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ORIGINAL ARTICLE

Adjuvant gemcitabine monotherapy for resectable perihilar cholangiocarcinoma with lymph node involvement: a propensity score matching analysis

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Abstract
Purpose The aim of this study was to evaluate the efficacy of adjuvant gemcitabine monotherapy following resection for perihilar cholangiocarcinoma with lymph node involvement.
Methods We performed a retrospective analysis of 180 patients undergoing resection for perihilar cholangiocarcinoma with lymph node involvement between 2001 and 2012. The patients were divided into two groups according to the presence ($n = 67$) or absence ($n = 113$) of adjuvant gemcitabine monotherapy. Univariate and multivariate analyses were performed followed by a propensity score matching analysis to adjust for the differences in the baseline characteristics of the groups.
Results The overall survival rates after surgery and the median survival times in patients who were treated with adjuvant chemotherapy were significantly longer than those who were treated without adjuvant chemotherapy (32.9 vs. 15.0 % at 5 years, 37 vs. 20 months, $P = 0.001$). A multivariate analysis indicated that adjuvant chemotherapy, a residual microscopic tumor, and pathological T stage were independent prognostic factors for survival. After two new cohorts of 32 patients were generated following 1:1 propensity score matching, the overall survival rate in the adjuvant chemotherapy group was found to be significantly longer than that in the surgery alone group (43.2 vs. 15.6 % at 5 years, $P = 0.001$).
Conclusion Adjuvant gemcitabine monotherapy may improve survival in node-positive perihilar cholangiocarcinoma patients.

Keywords Perihilar cholangiocarcinoma · Adjuvant therapy · Gemcitabine hydrochloride

Introduction

Surgical resection is the only curative option for perihilar cholangiocarcinoma (PHC). Many surgeons have adopted an aggressive approach to PHC [1–14]; however, recurrence is common, even after curative resection and the rate of survival after resection remains unsatisfactory, with a 5-year survival rate of 26–56 % [3, 13, 15–18]. Lymph node metastasis is reported to be one of the most important prognostic factors, and overall survival following resection in patients with lymph node involvement is significantly worse than that in patients without lymph node involvement [2, 3, 6, 7, 13, 14, 17, 19, 20]. Surgery alone is, therefore, not sufficient for improving the survival of lymph node-positive PHC patients. At present, however, there is little evidence of the efficacy of adjuvant chemotherapy in patients with biliary malignancy after resection [21–23]. In the present study, we retrospectively analyzed the efficacy of adjuvant gemcitabine monotherapy after resection in PHC patients with lymph node involvement.

Methods

Patients

Between January 2001 and December 2012, 484 patients underwent surgical resection with curative intent for PHC.

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Three hundred four of these patients were excluded from the present study, due to postoperative mortality ($n = 10$; 2.1 %), liver metastasis and/or local dissemination (pM1 disease) ($n = 30$), R2 resection ($n = 8$), the absence of lymph node involvement ($n = 238$), incomplete data regarding recurrence or survival ($n = 14$), and chemotherapy other than gemcitabine monotherapy ($n = 4$). Thus, the remaining 180 patients, who accounted for 37.2 % of the patients who underwent resection, were included in this retrospective study. Twenty-nine patients with distant lymph node (celiac artery, superior mesenteric artery, and/or periaortic lymph node) metastasis were included in this study because the results of our previous study indicated that the survival rates of patients with regional node metastasis alone and those with distant node metastasis did not differ to a statistically significant extent [19].

Surgery

The procedures used for resection depended on the location of the primary tumor [24, 25]. In principle, right hepatectomy was applied to Bismuth type I, II, and IIIa tumors [4], whereas left hepatectomy was applied to Bismuth type IIIb tumors. In Bismuth type IV tumors, the type of hepatectomy was determined based on the predominant tumor location, the presence or absence of portal vein and/or hepatic artery invasion, and liver function. Right-sided hepatectomy was applied to Bismuth type IV tumors with a right-sided predominance or even extension, whereas left-sided hepatectomy was selected for Bismuth type IV tumors with a left-sided predominance [26].

All of the 180 study patients underwent several types of hepatectomy with *en bloc* resection of the caudate lobe and the extrahepatic bile duct. Combined pancreatoduodenectomy [27, 28], and combined vascular resection with reconstruction [11, 29, 30] were also performed as necessary.

On laparotomy, we first examined frozen sections of the periaortic lymph nodes in all patients. In principle, we gave up resection when metastasis was found. In some patients, however, we performed resection, provided that it was considered likely to improve the patient's quality of life and was not deemed to be too risky. Periaortic node dissection, primarily based on the preference of the surgeon, was performed in early 2000. Periaortic node dissection was not performed after 2005 because several studies [31, 32] showed that periaortic node dissection has no impact on survival.

Histologic assessment

The extrahepatic bile duct of the resected specimen was opened longitudinally from the distal resection margin up to the proximal margin, to accurately evaluate the ductal margin status [33]. The resected specimens were then fixed in 10 % formalin for several days and serially sectioned at 5-mm intervals. The specimens were prepared for microscopic examination using hematoxylin and eosin staining. Positive ductal margins with carcinoma in situ ($n = 15$) were treated as "negative" because it is evident that residual carcinoma in situ has no survival impact [34]. Lymph node groups and staging were evaluated using the TNM classification of perihilar cholangiocarcinoma (seventh edition) by the UICC [35].

Adjuvant gemcitabine monotherapy

Adjuvant gemcitabine monotherapy was administered to 67 patients (37.2 %), who mainly underwent resection from 2007. Gemcitabine (1000 mg/m^2) was administered as a 30-min infusion on days 1, 8, 15 every 4 weeks. The patients received 6 cycles of gemcitabine monotherapy. The attending doctors allowed dose modifications and delays when adverse effects were observed. Treatment was discontinued at the completion of the treatment or because of recurrence, the choice of the patient or clinician, or due to unacceptable toxic effects.

Postoperative follow-up

Patients were followed up regularly. Follow-up examinations, including physical examinations, laboratory tests, tumor marker level tests, and computed tomography were performed at intervals of 3–6 months. The median follow-up period for the censored patients was 55 months. Recurrence was defined based on radiological and/or cytological evidence. A diagnosis of recurrence was not made before reviewing radiological and/or cytological evidence, even when the tumor marker levels increased above the normal limits.

Statistical analysis

Continuous variables were expressed as the medians and ranges. The Mann–Whitney *U* test, Chi-squared test, and Fisher's exact probability test were performed as appropriate. Recurrence-free and overall survival were calculated using the Kaplan–Meier method. Differences in survival curves were compared using the log-rank test. A multivariate analysis was performed using a Cox proportional hazards model to identify the factors that were independently associated with survival. *P* values of <0.05 were considered to indicate statistical significance.

After comparing the clinicopathological data between the surgery alone and the adjuvant gemcitabine monotherapy patients, rigorous adjustments were made via propensity score matching for the baseline characteristics that showed

significant differences between the two groups [36–38]. A multivariate logistic regression analysis was performed to estimate the propensity scores for these patients. The following 11 perioperative variables were included in the model: age, gender, Bismuth type, vascular resections, combined pancreatoduodenectomy, adjuvant external beam radiotherapy, histological grade, pathological T stage, distant lymph node metastasis, the presence of a residual microscopic tumor, and time period. Subsequently, a one-to-one match between the two groups was performed using the nearest-neighbor matching method within 0.05 standard deviation units. All of the statistical analyses were performed using the SPSS software program (version 23, IBM Japan, Tokyo, Japan).

Results

Patients demographics

The study population consisted of 109 male patients and 71 female patients with a median age of 66 years (range: 33–83 years). The Bismuth classifications were as follows: type I ($n = 6$), type II ($n = 11$), type III ($n = 65$), and IV ($n = 98$). Right-sided hepatectomy was performed in 66 patients, and left-sided hepatectomy was performed in 111 patients. The remaining 3 patients underwent central bisegmentectomy. Combined vascular resection with reconstruction was also performed in 100 patients (55.6 %), including the portal vein in 48 (26.7 %) patients, the hepatic artery in 13 (7.2 %) patients, and the simultaneous resection of the portal vein and hepatic artery in 39 (21.7 %) patients. Adjuvant external beam radiation therapy (EBRT) was applied to the margin-positive site in 3 patients (1.7 %). Combined adjuvant gemcitabine monotherapy and radiation therapy was used in 11 patients (6.1 %).

With regard to the histological examination, there were 39 (21.7 %) patients with a histologically positive margin. Distant lymph node metastasis was found in 29 (16.1 %) patients. The demographic information of patients, according to the adjuvant treatment, is shown in Table 1.

There were no significant differences with regard to age, gender, Bismuth type, the type of hepatic resection, combined PD, the presence of a microscopically positive margin, the pathological T stage, or the presence of distant lymph node metastasis between the chemotherapy group and the surgery alone group. As mentioned above, the patients mainly underwent adjuvant chemotherapy from 2007 ($P < 0.0001$). Combined vascular resection with reconstruction ($P = 0.020$), adjuvant extra beam radiotherapy ($P = 0.002$) were performed more frequently in the patients who received adjuvant chemotherapy. The surgery alone group included a greater number of well-differentiated adenocarcinoma cases ($P = 0.046$).

Delivery of adjuvant gemcitabine monotherapy

Among the 67 patients who received gemcitabine, 44 (66 %) patients completed the protocol; therapy was discontinued for the remaining 23 patients due to adverse effects ($n = 18$, 27 %), or recurrence ($n = 5$, 7 %). The main treatment-related adverse effects that led to discontinuation were neutropenia ($n = 12$), anorexia ($n = 3$), fatigue ($n = 2$), and refractory cholangitis ($n = 1$).

Recurrence and overall survival

Recurrent disease was identified during the study period in 149 of the 180 patients (82.8 %). The sites of the first recurrence were as follows: local ($n = 61$), the peritoneum or pleura ($n = 44$), the liver ($n = 25$), the periaortic lymph nodes ($n = 22$), the lung ($n = 13$), and other sites ($n = 8$). There was no statistically significant difference in recurrence site between the groups.

The 3-year recurrence-free survival rate and median recurrence-free survival times were 32.8 % and 19 months, respectively, in patients with adjuvant chemotherapy, and 22.1 % and 13 months, in patients without adjuvant chemotherapy. The Kaplan–Meier curves were initially dissociated; however, they crossed each other at 58 months after surgery. The difference was not statistically significant ($P = 0.40$) (Fig. 1).

Following recurrence, the patients underwent chemotherapy ($n = 82$), radiation therapy ($n = 31$), and resection of the recurrence ($n = 14$). Forty-three patients received the best supportive care alone. The patients in the adjuvant chemotherapy group more frequently received chemotherapy after recurrence than the patients in the surgery alone group ($P < 0.0001$).

The overall survival of the patients who received adjuvant chemotherapy was significantly better than that of those who did not receive adjuvant chemotherapy (32.9 vs. 15.0 % at 5-year; 37 vs. 20 months of median survival time, $P = 0.001$) (Fig. 2).

The univariate and multivariate analyses of the risk factors for survival

Table 2 shows the results of the univariate and multivariate analyses for the risk factors in the patients with lymph node involvement. The pathological T stage, the presence of a microscopic residual tumor, and the administration of adjuvant chemotherapy were the independent factors that influenced the overall survival after resection.

The propensity score matching analysis

As mentioned above, significant differences were observed in the baseline clinicopathological characteristics of the

Table 1 The demographic information of the 180 study patients according to the adjuvant treatment

	Surgery alone ($n = 113$)	Adjuvant chemotherapy ($n = 67$)	P value
Age (years)			
Median (range)	67.0 (33–83)	65.0 (38–79)	0.190
Sex			
Female	44	27	0.876
Male	69	40	
Time period			
2001–2006	76	1	<0.0001
2007–2012	37	66	
Bismuth type			
I–III	54	28	0.444
IV	59	39	
Type of hepatic resection			
Right-sided	43	23	0.333
Left-sided	67	44	
Others	3	0	
Vascular resection[a]			
No	58	22	0.020
Yes	55	45	
Combined PD			
No	99	57	0.655
Yes	14	10	
Adj. EBRT			
No	110	56	0.002
Yes	3	11	
Microscopic margin			
Negative	90	51	0.580
Positive	23	16	
pT[b]			
2a/2b	33	11	0.148
3	6	5	
4	74	51	
Distant N[b]			
No	93	58	0.533
Yes	20	9	
Histological grade[b]			
G1	26	6	0.046
G2	72	53	
G3	15	8	

EBRT external beam radiotherapy, *PD* pancreatoduodenectomy

[a] Vascular resection includes the resection/reconstruction of the portal vein and/or hepatic artery

[b] According to the classification of UICC 7th edition

surgery alone and adjuvant gemcitabine monotherapy groups. To reduce these baseline differences, 1:1 propensity score matching was performed and two new groups were obtained, each with 32 patients. The baseline characteristics were then compared between the groups (Table 3).

After propensity score matching, the 3-year recurrence-free survival rate and median recurrence-free survival times of the patients who received adjuvant gemcitabine monotherapy were significantly better than of the patients who did not receive adjuvant gemcitabine monotherapy (46.9 vs. 15.6 %, 25.4 vs. 9.9 months, respectively, $P = 0.01$) (Fig. 3a). The overall survival rate of the patients who received adjuvant therapy was also significantly higher than that of the patients who did not receive adjuvant

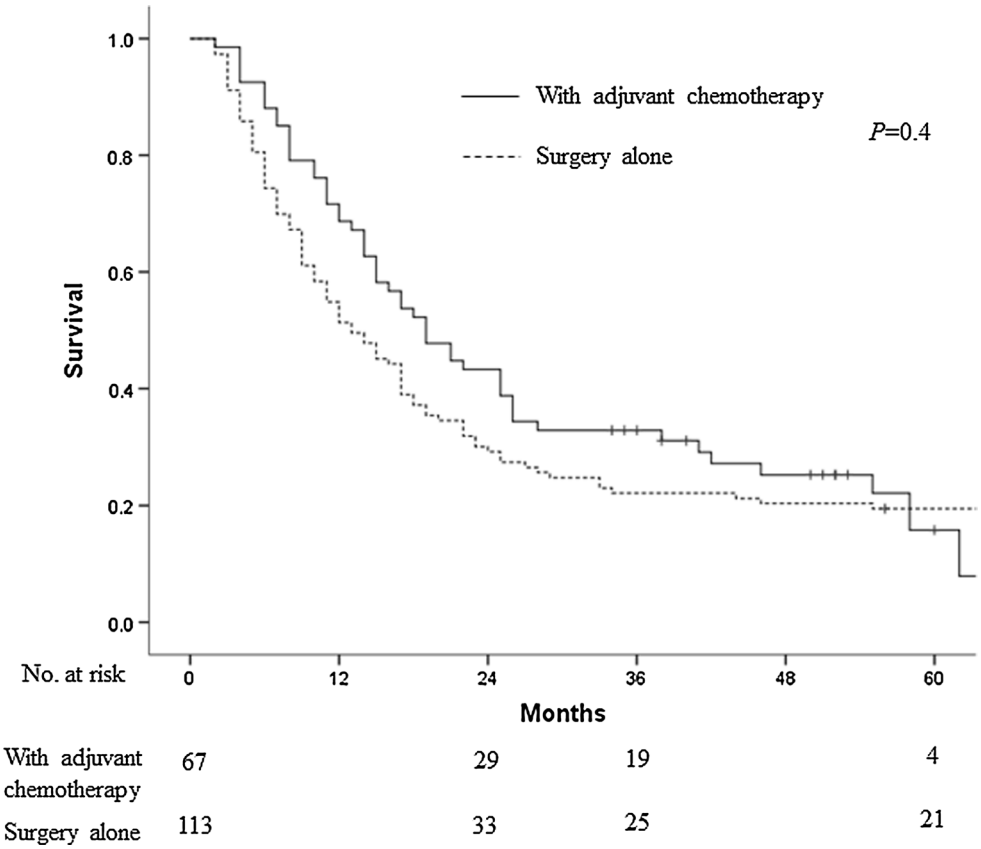

Fig. 1 The Kaplan–Meier curves for recurrence-free survival according to the adjuvant treatment

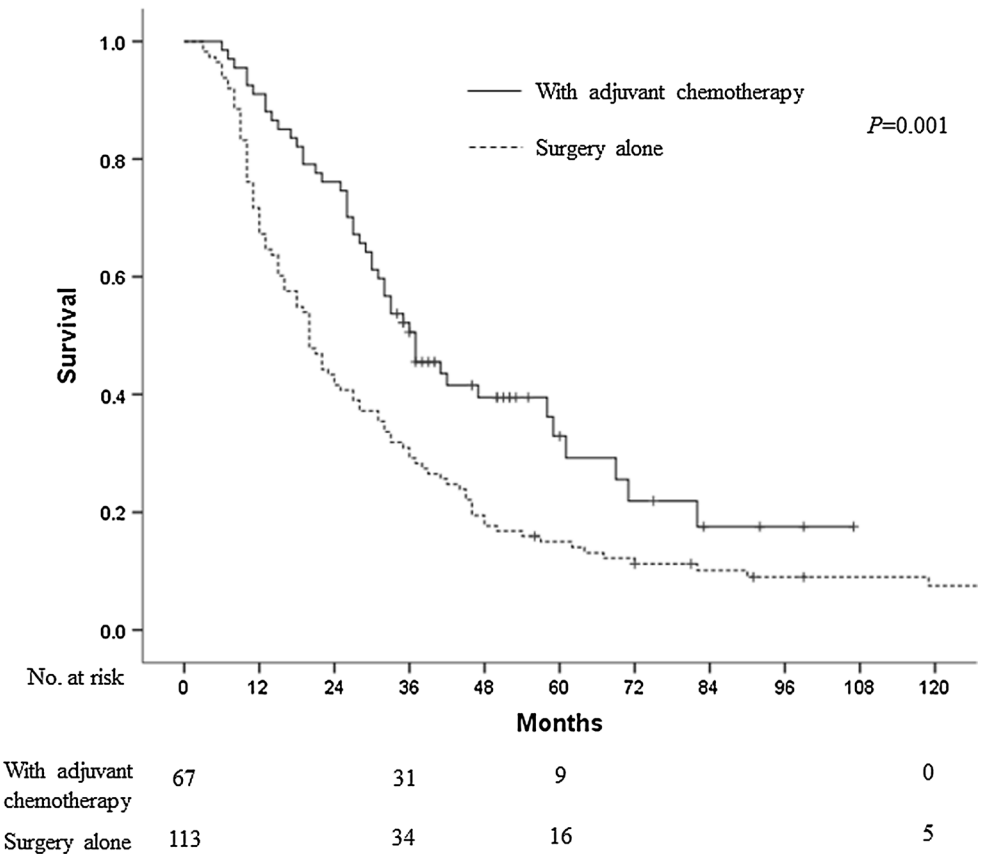

Fig. 2 The Kaplan–Meier curves for overall survival according to the adjuvant treatment

Table 2 The prognostic factors of the 180 study patients

	Univariate			Multivariate		
	n	MST	*P*	HR	95 % CI	*P* value
Gender						
Female	71	29	0.54			
Male	109	27				
Bismuth type						
I–III	82	30	0.09			
IV	98	26				
Time period						
2001–2006	77	20	0.003			
2007–2012	103	33				
Vascular resection						
No	80	31	0.088			
Yes	100	25				
Combined PD						
No	156	26	0.162			
Yes	24	37				
pT[a]						
2, 3	55	35	0.016	1.71	1.18–2.48	0.004
4	125	25				
Distant N[a]						
No	151	28	0.023			
Yes	29	20				
Histological grade[a]						
G1	32	31	0.405			
G2	125	28				
G3	23	16				
Microscopic margin						
Negative	141	30	0.023	1.57	1.01–2.17	0.46
Positive	39	20				
Adj. EBRT						
No	166	27	0.336			
Yes	14	27				
Adjuvant gemcitabine monotherapy						
No	113	20	0.001	0.49	0.35–0.72	<0.0001
Yes	67	37				

MST median survival time, *HR* hazard ratio, *CI* confidence interval, *PD* pancreatoduodenectomy, *EBRT* external beam radiotherapy

[a] According to the classification of UICC 7th edition

gemcitabine monotherapy (43.2 vs. 15.6 % at 5 years, $P = 0.001$) (Fig. 3b).

Discussion

Lymph node involvement has been reported to be one of the strongest poor prognostic factors in PHC patients who underwent resection [2, 3, 6, 7, 13, 14, 17, 19, 20]. Effective postoperative adjuvant treatment is, therefore, necessary to prolong survival. However, the efficacy of the adjuvant chemotherapy for biliary malignancies remains controversial because of a lack of evidence based on a phase III prospective randomized control study.

More than 10 years ago, Takada et al. prospectively compared therapy with mitomycin C and 5-FU to surgery alone after the radical resection of biliary carcinoma. They reported that the 5-year survival rate of gallbladder carcinoma patients was significantly better in the chemotherapy group (26 %) in comparison to the surgery alone group

Table 3 The clinicopathological features according to the adjuvant treatment after propensity score matching

Variables	Surgery alone ($n = 32$)	Adjuvant chemotherapy ($n = 32$)	P value
Propensity score			
Median (25–75th percentile)	0.534 (0.429–0.661)	0.539 (0.434–0.666)	1.000
Age			
<65 years	8	9	1.000
65 years	24	23	
Sex			
Female	11	11	1.000
Male	21	21	
Time period			
2001–2006	1	2	1.000
2007–2012	31	30	
Bismuth type			
I–III	14	18	0.617
IV	17	15	
Vascular resection			
No	11	11	1.000
Yes	21	21	
Combined PD			
No	28	27	1.000
Yes	4	5	
Adj. EBRT			
No	31	30	1.000
Yes	1	2	
Microscopic margin			
Negative	27	29	0.708
Positive	5	3	
pT[a]			
2, 3	8	10	0.782
4	24	22	
Distant N[a]			
No	29	31	0.613
Yes	3	1	
Histological grade[a]			
G1	4	4	0.601
G2	21	24	
G3	7	4	

Vascular resection includes the resection/reconstruction of the portal vein and/or hepatic artery

EBRT external beam radiotherapy, *PD* pancreatoduodenectomy

[a] According to the classification of UICC 7th edition

(14 %), but that the survival benefit was not found in bile duct carcinoma patients or ampullary carcinoma patients. [39]. The European Study Group for Pancreatic Cancer-3 trial, the largest randomized trial, was conducted in patients with resected periampullary adenocarcinomas. Four hundred twenty-eight patients with periampullary malignancies (96 bile duct cancers) were randomly assigned to one of three arms: observation, 6 months of leucovorin-modulated FU or 6 months of gemcitabine monotherapy. The use of adjuvant treatment was associated with a potential, but not statistically significant advantage (median 43 vs. 35 months, HR 0.86, 95 % CI: 0.66–1.11). However, a multivariate analysis showed that chemotherapy specifically gemcitabine achieved a statistically significant survival benefit [40]. Murakami et al. evaluated adjuvant chemotherapy consisting of 10 cycles of gemcitabine plus S-1 (intravenous gemcitabine 700 mg/m^2 on day 1 and per oral S-1 50 mg/m^2 for consecutive days, followed by

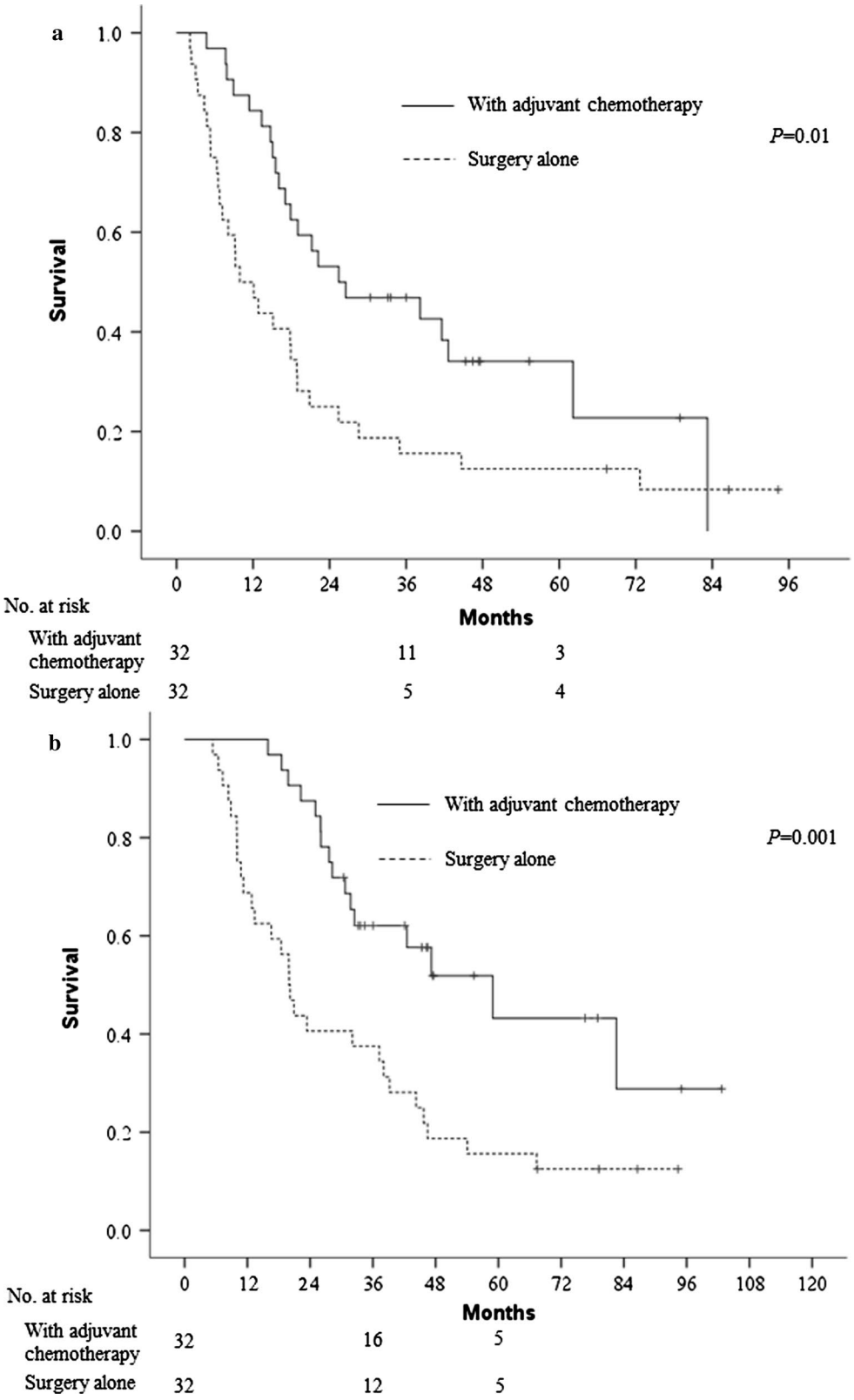

Fig. 3 The Kaplan–Meier curves for recurrence-free survival (**a**) and overall survival (**b**) according to the adjuvant treatment in matched cohorts

a 1-week rest) in patients with UICC stage II biliary cancer after resection. They reported that the 5-year survival rate of the patients who received adjuvant chemotherapy was significantly better than that of the patients who did not receive adjuvant chemotherapy (57 vs. 24 %, $P < 0.001$) [21]. A recent large-volume meta-analysis indicated the

efficacy in patients with nodal metastasis (pN1) and/or with R1 resection [23].

In this study, the overall survival rate for patients who received adjuvant gemcitabine monotherapy was significantly better than that of the patients who did not. Although the result did not reach statistical significance, recurrence-free survival in the former patients was 6 months longer than that in the latter patients. These observations indicate the efficacy of adjuvant chemotherapy for a high-risk subset of patients with biliary malignancies, and support the results of the meta-analysis [23]. However, there were significant differences in the treatments that were administered after recurrence, which might have affected overall survival.

To overcome the significant underlying differences in the baseline data of the two groups, we conducted a propensity score matching analysis [36–38] using clinicopathological factors that potentially affected the choice of adjuvant treatment. A subsequent analysis after propensity score matching clearly demonstrated improved recurrence-free and overall survival in the patients who received adjuvant chemotherapy, which implies the survival benefit of adjuvant chemotherapy in node-positive PHC patients.

The safety of gemcitabine monotherapy after major hepatectomy has not been established. Several previous clinical trials and case reports showed that patients who had undergone major hepatectomy for biliary malignancy did not tolerate the standard dose of gemcitabine (1000 mg/m^2 on days 1, 8, 15 every 4 weeks or 1000 mg/m^2 on days 1, 8 every 3 weeks) because of the development of severe toxicities [21, 22, 41]. In this study, adjuvant chemotherapy was discontinued in 27 % of the patients because of adverse effects. This result was consistent with the previous studies. Recently, a Japanese multicenter study group conducted a phase I trial [42] and pharmacokinetic study [43] on gemcitabine in patients with biliary tract cancers undergoing major hepatectomy, and have reported that the dose of gemcitabine should be reduced to 1000 mg/m^2 biweekly. A modification of the dose of gemcitabine would, therefore, be required for biliary malignancy patients after resection depending on the procedure that was performed.

Several investigators have reported the efficacy of the adjuvant extra beam radiotherapy (EBRT) [44, 45] or chemoradiotherapy [46] after R1/2 resection. However, the efficacy of these therapies is also controversial. In our series, only 14 patients with a positive margin received additional radiotherapy (EBRT, $n = 3$; chemoradiotherapy, $n = 11$). Due to the limited number of patients in the present study, it was difficult to evaluate the efficacy of additional radiotherapy. Further investigation is needed to determine whether chemotherapy or chemoradiotherapy would be more effective for the treatment of patients with lymph node positivity and/or a microscopically positive margin.

The present study is associated with some limitations. First, it was a non-randomized retrospective analysis with a relatively small number of patients. However, the results of the present study support the current clinical guidelines, and may strengthen the recommendation for adjuvant treatment in node-positive perihilar cholangiocarcinoma patients after resection. Besides, the results indicated that lymph node involvement should be a stratifying factor when planning a future prospective randomized trial for adjuvant chemotherapy for biliary tract cancer. At present, there are several ongoing randomized controlled studies that aim to evaluate the efficacy of adjuvant chemotherapy after surgical resection in biliary carcinoma patients [23]. These studies have enrolled patients with various types of biliary malignancies despite the different prognosis of each primary tumor site [2, 47]. The stages of our subjects were relatively homogenous and the primary sites were identical; thus, the results of the present study can contribute to the analysis of the upcoming results of the randomized studies.

In conclusion, adjuvant gemcitabine monotherapy may have the potential to improve survival in node-positive PHC patients.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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