Japanese Journal of Gastroenterology and Hepatology

Research Article

Adjuvant Chemotherapy in the Treatment of Perihilar Cholangiocarcinoma with Lymph Node Involvement

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Received: 30 May 2020

Accepted: 09 June 2020

Published: 12 June 2020

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1. Abstract

1.1. Aims: To study the application of adjuvant chemotherapy in the treatment of Perihilar cholangiocarcinoma (pCCA).

1.2. Methods: We retrospectively collected the data of 86 patients who underwent surgery for perihilar cholangiocarcinoma in our department between 2012 to 2017. The patients were divided into surgery alone group (n=44) and adjuvant chemotherapy group (n=42). Univariate and multivariate analyses were performed and propensity score matching was used to decrease the influence of potential confounding factors. Kaplan-Meier method was used to evaluate the survival of patients. For those 34 patients with lymph node involvement, similar analyses were performed.

1.3. Results: The median survival time of adjuvant chemotherapy was significantly longer than the surgery alone group (19.5 vs 13 months, p=0.0195). The result of multivariate analysis suggested that lymph node involvement and adjuvant chemotherapy were independent prognostic factors. After the propensity score matching, 28 pairs of patients were selected. The median survival time of adjuvant chemotherapy group was significantly longer than the surgery alone group (22 vs 9 months, p=0.0010). For those patients with lymph node involvement, the propensity score-matched cohort was composed of 14 surgery alone patients and 14 adjuvant chemotherapy patients, and the median survival time of adjuvant chemotherapy was significantly longer than the surgery alone group(18.5 vs 8.5 months, p=0.0158).

1.4. Conclusions The application of adjuvant chemotherapy may improve the survival of perihilar cholangiocarcinoma patients and those patients with lymph node involvement.

2. Keywords: Perihilar cholangiocarcinoma; Surgery; Adjuvant chemotherapy; Survival analysis

3. Introduction

Perihilar cholangiocarcinoma (pCCA) is a challenging malignant tumor that accounts for about 50% of biliary tract cancer [1]. Obstructive jaundice and itch are the most common symptoms [2, 3]. Surgery is the only curative option for pCCA [4]. Preoperative biliary drainage, extensive hepatectomy, hilar lymph node dissection and hilar vascular resection and reconstruction were key techniques to improve the surgical safety and R0 resection rate. However, due to the location and aggressive property, hilar vessels and bile ducts invasions are very common which contributes to the difficulty of surgical resection [5-7]. The resection rate of perihilar cholangiocarcinoma was relatively low as most patients were unsuitable for surgical resection at the time of diagnosis and the 5-year survival rate after surgical resection of perihilar cholangiocarcinoma ranges from 12 to 48% [4, 8-9]. Moreover, lymph node metastasis is reported to be one of the most important prognostic factors and patients with lymph node involvement would have a worse overall survival after surgery resection than those without it [4, 10-11].

The poor prognosis was reported to be associated with tumor cells in the blood, and some researchers have reported the application of adjuvant chemotherapy in these patients [12, 13]. However, due to the limited number of cases and difficulty of surgical resection, most studies were retrospective studies and most of the clinical trials have include all biliary tract tumors as one entity and

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there were no special studies for perihilar cholangiocarcinoma [9, 13]. However, the effect of adjuvant chemotherapy is still controversial1, [14]. Here in, we retrospectively collected the data of all pCCA patients in our department from 2012 to 2017 and analyzed the effect of adjuvant chemotherapy on patient'sprognosis.

4. Methods

4.1. Data collection

From January 2012 to December 2017, 86 patients underwent surgical resection for perihilar cholangiocarcinoma in our department and 42 patients (48.8%) have underwent adjuvant chemotherapy after excluding those didn't underwent surgery or only palliative resection, incomplete data. There were only 34pCCA patients with lymph node involvement and 16 of them have underwent adjuvant chemotherapy. All the relevant data of these patients were retrospectively collected.

4.2. Surgery

The surgical procedures for radical resection were mainly depended on the invasion area of tumor and Bismuth type. Usually, right hepatectomy was applied to Bismuth type I, II tumor. Right hepatectomy accompanied with caudate lobectomy was applied to Bismuth type III a and type IV tumor with right-sided predominance. Left hepatectomy accompanied with caudate lobectomy was applied to Bismuth type III b and type IV tumor with left-sided predominance. Perihilar lymph nodes were all resected and extra hepatic bile duct and vessels resection and reconstruction were combined when needed.

4.3. Adjuvant chemotherapy

There were mainly three kinds of adjuvant chemotherapy as follows: gemcitabine combined with cis-platinum, gemcitabine combined with tegafur, and oxaliplatin combined with tegafur and folinate. The specific regimens were decided by the clinician and could be modified when recurrence or unacceptable side effects occur.

4.4. Follow-up

Patients were followed up regularly after the surgery. Patients would have physical examinations, tumor marker tests, biochemistry tests, and blood routine and image examinations at 1 month, three months, half year and every 3 months later.

5. Statistical Analysis

Chi-square test, T test and non-parameter test were used to compare the differences between basic characteristics of two groups. The overall survival of two groups was analyzed using the Kaplan-Meier method. A multivariate analysis was also performed using Cox regression.

1:1 propensity score matching was performed to minimize the influence of confounding factors15.The matched factors include age, sex, bismuth type, preoperative biliary drainage (PBD), T stage, R0 resection lymph node involvement and histological grade. All of the statistical analysis was performed using the SPSS software (version 25.0). $p<0.05$ was considered to suggest statistical significant difference.

6. Results

52 male patients and 34 female patients were included in this study, with a median age of 60 (range: 28-79). Among them, there were 42 Bismuth type IV patients, 33 Bismuth type III patients 5 Bismuth type II patients and 6 Bismuth type I patients. 28 patients (32.6%) had gone through preoperative biliary drainage.

According to the postoperative histological examination, 44 patients (51.2%) had achieved R0 resection. The histological grades were as follows: well differentiated (n=20), moderately differentiated (n=54) and poorly differentiated (n=12). The primary tumor T classifications were as follows: T1 (n=5), T2 (n=55), T3 (N=15) and T4 (n=11).

The adjuvant chemotherapy regimens were as follows: gemcitabine combined with cis-platinum (n=11), gemcitabine combined with tegafur (n=23), and oxaliplatin combined with tegafur and folinate (n=8).

The basic characteristics according to the adjuvant chemotherapy are shown in (Table 1). No significant statistical differences were found with regard to age, sex, Bismuth type, preoperative biliary drainage, pathological T stage, R0 resection, lymph node involvement and histological grade.

(Table 2) shows the results of univariate and multivariate analyses of the prognostic factors of 86 pCCA patients. The univariate analyses showed that lymph node involvement, histological grade and adjuvant chemotherapy were risk factors of patient survival. While multivariate analyses showed that only lymph node involvement and adjuvant chemotherapy were independent factors of overall survival after resection.

According to the follow-up results, the 1-year survival rate (73.8% vs 54.5%) and 2-year survival rate (38.1% vs 25%) of adjuvant chemotherapy group were higher than the surgery alone group. As shown in the (Figure 1), the overall survival of patients in adjuvant chemotherapy group was significantly better than that in the surgery alone group (19.5 vs 13 months of median survival time,$p=0.0195$).

On the basis of previous univariate and multivariate analyses, lymph node involvement, histological grade and adjuvant chemotherapy were risk factors that may influence the patient's survival. To reduce the influence of potential confounding factors, 1:1 propensity score matching was performed and there were 28 patients in each new group. The basic characteristics of two groups after propensity score matching is shown in (Table 3).

After the propensity score matching, the 1-year survival rate (78.6% vs 46.4%) and 2-year survival rate (14.3% vs 42.9%) of adjuvant chemotherapy group was higher than the surgery alone group. As shown in the (Figure 2), the overall survival of patients in adjuvant chemotherapy group was significantly better than that in the surgery alone

group (22 vs 9 months of median survival time, p=0.0010).

For those patients with lymph node involvement, the basic characteristics of patients were shown in (Supplementary Table 1), and the median survival time of adjuvant chemotherapy group was significantly longer than that the surgery alone group (18.5 vs 5.75 months, p=0.0014) (Figure 3). After 1:1 propensity score matching, there were 14 patients in each group (Supplementary Table 2) and the overall survival of patients in adjuvant chemotherapy group was significantly better than that in the surgery alone group (18.5 vs 8.5 months of median survival time, p=0.0158) (Figure 4).

Table 1: Basic characteristics of patients according to the adjuvant.

	Surgeryalone (n=44)	Adjuvant chemotherapy (n=42)	P value
Age (years)			
Median(range)	59(51.5-67.25)	62(55.25-68)	0.67
Sex			
Male	29	23	0.291
Female	15	19	
Bismuth type			
I-III	24	20	0.521
IV	20	22	
PBD[a]			
Yes	12	16	0.284
no	32	26	
T4 grade[b]			
Yes	4	7	0.293
No	40	35	
R0 resection			
Yes	24	20	0.521
No	20	22	
Lymph node involvement			
Yes	18	16	0.79
no	26	26	
Histological grade[b]			
G1	9	11	0.799
G2	29	25	
G3	6	6	

a. PBD: preoperative biliary drainage
b. According to the classification of AJCC 8th edition

Table 2: The prognostic factors of the 86 patients

		Univariate			Multivariate	
	n	MST	P value	HR	95%CI	P value
Age						
<65Y	58	16	0.246	1.313	0.745-2.315	0.346
≥65Y	28	13				
Sex						
Male	52	13	0.963	1.153	0.657-2.025	0.62
Female	34	18				
Bismuth type						
I-III	44	16	0.575	1.167	0.692-1.969	0.563
IV	42	15				
PBD[a]						
Yes	28	15	0.659	0.789	0.456-1.365	0.397
no	58	16				
T4 grade[b]						
Yes	11	11	0.158	1.489	0.697-3.183	0.304
No	75	18				
R0 resection						
Yes	44	19	0.321	1.003	0.598-1.683	0.99
No	42	13				
Lymph node involvement						
Yes	34	12	0.047	1.903	1.101-3.289	0.021
No	52	19				
Histological grade[b]						
G1	20	20	0.029	1.53	0.962-2.433	0.072
G2	54	15				
G3	12	8				
Adjuvant chemotherapy						
Yes	42	19	0.019	0.343	0.147-0.797	0.013
No	44	13				

MST median survival time, HR hazard ratio, CI confidence interval
a. PBD: preoperative biliary drainage
b. According to the classification of AJCC 8th edition

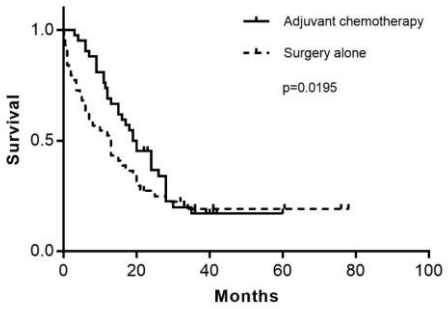

Figure1: The Kaplan–Meier curves for overall survival according to the adjuvant treatment.

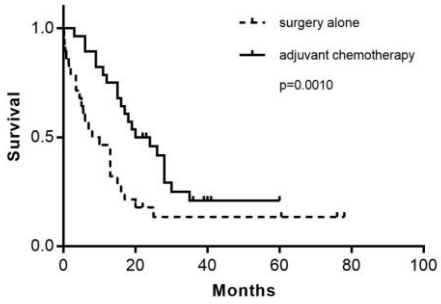

Figure 2: The Kaplan–Meier curves for overall survival according to the adjuvant treatment after propensity score matching

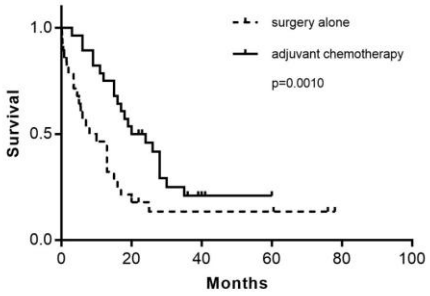

Figure 3: The Kaplan–Meier curves for overall survival of patients with lymph node involvement according to the adjuvant treatment.

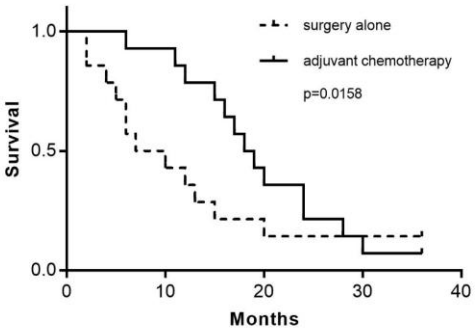

Figure 4: The Kaplan–Meier curves for overall survival of patients with lymph node involvement according to the adjuvant treatment after propensity score matching

Supplementary Table 1: Basic characteristics of patients with lymph node involvement.

	Surgery (n=18)	Adjuvant chemotherapy (n=16)	P value
Age (years)			
Median(range)	61.5(49-73)	57.5(35-74)	0.052
Sex			
Male	8	6	0.738
Female	10	10	

Bismuth type			
I-III	10	8	1
IV	8	8	
P^BDa			
Yes	6	6	1
no	12	10	
T4 grade[b]			
Yes	4	4	1
No	14	12	
R0 resection			
Yes	7	7	1
No	11	9	
Histological grade[b]			
G1	4	4	0.968
G2	12	10	
G3	2	2	

a. PBD: preoperative biliary drainage
b. According to the classification of AJCC 8th edition

Supplementary Table 2: Basic characteristics of patients with lymph node involvement after propensity score matching.

	Surgery (n=14)	Adjuvant chemotherapy (n=14)	P value
Age (years)			
＜65 Y	12	12	1
≥65 Y	2	2	
Sex			
Male	6	5	1
Female	8	9	
Bismuth type			
I-III	7	7	1
IV	7	7	
PBD[a]			
Yes	6	5	1
no	8	9	
T4 grade[b]			
Yes	3	3	1
No	11	11	
R0 resection			
Yes	6	5	1
No	8	9	
Histological grade[b]			
G1	3	4	0.904
G2	9	8	
G3	2	2	

a. PBD: preoperative biliary drainage
b. According to the classification of AJCC 8th edition

7. Discussion

Perihilar cholangiocarcinoma is a kind of malignant tumor with a low rate of resection and high rate of recurrence or metastasis, and the actual 5-year survival rate was 12% by [4]. Lymph nodes invasion of these patients would indicate a worse prognosis [16-19]. Herein the application of adjuvant chemotherapy to improve the prognosis of these patients was proposed.

Some have reported that adjuvant chemotherapy could help improve the survival of perihilar cholangiocarcinoma patients [20], but there were also studies that were opposed to it [21]. A recent meta-analysis included three randomized clinical trials showed that adjuvant chemotherapy could improve the recurrence free survival of bile duct tumor patients but have no effect on overall survival [22]. However, another meta-analysis had supported the application of adjuvant chemotherapy in bile duct tumors 9. The attitude of clinical guidelines about adjuvant chemotherapy in perihilar cholangiocarcinoma was still vague and there were no standard regimens [1, 14].

Moreover, due to the small number of perihilar cholangiocarcinoma patients with lymph node involvement and the low rate of surgical resection, the study of adjuvant chemotherapy in these patients were very rare [13, 22]. Previous studies usually include all bile duct tumors as a whole [9, 23], and neglect the heterogeneity of these tumors [21, 24].

In this study, we have collected the data of all perihilar cholangiocarcinoma patients and divided them into adjuvant chemotherapy group and surgery alone group. There was no statistical difference between the basic characters of two groups. Adjuvant chemotherapy and lymph node involvement were prognostic factors according to the prognosis analyses. The overall survival of patients in the adjuvant chemotherapy group was significantly longer than the patients in the surgery alone group, which was consistent with the result of previous studies [13, 25-27]. Furthermore, in order to reduce the influence of possible confounding factors, 1:1 propensity score matching was performed [15]. The survival analysis of two new generated groups has also supported the superiority of adjuvant chemotherapy. The similar analysis of patients with lymph node involvement was also performed and came to the same conclusion that adjuvant chemotherapy could improve the prognosis of this group of patients.

Different chemotherapy regimens were used in previous studies, including capecitabine, gemcitabine, oxaliplatin and 5-FU [20-21, 28]. Valle et al have reported that cisplatin combined with gemcitabine could significantly improve the overall survival compared to gemcitabine alone in patients with unresectable or metastatic bile duct tumor [29]. There were no standard chemotherapy regimens for perihilar cholangiocarcinoma and new prospective randomized clinical trials are needed to complete alternative chemotherapy regimens and prove their efficacy [22, 30].

The present study has the following limitations that must be taken into account. Firstly, this was a non-randomized retrospective study and the influence of placebo effect and confounding factors can't be neglected. Propensity score matching method was applied to decrease the potential bias. Secondly, the number of patients included is relatively small. This can be attributed to the low morbidity of pCCA patients with lymph node involvement and low surgical resection rate [1, 8-9]. Thirdly, the time of follow-up is not long enough. Fourthly, the chemotherapy regimens of included patients were different between patients. However, we think the result of this study could support the application of adjuvant chemotherapy in these patients. Moreover, the results indicated that lymph node involvement should be considered as a stratifying factor when designing a future randomized controlled trial of perihilar cholangiocarcinoma. There was no randomized controlled trial of adjuvant chemotherapy specifically for hilar cholangiocarcinoma, which we think may be caused by the small number of cases in one single center. Different centers could

cooperate to carry out clinical research about adjuvant chemotherapy for hilar cholangiocarcinoma in the future.

In conclusion adjuvant chemotherapy may be able to improve the survival of perihilar cholangiocarcinoma patients and those patients with lymph node involvements. Further prospective randomized studies are needed to determine the standard chemotherapy regimens.

8. Funding

This work was supported by: The Special Research Foundation of the National Nature Science Foundation of China (grant number 81972255); Grant from Sun Yat-sen University Clinical Research Project 5010 (grant number 2018008).

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