The purpose of this study is to evaluate the therapeutic results of small hepatocellular carcinoma (HCC) treated with hyperfractionated three-dimensional conformal radiotherapy (3-D conformal RT). This retrospective study was to review 39 small HCC (tumor ≤ 5 cm in size) patients who had been treated with hyperfractionated 3-D conformal RT from October 1999 to December 2000. The mean age was 59.79 ± 10.45 years old (range 35-80 years old). Patients had the mean follow-up period of 511.67 ± 104.81 days (range 307-812 days). Hyperfractionated 3-D conformal RT was delivered using 6 or 10 MV photons at 1.5 Gy per fraction, twice a day on 5 days of the week for a total dose of 45-75 Gy. The mean treatment volume was 137.22 ± 76.40 ml (ranged 26.93-334.06 ml). The cumulative survival rates were 100.0% for 180 days, 97.44% for 360 days and 62.64% for 720 days, respectively. The overall median survival time was 495 days. Acute radiation toxicity included 10 patients (25.6%) leukopenia, 9 patients (23.1%) had elevation in liver function tests, 3 patients (7.7%) had fever and 13 patients (33.3%) complained GI toxicity. Late complications were occurred in 3 patients (2 RT enteritis, 1 UGI bleeding). Our experience concludes that hyperfractionated 3-D conformal RT may be a safe, effective treatment modality in small HCC patients with preserved liver function even if they have already been treated with other therapies. The preliminary data shows quite promising and is valuable to study the potential role of 3-D conformal RT in strengthening the therapeutic efficacy when combined with other therapy.

Key words: Conformal radiotherapy, hepatocellular carcinoma, hyperfractionation, radiation toxicity

Hepatocellular carcinoma (HCC) is one of the world’s most common malignancies, especially in Asian countries. Surgical resection remains the treatment of choice for long-term control of the disease. However, less than 20% of patients are amenable to surgery at diagnosis [1-2]. Formerly, conventional radiotherapy (RT) has a limited role in the treatment of HCC because of poor tolerance of normal liver tissue. With the introduction of advanced computed tomography assisted radiation three-dimensional (3-D) treatment planning, the fractionated stereotactic RT is used for patients with advanced HCC [3]. Moreover, HCC is known to have a doubling time of approximately 41 days [4]. This rapid cell division suggested that hyperfractionated radiation might add an advantage in gaining remission of this malignancy. In this pilot study, 39 small HCC patients were treated with hyperfractionated three-dimensional conformal radiotherapy (3-D conformal RT) in order to determine the potential role of this new treatment modality.

MATERIALS AND METHODS

Patient characteristics

From October 1999 through December 2000, totally 39 patients with small HCC (tumor ≤ 5 cm)
were recruited into this study. Eleven patients had no previous treatment. Nineteen patients received transcatheter arterial embolization (TAE) or transcatheter arterial chemoembolization (TACE), 3 patients received percutaneous ethanol injection (PEI) and the other 2 patients received hepatectomy before 3-D conformal RT. Moreover, two patients received TAE and PEI; the other 2 patients received hepatectomy and TAE. The eligibility criteria required the leukocyte > 2,500 /µL, the platelet count > 80,000 /µL, serum total bilirubin ≤ 3.0 mg/dL, ALT ≤ 100 kU, AST ≤ 100 kU and at least 30 elapsed days if previous treatments were performed. There were 27 men and 12 women with an age range from 35 to 80 years old and with the mean age of 59.79 ± 10.45 years old. Patients had the mean follow-up period of 511.67 ± 104.81 days in a range from 307 to 812 days. The characteristics of all the patients are illustrated in Table 1.

The response assessment was based on serial abdominal CT scan obtained at the initiation of the treatment and 3-6 months later after R/T completed. The responses of the tumor were classified as follows: (1) complete response (CR): more than 75% decrease of the tumor; (2) partial response (PR): more than 50% and less than 75% decrease of the tumor; (3) stationary disease (SD): less than 50% decrease of the tumor.

**RT technique**

The patient is treated in the supine position with the arm toward the head and immobilized with the individual vacuum cushion on the patient tray. BrainLab ExacTrac system was used for immobilization and reposition during CT scans and 3-D conformal RT. A treatment-planning CT scan with 5mm slices was performed that included a portion of the inferior chest and the entire abdomen for planning the non-coplanar fields. All CT images were transferred to BrainLab planning workstation (BrainSCAN version 4.0) via DICOM transfer. The gross tumor volume (GTV) is defined as radiographically abnormal area seen on the CT images. The clinical target volume (CTV) is defined as the GTV plus 0.5 cm margin for subclinical tumor. The planning target volume (PTV) includes the CTV plus 0.5 cm for daily patient set-up variation and between 0.5-2.5 cm (determined under fluoroscopy) in the cranial-caudal dimension to account for the ventilatory motion of liver. Treatment plans were designed for each patient in which the high-dose region encompassed the PTV and maximally spared normal liver outside of the PTV. Radiation techniques for 35 patients were used coplanar beams, and the other 4 patients were used non-coplanar beams. All treatment was delivered by a linear accelerator with 6 or 10 MV photons. For all patients, RT was delivered at 3 Gy per day on 5 days a week in two 1.5 Gy fractions each day, separated by at least 6 hours. Radiation dosage to the target volume ranged from 45-75 Gy depending on the tolerance of the patients and the functional reserve of the liver. Treatment volume was ranged from 26.93 to 334.06 ml with the mean volume of 137.22 ± 76.40 ml. Treatment portals were ranged from 3 to 6 with the mean portals of 4.56 ± 0.99.

### Statistical Methods

Actuarial survival was calculated using the method of Kaplan and Meier. Survival statistical multivariate analysis was made by the Cox regression model. Survival duration was measured from the first day of RT until the day of death or last contact with the patient. Comparisons of different factors that influence toxicity were performed by backward stepwise method of binary logistic regression. A value of P < 0.05 was regarded as significant.

### RESULTS

There was 9 patients (9/39, 23.1%) showed CR of the tumor responded to 3-D conformal RT. In addition, there were 23 (23/39, 59.0%) and 7 (7/39, 17.9%) patients revealed PR and SD after 3-D conformal RT. The shrinkage of tumors were showed as figure 1 and figure 2.

The cumulative survival values were 100.0% for

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<td>35-80 year old (59.79 year old)</td>
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<td>Sex</td>
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<td>Karnofsky performance status</td>
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<tr>
<td>Normal liver volume (mean)</td>
<td>728.27-2156.4 ml (1154 ml)</td>
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<td>Tumor volume (mean)</td>
<td>26.93-334.06 ml (137.22 ml)</td>
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<td>Pre-treatment albumin level (mean)</td>
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180 days, 97.44% for 360 days and 62.64% for 720 days, respectively (Fig. 3). The median survival time was 495 days. Three patients were dead with the disease during the follow-up periods (307, 566 and 674 days after the initiation of RT).

Radiation toxicity was assessed using the acute radiation morbidity scoring criteria of the Radiation Therapy Oncology Group (RTOG). Acute radiation toxicity was evaluated during treatment weekly to 3 months following the treatment. Ten patients (25.6%) had leukopenia (6 grade I, 3 grade II, 1 grade III) during 3-D conformal RT. Nine patients (23.1%) had transient elevation in liver function tests (5 grade I, 2 grade II, 2 grade III). Fever in absence of infection (all 3 grade II) was found in 3 patients (7.7%). The characteristics of fever were low grade (equal or below than 38.5°C) and occurred within 3-5 weeks after initiation of RT. Thirteen patients (33.3%) complained gastrointestinal toxicity (6 grade I, 5 grade II, 2 grade III). Late complications were occurred in 3 patients (7.7%). Two patients had grade II RT enteritis and the other one had upper gastro-intestinal bleeding (grade II).

Multivariate analysis demonstrated all factors that including age, gender, site, normal liver volume, tumor volume, Child classification, Karnofsky performance status, pre-treatment albumin level and AFP (divided into positive and negative) did not appear to predict outcome significantly. Logistic regression analysis showed that RT complications were not significantly affected by age, gender, normal liver

Figure 1. A 46-year-old male patient with right side small HCC. a. The CT images show right liver mass before 3-D conformal RT (arrow). b. The CT images show elimination of right liver mass after 3-D conformal RT (arrow).

Figure 2. A 61-year-old male patient with right side small HCC. a. The CT images show right liver mass before 3-D conformal RT (arrow). b. Shrinkage of right liver mass after 3-D conformal RT (arrow).
volume, tumor volume, Child classification, Karnofsky performance status, pre-treatment albumin level and AFP. Only tumor site significantly influenced the complications (p=0.008).

DISCUSSION

The overall incidence rate of neoplasm of liver and intrahepatic bile ducts was 28.54% per million populations and the second most frequent cause of cancer deaths in Taiwan in 1997. Indeed, of the various solid cancers, HCC may be the most difficult to treat because of frequently associated cirrhosis especially in Taiwan. With the progress in imaging techniques and tumor markers in recent years, small HCC have come to be detected [5-6]. Although most authorities agree that surgical treatment is the most effective treatment for patients with HCC [7-8], various therapeutic modalities other than surgery have been developed with improvement [9-12].

PEI is highly used for patients with one to three nodules smaller than 3 cm. However, because of underlying lung and the risk of pneumothorax, tumors at the dome of the liver are difficult to treat by this method. In addition, patients with ascites, bleeding tendency, and obstructive jaundice are poor candidates for PEI, as the risk of post-procedural bleeding and bile peritonitis. Cryosurgery could be treated relatively larger size of tumor than PEI. However, the major disadvantage of cryosurgery is the need for general anesthesia and laparoscopy or laparotomy. Furthermore, not only freezing of tumors near major vascular channels is difficult because of the risks of bleeding, but complete freezing is virtually impossible because warm blood circulates in the vessels. Since TAE is useful for the treatment of unresectable tumors, some reports for small HCC have been encouraging [13-14]. However, it is almost impossible to achieve complete tumor necrosis with conventional TAE, and repeat TAE has an adverse effect on liver function [14-15]. Moreover, it has been reported that small lesions around the tumor, such as intrahepatic metastases or tumor emboli in the intrahepatic portal vein, as resistant to TAE [16-17]. With respect to blood supply to the tumor, it was suggested that the experimental small HCC was supplied not only by the hepatic artery but also by the portal vein. These results indicate that TACE might be ineffective against small HCC [18].

Formerly, the role of conventional RT in HCC has always been limited by the inability of the whole liver and its innocent bystander hepatocytes to tolerate a therapeutic dose of radiation. With elegant 3D radiation treatment planning, we are able to design portals at the beam’s eye view with various angles and in non-coplanar fashion for concentrating high dose to the tumor areas and keeping dosages to surrounding normal tissue as small as possible. Preliminary data also suggest that the targeting of tumor and sparing of uninvolved liver can be accomplished [3, 9, 11, 12, 19].

In series of 28, 62, and 144 patients with small HCC, Shinagawa et al [5], Lee et al [20], and Tang et al [21] reported operative mortality of 10%, 6%, and 2.3% and 1-year survival rates of 78%, 86% and 91.8%, respectively. Zhou et al [22] reported the treatment of 30 small HCC patients by cryosurgery, the 1-year, 3-year, and 5-year survival rates were 92.6%, 66.6%, and 50.8%, respectively. Ohnishi et al [23] reported treating 25 patients with solitary HCC of 3 cm or less in diameter by ultrasound-guided percutaneous acetic acid injection (PAI). The 1-year and 2-year survival rates were 100% and 92%, respectively, for the 23 patients who did not undergo surgery. The results of treatment for small HCC (less than 2 to 5 cm) by PEI have been reported in different series with a 3-year survival rate of 55% to 70% [24-26]. Nakao et al [13] reported treating 108 patients with small HCC (less than 3 cm) by TAE, the 1-year, 2-year, and 5-year survival rates were 73%, 64%, and 9%, respectively. Matsui et al [14] reported that 1-year, 2-year and 4-year survival rate for the 82 patient of small HCC (less than 4 cm) with Child class A or B disease treated by TAE were 100%, 92%, and 67%, respectively. In our study, the cumulative survival values were 100.0% for 180 days, 97.44% for 360 days and 62.64% for 720 days, respectively. It is comparable with other treatment modality. To our knowledge,
One page of a document is presented. The text includes a discussion on the efficacy of 3-D conformal RT (cRT) for small HCC (hepatocellular carcinoma). It references various studies and authors, discussing factors such as AFP (alpha-fetoprotein), tumor size, and Child-Pugh grade in relation to survival. The text also mentions potential limitations due to small sample size and the need for further research.

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**Reference**

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小型肝癌之多分次三度空間順形放射治療：前導研究

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台中澄清綜合醫院 放射腫瘤科1 放射線科2 內科4 一般外科5
台北市立中興醫院 放射腫瘤科3

本研究之目的為評估多分次三度空間順形放射治療對小型肝癌的治療成效。

此回溯性研究乃針對1999年10月至2000年12月，39位實行多分次三度空間順形放射治療之小型肝癌（腫瘤小於5公分）病患。病患平均年齡為59.79 ± 10.45歲（從35至80歲），平均追蹤日數為511.67 ± 104.81天（從307至812天）。多分次三度空間順形放射治療利用6至10百萬伏特光子射線，以每次1.5戈雷，每天2次，每週5天，總劑量45至75戈雷之方式施行。平均治療體積為137.22 ± 76.40毫升（從26.93至334.06毫升）。

180天、360天和720天之累積存活率分別為100.0%、97.44%和62.64%。整體中位存活期間為495天。急性放射副作用，包括：10位病患白血球降低（25.6%）、9位病患肝功能檢查上升（23.1%）、3位病患為發燒（7.7%）和13位病患有腸胃反應。三位病患（2位放射線引起之腸炎、1位上消化道出血）發生晚期副作用。

我們的經驗指出對即使已接受其他方式治療，其肝功能仍屬正常之小型肝癌病患，多分次三度空間順形放射治療是安全有效之治療模式。初步資料顯示當併用其他療法時，研究三度空間順形放射治療於治療效果上所扮演的潛在角色是極具價值且有成功的希望。

關鍵詞：順形放射治療，肝癌，多分次，放射毒性