Peer Review File

Article information: http://dx.doi.org/10.21037/ls-20-139

Reviewer A

Comments to the authors:

1. There are a number of errors in grammar and syntax. Although none of these are major they are frequent and consistent enough that it would greatly behove the authors to have the manuscript reviewed for consistency and accuracy of the English language. One typical example is the 3rd sentence of the abstract. The occurrence of spontaneous or iatrogenic rupture may explain this heterogeneity in survival and recurrence rates in "the" Literature. The "the" is missing and Literature should not be capitalized.

Reply: thanks for your comment. The manuscript has been reviewed.

Changes in the text: see manuscript.

2. it is not clear to me why you say on page 5 that due to the limitations of the staging systems in this disease, they are rarely used, especially in European countries. I am not aware of this being limited to European countries.

Reply: we agree with the reviewer, this sentence may be misleading and, hence, it was accordingly amended.

Changes in the text: Page 5, lines 115-117.

3. In discussing the results of the Mccarter et al paper first you say that 3yr recurrence free survival is worse in patients that have tumor rupture.. It would be nice to see those numbers

Reply: thanks for the useful suggestion; the relevant data were added in the table 1 (see comment#4)

Changes in the text: see Table 1.

4. Again, in the subsequent paragraph you discuss the results of the meta-analysis. It would again be nice to see some of those actual numbers. I may be helpful to the reader to put some of these actual numbers in a table

Reply: thank you for your suggestion but we preferred to report in table 1 only results from more recent studies and not to replicate those from the meta-analysis by Zhi.

Changes in the text: see Table 1.

5. I am concerned that the description of the pseudo-capsule as a natural barrier to tumor cells could mislead the reader. The pseudo-capsule is a very weak barrier -that is why it is a pseudo capsule. I think this needs to be clearer

Reply: thanks a lot for the comment; we absolutely agree with the reviewer as this description may be misleading. We accordingly modify the manuscript.

Changes in the text: see page 8, lines 186-190.

6. The discussion on "intentional" R1 resection is inherently somewhat

counterintuitive. For example, to say that man R1 resection may be reasonable in small GISTS but it should be done by oncologic principles is an oxymoron - by definition an R1 resection does not follow oncologic principles. I think this section needs to be expanded and also explained more clearly

Reply: thank you for your suggestion. We tried to make the concept clearer.

Changes in the text: see page 11, lines 264-265.

Reviewer B

Comments to the authors:

This is a potentially useful review concerning the importance of margin status in determining the prognosis of resected GIST. Much of the data presented are also to be found in the paper by Nishida et al "Defining Rupture in Gastrointestinal Stromal Tumor" Ann Surg Oncol 2019;26:1669-75), although this review goes further in discussing surgical management per se.

The most important message is probably the conclusion from studies in Norway and elsewhere that the adverse impact of an R1 or microscopic margin, is due to tumour rupture. The classification of tumour rupture by the Oslo Sarcoma Group appears useful and if applied prospectively in future clinical trials could further clarify this issue. The authors acknowledge the recommendation in the ESMO guidelines that patients with frank tumour rupture effectively have peritoneal disease and require indefinite adjuvant treatment with imatinib, Another important message is the recommendation that when laparoscopic resection should be actively discouraged in the case of larger tumours, because of the increased risk of tumour rupture.

In the abstract it is listed under everyday practice – "patients may undergo piecemeal resection by endoscopists with no expertise on (in the treatment of??) GIST" – surely this is not "everyday clinical practice" no tumours should be excised in this fashion, whether GIST of not and such practice has no place. It is inappropriate to list it in this fashion, although inadvertent removal of what is believed to be a benign mass may sometimes occur like this, perhaps. It would be better to state that GISTs should be managed by centres experienced in the multidisciplinary care of this disease.

Reply: thank you for the comment. We removed that sentence as it could have been misinterpreted.

Changes in the text: see page 3, lines 61-66.

In line 159 and following the impression is given that the pseudo-capsule represents a barrier to tumour penetration. It may be a barrier to tumour rupture, but it may also contain tumour cells and certainly in resection of extremity soft tissue sarcomas the pseudo-capsule is regarded as part of the tumour, in that resection should performed be through normal tissue beyond it. "Shelling" out a tumour by its pseudo-capsule almost invariably results in local recurrence. This is in fact explained in a way in lines 259,

260. The risk of shelling out a GIST needs to be emphasised here too because the pseudo-capsule may be contaminated. This needs to be better expressed in line 260 – see below

Reply: As suggested also by reviewer A, we tried to better explain this concept.

Changes in the text: page 8, lines 185-189; page 9 lines 264-268.

Where I believe the authors are completely wrong is the statement in lines 247, 248 that the SSGXVIII /AIO trial proves that >3 years of adjuvant therapy is of no value in patients with tumour rupture. They reference an opinion paper by Eisenberg rather than the study report from 2012 by Joensuu and colleagues. This study did not investigate treatment beyond 3 years, patients with tumour rupture had a statistically significant improvement in recurrence-free survival (p=0.02) and in the Discussion it is stated that there are patients who may benefit from a longer duration of treatment but that this is best studied in a randomised clinical trial – as indeed is being done. The authors need to read source data, not rely on someone else's interpretation, if indeed they have correctly reported what Eisenberg concluded. This error needs to be corrected. A similar erroneous conclusion is to be found in the paper by Nishida et al, in which it is stated that prolonged, i.e. 3 years, of treatment did not benefit patients with tumour rupture. This is not what the data show, although the difference in recurrence-free survival was much greater in patients without tumour rupture.

Reply: Thank you for your careful revision of our paper. We are sorry, the data we reported was not correct. We modified the text and decided to remove the comment since we thought it was not essential in the discussion.

Changes in the text: see page 11, lines 252-253.

There are some stylistic issues, some of which alter the sense and should be addressed – suggested alteration are below:

Line 54 – It is clear, not If it is ..

Line 62 - …achievable.. rather than reasonably pursuable?

Lines 63, 64 - ..may result in spillage of neoplastic cells into the abdominal cavity

Line 82 – "Nearly all" should be removed

Line 88 – microscopic residual *disease* left behind *after* surgery…

Line 92 – redo this sentence it is ungrammatical

Line 101 – greatly, not largely, which means mostly, but incompletely

Line 135 – replace comprehending – perhaps encompassing, or comprising, comprehending means understanding

Line 139 - replace appreciated with observed

Line 153 – suggest remove "probably, also"

Line 193 – widely employed not wide-employed

Line 204 - significantly not significant

Line 239 – in the literature

Line 243 – occult, not occults
Line 245 – replace recognise with consider
Line 260 – consider rewriting this sentence – perhaps what is meant is "because it may leave neoplastic cells behind owing to infiltration of tumour into or beyond the pseudo-capsule"?
Line 270 – classification – singular
Reply: again, thank you for your careful revision. We modified the text as suggested.
Changes in the text: lines 57, 63, 64, 83, 89, 93, 102, 138, 142, 201, 212, 246, 252, 267-268, 277.

Reviewer C
Comments to the authors:
In this review article written by authors not disclosed to this reviewer, the significance of surgical margins in GIST is addressed. Several important papers on this topic have been published lately, and a comprehensive review would be welcome. Unfortunately, this manuscript does not fill that need. Most importantly, its linguistic quality is not up to publishing standards – there are paragraphs which are almost unintelligible, e.g. the one beginning on line 118; moreover, the presentation lacks a stringent line of thought. Furthermore, there are statements which are dubious or incorrect:

1. It is stated that the TNM system is of limited usefulness. Actually, this system performs very well (Yanagimoto et al. *Gastric Cancer* 2014).
   Reply: We meant to say it is not widely used, and not that it does not perform well.
   Changes in the text: the sentence has been deleted.
2. With reference to the modified NIH criteria (lines 88-89), the variables mitotic index, tumour size and location are mentioned – tumour rupture is omitted.
   Reply: thank you for your careful revision; we accordingly corrected the manuscript.
   Changes in the text: page 5, lines 112-117
3. It is stated that the role of R1 resection has not been systematically studied. There are at least three important studies: McCarter et al. *Am Coll Surg* 2012; Hølmebakk et al. *Br J Surg* 2019; and Gronchi et al. *JAMA Surg* 2020.
   Reply: we rephrased the sentence; all of the suggested papers have been cited in the manuscript.
   Changes in the text: page 6, lines 125-127.
4. The study by Gronchi et al. is not cited or discussed.
   Reply: the study by Gronchi et al has been cited.
   Changes in the text: page 6, lines 146-149.

5. From what the authors say in lines 139-142, one is inclined to believe that the R system applies differently to epithelial and mesenchymal malignancies. This is not the case – involvement of the serosal surface is without consequence for the R status but may indicate tumour rupture.
   Reply: Thank you for your comment. We rephrased the sentence in order to better explain the concept: the R system applies in the same way, but the two neoplasms present different characteristics.
   Changes in the text: pages 7-8, lines 171-178.
6. It is stated that an endoscopic piecemeal resection could be classified as R0. This is controversial at best; and whether it is considered tumour rupture is also controversial – according to the Oslo criteria it is not unless there is communication to the abdominal cavity.
   Reply: thank you for the comment. We modified the sentence in order to better explain the concept.
   Changes in the text: page 11, lines 254-265
7. It is stated that the SSGXVIII/AIO trial proved that patients with rupture did not benefit from adjuvant therapy extended for more than 3 years. Actually, this was not investigated in that trial.
   Reply: thank you for the comment. See response to reviewer B.
   Changes in the text: See response to reviewer B.
8. In the conclusion, it is stated that the impact of positive resection margins and tumour rupture have to be clarified. In the opinion of this reviewer, both matters are settled: R1 resection does not influence prognosis; tumour rupture definitely does.
   Reply: we also believe that tumor rupture has a negative influence on prognosis and results from studies we cited support the fact that R1 margins without tumour rupture do not worsen RFS. The evidence we may obtain could be even stronger (and maybe more precise) if derived from uniformly defined data.
   Changes in the text: see page 12, lines 285-286.