Gallbladder Cancer (analysis of 55 cases)

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Abstract

Introduction

Gallbladder cancer (GBC) is the most frequent neoplasm of the biliary tract, appearing essentially in Latin America, unlike in western regions, including Portugal. Its prognosis is poor and the 5-year survival varies between 16% to 20%.

Objectives

Contribute to the characterization of GBC in Portugal through a retrospective analysis of patients with GBC registered at the CHUSJ, in the last 10 years.

Material and Methods

Data from 55 clinical files were reviewed according to the CHUSJ Registry of Tumors from January 2007 to December 2017, regarding the following variables: age, gender, symptomatology, risk factors, stage, type of surgery, morbidity and survival.

Results

There was a higher incidence in women (67.3%), the mean age was 67 years and in 60% of the cases were associated to lithiasis. Among the 55 neoplasms analyzed, 12 (21.8%) were considered unresectable.

On the 43 patients operated, the performed surgery corresponded to 25 laparoscopic cholecystectomies and 18 open holecystectomies, of which 19 and 10 were, associated with bisegmentectomies IV and V, respectively. The diagnosis of GBC was incidental in 29 cases (67.4%). Immediate postoperative morbidity was reported in 4 cases (9.3%) with 3 deaths (7%). The overall survival rate was 36, 43 and 6 months, in all the patients, in the operated and in the unresectable, respectively. Survival after 1, 3 and 5 years after surgery was 60.4%, 34.9% and 18.6%, respectively.
Discussion / Conclusion

Gallbladder cancer is very uncommon in western regions, including Portugal, unlike in Latin American countries such as Chile and Bolivia.

Our results confirm their poor prognosis with a non-negligible incidence of irresectability and low survival in the operated patients. Simple or radical cholecystectomy is the only recommended therapy, with an increasing use of the laparoscopic approach. Its diagnosis was incidental in an appreciable number of cases, and it is recommended to perform early surgery in the gallbladder pathology associated with risk factors.

Keywords: Gallbladder cancer; gallbladder lithiasis; polyps; cholecystectomy.

Introduction

Gallbladder Cancer, first described by Stoll in 1779 [1] occupies the sixth place among digestive tumors and is the most frequent malignant neoplasm of the biliary tract [2]. It appears with high incidence in the populations of Chile, Bolivia, American Indians of New Mexico, Eastern Europe and Israel [3-6]. It is much less frequent in western regions, namely the USA, UK, Australia, Canada and New Zealand [7]. In the USA, there were 11,740 gallbladder cancers with 3,830 deaths in 2017 [8]. In Portugal, it appears in 1.5 / 100,000 inhabitants [9]. According to the International Agency for Research on Cancer (IARC), the number of new cases in 2018 worldwide was 219,420, corresponding to an incidence of 1.2 per 100,000 populations [10].

The vast majority of the published series only have a number below 100 patients [11-16], with only three multicenter studies with a greater number of cases [17-19]. Interest in this neoplasm led to the particular attention given to it at the 26th IASGO (International Association of Surgeons, Gastroenterologists and Oncologists) Congress in South Korea. [20]

Among the various risk factors are: cholelithiasis [21], polyps [22], porcelain vesicle [23,24], obesity [25], exposure to heavy metals [26], genetic factors [27], infections and biliopancreatic junction anomalies [4].

The incidence of lithiasis in gallbladder cancer varies from 0.3 to 3% [21], with the relative risk of its appearance in relation to the normal population of 8.3 [28]. The diameter of the stones, in particular with more than 30 mm, in the elderly over 75 years should be valued.

Regarding polyps, their coexistence was reported in 13% of patients operated on due to gallbladder neoplasia [6], with special attention to those with a diameter greater than 10 mm, sessile and solitary. Chou [22], in 1204 polyps, registered malignancy in 13.4%.

The porcelain gallbladder was long considered a risk factor arising in 13% [23] of gallbladder cancer. However, more recent studies have not confirmed this incidence, occurring in only 2% of cases [24].

Its diagnosis is not always easy and is often performed incidentally during the histological examination of the specimen of the cholecystectomy.

Surgery is the only possibility of a cure consisting of simple or radical cholecystectomy, enlarged to segments IV and V and lymphadenectomy according to tumor stages [29]. It appears with poor prognosis, being only mentioned in some series 10% of the cases with indication for curative surgery [30]. Their survival at 5 years does not exceed 16% [31].

Aims

The main objective of the study is to contribute towards the characterization of Gallbladder cancer concerning age, gender, symptomatology, imageology, pathology, surgery, morbidity and survival.

Material and methods

Retrospective analysis of 55 patients with histological confirmation of gallbladder cancer over a period of 10 years from January 2007 to December 2017, coded in the CHUSJ Tumor Registry.

Data collection took place in November 2018, after previous consent obtained from the CHUSJ Ethics Committee in October 2018.

Statistical analysis
The statistical analysis was based on processes of descriptive analysis and comparison of proportions, using the binomial test. Survival analysis was performed using the Kaplan-Meier method. Positive values were considered for p<0.05.

**Results**

The results were analyzed in 58 cases, excluding 3; 2 because they had previously been operated on the gallbladder in other hospitals and another because there was insufficient information in the clinical process.

Of these 55 individuals, 12 (21.8%) were considered to be unresectable having been diagnosed by biopsy performed during laparotomy, exploratory laparoscopy or percutaneously.

There were 37 females (67.3%) and 18 males (32.7%) (p=0.076). The mean age was 67 years [47-95]. The distribution of age by the various age groups is shown in Figure 1.

![Figure 1: Distribution of patients by age groups](image)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithiasis</td>
<td>33 (60%)</td>
<td>p=0.0885</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>19 (34.5%)</td>
<td>p=0.0150</td>
</tr>
<tr>
<td>Obesity</td>
<td>15 (27.3%)</td>
<td>p=0.0005</td>
</tr>
<tr>
<td>Gallbladder polyps</td>
<td>4 (7.3%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>1 (1.8%)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

**Table 1: Risk factors and coexisting diseases (n=55)**

There was a tumor in a patient who had undergone right hemicolectomy 8 months previous because of cancer of the colon.

The following preoperative examinations were performed: echography, in all patients, using either CT alone or with contrast in non-incidental forms; NMR in 22 individuals, associated with cholangiography in 4 of them; angiography in 2; Endoscopic Retrograde Cholangiopancreatography (ERCP) in 3; Transhepatic Percutaneous Cholangiography (PTC) in 5; aspiration biopsy under ultrasound control in 1.

There were 49 adenocarcinomas (90%), 2 neuroendocrine carcinomas (3.6%), 2 poorly differentiated carcinomas (3.6%), 1 carcinosarcoma (1.8%) and 1 carcinoma in signet cells (1.8%). The values of tumor markers were only high in cases of advanced neoplasms and diagnosed non-incidentally.
In relation to the symptomatology, there was the appearance of pain or cramps in the right hypochondrium in 69.1%, jaundice in 34.5% and vomiting in 21.8%.

Of the 55 cases, 12 (21.8%) were considered inoperable or unresectable evidenced by imaging or in the course of laparotomies or exploratory laparoscopies.

Gallbladder cancer was diagnosed incidentally, in 29 cases (67.4%) during the histological examination following cholecystectomies, performed by lithiasis, acute cholecystitis, acute pancreatitis and also by occlusion in the course of cholecysto-enteric fistula with a gallstone ileus.

In the 43 operated patients, surgical management was as follows: 25 (58.1%) initial laparoscopic cholecystectomy, 6 simple and 19 associated with bisegmentectomies IV and V; 18 (41.9%) open cholecystectomies, 8 simple and 10 associated with bisegmentectomies IV and V. (Table 2)

Bisegmentectomies IV and V were performed in a second step and always by open approach; 10 cases were associated with lymphadenectomy and excision of the main bile duct in 2. Three laparoscopic cholecystectomy required conversion.

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>n</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>LC + SEG</td>
<td>19</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>1</td>
<td>16</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>OC</td>
<td>8</td>
<td>-</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>OC + SEG</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>-</td>
<td>8</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>total</td>
<td>43</td>
<td>5</td>
<td>18</td>
<td>18</td>
<td>2</td>
<td>33</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

**LC**: Laparoscopic Cholecystectomy; **OC**: Open Cholecystectomy; **SEG**: Segmentectomy IV and V

Initial LC vs. Initial OC (p=0.1801)

**Table 2**: Surgical management and TNM staging (n=43)

Tumor staging according to the TNM classification was as follows:

- T1-5, T2-18, T3-18, T4-2, N0-33, N1-9, N2-1, M1-0.
- (T1 + T2) - 23 (53.5%) vs. (T3 + T4) - 20 (46.5%) p=0.3804

Immediate postoperative morbidity was reported in 7 cases (16.3%, p<0.0001), 3 deaths (7%) (Table 3).

Eight patients underwent an R1 resection (non-curative resection).

<table>
<thead>
<tr>
<th>n=7</th>
<th>Surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary fistula</td>
<td>2</td>
</tr>
<tr>
<td>Hemoperitoneum</td>
<td>1</td>
</tr>
<tr>
<td>Vena cava thrombosis</td>
<td>1 (death)</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>2 (1 death)</td>
</tr>
<tr>
<td>Perforation of gastric ulcer</td>
<td>1</td>
</tr>
</tbody>
</table>

**CL**: Laparoscopic cholecystectomy; **CA**: Open Cholecystectomy; **SEG**: Segmentectomy IV and V

**Table 3**: Major morbidity

The overall survival rate was 36, 43 and 6 months, in all the patients, in the operated and in the unresectable, respectively (Fig. 2).

Survival after 1, 3 and 5 years after surgery was 60.4%, 34.9% and 18.6%, respectively. The relationship between survival and stage is shown in Fig. 3, with higher values in T1 + T2 group than in T3 + T4 group. However, the p value was = 0.432, indicating that there was no statistically significant

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difference in the survival curve as a function of the two groups of T (T1 + T2 and T3 + T4).

It should be noted that of the 8 patients with a survival of 5 years or more, two died 8 and 9 years after the surgical procedure. The occurrence of 2 relapses at the common bile duct and 2 at the gallbladder hepatic bed should be recorded.

Of the 8 R1, seven were dead at the end of one year and the other (with invasion of the cystic stump) remained alive 3 years after the surgery.

In the clinical history of a patient undergoing endocrine carcinoma, it should be noted that there was a death of the father due to gallbladder cancer and an uncle due to cholangiocarcinoma.

Adjuvant chemotherapy was used in 12 cases (28%).

Figure 2: Overall survival of all the patients (n=55), operated (n=43) and unresectable (n=12).

Figure 3: Survival and staging (T1+T2 vs. T3+T4)
Discussion

The diagnosis of gallbladder cancer is not always easy, thus justifying the small number of publications, including Portugal. Thus, it was only possible to register a multicentric investigation with more than three hundred cases [17], included in records of ten US surgical centers.

The circumstances that the Hepato-biliary Surgery Unit of the Surgery Department of CHUSJ is a reference center in this pathology allowed a relatively significant series of 55 cases to be collected.

The analysis of the results obtained on these patients allows for several comments.

First of all, 21.8% of the patients were considered unresectable, similar to that which occurred with 33% of the tumors referred in the Clinica Alemana de Chile by Aretxabala [32]. This confirms the high malignancy of these neoplasms and the difficulty of their early diagnosis in time to allow curative resection of the tumor, as reported by Zuh [30] in 10% of cases.

We verified, according to the generally mentioned predominance of gallbladder cancer in the female sex (67.2%) and over the age of 60 years.

In the analysis of this series, in addition to the presence of lithiasis in 60% of cases, there was association with gallbladder polyps (7.2%), obesity (27%), acute pancreatitis (1.8%) and mainly with acute cholecystitis (34.5%); therefore, this last situation was properly valued by Iago Justo [15] and Tamura [33].

Histological examination revealed adenocarcinomas predominantly in 95% of the cases, with two neuroendocrine carcinomas, one carcinoma of the signet cells, two small differentiated carcinomas and one carcinosarcoma.

The diagnosis of these neoplasias was incidental in 51% of the cases corresponding to surgery caused by uncomplicated lithiasis or associated with acute cholecystitis, acute pancreatitis or even the cholecysto-enteric fistula, causing ileo-biliary occlusion. In several published series, the appearance of these tumors in the operative specimens of cholecystectomy has been equally valued. Thus, this fact was reported by Charfi in 155 of 2584 cholecystectomies (0.8%) [18]. In the CHUSJ Surgery Department, during 6035 cholecystectomies performed between 2007 and 2017, there were 29 (0.5%) incidental cancers of the gallbladder.

For the diagnosis of non-incidental cases, the data revealed by the CT scan associated with contrast and NMR, with or without cholangiography, were important. The use of aspiration biopsy, actually previously proposed by Kumar [34], has also been useful.

The fact that 36 cases belong to stages T2 and T3 (83.7%) justifies the association of bisegmentectomy IV and V in 29 patients (67.4%); the same happens with lymphadenectomy by 9 N1 and 1 N2; the spread of neoplasia to the cystic stump led to the excision of BPV in 2 cases.

The bisegmentectomies were performed by an open procedure and in a second surgical step, with the time elapsed between the first and second intervention as short as possible.

Laparoscopic surgery plays an important role in biliary pathology and its use has recently been advocated not only in acute cholecystitis [35] but more recently in gallbladder cancer by Aretxabala [36] and Gumbs [37]. The initial skepticism was caused by the risk of relapses, namely at the level of the "ports" during the extraction of the gallbladder. Currently it is followed with success in several surgical centers including both simple and radical cholecystectomy [38]. At the IASGO meeting in Seoul, there was consensus that the results are the same as those provided by open surgery [39]. However, several contraindications to its use [40] are referred to as bulky tumors, invasion of the cystic, visceral invasion, previous surgery and acute cholecystitis; the fact that we recorded two relapses at the level of the hepatic vesicular bed justifies the need to involve the resected vesicle in a plastic bag.

This surgery is surrounded at times in great complexity with no negligible morbidity. Thus, there were 18.6% of complications with 7.6% mortality, results similar to the 10% reported in the literature [15].

It is sometimes difficult to compare the results of survival in the various investigations, since they are not always sufficiently enlightening, including in some series operated and unresectable patients and even curative and residual surgery.

The analysis of the survival of these patients demonstrated quite clearly the poor prognosis of this neoplasia. Thus, an
The Chemotherapy, used in 12 cases, was not able to produce significant results according to what is referred in literature [41].

Conclusion

In conclusion, the high malignancy of these neoplasms and the small percentage of patients alive 5 years after surgery was confirmed. Simple cholecystectomy or associated with IV and V segmentectomies is the only recommended therapy. It is important to mention the need to increase surgery in lithiasis patients with predisposing risk factors for these tumors.

Acknowledgements

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References


20. IASGO (2016) 26th World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists (IASGO) Seoul, Korea 16: 8-10.


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