Journal of Gastrointestinal Cancer (2019) 50:451–457
https://doi.org/10.1007/s12029-018-0099-y

ORIGINAL RESEARCH

Prognostic Factors for Operated Gallbladder Cancer

Bala Basak Oven Ustaalioglu[1] · Ahmet Bilici[2] · Mesut Seker[3] · Umut Kefeli[4] · Dincer Aydin[5] · Serkan Celik[1] · Tarik Demir[3] · Burcak Erkol[1]

Published online: 10 April 2018

Abstract

Purpose The prognosis of gallbladder cancer is poor. Lymph node metastasis and the stage are known to be the strongest prognostic factors for survival. The aim of this study was to determine the importance of complementary surgery and other prognostic factors for survival of operated gallbladder cancer.

Material and Method We retrospectively analyzed 62 localized gallbladder cancers. The prognostic factors for survival were evaluated by univariate and multivariate analysis.

Results The 3-year overall survival (OS) and disease-free survival (DFS) rates were 52.8 and 43.5%, respectively. Totally, 37 patients (59.6%) were diagnosed incidentally during simple cholecystectomy which was performed for benign causes but only 56.4% of them underwent complementary surgery. 51.6% of the recurrence was detected during 18.4 months of follow-up time. R0 resection, T stage, and pathological stage were found to be related with both OS and DFS by univariate analysis. Grade, lymph node metastasis, and adjuvant chemotherapy were also related with DFS. Presence of recurrence, recurrence side, performance score (PS), and perineural invasion (PNI) were related with OS. Peritoneal metastasis, advanced stage disease, and lymph node metastasis were more common among patients who did not undergo complementary surgery. Adjuvant chemotherapy was given more frequently to patients who undergone complementary surgery group. The multivariate analysis indicated that grade, lymph node metastasis, stage, recurrence site, PS, and adjuvant chemotherapy stage were independent prognostic factors for DFS on the other and only stage was a prognostic factor for OS.

Conclusion Our results showed that incidental diagnosis or complementary surgery was not related with DFS or OS but stage was only an independent prognostic factor for both OS and DFS in resected gallbladder cancer.

Keywords Gallbladder · Cancer · Operation · Prognostic factors

Introduction

Gallbladder cancer is the most common biliary tract cancer and has a dismal prognosis because of low rate of patients that can undergo curative surgery [1]. Most gallbladder cancers are adenocarcinoma (80%) and tumors tend to invade adjacent structure like liver parenchyma, bile duct, and regional lymph nodes [2]. Only third of all gallbladder cancer can be diagnosed preoperatively [3]. In most patients, tumors are diagnosed by a pathologist after simple cholecystectomy which was performed for benign disease and termed as incidental gallbladder cancer [3]. In the literature, incidental gallbladder cancer has been reported to have a rate of 0.9–2.8% [4]. The prognosis of the incidental gallbladder cancer was related with tumor surgical approach which was performed complementarily and postoperatively or performed together with the first cholecystectomy that did not influence the prognosis as long as R0 resection is achieved [5].

Gallbladder cancer is a very aggressive tumor with a 5-year overall survival (OS) rate of 3–13% [6]; even after curative surgery, it is nearly 17 to 45% [7]. It was reported that only

✉ Bala Basak Oven Ustaalioglu
basakoven@yahoo.com

[1] Medical Oncology, Haydarpasa Numune Education and Research Hospital, Selimiye Mah, Şair Nesimi sok, Kardeşler Apt. No: 1, Daire:4, 34668, Uskudar, Istanbul, Turkey

[2] Medical Oncology, Medipol University, Istanbul, Turkey

[3] Medical Oncology, Bezm-i Alem Vakıf Gureba University, Istanbul, Turkey

[4] Medical Oncology, Kocaeli University, Istanbul, Turkey

[5] Medical Oncology, Kartal Education and Research Hospital, Istanbul, Turkey

16.5% of the patients who underwent curative surgery could survive 5 years [8].

Although simple cholecystectomy is considered to be curative for T1a tumor, deep invasion included muscular layer, radical cholecystectomy included hepatic resection, and lymphadenectomy and bile duct resection if involved are recommended [9]. The residual disease is the most important prognostic factor for recurrence [10]. Lymph node metastasis, surgical margin, grade, lymphovascular invasion (LVI), perineural invasion (PNI), and tumor stage have been reported as important prognostic factors for OS and disease-free survival (DFS) [5, 10–12].

Studies including adjuvant therapy in gallbladder cancer are mostly retrospective. The 5-year OS was reported better in the adjuvant chemotherapy group compared the control group in Japanese Phase III trial [13]. Adjuvant chemotherapy included gemcitabine, fluoropyrimidines, or combinations of them for gallbladder cancer after surgery has been recommended [14] especially for node-positive disease and R1 disease postoperatively [12].

Because of low incidence of gallbladder cancer, there are a few prospective studies about prognosis and treatment modalities of gallbladder cancer so there are some differences between prognostic factors, surgery modalities, and postoperative treatment strategies with respect to different oncology centers. We reviewed the survival and prognostic factors of gallbladder cancer patients who underwent surgery in five different centers in Istanbul.

Material and Methods

Totally, 62 gallbladder cancer patients who were treated in five different oncology departments in Istanbul between 2008 and 2017 were included study. All patients underwent surgery for gallbladder cancer and patients were classified according to diagnosis time as preoperative diagnosis or gallbladder cancer diagnosed incidentally postoperatively. The first patient was operated on February 16, 2008. The patients were excluded if they had inoperable disease, peritoneal seeding, and paraaortic lymph node metastasis at the diagnosis or had visceral metastasis. The presence of complementary surgery was evaluated if patients had been diagnosed incidentally after simple cholecystectomy. Most of the data of the patients (no: 26) were collected from Haydarpaşa Numune Education and Research Hospital, 14 from Medipol University, 8 from Kartal Education and Research Hospital, 7 from Vakıf Guraba University, and other 7 from Kocaeli University.

This study is a retrospective, observational, and reviewed-based study of medical records of patients in our institutions. Data included clinicopathological characteristics, about age, operation type, histopathology, tumor stage, tumor size, histological grade, lymph node metastasis, and survival, and treatment protocols were obtained from patients' chart after informed consent was received from patients or their relatives. The primary end points were DFS and OS.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. The relationship between clinicopathological factors and the presence of complementary surgery was analyzed by the chi-squared test and Fisher's exact test. Median follow-up time was calculated as the median observation time among all patients. DFS was defined as the time from surgery to the last follow-up and the time until recurrence. In addition, OS was described as the time from diagnosis to the date of the patient's death or last known contact. Survival analysis and curves were established according to the Kaplan-Meier method and compared by the log-rank test. Factors analyzed by univariate analysis were also examined with multivariate analysis by using the Cox proportional hazards model for predicting risk factors for relapse. Multivariate p values were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests and p values less than or equal to 0.05 were considered to be statistically significant.

Results

Totally, 62 patients with gallbladder cancer who underwent surgery were analyzed. The median age of the patients was 61.5 ranging from 38 to 86 years and 66.1% of them were female (41 patients). Gallbladder cancer was diagnosed incidentally in 37 patients (59.6%) who underwent simple cholecystectomy because of benign disease. On the other hand, cancer was known preoperatively in 25 patients (44.4%). Half of them had history of cholelithiasis or gallbladder polyp (9.7%). Operation types were simple cholecystectomy (59.7%), cholecystectomy and lymph node dissection (17.7%), cholecystectomy, lymph node dissection combined with liver resection (19.4%), and debulking surgery (3.2%). Totally, 6 patients underwent minimally invasive surgery. All of these were T1 tumor and these underwent R0 resection without complementary surgery. Although laparoscopic or robotic approaches are accepted approaches for cholecystectomy and lymph node dissection, robotic surgery has not been used standardly for all these centers in Istanbul.

While 41 patients could be operated with R0 resection (66.1%), 12 R1 (19.4%) and 9 R2 (14.5%) resection could be achieved. Gallbladder cancer was diagnosed incidentally after simple cholecystectomy in 37 patients (59.6%) and 12 of

the underwent postoperative complementary surgery defined as lymph node dissection combined with liver resection. Tumor surgery was performed in 35 of the 62 patients (56.4%), 23 of them were performed preoperatively. Among the 23 patients, tumor surgeries were cholecystectomies combined with only lymph node dissection (11 patients), only liver resection (7 patients), or liver resection combined with lymph node dissection (5 patients). On the other hand, 25 patients could not undergo complementary surgery because their surgeons had not recommended extended surgery or patients did not want to undergo surgery. Two debulking surgery was performed with R2 resection. Figure 2 shows the surgery type. The most frequent histopathological type was adenocarcinoma (88.7%) and over half of the tumors were intermediate grade. Nearly two thirds of the tumor was T1 (22.6%) and T2 (51.6%). Pathological stages were stages III (35.5%), II (21%), IV (25.8%), and I (17.7%) in order of frequency. Nearly half of the patients (30 patients) received adjuvant chemotherapy as gemcitabine monotherapy (58.6%), 5-fluorouracil (24.1%), and cisplatin-gemcitabine combination (17.2%). Table 1 shows the results of the descriptive analysis.

At the median follow-up of 18.4 months (range, 1–82.5), recurrence was detected in 32 patients (51.6%). The most common metastatic sites were the liver (8 patients, 57.1%), locoregional (4 patients, 28.6%), peritoneum (1 patient, 7.1%), and multiple (1 patient, 7.1%). The 3-year DFS and OS rates were 43.5 and 52.8%, respectively, and the median DFS and OS were 24.6 (19–30.1) and 74.6 (9.6–139.5), respectively. Figure 1 shows the DFS and OS curves. In the

Table 1 The results of the descriptive analysis

Median age 61.5 (38–86)		
Median DFS 15.1 (1–122)	Median OS18.6 (1–103)	
Characteristics	Number	%
Gender		
Female	41	66.1
Male	21	33.9
Diagnosis		
Incidental	37	59.6
Preoperative	25	40.4
PS		
0	35	56.5
1	23	37.1
2	4	6.5
Cholelithiasis		
Present	31	50
Absent	31	50
Polyp		
Present	6	9.7
Absent	56	90.3
Operation type		
Simple cholecystectomy cholecystectomy + lymph node dissection	37	59.7
Cholecystectomy + lymph node dissection + liver resection	11	17.7
Cholecystectomy + liver resection	12	19.4
Debulking surgery	2	3.2
Surgical margin		
R0	41	66.1
R1	12	19.4
R2	9	14.5
Complement surgery		
Present	35	56.4
Absent	27	43.6
Histopathology		
Adenocancer	55	88.7
Squamous cell cancer	2	3.2
Adenosquamous	4	6.5
Adeno + neuroendocrine	1	1.6
Lymphatic invasion		
Present	31	50
Absent	26	41.9
Unknown	5	.,1
Vascular invasion		
Present	23	37.1
Absent	33	53.2
Unknown	6	9.7
Perineural invasion		
Present	27	43.5
Absent	29	46.8
Unknown	6	9.7
Grade		
Unknown	1	1.6
Low	13	21
Intermediate	36	58.1
High	12	19.4
T stage		
T1a	5	8.1
T1b	9	14.5
T2	32	51.6
T3	15	24.2
T4	1	1.6
N stage		
N1	21	33.9
N2	4	6.5
N0	20	32.3
NX	17	27.4
N cat		
N0	25	40.3
N+	20	32.3
Stage		
1	11	17.7
2	13	21
3	22	35.5
4	16	25.8
Metastasis site		
Liver	8	57.1
Peritoneum	1	7.1
Locoregional	4	28.6
Multiple	1	7.1
Adjuvant chemotherapy		
Present	30	48.4
Absent	32	51.6
Adjuvant chemotherapy type		
Gemsitabine	17	58.6
FUFA	7	24.1
Sisplatin-gemsitabine	5	17.2
Recurrence		
Present	32	51.6
Absent	30	48.4

OS overall survival, *DFS* disease-free survival, *PS* performance score

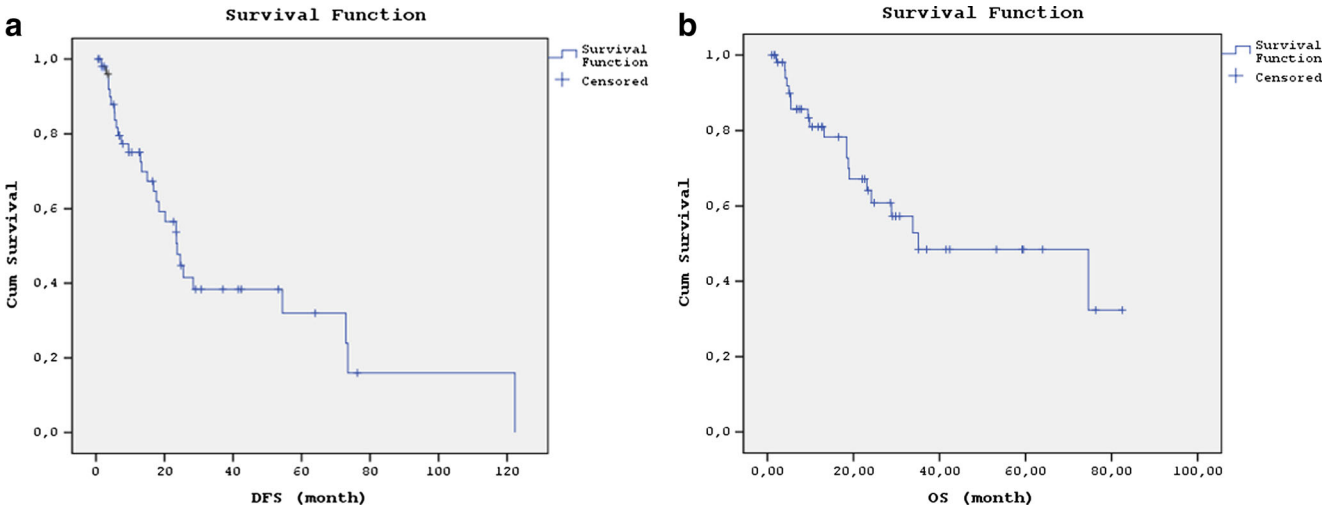

Fig. 1 **a** The DFS curve. **b** The OS curve

univariate analysis, surgical margin ($p = 0.01$), grade ($p = 0.04$), lymph node metastasis ($p = 0.05$), T stage ($p = 0.01$), pathological stage ($p < 0.001$), and presence of adjuvant chemotherapy ($p = 0.05$) were related with DFS; surgical margin ($p < 0.001$), PNI ($p = 0.05$), T stage ($p = 0.01$), pathological stage ($p < 0.001$), performance score (PS) ($p = 0.05$), recurrence ($p < 0.001$), and recurrence site ($p = 0.005$) were found to be important factors in predicting OS. The results of univariate analysis are shown in Table 2. We carried out the multivariate analysis with the Cox proportional hazards model in order to further determine the independent prognostic factors for OS and DFS. While only the pathological stage was the independent factor predicting OS, grade, lymph node metastasis, stage, recurrence site, adjuvant chemotherapy, and PS were all important factors for DFS.

PS ($p = 0.01$), diagnosis type ($p = 0.01$), lymph node metastasis ($p < 0.001$), stage ($p < 0.001$), and presence of chemotherapy ($p = 0.03$) were different between complementary surgery present and absent groups (Fig. 2). Table 3 shows the results of the chi-square test. Patient who underwent complementary surgery had good PS and advanced stage disease, and they had received more adjuvant chemotherapy and disease was diagnosed mostly preoperatively.

Among 35 patients who underwent complementary surgery, the clinicopathological factors were not different between preoperative or incidentally diagnosed groups by the chi-square test. In addition, both median OS ($p = 0.5$) and DFS ($p = 0.3$) were not different significantly. Liver resection also could not find to be related neither OS ($p = 0.3$) nor DFS ($p = 0.1$).

Discussion

Gallbladder cancer is aggressive and one of the most lethal cancers, which is mostly found in an advanced stage so potential curative surgery cannot be possible [15]. Although complete resection is curative for localized disease, there has been controversy worldwide about extend of surgery including liver resection, lymphadenectomy, and bile duct resection. The incidental gallbladder cancer was reported as 0.6–1.5% after cholecystectomy [4]. The survival rate of incidental gallbladder cancer was 21.2–60 months in the literature [16, 17]. Dorobisz et al. found 64 incidental gallbladder cancers among 7317 cholecystectomy material [4]. Because we did not examine all cholecystectomy material, we only reviewed pathology of patients with gallbladder cancer and we did not know true incidence of incidental gallbladder cancer. But nearly 60% of the diagnosis was incidental.

Butte et al. analyzed 261 gallbladder cancer patients who underwent resection in three different centers [15]. They found that the incidental gallbladder cancer rate was 58.2% (152 patients), and majority of the patients underwent complete resection (R0) (61.3%) similarly in our study (66.1%). While partial hepatectomy was performed in 61.5% of their study, only 42% of our patients (26 patients) could undergo hepatic resection. They compared clinicopathological characteristics for three different centers; although there were some differences among presentation, disease extent, and surgical treatment, disease-specific survival was not different. Although we included patients in five different centers, we could not compare the characteristics between different centers because of limited number of patients. In all five centers around Istanbul, patient characteristics and treatment modalities may reflect the other part of Turkey.

It is not clear whether incidental gallbladder cancer patients have a better prognosis compared with the same stage of nonincidental tumors. The median survival was reported as 26.5 months for incidental carcinoma but only 9.2 months for suspected gallbladder carcinoma [18]. On the other hand,

Table 2 The results of the univariate analysis

Characteristics	Median DFS (months)	Range	*p*	Median OS (months)	Range	*p*
Surgical margin			0.01			< 0.001
R0	28.4	0–56		na	na	
R1	na	na		23.1	4.1–42	
R2	6.4	0–13.7		9.7	1–18.4	
Grade			0.04			
Low	na	na				
Intermediate						
High						
Perineural invasion						0.05
Absent				74.6	na	
Present				na		
N categoric			0.05			
N+	18.3	7.8–2.9				
N0	72.9	11.2–134.6				
T stage	na	na	0.01	na	na	0.01
T1a						
T1b						
T2						
T3						
T4						
Stage			< 0.001			< 0.001
1	na	3.9–142		na	na	
2	72.9	13.6–33.3				
3	23.5	3.2–8.6				
4	5.9	19–30.1				
Adjuvant chemotherapy			0.05			
Present	18.3	8.3–28.3				
; Absent	72.9	20.2–125.6				
PS						0.05
0 1				74.6	18.2–130.3	
1 2				24.1	12.7–35.5	
				14.9	0–35.3	
Recurrence				na	na	< 0.001
Present						
Absent						
Recurrence side						0.005
Liver					na	
Multiple					16.1–32.1	
Locoregional					2.4–23.8	
Peritonitis carcinomatosa					3.6–63.9	

OS overall survival, *DFS* disease-free survival, *na* not available, *PS* performance score

the prognosis of the gallbladder cancer which was diagnosed preoperatively or diagnosed incidentally after simple cholecystectomy was not different if curative surgery was achieved [5]. Similar to the literature, the survival was not different between incidentally or preoperatively diagnosed patients in our study.

The recurrence rate after curative surgery was reported as 27–35% [1, 19]. The recurrence rate was higher (51.6%) in our study. It may be related to the complementary tumor surgery rate which was low because of patient refusal or surgical insufficiency. Complementary surgery was mostly performed in patients with better ECOG PS score and early stage disease, and they received more adjuvant chemotherapy than patients without complementary surgery.

Compatible with the literature, the most common recurrence sites of gallbladder cancer was the liver, peritoneum, and locoregional [19]. The recurrence site was also a prognostic factor for OS. While patients with multiple organ metastasis and peritoneal metastasis had the worse survival, patients with liver recurrence had the best survival. The median disease-specific survival was reported as 16.9 months in Butte's study. The 5-year survival of patients with N

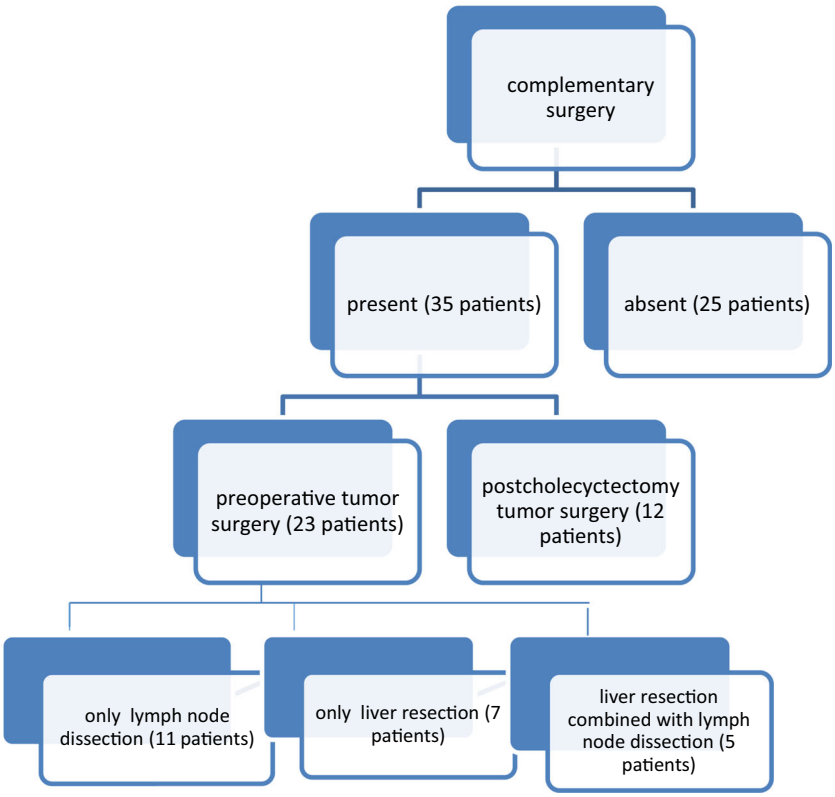

Fig. 2 The results of the complementary surgery

metastasis was reported as 34–42 and 66% for N0 disease [1]. We found the median DFS and OS were 24.6 months (19–30.1) and 74.6 months (9.6–139.5), respectively. OS was not different between patients with lymph node metastasis present or not in our study. On the other hand, the median DFS was longer in N0 patients (3-year DFS rate was 54.4 and 27.5%, respectively). The 3-year OS rates were 44.3 vs 60.3% for N1 vs N0 disease. Because of short follow-up (median 18.4 months) time, we could not report 5-year results.

Table 3 The comparison of the patient characteristics according to presence of complementary surgery

	Complementary surgery		
	Present (%)	Absent (%)	*p*
PS			0.01
0	24 (68.5)	11 (40.7)	
1	11 (31.5)	12 (44.4)	
2	0	4 (14.9)	
Stage			< 0.001
1	3 (8.5)	8 (29.6)	
2	7 (20)	6 (22.2)	
3	20 (57.1)	2 (7.4)	
4	5 (14.4)	11 (63)	
N categoric			< 0.001
N0	18 (51.4)	7 (25.9)	
N+	15 (42.8)	5 (18.5)	
Unknown	2 (5.8)	15 (55.6)	
Adjuvant chemotherapy			0.03
Present	21 (60)	9 (33.3)	
Absent	14 (40)	18 (66.7)	
Diagnosis			0.01
Incidentally	18 (51.4)	22 (81.4)	
Preoperatively	17 (48.6)	5 (18.6)	

In Ahn et al. study, 1.6% of incidental gallbladder cancer was diagnosed among 4629 patients who underwent cholecystectomy [20]. They found that advanced T stage, N stage, positive surgical margin grade, LVI, and PNI were risk factors for recurrence and overall survival but operation type did not affect the prognosis by univariate analysis for incidental gallbladder cancer. On the other hand, older age, lymph node metastasis, grade, and LVI were independent prognostic factors for poor prognosis [20]. In another study, surgical margin, grade, T stage, LVI, and PNI were reported as prognostic factors for DFS [19]. In our study, surgical margin, T stage, and pathological stages were all found to be prognostic for both OS and DFS. On the other hand, T stage and pathological stage were independent prognostic factors for both OS and DFS of patients similar to the literature [1]. Five-year OS rates were reported as 54–100% for T2, 16–63% for T3, and 8–25% for T4 disease (N60) and with respect to pathological stage 33–100% for stage I, 9–33% for II, 0–25% for III, and 0–5% for IV [21]. Three-year OS rates were 56% for T2 and 24% for T3 disease in our study. According to the pathological

stage, 3-year OS rates were 91% for stage I, 26% for II, and 12% for III.

Although R1/2 resected patients were reported to be alive 5.6% in 5 years [5], the 3-year survival rate of our patients was 65, 36, and 0% for R0, R1, and R2 resected patients, respectively ($p < 0.001$). In addition, grade, lymph node metastasis, recurrence site, adjuvant chemotherapy, and PS were all important independent factor for DFS by multivariate analysis. Extent of surgery was found to be related neither OS nor DFS compatible with the literature [19]. We know that adjuvant chemotherapy failed to improve the risk of survival [19]. Different from the literature, patients who received adjuvant chemotherapy had shorter DFS than patients who did not take. It may be related the adjuvant chemotherapy that was given to more advanced T stage tumor; on the other hand, T1 tumor that had better prognosis was observed without adjuvant chemotherapy in our study.

The major limitation of our study was to be retrospective nature, because the data were collected from 5 different hospitals around Istanbul; different surgery or treatment approaches may affect the results.

Conclusion

To the best of our knowledge, pathology reports of simple cholecystectomy should be monitored closely because of the high incidental gallbladder cancer ratio. In gallbladder cancer, tumor stage, lymph node metastasis, grade, and adjuvant treatment appear to be more important for DFS than presence of complementary surgery. Studies included larger number of patients that will be needed to confirm the results.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Nigri G, Berardi G, Mattana C, Mangogna L, Petrucciani N, Sagnotta A, et al. Routine extra-hepatic bile duct resection in gallbladder cancer patients without bile duct infiltration: a systematic review. Surgeon. 2016;14:337–44.
2. Ebata T, Ercolani G, Alvaro D, Ribero D, Di Tommaso L, Valle JW. Current status on cholangiocarcinoma and gallbladder cancer. Liver Cancer. 2016;6:59–65.
3. Goetze TO. Gallbladder carcinoma: prognostic factors and therapeutic options. World J Gastroenterol. 2015;21:12211–7.
4. Dorobisz T, Dorobisz K, Chabowski M, Pawłowski W, Janczak D, Patrzałek D, et al. Incidental gallbladder cancer after cholecystectomy: 1990 to 2014. Onco Targets Ther. 2016;9:4913–6.
5. Chen C, Geng Z, Shen H, Song H, Zhao Y, Zhang G, et al. Long-term outcomes and prognostic factors in advanced gallbladder cancer: focus on the advanced T stage. PLoS One. 2016;11:e0166361.
6. Wilkinson DS. Carcinoma of the gall-bladder: an experience and review of the literature. Aust N Z J Surg. 1995;65:724–7.
7. Lim H, Seo DW, Park DH, Lee SS, Lee SK, Kim MH, et al. Prognostic factors in patients with gallbladder cancer after surgical resection: analysis of 279 operated patients. J Clin Gastroenterol. 2013;47:443–8.
8. Sheinfeld W. Cholecystectomy and partial hepatectomy for carcinoma of the gall bladder with local liver extension. Surgery. 1947;22:48–58.
9. NCCN. Clinical Practice Guidelines in Oncology, Hepatobiliary cancer, version 2,2017, May 25,2017.
10. Clemente G. Unexpected gallbladder cancer: surgical strategies and prognostic factors. World J Gastrointest Surg. 2016;8:541–4.
11. Go SI, Kim YS, Hwang IG, Kim EY, Oh SY, Ji JH, et al. Is there a role for adjuvant therapy in R0 resected gallbladder cancer?: a propensity score-matched analysis. Cancer Res Treat. 2016;48:1274–85.
12. Kanthan R, Senger JL, Ahmed S, Kanthan SC. Gallbladder cancer in the 21st century. J Oncol. 2015;2015:967472.
13. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer. 2002;95:1685–95.
14. Aloia TA, Jarufe N, Javle M, Maithel SK, Roa JC, Adsay V, et al. Gallbladder cancer: expert consensus statement. HPB (Oxford). 2015;17:681–90.
15. Butte JM, Matsuo K, Gönen M, D'Angelica MI, Waugh E, Allen PJ, et al. Gallbladder cancer: differences in presentation, surgical treatment, and survival in patients treated at centers in three countries. J Am Coll Surg. 2011;212:50–61.
16. Choi SB, Han HJ, Kim CY, Kim WB, Song TJ, Suh SO, et al. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. World J Surg. 2009;33:2657–63.
17. Zhang WJ, Xu GF, Zou XP, Wang WB, Yu JC, Wu GZ, et al. Incidental gallbladder carcinoma diagnosed during or after laparoscopic cholecystectomy. World J Surg. 2009;33:2651–6.
18. Wullstein C, Woeste G, Barkhausen S, Gross E, Hopt UT. Do complications related to laparoscopic cholecystectomy influence the prognosis of gallbladder cancer? Surg Endosc. 2002;16:828–32.
19. Margonis GA, Gani F, Buettner S, Amini N, Sasaki K, Andreatos N, et al. Rates and patterns of recurrence after curative intent resection for gallbladder cancer: a multi-institution analysis from the US Extra-hepatic Biliary Malignancy Consortium. HPB (Oxford). 2016;18:872–8.
20. Ahn Y, Park CS, Hwang S, Jang HJ, Choi KM, Lee SG. Incidental gallbladder cancer after routine cholecystectomy: when should we suspect it preoperatively and what are predictors of patient survival? Ann Surg Treat Res. 2016;90:131–8.
21. Hensen D, Albores-Saaverda J, Corle D, et al. Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates. Cancer. 1992;70:1493–7.