Ann Surg Oncol (2012) 19:3486–3490
DOI 10.1245/s10434-012-2442-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Surveillance of Small Rectal Carcinoid Tumors in the Absence of Metastatic Disease

Sara E. Murray, MD[1], Rebecca S. Sippel, MD, FACS[1], Ricardo Lloyd, MD, PhD[2], and Herbert Chen, MD, FACS[1]

[1]Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI; [2]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI

ABSTRACT

Background. The incidence of rectal carcinoids is rapidly increasing, typically presenting as small (<1.0 cm), localized tumors. Although the evaluation of rectal carcinoids on presentation is well standardized, surveillance after resection has not been well established.

Methods. A prospective database documented patients with rectal carcinoids at our institution between January 1995 and September 2011. Information collected included patient and tumor characteristics, treatment method, surveillance schedule, recurrence, and survival.

Results. Twenty-eight patients with rectal carcinoid were identified. Ten patients were excluded for tumors >1 cm, known metastases at presentation, <6 months follow-up, or previous resections. The mean age of the remaining patients was 56 ± 3 years, and 61 % of the patients were female. All patients were diagnosed at endoscopy, with 50 % diagnosed incidentally on screening endoscopy. Treatment methods included endoscopic therapy ($n = 13$, 72 %), transanal excision ($n = 3$, 17 %), and transanal endoscopic microsurgery ($n = 1$, 5.5 %). One patient (5.5 %) received no additional invasive therapy after diagnostic endoscopy. The mean tumor diameter was 4.6 ± 0.5 mm. The average length of follow-up was 5.4 ± 0.9 years, with a median number of 2 follow-up endoscopies (range 0–6). Two patients (11 %) died within the follow-up period from noncarcinoid causes. Importantly, no surviving patients developed local or distant recurrence with up to 12.3 years of follow-up.

Conclusions. On the basis of this experience, patients presenting with small (≤1.0 cm), nonmetastatic rectal carcinoids are unlikely to develop local or distant recurrence after resection. Aggressive surveillance with repeat endoscopies or other imaging studies after resection may be unnecessary in this patient population.

Carcinoid tumors are neuroendocrine tumors of neural crest origin and arise from enterochromaffin cells.[1,2] The overall incidence of carcinoid tumors has been increasing over the past 40 years and is now estimated to be 2.47 to 4.48 per 100,000 population per year.[3–5] The gastrointestinal tract contains the largest population of enterochromaffin cells and thus harbors most carcinoid tumors (67.5 %).[5,6] According to the latest report from the Surveillance, Epidemiology, and End Results (SEER) program, rectal carcinoid tumors account for 18.5 % of all carcinoids.[5] Although these tumors represent only 1.3 % of all rectal neoplasms, their incidence is drastically increasing. The proportion of rectal carcinoid tumors to all rectal tumors increased 248 % on comparisons between the early SEER (1973–1991) and late SEER (1992–1999) subpopulations.[4,5] The definitive cause of this increase in unknown, although contributing factors may include improved availability of screening practices, increased awareness among physicians, the aging population, or variations in the reporting of these benign-appearing carcinoid tumors in the SEER database.[7]

Rectal carcinoids typically present as small, localized tumors, with previous reports demonstrating that 60–90 % measure <1.0 cm at the time of diagnosis.[5,8–10] This presentation is thought to be due to early endoscopic detection after symptoms of hematochezia, pain, or change in bowel patterns, as well as to the low propensity of these tumors to metastasize. Tumors of this size are reported to metastasize in less than 2 % of patients.[5]

Recurrence rates of small rectal carcinoid tumors have unfortunately not been reported in large series. However,

First Received: 20 April 2012;
Published Online: 16 June 2012

H. Chen, MD, FACS
e-mail: chen@surgery.wisc.edu

multiple single-institutional studies and one multi-institutional international collaboration demonstrated rare to no local or distant recurrences after resection.[11–16] Because rectal carcinoids often present as small and localized tumors that rarely recur after resection, rectal carcinoid tumors have the best prognosis among all carcinoid tumors with a 5-year survival rate at 88.3 %.[5] Moreover, in a study with 59 patients with node-negative tumors ≤1.0 cm, the 10-year survival rate was 100 %.[16] Of note, postresection surveillance and recurrence were not quantified for these patients.

Although the evaluation of rectal carcinoids at presentation is fairly well standardized and includes assessment for local invasion and metastatic disease, the follow-up surveillance schedule after resection has not been well established. Physician practices differ on the frequency, intensity, and modality of follow-up in these patients, and no guidelines have been established in the United States. We therefore reviewed our rectal carcinoid experience with the following objectives: to determine the recurrence rate of small (≤1.0 cm), nonmetastatic rectal carcinoid tumors; to evaluate the postresection surveillance regimens used at our institution; and to assess the utility of follow-up surveillance methods in the form of endoscopies or other imaging studies after resection.

METHODS

All patients with a rectal carcinoid tumor evaluated at our institution are documented in a prospective database. The current study is an Institutional Review Board approved retrospective review of patients ($n = 28$) with rectal carcinoid tumors evaluated at our institution between January 1995 and September 2011. Exclusion criteria included tumors >1.0 cm in diameter, known metastatic disease at the time of presentation, <6 months follow-up, or previous resections (Table 1). The only patients with tumors >1.0 cm in diameter ($n = 3$) also had metastatic disease on presentation and were therefore combined into a single group in Table 1. In total, 18 patients were included in our analysis.

The database included the following information: patient demographics, medical and surgical history, clinical presentation, modality of diagnosis, tumor characteristics, status of margins, treatment method, complications, adjuvant treatment, follow-up surveillance, recurrence, and survival. Any absent data were extracted from electronic hospital medical records. Pathologic features were obtained from the pathology reports. Tumor size was reported as the largest diameter recorded by the pathologist during processing of the specimen. The tumor, node, metastasis staging system of the American Joint Committee on Cancer was used for tumor classification.[17] Tumor margins were described as either positive, negative, or deemed indeterminate if the specimen was in fragments or the status of the margin was not specified in the pathology report. Margins were considered positive if tumor was present less than 0.1 cm from cauterized edge.

TABLE 1 Patients included in analysis

Total no. of carcinoid tumors	28
Exclusion criteria	
<6-mo follow-up	5
Known metastases/tumor size >1.0 cm	3
Previous resections	2
No. of patients analyzed	18

The treating physician determined the timing and modality of surveillance after resection. The follow-up period was calculated from the date of initial tissue diagnosis on endoscopy to the most recent carcinoid-specific clinic visit or endoscopy with the treating physician. This included gastroenterologists, general surgeons, or colorectal surgeons. Length of survival was calculated from the date of initial tissue diagnosis to the most recent patient encounter in our medical record system (e.g., clinic visit, telephone encounter, laboratory visit). The day of initial tissue diagnosis was chosen as day 0 for standardization purposes. As some patients in this series did not undergo complete (R0) resections with negative margins, the "date of complete resection" could not be used as a starting date.

Follow-up endoscopies were defined as the number of endoscopies obtained either after surgical resection, or >6 months after initial tissue diagnosis in patients managed endoscopically. It was assumed that endoscopies performed >6 months after diagnosis were used for the purpose of follow-up surveillance as opposed to an intention to treat the initial tumor. Data are expressed as mean with standard error (SEM). The status of final margins was compared between surgical and nonsurgical groups by two-sided Fisher's exact test, and comparison of continuous variables was made by Student's t test, with values of $P < 0.05$ considered significant.

RESULTS

Patient Characteristics

Eighteen patients were included in this analysis, and their characteristics are displayed in Table 2. As shown, 9 patients (50 %) were diagnosed incidentally at screening endoscopy, whereas 6 (33 %) experienced hematochezia, and 4 (22 %) experienced a change in bowel pattern leading to endoscopic evaluation. All 18 patients were diagnosed at endoscopic biopsy. None of the patients had carcinoid syndrome.

TABLE 2 Patient characteristics

Characteristic	Value
Age (y)	
Mean ± SEM	56 ± 3
Range	29–82
Sex, *n* (%)	
Female	11 (61)
Male	7 (39)
Symptoms at presentation, *n* (%)	
Asymptomatic	9 (50)
Hematochezia	6 (33)
Diarrhea	2 (11)
Constipation	2 (11)

Pathologic Tumor Information

The mean tumor diameter was 4.6 ± 0.5 mm (range 2–10 mm; median 4 mm), and additional tumor features are provided in Table 3. All tumors invaded the submucosa only, without extension into the muscularis propria. Resultantly, all tumors were classified as T1a with the exception of 1 tumor categorized as T1b for a tumor diameter of 10 mm.

Immunohistochemistry staining was performed on 50 % ($n = 9$) of the tumors. Unfortunately, information on lymphovascular invasion was not consistently recorded in the pathology reports, and this information was available for only 1 patient in which lymphovascular invasion was not present.

Treatment Methods

After diagnosis, patients were managed either surgically or endoscopically (Table 4). After initial diagnostic endoscopy, all 18 patients had either positive or indeterminate margins (Table 3). The 4 patients who underwent subsequent surgical excision all had an R0 resection performed. Of the 13 patients managed endoscopically, 5 (38 %) experienced margin clearance after repeat endoscopies (median 1; range 1–5). The other 8 patients did not undergo repeat biopsy at follow-up endoscopies as a result of lack of visualization of macroscopic disease, and they were therefore considered to have had an R1 resection (Table 5). Of note, 1 patient did not undergo additional therapy after a diagnostic endoscopy demonstrating indeterminate tumor margins. The patient was lost to follow-up before the recommended repeat endoscopy could be performed. Of note, no patients in this series underwent chemotherapy or radiotherapy after resection.

TABLE 3 Pathological information

Tumor characteristic	*n* (%)
Diameter[a]	
0–5 mm	15 (83)
6–10 mm	3 (17)
Depth of invasion[b]	
T1a	17 (94.5)
T1b	1 (5.5)
Initial margins	
Positive	7 (39)
Indeterminate[c]	11 (61)

[a] Mean tumor diameter ± SEM = 4.6 ± 0.5 mm

[b] *T1* tumor invades lamina propria or submucosa and size ≤2 cm; *T1a* tumor size <1 cm; *T1b* tumor size 1–2 cm[17]

[c] The tumor specimen was either in fragments, or the status of the margin was not specified in the pathology report

TABLE 4 Treatment methods

Intervention	*n* (%)
Endoscopic management	13 (72)
Transanal excision (TAE)	3 (17)
Transanal endoscopic microsurgery (TEM)	1 (5.5)
No additional invasive therapy after diagnostic endoscopy	1 (5.5)

There was one complication in this series. The patient experienced gastrointestinal bleeding after the initial diagnostic colonoscopy and sought care at the emergency department in stable condition. A colonoscopy demonstrated no active bleeding, and the patient was managed conservatively and recovered without further intervention or complications.

Follow-up, Recurrence, and Survival

The mean carcinoid-specific follow-up of patients in this series was 5.4 ± 0.9 (range 0.8–12.3; median 4.6) years, and the median number of follow-up endoscopies was 2 (range 0–6). Comparisons in follow-up between the surgically and endoscopically managed groups are outlined in Table 5.

TABLE 5 Comparisons between surgically and endoscopically managed patients

Characteristic	Surgical management ($n = 4$)	Endoscopic management ($n = 13$)	*P*
Tumor diameter, mm, mean ± SEM	4.5 ± 1.9	4.7 ± 0.4	0.73
Margin clearance, *n* (%)	4 (100 %)	5 (38 %)	0.08
Length of follow-up, y, mean ± SEM	7.9 ± 2.4	5.0 ± 1.0	0.20
No. of follow-up endoscopies, mean (median)	3.5 (4)	2.0 (1.5)	0.17

The mean length of disease-free survival was 6.9 ± 0.8 (range 1.4–12.9) years. There were 2 patient deaths in this series at 1.4 and 8.2 years after diagnosis, respectively, although neither was carcinoid specific. Importantly, of the 16 surviving patients, there were no carcinoid recurrences with a follow-up period of up to 12.3 years.

Imaging Studies and Laboratory Values

Patients were not regularly followed with imaging studies other than endoscopy. An abdominopelvic computed tomographic (CT) scan was obtained in 6 patients (33 %); 4 (22 %) were performed as part of the diagnostic assessment, and 2 (11 %) were performed within the follow-up period to evaluate abdominal or back pain. An endorectal ultrasound (EUS) was obtained in 2 patients (11 %), whereas another 2 (11 %) underwent ^{111}In-octreotide scans, all of which were done for staging purposes at diagnosis. All preresection imaging studies were negative for lymph node or distant metastasis, and those obtained after resection were unremarkable for recurrence.

Laboratory markers (e.g. serum chromogranin A [CgA], serum acid phosphatase, 24-hour urinary 5-hydroxyindoleacetic acid [5-HIAA]) were not consistently monitored. A 5-HIAA level was measured in only 1 patient (5.5 %) as a result of persistent diarrhea 2 years after resection. An elevated level resulted in a subsequent ^{111}In-octreotide scan and abdominopelvic CT, neither of which demonstrated any evidence of recurrence. This particular patient has been followed for over 10 years and has had 4 surveillance endoscopies and 5 abdominopelvic CT scans, all negative for recurrence.

DISCUSSION

These findings suggest that patients presenting with small (≤1.0 cm) rectal carcinoid tumors in the absence of regional or distant metastases are unlikely to develop local recurrence or metastases after resection. No recurrences were observed in this cohort after a mean follow-up of 5.4 years. This finding coincides with multiple previous studies that have reported no recurrences after resection of tumors ≤1.0 cm, over a median follow-up period of up to 6.4 years and a cohort as large as 84 patients.[13–15] Alternatively, Kwaan et al. reported 2 (4 %) of 48 patients with a rectal carcinoid tumor <1.0 cm had distant metastatic recurrence discovered at 5 and 13 years after resection.[12] The initial management and follow-up surveillance of these 2 patients is unclear. The authors' concluded that their standard postresection surveillance schedule includes proctoscopy every 6 months for 2 years and then annually for 5 years after resection. They further state that patients with higher risk tumors (possessing features such as muscular, lymphovascular, or perineural invasion) should undergo additional endoscopic ultrasonography or rectal magnetic resonance imaging (MRI) in conjunction with octreotide imaging annually for 3 years. Differences in management were not stratified on the basis of tumor size.

In 2008, the European Neuroendocrine Tumor Society (ENETS) released a consensus statement on the recommended surveillance of patients after resection of carcinoid tumors of the colon and rectum.[18] They concluded that tumors <1.0 cm and without lymph node involvement required no follow-up, whereas tumors 1.0–2.0 cm should be followed if they contained adverse features such as angioinvasion, invasion into muscularis, or atypical histopathology. Tumors >2 cm always required follow-up. Specific surveillance guidelines for tumors without adverse features (i.e., low risk) include one scan (e.g., rectal EUS, colonoscopy, or MRI) or serum marker (CgA or acid phosphatase if positive before resection) within the first year. For high-risk tumors patients should have a scan or serum marker every 4–6 months in the first year and then at least annually. Follow-up is typically for 10 years, although the authors cautioned that metastatic disease can occasionally occur after this period.

There was no consistent follow-up schedule used by physicians in this study. Endoscopy was the surveillance method of choice, whereas other imaging modalities and laboratory measurements were not regularly obtained. If imaging studies were performed on a patient after resection, it was due to symptoms of abdominal or back pain. Given that no recurrences were observed in this American cohort, we concur with the ENETS guidelines that patients with tumors <1.0 cm and without regional or distant metastases are unlikely to need scheduled follow-up after rectal carcinoid resection. This includes surveillance endoscopies and other imaging studies (e.g., EUS, CT, MRI, ^{111}In-octreotide scans). We are unable to make broad recommendations on tumors 1.0 cm in diameter, as only 1 patient in our series met this criterion. However, this particular patient had negative margins achieved on transanal excision (TAE) and was closely followed with 5 repeat endoscopies over 11.3 years with no evidence of recurrence.

It is clear from our study that not all physicians felt it necessary to obtain negative margins. In our series, margin clearance was achieved in only 9 patients (50 %), including 5 (38 %) of 13 patients treated with endoscopy alone. Consequently, 9 patients (50 %) were ultimately left with a positive or indeterminate margin. Despite this, no recurrences of local or distant disease were observed. There are no large series detailing R0 versus R1 recurrences, and the necessity of achieving microscopically negative margins has been questioned in the past.[6] However, the current consensus is that resection with microscopically negative margins should be done if possible.[6,12,19] This is because

resection offers the only chance of a cure. In addition, these tumors can evolve over a long period of time, and late recurrences are difficult to capture in the literature.[12,20]

Interestingly, despite the discrepancy in final margin status between patients treated surgically versus endoscopically, there was no significant difference in the number of follow-up endoscopies after resection. Although patients who underwent TAE or transanal endoscopic microsurgery (TEM) and had margin clearance underwent a greater number of follow-up endoscopies after resection than patients who were managed endoscopically, the longer length of follow-up in the surgical group likely accounts for this difference. Additional investigation is necessary to detail any potential differences in follow-up practices between surgeons and gastroenterologists, or variations in surveillance in the setting of a negative versus positive margin.

The major limitation of this study is the retrospective method of data collection. Additionally, because the majority of carcinoid tumors were discovered incidentally, common laboratory markers (CgA, acid phosphatase, 5-HIAA) were not regularly obtained and thus were not used as a surveillance modality. Furthermore, histopathologic information (lymphovascular invasion or mitotic rate) demonstrated to affect prognosis, and theoretically, recurrence of rectal carcinoid tumors was not consistently reported. However, because none of our patients experienced disease recurrence, our inability to distinguish between aggressive and nonaggressive tumor types did not effect the conclusions of the study. Lastly, the small sample size and limited length of follow-up make it difficult to draw broad conclusions on follow-up recommendations. As mentioned previously, recurrences of small rectal carcinoids have been reported 13 years after resection, although this is exceedingly rare. The implications of these uncommon recurrences on the follow-up regimen of the entire population of patients with rectal carcinoid tumors have not been established. Further investigation with larger cohorts and longer follow-up periods is warranted to determine accurate recurrence rates of small rectal carcinoid tumors and the timing of recurrence.

To our knowledge, there has not yet been a study dedicated to establishing guidelines for surveillance of small rectal carcinoid tumors after resection in the United States, and this study highlights the need for standardization. The long-term behavior of small ($\leq$1.0 cm), nonmetastatic rectal carcinoid tumors characterized in this study suggests that recurrence after endoscopic or surgical resection is low or absent. Therefore, a risk–benefit analysis examining the need for scheduled follow-up is essential, primarily because aggressive surveillance with repeat endoscopies or other imaging studies may be unnecessary in this patient population.

REFERENCES

1. Kulchitsky N. Zur Frage über den Bau des Darmkanals. *Arch F Mikroskop Anat Bd.* 1897;49.
2. Erspamer V, Asero B. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature.* 1952;169(4306):800–1.
3. Ellis L, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol.* 2010;105:2563–9.
4. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. *Cancer.* 1997;79:813–29.
5. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer.* 2003;97:934–59.
6. Moore JR, Greenwell B, Nuckolls K, et al. Neuroendocrine tumors of the rectum: a 10-year review of management. *Am Surg.* 2011;77:198–200.
7. Pinchot SN, Holen K, Sippel RS, et al. Carcinoid tumors. *Oncologist.* 2008;13:1255–69.
8. Jetmore AB, Ray JE, Gathright JB, et al. Rectal carcinoids: the most frequent carcinoid tumor. *Dis Colon Rectum.* 1992;35:717–25.
9. Soga J. Carcinoids of the rectum: an evaluation of 1271 reported cases. *Surg Today.* 1997;27:112–9.
10. Li AF, Hsu CY, Li A, et al. A 35-year retrospective study of carcinoid tumors in Taiwan: differences in distribution with a high probability of associated second primary malignancies. *Cancer.* 2008;112:274–83.
11. Sauven P, Ridge JA, Quan SH, et al. Anorectal carcinoid tumors. Is aggressive surgery warranted? *Ann Surg.* 1990;211:67–71.
12. Kwaan MR, Goldberg JE, Bleday R. Rectal carcinoid tumors: review of results after endoscopic and surgical therapy. *Arch Surg.* 2008;143:471–5.
13. Tsai BM, Finne CO, Nordenstam JF, et al. Transanal endoscopic microsurgery resection of rectal tumors: outcomes and recommendations. *Dis Colon Rectum.* 2010;53:16–23.
14. Onozato Y, Kakizaki S, Iizuka H, et al. Endoscopic treatment of rectal carcinoid tumors. *Dis Colon Rectum.* 2010;53:169–76.
15. Yoon SN, Yu CS, Shin US, et al. Clinicopathologic characteristics of rectal carcinoids. *Int J Colorectal Dis.* 2010;25:1087–92.
16. Shields CJ, Tiret E, Winter DC, et al. Carcinoid tumors of the rectum: a multi-institutional international collaboration. *Ann Surg.* 2010;252:750–5.
17. Edge SB, Byrd DR, Compton CC, et al. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
18. Ramage JK, Goretzki PE, Manfredi R, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumours: well-differentiated colon and rectum tumour/carcinoma. *Neuroendocrinology.* 2008;87:31–9.
19. Koura AN, Giacco GG, Curley SA, et al. Carcinoid tumors of the rectum: effect of size, histopathology, and surgical treatment on metastasis free survival. *Cancer.* 1997;79:1294–8.
20. Sippel RS, Chen H. Carcinoid tumors. *Surg Oncol Clin N Am.* 2006;15:463–78.