SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 2: 839-844

Stereotactic body radiotherapy combined with transarterial chemoembolization for huge (≥10 cm) hepatocellular carcinomas: A clinical study

NAN BAO ZHONG, GUANG MING LV and ZHONG HUA CHEN

Tumor Radiotherapy Center, Fuzhou General Hospital, Fuzhou, Fujian 350025, P.R. China

Received December 1, 2013; Accepted May 28, 2014

DOI: 10.3892/mco.2014.304

Abstract. This study was conducted to evaluate the safety and efficacy of stereotactic body radiotherapy (SBRT) combined with transarterial chemoembolization (TACE) for huge (≥10 cm) hepatocellular carcinomas (HCCs). Between May, 2006 and December, 2012, 72 patients with huge HCCs were treated by SBRT following incomplete TACE. The median total dose of 35.6 Gy was delivered over 12-14 days with a fractional dose of 2.6-3.0 Gy and 6 fractions per week. The patients were classified into those with tumor encapsulation (group A, n=33) and those without tumor encapsulation (group B, n=39). The clinical outcomes of tumor response, overall cumulative survival and toxicities/complications were retrospectively analyzed. Among the 72 patients, CR, PR, SD and PD were achieved in 6 (8.3%), 51 (70.8%), 9 (12.5%) and 6 patients (8.3%), respectively, within a median follow-up of 18 months. The objective response rate was 79.1%. The overall cumulative 1-, 3- and 5-year survival rates and the median survival time were 38, 12 and 3% and 12.2 months, respectively. In group A, the overall cumulative 1-, 3- and 5-year survival rates were 56, 21 and 6%, respectively, with a median survival of 19 months; in group B, the overall cumulative 1-, 3- and 5-year survival rates were 23, 4 and 0%, respectively, with a median survival of 10.8 months (P=0.023). The treatment was well tolerated, with no severe radiation-induced liver disease and no reported > grade 3 toxicity. Tumor encapsulation was found to be a significant prognostic factor for survival. In conclusion, the combination of SBRT and TACE was shown to be a safe and effective treatment option for patients with unresectable huge HCC.

Correspondence to: Professor Guang Ming Lv, Tumor Radiotherapy Center, Fuzhou General Hospital, 156 Xier Huan Road, Fuzhou, Fujian 350025, P.R. China
E-mail: brightlgming@hotmail.com

Key words: stereotactic body radiotherapy, huge hepatocellular carcinoma, transarterial chemoembolization, retrospective study

Introduction

Hepatocellular carcinoma (HCC) is most prevalent in developing countries; however, its incidence was reported to be on the increase in North America (1). HCC is one of the most common malignancies worldwide (2) and the third leading cause of cancer-related mortality (3), with an overall 5-year survival rate of merely 3-5% (4). It was reported that 10-20% of newly diagnosed HCCs are >10 cm in diameter (5). Although there are various treatments for HCC, including surgery (hepatic resection and liver transplantation), percutaneous ethanol injection (PEI), radiofrenquency ablation (RFA) and transarterial chemoembolization (TACE), the treatment options for huge (≥10 cm) HCCs are limited. PEI, RFA and liver transplantation are not considered suitable treatment modalities for large HCCs (6-8). Hepatic resection is considered the treatment of choice for HCC; however, a tumor recurrence rate of 50-60% remains a significant issue following curative resection (9). Furthermore, a number of patients have unresectable HCCs (10,11). TACE alone is unsatisfactory, particularly for large tumors (12). Therefore, there is a need for effective treatments for huge HCCs. Despite the lack of randomized controlled trials, radiotherapy is becoming recognized as a potentially curative treatment option (13). Conformal radiotherapy (CRT) for HCC was reported to exert a significant effect (14-16), as was SBRT (17-20). However, the number of studies on the application of CRT and SBRT for the treatment of huge HCCs is limited. Thus, it remains to be determined whether SBRT is feasible, safe and effective in the treatment of huge HCCs. In order to expand the use of SBRT as an effective treatment for patients with huge HCCs, in this study, we retrospectively analyzed the clinical outcomes of 72 such patients treated with a combination of SBRT and TACE.

Methods and materials

Patient eligibility. In this retrospective study, data were collected from the Tumor Radiotherapy Center of Fuzhou General Hospital. A total of 1,086 consecutive HCC patients were treated with gamma-ray SBRT between May, 2006 and December, 2012 and 72 patients were ultimately included in the study after a retrospective review following Institutional Review Board approval. The inclusion criteria were as follows: i) inoperable tumor; ii) tumor sized ≥10 cm; iii) Child-Pugh

class A or B; iv) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2; v) no extrahepatic metastasis; vi) treatment with SBRT combined with incomplete TACE; vii) no history of hepatic radiotherapy. The included patients had undergone contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and/or positron emission tomography of the abdomen. The blood tests included hepatitis B surface antigen, antibody to hepatitis C virus, serum α-fetoprotein (AFP), serum creatinine, albumin, alanine transaminase and total bilirubin. HCC was diagnosed by cytological/histological evidence (n=65), one radiological image showing the characteristic features of HCC together with an elevated AFP level (>400 ng/ml) (n=5), or at least 2 radiological images showing the characteristic features of HCC (n=2). The 72 patients were classified into those with and those without tumor encapsulation (group A, 33 patients and group B, 39 patients, respectively).

Treatment. TACE was performed with infusion of a mixture of 5-10 ml of iodized oil (Lipiodol; Laboratoires Guerbet, Roissy-Charles-de-Gaulle Cedex, France) and 1 mg/kg cisplatin (Dong-A Pharmaceutical Co. Ltd., Seoul, Korea), followed by gelatin sponge cubes (Gelfoam; Upjohn Co., Kalamazoo, MI, USA). The feeding arteries of the tumor were carefully selected for TACE in order to preserve the liver function as much as possible. TACE was performed without Lipiodol to prevent severe damage to normal liver when there was an arterial portal shunt. SBRT was administered using the total body gamma-ray stereotactic radiotherapy system 2-4 weeks after TACE. Briefly, the patients were immobilized by vacuum cushions and underwent a CT scan in the supine or prostrate position. The CT data were transferred to the SBRT Treatment Planning System (SGI; Southeast University, Nanjing, China). The body surface, tumor contour and important normal tissues were reconstructed to display three-dimensional representation. The clinical target volume (CTV) is defined as the macroscopic volume of the tumor. The planning target volume (PTV) was created by symmetrically expanding the CTV by 0.5 cm. The position, number and size of focused fields were elaborately selected to enhance the dose for the PTV but minimize the dose to the normal tissues and the irradiated volumes. The generated dose-volume histogram and isodose curves were used to evaluate the treatment planning. Dose prescription was normalized at 50 or 55% isodose curve. Verification films were taken to verify the tumor localization and the patient's position prior to SBRT. The median total dose of 35.6 Gy was delivered over 12-14 days with a fractional dose of 2.6-3.0 Gy and 6 fractions per week. The total and fractional dose depended on the predicted toxicity of normal tissues and the functional liver reserve. All the patients had one day of rest after every 6 consecutive fractions of treatment. Written informed consent was obtained from each patient prior to treatment with TACE and SBRT.

Evaluation of response, survival and toxicity. The patients were weekly assessed by complete blood counts and liver function tests during the course of the treatment. Tumor response within the radiotherapy field was based on CT and/or MRI scans 4 weeks after the completion of the treatment and at 1- to 3-month intervals thereafter. According to the World Health Organization criteria (21), complete response (CR) was defined as disappearance of the tumor, partial response (PR) as a >50% decrease in tumor size, progressive disease (PD) as a >25% of in-field tumor growth and stable disease (SD) as neither PR nor PD. The sum of CR and PR was defined as objective response (OR). Survival time was estimated from treatment initiation to the date of death or the last follow-up.

Acute and late toxicities were assessed using the National Cancer Institute Common Toxicity Criteria, version 2.0, and the Late Radiation Morbidity Scoring Scheme of Radiotherapy Oncology Group/European Organization for Research and Treatment of Cancer, respectively.

Statistical analysis. The overall survival (OS) rate was calculated using the Kaplan-Meier method. The log-rank test was used to identify the predictive factors for survival. For multivariate analysis to evaluate the association between the OS and various parameters, the stepwise procedure was performed using the Cox regression model. $P<0.05$ was considered to indicate a statistically significant difference. The statistical analyses were conducted using the SPSS 16.0 statistical software package (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics. The two groups of patients were compared by age, gender, tumor size, ECOG PS, Child-Pugh classification, fractional dose and delivered total dose. The characteristics of the investigated patients are compared in Table I.

Tumor response. Among the 72 patients, CR, PR, SD and PD were observed in 6 (8.3%), 51 (70.8%), 9 (12.5%) and 6 patients (8.3%), respectively, within a median follow-up of 18 months. The OR rate was 79.1%. In group A, 2 patients (6.1%) had in-field recurrence and 5 patients (15.2%) developed intra-and/or extrahepatic metastases within 1 year. In group B, 4 patients (10.3%) had in-field recurrence within 8 months and 13 patients (33.3%) developed intra-and/or extrahepatic metastases within 1 year. None of the patients in group B achieved a CR. The tumor responses in the two groups are compared in Table II.

Survival outcomes. The follow-up period ranged between 4 and 70 months (median, 18 months). The Kaplan-Meier survival analysis indicated an overall cumulative median survival of 12.2 months (range, 7.6-66.4 months; Fig. 1). The overall cumulative 1-, 3- and 5-year survival rates assessed by the life table (survival) analysis were 38, 12 and 3%, respectively. A multivariate analysis was performed using the Cox regression model. The results indicated that age, gender, ECOG PS, tumor size, delivered dose and AFP level were not associated with overall cumulative survival. However, patient grouping (A vs. B) was associated with overall cumulative survival. In group A, the overall cumulative 1-, 3- and 5-year survival rates were 56, 21 and 6%, respectively, with a median survival of 19 months. The results were significantly better compared to those in group B, in which the overall cumulative 1-, 3- and 5-year survival rates were 23, 4 and 0%, respectively, with a median survival of 10.8 months ($P=0.023$). Child-Pugh class (A vs. B) was also associated with overall cumulative survival;

Table I. Characteristics of the included patients.

Variables	Group A		Group B	
	Values	No. of patients (%)	Values	No. of patients (%)
Age, years range (mean)	41-69 (54)		38-66 (51)	
Gende				
Male		27 (81.8)		30 (76.9)
Female		6 (18.2)		9 (23.1)
ECOG PS				
0		3 (9.1)		0 (0.0)
1		22 (66.7)		29 (74.4)
2		8 (24.2)		10 (25.6)
Child-Pugh class				
A		24 (72.7)		28 (71.8)
B		9 (27.3)		11 (28.2)
AFP, ng/ml				
≥400		27 (81.8)		32 (82.1)
<400		6 (18.2)		7 (17.9)
HBsAg-positivity		25 (75.8)		29 (74.4)
Anti-HCV-positivity		4 (12.1)		5 (12.8)
C/H confirmation				
Yes		30 (90.9)		35 (89.7)
No		3 (9.1)		4 (10.3)
Delivered dose, Gy range (median)	33.8-39.0 (35.7)		33.8-39.0 (35.4)	
Fractional dose, Gy range (median)	2.6-3.0 (2.8)		2.6-3.0 (2.8)	
Tumor size, cm range (median)	10.8-16.5 (12.6)		10.2-17.6 (13.1)	

ECOG PS, Eastern Cooperative Oncology Group performance status; C/H, cytological/histological; AFP, α-fetoprotein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Table II. Response of huge HCCs treated by SBRT combined with TACE.

Type of response	No. of patients (%)	
	Group A	Group B
Complete response (CR)	6 (18.2)	0 (0.0)
Partial response (PR)	24 (72.7)	27 (69.2)
Stable disease (SD)	1 (3)	8 (20.5)
Progressive disease (PD)	2 (6.1)	4 (10.3)
Objective response (OR=CR+PR)	31 (90.9)	27 (69.2)

the overall cumulative 1-, 3- and 5-year survival rates of Child-Pugh class A patients were 57.2, 23.6 and 8.2%, respectively, vs. 35.4, 6.5 and 0% in Child-Pugh class B patients. However, the difference was not statistically significant (P=0.068). The overall cumulative survival of the two groups (A vs. B) and

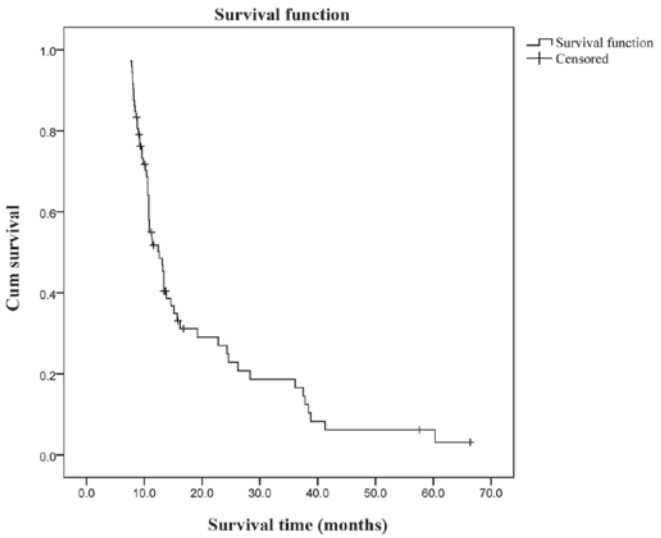

Figure 1. Overall survival of huge HCC treated with a combination of stereotactic body radiotherapy and transarterial chemoembolization. Cum, cumulative.

Table III. Complications and toxicities due to stereotactic body radiotherapy.

	Grade		
	1	2	3
Complication/toxicity	No. (%)	No. (%)	No. (%)
Edema	2 (2.8)		
Anemia	1 (1.4)		
Gastrointestinal toxicity	3 (4.2)	4 (5.6)	
Fatigue	18 (25.0)	10 (13.9)	
Nausea	6 (8.3)	4 (5.6)	
Dermatitis	5 (6.9)	13 (18.1)	3 (4.2)
Elevated liver function tests	1 (1.4)	3 (4.2)	

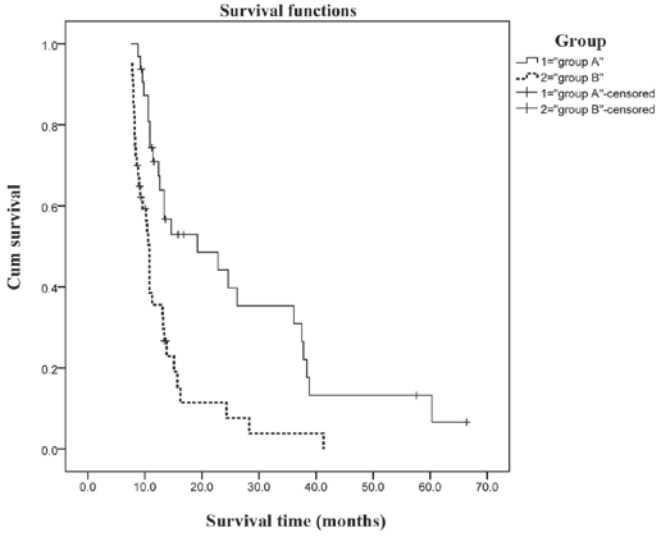

Figure 2. Overall survival stratified by group A (tumor with encapsulation) vs. group B (tumor without encapsulation). Cum, cumulative.

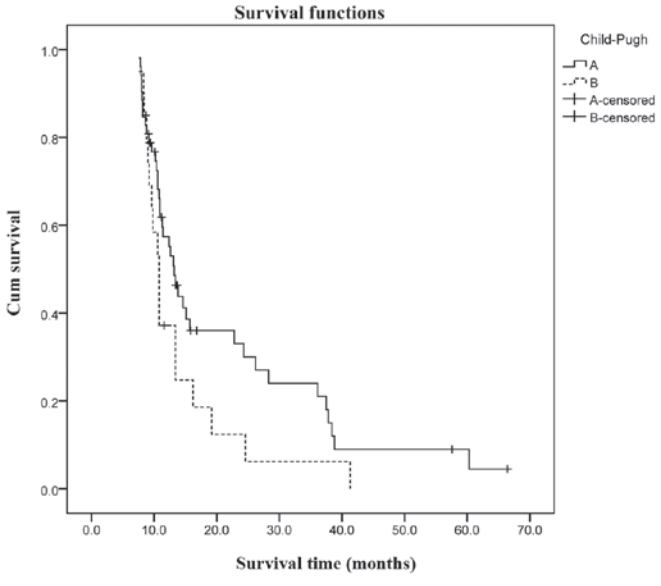

Figure 3. Overall survival stratified by Child-Pugh classification (class A vs. B). Cum, cumulative.

Child-Pugh classes (A vs. B) is shown in Figs. 2 and 3, respectively.

Toxicity. All the patients completed the treatment with no severe radiation-induced liver disease (RILD) observed during the median 18-month follow-up period (range, 4-70 months). Grade 1-2 liver and gastrointestinal toxicity were observed in 4 (5.6%) and 7 (9.8%) patients, respectively. The most common complication was fatigue, which was observed in 28 patients (38.9%). Dermatitis was also frequently encountered. The most severe complication was grade 3 dermatitis, which was observed in 3 patients (4.2%). The tumor diameter in those 3 patients was ≥16 cm (16.5, 16.8 and 17.6 cm, respectively) and the tumors were adjacent to the skin. The complications and toxicity are summarized in Table III.

Discussion

Treatment options for huge (≥10 cm) HCCs are limited. Large tumors are more likely to recur (22-25), as they harbor unrecognized small vessel tumor invasion (26). Furthermore, large tumors may portend worse biological behavior due to genetic factors which are currently unknown (27).

In this study, the outcomes of 72 patients with huge HCCs treated with a combination of TACE and SBRT were retrospectively analyzed. The rationale for this combined treatment was based on the following evidence: First, the efficacy of TACE alone for patients with unresectable HCC has been unsatisfactory (12,28,29); second, the deposit of iodized oil after TACE may help in more accurate contouring of the margin of gross tumor volume (GTV) in SBRT; and third, the irradiation dose delivered to the liver may be reduced, as the tumor often shrinks due to TACE.

The outcomes in this study demonstrated that huge HCCs treated with this combination therapy may achieve a high objective response rate (79.1%) and a low incidence of recurrence (8.3%). In addition, this combined modality may prolong patient survival (the overall cumulative median survival was 12.2 months and the overall cumulative 1-, 3- and 5-year survival rates were 38, 12 and 3%, respectively). Tumor encapsulation was found to be a significant prognostic factor for survival, as encapsulated tumors treated with this

combined therapy achieved better results compared to unencapsulated tumors, which is in accordance with previously reported results (30,31). In contrast to other findings (32), the Child-Pugh class was associated with overall cumulative survival in this study, although the difference was not statistically significant (P=0.068).

The survival of patients with encapsulated tumors in this study was comparable to the survival of patients with huge HCCs treated by resection; however, the incidence of recurrence of huge HCCs treated with the current combined modality was significantly lower compared to that following resection (33). In addition, the eligibility criteria for patients were significantly different, as patients treated by resection should be strictly selected (34). The outcomes in this study were also comparable to those previously reported (35). Of note, there was no severe toxicity observed in this study. This may be due to the fact that gamma-ray SBRT is able to easily meet the requirement of limiting the irradiation of normal liver; 30 beams of gamma-rays revolve around an axis and then shape the focused field, leading to the delivery of an increased dose to the target, while sparing the uninvolved liver. Additionally, the PTV is encompassed by a prescription isodose curve of 50 or 55%, but ≥70% isodose curves are all in the GTV. The dose delivered to the GTV was significantly higher compared to the dose delivered to normal tissue. The striking difference of the dose between GTV and normal tissue is considered to be the main reason that huge HCCs treated by this combined therapy achieve high response rates without accompanying severe toxicity. However, grade 3 dermatitis was observed in 3 patients (4.2%). The tumor diameters of those 3 patients were >16 cm (16.5, 16.8 and 17.6 cm) and the tumors were adjacent to the skin. Additionally, the fractional dose was as high as 3 Gy. The development of grade 3 dermatitis reflects the shortcomings of the technology in the treatment of such tumors (>16 cm) that are adjacent to skin. Although the beams of gamma-rays revolve around an axis and then shape the focused field, the direction of the axis is perpendicular. Several fields are required for a huge tumor, so that the prescription isodose curve (50 or 55%) encompasses the PTV. The skin (including the subcutaneous tissue) is at the entrance channel of each focused field. The dose delivered to the skin by each focused field is quite small, but dermatitis of proximal skin may be caused when numerous fields are merged. Dermatitis, particularly grade 3 dermatitis, may be avoided by lowering the fractional dose.

The delivered total dose and fractional dose in this study depended on the predicted toxicity of normal tissues and the functional liver reserve. In conventional radiotherapy, patients generally receive the treatment over 35-49 days (5-7 weeks) and 5 consecutive fractions per week, with a daily fraction of 2 Gy. Since the longer the treatment period, the more the dose is reduced, Toya *et al* (36) suggested that it may be more appropriate for HCC patients to be treated with radiotherapy over a shorter period of time. In the present study, all the patients received the SBRT treatment over 12-14 days, with a daily fraction of 2.6-3.0 Gy and 6 fractions per week. Although the fractional dose was higher compared to conventional radiotherapy, the treatment period was significantly shorter.

There were certain limitations to this study, mainly due to its retrospective design. For example, the treatment schedules were mainly determined by disease progression. In addition, the association between the radiation dose and the liver volume was not investigated. Therefore, a randomized trial may be required to determine the role of individual SBRT combined with TACE in the treatment of huge HCCs.

In summary, the outcomes demonstrate that combined treatment with SBRT and TACE is a safe, effective and promising option for unresectable huge HCCs. Further randomized trials are required to confirm the utility of this combined modality. Of note, patients with tumors >16 cm that are adjacent to the skin should be irradiated with a small fractional dose.

References

1. Sangiovanni A, Del Ninno E, Fasani P, *et al*: Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. Gastroenterology 126: 1005-1014, 2004.
2. Cormier JN, Thomas KT, Chari RS, *et al*: Management of hepatocellular carcinoma. J Gastrointest Surg 10: 761-780, 2006.
3. Pakin DM, Bray F, Ferlay J and Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108, 2005.
4. Llovert JM, Burroughs A and Bruix J: Hepatocellular carcinoma. Lancet 362: 1907-1917, 2003.
5. No authors listed: Predictive factors for long term prognosis after partial hepatectomy for patients with hepatocellular carcinoma in Japan. The Liver Cancer Group of Japan. Cancer 74: 2772-2780, 1994.
6. Bruix J and Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases: Management of hepatocellular carcinoma. Hepatology 42: 1208-1236, 2005.
7. Chirica M, Scatton O, Massault PP, *et al*: Treatment of stage IVA hepatocellular carcinoma: should we reappraise the role of surgery? Arch Surg 143: 538-543, 2008.
8. Mazzaferro V, Regalia E, Doci R, *et al*: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334: 693-699, 1996.
9. Yanaga K: Current status of hepatic resection for hepatocellular carcinoma. J Gastroenterol 39: 919-926, 2004.
10. Zhou ZD, Tang ZY, Yang BH, *et al*: Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. Cancer 91: 1479-1486, 2001.
11. Mazzaferro V, Chun YS, Poon RT, *et al*: Liver transplantation for hepatocellular carcinoma. Ann Surg Oncol 15: 1001-1007, 2008.
12. Trevisani F, De Notariis S, Rossi C and Bernardi M: Randomized control trials on chemoembolization for hepatocellular carcinoma: Is there room for new studies? J Clin Gastroenterol 32: 383-389, 2001.
13. Hawkins MA and Dawson LA: Radiation therapy for hepatocellular carcinoma: from palliation to cure. Cancer 106: 1653-1663, 2006.
14. Meng MB, Cui YL, Lu Y, *et al*: Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol 92: 184-194, 2009.
15. Ren ZG, Zhao JD, Gu K, *et al*: Three-dimensional conformal radiation therapy and intensity-modulated radiation therapy combined with transcatheter arterial chemoembolization for locally advanced hepatocellular carcinoma: an irradiation dose escalation study. Int J Radiat Oncol Biol Phys 79: 496-502, 2011.
16. Law AL, Ng WT, Lee MC, *et al*: Treatment of primary liver cancer using highly-conformal radiotherapy with kV-image guidance and respiratory control. Radiother Oncol 102: 56-61, 2012.
17. Yang ZX, Wang D, Wang G, *et al*: Clinical study of recombinant adenovirus-p53 combined with fractionated stereotactic radiotherapy for hepatocellular carcinoma. J Cancer Res Clin Oncol 136: 625-630, 2010.
18. Price TR, Perkins SM, Sandrasegaran K, *et al*: Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. Cancer 118: 3191-3198, 2012.
19. Son SH, Choi BO, Ryu MR, *et al*: Stereotactic body radiotherapy for patients with unresectable primary hepatocellular carcinoma: dose-volumetric parameters predicting the hepatic complication. Int J Radiat Oncol Biol Phys 78: 1073-1080, 2010.

20. Zhong NB, Chen ZH and LV GM: A clinical study on stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis. J Cancer Res Ther 1: 143-148, 2013.
21. WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No. 48 Geneva: World Health Organization; Geneva, 1979.
22. Shah SA, Greig PD, Galllinger S, *et al*: Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. J Am Coll Surg 202: 275-283, 2006.
23. Regimbeau JM, Abdalla Ek, Vauthey JN, *et al*: Risk factors for early death due to recurrence after liver resection for hepatocellular carcinoma: results of a multicenter study. J Surg Oncol 85: 36-41, 2004.
24. Yeh CN, Lee WC and Chen MF: Hepatic resection and prognosis for patients with hepatocellular carcinoma larger than 10 cm: two decades of experience at Chang Gung memorial hospital. Ann Surg Oncol 10: 1070-1076, 2003.
25. Shah SA, Wei AC, Cleary SP, *et al*: Prognosis and results after resection of very large (>or=10 cm) hepatocellular carcinoma. J Gastrointest Surg 11: 589-595, 2007.
26. Pawlik TM, Delman KA, Vauthey JN, *et al*: Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl 11: 1086-1092, 2005.
27. Llovet JM, Schwartz M and Mazzaferro V: Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 25: 181-200, 2005.
28. Harada T, Matsuo K, Inoue T, *et al*: Is preoperative hepatic arterial chemoembolization safe and effective for hepatocellular carcinoma? Ann Surg 224: 4-9, 1996.
29. Lee JK, Chung YH, Song BC, *et al*: Recurrence of hepatocellular carcinoma following initial remission by transcatheter arterial chemoembolization. J Gastroenterol Hepatol 17: 52-58, 2002.
30. Mok KT, Wang BW, Lo GH, *et al*: Multimodality management of hepatocellular carcinoma larger than 10 cm. J Am Coll Surg 197: 730-738, 2003.
31. Wu TH, Yu MC, Chen TC, *et al*: Encapsulation is a significant prognostic factor for better outcome in large hepatocellular carcinoma. J Surg Oncol 105: 85-90. 2012.
32. Ng KM, Yan TD, Black D, *et al*: Prognostic determinants for survival after resection/ablation of a large hepatocellular carcinoma. HPB (Oxford) 11: 311-320, 2009.
33. Chen XP, Qiu FZ, Wu ZD, *et al*: Long-term outcome of resection of large hepatocellular carcinoma. Br J Surg 93: 600-606, 2006.
34. Poon RT, Fan ST and Wong J: Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. J Am Coll Surg 194: 592-602, 2002.
35. Lee MT, Kim JJ, Dinniwell R, *et al*: Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol 27: 1585-1591, 2009.
36. Toya R, Murakami R, Baba Y, *et al*: Conformal radiotherapy for portal vein tumor thrombosis of hepatocellular carcinoma. Radiother Oncol 84: 266-271, 2007.