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# Optimal Timing for Lymphadenectomy in Non-Metastatic Pancreatic Neuroendocrine Tumors: Insights from a Population-Based Study by the German Clinical Cancer Registry Group

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## ABSTRACT

Determining which patients should undergo lymphadenectomy remains a debated issue in the management of pancreatic neuroendocrine tumors (pNETs), particularly with the increasing adoption of parenchyma-sparing and minimally invasive surgical techniques. This study utilized data from the German Cancer Registry Group, encompassing cases between 2000 and 2021. Only patients who underwent upfront resection for non-functional, non-metastatic pNETs were included. Among 5520 recorded pNET cases, 1006 fulfilled the inclusion criteria. Males represented 53% of the cohort, and the median patient age was 64 ± 17 years. Tumor grading revealed that 57% were G1, 37% G2, and 7% G3. Lymph node metastasis (LNM) occurred in 253 patients (24%) and emerged as an independent predictor of poorer disease-free survival (DFS) (HR 1.79, 95% CI 1.21–2.64, $p = 0.001$). DFS at 3, 5, and 10 years was notably higher in lymph node-negative patients compared with those positive for nodal involvement (82% vs. 53%, 75% vs. 38%, and 48% vs. 16%, respectively). The incidence of LNM increased with tumor stage—5% in T1, 25% in T2, and 49% in T3–T4 tumors. G1 predominated in T1 tumors (80%), whereas G2 and G3 accounted for 44% and 5% of T2 lesions. LNM was significantly associated with tumor location in the pancreatic head ($p < 0.001$), positive surgical margins ($p < 0.001$), tumor size exceeding 2 cm ($p < 0.001$), and higher histologic grade ($p < 0.001$). Multivariate analysis identified tumor size, grade, and anatomical location as independent risk factors for LNM, suggesting their potential use in preoperative prediction. LNM serves as a strong, independent negative prognostic marker for DFS in pNETs. Given the minimal LNM occurrence in small T1, G1 tumors (5%), limited parenchyma-preserving resections appear oncologically sufficient in such cases. Conversely, regional lymphadenectomy is advisable for patients with T2 or G2/G3 pNETs.

**Keywords:** Population-based analysis, Pancreatic neuroendocrine tumors (pNETs), Lymphadenectomy, Lymph node metastasis

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## Introduction

Pancreatic neuroendocrine tumors (pNETs) represent an uncommon form of pancreatic cancer, contributing only around 2–4% of all cases [1, 2]. Owing to advances in diagnostic technology and the wider use of cross-sectional imaging, their recorded incidence has grown approximately fivefold during the last thirty years, according to data from the SEER registry [3]. These tumors are broadly divided into functional and non-functional categories, based on whether they secrete hormones that produce clinical syndromes [4]. Non-functional pancreatic neuroendocrine tumors (NF-pNETs) constitute about 60–70% of all pNETs [5]. Since they do not cause hormone-related symptoms, they typically remain clinically silent until they become large enough to cause local pressure effects or are found incidentally during imaging performed for unrelated issues. The delay in diagnosis often results in presentation with advanced disease, including local invasion or distant metastasis, which is associated with a less favorable prognosis [6].

Although surgical removal is the preferred treatment for functional pNETs [7, 8], the optimal management of NF-pNETs remains a matter of debate. Existing guidelines differ regarding when surgery should be performed, how extensive the pancreatic resection should be, and whether systematic lymphadenectomy is necessary [7, 9, 10]. For small, well-differentiated tumors (<2 cm), several recommendations suggest a conservative "observation" strategy rather than immediate surgery [7]. However, inconsistencies across studies concerning the predictive and prognostic value of lymph node metastases, along with the uncertain links between tumor grade and size, have led to notable variation in international clinical practice.

The purpose of the current investigation was to determine preoperative variables associated with lymph node metastasis in patients with resected, non-metastatic pNETs and to examine their influence on survival outcomes, using population-based data from the German Clinical Cancer Registry Group.

## Materials and Methods

*Study design and data source*

This retrospective, multicenter analysis was performed under the coordination of the German Cancer Registry Group (GCRG) within the Society of German Tumor Centers (ADT). Data were obtained from 20 regional cancer registries covering the years 2000 to 2021, all in compliance with ADT data protection standards. Ethical approval was granted by the Ethics Committee of the University of Lübeck, Germany (reference number #2023-156).

Among all patients registered with pancreatic malignancies (ICD-O, 3rd Edition: C25.x), only those diagnosed with non-functional pNETs (ICD-O-3 morphology codes 8240-1/3, 8246, 8249/3) were included. Patients with functional tumors—such as insulinomas, gastrinomas, glucagonomas, VIPomas, and somatostatinomas—or with mixed neuroendocrine–non-neuroendocrine neoplasms and islet cell carcinoma (ICD-O-3 codes 8150–8156/3) were excluded [11]. The study focused solely on individuals who underwent primary surgical tumor resection without evidence of distant metastases.

Collected variables included demographic factors (age, sex), tumor characteristics (T-stage, grade, lymphangiosis, hemangiosis, and lymph node metastasis status), treatment-related information (tumor location, resection type, therapy details and margin status), and follow-up data (duration and survival outcome). For statistical analysis, certain variables were dichotomized: age (≤65 vs. >65 years), lymph node status (N0 vs. LNM), tumor site, and resection margin (R0 vs. R+). Because TNM classification criteria were updated during the study period, tumors categorized as T3 or T4 were merged since exact tumor size data for reclassification were unavailable.

*Statistical analysis*

All analyses were conducted using IBM SPSS Statistics version 28 (Armonk, NY, USA). Descriptive measures summarized baseline characteristics. The Chi-square test evaluated differences among categorical variables. Kaplan–Meier curves were generated to estimate survival, and comparisons were made using the log-rank test. Median survival was expressed in months.

Overall survival (OS) was defined as the interval between the initial diagnosis and death or last follow-up, while disease-free survival (DFS) represented the period from surgery to recurrence or last follow-up. Both univariable and multivariable Cox proportional hazards regression models were applied to identify independent prognostic factors. Statistical significance was determined at a two-sided p-value of <0.05.

## Results and Discussion

*Study population*

From a total of 5520 individuals diagnosed with pNETs in the registry, 1006 met all eligibility criteria and were included in the analysis. The cohort had a slight male predominance (53% male vs. 47% female). According to tumor stage, 40% (n = 404) had T1 tumors, 28% (n = 289) had T2 tumors, and 32% (n = 313) were classified as T3–T4. The median age at diagnosis was 64 years (±17). Tumor site was reported in 780 cases, with the pancreatic head being most common (40%, n = 313), followed by the tail (39%, n = 307) and the body (21%, n = 160).

Regarding surgical treatment, pancreatic head resection was carried out in 300 patients (37%), distal pancreatectomy in 478 (58%), and total pancreatectomy in 44 (4%). In 184 cases, a pancreatic resection was documented but the specific surgical procedure type was not reported. A detailed summary of patient demographics and surgical data is provided in **Table 1**.

**Table 1.** Patient characteristics and association of different variables with the presence of lymph node metastases (LNM) in pNETs.

| Variable | N0 | LNM | p |
|---|---|---|---|
| Age | | | 0.067 |
| <65 | 366 (73%) | 135 (27%) | |
| ≥65 | 394 (82%) | 111 (18%) | |
| Sex | | | 0.676 |
| Female | 356 (75%) | 119 (25%) | |
| Male | 404 (76%) | 127 (24%) | |
| Tumor Size | | | <0.001 |
| T1 | 384 (95%) | 20 (5%) | |
| T2 | 218 (75%) | 71 (25%) | |
| T3–T4 | 158 (51%) | 155(49%) | |
| Tumor Grade | | | <0.001 |
| G1 | 497 (87%) | 75 (13%) | |
| G2 | 237 (65%) | 87 (35%) | |
| G3 | 26 (39%) | 27 (61%) | |
| Resection margin | | | 0.005 |
| R negative | 724 (77%) | 208 (22%) | |
| R positive | 36 (49%) | 38 (51%) | |
| Location | | | <0.001 |
| Head | 207 (34.5%) | 106 (32.4%) | |
| Body/Tail | 386 (84.7%) | 81 (15.3%) | |
| Local recurrence | 23 (3%) | 18 (7%) | 0.003 |
| Distant metastasis * | 67 (11%) | 69 (35%) | <0.001 |

Legend: *p* indicates significance according to the $\chi^2$ test when comparing patients with and without lymph node metastasis (LNM). * Metastasis in the course of disease.

*Impact of lymph node metastasis (LNM) on overall and disease-free survival*

When comparing patients with node-negative versus node-positive pancreatic neuroendocrine tumors, overall survival at 3, 5, and 10 years was 84% versus 79% ($p = 0.505$), 80% versus 68% ($p = 0.89$), and 56% versus 52% ($p = 0.707$), respectively. In the univariable assessment, several variables showed significant correlations with diminished overall survival, including older patient age ($p < 0.001$), male sex ($p = 0.008$), higher tumor grade ($p < 0.001$), positive surgical margin ($p < 0.001$), and tumors located in the pancreatic head ($p < 0.001$). However, lymph node metastasis did not emerge as a statistically meaningful prognostic factor for overall survival.

Disease-free survival (DFS) data were available for 512 individuals. In this subgroup, the 3-, 5-, and 10-year DFS rates for node-negative tumors compared to node-positive tumors were 82% versus 53% ($p < 0.001$), 75% versus 38% ($p < 0.001$), and 48% versus 16% ($p < 0.001$), respectively. Univariable analysis demonstrated that the presence of lymph node metastasis ($p < 0.001$), larger tumor size ($p < 0.001$), higher grade ($p < 0.001$), positive resection margins ($p < 0.001$), and pancreatic head localization ($p = 0.003$) were all associated with shorter DFS. In the multivariable Cox regression model, several factors retained independent prognostic significance for reduced DFS: tumor size greater than 2 cm (HR 2.76, 95% CI 1.53–5.00, $p < 0.001$), positive resection margin (HR 1.80, 95% CI 1.01–3.23, $p = 0.045$), intermediate and high tumor grades (G2 vs. G1: HR 2.12, 95% CI 1.38–3.25, $p < 0.001$; G3 vs. G1: HR 3.73, 95% CI 2.11–6.53, $p < 0.001$), and lymph node metastasis (HR 1.88, 95% CI 1.27–2.78, $p = 0.001$). These findings indicate that while LNM does not significantly influence overall survival, it independently predicts poorer disease-free survival outcomes **(Table 2)**.

**Table 2.** Multivariable analysis for disease-free survival.

| Variable | Multivariable Analysis | | |
|---|---|---|---|
| | **HR** | **95% CI** | **p** |
| Age, <65 vs. ≥65 | 1.07 | 0.74–1.55 | 0.608 |
| Sex, male vs. female | 1.05 | 0.72–1.54 | 0.789 |
| Grading | | | |
| G2 vs. G1 | 2.15 | 1.40–3.30 | <0.001 |
| G3 vs. G1 | 3.45 | 1.95–6.66 | <0.001 |
| Tumor location, head vs. body/tail | 1.29 | 0.89–1.88 | 0–176 |
| LNM vs. N0 | 1.79 | 1.21–2.64 | 0.003 |
| Tumor size | | | |
| T2 vs. T1 | 2.09 | 1.10–3.98 | 0.024 |
| T3–T4 vs. T1 | 3.45 | 1.95–6.09 | <0.001 |

Legend: *p* according to Cox regression analysis comparing the specified variables. HR indicates hazard ratio.

*Factors related to lymph node metastasis (LNM)*

Out of the total 1006 patients analyzed, 253 individuals (24%) were found to have lymph node metastases. The likelihood of LNM rose notably with advancing tumor stage—appearing in only 5% of T1 tumors, increasing to 25% in T2, and reaching 49% among T3–T4 lesions **(Figure 1)**. A comparable escalation was seen with tumor grade, where nodal involvement occurred in 13% of G1, 35% of G2, and 61% of G3 tumors **(Table 3)**.

Tumor size and histologic grade also demonstrated a clear relationship. The majority of small (T1) tumors were well-differentiated (80% G1), whereas intermediate-sized (T2) tumors more frequently displayed G2 (44%) or G3 (5%) differentiation. Remarkably, even among T1 tumors, lymph node spread was not absent—occurring in 10% of T1 G2 and 20% of T1 G3 cases **(Figure 2)**.

From a statistical perspective, lymph node metastasis showed significant association with several clinicopathologic factors: tumor localization in the pancreatic head ($p = 0.002$), incomplete or positive resection margins ($p < 0.001$), tumor diameter exceeding 2 cm ($p < 0.001$), and increased tumor grade (both G2 vs. G1 and G3 vs. G1, $p < 0.001$).

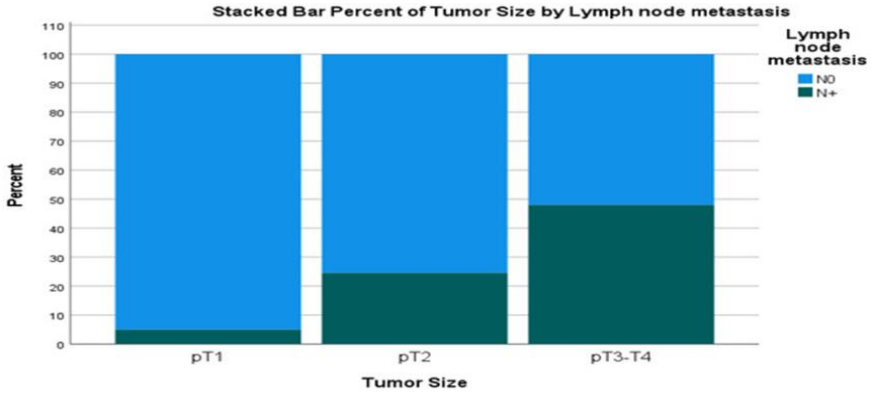



**Figure 1.** Distribution of lymph node metastasis (LNM) in pancreatic neuroendocrine tumors (pNETs) by tumor stage. Legend: N0 = absence of lymph node metastasis; LNM = presence of lymph node metastasis. The proportion of LNM increases with tumor size, occurring in 5% of T1 tumors, 25% of T2 tumors, and 49% of T3–T4 tumors.

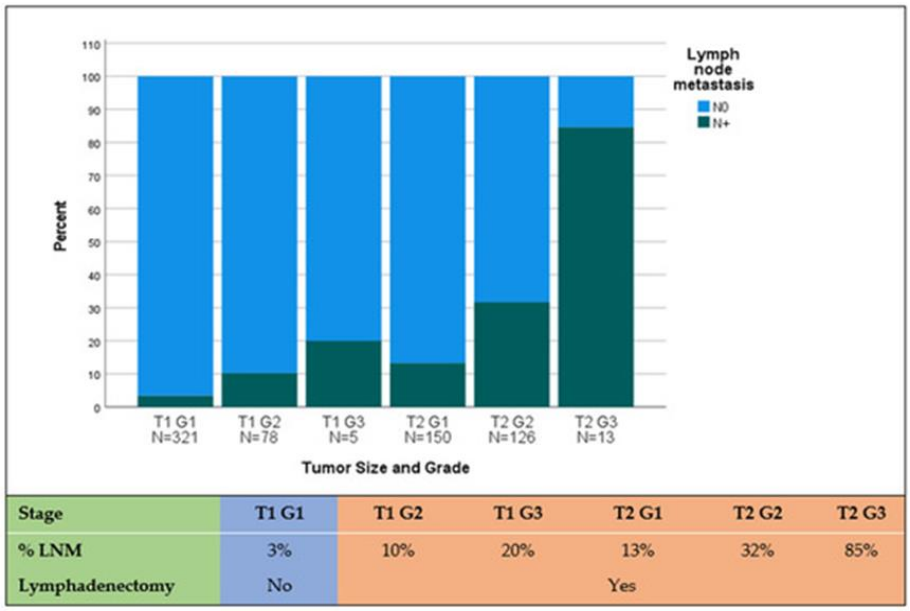


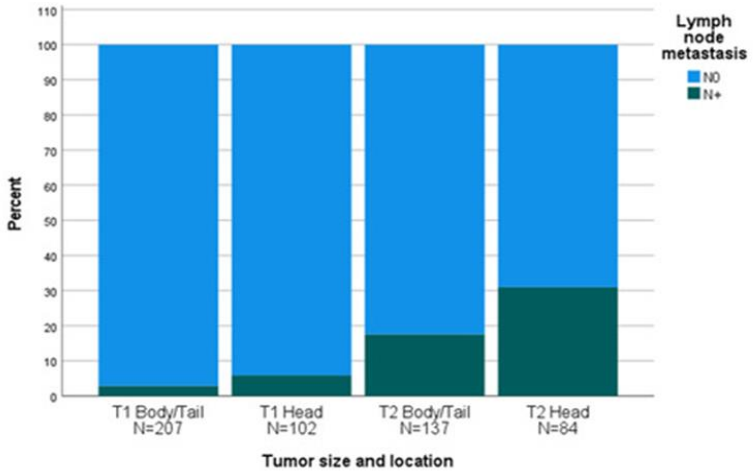

**Figure 2.** Relationship between lymph node metastasis (LNM) and tumor size when considered alongside tumor grade in pancreatic neuroendocrine tumors (pNETs). Legend: N0 = absence of lymph node metastasis; LNM = presence of lymph node metastasis; Orange = lymphadenectomy recommended; Blue = lymphadenectomy not indicated.

**Table 3.** Association of clinicopathologic parameters to lymph node metastasis in pNETs.

| Variable | N0 | LNM | p |
|---|---|---|---|
| Tumor Grade | | | <0.001 |
| G1 | 497 (87%) | 75 (13%) | |
| G2 | 237 (65%) | 130 (35%) | |
| G3 | 26 (39%) | 41 (61%) | |
| Location | | | <0.001 |
| Head | 207 (66%) | 106 (34%) | |
| Body/Tail | 386 (83%) | 81 (17%) | |
| Tumor Size | | | <0.001 |
| T1 | 384 (95%) | 20(5%) | |
| T2 | 218 (66%) | 71 (35%) | |
| T3–T4 | 158 (51%) | 155 (49%) | |
| Local recurrence | | | 0.022 |
| No recurrence | 625 (98%) | 186 (94%) | |
| Recurrence | 15 (2%) | 11 (6%) | |
| Distant metastasis (Progression) | | | <0.001 |
| No distant metastasis | 426 (88%) | 86 (55%) | |
| Distant metastasis | 60 (12%) | 69 (45%) | |

Legend: p according to the $\chi 2$ test when comparing patients with and without (N0) lymph node metastasis (LNM).

Tumor location showed a significant impact on lymph node metastasis in T2 pancreatic neuroendocrine tumors. Specifically, LNM occurred in 31% of T2 tumors situated in the pancreatic head, compared to 18% in tumors located in the body or tail of the pancreas **(Figure 3)**. In contrast, for T1 tumors, the incidence of LNM was low and comparable between locations (6% in the head vs. 3% in the body/tail), and the difference did not reach statistical significance, likely due to the small number of cases.




| Size and Site | T1 Body/Tail | T1 Head | T2 Body/Tail | T2 Head |
|---|---|---|---|---|
| % LNM | 3% | 6% | 18% | 31% |

**Figure 3.** Relationship between lymph node metastasis (LNM) and tumor location in T1 and T2 pancreatic neuroendocrine tumors (pNETs).

Multivariable analysis identified several independent predictors of lymph node metastasis in pNETs. Tumors located in the pancreatic head (HR 1.87, 95% CI 1.26–2.77, p < 0.001), intermediate-grade (G2 vs. G1: HR 2.23, 95% CI 1.45–3.43, p < 0.001), high-grade (G3 vs. G1: HR 3.65, 95% CI 1.79–7.32, p < 0.001), as well as tumor stage T2 (HR 5.31, 95% CI 2.69–10.59, p < 0.001) and T3–T4 (HR 14.84, 95% CI 7.67–28.72, p < 0.001) compared to T1, were all significantly associated with the presence of lymph node metastases **(Table 4)**.

**Table 4.** Multivariable analysis for prediction of lymph node metastasis in pNETs.

| Variable | Multivariable Analysis | | |
|---|---|---|---|
| | **OR** | **95% CI** | **p** |
| Age, <65 vs. ≥65 | 0.79 | 0.53–1.16 | 0.232 |
| Sex, male vs. female | 1.14 | 0.78–1.70 | 0.498 |
| Resection margin, positive vs. negative | 3.07 | 1.56–6.05 | <0.001 |
| Grading, | | | |
| G2 vs. G1 | 2.23 | 1.45–3.43 | <0.001 |
| G3 vs. G1 | 3.65 | 1.79–7.32 | <0.001 |
| Tumor location, Head vs. Body/Tail | 1.87 | 1.26–2.77 | 0.002 |
| Tumor size, | | | |
| T2 vs. T1 | 5.31 | 2.69–10.59 | <0.001 |
| T3–T4 vs. T1 | 14.84 | 7.67–28.72 | <0.001 |

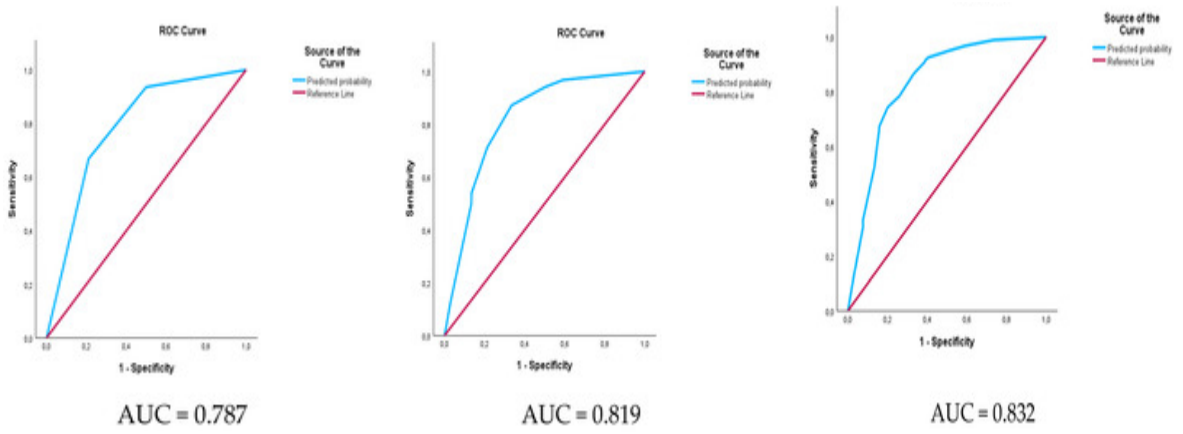
Legend: *p* according to binary logistic regression analysis comparing the specified variables. HR indicates hazard ratio.

*Preoperative prediction of lymph node metastasis*

Multivariable analysis revealed that lymph node metastasis (LNM) was significantly associated with tumor size, histologic grade, and tumor location. Importantly, these three factors can often be assessed before surgery using cross-sectional imaging and biopsy, providing valuable insight into the likelihood of nodal involvement. To explore this, we developed a predictive model based on these preoperatively identifiable parameters, although in our cohort, the data were derived from postoperative histology.

For this analysis, 780 patients with complete information on tumor size, grade, and location were included. We evaluated prediction models using tumor size alone, tumor size combined with location, and a model incorporating all three variables (size, location, and grade) **(Figure 4)**. The model integrating tumor size, grade, and location

demonstrated the highest predictive accuracy for LNM, with an area under the curve (AUC) of 0.832 (95% CI 0.80–0.86, $p < 0.001$).




a) b) c)

**Figure 4.** Receiver operating characteristic (ROC) analysis for predicting lymph node metastasis using tumor size and grade. Legend: AUC represents predictive accuracy for LNM; (a) model based on tumor size alone, (b) tumor size combined with grade, and (c) tumor size, grade, and location combined.

*Clinical versus histopathological nodal stage*

Preoperative clinical lymph node staging (cN) was available for 156 patients. Among 109 patients staged as cN0, 14 were found to have histologically positive nodes (pN1). Conversely, of 34 patients staged as cN1, 12 had no histopathologic nodal involvement (pN0). The diagnostic performance of preoperative nodal assessment showed a sensitivity of 61.1%, specificity of 90.1%, positive predictive value of 64.7%, and negative predictive value of 88.6%. The specific imaging or staging modality used was not reported.

*Relationship between lymph node metastasis and recurrence*

The impact of LNM on recurrence after surgical resection was evaluated by tumor size. In small pNETs (<2 cm), LNM did not significantly affect local recurrence (2% vs. 0%, p = ns), but was associated with higher rates of distant metastasis (13% vs. 3%, $p = 0.031$). For tumors larger than 2 cm, LNM was linked to increased rates of both local recurrence (5% vs. 8%, $p = 0.034$) and distant metastasis (19% vs. 37%, $p < 0.001$).

Guidelines for the surgical management of non-metastatic, non-functional pancreatic neuroendocrine tumors (NF-pNETs) remain inconsistent. ENETS recommends resection for tumors larger than 2 cm but provides limited guidance on lymphadenectomy or the extent of pancreatic resection [7], whereas NANETS and NCCN suggest resection with lymph node dissection for all tumors exceeding 2 cm [9, 10, 12]. The prognostic relevance of lymph node metastasis (LNM) has been debated, with prior studies producing conflicting results, partly due to small sample sizes and variable follow-up durations. To address this, we analyzed data from 20 German cancer registries and identified four key findings regarding LNM and its clinical significance.

First, LNM did not correlate with overall survival (OS) but was an independent predictor of disease-free survival (DFS), a more appropriate endpoint given the typically indolent nature of pNETs [13]. Past reports have been inconsistent: some studies link nodal positivity to worse survival [14, 15], whereas others do not [16–18]; however, a recent meta-analysis indicated significantly reduced survival in patients with NF-pNETs and nodal involvement [19].

Second, LNM incidence increased with tumor stage: 5% in T1 tumors, 25% in T2, and 45% in T3–T4 tumors, aligning with prior literature reporting 10–14% for tumors <2 cm and up to 25% for tumors >2 cm [14, 19–21]. We also observed that tumor grade shifted sharply in larger tumors; while 80% of T1 tumors were G1, over half of T2 tumors were G2/G3, which independently predicts worse DFS and OS [13, 22, 23]. This pattern parallels early colorectal cancer, where T1 rectal cancers with high-risk features undergo oncologic resection due to a 10–20% risk of nodal metastasis [24–26], suggesting that similarly sized pNETs with a 25% LNM risk warrant consideration for lymphadenectomy.

Third, current imaging modalities—including contrast-enhanced CT, endoscopic ultrasonography, and ^68Ga-DOTATOC PET—show low sensitivity for preoperative detection of LNM in sporadic NF-pNETs (26%, 19%, and 12%, respectively) despite high specificity [27]. In our cohort of 156 patients with documented preoperative nodal status, sensitivity was 61%, supporting previous findings that clinical nodal staging is limited, particularly in tumors >2 cm, which have higher LNM rates and more frequent advanced tumor grades.

Fourth, tumor size, location, and grade emerged as independent predictors of LNM. Using these parameters in a predictive model, we achieved the highest accuracy when combining all three variables. For example, a T1 G2 tumor in the pancreatic head carried an 18% risk of LNM, compared to only 6% if located in the body or tail, highlighting the potential consequences of omitting lymphadenectomy in high-risk scenarios and the risk of early recurrence.

Recurrence patterns further support these findings: in tumors <2 cm, LNM was linked primarily to distant metastasis, whereas in tumors ≥2 cm, both local and distant recurrence were elevated. This likely reflects the higher frequency of G2/G3 tumors in larger lesions, which predisposes to lymphatic spread. Collectively, these observations suggest that minimally invasive or parenchyma-sparing resection without lymphadenectomy may be sufficient for small, low-grade pNETs (<2 cm), while tumors >2 cm—particularly those in the pancreatic head—should undergo regional lymphadenectomy along with pancreatic resection. The relative benefit of standard oncologic versus parenchyma-sparing pancreatic resection with lymphadenectomy remains to be clarified.

Several limitations should be acknowledged. Data were derived from 20 German registries, introducing potential variability in patient selection, surgical technique, pathological assessment, and reporting. Detailed information regarding treatment protocols, Ki67 proliferation index, or the number of harvested lymph nodes was unavailable, and parenchyma-sparing procedures were not specifically recorded. Nonetheless, the large cohort reflects routine surgical practice across Germany rather than only high-volume specialized centers. To our knowledge, this is the first study to integrate tumor size, grade, and location with LNM to model its impact on survival, providing practical guidance for lymphadenectomy in NF-pNETs.

## Conclusion

Lymph node metastasis is an independent negative prognostic factor for DFS in non-metastatic pNETs. For T1 G1 tumors, the low risk of LNM and recurrence supports parenchyma-sparing pancreatic resection without regional lymphadenectomy. In contrast, T2 or G2/G3 tumors, particularly those located in the pancreatic head, demonstrate high rates of LNM and recurrence, justifying regional lymphadenectomy in addition to pancreatic resection.

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**Ethics Statement:** None

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