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Original Article

Study on clinical effects and prognosis of Bismuth II and III hilar cholangiocarcinoma treated by small-scale hepatectomy combined with new-type hepatoportoenterostomy

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Abstract: Objective: To study the effects and prognosis of Bismuth II and III hilar cholangiocarcinoma treated by small-scale hepatectomy combined with new-type hepatoportoenterostomy. Methods: A total of 48 patients were randomly divided into standard therapy group (conventional radical hepatectomy) and experimental group (small-scale hepatectomy combined with new-type hepatoportoenterostomy) by computer-generated random number table method with 24 patients in each group. The basic information, postoperative complications, one-year, three-year and five-year survival rates in two groups were observed and compared; the median survival time in two groups was compared by survival analysis; the influencing factors of patients' survival time were explored by Cox regression analysis. Results: In experimental group, operative time, intraoperative blood loss and blood transfusion volume were less than those in standard therapy group (all $P<0.05$); the incidence of postoperative complications (8.33%) was lower than that in standard therapy group (41.67%, $P=0.008$); the survival rates in one-year ($P=0.018$), three-year ($P=0.029$) and five-year ($P=0.020$) as well as the median survival time ($P=0.014$) in experiment group were higher than those in standard therapy group. Cox regression analysis found that operative method was an independent factor that affected survival rate of patients ($P=0.002$, HR=101.75, the 95% confidence interval was (0.027, 0.554)). Conclusion: Small-scale hepatectomy combined with new-type hepatoportoenterostomy could reduce operative complications and improve postoperative survival rate.

Keywords: Small-scale hepatectomy, hepatoportoenterostomy, hilar cholangiocarcinoma

Introduction

Hilar cholangiocarcinoma, a kind of malignant tumor, is difficult to detect at early stage [1]. Most patients were confirmed when it has developed to middle and late stages [2, 3]. This disease is difficult to be treated by operation and its treatment effects are not satisfactory, because there are lots of blood vessels at hepatic portal, and surrounding hepatic tissues and lymph nodes are easily affected [4-6]. According to study reports, the prognosis of hilar cholangiocarcinoma treatment was poor and the five-year survival rate after treatment was less than 40% [7]. Small-scale hepatectomy combined with new-type hepatoportoenterostomy reduced the incidence of complications such as hepatic failure, biliary fistula and biliary tract infection. Besides, it was significantly better than large-scale hepatectomy in less hospitalization costs and less blood loss.

In the study, small-scale hepatectomy (segments of liver resection ≤3) combined with new-type hepatoportoenterostomy was used to treat Bismuth II and III hilar cholangiocarcinoma, and it achieved favorable clinical effects.

Materials and methods

General information

The study was approved by Ethics Committee of our hospital and informed consents were signed by patients or their families. Patients with Bismuth II and III hilar cholangiocarcinoma

Table 1. Assignment of each variable

Variable	Factor	Case
X1	Age	
	<50 years	24
	≥50 years	24
X2	Gender	
	Male	27
	Female	21
X3	Course of disease	
	<1 year	8
	≥1 year	40
X4	Bismuth type	
	Bismuth II	42
	Bismuth III	6
X5	Operative method	
	Standard therapy group	24
	Experimental group	24

who underwent operative treatment in our hospital from June 2010 to January 2012 were selected as study subjects. Inclusion criteria: Patients who met diagnostic criteria of hilar cholangiocarcinoma and the diagnosis was confirmed by imaging examination, laboratory examination and clinical examination of attending physicians; patients with Bismuth II or III, type III including IIIa and IIIb; patients with hilar cholangiocarcinoma, but without other diseases; patients who were willing to cooperate with us to complete the study. Exclusion criteria: Patients with mental illness; patients who failed to cooperate during follow-up period; patients who had history of hereditary disease, congenital heart disease and severe inflammation. A total of 48 patients were randomly divided into experimental group and standard therapy group with 24 patients in each group.

Treatment method

Patients in standard therapy group were treated with conventional radical operation. In other words, cancer lesions and gallbladder were removed simultaneously during operation. Then, the bile duct and jejunum were performed with Roux-en-Y anastomosis [8].

Patients in experimental group were treated with small-scale hepatectomy (the gall bladder was not removed) according to the lesion range of tumor; selective resection was conducted according to the position of tumor after lesions were totally removed [9]. For patients with Bismuth II, the invasive site was selectively removed according to invasive range of cancer cells [10]. For patients with Bismuth IIIa, their blood vessels were observed; if portal vein or hepatic artery was invaded, it was necessary to remove the invaded site according to the invasion of cancer lesions. In patients with Bismuth IIIb, left hepatic duct and blood vessels were usually invaded; invaded hepatic duct and blood vessels were removed according to the invasion of tumor. The method of anastomosis was to anastomose the two small-scale broken ends [11]. Briefly, closing the two clamps to make sure the broken ends (ready to anastomose) were not reversed. The mesenterium side of upper and lower broken ends were attached with one stitch of interrupted suture on the seromuscular layer by thin silk thread for traction; the opposite margin was also performed with one stitch; hemostatic forceps were used to clamp the two stitches for traction; ligation was not carried out yet. Then 0 catgut was used for interrupted full thickness suture anastomosis at the back walls of anastomotic stoma, with stitch length of 0.3-0.5 cm. After that, the traction lines on both sides of the intestinal canal were ligated. At last, the anterior walls of anastomotic stoma were sutured, starting at the mucosa of one end to complete the endothecium suture. The anastomotic position included the hepatic vessels and hepatic ducts.

Follow-up and observational index

Conventional postoperative treatment was given to patients who were included in the study. Incidence of complications (including infection, biliary fistula, hepatic failure, etc.) one month after operation was observed and counted. Survival data of patients were collected by telephone follow-up, outpatient reexamination, home follow-up and other ways after discharge from hospital. Follow-up was conducted once a month until the death of patients or the end of five-year follow-up period.

Primary observational indexes: incidence of postoperative complications and median survival time.

Secondary observational indexes: one-year, three-year and five-year survival rates.

Table 2. Comparison of basic information in two groups

Group	Standard therapy group (n=24)	Experimental group (n=24)	Statistical value	*P* value
Age (year)	47.95±4.29	49.58±2.39	t=-0.575	0.596
Sex (male/female)	13/11	14/10	χ^2=0.085	0.771
Disease course (year)	1.49±0.24	1.51±0.16	t=-0.12	0.910
Bismuth type			χ^2=0.762	0.383
Bismuth II	20	22		
Bismuth III	4	2		
Pathological type			χ^2=0.851	0.639
Well differentiated	10	8		
Moderately differentiated	8	9		
Poorly differentiated	6	5		
Mucinous carcinoma	0	2		
Nutritional status			χ^2=1.093	0.579
Good	9	10		
Medium	12	13		
Poor	3	1		

Table 3. Comparison of operative time, intraoperative blood loss and blood transfusion volume between two groups ($\bar{x}$ ± sd)

Group	Operative time (min)	Intraoperative blood loss volume (ml)	Intraoperative blood transfusion volume (ml)
Standard therapy group (n=24)	429.6±48.3	988.3±113.6	998.3±114.5
Experimental group (n=24)	303.6±49.6	657.3±103.7	658.8±143.9
t value	2.987	3.725	3.198
P value	0.040	0.020	0.033

Statistical methods

SPSS 17.0 was used for statistical analysis. Enumeration data were expressed as number of cases and percentage; measurement data were represented as mean ± standard deviation. Chi-square test and independent samples t-test were used in comparison of percentage and mean between two groups respectively. Kaplan-Meier survival analysis was used to compare the difference of median survival time between two groups. The difference was statistically significant when P<0.05.

Multifactorial Cox regression model was used to evaluate if surgical method was an independent influence factor of 5-year survival rate. This study selected four basic factors (age (X1), gender (X2), course of disease (X3), and Bismuth type (X4)) and operative method (X5) as initial variables, and the survival situation was regarded as outcome variable, death =1, and survival =0. Other assignments were as follows. The age <50 was assigned 0, and ≥50 was 1; for gender, male was assigned 0, and female was 1; for course of disease, less than a year was assigned to 0, and more than or equal to a year was 1; Bismuth II was assigned 0, and Bismuth III was 1; for operative method, standard therapy group was assigned to 0, and experimental group was 1. See **Table 1**. Stepwise regression method was used for independent variables selection ($\alpha_{introduction}$ =0.10, $\alpha_{elimination}$ =0.15).

Results

Comparison of general information between two groups

Age, sex, disease course, Bismuth types and other general information of two groups were demonstrated in **Table 2**, and all the inter-group comparisons had no statistical differences. In standard therapy group, there were 10 cases of well differentiated adenocarcinoma, 8 cases of moderately differentiated adenocarcinoma and 6 cases of poorly differentiated adenocarcinoma; in experimental group, there were 8 cases of well differentiated adenocarcinoma, 9 cases of moderately differentiated adenocarcinoma, 5 cases of poorly differentiated adenocarcinoma and 2 cases of mucinous carcinoma; the difference of pathological types between two groups was not statistically significant (P=0.639). See **Table 2**.

The difference of preoperative nutritional status between two groups had no statistical significance (P=0.579), details were as follows: standard therapy group (good nutritional status, n=9; moderate nutritional status, n=12;

Table 4. Comparison of postoperative complications between two groups (n, %)

Group	Infection	Biliary fistula	Hepatic failure	Others	Total
Standard therapy group (n=24)	5 (20.83)	3 (12.5)	1 (4.17)	1 (4.17)	10 (41.67)
Experimental group (n=24)	1 (4.17)	0	0	1 (4.17)	2 (8.33)
χ^2 value	3.048	3.200	1.021	1	7.111
P value	0.081	0.074	0.312	1	0.008

Table 5. Comparison of survival rates between two groups (n, %)

Group	1-year survival rate	3-year survival rate	5-year survival rate	Median survival time (month, $\bar{x}$ ± sd)
Standard therapy group (n=24)	19 (79.17)	13 (54.17)	9 (37.50)	26.49±3.14
Experimental group (n=24)	24 (100)	20 (83.33)	17 (70.83)	42.38±4.39
Statistical value	5.581	4.752	5.371	1.643
P value	0.018	0.029	0.020	0.014

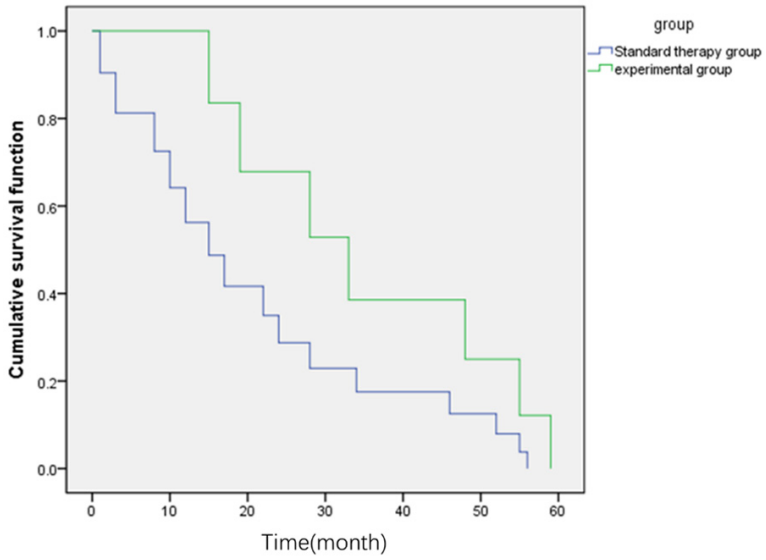

Figure 1. Medium survival time of two groups

poor nutritional status, n=3); experimental group (good nutritional status, n=10; moderate nutritional status, n=13; poor nutritional status, n=1). The data were with homogeneity. See **Table 2**.

Comparison of operative time, intraoperative blood loss and blood transfusion volume between two groups

The operative time, intraoperative blood loss and blood transfusion volume in standard therapy group were significantly higher than those in experimental group with significant differences (all P<0.05). See **Table 3**.

Comparison of postoperative complications between two groups

The incidence of postoperative complications in experimental group (8.33%) was significantly lower than that in standard therapy group (41.67%). See **Table 4**.

Comparison of survival rates between two groups

One-year, three-year and five-year survival rates as well as median survival time in experimental group were higher than those in standard therapy group (χ^2=1.643, P=0.014). See **Table 5** and **Figure 1**.

Multivariate analysis of factors influencing survival rate of patients

Multi-factor regression analysis showed that age, gender, course of disease and Bismuth type were not independent factors that affected survival rate of patients (P=0.648, P=0.934, P=0.205 and P=0.969). Nevertheless, operative method was an independent factor that affected survival rate of patients (P=0.002, HR=101.75, the 95% confidence interval was (0.027, 0.554)). So, it could illustrate that the differences of prognosis in this study mainly resulted from operative methods. The difference was significant with P<0.05. See **Table 6**.

Table 6. Multi-factor regression analysis of operative method

	B	Standard error	Wald	Degree of freedom	Significance	Exp (B)	95.0% confidence interval for Exp (B)	
							Lower limit	Upper limit
Operative method	4.623	4.198	1.212	1	0.002	101.751	0.027	0.554

Discussion

In 1965, hilar cholangiocarcinoma was first proposed by Klatskin and it was also called Klatskin tumor, which accounted for 55% to 75% of extrahepatic cholangiocarcinoma [11]. Hilar cholangiocarcinoma occurred from sites above the openings of cystic duct to sites between the beginnings of left and right hepatic ducts. It mainly invaded common hepatic duct, the bifurcation of common hepatic duct as well as left and right hepatic ducts. The features of hilar cholangiocarcinoma including location, infiltrative growth and closely related to hepatic hilar blood vessels caused to atypical clinical presentation, great operative difficulty and poor prognosis. Therefore, treatment and prognosis results of different operative methods on hilar cholangiocarcinoma were compared and analyzed in the study, aiming to investigate that shorter operative time, less postoperative complications and higher postoperative survival rate could be achieved by using small-scale hepatectomy combined with new-type hepatoportoenterostomy.

The study found that operative time, intraoperative blood loss and blood transfusion volume in experimental group were shorter and less than those in standard therapy group, with statistically significant differences, which was consistent with the study results of Wang et al., suggesting shorter operative time, less tissue injury and blood loss in experimental group [12]. But in standard therapy group, operative procedures were more difficult and time-consuming with long exposure time of intraperitoneal organs, which caused more blood loss of patients.

The study found that postoperative complications in experimental group were significantly decreased when compared with standard therapy group. The reason might be the scale of radical resection in standard therapy group was relatively large; remaining tissues and organs were under greater pressure. So, the overall physical quality and function of patients were decreased, and the incidence of complications increased. Besides, survival rate in standard therapy group was low from the long-term prognosis aspect. The possible reason was that large scale of resection led to remaining tissues and organs could not meet the needs of normal human activities. According to study reports of Nagakawa et al. and Kimura et al., the range of tissue injury of radical surgical resection was large with slow postoperative recovery and comparatively high incidence of postoperative complications, which was consistent with the results of this study [13, 14].

We also found that small-scale hepatectomy combined with new-type hepatoportoenterostomy could improve long-term survival rate of patients. However, some study reports about hilar cholangiocarcinoma regarded radical surgery as preferred surgical treatment method of Bismuth II and III [15, 16]. In previous clinical operation, surgical treatment could not be conducted if tumor lesions invaded blood vessels, but with the progress of medical technology, the surgery now can be implemented in such cases. In experimental group of this study, tumor lesions that invaded blood vessels were removed accordingly, and anastomosis was performed for blood vessels, so that the tumor lesions could be completely removed, and the surrounding blood supply would not be affected [17]. In general, small-scale resection was minimal resection after careful assessment of the tumor lesion range. The principle of new-type anastomosis was anastomosis of same tissues (anastomosis of blood vessel and blood vessel, anastomosis of hepatic duct and hepatic duct); in this way, anastomosis could achieve the best effect, and the completeness and function of each tissue and organ were ensured [18]. The prognosis of survival rate in patients was significantly improved; this study also found that one-year, three-year and five-year survival rates in experimental group were significantly higher than those in standard therapy group.

Operative method, pathological type, Bismuth type and infiltration condition of hepatic portal

vein were risk factors that affected survival rate and prognosis of patients with hilar cholangiocarcinoma according to the study of He et al. [19]. In this study, there was no statistically significant difference in comparisons of age, sex and pathological type between two groups. Cox regression analysis suggested that operative method was an independent risk factor that affected survival rate, and when compared with radical resection, postoperative complications in patients with Bismuth II and III hilar cholangiocarcinoma were significantly reduced when they were treated with small-scale hepatectomy combined with new-type hepatoportoenterostomy, and their survival rates were significantly increased. Study of Marubashi et al. found that serum CA199 indicator could also be used as an indication for the evaluation of prognosis [20].

The sample size of this study was small; some clinical data were incomplete or with poor accuracy; selection bias might exist; follow-up was failed in a small part of patients, which influenced the observation and comparison at terminal time. So, further improvement and analysis is needed.

In summary, small-scale hepatectomy combined with new-type hepatoportoenterostomy for the treatment of hilar cholangiocarcinoma can preserve the original tissues and organs as well as the completeness of function in maximum, increase body's ability of repair, play an important role in reducing the incidence of complications, improve the prognosis of patients at large extent, prolong long-term survival rate of patients and improve the quality of life of patients.

Disclosure of conflict of interest

None.

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