"Extended" radical cholecystectomy for gallbladder cancer: Long-term outcomes, indications and limitations

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Abstract

AIM: To delineate indications and limitations for "extended" radical cholecystectomy for gallbladder cancer: a procedure which was instituted in our department in 1982.

METHODS: Of 145 patients who underwent a radical resection for gallbladder cancer from 1982 through 2006, 52 (36%) had an extended radical cholecystectomy, which involved en bloc resection of the gallbladder, gallbladder fossa, extrahepatic bile duct, and the regional lymph nodes (first- and second-echelon node groups). A retrospective analysis of the 52 patients was conducted including at least 5 years of follow up. Residual tumor status was judged as no residual tumor (R0) or microscopic/macroscopic residual tumor (R1-2). Pathological findings were documented according to the American Joint Committee on Cancer Cancer Staging Manual (7th edition).

RESULTS: The primary tumor was classified as pathological T1 (pT1) in 3 patients, pT2 in 36, pT3 in 12, and pT4 in 1. Twenty-three patients had lymph node metastases; 11 had a single positive node, 4 had two positive nodes, and 8 had three or more positive nodes. None of the three patients with pT1 tumors had nodal disease, whereas 23 of 49 (47%) with pT2 or more advanced tumors had nodal disease, whereas 23 of 49 (47%) with pT2 or more advanced tumors had nodal disease. One patient died during the hospital stay for definitive resection, giving an in-hospital mortality rate of 2%. Overall survival (OS) after extended radical cholecystectomy was 65% at 5 years and 53% at 10 years in all 52 patients. OS differed according to the pT classification (P < 0.001) and the nodal status (P = 0.010). All of 3 patients with pT1 tumors and most (29 of 36) patients with pT2 tumors survived for more than 5 years. Of 12 patients with pT3 tumors, 8 who had an R1-2 resection, distant metastasis, or extensive extrahepatic organ involvement died soon after resection. Of the remaining four pT3 patients who had localized hepatic spread through the gallbladder fossa and underwent an R0 resection, 2 survived for more than 5 years and another survived for 4 years and 2 mo. The only patient with pT4 tumor died of disease soon after resection. Among 23 node-positive patients, 11 survived for more than 5 years, and of these, 10 had a modest degree of nodal disease (one or two positive nodes).

CONCLUSION: Extended radical cholecystectomy is indicated for pT2 tumors and some pT3 tumors with localized hepatic invasion, provided that the regional nodal disease is limited to a modest degree (up to two positive nodes). Extensive pT3 disease, pT4 disease, or marked nodal disease appears to be beyond the scope of this radical procedure.

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**INTRODUCTION**

The history of radical surgery for gallbladder cancer started with cholecystectomy combined with wedge resection of the gallbladder fossa (without regional lymphadenectomy) in the early 20th century[1-3]. However, outcomes after this procedure were disappointing even in tumors limited to the wall of the gallbladder, probably due to the lack of regional lymphadenectomy[4,5]. In 1954, Glenn et al[6] first proposed a radical resection procedure with intended regional lymphadenectomy (portal lymph node dissection), designated as "radical cholecystectomy" (Glenn operation), for localized gallbladder cancer. Pack et al[7] in 1955 and Fahim et al[8] in 1962 advocated radical resection consisting of hepatectomy and portal lymph node dissection, and this strategy remains the one recommended by the National Comprehensive Cancer Network (NCCN) for pathological T1b (pT1b) or more advanced gallbladder cancer[9]. Outcomes after such radical resections, however, remain unsatisfactory, particularly for node-positive patients[10-12].

In Japan, an aggressive attitude toward gallbladder cancer emerged and gradually grew among specialized hepatobiliary surgeons in the 1970s and 1980s[13]. In this context, "extended" radical cholecystectomy (designated as the modified Glenn operation) was instituted in 1982 in our department (Figure 1)[14-16], as a modification of the radical cholecystectomy described by Glenn et al[14]. The procedure involves en bloc resection of the gallbladder, gallbladder fossa, extrahepatic bile duct, and the regional lymph nodes as defined previously[11,13]. Although this procedure has been widely used for gallbladder cancer among Japanese surgeons[13,16-18], indications and limitations remain to be established.

This study aimed to delineate indications and limitations for the extended radical cholecystectomy procedure for gallbladder cancer by retrospectively analyzing the long-term outcomes of 52 patients who underwent this procedure in the study department. The study goal was to definitively establish the role of this particular procedure in surgical management strategies for gallbladder cancer.

**MATERIALS AND METHODS**

**Patient population**

From May 1982 through December 2006, 145 consecutive patients underwent a variety of radical resection procedures for gallbladder cancer (including cancer arising in the cystic duct[19]) in the study department (Table 1). A radical resection was defined as an en bloc resection of both the primary tumor and the regional lymph nodes. This study period was selected in order to evaluate long-term outcomes after resection; the follow-up period was at least 5 years in all the patients. Of these, 52 (36%) who underwent an extended radical cholecystectomy (modified Glenn operation; Figure 1) were selected as our study cohort. They comprised 39 women and 13 men ranging in age from 43 to 84 years (median, 66.5 years).

Among the 52 patients, 34 underwent the extended radical cholecystectomy as an initial radical resection and 18 underwent this procedure as a radical second resection after a prior simple cholecystectomy for presumed benign disease. Although early (pT1) tumors do not warrant radical resection[20], three patients with pT1 tumor underwent the extended radical cholecystectomy because pT2 or more advanced disease was not ruled out before resection.

**Scope of "extended" radical cholecystectomy**

Extended radical cholecystectomy involves a cholecystectomy, wedge resection of the gallbladder fossa with a rim of non-neoplastic liver tissue (approximately 2 cm in thickness or more), resection of the suprapancreatic segment of the extrahepatic bile duct (bile duct resection), and regional lymph node dissection in an en bloc fashion (Figure 1). The main differences between this procedure and the original radical cholecystectomy described by Glenn et al[14] comprise the extent of regional lymphadenectomy and the presence or absence of bile duct resection.

The regional lymph nodes of the gallbladder include the cystic duct, periholecdochal, posterior superior (posterosuperior) pancreaticoduodenal, retroportal, right celiac, and hepatic artery node groups[21,22]. The cystic duct and periholecdochal node groups have been regarded as the first-echelon nodes of the gallbladder, whereas the other node groups as the second-echelon nodes[21,22]. Extended radical cholecystectomy harvests both the first- and second-echelon nodes en bloc (Figure 1).

We perform a bile duct resection to facilitate the regional lymphadenectomy, to remove periholecdochal lymphatic vessels and nodes simultaneously, to remove the possible presence of ductal (periductal) involvement[23], and to avoid the occurrence of ischemic biliary stricture after aggressive periductal nodal dissection[24].

The extent of hepatectomy appears to be similar between the extended procedure and the original described by Glenn et al[14]. With regard to resection of the gallbladder fossa for invasive tumors, we emphasize the need for complete excision of the cystic plate to avoid violating the subserosal tumor plane (Figure 2).
Among the 52 patients who underwent an extended radical cholecystectomy, 19 with suspected (or confirmed) regional nodal disease also underwent a dissection of the paraaortic lymph nodes (cephalad to the origin of the inferior mesenteric artery). Paraaortic nodal disease was classified as N2 disease according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th edition)\[19\].

Pathological examination
Immediately after resection, the surgeon(s) retrieved lymph nodes from the node-bearing adipose tissues of the fresh surgical specimen. A total of 871 regional lymph nodes (excluding paraaortic nodes) were retrieved from the 52 patients (median 16, range 6 to 36 per patient). Resected specimens together with the retrieved lymph nodes were submitted for histological examination. Residual tumor status was judged as no residual tumor (R0) or microscopic residual tumor (R1-2). All pathological findings were documented according to the AJCC Cancer Staging Manual (7th edition)\[19\].

Patient follow-up
Adjuvant chemotherapy was administered to 23 patients at the discretion of the individual surgeon. No patients received adjuvant radiotherapy. Patients discharged to home were followed regularly in outpatient clinics every 1-6 mo for at least 5 years, with a median follow-up period of 188 mo (range: 82-351 mo).

Prognostic factors after extended radical cholecystectomy
To determine prognostic factors after extended radical cholecystectomy, the following 15 conventional variables were tested univariately and multivariately in 52 patients who underwent the procedure (Table 2): age, gender, gall-stone (absent vs present), timing of radical resection (initial resection vs second resection), adjuvant chemotherapy (absent vs present), size of the primary tumor (≤ 60 mm vs > 60 mm), pT classification, pathological regional lymph nodes (pN) classification, pathological distant metastasis (pM) classification, histological type, histological grade, lymphatic vessel invasion, venous invasion, perineural invasion, and residual tumor status.

Statistical analysis
Medical records and survival data were obtained for all 52 patients. Overall survival (OS) was defined as the interval between the date of definitive resection and the date of last follow up or death from any cause. The Kaplan-Meier method was used to estimate cumulative OS rates, and the log rank test was used to evaluate differences between groups. The Cox proportional hazards regression model using a step-backward fitting procedure was applied to

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Table 1: Radical resection procedures for 145 patients with gallbladder cancer

| Procedure                     | n  |
|-------------------------------|----|
| Extended cholecystectomy      |    |
| C + WR + BD + N'              | 52 |
| C + WR + N                   | 23 |
| C3 + BD + N                | 10 |
| C3 + N                        | 9  |
| More extensive resection      |    |
| C + H + BD + N               | 25 |
| C + WR + PD + N              | 15 |
| C + H + PD + N               | 9  |
| C3 + PD + N                  | 2  |

1Designated as 'extended' radical cholecystectomy (modified Glenn operation) since 1982\[11,15\]. Cholecystectomy with full-thickness dissection: cholecystectomy combined with removal of the cystic plate. C: Cholecystectomy; WR: Wedge resection of the gallbladder fossa; BD: Resection of the extrahepatic bile duct; N: Regional lymphadenectomy; H: Major hepatectomy defined as removal of two sections or more; PD: Whipple or pylorus-preserving pancreatioduodenectomy.

Figure 1 "Extended" radical cholecystectomy for gallbladder cancer. The dashed line indicates the scope of wedge resection of the gallbladder fossa (about 2 cm in thickness or more). The double-headed arrows indicate lines of division of the extrahepatic bile duct. The pale blue area indicates the extent of regional lymph node dissection, which achieves en bloc harvesting of both the first-echelon nodes (cystic duct and pericholedochal node groups) and the second-echelon nodes (posterosuperior pancreaticoduodenal, retroportal, right celiac, and hepatic artery node groups)\[11,15\]. GB: Gallbladder.

Figure 2 Wedge resection of the gallbladder fossa in "extended" radical cholecystectomy. The dashed line indicates the line of hepatic parenchymal division. The short double-headed arrow indicates the line of division of the cystic plate. The long double-headed arrows indicate lines of division of the extrahepatic bile duct. At the end of parenchymal division, the cystic plate is identified as a fibrous plate connecting with the right portal pedicle, and then divided at its base. Arabic numerals indicate the plate system of the liver (1: Cystic plate; 2: The dense fibrous sheath encircling the right portal pedicle; 3: Hilar plate). GB: Gallbladder; C: The triangle of Calot.
identify independent prognostic factors. In this model, a step-wise selection was used for variable selection with entry and removal limits of \(P < 0.05\) and \(P > 0.10\), respectively.

The IBM SPSS Statistics 19 software (IBM Japan, Tokyo, Japan) was used for all statistical evaluations. All tests were two-tailed, and \(P < 0.05\) was taken to indicate statistical significance.

## RESULTS

The \(pT\) was classified as \(pT1\) in 3 patients, \(pT2\) in 36, \(pT3\) in 12, and \(pT4\) in 1. Twenty-three patients had lymph node metastases, with the number of positive nodes per patient ranging from 1 to 41 (median, 2); 11 patients had a single positive node, 4 had two positive nodes, and 8 had three or more positive nodes. None of the three patients with \(pT1\) tumors had nodal disease, whereas 23 of 49 (47%) with \(pT2\) or more advanced tumors had nodal disease. One patient who underwent a radical second resection died during the hospital stay for definitive resection, giving an in-hospital mortality rate of 2%.

Long-term outcomes after extended radical cholecystectomy

Of the 52 patients who underwent an extended radical cholecystectomy, 34 survived for more than 5 years and 18 died within 5 years. OS following extended radical cholecystectomy was 65% at 5 years and 53% at 10 years (median survival time, not reached) across the study cohort. OS was significantly worse in the 5 patients undergoing a noncurative (R1-2) resection than in the 47 patients undergoing a potentially curative (R0) resection (\(P < 0.001\); Figure 3); the R1-2-resected patients died of recurrence within 5 years. This result indicated that R0 resection is a prerequisite for long-term survival after extended radical cholecystectomy.

We then focused on the subgroup of 47 patients who had undergone an R0 resection for subsequent survival analyses. OS after R0 resection differed according to the \(pT\) classification (\(P < 0.001\); Figure 4) and nodal status (\(P = 0.010\); Figure 5). At the time of last follow-up, 11 patients with node-positive disease had survived for more than 5 years, suggesting that regional lymphadenectomy could achieve an acceptable rate of long-term survival for node-positive patients given an R0 resection (Figure 5).
Five-year survival according to pT classification

All patients with pT1 tumor and most (29 of 36) patients with pT2 tumor survived for more than 5 years, while most (10 of 12) patients with pT3 tumor and the only patient with pT4 tumor died within 5 years (Table 3).

Of the 12 patients with pT3 tumors, 3 had an R1-2 resection, 2 had distant metastasis (pM1) in the liver, 2 had extensive extrahepatic organ involvement, and 1 had both an R1-2 resection and pM1 in the liver. All of these patients died within 5 years. Of the remaining four pT3 patients who had localized hepatic spread through the gallbladder fossa and underwent an R0 resection, 2 survived for more than 5 years, 1 survived for 4 years and 2 mo, and another succumbed to the cancer 4 mo after resection. Taken together, the above observations indicated that extended radical cholecystectomy was effective for most T1-2 lesions and some pT3 lesions with localized hepatic spread.

Five-year survival according to lymph node status

Among the eleven 5-year survivors with node-positive disease (Table 4), the number of positive lymph nodes was limited to one or two in 10 patients (patient No. 11 underwent an aggressive paraaortic lymphadenectomy for a total of nine positive paraaortic nodes), suggesting that extended radical cholecystectomy was effective in patients with up to a modest degree of regional nodal disease (up to two positive nodes).
both the first and the second echelon node groups of lymphadenectomy in the former procedure includes presence or absence of bile duct resection. The extent procedure in the extent of lymphadenectomy and the method (Figure 1) differs from the original Glenn and Hays procedure, designated as “radical cholecystectomy”, and found it to be effective for pT1-2 tumors and some pT3 tumors with localized hepatic invasion, provided that the nodal disease is absent or only present to a modest degree (one or two positive lymph nodes).

In 1954, Glenn et al[3] first proposed a radical surgical procedure, designated as “radical cholecystectomy”, where the gallbladder fossa and the node-bearing tissues within the hepatoduodenal ligament (portal lymph node dissection) were excised en bloc at the time of cholecystectomy. Extended radical cholecystectomy in our department (Figure 1) differs from the original Glenn and Hays procedure in the extent of lymphadenectomy and the presence or absence of bile duct resection. The extent of lymphadenectomy in the former procedure includes both the first- and the second-echelon node groups[21,26], but that in the original procedure was more limited[3,6,14]. The difference in the extent of lymphadenectomy may explain, in part, the acceptable rate of long-term survival (55%) achieved in our node-positive patients (Figure 5). Bile duct resection provides better local control by removing the possible presence of ductal (periductal) spread[20] as well as better clearance of nodal disease (especially periductal nodal disease). Thus, we believe that extended radical cholecystectomy confers oncological advantages over the original radical procedure.

The main modes of hepatic spread from resectable gallbladder cancer involve both direct invasion and portal tract invasion (lesions within the portal tracts of adjacent liver), the latter of which features intrahepatic lymphatic invasion[5,23,29]. We previously reported that the portal tract invasion is seen only in the vicinity (within about 1 cm) of the advancing margin of direct liver invasion[24,25]. Thus, a hepatectomy margin of approximately 2 cm or more in our extended radical cholecystectomy appears to be sufficient. The fact that local recurrence in hepatoma patients did not occur in any of our patients (data not shown) also supports the validity of our 2 cm hepatectomy margin. When performing a wedge hepatectomy for invasive tumor, the entire cystic plate should be resected (Figure 2) because incomplete excision of the cystic plate violates the subserosal plane of the gallbladder and thus may leave behind tumor cells in this plane. Also, complete excision of the cystic plate facilitates removal of the adipose tissue within the triangle of Calot, which usually contains cystic duct node(s).

The current study showed that most patients with pT2 gallbladder cancer who underwent an extended radical cholecystectomy survived for more than 5 years (Figure 4), suggesting that pT2 tumors are the best candidates for this procedure. Regarding pT3-4 tumors, we cannot draw a definitive conclusion due to the small number of patients analyzed in this study. However, the fact that three of the four pT3 patients with localized invasion of the liver through the gallbladder fossa survived for more than 4 years suggests that such pT3 patients may benefit from extended radical cholecystectomy, provided that they have no distant metastases and undergo an R0 resection. Our results also suggest that a considerable proportion of node-positive patients may benefit from this procedure (Figure 5). By analyzing 5-year survivors with nodal disease (Table 4), we realized that this procedure might clear only a modest degree of nodal disease (one or two positive nodes in our cohort). Taken together, the above observations indicate that the extended radical cholecystectomy undertaken in our department provides survival benefit for most patients with pT2 tumors and some patients with pT3 tumors with localized hepatic invasion, provided that the nodal disease is limited to a modest degree and an R0 resection is feasible.

In 2007, Yokomizo et al[28] argued that hepatectomy and/or bile duct resection could be withheld in radical surgery for pT2 gallbladder cancer provided that negative resection margins are achieved. The current NCCN guidelines[6] recommend hepatectomy and lymphadenectomy...
for pT1b or greater tumors, whereas bile duct resection is suggested as optional. We previously reported that a considerable proportion (40%) of pT2 patients could survive for more than 5 years after cholecystectomy alone if the resection margins are negative[10]. The above observations indicate that bile duct resection, hepatectomy, and even lymphadenectomy could be omitted for some pT2 patients. Indeed, some of our pT2 patients with advanced age or comorbid disease(s) had a less aggressive resection by omitting bile duct resection and/or hepatectomy (Table 1). However, considering the excellent outcomes after extended radical cholecystectomy for pT2 tumors (Figure 4), we now usually recommend application of the extended radical cholecystectomy to robust patients with pT2 gallbladder cancer.

The authors' policy on radical surgery for gallbladder cancer is to select a resection procedure for each patient based on the extent of tumor spread in the patient. Although extended radical cholecystectomy has been considered the standard procedure for fairly localized tumors in our department, only one-third (52 of 145) of our patients underwent this procedure (Table 1). The current study implies that extensive pT3 disease, pT4 disease, or marked nodal disease is beyond the scope of extended radical cholecystectomy. Such tumors may require more extensive resections (major hepatectomy, pancreatoduodenectomy, etc.) for clearance of the locoregional disease[31]. Adequate selection of a resection procedure in individual patients is mandatory to improve survival for gallbladder cancer.

The main limitations of the current study include the retrospective nature of the analysis and the small number of patients spanning a long period of time. We believe, however, that these limitations did not greatly affect the results of the study as the differences between the groups were too marked to have resulted from bias. In addition, the role of extended radical cholecystectomy in surgical management strategy for gallbladder cancer is now more clearly defined than previously[11,12,16]. Our results thus provide useful information for selecting an adequate resectional procedure for individual patients with gallbladder cancer.

In conclusion, extended radical cholecystectomy is indicated for gallbladder cancer patients with pT2 tumors and for some with pT3 tumors with localized hepatic invasion, provided that the regional nodal disease is limited to a modest degree (up to two positive nodes). Extensive pT3 disease, pT4 disease, or marked nodal disease appears to be beyond the scope of this procedure and thus may require more extensive resection. This study confirms that extended radical cholecystectomy plays a key role in the surgical management of invasive gallbladder cancer if the spread is moderate.

REFERENCES

1. Sheinfeld W. Cholecystectomy and partial hepatectomy for carcinoma of the gall bladder with local liver extension. Surgery 1947; 22: 48-58
2. Glenn F, Hays DM. Carcinoma of the extrahepatic biliary tract. Surg Clin North Am 1953: 479-492
3. Glenn F, Hays DM. The scope of radical surgery in the treatment of malignant tumors of the extrahepatic biliary tract. Surg Gynecol Obstet 1954; 99: 529-541
4. Pack GT, Miller TR, Brashfield RD. Total right hepatic lobectomy for carcinoma of the gallbladder; report of three cases. Ann Surg 1955; 142: 6-16
5. Fahim RB, McDonald JR, Richards JC, Ferris DOS. Carcinoma of the gallbladder: a study of its modes of spread. Ann Surg 1962; 156: 114-124
6. Benson AB, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM, Covey A, Curley SA, D’Angelica MI, Davila R, Ensminger WD, Gibbs JF, Laheru D, Malafa MP, Marrero J, Meranze SG, Mulvihill SJ, Park JO, Posey JA, Sachdev J, Salem R, Sigurdsson ER, Soffeles C, Vauthey JN, Venook AP, Goff LW, Yen Y, Zhu AX. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. J Natl Compr Canc Netw 2009; 7: 350-391
7. Bartlett DL, Fong Y, Fortner JC, Brennan MF, Blumgart LH. Long-term results after resection for gallbladder cancer. Implications for staging and management. Ann Surg 1996; 224: 639-646
8. Benoist S, Panis Y, Fagniez PL. Long-term results after curative resection for carcinoma of the gallbladder. French University Association for Surgical Research. Am J Surg 1998; 175: 118-122
9. Donohue JH, Nagorney DM, Grant CS, Tsushima K, Iklstrup DM, Adson MA. Carcinoma of the gallbladder. Does radical resection improve outcome? Arch Surg 1990; 125: 227-241
10. Frena A, La Guardia G, Martin F. Outcome of radical surgery for carcinoma of the gallbladder according to the tumor node metastasis and Japanese Society of Biliary Surgery
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11 Shirai Y, Wakai T, Hatakeyama K. Radical lymph node dissection for gallbladder cancer: indications and limitations. Surg Oncol Clin N Am 2007; 16: 221-232
12 Shirai Y, Yoshida K, Tsukada K, Muto T. Inapparent carcinoma of the gallbladder. An appraisal of a radical second operation after simple cholecystectomy. Ann Surg 1992; 215: 326-331
13 Shirai Y, Yoshida K, Tsukada K, Muto T, Watanabe H. Radical surgery for gallbladder carcinoma. Long-term results. Ann Surg 1992; 216: 565-568
14 Glenn F. Radical cholecystectomy for carcinoma of the gall-bladder. In: Atlas of biliary tract surgery. New York: The Macmillan Company, 1963: 86-88
15 Shirai Y, Yoshida K, Tsukada K, Ohtani T, Muto T. Identification of the regional lymphatic system of the gallbladder by vital staining. Br J Surg 1992; 79: 659-662
16 Shimada H, Endo I, Togo S, Nakano A, Izumi T, Nakagawara G. The role of lymph node dissection in the treatment of gallbladder carcinoma. Cancer 1997; 79: 892-899
17 Chijiwa K, Nakano K, Ueda J, Noshiro H, Nagai E, Yamaguchi K, Tanaka M. Surgical treatment of patients with T2 gallbladder carcinoma invading the subserosal layer. J Am Coll Surg 2001; 192: 600-607
18 Yamaguchi K, Chijiwa K, Saiki S, Nishihara K, Takashima M, Kawakami K, Tanaka M. Retrospective analysis of 70 operations for gallbladder carcinoma. Br J Surg 1997; 84: 200-204
19 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York: Springer, 2010
20 Wakai T, Shirai Y, Yokoyama N, Nagakura S, Watanabe H, Hatakeyama K. Early gallbladder carcinoma does not warrant radical resection. Br J Surg 2001; 88: 675-678
21 Shimizu Y, Ohtsuka M, Ito H, Kimura F, Shimizu H, Togawa A, Yoshidome H, Kato A, Miyazaki M. Should the extrahepatic bile duct be resected for locally advanced gallbladder cancer? Surgery 2004; 136: 1012-1017; discussion 1018
22 Ishizuka D, Shirai Y, Hatakeyama K. Ischemic biliary stricture due to lymph node dissection in the hepatoduodenal ligament. Hepatogastroenterology 1998; 45: 2048-2050
23 Cooper WA. Carcinoma of the gallbladder. Arch Surg 1937; 35: 431-448
24 Shirai Y, Tsukada K, Ohtani T, Watanabe H, Hatakeyama K. Hepatic metastases from carcinoma of the gallbladder. Cancer 1995; 75: 2063-2068
25 Wakai T, Shirai Y, Sakata J, Nagahashi M, Ajoka Y, Hatakeyama K. Mode of hepatic spread from gallbladder carcinoma: an immunohistochemical analysis of 42 hepatectomized specimens. Ann J Surg Pathol 2010; 34: 65-74
26 Yokomizo H, Yamane T, Hirata T, Hifumi M, Kawaguchi T, Fukuda S. Surgical treatment of pT2 gallbladder carcinoma: a reevaluation of the therapeutic effect of hepatectomy and extrahepatic bile duct resection based on the long-term outcome. Ann Surg Oncol 2007; 14: 1366-1373

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