



# Incidental gallbladder cancers: Our clinical experience and review of the literature

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## ABSTRACT

**Objective:** Gallbladder carcinomas are rare and aggressive neoplasms. They are usually advanced at the time of diagnosis. We aimed to evaluate incidental gallbladder cancers in our clinic, in terms of patients' demographics, diagnosis, treatment and follow-up, and compared our results with the literature.

**Material and Methods:** Patients who underwent laparoscopic cholecystectomy in the last 9 years were retrospectively reviewed, and features of the patients diagnosed with gallbladder cancer after histopathological evaluation were further evaluated.

**Results:** Thirteen patients were female and two were male. The mean age was 67 years. Additional treatment was applied in seven patients. All patients were operated on laparoscopically, with conversion to open surgery in four patients. The rate of incidental gallbladder cancer was 0.17% in our patients. Survival rates were found to be 22.2% in patients who had been operated at least 5 years ago.

**Conclusion:** Surgery is the only curative treatment in gallbladder cancers; however, they are usually at advanced stages at the time of diagnosis. In incidental gallbladder cancers, survival can be prolonged with appropriate treatment models if they are identified at early stages. The relatively low rates that have been reported in our population may be due to geographical differences and problems in study design.

**Keywords:** Incidental, gallbladder, cancer

## INTRODUCTION

Laparoscopic cholecystectomy is accepted as the gold standard for the treatment of benign gallbladder diseases in the world due to reduced postoperative pain, early oral intake, early discharge and better cosmetic results for the last 20 years, and is being implemented with low morbidity. There has not been a significant increase in the early detection rate of gallbladder cancer (GBC), which remains asymptomatic in early stages, despite advances in technology and widespread use of techniques such as ultrasound (US) and abdominal computed tomography (CT), with an incidence of 0,54-2,1% (1, 2). Overall, there is preoperative suspicion of GBC in only 30% of patients, while the remaining 70% are diagnosed in the postoperative pathologic examinations (3). In other words, in the literature it has been proven that 1 cancer is detected out of every 100 laparoscopic cholecystectomies (4). Maximillian Stoll has mentioned GBC for the first time in Vienna in 1777 (5). After many years, Nevin et al. (6) has defined the first GBC staging and survival rates after open cholecystectomy. Drouard et al. (7) showed port site metastases in 1991. Gallbladder cancer is a very aggressive disease, with a 5-year survival rate of 3-13% (8), and a mean survival of 3-11 months (9). However, especially with aggressive surgical approaches applied in some centers in Japan, satisfactory results can be obtained (10). The underlying cause of this rate is the too late emergence of symptoms such as pain and jaundice (6), and advanced stage on diagnosis (T3, T4).

Incidental GBC refers to cancers that were not diagnosed preoperatively but detected by postoperative pathologic examination. There is no effective treatment for GBC other than surgical resection, and complete resection seems to be the only curative method (11).

The aims of our study were to determine incidental GBC frequency in patients undergoing laparoscopic cholecystectomy in our center for symptomatic gallstones, to compare this with the literature data from our country and the world, to investigate the clinical and pathological characteristics, to determine prognostic factors effecting survival, and to detect the recurrence rate.

## MATERIAL AND METHODS

Patient files of 8698 patients who underwent laparoscopic cholecystectomy because of symptomatic gallstones at the Ministry of Health Istanbul Education and Research Hospital General Surgery Clinic between January 2005 and December 2013 were analyzed retrospectively, and the demographic characteristics and survival rates of 15 patients who were diagnosed with GBC on postoperative histopathological examination were determined and compared with the literature.

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Malignancy was not suspected in any of the patients in the preoperative physical examination, medical history, laboratory or radiologic examinations. None of the patients had intraoperative suspicion of cancer, and intraoperative frozen section examination was not conducted in any patients. All operations were performed by general surgeons, with the standard 4-port technique, by creating pneumoperitoneum with CO<sub>2</sub> at 14 mm Hg, but in 4 patients the laparoscopic surgery was converted to open surgery due to severe adhesions. Tumor staging was made according to the American Joint Committee on Cancer (AJCC) 7<sup>th</sup> edition criteria (12). Postoperative follow-up and treatment characteristics of patients were recorded by contacting practicing specialists.

## RESULTS

The demographic, clinical, histopathologic, and follow-up properties of patients included in this study are shown in Table 1. Accordingly, 13 of the patients were female (86.66%), and 2 of them were male (13.33%). The mean age was determined as 67 years (41-81). The rate of incidental gallbladder cancer rates in cases of cholecystectomy was found to be 0.17%. The most common tumor pathology was T2 adenocarcinoma, while one was consistent with MALT lymphoma (N15). During surgery, four patients were converted from laparoscopy to open surgery. One patient has been previously treated for acute pancreatitis, and 2 for acute cholecystitis. One patient was under follow-up for chronic hepatitis. Two patients were lost to follow-up in the postoperative period. One patient underwent additional surgical resection, and 6 of them received adjuvant therapy. 6 patients had an advanced stage disease by the time they have been contacted in the postoperative period after detection of the tumor, and they did not receive any further intervention. Six of the remaining 13 patients are still alive, with more than 5-year survival in one patient (22.2% when considered within 9 cases).

## DISCUSSION

Gallbladder cancer is a rare tumor with a worldwide incidence of 3 in 100,000 (13). The disease has a geographical distribution, being most common in Chile, Japan and North India (3). It is the most common cancer of the bile duct, and the 6<sup>th</sup> most common cancer of the gastrointestinal tract (14). Gallstones, advanced age, sclerosing cholangitis, porcelain gallbladder are well known risk factors for GBC. In general, the prognosis of GBC is quite poor, and tumor penetration depth and lymph node metastasis have been identified as the most important prognostic factors (6). Unexpected GBC after cholecystectomy was reported for the first time in 1961 (15). Today, only one third of GBCs can be diagnosed preoperatively (3). Most cases are diagnosed by histopathologic examination after laparoscopic cholecystectomy for benign pathologies. Theoretically, this group has the best prognosis (16).

The risk for GBC is 2-6 times higher in women in the general population, and its incidence increases with age (17). However, male gender is a significant poor prognostic factor in GBC, and is associated with shorter survival (17). In our study, the frequency of female patients was significantly greater and in contrast to the literature data men had better prognosis, however, the small number of male patients restricts the significance of this result. The most important risk factor for gallbladder cancer has been reported as chronic inflammation (18).

The presence of inflammation is associated with peroperative perforation and bile contamination, thus has a negative impact on prognosis. Calculi are detected within the gallbladder in 70-98% of cases (19). In our study, the rate of gallbladder calculi detection could not be related to prognosis, with no reports of perioperative perforation.

Curative surgical resection improves survival rate in GBC. Simple cholecystectomy is sufficient for T<sub>1A</sub> GBC (2), and 5-year survival rate has been reported to be 90-100% for these tumors (20). Two out of the 3 patients graded as in situ cancers in our study are still alive. Incidental GBC are usually early stage (T1) tumors (21). Their prognosis is better than GBCs with peroperative diagnosis (18), usually with a lower histologic grade (13, 22). In our study, laparoscopic surgery was planned in all cases, and when patients with conversion to open surgery were compared with the remaining patients no significant poor prognostic factors were identified. Port site metastases following laparoscopic cholecystectomy within a period of 10 months has been reported in the literature as 10-30% (23). The rate of port site metastasis is significantly lower in patients without peroperative perforation (24). In our study, an umbilical port site metastasis was detected in 1 patient (6.6%) at the 2<sup>nd</sup> postoperative year in the oncology clinic, and the patient died at 32 months after initial surgery (N1). The role of adjuvant chemotherapy in incidental GBC is not clear, in contrast to that of complementary resection (11). Six of our patients received postoperative adjuvant treatment. One patient with stage 1a (T1bN0) disease underwent liver wedge resection at postoperative 2 months with complementary lymphadenectomy (N4).

An important point we noticed in our study was that the 0,17% rate of incidental GBC was lower than the rate published in the literature (1, 2). However, we found that in other studies conducted in the Turkish population this ratio was consistent with ours and was lower than that in the literature (25-27). Genc et al. (25) reported the incidental gallbladder cancer rate in 5164 cholecystectomies as 0.09%, Dursun et al. (26) in 696 cases as 0.3%, while Akyurek et al. (27) detected the rate as 0,72% in 548 cases.

The wide range in the rate of incidental GBC detection has been attributed to various causes in the studies (26, 28, 29). The most prominent feature within these causes is the higher rate of in situ carcinomas in prospective studies as compared to retrospective studies, since sufficient sampling is not performed in the fundus and corpus section where cancer is most common as part of standard pathologic examination (26, 28). Also, gallbladder cancer is endemic in some countries, and thus average rates in these regions raise overall rates (3, 28, 29). So the low rate of detection of incidental GBC in our country as compared to the world is an expected result, however, we believe that with multicenter, prospective studies with large patient volume that will be carried out with the pathology department can yield findings similar to the literature rates.

We believe that the high proportion of patients who cannot be contacted and consequently not being able to apply additional surgical resection and early stage adjuvant treatment in the postoperative period is one of the limitations of our study. Only one patient underwent additional surgery, 5 of them were followed-up and treated by the Oncology Clinic, and one

Table 1. Demographic, clinical, histopathologic and follow-up data of patients

N	G	A	Symp	Op	Inf	Calculi	Patho	Diff	T	N	Adj	S (months)
1	F	74	No	LC	No	Yes	Adenoca	Well	T2	N0	No	32
2	F	80	Yes	LC	No	Yes	Adenoca	Well	In situ		No	26
3	F	69	Yes	LC	Yes	No	Adenoca	Poor	T3	N1	No	28
4	F	59	No	OC	Yes	Yes	Adenoca	Well	T1b	N0	*	A(32)
5	F	64	Yes	LC	Yes	Yes	Adenoca	Poor	T2	N0	No	30
6	F	82	Yes	LC	Yes	Yes	Adenoca	Well	T1a	N0	-	-
7	F	41	No	OC	Yes	Yes	Adenoca	Well	T2	N0	No	A(67)
8	F	73	Yes	OC	Yes	No	Adenoca	Moderate	T3	N0	No	18
9	F	58	Yes	LC	No	Yes	Adenoca	Well	T1b	N0	Yes	15
10	F	55	No	LC	No	No	Adenoca	Well	In situ		Yes	A(62)
11	M	54	No	LC	No	No	Adenoca	Well	In situ		Yes	A(49)
12	F	64	Yes	LC	No	Yes	Adenoca	Well	T2	N1	Yes	A(14)
13	F	81	Yes	OC	Yes	No	Adenoca	Well	T2	N0	No	29
14	F	74	Yes	LC	No	Yes	Adenoca	Moderate	T3	N0	-	-
15	M	77	Yes	LC	No	Yes	MALT				Yes	A(8)

N: number of patients; G: gender; A: age; Symp: symptomatic; Op: operation; Inf: presence of inflammation; Patho: pathologic diagnosis; Diff: Differentiation; Adj: adjuvant treatment; S: survival; LC: laparoscopic cholecystectomy; OC: open cholecystectomy; Adenoca: adenocarcinoma; A: alive; \*Additional surgical resection

by the Hematology Clinic. Six of the remaining 8 patients received no additional treatment, and 2 patients could not be reached even in the period of this manuscript preparation. We believe that the most important underlying cause of these negative consequences is perceiving laparoscopic cholecystectomy, which is performed too frequently with low rate of complications in our country in recent years, as a relatively insignificant procedure by patients and even surgeons, thus not paying enough attention to pursuing the results of pathology and to follow-up protocols in the postoperative period. Another restriction is the retrospective design of the study, since a higher rate of malignancy can be determined in prospective studies with more comprehensive pathological examination.

## CONCLUSION

In our study, older age, poor tumor differentiation, and advanced stage tumors had adverse effects, while additional surgical resection at the early stages and early adjuvant treatment had positive effects on survival. Our incidental GBC rate was lower than those reported in the literature, and was consistent with other studies in the Turkish population. Pathology results of cholecystectomies should be monitored closely, patients should be planned for follow-up visits without losing communication, pathologic examination should be performed beyond standard applications in patients with risk factors or those with perioperative suspicion, and once an incidental cancer is detected the treatment decision should be decided according to tumor spread and depth as well as the patient's age, additional health problems, and life expectancy.

**Ethics Committee Approval:** We did not have an ethics committee approval because of the fact that it was a retrospective study, and we acquired the data from patients' files.

**Informed Consent:** We did not have patients' consents because of the fact that it was a retrospective study.

**Peer-review:** Externally peer-reviewed.

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