Chemotherapy: Open Access
ISSN: 2167-7700

Osamu et al., Chemo Open Access 2015, 4:4
DOI: 10.4172/2167-7700.1000174

Research Article Open Access

Oral Adjuvant Chemotherapy with S-1 or Uracil-tegafur versus Surgery Alone in Patients with Biliary Tract Cancer

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Received date: 09 September, 2015, **Accepted date:** 28 November, 2015, **Published date:** 06 December, 2015

Abstract

Objective: We compared the influence of postoperative adjuvant chemotherapy with oral anticancer drugs (S-1 or uracil-tegafur [UFT]) and the influence of surgery alone on overall survival (OS) and disease-free survival (DFS) in patients with biliary tract cancer.

Methods: This retrospective study included 108 patients with gallbladder cancer (n=22) or bile duct cancer (n=86), who underwent curative resection. The patients were divided into surgery alone (n=58), UFT (n=39; 400 mg/m2/day), and S-1 groups (n=11; 80 mg/m2, days 1–28, twice daily), and outcomes and adverse effects were compared.

Results: The 2-year DFS rate was significantly higher in the S-1 group than in the surgery alone group for all patients (72.7% vs. 32.8%, p=0.046). For the patients with gallbladder cancer, the 2-year OS and DFS rates were significantly higher in the UFT group than in the surgery alone group (36.4% vs.0%, p=0.033 and 27.4% vs. 0% p=0.032, respectively; log-rank test). For patients with lymph node metastasis, the 2-year OS and DFS rates were significantly higher in the S-1 group than in the surgery alone group (71.4% vs. 18.2%, p=0.039 and 71.4% vs. 18.2%, p=0.026, respectively)

Conclusion: Postoperative adjuvant chemotherapy might improve both the OS and DFS rates, particularly in patients with gallbladder cancer and those with biliary tract cancer and lymph node metastasis.

Keywords: Uracil-tegafur; S-1; Adjuvant chemotherapy; Biliary tract cancer

Introduction

Extensive surgical resection of biliary tract cancer is performed in several high-volume centres, even for patients with advanced tumors that were formerly considered unresectable. However, although the surgical resection rate has increased, satisfactory improvements in survival have not yet been achieved. This indicates the limitations of surgical resection and emphasizes the need for adjuvant treatment. Previous studies comparing surgical resection combined with postoperative adjuvant chemotherapy and surgical resection alone have demonstrated that adjuvant treatment may be effective for prolonging survival [1]. Takada et al. reported that intraoperative - and post-operative intravenous chemotherapy could effectively prevent recurrence after resection and prolong survival in patients with gallbladder cancer, with a 5-year survival rate of 26% [1]. However, to the best of our knowledge, all previous reports on postoperative adjuvant chemotherapy for biliary tract cancer were pilot studies with a small numbers of patients and a variety of chemotherapy regimens [1-5].

In the present study, we compared the influence of postoperative adjuvant chemotherapy with oral anticancer drugs, (S-1 or uracil-tegafur ([UFT]), and the influence of surgery alone on overall survival (OS) and disease-free survival (DFS) in biliary tract cancer patients.

Methodology

Patient Population

This retrospective study included patients with biliary tract cancer who were admitted to our institution between January 1995 and April 2012. The eligibility criteria were as follows: postoperative diagnosis of carcinoma of the gallbladder or bile duct, with histological confirmation 2) pathological stage II–IV bile duct cancer or pathological stage III-IV gallbladder cancer 3) age<80 years 4) no previous surgery, radiotherapy, or chemotherapy for biliary tract cancer 5) no serious concomitant disease;6) no concurrent or non-concurrent multicentric tumor or double tumor 7) curative resection (CurA or CurB, defined according to the General Rules for Surgical and Pathological Studies of the Cancer of the Biliary Tract [6]) and 8) a leukocyte count>4000/mm^3, a platelet count>100,000/mm^3, liver enzymes levels (aspartate aminotransferase and alanine

aminotransferase)<100 U, and negative urinary protein at the start of treatment.

The surgical and histopathologic findings and the findings regarding curability were recorded in accordance with the General Rules for Surgical and Pathological Studies of the Cancer of the Biliary Tract [6]. In the present study, the term "curative resection" indicated complete removal of the tumor with a histologically clear surgical margin and removal of all metastatic primary and secondary lymph nodes.

Treatment Schedule

The patients who met the eligibility criteria were allocated to the postoperative adjuvant chemotherapy with UFT group (UFT group), postoperative adjuvant chemotherapy with S-1 group (S-1 group), or surgery alone group, according to the treatment. Adjuvant chemotherapy was used in patients with pathological stage II-IV bile duct cancer, or pathological stage III-IV gallbladder cancer, who provided informed consent. The UFT group received oral UFT (300 mg/body/day) on days 1-5 every week for approximately 1 year after surgery. The S-1 group received oral S-1 (80 mg/m^2) twice daily on days 1-28, for 4 weeks, followed by a 2-week rest, and the treatment was repeated every 6 weeks. Both S-1 and UFT were scheduled to be administered for over 6 months after surgery. The patients received UFT between 1995 and 2006 and S-1 between 2007 and 2011. The surgery alone group did not receive any drugs after surgery, including placebos. In the event of serious adverse drug reactions or abnormal laboratory findings, such as a leukocyte count<3000/mm^3, a platelet count<50,000/mm^3, aspartate aminotransferase and alanine aminotransferase levels>200 U, positive urinary protein, and the development of surgical complications, treatment was suspended or discontinued. With the exception of drugs for symptomatic treatment, the use of any concomitant therapy that might interfere with the evaluation of study results, such as anticancer drugs, immunotherapy, and radiotherapy, was prohibited.

Treatment Evaluation

The primary endpoint was OS. Survival time was calculated from the day of surgery, with deaths from all causes treated as events. The secondary endpoints were DFS and adverse effects. As a rule, patients were monitored monthly for disease recurrence, and this overall assessment included physical examination, radiography, ultrasonography, computed tomography, and laboratory examinations. Adverse drug reactions were assessed according to Common Terminology Criteria for Adverse Events v 4.0 [7]

Statistical Analysis

The durations of OS and DFS were calculated using the Kaplan–Meier method, and the log-rank test was used for comparisons. Patient characteristics, surgical methods, disease recurrence, and median follow-up durations were compared between the groups using the chi-square test, Fisher's exact test, Student's t-test, or Mann-Whitney U test. In the event that significant differences in OS and DFS were noted between the groups, the Cox proportional hazards model (multivariate analysis) was used to define whether postoperative chemotherapy was a true prognostic factor. All statistical analyses were performed using IBM SPSS Statistics software (version 22; IBM Corp, Armonk NY), and the level of significance was set at $p<0.05$.

Results

Clinicopathological Characteristics

A total of 108 patients (69 men and 39 women) with biliary tract cancer, who underwent resection with curative intent were analysed retrospectively. Of the 108 86 had bile duct cancer (50 in the surgery alone group, 28 in the UFT group, and 8 in the S-1 group) and 22 had gallbladder cancer (8 in the surgery alone group, 11 in the UFT group, and 3 in the S-1 group). The follow-up periods of the patients ranged from 0.24-134 months (median, 27.7 months years) in the surgery alone group, 5.28-125 months (median, 36.6 months) in the UFT group, and 4.44-57.9 months (median,33.96 months) in the S-1 group. Table 1 and 2 present the background characteristics of the evaluable patients for each disease. No significant differences were noted in patient factors and tumor factors, including T factor and disease stage, among the 3 groups. However, the tumor locations and operation types were significantly different among the 3 groups. Tumors tended to be near the liver in the surgery alone group and near the papilla of Vater in the S-1 group. Thus, hepatectomy was performed more often in the surgery alone group, and pancreatoduodenectomy was performed more often in the S-1 group.

		Surgery alone (n=50)	UFT group (n=28)	S-1 group (n=8)	p
Age (median)		67.4	62.7	64.5	0.551
Gender	Men Women	33 17	20 8	7 1	0.457
T	1	1	1	0	0.612
	2	18	7	2	
	3	17	7	4	
	4	14	13	2	
N	N0	32	11	3	0.07
	≥N1	18	17	5	
Stage	II	16	5	1	0.201

	III	15	9	4	
	IV	19	14	3	
Location	Porta hepatis	18	17	0	P<0.05
	Upper bile duct	4	2	0	
	Middle bile duct	4	3	0	
	Inferior bile duct	16	2	4	
	Vater papilla	8	4	4	
Operation	Hepatectomy + bile duct resection	17	17	0	P<0.01
	Bile duct resection	7	2	0	
	Panceratoduodenectomy	26	7	8	
	Hepatopancreatico-duodenectomy	0	2	0	
Curability	A B	32 18	16 12	4 4	0.685
Pathology	Well	18	6	0	0.190
	Moderate	25	19	7	
	Poor	7	3	0	
	Others	0	0	0	

Table 1: Clinicopathological characteristics of the patients with bile duct cancer in the surgery alone, uracil-tegafur (UFT), and S-1 groups; Curability A: There is no evidence of metastases in the liver, peritoneum, or elsewhere, and there is no evidence of residual tumors after surgery. Complete dissection of the lymph nodes includes removal of lymph node metastases and cancer-free- margins of more than 5 mm in width, defined according to the general rules for surgical and pathological studies of the cancer of the biliary tract; Curability B: There is no evidence of metastases in the liver, peritoneum, or elsewhere, and there is no evidence of residual tumors after surgery. Complete dissection of the lymph nodes includes removal of lymph node metastases and cancer-free- margins of 5 mm or less in width, defined according to the general rules for surgical and pathological studies of the cancer of the biliary tract; pathology: well: well differentiated carcinoma; moderate: moderately differentiated carcinoma; poor: poorly differentiated carcinoma; others: one case was of papillary adenocarcinoma, and the other was of solid adenocarcinoma.

		Surgery alone (n=8)	**UFT group (n=11)**	**S-1 group (n=3)**	**p**
Age (median)		73	67.3	74.7	0.173
Gender	Men Women	5 3	3 8	1 2	0.292
T	2	0	2	1	0.630
	3	3	4	1	
	4	5	5	1	
N	N0	4	3	1	0.592
	≥N1	4	8	2	
Stage	III	2	6	2	0.587
	IV	4	5	1	
Operation	Right hepatectomy	3	4	0	0.365
	Extended cholecystectomy	5	5	3	

	HepatoPanceratioduodenectomy	0	2	0	
Curability	A B	4 4	7 4	2 1	0.803
Pathology	Well	4	2	2	0.278
	Moderate	3	7	0	
	Poor	1	1	0	
	Others	0	11	12	

Table 2: One case was of papillary adenocarcinoma; one case was of solid adenocarcinoma; Curability A: There is no evidence of metastases in the liver, peritoneum, or elsewhere, and there is no evidence of residual tumors after surgery. Complete dissection of the lymph nodes includes removal of lymph node metastases and cancer-free- margins of more than 5 mm in width, defined according to the general rules for surgical and pathological studies of the cancer of the biliary tract; Curability B: There is no evidence of metastasies in the liver, peritoneum, or elsewhere, and there is no evidence of residual tumors after surgery. Complete dissection of the lymph nodes includes removal of lymph node metastases and cancer-free margins of 5 mm or less in width, defined according to the general rules for surgical and pathological studies of the cancer of the biliary tract; pathology: well: well-differentiated carcinoma; moderate: moderately differentiated carcinoma; poor: poorly differentiated carcinoma; others: one case was of papillary adenocarcinoma, and the other was of solid adenocarcinoma.

Surgical Procedures

Among the 86 patients with bile duct cancer,34 (39.5%) underwent hepatectomy with bile duct resection, including 33 with caudate lobe resection, 41 (47.7%) underwent pancreaticoduodenectomy, 9 (10.5%) underwent extrahepatic bile duct resection, and 2 (2.3%) underwent hepatopancreaticoduodenectomy. Among the 22 patients with gallbladder cancer, 7 (31.8%) underwent right hepatectomy, 13 (59.1%) underwent extended cholecystectomyies, and 2 (9.1%) underwent hepatopancreaticoduodenectomy There was a significant difference in the distribution of surgical procedures; however, there was no difference in the distribution of curability. The morbidity rate was 46.6%, and the mortality rate was 1.9%.

Treatment Compliance

UFT was administered for 3-108 months (mean, 18 months). Of the 39 patients administered UFT, 1 (2.6%) required a dose reduction. The continuation rate of UFT treatment over 6 months was 61.5%, with no major differences noted between disease categories. S-1 was administered for 2-19 months (mean, 10 months). Of the 11 patients administered S-1, 6 (54.5%) required a dose reduction. The continuation rate of S-1 treatment over 6 months was 72.7%.

Adverse Effects

A total of 39 patients in the UFT group and 11 patients in the S-1 group were evaluated with regard to adverse effects. In the UFT group, grade 3 or 4 toxicities (defined according to Common Terminology Criteria for Adverse Events) included diarrhea (2.6%) and leukopenia (2.6%). In the S-1 group, grade 3 or 4 toxicities included diarrhea (18.1%) and skin rash (18.1%). There were no treatment-related deaths in either chemotherapy group.

Survival

The OS and DFS rates of patients were compared among the S-1, UFT, and surgery alone groups (Figures 1-3). The 2-year DFS rate was significantly higher in the S-1 group than in the surgery alone group (72.7% vs. 32.8%, p=0.046; log-rank test) (Figure1B).

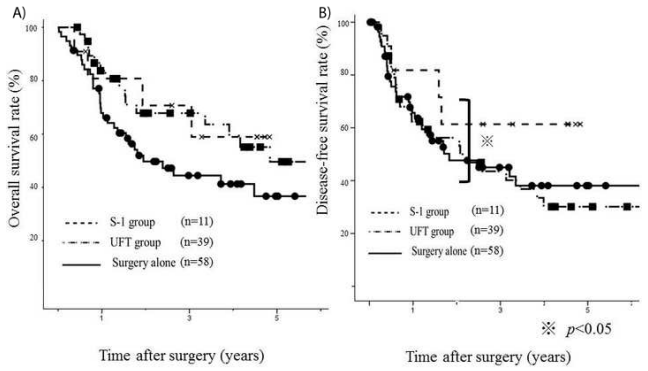

Figure 1: Comparison of postoperative overall survival (OS) and disease-free survival (DFS) rates among the S-1 group (n = 11), uracil-tegafur (UFT) group (n = 39), and surgery alone group (n = 58); The OS (A) and DFS (B) rates are compared among the S-1, UFT, and surgery alone groups. There are no significant differences in the OS rates among the 3 groups. However, the 2-year DFS rate is significantly higher in the S-1 group than in the surgery alone group (67.3% vs. 33.3%, p = 0.04; log-rank test).

For patients with bile duct cancer, there was no significant difference in survival among the 3 groups (Figure 2). For patients with gallbladder cancer, the 2-year OS and 2-year DFS rates were significantly higher in the UFT group than in the surgery alone group (36.4% vs. 0% p=0.033 and 27.4% vs. 0%, p=0.032, respectively; log-rank test. The 2-year OS and 2-year DFS rates were the highest in the S-1 group; however, the rates in the S-1 group were not statistically different from those in the UFT and surgery alone groups, probably because of the small number of patients in the S-1 group.

There were 54 patients with lymph node metastasis. The OS and DFS rates of these 54 patients were compared among the S-1, UFT and surgery alone groups (Figures 3-5). The 2-year OS and 2-year DFS rates were significantly higher in the S-1 group than in the surgery alone group (71.4% vs. 18.2%, p=0.039 and 71.4% vs. 18.2%, p=0.026,

respectively; log-rank test) (Figures 4A and 4B). For patients with bile duct cancer, the 2-year DFS rate was significantly higher in the S-1 group than in the surgery alone group (80.0% vs. 22.2%) (p=0.044; log-rank test) (Figure5B). For patients with gallbladder cancer, the 2-year OS and 2-year DFS rates were significantly higher in the UFT group than in the surgery alone group (17.1% vs. 0%, p=0.039 and 25.0% vs. 0%, p<0.001; log-rank test).

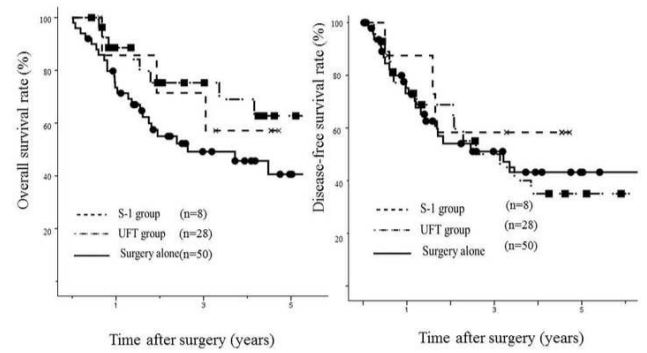

Figure 2: Comparison of postoperative overall survival (OS) and disease-free survival (DFS) rates among the S-1 group (n=8), uracil-tegafur (UFT) group (n=28), and surgery alone group (n=50) for patients with bile duct cancer; The OS (A) and DFS (B) rates are compared among the S-1, UFT, and surgery alone groups. There are no significant differences in the OS rates among the 3 groups. However, the 2-year DFS rate is significantly higher in the S-1 group than in the surgery alone group (67.3% vs. 33.3%, p=0.04; log-rank test).

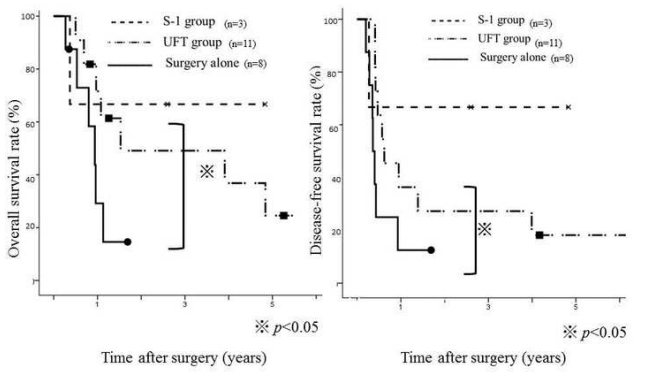

Figure 3: Comparison of postoperative overall survival (OS) and disease-free survival (DFS) rates among the S-1 group (n=3), (UFT) group (n=11), and surgery alone group (n=8) for patients with gallbladder cancer The OS (A) and DFS (B) rates are compared among the S-1, UFT, and surgery alone groups. The 2-year OS and 2-year DFS rates are significantly higher in the UFT group than in the surgery alone group (36.4% vs. 0% p=0.033 and 27.4% vs. 0% p=0.032, respectively; log-rank test). The 2-year OS and 2-year DFS rates are the highest in the S-1 group.

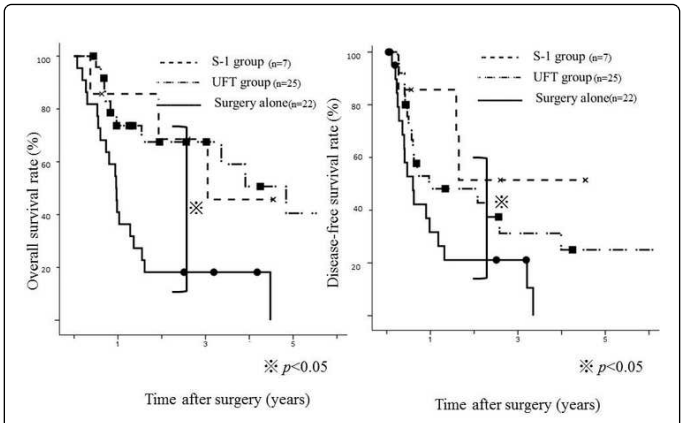

Figure 4: Comparison of postoperative overall survival (OS) and disease-free survival (DFS) rates among the S-1 group (n=7), uracil-tegafur (UFT) group (n=25), and surgery alone group (n=22) for patients with lymph node metastasis; The OS (A) and DFS (B) rates are compared among the S-1, UFT, and surgery alone groups. There are no significant differences in the OS rates among the 3 groups. However, the 2-year OS and 2-year DFS rates are significantly higher in the S-1 group (71.4%) than in the surgery alone group (71.4% vs. 18.2%, p=0.039 and 71.4% vs. 18.2%, p=0.026; log-rank test.

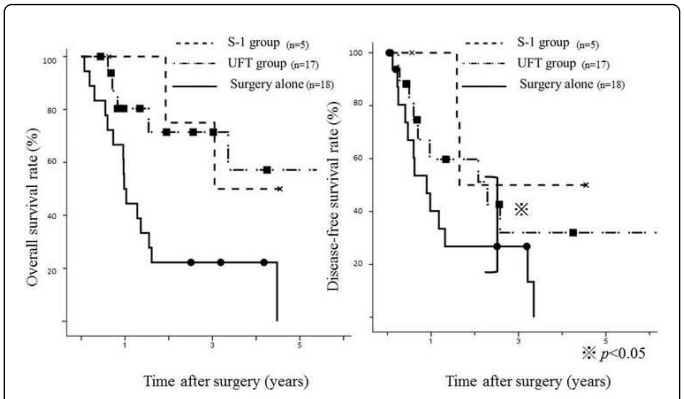

Figure 5: Comparison of postoperative overall survival (OS) and disease-free survival (DFS) rates among the S-1 group (n=5), uracil-tegafur (UFT) group (n=17), and surgery alone group (n=18) for patients with bile duct cancer and lymph node metastasis; The OS (A) and DFS (B) rates are compared among the S-1, UFT, and surgery alone groups. There are no significant differences in the OS rates among the 3 groups. However, the 2-year DFS rate is significantly higher in the S-1 group than in the control group (80.0% vs. 22.2%, p=0.044; log-rank test).

Multivariate Analysis

We performed a multivariate analysis to identify the prognostic factors among biliary cancer patients with regard to the durations of OS and DFS. The factors analyzed included postoperative chemotherapy, histologic depth of tumor invasion, histologic lymph node metastasis, and final disease stage (Tables 3 to 5). In all patients

and in patients with bile duct cancer, histologic lymph node metastasis was identified as a significant factor influencing OS and DFS, and postoperative chemotherapy was identified as a significant factor influencing DFS. In patients with gallbladder cancer postoperative chemotherapy was identified as a significant factor influencing both OS and DFS. Factor (all patients)

	OS		DFS	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
Factor	p-values	p-values	p-values	p-values
Age, Years	0.051	0.060	0.087	0.202
Sex, male/female	0.491	0.652	0.529	0.633
T	0.101		0.048	0.013
N	0.006	0.009	0.002	0.000
Stage	0.024	0.198	0.004	0.709
Location	0.523		0.802	
Operation	0.615		0.209	
Pathology Well/moderate/poor/others	0.271		0.270	
Adjuvant yes/no	0.129		0.068	
Adjuvant no/UFT/S-1	0.073		0.031	0.000

Table 3: Parameters influencing the overall survival and disease-free survival rates of all patients in univariate and multivariate analyses OS, overall survival; DFS, disease-free survival; UFT, uracil-tegafur.

	OS		DFS	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
Factor	p-values	p-values	p-values	p-values
Age, Years	0.082	0.077	0.200	0.512
Sex, male/female	0.430	0.788	0.371	0.611
T	0.432		0.333	
N	0.006	0.010	0.012	0.019
Stage	0.115		0.082	
Location	0.242		0.070	
Operation	0.323		0.112	
Pathology Well/moderate/poor/others	0.565		0.576	
Adjuvant yes/no	0.243		0.099	
Adjuvant no/UFT/S-1	0.167		0.065	0.000

Table 4: Parameters influencing the overall survival and disease-free survival rates of patients with bile duct cancer in univariate and multivariate analyses OS, overall survival; DFS, disease-free survival; UFT, uracil-tegafur; Factors (Bile duct carcinoma patients).

	OS		DFS	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
Factor	p-values	p-values	p-values	p-values
Age, Years	0.837	0.850	0.690	0.928
Sex, male/female	0.223	0.475	0.276	0.518
T	0.183		0.081	
N	0.680		0.257	
Stage	0.304		0.021	0.050
Operation	0.863		0.477	
Pathology Well/moderate/poor/others	0.347		0.274	
Adjuvant yes/no	0.017	0.027	0.016	0.027
Adjuvant no/UFT/S-1	0.023	0.507	0.018	0.409

Table 5: Parameters influencing the overall survival and disease-free survival rates of patients with gallbladder cancer in univariate and multivariate analyses OS, overall survival; DFS, disease-free survival; UFT, uracil-tegafur; Factors (gall bladder carcinoma patients).

Discussion

In the present study, we demonstrated the survival benefit of oral chemotherapy administered as postoperative adjuvant treatment in patients with biliary tract cancer. Lymph node metastasis was a significant prognostic factor for poor survival, and the number of patients with lymph node metastasis was higher in the 2 postoperative adjuvant chemotherapy groups than in the surgery alone group. Nevertheless, the results demonstrated that the 2-year OS and 2-year DFS rates were significantly higher with surgery plus S-1 than with surgery alone among patients with lymph node metastasis, additionally, the 2-year DFS rate was significantly higher with surgery plus S-1 than with surgery alone among patients with biliary tract cancer. Moreover, both the 2-year OS and 2-year DFS rates were significantly higher with surgery plus UFT than with surgery alone among patients with gallbladder cancer. Furthermore, the results of the multivariate analysis demonstrated that postoperative adjuvant chemotherapy significantly reduced the risk of death, especially in patients with gallbladder cancer. There have been no large-scale studies of adjuvant chemotherapy in patients with biliary tract cancer; therefore, we believe that these findings of this study are extremely important and indicate the potential usefulness of postoperative oral adjuvant chemotherapy, especially with S-1, in the treatment of patients with biliary tract cancer.

Previous studies have reported the use of 5-fluorouracil (5-FU), mitomycin C, and gemcitabine for the treatment of patients with biliary tract cancer [8-13]; however, we assessed orally administered adjuvant chemotherapy with UFT or S-1 because of the ease of administration. Administration of oral chemotherapy drugs can reduce the number of hospital visits, and fewer adverse effects are generally associated with oral chemotherapy than with intravenous chemotherapy. Adverse events of grade 3 or 4 occurred in less than 5% of the patients in the S-1 group [14]. The use of oral chemotherapy drugs simplified the initiation and discontinuation of postoperative adjuvant chemotherapy because the patients could continue taking these drugs for over 6 months.

No adjuvant chemotherapy regimen has been proven to be effective for the treatment of biliary tract cancer. A potential adjuvant chemotherapy regimen for patients with resected biliary tract cancer is cisplatin plus gemcitabine, because this regimen has been proven effective in patients with advanced biliary tract cancer (ABC01 study) [15]. However, the rate of grade 3 or 4 adverse effects with this regimen is 70.7%. Moreover, administration of this regimen to patients after resection may be difficult because of the morbidities associated with biliary tract cancer surgery.

Recent studies have demonstrated the efficacy of orally administered anticancer drugs for the treatment of other cancer types [14, 16]. UFT (tegafur combined with uracil in a molar ratio of 1:4) is a second-generation oral 5-FU prodrug that is converted to 5-FU in tissues [17]. S-1, an oral anticancer drug containing tegafur as the 5-FU prodrug, was shown to yield substantially higher 5-FU concentrations in tumor specimens than in plasma or normal tissue specimens [18]. S-1 is theoretically more effective than UFT, and this is supported by the results of this study. However, UFT has been reported to be an effective postoperative adjuvant treatment for several cancers [16, 19, 20], and this study demonstrated higher survival rates in the UFT group than in the surgery alone group among patients with gallbladder cancer. In addition, the toxicity of UFT chemotherapy was milder than that of S-1 chemotherapy. These results demonstrate the potential of postoperative adjuvant chemotherapy with UFT for patients with resected biliary tract cancer, especially those with poor general conditions. Capecitabine is another possible candidate drug for adjuvant therapy. Previous reports have shown positive results after capecitabine treatment for advanced cancers [21-23]; however, there have been few reports on the use of capecitabine as adjuvant therapy.

Adjuvant chemotherapy is generally continued for 6 months; however, our patients received adjuvant chemotherapy for over 6 months, which may have contributed to the prevention of disease

recurrence or progression. The longest treatment duration in this study was 9 years (UFT chemotherapy). The oral chemotherapy investigated in this study had few side effects, and many patients could continue treatment for a long time. These drugs are not effective in the early stage, but have a slow effect, suggesting that long-term adjuvant chemotherapy may be effective in prolonging survival. Therefore, we have recently initiated a clinical trial investigating 1 year of S-1 adjuvant treatment in our hospital.

Conclusion

In conclusion, postoperative oral adjuvant chemotherapy, especially with S-1, might improve the short-term DFS rate in patients with of biliary tract cancer. In patients with gallbladder cancer and those with biliary tract cancer and lymph node metastasis, oral anticancer drugs might improve both the OS and DFS rates. However, further studies, including large-scale, randomized controlled studies focusing on postoperative adjuvant chemotherapy with UFT and/or S-1, are needed to confirm our findings.

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