal compression. Active performance of EUS is effective even for small SELs of ≤2 cm to ensure early detection of hypoechoic solid masses suspected to be GISTs [56]. If EUS imaging of a SEL with an endoscopically negative biopsy shows a hypoechoic solid mass of >1 cm, subsequent EUS-FNA is needed to obtain a conclusive tissue diagnosis of a GIST [21,56]. However, EUS-FNA for a subepithelial hypoechoic solid mass of <1 cm is technically difficult using a standard EUS-FNA

scope; thus, EUS-FNA is recommended for masses of >1 cm[53,88]. Small SELs of <1 cm are currently recommended to undergo periodic EUS follow-up (every 6 months or 1 year) [56,91] because EUS-FNA for small SELs of <1 cm is technically difficult.

Additionally, we have corrected typographical errors below.

#1. Title page, line 11
Tadashi Koga, Department of Pathology, >> Surgery

#2. Introduction, page 5, line 8
is >> it

#3. **Diagnostic process,** page 12, line 17
(Figure 2G, H) >> (Figure 2G, H)

#4. **Management of small SELs suspected TO BE GISTs**, page 16, line 7
GISTs registered >> GISTs of <2 cm registered

#5. One repeated reference (Original Ref 83) was deleted.

We are sending herewith a cover letter (including our responses to the reviewers), revised manuscript entitled "**Current clinical management of gastrointestinal stromal tumor**" (38987-Revised manuscript, Table 1, Figs. 1-8, VTR 1), and all required documents, which we would like you to consider for publication in the *World Journal of Gastroenterology*.

Thank you very much for your consideration.

Yours sincerely,

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