Impact of High-Risk Features for Stage II Adenocarcinoma of the Appendix

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Abstract

Background: Clinico-pathological high-risk features are frequently utilized in adjuvant chemotherapy (AC) decisions in stage II colorectal cancer and their utility in stage II appendiceal adenocarcinoma (AA) is not established. The aim of this study is to determine the impact of high-risk features in clinical outcomes and whether high risk features are predictive of AC benefit in stage II AA.

Methods: Patients with pathological stage II AA between 2010-2015 were identified from the National Cancer Database (NCDB) using ICD-O-3 morphology and topography codes: 8140, 8480 and C18.1. High risk stage II AA was defined as having at least one of the following clinicopathological features: T4 tumor, <12 lymph nodes examined, poorly differentiated histology, positive margins, or lymphovascular invasion. Patients with none of these features were defined as low-risk.

Results: A total of 1,040 patients with pathological stage II AA were identified. 51.0% males, 84.5% Caucasian; median age 61 (range, 19-90). 46.4% were determined to have high-risk stage II AA. High-risk status was associated with worse OS compared to low-risk in univariate (HR 1.55; 95% CI 1.18-2.02; $p=0.001$) and multivariable analyses (HR 1.36; 95% CI 1.03-1.79; $p=0.028$). High-risk stage II AA patients had significantly worse 5-year OS compared to low-risk patients (67.1% vs. 74.5%, $p=0.0013$). AC was administered in 34.4% ($n=166$) of high-risk patients and in 36.5% ($n=203$) of low-risk patients. Among high-risk patients, AC was not associated with better OS in univariate (HR 0.86; 95% CI 0.59-1.26; $p=0.448$) and multivariable analyses (HR 1.35; 95% CI 0.90-2.04; $p=0.151$) compared to no AC. Similarly, among low-risk patients, AC was not associated with better OS in univariate (HR 0.92; 95% CI 0.60-1.39; $p=0.679$) and multivariable analyses (HR 1.27; 95% CI 0.81-2.02; $p=0.299$) compared to no AC. For high-risk patients, 5-year OS was 68.3% in patients that received AC vs. 66.5% in patients that did not ($p=0.722$). For low-risk patients, 5-year OS was 74.0% in patients that received AC vs. 76.3% in patients that did not ($p=0.813$).

Conclusion: High-risk stage II AA patients had significantly worse 5-year OS compared to low-risk patients. AC did not improve survival regardless of high-risk features in stage II AA.

Background

Appendiceal neoplasms are rare and have various histologic types such as adenocarcinoma, neuroendocrine tumors, goblet/ex-goblet cell carcinoid, mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)(1, 2). Appendiceal adenocarcinoma (AA) constitutes around 0.5% of all gastrointestinal tract neoplasms(3, 4). AA is frequently diagnosed incidentally at histologic assessment of the surgical specimen following appendectomy for suspected or diagnosed appendicitis(5). Despite being a rare disease, AA has various histological subtypes with distinct clinical behaviors such as mucinous adenocarcinoma, colonic subtype (non-mucinous adenocarcinoma) and signet-ring adenocarcinoma(6–9). Colonic subtype behaves like colon cancer clinically, whereas mucinous subtype often involves peritoneal cavity and rarely metastasizes outside of peritoneal cavity(6, 7). Signet-ring

adenocarcinoma subtype is usually more aggressive and has the worst survival. Despite differences in stage distribution, cancer specific survivals are similar for mucinous and non-mucinous AA(8). Up to half of the AA patients present with advanced stage disease and in the advanced setting clinical management can be unique based on histological subtype with different survival outcomes between subtypes(6). In the absence of distant metastasis, right hemicolectomy is recommended, with at least 12 lymph nodes typically considered adequate for accurate staging(7). Almost half of the AA patients present with locoregional disease with no established post-surgical management, which is usually extrapolated from colon cancer management(6, 7).

Adjuvant chemotherapy (AC) is standard of care in stage III colon adenocarcinoma and provides a 22–32% overall survival (OS) benefit, and a 30% relative risk reduction in disease recurrence(10). AC with 5-fluorouracil/leucovorin or capecitabine with oxaliplatin is included in post-surgical management of stage III AA if deemed medically fit(7). This approach is extrapolated from management of stage III colon adenocarcinoma(11). Not all patients with stage II colon cancer benefit from AC, and it is crucial to identify high-risk subgroups that might benefit from AC(11). Clinico-pathological high risk features have been defined as pathologic T4 (pT4) tumors, perforation, lymphovascular invasion (LVI), perineural invasion (PNI), less than 12 lymph nodes examined, high-grade tumors, positive margins, and obstruction(12–15). High-risk features are frequently utilized in AC decisions in stage II colon cancer(13). Despite lack of definitive evidence from randomized trials, several mostly retrospective studies suggested that stage II colon cancer with high-risk features might achieve improved survival with AC(14–19). Similar to colon adenocarcinoma, AC is also often considered for stage II AA patients with high-risk features, especially younger patients and those with inadequate nodal staging(7). This approach is extrapolated from management of stage II colorectal cancer (CC) and the exact role of high-risk features is less established in stage II AA. The aim of this study is to determine the impact of high-risk features on clinical outcomes and whether high-risk features are predictive of AC benefit in stage II AA.

Methods

Patients with pathological stage II AA between 2010 and 2015 who underwent surgery were identified from the National Cancer Database (NCDB). The NCDB contains clinical and demographic information on 70% of all incident cancers in the United States from > 1500 Commission-on-Cancer-accredited cancer centers. It is a joint quality improvement initiative of the American College of Surgeons Commission on Cancer and the American Cancer Society. Eligibility was obtained using the following ICD-O-3 morphology and topography codes were utilized: 8140/3 (adenocarcinoma), 8480/3 (mucinous adenocarcinoma) and C18.1 (Fig. 1). All other histology types such as goblet/ex-goblet cell, neuroendocrine tumor etc. were excluded. Patients treated with neoadjuvant systemic and/or radiation therapy and adjuvant radiation were excluded. High-risk was defined as having at least one of the following clinico-pathological features: T4 tumor, < 12 lymph nodes examined, poorly differentiated histology, positive margins, or lymphovascular invasion. Patients with none of the above features were defined as low-risk. The primary outcome was overall survival (OS) of patients with high-risk features compared to low-risk features. The secondary outcome was OS of patients who received adjuvant chemotherapy compared to patients that

received no treatment stratified by risk group. The following patient-specific covariates were included: sex, race, age at diagnosis, AJCC pathologic stage, microsatellite stability status, nodes examined, primary payor, chemotherapy, surgery of primary site, tumor size, and Charlson-Deyo score (Table 1). Microsatellite stability status was divided into microsatellite stable (MSS) which included MSI stable (code 020) and MSI unstable low positive (code 040). Microsatellite instable (MSI-H) status included MSI unstable high positive (code 050) and MSI unstable positive (code 060). No ethical approval was required for the study as de-identified patient information in the NCDB is legally accessible to the public.

Table 1
Baseline clinicopathological characteristics

Variable	Level	Entire cohort N (%) = 1040
Sex	Male	530 (51.0)
	Female	510 (49.0)
Race	Caucasian	879 (84.5)
	African American	126 (12.1)
	Other/Unknown	35 (3.4)
Histology	Adenocarcinoma (not otherwise specified)	484 (46.5)
	Mucinous adenocarcinoma	556 (53.5)
Grade	Well differentiated	343 (33.0)
	Moderately differentiated	565 (54.3)
	Poorly differentiated	119 (11.4)
	Undifferentiated	13 (1.3)
Risk Group	Low	557 (53.6)
	High	483 (46.4)
Microsatellite Instability (MSI)	MSI stable	152 (14.6)
	MSI high	14 (1.3)
	Undetermined	874 (84.0)
AJCC Pathologic T	p2	4 (0.4)
	p3	547 (52.6)
	p4	62 (6.0)
	p4A	280 (26.9)
	p4B	147 (14.1)
AJCC Pathologic N	p0	967 (93.0)
	p1	1 (0.1)
	pX	72 (6.9)

Variable	Level	Entire cohort N (%) = 1040
AJCC Pathologic M	p1	6 (0.6)
	p1A	5 (0.5)
	p1B	1 (0.1)
	pX	1028 (98.8)
Lymph Nodes Examined	< 12	313 (30.1)
	≥ 12	727 (69.9)
Lymphovascular Invasion	Not present	931 (89.5)
	Present	109 (10.5)
Year of Diagnosis	2010–2012	439 (42.2)
	2013–2015	601 (57.8)
Facility Type	Community Cancer Program	95 (9.1)
	Comprehensive Community Cancer Program	435 (41.8)
	Academic/Research Program	269 (25.9)
	Integrated Network Cancer Program	165 (15.9)
	Unknown	76 (7.3)
Insurance Status	Unknown/Not Insured	63 (6.1)
	Private Insurance	536 (51.5)
	Government Insurance	441 (42.4)
Charlson-Deyo Score	0	818 (78.7)
	1	160 (15.4)
	2+	62 (6.0)
Tumor Size (cm)	< 5	601 (57.8)
	≥ 5	273 (26.3)
	Unknown	166 (16.0)
Chemotherapy	No	637 (61.3)
	Yes	369 (35.5)
	Unknown	34 (3.3)

Variable	Level	Entire cohort N (%) = 1040
Chemotherapy Treatment	No	637 (61.3)
	Number & type unknown	20 (1.9)
	Single-agent chemotherapy	108 (10.4)
	Multiagent chemotherapy	241 (23.2)
	Unknown	34 (3.3)
Surgery at Primary Site	Appendectomy	305 (29.3)
	Right hemicolectomy	643 (61.8)
	Total colectomy	33 (3.2)
	Surgery NOS	59 (5.7)
Surgical Margin	Negative	934 (89.8)
	Positive	93 (8.9)
	Not evaluable	13 (1.3)
Age at Diagnosis	Mean	60.48
	Median	61.00
	Minimum	19.00
	Maximum	90.00
	Std Dev	13.86

Statistical Analysis

Eligible patients' demographic and disease information were described with appropriate descriptive statistics. Numeric variables were presented with mean, standard deviation, median and range, while categorical variables were presented with frequency and percentage. ANOVA tests were conducted for comparisons of numeric covariates, while Chi-square tests were utilized for categorical covariates. Univariate (UVA) and Multivariate (MVA) analyses and Cox Proportional-Hazards models were fitted to explore the association between each covariate and OS, which is defined as months from diagnosis to death or last contact. High risk group, chemotherapy, microsatellite status, sex, Charlson-Deyo score, race, year of diagnosis, tumor size, facility type, insurance status, and age at diagnosis were included in UVA and MVA models, with a backward elimination approach with the alpha level of 0.20 for covariate selections in MVA. Kaplan-Meier curves were also generated to compare UVA association with OS, with Log-rank test determining statistical significances. All analyses were done using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) with a significant level of 0.05.

Results

Patient Demographics and Tumor Characteristics

A total of 1,040 patients with resected pathological stage II AA were identified (Fig. 1). Baseline clinicopathological characteristics are summarized in Table 1. The median age at diagnosis was 61 (range, 19–90) years, with males accounting for 51%. About 84.5% were Caucasian and distribution across high and low risk status was 46.4% (N = 483) and 53.6% (N = 557), respectively. MSS accounted for 14.6%; MSI-H 1.3%; MSI status undetermined 84%. 50.9% of the patients were treated at community practices and 25.9% were treated at academic or research cancer centers. Insurance coverage was mostly private (51.5%) in comparison to government insurance (42.4%) and no insurance (6.1%). A higher number of patients were diagnosed between 2013–2015 (57.8%) compared to 2010–2012 (42.2%). Charlson-Deyo score was 0 for most patients (78.7%) compared to ≥ 1 in 21.4% of patients. Tumors were < 5 cm in 57.8% of cases and ≥ 5 cm in 26.3% (Table 1).

MSI-H accounted for 1.26% of low risk and 1.45% of high-risk tumors ($p = 0.008$). Covariates such as year of diagnosis, primary payor, sex, race, age at diagnosis and Charlson-Deyo score demonstrated similar proportions amongst high and low risk groups. Baseline clinicopathological characteristics stratified by risk status are summarized in Table 2.

Table 2
Univariate Association with Risk Status

Covariate	Level	Low Risk Group N (%) = 557	High Risk Group N (%) = 483	Parametric P-Value
Sex	Male	281 (50.45)	249 (51.55)	0.481
	Female	276 (49.55)	234 (48.45)	
Race	Caucasian	476 (85.46)	403 (83.44)	0.579
	African American	62 (11.13)	64 (13.25)	
	Other	19 (3.41)	16 (3.31)	
Year of Diagnosis	2010–2012	228 (40.93)	211 (43.69)	0.370
	2013–2015	329 (59.07)	272 (56.31)	
Facility Type	Community Cancer Program	44 (7.90)	51 (10.56)	0.267
	Comprehensive Community Cancer Program	224 (40.22)	211 (43.69)	
	Academic/Research Program	149 (26.75)	120 (24.84)	
	Integrated Network Cancer Program	97 (17.41)	68 (14.08)	
	Unknown	43 (7.72)	33 (6.83)	
Insurance Status	Not Insured/Unknown	28 (5.03)	35 (7.25)	0.318
	Private Insurance	292 (52.42)	244 (50.52)	
	Government Insurance	237 (42.55)	204 (42.24)	
Charlson-Deyo Score	0	443 (79.53)	375 (77.64)	0.714
	1	81 (14.54)	79 (16.36)	
	2+	33 (5.92)	29 (6.00)	

Covariate	Level	Low Risk Group N (%) = 557	High Risk Group N (%) = 483	Parametric P-Value
Tumor Size (mm)	Mean	43.73	40.57	0.336
	Median	35	30	
	Minimum	1	1	
	Maximum	665	989	
	Std Dev	41.84	55.13	
Chemotherapy	No	337 (60.5)	300 (62.11)	0.596
	Number & type unknown	9 (1.62)	11 (2.28)	
	Single-agent chemotherapy	65 (11.67)	43 (8.90)	
	Multiagent chemotherapy	129 (23.16)	112 (23.19)	
	Unknown	17 (3.05)	17 (3.52)	
Microsatellite Instability (MSI)	MSI stable	99 (17.77)	53 (10.97)	0.008
	MSI high	7 (1.26)	7 (1.45)	
	Undetermined	451 (80.97)	423 (87.58)	
Age at Diagnosis	Mean	60.18	60.82	0.456
	Median	62	61	
	Minimum	19	21	
	Maximum	90	90	
	Std Dev	13.43	14.35	

Risk Status and Overall Survival

In the total cohort, high-risk status was associated with worse OS compared to low-risk in univariate (HR 1.55; 95% CI 1.18–2.02; $p = 0.001$) and multivariable analyses (HR 1.36; 95% CI 1.03–1.79; $p = 0.028$) (Table 3). High-risk stage II AA patients had significantly worse 5-year OS compared to low-risk patients (67.1% vs. 74.5%, $p = 0.0013$) (Fig. 2). To adjust for the confounding effect of chemotherapy, a separate analysis was conducted to compare high and low-risk status among patients who only underwent surgery without being treated with chemotherapy. In patients who only underwent resection, high-risk status was still associated with worse OS compared to low-risk in univariate analysis (HR 1.62; 95% CI 1.15–2.29; $p = 0.006$) and a similar direction was seen on multivariable analysis, without reaching

statistical significance (HR 1.32; 95% CI 0.91–1.90; $p = 0.147$) (Supplemental Table 1). High-risk patients still had significantly worse 5-year OS compared to low-risk patients after eliminating chemotherapy as a confounding variable (66.5% vs. 76.3%, $p = 0.0057$) (Fig. 3).

Table 3
Univariate and Multivariate Association with Overall Survival (Total Cohort)

Covariate	Level	Univariate Analysis Hazard Ratio (95% CI) p-value	Multivariate Analysis Hazard Ratio (95% CI) p-value
Risk Status	High Risk Low Risk*	1.55; 1.18–2.02; p = 0.001	1.36; 1.03–1.79; p = 0.028
Chemotherapy	Yes Unknown No*	0.88; 0.67–1.17; p = 0.380 1.18; 0.58–2.41; p = 0.648	-
Microsatellite Instability (MSI)	MSI high Undetermined MSI stable*	0.82; 0.20–3.44; p = 0.786 1.03; 0.70–1.53; p = 0.873	-
Sex	Female Male*	0.80; 0.61–1.04; p = 0.096	0.75; 0.57–0.98; p = 0.037
Race	African American Other Caucasian*	1.37; 0.92–2.04; p = 0.124 1.26; 0.62–2.56; p = 0.521	1.69; 1.12–2.55; p = 0.013 1.18; 0.58–2.42; p = 0.647
Year of Diagnosis	2010–2012 2013–2015*	0.96; 0.71–1.29; p = 0.782	-
Facility Type	Community Cancer Program Academic/Research Program Integrated Network Cancer Program Unknown Comprehensive Community Cancer Program*	0.91; 0.56–1.47; p = 0.690 0.89; 0.64–1.24; p = 0.495 0.97; 0.66–1.43; p = 0.894 0.43; 0.21–0.89; p = 0.023	-
Insurance Status	Not Insured/Unknown Government Insurance Private*	0.96; 0.50–1.85; p = 0.902 2.23; 1.69–2.96; p < 0.001	-

*Reference

Covariate	Level	Univariate Analysis	Multivariate Analysis
		Hazard Ratio (95% CI) p-value	Hazard Ratio (95% CI) p-value
Charlson-Deyo Score	1	1.32; 0.93–1.88; p = 0.118	-
	2+		
	0*	2.23; 1.45–3.42; p < 0.001	
Tumor Size (cm)	≥5	0.88; 0.64–1.21; p = 0.419	-
	Unknown		
	< 5*	1.95; 0.80–4.74; p = 0.142	
Age at Diagnosis	>65	3.01; 2.30–3.95; p < 0.001	-
	≤ 65*		
*Reference			

Adjuvant Chemotherapy in High and Low Risk Stage II AA

AC was administered in 34.4% (n = 166) of high-risk patients and in 36.5% (n = 203) of low-risk patients (p = 0.742) (Table 2). Among high-risk patients, AC was not associated with better OS in univariate (HR 0.86; 95% CI 0.59–1.26; p = 0.448 and multivariable analyses (HR 1.35; 95% CI 0.90–2.04; p = 0.151 compared to no AC (Table 4). Similarly, among low-risk patients, AC was not associated with better OS in univariate (HR 0.92; 95% CI 0.60–1.39; p = 0.679 and multivariable analyses (HR 1.27; 95% CI 0.81–2.02; p = 0.299) compared to no AC (Table 5). For high-risk patients, 5-year OS was 68.3% in patients that received AC vs. 66.5% in patients that did not (p = 0.722) (Fig. 4). For low-risk patients, 5-year OS was 74.0% in patients that received AC vs. 76.3% in patients that did not (p = 0.813) (Fig. 5).

Table 4
Univariate and Multivariate Association with Overall Survival (High Risk)

Covariate	Level	High Risk Univariate Analysis Hazard Ratio (95% CI) p-value	High Risk Multivariate Analysis Hazard Ratio (95% CI) p-value
Chemotherapy	Yes	0.86; 0.59–1.26; p = 0.448	1.35; 0.90–2.04; p = 0.151
	Unknown		
	No*	1.09; 0.40–2.99; p = 0.865	1.41; 0.51–3.89; p = 0.512
Microsatellite Instability (MSI)	MSI high	1.21; 0.27–5.31; p = 0.803	-
	Undetermined	0.83; 0.48–1.46; p = 0.522	
	MSI stable*		
Sex	Female	0.67; 0.47–0.97; p = 0.032	0.63; 0.44–0.91; p = 0.014
	Male*		
Race	African American	0.41; 0.85–2.33; p = 0.181	2.01; 1.19–3.38; p = 0.009
	Other	1.47; 0.60–3.61; p = 0.402	1.28; 0.51–3.21; p = 0.593
	Caucasian*		
Year of Diagnosis	2010–2012	0.83; 0.57–1.21; p = 0.332	-
	2013–2015*		
Facility Type	Community Cancer Program	0.84; 0.45–1.57; p = 0.595	-
	Academic/Research Program	1.09; 0.71–1.69; p = 0.682	
	Integrated Network Cancer Program	0.89; 0.52–1.53; p = 0.683	
	Unknown		
	Comprehensive Community Cancer Program*	0.31; 0.10–1.00; p = 0.050	
Insurance Status	Not Insured/Unknown	1.03; 0.46–2.28; p = 0.948	-
	Government Insurance	2.28; 1.56–3.33; p < 0.001	
	Private*		

*Reference

Covariate	Level	High Risk Univariate Analysis Hazard Ratio (95% CI) p-value	High Risk Multivariate Analysis Hazard Ratio (95% CI) p-value
Charlson-Deyo Score	1	1.52; 0.98–2.35; p = 0.059	-
	2+		
	0*	2.11; 1.15–3.88; p = 0.015	
Tumor Size (cm)	≥5	0.87; 0.56–1.36; p = 0.538	-
	Unknown		
	< 5*	0.60; 0.36–0.99; p = 0.048	
Age at Diagnosis	>65	3.21; 2.23–4.61; p < 0.001	-
	≤ 65*		
*Reference			

Table 5
Univariate and Multivariate Association with Overall Survival (Low Risk)

Covariate	Level	Low Risk Univariate Analysis	Low Risk Multivariate Analysis
		Hazard Ratio (95% CI) p-value	Hazard Ratio (95% CI) p-value
Chemotherapy	Yes	0.92; 0.60–1.39; p = 0.679	1.27; 0.81–2.02; p = 0.299
	Unknown		
	No*	1.24; 0.45–3.43; p = 0.676	1.97; 0.68–5.70; p = 0.210
Microsatellite Instability (MSI)	MSI high	0.00; 0.00–; p = 0.984	-
	Undetermined		
	MSI stable*	1.12; 0.64–1.94; p = 0.697	
Sex	Female	0.99; 0.67–1.49; p = 0.980	-
	Male*		
Race	African American	1.26; 0.65–2.44; p = 0.493	-
	Other		
	Caucasian*	1.12; 0.35–3.54; 0.852	
Year of Diagnosis	2010–2012	1.12; 0.70–1.79; p = 0.628	-
	2013–2015*		
Facility Type	Community Cancer Program	0.98; 0.46–2.09; p = 0.963	1.27; 0.58–2.77; p = 0.551
	Academic/Research Program		
	Integrated Network Cancer Program	0.72; 0.43–1.21; p = 0.214	0.60; 0.35–1.04; p = 0.070
	Unknown	1.15; 0.66–1.99; p = 0.628	0.88; 0.50–1.54; p = 0.650
	Comprehensive Community Cancer Program*	0.59; 0.23–1.50; p = 0.270	2.66; 0.82–8.63; p = 0.104
Insurance Status	Not Insured/Unknown	0.78; 0.24–2.52; p = 0.676	-
	Government Insurance		
	Private*	2.20; 1.45–3.33; p < 0.001	

*Reference

Covariate	Level	Low Risk Univariate Analysis	Low Risk Multivariate Analysis
		Hazard Ratio (95% CI) p-value	Hazard Ratio (95% CI) p-value
Charlson-Deyo Score	1	1.04; 0.56–1.91; p = 0.908	0.57; 0.29–1.12; p = 0.102
	2+		
	0*	2.35; 1.27–4.33; p = 0.006	1.76; 0.92–3.35; p = 0.088
Tumor Size (cm)	≥5	0.96; 0.61–1.51; p = 0.857	-
	Unknown		
	< 5*	0.80; 0.42–1.52; p = 0.487	
Age at Diagnosis	>65	2.80; 1.86–4.20; p < 0.001	-
	≤ 65*		
*Reference			

Discussion

Appendiceal adenocarcinoma is a rare malignancy with complex clinical management. Significant increase has been reported in annual incidence of all appendiceal tumors from 1973 to 2014(6). Almost half of the patients present with locoregional disease and post-surgical management is less established. Clinicopathological high-risk features of colon adenocarcinoma as described in national guidelines(13, 20, 21) are often utilized in stage II appendiceal adenocarcinoma management despite lack of data(7). The presence of traditional “high-risk” pathologic features in stage II colon cancer can identify a subgroup of patients with a recurrence risk approximating that of stage III disease(22). The results in this study similarly demonstrated that patients with high-risk AA had significantly worse OS compared to their low-risk counterparts in multivariable analysis. High-risk stage II AA patients also had significantly worse 5-year OS compared to low-risk patients (67.1% vs. 74.5%, p = 0.0013). Thus, high-risk features are prognostic in stage II AA. In addition to clinico-pathological high-risk features high-quality prognostic biomarkers could also be useful clinically to estimate proper therapeutic strategies or to predict prognosis(23). A nomogram predict model proposed by Xie et al, who collected data for 1404 patients with adenocarcinoma of the appendix from the Surveillance, Epidemiology, and End Results Program (SEER) database, noted that different stages meant disparate therapies and discrepant prognosis between low- and high-risk patients, especially in stage I-III adenocarcinoma of the appendix(23). Their novel nomogram prognosis prediction model contained seven clinical factors (age, marital status, depth of tumor invasion, total number of resected regional lymph nodes, number of metastatic lymph nodes, histological grade and distant metastases), in patients who underwent surgical treatment, that were more accurate than those generated using the traditional AJCC TNM Staging system(23). However, due to the

limitations of the SEER database, information regarding the administration of chemotherapy could not be obtained(23).

The American Society of Colon and Rectal Surgeons (ASCRS) clinical practice guidelines recommend that patients with non-metastatic adenocarcinoma of the appendix should undergo right hemicolectomy(24). However, there are no published guidelines regarding AC for stage II AA due to lack of prospective trials. Management of stage II AA is extrapolated from stage II CC but studies examining role of high-risk features in stage II AA are lacking in adjuvant setting. To the best of our knowledge, this study is the first to describe the prognostic use of clinicopathological high-risk features in stage II AA. The results of this study demonstrated that clinicopathological high-risk features are prognostic in stage II AA. Neither resected high or low-risk stage II AA benefit from AC compared to no treatment in this study. Asare et al. reported that patients with mucinous and non-mucinous stage II and III appendiceal AA benefited from adjuvant systemic chemotherapy in their study examining impact of mucinous histology, grade and stage on all stages of AA(25). However, clinicopathological features of stage II AA patients who would benefit from adjuvant treatment was not studied.

Despite the novel findings of this study, this is a retrospective study with its inherent limitations. The limitations of this study include lack of specific chemotherapy regimen data, duration of chemotherapy and data about adverse effects of chemotherapy. The analysis was primarily based on receipt of any chemotherapy and does not account for early discontinuation of prescribed treatment, which possibly could impact the survival benefit. Certain high-risk features, such as clinical presentation with obstruction or perforation are not included in the NCDB. In addition, disease-specific mortality, recurrence indices, and response to treatment are not captured in the NCDB. Despite these limitations, this study is the largest collective series currently available for pathological stage II AA classified by low- and high-risk features. Furthermore, this study can assist clinicians with adjuvant treatment decisions in stage II AA.

Conclusion

High-risk stage II AA patients had significantly worse 5-year OS compared to low-risk patients. AC did not appear to improve survival regardless of high-risk features in stage II AA

List Of Abbreviations

Adjuvant chemotherapy (AC)

Appendiceal adenocarcinoma (AA)

National Cancer Database (NCDB)

Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)

Overall survival (OS)

Pathologic T4 (pT4) tumors

Lymphovascular invasion (LVI)

Perineural invasion (PNI)

Colorectal cancer (CC)

Microsatellite stable (MSS)

Microsatellite instable (MSI-H)

Univariate analysis (UVA)

Multivariate analysis (MVA)

American Society of Colon and Rectal Surgeons (ASCRS)

Declarations

Ethics approval and consent to participate: No ethical approval was required for the study as de-identified patient information in the NCDB is legally accessible to the public.

Consent for publication: Not applicable.

Availability of data and materials: Part of data presented in this study was presented at the 2020 GI ASCO Annual Meeting in San Francisco, CA. The manuscript's abstract was published in "Abstracts" in Journal of Clinical Oncology: J Clin Oncol 38, 2020 (suppl 4; abstr 795). Research reported in this publication was supported in part by the Winship Research Informatics Shared Resource of Winship Cancer Institute of Emory University and NIH/National Cancer Institute under award numbers P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The data used in the study are derived from a de-identified NCDB file. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

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Authors' contributions: MA was involved in conceptualization, data curation, formal analysis, investigation, project administration, supervision, validation and writing - review and editing. KZ was involved in conceptualization, data curation, formal analysis, investigation, project administration, supervision, validation and writing - review and editing. MP was involved in data curation, methodology,

software, writing - original draft, and writing - review and editing. RJ was involved in data curation, methodology, software, writing - original draft, and writing - review and editing. OBA was involved in the methodology, investigation, original draft, and writing - review and editing. WLS was involved in the methodology, investigation, original draft, and writing - review and editing. CW was involved in the methodology, investigation, original draft, and writing - review and editing. MB was involved in the conceptualization, project administration, investigation, validation, review and editing. BFER was involved in the methodology, investigation, original draft, and writing - review and editing. All authors read and approved the final manuscript.

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Supplemental Table

Covariate	Level	Univariate Analysis		Multivariate Analysis	
		Hazard Ratio (95% CI)		Hazard Ratio (95% CI)	
		p-value		p-value	
Risk Status	High Risk	1.62;	1.15-2.29;	1.32;	0.91-1.90;
	Low Risk*	p=0.006		p=0.147	
Microsatellite Instability (MSI)	MSI high	0.73;	.010-5.47;	-	
	Undetermined	p=0.760			
	MSI stable*	1.00;	0.61-1.65;		
		p=0.996			
Nodes Examined	<12	1.62;	1.15-2.28;	-	
	≥12*	p=0.006			
Surgical Margins	Positive	2.41;	1.51-3.85;	-	
	Negative*	p<0.001			
Sex	Female	0.70;	0.50-0.99;	0.68;	0.48-0.98;
	Male*	p=0.045		p=0.041	
Race	African American	1.39;	0.85-2.26;	2.06;	1.23-3.46;
	Other	p=0.192		p=0.006	
	Caucasian*	1.55;	0.68-3.54;	1.28;	0.55-3.00;
		p=0.296		p=0.566	
Year of Diagnosis	2010-2012	1.17;	0.80-1.71;	-	
	2013-2015*	p=0.407			
Facility Type	Community Cancer Program	0.86;	0.48-1.53;	1.05;	0.57-1.91;
	Academic/Research Program	p=0.603		p=0.878	
	Integrated Network Cancer Program	0.83;	0.54-1.29;	1.09;	0.69-1.74;
	Unknown	p=0.413		p=0.711	
	Comprehensive Community Cancer Program*	0.61;	0.36-1.04;	0.56;	0.32-0.96;
		p=0.067		p=0.036	
Insurance Status	Not Insured/Unknown	0.38;	0.12-1.21;	4.27;	1.12-16.32;
	Government Insurance	p=0.102		p=0.034	
	Private*	3.22;	2.17-4.78;	-	
		p<0.001			
Charlson-Deyo Score	1	1.26;	0.80-1.98;	1.05;	0.66-1.69;
	2+	p=0.320		p=0.829	
	0*	2.63;	1.63-4.24;	1.84;	1.11-3.03;
		p<0.001		p=0.017	
Tumor Size (cm)	≥5	1.05;	0.70-1.57;	-	
	Unknown	p=0.822			
	<5*	0.55;	0.31-0.99;		
		p=0.045			
Age at Diagnosis	>65	3.90;	2.67-5.68;	-	

≤65*

p<0.001

*Reference

Supplemental Table 1: Univariate and Multivariate Association with Overall Survival (Surgery Only, No Chemotherapy Cohort)

Figures

Figure 1

Consort diagram outlining the study selection

	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
Low Risk (0)	557	96 (17%)	461 (83%)	NA (86.8, NA)	98.2% (96.6%, 99.0%)	74.5% (69.0%, 79.3%)
High Risk (1)	483	122 (25%)	361 (75%)	NA (84.5, NA)	93.3% (90.6%, 95.2%)	67.1% (61.4%, 72.1%)

Figure 2

Overall Survival by Risk Group (Total Cohort)

	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
Low risk (0)	337	56 (17%)	281 (83%)	86.8 (82.1, NA)	97.9% (95.6%, 99.0%)	76.3% (69.1%, 82.1%)
High risk (1)	300	76 (25%)	224 (75%)	84.5 (75.4, NA)	91.6% (87.8%, 94.3%)	66.5% (58.9%, 73.0%)

Figure 3

Overall Survival by Risk Group (Surgery Only, No Chemotherapy Group)

Chemotherapy	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
No	300	76 (25%)	224 (75%)	84.5 (75.4, NA)	91.6% (87.8%, 94.3%)	66.5% (58.9%, 73.0%)
Unknown	17	4 (24%)	13 (76%)	NA (18.6, NA)	93.3% (61.3%, 99.0%)	70.0% (38.2%, 87.6%)
Yes	166	42 (25%)	124 (75%)	NA (71.2, NA)	96.2% (91.8%, 98.3%)	68.3% (58.8%, 76.1%)

Figure 4

Overall Survival by Treatment (High Risk)

Chemo Yes or No	No. of Subject	Event	Censored	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
No	337	56 (17%)	281 (83%)	86.8 (82.1, NA)	97.9% (95.6%, 99.0%)	76.3% (69.1%, 82.1%)
Unknown	17	4 (24%)	13 (76%)	NA (33.9, NA)	94.1% (65.0%, 99.1%)	58.1% (20.4%, 83.1%)
Yes	203	36 (18%)	167 (82%)	NA (76.5, NA)	99.0% (96.0%, 99.7%)	74.0% (64.8%, 81.2%)

Figure 5

Overall Survival by Treatment (Low Risk)