Original Article

Unsuspected Gallbladder Cancer: A Clinical Retrospective Study

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Abstract

Background: The morbidity of unsuspected gallbladder carcinoma (UGC) has increased. This study was aimed to explore the factors which may influence the therapeutic strategies and prognosis of UCG. Additionally, long-term prognosis of laparoscopic and open surgeries of UGC was comparatively investigated.

Methods: Thirty-eight cases of UGC were enrolled in this study. Statistical analysis of survival was performed using the Kaplan–Meier test and the results were examined using the log-rank test.

Results: The morbidity of UGC was 0.43 %. The cancer stagings were: pT1a (one), pT1b (11), pT2 (14), pT3 (10), pT3N1 (one), and pT4 (one). The median lifespan of the entire cohort was 20.0 ± 6.5 months, one-year survival rate was 44 %, and five-year survival rate was 11 %. One-year recurrence- free survival rate was 44 % and three-year recurrence- free survival rate was 0 %. Twenty-eight patients sustained cancer recurrence and three patients sustained port-site cancer recurrence. The cancer staging ($P < 0.01$) and radical resection ($P < 0.01$) were independent factors for both overall and recurrence-free survival. Radical resection improved the prognosis of the patients with pT2 stage UGC ($P < 0.05$), but no significant impact on the prognosis of the patients with pT1b ($P = 0.362$) or pT3 stage ($P = 0.221$) UGC. Survival rates were not significantly affected by the first operation no matter it was laparoscopic surgery or open surgery ($P = 0.12$).

Conclusion: Radical resection surgery is recommended in pT2 stage UGC. There is no difference for the long-term prognosis between laparoscopic surgery (cholecystectomy) and open surgery of UCG.

Keywords: Laparoscopic cholecystectomy, open cholecystectomy, unsuspected gallbladder carcinoma

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Introduction

Gallbladder cancer is a very common cancer in the digestive system. In China, gallbladder cancer is the 16th most commonly diagnosed cancer. But due to its highly invasive characteristics and poor early diagnostic rate, the prognosis of gallbladder cancer is relatively poor.[1] The unsuspected gallbladder cancer (UGC) or incidentally detected gallbladder cancer refers to the cancer which is diagnosed by pathologic examination during or after the cholecystectomy. With the increasing number of cholecystectomies, reported cases of UGC have increased. The morbidity rate is between 0.2 % – 0.91 %.[2–7]

The cancer staging is usually determined with TNM stage according to UICC/AJCC criteria. This staging is considered to be one of the independent factors for the overall survival.[5,8] Radical resection surgery which is defined as cholecystectomy plus wedge resection of the liver and regional lymphadenectomy (lymph nodes in the ligamentum hepatoduodenale) is a common treatment for gallbladder carcinoma.[9] But whether the radical resection should be carried out for the patients with UGC and whether it could confer better prognosis are still under debate.

In this study, we aimed to explore the factors which may influence the prognosis of UCG patients including the TNM staging, radical resection, age, and the differentiation of cancer. Additionally, long- term prognosis of laparoscopic and open surgeries of UGC was also considered.

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Patients and Methods

General information

From January 2006 through December 2012, 38 patients with UGC were enrolled. Within this cohort, 10 were diagnosed during or post-laparoscopic cholecystectomy (LC) and 28 patients were diagnosed after open cholecystectomy (OC). All the patients were followed up via telephone, until April 2013, the clinical follow-up rate was 92.1 %.

Statistical analysis

Cox multiple factors analysis model was used to test the factors that impact lifespan. Statistical analysis of survival was performed by the Kaplan–Meier test and the results were examined using the log-rank test. A P-value less than 0.05 was considered statistically significant.

Results

Clinical information

Eighteen patients had primary cholecystectomy surgery in our hospital (LC: eight cases, OC: 10 cases). Twenty patients took the primary surgery in other hospitals and sought further diagnosis and therapy in our hospital. The total number of cholecystectomy surgery between January 2006 and January 2013 was 4221 cases, the total morbidity of UCG in our hospital was 0.43 % (LC: 1666 cases, the morbidity was 0.48 %; OC: 2556 cases, the morbidity

Table 1. Surgical method for the patients

	LC UGC	OC UGC	Total
Only cholecystectomy	5	24	**29**
Radical resection during the first operation	1	0	**1**
Radical resection during the second operation	4	4	**8**
Total	**10**	**28**	- - -

Table 2. Cox multiple factors analysis for overall survival

	β	Standard Error	Wald	df	P-value	relative risk
Age	0.053	0.552	0.009	1	0.923	1.055
Differentiation	0.451	0.405	1.237	1	0.266	1.569
TNM staging	1.044	0.328	10.104	1	0.001	2.841
Radical resection	2.786	1.070	6.780	1	0.009	16.213

Table 3. Cox multiple factors analysis for recurrence-free survival

	β	Standard Error	Wald	df	P-value	relative risk
TNM staging	1.866	0.712	6.861	1	0.009	6.461
Radical resection	1.287	0.346	13.822	1	0.000	3.621
Age	0.394	0.394	0.998	1	0.318	1.483
Differentiation	0.224	0.604	0.137	1	0.711	1.251

Table 4. Overall survival with different UGC staging

	Case number	One-year survival rate	Patients still alive	Longest survival lifespan (month)
pT1a	1	- - -	1	12
pT1b	11	73 %	8	42
pT2	14	37 %	4	60
pT3	10	20 %	3	44
pT3N1	1	- - -	1	52
pT4	1	- - -	0	2

was 0.39 %).

Seven male and 31 female patients were enrolled, the median age was 61.23 years (the youngest age: 37 years, the oldest age: 87 years). The courses of disease lasted between two months to 15 years. Clinical symptoms mainly included right upper quadrant abdominal pain: 36 cases, mild jaundice: one case, and fever: one case. The ultrasonographic diagnosis included multiple cholecystolithiasis: 25 cases, single cholecystolithiasis: eight cases, polyp: three cases, hydrops: two cases. Two of the patients had a positive test of CA19-9. No patient had a history of malignant tumor. The admitting diagnosis before cholecystectomy was chronic calculous cholecystitis for 35 patients and polyps of the gallbladder for three cases.

All the patients received surgical treatment. Twenty-nine patients had only cholecystectomy, one patient took radical resection during the first operation, eight patients received a second operation for radical resection within four to 30 days after cholecystectomy (Table 1). TNM staging was determined according to the International Union Against Cancer criteria. The numbers of UCG patients with different stages were: pT1a one case (2.6 %), pT1b 11 cases (29.1 %), pT2 14 cases (36.8 %), pT3 10 cases (26.3 %), pT3N1 one case (2.6 %), and pT4 one case (2.6 %). The pathology diagnoses were: well-differentiated adenocarcinoma in nine cases, moderately-differentiated adenocarcinoma in 19 cases, and poorly- differentiated adenocarcinoma in nine cases.

Survival analysis

The median lifespan for the entire cohort was 20.0 ± 6.5 months, one-year survival rate was 44 %, three- year survival rate was 39 %, and five-year survival rate was 11 %.

The meadian recurrence-free lifespan was 19.0 ± 5.9 months, one-year recurrence-free survival rate was 44 %, and three-year recurrence-free survival rate was 0 %. Recurrence-free lifespan was defined as the survival time before cancer recurrence was diagnosed by medical imageology tests.

Twenty-eight patients (17 OC UGC and 11 LC UGC patients) sustained cancer recurrence: cancer recurrence as local erosion on the liver was found in 11 patients; intrahepatic metastasis in six patients; lymph metastasis in eight patients, and port-site cancer recurrence in three patients (all three were LC UGC) (Figure 1).

Factors affecting survival

Analysis by the Cox modal: the TNM staging ($P < 0.01$) and radical resection ($P < 0.01$) were the independent factors for overall survival; however, age ($P = 0.923$) and differentiation of the cancer ($P = 0.266$) were not (Table 2).

The TNM staging ($P < 0.01$) and radical resection ($P < 0.01$) were the independent factors for recurrence-free survival; however, age ($P = 0.318$) and differentiation of the cancer ($P = 0.711$) were not (Table 3).

Survival analysis with different UGC staging

One patient with pT1a staging UGC had cholecystectomy without radical resection. His recurrence-free survival lifespan was 12 months and currently is alive without relapse. The one-year survival rate of 11 patients with pT1b stage UGC was 73 %; up until the completion of this study, eight patients are still alive and the longest survival lifespan is 41 months. The one-year survival rate of 14 patients with pT2 stage UGC was 37 %; up until the completion of this study, four patients are still alive and the longest

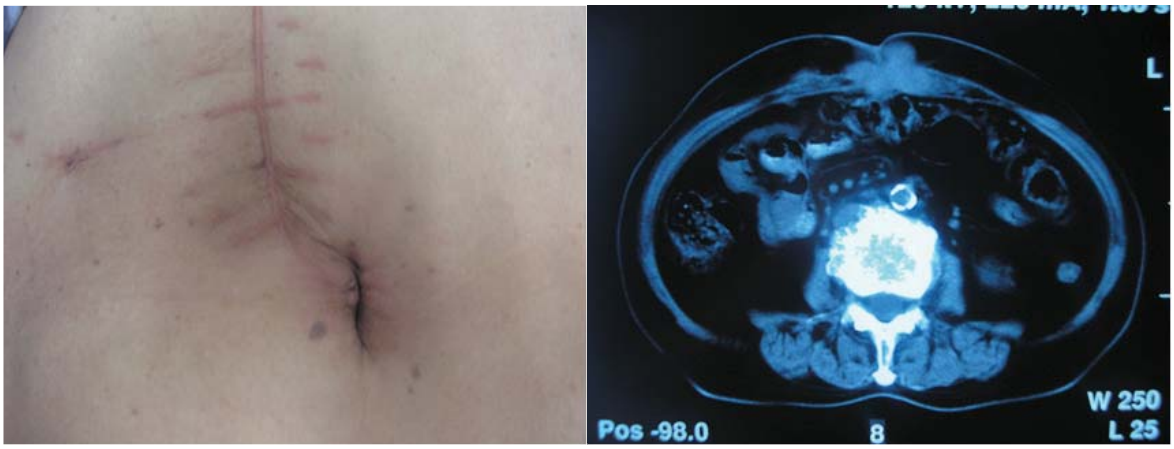

Figure1. Port-site recurrences of the UGC.

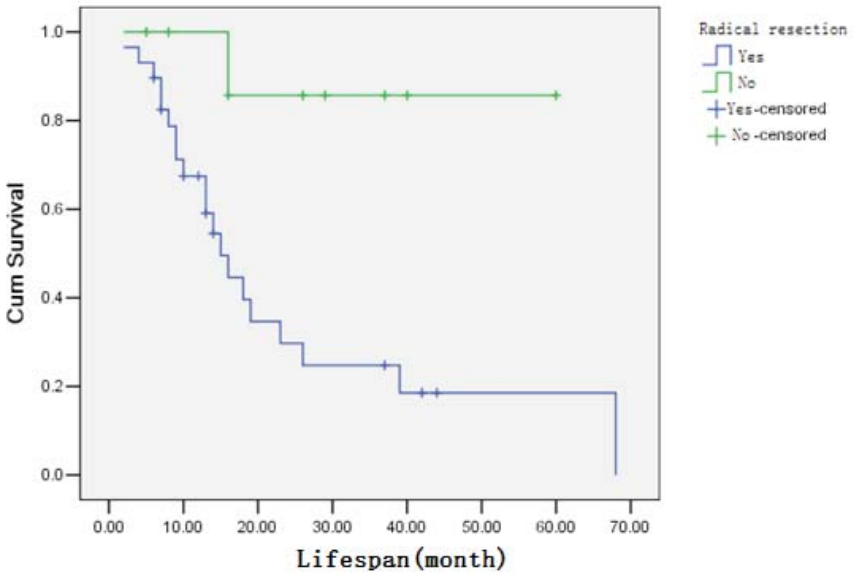

Figure 2. Survival curve for patients with or without radical resection.

survival lifespan is 60 months. The one-year survival rate of 10 patients with pT3 stage UGC was 20 %; up until the completion of this study, three patients are still alive and the longest survival lifespan is 44 months. One patient who had pT3N1 stage UGC was 60 years old and took the radical resection within six days after LS. Four years later she was diagnosed with abdominal lymph node metastasis and treated with chemotherapy. She is currently alive. One patient had pT4 stage UGC with rectum erosion and he died two months after the OC (Table 4).

Radical resection and the prognosis

Using the log-rank test, the radical resection had a predominant impact on the prognosis of the patients with UGC ($P < 0.01$). The patients who undertook the radical resection surgery had a better prognosis (Figure 2).

Analysis with the log-rank test showed that the radical resection had a significant impact on the prognosis of the patients with pT2 stage UGC ($P < 0.05$). The patients who undertook the radical resection surgery had a better prognosis. Radical resection had no impact on the prognosis of patients with pT1b ($P = 0.362$) or pT3 stage ($P = 0.221$) UGC.

Prognosis of LC and OC UGC

For the 10 LC UGC patients and the 28 OC UGC, the one-year survival rate was 50 % and 42.8 %, respectively. There was no statistically significant difference for the long-term prognosis between all LC and OC UGC patients ($P = 0.12$), (Figure 3). Additonally, there was no statistically significant difference for the long-term prognosis between LC and OC patients with pT1b ($P = 0.30$) and pT3 stage ($P = 0.95$). However, LC UGC patients with pT2 stage had a better survival rate ($P = 0.03$).

Discussion

One of the underlying reasons that why UGCs are currently difficult to diagnose early is due to a lack of specific clinical symptoms.[10] Without certain biologic markers and imaging characteristics, the laboratory and radiologic examinations usually

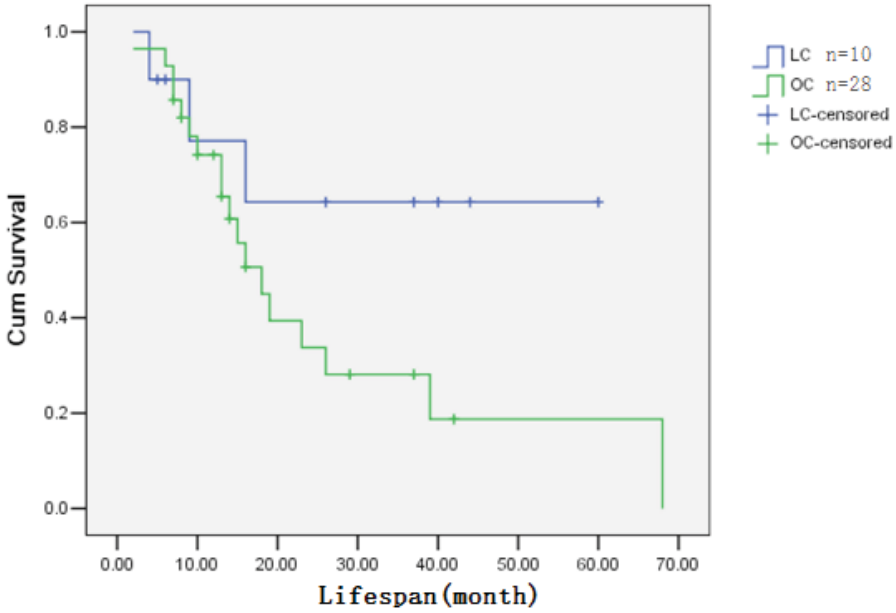

Figure 3. Survival curve for all patients with LC and OC.

cannot provide sufficient information for diagnosis. Kokudo, et al. reported that the diagnostic rate with the radiologic examinations for pT1 stage cancer is 37.2 % and for pT2 stage caner is 33.9 %.[11] Assaying for telomerase reverse transcriptase mRNA and cytology using bile obtained by endoscopic transpapillary catheterization into the gallbladder has the potential for early diagnosis.[12] However, this procedure needs a very high-level skill of endoscopic retrograde cholangiopancreatography which may limit its practicality. During cholecystectomy, UGC is still very hard to detect even with frozen section test. The overall diagnostic rate is less than 10 %. Cavallaro, et al. reported only one out of 10 UGC patients were detected by the frozen section test.[3] Another study reported that amongst 297 UGC cases, only four cases were diagnosed by the frozen section test.[13] In our study, only one case out of 38 patients was detected during the cholecystectomy by the frozen section test.

As we discussed before, the UGC is difficult to be detected both before and during the cholecystectomy surgery; the question whether the surgeons should do the secondary radical resection surgery is strongly concerned. In our study, we found that the radical resection had a good impact on the prognosis of the UGC by analyzing the survival of all the patients. But more attention is paid to the patients who already have neoplastic metastasis, and their prognosis after the radical resection surgery. A routine is to make the surgery plan with the UGC staging.[14]

Most of the studies show that patients with pT1 stage UGC have a good prognosis with primary cholecystectomies.[15,16] The patient with pT1 stage in our cohort had a similar prognosis. In other studies, hepatic partial resection and lymph node excision surgery for patients with pT1b stage UGC is recommended.[17] However, Wakai, et al. performed a long-term clinical trial for 25 pT1b stage UGC patients with a 95- month follow-up and found no difference between patients who undertook the radical resection and ones who did not.[18] In our study, we also found that the radical resection had no influence on the prognosis of the patients with pT1b stage UGC. Therefore, it is necessary to perform studies with large sample size and longer follow-ups to determine the treatment strategy for the pT1b stage UGC.

The majority of retrospective studies show that it is necessary for pT2 stage UGC patients to have the radical resection surgery.[19] Kiyoaki, et al. enrolled 498 patients with UGC and found a better prognosis for the pT2 stage patients who underwent the radical resection.[15] Pawlik, et al. performed a retrospective research including 115 UGC patients and reported that 10 % of the pT2 patients had liver invasion and 30 % had lymphatic metastasis.[20] They strongly recommended performing the radical resection for these patients. In our cohort, two out of 14 patients had pT2 stage UGC and the patient who took the radical resection had a better prognosis.

A small number of studies shows that patients with T3 or T4 stage UGC have a better prognosis if they have radical resection surgery. Yi, et al. found that radical resection showed a significant benefit in overall survival for the pT3 group.[17] On the contrary, we found that the radical resection had no influence on the prognosis of the patients with pT3 stage UGC. One study in Japan shows a 19 % in-hospital mortality for the patients with stage IV of gallbladder cancer after radical resection surgery.[9,21] Therefore, such surgical intervention for T3 or T4 stage UGC patients should be considered.

LC UGC is inherently considered to have a worse prognosis than OC UGC, because LC UGC has a high risk (7 % – 17.1 %) of port-site or local recurrence decreasing the overall survival.[13,22–24]. Povoski, et al. compared 210 OC and 60 LC UGC; the local recurrence rate was 6.5 % and 15 %, respectively.[25] The mechanisms of port-site recurrence after LC are attributed to carbon dioxide pneumoperitoneum,[24,26] trocar displacement,[24] and rupturing gallbladder[11] during the surgery. The one-year survival rate of patients with port-site recurrence is less than 30 %.[23,25] In our study, three patients suffered from this problem and only one of them survived over one year. Radical resection surgery is highly recommended if port-site recurrence is diagnosed.[25,27]

In the last few years, a series of studies demonstrated that the

overall survival of OC and LC UGC is almost similar. Sarli, et al. performed a retrospective clinicopathologic study on 9 LC and 11 OC UGC patients. The results showed that there was no statistically significant relation between survival rate and the primary surgery.[28] Ouchi, et al. analyzed the five-year survival rates of 498 LC UGC patients and found that LC did not have any adverse effects on the long-term outcomes of the patients with pT1a (99 % for LC and 100 % for OC), pT1b (95 % for LC and 75 % for OC), pT3 (20 % for LC and 17 % for OC), and pT4 (0 % for LC and 0 % for OC) UGC[15]. Cucinotta, et al. study of five LC and eight OC UGC patients and de Aretxabala, et al. follow-up of 24 LC and 40 OC UGC patients also reported the same conclusion that LC does not worsen the prognosis of UGC.[29,30] Goetze, et al. compared the five-year survival rates of the three groups of patients: 492 underwent LC, 200 underwent OC, and 142 initially underwent LC and converted to OC. They found that LC was associated with a better survival, the five-year survival rates for the three groups were 37 %, 25 %, and 29 %, respectively.[5] In our study, we found no significant difference for the total survival comparison between LC and OC UGC but a better survival for the pT2 stage LC UGC patients. Most of the pT2 stage LC UGC patients took the radical resection which may lead to a better prognosis.

In conclusion, the radical resection shows a significant benefit in overall survival for the patients with pT2 stage UGC. There is no difference for the long-term prognosis between LC and OC UCG, but if port-site recurrence is diagnosed, the radical resection surgery is recommended.

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