Clinical and Prognostic Features of Rectal Neuroendocrine Tumors

Brett Weinstock^a Stephen C. Ward^b Noam Harpaz^b Richard R.P. Warner^a
Steven Itzkowitz^a Michelle Kang Kim^a

^aDivision of Gastroenterology, Department of Medicine, and ^bDepartment of Pathology, Mount Sinai School of Medicine, New York, N.Y., USA

Key Words

Rectal neuroendocrine tumors · Carcinoids · Stage · Grade · Size · Prognosis · Survival

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.

© 2013 S. Karger AG, Basel

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

Table 1. NANETS tumor and stage guidelines

TNM staging			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor invades lamina propria or submucosa and size 2 cm or less		
T1a	Tumor size <1 cm in greatest dimension		
T1b	Tumor size 1–2 cm in greatest dimension		
T2	Tumor invades muscularis propria or size >2 cm with invasion of lamina propria or submucosa		
T3	Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues		
T4	Tumor invades peritoneum or other organs; for any T, add (m) for multiple tumors		
N0	No nodal involvement		
N1	Nodal involvement		
M0	No metastatic disease		
M1	Metastatic disease		

Tumor staging			
Stage	T stage	N stage	M stage
0	T0	N0	M0
I	T1a or T1b	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	any T	N1	M0
IV	any T	any N	M1

Tumor grading		
Grade	Mitotic rate per 10 high-power fields	Ki67 index, %
G1	<2	<3
G2	2–20	3–20
G3	>20	>20

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.

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 =

Table 2. Clinicopathological characteristics of 141 patients with rectal NETs

Median age, years	52.7 (13–88)
Sex	
Male	61 (43.3)
Female	80 (56.7)
Primary symptom	
Incidental finding	98 (69.5)
Change in bowel habits	18 (12.8)
Rectal bleeding	9 (6.4)
Abdominal/rectal pain	7 (5.0)
Tumor size	
Mean, cm	0.88 (0–5.3)
<1.0 cm	99 (75.6)
1.0–2.0 cm	14 (10.8)
≥2 cm	18 (13.8)
T classification	
Tx	7
T1a	102 (75.6)
T1b	10 (7.4)
T2	4 (3.0)
T3	12 (8.9)
T4	7 (5.2)
Nodal involvement	
Nx	2
N0	120 (86.3)
N1	19 (13.7)
Distant metastasis	
M0	123 (87.2)
M1	18 (12.8)
Stage	
I	112 (79.4)
II	4 (2.8)
III	7 (5.0)
IV	18 (12.8)
Grade	
G1	74 (88.1)
G2	7 (8.3)
G3	3 (3.6)
Not available	57

Figures in parentheses indicate percentage or range.

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 non-metastatic tumors ($p < 0.001$).

Table 3. Comparison of characteristics of nonmetastatic NETs (n = 123) and metastatic NETs (n = 18)

	Non-metastatic tumors (M0)	Distant metastatic tumors (M1)	p value
Mean age, years	52.6	56.2	0.292
Mean tumor size, cm	0.7	2.6	<0.001
Symptoms at diagnosis	23.6%	77.8%	<0.001
Endoscopic treatment	64.2%	28.6%	0.006
Survival			
5-year survival	87.6%	25.2%	<0.001
Total survival to date, years	7.6	5.3	<0.001

Table 4. Clinical characteristics by treatment types

	Endoscopy (n = 83)	Transanal resection (n = 20)	Surgery (n = 27)	p value
Age				
≤60 years	64 (77%)	14 (70%)	17 (63%)	0.335
>60 years	19 (23%)	6 (30%)	10 (37%)	
Sex				
Male	49 (59%)	12 (60%)	12 (44%)	0.386
Female	34 (41%)	8 (40%)	15 (56%)	
Tumor size				
<1.0 cm	67 (81%)	13 (68%)	12 (44%)	0.003
1–2 cm	6 (7%)	3 (16%)	3 (11%)	
≥2 cm	10 (12%)	3 (16%)	12 (44%)	
T classification				
T1a	73 (90%)	12 (67%)	10 (37%)	<0.001
T1b	5 (6%)	2 (11%)	2 (7%)	
T2	0 (0%)	2 (11%)	2 (7%)	
T3	2 (2%)	1 (6%)	9 (33%)	
T4	1 (1%)	1 (6%)	4 (15%)	
Nodal involvement				
N0	79 (96%)	18 (90%)	14 (52%)	<0.001
N1	3 (4%)	2 (10%)	13 (48%)	
Distant metastasis				
M0	79 (95%)	16 (80%)	20 (74%)	0.005
M1	4 (5%)	4 (20%)	7 (26%)	
Grade				
G1	48 (96%)	10 (91%)	9 (60%)	0.002
G2	1 (2%)	1 (9%)	4 (33%)	
G3	1 (2%)	0 (0%)	2 (13%)	

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

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 ($p = 0.004$).

Table 5. Univariable and multivariable analysis

	Univariable analysis		Multivariable analysis	
	odds ratio	95% confidence interval	odds ratio	95% confidence interval
Stage	2.543	2.27 to 2.81	2.478	2.06 to 2.89
Grade	5.992	5.22 to 6.76	0.902	0.44 to 1.35
Size	1.448	1.23 to 1.67	0.855	0.53 to 1.17
Symptoms	3.215	2.54 to 3.89	1.207	0.33 to 2.08
Endoscopy	0.269	−0.45 to 0.99	0.615	−0.25 to 1.48

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 6. Survival characteristics of rectal NETs by stage and grade

	1-year survival, %	3-year survival, %	5-year survival, %	Estimated cumulative survival, years	Standard deviation, years
Overall survival	97.2	89.6	84.4	21.7	2.9
Stage 1	100.0	97.2	92.7	25.8	3.5
Stage 2	75.0	75.0	75.0	5.5	1.9
Stage 3	71.4	57.1	42.9	5.8	1.8
Stage 4	94.4	56.9	33.2	4.0	0.7
Grade G1	97.3	92.8	87.7	14.1	0.7
Grade G2	85.7	71.4	47.6	6.4	1.8
Grade G3	100.0	66.7	33.3	4.0	0.8

Fig. 2. Kaplan-Meier curve of overall survival by tumor size. Patients with tumors <1 cm had greater survival than patients with tumors ≥1 cm ($p < 0.001$).

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.

Fig. 3. Kaplan-Meier curve of overall survival by treatment group. Patients who received endoscopic treatment had greater survival than patients treated by transanal excision or surgery ($p < 0.001$).

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.

Acknowledgements

The authors of this paper would like to formally acknowledge the assistance of the Carcinoid Cancer Foundation (CCF) for access to the CCF database.

References

- 1 Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM: The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011;40:1,18, vii.
- 2 Niederle MB, Hackl M, Kaserer K, Niederle B: Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society Classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer* 2010;17:909–918.

- 3 Scherübl H: Rectal carcinoids are on the rise: early detection by screening endoscopy. *Endoscopy* 2009;41:162–165.
- 4 Shields CJ, Tired E, Winter DC, International Rectal Carcinoid Study Group: Carcinoid tumors of the rectum: a multi-institutional international collaboration. *Ann Surg* 2010;252:750–755.
- 5 Yoon SN, Yu CS, Shin US, Kim CW, Lim SB, Kim JC: Clinicopathological characteristics of rectal carcinoids. *Int J Colorectal Dis* 2010;25:1087–1092.
- 6 Pinchot SN, Holen K, Sippel RS, Chen H: Carcinoid tumors. *Oncologist* 2008;13:1255–1269.
- 7 Chung TP, Hunt SR: Carcinoid and neuroendocrine tumors of the colon and rectum. *Clin Colon Rectal Surg* 2006;19:45–48.
- 8 Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB: 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.
- 9 Modlin IM, Sandor A: An analysis of 8305 cases of carcinoid tumors. *Cancer* 1997;79:813–829.
- 10 Modlin IM, Lye KD, Kidd M: A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003;97:934–959.
- 11 Godwin JD 2nd: Carcinoid tumors. An analysis of 2837 cases. *Cancer* 1975;36:560–569.
- 12 Landry CS, Brock G, Scoggins CR, McMasters KM, Martin RC 2nd: A proposed staging system for rectal carcinoid tumors based on an analysis of 4701 patients. *Surgery* 2008;144:460–466.
- 13 Shebani KO, Souba WW, Finkelstein DM, Stark PC, Elgadi KM, Tanabe KK, OTT MJ: Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. *Ann Surg* 1999;229:815.
- 14 Konishi T, Watanabe T, Muto T, Kotake K, Nagawa H: Site distribution of gastrointestinal carcinoids differs between races. *Gut* 2006;55:1051–1052.
- 15 Sauven P, Ridge JA, Quan SH, Sigurdson ER: Anorectal carcinoid tumors. Is aggressive surgery warranted? *Ann Surg* 1990;211:67–71.
- 16 Rindi G, Kloppel G, Couvelard A, Komminoth P, Korner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B: TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007;451:757–762.
- 17 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A: AJCC (American Joint Committee on Cancer) Cancer Staging Manual, ed 7. New York, Springer, 2010, p 181.
- 18 Bosman FT, Carneiro F, Hruban RH, Theise ND (eds): WHO Classification of Tumours of the Digestive System, ed 4. Geneva, WHO, 2010.
- 19 Sobin LH, Gospodarowicz MK, Wittekind C, International Union against Cancer: TNM Classification of Malignant Tumours, ed 7. Hoboken, Wiley-Blackwell, 2009.
- 20 Konishi T, Watanabe T, Nagawa H, Oya M, Ueno M, Kuroyanagi H, Fujimoto Y, Yamaguchi T, Muto T: Treatment of colorectal carcinoids: a new paradigm. *World J Gastrointest Surg* 2010;2:153–156.
- 21 Anthony LB, Strosberg JR, Klimstra DS, Mables WJ, O’Dorisio TM, Warner RR, Wiseman GA, Benson AB 3rd, Pommier RF: 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.
- 22 Caplin M, Sundin A, Nillson O, Baum RP, Klose KJ, Kelestimur F, Plockinger U, Papotti M, Salazar R, Pascher A: ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: colorectal neuroendocrine neoplasms. *Neuroendocrinology* 2012;95:88–97.
- 23 Jann H, Roll S, Couvelard A, Hentic O, Pavel M, Muller-Nordhorn J, Koch M, Rocken C, Rindi G, Ruszniewski P, Wiedenmann B, Pape UF: Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *BMC Cancer* 2011;117:3332–3341.
- 24 Bernick PE, Klimstra DS, Shia J, Minsky B, Saltz L, Shi W, Thaler H, Guillem J, Paty P, Cohen AM, Wong WD: Neuroendocrine carcinomas of the colon and rectum. *Dis Colon Rectum* 2004;47:163–169.
- 25 Koura AN, Giacco GG, Curley SA, Skibber JM, Feig BW, Ellis LM: Carcinoid tumors of the rectum: effect of size, histopathology, and surgical treatment on metastasis free survival. *Cancer* 1997;79:1294–1298.
- 26 Zhong DD, Shao LM, Cai JT: Endoscopic mucosal resection (EMR) versus endoscopic submucosal dissection (ESD) for rectal carcinoid tumours: a systematic review and meta-analysis. *Colorectal Dis* 2013;15:283–291.
- 27 Jeon SM, Lee JH, Hong SP, Kim TI, Kim WH, Cheon JH: Feasibility of salvage endoscopic mucosal resection by using a cap for remnant rectal carcinoids after primary EMR. *Gastrointest Endosc* 2011;73:1009–1014.
- 28 Choi CW, Kang DH, Kim HW, Park SB, Jo WS, Song GA, Cho M: Comparison of endoscopic resection therapies for rectal carcinoid tumor: endoscopic submucosal dissection versus endoscopic mucosal resection using band ligation. *J Clin Gastroenterol* 2013;47:432–436.
- 29 Lee WH, Kim SW, Lim CH, Kim JS, Cho YK, Lee IS, et al: Efficacy of endoscopic mucosal resection using a dual-channel endoscope compared with endoscopic submucosal dissection in the treatment of rectal neuroendocrine tumors. *Surg Endosc* 2013, E-pub ahead of print.
- 30 Christensen M, Bulow S: Carcinoid tumors of the colon and rectum. *Ugeskr Laeger* 1998;160:4605–4609.
- 31 Kulke MH, Mayer RJ: Carcinoid tumors. *N Engl J Med* 1999;340:858–868.
- 32 Kim KM, Eo SJ, Shim SG, Choi JH, Min BH, Lee JH, et al: Treatment outcomes according to endoscopic treatment modalities for rectal carcinoid tumors. *Clin Res Hepatol Gastroenterol* 2013;37:275–282.
- 33 Son HJ, Sohn DK, Hong CW, Han KS, Kim BC, Park JW, et al: Factors associated with complete local excision of small rectal carcinoid tumor. *Int J Colorectal Dis* 2013;28:57–61.