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Prevalence of gallbladder cancer In patients submitted to cholecystectomy: experience of the University Hospital, Faculty of Medical Sciences, State University of Campinas – UNICAMP

Prevalência do câncer de vesícula biliar em pacientes submetidos à colecistectomia: experiência do Hospital de Clínicas da Faculdade de Ciências Médicas da Universidade Estadual de Campinas – UNICAMP

Márcio Apodaca-Rueda[1]; Everton Cazzo[2]; Rita Barbosa De-Carvalho[2]; Elinton Adami Chaim, TCBC-SP[2].

A B S T R A C T

Objective: *to evaluate the prevalence of gallbladder carcinoma in patients submitted to cholecystectomy for chronic cholecystitis at the University Hospital of the State University of Campinas.* **Methods:** *we conducted a retrospective prevalence study through the analysis of histological specimens from January 2010 to May 2015.* **Results:** *we analyzed 893 patient reports. Emergency cholecystectomies amounted to 144, and elective ones, 749 (16.2% and 83.8%, respectively). Regarding gender, 72.8% were female and 27.2% male. Gallbladder adenocarcinoma occurred in 12 patients (1.3%) and non-Hodgkin's lymphoma in one (0.1%). In patients with cancer, seven (53.8%) were associated with cholelithiasis and two (15.3%) with gallbladder polyps.* **Conclusion:** *prevalence results of gallbladder adenocarcinoma in this study were similar to those of Western studies and the main risk factor was cholelithiasis, followed by the presence of gallbladder polyps.*

Keywords: *Gallbladder Neoplasms. Cholelithiasis. Gallstones. Prevalence*

INTRODUCTION

Gallbladder cancer (GBC) is a rare condition and ranks fifth in neoplasms of the gastrointestinal tract. However, it is the most frequent malignant neoplasm that affects the bile ducts[1]. The most common histological type is adenocarcinoma, representing approximately 90% of the cases and classified as papillary, tubular and mucinous. The frequency of the other histological types (anaplastic, squamous and adenosquamous carcinoma) is extremely low[2]. GBC affects patients older than 60 years. The incidence in women is greater when compared to male patients in the approximate ratio of 3:1[3,4]. Among its risk factors, the most common are cholecystolithiasis, followed by the presence of polyps in the gallbladder and the gallbladder in porcelain. Several studies have demonstrated that the infection of the bile ducts with *Salmonella sp.* and *Helicobacter pylori* would be related to the increased incidence of the disease. The genetic component is also an important risk factor for the development of this neoplasm[6-8].

The incidence of GBC is variable when analyzed in different geographic regions and in certain ethnic groups. It is low in Western countries such as the United States, where it affects 0.9 women and 0.5 men per 100,000 inhabitants. The United Kingdom also has a similar incidence. However, indigenous populations of the US, Hispanic American countries like Mexico, Chile, Peru, northern Argentina and Bolivia, Ecuador, Colombia, some Eastern European countries like Poland and Slovakia and in Asia, Japan, India and Pakistan, have a high incidence of GBC[9].

Due to the disease's characteristics, the lack of specificity of the clinical picture and, fundamentally, its late diagnosis, the prognosis of gallbladder cancer is poor[10]. In the vast majority of cases, the diagnosis comes late and in advanced stages, thus compromising treatment results and consequently increasing morbidity and mortality[11]. It is estimated that 85% of patients die one year after being diagnosed[12].

In Brazil, there are no population studies analyzing the incidence of gallbladder cancer. There

1 - State University of Campinas, Department of Surgery, Faculty of Medical Sciences, Campinas, São Paulo State, Brazil. 2 - Pontifical Catholic University of Campinas, Faculty of Medicine, Campinas, São Paulo State, Brazil.

Table 1 - *Gallbladder neoplasms' histological types.*

Histological type	N	%
Adenocarcinoma	12	92.3
Non-Hodgkin's Lymphoma	1	7.7
Total	13	100

are, however, some studies of regional prevalence and incidental diagnosis, with different results when compared with each other[13-17]. Therefore, the real incidence of gallbladder cancer in our country remains unknown.

The objective of this study is to analyze the prevalence of gallbladder cancer in patients undergoing cholecystectomy, as well as risk factors associated with GBC, in the Clinics Hospital of the Faculty of Medical Sciences of the State University of Campinas – UNICAMP.

METHODS

We conducted a cross-sectional, descriptive study, with retrospective data collection. We reviewed the reports of histopathological specimens from patients submitted to elective or emergency cholecystectomy and sent to the Department of Pathology of the Clinics Hospital, UNICAMP, from January 2010 to May 2015. In reports with diagnosis of gallbladder neoplasia, we performed an analysis of the medical record in the medical archive service. This project was approved by the Ethics in Research Committee and is registered in the "Plataforma Brasil" under the CAAE number 48103614.6.0000.5404. We collected the data in protocol sheets and organized them into Excel spreadsheets. We performed the statistical analysis with the software SPSS Statistics 20.0. We present quantitative variables as mean ± standard deviation, and qualitative variables, as frequency and percentage.

RESULTS

During the study period, 893 cholecystectomies were performed. Of these, 749 (83.8%) were elective and 144 (16.2%) were emergency ones. According to the gender, 650 (72.8%) were female and 243 (27.2%), male.

Upon analyzes of the histopathology reports of the surgical specimens, we found that 13 (1.4%) had a diagnosis of gallbladder neoplasia. Regarding histological type, 12 (92.3%) patients had gallbladder adenocarcinoma, and one (7.7%), non-Hodgkin's lymphoma (Table 1). The study group had a mean age of 60.23 years, with a variability of 35 to 85 (median age 59 years and standard deviation 12.93). As for gender, 10 (77%) patients were women, and three (23%), men (Table 2).

The analysis of the clinical presentation of such patients in the preoperative period showed that seven (53.84%) had moderate abdominal pain located in the right hypochondrium; two patients (15,38) presented with nonspecific dyspeptic condition; another two (15.38%) in addition to complaints of abdominal pain, had jaundice and coluria; one patient (7.7%) was admitted to the emergency room with acute cholangitis; and one patient (7.7%) was asymptomatic.

Regarding the preoperative ultrasonographic findings, four patients (30.8%) had a diagnosis of cholecystolithiasis, and two (15.4%), of polyps in the gallbladder. In four (30.8%), there was suspicion of gallbladder neoplasia. Finally, three other patients (23%) were suspected of having gallbladder neoplasia and cholecystolithiasis. In the study group, seven

Table 2 - *General characteristics of the studied population.*

Variable	N° (%)
Gender	
Female	650 (72.8)
Male	243 (27.2)
Histopathology	
Inflammatory cholecystopathy	880 (98.6)
Neoplasm	13 (1.4)
Age	M* 59 (35-85). SD** ±12.93
Total	893 (100)

** M = median, ** SD = standard deviation.*

patients had a suspicion of gallbladder cancer in the preoperative period, corresponding to 53.84%. However, six patients (46.16%) had their diagnosis confirmed only after the histopathological analysis of the surgical specimen. All surgeries of the studied group were performed in an elective manner.

DISCUSSION

Bile duct neoplasms are rare conditions that in most cases originate from the biliary lining epithelium, being classified according to their location in intrahepatic, extrahepatic and of the gallbladder, the latter being the most common. The predominant histological type is adenocarcinoma[18,19]. In the present study, only one patient (7.7%) presented a different histological type. Because of its late diagnosis and the tumor biological behavior, GBC continues to display poor prognosis and low long-term survival[20,21]. The incidental diagnosis of GBC has apparently increased, ranging from 0.3% to 2% of cholecystectomies due to cholecystolithiasis[22].

In our series, all patients were treated electively. In two patients, the approach was laparoscopic, and in eleven, laparotomic. In seven patients (53.84%), there was a diagnostic suspicion of neoplasia still in the preoperative period. I four of these, cholecystectomy was performed with regional lymphadenectomy associated with resection of the extrahepatic biliary tract with Roux-en-Y biliodigestive anastomosis. Three of them, in addition to the aforementioned procedures, were submitted to wedge resection of the gallbladder's hepatic bed. In six patients (46.16%), the diagnosis was defined after a histopathological study of specimens from patients undergoing cholecystectomy due to cholecystolithiasis. Of these, five had mucosal-restricted neoplasia (carcinoma in situ) and one had a diagnosis of non-Hodgkin's lymphoma, being referred to the Oncology service for adjuvant therapy. The incidental diagnosis in patients electively submitted to cholecystectomy due to cholecystolithiasis in this sample was 0.67%, similar to those published in other Western countries[23-25]. Recently, Martins-Filho *et al.*, in a study of the population of the State of Pernambuco, reported prevalence for incidental GBC of 0.34% [26].

Gallbladder cancer affects patients over 50 years of age at approximately 90% of the time, and female. In our study, 77% of the patients were female, with a mean of 60.23 years of age. Of these, 84% were older than 50 years.

Due to the lack of specificity of the clinical picture and the absence of symptoms suggestive of the disease in the early stages, the diagnosis of GBC is most often reached late and at an advanced stage. This invariably compromises prognosis, increases treatment morbidity and decreases long-term survival, of 5% when analyzed in a global manner. In this study, in 53.8% of cases the disease was advanced at the time of surgery. Among the symptoms these patients usually present with, abdominal pain localized mainly in the right hypochondrium, of continuous character, associated to the weight loss, are the most frequent. The presence of cholestatic symptoms usually suggests advanced disease. In this study, abdominal pain was present in all of those in whom the neoplasia was suspected in the preoperative period, followed by the presence of dyspeptic symptoms in 15.38%. In three patients, cholestatic symptoms were predominant.

The incidence of this neoplasia varies according to the region studied. Hispanic-American populations have a high incidence. In our continent, it is noteworthy the high incidence in countries such as Chile, 25/100,000 women and 9/100,000 men, and in Native American of the New Mexico, of 14.5/100,000. In Europe, Poland shows an incidence of 14/100,000. In Asia, India has 10/100,000 and Japan, 7/100,000, figures very different from those published in Western populations. This population variability of the disease reinforces the theory of the genetic component in the disease's etiology.

In our country, there are no population studies assessing GBC incidence. The few that exist analyzed the disease's prevalence in certain regions of the country or the incidental diagnosis of this neoplasia. Jukemura *et al*.[15], studying 475 patients who underwent cholecystectomy due to cholecystolithiasis

in São Paulo, found incidental GBC in 1.68%. Weston *et al*.[16] showed an incidental diagnosis of the disease of 0.012% in a study carried out in a population of the State of Rio Grande do Sul. Torres *et al*.[17], in a study similar to ours, found a prevalence of 2.3% in patients from São Luiz, Sate of Maranhão. The difference between the values in the different population samples studied once again suggests the importance of the ethnic-genetic component of the neoplasia. It is possible to infer that the intermediate prevalence of 1.4% found in our sample is explained by the miscegenation characteristics of the Campinas population, similar to that of the city of São Paulo.

Among the risk factors associated with gallbladder cancer, the most important is cholecystolithiasis, which is present in more than 70% of the time. In our country, Ziliotto Jr *et al*.[27] found an association of chronic cholecystolithiasis and gallbladder neoplasia in 40.9% of the cases. Carneiro *et al*.[14], in 1994, found a 68% association. Ours was 53%. Another risk factor related to GBC is the presence of gallbladder adenomatous polyps, considered pre-neoplastic lesions for the development of the disease, representing 30.8% of cases and being directly related to their size. In our sample, 15.4% had a diagnosis of gallbladder polyp at the ultrasound examination, which was confirmed in the histopathological study. Other risk factors such as porcelain gallbladder, anatomical anomalies of the biliary tract, *Salmonella sp*. and *Helicobacter pylori* infection, and genetic alterations, were not studied in our series.

The main limitation of this study is its retrospective design, which negatively influences the quality of data available. In addition, since the global incidence of GBC is low, the small absolute number of patients affected by it also makes it difficult to perform deeper analyzes. On the other hand, the availability of a large absolute number of histopathological specimens, in a study carried out in a regional and state reference service, partially attenuates this limitation. Due to Brazil's continental dimensions and ethnic diversity, there is a need for multicenter studies with larger population samples including the different geographic regions, to determine the real incidence of gallbladder cancer in our country.

R E S U M O

Objetivo: estudar a prevalência do câncer de vesícula biliar em pacientes submetidos à colecistectomia no Hospital de Clínicas da Universidade Estadual de Campinas. **Métodos:** estudo de prevalência retrospectivo a partir da análise de laudos de espécimes histopatológicos de pacientes submetidos à colecistectomia, no período de janeiro de 2010 a maio de 2015. **Resultados:** foram analisados 893 laudos de pacientes submetidos à colecistectomia, dos quais 144 de urgência e 749 eletivas (16,2% e 83,8%, respectivamente). Segundo o sexo, 72,8% correspondiam ao feminino e 27,2%, ao masculino. Em 12 pacientes (1,3%) foi evidenciado o diagnóstico de adenocarcinoma de vesícula biliar e, em um (0,1%), o diagnóstico de linfoma não Hodgkin. Dos 13 pacientes com neoplasia, sete (53,8%) apresentaram colecistolitíase associada. Em dois doentes (15,3%) foi constatado pólipo de vesícula biliar. Sete (53,8%) doentes foram operados com a hipótese diagnóstica de neoplasia de vesícula biliar. **Conclusão:** a prevalência do adenocarcinoma de vesícula biliar no presente estudo foi semelhante à dos estudos ocidentais e o principal fator de risco foi a colecistolitíase, seguido pela presença de pólipos de vesícula biliar.

Descritores: Neoplasias da Vesícula Biliar. Colecistolitíase. Cálculos Biliares. Prevalência.

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Mailing address:
Elinton Adami Chaim
E-mail: chaim@hc.unicamp.br / apodaca.r@hotmail.com