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Original Research Article

Adenosquamous carcinoma: An aggressive histologic sub-type of colon cancer with poor prognosis

Yosef Nasseri [a, b, *], Brian Cox [a], Wesley Shen [a, b], Ruoyan Zhu [a, b], Isabella Stettler [a, b], Jason Cohen [a, b], Avo Artinyan [c, d], Alexandra Gangi [a]

[a] Cedars-Sinai Medical Center, Los Angeles, CA, USA
[b] Surgery Group Los Angeles, Los Angeles, CA, USA
[c] Adventist Health Glendale, Glendale, CA, USA
[d] Academic Surgical Associates, Glendale, CA, USA

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ABSTRACT

Background: Studies have reported worse overall survival (OS) for adenosquamous carcinoma (ASC) compared to adenocarcinoma (AC) of the colon, but none have analyzed a national dataset for over 30 years.

Methods: The National Cancer Database was queried from 2004 to 2016 for patients with ASC and AC of the colon. Kaplan-Meier survival analysis was performed to assess OS. Descriptive variables were evaluated using independent T-test and Chi-square analyses.

Results: 332 ASC patients were compared to 496,950 AC patients. AC patients were older than ASC patients (68.6 vs. 64.4 years); $p < 0.001$. Most ASC cancers presented with stage IV (41.3%) and poorly-differentiated disease (57.5%) compared to AC (22.4% and 17.7%). OS of the ASC cohort was 13.9 months. Median OS for stage IV AC versus stage IV ASC was significantly better (14.1 vs. 8.0 months); $p < 0.0001$.

Conclusion: This is the largest national database study to compare ASC with AC. Our findings confirm that unlike AC, ASC most frequently presents late stage, as poorly-differentiated lesions, and have worse OS.

Introduction

Adenocarcinoma (AC) is the most common pathologic subtype of colon cancer.[1] Rarer epithelial subtypes of colon cancer include neuroendocrine tumors, sarcomas, and lymphoid tumors.[2] Adenosquamous carcinoma (ASC) is an extremely rare form of colon cancer with an incidence reported between 0.025 and 0.1% of all colon cancers.[3] It is characterized pathologically as featuring both glandular and squamous histological components.[3] ASC is characterized by the unusual presence of neoplastic squamous epithelium arising within the glandular colonic mucosa. Proposed theories of the histogenesis of colonic ASC include the presence of embryonic nests in the ectoderm, squamous metaplasia of the intestinal mucosa, or the presence of pluripotent stem cells of endodermal origin capable of multidirectional differentiation.[3] However, the rarity of the lesion and lack of a low-grade precursor prevents further clarification.[3]

The first reported case of ASC was documented in 1907 by Herxheimer who reported squamous cell carcinoma in the cecum.[4] Multiple case studies have since reported the aggressive nature and poor prognosis of ASC.[5,6] However, there is a paucity of large data analysis of this entity. Cagir et al. published the first NCI SEER database study of colorectal and anal ASC in 1999, identifying 145 cases.[3] The most recent database study was conducted in 2012 by Masoomi et al. and reported 99 cases of colorectal ASC.[2] Collating the numbers, there have been approximately 600 documented cases of colorectal and anal ASC over the last 30 years.[2,3,4] For comparison, over 95% of the estimated 134,490 colorectal cancer cases in the United States each year are classified as AC (~127,765).[7] Given their rarity and lack of robust data, we sought to gain a broader understanding of the presentation, prognosis and oncological outcome of ASC by re-examining the much larger dataset of

* Corresponding author. 8635 W. Third Street, Suite 880W, Los Angeles, CA, 90036, USA.
E-mail address: Yosef.Nasseri@cshs.org (Y. Nasseri).

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Table 1
Demographic characteristics of ASC vs. AC

	Adenosquamous	Adenocarcinoma	
	N = 332	N = 496950	
	Mean (STD)	**Mean (STD)**	***P***
Age	64.43 (14.59)	68.59 (13.44)	<0.0001
	N (%)	**N (%)**	***P***
Gender			0.784
Male	159 (47.9%)	242386 (48.8%)	
Female	173 (52.1%)	254564 (51.2%)	
Race			0.814
White	277 (83.4%)	412478 (83.0%)	
Black	42 (12.7%)	62313 (12.7%)	
Chinese	2 (0.6%)	2569 (0.3%)	
Japanese	2 (0.6%)	1768 (0.4%)	
Other	6 (1.8%)	13760 (2.8%)	
Unknown	3 (0.9%)	4062 (0.8%)	
Charlson-Deyo			0.295
0	234 (70.5%)	344515 (69.3%)	
1	77 (23.2%)	110188 (22.2%)	
2	12 (3.6%)	30309 (6.1%)	
3+	9 (2.7%)	11938 (2.4%)	

patients now recorded in the National Cancer Database (NCDB). We also compared clinicopathological outcomes of patients diagnosed with ASC and AC of the colon, making this the largest comparative study of ASC.

Methods

Data was obtained from the National Cancer Database (NCDB) registry from 2004 to 2016.

Selection of study cohort

The study cohort was derived from a cohort of 497,282 patients with colon cancer (International Classification of Diseases for Oncology 3rd Edition; disease topography code C18.0). Utilizing histologic code 8140/3, all patients with invasive ASC and AC of the colon were identified. Lesions involving appendix and the rectum were excluded from the study cohort. Patients who were classified as AJCC 7th Edition Stage 0 or 'Not Applicable' were also excluded. A

Table 2
Clinicopathological characteristics and survival of ASC vs. AC

	Adenosquamous	Adenocarcinoma	
	N = 332	N = 496950	
	N (%)	**N (%)**	***P***
Site			<0.0001
Cecum	93 (28.0%)	104725 (21.6%)	
Ascending	84 (25.3%)	103027 (20.7%)	
Hepatic Flexure	21 (6.3%)	24.38 (4.9%)	
Transverse	29 (8.7%)	49514 (10.0%)	
Splenic Flexure	10 (3.0%)	17409 (3.5%)	
Descending	13 (3.9%)	31368 (6.3%)	
Sigmoid	58 (17.5%)	138025 (27.8%)	
Unspecified	24 (7.2%)	25814 (5.2%)	
Laterality			<0.0001
Right	227 (68.4%)	284334 (57.2%)	
Left	81 (24.4%)	186802 (37.6%)	
Unspecified	24 (7.2%)	25814 (5.2%)	
Grade			<0.0001
Well-diff	8 (2.4%)	39400 (7.9%)	
Mod-diff	78 (23.5%)	323131 (65.0%)	
Poor-diff	191 (57.5%)	87788 (17.7%)	
Undiff	36 (10.8%)	10078 (2.0%)	
Unspecified	19 (5.7%)	36553 (7.4%)	
AJCC Stage			<0.0001
1	14 (4.2%)	86896 (17.5%)	
2	71 (21.4%)	151310 (30.4%)	
3	110 (33.1%)	147769 (29.7%)	
4	137 (41.3%)	110975 (22.3%)	
Survival			<0.0001
Alive	90 (29.6%)	225272 (45.3%)	
Dead or Lost to FU	214 (70.4%)	229341 (46.1%)	
Missing	28 (8.4%)	42337 (8.5%)	

total of 332 ASC (0.067%) and 496,950 AC patients from 2004 to 2016 met inclusion criteria.

Analysis

Patient characteristics were reported as means, medians, and standard deviations for continuous variables. Comparisons were performed using independent samples T-tests and Pearson Chi-Square tests for continuous and categorical variables. Overall survival (OS) was computed using Kaplan-Meier methods. All tests were conducted in SPSS v26 at a nominal significance level of 0.05.

Results

Characteristics of adenosquamous and adenocarcinoma cohorts

Table 1 details the demographics of both ASC and AC cohorts. ASC study patients (N = 332) were predominantly female (Ratio: 1.1:1). The overall mean age of ASC patients was 64 years, with no significant difference in mean age between males and females: 62.0 years and 66.6 years, respectively ($p = 0.644$). The reported population was primarily Caucasian (83.4%) and lacked comorbidities (Charlson-Deyo score 0–1: 93.7%).

The cohort of AC patients was also predominantly female (N = 496950, ratio: 1.05:1). The overall mean age of AC patients was 68.6 years, with a significant difference in mean age between males and females: 67.5 years and 69.7 years, respectively ($p < 0.001$). The reported population was primarily Caucasian (83.0%) and lacked comorbidities (Charlson-Deyo score 0–1: 91.5%).

Characteristics of adenosquamous and adenocarcinoma lesions

Table 2 details the clinicopathological comparisons between ASC and AC. ASC were widely disbursed throughout the colon with primary sites including the cecum (28.0%) and ascending colon (25.3%), followed by sigmoid colon (17.5%). Primary sites for AC were the sigmoid (27.8%) and cecum (21.6%), followed by the ascending colon (20.7%). In general, ASC tended to favor the right side of the colon more so than AC (68.4% vs. 57.2% respectively, $p < 0.0001$). Most ASC lesions were histologically characterized as poorly differentiated and undifferentiated (68.3%) and presented as stage IV disease (41.3%). In contrast, AC most frequently presented as moderately differentiated (65.0%) and at an earlier stage, with only 22.3% presenting at advanced Stage IV disease.

Overall survival (OS) and hazard ratio (HR)

Median OS of the ASC cohort was 13.9 months (95% CI: 10.98–16.83). There was no difference in OS between male or female patients; 13.01 and 16.36 months, respectively ($p = 0.099$). Stage IV patients performed significantly worse than stage II and III patients, with a median OS of 8.02 versus 71.82 and 19.75 months, respectively ($p < 0.001$). Median OS for stage I could not be calculated. ASC patients have significantly poorer prognosis than AC patients. At Stage III disease, ASC patients had a median OS of 19.75 months, compared to 76.16 for that of AC patients (Fig. 1). After adjusting for age, gender, and Charlson-Deyo score, a Cox Regression hazard function shows the risk of death in patients with ASC is approximately double that of their AC counterparts; HR: 2.2, $p < 0.001$. When comparing Stage IV patients, ASC continued to show an increased risk of death; HR: 1.7, $p < 0.001$.

Discussion

ASC is an aggressive histologic subtype of colon cancer.[3,4] To our knowledge, this is the largest retrospective cross-sectional examination of ASC from a national database for over 30 years. A 1999 paper by Cagir et al. was one of the first to report the demographic and clinicopathological features of 145 cases of colorectal and anal ASC, as well as highlight the disparities in survival between ASC and

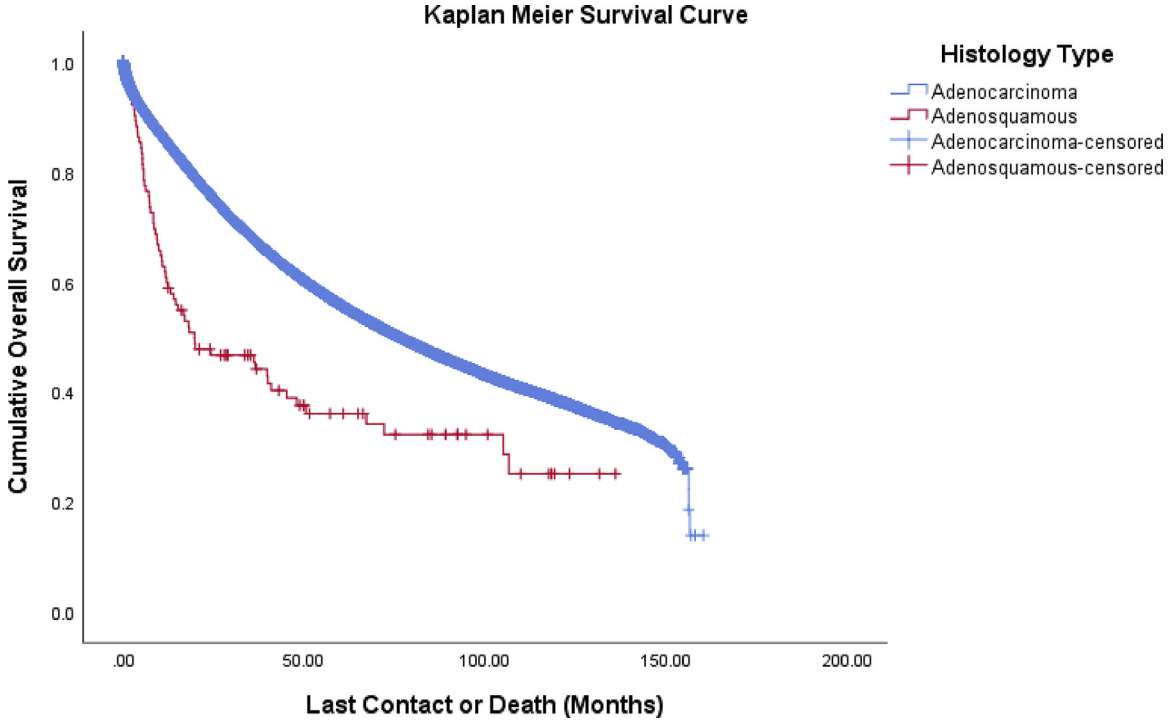

Fig. 1. Stage III survival rate in ASC vs. AC.

AC.3 For comparison, our updated study features a much larger dataset, comprising of more than double the original number of ASC cases reported by Cagir et al. (332).[3] A similar study on 44 cases of colorectal ASC by Frizelle et al., in 2001 supported the worse prognosis for ASC, especially with node-positive disease.[4] A more recent 2012 California Cancer Registry database study of 111,263 colorectal cases (99 ASC & 111,164 AC) by Masoomi et al. showed that ASC presented with poorer tumor grade and more advanced staging, which translated to increased overall mortality.[2] Multiple case reports (Toumi et al. & Kang et al.) align with the findings that ASC presents at an advanced stage and behaves aggressively.[5,6] To our knowledge, our study is the largest to quantify the differential overall survival between Stage I-IV disease, and to clearly demonstrate the increased risk of death when compared to conventional AC of the colon. Even in advanced Stage IV disease ASC showed a significant increase in risk of death (HR: 1.7, $p < 0.001$) when compared to AC. Lesion-specific surrogate markers of aggressive behavior (i.e. lymphovascular invasion, nodal disease, etc.) were examined; however, the disparate total numbers between the cohorts were prone to bias and not included in the results.

Our demographic findings largely corroborated that of other studies. We found that ASC patients (64.4) were significantly younger than their AC counterparts (68.6), with no differences in gender distribution. In Cagir et al.'s review, ASC patients were younger (67) than AC patients (70), though the difference was not significant.3 Masoomi et al. also found that ASC patients were generally younger (67 vs. 69.5, not significant) and had no differences in gender profile.[2] Given that our query yielded a substantially larger number of cases across an updated national database, we believe our result to be the most accurate one. Regarding clinicopathological features, the majority of ASC cancers in our review presented as poorly/un-differentiated (68.3%) and at Stage IV disease (41.3%). Massomi et al.'s analysis mirrored these numbers, with 65.96% poorly-differentiated and 36.56% Stage IV tumors.[2] Though Cagir et al. used an older staging system, they found that 41% had "distant disease" (Stage IV).[3] Thus, the consensus is that ASC tumors most commonly present with poor grade differentiation and with advanced metastases.

Based on our findings and previous studies, it is evident that the prognosis for ASC is worse than that for AC. Median OS and 5-year OS rate for our ASC cohort was 13.9 months and 29.6%. Cagir et al. similarly reported that the mean OS from diagnosis was 12 months, with a 5-year OS of 30.7%.[3] In their study, patients with distal segment lesions had significantly longer survival compared with those with right sided or transverse colon tumors.[3] This may be due to the earlier diagnosis of adenosquamous carcinomas in the distal segment. Another study by Frizelle et al. suggested that prognosis was dependent on stage of disease, reporting a 5-year OS of 34% (including all stages).[4] For stage I and II tumors, the prognosis was similar to that of colorectal AC.4 However, when nodal disease occurred, the prognosis was worse for ASC than that for AC of similar stage.[4] For node-positive and node-negative disease, the 5-year OS rates were 23% and 85%, respectively.[4] Specifically, stage IV mean OS was found to be 8.5 months.[4] Similarly, Cagir et al.'s analysis arrived at significantly poorer survival for staged B2 through D ASC compared to AC, reporting a measly 5-year OS of 1.7% for stage D (metastatic disease).[3] Our study confirms that even at Stage IV, ASC continue to exhibit increased risk of death compared to AC (HR: 1.7).

The California Cancer Registry study by Masoomi et al. yielded a 5-year OS of 23.5% for ASC, lower than our result (29.6%) and that of previous studies.[2] Conversely, they reported a median OS of 35.3 months, a figure that is substantially higher than ours (13.9).[2] While they also established that ASC carried a higher risk of overall mortality compared to AC (HR: 1.67), this was lower than our calculated risk (HR: 2.2).[2] One explanation for these disparities is that rectal ASC cases were included in their study and excluded from our own. This suggests that rectal ASC may have a better prognosis than colonic ASC, potentially due to higher rate of treatment with neoadjuvant chemoradiotherapy. Additionally, their profile demonstrates the clinical characteristics of CRC solely in California, whereas our study was queried from a national database and therefore more representative of the general population. Nonetheless, their study supplements our findings of overall worse prognosis for ASC compared to AC across stages. In other smaller studies, features predicting a poor prognosis included right-sided lesions, ulcerated or annular carcinomas, node-positive disease, grade 3 or 4 cancer and stage IV disease.[2–4] Overall, these findings are consistent with our analysis.

Because of the rarity of ASC malignancies, the effectiveness of chemoradiation therapy and a defining treatment strategy remains largely unclear. In two case studies, ASC was treated with resection and adjuvant chemotherapy (FOLFOX regimen).[5,6] In the California Cancer Registry study, 9% of ASC patients received radiation and 41% received chemotherapy.[2] The majority of those patients (80%) received either partial or subtotal colectomy.[2] Given the aggressive nature and poor prognosis of ASC, a more invasive, multimodal treatment approach may be warranted. Future clinical studies should examine the benefits of chemotherapy/radiation interventions and more radical resections.

Our study's limitations stem mostly from the use of the NCDB.[8] There exist inherent data entry errors associated with all large database studies, which must be taken into consideration. Additionally, the NCDB is limited in capturing specific health associated factors and providing indications for particular interventions.[7] Also, when studying stage IV patients, we did not evaluate the use of systemic therapies in ASC vs. AC patients. As such, treatment differences have not been evaluated within this study.

Conclusion

ASC of the colon is a very rare but aggressive type of colon cancer. Compared to AC, ASC commonly presents at stage IV and as poorly-differentiated tumors. ASC has significantly worse overall survival than AC across all stages, with advanced, node-positive stages accounting for most of the poor prognosis. Thus, more aggressive treatment options may be warranted for these types of malignancies. Surgical resection remains the mainstay of treatment for ASC. However, given the aggressiveness of this malignancy, further studies should be conducted to elucidate the treatment role of chemoradiation therapy.

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