

Incidental gallbladder cancer during laparoscopic cholecystectomy: Managing an unexpected finding

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Abstract

AIM: To evaluate the impact of incidental gallbladder cancer on surgical experience.

METHODS: Between 1998 and 2008 all cases of cholecystectomy at two divisions of general surgery, one university based and one at a public hospital, were retrospectively reviewed. Gallbladder pathology was diagnosed by history, physical examination, and laboratory and imaging studies [ultrasonography and computed tomography (CT)]. Patients with gallbladder cancer (GBC) were further analyzed for demographic data, and type of operation, surgical morbidity and mortality,

histopathological classification, and survival. Incidental GBC was compared with suspected or preoperatively diagnosed GBC. The primary endpoint was disease-free survival (DFS). The secondary endpoint was the difference in DFS between patients previously treated with laparoscopic cholecystectomy and those who had oncological resection as first intervention.

RESULTS: Nineteen patients (11 women and eight men) were found to have GBC. The male to female ratio was 1:1.4 and the mean age was 68 years (range: 45-82 years). Preoperative diagnosis was made in 10 cases, and eight were diagnosed postoperatively. One was suspected intraoperatively and confirmed by frozen sections. The ratio between incidental and nonincidental cases was 9/19. The tumor node metastasis stage was: pTis (1), pT1a (2), pT1b (4), pT2 (6), pT3 (4), pT4 (2); five cases with stage I a (T1 a-b); two with stage I b (T2 N0); one with stage II a (T3 N0); six with stage II b (T1-T3 N1); two with stage III (T4 Nx Nx); and one with stage IV (Tx Nx Mx). Eighty-eight percent of the incidental cases were discovered at an early stage (\leq II). Preoperative diagnosis of the 19 patients with GBC was: GBC with liver invasion diagnosed by preoperative CT (nine cases), gallbladder abscess perforated into hepatic parenchyma and involving the transversal mesocolon and hepatic hilum (one case), porcelain gallbladder (one case), gallbladder adenoma (one case), and chronic cholelithiasis (eight cases). Every case, except one, with a T1b or more advanced invasion underwent IVb + V wedge liver resection and pericholecystic/hepatoduodenal lymphadenectomy. One patient with stage T1b GBC refused further surgery. Cases with Tis and T1a involvement were treated with cholecystectomy alone. One incidental case was diagnosed by intraoperative frozen section and treated with cholecystectomy alone. Six of the nine patients with incidental diagnosis reached 5-year DFS. One patient reached 38 mo survival despite a port-site recurrence 2 years after original surgery. Cases with non in-

cidental diagnosis were more locally advanced and only two patients experienced 5-year DFS.

CONCLUSION: Laparoscopic cholecystectomy does not affect survival if implemented properly. Reoperation should have two objectives: R0 resection and clearance of the lymph nodes.

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Key words: Incidental gallbladder cancer; Laparoscopic cholecystectomy; Lymph nodes; Hepatic resection; Management; Outcome

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INTRODUCTION

The widespread use of laparoscopic techniques has led to an increase in referrals for cholecystectomy. As a consequence, the incidental finding of gallbladder cancer (GBC) at an earlier stage has altered the management and the outcome of the disease. However, GBC remains a lethal disease associated with a dismal prognosis. Controversies exist on the optimal treatment of this unexpected finding during routine laparoscopic cholecystectomy. The management is difficult because no guidelines have been established and some authors have reported worse overall prognosis when the patient was not adequately treated during the first operation. If GBC is suspected preoperatively, open cholecystectomy must be performed to enable a complete evaluation of the disease extent and to allow radical resection, if necessary.

Simple cholecystectomy may be adequate treatment only for the earlier stages: T_{is} and T_{1a}. Reoperation is recommended in cases of T₂ tumors and more advanced stages of disease. On the contrary, controversies still exist on the need for more radical resection for T_{1b} GBC. During reoperation it is also unclear what the appropriate extent of hepatic resection is, and whether hepatic resection can prevent liver recurrence.

We report our 10 years experience (19 cases) in the treatment of GBC, and we present a systematic review to evaluate the role of extended surgery in the treatment of the incidental GBC. A Medline search was performed using the keywords "Incidental gallbladder cancer", "laparoscopic cholecystectomy", "lymph nodes dissection" and "hepatic resection".

Reviewing the literature, we focused on the following key points, which are still considered controversial in the management of GBC: (1) How laparoscopy has modified the presentation, the outcome, and the management of the patients with gallbladder cancer? (2) What is an appropriate extent of hepatic resection during reoperation, and can hepatic resection prevent liver recurrence? (3) What is the optimal extent of lymph node dissection? (4) When is resection of the common bile duct necessary? (5) Which type of surgical strategy should be used according to depth invasion? (6) Does laparoscopic cholecystectomy worsen prognosis? (7) Are port-site metastases a real problem? and (8) When is additional radical resection not indicated?

MATERIALS AND METHODS

Ethics

This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. All patients provided informed consent.

Data collection

From 1998 to 2008, in the Department of General Surgery of Catania University Hospital and in the General Surgery Unit of Taormina Hospital, 1490 patients underwent cholecystectomy. Within this group of patients, all the cases of GBC were retrospectively reviewed. Patients' demographic data, as well as type of operation, surgical morbidity and mortality, histopathological classification, and survival data were collected in a database for further analysis. The diagnosis of gallbladder pathology was made by history, physical examination, and laboratory and imaging studies [ultrasonography and computed tomography (CT)].

Disease-free survival analysis

The patients were divided in two groups: incidental diagnosis of gallbladder carcinoma, and known or suspected diagnosis preoperatively. The primary endpoint of the study was disease-free survival (DFS) at different stages of diagnosis. The secondary endpoint was the difference in DFS between patients previously treated with laparoscopic cholecystectomy and patients who had oncological resection as their first intervention. The results are reported in percentages and means.

RESULTS

GBC was diagnosed in 19 patients, 11 women and eight men. The male to female ratio was 1:1.4 and the mean age was 68 years (range: 45-82 years).

According to tumor node metastasis staging of the 6th edition of the American Joint Committee on Cancer (AJCC), our patients were divided into: pT_{is} (1), pT_{1a} (2), pT_{1b} (4), pT₂ (6), pT₃ (4), pT₄ (2); five cases with stage I a (T₁ a-b); two with stage I b (T₂ N₀); one with stage II a (T₃ N₀); six with stage II b (T₁-T₃ N₁); two

Table 1 Patient characteristics with gallbladder cancer *n* (%)

	IGBC	NIGBC
No. of patients (<i>n</i> = 19)	9	10
Polyposis lesions	7 (77.8)	5 (50)
Nonpolyposis lesions	1 (11.1)	5 (50)
Histopathological grade		
G1	3 (33.3)	1 (10)
G2	6 (66.7)	3 (30)
G3	0	6 (60)
Lymphatic invasion		
+	2 (22.2)	4 (40)
-	7 (77.8)	6 (60)
Vessel invasion		
+	1 (11.1)	1 (10)
-	8 (88.9)	9 (90)
Perineural invasion		
+	1 (11.1)	3 (30)
-	8 (88.9)	7 (70)
Stage		
0	1 (11.1)	0
I A	4 (44.4)	2 (20)
I B	1 (11.1)	1 (10)
II A	0	1 (10)
II B	2 (22.2)	4 (40)
III	0	1 (10)
IV	1 (11.1)	1 (10)

IGBC: Incidental gallbladder cancer; NIGBC: Nonincidental gallbladder cancer. +: Positive; -: Negative.

with stage III (T4 Nx Nx); and one with Stage IV (Tx Nx Mx). Eighty-eight percent of the incidental cases were discovered at an early stage (\leq II). A preoperative diagnosis was possible only in 10 cases; eight were diagnosed postoperatively during the pathological examination; and one was suspected intraoperatively and then confirmed by frozen sections. The ratio between incidental and nonincidental cases was 9/19, with eight cases discovered after laparoscopic cholecystectomy. The preoperative diagnosis of the 19 patients with GBC was: GBC with liver invasion diagnosed by preoperative CT (nine cases); gallbladder abscess perforated into hepatic parenchyma and involving the transversal mesocolon and hepatic hilum (one case); porcelain gallbladder (one case); gallbladder adenoma (one case); and chronic cholecystolithiasis (eight cases).

Pathological characteristics of the tumors were: one *in situ* cancer; three well-differentiated polypoid adenocarcinoma (G1); one well-differentiated nonpolypoid adenocarcinoma of the gallbladder fundus (G1); seven moderately differentiated polypoid adenocarcinoma (G2-G3); one moderately differentiated nonpolypoid adenocarcinoma (G2); and one and five polypoid and nonpolypoid poorly differentiated GBC (G3), respectively (Table 1).

Every case, except one, with a T1b or more advanced invasion underwent IVb + V wedge liver resection and pericholedochic/hepatoduodenal lymphadenectomy. One patient with stage T1b refused further surgery. Cases with Tis and T1a involvement were treated with cholecystectomy alone. One incidental case was diagnosed by intraoperative frozen section and treated with cholecystectomy alone. Six of the nine patients with in-

cidental diagnosis reached 5-year DFS. Surprisingly, one patient reached 38 mo survival despite a port-site recurrence 2 years after the original surgery requiring further resection. Cases with nonincidental diagnosis were more locally advanced and only two patients experienced 5 years DFS (Tables 2 and 3).

DISCUSSION

How laparoscopy has modified presentation, outcome and management of patients with GBC

Presentation and outcome: The widespread use of laparoscopic cholecystectomy has led to discovery of this deadly disease at an earlier stage, altering the management and the outcome of these patients. GBC is an incidental finding in 0.25%-3% of patients and almost half of these cases are occasionally discovered during or after laparoscopic cholecystectomy for benign disease, such as gallstones and their complications (47% in the series of Memorial Sloan-Kettering Cancer Centre, 50% in the series of Johns Hopkins)^[1,2]. The earlier discovery results in an earlier pathological stage, and consequently, increased long-term survival^[2-4]. Patients with incidental GBC had a significant increase in survival when compared with those who had a preoperative diagnosis (overall 5-year survival 15% *vs* 33%)^[2]. Therefore, the general surgeon should be prepared to deal with GBC suspected or diagnosed incidentally, following a well-established treatment algorithm^[5-8]. It is paramount not to violate oncological principles during the first operation, if a two-stage approach is necessary. For this reason, the surgeon during video-laparoscopic cholecystectomy should always follow these simple rules: (1) perform a thorough preoperative diagnosis; (2) when in doubt, give up the laparoscopy to open access; (3) try to preserve the integrity of the gallbladder, handling it as little as possible; (4) close possible breaches of the wall with clips or endoloops; (5) always use the endobag for the removal of the gallbladder; (6) carefully inspect the gallbladder once extracted; (7) if in doubt, perform a histological examination impromptu; and (8) desufflate the pneumoperitoneum with the trocars *in situ*. During cholecystectomy, accidental opening of the gallbladder is described in 25%-30% of the cases, which clearly have a worse prognosis^[3,9].

Management: The approach to incidental GBC is still controversial because of the difficulty of comparing data deriving from nonuniform case studies. Particularly discordant are the data deriving from western cancer registries with respect to the Japanese ones^[3,4,10-13]. The only constant element seems to be that the prognosis strongly depends on the stage and on the possibility of achieving R0 oncological resection^[3,4]. When incidental GBC is diagnosed afterwards by the pathologist, it is essential to restage the patients carefully by CT, magnetic resonance imaging and positron emission tomography, with a targeted study of the liver bed, peritoneum and of orifices of the trocars^[14,15]. Moreover, a reassessment of

Table 2 Patient characteristics: Demographic data, histopathological classification, tumor node metastasis staging

Patient	Gender	Age (yr)	Incidental	TNM 6th edition	Cystic duct	Resection	Size (mm)	Grade	Lymphatic	Vessel	Perineural	5-yr survival
1	M	63	No	pT2 N1 Mx	R0	R0	10 (NP)	G3	No	R0	No	Alive, 15 mo
2	F	82	No	pT4 N2 M1	R0	R1	45 (NP)	G3	Yes	Yes	Yes	Dead, 3 mo
3	F	60	No	pT3 N1 Mx	R1	R1	60 (P)	G3	No	No	Yes	Dead, 6 mo
4	F	72	No	pT3 N1 Mx	R0	R1	32 (NP)	G3	Yes	No	No	Dead, 8 mo
5	M	76	No	pT4 N1 Mx	R0	R1	49 (NP)	G3	Yes	No	Yes	Dead, 7 mo
6	M	81	No	pT3 N0 Mx	R0	R1	44 (NP)	G3	No	No	No	Dead, 9 mo
7	F	77	No	pT2 N0 Mx	R0	R0	20 (P)	G2	No	No	No	Dead, 24 mo
8	F	45	No	PT1a N0 Mx	R0	R0	25 (P)	G1	No	No	No	Alive, no recurrence at 5 yr
9	F	81	No	PT3 N1 Mx	R0	R1	24 (P)	G2	Yes	No	No	Dead, 28 mo
10	F	66	No	pT1b N0 Mx	R0	R0	7 (P)	G2	No	No	No	Alive, no recurrence at 5 yr
11	M	69	Yes	pT1b N0 Mx	R0	R0	15 (NP)	G1	No	No	No	Alive, 38 mo (disease recurrence)
12	M	65	Yes	PT1a Nx Mx	R0	R0	18 (P)	G1	No	No	No	Alive, no recurrence at 6 yr
13	F	72	Yes	pT2 N0 Mx	R0	R0	10 (NP)	G2	No	No	No	Alive, no recurrence at 5 yr
14	M	55	Yes	pT2 N0 M1	R1	R1	30 (P)	G2-3	No	Yes	Yes	Dead, 8 mo
15	F	78	Yes	pT2 N1 Mx	R0	R0	14 (P)	G2-3	Yes	No	No	Dead, 26 mo
16	F	57	Yes	pT1b N0 Mx	R0	R0	30 (P)	G2-3	No	No	No	Alive, no recurrence at 5 yr
17	M	71	Yes	pT2 N1 Mx	R0	R0	20 (P)	G2-3	Yes	No	No	Dead, 23 mo
18	F	61	Yes	pTis Nx Mx	R0	R0	12 (P)	G1	No	No	No	Alive, no recurrence at 5 yr
19	M	69	Yes	pT1b N0 Mx	R0	R0	5 (P)	G2	No	No	No	Alive, no recurrence at 5 yr

TNM: Tumor node metastasis; M: Male; F: Female; NP: Non polypoid; P: Polypoid.

the histological examination has to be performed, with a possible second opinion. This is important in order to: (1) confirm the pT; (2) specify the exact site of the tumor (hepatic side, bottom, infundibulum); (3) have a thorough evaluation of the cystic duct; and (4) evaluate whether the cystic lymph node is included in the histological examination. Today reoperation for incidental GBC should have two fundamental objectives: R0 resection of the liver parenchyma with the other adjacent structures, and clearance of the locoregional lymph nodes^[7,8].

What is an appropriate extent of hepatic resection during reoperation and can hepatic resection prevent liver recurrence?

Hepatic resection for GBC must have two main aims: resect the tumor that has directly invaded the liver from the gallbladder bed, and prevent micrometastases that may recur around the gallbladder bed^[3]. However, it remains unclear what an appropriate extent of hepatic resection is, and whether hepatic resection can prevent liver recurrence. Generally, operative procedures for incidental GBC include: extended cholecystectomy or Glenn resection (i.e., cholecystectomy plus partial resection of liver segments 4 and 5, approximately 2-3 cm from the gallbladder bed); anatomic resection of liver segment 5 and lower part of segment 4 when GC invades the liver bed to a depth of 2 cm or more; right hepatectomy when GC invaded the right Glisson capsule^[3,7,8].

As noted in the literature, the preference today is for

parenchyma-sparing operations, such as no anatomical wedge resection^[1,3]. Araida *et al*^[16] showed in a multi-center retrospective study, that there was no significant differences in survival and in recurrence rates of liver metastasis between patients that underwent resection of the gallbladder bed, anatomical segmentectomy 4b + 5 and hepatectomy for pT2 and pT3 GBC. He also proved that there were no particular preferences of recurrent liver metastasis for segment 4a + 5. Similarly, other authors have reported that there was no association between major hepatectomy and long-term survival, and that there was an increased association between major hepatic surgery and perioperative morbidity^[1,3].

In order to support this, Pawlik *et al*^[5] have proved that patients who had undergone major hepatic resection (anatomical segmentectomy of 4a + 5 or hemihepatectomy) had a similar risk of specific death as patients who underwent hepatic wedge resection, on both univariate and multivariate analyses. Rather than the type of hepatic resection, the most important factor that determines the final outcome is to obtain R0 resection. In fact, R1/R2 margin status is associated with decreased long-term survival^[17].

In conclusion, for gallbladder cancer without hepatoduodenal ligament invasion and without any locoregional liver involvement, the wedge resection of the gallbladder bed (3 cm) is preferable to hepatectomy^[3,5,17]. With regard to GBC that has invaded the gallbladder bed, in order to obtain negative histological margins, the preferred approach is nonanatomical resection of hepatic parenchyma, with a distal clearance of at least 2 cm^[3,5,17].

Table 3 Patient characteristics: Type of operation and survival data

Patient	Gender	Age (yr)	Incidental	TNM 6th edition	Cystic duct	Resection	Surgery	5-yr survival
1	M	63	No	pT2 N1 Mx	R0	R0	Wedge res. (IVb + V) + lymphadenectomy (I stage)	Alive, 15 mo
2	F	82	No	pT4 N2 M1	R0	R1	Wedge res. (IVb + V) + lymphadenectomy (I stage) + CBD res.	Dead, 3 mo
3	F	60	No	pT3 N1 Mx	R1	R1	Wedge res. (IVb + V) + lymphadenectomy (I stage)	Dead, 6 mo
4	F	72	No	pT3 N1 Mx	R0	R1	Wedge res. (IVb + V) + lymphadenectomy (I stage)	Dead, 8 mo
5	M	76	No	pT4 N1 Mx	R0	R1	Wedge res. (IVb + V) + lymphadenectomy (I stage)	Dead, 7 mo
6	M	81	No	pT3 N0 Mx	R0	R1	Wedge res. (IVb + V) + lymphadenectomy (I stage)	Dead, 9 mo
7	F	77	No	pT2 N0 Mx	R0	R0	Wedge res. (IVb + V) + lymphadenectomy (I stage)	Dead, 24 mo
8	F	45	No	PT1a N0 Mx	R0	R0	Cholecystectomy, no further surgery	Alive, no recurrence at 5 yr
9	F	81	No	PT3 N1 Mx	R0	R1	Wedge res. (IVb + V) + lymphadenectomy (I stage)	Dead, 28 mo
10	F	66	No	pT1b N0 Mx	R0	R0	Wedge res. (IVb + V) + lymphadenectomy (I stage)	Alive, no recurrence at 5 yr
11	M	69	Yes	pT1b N0 Mx	R0	R0	LC (stage) - wedge res. (IVb + V) + lymphadenectomy (II stage) + PS exc	Alive, 38 mo (disease recurrence)
12	M	65	Yes	PT1a Nx Mx	R0	R0	Cholecystectomy	Alive, no recurrence at 6 yr
13	F	72	Yes	pT2 N0 Mx	R0	R0	LC (stage) - wedge res. (IVb + V) + lymphadenectomy (II stage) + PS exc	Alive, no recurrence at 5 yr
14	M	55	Yes	pT2 N0 M1	R1	R1	LC (stage) - wedge res. (IVb + V) + lymphadenectomy (II stage) + CBD and PS exc	Dead, 8 mo
15	F	78	Yes	pT2 N1 Mx	R0	R0	Cholecystectomy, refused further surgery	Dead, 26 mo
16	F	57	Yes	pT1b N0 Mx	R0	R0	LC (stage) - wedge res. (IVb + V) + lymphadenectomy (II stage) + PS exc	Alive, no recurrence at 5 yr
17	M	71	Yes	pT2 N1 Mx	R0	R0	LC (stage) - wedge res. (IVb + V) + lymphadenectomy (II stage) + PS exc	Dead, 23 mo
18	F	61	Yes	pTis Nx Mx	R0	R0	LC	Alive, no recurrence at 5 yr
19	M	69	Yes	pT1b N0 Mx	R0	R0	Cholecystectomy, refused further surgery	Alive, no recurrence at 5 yr

TNM: Tumor node metastasis; M: Male; F: Female; CBD: Common bile duct; PS: Port site; LC: Laparoscopic cholecystectomy; res: Resection of segments; exc: Excision.

Optimal extent of lymph node dissection?

In GBC, besides radical R0 resection, another main aim of surgery is to obtain complete clearance of the locoregional lymph nodes. GBC spreads through different pathways: direct locoregional invasion to lymphatic, vascular and neural invasion. The most common route of dissemination is lymphatic diffusion. This is facilitated by lymphatic channels in both the muscular and subserosal layers of the gallbladder. In addition, neoplastic cells, even without evident transmural invasion, often spread superficially to the other lymph nodes along the bile ducts^[18-20]. The lymph nodes involved in the locoregional spread of GC can be divided into three: (1) cystic, pericholedochal and hilar lymph nodes; (2) lymph nodes around the portal vein, the common hepatic artery and periduodenal and peripancreatic lymph nodes; and (3) celiac, superior mesenteric artery and the para-aortic lymph nodes^[18-20].

Although the cystic and pericholedochal lymph nodes are the first key station, the pathways of lymph node involvement from the first site of diffusion to the hepatoduodenal ligament (cystic, pericholedochal and hilar lymph nodes) tend to be highly variable^[21]. In fact, GBC can spread directly to the third level of lymph nodes, along the perivascular soft tissue (celiac, superior mesenteric artery and the para-aortic lymph nodes), according to the three pathways of lymphatic drainage proposed

by Ito *et al*^[21]: cholecysto-retropancreatic pathway (main pathway), cholecysto-celiac and cholecysto-mesenteric pathways (accessory pathways). The incidence of occult lymphatic metastasis discovered during reoperation for incidental GBC can vary from 0% to 85% in relation to the depth of organ invasion (pT).

In fact, the reported incidence of occult lymphatic metastasis by stage is as follows: for T1a 0%-2.5%, for T1b 15%-25%, for T2 30%-50%, for T3 45%-75%, and for T4 > 85%^[5,18,22-26] (Table 4). Similarly to other cancers, lymphadenectomy not only provides important staging information, but more importantly, may decrease the risk of locoregional recurrence. In fact, after tumor resection, the level of lymph node metastasis correlates with overall prognosis within the same pT stage category^[25,26]. Miyakawa *et al*^[27] reported 5-year survival of 60.3% for pN0 patients, 30.0% for pN1, 16.8% for pN2, and 5.9% for pN3. Hence, little controversy exists on the optimal management of T1a GBC. In fact, cholecystectomy alone is sufficient^[3]. On the contrary, controversy still exists on the need for more radical resection in T1b GBC^[24,26]. Moreover, different authors have advocated that not all T1b stages are the same, and treatment should be individualized. In fact, due to the strong correlation between lymphatic invasion and lymph node metastasis, Shibata *et al*^[20] have advocated the use of

Table 4 Residual disease in the lymph nodes after re-resection for each pT (%)

Pathological T	Ogura <i>et al.</i> ^[22]	Tsukada <i>et al.</i> ^[18]	Foster <i>et al.</i> ^[23]	Pawlik <i>et al.</i> ^[5]	You <i>et al.</i> ^[24]	Liang <i>et al.</i> ^[25]	Erich <i>et al.</i> ^[26]
Tis							
T1a	2.5	0			0	0	0
T1b	15.5	0			3.8	0	24.4
T1 (tot)	18	0		12.5	3.8	0	24.4
T2	44.3	46	33	31.3		29.2	44.9
T3	72		75	45.5		58.7	63.7
T4						85.36	

lymphatic invasion as guidance for additional radical resection. However, this remains controversial because the absence of lymph node invasion does not exclude other recurrence such as liver metastases, peritoneal carcinomatosis or recurrence at the port sites, or expression of other forms of diffusion of GBC^[28,29].

Based on our review, we believe that resection of the gallbladder bed with regional lymph node dissection is the best choice for treatment of T1b GBC. In Western countries, lymphadenectomy is usually confined to the hepatoduodenal ligament around the hilar area (N1 lymph nodes: cystic, pericholedochal and hilar lymph nodes). Extended radical lymphadenectomy of N2 lymph nodes (including lymph nodes around the portal vein, common hepatic artery, and periduodenal and peripancreatic lymph nodes) is not routinely advocated^[3,4]. Currently, according to the 7th edition of AJCC staging, N2 involvement is considered as M1 metastasis, and represent a potential contraindication to additional radical surgery^[30].

When is resection of the common bile duct necessary?

Resection of the common bile duct performed at the time of the hepatic resection and lymphadenectomy is controversial^[31-33]. GC has a strong tendency to invade the hepatoduodenal ligament in the form of perineural invasion or lymph node metastasis, therefore, *en bloc* resection of the regional lymph nodes together with excision of the connective tissue around the portal and hepatic artery should be performed, whenever lymph node dissection of the hepatoduodenal ligament is entertained^[34-36]. Dissection of the hepatoduodenal ligament implies a risk of inducing ischemic damage to the common bile duct, therefore, Shimizu *et al.*^[10] proposed routine resection of the extrahepatic bile duct to facilitate lymphadenectomy, avoiding common bile duct ischemia, and increasing the number of lymph nodes harvested. However, these benefits have not been confirmed in other studies^[32,33]. Pawlik *et al.*^[5] showed that the median number of lymph nodes harvested at the time of lymphadenectomy was the same ($n = 3$), regardless of whether the common bile duct was or was not resected concomitantly with lymph node dissection ($P = 0.35$). Araida *et al.*^[31] found that, in patients with advanced GBC, who did not have direct invasion of the hepatoduodenal ligament and/or of the cystic duct, bile duct resection did not result in any differences in terms of recurrence and overall survival, but it only exposes patients to the potential complications of the bilioenteric anastomosis.

In conclusion, bile duct resection should be performed only when the patients have a positive involvement of the cystic duct margins, discovered either on the pathological review of the initial cholecystectomy or through biopsy of the cystic duct at the time of the second operation^[3,32,33]. In fact, microscopic involvement of the cystic duct margin is associated with a residual and/or additional disease in the common bile duct in over one-third of the cases^[32,33].

Type of treatment according to depth invasion

Contrary to other gastrointestinal carcinomas, the depth of invasion of GBC dictates the extent of surgical resection. In cases of carcinoma *in situ* or tumor invading the mucosa (Tis and T1a), simple cholecystectomy with negative surgical margins can be considered as curative surgery^[3,4,23,37].

The 5-year survival after simple cholecystectomy is between 99% and 100%^[23,37]. When the muscularis layer is involved (T1b), a 20%-50% local-regional recurrence can be expected after simple cholecystectomy^[3,6,37] (Table 5). At the time of reoperation, it has been shown that there is a 10% incidence of residual disease in the liver bed associated with a 15%-25% incidence of residual metastatic lymph node involvement^[22,24,26]. The 5-year survival after simple cholecystectomy is between 40% and 50%^[6,23,36-39]. Therefore, the recommended procedure is cholecystectomy associated with resection of at least 3 cm of liver parenchyma (wedge resection), plus adequate lymphadenectomy (Glenn's resection)^[37-39]. When the tumor extends beyond the serosa and invades the liver or an organ or an adjacent structure (T3), there is a 36% incidence of residual disease at the liver level and 45%-75% incidence of lymph node dissemination^[5,22,25,26]. The goal of surgical intervention is to obtain R0 resection, hence, mandatory steps include extended lymphadenectomy and extended hepatic resection, associated with resection of other organs and structures, when necessary^[35]. T3 patients are at high risk of peritoneal metastases, therefore, explorative laparoscopy should be considered in order to avoid unnecessary laparotomy. The 5-year survival after simple cholecystectomy is 0%-15%, and reaches 25%-65% after extended resection^[5,23,36] (Table 5).

Does laparoscopic cholecystectomy worsen prognosis?

More cases of GBC are incidentally diagnosed during laparoscopic cholecystectomy, thus, the question arises whether laparoscopic cholecystectomy worsens the prog-

Table 5 Five-year survival according to both stage of gallbladder cancer and type of surgery (%)

Author	T1a LC	T1b LC	T2 LC	T2 extended resection
Fong <i>et al</i> ^[36]			19	61
Waghlikar <i>et al</i> ^[37]	100	41.67		
Fong <i>et al</i> ^[38]			20	60
Foster <i>et al</i> ^[23]	100	50	38	78
Chijiwa <i>et al</i> ^[39]			17	75

LC: Laparoscopic cholecystectomy.

nosis of these patients. Drouard *et al*^[40] first described the development of port-site metastases in 1991, and additional proof came in 1994^[41]. This contributed to the loss of interest in approaching malignancy laparoscopically. Furthermore, excessive manipulation of the organ and perforation can cause intraperitoneal spread of malignant cells, resulting in a worse long-term survival^[42]. In fact, the incidence of port-site recurrence increased from 9% in patients without intraoperative perforation to 40% in those in whom perforation could be demonstrated^[43]. Other studies proved that pneumoperitoneum significantly increased tumor cell implantation at trocar sites, and tumor growth in the peritoneum^[44-46]. However, laparoscopic cholecystectomy, if correctly performed, did not influence the long-term prognosis of early stage tumors (T1a, T1b, T2)^[7,8]. Also, radical re-resection, performed several months after laparoscopic cholecystectomy, has similar results to radical resection in one stage, and long-term survival can be achieved in tumors with infiltration of the liver in patients who have previously undergone noncurative surgery^[1,7,8,23]. Survival is strictly related to the depth of parietal invasion of the tumor, but there is no significant difference between patients with incidental GBC discovered during or after cholecystectomy ($P = 0.235$)^[7]. The real problem is to have a clear understanding of how to deal with this eventuality.

Are port-site metastasis a real problem?

Port-site metastasis is the most common form of parietal recurrence (Table 6). It has been reported at all stages of gallbladder carcinoma and at any of the trocar sites. It generally presents after latency, ranging from a few months to 3-4 years. Many factors can contribute to port-site metastasis. One of the most important is intraoperative spillage of bile from gallbladder wall perforation, which has been described in 30% of laparoscopic cholecystectomy cases, and it has been linked to port-site metastasis^[43,44,47,48]. Intraoperative manipulation of the tumor, in the form of tension, dissection and isolation, often leads to the disintegration of a certain proportion of cancer cells, as confirmed by the presence of granular cells in 40% of laparoscopic instruments^[49,50]. The increased intraperitoneal pressure induced by the CO₂ pneumoperitoneum can spread and redistribute cancer cells within the peritoneal cavity and in damaged surfaces. Finally, evidence exists on the immunosuppressive action of CO₂ which would favor the implantation of tumor

Table 6 Metastasis at port-site and at subcostal laparotomy (%)

Author	Metastasis at port-site	Metastasis at subcostal laparotomy
Z'graggen <i>et al</i> ^[43]	14	
Wu <i>et al</i> ^[44]	16	6.5
Paolucci <i>et al</i> ^[47]	17.1	
Paolucci <i>et al</i> ^[48]	14	12

cells^[50]. The median survival after port-site metastasis is approximately 1 year, and it is mandatory to perform resection at the time of reintervention in patients previously treated with laparoscopic cholecystectomy^[3,7,8].

Contraindications to additional radical resection

With the primary goal of surgery in mind (R0 resection), the only contraindication to additional surgery is the inability to obtain radical R0 resection. In particular, the presence of peritoneal metastasis, distant metastasis, locally advanced GBC with N2 or M1 (according to the 7th edition of AJCC staging), lymph node invasion along the hepatic artery, portal vein and celiac and mesenteric vessels are all considered contraindications to radical resection^[35,51-53]. On the other hand, the presence of peripancreatic (head only) lymph node disease is not a contraindication to surgical excision, and radical lymphadenectomy and pancreaticoduodenectomy can be carried out together with liver resection^[35,53]. Also, the depth of liver involvement and multiorgan locoregional involvement do not represent a contraindication for additional radical resection^[51,52]. Combined pancreaticoduodenectomy, right hemicolectomy and major hepatectomy are effective treatment for GBC with direct invasion of the adjacent organs (stomach, duodenum, pancreas, colon and liver), but only if potentially curative resection (R0) is feasible. In these cases of multiorgan resection for GBC, given radical R0 resection, the long-term survival will depend on bile duct involvement^[35,51-53]. In fact, stromal invasion of the extrahepatic bile ducts is sometimes a prelude to hepatoduodenal ligament involvement, and is also associated with a higher rate of metastases to para-aortic nodes with a high incidence of residual tumor and poor outcome after surgery^[32].

In conclusion, incidental carcinoma of the gallbladder, as our experience confirms, generally is diagnosed at an earlier stage and carries a better prognosis than non-incidentally found cancer. Laparoscopic cholecystectomy does not affect survival if implemented with proper technique. Simple cholecystectomy may be an adequate treatment only for earlier stage GBC: Tis and T1a. All other stages, starting from T1b should be treated with lymphadenectomy and resection of at least 2-3 cm of liver parenchyma around the liver bed, provided that no residual microscopic cancer (R0) remains. Resection of the main bile ducts could be necessary in hilum-type cancers with positive margins of the cystic duct. More extensive liver resection or performance of multiorgan resection can be pursued in order to achieve R0 resection.

COMMENTS

Background

Gallbladder carcinoma remains a rare, but highly aggressive disease. Its dismal prognosis is associated with the advanced stage of the disease at the time of diagnosis.

Research frontiers

Controversy exists about the optimal management of the disease. In particular, the debate involves the extent of surgical resection of the liver and surrounding organs, the need for resection of the main bile duct, the extent of lymph node removal, and the potential for negative effects of previous laparoscopic cholecystectomy. It is also unclear when surgery is not indicated at all.

Innovations and breakthroughs

Previous studies have proved how simple cholecystectomy is sufficient treatment for early stages of gallbladder carcinoma. Also, it seems that, at more advanced stages, it is paramount to obtain complete gross oncological resection (R0) without the need for anatomical hepatic resection. In order to minimize port-site metastasis, the laparoscopic approach to apparently benign gallbladder disease has to follow specific principles: minimal manipulation of the gallbladder; avoidance of rupture of the gallbladder and bile spillage; extraction of the specimen with a protective bag to avoid contact with the skin; and evacuation of the intraperitoneally insufflated gas via the cannulae.

Applications

The authors conclude that gallbladder cancer can be adequately cured when the diagnosis is early and the treatment is standardized by stage. Incidental carcinoma of the gallbladder is generally diagnosed at an earlier stage and carries a better prognosis than nonincidentally found cancer. Laparoscopic cholecystectomy does not affect survival if implemented with proper technique. Simple cholecystectomy may be adequate treatment only for the earlier stages. All other stages should be treated with lymphadenectomy and resection of at least 2-3 cm of liver parenchyma around the liver bed, provided that no residual microscopic cancer remains. Resection of the main bile ducts could be necessary in cancers with positive margins of the cystic duct. More extensive liver resection or performance of multiorgan resection can be pursued in order to achieve complete resection of the tumor. This research can certainly guide surgeons that encounter this rare entity unexpectedly. In fact, as long as the appropriate referrals are made, the prognosis does not worsen. This can also increase awareness of this rare, but potentially lethal disease.

Terminology

R0 is the surgical removal of all the grossly apparent tumor cells. Port-site metastasis refers to implantation of tumor cells at the skin incisions utilized to place the laparoscopic trocars.

Peer review

The authors present solid experience with a rare disease. Their clinical analysis, along with a thorough review of the literature, provides a clear algorithm to approach the disease at different stages.

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