tion (total bilirubin level ≥3.0mg/dL); and adequate bone marrow reserve (white blood cell count ≥4,000/μL, platelet count ≥100,000/μL, hemoglobin ≥11g/dL). Patients with an elevated serum bilirubin level at the time of pretherapy evaluation were considered eligible for this study if the bilirubin level could be reduced to within 3.0mg/dL after biliary drainage. All patients were required to provide written informed consent.

Exclusion criteria were as follows: uncontrollable pleural effusion or ascites; known metastases of the central nervous system; gastrointestinal bleeding; severe complications such as infection, heart disease, and renal disease; active concomitant malignancy; severe mental disorder; and pregnancy.

Treatment schedule

All therapies were administered on an in-patient basis. 5-FU was administered by continuous intravenous (IV) infusion at a dose of 500mg/m² on days 1 through 5. Epirubicin was administered by IV infusion at a dose of 50mg/m² on day 1, and cisplatin was administered by IV infusion at a dose of 80mg/m² over a 2-h period on day 1 with standard hydration. The dose of epirubicin was adjusted to the hematological toxicities observed; patients who experienced grade 4 leukocytopenia and/or neutropenia received 40mg/m² in subsequent courses. If there was no evidence of tumor progression or unacceptable toxicity, the treatment was repeated every 4 weeks, to a maximum of 6 courses.

Response and toxicity evaluation

Tumor size was measured by computed tomography (CT), and tumor response was assessed every 4 weeks after the beginning of chemotherapy. Response and toxicity were evaluated according to the World Health Organization guidelines (11).

Statistical Design

The primary endpoint was the efficacy and toxicity of CEF therapy in patients with advanced ICC. The number of patients to be enrolled was planned using a Simon's two-step design (12), based on the assumptions that the expected response rate would be 20%, the response rate judged as no activity would be 5%, alpha error would be 10% (one-tailed), and β error would be 10% (one-tailed).

Interim analysis was planned when 12 patients were enrolled. If none of the first 12 patients had a partial or complete response, the study was to be ended. If a response was detected in any of the first 12 patients studied, an additional 25 patients were to be studied in a second stage of accrual to estimate more precisely the actual response rate. The time to progression and survival time were also calculated from the start of treatment by the Kaplan-Meier method.

RESULTS

Thirty-nine patients were enrolled in this study at the National Cancer Center Hospital between May 1992 and November 2001. Patient characteristics are summarized in Table 1.

TABLE 1 Patient Characteristics

No. of patients		39
Sex	Men	25
	Women	14
Age (yrs)	Median (range)	60 (37-75)
ECOG PS	0	19
	1	20
Metastatic organ	Lymph node	14
	Lung	10
Prior surgery +		13
Biliary drainage +		5
Albumin (g/dl)	Median (range)	3.7 (2.6-4.5)
Total bilirubin (mg/dl)	Median (range)	0.8 (0.3-3.0)
CEA (ng/ml)	Median (range)	3 (0.8-7100)
CA19-9 (U/ml)	Median (range)	109 (1-382720)

ECOG: Eastern Cooperative Oncology Group; PS: performance status; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

All patients had histologically confirmed adenocarcinoma. The population consisted of 25 men and 14 women with a median age of 60 yrs (range: 37-74). Before chemotherapy, 13 patients had undergone prior hepatic resection and 5 patients had undergone biliary drainage for obstructive jaundice. All patients were deemed unsuitable candidates for surgical resection for one of the following reasons: extrahepatic metastasis (14 patients), huge tumor extending across the bilobes of the liver (12 patients), or intrahepatic recurrence after hepatic resection (13 patients).

The 39 patients were given a total of 127 courses, with a median of 3 courses each (range: 1-6; Table 2). The dose of epirubicin was modified to 40mg/m² according to the protocol in 9 patients (23%). The reasons for treatment discontinuation were: completion of treatment (6 courses) (8 patients, 21%); disease progression (26 patients, 67%); patient's refusal of treatment (1 patient, 3%); and treatment-related death (2 patients, 5%).

Thirty-eight patients were evaluable for response. One patient was evaluable for toxicity alone but not for response because she died due to treatment-related sepsis before the response evaluation. No complete

TABLE 2 Number of Treatment Courses

Courses	Number of patients (%)
1	9 (23)
2	8 (21)
3	7 (18)
4	4 (10)
5	3 (7)
6	8 (21)

TABLE 3 Toxicity

Grade	1	2	3	4
Hematological toxicity				
Per patient				
Hemoglobin	11 (28%)	14 (36%)	1 (3%)	1 (3%)
Leukocytes	7 (18%)	7 (18%)	16 (41%)	4 (10%)
Neutrophils	0 (0%)	2 (5%)	13 (33%)	16* (41%)
Platelets	10 (26%)	2 (5%)	7 (18%)	2 (5%)
Non-hematological toxicity				
Per patient				
Gastrointestinal				
Total bilirubin	8 (21%)	0 (0%)	0 (0%)	1 (3%)
AST	12 (31%)	4 (10%)	0 (0%)	0 (0%)
ALT	6 (15%)	4 (10%)	3 (8%)	0 (0%)
ALP	6 (15%)	8 (21%)	3 (8%)	0 (0%)
Renal/Genitourinary				
BUN	2 (5%)	2 (5%)	0 (0%)	0 (0%)
Creatinine	3 (8%)	1 (3%)	0 (0%)	0 (0%)
Nausea/Vomiting	18 (46%)	9 (23%)	2 (5%)	2 (5%)
Stomatitis	19 (49%)	4 (10%)	0 (0%)	0 (0%)
Diarrhea	5 (13%)	1 (3%)	0 (0%)	0 (0%)
Infection	8 (21%)	3 (8%)	0 (0%)	3 (8%)
Malaise/Fatigue	17 (44%)	11 (28%)	5 (13%)	1 (3%)

*Two patients died of neutropenic sepsis.
AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; BUN: blood urea nitrogen.

response was noted. A partial response was obtained in 4 patients (10%, 95% CI: 3-24%) with a median duration of 2.3 months (range: 1–8 months). Twenty-seven (69%) patients showed no changes, with a median duration of 7.8 months (range: 1-19 months). Seven patients (18%) showed progressive disease.

Toxicities are listed in Table 3. CEF therapy was generally well tolerated although 2 patients died of neutropenic sepsis, on day 10 of the 3rd course and on day 27 of the 1st course, respectively. Grade 4 leukocytopenia, neutropenia and thrombocytopenia occurred in 4 (10%), 16 (41%) and 2 (5%) patients, respectively. However, these toxicities were generally brief and reversible. Anemia was infrequent and mild. No cumulative tendency of myelosuppression was noted as the treatment courses continued. Severe non-hematological toxicities of CEF therapy were infrequent, and nausea/vomiting and malaise were the most common non-hematological toxicities.

All enrolled patients were included in the survival assessment. Thirty-six patients had died, and 3 patients were alive at the time of analysis. The median survival time was 9.1 months (range: 0.9-40.7 months) and the 1-year survival rate was 23% (Figure 1). The progression-free survival time was 5.1 months.

DISCUSSION

Hepatobiliary cancer is one of the most common malignancies in Japan. The annual incidence of hepatobiliary cancer has been steadily increasing in this nation, from 15.8 per 100,000 in the year 1989 to 18.2 per 100,000 in 1999 (2). ICC is, however, a rare malignancy accounting for approximately 3.3% of all primary hepatobiliary malignancies and 0.03% of all cancers in Japan (1). Due to the rarity of ICC, it is not surprising that there have been few prospective trials of systemic chemotherapy for ICC.

Gemcitabine is the only chemotherapeutic agent that has been evaluated in a disease-oriented study for ICC. In a phase II trial, the objective response rate was 30% (7/15) with a median time to tumor progression of 6.8 months and a median survival time of 9.3 months (20). Other chemotherapeutic agents have been investigated for BTC including cancers of the gallbladder and the intra- and extra-hepatic bile duct. 5-FU has been the most extensively studied single agent for this disease, with published objective response rates ranging from 10 to 24% (13-15). Mitomycin C has also been a commonly studied drug for BTC; a phase II study conducted by Crooke *et al.* showed a response rate of 47% (7/15) (16). However, a study by the European Organization for Research and Treatment of Cancer, testing mitomycin C in 30 patients showed only 3 (10%) responses (17). Some newer drugs have also demonstrated no significant efficacy as a single-agent therapy. Paclitaxel demonstrated no activity in 15 patients (18), and a phase II study of docetaxel likewise demonstrated no activity in 17 patients (19). Therefore, no single agent has reproducibly induced a sufficient antitumor response against BTC including ICC.

Due to the rather sobering results obtained with single-agent chemotherapy, various combination chemotherapies have been investigated in order to enhance response and to prolong survival in patients with BTC (21-30). In an ECOG study, 8 (9%) of the 89 patients showed a response in 5-FU-based chemotherapy using oral 5-FU or oral 5-FU plus either streptozotocin or methyl-CCNU. There were no significant differences in the types of drugs used with respect to response and survival (15). Recombinant interferon-α, which is a potent biochemical modulator of 5-FU, was tested in combination with 5-FU for 41 patients, and 8 patients (21%) achieved an objective response (22). However, the addition of cisplatin and adriamycin to the combination of 5-FU and interferon-α did not enhance antitumor activity: only 2 (14%)

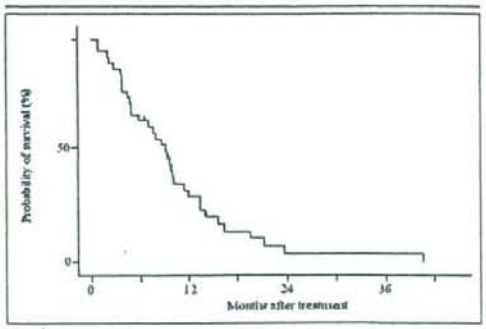


FIGURE 1 Overall survival curve of the 39 patients who received CEF therapy for ICC.

of the 14 patients showed an objective response in a recent phase II study (23). The combination of 5-FU, mitomycin C, and doxorubicin has also been evaluated: one study analyzing this combination for 13 patients showed 4 partial responses (31%) (24). Conversely, in a more recent trial in 14 patients, a modified regimen using these three agents demonstrated only 2 (14%) objective responses (25). A combination chemotherapy of epirubicin, methotrexate, and 5-FU showed no responses in 21 patients (26). For patients with advanced BTC including ICC, there is currently no standard chemotherapy.

Cisplatin has also been attempted, alone or in combination, in clinical trials for patients with BTC. One report showed 6 partial responses (33%) in 18 patients treated with continuous-infusion 5-FU and cisplatin (27). In another report, the addition of leucovorin to the combination of 5-FU and cisplatin showed 1 complete response and 9 partial responses (34%) in 21 patients (28). The activity of CEF therapy in hepatobiliary cancers has been reported in two phase II studies. In an English trial that was conducted for hepatobiliary cancers including ICC, partial response was achieved in 8 (40%) of the 20 patients, with a median survival time of 11 months (29). In another trial that was conducted in our hospital for BTC other than ICC, the results showed 7 partial responses (19%) in the 37 patients (30). These results suggest that 5-FU-based chemotherapy including cisplatin may have a favorable antitumor effect against BTC.

Our current study is the first disease-specific phase II trial for ICC treated with multi-agent chemotherapy including cisplatin. However, the results of the present study were very disappointing. This study failed to demonstrate significant antitumor activity; only 4 patients (10%) achieved a partial response, although the expected response rate was 20%. Although the CEF therapy was generally well tolerated, grade 3/4 myelotoxicity was frequent. Grade 4 neutropenia was noted in 16 patients (41%), and 2 of them died of sepsis caused by pneumonia. Nausea/vomiting and malaise were the most common non-hematological toxicities, and grade 3/4 nausea/vomiting was noted in 4 patients (10%). Grade 4 bilirubin elevation was noted in 1 patient (3%), who was diagnosed as having biliary pyogenic cholangitis caused by drainage tube obstruction. Grade 3 liver dysfunction was observed in 3 patients (8%), but their liver functions recovered to initial levels within 2 weeks.

ICC can be one of the most difficult cancers to treat effectively with chemotherapy, given the rapid progressive and chemoresistant nature of this disease. In the patients with BTC treated with CEF in the England trial, only 2 of the 9 patients with cholangiocarcinoma (22%) achieved a response, while 6 of the 11 patients with other BTC (55%) responded.

The conclusion of the current study is that CEF therapy has only marginal antitumor activity against advanced ICC, although hematological toxicity is the major and most frequent toxicity. Therefore, this regimen may not be adequate for recommendation as a standard. Further studies with new agents including gemcitabine are needed, and the expanding understanding of molecular biology should facilitate research to develop novel target-based agents for this disease.

REFERENCES

1 **The Liver Cancer Study Group of Japan:** Follow-up investigation of primary liver cancer 15th report. Kanzo 2003; 44:157-175. (In Japanese)

2 Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare. Vital statistics of Japan 2002. Tokyo: Ministry of Health and Welfare, 2004. (In Japanese)

3 **Okada S, Ishii H, Nose H, Yoshimori M, Okusaka T, Aoki K, Iwasaki M, Furuse J, Yoshino, M:** A phase II study of cisplatin in patients with biliary tract carcinoma. Oncology 1994; 51:515-517.

4 **Scanlon KJ, Newman EM, Lu Y, Priest DG:** Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. Proc Natl Acad Sci USA 1986; 83:8923-8925.

5 **Kish JA, Weaver A, Jacobs J, Cummings G, Al-Sarraf M:** Cisplatin and 5-fluorouracil infusion in patients with recurrent and disseminated epidermoid cancer of the head and neck. Cancer 1984; 53:1819-1824.

6 A randomized, comparative study of combination chemotherapies in advanced gastric cancer: 5-fluorouracil and cisplatin (FP) versus 5-fluorouracil, cisplatin, and 4'-epirubicin (FPEPIR). Kyoto Research Group for Chemotherapy of Gastric Cancer (KRGCGC). Anticancer Res 1992; 12:1983-1988.

7 **Findlay M, Cunningham D, Norman A, Mansi J, Nicolson M, Hickish T, Nicolson V, Nash A, Sacks N, Ford H, et al:** Phase II study in advanced gastroesophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994; 5:609-616.

8 **Bamias A, Hill ME, Cunningham D, Norman AR, Ahmed FY, Webb A, Watson M, Hill AS, Nicolson MC, O'Brien ME, Evans TC, Nicolson V:** Epirubicin, cisplatin, and protracted venous infusion of 5-fluorouracil for esophagogastric adenocarcinoma: response, toxicity, quality of life, and survival. Cancer 1996; 77:1978-1985.

9 **Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M:** Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997; 15:261-267.

10 **Ross P, Nicolson M, Cunningham D, Valle J, Seymour M, Harper P, Price T, Anderson H, Iveson T, Hickish T, Lofts F, Norman A:** Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002; 20:1996-2004.

11 **Miller AB, Hoogstraten B, Staquet M, Winkler A:** Reporting results of cancer treatment. Cancer 1981; 47:207-214.

12 Simon R: How large should a phase II trial of a new drug be? Cancer Treat Rep 1987; 71:1079-1085.

13 **Davis HL, Jr., Ramirez G, Ansfield FJ:** Adenocarcinomas of stomach, pancreas, liver, and biliary tracts. Survival of 328 patients treated with fluoropyrimidine therapy.

Cancer 1974; 33:193-197.
14 Haskell CM: Cancer in the liver. In: Haskell CM (Ed). Cancer Treatment: A Multidisciplinary Approach. Philadelphia, USA: WB Saunders Co., 1980; p. 319.
15 Falkson G, MacIntyre JM, Moertel CG: Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. Cancer 1984; 54:965-969.
16 Crooke ST, Bradner WT: Mitomycin C: a review. Cancer Treat Rev 1976; 3:121-139.
17 Taal BG, Audisio RA, Bleiberg H, Blijham GH, Neijt JP, Veenhof CH, Duez N, Sahmoud T: Phase II trial of mitomycin C (MMC) in advanced gallbladder and biliary tree carcinoma. An EORTC Gastrointestinal Tract Cancer Cooperative Group Study. Ann Oncol 1993; 4:607-609.
18 Jones DV, Jr, Lozano R, Hoque A, Markowitz A, Patt YZ: Phase II study of paclitaxel therapy for unresectable biliary tree carcinomas. J Clin Oncol 1996; 14:2306-2310.
19 Pazdur R, Royce ME, Rodriguez GI, Rinaldi DA, Patt YZ, Hoff PM, Burris HA: Phase II trial of docetaxel for cholangiocarcinoma. Am J Clin Oncol 1999; 22:78-81.
20 Kubicka S, Rudolph KL, Tietze MK, Lorenz M, Manns M: Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. Hepatogastroenterology 2001; 48:783-789.
21 Raderer M, Hejna MH, Valencak JB, Kornek GV, Weinlander GS, Bareck E, Lenauer J, Brodowicz T, Lang F, Scheithauer W: Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. Oncology 1999; 56:177-180.
22 Patt YZ, Jones DV, Jr., Hoque A, Lozano R, Markowitz A, Raijman I, Lynch P, Charnsangavej C: Phase II trial of intravenous flourouracil and subcutaneous interferon alfa-2b for biliary tract cancer. J Clin Oncol 1996; 14:2311-2315.
23 Patt YZ, Hassan MM, Lozano RD, Waugh KA, Hoque AM, Frome AI, Lahoti S, Ellis L, Vauthey J, N.Curley SA, Schnirer II, Raijman I: Phase II trial of cisplatin, interferon alpha-2b, doxorubicin, and 5-fluorouracil for biliary tract cancer. Clin Cancer Res 2001; 7:3375-3380.
24 Harvey JH, Smith FP, Schein PS: 5-Fluorouracil, mitomycin, and doxorubicin (FAM) in carcinoma of the biliary tract. J Clin Oncol 1984; 2:1245-1248.
25 Takada T, Nimura Y, Katoh H, Nagakawa T, Nakayama T, Matsushiro T, Amano H, Wada K: Prospective randomized trial of 5-fluorouracil, doxorubicin, and mitomycin C for non-resectable pancreatic and biliary carcinoma: multicenter randomized trial. Hepatogastroenterology 1998; 45:2020-2026.
26 Kajanti M, Pyrhonen S: Epirubicin-sequential methotrexate-5-fluorouracil-leucovorin treatment in advanced cancer of the extrahepatic biliary system. A phase II study. Am J Clin Oncol 1994; 17:223-226.
27 Rouger P, Fandi A, Ducreux M, et al: Demonstrated efficiency of 5-fluorouracil continuous infusion and cisplatin in patients with advanced biliary tract carcinoma. Proc Am Soc Clin Oncol 1995; 14:205.
28 Taïeb J, Mitry E, Boige V, Artru P, Ezenfis J, Lecomte T, Clavero-Fabri MC, Vaillant JN, Rougier P, Ducreux M: Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5-FU and cisplatin (LV5FU2-P regimen) in patients with biliary tract carcinoma. Ann Oncol 2002; 13:1192-1196.
29 Ellis PA, Norman A, Hill A, O'Brien ME, Nicolson M, Hickish T, Cunningham D: Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. Eur J Cancer 1995; 31:1594-1598.
30 Morizane C, Okada S, Okusaka T, Ueno H, Saisho T: Phase II study of cisplatin, epirubicin, and continuous-infusion 5-fluorouracil for advanced biliary tract cancer. Oncology 2003; 64:475-476.

19 胆道癌の補助化学療法

切除不能胆道癌や切除後の補助療法として確立されている化学療法はあるのでしょうか？

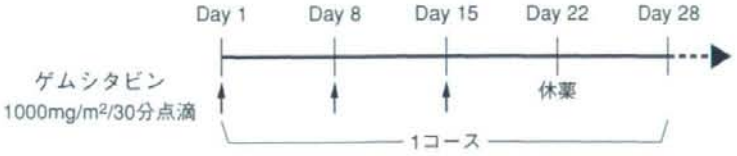
現在胆道癌に対しては切除不能例に対しても，補助療法としても標準的な治療法は確立していない．本稿では切除不能例に対する化学療法と，補助療法としての化学療法に分けて現在までの治療開発状況をまとめる．

A 切除不能胆道癌に対する全身化学療法

現在までに切除不能胆道癌に対する化学療法について，多くの研究が行われてきた．しかし標準治療が確立するには第 III 相試験（無作為化比較試験）により有効性が証明される必要がある．残念なことに今まで胆道癌領域でなされた臨床試験は対照群のない試験や，小規模な比較試験のみで大規模な第 III 相試験の報告はない．今までの報告によると，単剤では 5-FU 系薬剤やゲムシタビンにおいて比較的良好な成績が報告されており，日常診療の現場でも多く用いられている．

B 切除不能胆道癌に対するゲムシタビン

ゲムシタビンはわが国では 1999 年に肺癌への適応が承認され，2001 年には膵癌への適応が追加になっていた．その後，進行胆道癌患者を対象に後期第 II 相試験が多施設共同で行われ奏効割合 17.5 %，生存期間中央値 7.6 カ月と良好な治療成績が報告され，2006 年 6 月に胆道癌への適応が追加された．それ以降，わが国では標準治療ではないながらもゲムシタビンが広く臨床応用されている（図 1）．国際的にもゲムシタビンは標準治療薬の候補として高い期待が寄せられている．英国を中心に行われたゲムシタビン単剤とゲムシタビン＋シスプラチンのランダム化第 II 相試験（ABC-01 試験）の結果が 2006 年に学会報告された（図 2）．この成績を基にゲムシタビン単剤とゲムシタビン＋シスプラチン併用療法の第 III 相試験（ABC-02 試験）が現在進行中である．この試験の結果，どちらかの群の延命効果が示された場合は胆道癌に対する標準療法として受け入れられると予想される．



上記スケジュールで，病変の明らかな増悪が認められない限り治療を継続する．

図 1 ゲムシタビン単剤療法

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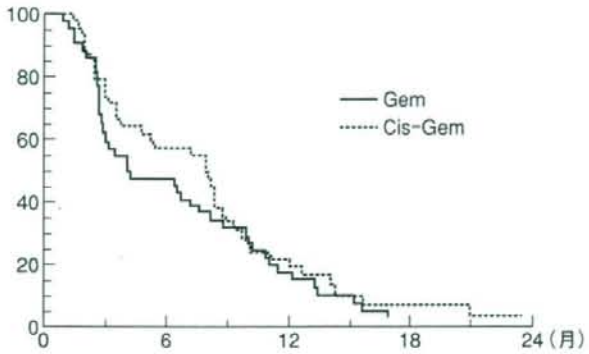


	ゲムシタビン単剤療法群	ゲムシタビン＋シスプラチン併用療法群
奏効割合	15.2%	24.3%
増悪までの期間	4.0mo	8.0mo
6カ月無増悪生存割合	47.7%	57.1%

図 2 ABC-01 試験の成績：無増悪生存期間
ゲムシタビン＋シスプラチン併用療法群 vs ゲムシタビン単剤療法群

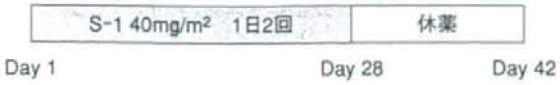
わが国でも海外のデータの再現性を評価することを目的にゲムシタビン単剤療法とゲムシタビン＋シスプラチンの併用療法のランダム化第 II 相試験が進行中である．

C 切除不能胆道癌に対する 5-FU 系薬剤

一方，5-FU 系薬剤としては，わが国では S-1 に期待が寄せられている．進行胆道癌患者を対象として前期および後期第 II 相試験が行われ，それぞれ奏効割合 21 %，35 %，生存期間中央値 8.3 カ月，9.4 カ月と良好な成績が報告された．これらの結果をもとに 2007 年 8 月に S-1 の効能・効果に胆道癌が追加された（図 3）．今後，日常診療でも多用される可能性があるが，延命効果を有するか否かの評価や，適切な使用方法（ゲムシタビンと併用すべきか，単剤で用いるべきか，など）についての検討が必要である．それ以外の 5-FU 系薬剤としては，カペシタビンがあげられる．現在海外では NCI-Canada でゲムシタビン＋カペシタビンの併用療法対ゲムシタビン単剤療法の第 III 相試験が行われており，結果が待たれている．

D 切除不能胆道癌に対する化学療法のまとめ

現在標準治療は確立していないが，ゲムシタビンに対する国際的な期待が高まっており，日常診療でもゲムシタビンがすでに広く用いられている．現在海外で行われているゲムシタビン単剤とゲムシタビン＋シスプラチン併用療法の第 III 相試験（ABC-02 試験）の結果により標準治療が確立する可能性があり，注目されている．また，S-1 やカペシタビンなど，5-FU 系薬剤に対する今後の治療開発にも期待が寄せられている．



体表面積（m^2）	初回基準量（テガフール相当量）
＜1.25m^2	40×2mg/日
1.25m^2～＜1.5m^2	50×2mg/日
1.5m^2≦	60×2mg/日

図 3 S-1 単剤療法

S-1 の投与は，40 mg/m^2 に相当する投与量を 1 日 2 回，28 日間連日経口投与し，14 日間休薬する．これを 1 コースとして，治療を続行する．

E 胆道癌に対する補助療法

進行胆道癌同様，胆道癌切除例に対する補助療法については現在確立した指針がない．胆道癌の補助療法に関する第 III 相試験は，膵癌も対象疾患に含めて行われたものが 2 本存在するにすぎない．わが国で高田らにより行われた第 III 相試験の結果[1]と，EORTC（European Organization for Research and Treatment of Cancer）による第 III 相試験の結果[2]である．それぞれの報告を以下にまとめる．

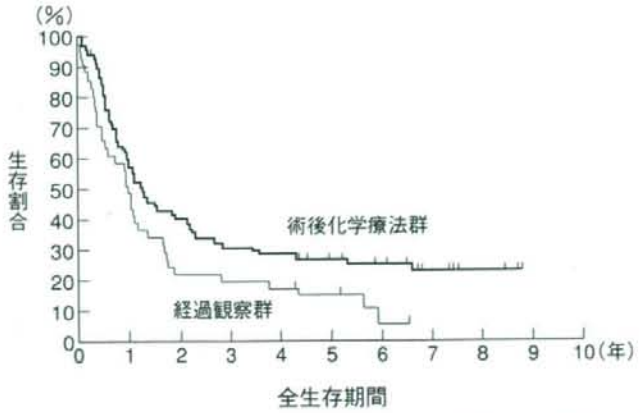
1）高田らによる報告[1]

膵臓癌 173 例，胆管癌 139 例，胆嚢癌 140 例，乳頭部癌 56 例の計 508 例を対象に，術後 5-FU ＋マイトマイシン C を投与する群と切除単独群で比較が行われた．登録症例全例を解析対象に含めた intent-to-treat 解析では，いずれの臓器においても生存期間，無再発生存期間に有意差は認められなかったが，登録後に Stage I などの不適格症例を除いた解析では，胆嚢癌のみにおいて術後補助療法群が切除単独群に比べて生存期間，無再発生存期間が有意に良好であった（図 4，5 年生存率 26 %対 14.4 %，p ＝ 0.0367，5 年無再発生存率 20.3 %対 11.6 %，p ＝ 0.021）．さらに治癒切除群と非治癒切除群に分けてサブグループ解析を行うと，胆嚢癌における非治癒切除群のみにおいて生存期間に有意差が，胆管癌と胆嚢癌における非治癒切除群のみにおいて無再発生存期間に有意差が認められた．

2）EORTC による報告[2]

膵臓癌と傍乳頭癌（下部胆管癌，乳頭部癌，十二指腸癌）218 例を対象に術後 5-FU 併用放射線療法施行群と切除単独群で比較された．しかし，膵癌と傍乳頭癌いずれにおいても術後化学放射線療法による延命効果は示されなかった．

以上の成績を考慮すると，胆道癌において現時点では予後を改善する補助療法は確立していないのが現状である．高田らの報告によれば非切除に終わった胆嚢癌に対しては 5-FU ＋マイトマイシン C 併用療法が有効とされているが，多重検定に関する統計学的な考慮がなされていないため，解釈は慎重にする必要がある．胆道癌の術後補助療法は，現時点では確立したものがないので，適切な臨床



	術後化学療法群	経過観察群	p
5年生存割合	26 %	14.4%	0.0367
5年無再発生存割合	20.3%	11.6%	0.021

図 4 高田らによる胆道，膵癌術後化学法の比較試験，胆嚢癌の治療成績

術後化学療法群 vs 切除単独群

試験に参加して補助療法を行うか，補助療法は行わずに経過観察をするのが適切と考えられる．

まとめ

胆道癌の化学療法に関する治療開発が進み，一刻も早く有効な治療法が確立することが望まれる．頻度の低い難治癌であるため，多施設共同試験や国際共同試験の体制作りも急務である．

■文献

1) Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer. 2002; 95: 1685-95.

2) Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999; 230: 776-82; discussion. 782-4.

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胆道癌

肝外の胆道系に原発した癌のことを「胆道癌」と呼び，そのなかで胆嚢，肝外胆管，乳頭部に発生したものをそれぞれ「胆嚢癌」，「胆管癌」，「乳頭部癌」と呼ぶ．図18に胆道癌取扱い規約による肝外胆道系の区分を示す．肝内の胆管に発生した癌は「肝内胆管癌（胆管細胞癌）」と呼ばれ，原発性肝癌として扱われる．胆道癌の好発年齢は50～60歳代で，胆嚢癌は女性に，胆管癌は男性に多い．切除困難な進行癌として発見されることが多いため，予後は一般に不良である．本項では，胆道癌のなかで頻度の高い胆嚢癌と胆管癌について述べる．なお，胆道癌に対する標準的な診断の指針となる胆道癌診療ガイドラインが2007年に出版されている．

胆嚢癌

胆嚢癌は肉眼的形態により，乳頭型，結節型，平坦型，充満型，塊状型などに分類される．また，癌が粘膜内または固有筋層内に限局するものを早期胆嚢癌と呼ぶ．

胆嚢癌は高率（50～70％）に胆石を合併することが知られている．また，膵胆管合流異常★1は胆嚢癌や胆管癌の高危険因子とされている．

★1 膵胆管合流異常
膵・胆道系の発生異常に起因する先天性疾患で，オッディ（Oddi）括約筋の影響の及ばない高位で膵管と胆道が合流するため膵液と胆汁の相互逆流が起こり，胆道または膵にさまざまな病態を起こす．

症状

初期には無症状のことが多いが，胆石合併例では胆石による腹痛を主訴に来院し，偶然，胆嚢癌が発見されることがある．また，近年は超音波検査の普及により，無症状で発見される胆嚢癌が増えている．

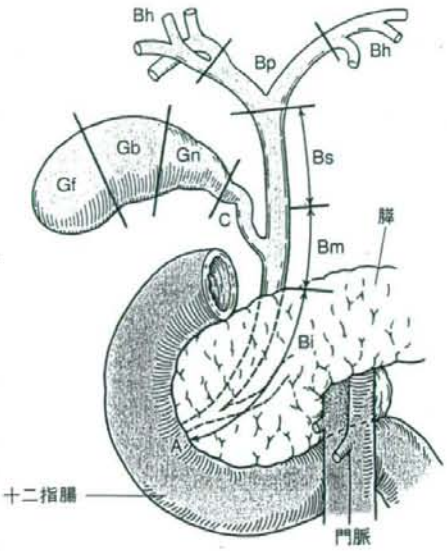
進行した胆嚢癌では，右季肋部痛，右季肋部腫瘤を主訴とすることが多い．胆管への浸潤や腫瘍またはリンパ節転移による胆管の圧排があれば，閉塞性黄疸が出現する．そのほか，病状の進行により，体重減少，食欲不振，全身倦怠感などの症状が出現する．

検査所見

血液生化学的検査

初期には異常を認めないことが多い．閉塞性黄疸例では，ALP（アルカリホスファターゼ）やγ-GTPなどの胆道系酵素の上昇や直接型ビリルビンの上昇を認める．癌が進行し，肝浸潤，肝転移をきたした場合は，GOT（AST），GPT（ALT），LDH（乳酸脱水素酵素）

図18　肝外胆道系の区分



肝外胆道系は，肝外胆管，胆嚢，乳頭部に大別される．肝外胆管はさらに，肝門部胆管（Bp），上部胆管（Bs），中部胆管（Bm），下部胆管（Bi）に，胆嚢は胆嚢底部（Gf），胆嚢体部（Gb），胆嚢頸部（Gn），胆嚢管（C）に分けられる．Bh：肝内胆管．

（日本胆道外科研究会編：胆道癌取扱い規約．第5版．東京：金原出版；2003.）

などの上昇がみられる．

腫瘍マーカーは初期には正常なことが多いが，進行例ではCEA（癌胎児性抗原），CA19-9（carbohydrate antigen 19-9）などの上昇を認める．

超音波検査（US）

侵襲が少なく簡便に施行できるUSは，胆嚢癌のスクリーニング検査だけでなく，質的診断や進展度診断にも有用である（図19）．

隆起性病変を認めた場合，表面が不整で広基性の病変や，径が10mm以上の病変は癌である可能性が高く，精査が必要である．胆嚢壁内を浸潤性に発育する例では，胆嚢壁は不均一に肥厚し，壁エコーの内側は不鮮明となる．肝への直接浸潤がある場合は，胆嚢壁が不連続性になり肝内に低エコー部が認められる．進行癌の多くはUSにて診断可能であるが，小隆起性病変や壁肥厚病変はUSのみでは質的診断が困難である．また，胆嚢内に胆石が充満している場合はUSでの観察が困難となるため，CTなどのほかの検査を行うべきである．

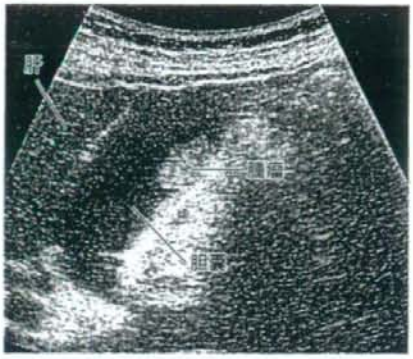
超音波内視鏡検査（EUS）

胆嚢壁はEUSにより粘膜，固有筋層，漿膜下層・漿膜の三層構造に描出される．局所に関して高い解像能を有することから，小さな隆起病変の鑑別や，深達度診断などを主な目的として施行される．

CT検査

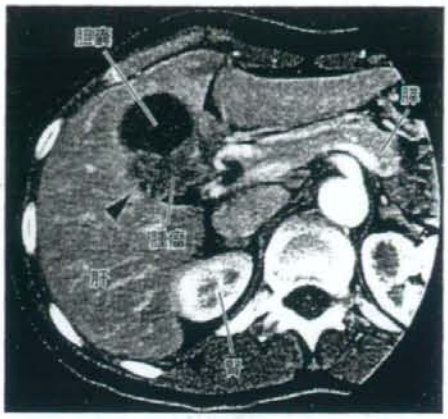
近年機器の進歩，特にMDCT（multi detector-row CT）の登場に

図19　胆嚢癌の超音波像



右肋間走査にて，胆嚢底部～体部に比較的均一な内部エコーを示す径15mmの隆起性病変を認め，病理組織学的に胆嚢癌と診断された．

図20　胆嚢癌のCT像



胆嚢頸部に腫瘍を認める．腫瘍は造影CTにて不均一な濃染像を呈し，一部が肝へ浸潤している（►）．

より，その有用性はますます高くなっている．胆嚢癌はCTにて，胆嚢内の隆起，壁の不整な肥厚，胆嚢内腔を占める腫瘤などとして描出され，造影CTでは濃染することが多い（図20）．進行した癌では，肝内直接浸潤や肝転移，リンパ節転移などがCTにて診断可能であり，進展度診断に有用である．

MRI検査

胆嚢癌はMRIにてT_1強調像で低信号，T_2強調像で高信号を呈し，造影剤にて濃染することが多い．MRCP（MR膵胆管造影）★2は低侵襲的に胆管の情報を得ることができるため，特に胆管への浸潤が疑われる場合の診断に有用である．また，胆嚢癌の高危険因子である膵胆管合流異常の診断にも有用である．

内視鏡的逆行性膵胆管造影（ERCP）

内視鏡的逆行性膵胆管造影（endoscopic retrograde cholangiopancreatography；ERCP）により隆起性病変は陰影欠損として描出される．胆嚢管や胆管への癌の浸潤を診断するうえで有用であるが，近年は低侵襲的なMRCPに取って代わられることが多い．

PET

胆嚢癌診断におけるPETの役割はまだ明らかではないが，PET-CTは遠隔転移や再発の診断に優れている．

細胞診，生検

胆嚢癌が疑われるが確定診断がつかないときに，体表面から胆嚢を穿刺し胆道鏡を挿入する経皮経肝胆嚢鏡を施行して，直視下観察および生検を行うことがある．診断率は高いが，侵襲性，胆汁性腹膜炎などの合併症，穿刺経路からの癌播種などの問題があり，一般的ではない．

★2 MRCP

magnetic resonance cholangiopancreatographyの略．MRによる膵胆道系の画像構築法．従来の膵胆道造影法に比べて，①造影剤を必要とせず低侵襲的である，②膵炎・胆管炎の急性期にも施行可能である，③閉塞部より対側の胆管・膵管の描出が可能である，などの利点を有する．

表6　胆嚢癌のTNM臨床分類

T-原発腫瘍

TX	原発腫瘍の評価が不可能
T0	原発腫瘍を認めない
Tis	上皮内癌
T1	粘膜固有層または筋層に浸潤する腫瘍
T1a	粘膜固有層に浸潤する腫瘍
T1b	筋層に浸潤する腫瘍
T2	筋層周囲の結合組織に浸潤するが，漿膜を越えた進展や肝臓への進展のない腫瘍
T3	漿膜（臓側腹膜）を貫通した腫瘍，肝臓，および/または肝臓以外の1つの隣接臓器（胃，十二指腸，結腸，膵臓，大網，肝外胆管）に直接進展する腫瘍
T4	門脈本幹または肝動脈に浸潤する腫瘍，あるいは肝臓以外の2つ以上の隣接臓器に進展する腫瘍

N-所属リンパ節

NX	所属リンパ節転移の評価が不可能
N0	所属リンパ節転移なし
N1	所属リンパ節転移あり

M-遠隔転移

MX	遠隔転移の評価が不可能
M0	遠隔転移なし
M1	遠隔転移あり

病期分類

Stage	T因子	N因子	M因子
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1，T2，T3	N1	M0
III	T4	Nに関係なく	M0
IV	Tに関係なく	Nに関係なく	M1

（UICC：TNM 悪性腫瘍の分類．第6版．東京：金原出版；2003.）

病期分類

上記検査の結果を総合し，腫瘍の大きさ，広がりなどから病期を判定する．病期分類には，UICCのTNM分類（表6）や日本胆道外科研究会の胆道癌取扱い規約の分類がある．

鑑別診断

胆嚢良性隆起性病変：コレステロールポリープは小さな桑実状の隆起で細い茎をもち，多発することが多い．腺腫，炎症性ポリープとの鑑別は難しいが，腫瘍径が10mmを超えると癌である可能性が高い．

★3 胆嚢腺筋腫症
ロキタンスキー-アショフ洞の増生とその周囲の筋・腺組織の増殖性病変を胆嚢腺筋腫症と呼ぶ．病変の広がりから，底部型，分節型，広範型に分けられる．

慢性胆嚢炎，胆嚢腺筋腫症★3：胆嚢壁肥厚を認めるが，壁肥厚は一様で不整ではない．癌と比べ良性疾患では造影CTで壁の濃染像が強いことが多い．また，MRCPはロキタンスキー-アショフ洞（Rokitansky-Aschoff sinus；RAS）の描出に優れているため，胆嚢腺筋腫症の診断に有用である．

原発性肝癌：胆嚢癌が肝に直接浸潤した場合，CT上は肝内の低吸収域として認められ，原発性肝癌と鑑別困難なことがある．

胆管癌

胆管癌は発症部位により，肝門部胆管癌，上部胆管癌，中部胆管癌，下部胆管癌に分けられる（**図18**）．また，肉眼的形態により，乳頭型，結節型，平坦型，その他（潰瘍型など）に分類される．組織学的深達度が粘膜内または線維筋層内にとどまるものを早期胆管癌と呼ぶが，早期癌で発見されることはまれである．

症状

ほとんどの例では閉塞性黄疸が初発症状である．黄疸は持続性，進行性であり，皮膚瘙痒感，灰白色便，褐色尿などを伴う．また，黄疸発症前に胆管狭窄による胆汁うっ滞が原因で胆管炎が起こり，発熱をきたすことがある．そのほか，病態の進行により，心窩部痛，右季肋部痛，全身倦怠感，食欲不振などが出現する．

検査所見

血液生化学的検査

多くの例で閉塞性黄疸のパターンを示すが，病初期には胆道系酵素のみが上昇し，ビリルビン値は正常なことがある．胆管炎を合併した例では白血球数の増加，C反応性蛋白（CRP）の上昇を認め，緊急の胆道ドレナージ（後述）が必要である．

腫瘍マーカーは，CEA，CA19-9などが進行癌で上昇する．CA19-9は良性の胆道疾患でも高値を示すことがあり，注意が必要である．

超音波検査（US）

USは黄疸の鑑別に有用であり，閉塞性黄疸では肝内および肝外胆管の拡張を認める．胆管癌は低エコーの腫瘤としてみられることが多く，上部および中部胆管癌では描出されやすいが，下部胆管癌は消化管ガスのため描出されにくい．進行癌では，肝転移，リンパ節転移，門脈浸潤などを認め，USにより進展度診断が可能である．

CT検査

USと同様に拡張した胆管の診断は容易であり，肝内では門脈に沿って走行する低濃度の管状構造として描出される．乳頭型の胆管癌

は拡張した胆管の中に造影剤で濃染する隆起として描出されるが，明らかな腫瘤を形成せずに胆管壁を浸潤性に発育する腫瘍はMDCTでも描出が困難な場合がある．進行した大きな腫瘍では，周囲臓器への直接浸潤，肝転移，リンパ節転移，脈管浸潤などがCTで診断される．

MRCP

MRCPはUSやCTで胆管癌が疑われた場合，胆管の閉塞部位や病変の質的診断を目的として施行される．近年，機器の進歩により良好な画像が得られるようになっており，直接胆道造影と比較し，低侵襲的であることや閉塞部の対側の情報が得られるといった利点を有する．

経皮経肝胆道造影（PTC），内視鏡的逆行性膵胆管造影（ERCP）

経皮経肝胆道造影（percutaneous transhepatic cholangiography；PTC）やERCPは直接的に胆道を造影する検査であり，胆管の閉塞部位と病変の質的診断に有用である．胆管癌の基本的な所見は，胆管の狭窄・閉塞，陰影欠損像であり，狭窄部や閉塞部は通常，不整あるいは結節状を呈する．閉塞性黄疸例では，胆道造影後に引き続いて経皮経肝胆道ドレナージ（PTBD）★4や内視鏡的逆行性胆道ドレナージ（ERBD）★5を施行し，減黄を図る．

PET

早期診断への有用性は明らかでないが，PET-CTはCTに比べて遠隔転移の診断に優れている．原発巣についていえば，腫瘍形成性の腫瘍に対しては優れた検出能を有するが，浸潤型のものについては有用性に乏しい．

細胞診，生検

胆道ドレナージから胆汁を採取して細胞診を行う．胆管癌の陽性率は高いが，陰性でも癌は否定できない．PTCを施行すれば直視下の観察と生検による確定診断が可能である．

病期分類

上記検査の結果を総合し，腫瘍の大きさ，広がりなどから病期を判定する（表7）．

鑑別診断

膵癌の胆管浸潤：膵癌では，膵頭部に腫瘍を認め，尾側膵管が拡張していることが多いが，胆管癌で膵管に異常を認めることは少ない．そのほか，乳頭部癌や胆嚢癌の胆管浸潤例でも閉塞性黄疸をきたすことがあり，十二指腸内視鏡，US，CTなどにて鑑別診断を行う．

良性胆管狭窄：原発性硬化性胆管炎★6は，経過が長く，胆管の狭窄

★4 PTBD

percutaneous transhepatic biliary drainageの略．閉塞性黄疸の減黄を目的とした治療法．経皮経肝的に肝内胆管を穿刺した後，ガイドワイヤーを利用してドレナージチューブを胆管内に挿入・留置し，胆汁を体外へ排泄する．

★5 ERBD

endoscopic retrograde biliary drainageの略．内視鏡的にドレナージチューブを乳頭から胆管内に挿入・留置し，胆汁を十二指腸へ排泄する．なお，胆汁を経鼻チューブにて体外へ排泄する方法を経鼻的内視鏡的胆道ドレナージ（endoscopic nasobiliary drainage；ENBD）と呼ぶ．

★6 原発性硬化性胆管炎

肝内外の胆管の線維性狭窄をきたす原因不明の慢性炎症性疾患．基本的には肝内外胆管のびまん性病変であるが，限局性にみられることもある．

表7　肝外胆管癌のTNM臨床分類

T-原発腫瘍

TX	原発腫瘍の評価が不可能
T0	原発腫瘍を認めない
Tis	上皮内癌
T1	胆管壁に限局する腫瘍
T2	胆管壁をこえて浸潤する腫瘍
T3	肝臓，胆嚢，膵臓，および/または門脈または肝動脈の片側の支流（右または左）に浸潤する腫瘍
T4	門脈本幹または両側の支流，総肝動脈，または他の隣接臓器（結腸，胃，十二指腸，腹壁）のいずれかに浸潤する腫瘍

N-所属リンパ節

NX	所属リンパ節転移の評価が不可能
N0	所属リンパ節転移なし
N1	所属リンパ節転移あり

M-遠隔転移

MX	遠隔転移の評価が不可能
M0	遠隔転移なし
M1	遠隔転移あり

病期分類

Stage	T因子	N因子	M因子
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1，T2，T3	N1	M0
III	T4	Nに関係なく	M0
IV	Tに関係なく	Nに関係なく	M1

（UICC：TNM 悪性腫瘍の分類．第6版．東京：金原出版；2003.）

が広範囲である．胆嚢摘出術後の胆管狭窄は，総肝管，胆嚢管，総胆管が合流する3管合流部にみられる．慢性膵炎によって総胆管の狭窄が起こることがあるが，総胆管の狭窄はなめらかで，閉塞性黄疸が出現することはまれである．

（上野秀樹，奥坂拓志）

参考文献

1）日本胆道外科研究会編：胆道癌取扱い規約．第5版．東京：金原出版；2003.
2）胆道癌診療ガイドライン作成出版委員会編：胆道癌診療ガイドライン．第1版．東京：医学図書出版；2007.

Expansion of metallic mesh stent hole using a Soehendra stent retriever in multiple stenting of biliary hilar obstruction

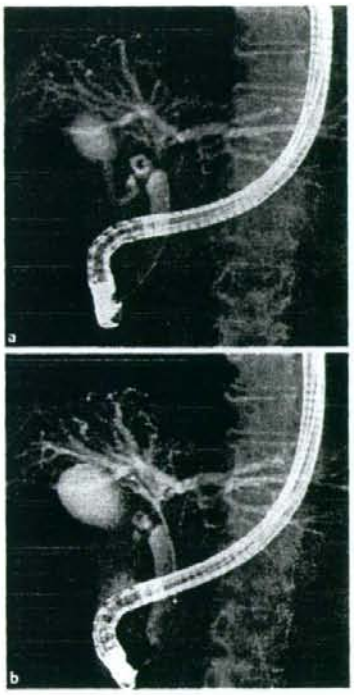


Fig. 1 **a** Cholangiogram showing a Bismuth type III hilar stricture. **b** A metallic mesh stent was placed in the right biliary tree.

A malignant hilar biliary stricture is usually unresectable at the time of diagnosis and requires multiple biliary stentings. Metallic mesh stents remain patent for a relatively long time in the biliary stricture compared to tube stents [1]. However, employing multiple metallic mesh stents is sometimes very difficult because of their small lumen, which impedes the delivery of a catheter. The Soehendra stent retriever (Soehendra SR; Wilson-Cook Medical Inc., Winston-Salem, North Carolina, USA) is useful for dilating a stenosed biliary or pancreatic duct [2–4]. We used it to expand the mesh holes in metallic mesh stents placed in patients with malignant biliary hilar stricture who were undergoing multiple stenting.

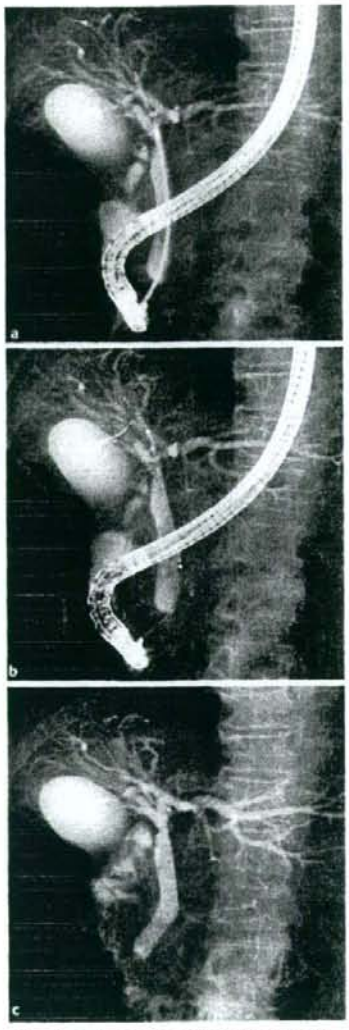


Fig. 2 **a** A Soehendra stent retriever was advanced along the guide wire to expand the mesh holes of the first metallic mesh stent. **b** A metallic mesh stent delivery catheter was then easily introduced into the left biliary tree. **c** Multiple stenting was successfully accomplished.

We used the retriever in three patients with unresectable hilar biliary carcinoma. ○ **Fig. 1a** shows the endoscopic cholangiogram of a patient with a Bismuth type III stricture. A guide wire was negotiated into the right biliary tree and a metallic mesh stent inserted (JoStent SelfX stent; Abbott Vascular Devices, Redwood City, California, USA) (○ **Fig. 1b**). Then, a second guide wire was negotiated into the left biliary tree through a mesh hole in the first stent. Despite several attempts using dilation catheters, it was not possible to insert them into the left biliary tree because of the small mesh holes of the stents. We therefore introduced a Soehendra SR and advanced it along the guide wire, turning it clockwise to allow the threads at the end of the device to engage the mesh and expand the stent hole (○ **Fig. 2a**). After expansion, a metallic mesh stent delivery catheter was easily introduced into the biliary tree (○ **Fig. 2b**) and multiple stenting was achieved (○ **Fig. 2c**). We successfully carried out multiple stenting using metallic mesh stents in two other patients and no relevant complications were encountered. Our results indicate that the Soehendra SR was useful in expanding the mesh holes of a metallic stent in patients requiring multiple stenting with metallic mesh stents.

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References

1 *Kaassis M, Boyer J, Dumas R et al.* Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc 2003; 57: 178–182
2 *Soehendra N, Mayde A, Eckmann B et al.* A new technique for replacing an obstructed biliary endoprothesis. Endoscopy 1990; 22: 271–272
3 *Faigel DO, Ginsberg GG, Kochman ML.* Innovative use of the Soehendra stent retriever for biliary stricture recannalization. Gastrointest Endosc 1996; 44: 635
4 *Brand B, Thonke S, Obytz KF et al.* Stent retriever for dilation of pancreatic and bile duct strictures. Endoscopy 1999; 31: 142–145

Bibliography
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Postoperative adjuvant treatments for biliary tract cancer

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Abstract
Surgery currently remains the only potentially curative treatment for biliary tract cancer, and most patients develop recurrence. Thus, effective adjuvant therapy is required to increase the curability of surgery and to prolong the survival in these patients. However, to date, no standard postoperative adjuvant therapy regimen has been established for patients with biliary tract cancer. Based on favorable results reported from phase II trials, gemcitabine and S-1 are currently available as promising agents for the treatment of unresectable biliary tract cancer in Japan. Both agents are also expected to be effective in the postoperative adjuvant therapy setting for biliary tract cancer, and well-designed randomized controlled trials (phase III trials) to determine the efficacy of these agents in the postoperative adjuvant setting should be pursued vigorously. In phase III trials, appropriate stratification of patients is important, and the primary disease (gallbladder cancer versus nongallbladder cancers), curability (R0 or R1), and presence/absence of lymph node metastasis should be taken into account.

Key words Biliary tract cancer · Systemic chemotherapy · Adjuvant chemotherapy

Introduction

The term "biliary tract cancer (BTC)" includes bile duct cancer, gallbladder cancer, and ampullary cancer, which arises from the extrahepatic biliary tract.[1,2] While intrahepatic cholangiocarcinoma is classified as primary liver cancer in the *General rules for the clinical and pathological study of primary liver cancer* published by the Liver Cancer Study Group of Japan[3] and the *TNM classification of malignant tumours* established by the International Union Against Cancer,[1] it is often included as BTC in clinical trials of chemotherapy. While BTC is generally rare in Western countries, it is one of the common causes of cancer deaths in Japan, with an estimated 16000 deaths from this cancer annually,[4] as compared to 3340 in the United States.[5]

Currently, surgery remains the only potentially curative treatment, and most patients develop recurrence. Thus, effective postoperative adjuvant therapy is required to increase the curability of surgery and to prolong survival in patients with BTC undergoing surgery. However, no standard postoperative treatment has been established yet. Some promising regimens have recently been reported for advanced unresectable BTC, and these are also expected to be investigated in the adjuvant setting.

Outcome of surgery for biliary tract cancer (BTC)

Surgical resection is the treatment of first choice for BTC, and the resection rate is reported to be relatively high, at 69.8% for gallbladder cancer, 67% for bile duct cancer, and 91.2% for ampullary cancer.[6] However, the rate of curative resection remains poor; it is reported to be 37.7% for gallbladder cancer, 30.4% for bile duct cancer, and 78.5% for ampullary cancer.[6] In particular, for hilar cholangiocarcinoma and gallbladder cancer, diagnosis in the early stage is often difficult because of the lack of specific symptoms. In patients with these cancers, the cancer often invades the segmental branches, producing obstructive jaundice. Thus, the additional difficulty of managing the obstructive jaundice makes the resection rate poor.

However, the development of surgical techniques and the use of supportive treatments have brought down the mortality rate, and deaths presumed to result directly from surgery have been reported to occur at a rate of only 1.7% in patients with BTC.[6] On the other hand, according to the BTC statistics registry in Japan,

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the 5-year survival rates after resection remain poor in these patients, being 26% for bile duct cancer, 42% for gallbladder cancer, and 51% for ampullary cancer.[6] The major reason for these poor outcomes of surgery in patients with BTC remains cancer recurrence, which is observed in more than 50% of the patients, and is observed even in those undergoing curative resection.[7] Furthermore, even long-term survivors remain at a significant risk of death from tumor recurrence.[8] Thus, it is necessary to develop effective postoperative adjuvant treatments to prolong the survival of patients with BTC.

Chemotherapy for unresectable biliary tract cancer (BTC)

In the consideration of postoperative adjuvant therapy after surgery, useful information can be obtained from the results of chemotherapy for advanced unresectable cancer. Although no standard chemotherapy for BTC has been established because there have been few randomized controlled trials (RCTs) with a large number of patients, many phase II studies have been conducted, and some promising regimens have been identified.

Recently, many clinical trials have been conducted with gemcitabine (Table 1). Although the methods of administration of gemcitabine have varied among studies, relatively good results have been reported with this drug. A phase II study of gemcitabine administered alone was carried out in Japan;[11] a response rate of 17.5% (95% confidence interval [CI], 7.3%–32.8%) and median overall survival (OS) of 7.6 months were achieved with administration of the standard dose of 1000 mg/m^2 as a weekly intravenous 30-min infusion, with treatment given for 3 consecutive weeks, followed by a week's rest. The results of this Japanese trial of gemcitabine were similar to those of trials of the drug reported from abroad.[9–17] The drug was well tolerated, with the major toxicities being myelosuppression and gastrointestinal toxicity, including nausea and anorexia. Based on these results, gemcitabine was approved by the Japanese Ministry of Health, Labour, and Welfare for the treatment of BTC in June 2006. Furthermore, in trials of gemcitabine-based combinations, the time-to progression (TTP) and OS were relatively good in the subjects who received gemcitabine-based combination chemotherapy as compared with these outcomes in trials in which subjects received gemcitabine alone. Favorable results were achieved, with response rates of 27.5%–36.6% and median OS of 4.6–11.0 months in

Table 1. Gemcitabine-based chemotherapy for unresectable advanced biliary tract cancer

Regimen	*n*	Response rate	Median PFS/TTP (months)	Median OS (months)	Author (year)
Gemcitabine alone					
*1000 mg/m^2, D 1, 8, 15, q 4 wks	25	36.0%	—	6.9	Gallardo (2001)[9]
*1000 mg/m^2, D 1, 8, 15, q 4 wks	24	12.5%	2.5	7.2	Lin (2003)[10]
*1000 mg/m^2, D 1, 8, 15, q 4 wks	40	17.5%	2.6	7.6	Okusaka (2006)[11]
*1200 mg/m^2, D 1, 8, 15, q 5 wks	19	16.0%	2.5	6.5	Raderer (1999)[12]
*2200 mg/m^2, biweekly	32	21.9%	5.6	11.5	Penz (2001)[13]
*800 mg/m^2, weekly	30	30.0%	7.0	14.0	Tsavaris (2004)[14]
FDR Gemcitabine (1500 mg/m^2), D1, 8, 15, q 4 wks	15	0%	2.1	4.6	Eng (2004)[15]
1000 mg/m^2, 60-min infusion, D 1, 8, q 3 wks	23	26.1%	8.1	13.1	Park (2005)[16]
1000 mg/m^2, 24-h infusion, D1, 8, 15, q 4 wks	19	5.5%	3.6	7.5	von Delius (2005)[17]
Gemcitabine-based combination					
Gemcitabine/5-FU	27	33.3%	3.7	5.3	Knox (2004)[18]
Gemcitabine/5-FU/LV	30	21.4%	3.7	4.7	Hsu (2004)[19]
Gemcitabine/5-FU/LV	42	11.9%	4.6	9.7	Alberts (2005)[20]
Gemcitabine/capecitabine	45	31.1%	7.0	14.0	Knox (2005)[21]
Gemcitabine/capecitabine	45	31.8%	6.0	14.0	Cho (2005)[22]
Gemcitabine/cisplatin	30	36.6%	4.1	4.6	Doval (2004)[23]
Gemcitabine/cisplatin	40	27.5%	4.7	8.3	Thongprasert (2005)[24]
Gemcitabine/cisplatin	29	34.5%	3.0	11.0	Kim ST (2006)[25]
Gemcitabine/cisplatin	27	33.3%	5.6	10.0	Park BK (2006)[26]
Gemcitabine/oxaliplatin	33	33.3%	5.7	15.4	Andre (2004)[27]
Gemcitabine/oxaliplatin/bevacizumab	26	27.3%	7.6	—	Clark (2007)[28]
Gemcitabine/docetaxel	43	9.3%	5.2	11.0	Kuhn (2002)[29]
Gemcitabine/pemetrexed	58	11%	3.8	6.6	McWilliams (2007)[30]

D, day; wks, weeks; FDR, fixed-dose-rate infusion (10 mg/min infusion); PFS, progression-free survival; TTP, time to progression; OS, overall survival; 5-FU, fluorouracil; LV, leucovorin
*30-min infusion

Table 2. Oral fluoropyrimidine-based chemotherapy for unresectable advanced biliary tract cancer

Regimen	*n*	Response rate	Median PFS/TTP (months)	Median OS (months)	Author (year)
UFT/LV	13	0%	2.1	6.5	Mani (1999)[32]
UFT/LV	16	0%	2.2	4.5	Chen (2003)[33]
UFT	19	5.3%	1.0	8.8	Ikeda (2005)[34]
Capecitabine	26	19.2%	NA	CC, 8.1; GB, 9.9	Patt (2004)[35]
S-1	19	21.1%	3.7	8.3	Ueno (2004)[36]
S-1	40	32.5%	3.7	9.4	Furuse (2008)[37]
UFT/doxorubicin	24	12.5%	2.5	7.6	Furuse (2006)[38]
Capecitabine/oxaliplatin	65	20.0%	GB, 2.2; CC, 6.5	GB, 5.2; CC, 12.8	Nehls (2006)[39]
S-1/cisplatin	51	29.4%	4.8	8.7	Kim YJ (2008)[40]

PFS, progression-free survival; TTP, time to progression; OS, overall survival; UFT, uracil-tegafur; LV, leucovorin; S-1, tegafur/gimeracil/oteracil potassium; GB, gallbladder; CC, cholangiocarcinoma; NA, not available

trials with a gemcitabine + cisplatin regimen.[23–26] Currently, a large RCT comparing gemcitabine alone and gemcitabine + cisplatin is being conducted chiefly by a United Kingdom group and is drawing attention.[31] In Japan also, a randomized phase II study has been conducted using the same regimens.

Another key drug class is that of the fluoropyrimidines, and some oral fluoropyrimidines have been developed (Table 2). Clinical trials of tegafur/gimeracil/oteracil potassium (S-1), an oral anticancer drug containing tegafur (FT) as the prodrug of fluorouracil, 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo), have been conducted in Japan.[36,37] S-1 was administered orally at the dose of 80 mg/m^2 per day for 28 days followed by 14 days' rest. In a late phase II trial, favorable results were reported, with a response rate of 30% and median OS of 9.4 months in a multicenter phase II study of 40 patients.[37] Based on these results, insurance coverage for the use of this agent in the treatment of BTC was endorsed by the Government of Japan in August 2007.

Adjuvant therapy after surgery

Although further development of effective measures for preventing recurrence through establishing effective postoperative adjuvant therapies for BTC has been eagerly anticipated, few RCTs of postoperative adjuvant therapy have been conducted. In 2002, Takada et al.[41] reported the results of an RCT of postoperative adjuvant chemotherapy in patients with pancreatic cancer and BTC, including extrahepatic bile duct cancer, gallbladder cancer, and ampullary cancer (Table 3). In this trial, 508 patients were assigned to either a combination chemotherapy arm of 5-FU and mitomycin C (MF group) or an observation arm treated by surgery alone (control group). The 5-year OS rates were analyzed independently for individual diseases in the eligible patients; namely, 158 patients with pancreatic cancer, 118 patients with bile duct cancer, 112 patients with gallbladder cancer, and 48 patients with ampullary cancer. The OS rate in the MF arm was statistically significantly higher than that in the control arm only for gallbladder cancer; furthermore, this significant difference was found only in patients who had undergone noncurative resection. According to the results of intent-to-treat analysis, no significant difference was observed between the MF and control groups in the patients with gallbladder cancer. Thus, while MF therapy has not yet been established as the standard postoperative adjuvant therapy for patients with BTC, the efficacy of postoperative adjuvant therapy was suggested by this trial.

Table 3. Randomized clinical trials of adjuvant chemotherapy for pancreatic and biliary tract cancer[41]

	n	5-Year survival rate	*P* value
Pancreatic cancer			
Mitomycin C/5-FU	81	11.5%	NS
Surgery alone	77	18.0%	
Gallbladder cancer			
Mitomycin C/5-FU	69	26.0%	0.037
Surgery alone	43	14.4%	
Bile duct cancer			
Mitomycin C/5-FU	58	26.7%	NS
Surgery alone	60	24.1%	
Ampullary cancer			
Mitomycin C/5-FU	24	28.1%	NS
Surgery alone	24	34.3%	

5-FU, fluorouracil; NS, not significant

At the present time, no recommendable postoperative adjuvant therapy has been identified, and a guideline for BTC treatment recommends that trials of adjuvant chemotherapy be carried out.[42] Based on the results of phase II studies in patients with unresectable BTC, gemcitabine and S-1 are considered to have activity against BTC, and both agents are currently available