

## GALLBLADDER ADENOCARCINOMA: EVALUATION OF THE PROGNOSTIC FACTORS IN 100 RESECTABLE CASES IN BRAZIL

*Adenocarcinoma da vesícula biliar: avaliação dos fatores prognósticos em 100 casos ressecados no Brasil*

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**ABSTRACT – Background** – In spite its relative rarity, gallbladder adenocarcinoma is a neoplasm who presents an aggressive biologic behavior. The single curative treatment has been radical surgical resection with free margin. Prognostic factors has been studied because are very important to identify long-term survival patients which may benefit of aggressive surgical resection. **Aim** - To evaluate long-term prognostic predictors from gallbladder cancer. **Methods** - The medical records of all patients that presented confirmed histological diagnosis of gallbladder adenocarcinoma operated over a 14 year period were identified and retrospectively reviewed. Uni and multivariate analysis was done. **Results** - Total sample was 100 patients. Median age was 71 years (34 to 93). There were 17 men and 83 women. Lesion distribution according to TNM stage system was: I (n=22), II (n=59), III (n=6), IV (n=4) and unknown (n=9). Fifty two patients underwent radical resection (R0) while 48 to palliative surgery (R1-R2). Overall major morbidity was 14%, while postoperative surgical mortality rate (30th postoperative day) was 12 %. Five-year survival rate was 28% while median of survival was 10 months. Multivariate analysis identified six prognostic factors: T stage, serum level of CA 19.9, gallbladder perforation, lymphatic embolization, surgical historical cohort (after 2002) and hilar lymphadenectomy. **Conclusion** - Prognostic factors were: T stage, serum level of CA 19.9, gallbladder perforation, lymphatic embolization, surgical historical cohort and hilar lymphadenectomy.

**HEADINGS** - Gallbladder neoplasms. Adenocarcinoma. Hepatectomy.

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Financial source: none  
Conflicts of interest: none

Received for publication:  
Accepted for publication:

**RESUMO – Racional** - A despeito da sua relativa raridade, o adenocarcinoma de vesícula biliar é neoplasia que apresenta comportamento biológico agressivo. O único tratamento curativo tem sido a ressecção cirúrgica radical com margem livre. Fatores prognósticos têm sido estudados por serem importantes para identificar pacientes que podem se beneficiar de ressecção cirúrgica agressiva. **Objetivo** - Avaliar preditores prognósticos em longo prazo de pacientes com câncer da vesícula biliar. **Métodos** - Foram identificados e retrospectivamente revisados os prontuários médicos de todos os doentes submetidos a tratamento cirúrgico que apresentavam diagnóstico histológico confirmado de adenocarcinoma de vesícula biliar durante período de 14 anos. Os dados foram submetidos à análise estatística uni e multivariada. **Resultados** - A amostra total foi de 100 doentes. A mediana de idade foi de 71 anos (34 a 93). Houve 17 mulheres e 83 homens. A distribuição das lesões de acordo com o sistema de estadiamento TNM foi: I (n=22), II (n=59), III (n=6), IV (n=4) e desconhecido (n=9). Cinquenta e dois doentes foram submetidos à ressecção radical (R0) enquanto 48 à cirurgia paliativa (R1-R2). A morbidade global foi de 14% enquanto que a mortalidade pós-operatória (até 30º dia do pós-operatório) foi de 12 %. A taxa de sobrevida em cinco anos foi de 28% enquanto a mediana de sobrevida foi de 10 meses. A análise multivariada identificou seis fatores prognósticos: estágio T, nível sérico de CA 19.9, perfuração da vesícula biliar, embolização linfática, coorte cirúrgico histórico e linfadenectomia hilar. **Conclusão** - O tratamento do câncer de vesícula biliar apresenta alta morbimortalidade. Os fatores prognósticos foram: estágio T, nível sérico de CA 19.9, perfuração da vesícula biliar, embolização linfática, coorte cirúrgico histórico e linfadenectomia hilar.

**DESCRITORES** - Neoplasia da vesícula biliar. Adenocarcinoma. Hepatectomia.

## INTRODUCTION

**G**allbladder carcinoma (GBC) is the most common malignant biliary neoplasm and the 7<sup>th</sup> most common gastrointestinal cancer<sup>20</sup>. Tumor resection with free margins remains curative therapy. Nevertheless GBC at an early stage may be cured by simple cholecystectomy. Generally it is diagnosed at an advanced stage, when major resections including hepatectomy should be necessary for attaining free margins<sup>4,5,8,11,12,20</sup>. Although safety of these surgical procedures has improved over last years – due to major advances in both operative and perioperative management –, the overall mortality for advanced GBC remains high, when compared with other gastrointestinal surgeries<sup>9,10,11</sup>. Generally, it is more commonly found in elderly patients with several clinical comorbidities. Furthermore the outcome of patients with advanced disease requiring major resection is dismal<sup>1,13,25</sup>. Prognostic factors have been studied such as epidemiology/demography (age, gender), management treatment (radical operative procedures, adjuvant therapy) and histological (TNM stage, grade, perineural or vascular-lymphatic embolization). These prognostic factors along the time had represented the most important predictors of GBC in long follow-up<sup>3,4,10,11,12,14,21,22,23,24,25</sup>.

The aim of this study was to identify prognostic factors in long-term survival in GBC in Brasil.

## METHODS

A retrospective analysis of the prognostic factors in 100 patients treated at São Paulo Francisco Morato de Oliveira Hospital – HSPE-FMO with confirmed histological diagnosis of gallbladder adenocarcinoma was performed. The study period was between January 1995 and January 2009. This study was approved by ethic committees of both HSPE-FMO and Federal University of São Paulo. All patients were identified from both HSPE-FMO cancer registry and Department of Pathology.

Only adenocarcinomas histologically proven were included. Only underwent surgical treatment patients were considered to the final analysis. Patients who underwent both radical (R0) and palliative surgery (R1-R2) were included. Preoperative metastatic disease was also excluded. Information extracted to find possible long-term prognostic factors were: 1) demographics data (age, sex, ethnicity, MCI, ASA, pre-operative diagnosis, incidental diagnosis, historical surgical cohort); 2) laboratory analysis (serum levels of bilirrubins, albumin and tumor markers); 3) surgical treatment (type of surgery, previous surgery, surgical time, blood loss, transfusions, morbidity); 4) histology (localization, status of the surgical margins, TNM stage, macroscopic type, grade, lymphatic or vascular

embolization, perineural invasion, inflammatory process, gallbladder perforation or necrosis); 5) adjuvant treatment.

Sixth edition of the AJCC TNM staging manual was employed. The types of surgery were simple cholecystectomy or partial hepatectomy (bisegmentectomy IV-V or right hepatectomy). When hilar lymphadenectomy (HL) was indicated, resection of porta hepatis and supraduodenal nodes were performed (N1). If N2 nodes were suspected, additional lymphadenectomy was done. Bile duct resection was performed only if there were bile duct invasion or even the surgical margin was close. Reconstruction with 70 cm Roux-en-Y biliary enteric bypass was performed when bile duct resection was done. Completeness of resection was classified as R0, R1 or R2 always depending on the margin status and intraoperative impression of the surgical team that were confirmed in definitive histological analysis. R0 was defined as no residual disease, R1 as microscopically positive margin and finally R2 as macroscopically residual disease. All of the hepatectomies were performed by senior oncology surgeon team.

Overall survival was measured from the day of operation to death, including cancer death and other causes, and to the last day of follow-up considered so until last medical return or death.

Survival curves were estimated using the Kaplan-Meier method and compared using log-rank test. Cox regression analysis was carried out to determine which factors were the best prognostic determinants.  $P < 0,05$  was considered statically significant. All statistics analyzes were performed using SPSS 17.0 software (SPSS-USA).

## RESULTS

One hundred sixteen GBC patients were identified. However, 16 patients were excluded due uncompleted records ( $n=14$ ) and no-adenocarcinoma ( $n=2$ ) at histology. Consequently, 100 patients who underwent surgical resection were the aim of the present study (Table 1).

The distribution of the gender was: 83 females (83%) and 17 males (17%). Median age was 71 years (34 to 93), while mean age was 69 years. Ninety five patients were caucasians and five no. Fifty four presented associated diseases: systemic arterial hypertension ( $n=47$ ), diabetes ( $n=12$ ), coronary insufficiency ( $n=3$ ), congestive cardiac insufficiency (3), mental demency ( $n=2$ ), renal chronic insufficiency ( $n=1$ ), and sclerodermia ( $n=1$ ). The BMI was 27.8 ranging from 18 to 43. The ASA classification showed 46 patients in ASA 1, 30 in ASA II and 21 in ASA III. The clinical findings were: jaundice in 42 patients, acute cholecistitis in 36, weight loss in 21, acute cholangitis in six and acute pancreatitis in one patient. The mode of presentation was: incidental finding in 63 patients,

localized mass (advanced lesion) in 37. The laboratory findings were: bilirrubines (ng/dl) 0,7 (0,2-28), albumin (ng/dl) 3,5 (1,3-4,7), ACE (ng/dl) 4,5 (0,2-535) and CA 19.9 (ng/dl) 35,6 (1,2-24150).

Were done 52 hepatectomies (21 with en-bloc biliary resection plus biliary reconstruction) and 48 simple cholecystectomies. Fourty seven operations were bisegmentectomy IV + V, while five right hepatectomies. There were 73 elective surgeries while 27 patients were operated in emergency situation due to complications of their gallstone disease. Seven patients underwent some type of hilar lymphadenectomy. There were 52 R0 resections and 48 in R1-R2. Overall morbidity was 46%, in which 14 had major complications (14%) that needed reoperation during their hospital stay. Overall postoperative mortality (30 days) was 12%. Elective surgery mortality was 5%. All patients submitted to emergency surgery to treat acute cholangitis (n=6) died due infectious complications. Overall mortality rate of the first period (cohort before 2002) was 25 % while in second period (cohort after 2002) was 3,3%.

Surgical treatment characteristics were: simple cholecistectomy in 48 patients, resection of segments IV + V in 47, formal right hepatectomy in five, bile duct resection + biliary bypass in 21, hilar lymphadenectomy in 70, multivisceral resection in four and biliary bypass in six patients.

The surgical findings were: median operative time (min): 185 (58-510); median operative bleeding (ml): 400 (0-4000); median hospital stay (days): 18 (1-75); major morbidity: 14 (14%); reoperation: 14 (14%) and overall mortality: 12 (12%).

Seventeen patients (17%) underwent adjuvant treatment (radiotherapy or/and chemotherapy).

Histological characteristics are shown in Table 1.

Fifty six patients presented documented tumor recurrence distributed as: multiple (two sites minimum)=29, peritoneum=14, liver=10, lymph nodes=2, biliary system=1. Nineteen patients presented no recurrence in 40 months median follow-up period (5 to 120 months). Median survival time was 10 months, while de 5-year survival was 28%. The Kaplan-Meier curve is shown on Figure 1A.

#### Analysis of prognostics factors

Twenty nine variables were analyzed related to possible prognostic factors in this sample. On univariate analysis, it was found that T-stage, no billiary resection, radicality (R1), blood transfusions, CA 19.9>40 ng/dl, bilirrubines>4 ng/dl, gallbladder perforation, tumor grade, lymphatic embolization, surgical cohort<2002, obesity, TNM classification, no fundic location, positive lymph node, and reoperation due postoperative complication were statically significant factors for dismal survival (Table 2).

On multivariate analysis, were identified as

TABLE 1 - Histological characteristics (n=100)

Number of patients	100
<b>Grade tumor</b>	
I	33
II/III	77
<b>Tumor-stage</b>	
T1	6
T2	24
T3	66
T4	4
<b>Clinical stage (TNM)</b>	
I	22
II	59
III	6
IV	4
No-defined	9
<b>Macroscopic findings</b>	
<b>Local of the lesion</b>	
Fundus	31
Neck	8
Infundibulum	26
Difuse	35
<b>Macroscopic type</b>	
Papilifer-fungoid	13
Nodular	23
Infiltrative	40
No especific	24
<b>Microscopic findings</b>	
Perineural invasion	57
Vascular invasion	45
Lymphatic embolization	58
Peri-tumoral inflamation	34
Necrosis	42
Gallbladder perfuration	41
<b>Lymph nodes</b>	
No	43
N1	48
Nx	9

TABLE 2 - Univariate analysis

Variable	P	Odds Ratio (Exp B)	IC 95% to Exp (B)	
			Inferior	Superior
T-stage	,092	6.238	,743	52.357
Age	,120	,944	,877	1.015
Gender	,240	,357	,064	1.993
Body mass index	,172	,829	,633	1.085
Hepatectomy	,639	,626	,088	4.436
Pre-operative diag	,075	,135	,015	1.223
Bile duct resection.	,966	1.036	,203	5.297
Radicality (R0/R1)	,031	6.078	1.183	31.216
Blood transfusions	,166	3.800	,575	25.099
CA19.9>40	,000	233.063	13.884	3912.330
Antigen carcinoembrionary>20	,014	,083	,011	,604
Bilirrubines>04	,026	8.846	1.293	60.535
Albumine<3	,173	,289	,048	1.727
Gallbladder necrosis	,047	,009	,000	,933
Gallbladder perfuration	,147	38.261	,279	5247.573
Grade	,847			
Grade (1)	,614	1.969	,141	27.509
Grade (2-3)	,826	,806	,117	5.531
N-stage	,130	,226	,033	1.547
Lymphatic embolization	,002	506.393	9.904	25892.924
Perineural invasion	,013	,018	,001	,421
Inflammatory reaction	,002	,033	,004	,287
Surgical time>80	,261	,353	,057	2.171
Surgical cohort<2002	,001	29.134	3.883	218.596
Colestasis	,059	,053	,003	1.113
Obesity	,036	37.305	1.267	1098.629
UICC-TNM	,798	1.586	,046	54.316
Gallbladder localization (fundus or no)	,694	1.570	,165	14.914
Lymphadenectomy	,000	255.652	15.398	4244.538
Reoperation	,029	11.043	1.272	95.878
Adjuvant treatment	,007	,020	,001	,338

TABLE 3 - Multivariate analysis – logistic regression

	p	Odds Ratio (Exp B)	IC 95% to Exp (B)	
			Inferior	Superior
T stage	0.005	2.759	1.364	5.579
CA 19.9 (> 40ng/dl)	0.000	6.386	2.630	15.506
Gallbladder perforation	0.005	3.082	1.412	6.723
Lymphatic embolization	0.038	2.923	1.058	8.075
Surgical cohort (<2002)	0.000	5.477	2.229	13.460
Lymphadenectomy	0,0027	3.624	1.156	11.362

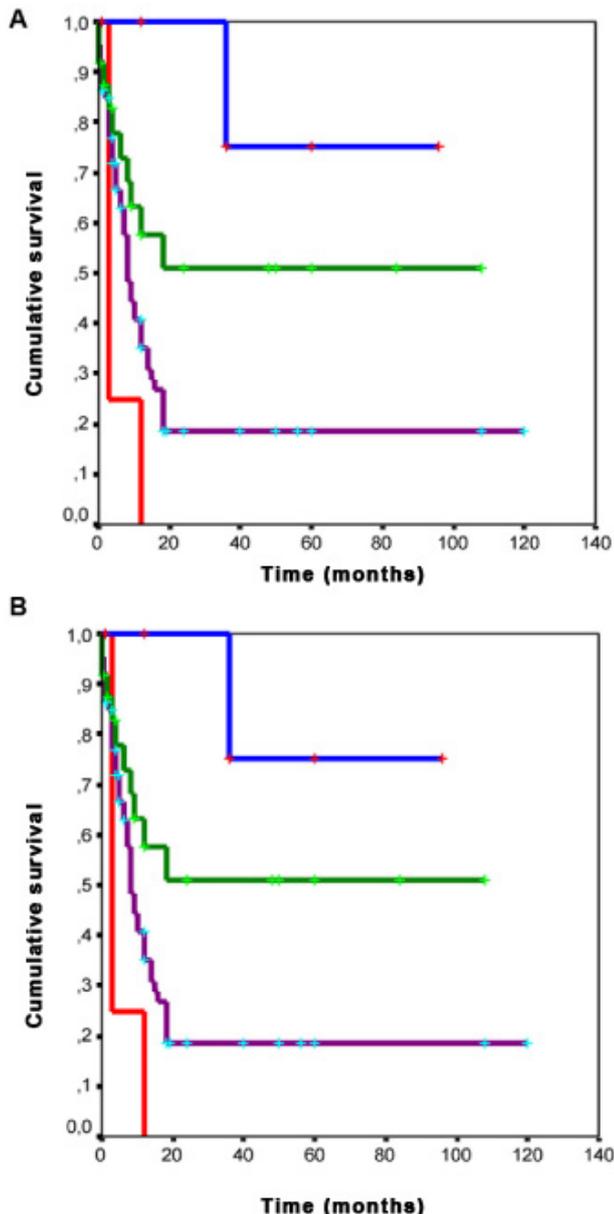


FIGURE 1 - A) Kaplan-Meier curve of cumulative overall survival time (n=100): 28% in 5-years (median of survival time: 10,0 months - IC 95%: 6,6 to 13,3 months); B) Kaplan-Meier curves of the 100 patients undergoing resection of GBC by T-stage (TNM-UICC): T1=75% - 5-years (n=6), T2=51% - 5-years (n=24), T3=18% - 5-years (n=66), T4=5% - 1-year (n=4)

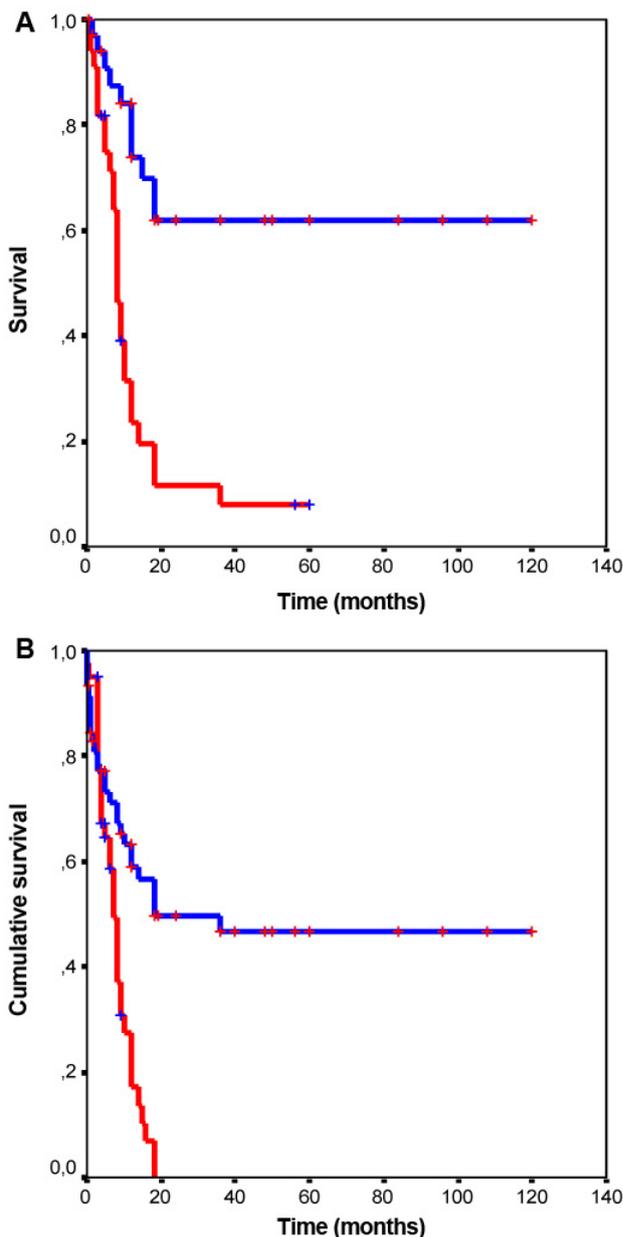


FIGURE 2 -A) Kaplan-Meier curves by serum level of CA 19.9: < 40ng/dl=62% - 5-years X CA19.9>40 ng/dl=7,8% in 5-years; B) Kaplan-Meier curves by gallbladder perforation: negative=46% in 5-years (median of survival time=18,0 months) X positive=0% in 5-years (median of survival time=7,0 months)

significant independent prognostic factors (Table 3): survival time and T-stage (Figure 1A and 1B), CA 19.9 >40,0 ng/dl and gallbladder perforation (Figure 2A and 2B), lymphatic embolization and surgical cohort <2002 (Figure 3A and 3B) and, finally, no lymphadenectomy (Kaplan-Meier according hilar lymphadenectomy: positive=28% in 5-years (median of survival time=12,0 months) X negative=26% in 5-years (median of survival time=7,0 months).

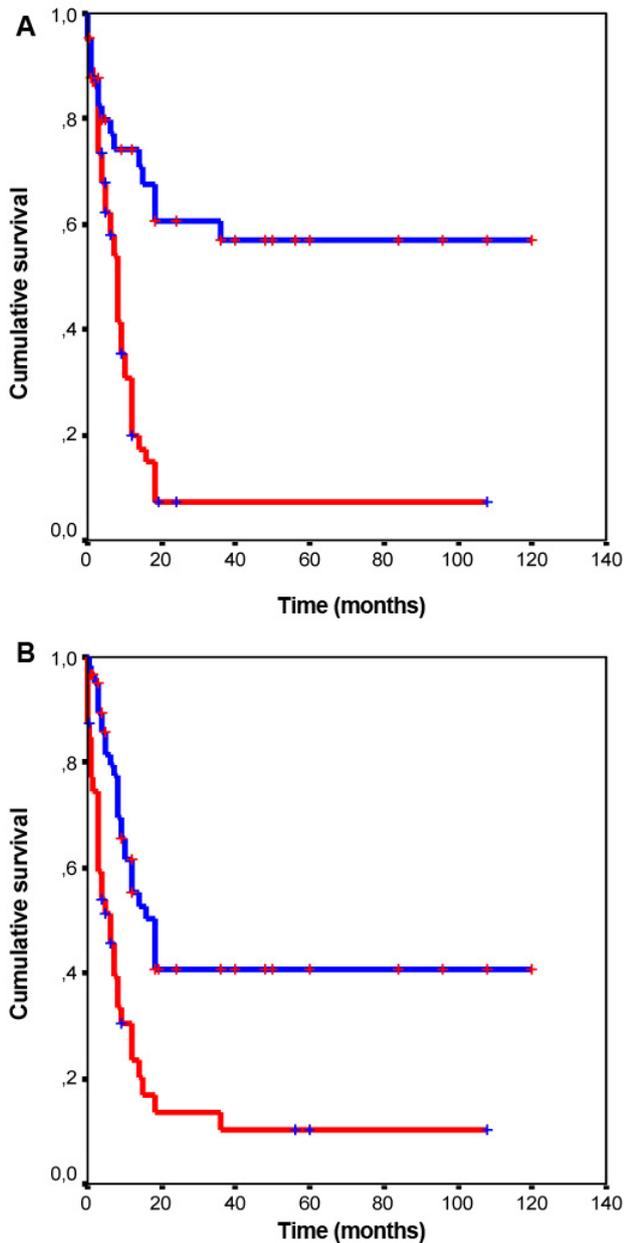


FIGURA 3 - A) Kaplan-Meier curves by lymphatic embolization: negative=57% in 5-years X positive=7% in 5-years; B) Kaplan-Meier curves by historical surgical cohort: after 2002=41% in 5-years ((median of survival time=18,0 months) X before 2002=10% in 5-years (median of survival time=6,0 months)

## DISCUSSION

Few studies have been reported about prognostic factors in GBC. Perhaps, because it is relatively rare tumor found on occidental countries (except some areas as Chile, Bolivia, Mexico, and east Europe) few studies has been conducted in Occident.

Real knowledge of the prognostic factors could lead to make a therapeutic decision that could avoid expensive costs. It could save patients of the

unnecessary large surgical procedure. For example, in oriental countries as Japan, all efforts have been done to perform ultra-radical operations (extended surgeries) for treating advanced GBC. Even there surgery carried high morbidity, high mortality rates and poor outcome. Radical resection seems to be limited in patients with advanced GBC. Thus with adequate selection, referential centers can treat advanced GBC with radical surgery identifying the prognostic factors to select the patients<sup>1,3,5,7,10,11,14,19,20,21,22,23,24,25</sup>.

Although, simple cholecystectomy seems to be enough for treating GBC restricted to mucosa (T1a), radical surgery with hepatic resection and hilar lymphadenectomy has been considered the gold standard therapeutic choice in more advanced stages (T1b-T3 or few T4). Despite great rates of specific surgical complications, these extended procedures are the single option to cure.

Though overall mortality has been decreased in recent studies, the morbidity seems high<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19</sup>. In according with Chan et al.<sup>4</sup>, the overall postoperative mortality with radical surgery for gallbladder cancer ranged 1% to 8,3%. The overall mortality of the present study (to the elective surgery) of 5,7% is similar to the one found in the literature. More recently, Pais-Costa et al.<sup>16,17</sup> shown in two small series of selected T2 and T3 GBC patients submitted to hepatectomy, 0% of the mortality rate in Brazil. Nevertheless, the high morbidity seems still stable; it has ranged among 12% and 33% in different series<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21</sup>. Major morbidity was similar to recent reports<sup>4</sup>. Concomitantly, extended procedure series improved in reports over recent years<sup>4,19,20</sup>. Like Konstantinidis et al.<sup>12</sup>, was observed a significant improve in hepatectomy aiming GBC treatment on recent years. Before 2002 only 17 hepatectomies were performed versus 37 hepatectomies after 2002. Therefore with improve of the experience on enlarged resection associated to decrease of overall mortality, has been observed major freedom to indicate more frequently extended resections in Brazil<sup>16,17</sup>.

Median survival time in present series was low (10 months), perhaps due to high mortality of emergency surgeries; similar results had Duffy et al.<sup>8</sup> as Liang et al.<sup>21</sup>. Overall 5-year survival rate of 28 % was comparable with recent studies (26% and 35%<sup>12,13,14,23</sup>).

Previous reports identified many prognostic factors. They were: age, gender, jaundice, depth of invasion, hepatic invasion, bile duct invasion, hepatoduodenal ligament invasion, lymph node metastasis, distant metastasis, residual disease, type of surgery (R0, R1 and R2), type of diagnosis (incidental or no), lymphadenectomy, perineural invasion, vascular invasion, lymphatic invasion, grade of differentiation<sup>4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19</sup>.

Like other authors, these authors preferred to exclude patients with distant metastasis considering that no therapeutic surgery should be done in these

situations<sup>8</sup>. T stage has been described with a strong predictor of long-term survival for many tumors. Basically, deep invasion of gallbladder layer is the most valuable predictor of both loco-regional and systemic dissemination. This observation was evident in this study, where survival time was significantly decreased with an increase of the T stage. The 5-year survival time was 75% to the T1 versus 51% and 18% respectively to the T2 and T3 stages. Only 25% of the T4 patients survived one year (median of three months). Recently, in China, Liang et al.<sup>13</sup> observed that T stage was the strongest survival predictor. These authors shown that for T1 tumors the 5-year survival was 100% against 78% for T2 and only 17% for T3 ( $p < 0,000$ ). Kayahara et al.<sup>11</sup> in a large multicentre study of 4770 patients in Japan observed that TNM stage was the strongest long-term predictor at multivariate analysis ( $p < 0.0001$ ). T stage also increases probability of lymph node disease. This paper observed that lymph nodes were respectively comprised on 0% at T1, 33% at T2 and 57% at T3 stages, similarly to other authors in literature<sup>4,7,9</sup>.

Nevertheless, lymph node metastasis has been considered predictor of dismal prognosis for patients with advanced GBC<sup>7,14,21</sup>, here no association was found. Perhaps, when multivariate analysis was done lymphatic invasion could be one confused variable at logistic regression. Like recently described by Shibata et al.<sup>24</sup> was observed that lymphatic embolization was one independent prognostic factor at multivariate analysis. Controversies have remained about role of the lymphadenectomy for treating GBC. Few Western reports have found node positive long-term survivors who underwent hilar lymphadenectomy. For example, Benoist et al.<sup>2</sup> advocated that radical resection should only be performed if there are no comprised loco-regional nodes. On the contrary, Japanese school has shown an improvement of the overall prognosis in patients which underwent lymph node dissection when lymph node metastasis were limited to the lymph nodes within the hepatoduodenal ligament<sup>14,21</sup>. Like other gastrointestinal cancers, controversies about the aim of the lymphadenectomy seem difficult to solve. Similarly to Japanese studies, was here observed improvement of the overall prognosis in patients which hilar lymphadenectomy even with compromised nodes. Perhaps, this finding could favor the therapeutic role of the systematic lymphadenectomy. Hilar lymphadenectomy has been considered important as prognosis in adjuvant treatment. In the present study, like in Sakata et al.<sup>21</sup> paper, hilar lymphadenectomy was found independent prognostic factor for long-term survival. This fact could also explain that there was no significance in node positive as independent prognostic factor. Therefore, the authors of this study think that it could present therapeutic potential role, as far as hilar lymphadenectomy was considered independent prognostic variable at multivariate analysis.

Although CA 19.9 has been associated with

prognosis in other gastrointestinal cancers - mainly colorectal cancer -, the real prognostic value of the serum levels of the CA 19.9 to the GBC remains unclear. Few studies associated serum levels of the CA 19.9 with prognosis of resectable GBC. Hatazara et al.<sup>9</sup> observed that the value of CA 19.9 > 35 ng-dl was the single significant long-term prognostic factor to the biliary tumors. They observed a very low long-term survival in the patients who underwent a radical surgery but preoperative levels of CA 19.9 were higher than 35 ng/dl (15.1 months X 67.4 months). In this paper was observed a poor long-term prognosis in patients presenting high preoperative serum levels of the CA 19.9 (>40 ng-dl). When it was higher than 40 ng/dl was found dismal overall prognosis.

In general lines, tumor perforation could lead peritoneal dissemination worsening overall long-term prognosis. This question has been discussed mainly in colorectal cancer<sup>18</sup>. In present study, gallbladder perforation showed worse prognosis, with seven months of median of survival time. More recently, occidental school has treated GBC by more aggressive surgical procedures<sup>8,12,19,20</sup>. Initially, occidental surgical institutions thought that radical resection of GBC with extended surgeries was not effective because the dismal prognosis independently of major resections for treating this neoplasm<sup>15,20</sup>. However, in this study neither hepatectomy nor R0 surgery were independent prognostic factors, although the second surgical cohort (after 2002) had presented better prognosis than first one (before 2002). More proportionally numbers of hepatectomies were performed in second period (3:1). Possibly, best long term survival has been obtained with more radical surgeries like previously published studies<sup>10,25</sup>. Kostatinidis et al.<sup>13</sup> observed in four historic moments that there was an improving of the overall survival with more radical surgery performed in recent periods. This paper observed proportionality in radical surgery with hepatectomy and hilar lymphadenectomy after 2002. Additionally, the second historical cohort (after 2002) was an independent prognostic factor for long-term survival at multivariate analysis. This fact has also been confirmed in more recent occidental studies<sup>8,12,19,20</sup>.

## CONCLUSION

Prognostic factors were: T stage, serum level of CA 19.9, gallbladder perforation, lymphatic embolization, surgical historical cohort and hilar lymphadenectomy.

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