The American Journal of Surgery (2016) 211, 877-885

The American Journal of Surgery®

North Pacific Surgical Association

Surgical management of rectal carcinoids: trends and outcomes from the Surveillance, Epidemiology, and End Results database (1988 to 2012)

Yarrow J. McConnell, M.D., M.Sc., F.R.C.S.C.*

Department of Surgery, University of British Columbia, 5th Floor, 2775 Laurel St., Vancouver, British Columbia, V5Z 1M9, Canada

KEYWORDS:
Carcinoid;
Neuroendocrine tumor;
Rectum;
Outcomes;
Epidemiology;
Transanal excision

Abstract

BACKGROUND: Local excision of small (<10 mm) rectal carcinoids is a standard treatment. Actual patterns of care and outcomes are understudied because of the rarity of this tumor.

METHODS: Surveillance, Epidemiology, and End Results database (1988 to 2012) was interrogated for rectal carcinoid patients. Chi-square testing and Kaplan-Meier survival analysis were used to compare survival outcomes.

RESULTS: Of all, 11,329 patients were identified—9,605 with only localized disease. The majority (77%) underwent local excision only. Full rectal resection was performed more frequently for tumors greater than 10 mm (11.7% to 12.2%) than for tumors less than 10 mm (4.5% to 4.9%, $P < .001$), and for higher T stage (T1: 4.0%, T2: 11.4%, T3/4:30.4%, $P < .001$). Nonoperative management was more common after year 2000 (11.2% to 13.7%) than prior (7.4% to 8.5%, $P < .001$). Cancer-specific survival improved across time periods but did not differ between nonoperative, local excision, or surgical resection.

CONCLUSIONS: Nonexcisional management of small, localized rectal carcinoids is becoming more common and may offer equivalent survival to excision or resection.

Carcinoid tumors arise throughout the gastrointestinal tract and bronchial tree, with an overall age-adjusted incidence of 1.31 to 4.48 per 100,000.[1] These tumors arise from neuroendocrine cell lineage and are identifiable histologically as solid nests of small uniform cells that stain for chromogranin A and/or synaptophysin, and generally have a low mitotic index. They generally have indolent behavior but high-grade variants do arise—characterized by high mitotic rate, necrosis, and poorly differentiated histology. Some carcinoid tumors, particularly those arising from the midgut, can produce substantial quantities of serotonin, leading to a "carcinoid syndrome" of flushing, profuse diarrhea, and eventual right heart failure, if sufficient levels of serotonin reach the systemic circulation.

Carcinoid tumors arising in the rectum form a small but important subgroup of this larger classification. The age-adjusted incidence of rectal carcinoid is .31 to 1.22 per 100,000,[1] making it the most common site for carcinoid occurrence in the hindgut. The incidence of rectal carcinoid appears to be increasing, likely due to increased detection on screening endoscopy.[2] In the great majority of cases, rectal carcinoid tumors remain localized (65% to 90%)

The authors declare no conflicts of interest.

* Corresponding author. Tel.: 604-875-5880; fax: 604-875-4036.
E-mail address: yarrow.mcconnell@vch.com

Manuscript received November 20, 2015; revised manuscript January 8, 2016

0002-9610/$ - see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjsurg.2016.01.008

and only a small percentage develop metastases to regional lymph nodes (2% to 3%) or distant sites (1% to 2%).[1,3] This translates into better long-term outcomes than other sites of carcinoid. Historically, 5-year survival for rectal carcinoid has been 75% to 97%, compared with 51% to 78% for other gastrointestinal sites of disease.[1,3] These data are from the 1990s and earlier but contributed to the recent trend toward managing rectal carcinoids with local excision or close observation alone. These approaches, aided by the development of improved techniques for transanal excision, avoid many of the short- and long-term morbidity risks associated with traditional rectal resection. But they run the risk of leaving residual disease in situ, either at the primary site or in adjacent lymph nodes, which may contribute to worse survival outcomes in the long term.

With the recent release of Surveillance, Epidemiology, and End Results (SEER) data for patients diagnosed between 2008 and 2012, much larger cohorts of rarer tumors are now available for analysis. The aim of this study was therefore to use the updated SEER database to evaluate trends in the demographics, staging, and management of rectal carcinoid, and to examine the associated survival outcomes.

Methods

Individual case data were extracted from the SEER database for patients diagnosed with rectal carcinoid tumor between January 1, 1988 and December 31, 2012. Codes used to identify these patients were a rectal primary site (C20.9) and *International Classification of Diseases for Oncology, 3rd edition* code 8240/3—"carcinoid tumor, malignant".

For the resulting cohort of 11,329 patients, data were extracted for age at diagnosis, gender, race, extent of disease and stage at presentation, size of primary lesion, and surgical procedure for the primary lesion. Data regarding lymphovascular invasion and tumor grade were also extracted but were missing for more than 80% of patients, and hence excluded from further analysis. Tumor-specific and surgical data in the SEER database have been abstracted by trained and audited coding professionals based on information gathered from clinical, radiologic, operative, and pathologic reports. Critical reviews suggest that SEER data accurately reflect surgical cancer management, both when operative resection is undertaken and when it is avoided.[4]

Variables

Age at diagnosis was classified into 3 categories ($\leq$49, 50 to 69, and $\geq$70 years) based on clinically relevant thresholds for decision-making regarding rectal resection. The SEER coding for 3 categories of race—white, black, and other—was used.

The extent of disease at presentation was classified as "local", "regional", or "distant" based on the maximal value from the SEER fields "EOD 10 - extent (1988 to 2003)", "EOD 10 - nodes (1988 to 2003)", "SEER summary stage 1977 (1995 to 2000)", and "Summary stage 2000 (1998+)". Nodal status, derived from SEER fields "derived AJCC N, 7th edition (2010+)", "EOD 10 - nodes (1988 to 2003)", and "CSlymphnodes2004", was used to check the designation of "regional" disease to include only those with lymph node involvement but without distant metastatic disease or only localized disease.

Primary tumor size was collated, where available, from the SEER fields "EOD 10 - size (1988 to 2003)" and "CS tumor size (2004+)". Tumor size was then classified into 4 groups, based on clinically relevant thresholds and previous reports of worse outcomes for tumors 10 to 19 and 20 mm or more in size.[3,5]

T stage was derived from the SEER fields "derived AJCC T, 7th edition (2010+)", "EOD 10 - extent (1988 to 2003)" and "CS extension (2004+)". Where data coding indicated only depth of invasion, the AJCC 7th edition definitions for T stage were applied. Given the small number of patients with T3 or T4 tumors, these categories were combined for analysis.

Data regarding definitive surgical procedure were derived from the SEER fields "RX Summ–Surg Prim Site (1998+)", "site specific surgery (1983 to 1997)", and "RX Summ–Scope Reg LN Sur (2003+)". Patients were classified as having undergone "biopsy only" if their diagnosis was made by needle biopsy but no cancer-directed polypectomy, surgical excision, destruction, or resection was undertaken. Any patient who underwent excisional biopsy, including polypectomy, or any other form of local excision or destruction without traditional rectal resection, was classified as "local excision". Any patient with record of a traditional resection and/or resection of regional lymph nodes, was classified as having undergone "rectal resection".

Univariate analysis by year of diagnosis

Patients were grouped into evenly spaced time periods based on their year of diagnosis, to allow comparisons over time. Data from each period cover several SEER coding changes and changes in field names. As described previously, these were integrated and summary fields used for analysis. Also as described previously, the number of missing data points were analyzed to assess for potential gaps because of unrecognized coding changes and to enable transparent communication of the limitations of the available data.

For each clinical and demographic factor, univariate analysis was undertaken to compare time periods using chi-square analysis. For the end point of surgical procedure, multivariate logistic regression was performed, incorporating all available clinical and pathologic parameters.

Given the substantial sample size, and thus potential for statistically significant findings where no clinical significance is present, a threshold P value of .01 was chosen to declare statistical significance for all analyses.

Overall and disease-specific survival analysis

Given the finding of significant changes in clinical and demographic factors, the period of diagnosis was included as a cofactor for survival analyses.

Kaplan-Meier survival analysis was used to estimate the 5- and 10-year overall and disease-specific survival (DSS) across each cofactor. Crude survival was derived from the SEER field "survival months". Overall survival (OS) was defined, as per SEER guidelines, from the date of diagnosis to the date of death or date of last follow-up, whichever came first, with all causes of death treated equally. DSS was defined the same way, except only deaths attributable to the rectal carcinoid tumor were treated events, with deaths from any other cause treated as a censorship event. Log-rank testing was used to compare groups within each covariate for univariate differences in survival. Again, given the large sample size, a P value of .01 was chosen as the threshold for declaring statistical significance.

Multivariate Cox proportional hazards modeling was conducted for the 2 end points of OS and DSS, with all cofactors included in the model. Ninety-five percent confidence intervals were calculated, and a P value of .01 used as a threshold for statistical significance. Postestimation testing of the assumption that the multivariate model was independent of time was undertaken using likelihood-ratio testing.

Results

Descriptive

Data for 11,329 patients with rectal carcinoid tumors were extracted and analyzed. Most of the analyzed cases were diagnosed since 2000, with 5,345 (46.4%) being extracted from the most recent data set added to the SEER database (2008 to 2012). Demographic and clinical characteristics are summarized in Table 1.

Overall, median age at diagnosis was 55 years. Age at diagnosis was 49 years or less in 24.2%, 50 to 69 years in 62.4%, and 70 years or more in 13.4% of patients. The proportion of patients aged 70 years or more at diagnosis declined over the period of data extraction—from 18.5% in 1988 to 1994 to 10.9% in 2007 to 2012. This was mirrored by a similar rise in the proportion of patients aged 50 to 69 years at diagnosis—from 48.1% in 1988 to 1994 to 67.4% in 2007 to 2012 ($P < .001$). The gender ratio for the entire cohort was 1:1, and remained so across all time periods ($P = .08$). Most of the patients (56.6%) were white, with 21.0% black, and 15.2% of another racial group.

The great majority of patients presented with only local disease (84.8%). A small proportion (4.2%) had regional lymph node involvement and an even small proportion (1.3%) had distant metastases at the time of diagnosis. Over the entire cohort, the rate of missing data for this cofactor was 9.7%—with a decrease over time from 14.1% in 1988 to 1994 to 8.8% in 2007 to 2012 ($P = .009$).

The measured tumor size was 5 mm or less in 49.7% of patients where this data point was available (2,585/5,199). Tumor size was 6 to 10 mm in 34.7%, 11 to 19 mm in 7.9%, and 20 mm or more in 7.6%. This data point was missing in 54.1% of patients, although this proportion declined over time—from 63.9% in 1988 to 1994 compared with 48.0% in 2007 to 2012. Tumor size and extent of disease were strongly related. Nodal involvement was present in 2.4% of patients with tumors 10 mm or less, 8.2% of patients with tumors 11 to 19 mm, and 11.7% in those with tumors 20 mm or more in size ($P < .001$). Distant metastatic disease was present .2% of those with tumors 10 mm or less, 2.4% of those with tumors 11 to 19 mm, and 12.0% of those with tumors 20 mm or more ($P < .001$).

The primary rectal tumor was T1 in 95.9% of patients with available T stage data (7,389/7,791), T2 in 3.6%, and T3 in 1.4%, and T4 in .1%. The proportion of patients with T3/4 tumors at presentation declined over time—from 4.1% in 1988 to 1994 to 1.1% in 2007 to 2012. The proportion of patients with T1 tumors rose over the same time period, whereas T2 tumor rates remained stable ($P < .001$). T stage data were missing for 3,538 patients (31.2%) of the entire cohort, but there was a declining rate of missing data for this cofactor between 1988 and 94 (40.3% missing) and 2007 to 2012 (30.2% missing). T stage was also strongly associated with the rate of nodal and distant metastases. Nodal involvement was present in .5% of T1, 6.7% of T2, and 41.5% of T3/4 tumors ($P < .001$). Distant metastases were present in .3% of T1, 3.2% of T2, and 14.7% of T3/4 tumors ($P < .001$).

Rectal resection was performed for 5.2% of patients overall, with a declining rate over time—9.0% in 1988 to 1994 vs 4.7% in 2007 to 2012. Most of the patients underwent local excision with a stable rate over time—73.9% in 1988 to 1994 to 75.4% in 2007 to 2012. The rate of nonoperative (biopsy only, no excision or resection) management, rose from 17.1% of patients in 1988 to 1994 to 19.8% of patients in 2007 to 2012 ($P < .001$).

Overall and disease-specific survival

Median OS was 64-month overall, but ranged from 26 months for those presenting with distant metastases, to 47.5 months for those with regional lymph node involvement, and 65 months for those with only local disease. The longest recorded survivor, at 300 months (25 years), presented with local disease. But there are also long-term survivors among those presenting with nodal involvement (maximum 286 months or 23.8 years) and distant metastases (maximum 206 months or 17.2 years).

Table 1 Demographic and clinical characteristics of all patients with rectal carcinoid, SEER database, 1988 to 2012, with missing data noted

	N	1988–94	1995–2000	2001–06	2007–12	*P*
Overall	11,329	690 (6.1%)	1,398 (12.3%)	3,896 (34.4%)	5,345 (46.4%)	-
Age, y						
≤49	2,737 (24.2%)	230 (33.3%)	383 (27.4%)	963 (24.7%)	1,161 (21.7%)	**<.001**
50–69	7,074 (62.4%)	332 (48.1%)	765 (54.7%)	2,375 (61.0%)	3,602 (67.4%)	
≥70	1,518 (13.4%)	128 (18.5%)	250 (17.9%)	558 (14.3%)	582 (10.9%)	
Gender						
Female	5,743 (50.7%)	330 (47.8%)	688 (49.2%)	1,955 (50.2%)	2,770 (51.8%)	.08
Male	5,586 (49.3%)	360 (52.2%)	710 (50.8%)	1,941 (49.8%)	2,575 (48.2%)	
Race						
White	6,410 (56.6%)	410 (59.4%)	819 (58.6%)	2,327 (59.7%)	2,854 (53.4%)	**<.001**
Black	2,598 (22.9%)	145 (21.0%)	309 (22.1%)	838 (21.5%)	1,304 (24.4%)	
Other	1,726 (15.2%)	121 (17.6%)	233 (16.7%)	567 (14.5%)	805 (15.1%)	
Missing	597 (5.3%)	14 (2.0%)	37 (2.6%)	164 (4.2%)	382 (7.1%)	
Extent of disease at presentation						
Local	9,605 (84.8%)	565 (81.9%)	1,168 (83.5%)	3,320 (85.2%)	4,552 (85.2%)	**.009**
Regional	473 (4.2%)	15 (2.2%)	41 (2.9%)	147 (3.8%)	270 (5.0%)	
Distant	147 (1.3%)	13 (1.9%)	20 (1.4%)	59 (1.5%)	55 (1.0%)	
Missing	1,104 (9.7%)	97 (14.1%)	169 (12.1%)	370 (9.5%)	468 (8.8%)	
Size of primary						
≤5 mm	2,585 (22.8%)	76 (11.0%)	223 (16.0%)	795 (20.4%)	1,491 (27.9%)	**<.001**
6–10 mm	1,804 (15.9%)	100 (14.5%)	185 (13.2%)	610 (15.7%)	909 (17.0%)	
11–19 mm	413 (3.7%)	30 (4.4%)	54 (3.9%)	134 (3.4%)	195 (3.6%)	
≥20 mm	397 (3.5%)	43 (6.2%)	48 (3.4%)	119 (3.0%)	187 (3.5%)	
Missing	6,130 (54.1%)	441 (63.9%)	888 (63.5%)	2,238 (57.4%)	2,563 (48.0%)	
T stage, AJCC 7th edition						
T1	7,389 (65.2%)	376 (54.5%)	905 (64.7%)	2,568 (65.9%)	3,540 (66.2%)	**<.001**
T2	284 (2.5%)	19 (2.7%)	33 (2.4%)	87 (2.2%)	145 (2.7%)	
T3/4	118 (1.0%)	17 (2.5%)	18 (1.3%)	39 (1.0%)	44 (.8%)	
Missing	3,538 (31.2%)	278 (40.3%)	422 (31.6%)	1,202 (30.9%)	1,616 (30.2%)	
Surgical procedure						
Biopsy only	2,035 (18.1%)	118 (17.1%)	205 (14.7%)	668 (17.3%)	1,044 (19.8%)	**<.001**
Excision	8,603 (76.6%)	510 (73.9%)	1,117 (80.1%)	2,999 (77.5%)	3,977 (75.4%)	
Resection	587 (5.2%)	62 (9.0%)	203 (5.2%)	203 (5.2%)	250 (4.7%)	

AJCC = American Joint Committee on Cancer; SEER = Surveillance, Epidemiology, and End Results.

Estimated 5- and 10-year OS for the entire cohort were 91.5% and 82.3%, respectively. On univariate analysis, worse OS was associated with an earlier year of diagnosis (10-year OS, 76.1% vs 84.0% for 1988 to 1994 vs 2001 to 2006, $P < .001$), advanced age (10-year OS, 93.2% vs 51.7% for patients aged 49 or less vs 70 years or more at diagnosis, $P < .001$), and male gender (10-year OS, 80.1% vs 84.4% for males vs females, $P < .001$). These associations were substantially decreased when 10-year DSS was estimated (Table 2), suggesting that most of the observed differences in OS were due to competing risks.

In terms of racial disparities, patients of black race had worse 10-year OS and DSS (75.7% and 95.3%) compared with both patients of white race (82.9% and 97.4%), and the combined group of all other races (96.8% and 99.7%, $P < .001$).

Patients presenting with metastatic disease had worse 5- and 10-year OS (35.0% and 11.2%, respectively) compared with patients presenting with regional nodal involvement (86.3% and 73.3%, respectively) and those with only local disease (92.8% and 83.8%, respectively, $P < .001$). This substantive difference persisted when 5- and 10-year DSS were estimated (44.1% and 20.1%, respectively, for metastatic disease; 96.7% and 91.2%, respectively, and for regional disease; 99.3% and 98.2%, respectively, for local disease; $P < .001$). The 5- and 10-year OS and DSS values for the subgroup of patients missing data on the extent of their disease were intermediate between those of patients with local and regional disease (see Table 2).

The size of the primary tumor, when available, was inversely related to OS and DSS on univariate analysis. With each increasing size category, OS and DSS declined. Ten-year OS was 89.1% for tumors 5 mm or less, 82.1% for those 6 to 10 mm, 71.5% for those 11 to 19 mm, and 58.6% for those 20 mm or more ($P < .001$). Ten-year DSS was 99.4% for tumors 5 mm or less, 97.9% for those 6 to 10 mm, 93.7% for those 11 to 19 mm, and 72.2% for those 20 mm or more ($P < .001$). Patients with data missing for this field had 10-year OS and DSS similar to those with 6 to 10-mm tumors.

Table 2 Overall and disease-specific survival for all patients, estimated by Kaplan-Meier survival analysis, at 5 and 10 years

		Overall survival			Disease-specific survival		
	n	5 y	10 y	Cox HR (CI)	5 y	10 y	Cox HR (CI)
Overall	11,329	91.5%	82.3%	No. of events: 1,592	98.4%	97.1%	No. of events: 251
Year of diagnosis							
1988–1994	690	86.7%	76.1%	Ref	96.4%	94.2%	Ref
1995–2000	1,398	89.7%	78.8%	.87 (.74, 1.02)	98.3%	96.8%	**.56 (.37, 0.84)**
2001–2006	3,896	91.8%	84.0%	**.62 (.52, 0.73)**	98.6%	97.4%	**.34 (.23, 0.51)**
2007–2012	5,345	93.0%	NC	**.60 (.49, 0.74)**	98.8%	NC	**.40 (.24, 0.67)**
Age, y							
≤49	2,737	96.3%	93.2%	Ref	99.0%	98.6%	Ref
50–69	7,074	93.3%	85.3%	**2.39 (2.01, 2.85)**	98.8%	97.5%	2.00 (1.35, 2.97)
≥70	1,518	75.4%	51.7%	**9.45 (7.89, 11.32)**	95.7%	91.8%	**5.96 (3.91, 9.09)**
Gender							
Female	5,743	93.1%	84.4%	Ref	98.5%	97.2%	Ref
Male	5,586	90.0%	80.1%	**1.49 (1.34, 1.65)**	98.4%	96.9%	1.27 (.97, 1.67)
Race							
White	6,410	92.3%	82.9%	Ref	98.7%	97.4%	Ref
Black	2,598	87.5%	75.7%	**1.58 (1.40, 1.78)**	97.3%	95.3%	**1.81 (1.34, 2.45)**
Other	1,726	92.7%	86.2%	.86 (.73, 1.00)	98.6%	97.6%	.98 (.65, 1.49)
Missing	597	98.8%	96.8%	**.20 (.10, 0.39)**	99.7%	99.7%	.25 (.03, 1.82)
Extent of disease at presentation							
Local	9,605	92.8%	83.8%	Ref	99.3%	98.2%	Ref
Regional	473	86.3%	73.3%	**1.40 (1.07, 1.84)**	96.7%	91.2%	**2.07 (1.19, 3.60)**
Distant	147	35.0%	11.2%	**8.66 (6.64, 11.28)**	44.1%	20.1%	**33.1 (20.4, 53.6)**
Missing	1,104	90.1%	81.2%	.95 (.77, 1.17)	98.0%	97.5%	.88 (.50, 1.53)
Size of primary							
≤5 mm	2,585	95.0%	89.1%	Ref	99.8%	99.4%	Ref
6–10 mm	1,804	92.3%	82.1%	1.26 (1.02, 1.54)	99.1%	97.9%	2.12 (.99, 4.52)
11–19 mm	413	84.9%	71.5%	**1.56 (1.18, 2.05)**	96.7%	93.7%	**3.18 (1.39, 7.27)**
≥20 mm	397	74.8%	58.6%	**2.01 (1.53, 2.63)**	84.0%	72.2%	**5.79 (2.75, 12.2)**
Missing	6,130	91.4%	82.1%	1.28 (1.08, 1.51)	98.7%	97.6%	2.20 (1.14, 4.25)
T stage, AJCC 7th edition							
T1	7,389	92.9%	83.9%	Ref	99.3%	98.6%	Ref
T2	284	88.3%	77.1%	1.02 (.74, 1.42)	95.8%	91.6%	1.92 (.99, 3.70)
T3/4	118	67.5%	42.9%	**1.83 (1.32, 2.53)**	82.9%	61.9%	**3.08 (1.76, 5.41)**
Missing	3,538	89.8%	80.7%	.97 (.85, 1.12)	97.3%	95.6%	1.40 (.96, 2.04)
Surgical procedure							
Biopsy only	2,035	87.8%	79.5%	Ref	96.5%	95.6%	Ref
Excision	8,603	92.8%	83.8%	**.77 (.66, 0.89)**	99.3%	98.3%	**.54 (.37, 0.79)**
Resection	587	84.2%	67.9%	.85 (.67, 1.08)	92.3%	84.3%	.91 (.59, 1.42)

For multivariate Cox proportional hazards modeling, hazards ratios and 95% confidence intervals are marked in bold if $P \leq .01$.
AJCC = American Joint Committee on Cancer.

Advanced T stage (T3/4) was associated with worse 5- and 10-year OS and DSS (see Table 2). Ten-year OS was 42.9% for T3/4 lesions, vs 77.1% for T2 lesions, and 83.9% for T1 lesions ($P < .001$). Ten-year DSS for T3/4 lesions was 61.9%, vs 91.6% for T2 lesions, and 98.6% for T1 lesions ($P < .001$). Patients missing T stage data had OS and DSS outcomes intermediate between those for T1 and T2 lesions, suggesting that few of these patients had locally advanced disease.

Formal surgical excision was associated with better 5- and 10-year OS and DSS compared with biopsy alone. Ten-year OS was 83.8% with excision vs 79.5% with biopsy alone ($P < .001$), whereas 10-year DSS was 98.3% with excision vs 95.6% without excision ($P < .001$). Full rectal resection was associated with worse survival outcomes than excision alone (10-year OS and DSS, 67.9% and 84.3%, respectively, $P < .001$). Rectal resection was very strongly associated with node positivity. Among node-positive patients, 80.4% had a rectal resection, whereas only 4.8% of node negative patients had a rectal resection ($P < .001$).

On multivariate Cox proportional hazard modeling for all patients, worse 10-year OS was associated with earlier year of diagnosis, older age, male gender, black race, distant disease at presentation, primary tumor size greater than 10 mm, and T3/4 stage (Table 2). Worse 10-year DSS

remained significantly associated with earlier year of diagnosis, age 70 years or more, black race, regional and distant disease at presentation, primary tumor size greater than 10 mm, and T3/4 stage. As well, surgical excision remained associated with improved 10-year OS and DSS compared with biopsy alone, but rectal resection was not associated with any change in outcome compared with biopsy alone.

Surgical treatment of localized disease

In patients with only localized disease, rectal resection was performed more frequently in those with T3/T4 tumors ($P < .001$, see Table 3), and those with tumor size greater than 10 mm ($P < .001$). Biopsy alone was implemented more frequently in more recent years (13.7% in 2007 to 2012 vs 8.5% in 1988 to 1994, $P < .001$).

On multivariate logistic regression, year of diagnosis and T stage remained significantly associated with choice of surgical procedure, whereas tumor size was no longer significantly associated (see Table 3).

Among the 9,568 patients with only localized disease, disease-specific mortality occurred in 107 patients (1.1%). The median time to disease-specific death was 64 months, with 75th and 95th percentiles at 103 and 185 months, respectively. On Kaplan-Meier analysis, formal rectal resection was associated with worse estimated 10-year OS and DSS, compared with excision or biopsy alone. This likely relates to the finding, previously, that rectal resection was performed more frequently for higher T stage tumors and larger tumors. When broken down by tumor and clinical factors (see Table 4), localized T3/4 tumors had a 10-year OS of 28.3% compared with 83.3% for T1 tumors and 63.2% for T2 tumors ($P < .001$) after rectal resection. The corresponding 10-year DSS values were 42.1% for T3/4 tumors vs 71.4% for T2 tumors and 98.3% for T1 tumors ($P < .001$). In all cases, the 10-year OS and DSS outcomes were better for patients who had biopsy only, or excision, across all T stages. The same, seemingly paradoxical, relationship was observed when outcomes were analyzed by tumor size (Table 4).

On multivariate Cox proportional hazard modeling for patients with only localized disease, worse 10-year OS was

Table 3 Clinical and demographic characteristics of patients with only local disease at presentation, by surgical procedure performed

		Surgical procedure			Univariate	Multivariate
	N	Biopsy	Excision	Resection	*P*	*P*
Overall	9,568	1,124 (11.7%)	8,033 (84.0%)	411 (4.3%)	-	-
Year of diagnosis						
1988–94	565	48 (8.5%)	487 (86.2%)	30 (5.3%)	**<.001**	**<.001**
1995–2000	1,166	86 (7.4%)	1,035 (88.8%)	45 (4.4%)		
2001–06	3,309	370 (11.2%)	2,793 (84.4%)	146 (4.2%)		
2007–12	4,528	620 (13.7%)	3,718 (82.1%)	190 (4.3%)		
Age, y						
≤49	2,310	245 (10.6%)	1,971 (85.3%)	94 (4.1%)	.2	.24
50–69	6,036	719 (11.9%)	5,054 (83.7%)	263 (4.4%)		
≥70	1,222	160 (13.1%)	1,008 (82.5%)	54 (4.4%)		
Gender						
Female	4,863	560 (11.5%)	4,088 (84.1%)	215 (4.4%)	.6	.57
Male	4,705	564 (12.0%)	3,945 (83.8%)	196 (4.2%)		
Race						
White	5,474	599 (10.9%)	4,643 (84.8%)	232 (4.2%)	.02	.31
Black	2,145	285 (13.3%)	1,758 (82.0%)	102 (4.8%)		
Other	1,514	152 (10.0%)	1,289 (85.1%)	73 (4.8%)		
Missing	439	88 (20.2%)	343 (78.8%)	4 (.9%)		
Size of primary						
≤5 mm	2,448	211 (8.6%)	2,118 (86.5%)	119 (4.9%)	**<.001**	.86
6–10 mm	1,710	120 (7.0%)	1,513 (88.5%)	77 (4.5%)		
11–19 mm	350	17 (4.9%)	292 (83.4%)	41 (11.7%)		
≥20 mm	246	27 (10.9%)	189 (76.8%)	30 (12.2%)		
Missing	4,814	749 (15.6%)	3,921 (81.4%)	144 (3.0%)		
T stage, AJCC 7th edition						
T1	7,305	742 (10.2%)	6,268 (85.8%)	295 (4.0%)	**<.001**	**<.001**
T2	254	24 (9.4%)	201 (79.1%)	29 (11.4%)		
T3/T4	46	4 (8.7%)	28 (60.9%)	14 (30.4%)		
Missing	1,963	354 (18.0%)	1,536 (78.2%)	73 (3.7%)		

Missing data are indicated where applicable. *P* values are for chi-square testing, and marked in bold if less than .01.
AJCC = American Joint Committee on Cancer.

Table 4 Overall and disease-specific survival for patients with local disease at presentation, estimated by Kaplan-Meier survival analysis, at 10 years, by surgical procedure performed

		10-year overall survival				10-year disease-specific survival			
	N	None	Excision	Resection	Cox HR (CI)	None	Excision	Resection	Cox HR (CI)
Overall	9,568	83.1%	84.2%	**78.3%**	No. of events: 1,202	98.2%	98.5%	**93.5%**	No. of events: 130
Year of diagnosis									
1988–1994	565	63.3%	80.2%	73.3%	Ref	95.4%	96.8%	89.1%	Ref
1995–2000	1,166	78.9%	81.0%	72.1%	.99 (.82, 1.20)	97.2%	98.2%	94.7%	.75 (.42, 1.32)
2001–2006	3,309	**82.6%**	**86.2%**	81.5%	**.77 (.64,0.93)**	97.7%	99.0%	93.7%	.53 (.29, 0.95)
2007–2012	4,528	NC	NC	NC	**.70 (.55, 0.88)**	NC	NC	NC	.59 (.28, 1.26)
Age, y									
≤49	2,310	98.2%	95.9%	88.1%	Ref	100%	100%	94.7%	Ref
50–69	6,036	92.0%	91.8%	83.8%	**2.19 (1.50, 3.21)**	99.0%	99.1%	93.0%	**7.75 (1.06, 56.8)**
≥70	1,222	**71.3%**	**69.6%**	72.1%	**8.52 (5.87, 12.4)**	**96.5%**	**97.1%**	94.2%	**21.5 (2.97, 156.7)**
Gender									
Female	4,863	85.1%	85.9%	81.6%	Ref	98.4%	98.4%	92.6%	Ref
Male	4,705	82.7%	**82.5%**	76.8%	**1.40 (1.24, 1.58)**	97.7%	98.6%	95.2%	.95 (.65, 1.40)
Race									
White	5,474	87.4%	84.3%	82.7%	Ref	97.7%	98.6%	96.4%	Ref
Black	2,145	**73.4%**	**78.4%**	71.8%	**1.54 (1.34, 1.77)**	97.8%	97.8%	87.2%	1.59 (.99, 2.40)
Other	1,514	84.2%	88.8%	77.8%	.81 (.68,0.97)	100%	98.6%	94.1%	.84 (.47, 1.49)
Missing	439	**98.4%**	**97.5%**	100%	**.15 (.06, 0.37)**	100%	100%	100%	NC
Size of primary									
≤5 mm	2,448	84.1%	91.0%	81.7%	Ref	98.9%	99.6%	100%	Ref
6–10 mm	1,710	77.2%	83.9%	80.7%	1.28 (1.04, 1.60)	97.7%	98.2%	98.3%	2.35 (1.01, 5.47)
11–19 mm	350	**34.0%**	**75.1%**	79.4%	**1.83 (1.34, 2.50)**	**80.0%**	97.7%	88.2%	**3.74 (1.36, 10.3)**
≥20 mm	246	**80.3%**	**76.2%**	**57.1%**	**2.04 (1.83, 3.56)**	**88.0%**	**93.6%**	**60.0%**	**13.5 (5.62, 32.3)**
Missing	4,814	86.6%	82.5%	81.8%	**1.41 (1.14, 1.62)**	98.9%	98.4%	97.3%	2.16 (1.02, 4.56)
T stage, AJCC 7th edition									
T1	7,305	83.5%	84.4%	83.3%	Ref	98.2%	98.7%	98.3%	Ref
T2	254	80.0%	79.8%	**63.2%**	1.08 (.75, 1.54)	100%	97.2%	**71.4%**	1.74 (.76, 3.98)
T3/T4	46	100%	82.3%	**28.3%**	**1.66 (.96, 2.88)**	100%	100%	**42.1%**	**4.15 (1.58, 10.9)**
Missing	1,963	84.5%	84.0%	83.4%	1.02 (.88, 1.18)	97.7%	97.7%	98.3%	1.32 (.8, 2.09)
Surgical procedure									
None	1,095	-			Ref	-			Ref
Excision	8,061		-		.84 (.69, 1.03)		-		.66 (.35, 1.24)
Resection	449			-	.86 (.62, 1.18)			-	1.31 (.58, 2.98)

For univariate log-rank testing, 10-year survival rates are marked in bold if $P \leq .01$. For multivariate Cox proportional hazards modeling, hazards ratios and 95% confidence intervals are marked in bold if $P \leq .01$.

NC: not calculable because of short period of follow-up for more recent cases and/or insufficient sample size.

AJCC = American Joint Committee on Cancer.

associated with earlier year of diagnosis, older age, male gender, black race, primary tumor size greater than 10 mm, and T3/4 stage. Worse 10-year DSS was associated with older age, tumor size 20 mm or more, and T3/4 stage. Surgical procedure was not significantly related with either OS or DSS on this multivariate analysis, once controlled for the other clinical and tumor-related factors (see Table 4).

In the subset of patients with only localized disease and a tumor 11 mm or more in size and/or T3 stage or more, local excision was associated with a 10-year OS and DSS of 76.6% and 96.3%, significantly higher than with biopsy alone (52.0% and 82.8%, respectively, $P < .05$). Rectal resection was associated with worse outcomes than local excision in these patients (10-year OS and DSS, 65.9% and 75.9%, respectively, $P < .01$). On multivariate Cox proportional hazard modeling, controlling for year of diagnosis, age, race, gender, and tumor size; surgical procedure had no residual association with OS but there remained a benefit of local excision over biopsy for the endpoint of DSS (hazard ratio [HR] .24, 95% confidence interval [CI] .06, .94). When rectal resection was used as the referent surgical procedure, local excision also retained its DSS benefit on multivariate analysis (HR .23, 95% CI .09, .57).

Surgical treatment of node-positive disease

In patients with node-positive disease, 10-year OS was 80.7%, 79.9%, and 56.4%, respectively with biopsy alone, local excision, and rectal resection ($P < .001$). Similarly, 10-year DSS was 98.4% with biopsy alone, 79.9% with

local excision, and 56.4% with rectal resection ($P < .001$). On multivariate analysis, controlling for year of diagnosis, age, gender, race, size of primary tumor, and T stage; rectal resection continued to be associated with a worse OS (HR = 2.52, 95% CI = 1.13, 5.65) but not a worse DSS (HR = 4.63, 95% CI = .81, 26.5).

Comments

This review of data derived from the SEER database includes the largest number of rectal carcinoid patients ever included in an analysis of surgical management and survival. It has allowed a multivariate examination of survival related to key clinical, staging, and surgical parameters, which has not been previously possible.

One of the most notable findings was that the proportion of tumors 10 mm or more in size, and without involvement beyond the submucosa (T1) is rising over time—accounting for 45% to 65% of patients in recent years. These small localized tumors are associated with a very low rate of lymph node involvement (.5% to 2.4%) and have been increasingly managed by biopsy alone—without formal local excision. On multivariate analysis, local excision was not associated with an improvement in overall or DSS compared with biopsy alone. This finding suggests that formal excision may not be necessary for these lesions, a strategy that has obviously been in use for some time by many clinicians but not previously supported by any substantive data. This observation of current practice is a departure from recommended treatment algorithms[6] but represents a practical response to the relatively frequent finding of a small rectal carcinoid tumor. With the accurate measurement and T staging provided by experienced endorectal ultrasound operators, it may be reasonable to simply perform a diagnostic biopsy for lesions less than 10 mm with T1 staging and no suggestion of perirectal lymphadenopathy.

In patients with slightly larger tumors (11 to 19 mm and/or T2), the rate of lymph node involvement was substantially higher (6.7% to 8.2% of the patients). On multivariate analysis for OS and DSS, this intermediate tumor size was significantly associated with worse outcome, even after controlling for the presence of metastases, and lymph node involvement. When only patients with localized disease were analyzed, a tumor size of 11 to 19 mm remained associated with worse outcomes on multivariate analysis (Table 4). This suggests that there is a survival deficit associated with 11 to 19-mm tumors independent of their association with node involvement, and likely representing an inherent metastatic capacity. This supports the findings of an earlier study where this intermediate size category was a predictor of poorer survival, independent of nodal and distant metastases.[3,7] Again, it speaks to the paramount importance of high quality endorectal ultrasound and careful sizing and local staging of these tumors. Unfortunately, formal rectal resection does not appear to improve survival in this intermediate risk group, and surveillance is our only potentially useful tool. The SEER database does not provide detailed recurrence data, but the lengthy time to cancer-specific death observed here (median 64 months, 95th percentile 185 months) suggests that recurrences can occur many years after initial presentation.

In the subset of patients with tumors more than or equal to 11 mm and/or more than or equal to T3, local excision appears to offer a DSS benefit over biopsy alone, but rectal resection does not. This likely reflects uncaptured clinical factors contributing to the decision for local excision over biopsy alone for these larger localized tumors. For instance, in patients with multiple comorbidities presenting with larger localized tumors, where rectal resection is not be feasible, biopsy alone may have been chosen. Given the retrospective nature of administrative databases, it is possible that other clinical or pathologic features were associated with the choice of rectal resection, and contributing to the worse outcome seen for these patients. Unfortunately, information regarding tumor grade and lymphovascular invasion were not available for the great majority of rectal carcinoid patients in SEER. Requirement for reporting of these features will be necessary before their impact on prognosis and surgical decision-making in large cohorts of patients can be analyzed.

Unfortunately, the exact technique used for local excision procedures is not yet captured by SEER coding practices. Several studies and a recent meta-analysis suggest that these tumors are more completely excised when techniques aimed at complete submucosal dissection are applied compared with more traditional techniques aimed at mucosal lesions.[8]

In node-positive patients, our analysis suggests that local excision is not associated with any improvement in outcomes over biopsy alone. The finding that rectal resection is associated with a substantially worse OS and DSS in these patients appears paradoxical but likely reflects uncaptured clinical factors. Node positivity in patients who underwent only biopsy or local excision has been coded on the basis of radiological reports, plus needle biopsy of nodes in some patients. In contrast, node positivity in patients who underwent rectal resection is coded on the basis of detailed surgical pathology reports. This difference undoubtedly introduces some degree of stage migration, which can strongly influence measurement of outcomes. Given that age, gender and race distribution did not vary across choice of surgical procedure, it is unlikely that these factors contributed to the worse outcomes with rectal resection. A randomized clinical trial is the only method to accurately determine whether rectal resection benefits patients with node-positive or locally advanced tumors. In the absence of such a trial, and recognizing that one is highly unlikely to occur, the standard treatment of locally advanced or radiographically node-positive patients, in the absence of distant metastatic disease, should continue to be full rectal resection with a total mesorectal excision approach.

The limitations of this study are many. It is based on administrative data which, although demonstrated to be highly accurate,[4] are limited in their breadth of data capture. Of particular interest in rectal carcinoids, the low level of capture for grade and lymphovascular invasion data fields is especially troublesome. Given the level of emphasis on these factors in modern neuroendocrine tumor staging systems,[6,9] SEER oversight committees should strongly consider making such fields mandatory reporting for these tumors.

The second major limitation is the retrospective nature of such analyses. Survival appears to be improving over time and this may be variably attributable to earlier detection, improved preoperative staging, changes in surgical technique, and improved treatments for patients with advanced stage disease. The choice of surgical procedure has been made, at an individual level, based on a host of factors that cannot be captured by such a review.

In summary, the current review of SEER data over a 25-year period highlights the utmost importance of accurate tumor size measurement and local staging in the management of rectal carcinoid. The growing majority of patients have small (<1 cm), likely incidental, tumors found on screening endoscopy. These are likely sufficiently treated with biopsy alone and may not require formal transanal submucosal excision. Patients with larger tumors (>1 cm) appear to benefit from formal local excision but the role of full rectal resection remains unclear. The standard approach of rectal resection for any tumor more than 2 cm in size or with evidence of lymph node involvement should be continued until we have sufficient data to debate its utility. The presence of distant metastatic disease portends a dismal prognosis and it is unlikely that any local therapy, other than for symptom control, is of benefit to such unfortunate patients.

References

1. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–59.
2. Scherübl H, Klöppel G. [Rectal carcinoids on the rise—update]. Z Gastroenterol 2009;47:365–71.
3. Landry CS, Brock G, Scoggins CR, et al. A proposed staging system for rectal carcinoid tumors based on an analysis of 4701 patients. Surgery 2008;144:460–6.
4. Cooper GS, Virnig B, Klabunde CN, et al. Use of SEER-Medicare data for measuring cancer surgery. Med Care 2002;40(8 Suppl). IV-43–8.
5. Gleeson FC, Levy MJ, Dozois EJ, et al. Endoscopically identified well-differentiated rectal carcinoid tumors: impact of tumor size on the natural history and outcomes. Gastrointest Endosc 2014;80:144–51.
6. Anthony LB, Strosberg JR, Klimstra DS, et al. 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;39:767–74.
7. 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.
8. He L, Deng T, Luo H. Efficacy and safety of endoscopic resection therapies for rectal carcinoid tumors: a meta-analysis. Yonsei Med J 2015;56:72–81.
9. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010;39:707.

Discussion

Discussant

Liana Tsikitis, MD, (Portland, OR): In this retrospective descriptive study of the Surveillance, Epidemiology, and End Results database, the author examines the treatment trends of rectal carcinoids with particular interest of small lesions, less than 1 cm, between the years 1988 and 2012. The resulting cohort includes 11,329 patients and the data extracted are age at diagnosis, gender, race, disease stage, tumor size, and surgical procedure.

Because of the long period of study with changes of the staging system, it is hard to maintain consistency with the data captured on tumor size and lymph node involvement of rectal carcinoids. The author tries to summarize the cohorts of different stages by using the staging extent of disease for the years 1988 to 2003, collaborative stage lymph node for the years 2004 to 2010, and finally, the American Joint Committee on Cancer 7th edition for the years 2010 to 2012.

The issue of missing data is significant among the years (more than 40% for tumor size or lymph node status) and the author tries to address this by assigning a stringent *P* value for her analysis, which may not be the most appropriate statistical approach as multiple imputations.

Results show that treatment does not seem to have significantly changed over the years as the rate of local excision for small lesions seems to have stayed stable to about 75%. The author finds on univariate analysis associations of overall survival and disease free survival with T stage tumor size and overall stage as one would expect. On multivariate analysis, worse 10-year overall survival is associated with earlier year of diagnosis, older age, tumor size greater than 10 mm, T3/T4 stage, and surgical procedure.

Questions for the author:

1. How does the author interpret the fact that rectal resection for localized and nodal positive disease is associated with worse survival?
2. If a small carcinoid less than 10 mm is found the author recommends biopsy and not excision. What are the author's recommendations of surveillance? The lack of 100% sensitive and specificity of endorectal ultrasound to accurately stage tumor size, and the knowledge that 11 to 19 mm of tumors have much more prognosis should local excision be the mainstay treatment?