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Improving the AJCC/TNM staging for adenocarcinomas of the appendix: the prognostic impact of histological grade

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Abstract

Purpose—Though histological grade is known to have a major prognostic impact in metastatic mucinous appendiceal adenocarcinomas; the prognostic impact of grade in localized disease, and the validity of the AJCC Cancer Staging Manual 7th edition decision to combine moderately and poorly differentiated mucinous adenocarcinomas into a single mucinous high-grade category, is not known.

Methods—Patients with adenocarcinoma of the appendix diagnosed between 1988-2007 were identified from the SEER database. Cancer-specific survival (CSS) stratified by histological subtype, stage and grade were calculated; and Cox proportional hazards regression analyses were performed.

Results—We analyzed a total of 2,469 appendiceal adenocarcinomas, of which 1,375 had mucinous histology and 860 had non-mucinous histology. Though overall CSS was similar for mucinous and nonmucinous subtypes, differences in stage distribution and stage-stratified CSS were seen. Female gender, stage IV disease, and well differentiated histology were more common for mucinous adenocarcinomas. Histological grade had a strong prognostic impact, especially in patients with stage IV mucinous adenocarcinoma. The adjusted hazard ratios for stage IV moderately and poorly differentiated histological grade were 1.63 (95%CI: 1.14-2.34) and 4.94 (95%CI: 3.32-7.35) for mucinous histology, in comparison to 1.44 (95%CI: 0.82-2.52) and 1.90 (95%CI: 0.95-3.80) for non-mucinous histology, respectively.

Conclusion—The strong prognostic impact of histological grade for mucinous adenocarcinomas is primarily restricted to stage IV disease. Stage IV moderately and poorly differentiated mucinous adenocarcinomas have distinctly different CSS and this data does not support the combination of these two histological grades in the recent AJCC 7th edition.

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appendiceal carcinoma; mucinous; grade; survival

INTRODUCTION

Malignancy of the appendix is rare, with an age-adjusted incidence of 0.12 cases per 1,000,000 person years.¹ Often the diagnosis is unexpected, and it is found in approximately 1% of all appendectomy specimens.^{2, 3} Adenocarcinomas represent approximately two-thirds of these cases and can be subdivided into mucinous, non-mucinous (or colonic-type), and signet-ring cell histological subtypes.¹ Although signet-ring cell adenocarcinomas are known to have a worse prognosis, the prognostic impact of mucinous and non-mucinous histological subtypes has not been well studied.

Retrospective series have demonstrated both better⁴⁻⁶ and worse^{7, 8} prognoses in patients with mucinous as opposed to non-mucinous histological subtypes. An analysis of the Surveillance, Epidemiology and End-Results (SEER) registry from 1973 to 1988 demonstrated no difference in all-cause survival for patients with mucinous and non-mucinous adenocarcinomas.¹ However, this finding contrasts with the distinctly different clinical behaviors that can be seen between mucinous and non-mucinous metastatic appendiceal adenocarcinomas.

In particular, metastatic well-differentiated mucinous adenocarcinomas of the appendix frequently present with the clinical syndrome of pseudomyxoma peritonei, which is characterized by the slow and progressive accumulation of mucinous ascites. For this subgroup of mucinous appendiceal adenocarcinomas, cytoreductive surgery can result in cure, with 5-year overall survival rates of 30-35%.^{9,10} However, the relative impact of the various histological grades in mucinous adenocarcinomas has not been well characterized, and how histological grade may affect the outcome of non-mucinous appendiceal adenocarcinomas is unknown. In addition, no data are available regarding the prognostic impact of histological grade on prognosis for localized or regional appendiceal adenocarcinomas.

In the seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual, appendiceal carcinomas are now classified separately from colorectal carcinomas.¹¹ In particular, this new edition incorporates histological grade into the staging of stage IV disease and classifies mucinous carcinomas into two distinct groups: low-grade, composed of well differentiated carcinomas, and high-grade, composed of moderately and poorly differentiated carcinomas. Though moderately and poorly differentiated mucinous adenocarcinomas are known to have worse outcomes than well differentiated mucinous adenocarcinomas, it is not known whether the outcomes for moderate and poorly differentiated mucinous adenocarcinomas differ.¹²

The purpose of this study, therefore, was to perform a population-based evaluation of outcomes of patients with appendiceal adenocarcinomas stratified by stage, grade, and histological subtype.

PATIENTS AND METHODS

Data Source and Case Identification

Data from the SEER Program of the National Cancer Institute, release 2010, were utilized for this study.¹³ SEER, a population-based cancer registry, collects cancer incidence and

survival data from 18 regional population-based registries that now cover approximately 26% of the U.S. population. The SEER registry routinely collects data on patient demographics, primary tumor site, tumor morphology, disease stage at diagnosis (per the *AJCC Cancer Staging Manual*, since 1988), first course of treatment (radiotherapy and surgery within the 4 months after cancer diagnosis), and follow-up for vital status. SEER does not collect data on chemotherapy or cytoreductive surgery, which was therefore not evaluated in this study.

Patients eligible for the study included all those with appendiceal carcinomas (ICD-O-3: C18.1) diagnosed between January 1988 and December 2007. The inclusive study dates were chosen because 1988 was the first year SEER coded data elements that would allow restaging using the *AJCC Cancer Staging Manual* 7th edition and 2007 was the latest available SEER release for our analysis. Data were not available to classify metastases into the 7th edition subcategories of peritoneal-only metastases (M1a) and nonperitoneal metastasis (M1b).

Appendiceal adenocarcinomas were classified into mucinous (histology type 8470, 8480, and 8481) and non-mucinous (histology type 8010, 8013, 8020, 8140-1, 8144, 8210-1, 8255, 8260-3, 8310, 8440, 8460, 8471-72, 8560, and 8574). Because goblet cell carcinoids (histology type 8243) demonstrated a distinctly different cancer-specific survival (CSS) than non-mucinous adenocarcinomas, they were not included in this analysis. As signet-ring cell histological subtype (histology type 8490) had a uniquely poor prognosis, we separately evaluated them.

Exclusion criteria included age younger than 18 years or older than 90 years, lack of histological confirmation, survival time <30 days and if the incident diagnosis of appendiceal cancer was not their first and only occurrence of malignant disease. Cases were also excluded if the cancer reporting source was a nursing home, hospice, autopsy, or death certificate as these patients would not have been likely to receive cancer-directed therapy (Supplementary Table 1).

For comparative purposes we applied the same criteria to all colon adenocarcinomas from the same period in the SEER registry: cecum (C18.0), ascending colon (C18.2), hepatic flexure of colon (C18.3), transverse colon (C18.4), splenic flexure of colon (C18.6), sigmoid colon (C18.7), overlapping lesion of colon (C18.8), and colon not otherwise specified (C18.9).

Analysis

We compared demographic and tumor factors by histological subtype (mucinous, non-mucinous, and signet-ring cell). Cox regression analyses to evaluate the risk of cancer-specific death included patients' age (<50 years, 50-75 years, >75 years), gender, race (white, black, other), tumor grade (well, moderately, poorly, undifferentiated and unknown), total number of lymph nodes evaluated (0, 1, unknown), year of diagnosis (1988-1991, 1992-1995, 1996-1999, 2000-2003, 2004-2007), and surgery received (no surgery/local tumor destruction/local excision/unknown, appendectomy, hemicolectomy, total colectomy/proctocolectomy). Within SEER, an appendectomy is not specifically recorded and is defined in this report as representing the SEER surgical code of partial colectomy less than hemicolectomy. Models were built separately for stage I-III disease and stage IV disease.

The SEER registry does not have a specific category for appendiceal cancer deaths which are therefore classified as colorectal cancer. These codes yielded a total of 786 deaths, representing 81.8% of all defined cancer-specific deaths for CSS calculation. In addition the distribution of the cause of death coding was evaluated to determine other relevant cancer-

specific causes of death, and this identified a total of 174 cancer specific deaths, accounting for the remaining 18.2% of all predefined cancer-specific deaths (Supplementary Table 2). Cases were censored if death were from a cause other than those specified above or if the patient were alive at the last follow-up. To account for the possible unreliable cause of death information in SEER, we exclusively used multivariate relative survival regression modeling with the Poisson assumption for the observed number of deaths to confirm our finding.¹⁴

Within population based data, appendiceal cancer is associated with a significant proportion of patients with missing data regarding tumor grade. To address the impact of missing histological grade on survival we performed three separate analyses that alternatively excluded all cases of unknown histological grade, included all cases of unknown grade as a separate grade category, and included all cases of unknown grade by multiple imputation.¹⁵ Specifically, for the multiple imputation method we replaced missing grade with distributions of plausible values that accounted for the uncertainty about the imputed value. The missing values were imputed with 100 sets of plausible values based on the Bayesian posterior predictive distribution derived from the imputation model adjusted for age, gender, race, stage, number of total lymph nodes evaluated, year of diagnosis, surgery received, time to cancer-specific death and death indicator. The imputation models were built separately by stage (stage I-III or stage IV) and histological subtype (mucinous or non-mucinous).

Statistical analyses were performed using Stata SE version 11.0 (release 2010, College Station, TX). Because the study used preexisting data with no personal identifiers, this study was exempt from review by our institutional review board.

RESULTS

Clinicopathologic Characteristics

A total of 2,469 patients with appendiceal carcinomas met the eligibility criteria. Baseline characteristics stratified by histological subtype are shown in Table 1. The median age was 58 years (interquartile range 48-70 years) and was similar across the different histological subtypes. Female sex was more common in mucinous (57%) and in signet-ring cell (62%) than in non-mucinous adenocarcinomas (45%). The overall stage distribution was 8% stage I, 22% stage II, 11% stage III, 41% stage IV, and 18% unstaged. The primary reason for being classified as unstaged was the lack of information regarding nodal status (Nx, 97% of unstaged cases). Stage distribution varied by histological subtype, with stage IV disease being more common in mucinous and signet-ring cell adenocarcinomas (48% and 59%, respectively) than in non-mucinous adenocarcinomas (25%). Stage III disease was uncommon for the mucinous histological subtype, representing only 6% of cases, and this finding was more pronounced for the well-differentiated mucinous adenocarcinomas, with only 9 cases (1.2%).

The histological grade was well-differentiated in 22% of patients, moderately differentiated in 30%, poorly differentiated in 18%, and not otherwise specified in 29%. The rate of unspecified histological grade for mucinous, signet ring cell, and non-mucinous histological subtypes was, 35%, 38%, and 17%, respectively. For mucinous and non-mucinous histological subtypes, the cases with missing histological grade were most commonly those identified as stage IV disease, 53% and 46%, or unknown stage, 22% and 24%, respectively. Well-differentiated adenocarcinomas were more frequently seen with the mucinous histological subtype (31%) than with the signet-ring cell (1%) and non-mucinous (14%) subtypes.

The type of surgical resection for stage unknown, I, II, or III disease was an appendectomy in 30%, hemicolectomy in 41%, total colectomy/ proctocolectomy in 14%, and local

resection/local tumor destruction/no surgery/unknown surgery in 15%. In the 458 cases with locoregional disease who underwent an appendectomy, 46%, 36%, and 18% had unknown nodal evaluation (Nx), 1-12 lymph nodes evaluated, and >12 lymph nodes evaluated in the pathological specimen, respectively.

Cancer Specific Survival

CSS rates stratified by histological subtype, stage, and grade are shown in Figure 1. Mucinous and nonmucinous adenocarcinomas demonstrated similar 5-year CSS rates of 56% (mucinous) and 54% (nonmucinous), respectively, whereas signet-ring cell carcinomas had a worse outcome (22%, Figure 1A). Surprisingly, stage stratified CSS demonstrated similar outcomes for stage III and stage IV disease (Figure 1B). However, this finding was confounded by the histological subtype, as stage III cases were more commonly non-mucinous (52%) versus mucinous (32%, $P<.001$) and stage IV cases were more commonly mucinous (65%) versus non-mucinous (21%, $P<.001$).

In comparison to histological subtype- or stage-stratified CSS, histological grade-stratified CSS appears to provide the best discrimination of CSS (Figure 1C). However grade-stratified CSS was also influenced by histological subtype with mucinous adenocarcinomas being most commonly well (31%) or moderately (24%) differentiated, while non-mucinous adenocarcinomas were moderately (47%) or poorly (22%) differentiated and signet-ring cell adenocarcinomas were poorly differentiated (52%, Table 1).

Stage-stratified CSS rates for both mucinous and non-mucinous histological subtypes (excluding signet-ring cell histological subtype and cases with undifferentiated grade) are shown in Figure 2. Though CSS rates were similar for stages I, II and III disease, the CSS rates for stage IV disease differed dramatically between histological subtypes.

Stage- and Grade-Stratified Cancer Specific Survival

Because of the strong prognostic impact of both histological grade and stage, in addition to the interplay between these factors, grade- and stage-stratified CSS were analyzed for both mucinous and nonmucinous adenocarcinomas. The impact of histological grade upon CSS for stage I-III mucinous and nonmucinous carcinomas was similar (Figure 3A and 3C). The 5-year CSS rates for stage I-III well-differentiated, moderately differentiated, and poorly differentiated mucinous adenocarcinoma were 82%, 64%, and 50%, respectively, while for non-mucinous adenocarcinoma the 5-year CSS rates were 69%, 73%, and 55%.

For stage IV mucinous and non-mucinous adenocarcinomas, histological grade had a differential impact, with well-, moderately and poorly differentiated mucinous adenocarcinomas having distinctly different CSS, whereas CSS for moderately and poorly differentiated non-mucinous adenocarcinomas were similar (Figure 3). Well-differentiated stage IV non-mucinous adenocarcinomas represented a small subset with only 17 cases. Five-year CSS rates stratified by well, moderate, or poor tumor grade, was 71%, 51%, and 0%, respectively, for mucinous adenocarcinomas and 48%, 9%, and 5% for non-mucinous adenocarcinomas, respectively.

Multivariate Analysis

To further evaluate the impact of grade and stage for mucinous and non-mucinous appendiceal adenocarcinomas a multivariate model utilizing unknown grade as a separate grade category was constructed and hazard ratios are shown in Table 2. To confirm these findings we also analyzed histological grade in our multivariate model after multiple imputation or after exclusion (Table 2). With all three methods our results remained

unchanged. In addition we also performed multivariate relative survival regression analysis and confirmed these findings (Supplementary Table 3).

Histological grade was a stronger prognostic factor for mucinous than for non-mucinous appendiceal adenocarcinomas. This was most dramatically seen with stage IV mucinous adenocarcinoma where the CSS hazard ratios for moderately differentiated and poorly differentiated histological grade were 1.63 (95% CI: 1.14-2.34) and 4.93 (95% CI: 3.31-7.34), in comparison to 1.45 (95% CI: 0.83-2.2.54) and 1.92 (95% CI: 0.96-3.83) for non-mucinous adenocarcinomas, respectively.

To better understand the relative impact of grade in mucinous and non-mucinous appendiceal adenocarcinomas we performed the same analysis for adenocarcinomas of the colon (Supplementary Table 4). The impact of grade for colon adenocarcinomas was similar between mucinous and nonmucinous histological subtypes with poorly differentiated mucinous and non-mucinous having CSS hazard ratios of 1.66 (95% CI: 1.56-1.77) and 1.64 (95% CI: 1.42-1.88), respectively for stage I-III, and 1.71 (95% CI: 1.6-1.84) and 1.82 (95% CI: 1.54-2.15), respectively for stage IV.

DISCUSSION

This analysis highlights the interplay between histological type (mucinous or non-mucinous), stage, and grade for patients with appendiceal adenocarcinoma. The analysis also shows that the relationships amongst these factors are empirically not independent. The prognostic implication of histological grade is greater for mucinous than for non-mucinous appendiceal adenocarcinomas. Notably, this impact is primarily due to the improved outcome of moderately and well differentiated stage IV mucinous but not non-mucinous appendiceal adenocarcinomas. Furthermore, within each stage poorly differentiated appendiceal adenocarcinomas are associated with poor outcomes irrespective of histological subtype. Finally, the distinctly different outcomes for moderately as opposed to poorly differentiated mucinous appendiceal adenocarcinomas suggests that these two histological grades should not be combined into a single high-grade mucinous category as is currently recommended in the *AJCC Cancer Staging Manual*, 7th edition.

Consistent with previous reports, we identified a number of differences between mucinous and non-mucinous appendiceal adenocarcinomas with female sex, stage IV disease, and well differentiated histology being more common for mucinous adenocarcinomas.^{1, 16} Interestingly, mucinous adenocarcinomas are more than two times more likely to present with stage IV disease as non-mucinous adenocarcinomas (48% vs. 25%, respectively). Yet, stage III disease at presentation was extremely rare for mucinous adenocarcinomas (6%), and this was even more evident for well-differentiated mucinous adenocarcinomas (1.2%), suggesting a strong propensity for peritoneal rather than lymphatic metastases. From the data presented here, the apparent similarity in overall CSS for mucinous and non-mucinous appendiceal adenocarcinomas likely does not reflect similar disease biology but rather the higher rate of localized disease for non-mucinous adenocarcinomas than for mucinous adenocarcinomas and the improved CSS for stage IV mucinous adenocarcinomas compared with stage IV non-mucinous adenocarcinomas. Little is known about appendiceal adenocarcinomas at the molecular level and only one prior study has directly compared the molecular patterns of mucinous and non-mucinous histological subtypes, observing similar rates of K-ras mutations, microsatellite instability, and p53 overexpression.⁵

A notable finding from these data was the stage-dependent impact of grade on survival for patients with mucinous adenocarcinomas. Although poor differentiation was associated with worse outcome in all stages, the magnitude of this impact was very stage-dependent as

reflected by adjusted hazard ratios (compared to well-differentiated) of 1.90 and 4.94 for stage I-III and stage IV, respectively. This finding was not seen for non-mucinous appendiceal adenocarcinomas where the impact of histological grade on survival was stage-independent. In order to better understand the impact of mucinous histology and grade in appendiceal adenocarcinomas we performed the same analysis in colon adenocarcinomas. The impact of grade on survival outcomes of colon adenocarcinomas was independent of stage and mucinous histology. In fact the prognostic impact of grade in colon adenocarcinomas appears similar to that seen for non-mucinous adenocarcinomas of the appendix. These findings further support the unique biological behavior of mucinous adenocarcinomas of the appendix.

In the 7th edition of the *AJCC Cancer Staging Manual*, appendiceal carcinomas are classified separately from colorectal carcinomas with: (1) a distinction made between mucinous and non-mucinous histological subtypes, (2) classification of histological grade for mucinous carcinomas as either low or high, and (3) substratification of metastases into intraperitoneal and extraperitoneal categories.¹¹ As the SEER registry does not provide information on sites of metastatic disease, we were not able to evaluate the impact of metastatic site on outcome. However, prior data for appendiceal adenocarcinomas have suggested a low rate of extraperitoneal dissemination.^{17, 18} This analysis has confirmed the unique clinical behaviors of mucinous versus non-mucinous subtypes and supports their distinction. However, the merging of moderately and poorly differentiated grades into a single high-grade category is not supported by our data. In patients with stage IV mucinous adenocarcinomas, statistically significant differences in CSS were demonstrated for moderate and poor differentiation. No statistically significant difference was seen for stage I-III mucinous adenocarcinomas, though this analysis was limited by sample size.

A potential limitation of this analysis relates to the high rate of cases with unknown histological grade. As the histological classification of mucinous appendiceal neoplasm represents a diagnostic challenge, a number of classification systems exist.^{12, 19-21} It is possible that some cases of unknown grade may reflect the use of alternative grading systems using such terms as peritoneal mucinous carcinomatosis (PMCA)-1 or PMCA-2 as proposed by Ronnett *et al.*, or mucinous carcinoma peritonei low grade or high grade as proposed by Bradley *et al.*^{12, 19} In either instance, such histological grading would be recorded in SEER under the category of unknown grade. In order to evaluate the impact of missing histological grade, we utilized three separate techniques for handling missing data and constructed separate multivariate logistic regression models examining missing histological grade as an included, excluded, or imputed data.¹⁵ In strong support of our findings, we found consistent findings across all three models. An additional area of confusion regarding histological classification of mucinous appendiceal neoplasms relates to cases in which microscopic evaluation of the appendix reveals a neoplasm with bland or low-grade cytological features which lacks the architectural abnormalities characteristic of invasive carcinoma (i.e. destructive invasion with associated desmoplasia), yet there is intraperitoneal dissemination of abundant mucinous material containing neoplastic cells with bland or low-grade dysplastic features. In one of the most common classification systems, these neoplasms have been termed disseminated peritoneal adenomucinosis (DPAM).¹⁹ As SEER does not capture data on cases with histologically benign or uncertain malignant potential, this subgroup of neoplasms is not represented in this analysis.

As in other malignancies, including colorectal cancer, the distinction between well, moderately, and poorly differentiated carcinomas represents a subjective assessment with interobserver variation.^{22, 23} However, despite this limitation, histological grade has consistently been identified as a statistically significant independent marker of colorectal cancer prognosis.²⁴⁻²⁶ Though it is likely that subjectivity in the histological grading of

moderately and poorly differentiated mucinous adenocarcinomas exists, our data show that this distinction, as determined by a multitude of pathologists across the SEER reporting sites, is prognostically relevant.

As with most registry-based observational studies, there are both strengths and limitations to our analysis. There are clinical variables that are not included within the SEER registry which may affect comparison of outcomes including the receipt of cytoreductive surgery with or without intraperitoneal chemotherapy for carcinomatosis or systemic chemotherapy. However the decisions for cytoreductive surgery and systemic chemotherapy are subject to influence by histological grade and histological subtype (i.e. poorly differentiated or non-mucinous cancers with carcinomatosis are generally not treated with cytoreductive surgery). The biologic rationale for these treatment decisions only support our observations regarding the importance of grade and histology for stage IV disease particularly with respect to the merging of moderately- and poorly-differentiated mucinous adenocarcinomas into a single high-grade category. Secondly, there were a number of incompletely staged cases which can potentially skew the data. The primary reason for lacking stage assignment was missing information regarding nodal status and the proportion of unstaged patients was similar amongst the histological subtypes. Finally, within SEER surgical resection for appendiceal adenocarcinomas are imperfectly classified, as both appendectomy and cecectomy are recorded as a partial colectomy. In addition, it is possible that a number of unstaged cases were treated by an appendectomy alone, as these cases could represent cases with localized disease that did not have nodal staging information. Though the exact rate of cases treated with an appendectomy cannot be determined, similar rates of partial colectomy and unstaged cases were seen between mucinous and non-mucinous histological subtypes suggesting that this was not a significant limitation to our analysis. Despite these limitations, the large sample size of nearly 2,000 patients and the ability to perform stratified adjusted survival analysis to account for the interplay between the clinically important prognostic variables is an important advantage of the SEER registry.

CONCLUSION

In conclusion, there is a strong prognostic impact of grade in appendiceal adenocarcinomas that is predominantly limited to stage IV mucinous adenocarcinomas. In this setting, mucinous adenocarcinomas demonstrate a markedly different outcome from those of non-mucinous appendiceal adenocarcinomas and both mucinous and non-mucinous colon adenocarcinomas. These data demonstrate that stage IV moderately and poorly differentiated mucinous appendiceal adenocarcinomas are associated with significantly different cancer specific survival rates, and suggests that contrary to the 7th edition of the *AJCC Cancer Staging Manual*, these two histological categories should not be classified together.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cancer-specific survival stratified by (A) tumor subtype, (B) stage, and (C) histological grade

Figure 2. Cancer-specific survival for mucinous and non-mucinous adenocarcinomas stratified by (A) stage I, II, and III and (B) stage IV

3A

3B

Figure 3. Histological grade stratified cancer-specific survival for mucinous adenocarcinomas (A) Stage III and (B) Stage IV, and non-mucinous (C) stage I-III and (D) Stage IV

Table 1

Baseline Characteristics for Patients Diagnosed with Adenocarcinoma of the Appendix

Characteristics	Mucinous (n=1,375)		Non-mucinous (n=860)		Signet-ring cell (n=234)	
	n	%	n	%	n	%
Age at diagnosis (yr)	$X^2=18.7$, P -value=0.001					
<50	411	30	214	25	78	33
50-75	781	57	493	57	134	57
>75	183	13	153	18	22	9
Gender	$X^2=38.7$, P -value<0.001					
Male	597	43	475	55	88	38
Female	778	57	385	45	146	62
Ethnicity	$X^2=17.9$, P -value<0.001					
White	1,166	85	698	81	206	88
Black	102	7	104	12	15	6
Asian/Pacific Islander/Others	107	8	58	7	13	6
Tumor grade	$X^2=561.4$, P -value<0.001					
Well differentiated	422	31	117	14	3	1
Moderately differentiated	328	24	402	47	14	6
Poorly differentiated	125	9	192	22	121	52
Undifferentiated	13	1	7	1	6	3
Unknown	487	35	142	17	90	38
Stage (AJCC 7th edition)	$X^2=225.6$, P -value<0.001					
I	87	6	112	13	5	2
II	281	20	231	27	23	10
III	89	6	143	17	43	18
IV	660	48	212	25	137	59
Unknown	258	19	162	19	26	11
Total lymph nodes evaluated	$X^2=62.0$, P -value<0.001					
0	595	43	241	28	72	31
1-12	403	29	323	38	86	37
12	299	22	254	30	62	26
Unknown	78	6	42	5	14	6
Year of diagnosis	$X^2=7.6$, P -value=0.47					
1988-1991	74	5	66	8	12	5
1992-1995	140	10	94	11	25	11
1996-1999	175	13	108	13	24	10
2000-2003	470	34	278	32	78	33
2004-2007	516	38	314	37	95	41
Type of surgery (Stage unknown + I-III)	$X^2=25.7$, P -value<0.001					

Characteristics	Mucinous (n=1,375)		Non-mucinous (n=860)		Signet-ring cell (n=234)	
	n	%	n	%	n	%
No surgery/local excision/unknown	83	12	44	7	8	8
Appendectomy *	230	32	200	31	28	29
Hemicolectomy	339	47	368	57	47	49
Total colectomy/proctocolectomy	63	9	36	6	14	14

* defined by SEER as appendectomy or partial colectomy less than hemicolectomy.

Table 2

A Comparison of Adjusted Hazard Ratios (95% Confidence Interval) for Cancer-specific Survival for Mucinous and Non-mucinous Appendiceal Adenocarcinoma, Stratified by Stage with Unknown Grade Analyzed as an Included, Imputed or Excluded Variable.*

Tumor grade	Stage I-III		Stage IV	
	Mucinous	Non-mucinous	Mucinous	Non-mucinous
Unknown grade included				
Well differentiated	1	1	1	1
Moderate differentiated	1.44 (0.82-2.52)	0.95 (0.52-1.71)	1.63 (1.14-2.34)	1.8 (0.87-3.72)
Poorly differentiated	1.9 (0.95-3.80)	1.36 (0.71-2.60)	4.94 (3.32-7.35)	2.03 (1.00-4.14)
Unknown grade	1.41 (0.66-3.00)	0.73 (0.38-1.37)	1.64 (1.21-2.23)	1.08 (0.51-2.29)
Multiple imputation				
Well differentiated	1	1	1	1
Moderate differentiated	1.46 (0.81-2.62)	0.94 (0.52-1.69)	1.56 (1.08-2.25)	1.73 (0.83-3.60)
Poorly differentiated	1.89 (0.91-3.91)	1.36 (0.71-2.58)	5.15 (3.45-7.68)	1.93 (0.94-3.97)
Unknown grade excluded				
Well differentiated	1	1	1	1
Moderate differentiated	1.49 (0.84-2.63)	1 (0.55-1.81)	1.67 (1.16-2.41)	1.72 (0.81-3.66)
Poorly differentiated	1.8 (0.88-3.68)	1.37 (0.72-2.63)	5.39 (3.55-8.18)	2.16 (1.03-4.50)

* Adjusted by age, sex, race, number of total LN evaluated, tumor stage, year of diagnosis, and surgery received.