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# Radical Surgery for Gallbladder Carcinoma

## Long-term Results

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The authors' objective was to evaluate the effectiveness of radical surgery with lymph node dissection for gallbladder carcinoma. Long-term results were analyzed in 40 patients in a 5-year study. The authors divided the 40 cases into two groups: 20 without positive nodes and 20 with positive nodes. In the group without positive nodes, one patient who underwent R1 resection died of a recurrence at 1 year 7 months. Seventeen of the 19 patients treated with R0 resection survived more than 5 years. The 5-year survival rate was 85% (17/20). In the group with positive nodes, 9 of the 13 patients treated with R0 resection survived more than 5 years, whereas the seven patients treated with R1 or R2 resection died within 5 years. The 5-year survival rate was 45% (9/20). Patients treated by R0 resection showed a 5-year survival rate of 69% (9/13). Thus we documented the favorable long-term results of radical surgery. R0 resection is a prerequisite for long-term survival. The results justify radical surgery with lymph node dissection.

**G**ALLBLADDER CARCINOMA IS a highly lethal disease, with numerous authors pointing out the dismal outcome of surgery.<sup>1-4</sup> Although some investigators have reported long-term survivors after surgery, most of the patients had received only cholecystectomy for early carcinoma.<sup>5-9</sup> There are few reports of long-term survivors of advanced gallbladder carcinoma. In a literature review, we found only 13 5-year survivors with advanced gallbladder cancer who had presented with nodal metastasis.<sup>7,10-19</sup> Although some authors have advocated radical surgery for gallbladder carcinoma, the long-term benefit has not been satisfactorily documented.<sup>5,12,17-21</sup> Thus, the advantages of radical surgery for cancer of the gallbladder remain controversial.<sup>4,18,22</sup>

We report the long-term results of radical surgery for gallbladder carcinoma, documenting nine 5-year survivors who presented with nodal metastasis and their clinicopathologic characteristics. Our objective was to evaluate

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the effectiveness of radical surgery for gallbladder carcinoma with resection of regional lymph nodes.

### Patients and Methods

A total of 81 patients with gallbladder carcinoma (GBC) underwent radical surgery in our department between 1981 and 1990. The postoperative follow-up period was at least 5 years in 40 patients who had such surgery before October 1986. To evaluate the long-term results, we selected these 40 as our study subjects. There were 22 women and 18 men, whose ages ranged from 39 to 78 years (average, 66.1 years).

The operative procedures employed are listed in Table 1. The standard radical operation for gallbladder cancer (GBC) in our department consists of cholecystectomy, wedge resection of the gallbladder bed, resection of the suprapancreatic segment of the extrahepatic bile duct, and *en bloc* dissection of the regional lymph nodes.<sup>23</sup> Bile duct resection or wedge resection of the gallbladder bed was spared in some cases of early-stage disease. Major hepatic resection or pancreatoduodenectomy was carried out when the cancer had invaded such neighboring organs as the liver, the head of the pancreas, and the duodenum. We have documented the extent of the dissection of regional lymph nodes in previous publications.<sup>23,24</sup>

The names of the regional lymph nodes of the gallbladder have not been standardized internationally. Therefore, we used the names that we proposed previously.<sup>24</sup> This nomenclature is a modification of Fahim and his associates'.<sup>25</sup>

One of the authors (HW), a pathologist, examined all of the resected specimens. The depth of the lesion and the presence or absence of residual tumor were determined on multiple sections of the whole lesion. Dissected lymph

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TABLE 1. Operative Procedures in 40 Patients With Gallbladder Carcinoma, 1981-1986

Procedure*	No. of Patients
C + N	3
C + L + N	9
C + BD + N	2
C + L + BD + N	18
C + L + PD + N	7
C + H + PD + N	1
Total	40

\* C, cholecystectomy (full thickness); N, dissection of regional lymph nodes; L, wedge resection of gallbladder bed; BD, resection of the bile duct; PD, pancreatoduodenectomy; H, extended right hepatic lobectomy.

nodes were examined histologically to detect metastatic foci on a single representative section per lymph node.

The TNM (tumor, nodes, metastases) staging system<sup>26,27</sup> was used, and the extent of tumor spread was described by the TNM (pTNM) system. "R0 resection" refers to the complete removal of locoregional tumor spread. "R1 resection" and "R2 resection" indicate an incomplete removal with microscopic residual tumor and macroscopic residual tumor, respectively. We used the terms "early stage" for pT1 lesions and "advanced stage" for pT2 or more advanced lesions.

Clinical records and follow-up data were obtained for all 40 patients. Survival rates were calculated by the direct method.

### Results

The 40 patients were divided into two groups according to the absence or presence of lymph node metastasis. They are listed in Table 2 according to the extent of disease. No operative deaths were encountered in this series.

#### Cases of GBC Without Lymph Node Metastasis (n = 20)

Of the 20 patients without lymph node metastases, six had early stage lesions and 14 had advanced stage lesions.

R0 resection was performed in all but one patient. This patient had GBC of pT3pN0M0 with marked invasion of the bile duct. Pancreatoduodenectomy was performed, combined with cholecystectomy, wedge resection of the gallbladder bed, and lymph node dissection. Histologic examination, however, showed microscopic residual tumor on the resection margin around the portal vein. This operation was judged as an R1 resection. The patient died of local recurrence and peritonitis carcinomatosa 19 months after operation.

Of the 19 patients treated by R0 resection, 17 (six with early stage and 11 with advanced stage disease) survived more than 5 years without recurrence. One patient died of cardiac failure of unknown cause and malnutrition 4

years and 8 months after the operation. The major operative procedure, which consisted of an extended right hepatic lobectomy combined with pancreatoduodenectomy, had probably led to the long-standing postoperative malnutrition. Autopsy showed no recurrent disease. The remaining patient died of peritonitis carcinomatosa 3 months after R0 resection (the standard radical operation). Histologic examination of the resected specimen showed cancerous invasion of the serosa of the gallbladder.

In these 20 patients, the 5-year survival rate was 85% (17 of 20 patients). The 19 patients who underwent R0 resection showed a 5-year survival rate of 89% (17 of 19 patients).

#### Cases of GBC With Lymph Node Metastasis (n = 20)

All 20 patients with lymph node metastases had advanced-stage GBC.

R0 resection was performed in 13. An incomplete resection (R1 or R2) was carried out in seven: R1 resection in five and R2 resection in two, respectively.

Of the 13 patients treated by R0 resection, four patients died of recurrence. Three of the four died of peritonitis carcinomatosa combined with local recurrence 1 year 1 month, 2 years 11 months, and 3 years 7 months after operation. A remaining patient who had pancreatoduodenectomy combined with cholecystectomy and a wedge resection of the gallbladder bed died of pulmonary metastasis 4 years 9 months after the operation. Two of the four patients had metastases to the retroportal and the right celiac nodes, and two had metastases to the pericholedochal and the cystic nodes. The remaining nine patients survived more than 5 years after the operation. The clinicopathologic characteristics of these long-term survivors are summarized in Table 3. None of these long-term survivors showed metastatic disease to the retroportal or the right celiac nodes (Table 3).

None of the seven patients who were treated by R1 or R2 resection survived 5 years after the operation. Five of

TABLE 2. Staging of Gallbladder Carcinoma in 40 Patients

Extent of Disease	No. of Patients
Gallbladder carcinoma without positive nodes (n = 20)	
pT1a pN0 M0 = Stage I	5
pT1b pN0 M0 = Stage I	1
pT2 pN0 M0 = Stage II	13
pT3 pN0 M0 = Stage III	1
Gallbladder carcinoma with positive nodes (n = 20)	
pT2 pN1a M0 = Stage III	10
pT2 pN1b M0 = Stage III	3
pT3 pN1a M0 = Stage III	6
pT4 pN1b M0 = Stage IV	1
Total	40

TABLE 3. Clinicopathological Characteristics of Nine Long-term Survivors With Gallbladder Carcinoma With Nodal Involvement

Patient	Age	Sex	pT	pN	M	Stage	Positive Nodes*	Surgery*	Residual Tumor	Status
1	72 yr	F	2	1a	0	III	Cystic node, pericholedochal node	C + L + N	0	Alive 10 yr, 2 mo
2	58 yr	M	2	1a	0	III	Node along hepatic artery	C + L + BD + N	0	Alive 7 yr, 11 mo
3	69 yr	F	2	1a	0	III	Pericholedochal node	C + L + N	0	Alive 7 yr, 10 mo
4	58 yr	M	3 (liver)	1a	0	III	Pericholedochal node	C + L + PD + N	0	Alive 7 yr, 8 mo
5	75 yr	F	2	1a	0	III	Cystic node	C + L + N	0	Alive 6 yr, 2 mo
6	77 yr	M	3 (liver)	1a	0	III	Cystic node	C + L + BD + N	0	Alive 5 yr, 10 mo
7	67 yr	F	2	1a	0	III	Cystic node	C + L + BD + N	0	Alive 5 yr, 4 mo
8	54 yr	F	2	1a	0	III	Cystic node, pericholedochal node	C + L + PD + N	0	Dead 5 yr, 2 mo (recurrence)
9	75 yr	F	3 (liver)	1a	0	III	Pericholedochal node	C + L + BD + N	0	Alive 5 yr, 1 mo

The pericholedochal nodes include the node of the hiatus and the superior pancreaticoduodenal node.<sup>25</sup>

\* Refer to Table 1 for abbreviations of surgical procedures.

the seven had GBC with invasion of the hepatoduodenal ligament. The skeletonization of the portal vein and the hepatic artery in the involved hepatoduodenal ligament left microscopic infiltrating tumor tissue around the portal vein and the hepatic artery. Four of the five patients died of a local recurrence within 15 months. Another patient died of unknown causes 2 years after the operation. The remaining two patients who underwent the standard radical operation demonstrated microscopic residual tumor at the cut stumps of the bile duct on postoperative histologic examination. This residual tumor was confined to the wall of the bile duct. One of these patients died of local recurrence 4 years 11 months after operation, and the other died of pulmonary metastasis of concomitant renal cell carcinoma 3 years 8 months after the operation. A positive cut stump of the bile duct was a better prognostic factor than infiltrating residual tumor in the hepatoduodenal ligament.

Overall, the 5-year survival rate was 45% (9 of 20 patients). The patients who underwent R0 resection showed a 5-year survival rate of 69% (9 of 13 patients).

### Discussion

Although most surgeons have a pessimistic view of radical surgery for GBC,<sup>1-4,22</sup> some advocate this approach.<sup>5,11,17-21,28</sup> Radical surgery has cured selected patients with advanced disease.<sup>5,17-21,28</sup> The long-term results, however, have failed to justify such radical surgery for GBC. Therefore, we conducted this study to evaluate the effectiveness of the radical procedure that is routinely performed in Japan for advanced-stage GBC.<sup>17,19,23,24,28</sup>

Some authors believe that patients with inapparent GBC that is treated by simple cholecystectomy may have a chance of long-term survival.<sup>5-9</sup> We found, however, that those with GBC metastatic to the cystic node and who underwent simple cholecystectomy did not survive long-term.<sup>23</sup> Simple cholecystectomy thus cannot offer the hope of long-term survival in patients with nodal involve-

ment, even though this operation is potentially curative. There are few reports of long-term survivors with nodal involvement who have had radical surgery.<sup>7,10-18</sup> We found in the literature only 13 patients who had GBC with nodal involvement and who survived more than 5 years after resection.<sup>7,10-19</sup>

In 1981, we began performing radical surgery for GBC with the objective of effecting a cure.<sup>23,24,28</sup> At this writing, we have performed radical procedures in 92 patients, of whom we report 40 whose follow-up period was beyond 5 years to clarify the long-term results. Our results clearly showed the following: (1) lymph node dissection can achieve an acceptable rate of long-term survival, even in patients with nodal metastasis; (2) R0 resection is a prerequisite for long-term survival.

Glenn and Hays<sup>20</sup> proposed the importance of lymph node dissection in surgery for GBC in 1954. The procedure was referred to as "skeletonization of the lesser omentum." Fahim et al.<sup>5</sup> also advocated the nodal dissection for GBC in 1963.<sup>5</sup> In Japan, radical resection with nodal dissection for GBC has been widely accepted. An acceptable rate of long-term survival has not been reported, however.<sup>17,19</sup> Thus, western surgeons have remained pessimistic about the radical procedure.<sup>22</sup> We first proved that radical surgery with lymph node dissection could control the locoregional spread of GBC in a considerable number of patients. Nodal dissection was able to control the metastasis to the cystic and pericholedochal nodes, although it could not control the metastasis to the retroportal or right celiac nodes. This shows that patients with N1a lesions are good candidates for nodal dissection.

Recently we have also resected the interaortocaval nodes, in addition to the usual dissection of regional lymph nodes (the nodes located in the hepatoduodenal ligament and on the posterosuperior aspect of the head of the pancreas), because we have found that the interaortocaval nodes were the final regional nodes of the gallbladder.<sup>24</sup> Moreover, we have performed pancreaticoduodenectomy in patients with marked nodal involvement

around the head of the pancreas and have obtained good short-term results using the extended procedures described above, although the period of follow-up is still short (unpublished data). We expect that the extended nodal dissection may achieve favorable long-term results in patients with regional spread that reaches the retroportal nodes, the right celiac nodes, or more distant nodes. Further investigation is needed to resolve the issues concerning the indications and limitations of lymph node dissection.

R0 resection is required for the long-term survival of the patient with GBC. Direct invasion of the liver can be treated with liver resection. Wedge resection of the gallbladder bed can control a small amount of invasion (Table 3). Extended right hepatic lobectomy is applied to a massive invasion of the liver or to the invasion of the right main branches in the hepatic pedicle. A combined resection of the involved organs (pancreatoduodenectomy, colectomy, etc.) can achieve R0 resection for T3 or T4 lesions. Extended procedures to obtain R0 resection are employed increasingly in our department (unpublished data). Further investigations are mandated to evaluate the long-term value of these extended procedures.

Invasion of the bile duct or of the hepatoduodenal ligament is difficult to resect by the R0 procedure. In this study, most of the recurrences after radical procedures showed infiltrating residual tumor (positive resection margin) around the portal vein or the hepatic artery, or on the cut stump of the bile duct. In three cases, the meticulous skeletonization of the portal vein and the hepatic artery could not eradicate residual tumor in the hepatoduodenal ligament. Combined resection and reconstruction of large blood vessels should be considered to obtain R0 resection in selected cases. Of course, surgery alone cannot remove all the tumor cells that infiltrate the ligament. A multidisciplinary approach, which includes preoperative radiochemotherapy, may allow us to increase the rate of curative R0 resection in the near future, although this has not been proven. In contrast to the early death of patients with infiltrating residual tumor in the ligament, two patients with residual tumor confined to the wall of the bile duct survived tumor free for more than 3 years. This suggests that the biologic behavior of tumor cells differs according to the site of invasion.

### Conclusions

We have documented our favorable long-term results with radical surgery for GBC. R0 resection is prerequisite for long-term survival. These results justify using the radical procedure for GBC.

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