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RESEARCH ARTICLE

CLINICOPATHOLOGICAL CHARACTERISTICS AND OUTCOMES OF GALLBLADDER CANCER: A SINGLE-INSTITUTION EXPERIENCE

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ABSTRACT

Background/Aim: This study aims to determine the clinicopathological characteristics and outcomes of gallbladder cancer during the last nine years. **Settings and Design:** Retrospective chart review of the demographic and clinical profiles of gallbladder patients followed up at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, for the period of 2008–2017. **Methods and Material:**We collected data demographic and clinical data (histopathological features, radiological findings, date of diagnosis, type of surgical treatment offered, type of chemotherapy, radiation therapy, intervention used, disease progression, date of the last follow up, date of recurrence, and date of death). **Statistical Analysis:** The Cox proportional hazards model was used for the univariate analysis and multivariate analysis model building. **Results and Conclusions:** A total of 21 patients were included in this study, with females representing 66.7% of the sample. The mean age of the patients was 57 years. Among the cases, 13 (61.9%) were identified as adenocarcinoma, and five (23.8%) were classified as dysplasia; the least frequent histologic diagnosis wascarcinosarcoma (n = 1, 4.8%).Tumor resection was performed in 14patients. Of these, 13 had a laparoscopic cholecystectomy, whereas only one case hadhepaticoenterostomy. Univariate analysis did not demonstrate significant differences in overall survival by age, gender, histologic subtype, tumor grade, surgical margin status, lymph node invasion, or tumor marker status. We did not identify predictors of outcome in patients who were followedup and treated for gallbladder cancer at our institution. Future larger studies are warranted to study the patterns of outcome in our context.

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INTRODUCTION

The actual incidence rates of gallbladder cancer are not well established because, in most registries, gallbladder cancersareusually classified as hepatobiliary tumors (https://seer.cancer.gov/statfacts/html/livibd.html; Al-Shahrani, 2014). In 2017, the estimated rates of hepatobiliary tumors among all other cancers in the United States was 40,710 (https://seer.cancer.gov/statfacts/html/livibd.html). In 2014, hepatobiliary cancers ranked sixth among Saudi males and ninth among Saudi females (Al-Shahrani, 2014). A total of 466 liver cancer cases accounted for 4.0% of all cancer incident cases diagnosed among Saudi nationals in 2014. Liver cancer affected 310 males (66.5 %) and 156 females (33.5%). The age-standardized incidence rate was 4.8/100,000 for males and 2.4/100,000 for females. Gallbladder cancer is a rare gastrointestinal tract malignancy (Perisetti, 2018); however, its incidence is high in Ecuador (12.9/100,000), Pakistan (13.8/100,000), and India (21.5/100,000) (Randi, 2006).

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It is the sixth most common cancer among gastrointestinal tract malignancies, and it is also the most common cancer of the biliary tract, with an annual rate of 2.2 per 100,000 people worldwide (Noel, 2016; Ferlay, 2012). Adenocarcinoma is the most common histologic type, accounting for 76–90% of all gallbladder tumors.[7]Other subtypes that have been identified include papillary, mucinous, squamous, and adenosquamous subtypes (Samuel, 2018; Yang, 2014). However, there is a paucity of data on the clinical behavior and outcomes of papillary and adenosquamous or squamous gallbladder cancers due to the rarity of these histologic subtypes. Most of the available data is limited to case reports or single hospital-based studies (Yang *et al*., 2014; Song *et al*., 2015; Onuma *et al*., 2013; Adsay *et al*., 2012). According to one report, the prognostic outcome of patients with adenosquamousor squamous cell carcinoma is worse than that of those with adenocarcinomas (Roa *et al*., 2011). In this era when laparoscopic cholecystectomy is used for the treatment of benign diseases, the incidental diagnosis of gallbladder carcinoma has increased substantially (Panebianco *et al*., 2013). This increase has allowed physicians to detect cancer at an early stage and, ultimately, improve the prognosis.

This study aims to determine the clinicopathological characteristics and outcome of gallbladder cancer at King Abdulaziz University Hospital during the last nine years.

MATERIALS AND METHODS

This retrospective chart review was conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Approval to conduct this study was granted by the Research Ethics Committee of King Abdulaziz University. Charts from patients with all bladder cancer as per the Pathology Department's database and electronic healthcare systems for the period of 2008–2017 were extracted and reviewed.

Data Collection: The data elements used in this study included the patients' demographic characteristics(date of birth and gender), histopathological features (specimen type, TNM staging, histopathological grading, type of grading system utilized, histologic subtype, surgical margins, and tumor markers), and radiological findings from computed tomography (CT) scans. Computed tomography and tumor marker data were included in the analysis if they had been performed within one month of diagnosis. We also collected the following data: date of diagnosis, possibility of resection, type of surgical treatment offered, type of chemotherapy, radiation therapy, intervention used, disease progression, date of the last follow-up, date of recurrence, and date of death.

Statistical analysis: The data were entered and analyzed using Strata/IC Version 15.1. (College Station, TXT, USA). The Cox proportional hazards model was used for the univariate analysis and multivariate analysis model building. Multivariate analysis was conducted using a stepwise model to eliminate irrelevant variables affecting the overall survival (OS), with a probability to eliminate variables at p-value >0.2.

RESULTS

Demographic characteristics of the patients and clinical variables: A total of 21 patients were included in this study, with females representing 66.7% of the sample (n = 14).The mean age of the patients was 57 years. Among the cases, 13 (61.9%) were identified as adenocarcinoma, and five (23.8%) were classified as dysplasia; the least frequent histologic diagnosis was carcinosarcoma, which was identified in one patient (4.8%). As shown in Table 1, the tumor marker carcinoembryonic antigen 19-9 (CA19-9) was measured in 11 cases (mean value, 1245.5 U/mL), whereas carcinoembryonic antigen (CEA) was measured in nine cases (mean value, 43.0 U/mL); alpha-fetoprotein was measured in eight cases (mean value, 3.2 ng/mL). Only six of the 21 patients presented with jaundice (28%). Tumor resection was performed in 14patients.Of these, 13 had a laparoscopic cholecystectomy, whereas only one case hadhepaticoenterostomy. The remaining seven cases did not undergo surgery. One patient had lymph node enlargement (16.7%), two patients had lymph node enlargement with vascular invasion (33.3%), one had lymph node enlargement and metastasis to another organ (16.7%), and one patient had an invading tumor to surrounding structures (16.7%). Three patients out of 14 who underwent tumor resection received adjuvant chemotherapy (21.4%), while four had percutaneous transhepatic cholangiography as an intervention. The surgical margin status was positive in six patients (28.6%) and negative in eight patients (38.1%).Three patients (14.3%) had lympho-vascular invasion, and two (9.5 %) had a perineural invasion.

Table 1. Demographic characteristics and clinical variables

Demographic data	Frequency (n = 21)	Percent (100%)
Gender		
Male	7	33.3%
Female	14	66.7%
Histologic type		
Adenocarcinoma	13	61.9%
Dysplasia	5	23.8%
Squamous cell carcinoma	2	9.5%
Carcinosarcoma	1	4.8%
Tumor markers (elevated)		
CEA	9	43.0%
CA19-9	11	52.4%
Alpha-fetoprotein	6	3.19%
Tumor grade		
Grade 1	8	38.1
Grade 2	7	33.3
Grade 3	6	28.6
Jaundice		
Yes	6	28.6%
Was the tumor resected?		
Yes	14	66.7%
Type of surgery		
Laparoscopic cholecystectomy	13	92.9%
Hepaticoenterostomy	1	7.1%

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen.

Table 2.Univariate analysis of overall survival

Variables	Hazard Ratio	95% CI	p-value
Age	1.02	0.95–1.10	0.55
Male	2.29	0.50–10.47	0.29
Adenocarcinoma	0.56	0.06–4.88	0.60
Carcinosarcoma	1.77	0.20–15.31	0.60
Grade histopathology	1.46	0.62–3.48	0.38
Margins	1.15	0.10–12.83	0.91
LVI	2.33	0.21–26.16	0.49
PNI	2.33	0.21–26.16	0.49
TNM stage	2.18	0.69–6.91	0.18
CEA	1.00	0.99–1.01	0.84
CA199	1.00	0.99–1.00	0.81
Alpha fetoprotein	0.91	0.57–1.49	0.73

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CI, confidence interval; LVI, lymph node invasion; PNI, perineural invasion.

Table 3. Univariate analysis of overall survival in patients with resected tumors

Variables	Hazard Ratio	95% CI	p-value
Age	0.99	0.90–1.08	0.76
Male	1.49	0.13–16.93	0.74
Adenocarcinoma	0.32	0.03–3.61	0.35
Carcinosarcoma	3.08	0.28–34.39	0.35
Grade histopathology	1.28	0.35–4.66	0.70
Margins	1.15	0.10–12.83	0.91
LVI	2.34	0.21–26.26	0.49
PNI	2.34	0.21–26.16	0.49
TNM stage	2.19	0.69–6.91	0.18
CEA	3.07	0.00–0.00	1.00
CA199	1.88e-10	-	-
Alpha fetoprotein	1.00	-	-

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CI, confidence interval; LVI, lympho-vascular; PNI, perineural invasion.

The overall survival rate was 52.6% at 24 months (Figure 1), and the median follow up was 6.1 months (95% confidence interval 1.9–14.1). The univariate analysis did not demonstrate significant differences in overall survival by age, gender, histologic subtype, tumor grade, surgical margin status, lymph node invasion, or tumor marker status (Table 2). Further analysis showed that in patients with resected tumors, no significant difference was found in overall survival by age, gender, histologic subtype, tumor grade, surgical margin status, lymph node invasion, or tumor marker status (Table 3).

Table 4. Univariate analysis of overall survival in patients with non-dysplastic carcinoma

Variables	Hazard Ratio	95% CI	p-value
Sex	1.33	0.29–6.06	0.711
Adenocarcinoma	0.56	0.07–4.88	0.60
Carcinosarcoma	1.77	0.20–15.31	0.60
Grade histopathology	1.58	0.60–9.90	0.35
Margins	1.15	0.10–12.83	0.90
LVI	2.34	0.21–26.16	0.49
PNI	2.34	0.21–26.16	0.49
TNM	1.77	0.44–7.12	0.42
CEA	1.00	0.99–1.00	0.84
CA199	0.99	0.99–1.00	0.96
Alpha fetoprotein	0.83	0.50–1.00	0.46

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CI, confidence interval; LVI, lympho-vascular; PNI, perineural invasion; T, tumor.

Table 5.Univariate analysis of overall survival in patients with resected non-dysplastic carcinoma

Variables	Hazard Ratio	95% CI	p-value
Sex	0.91	0.08–10.26	0.93
Adenocarcinoma	0.32	0.03–3.60	0.36
Carcinosarcoma	3.09	0.28–34.39	0.35
Grade histopathology	1.20	0.30–4.78	0.80
Margins	1.15	0.10–12.83	0.91
LVI	2.34	0.21–26.16	0.49
PNI	2.33	0.21–26.16	0.49
TNM	1.77	0.44–7.12	0.42
CEA	3.07	0.00–0.00	1.00
CA199	2.61e-10	0.00–0.00	1.00
Alpha fetoprotein	1	-	-

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CI, confidence interval; LVI, lympho-vascular; PNI, perineural invasion; T, tumor.

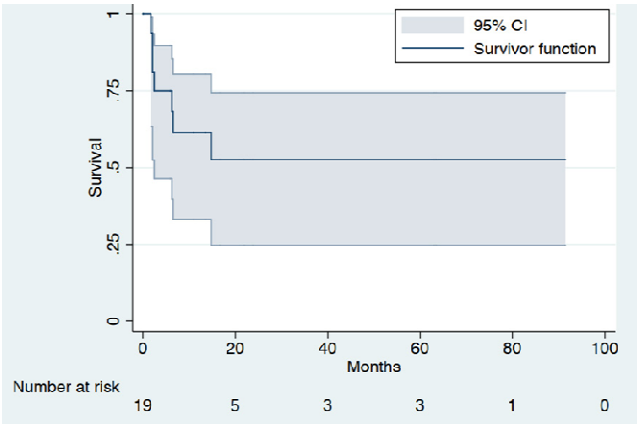

Figure 1. Kaplan-Meier survival curve for the 21 patients included in this study

In the same line, we did not find a significant difference in overall survival in patients with non-dysplastic carcinoma (Table 4) or those with resected non-dysplastic carcinoma (Table 5) stratified by age, gender, histologic subtype, tumor grade, surgical margin status, lymph node invasion, or tumor marker status.

DISCUSSION

We found that females were mainly represented in the sample, which is in line with reports from single-center studies conducted in Saudi Arabia (Aldossary *et al*., 2018) and abroad (Panebianco, 2013; Cha, 2015; Khan, 2013). Findings from epidemiological studies have also reported a preponderance of the disease in females (Lai, 2008; Miller, 2008). According to one report, females are three times more likely to be diagnosed with gallbladder cancer than males (Miller, 2008). Additionally, a retrospective analysis of data from the Surveillance, Epidemiology, and End Results database showed that survival rates were higher in females (hazard ratio 0.82, confidence interval 0.70–0.96, p-value = 0.02) (Downing, 2011). Patients with adenocarcinoma were heavily represented in our sample, constituting approximately 61.9% of the cases. Other common histologic types includeddysplasia (23.8%), squamous cell carcinoma (9.5%), and carcinosarcoma (4.8%). Unfortunately, reports from other health institutions in our region are rare, and only a recent study conducted at a tertiary hospital in Dammam, Eastern Province of Saudi Arabia (2018), reported that adenocarcinoma not otherwise specified was the most common histopathologicalsubtype (75.0%). This subtype was followed by papillary adenocarcinoma (9.2%), mucinous adenocarcinoma (3.9%), and carcinosarcoma (3.9%); all other subtypes were each identified in approximately 1.3% of the cases. In this modern era of imaging and laparoscopy, it is estimated that approximately 1.5% of cases of gallbladder cancer are incidentally discovered during laparoscopic cholecystectomy (Kwon, 2008). Furthermore, improved imaging techniques and awareness of this cancer by clinicians have also contributed to its higher detection rates (Konstantinidis, 2009). At King Abdulaziz University Hospital, clinicianstypically use ultrasonography to image gallbladders. In cases where an ultrasound examination suggests neoplasm of the gallbladder, the clinician should perform a further examination usinga CT scan,magnetic resonance imaging/magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound as was the case in our patients. The general recommendation is to perform radical resection in cases that are discovered incidentally during or after a cholecystectomy, and the clinician should consider aggressive resection either during the surgery or during a subsequent one (Qadan, 2016).

Open cholecystectomy is the preferred option because it will decrease the likelihood of bile spillage with possible liver resection, depending on the cancer stage. Indeed, port site metastases have been reported in several cases following laparoscopic cholecystectomy (Lundberg, 2001; Paolucci *et al*., 1999). Among the 21cases diagnosed at our institution, tumor resection was performed in 14patients, of which 13 had laparoscopic cholecystectomy. While we attempted to explore outcomes based on variables such as age, gender, histologic subtype, tumor grade, surgical margin status, lymph node invasion, and tumor marker status, wedid not find significant differences, probably owing to our small sample size. In a single-center study conducted in Dammam (Aldossary *et al*., 2018), the investigators reported a poor outcome, with 57.9% of the patients having advanced disease at diagnosis. Additionally, the investigators reported a five-year survival rate of 20.5%, with the rate being significantly higher in patients who had undergone surgical resection compared with those in whom resection was not performed. In another study conducted at Massachusetts General Hospital (Konstantinidis, 2009), the investigators reported a five-year survival of 35% in patients who had undergone resection (R0 and R1); the overall median survival for these patients was 24 months. Although survival is largely dependent on early diagnosis of the disease, most patients with gallbladder cancer have advanced disease at diagnosis, and recurrence is high despite surgery (Hundal, 2014). Re-resection has proven not to increase survival, and outcomes are rather dismal. Adjuvant treatment has also been reported to be largely ineffective, with response rates of

<30%.[26]In previous studies, investigators demonstrated a significant survival benefit for extended cholecystectomy in patients with early gallbladder cancer (Downing, 2011; Shirai, 2012). Other factors such as old age (> 60 years), advanced disease (T1 and T2), and disease-positive lymph nodes (regional and regional) have been shown to be associated with decreased survival (Downing, 2011). This study has limitations inherent to retrospective studies. Additionally, our analyses are limited by the small sample size, making it difficult for us to deduce relevant conclusions. However, these data may serve as preliminary insights in this context. Overall, this retrospective study did not identify predictors of outcome in patients who were followed up and treated for gallbladder cancer at our institution. Although our cases have similar clinicopathological characteristics to gallbladder patients in single-institution studies conducted locally and abroad, we believe that future larger studies are warranted to study the patterns of outcome in our context.

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