The Purpose of this work is to evaluate the response and therapeutic results of hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT) treated with 3-Dimensional (3-D) conformal radiotherapy (RT).

Twenty-four HCC patients with PVT who had been treated with 3-D conformal RT from October 1998 to September 2000 were reviewed. The mean age was 54.1 years old (range 30-73 years old). Patients had the mean follow-up period of 265 days (range 68-689 days). Three-dimensional conformal RT was delivered using 6 or 10 MV photons at 1.8- 2 Gy per fraction, once a day on 5 days of the week for a total dose of 43.2- 75 Gy. The mean treatment volume was 455.76 ml (ranged 62.39-1436.76 ml).

In general, the HCC patients with PVT who received 3-D conformal RT had good responses (63%, 15/24). By multivariate analysis, intrahepatic or extrahepatic involvement was the only significant factor that influenced the response of PVT (p=0.025). The 180 and 360 days survival rates were 72.0% and 55.4%. The median survival time was 215.5 days. Using Cox's regression model for multivariate survival analysis, treatment dose (p=0.011), intrahepatic or extrahepatic involvement (p=0.041) and treatment volume (p=0.032) were found to affect the prognosis. When treatment volume was divided into less than 500 ml and equal or more than 500 ml subgroups, the survival curves showed statistical significance (p=0.029). Radiation-induced acute complications, including leukopenia, transient liver dysfunction, and epigastralgia, were mild and reversible.

Our experience concludes that 3-D conformal RT may be a safe and effective treatment modality for unresectable HCC patients with PVT. The preliminary data shows quite promising and it is valuable to study the potential role of 3-D conformal RT in the treatment strategy for HCC at various stages.

Key words: Conformal radiotherapy, hepatocellular carcinoma, portal vein thrombosis

Hepatocellular carcinoma (HCC) is one of the world’s most common malignancies and the leading cause of cancer death in Taiwan. Surgical resection remains the treatment of choice. However, approximately only one of five patients is amenable to surgery at the time of diagnosis because of the advanced stage of HCC and/or the poor hepatic reserve function of underlying liver [1-2]. In cases of unresectable HCC, treatment combining transarterial embolization (TAE) and transarterial chemoembolization (TACE) might be very effective [3]. But those treatments are not feasible...
for patients with thrombosis of portal vein because of the possibility of hepatic failure following embolization. For the treatment of HCC patients with portal vein thrombi, systemic chemotherapy using various anti-cancer agents have been tried but the results were not convincing [4-5].

Radiotherapy (RT) has a limited role in the treatment of HCC formerly. The major problem is poor tolerance of normal liver tissue. Hence, the dose of conventional RT in HCC has been no more than 35 Gy to whole liver, and it is less likely to obtain the desired therapeutic effect. Taking the advantage of computed tomography assisted radiation three-dimensional (3-D) treatment planning, the fractionated stereotactic RT is used for patients with advanced HCC [6]. In this pilot study, 24 HCC patients with portal vein thrombosis (PVT) were treated with 3-D conformal RT in order to determine the potential role of this new treatment modality.

**MATERIALS AND METHODS**

From October 1998 through September 2000, totally 24 HCC patients with PVT were enrolled in this study. There were 19 men and 5 women with an age range from 30 to 73 years old and with the mean age of 54.1 ± 11.9 years old. Patients had the mean follow-up period of 265 ± 184 days in a range from 68 to 689 days. The characteristics of all the patients are illustrated in Table 1. Eleven patients had no previous treatment. Ten patients received TACE and the other 3 patients received hepatectomy before 3-D conformal RT. The eligibility criteria required the leukocyte > 3,000 /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 after completion of prior TACE.

Prior to entry into this study, all patients underwent complete medical history taking, physical examination, routine blood tests, and biochemical liver function tests, serum alpha-fetoprotein (AFP) assessment, abdominal sonography, and CT imaging studies. According to ultrasound and/or CT scan, the portal vein thrombi were confirmed. The HCC lesions are classified into 3 major types: expansive nodular type, infiltrative type, and diffuse type.

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 (Figure 1). ExacTrac system by BrainLab, Inc. was used for immobilization and reposition during CT scans and treatment. Liver CT for each patient was performed and CT-images were transferred to software planning system BrainSCAN (version 4.0). The gross tumor volume (GTV) is defined as radiographically primary tumor plus abnormal portal areas seen on the CT images. The clinical target volume (CTV) is defined as the GTV plus 1 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 1 and 2.5 cm (determined under fluoroscopy) in the cranial-caudal dimension to account for liver motion resulting from breathing. The treated volume is defined as the volume enclosed by an isodose surface (usually 90%, in our study), selected and specified by the radiation oncologist. Because of limitation of irradiation techniques, the treated volume does not generally match the PTV. We choose the plan that treated volume encompasses PTV in this study. Radiation techniques for all patients were used coplanar beams. All treatment was delivered by a linear accelerator.
Table 1 The characteristics in 24 patients treated with 3-D conformal RT

<table>
<thead>
<tr>
<th>Gender/age</th>
<th>Previous Tx.</th>
<th>Tumor Pattern</th>
<th>Tx. Dose (cGy)</th>
<th>Tx. Volume (ml)</th>
<th>Thrombi Location</th>
<th>No. of Portals</th>
<th>AFP level</th>
<th>Albumin level</th>
<th>KPS (%)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. M/35</td>
<td>Nil</td>
<td>Expansive nodular</td>
<td>4500</td>
<td>675.21</td>
<td>RPV</td>
<td>4</td>
<td>35350</td>
<td>4.0</td>
<td>80</td>
<td>PR</td>
</tr>
<tr>
<td>2. M/69</td>
<td>Nil</td>
<td>Infiltrative</td>
<td>7500</td>
<td>62.39</td>
<td>RPV</td>
<td>6</td>
<td>94.6</td>
<td>4.1</td>
<td>90</td>
<td>SD</td>
</tr>
<tr>
<td>3. M/64</td>
<td>TACE</td>
<td>Infiltrative</td>
<td>4500</td>
<td>210.59</td>
<td>RPV</td>
<td>4</td>
<td>3.0</td>
<td>4.0</td>
<td>90</td>
<td>SD</td>
</tr>
<tr>
<td>4. M/31</td>
<td>Nil</td>
<td>Expansive nodular</td>
<td>4500</td>
<td>746.56</td>
<td>MPV, IVC</td>
<td>2</td>
<td>6530.0</td>
<td>4.2</td>
<td>80</td>
<td>CR</td>
</tr>
<tr>
<td>5. M/59</td>
<td>TACE</td>
<td>Expansive nodular</td>
<td>4500</td>
<td>560.19</td>
<td>MPV, IVC</td>
<td>6</td>
<td>3.9</td>
<td>4.0</td>
<td>90</td>
<td>CR</td>
</tr>
<tr>
<td>6. M/68</td>
<td>Nil</td>
<td>Diffuse</td>
<td>4500</td>
<td>189.08</td>
<td>RPV</td>
<td>4</td>
<td>34435</td>
<td>4.4</td>
<td>80</td>
<td>MR</td>
</tr>
<tr>
<td>7. F/62</td>
<td>Nil</td>
<td>Infiltrative</td>
<td>4800</td>
<td>227.22</td>
<td>MPV, IVC</td>
<td>5</td>
<td>35350</td>
<td>4.0</td>
<td>90</td>
<td>MR</td>
</tr>
<tr>
<td>8. M/58</td>
<td>TACE</td>
<td>Infiltrative</td>
<td>5500</td>
<td>128.14</td>
<td>RPV</td>
<td>6</td>
<td>6809.7</td>
<td>4.1</td>
<td>80</td>
<td>PR</td>
</tr>
<tr>
<td>9. M/45</td>
<td>TACE</td>
<td>Infiltrative</td>
<td>7500</td>
<td>790.25</td>
<td>RPV</td>
<td>6</td>
<td>13.1</td>
<td>4.0</td>
<td>80</td>
<td>SD</td>
</tr>
<tr>
<td>10. M/47</td>
<td>TACE</td>
<td>Expansive nodular</td>
<td>7500</td>
<td>534.16</td>
<td>RPV</td>
<td>5</td>
<td>16.1</td>
<td>4.3</td>
<td>80</td>
<td>SD</td>
</tr>
<tr>
<td>11. F/64</td>
<td>TACE</td>
<td>Infiltrative</td>
<td>4800</td>
<td>475.78</td>
<td>LPV</td>
<td>5</td>
<td>17299</td>
<td>3.9</td>
<td>90</td>
<td>SD</td>
</tr>
<tr>
<td>12. M/63</td>
<td>TACE</td>
<td>Infiltrative</td>
<td>4500</td>
<td>96.59</td>
<td>RPV</td>
<td>6</td>
<td>403.0</td>
<td>4.7</td>
<td>90</td>
<td>PR</td>
</tr>
<tr>
<td>13. M/48</td>
<td>Hepatectomy</td>
<td>Infiltrative</td>
<td>4500</td>
<td>478.13</td>
<td>MPV, IVC</td>
<td>3</td>
<td>4.3</td>
<td>4.6</td>
<td>80</td>
<td>MR</td>
</tr>
<tr>
<td>14. M/44</td>
<td>Nil</td>
<td>Infiltrative</td>
<td>7500</td>
<td>476.70</td>
<td>RPV</td>
<td>3</td>
<td>35350</td>
<td>4.0</td>
<td>80</td>
<td>PR</td>
</tr>
<tr>
<td>15. F/58</td>
<td>Nil</td>
<td>Expansive nodular</td>
<td>7500</td>
<td>112.50</td>
<td>MPV, IVC</td>
<td>3</td>
<td>3.9</td>
<td>3.7</td>
<td>90</td>
<td>CR</td>
</tr>
<tr>
<td>16. M/53</td>
<td>Nil</td>
<td>Diffuse</td>
<td>7500</td>
<td>361.87</td>
<td>RPV</td>
<td>4</td>
<td>11.7</td>
<td>4.2</td>
<td>80</td>
<td>SD</td>
</tr>
<tr>
<td>17. M/58</td>
<td>Hepatectomy</td>
<td>Infiltrative</td>
<td>4800</td>
<td>705.85</td>
<td>LPV</td>
<td>2</td>
<td>1993.9</td>
<td>4.3</td>
<td>80</td>
<td>SD</td>
</tr>
<tr>
<td>18. M/30</td>
<td>TACE</td>
<td>Diffuse</td>
<td>7500</td>
<td>272.70</td>
<td>LPV, MPV</td>
<td>4</td>
<td>25.4</td>
<td>5.1</td>
<td>90</td>
<td>CR/SD*</td>
</tr>
<tr>
<td>19. M/73</td>
<td>Nil</td>
<td>Diffuse</td>
<td>4500</td>
<td>1436.76</td>
<td>RPV</td>
<td>3</td>
<td>12.5</td>
<td>4.5</td>
<td>80</td>
<td>SD</td>
</tr>
<tr>
<td>20. F/58</td>
<td>Nil</td>
<td>Expansive nodular</td>
<td>4500</td>
<td>893.55</td>
<td>RPV, MPV, IVC</td>
<td>4</td>
<td>2.5</td>
<td>3.8</td>
<td>80</td>
<td>MR/SD*</td>
</tr>
<tr>
<td>21. F/44</td>
<td>Hepatectomy</td>
<td>Expansive nodular</td>
<td>5500</td>
<td>71.66</td>
<td>MPV, IVC, right atrium</td>
<td>5</td>
<td>4.2</td>
<td>3.9</td>
<td>80</td>
<td>CR</td>
</tr>
<tr>
<td>22. M/66</td>
<td>Nil</td>
<td>Expansive nodular</td>
<td>4320</td>
<td>640.15</td>
<td>LPV</td>
<td>3</td>
<td>10231</td>
<td>4.3</td>
<td>80</td>
<td>MR</td>
</tr>
<tr>
<td>23. M/47</td>
<td>TACE</td>
<td>Diffuse</td>
<td>4500</td>
<td>320.47</td>
<td>MPV, IVC</td>
<td>4</td>
<td>35350</td>
<td>4.0</td>
<td>80</td>
<td>MR</td>
</tr>
<tr>
<td>24. M/55</td>
<td>TACE</td>
<td>Infiltrative</td>
<td>4500</td>
<td>216.92</td>
<td>MPV, IVC, right atrium</td>
<td>6</td>
<td>15.1</td>
<td>4.2</td>
<td>80</td>
<td>PR</td>
</tr>
</tbody>
</table>

KPS: Karnofsky performance status; M, male; F, female; TACE, trans-arterial chemoembolization; RPV, right portal vein; LPV, left portal vein; MPV, main portal vein; IVC, inferior vena cava; CR: complete response; PR: partial response; MR: minimal response; SD: stationary disease; * extrahepatic/ intrahepatic responses
with 6 or 10 MV photons. Radiotherapy was given five times a week at 1.8-2 Gy per day. Radiation dosage to the target volume ranged from 43.2-75 Gy (mean dosage: 53.9 ± 12.8 Gy, median dosage: 48 Gy) depending on the tolerance of the patients and the functional reserve of the liver. Treatment volume was ranged from 62.39 to 1436.76 ml with the mean volume of 455.76 ± 328.41 ml. Treatment portals were ranged from 2 to 6 with the mean portals of 4.3 ± 1.3.

The response assessment was based on serial abdominal CT scan obtained at the initiation of the treatment and 1-6 months later after R/T completed. The responses of the PVT were classified as follows: (1) complete response (CR): more than 75% decrease of the PVT; (2) partial response (PR): more than 50% and less than 75% decrease of the PVT; (3) minimal response (MR): more than 25% and less than 50% decrease of the PVT; (4) stationary disease (SD): less than 25% increase or decrease of the PVT.

Actuarial survival was calculated using the method of Kaplan and Meier. The log-rank test was used to test the null hypothesis of similarity of survival curves among different factors of patients. Survival duration was measured from the first day of RT until the day of death or last contact with the patient. Multivariate analysis was performed by Cox regression model. For the study of PVT elimination, we assume the medium as the response of PVT, e.g., complete response as 87.5%, partial response as 62.5%. Multivariate analysis of PVT elimination was performed by stepwise method of regression model. A value of P < 0.05 was regarded as significant.

**RESULTS**

**The response of PVT**

In general speaking, sixty-three percent (15/24; 5 CR, 5 PR, 5 MR) of patients responded to 3-D conformational RT. When therapeutic outcome was determined by the changes of PVT from the initiation of RT, it revealed intrahepatic involvement responded with 37.5% (6/16; 4 PR, 2 MR, 10 SD) of the patients and 90% (9/10; 5 CR, 1 PR, 3 MR, 1 SD) of the patients showed improvement of extrahepatic involvement (both extrahepatic and intrahepatic involvement were found in 2 patients). The response of tumor thrombi was showed as figure 2 and figure 3.

Multivariate analysis showed that response of PVT was not significantly affected by age (p=0.092), gender (p=0.276), tumor types (p=0.271), treatment dose (p=0.765), treatment volume (p=0.069). Intrahepatic or extrahepatic involvement significantly influenced the response of PVT (p=0.025).

**Survival**

The cumulative survival values were 72.0% for 180 days and 55.4% for 360 days, respectively (Fig. 4). The median survival time was 215.5 days. Ten patients died of this disease during the follow-up periods. Two patients were dead with other diseases. One patient died of cerebrovascular accident and the other one died of later TACE complication. Multivariate analysis demonstrated age (p=0.835), gender (p=0.091), tumor types (p=0.435), Karnofsky performance status...
(p=0.148), pre-treatment albumin level (p=0.374), AFP (divided into less than 10,000 ng/ml and equal or more than 10,000 ng/ml subgroups, p=0.875) did not influence survival significantly. Treatment dose (p=0.011), intrahepatic or extrahepatic involvement (p=0.041) and treatment volume (p=0.032) were the significant factors (Fig. 5). When treatment volume was divided into less than 500 ml and equal or more than 500 ml subgroups, the survival curves showed statistical significance (p=0.029, Fig. 6). When treatment dose was divided into less than 5000 cGy and equal or more than 5000 cGy subgroups, the survival curves showed statistical significance (p=0.011, Fig. 7).

**Acute complication**

Acute radiation toxicity was evaluated during treat-

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**Figure 3.** A 30-year-old male HCC patient with right portal vein thrombi. **a.** The CT images show tumor thrombi of right portal vein before 3-D conformal RT (arrow). **b.** Shrinkage of right portal vein thrombi after 3-D conformal RT (arrow).

**Figure 4.** The overall survival curve in 24 HCC patients with PVT whom treated with 3-D conformal RT.

**Figure 5.** Comparison of survival rates between intrahepatic involvement (n=16) and extrahepatic involvement (n=10). Both extrahepatic and intrahepatic involvements were found in 2 patients. (P=0.041)

**Figure 6.** Differences in survival rates for patients with treatment volume < 500 ml (n=15) and treatment volume ≥ 500 ml (n=9). There was significant difference between both groups (P=0.029).

**Figure 7.** Differences in survival rates for patients with treatment dose < 50 Gy (n=16) and treatment dose ≥ 50 Gy (n=8), (P=0.011).
ment weekly to 3 month following treatment. According to the Radiation Therapy Oncology Group (RTOG) criteria, 4 patients (16.6%) had leukopenia (3 grade II, 1 grade III) during 3-D conformal RT. Six patients (25.0%) had transient elevation in liver function tests (4 grade I, 1 grade II, 1 grade III). Fever was found in 3 patients (12.5%). The characteristics of fever were low grade (below than 38.5°C) and occurred with in 3-4 weeks after initiation of RT without infection signs. Seven patients (29.2%) complained epigastralgia (4 grade I, 3 grade II). The symptom was subsided after medication. No definite radiation-induced liver disease was found in this study.

DISCUSSION

Approximately 6.5% of HCC patients have combined with PVT at the time of diagnosis [7]. The proportion for cirrhotic patients who develop PVT was estimated to be as high as 16.6% [8]. In the setting of cirrhosis and HCC, the clinical course of PVT may be dramatic: severe liver dysfunction, hepatic encephalopathy and eventually death may follow from intractable ascites and repeated bouts of esophageal variceal hemorrhage [9]. Indeed, advanced HCC patients who didn’t undergo any treatment have poor life expectancy, about four months after the onset of initial symptoms. Moreover, several retrospective studies have shown that presence of PVT may significantly affect prognosis [10-11]. The treatment options for patients with HCC include surgical resection, TACE, and intratumor ethanol injection. However, in the patients with PVT complicating HCC, all the above treatments are associated with the worse prognosis [12-13].

Formerly, conventional RT has limited role in treatment of unresectable hepatoma because the limitation of portal arrangement and portal design. With the development of 3D-treatment planning system, we are able to design portals at the beam’s eye view with various angles and in non-coplanar fashion for concentration of high dose to the PVT and keeping dosages to surrounding normal tissue as small as possible.

In our study, intrahepatic or extrahepatic involvement was the only factor that influenced the response of PVT. Witte et al [9] reported PVT might ensue by direct tumor invasion of the portal vein. Moreover, extrahepatic blood flow and lumen was larger than intrahepatic site. Hence, the elimination of extrahepatic tumor thrombi was faster and more than intrahepatic tumor thrombi.

Lee et al [14] reported the survival rates of the HCC patients with PVT after TACE were 35.5% for 6 months and 22.6% for 9 months. They also found the 6-month and 9-month survival rates with untreated patient were 25.0% and 12.5%, respectively. The medial survival time was 150 days in the TACE group and 90 days in the untreated group. Chung et al [15] reported that 1-year survival rate for the patient of HCC with PVT after TACE and systemic interferon-α was 27.0%. The medial survival period was 19 weeks (133 days) and 5 weeks (35 days) in treated and conservative treatment group. Cheng et al [16] reported seven HCC patients with PVT, their survival after RT ranged from 2-15 months, median 5 months. In our series, the 180-days and 360-days survival rates were 72.0% and 55.4%, respectively. The median survival time was 215.5 days. The survival time seemed to be relatively longer with 3-D conformal RT for HCC patients with PVT. However, because it lacks of a control group in our series, further research is required to support this issue.

Several series have reported the prognostic factors of HCC. Stuart et al [11] reported albumin, AFP and PVT were independent risk factors. Liado et al [17] reported AFP (>400 U/L), tumor size (> 50%), Child-Pugh grade (Child C), and PVT were significantly associated with survival. Lee et al [14] reported tumor type had the greatest prognostic significance. In our study, treatment dose, intrahepatic or extrahepatic involvement and treatment volume <500 ml were significant factors. The response of extrahepatic tumor thrombi was faster and more than intrahepatic tumor thrombi, whereas the survival of extrahepatic involvement was worse than intrahepatic involvement. This might be due to more advance of the disease and the tendency of distant metastasis in extraphepatic involvement group. Therefore, although extrahepatic tumor thrombi were good response for RT, the survival was still poor.

To the best of our knowledge, we are the first to document that 3-D conformal RT was performed in HCC patients with PVT. We agree that the radiation dosage > 40 Gy may achieve tumor regression [16]. However, the dosage that will eradicate cancer cells or tumor thrombi completely is as yet unknown. In our study, treatment dose was a significant factor for survival. Other studies also have found that the dose-response relationship may exist for HCC [18, 19].

Lawrence et al [20] reported that all nine of the patients developing radiation hepatitis in their analysis received whole-liver irradiation to doses of 37 Gy or greater. Moreover, there have been 2 reports of potentially fatal liver dysfunction developing more than 2 year after whole liver irradiation using the moving
strip technique [21, 22]. The late side effects of RT, including gastrointestinal bleeding, large bowel bleeding, were mentioned by Cheng et al [16]. In our study, radiation-related acute hepatic toxicity was mild and reversible. Similar complications have been reported as our previous experience and Cheng et al [6, 16]. Because the periods of follow-up were not long enough in this study, the late complication of RT needs further evaluation.

In conclusion, 3-D conformal RT may be a safe and effective modality compared with conventional RT for the treatment of unresectable HCC patients with PVT. Most of the acute complications were transient, well tolerated and medication controllable.

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REFERENCES

三度空間順形放射治療對肝癌合併肝門靜脈栓塞之初步成果

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本文目的在於評估三度空間順形放射治療對肝癌合併肝門靜脈栓塞之反應與治療成效。
從1998年10月至2000年9月，24位肝癌合併肝門靜脈栓塞的病患施行三度空間順形放射治療。病患平均年齡為54.1歲（從30至73歲），平均追蹤日數為265天（從68至689天）。三度空間順形放射治療利用6至10百萬伏特光子射線，以每週3次，每天1次，每次1.8至2戈雷，總劑量43.2至75戈雷之方式施行。平均治療總體為455.76銅（從62.39至1436.76銅）。
一般而言，病患接受三度空間順形放射治療後反應良好（63%，15/24）。利用多變項分析，肝內或肝外侵犯是影響肝門靜脈栓塞反應的唯一顯著因子（P=0.025）。180天和360天之存活率分別為72.0%和55.4%，中位存活時間為215.5天。使用多變項存活分析之Cox's迴歸模式，發現治療劑量（p=0.011）、肝內或肝外侵犯（p=0.041）和治療總體（p=0.032）影響預後。當治療總體分為小於500銅及等於或大於500銅時，存活曲線有統計意義（p=0.029）。放射引起的急性副作用，包括：白血球降低、暫時肝功能障礙和上腹痛，均屬輕微且可逆。
我們的經驗指出對無法切除之肝癌合併肝門靜脈栓塞之病患，三度空間順形放射治療是安全有效之治療模式。初步資料顯示研究三度空間順形放射治療在不同期別之肝癌的治療策略所扮演的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，肝門靜脈栓塞