



The prognostic relevance of examined lymph nodes for accurate staging of resected pancreatic adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC) is a disease with a particular aggressive cancer biology and, unfortunately, a very poor prognosis for most patients. There is no question about the lethality of pancreatic cancer. However, the question why this malignancy is so deadly remains a biological puzzle both to investigators and caretakers alike. Staging of pancreatic cancer undergoing resection—while important to compare cohorts across studies and trials—also allows for a clinical clue about the progress of the disease. Yet, still, current staging imperfectly splits prognosis and outcomes and fails to illuminate the biological mechanisms behind the patterns (1). Hence, continued refinement of available staging systems is attempted across several clinical series and different patient cohorts. Indeed, pancreatic cancer seems to be a systemic disease from the very onset or, at least, even at the earliest stages of invasive disease (2). Also, it seems that the more nodes investigated per specimen for PDAC, the higher the likelihood to find node metastasis—and, hence, a better staging. In a large series on two nationwide cancer registries from the United States and The Netherlands (3), the investigators found an association between examined lymph nodes and the risk of having metastatic lymph node disease, with a minimal threshold for a sufficient number of nodes found at a cut-off of 11 nodes and an optimal cut-off (to avoid understaging) at 19 lymph nodes.

Along the lines of other cancer forms, the impact of

lymph nodes has been the matter of much debate, and investigation intensively also in pancreatic cancer (4-7). Several metrics and defined criteria have been used to call out node status as an indicator of quality or to indicate prognosis, some of which are listed in *Table 1*. Indeed, the presence of lymph node metastases in pancreatic cancer has prognostic value, with higher risk of disease recurrence after resection and indicating worse long-time survival (8). Lymph node sampling plays an important role in both accurate staging and may (at least in theory) have a curative effect in the setting of resectable pancreatic carcinoma by removing potential metastases—at least that is the main thinking behind the rationale for extended lymphadenectomy—yet randomized trials failed to demonstrate a benefit on survival (5,9).

Nonetheless, the number of examined lymph nodes seems to be an important tool for accurate staging and assessing surgical quality. Although guidelines for acceptable standard minimal numbers of examined lymph nodes exist for various cancer specimens, according to the AJCC Cancer Staging Manual 8th edition [2017], there is an ongoing debate around the nodal staging in pancreatic cancer (10). International guidelines show striking variability among recommendations for the threshold of ELN (examined lymph nodes), as AJCC recommends examination of at least 12 LN, while the European Society of Medical Oncology (ESMO) practice guidelines (11)

Table 1 Several metrics and roles of lymph nodes in PDAC

Item	Description	Rationale	Role
Number of nodes	Total number of lymph nodes sampled	Accurate staging. Surgical quality Pathology quality	Quality metric
Number of metastatic nodes	pN0 = no LN mets pN+ = presence of mets N1 = 1–3 node mets N2 = 4 or more node mets	Systemic disease; tumor burden	Prognostication
LNR	Ratio of metastatic to total LNs	Potentially more accurate assessment than pN with insufficient lymph nodes examined	Prognostication
LODDS	The logarithmic of the ratio between the probability of pN+/ pN0 when one LN is retrieved	Better prognostic stratification compared to LNR in node negative patients	Prognostication
PALN	Node(s) in the aorto-portal window	Suggests distant metastases; systemic disease	Prognostication; poor survival
Location of LN	Specific lymph node stations	Named location; patterns of dissemination	Prognostication; systemic disease
Sentinel node	Accurate assessment of draining lymph nodes	Sentinel lymph node most likely location for lymphatic spread. Precision of surgical resection and extent of lymphadenectomy?	Little or none in PDAC

PDAC, pancreatic ductal adenocarcinoma; LN, lymph node; LNR, lymph node ratio; LODDS, logarithmic odds of metastatic lymph nodes; PALN, periaortal lymph node.

and the International Study Group on Pancreatic Surgery (ISGPS) consensus favor a minimum of 15 LN (12), with lower numbers accepted after neoadjuvant therapy. More recently, the updated TNM 8th classification for pancreatic adenocarcinoma has been revised as the number of positive lymph nodes has been shown to have prognostic value, with ≥ 4 positive lymph nodes (pN2) being associated with reduced overall survival (13).

Previously conflicting results regarding the impact of ELN on long-term survival, especially in lymph node negative disease (4,14), are currently overthrown by studies with larger sample size and stratified analysis that point to the more nodes evaluated the better and emphasize the need for reevaluating and refining current recommendations. The study by Huang *et al.* (3) is based on a large, international sample size from two national cancer registers (SEER from the US; NCR from The Netherlands) to better understand the implications of ELN in pancreatic cancer. In an analysis of 16,241 patients, the investigators show that higher ELN numbers were associated with larger proportion of identifying lymph node positive disease and better stage stratifying with correlation to survival. A robust

statistical analysis with adjustment for multiple confounding variables, like sex, age, tumor location, T stage, harvested and metastatic lymph node numbers, showed similar results regardless of operation type (pancreatoduodenectomy *vs.* distal pancreatectomy). Furthermore, their suggested cut-off of minimum 11 ELN to achieve accurate staging seems a feasible goal for pathologists, keeping in line with current AJCC guidelines. However, when looking at thresholds of ELN associated with better survival and decreased mortality, the optimal cutoff was set to >19 LN, which falls in the interval supported by previous studies (15,16).

The problematic area of node negative disease remains, as the association between higher ELN count and better survival was seen in both node positive disease and node negative disease in the US cohort; this was not the case for node negative disease in The Netherlands. Stage migration may account for some of the differences, however, other variations between the two countries, like the higher mean numbers of ELN in the US underscore that other factors might influence nodal sampling. Operative technique and lymph node sampling may vary between institutions. One may argue that high volume centers

will retrieve higher numbers of LN and thus find more pN+ disease. The investigators in comment that the most probable explanation is different pathology practice in the Netherlands, with greater variation, where the number of nodes sampled was lower. As mentioned previously (7), lymph node sampling is deeply investigator-dependent and a preset requirement of a low number could allow the pathologist to settle for less and deem a lower number of nodes as sufficient rather than search for more nodes. In addition, variations in macroscopic specimen examination protocols contribute to the differences in total number of lymph nodes sampled. Efforts to standardize dissection of surgical pancreas specimens may lead to improved LN sampling (17,18).

Despite standardization of both surgery and pathology practice, that may be delivered to optimal and state-of-the-art standards, there are still unknown variables in the equation of sampling accuracy (7,19). There might be a biological variation in absolute number and distribution of LN around the pancreas (20). Also, clinical attempts to perform extensive lymphadenectomy have not demonstrated better survival in randomized trials, despite obtaining more LNs (9). However, the technical details and minute accuracy to counting node status can only take us this far to impact the patients' outcome. Although the study by Huang and colleagues (3) underscores the importance of sampling higher lymph node numbers for improving staging and better stratifying patients according to their possible outcome, other factors are likely just as important in defining the aggressive nature of pancreas cancer like tumor biology and molecular pathways. Comparing 5-year survival of patients with breast cancer with lymph node metastases and pancreas cancer with lymph node metastases, the latter has a much lower estimated survival. Hence, lymph node metastasis per se may not account for the large difference observed in survival for patients with PDAC.

The biology behind the aggressive behavior in pancreatic cancer remains difficult to understand. Lymph nodes and their metastases may represent a spectrum or parts of biological processes that we have yet to fully elucidate. As the pursuit for a better understanding of this disease continues, the obsession of counting nodes should maybe seize for a while and allow us to reflect on the true mechanisms driving this process forward. Maybe when we eventually better understand the tumor intrinsic factors and the complex interplay between the host, the tumor cells, the immune system and the lymphatic network, we will also

truly arrive at novel ways of treating this disease. Hence, the lymph nodes may hold parts of the code—if not the very key—to paving a way for further translational advances from disease biology to effective management. In the end, this may change the outcome for patients suffering from this unfortunate disease.

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