Predictive Factors Relating to Tumor-Free Survival Rates and the Clinical Management of Small Cancer of the Liver after Hepatectomy

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OBJECTIVE To investigate factors associated with tumor-free survival rates and methods of treatment for small cancer of the liver.

METHODS A total 105 cases of small cancer of the liver (maximum diameter ≤5 cm in a solitary nodule or the sum of maximum diameters in double nodules ≤5 cm) were studied between 1983 and 2000. Patients were divided into an invasive group (primary tumor accompanied by any one or more of the following features: satellite nodules, venous invasion, adjacent organ involvement and double nodules) and a non-invasive group.

RESULTS Three patients died from liver failure within 30 days after operation and 100 of the other patients were followed-up. The 1, 3, 5, 7 and 10-year survival rates after the first resection were 95.8%, 64.8%, 48.8%, 39.4% and 34.3% respectively. The main factors influencing tumor-free survival after radical resection were tumor size, presence or absence of satellite nodules or vascular invasion, the incisal edge, the UICC TNM stage, and the number of tumor nodules. The survival rate of the invasive group was significantly lower than that of the non-invasive group. Tumors of fifty-one cases recurred after radical resection. For the recurrent patients, treatments included a repeated resection for 17 cases, transcatheter artery chemotherapy and embolization (TACE) for 18 cases and no treatment or chemotherapy for 18 cases. The 1, 3 and 5-year survival rates after repeated hepatectomy for recurrent patients were 82.4%, 51.3% and 34.2% respectively, which were higher than those in the non-resected group.

CONCLUSIONS Factors that influence postoperative tumor-free survival rate were concluded to be early stage detection, tumor invasive or non-invasive traits and the incisal edge. For the recurrent patients, active treatment especially a second hepatectomy, is safe and feasible, and can improve the 5-year survival rate by 10 percent. The categorization of invasive and non-invasive groups for small cancer of the liver is useful in clinical work. For patients with invasive small cancer of the liver, postoperative close surveillance and follow-up is the key to improve the prognosis.

KEYWORDS: small cancer of the liver, tumor-free survival, prognosis.

In the present study, postoperative tumor-free survival rates were employed as the evaluating standard to explore the factors influencing prognosis of small cancer of the liver, so as to formalize proper clinical management.

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MATERIALS AND METHODS

Clinical materials

A Total of 116 patients with small cancer of the liver who were admitted to our department between January 1983 and December 2000 were included in this study. Among these, 105 (male =94) underwent surgical resection. The diagnostic standard for small cancer of the liver was as follows: the maximal diameter ≤5 cm in a solitary nodule or the sum of maximal diameters in double nodules ≤5 cm [1].

The mean age for the 105 selected patients was 52.4 ±11.4 years, ranging from 10 to 71. HBV biomarker tests for 104 cases resulted in a HBsAg positive rate of 76.9% (80/104). Thirty-five cases (65.7%)were AFP positive(>20 ng/ml).Among all the AFP positive patients, 32 cases had 21-400 ng/ml (31.4%), and 35 cases had > 400 ng/ml (34.3%).

There were 96 cases with a solitary nodule measuring ≤5 cm in maximal diameter (of whom 36 cases were ≤3 cm) and 9 cases had the sum of maximum diameters ≤5 cm in double nodules. Sixty-eight cases had a tumor in the right lobe, 32 cases in the left lobe, 3 cases in the caudate lobe and 2 cases with one nodule in both left and right lobes. Hemihepatectomy was performed in 8 patients (one case right hepatectomy); hepatic segmentectomy (including combined segments) was performed on 32 cases (12 cases of whom received a left lateral lobectomy); 65 cases underwent subsegmental or focal resection. Four of the 105 cases underwent palliative resection and 3 failed to become AFP negative. One was found to have residual satellite nodules on the resection edges. Three patients died of liver failure during the first month after operation. At the operations for 18 cases, catheters were detained in the gastro-omental vessels and subcutaneous pumps were implanted to carry out sequential focal assistant chemotherapy.

Pathological examinations

There were 98 hepatocellular carcinoma cases, 4 cholangiocarcinoma cases and 3 mixed carcinoma cases. Satellite nodules were seen in 8 cases. Blood vessel infiltration was seen in 7 cases, 4 in whom tumor cells were discerned in hepatic sinusoids. Two cases were accompanied by adjacent organ invasion, one in the gallbladder and the other in the right adrenal gland. Peri-tumor tissue histological examination: 77 cases involved liver cirrhosis, accounting for 73.3%.

Statistical analysis

All data were analyzed using SPSS 8.0 for windows software [2]. Survival curves were evaluated by the Kaplan-Meier method and compared by a Long-rank test. The tumor-free survival rate was defined as the time relapsed between the date of surgical operation and the date of death or the date of the latest follow-up visit[3].

RESULTS

Of the 102 cases of which follow-up were attempted, 2 cases were lost by the end of the year 2000. The follow-up rate was 98.1%. The median follow-up time was 53 months (1~174 months), 93.2% with a follow-up period over 1 year. During the follow-up period, 49 cases had died and 51 cases were alive(5 of whom were tumor-bearing survival). Thirty-two cases survived for over 5 years and 1 case was still alive 14 and a half years after their operation. The total postoperative 1, 3, 5, 7 and 10-year survival rates were 95.8%, 64.8%, 48.8%, 39.4% and 34.3% respectively. For the radical resectioned patients, 1, 3, 5, 7 and 10-year survival rates and tumor-free survival rates were 97.8%, 68.7%, 51.8%, 44.7%, 36.4% and 80.3%, 48.6%, 40.6%, 37.3%, 26.7%, respectively.

Eighty-eight cases with a solitary nodule were treated with a radical resection. Tumor size, presence or absence of satellite nodules, vascular invasion and resection edges (≥1 cm or <1 cm) were statistically associated with the prognosis; sex, hepatitis history, the method by which the tumor was detected (by physical examination or obvious symptoms), tumor site and liver cirrhosis were not statistically associated with the prognosis. In 96 radical resection cases, tumor-free survival rates were significantly associated with the nodular amount and the UICC TNM stage, in a manner that was highly statistically significant. So, in the present study, small cancer of the liver was further divided into an invasive group (primary tumor accompanied by any one or more of features such as: micro-satellite nodules, venous invasion, adjacent organ involvement and double nodules) and a non-invasive group. The 2 groups showed significantly statistical differences in prognosis (Table 1).

During the follow-up period, 51 radically-resectioned patients had a recurrence, the rate being 53.1% (51/96). Surgical procedures were repeated for 17 recurrent cases, one died of upper gastro-intestinal bleeding one month after the repeated operation, one suffered from a biliary fistula and died 4 months later.

Table 1. Relation of factors with the survival rate

Classification	Cases	Tumor-free survival rate(%)				Median tumor-free survival time 95%CI(month)	χ^2	*P* value
		1-year	2-year	3-year	5-year			
Tumor size								
≤3 cm	36	82.3	68.5	64.7	64.7	119(0-179)		
3.1-5 cm	52	82.0	65.0	48.1	36.8	31(16-46)	5.02	0.0359
Microsatellite nodules								
Absent	82	80.7	66.0	56.8	49.2	52(13-91)		
Present	6	50.0	0	0	0	20(7-33)	4.61	0.0317
Venous invasion								
Absent	81	80.5	66.7	57.0	48.9	52(8-96)		
Present	7	57.1	42.9	28.6	28.6	18(0-39)	3.84	0.0501
Tumor number								
Single	88	78.5	64.7	54.3	47.0	76(19-81)		
Double	8	50.0	45.0	0	0	21(18-22)	4.99	0.025
UICC TNM stage								
I	11	100.0	87.5	87.5	87.5	119(72-140)		
II	63	82.2	68.9	56.8	47.0	50(13-87)		
III	17	58.8	39.7	13.2	13.2	16(8-30)		
IV	5	50.0	0	0	0	7(3-19)	18.80	0.0003
Cutting margins								
≥1 cm	52	84.4	71.1	61.3	58.5	96(50-188)		
≤1 cm	36	69.7	54.5	41.5	20.8	28(12-44)	5.66	0.0174
Invasive characteristic								
Negative	73	84.2	71.2	60.8	52.1	85(65-105)		
Positive	23	59.1	35.8	11.9	11.9	23(15-25)	15.4	0.0001

The 1, 3 and 5-year cumulative survival rates were 82.4%, 51.3% and 34.2% for the other 15 cases. TACE treatment was employed for 18 cases with 1 and 2 -year survival rates of 48.3% and 16.1% respectively. There were 16 cases who received no treatment or merely chemotherapy, followed by 1 and 2 -year survival rates of 43.7% and 6.25% respectively. No cases survived for more than 3 years in the latter two groups. For recurrent cases, the reoperated group showed better prognosis than the non -operated group. The statistical difference was significant (χ^2 =14.74, *P*=0.0006).

DISCUSSION

When effects of secondary treatment after a recurrence is excluded, a tumor recurrence can provide information regarding the biological characteristics of the primary tumor and also in evaluating the effects of the initial treatment to the prognosis. In this study, 6 factors were found to be associated with the prognosis as follows: early detection (including tumor size, UICC TNM stage), invasive or non -invasive traits (satellite nodules, tumor nodule amount, vascular invasion and adjacent organ involvement) and the incisal edge.

Active postoperative combined therapy, especially repeated resection, can improve the overall prognosis for patients. Paguet *et al.*[4] reported a study of 34 cases with single-nodular cancer of the liver with a diameter ≤5cm and the operation mortality was 11.8%. In follow-up for 11 years, 18 cases died (1.5~10 years), and the 5 and 10-year survival rates were 50.0% and 34.0% respectively. Factors influencing prognosis included: being HBsAg positive, liver function grade, blood transfusion, histological grading of tumor, vascular invasion, satellite nodules and mitotic index. Zhou *et al.*[5] reported their experience with one -thousand hepatectomies for small cancer of the liver. Using a COX model multi-factor analysis, the results implied that γ-GT, liver cirrhosis, tumor number and portal vein tumor thrombus influenced postoperative

prognosis significantly. These researches cited have suggested that three factors influenced prognosis for patients with small cancer of the liver: liver function reserve of the patients, early detection and biological characteristics of the tumor and whether proper treatment was administrated.

Previous studies showed a 5-year postoperative recurrent rate as high as 40.0% ~60.0% . Of these, 70.0% of the recurrent sites were limited intrahepatically [6]. In our study, the postoperative recurrent rate was 53.1% after radical resection and 90.0% after an intrahepatic procedure. Operations remained the predominant treatment for resectable recurrent liver cancer [7]. Five years after radical resection, the overall survival rate was 51.7% ; the tumor-free survival rate was 40.6% . Repeated operations had a complication rate of 11.8% (2/17), no liver failure occurred, suggesting that active postoperative treatment, especially repeated resection, was safe and effective, and could improve the 5-year survival rate by over 10.0%.

Thorough imaging examination, careful and comprehensive exploration at operation and real time type B ultrasound application to avoid residual tumor tissue are basic preoperative methods to prevent a recurrence. However, imaging examinations have their limitations, for space-occupying lesions in the liver because of resolution. Even if DSA is applied, only tumors of the size of 0.5 cm×0.6 cm can be detected[8]. Minute small cancer of the liver and micro-portal vein thrombi are difficult to detect using present imaging techniques [9]. Thus some readily diagnosed cases are not small cancer of the liver at all. Tumor residues are the root cause of early recurrence after a surgical operation. It is critical for the choice of a repeated operation to verify whether the recurrent tumor is caused by a monofocal heterochronia or tumor metastasis. The recurrent time and compulsory radiological examinations also may be helpful in this regard. Arii *et al.* [10] reported that postoperative-infusion chemotherapy helped to prolong the postoperative survival time with a 5-year survival rate of 48.7 compared to 19.5% in the control group. Li *et al.*[11] reported their results based on 81 primary liver cancer patients who received an operation. There were two groups treated with chemotherapy in their study. A postoperative group treated with combined transcatheter artery chemotherapy and embolization (TACE) and a group treated with portal vein chemotherapy (PVC) plus TACE. When compared with a group receiving no chemotherapy, the authors found that the TACE + PVC group and the group only receiving TACE had a lower 1-year recurrent rate than the group not treated with chemotherapy (4.4%, 6.8% and 14.3%), and the TACE+PVC group showed a remarkably lower 2-year recurrent rate than both the group only receiving TACE and the non-specially treated group (8.7%, 20.0%, 28.6%). The type of procedures used was not associated with the long-term postoperative recurrent rate, which implies that TACE and PVC alone decreased the early postoperative recurrent rate for liver cancer. In our study, 18 cases were treated with regional chemotherapy using catheters detained in the gastro-omental vessels (artery or vein) or using implanted subcutaneous pumps. Initial results revealed that the 1-year recurrent rate was lower for the pump-implanted group than for the non-chemotherapy group (16.8% versus 31.5%); the 2-year recurrent rates were 38.9% versus 42.8% . There were no statistical differences in terms of improvement of the tumor-free survival rate. Based on these findings, we conclude that postoperative TACE therapy is more effective for invasive and occult small cancer of the liver, and prolongs the tumor-free survival rate.

The diagnostic criteria for small cancer of the liver have been different in various studies [1, 12, 13]. Okuda *et al.*[12] reported small cancer of the liver as: monofocal tumor with a diameter not exceeding 4.5 cm or multinodular tumors (not exceeding four) with a maximal diameter not exceeding 3.5 cm. Tang *et al*[13] proposed the following criteria: the maximal diameter ≤5 cm in a solitary nodule or the sum of maximal diameters in double nodules ≤5 cm. The pathological diagnostic standard for a small cancer of the liver is: the maximal diameter ≤3 cm in a solitary nodule or the sum of two adjacent nodules ≤3 cm [1]. The UICC TNM suggests T1 stage liver cancer should be defined at the diameter of 2 cm [1]. In recent years, molecular pathological studies have shown that liver cancer measuring less than 3 cm exhibits more features of small cancer of the liver, such as its expansive growth, presence of capsules, vascular invasion, rare intrahepatic metastasis and a diploid-dominant DNA concentration [14, 15]. The present study showed that the outcome for monofocal tumors ≤3 cm was obviously better than tumors ≤5 cm. So, a solitary nodule ≤3 cm in diameter as a standard for small cancer of the liver may be a more optimal size to use for current liver cancer research and treatment [15]. The latest clinical liver cancer staging standard suggested by the 8th National Liver Cancer Learning Session also

defined 3 cm, monofocal, no vascular tumor thrombi as the criterion of a Ia stage (Guangzhou, September 2001). Data presented in our study demonstrated that small cancer of the liver showed distinct differences in prognosis, with a 5-year tumor-free survival rate ranging from 64.7% for small cancer of the liver to 11.9% for an invasive group and to 0% for double-nodular IV stage small cancer of the liver. Those results indicate that for solitary-nodular ≤3 cm diameter small cancer of the liver, there is a problem of staging variance and tumor heterogeneity [16]. Though it is far from sufficient to define small cancer of the liver merely by diameter measurements, however much comprehensive or complicated clinical diagnostic criteria may be obscure for practical clinical application. We suggest dividing small cancer of the liver into two subtypes: non-invasive favorable-prognostic and invasive-poor prognostic seems to be appropriate. Preliminary studies have indicated that compared with the non-invasive group, the invasive group possessed higher p16 and p21 oncogene mutation rates, which were 64.3% versus 10.0% and 43.2% versus 16.7% respectively. The invasive group showed poorer prognosis [17]. In conclusion, for patients with poor-prognostic small cancer of the liver, active postoperative combined therapy should be the key to improve the tumor-free survival rate.

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