



Radical Second Resection Provides Survival Benefit for Patients with T2 Gallbladder Carcinoma First Discovered after Laparoscopic Cholecystectomy

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Abstract. Port site recurrence or peritoneal seeding is a fatal complication following laparoscopic cholecystectomy for gallbladder carcinoma. The aims of this retrospective analysis were to determine the association of gallbladder perforation during laparoscopic cholecystectomy with port site/peritoneal recurrence and to determine the role of radical second resection in the management of gallbladder carcinoma first diagnosed after laparoscopic cholecystectomy. A total of 28 patients undergoing laparoscopic cholecystectomy for gallbladder carcinoma were analyzed, of whom 10 had a radical second resection. Five patients had recurrences; port site/peritoneum recurrence in 3 and distant metastasis in 2. The incidence of port site/peritoneal recurrence was higher in patients with gallbladder perforation (3/7, 43%) than in those without (0/21, 0%) ($p = 0.011$). The outcome after laparoscopic cholecystectomy was worse in 7 patients with gallbladder perforation (cumulative 5-year survival of 43%) than in those without (cumulative 5-year survival of 100%) ($p < 0.001$). Among 13 patients with a pT2 tumor, the outcome after radical second resection (cumulative 5-year survival of 100%) was better than that after laparoscopic cholecystectomy alone (cumulative 5-year survival of 50%) ($p = 0.039$), although there was no survival benefit of radical second resection in the 15 patients with a pT1 tumor ($p = 0.65$). In conclusion, gallbladder perforation during laparoscopic cholecystectomy is associated with port site/peritoneal recurrence and worse patient survival. Radical second resection may be beneficial for patients with pT2 gallbladder carcinoma first discovered after laparoscopic cholecystectomy.

Since the first report by Drouard et al. [1] in 1991, port site and/or peritoneal (port site/peritoneal) recurrence has been recognized as a major problem associated with laparoscopic cholecystectomy (LC) for gallbladder carcinoma [2–5]. Although it usually occurs among patients with pathologic T2 (pT2) or more advanced tumors [6, 7], recently cases of such recurrence among those with early (pT1) lesions have been reported [2, 3, 8–21]. Suzuki et al. [6] demonstrated a significant association between gallbladder perforation during LC and port site/peritoneal recurrence, whereas others argue against this association [16, 22]. Thus, controversy remains regarding the risk associated with gallbladder perforation during LC and later recurrence.

Clinically overt gallbladder carcinoma is often far advanced and beyond the scope of resection [23]. In contrast, gallbladder carcinoma unsuspected before cholecystectomy tends to be in the early

stages, most of the cases of unsuspected cancer belonging to category pT1 or pT2 [2, 23]. In 1992, we clarified that radical second resection provides a survival benefit for patients with gallbladder carcinoma discovered after open cholecystectomy [23]. Whether radical second resection is also effective for unsuspected carcinoma discovered after LC remains unclear, although a few reports have dealt with this issue [7, 24].

The aims of this retrospective analysis were to examine the association of gallbladder perforation with port site/peritoneal recurrence and to determine whether radical second resection is beneficial for patients with gallbladder carcinoma first discovered after LC for presumed benign disease.

Patients and Methods

Patients

A total of 165 patients with gallbladder carcinoma underwent surgical resection at Niigata University Medical Hospital and its affiliated institutions between June 1992 and July 1999. Of these patients, 28 (17%) had gallbladder carcinoma first diagnosed after LC for presumed benign disease; these patients formed the basis of this study, including 9 men and 19 women with ages ranging from 49 to 91 years (median age, 72 years).

Preoperative Assessment

All patients underwent ultrasonography before LC. Intravenous cholangiography, computed tomography, and/or endoscopic retrograde cholangiography was also performed when considered necessary. The preoperative diagnosis was gallstone disease in 24 patients, gallbladder polyps in 3, and both gallstone disease and polyps in 1.

Laparoscopic Procedure

A standard four-port technique with pneumoperitoneum was used. In one patient, LC was converted to open surgery owing to severe inflammation despite no suspicion of tumor. Gallbladder

perforation occurred in 7 of 28 patients (25%), during dissection of the viscus in 6 patients and during retrieval of the viscus in 1. Malignant disease was not suspected during the laparoscopic procedure in any patient. No retrieval bag was used in any of our patients.

Histologic Examination of Laparoscopically Resected Specimens

Laparoscopically resected specimens were submitted to the Department of Pathology in our institution for histologic examination. Depth of invasion was determined by examination of multiple sections of the whole lesion in each patient and was described according to the tumor-nodes-metastases staging system [25]. The sections were embedded in paraffin, sliced into 3- μ m-thick sections, and stained with hematoxylin and eosin (H & E). Depth of invasion was pathologic T1a (pT1a) in 13 patients, pT1b in 2, and pT2 in 13. Microscopic lymphatic vessel invasion was found in 6 patients, microscopic blood vessel invasion in 7, and perineural invasion in 3. None of the patients with pT1 tumors had such invasion. The primary tumor was adenocarcinoma in all patients. Histopathologic grade was well differentiated in 25 patients, moderately differentiated in 2, and poorly differentiated in 1. There were 9 cases in which the cholecystectomized specimen included a cystic lymph node. Metastasis to the lymph node was found in 3 patients with pT2 tumors. Resection margin status was negative in all specimens.

Procedures for Radical Second Resection

After gallbladder carcinoma was diagnosed histologically following LC, a radical second resection was performed in 10 patients, including 2 with a pT1a tumor, 1 with a pT1b tumor, and 7 with a pT2 tumor. Surgeons in our hospital and its affiliated institutions, based on the results of our previous studies [23, 26], consider that pT2 gallbladder cancer discovered after cholecystectomy is an indication for radical second resection. In this series, all the 13 patients with pT2 tumors were advised to have a radical second resection, and 7 of them consented to it. Some surgeons involved in this study think that pT1 tumor is also an indication for radical second resection, while others do not. This explains why 3 patients with pT1 tumor underwent radical second resection in this series. The interval between initial LC and radical second resection ranged from 9 to 140 days (median 53 days).

A radical second resection was defined as an additional resection with radical lymphadenectomy, including wedge resection of the gallbladder bed in 3 patients, resection of the extrahepatic bile duct in 4, and combined resection of the gallbladder bed and the extrahepatic bile duct in 3. The extent of regional lymph node dissection included the lymph nodes in the hepatoduodenal ligament and those posterosuperior to the head of the pancreas [23, 26]. No patients received paraaortic lymph node dissection. Excision of the port sites at the time of radical second resection was not performed in any of our patients.

Histologic Examination of Radical Second Resection Specimens

Multiple tissue sections of the resected liver and bile ducts were examined histologically. No cancer involvement was found in

these sections. A total of 93 dissected regional lymph nodes (median; 10 per patient) were examined histologically. One representative section per node was examined for metastasis using H & E staining. A total of 3 positive lymph nodes from 2 patients with a pT2 tumor were found. The positive nodes were the pericholedochal nodes in 1 patient and the peripancreatic nodes in 1. Resection margin status was negative in all patients.

Postoperative Follow-up

Although there were no in-hospital deaths after LC, there was one in-hospital death from disseminated intravascular coagulation after radical second resection for a pT1a tumor. Recurrences were found in 5 (18%) of the 28 patients. The initial sites of recurrence were the port site in 1 patient, the peritoneum in 1, the port site and peritoneum in 1, and distant organs in 2. Thus, the incidence of port site/peritoneal recurrence was 11% (3/28) in this series. Among the 18 patients undergoing an LC alone, 4 died of recurrent gallbladder disease, 2 died of other causes with no recurrent disease, and 12 were alive with no evidence of recurrent disease. Among the 10 patients undergoing a radical second resection, 2 died of other causes with no recurrent disease and the other 8 were alive with no evidence of recurrent disease. No patients underwent adjuvant chemotherapy or radiotherapy. Patients were regularly followed in outpatient clinics every 3 to 6 months. The follow-up periods ranged from 9 to 103 months (median, 68 months).

Statistical Analysis

Medical records and survival data were obtained for all 28 patients. The cause of death for the 8 patients who died was determined from medical records. Survival time was defined as the interval from the date of LC. Survival curves were constructed using the Kaplan-Meier method. Patients who died from other causes were treated as censored cases. Differences in survival were evaluated using the log-rank test. Fisher's exact test was used to test the association between two variables. Statistical evaluation was performed using the SPSS 9.0J (SPSS Japan Inc., Tokyo) software package. A p value < 0.05 was considered statistically significant.

Results

The clinicopathologic characteristics of 18 patients who underwent LC alone were comparable with those of 10 patients who underwent radical second resection (Table 1).

Impact of Gallbladder Perforation on Port Site/Peritoneal Recurrence and Patient Outcome

The incidence of port site/peritoneal recurrence was significantly higher in patients with gallbladder perforation (3/7, 43%) than in those without (0/21, 0%) ($p = 0.011$). The outcome after resection was significantly better in 21 patients without gallbladder perforation (cumulative 5-year survival of 100%) than in 7 with (43% survival) ($p < 0.001$).

Table 1. Clinicopathologic characteristics of 28 patients with laparoscopically discovered gallbladder carcinoma.

Variable	LC alone (n = 18)	Radical resection (n = 10)	p
Age (years)			
< 70	8	4	
≥ 70	10	6	> 0.999
Gender			
Male	6	3	
Female	12	7	> 0.999
Gallstone			
Absent	1	1	
Present	17	9	> 0.999
Gallbladder perforation			
Absent	12	9	
Present	6	1	0.364
pT classification ^a			
pT1	12	3	
pT2	6	7	0.114
Histologic grade ^a			
Well differentiated	16	9	
Moderately to poorly differentiated	2	1	> 0.999
Tumor size (cm)			
< 6.0	10	4	
≥ 6.0	8	6	0.695
Lymphatic vessel invasion			
Absent	16	6	
Present	2	4	0.147
Blood vessel invasion			
Absent	15	6	
Present	3	4	0.207
Perineural invasion			
Absent	17	8	
Present	1	2	0.284
Resection margin status			
Negative	18	10	
Positive	0	0	> 0.999

LC: laparoscopic cholecystectomy; pT classification: pathologic primary tumor classification.

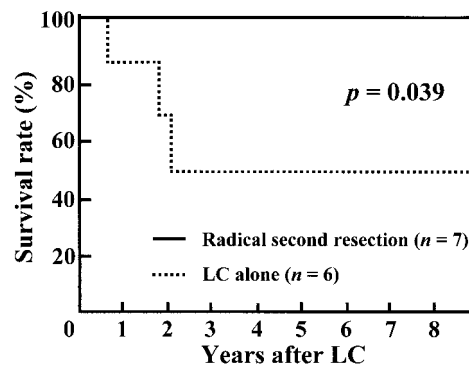
^aAccording to the tumor-nodes-metastases (TNM) staging system [25].

Pattern of Relapse among Patients Undergoing LC Alone

Recurrences were found in 4 (22%) of the 18 patients undergoing an LC alone, including 1 with a pT1a tumor and 3 with a pT2 tumor. The initial sites of recurrence were port site/peritoneum in 2 patients, the liver and pericholedochal lymph nodes in 1, and the lung and supraclavicular lymph nodes in 1. The patient with a pT1a tumor died of peritoneal recurrence 52 months after LC. The remaining 3 patients with a pT2 tumor died of disease at 8.5, 22, and 25 months after LC.

Pattern of Relapse among Patients Undergoing Radical Second Resection

Recurrences developed in only one of the 10 patients undergoing a radical second resection. The patient with a pT2 tumor had a subcutaneous recurrence at the epigastric port site, from which the viscus was retrieved, 44 months after LC. She underwent a resection of the recurrence as the third resection 49 months after LC and was alive with no evidence of disease 68 months after LC, as previously reported [27].



No. at risk	0	1	2	3	4	5	6	7	8
Radical second resection	7	7	7	7	7	7	2	2	0
LC alone	6	5	4	3	3	1	1	1	0

Fig. 1. Kaplan-Meier patient survival curves for 13 patients with pT2 gallbladder carcinoma according to the procedure performed. LC: laparoscopic cholecystectomy.

Long-term Survival Analysis

Among the 15 patients with a pT1 tumor, the outcome after LC alone (cumulative 5-year survival of 90%) was comparable to that after radical second resection (100% survival) ($p = 0.65$).

The median length of survival was 37 months, with a cumulative 5-year survival rate of 50% in 6 patients with a pT2 tumor undergoing an LC alone. The median length of survival was 68 months with a cumulative 5-year survival rate of 100% in 7 patients with a pT2 tumor undergoing a radical second resection. The outcome after radical second resection was significantly better than that after LC alone among the 13 patients with a pT2 tumor ($p = 0.039$) (Fig. 1).

Discussion

This study clearly demonstrated that radical second resection may provide a survival benefit for patients with a pT2 tumor unsuspected before or during LC, although no survival benefit of radical second resection was recognized in patients with a pT1 tumor. In 1992, we reported the effectiveness of radical second operation for gallbladder carcinoma discovered after open cholecystectomy [23]. However, the role of radical second resection in the management of patients with gallbladder carcinoma discovered after LC remained undetermined. This prompted us to conduct the current study.

Spillage of tumor-laden bile may be a cause of port site/peritoneal recurrence following LC [3, 19, 28]. The incidence of gallbladder perforation (or bile spillage) during LC ranges from 14% to 44% [6, 8, 16, 19] and was 25% in our series. Wibbenmeyer et al. [19] reported that the incidence of bile spillage during LC was significantly higher in patients with gallbladder cancer (44%) than in those with cholelithiasis. The association between gallbladder perforation and port site/peritoneal recurrence has been unclear, probably because of the small sample sizes and shorter follow-up time in earlier reports [8, 16, 19]. In 2000, Suzuki et al. [6] first documented a significant association between gallbladder perforation and port site/peritoneal recurrence, an association the current study has confirmed. In addition, gallbladder perforation was associated with worse patient survival, as suggested in the current

study and a recent report by Sarli et al. [29]. Gallbladder perforation during LC may lead to port site/peritoneal recurrence and a worse prognosis.

The question of whether the use of a plastic bag at the time of retrieval of specimens reduces the incidence of port site/peritoneal recurrence remains unresolved. Several authors [1, 3, 5, 13, 18, 30] advocate the use of a plastic bag to prevent tumor seeding, although they have provided no evidence that it actually reduces the incidence of seeding. Paolucci et al. [2] and Sarli et al. [9] suggested that the use of a plastic bag does not exclude the risk of port site recurrences. Suzuki et al. [6] identified no significant association between the use of a plastic bag and abdominal wall recurrences. Because most gallbladder perforations occur not at the time of retrieval of the specimen but during dissection of the viscus as shown in this series, we do not think that the use of a plastic bag effectively prevents port site/peritoneal recurrences, and the use of this approach therefore remains a matter for debate.

The incidence of port site/peritoneal recurrence after LC for gallbladder carcinoma is unexpectedly high, ranging from 10% to 18.6% [2, 6, 12, 16, 30], and was 11% in this series. In 1999, Paolucci and colleagues [2], in a large European series, documented port site/peritoneal recurrence in 76 (18.6%) of 409 patients with laparoscopically resected gallbladder carcinoma. In contrast, none of 98 patients with unsuspected gallbladder carcinoma after open cholecystectomy developed wound metastases [23, 31]. Laparoscopic cholecystectomy for cancer appears to increase the risk of parietal seeding when compared to open cholecystectomy [2, 19]. Schaeff et al. [14] reported that out of 59 cases of port site recurrence after LC, 15% were secondary to pT1 tumors. Open surgery is therefore a wiser option for known or suspected gallbladder carcinoma, even though it is considered to be an early carcinoma.

Fong et al. [7, 24] showed the effectiveness of aggressive second resection for patients with laparoscopically resected gallbladder carcinoma. However, their patients appear different from our series; in their series of 42 patients, 32 had a pT3–4 tumor, and only 20 had a tumor discovered after LC. Their results imply that aggressive second resection may provide a survival benefit for patients with a pT2–4 tumor. Considering the effectiveness of radical second resection for pT2 tumor in our series, radical second resection may be beneficial for patients with laparoscopically resected pT2–4 gallbladder carcinoma.

Many authors recommend excision of port sites at the time of radical second resection [6–8, 19, 30]. Excision of port site recurrence may prolong survival [6, 19, 32]. However, none of our patients undergoing radical second resection had excision of port sites. From the experience of one port site recurrence in this series, we think that port sites should be excised at the time of radical second resection in future patients.

The main limitations of this study were, first, that it was a retrospective analysis of a small number of patients, and second that the follow-up period in 8 patients was less than 60 months. To our knowledge, however, the current study is one of the largest series of patients with gallbladder carcinoma discovered after LC with the longest follow-up period, and thus delineates the impact of radical second resection on long-term patient survival.

In conclusion, gallbladder perforation during LC is strongly associated with both the development of port site/peritoneal recurrence and worse patient survival. Radical second resection may

be beneficial for patients with pT2 gallbladder carcinoma first discovered after LC.

Résumé. La récurrence au niveau de l'orifice de trocart ou du péritoine est une complication grave, fatale, après cholécystectomie laparoscopique pour cancer de la vésicule biliaire. Les buts de cette étude rétrospective ont été de déterminer les rapports entre la perforation pendant une cholécystectomie et la récurrence de l'orifice et/ou péritonéale, et de déterminer le rôle de la résection radicale secondaire dans le traitement du cancer de la vésicule biliaire diagnostiqué après cholécystectomie laparoscopique. On a analysé les résultats de 28 patients, dont 10 ont eu une résection radicale secondaire après cholécystectomie laparoscopique. Cinq patients ont eu une récurrence, au niveau des orifices de trocart et/ou péritonéal chez trois patients, et des métastases à distance, chez deux. L'incidence des récurrences au niveau des orifices/péritonéales a été plus élevée chez les patients ayant une perforation (3/7, 43%) que chez les patients sans (0/21, 0%) ($p = 0.011$). L'évolution après cholécystectomie laparoscopique a été moins bonne chez sept patients ayant une perforation (survie cumulative à 5 ans = 43%) que chez ceux sans (100%) ($p < 0.001$). Parmi 13 patients ayant une tumeur pT2, l'évolution après résection radicale secondaire (survie cumulative à 5 ans de 100%) était meilleure qu'après cholécystectomie laparoscopique seule (50%) ($p = 0.039$), bien qu'il n'y avait aucun bénéfice de survie en rapport avec la résection radicale secondaire chez les 15 patients ayant une tumeur pT1 ($p = 0.65$). En conclusion, le taux de récurrence au niveau des orifices de trocart, ou péritonéale lors d'une cholécystectomie laparoscopique est élevé et la survie plus mauvaise. On recommande la résection radicale secondaire pour les patients ayant une tumeur pT2 de la vésicule biliaire découverte après une cholécystectomie laparoscopique.

Resumen. La recurrencia en los sitios de los puertos o la siembra peritoneal constituye una complicación fatal luego de colecistectomía laparoscópica en pacientes con carcinoma de la vesícula biliar. El propósito de este análisis retrospectivo fue determinar la asociación de la perforación de la vesícula en el curso de la colecistectomía laparoscópica con la recurrencia en los sitios de los puertos y la recurrencia peritoneal, y determinar el papel de una segunda resección radical en el manejo del carcinoma de la vesícula biliar diagnosticado luego de una colecistectomía laparoscópica. Se analizaron 28 pacientes, 10 de los cuales fueron sometidos a segunda resección luego de la colecistectomía laparoscópica. Cinco desarrollaron recurrencia, 3 en los sitios de puertos/peritoneo y 2 en sitios distantes. La incidencia de recurrencia de sitio de puerto/peritoneo fue mayor en los pacientes con perforación de la vesícula (3/7, 43%) que en los que esto no ocurrió (0/21, 0%) ($p = 0.011$). El resultado luego de la colecistectomía laparoscópica fue peor en 7 pacientes con perforación de la vesícula (supervivencia acumulativa a 5 años de 43%) que en aquellos sin perforación (100%) ($p < 0.001$). En 13 pacientes con tumor pT2, el resultado luego de la segunda resección radical (supervivencia acumulativa a 5 años de 100%) fue mejor que la de los que sólo recibieron la colecistectomía laparoscópica (50%) ($p = 0.039$) aunque no se observó beneficio de supervivencia con la segunda operación radical en los 15 pacientes con tumor pT1 ($p = 0.65$). En conclusión, la perforación de la vesícula biliar durante una colecistectomía laparoscópica se asocia con recurrencia en los sitios de los puertos/peritoneo y peor supervivencia. La segunda resección radical está indicada en pacientes con carcinoma pT2 de la vesícula biliar que es descubierto luego de una colecistectomía laparoscópica.

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