

**We thank the reviewers for their questions and remarks. We have answered to each remark and altered the manuscript accordingly if needed.**

**We have uploaded two versions of the manuscript: one 'clean' version, and one version with all the modifications recorded.**

**→ Reviewer #1:**

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** Drubay et al prepared a well-updated review on a very hot topic issue in gastric cancer research: signet ring cell histology. They explored thoroughly all the aspects of literature the SRC pattern, from histological to therapeutical point of view. The paper appears well organized, even if it is too long to read. Anyway, it includes all the informations according to specific histotype of gastric cancer.

\* The review is well written and organized, but the reading is too poor of "Authors' perspectives" and I Would recommend the Authors to add several personal discussions to really improve as well as personalize the entire study.

**ANSWER: Several personal discussions have been added throughout the manuscript:**

\* WHO and Verona classifications:

*'The importance of this consensus definition cannot be underestimated, since it will enable future studies to standardize results and facilitate comparison between studies in order to avoid the major heterogeneity that has characterized studies concerning SRC-GC for the past few decades.'*

\* Linitis plastica

*'However, we believe that the current definition of SCR-GC should be used systematically. The term 'linitis plastica' can be additionally used when applicable.'*

\* Additionally, some issues should be addressed: - the abstract seems to be only a super-summary of the entire work. Since it is one of the most important parts of work, I invite Authors to rewrite it in a more attractive fashion and in present verbal form.

**ANSWER: the abstract has been rewritten with attention to highlight the specific key messages of this review.**

\* The reference number 1 is too old; please replace the epidemiological data with more recent reference;

**ANSWER: The reference has been updated by a more recent reference.**

Thrift AP, El-Serag HB. Burden of Gastric Cancer. Clin Gastroenterol Hepatol. 2020 Mar;18(3):534-542. doi: 10.1016/j.cgh.2019.07.045. Epub 2019 Jul 27. PMID: 31362118; PMCID: PMC8859863.

\* Page 5 line 7: it is reported that studies reporting more/equal than 30 cases were prioritized. Since it is not clear, please delete this criterion or please state if papers with less than 30 cases were excluded.

**ANSWER: the criterion has been clarified:**

*'Studies reporting on < 30 cases were excluded.'*

\* Page 5: the last sentence "the definition...." should be deleted since it is a repetition of the previous sentence.

**ANSWER: the sentence has been deleted.**

\* Page 15: please check the sentence: "however, the definition of SRC in the FLOT..." since it is not clear why the presence of any SRC is finally close to the recent definition of PCC-GC: it is wrong.....

**ANSWER: indeed, the contrary meaning was intended. This has been corrected:**

*'However the definition of SRC in the FLOT trial was presence of any SRC in the pathological report which does not correlate with the recent definition of PCC-GC<sup>[12]</sup>.'*

\* Page 16:"A retrospective study suggested no tumor response of pure SRC-GC....." ,please specify in that study how is the definition of "pureSRC".

**ANSWER: in the study no exact definition of the SRC and mixed SRC group is mentioned.**

**This nuance has been added in the manuscript:**

'A retrospective study suggested no tumor response of SRC-GC to either oxaliplatin or docetaxel adjuvant based chemotherapy, whereas the mixed SRC-GC group responded to both regimens with even better improved survival with the docetaxel-based regimen <sup>[98]</sup>. Although the exact definition of SRC-GC and mixed SRC-GC was not mentioned in this study, it supports the fact that PCC-GC could behave differently according to the percentage of SRC and underlines the potential benefit of taxane-based CT in PCC-GC.'

\* Pag 19 line 5: a total of 200 pts with "localized".....: do you mean "non metastatic"? It would be better term to indicate that condition.

**ANSWER: indeed, non-metastatic is intended. This has been changed in the text.**

*'The currently ongoing PREVENT trial (FLOT-9) (NCT04447352) is a multicenter, randomized, controlled, open-label study including a total of 200 pts. with localized and locally advanced non-metastatic diffuse or mixed type (Lauren's classification) adenocarcinoma of the stomach and Type II/III esogastric junction tumors.'*

\* Pag. 21 paragraph 3.5.1. first sentence: "SRCC":please indicate these tumors as already used: SRC-GC

**ANSWER: the terminology has been altered:**

*'Several studies demonstrated that SRC-GC had different infiltrative and metastatic mechanisms than non-SRC-GC.'*

\* Please correct misspelling errors throughout the paper - An English polishing would be appreciated

**ANSWER: Sever misspelling errors as well as grammatical errors have been corrected throughout the manuscript.**

\* Please rewrite the "Conclusions" in a more "Arguing" fashion, highlighting the proposals forfeiture studies.

**ANSWER: Several proposals from the authors point of view have been added to the conclusion section:**

*'In contrast to GC in general, the relative incidence of PCC-GC has risen over the past few decades. PCC-GC represents a distinct pathological entity within the GC spectrum, characterized by specific epidemiological and clinical features, including younger age at presentation and a significantly worse prognosis, mostly due to peritoneal dissemination early on in the disease. In light of these distinct features, the recently redefined pathological definition of PCC-GC by the WHO and the European chapter of IGCA will facilitate methodological standardization in future studies, which in turn will help to identify which therapeutic strategies for GC in general are applicable to PCC-GC. **We believe that the updated definition will help standardize future research concerning the prognostic results of SRC-EGC in Western populations as well as in evaluating the correlation between pre-therapeutic biopsies and the final pathology result.** Concerning the pre-therapeutic evaluation, the infiltrative growth pattern of PCC-GC along with early peritoneal dissemination justifies the use of repeat endoscopies with deep biopsies, CT-graphic imaging as well as systematic staging laparoscopy with peritoneal lavage. **Since correct PCI determination is essential for therapeutic management, a small incision with palpation of the entire small bowel should be considered.** Surgery is considered the mainstay of curative treatment for PCC-AGC. **The role of the extent of the lymphadenectomy however in PCC-AGC should be evaluated in future studies.** For PCC-EGC, no endoscopic treatment is currently advocated. The added value of peri-operative CT for PCC-GC with FLOT regimen is probable*

*but should be further confirmed using histological reassessment. No role of adjuvant radiotherapy has been demonstrated in PCC-GC. In case of peritoneal disease, IPC by means of HIPEC, PIPAC offer a valuable treatment option, on the condition that patients are well selected. To what extent the promising results of immunotherapy could be applicable to PCC-GC needs to be confirmed in future studies. PCC-GC in general requires a highly individualized diagnostic and therapeutic approach to optimize the inherent poor prognosis of this disease in the future. **Molecular and genetic differentiation will be of importance to offer an patient tailored therapeutic strategy.***

Reviewer #2:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** Very relevant and interesting review manuscript. The authors studied a large number of articles (198). The authors also discussed histological, molecular genetic classifications of gastric cancer, reviewed and analyzed modern surgical, endoscopic, immune, radiation, chemotherapeutic, and targeted methods of treatment. An interesting assessment of the prognosis of the development of the disease. The manuscript is recommended for publication in the World Journal of Gastrointestinal Oncology.

**1) Science editor:**

The review is well written and well organized, but the length of the article is too long and the authors need to refine the relevant research and remove redundancy. It is also suggested that the authors add a few personal discussions to really improve the personalization of the whole study.

**ANSWER: Several paragraphs have been shortened to reduce the length of the article. Especially in the conclusion personal discussion has been added, with a specific point of view on future studies.**