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CLINICAL INVESTIGATION **Liver**

IS LOCAL RADIOTHERAPY STILL VALUABLE FOR PATIENTS WITH MULTIPLE INTRAHEPATIC HEPATOCELLULAR CARCINOMAS?

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Purpose: To investigate whether local radiotherapy (RT) is valuable for patients with multiple hepatocellular carcinomas (HCCs).

Methods and Materials: From July 1992 to August 2006, 107 patients with unresectable HCC were treated with local RT after incomplete transcatheter arterial chemoembolization (TACE). The RT field included a main tumor with or without other tumor nodules, depending on the effectiveness of TACE. The median RT dose was 50.4Gy in conventional fractionation. Patients were categorized into four groups: Group 1, single tumor (39 patients); Group 2, multiple tumors within the RT field (25 patients); Group 3, controlled tumors out of the RT field (19 patients); and Group 4, tumors that remained viable out of the RT field (24 patients).

Results: Group 1 showed the best survival rate (MST, 35 months; 2-year OS, 60%) and Group 4 the worst (MST, 5 months; 2-year OS, 16%). Group 2 and Group 3 showed similar survival (MST, 13 vs. 19 months; 2-year OS, 35% vs. 46%; $p = 0.698$). Significantly worse intrahepatic control in Group 4 was observed. The survival in Groups 2 and 3 (MST, 16 months) was significantly different from that in Group 4 ($p = 0.004$), and was marginally significant compared with that in Group 1 ($p = 0.051$).

Conclusions: Local RT to the main tumor could be applicable in well-controlled intrahepatic tumors out of the RT field. Patients with viable intrahepatic tumors out of the RT field showed worse survival. In future clinical trials, these patients need to be excluded.

Radiotherapy, Transcatheter arterial chemoembolization, Hepatocelluar carcinoma, Multiple intrahepatic tumors, Survival.

INTRODUCTION

Hepatocellular carcinoma (HCC) usually develops in patients with underlying cirrhosis or chronic active hepatitis. HCC is considered a pathologic organ condition, and the first nodule detected seems to progress to multiple lesions (1). In addition, multiple intrahepatic tumors can result because of intrahepatic metastasis or metachronous multicentricity of HCC (2). Even for patients who have undergone resection, multicentricity is already present in 50% of early-stage patients, and approximately 30% to 70% will eventually present with other nodules in the liver as metachronous tumors or intrahepatic metastasis (1, 3).

Transcatheter arterial chemoembolization (TACE) has been widely used in the treatment of multiple intrahepatic tumors, and its efficacy in enhancing survival has been reported (4–8). However, TACE alone is less satisfactory, particularly for large tumors that have a complicated blood supply and show a high incidence of residual viable tumor even after repeated treatment (9–12). With the advance of selective (segmental and subsegmental) TACE, satellite or daughter nodules can be effectively treated (13). Therefore, multiple intrahepatic tumors, which consist of large main tumor and satellite nodules, need tailored strategies for each lesion. A combination of different modalities to large tumors with unsatisfactory TACE response is still necessary, even in multiple intrahepatic tumors.

The combination of TACE and three-dimensional conformal radiotherapy (RT), which enables delivery of higher doses to a targeted portion of the liver, has been reported to have a substantial effect (14–18). Despite the lack of randomized controlled trials, RT is becoming recognized as a potentially curative option (19). However, the efficacy of local RT

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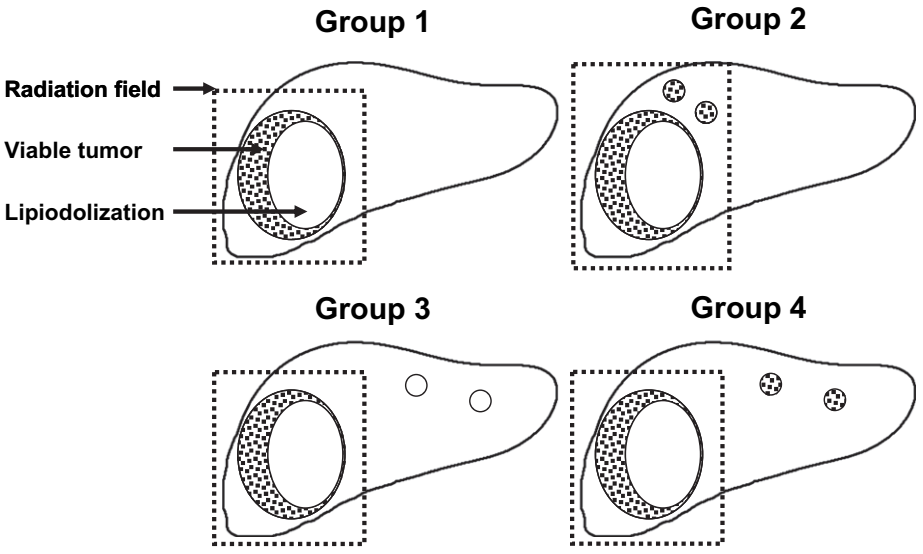

	Group 1	Group 2	Group 3	Group 4
Number of tumor	single	multiple	multiple	multiple
Location of tumor related with RT field	within field	within field	out of field	out of field
Tumor status out of radiation field	none	none	controlled	viable

Fig. 1. Classification of patients according to the number of tumors, and presence and viability of intrahepatic tumors outside the radiation field. The dotted area indicates viable tumor and the white area indicates complete lipiodolization.

to supplement an incomplete response to TACE in patients with multiple intrahepatic tumors has not been defined.

The purpose of this study was to evaluate the clinical outcome of local RT directed only to the main tumor area in patients with multiple intrahepatic tumors. We investigated whether the presence and viability of HCC out of the RT field affected survival, and we evaluated the benefits of local RT in patient subgroups.

METHODS AND MATERIALS

Patient selection

Between February 1992 and December 2006, 302 patients with unresectable HCC underwent local RT with TACE. After retrospective chart review with institutional review board approval, 107 patients were included in this study. The diagnosis of HCC was based on histologic features or HCC-compatible radiologic findings in computed tomography (CT), magnetic resonance imaging (MRI), or hepatic angiography, and a serum alpha-fetoprotein (AFP) values of >400 IU/ml. In patients with an AFP levels ≤400 IU/ml, a diagnosis of HCC was made if radiologic findings compatible with HCC were observed in at least two imaging modalities. Eligibility criteria included the following: Child-Pugh class A or B, Eastern Cooperative Oncology Group (ECOG) performance score 0 to 2, tumor size >5 cm, T2 or T3 stage by the Liver Cancer Study Group of Japan, TACE as the primary treatment before RT, and local RT targeting the major tumor with incomplete TACE. Failure of TACE was based on incomplete tumor filling with lipiodol or presence of a viable tumor area on angiography, CT, or MRI. Exclusion criteria were ECOG performance score of 3 or 4 (3 patients), Child-Pugh class C (18 patients), tumor thrombi to the main or first branch of portal vein, main hepatic vein, or inferior vena cava (93 patients), extrahepatic metastasis including lymph nodes (30 patients), suboptimal RT dose <30 Gy (33 patients), and no TACE as initial treatment (35 patients). Pretreatment evaluation consisted of a complete medical history and physical examination, routine blood counts and liver function tests, and a dynamic helical CT scan of the liver and/or hepatic angiography. Radiography or CT of the chest, whole-body bone scan, and/or positron emission tomography were performed when indicated. All tumors were staged before RT according to the Liver Cancer Study Group of Japan (20).

The median patient age was 56 years (range, 31–75 years), and the majority of patients were male (85 patients, 79%). The numbers of patients in ECOG scales 0, 1, and 2 were 6, 78, and 23, respectively. Most patients were in Child-Pugh class A (93 patients, 87%). Median tumor size was 8 cm (range, 5–18 cm). In T staging according to the Liver Cancer Study Group of Japan, stage T2 was observed in 39 patients (36%) and T3 in 68 patients (64%).

RT and multimodality therapy

Total dose was determined by the fraction of the non-tumor liver tissue that received 50% of the isocenter dose as follows: if the