The Effects of Carbon Ion Irradiation Revealed by Excised Perforated Intestines as a Late Morbidity for Uterine Cancer Treatment

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Abstract

Purpose. Clinical trials of carbon ion therapy have been performed due to the advantages of high-dose energy delivery with precise localization control to targeted organs and strong cell-killing activities to cancers. Perforated intestines as a late morbidity after carbon ion radiotherapy for uterine cancers were examined to reveal the biological characteristics of carbon ion for future applications for the treatment of gastrointestinal cancers.

Methods. Between June 1995 and December 2004, 94 patients with carcinoma of the uterine cervix or corpus were treated with carbon ion therapy. Among them, 9 patients (9.6%) developed major late gastrointestinal (GI) complications. Four out of 9 patients had intestinal perforations excised operatively at our institute. The postoperative clinical courses and histopathological findings of the excised intestine were investigated.

Results. Carbon ion irradiation severely damaged smooth muscle layers by coagulation necrosis as well as atrophy of the intestinal epithelium and middle-sized arterial thromboses of the intestines. After evaluating late complications, the dose constraints on the GI tracts were set under 60 GyE to prevent major complications. Thereafter, the incidence of major GI complications markedly decreased.

Conclusion. Our findings demonstrated the characteristic histopathological effects of carbon ion radiotherapy and thus are expected to facilitate future additional applications of carbon ion radiotherapy for the treatment of gastrointestinal cancers.

Key words Carbon ion radiotherapy · Heavy ion medical accelerator in Chiba (HIMAC) · Late morbidity · Uterine cancer treatment · Clinical trials

Introduction

Carbon ion radiotherapy has several advantages in comparison to conventional photon radiotherapy, such as better physical dose distribution and a higher biological efficiency in tumor cell killing.1–4 In other words, carbon ion, high-linear energy transfer (LET) radiation, has several advantageous biological characteristics such as a decreased oxygen enhancement ratio, a diminished capacity for sublethal and potentially lethal damage repair, and a diminished cell cycle-dependent radiosensitivity in comparison to those observed with low LET radiation. The carbon ion beam possesses the unique physical properties of a well-defined range and insignificant scatter in tissues, and a significant energy release at the end of its range that is well known as the “Bragg peak.”5

At the Heavy Ion Medical Accelerator in Chiba (HIMAC), the world’s first carbon ion accelerator complex dedicated to medical use in a hospital environment, established in 1994, carbon ion radiotherapy has been studied in clinical trials and it has shown major beneficial effects for more than 1700 cancer patients who were not indicated for an operation.6 So far, the treatment efficiency of carbon ion radiotherapy has been excellent, especially for head and neck tumors,7 bone and soft tissue sarcomas,8 esophageal cancers, non-small cell lung cancers,9–11 uterine cancers,12–14 and recurrent rectal cancers in the pelvis.6 However, the adverse effects and biological assessment of carbon ion radiotherapy have

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not yet been completely elucidated. Few reports have been published concerning the histopathological changes after carbon ion irradiation, in contrast to numerous publications regarding conventional X-ray irradiation.

To reveal the effects of carbon ion on the intestines for gastrointestinal cancer treatment, we examined the histopathological changes as well as the clinical aspects of four patients with intestine perforation caused by carbon ion irradiation as a late morbidity for uterine cancer treatment. Our findings demonstrated the characteristic histopathological effects of carbon ion radiotherapy, and thus are expected to facilitate future additional applications of carbon ion radiotherapy for the treatment of gastrointestinal cancers.

**Materials and Methods**

**Patient Characteristics**

Clinical trials of carbon ion irradiation protocols have been applied to advanced uterine cancers at HIMAC since 1994, and an acceptable outcome has been obtained in a large proportion of cases. The eligibility criteria for carbon ion radiotherapy are as follows: (1) histologically confirmed squamous cell carcinoma or adenocarcinoma of the uterus, (2) stage IIB ≥ 4 cm in diameter, stage IIIB ≥ 4 cm in diameter, and stage IVA disease, (3) a patient performance status of 0 to 3 according to the World Health Organization classification, (4) an age of less than 80 years, (5) no prior chemotherapy, surgery, and/or radiotherapy to the pelvis, (6) more than 6 months of life expectancy with this treatment, and (7) no severe concomitant illness, such as severe infection in the pelvis or active double cancer.

Between June 1995 and November 2004, a total of 94 patients with carcinoma of the uterine cervix or corpus were treated with carbon ion radiotherapy. All patients had tumors measuring 4–10 cm in diameter by magnetic resonance imaging (MRI). The median follow-up period for all and surviving patients was 26.2 months (range, 4.1–122.8 months) and 54.4 months (range, 7.9–122.8 months), respectively. Among these 94 patients, nine patients (9.6%) developed intestinal perforations or fistulae; 3 rectovaginal fistulae, 2 rectal ulcers, 1 sigmoid perforation, 1 sigmoid-vesical fistula, 1 ileum perforation, and 1 both ileum and sigmoid perforations, respectively. Four out of 9 patients were operated on at our hospital.

**Treatment and Clinical Courses**

HIMAC is the world’s first heavy ion accelerator complex dedicated to medical use in a hospital environment. The energy of carbon ion beams used for the treatment of the uterine cancer was 350–400 MeV. The range of the 350-MeV beam is approximately 20 cm in water and that of the 400-MeV beam is 25 cm. The clinical target volume (CTV) included the primary tumor, uterus, parametrium, at least the upper half of the vagina, and pelvic lymph nodes (common, internal, and external iliac lymph nodes, and presacral lymph nodes). A margin of 5 mm was usually added to the CTV to create the planning target volume (PTV). The rectum, bladder, and small intestine in the pelvis were excluded from the PTV as much as possible (Fig. 1). Carbon ion radiotherapy was given once a day, 4 days a week, for a fixed 20–24 fractions over a 5–6-week period (overall treatment time). Dose escalation was carefully conducted. A total dose of 35.2–48.0 GyE (Gray equivalent; units express the carbon dose in terms comparable to ordinary photon beams) was delivered to the pelvic lymph nodes, and a total of 52.8–72.8 GyE was delivered to the primary tumor (Table 1).

The four patients of this study suffered from uterine cancer and underwent carbon ion radiotherapy between May 1997 and June 2003 at HIMAC, Japan. The histopathological diagnosis of three patients was squamous cell carcinoma of the cervix, and the other was adenocarcinoma of the corpus. The clinical stages of all four cases were IIIB, III, or IVA according to the Federation of Gynecology and Obstetrics (FIGO) staging system, and all were considered to not be indicated for an operation.

**Results**

Three of the patients suffered from anal bleeding following the sudden onset of abdominal pain due to intestinal perforations 9–14 months after the carbon ion irradiation (Table 2), and they were referred to the Department of Frontier Surgery, Chiba University. They all underwent an emergency operation and recovered without any significant complications (Table 2). Three of them are alive at the time of this investigation (August 1, 2005), and one patient died due to a myocardial infarction without uterine cancer recurrence.

**Clinical Follow-up and Histopathological Findings**

Carbon ion radiotherapy was effective in all four uterine cancer patients experienced in this study (Table 2). In cases 1, 2, and 3, the tumor masses in the pelvis had disappeared completely and were not detected by a computed tomography (CT) scan after carbon ion radiotherapy. In case 4, the tumor mass in the pelvis had also disappeared completely, but lymph node metastasis along the abdominal aorta was found outside of the