Peer Review File

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Reviewer A

Mr. Russell and colleagues have submitted a wonderfully written narrative review of selected factors impacting outcomes following PD for malignancy. There are small points to be made here and there which may serve to improve engagement with the readership. These include (1) a consideration of blood transfusion as a potentially modifiable risk factor (haemoglobin transfusion trigger adjustment, decreased utilization of 'prophylactic' intraoperative transfusion practices, adjustment of intraoperative techniques to modify EBL, utilization of practices that restrict crystalloid volume during perioperative care, etc.),

The section on blood transfusion has been expanded to reflect the complexity of the topic and further studies have been included. A paragraph has now been included which outlines the findings of a Finnish study which investigated how transfusion protocols varied between small-, medium- and large centres (Lammi et al).

We conducted a further literature search and could not find any recent articles which specifically commented on the impact of the decreased use of prophylactic intraoperative transfusion practices on PD outcomes. We have now included a paragraph on estimated blood loss and included recent articles which have described operative techniques which can be used to minimise this.

(2) the safety/risk profile during the application of MIS technologies (both laparoscopic and robotic) are dependent upon the surgeon/centre expertise and practice patterns,

This has been clarified at the end of the “open versus minimally invasive technique” section and throughout the article.

(3) NAT is standard of care in BRPC and LAPC

The sentence in the vascular resection section has been changed to reflect this. Throughout the article it has been made clear that NAT is now standard of care in BR and LA patients.

(4) a more nuanced discussion of the selective use of PD in octogenarians and older (this is admittedly more difficult to do without expanding on the other factors of

outcomes as mentioned below), etc.

For the sake of this article, we have not considered age as we have considered this a "pre-operative factor" which we have covered in another article which has been submitted to APC (revision recently submitted).

When we say "peri-operative" what we really refer to is "intra-operative" for the most part and hence the title of the article has been changed. The methods section has been altered to make this clear.

The major aspect of the work that precludes my great excitement for an immediate accept are two-fold that, I would hazard a guess, are beyond the scope of the authors' intended work. First, the number of factors they explore in the narrative review are, while explored to a fair depth, limited to such an extent that the readership may be erroneously lead to believe the list is comprehensive. In fact, there are at least twice as many factors left out as there are included, with many of the most important omitted. These include drilling down onto the other preoperative patient factors that can enable safe patient selection at the extremes of age and comorbid conditions and the highly important utilization of optimal pathways (and the components therein) for perioperative patient care.

We have only included factors that will be investigated by the Recurrence After Whipple's study. We have now made this clear in the methods section. We have also updated the limitations paragraph to acknowledge that we will not have covered all known variables which affect PD outcomes.

As previously mentioned, we have not included age as we have categorized this as a "pre-operative factor", this is covered in an additional article which has been submitted to APC.

The second major limitation is that this is not a formal systematic review. Though the scope of work would be vastly different, the narrative format here leaves such to be desired (as above) that it may be preferable to select one or two factors and perform a formal systematic review. As it stands, this would fit best as an invited commentary on some of the more recent work looking at independent factors and the editors may consider holding this until such a primary work is obtained to pair this with.

The aim of this review was to provide a broad overview rather than answer a specific research question. As such, a narrative review framework has been used. We appreciate that this is not as robust as a formal systematic review but wanted to cover a broad range of topics.

Reviewer B

The authors produced a narrative review on Peri-operative factors affecting outcomes following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. The manuscript is globally well composed, the narration is clear, the content informative and, globally, it adds some interesting insights into these matters.

Here are some suggestions:

1) Abstract:

" Most newly diagnosed patients are not candidates for surgical resection " specify in the abstract what is the % of newly diagnosed patients not candidates for surgery. This will make the abstract more informative and precise.

A figure of “approximately 85%” has been included.

Same applies a few lines after for morbidity and disease recurrence rates

“Around half” has been provided for overall morbidity and “less than two years” for overall survival.

2) Introduction:

"Pancreatic ductal adenocarcinoma (PDAC) is predicted to become the UK’s fourth 41 biggest cancer killer by 2030" Add similar data for other geographic regions: e.g., US, Asia ... This will add useful information for readers outside the UK.

A worldwide incidence rate has now been quoted and it has been highlighted that that the number of cases in all countries is expected to rise. Furthermore, it has been made clear that PDAC will become one of the most common causes of cancer-related death in high-income countries in Europe, North America and Oceania in the near future.

3) Methods:

Specify the inclusion and exclusion criteria.

These have now been specified in the methods section.

4) Limitations: " Since the subject matter is so broad a formal systematic review has not been carried out and meta-analysis was not possible " . I would remove this statement, you conducted a narrative review. I would not venture into discussing what was not done or what may be possible or may not be possible for other authors.

The limitations paragraph has been moved to the end of the discussion section. We now highlight that we have pre-selected certain factors and have not considered all possible variables. We have removed the sentence on possible systematic review/meta-analysis.

5) Conclusions:

I would add some specific future perspectives: e.g., given some of the limitations of the current literature, which kind of studies do we need in the future to improve our understanding of the topic.

The original conclusion has been added to.