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Importance of Histologic Subtype in the Staging of Appendiceal Tumors

Kiran K. Turaga, MD, MPH, Sam G. Pappas, MD, and T. Clark Gamblin, MD, MS

Division of Surgical Oncology, Medical College of Wisconsin, Milwaukee, WI

ABSTRACT

Background. Malignant neoplasms of the appendix have different behavior based on their histologic subtypes in anecdotal series. Current staging systems do not capture the diversity of histologic subtypes in predicting outcomes.

Methods. We queried all patients with appendiceal malignancies captured in the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2007. Tumors were classified as colonic type adenocarcinoma, mucinous adenocarcinoma, signet ring cell type, goblet cell carcinoid, and malignant carcinoid. We compared incidence, overall survival, and disease-specific survival for these tumors on the basis of patient, tumor, and therapy characteristics. Estimates from Cox proportional hazard modeling were used to predict hazard ratios for differing histologic subtypes with similar tumor, node, metastasis system (TNM) stages.

Results. Of the 5672 patients identified, we included 5655 (99%) in our analysis. The 5-year disease-specific survival rates were 93% for malignant carcinoid, 81% for goblet cell carcinoid, 55% for colonic type adenocarcinoma, 58% for mucinous adenocarcinoma, and 27% for signet ring cell type. Predicted estimates of adjusted hazard ratios revealed an 8-fold difference between histologic subtypes for similar TNM stages.

Conclusions. Histologic subtype is an important predictor of disease-specific survival and overall survival in patients with appendiceal neoplasms. Addition of the histologic subtype to the TNM staging is simple and may improve prognostication.

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K. K. Turaga, MD, MPH
e-mail: kturaga@mcw.edu

The use of the tumor, node, metastasis system (TNM) classification has become ubiquitous as a result of its applicability to a variety of tumors, its simplicity of use, and its validity in predicting survival outcomes for malignant tumors.[1] Appendiceal adenocarcinomas are generally staged in a manner similar to colonic adenocarcinomas, while novel TNM staging strategies have been proposed for appendiceal carcinoids, which in the 7th edition of the staging system include tumor grade, proliferation index, and tumor mitotic rate as well as the incorporation of mucinous histology.[2–4] Nevertheless, a high proportion of tumors, including goblet cell carcinoids and signet cell adenocarcinoma, remain in orphan status, and clinicians are often forced to stage disease on the basis of existing TNM staging guidelines, which may over- or understage tumors in terms of survival outcomes.

More than 280,000 appendectomies are performed in the United States every year, and appendiceal tumors are noted in 0.9–1.4% of the tumors operated on.[5,6] Despite the application of laparoscopic appendectomies and early use of computed tomographic scans in the diagnosis of appendicitis, the rates of perforated appendicitis have stayed similar over the last 3 decades.[6] The variability in the median survival for perforated malignant appendiceal tumors can vary from 6 months in patients with signet cell adenocarcinoma to >8 years in patients with mucinous neoplasms (disseminated peritoneal adenomucinosis [DPAM]/peritoneal mucinous carcinomatosis [PMCA]) This variability is poorly captured in the current staging systems.[7] Additionally, the application of hyperthermic chemoperfusion for appendiceal epithelial neoplasms has become more widely accepted in the setting of ruptured appendiceal tumors with positive peritoneal disease, and appropriate risk staging might help determine the timing and aggressiveness of therapy.[8]

We hypothesized that the histologic characteristics of appendiceal neoplasms are strong predictors of survival and proposed that histology should be included in the staging of patients with appendiceal tumors.

METHODS

We obtained an institutional review board exemption for the purposes of the study because the Surveillance, Epidemiology, and End Results (SEER) program provides deidentified data. The SEER program collects data from 17 registries that currently include approximately 28% of the U.S. population. The methodology of the SEER database and its external validity have been previously reported.[9]

Cases of malignant neoplasms of the appendix reported to the SEER program between 1973 and 2007 were included in the study. The SEER*Stat program was used to abstract data from all patients with site of disease recorded as the appendix in all 17 registries. We included all patients with complete data for analysis. Missing data were not interpolated and were treated as missing variables. Patients with year of diagnosis before 1983 had limited data and were excluded from detailed analysis.

Incidence rates were calculated by the incidence rate function provided by the SEER*Stat program. Incidence rates for the entire study period were obtained from 9 SEER registries, and updated incidence rates were obtained from 17 registries for the period 2000–2007.

Histologic subtypes were classified by ICD oncology codes. The histologic subtypes classified were as follows: malignant carcinoid tumors (8240, 8241, 8249), goblet cell carcinoid (including adenocarcinoid and neuroendocrine carcinoma) (8243, 8244, 8245, 8246, 8574, 8013), adenocarcinoma (8010, 8020, 8140, 8141, 8144, 8211, 8210, 8255, 8260, 8261, 8262, 8263, 8310, 8440, 8460, 8550, 8560), mucinous adenocarcinoma (8470, 8471, 8472, 8480, 8481), and signet ring cell adenocarcinoma (8490). We excluded patients with an ICD diagnosis of 8000 (malignant neoplasm, $n = 12$), 8800 (sarcoma, $n = 1$), 8890 (leiomyosarcoma, $n = 1$), 8936 (gastrointestinal stromal tumor, $n = 1$), and 9140 (Kaposi sarcoma, $n = 0$)

Age was investigated using graphical means, and linear splines were created to allow for analysis in the subgroups of <20, 20–39, 40–59, and ≥ 60 years of age. Tumor size, tumor extension, nodal disease, and metastasis were available only for patients diagnosed after 1983, and these data were included. Tumor extension was classified consistent with the current American Joint Committee on Cancer (AJCC) proposed guidelines into T0 or Tis (intramucosal cancer), T1 (involving submucosa), T2 (involving muscularis propria), T3 (invading through muscularis and/or serosa), and T4 (involving adjacent organs). Nodal disease and metastatic disease were classified as a binary variable.

The type of surgical resection was obtained by using classification codes available after 1983. This was classified broadly into no surgery, local surgery (excision, destruction, curettage), partial colectomy (including appendectomy), segmental colectomy (right colectomy or subtotal colectomy), total proctocolectomy, and colectomy plus resection of contiguous organ. We considered appendectomies as partial colectomies, which fitted the definition better in the coding manuals and also occurred with an expected frequency of 32%.

Data abstracted by the SEER*Stat program were imported into Stata 9.0 (Houston, TX), and logic checks were used to verify the imported data. Continuous variables were assessed by the t-test, and nonparametric tests, including the chi-square test, were applied as appropriate. Survival analysis was performed by Cox proportional hazard modeling with robust standard errors. Although analysis was performed for both overall survival and disease-specific survival, we report the results of the latter. Postestimation linear combination was used to predict point estimates, hazard ratios (HRs), and standard errors after modeling. In concordance with epidemiologic convention, the survival of patients recorded as null was changed to 0.5 months to capture data ($n = 179$).[10]

The alpha error was set at 0.05, and all P values indicate two-sided tests. Multivariate survival modeling was limited by loss of data from missing variables with regard to size and nodal status, and limited inferences were drawn from the multivariate models.

RESULTS

Our original query resulted in 5672 patients recorded as having tumors arising in the appendix; of these, we excluded 15 patients as a result of sarcomatous or poorly defined ICD oncology histologic codes. We had limited tumor characteristic data for 596 patients with tumors diagnosed before 1983 (10%), and data from this group of patients were used for demographic comparisons only.

The age-adjusted incidence rate (to the U.S. population 2000) for the entire study period was 4 cases per 1,000,000 population and varied from 2 cases/1,000,000 in 1973 to 5–6 cases/1,000,000 in 2006–2007; Fig. 1). In the abbreviated registries, the overall age-adjusted incidence was 6 cases/1,000,000 patients. The histologic subgroups had low individual incidences (0–2 cases/1,000,000), and hence discrimination of trends was not possible by disease subtype.

The median age of the population was 46 years (interquartile range 58–70), and the predominant histologic subtype was mucinous adenocarcinoma (37%, $n = 2101$). Demographic and therapeutic characteristics by histologic subtype are shown in Table 1. Patients with signet ring cell carcinoma were more likely to have poorly differentiated histology (50%), locally advanced (T4) lesion (56%), and node-positive disease (61%), and they were likely to have

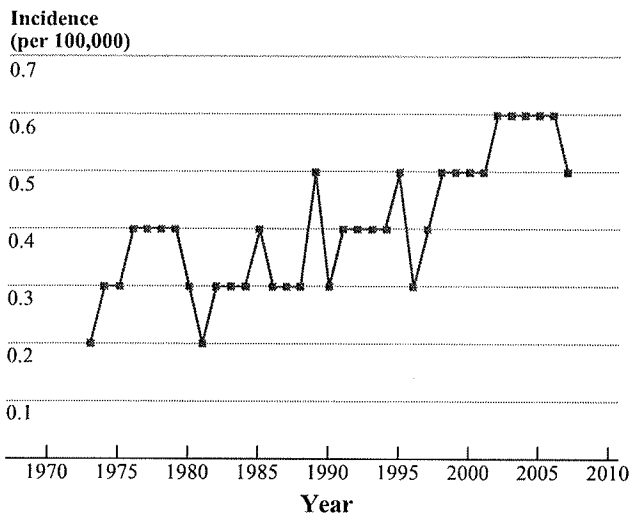

FIG. 1 Age-adjusted incidence rates for appendiceal tumors from 1973 to 2007 from 9 SEER registries (per 100,000 population)

metastases (56%). In contrast to nonmucinous adenocarcinomas, mucinous tumors were more likely to have metastatic disease and be well-differentiated tumors, but less likely to have nodal involvement (Table 1).

The median overall survival of the group of patients was 85 months (range 0.5–418 months), while the mean disease-specific survival was 90 months (range 0.5–418 months). The median survival of patients with malignant carcinoids was not reached in the data set, with 75th quartile survival of 240 months (20 years or more), while the median survival for goblet cell carcinoids was 174 months. The median survival of patients with adenocarcinoma not otherwise specified, mucinous adenocarcinoma, and signet ring cell carcinoma was 48 months, 61 months, and 24 months, respectively, while the disease-specific survival was 93 months, 103 months, and 25 months (Fig. 2). The 5-year disease-specific survival rates were 93% for malignant carcinoid, 81% for goblet cell carcinoid, 55% for adenocarcinoma, 58% for mucinous adenocarcinoma, and 27% for signet ring cell adenocarcinoma.

The effect of surgery was investigated by univariate analysis to determine appropriateness of surgery by T and N stage (Table 2). Survival modeling was performed by Cox proportional hazard modeling. We excluded patients who underwent total colectomy ($n = 59$) because the survival functions were not proportional. In the remaining 4823 patients, the age, gender, and histologic subtype-adjusted HR, compared to the referent group with no surgery, were as follows: local surgery HR 0.36 [95% confidence interval (CI) 0.28–0.47], partial colectomy/appendectomy HR 0.26 (95% CI 0.21–0.31), right colectomy/subtotal colectomy HR 0.27 (95% CI 0.22–0.32), and colectomy with contiguous organ resection HR 0.57 (0.46–0.68) ($P < 0.001$ for all HRs). The median survival for patients who underwent total colectomies was 152 months, which was longer than those who underwent resection of contiguous organs, which was 42 months.

Multivariate Cox proportional hazard modeling was performed; we excluded patients who had total colectomies ($n = 59$) for the purposes of the model. We built two separate models, one using tumor extension and the other using tumor size (Table 3).

On the basis of estimates derived from the multivariate Cox models, age, gender, and surgery-adjusted hazard revealed that the magnitude of HRs varied by histologic subtype in addition to node positivity and metastatic disease (Table 4).

DISCUSSION

The SEER database has been a valuable resource for the study of rare tumors such as appendiceal tumors, and we present our analysis of the SEER database for such tumors after previous comprehensive analyses performed in 2002 and 2005.[7,11] The update over the last 8 years reveals a continued trend toward an increasing number of incident cases, which may be a function of increasing disease incidence but may also reflect better detection through computed tomographic scans, colonoscopies, and other imaging modalities, as well as the generous use of laparoscopy, which allows surgeons complete visual access to the peritoneal cavity. Nevertheless, despite the rising incidence of appendiceal tumors, their rarity maintains its orphan status.

Marked advances have been made in the management of appendiceal epithelial neoplasms, primarily as a result of the efforts of Sugarbaker.[8] The application of cytoreductive surgery and hyperthermic chemoperfusion to appendiceal and colon primary tumors with improved survival benefit has led to an increased number of studies on histology to predict outcomes.[12] Ronnett et al. proposed a histopathologic classification of mucinous tumors of the appendix, and the role of histology in predicting outcomes has been reported by several institutions, with survival varying between 5-year 60% survival for DPAM variants to 30% for the PMCA variants.[13]

Staging of appendiceal tumors is extremely difficult, given the varied histologies that occur with almost similar frequencies (37% mucinous, 27% adenocarcinoma, 19% goblet cell carcinoid) and the markedly different histologic characteristics. The use of proliferation index (Ki-67), mitotic rate, and grade has already been proposed and incorporated into the staging of midgut neuroendocrine tumors.[4] This enhances the staging system but introduces an element of complexity that makes a staging system unwieldy and difficult to use. On the basis of the importance of histologic subtypes in predicting outcomes, we envision a two-tier system of staging. Tumors will be staged as carcinoids or

TABLE 1 Demographic and tumor/therapy characteristics by histologic subtype

Characteristic	Overall ($n = 5655$)	Malignant carcinoid ($n = 625$)	Goblet cell carcinoid ($n = 1072$)	Adenocarcinoma ($n = 1544$)	Mucinous adenocarcinoma ($n = 2101$)	Signet ring cell ($n = 313$)	P
Age at diagnosis, year, median (range)	46 (58–70)	27 (40–54)	43 (53–64)	53 (64–75)	49 (59–72)	48 (57–68)	<0.001 (ANOVA)
Male gender	47%	31%	50%	55%	45%	40%	<0.001
Diagnosed after 1983	89%	61%	98%	89%	92%	99%	<0.001
Tumor grade							<0.001
Well differentiated	17% ($n = 962$)	5% ($n = 31$)	5% ($n = 54$)	16% ($n = 251$)	29% ($n = 621$)	1.6% ($n = 5$)	–
Moderately differentiated	21% ($n = 1200$)	1% ($n = 8$)	3% ($n = 36$)	42% ($n = 653$)	23% ($n = 484$)	6% ($n = 19$)	–
Poorly differentiated	12% ($n = 681$)	1% ($n = 4$)	6% ($n = 66$)	18% ($n = 275$)	8% ($n = 178$)	50% ($n = 158$)	–
Unknown	49% ($n = 2761$)	93% ($n = 581$)	85% ($n = 909$)	23% ($n = 352$)	38% ($n = 800$)	38% ($n = 119$)	
Tumor size							<0.001
<2 cm	32% ($n = 751$)	69% ($n = 174$)	52% ($n = 270$)	23% ($n = 149$)	17% ($n = 138$)	14% ($n = 20$)	
2–3.9 cm	28% ($n = 667$)	21% ($n = 54$)	25% ($n = 130$)	38% ($n = 241$)	25% ($n = 195$)	34% ($n = 47$)	
≥4 cm	39% ($n = 919$)	10% ($n = 24$)	22% ($n = 116$)	39% ($n = 249$)	58% ($n = 457$)	52% ($n = 73$)	
Tumor extension							<0.001
Intramucosal	1% ($n = 48$)	2% ($n = 8$)	1% ($n = 10$)	2% ($n = 18$)	1% ($n = 11$)	0.5% ($n = 1$)	
T1	17% ($n = 659$)	28% ($n = 92$)	22% ($n = 207$)	15% ($n = 174$)	14% ($n = 175$)	5% ($n = 11$)	
T2	10% ($n = 378$)	11% ($n = 37$)	9% ($n = 87$)	14% ($n = 164$)	7% ($n = 84$)	3% ($n = 6$)	
T3	40% ($n = 1548$)	46% ($n = 151$)	49% ($n = 463$)	40% ($n = 457$)	33% ($n = 407$)	35% ($n = 70$)	
T4	32% ($n = 1222$)	13% ($n = 42$)	19% ($n = 178$)	28% ($n = 317$)	46% ($n = 572$)	56% ($n = 113$)	
Nodal status							<0.001
N0	74% ($n = 2990$)	69% (208)	81% ($n = 708$)	71% ($n = 835$)	80% ($n = 1143$)	39% ($n = 96$)	
N1	26% ($n = 1037$)	31% ($n = 94$)	19% ($n = 170$)	29% ($n = 340$)	20% ($n = 282$)	61% ($n = 151$)	
Metastatic disease							<0.001
M0	69% ($n = 3393$)	88% ($n = 316$)	88% ($n = 902$)	78% ($n = 1045$)	54% ($n = 994$)	44% ($n = 136$)	
M1	31% ($n = 1506$)	12% ($n = 45$)	12% ($n = 128$)	22% ($n = 299$)	46% ($n = 863$)	56% ($n = 171$)	
Type of surgery performed							<0.001
No surgery	5% ($n = 253$)	4% ($n = 13$)	2% ($n = 19$)	4% ($n = 60$)	7% ($n = 138$)	8% ($n = 23$)	
Local surgery (excision, destruction, curettage)	7% ($n = 331$)	16% ($n = 57$)	8% ($n = 78$)	6% ($n = 84$)	6% ($n = 104$)	3% ($n = 8$)	
Partial colectomy (including appendectomy)	32% ($n = 1578$)	40% ($n = 141$)	38% ($n = 385$)	31% ($n = 421$)	30% ($n = 562$)	23% ($n = 69$)	
Right colectomy, subtotal colectomy	39% ($n = 1905$)	29% ($n = 103$)	43% ($n = 435$)	46% ($n = 620$)	34% ($n = 631$)	35% ($n = 105$)	
Total colectomy	1% ($n = 59$)	2% ($n = 6$)	1% ($n = 7$)	1% ($n = 15$)	1% ($n = 27$)	1% ($n = 4$)	
Colectomy + resection of contiguous organ	15% ($n = 754$)	9% ($n = 31$)	9% ($n = 95$)	11% ($n = 153$)	21% ($n = 386$)	30% ($n = 89$)	

ANOVA analysis of variance

carcinomas, as they currently are in the AJCC 7th edition, but they will be further subclassified into A subgroup (carcinoid, carcinoma/mucinous carcinoma) and B subgroup (goblet cell carcinoid, signet cell carcinoma), respectively. The B subgroup for carcinoids has a 3 times HR for all stages, while for carcinoma, it has a 30% higher HR for all stages (Table 4).

Tumors of the appendix are also prone to rupture, and metastatic disease from mucinous tumors of the appendix, even though classified as M1 disease, has a far better prognosis than systemic metastasis; this adds to the heterogeneity to the staging system, which is histology specific. Aggressive cytoreduction and chemoperfusion can often control the peritoneal carcinomatosis and provide durable survival benefit; this component of treatment is not captured, which makes prognostication based on national data difficult.[8] It thus comes as no surprise that histologic subtype is extremely important in predicting outcomes for patients with appendiceal tumors.

Our report contradicts the previous comprehensive report in 2002 and has differences from the report in 2005, where the histologic subtype (other than signet ring cell carcinoma and malignant carcinoid) did not greatly affect survival.[7,11] There are several differences between our studies. In addition to being newer and having recent data, our studies classified patients slightly differently. Our inclusion criteria for patients with goblet cell carcinoid and malignant carcinoid were much wider, and we included more patients. Additionally, we included the extent of surgery in our models to help obtain a better fit of the data because it is an important factor in predicting survival. Additionally, nodal status and metastatic disease were not

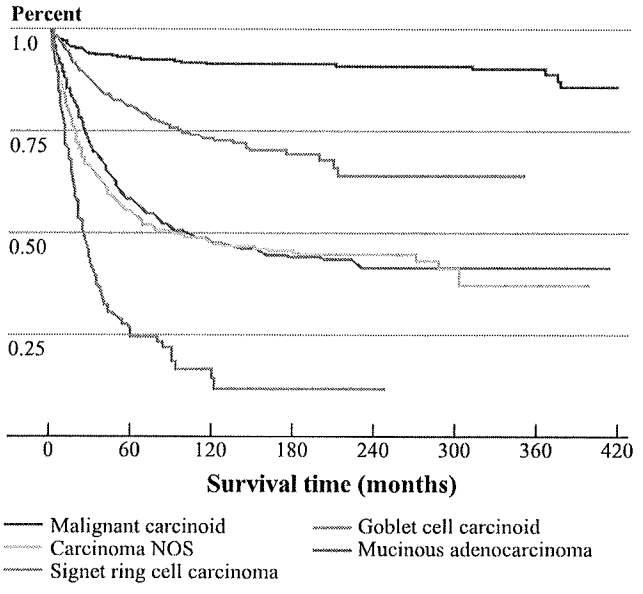

FIG. 2 Disease-specific survival by histologic subtype

TABLE 2 Assessment of appropriateness of surgery by tumor extension and nodal status

Variable	No surgery	Local surgery	Partial colectomy	Right hemicolectomy	Total colectomy	Colectomy + resection of contiguous organs	*P*
Tumor extension							
T3 or less	37% ($n = 27$)	84% ($n = 192$)	75% ($n = 970$)	71% ($n = 1159$)	56% ($n = 22$)	38% ($n = 181$)	<0.001
T4 lesions	63% ($n = 46$)	16% ($n = 38$)	25% ($n = 317$)	29% ($n = 479$)	44% ($n = 17$)	62% ($n = 294$)	
Nodal status							
N0	81% ($n = 75$)	93% ($n = 183$)	84% ($n = 990$)	69% ($n = 1246$)	63% ($n = 26$)	62% ($n = 379$)	<0.001
N1	19% ($n = 18$)	7% ($n = 14$)	16% ($n = 188$)	31% ($n = 551$)	37% ($n = 15$)	38% ($n = 235$)	

TABLE 3 HRs by histologic subtype after multivariate modeling[a]

Histologic subtype	Adjusted for tumor extension ($n = 3260$)		Adjusted for tumor size ($n = 1984$)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Malignant carcinoid	Ref.	–	Ref.	–
Goblet cell carcinoid	3.8 (1.8–7.8)	<0.001	3.1 (1.7–5.7)	<0.001
Colonic adenocarcinoma	7.4 (3.6–15.3)	<0.001	5.1 (2.8–9.2)	<0.001
Mucinous adenocarcinoma	5.8 (2.8–12.1)	<0.001	4.1 (2.2–7.4)	<0.001
Signet ring cell carcinoma	7.8 (3.6–16.5)	<0.001	4.8 (2.6–9.0)	<0.001

HR hazard ratio, *CI* confidence interval

[a] Both models include age splines, gender, node positivity, metastatic disease, and extent of surgery

TABLE 4 Application of linear combination of coefficients to predict hazard ratios on the basis of the current AJCC 7th edition of the TNM staging system

Coefficient	Unadjusted		Adjusted[a]	
Carcinoid				
AJCC stage based on tumor size (except T4 based on extension)	Malignant carcinoid	Goblet cell carcinoid	Malignant carcinoid	Goblet cell carcinoid
Stage 1				
T1N0M0	Referent	3.4 (1.7–6.8)	Referent	2.8 (1.4–5.7)
Stage 2				
T2N0M0	1.5 (0.7–3.2)*	5.4 (2.1–13.5)	1.5 (0.7–3.5)*	4.3 (1.5–12.5)
T3N0M0	3.1 (1.6–5.9)	10.72 (4.2–27.3)	2.3 (1.1–4.9)	6.5 (2.1–19.8)
Stage 3				
T4N0M0	2.9 (1.6–5.4)	10.1 (4.4–23.3)	2.5 (1.3–4.8)	6.9 (2.7–17.7)
T4N1M0 (worst case)	12.4 (6.0–25.5)	42.6 (14.1–128.8)	13.0 (5.9–28.7)	36.4 (11.2–118.9)
Stage 4				
T1N0M1 (best case)	4.2 (2.6–6.9)	14.6 (7.3–29.3)	3.6 (2.2–6.0)	10.2 (4.6–22.5)
T4N1M1 (worst case)	52.6 (29.1–95.1)	180.9 (73.2–447.1)	47.5 (21.9–102.8)	133.1 (44.2–401.2)
Carcinoma				
AJCC stage based on tumor extension	Carcinoma (including mucinous)	Signet ring cell carcinoma	Carcinoma (including mucinous)	Signet ring cell carcinoma
Stage 1				
T1N0M0	Referent	1.3 (1.0–1.7)	Referent	1.2 (1.0–1.6)*
T2N0M0	0.6 (0.4–1.0)*	0.8 (0.5–1.4)*	0.7 (0.4–1.2)*	0.9 (0.5–1.6)*
Stage 2				
T3N0M0	1.4 (1.0–1.8)	1.8 (1.2–2.7)	1.6 (1.1–2.2)	2.0 (1.3–3.0)
T4N0M0	2.1 (1.6–2.8)	2.8 (1.9–4.1)	2.3 (1.7–3.2)	2.9 (1.9–4.4)
Stage 3				
T1N1M0 (best case)	2.8 (2.3–3.3)	3.7 (2.8–4.8)	3.1 (2.6–3.6)	3.8 (2.9–5.1)
T4N1M0 (worst case)	5.8 (4.3–8.0)	7.8 (5.4–11.3)	7.1 (5.1–10.0)	8.9 (6.0–13.3)
Stage 4				
T1N0M1 (best case)	1.9 (1.5–2.4)	2.5 (1.8–3.5)	1.9 (1.5–2.5)	2.4 (1.7–3.4)
T4N1M1 (worst case)	11.1 (7.8–15.8)	14.8 (9.8–22.1)	13.8 (9.3–20.5)	17.3 (11.1–26.9)

TNM tumor, node, metastasis system, *AJCC* American Joint Committee on Cancer

[a] Adjusted for age, gender, and therapy (T status based on size)

* $P > 0.05$

considered by the older study, which would weaken the conclusions. The strength of our study, however, lies in the fact that we demonstrated similar, albeit higher, HRs for the aggressive subtypes including signet ring cell carcinoma and goblet cell carcinoids, and several findings are consistent with previously reported literature.

Our study suffers from the limitations of any study that uses a large national database.[14] In addition to temporal bias and classification bias, we believe that capturing accurate treatment is difficult in studies of this nature; this is amplified by the use of surgery in the metastatic setting ($n = 1249$), which may indicate cytoreductive surgery or metachronous development of metastatic disease. Also, missing data may bias our findings directionally; however, previous studies from the national database provide evidence that the bias is nondirectional and likely small.

Distinguishing between the behavior of mucinous adenocarcinoma and colonic adenocarcinoma has been difficult, and our study lends credence to the fact that the two histologies differ in their characteristics. The effect of histology on outcomes from hollow visceral gastrointestinal malignancies is often studied, but the systematic application of histology to obtain prognostic information is not as widespread. Almost every gastrointestinal malignancy has histologic variants that portend a different outcome; for instance, intestinal type gastric cancer behaves differently from signet ring cancer, and acinar cell cancers of the pancreas behave differently from adenocarcinoma.

In our study, mucinous adenocarcinoma, although more likely to have metastatic disease and less likely to have nodal disease, were more often well-differentiated tumors. Again, this is consistent with the peritoneal seeding of these tumors of relatively good tumor biology with higher survival compared to metastatic colorectal adenocarcinoma.

Our application of the model to the TNM staging is unique and offers two functions: it highlights the marked differences between same-stage tumor histologies, but can also act as a clinical tool for physicians to prognosticate the disease process. This would need to be validated prospectively to ensure validity.

Overall, our analysis highlights the importance of histology in staging appendiceal tumors. We suggest that the prognosis of patients with such disease must take the histologic subtype into account.

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