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Post-radiation survival time in hepatocellular carcinoma based on predictors for CT-determined, transarterial embolization and various other parameters

Ting-Kai Leung, Chi-Ming Lee, Li-Kuo Shen, Hsi-Chi Chen, Yu-Cheng Kuo, Jeng-Fong Chiou

Ting-Kai Leung, Chi-Ming Lee, Li-Kuo Shen, Hsi-Chi Chen, Department of Diagnostic Radiology, Taipei Medical University Hospital, Taipei, Taiwan, China
Yu-Cheng Kuo, Jeng-Fong Chiou, Department of Radiation Oncology, Taipei Medical University Hospital and Wan Fang Hospital, Taipei, Taiwan, China
Correspondence to: Chi-Ming Lee, M.D., Department of Diagnostic Radiology, Taipei Medical University Hospital, Wu-Hsin Street 250, Taipei, Taiwan, China. vd142098@yahoo.com.tw
Telephone: +886-2-27372181-1131 Fax: +886-2-23780943
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Abstract

AIM: In this retrospective study of unresectable hepatocellular carcinoma (HCC), we have investigated the efficacy of CT-derived parameters, laboratory measurements, clinical assessment and associated transarterial embolization (TAE) as predictors of post-radiotherapy survival time.

METHODS: Sixty-six patients diagnosed with unresectable HCC that had undergone radiotherapy at two medical university hospitals in Taipei were enrolled in the study. Using multivariate analysis, pre-treatment parameters including tumor number and CT confirmation of PVT and ascites were compared. Multivariate analysis was also used for comparison of the mean pretreatment values for laboratory measurements, including alpha-fetoprotein, direct/total bilirubin and GOT/GPT levels, and clinical history of chronic hepatitis across the three survival-time categories. The χ^2 was used to test the significance of the relationship between survival time and TAE procedure. The *P* values for the above tests were deemed statistically significant where *P* < 0.05.

RESULTS: Portal vein thrombosis (*P* = 0.032) and ascites (*P* < 0.05) were negative predictors of post-radiation survival time. Low-grade liver cirrhosis (A or B), lower tumor volume and low levels of AFT, GOT/GPT, and total bilirubin were predictors of longer post-radiation survival time (*P* < 0.05).

CONCLUSION: The CT and clinical and laboratory assessment provide a reference for, and enable estimation of, probable survival times in HCC patients after radiotherapy. Tumor volume, severity of liver cirrhosis, status with respect to portal vein thrombosis and ascites and AFT, GOT/GPT and total bilirubin values were significant predictors of survival in this study.

INTRODUCTION

Radiotherapy treatment for hepatocellular carcinoma (HCC)^[1] is still considered unorthodox in Taiwan. However, there has been a trend towards increased utilization in unresectable and TAE-nonsusceptible cases.

In this study, we share our experience over the past six years with HCC irradiation to provide a reference for prediction of survival time based on clinical, laboratory, and image-derived information^[2], and particularly to discuss the value of pre-TAE treatment.

We also compared our results with those of other analogous research^[1].

MATERIALS AND METHODS

Patients

From June 1998 to June 2004, radiotherapy for a total of 66 patients diagnosed with unresectable HCC was performed at Taipei Medical University Hospital (TMUH) and Taipei Wan-Fang Hospital (TWH).

The mean age for the 35 male (53%) and 31 female (47%) patients was 58 years. Diagnosis was based on cytology, high serum alpha-fetoprotein and image findings characteristic of malignancy (including angiography and CT follow-up).

Various factors were considered, including: laboratory data for alpha-fetoprotein, total bilirubin, and GOT/GPT; tumor number and volume and existence of portal vein thrombosis (PVT) and ascites, based on pre-treatment CT; clinical grade of liver cirrhosis (Child's A, B, C); history of chronic hepatitis; and status for the associated therapeutic factor, transarterial embolization (TAE).

Pre-treatment spiral CT examination (5-mm slices) was

performed, and the following parameters recorded: tumor number and volume (as described below), and presence of PVT or ascites.

VARIAN Eclipse 7.1.35.7 software (Integrated Treatment Planning System) was used for CT-based measurement of tumor volume, with the images made available on a large screen monitor. The distance-reference line on the CT images was used to calculate the pixel size. The tumor outlines were traced manually on the screen using a mouse-controlled cursor. Tumor volume was calculated by multiplying the sum of the traced areas by the image reconstruction interval (summation-of-areas technique). All three-dimensional reformation volumes were calculated in milliliters.

The patients were treated using limited-field radiotherapy mostly irradiated with daily fractions of 180/250 cGy to a total dose of 5 000 cGy.

Survival time after radiation was divided into three categories: (1) 6 mo; (2) 6-24 mo; (3) >24 mo; with these considered dependent variables. Other variables included PVT, ascites, hepatitis, liver cirrhosis (A, B or C) and tumor number ($n = 1, 2, \text{ or } >2$) with multivariate analysis used to determine statistical significance as independent predictors where $P < 0.05$. Mean AFP, tumor size, and GOT/GPT and total bilirubin [Bili(T)] levels were compared for each of the three survival categories, with multivariate analysis used to verify statistical significance as independent predictors where $P < 0.05$.

Statistical significance was also determined for the associated therapeutic factor, TAE, for the three survival-time categories. The significance of the relationship between TAE and survival time was evaluated using the χ^2 ($P < 0.05$).

RESULTS

The overall survival rates for the 66 irradiation patients^[3] for <6, 6-24 and >24 mo were 18%, 32% and 50% respectively. Of these 66 cases: 46 (70%) involved single lesions detected by pre-treatment spiral CT; 12 patients (18%) had two visible tumors; and, 8 individuals (12%) had multiple or diffuse lesions. Tumor volumes ranged from 4-1 948 mL. Pre-treatment CT scan was used for 16 (24%)

Table 1 Parameters of CT findings

Parameters	Survival time	<0.5 yr	0.5-2 yr	>2 yr	P
Tumor number	1	2	4	9	0.31
	2	2	6	4	0.38
	Multiple or diffuse	1	4	3	0.24
PVT		7	8	1	0.032
Ascites		7	16	6	0.025

Table 2 Parameters of clinical assessment

Parameters	Survival time	<0.5 yr	0.5-2 yr	>2 yr	P
Hepatitis		8	11	14	0.37
Cirrhosis	A	3	5	22	0.03
	B	5	13	6	0.02
	C	1	0	0	0.28

and 29 instances (44%) of portal vein thrombosis and ascites respectively (Table 1).

The clinical assessments and grading for the liver cirrhoses are presented in Table 2. A total of 40 cases (61%) were associated with TAE treatment^[4] before or during radiation therapy^[5].

The pre-treatment laboratory data for alpha-fetoprotein, direct/total bilirubin, GOT/GPT and clinical history of chronic hepatitis are presented in Tables 2, 3.

We found that, for our sample, PVT^[6] ($P = 0.032$) and ascites ($P = 0.025$) were predictors^[7] of shorter survival time^[8] after radiation therapy (Table 1). By contrast, the early stages of liver cirrhosis (A or B; $P = 0.03$ and 0.02 respectively) were predictors of longer survival time. The variant factors of chronic hepatitis and tumor numbers were, however, not significant predictors. Mean values for the study parameters were compared across the three survival times using multiple analysis (Tables 1, 2). It was demonstrated that AFP <91.8 ng/mL, tumor volume <178 mL; GOT <59 IU/L; GPT <43.5 IU/L, and total bilirubin <0.799 mg/dL were predictors of longer survival time post radiation therapy.

We found that the associated procedure for TAE did not predict survival time after radiation therapy (Table 4).

DISCUSSION

Our results may provide a reference for prediction of outcome after radiotherapy for HCC, based on CT and clinical and laboratory assessment.

In this retrospective study, the number of eligible cases from the radiation oncology departments at TMUH and TWH was scarcely sufficient. In comparison to the reference study of Guo and colleagues^[1], high grade criteria were not set to exclude advanced or terminal-stage disease from our sample.

Table 3 Parameters of laboratory data

AFP	<0.5 yr	0.5-2 yr	>2 yr	P
Range	2.7-146 700	10-265 891	2.3-40 248	<0.0001
Mean	23 844	47 594.8	91.8	
Tumor size	<0.5 yr	0.5-2 yr	>2 yr	P
Range	126-916	4-1 948	19-1 405	<0.0001
Mean	365	178	204	
GOT	<0.5 yr	0.5-2 yr	>2 yr	P
Range	20-330	2.1-270	20-153	<0.0001
Mean	99	59	59.8	
GPT	<0.5 yr	0.5-2 yr	>2 yr	P
Range	31-92	0.8-138	22-442	<0.0001
Mean	50	43.5	94.2	
Bili (T)	<0.5 yr	0.5-2 yr	>2 yr	P
Range	0.4-2	0.5-21	0.19-1.84	<0.0001
Mean	1.39	1.12	0.799	

Table 4 Parameters of TAE treatment

Parameters	Survival time	<0.5 yr	0.5-2 yr	>2 yr	Total	P
TAE	Performance	9	13	18	40	0.47
	Not performance	3	8	15	26	

The two studies differed in terms of overall survival rate, with markedly shorter post-RT survival time demonstrated for our sample population. Basically, this is due to fundamental differences in the two studies. In the above-mentioned study, the cases were first treated in the same hospital. By contrast, the source of our cases could be divided into two categories. The first consisted of referrals from other hospitals or medical units without initial treatment at our two institutions, such that, in most cases, we were not able to take advantage of the 'golden period' in terms of successful TAE treatment. Further, many patients had already undergone multiple sequential TAE procedures and as such, poor response to further TAE could be anticipated. Further, we also suggest that our cases were more severe and more advanced in terms of HCC stage as determined from CT and clinical and laboratory parameters. Our second category of patients were initially treated in the same hospital after HCC was proven, as in the study of Guo and colleagues^[1], with some of these referred to diagnostic radiation departments for TAE. Unfortunately, the first group outnumbered the second by more than nine-fold in our study, resulting in a significant decrease in prediction of success rate for our TAE cases, as well as, shorter median survival time post-RT treatment, compared to the reference study. Therefore, it appears reasonable to assume that the difference in patient-selection criteria explains the disparity between these two otherwise similar studies.

In conclusion, we found that the presence of PVT ($P = 0.032$)^[9] and ascites ($P = 0.025$) after radiation therapy were predictors of shorter survival time. By contrast, the early stages of liver cirrhosis (A and B; $P = 0.03$ and 0.02 respectively) were predictors of longer survival time^[10].

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