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BRIEF ARTICLE

Hepatocellular carcinoma: Clinical study of long-term survival and choice of treatment modalities

Ke-Tong Wu, Cun-Chuan Wang, Li-Gong Lu, Wei-Dong Zhang, Fu-Jun Zhang, Feng Shi, Chuan-Xing Li

Ke-Tong Wu, Wei-Dong Zhang, Fu-Jun Zhang, Feng Shi, Chuan-Xing Li, Department of Medical Imaging and Interventional Radiology, Cancer Center and State Key Laboratory of Oncology in South China, Sun Yat-sen University, Guangzhou 510060, Guangdong Province, China
Cun-Chuan Wang, the Center of Minimally Invasive Surgery, First Affiliated Hospital of Jinan University, Guangzhou 510630, Guangdong Province, China
Li-Gong Lu, Cancer Center, Guangdong General Hospital, Guangzhou 510080, Guangdong Province, China
Author contributions: Wu KT, Wang CC and Lu LG contributed equally to this work; Wu KT, Wang CC and Lu LG performed the majority of the study and wrote the manuscript; Zhang WD, Zhang FJ and Shi F were involved in editing the manuscript; Li CX contributed to data acquisition, analysis and interpretation; all authors were involved in revising and approving the final version for publication.
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Correspondence to: Chuan-Xing Li, MD, Department of Medical Imaging and Interventional Radiology, Cancer Center and State Key Laboratory of Oncology in South China, Sun Yat-sen University, 651 Dongfeng Road, East, Guangzhou 510060, Guangdong Province, China. lichuanh@mail.sysu.edu.cn
Telephone: +86-20-87343272 Fax: +86-20-87343272
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Abstract

AIM: To analyze the prognostic factors of 5-year survival and 10-year survival in hepatocellular carcinoma (HCC) patients, and to explore the reasons for long-term survival and provide choice of treatment modalities for HCC patients.

METHODS: From January 1990 to October 2012, 8450 HCC patients were included in a prospective database compiled by the Information Center after hospital admission. Long-term surviving patients were included in a 10-year survival group (520 patients) and a 5-year survival group (1516 patients) for analysis. The long-term survival of HCC patients was defined as the survival of 5 years or longer. Clinical and biologic variables were assessed using univariate and multivariate analyses. The survival of patients was evaluated by follow-up data.

RESULTS: The long-term survival of HCC patients was associated with the number of lesions, liver cirrhosis and Child-Pugh classification. It was not found to be associated with tumor diameter, histological stage, and pretreatment level of serum α-fetoprotein. The differences in clinical factors between the 5-year survival and the 10-year survival were found to be the number of lesions, liver cirrhosis, Child-Pugh classification, and time elapsed until first recurrence or metastasis. The survival period of different treatment modalities in the patients who survived for 5 years and 10 years showed significant differences: (in order of significance) surgery alone > surgery-transcatheter arterial chemoembolization (TACE) > TACE-radiofrequency ablation (RFA) > TACE alone > surgery-TACE-RFA. The 10-year survival of HCC patients was not associated with the choice of treatment modality.

CONCLUSION: This retrospective study elucidated survival outcomes, prognostic factors affecting survival and treatment modalities in HCC patients.

Key words: Hepatocellular carcinoma; Surgery; Radiofrequency ablation; Transcatheter arterial chemoembolization; Statistical analysis; Clinical study

Core tip: This manuscript was a retrospective analysis and it revealed that the long-term survival of hepatocellular carcinoma (HCC) patients was associated with the number of lesions, liver cirrhosis and Child-Pugh classification, whiletumor diameter, histological stage, and pretreatment level of serum α-fetoprotein

were not related. Conditions for long-term survival of HCC patients were: age over 50 years, no cirrhosis, a uninodular lesion, no vessel invasion, tumor-node-metastasis stage Ⅰ or Ⅱ, Child-Pugh classification Class A, and appropriate treatment. The best treatment modality for more than 10 years survival compared with 5 years survival were surgery alone > surgery-transcatheter arterial chemoembolization (TACE) > TACE-radiofrequency ablation (RFA) > TACE alone > surgery-TACE-RFA.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide. The prognostic factors of primary HCC have been studied by many researchers worldwide. Several reports conducted in the 1990s in both Eastern and Western centers have documented a 5-year overall survival rate of 26% to 44% after HCC resection[1-5]. Studies performed from 1975 to the present[6-15] showed that age, gender, metastasis, bilirubin levels, ascites, tumor thrombus of the portal vein, neoplasm staging, Child-Pugh classification, and serum levels of γ-glutamyltransferase (GGT), alkaline phosphatase, and lactate dehydrogenase may all have significant effects on the prognosis of HCC patients.

There are many different modes of HCC treatment and types of primary HCC. The effects of treatment and survival rate have seen only limited improvements[16-21]. Curative surgical therapies have shown the best long-term survival rates. However, most patients do not meet the selection criteria for these treatments. Surgical resection is not available to HCC patients with severe liver cirrhosis, multiple lesions located in different parts of the liver, or lesions located near a large vein or the junctions of large portal veins[22,23]. For this reason, effective, minimally invasive therapeutic options are essential to improving the prognosis in HCC patients. Existing minimally invasive local treatments for primary HCC include radiofrequency ablation (RFA), microwave ablation, cryoablation, transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection therapy, and high-intensity focused ultrasound ablation. In recent years, preliminary clinical trials have suggested that targeted drugs may have certain curative effects in the treatment of HCC[24-26].

This study discusses the factors relevant to duration of survival in these primary HCC patients. The method of treatment, the tumor's general prognostic factors, and the tumor's own characteristics were found to determine duration of survival. Therefore, the purpose of the present study was to analyze and compare the prognostic factors between 5-year survival and 10-year survival groups, to explore the clinical reasons for long-term survival and the choice of treatment modalities for HCC patients.

MATERIALS AND METHODS

Patients

From January 1990 to October 2012, 8450 HCC patients from Sun Yat-Sen University Cancer Center, First Affiliated Hospital of Jinan University, and Guangdong General Hospital were included in a prospective database after hospital admission. Long-term surviving patients were those who survived more than 5 years and they were identified and included in a 10-year survival group (520 patients) and 5-year survival group (1516 patients)for analysis. The long-term survival of HCC patients was defined as survival of 5 years or longer. This study was approved by the internal review board and ethics committee of the hospital. Informed consent was not required because of the retrospective and anonymous nature of the study, although these data were derived from prospective statistics for inpatients.

The diagnosis of HCC was confirmed in all patients either by histopathological findings or by the appearance of a liver tumor with arterial hypervascularization on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with a serum α-fetoprotein (AFP) value exceeding 400 ng/mL. Liver cirrhosis was diagnosed by histological or clinical features and liver function was evaluated according to the Child-Pugh score. All patients were evaluated according to European Association for the Study of the Liver criteria up to 2005[27], and to American Association for the Study of Liver Diseases criteria from January 2006[28]. We reviewed the patients' records for demographic parameters (age, sex), hepatitis B serology, Child-Pugh stage, AFP, tumor morphology and extension, including maximum diameter, tumor number, and vessel invasion determined by imaging studies (abdominal arteriography, CT during hepatic arteriography, and the portal phase of superior mesenteric arteriography), treatment modality, complications after treatment, hospital mortality, and time of recurrence. Patient characteristics of both survival groups are shown in Table 1.

Treatment

Surgical resection: Surgery was performed with patients under general anesthesia using a right subcostal incision with a midline extension with the aid of intraoperative ultrasound. Anatomic resection was performed using a target resection margin of at least 1 cm. Pringle's maneuver was routinely used with a clamp time of 10 min and an unclamp time of 5 min. Suturing and fibrin glue were used to establish hemostasis on the surface of the liver[29].

TACE: Chemoembolization involves the delivery of chemotherapeutic agents to liver tumors through the hepatic artery. Seldinger's method was used to insert a catheter

Table 1 Baseline characteristics of the patients

Characteristics	5-yr survival group	10-yr survival group	*P* value
No. of patients	1516	520	
Mean age (yr)	50.45 ± 12.32	50.37 ± 11.59	0.102
Female/male patients	166/1350	58/462	0.935
No. of tumors			0.000
1	1285	484	
2	206	33	
⩾ 3	25	2	
No. of treatments			0.000
Surgery	1100	410	
TACE	2356	576	
RFA	656	109	
Mean	2.71 (4112/1516)	2.11 (1095/520)	
Microvascular invasion	7	3	
Histology			0.381
Well	320	104	
Moderate	580	184	
Poor	382	144	
HBsAg			0.104
Positive	948	342	
Negative	568	178	
Cirrhosis			0.000
Absence	1396 (91.1%)	508 (97.7%)	
Present	120 (7.9%)	12 (2.3%)	
Position of lesion			0.246
Left lobe	87	126	
Right lobe	1334	423	
Both lobes	25	5	
Lesion diameter, *n* (cm)			0.651
⩽ 3	214 (2.26 ± 0.62)[1]	82 (2.27 ± 0.69)[1]	
> 3-⩽ 5	404 (4.22 ± 0.60)[1]	143 (4.20 ± 0.61)[1]	
> 5-< 10	560 (12.44 ± 1.98)[1]	190 (7.31 ± 1.28)[1]	
⩾ 10	338 (7.24 ± 1.40)[1]	105 (11.94 ± 1.80)[1]	
Mean	1516 (6.89 ± 3.69)	520 (6.58 ± 3.44)	
Child-Pugh classification			0.383
Class A	1466	505	
Class B	50	15	
TNM stage			0.109
Ⅰ	387	90	
Ⅱ	1096	422	
Ⅲ	33	8	
α-fetoprotein, ng/mL			
⩽ 100	712 (22.50 ± 23.59)[1]	261 (19.78 ± 17.93)[1]	0.528
100-400	186 (257.92 ± 92.89)[1]	48 (204.91 ± 81.92)[1]	0.129
⩾ 400	618 (16661.32 ± 28889.57)[1]	211 (15302.74 ± 23346.16)[1]	0.853
Liver function, mean ± SD			
Total bilirubin, mg/dL	19.65 ± 10.03	21.04 ± 38.16	0.080
AST, U/L	50.82 ± 26.46	51.72 ± 37.24	0.145
ALT, U/L	48.71 ± 27.35	45.32 ± 30.95	0.053
γ-glutamyltransferase, U/L	71.54 ± 43.62	64.42 ± 46.07	0.069

[1]There is significant difference within each group. RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen.

through the femoral artery. Angiography of the celiac and superior mesenteric arteries was routinely performed to determine the tumor blood supply, distribution of hepatic arteries, and collateral circulation routes[30]. The tumor's primary artery was selected for catheter placement. Patients were given a standard drug regimen of emulsified THP (40-60 mg), DDP (20-60 mg) and lipiodol (5-40 mL) through the hepatic artery.

Radiofrequency ablation: The size and position of the tumors and the position and direction of the needle were confirmed by CT. RFA treatment was performed with patients under general anesthesia to prevent the patient from experiencing pain and to ensure immobilization. CT was used to guide the insertion of a radiofrequency electrode into each tumor. The diameter of the needle was adjusted for tumor size. The range of ablation was extended 0.5-1 cm into the non-cancerous tissue to ensure complete coverage[31]. Patients underwent enhanced CT scans 4 wk after TACE treatment to determine the distribution of lipiodol and the status of any remaining tumor. If living tumor tissue was found, RFA was repeated[32].

Follow-up and recurrence

Dual-phase spiral CT was performed 4 wk after treatment and every 2 mo thereafter for the next 2 years. Each of these follow-up visits included blood tests, including liver function tests and serum AFP tests. Residual viable tumor tissue was considered present upon the first CT assessment at 4 wk after treatment if enhancement areas were seen within the tumor at either the arterial or the portal venous phase. MRI was performed if CT results were unclear on whether residual viable tumor tissue was presentAdditional treatment with RFA was given in these cases. If residual viable tumor was still present after repeated treatments, patients were given TACE[33].

The level of serum AFP and CT scans were regularly assessed to determine tumor recurrence. Recurrence was defined as the presence of hypervascular or early washout tumors on dynamic CT, MRI or angiography, or by a diagnosis of HCC by a radiologist. In this way, the diagnosis of recurrence was based on typical imaging findings on CT or arteriography, and, if necessary, percutaneous fine-needle aspiration cytology. Treatment modalities for HCC included surgery alone, TACE alone, surgery-TACE, TACE-RFA and surgery-TACE-RFA.

Statistical analysis

Patient characteristics are presented as mean ± SD. χ^2 tests and the Wilcoxon rank sum test were used to compare the characteristics of patients in the 5-year and 10-year survival groups. Overall survival was calculated by the Kaplan-Meier method from the beginning of treatment. Death from any cause was considered an event. The differences in survival between groups were compared by the generalized Wilcoxon's test. A stratified Cox's proportional hazards regression model was used for multivariate analysis of prognostic parameters identified by the survival analysis. SPSS statistical software, version SPSS 19.0 for Windows (IBM Corp., Armonk, NY, United States), was used. A P value < 0.05 was considered significant.

RESULTS

Patient characteristics and clinical features

As shown in Table 1, there were 520 patients in the10-

Table 2 Comparison of treatment modalities between 5-year survival group and 10-year survival group for hepatocellular carcinoma

Treatment modalities by tumor type	5-yr survival group	10-yr survival group	*P* value between groups	*P* value between overall groups
No. of treatment modalities				0.092
Surgery alone	609	235		
TACE alone	214	80		
Surgery + TACE	458	125		
TACE + RFA	85	28		
Surgery + TACE + RFA	150	52		
Tumor size ≤ 5 cm (maximum diameter)				0.097
Surgery alone	244 (3.53 ± 1.03)	100 (3.48 ± 1.06)	0.217	
TACE alone	92 (2.59 ± 1.16)	38 (3.58 ± 1.16)	0.087	
Surgery + TACE	133 (3.90 ± 1.02)	43 (3.47 ± 1.03)	0.192	
TACE + RFA	72 (3.10 ± 1.16)	21 (2.93 ± 1.10)	0.824	
Surgery + TACE + RFA	82 (3.88 ± 0.91)	26 (3.42 ± 0.98)	0.314	
Tumor size > 5 cm (maximum diameter)				0.106
Surgery alone	365 (8.16 ± 2.27)	135 (8.532 ± 2.71)	0.130	
TACE alone	122 (9.31 ± 2.94)	42 (9.36 ± 2.26)	0.925	
Surgery + TACE	325 (9.59 ± 3.16)	82 (9.09 ± 2.50)	0.624	
TACE + RFA	13 (11.68 ± 3.74)	7 (10.47 ± 5.59)	0.548	
Surgery + TACE + RFA	68 (7.19 ± 3.02)	26 (10.65 ± 4.63)	0.131	
Uninodular HCC				0.039
Surgery alone	531	223		
TACE alone	178	75		
Surgery + TACE	382	113		
TACE + RFA	57	24		
Surgery + TACE + RFA	100	50		
Multinodular HCC				
Surgery alone	78	12		
TACE alone	36	5		
Surgery + TACE	76	12		
TACE + RFA	28	4		0.445
Surgery + TACE + RFA	50	2		
AFP > 400 ng/mL (AFP value)				0.289
Surgery alone	280 (16053.09 ± 27804.11)	102 (18092.07 ± 26818.62)	0.450	
TACE alone	66 (15876.11 ± 30406.63)	28 (10984.83 ± 18402.28)	0.270	
Surgery + TACE	188 (21164.79 ± 31964.15)	47 (25114.26 ± 31807.02)	0.385	
TACE + RFA	32 (742.50 ± 0.00)	12 (22597.20 ± 28745.64)	0.667	
Surgery + TACE + RFA	56 (1884.33 ± 953.25)	19 (8789.88 ± 21862.41)	0.091	
AFP < 400 ng/mL (AFP value)				0.065
Surgery alone	329 (45.50 ± 71.08)	133 (56.35 ± 91.86)	0.853	
TACE alone	148 (38.60 ± 71.56)	52 (38.09 ± 48.30)	0.355	
Surgery + TACE	270 (66.35 ± 98.86)	78 (43.02 ± 74.45)	0.738	
TACE + RFA	69 (133.34 ± 145.64)	16 (44.81 ± 43.02)	0.579	
Surgery + TACE + RFA	94 (96.06 ± 138.35)	33 (15.43 ± 8.21)	0.064	

AFP: α-fetoprotein; TACE: Transcatheter arterial chemoembolization; RFA: Radiofrequency ablation; HCC: Hepatocellular carcinoma.

year survival group. Single lesions were present in 93.1% and multiple lesions in 6.7%. Lesions located in only one lobe of the liver were present in 93.1%, and lesions located in two lobes were present in 0.9%. A portal vein tumor thrombus was present in 2.3%. Child-Pugh classification class A applied to 97.1% and class B to 2.9%. tumor-node-metastasis (TNM) stage I or Ⅱ applied to 98.5% patients. Among the 1516 patients who survived for 5 years, 84.8% had one lesion, 13.6% had two lesions, 1.6% had three lesions, 98.6% had lesions located in one lobe of the liver, 1.4% had lesions located in the two lobes, 1.1% had vessel invasion, 96.7% had Child-Pugh classification class A, 3.3% had class B, and 97.8% had TNM stage I or Ⅱ. In this way, the survival period of both groups showed some correlation with the number of tumor lesions and liver cirrhosis. No statistically significant differences were observed with respect to maximum tumor diameter in either group. In the 5-year group, vessel invasion appeared in 1.1% of patients. In the 10-year group, vessel invasion appeared in 2.1% of patients. This suggests that patients with vessel invasion seldom survived for 5 years. In the 10-year survival group, 97.1% of patients were described as Child-Pugh classification class A and 2.9% as class B. TNM stage I and Ⅱ was applied to 98.5% of patients. In the 5-year survival group, 96.7% of patients were described as Child-Pugh classification class A, 3.3% as class B, and 97.8% as TNM stage I or Ⅱ. The survival periods of both groups may be related to Child-Pugh classification class A and TNM stage I or Ⅱ.

Treatment modalities

As shown in Table 2, treatment modalities such as surgery alone, TACE alone, surgery-TACE, surgery-TACE-RFA, and TACE-RFA, showed no statistically significant

Table 3 Comparison of treatmentefficacy between the 5-year survival group and 10-year survival group for hepatocellular carcinoma

Characteristics	5-yr survival group	*P* value	10-yr survival group	*P* value	*P* value between groups
AFP the first time before and after treatment (ng/mL)					
Surgery		0.002		0.000	
Before surgery	1020 (4596.63 ± 17193.11)		358 (7419.90 ± 18412.64)		0.049
After surgery	1020 (1133.25 ± 4530.36)		358 (1255.09 ± 4337.24)		0.070
TACE		0.039		0.002	
Before TACE	496 (4510.68 ± 15115.73)		162 (2827.99 ± 9506.04)		0.446
After TACE	496 (1732.58 ± 7631.56)		162 (502.21 ± 1526.13)		0.711
Liver function the first time before and after treatment					
Total bilirubin (mg/dL)		0.721		0.353	
Before treatment	68.32 ± 58.98		19.63 ± 12.65		0.078
After treatment	67.22 ± 69.45		18.76 ± 11.56		0.120
AST (U/L)		0.983		0.730	
Before treatment	51.99 ± 28.41		52.69 ± 40.86		0.137
After treatment	50.87 ± 27.50		52.42 ± 39.77		0.695
ALT (U/L)		0.104		0.262	
Before treatment	52.46 ± 37.21		50.69 ± 53.10		0.291
After treatment	54.60 ± 42.26		51.16 ± 50.09		0.126
γ-glutamyltransferase (U/L)		0.366		0.017	
Before treatment	19.30 ± 8.09		69.85 ± 93.75		0.122
After treatment	19.53 ± 8.32		58.79 ± 67.08		0.670
Time to first tumor recurrence or metastasis (d)		0.012		0.045	
Surgery alone	90 (1031.36 ± 662.61)		38 (3246.38 ± 2047.29)		0.003
TACE alone	32 (675.64 ± 412.31)		12 (1882.77 ± 1324.08)		0.015
Surgery + TACE	225 (1012.00 ± 818.86)		70 (2778.30 ± 6296.35)		0.007
Surgery + TACE + RFA	90 (798.41 ± 492.01)		52 (2553.20 ± 1746.48)		0.016

RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

differences between the 5-year survival group and 10-year survival group, but there were significant differences in treatment modalities of uninodular lesions between the 5-year survival group and 10-year survival group. Surgery alone, TACE alone, surgery-TACE, TACE-RFA and surgery-TACE-RFA showed no statistical differences in the maximum diameter of the tumor for the two groups. The survival period had no relationship with tumor size. Similarly, the survival period had no relationship with the level of the serum AFP in patients treated with different modalities. The patients of the two groups showed statistically significant differences in survival period depending on the different treatment modalities, but only among patients with only one lesion. The patients of the groups showed statistically significant differences in survival period depending on liver cirrhosis. Survival period did not differ significantly across the 5-year survival and 10-year survival groups in patients multiple lesions. In short, different treatment modalities were found to have an effect on patients with only one lesion, and no effect on patients with multiple lesions.

Effects of initial treatment

As shown in Table 3, serum levels of AFP and GGT differed significantly before and after the first treatment, but the levels of serum total bilirubin, aspartate aminotransferase, and alanine aminotransferase showed no statistically significant differences regardless of whether the first treatment was surgery or TACE and regardless of whether the patient survived for 5 or 10 years. The level of pre-surgery serum AFP showed statistically significant differences between 5-year survival and 10-year survival groups. After the first surgery, the two groups showed no statistically significant differences from each other. The time of the first recurrence or metastasis showed significant differences between the 5-year and 10-year survival groups. Different treatments for each treatment group also showed statistically significant differences in the time of the first recurrence or metastasis: (in order of significance) surgery alone > surgery-TACE > TACE alone > surgery-TACE-RFA.

Prognostic analysis

The influence of patient and tumor related factors on overall survival are shown in Table 4. Analysis of patients who survived for 5 years or longer showed that survival rates differed significantly with age, Child-Pugh classification, vessel invasion, liver cirrhosis, TNM stage, treatment method, and number of tumors. Statistical results also showed that, among patients who survived 5 years or longer, no significant differences could be attributed to sex, diameter of the largest tumor, or to pretreatment serum levels of AFP. Analysis of 10 years survival showed statistically significant differences in survival rates with respect to vessel invasion, number of tumors and Child-Pugh classification. No significant differences could be attributed to age, sex, tumor diameter, or pretreatment level of serum AFP. Multivariate analysis of patients who lived 5 years or longer showed survival rates to be related to age, vessel invasion, liver cirrhosis, TNM stage, Child-Pugh classification, treatment method, and number of tumors. Multivariate analysis of patients who survived

Table 4 Comparison of univariate analysis for various prognostic factors between 5-year survival and 10-year survival groups for hepatocellular carcinoma

Factor	5-yr survival group		10-yr survival group	
	Exp (B) 95%CI	*P* value	Exp (B) 95%CI	*P* value
Sex (men and women)	0.787 (0.678-0.913)	0.002	0.875 (0.667-1.146)	0.332
Age (yr) (< 50 and ≥ 50)	0.516 (0.462-0.575)	0.000	1.097 (0.838-1.438)	0.500
Diameter of largest tumor	0.971 (0.921-1.023)	0.274	0.961 (0.879-1.051)	0.384
Child-Pugh classification	0.070 (0.060-0.082)	0.000	0.559 (0.334-0.938)	0.028
No. of tumors	1.452 (1.284-1.642)	0.000	0.390 (0.261-0.582)	0.000
Pretreatment serum AFP level	1.041 (0.987-1.099)	0.138	0.933 (0.851-1.022)	0.137
Cirrhosis	0.832 (0.775-0.893)	0.000	10.539 (8.164-13.606)	0.000
TNM stage	0.739 (0.662-0.862)	0.000	0.911 (0.739-1.124)	0.384
Treatment methods	1.152 (1.109-1.197)	0.000	1.043 (0.975-1.115)	0.220
Microvascular invasion	1.038 (0.494-2.181)	0.922	1.233 (0.396-3.838)	0.718

AFP: α-fetoprotein; TNM: Tumor-node-metastasis.

Table 5 Comparison of multivariate analysis for various prognostic factors between 5-year survival and 10-year survival groups for hepatocellular carcinoma

Group	Sex	Age	Micro-vascular invasion	Pretreatment AFP level	Diameter of tumor	Treatment methods	TNM stage	Child-Pugh classification	No. of tumors	Cirrhosis
5-yr survival (*P* value)	0.344	0.004	0.033	0.080	0.211	0.000	0.001	0.000	0.040	0.000
10-yr survival (*P* value)	0.983	0.962	0.370	0.783	0.847	0.215	0.695	0.029	0.025	0.000

AFP: α-fetoprotein; TNM: Tumor-node-metastasis.

10 years or longer showed survival rates to be related to Child-Pugh classification, liver cirrhosis and to the number of tumors.

Overall survival

Table 1 show that patients with only one lesion, 2 lesions, or 3 lesions showed statistically significant differences with respect to duration of survival period in both groups. Patients who had only one lesion survived significantly longer than other patients. Patients who had 2 lesions seldom survived 5 years. Patients with 3 lesions seldom survived 5 years. Patients who survived more than 5 years were associated with more influencing factors than those in the 10-year survival group. Factors associated with long-term survival among HCC patients included age over 50 years, single rather than multiple lesions, no vessel invasion, TNM stage I or Ⅱ, Child-Pugh classification Class A, and only 1-3 rounds of treatment. Long-term survival of patients for HCC was found to be related to the number of lesions, liver cirrhosis and methods of treatment, not to tumor diameter or level of serum AFP.

Statistical results showed that, among patients who survived 10 years or longer, no significant differences could be obtained from the different treatment modalities (P = 0.202). The survival period of different treatment modalities in the patients who survived between 5 years and 10 years showed statistically significant differences: (in order of significance) surgery alone > surgery-TACE > TACE-RFA > TACE alone > surgery-TACE-RFA (Figure 1). Therefore, the 10-year survival of HCC patients was not associated with the choice of initial treatment modality. However, different treatment modalities had a significant effect on the survival of HCC patients who survived between 5 and 10 years (Table 5).

DISCUSSION

There is a variety of treatment methods and models of HCC. Surgical resection is the preferred treatment for HCC. TACE, however, has broader indications. RFA, microwave ablation, cryoablation, radiation therapy, and high intensity focused ultrasound therapy have been widely used in clinical treatment[34-37]. When HCC is diagnosed early, the curative effects enjoyed by some HCC patients improve, as does the prognosis. However, improvements to the survival rate are very limited and the prognosis remains poor. By evaluating criteria to more accurately predict prognosis, patients at high risk of recurrence would be identified more easily and effective prevention and control measures could be implemented.

The results of this study show the 5-year and 10-year survival groups to have the following common features: lesions located in only one lobe of the liver, single lesions, no vessel invasion, no liver cirrhosis, TNM stage I or Ⅱ, Child-Pugh classification class A, and 1 to 3 treatments. Long-term survival factors are assessed by using univariate and multivariate Cox proportional hazard regression analyses. Multivariate analysis indicated that survival for more than 10 years was associated with treatment modal-

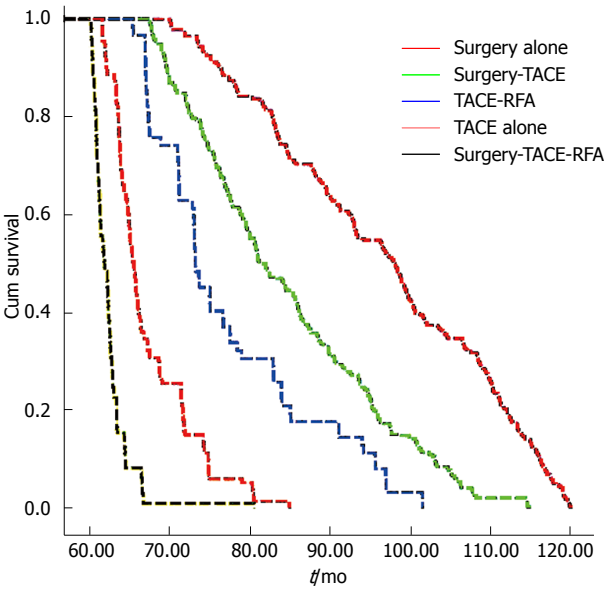

Figure 1 Kaplan-Meier curve shows overall survival rates of different treatment modalities in hepatocellular carcinoma patients who survived between 5 years and 10 years. Different treatment models showed statistically significant differences in the survival period: surgery alone > surgery-transcatheter arterial chemoembolization (TACE) > TACE-radiofrequency ablation (RFA) > TACE alone > surgery-TACE-RFA.

ity, number of lesions, vessel invasion, age, and Child-Pugh classification. Survival for more than 5 years wasassociated with number of lesions, no liver cirrhosis and treatment modalities. The independent prognostic factors of both groups included method of treatment, liver cirrhosis and number of lesions. The diameter of the largest tumor and serum level of AFP were not associated with survival period in either group.

Patients with multiple lesions or lesions located in more than one lobe of the liver showed poorer prognosis and did not always survive 5 years. The treatment modalities showed that the most effective type of treatment was surgery. The three typesof combination therapy were used in 412/520 (79.2%) of the patients who survived for 10 years or longer and in 1244/1516 (82.1%) of the patients who survived for 5 years or longer. The survival period for different treatment modalities in both groups also showed statistically significant differences: surgery alone > surgery-TACE > TACE-RFA > TACE alone > surgery-TACE-RFA. When a single lesion is present and that lesion can be removed by surgery, surgical resection should be the preferred method. Surgical resection is the preferred treatment for HCC. TACE should be performed in the treatment of the relapse or metastatic lesions after surgical resection.

The initial effects of treatment in both 10-year and 5-year survival groups showed serum levels of AFP and GGT to be significantly different before and after the first treatment regardless of whether this first treatment was surgery or TACE. The level of serum AFP showed statistically significant differences between 10-year group and 5-year survival groups before the first surgical operation, but no statistically significant differences between the two groups were detected after the first surgical operation. This suggests that the serum level of AFP decreased quickly after surgical resection in the 10-year survival group, an ideal curative effect. With all five kinds of treatment, surgery alone, surgery-TACE, TACE-RFA, TACE alone, or surgery-TACE-RFA, the first relapse or metastasis showed statistically significant differences between the 5-year and 10-year survival groups. The first relapse or metastasis tended to occur later in the 10-year survival group than in the 5-year survival group. The time to tumor recurrence or metastasis was found to significantly affect the patients' survival periods.

The prognosis of HCC here showed heterogeneity caused by the interactions between many factors and by the interplay between the tumor and the rest of the body. Factors that affect prognosis have been found to be different, but this may be because the studies evaluating them had different goals and factors[38-40]. Lau *et al*[41] reported that the factors that affect the curative effect of mid-to-late HCC are tumor type, portal vein tumor thrombus, treatment method, and hepatic function. Yamamoto *et al*[42] found that portal vein tumor thrombus, tumor type, traces of iodized oil, and hepatic function all influence the survival and prognosis of the HCC patients.

This study evaluated patient age, gender, TNM stage, Child-Pugh classification, portal vein tumor thrombus, serum AFP level, number of tumor lesions, tumor diameter, and treatment method, all of which may have some relationship with prognosis. The independent prognostic survival factors of both the patients who survived more than 10 years and those who survived 5 years can be said to be related to treatment method and to the number of lesions. The number of lesions was found to be a common risk factor in the 10-year and 5-year survival groups. One possible reason for this may be that most of the intrahepatic tumor lesions had undergone intrahepatic metastasis. Multiple lesions tended to be caused by intrahepatic metastasis. Even when tumors were completely removed, subclinical tumor lesions remained in the liver and the tumor cells may have entered the bloodstream. The survival period showed obvious differences in patients who received different treatments. The treatments, in decreasing order of favorability, were as follows: surgery alone > surgery-TACE > TACE-RFA > TACE alone > surgery-TACE-RFA. The patients who survived more than 10 years were found to have more influencing factors than those in the 5-year group. The patients who were more than 50 years old, who had no portal vein tumor thrombus, who had Child-Pugh class A tumors, who had only one lesion, and who underwent appropriate treatment tended to live longer than other patients.

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COMMENTS

Background

Hepatocellular carcinoma (HCC) is one of the most common digestive malignancies cancer, which do serious threat to the people's life and health. Therefore, it has been studied by many scholars, but people still do not know what is the reason for the long-term survival and whether it has an optimal treatment.

Research frontiers

There are various prognosis factors for HCC, some researchers suggesting that age, sex and α-fetoprotein (AFP) level play a critical role, while others suggest that the long-term survival of HCC is related to treatment modality or the biological nature of the tumor.

Innovations and breakthroughs

This manuscript reveals the long-term survival of HCC patients was associated with the number of lesions, liver cirrhosis and Child-Pugh classification. It was not found to be associated with tumor diameter, histological stage, and pretreatment level of serum AFP. Conditions associated with long-term survival of HCC patients were: age over 50 years, no cirrhosis, uninodular lesion, no vessel invasion, tumor-node-metastasis stage Ⅰ or Ⅱ, Child-Pugh classification class A, and appropriate treatment. The clinical reasons for the differences between the 5-year survival and the 10-year survival were found to be the number of lesions, liver cirrhosis, Child-Pugh classification, and time elapsed until first recurrence or metastasis for HCC. The survival period of different treatment modalities in the patients who survived between 5 years and 10 years showed statistically significant differences: surgery alone > surgery-transcatheter arterial chemoembolization (TACE) > TACE-radiofrequency ablation (RFA) > TACE alone > surgery-TACE-RFA. The 10-year survival of HCC patients was not associated with the choice of treatment modality.

Applications

This study retrospectively studied HCC patients treated in the past 20 years, and the ultimate conclusion is that the long-term survival of HCC patients was associated with the number of lesions, liver cirrhosis and Child-Pugh classification, patients who survived for 5 and 10 years showed statistically significant differences in types of treatments. The 10-year survival of HCC patients was not associated with the choice of treatment modality. The results can provide information on the treatment choice of HCC patients.

Terminology

TACE is short for transhepatic arterial chemotherapy and embolization, used in the treatment of HCC patients especially for the terminal cancer patients; RFA is a treatment method for HCC patients which uses a RFA needle to send high radiofrequency waves to heat the tumor and cause cell degeneration and necrosis. It is widely used for small HCC tumor (diameter < 3 cm).

Peer review

This study was performed as a retrospective analysis of prognostic factors including individual therapy for patients with HCC who survived for 5 years or longer and 10 years or longer. A large population of more than 2000 patients was selected from over 8000 HCC patients, and thus this study is likely to give interesting and reliable data.

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