Showa Univ J Med Sci **31**(4), 323～328, December 2019

Original

The Prognosis for Unexpected Gallbladder Carcinoma with Bile Spillage during Laparoscopic Cholecystectomy

Tomotake KOIZUMI*, Takeshi AOKI, Yuta ENAMI,
Akira FUJIMORI, Tomokazu KUSANO, Kazuhiro MATSUDA,
Kosuke YAMADA, Koji NOGAKI, Yoshihiko TASHIRO
and Masahiko MURAKAMI

Abstract: Here we review the prognosis of patients with unsuspected gallbladder carcinoma (GBC), detected after laparoscopic cholecystectomy (LC) in a single institute. We reviewed the medical records of patients diagnosed with gallbladder stones on admission, who underwent LC. Carcinoma involving the gallbladder was found in 22 of 2,770 patients (0.9%) via postoperative pathological examination. This GBC group spanned 58–87 years of age (mean, 75 years; 13 females and 9 males). The preoperative diagnosis was gallbladder stones with acute / chronic cholecystitis or adenomyomatosis of the gallbladder in all patients. We performed an additional surgery in 6 of 15 patients with pT2 and T3 disease; of these, 3 patients with pT2 disease and 1 with pT3 experienced bile spillage during the LC. The mean survival of patients with unexpected GBC was 21 months, with bile spillage occurring as a complication of LC identified as a potential risk factor for shorter survival (15.3 vs. 32.5 months). We identified patients with pT2 and pT3 disease after LC, and two patients with pT2 and 1 with pT3 who had bile spillage during LC died of peritoneal dissemination within 28 months, despite additional surgery. Occasional seeding caused by bile spillage during LC should be carefully avoided to minimize the risk of developing unsuspected GBC after LC.

Key words: unexpected gallbladder carcinoma, gallbladder carcinoma, bile spillage, laparoscopic cholecystectomy

Introduction

Laparoscopic cholecystectomy (LC) is a standard treatment for symptomatic gallstones. Recently, the increased use of LC and difficulties in preoperatively diagnosing gallbladder cancer (GBC) has increased the incidental discovery of GBC during and after LC, with a reported incidence of 0.23–2.85%[1–5].

Unfortunately, unexpected LC-related GBC can worsen the disease prognosis[3, 4, 6–11], manifesting as a reported increase in port site metastases[5, 12] and early peritoneal dissemination[13–15]. This increased risk even extends to patients with carcinoma *in situ* and pathological T1 carcinoma[14].

Department of Surgery, Division of General and Gastroenterological Surgery, Showa University School of Medicine, 1–5–8 Hatanodai, Shinagawa-ku, Tokyo 142–8666, Japan.
* To whom corresponding should be addressed.

Therefore, special attention should be paid to the LC findings because factors such as bile spillage, excessive tumor manipulation, and direct gallbladder contact at the time of extraction could influence the prognosis of GBC[4, 7]. In contrast, other studies found no change in the survival rate of patients diagnosed with GBC after LC[1, 2, 16–19]. The present study therefore investigated the prognosis associated with incidental GBC after LC with complications, such as bile spillage.

Patients & methods

From January 2000 to December 2014, 2,770 patients with gallbladder disease underwent LC at Showa University Hospital. Preoperative evaluations included abdominal ultrasound (US), computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP). We retrospectively analyzed medical records, imaging data, surgical records, pathological findings, and long-term outcomes. The tumors were staged according to the Union for International Cancer Control system and General Rule for Clinical and Pathological Studies on Cancer of the Biliary Tract, based on the hematoxylin and eosin staining. This study protocol was approved by the Institutional Ethical Committee at Showa University, Japan (notice of approval of IRB protocol numbers, 2865). Categorical and continuous data were compared using Mann-Whitney U test. A P value < 0.05 was considered statistically significant.

Results

Preoperative diagnosis

The preoperative diagnosis was acute / chronic cholelithiasis or adenomyomatosis of the gallbladder in the total group of 2,770 patients. Of these, 22 patients were diagnosed with unexpected GBC postoperatively, following a preoperative diagnosis of cholelithiasis. No patients exhibited polypoid lesions on abdominal US or CT. Moreover, there was no clear evidence of cancer, and all 22 therefore underwent LC.

Intraoperative findings

LC was performed with CO_2 pneumoperitoneum. Bile spillage occurred in 4 of the 22 patients (18%) during LC, caused by gallbladder perforation during dissection of the gallbladder bed or by the grasping forceps. A retrieval bag was used with all patients to extract the resected gallbladder. LC was converted to open surgery intraoperatively in 4 of 22 cases. None of the patients showed preoperative evidence of malignancy, and GBC was recognized only upon postoperative pathological examination.

Pathological characteristics after LC

Of the 2770 patients in whom LC was attempted, 22 (0.8%) had pathologically malignant lesions of the resected gallbladder; Table 1 details the patient characteristics and pathological diagnoses of these 22 cases. In brief, their median age was 75 years (range, 58–87), with 13 females and 9 males. The tumor stage was pT1a in 4 patients, pT1b in 3 patients, pT2 in 14

patients, and pT3 in 1 patient. Further investigation showed lymphatic invasion in 6 patients, and venous invasion in 6 with pT2 or pT3 disease (Table 2).

Additional surgery

After the diagnosis of GBC, 6 of the 22 patients underwent additional surgeries (liver bed resection and regional lymphadenectomy). These included 5 patients with pT2 tumors and 1 patient with a pT3 tumor. The median interval between LC and the additional surgeries was 38.1 days (28–77 days). Malignant cells were found in the additionally resected specimens of two

Table 1. Clinical findings of incidental gallbladder carcinoma diagnosed after laparoscopic cholecystectomy

Patient characteristics	n = 22
Median age (range, years)	75.4 (58–87)
Male / female (n)	9 / 13
Histology	
M (T1a)	4
MP (T1b)	3
SS (T2)	14
SE (T3)	1

M (T1a), tumor invades lamina propria; MP (T1b), T1b, tumor invades muscular layer; SS (T2), tumor invades perimuscular connective tissue, with no extension beyond the serosa (visceral peritoneum) or into the liver; subserosa invasion; SE (T3), tumor perforates the serosa and/or directly invades the liver and/or one other adjacent organ or structure, such as stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts.

Table 2. Pathological findings and outcome for six cases of incidental gallbladder carcinoma diagnosed after laparoscopic cholecystectomy

Case	Differentiation	Depth	bm	binf	hinf	v	ly	Additional operation	Bile leakage	Port site recurrence	Type of recurrence	Outcome
1	pap	SS	0	0	0	1	1	Lymphadenectomy	(+)	(−)	Peritoneal	Death
2	pap	SS	0	0	0	1	1	Liver bed resection, lymphadenectomy	(+)	(−)	Peritoneal	Death
3	tub	SS	0	0	0	0	2	Liver bed resection, lymphadenectomy	(−)	(−)	Peritoneal	Death
4	tub	SE	0	2	1	1	2	Laparotomy	(+)	(+)	Peritoneal	Death
5	pap	SS	0	0	0	1	3	Liver bed resection, lymphadenectomy	(−)	(−)	No	Alive
6	pap	SS	1	0	0	0	1	Liver bed resection, lymphadenectomy	(+)	(−)	No	Alive

pap, papillary adenocarcinoma; tub, tubullary adenocarcinoma; SS (T2), tumor invades perimuscular connective tissue, with no extension beyond the serosa (visceral peritoneum) or into the liver; subserosa invasion; SE (T3), tumor perforates the serosa and / or directly invades the liver and / or one other adjacent organ or structure, such as stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts; bm, biliary margin; hinf, hepatic infiltration; binf, biliary infiltration; v, metastasis of vein; ly, metastasis of lymph duct

patients with pT2 disease and one patient with pT3 disease. Three patients also had metastases to the lymph nodes surrounding the common hepatic artery[8] and the portal vein (12p).

Outcomes after additional surgery

The follow-up time ranged from 9 to 88 months (mean, 31 months), and there were no operative deaths. After the additional surgery, recurrence was found in 4 (66%) of the 6 patients, including 3 with pT2 disease and 1 with pT3 disease. Three patients with pT2 who showed bile spillage during the laparoscopic surgery subsequently died due to involvement of the peritoneal wall. The site of recurrence was the abdominal wall in 4 patients, 3 with pT2 disease and 1 with pT3 disease. Bile spillage occurred during the procedure in 4 patients, requiring use of an isolation sac (Table 2), and there tended to be a relationship between abdominal wall recurrence and bile spillage. Patients with unexpected GBC who suffered intraoperative complications (n=4) during LC also tended to have shorter survival times than those without such complications. (15.2 vs. 38.5 months, mean survival $P=0.04$).

Port site metastasis

Of the 22 patients who were diagnosed as GBC after LC, 1 patient with pT3 had a port site recurrence.

Discussion

In the present study, 22 of 2,770 patients (0.8%) who underwent LC for gallbladder disease showed pathologically malignant lesions of the resected specimens. The rate of incidental GBC after LC was previously reported as 0.23%-2.85%[1-5]. Patients with gallbladder polyps were not included in our study population; however, gallstones resulting from a distinct local mucosal irritation and chronic bacterial infection are potentially associated with the malignant transformation of cells[20-22]. Therefore, re-examination of such patients would reveal more cases, and collaboration with other institutions will be necessary because there are very few cases of incidental GBC.

LC can potentially worsen the prognosis of GBC[3, 4, 6-11], while not adversely influencing the rate of unsuspected GBC after LC[1, 2, 16-19]. In this study, we reviewed the medical records of patients with incidental GBC detected after LC to determine whether complications such as bile spillage affected the prognosis in patients with incidental GBC. There was no incidence of bile spillage in patients with pT1 disease in this study, but special attention should be paid to avoid bile spillage during LC, even for cases of T1 disease because the risk of early peritoneal dissemination is eminent in any progression of GBC due to bile spillage[4, 7].

Port site recurrence is also a risk of laparoscopic surgery[5, 12-15, 20, 23], and herein we report no such complications in patients with pT2 disease, but one case of pT3 disease with a port site recurrence. Most port site recurrences occur at the site of specimen or port removal; however, Ricardo *et al*[17] found no statistically significant differences when comparing the incidence of abdominal wall recurrences among surgical procedure categories (laparoscopic vs. open vs.

laparoscopic converted to open), suggesting no increase in abdominal wall implantations following laparoscopic surgery, and a more likely cause being the aggressive nature of this tumor. Paolucci *et al*[5] also suggested that abdominal wall metastases of GBC are not a specific complication of laparoscopy[5], although when unsuspected invasive GBC is found after LC, laparoscopic port sites should be inspected at reoperation, or at a minimum, the port site through which the gallbladder was removed should be widely excised[24].

It is very important to determine if LC influences the prognosis in patients with GBC. At the Organizing Committee of the 30th Annual Congress of the Japanese Society of Biliary Surgery, the 5-year survival rates of patients after LC, according to the depth of invasion, were as follows: 99% in those with pT1a (limited to the mucosa), 95% in those with pT1b (muscularis), 70% in those with pT2 (subserosa), 20% in those with pT3 (serosa), and 0% in those with pT4 (serosa with invasion to adjacent organs)[18]. It is therefore unlikely that LC could worsen survival among patients with GBC, compared with patients who underwent a standard open radical procedure, as long as additional excision was conducted for those with laparoscopically removed pT2 or pT3 GBCs[18]. Shimada *et al*[25] found that systemic dissection of N1 and posterior pancreaticoduodenal lymph nodes as well as lymph nodes around the common hepatic artery and portal vein was necessary among patients with N2 disease to improve the prognosis of patients with GBC and pT2 disease. In our study, five patients with pT2 disease underwent lymphadenectomy, and three died because of peritoneal dissemination. Sarli[16] also found no significant difference between LC and open laparotomy in cases of GBC detected after LC; however, 3 of our 4 patients with bile spillage during LC died within 28 months because of recurrent peritoneal cancer despite undergoing additional surgeries. Therefore, surgeons who perform LC should take great care to prevent inadvertent bile spillage into the surgical field and to avoid excessive manipulation of the gallbladder.

In conclusion, we demonstrated that a cautious surgical approach is desirable during LC, particularly to avoid gallbladder perforation. Such an approach reduces the risk of peritoneal dissemination of incidental GBC.

Conflict of interest disclosure

The authors declare that they have no conflicts of interest.

References

1) Suzuki K, Kimura T, Ogawa H. Long-term prognosis of gallbladder cancer diagnosed after laparoscopic cholecystectomy. *Surg Endosc.* 2000;**14**:712-716.
2) Mori T, Souda S, Hashimoto J, *et al*. Unsuspected gallbladder cancer diagnosed by laparoscopic cholecystectomy: a clinicopathological study. *Surg Today*. 1997;**27**:710-713.
3) Paolucci V, Schaeff B, Schneider M, *et al*. Tumor seeding following laparoscopy: international survey. *World J Surg*. 1999;**23**:989-995; discussion 996-997.
4) Wibbenmeyer LA, Wade TP, Chen RC, *et al*. Laparoscopic cholecystectomy can disseminate in situ carcinoma of the gallbladder. *J Am Coll Surg*. 1995;**181**:504-510.

5) Paolucci V. Port site recurrences after laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Surg*. 2001;**8**:535-543.
6) Braghetto I, Bastias J, Csendes A, *et al*. Gallbladder carcinoma during laparoscopic cholecystectomy: is it associated with bad prognosis? *Int Surg*. 1999;**84**:344-349.
7) Wullstein C, Woeste G, Barkhausen E, *et al*. Do complications related to laparoscopiuc cholecystectomy influence the prognosis of gallbladder cancer? *Surg Endosc*. 2002;**16**:828-832.
8) Z'graggen K, Birrer S, Maurer CA, *et al*. Incidence of port site recurrence after laparoscopic cholecystectomy for preoperatively unsuspected gallbladder carcinoma. *Surgery*. 1998;**124**:831-838.
9) Pezet D, Fondrinier E, Rotman N, *et al*. Parietal seeding of carcinoma of the gallbladder after laparoscopic cholecystectomy. *Br J Surg*. 1992;**79**:230.
10) Clair DG, Lautz DB, Brooks DC. Rapid development of umbilical metastases after laparoscopic cholecystectomy for unsuspected gallbladder carcinoma. *Surgery*. 1993;**113**:355-358.
11) Fong Y, Brennan MF, Turnbull A, *et al*. Gallbaldder cancerdiscovered during laparoscopic surgery. *Arch Surg*. 1993;**128**:1054-1056.
12) Garcia FR, Diaz TM, Lapena VJA, *et al*. Port site metastases after laparoscopic cholecystectomy for an unexpected gallbladder carcinoma. *Abdom Imaging*. 1999;**24**:404-406.
13) Sailer M, Debus S, Fuchs KH, *et al*. Peritoneal seeding of gallbladder cancer after laparoscopic cholecystectomy. *Surg Endosc*. 1995;**9**:1298-1300.
14) Sano T, Ajiki T, Hirata K, *et al*. A recurrent case of an early gallbladder carcinoma after laparoscopic cholecystectomy. *Hepatogastroenterology*. 2004;**51**:672-674.
15) Ohtani T, Takano Y, Shirai Y, *et al*. Early intraperitoneal dissemination after radical resection of unsuspected gallbladder carcinoma following laparoscopic cholecystectomy. *Surg Laparosc Endosc*. 1998;**8**:58-62.
16) Sarli L, Contini S, Sansebastiano G, *et al*. Does laparoscopic cholecystectomy worsen the prognosis of unsuspected gallbladder cancer? *Arch Surg*. 2000;**135**:1340-1344.
17) Ricardo AE, Feig BW, Ellis LM, *et al*. Gallbladder cancer and trocar site recurrence. *Am J Surg*. 1997;**174**:619-623.
18) Ouchi K, Mikuni J, Kakugawa Y, *et al*. Laparoscopic cholecystectomy for gallbladder carcinoma: results of a Japanese survey of 498 patients. *J Hepatobiliary Pancreat Surg*. 2002;**9**:256-260.
19) Suzuki K, Kimura T, Ogawa H. Is laparoscopic cholecystectomy hazardous for gallbladder cancer? *Surgery*. 1998;**123**:311-314.
20) Goetze TO. Gallbladder carcinoma: prognostic factors and therapeutic options. *World J Gastroenterol*. 2015;**21**:12211-12217.
21) Zatonski WA, Lowenfels AB, Boyle P, *et al*. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH program of the international agency for research on cancer. *J Natl Cancer Inst*. 1997;**89**:1132-1138.
22) Espinoza JA, Bizama C, Garcia P, *et al*. The inflammatory inception of gallbladder cancer. *Biochim Biophys Acta*. 2016;**1865**:245-254.
23) Suzuki K, Kimura T, Hashimoto H, *et al*. Port site recurrence of gallbladder cancer after laparoscopic surgery: two case reports of long-term survival. *Surg Laparosc Endosc Percutan Tech*. 2000;**10**:86-88.
24) Wade TP, Comitalo JB, Andrus CH, *et al*. Laparoscopic cancer surgery. Lessons from gallbladder cancer. *Surg Endosc*. 1994;**8**:698-701.
25) Shimada H, Endo I, Togo S, *et al*. The role of lymph node dissection in the treatment of gallbladder carcinoma. *Cancer*. 1997;**79**:892-899.

[Received May 17, 2019 : Accepted July 30, 2019]