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EDITORIAL

Mesopancreas: A boundless structure, namely the rationale for dissection of the paraaortic area in pancreaticoduodenectomy for pancreatic head carcinoma

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Abstract

This review highlights the rationale for dissection of the 16a2 and 16b1 paraaortic area during pancreaticoduodenectomy (PD) for carcinoma of the head of the pancreas. Recent advances in surgical anatomy of the mesopancreas indicate that the retropancreatic area is not a single entity with well defined boundaries but an anatomical site of embryological fusion of peritoneal layers, and that continuity exists between the neuro lymphovascular adipose tissues of the retropancreatic and paraaortic areas. Recent advances in surgical pathology and oncology indicate that, in pancreatic head carcinoma, the mesopancreatic resection margin is the primary site for R1 resection, and that epithelial-mesenchymal transition-related processes involved in tumor progression may impact on the prevalence of R1 resection or local recurrence rates after R0 surgery. These concepts imply that mesopancreas resection during PD for pancreatic head carcinoma should be extended to the paraaortic area in order to maximize retropancreatic clearance and minimize the likelihood of an R1 resection or the persistence of residual tumor cells after R0 resection. In PD for pancreatic head carcinoma, the rationale for dissection of the paraaortic area is to control the spread of the tumor cells along the mesopancreatic resection margin, rather than to control or stage the nodal spread. Although mesopancreatic resection cannot be considered "complete" or "*en bloc*", it should be "extended as far as possible" or be "maximal", including dissection of 16a2 and 16b1 paraaortic areas.

Key words: Pancreatic carcinoma; Mesopancreas; Mesopancreas resection; Paraaortic area; Paraaortic dissection

Core tip: The rationale for dissection of the 16a2 and 16b1 paraaortic areas in pancreaticoduodenectomy for pancreatic head carcinoma is to control tumor spread along the mesopancreatic resection margin (R factor), rather than to control or stage the nodal spread (N factor).

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PROGNOSTIC ACCURACY OF N-LINKED VARIABLES DEPENDS ON THE NUMBER OF EXAMINED NODES: THE RATIONALE FOR EXTENDED LYMPHADENECTOMY

Lymph node (LN) involvement is one of the most important prognostic factors in gastrointestinal cancers and has been reported to range from 50% to 80% in resected pancreatic ductal adenocarcinoma. Pancreatic cancer dissemination is characterized not only by lymphatic involvement, but also by perineural invasion that might be a pathway for lymphatic spread of cancer cells. Therefore, simple nodal resection without resection of the peripancreatic soft tissues has been considered oncologically inadequate. Skeletonization of the regional vessels with removal of LNs and perivascular neural and soft tissues is necessary during lymphadenectomy for pancreatic cancer[1-3]. However, the optimal extent of lymphadenectomy in pancreatic carcinoma remains controversial.

A long-term survival benefit of extended *vs* standard lymphadenectomy in pancreaticoduodenectomy (PD) for pancreatic head adenocarcinoma was not shown in five recently published prospective randomized controlled trials (RCTs) and four meta-analyses, while morbidity and mortality were comparable[4-14]. Moreover, no significant difference was found in local recurrence rates between standard and extended lymphadenectomy[8,10].

According to these results, standard lymphadenectomy has been recommended for resectable ductal pancreatic carcinoma[15,16]. However, no standard definition of "extended" or "standard" lymphadenectomy was adopted in the RCTs; the extent of nodal dissection was different in each RCT and often too few LNs were retrieved or too few cases were included. The RCTs also differed with regard to the use of adjuvant chemotherapy[17,18]. In addition, it has been calculated that an adequately powered RCT to evaluate the potential benefit of extended lymphadenectomy would require a prohibitively large sample size[19]. Extended lymphadenectomy was shown to be associated with higher R0 resection in one RCT[6], while a trend towards fewer positive resection margins in an extended lymphadenectomy group was shown in another RCT[10] and one meta-analysis[12]. In another meta-analysis no significant difference was found between standard and extended lymphadenectomy in resection margin status[14]. However, no homogeneous definition of microscopic resection margin involvement and no standardized assessment protocol of resection margin status were adopted.

An association between better postoperative long-term survival and a larger number of examined nodes has been reported in several N0 malignancies, including pancreatic carcinoma. This may be due to a more accurate staging, with a lower probability of missing a metastatic LN as the number of examined LNs increases[20-25]. In node-positive pancreatic carcinoma, the LN ratio compared to the number of positive LNs (PLNs) is less influenced by biases of the number of examined nodes and is a more accurate predictor of survival. However, a positive or negative nodal status (N0/N+), PLNs and LN ratio are influenced by the total number of examined LNs; the prognostic accuracy of each of these LN-linked variables depends on an adequate number of LN examined[22,23,25-27] and then on the extent of lymphadenectomy[26,28] and thoroughness of the pathologist's examination[21]. Apart from understaging of disease due to inadequate lymphadenectomy or inadequate pathological examination, a not negligible rate of LN micrometastasis remains undetected by conventional pathological examination. However, the impact on survival of nodal micometastasis, particularly in pN0 pancreatic carcinoma, is debated[29-31]. Thus, although the therapeutic effect of lymphadenectomy has not been proven and the number of retrieved nodes cannot be considered a measure of successful cancer surgery, an adequate LN count is necessary for accurate N-staging[22,25,32].

PROGNOSTIC IMPACT OF PARAAORTIC NODAL METASTASIS IN PANCREATIC HEAD CARCINOMA: THE RATIONALE FOR PARAAORTIC LN SAMPLING OR DISSECTION

Paraaortic LN involvement is considered to be a next step in lymphatic spread of pancreatic cancer, after peripancreatic and superior mesenteric artery (SMA) node involvement[33,34]. The prognostic impact of paraaortic nodal metastasis in carcinoma of the pancreatic head has been shown in some studies[31,35], and refuted in others[36,37]. Paraaortic LN metastases have been found to be associated with early recurrences and poor survival, and have been considered a contraindication to pancreatic resection. Thus, paraaortic LN sampling with frozen-section examination at laparotomy has been routinely recommended to assess distant nodal status and select patients who would benefit from curative resection[31,35]. Conversely, there are some long-term survivors among patients who underwent resection of metastatic para-aortic nodes[38], and adjuvant chemotherapy may improve the survival of patients with limited paraaortic node involvement[36,39].

MAXIMIZING MESOPANCREAS RESECTION IN PANCREATICODUODENECTOMY FOR PANCREATIC HEAD CARCINOMA: THE RATIONALE FOR DISSECTION OF THE PARAAORTIC AREA

The assessment of R status after PD for pancreatic head carcinoma is a surgical and histopathological challenge. Lack of international consensus on the definition of microscopic margin involvement, components of the resection margins and a standardized protocol for pathological examination of the PD specimens contribute to the variability of the reported rate of R1 resection and its variable impact on long-term survival[40-42].

The so-called mesopancreatic resection margin has been indicated as the primary site for R1 resection in pancreatic head cancer[43]; total excision of the mesopancreas with circumferential lymphadenectomy of the SMA has been proposed to achieve an adequate retropancreatic margin clearance and minimize the likelihood of an R1 resection[44] and local recurrence[45,46].

The term mesopancreas refers to retropancreatic tissue, microscopically consisting of areolar and adipose tissue, peripheral nerves and plexuses, blood and lymphatic vessels or capillaries, and LNs: there is no fibrous sheath or fascia surrounding these structures[43,47,48]. The mesopancreas has been variously described as a definite anatomical entity extending from the posterior surface of the head, neck, and uncinate process of the pancreas behind the superior mesenteric vein, to the right or left side of the SMA, and to the inferior vena cava, aortocaval groove and aorta[43-45,47-49].

In our experience, the so-called mesopancreas does not have well defined boundaries but is continuous and connected through its components with the paraaortic area[50-52]. Our findings are consistent with the concept of the retropancreatic area as an anatomical site of embryologic fusion of peritoneal layers (the Treitz fusion fascia), and the absence of a real "meso" of the pancreas[47].

The mesopancreatic resection margin that includes the different named components of the circumferential resection margin obtained from PD (*i.e.*, SMA, retroperitoneal, uncinate, posterior, and portal vein groove margins) is a true histopathologic structure which results from a necessary and extensive surgical dissection of the retropancreatic area[51].

Lack of anatomical boundaries of the mesopancreas could explain the difficulty in obtaining an R0 mesopancreatic resection margin. The cause of loco-regional recurrences after PD with clear margins (R0) have been attributed to extrapancreatic spread of the tumor to LNs, soft tissues, lymphovascular and perineural structures, *i.e.*, all components of the mesopancreas[38,42,53]. Moreover, epithelial-mesenchymal transition-related processes involved in tumor progression may impact on the prevalence of an R1 resection or local recurrence after R0 surgery for pancreatic carcinoma in the following ways[54]: (1) occurrence of tumor budding, or the presence of de-differentiated, isolated single cells or small cell clusters (up to five cells) scattered in the stroma at the invasive tumor front[55]; (2) formation of tumor deposits, *i.e.*, macroscopic or microscopic nests or nodules found in the lymph drainage area of a primary carcinoma without evidence of residual LNs in the nodules[56,57]; and (3) a dispersed pattern of growth in the tumor periphery[58]. Our concept of the mesopancreas entails the need for extended dissection of the paraaortic area to maximize the posterior clearance and minimize the likelihood of an R1 mesopancreatic resection margin or the risk of tumor cells left beyond a negative (R0) mesopancreatic resection margin[50,51].

Although the goal of mesopancreas excision is to control R1 retropancreatic margin rates and the goal of lymphadenectomy is at least to evaluate, if not to control, the tumor spread in the nodal basin, due to the peculiar way of loco-regional spread of pancreatic carcinoma, paraaortic clearance achieved during maximal mesopancreatic excision corresponds with neuro lymphovascular and soft tissue clearance during lymphadenectomy of the 16a2-16b1 paraaortic area. Thus, in PD for pancreatic head carcinoma the rationale for paraaortic area dissection is to control tumor spread along the mesopancreatic resection margin (R factor), rather than to control or stage the nodal spread (N factor). With this perspective, 16a2 and 16b1 paraaortic dissection in pancreatic head carcinoma may impact on R classification, rather than N classification. This is in accordance with a previously reported association of LN involvement of the paraaortic area with a positive posterior resection margin[35,37], suggesting that 16b1 LN involvement may be a reflection of local invasion through the fascia of Treitz, rather than true second order node involvement in lymphatic spread[37]. Although the need for an "*en bloc*" resection of the mesopancreas has been recently emphasized[44,45,49], we highlight that the lack of anatomic boundaries of the mesopancreas and the continuity of the mesopancreatic and paraaortic area implies that, regardless of the preferred surgical procedure, mesopancreatic excision is necessarily performed through the mesopancreas and contents of the mesopancreatic area and that "*en bloc*" dissection of the mesopancreas is not possible. On the other hand, no difference in survival was found between patients undergoing an R0 *en bloc* resection and an R0 after reexcision of an initial positive margin[59].

Our technique of PD with mesopancreatic excision entails early dissection of para-aortic 16a2 and 16b1 areas followed by classical demolitive procedure with regional lymphadenectomy including lymphatic and

perineural tissues of the hepatoduodenal ligament, common hepatic artery, celiac axis and final approach to the SMA; circumferential exposure of the SMA is performed after division of the pancreas and dissection of the mesopancreatic tissues off the portal and superior mesenteric veins. Although mesopancreatic resection can never be "complete" or "*en bloc*", it should be "as far extended as possible" or "maximal", including 16a2 and 16b1 paraaortic area dissection.

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