Peer Review File

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Reviewer A

Comment 1

Clarification on Mesopancreas Definition: The concept of the mesopancreas and its role in PDAC recurrence and surgery complications could be further clarified. Providing a more detailed description of the mesopancreas, including its anatomical boundaries and significance in PDAC surgery, would enhance the reader's understanding. Does mesopancreas include ganglion? In some articles, mesopancreas include nerve plexus connecting CHA,SMA and uncinate portion.

Reply 1

Fernandes ESM, Strobel O, Girão C, Moraes-Junior JMA, Torres OJM. What do surgeons need to know about the mesopancreas. *Langenbecks Arch Surg*. 2021;406(8):2621-2632. doi:10.1007/s00423-021-02211-y

The term mesopancreas is not widely accepted in the literature. This region, firstly defined as mesopancreas by Gockel, can also be known as pancreatic head plexus (Japan Pancreas Society), Mesopancreatic resection (Gaedcke) , or as a nonexistent region due to the lack of precise anatomic borders(Agrawal).

Gockel (**Gockel I, Domeyer M, Wolloscheck T, Konerding MA, Junginger T (2007) Resection of the mesopancreas (RMP)**: a new surgical classification of a known anatomical space. World J Surg Oncol 5:44) first defined the term *mesopancreas*, in 2007, as a rigid and richly vascularized peripancreatic arrangement composed of: fatty tissue with vascular structures, nerve fibres, lymph nodes as well as lymphatic vessels on the fusion fascia of the Treitz. The Japan Pancreas Society refers this region as the pancreatic head plexus, which is an area situated behind the pancreatic head, celiac plexus, and the pancreatic head plexus II including the region behind the uncinate process, superior mesenteric artery and inferior pancreatoduodenal artery. (**Japan Pancreas Society (2017) Classification of pancreatic carcinoma, 4th edn. Kanehara & Co., Ltd., Tokyo**)

The anatomical limits of the mesopancreas include: the medial and posterior aspect of the uncinate process and pancreatic heart (lateral delimitations), the right aspect of the

superior mesenteric vein and superior mesenteric artery (medial limits), the origin go the celiac trunk (cephalic limit), the beginning of the mesenteric root (caudal limit) and the left renal vein(posterior delimitation).

The total mesopancreas excision (TME) includes the resection of the mesopancreas, the main site of a positive resection margin, as well as the peripancreatic lymphatic structures located along the neuronal plexus, posterior to the pancreatic head and on the right side of the superior mesenteric artery. Therefore, the TME is considered a favorable surgical approach for patients with pancreatic ductal adenocarcinoma, because this area is an important location of perineurial tumor cell infiltration in patients with pancreatic head adenocarcinoma and the perineurial tumor invasion rate in pancreatic cancer can be up to 75%.

We added some data in page 2.

Comment 2

Figures of preoperative imaging studies and surgical photograph should be added to strengthen the validity for performing such invasive surgery.

Unfortunately, we didnt have acess to the photographs in time

Comment 3

Detailed Description of Management Strategies: While the article mentions effective management leading to recovery from neurogenic shock, specific details regarding the management strategies employed (beyond the mention of sympathomimetics and fludrocortisone) would be valuable. Including such details could provide insights into best practices for managing similar cases in the future.

Reply 3

The neurogenic shock is defined as a hypo perfused state of the organ tissue as a result from the interruption or deregulation of the autonomic nervous system control over the vascular tone. This condition consists of the lack of sympathetic tone, due to a spine or plexus lesion, for example, resulting in an uncontrolled/unopposed parasympathetic system, which leads to an unbalanced autonomic nervous system activity. This decline in sympathetic control over the vascular tone, **induces the**

dilation of capacitance blood vessel in the lower body extremities. This results in decreased cardiac filling, which leads to hypotension and shock. Furthermore, the diminished sympathetic control over the heart leads to a state in which the unopposed vagal influence causes bradycardia.

The main goal in the initial management of neurogenic shock is hemodynamic stability. The first line of treatment for hypotension consists of intravenous fluid resuscitation, which aims at the vasogenic dilation typically observed in a neurogenic shock. Nevertheless, an excessive and overly aggressive fluid reposition can lead to complications. The second line of treatment involves the use of vasopressors and inotropes, which changes the force of the heart's contractions, enhancing or weakening the force of the heartbeat. This medications are used when the hypotension remains even after euvolemia. Phenylephrine, a pure alpha 1 agonist, is frequently used to induce peripheral vasoconstriction and alleviate the lack of sympathetic activity. Another pillar of neurogenic shock management consists of prevention. The patients with this condition should stay well hydrated, minimize abrupt movements and adhere to prescribed medications such as sympathomimetics.

Dave S, Dahlstrom JJ, Weisbrod LJ. Neurogenic Shock. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; October 29, 2023.

We added some data in page 6.

Comment 4

Long-term Follow-up and Quality of Life Assessment: The article briefly mentions the patient's demise due to liver metastases but lacks a comprehensive discussion on the long-term follow-up, including quality of life assessments post-recovery from neurogenic shock. Incorporating information on long-term outcomes and quality of life could offer a more complete picture of the patient's postoperative journey.

Reply 4:

The patient returned to her hometown and maintained an excellent quality of life for approximately 9 months, during which time her family kept in touch with the medical team, sending photos and videos of the patient asymptomatic and participating in

significant family events without any symptoms. This was considered a success, given the high risk of recurrence (pT3pN2) and the high likelihood that, in the absence of response to systemic therapy, it could lead to compressive symptoms and loss of quality of life, being well controlled with surgical treatment during the reported time.

We added some data in page 4.

Comment 5

Discussion on Decision-making for Elderly Patients: The decision to perform extensive surgery on elderly patients, especially those with significant comorbidities, is complex. The article would benefit from a deeper discussion on the ethical considerations and decision-making processes involved in pursuing aggressive surgical options for elderly patients with PDAC.

Reply 5:

The decision for surgical management of the disease was made in a multidisciplinary approach and in joint decision with patients and family members. It is known that the only curative treatment for pancreatic adenocarcinoma is surgical, and in cases where it can be performed in a center with a surgeon experienced in the procedure, using robotic assistance, it should be considered whenever feasible. Also, the patient was against systemic therapy, which motivated the team to proceed with the surgical plan.

We added some data in page 3

Comment 6

Comparison with Existing Literature: While the article presents this case as potentially unique, a more thorough comparison with existing literature on postoperative dysautonomia and neurogenic shock following pancreatic surgery could provide context. Highlighting how this case adds to or contrasts with existing knowledge would strengthen the article's contribution to the field.

Reply 6

To our knowledge, this is the only reported case evidencing recurrent neurogenic shocks in the postoperative period of curative oncological surgery for pancreatic adenocarcinoma."

We added some data in page 4

Reviewer B

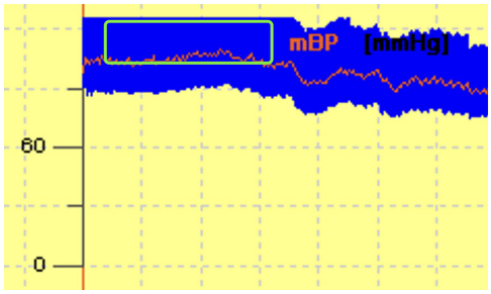
1. Please add “a case report” in the Title, as required in the CARE checklist. - OK

2. Please provide the full names of “PDAC” “AJCC” “ICU” in the main text. Please also check through your article to make sure **all the abbreviated terms** have been defined when they **FIRST** appear in the Abstract and the main text.

   OK

3. The citation of **Reference 5** and **13** is missing in the text.
   OK

4. Figure
   - The citation of Figure 1 is missing in the text. OK
   - The description is missing in Figure 1A.



   OK

   - Please check if “LF/HF” needs to be added in Figure 1B legend.

; RRI (R-R interval [ms]); dBP: diastolic blood pressure, LFnu-dBP / HFnu-RRI (low-frequency band heart rate / high-frequency band heart rate [%]) and BRS Lag0 lines regarding autonomic responses (left)versus tilt-test (right).

   OK

- Please double check the full names of “LFnu-dBP” and “HFnu-RRI”. Or please provide the full name of “LFnu” “HFnu”.

;LFnu-dBP / HFnu-RRI: low-frequency band heart rate / high-frequency band heart rate [%];

OK