PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2004;10(15):2184-2189
World Journal of Gastroenterology
 ISSN 1007-9327

• LIVER CANCER •

Therapeutic effects and prognostic factors in three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma

De-Hua Wu, Li Liu, Long-Hua Chen

De-Hua Wu, Long-Hua Chen, Department of Radiation Oncology, Nanfang Hospital, First Military Medical University, Guangzhou 510515, Guangdong Province, China
Li Liu, Department of Pathology, First Military Medical University, Guangzhou 510515, Guangdong Province, China
Supported by the Natural Science Foundation of Guangdong Province, No. 013056
Correspondence to: Dr. Long-Hua Chen, Department of Radiation Oncology, Nanfang Hospital, First Military Medical University, Guangzhou 510515, Guangdong Province, China. flclh@fimmu.com
Telephone: +86-20-61642136 **Fax:** +86-20-61642131
Received: 2003-12-10 **Accepted:** 2004-02-01

Abstract

AIM: To evaluate the therapeutic efficacy of three-dimensional conformal radiotherapy (3D-CRT) combined with transcatheter arterial chemoembolization (TACE) on the patients with hepatocellular carcinoma (HCC).

METHODS: Between 1998 and 2001, 94 patients with HCC received 3D-CRT combined with TACE. A total 63 patients had a Okuda stage I lesion and 31 patients had stage II. The median tumor size was 10.7 cm (range 3.0-18 cm), and liver cirrhosis was present in all the patients. There were 43 cases of class A and 51 class B. TACE was performed using lipiodol, 5-fluorouracil, cisplatin, doxorubicin hydrochloride and mitomycin, followed by gelatin sponge cubes. Fifty-nine patients received TACE only one time, while the others 2 to 3 times. 3D-CRT was started 3-4 wk after TACE. All patients were irradiated with a stereotactic body frame and received 4-8 Gy single high-dose radiation for 8-12 times at the isocenter during a period of 17-26 d (median 22 d).

RESULTS: The median follow-up was 37 mo (range 10-48 mo) after diagnosis. The response rate was 90.5%. The overall survival rate at 1-, 2-, and 3- year was 93.6%, 53.8% and 26.0% respectively, with the median survival of 25 mo. On univariate analysis, age (P=0.026), Child-Pugh classification for cirrhosis of liver (P=0.010), Okuda stage (P=0.026), tumor size (P=0.000), tumor type (P=0.029), albuminemia (P=0.035), and radiation dose (P=0.000) proved to be significant factors for survival. On multivariate analysis, age (P=0.024), radiation dose (P=0.001), and tumor size (P=0.000) were the significant factors.

CONCLUSION: 3D-CRT combined with TACE is an effective and feasible approach for HCC. Age, radiation dose and tumor size were found to be significant prognostic factors for survival of patients with HCC treated by 3D-CRT combined with TACE. Further study for HCC is needed to improve the treatment efficacy.

Wu DH, Liu L, Chen LH. Therapeutic effects and prognostic factors in three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol* 2004; 10 (15): 2184-2189
http://www.wjgnet.com/1007-9327/10/2184.asp

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health threat in Africa and China where rates of hepatitis B infection have always been high[1]. Although early diagnosis and curative surgical resection can achieve the best prognosis, the number of patients who could undergo resection is still limited, even for those with small tumors because of the unique characteristics of this tumor, such as multifocality, early vascular invasion, and concurrent liver cirrhosis[2]. Nonsurgical therapies, such as percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), have been tried for unresectable HCC[3,4]. TACE has achieved improved survival; however, the antitumor effect of TACE alone has frequently been incomplete, even after repeated treatments[5,6]. Radiotherapy used for HCC has been attempted for more than 4 decades. Early trials adopted whole liver irradiation but the radiation dose was inadequate[7]. Because of the unsatisfactory results obtained with this low-dose whole liver irradiation, doctors have not long applied it in their treatment of HCC. The advanced technique of three-dimensional conformal radiotherapy (3D-CRT), however, has made it possible to deliver a higher dose of radiation to part of the liver accurately without a significant dose increase in the other intra-abdominal critical structures. Several studies reported that 3D-CRT could tolerate higher radiation levels with a substantial tumor response[8-17]. Their findings indicate that 3D-CRT can be an effective component of the treatment strategy for HCC. The principle for 3D-CRT was to escalate the radiation dose in an attempt to elevate the rate of tumor response without damaging the normal liver cells. Stereotactic radiosurgery or hypofractionated radiotherapy has 80-90% local control rate, even for so-called radioresistant tumors, such as renal cell carcinoma and melanoma[18,19]. Because of its success, small-volume radiotherapy has been applied to extracranial lesions, such as lung and liver tumors[20, 21]. Although the role of 3D-CRT in the management of HCC has been increasingly recognized, there are still several questions to be solved, one of which involves the identification of prognostic factors so as to improve the therapeutic effects of the management for HCC after 3D-CRT combined with TACE. Another is how to assess the exact effectiveness and toxicity of 3D-CRT combined with TACE. In our department, 3D-CRT combined with TACE has been actively applied for the treatment of HCC since the 1998. In this retrospective study, we aimed to analyze the effects and prognostic factors affecting survival in 94 HCC patients treated with this therapy.

MATERIALS AND METHODS

Patients

The diagnosis of HCC was based on histological features or

on radiologic findings (liver tumor CT scan, as well as hypervascular mass in hepatic angiography) and on a serum alpha-fetoprotein (AFP) level exceeding 400 ng /mL. All tumors with an AFP less than 400 ng /mL underwent a biopsy for diagnosis. The exclusion criteria included were as follows: (1) the presence of extrahepatic metastasis; (2) liver cirrhosis of Child-Pugh class C; (3) tumors occupying more than two-thirds of the liver; and (4) a score of Karnofsky performance status of less than 60.

Table 1 Patient data before initiation of radiotherapy (n =94)

Data	n(%)
Age (yr)	
<60	78(83.0)
≥60	16(17.0)
Gender	
Male	84(89.4)
Female	10(10.6)
Alpha-fetoprotein	
>400 ng / mL	64 (68.1)
≤400 ng / mL	30(31.9)
Child-Pugh classification for cirrhosis of liver	
Class A	43(45.7)
Class B	51(54.3)
Karnofsky performance score	
>70	90(95.7)
<70	4(4.3)
Okuda stage	
I	63(67.0)
II	31(33.0)
Tumor size (cm)	
<5	17(18.1)
5-10	40(42.6)
>10	37(39.3)
Tumor type	
Massive	66(70.2)
Multinodular	28(29.8)
PVT	
Yes	12(12.8)
No	82(87.2)
Albuminemia	
<3 g / dL	15(16.0)
>3 g / dL	79(84.0)
Bilirubinemia	
<3 mg / dL	29(30.9)
>3 mg / dL	65(69.1)
Chronic hepatitis in serum virology	
Type B	90(95.7)
Type C	4(4.3)
Radiation dose	
60 Gy	34(36.2)
56 Gy	34(36.2)
48 Gy	26(27.6)
TACE	
1 fraction	59(62.8)
>1 fraction	35(37.2)

Ninety-four patients (84 male and female) who received 3D-CRT combined with TACE in our department between August 1998 and August 2001 were enrolled in this study. The patient data are shown in Table 1. Their median age was 51.5 years (range 23–73 years). Sixty-four patients had an serum AFP level >400 ng/mL. Liver cirrhosis was present in all patients, with 43 patients of Child-Pugh class's A. Most patients had good performance status, and 90 patients had a Karnofsky performance score (KPS) of more than 70. The Okuda stage I was in 66 patients and II in 28 patients. The tumor size was calculated according to the mean of three orthogonal diameters on CT. It was <5 cm in 7 patients, 5-10 cm in 30 patients, and >10 cm in 57 patients, with the median tumor size of 10.7 cm (range 3.0-18 cm). The massive tumor was the most frequent type, which was found in 82 patients (87.2%). Portal vein thrombosis (PVT) was present in 12 patients (12.8%). Chronic hepatitis in serum virology was present in 90 patients with type B (95.7%), and in 4 patients with type C (4.3%).

TACE procedures

TACE was performed with the infusion of a mixture of 5–20 mL of iodized oil contrast medium (Lipiodol, Huaihai Pharmaceutical Factory, Shanghai, China), 1.0 g of 5-fluorouracil (5-Fu, Xudong Haipu Pharmaceutical Inc., Shanghai, China) and 40-60 mg of cisplatin (CDDP, Qilu Pharmaceutical Factory, Jinan, China) or 30-50 mg of doxorubicin hydrochloride (Adriamycin, Main Luck Pharmaceutical Inc., Shenzhen, China), and 10 mg of mitomycin (Mytomycin-C C, Kyowa Hakko Kogyo, Tokyo, Japan), followed by 1 mm×1 mm×10 mm of gelatin sponge cubes (Gelfoam. the 3rd Pharmaceutical Factory of Nanjing, Nanjing, China) embolization. To preserve liver function as much as possible, we performed superselective TACE for the feeding arteries of each intrahepatic tumor. When there was an arterial portal shunt or main branch PVT, we performed TACE without lipiodol to prevent severe damage to the normal liver. TACE procedures were performed with a 4-wk interval, and the patients received 1 to 3 times.

Radiotherapy

Radiation treatment was given to patients placed in a supine position, with both arms raised above the head and the head in a natural position. The patients were immobilized in this position using a vacuum pillow (TN-1, TOPSLANE, Shanghai, China) with an oxygen mask (3 000–5 000 cc/min) for respiratory suppression for CT simulator (PQS 2000, Picker, USA). CT data were all transferred to a 3D–radiation treatment planning system (STP 3.0, Leibinger, Freiburg, Germany) by the network. The hepatic tumor, liver, kidneys, spinal cord, and gastroduodenal intestine of each patient were contoured and reconstructed to form a 3D representation. The radiation treatment volumes and treatment angles were designed according to the beam's-eye view technique to minimize critical organ injury. Each beam's shape was designed using a multileaf collimator or custom-made block. Three-dimensional CT-based computerized treatment planning was used to determine the best combination of coplanar and noncoplanar portals. A dose-volume histogram (DVH) was generated from the stereotactic treatment planning system for each patient. Gross tumor volume (GTV) was defined as the hepatic tumor volume, visualized by three-dimensional computation of contrast CT-defined contours. Clinical target volume (CTV) was defined as GTV plus a 0.5 cm margin. Planning target volume (PTV) was defined as CTV plus a 0.5 cm margin at medial/lateral/ventral/dorsal sides, but plus a 1.5-2 cm margin at cranial/caudal sides to account for daily setup error and respiratory organ motion. Dose inhomogeneity of PTV should be within ±7% of isocenter dose. Normal liver was defined as the total liver volume minus the GTV. The average volume of GTV for these 94 patients was 979±623 mL. The average volume of whole liver was 1 790±645 mL. The number of portals used for radiation treatment ranged from 2 to 6, with a median of 5. Ultimately, the radiotherapy volume involved a portion of the liver, and whole liver radiation was always avoided. 3D-CRT was started within 3-4 wk after TACE using a 6-MV linear accelerator (CLINAC 600C/D, Varian Assoc, USA).

A dose of 4-8 Gy was applied each time and 3 times a week to deliver a total dose of 48-60 Gy. The total dose was determined by the fraction of the nontumorous liver receiving >50% of the isocenter dose. The guidelines were as follows: if <25% of the nontumorous liver received >50% of the isocenter dose, the total dose was increased to 60 Gy with 7.5 Gy each time; if 25-50%, the dose was 54 Gy with 6 Gy each time; if 50-75%, the dose was 48 Gy with 4 Gy each time; and if >75%, no treatment was given. This guideline was more strictly followed after the application of three-dimensional planning. The total radiation dose ranged from 48 to 60 Gy, and the median tumor dose was 56 Gy. During treatment, patients were monitored weekly with complete blood counts and liver function tests and AFP test.

Evaluation

The evaluation of tumor response was based on the change in mean tumor size (calculated according to the mean of three orthogonal diameters) on serial CT scans which are first started 4-6 wk after treatment completion and then performed at 1-, 3-mo interval. The evaluation of the change in tumor size was done at 3 mo after the treatment. Complete disappearance of the tumor was considered a complete response (CR), a decrease of >50% in tumor size was defined as a partial response (PR), a decrease of <50% in tumor size or no change was defined as stable disease (SD), and progression was defined as progressive disease (PD). CR and PR were considered to be responsible, whereas SD or PD not to be responsible. Acute toxicity was that occurred during treatment and 1 mo after the treatment. Subacute or chronic toxicity was defined as that occurring from 1 mo after radiotherapy.

Statistics

Statistical analysis was performed using SPSS 10.0. Overall survival was estimated from the date of diagnosis according to the Kaplan-Meier method. Log-rank statistics were used to identify the prognostic factors important for survival. Cox proportional models using enter stepwise regression were applied to all potentially significant variables for the multivariate analysis. $P<0.05$ was considered statistically significant.

RESULTS

Tumor response

As shown in Table 2, tumor response (CR+PR) was evaluated by the change in mean tumor size on CT 3 mo after treatment completion.

Table 2 CT response of HCC to 3D-CRT combined with TACE

Response	No of patients (%)
Complete	12(12.8)
Partial	73(77.7)
Stable disease	6(6.4)
Progressive disease	3(3.1)

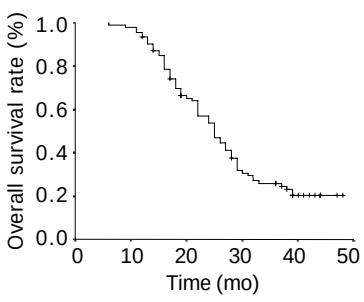

Figure 1 Actuarial survival of 94 patients treated with 3D-CRT combined with TACE.

Overall survival

The median follow-up was 37 mo (range 10-48 mo) after diagnosis. The overall survival rates of 1-, 2-, and 3-year were 93.6%, 53.8%, and 25.9%, respectively (median survival 25 mo, Figure 1).

Factors affecting overall survival

The results of univariate and multivariate analyses of prognosis factors for overall survival are shown in Table 3. On univariate analysis, age (P=0.026, Figure 2), Child-Pugh classification for cirrhosis of liver (P=0.01, Figure 3), Okuda stage (P=0.008, Figure 4), tumor size (P=0.000, Figure 5), tumor type (P=0.029, Figure 6), albuminemia (P=0.035, Figure 7), and radiation dose (P=0.000, Figure 8) were shown as significant factors. Multivariate regression identified the following independent favorable prognostic factors: younger age (P=0.024), high radiation dose (P=0.001), and small tumor size (P=0.000).

Table 3 Univariate and multivariate analyses of prognosis factors for overall survival

Univariate analysis	Multivariate analysis		
	P	R (95% *CI*)	*P*
Age (yr)	0.026	2.377	0.024
Tumor size	0.000	6.183	0.000
Radiation dose	0.000	0.491	0.001
Child-Pugh classification for cirrhosis of liver	0.010		
Karnofsky performance status	0.913		
Okuda stage	0.008		
Gender	0.202		
Tumor type	0.029		
PVT	0.235		
Albuminemia	0.035		
Bilirubinemia	0.305		
Chronic hepatitis in serum virology	0.060		
Alpha-fetoprotein	0.861		
TACE	0.892		

HR: Hazard ratio; 95% *CI*: Confidence interval.

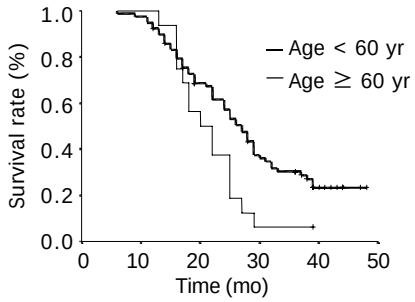

Figure 2 Univariate analysis of age on survival of patients treated with 3D-CRT combined with TACE.

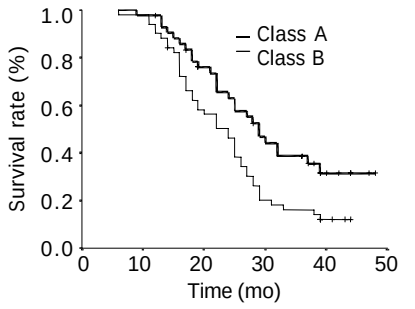

Figure 3 Univariate analysis of Child-Pugh classification on survival of patients treated with 3D-CRT combined with TACE.

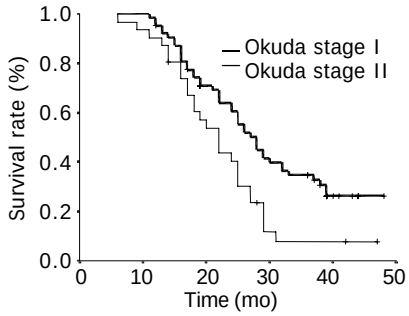

Figure 4 Univariate analysis of Okuda stage on survival of patients treated with 3D-CRT combined with TACE.

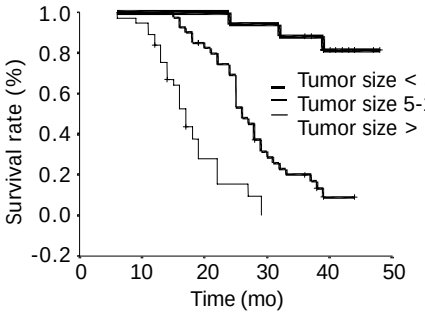

Figure 5 Univariate analysis of tumor size on survival of patients treated with 3D-CRT combined with TACE.

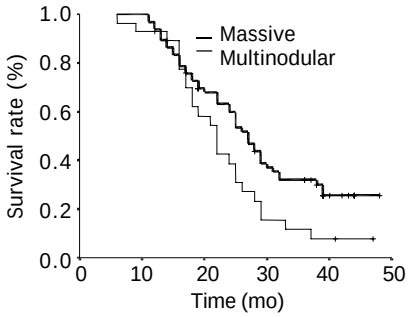

Figure 6 Univariate analysis of tumor type on survival of patients treated with 3D-CRT combined with TACE.

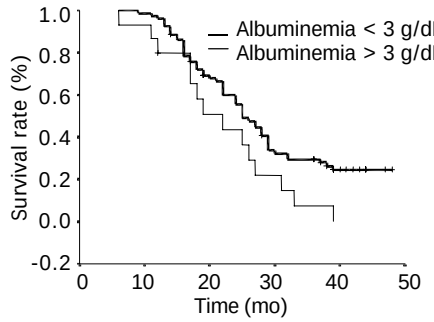

Figure 7 Univariate analysis of albuminemia on survival of patients treated with 3D-CRT combined with TACE.

Toxicity

In terms of acute toxicity, alterations in the liver function test (23 patients, 24.5%) and fever (51 patients, 54.3%) were frequently found in patients during the early time after TACE. These effects were transient and most patients recovered within 1-2 wk. Hematologic toxicity involved thrombocytopenia (platelets <50 000/mm^3) in 13 patients and leucopenia (white blood cells <2 000/mm^3) in 2 patients. Subacute and chronic toxicity involved radiation-induced liver disease (RILD) in 12 patients, 4 of whom died from RILD, and gastroduodenal ulcer in 5 patients. The patients other than the 4 victims of RILD were treated conservatively, and no death was found related to the treatment.

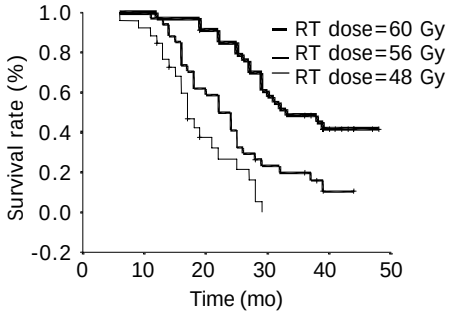

Figure 8 Univariate analysis of radiation dose on survival of patients treated with 3D-CRT combined with TACE.

DISCUSSION

Although TACE has been proved to be effective in treating HCC, and selectively and repeatedly used for patients with unresectable HCC, no survival benefits have been observed in at least two randomized trials of TACE[22,23]. TACE is not a curative method and its limitation has also been well documented. After TACE, the tumor cells remain viable, especially in and around the capsule, and tumors may recur by the blood supply from the collateral circulation or portal vein or recanalization of the originally embolized artery[6,24,25]. In advanced HCC, it is almost impossible to achieve a measurable response with TACE[26].

Local radiotherapy can be an effective adjunct to the palliative treatment of HCC, even with portal vein thrombosis. Some studies of local radiotherapy, however, as either combination therapy with TACE or salvage therapy following TACE, have not shown a survival benefit, despite tumor response[4-17]. This is because HCC eradication requires at least 50 Gy of radiation[1,2]; but 33 Gy is a sufficient dose to induce RILD for whole liver radiation. With three-dimensional radiation planning, conformal radiotherapy can minimize scattering, limit unnecessary exposure of normal tissue, and deliver higher doses (40-80 Gy) to tumors[27,28]. Therefore, it can be a feasible approach in the treatment of HCC with high dosage of radiation.

3D-CRT has been reported by a few studies to be effective in treatment of primary and metastatic tumors of lung and liver[20, 21], but it has not been common to be applied in the treatment of HCC. The common therapy for HCC has been reported to be a daily dose of 1.8-2 Gy, 5 fractions per week, to a total delivered dose of 40-60 Gy[4-17]. In our study of the 94 cases of HCC, we suggested that employing 3D-CRT could be beneficially combined with TACE with the following considerations.

Firstly, the combination of 3D-CRT with TACE may remedy the limitation of each alone and has synergistic effects. Secondly, tumor shrinkage after TACE allows the use of smaller irradiation fields, which permits higher tumor doses and improves the normal liver tolerance. Thirdly, combination therapy may also serve the purpose of eliminating residual cancer cells after TACE. Furthermore, the anticancer drug retained in the tumor may have a documented radiosensitizing effect[6,29]. The anticancer drug, when mixed with lipiodol, has been reported to maintain relatively high concentrations in tumors as long as 27 d and decrease to a trace level after 47 d[30]. Guo *et al.*[6] reported that TACE followed by irradiation was a promising approach for large HCC and confirmed that TACE combined with radiotherapy was more effective than TACE alone.

In discussing the factors affecting the prognosis, we are not going to deal with the commonly known ones, which were also found in our study, such as age, Child-Pugh classification for cirrhosis of liver, Okuda stage, tumor size and type, and albuminemia. Only radiation dose is to be discussed, for it is of clinical importance in exploration of a better therapeutic method for HCC. In our present study, the radiation dose started at 60 Gy in 8 fractions within 17 d in cases with <25% of the nontumorous liver receiving >50% of the isocenter dose, at 56 Gy in 9 fractions within 19 d in cases with 25-50%, and 48 Gy in12 fractions within 26 d in cases with 50-75%. Using the linear quadratic model, the biologic effective dose (BED) was here defined to be nd $(1+d/\alpha/\beta)$ in Gray, where n is the fractionation number, d is the daily dose, and α/β ratio is assumed to be 10 for tumors. The BEDs for our 3 different dose groups were equivalent respectively to those for 87.5 Gy total doses, 72 Gy total dose and 56 Gy total dose with a daily fraction of 2 Gy. The univariate and multivariate analyses of prognosis factors for overall survival showed that radiation dose is closely related to the prognosis. It seems clear that our virtually high total doses resulted in better response rates and overall survival. In our study, the radiologically documented response rates were 90.5%, our survival rates at 1-, 2-, and 3-year were 93.6%, 53.8%, and 25.9%, respectively, and our median survival rate was 25.0 mo. Besides better survival effect, hypofractionated 3D-CRT offers advantages of a shorter treatment course than a conventional radiotherapy and higher acceptance on the part of the patients without increasing side effects.

It has been reported that if less than 25% of the normal liver is treated with radiotherapy, then there may be no upper limit on dose associated with RILD; if 33%, 67%, or the whole liver is under uniform irradiation of 90 Gy, 47 Gy, or 31 Gy, respectively, there may be 5% risk of RILD associated with the treatment[31]. In analyzing the correlation of RILD with patient-related and treatment-related dose-volume factors, Cheng *et al*.[15] showed that after 3D-CRT, 12 of 68 patients developed RILD which was not found to be associated with their tumor volume. Compared with the documented ones, our results showed no increased toxicity in spite of the increased dose per fraction. This indicated that 3D-CRT played a critical role in the treatment of HCC.

In conclusion, 3D-CRT hypofractionated combined with TACE is a very safe and effective treatment method in higher tumor control and similar normal-tissue toxicity to conventional radiotherapy for HCC.

ACKNOWLEDGEMENTS

We thank Professor Liang Ping for his revision of the English version and An Sheng-li for his help in statistical analysis in the present study.

REFERENCES

1 **Oberfield RA,** Steele G Jr, Gollan JL, Sherman D. Liver cancer. *CA Cancer J Clin* 1989; **39:** 206-218
2 **Tang ZY**. Small hepatocellular carcinoma: current status and prospects. *HePatobiliary Pancreat Dis Int* 2002; **1:** 349-353
3 **Mok KT**, Wang BW, Lo GH, Liang HL, Liu SI, Chou NH, Tsai CC, Chen IS, Yeh MH, Chen YC. Multimodality management of hepatocellular carcinoma larger than 10 cm. *J Am Coll Surg* 2003; **197:** 730-738
4 **Qian J**, Feng GS, Vogl T. Combined interventional therapies of hepatocellular carcinoma. *World J Gastroenterol* 2003; **9:** 1885-1891
5 **Seong J**, Park HC, Han KH, Chon CY, Chu SS, Kim GE, Suh CO. Clinical results of 3-dimensional conformal radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma in the cirrhotic patients. *HePatol Res* 2003; **27:** 30-35
6 **Guo WJ**, Yu EX, Liu LM, Li J, Chen Z, Lin JH, Meng ZQ, Feng Y. Comparison between chemoembolization combined with radiotherapy and chemoembolization alone for large hepatocellular carcinoma. *World J Gastroenterol* 2003; **9:** 1697-1701
7 **Stillwagon GB**, Order SE, Guse C, Klein JL, Leichner PK, Leibel SA, Fishman EK. 194 hepatocellular cancers treated by radiation and chemotherapy combinations: Toxicity and response: A Radiation Therapy Oncology Group Study. *Int J Radiat Oncol Biol Phys* 1989; **17:** 1223-1229
8 **Seong J**, Park HC, Han KH, Chon CY. Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma: a retrospective study of 158 patients. *Int J Radiat Oncol Biol Phys* 2003; **55:** 329-336
9 **Cheng JC**, Wu JK, Huang CM, Liu HS, Huang DY, Tsai SY, Cheng SH, Jian JJ, Huang AT. Dosimetric analysis and comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy for patients with hepatocellular carcinoma and radiation-induced liver disease. *Int J Radiat Oncol Biol Phys* 2003; **56:** 229-234
10 **Yamada K**, Izaki K, Sugimoto K, Mayahara H, Morita Y, Yoden E, Matsumoto S, Soejima T, Sugimura K. Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2003; **57:** 113-119
11 **Li B**, Yu J, Wang L, Li C, Zhou T, Zhai L, Xing L. Study of local three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for patients with stage III hepatocellular carcinoma. *Am J Clin Oncol* 2003; **26:** E92-99
12 **Park HC**, Seong J, Han KH, Chon CY, Moon YM, Suh CO. Dose-response relationship in local radiotherapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2002; **54:** 150-155
13 **Seong J**, Park HC, Han KH, Lee DY, Lee JT, Chon CY, Moon YM, Suh CO. Local radiotherapy for unresectable hepatocellular carcinoma patients who failed with transcatheter arterial chemoembolization. *Int J Radiat Oncol Biol Phys* 2000; **47:** 1331-1335
14 **Yamada K**, Soejima T, Minami T, Yoden E, Watanabe Y, Takenaka D, Imai M, Okayama T, Fujii M, Sugimura K. Three-dimensional treatment planning using electrocardiographically gated multi-detector row CT. *Int J Radiat Oncol Biol Phys* 2003; **56:** 235-239
15 **Cheng JC**, Wu JK, Huang CM, Liu HS, Huang DY, Cheng SH, Tsai SY, Jian JJ, Lin YM, Cheng TI, Horng CF, Huang AT. Radiation-induced liver disease after three-dimensional conformal radiotherapy for patients with hepatocellular carcinoma: dosimetric analysis and implication. *Int J Radiat Oncol Biol Phys* 2002; **54:** 156-162
16 **Chia-Hsien Cheng J**, Chuang VP, Cheng SH, Lin YM, Cheng TI, Yang PS, Jian JJ, You DL, Horng CF, Huang AT. Unresectable hepatocellular carcinoma treated with radiotherapy and/or chemoembolization. *Int J Cancer* 2001; **96:** 243-252
17 **Guo WJ**, Yu EX. Evaluation of combined therapy with chemoembolization and irradiation for large hepatocellular carcinoma. *Br J Radiol* 2000; **73:** 1091-1097
18 **Aoyama H**, Shirato H, Onimaru R, Kagei K, Ikeda J, Ishii N, Sawamura Y, Miyasaka K. Hypofractionated stereotactic radiotherapy alone without whole-brain irradiation for patients with solitary and oligo brain metastasis using noninvasive fixation of the skull. *Int J Radiat Oncol Biol Phys* 2003; **56:** 793-800
19 **Vesagas TS**, Aguilar JA, Mercado ER, Mariano MM. Gamma knife radiosurgery and brain metastases: local control, survival, and quality of life. *J Neurosurg* 2002; **97**(5 Suppl): 507-510
20 **Kelsey CR**, Schefter T, Nash R, Russ P, Baron AE, Zeng C, Gaspar LE. Retrospective clinicopathologic correlation of gross tumor size of hepatocellular carcinoma: implications for extracranial stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2003; **57**(2 Suppl)**:** S283
21 **Onimaru R**, Shirato H, Shimizu S, Kitamura K, Xu B, Fukumoto S, Chang TC, Fujita K, Oita M, Miyasaka K,

Nishimura M, Dosaka-Akita H. Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. *Int J Radiat Oncol Biol Phys* 2003; **56:** 126-135

22 **Pelletier G**, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, Lenoir C, Attali P, Etienne JP. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol* 1990; **11:** 181-184

23 Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995; **332:** 1256-1261

24 **Ernst O**, Sergent G, Mizrahi D, Delemazure O, Paris JC, L'Hermine C. Treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization: comparison of planned periodic chemoembolization and chemoembolization based on tumor response. *Am J Roentgenol* 1999; **172:** 59-64

25 **Yu YQ**, Xu DB, Zhou XD, Lu JZ, Tang ZY, Mack P. Experience with liver resection after hepatic arterial chemoembolization for hepatocellular carcinoma. *Cancer* 1993; **71:** 62-65

26 **Seong J**, Keum KC, Han KH, Lee DY, Lee JT, Chon CY, Moon YM, Suh CO, Kim GE. Combined transcatheter arterial chemoembolization and local radiotherapy of unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 1999; **43:** 393-397

27 **Aguayo A**, Patt YZ. Nonsurgical treatment of hepatocellular carcinoma. *Semin Oncol* 2001; **28:** 503-513

28 **McGinn CJ**, Ten Haken RK, Ensminger WD, Walker S, Wang S, Lawrence TS. Treatment of intrahepatic cancers with radiation doses based on a normal tissue complication probability model. *J Clin Oncol* 1998; **16:** 2246-2252

29 **Seong J**, Kim SH, Suh CO. Enhancement of tumor radioresponse by combined chemotherapy in murine hepatocarcinoma. *J Gastroenterol Hepatol* 2001; **16:** 883-889

30 **Raoul JL**, Heresbach D, Bretagne JF, Ferrer DB, Duvauferrier R, Bourguet P, Messner M, Gosselin M. Chemoembolization of hepatocellular carcinomas. A study of the biodistribution and pharmacokinetics of doxorubicin. *Cancer* 1992; **70:** 585-590

31 **Dawson LA**, Ten Haken RK, Lawrence TS. Partial irradiation of the liver. *Semin Radiat Oncol* 2001; **11:** 240-246

Edited by Kumar M and Chen WW **Proofread by** Xu FM