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ORIGINAL ARTICLE – COLORECTAL CANCER

Survival Outcomes and Patterns of Management for Anal Adenocarcinoma

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ABSTRACT

Background. Anal adenocarcinoma (AA) is a rare histologic subtype of anal cancer believed to have worse outcomes than anal squamous cell carcinoma (AS). This study aimed to examine practice patterns and treatment outcomes for this rare subtype using the National Cancer Data Base (NCDB).

Methods. Patients who had new diagnoses of anal cancer treated with chemoradiation were selected from the NCDB from 2004 to 2015. The patients were divided into two histologic groups (AA or AS). Statistics included the Chi square test to analyze categorical proportions in demographic information, Kaplan–Meier analysis to evaluate overall survival (OS), and Cox proportional hazards modeling to determine variables associated with OS.

Results. The study analyzed 24,461 patients. Compared with AS patients, AA patients were more likely to be male, to present with a higher cancer stage, to be older (> 65 years), and to undergo surgery with an abdominoperineal resection (APR). The median OS was 72.5 months for the AA patients and 143.8 months for the AS patients ($P < 0.001$). Survival was longer for the AA patients undergoing APR within 6 months after chemoradiation (CRT) than for the AA patients who had an APR 6 months after CRT (88.3 vs. 58.1 months; $P < 0.001$). In the multivariable analysis, the factors associated with worse survival included adenocarcinoma subtype, age of 55 years or older, male gender, T stage of 3 or higher, comorbidity score of 1 or higher, lower income, and treatment at a nonacademic institution.

Conclusions. In this largest study of anal adenocarcinoma to date, trimodality therapy was associated with better survival than chemoradiation alone.

Anal cancer is a relatively rare malignancy, representing only 1% of gastrointestinal cancer cases.[1] The vast majority of anal cancer cases are of squamous cell carcinoma histology. However, due to the unique anatomy and histology of the anal canal, characterized by the transition of columnar cellular epithelium to squamous cellular epithelium, other histologies of cancer have been observed.[2] Adenocarcinoma of the anus (AA), a rare subtype of anal cancer, is thought to represent 5 to 10% of all anal cancer cases.[3] Previous studies have reported that AA carries a worse prognosis than anal squamous cell carcinoma (AS).[3,4]

Unfortunately, due to the rarity of AA, no evidence-based treatment guidelines exist currently. The treatment for AS is definitive chemoradiation based on the seminal work reported by Nigro et al.[5] in the 1970s. Abdominoperineal resection (APR) is reserved for the salvage setting.

In contrast, AA typically has been treated similarly to a low-lying rectal adenocarcinoma using trimodality therapy with neoadjuvant chemoradiation followed by APR. This aggressive approach may be due to the reported worse survival outcomes necessitating the use of all lines of therapy. Given the disease rarity and the lack of defined management guidelines, we aimed to use the National Cancer Data Base (NCDB) to examine practice patterns and outcomes.

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MATERIALS AND METHODS

This study used the NCDB, a hospital-based cancer registry sponsored by the American College of Surgeons (ACoS) and the American Cancer Society. The NCDB collects data from more than 1500 hospitals with ACoS-accredited cancer programs, accounting for 70% of all newly diagnosed cancers in the United States.[6–12] The most recent data from the NCDB included data from 2004 to 2015. Institutional review board approval was not required for this study because only de-identified information is stored in the database.

Only patients with newly diagnosed, non-metastatic anal cancer treated with upfront chemoradiation were included in this study. The patients were required to have histologic diagnostic confirmation, treatment with upfront chemoradiotherapy, and a recorded vital status. The patients were divided into two cohorts: those with AA histology and those with AS histology. The information collected on each patient included demographic data, comorbidity information, clinicopathologic tumor parameters, and treatment facility characteristics. Academic versus nonacademic facilities was defined using a classification scheme from other published studies using the NCDB.[13]

All statistical tests were two-sided, with a threshold P value lower than 0.05 for statistical significance, and were performed using STATA version 14 (StataCorp LLC, College Station, TX, USA). The Chi-square test analyzed categorical proportions between groups. Uni- and multivariable logistic regression modeling was used to determine characteristics predictive for receipt of radiotherapy (RT). The Kaplan–Meier method was used for survival analysis, and comparisons between the two treatment paradigms were performed with the log-rank test for all patients. Overall survival (OS) was defined as the interval between the date of diagnosis and the date of death or last contact. Multivariable Cox proportional hazards modeling was additionally used to identify variables associated with OS in the entire cohort.

RESULTS

The selection requirements were met by 24,461 anal cancer patients. Of these patients, 1183 (4.8%) had adenocarcinoma, and 23,278 (95.2%) had squamous cell carcinoma. Table 1 displays the clinical characteristics of the analyzed patients. The majority of the patients were older than 55 years and Caucasian, had a Charlson-Deyo Comobidity Score of 0, and were treated in a nonacademic facility. Compared with the AS patients, the AA patients were more likely to be male, to present at a higher stage, to be older (> 65 years), and to undergo surgery with an abdominoperineal resection (APR) ($P < 0.05$). These factors are summarized in Table 2.

Of the AA patients undergoing APR, 96.2% underwent APR within 6 months after completion of upfront chemoradiation (CRT). The clinical characteristics of the AA patients with a recorded surgery type ($n = 1155$) are included in Table S1. The AA patients undergoing APR were more likely to be younger, to have a higher T stage, to have a higher stage of cancer, and to have private insurance. The median OS was 72.5 months for the AA patients and 143.8 months for the AS patients ($P < 0.001$) (Fig. 1). Survival was longer for the AA patients undergoing APR within 6 months after chemoradiation (CRT) than for the AA patients who had an APR 6 months after CRT (88.3 vs. 58.1 months; $P < 0.001$; Fig. 2a). In the multivariable analysis, the factors associated with worse survival included adenocarcinoma subtype, age of 55 years or older, male gender, T stage of 3 or higher, comorbidity score of 1 or higher, lower income, and treatment at a nonacademic institution.

To account for selection bias in the AA patients undergoing APR, propensity score-matching was performed using age, T stage, and stage group as the matched variables. Even after matching by age, T stage, and stage group, the patients with AA undergoing APR within 6 months after CRT showed significantly better OS than all the other AA patients (60.1 vs. 43.7 months; $P < 0.001$; Fig. 2b).

DISCUSSION

Given the lack of clear evidence for the management of AA, using a large data set is useful for examining patterns of care to determine possible management options. To our knowledge, this is the largest study to examine the incidence, patterns of management, and survival outcomes to date for patients with AA.

Several observations can be made from our analysis. First, in accordance with the existing literature, survival outcomes of AA are poor.[3,4] Patients with AA do substantially worse than patients with AS. This survival difference remained even when this study accounted for other factors that affect survival including age, race, cancer stage, and the presence of comorbidities. The reasons for this are not clear. Histology alone cannot explain the difference because AA patients also do worse than rectal adenocarcinoma (RA) patients.[3] As a result, it may be speculated that AA may have unique biologic or molecular characteristics that could help explain the difference in outcomes compared with AS or RA. As newer

TABLE 1 Baseline characteristics of the patients in each of the cohorts

Characteristic	Adenocarcinoma (n = 1183) n (%)	Squamous cell (n = 23,308) n (%)	P value
Age (years)			
< 55	269 (22.8)	8262 (35.5)	< 0.001
55–64	339 (28.7)	7554 (32.5)	
65 +	573 (48.5)	7464 (32.1)	
Sex			
Male	664 (56.2)	7179 (30.8)	< 0.001
Female	517 (43.8)	16,101 (69.2)	
Race			
White	977 (82.7)	20,543 (88.2)	< 0.001
African American	157 (13.3)	2227 (9.6)	
Other/not recorded	47 (4.0)	510 (2.2)	
T Stage			
T1–2	586 (49.6)	16,056 (69.0)	< 0.001
T3–4	595 (50.4)	7224 (31.0)	
N stage			
N0	754 (63.8)	15,582 (66.9)	0.028
N+	427 (36.2)	7698 (33.1)	
Stage			
1	130 (11.0)	4149 (17.8)	< 0.001
2	551 (46.7)	10,559 (45.4)	
3	500 (42.3)	8572 (36.8)	
Charlson Deyo score			
0	961 (81.4)	1886 (81.1)	< 0.001
1	159 (13.5)	2857 (12.3)	
2	43 (3.6)	626 (2.7)	
≥ 3	18 (1.5)	911 (3.9)	
Facility type			
Nonacademic	738 (62.5)	15,145 (65.1)	0.192
Academic	403 (34.1)	7425 (31.9)	
Not recorded	40 (3.4)	710 (3.1)	
Income ($)			
≤ 62,999	826 (69.9)	16,313 (70.1)	0.574
63,000 +	345 (29.2)	6827 (29.3)	
Not recorded	10 (0.9)	140 (0.6)	
Insurance			
Medicaid	81 (6.9)	2176 (9.4)	< 0.001
Medicare	539 (45.6)	8287 (35.6)	
Private	454 (38.4)	10,697 (46.0)	
Uninsured	67 (5.7)	1259 (5.4)	
Government/other	40 (3.4)	861 (3.7)	
APR			
Yes	538 (45.6)	453 (2.0)	< 0.001
No	617 (52.2)	22,638 (97.2)	
Not recorded	26 (2.2)	189 (0.8)	

APR abdominoperineal resection

TABLE 2 Cox multivariable analysis of factors predictive of overall survival in the entire cohort (for both AA and AS patients)

Characteristic	HR	95% CI	*P* value
Histology			
Squamous cell	1 (reference)		
Adenocarcinoma	1.19	1.077–1.316	0.001
Age (years)			
< 55	1 (reference)		
55–64	1.187	1.105–1.274	< 0.001
65 +	1.685	1.552–1.829	< 0.001
Sex			
Male	1 (reference)		
Female	0.67	0.634–0.707	< 0.001
Race			
White	1 (reference)		
African American	1.054	0.970–1.145	0.217
Other/not recorded	0.854	0.708–1.030	0.098
T Stage			
*T*1–2	1 (reference)		
*T*3–4	1.533	1.447–1.624	< 0.001
N stage			
*N*0	1 (reference)		
N+	1.056	0.944–1.182	0.341
Stage			
1	1 (reference)		
2	1.404	1.287–1.530	< 0.001
3	1.916	1.667–2.202	< 0.001
Charlson-Deyo score			
0	1 (reference)		
1	1.399	1.303–1.502	< 0.001
2	1.832	1.615–2.077	< 0.001
≥ 3	1.891	1.685–2.121	< 0.001
Facility type			
Nonacademic	1 (reference)		
Academic	0.859	0.812–0.910	< 0.001
Not recorded	1.039	0.895–1.206	0.617
Income ($)			
≤ 62,999	1 (reference)		
63,000 +	0.857	0.807–0.910	< 0.001
Not recorded	2.784	2.211–3.504	< 0.001
Insurance			
Medicaid	1 (reference)		
Medicare	0.996	0.900–1.102	0.937
Private	0.61	0.555–0.670	< 0.001
Uninsured	0.858	0.755–0.976	0.02
Government/other	0.729	0.622–0.855	< 0.001

AA anal adenocarcinoma, *AS* anal squamous cell carcinoma, *HR* hazard ratio, *CI* confidence interval

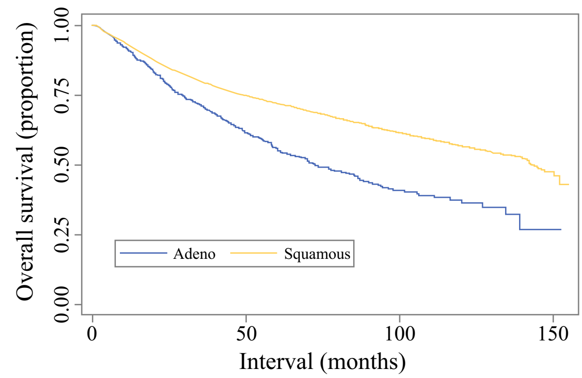

FIG. 1 Kaplan–Meier overall survival curves comparing anal adenocarcinoma and anal squamous cell carcinoma

genetic/molecular profiling techniques are developed, further research into these biologic differences can be performed.

Second, the lack of a consistent management approach for AA (due to its rarity) may contribute to the poor survival outcomes. It appears that AA patients are managed similarly to either AS (with definitive chemoradiation) or RA (with surgery ± neoadjuvant chemoradiation). Almost half of the AA patients (45.6%) in this study underwent APR, whereas the remaining 52.2% did not. The AA patients undergoing APR were more likely to be younger and to have a more advanced T stage and a higher stage of cancer. This suggests that younger patients and patients with more advanced disease are treated aggressively possibly to maximize survival outcomes. In contrast, patients with older or less advanced disease are more likely to be treated with chemoradiation alone. Possibly the goal has been to surveil these patients for a complete clinical response to avoid a morbid surgery (as is the standard of care for AS patients, and is being explored for rectal adenocarcinoma patients).

Although the exact reasoning for APR cannot be ascertained using the information present in the NCDB, it is important to note that 96.2% of the patients undergoing APR did so within 6 months after completion of chemoradiation, suggesting that this was a planned surgery and not surgery performed for salvage. The optimal management paradigm for patients with AA is uncertain. It could be argued that the rarity of AA prohibits more aggressive management (i.e., APR) without more definitive clinical evidence. This is especially important given the significant morbidity and quality-of-life changes associated with an APR.[14] Several series have reported respectable outcomes for patients with AA using

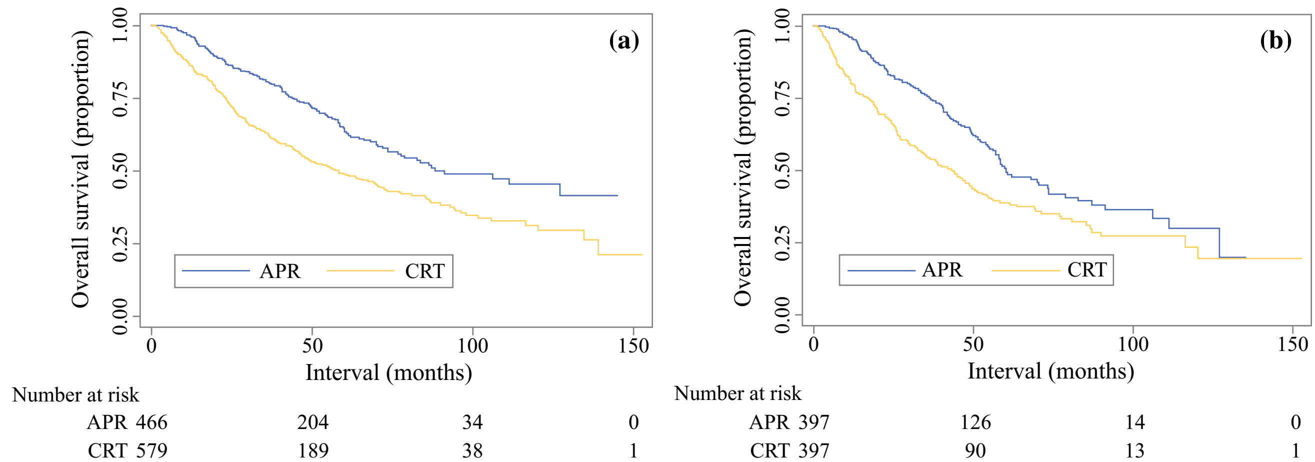

FIG. 2 **a** Kaplan–Meier overall survival curves comparing anal adenocarcinoma patients undergoing abdominoperineal resection (APR) within 6 months after upfront chemoradiation and all other anal adenocarcinoma patients. **b** Kaplan–Meier overall survival curves comparing anal adenocarcinoma patients undergoing APR within 6 months after upfront chemoradiation and all other anal adenocarcinoma patients in the propensity score-matched cohort

TABLE 3 Previous literature on adenocarcinoma of the anus

Study	Cases (*n*)	Median age (years)	Treatment paradigm	Median DFS (months)	Median OS (months)	OS (%)	Median follow-up
Su et al. (2017)[20]	112	55.5	67 patients: local surgery/APR alone	–	–	64.5% at 5 years	30 months
			18 patients: CRT alone				
			27 patients: CRT ± local surgery/APR				
Franklin et al. (2016)[3]	462	69	RT ± local surgery/APR	–	33	30.2% at 5 years	–
Chang et al. (2009)[19]	28	64	CRT + local surgery	13	–	43% at 5 years	37 months
			CRT + APR	32		63% at 5 years	
Kounalakis et al. (2009)[18]	30	67.6*	APR alone	–	Not reached	58% at 5 years	40 months
	42	57.5*	APR ± CRT		56	50% at 5 years	32 months
	93	69*	CRT alone		39	30% at 5 years	31 months
Beal et al. (2003)[21]	13	59	CRT ± local surgery/APR	–	26	62% at 2 years	19 months
Papagikos et al. (2003)[17]	16	58	RT ± local surgery/APR/ chemotherapy	15	63	64% at 5 years	45 months
Belkacémi et al. (2003)[15]	6	66	APR alone	–	–	21% at 5 years	4.6 years
	45	78	RT + local surgery/APR			29% at 5 years	3.6 years
	31	69	CRT alone			58% at 5 years	4.7 years
Joon et al. (1999)[16]	6	69*	RT or CRT	Not reached	Not reached	83% at 3.5 years	6.6 years
Klas et al. (1999)[22]	36	58*	Local surgery/APR ± CRT	–	–	63% at 5 years	48 months
Basik et al. (1995)[23]	10	59	Local surgery/ APR ± chemotherapy	–	29	–	35 months

DFS disease-free survival, *OS* overall survival, *APR* abdominoperineal resection, *CRT* chemoradiation, *RT* radiation

* denote mean age values

chemoradiation alone.[15–17] In contrast, other retrospective series have suggested improvement in survival when an APR is part of the management paradigm.[3,18,19]

The previous literature on AA is presented in Table 3. Based on our data, AA patients who underwent an APR within 6 months after chemoradiation (i.e., as part of upfront management) had better median survival than all other AA patients. This finding remained after propensity score-matching was performed. These findings suggest, in accordance with previous retrospective data, that trimodality treatment with chemotherapy, radiation, and radical surgery results in the best probability of long-term survival for AA patients and that AA may best be managed similarly to RA.

Given the rarity of AA, large retrospective series may represent the best data on the proper treatment paradigm for these patients. When it comes to the management of a single patient, multidisciplinary treatment planning by a team that includes a surgeon, medical oncologist, and radiation oncologist as well as a frank and open discussion with the patient should be performed to optimize the care for that particular patient. Further research into the genetic/molecular profile of this rare disease subtype may provide clues that result in the development of more effective treatment and prevention strategies.

This study had several limitations. First, selection bias is always an important consideration when retrospective data sets are analyzed. Propensity score-matching was performed to minimize the effects of selection bias, although it is still possible that a selection bias may be confounding the results. Second, unfortunately, no information is available on other important variables for examining practice patterns, including the reasoning behind treatment decisions as well as the use of targeted or salvage treatments. Third, end points such as treatment toxicity, cancer-specific survival, and local/regional control are not included in the NCDB. Finally, although the NCDB accounts for 70% of new cancer diagnoses in the United States, only CoC-accredited facilities collect data for the NCDB. Overall, these limitations do not diminish the need for further investigations into the proper management of anal adenocarcinoma.

CONCLUSION

Anal adenocarcinoma is a rare disease subtype with worse survival outcomes than AS. In addition, AA patients are more likely to be male, to present at a higher stage, to be older (>65 years), and to undergo surgery with an abdominoperineal resection. In the multivariable analysis, the factors associated with worse survival included adenocarcinoma subtype, age of 55 years or older, male gender, T stage of 3 or higher, comorbidity score of 1 or higher, lower income, and treatment at a nonacademic institution. This study is the largest study of AA to date, and our findings suggest that upfront chemoradiation followed by abdominoperineal resection within 6 months results in the best probability of long-term survival.

DISCLOSURE There are no conflicts of interest.

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