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The effect of external radiotherapy in treatment of portal vein invasion in hepatocellular carcinoma

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Abstract. To investigate the effect of external radiotherapy in the control of portal vein invasion (PVI) in hepatocellular carcinoma (HCC), ten patients with cytologically confirmed unresectable HCC were recruited for study. All of the patients were assigned Pugh's classification A, and all had only unilateral PV involvement. The main tumors were treated by transcatheter arterial embolization. The PVI was irradiated with a dose of 3000–5000 cGy using a linear accelerator under localization by real-time ultrasound. All ten patients responded to the external irradiation, with complete disappearance of the PVI occurring in five and partial shrinkage, in the other five. However, the HCC extended to the contralateral PV in two patients, although the irradiated lesion had shrunk. Both patients had shown involvement of the main PV in the initial study. Six patients died after 3, 6, 7, 7, 8, and 10 months, respectively, due to advance of the HCC, rupture, liver failure, and respiratory failure. The others survived for longer than 6 months and remain under follow-up. The branch of PVI at discovery might have an important bearing on the effect of the radiotherapy. No postirradiation hepatitis or other complication was observed.

Introduction

Portal vein invasion (PVI) is frequently seen in patients with hepatocellular carcinoma (HCC) [9, 12]. The presence of PVI is associated with a poor prognosis [3]. Although intra-arterial chemotherapy (IA), transcatheter arterial embolization (TAE),and surgery have been tried [7, 8], the results have not been satisfactory. Radiotherapy was considered to be ineffective against HCC in earlier reports [1, 6]. However, recent reports have shown some favorable effect of radiotherapy on HCC and its metastases [5, 11]. We performed this study to evaluate the effect of external radiotherapy in the control of PVI in HCC.

Materials and methods

The patients selected for this study included those with cytopathologically confirmed unresectable HCC and those whose tumor embolus extended into unilateral PV branches but not beyond the intrahepatic main PV. PVI was detected by real-time ultrasound (US), which has been shown to be as accurate as angiography [2, 4]. All patients underwent TAE and irradiation after granting informed consent. The field and the depth of the irradiation were decided by US. The field size ranged from 4.5×4.7 to 8.5×11.9 cm. The median field size was 4.5×8.3 cm. The vertical direction was selected for irradiation of the left PVI, whereas the right 45° direction was employed for irradiation of the right PVI. The irradiation dose consisted of 200 cGy daily to a total dose of at least 3000 cGy. The response of the PVI after irradiation was examined by serial US and evaluated as complete disappearance, a partial response, no change, and progressive disease.

Results

As listed in Table 1, this study included ten patients, of whom eight were men and two were women. Their mean age was 48.4 years. Eight were HBsAg-positive. The alpha-fetoprotein level was higher than 700 ng/ml in six patients. The type of tumor was a single nodule with local infiltration in one patient, multiple nodules in four patients, and the massive type with daughter nodules in five patients.

After irradiation, five patients showed complete disappearance of the PVI (Fig. 1) and another three patients achieved partial shrinkage of the PVI (Fig. 2). In two patients with main PVI, the PVI spread to the contralateral PV, although the irradiated lesion had shrunk. The time until the PV tumor regression was observed was 15–88 days after the start of radiotherapy. Six patients died at 3, 6, 7, 7, 8, and 10 months, respectively, due to uncontrolled liver involvement, tumor rupture, liver failure, and respiratory failure. No elevation of transaminase, jaundice, or other major complication was observed during the radiotherapy.

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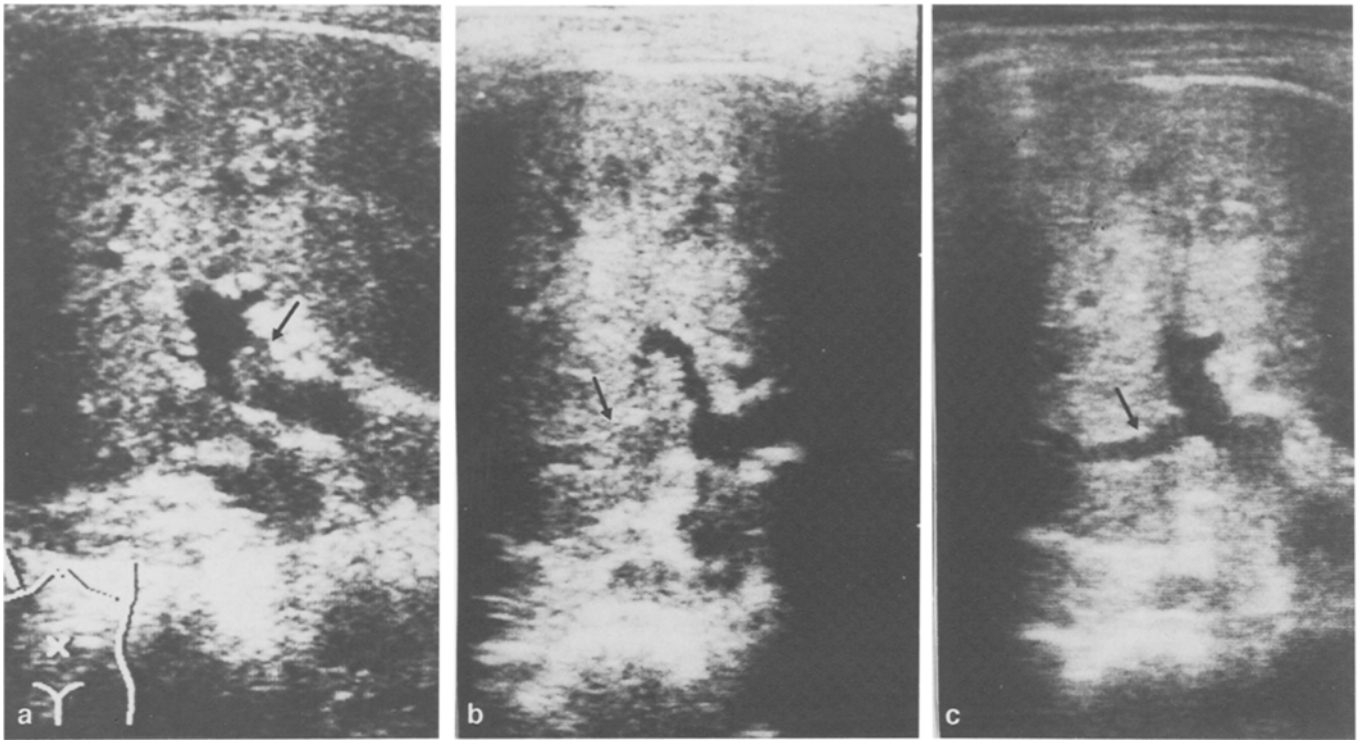

Fig. 1. A patient showing complete disappearance of a PV lesion after radiotherapy. (**a**) Small thrombus (*arrow*) in a bifurcation of the right PV (**b**) The tumor in the PV extended into the anterior and posterior branches 12 days later, before the start of irradiation. The posterior PV was enlarged (*arrow*) (**c**) Complete disappearance was observed on the 34th day. The posterior PV returned to its initial diameter (*arrow*)

Table 1. Basic data on the site of PVI, irradiation dose, and response to external radiotherapy in patients with HCC

Case no.	Age (years)	Sex	HBsAg	AFP (ng/ml)	Tumor		Irradiation		Day of response	Result	Outcome
					Type	Size	PVI	Doses (cGy)			
1	63	M	+	>700	NL	5 cm	R, 1st	3600	?	CD	ly a
2	68	M	+	>700	MN	25–50%	R, 1st	4400	15	CD	10m d
3	53	M	+	14480	MN	50%	L, Umb	5000	31	CD	7m d
4	29	M	–	190860	MS	>10 cm	R, 1st(c)	4400	88	PS	10m a
5	36	M	+	3.2	MS	>10 cm	R + M(c)	5000	35	PS	8m d
6	34	M	+	>700	MS	>10 cm	R + M(c)	4000	41	PS	7m d
7	56	F	+	236	MN	<25%	L, Umb	3400	28	CD	8m a
8	57	F	–	60155	MS	>10 cm	R, 2nd(c)	3000	27	CD	6m d
9	34	M	+	49	MN	50%	L, 1st(c)	5000	33	PS	3m d
10	54	M	+	266	MS	>10 cm	R, 1st(c)	5000	32	PS	6m a

?, The first echo after 9 months showed complete disappearance of the PVI; NL, nodule with local invasion; MN, multiple nodules; MS, massive type with satellite nodules; R, right; L, left; M, main PV; 1st, first-order branch of the PV; Umb, umbilical part of the left PV; 2nd, second branch of the PV; (c), complete obstruction of the PV lumen; CD, complete disappearance; PS, partial shrinkage; a, alive; d, dead; M, months; y, year

Discussion

The incidence of PVI in HCC is about 60% in Taiwan [3, 9]. It is a bothersome problem in the treatment of HCC not only because it might represent spread of the tumor through the PV but also because it might impair the liver blood supply. The survival of HCC patients with PVI is poor with current therapeutic modalities. This study tested radiotherapy in the control of PVI in HCC. The PV lesions in all ten patients showed some degree of response to the radiotherapy. Although all of the patients had also been treated by TAE for their parenchymal tumors, the responses seen in this study were considered to be unrelated to the TAE. TAE and IA have been tried in various studies, but the response has varied [7]. Surgical resection has also been tried [8]. However, most cases of HCC in Taiwan are complicated by liver cirrhosis [9], and the recurrence rate after surgical resection is quite high.

In this study, six patients died at 3, 6, 7, 7, 8, and 10 months after the irradiation, respectively. One patient died of hepatic failure after repeated TAE. Four patients died of progressive liver involvement due to hypovascular

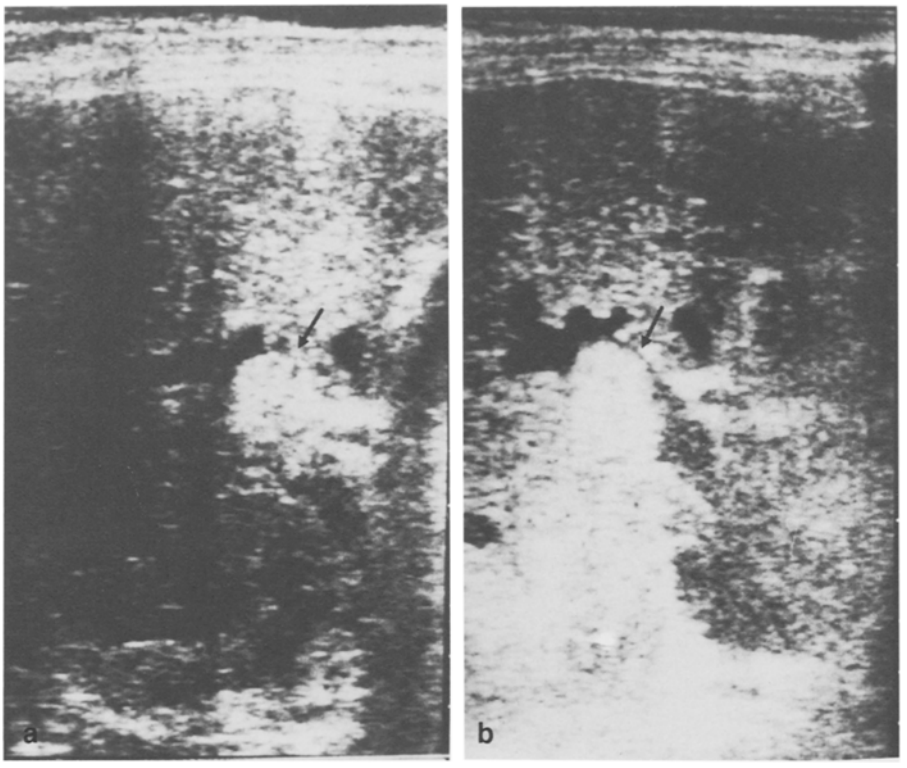

Fig. 2. (**a**) Real-time ultrasound in a 54-year-old men demonstrated a highly echoic tumor thrombus in the right PV with complete obstruction of the lumen (*arrow*) (**b**) After irradiation, minimal regression of the tumor, with a visible lumen (*arrow*), was identified

HCC, technical problems, or complete obstruction of the main PV, which prevented further TAE. One patient died of cachexia due to loss of the will to live after the development of lung metastasis. Four patients were alive and well and continued TAE therapy.

The survival seems limited, however, since most patients had extensive tumor involvement and only two patients actually died due to advance of the PVI that prevented further treatment. We believe that irradiation is a good complementary therapy in combination with other effective therapies for the treatment of HCC with PVI. Patients might thereby survive longer or have the opportunity to receive curative therapy.

The time of treatment of PVI in HCC is important. Complete disappearance of the tumor PVI was observed in five patients, and four of them had not initially been completeley obstructed. In contrast, only one of six patients with complete obstruction of the PV lumen achieved complete disappearance. That case was a patient with PVI in a small branch. Moreover, in two patients with main PV involvement, HCC extended to the contralateral PV, although the irradiated PV lesion had shrunk. Possible explanations for the continued invasion were that (1) the tumor had initially invaded the contralateral PV but was not detected, and (2) the effect of the irradiation did not appear immediately. Shrinkage of the PVI after irradiation was seen as early as on the 15th day, but it was also seen as late as at 3 months (Fig. 3). Usually, shrinkage was first seen after the 4th week. The irradiation field should be larger and should cover part of the patent PV if the tumor has invaded the main PV. The best time to treat PVI in HCC is before the HCC has spread into the main PV. Screening for PVI in HCC should be performed regularly.

A high dose irradiation might induce radiation hepatitis and liver function impairment [10]. Liver function impairment might preclude further TAE or surgery. In the present ten patients, US localization was performed to avoid irradiation of the nontumorous liver, and no major complication was observed. However, atrophy of the local liver parenchyma was noted in four patients. Irradiation of PVI in HCC should be performed carefully in patients with a small liver function reserve.

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