



About Extended Lymph-Node Dissection for Pancreatic Ductal Adenocarcinoma

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Received: September 19, 2020

Published: September 29, 2020

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignant tumors in the human organism and is the most prevalent neoplastic disease of the pancreas accounting for approximately 90% of all pancreatic malignancies. To date, pancreatic cancer is the seventh most common cause of cancer-related deaths worldwide. The incidence of PDAC demonstrates annual 5 - 6% absolute increase worldwide and is expected to rise further in the future.

As noted above PDAC represents a cancer entity of extraordinarily high malignancy and albeit the development of novel treatment strategies the overall prognosis and survival rate of PDAC patients still remains scanty with 5-year overall survival of less than 8%. Surgical resection followed by adjuvant chemotherapy is the only possible curative therapy available, yet only 10 - 20% of PDAC patients are detected at resectable stages, while the less part of the remaining 80 - 90% demonstrates locally advanced, non-resectable stage and the greater part - distant metastases. One of the prominent features of PDAC is its early progression to metastatic disease and the key mechanisms of PDAC-metastasis formation are still poorly understood. Regardless of its mechanisms hematogenous metastases are the main barrier to curing the patients with PDAC.

According to the popular opinions the only realistic chance of a cure for patients suffering from PDAC is the radical resection of the tumor despite the anecdotal cases of eradication of PDAC after chemotherapy without recurrence, including our unpublished two cases without recurrence for more than 12 and 6 years, re-

spectively. Despite the encouraging trend in resectability rate and improvement of long-term results with adjuvant chemotherapy PDAC treatment strategies are one of the greatest challenges in the current oncological research. Whether the increasing resectability rate of PDAC is due to more proportion of patients detected at early stages or to more aggressive surgical behavior is not fully clear. In any case there is no reliable "marker" confirming that the increasing resectability rate is related to detecting more of PDAC cases at early stages. Theoretically decreasing of proportion of patients with pancreatic head cancer complicated with obstructive jaundice with time can serve as a clinical "marker" indicating that the increasing resectability rate is related to detection of more patients at early stages. We compared proportions of appropriate patients with obstructive jaundice with >30 year interval and revealed that the indicated parameter dropped only by 3% (82% vs 79%) during this period of time, that theoretically confirms that the difference in resectability rate hardly can be related to detection of more cases at early stages.

Lymph node dissection is considered to be essential for PDAC to achieve curative intent surgery. By analyzing the frequency of lymph-node involvement in PDAC, it can be seen that the rate of the lymph-node involvement is around 70% in the patients undergone resection. There is a frequent lack of correlation between tumor diameter and lymph-node positivity, which, in some case series, may be present in as many as 50% of cases of small tumors ($T < 2$ cm). According to opinions of some researchers the risk of false lymph-node negativity can result from the lack of anatomical contiguity in the lymphogenic-metastasis pattern of PDAC, with possible posi-

tivity in remote lymph-node stations together with negative peripancreatic lymph nodes. Therefore, the extent of lymph node dissection during pancreatic resection remains a hotly debated issue.

Theoretically, lymph-node dissection is essential for the treatment of the adenocarcinomas, including PDAC. Whether extended lymph-node dissection can provide eradication of PDAC cells and increase the long-term survival remains an issue of controversial opinions. Some Eastern specialists report that an extensive lymph-node dissection including areas 14 and 16 is necessary for radical resection in patients with pancreatic cancer. In the literature there is also opinion that standard Whipple surgery successfully removes 80% of the lymph-node sites most commonly involved. Non-performance of a standard lymphadenectomy in all patients with PDAC in Western series is interpreted by some authors as the result of both a non-homogeneous surgical approach and definitions used for the standard and extended procedures by surgeons. Moreover, a major intra-abdominal lipid component formed for anthropomorphic and dietetic reasons, is comparatively more frequent in Western populations. Some researchers consider that this technical obstacle sometimes proves insurmountable in terms of harvesting lymph nodes properly along with the elevating the related operative times and risks, at least theoretically. In any case differences in the long-term survival of appropriate patients can serve as an "indicator" for the obligatoriness of lymph-node dissection and its extent.

According to the general opinions the "standard" surgery for pancreatic head adenocarcinoma means to include anterior and posterior pancreaticoduodenal, pyloric, main bile duct, superior and inferior head and body nodes; the "extended" means to include also the nodes stations located at the liver hilum along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery, celiac trunk, superior mesenteric artery and both renal hili. Some Japanese researchers however, stress that, in order to offer the individual patient the maximum chance of survival, surgeons cannot confine themselves to extended lymphadenectomy alone, but must also remove the retroperitoneal laminar tissue including the celiac nerve plexus. The benefit of this extent in terms of survival is questioned by the Japanese authors themselves as these patients experience devastating diarrhea requiring periods of long hospitalization. By contrast, in Western countries few authors suggest more radical approach than a standard. So because of the yet unclear pattern of lymph-node involvement and its effective prog-

nostic role in PDAC, the value of extended lymph-node dissection is still a much debated issue.

Results of some retrospective, nonrandomized studies suggest a survival benefit from extended lymph node dissection for localized pancreatic cancer. Unfortunately, a pooled retrospective experience from 59 Japanese centers has revealed that extended lymphadenectomy for pancreatic cancer < 2.0 cm do not demonstrate a clear survival advantage to standard surgery. Moreover, some researchers suppose that careful analysis of the published clinicopathologic data and outcome analysis of patients undergoing resection for node-positive PDAC suggest that this issue cannot be settled by a logistically feasible randomized clinical trial.

According to the opinions of some Western researchers extracted from multicentric, prospective, randomized studies extended lymphadenectomy can increase the survival rate in node-positive patients with PDAC. However recent molecular analyses of resected lymph nodes for K-ras oncogene mutations using polymerase chain reaction and analysis for restriction fragment length polymorphisms have indicated that approximately two thirds of patients with histologically negative lymph nodes harbor molecular micrometastases in at least one regional lymph node in cases of PDAC. Thus, standard histologic staging understates the percentage of node-positive patients.

As mentioned above PDAC is a type of cancer with very high potential of occult metastases – micrometastases. Unlike hematogenous occult metastases lymphogenic micrometastases can be detected by current immunohistochemical analysis and molecular assays after surgery. Existence of hematogenous micrometastases can't be detected before or immediately after surgery, they can be revealed in the follow-up period as an obvious metastases. Therefore, percentage of patients developing distant metastases after radical intent pancreatectomy corresponds to the rate of hematogenous occult metastases before surgery. So the percentage of hematogenous occult metastases can only be assessed indirectly, later long after the surgery and in approximate ranges. We retrospectively analyzed the percentage of postoperative hematogenous metastases in 12 patients undergone Whipple surgery with extended lymphadenectomy and revealed that all patients developed hematogenous metastases during 16 months following surgery with 0% 3-year survival that indirectly confirm that all the patients had had hematogenous micrometastases before surgery. Therefore

one of the reliable parameters justifying whether to perform extended lymphadenectomy routinely in patients with PDAC can be difference between the rates of detectable hematogenous metastases following standard surgery and extended lymphadenectomy.

In summary it appears reasonable to conclude that almost all arguments drawn from the literature are not in favor of performing extended lymphadenectomy routinely in patients with resectable PDAC unlike the other gastrointestinal adenocarcinomas. It is mainly just because most of the patients with PDAC requiring extended lymphadenectomy theoretically have simultaneous occult hematogenous metastases that can't be detected by current diagnostic modalities.

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