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A Single-center Analysis of the Survival Benefits of Adjuvant Gemcitabine Chemotherapy for Biliary Tract Cancer

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Abstract

Background Surgical resection is the only curative treatment of biliary tract cancer. However, the prognosis of biliary tract cancer is unsatisfactory. The aim of this study was to evaluate the benefits of adjuvant gemcitabine chemotherapy for biliary tract cancer.

Methods We performed a historical cohort study that involved 198 patients who underwent R0 surgical resections. Patients who underwent major hepatectomies were administered biweekly intravenous gemcitabine at a dose of 800 mg/m². Otherwise, patients were administered intravenous gemcitabine at a dose of 1,000 mg/m² in 3 weekly infusions, which were followed by a 1-week pause. The primary outcome was overall survival. The hazard ratio of adjuvant chemotherapy was estimated by propensity score-stratified Cox regression that was adjusted for confounders.

Results Forty patients received adjuvant chemotherapy. The hazard ratio of adjuvant chemotherapy was 0.47 (95% confidence interval, 0.28-0.95; P = 0.03). The subgroup analysis showed that the survival benefits were possibly modified by lymph node positivity (hazard ratio, 0.19; 95% confidence interval, 0.07-0.58; interaction, P = 0.22), Stage III (hazard ratio, 0.11; 95% confidence interval, 0.02-0.50; interaction, P < 0.01), intrahepatic cholangiocarcinoma (hazard ratio, 0.09; 95% confidence interval, 0.01-0.67; interaction, P = 0.05), and a poorly differentiated tumor (hazard ratio, 0.16; 95% confidence interval, 0.03-0.85; interaction, P = 0.13).

Conclusions Adjuvant gemcitabine chemotherapy for biliary tract cancer may be effective,

particularly for patients with Stage III and intrahepatic cholangiocarcinoma.

Mini-abstract

Adjuvant gemcitabine chemotherapy for biliary tract cancer may be effective, particularly for patients with Stage III and intrahepatic cholangiocarcinoma. Biweekly 800 mg/m² gemcitabine to patients with major hepatectomies was tolerable.

Key words: gemcitabine, adjuvant chemotherapy, biliary tract cancer

2017 Words, 1 Table, 2 Figures

Introduction

Biliary tract cancer (BTC) is a common cancer, and approximately 15,000 people have died of BTC in Japan in a year.^{1,2} BTC was recently thought to be composed of intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), gallbladder cancer, and ampulla of Vater cancer. Surgical resection is the only curative treatment of BTC. However, 60% of the patients with hilar cholangiocarcinomas developed distant metastasis after R0 resection.³ The 5-year survival rate for resectable patients is around 30%.⁴⁻⁶ The prognosis of BTC is unsatisfactory, and adjuvant chemotherapy is expected to improve the long-term survival of these patients.

Several chemotherapeutic regimens have been tested for unresectable BTC. Chemotherapeutic agents, such as gemcitabine (GEM), 5-fluorouracil (5-FU), oxaliplatin, and cisplatin (CDDP) have survival benefits for patients with advanced BTC.⁷⁻¹⁰ Among them, GEM is the most promising agent for BTC. We previously conducted a phase-I study in order to determine the maximum-tolerated dose and the recommended dose of GEM for resected BTC (UMIN000004682). The results of the study indicated that patients who underwent surgical resections for BTC could not tolerate the standard dose and schedule of GEM for unresectable BTC. In particular, patients who underwent major hepatectomies hardly received an administration on day 8 because of neutropenia.

Thus, we decided to administer biweekly intravenous GEM at a dose of 800 mg/m² to

patients who underwent major hepatectomies in clinical settings. The aim of this study was to evaluate the survival benefits of adjuvant GEM chemotherapy for BTC.

Patients and methods

Study design and eligibility criteria

The Kyoto University Graduate School and Faculty of Medicine Ethics Committee approved this study (E-1229) in accordance with the ethics guidelines for epidemiologic studies in Japan. We performed a historical cohort study in order to assess the survival benefits of adjuvant GEM chemotherapy for BTC. Patients at Kyoto University Hospital who were diagnosed with BTC and who underwent surgical resections between June 2001 and August 2010 were selected for this study. Among the 273 consecutive patients who underwent surgical resections for BTC, 211 patients had R0 surgical resections. The following 10 patients were excluded because they were treated with the following other chemotherapeutic agents in an adjuvant setting: 3 patients, Tegafur-uracil; 5 patients, leucovorin/5-FU; and 2 patients, 5-FU/CDDP. Three patients who died in hospital after the surgical resections were also excluded. Thus, 198 patients were included in this study. We basically performed adjuvant GEM chemotherapy except for patients with Stage-I- BCT, because even the prognosis for the patients with stage-II-BCT was unsatisfactory.

Adjuvant Chemotherapeutic Regimen

The adjuvant GEM chemotherapy was started within 12 weeks after the surgical resection. Before the administration of GEM, we confirmed that all drainage tubes were removed and that no abscesses were observed in the abdominal cavity. Patients who underwent major hepatectomies were treated with biweekly intravenous GEM at a dose of 800 mg/m². Patients who did not undergo hepatectomies were treated with intravenous GEM at a dose of 1,000 mg/m² in 3 weekly infusions, which were followed by a 1-week pause. The dose and schedule of chemotherapy was adjusted by individual physicians in response to the adverse events that were observed in the previous cycle. Toxicity was assessed based on the National Cancer Institute Common Toxicity Criteria scale, version 4.

Statistical analysis

The primary outcome measure was overall survival (OS), which was defined as the time from the date of surgery to the date of death from any cause. All patients were followed until August 2011. Patients who failed to undergo follow-up procedures were censored on the last day when they were confirmed to be alive.

In the primary analysis, bias due to confounding factors was adjusted for propensity score stratification, which stratifies patients according to their propensity scores, the probability that a

patient would undergo adjuvant GEM chemotherapy. This method attempts to mimic randomization by creating strata of patients that received the adjuvant chemotherapy that is comparable on all observed confounders to strata of patients that did not receive the adjuvant chemotherapy. We estimated the propensity score for each patient by a multivariable logistic regression that included age, gender, Child–Pugh classification, primary lesion, T factor, N factor, Stage, tumor differentiation, operative procedures, and postoperative complications as confounders. These variables, other than the Child–Pugh classification, were examined after the surgical resection. The T factor, N factor, and Stage were estimated based on the International Union Against Cancer classification, 7th edition. The C statistics of the multivariate logistic regression was 0.760. The hazard ratios (HR) for the OS of the adjuvant chemotherapy group compared to those for the OS of the nonadjuvant chemotherapy group were estimated by Cox proportional hazard models that were stratified to the quintiles of the propensity scores. We also performed a subgroup analysis that was stratified for the clinical variables by using a test of the interaction terms in the Cox proportional hazard models, unless a stratum included less than 5 patients in either group. We used chi-square tests (without Yates' correction) for the categorical comparisons of patient characteristics. The probability of survival was calculated by the Kaplan–Meier method. A P-value less than 0.05 indicated statistical significance. All tests were two-tailed. JMP for Windows software ver. 8.0 and SAS ver.9.2 were used for all statistical analyses.

Results

Patients

Forty patients received adjuvant GEM chemotherapy (the adjuvant chemotherapy group) and 158 patients did not receive any adjuvant chemotherapy (the nonadjuvant chemotherapy group). There were significant differences in age, T factor, and Stage between the groups. Patients in the adjuvant chemotherapy group were younger and had higher Stage of BTC. No significant differences were present in the primary lesion, operative procedure, or postoperative complications. The patient characteristics are shown in Table 1.

Recurrence

The probability of recurrence was 41.8% (66/158) in the nonadjuvant chemotherapy group and 57.5% (23/40) in the adjuvant chemotherapy group. Twenty-eight patients in the nonadjuvant chemotherapy group were administered GEM after tumor recurrence. The probabilities of the 1-, 2- and 3-year survival of the patients with recurrent BTC who were administered GEM chemotherapy in the nonadjuvant chemotherapy group were 88.9%, 69.8%, and 46.8%, respectively. Patients in the adjuvant chemotherapy tended to have a longer life expectancy without recurrence, although this was not significant ($P = 0.16$).

Survival

During the follow-up period, which had a median length of 3.2 years, 13 patients in the adjuvant chemotherapy group and 66 patients in the nonadjuvant chemotherapy group died. The probabilities of 1-, 2-, and 3-year survival in the adjuvant chemotherapy group were 97.5%, 79.6%, and 68.0%, while those in the nonadjuvant chemotherapy group were 87.1%, 76.9%, and 68.7%, respectively (Figure 1). These survival probabilities were not comparable as the adjuvant chemotherapy group included patients with higher stages. In the propensity score analysis that was adjusted for the differential patient characteristics, the HR was 0.47 (95% confidence interval [CI], 0.23-0.95; $P = 0.04$), suggesting a significant increase in survival by the administration of adjuvant GEM chemotherapy. The subgroup analysis according to the clinical variables is presented in Figure 2. The HRs were lower in female patients (HR, 0.17; 95%CI, 0.05-0.60; interaction, $P = 0.90$), patients with ICC (HR, 0.09; 95% CI, 0.01-0.67; interaction, $P = 0.05$), patients with lymph node positivity (HR, 0.19; 95% CI, 0.07-0.58; interaction, $P = 0.22$), patients with Stage III BTC (HR, 0.11; 95% CI, 0.02-0.50; interaction, $P < 0.01$), and patients with poorly differentiated tumors (HR, 0.16; 95% CI, 0.03-0.85; interaction, $P = 0.13$). In the patients with ICC, the probability of 2-year survival in the adjuvant chemotherapy group was 91.7%, while that in the nonadjuvant chemotherapy group was 68.2% ($P = 0.04$).

Adverse events

The grade of toxicity was not estimated for 4 patients because they were not administered

adjuvant GEM chemotherapy at Kyoto University. Toxicities of grade 3 or more were observed in 13 patients (13/36, 36.1%); neutropenia in 8 patients, thrombocytopenia in 2 patients, and other events (liver abscess, pancreatitis, vertigo) in 1 patient each. The toxicities were seen in 10 patients with hepatectomy (10/28, 35.7%) and 3 patients without hepatectomy (3/8, 37.5%), respectively. Two patients (2/36, 5.6%) had grade-4 hematological toxicities. There were no treatment-related deaths.

Discussion

A GEM-based regimen is the main chemotherapeutic agent for BTC. GEM combined with CDDP has recently been used as the first-line treatment for unresectable BTC in clinical practice due to the results of the ABC-02 trial.⁸ There have been few articles regarding adjuvant chemotherapy for BTC. Adjuvant GEM plus S-1 chemotherapy has been reported to improve outcomes after surgical resections of BTC.¹¹ A phase-III trial indicated that adjuvant mitomycin C and 5-FU chemotherapy may have survival benefits in patients with gallbladder cancer who underwent noncurative resections.¹² However, prospective trials have not been reported concerning adjuvant GEM chemotherapy. Therefore, there is no definitive regimen of adjuvant chemotherapy for BTC and the efficacy of the adjuvant chemotherapy has not been established. However, there have been several reports of adjuvant radiation and chemoradiation therapy for BTC, and some of them may be promising.¹³⁻¹⁵

In cases of adjuvant GEM chemotherapy in patients who underwent resections of pancreatic cancer, 62% of the patients were given the full number of cycles of intravenous GEM, which consisted of a dose of 1,000 mg/m² in 3 weekly infusions, which was followed by a 1-week pause, for 6 cycles.¹⁶ The average weekly dose was 700 mg/m², and the median relative-dose intensity was 86%.¹⁶ However, the phase-I study we previously conducted revealed that patients who were resected for BTC could not tolerate the standard dose. GEM is catalyzed to inactivate metabolite dFdU by cytidine deaminas in the liver. Patients with elevated bilirubin levels had significant deterioration in liver function after GEM therapy and a dose reduction is recommended.¹⁷ We have clinically administered biweekly intravenous GEM at a dose of 800 mg/m² to patients who underwent major hepatectomies. This dose reduction was well tolerated. The HR of patients with hepatectomies was 0.60 (95% CI, 0.28-1.29) in this study. Therefore, we think that this dose reduction regimen is useful for patients who underwent major hepatectomies for BTC.

A randomized phase-III trial of adjuvant chemotherapy with GEM vs. observations in patients with resectable bile duct cancer (UMIN000000820) is now being conducted in Japan. This study is examining whether adjuvant GEM chemotherapy increases the life expectancy of patients with bile duct cancer. However, ICC is not included in the eligibility criteria of this study. In patients with ICC who underwent surgical resections, it has been reported that an aggressive approach to recurrence can significantly prolong survival.¹⁸ However, there is no effective adjuvant regimen for

ICC.¹⁹ This study indicated that adjuvant GEM chemotherapy was significantly associated with an increased OS of patients with ICC. It is highly expected that adjuvant GEM chemotherapy may have survival benefits for patients with ICC. Furthermore, previous studies have revealed that lymph node metastasis is an important prognostic factor in BTC.^{4,6} Patients with lymph node metastasis are required to be treated with adjuvant therapies. The subgroup analysis showed that adjuvant GEM chemotherapy improved the OS of patients with lymph node positivity and patients with Stage III. Further assessments of the effects of adjuvant GEM chemotherapy are needed to overcome the poor prognosis of patients with lymph node metastasis.

There were some limitations to this study. This study was a retrospective study, and the effects of adjuvant chemotherapy could not be directly evaluated, although the associations could be evaluated. We included postoperative complications and age in the clinical variables because they are thought to be related to the selection of adjuvant chemotherapy. The HR of adjuvant chemotherapy was estimated by a propensity score-stratified Cox regression, which was adjusted for confounders. However, unselected variables are not adjusted that might affect the survival benefits of adjuvant GEM chemotherapy.

In conclusion, adjuvant GEM chemotherapy may be effective for patients with BCT who underwent R0 resection, particularly for patients with Stage III and ICC. Biweekly intravenous GEM at a dose of 800 mg/m² to patients who underwent major hepatectomies was tolerable. A prospective

clinical trial of adjuvant GEM chemotherapy of BTC is needed to confirm these results, and it should be designed to include lymph node and primary lesions in addition to ICC as prescribed baseline factors.

Conflict of interest

The authors declare that they have no conflict of interest.

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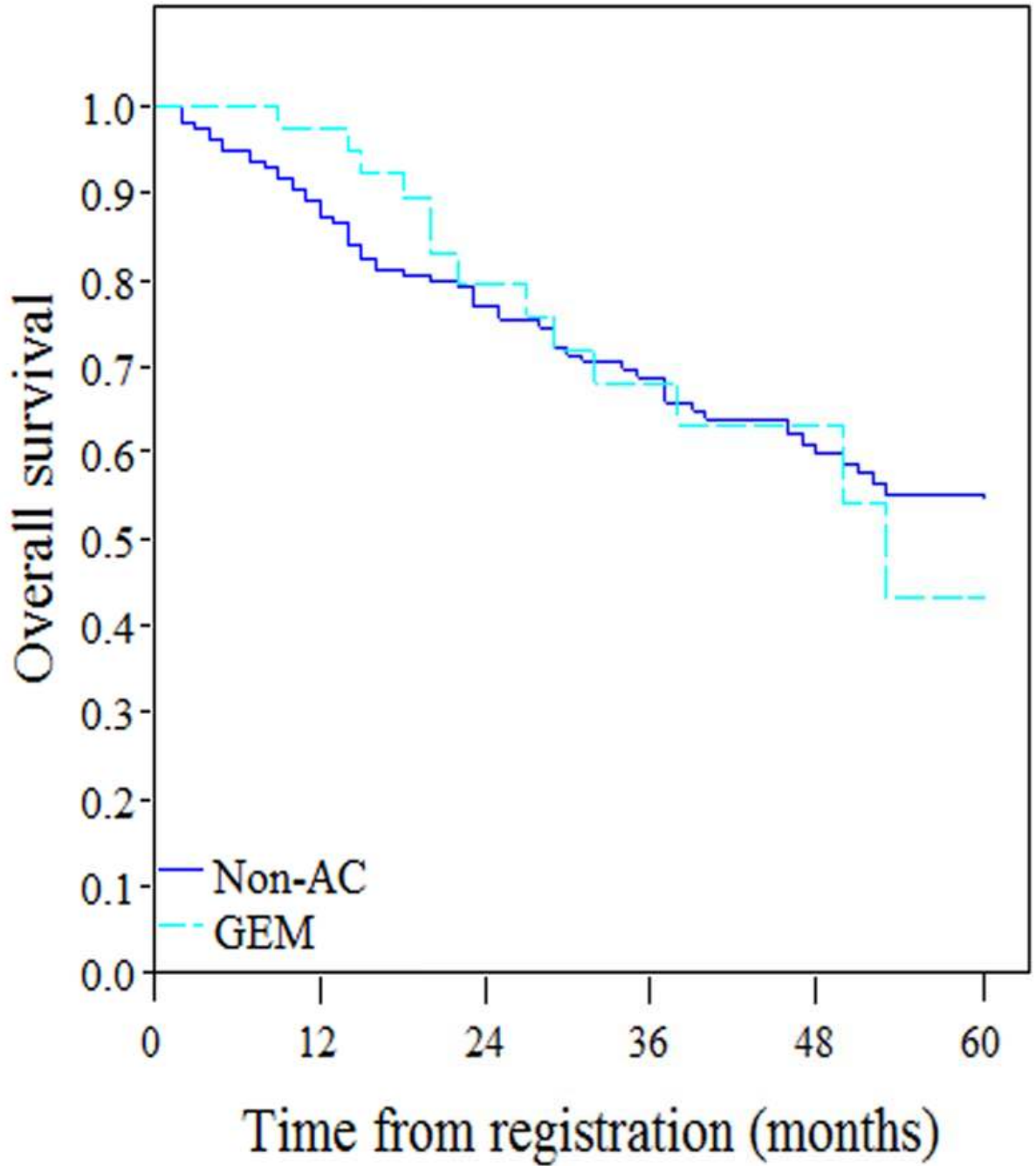
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Figure legends

Figure 1. Unadjusted overall survival of adjuvant gemcitabine chemotherapy compared to nonadjuvant chemotherapy

Figure 2. Hazard ratio of adjuvant gemcitabine chemotherapy compared to nonadjuvant chemotherapy according to the clinical variables



No. at Risk
Non-AC
GEM

158	137	103	75	55	42
40	39	24	15	8	1

Figure 1

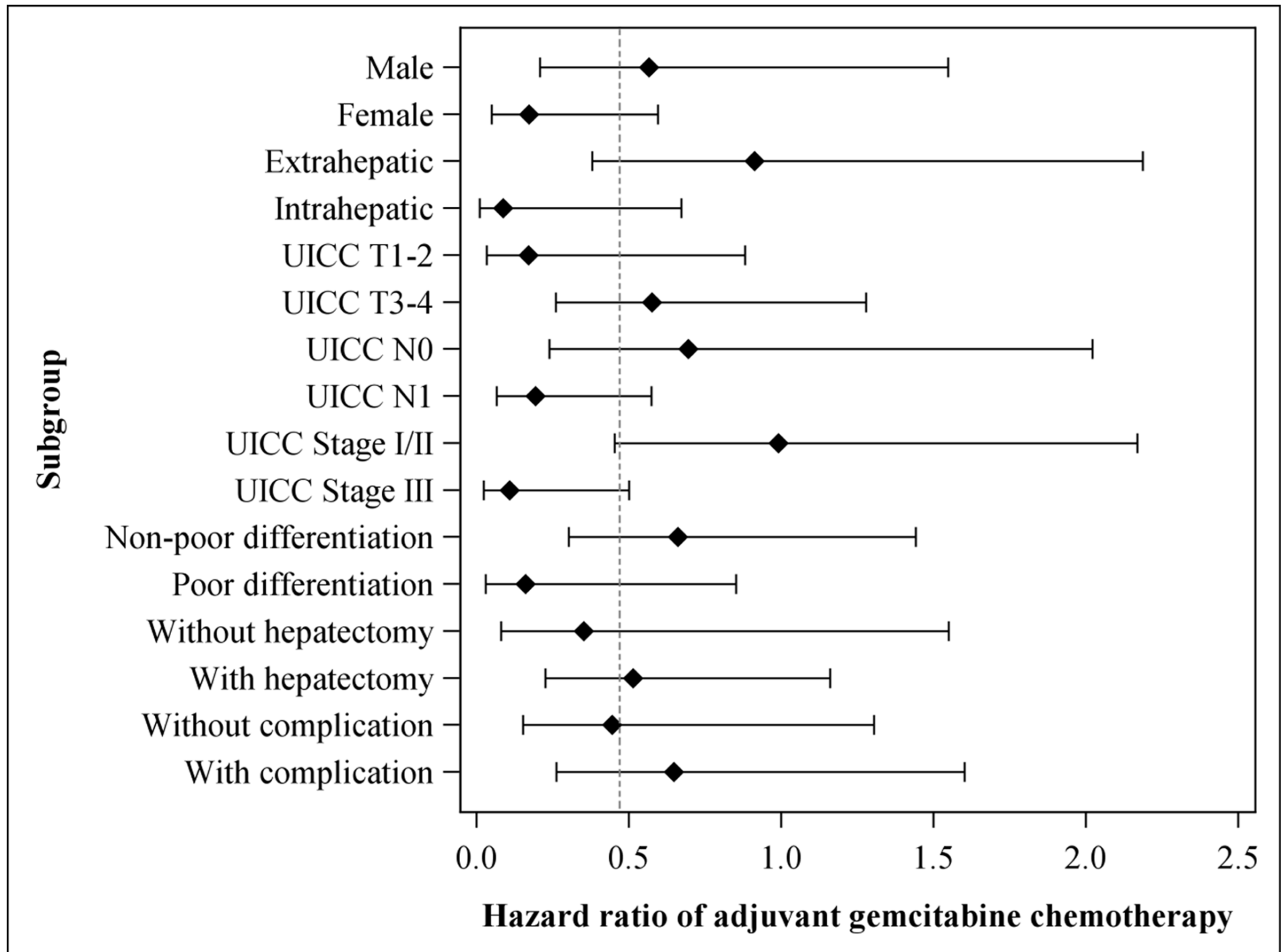


Figure 2

Table 1. Patient characteristics

		Nonadjuvant chemotherapy (n = 158)	Adjuvant GEM chemotherapy (n = 40)	P-value
Age	<75	121 (76.6)	39 (97.5)	<0.01*
	≥75	37 (23.4)	1 (2.5)	
Gender	Male	88 (55.7)	20 (50.0)	0.52
	Female	70 (44.3)	20 (50.0)	
Child–Pugh classification	A	134 (84.8)	36 (90.0)	0.39
	B	24 (15.2)	4 (10.0)	
Primary lesion	Extrahepatic	61 (38.6)	18 (45.0)	0.39
	Intrahepatic	51 (32.3)	15 (37.5)	
	Gallbladder	30 (19.0)	6 (15.0)	
	Ampulla of Vater	16 (10.1)	1 (2.5)	
UICC T	T1–2	111 (70.3)	19 (47.5)	<0.01*
	T3–4	47 (29.7)	21 (52.5)	
UICC N	N0	120 (76.0)	25 (62.5)	0.09
	N1	38 (24.0)	15 (37.5)	
UICC Stage	Stage I	76 (48.1)	9 (22.5)	<0.01*
	Stage II	60 (38.0)	19 (47.5)	
	Stage III	22 (13.9)	12 (30.0)	
Tumor differentiation	Nonpoor	138 (87.3)	31 (77.5)	0.16
	Poor	20 (12.7)	9 (22.5)	
Operative procedures	Without Hepatectomy	47 (29.8)	10 (25.0)	0.55
	With Hepatectomy	111 (70.2)	30 (75.0)	
Postoperative complications	Yes	88 (55.7)	17 (42.5)	0.14
	No	70 (44.3)	23 (57.5)	

UICC, International Union Against Cancer; GEM, gemcitabine