Predictors of Lymph Node Metastasis Warranting Lymphadenectomy in Pancreatic Neuroendocrine Tumors

Walid Akmal Shafie, MD; Fouad Abdelshahid Fouad, MD; Islam Ali Soliman, MD; Aly El Faqeh Mohamed Okasha, MD
Department of Surgical Oncology, National Cancer Institute, Cairo University, Cairo, Egypt

Introduction: Pancreatic neuroendocrine tumors (PNETs) represent about 1–3% of all pancreatic tumors. The optimal extent of surgical resection remains uncertain, largely due to difficulties in reliably predicting lymph node metastasis (LNM) before surgery—a critical determinant of patient prognosis. Precise preoperative assessment of LNM is essential to guide appropriate surgical planning and minimize unnecessary intervention in patients with a low risk of metastasis.

Aim of work: To study the predictor factors of lymph made metastasis in pancreatic neuro endocrine tumour and hence the need for lymphadenectomy.

Patients and methods: This retrospective study included patients who underwent curative-intent pancreatic resection for PNETs at the National Cancer Institute, Cairo University, from January 2004 to December 2024. We analyzed associations between LNM and variables including age, tumor size, location, grade, Ki-67 index, lymphovascular invasion (LVI), perineural invasion, and tumor stage.

Results: Among 28 patients, 9 (32.1%) had positive lymph nodes. LNM was significantly associated with higher Ki-67 index, grade 2–3 tumors, stage 3–4 disease, LVI, and perineural invasion. No significant association was found between LNM and tumor size, location, or type of surgery.

Conclusion: Tumor biology—specifically grade, Ki-67 index, stage, LVI, and perineural invasion—are significant predictors of LNM in PNETs. These factors should guide decisions regarding lymphadenectomy rather than tumor size or location alone.

Key words: Pancreatic neuroendocrine tumor, lymph node metastasis, lymphadenectomy.

Introduction

Pancreatic neuroendocrine tumors (PNETs), originating from the neuroendocrine cells within the pancreas, comprise roughly 1–3% of all pancreatic tumors and are recognized as the second most common type of pancreatic cancer.[1-3] Among these, non-functioning PNETs (NF-PNETs) are far more prevalent than functioning variants, accounting for approximately 70–90% of diagnosed cases.[4]

Surgical resection remains the only potentially curative option for PNETs. Nevertheless, the most effective surgical approach continues to be a subject of debate.[5,6] A major challenge in surgical planning lies in the preoperative assessment of lymph node metastasis (LNM), which has been firmly established as a key prognostic indicator influencing patient outcomes.[7]

Current guidelines from the European Neuroendocrine Tumor Society (ENETS) recommend performing a pancreatectomy with regional lymph node dissection for tumors larger than 2 cm.[7] Similarly, the National Comprehensive Cancer Network (NCCN) advises extensive surgical resection, including regional lymphadenectomy, for lesions over 2 cm or those with known nodal involvement. For tumors between 1 and 2 cm, consideration of lymph node dissection is also suggested.[8] Given the impact of lymph node involvement on prognosis and treatment strategy, accurate preoperative identification of LNM is essential to guide the extent of surgery and prevent unnecessary overtreatment in patients at lower risk. Prior research has highlighted several predictors of lymph node metastasis in PNETs, including tumor size, histologic grade, and the Ki-67 proliferation index.[9-14]

Aim of work: To study the predictor factors of lymph made metastasis in pancreatic neuro endocrine tumour and hence the need for lymphadenectomy.

Patients and methods

This study is a retrospective analysis that compares clinicopathological factors associated with predicting lymph node metastasis in patients diagnosed with histologically confirmed pancreatic neuroendocrine tumors (PNETs). All patients underwent curative-intent surgical resection at the Department of Surgical Oncology, National Cancer Institute, between January 2004 and December 2024 (Covering a 20-year period of NCI experience). Out of 34 initially identified cases, 6 were excluded due to the absence of lymph node dissection, leaving 28 patients for final analysis.

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Preoperative assessments were conducted using imaging tools such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS). Definitive diagnoses were based on pathological evaluation of the resected tissues. Tumors were categorized as functional PNETs if clinical symptoms indicated hormonal excess along with elevated serum hormone or peptide levels. In contrast, tumors without such features were classified as non-functional PNETs.

Surgical strategies were chosen based on tumor location, size, and the patient's overall clinical condition. Pancreatic resection was regarded as the primary treatment option. The type of surgery performed was determined by tumor characteristics and the presence of metastases. Procedures included pancreaticoduodenectomy (Whipple procedure) for tumors in the pancreatic head and distal pancreatectomy—with or without splenectomy—for tumors in the body or tail of the pancreas, particularly if liver metastases were present.

The study examined various factors that could predict lymph node metastasis (LNM), such as patient age, tumor size, primary tumor location, tumor grade, Ki-67 index, presence of lymphovascular invasion (LVI), perineural invasion, and tumor stage. Statistical analysis was conducted using SPSS (Version 28). Categorical data were analyzed using the Chi-square test, while numerical data were presented as mean ± standard deviation or median (Range), with comparisons made using the Student's t-test or Mann–Whitney U test depending on the data distribution. A p-value of ≤ 0.05 was considered statistically significant.

Results

The study analyzed 28 patients diagnosed with pancreatic neuroendocrine tumors who underwent curative-intent surgical resection, including lymph node dissection. Of these, 9 patients (32.1%) were found to have lymph node metastases, while the remaining 19 patients (67.9%) had no lymph node involvement. The mean age of participants was 56.3 ± 14 years, and approximately two-thirds were female **(Table 1).**

A significantly greater number of lymph nodes were identified in patients with lymph node metastasis compared to those without. Similarly, patients with lymph node involvement exhibited notably higher Ki-67 index values than those with negative lymph nodes.

The incidence of perineural invasion was substantially greater in the lymph node-positive group (55.6%) compared to the negative group (15.8%, p = .012). Moreover, lymphovascular invasion was present in 100% of cases with positive lymph nodes, significantly higher than the 31.6% observed in the negative group (p < .001).

Additionally, there was a statistically significant association between higher tumor grades (Grades 2–3) and more advanced tumor stages (Stages 3–4) with lymph node positivity. However, no meaningful association was detected between lymph node status and tumor size, surgical type, or the presence of a positive lymph node **(Table 2).**

Table 1: Sociodemographic characteristics of the participants

	Total (n=28)	Negative (n=19)	Positive (n=9)	P-value
Age (years)				
Mean ±SD	56.3±14	56±10.4	57±20.5	.962
Median (range)	57 (28-95)	57 (31-71)	54 (28-95)	
Gender				
Female	17 (60.7%)	13 (68.4%)	4 (44.4%)	.225
Male	11 (39.3%)	6 (31.6%)	5 (55.6%)	

Table 2: Clinicopathological Factors among the studied group

	Total (n=28)	Negative (n=19)	Positive (n=9)	P-value
Tumor site				
Body or tail	12 (42.9%)	9 (47.4%)	3 (33.3%)	.483
Head or uncinate	16 (57.1%)	10 (52.6%)	6 (66.7%)	
Tumor size (cm)				
Mean ±SD	5.7±2.8	5.8±3.4	5.6±1.1	1.000
Median (range)	5.3 (1.5-16)	6 (1.5-16)	5 (4.5-7.5)	
Ki-67 index				
Mean ±SD	11.3±12.5	9.7±14.1	14.6±7.9	.037
Median (range)	6 (1-54)	3 (1-54)	10 (5-25)	
Type of surgery				
Distal pancreatectomy and splenectomy	12 (42.9%)	9 (47.4%)	3 (33.3%)	.483
Whipple procedure	16 (57.1%)	10 (52.6%)	6 (66.7%)	
Total lymph node				
Mean ±SD	9.1±6.5	7.4±6.5	12.4±5.3	.012
Median (range)	6.5 (1-25)	5 (1-25)	11 (6-21)	
Perineural invasion				
Negative	20 (71.4%)	16 (84.2%)	4 (44.4%)	.030
Positive	8 (28.6%)	3 (15.8%)	5 (55.6%)	
Lymphovascular invasion				
Negative	13 (46.4%)	13 (68.4%)	0 (0%)	.001
Positive	15 (53.6%)	6 (31.6%)	9 (100%)	
Surgical margin				
Negative	21 (75%)	14 (73.7%)	7 (77.8%)	.815
Positive	7 (25%)	5 (26.3%)	2 (22.2%)	
TNM staging				
1&2	15 (53.6%)	15 (78.9%)	0 (0%)	<.001
3&4	13 (46.4%)	4 (21.1%)	9 (100%)	
Grade				
1	11 (39.3%)	10 (52.6%)	1 (11.1%)	.036
2&3	17 (60.7%)	9 (47.4%)	8 (88.9%)	
3&4	20 (71.4%)	11 (57.9%)	9 (100%)	

Discussion

In this retrospective cohort study spanning 20 years, we identified several clinicopathologic factors associated with lymph node metastasis (LNM) in pancreatic neuroendocrine tumors (PNETs). Our findings are in line with and contribute to the existing body of evidence.

Consistent with prior studies (e.g., Tanaka et al., 2021; Lopez-Aguiar et al., 2019),[15,13] we found that Ki-67 index, tumor grade and tumor stage were significantly associated with LNM. The higher proportion of LNM in grade 2–3 tumors (88.9% in our study) support the well-documented role of tumor grade as an independent predictor of nodal involvement. Similarly, all patients with stage 3–4 disease in our cohort had positive lymph nodes, highlighting the importance of staging in surgical planning as highlighted by Postlewait et al. (2016).[14]

Importantly, we demonstrated that lymphovascular invasion (LVI) and perineural invasion were significantly associated with LNM (100% LNM in cases with LVI, p = 0.001; and 55.6% LNM with perineural invasion, p = 0.03). This aligns with the findings of Parekh et al. (2012),[12] and Wong et al. (2014),[11] who reported that LVI is a strong predictor of nodal metastasis and may guide the extent of lymphadenectomy.

In contrast to several reports (e.g., Kwon et al., 2021),[9] ENETS guidelines), tumor size in our study did not show a significant association with LNM.

This may reflect the relatively small sample size or potential selection bias, as most tumors in our cohort were large at presentation (Mean size ~5.7 cm). Similar findings were reported by Lopez-Aguiar et al. (2019),[13] where tumor size alone was not a reliable predictor when other aggressive features were present.

We also found no significant association between tumor location or type of surgery and LNM, which is consistent with the conclusions of Postlewait et al. (2016),[14] suggesting that location alone should not dictate the extent of lymphadenectomy.

Our findings highlight that tumor grade, stage, lymphovascular invasion, perineural invasion, and Ki-67 index are significantly associated with lymph node metastasis, consistent with prior multicenter studies and meta-analyses (Tanaka et al., 2021; Lopez-Aguiar et al., 2019).[15,13] The absence of correlation between tumor size and nodal status contrasts with ENETS and NCCN guidelines, which use size as a primary determinant for lymphadenectomy (Partelli et al., 2017; NCCN 2021).[7]

Our study supports the growing view that tumor biology (grade, proliferation index, invasion patterns) may be more critical than size or location in guiding lymphadenectomy decisions. The significantly higher Ki-67 index among node-positive patients in our series reinforces its role as a valuable marker of tumor aggressiveness, as highlighted in multiple studies (Wong et al., 2014; Poultsides et al., 2012).[11,10]

Given these findings, consideration should be given to individual risk stratification rather than uniform size-based surgical strategies. However, this study is limited by its retrospective design and the small sample size, which may affect the statistical power and generalizability of the findings. The data reflects the experience of a single institution over a long period during which diagnostic and surgical practices may have evolved. Future prospective, multicenter studies with larger cohorts are needed to validate these results and to establish robust predictive models applicable to different clinical settings.

Conclusion

This study highlights that tumor grade, stage, lymphovascular invasion, perineural invasion, and Ki-67 index are significant predictors of lymph node metastasis in pancreatic neuroendocrine tumors. In contrast, tumor size and location showed no significant association with nodal involvement in our cohort. These findings suggest that surgical decisions regarding lymphadenectomy should be guided by tumor biology and invasion characteristics rather than size alone. Further multicenter studies with larger cohorts are recommended to validate these results and refine surgical guidelines for this rare tumor entity.

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Author contribution

Walid Akmal Shafie developed the main concept of the study and drafted the manuscript. Aly El Faqeh Mohamed Okasha performed the data collection and analysis. Fouad Abdelshahid Fouad and Islam Ali Soliman contributed to the editing and critical revision of the manuscript. All authors reviewed and approved the final draft.

Ethical committee approval

All data were collected and analyzed after approval of the Institutional Review Board and Ethical Research Committee (IRB Review Number: 2506-510-111-200).

Data and material availability

All data associated with this study are present in the paper.

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This study has not received any external funding.

Conflict of interst

Authors declare that there is no conflict of interests.

Consent for publication

Authors agree for publication of this study.

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