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Incidental Gallbladder Cancer after Laparoscopic Cholecystectomy for Cholelithiasis, and Factors Affecting the Prognosis: A Single-center Experience

Kolelitiyazis için Uygulanan Laparoskopik Kolesistektomi Sonrası Rastlantısal Safra Kesesi Kanseri ve Prognozu Etkileyen Faktörler: Tek Merkez Deneyimi

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Abstract

Aim: Despite surgical and radiological innovations, gallbladder cancer (GC) is usually diagnosed incidentally by the pathological examination of the cholecystectomy specimens, and it is defined as incidental GC (IGC).

Methods: Medical files of patients, who underwent cholecystectomy, were analyzed retrospectively. We investigated the relationship between clinicopathological features and survival in patients with IGC.

Results: We performed cholecystectomy surgery in 6225 patients in 20 years. Only 21 patients with IGC were included in this study. The distribution of the tumor stages was as follows: *in situ* cancer (n=1), T1 (n=2), T2 (n=7), and T3 (n=11). Tumor subtypes were identified as adenocarcinoma (n=16), neuroendocrine tumor (n=2), mucinous carcinoma (n=2), and adenosquamous carcinoma (n=1). Advanced ''T stage'', conversion of laparoscopic cholecystectomy to open cholecystectomy (OCC), positive surgical margins, positive lymphovascular invasion and increased levels of pre-operative alkaline phosphatase (ALP) were found to be associated with poor survival.

Conclusion: In case of OCC or high preoperative ALP activity in cholelithiasis, IGC should be kept in mind. Pathology report on IGC should give information on all histopathological prognostic features in order to avoid loss of time associated with re-examination of specimens due to absence of sufficient information in the initial pathology report and enable the surgical team to perform re-operation for T1b tumors or more advanced IGC in a timely fashion.

Keywords: Cholelithiasis, incidental gallbladder carcinoma, neuroendocrine carcinoma, lymphovascular invasion, laparoscopic cholecystectomy, alkaline phosphatase

Öz

Amaç: Cerrahi ve radyolojik yeniliklere rağmen, safra kesesi kanseri (GC) kolesistektomi sonrası patolojik incelemede genellikle rastlantısal olarak teşhis edilir ve rastlantısal GC (IGC) olarak tanımlanır.

Yöntemler: Kolesistektomi yapılan hastaların tıbbi dosyaları retrospektif olarak incelendi. IGC'de klinikopatolojik özellikler ile sağkalım arasındaki ilişkiyi araştırdık.

Bulgular: Yirmi yılda 6225 hastaya kolesistektomi uyguladık. Bu çalışmaya sadece 21 IGC hastası dahil edildi. Tümör evrelerinin dağılımı: *in situ* kanser (n=1), T1 (n=2), T2 (n=7) ve T3 (n=11) olarak bulundu. Tümör alt tipleri, adenokarsinom (n=16), nöroendokrin tümör (n=2), müsinöz karsinom (n=2), adenoskuamöz karsinom (n=1) olarak tanımlandı. İleri evre T evresi, laparoskopik kolesistektomide açık kolesistektomi dönüş (OCC), pozitif cerrahi sınır, pozitif lenfovasküler invazyon ve preoperatif alkalen fosfatazın (ALP) yüksek aktivitesinin sağkalım süresini kısalttığı saptadık.

Sonuç: Kolelitiaziste OCC veya preoperatif ALP'nin yüksek aktivitesi durumunda, IGC'yi aklımızda tutmalıyız. Patologlar, IGC'yi teşhis ettiklerinde tüm histopatolojik prognostik faktörleri içeren bir rapor sunmalıdırlar. Böylece revizyon patolojisi için zaman kaybedilmeyecek, T1b veya daha ileri T-evreleri için re-operasyon uygun zamanda uygulanabilecektir.

Anahtar Sözcükler: Kolelitiyazis, rastlantısal safra kesesi karsinomu, nöroendokrin karsinom, lenfovasküler invazyon, laparoskopik kolesistektomi, alkalen fosfataz

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Introduction

Gallbladder carcinoma (GC) is the fifth most common cancer of the gastrointestinal tract (1-5) and the most common malignancy of the biliary tract (3,5). The overall incidence of GC is 2.5-3 per 100,000 people (3,4,6). The most important curative treatment for GC is surgical resection; the curative efficacy of both radiation therapy and systemic chemotherapy are still uncertain (6,7). The 5-year survival rate for all stages of GCs is 2.7-15% (1-4,8,9).

Gallbladder cancer, incidentally diagnosed during pathological examination of the gallbladder specimen after cholecystectomy performed for other indications, is defined as incidental GC (IGC) (1,8,10-12). It was first defined by Marcial-Rojas (13) in 1961. 27-41% of the GC cases are diagnosed primarily as IGC, however, this rate, ranges from 10% to 93% depending on the different series reported (7,8,14). While physicians suspect GC preoperatively in 30% of all cases, it is diagnosed in pathological examination of cholecystectomy specimens in the majority of cases (4,6).

The presence of gallstones, calcification, inflammation, anomalous pancreatobiliary junction, and polyps are the known risk factors for the development of GC. In addition, advanced age, female gender, obesity, ethnicity (such as Hispanic race) and various geographical regions (such as Chile, Northern India) are also related with higher incidence of GC (3,8,14,15). Goetze (8) defined gallstones and chronic cholecystitis, as the most important risk factors for the development of the GC. Moreover, it was proposed that any increase in the size of gallstones would be associated with high risk of developing GC. The incidence of GC presenting with acute cholecystitis (AC) is higher than that of diagnosed during elective cholecystectomy for cholelithiasis (16). A recent study performed by Kim et al. (16) concluded that both GC and AC cause thickening of the gallbladder wall rendering the differential diagnosis of these two diseases complicated. Gallstones are found in 70-98% of patients with GC (5,9). The most important risk factor for GC has been reported to be cholelithiasis (17). The incidence of GC related to cholelithiasis varies from 0.3% to 12% (6). The preoperative diagnosis of GC in these patients could be difficult due to the fact that the clinical and radiological presentation may be masked by acute or chronic cholecystitis (12,14,18). Laparoscopic cholecystectomy (LC) has received broad acceptance. In the Western countries, LC constitutes almost 90% of all cholecystectomies (8,14,19). With the widespread use of LC, the diagnosis of IGC at early stages has become easier (6,17). However, the widespread use of LC has not changed the prevalence of GC considerably (14).

Treatment of IGC includes surgical methods varying from simple cholecystectomy to radical cholecystectomy (1,2). The objective of re-exploration and definitive resection is to eliminate likely areas locoregional residual disease (11). Radical resections may improve survival in patients with T4 stage tumors without remote metastases or dissemination (20). Tumor stage is the strongest predictor of overall survival (21).

We investigated the relationship between clinicopathological features and survival in patients with IGC. Our objective was also to determine prognostic factors in patients who received the diagnosis of IGC after cholecystectomy.

Methods

This retrospective study was carried out in accordance with the principles of the Declaration of Helsinki and after obtaining approval of the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Faculty of Medicine-Institutional Review Board (Number: 83045809/604.01/02-82599). Medical records of 6225 patients, who underwent cholecystectomy for benign gallbladder pathologies between January 1998 and January 2018, were screened. Patients with suspected malignant diseases, AC and acalculous cholecystitis, those who underwent open cholecystectomy (OC), frozen procedure, re-operation and LC for polyp, and those who were lost to follow-up were excluded from the study. Only 21 IGC patients were included in our study (Figure 1).

We routinely perform LC using the four-trocar technique. We use a retrieval bag for LC during extraction. We place a drain in the subhepatic space in patients with high risk of bleeding.

Personal address and contact details of the patients who underwent LC were obtained from the institutional records. Patients or their relatives were contacted via telephone calls to determine their survival status. The health status of the patients who survived during the interview, date of death and the causes of death were investigated. One patient who could not be contacted directly and/or through her care giver was excluded from the study. Survival time was determined from the date of diagnosis to the date of death or to the date of last follow-up.

All cases were re-evaluated according to the tumor, nodes, metastases (TNM) system designed by the American Joint Committee on Cancer (AJCC) for staging GC. The TNM system classifies cancers by the size and extent of the primary tumor (T), involvement of regional lymph node (LN), and the presence or absence of distant metastases (M), supplemented in recent years by carefully selected non-anatomic prognostic factors. For this

purpose, the ''7th edition of the AJCC staging'' system was used (22).

The demographic data, operative data and preoperative clinical laboratory results, such as serum albumin, lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and blood hemoglobin (Hb), preoperative radiological examination reports and their related pathology results were also evaluated. Serum LDH, ALP and albumin levels were assayed in Roche c8000® auto analyzer. Hb concentrations were estimated in the Beckman LH 780® autoanalyzer using the cyanmethemoglobin method. Values of LDH ≥250 IU/L, albumin <530 µmol/L, ALP ≥105 IU/L, and Hb ≤120 g/L were all considered diagnostic cut off points.

Statistical Analysis

We performed statistical analyses using the SPSS software version 20 (IBM Analytics, Armonk, New York, USA). The categorical variables were expressed as frequencies (%), and the continuous variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk test) to determine whether they were normally distributed. If values were normally distributed, we used mean and standard deviation to express data. If not, we used median to express our data. Clinical chemistry parameters were compared between dichotomous categorical variables using the Mann-Whitney U test. Survival outcomes were compared using the Kaplan-Meier method with the log-rank test, and potent survival factors were verified using the Cox regression model. A p value of less than 0.05 was considered statistically significant.

Results

Of the 6225 patients, 749 (12%) underwent OC. LC (88%) was done in 5476 patients; in 183 (3%) of whom the technique was converted to OC (OCC). IGC was diagnosed in 43 (0.78%) of these patients. The incidence of IGC was found to be 5.5% in our patients with OCC. Of patients who underwent LC, 3723 (68%) were women and 1753 (32%) men.

Only 21 IGC patients (15 female, six male) with the mean age of 69.67±12.86 years were included in the study (Figure 1). The median survival was 7.00±3.81 months. The

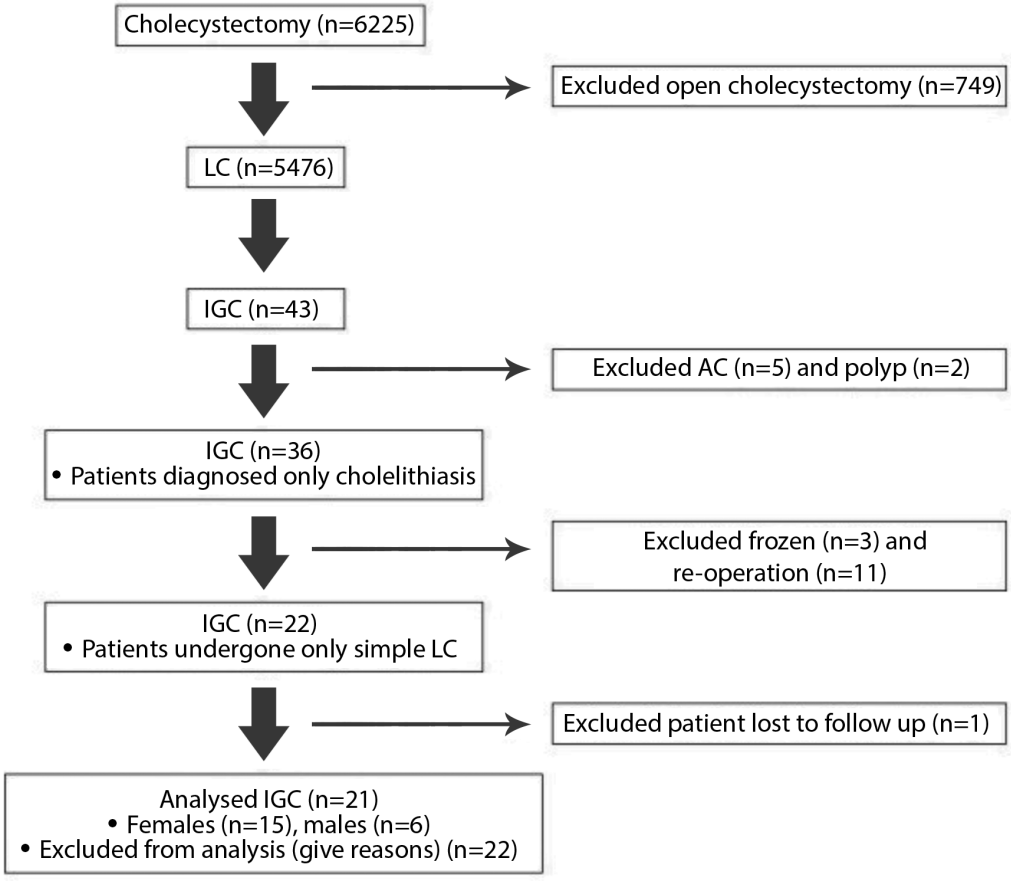

Figure 1. Flowchart for patient selection (LC: laparoscopic cholecystectomy; IGC: incidental gallbladder carcinoma; AC: acute cholecystitis)

median survival was 6.00±2.15 months in female patients. Sixteen were geriatric patients. The median survival in the non-geriatric population was 9.00±5.48 months, whereas, it was 6.00±3.00 months in the geriatric population. We have not found any effect of gender, age and being in the geriatric population on survival in our study.

In 11 of the patients, LC was successfully completed, however, an OCC was deemed necessary in 10 of the patients. Survival was significantly longer in patients whose LC procedures were completed successfully (p=0.009) (Figure 2). The median survival was 60.00±37.89 months after LC and 2.00±0.95 months after OCC.

Survival analyses for the location of IGC at the fundus, body, and neck regions of the gallbladder could not be performed. IGC was detected in the fundus, body and the neck regions in 3, 16, and two of patients, respectively. IGC involved the peritoneal surface (n=14) or the hepatic bed (n=7). Involvement of the hepatic bed or the peritoneal surface seems not to be a statistically significant factor determining survival. However, survival was found to be longer in patients with IGC involving the peritoneal surface (Table 2).

Gallbladder perforation (GP) occurred in 6 patients during surgery. The median survival was found to be 2.00±3.67 months in patients with GP, and it was 9.00±5.15 months in patients without GP (p=0.548). Although it seems not statistically significant, it was noteworthy that survival was shorter in patients with IGC complicated with the occurrence of GP.

Histopathological type and T stage distributions of the cases are given in Table 1. One patient with Tis and 2 with T1b were excluded from the survival analysis due to the small sample size. The median survival was longer in patients with T2 IGC than in those with T3 IGC (Figure 3). The patient with Tis was in the postoperative (PO) 186th month and those with T1b were in the PO 12th and 36th months. In patients with only adenocarcinoma, there was no significant difference in survival between T2 and T3 stages (p=0.091). One of the two patients with mucinous adenocarcinoma was found to be still alive in the 31st PO month in the T2 stage, however, the other one died in the PO first month in the stage T3. The patient with adenocarcinoma had T3 tumor and died 6 months after the definitive operation. The patients with neuroendocrine carcinoma had stage T3 disease and lost their lives within the PO first and fourth months.

According to histologic grading, 11 patients had well-differentiated ICG, four had moderately differentiated, and 6 patients had poorly differentiated ICG. Although we found no statistically significant effects of the grades

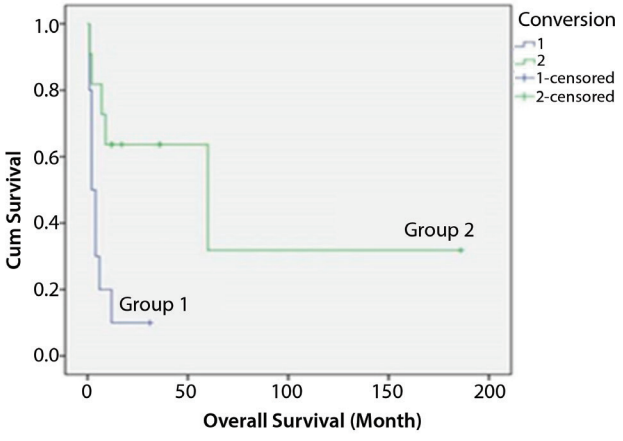

Figure 2. Kaplan-Meier survival curves according to conversion from laparoscopic cholecystectomy (Group 2) to open cholecystectomy (Group 1)

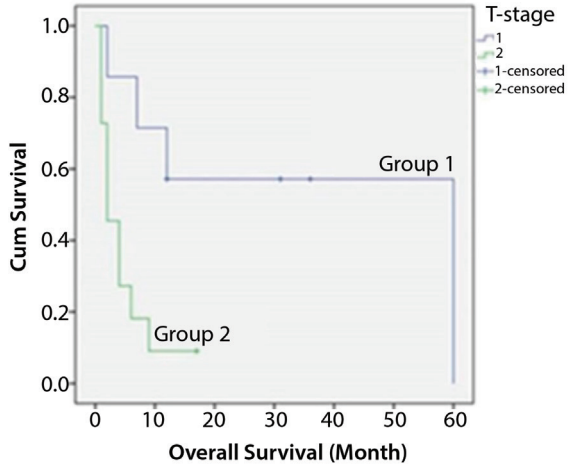

Figure 3. Kaplan-Meier survival curves according to T-stages (Group 1, T2 patients; Group 2, T3 patients)

Table 1. T stages and histopathological types in incidental gallbladder cancer

	Adenocarcinoma (n=16)	Mucinous adenocarcinoma (n=2)	Adenosquamous carcinoma (n=1)	Neuroendocrine carcinoma (n=2)	Total (n=21)
Tis	1	-	-	-	1
T1b	2	-	-	-	2
T2	6	1	-	-	7
T3	7	1	1	2	11

on survival, it was noteworthy that survival was longer in patients with well-differentiated tumors (Table 2).

The median of tumor diameter (TD) was 35000 µ. Of the IGC patients, nine of them have had tumors measuring 35000 µ in diameter or larger. Although the difference was not statistically significant (Table 2), patients with tumors <35000 µ had longer survival.

In 12 of the cases, regional LN could not be evaluated. Four of the cases had positive LN metastasis but five were LN-negative. The effect of regional LN involvement on survival could not be assessed. Perineural invasion (PI) was found in 11 patients. No significant difference was found in survival between patients with and without PI (Table 2). Nevertheless, it seems that patients without PI had longer survival. Lymphovascular invasion (LVI) was identified in 12 patients. The median survival in patients with LVI was 2.00±0.75 months, shorter than that in patients without LVI (Table 2 and Figure 4). Surgical margins (SM) were positive in nine of the patients. SM-positive patients had shorter survival durations (Table 2 and Figure 5).

The mean activity of LDH was 341±142.45 IU/L, and the median survival was found to be 4.00±3.00 months for patients with high LDH levels (p=0.242). The mean serum albumin concentration was 600±85 µmol/L and the median survival was found to be 9.00±5.00 months in patients with low albumin levels (p=0.125). The mean

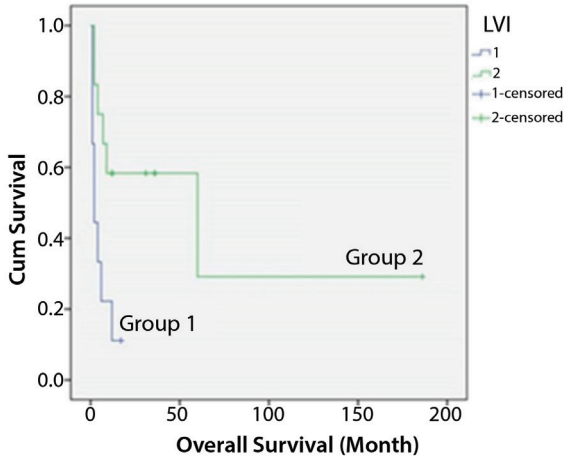

Figure 4. Kaplan-Meier survival curves according to lymphovascular invasion. (Group 1 positive LVI, Group 2 negative LVI)
LVI: Lymphovascular invasion

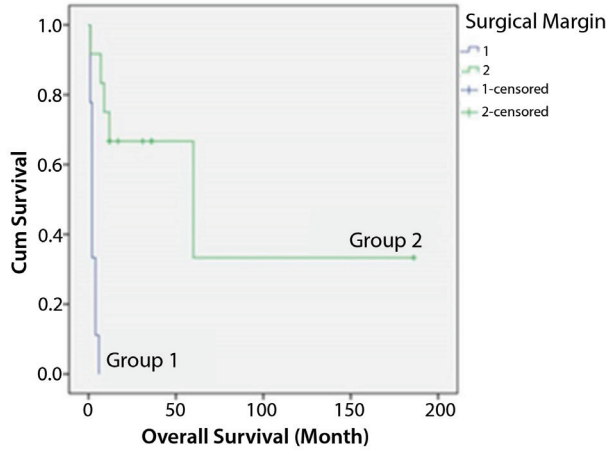

Figure 5. Kaplan-Meier survival curves according to the surgical margins (SM). (Group 1 positive SM, Group 2 negative SM)

Table 2. Survival analysis of the patients according to their histopathological features

		Number of patients (n)	Median survival (Months)	p
The median survival of patients		21	7.00±3.81	
T staging	T2	7	60.00±0.00	0.011
	T3	11	2.00±0.99	
Histologic grading	Well differentiation	11	60.00±41.60	0.092
	Moderate differentiation	4	6.00±2.50	
	Poor differentiation	6	2.00±1.84	
Tumor location	Peritoneal surface	14	9.00±22.03	0.173
	Hepatic bed	7	4.00±1.19	
Tumor diameter	<35 mm	12	60.00±39.65	0.053
	≥35 mm	9	4.00±1.49	
Perineural invasion	Positive	11	4.00±2.20	0.087
	Negative	10	60.00±39.90	
Lymphovascular invasion	Positive	12	2.00±0.75	0.011
	Negative	9	60.00±38.15	
Surgical margin	Positive	9	2.00±0.35	0.016
	Negative	12	60.00±35.32	

level of Hb was 124.9±12.2 g/L. No effects of low levels of Hb on survival was identified (p=0.276). The mean ALP activity was 176.57±119.83 IU/L. The median survival was found to be 4.00±0.95 months for patients with high ALP levels. High levels of ALP were found to be significantly related to shorter survival (p=0.009) (Figure 6).

Discussion

Despite considerable improvement achieved in the early diagnosis of GC with the use of radiologic advancements, the incidence of IGC is still 0.2-3% worldwide (2,12,16). LC as a surgical treatment for cholelithiasis has replaced OC lately (12,16,18,23,24). It is estimated that the incidence of IGC after LC varies from 0.09 to 2% (3,16,25). The incidence of IGC in our 20-year of cholecystectomy series was 0.78%.

In many studies, female gender or age 65 years or older has been considered risk factors for IGC (2,3,14,17). In our cases, fifteen patients were female and their median age was 69.67±12.86 years. We did not find a statistically significant effect of gender or advanced age on survival.

Ahn et al. (2) emphasized that operative procedures should be considered independent prognostic factors. In our cases, OCC was done in 10 patients. IGC incidence was found to be 5.5% in our patients with OCC and the duration of survival in the OCC patients was found to be shorter than in LC patients. Goetze and Paolucci (26) emphasized the safety of LC as reliable as OC as a surgical method, independent of T stage in patients with IGC. In their study including 91.260 patients, Pitt et al. (14) reported an OCC rate of 2% in 91.260 patients who underwent cholecystectomy and an IGC incidence of 0.6% in patients with OCC. In the present study, we observed

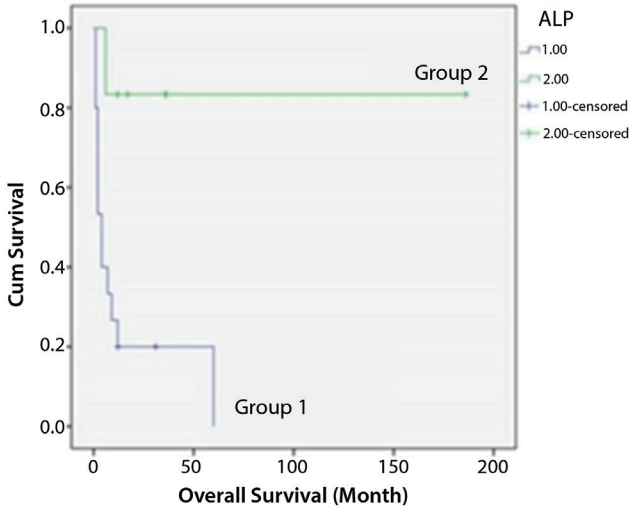

Figure 6. Kaplan-Meier survival curves by the activities of alkaline phosphatase (ALP). (Group 1 high ALP activity, Group 2 normal ALP activity)

that within the first 6 months after LC surgery, the survival rate was 63%, whereas it was 30% in OCC cases.

GP during surgery should be considered as a poor prognostic factor for the probability of recurrence or survival (2). Shimizu et al. (19) concluded that prevention of peritoneal recurrences and favorable prognosis were strongly related with the prevention of intraperitoneal bile spillage during LC. Goetze and Paolucci (26) reported an intraoperative perforation rate of 23% for LC, 21% for OC, and 35% for OCC. However, one study has not found a relationship between survival and an intraperitoneal spillage (16). In our study, the rate of GP was 28.6%. In our surgical series of LC, GP occurred in six patients intraoperatively. We did not find a statistically significant relationship between the GP and survival (p=0.548). However, we found shorter survival in our cases of GP, although it was not statistically significant.

Lymph node metastasis in GC is considered to be one of the most important prognostic factors (2). However, LN evaluation is limited in IGC specimens, because LN dissection is not carried out in standard cholecystectomies. In 12 of our IGC cases, no information on regional LN involvement could be found in the reports of pathological specimens.

Butte et al. (11) reported that re-examination of the initial cholecystectomy specimen showed PI in 42.2% of 83 patients and observed a higher rate of OCC in patients with residual disease. Additionally, D'Hondt et al. (27) suggested that PI should be considered a significant prognostic factor for survival. We found no effects of PI on survival (Table 2). However, PI was determined in seven of the OCC cases. Although not statistically significant, we have found that PI-negative patients had longer survival.

Gallbladder anatomy facilitates early hepatic infiltration, since there is no muscularis mucosa or serosal layer in the liver attached to the gallbladder (10,28). Kondo et al. (20) classified the pattern of dissemination of tumor with a focus on surgical strategy in surgical specimens from 112 patients who underwent curative resection for GC. They reported the median survival of 18 months for the whole series, 2 months for the LN dissemination type, and 11 months for the hepatic bed dissemination type (20). Seven of our cases were bed type tumors. Whether on the liver bed or on the peritoneal surface, location of the tumor was not found to be a prognostic factor for survival in the current study. However, survival was found to be some longer in patients with IGC involving the peritoneal surface.

The most common histopathological type of GC is adenocarcinoma (80-97%). The remaining (3-20%) histopathological types of GC comprise of squamous-cell, adenosquamous-cell carcinoma, or papillary carcinoma. Histopathological types of our IGC consisted

of adenocarcinoma (85.7%), neuroendocrine carcinoma, and adenosquamous carcinoma (Table 2).

Chatelain et al. (29) assesses the accuracy of pathology reports in 100 patients who received the diagnosis of IGC and reported that 93% of reports had a conventional format without any standardization and lacked important information on key histological prognostic factors such as exact tumor site, depth of tumor infiltration within the gallbladder wall, surgical margins, tumor differentiation, vascular invasion and perineural invasion in 55%, 10%, 40%, 28%, 52%, and 51 of cases. Only 30% of the reports gave information on T stage with margin status and tumor location. They found that the turnaround time for pathology reports was 1-35 days (mean 7 days). TNM, R status, tumor location and histopathological prognostic factors were mentioned in the pathology reports of our patients. We linked this phenomenon to the fact that our institution was a tertiary hospital.

One of the most important factors for survival in patients with IGC is the depth of tumor invasion (T stage) (27,30). IGC is often detected in T2 and T3 stages (10,14,18). Due to the widespread use of LC, IGCs are detected more frequently in early stages (T1 or T2) nowadays (6,16,17,31). We found that the rate of stages T2 and T3 was 33.3% and 52.4%, respectively. Due to the exclusion of re-operated cases, T3 IGC was more frequently diagnosed than other T stages. Non-resected GC is known to be a rapidly disseminating and fatal disease (27). The median survival for IGC has been reported to be either more favorable or similar when compared to non-incidental GC (2,7,21,27,32). D'Hondt et al. (27) reported a mean survival of 25.8 months in their patients with IGC and 4.4 months in non-incidental GC patients. The median survival in our cases was 7.00±3.81 months. The short duration of median survival in our cases clearly indicates the importance of re-operation. For patients with T1a or Tis disease, the standard curative procedure is a simple cholecystectomy with negative SM. (8,10,15,30-32). Liver resection and LN dissection are recommended by the National Comprehensive Cancer Network (NCCN) (33). We had two T1b IGC cases in our LC series. The tumors were located in the fundus and body on the peritoneal surface of the gallbladder. In both patients, there were no LVI or PI. Both patients had a regional LN, found to be metastasis-free in the pathology examination. The histopathological type of the tumor was well-differentiated adenocarcinoma and the patients underwent simple LC. ALP activity in these patients was within the normal range. We have not performed re-operation, since the patients did not give consent for further surgery.

Hamdani et al. (5) and Pitt et al. (14) stressed that higher ALP activity was a significant risk factor for IGC. Moreover, they reported that higher GGT and/or ALP activity may occur even in the absence of jaundice (5). The mean ALP activity was 177±120 IU/L in our study. We also did not detect jaundice in our patients with higher ALP activity. We found that high ALP activity was strongly associated with poor survival.

Study Limitations

Small number of patients with T1 and T4 IGC and its retrospective design were the limitations of our study.

Conclusion

In summary, female gender and advanced age were common in our series.

OCC, high ALP, advanced T stage, LVI and positive of SM are statistically significant poor prognostic factors. Although not statistically significant, development of GP during surgery, poor differentiation histologic grade, TD≥35 mm, location of the tumor in the hepatic bed and, PI shorten survival. Pathology reports should provide information about all of these histopathologic prognostic factors to avoid loss of time associated with re-examination of specimens due to absence of sufficient information in the initial pathology report.

The poor overall survival in our cases obviously demonstrates the importance of re-operation in patients with T2 or T3 IGC.

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Authorship Contributions

Design: S.D., O.A., N.K., I.T. Concept: S.D., O.A., N.K., I.T. Data Collection or Processing: S.D., O.A., N.K. Analysis or Interpretation: S.D., I.T. Literature Search: S.D. Writing: S.D.

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