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## Original article

## Gallbladder cancer in a regional hospital

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## A B S T R A C T

**Objectives:** To assess the management of gallbladder cancer (GBC) in our region.

**Material and methods:** Data on 372 patients who underwent cholecystectomy were identified from our database (January 2003 to February 2008) and 6 patients were found to have GBC.

**Results:** Four patients had incidental carcinoma, one case was preoperatively suspected, and one patient presented with jaundice and locally advanced neoplasia. The incidence was 2 per 100 000 inhabitants per year; incidental carcinoma in 1.1% of cholecystectomies. The ultrasonography showed multilithiasis in 2 patients, sludge and neoplasia in 1, gallstones more than 3 cm in 2, and tumor mass only in 1 case. T stage: one case of T0 (in situ), 1 of T1, 2 of T2, and one T4. Incidental carcinomas were reoperated on when a T2 was established: two underwent lymphadenectomy and cystic stump resection, 1 segmentectomy IVb-V and lymphadenectomy. In the preoperative suspected neoplasia a cholecystectomy, lymphadenectomy, and partial hepatic gallbladder bed resection was initially performed.

**Conclusions:** GBC has a low incidence but it will be found in 1% of cholecystectomies. There is no adjuvant treatment and T-based surgical treatment is the only opportunity to reach cure in those patients. A national GBC database would be helpful in the publication of national guidelines for this disease.

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## Cáncer de vesícula biliar en un hospital comarcal

## R E S U M E N

**Objetivo:** Evaluar el tratamiento del cáncer de vesícula biliar (CVB) en nuestro medio.

**Material y métodos:** De 372 pacientes a los que se les realizó colecistectomía (enero de 2003 a febrero de 2007), 6 presentaron un CVB.

**Resultados:** En 4 casos el carcinoma fue incidental, en un paciente se tuvo sospecha diagnóstica antes de la colecistectomía, y un paciente comenzó con ictericia obstructiva secundaria a neoplasia avanzada. Incidencia: 2 casos por 100.000 habitantes por año; cáncer inci-

## Palabras clave:

Cáncer de vesícula biliar

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dental en el 1,1% de las colecistectomías. La ecografía mostró multilitiasis en 2 pacientes, barro biliar y neoplasia en un paciente, litiasis mayor de 3 cm en 2 pacientes y sólo masa tumoral en un paciente. Grados T: un caso T0 (in situ), un caso T1, 3 casos T2 y un caso T4. En los T2 incidentales se practicó ampliación quirúrgica: en 2, linfadenectomía, y en uno, segmentectomía IVb-V con linfadenectomía. En la sospecha preoperatoria se practicó colecistectomía, linfadenectomía y resección del lecho vesicular.

**Conclusiones:** El CVB presenta baja incidencia pero es un hallazgo incidental en el 1% de las colecistectomías. No existe tratamiento adyuvante, por lo que la cirugía basada en el grado T es la única oportunidad de curación. No es infrecuente que tumores supuestamente T2 sean luego T3 al existir células malignas en el lecho vesicular hepático. Su extirpación mantiene la oportunidad de curación. La creación de una base de datos nacional de cáncer de vesícula ayudaría a establecer recomendaciones terapéuticas propias para esta enfermedad.

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## Introduction

Gallbladder carcinoma is an aggressive disease of ominous prognosis. No chemotherapeutic regimen has currently rendered acceptably optimistic results; gemcitabine-oxaliplatin is the most commonly used combination but has not proven to be effective. This type of cancer is resistant to radiotherapy. Surgery is the only therapeutic hope for the time being. However, curative surgery is not always possible. Surgical interventions offer no benefit at advanced stages. Because of this, many surgeons have a very pessimistic attitude toward gallbladder cancer, mostly concerning therapeutic treatment.

Gallbladder cancer (GBC) found unexpectedly after a cholecystectomy for biliary lithiasis, unsuspected at preoperative stage, is known as incidental cancer. One in 100 samples analysed after cholecystectomy test positive for GBC.<sup>1,2</sup> This incidental cancer provides the opportunity to improve prognosis for this disease, as long as the treatment adjusts to the recommendations published about it. These recommendations are based mainly on surgical procedures that vary depending on depth of tumoral infiltration into the vesicular wall (T in TNM [Tumour Node Metastasis] classification). When the pathologist informs about a tumour T1 in a sample after cholecystectomy, no more treatment apart from the cholecystectomy just performed is necessary. But if it is pT2, chances to cure it are significantly reduced unless surgery is not converted to an open surgery.<sup>3-5</sup> Despite repercussions derived from prognosis for this patient subgroup, the application of these recommendations is not much widespread within the surgical community.<sup>6,7</sup>

The objective of the present work is to evaluate gallbladder malignant disease in our centre (county hospital) and, to that end, incidence, presentation, relation with biliary lithiasis, and treatment performed were analysed.

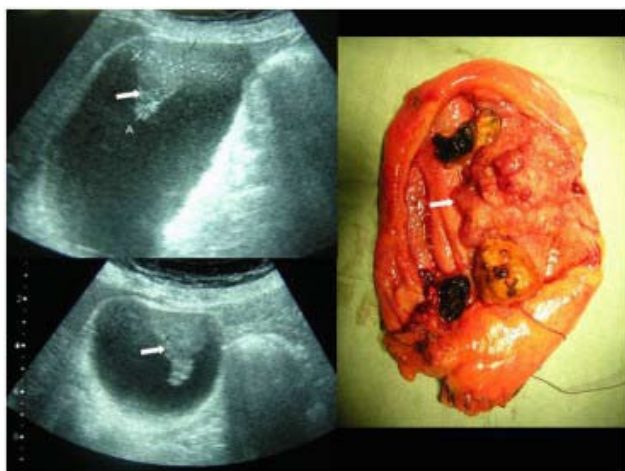
## Material and methods

A retrospective study was carried out. From our service database those cases with gallbladder cancer admitted from

January 2003 to February 2008 were selected. Other parameters included the number of cholecystectomies performed in our centre during that period, and the population treated in our hospital. From the health histories of those cases diagnosed with gallbladder cancer the following were analysed: incidental finding (preoperative unsuspected cholecystectomy), ecography, preoperative exams, anatomopathological results, treatment, and survival.

## Results

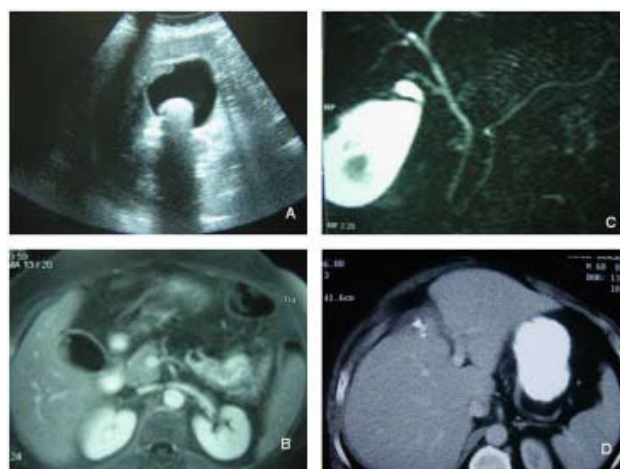
Three hundred and seventy-two cholecystectomies were performed during the period indicated above. The anatomopathological analysis revealed 4 samples with adenocarcinoma (1.1% incidental carcinoma). The following were added to these cases: a male patient preoperatively suspected of gallbladder neoplasia by echographic imaging, diagnosed from an episode of acute pancreatitis (Figure 1), and a female patient presenting with obstructive jaundice secondary to advanced neoplasia (Figure 2). Incidence in our population was of 2 cases out of 100 000 people per year. The following preoperative echographic characteristics were observed in the patients in this series: multilithiasis in 2 patients, biliary-lithiasis sludge and neoplasia suspicion in one patient, lithiasis of more than 2 cm in 2 patients, and no lithiasis found in the case with advanced neoplasia, where ecography showed tumoral mass (Table). Classification T of TNM for tumours in this series is shown in Table. Patients with incidental carcinomas T2 underwent conversion to open surgery: two underwent hepatic pedicle lymphadenectomy and cystic stump resection, and 1 segmentectomy IVb-V with pedicle lymphadenectomy. In this last female patient the initial finding was a vesicular polyp with 3 cm lithiasis (Figure 3), due to an episode of acute abdomen that turned out to be jejunal perforation. An NMR performed after resolution of acute symptoms showed possible Rokitsky-Aschoff nodules, as the mass gave no contrast (Figure 3). Given the lithiasis size and in spite of the NMR results, cholecystectomy was recommended. The result was a carcinoma pT2. Conversion to open surgery resulted in



**Figure 1 – Echography and surgical sample from patient that started with acute pancreatitis. Arrow points at tumour in ultrasonography and in gallbladder lumen. Biliary calculus can be observed. PA indicates papillary adenocarcinoma.**

tumour classification changing from T to T3 (malignant cells in the hepatic bed) and one positive adenopathy out of the 4 isolated lymph nodes in the hepatoduodenal ligament. In the preoperative suspected neoplasia case (where patient started with an episode of acute pancreatitis of no enolic aetiology), cholecystectomy, lymphadenectomy, and gallbladder bed resection were performed, that is, a wedge 3 cm resection as thick as the hepatic bed area adjacent to where the vesicular tumour was sitting, accompanied by intraoperative histologic study.

The female patient with suspected advanced carcinoma started with jaundice. It was opted for an exploratory surgery. As the neoplasia was unresectable, biopsies were taken and a biliary and intestinal bypass was performed. The patient died at home 3 months after palliative surgery. The rest of the patients are alive (Table), but one female patient presented with liver metastasis 12 months after surgical cholecystectomy open procedure.



**Figure 3 – A. Echographic image of 3 cm lithiasis and sessile polyp on posterior hepatic wall of gallbladder. B. NMR portal phase with gadolinium: polyp prevents contrast to be observed. C. Cholangiogram-MR Superior sessile polyp and lithiasis in gallbladder lumen. D. CAT 3 weeks after resection IVb-V (no postoperative complications appeared).**

**Figure 2 – CAT image of locally advanced neoplasia. Dilatation of biliary tract (thin arrows). Gallbladder occupied by tumoral mass extended over neighbouring areas (thick arrows).**

**Table 3 – Echographic findings, pT postcholecystectomy, and type of tumour**

Cases	Sex	Age	Symptoms	US Findings	T	Follow-up months
1	H	67	Biliary colic	Multiple lithiasis	T2	53
2	M	58	Biliary colic	Multiple lithiasis	T2	41
3	H	72	Pancreatitis	Microlithiasis+neoplasia	T1	21
4	M	49	Biliary colic	2.6 cm single lithiasis	Tis	7
5	M	59	Incidentaloma	3 cm lithiasis-polyp	T2 <sup>b</sup>	13 <sup>c</sup>
6	M	78	Jaundice	Infiltrating mass, dilatation of BT	T4	3 (death) <sup>d</sup>

BT indicates biliary tract; F, female; M, male.

<sup>a</sup>Female patient diagnosed with polyps by study of hollow viscus perforation; opening diagnosed with NMR ruled out malignancy suspicion.

<sup>b</sup>T moved up to T3 upon opening surgery, and positive porta hepatis adenopathy appeared.

<sup>c</sup>Disease relapse with 3 minor 1 cm hepatic lymph nodes, segments VI and VII 12 months after hepatic resection.

<sup>d</sup>Death 3 months after palliative surgery.

## Discussion

Gallbladder adenocarcinoma is accompanied by ominous prognosis, except in those early staging cases (T1 and T2 with negative nodes). Indeed, when the disease is advanced, therapeutic expectation lowers considerably. When tumoral infiltration clearly classifies as T4, resection would not be indicated for most surgical groups.<sup>8,9</sup> Furthermore, when a patient presents with N2 nodal positive (peripancreatic, periduodenal, periportal, celiac artery, superior mesenteric artery) resection is not indicated, due to negative results regarding survival.<sup>9-11</sup> The problem lies in identifying those patients with tumour T4 or nodes N2. When the abdominal mass can be felt by palpating it, the tumour is usually inoperable. If preoperative imaging shows a locally advanced stage and non-surgical palliative treatment can be useful, thin-needle aspiration biopsy (TNAB) radiologically guided could prevent laparotomy, as shown by de la Cruz et al<sup>12</sup> in a retrospective study carried out in Spain. There is an example of this in the small series presented by our group. With our patient, however, a traditional attitude was taken and we performed laparotomy to obtain biopsies, confirm inoperability suspicions and set a biliary and intestinal bypass as a palliative surgical procedure, with which the patient survived for 3 months after surgery. An approach closer to current techniques to biopsy and biliary bypass by interventionist radiology would have avoided laparotomy, probably with similar results.

There exists great variability as to the extension of lymphadenectomy clinically practiced everyday, which ranges from only removing a cystic node to duodenopancreatectomy to resect nodes in the pancreaticoduodenal area. It is important to note that performing procedures as aggressive as this last one, in the context of CVB, is not justified considering the benefits obtained. Regional lymphadenectomy covering dissection of hepatic pedicle seems to be enough to correctly stage these patients and treat their disease with expectation of cure. Biliary tract resection to open onto lymphadenectomy has not shown differences regarding the number of nodes obtained against no resection.<sup>14</sup> Therefore, if no adenopathy N2 sample is obtained, not to resect tumours affecting these nodal areas should not be recommended. An attitude in accordance with this respect would be to perform hepatic pedicle lymphadenectomy and add up a sampling of macroscopic or suspicious nodes in an elective manner in N2 areas with preoperative histologic test of these last ones; an attitude we are currently having while waiting for clinical guidelines to be written about it (which is an issue open to discussion).

Treatment of incidental carcinoma adapted to the recommended guidelines for open surgery procedure depending on parietal infiltration of bladder significantly increases survival.<sup>13</sup> In a study by Pawlik et al<sup>14</sup> no residual disease was found when opening surgical procedure for T1 cases, but 10.4% of T2 and 36.4% of T3 presented with additional disease after resection. In other recent study Frena et al<sup>15</sup> retrospectively evaluated a period of 20 years where out of 3012 cholecystectomies 20 gallbladder cancer cases

were found. Five-year survival was 26% for those patients who underwent simple cholecystectomy and 66% for those who were practiced open surgical procedure.

In addition, open surgical procedure with lymphadenectomy is the only way to obtain real staging to assess individual prognosis. This can be observed in the results from the study by Pawlik et al where an unexpected additional disease appeared.<sup>13</sup> Thus, as it happened with one of the cases in our series, a change in staging may occur after cholecystectomy, moving onto higher T classification after surgical completion. As is the case here, a stage considered postcholecystectomy such as T2Nx may turn out to be T3N1, with a radically different prognosis. As a result, in order to achieve survival increase those recommendations given by groups with experience in this disease should be followed. These recommendations are mainly of surgical nature, as there is not for the time being an effective chemotherapeutic treatment. New agents are being studied, such as bevacizumab, a monoclonal antibody anti-vascular endothelial growth factor, associated with other chemotherapeutic agents such as gemcitabine, but there are no results as yet.<sup>16</sup> Meanwhile, the most frequently used regime is gemcitabine with oxaliplatin, which is substituting gemcitabine and cisplatin, but, as it has been pointed out, the results with these therapies are not well defined in the medical literature, and they are quite poor in clinical practice. Indeed, in national centres with experience in this type of disease<sup>8</sup> no treatment adjuvant to radiotherapy or chemotherapy has been adopted yet, being surgery the only therapy to adopt. Surgical procedure depending on the degree of tumoral infiltration is as important to obtain real staging as it is to offer patients an option for cure.

Gallbladder cancer is a low incidence disease, but it represents an incidental finding in 1% of cholecystectomies performed for benign diseases. This figure should be taken into consideration when communicating with pathologists to have them carry out detailed revision of surgical samples for bladder disease, because it is likely that by so doing we increase the number of patients whom we can offer solutions to a so-far catastrophic disease. A female patient in this study was considered within the group of incidental cancer when, in reality, the preoperative echographic image and CAT confirmed the presence of a polypoid sessile mass. However, we have kept this patient in the incidental group, since the preoperative suspicious diagnosis was ruled out in the extension study by NMR (Figure 3). This case also sets in the discussion of intraoperative exam results. The procedure of choice with this patient was to wait for the final exams, as she had previously been informed of the negative results regarding malignity of polypoid mass and no macroscopic infiltration of the gallbladder bed was observed in the cholecystectomy. It has been demonstrated that deferred surgery after cancer diagnosis does not give differences in results against that performed in one intervention.<sup>10,14</sup>

When finding an incidental carcinoma after laparoscopic cholecystectomy it has been recommended to remove laparoscopic portal of entry. Abstaining from so doing has not been associated to relapse in these areas in such series as

that published by de la Cruz et al.<sup>12</sup> We consider that exeresis of the exact trocar path, not only over skin, is a procedure of difficult precision, and, therefore, that it lacks preventive capacity regarding implants. Furthermore, its performance does not rule out the appearance of these in incisions to make them at the moment of the deferred open surgery, as shown in a well documented case by Ramia et al.<sup>17</sup>

In summary, given the low incidence of this disease, its aggressiveness and the emergency factor from the incidental gallbladder cancer, the creation of a national database of gallbladder cancer would provide the possibility to improve therapeutic recommendations for this disease; the main controversial points are the need to convert surgery to open surgery, and, in particular, lymphadenectomy extension and extirpation of laparoscopic portal of entry. Treatment of choice is, for the moment, mainly surgical. The anatomopathological exam of any sample obtained after cholecystectomy is extremely important to screen gallbladder neoplasia, since early findings offer the possibility to convert the procedure into an open surgery if indicated and thus increase survival over this aggressive disease.

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