ORIGINAL CONTRIBUTION

Predictors of Metastases in Rectal Neuroendocrine Tumors: Results of a National Cohort Study

Seth J. Concors, M.D.[1,2] • Andrew J. Sinnamon, M.D., MSCE[1,2] • Ian W. Folkert, M.D.[1,2]
Najjia N. Mahmoud, M.D.[1,2] • Douglas L. Fraker, M.D.[1,2] • E. Carter Paulson, M.D., MSCE[1,2]
Robert E. Roses, M.D.[1,2]

1 Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
2 Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

BACKGROUND: Rectal neuroendocrine tumors are often found incidentally. Local excision alone has been advocated for lesions ≤2 cm; however, the evidence base for this approach is limited.

OBJECTIVE: Associations among tumor size, degree of differentiation, and presence of distant metastatic disease were examined.

DESIGN: This was a retrospective cohort study.

SETTINGS: This study was conducted using a nationwide cohort.

PATIENTS: A total of 4893 patients with rectal neuroendocrine tumors were identified in the National Cancer Database (2006–2015).

MAIN OUTCOME MEASURES: Logistic regression analyses were used to evaluate associations among tumor size, degree of differentiation, and presence of regional and distant metastatic disease. Cut point analysis was performed to identify an optimal size threshold predictive of distant metastatic disease.

RESULTS: Of patients included for analysis, 3880 (79.3%) had well-differentiated tumors, 540 (11.0%) had moderately differentiated tumors, and 473 (9.7%) had poorly differentiated tumors. On logistic regression, increasing size was associated with a higher likelihood of pathologically confirmed lymph node involvement (among patients undergoing proctectomy), and both size and degree of differentiation were independently associated with a higher likelihood of distant metastatic disease. The association between tumor size and distant metastatic disease was stronger for well-differentiated and moderately differentiated tumors (OR = 1.4; $p < 0.001$ for both) than for poorly differentiated tumors (OR = 1.1; $p = 0.010$). For well-differentiated tumors, the optimal cut point for the presence of distant metastatic disease was 1.15 cm (area under the curve = 0.88; 88% sensitive and 88% specific). Tumors ≥1.15 cm in diameter were associated with a substantially increased incidence of distant metastatic disease (72/449 (13.8%)). For moderately differentiated tumors, the optimal cut point was also 1.15 cm (area under the curve = 0.87, 100% sensitive and 75% specific).

LIMITATIONS: This study was limited by its retrospective design.

CONCLUSIONS: Tumor size and degree of differentiation are predictive of regional and distant metastatic disease in rectal neuroendocrine tumors. Patients with tumors >1.15 cm are at substantial risk of distant metastasis and should be staged and managed accordingly. See **Video Abstract** at http://links.lww.com/DCR/A778.

KEY WORDS: Differentiation; Metastasis; Neuroendocrine; Proctectomy; Rectal.

Rectal neuroendocrine tumors (rNETs) account for between 14% and 55% of all neuroendocrine tumors and are increasing in incidence.[1,2] In contrast to other GI neuroendocrine tumors, rNETs do not typically present with symptoms of carcinoid syndrome, and many lesions are asymptomatic at the time of diagnosis.[3] The rising incidence of rNETs is, at least partially attributable to an increasing use

CME Earn Continuing Education (CME) credit online at cme.lww.com.

Funding/Support: None reported.

Financial Disclosure: None reported.

Podium presentation at the meeting of The American Society of Colon and Rectal Surgeons, Nashville, TN, May 19 to 23, 2018.

Correspondence: Robert E. Roses, M.D., 3400 Spruce St, 4 Silver, Philadelphia, PA 19104. E-mail: Robert.Roses@uphs.upenn.edu

Dis Colon Rectum 2018; 61: 1372–1379
DOI: 10.1097/DCR.0000000000001243

of screening colonoscopy, leading to the discovery of asymptomatic lesions.[4,5] Small lesions, particularly those <2 cm, are commonly endoscopically resected.[6] Transabdominal or transperitoneal resection has been advocated for lesions >2 cm because of a perceived increase in the risk of regional nodal metastasis at this size cut point.[7] Evidence supporting this approach, however, is limited to small institutional series.[8,9]

The risk of metastasis and survival has been correlated with tumor size and depth of invasion. This is reflected in the American Joint Cancer Commission TNM staging guidelines for colon and rNETs, with tumor size and depth of invasion influencing T stage.[7] Although overall 5-year survival in rNETs is high, from 62% to 88%, it is markedly worse (24%–33%) when regional or distant metastatic disease is present.[2,5,7,10,11] Several groups have previously sought to identify patients who should be more extensively staged and followed for distant spread after a diagnosis of rNET. Increasing tumor grade, signified by Ki67, lymphovascular invasion, and depth of invasion beyond the muscularis layer, predict poorer survival.[2,7,10,12,13] However, despite data supporting patient- and tumor-specific factors impacting local and distant spread, a clear understanding of which patients are at highest risk for disseminated disease is elusive. The aim of this study was to identify predictors of regional lymph node and distant metastatic spread in patients with rNETs in a large national cohort.

PATIENTS AND METHODS

Data Source

After institutional review board approval, data from 2006 to 2015 were identified in the rectal participant use file of the National Cancer Data Base (NCDB), a joint effort between the American Cancer Society and the American College of Surgeons Commission on Cancer. Established in 1989, the NCDB is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually.[14]

Patient Selection

Patients diagnosed with rNETs from 2006 to 2015 were selected, as defined by the *International Classification of Diseases for Oncology, 3rd Revision*.[15] Patients with incomplete information data regarding tumor size and tumor differentiation were excluded. Of note, survival analysis included only patients for which ≥6 months of follow-up data was available. For the analysis related to lymph node metastasis, only patients who had lymph nodes sampled at the time of surgical resection and without distant metastases were included (Fig. 1).

Variables

Demographic, cancer-specific, and facility-related variables available in the NCDB have been defined previously, and include age, sex, race, Charlson–Dayo comorbidity score, tumor histology, tumor size, tumor differentiation, American Joint Committee on Cancer tumor stage, surgery type, and lymph nodes status.[14] Patients were classified as having a surgical resection (segmental colectomy, low anterior resection, abdominoperineal resection, total proctectomy, or proctocolectomy), a local excision, or no surgery.

Statistical Methods

Descriptive statistics are displayed as frequencies for categorical variables and medians with interquartile ranges for continuous variables. Univariate analysis was performed using the χ^2 test or Student *t* test. Multivariable logistic regression was then performed to assess the association between demographic/clinical factors and surgical procedure performed, as well as the presence of lymph node metastasis or distant metastasis at the time of diagnosis. For the multivariable model, size was divided into <1.00 cm, 1.01 to 1.99 cm, and >2.00 cm. Continuous variables were dichotomized at the optimal cut point, which was determined using the Liu method, which optimizes the product of sensitivity and specificity for a given test.[16]

The Kaplan–Meier method was used to estimate the overall survival function. *Overall survival* was defined as time from diagnosis to death, with patients alive at time of last follow-up censored. Cut point analysis identified a discriminatory difference above and below 1.15 cm; however, for survival analysis, this was rounded to the more clinically appropriate value of 1.00 cm. A p value of <0.05 was considered statistically significant. All of the statistics were formed with STATA MP (StataCorp LLC, College Station, TX).

RESULTS

Descriptive Statistics

A total of 4893 patients were identified as meeting study criteria and were included for analysis. The median age was 55 years (interquartile range, 50–63 y), and a majority of patients were male (52.4%) and white (52.7%). Most of the tumors were well differentiated (79.3%) and ≤1 cm (75.7%); median tumor size was 0.6 cm (interquartile range, 0.4–1.0 cm). A subset of patients had distant metastatic disease at time of presentation (8.0%; Table 1).

Determinants of Procedure Type

The majority of patients, 3569 (86.0%), underwent local excision, and 582 (14.0%) underwent proctectomy. No significant differences in patient race, sex, Charleson–Dayo score, geographic location, or facility type (academic or nonacademic facility) were observed in the local excision and proctectomy groups. On univariate analysis, age, private insurance type, increasing tumor size, and worsening

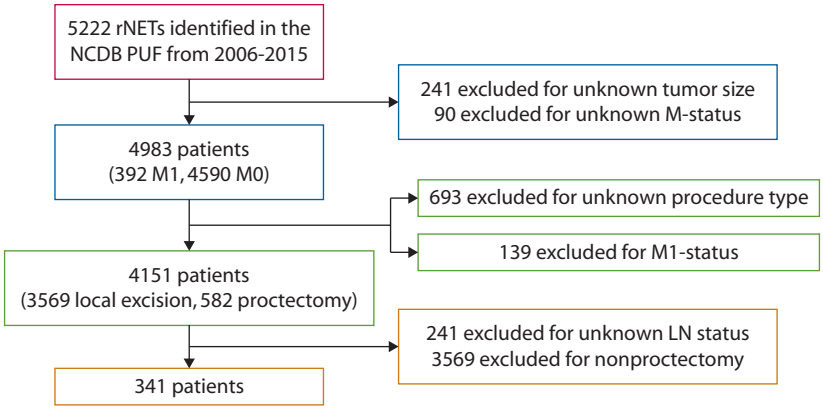

FIGURE 1. Flow chart of cohort. rNET = rectal neuroendocrine tumor; NCDB = National Cancer Data Base; PUF = Participant User File; LN = lymph node.

differentiation were associated with performance of proctectomy. On multivariable analysis, factors that remained significantly associated with performance of proctectomy were increasing tumor size 1.01 to 1.99 cm (OR = 3.2 (95% CI, 2.4–4.3); $p < 0.001$), >2.00 cm (OR = 11.5 (95% CI, 8.7–15.1); $p < 0.001$), moderate differentiation (OR = 1.8 (95% CI, 1.4–2.4); $p < 0.001$), and poor differentiation (OR = 9.6 (95% CI, 6.0–15.4); $p < 0.001$). Uninsured (OR = 0.4 (95% CI, 0.2–0.7); $p < 0.01$) and Medicaid patients (OR = 0.6 (95% CI, 0.4–0.9); $p < 0.05$) were more likely to undergo local excision, with Medicare nonpredictive of procedure type (Table 2).

TABLE 1. Demographic and clinical characteristics of the overall cohort

Parameter	*Data*
Age, median (IQR), y	55 (55–63)
Sex, n (%)	
Men	2562 (52.4)
Women	2331 (47.6)
Race, n (%)	
White	2576 (52.7)
Black	1390 (28.4)
Hispanic	388 (7.9)
Other/unknown	539 (12.0)
Charlson–Dayo score, n (%)	
0	4038 (82.5)
1	680 (13.9)
>2	175 (3.5)
Tumor size, n (%), cm	
≤1.00	3706 (75.7)
1.01–1.99	393 (8.0)
≥2.00	794 (16.2)
Tumor differentiation, n (%)	
Well differentiated	3880 (79.3)
Moderately differentiated	540 (11.0)
Poorly/undifferentiated	473 (9.7)
Metastatic disease at diagnosis, present	392 (8.0)
Procedure type, n (%)	
No surgery	589 (12.0)
Local excision	3605 (73.7)
Proctectomy (LAR, APR, etc)	685 (14.0)
Unknown	14 (0.3)

IQR = interquartile range; LAR = low anterior resection; APR = abdominoperineal resection.

Predictors of Lymph Node Metastasis

To determine predictors of lymph node metastasis, a subset analysis was performed including the cohort of patients who underwent curative-intent resection of clinically localized tumors, with lymph nodes sampled, and who did not have distant metastatic disease. Among 341 patients, 187 (54.8%) had positive lymph nodes. On univariate analysis, both increasing tumor size ($p < 0.0001$) and poorer differentiation ($p < 0.005$) were associated with increased rate of lymph node positivity. On multivariate analysis, size was the only predictor of lymph node metastasis; tumor size of 1.00 to 1.99 cm (OR = 5.1 (95% CI, 2.4–11.0); $p < 0.005$) and ≥2.00 cm (OR = 4.9 (95% CI, 2.6–9.1); $p < 0.005$) were both predictive (Table 3). Cut point analysis identified an increased risk of lymph node metastasis for tumors >1.5 cm (sensitivity = 82%, specificity = 51%), with 29.7% of patients below this size having positive lymph nodes, and 67.0% of patients with positive lymph nodes above this cut point.

Predictors of Distant Metastasis

Examining the entire cohort of patients, univariate analysis identified associations among patient age, male sex, tumor size, worsening differentiation, and distant metastatic disease at time of diagnosis. On multivariable analysis, male sex (OR = 1.4 (95% CI, 1.1–1.8); $p < 0.05$), size 1.01 to 1.99 cm (OR = 16.6 (95% CI, 8.9–30.9); $p < 0.005$), size >2.00 cm (OR = 77.7 (95% CI, 45.1–133.9); $p < 0.005$), moderate differentiation (OR = 2.05 (95% CI, 1.4–3.1); $p < 0.005$), and poor differentiation (OR = 5.0 (95% CI, 3.6–7.0); $p < 0.005$) were associated with distant metastatic disease (Table 4).

Evidence of effect modification of tumor differentiation on the impact of tumor size on the presence of metastasis was identified ($p < 0.001$); the association between tumor size and distant metastatic disease was stronger for well-differentiated and moderately differentiated tumors (size

TABLE 2. Determinants of local excision versus proctectomy among the subset of patients who had a procedure performed

				Multivariate	
Parameter	*Local excision, n (%)*	*Proctectomy, n (%)*	*Univariate p*	*OR (95% CI)*	*p*
Age, median (IQR), y	54 (50–62)	56 (50–66)	<0.001	1.0 (1.0–1.0)	0.64
Men	1651 (53.7)	285 (49.0)	0.22		
Race					
White	1822 (51.1)	328 (56.4)	0.13		
Black	1033 (28.9)	143 (24.6)			
Hispanic	290 (8.1)	50 (8.6)			
Other	365 (10.2)	53 (9.1)			
Charlson–Dayo score					
0	2984 (83.6)	477 (82.0)	0.48		
1	476 (13.3)	85 (14.6)			
2	73 (2.1)	16 (2.8)			
≥3	36 (1.0)	4 (0.7)			
Facility location					
Northeast	760 (23.3)	138 (15.1)	0.08		
South	1061 (32.4)	231 (17.8)			
Midwest	889 (27.1)	163 (15.4)			
West	567 (17.3)	106 (15.5)			
Facility type					
Academic	1408 (43.0)	232 (42.9)	0.97		
Nonacademic	1869 (57.0)	309 (57.1)			
Insurance type			0.005		
Private	2288 (64.1)	351 (60.3)			
Medicare	751 (21.0)	153 (26.3)		0.9 (0.6–1.2)	0.30
Medicaid	305 (8.6)	41 (7.0)		0.6 (0.4–0.9)	0.015
Uninsured	115 (3.2)	11 (1.9)		0.4 (0.2–0.7)	0.006
Unknown	110 (3.1)	26 (4.5)		1.7 (1.0–2.7)	0.040
Tumor differentiation			<0.001		
Well differentiated	3174 (88.9)	362 (62.2)			
Moderately differentiated	365 (10.2)	96 (16.5)		1.8 (1.4–2.4)	<0.001
Poorly differentiated	30 (0.8)	124 (21.3)		9.6 (6.0–15.4)	<0.001
Tumor size, cm			<0.001		
<1.00	3170 (88.8)	277 (47.6)			
1.00–1.99	263 (7.4)	79 (13.6)		3.2 (2.4–4.3)	<0.001
>2.00	136 (3.8)	226 (38.8)		11.5 (8.7–15.1)	<0.001

IQR = interquartile range.

treated as a continuous variable in centimeters; OR = 1.4, $p < 0.001$, for both) than for poorly differentiated tumors (OR = 1.1; $p = 0.010$). For well-differentiated tumors, the optimal cut point was 1.15 cm, which had good discriminative capacity in predicting distant metastatic disease (area under the curve = 0.88; 88% sensitive and 88% specific). Above this cut point, 79 (15.4%) of 514 patients had distant metastatic disease, with 10 (0.3%) of 3366 patients <1.15 cm having distant metastatic disease at the time of diagnosis. For moderately differentiated tumors, the optimal cut point was 1.15 cm as well (area under the curve = 0.87; 100% sensitive, 75% specific). Above this cut point, 53 (30.5%) of 174

TABLE 3. Predictors of lymph node metastasis in the cohort of patients who underwent resection procedure

				Multivariate	
Parameter	*Lymph node negative*	*Lymph node positive*	*Univariate p*	*OR (95% CI)*	*p*
Age, median (IQR), y	60 (50–69)	57 (50–67)	0.06	0.97 (0.95–0.99)	0.002
Men, n (%)	72 (46.8)	94 (50.3)	0.52		
Size, median (IQR), cm	1.35 (0.6–3.1)	3 (1.5–4.5)	<0.005		
1.00–1.99				5.1 (2.4–11.0)	<0.005
>2.00				4.9 (2.6–9.1)	<0.005
Differentiation, n (%)					
Well differentiated	86 (52.8)	77 (47.2)	<0.01		
Moderately differentiated	30 (46.2)	35 (53.9)		0.96 (0.50–1.8)	0.90
Poorly differentiated	38 (33.6)	75 (66.4)		1.66 (0.89–3.11)	0.11

IQR = interquartile range.

TABLE 4. Predictors of distant metastasis in the entire cohort

				Multivariate	
Parameter	*Nonmetastatic*	*Metastatic*	*Univariate p*	*OR (95% CI)*	*p*
Age, median (IQR), y	55 (50–63)	59 (50–70)	<0.005	1.0 (1.0-1.0)	0.077
Men	2018 (90.4)	223 (9.6)	<0.005	1.4 (1.1–1.8)	0.02
Size, median (IQR), cm	0.6 (0.4–0.9)	4.45 (2.9–6.5)	<0.005		
1.00–1.99				16.6 (8.9–30.9)	<0.005
>2.00				77.7 (45.1–133.9)	<0.005
Differentiation, n (%)					
Well differentiated	3791 (97.7)	89 (2.3)	<0.005		
Moderately differentiated	487 (90.2)	53 (9.8)		2.1 (1.4–3.1)	<0.005
Poorly differentiated	223 (47.2)	250 (52.9)		5.0 (3.6–7.0)	<0.005

IQR = interquartile range.

patients had distant metastatic disease, with 0 (0%) of 366 patients <1.15 cm having distant metastatic disease at the time of diagnosis. For poorly differentiated tumors, no optimal cut point was identified (area under the curve = 0.53).

Tumor Size and Differentiation Predict Overall Survival

Overall 5- and 10-year survival rates for patients with nonmetastatic rNETs were 89.2% (95% CI, 87.8%–90.4%) and 77.8% (95% CI, 73.6%–81.2%). In contrast, the presence of distant metastatic disease resulted in a very poor 5- and 10-year survival, at 15.4% (95% CI, 10.8%–20.6%) and 12.6% (95% CI, 8.2%–18.0%; Fig. 2).

When accounting for differentiation, the nonmetastatic well-differentiated patients had the best 5- and 10-year overall survival rates at 93.6% (95% CI, 92.4%–94.7%) and 83.0% (95% CI, 78.5%–86.7%), followed by moderately differentiated patients at 88.7% (95% CI, 83.5%–92.3%) and 69.9% (95% CI, 52.6%–81.8%). Poorly differentiated patients had the poorest 5- and 10- year survival rates, at 28.6% (95% CI, 21.9%–35.5%) and 21.3% (95% CI, 14.6%–28.8%).

Among patients with nonmetastatic well- and moderately differentiated tumors, a 1-cm size cutoff correlated with overall survival. Well-differentiated tumors <1 cm had a 5-year survival of 94.5% (95% CI, 93.1%–95.5%). In patients with tumors ≥1 cm, this decreased to 89.0% (95% CI, 84.1%–92.5%). Among patients with moderately differentiated tumors <1 cm, 5-year survival was 93.7% (95% CI, 88.1%–96. 7%). In patients with tumors ≥1 cm, this decreased to 78.4% (95% CI, 66.7%–86.4%; Fig. 3).

DISCUSSION

The present study, from a large national cohort, affirms that tumors >1.5 cm are more likely to metastasize to regional nodes, and less-differentiated and larger tumors are more likely to be associated with distant metastatic disease. Notably, the notion that 2 cm is a meaningful threshold

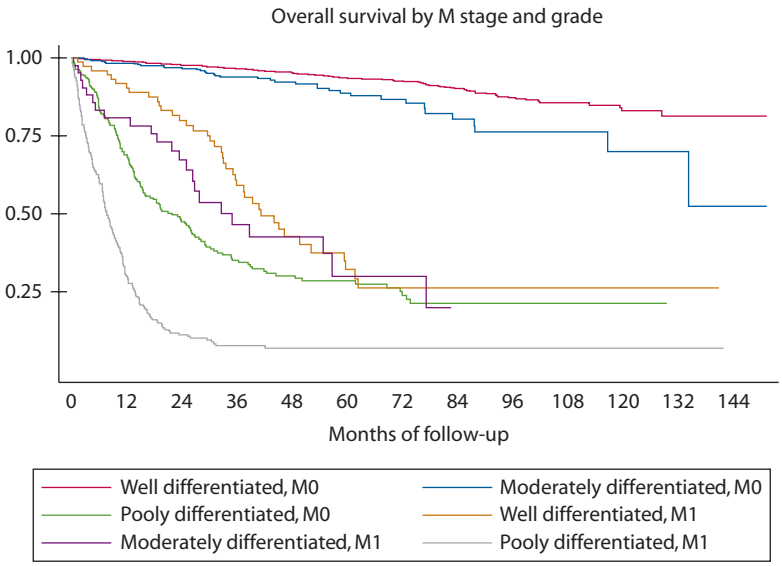

FIGURE 2. Kaplan–Meier survival analysis of metastatic (n = 392) and nonmetastatic disease (n = 4501) demonstrates extremely poor survival in the subset of metastatic patients.

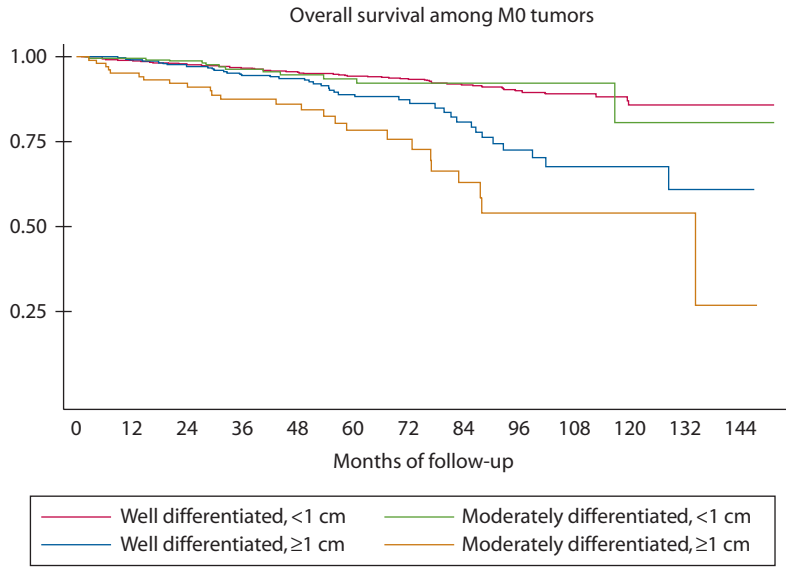

FIGURE 3. Kaplan–Meier survival analysis of well- and moderately differentiated tumors above and below 1 cm, demonstrating significantly decreased survival for both groups in larger tumors ($p < 0.001$).

above which risk of distant metastatic disease is substantial is not corroborated; a 1.15-cm cut point appears to be more relevant.

There are conflicting data and guidelines regarding the management of well-differentiated tumors. The North American Neuroendocrine Tumors Society guidelines conclude that tumors <2 cm and confined to the mucosa or submucosa are associated with very little risk of local and metastatic spread, and metastatic screening or follow-up are not recommended after local resection.[7] In contrast, the National Comprehensive Cancer Network guidelines suggest that all patients be screened with colonoscopy plus either abdominal/pelvic CT/MRI and endorectal ultrasound or endoscopic ultrasound. In addition, for lesions ≤2 cm, the National Comprehensive Cancer Network suggests transanal excision if possible, with no follow-up for lesions <1 cm, and follow-up at 6 and 12 months for local recurrence with rectal MRI or endoscopic ultrasound for lesions between 1 and 2 cm.[17] In practice, most lesions <2 cm are endoscopically resected without lymph node harvest.[18]

Although the North American societies suggest that patients with well-differentiated tumors between 1.0 and 2.0 cm are at low risk of metastasis, several retrospective North American studies have suggested a substantial risk of regional or distant metastatic disease with tumors between 1.1 and 1.9 cm.[18,19] In addition, literature from Japan suggests that such patients are at high risk of regional and distant spread and should be treated more aggressively. One large series demonstrated a 30% risk of lymph node metastasis for tumors 1 to 2 cm.[20] This prompted Fujimoto et al[21] to advocate for mesorectal excision in all patients with tumors >1 cm, ultimately reporting positive lymph node metastasis in 8 of 9 patients in a small series. These findings may reflect a difference in biology, however, because Mani et al[22] reported a 10% to 15% rate of lymphatic spread with tumors between 1.0 and 1.9 cm in a series of American patients. Both Japanese and American series demonstrate excellent survival in patients with tumors <1 cm after proctectomy, with 5-year survival approaching 100%.[23]

Importantly, tumor differentiation or grade also has a substantial impact on risk of progression, as acknowledged in the World Health Organization classification scheme for staging of rNET,[7] as well as a risk stratification score developed by Konishi et al.[24] The present series affirms the predictive capacity of tumor differentiation, both for regional and distant dissemination; it is a univariate predictor of lymph node metastasis and part of a multivariate predictive model of distant metastatic disease. Size cut points for the prediction of distant metastatic disease appear to be most relevant with well-differentiated and moderately differentiated tumors but do not have a discriminatory capacity for poorly differentiated tumors. In patients with poorly differentiated tumors, no receiver operator curve could be identified creating a clinical useful cut point, with acceptable sensitivity and specificity, reflecting the extremely high rates of locoregional spread (75/113) and distant spread (250/473).

There are several important limitations of the present study that bear emphasis. In 2010 the World Health Organization classification shifted from tumor differentiation, which was a more subjective measure reflecting cell morphology, growth patterns, and tumor circumscription, to tumor grade, based on Ki-67 and mitoses per high-powered field.[25] The NCDB only reports the differentiation of

tumors, not the Ki-67 or mitotic indices, and the present analyses, which depend on differentiation, may be less reproducible or generalizable. In addition, the NCDB, as designed, captures malignancies only at Commission on Cancer–accredited facilities. As such, the patients in this database are a selected population, possibly with more aggressive tumors, justifying referral to a center with expertise. Risk of regional and distant metastasis for smaller-sized tumors may, therefore, be overestimated. The potential for referral bias may be greatest in analyses of patients referred for proctectomy where uncaptured clinical factors may have suggested aggressive tumor biology and driven the surgical approach.

Several more general limitations inherent to retrospective database analyses may have influenced the findings of this study as well. Despite efforts to ensure data quality and accuracy, retrospective registry data is subject to omitted entries and coding inconsistency. Disease-specific survival could not be ascertained, and overall survival is an imperfect surrogate. In addition, although collected, the NCDB does not report information regarding the development of local or distant metastatic disease after the time of diagnosis, limiting conclusions regarding the ultimate risk of metastatic disease in at-risk individuals. In particular, this limited the ability to investigate the risk of developing locoregional disease, because only lymph node metastasis at the time of diagnosis in patients selected to undergo resection procedure could be ascertained.

Despite these limitations, the present study indicates that well- and moderately differentiated tumors >1.15 cm in diameter are associated with an increased risk of distant metastatic disease. More extensive staging is likely justified in patients with such tumors. Use of 68-Gallium Dotatate scans, which have high sensitivity for metastatic disease, and other emerging imaging techniques in neuroendocrine tumors may be of value in this setting.[26,27] Additional studies are needed to determine whether patients with 1- to 2-cm tumors benefit from more aggressive surgical approaches.

REFERENCES

1. Tsikitis VL, Wertheim BC, Guerrero MA. Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: a SEER analysis. *J Cancer*. 2012;3:292–302.
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003;97:934–959.
3. Wang AY, Ahmad NA. Rectal carcinoids. *Curr Opin Gastroenterol*. 2006;22:529–535.
4. Scherübl H. Rectal carcinoids are on the rise: early detection by screening endoscopy. *Endoscopy*. 2009;41:162–165.
5. 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;26:3063–3072.
6. Kwak MS, Chung SJ, Yang JI, et al. Long-term outcome of small, incidentally detected rectal neuroendocrine tumors removed by simple excisional biopsy compared with the advanced endoscopic resection during screening colonoscopy. *Dis Colon Rectum*. 2018;61:338–346.
7. Anthony LB, Strosberg JR, Klimstra DS, et al.; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. *Pancreas*. 2010;39:767–774.
8. Naunheim KS, Zeitels J, Kaplan EL, et al. Rectal carcinoid tumors: treatment and prognosis. *Surgery*. 1983;94:670–676.
9. Schindl M, Niederle B, Häfner M, et al. Stage-dependent therapy of rectal carcinoid tumors. *World J Surg*. 1998;22:628–634.
10. Weinstock B, Ward SC, Harpaz N, Warner RR, Itzkowitz S, Kim MK. Clinical and prognostic features of rectal neuroendocrine tumors. *Neuroendocrinology*. 2013;98:180–187.
11. Shebani KO, Souba WW, Finkelstein DM, et al. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. *Ann Surg*. 1999;229:815–822.
12. Fahy BN, Tang LH, Klimstra D, et al. Carcinoid of the rectum risk stratification (CaRRs): a strategy for preoperative outcome assessment. *Ann Surg Oncol*. 2007;14:1735–1743.
13. Tsang ES, McConnell YJ, Schaeffer DF, Yin Y, Speers CH, Kennecke HF. Prognostic factors for locoregional recurrence in neuroendocrine tumors of the rectum. *Dis Colon Rectum*. 2018;61:187–192.
14. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683–690.
15. World Health Organization. *International Classification of Diseases for Oncology,* 3rd edition, first revision. Geneva, Switzerland: World Health Organization; 2013.
16. Liu X. Classification accuracy and cut point selection. *Stat Med*. 2012;31:2676–2686.
17. National Comprehensive Cancer Network. Neuroendocrine tumors (version 1.2015). https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed March 2, 2018.
18. Gleeson FC, Levy MJ, Dozois EJ, Larson DW, Wong Kee Song LM, Boardman LA. Endoscopically identified well-differentiated rectal carcinoid tumors: impact of tumor size on the natural history and outcomes. *Gastrointest Endosc*. 2014;80:144–151.
19. Al Natour RH, Saund MS, Sanchez VM, et al. Tumor size and depth predict rate of lymph node metastasis in colon carcinoids and can be used to select patients for endoscopic resection. *J Gastrointest Surg*. 2012;16:595–602.
20. Konishi T, Watanabe T, Kishimoto J, Kotake K, Muto T, Nagawa H; Japanese Society for Cancer of the Colon and Rectum. Prognosis and risk factors of metastasis in colorectal carcinoids: results of a nationwide registry over 15 years. *Gut*. 2007;56:863–868.
21. Fujimoto Y, Oya M, Kuroyanagi H, et al. Lymph-node metastases in rectal carcinoids. *Langenbecks Arch Surg*. 2010;395:139–142.
22. Mani S, Modlin IM, Ballantyne G, Ahlman H, West B. Carcinoids of the rectum. *J Am Coll Surg*. 1994;179:231–248.
23. Matsuhashi N, Takahashi T, Tomita H, et al. Evaluation of treatment for rectal neuroendocrine tumors sized under 20 mm in comparison with the WHO 2010 guidelines. *Mol Clin Oncol*. 2017;7:476–480.

24. Konishi T, Watanabe T, Nagawa H, et al. Treatment of colorectal carcinoids: a new paradigm. *World J Gastrointest Surg.* 2010;2:153–156.
25. Kim JY, Hong SM. Recent updates on neuroendocrine tumors from the gastrointestinal and pancreatobiliary tracts. *Arch Pathol Lab Med.* 2016;140:437–448.
26. Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. *Am J Nucl Med Mol Imaging.* 2014;4:426–434.
27. Srirajaskanthan R, Kayani I, Quigley AM, Soh J, Caplin ME, Bomanji J. The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. *J Nucl Med.* 2010;51:875–882.