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ORIGINAL RESEARCH

Adenosquamous carcinoma of the bile duct: a population-based study

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Introduction: Adenosquamous carcinoma (ASC) of the bile duct is a rare diagnosis with poorly understood clinicopathological characteristics and disease progression, so identification of the features associated with ASC patient survival is warranted.

Materials and methods: A population cohort study was performed using prospectively extracted data from the Surveillance, Epidemiology and End Results (SEER) database for patients with histological diagnoses of ASC of the bile duct from 1973 to 2013.

Results: A total of 106 patients with ASC of the bile duct were included (mean age 68.1±13.5 years). Lesions from 58 patients were in the extrahepatic bile duct and 34 were located at the ampulla of Vater. Fifty-seven patients were categorized with a regional stage, 15 had localized disease, and 30 had distant disease. Most (60.4%) patients received cancer-directed surgery, and radiation was performed in 14.1% of cases. The 1-year, 2-year, and 5-year overall survival (OS) for patients with ASC of the bile duct was 30.1%, 11.3%, and 3.7%, respectively. Cancer-directed surgery offered 10 additional months of OS for patients with ASC of the bile duct and median OS was 14.0, 6.0, and 6.0 months for ampulla of Vater, extrahepatic bile duct, and intrahepatic bile duct cases, respectively. A multivariate Cox analysis showed that lesions in the ampulla of Vater (HR=0.51, 95% CI 0.26–0.99) and having surgery (HR=0.34, 95% CI 0.14–0.81) were independent protective prognostic factors for these patients.

Conclusion: Cancer-directed surgery and a primary lesion site of the ampulla of Vater may suggest favorable prognosis for patients with ASC of the bile duct.

Keywords: adenosquamous carcinoma, bile duct, prognosis, SEER database

Introduction

Adenosquamous carcinoma (ASC) is a rare bile duct cancer characterized by the presence of variable proportions of two malignant components: adenocarcinoma and squamous cell carcinoma (SCC).[1] ASC can arise from primary sites with a glandular epithelium such as the stomach, pancreas, colon and rectum, and breast.[2–6] ASC of the bile duct has been described as an infiltrative bile duct cancer composed of a squamous component and a glandular component. Based on the WHO classification of tumors of the digestive system, ASC of the ampulla of Vater is defined as having a tumor of at least 25% SCC.[7,8]

ASC of the extrahepatic bile duct has been reported to account for approximately 2% of extrahepatic bile duct carcinomas, and ASC of the ampulla of Vater is more rare and most studies on ASC at this site focused on a small series or case report[9–11] and prognosis is rarely mentioned. The SCC component of ASC of the bile duct is associated with local invasiveness, tumor progression, and metastasis.[7] Also, ASC of this

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nature is clinically more aggressive with a worse prognosis than those with adenocarcinoma. Even so, clinicopathological characteristics and prognosis for ASC of the bile duct remains unclear due to a scarcity of reports. To address this, we offer a descriptive, retrospective analysis of patients with ASC of bile duct registered in the Surveillance, Epidemiology and End Results (SEER) database. The purpose of this report is to characterize overall survival (OS) for these patients and delineate features influencing OS.

Methods and materials

Participants

The SEER program is supported by the National Cancer Institute and collects information including cancer incidence and survival from 18 population-based cancer registries throughout the US which covers approximately 28% of the US population. All patients with a diagnosis of ASC of the bile duct according to the ICD-0–3/WHO 2008 were identified in the SEER database between 1973 and 2013. Demographic features and clinicopathological characteristics of these patients were collected including age, gender, ethnicity, primary site, pathological differentiation, TNM stage, lymph node metastases, distant metastases, and types of therapeutic strategy (radiation and surgery). The SEER database reported cancer-specific survival, which was defined as the interval from diagnosis until death due to this kind of cancer or until the last follow-up. The SEER database holds no identifying patient information, all data are anonymous and the Institutional Review Board of Shanghai Changzheng Hospital approved this study.

Statistical analysis

Continuous data were compared using a Student's *t*-test, and categorical data were compared using a Chi-square test. Age at diagnosis, gender, ethnicity, primary site, pathological differentiation, TNM stage, lymph node metastases, distant metastases, surgery and radiation were included in the survival analysis. Survival probabilities were estimated using the Kaplan-Meier method and a log-rank test was used to assess any significant differences in OS stratified by each covariate. Cox proportional hazards models were used to analyze associations between clinicopathological characteristics with patient survival. HRs and 95% CIs were estimated using univariate and multivariable models. Statistical analysis was performed using the software MedCalc (version 15.2.2; MedCalc Software, Mariakerke, Belgium), and $p<0.05$ was considered statistically significant.

Results

Patients' characteristics

A total of 106 cases of ASC of the bile duct were identified and patient data appear in Table 1. Eighty-nine patients were white and 55 were women. The age at diagnosis for all patients with ASC of the bile duct was 68.1±13.5 years. Lesions from 58 patients were in the extrahepatic bile duct, 34 were located at the ampulla of Vater, and six were in the intrahepatic bile duct. According to the SEER historic staging, 57 patients were categorized with a regional stage, 15 had localized disease, and 30 had distant disease.

Next, we compared characteristics across SEER historic stages and distribution by stage of ASC did not differ significantly by age, gender, ethnicity, pathological differentiation, lymph node metastases, primary site, or radiation (Table 2). However, patients who presented with distant disease were more likely to be at a later stage and with distant metastases, and less likely to undergo surgical resection ($p<0.01$ for all).

Treatment

Table 3 shows treatment data. Of all patients, 60.4% received cancer-directed surgery, radiation treatment was performed in 14.1% of all included patients, and both surgery and radiation were performed in 11.3%. Due to limited data, surgery types were not clear but comparison analysis revealed that patients who received surgery were more likely to be without distant metastases and a regional summary stage.

OS

We extracted survival data for patients with adenocarcinoma. SCC of the bile duct from the SEER database and patients with ASC of the bile duct had a significantly poorer prognosis than those with adenocarcinoma ($p<0.01$). Conversely, patients with ASC had a relatively better prognosis than those with SCC, but this was not significant ($p=0.135$, Figure 1A). However, the multivariate Cox analysis did not demonstrate that ASC tumor type was an independent prognostic factor for these patients (HR=0.65, 95% CI 0.34–1.24).

The 1-year, 2-year, and 5-year OS of all patients with ASC of the bile duct were 30.1%, 11.3%, and 3.7%, respectively. Kaplan-Meier curves for survival stratified by SEER historic stage A classification appear in Figure 1B. The 1-year, 2-year, and 5-year survival rates for patients with localized, regional disease were 45.6%, 15.8%, 5.2% and 40.0%, 20%, 6.6%, respectively. Patients with distant stages did not survive more than 1 year so they had significantly poorer prognoses than those with localized or regional disease ($p<0.01$ for both).

Table 1 Characteristics of patients with ASC, AC, and SCC of the bile duct

Characteristics	ASC	AC	SCC	*p*-value
Number	106	17,054	35	
Age (years)	68.1±13.5	69.9±12.6	67.7±13.2	0.20
Gender				
Female	55 (51.8%)	8,060 (47.3%)	17 (48.6%)	0.629
Male	51 (48.2%)	8,994 (52.7%)	18 (51.4%)	
Ethnicity				
White	79 (74.6%)	13,918 (81.8%)	22 (62.9%)	0.02
Black	10 (9.4%)	1,215 (7.1%)	4 (11.4%)	
Other (American Indian/Alaskan Native, Asian/Pacific Islander)	17 (16%)	1,881 (11.1)	9 (25.7%)	
Unknown	0	40	0	
Primary site				
Extrahepatic bile duct	58 (59.2%)	7,447 (48.6%)	19 (70.4%)	0.03
Ampulla of Vater	34 (34.7%)	6,562 (42.8%)	5 (18.5%)	
Intrahepatic bile duct	6 (6.1%)	1,310 (8.6%)	3 (11.1%)	
Bile duct, not otherwise specified	8	1,735	8	
Pathological differentiation				
Well	3 (4.8%)	6,826 (44.8)	1 (5.3%)	<0.01
Moderate	21 (33.3%)	4,920 (32.3%)	7 (36.8%)	
Poor	37 (58.7%)	3,374 (22.1%)	11 (57.9%)	
Undifferentiated	2 (3.2%)	124 (0.8%)	0 (0)	
Unknown	43	1,810	16	
Summary stage				
Distant	30 (29.4%)	4,294 (29.0%)	12 (41.4%)	0.31
Regional	57 (55.9%)	7,454 (50.3%)	13 (44.8%)	
Localized	15 (14.7%)	3,082 (20.7%)	4 (13.8%)	
Unstaged	4	2,224	6	
TNM stage				
I	5 (10.4%)	1,848 (26.0%)	0 (0)	0.02
II	21 (43.8%)	1,898 (26.7%)	3 (33.3%)	
III	11 (22.9%)	1,165 (16.4%)	2 (22.2%)	
IV	11 (22.9%)	2,199 (30.9%)	4 (44.5%)	
Unknown	58	9,944	26	
Lymph node metastases				
Yes	22 (47.8%)	2,432 (35.5%)	6 (66.7%)	0.03
No	24 (52.2%)	4,412 (64.5%)	3 (33.3%)	
Unknown	60	10,210	26	
Distant metastases				
Yes	11 (22.4%)	2,199 (28.9%)	6 (60.0%)	0.06
No	38 (77.6%)	5,432 (71.1%)	4 (40.0%)	
Unknown	57	9,423	25	
Surgery				
Yes	64 (60.4%)	7,059 (42.4%)	10 (30.3%)	<0.01
No	42 (39.6%)	9,574 (57.6%)	23 (69.7)	
Unknown	0	421	2	
Radiation				
Yes	14 (13.7%)	3,176 (19.0%)	2 (5.9%)	0.07
No	88 (86.3%)	13,569 (81.0%)	32 (94.1%)	
Unknown	4	309	1	

Abbreviations: ASC, adenosquamous carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma.

Figure 1C shows the Kaplan-Meier curves grouped by surgery. Cancer-directed surgery improved OS for patients with ASC of the bile duct by almost 10 months. However, there was no significant difference in prognosis between patients who received radiation and those who did not (p=0.30). Patients with a lesion of the ampulla of Vater had better survival compared to those with extrahepatic bile duct lesion (p<0.01) and intrahepatic bile duct lesion (p=0.10). Figure 1D depicts OS for these three groups and the median OS was 14.0, 6.0, and 6.0 months, respectively.

Table 2 Patient characteristics by the SEER historic stage

Characteristics	Localized	Regional	Distant	*p*-value
Number	15	57	30	
Age	70.7±12.1	66.4±13.2	69.8±13.9	0.37
Gender				
Female	5 (33.3%)	28 (49.1%)	20 (66.7%)	0.09
Male	10 (66.7%)	29 (50.9%)	10 (33.3%)	
Ethnicity				
White	12 (80.0%)	40 (70.2%)	23 (76.7%)	0.92
Black	1 (6.7%)	6 (10.5%)	3 (10.0%)	
Other (American Indian/Alaskan Native, Asian/Pacific Islander)	2 (13.3%)	11 (19.3%)	4 (13.3%)	
Primary site				
Extrahepatic bile duct	8 (53.3%)	36 (63.2%)	11 (47.8%)	0.50
Ampulla of Vater	6 (40.0%)	19 (33.3%)	9 (39.1%)	
Intrahepatic bile duct	1 (6.7%)	2 (3.5%)	3 (13.1%)	
Bile duct, not otherwise specified	0	0	7	
Pathological differentiation				
Well	1 (16.7%)	1 (2.2%)	1 (8.4%)	0.28
Moderate	2 (33.3%)	15 (33.3%)	4 (33.3%)	
Poor	2 (33.3%)	28 (62.3%)	7 (58.3%)	
Undifferentiated	1 (16.7%)	1 (2.2%)	0	
Unknown	9	12	18	
TNM stage				
I	3 (100.0%)	2 (6.5%)	0	<0.01
II	0 (43.8%)	21 (67.7.3%)	0	
III	0 (22.9%)	8 (25.8%)	3 (21.4%)	
IV	0 (22.9%)	0	11 (78.6%)	
Unknown	12	26	16	
Lymph node metastases				
Yes	0 (0.0%)	16 (50.0%)	6 (60.0%)	0.19
No	3 (100.0%)	16 (50.0%)	4 (40.0%)	
Unknown	12	25	20	
Distant metastases				
Yes	0 (0%)	0	11 (78.6%)	<0.01
No	3 (100.0%)	31 (100.0%)	3 (21.4%)	
Unknown	12	26	16	
Surgery				
Yes	7 (46.7%)	49 (86.0%)	7 (23.3%)	<0.01
No	8 (53.3%)	8 (14.0%)	23 (76.7%)	
Radiation				
Yes	1 (7.1%)	11 (20.0%)	3 (10.3%)	0.33
No	13 (92.9%)	44 (80.0%)	26 (89.7%)	
Unknown	1	2	1	

Abbreviation: SEER, Surveillance, Epidemiology and End Results.

Variables potentially influencing OS were analyzed using univariate Cox proportional hazards analysis and Table 4 shows that distant SEER historic stage, late TNM stage (III and IV), lymph node and distant metastasis were significantly associated with poor prognosis for patients with ASC of the bile duct ($p<0.01$ for all). Conversely, lesions at the ampulla of Vater and surgery were protective factors ($p<0.01$ for both). TNM stage and lymph node and distant metastases were omitted for multivariate Cox analysis due to covariance with SEER historic stage. The results of multivariate Cox analysis are presented in Table 5, which show that lesions at the ampulla of Vater (HR=0.51, 95% CI 0.26–0.99) and surgery (HR=0.34, 95% CI 0.14–0.81) were independent protective factors for ASC patients.

Discussion

Most studies of ASC of the bile duct have been small series or single case reports because of its rarity. Therefore, clinicopathological features and outcomes of this entity remain unclear. In the present study, we described clinical characteristics of patients with ASC of the bile duct and identified variables affecting OS using data from SEER. Only 106

Table 3 Patient characteristics by surgery treatment

Characteristics	Surgery	Non-surgery	*p*-value
Number	64	42	
Age (years)	65.3±12.5	72.2±13.8	0.01
Gender			
Female	32 (50.0%)	23 (54.8%)	0.69
Male	32 (50.0%)	19 (54.2%)	
Ethnicity			
White	47 (74.6%)	32 (76.2%)	0.92
Black	6 (9.4%)	4 (9.5%)	
Other (American Indian/ Alaskan Native, Asian/ Pacific Islander)	11 (16%)	6 (14.3%)	
Primary site			
Extrahepatic bile duct	37 (59.7%)	21 (58.3%)	0.27
Ampulla of Vater	23 (37.1%)	11 (30.5%)	
Intrahepatic bile duct	2 (3.2%)	4 (11.2%)	
Bile duct, not otherwise specified	2	6	
Pathological differentiation			
Well	2 (10.4%)	1 (7.1%)	0.74
Moderate	17 (43.8%)	4 (28.6%)	
Poor	29 (22.9%)	8 (57.2%)	
Undifferentiated	1 (22.9%)	1 (7.1%)	
Unknown	15	28	
Summary stage			
Distant	7 (29.4%)	23 (59.0%)	<0.01
Regional	49 (55.9%)	8 (20.5%)	
Localized	7 (14.7%)	8 (20.5%)	
Unstaged	1	3	
TNM stage			
I	3 (10.4%)	2 (13.3%)	<0.01
II	21 (43.8%)	0	
III	8 (22.9%)	3 (20.0%)	
IV	1 (22.9%)	10 (66.7%)	
Unknown	31	27	
Lymph node metastases			0.32
Yes	18 (47.8%)	4 (33.3%)	
No	16 (52.2%)	8 (66.7%)	
Unknown	30	30	
Distant metastases			
Yes	1 (22.4%)	10 (62.5%)	<0.01
No	32 (77.6%)	6 (37.5%)	
Unknown	31	26	
Radiation			
Yes	12 (13.7%)	2 (4.9%)	0.04
No	49 (86.3%)	39 (95.1%)	
Unknown	3	1	

patients recorded in SEER between 1973 and 2013 were extracted from the database. Compared with 17,069 cases with adenocarcinoma of the bile duct, the prevalence of ASC of the bile duct was very low.

According to our results, age at diagnosis of patients ranged from 32 to 97 years, and the mean age of all patients was 58 years, which agrees with Hong et al and Okabayashi et al's reports of an average age of 60 years.[9,12] In this cohort, white patients accounted for the largest proportion (~74.6%), which was consistent with the distribution of races in the Western population. Although the sample size was smaller, only 36 and 12 cases, Okabayashi et al and Hong et al reported series of patients with ASC of the bile duct with a female to male ratio of 1.4:1 and 2:1, respectively. We found 106 cases with more females affected than males, but the difference was small (55:51). Lesions of most ASC of the bile duct were located in the extrahepatic bile duct, and next to the ampulla of Vater. Most ASC patients received surgery and 13.7% received radiation. Early stage patients with regional and localized tumors accounted for 70.9% of ASC patients.

ASC is more clinically aggressive and offers less favorable prognosis than adenocarcinoma (AC) of other origins. The median OS for patients with ASC of the pancreas was nearly half that of patients with pancreatic ductal adenocarcinomas.[13] We found that ASC patients have poorer prognosis than those with AC, but better prognosis than SCC patients. Thus, ASC has greater malignant potential than adenocarcinoma of the bile duct. Likely, SCC grows twice as fast as adenocarcinoma and once adenocarcinoma transforms to AC, the carcinoma is highly malignant.[12,14] Moreover, previous studies have reported significantly shorter doubling times of SCC than adenocarcinomas in lung cancer.[15,16]

Univariate analysis revealed that distant stages of SEER historic stages, late TNM stages (III and IV), lymph node and distant metastasis were associated with poor prognosis for patients with ASC of the bile duct. The American Joint Committee on Cancer (AJCC) method is more commonly used in the clinical setting, and the SEER historic stage has standardized and simplified staging to ensure consistent definitions over time. Both can be used to provide a measure of disease progression and both were associated with poor prognosis of ASC patients. Among 106 ASC patients, 58 and four patients had not been categorized by AJCC stage or SEER historic staging, respectively. Thus, we included SEER historic stage in the multivariate Cox analysis and after adjusting for other variables, the analysis showed that SEER historic stage likely portends a less favorable prognosis, but without statistically significant difference. Although ASC of the bile duct has a different etiology and biological features compared with AC, treatment of ASC patients is similar to that for AC patients. Because ASCs are relatively uncommon tumors with a poor prognosis, outcomes related to various therapeutic interventions are not well defined and no standard therapeutic strategies have been established. In the present study, a significantly longer OS was found for patients who received surgery. Similar to other

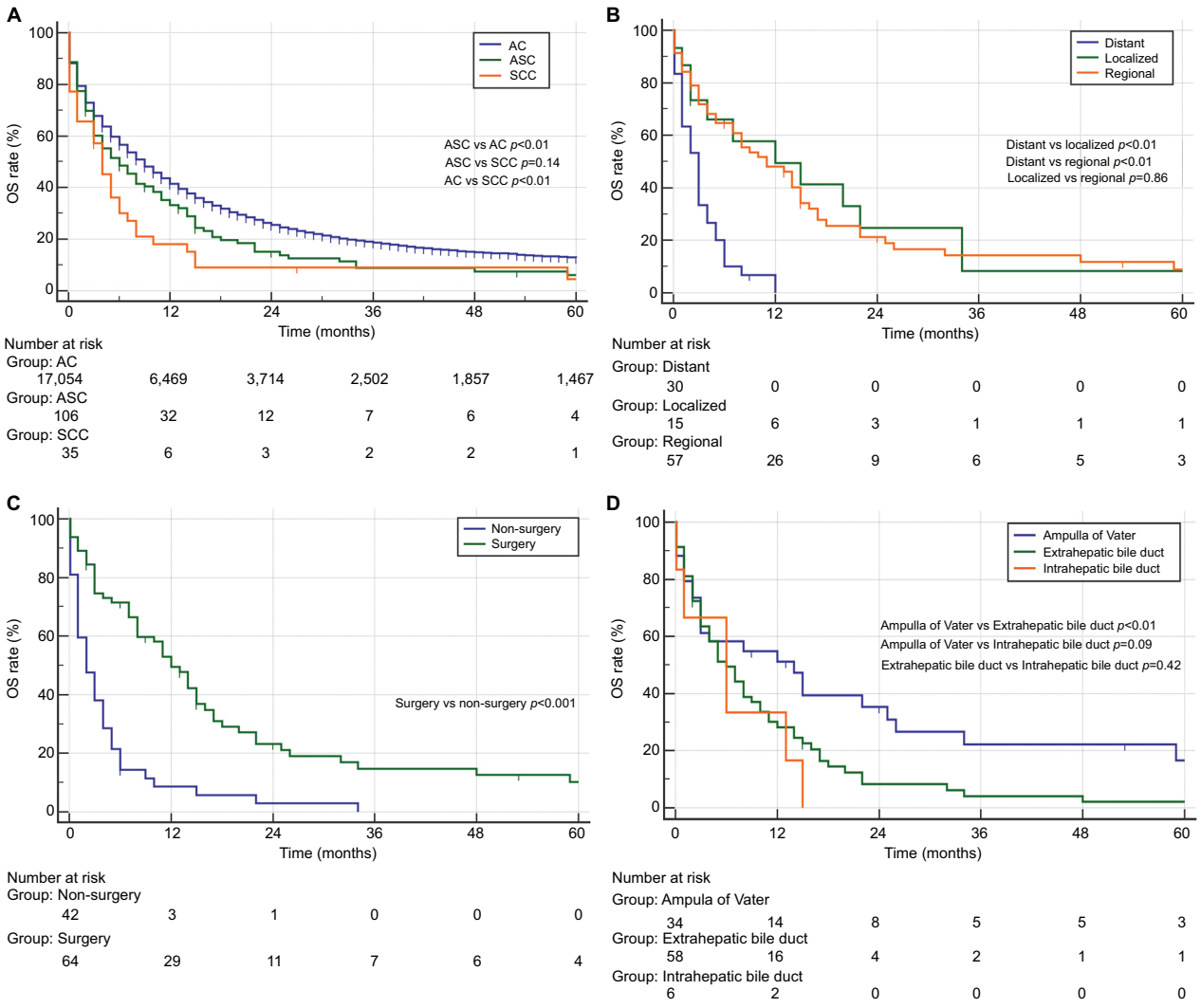

Figure 1 (**A**) OS for patients with ASC and other bile duct cancer; (**B**) OS for patients with distant, regional, localized stages; (**C**) OS for patients who received surgery and those who did not; (**D**) OS for ASC patients with different primary lesion sites.
Abbreviations: ASC, adenosquamous carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma; OS, overall survival.

Table 4 Univariate Cox proportional hazard analyses of clinical characteristics for OS in patients with ASC of the bile duct

Factor	Category	Univariate	
		HR (95% CI)	*p*-value
Age	>58/<58	1.44 (0.96–2.17)	0.08
Gender	Male/female	1.22 (0.82–1.83)	0.33
Race	White/Black and other	0.67 (0.42–1.07)	0.10
Primary site	Ampulla of Vater/extrahepatic, intrahepatic bile duct	0.50 (0.31–0.81)	<0.01
Pathological differentiation	Poor and undifferentiated/well and moderate	1.35 (0.76–2.39)	0.31
Summary stage	Distant/localized and regional	3.60 (2.15–6.02)	<0.01
TNM stage	III and IV/I and II	2.43 (1.24–4.77)	0.01
Lymph node metastases	Yes/No	2.00 (1.23–3.23)	<0.01
Distant metastases	Yes/No	6.54 (2.66–16.0)	<0.01
Surgery	Yes/No	0.32 (0.21–0.50)	<0.01
Radiation	Yes/No	0.75 (0.42–1.32)	0.31

Abbreviations: ASC, adenosquamous carcinoma; OS, overall survival.

Table 5 Multivariate Cox proportional hazard analyses of clinical characteristics for OS in patients with ASC of the bile duct

Factor	Category	Multivariate	
		HR (95% CI)	*p*-value
Age (years)	>58/<58	1.41 (0.79–2.53)	0.25
Gender	Male/female	1.44 (0.62–3.36)	0.25
Race	White/black and other	0.59 (0.30–1.13)	0.11
Primary site	Ampulla of Vater/extrahepatic and intrahepatic bile duct	0.51 (0.26–0.99)	0.04
Pathological differentiation	Poor and undifferentiated/well and moderate	1.60 (0.87–2.95)	0.13
Summary stage	Distant/localized and regional	2.40 (0.93–6.17)	0.07
Surgery	Yes/No	0.34 (0.14–0.81)	0.02
Radiation	Yes/No	0.69 (0.30–1.61)	0.39

Abbreviations: ASC, adenosquamous carcinoma; OS, overall survival.

cancers, younger patients with early disease stage (regional and localized disease, or early TNM stage) and non-distant metastases were more likely to be managed with surgery. Except for these factors, there was no difference in features between patients who had surgery and patients who did not. However, we did not observe that radiation significantly affected OS of ASC patients. This result is consistent with Guglielmi et al's report that curative resection of intrahepatic cholangiocarcinoma is the only therapy that can achieve long-term survival.[17]

We noted that the ampulla of Vater was an independent prognostic protective factor for ASC patients. Several case reports of ASC of the ampulla of Vater suggest that resection and surgery remains the mainstay therapy for this disease. Surgical interventions do not appear to improve patient survival and most patients experienced early distal metastasis and short survival after surgery. OS ranged from 6 to 48 months and median OS was 10 months.[11,18,19] In our study, the median OS of ASC patients of the ampulla of Vater was relatively longer; almost 16 months. Okabayashi et al's group reported the median survival of patients with ASC of extrahepatic bile duct was 13 months, which is relatively longer than that in our cohort (6 months). This may be explained by racial differences as Okabayashi et al's study included East Asian people. Also, 36.2% of patients did not receive surgery in our cohort, whereas all patients received surgery in Okabayashi et al's study.

Besides, tumor etiology is unclear, but several hypotheses have been offered to explain the histogenesis of ASC. Currently, the most reliable theories are persistent adenocarcinoma undergoing squamous metaplasia or transformation, and squamous metaplasia of the bile duct epithelium caused by chronic inflammation due to infection, gall stones or a choledochal cyst undergoing a malignant transformation.[14,20–22] Other potential mechanisms included pluripotent stem cells capable of inducing adenocarcinoma and SCC transformation, or a collision of both malignant tumor types.[23]

Similar to other studies using SEER as a data source, we had limitations that require clarification for accurate interpretation of the results. First, we lacked a pathological grade and TNM stage for some patients. For example, there were 43 patients with unknown pathological differentiation, and 58 patients had no recorded TNM stage. Therefore, when we conducted multivariate Cox analysis, we included SEER historic stage rather than TNM stage. Second, the retrospective nature of this study and the inability to account for other relevant variables such as performance status were weaknesses. We also lacked information about chemotherapy, and we could not account for the effect of potential advances in chemotherapy, thus limiting our ability to describe treatment patterns for ASC. Responses to treatment and recurrence rates could not be ascertained from SEER.

Conclusion

Despite the exceptionally rare occurrence of this disease, a population-based approach provided reasonable statistical utility for crude stratification of prognosis based on commonly identified variables. Cancer-directed surgery and a primary site of the ampulla of Vater may be favorable for prognosis for patients with ASC of the bile duct.

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Disclosure

The authors report no conflicts of interest in this work.

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