Abstract
Prognosis of biliary tract cancer has generally been poor, and effective chemotherapy has not yet been established. A 64 year-old woman was admitted to our hospital for indications of gallbladder wall thickness. The diagnosis on computed tomography and ultrasonography was gallbladder cancer with liver metastasis in the inferior anterior segment. A cholecystectomy with partial hepatectomy was performed, and lymph nodes associated with the hepatoduodenal ligament, periampullary lesion, and common hepatic artery were dissected.

Chemotherapy with gemcitabine after resection biweekly was administered. After 4 months, liver metastases in the anterior segment was recognized. A right hepatic lobectomy was performed. After another 4 months, lymph node metastases of posterior lesions of the pancreas head, and caudate lobe metastasis were found. We initiated combination chemotherapy using gemcitabine plus tegafur・gimeracil・oteracil potassium (S-1). Complete response to chemotherapy was confirmed after 12 cycles. CA19-9 values reverted to normal levels. No major events of toxicity were seen. After 15 months, complete response had been maintained. Biweekly gemcitabine plus S-1 combination chemotherapy was effective and well tolerated.

Key words: gallbladder cancer, S-1, gemcitabine

Introduction
For biliary tract cancer (BTC), chemotherapy or radiotherapy has not shown substantially improved outcomes. Therefore surgical resection remains as the only curative treatment. However, prognosis after surgery of BTC is extremely poor, and standard chemotherapy regimens for advanced BTC need to be established. Gemcitabine (GEM) and tegafur・gimeracil・oteracil potassium (S-1) monotherapy were reported to be active and well tolerated for BTC. In Japan, GEM and S-1 are the only drugs approved by insurance for treating BTC. Therefore GEM and S-1 combination chemotherapy is under active investigation. Sasaki et al. reported that GEM plus S-1 for advanced BTC had promising efficacy and tolerability. We report here on the effectiveness of GEM plus S-1 combination chemotherapy for a patient with recurrent cancer of the gallbladder.

Case report
A 64 year-old woman was admitted to our hospital for a suspected gallbladder problem. Enhanced ultrasonography (US) and computed tomography (CT) revealed irregular enhanced gallbladder wall thickness with a 12 mm sized elevated lesion, and an enhanced tumor as an elevated lesion in the fundal portion. US with Sonazoid® and CT showed 3 tumors in the inferior anterior segment of the liver. The diagnosis was gallbladder cancer with liver metastases. A cholecystectomy with partial hepatectomy was performed, and lymph nodes associated with the hepatoduodenal ligament, periampullary lesion, and common hepatic artery were dissected (T2,N1,M1 stage IV). Adjuvant chemotherapy with GEM 800 mg/m² biweekly was started 39 days af-
ter surgery, and was administered 6 times. At 4 months after surgical resection, 2 metastatic liver lesions in the anterior segment were recognized on CT. A right hepatic lobectomy was performed for liver metastases. After liver resection, she declined to be treated with chemotherapy.

At 4 months after the second surgical resection, CT found caudate lobe metastasis and lymph node metastases of posterior lesions of the pancreas head (Fig. 1a, b).

Combination chemotherapy was initiated using GEM plus S-1. A cycle of chemotherapy consisted of intravenous GEM 1000 mg/m² on day 1 and oral S-1 80 mg/m² for 7 consecutive days, followed by a 1-week break from chemotherapy. CT confirmed a partial response after 6 cycles, and a complete response after 12 cycles (Fig. 2a, b). CA19-9 reverted to normal level (7.6 U/ml) from 176.9 U/ml which was the value before combination chemotherapy. No major events of toxicity were observed by this regimen of chemotherapy. Leukopenia and pigmentation, nausea (grade 1) appeared, but severe adverse effects (grades 3 or 4) were not recognized. All adverse effects were improved soon. Complete response of chemotherapy was still maintained fifteen months from the start of chemotherapy.

Discussion
As standard chemotherapy for pancreatic cancer was established, studies have turned to chemothera-
py for advanced BTC. GEM monotherapy for advanced BTC showed a response rate (RR) of 12.5% ~ 36% and median overall survival (OS) was 6.9 months ~ 7.2 months\(^2,6,7\). S-1 monotherapy for advanced BTC had a RR of 21 ~ 35% and the median OS was 8.3 ~ 9.4 months\(^3,4\). Therefore, S-1 monotherapy was considered to be a feasible and efficacious treatment for BTC as a first or second line chemotherapy regimen\(^8\).

To establish a standard chemotherapy for advanced BTC, various regimens of combination chemotherapy have been investigated. Pooled analyses of these trials revealed combination chemotherapy with GEM and cisplatin had an effective response for advanced BTC\(^9\). A phase III trial of GEM alone and combination chemotherapy of cisplatin plus GEM (ABC-02) was reported by Valle\(^10\). The median OS's of GEM alone and cisplatin plus GEM were 8.1 and 11.7 months (p<0.001) and the median progression-free survivals (PFS) were 5.0 and 8.0 months respectively (p<0.001). In addition, the rate of tumor control among patients in the cisplatin plus GEM combination group was significantly increased (81.4% vs 71.8%, p=0.049). Valle reported cisplatin plus GEM was associated with a significant survival advantage without substantial toxicity compared with GEM alone. In Japan, a Phase II trial of GEM alone and cisplatin plus GEM combination chemotherapy (BT-22) confirmed the efficacy of cisplatin plus GEM combination as described in the ABC-02 report\(^11\).

Because they are the only insurance approved drugs for treating BTC in Japan, GEM and S-1 in combination chemotherapy were investigated\(^15\). GEM was administered intravenously at a dose of 1000 mg/m\(^2\) over 30 min on day 1 and 15, and S-1 80 mg/m\(^2\) for 14 consecutive days, repeated every 4 weeks. RR was 34.3% and the overall disease control rate was 82.9%. The median OS was 11.6 months and the median time to progression was 5.9 months. GEM plus S-1 combination chemotherapy was equivalent to results reported in ABC-02 and BT-22.

At present, there is no established adjuvant chemotherapy for BTC. GEM has been the current standard anticancer drug for adjuvant chemotherapy for patients with resected pancreatic cancer since the randomized phase III clinical study reported by Oettle et al\(^13\). We reported that adjuvant chemotherapy using GEM at a dose of 800 mg/m\(^2\) for resected pancreatic cancer contributed to prolonged PFS, MST, and overall survival\(^13\). Murakami et al\(^14\) had used intravenous GEM at a dose of 700mg/m\(^2\) biweekly and reported that postoperative adjuvant gemcitabine-based chemotherapy may be a promising strategy to improve survival after surgical resection for hilar cholangiocarcinoma. Therefore, in our case biweekly chemotherapy was performed using GEM at a dose of 800 mg/m\(^2\) with the aim of avoiding adverse effects as nausea, general fatigue.

A randomized study of GEM plus S-1 combination therapy vs. S-1 in advanced BTC was started by Takashima et al\(^15\). GEM plus S-1 combination therapy was considered to have a better response rate than S-1 monotherapy. Although GEM is a standard chemotherapy agent for advanced BTC, maintenance with a standard drug like 5FU or leucovorin for colorectal cancer on second-line chemotherapy was considered necessary. Therefore GEM plus S-1 combination therapy was used in the present case on second line chemotherapy.

It should be noted that extensive surgical procedures, including major hepatectomy or pancreaticoduodenectomy, are closely associated with a high incidence of postoperative chemotherapy-induced toxicity\(^16\) and sometimes these patients are unable to tolerate combination chemotherapy. We used GEM plus S-1 combination chemotherapy at biweekly GEM 1000 mg/m\(^2\) and S-1 80mg/m\(^2\) for 7 consecutive days, and therefore successfully avoided serious adverse effects of chemotherapy.

A randomized control study of GEM and S-1 combination chemotherapy versus the combination of GEM and cisplatin is needed to identify the best treatment for advanced BTC.

Conflict of interest: The authors have no potential conflicts of interest.

References
Gemcitabine plus S-1 combination chemotherapy for recurrent gallbladder cancer


