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CLINICAL INVESTIGATION **Kidney**

CARBON ION RADIATION THERAPY FOR PRIMARY RENAL CELL CARCINOMA: INITIAL CLINICAL EXPERIENCE

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Purpose: Renal cell carcinoma (RCC) is known as a radioresistant tumor, and there are few reports on radiotherapy for primary RCC. We evaluated the efficacy of carbon ion radiotherapy (CIRT) for patients with RCC.
Methods and Materials: Data for patients with RCC who received CIRT were analyzed. A median total dose of 72 GyE (gray equivalents) in 16 fractions was administered without any additional treatment. Clinical stage was determined based on TNM classification by the International Union Against Cancer (UICC). Local recurrence was defined as definite tumor regrowth after treatment.
Results: Data for 10 patients were included in the analyses, including 7 patients with Stage I and 3 patients with Stage IV (T4NxM0 or TxN2M0) disease. The median maximum diameter of the tumor was 43 mm (24–120 mm). The median follow-up for surviving patients was 57.5 months (9–111 months). The 5-year local control rate, progression-free survival rate, cause-specific survival rate, and overall survival rates were 100%, 100%, 100%, and 74%, respectively. Interestingly, treated tumors showed very slow shrinkage, and the tumor in 1 case has been shrinking for 9 years. One patient with muscular invasion (T4 tumor) developed Grade 4 skin toxicity, but no other toxicity greater than Grade 2 was observed.
Conclusions: This is one of the few reports on curative radiotherapy for primary RCC. The response of the tumor to treatment was uncommon. However despite inclusion of T4 and massive tumors, favorable local controllability has been shown. The results indicate the possibility of radical CIRT, as well as surgery, for RCC. **© 2008 Elsevier Inc.**

Renal cell carcinoma, Carbon ion radiotherapy, Particle radiotherapy, Survival analysis, Tumor response.

INTRODUCTION

The incidence of renal cell carcinoma (RCC) is about 30,000 per year in the United States and about 10,000 per year in Japan; RCC is a relatively rare disease that accounts for less than 3% of all cancer deaths (1, 2). Although the classical triad of RCC comprises hematuria, pain, and mass, the frequency of incidental RCC is increasing because of the increase in medical examinations, and it has been reported that incidental RCC accounts for more than 50% of all RCC cases (3).

Because RCC accounts for 80% to 90% of all renal cortical tumors and typical RCC is easy to differentiate from other tumors, there are many cases in which surgical resection is performed without biopsy (4). Recently not only radical nephrectomy but also partial nephrectomy or laparoscopic nephrectomy has been performed for the treatment of RCC, with favorable outcomes (5–7).

It is known that RCC is highly resistant to chemotherapy, and no chemotherapeutic agent should be considered standard in treatment for RCC. Interferon-α or interleukin-2 is used for additional treatment, but the response rate is not high (8). It is considered that RCC is resistant to radiotherapy with photon beams (9–11). Although there are reports of radiotherapy for the treatment of metastatic RCCs (*e.g.,* those in the brain or bone), there are few reports of curative radiotherapy for primary RCC (12). We report our experience with curative treatment for primary RCC using carbon ion radiotherapy (CIRT).

METHODS AND MATERIALS

Heavy Ion Medical Accelerator in Chiba and CIRT

The Heavy Ion Medical Accelerator in Chiba (HIMAC) is the first heavy ion accelerator complex for medical use in the world. Although various heavy ions can be accelerated in HIMAC, only

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carbon ion (mass number, 12; atomic number, 6) is now used for clinical treatment. Carbon beams of 290 mega-electron volts (MeV), 350 MeV, and 400 MeV are used in HIMAC, and these beams are properly administered according to depth of the lesion.

Figure 1A shows depth–dose curves of a carbon beam and a photon beam. X-ray (Fig. 1A: blue broken line, 10-MV photon) that is used for general radiotherapy shows its peak dose at a depth of 3 to 4 cm from the body surface, and the dose decreases as the depth increases. On the other hand, a characteristic of particle beams such as a carbon beam or proton beam is that they show a smaller dose at the upper stream of the peak dose. They also show a sudden increase in dose, called the ''Bragg peak,'' and the dose suddenly decreases at an area deeper than the Bragg peak. The Bragg peak can be spread out to an optimum range that is called ''spread-out Bragg peak (SOBP; Fig. 1A, red solid line),'' and the target (tumor) is covered with this SOBP in treatment.

Cell mortality rate in a carbon ion beam is higher than that in a photon beam when the same physical dose is irradiated. This ratio of cell killing effect is expressed by the relative biological effectiveness (RBE), and the RBE of a carbon ion beam has been reported to be 2 to 3, which means that the cell-killing effect of a carbon beam is two to three times stronger than that of a photon beam (13). Because the clinical dose of CIRT is calculated by multiplying the RBE by the physical dose, the clinical dose is different from the physical dose in gray (Gy), as shown in Fig. 1A (black solid line); thus the clinical dose of CIRT is expressed by gray equivalents (GyE) to distinguish between clinical dose and physical dose (14).

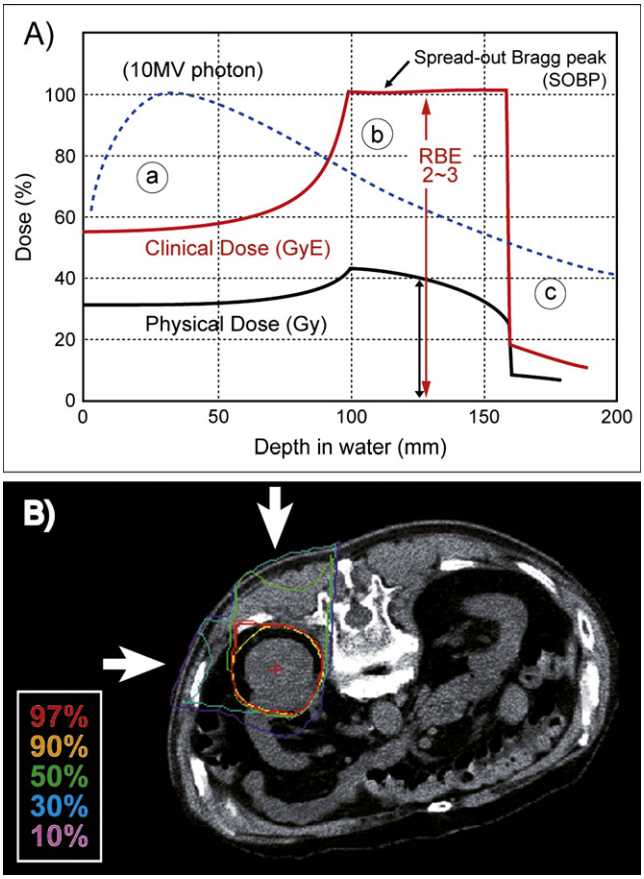

Fig. 1. (A) Depth–dose curves of X-ray (blue broken line), physical dose of carbon beam (black solid line), and clinical dose of carbon beam (red solid line). In the upper stream of the target (a), the dose of the carbon beam can be suppressed to less than that of the X-ray. In (b), targets are covered by the spread-out Bragg peak (SOBP) of the carbon beam, with higher dose intensity than that of the X-ray. In the area beyond the target (c), the dose of carbon beam suddenly decreases to a level lower than that of the X-ray. As shown in the graph, it is easy to concentrate the dose of the carbon beam on the tumor with preservation of surrounding tissues. (B) Dose distribution of carbon ion radiotherapy for localized renal cell carcinoma. A horizontal port and a vertical port are used in this plan, and well-localized dose distribution has been achieved.

CIRT planning

Resinous shells for immobilization were individually made for all patients, and the patients were immobilized during computed tomography (CT) for treatment planning and during irradiation. All patients underwent diagnostic contrast-enhanced CT and/or magnetic resonance imaging (MRI) before treatment; nonenhanced CT with a slice thickness of 5 mm was used for treatment planning. Dose distribution was calculated by HIPLAN, a heavy ion treatment planning system at HIMAC, which was developed for CIRT in this institution (15). Figure 1B shows typical planning and dose distribution for treatment of RCC.

In cases without definite lymph node metastasis, the target was limited to the tumor, and regional lymph node area was not included in the irradiation field. The clinical target volume included a margin of 10 to 15 mm around the macroscopic tumor (gross target volume), and the planning target volume included a margin of 5 mm in the craniocaudal direction around the clinical target volume; the whole kidney was not included in the irradiation field. An optimum ridge filter was used for adjustment of SOBP; a resinous bolus was manufactured for adjustment of depth and shape of irradiation field; and a multileaf collimator or metallic collimator was used for shaping the irradiation field. One or more iridium needles (3 mm in length and 1 mm in diameter) were always implanted under local anesthesia in the ipsilateral renal cortex around the tumor as target markers, and all irradiations were performed identifying these permanent markers by X-ray radiography. Because of respiratory organ motion, respiration-synchronized irradiation using a respiration sensing system was always performed (16). Irradiation was delivered once per day and 4 times per week (*i.e.,* Tuesday through Friday).

Patients

Data for all patients with RCC without distant metastasis (Tx Nx M0) who were treated with CIRT were included in the analysis from 1994, when operation of HIMAC began. Diagnosis was confirmed using CT, MRI, ultrasonography, angiography, and needle biopsy, but biopsy was not performed when radiographic findings were typical of RCC. Clinical stage was determined according to TNM classification by the International Union Against Cancer (UICC), and toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 from the National Cancer Institute (17).

Written informed consent was obtained from all patients or the patients' families. All patients were hospitalized during CIRT. No additional treatments, including chemotherapy, were combined with CIRT. Three-dimensional tumor size (cm) was measured using CT or MRI, and tumor volume (cc) was calculated as follows: [(x*y*z)*π/6]. After CIRT, follow-up imaging with CT and/or MRI) was performed at least twice per year in all patients. The date of local failure was defined as the day when definite re-enlargement of the tumor was observed, and the date of progression was defined as the day when definite local failure or distant metastasis was observed. Presence of residual tumor without re-enlargement was not defined as local failure. The final follow-up date was June 30,