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Original articles

Unsuspected gallbladder carcinoma after laparoscopic cholecystectomy

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Abstract
Background/Purpose. Many cases have been reported of disastrous port-site recurrence after laparoscopic cholecystectomy (LC) revealed unsuspected gallbladder carcinoma (GBC). Some investigators have reported that the prognosis of patients after LC showed unsuspected GBC is not worsened by laparoscopic procedures. We retrospectively reviewed our cases and the literature to reconfirm the intrinsic risks of LC for unsuspected GBC.
Methods. Of 1663 patients who underwent LC from January 1991 to December 2003 in a single institution, 9 (0.54%) with unsuspected GBC were reviewed.
Results. These 9 patients consisted of 5 men and 4 women, whose ages ranged from 58 to 87 years, with a median age of 73 years. Two patients with a pT1a tumor (limited to mucosa) and 2 patients with a pT1b tumor (muscle layer) underwent no further operation. The remaining 5 patients with a pT2 tumor (subserosa) underwent further operations with lymph node dissection. Five patients (2 patients with pT1b and 3 patients with pT2) developed recurrence and all of them died within a median period of 19 months (range 14–37 months) after LC. The causes of death were bone metastases in 1 patient (pT2), local recurrence in 2 patients (pT1b and pT2), and peritoneal metastasis in 2 patients (one elderly patient with pT1b who underwent laparoscopic common bile duct exploration, and one patient with pT2 in whom the cystic duct was damaged during surgery). Four patients (2 with pT1 and 2 with pT2) have been doing well with a median follow-up of 39.5 months (range 12–99 months) after LC.
Conclusions. Surgeons should always prevent bile spillage during LC and when removing the resected gallbladder. When laparoscopic common bile duct exploration is planned, especially for elderly women, surgeons should also bear in mind the increasing possibility of unsuspected GBC.

Key words Unsuspected gallbladder carcinoma · Port-site metastasis · Laparoscopic common bile duct exploration (LCBDE)

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Introduction

Since its introduction in 1988,[1] laparoscopic cholecystectomy (LC) has become the surgical procedure of choice worldwide for uncomplicated diseases of the gallbladder. It has been reported that gallbladder carcinoma (GBC) is discovered incidentally in about one of every 100 open cholecystectomies,[2] but in the past there were few reports addressing the issue of wound metastasis after cholecystectomy. Since 1991,[2–8] in the era of laparoscopic surgery, many reports have drawn attention to port-site metastases or inadvertent dissemination of preoperatively undiagnosed GBC even if the tumor was at an early stage.[2,3,9] Laparoscopic surgery for gastrointestinal malignancy has also been associated with late abdominal wall recurrence, which is rarely found after standard laparotomy,[10–12] and it is likely that laparoscopic surgery adversely affects the prognosis of malignant tumors. Some recent multicenter evaluations have demonstrated that LC does not always affect the prognosis of patients with unsuspected GBC.[9,13–15] We have evaluated the outcome and pattern of recurrence in patients with laparoscopically discovered GBC in a single institution and reviewed the literature in an attempt to verify the intrinsic risks of LC for unsuspected GBC.

Patients and methods

Between January 1991 and December 2003, 1829 patients with gallbladder diseases underwent cholecystectomy at Tohkai Hospital. Of these, 1663 (91%) patients were treated by laparoscopic surgery, and 166 (9%) patients by open surgery. Of the 1663 patients in whom we attempted or completed laparoscopic cholecystectomy, 9 (0.54%) had histologically malignant lesions of the resected gallbladder. These patients included 5 men and 4 women, with a median age of 73 years (range 58–

Table 1. Clinical data of patients with unsuspected gallbladder carcinoma who underwent laparoscopic cholecystectomy

Patient no.	Age (years)	Sex	Preoperative diagnosis	Operation	Bile spillage	Retrieval bag
1	78	F	Cholelithiasis in the cystic duct	LC → OC	–	Not used
2	62	M	Cholelithiasis	LC	–	Not used
3	78	M	Adenomyomatosis	LC + DUe	–	Not used
4	70	F	Cholelithiasis, chronic cholecystitis	LC	+	Used
5	75	M	Cholelithiasis, adenomyomatosis	LC	–	Not used
6	87	F	Cholecysto-choledocholithiasis	LCBDE	+	Used
7	60	F	Cholelithiasis	LC	–	Not used
8	62	M	Cholelithiasis, acute cholecystitis	LC	–	Used
9	73	M	Cholecysto-choledocholithiasis, acute cholecystitis	LC	–	Used

M, male; F, female; LC, laparoscopic cholecystectomy; OC, open cholecystectomy; LCBDE, laparoscopic common bile duct exploration; LC → OC, LC converted to OC; DUe, excision of the duodenum

87 years, Table 1). The medical records, imaging data, surgical records, pathologic findings and long-term outcome were reviewed.

The preoperative diagnosis was chronic cholelithiasis in 5 patients, acute cholecystitis in 2 patients, and cholecysto-choledocholithiasis and adenomyomatosis in 1 patient each (Table 1). Preoperative imaging modalities such as abdominal ultrasonography, computed tomography (CT), drip infusion cholangiography (DIC), and/or endoscopic retrograde cholangiography (ERC) were performed in all patients. The gallbladder was not visualized on preoperative ERC in 2 patients who had an atrophic gallbladder with impacted stones in the cystic duct. Two patients with acute cholecystitis underwent preoperative percutaneous transhepatic gallbladder drainage (PTGBD), and one of them underwent endoscopic sphincterotomy for the clearance of a common bile duct stone prior to surgery.

The depths of cancer invasion were determined by taking serial sections, 5 mm thick, from the gallbladder. The tumor stage was classified according to the pathologic tumor system[16]: pTis, carcinoma in situ; pT1, tumor is within the mucosa or invades the muscle layer (pT1a, tumor is confined to the mucosa; pT1b, tumor reaches to the muscle layer); pT2, tumor infiltrates the subserosal layer but does not extend beyond the serosa; pT3, tumor invades tissues beyond the serosa or adjacent organ (extending 2 cm or less into the liver); pT4, tumor extends more than 2 cm into the liver and/or into 2 or more adjacent organs.

Results

Laparoscopic procedure

Eight patients were successfully treated with laparoscopic surgery, including cholecystectomy in 6 patients, and cholecystectomy with common bile duct exploration and cholecystectomy with combined partial excision of the duodenal wall in 1 patient each. One patient underwent conversion from LC to open cholecystectomy (OC) after a diagnosis of suspected carcinoma of the cystic duct.

Bile spillage due to accidental perforation of the gallbladder did not occur in any patient during the laparoscopic procedure, whereas spillage of tumor-laden bile might have occurred in 2 patients in other situations (Table 1). Bile spillage was caused by laceration of the cystic duct during the laparoscopic procedure in one patient, and by laparoscopic choledochotomy itself in another patient. These two patients eventually developed peritoneal metastasis. A retrieval bag to extract the gallbladder was used in 4 patients.

Histological stage

Postoperative permanent histologic examinations revealed adenocarcinoma in all these patients. The lesion was adenocarcinoma in situ in 1 patient, well-differentiated tubular adenocarcinoma in 3 patients, moderately differentiated tubular adenocarcinoma in 4 patients, and papillary adenocarcinoma in 1 patient. The histological tumor stages in these patients are shown in Table 2, i.e., pTis in 1 patient, pT1a in 1 patient, pT1b in 2 patients, and pT2 in 5 patients. No patient had pT3 or pT4 disease. Lymphatic invasion was found in 2 patients with pT1b and pT2, while no venous invasion or perineural invasion was found in any patient.

Additional surgery

Four patients, one with pTis and three with pT1, underwent no additional surgery. Five patients with pT2 underwent further operations involving regional lymphadenectomy. Two patients underwent excision of the

Table 2. Histological findings, reoperation, and outcome for patients with unsuspected gallbladder carcinoma

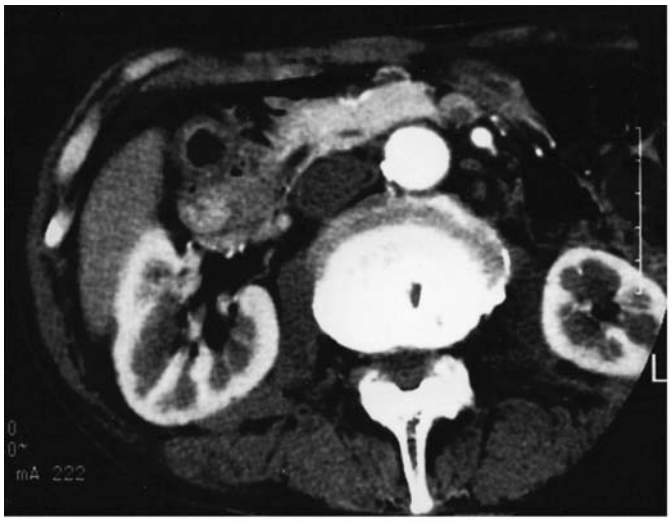
Patient no.	Location	Histology	Depth	ly	v	pn	Additional surgery	Residual tumor	Lymph node	Outcome
1	C	Mod. diff. adenocarcinoma	pT2 (ss)	0	0	0	Bx+D2	+	N0	DOR, 14 m
2	Gf	Well-diff. adenocarcinoma	pT1a (m)	0	0	0	—			NED, 99 m
3	Gfb	Papillary adenocarcinoma	pT1b (mp)	0	0	0	—			DOR, 15 m
4	Gf	Mod. diff. adenocarcinoma	pT2 (ss)	0	0	0	Hx (S4a+S5) Bx+D2	+	N0	DOR 37 m
5	Gf	Mod. diff. adenocarcinoma	pT2 (ss)	0	0	0	LBx, PE D2+16	–	N0	DOR, 36 m
6	Gfn	Well-diff. adenocarcinoma	pT1b (mp)	2	0	0	—			DOR, 19 m
7	Gf	Adenocarcinoma in situ	pTis	0	0	0	—			NED, 41 m
8	Gf	Mod. diff. adenocarcinoma	pT2 (ss)	0	0	0	LBx, PE D2+16	–	N0	NED, 38 m
9	Gfb	Mod. diff. adenocarcinoma	pT2 (ss)	2	0	0	Bx, PE D2+16	–	N0	NED, 12 m

C, cystic duct; Gf, fundus of the gallbladder (GB); Gfb, fundus and body of the GB; Bx, bile duct excision; Hx, hepatectomy; LBx, excision of the liver bed; PE, excision of the port site; D, lymph node dissection; NED, no evidence of disease; DOR, died of recurrence; mod. diff., moderately differentiated; m, months

liver bed, and one patient underwent resection of segments 4a and 5 of the liver. Bile duct resection, with or without hepatic resection, was performed in 3 patients. The patient who was converted to OC underwent cholecystectomy and choledochotomy with T-tube drainage at the time of initial surgery because malignancy was not detected in the frozen section. However, the final histopathological examination of the fixed specimen revealed findings compatible with a diagnosis of adenocarcinoma, and the patient underwent bile duct resection with regional lymph node dissection 12 days after initial surgery. The port site (subxiphoid point) through which the gallbladder was extracted was also simultaneously excised at the time of radical resection in 3 patients. The median interval between the laparoscopic procedure and additional surgery was 37 days (12–54 days). Cancer was found in the resected tissues in 2 patients with pT2 disease: in the tissue around the right hepatic artery in one patient (perineural infiltration), and in the remnant cystic duct of the gallbladder in another patient (a residual primary neoplasm). No microscopic implantation of cancer was found in the tissue excised from around the port sites.

Outcome

There were no operative deaths, and all patients were followed up. The follow-up time ranged from 12 to 99 months (median 36 months). Unfortunately, the cancer recurred in 2 patients with a pT1b tumor. One patient, a 78-year-old man, had undergone LC with a preoperative diagnosis of adenomyomatosis (Fig. 1). A histological examination had revealed a papillary adenocarcinoma that invaded the muscle layer without lymphatic or perineural invasion. Although histologically there was no tumor invasion of the cystic duct, he presented with jaundice 14 months after laparoscopic surgery and was admitted to another hospital. Cholangiography via percutaneous transhepatic biliary drainage (PTBD) revealed an obstruction of the common hepatic duct. CT also showed multiple lymph node metastases around the abdominal aorta. He was operated on, and underwent left hepatic cholangiojejunostomy. He was found to have developed a recurrent tumor near the GB bed without any peritoneal metastases. He died of pulmonary embolism 1 month after the second surgery. The other patient, an 87-year-old woman, underwent laparoscopic common bile duct exploration (LCBDE) after a preoperative diagnosis of chronic cholecystitis with cholecystcholedocholithiasis, because clearance of the common bile duct (CBD) stone by endoscopic sphincterotomy was not possible (Fig. 2). A histological examination revealed a well-differentiated tubular adenocarcinoma in the fundus and neck of the gallbladder. The tumor in the fundus was carcinoma in-situ, while the one in the neck invaded the muscle layer (Fig. 2). The patient presented with intestinal obstruction due to peritoneal dissemination 18 months after laparoscopic choledocholithotomy and died 1 month later.



a

c

b

Fig. 1a–c. Case 3. **a** Computed tomography (CT) showing a thickened wall in the body and fundus of the gallbladder. **b** Endoscopic retrograde cholangiography (ERC) showing no visualization of the fundus of the gallbladder. The patient was diagnosed as having adenomyomatosis by CT, ERC, and endoscopic ultrasonogrpahy. **c** The resected specimen presented a granular mucosa in the body and fundus area

Peritoneal seeding might have been derived from intraoperative bile spillage during choledochotomy. The remaining two patients, one with a pTis tumor and the other with a pT1a tumor, have been doing well for 41 and 99 months, respectively, with no sign of recurrence.

Recurrence developed in 3 of the 5 patients with pT2 tumors. The first patient, who underwent radical reoperation for carcinoma of the cystic duct, developed a local recurrence in the hepatic hilum and died of the disease 14 months after the initial surgery. The second patient, who underwent additional excision of segments 4a and 5 with combined resection of the bile duct after LC, presented with an abdominal wall mass in the right upper quadrant 17 months after the reoperation (Fig. 3). In this patient, the atrophic gallbladder tore at the cystic duct as it was pulled during the initial LC, probably following a little bile spillage. The recurrence site was not the port site used for specimen withdrawal, but the port site used to insert the instruments. Histological findings from the parietal nodule confirmed that this was metastasis from GBC. At the time of excisional surgery for the abdominal wall tumor, exploration of the abdomen disclosed two peritoneal metastases near the stump of the jejunal limb. This patient died of peritoneal dissemination 37 months after LC. There was no abdominal wall recurrence in any other patient apart from this patient. The third patient died of multiple

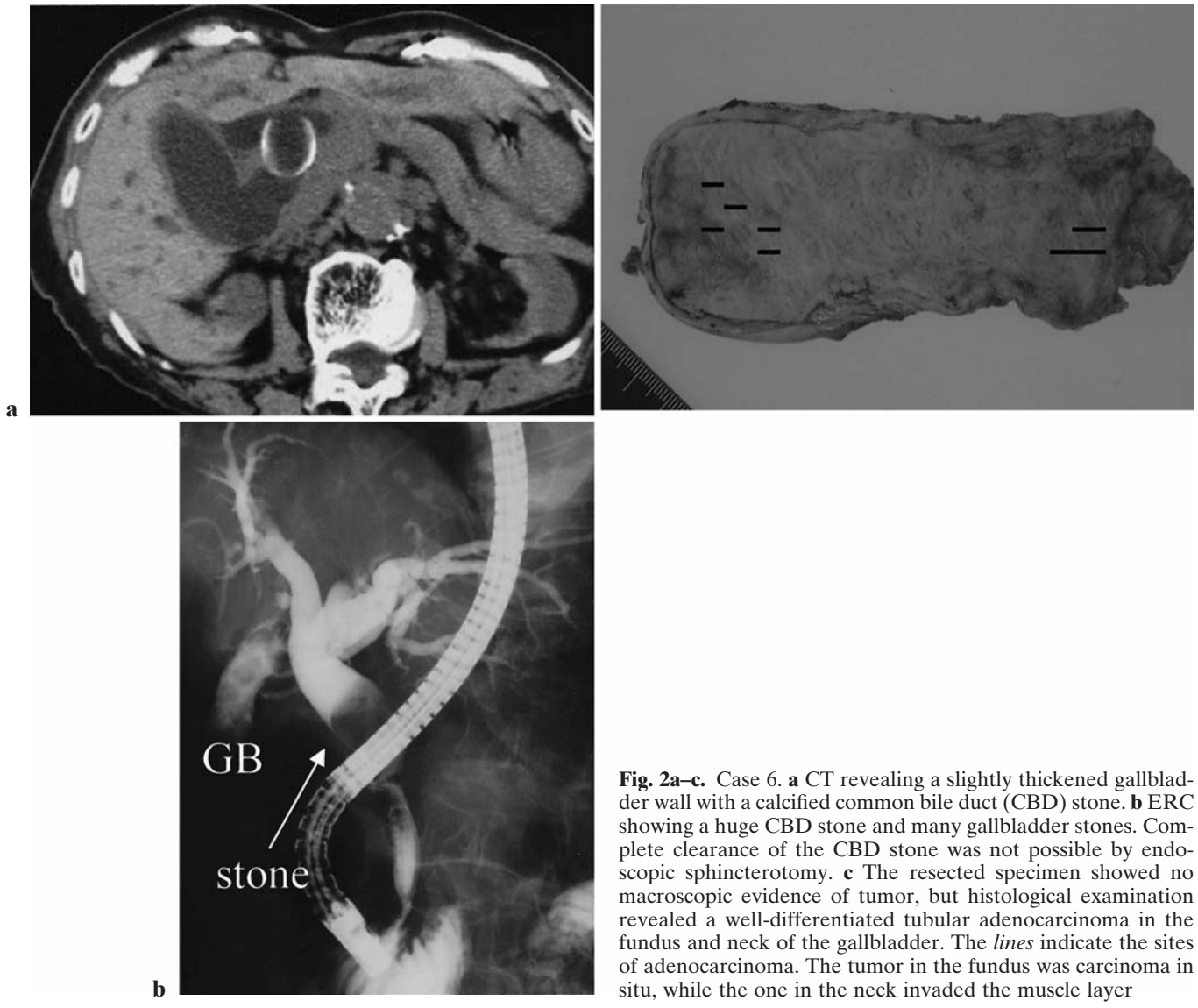


Fig. 2a–c. Case 6. **a** CT revealing a slightly thickened gallbladder wall with a calcified common bile duct (CBD) stone. **b** ERC showing a huge CBD stone and many gallbladder stones. Complete clearance of the CBD stone was not possible by endoscopic sphincterotomy. **c** The resected specimen showed no macroscopic evidence of tumor, but histological examination revealed a well-differentiated tubular adenocarcinoma in the fundus and neck of the gallbladder. The *lines* indicate the sites of adenocarcinoma. The tumor in the fundus was carcinoma in situ, while the one in the neck invaded the muscle layer

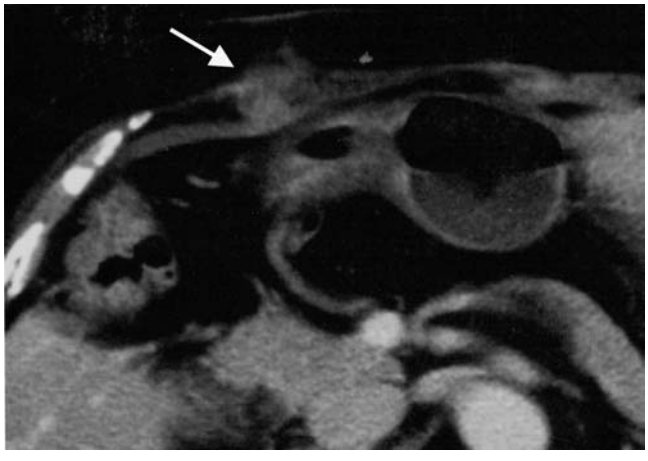


Fig. 3. Case 4. CT showing a mass (*arrow*) in the right upper quadrant incision site 19 months after laparoscopic cholecystectomy (LC)

bone metastases 35 months after the initial LC (33 months after additional surgery) without any sign of intraabdominal recurrence on abdominal CT. The remaining 2 patients with pT2 are currently free of disease 12 and 38 months after LC.

Discussion

In the era of laparoscopic surgery, gallbladder cancer is found unexpectedly in 0.3%–0.8% of patients during or after LC.[3,7,13,17–19] According to reports of large series including more than 2000 laparoscopic cholecystectomies, the rate of unsuspected GBC ranges from 0.3% to 0.5% in Western countries,[3,7,18,19] but in Japan it is slightly higher (0.8%–0.9%) (Table 3).[13,17]

As to the occurrence of tumor implantation in the abdominal wall associated with cholecystectomy, some

Table 3. Unsuspected gallbladder carcinoma (GBC) detected after laparoscopic cholecystectomy: occurrence, average age, and male to female ratio

Author	Year	No. of laparoscopic cholecystectomies	Unsuspected GBC (%)	Average age (range)	Male : female
Yamaguchi et al.[17]	1996	2616	24 (0.9%)	65.4 (36–91)	1:1.2
Z'graggen et al.[19]	1998	10925	37 (0.34%)	67 (51–87)	1:3.6
Paolucci et al.[3]	1999	117840	409 (0.35%)	—	—
Lundberg and Kristoffersson[7]	1999	11976	55 (0.5%)	—	—
Suzuki et al.[13]	2000	5027	41 (0.84%)	65.9 (39–86)	1:3.5
Sarli et al.[18]	2000	2300	9 (0.39%)	62.3 (36–75)	1:2
Wullstein et al.[24]	2002	1448	5 (0.35%)	67 (54–96)	1:3
Ouchi et al.[30]	2002	—	498	63.6 (17–90)	1:1.7

Table 4. Case reports of port-site metastasis after laparoscopic cholecystectomy for patients with unexpected pTis or PT1 gallbladder carcinoma

Author	Year	Age	Sex	Stage	Bile spillage	Duration	Recurrent site	Treatment for recurrence	Outcome
Fligelstone et al.[32]	1993	61	F	pT1	?	?	Port site, peritoneum	?	Died (?)
Nduka et al.[33]	1994	61	F	pTis	–	?	Port site, peritoneum	Radiation	Died (8 m)
Wibbenmeyer et al.[2]	1995	76	F	pTis	+	9 m	Port site, peritoneum	?	Died (10 m)
Principe et al.[34]	1997	61	F	pT1b	?	?	Port site		?
Z'graggen et al.[19]	1998	61	F	pT1b	–	6 m	Port site, peritoneum		Died (12 m)
Figueiras et al.[5]	1999	76	F	pT1b	?	8 m	Port site	Excision	?
Paolucci et al.[3]	1999			pT1a (3 pats)			Port site		?
	1999			pT1b (10 pats)			Port site		?
Jeon et al.[9]	1999	65	F	pT1b	?	47 m	Port site	Excision	?
Sarli et al.[18]	2000	36	F	pT1b	+	?			Died (16 m)
		75	F	pT1b	–	?			Died (13 m)
Yoshida et al.[15]	2000	79	F	pT1b	+	12 m	Port site, peritoneum	LBx+D	Died (24 m)
Ouchi et al.[30]	2002	?	?	pT1a	+	?	Port site, peritoneum		Died
		?	?	pT1b	+	?	Port site, peritoneum		Died
Wullstein et al.[24]	2002	?	?	pT1a	+	36 m	Port site, peritoneum liver metastases		Died (39 m)
		?	?	pT1b	+	24 m	Port site, local rec. in HDL		Died (28 m)

pats, patients; m, months

authors[3,20,21] have reported that it did not increase after laparoscopic surgery. However, some investigators have stated that laparoscopic surgery in patients with pneumoperitoneum induced by carbon dioxide (CO_2) would promote the dissemination of malignancy,[22,23] and other investigators[18,24] have verified that bile spillage and excessive manipulation of the gallbladder during LC significantly affected the prognosis of patients with unsuspected GBC. It has been reported that the rate of gallbladder perforation during LC is about 32%–40%,[25] and therefore we prefer not to perform LC on patients with preoperatively suspected GBC.

In this study, cancer recurred in two patients with pT1b tumors, including local recurrence in one and peritoneal seeding in the other. Although there is now a consensus in that cholecystectomy alone is the treatment of choice for pT1 gallbladder carcinoma,[15,26,27] some authors have warned that LC might contribute to the development of abdominal wall metastases even in patients with pT1 tumors.[4,15,19,24] In a review of the literature, we encountered many case reports of port-site metastasis or peritoneal metastasis in patients with pTis or pT1 tumors, and most of them died of the disease (Table 4). In many there was intraperitoneal bile spillage during LC. Z'graggen et al.[19] reported that the occurrence of port-site recurrence increased from 9% in patients without intraoperative gallbladder perforation to 40% in patients with documented intraoperative gallbladder perforation. Hence, bile spillage due to disruption of the gallbladder seemed to be the main cause of port-site metastases or peritoneal metastases in these patients with pT1.[24] In our patient with pT1b (case 3),

we speculate that an unrecognized exfoliation of tumor cells at the stump of the cystic duct might have been the cause of a local recurrence near the GB bed, because the resection margin was histologically free from tumor without lymphatic or perineural invasion. Some authors[5,9] insist that excision of all layers of the trocar sites is also advisable, and continuous follow-up is necessary even for patients with early GBC.

LCBDE is now widely used to remove CBD stones.[28,29] In our series, an old woman with pT1b who underwent LCBDE via a choledochotomy to remove a CBD stone unfortunately suffered from an intestinal obstruction due to peritoneal seeding of GBC cells 1 year later. Jones[27] demonstrated that the mean age of patients with GBC is 65.2 years, with the highest incidence of the disease being observed in the seventh and eighth decades of life. Several reports[2,9,13,17–19,24,30] have stated that the average age is 63.0–68.6 years, and that the male to female ratio is 1:1.7–3.6. Our experience of disastrous peritoneal recurrence after LCBDE suggests that surgeons must be alert for the possibility of GBC in elderly women, and should deliberate whether or not to do an LCBDE, especially if there is any finding such as wall thickening which might be indicative of GBC. We consider that endoscopic sphincterotomy or open definitive choledocholithotomy would be the ideal procedure for patients in this age group.

In our series, abdominal wall metastasis developed in one patient (case 4), at the right subcostal incision site, through which the gallbladder was not extracted, but probably through which the instruments were passed or the drain was placed. Although most of the port-site recurrences occur at the sites through which the specimen was removed, the recurrences do not always develop in the removal port sites.[3] Indeed, the use of a protective retrieval bag is considered ideal during extraction of the GB, but this precaution does not always exclude an intraperitoneal seeding event. Moreover, this is not feasible for all laparoscopic cholecystectomies, because the prevalence of unsuspected GBC is low (between 0.3% and 0.8% of laparoscopic cholecystectomies). What is most important is that surgeons are always meticulous during LC, with care being taken to prevent inadvertent bile spillage in the surgical field and to avoid excessive manipulation of the gallbladder. For example, we always hold the stump of the cystic duct with craw forceps when the gallbladder is dragged from the abdomen, and will never retrieve the gallbladder unless we put the stump of the cystic duct into the trocar sheath to avoid contact of the bile with the subcutaneous tissue.

Shirai et al.[26] have shown that the outcome of unsuspected GBC is determined by the pathological stage, while a second radical operation after open cholecystectomy (OC) brought about a better outcome, especially in the case of pT2 tumors. Although dissemination of the disease is a potential complication associated with laparoscopic surgery, as mentioned above, recent studies[13,15,30,31] have also shown that LC is not likely to have a negative effect on the survival of patients with unsuspected GBC as long as additional surgery is conducted according to the pathological stage. In fact, the 5-year survival rate of patients with pT2 in OC was 40%,[26] whereas those with pT2 in LC was 70%.[30] This would seem to suggest that GBC is a highly lethal malignancy, but we should also have reasonable confidence in performing LC, and additional surgery matched to the pathological stage should be carried out after LC.

In conclusion, laparoscopic surgeons should always prevent bile spillage, which might contain cancer cells, in the abdominal cavity or at port sites when removing the gallbladder. Even if confronted with unsuspected GBC during LC, the prognosis of the patients is not always affected provided one selects the appropriate treatment in accordance with the pathological stage of the GBC. Moreover, one should deliberate carefully whether or not to do LCBDE in elderly patients (over 65 years), especially those with questionable findings such as a thickened gallbladder wall.

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