PERSPECTIVE

An outlook on the lymph nodes dissection during the pancreatectomy for pancreatic cancer

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1 | INTRODUCTION

Pancreatic cancer is likely to be one of the most highly lethal diseases in the world.1,2 Radical pancreatectomy with adjuvant chemotherapy is a curative treatment for pancreatic cancer.2 Lymphadenectomy is an indispensable procedure in radical resection for pancreatic cancer. It is obvious that lymph node dissection is essential. According to the eight edition of the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging system, the number of positive lymph nodes (PLNs) is related to the prognosis of the patients.3 Moreover, a standard lymphadenectomy reduces the incidence of local lymph node recurrence.4,5 However, in some cases, the current guidelines or consensus cannot be satisfied in clinical practice. Thus, in this brief literature review, we summarize the current status of lymph nodes dissection in pancreatectomy while focusing on the further development of research.

2 | NUMBER OF PLNs, NUMBER OF EXAMINED LYMPH NODES, AND LYMPH NODE RATIO (LNR)

The AJCC TNM staging system is the most worldwide used system that provides us a relatively accurate prognosis of the patients. The latest version is the eight edition of the TNM staging system.3 The main revision to the seventh edition is the modification of the N status in the system. Previously, in the seventh edition, the N status was separated into N0/N1 depending on whether regional metastatic lymph nodes were found in the operation. The impact of the number of PLNs on the prognosis was ignored. Currently, in the eight edition, the N status is divided into N0/N1/N2 based on the number of PLNs. The patients without lymph node metastasis are stated in the N0 stage. The patients with four or more PLNs are classified into the N2 stage, which implied poor survival. The rest are in the N1 stage whose PLNs are less than four.

In order to acquire accurate PLNs, a certain number of lymph nodes should be harvested. The optimal lymphadenectomy was disputed until a consensus statement on the extent of lymphadenectomy for pancreatectomy was published by the International Study Group on Pancreatic Surgery (ISGPS) in 2014.4 In this statement, the study group has affirmed the extent of lymph node dissection for the pancreatectomy. Based on the nomenclature for nodal stations of the Japanese Pancreas Society,5 a standard lymphadenectomy should include lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a right lateral side, 14b right lateral side, 17a, and 17b during the pancreatectoduodenectomy (PD), while a standard lymphadenectomy during the...
distal pancreatectomy should include lymph node stations 10, 11 and 18 for the tumor located in the body and tail of the pancreas. Furthermore, the minimal number of examined lymph nodes (MNELN) for the PD was considered to be at least 15. With the increase of the number of regional lymph nodes retrieved, the accuracy of PLNs raised up.\(^7\)

Except for the number of PLNs and the number of examined lymph nodes, the lymph node ratio is another important factor of survival prediction. In many former researches,\(^8\)–\(^11\) the lymph node ratio that referred to the number of PLNs involved to the number of examined lymph nodes was considered as an independent risk factor of patients’ disease-free survival and overall survival. However, among the number of PLNs, the number of examined lymph nodes, and the lymph node ratio, only the first one is mentioned in the TNM stagings system.

Thus, the accuracy of the N status in the eight edition TNM staging system is totally dependent on the exact number of PLNs. Moreover, the number of regional lymph nodes retrieved determines the quality of lymph node dissection. Nevertheless, is optimal lymphadenectomy easy to be achieved in clinical practice? As the predictive factors, is the number of PLNs more significant than the lymph node ratio in the survival prediction? Is the current eight edition TNM staging system good enough to satisfy all the clinical conditions? All these problems need to be solved.

3 | DEFICIENCIES IN THE TNM STAGING SYSTEM

3.1 | Inadequate examined lymph node

As mentioned above, the optimal MNELN for the PD is 15. However, occasionally the MNELN could not be achieved in clinical practice. A standard lymphadenectomy during the pancreatectomy cannot ensure enough examined lymph nodes. Thus, we would like to name this state as an “inadequate examined lymph node,” which means the MNELN cannot be realized in a standard lymphadenectomy.

According to our previous research based on the data of nearly 10,000 patients who underwent PD during 2004 to 2013 from the US Surveillance, Epidemiology, and End Results registry, the inadequate examined lymph node occurred in more than half of these patients due to the racial or individual variances, oncological behaviors, pathological manipulations, and so forth.\(^12\) C the extended lymph node dissection become a solution? Several researches have been carried out to compare the outcomes between extended and standard lymphadenectomy in the PD.\(^13\)–\(^17\) The results were familiar. The number of examined lymph nodes in the extended lymphadenectomy was higher than that in the standard lymphadenectomy. However, no survival benefits were reported in the extended lymphadenectomy. Therefore, without regard to the survival benefit, the extended lymphadenectomy might be performed as a solution to the inadequate examined lymph node.

3.2 | Estimation of the accuracy of nodal positivity

Since the inadequate examined lymph node seems inevitable, the estimation of the prognosis of these patients should be reconsidered. In our previous research, we found that the inadequate examined lymph node could result in underestimation of the N stage, and this would have an adverse impact on recurrence, the efficacy of postoperative treatment, and even overall survival.\(^12\)

Several look-up tables that included the observed PLNs, the number of examined lymph nodes, and the tumor size were provided for the surgeons to estimate the nodal accuracy. Each examined lymph node from 4 to 14 was listed separately in these tables. The probability of four or more PLNs and the accuracy of the number of PLNs observed in patients with T1-3 tumor could be easily found in these tables.\(^12\) In this way, the possibility of undetected PLNs could be estimated. However, it should be noticed that the estimation of the accuracy of nodal positivity was carried out only after the operation. If the nodal inaccuracy was affirmed, it would be tough to make the discussion to do the secondary operation. The worth of the re-operation should be well-considered.

3.3 | Supplementary staging system

Former researchers have announced the deficiency of the current TNM staging system.\(^8,18\) The main reason was that the current system could not distinguish patients of all kinds. Therefore, they have tried several methods to modify or ameliorate the staging system. In our opinion, we firmly believe the insufficiency of the staging system is mainly caused by the inadequate examined lymph node.

In our recent research, the eight edition of the TNM staging system is suitable for patients with sufficient examined lymph nodes but not applicable for patients with an inadequate examined lymph node.\(^19\) According to the estimation of the accuracy of nodal positivity, the probability of undetected PLNs might be pretty high in patients with an inadequate examined lymph node.\(^12\) Thus, for these patients, the number of PLNs was no longer appropriate for the nodal assessment in the TNM staging system. The number of PLNs could be replaced by the lymph node ratio in
the supplementary staging system. A new N staging system was proposed based on the lymph node ratio. N’ status in the supplementary staging system was established. N’0 referred to LNR = 0, while N’1 as 0 < LNR < 0.18 and N’2 as LNR ≥ 0.18. The results of this study showed that the supplementary staging system could perfectly distinguish the patients with an inadequate examined lymph node.19

3.4 | Lymph node status in distal pancreatectomy

For the distal pancreatectomy, the optimal MNELN is unknown. As mentioned before, the extent of lymphadenectomy in distal pancreatectomy is totally different from that in PD. Thus, the MNELN in distal pancreatectomy should be reanalyzed. Previous studies have reported that the MNELN ranged from 11 to 18 nodes for distal pancreatectomy,8,20–22 but the methods they performed were not sufficiently convincing. The data sources were not multi-centric, and the sample size was not big enough in some researches. Therefore, a retrospective study with a huge sample size from multiple centers should be carried out to verify the MNELN.

4 | BRAINSTORMING FOR THE “OPTIMAL” LYMPHADENECTOMY

The “optimal” or “ideal” lymphadenectomy should be defined as a method of acquiring the adequate number of PLNs with little trauma during the dissection and reducing the potential postoperative lymph node recurrence. The “optimal” lymphadenectomy should have characteristics listed as below.

4.1 | Individualized

The standard lymphadenectomy is not a fetter to the surgeons. In fact, it is impossible to neglect the enlarged lymph nodes in the other lymph node station besides the standard ones. Individualized should be an important characteristic of “optimal” lymphadenectomy.

The extent of lymphadenectomy depends on the tumor location. For the tumor located at the head of the pancreas, lymph node stations 5, 6, 8a, 12b, 12c, 13a, 13b, 14a, 14b, 17a, and 17b should be retrieved. While for the tumor located at the body/tail, lymph node stations 10, 11, and 18 should be included in the lymphadenectomy. With our efforts, the extent of lymphadenectomy could be more refined.

According to embryonic development, the head of the pancreas combines with the dorsal and ventral parts. The lymph node reflux of these two parts are different: Cancer in the dorsal part spreads through lymph node stations 8 and 12 (lymph nodes along the common hepatic artery and lymph nodes along the hepatic duodenal ligament), while cancer in the ventral part spreads through lymph node station 14 (lymph nodes along the superior mesenteric artery).23 In our work, we detailed the extent of lymphadenectomy for pancreatic head cancer. We found it necessary to dissect the lymph node station 14 when cancer located in the ventral head of the pancreas. Contrarily, when cancer is located in the dorsal, the dissection of lymph node station 14 was left to the discretion of the surgeon.24

The consensus by ISGPS has stated that lymph node station 9 is only suggested to be included in the resection when tumors are confined to the area of the body of the pancreas.4 However, the area of the pancreas body was not detailed. Should a standard lymphadenectomy include lymph node station 9 (lymph nodes around the celiac artery)? A retrospective study was carried out and found that when cancer is located in the neck or the body/tail of the pancreas with margin-to-bifurcation-distance less than or equal to 2.5 cm, the involvement rate for lymph node station 9 was high. Standard lymphadenectomy should include the lymph node station 9.25

It can be predicted that under further investigation, each lymph node station would be discussed separately and lymphadenectomy would be more individualized.

4.2 | Early/preoperative detection

One of the objectives of lymph node dissection is to detect the potential PLNs. If the PLNs could be detected previously, it would be a great change to the clinical treatment strategy.

The early/preoperative detection of lymph node metastasis could optimize the regional lymphadenectomy. The lymph node dissection would be more precise. Furthermore, if the patient is diagnosed in the N2 stage (four and more PLNs) before the operation, which means sharing the same prognosis with patients in the T4 stage (borderline resectable or local advanced cancer), the neoadjuvant therapy might be profitable for these patients. However, at the present, the sensitivity and specificity of the radiography (computer tomography, CT and magnetic resonance, MR) are not high enough to diagnose the lymph node metastasis. The role of positron emission tomography, PET/CT and PET/MR remains unclear.5 There is no significant correlation between the lymph node metastasis and imaging features.
Radiomics might provide another solution. A few studies have tried to reveal the effect of radiomics in the prediction of lymph node involvement.\textsuperscript{26–30} Among them, Bian et al.\textsuperscript{30} found a significant association between the arterial radiomics score and lymph node metastasis. However, their study still could not tell the exact location of the PLN. Compared with radiomics in the lung, the images of pancreas are more difficult to obtain because the imaging features of the other organs in the abdomen have a great influence on the pancreas. More studies need to be carried out.

4.3 Visualization

During lymphadenectomy, the surgeons will not ignore the enlarged lymph nodes. Some of them are metastatic, but the others are inflammatory. It is hard to tell them apart during the operation. Excessive lymph node dissection may lead to postoperative hemorrhage and chyle fistula. To avoid these complications, a visualized lymphadenectomy is required.

For pancreatic diseases, Lu et al.\textsuperscript{31} provided the first clinical use of panitumumab-IRDye800CW for detecting pancreatic ductal adenocarcinomas, which was feasible and safe in the surgery. Although their study was still in phase 1, the researches on tumor-specific fluorescence-guided surgery for pancreatic diseases have commenced. In the future, tumor-specific fluorescence visualization could lead the surgeons to accomplish the “optimal” lymphadenectomy.

5 SUMMARY

The lymph nodes dissection is an essential procedure in the radical pancreatectomy. At present, under the guidance of many guidelines and consensus, lymph node dissection has gradually been standardized. However, there are still some deficiencies that can be overcome stepwise. We are looking forwards to achieving an “optimal” lymphadenectomy in the future.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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