

Peer Review File

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Reviewer A

The authors have reviewed the current status on the perioperative and long-term outcomes related to arterial resection for proximal pancreatic tumours. The level of evidence is not high because previous reports are limited to retrospective observational studies with a small number of cases. However, this review article is thought to be useful in understanding the current situation in which concomitant arterial resections are being performed with some degree of safety in high-volume centers.

Reply: We thank the reviewer for his comments.

Reviewer B

This article addresses a relevant topic using acceptable methods. However it could more deeply investigate arterial resection by providing relevant information to the readers.

I would suggest major revisions.

This article is a Systematic Review of the literature about perioperative outcomes after arterial resection for the treatment of pancreatic head/uncinate neoplasms. The Review considered 8 published papers from 2000 to 2022 with a total of 171 patients undergoing pancreaticoduodenectomy (136 patients) and total pancreatectomy (35 patients) and receiving arterial resection.

Authors conclude that although arterial resection can be performed with an acceptable peri-operative morbidity and mortality, survival outcomes are still not convincing and future efforts should concentrate on patient and disease biology selection.

The authors deserve to be congratulated for their effort in investigating an interesting topic still presenting unsolved issues.

Some criticisms rose during revision and need to be clarified or improved:

Comment1: - row 58: coeliac axis should be abbreviated (CA) as reported above (row 53)

Reply: Thank you, this has been addressed

Changes in the text: row 58 – “coeliac axis” → CA

Comment 2: - Authors reported that arterial resection was carried out in a total of 171 patients (median 18, interquartile range (IQR) 15-21.5); please report the rate of patients receiving arterial resection in each study

Reply: The number of arterial resections for each study are highlighted in Table 1. A reference to table 1 has been added in the manuscript

Changes in the text: Row 103-104. Arterial resection was carried out in a total of 171 patients (median 18, interquartile range (IQR) 15-21.5) (6,7,8,9,10,11,12,13) → Arterial resection was carried out in a total of 171

patients (median 18, interquartile range (IQR) 15-21.5) (6,7,8,9,10,11,12,13) (Table 1).

Comment 3: - Neoadjuvant chemotherapy was performed only in 45% of patients receiving arterial resection; this data is quite surprising. Please report, where possible, reasons that justified arterial resection in patients not receiving neoadjuvant therapy. This could potentially affect the poor reported oncological outcomes

Reply: The authors agree with this comment and have dedicated a paragraph in the discussion section to this. Unfortunately most papers did not necessarily indicate the rationale for not undergoing neoadjuvant chemotherapy. Yang et al, Ramia et al and Zhang et al have all suggested decision regarding neoadjuvant chemotherapy were down to unit policy and a sentence on this has been added in the manuscript.

Changes in the text: Row 206: of neoadjuvant chemotherapy. The lack of adequate disease biology selection may explain the recorded... → of neoadjuvant chemotherapy. Whilst most studies did not report their rationale for patients not receiving neoadjuvant chemotherapy, three of them suggested it was down to unit policy^{7,9,10}. The lack of adequate disease biology selection may explain the recorded...

Comment 4: - The authors correctly reported the imaging modalities for perioperative staging but they did not report about resectability characteristics. How were patients preoperatively classified (resectable/borderline/unresectable)? And which classification various studies used to define resectability?

Reply: Only a few authors provided sufficient information to answer this question. The classification stated by all authors was NCCN guidelines.

Changes in the text: row 103 - head been the commonest reported location. Three studies reported the classification of tumours, with the most commonly reported tumor being borderline resectable^{6,9,12}. Where reported NCCN guidelines were used to classify each cancer^{6,9}.

Comment 5: - Please report about the number of cycles of chemotherapy administered and resection strategies.

Reply: FOLFIRINOX and gemcitabine-based regimens were both reported in the studies, however they were not reported for each type of resection. It is therefore not possible to extract the specific information for pancreatic head resections alone. Furthermore, specific details on the chemotherapy regimens, such as cycles per patient or possible dose reduction due to intolerance were not reported in the studies.

Changes in the text: none

Comment 6: - Why was total pancreatectomy preferred upon PD in 35 patients?

Better radicality? Prevention of POPF? In patients undergoing total pancreatectomy, was splenectomy associated or not?

Reply: Amano and Ramia et al both reported a sizable number of total pancreatectomies, however the rationale for proceeding to total pancreatectomy in both papers was not mentioned

Changes in text: none

Comment 7: - Was arterial resection a first choice or a rescue strategy due to the impossibility to perform arterial divestment?

Reply: Arterial divestment is preferred as the first approach in general. Arterial resection can be a planned approach if divestment cannot be performed based on the intraoperative findings or even a rescue strategy for example in cases where an arterial injury is caused from the divestment. The studies included have not provided any information on this.

Changes to text: none

Comment 8: - The authors put together CHA/CA/SMA resection with aRHA resection. The latter group could deserve a more specific attention: were these aRHA replaced or accessory? Were they reconstructed or just resected?

Reply: Of the 4 studies that reported aRHA, Marichez et al and Amano et al reported these as being replaced. This has been added in the manuscript.

Changes to text:

Row 120: The types of arterial resections performed can be found on **Table 2**. The median... → The types of arterial resections performed can be found on **Table 2**. Of the 4 studies that reported aRHA resection (6, 8, 9, 12), only two clarified that this was a replaced rather than an accessory artery (6, 12). The median...

Comment 9: - What about the choice of one reconstruction technique over the others?

Reply: Two studies reported justification in reconstruction technique.

Changes to text: The most frequently reported reconstruction was a primary end to end anastomosis (9,10,11,12), followed by autologous venous interposition graft with great saphenous vein (8,10), while the use of autologous internal iliac artery, splenic artery (12) or synthetic graft (8) were also reported. → The most frequently reported reconstruction was a primary end to end anastomosis (9,10,11,12) if adequate vessel length was available (10) , followed by autologous venous interposition graft with great saphenous vein (8,10), while the use of autologous internal iliac artery, splenic artery (12) or synthetic graft (8) were also reported. The rational for use of each type of graft was not mentioned.

Reviewer C

Comment 1: Perioperative 34 morbidity was 4.5% and mortality was 43.5% --> Please check it.

Reply: corrected

Changes to text: morbidity was 4.5% and mortality was 43.5%. → morbidity was 43.5% and mortality was 4.5%.

Comment 2: Arterial resection can be performed with an acceptable peri-operative morbidity and mortality. --> around 5% mortality is not thought to be acceptable considering long-term oncologic efficacy. Please modify.

Reply: The authors do not agree with this statement. For early stages of pancreatic cancer (NCCN resectable) peri-operative mortality is quoted 1-4% in the literature and up to 8% for elderly patients. In these cases OS with the surgery first approach is 22-26 months. In this context a 5% peri-operative mortality for arterial resection is certainly acceptable and oncological long term outcomes not substantially worse than the earlier stages of the disease.

Changes to text: none

Comment 3: The rates for overall 3-year and 5-year survival in this review remain low at 6.6% (range, 0-42.4) and 3.3% (range, 0-6.6) respectively (9,11,13), while in one study no statistical difference in 5 year-survival (P=0.008) was identified between the arterial resection and the arterial palliation groups (13).

--> Please check it out, P=0.008? 0.08?

Reply: P value is correct, the text is a typo error and corrected

Changes to text: Row 216 - The rates for overall 3-year and 5-year survival in this review remain low at 6.6% (range, 0-42.4) and 3.3% (range, 0-6.6) respectively (9,11,13) and in one study a statistical difference in 5 year-survival (P=0.008) was observed between the arterial resection and the arterial palliation groups (13).

Comment 4: Arterial involvement is no longer considered a contraindication to surgical treatment for locally advanced pancreatic cancer of the head and uncinate process. Arterial resection can be performed with an acceptable peri-operative morbidity and 90 day mortality. However, oncological outcomes (OS and DFS) are still not convincing and future efforts should concentrate on patient and disease biology selection. --. Please modify. Technical feasibility is acceptable, but indication for surgical extirpation based on disappointing long-term oncologic outcomes (very similar to results of palliative chemotherapy in mPC) should not be recommended. If author can do, it would be better to summarize type of arterial resection for example, CHA, SMA...

Reply: the authors do not agree with this suggested modification. There are selected cases that benefit from aggressive surgical treatment. A blanket approach with arterial resection to every case is certainly not advisable, however a case selection approach with focus on patient and disease selection can yield improved oncological outcomes. This should be the focus of future studies.

Changes to text: none