

Gallbladder cancer: 10 years of experience at an Amazon reference hospital

Câncer de vesícula biliar: experiência de 10 anos em um hospital de referência da Amazônia

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A B S T R A C T

Objective: To evaluate the epidemiological aspects of surgical patients with gallbladder cancer (GC) enrolled in a University Hospital in Belém (State of Pará – PA), in the period 1999-2009. **Methods:** observational, retrospective, descriptive and analytical study of secondary sources of patients with GC in the period 1999-2009. We analyzed 75 medical records, with 34 patients studied. The information collected was used for the TNM tumor staging of GC and to characterize the clinical and surgical population. **Results:** 79% were female, mean age 66.2 ± 11 years and duration of symptoms was 10.8 ± 17.2 months, with no statistical relationship with the stage of disease. Pain in right upper quadrant, nausea and jaundice prevailed as signs / symptoms. Gallstones were present in 91% of cases and were positive in 100% of patients with stage I / II. The sensitivity of ultrasound to preoperatively suggest GC was 14.28%. The simplest operation performed was cholecystectomy, with the predominant intraoperative finding being hepatic invasion. Adenocarcinoma was the predominant histologic type, especially for stages III and IV. **Conclusion:** The present study showed high incidence of gallstone disease. Advanced stage adenocarcinoma was the most prevalent. This resulted in a low rate of operations with curative intent, in 30% of the patients, and a mortality rate of 21%. The appreciation of symptoms and early investigation by imaging could facilitate treatment in early stages of GC, providing a better prognosis for patients.

Key words: Neoplasms of the gallbladder. Neoplasm staging. Surgery.

INTRODUCTION

The neoplasm of gallbladder is a relatively rare disease, despite being the most common tumor of the biliary tract and the fifth most frequent of the gastrointestinal tract. It shows a high rate of mortality, as in most cases the patient presents with nonspecific symptoms and already in advanced disease stages¹⁻³.

The higher incidence of malignant neoplasm of the gallbladder occurs in women over 65 years. It also displays a large ethnic variation. The populations of countries such as Bolivia, Chile, Mexico, and Native Americans have a high mortality from this disease. In Europe, on its turn, there is a characteristically lower incidence. As risk factors, one may cite as the most important the presence of cholelithiasis, which would be responsible for a process of chronic inflammation with consequent formation of dysplasia-adenocarcinoma, this risk being even higher when there is presence of calculi above 3 cm. The porcelain

gallbladder is also a risk factor for gallbladder cancer (GC) – due to extensive calcification of its walls – and so is the presence of polyps – because of adenoma-adenocarcinoma progression. It is also noted that the presence of histological alterations can be linked to GC. Despite the scarcity of studies, obesity and high BMI, mainly grades II and III, and multiparity are present in patients with gallbladder cancer and may constitute risks as well. Some studies have shown an increased GC incidence in patients with chronic *Salmonella sp.* or *Helicobacter pylori*, purportedly by degradation of bile acids induced by these bacteria¹⁻⁴.

More than 90% of cases are represented by a histological pattern of adenocarcinoma, which can be characterized in tubular, mucinous or papillary. The anaplastic, the squamous and the adenosquamous carcinomas are the less common types⁴.

Therefore, we decided to analyze the demographic and clinical-surgical aspects of patients with malignant neoplasm of the gallbladder attended in a

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university hospital of Belém – PA, in the period from 1999 to 2009.

METHODS

The survey obeyed the ethical precepts of the Declaration of Helsinki and Nuremberg Code. The standards of Research Involving Humans (Res. CNS 196/96) of the Brazilian National Health Council were met, with the approval of the Ethics in Research Committee of the João de Barros Barreto University Hospital (HUIBB) on January 12, 2009 (Protocol No. 3774/08).

The study was of retrospective type, observational, descriptive-analytical secondary source (analysis of medical records of the Department of Medical and statistical Archive of the João de Barros Barreto University Hospital – DAME – HUIBB).

The universe of study contained patients treated at the HUIBB with a diagnosis of GC (ICD-10 C23), in the period from 1999 to 2009. We studied 75 patient records, of which 44 were diagnosed with GC, of which 10 were excluded for inaccurate/incomplete medical information and/or absence of histopathological reports confirming the presence of GC.

The search protocol used aimed to raise patients' epidemiological data, as well as comorbidities, familiar and personal pathological background, clinical symptoms and signs, time of symptoms, biochemical exams, ultrasound and tomography diagnosis. One or more of four following features were considered suggestive of GC at ultrasound: irregularity of the gallbladder wall; irregular thickening; polyps; and mass occupying the interior of the organ.

We also examined: surgical treatment, surgical time, intraoperative findings, postoperative complications, histologic type and tumor differentiation of the lesions. The information collected was used for TNM staging of GCs and epidemiological and clinical-surgical characterization of the studied population⁵.

In some analyses patients were distributed into two groups: Group A, containing patients belonging to GC stages I and II; and Group B, containing patients belonging to stages III and IV. This Division was intended to generate a differentiated view on the group for which surgical curative intent has high rates of success (Group A) and the one for which palliation or biopsy are but the few options (Group B).

For statistical analysis were applied descriptive and inferential statistical methods. The descriptive statistics was applied through numerical calculation of the main measures (mean, standard deviation). Statistical inference was implemented through hypothesis testing: the G Test compared the proportions within the sample and between two independent samples according to the case analyzed. Student's t-test was used to analyze the difference between

two arithmetic means. A level of significance $\alpha = 0.05$ was previously established to reject the null hypothesis.

RESULTS

Of the 34 cases studied, 79% (27/34) were female and 21% (7/34) male, with a ratio of 3.85:1. The average age was 66.2 ± 11 years, 66.5 ± 10.9 being female and 64.9 ± 12.1 male. The average time of symptoms was 10.8 ± 17.2 months, 19 ± 20.8 months among men and 8.1 ± 14.5 months among women. The average time of symptoms was 8.6 months in patients with advanced disease (stages III or IV), however, there was no statistical significance on this data ($p = 0.24$). Preoperative clinical signs and symptoms are shown in table 1.

Biliary calculi were found in 90.91% (30/33) of the population studied, with one of the medical records lacking this information.

Ultrasound sensitivity to preoperatively suggest GC was 14.28% (4/28), not being suggestive in 85.72% (24/28), both without statistical significance ($p > 0.05$). Ultrasound information could not be found in six medical records.

A cholecystectomy was performed in most patients, 41.17%. In 23.5% of patients a laparotomy with biopsy was carried out (Table 2). In 20.5% (7/34) of cases we opted for a palliative procedure associated with the main surgery, a biliodigestive anastomosis in 43% (3/7) and biliary drainage in 57% (4/7).

Key intraoperative findings are presented in table 3. We found the following recorded postoperative complications: jaundice (56%), fever (32%), sepsis (9%), and hemorrhage (9%). Seven patients (21%) died.

The histopathological diagnosis showed: adenocarcinoma in 91% of patients, epidermoid carcinoma in 6% and undifferentiated carcinoma in 3%.

The tumoral staging showed that stage IV was present in 44% of specimens examined (Table 4).

Table 1 – Distribution of main preoperative clinical signs and symptoms.

Signs / Symptoms	n	%
Weight loss	9	26%
Pruritus	9	26%
Acholia	10	29%
Abdominal discomfort	10	29%
Fever	11	32%
Choluria	15	44%
Vomiting	17	50%
Jaundice	19	56%
Nausea	19	56%
Pain in the right upper quadrant	26	76%

Table 2 – Main surgical procedures performed.

Operation Performed	n	%
Radical Cholecystectomy (IVb/V)	7	20.58%
Simple Cholecystectomy	14	41.17%
Cholecystectomy + Hepatic Wedge resection	4	11.80%
LE * + Bx **	8	23.50%
Whipple surgery	1	2.90%
Total	34	100.00%

* LE: Exploratory Laparotomy

** BX: Biopsy

The clinical outcome of each case was hampered by the loss to follow-up of a great part of the sample before completing five postoperative years, which prevented us from estimating the curative and mortality indexes of patients undergoing surgery with curative intent.

DISCUSSION

The signs and symptoms of GC, according to the literature, are not specific and generally arise late in the disease clinical course. Thus, the majority of cases are diagnosed in advanced stages, resulting in unfavorable prognosis^{1,2,6-8}. The population of this study showed 85% of cases in advanced stage, a fact that may be favored by symptoms that do not always express the severity of the disease, with consequent late suspicion. It is noteworthy that factors as delay in specialized medical care within the public health services could contribute with a high index of patients diagnosed in advanced and/or terminal stages, where alleviation emerges as the sole alternative.

Still in the aspect of the clinical picture associated with the GC, the most common symptoms associated with malignant neoplasm of the gallbladder are abdominal pain and/or biliary colic^{9,10}. However, patients with advanced disease may exhibit jaundice, from both the invasion of the biliary tree and metastasis to the hepato-duodenal ligament. Systemic manifestations such as weight loss, anorexia and asthenia may also be found^{9,10}.

Therefore, abdominal pain, mainly in the right upper quadrant, seems to be the great "marker", however non-specific, for gallbladder disease referred to in much of the literature, whether in calculus disease or in cancer.

In most series, the pain, a finding in part poorly conclusive, takes little space featured among complaints from patients, reaching figures of up to 95% of cases with GC. Proper appreciation of this symptom may allow earlier diagnosis and therapeutic results.

The gallbladder pain is in general closely associated with calculus disease and the literature shows an association of approximately 95% of cases of GC with cholelithiasis^{4,9,10}, which causes many studies to place calculi

Table 3 – Key intraoperative findings.

Intraoperative Findings	n	%
Liver invasion	14	41%
Invasion of other organs	13	38%
Invasion of extra-hepatic biliary tree	11	32%
Ascites	7	21%
Mass in topography of gallbladder	5	15%
Invasion of hepatic vascular pedicle	5	15%
Peritoneal carcinomatosis	5	15%
Adhesions	5	15%
No relevant findings	4	12%
Outros	3	9%

Table 4 – Gallbladder Cancer Tumor Staging.

Tumor Staging	n	%
Stage IA	1	3%
Stage IB	1	3%
Stage IIA	2	6%
Stage IIB	1	3%
Stage III	13	41%
Stage IV	14	44%
Total	32 *	100%

*Two patient records contained no information regarding stage.

in the position of a risk factor of great importance in the development of malignant neoplasm of the gallbladder.

Other associated symptoms such as jaundice and weight loss make the diagnostic suspicion easier. However, these are milestones of advanced disease and contribute little to an early diagnosis and better therapeutic management.

In cases of locally advanced disease, abdominal ultrasound (US) has a sensitivity of 85% and an accuracy of 80% in diagnosing GC, according to an American review held by Miller *et al.*⁴. However, in this series, they found a US sensitivity on suspicion of malignant neoplasm of the gallbladder next to only 14%. Nevertheless, when comparing the suspicion at US with the disease stage, it was realized that the sensitivity of

the US was 0% for suspicion of cancer stages I and II and only 13.3% for suspicion in stages III and IV, both data without statistical significance ($p > 0.05$).

Even with these poor results, one may infer that the cancer in stages III and IV is more suspected in US when compared to cancer in stages I and II, which again reinforces the reason for a late diagnosis in most cases the GC.

In accordance with revisions on the histopathology of GC, adenocarcinoma accounts for 80 to 90% of cases, the remaining 10-20% corresponding to squamous cell carcinoma, adenosquamous carcinoma, small cell carcinoma, undifferentiated carcinoma and more rarely, rhabdomyosarcoma^{4,9}. No different, the sample of patients with GC in this study showed a prevalence of 91% of adenocarcinoma, and epidermoid carcinoma in second place with only 6%. All epidermoid carcinoma cases were diagnosed in advanced stages, deeming it impossible to identify differences in clinical biological behavior, clinical manifestations and therapeutic results between different histological types.

Unlike expected, it was noted that the average time of symptoms was smaller (8.6 months) in patients with advanced disease (stages III or IV). However, there was no statistical significance on this data ($p = 0.24$), so that the real relationship between the symptomatic time frame and the stage at the time of diagnosis remains uncertain.

The finding of more symptomatic time in the group of stages I and II may be due to the association of symptoms to cholelithiasis, while the group with stages III or IV showed symptoms already associated with the

presence of advanced malignant neoplasm, which possibly lead to underestimation of prior, less relevant symptoms.

As for the therapy employed, it was noted that the main procedure was simple cholecystectomy in 41% of cases, possibly due to the large number of cases in advanced stages, preventing the realization of radical surgery^{9,11-15}.

We must point out that many patients had been previously operated in other non-specialized hospitals and had widespread disease in the abdominal cavity as the new operative finding. In these situations, as recommended, only alleviation and tumor histopathological diagnosis are plausible options^{16,17}.

The GC had higher prevalence in females, showing, as main symptoms and signs, the same found in calculous cholecystitis. The high incidence of biliary calculi can be linked to the cause of this neoplasm. Unlike expected, the average time of symptoms was lower in the group stage III and IV, but with no statistical significance, its role remaining uncertain on in this disease tumor advance. The advanced stage adenocarcinoma was more prevalent and likely related to the high incidence of death still in the hospital.

The series examined showed high incidence of biliary calculi and advanced stage adenocarcinoma was the most prevalent, leading to a small index of operations with curative intent, 30% of patients operated, and a mortality rate of 21%. The appreciation of symptoms and early investigation by imaging examinations could facilitate treatment in the initial stages of GC, providing an improved prognosis for the operated patients.

R E S U M O

Objetivo: Analisar os aspectos epidemiológicos-cirúrgicos dos pacientes com câncer de vesícula biliar (CAVB) atendidos em um Hospital Universitário de Belém/PA, no período de 1999-2009. **Métodos:** estudo observacional, retrospectivo, descritivo-analítico de fonte secundária dos pacientes com diagnóstico de CAVB, no período de 1999-2009. Foram analisados 75 prontuários, sendo 34 pacientes estudados. As informações coletadas foram utilizadas para o estadiamento tumoral TNM do CAVB e para a caracterização clínico-cirúrgica da população estudada. **Resultados:** 79% eram do sexo feminino, com média de idade de 66,2±11 anos e tempo de sintomatologia de 10,8±17,2 meses, não obtendo relação estatística com o estádio da doença. Dor no hipocôndrio direito, náuseas e icterícia predominaram como sinais/sintomas. A litíase biliar esteve presente em 91% dos casos, sendo positiva em 100% dos pacientes com estádios III. A sensibilidade ultrassonográfica para sugerir o CAVB no pré-operatório foi 14,28%. A operação mais executada foi a colecistectomia simples, tendo como achado intra-operatório predominante, invasão hepática. O adenocarcinoma foi o tipo histológico preponderante, com destaque para os estádios III e IV. **Conclusão:** A série estudada apresentou alta incidência de litíase biliar, o adenocarcinoma com estádio avançado foi o mais prevalente. acarretando um pequeno índice de operações com intenção curativa, 30% dos pacientes operados, e uma taxa de mortalidade de 21%. A valorização dos sintomas e a investigação precoce por exames de imagem poderiam favorecer o tratamento, em fases iniciais do CAVB, proporcionando um melhor prognóstico para os pacientes operados.

Descritores: Neoplasias da vesícula biliar. Estadiamento de neoplasias. Cirurgia.

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