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Original Research Article

Extended cholecystectomy in gallbladder cancer: survival and surgical results in two time periods

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ABSTRACT

Background: Describe the surgical results in terms of postoperative morbidity and mortality and survival of patients undergoing an EC in two time periods. Gallbladder cancer is a rare disease in the world and highly lethal. T1b and T2 tumors require an extended cholecystectomy (EC) for staging and eventual treatment with adjuvant chemotherapy and/or radiation according to lymph node involvement.
Methods: Case series with follow-up of patients undergoing EC between January 2006 and December 2010 (Group A) and between January 2011 and December 2016 (group B) at the Hospital Dr. Hernan Henriquez Aravena and Clinica Alemana in Temuco. Biodemographic, surgical and clinical evolution variables were recorded. Descriptive statistic was used with measures of central tendency and dispersion and analysis with Kaplan-Meier curves for survival.
Results: The series consists of 31 patients, 11 in the first time period (group A) and 20 in the second (group B). Total female patients 28. Mean age 60.5±8.5 years in group A and 58.4±9.1 in group B. The mean number of days between cholecystectomy and EC was 123.1±59.1 days in group A and 119.3±48.6 in group B. In group A there was morbidity in 6 patients (54%) and 4 patients (20%) in group B. With an average follow-up of 54.8±41 months in both groups, 2 patients died.
Conclusions: Author presented results of similar morbidity and mortality in both study groups and in the literature in national and international studies.

Keywords: Case series, Cancer, Extended cholecystectomy, Gallbladder cancer, Survival analysis

INTRODUCTION

Gallbladder cancer (GBC) is a rare pathology in Europe and the United States (rate in the US of 1.2 per 100,000 inhabitants) and of little scientific interest; nevertheless, it has a strong impact on areas of South America like Chile, where it is the primary cause of death by cancer in women.[1] In particular, the region of the Araucanía presents the highest reported mortality rate in the world (35 per 100,000 inhabitants).[1] Other regions with a high rate of GBC are Bolivia, Peru, Ecuador, Colombia, Brazil and India.

The prognosis for GBC continues to be very unfavorable, with an overall 5year survival of only 5%.[1,2] Even in patients with curative intent in early stages (T2N0M0), 5-year survival does not reach 30%, which reflects that a high percentage of the patients will present relapses.[2] Many patients are diagnosed at advanced stages, beyond the reach of surgery, which is the only curative tool.

Despite this poor prognosis, there is a subgroup of patients with significant long-term survival.[2] Most patients in this group with a potentially curable disease are diagnosed by the histopathological report. On rare occasions, there is a preoperative suspicion of GBC. Of these patients, those with T1b and T2 (muscle or subserosal invasion) are a group with an intermediate and likely important prognosis regarding long-term survival. The cholecystectomy by itself is the treatment adapted for the T1a gallbladder tumors. In patients with T1b and T2 tumors, the extended cholecystectomy (EC) has an important role as a staging surgery for adjuvant treatment, but the real effect on survival is debatable.

The aim of this work was to describe surgical outcomes in terms of postoperative morbimortality and survival of patients who underwent an EC in two time periods: 2006-2010 and 2011-2016.

METHODS

This study was case series with follow-up. Patients who underwent a laparotomic EC between January 2006 and December 2010 in the first period (group A) and later between January 2011 and December 2016 in the second period (group B) at Hospital Dr. Hernán Henríquez Aravena and Clínica Alemana, Temuco.

Biodemographic, surgical and clinical evolution variables were recorded. All the patients were evaluated with a delayed histopathological report, Computed Tomography (CT) of the thorax, abdomen and pelvis for staging (nuclear magnetic resonance in special cases) and tumor markers (alpha-fetoprotein, carcinoembryonic antigen, CA19-9 and CA-125) in a meeting of the hepatobiliary (HPB) surgical team. Follow-up was done in the HPB surgery polyclinic and the oncology committee to define adjuvant treatment.

The EC team performs consists of a complete lymph node dissection of the hepatic pedicle plus a S4 and S5 sub-segmentectomy. Initially, an abdominal exploration was done in search of ascites, peritoneal carcinogenesis, hepatic metastatic lesions or peritoneal nodules. Then, author turned to the intercaval-aortic space for a frozen-section biopsy.If it was negative, author performed the lymph node dissection of the hepatic pedicle with resection of all the tissue surrounding the hepatic artery, bile duct and portal vein (Figure 1). Next, author send the cystic remnant for a frozen-section biopsy (in case of involvement of the cystic remnant, author performed a resection of the bile duct) and finally they do the 4b and 5 sub-segmentectomy.

This series was performed with open surgery. however, this equipment was initiating the EC protocol laparoscopically. Descriptive statistics were used with measures of central tendency and dispersion and Kaplan-Meier curves to calculate survival. A database was designed in Excel® 14.4.1; Stata® 10.0 for data analysis.

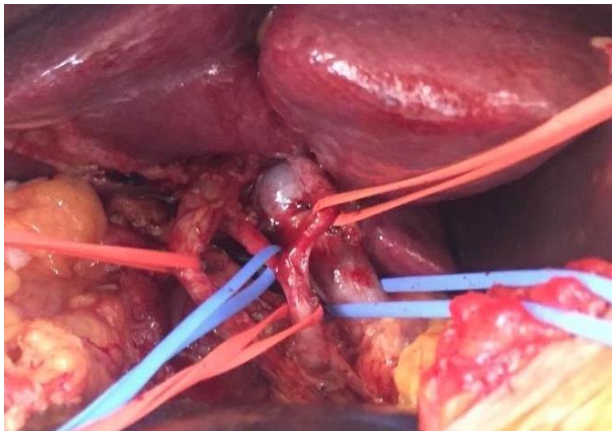

Figure 1: Lymph node resection showing elements of the hepatic pedicle.

This study was reviewed and approved by the Institution Review Board of Hernán Henríquez Aravena Hospital and Department of Surgery of Universidad de la Frontera. All study participants or their legal guardian provided informed written consent prior to study enrollment.

RESULTS

Author series consists of 31 patients (11 in group A and 20 in group B) with an average age in group A of 60.5±8.5 years and 58.4±9.1 years in group B. 28 patients were women (90.3%). Only 1 patient had no association with lithiasis in group B (3%).

There was preoperative suspicion of a likely gallbladder neoplasia in 2 patients (6%), both in Group B, one with suspicion from an abdominal ultrasound with thickening of the gallbladder fundus (gallbladder cancer vs. adenomyomatosis) and in the other patient an abdominal CT also showed thickening of the gallbladder fundus, and proliferative neoplasia could not be discounted.

There were 2 patients who did not undergo an EC (intercaval-aortic lymph node positive and a peritoneal nodule positive for metastasis), one in each group, which was not considered in the final results.

With respect to the initial surgery, an open cholecystectomy was performed on 18 patients (13 in group A and 5 in group B), laparoscopic cholecystectomy on 11 patients (2 in group A and 9 in group B) and 2 other patients underwent laparoscopic surgery but this had to be changed to laparotomic due to difficulty in identifying structures in the cystohepatic triangle both in group B.

Regarding the depth level, there were 7 (23%) patients with muscle invasion (T1b), 2 in group A and 5 in group B and 24 (77%) patients with subserosal invasion (T2), 11 in group A and 13 in group B. Of the histological type of the biopsy, there were 29 patients with adenocarcinoma (94%) and 2 patients with

adenosquamous carcinoma (both of the Group B). The time between the initial surgery and the EC was 123.1±59.1 days in group A and 119.3±48.6 days in group B.

From the biopsy of the EC and according to the TNM classification: 7 patients T1bN0M0 (3 in group A and 4 in group B), 20 patients T2N0M0 (9 in group A and 11 in group B) and 4 patients T2N1M0 (2 patients in each group), who later received adjuvant chemotherapy with a protocol of gemcitabine plus cisplatin.[12] The average of resected lymph nodes was 5.5 (range 2-14) in the total group. There was no postoperative mortality in this sample. Follow-up was 54.8±41 months for both groups. Six patients had some type of morbidity in group A: 2 with a surgical site infection, 1 with abdominal collection, 1 pneumonia, 1 biliary fistula and 1 urinary tract infection. In group B, 4 patients had some type of morbidity: 2 with infection of the lower urinary tract and 2 with pneumonia. Table 1 details the morbidity according to the Clavien-Dindo classification.[3] From the overall survival of this series, author obtained a 71% likelihood of survival at 5years in T2 patients with the EC (Figure 2) in group A and a 75% likelihood of survival in group B (Figure 3).

Table 1: Morbidity according to Clavien-Dindo.

Variable	Group A n=11	Group B n= 20	N (%)
Clavien-Dindo[3]			
Grade I	3	0	3 (9.6%)
Grade II	1	3	4 (12.9%)
Grade III			
Grade IIIa	0	0	0 (0%)
Grade IIIb	0	3	3 (9.6%)
Grade IV			
Grade IVa	0	0	0 (0%)
Grade IVb	0	0	0 (0%)
Grade V	0	0	0 (0%)
No complication	7	14	21 (67.7%)
Total	11	20	31 (100%)

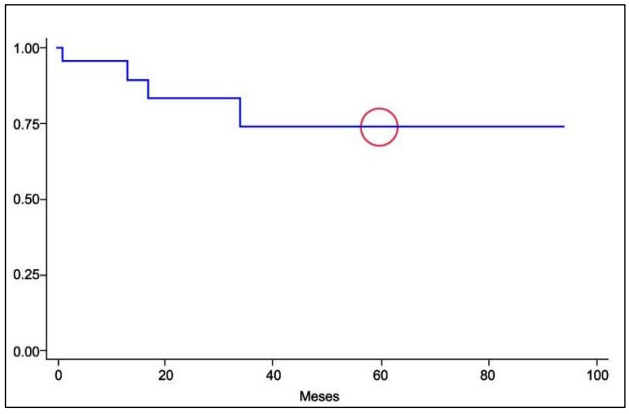

Figure 2: Likelihood of survival 71% (group A) at 5 years (0.38-0.88) CI 95%.

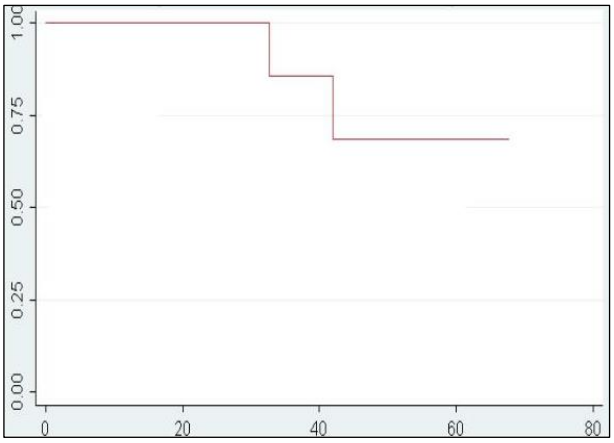

Figure 3: Likelihood of survival 75% (group B) at 5 years (0.39-0.91) IC 95%.

DISCUSSION

Among the reasons that explain the low survival in patients with GBC, the delayed diagnosis has been mentioned in many articles as one of the most important.[4-7]

In this patient series, the diagnosis of GBC was detected largely after the histopathological report of the intraoperative specimen from the cholecystectomy. This reveals the low yield obtained from preoperative imaging (abdominal ultrasound or CT) in the detection of small lesions. The high percentage of flat or non-visible lesions under macroscopic examination makes it difficult to detect suspicious lesions, in addition, the indication of the cholecystectomy in a not insignificant number of patients occurs in acute episodes where the inflammation of the gallbladder wall contributes to the difficulty of visualizing potential neoplastic lesions.[7,8]

It has been described and published that T1b and T2 patients are indicated for an EC as a staging surgery to determine the need for adjuvant treatment.[2] From the point of view of the survival of those patients who undergo an EC vs. those who do not, there are no randomized clinical trials comparing these two groups and that can answer this question. The gallbladder resection associated with the EC was also a discussion point. In this patient series, author send a frozen-section biopsy of the cystic duct remnant to perform the gallbladder resection in case this is (+) for neoplasia. All the biopsies were (-), which was why there were no gallbladder resections.

Resection of the lymph nodes of the tissue surrounding the biliary tract could be done better if the biliary tract were resected. From the theoretical point of view, this discussion could have some type of foundation but from the clinical or surgical point of view, resection of the biliary tract may be associated with greater morbidity than for patients on whom it was not done.[9]

At present, the laparoscopic cholecystectomy is the gold standard for the treatment of the cholelithiasis. However, its role in the subsequent resectability and prognosis of patients with GBC is unknown.[10,11]

Traditionally, 5-year survival of patients with GBC is approximately 10%.[1] These outcomes occur because the diagnosis is made at very advanced stages of the disease. In countries like Chile, where this pathology is more commonly detected, there are stages of the disease with higher survival rates because it is detected at earlier stages. In this center involvement up to the sub-serosa (T2) is found in approximately 30% of all patients with GBC.

The overall survival of the patient series was 75% for T2 stages. This outcome was a result of the disease being detected at early stages, which leads to a cholecystectomy for a suspected benign disease (cholelithiasis or acute cholecystitis). It was worth noting that lymph node involvement was an important prognostic factor.[9,12] In this study, 4 had lymph node involvement who later went on to adjuvant treatment (chemotherapy and radiation). Lymph node involvement generally has a constant pattern: initially those located in the cystic duct remnant, then in the chole-docoduodenal region and finally the paraaortic lymph nodes via the retro pancreatic lymph nodes.[9,13] The number of resected lymph nodes in this study (5.5 in average) was similar to that described in the literature. The range was variable (2-14), which was to be expected due to anatomical variations in the hepatic pedicle that make the dissection more complex.

In relation to morbidity, several studies show similar results with the presence of surgical site infections, pneumonias or urinary tract infections.[9,12-14] Regarding hospital stay, it has been described that patients who undergo a laparoscopic EC have a shorter hospital stay and less postoperative pain than those who undergo open surgery, advantages associated with the laparoscopic surgery itself.[11,15,16]

In terms of the possible role of the EC in patients in early stages of the disease (T1a tumors), in patients with Rokitansky-Aschoff (RA) sinus involvement, there is no categorical consensus as to whether or not they benefit from the EC.[11,15] An exhaustive review of the intraoperative specimen in pathology is important to determine the depth of invasion of these RA sinuses. It is feasible to think that those patients in whom RA sinus invasion has reached the tunica muscularis or the subserosal layer would benefit from the EC.

This series corresponds to a patient using the laparotomic approach; nevertheless, there was evidence that the laparoscopic EC presents oncological outcomes similar to those of open surgery, with the benefits of laparoscopic surgery.[17] Present team has already begun experience with the laparoscopic EC and author expected to present the results in the next few years.

CONCLUSION

The survival at 5 years of patients with T1b and T2 GBC treated with the EC is around 75%. The morbimortality figures are comparable to international studies.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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