Gallbladder Cancer: An Analysis of a Series of 139 Patients With Invasion Restricted to the Subserosal Layer

Xabier de Aretxabala, M.D., F.A.C.S., Ivan Roa, M.D., Luis Burgos, M.D., F.A.C.S., Hector Losada, M.D., Juan Carlos Roa, M.D., Javier Mora, M.D., Juan Hepp, M.D., F.A.C.S., Jorge Leon, M.D., F. Maluenda, M.D., F.A.C.S.

The goal was to study our experience in the management of a series of patients with a potentially curative subserosal gallbladder cancer who were prospectively treated by the authors. Between April 1988 and July 2004, 139 patients were enrolled in our prospective database. Of the above, 120 were operated on with an open procedure and the rest with laparoscopic surgery. In only eight patients was the diagnosis suspected before the cholecystectomy. The majority of tumors were adenocarcinoma. Six patients had an epidermoid tumor, and one had a carcinosarcoma. Of the patients, 74 underwent reoperation, while in 55 (70.2%) it was possible to perform an extended cholecystectomy with a curative aim. Operative mortality was 0%, and operative morbidity was 16%. Lymph node metastases were found in 10 (18.8%), while in 7 (13.2%) the liver was involved. The overall survival rate was 67.7%, while in those who underwent resection, the survival rate was 77%. Through the use of a multivariate analysis, the presence of lymph node metastasis was found to be an independent factor with respect to prognosis. The feasibility of performing an extended cholecystectomy in patients with gallbladder cancer and invasion of the subserosal layer allows for a good survival rate. The presence of lymph node metastases represents the main poor prognosis factor, and some type of adjuvant therapy should be studied in this particular group.

KEY WORDS: Gallbladder cancer, survival outcomes, hepatic resection, lymph nodes

Gallbladder cancer (GC) is a very common disease in countries such as Chile, Japan, and India; however, it is uncommon in the United States.[1–3] Despite its generally poor prognosis, there is a subset of cases with long-term survival. The majority of patients with a potentially curable disease are detected after the examination of the cholecystectomy specimen. Of these patients, those with a T2 tumor (invasion restricted to the subserosal layer) are a group characterized by an intermediate prognosis and hope for long-term survival.[4,5]

Cholecystectomy alone is an adequate treatment for T1 GC (invasion through to the muscular layer). Radical second resection has been advocated in T2 patients, but its real effect on survival is discussed. Despite the lack of statistical evidence, most surgeons agree that the extended cholecystectomy would be useful as treatment.[5–8] Since 1988,

From the Department of Surgery, German Clinic (X.deA., J.H., J.L., F.M.), Santiago, Chile; Department of Pathology, Universidad de la Frontera and German Clinic (I.R., J.C.R.), Santiago, Chile; Department of Surgery, Hospital Regional (L.B., H.L., J.M.), Temuco, Chile; and Department of Surgery, University of Chile (X.deA., F.M.), Santiago, Chile.

Supported by the generosity of the German Clinic, Santiago, Chile.

Reprint requests: Dr. Xabier de Aretxabala, Department of Surgery, German Clinic, Vitacura 5951, Santiago, Chile. e-mail: xdearetxabala@alemana.cl

Table 1. Protocol of management

Cholecystectomy and specimen biopsy	
Cancer diagnosis	
Wall infiltration of the tumor	**Procedure**
Mucosa	Only cholecystectomy
Muscle	Only cholecystectomy
Subserosa	Only cholecystectomy or reoperation
Serosa	Only cholecystectomy or reoperation

a prospective protocol of pathological diagnosis and treatment has been conducted by two of the authors (X.deA., I.R.). In general terms and as a part of the protocol, the extended cholecystectomy is offered to patients with GC and invasion deeper than the muscular layer in whom diagnosis is performed after studying the cholecystectomy specimen and are able to get a curative operation (Table 1).

The purpose of this study was to evaluate the results obtained in a cohort of potentially resectable patients with invasion limited to the subserosal layer (T2).

MATERIAL AND METHODS

We analyzed a series of 139 patients harboring a potentially resectable subserosal T2 GC detected after examination of the cholecystectomy specimen. The selection of patients was restricted to those with invasion limited to the subserosal layer (peritoneal side). We did not include patients in whom invasion was located in the adipose tissue at the hepatic side of the gallbladder. These patients were obtained from a database that included 334 patients with a potentially resectable GC enrolled prospectively over a 16-year period (April 1988–July 2004). A potentially resectable tumor is defined as a tumor in a completely resected gallbladder with no macroscopic residual tumor, or, if there is a residual tumor, it is located in areas that can be extirpated during a second operation. All patients underwent a simple cholecystectomy either open or laparoscopically in the first operation. The type of surgery depended on the surgeon choice and availability. Patient survival data were obtained from personal interviews with patients, from the clinical charts, or from the Chilean death master file. Most patients underwent a cholecystectomy at the Temuco Regional Hospital by different surgeons yet all were reoperated on by one of the authors (X.deA.).

Surgical mortality was considered as death occurring within 30 days of surgery. The interval between the cholecystectomy and the reoperation ranged between 1 and 11 months, with most undergoing surgery between 3 and 5 months.

Preoperative assessment included history, physical examination, and radiographic studies (computed tomography scan of abdomen and thorax radiograph).

An extended cholecystectomy was planned for the reoperation. Para-aortic lymph node samples were obtained from all patients as a first step during the operation.

The presence of distant tumor compromise or the impossibility of performing a curative surgery (complete resection with no gross residual cancer upon completion of surgery) was an indication to finish the operation.

An extended cholecystectomy consists of a liver wedge resection that included segments V and IVb along with a lymphadenectomy of the nodes located in the hepatic pedicle. Previous laparoscopic port sites were resected if present. Liver transection was performed using a crush clamp technique. Later, parenchymal division was accomplished using an ultrasonic dissector. Central venous pressure was maintained at 5 cm H_2O or less during the transection. The common bile duct was not resected. Adjuvant and neoadjuvant therapies were not used to any great extent in this series, making them unlikely to affect the analysis.

Numerical data are expressed as the mean, median, standard deviation, and ranges. Differences were considered significant at $P < .05$. The survival curves for selected patient groups were determined using Kaplan-Meier method. Survival durations for these groups were derived from the corresponding Kaplan-Meier curves and compared using the log-rank test.

Cox proportional hazard regression modeling was used to assess the effect that independent covariates had on the dependent variable of survival. Comparisons of patient survival curves were made using the log-rank test. Statistical analysis was performed using Stata 8.0 software (Stata Corporation, College Station, TX).

RESULTS

Patients

There were 17 men and 122 women with an average age of 58 years at presentation (range, 31–88 years). Nine patients were younger than 40.

Table 2. Presenting diagnosis of patients harboring a T2 gallbladder cancer

Diagnosis	No. of patients
Cholelithiasis	48
Acute cholecystitis	67
Cholangitis	4
Empyema	2
Jaundice	4
Neoplasia or polyp	8
Other	6

Table 3. Reasons to exclude patients from resection

Reason	No. of patients
Diffuse compromise of the bile duct	8
Paraaortic compromise	4
Port site invasion along with peritoneal compromise	2
Choledocoduodenal lymph node compromise	1
Miscellaneous	4

Presenting Symptoms and Preoperative Diagnosis

Of the patients, 120 (86%) underwent an open procedure, while the rest (19 patients) underwent a laparoscopic cholecystectomy. Of the latter, three had to be converted to an open procedure because cancer was suspected at the moment of the cholecystectomy. Most patients were operated on due to a cholelithiais (48 patients) or acute cholecystitis (67 patients). Of the 139 patients, only eight diagnoses were suspected prior to the cholecystectomy. In two of these eight patients, the lesion was suspected to be a polyp, while in six it corresponded to a gallbladder mass (Table 2). With respect to the postoperative diagnosis, in only 15 patients was the diagnosis of tumor suspected during the cholecystectomy. In the rest, diagnosis of tumor was made during the analysis of the cholecystectomy specimen. Of these patients, in 61 patients the lesion was detected only after the histologic examination, being completely unsuspected during the macroscopic examination of the gallbladder mucosa performed by the pathologist.

Pathology

Most patients had an adenocarcinoma, while six patients had an epidermoid tumor and one had a carcinosarcoma. Among the patients with an adenocarcinoma, 72 (54.5%) had a moderately differentiated tumor.

Therapeutic Procedures and Pathologic Findings

Of all of the patients, 74 (53.2%) underwent reoperation with the aim of performing an extended cholecystectomy. The rest did not undergo reoperation due to their refusal or their advanced age (older than 65). Of those who underwent reoperation, 55 (70.2%) were resected. Reasons for not undergoing the resection were diffuse common bile duct extension in eight patients, para-aortic lymph node compromise in four, port site compromise along with peritoneal compromise in two, and others (Table 3). Among the last patients, it is important to draw attention to one patient with liver cirrhosis and another patient who presented with a diffuse inflammatory compromise of the upper abdominal cavity, probably secondary to an asymptomatic biliary leak. In these patients, the risk of bleeding and liver failure and the technical difficulties derived from the inflammation were considered, respectively, to avoid the resection. Furthermore, in two patients, only a lymphadenectomy was performed, the reason being thrombosis of the hepatic artery and persistent intraoperative hemodynamic instability. Among the patients who underwent a lymphadenectomy, metastases were found in 12 (18.8%). The total number of lymph nodes dissected ranged between 2 and 21 nodes, with an average of 8.6 nodes. All patients with lymph node compromise had lymph node involvement in the hepatic pedicle. No skip metastases were observed in this series. Liver infiltration was found in 7 of the 53 who underwent liver resection (13.2%). The volume of liver resection was calculated from the weight of the specimen, with the average weight being 100 g (Table 4).

Perioperative Complications

Operative mortality was 0%. Morbidity for those undergoing resection was 16.6%. Transient biliary leakage was observed in three patients, and lymphorrhea, abdominal collection, pneumonia, and fever of unknown origin were seen in one patient each,

Table 4. Pathologic findings in patients undergoing resection

	No.	Positive
Lymph nodes	55	10 (18.8%)
Liver tissue	53	7 (13.2%)

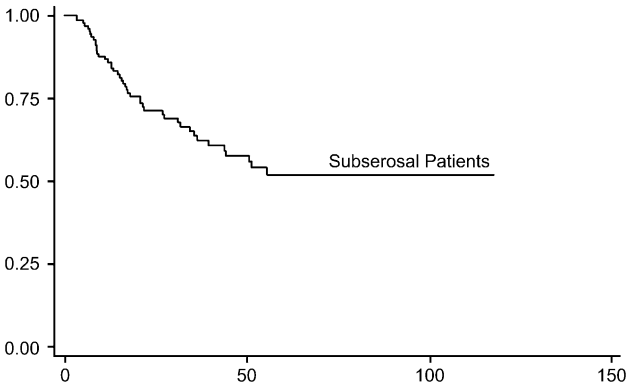

Fig. 1. Kaplan-Meier estimates of overall survival for the entire cohort.

respectively. The only patient to undergo reoperation was the one with lymphorrhea; the reason for the operation was the presence of intense abdominal pain. At reoperation, a small amount of a liquid with lymphatic characteristics was found in the minor pelvis. The abdominal abscess was drained percutaneously.

Survival

Mean follow-up of the patients in the study was 20.8 months, ranging between 2 and 116 months (SD, 27.95 months). The overall survival rate in the series was 67.7% (Fig. 1). Figure 2 shows the survival curve of patients who underwent resection versus those who underwent only cholecystectomy. Those undergoing resection had a greater 5-year survival rate but with no statistical significance ($P = 0.07$).

The presence of lymph node metastases and liver involvement were associated with a worse prognosis when survival in groups with and without invasion was studied (45% versus 70% 5-year survival rate for patients with lymph node compromise versus no lymph node involvement [$P = 0.06$] and a 42% versus 82% 5-year survival rate in those with invasion of the liver versus those without invasion [$P = 0.002$]) (Figs. 3, 4).

Prognostic Factors

To know the true value of prognostic factors, a Cox proportional hazard regression model was designed according to the following factors: (1) macroscopic type, (2) lymph node status, (3) liver infiltration, and (4) age older than 50. In this model, the absence of lymph node compromise was associated with significant improvement in overall survival. The P values and relative risks are shown in Table 5.

DISCUSSION

Among the reasons to explain the lower survival rate of patients with GC, late diagnosis has been cited as one of the most important.[9,10] In this series, the diagnosis of GC was mainly performed after the pathologic examination of the cholecystectomy specimen. This factor stresses the poor value that examinations such as ultrasonography and computed tomography scanning have in the detection of small lesions. The higher percentage of flat and

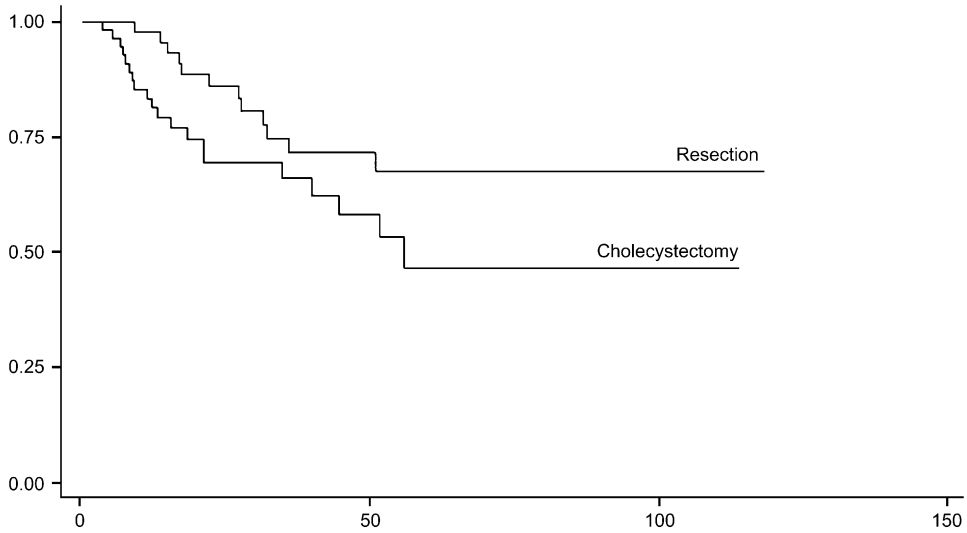

Fig. 2. Kaplan-Meier estimates of overall survival, comparing those who underwent resection with those who underwent only cholecystectomy ($P = 0.07$).

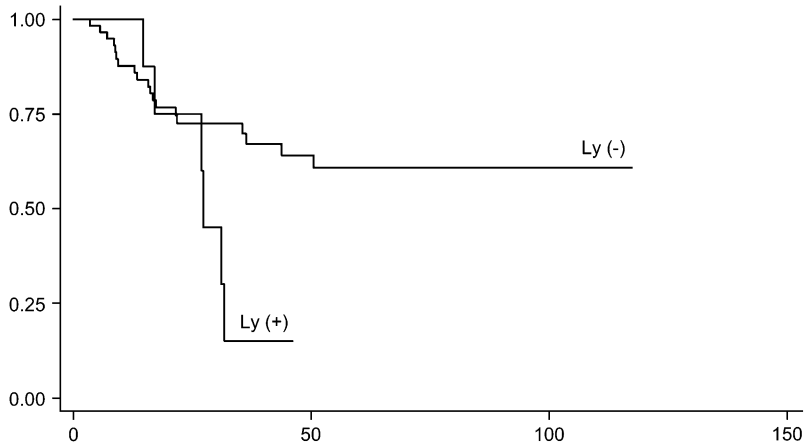

Fig. 3. Kaplan-Meier estimates of overall survival for patients who underwent resection comparing those with lymph node compromise [Ly (+)] versus those without compromise [Ly (−)] ($P = 0.06$).

nonapparent lesions, many of which were not recognized during the macroscopic examination of the gallbladder mucosa, explains the above results. Moreover, inflammation of the gallbladder wall contributes to the poor visualization.

This lower rate of preoperative suspicions makes greater the possibility of finding an unapparent tumor and increases the number of technical considerations that Chilean surgeons need to take into account when performing a cholecystectomy. Among patients older than 60 undergoing a cholecystectomy, the proportion of coincident GC is almost 10%.[11,12]

There is almost universal agreement to use an extended cholecystectomy for the management of patients with resectable GC; however, there is no scientifically proven evidence to support this management. Most series compare patients who underwent resection with a group treated only by a cholecystectomy, and we have no information about their potential resectability.[5,13,14] This study performed similar analyses and obtained similar results. However, an extended cholecystectomy is the most commonly used procedure for treatment. The definitive answer regarding its real value should come from a randomized trial comparing patients with and without reoperation.

The resection of the common bile duct associated with an extended cholecystectomy is another point of discussion: the complete excision of lymphatics around the duct would be better performed if the duct were excised. However, such a statement is based largely on theory rather than on clinical or pathologic studies. On the other hand, the addition of common bile duct resection could be associated with higher morbidity compared with the morbidity of patients without resection.

At present, the laparoscopic cholecystectomy is the "gold standard" in the treatment of gallstone disease. However, concern about its influence on the prognosis has been mentioned in a number of reports.[15–17] Because open procedures are largely used in patients undergoing emergency surgery in Chile, most patients in this series were treated in this manner. Perhaps a greater use of the laparoscopic cholecystectomy is associated with a poorer resectability and prognosis.

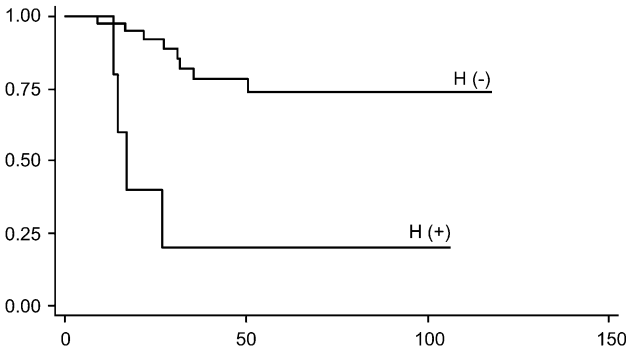

Fig. 4. Kaplan-Meier estimates of overall survival for patients who underwent resection comparing those with hepatic compromise [H (+)] versus those without compromise [H (−)] ($P = 0.002$).

Table 5. Cox's proportional hazards model

Factor	Hazards ratio	*P* Value	95% Confidence interval
Lymph node status	5.65	0.014	1.42–22.36
Liver infiltration	3.93	0.071	0.89–17.35
Age >50 y	1.03	0.960	0.26–4.02
Macroscopic type	1.24	0.800	0.23–6.56

Traditionally, the overall 5-year survival of patients with GC has been less than 10%.[9] These dismal results are mainly due to the advanced stage of the disease at the moment of diagnosis. In countries such as Chile, however, where GC is commonly detected, a higher proportion of GC cases correspond to early forms associated with longer survival.[11,12] This fact is clearly observed from the analysis of the percentage of early tumors among those with GC. At our center, mucosal and muscular tumors comprise 23% of the total number of gallbladder tumors.[18]

In this series, an overall survival rate of 67.7% was observed. This result is a consequence of the detection of patients with early forms of GC among those who underwent a cholecystectomy for a presumed benign disease.

From our results, we can also point out the importance of lymph nodes as a prognostic factor. All patients with lymph node compromise had involvement of lymph nodes located in the hepatic pedicle, mainly in the cystic and the choledocoduodenal node. The involvement of lymph nodes along the hepatic pedicle follows a constant pathway, first compromising those located near the cystic duct and then the choledocoduodenal node to reach the para-aortic nodes through the retropancreatic lymph nodes.

Despite the fact that the same surgeon operated on all the patients, there were variations in the number of dissected lymph nodes. This variation could be due to local changes in the hepatic pedicle that make dissection more difficult. The presence of fibrosis secondary to the surgical trauma or to the existence of a T-tube may be responsible for this numerical variation.

The 5-year survival rate of patients who underwent resection but had lymph node compromise was significantly worse than the survival rate in the same group without lymph node compromise. By using this factor, we can distinguish two different types of populations among those who have lymph nodes evaluated. From the analysis of our lymph node compromise rate, we realized the lower percentage of lymph node compromise observed in our patients. Only 10 (18.8%) patients undergoing dissection had lymph node metastases. This rate is lower than that published in other reports, which could be explained by the fact that all of the patients in our series had undergone a previous cholecystectomy. This first surgical approach would permit a more precise staging, meaning that only patients about whom a more precise knowledge of their disease extension is available would receive reoperation. Furthermore, our series of patients was restricted to those where invasion was located on the peritoneal side of the gallbladder. In previous studies, we observed a worse prognosis for patients with tumor invasion of the hepatic side of the gallbladder.[5] This fact is reinforced by our higher resectability.

Liver extension was also observed to be associated with a worse prognosis, although there is no statistical significance.

CONCLUSION

Despite the generally poor survival rate of patients with lymph node metastases, the study of patients with intermediate forms of the disease, such as subserosal tumors, allows us to obtain a selected group with good survival. This particular group of patients is obtained in areas where the disease is more prevalent and the cholecystectomy specimen is deeply studied.

Unfortunately, the type of treatment for the disease is mainly supported by expert opinions and analysis of dissemination routes, lacking the development of a randomized trial that challenges the true value of the extended cholecystectomy.

Given the existence of poor prognostic factors among patients undergoing curative resection, adjuvant strategies must be studied in these groups of patients.

REFERENCES

1. de Aretxabala X, Roa I, Burgos L, et al. Gallbladder cancer in Chile. A report on 54 potentially resectable tumors. Cancer 1992;69:60–65.
2. Wistuba I, Gazdar AF. Gallbladder cancer: lessons from a rare tumor. Nat Rev J Cancer 2004;4:695–705.
3. Ito H, Matros E, Brooks DC, et al. Treatment outcomes associated with surgery for gallbladder cancer. J Gastrointest Surg 2004;8:183–190.
4. Wakai T, Shirai Y, Yokoyama N, et al. Depth of subserosal invasion predicts long term survival after resection in patients with T2 gallbladder carcinoma. Ann Surg Oncol 2003;10: 447–454.
5. de Aretxabala X, Roa Y, Burgos L, et al. Curative resection in potentially resectable tumours of the gallbladder. Eur J Surg 1997;163:419–426.
6. Dixon E, Vollmer CM, Sahajpal A, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer. A 12 year study at a North American center. Ann Surg 2005;241:385–394.
7. Nakamura S, Sakaguchi S, Suzuki S, et al. Aggressive surgery for carcinoma of the gallbladder. Surgery 1989;106:467–473.
8. Matsumoto Y, Fujii H, Aoyama H, et al. Surgical treatment of primary carcinoma of the gallbladder based on histologic analysis of 48 surgical specimens. Am J Surg 1992;163: 239–245.
9. Cubertafond P, Gainant A, Cucchiaro G. Surgical treatment of 724 carcinomas of the gallbladder. Results of the French surgical association survey. Ann Surg 1994;219:275–280.
10. Donohue JH. Present status of the diagnosis and treatment of gallbladder carcinoma. J Hepatobiliary Pancreat Surg 2001;8:530–534.

11. Roa I, Araya JC, Villaseca M, et al. Preneoplastic lesions and gallbladder cancer: an estimate of the period required for progresion. Gastroenterology 1996;111:232–236.
12. de Aretxabala X, Roa I, Mora J, et al. Manejo de pacientes con invasion de la tunica muscular. Rev Med Chile 2004; 132:183–188.
13. Shirai Y, Yoshida K, Tsukada K, et al. Inapparent carcinoma of the gallbladder. An appraisal of a radical second operation after simple cholecystectomy. Ann Surg 1992;215:326–331.
14. Fong Y, Jamagin W, Blumgart LH. Gallbladder cancer. Comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention Ann Surg 2000;232:557–569.
15. Clair DG, Lautz DB, Brooks DC. Rapid development of umbilical metastases after laparoscopic cholecystectomy for unsuspected gallbladder carcinoma. Surgery 1993;113: 355–357.
16. Wiebbenmeyer LA, Wade TP, Chen RC, et al. Laparoscopic cholecystectomy can disseminate in situ carcinoma of the gallbladder. J Am Coll Surg 1995;181:504–510.
17. de Aretxabala X, Roa I, Mora J, et al. Laparoscopic cholecystectomy: its effect on the prognosis in gallbladder cancer. World J Surg 2004;28:544–547.
18. de Aretxabala X, Roa I, Burgos L. Gallbladder cancer: management of early tumors. Hepatogastroenterology 1999;46: 1547–1551.