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Adeno-squamous and squamous cell carcinoma of the gallbladder: The importance of histology in surgical management

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ABSTRACT

Background: Although gallbladder adenocarcinoma (AC) is potentially curable with resection, outcomes of squamous histologies are poorly described.
Methods: We retrospectively analyzed all gallbladder cancers which underwent resection-for-cure in our health system from 2007 to 2017. We compared outcomes of AC to adeno-squamous (ASC)/squamous (SC) histologies.
Results: 91 patients met criteria; 76 AC, 15 ASC/SC. Compared to AC, ASC/SC tumors were larger (58 vs. 28 mm), with more frequent liver invasion (73% vs. 37%), pN+ (60% vs. 32%), higher stage (III/IV 73% vs. 52%), and displayed more LVI (60% vs. 36%), $p < 0.05$. For stage III/IV disease, provided R0 was achieved, survival was durable and similar for ASC/SC and AC (OS median 28mo ASC/SC vs. 25mo AC, $p = 0.132$; PFS median 21mo ASC/SC vs. 13mo AC, $p = 0.206$). Pure SC had considerably poorer median OS (<5mo) than ASC (23mo) and AC (28mo).
Discussion: Squamous variants of gallbladder cancer confer aggressive and advanced disease and often require more radical resections to achieve R0. Durable survival is possible in ASC provided R0 is achieved. Pure SC has dismal survival even with R0 resection.

Introduction

Gallbladder cancer (GBC) is a relatively uncommon hepatobiliary malignancy, with an annual incidence of around 2/100,000 cases in the United States.[1] The most common histologic subtype is adenocarcinoma (AC) accounting for 90–95% of GBC,[2] and its clinicopathologic features and survival outcomes are relatively well-studied. Data have demonstrated that durable oncologic outcomes are possible after resection for cure, especially for patients with early stage disease who achieve negative surgical margins.[3]

Squamous cell (SC) and adeno-squamous carcinomas (ASC) of the gallbladder are much rarer, making up around 1.4–10.6% of GBC.[4,5] Squamous variants of other malignancies exhibit completely different biology depending on the primary tumor origin. For example, squamous carcinomas originating from the gynecologic tract exhibit more favourable outcomes compared to adenocarcinomas of the same site[6] whereas squamous malignancies arising from the pancreas exhibit poorer survival than conventional adenocarcinomas.[7] Owing to the rarity of SC of the gallbladder, a paucity of data exists on the features and outcomes of this histologic subtype. The majority of literature to date consists of case reports and small case series and only very few studies have compared AC to ASC or SC GBC.[4,8–14] There is also currently no standardised definition for squamous tumors of the gallbladder and as such it is unclear if it is solely the presence of squamous cells which changes the overall biology of tumour, or if pure squamous cell tumors have poorer outcomes than those with a component of adenocarcinoma.

The purpose of this study was to compare clinicopathologic characteristics and survival outcomes of patients within our institution who underwent resection with curative intent for AC GBC to those with squamous histologies (ASC/SC) and to determine any differences in survival between ASC and SC tumors. We hypothesized that, similar to squamous cell pancreatic tumors, squamous variants of GBC would be more aggressive with poorer prognosis.

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Materials and methods

This is a retrospective study conducted at multiple hospitals within the Mount Sinai healthcare system of all consecutive patients with non-metastatic GBC who underwent surgical resection with curative intent between February 2007 and April 2017. Patients with perforated gallbladder cancer at diagnosis were considered metastatic and therefore were excluded from the study. Only pathologically confirmed pure adenocarcinoma or squamous types were included (Fig. 1). Patients were classified into two histological cohorts; AC and squamous variants (ASC/SC). All patients were discussed preoperatively at the same multidisciplinary hepatobiliary disease management conference. This study was approved by the Mount Sinai School of Medicine institutional review board.

Operative procedure

All patients underwent resection with curative intent. All definitive oncologic operations were performed by surgeons experienced in hepatobiliary surgery. The extent of hepatic and en bloc resection was determined by the ability to achieve a margin negative resection. The extent of lymphadenectomy was at the discretion of the operating surgeon, driven by preoperative imaging and gross intraoperative findings. Histopathologic examination of specimens was centralized and performed at a single site. Tumors were classified as AC when no malignant squamous cells were identified, SC when no AC areas were identified and ASC when there were both AC and SC features present. Perioperative complications were graded according to the Clavien-Dindo classification system,[15] and were defined as occurring within 30 days of definitive surgery.

Data collection

Detailed clinicopathologic data encompassing the preoperative, operative, and postoperative course was collected retrospectively and maintained within a database. TNM stage was based on the AJCC 7th edition.

Outcomes

The primary endpoints were histopathologic features, rate of curative (R0) resection and overall survival (OS). OS was defined as time from surgery to death from any cause or last follow-up. Secondary endpoints were extent of surgical resection, progression-free survival (PFS) and to determine factors predictive of OS and PFS. PFS was defined as time from surgery to disease progression or relapse (diagnosed on imaging or re-operation). The censoring date was determined by the date of the last note or investigative study performed in the patient's chart.

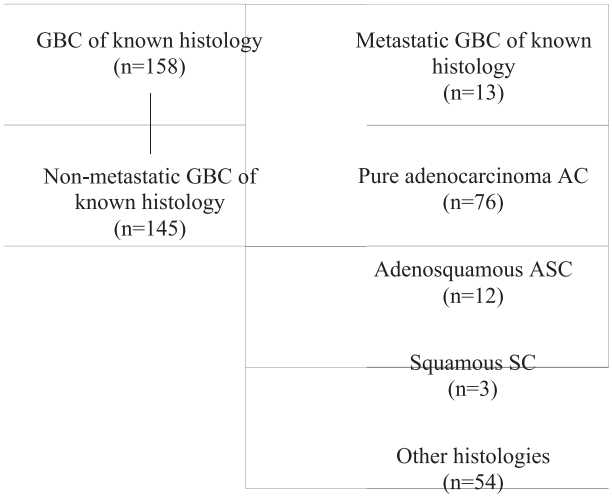


Fig. 1. Flow chart of all GBC of known histology at our institution from 2007 to 2017.

Statistical analysis

All statistical analyses were performed using SAS® software, version 9.4. Categorical variables were compared using Chi Squared and Fisher's exact tests and are reported as totals with percentages. Continuous variables were compared using student's t-tests when data were normally distributed and Wilcoxon Mann-Whitney rank sum tests when data were not normally distributed, and are reported as median values with interquartile ranges (IQR). Normality of distribution was assessed using Shapiro-Wilk tests. Kaplan-Meier estimates were used to analyze PFS and OS and survival curves calculated using the log-rank test. Cox-proportional hazards models using backwards elimination were used to create multivariate models for factors predictive of PFS and OS. A p value of <0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 91 consecutive patients underwent surgical resection with curative intent for GBC with AC ($n = 76$) or ASC/SC ($n = 15$). Patient demographics are displayed in Table 1. Patients in the two cohorts were of similar age, gender and ASA score. The ASC/SC cohort were significantly more likely to present with weight loss (40% vs. 9% AC, $p = 0.007$) and be diagnosed with cancer on preoperative imaging (80% vs. 36% AC) rather than incidentally after non-oncologic cholecystectomy (20% vs. 64% AC), $p = 0.003$. Overall, most GBC patients had concomitant cholelithiasis. There was no significant difference in preoperative CA 19-9 levels between the two cohorts.

Extent of resection

Table 2 reports intraoperative surgical outcomes and histopathologic tumor features. The extent of surgery was similar across all cohorts in terms of need for (and type of) liver resection, common bile duct resection and lymphadenectomy. However, compared to AC, patients with ASC/SC were much more likely to require adjacent organ resection (40% vs. 7% AC, $p < 0.001$) for a comparable rate of R0 (73% vs. 66% AC, $p = 0.988$). The adjacent organs most frequently resected were duodenum ($n = 3$) and omentum ($n = 4$) in the AC cohort and colon ($n = 3$) and omentum ($n = 3$) in the ASC/SC cohort. These organs were partially excised because they were adherent to the gallbladder at the time of surgery. Despite undergoing more extensive surgical resection, the ASC/SC cohort did not have an increased rate of major perioperative complications (Clavien III-V 33% vs. 16% AC, $p = 0.230$).

Histopathologic characteristics

Tumors with ASC/SC histology were considerably larger at diagnosis (median 58 mm vs. 28 mm AC, $p = 0.021$) and trended towards being more often multifocal than at a single location within the gallbladder. They were more advanced at diagnosis with higher rates of liver invasion (73% ASC/SC vs. 37% AC, $p = 0.036$),

Table 1
Demographics of AC, ASC and SC cohorts.

Variable	AC (n = 76)	ASC/SC (n = 15)	p value
Age at surgery, years	69 (59–76)	61 (56–77)	0.189
Gender (*Male/Female*)	26 (34)/50 (66)	9 (60)/5 (40)	0.082
ASA score III/IV	35 (46)	3 (21)	0.104
Discovery of GBC			0.003*
Non-oncologic cholecystectomy	49 (64)	3 (20)	
Preoperative imaging	27 (36)	12 (80)	
Preoperative symptoms			
Abdominal pain	51 (67)	12 (80)	0.378
Fatigue	7 (9)	1 (7)	0.751
Weight loss	7 (9)	6 (40)	0.007*
Jaundice	16 (21)	3 (20)	0.927
Preoperative CA 19-9	110 (11–355)	168 (52–461)	0.414
Preoperative gallstones	51 (67)	13 (87)	0.130
Neoadjuvant chemotherapy	5 (7)	1 (7)	0.990
Adjuvant therapy			1.000
Chemotherapy	13 (17)	4 (27)	
Chemoradiation	15 (20)	5 (33)	
Radiation	1 (1)	0 (0)	

AC adenocarcinoma, ASC adeno-squamous carcinoma, SC squamous cell carcinoma, GBC gallbladder cancer.

higher TNM stages (stage III/IV 73% ASC/SC vs. 52% AC, p = 0.011), more perineural invasion (53% ASC/SC vs. 37% AC, p = 0.041) and a trend towards more lymphovascular invasion (60% ASC/SC vs. 36% AC, p = 0.160) and poorer differentiation (G3 73% ASC/SC vs. 43% AC, p = 0.111). There was also a trend towards more lymph node involvement in the ASC/SC cohort (60% vs. 32% AC, p = 0.140).

Survival

Median follow-up time for the whole cohort was 17 months. There was a trend towards poorer survival in patients with squamous features, though statistical significance was not reached. The ASC/SC cohort had a slightly shorter OS (median 23 months, 1-year 65%, 3-year 22%, 5-year 22%) than the AC cohort (median 28 months, 1-year 72%, 3-year 46%, 5-year 37%), p = 0.287 (Fig. 2a). When the ASC/SC cohort was separated by histological subtype, the ASC cohort OS was similar to AC (ASC median 23 months, 1-year 68%, 3-year 23%, 5-year 23%), however, the SC cohort had considerably poorer OS (median <5 months, 1-year 0%, 3-year 0%, 5-year 0%) with no patients alive at 12 months postoperatively. Similar findings were exhibited for PFS (Fig. 2b). There was a trend towards shorter PFS in the ASC/SC cohort (median 7 months, 1-year 34%, 3-year 9%, 5-year 9%) than the AC cohort (median 15 months, 1-year 55%, 3-year 35%, 5-year 23%), p = 0.077, though again statistical significance was not reached. For stage III/IV disease, there was no difference in OS (median 24 months ASC/SC vs. 24 months AC, p = 0.980) or PFS (median 6 months ASC/SC vs. 12 months AC, p = 0.650) between the two cohorts. Of note, the use of neo-adjuvant and adjuvant (chemotherapy, radiation) therapies was similar between the cohorts, p > 0.05 (Table 1). In the AC cohort, of those patients who received adjuvant chemotherapy, the most common regimens used were gemcitabine (n = 14, 70%) and cisplatin (n = 6, 30%); similar to the ASC/SC cohort (gemcitabine n = 7, 78%, cisplatin n = 4, 45%).

Tables 3a and 3b displays cox-proportional hazards models for factors predictive of survival. On multivariate analysis, significant independent predictors of OS were tumor size (HR 1.05, CI 1.02–1.09), pTNM stage, no LVI (HR 0.16, CI 0.04–0.64), no PNI (HR 0.18, CI 0.04–0.84), R0 resection (HR 0.01, CI 0.00–0.08) and no tumor recurrence (HR 0.02, CI 0.00–0.12), p < 0.05. Only tumor size (HR 1.02, CI 1.00–1.04) and no LVI (HR 0.19, CI 0.06–0.59) were significant predictors of PFS, p < 0.05.

R0 resection was achieved in 66% of AC patients and 73% of ASC/SC patients. ASC/SC who underwent R0 resection had significantly longer survival (OS median 24 months, 1-year 75%; PFS median 8 months, 1-year 46%) than ASC/SC patients who only achieved R1 (OS median 14 months, 1-year 50%; PFS median 6 months, 1-year 0%), p < 0.05. For stage III/IV disease, provided that R0 was achieved, the ASC/SC cohort achieved a similar OS (median 28 months ASC/SC R0, 25 months AC R0, 14 months ASC/SC R1, 11 months AC R1, p = 0.132, Fig. 2c) and PFS (median 21 months ASC/SC R0, 13 months AC R0, 6 months ASC/SC R1, 12 months AC R1, p = 0.206, Fig. 2d).

Table 2
Surgical and histopathologic characteristics of GBC variants.

Variable	AC (n = 76)	ASC/SC (n = 15)	p value
Extent of resection			
Liver resection			0.739
IVB/V wedge resection	39 (51)	10 (83)	
Anatomic lobectomy	6 (8)	2 (17)	
Extended hepatectomy	1 (1)	0 (0)	
Common bile duct excision	18 (21)	3 (20)	0.946
Lymphadenectomy	43 (57)	11 (73)	0.476
Adjacent organ resection	5 (7)	6 (40)	<0.001*
Histopathology			
Tumor location			0.933
Fundus/body	31 (41)	5 (33)	
Neck	13 (17)	2 (13)	
Multifocal	10 (13)	3 (20)	
Tumor size, mm	28 (16–43)	58 (38–82)	<0.021*
Liver invasion	28 (37)	11 (73)	0.036*
pN + disease	24 (32)	9 (60)	0.140
Lymph node yield	1 (0–3)	4 (1–6)	0.085
pTNM stage			0.011*
I/II	11 (14)/25 (33)	1 (7)/3 (20)	
IIIA/IIIB	16 (21)/20 (26)	2 (13)/4 (27)	
IVA/IVB	0 (0)/4 (5)	2 (13)/3 (20)	
Lymphovascular invasion	27 (36)	9 (60)	0.160
Perineural invasion	28 (37)	8 (53)	0.041*
Differentiation			0.111
Well	10 (13)	0 (0)	
Moderate	30 (42)	4 (27)	
Poor	33 (43)	11 (73)	
Biliary tree invasion	14 (18)	2 (13)	0.771
R0 resection	50 (66)	11 (73)	0.988

AC adenocarcinoma, ASC adeno-squamous carcinoma, SC squamous cell carcinoma.

Discussion

Squamous cell carcinomas have extremely different tumor biology and survival outcomes depending on their primary cell of origin.[6,7] Treatment algorithms differ from favourable and early stage tumors being amenable to limited surgery to more aggressive and locally invasive tumors requiring extensive resection with or without locoregional and systemic non-operative therapies. Squamous variants of gallbladder cancer are very uncommon and data on their incidence, histopathology and outcomes after surgical management still remains extremely limited.[4,5,8–14] A 2011 study by Roa et al.[5] reported on 606 patients with invasive GBC and found that squamous differentiation (ASC) was seen on pathology in 7% of cases; 1% were pure SC. The growth rate of SC in GBC has been shown to be more than twice as fast (doubling time of 81 days) than in adenocarcinomas (doubling time of 166 days),[16] and immunostaining has revealed a significantly higher positive rate of proliferating cell nuclear antigen in the squamous component (51%) than the adenocarcinoma component (3%) for ASC tumors.[17] As such, multiple studies have demonstrated that ASC/SC GBC are typically diagnosed at more advanced stages than AC tumors, primarily due to the high proliferative index of the squamous component.[5,11–13]

Kalayarasan et al.[11] compared 14 patients with ASC/SC to 122 patients with AC and found that patients with a squamous cell component had significantly larger tumors (7.9 cm vs. 4.8 cm, $p = 0.01$) which presented at higher TNM stages (T4 57% vs. 16%). These findings were echoed by Kim et al.[12] who compared 16 patients with ASC/SC to 32 with adenocarcinoma and found that the ASC/SC patients had larger tumors (5.03 cm vs. 3.34 cm, $p = 0.023$) and the majority (69%) had local infiltration of the liver. Other authors have also corroborated these findings.[5,13]

The influence of nodal involvement in GBC is well understood to be an important prognostic factor in survival after surgical resection of adenocarcinoma.[18,19] However, the mode of spread in SC appears to be undefined. Oohashi et al.[13] amongst others[11,20] found lower rates of nodal metastases and suggested that SC has less metastatic potential than AC as it invades by direct infiltration of adjacent organs from gallbladder wall extension rather than spreading via lymphatics. Kim et al.[12] and Chan et al.,[4] however, have found the contrary with considerably higher rates of positive

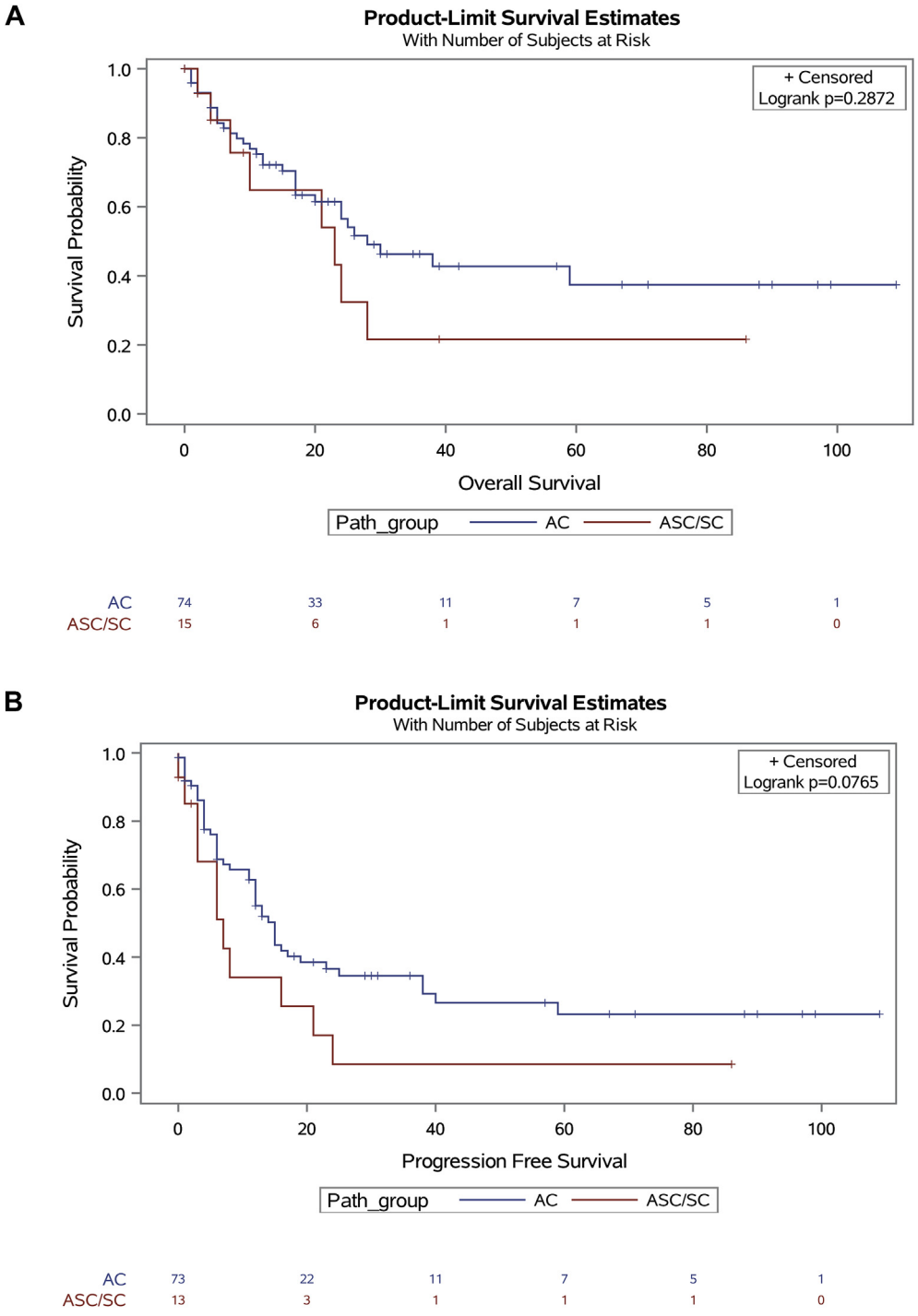
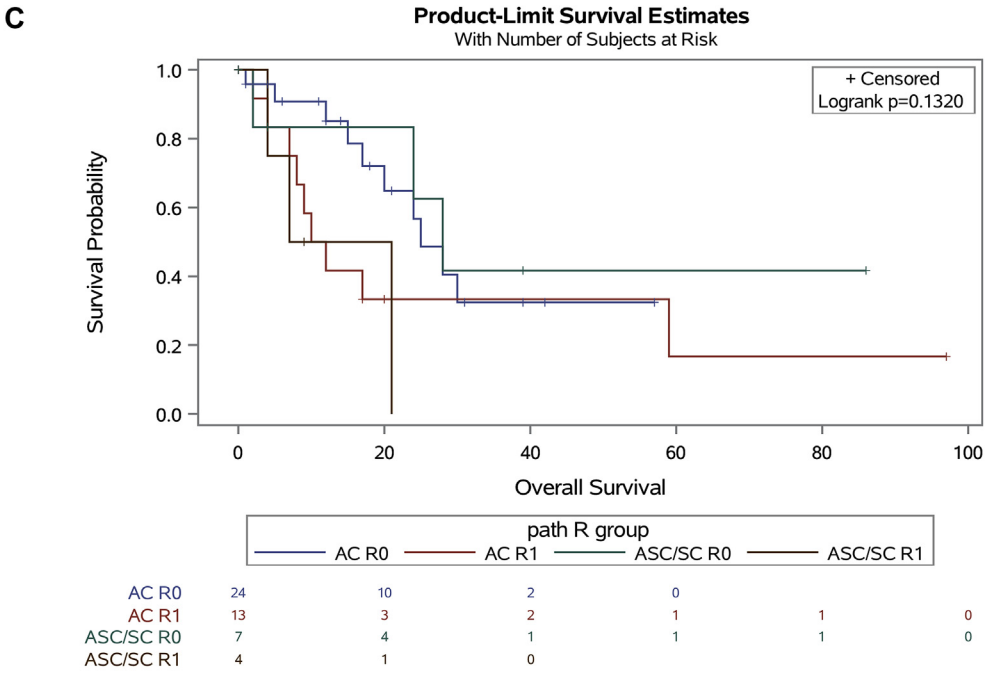


Fig. 2. Kaplan-Meier curves for survival. **a:** Overall survival for all cohorts by pathologic variant, **b:** Progression-free survival for all cohorts by pathologic variant, **c:** Overall survival for TNM stage III/IV by pathologic variant and R status, **d:** Progression-free survival for TNM stage III/IV by pathologic variant and R status.



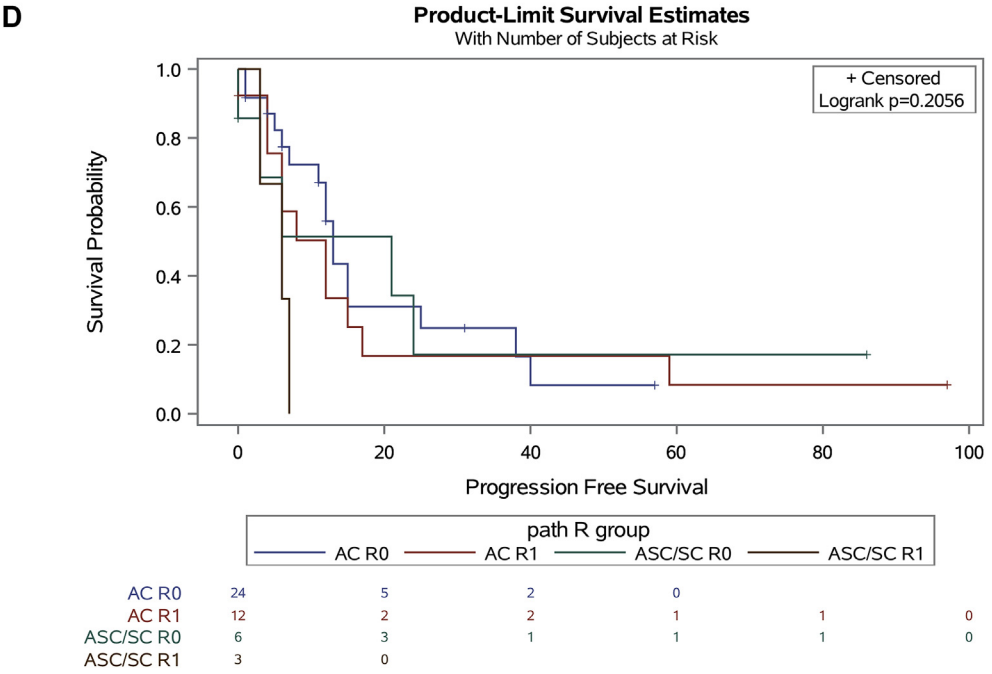


Fig. 2. (*continued*).

lymphadenopathy in SC compared to AC, up to 86%.[4,12]

In our study we found that ASC/SC patients presented with more bulky disease; they had larger tumors (58 mm vs. 28 mm), more liver infiltration (73% vs. 37%) and a higher rate of pTNM stage IV disease (33% vs. 5%), $p < 0.05$. ASC/SC tumors had almost double the rate of lymph node involvement compared to AC tumors (60% vs. 32%). 80% of ASC/SC patients were diagnosed preoperatively with the presence of symptoms, and significantly more patients presented with weight loss (suggesting more advanced disease) than in the AC cohort. Our data suggest that a squamous histological component of GBC infers locally infiltrative disease with a higher likelihood of lymphatic spread.

The ability to achieve a negative surgical margin is an important oncologic principle for patients with GBC. Given that patients with ASC/SC present with more locally advanced disease at diagnosis, it is not surprising that more extensive surgical resection is generally required in order to achieve R0 surgical margins. Kalayarasan et al.[11] found that squamous variants required significantly higher rates of bile duct (43% vs. 20%) and adjacent organ resection ($p < 0.01$). However, the invasive nature of squamous tumors often precludes R0 resection. Kim et al.[12] found that despite aggressive surgical resection in ASC/SC (13% common bile duct, 6% colon, 6%

Table 3
Cox-proportional hazards models for factors predictive of survival outcomes. a: Overall Survival. b: Progression-Free Survival a.

<!–Col Count:4–>Variable	Univariate Analysis	Multivariate Analysis	
	p value	HR [CI]	p value
Liver resection	0.170		
Adjacent organ resection	0.060		
Tumor size	0.001*	1.05 [1.02–1.09]	0.001*
pTNM stage	0.009*		
II		0.02 [0.01–0.36]	0.007*
IIIA		0.01 [0.01–0.16]	0.002*
IIIB		0.00 [0.01–0.03]	<0.001*
IVB		0.01 [0.02–0.04]	<0.001*
No lymphovascular invasion	0.009*	0.16 [0.04–0.64]	0.009*
No perineural invasion	0.030*	0.18 [0.04–0.84]	0.030*
Differentiation	0.098		
R0 resection	<0.001*	0.01 [0.01–0.08]	<0.001*
Histologic group	0.523		
No recurrence	<0.001*	0.02 [0.00–0.12]	<0.001*
b:			
Liver resection	0.199		
Adjacent organ resection	0.194		
Tumor size	0.042*	1.02 [1.00–1.04]	0.042*
pTNM stage	0.008*		
II		0.73 [0.12–4.58]	0.741
IIIA		1.83 [0.32–10.58]	0.501
IIIB		0.45 [0.06–03.59]	0.452
IVB		5.48 [0.94–32.12]	0.059
No lymphovascular invasion	0.004*	0.19 [0.06–0.59]	0.004*
No perineural invasion	0.768		
Differentiation	0.920		
R0 resection	0.579		
Histologic group	0.166		

duodenum), R0 resection was only achieved in 50% of patients. In our study, 73% of ASC/SC patients were able to undergo R0 resection, similar to AC patients, however, they more frequently required adjacent organ resection (overall 40% vs. 7%, $p < 0.05$; 20% colon, 7% duodenum, 7% stomach) in order to achieve this. Previous studies have demonstrated that in the setting of a pathologically negative margin, ASC/SC patients can have similar survival outcomes to AC patients,[4,11,12] with a median overall survival of around 14–28 months. Our data demonstrated that ASC/SC patients had similar median OS (24 months vs. 24 months AC) and PFS (median 6 months vs. 12 months AC), even in stage III/IV disease ($p > 0.05$). Moreover, when R0 resection was achieved, durable long-term survival outcomes were possible for advanced squamous malignancies (pTNM stage III/IV median OS 28 months, PFS 21 months); equivalent to AC (pTNM stage III/IV median OS 25 months, PFS 13 months), $p > 0.05$.

There are no studies to date, however, which compare the outcomes of patients with pure squamous cell carcinomas (SC) to those with a component of adenocarcinoma (ASC). Though there were only three patients in our study who had pure SC, they had a clear survival disadvantage compared to ASC even with similarly high rates of R0 resection (67% SC vs. 75% ASC). The median survival was considerably shorter in SC patients (OS < 5 months, PFS 1 month) than in ASC patients (OS 23 months, PFS 8 months), with no patients alive at 1 year (vs. 68% AC). Although the very small number of SC patients may limit generalization of our results, our data does provoke the question of whether pure SC malignancies behave in a much more aggressive fashion than ASC, and therefore perhaps these cancers are not candidates for surgical resection considering their survival outcomes are no better than chemotherapy alone,[21] even in the setting of negative surgical margins.

Limitations of this study, similar to the other reported series, are its retrospective nature, small sample size and difference in size of the two cohorts. The rarity of squamous variants makes this an inherent limitation when studying this patient population. However, the authors feel that despite the small sample size, the many significant differences between the two cohorts are unlikely to have resulted from chance. Larger studies are needed to corroborate the impact of squamous variants of GBC on patient outcomes in order to better guide management.

Despite these limitations, this study addresses an important yet underdiscussed topic. Our data highlights the significance of histopathology in operative planning and survival outcomes in GBC. Although patients with ASC present with more locally infiltrative and higher stage disease and more lymph node positivity, surgical resection offers survival benefits equivalent to AC. However, operative planning for a more radical resection (including adjacent organs) will likely be necessary in order to achieve a negative surgical margin. Locoregional therapies (such as radiation) and systemic chemotherapy may also benefit this patient population. Pure SC malignancies may not benefit from surgery even with an R0 resection, and pre-operative identification of this aggressive histology may prevent unnecessary morbid operations.

Conclusions

Squamous cell variants of GBC (ASC, SC) typically present at more advanced stages and are locally infiltrative with a higher rate of lymphatic spread. Durable survival outcomes, similar to AC, are possible for ASC when R0 resection is achieved. However, SC has dismal survival even after resection to negative margins.

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Declaration of competing interest

None.

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