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Prognostic Factors in Gallbladder Cancer

Osman Bandırmalı¹ , Zeki Yılmaz² , Türkmen Bahadır Arıkan³

ABSTRACT

Objective: Gallbladder cancer (GBC) is a tumor with poor prognosis, which is rarely seen and challenging to diagnose. Gallbladder cancer is followed by stomach, colon and pancreatic cancers among gastrointestinal system cancers with different geographical distribution. There are different approaches in surgical treatment. Thus, our clinic's experience of GBC has been evaluated retrospectively.

Materials and Methods: Patients with GBC who were referred to Erciyes University Faculty of Medicine between 2003 and July 2018 were evaluated concerning their demographic characteristics, symptoms, diagnostic methods, surgical treatment, morbidity, mortality and follow-up results.

Results: Of the 1979 cholecystectomy performed in our clinic, 40 (2.0%) had GBC. Of all cases, 21 were male, 19 were female and the mean age was 67 (56–94). The most common symptom was abdominal pain (30%) and jaundice (15%). Abdominal ultrasonography, CT (computerized tomography) or MR (magnetic resonance imaging) were performed for diagnostic purposes. In addition to the diagnosis of cholelithiasis or cholecystitis, 10 (25%) of these patients had asymmetric wall thickness, CA 19–9 height or a tumor mass in the gallbladder, suggesting malignancy in preoperative examinations. Adenocarcinoma and subtypes were found in 33 cases and other malignant types in three cases and dysplasia in four cases after pathologic evaluation. In the follow-up, 31 cases were lost in 0–48 (mean 14.4) months. Nine cases have been monitored for 0–48 (mean 27) months as they are alive.

Conclusion: GBC is a complicated disease with poor prognosis, which is usually diagnosed post-operative, despite surgical treatment.

Keywords: Cancer, gallbladder, histological type, stage

Cite this article as:
Bandırmalı O, Yılmaz Z, Arıkan TB. Prognostic Factors in Gallbladder Cancer. Erciyes Med J 2020; 42(4): 457-62.

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Submitted
09.12.2019

Accepted
30.06.2020

Available Online Date
27.10.2020

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INTRODUCTION

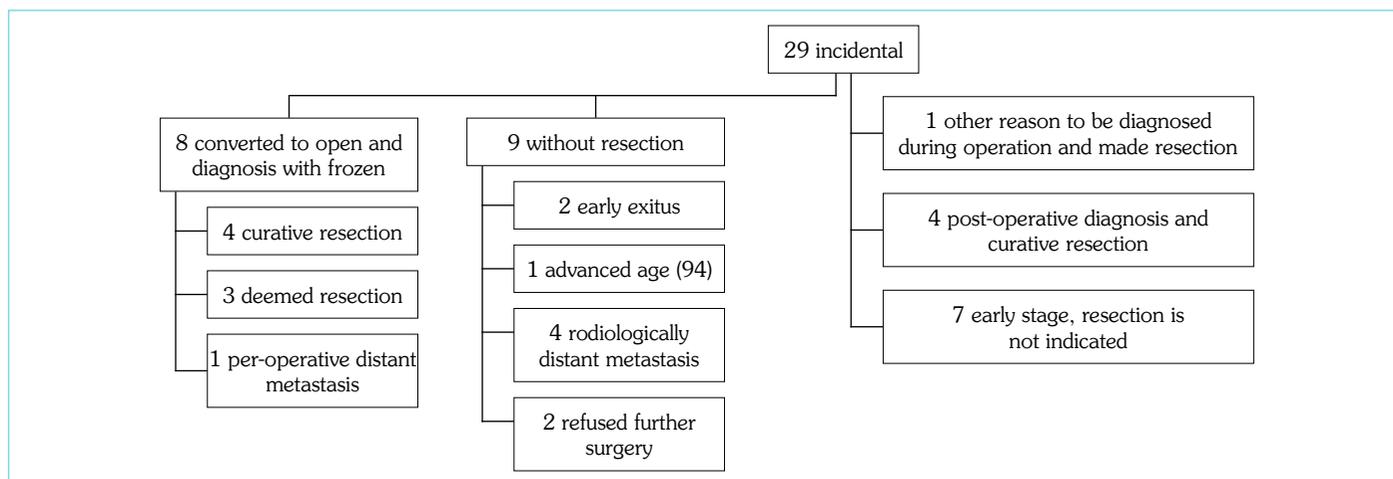
Gallbladder cancer (GBC) is a rare adenocarcinoma originating from the bile duct mucosa. GBC differs from occlusion and clinical manifestations without reaching large sizes. The cases are most frequently present with clogged hunger. Due to the progression of clinical, radiologic imaging (1), the rate of biliary cancer diagnosis and resectability is now increasing. Systemic pathology is a frequent group of diseases that may cause complaints, such as jaundice, pruritus, right upper quadrant pain, nausea, vomiting. The most common causes are stones, inflammation and tumors. Treatment should be directed in this direction by exposing the cause quickly and accurately. Today, liver resection is defined as a standard curative surgical treatment for bile duct surgery, where it is indicated and feasible. Surgical resection is the only treatment option that increases survival in biliary cancer. This study aims to investigate the factors that determine prognosis in bile duct cancer, to investigate the effects of the surgery on the survival and the other factors affecting the survival, to increase survival and share our 15 years of experience. This study included cases diagnosed with biliary cancer of the Erciyes University Faculty of Medicine or surgical resection.

MATERIALS and METHODS

This study was conducted with the decision of the ethics committee of Erciyes University Faculty of Medicine numbered 2018/257. Forty patients with biliary cancer or premalign who were admitted to the Erciyes University Faculty of Medicine between 2003 and 2018 were included in this study. The electronic and written files of these patients were retrospectively reviewed and pre-operative and post-operative information was compiled. In the cases, age, sex, preoperative radiological diagnosis, post-operative pathologic diagnosis, tumor stages, postoperative survival times, preoperative serum bilirubin, and CA 19–9 values were evaluated. TNM system of AJCC (The American Joint Committee on Cancer) was used in the tumor stage. In post-operative pathology reports, data were recorded by removing haematoxylin-eosin stained preparations from the pathology archive of patients whose invasion status was not clearly evaluated and re-evaluating them.

Table 1. Comparison of demographics and symptoms at presentation

	Incidental (n=29)		Non-incidental (n=11)		Total (n=40)		p
	n	%	n	%	n	%	
Age (years)	66.8 (±16.8)		63.0 (±12.0)		67 (±15.6)		0.310
Gender							
Male	17	58.6	4	36.3	21	52.5	0.214
Female	12	41.3	7	63.6	19	47.5	
Pain	7	24.1	7	63.6	14	35	0.912
Jaundice	1	3.4	6	54.5	7	17.5	<0.001
Cholelithiasis	1	3.4	7	63.6	8	20	0.484

**Figure 1.** Classification of incidental 29 GBC patients

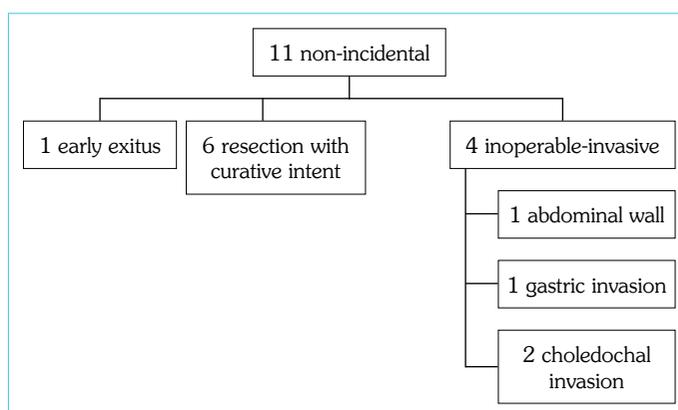
Statistical Analysis

For statistical study purposes, age, sex, pathology types, stages and survival were compared in the cases. One way ANOVA test, chi-square test and Kruskal-Wallis test were used for this purpose. Statistical evaluation of the findings was performed using the IBM SPSS 22.0 package program. A statistically significant relationship/difference was accepted when $p < 0.05$ in the analyses performed. The normality test, in which the numerical data were normally distributed, was evaluated. Median survival was calculated using the Kaplan-Meier test.

RESULTS

Of the 1979 cholecystectomy performed in our clinic, 40 (2.0%) cases had gallbladder cancer or pre-malignant lesions. Thirty-five adenocarcinomas and five pre-malign lesions were detected. Of all cases, 21 were male and 19 were female. The most common symptom was abdominal pain (30%) and jaundice (15%) (Table 1). Abdominal ultrasonography, CT (computerized tomography) or MR (magnetic resonance imaging) were performed for diagnostic purposes. Eleven patients (28%) were diagnosed with a pathological examination of the lesion during the operation (frozen section). One case was diagnosed with tru-cut biopsy and all remaining cases were laparotomized.

Age distribution of the 35 patients who came as pathologic adenocarcinoma was 30–39 (1 patient), 40–49 (3 patients), 50–59

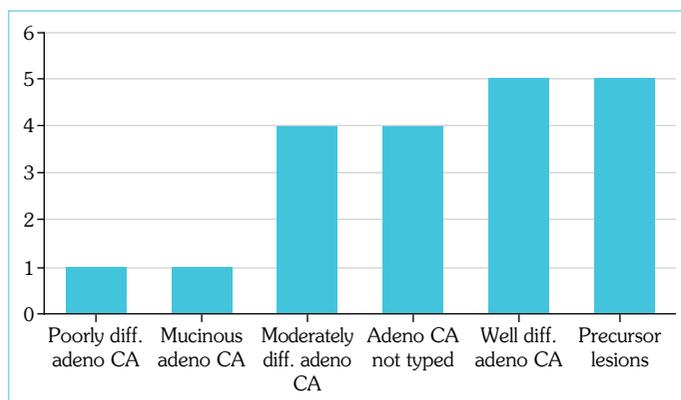
**Figure 2.** Classification of non-incident 11 GBC patients

(7 patients), 60–69 (11 patients), 70–79 (6 patients), 80–89 (6 patients), and over 90 (1 patient). The disease was most frequently found in the 60–69 age group (31.4%). 88% of the cases are over 50 years old. Figure 1 shows the classification of incidental 29 GBC patients. Figure 2 shows the classification of non-incident 11 GBC patients. R0 resection means microscopic margin negative resection (Table 2). There were pre-operatively five (70%) bilirubin and CA 19–9 elevations in seven patients who had radiologic findings and preoperative malignancy preoperatively, which could be compatible with gall bladder cancer. In the radiological findings of these patients, findings, such as asymmet-

Table 2. Comparison of resections in patients with incidental versus nonincidental GBC

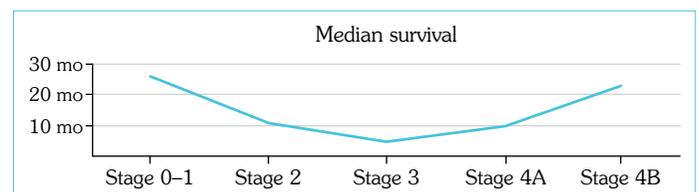
	Incidental (n=29)		Non-incidental (n=11)		Total (n=40)		p
	n	%	n	%	n	%	
R 0 resection	10	34.5	2	18.1	12	30	0.832
Liver resection	8	27.6	6	54.5	14	35	0.115
Stage 0–I	6	20.6	1	9	7	17.5	0.005
Stage II	5	17.2	0	0	5	12.5	
Stage III	12	41.3	5	45.4	17	42.5	<0.001
Stage IV	6	20.7	5	45.4	11	27.5	0.002

GBC: Gallbladder cancer

**Figure 3.** Post-operative pathology types of 20 patients who underwent cholecystectomy for benign causes and pathologic malignancy or pre-malignancy

ric thickening on the gallbladder wall of the USG, CT or MR, or mass on invasive bile were detected in the liver. Three of these seven patients had a liver 4B-5 resection, but the remaining four patients were not suitable for resection because one patient had abdominal wall invasion, one patient had gastric invasion and two patients had a choledochal invasion. These seven patients had TNM stages: Stage I (1 patient), Stage II (1 patient), Stage III (3 patients), Stage IV (2 patients). The survival rate of six patients was 10 months on average. The mean age of the resectionable group was 63.6 (excluding living), and the mean age of inoperable patients was 74. Patients with the resectable group were found to have stage I. Others advanced stage III (1 patient), stage IV (2 patients), inoperable patients stage II (1 patient), stage III (2 patients). The mean survival of the resectable group was 14 months (except for live), and the mean survival of inoperable patients was 6.6 months, but not statistically significant ($p=0.915$).

The number of patients with malignancy after post-operative pathology was 20 after benign causes (stone, cholecystitis, hydrops gall bladder) cholecystectomy in our clinic or external center. In the pathology results of these patients, five were well-differentiated adenocarcinoma, four were moderately differentiated adenocarcinoma, one was poorly differentiated adenocarcinoma, one was mucinous adenocarcinoma, four were non-typing adenocarcinoma, three were high-grade dysplasia, one was low-grade dysplasia, one was intracystic papillary neoplasm (Fig. 3).

**Figure 4.** Median survival distribution according to the stage of 40 patients with GBC

One patient was lost in the post-operative early period and no resection was performed. Two patients were considered inoperable because of the metastasis of PET-CT after the first surgery, and one of them had peripancreatic LAP resultant metastasis on post-operative follow-up. Post-operative pathology was diagnosed as mucinous adenocarcinoma in one patient and it was determined as inoperable because it was a peritoneal implant and CT was taken on the first surgery. After that, tumor recurrence was detected at the epigastric port site in the follow-up post-op one year. One patient underwent pre-operative pulmonary adenocarcinoma diagnosis and follow-up cholecystectomy pathology did not plan for advanced surgery due to bile duct adenocarcinoma and was directed to oncology. One patient with stage 4A who underwent complementary resection in our clinic was followed up for 11 months as alive.

Eleven patients received a malignant diagnosis due to a frozen section sent peroperatively after being operated for benign reasons. Six of these patients underwent surgery for hepatic segment 4B-5 resection. Three of these patients were stage III, three of them were stage IV, and the mean survival was 11.8 months. Five of these 11 patients were not eligible for resection because three patients had duodenum-small intestines invasion, one was unresectable, and one had omental implants. Stages of five patients without complementary resection; stage III (3) and stage IV (2). Mean survival was 43 months and the right four months survival was six months, but no statistically significant difference was found ($p=0.825$).

Mean survivals according to the stages of 40 patients with GBC are shown in Figure 4, Figure 5, Figure 6, Table 3 and Table 4. Mean survival rates of 40 patients with GBC compared to each other are shown and the comparison of Stage 3 and Stage 0–1 groups was statistically significant ($p=0.015$), while the others were not significant.

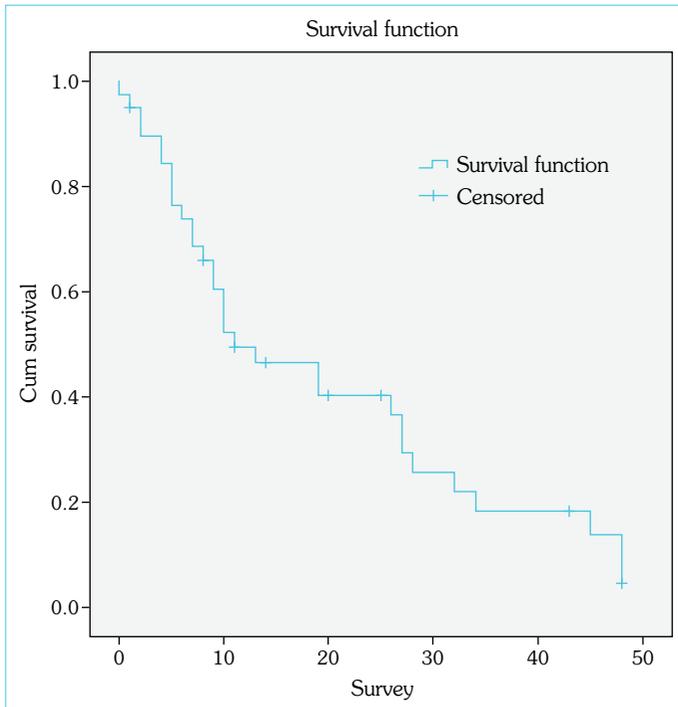


Figure 5. Cumulative survival totally

DISCUSSION

An estimated 386,300 new cases and 150,200 deaths from gallbladder cancer occurred in 2008 worldwide. Incidence and mortality age-standardized rates (ASR) are higher in females worldwide, except in some Asian countries like the Republic of Korea and Japan, where the highest ASR values are in men (2). However, in our study, it was seen that the ratio of female to male was 19/21. The incidence of gallbladder cancer in patients undergoing cholecystectomy varies from 0.19% to 3.3% in the literature (3). Of the 1979 cholecystectomies performed in our series, 40 (2.0%) had biliary cancer or premalign lesions. Biliary cancer has been reported in approximately 1% of acute cholecystitis cases (4). In our series, five patients underwent surgery for acute cholecystitis and underwent a frozen section for gallbladder cancer. Those with a diameter greater than 10 mm in biliary polyps carry the risk of GBC (5). In our study, 2.5 cm polyps were detected in the preoperative USG of one patient included. The survival of the patient was 45 months. Stage II, well-differentiated adenocarcinoma was detected in the post-operative pathology of this patient. More than two-thirds of individuals diagnosed with gallbladder cancer are over the age of 65 years, with the average age of diagnosis being 72 years (6). In our study, peak age range was seen as 60–69 age group (27%).

GBC causes diagnostic confusion with biliary sickness being associated with other diseases. Clinical findings of the cases are mixed with gallstones and bile duct stones. The most common clinical finding is pain, nausea, vomiting, jaundice and a palpable mass in the right hypochondrium. In our series, abdominal pain was seen in most cases, followed by jaundice. Clinical findings, however, did not help the differential diagnosis. Thus, preoperative radiological examinations are investigated, but preoperative diagnosis is not possible at a significant rate (1). Ultrasonography (USG) is the most commonly used imaging modality in cases with complaints related

Table 3. Survival time for groups and in total

	Patients (n=40)	Median (min.–max.)	Mean±SD
Stage 0–I	7	25 (9–48)	28.72±5.85
Stage II	5	9.5 (5–45)	27.50±8.05
Stage III	17	4.5 (0–48)	14.60±4.87
Stage IV	11	11 (1–32)	16.90±3.43
Total	40	27 (0–48)	19.70±2.76

SD: Standard deviation. The results are given in months as both median (minimum-maximum) and mean±SD

Table 4. Survival analysis with Kaplan Meier and Logrank Test

Groups	p
Stage 0–I vs II	0.091
Stage II vs III	0.668
Stage III vs IV	0.807
Stage I vs III	0.015
Stage I vs IV	0.052
Stage II vs IV	0.283

to biliary diseases, whereas the sensitivity of USG in biliary cancer is 44% (7). In addition, the status of ultrasound should be discussed in the definition of resectability. If pre-operative GBC can be diagnosed, unnecessary laparotomy should be avoided in unresectable cases. In our series, eleven patients who underwent cholecystectomy for benign causes and diagnosed with malignancy during the operation were re-evaluated, and bilirubin and CA 19–9 were elevated in preoperative examinations. In USG of four patients, solid tumor suspicion or bile duct fundus thickening was detected. When retrospectively re-evaluated pre-operative CT images of these 11 patients, asymmetric wall thickening was detected in five patients, which may be confused with malignancy. In our cases, preoperative USG findings were found to be inoperable in five of benignly reported patients such as cholelithiasis or cholecystitis. USG and CT had low sensitivity in GBC (36% and 45%). When CT is also ionisable and contrast-related complications are considered, there is a need to investigate other imaging modalities, such as MRCP or cholescintigraphy (HIDA), when these patients are detected preoperatively. In our series, MRCP was not performed in patients. CA 19–9 and bilirubin elevation were suspicious for GBC and malignancy, but sensitivity was low (18%). More sensitive and specific tests are needed for the diagnosis of GBC.

GBC should be evaluated using CT or MR with preoperative USG in elderly patients who are referred for cholelithiasis or cholecystitis because of their more frequent appearance in older ages and surgical planning should be made carefully. Because of the lack of specific signs and symptoms in biliary cancer, early diagnosis is very rare. Laparoscopy was frequently used to evaluate the origins and spread of gastrointestinal tumors in previous years. Ultrasonography and CT, however, nowadays have been replaced by laparoscopy in many cases. However, laparoscopy seems to be more advantageous than open exploration and biopsy because of its relatively minimal invasive procedure, especially for advanced bile duct

cancers, which cannot be used for surgery in patients with comorbid diseases. In addition, diagnostic laparoscopy can also free the patient from an unnecessary laparotomy and evacuate the external bilateral drainage in the same session. Today, interventional radiology is also a non-invasive technique. In our series, one patient was diagnosed with a true-cut biopsy by interventional radiology.

No additional operation is needed when in situ bile duct cancer (stage 0) is detected incidentally after cholecystectomy. In our series, in situ cancer was detected in five patients (12.5%). Laparoscopic cholecystectomy was performed in this patient and the patients were followed up alive at 10, 25, 26, 27 and 48 months. Cholecystectomy is the only surgical option in stage I patients (8). Five years of survival in patients treated in this way is 100%. In our series, two patients were diagnosed as stage I, histologically well-differentiated adenocarcinoma according to pathology after laparoscopic cholecystectomy and these patients were followed for 19 months and 48 months alive. In GBC, four and five liver segments are the most commonly involved sites. At the time of diagnosis, penetration depth and lymph node involvement are directly proportional to the tumor. In our series, 36–65% of the cases were diagnosed with lymph node involvement, and 45% to 67% of the cases had liver spread and 30% had peritoneal metastasis.

Some categorizations based on primary tumor spread, lymph node involvement and metastatic spread have been done to define the prevalence of GBC. Thus, it has been tried to determine the prognosis and treatment modalities of GBC. However, there are difficulties with GBC. In addition to preoperative diagnosis with USG and CT, some of the cases are suspected of having difficulty in the dissection of the gall bladder during surgery, metastatic spread in the peritoneum and detection of tumoral occlusion. Only five (12.5%) patients were referred to PET-CT or MR for metastasis or liver invasion in our series.

Cholecystectomy is recommended for stage I patients, and extended cholecystectomy is recommended for stage II patients. It is emphasized that hepatectomy is necessary for the cure in hilus involvement when it is sufficient to remove GBC with a 2 cm release limit (9). Of the 40 retrospective patients studied in our study, five of 11 patients who were suspected of biliary cancer as a preoperative option were found to be inoperable and six were operable in terms of complementary liver resection. The mean survival of these patients was six months (1 patient alive) and 11.8 months, respectively, but no statistically significant difference was found between them. Of these five inoperable patients, three were invasive to the duodenum-small intestine, one was unresectable, and one had an omental implant. All of the 11 patients who were operated on for benign causes and malignancy during the operation were in advanced stage (stage III-IV). Mean survival (excluding one patient who followed alive) was 9.5 months. When the preoperative difference was noticed, it was observed that the disease was advanced stage and the survival of these patients was low.

There were statistically significant differences between the median survival of the 40 patients with GBC compared to each other, and the median survival of Stage 0-I and Stage III patients. According to this, as the stage progresses, median survival decreases in GBC. The lack of a statistically significant difference in the comparison

between the other groups may be due to the small number of patients. We think that this difference will be significant in a larger series. While the median survival of patients in Stage III and Stage IV is expected to decrease, survival in our series is increasing, which we think may be caused by patients with a median survival of 32 months and 43 months in Stage III and IV.

In addition to cholecystectomy, only two of 14 patients who had a pre-operative diagnosis, frozen section and decision-making or post-operative diagnosis and complementary surgery were early-stage. GBC is predominantly (85%) advanced at diagnosis at the time of diagnosis, even if it is diagnosed as complementary surgery.

The most common gallbladder cancer is adenocarcinoma. Known histological subtypes include: biliary, intestinal, gastric foveolar, mucinous, stony ring cell, clear cell, cribriform, adenosquamous, squamous, hepatoid, carcinosarcoma and undifferentiation. In our cases, adenocarcinoma was found in 26 cases (65%) and mucinous adenocarcinoma (10%) in four cases, anaplastic cancer in one case (2.5%) and undifferentiated large cell cancer in one case (2.5%).

Prognosis is good if gallbladder cancers are limited to mucosa only. However, the prognosis is poor if cancer has retained the musculature and serosa. Prognosis is poor if peritoneal spread, fat layer involvement between the bile duct and liver tissue. In addition, hepatic parenchymal and lymphatic plexus involvement is quite rapid. In a mucosal limited early-stage gallbladder cancer, the 5-year survival rate is 100%, but in cases with serosal involvement, this rate falls below 5% (10). In our series, two patients with mucosa-limited carcinoma (stage I) were followed alive (100%), only three patients were followed for 11 months, 34 months, and 43 months, respectively, in the more advanced stage (8.5%).

In the cases where GBC is detected after the operation, it should be discussed whether reoperations should be performed or not. Resection of the tumor with a negative surgical margin was reported to prolong survival (10). In our series, 20 patients with benign causes and post-operative pathologic malignancies were able to undergo complementary resection in three (9%) of the advanced stage (stage III-IV) (33%). One case of this group was followed for 11 months as alive.

The use of laparoscopic cholecystectomy increases the number of post-operative GBC. However, the removal of the gall bladder without using endobag causes the tumor cells to plant the surgical field, contamination and worsens the prognosis (11). Various isolation methods are used to prevent the bile duct tumor from spreading during surgery. Care is taken that the tumor does not come into contact with the incision. Benign laparoscopy can be performed with the endobag of the sac outside the abdomen. However, this procedure is not routinely used. In our study, one patient with a diagnosis of mucinous adenocarcinoma was diagnosed as inoperable because of the presence of a peritoneal implant on the CT of the first surgery, and the oncologic orientation of the patient was followed up, tumor recurrence at the site of the epigastric port at the first postoperative year.

If gallbladder cancer is suspected in patients with benign laparoscopic cholecystectomy, cholecystectomy should be completed, and cholecystectomy should be extended if it is proven to be fro-

zen. Patients who underwent cholecystectomy should be careful after discharge, and surgical treatment should be planned early in patients who require complementary surgery.

The most significant factor showing the effectiveness of surgical treatment that determines the prognosis in biliary cancer is the tumor's stage. The 5-year survival rate for tumors limited to the mucosa and musculoskeletal is about 100%, while 5-year survival rates for tumors invading the liver using adjacent neoplasms or lymph node spread are 10%. Therefore, patients with distant metastases (M1) should not be considered candidates for a curative surgery because of the radiological or clinical evidence of para-aortic ganglion metastasis (12). In our series, five patients with stage 4 were considered inoperable for the mentioned reasons.

CONCLUSION

The prognosis of gallbladder cancer is very poor. Histopathological follow-up of all cholecystectomy materials should be prepared carefully considering the correlation with gallstones. Surgical treatment of gallbladder cancer is still an outstanding treatment. Because gallbladder cancer is relatively rare compared to other cancers of the digestive system, surgical treatment does not allow for a randomized, prospective study of options. By increasing the number of studies and case series in this subject, the factors affecting the diagnosis, treatment and results will be clarified more clearly.

Ethics Committee Approval: Ethics committee approval was fort his study from the ethics committee of Erciyes University Faculty of Medicine (date: 09.05.2018, number: 2018/257).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ZY, OB; Design – ZY, OB, TBA; Supervision – ZY, OB, TBA; Materials – ZY; Data Collection and/or Processing – OB; Analysis and/or Interpretation – OB, TBA; Literature Search – OB, TBA; Writing – OB; Critical Reviews – ZY, OB, TBA.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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