Clinical and Prognostic Features of Rectal Neuroendocrine Tumors

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Abstract

Background: Rectal neuroendocrine tumors (NETs) are among the most common NETs. The aim was to validate European Neuroendocrine Tumor Society (ENETS)/North American Neuroendocrine Tumor Society (NANETS) staging and grading systems with regard to clinical outcomes. Methods: A comprehensive database was constructed from existing databases of the Mount Sinai Division of Gastrointestinal Pathology and the Carcinoid Cancer Foundation. Analysis was performed on 141 patients identified with rectal NETs seen at Mount Sinai Hospital between 1972 and 2011. Results: The median age was 52.7 years; 43% were males. Average tumor size was 0.88 cm. NETs <1 cm accounted for 75.6% of the tumors. Stage I, II, III and IV accounted for 79.4, 2.8, 5.0 and 12.8% of the tumors, respectively. G1 tumors accounted for 88.1%, G2 8.3% and G3 3.6%. Of G1 tumors, 94.6% were stage I and 5.4% were stage IV. The median survival time for all 141 patients was 6.8 years (range, 0.8–34.7 years). The overall 5-year survival rate was 84.4%. The 5-year survival rates for patients in stages I–IV were 92.7, 75.0, 42.9 and 33.2%, respectively. The 5-year survival rates for patients with G1–G3 tumors were 87.7, 47.6 and 33.3%, respectively. Univariate analysis of increased survival showed significance for lower stage, lower grade, smaller size, absence of symptoms and endoscopically treated tumors. Multivariate analysis showed that stage alone was statistically significant as the strongest predictor of survival. Conclusion: The results of our study validated ENETS/NANETS guidelines for staging and grading of rectal NETs in the US setting of a tertiary referral center. Staging according to ENETS/NANETS guidelines should be used in the treatment algorithm rather than size alone.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) signify the majority of all NETs, traditionally referred to as carcinoid tumors. In a recent study, the rectum was the site of overall highest GEP frequency, representing 17.7% of neoplasms of all NETs and 29.0% of GEP-NETs [1]. In another recent study, rectal NETs represented 14% of GEP-NETs [2]. According to studies using the National Cancer Institute’s Surveillance, Epidemiology and End Results registry, the incidence rate of rectal NETs in the US has risen, largely due to an increased number of screening colonoscopies, allowing for identification of smaller lesions [3, 4]. This trend can be expected to
continue as colonoscopy continues to be performed in screening for colon cancer [5–7]. A large registry study by Yao et al. [8] cited 5-year overall survivals of 90 and 62% for localized and regional diseases, respectively. Although patients frequently have excellent survival, these tumors still have a risk of metastasis, mainly to the liver, for whom 5-year survival drops to 24% [8–12].

The management of rectal NETs continues to evolve. Clinicians have frequently used tumor size as a guide for further treatment. Most guidelines agree that tumors <1 cm can be appropriately treated by local excision, while tumors >2 cm generally require a more invasive surgical procedure. Endoscopic ultrasound may be used to measure tumor size and depth [13]. Some studies suggest that malignant potential increases with increased tumor size and depth [4, 14, 15].

In 2005, a multidisciplinary team of 57 NET experts developed consensus guidelines at an international conference. These were published in written form as the European Neuroendocrine Tumor Society (ENETS) Consensus Statement in 2007 [16]. From 2009 to 2010, The International Union of Cancer Control, World Health Organization and the American Joint Committee on Cancer adopted the guidelines proposed by ENETS [16–20]. In 2011, Anthony et al. [21] published the North American Neuroendocrine Tumor Society (NANETS) Consensus Guidelines based on ENETS staging guidelines (table 1) [16, 22]. Essentially, these guidelines are identical. Collectively, these studies define a system for staging and grading NETs of the rectum which characterize tumors based on their size, depth, location, and histologic morphology. For that reason, stage and grade may provide more accurate prognostic information than size alone. A retrospective multi-institution study in Berlin and France validated these criteria [23]. To our knowledge, no such review has been done in the US.

The principal aim of this study was to validate these guidelines in a cohort of patients with rectal NETs seen at a tertiary referral center. A secondary aim was to identify prognostic factors associated with metastatic disease.

**Methods**

**Data Collection**

This research was approved by the Institutional Review Board at Mount Sinai Hospital in New York, N.Y. We performed a retrospective chart review of 141 patients with a confirmed histopathological and immunohistochemical staining diagnosis of primary rectal NET. Cases were identified by querying existing databases. The Mount Sinai Gastrointestinal Pathology Database is a prospectively maintained database containing pathology records from patients seen at Mount Sinai Hospital. The Carcinoid Cancer Foundation Database has clinicopathological information on over 2,000 patients with NETs. Individual patient records were reviewed to ascertain any other information not available in the database. The data gathered on each patient included demographics, symptoms at presentation, size of tumor, depth of invasion, diagnostic method, treatment method, pathological stains and margins, and follow-up information. Overall survival information was ascertained using medical records and the Social Security Death Index.

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**Table 1. NANETS tumor and stage guidelines**

<table>
<thead>
<tr>
<th>TNM staging</th>
<th>Tumor staging</th>
<th>Stage</th>
<th>T stage</th>
<th>N stage</th>
<th>M stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td>0</td>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>I</td>
<td>T1a or T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa and size 2 cm or less</td>
<td>IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor size &lt;1 cm in greatest dimension</td>
<td>IIIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor size 1–2 cm in greatest dimension</td>
<td>IIIA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria or size &gt;2 cm with invasion of lamina propria or submucosa</td>
<td>IIIB</td>
<td>any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues</td>
<td>IV</td>
<td>any T</td>
<td>any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor grading</th>
<th>Grade</th>
<th>Mitotic rate per 10 high-power fields</th>
<th>Ki67 index, %</th>
</tr>
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<tbody>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>&lt;3</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>2–20</td>
<td>3–20</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
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</table>
Patient and Tumor Characteristics
Clinicopathologic characteristics were studied and divided into subgroups. Symptoms at presentation were categorized based on chief complaint. In asymptomatic patients undergoing age-appropriate screening colonoscopies, NETs were characterized as incidental findings.

Local treatments included colonoscopy or sigmoidoscopy with biopsy or snare polypectomy, and transanal excision. Regional treatments included surgical approaches such as low anterior resection, abdominoperineal resection, proctocolectomy.

Tumor-node-metastasis (TNM) staging (table 1) was performed in accordance with the established guidelines [16, 19, 24]. Tumors were graded G1, G2, or G3 (table 1) using mitotic rate and Ki67 in accordance with ENETS, NANETS, and American Joint Committee on Cancer guidelines [16, 18, 19, 21, 22]. Slides were retrieved whenever possible (n = 84) from the archives and graded by a single pathologist (S.C.W.). Grade was determined by mitotic rate and Ki67; staining for chromogranin A and synaptophysin was performed on diagnosis.

Overall survival was calculated based on the Social Security Death Index.

Statistical Analysis
Statistical analysis was performed using SPSS (release 18.0.0, PASW Statistics 18, Polar Engineering and Consulting). Comparison of means between paired groups was done using the independent-sample t test. The cutoff for p value significance was p < 0.05. Univariate and multivariate analysis was performed. Kaplan-Meier curves were constructed and log-rank testing was used to assess survival differences between groups.

Results
Patient and Tumor Characteristics
We identified 141 patients with rectal NETs. Table 2 presents the demographic and clinicopathologic characteristics of these patients. The median age of patients with primary rectal NET was 52.7 years (range 13–88; table 2), and 43.3% (n = 61) were male. Of the patients for whom racial data were available, 63.8% (n = 44) were Caucasian, 13.0% (n = 9) were Asian, 11.6% (n = 8) were African-American, and 11.6% (n = 8) were Hispanic.

The average size of primary NET was 0.88 cm. A total of 99 (75.6%) rectal NETs were <1 cm, 14 (10.8%) were 1–2 cm and 18 (13.8%) were >2 cm. There were three NETs staged as pT1a (<1 cm) but were excluded from size analysis because the exact size of tumor was not available.

pT1a NETs accounted for 102 (76.1%) of the tumors, all of which were found to have no nodal or distant metastases. Stage I, II, III and IV accounted for 79.4, 2.8, 5.0 and 12.8% of the tumors (n = 112, 4, 7 and 18), respectively. Grading was available in 84 (59.5%) tumors. G1 tumors accounted for 88.1%, G2 8.3%, and G3 3.6% (n = 74, 7 and 3). Of G1 tumors, 70 (94.6%) were stage I and 4 (5.4%) were stage IV. There were 57 patients for whom grading could not be done due to unavailability of original slides.

There were 123 patients with nonmetastatic disease and 18 patients with metastatic disease (table 3). Of the 18 metastatic tumors, the average size was 2.6 cm. This result was significantly larger than the 0.7 cm for nonmetastatic tumors (p < 0.001).
Clinical Presentation and Treatment

Of the 141 patients, 98 (69.5%) presented incidentally on screening colonoscopy. Other clinical presentations included change in bowel habits (n = 18, 12.8%), rectal bleeding (n = 9, 6.4%), abdominal/rectal pain (n = 7, 5.0%), unexplained weight loss (n = 3, 2.1%), and other (n = 6, 4.2%). Of the 123 patients with nonmetastatic disease, 94 (76.4%) presented without symptoms. Significantly fewer patients with metastatic disease, only 4 of 18 (22.2%), were asymptomatic (p < 0.001).

Treatments were categorized as endoscopy, transanal excision, or open surgery (table 4). There were 11 patients for whom no treatment data were available. Local treatments included endoscopic or transanal excision and accounted for 79.2% (n = 103) of the cases. Within this group, 80.6% (n = 83) were treated endoscopically, and 19.4% (n = 20) were treated by transanal excision. The regional treatment group included more invasive surgical procedures and accounted for 20.8% (n = 27) of treatments. When comparing patients with metastatic NETs with patients with nonmetastatic disease, significantly fewer metastatic patients received endoscopic treatment (p = 0.006). Only 28.6% (n = 5) of metastatic tumors were treated endoscopically, while 64.2% (n = 79) of nonmetastatic tumors were treated endoscopically.

Survival Analysis

The median survival time for all 141 patients was 6.8 years (range, 0.8–34.7 years). The overall 5-year survival rate was 84.4% (fig. 1a). The 5-year survival rates for patients in stages I, II, III and IV were 92.7, 75.0, 42.9 and 33.2%, respectively. Kaplan-Meier analysis showed a significant difference in survival according to tumor stage when comparing stage I with stage II tumors (p < 0.001; fig. 1b). Analysis between stage II, III and IV tumors showed no statistical difference in survival (n = 29).

Lower tumor grade was also predictive of improved survival as compared to higher tumor grade (fig. 1c). The 5-year survival rates for patients with G1, G2 and G3 tumors were 87.7, 47.6 and 33.3%, respectively. Kaplan-Meier analysis and Cox regression showed significant difference between low-grade and either medium- or high-grade tumors (p = 0.004; fig. 1c).

Univariate analysis showed significance for stage, grade, size, symptoms and treatment modality (table 5). Multivariate analysis showed that stage alone was statistically significant as the strongest predictor of survival. Estimated cumulative survival was greatest for stage 1 tumors (table 6).

log-rank analysis also showed significant differences between size grouping <1 cm and >1 cm (p < 0.001; fig. 2), but failed to show a difference between groups 1–2 cm and ≥2 cm. There was a significant difference in overall survival according to tumor grade (p < 0.001; fig. 1c).

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survival time between patients with metastatic tumors and nonmetastatic tumors (average 3.4 vs. 7.9 years, respectively, p < 0.001).

Kaplan-Meier curves were also generated to look for differences in survival between diagnostic modality groups. Patients who presented without symptoms had a significantly greater overall survival (p < 0.001). Additionally, survival time between treatment groups showed significantly greater survival in patients who were treated endoscopically, with average survival being 8.5 versus 5.9 years (p < 0.001).

**Table 5.** Univariable and multivariable analysis

<table>
<thead>
<tr>
<th></th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>odds ratio 95% CI</td>
<td>odds ratio 95% CI</td>
</tr>
<tr>
<td>Stage</td>
<td>2.543 (2.27 to 2.81)</td>
<td>2.478 (2.06 to 2.89)</td>
</tr>
<tr>
<td>Grade</td>
<td>5.992 (5.22 to 6.76)</td>
<td>0.902 (0.44 to 1.35)</td>
</tr>
<tr>
<td>Size</td>
<td>1.448 (1.23 to 1.67)</td>
<td>0.855 (0.53 to 1.17)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>3.215 (2.54 to 3.89)</td>
<td>1.207 (0.33 to 2.08)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>0.269 (−0.45 to 0.99)</td>
<td>0.615 (−0.25 to 1.48)</td>
</tr>
</tbody>
</table>

**Fig. 1.** Kaplan-Meier analysis of survival. 

- **a** Overall survival of all patients with 5-year survival rate was 84.4%.
- **b** Overall survival by tumor stage. Patients with stage I disease had greater survival than patients with stages II–IV (p < 0.001).
- **c** Overall survival by tumor grade. Patients with grade I disease had greater survival than patients with grades II–III (p = 0.004).
Discussion

Rectal NETs have rapidly increased in incidence, with more than 10-fold rise in the last 30 years [1]. The staging and grading guidelines set by NET societies have not yet been validated in a US tertiary care population. This study represents the first known US validation of the ENETS/NANETS guidelines for rectal NETs. Overall, 5-year survival rate was 84.4%, consistent with 88% cited by NET societies and review articles [1, 8, 11, 14, 25]. In our study using these criteria, tumor stage and grade accurately predicted clinical outcome and survival, with advanced stage and grade associated with worse outcomes in agreement with the confirmatory European study by Jann et al. [23].

Multivariate analysis showed stage to be the strongest predictor of survival. Stage I, II, III and IV tumors accounted for 79.4, 2.8, 5.0 and 12.8%, respectively. The 5-year survival rates for patients in stages I, II, III and IV were 92.7, 75.0, 42.9 and 33.2%, respectively. Stage I showed statistically significant increase in survival over stage II. It was also significant when compared to stages III and IV. There was no statistical difference in survival between tumors staged II–IV despite an apparent separation in survival curves. There appeared to be trends towards poorer survival for more advanced stage tumors, but this was not statistically significant because of the small number of events.

G1 tumors accounted for 88.1%, G2 8.3% and G3 3.6%. The 5-year survival rates for patients with G1, G2 and G3 tumors were 87.7, 47.6 and 33.3%, respectively. In agreement with the consensus guidelines, we found that lower-grade tumors were associated with improved survival as compared to higher-grade tumors. We did not find statistically significant differences in survival between G2 and G3 tumors; this likely reflects the small numbers of G2 and G3 tumors (only 10 tumors in all).

In our study, treatment modality was associated with tumor stage. Stage IV tumors were less frequently treated endoscopically and required more invasive procedures to treat the primary tumor, consistent with ENETS and NANETS staging and treatment recommendations [21, 22]. Evolving therapies using endoscopic resection and submucosal dissection are treatments reserved for more limited disease and have proven to be effective when warranted [26–29]. The main limiting factor in treatment of localized disease is tumor depth. Positive deep margins on endoscopic biopsy require more invasive treatment.
Not surprisingly, those patients treated with surgery showed significantly worse survival as this patient population reflected more advanced stage (fig. 3).

This study showed that increased tumor size was associated with metastatic disease; the majority (n = 11, 61%) of tumors >2 cm demonstrated evidence of distant metastases. Importantly, there is still a small risk of metastasis for NETs <1 cm. In this study, only 1 of 99 NETs <1 cm had metastasized (1.0%), though figures ranging from 1.7 to 3.4% have been cited in other studies [12, 30, 31]. This is a small but real risk. Stage IV tumors were also associated with symptomatic presentation at diagnosis.

NETs found on screening colonoscopy were often small and endoscopically resectable. Patients with these tumors had early stage disease and better survival. Still, as screening sigmoidoscopy or colonoscopy becomes more prevalent, these early-stage tumors will likely be more commonly detected as has been suggested by Scherübl [3]. Noninvasive treatment with endoscopy will continue to be a useful treatment for this group of patients. Future studies should address the follow-up necessary for these early-stage patients.

One limitation of this study is the databases included patients treated over nearly 4 decades from 1972 to 2011. In this time, practice patterns have changed. Endoscopic modalities and treatments have become increasingly sophisticated. Endoscopic therapy in our study was largely endoscopic polypectomy or biopsy. Several recent studies have demonstrated the utility of endoscopic mucosal resection and even endoscopic submucosal dissection [26–28, 32]. Results remain divided as to which endoscopic modality might have the best outcomes, with endoscopic mucosal resection having shorter procedure time and endoscopic submucosal dissection having a higher rate of complete resection [26]. In addition, transanal endoscopic microsurgery has only recently become available as a less invasive surgical procedure with high rates of complete resection [33]. Now, localized disease can be treated by transanal procedures that used to require an open surgical approach. Another limitation to the study is that cause of death was not available for deceased patients. This prevents the assessment of disease-specific survival in this population. Additionally, small sample size with lack of events prevented statistically significant outcomes between stage II–IV disease.

Conclusions

The results of our study validated ENETS/NANETS guidelines for staging and grading of rectal NETs in the US setting of a tertiary referral center. Staging according to ENETS/NANETS guidelines should be used in the treatment algorithm rather than size alone. Additionally, clinicians should be more suspicious of advanced disease if the patient presents symptomatically, in which case tumor grading and special staining can be considered.

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References

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