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Reviewers 1

I think this manuscript is very interesting and offers us a wide state of the art about the problem of the free peritoneal cells in colorectal cancer. There are some grammar mistakes that must be corrected. The discussion around the statement of the proactive peritoneal treatment if IFCC are present is poor. I think the authors must give a deeper discussion about this topic.

Answer

1. Thank you for your kind words we are pleased to learn that you found this manuscript engaging , we were delighted by your suggestions as it was a useful opportunity to improve our work and enhance it to the next level.
We revised the article and corrected the grammar mistakes.
2. We widened the discussion about possible proactive peritoneal treatment when IFCC are present as you requested .

Reviewer 2

Minor issues: 1. In the "Abstract" section, " Positive peritoneal washing" should be identified with a more detailed description. 2. In the "Core Tip", The methods of detections based on real time PCR, will surely add power to conventional citology and...., what's the "citology"? 3. In "- Mechanism of peritoneal shedding, circulation and seeding of cancer cells", Down regulation of cell-cell adhesion molecules, such as e-cadherin,....., the e-cadherin should be replaced by "E-cadherin". 4. In "Conventional cytology and cytology following immune-markers staining", Immuno-stains for CK7 and CK20 yield a negative and a positive staining result, respectively. A negative and a positive staining result for what? 5. Please give a short explanation of Figure 1.

Answers

1. We revised as well the "Abstract" section, adding as you suggested some details on "Positive peritoneal washing" .
2. Of course the term "citology" has been replaced with the correct "cytology".
3. The term "e-cadherin" has been replaced with "E-cadherin" ; we are sorry you had to face such mistakes in your read.
4. The result of stainings is referred to the presence or absence of CK7 and CK20 expression on IFCC when matched with monoclonal antibodies for these cytokeratines, we hope that the explanation is clear now.
5. We added a few words about Figure 1, in reference to your observation .

Reviewer 3

In general, article is good. It shows us your projects and makes sense. It has newness, concision, and readability in each part. But it also has some flows which should be noticed or improved. Firstly, there are many grammar and written mistakes in manuscript should be

noticed and corrected. Secondly, body text has clarified five detection methods and clinical significance of free peritoneal tumor cells found during colorectal cancer surgery which is clear and obvious, however, its lack of sufficient statistics conclusion to analyze the topic deeply. What's more, conclusions discussed the present problems and challenges which should give readers more deep analysis. If the authors bring up more projects about further research in needed, it would be better.

Answers

1. We appreciate your kind words, we tried to ameliorate those flaws you mentioned. Thus grammar mistakes have been checked and corrected.
2. We reported the available statistics; still unfortunately there is not enough evidence in order to suggest a "gold standard" for IFCC detection or to perform a routinely peritoneal washing with conventional cytology for colorectal cancer staging. Authors believe that conventional cytology remains the most cost-effective suitable procedure, especially if associated with MMP-7 detection, which may increase its specificity. Detection of IFCC seems to have clinical significance since it worsen prognosis, whether it is not clear if it is associated with higher local recurrence rates or not.
3. Further researches about role and setting of IFCC detection are reported, as well as those about proactive treatment when IFCC are found, based on your appropriate suggestions.

Reviewer 4

Dr. Simone et al. reported an editorial article about intraperitoneal free cancer cell (IFCC). This article is well written and comprehensively reviewed for this hot topic. However, some questions and comments are written below. 1. Is the term "IFCC" an abbreviation for "intraperitoneal free cancer cells" or "free intra-peritoneal cancer cells" the authors stated? 2. In the last sentence of abstract, the authors stated about adjuvant chemotherapy. However, no evidence of survival benefit by adjuvant chemotherapy is shown so far. The reviewer recommends that the authors adds the sentence about the need for blushing up the detection of positive cytology and need for further studies, as mentioned in conclusion of text. 3. In page 11 line 19-21, the authors stated that "this reflected on survival analysis which lead worse survival in patients with positive cytology ($p < 0.0001$)(40)". EVOCAPE 2 study is a negative study. This study showed that positive cytology was not an independent factor on survival. This sentence was a result of univariate analysis and it can mislead for readers. 4. In page 12 line 10-11, the authors stated that "When positive cytology is found, a prophylactic intraperitoneal chemotherapy may be considered." Did the authors have any clinical data of prophylactic intraperitoneal chemotherapy as a prospective study? If only retrospective study data, the reliability of the evidence is quite low. 5. In page 12 line 16-18, the authors stated that "Results are promising in terms of overall and disease free survival and peritoneal recurrence rate (18-20)". However, these studies (ref 18-20) are not randomized controlled trials. These results seems to be not promising.

Answers

We are very pleased we received your valuable help, it was definitely advantageous, pragmatic and effective. Thank you.

1. In fact as you noticed, the term "IFCC" is an abbreviation for "intraperitoneal free cancer cells", of course the text has been corrected.
2. We provided the addition of a sentence stating the need for further studies at the end of the Abstract, as you suggested.
3. The sentence has been better specified, as we noticed as well that it could mislead readers .
4. Absolutely, you may be right in deducing these assumptions ; however Clinical data from prospective study about proactive intraperitoneal chemotherapy are available for patients at high risk of peritoneal metastasis, namely those with positive peritoneal washing in the study by Sammartino et al., now cited in the reference n.19. That study was a prospective preliminary one whose long term results are reported in a second study (reference n.18). Furthermore a large prospective multicenter randomized controlled trial (ProMenade trial) has been proposed on its basis and it has started recruitment of patients in May, 2015. It is early to propose a proactive treatment outside clinical trials but such treatment "may be considered in selected cases within clinical trials" .
5. Sentence has been amended.