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Original Article

Single factor and multi-factor analysis of survival and recurrence after primary hepatocellular carcinoma operation

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Abstract: Objective: We aimed to analyze the single factor and multi-factor survival and recurrence after radical operation for primary hepatocellular carcinoma (PHC). Methods: A total of 115 PHC patients treated with radical operation for PHC in our hospital were selected as subjects of study to analyze the influencing factors of recurrence within 2 years (early recurrence) and post 2 years (late recurrence) to explore the postoperative survival of patients. Results: The recurrence rate of the 115 PHC patients in this group was 71.30%, 4 years after operation. The early recurrence rate and late recurrence rate were respectively 49.57% and 21.74%. The disease-free survival (DFS) of 115 patients was respectively 64.35%, 38.26% and 22.61% at 1 year, 2 years and 4 years after operation and the overall survival (OS) was respectively 83.48%, 60.87% and 53.91%. The OS of patients with late recurrence was higher than that of patients with early recurrence at 1 year, 2 years and 4 years after operation ($P<0.05$). The analysis on influencing factors showed that AFP/V, number of tumors and vascular invasion were independent influencing factors of early recurrence and liver cirrhosis (LC) was the independent influence factor of late recurrence ($P<0.05$). Conclusion: There was obvious difference in the survival of patients with early recurrence and those with late recurrence after radical operation for PHC. The independent risk factors of early recurrence included vascular invasion, number of tumors and AFP/V and the independent risk factor of late recurrence was LC. Therefore, risk factors are important to emphasize in clinical practice to carry out targeted prevention and treatment.

Keywords: Radical operation for primary hepatocellular carcinoma, survival, recurrence, single factor, multi-factor, analysis

Introduction

PHC ranks fifth in the incidence in all malignant tumors and the frequency of male patients is much higher than that of females. This malignant tumor shows a very high death rate, only second to lung cancer [1]. The pathogenesis of PHC is still unclear in clinical practice, but it has been verified in a lot of research that the occurrence and progression of PHC are closely related with hepatitis B virus infection, hepatitis C virus infection and infection-induced LC [2].

According to statistics, PHC patients complicated with hepatitis B virus infection or hepatitis C virus infection account for over 80% of cases. The former occurs more frequently in China and the latter in Europe and America [3]. There are a variety of clinical treatment methods for PHC and operation comes first. With the gradual progress in medical technology and the continuous increase in clinical experience, the death rate of PHC has decreased gradually in perioperative period and the survival of patients is much improved [4]. It has also been found clinically that the recurrence rate is still very high after radical operation for PHC, respectively about 25% and 70% within 1 year and 5 years [5]. The death rate is seriously increased and the OS is obviously decreased due to the recurrence after radical operation for PHC [6].

However, there is little research about risk factors for recurrence after radical operation for

PHC. New ideas and reference information are needed for clinical intervention. It was intended from this study that important evidence could be provided for scientific prevention and treatment of liver cancer by emphatically analyzing the risk factors for recurrence after radical operation for PHC. Therefore, 115 PHC patients admitted to our hospital were included in this study to analyze the recurrence, survival and risk factors for recurrence after radical operation for PHC.

Materials and methods

Materials

A total of 115 PHC patients admitted to our hospital from January, 2013 to December, 2015 were selected as research subjects. Inclusion criteria: patients who met the diagnostic criteria of liver cancer; those who had primary hepatic carcinoma; and those who were aged over 18 years. Patients or their families signed an informed consent to participate in the study. The study was approved by the hospital ethics committee. Exclusion criteria: patients who received other treatments before surgery; those with surgical contraindications; those with secondary hepatic carcinoma; those combined with other serious systemic diseases; and those who had incomplete follow-up data. This study has been approved by the Ethics Committee of Peking University International Hospital.

The selected subjects included 101 males and 14 females. They were aged 23-70 years old, with an average age of (46.83±20.19). The AFP of 75 patients was≥20 ng/ml and the diameter of tumor in 75 patients was≥5 cm. The hepatitis B surface antigen (HBs Ag) of 97 patients was positive, of which 11 ones were complicated with positive hepatitis Be antigen (HBe Ag). Child grading for liver function: 112 patients were in Grade A and 3 were in Grade B. Severity of LC: 46 patients suffered from mild LC, 48 ones suffered from moderate LC and 21 suffered from severe LC. Number of tumors: 91 patients had 1 tumor and 24 ones had 2 or more tumors. Microvascular invasion was shown in the postoperative pathological examination of 11 patients. All the patients were eligible for the radical operation for PHC [7]. Hepatectomy: 88 patients were treated with non-anatomic resection of tumor, with the incisal margin of over 1 cm. The postoperative pathological examination showed a negative margin. There were 27 patients that received regular resection of tumor, including 6 that were treated with left lateral hepatic lobectomy, 5 with left hemihepatectomy, 6 with right hemihepatectomy, 8 with right posterior lobectomy and 2 with hepatic caudate lobectomy. All 115 patients were definitely diagnosed with PHC through postoperative pathological examination.

Methods

The 115 patients received regular follow-up visits and reexamination after operation. B-ultrasonic examination, liver function examination and serum AFP examination were performed approximately every 5 weeks within 24 months after operation. And chest x-ray film examination was performed every 10 weeks. The follow-up visits lasted for 4 years and ended in December, 2019. Patients were admitted to hospital immediately upon the recurrence during follow-up period. Patients with recurrence within 1 year after operation received micro-wave coagulation, percutaneous radiofrequency ablation guided by B-ultrasound, TACE, local injection of absolute alcohol and other minimally invasive therapies; and those with recurrence greater than 1 year after operation received secondary hepatectomy if they had good liver function.

The threshold of this study was 2 years after operation, including early recurrence referring to the recurrence within 2 years and late recurrence referring to that after 2 years.

Observation targets

Postoperative recurrence: The total recurrence of 115 PHC patients was recorded during postoperative follow-up period to compare the early recurrence rate and late recurrence rate.

Postoperative survival: OS and DFS were analyzed among 115 PHC patients at 1 year, 2 years and 4 years after operation. Overall survival time referred to the interval from random grouping to death from any cause [8]; and disease-free survival time referred to the interval from date of operation to tumor recurrence or tumor metastasis [9]. The OS was compared

Table 1. Analysis on postoperative recurrence of 115 PHC patients (case, %)

Recurrence	Early recurrence	Late recurrence	Total recurrence
Number of cases	57	25	82
Proportion	49.57	21.74	71.30
X^2	19.407		/
P	<0.000		/

between patients with early recurrence and those with late recurrence.

Single factor analysis on postoperative recurrence: Patients with early postoperative recurrence and those with late postoperative recurrence were compared in AFP level, AFP/V level, diameter of tumor, number of tumors, vascular invasion, differentiated degree, liver function grading, severity of LC, HBs Ag, hepatectomy and intraoperative blood transfusion.

Multi-factor analysis on postoperative recurrence: Factors with statistical significance were selected for dichotomy on the basis of single factor analysis and Logistic regression analysis was conducted to accomplish multi-factor analysis.

Statistical methods

SPSS 23.0 was used for statistical analysis. The measurement data were represented by ($\bar{x}\pm s$) and the results were compared through independent-samples *t* test. The enumeration data were represented by [n (%)] and the results were compared through chi-squared test. Logistic regression analysis was used for multi-factor analysis; Kaplan-Meier survival analysis was used for survival analysis; and Graphpad Prism 8 was used for illustration of figures. *P*<0.05 meant that the difference had statistical significance.

Results

Early postoperative recurrence was higher than late recurrence

Among the 115 PHC patients in this group, 82 suffered from recurrence during the postoperative follow-up period, showing a recurrence rate of 71.30% (82/115). There were 57 with recurrence within 2 years, with an early recurrence rate of 49.57% (57/115); and 25 with recurrence after 2 years, with a late recurrence rate of 21.74% (25/115). Early recurrence rate was much higher than late recurrence rate, showing statistical difference (*P*<0.05) (**Table 1** and **Figure 1**).

The OS of late postoperative recurrence was higher than early recurrence

The DFS of 115 PHC patients was respectively 64.35%, 38.26% and 22.61% at 1 year, 2 years and 4 years after operation and the OS was respectively 83.48%, 60.87% and 53.91%. It was found by analyzing the OS of patients with early recurrence and those with late recurrence that the OS of the latter was much higher than that of the former at 1 year, 2 years and 4 years after operation (*P*<0.05) (**Table 2** and **Figures 2**-**4**).

Single factor analysis of early and late postoperative recurrence

The single factor analysis on postoperative recurrence of 115 patients showed that the risk factors of early postoperative recurrence included AFP≥20 ng/ml, AFP/V≥14 ng/mlcm^3, diameter of tumor≥5 cm, number of tumors≥2, vascular invasion, tumor differentiation, positive HBs Ag and no intraoperative blood transfusion (*P*<0.05). The risk factors of late postoperative recurrence included AFP≥20 ng/ml and LC (*P*<0.05) (**Table 3**).

Multi-factor analysis of early and late postoperative recurrence

Factors with statistical significance in single factor analysis were selected for multi-factor Logistic regression analysis through dichotomy. The results showed that AFP/V, number of tumors and vascular invasion were independent influence factors of early recurrence, showing a negative correlation (*P*<0.05). LC was the independent influence factor of late recurrence, showing a positive correlation (*P*<0.05) (**Table 4**).

Discussion

Patients who suffered from recurrence after radical operation for PHC had a significantly higher fatality rate, which directly affected the

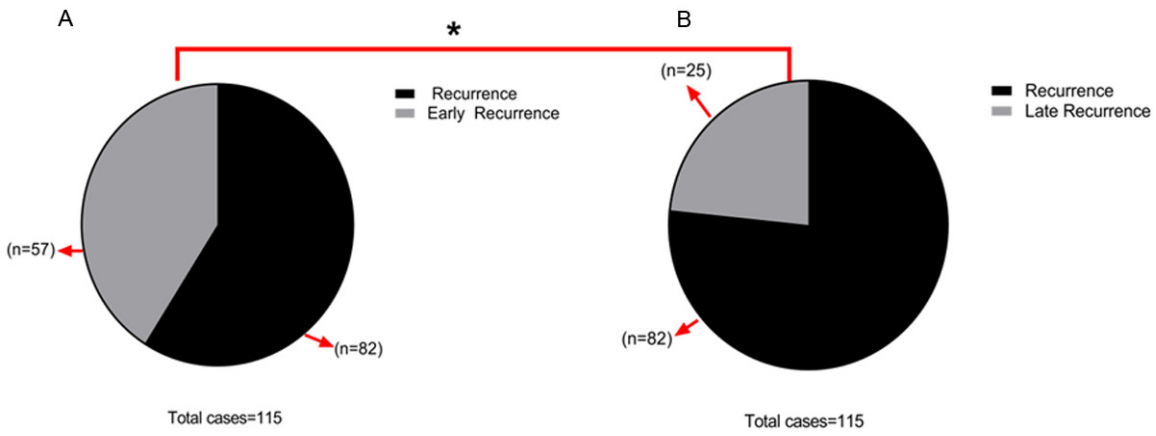

Figure 1. Postoperative recurrence. The late postoperative recurrence was 21.74% (25/115) (B), which was much lower than 49.57% (57/115) (A) of early postoperative recurrence (P<0.05). * referred to *P*<0.05 in comparison of two groups.

Table 2. Analysis on postoperative survival of 115 PHC patients (case, %)

Survival	1 year after operation	2 years after operation	4 years after operation
DFS (n=115)	74 (64.35)	44 (38.26)	26 (22.61)
OS (n=115)	96 (83.48)	70 (60.87)	62 (53.91)
OS of early recurrence (n=57)	37 (64.91)	13 (22.81)	11 (19.30)
OS of late recurrence (n=25)	25 (100.00)	22 (88.00)	18 (72.00)

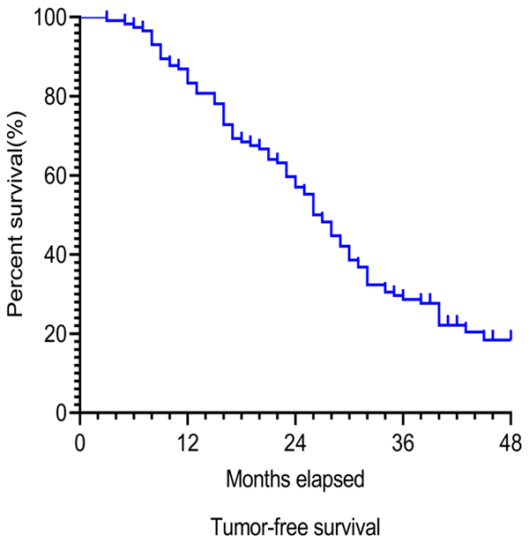

Figure 2. 4-year DFS of 115 patients.

postoperative OS of patients [10]. In the present study, the 4-year recurrence rate of 115 PHC patients was 71.30%, among which the recurrence rate was 49.57% within 2 years and 21.74% after 2 years. Other studies have shown similar results, with the recurrence rate of over 50% within 2 years after operation [11], indicating that PHC had a higher postoperative recurence rate and the highest recurrence period was 2 years after operation.

According to research, there are two types of postoperative recurrence for PHC. The first one is multicentric tumorigenesis. The residual liver will induce new tumors under the common influence of lesions and various tumorigenic factors. It generally occurs 2 years after operation and is an important manifestation of late recurrence [12, 13]. The second one is recurrence caused by intrahepatic metastasis and portal vein spread of the primary tumor. This generally happens soon after operation when cancer cells enter into the intrahepatic portal vein system due to tumor compression during operation or because some small lesions are not found during the first operation [14, 15]. Intrahepatic metastasis occurs at a higher rate, 1 year and 2 years after operation. It is a crucial manifestation of early recurrence and basically related to the biological characteristics of tumor. The prognosis is mostly poor [16, 17]. By contrast, there is almost no capsular invasion or vascular invasion in the latter case, with a better prognosis. In this study, the OS of patients with late recurrence was respectively 100.00%, 88.00% and 72.00% at 1 year, 2 years and 4 years after operation, which were significantly higher than those of patients with early recurrence of 64.91%, 22.81% and 19.30% (*P*<0.05), which

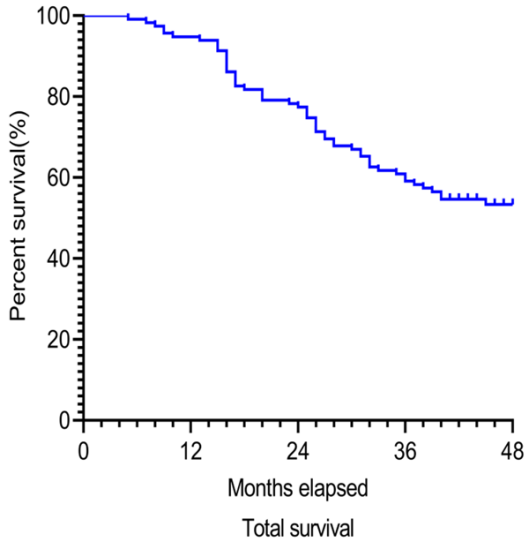

Figure 3. 4-year OS of 115 patients.

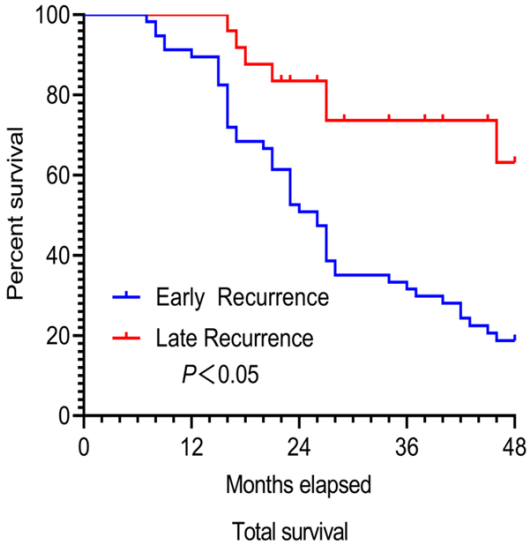

Figure 4. Comparison of 4-year OS between early recurrence group and late recurrence group. The 4-year OS of late recurrence group was much higher than that of early recurrence group ($P<0.05$).

was consistent with the above discussion. Similar studies have also shown that the survival of patients with late recurrence was better than that of patients with early recurrence [18], suggesting that the prognosis of patients with late recurrence was better than that of patients with early recurrence. The risk factors of recurrence were analyzed in this study on the basis of recurrence rate. The single factor and multi-factor analyses showed that AFP/V, number of tumors and vascular invasion were independent influencing factors for early postoperative recurrence. Among them, AFP was an important index in the diagnosis, determination of therapeutic effect and evaluation of prognosis of PHC. Studies have shown that higher AFP levels per unit volume of the tumor indicate higher risk of early postoperative recurrence and poorer prognosis [19]. Studies believed that the number of tumors was related with vascular invasion, and multiple tumors had a higher risk of vascular invasion [20]. Studies have found that the possibility of vascular invasion might be over 80% if there were more than 1 tumor even in the same lung lobe [21]. In this study, 10 of the 11 patients with vascular invasion recurred within 2 years after operation. It was believed in this study that the feasibility of operation should be considered comprehensively if the preoperative examination showed vascular invasion or multiple tumors. If there are more than 2 tumors or if tumors are located in different liver lobes, it is basically difficult to perform radical operation. In this case, it is suggested to perform microwave therapy or TACE therapy.

For PHC with late recurrence, the multi-factor analysis showed that LC was the risk factor. Studies have suggested that HBV replication was closely associated with the recurrence after radical operation for PHC, and massive virus replication significantly increased the risk of postoperative recurrence [22]. Generally, the postoperative recurrence caused by LC is basically multicentric tumorigenesis. In addition to the collaborative influence of other tumorigenic factors, there will be new tumors with identical or different biological characteristics to or from the primary tumor in residual liver [23, 24]. It was thought in this study that such patients must receive antiviral treatment and liver protection therapy and that dynamic monitoring should be performed for HBV-NDA level. Research has shown that tumor recurrence could be prevented effectively by performing interferon therapy in patients treated with radical operation for PHC [25].

In conclusion, there were a variety of risk factors for postoperative recurrence after radical operation for PHC. The risk of early postoperative recurrence could be increased due to high AFP/V level, large numbers of tumors and

Table 3. Single factor analysis on postoperative recurrence of PHC patients (case, %)

Factor		Recurrence within 2 years (n=57)	No recurrence within 2 years (n=58)	X^2	*P*	Recurrence after 2 years (n=25)	No recurrence after 2 years (n=33)	X^2	*P*
AFP (ng/ml)	≥20 (n=75)	47 (82.46)	28 (48.28)	14.806	0.000	16 (64.00)	11 (33.33)	5.376	0.020
	<20 (n=40)	10 (17.54)	30 (51.72)			9 (36.00)	22 (66.67)		
AFP/V (ng/mlcm^3)	≥14 (n=37)	28 (49.12)	9 (15.52)	14.877	0.000	4 (16.00)	4 (12.12)	0.180	0.671
	<14 (n=78)	29 (50.88)	49 (84.48)			21 (84.00)	29 (87.88)		
Diameter (cm)	≥5 (n=75)	44 (77.19)	31 (53.45)	7.145	0.008	14 (56.00)	16 (48.48)	0.322	0.571
	<5 (n=40)	13 (22.81)	27 (46.55)			11 (44.00)	17 (51.52)		
Number	Single (n=91)	38 (80.85)	53 (91.38)	10.631	0.001	22 (88.00)	29 (87.88)	0.000	0.989
	Multiple (n=24)	19 (19.15)	5 (8.62)			3 (12.00)	4 (12.12)		
Vascular invasion	Yes (n=11)	10 (17.54)	1 (1.72)	8.317	0.004	1 (4.00)	0 (0.00)	1.343	0.246
	No (n=104)	47 (82.46)	57 (98.28)			24 (96.00)	33 (100.00)		
Differentiated degree	High (n=51)	19 (33.33)	32 (55.17)	4.516	0.038	11 (44.00)	20 (60.61)	1.072	0.361
	Moderate (n=37)	19 (33.33)	18 (31.03)			10 (40.00)	8 (24.24)		
	Low (n=27)	20 (35.09)	7 (12.07)			4 (16.00)	5 (15.15)		
Child grading	A (n=112)	56 (98.25)	56 (96.55)	0.325	0.569	24 (96.00)	30 (90.91)	0.574	0.449
	B (n=3)	1 (1.75)	2 (3.45)			1 (4.00)	3 (9.09)		
LC	Mild (n=46)	20 (35.09)	26 (44.83)	1.854	0.129	6 (24.00)	20 (60.61)	4.638	0.025
	Moderate (n=48)	26 (45.61)	22 (37.93)			11 (44.00)	9 (27.27)		
	Severe (n=21)	11 (19.30)	10 (17.24)			8 (32.00)	4 (12.12)		
HBs Ag	Negative (18)	5 (8.77)	13 (22.41)	4.222	0.040	5 (20.00)	7 (21.21)	0.013	0.910
	Positive (97)	52 (91.23)	44 (77.59)			20 (80.00)	26 (78.79)		
Hepatectomy	Regular (n=27)	16 (28.07)	11 (19.30)	1.326	0.249	3 (12.00)	7 (21.21)	0.846	0.358
	Local (n=88)	41 (71.93)	47 (80.70)			22 (88.00)	26 (78.79)		
Intraoperative blood transfusion	Yes (n=30)	22 (38.60)	8 (13.79)	9.172	0.002	4 (16.00)	2 (6.06)	1.515	0.218
	No (n=85)	35 (61.40)	50 (86.21)			21 (84.00)	31 (93.94)		

Table 4. Multi-factor Logistic regression analysis on postoperative recurrence

Type of recurrence	Factor	β	OR	95% CI	*P*
Early recurrence	AFP	0.657	1.082	0.326-2.741	0.128
	AFP/V	-1.756	0.173	0.071-0.431	0.016
	Diameter of tumor	0.416	1.635	0.639-3.528	0.326
	Number of tumors	-1.728	0.169	0.062-0.552	0.008
	Vascular invasion	-2.714	0.065	0.008-0.543	0.011
	Tumor differentiation	1.623	1.857	0.638-2.849	0.338
	HBs Ag	1.234	0.891	1.366-2.818	0.120
	Intraoperative blood transfusion	1.978	1.238	0.338-1.724	0.071
Late recurrence	AFP	0.639	0.028	0.519-3.641	0.119
	LC	1.035	0.421	1.287-6.351	0.005

occurrence of vascular invasion. The high severity of LC could obviously increase the risk of late postoperative recurrence. There was obvious difference in the survival of early postoperative recurrence and late postoperative recurrence. This implied that prevention and treatment measures should be carried out in a timely manner to discover the signs of postoperative recurrence and thus implement strict and close follow-up visits so as to achieve early diagnosis and treatment and improve the survival of patients. However, this study also has some limitations. Few subjects were included in this study and they were grouped according to the threshold of 2 years after operation, so it was unknown whether grouping under other standards would get the same conclusion. Therefore, objects shall be grouped in more detail in the future to explore the recurrence in more groups and thus obtain more accurate results and provide more reference information for the prevention and treatment of postoperative recurrence among PHC patients.

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Disclosure of conflict of interest

None.

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