



May 21, 2016

FACULTY OF MEDICINE

Lund University

Medical Faculty

Department of Surgery, Clinical Sciences, Lund

Roland Andersson, MD, PhD

Professor of Surgery

Ya-Juan Ma

Science Editor, Editorial Office

World Journal of Gastroenterology

Dear Editor,

We were pleased to learn that there was interest in our manuscript “Early stage pancreatic cancer – what determines outcome?”. Enclosed is a revised version of our manuscript. We appreciate the constructive comments provided by the reviewers and the manuscript has been carefully revised according to their comments. The title has been updated to “Re-evaluation of classical prognostic factors in resectable ductal adenocarcinoma of the pancreas” following the suggestion made by one of the reviewers. We believe that the manuscript should be categorized as a regular review rather than a “systematic review”. All sections in the manuscript that have been revised have been marked in red.

We have addressed all issues, and below please find a point-by-point reply to the points raised by the reviewers, indicating in detail our response. By that, we hope that our manuscript will be found suitable for publication in World Journal of Gastroenterology and we look forward to hearing your final decision.

Sincerely yours,

Roland Andersson

Roland Andersson, MD, PhD

Professor of Surgery

Corresponding author

Reviewer 1

The manuscript by Åkerberg and coworkers reviews prognostic factors in early stage pancreatic cancer. The manuscript is – in general- well written and the topic is timely and of interest.

There are a few points to consider:

Regarding lymph node status: there are obviously different approaches to lymphadenectomy in pancreatic cancer. Do the authors have any information regarding this for the included studies?

Response: The statement regarding standard and extended lymphadenectomy according to ISGPS is now included in the manuscript (page 5, paragraph 3).

Regarding R0/R1 status: there are obviously different protocols and definitions of involved resection margins in pancreatic cancer. Do the authors have any information regarding this for the included studies?

Response: Table 6 has been updated to include the various R1 definitions used in different studies.

I certainly agree with the authors' conclusion that a unifying way of reporting data on prognostic factors should be used in the future. I would also like the authors to include statements regarding unifying ways of therapy and acquiring data. For example, the international study group for pancreatic surgery has made efforts to define standard (and extended) lymphadenectomy for pancreatic cancer, which are now widely accepted. In contrast, histopathological reporting is still defined differently in various national guidelines. Further, to the best of my knowledge, there is no uniform definition of how to evaluate perineural or perivascular invasion. Indeed, some pathologists would argue that you would find that in close to 100% of cases, if you look hard enough.

Response: We agree that standardization of histopathological reporting would be essential. We have updated the tables in the manuscript to depict the relative frequency of each prognostic, e.g. the rate of perineural invasion ranging from 30-96%.

Reviewer 2

Comments to authors: No.

Reviewer 3

This review by Akerberg D, et al. discussed the impact of conventional prognostic factors on survival of early stage pancreatic cancer. The manuscript is well-written.

Several comments are listed below.

1. The title focused on early stage pancreatic cancer, while the context discussed resectable PDAC. The main concern is that resectable PDAC does not equal to early stage pancreatic cancer.

Response: Thank you for this remark. The title has been changed to " Re-evaluation of Classical Prognostic Factors in Resectable Ductal Adenocarcinoma of the Pancreas" in order to accurately capture the content of the article.

2. Although pancreatic tumors include a wide range of histopathologic subtypes, distal bile duct, duodenum and ampulla of Vater are actually not belong to these tumors. Pancreatic cancers include exocrine and neuroendocrine tumors, and solid pseudopapillary carcinomas, et al. This review mainly focused on PDAC. Thus, the title maybe more appropriate if pancreatic cancer is changed as PDAC.

Response: We agree with the reviewer. The title now includes the term " ductal adenocarcinoma of the pancreas" .

3. This study included five conventional prognostic factors, however, tumor location, tumor grade and CA19-9 level are as important as these factors. Why did the authors select these factors?

Response: Following the suggestion by the reviewer, we have now included a section on tumor grade (page 6, paragraph 2). The primary objective of this review was to analyze the prognostic role of classical morphological factors. This has been clarified in the manuscript. The prognostic role of tumor location is controversial. The analysis of CA 19-9 is beyond the scope of this article.

4. The systematic reviews may omit several studies. For example, a total of 14 studies were identified about vascular involvement and survival. A recent meta-analysis published in British Journal of Surgery included 27 studies comparing the results of PV/SMV resection (+) with those of PV/SMV resection (-) during pancreatic resection.

Response: We agree with the reviewer. The challenge with the analysis of common prognostic factors is that they are often used as co-variables in survival analysis for other factors, therefore many studies may be omitted that do not analyze these factors as the primary variable. Therefore, a narrative review may be more appropriate for our purposes selecting key references published in recent years. We have also gone through the article in British Journal of Surgery and selected several important trials of vascular resection that are now shown in Table 4.

5. In table 3, the first two studies are duplicated. In line Kelly [82], "R1+" should be "R1".

Response: This has been changed.

