Gallbladder carcinoma: clinicopathological study of 24 cases

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Carcinoma da vesícula biliar: estudo clinicopatológico de 24 casos

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key words

Gallbladder

Carcinoma

Surgical pathology

abstract

Introduction: Despite preoperative procedures, gallbladder carcinoma is commonly detected intraoperatively or on anatomopathologic examination after cholecystectomy. **Objective:** To study the clinical-morphological aspects and evolution of patients with primary gallbladder carcinoma. **Methods:** We reviewed medical records and pathologic material of all patients diagnosed with gallbladder carcinoma at our institution from 1997 to 2008. **Results:** Twenty-four cases with primary carcinoma were studied, predominantly among female patients, mean age of 61.1 years. The most common clinical symptom was upper right hypochondriac pain. Five patients were diagnosed in early stages and 19 were in advanced stages. Only seven patients were diagnosed with carcinoma preoperatively, all of them in advanced stages. As to macroscopic examination, three early cases were identified as type IIa, two type IIb and 13 advanced cases were flat and infiltrating. Histologically, there were 23 adenocarcinomas and one adenosquamous carcinoma. Simple cholecystectomy was performed in seven patients, extended cholecystectomy in four patients, cholecystectomy and omentectomy in one patient, and tumor biopsy in only two patients. The median survival rate for patients in early stages was 59 months, and for pT2, pT3 and pT4 stages were 22 months, nine months and three days, respectively. **Conclusion:** There was a prevalence of advanced neoplasias diagnosed through anatomopathological examinations with poor prognosis. Furthermore, earlier detection contributed to higher survival rate. Investigation of anatomopathologic features, specially the macroscopic patterns of gallbladder carcinoma, is essential to improve diagnostic accuracy and to provide a definite treatment.

unitermos

Vesícula biliar

Carcinoma

Patologia cirúrgica

resumo

Introdução: *Não obstante estudos pré-operatórios, o câncer da vesícula biliar é frequentemente detectado durante a cirurgia ou no exame anatomopatológico após colecistectomias.* ***Objetivo:*** *Avaliar as principais apresentações clinicomorfológicas e a evolução de pacientes com carcinoma da vesícula biliar.* ***Métodos:*** *Foram revisados prontuários médicos e material anatomopatológico de todos os pacientes com carcinoma de vesícula biliar diagnosticados em nosso hospital de 1997 a 2008.* ***Resultados:*** *Foram encontrados 24 carcinomas primários, com predomínio em mulheres, média de idade de 61,1 anos. A apresentação clínica mais frequente foi de dor em hipocôndrio direito. Cinco pacientes foram diagnosticados em estádios precoces e 19, em estádios avançados. O diagnóstico pré-operatório de câncer foi realizado em sete pacientes, todos em estádios avançados. Ao exame macroscópico, três cânceres precoces eram tipo IIa e dois, IIb. Treze casos avançados eram aplanados e infiltrantes, 23 eram adenocarcinomas e um era adenoescamoso. Colecistectomia simples foi realizada em sete pacientes, colecistectomia associada à ressecção do leito hepático em quatro, colecistectomia e omentectomia em um e apenas biópsia do tumor em dois pacientes. A média de sobrevida para os pacientes em estádio precoce foi de 59 meses e para os pT2, pT3 e pT4 foram 22 meses, nove meses e três dias, respectivamente.* ***Conclusão:*** *Salienta-se a prevalência de neoplasias avançadas, com prognóstico ruim, diagnosticadas ao exame anatomopatológico. Detecção mais precoce contribuiu para melhor sobrevida. Conhecimento das características anatomopatológicas, especialmente dos padrões macroscópicos do câncer da vesícula biliar, é essencial para melhorar a acuidade diagnóstica e permitir o tratamento radical definitivo.*

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Introduction

The prevalence of gallbladder carcinoma is highly variable across the world and remains the most common malignancy of the biliary tract worldwide. Very high incidence rates are found in Northern India and Chile[13]. Gallbladder cancer has been frequently referred as a lethal and incurable disease. However, most series reported in the literature only included advanced-stage carcinomas, what is partially responsible for the general pessimism surrounding this disease[14]. Several studies, mostly in Japan and Chile have shown that when detected and treated in its early stages the 5-year survival is higher than 90%[3, 8, 9, 11, 14, 15, 20]. Patients with early carcinoma – defined as tumor confined to the mucosa or the *muscularis propria* according to the TNM staging system – have a real chance of curative treatment. Long-term survival with radical surgical approach has been reported even with T3 and T4 tumors[5, 8, 9, 15].

Despite the advances in medical imaging most cases (70%-80%) of gallbladder cancer are only discovered incidentally on histopathological examination after cholecystectomy performed for presumed benign biliary disease[14]. Therefore, the morphologic study has a significant impact in the diagnosis of this cancer, lowering the number of cases that could be underdiagnosed[14] and guiding extent of surgical resection.

Objective

The objective of this retrospective analysis is to study the clinicopathological features and outcome of patients with primary gallbladder carcinoma.

Materials and methods

Twenty-four consecutive cases of gallbladder carcinoma were identified from the files of the Anatomic Pathology Department of the Hospital de Base do Distrito Federal, Brasília, DF, from January 1997 to April 2008, all of which were included in this study. Four of these cases were resected at other public hospitals of the Health Secretary of the Federal District and the specimens examined and diagnosed at our department.

Clinical records and pathologic material were reviewed and the following data was analyzed: patient age, gender, and presenting signs and symptoms, gross and histopathologic patterns, size and location of the tumors, angiolymphatic and perineural invasion, surgical margins, association to cholelithiasis, pathologic stage and survival. The macroscopic patterns of the tumors were determined in accordance with the classification of the Japanese Society of Biliary Surgery[7] (**Figures 1** and **2**). Histological examination was done on multiple sections (average of 10 sections) stained by H&E, obtained from the tumor and the cystic duct, the gallbladder neck, body and fundus.

The TNM staging system (AJCC 5th edition) was used to classify the extent of cancer. However, N (nodes) and M (metastases) categories could not be assessed in several cases. Thus the authors adopted the pathologic T category (pT) to define the local extent of the primary tumor as follows:

- pTX – primary tumor cannot be assessed;
- pT0 – no evidence of primary tumor;
- pTis – carcinoma *in situ*;
- pT1 – tumor invades *lamina propria* (T1a) or muscle layer (T1b);

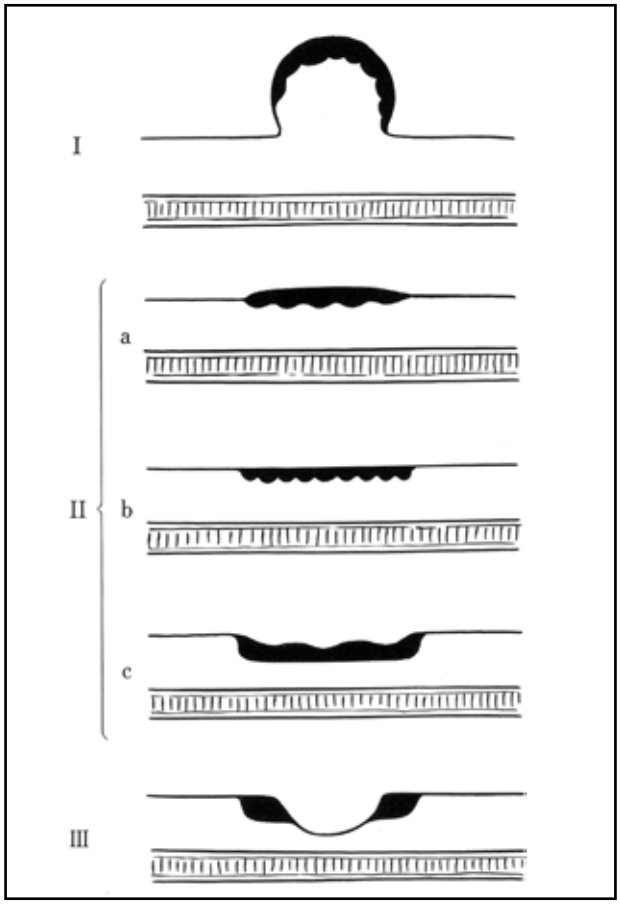

Figure 1 – *Macroscopic classification of early gallbladder cancer*[7]

(I) Protruded type (height ≥ 3 mm); (II) superficial type (height < 3 mm); (IIa) superficially elevated; (IIb) flat; (IIc) superficially depressed; (III) depressed type.

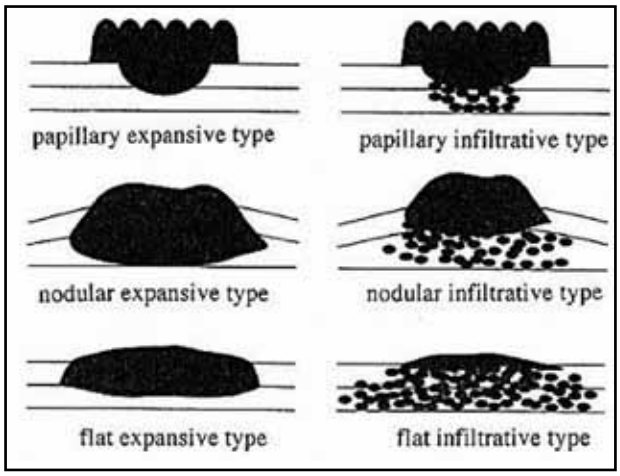

Figure 2 – *Macroscopic classification of advanced gallbladder cancer*[7]

- pT2 – tumor invades perimuscular connective tissue; no extension beyond serosa or into liver;
- pT3 – tumor perforates the serosa (visceral peritoneum) or directly invades one adjacent organ or both (extension of 2 cm or less into liver), or both;
- pT4 – tumor extends more than 2 cm into liver, and/or into two or more adjacent organs (stomach, duodenum, colon, pancreas, omentum, extra hepatic bile ducts, and any involvement of liver), or both.

Mortality data that could not be obtained from the hospital files were provided by nominal consultation of the databases of the Mortality System of the Health Secretary of the Federal District and of the Ministry of Health. The postoperative survival rate was calculated by the Kaplan-Meier method, without discrimination between deaths resulting from gallbladder cancer or other causes. The overall survival rate was obtained by considering the date of surgery and the date of death. Differences in frequency were detected by the chi-square test. A *p* value of 0.05 was considered significant. The BioEstat[2] program, version 5.0, was used for statistical analysis.

The study was approved by the Research Ethics Committee of the Health Secretary of the Federal District, number 196/2008.

Results

Twenty-four patients with primary gallbladder carcinoma were identified: 20 women and four men mean age at diagnosis of 61.1 years, range 24-88 years. The most common presenting symptoms included right upper quadrant pain or abdominal discomfort in 20 patients, followed by jaundice in seven and nausea and vomiting in four patients.

Early-stage tumors

Five patients (20.8%) were diagnosed in early stages (one pTis, three pT1a, one pT1b), mean age of 51.4 years. Two of them were men, mean age of 66 years and three women, mean age of 41.6 years. Three early cancers showed macroscopic type IIa and two type IIb. None of the early-stage tumors showed angiolymphatic or perineural invasion. Simple cholecystectomy was performed in all patients. Histologically, all of them were adenocarcinomas, well or moderately differentiated (**Figure 3**). Association with chronic or acute cholecystitis was demonstrated in all five patients; in three of them with cholelithiasis. The median survival for early-stage patients was 59 months.

Advanced-stage tumors

Nineteen patients (79.2%) were diagnosed with advanced-stage cancer, mean age of 63.6 years. The difference in mean ages, between early and advanced-stages patients was not statistically significant ($\chi^2 = 1.29$; $p = 0.29$). In seven of the advanced-stage patients (29% of all patients) there was a preoperative suspicion of malignancy by imaging techniques (ultrasonography, computerized tomography or magnetic resonance), two of them already unresectable. In most cases malignancy was diagnosed postoperatively after pathological examination of the resected gallbladder.

The following surgical procedures were performed: simple cholecystectomy in twelve patients; extended cholecystectomy, which included a liver wedge resection and regional lymphadenectomy in four patients;

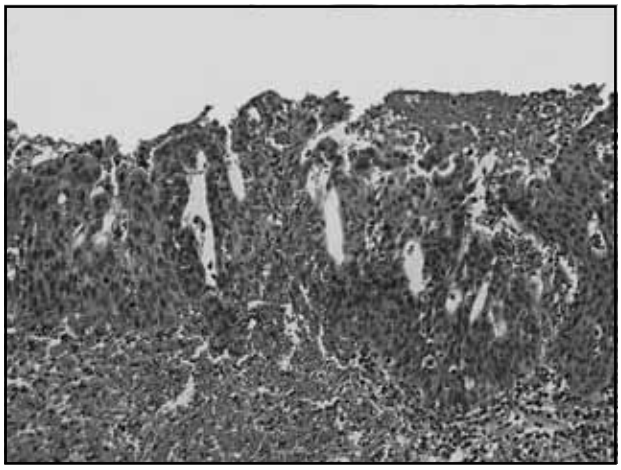

Figure 3 – *Early gallbladder cancer, limited to the mucosa (H&E, 10×).*

cholecystectomy and omentectomy in one patient, and a biopsy of the tumor in two patients.

Revision of the descriptions of macroscopic patterns of the carcinomas combined with the gross histologic patterns on the cut surfaces revealed 13 flat infiltrative type tumors, three nodular infiltrative and one papillary infiltrative advanced cancers centered on the fundus or body, or diffusely infiltrating the gallbladder.

The dimensions of the elevated tumors (nodular and papillary) varied from 1.2 cm to 4 cm in maximum diameter and the wall thickness from 0.4 cm to 2 cm.

Histologically, eighteen were adenocarcinomas, mainly moderately differentiated (**Figure 4**), and one was adenosquamous carcinoma. Lymphatic or vascular invasion was observed in all cases and perineural invasion in eight. Positive surgical margins of the cystic duct were observed in four patients with advanced tumors.

Of the 19 patients with advanced-stage tumors, four were in stage pT2, twelve in stage pT3 and three in stage pT4.

The median survival for patients stages pT2, pT3 and pT4 were 22 months, nine months and three days, respectively, the differences been statistically significant (pT1-pT2 $p < 0.0001$; pT2-pT3 $p = 0.03$; pT3-pT4 $p < 0.0001$). The median survival for all patients in this study, independent of stage or type of treatment was 21.2 months.

Association with chronic or acute cholecystitis was demonstrated on histologic examination in all 19 patients, two with cholesterolosis. Gallstones were sent to the laboratory or referred by the surgeon in eight patients.

Discussion

In this study, similar to others, most gallbladder carcinomas were detected incidentally on specimens removed for presumed benign biliary disease. This was partially due to the disease's non-specific presentation. The most frequent presenting symptom was right upper quadrant pain, followed by jaundice and nausea. The most frequent preoperative diagnoses were cholecystitis/cholelithiasis found associated with the carcinoma in most patients. A correct preoperative diagnosis of cancer was made in only seven patients with advanced tumors, a diagnostic accuracy of 29.2%. Three of these patients had metastatic disease and severe weight loss.

Despite the advances in medical imaging it is still difficult to diagnose gallbladder cancer preoperatively. A

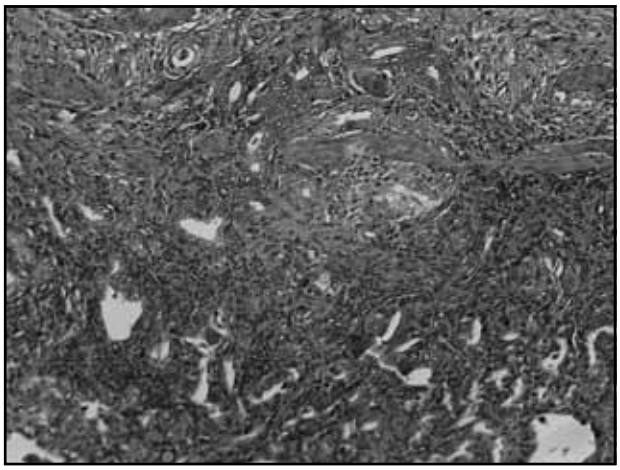

Figure 4 – *Advanced gallbladder cancer. Malignant glandular structures invade the gallbladder wall (H&E, 10×)*

gallbladder carcinoma is suspected preoperatively in only 20%-30% of all patients, the other 70%-80% of all cases are detected intraoperatively, or incidentally discovered by the pathologist[6, 14], consistent with our results. Through the anatomopathologic examination directed to this disease it has been demonstrated that nearly 25% of these carcinomas can be detected in early stages[14]. Therefore, the morphologic study has a significant impact in the diagnosis of this cancer, lowering the number of cases that could be underdiagnosed[14]. Knowledge concerning macroscopic features of gallbladder cancer is useful in detecting suspicious lesions and is essential to facilitate diagnosis by means of medical imaging. In the present study, the majority of the advanced-stage lesions were classified into flat infiltrative, with localized or diffuse thickening of the gallbladder wall, and the early-stage tumors were classified into IIa (superficially elevated) and IIb (superficial and flat) similar to other reports[1, 16, 17]. The advanced tumors diagnosed by imaging techniques were types nodular infiltrative and flat infiltrative. The majority of the carcinomas was located in the fundus and/or body of the gallbladder; only two occurred in the neck.

Optimal surgery for gallbladder carcinoma depends on extent of disease. General principles guiding extent of resection can be based on TNM classification T stage of disease, but also of use is consideration of location of tumor, and its growth pattern[12]. Infiltrative growth pattern is of most relevance in deciding extent of hepatic resection in T2 and T3 tumors[12]. Characterization of the macroscopic patterns is thus essential to improve diagnosis and to permit a radical surgical approach to be carried out definitively.

The stage at which the disease presented certainly had a direct impact on the survival of the patients. Consistent with

other investigations earlier detection contributed to better survival. Three of the five patients in stage pT1 are alive, with a median survival of 59 months; one was lost to follow-up and one died at 13 months due to unrelated cause. A number of authors have reported between 80% and up to 100% 5-year survival when the gallbladder carcinoma is detected and treated in its early stages both following a simple or extended cholecystectomy[3, 6, 8-11, 14, 18, 20], as well as survival over 90% in 10 years for early cancers[14, 18]. Long-term survivals after radical resection have been reported even among the group of patients with advanced-stage disease[5, 8-11, 19]. In this subgroup of patients the paradigm of gallbladder carcinoma as a uniformly fatal neoplasm cannot be applied. The nihilistic attitude of physicians should not prevent patients from being offered an aggressive procedure to achieve a margin-negative (R0) curative resection.

It is important to note that, in this investigation, 15 patients had positive surgical margins (of the cystic duct or gallbladder bed) and one of the four patients in which lymphadenectomy was performed (pT3) had already nodal involvement. Lymphatic or/and venous invasion was observed in all patients with advanced-stage cancers and perineural infiltration in eight patients. In contrast, no lymphatic, venous or perineural invasion was observed in the early-stage tumors.

Conclusion

Most carcinomas were detected in advanced stages associated with poor prognosis. Earlier detection contributed to better survival. To improve the prognosis of patients with gallbladder carcinoma it is necessary to detect the cancer in earlier stages. Better recognition of the anatomopathologic features, specially of the macroscopic patterns of gallbladder carcinoma is essential to improve early diagnosis and to permit a rational and effective radical surgical approach to be carried out definitively.

Acknowledgments

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