

---

# Inapparent Carcinoma of the Gallbladder

## *An Appraisal of a Radical Second Operation After Simple Cholecystectomy*

---

YOSHIO SHIRAI, M.D., KEISUKE YOSHIDA, M.D., KAZUHIRO TSUKADA, M.D., and TERUKAZU MUTO, M.D.

---

This study was designed to investigate issues concerning "inapparent carcinoma" of the gallbladder and the effectiveness of a radical second operation in the treatment of inapparent carcinoma. Ninety-eight patients with inapparent carcinoma were analyzed according to the "pT" category of TNM (tumor, nodes, and metastases) classification. Eighty patients underwent cholecystectomy alone, and 14 patients had a subsequent radical operation. After cholecystectomy alone it was found that (1) Patients with pT1 cancer had a 5-year survival rate (5ysr) of 100%; (2) In patients with pT2, 5ysr was 40%; and (3) Patients with pT3 showed 5ysr of 0%. Results of a radical second operation showed that (1) Patients with pT2 cancer showed a 5ysr of 90%, significantly better ( $p < 0.05$ ) than pT2 treated with cholecystectomy alone; (2) There was a prolongation of survival in patients with pT3 or pT4. It was concluded that a radical second operation should be carried out for pT2 or more advanced inapparent carcinoma, whereas follow-up without a second operation is recommended for pT1 cancer without positive margin.

**C**ARCINOMA OF THE GALLBLADDER has been considered to be a highly lethal disease.<sup>1-3</sup> Although a few long-term survivors have been reported, most of them were patients with gallbladder carcinoma first diagnosed on microscopic examination after simple cholecystectomy, that is, "inapparent carcinoma" of the gallbladder.<sup>4-7</sup> It has been clear, however, that the prognosis in inapparent carcinoma was not uniformly good, and many of the reported patients died of recurrence.<sup>5-7</sup>

Reoperation after first cholecystectomy for inapparent carcinoma has been recommended by some investigators,<sup>6-10</sup> but there has been no study thus far that clearly demonstrates whether reoperation with a radical procedure could improve the prognosis for inapparent carcinoma of the gallbladder.

*From the Department of Surgery, Niigata University School of Medicine, Niigata, Japan*

---

The present study was designed to address issues concerning inapparent carcinoma: (1) the prognosis for inapparent carcinoma treated with cholecystectomy alone, (2) the types of inapparent carcinoma that can be cured with cholecystectomy alone, and (3) does the radical second operation improve the survival of patients with inapparent carcinoma?

### Patients and Methods

Two hundred forty-one patients with gallbladder carcinoma underwent surgical resection in Niigata university hospital and its affiliated institutions from 1981 to 1989. A summary of these cases is provided in Table 1. In the present study, "inapparent carcinoma" of the gallbladder was defined as a carcinoma unrecognized before and at the time of operation, but diagnosed later on microscopic examination of the specimen. Therefore, 98 cases (41%) of "inapparent carcinoma" were included in this study. Clinical records and follow-up data could be obtained for all of them.

Histologic examination of these specimens was done in the first department of pathology of our institute. In 86 cases 5-mm stepwise tissue sections of the whole gallbladder were embedded in paraffin and cut into 4- $\mu$ m slices. The depth of cancer invasion was carefully determined in these sections. In the remaining 12 cases, depth of invasion was judged using three to four representative sections containing evidence of cancer.

We used the TNM (tumor, nodes, metastases) system<sup>11,12</sup> to describe the extent of the cancer. Depth of cancer invasion corresponds with the "T" category in this system. However, "N" and "M" categories of inapparent carcinoma could not be assessed in almost all cases, because the cancer had not yet been noticed at the time of the first operation. It also follows that the "Stage" could

---

Supported in part by the Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Science and Culture of Japan, account no. 02770776.

Address reprint requests to Yoshio Shirai, M.D., Department of Surgery, Niigata University, School of Medicine, Asahimachi 1, Niigata, 951, Japan.

Accepted for publication August 26, 1991.

TABLE 1. Patients Who Underwent Resection for Gallbladder Carcinoma at the Department of Surgery, Niigata University, 1981-1989

Time of Diagnosis	No. of Cases
Before operation	102
At the time of operation	41
After operation (inapparent carcinoma)	98
Total	241

not be determined in many of the cases. The authors therefore adopted the pathologic T category (pT) alone to describe the extent of inapparent cancer of the gallbladder. The pT system is defined in TNM system as follows<sup>11,12</sup>: pT1: tumor invades mucosa or muscle layer; pT2: tumor invades perimuscular connective tissue; no extension beyond serosa or into liver; pT3: tumor invades beyond serosa or into one adjacent organ, or both (extension 2 cm or less into liver); and pT4: tumor extends more than 2 cm into liver, or into two or more adjacent organs.

The survival curves were calculated using the Kaplan-Meier method. Differences in survival curves were measured using the generalized Wilcoxon test.

### Results

Ninety-eight cases of inapparent carcinoma are categorized according to their "T" classification and type of operation performed in Table 2. There were 24 men and 74 women. The age of these patients ranged from 37 to 87 years, with a mean of 68.5 years.

Eighty patients had cholecystectomy alone, and 14 patients had a radical second operation after pathologic confirmation of the specimen removed at the time of cholecystectomy. The remaining four patients also underwent reoperation after histologic confirmation of cancer. They had no radical procedure, however, but sampling of pericholedochal lymph nodes alone at the time of reoperation, with regard to no macroscopic evidence of residual cancer.

TABLE 2. Distribution of pT Category of 98 Patients With Inapparent Carcinoma According to Operations Performed

pT	Operations Performed			Total
	Cholecystectomy Alone	Second Radical Operation	Other Operations*	
pT1	39	1	—	40
pT2	35	10	3	48
pT3	6	2	1	9
pT4	—	1	—	1
Total	80	14	4	98

\* Refer to the text for the details of the operations.

### Cholecystectomy Alone

Follow-up data of the 80 inapparent cancer patients who underwent cholecystectomy alone is presented according to their "pT" classification in Figure 1. There were no pT4 patients.

The 39 patients with pT1 cancer had a 5-year survival rate (5ysr) of 100%. There were 35 cases of cancer rated as pT1a and 4 cases of pT1b. Only two patients with pT1a cancer died, one at 19 months and the other 66 months after surgery; the former, who had mucosal cancer with a free surgical margin, died of an unrelated cause, and the latter, who had a mucosal cancer with a positive margin at the cut stump of the cystic duct, died of recurrence of the tumor at the hilus of the liver. There was no recurrence among the pT1b patients; the longest period of survival so far is 98 months. In the 35 patients with pT2 cancer, 5ysr was 40%, and 17 patients died of recurrent disease within 55 months postoperatively. All of the six patients in the pT3 group died of recurrence within 27 months after cholecystectomy.

There were significant differences between pT1 and pT2 groups ( $p < 0.001$ ) and between pT2 and pT3 groups ( $p < 0.01$ ), respectively (Fig. 1).

There were 36 cases in which the cholecystectomized specimen included a cystic lymph node. In six cases, there was evidence of metastasis to the lymph node; five of these patients died within 45 months from recurrence, and only one has survived 36 months so far. The remaining 30 patients who had no metastasis to the node showed a significantly better ( $p < 0.001$ ) prognosis, and a 5ysr of 84%.

### Radical Second Operation

A radical second operation (after cholecystectomy) was carried out in 14 of the 98 cases with inapparent carcinoma. Table 3 presents a brief summary of the 14 patients. The radical second operation was performed for pT2, 3, or 4 inapparent cancer or a positive surgical margin.

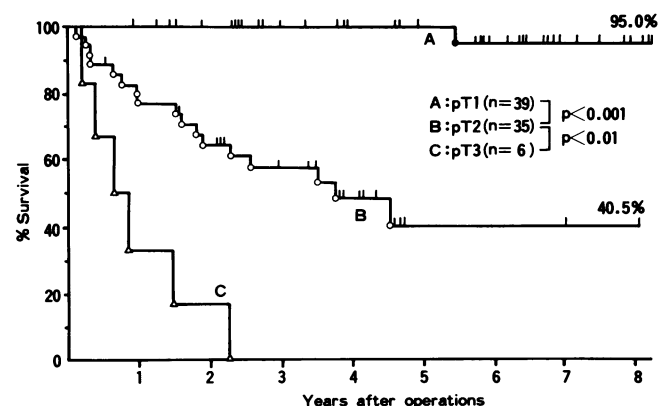


FIG. 1. Survival curves by pT category in 80 patients with inapparent carcinoma treated by cholecystectomy alone.

TABLE 3. Patients With Inapparent Carcinoma Treated by Second Radical Operation

Patient	Age (yr)	Sex	pT	pN	M	Stage	Cancer Tissue in Reresected Specimen	Residual Tumor (R) at 2nd Resection	Survival	Status	Cause of Death
1	72	M	1a	0	0	I	Not detected	R0	56 mo	Alive	—
2	37	F	2	0	0	II	Not detected	R0	18 mo	Alive	—
3	72	F	2	0	0	II	Detected: C	R0	22 mo	Alive	—
4	62	M	2	0	0	II	Not detected	R0	63 mo	Alive	—
5	58	M	2	0	0	II	Not detected	R0	65 mo	Alive	—
6	62	F	2	0	0	II	Not detected	R0	67 mo	Alive	—
7	69	F	2	0	0	II	Not detected	R0	86 mo	Alive	—
8	45	F	2	0	0	II	Not detected	R0	91 mo	Alive	—
9	76	F	2	1a	0	III	Detected: N, B	R1	44 mo	Dead	Renal cell cancer
10	72	F	2	1a	0	III	Detected: N, C	R0	105 mo	Alive	—
11	66	F	2	1b	0	III	Detected: N	R0	13 mo	Dead	Recurrence
12	66	F	3	0	0	III	Detected: C, L	R2	14 days	Dead	Complications after operation
13	74	M	3	1a	0	III	Detected: B, C	R1	59 mo	Dead	Recurrence
14	70	F	4	1b	0	IV	Detected: N, B, C, L	R2	17 mo	Dead	Recurrence

C, invasion of connective tissue around the gallbladder; N, metastasis

to regional lymph nodes; B, invasion of bile duct; L, invasion of liver parenchyma.

The "standard" radical operation in our department since 1982 adopted as a first operation for preoperatively diagnosed gallbladder carcinoma is illustrated in Figure 2. The operation is composed of a cholecystectomy, wedge resection of the gallbladder bed (including about 2 cm thickness of liver parenchyma), resection of the supra-duodenal segment of the extrahepatic bile duct, and an *en bloc* and thorough dissection of the regional lymph nodes (No. 1a and 1b nodes). As a surgical approach to management of inapparent cancer, the "standard" radical second operation was therefore composed of bile duct resection, wedge resection of the gallbladder bed, and an *en*

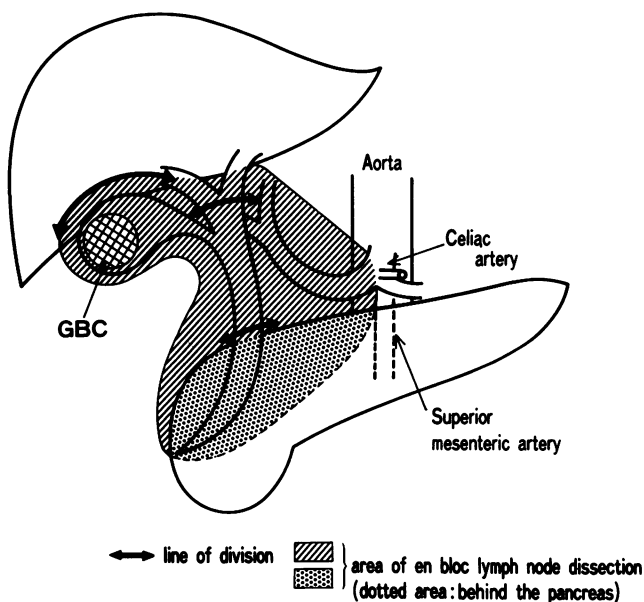


FIG. 2. Schematic representation of the extent of surgical resection in patients with gallbladder cancer.

*bloc* dissection of regional lymph nodes (No. 1a and 1b nodes). All patients except patients 1 and 10 listed in Table 3 underwent the "standard" radical second operation. In patient 1, the second resection was indicated because of a positive margin at the cystic duct, and a wedge resection of gallbladder bed was deferred in consideration of the depth of cancer invasion (pT1a). Bile duct resection was not performed in patient 10 because, in 1981, the standard for the radical operation had not been established.

As shown in Table 3, cancer tissue could be histologically proven in the tissue resected in the radical second operation in seven patients. In four of the seven patients, complete removal of the cancerous tissue could not be achieved by the second operation, and microscopic or macroscopic residual tumor (R1, R2) was identified. All of the 4 patients died by 59 months after the second resection; 2 of them died of recurrence of gallbladder cancer, 1 died of renal cell carcinoma, and another died of a post-operative complication (bleeding).

Thus far, one case of pT1 cancer survives 56 months after the second operation, and eight of the ten cases of pT2 continue to survive, with the longest time of survival being 105 months. All three cases with pT3 and pT4 have died.

To evaluate the efficacy of a radical second operation, the survival of patients with pT2 inapparent cancer treated by cholecystectomy alone were compared with those treated by the radical second procedure (Fig. 3). Survival of the group receiving the radical second operation was significantly better than cholecystectomy alone ( $p < 0.05$ ).

## DISCUSSION

In Japan, many gastroenterologists have a great interest in the early diagnosis of gallbladder carcinoma (GBC) be-

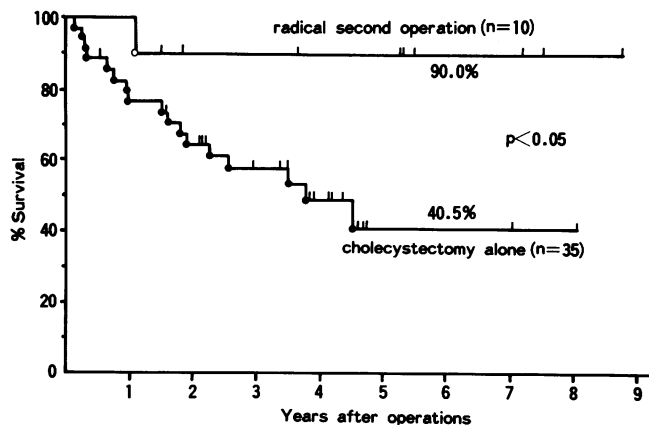


FIG. 3. Comparison of survival curves of patients with pT2 inapparent gallbladder carcinoma undergoing cholecystectomy alone and cholecystectomy combined with a radical second surgical resection.

cause of the high mortality rate of GBC in the Japanese population.<sup>13</sup> In spite of recent developments of diagnostic imaging, it is still difficult to diagnose GBC preoperatively. The present study showed that the preoperative diagnostic rate was rather low, 42% (102 of 241), and inapparent carcinoma was present in 41% of our patients.

It has been widely accepted that some cases of inapparent cancer have a good chance to be cured, and clinically overt cancer is often far advanced and beyond the scope of resection.<sup>1-3</sup> It is likely that inapparent cancer tends to be in the early stages.<sup>10</sup> Many of the cases of inapparent cancer observed in this study belonged to pT1 or pT2 (Table 2).

There are two issues concerning the treatment of inapparent carcinoma of the gallbladder. The first issue is that there are many patients with inapparent carcinoma who cannot currently be diagnosed preoperatively, and the second issue is that inapparent carcinoma is a good candidate for radical surgery because of the demonstrated predominance of earlier stages. A radical second operation for inapparent carcinoma, therefore, appears to be an effective way to improve the poor prognosis of GBC.

Most long-term survivors of GBC have been considered to be patients with inapparent cancer treated with cholecystectomy alone.<sup>4-7</sup> Nevin et al.<sup>14</sup> proposed a staging system and reported that the prognosis of GBC depended mainly on the depth of cancer invasion. Carcinoma confined to the mucosa or the tunica muscularis showed an excellent prognosis after being treated by cholecystectomy alone, but once the cancer involved all three layers, liver, or any other organ, the results of surgery were poor. Some investigators also have reported good results with surgery for patients with carcinoma confined to the mucosa or the tunica muscularis.<sup>9,15</sup>

The present study demonstrated that cholecystectomy

alone provided excellent results in patients with pT1 cancer. For this reason, a radical second operation should be avoided in the pT1 inapparent cancer group. However, pT2 and pT3 inapparent cancer had little chance to be cured by cholecystectomy alone and so a radical second operation should be considered if possible.

Glenn and Hays<sup>16</sup> proposed radical surgery for GBC in an excellent paper published in 1954. This radical procedure, commonly called "Glenn's operation," seems to have been widely accepted. This operation has been thought to be an adequate operation for GBC in early stages. The lymph node dissection in this operation is commonly referred to as "skeletonization of the lesser omentum."

In our department, the operation illustrated in Figure 2 has been adopted as the standard operation for "apparent" GBC except in pT1 tumor. This operation differs from Glenn's in that bile duct resection is performed in our operation to clear the lymphatics around bile duct and possible presence of invasion of bile duct, and lymphatic system behind the upper part of the head and neck of the pancreas is removed *en bloc*. We designed the scope of the nodal dissection on the basis of the data from Fahim et al.<sup>17</sup> and our own data (unpublished observations) relating to the routes of lymphatic drainage from the gallbladder and patterns of nodal metastasis in GBC.

In the radical second operation, the same degree of nodal dissection as in the operation illustrated in Figure 2 should be performed. Although it was impossible to remove completely cancerous tissue even in the radical second operation in some patients, it was thought that the results justified the surgical intervention (Table 3). Tsunoda et al.<sup>8</sup> reported on three patients with inapparent cancer who underwent a second-look operation. The authors, however, could not definitely comment on the efficacy of the second-look operation due to the small sample size. De Aretxabala et al.<sup>10</sup> aggressively performed a radical second operation including lymph node dissection and hepatic wedge resection for patients with inapparent GBC. They did not report long-term results of the operation, however, and concluded that further follow-up was required to assess the long-term value of this approach. In the present study, we were able to demonstrate that the radical second operation was especially effective against pT2 cancer (Fig. 3). Although the number of pT3 and pT4 cancers treated with the radical second operation was small, it is important to note that one case of pT3 and one case of pT4 survived 59 months and 17 months, respectively, after the operation. In consideration of the extremely poor prognosis (Fig. 1) of pT3 inapparent cancer patients who underwent cholecystectomy alone, the results (Table 3) of the radical second operation in pT3 and pT4 suggest a prolongation of survival time.

### Indications for a Radical Second Operation for Inapparent Cancer

Based on the results of this study, indications for a radical second operation for inapparent carcinoma are proposed in Table 4. It was demonstrated that pT1 cancer patients had an excellent survival with cholecystectomy alone. Therefore, if the depth of cancer invasion is judged to be limited to the mucosa or the muscle layer and the surgical margin, on histologic examination, is negative, the patient should be followed without recourse to a radical second operation. Prognosis of pT2 and pT3 cancer treated by cholecystectomy alone was unfavorable and was improved by a radical second operation. Therefore, the radical second operation should be indicated for pT2 or more advanced inapparent GBC. A second resection also should be considered for inapparent cancer with positive margin, regardless of the depth of invasion. When a carcinoma is found in the gallbladder removed for presumed benign disease, the cystic duct node, when found, should be examined histologically. In the case of a positive cystic node, which indicates short-term recurrence, a radical second operation should be considered.

Once a carcinoma was found in a gallbladder removed for benign disease, the depth of cancer invasion, the resection margin, and the state of the cystic node should be precisely determined by detailed pathologic examination. The depth of cancer invasion in the specimen is the most reliable criterion for a radical second operation. Although some authors<sup>5,8,18</sup> have reported some recurrences in patients with carcinoma invading the muscular layer (pT1b), others<sup>14,15</sup> have reported good results in patients with pT1a and pT1b cancers treated with cholecystectomy alone. On the basis of the results of cholecystectomy alone for pT1 cancer in this study, we do not think that a radical second operation is indicated for pT1 cancer with negative margin. The sample size of pT1b cancer, however, is so small and the follow-up period is so short that further investigation is required to conclude the indication of the radical second operation for pT1b inapparent cancer.

On histologic evaluation of the depth of invasion of GBC, it is often difficult to distinguish pseudoinvasion into the Rokitansky-Aschoff sinus (RAS) (*i.e.*, RAS involvement) from true, stromal invasion. Shirai<sup>19</sup> previously reported an attempt at a histologic differentiation of these two. RAS involvement is not a stromal invasion but an intraepithelial spread, that is, carcinoma *in situ*.

TABLE 4. Indications for Radical Second Operation for Inapparent Carcinoma of the Gallbladder

pT2 or more advanced carcinoma
Positive surgical margin
Positive cystic duct node (if examined)

Gallbladder carcinoma with RAS involvement in the muscle layer and subserosal layer, without stromal invasion, therefore, is judged to be a mucosal cancer (pT1) and is not a candidate for the radical second operation in our department.

One patient who underwent the radical second operation for stage III cancer died of bleeding within a month after operation in the present study. The operative procedure of the radical second operation is difficult because of adhesions caused by the first operation. We think that indications for the radical second operation should be carefully weighed.

The resected gallbladder should be examined intraoperatively in all cases of cholecystectomy for presumed benign disease to detect "inapparent gallbladder cancer" to avoid a second operation. The surgeon should open the gallbladder immediately after removal and observe the mucosa to detect unexpected cancer. Some investigators reported that the predominant macroscopic shape of early-staged carcinoma of the gallbladder was the superficial type.<sup>20,21</sup> Knowledge concerning macroscopic features of gallbladder cancer<sup>20,21</sup> is useful in detecting suspicious lesions. Histologic examination of a frozen section of the lesion is mandatory to prevent overlooking a cancer.

Because the number of patients who underwent the radical second operation is small in this study, further investigation is warranted to clarify the true indications and the advantages of the radical second operation.

### Conclusions

It was concluded that a radical second operation should be carried out for pT2 or more advanced inapparent carcinoma of the gallbladder whenever possible. Follow-up without a second resection is the treatment of choice for pT1 cancer with free margins. The radical second operation should contribute to a better salvage rate in this lethal disease.

### Acknowledgments

The authors thank Dr. Tetsuya Ohtani, Mr. Junichi Konno, Miss Keiko Itoh, and Mrs. Kumiko Shirai for preparation of the manuscript.

### References

1. Perpetuo MDCMO, Valdivieso M, Heilbrun LK, et al. Natural history study of gallbladder cancer: a review of 36 years experience at M.D. Anderson Hospital and Tumor Institute. *Cancer* 1978; 42:330-335.
2. Wanebo HJ, Castle WN, Fechner RE. Is carcinoma of the gallbladder a curable lesion? *Ann Surg* 1982; 195:624-631.
3. Tarpila E, Borch K, Kullman E, Liedberg G. Gallbladder cancer: current status in clinical practice. *Eur J Surg Oncol* 1988; 14:51-54.
4. Appleman RM, Morlock CG, Dahlin DC, Adson MA. Long term

- survival in carcinoma of the gallbladder. *Surg Gynecol Obstet* 1963; 117:459-464.
5. Frank SA, Spjut HJ. Inapparent carcinoma of the gallbladder. *Am Surg* 1967; 33:367-372.
  6. Kott I, Urca I. Carcinoma in situ of the gallbladder and routine cholecystectomy. *Med Chir Dig* 1974; 3:181-182.
  7. Bergdahl L. Gallbladder carcinoma first diagnosed at microscopic examination of gallbladders removed for presumed benign disease. *Ann Surg* 1980; 191:19-22.
  8. Tsunoda T, Tsuchiya R, Harada N, et al. The surgical treatment for carcinoma of the gallbladder: rationale of the second-look operation for inapparent carcinoma. *Jpn J Surg* 1987; 17:478-486.
  9. Piehler JM, Crichlow RW. Primary carcinoma of the gallbladder. *Arch Surg* 1977; 112:26-30.
  10. de Aretxabala X, Roe I, Araya JC, et al. Operative findings in patients with early forms of gallbladder cancer. *Br J Surg* 1990; 77:291-293.
  11. UICC. TNM Classification of Malignant Tumours. 4th Edition. Berlin: Springer-Verlag, 1987.
  12. AJCC. Manual for Staging of Cancer. 3rd Edition. Philadelphia: JB Lippincott, 1988.
  13. Kato K, Akai S. Geographical distribution of biliary tract cancer in Niigata prefecture. *Jpn J Clin Oncol* 1990; 20:67-71.
  14. Nevin JE, Moran TJ, Kay S, King R. Carcinoma of the gallbladder: staging, treatment, and prognosis. *Cancer* 1976; 37:141-148.
  15. Yamaguchi K, Enjoji M. carcinoma of the gallbladder: a clinicopathology of 103 patients and a newly proposed staging. *Cancer* 1988; 62:1425-1432.
  16. 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.
  17. Fahim RB, McDonald JR, Richards JC, Ferris DO. Carcinoma of the gallbladder: a study of its modes of spread. *Ann Surg* 1962; 156:114-124.
  18. Kimura W, Shimada H. A case of gallbladder carcinoma with infiltration into the muscular layer that resulted in relapse and death from metastasis to the liver and lymph nodes. *Hepatogastroenterology* 1990; 37:86-89.
  19. Shirai Y. Histological differentiation of Rokitansky-Aschoff sinus involvement from stromal invasion of carcinoma of the gallbladder. *Journal of the Japanese Surgical Society* 1987; 88:970-981 (in Japanese).
  20. Tsuchiya Y. Early carcinoma of the gallbladder: macroscopic features and US findings. *Radiology* 1991; 179:171-175.
  21. Shirai Y, Watanabe H, Kijima H, et al. Macroscopic features and imaging diagnosis of early gallbladder carcinoma. *Journal of Biliary Tract and Pancreas* 1985; 6:503-512 (in Japanese).