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ORIGINAL ARTICLE

Prognostic factors in patients with advanced biliary tract cancer receiving chemotherapy

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Abstract
Purpose Prognostic factors for patients with advanced biliary tract cancer receiving chemotherapy are presently not well established. Gallbladder cancer and intra-hepatic cholangiocarcinoma are previously reported prognostic factors of poor prognosis; however, tumor volume has not been analyzed in these previous reports.
Methods We analyzed 56 consecutive patients with advanced biliary tract cancer who had received gemcitabine and S-1 combination chemotherapy as first-line palliative chemotherapy. Prognostic factors, including the baseline sum longest diameter (BSLD) representing tumor volume in Response Evaluation Criteria in Solid Tumor, were evaluated.
Results By multivariate analysis, age $\geq$70 (HR 3.01, 95% CI 1.25–7.31, $P = 0.014$) and larger BSLD (HR 1.09, 95% CI 1.01–1.18, $P = 0.021$) were statistically significant independent predictors of poor prognosis. Primary biliary site was not identified as a prognostic factor ($P = 0.728$). Median survival times of patients with BSLDs $\leq$ 9.0 cm and BSLDs $>$ 9.0 cm were 18.7 and 8.8 months, respectively ($P = 0.024$).
Conclusions Age and BSLD were identified as strong prognostic factors for patients with advanced biliary tract cancer receiving chemotherapy. Tumor volume might be more important than primary biliary site for the prognosis of advanced biliary tract cancer.

Keywords Biliary tract cancer · Tumor volume · Prognostic factor · Chemotherapy

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Introduction

Biliary tract cancer (BTC) is a rare cancer worldwide, and there exists little data regarding the treatment of this condition using chemotherapy [1, 2]. In 2009, the first large phase III study (ABC-02) demonstrated the superiority of gemcitabine and cisplatin combination chemotherapy to single-agent gemcitabine in the treatment of BTC, which has made this combination chemotherapy a standard of care for the treatment of advanced BTC [3]. S-1, an oral fluoropyrimidine, is another treatment option for advanced BTC in Japan [4–6], wherein combination chemotherapy of S-1 and gemcitabine has demonstrated good efficacy in our phase II study [7].

Due to the difficulty of conducting clinical trials for advanced BTC, most previous studies, including the ABC-02 study, have analyzed all biliary tract cancers in

the same study population, regardless of primary biliary site and disease status. Due to the heterogeneity of the study population, data regarding patient characteristics are necessary, and prognostic factors should be identified for patients with advanced BTC receiving palliative chemotherapy. Several clinical trials evaluating chemotherapeutic regimen and several studies investigating prognostic factors for patients receiving palliative chemotherapy for advanced BTC have been reported; however, most previous studies do not discuss tumor volume [2, 3, 8–12], and we have experienced that patients with large tumor volumes typically show poor prognoses.

The baseline sum longest diameter (BSLD) was evaluated as a measure of tumor volume when judging tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) [13]. BSLD was usually measured in the most recent clinical trials and is not as complicated as other measurement methods [e.g., computed tomography (CT) volumetry] for measuring tumor volumes. Therefore, we evaluated the importance of tumor volume by using BSLD as a prognostic factor for patients with advanced BTC receiving first-line palliative chemotherapy.

Patients and methods

Study population

Fifty-six consecutive patients with advanced BTC who received gemcitabine and S-1 combination chemotherapy as first-line chemotherapy at five institutions in Tokyo, Japan, between January 2007 and July 2009, were included in the study. All patients provided written informed consent, and the trial was conducted in accordance with the Declaration of Helsinki. Each participating institution was required to receive approval from their respective local research ethics committees.

The inclusion criteria for the current study included the following: (1) patients exhibited advanced BTC and were not amenable to potentially curative surgery or refractory for surgery; (2) pathologically demonstrated BTC or graphically confirmed BTC; (3) the presence of measurable lesions defined by RECIST criteria; (4) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ranging from zero to two; and (5) adequate bone marrow and organ function (white blood count $> 3{,}000/mm^3$, hemoglobin > 9.0 g/dL, platelet count $> 100{,}000/mm^3$, total bilirubin $<$ three times the upper limit of normal (ULN), aspartate/alanine transaminases $<$ five times ULN, and creatinine < 1.2 mg/dL or creatinine clearance $>$ 50 mL/min). Exclusion criteria included age < 20 years, a prior history of chemotherapy or radiotherapy, uncontrolled infection, active ulcer of the gastrointestinal tract, gastrointestinal obstruction compromising oral ingestion, pregnancy or lactation, a history of drug hypersensitivity, active concomitant malignancy, and concurrent severe medical conditions.

Treatment

Gemcitabine was given intravenously at 1,000 mg/m^2 over 30 min on days 1 and 15, and repeated every 4 weeks. S-1 was administered orally twice daily from days 1 to 14, followed by a 2-week rest [7, 14]. Three doses of S-1 were established according to body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; 1.25 m$^2 \leq$ BSA < 1.5 m^2, 100 mg/day; and BSA ≥ 1.5 m^2, 120 mg/day. Dose reduction was based on adverse effects that were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. In case of grade III/IV hematological toxicity or grade II or higher non-hematological toxicity, treatment was temporarily suspended. After confirming a grade I toxicity level or lower, treatment was resumed at a reduced dose. At first, S-1 was reduced to the following doses: BSA $<$ 1.25 m^2, 60 mg/day; 1.25 m$^2 \leq$ BSA < 1.5 m^2, 80 mg/day; and BSA ≥ 1.5 m^2, 100 mg/day. If toxicity occurred despite S-1 reduction, gemcitabine was reduced to 800 mg/m^2. If further toxicity was experienced, S-1 was reduced to the following doses: BSA < 1.25 m^2, 40 mg/day; 1.25 m$^2 \leq$ BSA < 1.5 m^2, 60 mg/day; and BSA ≥ 1.5 m^2, 80 mg/day, and gemcitabine was reduced to 600 mg/m^2. If further dose reduction was needed, the study treatment was put on hold. No dose re-escalation was allowed. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal occurred.

Data collection and statistical analysis

Pretreatment evaluation included age, gender, ECOG PS, primary biliary site, disease status, metastatic site (liver, lung, lymph node, peritoneum, and others), carbohydrate antigen 19-9 (CA19-9) levels, carcinoembryonic antigen (CEA) levels, and BSLD. All target lesions (10 mm or larger in the longest diameter, up to a maximum of 5 lesions per organ and 10 lesions in total) and non-target lesions at baseline were identified and measured by CT scans using 5-mm slices within 4 weeks before starting chemotherapy. The BSLD was defined as a sum of the longest diameter for all target lesions identified at baseline.

Overall survival and time-to-progression was calculated using the Kaplan–Meier method, and differences were evaluated using the log-rank test. Overall survival was defined as the time from initiation of therapy to final follow-up, or else until death from any cause. Time-to-progression was calculated from the start of the

treatment to the first date of documented disease progression. Tumor response was evaluated according to RECIST criteria. All the analysis was based on follow-up information received prior to September 2009.

The Mann–Whitney *U* test or Kruskal–Wallis test was used to compare quantitative variables, as appropriate. The univariate and multivariate analyses of prognostic factors using a Cox proportional hazard model were used to calculate hazard risks (HRs) and their 95% confidence interval (95% CI). Factors with substantial impacts ($P < 0.1$) in the univariate analysis were subsequently evaluated with multivariate analysis. A P value of less than 0.05 was considered statistically significant, and all tests were two-sided. The following 12 categories were examined: age (<70 or ≥70), gender (male or female), ECOG PS (0–1 or 2), disease status (metastatic or locally advanced/recurrent), primary biliary site (gallbladder/intra-hepatic bile duct or extra-hepatic bile duct/ampulla of Vater), liver metastasis, lung metastasis, lymph node metastasis, other metastasis, CA19-9 level (<1,000 or ≥1,000 U/mL), CEA level (<5 or ≥5 ng/mL), and BSLD (as a continuous variable). The JMP 8.0 statistical software program (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Patient characteristics

Patient characteristics are listed in Table 1. All patients except two exhibited pathologically confirmed BTC. The median age was 67 years (range, 24–83 years) and 35 patients (63%) were men. The primary biliary sites were located in the gallbladder in 22 patients (39%), the intra-hepatic bile duct in 19 patients (34%), the extra-hepatic bile duct in 14 patients (25%), and the ampulla of Vater in 1 patient (2%). The median BSLD was 9.0 cm (range 1.5–26 cm). The median BSLDs of gallbladder cancers, intra-hepatic cholangiocarcinomas, and extra-hepatic cholangiocarcinomas were 10.0 cm (range 3–24 cm), 11 cm (range 3–26 cm), and 3.7 cm (range 1.5–8.3 cm), respectively. The BSLD of the ampulla of Vater was 3 cm. The BSLD was significantly different between each primary biliary site (Fig. 1; $P < 0.001$).

Table 1 Patient characteristics ($n = 56$)

Age (years)	
Median (Range)	67 (24–83)
Gender	
Male	35
Female	21
ECOG performance status	
0	27
1	27
2	2
Primary biliary site	
Gallbladder	22
Intra-hepatic bile duct	19
Extra-hepatic bile duct	14
Ampulla of Vater	1
Disease status	
Locally advanced	6
Metastatic	41
Recurrent	9
Metastatic sites	
Liver	24
Lung	14
Lymph node	42
Others (Peritoneum, Bone, Adrenal gland)	12
CA19-9 (U/mL)	
Median (Range)	157.5 (1–311,276)
CEA (ng/mL)	
Median (Range)	6.5 (0.9–1570.8)
BSLD (cm)	
Median (Range)	9.0 (1.5–26.0)

ECOG Eastern Cooperative Oncology Group, *CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *BSLD* baseline sum longest diameter

Overall survival and analysis of prognostic factors

The median overall survival time was 12.3 months (95% CI, 9.2–17.9 months). Of all 56 patients, 29 patients (52%) had died at the time of data analysis. Variables significantly associated with overall patient's survival in the univariate analysis were age, ECOG PS, primary biliary site, lymph node metastasis, CA19-9 level, and BSLD (Table 2). In the multivariate analysis, age ≥ 70 (HR 3.01, 95% CI 1.25–7.31, $P = 0.014$) and larger BSLD (HR 1.09, 95% CI 1.01–1.18, $P = 0.021$) were extracted as statistically significant independent poor prognosis factors (Table 3). Primary biliary site was not extracted as a prognostic factor ($P = 0.728$).

When the study population was separated into two groups by a BSLD of 9 cm (one group consisting of patients with BSLDs ≤ 9 cm and the other with BSLDs > 9 cm), which was the median of the BSLD in the current study population, the overall survival curves were clearly separated with statistical significance (Fig. 2). Median survival times of the smaller BSLD group (≤9 cm) and larger BSLD group (>9 cm) were 18.7 and 8.8 months, respectively ($P = 0.024$).

In order to exclude the impacts of primary biliary site, gallbladder cancer and intra-hepatic cholangiocarcinoma,

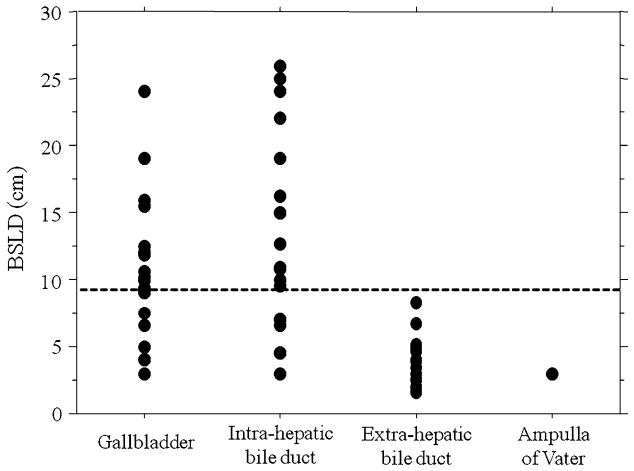

Fig. 1 Scatter plots demonstrating the relation between BSLD and primary biliary site in the current study population. The *dashed line* indicates the median BSLD (9 cm) of the current study population. The BSLDs of each primary biliary site were significantly different ($P < 0.001$)

which have been previously reported as poor prognostic factors, were extracted, and the same analysis was performed. Median survival times of the smaller BSLD group (≤9 cm) and larger BSLD group (>9 cm) were 17.2 and 8.8 months, respectively ($P = 0.142$), when the impacts of primary biliary site were excluded from median survival times.

Time-to-progression and BSLD

The median time-to-progression was 5.9 months (95% CI, 5.0–6.3 months). Of all 56 patients, 35 patients (63%) experienced disease progression at the time of data analysis. Variables significantly associated with time-to-progression in the univariate analysis were disease status (metastatic) (HR 2.66, 95% CI 1.17–7.14, $P = 0.018$), liver metastasis (HR 2.00, 95% CI 1.02–3.91, $P = 0.044$), and a larger BSLD (HR 1.07, 95% CI 1.01–1.13, $P = 0.026$). In the multivariate analysis, none of these clinical parameters were extracted as significant variables for time-to-progression. Median time-to-progression curves of the smaller BSLD group (≤9 cm) and the larger BSLD group (>9 cm) were 5.9 and 4 months, respectively ($P = 0.048$).

Tumor response and BSLD

Overall, two patients (3.6%) achieved complete responses, and 15 (26.8%) showed partial responses. Stable diseases were observed in 26 patients (46.4%), and progressive diseases were observed in 10 patients (17.9%). Three patients who stopped the treatment within 1 week were judged "not evaluable." The overall response and disease control rates of the current study population were 30.4 and 76.8%, respectively. When the study population was separated into two groups by a BSLD of 9 cm, the response rates and the disease control rates were clearly different in each BSLD group. The response rates of the smaller BSLD group (≤9 cm) and the larger BSLD group (>9 cm) were 41.4 and 18.5%, respectively. The disease control rates of the smaller BSLD group (≤9 cm) and the larger BSLD group (>9 cm) were 89.7 and 63.0%, respectively (Table 4).

Discussion

Early diagnosis is essential to achieving a good prognosis; however, most cases of BTC are diagnosed at advanced stages and usually demonstrate poor prognoses. Recently, several clinical trials of chemotherapy to improve the prognosis of advanced BTC have been reported [1–3, 7, 11]. In most of these trials, primary biliary site and disease status were analyzed together due to the rarity of BTC. Consequently, a small metastasis site (e.g., small lung metastasis) and a large primary site (e.g., unresectable intra-hepatic cholangiocarcinoma of more than 10 cm in size) were analyzed together. In fact, the BSLD was significantly different between each primary biliary site in the current study (Fig. 1). For this reason, some information of tumor volume should be involved in the reports of chemotherapy for advanced BTC; however, few previous reports have mentioned tumor volume.

BSLD was selected as the measure of tumor volume because most of the clinical trials using RECIST criteria evaluated BSLD. Other modalities, like CT volumetry, might more accurately assess tumor volume; however, this technique is more complicated in comparison with BSLD measurement. There have been some instances of immeasurable BTC, like diffuse cholangiocarcinoma, although the incidence of these tumors is limited. BSLD has also been evaluated as an independent prognostic factor of patients with metastatic colorectal cancer after systemic chemotherapy [15].

In the present study, tumor volume represented by BSLD was extracted as a prognostic factor (HR 1.09, 95% CI 1.01–1.18, $P = 0.021$). Median survival times of patients in the group with smaller BSLDs (≤9 cm) and the group with larger BSLDs (>9 cm) were 18.7 and 8.8 months ($P = 0.024$), respectively. These differences in median survival time are remarkable. A larger tumor size has also been reported as a poor prognostic factor in patients with intra-hepatic cholangiocarcinoma receiving *trans*-catheter arterial chemo-embolization or chemo-infusion [16]. Previous studies evaluating prognostic factors of advanced BTC receiving chemotherapy concluded that

Table 2 Univariate analysis of prognostic factors

Variable	*N*	Median OS (months)	Hazard ratio (95% CI)	*P* value
Age (years)				0.004
<70	35	22.6	1	
≥70	21	9.3	3.04 (1.43–6.56)	
Gender				0.119
Male	35	11.5	1	
Female	21	15.4	0.54 (0.24–1.16)	
ECOG performance status				0.061
0–1	54	14.4	1	
2	2	5.4	5.87 (0.90–22.0)	
Primary biliary site				0.069
Extra-hepatic bile duct/ampulla of Vater	15	Not reached	1	
Gallbladder/intra-hepatic bile duct	41	11.3	2.29 (0.94–6.81)	
Disease status				0.118
Locally advanced/recurrent	15	18.7	1	
Metastatic	41	11.1	1.97 (0.85–5.35)	
Liver metastasis				0.154
No	32	14.9	1	
Yes	24	7.2	1.72 (0.81–3.60)	
Lung metastasis				0.609
No	42	12.3	1	
Yes	14	13.9	0.80 (0.32–1.80)	
Lymph node metastasis				0.025
No	14	Not reached	1	
Yes	42	9.7	2.92 (1.13–9.94)	
Other metastasis				0.356
No	44	14.4	1	
Yes	12	11.2	1.57 (0.57–3.71)	
CA19-9 (U/mL)				0.005
<1,000	36	18.7	1	
≥1,000	20	8.8	3.15 (1.41–7.21)	
CEA (ng/mL)				0.113
<5	26	22.6	1	
≥5	30	10.7	1.82 (0.87–3.91)	
BSLD (cm; continuous)	56	–	1.07 (1.01–1.13)	0.016

N number of patients, *OS* overall survival, *95% CI* 95% confidence interval, *ECOG* Eastern Cooperative Oncology Group, *CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *BSLD* baseline sum longest diameter

gallbladder cancer or intra-hepatic cholangiocarcinoma is associated with a poor prognosis in patients with advanced BTC [9, 10, 12]. It is difficult to interpret whether primary biliary site or tumor volume affect prognosis, because the tumor volume of each primary biliary site was usually different (Fig. 1). In the current study, primary biliary site, including gallbladder and intra-hepatic cholangiocarcinoma, was not extracted as a prognostic factor in the multivariate analysis ($P = 0.728$). Additionally, in patients with either gallbladder cancer or intra-hepatic cholangiocarcinoma, previously reported as poor prognostic factors for primary biliary cancer, the group of patients with larger BSLDs also demonstrated poorer prognosis in comparison with the group of patients with small BSLDs (8.8 vs. 17.2 months). Therefore, tumor volume seems to be more important than primary biliary site for the prognosis of advanced BTC receiving chemotherapy.

Larger BSLD was also demonstrated as a statistically significant poor predictor of time-to-progression, although it was not extracted by multivariate analysis. This result could have been caused by the small size of study population and the small proportion of the patients with progressive disease. Tumor response was also associated with BSLD size in the current study. The response rates and disease control rates of each BSLD group (≤9 vs. >9 cm) were quite different. These results indicate that tumor volume markers, like BSLD, should be evaluated in the study of advanced BTC receiving chemotherapy.

Table 3 Multivariate analysis of prognostic factors

Variable	*N*	Hazard ratio (95% CI)	*P* value
Age (years)			0.014
<70	35	1	
≥70	21	3.01 (1.25–7.31)	
ECOG performance status			0.378
0–1	54	1	
2	2	2.16 (0.32–9.05)	
Primary biliary site			0.728
Extra-hepatic bile duct/ampulla of Vater	15	1	
Gallbladder/intra-hepatic bile duct	41	1.22 (0.40–4.18)	
Lymph node metastasis			0.431
No	14	1	
Yes	42	1.54 (0.55–5.51)	
CA19-9 (U/mL)			0.093
<1,000	36	1	
≥1,000	20	2.21 (0.88–5.67)	
BSLD (cm; continuous)	56	1.09 (1.01–1.18)	0.021

N number of patients, *95% CI* 95% confidence interval, *ECOG* Eastern Cooperative Oncology Group, *CA19-9* carbohydrate antigen 19-9, *BSLD* baseline sum longest diameter

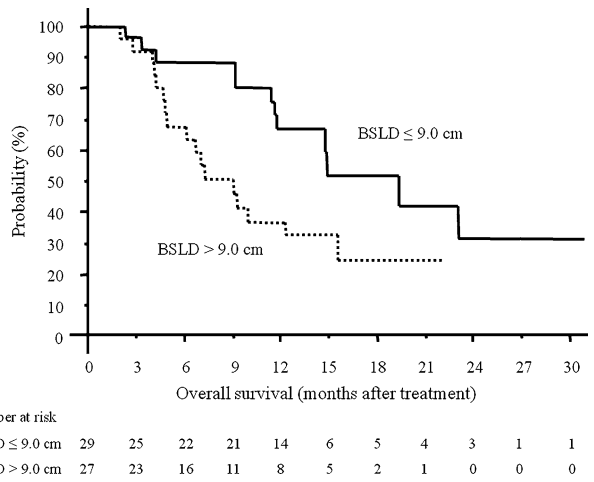

Fig. 2 Overall survival curves of patients with BSLDs ≤ 9 cm (*solid line*) and BSLDs > 9 cm (*dashed line*). Median survival times of patients with BSLDs ≤ 9 cm and BSLDs > 9 cm were 18.7 and 8.8 months, respectively ($P = 0.024$)

A limitation of the current study was the small size of the study population. Because the study population of advanced BTC is typically heterogeneous, we attempted to include patients receiving the same chemotherapeutic regimen. The study population of patients receiving gemcitabine and S-1 combination chemotherapy was selected, because gemcitabine and cisplatin combination chemotherapy, a standard of care for advanced BTC, was not approved by the Japanese Ministry of Health, Labor, and Welfare for the treatment of advanced BTC in 2009. In Japan, gemcitabine and S-1 combination chemotherapy was expected to be a competitive regimen to gemcitabine and cisplatin combination chemotherapy.

Table 4 Tumor response and BSLD

	CR	PR	SD	PD	NE	RR (%)	DCR (%)
BSLD ≤ 9 cm	2	10	14	3	0	41.4	89.7
BSLD > 9 cm	0	5	12	7	3	18.5	63.0

BSLD baseline sum longest diameter, *CR* complete response, *PR* partial response, *SD* stable disease *PD* progressive disease, *NE* not evaluable, *RR* response rate, *DCR* disease control rate

Additional attention was needed when RECIST version 1.1 was adopted to measure BSLD [17]. In RECIST version 1.1, the number of target lesions required to assess tumor volume was reduced from a maximum of 10 to a maximum of 5 lesions. The number of target lesions per organ was also reduced from a maximum of five lesions to a maximum of two lesions. Moreover, the method for measuring pathological lymph nodes was changed. These changes to the RECIST criteria may have affected the impact of BSLD as a prognostic factor, and therefore, further assessment is needed in future studies using RECIST version 1.1.

In conclusion, age and BSLD were identified as two independent prognostic factors for advanced BTC receiving chemotherapy. Tumor volume seems to be more important than primary biliary site for assessing the prognosis of advanced BTC.

Conflict of interest statement None.

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