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# Gallbladder cancer who is really cured?

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## Abstract

**Background:** Although gallbladder cancer (GBCA) is characterized by a dismal prognosis, there is a proportion of patients who are cured. The aim of this study was to analyze the profile of these patients.

**Methods:** A database was queried for patients who underwent curative resection with a follow-up of at least 5 years. Patients were prospectively treated and registered by the same surgical team. A multivariate regression analysis was used to identify factors associated with long-term survival.

**Results:** From 1988 to 2013, 461 patients were evaluated and 112 who underwent resection were analyzed. Among the patients, five year survival was 57% while lymph node and liver compromise were the only independent factors associated with survival. On the other hand, the elapsed time between the cholecystectomy and the resection, the differentiation grade and the level of wall invasion did not have an independent effect on the prognosis.

**Conclusion:** Despite its poor prognosis, a subset of patients can be cured of GBCA. R0 resection of patients without lymph and liver infiltration are key to GBCA survival.

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## Introduction

Although considered a rare disease with an estimated incidence of 1.2 per 100.000 people each year, GBCA is common in some countries of South America, India and Western Europe.[1–4]

The prognosis of the disease is poor due to its early spread via lymphatic, hematogenous, and peritoneal pathways.[5–8] Nevertheless, the prognosis is better in those patients harboring an early gallbladder cancer which is generally detected during the pathology exam of a cholecystectomy specimen and undergoing an R0 resection.[8–12] During the last two decades, the detection of GBCA has increased in line with the increases in cholecystectomy rates.[11]

Due to its lower incidence, most of series studying GBCA includes a small number of patients and incomplete follow up. On the other hand, larger series comprise retrospective data from patients obtained from multiple centers.[7,13–15]

With the focus on patients considered to be cured of the disease, we performed an analysis of a series of patients harboring GBCA who underwent lymphatic dissection and resection of the gallbladder bed with a follow-up of at least 5 years.

The aim of the study was to identify clinical and pathologic characteristics to select patients likely to be cured of GBCA.

## Method

Since 1989 the main author has directed a prospective database of patients referred to him with potentially curable GBCA. This database contains demographic, pathological, operative, perioperative, and survival information. To classify a tumor as potentially resectable, after a cholecystectomy, the gallbladder had to have been removed and there could be no tumor spread beyond the area to be resected during the reresection.

461 patients with gallbladder cancer were treated in two different centers according to the date of the definitive surgery, From 1989 to 2003, patients were treated at Temuco Regional Hospital, whereas from 2004 to date, patients have been treated at the Clinica Alemana in Santiago. In both centers, the surgeon in charge of patients was the main author.

After the pathological diagnosis of gallbladder cancer performed elsewhere, patients were referred for evaluation. At this time the therapeutic plan was explained and patients were free to accept or decline the therapy.

The staging was based on a helicoidal multi-slice CT of the chest and abdomen in addition to a complete physical exam and common blood tests. An open approach was the way to perform

 

the re-exploration until 2005 while a laparoscopic approach has since become the preferred method. During the abdominal exploration, non-resection signs included: peritoneal dissemination, adjacent organ infiltration, and para-aortic lymph node compromise. Para aortic lymph nodes were routinely extirpated for frozen biopsy. Surgical techniques have already been shown in detail elsewhere.[16–18]

Among the patients, 62 were not included in the analysis because they had a follow-up shorter than 5 years. Of the 399 patients who were evaluated for reoperation, 189 were able to undergo reoperation while 210 patients did not. The Reason for not undergoing surgery were: 100 had the tumor confined to mucosal or muscular, 37 had inoperability signs observed during the evaluation for staging, 44 refused to undergo reoperation, 29 were older or had a medical condition making the surgery risky.

Among those undergoing reoperation 112 were resected, while 77 patients had operative findings precluding the resection.

Of the patients, all except one underwent a cholecystectomy during the first procedure while the other only had an exploratory laparoscopy. Neoadjuvant or adjuvant chemotherapy was not considered the standard of care and was administered in some patients based on the presence of risk factors such as lymph nodes or liver compromise.

Classification of the disease was performed according to the 8th edition of the American Join Committee on cancer (AJCC) manual.[19]

This study was performed according to the ethics guidelines of the Declaration of Helsinki and was approved by the investigational review board of ethics committee.

Native Mapuche ethnic origin was catalogued based on the presence of at least one Mapuche family name.

Patient characteristics were described using counts and percentages for categorical variables and median, range and standard deviation (SD) for continuous variables. Survival was calculated from the index cholecystectomy until death. P-values were considered statistically significant when <0.05. A multivariate logistic regression analysis was employed to identify independent factors associated with prognosis.

## Results

The cohort was composed of 93 (83%) female and 19 male patients, age ranging from 76 to 30 years old, (mean 55 SD: 9.74). Of these, 18 had at least one Mapuche family name.

Concerning the preoperative diagnosis, a gallbladder tumor was suspected in four patients before the cholecystectomy, while acute cholecystitis was the indication for surgery in 39 patients. Gallstone associated diseases were observed in 111 of the patients.

Open cholecystectomy was performed as the initial procedure in 76 patients while the rest underwent a laparoscopic procedure.

In terms of diagnosis, only 19 patients was a tumor suspected during the procedure. Of these patients, 18 underwent cholecystectomy while the other in whom a tumor was suspected, only an exploratory laparoscopy was performed as an initial procedure, and then radical surgery was indicated. 83 patients had a pathological T stage of pT2 and were most commonly moderately differentiated. Among the pT2 patients, tumor location within the gallbladder was available for 61 patients (73.5%). Of these cases, 53 (86,8%) tumors were most commonly localized on the peritoneal side. On the other hand, 8 were localized on the hepatic side.

Residual tumor in both lymph nodes and liver were statistically related to the depth of wall invasion. Among patients with pT2 invasion, lymph nodes and liver were involved in 21 and 13 respectively (Table 1).

The elapsed time between cholecystectomy and reoperation ranged between 15 and 283 days (mean 84.8 S.D. 51,1). In 69 (61,6%) patients the time between the two surgeries was less than 90 days. To evaluate the effect of the elapsed time on the presence of residual tumor, we divide the patients into three groups, observing no relation between the elapsed time and the presence of residual tumor (Table 2).

In 89 patients, an open approach was the method used to perform the resection, while in 23 the method was laparoscopic. Of these patients, 14 were converted before finishing the resection whereas in 9 the resection was completely performed by laparoscopy.

Of the patients 64 (57.1%) were alive at five years, while 11 died during the first year after the cholecystectomy.

The number of dissected lymph nodes ranged between two and 21 (mean 8.9 SD. 4.3). 30 patients had at least one lymph node involved. The number of involved nodes ranged between one and eight. No relation was observed between the total number of dissected lymph nodes and the presence of lymph node compromise (Table 3).

Of the 30 patients with at least one lymph nodes involved, 24 died during the follow-up, while 6 completed 5 years of follow-up. On the other hand, the two patients with n2 compromise died within the follow-up period.

With regard to liver compromise, 23 patients had liver infiltration in the specimen and it was completely resected. Of these patients, four were alive after follow-up.

71 (62,8%) patients showed no residual tumor neither lymph nodes nor liver during the pathological study. Of these

**Table 1** Residual tumor according level of wall infiltration

| | Liver (+) | Lymph nodes (+) |
|---|---|---|
| All | 23/112 | 30/112 |
| T1b | 1/12 | 1/12 |
| T2 | 13/83 | 21/83 |
| T3 | 9/17 | 8/17 |

Liver P:0.0013.
Lymph P:0.019.

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

| Days | Total patients | Ly (+) | H (+) |
|---|---|---|---|
| 1–60 | 42 | 12 | 10 |
| 61–90 | 27 | 3 | 7 |
| >91 | 42 | 15 | 6 |

P = 0.119 (Ly).
P = 0.417 (H).

**Table 3** Number of lymph nodes dissected versus number of patients with positive lymph nodes

| Number of nodes dissected | N (–) | N (+) | Number of patients |
|---|---|---|---|
| 2 | 1 | 1 | 2 |
| 3 | 3 | 3 | 6 |
| 4 | 6 | 2 | 8 |
| 5 | 9 | 2 | 11 |
| 6 | 5 | 1 | 6 |
| 7 | 9 | 4 | 13 |
| 8 | 9 | 6 | 15 |
| 9 | 11 | 1 | 12 |
| 10 | 5 | 2 | 7 |
| 11 | 4 | 1 | 5 |
| 12 | 4 | 2 | 6 |
| 13 | 3 | 2 | 5 |
| 14 | 2 | 0 | 2 |
| 15 | 1 | 2 | 3 |
| 17 | 6 | 1 | 7 |
| 19 | 1 | 0 | 1 |
| 20 | 1 | 0 | 1 |
| 21 | 2 | 0 | 2 |

P = 0.078.

patients, 16 did not complete the 5 years follow-up and died during the observation period. Table 4, provides details of patients with lymph node involvement that survived more than 5 years.

To study independent factors associated with survival, the following factors were studied: age less than 55 years, type of cholecystectomy (open or laparoscopic), type of resection (open, laparoscopic or converted), acute cholecystitis as the primary diagnosis, elapsed time between cholecystectomy and resection (less than 60 days, 61 and 90 days, more than 90 days), differentiation grade, pT classification, lymph node compromise, liver compromise, neoadjuvant or adjuvant chemotherapy, and place and time where the resection was performed. Among these factors, only lymph node and liver compromise were identified as independent prognostic factors Table 5.

## Discussion

Although GBCA is considered a disease associated with a poor prognosis, patients with long-term survival are reported and surgery is the only way to achieve curative results.[6,17,20]

A simple cholecystectomy is an effective therapy in patients with mucosal tumors, while controversy exists on its use in the therapy of muscular lesions.[10,20–23] In cases with subserosal and more advanced tumors, a simple cholecystectomy would be insufficient as treatment, and the dissection of the hepatic pedicle lymph nodes along with the resection of the gallbladder bed is advocated. Despite this having agreed by the surgical community, no strong evidence supports the indication of such therapy, and a randomized clinical trial has never been performed.[11,13,23]

The introduction of the subdivision of T2 into pT2a and pT2b has further complicated the discussion. Patients with pT2b tumors have a poorer prognosis than those with a pT2a, opening the discussion up to for different management categories in both groups.[24]

Preoperative diagnosis of early forms of GBCA is considered a difficult task, and even during the cholecystectomy, a tumor diagnosis is rarely made. An explanation for this could be the higher proportion of macroscopic flat lesions, which are not observed in a chronically inflamed mucosa. In the present report, this fact is clearly highlighted, only in four patients, was a tumor suspected prior to the cholecystectomy. This reinforces that the routine rather than the selective histopathology exam detects more incidental tumors.[25]

On the other hand, in high incidence countries, cholecystectomies should be performed, bearing the possibility of a tumor in mind.

Although GBCA is considered a disease associated with a poor prognosis, more than half of our patients lived for more than five years. Among the factors related to the prognosis, lymph node compromise is stands out as the most important. In this report, a multivariate analysis reinforces the concept showing that lymph node compromise was the most important prognosis-related factor. In the present series, only 6 patients with lymph node involvement were alive after five years. However, the absence of lymph node involvement did not guarantee survival: 24 patients who did not show lymph node involvement died during follow-up. Tran,[15] highlights the value of the lymphadenectomy and showed that only 7.7% of patients in his series had 4 or more examined, whereas 62.5% had no lymph node evaluated. Similarly, Tsilimigras[18] shows the value that the number of lymph nodes examined has in terms of survival, suggesting that patients with 4 or more lymph nodes evaluated were likely better staged.

Among our patients, a residual tumor was found in 26.7% of all examined lymph nodes, and the positivity rate increased concomitantly with the pT stage. Our positivity rate for lymph nodes contrasts with other series, which showed higher lymph node involvement rates. In our series, although the surgical

**Table 4** Patients surviving more than 5 years with positive lymph nodes

| Gender | age | t | Cholecystectomy | Total Lymph nodes dissected | Total Lymph nodes positive | H | Resection |
|---|---|---|---|---|---|---|---|
| Male | 60 | t2a | Open | 4 | 1 | Negative | Open |
| Male | 57 | t2a | Laparoscopic | 8 | 1 | Positive | Laparoscopy |
| Female | 53 | t1b | Laparoscopic | 9 | 1 | Negative | Laparoscopy |
| Male | 64 | t2a | Laparoscopic | 3 | 1 | Negative | Open |
| Female | 65 | t2b | Laparoscopic | 17 | 2 | Positive | Open |
| Female | 54 | t2a | Laparoscopic | 3 | 1 | Negative | Laparoscopic |

**Table 5** Logistic regression analysis Factors related to prognosis

| | Odds ratio | 95% CI | p Value |
|---|---|---|---|
| Type of cholecystectomy | | | |
| Open cholecystectomy | 1 | | |
| Lap cholecystectomy | 0.623 | 0.115–3.36 | 0.583 |
| Type of resection: | | | |
| Open | 1 | | |
| Laparoscopy, | 0.241 | 0.011–5.06 | 0.36 |
| Converted | 4.74 | 0.366–61.38 | 0.234 |
| Age | | | |
| <=55 | 1 | | |
| > 55 | 1.72 | 0.528–5.65 | 0.365 |
| No | 1 | | |
| Acute Cholecystitis | 0.677 | 0.196–2.33 | 0.537 |
| Time between surgery | | | |
| 1–60 days | 1 | | |
| 61–90 days | 3.24 | 0.71–14.83 | 0.129 |
| >90 days | 1.06 | 0.27–4.09 | 0.928 |
| Differentiation grade | | | |
| Poor | 1 | | |
| Moderate | 2.95 | 0.519–16.78 | 0.22 |
| Well | 0.29 | 0.298–2.88 | 0.288 |
| H0 | 1 | | |
| H1 | 7.27 | 1.43–36.78 | 0.016 |
| N0 | 1 | | |
| N1 | 12.35 | 2.11–72.15 | 0.005 |
| No neo and adjuvant chemotherapy | 1 | | |
| Neo and adjuvant chemotherapy | 1.33 | 1.33–5.30 | 0.678 |
| Place of treatment | | | |
| Santiago | 1 | | |
| Temuco | 2.79 | 0.50–15.35 | 0.237 |
| T 1b | 1 | | |
| T2 | 2.18 | 0.34–14.01 | 0.41 |
| T3 | 5.36 | 0.46–61.6 | 0.177 |

intention was the performance of an extended dissection, eight patients had fewer than four nodes examined. Despite the surgical technique being the same; the harvest of lymph nodes differed among patients possibly due to anatomical considerations. The role of the lymphadenectomy in survival has not yet been clearly confirmed yet and its main role is probably associated with staging accuracy.[11]

In our series, we did not find a relation between the number of lymph nodes harvested and the detection of malignancy in the lymph nodes. Possibly, the macroscopic appearance of involved lymph nodes is what makes the surgeon dissect them primarily.

When we focused on liver infiltration, only 23 patients had liver infiltration in the resected liver, and most of them did not survive 5 years.

Compared to other publications, our findings showed a lower incidence of residual tumor in both lymph nodes and liver.[7,11] The accuracy of the cholecystectomy specimen analysis could be responsible for this difference. Down staging secondary to an incomplete pathology specimen study could be responsible for the change in the results.

The time between cholecystectomy and the reresection ranged between 0,5 and 6 months. Management of an incidental tumor should come with urgency; however, there are no data supporting that early management is associated with a better outcome. On the contrary, in a multicenter study, Ethum[26] showed a lower survival for those patients undergoing resection within 4 weeks from the cholecystectomy. Likewise, Ausania,[27] suggested a 3-month repeat staging CT before surgery in patients with incidental tumors as a way of evaluating the biological characteristics of the tumor. From our results, we realize that it is the pT stage rather than the elapsed time between the two surgeries that determined the residual tumor. A period of more than 4 weeks between the two surgeries could be beneficial by allowing not only the existence of unresectability to be discovered, but also the resolution of inflammation originating in the previous cholecystectomy.

After the introduction of the laparoscopy, the question emerged whether laparoscopy worsened the prognosis in those patients in whom a tumor was discovered from the histopathological exam of a cholecystectomy specimen. Although wall perforation has been associated with peritoneal dissemination

and poor survival, if correctly performed a laparoscopic cholecystectomy would not influence survival.[28]

Concerning the employment of any type of adjuvant therapy, most of the information is derived from series grouping of all types of biliary tumors. To date, the use of any kind of adjuvant therapy is not known based on current information.[11,29,30]

Limitations of this study are the retrospective analysis and the lack of recurrence data. However, the main strengths are that therapy was done under the same standard of care and that patients who are alive had a complete follow-up of five years.

In conclusion, we can highlight that, when certain conditions are met GBCA can be cured. Early diagnosis and absence of lymph nodes and liver compromise are the most important, while factors such as type of surgery, differentiation grade and elapsed time between cholecystectomy and resection did not show any independent effect.

## Conflicts of interest

None to declared.

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