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Long-term results and prognostic factors after surgical treatment for gallbladder cancer

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ABSTRACT

Objective: Gallbladder cancer is relatively rare and traditionally regarded as having poor prognosis. There is controversy about the effects of clinicopathological features and different surgical techniques on prognosis. The aim of this study was to investigate the effects of clinicopathological characteristics of the patients with surgically treated gallbladder cancer on long-term survival.

Material and Methods: We retrospectively analyzed the database of gallbladder cancer patients treated at our clinic between January 2003 and March 2021.

Results: Of 101 evaluated cases, 37 were inoperable. Twelve patients were determined unresectable based on surgical findings. Resection with curative intent was performed in 52 patients. The one-, three-, five-, and 10-year survival rates were 68.9%, 51.9%, 43.6%, and 43.6%, respectively. Median survival was 36.6 months. On univariate analysis, poor prognostic factors were determined as advanced age; high carbohydrate antigen 19-9 and carcinoembryonic antigen levels; non-incidental diagnosis; intraoperative incidental diagnosis; jaundice; adjacent organ/structure resection; grade 3 tumors; lymphovascular invasion; and high T, N1 or N2, M1, and high AJCC stages. Sex, IVb/V segmentectomy instead of wedge resection, perineural invasion, tumor location, number of resected lymph nodes, and extended lymphadenectomy did not significantly affect overall survival. On multivariate analysis, only high AJCC stages, grade 3 tumors, high carcinoembryonic antigen levels, and advanced age were independent predictors of poor prognosis.

Conclusion: Treatment planning and clinical decision-making for gallbladder cancer requires individualized prognostic assessment along with standard anatomical staging and other confirmed prognostic factors.

Keywords: Biliary tract surgical procedures, gallbladder neoplasm, prognostic factors, survival

INTRODUCTION

Gallbladder cancer (GBC) is relatively rare form of cancer with a worldwide incidence of less than 2/100.000 people (1). Surgical resection is the only treatment with curative potential, and success depends on the biology of the tumor and the completeness of the resection (2). However, there is controversy about the effects of clinicopathological features and different surgical techniques on prognosis. The evaluation of such variables predicted to affect prognosis and long-term survival outcomes may provide valuable data, which can be used to develop effective survival prediction models, allowing individual evaluation beyond standard anatomical staging and possibly affecting treatment algorithms. This single-center retrospective study on GBC patients treated with surgery aimed to determine prognostic factors by evaluating long-term survival outcomes.

MATERIAL and METHODS

We retrospectively analyzed the hospital database for GBC patients treated and followed up in our tertiary referral surgery center between January 2003 and March 2021. Approval for the study was obtained from the institutional ethics committee of the University of Health Sciences Haydarpaşa Numune Training and Research Hospital 2021/65).

Patients and Surgical Approach

Patients who were inoperable at presentation due to unresectable or metastatic disease were referred for supportive care and palliative treatment. Patients who

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were considered operable at the initial workup were operated on after being prepared for curative surgical treatment. The American Joint Committee on Cancer Staging (AJCC) 8th Edition Manual was used for the patients' clinical and pathological staging (3). While simple cholecystectomy was considered sufficient for Tis and T1a cases, radical cholecystectomy was required for more advanced cases. While standard radical cholecystectomy was sufficient in most cases for curative R0 resection, some advanced cases required extended resection. Patients were then evaluated in a multidisciplinary manner and referred for postoperative adjuvant treatment when necessary.

Statistical Analysis

Data analysis was performed using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Categorical data were expressed as numbers (n) and percentages (%), and quantitative data as mean ± standard deviation (SD) and median (interquartile range, 25th-75th percentiles). Shapiro-Wilk test was used to investigate whether the normal distribution assumption was met. Mean differences between the groups were compared using Student's t-test. In all 2 × 2 contingency tables used to compare categorical variables, the continuity corrected $\chi 2$ test was used when one or more of the cells had an expected frequency of 5-25; Fisher's exact test, ≤5. In all R × C contingency tables used to compare categorical variables, Fisher Freeman Halton test was used when one quarter or more of the cells had an expected frequency of ≤5. Kaplan-Meier survival analysis via the log-rank test was used to determine whether categorical variables had a statistically significant effect on prognosis [i.e., recurrence-free and overall survival (OS)]. Cumulative one-, three-, five-, and 10-year survival rates, mean expected duration of life, and 95% confidence intervals (CIs) were computed. Kaplan-Meier survival curves were generated using STATA 16.1 (Stata Corp., College Station, TX, USA). Whether the potential factors had a statistically significant effect on prognosis was investigated using univariate Cox's proportional hazard regression models. Multiple Cox's proportional hazard regression models via the backward stepwise elimination procedure were obtained to determine the best independent predictors that affected prognosis. Any variable (except for those with missing values) whose univariable test had a p-value <0.25 was accepted as a candidate for the multivariable model. Hazard ratios (HR) and 95% CIs for each independent variable were also calculated. P values <0.05 were considered statistically significant.

RESULTS

Of the 101 GBC patients, 37 patients (36.6%) were deemed inoperable at baseline and referred for palliative treatment and supportive care, while the other 64 (63.4%) were operable. Inoperable and operable patient groups were comparable in terms of age and sex. Mean age was 64.6 ± 13.5 years (64.7 ± 15.4 years for inoperable and 64.6 ± 12.4 years for operable group, p= 0.986). Sixty-three patients (62.4%) were females (62.2% of inoperable and 62.5% of operable group, p> 0.999).

Twelve of the 64 operable patients were determined unresectable based on surgical findings and received only palliative surgery or exploration. The other 52 patients underwent resection with curative intent. R0 resection was achieved in 50 patients, but in the other two patients, surgical margin was reported as R1 on final pathology. Among 52 patients, a total of 20 patients received adjuvant therapy (chemotherapy, n= 15; chemoradiotherapy, n= 5). However, due to the diversity of therapy protocols and treatment centers, prognostic effect of adjuvant therapy was not evaluated in this study.

Twenty-nine of the patients in the operable group (45.3%) were incidentally diagnosed during cholecystectomy performed due to cholelithiasis and/or a polyp [incidental GBC (IGBC)]: Five (17.2%) intraoperatively versus 24 (82.8%) during postoperative pathological evaluation. Thirty-five patients (54.7%) undergoing surgery with a preoperative diagnosis of GBC constituted the non-incidental (non-IGBC) group.

The most frequent symptom in the operable group was abdominal pain [n= 58 (90.6%)], 52 (81.3%) had gallbladder stones, and 15 (23.4%) had jaundice at admission. Table 1 and Table 2 show descriptive statistics of serum tumor markers and surgical procedures, and pathological characteristics, respectively.

Seven of the operated patients (10.9%) died postoperatively in the hospital. Median follow-up time for 57 patients included in the survival analysis was 29.8 months (interquartile range, 2.3-198.4). Recurrence occurred in 23 patients (40.4%) after curative resection. Median recurrence-free survival (RFS) was not statistically computable, while the one-, three-, five-, and 10-year RFS rates were 68.5%, 52.1%, 49.2%, and 49.2%, respectively.

Table 3 shows cumulative one-, three-, five-, and 10-year survival rates and the overall median and mean life expectancy according to operable or inoperable status, curative or non-curative surgery, IGBC or non-IGBC, absence or presence of jaundice, and AJCC 8th ed. stages. Kaplan-Meier survival curves are shown for IGBC versus non-IGBC (Figure 1) and AJCC stages (Figure 2A-D).

When the IGBC and non-IGBC groups were compared, no statistically significant difference was observed in terms of mean age, sex distribution, jaundice, curative or non-curative operation rates, N and M stage, perineural invasion (PNI), or grade (p> 0.05). In contrast, T stage, lymphovascular invasion (LVI) incidence, AJCC stage, and mortality incidence in the non-IGBC group were significantly higher than in the IGBC group (p< 0.05) (Table 4).

When different categorical variables that may affect prognosis were evaluated by univariate statistical analyses, mortality rate

Table 1. Serum tumor markers in operable patients and the surgical procedures applied

	n= 64 (%) or mean (95% CI)
Serum CA19-9 (U/mL)	20.3 (6.6-125.5)
Serum CEA (U/mL)	2.84 (1.71-7.67)
Type of surgery	
Curative (R0)	50 (78.1%)
Non-curative	14 (21.9%)
R1	2
Palliative or explorative surgery	12
Surgical procedure details	
Procedures with curative intent	52 (81.3%)
Simple cholecystectomy (LC/open)	4 (6.3%)
Standard radical cholecystectomy	38 (59.4%)
Hepatic wedge resection	7
Segment IVb/V segmentectomy	31
Extended radical resection	10 (15.6%)
Hepatopancreatoduodenectomy	6
Right hepatic trisectionectomy	1
Right hepatectomy plus segment IVb segmentectomy	1
Central hepatectomy	1
Segment IVb/V plus segment VI segmentectomy	1
Palliative or explorative surgery	12 (18.8%)
Simple cholecystectomy (LC/open)	6
Gastrojejunostomy	2
Explorative laparoscopy or laparotomy	4
Liver resection plus en bloc adjacent organ or structure resection	29 (45.3%)
EHBD resection	20 (31.3%)
Duodenum wedge resection	11 (17.2%)
Colon wedge or segmental resection	9 (14.1%)
Right hepatic artery	4 (6.3%)
Portal vein	3 (4.7%)
Others (Distal gastrectomy, omentum, abdominal wall and small intestine segmental resections)	9 (14.1%)
Lymphadenectomy	
No	14 (21.9%)
Standard dissection	38 (59.4%)
Standard dissection plus paraaortic dissection	12 (18.8%)
Total number of lymph nodes	8.0 (4.0-13.0)

CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, LC: Laparoscopic cholecystectomy, EHBD: Extrahepatic bile duct.

increased in direct proportion with advanced age (≥60 years), high serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels, non-IGBC versus IGBC, intraoperative versus postoperative incidental diagnosis, presence of jaundice, non-curative surgery, resection of adjacent organ or structure, grade 3 versus grade 1-2 tumors, presence of LVI, high T, stage N1 or N2 instead of N0, stage M1, and high AJCC stage ($p< 0.05$) (Table 5).

All variables with values of $p< 0.25$ on univariate statistical analyses were included in the multivariate Cox proportional hazards regression model. The following most determinant factors for OS were determined via the backward stepwise elimination procedure: High AJCC stage, grade 3 tumor, elevated serum CEA level, and advanced age (Table 6).

DISCUSSION

Median survival of the patients on whom we performed curative resection was 36.6 months, and their five-year survival rate was 51.9%; in contrast, in the group that underwent non-curative surgery, median survival was 7.2 months, and no patients survived five years later ($p< 0.001$). These suggest that

Table 2. Pathological characteristics of operable patients

	n= 64 (%)
Location	
Fundus	17 (27.0%)
Corpus	27 (42.9%)
Neck	4 (6.3%)
Multiple	3 (4.8%)
Diffuse	12 (19.0%)
Histologic type	
Adenocarcinoma	58 (90.6%)
Squamous cell	2 (3.1%)
Carcinosarcoma	1 (1.6%)
Neuroendocrine	3 (4.7%)
Grade	
1-2	46 (75.4%)
3	15 (24.6%)
AJCC 8th ed. stage	
0-I	6 (9.4%)
II	12 (18.8%)
III	14 (21.9%)
IV	32 (50.0%)
T stage	
T_{is}-T_{1a}	4 (6.3%)
T_{1b}-T_2	21 (32.8%)
T_3-T_4	39 (60.9%)
N stage*	
N_0	24 (50.0%)
N_1-N_2	24 (50.0%)
M stage	
M_0	47 (73.4%)
M_1	17 (26.6%)
LVI	
Absent	23 (40.4%)
Present	34 (59.6%)
PNI	
Absent	23 (40.4%)
Present	34 (59.6%)

AJCC 8th ed.: American Joint Committee on Cancer 8th edition, LVI: Lymphovascular invasion, PNI: Perineural invasion.
*NX was excluded from the calculation.

curative resection is a prerequisite for the treatment of GBC, as demonstrated in many other series (4-9). Herein, simple cholecystectomy was considered sufficient for curative resection in Tis and T1a cases, while radical resection was performed in T1b and more advanced cases. This practice was consistent with the Guidelines of the National Comprehensive Cancer Network recommendations and the Expert Consensus Statement derived from the Americas Hepato-Pancreato-Biliary Association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO)/American Society of Clinical Oncology (ASCO) Consensus Conference (10,11). When the effects of AJCC stage and the T, N, and M stages on survival were evaluated separately, the negative effect of a high AJCC stage, high T stage, N1 or N2 stage, or M1 stage on survival was demonstrated in the univariate analysis, whereas only a high AJCC stage was an independent factor with a negative effect on survival in the multivariate analysis. These results were consistent with those of previous studies that revealed AJCC stage as the strongest prognostic factor (4-6). In our series, the high number of stage T3-T4, N1-N2, and M1 patients was noteworthy, while 50% of the patients had stage IV disease. Median survival of stage IV patients was 8.1 months, their one-year survival rate was 36%, and their three-, five-, and 10-year survival rates were 10.7%. In the Nagoya series, which is considered one of the main series in the surgical treatment of stage IV patients, median survival has been found as 9.6 months and three-, five-, and 10-year survival rates as 19%, 12%, and 10%, respectively (12). To provide a chance of survival for such advanced GBC cases, surgical treatment may be recommended if R0 resection is possible (13).

An estimated 25-50% of GBC patients present with jaundice. It has been found that the chance of resectability is lower and the incidence of metastatic disease and locally advanced disease is higher in jaundiced patients than in those without jaundice. In addition, when curative resection is performed, morbidity and mortality rates are higher and median survival is lower. As such, some studies have suggested that jaundice is a relative contraindication for resection (2,14). Mishra et al. have demonstrated that jaundice is an independent negative predictor of resectability; however, it is not an independent prognostic factor for post-resection survival (14). In our series, 23.4% of the patients had jaundice, among whom R0 curative resection was achieved in 80%. All patients required extrahepatic bile duct (EHBD) resection, and three patients needed hepatopancreatoduodenectomy (HPD) to achieve R0 resection. Mortality rate for these patients was 16.6%, median survival was 7.6 months. These results are significantly worse than those of the patients without jaundice. While jaundice was a negative prognostic factor in the univariate analyses, it was not an independent factor in the multivariate analysis for this group, which mostly consisted of stage IV patients.

Here, six HPD procedures were performed to achieve R0 curative resection: Two patients died during the postoperative period in the hospital, three died in the first year, and one remained alive at month 64. The cause of mortality was intraabdominal sepsis due to pancreaticojejunal anastomotic leakage. There were an insufficient number of HPD cases for analysis in our series; however, the literature demonstrates mortality rates

Table 3. Kaplan-Meier survival analyses of overall survival via log-rank test

	n	Cumulative survival rates				Expected duration of life		Log-rank	p
		One-year	Three-year	Five-year	10-year	Median (95% CI)	Mean (95% CI)		
Groups								51.408	**<0.001**
Operable	57	61.4	42.2	35.5	35.5	25.7 (9.2-42.2)	76.8 (53.6-100.1)		
Inoperable	37	5.4	N/A	N/A	N/A	3.0 (1.7-4.3)	4.6 (3.2-5.9)		
Operation								13.633	**<0.001**
Curative	45	68.9	51.9	43.6	43.6	36.6 (7.1-66.1)	92.5 (65.8-119.3)		
Non-curative	12	33.3	N/A	N/A	N/A	7.2 (3.7-10.8)	9.1 (5.9-12.5)		
Diagnosis								6.905	**0.009**
Incidental	29	75.9	57.4	49.2	49.2	N/A	106.5 (72.2-140.8)		
Non-incidental	28	46.4	26.0	21.6	21.6	8.3 (2.1-14.6)	48.9 (20.8-77.0)		
Jaundice								10.568	**<0.001**
Absent	44	70.5	51.1	45.2	45.2	44.7 (0.0-117.4)	94.3 (67.0-121.6)		
Present	13	30.8	10.3	N/A	N/A	7.7 (3.4-12.0)	13.8 (6.8-20.8)		
AJCC 8th ed. stage								25.181	**<0.001**
0-I	6	100.0	100.0	100.0	100.0	N/A	N/A		
II	12	100.0	75.0	75.0	75.0	N/A	154.4 (111.2-197.6)		
III	14	57.1	34.3	12.9	12.9	15.1 (1.5-28.8)	27.5 (13.2-41.7)		
IV	25	36.0	10.7	10.7	10.7	8.1 (6.3-9.9)	29.7 (6.3-53.1)		
T stage								18.620	**<0.001**
T_{is}-T_{1a}	4	100.0	100.0	100.0	100.0	N/A	N/A		
T_{1b}-T_2	19	94.7	67.4	56.1	56.1	N/A	121.2 (80.8-161.5)		
T_3-T_4	34	38.2	19.9	14.9	14.9	8.1 (7.1-9.1)	37.9 (14.7-61.1)		
N stage*								12.079	**<0.001**
N_0	23	87.0	67.9	67.9	67.9	181.6 (0.0-391.7)	134.2 (99.0-169.4)		
N_1-N_2	19	47.4	21.3	14.2	14.2	9.3 (0.0-20.7)	23.0 (10.9-35.2)		
M stage								6.304	**0.012**
M_0	43	69.8	49.7	40.8	40.8	33.3 (6.5-60.0)	91.2 (63.0-119.2)		
M_1	14	35.7	19.0	19.0	19.0	7.2 (1.7-12.7)	41.7 (2.4-81.0)		

AJCC 8th ed.: American Joint Commission on Cancer 8th edition, CI: Confidence interval, N/A: Not applicable.
*NX was excluded from the calculation.

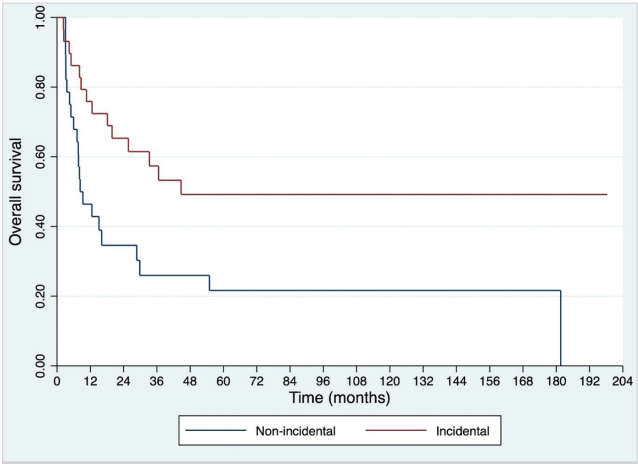

Figure 1. Kaplan-Meier survival curves of overall survival of patients with incidental versus non-incidental gallbladder cancer (p= 0.009).

of 0-60% and five-year survival rates of 0-39.8% were reported after HPD for advanced GBC cases (13).

In our series, another extended radical resection method was major hepatectomy; however, the low number and diversity prevented statistical evaluation. In standard radical cholecystectomy, the most common hepatic resection method was segment IVb/V resection. Although this resection method tended to lead to longer OS than wedge resection, the difference was not statistically significant. Segment IVb/V resection, which was previously recommended considering that potential micrometastases to this region through the venous drainage of the gallbladder by segment IVb/V resection would be also resected, provided no survival advantage over wedge resection; therefore, recommendations of Expert Consensus Statement derived from the AHPBA/SSAT/SSO/ASCO Consensus Conference and version 3 of the Clinical Practice Guidelines for the Management of Biliary Tract Cancers of the Japanese Society of Hepato-Biliary-Pancreatic Surgery have proposed that gallbladder bed resection would be sufficient provided that negative surgical margins are achieved (11,15-17). In 29 (45.3%) of our cases, combined en bloc adjacent organ or struc-

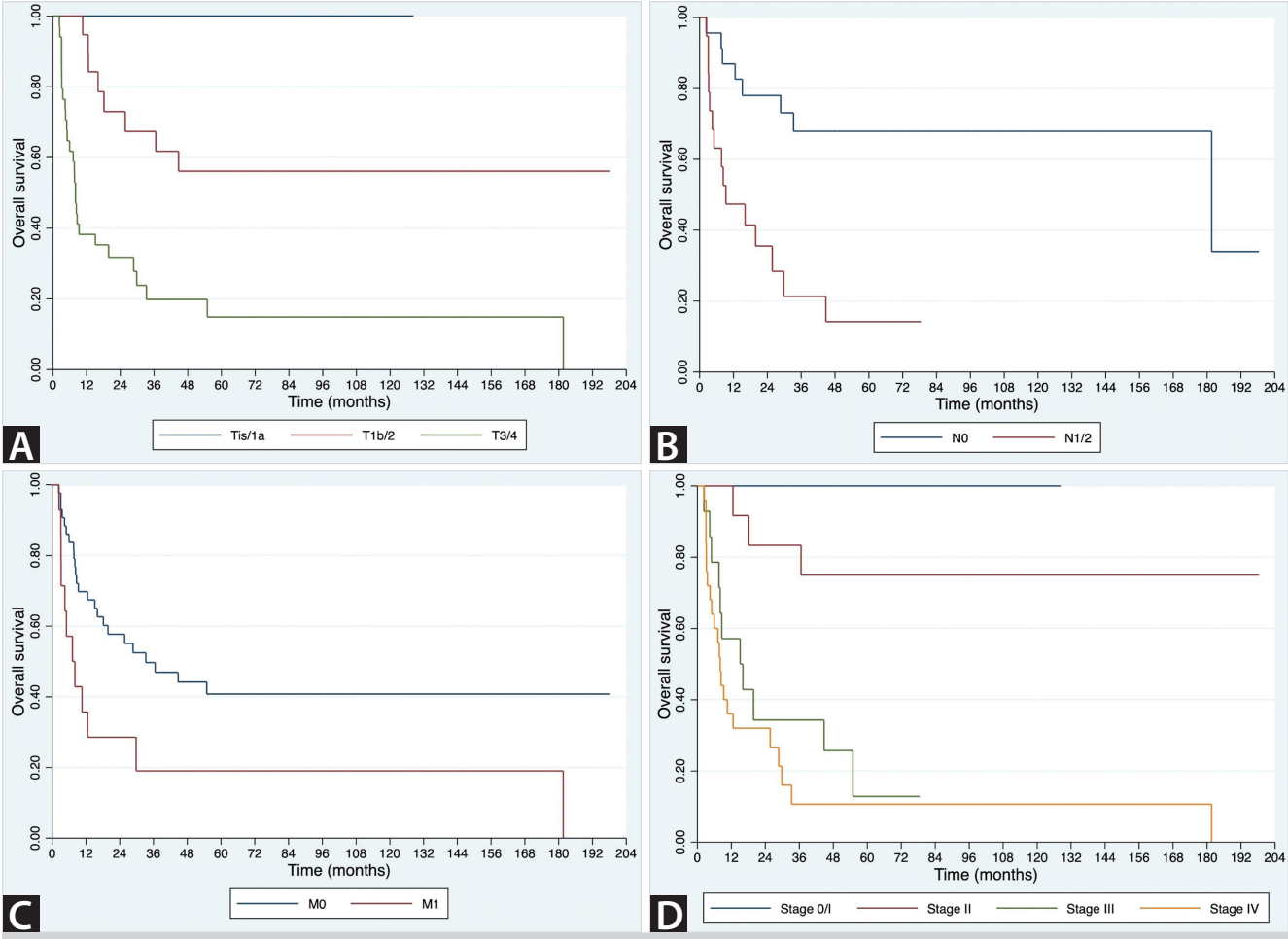

Figure 2. Kaplan-Meier survival curve of overall survival according to T stage (p< 0.001) **(A)**, N stage (p< 0.001) **(B)**, M stage (p= 0.012) **(C)**, and American Joint Commission on Cancer stage (p< 0.001) **(D)**.

Table 4. Patients' demographic and clinical characteristics of incidental versus non-incidental groups

	Incidental (n= 29) n (%) or mean ± SD	Non-incidental (n= 35) n (%) or mean ± SD	p
Age	63.1 ± 12.1	65.9 ± 12.6	**0.365†**
Female sex	18 (62.1%)	22 (62.9%)	**>0.999‡**
Jaundice	3 (10.3%)	12 (34.3%)	**0.051‡**
Curative operation	24 (82.8%)	26 (74.3%)	**0.608‡**
T stage			**0.002¶**
T_{is}-T_{1a}	3 (10.3%)	1 (2.9%)	
T_{1b}-T_2	15 (51.7%)	6 (17.1%)	
T_3-T_4	11 (38.0%)	28 (80.0%)	
N stage*			**0.143‡**
N_0	13 (65.0%)	11 (39.3%)	
N_1-N_2	7 (35.0%)	17 (60.7%)	
M stage			**0.210‡**
M_0	24 (82.8%)	23 (65.7%)	
M_1	5 (17.2%)	12 (34.3%)	
LVI			**0.013‡**
Absent	16 (59.3%)	7 (23.3%)	
Present	11 (40.7%)	23 (76.7%)	
PNI			**0.159‡**
Absent	14 (51.9%)	9 (30.0%)	
Present	13 (48.1%)	21 (70.0%)	
Grade			**0.060‡**
1-2	24 (88.9%)	22 (64.7%)	
3	3 (11.1%)	12 (35.3%)	
AJCC 8th ed. stage			**0.002¶**
0-I	4 (13.8%)	2 (5.7%)	
II	10 (34.5%)	2 (5.7%)	
III	7 (24.1%)	7 (20.0%)	
IV	8 (27.6%)	24 (68.6%)	
Mortality	0 (0.0%)	7 (20.0%)	**0.013¥**

†Student's t test, ‡Continuity-corrected $\chi 2$ test, ¶Fisher Freeman Halton test, ¥Fisher's exact test.

SD: Standard deviation, LVI: Lymphovascular invasion, PNI: Perineural invasion, AJCC 8th ed.: American Joint Committee on Cancer 8th edition.

*NX was excluded from the calculation.

ture resections other than HPD were also needed for R0 resection. The most common ones were EHBD resection in 20 cases, duodenal wedge resection in 11, and colon wedge or segmental resection in nine. In the univariate analysis, OS was significantly poor in the group subjected to en bloc adjacent organ or structure resection (p= 0.012). This may have been due to the more aggressive tumor characteristics in the EHBD resection group compared to the non-resected group as reported by Choi et al (18).

It is recommended that a minimum of six lymph nodes be resected to ensure sufficient staging in the lymphadenectomy part of radical cholecystectomy for GBC (10,11). Some studies have asserted that the number of lymph nodes resected during lymphadenectomy affects both staging and survival (19,20). In our study, a mean eight lymph nodes were resected for each patient, and the number of resected lymph nodes did not have a significant effect on OS. In their study comparing standard regional lymphadenectomy with extended regional lymphadenectomy including paraaortic lymphadenectomy, Wang et al. have reported that the latter provided significantly higher survival in patients with nodal positive stage III and IV disease without distant metastases (21). In our study, the survival effect

Table 5. Univariate Cox proportional hazard regression analysis of overall survival

	HR	95% CI for HR		Wald	p
		Lower limit	Upper limit		
Age ≥60 years	2.685	1.220	5.909	6.026	**0.014**
Female sex	1.168	0.591	2.309	0.199	0.656
Serum CA19-9*	1.013	1.0003	1.026	4.011	**0.045**
Serum CEA	1.020	1.009	1.030	13.584	**<0.001**
Non-incidental diagnosis	2.411	1.225	4.748	6.482	**0.011**
Intraoperative versus postoperative diagnosis	3.734	1.158	12.038	4.865	**0.027**
Jaundice	3.126	1.515	6.451	9.512	**0.002**
Non-curative operation	3.929	1.794	8.605	11.703	**<0.001**
Wedge resection versus segment IVb/V	2.395	0.923	6.210	3.226	0.072
Adjacent organ or structure resection	2.343	1.202	4.570	6.246	**0.012**
Grade 3 versus grade 1-2	3.376	1.671	6.820	11.504	**<0.001**
LVI	3.235	1.485	7.046	8.740	**0.003**
PNI	2.005	0.958	4.197	3.407	0.065
Location					
Corpus	1.689	0.727	3.924	1.486	0.223
Neck	0.901	0.190	4.266	0.017	0.896
Multiple	N/A	-	-	-	-
Diffuse	1.969	0.754	5.138	1.915	0.166
Total number of lymph nodes	0.990	0.952	1.029	0.280	0.597
Standard plus paraaortic lymphadenectomy	0.727	0.274	1.928	0.411	0.521
AJCC 8th ed. stage	2.696	1.740	4.177	19.708	**<0.001**
T stage	4.376	2.066	9.267	14.866	**<0.001**
N stage	4.456	1.784	11.128	10.239	**<0.001**
M stage	2.408	1.187	4.886	5.926	**0.015**

CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, LVI: Lymphovascular invasion, PNI: Perineural invasion, AJCC 8th ed.: American Joint Committee on Cancer 8th edition, CI: Confidence interval, HR: Hazard ratio, N/A: Not applicable.

*The effect of every 100-unit increase in carbohydrate antigen 19-9 level on overall survival.

Less than 60 years for age, male factor, incidental diagnosis, postoperative diagnosis, curative operation, the resection of segment IVb/V, Grade 1-2, location in the fundus, standard lymphadenectomy, M0 for M stage and the absence of jaundice, adjacent organ or structure resection, LVI, and PNI were taken considered as reference category. The measurements of serum CA 19-9, serum CEA and total number of lymph nodes were taken into the model as continuous variables. On the other hand, AJCC 8th ed. stage, T stage and N stage were treated as ordinal variables.

Table 6. Results of multivariate Cox proportional hazards regression model via the backward stepwise elimination procedure for determining predictors affecting overall survival

	HR	95% CI for HR		p
		Lower limit	Upper limit	
Age≥ 60 years	4.506	1.127	18.023	**0.033**
Serum CEA*	1.041	1.005	1.078	**0.023**
Grade 3 versus grade 1-2	5.144	1.641	16.127	**0.005**
AJCC 8th ed. Stage**	2.568	1.354	4.870	**0.004**

CEA: Carcinoembryonic antigen, AJCC: American Joint Commission on Cancer 8th edition, CI: Confidence interval, HR: Hazard ratio.

Less than 60 years for age, and Grade 1-2 were taken as reference category.

*Effect of each 1-unit increase in serum CEA on overall survival

**Effect of each 1-step (e.g., Stage 2 vs 3 or Stage 3 vs 4 etc.) increase in AJCC stage on overall survival.

of extended regional lymphadenectomy was evaluated without any discrimination of stages due to the insufficient number of cases, and no significant effect on survival was found.

Advanced patient age and high tumor grade have been shown to be independent poor prognostic factors reducing OS in the literature (22,23). We also found that being ≥60 years of age and having grade 3 tumor were independent factors that reduced OS. Ouchi et al. have found that LVI and PNI, in addition to high tumor grade, were significantly associated with lower survival (24). Choi et al. have shown that LVI was an independent prognostic factor for OS; however, they did not find the effect of PNI to be significant (18). In our series, LVI significantly shortened OS; however, although such a trend was detected for PNI, it was not significant.

Univariate and multivariate analyses revealed that high serum CA19-9 and CEA levels were significantly associated with poor prognosis in resectable GBC, suggesting that they can be used as independent prognostic markers (25). In the present study, both were significantly associated with poor prognosis on the univariate analysis, whereas only CEA was an independent factor on the multivariate analysis.

IGBC has a better prognosis overall than does non-IGBC, which may result from its tendency to be detected at earlier stages (5,6). In our series, IGBC cases comprised 45.3% of all cases, and the incidence of advanced T stage, advanced AJCC stage, and LVI was significantly higher in non-IGBC patients. The incidence of jaundice, N stage, M stage, grade 3, and PNI also tended to be higher, but the difference was not statistically significant. In the univariate analysis of survival of patients with non-IGBC and IGBC, non-IGBC was a predictor of poor prognosis and was not an independent factor in the multivariate analysis. Patients with IGBC who were diagnosed intraoperatively and underwent radical resection simultaneously had significantly worse survival than those who were diagnosed postoperatively and underwent radical resection as a secondary operation. These results were similar to those reported by Schauer et al. (5) and He et al (26). He et al. have suggested that this may have been because the postoperative diagnostic group was subjected to a more comprehensive preoperative radiographic evaluation and underwent higher quality surgical procedures (26).

The present study has some limitations. First, it is a retrospective study, which carries an inherent risk of selection bias. Second, it includes data from a single center and a relatively low number of patients, precluding subgroup assessments.

CONCLUSION

In conclusion, individualized prognostic assessment is necessary in the treatment of GBC. Well-established prognostic factors whose effects have been confirmed along with standard anatomical staging may be of benefit in treatment planning and clinical decision-making.

Ethics Committee Approval: Approval for the study was obtained from Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Protocol number: 2021/65, Approval date: 02.15.2021).

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ORİJİNAL ÇALIŞMA-ÖZET
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Safra kesesi kanserinin cerrahi tedavisi sonrasında uzun dönem sonuçlar ve prognostik faktörler

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ÖZET

Giriş ve Amaç: Safra kesesi kanseri nispeten nadir olup, geleneksel olarak kötü bir prognoza sahip olduğu kabul edilir. Klinikopatolojik özelliklerin ve farklı cerrahi tekniklerin prognoza etkileri konusunda tartışmalar mevcuttur. Bu çalışmanın amacı, cerrahi olarak tedavi edilen safra kesesi kanserli hastaların klinikopatolojik özelliklerinin uzun dönem sağkalımları üzerine etkilerini araştırmaktır.

Gereç ve Yöntem: Kliniğimizde Ocak 2003 ile Mart 2021 tarihleri arasında tedavi edilen safra kesesi kanseri hastalarının veri tabanını geriye dönük olarak analiz ettik.

Bulgular: Değerlendirilen 101 vakanın 37'si inoperabl idi. On iki hasta cerrahi bulgulara göre anrezektabl olarak saptandı. Elli iki hastaya küratif amaçlı rezeksiyon yapıldı. bir, üç, beş ve 10 yıllık sağkalım oranları sırasıyla %68,9, %51,9, %43,6 ve %43,6 idi. Medyan sağkalım 36,6 aydı. Tek değişkenli analizde; ileri yaş, yüksek karbonhidrat antijeni 19-9 ve karsinoembriyonik antijen seviyeleri, non-insidental tanı, insidental vakalarda intraoperatif tanı, sarılık, komşu organ/yapı rezeksiyonu, *grade* 3 tümörler, lenfovasküler invazyon, yüksek T, N1 veya N2, M1 ve yüksek AJCC evreleri kötü prognostik faktörler olarak bulundu. Cinsiyet, *wedge* rezeksiyon yerine IVb/V segmentektomi yapılması, perinöral invazyon, tümör lokasyonu, çıkarılan lenf nodu sayısı ve genişletilmiş lenfadenektomi genel sağkalımı anlamlı olarak etkilemedi. Çok değişkenli analizde, sadece yüksek AJCC evreleri, *grade* 3 tümörler, yüksek karsinoembriyonik antijen seviyeleri ve ileri yaş kötü prognozun bağımsız öngörücüleriydi.

Sonuç: Safra kesesi kanseri için tedavi planlaması ve klinik karar verme, standart anatomik evreleme ve diğer doğrulanmış prognostik faktörlerle birlikte bireyselleştirilmiş bir prognostik değerlendirme gerektirir.

Anahtar Kelimeler: Safra yolu cerrahi prosedürler, safra kesesi neoplazmı, prognostik faktörler, sağkalım

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