Practice Patterns and Guideline Non-Adherence in Surgical Management of Appendiceal Carcinoid Tumors

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BACKGROUND: Surgical management of appendiceal carcinoid tumors is heavily debated, despite National Comprehensive Cancer Network guidelines recommending aggressive resection of tumors >2 cm. We investigated national practice patterns and the predictors and impact of guideline non-adherence.

STUDY DESIGN: The National Cancer Database was queried for cases of appendiceal carcinoids diagnosed from 2004 to 2015 treated with either appendectomy or hemicolectomy. Multivariable logistic regression, adjusted for demographic and clinical factors, identified associations with the procedure type among patients stratified by tumor size ≤2 cm and >2 cm. Cox Proportional Hazards then identified associations with overall survival among stratified patient groups.

RESULTS: Of 3,198 cases of appendiceal carcinoids, 1,893 appendectomies and 1,305 hemicolectomies were identified. Contrary to National Comprehensive Cancer Network guidelines, 32.4% of tumors ≤2 cm were treated with hemicolectomy and 31.3% of tumors >2 cm were treated with definitive appendectomy. Hemicolectomy for small tumors was associated with age 65 years and older (odds ratio [OR] 2.4; 95% CI 1.7 to 3.3; reference group age 18 to 39 years), history of malignancy (OR 2.0; 95% CI 1.6 to 2.6), tumor size 1.1 to 2 cm (OR 2.8; 95% CI 2.3 to 3.4; reference group size ≤1 cm), and lymphovascular invasion (OR 2.2; 95% CI 1.6 to 3.2); appendectomy for large tumors was associated with age 65 years and older only (OR 2.2; 95% CI 1.1 to 4.2). Procedure type was not associated with survival for small or large tumors (hazard ratio 1.0; 95% CI 0.7 to 1.4 and hazard ratio 1.1; 95% CI 0.6 to 2.0, respectively).

CONCLUSIONS: Despite well-known size-based treatment guidelines for appendiceal carcinoids, one-third of patients in the US undergo hemicolectomy for small tumors and appendectomy for large tumors. Guideline non-adherence, however, is not associated with overall survival. Reasons for these practice patterns should be explored, and guidelines revisited. (J Am Coll Surg 2019;228:839–851. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms
HR = hazard ratio
NCDB = National Cancer Data Base
OR = odds ratio
OS = overall survival

Carcinoids, a histologic subset of the rare neuroendocrine tumors, are the most common tumor of the appendix. Unlike mixed-type goblet cell or adenocarcinoids, pure appendiceal carcinoids portend a highly favorable prognosis, with 5-year survival approximating 90%.[1,2] Such prolonged survival depends on treatment by adequate surgical resection—a topic of surprising literature debate.

Choice of resection procedure for appendiceal carcinoids has long been dictated by tumor size, an established prognostic determinant. In the 1987 landmark study by Moertel and colleagues,[3] after more than 25 years follow-up, only tumors >2 cm were associated with distant metastases. Numerous studies thereafter demonstrated association of size >2 cm with lymph node metastases and reduced survival.[4-9] Naturally, these data were incorporated into clinical practice guidelines developed by the National Comprehensive Cancer Network[10] and the North American Neuroendocrine Tumor Society,[11] which recommended simple appendectomy for small tumors (≤2 cm) and more aggressive right hemicolectomy for large tumors (>2 cm; or positive margins after appendectomy) (Fig. 1). They also recommended judicious consideration of hemicolectomy for intermediate-sized tumors (1.1 to 2 cm) with aggressive features like lymphovascular and mesoappendiceal invasion,[2,10-12] which have also been associated with lymph node metastases.[5-7]

Despite the existence of size-based surgical treatment guidelines since the year 2000,[13,14] choice of resection procedure for appendiceal carcinoids remains controversial. Several studies suggest that lymph node metastasis, although associated with intermediate and large tumors, might not impact survival.[6,9] Studies that demonstrate survival difference between patients with small and large tumors have failed to show an advantage of one procedure over another.[8,15,16] Some institutions challenge the necessity of the more morbid hemicolectomy, even for tumors >2 cm.

The aim of this study was to describe the reality of surgical treatment practices for appendiceal carcinoid in the US; that is, the degree to which established treatment guidelines are being followed. A secondary objective was to investigate whether resection procedure choice is associated with overall survival using currently available national data. We hypothesized that, given conflicting opinions and questionable survival benefit, there was a significant proportion of patients with small and/or large tumors being treated with a non-recommended surgical procedure. We also hypothesized that patient and disease characteristics unrelated to size, such as baseline health status and tumor aggressiveness, were associated with procedure choice.

METHODS

Data selection

Data for this study were drawn from the National Cancer Data Base (NCDB), a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society. This pooled data source captures approximately 70% of incident cancers in the US, and is highly advantageous for studying practice patterns in rare cancers like appendiceal carcinoid. The American College of Surgeons and Commission on Cancer are not responsible for the analytic methodologies used in this study or the conclusions drawn by the investigators.

For the years 2004 to 2015, cases of appendiceal carcinoid tumors were identified using the 2015 "colon" Participant User File (downloaded November 17, 2017). Histologies reflecting pure carcinoid tumors without adenomatous or sarcomatous features were selected, consistent with earlier studies.[5,8,9,15] Morphology codes from the *International Classification*

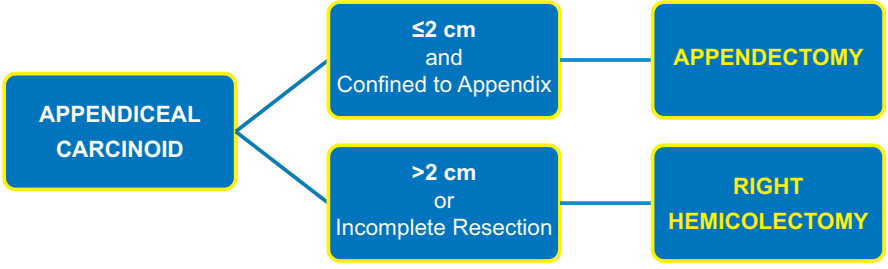

Figure 1. Depiction of the 2018 National Comprehensive Cancer Network surgical treatment guidelines for appendiceal carcinoid tumors.

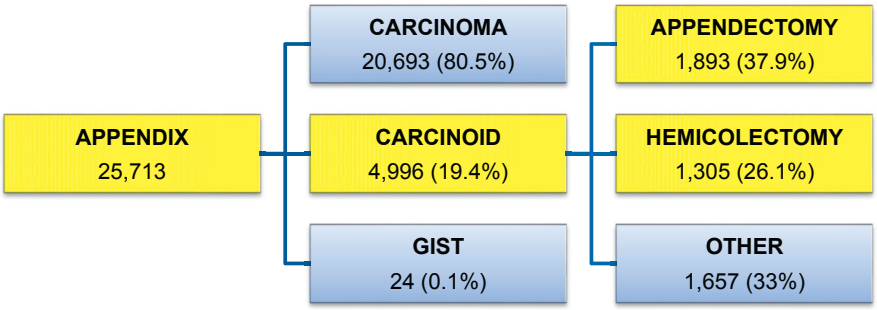

Figure 2. Process of identifying cases of appendiceal carcinoid tumor treated with appendectomy or hemicolectomy, as recorded in the National Cancer Data Base from 2004 to 2015. GIST, gastrointestinal stromal tumor.

of Diseases for Oncology, 3rd Edition[17] included: 8240 = carcinoid, 8241 = enterochromaffin cell carcinoid, 8242 = enterochromaffin-like cell carcinoid, 8246 = neuroendocrine carcinoma, and 8249 = neuroendocrine tumor. Finally, patients treated with appendectomy or formal right hemicolectomy were selected for study. In the context of appendiceal tumors, these procedures have been correlated previously with the Facility Oncology Registry Data Standards codes 30 to 32 for segmental resection (denoting appendectomy, cecectomy, and ileocecectomy) and codes 40 to 41 for hemicolectomy (denoting right and extended right hemicolectomy with oncologic lymphadenectomy).[5,8,15] Of note, the NCDB does not specify which patients underwent segmental resection as the first procedure followed by completion right hemicolectomy as the definitive procedure, so this statistic could not be reported.

Practice pattern analysis

The primary objective was to investigate surgical concordance with size-based treatment guidelines. Patients were stratified by tumor size ≤2 cm vs >2 cm, and the

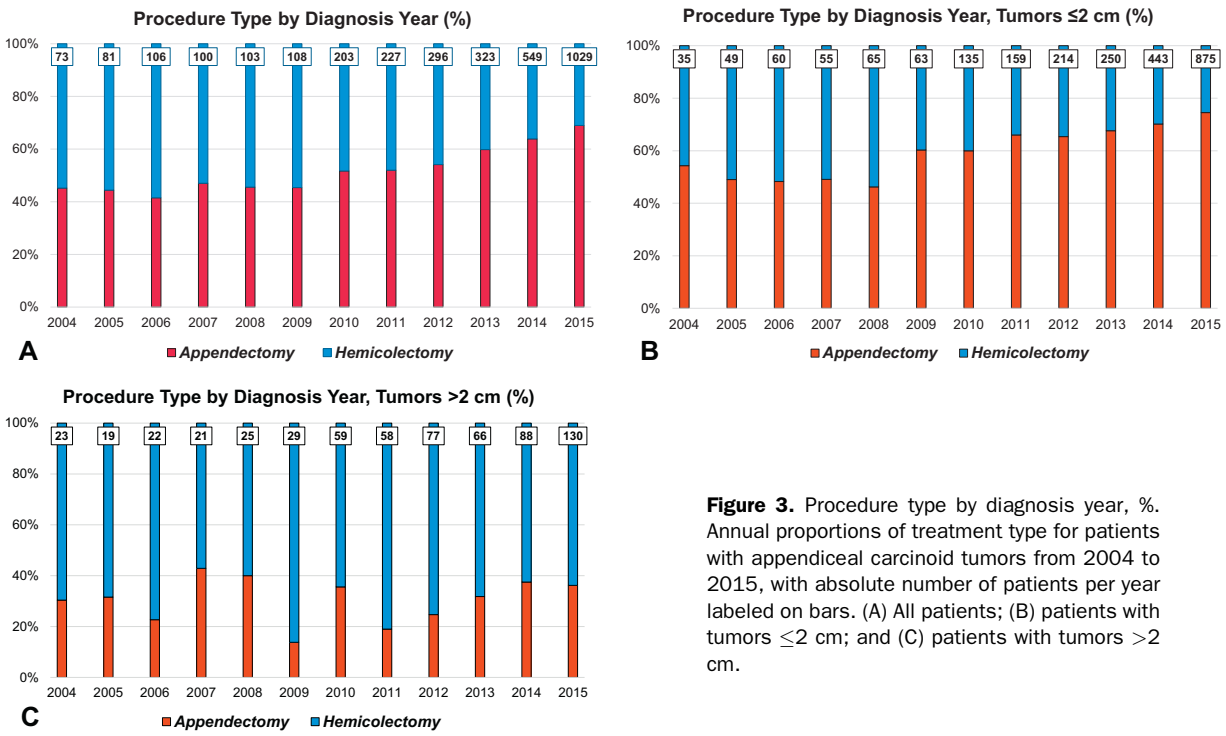

Figure 3. Procedure type by diagnosis year, %. Annual proportions of treatment type for patients with appendiceal carcinoid tumors from 2004 to 2015, with absolute number of patients per year labeled on bars. (A) All patients; (B) patients with tumors ≤2 cm; and (C) patients with tumors >2 cm.

Table 1. Univariable Analysis Showing Demographic and Clinical Characteristics of Patients Treated with Appendectomy vs Hemicolectomy for Small Tumors ≤2 cm (n = 2,403)

	Appendectomy		Hemicolectomy		
Characteristic	**n**	**%**	**n**	**%**	**p Value**
Total	1,625	67.6	778	32.4	—
Sex					0.99
Male	629	67.6	301	32.4	
Female	996	67.6	477	32.4	
Age group					<0.01
18–39 y	726	77.4	212	22.6	
40–64 y	668	65.9	346	34.1	
≥65 y	231	51.2	220	48.8	
Race					0.11
White	1,413	67.2	689	32.8	
Black	129	66.8	64	33.2	
Other	36	76.6	11	23.4	
Urbanicity					0.08
Metropolitan	1,437	68.5	660	31.5	
Urban/rural	166	62.9	98	37.1	
Missing	22	61.1	14	38.9	
Median income quartile					0.58
<$38,000	228	65.7	119	34.3	
$38,000–$47,999	298	65.9	154	34.1	
$48,000–$62,999	453	68.3	210	31.7	
≥$63,000	645	68.8	292	31.2	
Missing	1	25.0	3	75.0	
No high school degree					0.18
≥21%	232	66.5	117	33.5	
13.0–20.9%	345	66.9	171	33.1	
7.0–12.9%	554	66.0	285	34.0	
<7.0%	494	70.9	203	29.1	
Missing			2	100.0	
Insurance					<0.01
None	95	76.0	30	24.0	
Private	1,089	71.4	436	28.6	
Medicare/Medicaid/government	414	58.3	296	41.7	
Unknown	27	62.8	16	37.2	
Charlson/Deyo score					<0.01
0	1,427	69.3	632	30.7	
≥1	198	57.6	146	42.4	
Prior malignancy					<0.01
No	1,382	72.1	535	27.9	
Yes	243	50.0	243	50.0	
Year of diagnosis					<0.01
2004–2009	167	51.1	160	48.9	
2010–2015	1,458	70.2	618	29.8	
Histology					0.11
Carcinoid/enterochromaffin cell	1,248	68.8	573	31.6	
Neuroendocrine carcinoma	342	64.8	186	35.2	

(Continued)

Table 1. Continued

Characteristic	Appendectomy n	Appendectomy %	Hemicolectomy n	Hemicolectomy %	p Value
Tumor size					<0.01
2.1−3 cm	1,218	74.7	412	25.3	
≥3.1 cm	407	52.7	366	47.3	
Tumor grade					0.43
Low	1,119	70.0	480	30.0	
Intermediate/high	114	67.1	56	32.9	
Unknown	392	61.8	242	38.2	
Lymphovascular invasion					<0.01
No	1,124	73.0	416	27.0	
Yes	79	48.5	84	51.5	
Unknown or missing	421	60.4	276	39.6	

frequency of appendectomy vs hemicolectomy was calculated for each group. Tumor size was missing in 5.6% of the cohort; these patients were excluded from additional analysis.

In univariable analyses, demographic and clinical characteristics were compared between patients treated with appendectomy vs hemicolectomy for each tumor size group. Variables analyzed included sex, age, race, insurance, urbanicity, median income quartile, education level, Charlson/Deyo score, history of malignancy, year of diagnosis, histology, tumor size, tumor grade, and lymphovascular invasion. History of malignancy, extracted from the cancer "sequence number" field in the NCDB, was analyzed as a separate covariate from comorbidity score to capture the potential confounding effect of previous cancer on treatment or survival (eg patients with right colon cancer treated with hemicolectomy who were incidentally diagnosed with appendiceal carcinoid on pathologic review).[18]

Facility location, cancer-center type, and tumor location within the appendix were excluded from analysis due to >40% missing data. Two variables—tumor grade and lymphovascular invasion—were noted to have up to 26% and 35% unknown and/or missing data across the patient strata, respectively. Because grade and lymphovascular invasion are important markers of tumor aggressiveness that can drive surgical treatment choice, we used multiple imputations (PROC MI and PROC MIANALYZE, SAS, version 9.4, SAS Institute) to generate unknown and/or missing data, as has been previously proposed.[19] We further verified these results by performing sensitivity analyses, treating missing data as unique covariates within the grade and lymphovascular invasion categories. Results were consistent with those from the imputations.

Categorical characteristics of patients treated with appendectomy vs hemicolectomy were summarized and then compared using chi-square statistical tests. A 2-sided *p*-value <0.05 was considered statistically significant.

Variables were then entered into a backward stepwise logistic regression to assess their associations with treatment procedure for small and large tumors, respectively. Those with $p < 0.20$ remained in the final multivariable models, which ultimately included all variables from univariable analyses. Two logistic regression models were used: one that identified factors associated with hemicolectomy among patients with small tumors (≤2 cm), and another that identified factors associated with appendectomy among patients with large tumors (>2 cm). Odds ratios (OR) with a 95% CI that did not include 1.0 were considered statistically significant.

Survival analysis

After calculating the frequency of non-recommended procedures in the management of appendiceal carcinoids, we explored the impact of guideline non-adherence on survival. Using the Kaplan-Meier method, we first calculated unadjusted overall survival (OS) for the entire cohort, comparing patients with small vs large tumor size. This was replicated for small tumors (≤2 cm), intermediate tumors (1.1 to 2 cm), and large tumors (>2 cm), stratifying by appendectomy vs hemicolectomy to assess survival differences between the treatment arms and controlling for tumor size. The log-rank test with p value set at <0.05 was used to demonstrate a significant survival difference.

Cox proportional hazards models were then used to evaluate associations of demographic and disease factors with OS after adjusting for age, race, insurance, urbanicity, median income quartile, education level, Charlson/

Table 2. Univariable Analysis Showing Demographic/Clinical Characteristics of Patients Treated with Appendectomy vs Hemicolectomy for Large Tumors >2 cm (n = 617)

	Appendectomy		Hemicolectomy		
Characteristic	**n**	**%**	**n**	**%**	**p Value**
Total	193	31.3	424	68.7	—
Sex					0.90
Male	72	31.6	156	68.4	
Female	121	31.1	268	68.9	
Age group					0.49
18–39 y	65	30.0	152	70.0	
40–64 y	88	30.4	201	69.6	
≥65 y	40	36.0	71	64.0	
Race					0.73
White	162	31.0	360	69.0	
Black	27	34.2	52	65.8	
Other	3	42.9	4	57.1	
Urbanicity					0.02
Metropolitan	176	33.0	357	67.0	
Urban/rural	17	20.2	67	79.8	
Missing	5	35.7	9	64.3	
Median income quartile					0.97
<$38,000	26	32.9	53	67.1	
$38,000–$47,999	38	30.9	85	69.1	
$48,000–$62,999	56	31.8	120	68.2	
≥$63,000	71	30.3	163	69.7	
Missing	2	40.0	3	60.0	
No high school degree					0.64
≥21%	27	36.0	48	64.0	
13.0–20.9%	43	29.3	104	70.7	
7.0–12.9%	68	32.9	139	67.1	
<7.0%	54	29.2	131	70.8	
Missing	1	33.3	2	66.7	
Insurance					0.87
None	12	35.3	22	64.7	
Private	121	31.1	268	68.9	
Medicare/Medicaid/government	56	30.8	126	69.2	
Unknown	4	33.3	18	66.7	
Charlson/Deyo score					0.13
0	169	32.5	351	67.5	
≥1	24	24.7	73	75.3	
Prior malignancy					0.87
No	161	31.1	356	68.9	
Yes	32	32.0	68	68.0	
Year of diagnosis					0.99
2004–2009	41	29.5	98	70.5	
2010–2015	152	31.8	326	68.2	
Histology					0.26
Carcinoid/enterochromaffin cell	121	32.8	254	67.2	
Neuroendocrine carcinoma	62	28.4	156	71.6	

(Continued)

Table 2. Continued

Characteristic	Appendectomy n	Appendectomy %	Hemicolectomy n	Hemicolectomy %	p Value
Tumor size					0.03
2.1−3 cm	119	34.9	222	65.1	
≥3.1 cm	74	26.8	202	73.2	
Tumor grade					0.10
Low	114	32.5	237	67.5	
Intermediate/high	26	24.1	82	75.9	
Unknown	53	33.5	105	66.5	
Lymphovascular invasion					0.05
No	87	35.5	158	64.5	
Yes	41	26.3	115	73.7	
Unknown or missing	65	30.1	151	69.9	

Deyo score, history of malignancy, year of diagnosis, histology, tumor size, tumor grade, lymphovascular invasion, and procedure type. Hazard ratios (HRs) with 95% CI that excluded 1.0 were considered to be significantly associated with OS.

RESULTS

Cohort characteristics

Of 25,713 appendiceal tumors in the NCDB diagnosed between 2004 and 2015, 4,996 (19.4%) were pure carcinoids. A majority of surgically managed cases (37.8%) were treated with appendectomy, and a minority (26.1%) were treated more aggressively with hemicolectomy. The remainder of patients were treated with alternative therapies that were either unknown or coded as endoscopic removal or total colectomy, and they were excluded. The preliminary cohort of 3,198 patients was composed of 1,893 (59.2%) treated with appendectomy and 1,305 (40.8%) treated with hemicolectomy (Fig. 2).

Of this cohort, 1,968 (61.5%) were female, 2,779 (86.9%) were white, mean age was 47 years (SD 17.7), and 2,728 (85.3%) had no medical comorbidities. The majority of tumors with known histopathologic features were low grade (86.9%) and lacked lymphovascular invasion (84.7%). Three-thousand and twenty patients (94.4%) had known tumor size, roughly 80% of which measured ≤2 cm in largest diameter and 20% measured >2 cm; these patients made up the final analytic cohort.

During the first half of the study period from 2004 to 2009, the proportion of appendectomies represented roughly 45.0% of operations/year, ultimately growing to represent 69.0% of operations by 2015. The surge in appendectomy rate was largely seen among patients with small tumors (≤2 cm); among patients with large tumors (>2 cm), the proportions of appendectomy and hemicolectomy remained constant on average over time (Fig. 3).

Demographic and clinical associations with procedure type

After stratifying patients by tumor size, demographic and clinical characteristics were compared between the 2 treatment arms. Analysis of small tumors (≤2 cm) revealed that nearly one-third of patients had been treated with non-recommended hemicolectomy. Hemicolectomy was more prevalent during the first half of the study period and among older patients with medical comorbidities, history of cancer, government-provided health insurance, and tumors with intermediate size (1.1 to 2 cm) and lymphovascular invasion (Table 1).

Analysis of large tumors (>2 cm) revealed that a similarly high proportion of patients, nearly one-third, had been treated with non-recommended appendectomy. Several inverse associations were seen. Appendectomy rates were higher in healthy patients without comorbidities whose tumors were low grade and lacking lymphovascular invasion, although these variables did not reach statistical significance. Appendectomy was significantly associated with smaller tumors (2.1 to 3 cm) and metropolitan vs urban/rural setting (Table 2).

In multivariable analyses, many of the characteristics mentioned remained associated with non-recommended hemicolectomy in patients with small tumors and with non-recommended appendectomy in patients with large tumors. Among patients with small tumors (≤2 cm), the variable with the strongest association with hemicolectomy was intermediate tumor size (1.1 to 2 cm) (OR 2.8; 95% CI 2.3 to 3.4; reference group size ≤1 cm), followed by age older than 65 years (OR 2.3; 95% CI 1.7 to 3.2; reference group age 18 to 39 years), earlier year of

Table 3. Multivariable Analysis Showing Strength of Association between the Non-Recommended Treatment Procedure and Demographic/Clinical Characteristics of Patients with Small Tumors ≤2 cm and Large Tumors >2 cm, Respectively

	Hemicolectomy: tumor ≤2 cm		Appendectomy: tumor >2 cm	
Characteristic	**OR**	**95% CI**	**OR**	**95% CI**
Sex				
Male	ref	ref	ref	ref
Female	1.0	0.8–1.2	1.0	0.7–1.4
Age group				
18–39 y	ref	ref	ref	ref
40–64 y	1.6	1.3–2.0	1.2	0.8–1.9
≥65 y	2.3	1.7–3.2	2.3	1.2–4.4
Race				
White	ref	ref	ref	ref
Black	0.9	0.7–1.3	1.2	0.7–2.0
Other	0.7	0.4–1.1	0.7	0.2–2.3
Urbanicity				
Metropolitan	ref	ref	ref	ref
Urban/rural	1.2	0.9–1.6	0.5	0.3–0.9
Median income quartile				
<$38,000	ref	ref	ref	ref
$38,000–$47,999	1.0	0.7–1.4	1.0	0.5–2.0
$48,000–$62,999	1.0	0.7–1.4	0.9	0.5–1.8
≥$63,000	1.1	0.7–1.6	0.8	0.4–1.7
No high school degree				
≥21%	ref	ref	ref	ref
13.0–20.9%	0.9	0.7–1.3	0.7	0.4–1.3
7.0–12.9%	0.9	0.7–1.3	0.8	0.4–1.6
<7.0%	0.7	0.5–1.1	0.7	0.3–1.5
Insurance				
None	ref	ref	ref	ref
Private	1.0	0.7–1.5	0.9	0.4–1.7
Medicare/Medicaid/government	1.3	0.8–2.0	0.7	0.3–1.5
Charlson/Deyo score				
0	ref	ref	ref	ref
≥1	1.3	1.0–1.6	0.6	0.4–1.0
Prior malignancy				
No	ref	ref	ref	ref
Yes	2.0	1.6–2.6	1.0	0.6–1.6
Year of diagnosis				
2004–2009	ref	ref	ref	ref
2010–2015	0.5	0.4–0.7	1.1	0.6–2.1
Histology				
Carcinoid/enterochromaffin cell	ref	ref	ref	ref
Neuroendocrine carcinoma	1.1	0.9–1.4	0.9	0.6–1.3
Tumor size				
≤1 cm	ref	ref	—	—
1.1–2 cm	2.8	2.3–3.4	—	—
2.1–3 cm	—	—	ref	ref
≥3.1 cm	—	—	0.7	0.5–1.0

(Continued)

Table 3. Continued

Characteristic	Hemicolectomy: tumor ≤2 cm		Appendectomy: tumor >2 cm	
	OR	95% CI	OR	95% CI
Tumor grade				
Low	ref	ref	ref	ref
Intermediate/high	1.0	0.7−1.3	0.8	0.5−1.3
Lymphovascular invasion				
No	ref	ref	1.4	1.0−2.0
Yes	1.6	1.1−2.3	ref	ref

OR, odds ratio.

diagnosis from 2004 to 2009 (OR 0.5 for years 2010 to 2015; 95% CI 0.4 to 0.7), history of malignancy (OR 2.0; 95% CI 1.6 to 2.6), and presence of lymphovascular invasion (OR 1.6; 95% CI 1.1 to 2.3). For patients with large tumors (>2 cm), predictors of non-recommended appendectomy were age older than 65 years (OR 2.3; 95% CI 1.2 to 4.4), metropolitan setting (OR 0.5 for urban/rural setting; 95% CI 0.3 to 0.9), absence of lymphovascular invasion (OR 1.4; 95% CI 1.0 to 2.0), and tumor size 2.1 to 3 cm (OR 0.7 for size ≥3.1 cm; 95% CI 0.5 to 1.0) (Table 3).

Impact of procedure type on survival

Comparison of Kaplan-Meier curves revealed a significant difference in overall survival between patients with small and large tumors (log-rank = 0.02). At 10 years of

Table 4. Cox Proportional Hazards Models Showing Adjusted Effects of Demographic and Clinical Characteristics on the Survival of Patients with Appendiceal Carcinoid Tumors

Characteristic	All tumors	Tumor size		
		≤2 cm	1.1−2 cm	>2 cm
Age				
18−39 y	ref	ref	ref	ref
40−64 y	6.4 (3.2−12.9)	5.8 (2.4−13.7)	5.9 (1.3−26.8)	5.4 (1.6−18.3)
≥65 y	12.0 (5.6−25.7)	10.4 (4.0−26.8)	17.8 (3.2−97.8)	8.3 (2.2−31.9)
Charlson/Deyo Score				
0	ref	ref	ref	ref
≥1	1.9 (1.4−2.6)	1.9 (1.3−2.9)	2.9 (1.4−6.0)	2.4 (1.2−4.5)
Earlier malignancy				
No	ref	ref	ref	ref
Yes	1.9 (1.4−2.6)	2.5 (1.7−3.7)	3.4 (1.7−6.8)	1.3 (0.7−2.4)
Surgical treatment				
Appendectomy	ref	ref	ref	ref
Hemicolectomy	1.0 (0.8−1.4)	1.0 (0.7−1.4)	1.1 (0.6−2.2)	1.3 (0.7−2.3)
Histology				
Carcinoid	ref	ref	ref	ref
Carcinoma	1.7 (1.2−2.4)	1.6 (1.1−2.4)	2.0 (1.0−3.9)	1.9 (1.0−3.8)
Tumor size				
≤2 cm	ref	NA	NA	NA
>2 cm	1.2 (0.9−1.7)	NA	NA	NA
Tumor grade				
Low	ref	ref	ref	ref
Intermediate/high	2.0 (1.4−2.9)	1.3 (0.7−2.3)	1.3 (0.5−3.2)	3.3 (1.7−6.1)
Lymphovascular invasion				
No	1.1 (0.6−1.6)	1.3 (0.6−2.0)	1.1 (0.4−3.3)	0.6 (0.2−1.7)
Yes	ref	ref	ref	ref

Values are hazard ratio (95% CI). Only variables that reached statistical significance in unadjusted analyses are shown.
HR, hazards ratio; NA, not applicable.

follow-up, 84% of patients with small tumors were alive vs 77% of patients with large tumors ($p = 0.01$). In the Cox regression models, neither large tumor size (HR 1.2; 95% CI 0.9 to 1.7) nor treatment type (HR 1.0; 95% CI 0.8 to 1.4) had a significant impact on survival for the cohort. Instead, patient factors, including age older than 65 years (HR 12.0; 95% CI 5.6 to 25.7), history of malignancy (HR 1.9; 95% CI 1.4 to 2.6), and medical comorbidities (HR 1.9; 95% CI 1.4 to 2.6) were the predominant predictors. Disease characteristics, including intermediate/high tumor grade (HR 2.0; 95% CI 1.4 to 2.9) and carcinomatous histology (HR 1.7; 95% CI 1.2 to 2.4) were also significantly associated (Table 4, Fig. 4).

Among patients with small tumors (≤2 cm), 10-year OS was 88% for those treated with appendectomy and 84% for those treated with hemicolectomy ($p < 0.01$; log-rank < 0.01). Procedure type did not impact survival (HR 1.0; 95% CI 0.7 to 1.4). Variables that were predictive resembled those identified on the total cohort analysis, including age 65 years or older (HR 10.4; 95% CI 4.0 to 26.8), history of malignancy (HR 2.5; 95% CI 1.7 to 3.7), concomitant comorbidities (HR 1.9; 95% CI 1.3 to 2.9), and carcinomatous histology (HR 1.6; 95% CI 1.1 to 2.4) (Table 4, Fig. 4). When restricting the small tumor group to tumors measuring 1.1 to 2 cm, 10-year OS remained similar between patients treated with appendectomy and hemicolectomy (87% vs 89%; $p = 0.32$; log-rank = 0.63), and procedure type did not impact survival (HR 1.1; 95% CI 0.6 to 2.2) (Table 4, Fig. 4).

Among patients with large tumors (>2 cm), 10-year OS was 70% for those treated with appendectomy and 81% for those treated with hemicolectomy ($p = 0.75$). Despite this disparity, the log-rank test was not statistically significant ($p = 0.90$). Multivariable analysis again failed to show an impact of procedure type on survival (HR 1.3; 95% CI 0.7 to 2.3). Older age (HR 8.3; 95% CI 2.2 to 31.9), concomitant comorbidities (HR 2.4; 95% CI 1.2 to 4.5), intermediate/high tumor grade (HR 3.3; 95% CI 1.7 to 6.1), and carcinomatous histology (HR 1.9; 95% CI 1.0 to 3.8) all predicted poorer survival (Table 4, Fig. 4).

DISCUSSION

Using a large contemporary national data set, we found that >30% of patients with appendiceal carcinoids are treated by surgeons with a non-recommended procedure, as defined by recognized guidelines from the National Comprehensive Cancer Network and North American Neuroendocrine Tumor Society. This surprisingly large percentage applied to both patients treated with hemicolectomy for small tumors (≤2 cm) and appendectomy for large tumors (>2 cm). The former is certainly improving over time: hemicolectomy for small carcinoids has been on the downtrend since 2010. The same has not been true of appendectomy for large carcinoids, however, the proportion of which has remained relatively stable since 2004.

What is driving these practice patterns? Apart from the questionable survival benefit of hemicolectomy raised by previous studies,[8,15,16] other contributing factors may relate to demographic and disease characteristics. Among patients with small tumors, we identified older age, comorbidities, and cancer history as significantly associated with non-adherence to treatment guidelines. These associations might be partially explained by confounding effects: older, sicker patients might have concomitant right colonic diseases requiring hemicolectomy, with subsequent diagnosis of carcinoid. The uncertain nature of statistical associations is a drawback of all retrospective studies that use administrative-level data, and a clear limitation of our study. Still, the connection between older age and hemicolectomy is important to note, as it stands at odds with the original longitudinal investigations by Moertel and colleagues[3] in 1987 and Roggo and colleagues[4] in 1993, who recommended consideration of hemicolectomy for young patients to prevent long-term recurrence. Their admonition does not appear to play a large role in modern decision-making, the implications of which on recurrence are not yet known.

Other identified predictors of hemicolectomy for small tumors, intermediate tumor size and lymphovascular invasion, related to tumor aggressiveness. These associations are more readily interpretable as an attempt to completely eliminate occult disease and prevent recurrence.[6,12] They might also highlight ambiguity within the practice guidelines, which state in a footnote that "some institutions will consider more aggressive treatments for 1 to 2 cm with poor prognostic features,"[10] yet do not then offer an explicit treatment recommendation for such tumors. This ambiguity could be engendering confusion or apprehension around the treatment of small tumors with aggressive features, manifesting in more aggressive management.

Among patients with large tumors, predictors of undertreatment were fewer. Elderly patients were more prone to appendectomy, revealing that surgical risk seemed to outweigh cancer risk. Tumor size 2.1 to 3 cm and absence of lymphovascular invasion were also associated with less aggressive treatment. The clustering of appendectomy-treated large tumors in metropolitan locales, along with the stable proportion of appendectomies throughout the

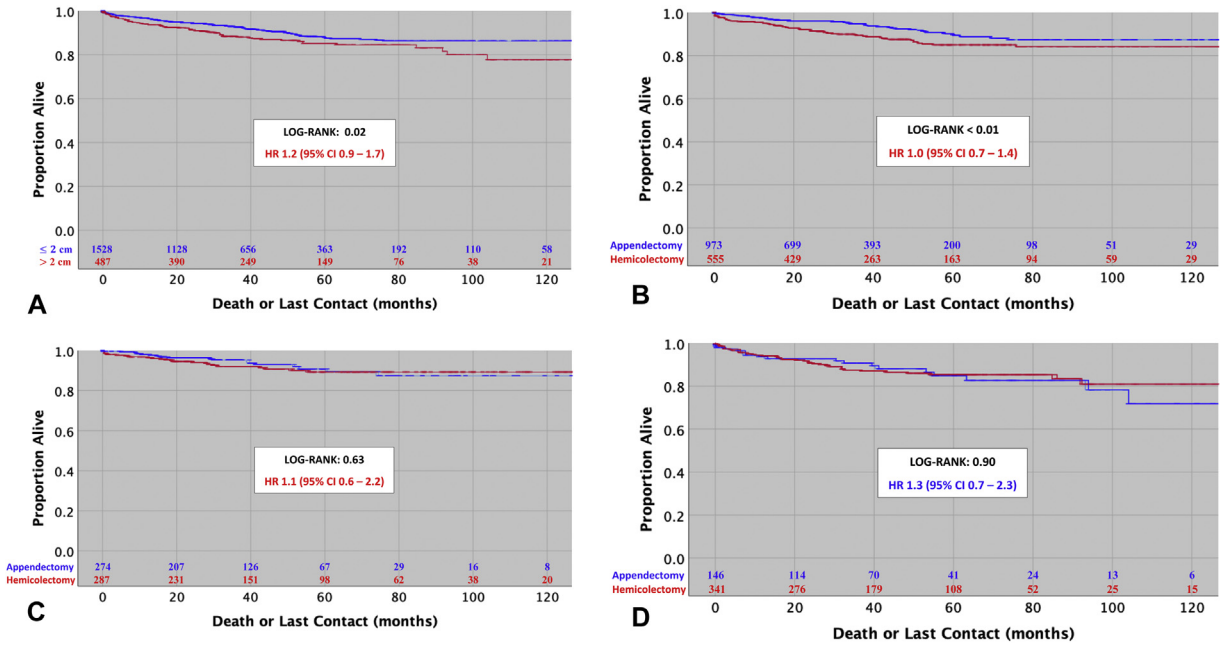

Figure 4. Unadjusted Kaplan-Meier survival curves represent: (A) all patients; (B) patients with tumors ≤2 cm; (C) patients with tumors 1.1 to 2 cm; (D) patients with tumors >2 cm.

study period, suggest that some institutions might categorically treat appendiceal carcinoids non-aggressively. Bamboat and Berger,[16] using single institutional data, and Ciarrocchi and colleagues,[8] using data from the Surveillance, Epidemiology, and End Results database, have supported such an approach.

More important than understanding what underlies guideline non-adherence is measuring the clinical impact. In the survival analysis of the total cohort, there was a 7% difference between patients with small and large tumors at 10 years of follow-up. At first glance, this suggested that aggressive oncologic resection was necessary to effectively treat large tumors. However, in the adjusted analysis, resection procedure did not appear to impact survival, nor did tumor size. The most frequently identified factors were not related to the disease but to the patients, such as their age, comorbidities, and history of malignancy. Life expectancy and overall health status dictated survival more than tumor characteristics, raising the possibility that, on average, large carcinoids might be a symptom rather than source of poorer health status and earlier death.

This theme persisted for each tumor size group—small, intermediate, and large. When stratifying each group by procedure type, the only meaningful survival difference emerged for large tumors, where patients treated with appendectomy saw a 11% reduction in 10-year survival. In the adjusted analyses of all size groups, however, baseline patient characteristics were the predominant predictors of survival. Resection procedure had no impact.

It must be noted that tumor factors were not entirely dissociated from survival in the Cox model. Although size, lymphovascular invasion, and treatment type were not significantly associated with survival, higher grade and carcinomatous histology were associated, specifically in the setting of large tumors. Although this finding aligns with the way oncologists generally view aggressive histopathologic markers, it still seems counterintuitive with the well-published finding that resection type does not impact survival. Unlike medical oncologists, who increasingly look to genomics to guide systemic treatment decisions, many surgeons still rely on clinical indicators of disease aggressiveness—size, histopathology, and lymph node status—to guide treatment decisions and improve survival. Such an approach does not appear to completely befit appendiceal carcinoids, yet the association of grade and histology with poorer outcomes cannot be ignored. Caution should be used in the setting of these less common variants, present in 12.5% and 24.7% of patients in our national data set, respectively. When present, we recommend consultation with a multidisciplinary tumor board to inform treatment approach, as a specific treatment procedure is not supported by our data or past literature.

Rare cancers make difficult study subjects. Accruing enough data to power a study with generalizability can

take decades, during which treatment modalities and guidelines evolve. National registry data have become essential for tracking practice and outcomes trends in rare diseases. The NCDB platform, capturing most US cancer cases and recording a variety of patient and tumor characteristics, suits this purpose well for appendiceal neuroendocrine tumors. Use of this registry is a key strength of our study compared with other studies that use single-institutional data. Naturally, it is also a limitation. Administrative-level data that have gone through several rounds of recoding lack granularity and are prone to processing errors and inconsistencies. This latter point is particularly important in the setting of rare tumors, for which the numbers are not always large enough to offset random coding error. For this reason, extreme specificity in selecting a study cohort and integrity of statistical methods is of the utmost importance. We strongly prioritized these elements in our study design.

Our data demonstrate that non-adherence to size-based treatment guidelines is widespread, though it might not alter the prognosis of patients with appendiceal carcinoid tumors. Appendectomy for all tumor sizes can actually suffice in a large number of cases. Expert disagreement around this issue can stem from dissimilar data being used across studies; for example, many include adeno- and goblet cell carcinoids, for which the prognosis is poorer than for pure carcinoids.[2-6,12] Tendencies of oncologists and surgeons to attach size-associated lymph node spread to a need for more aggressive treatment might also promote hemicolectomy without evidence of survival benefit. Additional investigation into outcomes of appendectomy vs hemicolectomy in treating appendiceal carcinoids must meticulously separate out biologically distinct histologies and use optimal statistical methods to avoid misinterpreting the clinical implications of tumor size associations.

CONCLUSIONS

Up to one-third of patients with appendiceal carcinoid tumors in the US are treated with a non-recommended surgical procedure by the standards of nationally recognized, size-based treatment guidelines. Variant study methodologies, paucity of data, and ambiguity or mistrust of the guidelines might be contributing to variability in practice. Despite such practice patterns, patient survival does not appear to be impacted negatively. This casts some doubt on the need for aggressive surgical resection of appendiceal carcinoids and calls for reassessment of the treatment guidelines.

Author Contributions

Study conception and design: Heller, Jean, Luo, Kurbatov, Grisotti, Jacobs, Chiu, Zhang, Khan
Acquisition of data: Heller, Jean, Khan
Analysis and interpretation of data: Heller, Jean, Luo, Kurbatov, Grisotti, Jacobs, Chiu, Zhang, Khan
Drafting of manuscript: Heller, Jean, Khan
Critical revision: Heller, Jean, Luo, Kurbatov, Grisotti, Jacobs, Chiu, Zhang, Khan

REFERENCES

1. Ruoff C, Hanna L, Zhi W, et al. Cancers of the appendix: review of the literatures. ISRN Oncol 2011;728579:1–6.
2. Griniatsos J, Michail O. Appendiceal neuroendocrine tumors: recent insights and clinical implications. World J GI Oncol 2010;2:192–196.
3. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med 1987;317:1699–1701.
4. Roggo A, Wood WC, Ottinger LW. Carcinoid tumors of the appendix. Ann Surg 1993;217:385–390.
5. Groth SS, Vernic BA, Al-Refaie WB, et al. Appendiceal carcinoid tumors: predictors of lymph node metastasis and the impact of right hemicolectomy on survival. J Surg Oncol 2011;103:39–45.
6. Sarshekeh AM, Advani S, Halperin DM, et al. Regional lymph node involvement and outcomes in appendiceal neuroendocrine tumors: a SEER database analysis. Oncotarget 2017;8:99541–99551.
7. Landry CS, Woodall C, Scoggins CR, et al. Analysis of 900 appendiceal carcinoid tumors for a proposed predictive staging system. Arch Surg 2008;143:664–670.
8. Ciarrocchi A, Pietroletti R, Carlei F, et al. Propensity adjusted appraisal of the surgical strategy for appendiceal carcinoids. Tech Coloproctol 2015;19:35–41.
9. Mosquera C, Fitzgerald TL, Vora H, Grzybowski M. Novel nomogram combining depth of invasion and size can accurately predict the risk for regional nodal metastases for appendiceal neuroendocrine tumors (A-NET). J Surg Oncol 2017;116:651–657.
10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology for Neuroendocrine and Adrenal Tumors, Version 2.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed May 24, 2018.
11. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013;42:557–577.
12. Kleiman DA, Finnerty B, Beninato T, et al. Features associated with metastases among well-differentiated neuroendocrine (carcinoid) tumors of the appendix: the significance of small vessel invasion in addition to size. Dis Colon Rectum 2015;58:1137–1143.
13. National Comprehensive Cancer Network (NCCN). Archive NCCN Practice Guidelines in Oncology for Neuroendocrine

and Adrenal Tumors, Version 1.2000. Plymouth Meeting, PA: NCCN; 2000.
14. National Comprehensive Cancer Network (NCCN). Archive NCCN Practice Guidelines in Oncology for Neuroendocrine and Adrenal Tumors, Version 1.2003. Plymouth Meeting, PA: NCCN; 2003.
15. Nussbaum DP, Speicher PJ, Gulack BC. Management of 1- to 2-cm carcinoid tumors of the appendix: using the National Cancer Data Base to address controversies in general surgery. J Am Coll Surg 2015;220:894–903.
16. Bamboat ZM, Berger DL. Is right hemicolectomy for 2.0-cm appendiceal carcinoids justified? Arch Surg 2006;141:349–352.
17. World Health Organization. International Classification of Diseases for Oncology, 3rd Edition. Available at: http://codes.iarc.fr/codegroup/2. Accessed May 24, 2018.
18. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–959.
19. Yuan YC. Multiple Imputation for Missing Data: Concepts and New Development (Version 9.0). Rockville, MD: SAS Institute; 2011.

Invited Commentary

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To bring surgical management of appendiceal carcinoids into the 21st century, Heller and colleagues, from the Yale School of Medicine, took a clever approach using the National Cancer Database (NCDB) to evaluate surgeon adherence to the current guidelines and the impact of any deviation on overall survival. The authors identified 3,189 patients in the NCDB with appendiceal carcinoid who underwent either appendectomy (n = 1,893) or right hemicolectomy (n = 1,305) as their definitive treatment. Contrary to National Comprehensive Cancer Network (NCCN) and North American Neuroendocrine Tumor Society (NANETS) guidelines, 32.4% of tumors $\leq$ 2 cm were treated with right hemicolectomy and 31.3% of tumors $>$ 2 cm were treated with appendectomy alone. On multivariate analysis, neither tumor size nor definitive surgical procedure were associated with overall survival for either small or large tumors. However, in both groups, age $\leq$ 65 years, medical comorbidity (including a history of a previous malignancy in the $\leq$ 2 cm group), tumor grade, and carcinomatous histology predicted poorer survival.

Current NCCN and NANETS guidelines for operative management of appendiceal carcinoids are still largely based on findings published by Moertel and colleagues[1] in 1987. One might argue that administrative-level data from a national registry lack the necessary granularity found in a single-institution study spanning more than 50 years to better understand the true natural history of such a rare and indolent tumor. It would certainly be helpful to know the progression-free and disease-specific survival of the 3,000 patients in this study, as this might, in fact, prove to be related to the type of surgical intervention for appendiceal carcinoids. It could also be argued, given both the latency of recurrence and relatively indolent nature of these tumors, that even with the large numbers of a national registry, there is still not enough power to demonstrate a true survival advantage due to surgical intervention. However, given the consistency of the authors' findings with Moertel and colleagues[1] and others who have not demonstrated a survival benefit associated with right hemicolectomy for appendiceal carcinoids $>$ 2 cm,[2-4] the authors appropriately suggest that tumor size may not be the most important determinant of oncologic outcome for appendiceal carcinoids. As shown in this study, the only tumor-based characteristics that were statistically significant were related to the biology of the tumor: higher grade and carcinomatous histology. This should come as no surprise because this is proving to be the case with most, if not all, other cancers as well. Through this manuscript, Heller and colleagues add another voice to the plea for more modern and precise guidelines for operative management of appendiceal carcinoids. Although their findings appear to support Moertel and coauthors' original 1987 statement that even among patients with $\geq$2 cm tumors, "simple appendectomy appears to be curative,"[1] until this is proven through 21st century technology, surgeons will have to continue to weigh the evidence for themselves and vote with their scalpels.

REFERENCES

1. Moertel CG, Weilan LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med 1987;317:1699–1701.
2. Bamboat ZM, Berger DL. Is right hemicolectomy for 2.0-cm appendiceal carcinoids justified? Arch Surg 2006;141:349–352.
3. Ciarrocchi A, Pietroletti R, Carlei F, et al. Propensity adjusted appraisal of the surgical strategy for appendiceal carcinoids. Tech Coloproctol 2015;19:35–41.
4. Groth SS, Virnig BA, Al-Refaie WB, et al. Appendiceal carcinoid tumors: Predictors of lymph node metastases and the impact of right hemicolectomy on survival. J Surg Oncol 2011;103:39–45.