



Importance of an appropriate number of examined lymph nodes in patients with pancreatic cancer – the more the better?

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Comment on: Huang L, Jansen L, Balavarca Y, *et al.* Significance of Examined Lymph Node Number in Accurate Staging and Long-term Survival in Resected Stage I-II Pancreatic Cancer-More is Better? A Large International Population-based Cohort Study. *Ann Surg* 2021;274:e554-63.

Submitted Apr 27, 2022. Accepted for publication May 12, 2022.

doi: 10.21037/hbsn-22-163

View this article at: <https://dx.doi.org/10.21037/hbsn-22-163>

Pancreatic cancer is a highly aggressive malignant cancer with a 5-year survival rate of approximately 10%. The outcome of patients diagnosed with resectable pancreatic cancer as per the National Comprehensive Cancer Network (NCCN) classification and those who underwent resection was not satisfactory. Similar to other abdominal malignant tumors, the stages of pancreatic cancer are defined by local extension, lymph node metastasis, and distant metastasis. The presence or absence of lymph node metastasis is diagnosed by pathological examination of the retrieved lymph, the quality of the diagnosis based on lymph node (N) staging depends on the surgical and pathological aspects (1). In other words, it is necessary to perform lymph node dissection in an oncologically appropriate area without overestimation during surgery; further, the pathologist must thoroughly check the lymph nodes that have been retrieved and provide an accurate diagnosis.

The importance of the number of dissected lymph nodes as an evaluation criterion in the diagnosis of gastric and colorectal cancer has been emphasized. A minimum number of 16 lymph nodes are required to ensure reliable node staging in patients with gastric cancer as per the eighth edition of TNM classification (2) and the most recent American Joint Committee on Cancer (AJCC) Staging System (3). In addition, the European Society for Medical Oncology (ESMO) guidelines (4) mentions that patients with stage II colorectal cancer and fewer than 12 lymph nodes dissected are considered as a high-risk group for recurrence; therefore, those patients are recommended to receive postoperative adjuvant chemotherapy. A low number

of retrieved lymph nodes could imply that either an optimal lymph node dissection had not been performed during surgery or that the dissected lymph nodes were not fully evaluated during pathological diagnosis; thus, increasing the likelihood of missing detection of potential lymph node metastases that may cause the risk of stage migration.

Huang *et al.* (5) published a study on the significance of examined lymph node (ELN) number in resected stage I–II pancreatic cancer conducted between 2003 and 2015 based on data collected from two large cohort studies: the US Surveillance, Epidemiology, and End Results (SEER)-18 program and The Netherlands National Cancer Registry (NCR). They observed that as the number of retrieved nodes increased over time, the number of metastasis-positive nodes increased; further, the odds ratio for negative-to-positive node stage migration increased, and the overall survival rate improved. These results suggest that a certain number of nodes must be dissected to diagnose the appropriate stage, and that dissection of an inadequate number of nodes may result in missing the detection of potential metastatic nodes.

In the previous study (5), a minimal and optimal cutoff (11 and 19, respectively) were identified to determine the different probabilities in survival and stage migration in both the US and The Netherlands cohorts. In the US cohorts, as the number of ELNs increased up to 19 the hazard ratio for overall survival consistently decreased and the odds ratio for stage migration consistently increased; however, both parameters flattened out when ELNs were ≥ 19 . Further, The Netherlands cohorts did not show

significant difference in survival rate between those with ≥ 19 and < 19 ELNs implying that the threshold of 19 ELNs was not appropriate in this cohort. This indicates that the optimal threshold may differ depending on the background and country of the target group.

The question is whether to allow extended lymph node dissection in patients with pancreatic cancer to ensure examination of an optimal number of nodes. Nimura *et al.* (6) performed a randomized controlled trial comparing a standard dissection group who underwent lymphadenectomy of anterior and posterior pancreatoduodenal nodes (No. 13a/b, 17a/b station) with an extended dissection group involving dissection of lymph nodes around common hepatic artery (CHA), celiac artery (CA), superior mesenteric artery (SMA), and abdominal aorta (No. 8a/p, 9, 12a/b/p, 14p/d, 16a2/b1 + total nerve dissection of CHA and SMA + right side nerve dissection of CA). The number of lymph nodes dissected in the extended dissection group was significantly higher than in the standard dissection group (40.1 *vs.* 13.3, $P < 0.0001$). Further, a longer surgery duration, increased blood loss, and no difference in overall survival or recurrence-free survival was observed in the extended dissection group. In 2015, Dasari *et al.* (7) performed a meta-analysis of five randomized controlled trials on extended lymph node dissection in pancreatic cancer and observed that 15.7 additional lymph nodes were retrieved in the extended dissection group than in the standard dissection group; however, the hazard ratio of the overall survival was not significantly different between the two groups (0.88, $P = 0.11$), and the risk ratio for postoperative complications was high (1.23, $P = 0.004$). Based on these studies, the superiority of performing extended lymph node dissection in patients with pancreatic cancer could not be ascertained; however, the appropriate lymph node dissection area is still being investigated.

The distribution of lymph node metastases in left-sided pancreatic cancer and the optimal areas for lymph node dissection have been previously studied (8). There was no metastasis to non-peripancreatic lymph nodes (No. 7, 8a/p, 9, 14p/d station) in distal pancreatic carcinoma that was more than 20 mm away from the left margin of the portal vein. In addition, patients with tumors located within 20 mm of the left border of the portal vein showing positive metastasis to the non-peripancreatic lymph nodes had a significantly poor prognosis in overall and recurrence-free survival as compared with the other groups. This indicates that non-peripancreatic lymph node dissection can be omitted in left-sided pancreatic cancer. In cases with

pancreatic body cancer, 20% of patients had metastasis to peri-pancreatic head lymph nodes (No. 13, 17 station) and its dissection was highly effective (9); therefore, pancreatoduodenectomy may be selected on a case-by-case basis. Recently, the optimal lymph node dissection area in pancreatic cancer has been increasingly studied, and further investigation through prospective studies is desired in the future.

Moreover, the procedure to identify the lymph nodes from the resected specimen should also be considered. In Japan, surgeons themselves separate lymph nodes from the excised specimen, map them according to each lymph node station and then submit it for pathological examination. Ambrosio *et al.* (10) compared the Japanese method (surgeons and pathologists working together to identify lymph nodes at each station) with the conventional method (the resected specimen is fixed in formalin and the pathologist identifies the lymph nodes) for resected gastric cancer specimens. The results showed that the Japanese method retrieved significantly more lymph nodes than the conventional method (79 *vs.* 29, $P = 0.001$). However, this method required more time because technicians had to prepare approximately 30 additional hematoxylin and eosin slides per case and the pathologists required additional time for examination of these slides; consequently, increasing the technical costs. In cases of pancreatoduodenectomy, the number of retrieved lymph nodes were reported to increase in education of pathologists and pathology assistants (11). Thus, it is clear that the number of ELNs depends on the handling of the resected specimen, and it may be necessary to develop a system that facilitates the evaluation of a higher number of lymph nodes from the same specimen.

As described by Huang *et al.* (5), observational analysis can show correlations between events but cannot establish causal relationships. However, in their large cohort study, the increase in ELN may allow for more accurate staging of pancreatic cancer and definition of quality metrics in the population. Recent a study has reported the need to determine an appropriate number of ELNs, even in the current era of preoperative therapy (12). Different countries, regions, and systems will have a varied opinion and procedures regarding lymph node dissection. The threshold for the appropriate number of nodes may vary, but an assessment involving limited number of lymph nodes will reduce the credibility of the diagnosis itself. Therefore, the evaluation of an appropriate number of lymph nodes is a collaborative effort of both surgeons and pathologists, and their recognition of its importance will contribute to

the maintenance of quality indicators in the treatment of pancreatic cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-163/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Ogura T, Ishida H, Takahashi A, Kawashima Y. Importance of an appropriate number of examined lymph nodes in patients with pancreatic cancer—the more the better? *HepatoBiliary Surg Nutr* 2022;11(4):605-607. doi: 10.21037/hbsn-22-163