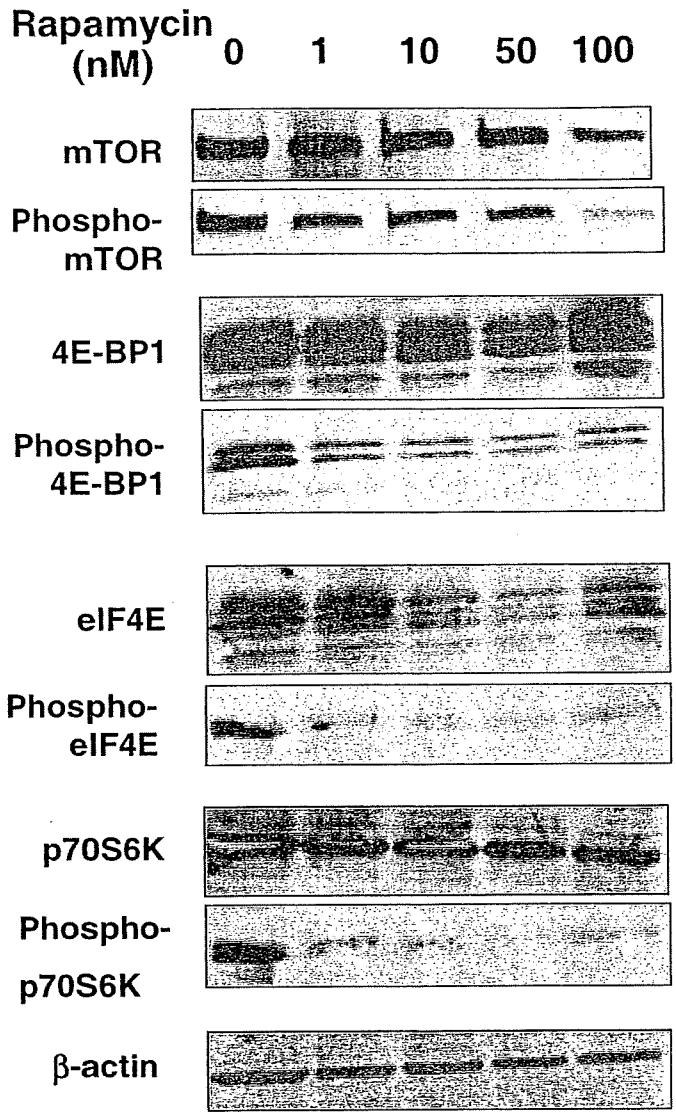

Fig. 2. Inhibition of the mammalian target of the rapamycin signal pathway by rapamycin in B13LM cells. Proteins were prepared from cells that were treated with a concentration gradient of rapamycin (0 nM, 1 nM, 10 nM, 50 nM, and 100 nM) for 48 h 50 mg of each protein was evaluated by sodium dodecylsulfate–polyacrylamide gel electrophoresis (SDS-PAGE) for the expression of the mammalian target of rapamycin, phosphor-mammalian target of rapamycin, initiation factor 4E-binding protein 1, phosphor-initiation factor 4E-binding protein 1, initiation factor 4E, phosphor-initiation factor 4E, p70S6K, and phospho-p70S6K. β-actin was also evaluated as a control. Slight dephosphorylation of mammalian target of rapamycin (mTOR) was observed in the B13LM cells treated with 1 nM of rapamycin. initiation factor 4E-binding protein 1, initiation factor 4E and p70S6K were also dephosphorylated in B13LM cells treated with 1 nM of rapamycin.

in vivo using a nude mouse model. The size of subcutaneous tumors in the rapamycin-treated mice became smaller than that of control mice at 20 days after the initiation of rapamycin treatment ($P = 0.009$), although it increased at the same rate as in the control mice until 16 days (Fig. 5a). To identify tumor-associated lymphatic vessels, we used immunohistochemistry using an antibody specific for mouse LYVE-1, which is a highly specific marker for mouse lymphatic vessels[44] (Fig. 5b). The computer-assisted quantitative analysis of lymphatic vessels revealed that rapamycin treatment reduced lymphangiogenesis in the xenografted tumors in nude mice. The number of lymphatic vessels was significantly decreased in the tumors of the rapamycin-treated mice compared with the control mice ($P < 0.001$). In addition, when we calculated the area of the lymphatic vessel lumen, it was significantly smaller in the tumors of the rapamycin-treated mice than in those of control mice ($P = 0.033$) (Fig. 5c). Finally, the occurrence of lymphatic metastasis was significantly decreased in the rapamycin-treated nude mice ($P = 0.049$). All control mice had one or two metastatic lymph nodes in the para-aortic area, whereas, three of 10 mice that were treated with rapamycin were free from lymph node metastasis and another one of the 10 had only one metastatic lymph node. Metastasis was not observed in lymph nodes in other areas, with the exception of the para-aortic area. No metastasis was observed in organs other than the lymph nodes. The mean size of the metastatic lymph nodes in mice with and without rapamycin treatment was 26.7 ± 21.3 mm^3 and 47.4 ± 77.8 mm^3, and the difference was not statistically significant (Table 2).

Discussion

Our experimental metastatic study using nude mice demonstrated that rapamycin has the potential to inhibit lymphatic metastasis of tumor cells, because the development of lymph node metastasis of B13LM cells was significantly reduced by intraperitoneal administration of rapamycin. Both the number and area of lymphatic vessels in the subcutaneous tumor were significantly smaller in the rapamycin-treated mice than in the control mice, indicating that *in vivo* rapamycin treatment inhibited the tumor-associated lymphangiogenesis.

VEGF-C and its receptor, VEFGR-3, are considered to be potent targets for the prevention of lymphatic metastasis, because the proliferating signals via VEGFR-3 promote lymphangiogenesis, and clinicopathological studies have indicated that VEGF-C/VEGFR-3 signal transduction has an important role in lymphatic metastasis.[1,17–24,45,46] Studies using experimental animal models have demonstrated that a decrease in lymphatic metastasis could be achieved by inhibiting VEGF-C/VEGFR-3 signal transduction.[47–49] Inhibition of the VEGF-C/VEGFR-3 interaction was experimentally realized by inhibitors including a soluble VEGFR-3 decoy receptor[47] and antagonistic antibody.[48] Tumor-derived VEGF-C is another therapeutic target, and VEGF-C-specific inhibition by small interfering RNA-mediated gene silencing has been shown to decrease lymphatic metastasis.[49] These results provide direct evidence of the significant role of the VEGF-C/VEGFR-3 signal transduction pathway in tumor-associated lymphangiogenesis and lymphatic metastasis. However, the methods of VEGF-C/VEGFR-3 inhibition in these studies were not immediately applicable to clinical therapy. The observed antimetastatic effect of rapamycin in our study thus has great meaning from a clinical point of view, because the analogs of rapamycin, such as CCI-779, have already progressed to the Phase III evaluation of antitumor activity.[50] In addition, it has been demonstrated that rapamycin and its derivatives have a potent antitumor action on a variety of solid tumors.[39–41] Furthermore, rapamycin and its analogs have been reported to increase the efficacy of a variety of chemotherapeutic agents, including cisplatin, doxorubicin, camptothecin, 5-fluorouracil, gemcitabin, and tamoxifen, in several types of cancers.[51–53]

The inhibitory effect of rapamycin on VEGF-C expression in B13LM cells is thought to be one of the mechanisms involved in the antilymphangiogenetic effect of rapamycin *in vivo*. There is a substantial body of evidence that tumor-derived VEGF-C plays a causal role in lymphangiogenesis and lymphatic metastasis.[1,17–24,45,46] However, because we used systemic administration of rapamycin in the present study, we cannot rule out the possibility that rapamycin affected the lymphatic endothelial cells. The decrease in the number of lymphatic vessels in the

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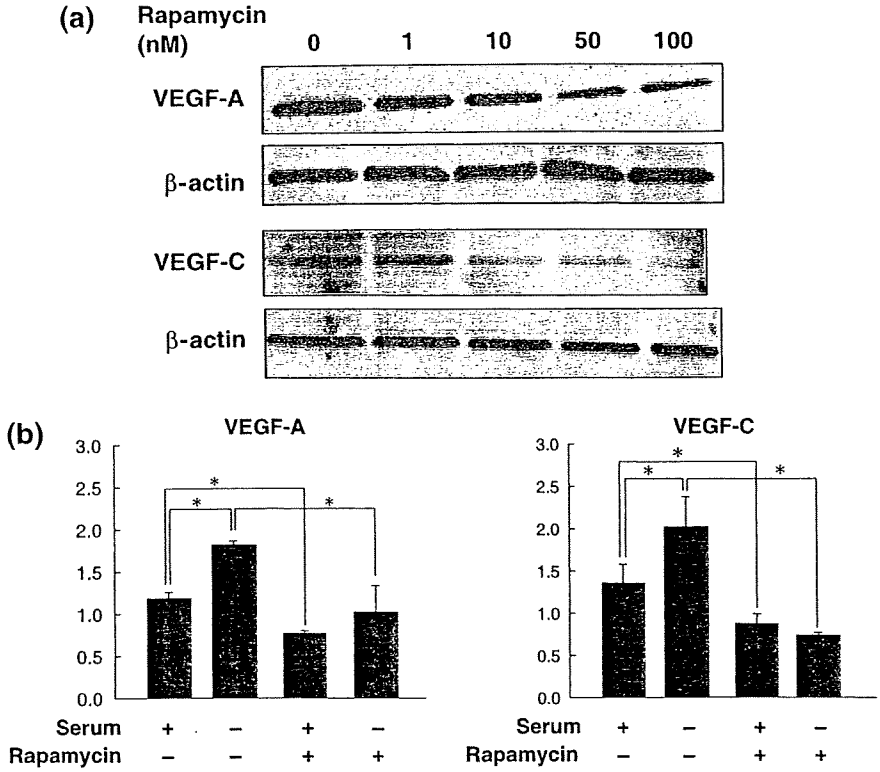

Fig. 3. Inhibition of vascular endothelial growth factor-A (VEGF-A) and vascular endothelial growth factor-C in B13LM cells by rapamycin. (a) Proteins were prepared from cells that were treated with a concentration gradient of rapamycin (0 nM, 1 nM, 10 nM, 50 nM, and 100 nM) for 48 h 50 μg of each protein was evaluated by sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) for the expression of VEGF-A and VEGF-C. β-actin was also evaluated as a control. The expressions of VEGF-A and VEGF-C were reduced by rapamycin in a dose-dependent manner. (a) Representative data of two experiments). (b) Cells were cultured in the medium with 10% (serum +), or with 0% (serum −) fetal bovine serum (FBS) for 24 h. The mRNA expressions of VEGF-A and VEGF-C were evaluated by quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis. Serum starvation-induced expression of VEGF-A was observed, and was partially repressed by rapamycin treatment. In contrast, the serum starvation-induced expression of VEGF-C was almost completely inhibited by rapamycin treatment. Note that rapamycin inhibited the constitutive expression of VEGF-A and VEGF-C in the culture condition with 10% serum. (*$P < 0.05$).

Table 1. Inhibition of vascular endothelial growth factor-C (VEGF-C) secretion by rapamycin

	Rapamycin	
	(+)	(−)
VEFG-C (pg/mL)	510.6	131.8

rapamycin-treated tumor could be mediated by a direct effect of rapamycin on lymphatic endothelial cells, because the growth signal via VEGFR-3 activates the Akt-dependent pathway and promotes the proliferation of lymphatic endothelial cells.[54,55] However, it remains to be determined whether rapamycin directly inhibits the proliferation of lymphatic endothelial cells.

The mTOR pathway in B13LM cells was activated under a normal culture condition, which was not surprising because up-regulation of the mTOR pathway is observed in many human cancers.[56–58] Inhibition of the mTOR pathway by rapamycin reduced the expression of VEGF-C and, furthermore, inhibited the VEGF-C expression that was induced by serum starvation. Increased phosphorylation by withdrawal of FBS suggested that the Akt pathway in B13LM cells was activated by serum starvation, although PI3K/Akt pathway would be usually inactivated under the serum starved-conditions. These results indicate the involvement of the mTOR pathway in the expressional regulation of VEGF-C in B13LM cells. This is not in conflict with the results of a previous study that showed that the PI3K pathway plays an important role in IGF-1-induced VEGF-C expression,[29] because activation of the PI3K/Akt pathway leads to mTOR signaling.

The exact mechanism of how rapamycin inhibits mTOR function is not fully understood. Evidence has been presented that kinases, including Akt, can phosphorylate mTOR at Ser2448 and that such phosphorylation is likely to have a regulatory role.[59–61] On the other hand, the complex of rapamycin and FKBP-12 binds directly to mTOR and inhibits the mTOR-mediated phosphorylation of S6K1 and 4E-BP1.[32] Rapamycin also weakens the interaction of mTOR and raptor (a componet of the mTOR complex), which results in the inhibition of mTOR functions.[62] In the B13LM cells treated with 1 nM of rapamycin, the downstream molecules of mTOR, such as 4E-BP1, eIF4E and p70S6K were dephosphorylated, suggested that 1 nM of rapamycin sufficiently inhibited the mTOR pathway, although phosphorylation of mTOR (at Ser2448) remained. It was suspected from these results that the dephosphorylation of mTOR was not necessarily in the inhibitory mechanism of rapamycin in B13LM cells. A similar observation was previously observed in the hepatoma cell, Hep-G2, that was activated by insulin.[63]

The expression of both VEGF-A and VEGF-C was increased under the serum starved-conditions. However, the contribution of the mTOR pathway in the regulation of VEGF-A and VEGF-C to serum-starvation stimuli seemed not to be same because the efficacy of suppression by rapamycin was different. The serum-starvation-inducing expression of VEGF-C was completely suppressed by rapamycin, whereas the inhibition of serum-starvation-inducing VEGF-A by rapamycin appeared partially. Interestingly, a previous study using colon carcinoma cells suggested that extracellular signal-regulated kinase (ERK)1/2 activation, but not Akt activation, is required for the induction of VEGF-A by serum starvation.[26]

The size of the subcutaneous tumors in nude mice was reduced at day 20 by the rapamycin treatment. One possible explanation for the suppression of the growth of the tumor may be that tumor angiogenesis was inhibited, because rapamycin has an antiangiogenic effect. A previous study using an animal tumor model showed a similar inhibition of tumor growth, in which rapamycin was considered to mainly affect the endothelial cells; VEGF-induced endothelial cell proliferation rather than tumor-derived VEGF-A expression was inhibited by rapamycin.[41] In our previous study, rapamycin inhibited the B13LM cell proliferation *in vitro*. Thus, a direct effect of rapamycin on cell proliferation should be also considered.

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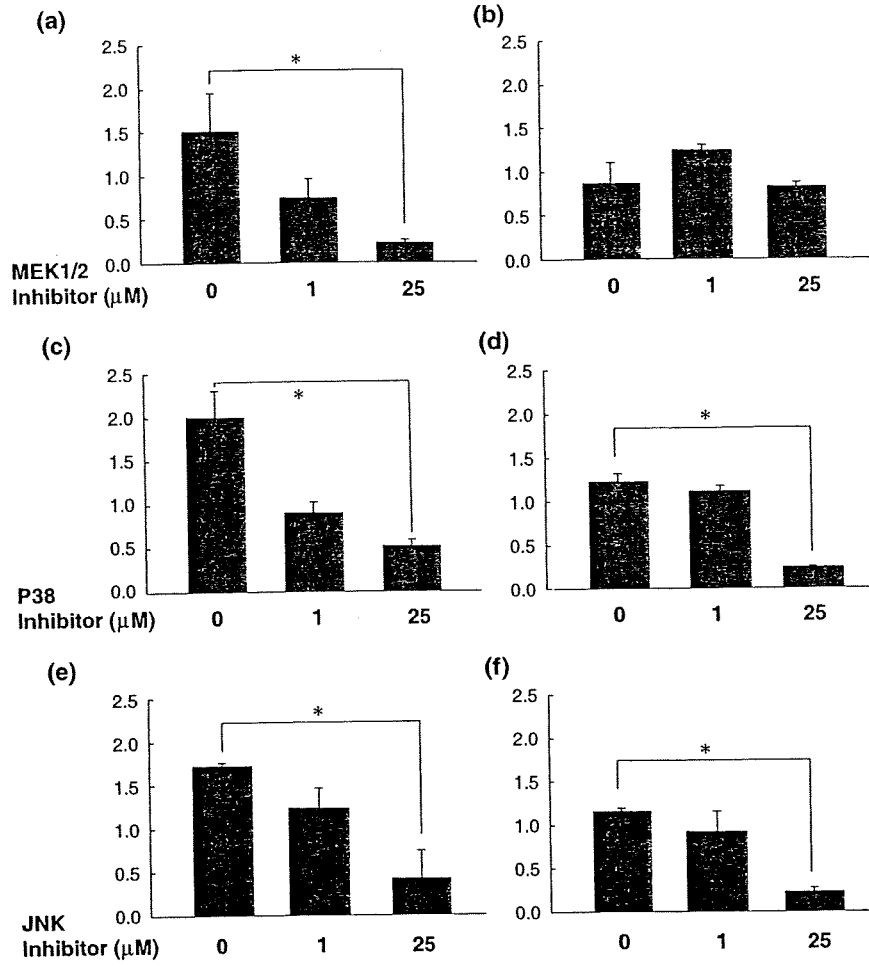
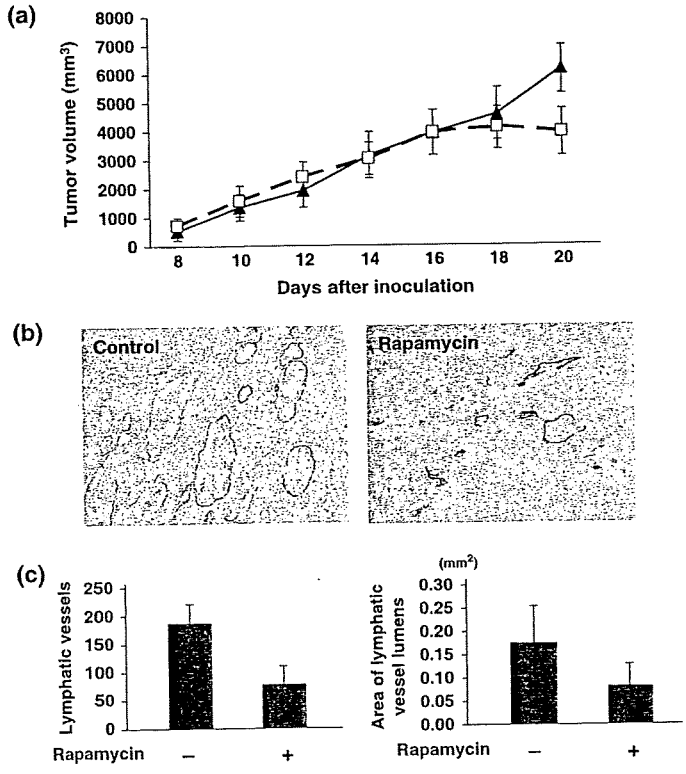


Fig. 4. mRNA expression of vascular endothelial growth factor-A (VEGF-A) (a, c, e) and VEGF-C (b, d, f) in B13LM cells treated by the MEK1/2 inhibitor (U0126) (a, b), p38 inhibitor (SB202190) (c, d), and JNK inhibitor (SP600125) (e, f). mRNA were prepared from cells treated with a concentration gradient of each inhibitor (0 nM, 1 nM, 25 nM) for 48 h. The expression level of each mRNA was adjusted using the level of β-actin mRNA, and expressed as ratio to β-actin mRNA. The inhibitors of MEK1/2, p38, and JNK inhibited VEGF-A expression in a dose-dependent manner. The inhibitors of p38 and JNK inhibited VEGF-C expression at their highest concentration (25 nM). However, the inhibitory effect of the MEK1/2 inhibitor was ambiguous. (*$P < 0.05$)



The stimulation by growth factors, including IGF-1, PDGF, EGF, and TGF-β, has been shown to induce mRNA expression of VEGF-C.[27] Stimulatory signals from these growth factors activate MAPK signal pathways, which in turn control the cell regulation, including proliferation, differentiation, and apoptosis. The results of our experiment using kinase inhibitors suggest that the signal transduction pathways of VEGF-A and VEGF-C are similar but not identical in B13LM cells. The inhibitors for JNK and p38 inhibited the expression of both VEGF-A and VEGF-C. However, it is notable that the inhibition of VEGF-C by the MEK1/2 inhibitor was not remarkable.

Fig. 5. Evaluation of the effect of rapamycin on intratumoral lymphangiogenesis and lymphatic metastasis using an experimental metastatic model in nude mice. 5.0×10.0^6 B13LM cells were injected subcutaneously into the left inferior limb. Tumors were allowed to grow for 7 days and then rapamycin (1.5 mg/kg per day) ($n = 10$) or the vehicle alone ($n = 11$) was intraperitoneally given to the mice every day. The subcutaneous tumor volume ([major axis] × [minor axis]^2 × $\pi/6$) was measured every other day (a). Inhibition of the tumor growth was observed in rapamycin-treated mice at day 20 ($P = 0.009$). After 3 weeks from the start of treatment, mice were killed. Lymphatic vessels in the subcutaneous tumors were evaluated using LYVE-1 immunostains and computer-assisted quantitative analysis. (b) Representative examples of LYVE-1 immunostains of the subcutaneous tumors (left, control mice; right, rapamycin-treated mice). The lymphatic vessels were less conspicuous in the tumor of rapamycin-treated mice than that of control mice. (c) Ten hot spots having the greatest number of LYVE-1-positive vessels were selected in each slide and evaluated. The number (left) and the area (right) of lymphatic vessels were significantly decreased in rapamycin-treated mice ($P < 0.001$ and $P = 0.033$, respectively).

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Table 2. Results of the experimental metastasis model

Lymph node	Lymph node metastasis	Size of metastatic lymph node (mm^3)
Rapamycin	7/10*[†]	26.7 ± 21.3
Control	11/11	47.4 ± 77.8

[†]The numbers of metastatic lymph nodes in each mouse with and without rapamycin treatment were 0, 0, 0, 1, 1, 1, 1, 1, 1, 1 and 1, 1, 1, 1, 1, 1, 1, 2, 2, respectively. The size of the metastatic lymph node is given as the mean ± SD; *$P = 0.049$.

Binding of growth factors to their receptor-type tyrosine kinase leads to Grb2/SOS/Ras interaction, which activates MEK1/2. Activated MEK1/2 then activates ERK1/2. Interestingly, a previous study has shown that IGF-1-induced VEGF-C expression in lung carcinoma cells is both PI3K- and ERK-dependent, but PI3K has the predominant role.[29] Another study has shown that the induction of Ras oncoprotein in fibroblasts or fibrosarcoma cells induced VEGF-A mRNA, but did not induce VEGF-C mRNA.[27,54]

In summary, rapamycin inhibited the expression of VEGF-C, a potent growth factor for lymphatic endothelial cells, *in vitro*. Lymphatic vessels in the primary tumors were significantly reduced, and finally the lymph node metastasis was decreased in our experimental animal model using lymphatic metastatic-prone B13LM cells. Our results provide the first preclinical data that rapamycin has the potential to suppress tumor-related lymphangiogenesis and lymph node metastasis. Further understanding of the signal transduction of VEGF-C/VEGFR-3 axis could prove invaluable for improving treatments that target lymphangiogenesis.

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Status of Surgical Treatment of Biliary Tract Cancer

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Key Words

Biliary tract carcinoma · Bile duct carcinoma, hilar, middle, distal · Gallbladder carcinoma · Papilla of Vater carcinoma · Biliary surgery, 5-year survival · Disease stage

Abstract

Complete surgical resection of biliary tract carcinoma remains the best treatment. The Japanese Society of Biliary Surgery has organized a registry project and established a classification of biliary tract carcinoma. We report here the status of biliary surgery in Japan. For hilar bile duct carcinoma, major hepatectomy is needed to increase the resection rate, and total caudate lobectomy is required for curative resection. The 5-year survival rate was 39.1%. Middle and distal bile duct carcinomas were treated with pancreatoduodenectomy (PD) or pylorus-preserving PD (PPPD) or bile duct resection alone. The 5-year survival rate was 44.0%. The treatment of gallbladder carcinoma with pT1 lesions is cholecystectomy. The treatment of pT2 lesions is extended cholecystectomy or various hepatectomy with or without extrahepatic bile duct resection along with lymphadenectomy. Treatment of pT3 and pT4 lesions includes hepatectomy with or without bile duct resection, combined with vascular resection, extended lymphadenectomy, and autonomic nerve dissection. Several groups in Japan have performed hepatopancreatoduodenectomy. The 5-year survival rate of pT1, pT2, pT3, and pT4 were 93.7, 65.1, 27.3, and 13.8%. PD or PPPD is the standard operation for carcinoma of the papilla of Vater. The 5-year survival rate was 57.5%.

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Introduction

Complete surgical resection of biliary tract carcinoma remains the best treatment for long-term survival. In Japan, the Japanese Society of Biliary Surgery (JSBS) is organized into 225 institutions. It performs registration of biliary tract carcinomas as one of its projects. In this project, the society has established guidelines for the treatment of cancer of the biliary tract based on the extent of involvement at each site. A total of 3,518 cases of biliary tract carcinoma were registered between 1998 and 2002; the site of carcinoma was the bile duct in 1,669, the gallbladder in 1,345, and the papilla of Vater in 504 cases. These cases were analyzed with regard to patient survival. We report the status of biliary surgery in Japan.

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Classification of Biliary Tract Carcinoma

As noted above, the JSBS established guidelines for the treatment of cancer of the biliary tract based on the extent of involvement at each site, according to the Classification of Biliary Tract Carcinoma currently used in Japan, and the 2nd English edition was published in 2004 [1]. The guidelines promoted in Japan for the treatment of biliary tract carcinoma are divided into three anatomical regions: the biliary duct, gallbladder, and papilla of Vater.

Bile Duct Carcinoma

Staging

Extrahepatic carcinomas have been subdivided into proximal or hilar, middle, and distal subgroups. The histological extent of tumor invasion around the bile duct (t category) in the classification of biliary tract carcinoma of JSBS is defined as the degree of tumor extension. According to the currently used Japanese classification of tumor invasion into the bile duct wall, serosal invasion is histologically divided into 5 stages, m, fm, ss, se, and si, in anatomical fashion. Furthermore, various types of direct invasion of the carcinoma into four structures present around the bile duct, i.e., invasion of the hepatic parenchyma (hinf), pancreatic parenchyma (panc), portal venous system (p), and arterial system (a), are graded from 0 to 3. Nodal involvement of carcinoma is classified into four groups. The stages of biliary tract carcinoma of JSBS are classified into five groups [1].

Hilar Bile Duct Carcinoma

Long-term survival with hilar bile duct carcinoma depends critically on complete resection with negative margins. The resection rate increases with the performance of major hepatectomy, and the likelihood of negative margins by performing it rises in hilar bile duct carcinoma. In addition, total caudate lobectomy is required for curative resection since caudate branches join the hilar bile duct [2, 3]. However, the risk of developing hepatic failure as a postoperative complication increases when major hepatectomy is performed. Therefore, when major hepatectomy is planned, portal vein embolization (PVE) is performed in many Japanese institutions. The main purpose of PVE is to induce compensatory hypertrophy of the future remnant liver and thus minimize postoperative liver dysfunction. In the recent literature from high-volume centers in Japan [4–11], the mortality rate ranged from 0 to 12%. The overall 3- and 5-year survival rates ranged from 26 to 54.8% and 23 to 40%, respectively. The proportion of stage IVa (5th edition of UICC) or over stage III (6th edition of UICC) ranged from 41 to 72%. A total of 255 cases of hilar bile duct carcinoma subjected to major hepatectomy were registered in the JSBS between 1998 and 2002 (table 1). The surgical procedure was left hepatectomy in 54 patients, extended left hepatectomy in 66 patients, left trisegmentectomy in 10 patients, right hepatectomy in 35 patients, extended right hepatectomy in 69 patients, right trisegmentectomy in 18 patients, and central bisegmentectomy in 3 patients. Bloc hepatic resection with pancreatoduodenectomy (HPD) was performed in 29 patients. Portal vein resection and reconstruction was performed in 167 patients. Resection of the right or left hepatic artery and reconstruction was performed in 78 patients. The overall the 1-, 2-, 3-, and 5-year survival rates of patients who underwent major hepatectomy were 77.3, 55.9, 46.7, and 39.1%, respectively. Patients were grouped according to the Japanese classification as stage I (n = 21, 8.2%), stage II (n = 45, 17.6%), stage III (n = 66, 25.9%), stage IVa (n = 86, 33.7%), or stage IVb (n = 37, 14.5%). The 5-year survival rate was 90.0% in stage I patients, 57.7% in stage II, 46.2% in stage III, 29.9% in stage IVa, and 17.0% in stage IVb patients (fig. 1). Compared with high-volume centers in Japan, the overall survival rate of the JSBS is good. This difference in survival rate is attributable to the higher percentage of cases of advanced cancer among those undergoing surgery at high-volume centers in Japan where aggressive surgery is often performed for advanced cancer.

Table 1. Surgical procedure for hilar bile duct carcinoma

Type of hepatectomy	Cases	With PD	With PV	With HA
Left hepatectomy	54	2	2	1
Extended left hepatectomy	66	9	6	3
Left trisegmentectomy	10	1	2	
Right hepatectomy	35	8	1	
Extended right hepatectomy	69	9	4	
Right trisegmentectomy	18	4	2	
Central bisegmentectomy	3			
Total	255	29	17	8

PD = Pancreatoduodenectomy; PV = resection and construction of the portal vein; HA = resection and construction of the hepatic artery.

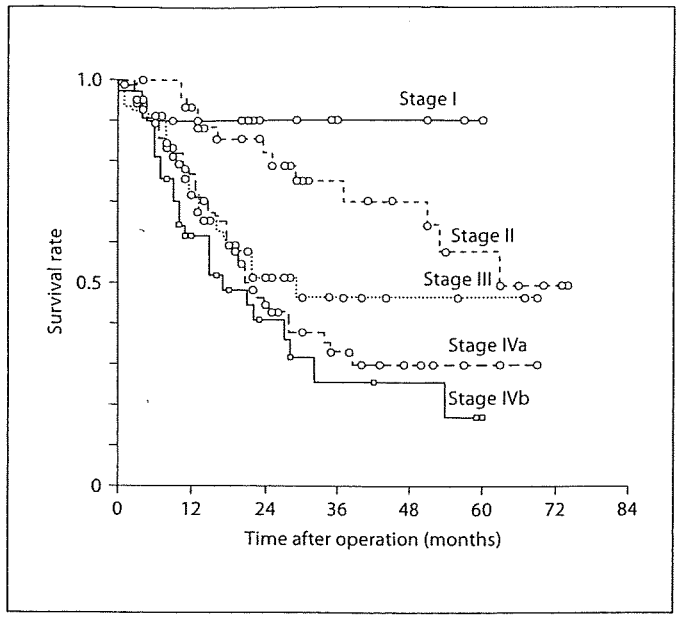

Fig. 1. Survival rates of hilar bile duct carcinoma according to stage.

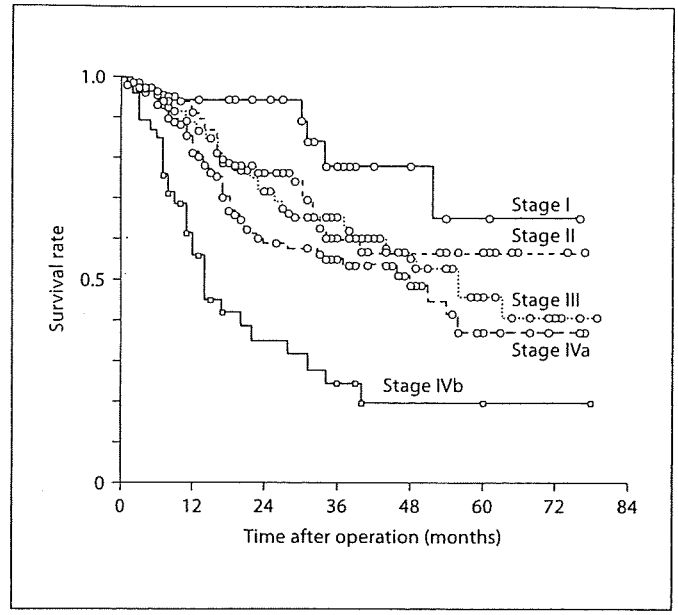

Fig. 2. Survival rates of middle and distal bile duct carcinoma according to stage.

Table 2. Studies of middle and distal bile duct carcinoma

Reference	Year	Location of tumor	Patients	3-Year survival, %	5-Year survival, %
Yamaguchi et al. [12]	1997	Distal	11	38	19
Yamaguchi et al. [12]	1997	Middle	11	33	11
Kayahara et al. [13]	1999	Middle and distal	50	47	35
Suzuki et al. [14]	2000	Middle and distal	99	50	37.4
Sasaki et al. [15]	2001	Middle and distal	59	42.6	33.6
Yoshida et al. [16]	2002	Distal	27	37	37
Sakamoto et al. [17]	2005	Middle and distal	55	52	24

Middle and Distal Bile Duct Carcinoma

Middle and distal bile duct carcinoma is treated with pancreatoduodenectomy (PD) or pylorus-preserving PD (PPPD) or bile duct resection alone. In Japan, some surgeons have advocated complete removal of the primary bile duct cancer with connective tissue clearance, including lymph nodes and neural plexus dissection. Recent results reported from high-volume centers in Japan are summarized (table 2) [12–17]. The overall 3- and 5-year survival rates ranged from 33 to 52% and 11 to 37.4%, respectively. 427 patients with middle and duct carcinoma, excluding those with insufficient data, who underwent PD or PPPD were registered in the JSBS between 1998 and 2002. The overall 1-, 2-, 3-, and 5-year survival rates were 83.5, 66.6, 57.9, and 44.0%, respectively. Patients were grouped according to the Japanese classification as stage I (n = 36, 8.4%), stage II (n = 82, 19.2%), stage III (n = 134, 31.4%), stage IVa (n = 130, 30.4%), or stage IVb (n = 45, 10.5%). The 5-year survival rates were 64.8% in stage I patients, 56.9% in stage II, 45.6% in stage III, 36.8% in stage IVa, and 19.5% in stage IVb (fig. 2).

Gallbladder Carcinoma

Staging

The histological extent of tumor invasion around the gallbladder (t category) in the classification of gallbladder carcinoma of the JSBS is defined as the degree of tumor extension. According to the currently employed Japanese

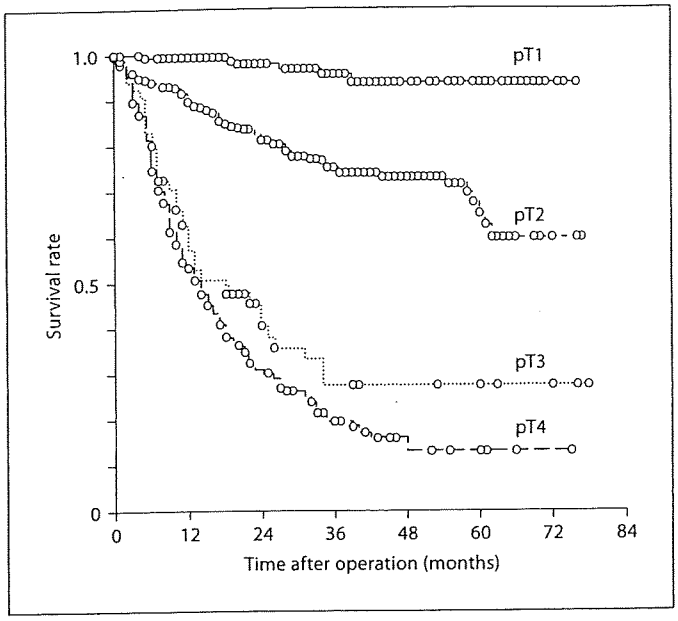

Fig. 3. Survival rates of gallbladder carcinoma according to depth of invasion.

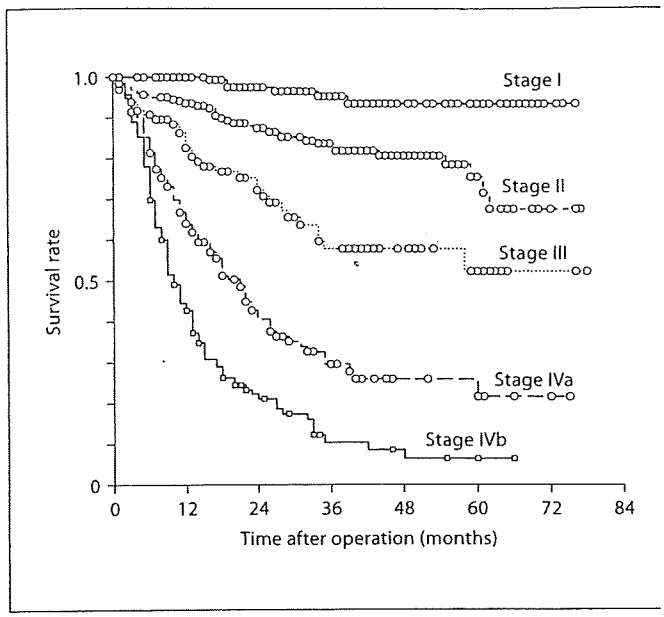

Fig. 4. Survival rates of gallbladder carcinoma according t stage.

classification of tumor invasion into the bile duct wall, serosal invasion is histologically classified into five stages, m, mp, ss, se, and si, in accordance with the anatomical structure. Furthermore, various types of direct invasion of carcinoma into four structures present around the bile duct are distinguished, i.e., invasion of the hepatic parenchyma (hinf), hepatoduodenal ligament (binf), portal venous system (p), and arterial system (a), which are graded from 0 to 3. Nodal involvement of gallbladder carcinoma is classified into four groups. The stages of biliary tract carcinoma of the JSBS are classified into five groups [1].

Surgery

Most surgeons agree that pT1 tumors are effectively treated with cholecystectomy. The 1-, 2-, 3-, and 5-year survival rates of pT1 patients (n = 160) registered with the JSBS were 99.4, 97.8, 95.4, and 93.7%, respectively (fig. 3). pT2 tumors often exhibit lymph node metastases. 30% (93/306) of the T2 tumors registered with JSBS were associated with lymph node metastases. Lymph node dissection is thus necessary for pT2 gallbladder carcinoma. Extended cholecystectomy or various types of hepatectomy with or without extrahepatic bile duct resection have been performed for pT2 patients in Japan. The range of liver resection required as part of radical surgery is still controversial. The 1-, 2-, 3-, and 5-year survival rates of T2 patients (n = 306) registered with the JSBS were 89.8 81.1, 75.2, and 65.1%, respectively (fig. 3). For pT3 an pT4 tumors, the surgical procedures currently used in Ja pan include various types of hepatectomy with or withou bile duct resection, combined vascular resection, extend ed lymphadenectomy, and autonomic nerve dissectior Several surgical groups in Japan have performed HPD fo locally advanced gallbladder carcinoma. The usefulnes of extrahepatic bile duct resection as part of radical sur gery for advanced gallbladder carcinoma is also still con troversial, particularly when there is no apparent extra hepatic bile duct involvement. The 1-, 2-, 3-, and 5-yea survival rates of pT3 patients (n = 66) registered with th JSBS were 57.7, 41.0, 27.3, and 27.3%, while those for pT patients (n = 228) were 53.6, 30.3, 19.5, and 13.8%, respec tively (fig. 3).

760 patients with gallbladder carcinoma, excludin those with insufficient data, who underwent resectio were registered in the JSBS between 1998 and 2002. Th overall 1-, 2-, 3-, and 5-year survival rates were 78.2, 66.: 58.9, and 52.6%, respectively. There are two papers cor cerning large numbers in Japan from different period The 5-year survival rate of 1,686 patients with resectio between 1979 and 1988 was 30.1% [18], while that of 3,24 patients with resection between 1988 and 1998 (JSBS) wa 42% [19]. Patients were grouped according to the Jap nese classification as stage I (n = 160, 8.4%), stage

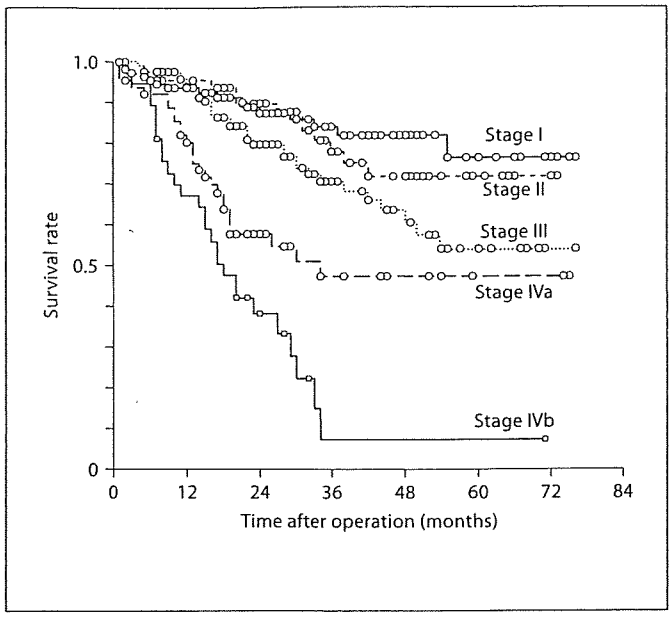

Fig. 5. Survival rates of carcinoma of the papilla of Vater according to stage.

Table 3. Studies of carcinoma of the papilla of Vater

Reference	Year	Patients	3-Year survival, %	5-Year survival, %
Kawarada et al. [20]	1993	89	63.6	57.4
Nakao et al. [21]	1994	26	57.7	52.3
Shirai et al. [22]	1996	35	60	
Kayahara et al. [23]	1997	36	66	56
Tanaka et al. [24]	2002	16	58.9	55

(n = 208, 19.2%), stage III (n = 98, 31.4%), stage IVa (n = 152, 30.4%), or stage IVb (n = 142, 10.5%). The 5-year survival rate was 93.6% in stage I patients, 80.8% in stage II, 52.6% in stage III, 21.5% in stage IVa, and 6.5% in stage IVb (fig. 4).

Carcinoma of the Papilla of Vater

Staging

The histological extent of tumor invasion around the papilla of Vater (t category) in the classification of gallbladder carcinoma of the JSBS is defined as the degree of tumor extension. Various types of histologically direct invasion of the carcinoma into two structures present around the papilla of Vater, i.e. the pancreatic parenchyma (panc) and duodenum (du), are graded from 0 to 3. Nodal involvement of gallbladder carcinoma is classified into four groups. The stages of biliary tract carcinoma of JSBS are classified into five groups [1].

Surgery

In most series, the resectability rate is higher than for other malignant tumors of the periampullary region. PD or PPPD is the standard operation for carcinoma of the papilla of Vater. Recent reports from high-volume centers in Japan are summarized (table 3) [20–24]. The overall 3- and 5-year survival rates ranged from 55 to 66% and from 40 to 60%, respectively. 404 patients with carcinoma of papilla of Vater, excluding those with insufficient data, who underwent PD or PPPD were registered in the JSBS between 1998 and 2002. The overall 1-, 2-, 3-, and 5-year survival rates were 89.3, 75.6, 66.0, and 57.5%, respectively. Patients were grouped according to the Japanese classification as stage I (n = 112, 27.7%), stage II (n = 65, 16.1%), stage III (n = 126, 31.2%), stage IVa (n = 64, 15.8%), or stage IVb (n = 37, 9.2%). The 5-year survival rates were 76.3% in stage I patients, 71.7% in stage II, 54.0% in stage III, 47.2% in stage IVa, and 7.4% in stage IVb (fig. 5).

Conclusion

We report the status of biliary surgery in Japan. Hilar bile duct carcinoma is one of the diseases on which Japanese biliary tract surgeons place particular emphasis. PVE performed during major hepatectomy and total caudate lobectomy have contributed to improving the outcome of treatment of hilar bile duct carcinoma. Middle and distal bile duct carcinomas are treated with PD or PPPD or bile duct resection alone. The treatment of gallbladder carcinoma with pT1 lesions is cholecystectomy. The treatment of pT2 lesions is extended cholecystectomy or various hepatectomy with or without extrahepatic bile duct resection, and lymphadenectomy. The treatment of pT3 and pT4 lesions includes various types of hepatectomy with or without bile duct resection combined vascular resection, extended lymphadenectomy, and autonomic nerve dissection. The usefulness of resection of the extrahepatic bile duct and the range of liver resection of gallbladder carcinoma are still controversial. Several groups in Japan perform HPD for locally advanced gallbladder carcinoma. PD or PPPD is the standard operation for carcinoma of the papilla of Vater.

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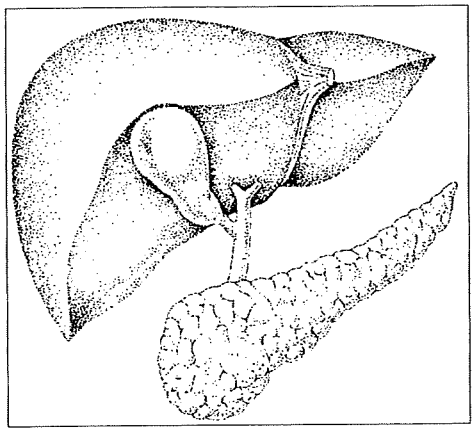

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Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese Society of Biliary Surgery classification

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Abstract

Background/Purpose. The role of aggresive surgery for stage IV gallbladder carcinoma remains controversial. Survival and prognostic factors were analyzed in patients with stage IV disease, based on the Japanese Society of Biliary Surgery (JSBS) classification, to identify the group of patients who could benefit from radical surgery.

Methods. A retrospective analysis was done of 79 patients with JSBS stage IV gallbladder carcinoma who had undergone surgical resection with curative intent at our institution. The standard procedures were anatomical S4a + S5 subsegmentectomy (n = 29) with extrahepatic bile duct resection and extended lymphadectomy, but when right Glisson's sheath and/or the hepatic hilum were involved, right extended hepatectomy (n = 34) or right trisegmentectomy (n = 3) was selected. To achieve a tumor-free margin combined pancreaticoduodenectomy was performed in 12 patients, and major vascular resection in 17 patients.

Results. In the patients with stage IV gallbladder carcinoma, the curative resection rate was 65.8% and the hospital mortality rate was 11.4%. The postoperative 5-year survival rate following curative resection was 13.7%. Univariate analysis indicated that curability, hepatoduodenal ligament invasion, nodal involvement, and vascular resection were significant prognostic factors. Neither hepatic invasion nor liver metastasis was a significant factor.

Conclusions. Aggressive surgical resection should be considered even in stage IV patients when hepatoduodenal ligament invasion and nodal involvement are absent or limited. Acceptable survival may be expected among such patients only when curative resection is achieved.

Key words Gallbladder carcinoma · Surgical resection · Stage IV · Hepatoduodenal ligament invasion · Liver metastasis

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Introduction

The majority of gallbladder carcinomas are diagnosed at advanced stages of the disease,[1–3] in spite of the recent advances in diagnostic modalities. This may be related to the lack of specific symptoms and signs,[1,4] and also the rapid growth of the tumor. Surgical approaches in resectable lesions remain the principal treatment for cure in gallbladder carcinomas, but prognosis is closely correlated with the extent of tumor invasion, suggesting that survival is stage-dependent.[1–8] In patients with early stages of the disease, surgical resection can achieve good outcome, but in advanced stages, the prognosis is apparently poor, even after radical resection.[2,3,8–12] Five-year survival rates in patients with advanced gallbladder carcinoma have been reported to range from 0% to 20%.[6,8,10–15]

In recent years, efforts have been made to increase the resectability of advanced gallbladder carcinoma, especially stage IV, by extending surgical procedures, such as extended right hepatectomy combined with pancreaticoduodenectomy and/or vascular resection and reconstruction.[16–18] According to the reports of Endo et al.[19] and Kondo et al.,[20] aggressive surgical approaches brought about some survival benefit among selected patients with advanced disease. On the other hand, extended surgical procedures carry a high risk of postoperative morbidity and mortality, especially in patients with obstructive jaundice.[15–21] The question therefore arises as to the indications for aggressive surgery in patients with stage IV disease, based on the balance between survival benefit and operative risk. At present, indications for radical resection of stage IV gallbladder carcinoma have not yet been fully defined.

The aim of the present study was to clarify which patients might benefit from radical surgery, and achieve long-term survival. We therefore analyzed our experience of surgical resection for stage IV gallbladder carcinoma, based on the Japanese Society of Biliary Surgery

(JSBS) staging system[22] (Table 1). Since 1980, we have performed aggressive surgical resections for 79 patients with stage IV disease (JSBS) with curative intent. In the present study, we retrospectively evaluated the effects of the aggressive surgery on prognosis, based on the medical records. Furthermore, as a strategy for analysis of tumor characteristics, stage IV tumors were divided into four subgroups, according to the extent of adjacent organ involvement, defined by the JSBS classification as follows: (1) hepatic-involvement type (pHinf 2-3, and pBinf 0-1), (2) biliary-involvement type (pBinf 2-3, and pHinf 0-1), (3) hepato-biliary type (pHinf 2-3 and pBinf 2-3), and (4) other. Surgical curability and postoperative morbidity and mortality were then investigated, and compared between the groups. The results of the present study may be helpful in evaluating candidates for aggressive surgical resection among stage IV patients in the future.

Patients and methods

Between 1980 and December 2005, 143 patients with gallbladder carcinoma underwent surgical resection with curative intent in the Department of General Surgery, Chiba University Hospital. During this period, surgical approaches were employed in all patients with gallbladder carcinoma unless there was involvement of the left and/or proper hepatic artery, peritoneal dissemination, or distant metastases. However, limited hepatic metastases or paraaortic lymph node metastases were resected with the primary tumor, but only if complete tumor resection was possible.

The latest International Union Against Cancer (UICC) staging system (sixth edition)[23] defines stage IV only by distant metastasis (M1), whereas stage IV as defined by the JSBS system comprises different extents of disease, as shown in Table 1. In the present study, the clinical stage of the disease was evaluated according to the JSBS classification. Among the patients with resected gallbladder carcinomas (n = 143), there were 7, 23, 34, and 79 with stage I, II, III, and IV, respectively. Therefore, the 79 patients classified as having stage IV (stage IVa, n = 42; and stage IVb, n = 37) were the subjects of this study, and their details were reviewed retrospectively. Patient age ranged from 44 to 83 years (mean, 67.8 years), and the ratio of men to women was 28: 51. None of the patients received chemotherapy before surgery. Furthermore, as a strategy for analysis of tumor characteristics, the 79 patients with stage IV tumors were stratified into subgroups according to the extent of adjacent organ involvement, defined by the JSBS, as follows: (1) hepatic-involvement type (pHinf 2-3, and pBinf 0-1), 32 patients; (2) biliary-involvement type (pBinf 2-3, and pHinf 0-1), 24 patients; (3) hepato-biliary type (pHinf 2-3 and pBinf 2-3), 17 patients; and (4) other, 6 patients. The surgical curability rates, as well as surgical morbidity and mortality rates, were then investigated, and compared between the groups.

The surgical procedures performed are listed in Table 2. Our standard procedures for advanced gallbladder carcinoma were anatomical S4a + S5 subsegmentectomy (n = 29) with extrahepatic bile duct resection and extended lymphadectomy including the N1 and N2 nodes (JSBS), and paraaortic node sampling. However, when right Glisson's sheath and/or the hepatic hilum was involved, right extended hepatectomy (n = 34) or right trisegmentectomy (n = 3) was performed. In addition, to achieve a tumor-free margin, pancreaticoduodenectomy was added in 12 patients, and major vascular resection and reconstruction of remaining liver was performed in 17 patients (portal vein for 14; hepatic artery for 4). The inferior vena cava was also partially resected and repaired by means of primary closure in 2 patients. "Curative resection", in which the surgical margin was histologically free from cancer involvement was achieved in 52 patients (65.8%), and noncurative resection was done in 27 patients (34.1%). Mean follow-up was 152 months (range, 6–288 months).

Survival curves were constructed using Kaplan-Meier analysis. Statistical assessment of survival was performed with the log-rank test. Cox univariate and multivariate analyses were performed to determine prognostic factors for survival. Surgical curability rates, as well as morbidity and mortality rates, were compared using the χ^2 test. A P value of less than 0.05 was considered significant.

Results

Survival

Cumulative survival curves according to stage of disease are shown in Fig. 1. Satisfactory results were achieved in patients with stage I and stage II diseases. The 5-year survival rates in patients with stage I and II were 86% and 49%, respectively. In contrast, the 5-year survival rate in patients with stage IV was only 9.1%, and a statistically significant difference was found when stage IV was compared to stage I and stage II ($P < 0.001$, respectively).

Cumulative survival curves for stage IV patients, according to curability, are shown in Fig. 2. The 5-year survival rate in patients who underwent curative resection (n = 52) was 13.7%, and a statistically significant difference was found between the curative and noncurative resection groups ($P = 0.023$). In addition, curative resection was possible more frequently in the hepatic involvement-type tumors, as compared to the other

Table 1. Classification systems for staging gallbladder carcinoma by the Japanese Society of Biliary Surgery (JSBS)

1. pT-category (primary tumor invasion)

pT_1:	m, mp	$pHinf_0$	$pBinf_0$	pPV_0/PV_0	pA_0/A_0
pT_2:	ss	$pHinf_{1a}$	$pBinf_0$	pPV_0/PV_0	pA_0/A_0
pT_3:	se	$pHinf_{1b}$	$pBinf_1$	pPV_0/PV_0	pA_0/A_0
pT_4:	any	$pHinf_{2,3}$	$pBinf_{2,3}$	$pPV_{1,2,3}/PV_{1,2,3}$	$pA_{1,2,3}/A_{1,2,3}$

1.1 Liver

$pHinf_0$: No direct invasion of the liver, or direct invasion limited to the muscularis propria of the gallbladder

$pHinf_1$: Direct invasion of the muscularis propria of the gallbladder and/or slight invasion of liver parenchyma (no more than 5 mm in depth)

$pHinf_2$: Direct invasion of the liver parenchyma, which invasion is 5 mm or more but not more than 20 mm in depth

$pHinf_3$: Direct invasion of the liver parenchyma, which invasion is 20 mm or more in depth

1.2 Hepatoduodenal ligament

$pBinf_0$: No invasion of the right margin of the hepatoduodenal ligament

$pBinf_1$: Invasion of the right margin of the hepatoduodenal ligament, but not to the left margin

$pBinf_2$: Invasion of the left margin of the hepatoduodenal ligament, but not to the entire ligament

$pBinf_3$: Invasion through the hepatoduodenal ligament

1.3 Portal veins

pPV_0: No invasion of portal veins

pPV_1: Invasion of the adventitia

pPV_2: Invasion of the media

pPV_3: Invasion of the intima and/or lumen

1.4 Hepatic arteries

pA_0: No invasion of hepatic arteries

pA_1: Invasion of the adventitia

pA_2: Invasion of the media

pA_3: Invasion of the intima and/or lumen

2. Lymph node metastasis

pN_0: No evidence of lymph node metastasis

pN_1: Metastasis in cystic duct and/or pericholedochal lymph node

pN_2: Metastasis in hepatoduodenal ligament except N1, superior retropancreas and/or along the common hepatic artery

pN_3: Metastasis in peripancreatic (except superior retropancreas), celiac, splenic, superior mesenteric, and/or paraaortic lymph nodes

3. Stage grouping

Final stage (fStage) should be classified according to the histopathological findings, in addition to the surgical findings.

	H0, P0, M (–)				
	pN0	pN1	pN2	pN3	H(+), P(+), M (+)
pT1	I	II			
pT2	II	III		IVa	
pT3			IVa		IVb
pT4	IVa				

types of tumors, and a statistically significant difference was found between the hepatic-involvement type (26/32) and the hepato-biliary type (8/17) of tumors (Table 3). However, the curative resection rate in the major vascular resection group ($n = 17$) was not significantly different from that in the non-vascular resection group, as shown in Table 4.

Prognostic factors

Univariate analysis of clinicopathological factors in the 79 stage IV patients revealed that operative curability ($P = 0.023$), hepatoduodenal ligament invasion (pBinf 1-2 vs pBinf 2-3; $P = 0.014$), vascular resection ($P = 0.016$), and lymph node metastasis ($P = 0.028$) were

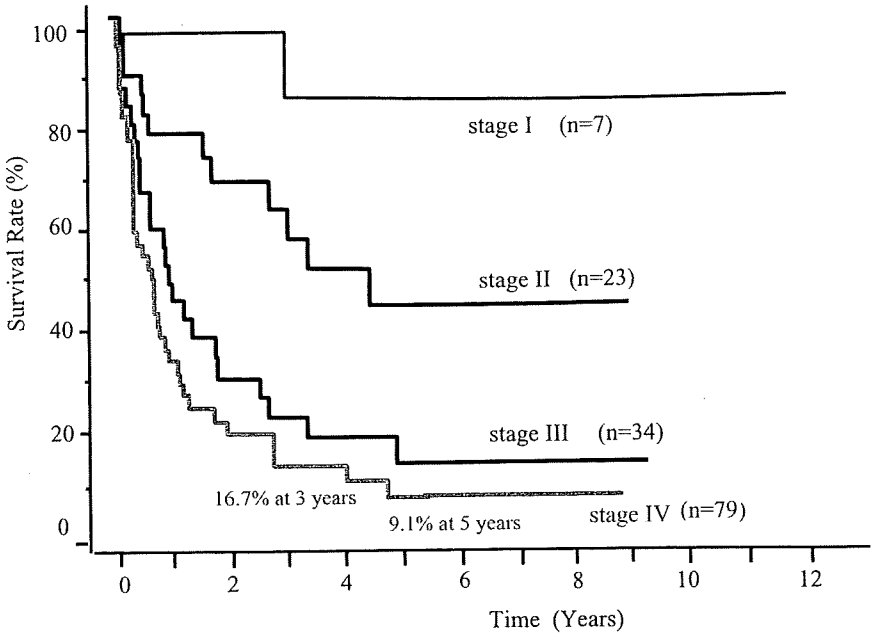

Fig. 1. Cumulative survival curves depending on the stage classified by the Japanese Society of Biliary Surgery (JSBS) system. A statistically significant difference was found between stage I and stage IV, and between stage II and stage IV ($P < 0.001$, respectively)

Table 2. Operative procedures for stage IV gallbladder carcinoma

Gallbladder bed resection	$n = 12$	(*n*)
None*		2
BDR		6
PD		4
Central inferior hepatectomy (S4a + S5)	$n = 29$	(*n*)
None		1
BDR		16
PD		4
colon resection		2
BDR + duodenum resection		3
PD + colon resection		1
BDR + colon resection + duodenum resection		2
Extended right hepatectomy	$n = 34$	(*n*)
BDR		24
BDR + colon resection		3
BDR + gastrectomy + colon resection		1
BDR + colon resection + duodenum resection		2
BDR + duodenum resection		2
PD		1
PD + colon resection		1
Right trisegmentectomy	$n = 3$	(*n*)
BDR		1
BDR + colon resection		1
PD + colon resection		1
Extended left hepatectomy	$n = 1$	(*n*)
BDR		1

*None, no combined resection
BDR, bile duct resection; PD, pancreaticoduodenectomy

found to be significant factors for prognosis. Neither hepatic invasion (pHinf 0-1 vs pHinf 2-3) nor liver metastasis was a significant prognostic factor (Table 5). According to multivariate analysis among these four

Table 3. Cancer extension patterns and surgical curability in stage IV gallbladder carcinoma

	n	Curative resection (%)
Hepatic-involvement type	32	26/32 (81.3%)*
Biliary-involvement type	24	14/24 (58.3%)
Hepato-biliary type	17	8/17 (47.1%)
Other type	6	4/6 (66.7%)
Total	79	52/79 (65.8%)

* $P < 0.03$ vs hepato-biliary type

Table 4. Surgical curability and vascular resection in stage IV gallbladder carcinoma

Vascular resection	(*n*)	Curative resection (%)
(−)	62	34/62 (54.8%)
(+)	17	9/17 (52.9%)
Total	79	52/79 (65.8%)

significant factors, no independent factor that correlated significantly with survival was found in our stage IV series.

Subgroup of stage IV patients expected favorable prognosis

Based on the present results, a favorable surgical outcome may be expected for stage IV patients who have neither hepatoduodenal ligament invasion nor nodal involvement, and for whom curative resection is possible without major vascular resection. Among the 79 patients with stage IV disease, patients who met these criteria were selected, and survival outcomes

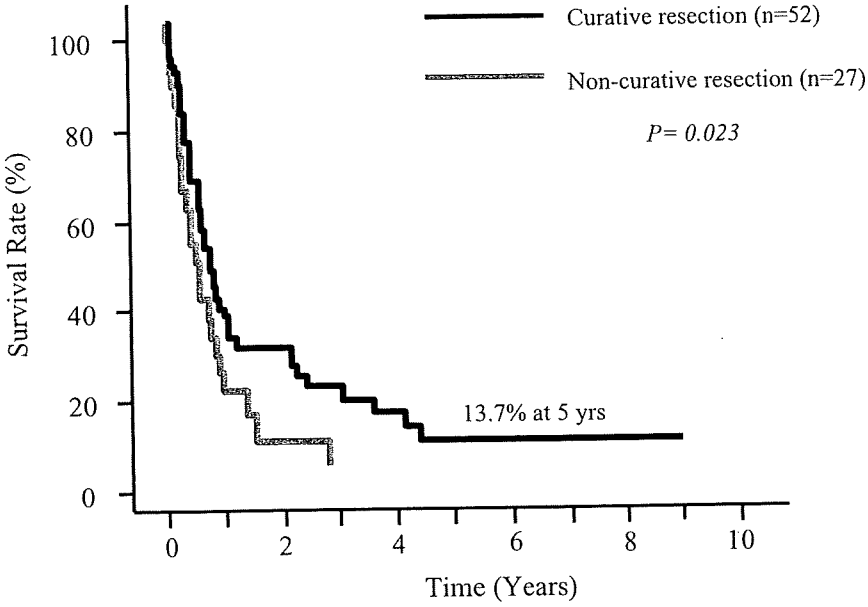

Fig. 2. Cumulative survival curves in patients with stage IV gallbladder carcinoma, according to operative curability

Table 5. Univariate analysis of prognostic factors in stage IV gallbladder carcinoma

Factors	Overall survival (%)		*P* value
	3 Years	5 Years	
Age (years)			
<60 (n = 56)	15.4	13.2	0.960
≦60 (n = 23)	11.8	5.9	
Sex			
Men (n = 29)	4.0	4.0	0.152
Women (n = 50)	21.0	15.8	
Curability			
Negative margin (n = 52)	21.5	13.7	0.023
Positive margin (n = 27)	5.7	0	
pBinf			
pBinf 0-1 (n = 43)	28.1	17.2	0.014
pBinf 2-3 (n = 36)	6.2	0	
pHinf			
pHinf 0-1 (n = 33)	22.2	7.4	0.249
pHinf 2-3 (n = 46)	13.0	9.7	
Liver metastasis			
(+) (n = 16)	14.4	14.4	0.514
(−) (n = 63)	17.0	7.9	
Vascular resection			
(+) (n = 17)	0	0	0.016
(−) (n = 62)	23	12.5	
N			
(+) (n = 51)	7.6	0	0.028
(−) (n = 28)	31.9	22.3	

were analyzed in our series. As shown in Fig. 3, acceptable survival was achieved among these highly selected patients (n = 12), and the 5-year survival rate was 35.6%.

Postoperative morbidity and mortality

The overall surgical morbidity rate for the stage IV patients was 48.1% (38/79). The most frequent postoperative complication was pleural effusion, as shown in Table 6. The surgical mortality rate for the stage IV patients was 11.4 % (9/79). The causes of death were postoperative hepatic failure in 7 patients, intraperitoneal bleeding in 1 patient, and respiratory complication in 1 patient. The surgical morbidity and mortality rates of patients with biliary involvement-type and hepatobiliary involvement-type tumors tended to be higher when compared to these rates in other groups, but no significant differences were found between the groups.

Discussion

Surgical results in stage IV gallbladder carcinoma have been reported to be extremely poor,[3,8,10–14] but complete resection of tumors may offer the only chance for long-term survival. In our series, various surgical procedures, including en-bloc resection of involved organs, were performed depending on the extent of tumor. Curative resection was achieved in 65.8% of patients with stage IV disease. In particular, curative resection rates for the hepatic involvement-type tumors were significantly higher than those for the biliary-type and hepatobiliary type tumors. Moreover, patients who underwent curative resection had a significantly better prognosis than those with noncurative resection, although the 5-year survival rate in our series was relatively low at 13.7%.

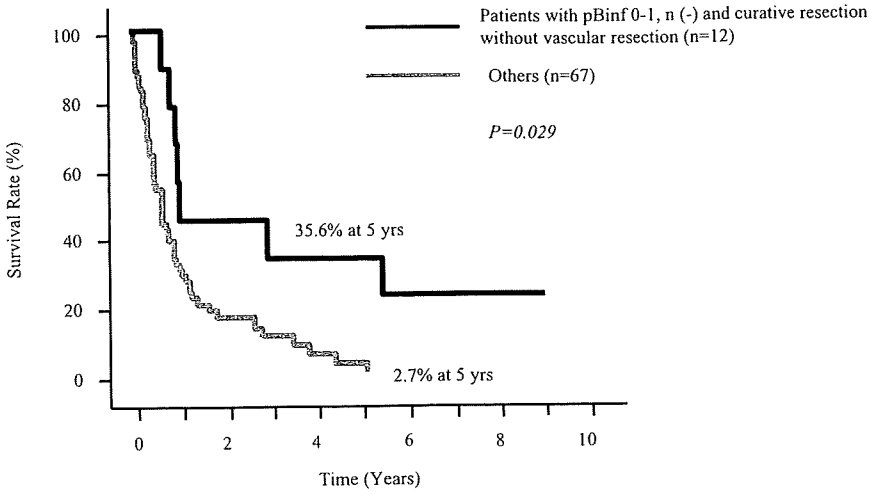

Fig. 3. Cumulative survival curves in patients with pBinfo-1 and n(–) who underwent curative resection without vascular resection (n = 12), and the remaining patients (n = 67)

Table 6. Cancer extension patterns and surgical morbidity and mortality in stage IV gallbladder carcinoma

	Cancer extension patterns				
	Hepatic-involvement type (n = 32)	Biliary-involvement type (n = 24)	Hepato-biliary involvement type (n = 17)	Other type (n = 6)	Total (n = 79)
Morbidity	14 (43.7%)	13 (54.2%)	9 (52.9%)	2 (33.3%)	38 (48.1%)
Hyperbilirubinemia	2	5	5	0	13
Anastomosis leakage	2	1	2	1	6
Intraabdominal abscess	4	2	4	1	11
Sepsis	1	0	1	0	2
DIC	3	0	2	0	5
Pleural effusion	12	9	8	0	29
Pneumonia	2	2	2	0	6
Wound infection	2	2	2	0	6
Mortality	2 (6.3%)	3 (12.5%)	3 (17.6%)	1 (16.7%)	9 (11.4%)

According to the JSBS staging system,[22] stage IV comprises different extents of disease, although the UICC system (sixth edition)[23] defines stage IV only by distant metastasis (M1). Liver metastasis, which is recognized as a discrete hepatic lesion separate from the primary tumor, is one of the factors defining stage IVb, according to the JSBS. Generally, gallbladder carcinoma with liver metastasis has no indication for surgical resection, because of poor outcome. However, in our series, "limited liver metastases" were resected with the primary tumor, but only when it was possible to achieve complete tumor resection. This treatment policy for advanced gallbladder carcinomas may be a major difference from that applied in Western countries. In our series, the 5-year survival rate in patients with liver metastasis (n = 16) was 14.4%, which was not significantly different from that in patients without liver metastasis (n = 63). Of our 16 patients with liver metastasis who underwent resection, a microscopically cancer-free margin was achieved in all except 3 cases. The sites of liver metastases were restricted to S4, S5, S8, or S6 of the liver, but the majority of the metastases were located within S4a and S5, near the gallbladder bed. Of these 16 patients, 2 patients survived for more than 4 years without recurrence (48 and 70 months), but most of the patients died, due to recurrence of carcinoma, within 1 year after surgery. Each of the long-term survivors had two metastatic lesions that were located in S5 near the gallbladder, and the tumors were node-negative and the hepatic-involvement type in both patients. Ohtsuka et al.[24] previously reported that early liver metastasis may occur along portal tracts of S4a or S5 from areas of hepatic involvement, but in patients with invasion of the hepatoduodenal ligament, extensive spread into the liver may easily occur though the right portal tract. Furthermore, Yoshimitsu et al.[25] have also clearly demonstrated that sites of liver metastases were well correlated with the areas of cholecystic

venous drainage. That is, early-stage liver metastasis from gallbladder carcinoma may occur via cholecystic venous flow, which commonly drains into the portal tract or sinusoids of S4a and S5.[26] Therefore, we believe that surgical resection should not be abandoned even in patients with liver metastasis, when the liver metastases are restricted to S4a and S5 of the liver, and also when the hepatoduodenal ligament is not involved, because the alternative therapy offers no chance of long-term survival. However, as the results in this study were obtained by evaluating only a small number of patients, it may be necessary to use multicenter databases to clarify the indications for radical surgery for patients with liver metastasis.

On the other hand, surgery must be performed without exposing the patient to unacceptable risks, otherwise the benefit of surgery may be offset by high risks of mortality and morbidity. In recent years, at our institution, preoperative portal embolization of the right lobe has been routinely performed to prevent postoperative hepatic failure in patients with obstructive jaundice who were scheduled for extended right hepatectomy. Portal embolization of the right lobe causes atrophy of the right lobe, and compensatory hypertrophy of the left lobe. Several studies have previously reported that preoperative portal embolization reduced operative mortality in patients with biliary tract carcinoma who underwent major hepatectomy.[27–30] In our series, there have been no cases of hospital death due to postoperative hepatic failure after portal vein embolization for the past 5 years.

In our present series of stage IV gallbladder carcinoma patients, hepatoduodenal ligament invasion (pBinf 2-3), vascular resection, and lymph node metastasis were significant factors for prognosis by univariate analysis. However, no significant independent factors were identified by multivariate analysis, although a number of independent factors have been reported in patients with resected advanced gallbladder carcinoma.[31–34] This difference may be related to the characteristics of the patients involved. The patients in the present study may have more advanced stage disease than those in these previous studies. However, our results suggest that the best candidates for radical surgery for stage IV gallbladder carcinoma may be patients with absent or slight invasion of the hepatoduodenal ligament (Binf 0-1) who are node-negative (N0), and also for whom curative resection is possible. Moreover, appropriate preoperative management, such as biliary drainage for ongoing cholangitis, and portal vein embolization scheduled for major hepatectomy, is also important to decrease postoperative morbidity and mortality.

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