

Value of Postoperative Radiotherapy in Locally Advanced Hepatic Hilar Cholangiocarcinoma

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Abstract Objective To evaluate the outcome of postoperative radiotherapy (RT) in locally advanced hepatic hilar cholangiocarcinoma. **Methods** Forty-four patients who had positive margin after surgery were divided into two groups, one group of 28 patients were treated with postoperative radiotherapy (S+RT, with a median dose of 50 Gy, range 45~62 Gy), and the other group of 19 cases were not treated with postoperative radiotherapy (S, 19 patients). The median follow-up was 30 months (ranged 4~113). **Results** The overall 5-year survival rate was 28%, with a median survival time of 19.6 months for the whole group. The 5-year survival rate of S+RT group and S group was 34% and 14%, with a median survival time of 29 and 10 months, respectively ($P=0.015$). The complication rate was 11% in either group. **Conclusion** Postoperative radiotherapy obviously prolongs the survival in hepatic hilar cholangiocarcinoma patients with positive microscopic surgical margins. Radiation toxicities are well tolerated.

Key words Bile duct neoplasms; Hepatic surgery; Radiotherapy; Prognosis

Hilar cholangiocarcinoma (proximal bile duct) is a malignant tumor located in the area of right, left hepatic duct and its confluence, which account for about 58%~75% of extrahepatic bile duct cancer^[1], the confluences malignant tumor of right and left hepatic duct is also called Klatskin tumor. At present, surgical excision is the only treatment for the radical cure of cholangiocarcinoma, but the occurrence of the disease is obscure and final diagnosis was made in advanced stage usually, in addition the anatomic relation is complicated in hepatic hilum, so the surgical resection rate and radical rate are low^[2]. With the extended radical resection used in hilar cholangiocarcinoma in recent years, for the reason of the residual tumor, the recurrence rate increased followed the increased resection rate. So, eradicating the residual tumor is the key point to enhance therapeutic efficacy. In this study, in order to expound the effect of radiotherapy for tumor bed after extended radical resection, 47 patients with stage IV hilar cholan-

giocarcinoma who had positive margin after surgery were treated with or without postoperative radiotherapy for retrospective study.

MATERIALS AND METHODS

Patient population

From March 1992 to December 1997, 76 patients with stage IV A (staged by TNM: T3N0-2M0) hepatic hilar cholangiocarcinoma underwent radical surgery were selected, and all of them were diagnosed as adenocarcinoma by pathological section after surgery. 29 of them had negative and 47 of them had positive in pathological section of surgery margin. Among the 47 patients, 20 females and 27 males, the average age of them was 61.4 years old (from 24 to 72), 28 patients were treated by postoperative (S+RT) radiotherapy and the other 19 patients underwent surgery only (S).

Preoperative therapy

Piliary decompression was performed on all the patients before surgery, and 30 patients of them were made decompression by percutaneous transhepatic biliary drainage (PTBD), others undergone the endoscopic ret-

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rograde biliary drainage (PTBD).

Exposure system

External irradiation with 6~15 MV X-ray was performed from 2 weeks to 4 weeks after surgery, the target site was determined by binding of silver clip labeling during operative and CT or(and)MRI preoperative, and added the lymph node of hepatic hilum, paraaortic, para-pancreatic into target site when found metastasis in it. Conventional irradiation technique was used or changed the angle to avoid the spinal cord. Irreglular shield was made or Multi Leaf Collimator was used to block irradiation of normal tissue efficiently. DVH of spinal cord was used to monitoring dose distribution in spinal, as the dose in spinal less than 36 Gy, reduced field or changed field to avoid spinal and control the irradiation in it less than 44 Gy. The target site was irradiated with 44-45 Gy, 1.8-2.0 Gy per time, one day apart, 5 times per week, and median dose was 52 Gy.

Follow-up visit

Median follow-up period after surgery was 30 months (from 4 months to 113 months).

Statistical methods

Kaplan-Meier was used to calculate survival rate, Logrank was used to analyze deviation, and Cox regression analysis was used to analyze prognostic factors.

RESULTS

5 years survival rate

To Feb, 2003, 47 patients, 5 years survival rate was 28%, and median survival time was 19.6 months. In S+RT group, 5 years survival rate and median survival time were 34%, 29 months and they were 14%, 10 months in the S group respectively, the difference was significant in statistics ($P=0.015$). In 29 patients with negative pathological sections, the 5 years survival and median survival time was 36% and 30.6 months respectively, compared with S+RT groups had no difference ($P=0.720$), and had significant difference with S groups ($P=0.014$).

Prognostic factors

Cox regression analysis indicated that the positive or negative for pathological sections and the postoperation radiotherapy for positive pathological section had significant effect for survival (table 2).

Postoperative complications and radiation reaction

The postoperative complications incidence in surgery group and postoperation radiotherapy group were 10.5% and 10.7% respectively, and had no statistically significant. To acute reaction, evaluated by PROG, there was no patient with grade 3 and 4 in postoperative radiotherapy group, and 14 patients with grade 2 (5 for stomachache and diarrhea, 14 for nausea and emesis). Radiation reaction in advance stage: during follow-up

Table1 The characteristic of 47 hilar cholangiocarcinoma in stage IV

Characteristic	S group	S+R group	χ^2	P
patients	19	28		
Sex			0.00	0.960
Male	11	16		
Female	8	12		
Age (year)	59.4±9.1	61.8±7.4	1.00#	0.323
Bismuth typing			1.10	0.776
I	0	1		
II	3	5		
III	11	13		
IV	5	9		
Pathological grading			0.10	0.948
G1	10	16		
G2	5	7		
G3 or G4	4	5		
Lymph node metastasis			0.54	0.762
N0	7	13		
N1	4	6		
N2	8	9		
Lobectomy of liver			0.29	0.593
Yes	13	17		
No	6	11		

was "t" value

Table2 The Cox regression analysis

Correlation factor	β	χ^2	P
Residual in cutting edge	1.703	8.66	0.003
Radiotherapy	0.849	4.56	0.033

period, 15 patients had gastrointestinal bleeding and 10 of them were diagnosed as tumor recurrence, 5 patients had roentgen ulcer. There was 1 patient in S+RT group who had obstructive jaundice after 3 years of postradiotherapy, was complete remission after cholangiojejunostomy, and had not detected tumor recurrence in pathology.

DISCUSSION

The resection rate of hepatic hilar cholangiocarcinoma was from 5% to 47%^[2]. In recent years, this rate reached 64.1% with the development of the operative techniques and method^[3]. However, the long-term survival rate of the patients was not significantly improved, because the anatomic structure of the hepatic hilum is very complex and the ambitus of the tumor is widely encroached. The extirpation rate of extended radical surgery for locally advanced hilar cholangiocarcinoma is not high enough. Over enlargement of the range of resection will result in complications and the increase of operative mortality. Schoenthaler *et al.*^[4] reported that the negative margins in patients undergone total resection was only 11%. It was reported by Todoroki *et al.*^[4] that the postoperative residual rate of Klatskin tumor in IV stage reached 97% (61/63) although the ranges of the operation were enlarged. Our study showed that the postoperative residual rate was 61.8% in 76 patients with hilar cholangiocarcinoma in IV stage. There is no randomization data at present about the postoperation radiotherapy for patients with positive margins, it was considered to be useless of radiotherapy after total correction^[6]. However, most retrospective data shows that postoperation radiotherapy plays a significant role for the survival of patients. Gonzalez *et al.*^[7] reported that the median survival times of patients with or without postoperation radiotherapy were 19 months and 8 months, respectively, and their 2-year survival rate was 42% and 18%, respectively ($P = 0.001$), and the median survival times reported by Schoenthaler *et al.*^[4] were 21.5 and 11.0 months, respectively ($P = 0.011$). By summarizing the experiences of Tsukuba University in the past 23 years (1976–1999), Todoroki *et al.*^[5] found that the 5-year survival rate in patients undergone postoperation

radiotherapy ($n = 17$) was 39%, which was significantly higher than that (13%) in patients undergone operation alone ($n = 13$, $P < 0.05$). Our results are similar with those reported in literatures, and it is suggested by COX regression analysis that postoperation radiotherapy affects the survival rate ($P = 0.033$). Do patients with negative margins need postoperation radiotherapy? Kim *et al.*^[8] reported that the 5-year survival rate and the median survival times in patients with negative and positive margins were 36% and 26 months, 35% and 24 months, respectively ($P = 0.780$), and this result is similar with ours. It is indicated by most retrospective data that postoperation radiotherapy can prolong the survival time of patients with positive margins but it is not valuable for those with negative margins.

Excess enlargement of the range of resection will result in complications and the increase of operative mortality. It was reported by Todoroki *et al.*^[5] that the mortality rates within 30 days after operation were 10.5% and 0% respectively in patients undergone enlarged radical cure and in those undergone postoperation radiotherapy. According to the RTOG standard, the common early reactions are nausea, vomiting, abdominal pain and diarrhea which were not more than the second degree with an incidence rate of 28~68%^[8,9], and those reactions can be relieved by handling with the symptoms. As to those reactions above the third degree, radiotherapy should be stopped and the schedule should be modified. In our study, no reactions above third or fourth degree were found, among the patients with reactions of the second degree, 5 of them were with abdominal pain and diarrhea and 14 of them were with nausea and vomiting. The complications at the advanced stage are mainly gastrointestinal bleeding and stenosis. In our study, the incidence rate of roentgen ulcer was 17.9%. Buskirk *et al.*^[10] reported that the incidence rate of gastrointestinal bleeding was 21%. Flickinger *et al.*^[11] found that the certain chance of duodenobulbar ulcer with symptoms within two years after operation was 29%, which may be due to the radiation dose, methods and the location and size of the tumor. They also found that the incidence rate of gastrointestinal ulcer was increased in patients whom were given a dose more than 55 Gy. Other studies suggested that the total tumor dose was not a risk

factor. For example, Schoenthaler *et al.*^[4] reported that complications in patients with tumor of distal bile duct were more than those with tumor of proximal bile duct. Stenosis of bile duct is mainly due to the operation as well as to tumor, and the incidence rate of stenosis increases with the prolongation of life span. In our study, one patient was found to have obstructive jaundice within three years after radiotherapy. Stenosis of stoma was found in the patient by retrograde cholangiography, and the symptoms were relieved by cholangiojejunostomy and recurrence of tumor was not found with pathology. Yoshihiro *et al.*^[12] reported that one patient undergone radical surgery and postradiotherapy was found to have radioactive stenosis of bile duct within 11 years, which was confirmed with pathology. The mechanisms involved was that fibroplasia and thickening of the bile duct wall after the injury of the submucous blood vessel resulted in the stenosis of lumens.

Postoperative radiotherapy obviously effects the survival of patients in locally advanced hepatic hilar cholangiocarcinoma. Because the incidence rate of hepatic hilar cholangiocarcinoma is low and the equipments and technical levels of the medical therapy units are irregular, polycentric cooperation should be strengthened in order to perform the study of prospective randomization, and further identify the indication of postoperative radiotherapy. The cooperation of oncosurgery, medical oncology, and radiation oncology are certainly needed to improve the long-term therapeutic efficacy to the patients.

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