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Radiation therapy in patients with unresectable hepatocellular carcinoma*

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Summary. From April 1978 through December 1989, a total of 17 patients with unresectable hepatocellular carcinoma (HCC) were treated with radiation therapy alone or radiation therapy in conjunction with percutaneous ethanol injection (PEI), transarterial infusion chemotherapy (TAI), or transarterial embolization (TAE) at the National Medical Center Hospital. The median survival of all patients was 13.8 months. The survival values determined at 1, 2, and 3 years were 58.8%, 26.1%, and 9.8%, respectively. Only the pretreatment liver function affected the survival value. Between patients who did not have liver cirrhosis (LC) as well as those who had LC of Child's class A and patients who had LC of Child's class B or C, the differences observed in the 1-year survival value and the median duration of survival were statistically significant ($P < 0.05$). The serum cholinesterase (ChE) level seemed to be a good indicator of liver function during the radiation therapy. A field size of 150 cm^2 and a total dose of 5000 cGy (TDF 82) seemed to be well tolerated by patients who did not have LC and those who had LC of Child's class A. The field size determined whether patients with poor liver function such as LC of Child's class B or C would develop severe hepatic deterioration after undergoing radiation therapy.

Introduction

Recently, the advent of new technologies for the diagnosis and management of hepatocellular carcinoma (HCC) has improved the resection rate. However, because of the frequent coexistence of cirrhosis with HCC and the resulting liver-function impairment, even early-stage tumors frequently cannot be resected. Moreover, in many cases the disease is so advanced that resection is not feasible. In such cases, transarterial infusion chemotherapy (TAI), transarterial embolization (TAE), or percutaneous ethanol injection (PEI) has commonly been attempted, although there is no widely accepted standard therapy for these patients. We thus investigated the usefulness of radiation therapy for unresectable HCC patients and report the results and the associated problems.

Patients and methods

Patients' characteristics. From April 1978 through December 1989, a total of 17 patients with unresectable HCC were treated with radiation therapy alone or radiation therapy in conjunction with PEI, TAI, or TAE at the National Medical Center Hospital. The characteristics of the patients are shown in Table 1. Eight patients had histologically confirmed HCC. The remaining nine patients were diagnosed on the basis of the results of α-fetoprotein (AFP) tests and imaging procedures such as computerized tomography (CT), ultrasonography (US), and angiography (AG). Three subjects had previously undergone surgery and were referred for radiation therapy due to recurrent disease. The ratio of men to women was 13 : 4 and the mean age was 62.6 years. In all, 12 patients (70.6%) had coexistent liver cirrhosis and were classified according to Child's criteria, with 5 belonging to Child's class A; 3, to Child's class B; and 4, to Child's class C. Six patients were treated with radiation therapy alone, eight underwent TAI and radiation therapy, two were subjected to TAE and radiation therapy, and one was treated with PEI and radiation therapy.

Treatment. For most of the patients, local irradiation included a generous margin outside the main tumor. The radiation fields were set up using the information obtained by CT, US, and AG. In some cases, arterial infusion of lipiodol was performed for precise identification of the involved area. Treatment portals and photon energy were determined on the basis of the isodose curves generated using a Therac 2300 planning computer. In all, 14 patients were treated with parallel opposed AP-PA fields and 3, with 4-field techniques. All patients were irradiated with a weekly dose of 900–1000 cGy by conventional fractionation. The total dose delivered ranged from 2600 to 6000 cGy (mean, 4620 cGy).

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Table 1. Patients' characteristics

Characteristic	Number of patients
Patients entered	17
Sex (M/F):	
M	13
F	4
Age (years):	
Mean	62.6
Range	48–76
Performance status:	
0–1	12
2–3	5
Child's class:	
A	5
B	3
C	4
Cirrhosis (–)	5
Tumor type:	
Nodular	11
Massive	5
Diffuse	1
Treatment:	
RT alone	6
RT + TAI	8
RT + TAE	2
RT + PEI	1

RT, Radiation therapy

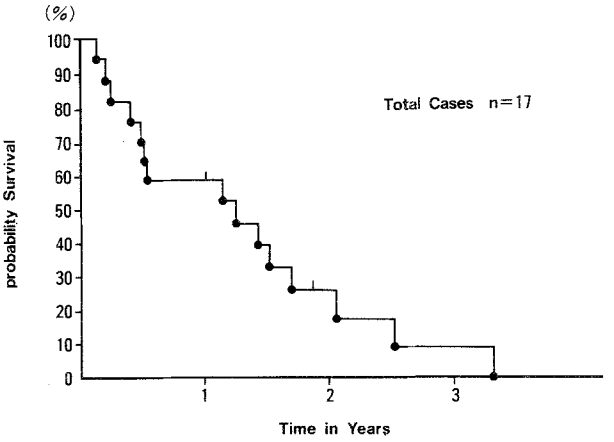

Fig. 1. Cumulative survival curve generated for all HCC cases (Kaplan-Meier)

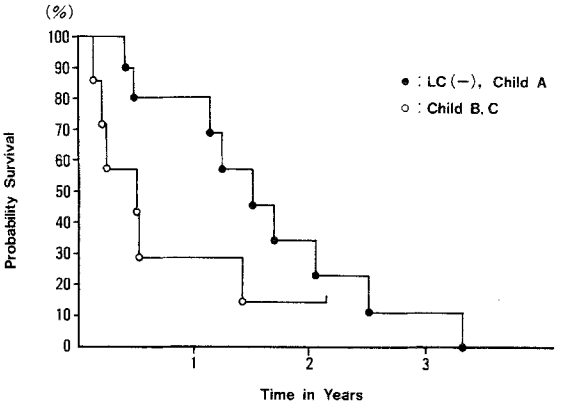

Fig. 2. Cumulative survival curves plotted as a function of the initial liver function (Kaplan-Meier)

Follow-up. All patients but one died. The follow-up period for the single living patient is currently 12 months.

Statistical analysis. Survival was calculated using the Kaplan-Meier method, and statistical significance was tested by the generalized Wilcoxon method, with a value of $P < 0.05$ representing significance.

Response. The responses to treatment were defined as follows: complete response (CR), the absence of any detectable tumor mass for more than 4 weeks; partial response (PR), a decrease of 50% or more in the product of two perpendicular diameters of the tumor or a decrease of 30% or more in one diameter for more than 4 weeks; no change (NC), a decrease of less than 50% or an increase of less than 25% in the product of two perpendicular diameters of the tumor or a decrease of less than 30% in one diameter; and progressive disease (PD), an increase of 25% or more in the product of two perpendicular diameters of the tumor or the appearance of new lesions.

Table 2. Responses to treatment

	CR	PR	NC	PD	Totals
LC (–)	0	1 (20%)	4 (80%)	0	5
LC (+):					
Child's class A	0	3 (60%)	1 (20%)	1 (20%)	5
Child's class B	0	1 (33%)	2 (67%)	0	3
Child's class C	0	1 (25%)	3 (75%)	0	4
Total	0	6 (35%)	10 (59%)	1 (6%)	17

Results

The cumulative survival curve constructed for all the patients is shown in Fig. 1. The overall median duration of survival was 13.8 months. The survival values determined at 1, 2, and 3 years were 58.8%, 26.1%, and 9.8%, respectively. The response data are shown in Table 2. A PR was observed in 6 patients (35%) and NC, in 10 subjects (59%), whereas PD was seen in 1 patient (6%). None of the patients achieved a CR. The cumulative survival curves plotted as a function of the initial liver function are shown in Fig. 2. Patients with good liver function constituted those who did not have LC and those who had LC of Child's class A. Subjects who had LC of Child's class B or C belonged to the group of patients with poor liver function. The respective survival values determined for these two groups were 80% and 29% at 1 year and 34% and 14% at 2 years. The median survival periods were 18.5 and 6.0 months, respectively, with the difference being statistically significant ($P < 0.05$).

The relationship between the TDF and the field size in all the patients is plotted in Fig. 3. In the 10 subjects with good liver function, the mean total dose delivered was 5020 cGy (TDF 86) and the average field size was

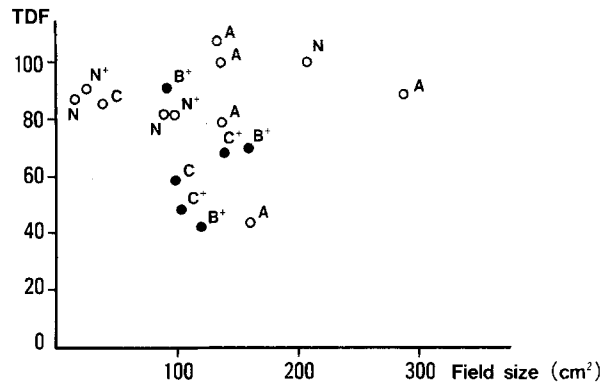

Fig. 3. Relationship between TDF and field size in all the patients

120 cm^2. None of these patients developed a severe decrease (less than 60% of the pretreatment level or less than 150 units/l) in serum cholinesterase (ChE) levels or liver failure after the radiation therapy. Of these 10 subjects, 8 survived for more than 12 months after the radiation therapy; 2 patients died within 6 months, 1 due to brain metastasis and the other due to cancer progression at the primary site. In contrast, 6 of the 7 patients who had LC of Child's class B or C developed a severe decrease in serum ChE levels after radiation therapy. In these 6 subjects, the mean total dose delivered was 3870 cGy (TDF 64) and the field size ranged from 95 to 156 cm^2 (mean, 123 cm^2); 5 of them died within 6 months after the radiation therapy. In all, 2 deaths occurred within 2 months due to progressive liver failure that was attributable to the radiation therapy.

Case 1

A 71-year-old man was admitted to the hospital due to right upper quadrant discomfort. He had a cirrhotic liver corresponding to Child's class A. On US and CT examinations, a 11.5- × 11.2-cm low-density mass was identified in the right lobe. On AG examination, the tumor showed hypervascularity and the portal vein was completely obstructed by a tumor thrombus. The tumor was confirmed to be HCC (Edmondson grade 3) by US-guided needle biopsy. The serum AFP level was 423 ng/ml. Radiation therapy alone was given with AP/PA opposed fields, and the field size was 19.0 cm × 15.5 cm. A total dose of 5400 cGy was delivered in 27 fractions (200 cGy/day). The tumor size decreased to 6.2 × 5.4 cm after this radiation therapy, and a PR was obtained. The serum ChE value was 235 units/l after the radiation therapy, which was 83% of the pretreatment level. The AG and US findings obtained prior to and after radiation therapy are shown in Fig. 4. After the radiation therapy, the portal vein was recanalized, and TAI was safely performed. At present, the patient is alive at 12 months after the radiation therapy.

Case 2

A 76-year-old woman with a serum AFP level of 1,478 ng/ml was revealed by CT to have a 5.4- × 3.8-cm low-density mass in the right lobe. She was not a candidate for surgical resection because she had LC of Child's class C. Radiation therapy was begun at 1 month after PEI. A 6- × 6.5-cm four-field box technique using ten MV X-rays was used to deliver a high dose to the tumor (Fig. 5). A total dose of 5200 cGy was delivered in 26 fractions 200 cGy/day). Although the response obtained was NC, the serum AFP level decreased to 189 ng/ml. The serum ChE value decreased to 97% of the initial value after radiation therapy without the subsequent development of liver failure. Hematological toxicity was minimal. The patient lived for 16 months after the radiation therapy.

Discussion

HCC is a frequent cause of morbidity and mortality in Japan. The availability of new technologies for diagnosis and management has increased the rate of resection in HCC. However, only about 25% of all cases of HCC are resectable. Resectability depends on several factors, such as the tumor size, the tumor site, the presence of vascular invasion, and the coexistence of LC. In such unresectable patients, TAI, TAE, and PEI are the main modalities commonly attempted.

Because HCC has traditionally been considered to be relatively radioresistant, radiation therapy for HCC has not been widely accepted. However, various investigators have reported the effectiveness of radiation therapy in patients with HCC [1, 4, 5, 9, 11, 13]. In the present study, a PR was observed in 6 patients (35%), and we thus surmise that HCC is not radioresistant when an adequate dose is delivered.

As judged from the literature, the tolerable dose of whole-liver irradiation in patients with otherwise normal liver function seems to lie in the range of 3000 to 3500 cGy [3, 6, 7, 10, 11]. Among patients with a metastatic liver tumor who did not have LC, Barone et al. [2] found that 3000 cGy (split course) was deleterious in two subjects who were treated with whole-liver irradiation and TAI. Volberding et al. [14] reported that two patients developed progressive liver failure due to radiation therapy after receiving 2100 cGy of whole-liver irradiation and TAI. In patients who undergo TAI, the tolerance of whole-liver irradiation appears to be somewhat lower. It is reasonable to speculate that a cirrhotic liver would display a lower level of tolerance for whole-liver irradiation, but there are few reports concerning this point.

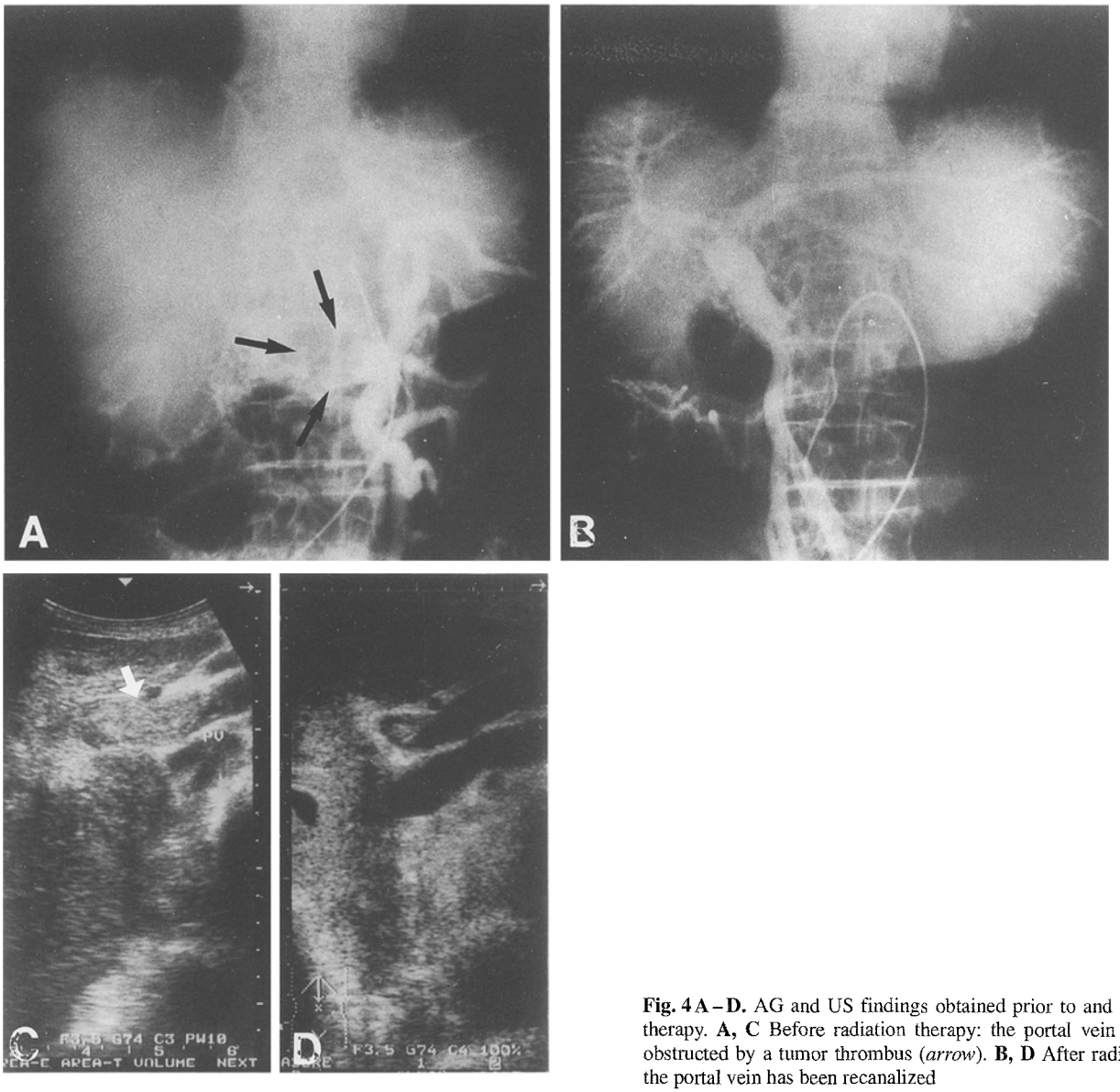

Fig. 4 A – D. AG and US findings obtained prior to and after radiation therapy. **A, C** Before radiation therapy: the portal vein is completely obstructed by a tumor thrombus (*arrow*). **B, D** After radiation therapy: the portal vein has been recanalized

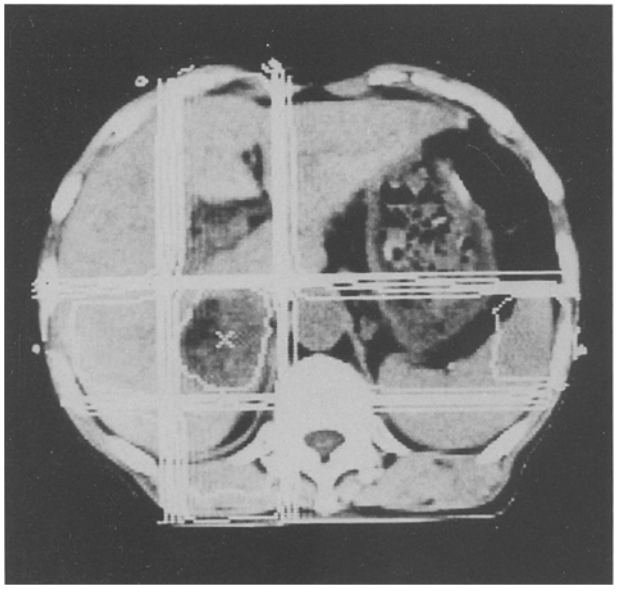

Fig. 5. Dose distribution in case 2 as drawn on a CT image using a Therac 2300 planning computer

Because the cirrhotic liver's tolerance of whole-liver irradiation is apparently lower than its tolerance of the tumor-sterilizing dose, we tried to irradiate only a portion of the liver as part of a multidisciplinary treatment regimen in the hope of increasing the tolerance and improving the local control of HCC. Some studies have examined the effects and problems of partial-liver irradiation.

Nagashima et al. [8] reported that partial-liver irradiation delivered at a dose of 5000 cGy (TDF 80) around the tumor thrombus was effective when patients were not suitable candidates for other treatment modalities bacause of the existence of a tumor thrombus. These authors observed liver failure due to radiation therapy in one patient with LC of Child's class C. Takara et al. [12] studied a series of 24 patients with HCC using partial-liver irradiation with a dose of 2700–5000 cGy as part of a multidisciplinary treatment regimen. These investigators reported that the 1-year survival value was 58% and that the pretreatment liver function and the field size determined whether the patient would develop liver failure after undergoing radia-

tion therapy. They also showed that a dose of 3000–5000 cGy was associated with improved survival. In our series, the mean dose delivered to ten patients who survived for longer than 1 year was 4820 cGy (TDF 83.4). A PR was achieved by 5 (50%) of these subjects. We thus conclude that a dose of about 5000 cGy is necessary to shrink the tumor volume and prolong survival.

It is necessary to take account of the patients' liver function before subjecting them to radiation therapy. As shown in our study, a decrease in serum ChE levels after radiation therapy tended to be associated with a poor prognosis. We consider that the serum ChE level is a very good indicator for predicting the occurrence of liver failure after radiation therapy. Progressive liver failure was encountered in patients with poor pretreatment liver function, whereas those with good initial liver function did not succumb to liver failure.

Our results demonstrate that a field size of 150 cm^2 and a dose of 5000 cGy (TDF 82) were well tolerated by patients who did not have LC and subjects who had LC of Child's class A. On the other hand, six of seven patients with LC of Child's class B or C developed a severe decrease in serum ChE levels after undergoing radiation therapy. As seen in case 2, a patient with LC of Child's class C, radiation therapy using small portals resulted in only a mild decrease in serum ChE levels, and this patient survived for 17 months after the radiation therapy. In patients with poor pretreatment liver function, the field size is a major factor contributing to the development of subsequent liver failure. We surmise that a field size larger than 100 cm^2 should not be recommended for patients with LC of Child's class B or C. Further investigation is needed to determine the tolerable field size for patients with poor pretreatment liver function.

References

1. Appelqvist P (1982) Primary carcinoma of the liver: clinical course and therapeutic results. J Surg Oncol 21: 87
2. Barone RM, Byfield JE, Goldfarb PB, Frankel S, Ginn C, Greer S (1982) Intra-arterial chemotherapy using an implantable infusion pump and liver irradiation for the treatment of hepatic metastases. Cancer 50: 862
3. Friedman MA, Cassidy M, Levine M, Phillips TL, Spivack S, Resser KJ (1979) Combined modality therapy of hepatic metastasis. Cancer 44: 906
4. Friedman MA, Volberding PA, Cassidy MJ, Resser KJ, Wasserman TH, Phillips TL (1980) Therapy of hepatocellular cancer with combined intrahepatic arterial chemotherapy and whole liver irradiation. Ann Acad Med 9: 260
5. Hatano K (1990) Therapeutic factors related to irradiation in primary and metastatic liver cancer using multivariate analysis. J Jpn Soc Cancer Ther 25: 1172
6. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA (1965) Radiation hepatitis. AJR 93: 200
7. Kaplan HS, Bagshaw MA (1968) Radiation hepatitis: possible prevention by combined isotopic and external radiation therapy. Radiology 91: 1214
8. Nagashima T, Ryu M, Mukai M, Ariga T, Koh Z, Amano H, Furukawa T, Maruyama T, Yamamoto Y, Odaka M, Isono K, Arimizu N, Uematsu S, Ishikawa T (1987) Therapy of hepatocellular carcinoma complicated with intravascular tumor emboli – effectiveness of radiotherapy for tumor emboli. Act Hepatol Jpn 28: 735
9. Niblett JS (1979) Radiation treatment of hepatoma in Papua New Guinea (Pilot study, 1974–1975). Australas Radiol 23: 242
10. Phillips R, Karnofsky DA, Hamilton LD, Nickson JJ (1954) Roentgen therapy of hepatic metastases. AJR 71: 826
11. Phillips R, Murikami K (1960) Primary neoplasms of the liver. Results of radiation therapy. Cancer 13: 714
12. Takara K, Ohto M, Yoshikawa M, Ebara M, Okuda K, Itami J, Arimizu N (1985) Clinical and pathological study of irradiation therapy in 24 patients with hepatocellular carcinoma. Jpn J Gastroenterol 83: 1473
13. Tang ZY (1980) Treatment of primary liver cancer – with special reference to the east part of China. Ann Acad Med 9: 251
14. Volberding PA, Friedman MA, Resser KJ, Phillips TL (1982) Therapy of liver tumors metastatic from colorectal cancer with whole-liver radiation combined with 5-FU, Adriamycin, and methotrexate. Cancer Chemother Pharmacol 9: 17