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Unsuspected Gallbladder Cancer Diagnosed After Laparoscopic Cholecystectomy: Focus on Acute Cholecystitis

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Abstract

Background The aim of the present study was to investigate clinicopathological features of patients who were diagnosed with unsuspected gallbladder cancer (UGC) after laparoscopic cholecystectomy (LC) and to clarify the relationship between acute cholecystitis (AC) and unsuspected gallbladder cancer.

Methods From June 1997 to March 2008, a total of 2,607 LCs were performed at Ajou University Medical Center. Twenty-six patients (1.0%) were diagnosed with gallbladder cancer after LC. We excluded patients with preoperatively or intraoperatively suspected gallbladder cancer.

Results Of 1,128 patients with AC, 19 (1.6%) were identified with gallbladder cancer after surgery. The preoperative diagnosis included a high rate of acute and severe acute cholecystitis ($n = 19$; 73.1%). The rate of conversion to open surgery was 15.4% (4/26), and bile spillage occurred in 14 of 26 patients (53.8%). Adenocarcinoma (92.3%) and pT2 (65.4%) were the most common pathological findings. In 19 UGC patients with AC, the most common pathological finding was also pT2 ($n = 12$; 63.1%). In addition, all 5 of the patients with positive resection margin belonged to the UGC with AC group. Two of 26 patients (7.7%) underwent additional surgery after LC, and 2 patients (7.7%) underwent excision of the port site/wound for recurrence. The overall median survival was 32 months (95% Confidence Interval [CI] = 21–43). There were no significant differences in age, the presence of acute cholecystitis, or bile spillage ($P > 0.05$) However, tumor differentiation was associated significantly with survival rate.

Conclusions The preoperative diagnosis included a high rate of acute and severe acute cholecystitis. Survival was not associated with the presence of AC and bile spillage. Therefore, we suggest that AC may not influence the prognosis of unsuspected gallbladder cancer after LC. Moreover, good tumor differentiation can guarantee favorable survival, even in UGC with AC.

Introduction

Laparoscopic cholecystectomy (LC) has been a treatment of choice for benign diseases of the gallbladder [1], and the indications for LC include both acute and gangrenous cholecystitis [2]. However, gallbladder cancer is found unexpectedly in 0.3–0.9% of patients during or after LC [3–8]. Furthermore, port site metastases and peritoneal dissemination develop after LC for unsuspected gallbladder cancer (UGC) [9–11], and bile spillage and damage to the gallbladder wall during LC are known to significantly influence the prognosis of patients with UGC [7, 12].

There are some reports about the outcome of patients with gallbladder cancer presenting with acute cholecystitis (AC) [13–16]. The incidence of gallbladder cancer presenting with AC is higher than in patients undergoing elective cholecystectomy for cholelithiasis. However, the relationship between AC and prognosis remains unclear. Therefore, the aim of this study was to investigate clinicopathological features of patients who were diagnosed

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with UGC after LC, and to clarify the impact of AC for survival.

Materials and methods

From June 1997 to March 2008, a total of 2,607 LCs were performed at Ajou University Medical Center. Twenty-six patients (1.0%) who had been diagnosed with gallbladder cancer after LC were identified. We excluded all patients who were preoperatively or intraoperatively suspected of having gallbladder cancer, and who were referred from other hospitals after the first operation. Unsuspected gallbladder cancer (UGC) was defined as a cancer that was detected first by microscopic examination of the gallbladders resected at LC for presumed benign disease. There were 8 men and 19 women whose ages ranged from 36 to 86 years. We retrospectively reviewed the medical records of all patients and analyzed data, including clinical characteristics, operative records, reports of pathology, and survival outcomes. The stages of gallbladder cancer were classified according to the TNM system proposed by the American Joint Committee on Cancer (AJCC) [17].

During the study, 1,128 patients who were diagnosed with acute cholecystitis (AC) underwent LC. Among them, 1.6% of patients (19/1,128) were identified with gallbladder cancer after surgery. Acute cholecystitis was diagnosed by fever and right upper quadrant abdominal pain as clinical signs, and by thickening of the gallbladder wall and pericholecystic fluid collections as computed tomographic (CT) findings. Both gangrenous and empyematous acute cholecystitis were defined as severe acute cholelecystitis (SAC) and were included as acute cholecystitis; SAC was confirmed by operative findings: inspection of gallbladder showed a change in wall color to dark green or gray and contained infected bile or pus. Finally, SAC was confirmed by postoperative pathologic findings.

We used abdominal CT or ultrasonography for the imaging study. Laparoscopic cholecystectomy was performed via the standard four-trocar technique. A retrieval bag for gallbladder extraction was used to avoid stone spillage during LC when perforation of the gallbladder was suspected or to prevent wound infection when there was severe inflammation and thickening of the gallbladder wall. All the gallbladders resected were examined immediately by the operating surgeon.

We recommended additional radical surgery when the tumor stage was over T2 (tumor invades the perimuscular connective tissue) or when the resection margins were positive for cancer. Oral/intravascular chemotherapy or radiotherapy was carried out in patients who refused reoperation and who presented with recurrence. Recurrence was defined as distant metastasis, widespread or local peritoneal seeding, or port-site/wound recurrence. The presence of neoplastic tissue in the surgical wound was considered to be port-site/wound recurrence, and the wound mass was resected immediately by reoperation.

Follow-up data were obtained from outpatient clinical records and telephone interviews with patients or members of their families. Furthermore, survival data of patients were obtained from National Cancer Center in Korea. Patients underwent abdominal CT 6 and 12 months after surgery, and once a year thereafter. The mean follow-up period was 26.6 months (range: 3–81 months).

Survival was determined from the date of diagnosis to the date of death or to the date of last follow-up. The categorical variables were expressed as frequencies (%), and the continuous variables were presented as median and range. The cumulative survival rates were calculated using the Kaplan–Meier method. To analyze correlations between survival rate and prognostic factors, a log rank test was used. A P value < 0.05 was considered statistically significant.

Results

Clinical characteristics of patients with UGC are presented in Table 1. The mean age was high (over 60 years), and the rate among female patients was higher than in men. The mean white blood cell count was 11,292 ± 5,169.3(/mm^3). There were 3 patients who had a preoperative diagnosis of gallbladder polyp; in each case the diameter of the polyps was less than 1 cm. Surprisingly, the preoperative diagnosis included a high incidence of acute and severe acute

Table 1 Clinical characteristics of patients with unsuspected gallbladder cancer (UGC) after laparoscopic cholecystectomy (LC)

	UGC after LC ($n = 26$)
Age, years (mean)	63.0 ± 14.4 (36–86)
Gender	
Male	8
Female	18
Preoperative diagnosis	
GB polyp	3 (11.5%)
GB adenomyomatosis	1 (3.8%)
GB stone	3 (11.5%)
Acute cholecystitis	9 (34.6%)
Severe acute cholecystitis	10 (38.5%)
Operation	
LC	22
Conversion to open	4 (15.4%)
Mean follow-up (months)	26.0 ± 23.6 (3–81)

GB gallbladder

cholecystitis (19 patients; 73.1%). Five of 19 patients underwent preoperative gallbladder drainage (PTGBD).

Laparoscopic cholecystectomy was successfully completed in 22 patients, and conversion to open surgery was necessary in 4 patients (15.4%). Patients who underwent conversion to open surgery initially presented with severe AC, and their pathology showed T2 (tumor invading the perimuscular connective tissue). The causes of conversion to open surgery included severe adhesion in 3 patients and common bile duct injury in one patient.

Intraoperative frozen section examinations were not performed in any of the patients. Bile spillage occurred in 14 of 26 cases (53.8%). The most common reason for bile spillage was perforation of the gallbladder by grasping forceps, because of an edematous and distended gallbladder wall.

As a preoperative diagnosis, acute and severe acute cholecystitis was present in 19 patients. The mean age was 64.7 ± 14.2 years. The white blood cell count was slightly higher than that of all patients [WBC: 1,3045.2 ± 5,061.8 (/mm^3)]. Early LCs within 72 h were performed in 10 patients (52.6%). Pathological findings of UGC with AC also showed a high incidence of pT2 tumors ($n = 12$; 63.1%) and moderate differentiation ($n = 11$; 57.8%). The mean tumor size was 2.69 ± 1.35 cm. In addition, all 5 patients with positive resection margins belonged to the UGC with AC group.

The most common cancer was adenocarcinoma (24 cases), followed by small cell carcinoma (1 case) and mucinous carcinoma (1 case). Tumor with pT2 was the most common finding (65.4%) (Table 2). However, only 2 of 19 patients with stage 2 cancer or higher underwent additional surgery, because the 17 patients chose not to undergo reoperation regardless of the tumor extension into the resection margin. Two of 26 patients (7.7%) underwent additional surgery because of final pathology (T2 and positive margin of cystic duct); resection of cystic duct, and resection of common bile duct with hepaticojejunostomy in each patient (on 1st and 2nd month after LC). However, there were no remnant tumors found in resected specimens of duct. Furthermore, the dissection of common bile duct was very difficult because of severe adhesions in the operative field. Port site/wound recurrences were present in 2 patients (7.1%); excision of port site/wound was carried out (3 and 9 month later, respectively). Surgical procedures were LC in one patient (Fig. 1) and open conversion in the other.

The overall median survival was 32 months (95% CI = 21–43) (Fig. 2). The associations between survival rate and prognostic factors were analyzed. As shown in Fig. 3, there were no significant differences in age (<65 versus > 65 years), gender (male versus female), WBC count (/mm^3) (<11,000 versus > 11,000), PTGBD, presence of AC, bile spillage, open conversion, early operation, and second operation ($P > 0.05$). However, tumor differentiation was associated significantly with survival rate (Fig. 4).

Table 2 Pathological findings in UGC after LC patients

	UGC after LC ($n = 26$)
Tumor size, cm (mean)	2.36 ± 1.34
Tumor stage	
In situ	1
1a	3
1b	3
2	17
3	2
Tumor differentiation	
Well	5
Moderately	12
Poorly	5
Papillary	1
Others	3
Regional lymph node metastasis	3
Microscopic invasion	
Lymphovascular invasion	7
Perineural invasion	2
Resection margin involvement	5

Discussion

Since LC was first developed, the incidence of UGC has increased to 2.9% [3–9]. However, some authors suggest that this tumor has a significantly better chance for cure if it is diagnosed as an incidental finding after LC [18, 19]. Advanced gallbladder cancer is preoperatively diagnosed in the range of 80–90% of cases [20]. In contrast, however, UGC tends to be in early stages, most of the cases belonging to pT1 or pT2 [3, 20]. In the present study, the incidence of UGC was found to be similar to that of other reports. Furthermore, tumors with pT2 accounted for two-thirds of UGC. We think that the high rate of UGC with AC can be attributed to the preoperative difficulty of differentiating between AC and gallbladder cancer. The clinical presentation of early gallbladder cancer is nonspecific, and symptoms are similar to those of acute or chronic cholecystitis. In addition, it is difficult to grossly differentiate between AC and gallbladder cancer, because thickening of the gallbladder wall is a common feature in both diseases [21].

In the present study, the rate of UGC with AC after LC was 73.1%, significantly higher than that of other studies

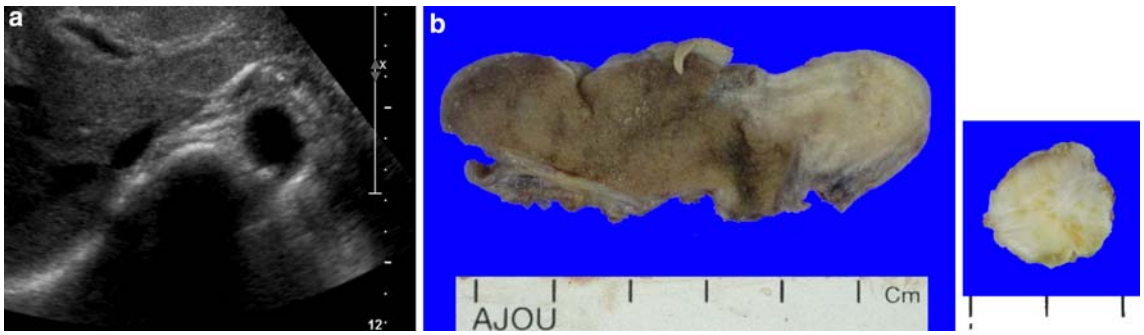

Fig. 1 Patient with port-site recurrence of gallbladder cancer (82-year-old woman). **a** Preoperative ultrasonogram showing diffuse thickening and septation of the gallbladder wall. **b** Resected gallbladder. On opening, the mucosa of the gallbladder shows ill-defined thickening, measuring about 3 × 2 cm, at the fundic area. Specimen after excision for port site recurrence (3 months later). The specimen consists of an irregular lump of soft tissue measuring 1.8 × 1.5 × 1 cm

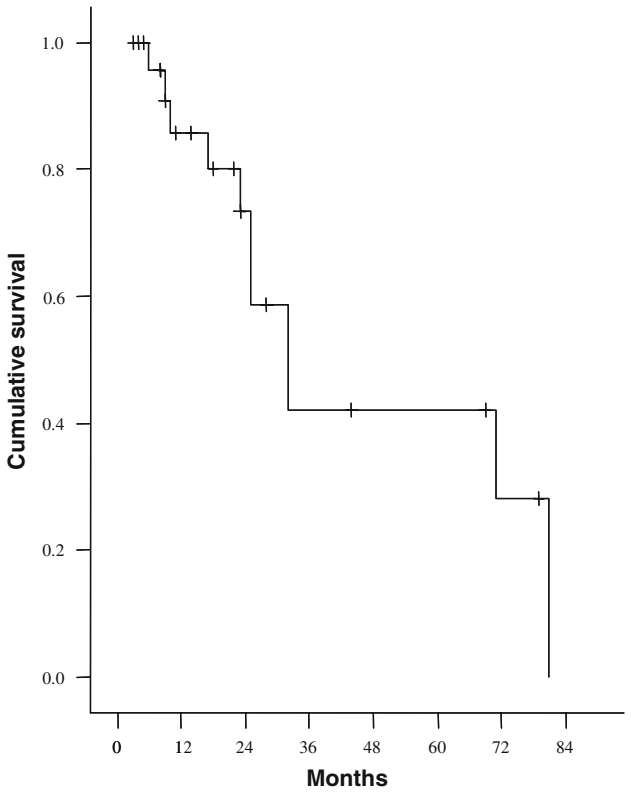

Fig. 2 Kaplan–Meier curves of survival

(4.1–34.1%) [5, 7, 22–25]. However, in some reports there are no detailed descriptions of AC [26]. What is worse is that preoperative diagnosis did not include AC in the study [27]. There are a few reports addressing the outcome of patients with gallbladder cancer presenting with AC [14–16]. A recent study carried out in Hong Kong showed a high incidence of gallbladder cancer with AC, and it indicated that long-term survival is possible in patients with early stage of the disease [13]. In the present study, we found that the presence of AC did not significantly influence the survival rate after LC. Nevertheless, a careful preoperative work-up and meticulous inspection of resected gallbladder are essential to detect gallbladder cancer in patients who undergo LC.

The treatment of UGC has been in dispute because of tearing of the gallbladder wall and bile spillage, which can increase the incidence of port site/peritoneal recurrence after LC [9–11, 19, 26]. However, many authors report that laparoscopic surgery may not worsen the prognosis of patients with UGC [5, 7, 23, 24, 28], although there are some opinions to the contrary [11, 29]. The incidence of port site/peritoneal recurrence of UGC ranges from 10 to 20% [3–6, 8, 30]. Because trocar-site recurrence or peritoneal dissemination appears early after the second operation [9–11], many authors recommend excision of the port site at the time of the second operation [5, 6, 29]. Moreover, several reports emphasize the conclusion that excision of the port site after recurrence may prolong survival [5, 29]. In contrast, Ricardo et al. [30] reported no significant difference in the incidence of port site/wound recurrence in patients undergoing different types of gallbladder operations (LC versus OC). In the present study, 2 cases of port site/wound recurrence occurred in two patients, one after LC and one after open conversion, suggesting that LC may not be associated with port site/wound recurrence. Sarli et al. [7] reported that none of their patients had port site recurrence after LC, even though they employed a plastic retrieval bag in only one case.

Analysis of survival after LC for UGC has been carried out by several authors. Wakai et al. [26] reported that gallbladder perforation during LC is associated with port site/peritoneal recurrence and worsens patient survival. Sarli et al. [7] reported that tumor stage and bile spillage are significantly correlated with prognosis. In the present study, however, we found that bile spillage was not associated with survival; the small number of cases may be a factor in this finding.

The survival rate of patients with UGC after LC is reported to be comparable with that of patients with UGC

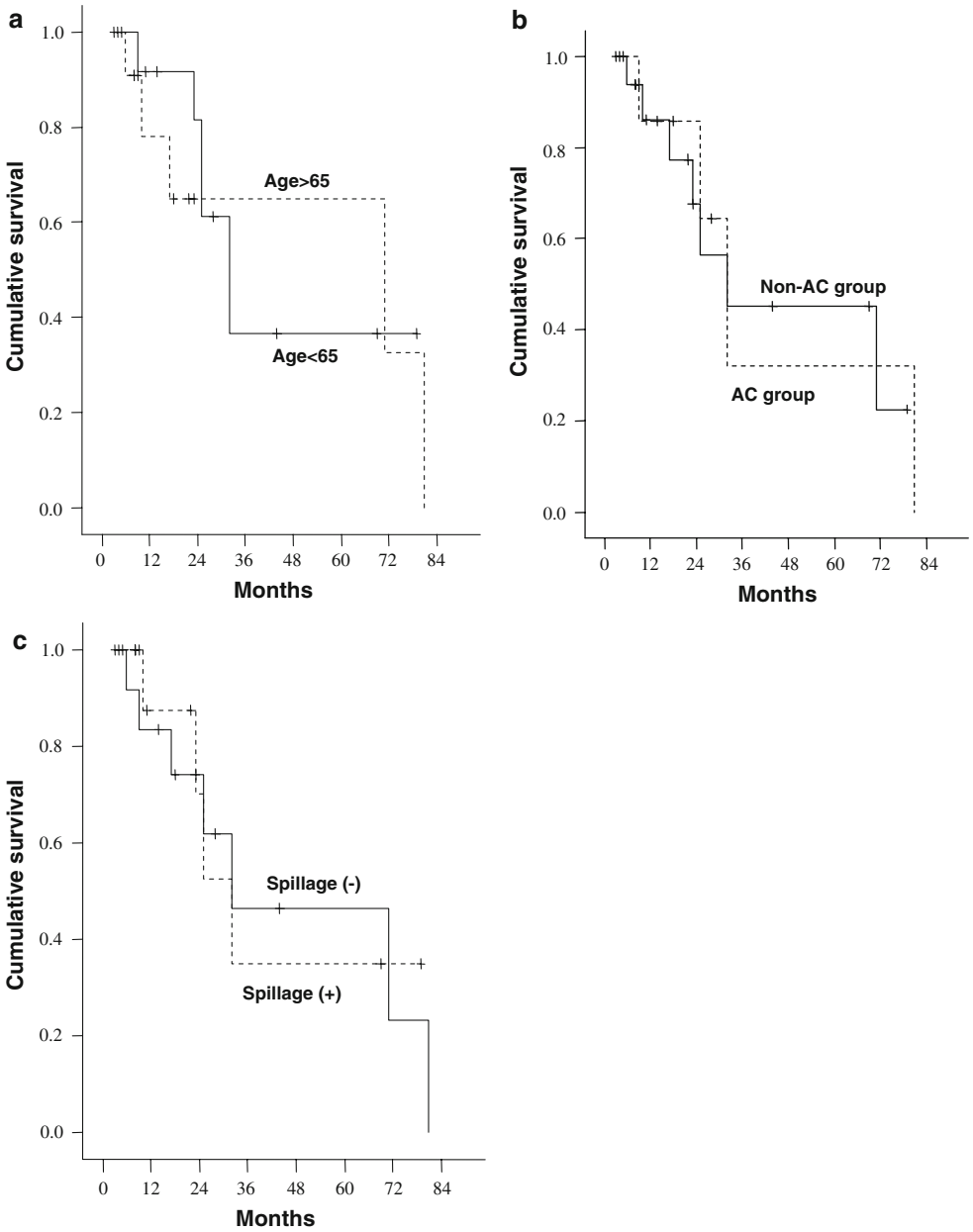

Fig. 3 Kaplan-Meier curves of survival. **a** Survival according to age ($P = 0.753$) **b** Survival according to the presence of acute cholecystitis ($P = 0.804$). **c** Survival according to bile spillage ($P = 0.905$)

after OC [19]. The 5-year survival rate after LC for UGC was 92% in patients with pT1 cancer and 59% in patients with pT2 cancer [5]. Cucinotta et al. [23] reported that the tumor stage is the most important prognostic factor. In the present study, however, tumor differentiation was found to be a significant prognostic factor.

To improve the prognosis of patients with T2 cancer, reoperation has been recommended after initial cholecystectomy by many investigators [5–7, 9]. Moreover, some authors report improved prognosis after the second operation for T2 cancer after LC [20, 25]. Among our patients, the frequency of reoperation was very low: Immediate reoperation was carried out in only two patients, both of whom had positive resection margins. In fact, our patients seemed reluctant to undergo reoperation, fearing death from cancer or from reoperation itself. The patient's general condition should be considered in deciding reoperation, and proper communication between surgeon and patient is needed.

In conclusion, we found that the number of UGC patients presenting with AC and pT2 was higher than reported in literatures. Survival was not associated with the presence of AC and bile spillage; however, tumor differentiation was associated with survival after LC for UGC. Therefore, we suggest that acute cholecystitis may not influence the prognosis of patients with unsuspected gallbladder cancer detected after laparoscopic cholecystectomy. Moreover, good tumor differentiation can guarantee

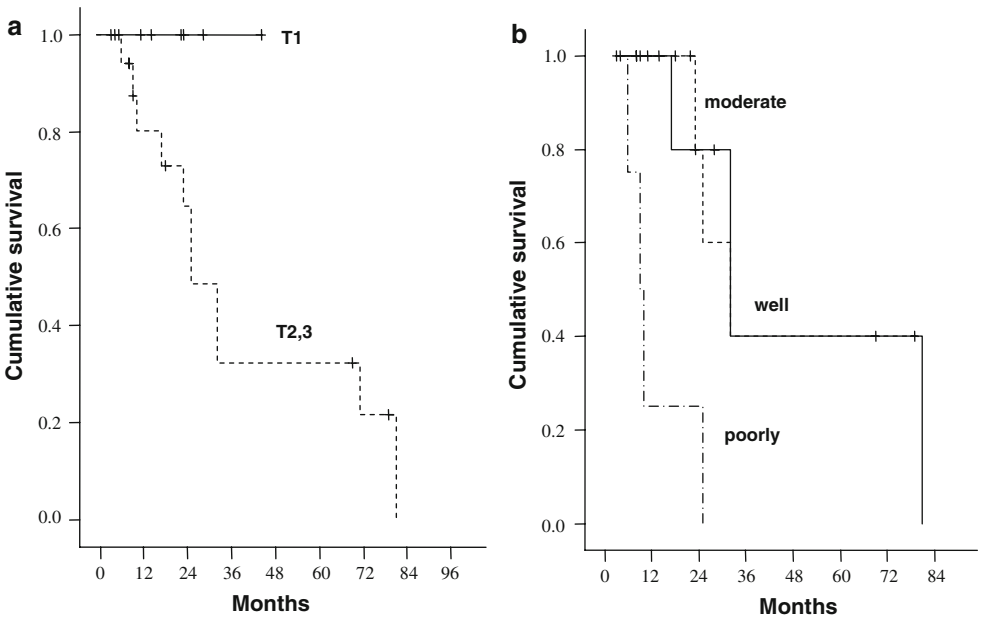

Fig. 4 Kaplan–Meier curves of survival. **a** Survival according to tumor stage ($P = 0.086$). **b** Survival according to tumor differentiation ($P = 0.005$)

good survival, even in unsuspected gallbladder cancer with acute cholecystitis.

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