



Laparoscopic Cholecystectomy: Its Effect on the Prognosis of Patients with Gallbladder Cancer

Xabier A. de Aretxabala, M.D.,¹ Ivan S. Roa, M.D.,² Javier P. Mora, M.D.,¹ Juan J Orellana,³ Juan P. Riedeman, M.D.,³ Luis A. Burgos, M.D.,¹ Veronica P. Silva, M.D.,⁴ Alvaro J. Cuadra, M.D.,¹ Harold J. Wanebo, M.D.⁵

¹Department of Surgery, Universidad de la Frontera, German Clinic Temuco, PO Box 54-D Temuco 4781176, Chile

²Pathology Unit, Universidad de la Frontera, PO Box 54-D, Temuco 4781176, Chile

³Epidemiology Unit, Universidad de la Frontera, PO Box 54-D, Temuco 4781176, Chile

⁴Department of Surgery, Hospital Quilpue, San Martin 1270, Quilpue 6540562, Chile

⁵Department of Surgery, Roger Williams Medical University, Boston University, 825 Chalkstone Avenue, Providence, Rhode Island 02908, USA

Published Online: May 19, 2004

Abstract. Numerous reports suggest more recurrences and a worse prognosis after laparoscopic cholecystectomy (LC) than after open cholecystectomy (OC). The objective of this study was to compare the survival rate of patients undergoing a laparoscopic procedure versus those undergoing an open operation. A series of 24 patients with gallbladder cancer detected after LC were compared with 40 consecutive patients with gallbladder cancer detected after OC. Patients were matched by wall invasion, age, and whether they underwent a reoperation or only cholecystectomy. The series included 2 patients with in situ tumors, 2 with mucosal tumors, 1 with muscular invasion, 13 with subserosal invasion, and 6 with serosal invasion. Recurrences were observed in 4 of the 10 patients with subserosal compromise who underwent reoperation. In contrast, in the OC group of 26 patients with subserosal invasion, 20 of whom were reoperated, only 2 had a recurrence. Of the six patients with serosal infiltration, three in the LC underwent reoperation, all of whom had recurrences that precluded resection. Of the 12 patients in the OC group who presented with serosal invasion, 6 were reoperated and 4 had a recurrence. Overall survival curves did not show differences when patients were compared according to the type of procedure performed. Similarly, the analysis of patients according to the level of wall invasion indicated that there was no significant difference in survival. Although multiple reports have shown a worse prognosis for patients with gallbladder cancer undergoing LC, this study did not show a significant survival difference between the two methods. Although there is a higher but insignificant recurrence rate among the patients who underwent LC, this is not translated into survival.

Gallbladder cancer is a disease characterized by its poor prognosis and late diagnosis [1–4]. In our center, 74% of the early forms of tumors are detected after histologic examination of the cholecystectomy specimen [1]. The introduction of laparoscopic cholecystectomy (LC) drew attention to the existence of recurrence sites related to the laparoscopic method itself [5, 6]. Metastatic wound implants most commonly arose from trocar sites [5–7]. Hence concern has been expressed that LC could adversely affect the prognosis. Because of the high incidence of gallbladder cancer in Chile

(12/100,000 inhabitants) the diagnosis of incidentally finding cancer in a “routine” cholecystectomy specimen is common [1, 3]. In view of these facts, the possible effect of laparoscopy on the prognosis represents a cause of concern among surgeons.

In the present study we evaluated the role of laparoscopy in the survival of patients with gallbladder cancer. We did so by comparing patients in whom cancer was detected after LC with a group of patients with similar clinical characteristics in whom cancer was diagnosed after open cholecystectomy (OC).

Materials and Methods

The medical records, imaging data, operative records, and pathologic findings were reviewed in 24 patients with a gallbladder cancer discovered after or during LC. To analyze the role of laparoscopy, these patients were compared with a series of 40 patients with gallbladder cancer detected after OC. Thus for every patient whose cancer was detected after or during LC, two patients with a cancer detected after or during an open procedure were recruited. To make the two groups comparable, patients were matched by level of wall invasion, age, and whether they had undergone reoperation. These variables were chosen because of their relation with the prognosis [1, 4]. Control patients were chosen correlatively from our database of gallbladder cancer patients. Because patients with in situ and mucosal infiltration who underwent LC and OC are alive and free of disease, we did not study this group. Furthermore, because the number of patients with muscular invasion was small, they were also excluded from the survival analysis. Follow-up data were obtained by personal contact with the patients or from their clinical records. In cases in which the gallbladder was completely resected, the surgical specimen was examined using stepwise sectioning of the whole gallbladder.

Tumors were classified according the level of wall invasion. The categories were in situ, mucosal, muscular, subserosal, and serosal invasion. The American Joint Commission for Cancer/Internation-

Correspondence to: Xabier A. de Aretxabala, M.D., e-mail: aretxaba@ufro.cl

Table 1. Patients who underwent laparoscopic cholecystectomy in whom cancer was diagnosed after or during the procedure.

Age (years)	Invasion	pT	Reoperation	Recurrence	Alive	Follow-up
56	In situ	Tis	No		Yes	24
48	In situ	Tis	No		Yes	60
54	Mucosa	T1a	No		Yes	60
67	Mucosa	T1a	No		Yes	20
63	Muscular	T1b	No		Yes	8
66	ss	T2	Yes	Yes	No	16
60	ss	T2	Yes	No	Yes	10
60	ss	T2	Yes	No	No	36
36	ss	T2	Yes	Yes	No	16
63	ss	T2	Yes	No	Yes	12
50	ss	T2	No		No	9
56	ss	T2	Yes	Yes	No	9
44	ss	T2	Yes	No	Yes	96
41	ss	T2	Yes	No	Yes	72
77	ss	T2	No		Yes	48
46	ss	T2	No		Yes	24
56	ss	T2	Yes	Yes	Yes	2
45	ss	T2	Yes	No	Yes	4
64	se	T3	Yes	Yes	No	11
69	se	T3	Yes	Yes	No	7
52	se	T3	No		No	5
72	se	T3	No		No	4
53	se	T3	No		Yes	24
64	se	T3	No		No	2

ss: subserosal; se: serosal.

tional Union Against Cancer (AJCC/UICC) classification was employed [8]. Patients were managed according to a previously reported protocol [1, 9, 10]. Thus for those with subserosal or deeper infiltration, a second operation with the aim of resecting potentially involved tissue was offered. The median follow-up ranged from 2 to 96 months.

The cumulative survival rate was calculated according the Kaplan-Meier method. To compare the survival curves for the two procedures, we performed a Cox proportional hazard model, adjusting the standard error for clustering on the matched variable. Recurrence was analyzed using Fisher's exact test. Differences between variables were considered statistically significant when $p < 0.05$.

Results

The 24 patients with gallbladder cancer detected after the laparoscopic procedure included 4 men and 20 women aged 36 to 77 years. The preoperative diagnosis in these patients was cholelithiasis in 22, gallbladder polyp in 1, and acute cholecystitis in 1.

Concerning the level of wall invasion, 2 patients had an in situ tumor (AJCC/UICC T0). 2 a mucosal tumor (T1a), 1 a muscular tumor (T1b), 13 a subserosal tumor (T2), and 6 a serosal lesion (T3) (Table 1).

All of the patients with in situ or mucosal tumors are alive and free of disease after a follow-up of 20 to 60 months. The patient with muscular invasion is also alive after 8 months of follow-up.

Among the patients in the LC group, 10 who had subserosal compromise underwent reoperation with the aim of resecting potentially compromised areas. Of these 10 patients, 4 had recurrences that precluded resection. The recurrences were observed at the site lateral trocar hole placement in one patient, in the prerenal fasciae

in another, and in the lymph nodes in two patients (Table 2). Among these four patients, those with recurrences in the prerenal fasciae, at the trocar holes, and in the paraaortic lymph nodes were dead after 9, 16, and 16 months of follow-up, respectively. The other patient is still alive but with a follow-up of only 2 months.

Of the six patients with serosal compromise, five were converted to open surgery because of intraoperative suspicious of tumor. The other patient completed the laparoscopic procedure, and the diagnosis was established after studying the cholecystectomy specimen. Three of these patients underwent reoperation, but in all three cases the tumors were unresectable because they were not suitable for a curative procedure.

The 40 patients whose cancers were detected after an open procedure comprised the control group. The group included 26 patients with subserosal compromise, 12 with serosal invasion, and 2 with muscular invasion.

The two patients with muscular invasion are alive after 23 and 50 months of follow-up, respectively. Of the 26 patients with subserosal tumors, 20 underwent reoperation; 18 of them were able to undergo resection, but the other 2 had infiltration outside the area to be resected. Although the proportion of patients whose lesions could be resected in the OC group was higher, differences did not reach statistical significance ($p = 0.141$). On the other hand, among the 12 patients with serosal infiltration, 6 underwent reoperation; and of these 6, only 2 were able to undergo resection ($p = 0.50$). The rest of the patients had a recurrence that precluded resection with a curative aim (Table 2).

The survival analysis did not show a higher risk of death for those who underwent laparoscopic surgery compared with those undergoing open surgery. Using Kaplan-Meier survival estimates, patients who underwent laparoscopic surgery had a risk of death of 1.22 (hazard ratio) compared with those undergoing open surgery. However, this was not statistically significant [$p = 0.598$; 95% confidence interval (CI) 0.58–2.571].

Figure 1 shows survival curves of patients according to the cholecystectomy technique. After 60 months of follow-up, 34.9% of the LC patients and 35.4% of the OC patients were alive ($p > 0.05$). Among the patients with infiltration restricted to the subserosal layer, survival was no different for those who underwent LC or OC (hazard ratio 1.01; $p = 0.97$; 95% CI 0.36–2.38) (Fig. 2). Analysis of those with invasion of the serosal layer also did not show any differences in survival for the LC and OC patients (hazard ratio 1.64; $p = 0.38$; 95% CI 0.54–4.92) (Fig. 3).

Discussion

The most frequent ways for gallbladder cancer to spread are local invasion, regional lymph node involvement, and distant metastasis [11]. Recurrences at the level of scars or trocar holes and by peritoneal infiltration are not common in patients with early-stage gallbladder cancer, although they have been described in those who have undergone LC [5–7, 12–15].

Intraoperative perforation of the gallbladder with spillage of bile seems to be an important event in the seeding of cells. According to the data of Z'graggen et al., the incidence of port-site recurrence increased from 9% in patients without intraoperative perforation to 40% in those in whom perforation could be demonstrated [13].

Although this was not a randomized trial, to distinguish the real effect of laparoscopy on the prognosis, we designed the study with the aim of comparing the same categories of patients according to

Table 2. Recurrences in patients undergoing reoperation.

Level of invasion	LC			OC			<i>p</i>
	Initial	Reoperation	Recurrence	Initial	Reoperation	Recurrence	
Subserosa	13	10	4	26	20	2	0.141
Serosa	6	3	3	12	6	4	0.50

LC: laparoscopic cholecystectomy; OC: open cholecystectomy.

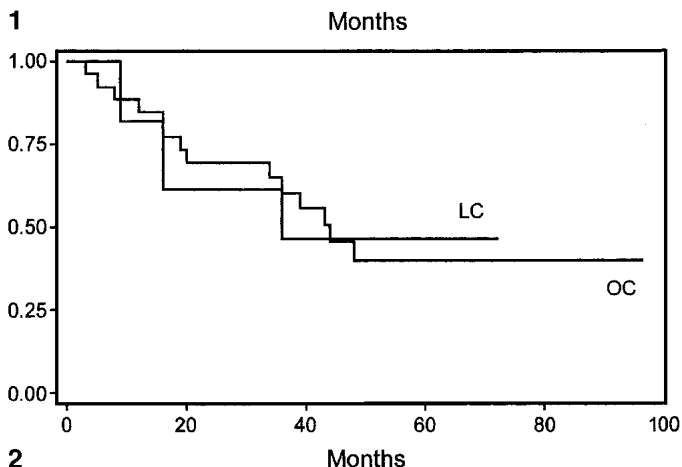
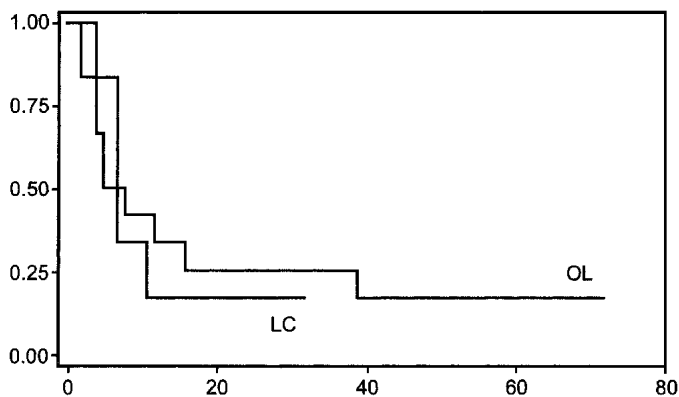


Fig. 1. Survival curves of patients with subserosal and serosal infiltration undergoing cholecystectomy by a laparoscopic procedure (LP) versus those who undergoing an open procedure (OC). $p = 0.598$.

Fig. 2. Survival curves of patients with subserosal infiltration undergoing cholecystectomy by a laparoscopic procedure compared with those undergoing cholecystectomy by an open procedure. $p = 0.974$.

the cholecystectomy technique used. The analysis of patients with early-stage tumors, such as mucosal or in situ lesions, showed that laparoscopy did not influence their outcome. Patients with small tumors undergoing laparoscopy had an excellent prognosis, as all were alive without evidence of recurrence. Although the total number of these patients is small, this fact is important because it shows that laparoscopy per se is not responsible for the unfavorable prognosis. Although it was not recorded in this study, bile spillage may be responsible for recurrences even with small tumors. This fact stresses the value of using meticulous technique in all LC cases. The analysis of patients with subserosal and serosal invasion who underwent reoperation showed a higher recurrence rate for patients who underwent the laparoscopic procedure. Although differences did not reach statistical significance, studying a larger number of

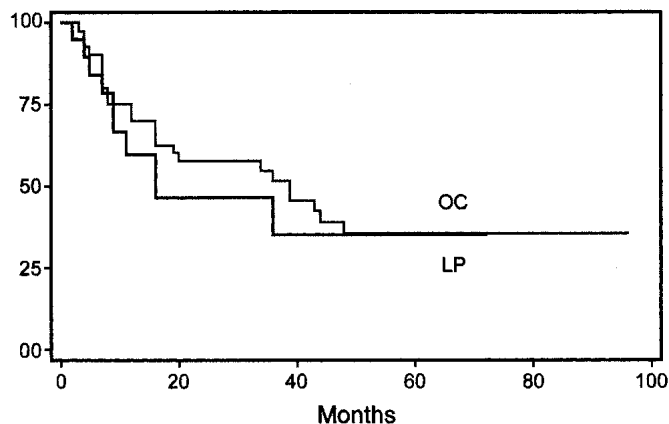


Fig. 3. Survival curves of patients with serosal infiltration undergoing cholecystectomy by a laparoscopic procedure compared with those undergoing cholecystectomy by an open procedure. $p = 0.38$.

patients might confirm the impression that patients with subserosal or serosal invasion undergoing LC are at a higher risk of recurrence than are those undergoing OC.

Among those with a potentially resectable gallbladder cancer, patients with subserosal infiltration had an intermediate prognosis. Survival analysis of patients who underwent LC did not show any difference in the prognosis compared with those who underwent OC.

Finally, those with serosal infiltration represent a poor-prognosis group independent of the operative method. These patients rarely survive longer than 1 year after the diagnosis, although exceptions occur when a large number of patients are evaluated. Although it was not statistically observed in this study, laparoscopy itself probably influences the outcome in this group of patients. Laparoscopic maneuvers can exfoliate malignant cells from the gallbladder surface, favoring implantation in the peritoneum. This fact is evident in reports that show glandular cells in 40% of laparoscopic instruments and in the filtrate of exhausting carbon dioxide [16, 17]. Other experimental studies demonstrated that pneumoperitoneum significantly increased implantation at trocar sites and tumor growth in the peritoneum [18, 19].

Conclusions

We emphasize here that laparoscopic cholecystectomy does not influence the prognosis in patients with small tumors, particularly among patients with less than subserosal wall infiltration. Patients with subserosal infiltration represent an interesting group in whom a high incidence of recurrence might be demonstrated if a larger number of patients with longer follow-up are studied. Those with serosal invasion might comprise a group in whom the safety of lap-

aroscopy should be examined. Therefore we suggest conversion to an open procedure for patients in whom gallbladder cancer is recognized prior to or during laparoscopy. For patients who have already undergone LC and have been diagnosed as having gallbladder cancer after the specimen is examined histologically, a poor prognosis is likely. This group may benefit from adjuvant chemotherapy with or without irradiation. Clinical trials are warranted to address this issue.

Résumé. De nombreuses publications suggèrent que les récidives du cancer de la vésicule biliaire sont plus fréquentes et d'un plus mauvais pronostic après cholécystectomie coelioscopique (CC) qu'après cholécystectomie par voie traditionnelle (CT). Le but de cette étude a été de comparer la survie des patients ayant eu une intervention sous coelioscopie par rapport à ceux ayant été opérés par CT. Vingt-quatre patients ayant un cancer de la vésicule biliaire détecté après CC ont été comparés à 40 patients consécutifs porteurs d'un cancer de la vésicule biliaire détecté après CT. Les patients ont été appariés selon le degré d'invasion pariétale, l'âge et selon qu'ils ont eu une réintervention ou seulement une cholécystectomie. La série a été composée de deux patients ayant une tumeur in situ, deux cas de tumeur de la muqueuse, un patient ayant une invasion de la musculaire, treize patients ayant une invasion de la sous-séreuse et six patients présentant une invasion de la séreuse. Une récidive a été constatée chez quatre des dix patients ayant une invasion de la sous-séreuse: ils ont été réopérés. En revanche, dans le groupe opéré par CT, des 26 patients porteurs d'une invasion de la séreuse, 20 ont eu une intervention itérative, mais seulement deux ont eu une récidive. Des six patients ayant une invasion de la sous-séreuse, trois patients, dans le groupe CC, ont eu une intervention itérative. Tous avaient des récidives qui interdisaient la résection. Des 12 patients qui ont eu une invasion de la séreuse dans le groupe CT, six ont eu une ré-opération et quatre ont récidivé. Les courbes de survie globale n'ont pas montré de différences lorsque les patients ont été comparés selon le type de procédé réalisé. De même, dans l'analyse des patients selon le degré d'invasion pariétale, il n'y avait aucune différence significative en ce qui concernait la survie. Bien qu'il existe plusieurs publications démontrant un plus mauvais pronostic pour les patients porteurs de cancer de la vésicule biliaire opérés sous coelioscopie par rapport à la chirurgie traditionnelle, cette étude ne montre pas une différence de survie significative entre les deux voies d'abord. Bien que le taux de récidive soit plus élevé chez le patient opéré sous coelioscopie, il n'y avait pas de différence en ce qui concernait la survie.

Resumen. La existencia de reportes que muestran un peor pronostico en aquellos pacientes en los que el diagnóstico de cáncer de la vesícula biliar (C.V.B) es efectuado luego de una colecistectomía Laparoscópica (C.L.), motivó la realización de un estudio que pretendía comparar un grupo de pacientes en los que el diagnóstico fue efectuado luego de una C.L. con otro en el que el diagnóstico fue efectuado luego de una Colecistectomía abierta (C.A.). Veinte y cuatro pacientes portadores de un C.V.B. diagnosticado luego de una C.L. fueron comparados con 40 pacientes portadores de un C.V.B. diagnosticados luego de una C.A. Los pacientes fueron pareados de acuerdo a la edad, nivel de infiltración de la pared y si fueron reoperados o no. La serie estuvo compuesta por dos pacientes con un tumor in situ, dos pacientes con un tumor mucoso, un paciente con invasión muscular, 13 con compromiso sub seroso, y 6 con invasión serosa. Recurrencias fueron observadas en 4 de 10 pacientes con invasión sub serosa que fueron sometidos a una reintervención. Por otra parte, en el grupo de pacientes sometidos a una C.A., de 26 pacientes, 20 fueron reoperados y solo dos tuvieron tumor residual. De los 6 pacientes con invasión serosa, tres en el grupo de C.L fueron sometidos a una reoperación, los tres tuvieron tumor residual. De los 12 pacientes en el grupo de C.A. 6 fueron reoperados, en 4 observándose tumor residual. El análisis de las curvas de supervivencia no mostró diferencias cuando los pacientes fueron comparados de acuerdo al

método en que fueron colecistectomizados. Cuando este análisis fue efectuado en sub grupos de acuerdo al nivel de invasión tampoco fueron observadas diferencias. A pesar de la existencia de reportes que muestran un peor pronóstico para los pacientes portadores de un C.V.B. detectado luego de una C.L. este análisis no mostró dichos resultados. Aunque existe un mayor número de tumor residual en los pacientes sometidos a una C.L. esto no se tradujo en una menor supervivencia.

Acknowledgments

This study was supported by grant 1010523 from Fondecyt Chile.

References

1. De Aretxabala X, Roa I, Burgos L, et al. Curative resection in potentially resectable tumors of the gallbladder. *Eur. J. Surg.* 1997;163:419-426
2. Benoist S, Panis Y, Fagniez PL, et al. Long term results after curative resection for carcinoma of the gallbladder. *Am. J. Surg.* 1998;175:119-122
3. Serra I. Ha disminuido la mortalidad por cáncer vesicular en Chile? *Rev. Med. Chile* 2001;129:1079-1084
4. Shirai Y, Yoshida K, Tsukada K, et al. Radical resection for gallbladder carcinoma: long term results. *Ann. Surg.* 1992;16:565-568
5. Nduka CC, Monson JRT, Menzies-Gow N, et al. Abdominal wall metastases following laparoscopy. *Br. J. Surg.* 1994;81:648-652
6. Clair DG, Lautz DB, Brooks DC, et al. Rapid development of umbilical metastases after laparoscopic cholecystectomy for unsuspected gallbladder carcinoma. *Surgery* 1993;113:355-358
7. Fong Y, Brennan M, Turnbull A, et al. Gallbladder cancer discovered during laparoscopic cholecystectomy: potential for iatrogenic tumor dissemination. *Arch. Surg.* 1993;128:1054-1056
8. Hermanek P, Hutter RVP, Sobin LH, et al. UICC TNM Atlas, 4th edition
9. 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
10. De Aretxabala X, Roa I, Burgos L, et al. Preoperative chemoradiotherapy in the treatment of gallbladder cancer. *Am. Surg.* 1999;65:241-246
11. Fahim RB, McDonald JR, Richards JC, et al. Carcinoma of the gallbladder: a study of its methods of spread. *Ann. Surg.* 1962;156:114-124
12. Ricardo AE, Feig BW, Ellis LM, et al. Gallbladder cancer and trocar site recurrences. *Am. J. Surg.* 1997;174:619-622
13. Z'graggen K, Birrer S, Maurer CA, et al. Incidence of port site recurrence after laparoscopic cholecystectomy for preoperatively unsuspected gallbladder carcinoma. *Surgery* 1998;124:831-838
14. Suzuki K, Kimura T, Ogawa H. Is laparoscopic cholecystectomy hazardous for gallbladder cancer. *Surgery* 1998;123:311-314
15. Wibbenmeyer 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
16. Doudle M, King G, Thomas WM, et al. The movement of mucosal cells of the gallbladder within the peritoneal cavity during laparoscopic cholecystectomy. *Surg. Endosc.* 1996;10:1092-1094
17. Champault G, Taffinder N, Zioli M, et al. Cells are present in the smoke created during laparoscopic surgery. *Br. J. Surg.* 1997;84:993-995
18. Wu JS, Brasfield EB, Guo LW, et al. Implantation of colon cancer at trocar sites is increased by low pressure pneumoperitoneum. *Surgery* 1997;122:1-7
19. Bouvy ND, Marquet RL, Jeekel J, et al. Laparoscopic surgery is associated with less tumor growth stimulation than conventional surgery: an experimental study. *Br. J. Surg.* 1997;84:358-361