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Duodenal Neuroendocrine Tumors: Impact of Tumor Size and Total Number of Lymph Nodes Examined

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Synopsis for Table of Contents: While the incidence of LNM directly correlated with tumor size, even patients with dNETs ≤1 cm had a 40% incidence of LNM. Regional lymphadenectomy of a least 8 LNs was needed to stage patients accurately.

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

Abstract

Background: The current study sought to investigate the impact of tumor size and total number of LN examined (TNLE) on the incidence of lymph node metastasis (LNM) among patients with dNET.

Methods: Patients who underwent curative resection for dNETs between 1997-2016 were identified from 8 high-volume U.S. centers. Risk factors associated with OS and LNM were identified and the optimal cut-off of TNLE relative to LNM was determined.

Results: Among 162 patients who underwent resection of dNETs, median patient age was 59 (IQR:51-68) years and median tumor size was 1.2 cm (IQR:0.7-2.0 cm); a total of 101 (62.3%) patients underwent a concomitant LND at the time of surgery. Utilization of

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LND increased relative to tumor size (≤1 cm:52.2% vs. 1-2 cm:61.4% vs. >2 cm:93.8%; p<0.05). Similarly, the incidence of LNM increased with dNET size (≤1 cm: 40.0% vs. 1-2 cm:65.7% vs. >2 cm:80.0%; p<0.05). TNLE≥8 had the highest discriminatory power relative to the incidence of LNM (AUC=0.676). On multivariable analysis, while LNM was not associated with prognosis (HR=0.9, 95%CI:0.4-2.3), G2/G3 tumor grade was (HR=1.5, 95%CI:1.0-2.1).

Conclusions: While the incidence of LNM directly correlated with tumor size, patients with dNETs ≤1 cm had a 40% incidence of LNM. Regional lymphadenectomy of a least 8 LN was needed to stage patients accurately.

Introduction

Duodenal neuroendocrine tumors (dNETs) represent up to 3% of all primary duodenal malignancies and 2-3% of all gastrointestinal neuroendocrine tumors (NETs).[1-3] The incidence of dNETs has increased from 0.027/100,000 in 1983 to 1.1/100,000 in 2010, perhaps reflecting the increased use of gastrointestinal endoscopy.[4,5] According to the latest population study in the United States, dNETs present most often in the 6th decade of life and males are slightly more predominant than females.[6] In turn, resection of dNETs generally represents the most common modality associated with the best chance at cure.

Although dNETs are usually small on presentation (i.e. 75% of cases ≤ 20 mm), regional lymph node (LN) metastasis has been reported in up to 40-80% of cases.[7-10] Current treatment guidelines recommend treatment strategies for dNETs that are similar to gastric NETs for non-functional tumors and similar to pancreatic NETs for functional dNETs.[11] For example, the European Neuroendocrine Tumor Society (ENETS) consensus guidelines generally recommend surgical treatment for large (>20 mm) and /

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or metastatic dNETs, as well as peri-ampullary dNETs.[11] More often dNET cases are now diagnosed, however, incidentally when the tumors are small in size (<10 mm), well-differentiated, limited to the mucosa and submucosa, and non-functioning. In turn, endoscopic local excision may be increasingly considered for these early stage tumors rather than surgical resection.[12] The impact of not staging the nodal basin in the setting of endoscopic excision remains poorly defined. Unfortunately, data on the clinical characteristics, tumor biology, treatment and prognosis of patients with dNETs have been limited largely to small, single center case series.[12-14] Therefore, the objective of the current study was to define the outcomes of patients who underwent curative-intent resection for peri-ampullary and non-ampullary dNETs using a large, multi-institutional database. Specifically, the aim was to characterize potential risk factors associated with the presence of lymph node metastasis (LNM), as well as identify the minimal number of LN needed to stage patients optimally.

Methods

Study cohort and data collection

Patients who underwent surgical resection for dNETs between 1997 and 2016 were identified from the U.S. Neuroendocrine Tumor Study Group (US-NETSG).[15] All patients were diagnosed with dNETs, which were confirmed by histological examination. Patients who presented with distant metastasis or underwent cytoreductive/palliative (R2) resection were excluded. The study was approved by The Institutional Review Boards at each participating institution.

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A standardized datasheet was utilized to collect the demographic, clinical and pathologic data at each institution. Largest tumor size, primary tumor location, the total number of LNs examined (TNLE), the number of LNM, perineural invasion, lymph-vascular invasion and surgical margin status were determined based on the final pathological report. The tumors were staged according to the eighth TMN stage scoring system[16] and classified as grade G1 (Ki-67 ≤2%), G2 (Ki-67 3-20%), and G3 (Ki-67>20%) according to the WHO 2010 classification.[17] Overall survival (OS) was calculated from the date of surgery to the date of death or date of last follow-up. Tumor recurrence was determined by suspicious imaging finding or biopsy-proven tumor.

Statistical analysis

Categorical variables were reported as totals and percentages and compared by $\chi 2$ test or Fisher exact test as appropriate. Continuous variables were expressed as median with interquartile ranges (IQRs) and compared using the Mann-Whitney U test. Kaplan-Meier survival curves were plotted and compared using the log-rank test. The receiver-operating characteristic curve (ROC) analysis was used to investigate the discriminatory ability of TNLE relative to the number of LNM. Risk factors associated with OS or LNM were identified by using Cox-proportional hazard regression models or Logistic regression models, respectively. Results were reported as hazard ratios (HRs) or odds ratio (OR) and 95% confidence intervals (95% CI). A *P*-value <0.05 (two-tailed) was considered statistically significant for all analyses. Statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA).

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Results

Baseline characteristics

Among 162 patients with dNETs, median patient age was 59 (IQR 51-68) years and 53.7% (n=87) of patients were male (**Table 1**). Roughly one-in-five (n=34/162, 21.0%) patients had a functional tumor; gastrinoma (n=31/34, 91.2%) was the predominant tumor type. The overwhelming majority of patients had no designated syndrome (n=146, 90.1%), whereas a small subset of individuals had Multiple Endocrine Neoplasia type 1 (MEN 1) (n=8, 4.9%) or neurofibromatosis syndrome (n=4, 2.5%). Abdominal pain (47.5%) was the most common symptom. The majority (n=127, 78.4%) of patients underwent an open surgical procedure. Surgical procedures included transduodenal resection (n=25, 15.4%), partial duodenectomy (n=20, 12.3%), segmental duodenectomy (n=33, 20.4%), and pancreaticoduodenectomy (PD) (n=52, 32.1%); 30 (18.5%) patients underwent an endoscopic resection. Based on final pathological assessment, median tumor size was 1.2 cm (IQR 0.7-2.0 cm). A total of 101 (62.3%) patients underwent a concomitant lymphadenectomy (LND) at the time of surgery (transduodenal resection, n=11; partial duodenectomy, n=14; segmental duodenectomy, n=26; PD, n=50); median TNLE was 10 (IQR 3-16). Among patients who underwent LND (n=101), at least one LNM was identified in 61 (60.4%) patients. The overall incidence of procedure-related complications was 48.1% (n=78) with 22.8% (n=37) of patients experiencing a severe Clavien-Dindo III-V complication.

Peri-ampullary versus non-ampullary dNETs

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In assessing the cohort, 127 (78.4%) patients had a dNET located in the duodenum away from ampulla of Vater, whereas 35 (21.6%) patients had a peri-ampullary dNET. Clinicopathologic characteristics and surgical procedures associated with non-peri-ampullary and peri-ampullary pNET tumors were largely comparable (**Table 1**). Perhaps not surprisingly, patients with peri-ampullary dNETs were more likely to present with clinical jaundice (22.9% vs. 1.6%, $p<0.001$) and abdominal pain (68.6% vs. 41.7%, $p=0.007$) versus patients with non-ampullary dNETs. In addition, more patients who had a peri-ampullary dNET underwent a PD (n=21, 60.0%) compared with only 24.4% (n=31) of patients with a non-ampullary dNET ($p<0.001$). In turn, patients with a peri-ampullary dNET had a higher TNLE compared with non-peri-ampullary dNET (median 15 vs. 7, respectively; $p=0.005$)(**Table 1**). In addition, patients with peri-ampullary dNETs were more likely to have a single tumor that was larger in size versus patients who had non-ampullary tumors (both $p<0.05$). In contrast, receipt of LND, as well as incidence and number of LNM were not different among patients with ampullary versus non-ampullary dNETs (**Table 1**).

Long-term survival

With a median follow-up of 27.2 (IQR 8.9-57.0) months, 1-, 3-, and 5-year OS was 94.2%, 86.9%, and 84.7%, respectively (**Figure 1a**). Of note, OS was similar among patients with peri-ampullary versus non-ampullary dNETs (5-year OS, 70.8% vs. 87.3%, $p=0.944$)(**Figure 1b**). In the subset of patients who underwent PD, OS was also comparable among patients with peri-ampullary (n=21) and non-ampullary (n=31) dNETs (5-year OS, 81.0% vs. 82.0%, $p=1.000$). On multivariable analysis, only G2/G3 WHO classification was associated with a higher risk of worse OS (Reference G1, HR

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1.5, 95%CI 1.0-2.1, p=0.032). In contrast, tumor location, size and number, AJCC T stages, nodal status, as well as treatment procedures were not associated with long-term survival of dNETs patients (**Table 2**).

Among the 18 (11.1%) patients who developed tumor recurrence during follow-up, 9 (50%) developed hepatic recurrence only, whereas 8 (44.4%) patients developed loco-regional resection site and/or LN recurrence; one (5.6%) patient had both loco-regional and distant metastasis. Tumor recurrence was no different among patients with peri-ampullary versus non-ampullary dNETs, or among patients undergoing different surgical procedures (both p>0.05).

Tumor size and nodal metastasis

As tumor size is a key indicator in defining the T category for dNETs in the AJCC staging manual,[16] the impact of tumor size on the proportion of LND, as well as the incidence of nodal metastasis, was further analyzed. Of note, LND were performed among almost all (93.8%) patients with dNET >2 cm compared with 61.4% of patients with tumors of 1-2 cm and 52.2% of patients with tumors ≤1 cm (both p<0.01)(**Figure 2a**). Patients with larger tumors were also more likely to have a higher TNLE (median TNLE, >2 cm 14 vs. 1-2 cm 7 vs. ≤1 cm 5, p<0.001)(**Figure 2b**). In addition, the incidence of LNM incrementally increased among patients with tumors ≤1 cm, 1-2 cm and >2 cm (LNM, 40.0% vs. 65.7% vs. 80.0%, p=0.003)(**Figure 2c**).

The likelihood to identify LNM was associated with TNLE. Specifically, TNLE ≥ 8 was associated with a higher incidence of identifying LNM (TNLE < 8: 20/45, 44.4% vs. TNLE ≥ 8: 41/56, 73.2%, p=0.004), as well as a higher number of LNM identified

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(median number of LNM, TNLE ≥ 8: 2 (IQR 1-5), vs. TNLE < 8: 1 (IQR 1-2), p<0.001). In addition, TNLE ≥ 8 had the highest discriminatory power relative to the incidence of LNM (area under the curve [AUC] 0.676, sensitivity 67.2%, specificity=65.0%)(**Figure 2d**). On multivariable analysis, tumor size (1-2 cm versus ≤1 cm (OR 2.8, 95%CI 1.0-8.0, p=0.048), >2 cm versus ≤1 cm (OR 4.6, 95%CI 1.4-15.0, p=0.012), as well as TNLE ≥8 versus <8 (OR 3.6, 95%CI 1.4-9.2, p=0.007) were associated with the likelihood of identifying LNM (**Table 3**).

Discussion

The AJCC TNM staging system for NET incorporates tumor size, nodal status and distant metastasis to stratify outcomes of patients with dNETs. The impact of tumor size and nodal status on prognosis has, however, not been fully investigated, partially due to the rarity of this disease. The current study was important as we utilized a large multi-institutional database to demonstrate that long-term survival of patients with dNETs was comparable among patients with peri- or non-ampullary dNETs. Rather than location or size, tumor grade G2/G3 was the main risk factor associated with worse prognosis. Among patients who underwent LND, three out of five patients had at least one LNM. Perhaps not surprisingly, LND was utilized incrementally more often among patients who had larger dNETs (≤1 cm, 52.2% vs. 1-2 cm, 61.4% vs. >2 cm, 93.8%) and the incidence of LNM also increased (≤1 cm, 40.0% vs. 1-2 cm, 65.7% vs. >2 cm, 80.0%). We noted that the TNLE with the best discriminatory power to ensure adequate staging of the nodal basin was a TNLE ≥ 8 (AUC 0.676). In fact, on multivariable analysis, in addition to tumor size, TNLE ≥8 versus <8 was independently associated with likelihood of identifying LNM. Collectively, data from the current study serves to highlight that

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patients with dNET generally have a favorably prognosis, however the incidence of LNM may be high. Tumor size was associated with LNM, especially among those patients with a dNET >1 cm, and the ability to identify LNM depended on the adequacy of the LND with TNLE ≥8 being the optimal TNLE to stage patients with dNETs.

Duodenal NETs have been anatomically classified most often as peri-ampullary versus non-ampullary. Perhaps not surprisingly, peri-ampullary tumor location was associated with higher likelihood of abdominal pain (80% vs. 73%) and clinical jaundice (22.9% vs. 1.6%) versus non-ampullary dNETs due to obstruction of bile and pancreatic ducts. Consistent with a previous population-based study,[18] the current study also noted that peri-ampullary dNETs were larger at the time of presentation compared with non-ampullary dNETs. Patients with peri-ampullary dNETs were also more likely to undergo PD, and had higher number of LNs examined than patients with non-ampullary dNETs. The incidence of LNM was, however, no different among patients with peri-ampullary versus non-ampullary dNETs. Consistent with previous data, we also noted that tumor grade was associated with long-term survival among patients with both peri-ampullary and non-ampullary dNETs after curative resection.[8] In contrast, Randle and colleagues failed to find an association of higher tumor grade and worse survival among patients with dNETs – especially as related to patients who had peri-ampullary versus non-ampullary dNETs.[18] The reason for these disparate results are likely multifactorial yet may be due to patients with peri-ampullary dNET in the current study being more likely to undergo a more extensive resection, such as PD, compared with patients included in the study by Randle et al. who more often underwent a local excision.[18]

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Prognosis following curative-intent resection of dNET was generally very good with a 5-year survival of 84.7%, which was comparable to previous data reported in the literature (66% to 93.8%).[8,19,20] Interesting, the impact of LNM on long-term outcome has been controversial. While some studies have suggested that LNM was associated with a worse prognosis,[7,16] data from the current study, as well as several other previous reports, have not demonstrated an association of LNM with long-term prognosis.[8,9,21] Given the low accuracy of preoperative imaging to detect LNM among dNETs patients, most surgeons advocate for routine LND at the time of surgical resection of dNETs.[12,22] To this point, LNM was present in over one-half of all patients with dNETs (60.4%). Perhaps of more interest, the data clearly demonstrated a strong correlation with dNET size and the likelihood of LNM, as patients with tumor >2 cm (80.0%) or 1-2 cm (65.7%) in size had a much higher incidence of LNM than patients with tumors ≤1 cm (40.0%) (p=0.003). Margonis et al. had similarly reported a higher incidence of LNM among NET tumors sized >1.5 cm,[10] while Burke et al. noted a difference in the incidence of LNM using tumor size using > 2 cm as the cut-off.[23] While 1 cm is currently used as the cut-off size to differentiate T1 from T2 in the AJCC staging manual,[11,16] there was still a relatively high incidence of LNM even among patients with small tumors (≤1 cm, 40.0%). Whereas surgical resection and lymphadenectomy has traditionally been recommended for only tumors >1 cm, data in the current study suggest that patients with dNETs ≤1 cm should also be considered for LND rather than local excision alone.

The minimal number of LNs needed to examine in order to achieve accurate staging of the nodal basin for patients with dNETs has not been defined in the latest NCCN guidelines.[11,16] The topic of TNLE has been an area of interest for several other

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hepatopancreatic diseases. In fact, TNLE among patients with pancreatic and small bowel NETs relative to recurrence-free survival and overall survival has been examined by our group and others.[15,24] Using a large multi-institutional database with external validation based on the Surveillance, Epidemiology and End Results (SEER) registry, we demonstrated that TNLE ≥8 had the highest discriminatory power relative to recurrence-free and overall survival among patients with pNET who had 1 to 3 LNM, and patients who had ≥4 LNM in both a multi-institutional dataset and the SEER database.[15] In the current study, we similarly noted that TNLE ≥8 had the strongest discriminatory power to ensure identification of possible LNM and optimally stage the nodal basin for patients with dNETs. Specifically, TNLE ≥ 8 versus TNLE<8 was associated with a higher chance of identifying LNM (73.2% vs. 44.4%), as well as a higher number of LNM identified. Taken together, LND as part of an operative procedure for patients with dNET should include examination of ≥ 8 LN to ensure adequate staging.

Several limitations should be considered when interpreting data in the current study. While a multi-institutional study increased the sample size of the analytic cohort, patient selection, surgical technique, as well as utilization of LND and pathologic examination of LN may have varied at different centers. All participatory centers were, however, major hepatopancreatic institutions who followed standard state-of-the-art care guidelines regarding the management of patients with NET. The current study also did not note a difference of long-term survival among patients with versus without LNM. The reason for this may have been due to a lack of statistic power (Type II error); however, other authors have noted a similar finding and attributed the lack of prognostic impact to the indolent nature of dNET and the very good overall prognosis.[8,9,21] The current study

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also only included patient who underwent curative-intent resection and therefore patients receiving non-surgical treatments were not available for comparison.

In conclusion, patients with a dNET had an overwhelmingly favorable prognosis after curative-intent resection, despite the relatively high incidence of associated LNM. While the incidence of LNM directly correlated with tumor size, even patients with dNET ≤1 cm had a 40% incidence of LNM. Regional lymphadenectomy of a least 8 LN was recommended to stage patients accurately. Interestingly, the presence of LNM was not, however, associated with long-term survival; rather, tumor grade was the factor that impacted prognosis. Collectively, data from the current study should help to inform the care of patients with dNETs.

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Reference

1. O'Toole D, Delle Fave G, Jensen RT. Gastric and duodenal neuroendocrine tumours. *Best Pract Res Clin Gastroenterol.* 2012;26:719-35.

2. Jensen RT, Rindi G, Arnold R, et al. Well-differentiated duodenal tumor/carcinoma (excluding gastrinomas). *Neuroendocrinology.* 2006;84:165-72.

3. Modlin IM, Lye KD, Kidd M. Carcinoid tumors of the stomach. *Surg Oncol.* 2003;12:153-72.

4. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer.* 2003;97:934-59.

5. Fitzgerald TL, Dennis SO, Kachare SD, Vohra NA, Zervos EE. Increasing incidence of duodenal neuroendocrine tumors: Incidental discovery of indolent disease? *Surgery.* 2015;158:466-71.

6. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26:3063-72.

7. Masui T, Sato A, Nakano K, et al. Comparison of Recurrence Between Pancreatic and Duodenal Neuroendocrine Neoplasms After Curative Resection: A Single-Institution Analysis. *Ann Surg Oncol.* 2018;25:528-34.

8. Dogeas E, Cameron JL, Wolfgang CL, et al. Duodenal and Ampullary Carcinoid Tumors: Size Predicts Necessity for Lymphadenectomy. *J Gastrointest Surg.* 2017;21:1262-9.

9. Untch BR, Bonner KP, Roggin KK, et al. Pathologic grade and tumor size are associated with recurrence-free survival in patients with duodenal neuroendocrine tumors. *J Gastrointest Surg.* 2014;18:457-62; discussion 62-3.

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10. Margonis GA, Samaha M, Kim Y, et al. A Multi-institutional Analysis of Duodenal Neuroendocrine Tumors: Tumor Biology Rather than Extent of Resection Dictates Prognosis. *J Gastrointest Surg.* 2016;20:1098-105.

11. Delle Fave G, O'Toole D, Sundin A, et al. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. *Neuroendocrinology.* 2016;103:119-24.

12. Rossi RE, Rausa E, Cavalcoli F, Conte D, Massironi S. Duodenal neuroendocrine neoplasms: a still poorly recognized clinical entity. *Scand J Gastroenterol.* 2018;53:835-42.

13. Massironi S, Campana D, Partelli S, et al. Heterogeneity of Duodenal Neuroendocrine Tumors: An Italian Multi-center Experience. *Ann Surg Oncol.* 2018;25:3200-6.

14. Dasari BVM, Al-Shakhshir S, Pawlik TM, et al. Outcomes of Surgical and Endoscopic Resection of Duodenal Neuroendocrine Tumours (NETs): a Systematic Review of the Literature. *J Gastrointest Surg.* 2018;22:1652-8.

15. Zhang XF, Xue F, Dong DH, et al. New Nodal Staging for Primary Pancreatic Neuroendocrine Tumors: A Multi-institutional and National Data Analysis. *Ann Surg.* 2019.

16. Amin MB. *American Joint Committee on Cancer.* Springer, New York; 2017.

17. Crippa S, Partelli S, Boninsegna L, Falconi M. Implications of the new histological classification (WHO 2010) for pancreatic neuroendocrine neoplasms. *Ann Oncol.* 2012;23:1928.

18. Randle RW, Ahmed S, Newman NA, Clark CJ. Clinical outcomes for neuroendocrine tumors of the duodenum and ampulla of Vater: a population-based study. *J Gastrointest Surg.* 2014;18:354-62.

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19. Milanetto AC, Pasquali C, Da Broi M, Brambilla T, Capretti G, Zerbi A. Ampullary neuroendocrine neoplasms: surgical experience of a rare and challenging entity. *Langenbecks Arch Surg.* 2018;403:581-9.

20. Kachare SD, Liner KR, Vohra NA, Zervos EE, Fitzgerald TL. A modified duodenal neuroendocrine tumor staging schema better defines the risk of lymph node metastasis and disease-free survival. *Am Surg.* 2014;80:821-6.

21. Burke CA, Beck GJ, Church JM, van Stolk RU. The natural history of untreated duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. *Gastrointest Endosc.* 1999;49:358-64.

22. Iwasaki T, Nara S, Kishi Y, Esaki M, Shimada K, Hiraoka N. Surgical treatment of neuroendocrine tumors in the second portion of the duodenum: a single center experience and systematic review of the literature. *Langenbecks Arch Surg.* 2017;402:925-33.

23. Burke AP, Sobin LH, Federspiel BH, Shekitka KM, Helwig EB. Carcinoid tumors of the duodenum. A clinicopathologic study of 99 cases. *Arch Pathol Lab Med.* 1990;114:700-4.

24. Zaidi MY, Lopez-Aguiar AG, Dillhoff M, et al. Prognostic Role of Lymph Node Positivity and Number of Lymph Nodes Needed for Accurately Staging Small Bowel Neuroendocrine Tumors. *JAMA Surg.* 2018.

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Figures:

Figure 1: (a), overall survival of the whole cohort (n=162); **(b),** overall survival of patients with peri-ampullary (n=35) or non-ampullary (n=127) duodenal neuroendocrine tumors.

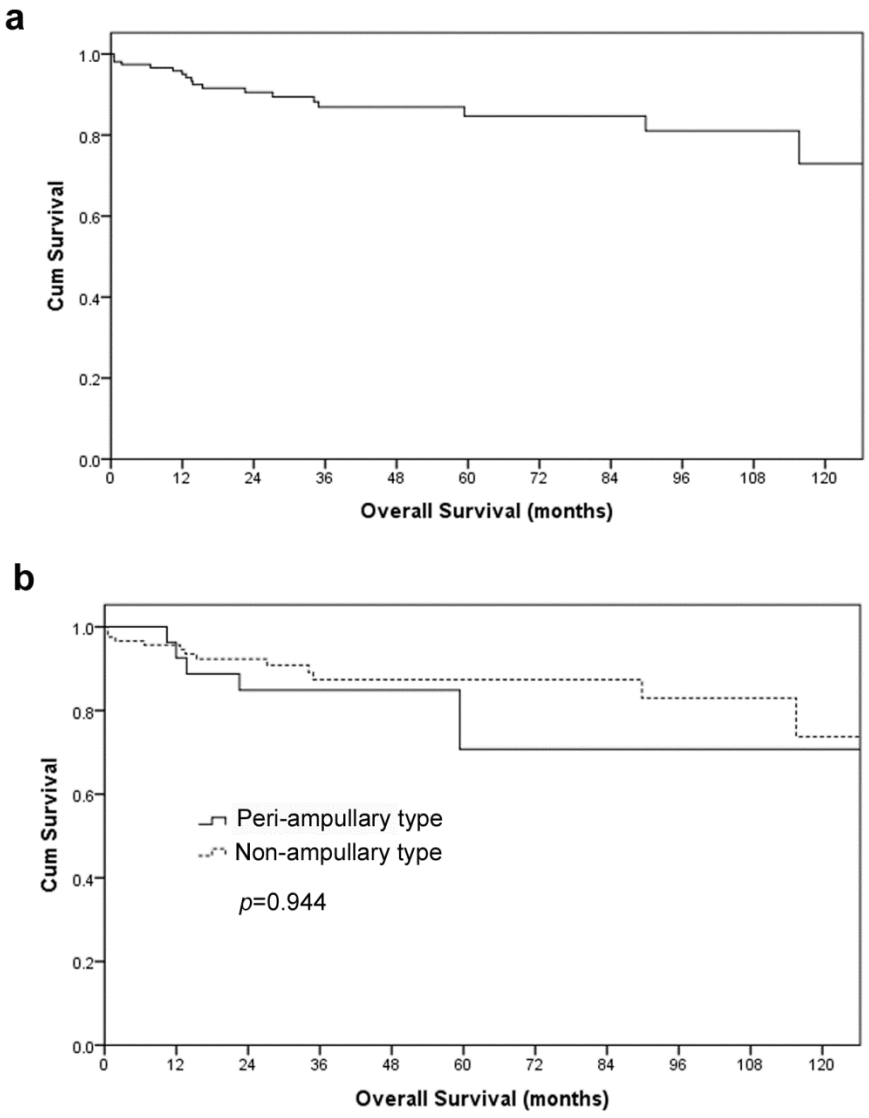

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Figure 2: The proportion of lymphadenectomy (LND) **(a)** and number of LND **(b)** among patients with different tumor size; **(c),** the incidence of lymph node metastasis (LNM) among patients with different tumor size; **(d),** Receiver operative characteristics (ROC) analysis illustrating that total number of lymph nodes examined (TNLE) ≥ 8 had the highest discriminatory power relative to LNM.

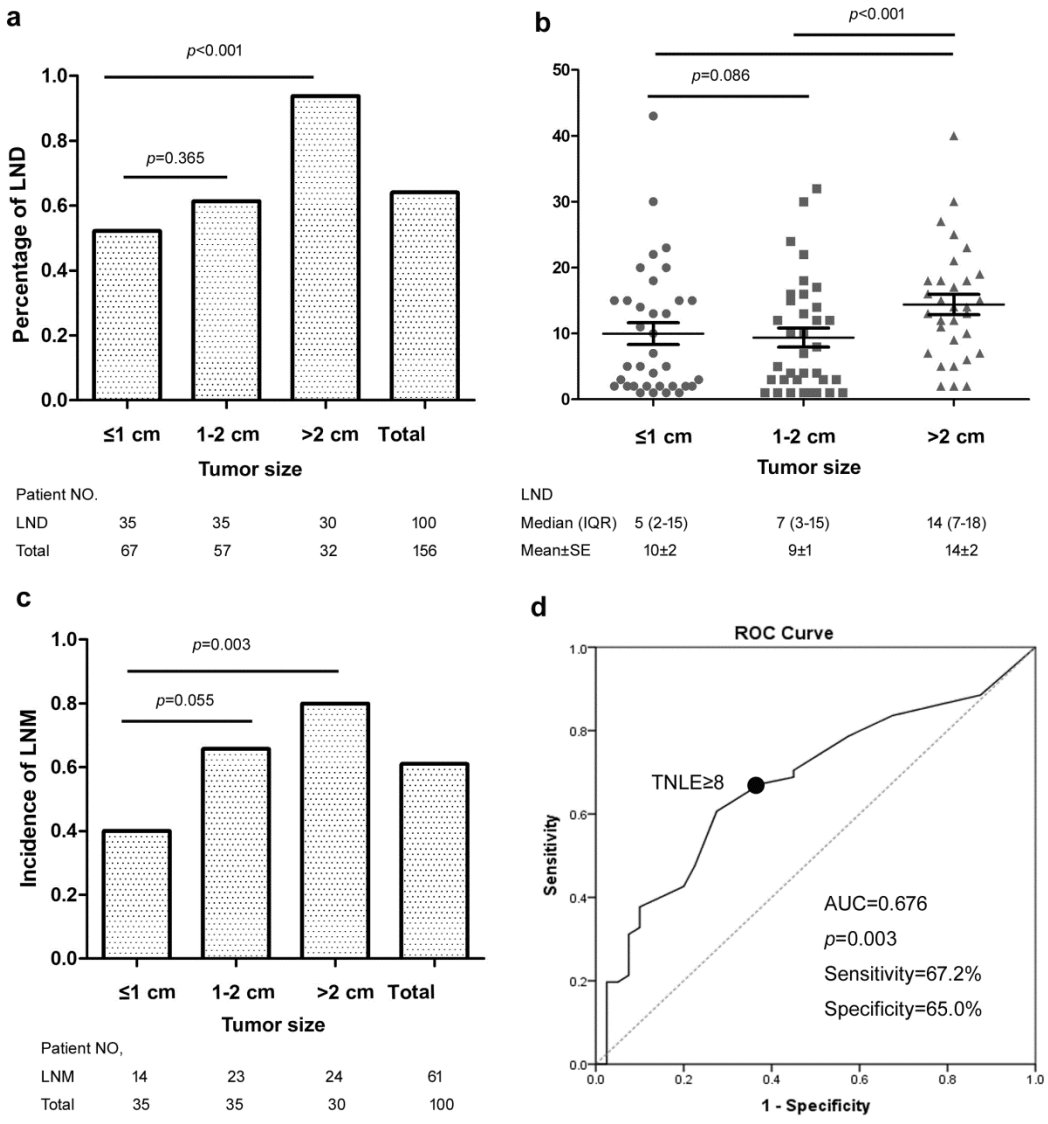

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Table 1 Clinicopathologic characteristics and surgical procedures

	Overall (n=162)	Peri-ampullary dNETs (n=35)	Non-ampullary dNETs (n=127)	P value
Age (years)	59 (51-68)	56 (50-70)	59 (52-68)	0.559
Gender				0.340
Male	87 (53.7%)	16 (45.7%)	16 (45.7%)	
Female	75 (46.3%)	19 (54.3%)	19 (54.3%)	
Non-functional tumor	128 (79.0%)	30 (85.7%)	98 (77.2%)	0.352
Functional tumor	34 (21.0%)	5 (14.3%)	29 (22.8%)	0.326
Gastrinoma	31 (19.1%)	4 (11.4%)	27 (21.3%)	
Somatostatinoma	2 (1.2%)	1 (2.9%)	1 (0.8%)	
Glucagonoma	1 (0.6%)	-	1 (0.8%)	
Genetic syndrome				0.059
None	146 (90.1%)	30 (85.7%)	116 (91.3%)	
MEN 1	8 (4.9%)	1 (2.9%)	7 (5.5%)	
Neurofibromatosis	4 (2.5%)	3 (8.6%)	1 (0.8%)	
NA	4 (2.5%)	1 (2.9%)	6 (2.4%)	

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Symptomatic	121 (74.7%)	28 (80.0%)	93 (73.2%)	0.515
Abdominal pain	77 (47.5%)	24 (68.6%)	53 (41.7%)	0.007
Clinical jaundice	10 (6.2%)	8 (22.9%)	2 (1.6%)	<0.001
Gastrointestinal bleeding	21 (13.0%)	2 (5.7%)	19 (15.0%)	0.254
Diarrhea	33 (20.4%)	7 (20.0%)	26 (20.5%)	1.000
Nausea/vomiting	37 (22.8%)	11 (31.4%)	26 (20.5%)	0.182
Preoperative FNA	47 (29.0%)	14 (40.0%)	33 (26.0%)	0.141
Primary location				
D1	76 (46.9%)	-	76 (59.8%)	
D2	26 (16.0%)	-	26 (20.5%)	
D1+D2	7 (4.3%)	-	7 (5.5%)	
D3/D4	4 (2.5%)	-	4 (3.1%)	
Surgery technique				0.267
Endoscopic	30 (18.5%)	4 (11.4%)	26 (20.5%)	
Open	127 (78.4%)	30 (85.7%)	97 (76.4%)	
Laparoscopic	4 (2.5%)	-	4 (3.1%)	

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Type of resection				<0.001
Endoscopic resection	30 (18.5%)	4 (11.4%)	26 (20.5%)	
Transduodenal resection	25 (15.4%)	9 (25.7%)	16 (12.6%)	
Partial duodenectomy	20 (12.3%)	-	20 (15.7%)	
Segmental duodenectomy	33 (20.4%)	-	33 (26.0%)	
Pancreaticoduodenectomy	52 (32.1%)	21 (60.0%)	31 (24.4%)	
Operation time (min)	200 (138-306)	250 (154-375)	196 (133-302)	0.082
Blood loss (ml)	125 (25-300)	200 (50-500)	100 (20-300)	0.074
Surgical margin				1.000
R0	131 (80.9%)	28 (80.0%)	103 (81.1%)	
R1	23 (14.2%)	5 (14.3%)	18 (14.2%)	
Largest tumor size (cm)	1.2 (0.7-2.0)	1.8 (1.2-2.5)	1.1 (0.7-1.7)	0.019
Tumor number				0.044
Single	141 (87.0%)	34 (97.1%)	107 (84.3%)	
multiple	21 (13.0%)	1 (2.9%)	20 (15.7%)	
Lymphadenectomy	101 (62.3%)	24 (68.6%)	77 (60.6%)	0.424

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NO. of lymph node examined	10 (3-16)	15 (11-21)	7 (2-15)	0.005
Lymph nodes status				0.241
Negative	40 (39.6%)	7 (29.2%)	33 (42.9%)	
Positive	61 (60.4%)	17 (70.8%)	44 (57.1%)	
NO. of positive lymph nodes	2 (1-4)	4 (2-6)	2 (1-3)	0.285
WHO classification				0.104
G1	106 (65.4%)	22 (62.9%)	84 (66.1%)	
G2	51 (31.5%)	10 (28.6%)	22 (32.3%)	
G3	5 (3.1%)	3 (8.6%)	2 (1.6%)	
AJCC T stage				0.018
T1	56 (34.6%)	5 (14.3%)	51 (40.2%)	
T2	61 (37.7%)	17 (48.6%)	44 (34.6%)	
T3	21 (13.0%)	8 (22.9%)	13 (10.2%)	
T4	6 (3.7%)	2 (5.8%)	4 (3.1%)	
Lymph-vascular invasion	31 (19.1%)	11 (31.4%)	20 (15.7%)	0.184
Perineural invasion	12 (7.4%)	3 (8.6%)	9 (7.1%)	1.000

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Postoperative morbidity	78 (48.1%)	18 (51.4%)	60 (47.2%)	0.705
Severe complication (III-V)	37 (22.8%)	10 (28.6%)	27 (21.3%)	0.432
Length of stay (d)	7 (5-11)	15 (7-21)	7 (4-11)	0.029

Table 2 Factors associated with overall survival after curative resection for duodenal neuroendocrine tumors (dNETs)

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (male vs. female)	1.3 (0.5-3.4)	0.535		
Functional status	0.4 (0.1-1.7)	0.202		
Symptomatic	0.5 (0.2-1.1)	0.083		
Genetic syndrome	0.4 (0.1-20.0)	0.309		
AJCC T categories				
T1	Ref.		Ref.	
T2	0.8 (0.3-	0.835	0.4 (0.1-	0.425

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	2.9)		1.7)	
T3-T4	1.9 (1.1-6.6)	0.024	0.9 (0.2-4.1)	0.924
Multiple lesions	0.7 (0.2-3.0)	0.623		
Tumor size (cm)				
≤1	Ref.			
1-2	0.9 (0.3-2.5)	0.831		
>2	0.9 (0.3-2.8)	0.913		
Tumor location		0.944		
Duodenum	Ref.			
Ampulla of Vater	1.0 (0.7-1.4)			
Surgery technique		0.732		
Endoscopic	Ref.			
Open/laparoscopic	1.3 (0.3-5.7)			
Surgical margin		0.537		
R0	Ref.			

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R1	0.6 (0.1-2.7)			
Lymphadenectomy		0.874		
No	Ref.			
Yes	0.9 (0.4-2.3)			
Nodal metastasis	0.5 (0.2-1.7)	0.260		
WHO classification				
G1	Ref.		Ref.	
G2/G3	1.7 (1.1-3.2)	0.025	1.5 (1.0-2.1)	0.032
Lymph-vascular invasion	2.5 (0.5-13.9)	0.282		
Perineural invasion	2.6 (0.4-15.6)	0.296		

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Table 3 Factors associated with lymph node metastasis (LNM) of duodenal neuroendocrine tumors (dNETs)

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Gender (female vs. male)	2.5 (1.1-5.6)	0.030	2.6 (1.0-6.4)	0.046
Functional status				
Symptomatic	1.1 (0.4-3.1)	0.805		
Genetic syndrome	2.1 (0.5-8.2)	0.297		
Multiple lesions	1.3 (0.4-4.2)	0.626		
Tumor size (cm)				
≤1	Ref.		Ref.	
1-2	2.9 (1.1-7.6)	0.033	2.8 (1.0-8.0)	0.048
>2	6.0 (2.0-18.4)	0.002	4.6 (1.4-15.0)	0.012
Tumor location		0.819		

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Duodenum	Ref.			
Ampulla of Vater	0.8 (0.6-1.1)			
Total number of LNs examined		0.004		0.007
<8	Ref.		Ref.	
≥8	3.4 (1.5-7.9)		3.6 (1.4-9.2)	
WHO classification				
G1	Ref.			
G2/G3	1.8 (0.6-5.7)	0.328		

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