ORIGINAL ARTICLE

T1b gallbladder cancer: is extended resection warranted?

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Abstract

Background: Although the prognosis for gallbladder cancer (GBCA) improves with early diagnosis and aggressive surgical treatment, the management of patients with muscle layer invasion (T1b) remains controversial. This study aimed to analyze the optimal surgical approach for these patients.

Methods: A database was queried for patients with early T1b GBCA treated at four Chilean hospitals. Patients were prospectively treated and registered by the same surgical team at each hospital. Clinical outcomes, including survival rates according to the type of surgery, were analyzed.

Results: Between 1988 and 2023, 129 Chilean patients were pathologically diagnosed with T1b GBCA. Simple cholecystectomy (SC) was performed in 86 patients (66.7 %), while extended cholecystectomy (EC) was performed in 43 patients. The overall 5-year survival rate was 83 %, with no significant difference between SC and EC patients.

Conclusion: Simple cholecystectomy demonstrated survival rates comparable to extended cholecystectomy for patients with T1b GBCA. More extensive resections did not improve the prognosis.

Received 16 July 2024; accepted 23 December 2024

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Introduction

Gallbladder cancer (GBCA) accounts for 80–95 % of biliary tract cancers worldwide; however, it remains relatively rare, with an estimated incidence of 1.2 per 100,000 people annually worldwide and 11.7 per 100,000 in Chile.[1–3]

GBCA is associated with a poor prognosis, with a median survival of only six months due to early dissemination through the lymphatic system, hematogenous routes, and the peritoneum.[2–5] Early diagnosis and aggressive surgical treatment, achieving an R0 resection, can significantly improve the prognosis.[6] Tumors are classified as early-stage when neoplastic cells are confined to the mucosa or muscular layers. Over the past 20 years, laparoscopic surgery has improved the diagnosis of incidental GBCA, thereby increasing the likelihood of curative resections.[6,7]

The depth of infiltration classifies early GBCA as either mucosal (T1a) or muscular (T1b). Current guidelines recommend simple cholecystectomy (SC) for T1a patients, with a five-year survival rate of approximately 95 %.[4,7–11] For tumors with deeper invasion, such as those extending into the perimuscular connective tissue (T2), extended cholecystectomy (EC) which includes resection of the gallbladder bed and lymphadenectomy of the hepatic pedicle is advised.[11,12] Despite aggressive therapy, the five-year survival rate for T2 patients does not exceed 60 %.[6,12,13]

However, the optimal management of T1b patients, whose tumors invade the muscle layer, remains controversial. This group represents an intermediate stage, and both SC and EC are considered valid options.[7,9,10] Due to the low incidence of GBCA, conducting randomized prospective trials to determine the effect of extended surgery on T1b outcomes is challenging.

This study aims to evaluate a series of patients with T1b GBCA, focusing on optimal surgical management and comparing survival outcomes between EC and SC in a multicenter cohort.

Materials and methods

Patients and data collection

This study utilized a prospective database containing information on patients diagnosed with potentially resectable GBCA since 1988. The database includes demographic, pathological, operative, perioperative, and survival data. Tumors were classified as potentially resectable if the gallbladder and tumor were completely excised with no residual tumor beyond the resection

margins. All specimens were analyzed by a pathologist with expertise in GBCA. The cholecystectomy was considered the index surgery for follow-up. A total of 129 patients with T1b GBCA, classified according to the 8th edition of the American Joint Committee on Cancer (AJCC), were included.[8]

The patients were treated at four Chilean hospitals: Hernán Henríquez Aravena Hospital, Clínica Alemana de Santiago, Padre Hurtado Hospital, and the Chilean Air Force Clinical Hospital. Between 1988 and 2023, all patients were managed by two surgeons (X de A and H L).

All patients underwent preoperative staging, which included a multi-slice helical CT scan, a comprehensive physical examination, and standard blood tests. The macroscopic tumor type was determined by visual inspection conducted by the pathologist.

Following SC, cases were reviewed in tumor boards. Given the lack of robust evidence regarding the benefits of EC for T1b patients, surgeons explained the current state of knowledge and outcomes for both SC and EC to the patients and their families. The final decision regarding reoperation was made jointly with the patient and their family.[7,9,10]

Surgical procedures

Open reoperations were performed until 2005, after which laparoscopic techniques became the standard method for re-exploration. Reoperations included resection of the gallbladder bed and lymphadenectomy, including lymph nodes along the hepatic pedicle.

Patients were excluded if they had a different TNM stage, were deemed unresectable, or had incomplete staging. Signs of non-resectability during reoperation included peritoneal dissemination, distant lymph node involvement, and invasion of adjacent organs. Neoadjuvant or adjuvant chemotherapy was not standard for T1b GBCA and was not administered.

Statistical analysis

Categorical variables were described using counts and percentages, while continuous variables were summarized using medians, ranges, and standard deviations (SD). Survival was calculated from the index cholecystectomy to death. *P*-values <0.05 were considered statistically significant. A multivariate logistic regression analysis was conducted to identify independent factors associated with prognosis. Five-year disease-specific survival was evaluated using Kaplan–Meier curves, and groups were compared using Mantel–Cox analysis.

Missing data were left unfilled, and no imputation methods were applied. Postoperative complications were classified according to the Clavien-Dindo criteria.[14]

Ethical considerations

This study was approved by the investigational review ethics committee and conducted in compliance with the Declaration of Helsinki (Protocol 010/2018). All patient data were kept confidential, and the procedures adhered to relevant laws and institutional guidelines.

Results

Patient characteristics

This study included 129 Chilean patients diagnosed with pathologically confirmed T1b GBCA between 1988 and 2023. The cohort comprised 23 men (17.8 %) and 106 women (82.2 %), with a mean age at diagnosis of 62 years (range: 30–92 years, SD: 12.12). Regarding preoperative diagnoses, acute cholecystitis was the indication for surgery in 46 patients (35.7 %), while cholelithiasis accounted for the remainder (Table 1).

Characteristics according to surgery performed

Open cholecystectomy was initially performed in 69 patients (53.5 %), while 48 underwent laparoscopic procedures, and three required conversion to open surgery. The type of cholecystectomy was not recorded for nine patients. One patient with a suspected tumor on preoperative evaluation underwent an extended resection during the same surgery as the cholecystectomy. For the remaining patients, the tumor diagnosis was not suspected before cholecystectomy, and simple cholecystectomy (SC) was performed initially.

In 85 patients (65.9 %), the macroscopic appearance of the tumor was inapparent or plain, and pathologists did not suspect GBCA until the histological examination.

Of the 129 patients, 86 (66.7 %) underwent SC as the definitive treatment, while 42 (32.6 %) underwent reoperation to resect the liver bed with associated lymphadenectomy. As previously mentioned, one patient underwent an extended resection immediately after the cholecystectomy.

Postoperative outcomes

No Clavien-Dindo postoperative complications higher than grade II were observed.

At five years, 114 patients (88.4 %) were alive, and 105 (81.4 %) were alive at the end of the follow-up period.

Among the patients who died during the follow-up, nine died from a GBCA; the remaining patients had diseases other than GBCA. Of the patients who underwent SC, four (4.6 %) died from GBCA, while among the 43 patients who underwent EC, five (11.6 %) patients died from GBCA. Regarding the timing of death, two patients died within 12 months of diagnosis, three between 12 and 24 months, and another three between 24 and 36 months. Notably, one patient survived for 15 years post-diagnosis but ultimately died from a recurrence in the biliary tract after undergoing SC. In the EC group, two patients had positive lymph nodes, and one had hepatic involvement. Of the two patients with lymph node involvement, one remains alive, while the other died during the follow-up period. The patient with hepatic involvement (with adenocarcinoma) died as a result of the disease.

Table 1 Comparison of the baseline characteristics for patients who underwent Simple Cholecystectomy and those who underwent Extended Cholecystectomy

	Simple cholecystectomy	Extended cholecystectomy	Total
Gender			
Male	15 (11.6 %)	8 (6.2 %)	23 (17.8 %)
Female	71 (55 %)	35 (27.1 %)	106 (82.2 %)
Age			
<65	44 (34.1 %)	30 (23.3 %)	74 (57.3 %)
≥65	42 (32.6 %)	13 (10.1 %)	55 (42.6 %)
First surgery			
Open cholecystectomy	50(38,8 %)	19 (14.7 %)	69 (53,5 %)
Laparoscopic cholecystectomy	26 (20.2 %)	21 (16,3%)	47 (36.4 %)
Extended cholecystectomy	0 (0 %)	1 (0.8 %)	1 (0.8 %)
Converted	1 (0.8 %)	2 (1.6 %)	3 (2.3 %)
Acute cholecystitis	38 (29.5 %)	8 (6.2 %)	46 (35.7 %)
Cholelithiasis	48 (37.2 %)	35 (27.1 %)	83 (64.3 %)
Died because of gallbladder cancer	4 (3.1 %)	5 (3.9 %)	9 (7 %)

Table 2 Operative findings and its relation with the elapsed time between cholecystectomy and reoperation

Days	Total patients	Ly (+)	H (+)
1–89	14	0	1
90–180	16	1	0
>180	12	1	0

Ly (+): positive lymph node.
H (+): hepatic involvement with adenocarcinoma.

Among the patients who died from gallbladder cancer after radical cholecystectomy, one was reoperated within three months, two were reoperated between three and six months, and two were reoperated after six months.

Surgical approaches in EC

Of the 43 patients treated with EC, 27 underwent an open approach, while 16 underwent laparoscopic surgery. Among the laparoscopic cases, three required conversion to open surgery, and 13 underwent complete laparoscopic resections.

The time between cholecystectomy and reoperation ranged from 23 to 277 days (median: 114 ± 79.96 days). In 14 patients (33.3 %), the interval was less than 90 days; in 16 (38.1 %), it ranged from 90 to 180 days, while in 12 patients (28.6 %), the interval exceeded 180 days (Table 2).

The median number of harvested lymph nodes was seven (range: 0–19). Among the EC patients, two (4.7 %) had positive lymph nodes (Ly+), with the involved nodes located in the hepatic pedicle (Fig. 1). Regarding hepatic involvement (H+), one patient had liver infiltration in the specimen.

Prognostic factors

The following factors were analyzed for their association with prognosis: age below 55 years, type of cholecystectomy (open or laparoscopic), type of resection (open, laparoscopic, or converted), acute cholecystitis as the primary diagnosis, tumor differentiation grade, lymph node involvement, hepatic infiltration, macroscopic tumor type, and the surgical approach used (SC or EC) (Table 3).

None of the analyzed factors were statistically associated with lower survival. The overall five-year survival rate was 83 %, with no significant differences between SC and EC patients ($P = 0.991$) (Fig. 2).

Discussion

Chile has one of the highest incidences of GBCA in the world, and as observed in this series, women are disproportionately affected. One possible explanation is the higher prevalence of gallstones among women in Chile.[3]

GBCA is known as a disease with a poor prognosis, and surgery remains the only curative treatment. Achieving an R0 resection is critical, as complete tumor removal significantly improves both overall and long-term survival.[6,7] However, preoperative diagnosis of early-stage GBCA is challenging. Even during cholecystectomy, a tumor is rarely identified. In this study, only one patient had a tumor suspected prior to cholecystectomy, and only a few tumors were observed during the macroscopic pathology examination. This reinforces the importance of routine, rather than selective, histopathological examinations in detecting incidental tumors.[15]

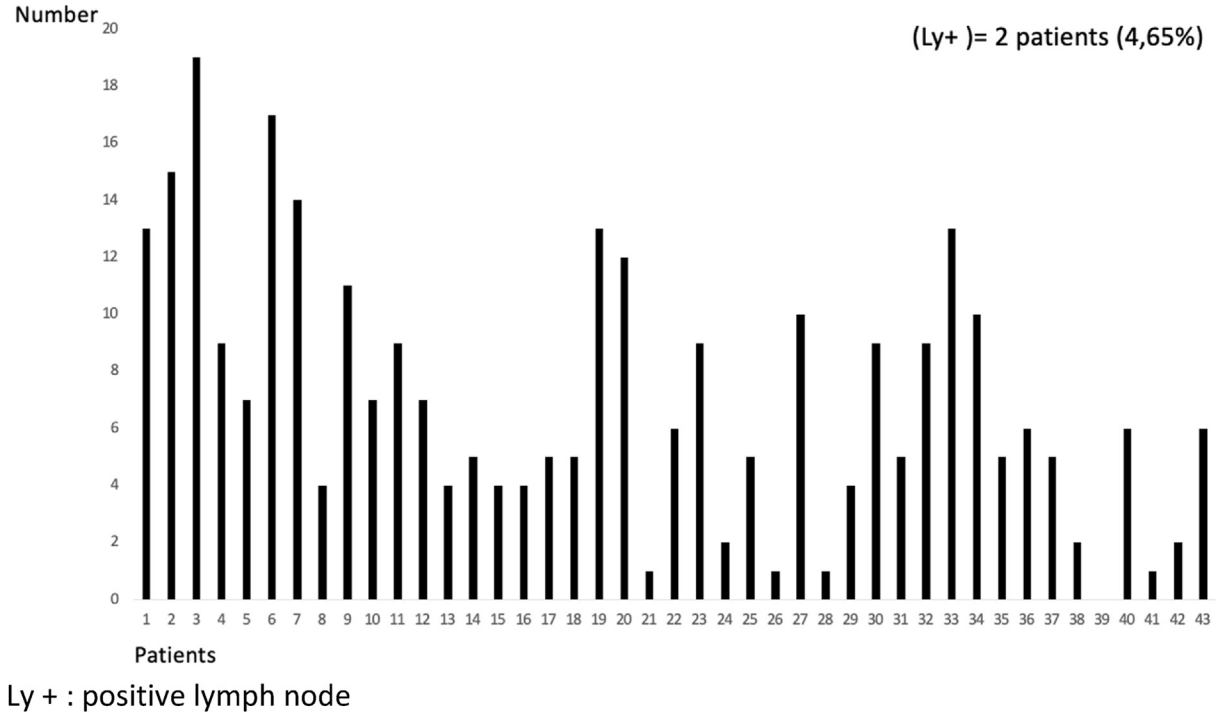

Figure 1 Number of harvested lymph nodes by patient treated with extended cholecystectomy

Table 3 Logistic regression analysis of factors related to prognosis

	n/%	Hazard Ratio (HR)	p Value	95 % CI HR
Type of surgery				
Simple cholecystectomy	86 (66.7 %)			
Extended cholecystectomy	43 (33.3 %)	1.00	0.99	0.41 a 2.45
Type of cholecystectomy (initial procedure)				
Open	69 (53.5 %)			
Laparoscopy	48 (37.2 %)	0.52	0.20	0.19 a 1.43
Converted	3 (2.3 %)	2.62	0.35	0.33 a 20.51
Unknown	9 (6 %)			
Type of extended cholecystectomy				
Open	27 (62.8 %)			
Laparoscopy	13 (30.2 %)	0.97	0.97	0.18 a 5.22
Converted	3 (6 %)	1.06	0.95	0.12 a 9.13
Age				
<65	74 (57.4 %)			
≥65	55 (42.6 %)	1.43	0.37	0.64 a 3.21
Gender				
Male	23 (17.8 %)			
Female	106 (82.2 %)	1.36	0.61	0.40 a 4.61
Acute cholecystitis	45 (35.7 %)	1.58	0.27	0.69 a 3.58

Table 3 (*continued*)

	n/%	Hazard Ratio (HR)	p Value	95 % CI HR
Differentiation grade				
Well	56 (43.4 %)			
Other (poor, moderate, unknown)	73 (56.6 %)	1.54	0.32	0.65 a 3.66
Lymph node stage				
Ly0	41 (95.4 %)			
Ly1	2 (4.7 %)	4.10	0.17	0.54 a 30.83
Lymph node harvested				
<7	110 (85.3 %)			
≥7	19 (14.7)	0.94	0.92	0.27 a 3.17
Macroscopic type				
Inapparent plane (e)	85 (65.9 %)	0.77	0.63	0.27 a 2.20
Other (a,b,c,d,unknown)	44 (33.3 %)			

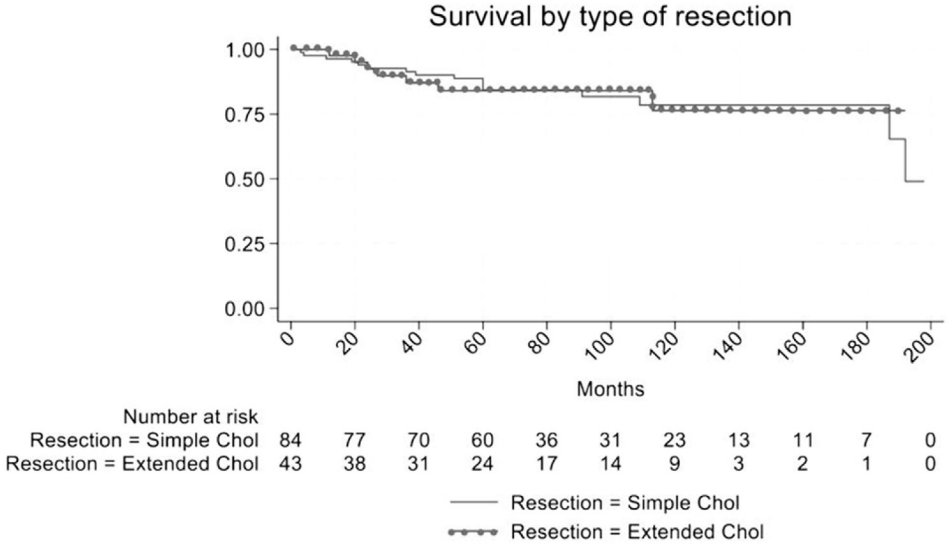

Figure 2 Survival by type of resection (EC or SC)

Tumor invasion (T), as defined by the American Joint Committee on Cancer (8th edition), plays a crucial role in management decisions. In alignment with NCCN guidelines,[4,8] SC is the standard treatment for patients with mucosal tumors, although its use for muscular lesions remains controversial. Optimal surgical management for T1b GBCA presents a clinical challenge, as the evidence remains inconclusive.[7,16–20] Conversely, EC, which includes liver wedge resection or segment 4b and 5 segmentectomy with dissection of hepatic pedicle lymph nodes, is required for subserosal involvement and more advanced tumors.[11,12,21]

In this study, SC showed no survival differences compared to more extensive procedures. Other authors have reported similar findings. A meta-analysis of 2578 patients concluded that SC and EC have comparable survival outcomes in T1 patients.[9] Additionally, an international multicenter study from specialized tertiary hospitals found no significant differences in five-year disease-specific survival between SC and EC for T1b patients.[10]

The ongoing debate regarding the surgical treatment of T1b GBCA may stem from challenges in achieving standardized pathological diagnoses. Estimating tumor depth in the gallbladder wall relies on comprehensive specimen mapping. Some tumors classified as T1b could potentially be T2 if thorough mapping were performed. This may explain why some studies associate T1b tumors with a worse prognosis than observed in our series.[22] In this study, all specimens underwent complete mapping.

Lymphatic involvement is another crucial prognostic factor in GBCA, strongly influencing survival. In the absence of lymphatic metastases, five-year survival rates range from 80 % to 100 %; however, with node involvement, survival drops significantly.[6,11,23,24] Previous studies report a 13 % lymph node

metastasis rate in T1b patients,[24] supporting EC with lymphadenectomy as an accepted management strategy. According to the AJCC (8th edition), the standard recommendation is to pathologically examine at least six lymph nodes. However, recent evidence suggests no survival benefit from lymphadenectomy in T1b tumors.[10] In this study, only two patients had lymph node metastases, highlighting the potential for selective management in T1b GBCA.

The lower rate of lymph node involvement in this study occurred despite a significant number of patients undergoing reoperation long after initial cholecystectomy. Only 14 patients underwent reoperation within 90 days post-cholecystectomy. Delayed reoperations may reflect limitations in Chile's healthcare system, where timely access to care is not always available, particularly in rural populations like this sample.

No survival differences were observed between patients who underwent open or laparoscopic reoperations. Increasing evidence supports both approaches as acceptable options for GBCA surgery. A large multi-institutional study on laparoscopic management of incidental GBCA found that laparoscopic re-resection in selected patients is safe, oncologically effective, and associated with morbidity rates similar to those of the open approach.[25] Both approaches offer comparable perioperative and long-term oncological outcomes, and a minimally invasive approach should be considered an acceptable standard of care.[26,27]

The main limitations of this study include the extended time frame required to gather sufficient patient data and potential selection bias in treatment decisions. Since the study's inception, patients were classified according to tumor depth, ensuring uniform classification over time. The study's strengths include the consistent methodology applied and adherence to standardized care practices. Additionally, pathologists and surgeons at participating centers were trained under a unified specimen evaluation methodology and surgical principles.

Conclusion

In this study, SC demonstrated survival outcomes comparable to EC for patients with T1b GBCA. More extensive resections did not improve the prognosis. Appropriate staging and histopathological evaluation are fundamental to guiding surgical decisions. While further large-scale, multicenter studies are needed to refine treatment guidelines, EC may not be necessary, as it does not appear to offer survival benefits for T1b tumors.

Funding sources

None.

Conflicts of interest

None declared.

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