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Editor-in-Chief
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Frequency, localization, and types of GIST-associated neoplasia – A systematic review

Dear Prof. Ruo-Yu Ma,

Thank you and your reviewers for the complaisant evaluation of our manuscript and for the valuable suggestions of improvement! According to the suggestions we made some changes to the manuscript (all were highlighted in yellow colour). Comments on formatting, references and figures were realized.

Please find below our answers (**A:**) to the reviewer comments.

Reviewer 1:
Very good review. Methodology is rigorous, all the relevant papers have been included in the analysis. Results are concise and straightforward. Discussion is clear and well organized. Few words are misspelled. Very good review. Methodology is rigorous, all the relevant papers have been included in the analysis. Results are concise and straightforward. Discussion is clear and well organized. Few words are misspelled.
A: Our manuscript has already been edited by a professional language service. Nevertheless, we carefully went through the text and could correct a few spelling mistakes.

Reviewer 2:
1. Over what time frame are the tumours being considered as a second neoplasia. Is it any within that patients lifetime? Please clarify.
A: Second neoplasms were considered regardless of the time frame between their occurrence and the occurrence of GIST. An according sentence was added to the methods part of the manuscript.

2. Please give the numbers and rate of synchronous tumour (?10%) as this is of clinical relevance for patients diagnosed with GIST and if we should be considering further investigation for a second lesion at time of diagnosis. Please also specify rates of GI-Tract and urogenital tract synchronous rates.
A: A rate of 6% (366 of 5131) of synchronous second neoplasias was detected for all GIST patients. Of these synchronous second neoplasias 77% (177 of 230) occurred in the GI-Tract and 7% (16 of 230) in the male and female urogenital tract. Unfortunately, the relevant data was not available in all studies.

3. In discussing the 4 studies with mutational status of the patients with a second neoplasia please specify that this is in keeping with normal GIST mutational frequency or add a sentence on this in the discussion.
A: In the discussion part of the manuscript the following sentence was already included: “The occurrence of GIST-specific mutations such as in the c-KIT or PDGFRα gene that we found

in the group of patients with GIST and second neoplasms were similar to those reported for GIST in general before.". We think this should provide the information you wanted. If not, please let us know.

4. Please make the discussion more concise and in particular needs reference to the clinical relevance, especially in the context that multiple primary tumours are known to occur in 2-17% of patients.(https://esmoopen.bmj.com/content/2/2/e000172.info) of patients and is already known to be highest in genitourinary and GI tract malignancies. I would focus on the synchronous tumours as this is interesting and clinically useful.
A: According to the review of Vogt et al. we added passage to the discussion part of the manuscript (all highlighted with yellow) regarding multiple primary tumors and included this article in our reference list [18].
We absolutely agree with the reviewer that it would be a meaningful approach to focus on synchronous tumors. However, the data for the localization of synchronous second tumors is only available for a relatively small number of patients which stands in the opposite to such a focus (230). Nevertheless, in the discussion part we recommend "to consider frequent controls or extended staging for early detection of second neoplasias, especially in the gastrointestinal and urogenital tract".

Sincerely yours,

Bruno Märkl and Johanna Waidhauser