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## ORIGINAL ARTICLE

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### Unsuspected Gallbladder Cancer During or After Laparoscopic Cholecystectomy

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**Key words:** laparoscopic cholecystectomy; gallbladder neoplasms; carcinoma; frozen sections; survival rate

**Objective** To summarize the clinical features and outcomes of unsuspected gallbladder carcinoma (UGC) detected during or after laparoscopic cholecystectomy.

**Methods** Medical records of 8005 patients, who underwent laparoscopic cholecystectomy in Peking Union Medical College Hospital between June 1993 and June 2011, were reviewed. Patients that pathologically diagnosed as UGC were retrospectively studied in terms of clinical features, preoperative and postoperative diagnosis, surviving period, and complications.

**Results** In the 8005 patients who received laparoscopic cholecystectomy, 36 (0.45%) were diagnosed as UGC during (25 patients) or after (11 patients) laparoscopic cholecystectomy. The gallbladder cancer was staged as T1 in 16 patients, T2 in 11 patients, and T3 in 9 patients. The 1-, 3-, and 5-year survival rates of all the patients were 88.9% (32/36), 63.9% (23/36), and 58.3% (21/36). The 5-year survival rates in T1 stage, T2 stage, and T3 stage patients were 100%, 75.0%, and 0.0%, respectively.

**Conclusions** The survival rate of UGC is associated with tumor stage, not with operation approaches. Laparoscopic cholecystectomy is appropriate for T1 patients.

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**W**ITH the advance of laparoscopic techniques, laparoscopic cholecystectomy (LC) has been widely popularized for its advantages of little trauma and quick recovery. Nowadays, early diagnosis of gallbladder carcinoma (GC) is still very difficult. The GC cases not diagnosed before surgery but confirmed unsuspectedly during or after LC are

called unsuspected gallbladder carcinoma (UGC).<sup>1</sup> Incidence of UGC is about 0.3%-2.9%.<sup>2,3</sup> However, controversy exists in whether LC will lead to tumor cell dissemination. It is reported that if UGC is found during LC, the risk of tumor spread or tumor implantation at trocar sites will be increased.<sup>4-6</sup> It is also reported, however, that the prognosis of GC after LC is not different from that after open cholecystectomy.<sup>7,8</sup> This retrospective study analyzed the clinical data of 36 UGC patients and reviewed relevant literatures.

## PATIENTS AND METHODS

### Patients

Patients who underwent LC between June 1993 and June 2011 in Peking Union Medical College Hospital were reviewed, and those diagnosed as having UGC were included. Clinical data including chief complaints, preoperative diagnosis, managements, postoperative diagnosis, and follow-up information were collected.

### Statistical analysis

Statistical analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). Descriptive analyses were used to characterize the study population. Survival analysis was performed using Kaplan-Meier method.

## RESULTS

In the period reviewed in the present study, 8005 cases of LC were performed in our hospital, among which 36 UGC (0.45%) were diagnosed during or after the operation, including 15 males and 21 females aged from 36 to 89 years (average, 64.7 years).

### Clinical features

Table 1 presents the clinical features of the UGC patients. Of the 36 UGC patients, 29 had complained about right upper quadrant pain, postprandial fullness and discomfort, and pain radiating to the back. The other 7 patients had no complaints of discomfort, and were all diagnosed as polypoid lesions of the gallbladder. Eight patients with fever and jaundice were diagnosed as multiple cholecystolithiasis due to the existence of bile duct stone, and the symptoms could be alleviated by conservative treatment. In the 36 patients, the longest history of upper abdominal pain was 25 years, and the shortest was 2 months (average, 84.2 months).

### Auxiliary examination

Liver function tests were performed for all the patients. The results showed normal liver function in 29 patients, and in the other 7 patients, alanine aminotransferase (maximum 77 U/L, normal range 5-40 U/L), aspartate aminotransferase (maximum 59 U/L, normal range 5-37 U/L), gamma-glutamyl transpeptidase (maximum 89 U/L, normal range 10-67 U/L), total bilirubin (maximum 32.6  $\mu\text{mol/L}$ , normal range 5.1-22.2  $\mu\text{mol/L}$ ), direct bilirubin (maximum 17.1  $\mu\text{mol/L}$ , normal range 0-8.6  $\mu\text{mol/L}$ ) were slightly increased.

**Table 1.** Clinical features of patients with unsuspected gallbladder carcinoma ( $n=36$ )

| Features                                 | Number of cases |
|------------------------------------------|-----------------|
| Gender                                   |                 |
| Male                                     | 15              |
| Female                                   | 21              |
| Pathological classification              |                 |
| T1                                       | 16              |
| T2                                       | 11              |
| T3                                       | 9               |
| General classification                   |                 |
| Polypoid lesion                          | 8               |
| Ulceration                               | 4               |
| Gallbladder wall thickening              | 9               |
| With cholecystolithiasis                 | 20              |
| Without cholecystolithiasis              | 16              |
| Intraoperative frozen pathology          |                 |
| Yes                                      | 27              |
| No                                       | 9               |
| Surgical approach                        |                 |
| LC                                       | 13              |
| LC+radical gallbladder carcinoma surgery | 20              |
| LC+laparotomy                            | 2               |
| LC (refuse second operation )            | 1               |
| Implantation at trocar sites             | 2               |
| Distant metastasis                       | 6               |
| Death                                    |                 |
| T1                                       | 0               |
| T2                                       | 3               |
| T3                                       | 11              |

LC: laparoscopic cholecystectomy

Tumor markers, including carbohydrate antigen 19-9 (CA19-9), carcino-embryonic antigen, and apha-fetoprotein, were tested in 12 patients, of whom 7 showed slightly increased level of CA19-9 (maximum 81 U/L, normal range 0-37 U/L).

Preoperative abdominal ultrasound scan revealed cholecystolithiasis in 22 patients, and 5 had stones larger than 3 cm in diameter. The ultrasound scan demonstrated thickening gallbladder walls in 8 patients, and single gallbladder polyp (9-26 mm in diameter) in 8 patients. Preoperative abdominal computed tomography was applied in 7 patients, which showed diffuse thickening of gallbladder walls with no space-occupying lesions, indicating chronic cholecystitis or gallbladder adenomyomatosis. Five patients with cholecystolithiasis or common bile duct stones received

endoscopic retrograde cholangiopancreatography, which showed normal gallbladder.

### Preoperative diagnosis

Preoperative diagnosis, such as cholecystolithiasis with cholecystitis, polypoid lesions of the gallbladder, gallbladder polyps, and adenomyomatosis were confirmed *via* imaging, such as abdominal computed tomography (Fig. 1), magnetic resonance imaging, and abdominal ultrasound.

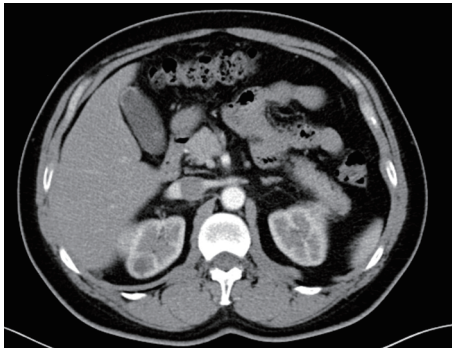


**Figure 1.** Preoperative computed tomographic scan of a patient shows diffuse gallbladder wall thickening.

### Postoperative diagnosis

Intraoperative frozen section examinations were applied when any of the following conditions existed: (1) shrinkage or ulceration in gallbladder mucosa; (2) local thickening over 4 mm at gallbladder wall; (3) replacement of normal gallbladder wall by connective tissue; (4) change in the color of gallbladder mucosa; (5) presence of polypoid lesions larger than 10 mm. Based on those criteria, intraoperative frozen section examinations were applied for 27 patients, and paraffin section examinations for all the 36 patients.

The results of frozen section examinations suggested that the gallbladder cancer in 8 patients was at stage T1 and LC was performed; the cancer in 9 patients was at stage T2 and open radical gallbladder carcinoma operation was performed accordingly; and in 8 patients was at stage T3, among which 6 received wedge resection of liver bed and regional lymph node dissection, 1 only received cholecystectomy due to widespread abdominal metastasis, and 1 underwent cholecystectomy, regional lymph node dissection, and common bile duct T tube drainage because the lesion was located at the neck of the gallbladder and the common bile duct lymph nodes were swollen. Intraoperative frozen section results in 2 patients suggested the need of paraffin section examination, and the results of paraffin section of the 2 patients showed gallbladder carcinoma at stage T2 and T3, respectively. They received

radical gallbladder carcinoma surgery 2 weeks after LC. The accuracy of intraoperative frozen section examination for UGC in the present study was 92.6% (25/27).

The other 9 patients did not have intraoperative frozen section examination, while postoperative paraffin section examination suggested gallbladder carcinoma. According to the results of postoperative paraffin section examination, 5 patients had stage T1 cancer and no further treatments were adopted, 2 had stage T2 cancer and thus received wedge resection of liver bed and regional lymph node dissection 2 weeks after LC, and the other 2 had stage T3 cancer, of whom 1 underwent wedge resection of liver bed and regional lymph node dissection, and the other one gave up operation due to advanced age (88 years old) without conservative therapy.

### Follow-up information

The patients were followed up for 4-144 months (average, 63.0 months). The total 1-, 3-, and 5-years survival rate of all the patients was 88.9% (32/36), 63.9% (23/36), and 58.3% (21/36), respectively. The 5-years survival rate of T1, T2, and T3 patients was 100.0%, 75.0%, and 0.0%, respectively (Fig. 2). The patient having the longest period of survival (144 months) was in stage T1. Three patients who had stage T2 gallbladder carcinoma were dead 16, 23, and 39 months after the operation, respectively. The mean survival time of stage T3 patients was  $14.1 \pm 5.9$  months, with the longest survival time in those patients being 24 months.

### Complications

Two patients had tumor implantation at laparoscopic trocar sites (1 having T2 cancer and the other having T3 cancer). The T2 patient had a reoperation to excise the tumor implantation and survived for 16 months. The T3 patient gave up surgery and survived for another 8 months.

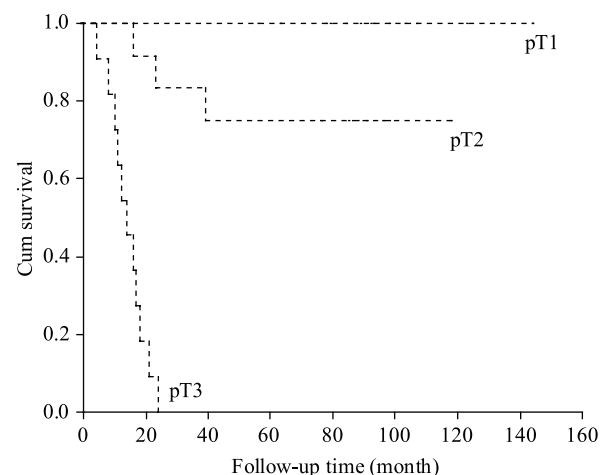


**Figure 2.** Kaplan-Meier survival rate of the patients with gallbladder carcinoma at different T stages.

## DISCUSSION

The incidence of gallbladder cancer is low. In the cases receiving cholecystectomy, 0.3%-1.5% are gallbladder carcinoma, and the incidence of UGC in those who receiving LC is 0.3%-2.9%.<sup>1-3,9</sup> In this retrospective study, the incidence of gallbladder carcinoma in LC-treated patients was 0.45%, of which 22 cases were diagnosed as cholecystolithiasis with cholecystitis, 8 cases as polypoid lesions of the gallbladder, 4 cases as cholecystolithiasis with polyps, and 2 cases as gallbladder adenomyomatosis before the operation. The clinical manifestations of cholelithiasis and cholecystitis are similar, which are also similar with the clinical manifestations of gallbladder cancer, making it difficult to diagnosis gallbladder cancer at an early stage.

Early preoperative diagnosis of gallbladder carcinoma with ultrasound or computed tomography is quite a challenge. Therefore during LC, gross observation to differentiate the gallbladder benign lesions from gallbladder carcinoma and intraoperative frozen section examination are important. If mucous changes or thickening of gallbladder wall are noticed during LC, frozen sections are needed. Aoki *et al*<sup>10</sup> reported that 7 cases were found to have gallbladder cancers in 990 cases receiving LC because of cholecystolithiasis, but the pathological results of intraoperative frozen section examination in the 983 benign cases showed that 4 had severe epithelial dysplasia. Therefore, it is difficult to distinguish gallbladder carcinoma *in situ* and atypical hyperplasia of gallbladder mucosa.<sup>11</sup>

In this study, the accuracy of intraoperative frozen section pathological examination was 92.6% (25/27). The previously reported accuracy of intraoperative frozen section pathology to assess the depth of the tumor infiltration was 70%-86%.<sup>12,13</sup> Therefore, the diagnosis based on frozen section pathological examination is not always accurate, probably because this examination can not cover the whole lesion of the gallbladder.

The surgical approach for gallbladder carcinoma, based on the depth of the tumor infiltration (T stages), determined the outcome of therapy to a great extent.<sup>14</sup> For the gallbladder carcinoma of T1 stage, simple LC is enough. In this study, the cases of stage T1 gallbladder carcinoma showed no recurrence or metastasis after LC. As for the gallbladder carcinoma of T2 stage, controversy exists in whether a radical resection is necessary.<sup>3,10</sup> According to the results of this study, a radical resection is beneficial for stage T2 patients, but not for stage T3 patients.

The incidence of gallbladder carcinoma implantation at trocar sites or abdominal implantation after LC is between

14%-20%.<sup>15,16</sup> In this study, there were 2 cases of tumor implantation at trocar sites (5.6%). It was reported that there is no difference in the recurrence of abdominal tumor implantation between LC and open cholecystectomy (OC) or LC-conversion-to-OC, and the operation strategies have no effect on prognosis.<sup>16,17</sup> It was also reported that the prognosis of UGC was not worse than gallbladder cancers found after OC.<sup>18,19</sup> The causes of tumor implantation at trocar sites include the damage of gallbladder wall and the wide use of the electrocautery in LC. To avoid trocar implantation of tumor, electrocautery should be less used and injury to the gallbladder wall avoided.<sup>20</sup> It was reported that the prognosis of patients is closely related to the tumor staging and the bile leakage, but not to the type of surgical approach.<sup>19,21</sup> Using retrieval bag during the operation appeared to be able to prevent tumor implantation at trocar sites.<sup>22</sup>

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