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Neuroendocrine Tumors in Meckel's Diverticulum: Recommendation for Lymphadenectomy Regardless of Tumor Size Based on the NCDB Experience

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Abstract

Background Meckel's diverticulum (MD) is an anomaly of the small intestine from which malignancy may arise. Among MD neoplasms, neuroendocrine tumors (NETs) are considered the most common. However, their metastatic potential and optimal surgical therapy remain ill-defined.

Methods In a retrospective analysis of the National Cancer Database (2004–2015), patients with a diagnosis of MD malignancy were identified. Clinicopathologic factors were extracted and tumors arising in MD were compared. In the subgroup of patients with NET, the association between tumor factors and node involvement was investigated.

Results Three hundred twenty primary MD malignancies were captured in the National Cancer Database, consisting of 280 (87.5%) NET. The median age at diagnosis was 64 years. Patients were predominantly male (207, 73.9%) and white (269, 96.1%). Most tumors were well-differentiated (118, 42.1%) and sub-centimeter (median size, 0.7 cm). Distant metastasis was present in a minority (16, 5.7%), and the median overall survival was 114 months in the entire cohort. The regional lymph node status was known in 87 NET patients, out of which 39 (44.8%) harbored node metastasis. Although the risk of node involvement increased with larger tumor size, it remained significant even among sub-centimeter (9 out of 34, 26.5%) and well-differentiated (18 out of 44, 41%) tumors. Regional node involvement was associated with the presence of distant metastasis ($p < 0.001$).

Conclusion Lymph node involvement was common irrespective of the size and grade of NET arising from Meckel's diverticulum. Therefore, regional lymphadenectomy should be considered in the curative-intent surgical management of these neoplasms regardless of tumor size and grade.

Keywords Neuroendocrine tumors · Carcinoid · Meckel's diverticulum · Small bowel · Small intestine · Lymphadenectomy · Lymph nodes

Introduction

Meckel's diverticulum (MD) is a true diverticulum of the small intestine found in 0.3–3% of the population.[1,2] MD is considered a high-risk area for tumorigenesis with malignancy 70 times more likely to develop in a MD than any other location along the ileum. Furthermore, cancers associated with MD are diagnosed with increasing frequency in recent decades.[2] Among these cancers, neuroendocrine tumors (NETs) are the most common as they account for 76.5% of all MD tumors captured in the Surveillance, Epidemiology, and End Results (SEER) database.[3] Adenocarcinomas, pancreatic carcinomas, intraductal papillary mucinous neoplasms (IPMNs), and gastrointestinal stromal tumors (GISTs) have also been reported, which speaks to the variety of ectopic tissues that can be found in this structure.[2]

The metastatic potential and optimal choice of surgical therapy remain poorly defined for NET arising in MD, particularly for small-sized tumors. Neuroendocrine tumors arising from another true diverticulum of the gastrointestinal tract, the appendix, have low metastatic potential at small size (< 2 cm)

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and are often treated with an appendectomy.[4,5] However, neuroendocrine tumors arising from the ileum, where MD is most commonly located, carry a high risk for metastasis regardless of size and are treated with segmental bowel resection and mesenteric lymphadenectomy.[4–6] Thus, the decision to treat small-sized Meckel's NET similar to ileal or appendiceal NET has been an ongoing debate in the literature.[3,7,8] Two small, single-institution case series suggest that even small-sized Meckel's NET can metastasize to the regional lymph nodes.[3,8] Therefore, current surgical doctrine dictates the performance of a regional lymphadenectomy when resecting a Meckel's NET as lymphadenectomy for small intestinal NET might be associated with improved survival.[6]

To our knowledge, there are no population-based studies investigating the relationship between tumor clinicopathologic factors and nodal metastasis for Meckel's NET. Thus, current treatment recommendations are based on small, single-institutional series. All the while, the incidence of MD cancer has steadily increased in recent decades.[2] We sought to study the association between clinicopathologic factors and risk of nodal metastasis in neuroendocrine tumors of the Meckel's diverticulum using the National Cancer Database (NCDB) in an effort to better define future management guidelines.

Materials and Methods

The NCDB has collected more than 34 million records for cancer patients and captures 70–88% of all cancer diagnoses in the USA.[9] After the approval of the study protocol by the Institutional Review Board (IRB), we performed a retrospective analysis of the 2004–2015 NCDB small intestine Participant User File (PUF). The database was queried for Meckel's diverticulum malignancies using the International Classification of Disease (ICD) site code C17.3. The malignancies discovered with the histology codes 8240, 8243, and 8246 were grouped as "Neuroendocrine Tumors," codes 8140, 8480, 8481, and 8490 were grouped as "Adenocarcinomas," histology code 8936 was listed as "Gastrointestinal Stromal Tumors (GISTs)," and codes 8245, 8890, and 9364 were grouped as "Other."

Patient demographics, as well as tumor- and treatment-related variables, were extracted from the database, including the following: year of diagnosis, age, gender, race, insurance coverage, treatment facility type, Charlson-Deyo Comorbidity Index score, tumor grade, tumor size, depth of invasion, T stage, regional lymph node status, number of regional lymph nodes assessed, presence of distant metastasis, type of surgical treatment received, status of surgical resection margins, and receipt of systemic chemotherapy. We defined surgical treatment received as follows: Facility Oncology Registry Data Standards (FORDS) codes 20 and 27 were grouped as "Local Tumor Excision," codes 30 and 40 were grouped as "Removal of Primary Site," and codes 50 and 60 were grouped as "Radical Resection."

To investigate the association between clinicopathologic factors and nodal metastasis, we studied the subset of NET patients that had regional lymph nodes assessed by excluding patients with unknown regional lymph node status. Continuous variables were expressed as median with interquartile ranges (IQRs) in parentheses and compared using the Mann Whitney *U* test. Categorical variables were presented as totals and percentages and compared with the chi-square test. Overall survival estimates were obtained with the Kaplan-Meier method and compared with the Log Rank test. Statistical significance was set at alpha = 0.05 across all tests. All statistical analyses were performed with SPSS software package (SPSS 23, IBM, Chicago, IL.)

Results

Patient and Tumor Characteristics

Sixty-four thousand seven hundred fifty-six small intestine malignancies were captured in the NCDB between 2004 and 2015, with MD malignancies accounting for 323 (0.5%) of all small bowel cancers (Fig. 1). The most common neoplasm arising from the MD was NET (280, 86.7%), followed by adenocarcinomas (22, 6.8%) and GIST (18, 5.6%). The annual rate of new cases did not differ across the study years, averaging 23 new diagnoses of Meckel's NET per year (Table 1).

Patients with Meckel's NET who had a median age of 64 years (IQR, 53–73) were mostly white (96.1%), male (73.9%), with no comorbidities (70%), and treated at non-academic centers (65%) (Table 2). Most tumors were well-differentiated (118, 42.1%), sub-centimeter (median size, 0.7 cm; IQR, 0.4–1.2), and characterized as T1 lesions (67, 23.9%). The status of the regional lymph nodes was unknown in the majority of the patients (193, 68.9%), while 39 patients (13.9%) had regional node metastasis. Distant metastasis was present in a minority of patients (16, 6.7%). Most patients were treated with surgical removal of the primary site (201, 71.8%), and a margin negative resection was achieved in the majority (240, 85.7%). Systemic chemotherapy was administered to 5 patients (1.8%), while none of the patients received radiation therapy as part of their treatment. The median overall survival (OS) in the entire cohort was 114 months, with 83% of the patients being alive at 1 year from diagnosis, 78% at 3 years, and 42% at 5 years.

Lymph Node Involvement

The status of the regional lymph nodes was known for 87 (31.1%) patients out of the entire cohort of Meckel's NET.

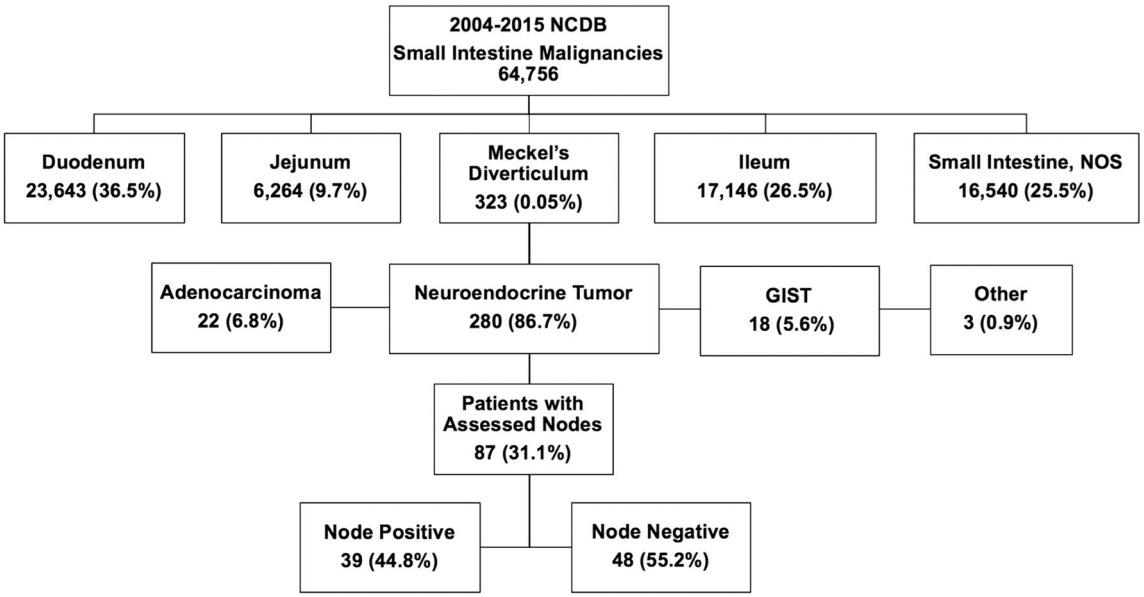


Fig. 1 Summary of small intestine malignancies captured in the NCDB between 2004 and 2015 and breakdown of the tumor histology subtypes arising from Meckel's diverticulum. NOS: not-otherwise specified; GIST: gastrointestinal stromal tumor

Among them, tumor metastasis was present in the regional nodes of 39 (44.8%) patients and not present in 48 (55.2%). Patients with nodal metastasis tended to be younger (median age, 60 vs 71 years; $p < 0.001$) and more often had private insurance (Table 3). Tumors with involved regional nodes were larger (median size, 1.5 vs 0.6 cm; $p = 0.001$) with a higher T stage ($p = 0.017$). Nevertheless, 9 out of 34 (26.5%) tumors less than 1 cm in size exhibited nodal metastasis, compared with 15 out of 28 (53.6%) tumors measuring 1–2 cm and 14 out of 19 (73.7%) tumors larger than 2 cm (Fig. 2). Therefore, although the risk of nodal metastasis increased with larger tumor size, it was still significant even among subcentimeter tumors. A well-differentiated tumor grade did not exclude the presence of nodal metastasis. The majority of tumors were well-differentiated in both groups, with 18 out of 44 (41%) well-differentiated tumors exhibiting nodal metastasis. Of note, a total of four non-well-differentiated NET all had positive regional nodes. The number of assessed lymph nodes did not differ significantly between the node positive and negative patients (median, 9 vs 7; $p = 0.469$). Distant metastasis was more likely to be present in the node-positive group (12% vs 2%; $p = 0.001$). The choice of surgical therapy did not differ among the two groups with the majority of patients receiving surgical removal of the primary site with negative resection margins. Chemotherapy was administered to a minority of patients in both groups (7.7% vs 4.2%; $p = 0.075$). The median overall survival was not reached in either group, with respective 1-, 3-, and 5-year overall survival estimates in the node positive versus negative groups: 94% vs 86%, 90% vs 77%, and 63% vs 43%, $p = 0.053$.

Table 1 New diagnoses of Meckel's neuroendocrine tumors (NETs) captured in the NCDB per year (2004–2015)

Year of diagnosis	Meckel's NET ($N = 280$)
2004	20
2005	19
2006	28
2007	21
2008	24
2009	26
2010	19
2011	20
2012	22
2013	25
2014	24
2015	32

Discussion

Neuroendocrine tumors are the most common malignancies arising in Meckel's diverticulum, but our understanding of their biologic behavior and, consequently, the appropriate choice of subsequent therapy after primary resection remain poorly defined. The incidence of these uncommon neoplasms has been found to be increasing based on previous analysis of the population-based SEER dataset, while the rate of new cases was found to be similar across the study years in our analysis of the hospital-based NCDB.[2] More importantly, limitations in previous studies, due to small sample size in addition to the absence of information related to nodal involvement of small-sized tumors, raise the question of a possible underestimation of regional metastatic presence. This

Table 2 Summary of patient and tumor characteristics of Meckel's neuroendocrine tumors (NETs) captured in the 2004–2015 NCDB. *Median (IQR). All other values total (%)

	Meckel's NET ($N = 280$)
Age (years)*	64 (53–73)
Gender	
Male	207 (73.9)
Female	73 (26.1)
Race	
White	269 (96.1)
Black	4 (1.4)
Other	2 (0.7)
Unknown	5 (1.8)
Insurance	
Private	121 (43.2)
Medicaid	8 (2.9)
Medicare	130 (46.4)
Not insured	12 (4.3)
Unknown	9 (3.2)
Treatment facility	
Academic	73 (26.1)
Non-academic	182 (65)
Unknown	25 (8.9)
Charlson-Deyo Score	
0	196 (70)
1	62 (22.1)
≥ 2	22 (7.9)
Grade	
Well-differentiated	118 (42.1)
Moderately differentiated	16 (5.7)
Poorly differentiated	1 (0.4)
Unknown	145 (51.8)
Tumor size (cm)*	0.7 (0.4–1.2)
Depth of invasion - T stage	
T1	67 (23.9)
T2	24 (8.6)
T3	28 (10)
T4	8 (2.9)
Unknown	153 (54.6)
Regional lymph node involvement	
Yes	39 (13.9)
No	48 (17.1)
Unknown	193 (68.9)
Distant metastasis	
Yes	16 (5.7)
No	255 (91.1)
Unknown	9 (3.2)
Treatment	
Local excision	59 (21.1)
Removal of primary site	201 (71.8)
Radical resection	14 (5)
Unknown	6 (2.1)
Resection margins status	
Negative	240 (85.7)
Positive	12 (4.3)
Unknown	28 (10)
Chemotherapy	
Yes	5 (1.8)
No	261 (93.2)
Unknown	14 (5)

underestimation has the potential to alter surgical judgment, influencing both the extent and quality of regional surgical treatment. In this population-based study of 280 Meckel's NET, we included 87 surgically resected tumors in which an assessment of the regional lymph nodes was performed. Of importance, the average number of lymph nodes assessed in both node positive and negative patients was 7. More importantly, the majority of the primary tumors were less than 2 cm in size, providing the opportunity to determine the metastatic potential of small tumors. Our analysis of the data reveals that sub-centimeter Meckel's NET carries a 26.5% risk of nodal metastasis, which increases to 53.6% for tumors 1–2 cm and to 73.7% for tumors larger than 2 cm.

Previous single-institutional series suggested that small-sized Meckel's NET might carry a significant risk of nodal metastasis. Lorenzen et al. reported on their experience with 7 Meckel's NET, out of which 6 had evidence of nodal metastasis, including 3 tumors that measured < 2 cm in size.[3] Similarly, Poncet et al. described a series of 8 Meckel's NET, where all > 1 cm tumors except one had regional nodal disease leading to their recommendation of resection with lymphadenectomy for tumors measuring more than 1 cm in diameter.[5] Our results confirm their findings of a significant rate of nodal metastasis in Meckel's NET > 1 cm but also reveal a substantial 25.6% risk of nodal spread for tumors less than 1 cm in size.

Staging gastrointestinal neuroendocrine tumors continues to rely heavily on features such as tumor size.[3,5,7,8] The College of American Pathologists used size as an important staging consideration in its 8th edition American Joint Committee on Cancer (AJCC) staging manual for neuroendocrine tumors of the small bowel.[10] Specifically, tumors less than 1 cm in size confined to the submucosa are characterized as T1, while tumors greater than 1 cm in the same location would be characterized as T2. Our study adds credence to the notion of using tumor size for staging purposes as we found a positive association between increasing tumor size and the

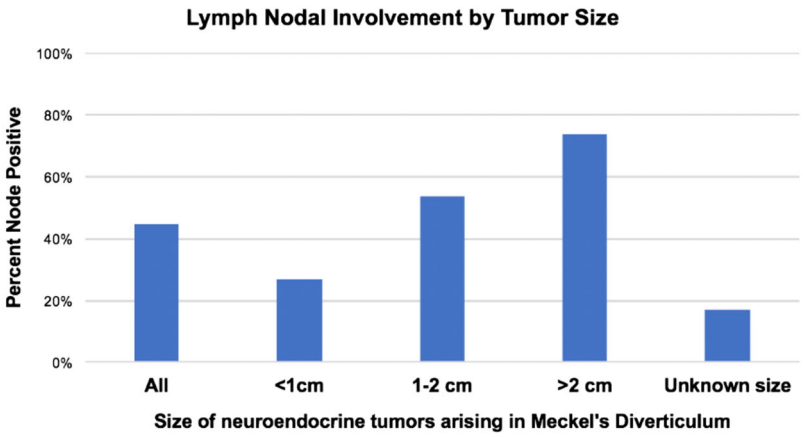
Table 3 Comparison of patient and tumor characteristics between node-positive and node-negative Meckel's neuroendocrine tumors. *Median (IQR). All other values total (%)

	Positive nodes ($n = 39$)	Negative nodes ($n = 48$)	p value
Age (years)*	60 (52–66)	71 (63–76)	< 0.001
Gender			
Male	29 (74.4)	37 (77.1)	0.768
Female	10 (25.6)	11 (22.9)	
Race			
White	39 (100)	46 (95.8)	0.435
Black	–	1 (2.1)	
Other	–	1 (2.1)	
Insurance			
Private	24 (61.5)	10 (20.8)	< 0.001
Medicaid	–	1 (2.1)	
Medicare	11 (28.2)	35 (72.9)	
Not insured	2 (5.1)	2 (4.2)	
Unknown	2 (5.1)	–	
Treatment facility			
Academic	12 (30.8)	19 (39.6)	0.694
Non-academic	26 (66.7)	28 (58.3)	
Unknown	1 (2.6)	2 (2.1)	
Charlson-Deyo Score			
0	33 (84.6)	33 (68.8)	0.179
1	5 (12.8)	10 (20.8)	
≥ 2	1 (2.6)	5 (10.4)	
Grade			
Well-differentiated	18 (46.2)	26 (54.2)	0.156
Moderately differentiated	3 (7.7)	–	
Poorly differentiated	1 (2.6)	–	
Unknown	17 (43.6)	22 (45.8)	
Tumor size (cm)*	1.5 (1.0–2.3)	0.6 (0.3–1.2)	0.001
Depth of invasion - T stage			
T1	1 (2.6)	11 (22.9)	0.017
T2	6 (16.7)	3 (6.3)	
T3	5 (12.8)	8 (16.7)	
T4	5 (12.8)	1 (2.1)	
Unknown	22 (56.4)	25 (52.1)	
Number of examined nodes*	9 (4–16)	7 (2–15)	0.469
Regional nodes examined			
< 8 nodes examined	19 (48.7)	25 (52.1)	0.232
≥ 8 nodes examined	20 (51.3)	20 (41.7)	
Unknown	–	3 (6.2)	
Distant metastasis			
Yes	12 (30.8)	2 (4.2)	0.001
No	27 (69.2)	46 (95.8)	
Treatment			
Local excision	2 (5.1)	6 (12.5)	0.318
Removal of primary site	31 (79.5)	39 (81.3)	
Radical resection	5 (12.8)	3 (6.3)	
Unknown	1 (2.6)	–	
Resection margins status			
Negative	33 (84.6)	43 (89.6)	0.696
Positive	4 (10.3)	4 (8.3)	
Unknown	2 (5.1)	1 (2.1)	
Chemotherapy			
Yes	3 (7.7)	2 (4.2)	0.075
No	29 (74.4)	44 (91.7)	
Unknown	7 (17.9)	2 (4.2)	

risk of lymph node metastasis. However, it must be emphasized that in this series, even sub-centimeter tumors were commonly associated with metastatic disease (Fig. 2).

Importantly, this study reveals that tumor grade was a poor predictor of nodal metastasis. We observed a significant rate of nodal metastasis (41%) among well-differentiated tumors. Therefore, we believe that the diagnosis of a well-differentiated NET in Meckel's diverticulum, even a small-sized one, should not provide reassurance to the surgeon as there is still a substantial risk of lymph node metastasis. Furthermore, all four non-well-differentiated tumors in our series had evidence of positive lymph nodes, and thus our data suggest that the diagnosis of a non-well-differentiated Meckel's NET should prompt a lymphadenectomy. Of note, one limitation of our study is the absence of information on the Ki-76 proliferation index of Meckel's NET. Whether the percentage of Ki-67-positive cells in the tumor will be a better predictor of metastasis than tumor size or grade remains to be answered by future studies.

When operating on a known or suspected neuroendocrine tumor in a Meckel's diverticulum, a regional lymphadenectomy should be considered based on our data as there is a substantial risk of nodal metastasis regardless of tumor size or grade. We recognize that in routine clinical practice, a sub-centimeter Meckel's NET may be diagnosed incidentally on a specimen resected for another indication. Until further evidence to the contrary, our findings support the argument that, in these patients, consideration should be given to performing a formal regional lymphadenectomy on a subsequent operation in order to accurately stage the tumor as they harbor a risk of nodal metastasis upwards of 25%. However, whether regional lymphadenectomy improves the overall survival of patients with gastrointestinal neuroendocrine tumors is still the subject of ongoing debate.[6] In our series, both node-positive and node-negative Meckel's NET exhibited similar rates of OS, although there was a trend towards paradoxically improved survival in the node-positive population. It should be noted that lymph node–positive patients were significantly younger in our cohort (median age, 60 vs 71 years) leading to a potential confounding effect on overall survival. A more refined metric to assess the effect of nodal involvement on



Patients with Positive Nodes	39	9	15	14	1
Patients with Assessed Nodes	87	34	28	19	6
Percent Node Positive	**44.8%**	**26.5%**	**53.6%**	**73.7%**	**16.7%**

Fig. 2 Association between tumor size and regional lymph node metastasis for neuroendocrine tumors arising from Meckel's diverticulum

prognosis would have been cancer-specific survival, but these data were not captured by the NCDB. Additionally, the NCDB does not provide data on cancer recurrence, and therefore, the effect of lymph node positivity on recurrence-free survival remains unknown. For these reasons, current curative-intent oncologic surgical principles would dictate performing a lymphadenectomy for a gastrointestinal neoplasm harboring a greater than 25% risk of nodal metastasis. Regardless of the effect of lymphadenectomy on survival, knowing the regional node status of a Meckel's NET could help guide the search for additional distant disease and inform surveillance frequency. These recommendations are based on our data demonstrating a significantly higher risk of harboring distant metastasis in the node-positive patients (12% vs 2%). Lastly, as emerging systemic, molecularly targeted therapies against neuroendocrine tumors evolve, the regional node status, as well as debulking through lymphadenectomy, may not only guide the decision to administer adjuvant treatment but also enhance the efficacy of therapy for high-risk tumors.[11] These recommendations should be carefully applied to the cohort of older patients with Meckel's NET, as advanced age was associated with a lower risk of nodal metastasis on our analysis of the NCDB. Specifically, in cases of incidentally discovered Meckel's NET treated with local excision, clinical equipoise should be applied when contemplating re-resection to include a regional mesenteric lymphadenectomy. We believe treatment decisions related to patient age should be made within the context of careful consideration of comorbidities, patient choice, and potential oncologic benefit. Our results can help educate patients with Meckel's NET on the risk of harboring residual lymph node disease and facilitate making informed decisions about their care, including the decision to pursue a regional lymphadenectomy in the case of initially locally resected tumors.

Finally, the optimal lymph node harvest when performing a regional lymphadenectomy for a Meckel's NET remains unknown. A recent analysis of the NCDB by Motz et al. determined that resecting at least 8 nodes was associated with improved survival in patients with small bowel NET.[6] However, Chen et al. advocate resecting at least 12 lymph nodes to improve survival in patients with small bowel NET based on SEER data.[12] It is unclear how the findings of these two studies specifically apply to neuroendocrine tumors of Meckel's diverticulum. In our series, 46% of the 87 patients with assessed nodes had greater than or equal to 8 regional lymph nodes assessed, which is the lower threshold of the two studies. Considering that 26.5% of this cohort had sub-centimeter tumors, it is unlikely that these tumors were known based on preoperative imaging. We speculate that intraoperative palpable lymph nodes might have driven the decision to perform a potentially limited lymphadenectomy for these patients or preoperative imaging revealed evidence of enlarged mesenteric lymph nodes that were subsequently excised.

In summary, we harnessed the power of the NCDB to collect a large series of Meckel's NET to gain insight into their metastatic potential and choice of optimal surgical therapy. Our study is inherently limited by the inability to retrospectively collect missing variables from the NCDB and by the absence of detailed information regarding factors driving treatment decisions. We believe future studies assessing the relationship between Ki-67 and node metastasis, as well as between node metastasis and the risk of recurrence, which

are not captured by the NCDB, may prove to be informative. Lastly, we would like to highlight the potential of NCDB analysis in expanding the opportunity to further understand low-incidence malignancies, such as Meckel's NET, by overcoming the inherent limitations of small-sized, single-institution case series.

Conclusion

Neuroendocrine tumors were the most common malignancy arising from a Meckel's diverticulum in the NCDB. Regional lymph node involvement was common for Meckel's NET, even among small-sized (< 1 cm) and well-differentiated tumors, and was associated with the presence of distant metastasis. Thus, regional lymphadenectomy should be considered in the curative-intent surgical management of these neoplasms regardless of tumor size and grade.

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Acquisition of data: Dogeas, Magallanes, Augustine
Interpretation of data: Dogeas, Magallanes, Porembka, Wang, Yopp, Polanco, Mansour, Choti, Zeh, Augustine
Drafting the work: Dogeas, Magallanes, Augustine
Final approval: Dogeas, Magallanes, Porembka, Wang, Yopp, Polanco, Mansour, Choti, Zeh, Augustine
Agreement to be accountable for all aspects of the work: Dogeas, Magallanes, Porembka, Wang, Yopp, Polanco, Mansour, Choti, Zeh, Augustine

Compliance with Ethical Standards

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