

Survival of a cohort of patients with Intermediate and advanced gall bladder cancer treated with a prospective therapeutic protocol¹

Sobrevida de uma coorte de pacientes com câncer na vesícula intermédio e avançado tratados com um protocolo terapêutico de natureza prospectiva

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ABSTRACT

Purpose: To evaluate the results of a prospective therapeutic protocol with long-term follow up in terms of survival rates in a cohort of patients treated with Intermediate and Advanced GBC (GBC). **Methods:** Prospective cohort of patients with intermediate and advanced stages of GBC treated between 1996 and 2006. All cases were treated with a partial hepatic segmentectomy on segments IVb and V and a regional lymph node dissection and six cycles of out-patient chemotherapy (5-FU and leukovorin). With an average follow-up of 31.5 months, the morbidity, operative mortality, hepatic and lymphatic infiltration and actuarial survival were measured. Descriptive statistics were applied as well as bivariate analysis applying Fisher's exact test and non-parametrical tests and Kaplan Meier survival curves. Also logistic regression and proportional risk of Cox were applied. **Results:** 40 patients were included in this protocol, with an average age of 59.5 years (40-85 years), of which 28 were women (70%). Depth of wall infiltration: muscular 8 patients (20%), subserosal 12 patients (30%), serosal 12 patients (30%) and perivesicular adipose tissue 8 patients (20%). The series morbidity was 27.5%. There was no operative mortality. The chemotherapy was well tolerated. The overall actuarial survival in the series was 50% at 60 months. **Conclusion:** Our protocol treatment has morbidity, mortality and survival rates similar to previously reported series.

Key words: Gallbladder Neoplasms. Hepatectomy. Chemotherapy, Adjuvant.

RESUMO

Objetivo: Avaliar os resultados de resultados da aplicação de um protocolo terapêutico de natureza prospectiva, com seguimento em longo prazo nos termos de taxas de sobrevivência em uma coorte de pacientes operados com carcinoma vesícula biliar (CVB) intermédio e avançado. **Métodos:** A coorte prospectiva de pacientes com estágios intermediários e avançados de CVB tratados entre 1996 e 2006. Todos os casos foram tratados com uma segmentectomia hepática parcial em segmentos IVb e V e uma dissecação linfonodal regional e seis ciclos de quimioterapia de ambulatorio (5-FU e leukovorin). Com um tempo de seguimento médio de 31,5 meses, a morbidade, mortalidade operatória, hepático e infiltração linfática e atuarial de sobrevida foram medidas. Estatísticas descritivas foram aplicadas, bem como análise bivariada aplicando o teste exato de Fisher, testes não-paramétricos, curvas de sobrevida Kaplan Meier e técnica de regressão logística e risco proporcional de Cox. **Resultados:** Foram incluídos 40 pacientes neste protocolo, com uma média de idade de 59,5 anos (40-85 anos), dos quais 28 eram mulheres (70%). Profundidade de infiltração parede: muscular 8 pacientes (20%), subserosal 12 pacientes (30%), serosas 12 pacientes (30%) e perivesicular no tecido adiposo, 8 pacientes (20%). A série morbidade foi de 27,5%. Não houve mortalidade operatória. A quimioterapia foi bem tolerada. A sobrevida global atuarial da série foi de 50% em 60 meses. **Conclusão:** Nosso protocolo tem tratamento morbidade, mortalidade e taxas de sobrevivência semelhantes às relatadas anteriormente série. **Descritores:** Neoplasias da Vesícula Biliar. Hepatectomia. Quimioterapia Adjuvante.

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Introduction

Gallbladder cancer (GBC) is the leading cause of cancer death in women over 40 years old in Chile. The prognosis is generally poor because of the diagnosis is made in advanced stages¹.

Most patients that survive long-term are those that had a

cholecystectomy for cholelithiasis and a nonapparent or incidental neoplasia were found in the histological examination².

There is evidence related to the overall survival of GCB patients suggesting that it is less than 60% at 5 years and for

advanced stages is around 20% to 30% (T₃ and T₄)³⁻⁵. This undoubtedly determines the need to permanently review and discuss the various therapeutic options currently available in order to offer progressively better results to our patients. However, in general terms, it can be said that those patients with GCB where the invasion affects only the tunica mucosa can be considered cured with a cholecystectomy; in those cases where the invasion is muscular (T₁), a 80% survival rate has been reported at 5 years^{6,7}, and in these cases there is no consensus regarding the need for complementary treatment; in those patients where the invasion is subserosal (T₂), a 50% survival rate has been reported at 5 years in treated patients^{4,6}, it seems that the complementary treatments would be useful; and for those where the serosal and/or perivesicular adipose tissue has been compromised, the use of complementary treatments is debatable because, in these cases, it is common to find tumoral extension to adjacent organs and hepatic metastasis during surgery, which make any additional treatment with poor results which renders any attempt at treatment practically ineffective^{3,5}.

Different protocols of treatment have been used. There is general coincidence to use surgical hepatic resection with or without adjuvant or neoadjuvant protocols⁵⁻¹⁰.

The objective of this study is to evaluate the results of a prospective therapeutic protocol with long-term follow up in terms of survival rates in a cohort of patients treated with Intermediate and Advanced GBC.

Methods

The series includes patients who underwent a cholecystectomy performed by the first author at the Hospital Clínico de la Frontera (Temuco, Chile) between July 1996 and December 2006. A GBC was confirmed histologically. All the patients were followed up on the basis of a protocol of clinical, laboratory and imaging examinations until the end of the study.

Study variables

The dependent variable or end-point was survival rate. Independent variables were disease stages, morbidity and mortality rates related to the treatment. Other in study variables (co-variables) were age, gender, biochemical variables, liver characteristics, resected liver infiltration, operating time, resected lymph node infiltration, post-operative morbidity, mortality and post-operative hospital stay.

Protocol

Once the neoplasia had been confirmed, the specimen was mapped in order to achieve the deepest wall infiltration level (Figure 1).

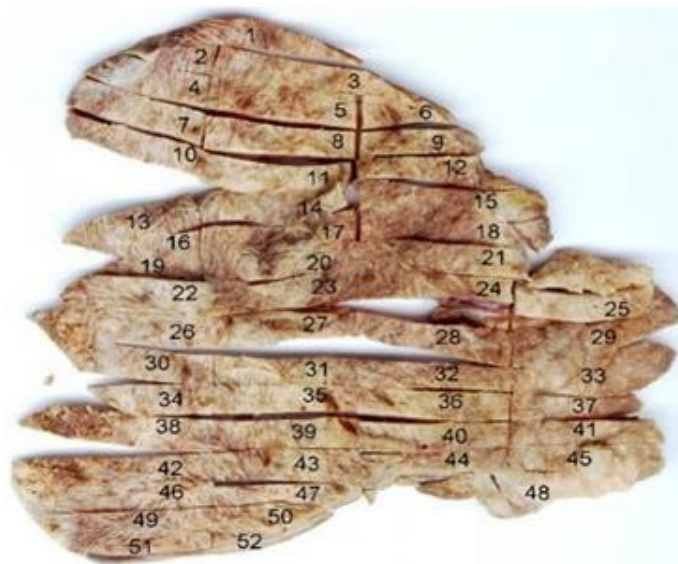


FIGURE 1 - Cholecystectomy specimen fixed in formalin, set and subsequently mapped in small fragments for independent study

Those subjects with an invasion as far as the tunica mucosa were considered “cured” with the cholecystectomy and did not enter into this protocol, so they were not included in this study. In those patients where the tumor invaded the muscular coats (T₁) (Figure 2A), subserosa (T₂) (Figure 2B), serosa (T₃) (Figure 2C) and perivesicular adipose tissue (T₄) (Figure 2D), the following therapeutic scheme was applied: resection of hepatic segments IVb and V and a local lymphadenectomy (intercavaoortic, choledochoduodenal, retropancreatic, hepatic pedicle and celiac trunk groups).

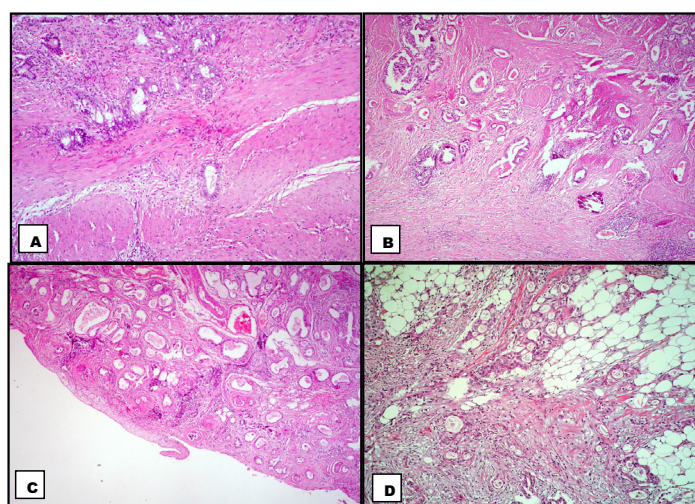


FIGURE 2 - Compound microphotograph showing the four categories group cases included in this study. **A.** Shows muscular layer infiltrated by neoplastic glands (pT₁). **B.** Shows the invasion of many neoplastic glandular structures in the subserosal layer (pT₂). **C.** Many neoplastic glands are in direct relationship with serosa (pT₃). **D.** The surrounding adipose tissue around gallbladder is infiltrated by neoplasia (pT₄)

In those patients whose neoplasia was discovered after a laparoscopic cholecystectomy, the resection of operative scars at corresponding laparoscopic ports was also added. After the second look surgery, 6 cycles of out-patient chemotherapy (5-FU and leukovorin) were administered, with the first cycle beginning between the third and fourth post-operative week.

Statistical analysis

Descriptive statistics were applied with a calculation of percentages, medians, extreme values and confidence intervals of 95% as well as the Kaplan Meier survival estimate. Furthermore, statistical analysis was applied using Fisher's test for categorical variables and non-parametrical tests for continuous variables. In addition logistic regression and Cox proportional risk for compare survival rates were applied.

Results

In the period analyzed, 1485 cholecystectomies for

cholelithiasis were performed in this hospital, 44 cases of GBC were diagnosed, which represents a disease prevalence of 3% for this period. The distribution according to the level of infiltration can be summarized as follows: 4 cases of intramucous cancer (T₁) (9.1%), 8 (18.2%) infiltrative as far as the muscular coat (T₁), 12 (27.3%) subserosal (T₂), 12 (27.3%) serosal (T₃) and 8 (18.2%) beyond the serosa (T₄). Intramucous cancer will be omitted because they did not receive a treatment with outcomes evaluated in this study.

Therefore, 40 patients were treated with this protocol, 28 female (70.0%) with an median age of 59.7 years (40-85 years). The distribution according to level of invasion of the main lesion was as follows: T₁ 8 patients (20%), T₂ 12 patients (30%), T₃ 12 patients (30%) and T₄ 8 cases (20%). These parameters and other clinical variables are outlined in Table 1.

In 22 patients (55%), liver parenchyma infiltration was found and in 23 patients (57.5%), lymph nodes metastases were confirmed (Table 1).

TABLE 1 - GBC. Infiltration level and association with categoric variables (N = 40)

Variable	Level of tumoral invasion				p
	T1 (n = 8)	T2 (n = 12)	T3 (n = 12)	T4 (n = 8)	
Gender (%)					
Male	12.5	33.3	16.7	62.5	0.098
Female	87.5	66.7	83.3	37.5	
Liver characteristics (%)					
Normal	75.0	66.7	83.3	62.5	0.679
Steatotic	25.0	33.3	16.7	37.5	
Resected liver infiltration (%)					
No infiltration	100.0	41.7	25.0	0.0	0.001
With infiltration	0.0	58.3	75.0	100.0	
Resected lymph node infiltration (%)					
No infiltration	87.5	41.7	16.7	0.0	0.001
With infiltration	12.5	58.3	83.3	100.0	
Post-operative morbidity (%)					
No	12.5	41.7	33.3	12.5	0.296
Yes	87.5	58.3	66.7	87.5	

In the preoperative study, a significant difference in T₄ patients was observed (red cells, hematocrits, total leukocyte count, alkaline phosphatases, transaminases and prothrombin) (Table 2).

The median of the surgical reintervention time and post-operative hospital stay was 215 minutes (90 to 480 mins) and 5 days (4 to 12 days), respectively. The longest hospital stay was observed in T₄ patients (Table 2).

TABLE 2 - GBC. Infiltration level and association with continuous variables (N = 40)

Variable	Level of tumoral invasion				p
	T1 (n = 8)	T2 (n = 12)	T3 (n = 12)	T4 (n = 8)	
Age (years)	57	64	62.5	55	0.5745
Red cells (10 ³)	4300	4330	4320	3650 *	0.0001
Hematocrit (%)	38	40	38	30 *	0.0001
Total leukocytes (mm ³)	8500	5900	9100	13350 *	0.0001
Platelets (10 ³)	252	196	240	255	0.0833
Total bilirubin (mg/dl)	0.8	0.8	1.0	1.1 *	0.0024
Alkaline phosphotase (U/L)	180	155	227.5	741 *	0.0001
ASAT (U/L)	23	20	25	180 *	0.0001
ALAT (U/L)	23	24	30	166 *	0.0001
Prothrombin (%)	95	90	97.5	71 *	0.0001
PTT (secs.)	29	30	34	40 *	0.0001
Operating time (mins.)	180	180	260	200	0.6725
Hospitalization (days)	5	5	5	10 *	0.0609

ASAT: Aspartate aminotransferase

ALAT: Alanine aminotransferase

PTT: Partial thromboplastin time

The values reported correspond to the variable medians.

* : Values that generate statistical differences

With a median follow-up of 31.5 months (3 to 133 months), we observed a morbidity of 27.5% (11 cases): three patients developed post-operative atelectasia, which improved with breathing exercises; three patients presented an infection of the operating site which improved with nursing care; one patient required an intervention for early bile peritonitis of non-specific etiology; and the four remaining patients developed an incisional hernia (three months after their surgery). No operative mortality was recorded.

Two T₄ patients, with hepatic metastasis (one with a perforation of the tumor at the hepatic angle of the colon and the other with infiltration of a coexistent hepatic hydatid cyst), did not manage to receive any cycle of adjuvant chemotherapy. Three T₄ patients only received two cycles of chemotherapy because they died before completing the complementary treatment. The rest of the subjects completed their adjuvant treatment without incident and it was well tolerated.

The overall actuarial survival in the series at 60 months was 50% (Figure 3).

When analyzing by stages, the following figures were confirmed: T₁ patients 100%, T₂ 85%, T₃ and T₄ 0% ($p < 0.001$) (Figure 4).

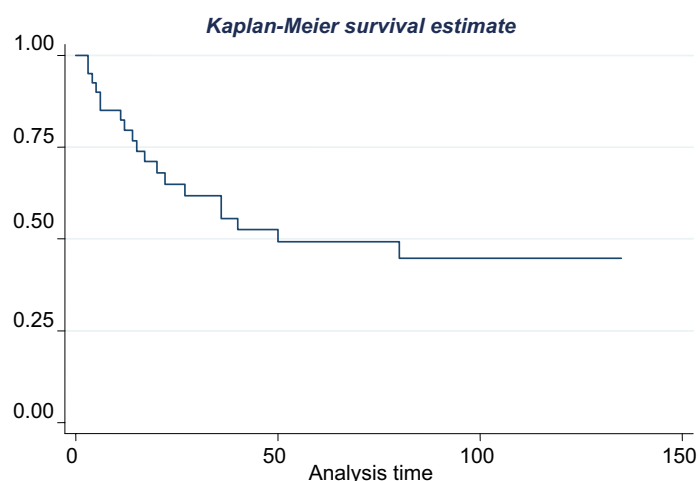


FIGURE 3 - Overall actuarial survival of the series, estimated using Kaplan Meier's method

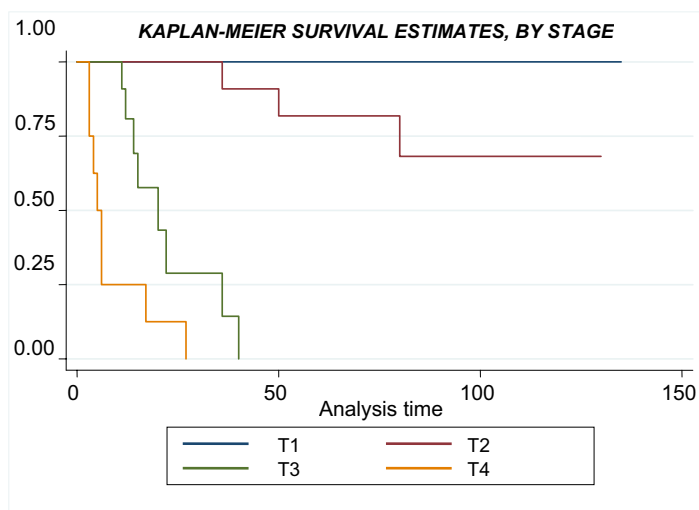


FIGURE 4 - Actuarial survival of the series according to the invasion level of the main lesion, estimated using Kaplan Meier's method and comparison applying Cox proportional risk

The survival median of the series was 31.5 months (95% CI 5.5 – 57.3). When analyzing by stages, the following medians were confirmed: 81 months (95% CI 20.8 – 131.8) for T₁ patients; 80 months (95% CI 50.0 – 104.3), for T₂ patients; 14.5 months (95% CI 11.1 – 21.8) for T₃ patients and 5.5 months (95% CI 3.0 – 20.5) for T₄ patients ($p = 0.0001$).

Discussion

GBC is the primary cause of cancer death in women in Chile and the mortality rate for this has not improved in the last 20 years^{1,2}. Early lesions of GBC can be considered the tumors with the best prognosis because in general the survival reported for these is almost 100% at 5 years³⁻⁵.

Classification based on infiltration level of the gall bladder⁷ yields interesting results because it seems to be concordant with the patients' prognosis and at the same time is operative in terms of therapy. Therefore, one can say that in some patients with invasion beyond the mucosa, an exclusive cholecystectomy is associated with the existence of a residual tumor and hence with a detriment to long-term survival. In this sense, the evidence justifies applying complementary therapies with the idea of improving survival rates.

This is a prospective cohort study that allows us to respond with a 2b level of evidence to the research question on the survival rate of patients with different stages of GBC treated with this protocol.

From the characteristics of our series, we can say that the behavior of the age and gender variables were no different to what has been reported previously^{5,7,9,11,12} because a clear predominance in females was observed; and the age was similar in the groups except for those with advanced cancer, who were 7 to 9 years younger, making it possible to suggest the development of more aggressive neoplasias in younger people – a fact that may present a selection bias, due to the sample size of this series.

Another interesting fact to consider is the relation to laboratory studies, which were seen to be significantly changed in

patients with advanced tumors, and we remind that these also presented other coexisting entities (tumoral perforation of the colon, infiltration in a coexistent hepatic hydatid cyst and residual choledocholithiasis).

The surgical times and hospital stays were similar for all the groups (except for T₄ group), which seems logical, given that despite a similar surgery being performed in the most advanced group, the surgical process was more difficult. All the groups evolved in good condition, with a post-operative hospital stay that was considered adequate.

The total morbidity reported (27.5%) seems reasonable if we consider that this includes not only problems investigated at the immediate post-operative stage, but also those that appeared later. The published series in general do not record this data except for some that mention early complications, with rates that fluctuate between 14% and 30%¹²⁻¹⁴; from this point of view; the operative morbidity of our series would only be 17.5%.

In relation to the overall actuarial survival of the series (50.0% at 60 months), it may be pointed out that it resembles other experiences, but this data must be carefully considered because for this calculation, the patients have different follow-up periods and because, as mentioned earlier, it deals with a small series of cases even though the follow-up was exhaustive. In fact, observing the survival by stage, one can see that the patients with T₃ and T₄ stages have an actuarial survival of 39% and 12.5%, respectively, which can be also explained using those reasons mentioned earlier. For all this, it seems to us that this information must be necessarily contrasted to the real survival expressed in medians with their respective confidence intervals of 95%, and this will give us information closer to what can be expected.

Analyzing the data from this perspective calls attention to the fact that the survival median is similar for patients with GBC with infiltration up to the muscle coat and subserosa. In these subgroups, the confidence intervals are different and this is related to the follow-up period with patients; but it could be also influence by other clinical and biological variables involved and it is impossible to hazard an opinion at this preliminary stage.

On the other hand, statistically significant differences in the survival median of T₃ (14.5 months) vs. T₄ (5.5 months) were verified; this leads us to think that as usual in medicine, each patient must be analyzed independently since factors such as these, added to age, general state of health, the coexistence of an associated pathology, etc. can mean modifying determined therapy management, particularly when there is still no consensus based on solid scientific evidence to support it.

After this experience, it seems to us that in T₄ patients with invasion beyond the serosa, surgery does not play a significant role beyond being a procedure to improve the quality of survival because the contribution in terms of increasing survival is very poor (median of 5.5 months).

With regards to the laparoscopic cholecystectomy, we can mention that 9 patients were primarily operated on this way (4 T₁ and 5 T₂ patients). In these subgroup, the second look surgery did not show evidence of spreading (including the port sites) and the clinical study with images did not reveal any evidence of tumoral implant or extension in contrast to that reported by other research groups¹⁵⁻¹⁸, which also explains the possible tumor-spreading mechanisms (vesicular perforation, air leakage when removing the trocars, etc.).

Therefore, the prevalence of GBC forces us to maximize precautions when we perform a laparoscopic cholecystectomy, the technique of choice in treating gallbladder pathology.

With reference to the complementary treatment, it seems to us of interest to comment that the use of adjuvant therapies after surgery is still a matter of some controversy which is why multicenter clinical trials must be conducted to compare the effectiveness of the different options versus surgery exclusively. The advent of gemcitabine has brought with it a new therapeutic opportunity so that adjuvant treatment could be involved not only in the traditional 5 FU but also gemcitabine, cisplatin and docetaxel¹⁹⁻²¹.

Conclusion

Our protocol treatment has morbidity, mortality and survival rates similar to previously reported series.

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