Carbon-ion radiotherapy for inoperable endometrial carcinoma

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ABSTRACT

This is a pooled analysis to evaluate the toxicity and efficacy of carbon-ion radiotherapy (C-ion RT) for inoperable endometrial carcinoma. Eligible patients had previously untreated Stage I–III endometrial carcinoma without para-aortic lymph node metastasis. Total dose to the tumor was 62.4–74.4 Gy [relative biological effectiveness (RBE)] in 20 fractions, and the dose to the gastrointestinal tract was limited to <60 Gy (RBE). Intracavitary brachytherapy was not combined in the present study. Fourteen patients with endometrial carcinoma were analyzed. Ten of the 14 patients were judged medically inoperable, and the others refused surgery. The numbers of patients with Stage I, II and III disease were 1, 9 and 4, respectively. Tumor size was 3.8–13.8 cm in maximum diameter. Median follow-up periods for all patients and surviving patients were 50 months (range, 12–218 months) and 78 months (range, 23–218 months), respectively. Two of three patients receiving 62.4–64.8 Gy (RBE) had local recurrence whereas none of 11 patients receiving 68.0 Gy (RBE) or more had local recurrence. Three patients developed distant metastases and one of them also had local recurrence. The 5-year local control, progression-free survival, overall survival, and cause-specific survival rates were 86%, 64%, 68% and 73%, respectively. No patient developed Grade 3 or higher acute or late toxicity. The present study showed that C-ion RT alone could be a safe and curative treatment modality for inoperable endometrial carcinoma.

Keywords: endometrial carcinoma; carbon-ion radiotherapy; inoperable case; particle radiotherapy

INTRODUCTION

Endometrial carcinoma is the most common gynecologic malignancy in developed countries [1]. Although surgery is the main treatment for endometrial carcinoma [2–4], there are certain risk factors related to operative indications, including obesity, diabetes, and older age [5, 6]. Hence, some patients with endometrial carcinoma are considered inoperable. In fact, an estimated 3–10% of patients are contraindicated for surgery because of medical comorbidities [7–10]. Definitive radiotherapy, including brachytherapy, is one of the curable options for those patients who are medically inoperable [4, 11–15]. However, there is a subgroup who are poor candidates for intracavitary brachytherapy because of an excessive risk of
general anesthesia, inability to undergo regional anesthesia, poor tolerance of dorsal lithotomy position, or refusal to undergo insertion of brachytherapy apparatus.

In 1994, carbon-ion radiotherapy (C-ion RT) was initiated at the National Institute of Radiological Sciences (NIRS) [16]. C-ion beams possess dose localization properties superior to photon beams, and can potentially produce favorable effects on tumors while minimizing normal tissue damage [17, 18]. Moreover, they possess a biological advantage due to their high linear energy transfer in the Bragg peak [19]. Utilizing the unique properties of C-ion beams, we have conducted a pooled analysis for inoperable endometrial carcinoma in a dose-escalation manner. Here, we report the toxicity and efficacy of C-ion RT for endometrial carcinoma.

MATERIALS AND METHODS

Patient eligibility
In the present study, we performed a pooled analysis of data from two trials: protocols 9704 and 9404. Patients enrolled in the present study were previously untreated, and had histologically proven International Federation of Gynecology and Obstetrics (FIGO 1988) Stage ≥IIIC endometrial carcinoma. Pathologists of the Working Group of the Gynecological Tumor reviewed the tumor specimens. All patients were judged as medically inoperable because of comorbidities, age, or refusal of surgery. Other eligibility criteria included estimated life expectancy of >6 months, and the tumor had to be grossly measurable. Eligibility criteria of protocol 9704 included World Health Organization performance status ≤ 3, and age ≤ 80, although protocol 9404 did not include the age restriction. Patients with severe pelvic infection, severe psychological illness, or active synchronous cancer were ineligible for the two protocols.

The initial work-up included an assessment of the patient's history, physical and pelvic examinations by gynecologists and radiation oncologists, biopsy, routine blood cell counts, chemistry profile, chest X-ray, cystoscopy, and rectoscopy. Bladder or rectal involvement was assessed by endoscopy. All patients were also examined by computed tomography (CT) of the abdomen and pelvis, and magnetic resonance imaging (MRI) of the pelvis. Patients with para-aortic lymph nodes >1 cm in minimum diameter on CT images were excluded from the present study. Staging laparotomy was not performed, and no histologic confirmation of CT-positive pelvic or para-aortic lymph nodes was performed in the present study. Tumor size was assessed by both pelvic examination and MRI, and tumor dimensions were measured according to T2-weighted and contrast-enhanced MRI images [20]. All patients gave written informed consent according to the institutional regulations.

Carbon-ion radiotherapy
Details of the treatment system of C-ion RT have previously been described [17, 18, 21]. Briefly, patients were fixed in the supine position using an individually tailored immobilization device. A set of CT images was taken for treatment planning for each patient. Up to 2011, the thickness of the CT slice was 5 mm, and it was changed to 2.5 mm in 2012. Three-dimensional treatment planning of C-ion RT was performed with HIPLAN software (National Institute of Radiological Sciences, Chiba, Japan) and was used until 2011, and the Xio-N system (ELEKTA, Stockholm, Sweden, and Mitsubishi Electric, Tokyo, Japan) was used from 2012 [22]. C-ion RT was carried out for 4 days per week (normally Tuesday through Friday). At each treatment session, the patient was laid on the treatment couch with the immobilization device, and the patient's position was verified with a computer-aided, on-line positioning system. Digital orthogonal X-ray images were taken, transferred to the positioning computer, and compared with reference images that were digitally reconstructed from the CT images acquired for treatment planning.

The treatment consisted of whole-pelvic irradiation and two steps of local boost. The gross tumor volume (GTV) was defined by MRI findings and clinical examination just before each treatment planning. The clinical target volume (CTV) of the whole-pelvic irradiation, named CTV-1, consisted of the primary site (GTV, whole uterus, parametrium, ovaries, and at least the upper half of the vagina) and the whole pelvic node region (common iliac, internal iliac, external iliac, obturator, and presacral node regions). The planning target volume (PTV) of the whole-pelvic irradiation (PTV-1) included the CTV-1 plus a 3-mm safety margin for positioning uncertainty and the uterus plus a 10-mm safety margin for intra- and inter-movement. After completing the sessions of whole-pelvic irradiation, the CTV for the first local boost (CTV-2) consisted of the primary site and the enlarged lymph nodes. A margin was added to CTV-2 to create PTV-2; this margin was expanded basically by 5–10 mm and modified to cover uterus movement. Finally, the CTV was shrunken to the GTV only (CTV-3), and no margin was added to PTV-3. The treatment plans of each treatment course for CTV-1, 2 and 3 were performed while referring to the MRI and CT images acquired just before initiation of each of the treatment courses. The radiation dose was calculated for the target volume and surrounding normal structures and was expressed in Gray [relative biological effectiveness (RBE)], which was defined as the physical dose multiplied by the RBE of the C-ions [23]. The dose to the gastrointestinal (GI) tracts was limited to <60 Gy (RBE) on the basis of dose–volume histogram analysis of an earlier study [24]. If PTV-1 and PTV-2 overlapped normal tissues, priority was given to the PTVs' coverage. However, the GI tracts were completely excluded from PTV-3 to limit the dose of GI tracts to under 60 Gy (RBE).

To minimize internal displacement of the uterus, tight vaginal packing was done at the treatment sessions. The cotton pads for vaginal packing were soaked in a contrast medium so that the surface of the uterine cervix could be visualized by X-ray images at the treatment sessions for the last eight fractions. Bladder volume was controlled with normal saline infusion by transurethral catheter to minimize any change in uterus position. Patients were also prescribed laxatives, as constipation might affect dose distribution by rectal stool gas.

The protocols were designed to identify the optimized dose for controlling the tumor in a dose-escalation manner. The dose to PTV-1 was fixed at 36.0 Gy (RBE) in 12 fractions in these protocols. With regard to PTV-2 and PTV-3, they each received 4 fractions in a dose-escalation manner; the dose per fraction of the successive levels was 3.3, 3.6, 4.0, 4.4 and 4.8 Gy (RBE). Therefore, the total dose to the GTV was 62.4–74.4 Gy (RBE) in 20 fractions. Dose escalation was carried out after careful observation of acute
normal tissue responses according to discussions of the Working Group of the Gynecological Tumor on a semi-annual basis.

**Patient characteristics**

Fourteen patients with endometrial carcinoma were treated by C-ion RT between July 1998 and October 2014. Ten of the 14 patients were judged as medically inoperable for reasons of advanced tumor invasion, older age, or severe concomitant illnesses. The other patients refused surgery. The median age of the patients was 70 years (range, 35–91 years). One patient had Stage I, 9 had Stage II, and 4 had Stage III disease. The median tumor size was 6.5 cm (range, 3.8–13.8 cm). Two of the 14 patients had pelvic lymph node metastases. Regarding total dose to the tumor, two patients received 62.4 Gy (RBE), one patient received 64.8 Gy (RBE), three patients received 68.0 Gy (RBE), three patients received 71.2 Gy (RBE), and five patients received 74.4 Gy (RBE). Figure 1 shows an example of the isodose curves of C-ion RT superimposed on CT images for the total irradiation plan. The median follow-up periods for all patients and surviving patients were 50 months (range, 12–218 months) and 78 months (range, 23–218 months), respectively. Characteristics of all patients are summarized in Table 1.

**Assessment of toxicity and efficacy**

After completing treatment, patients received follow-up every 1–3 months for 2 years, and every 3 or 6 months thereafter. Acute toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, with the highest toxicity within 3 months from the initiation of C-ion RT. Late toxicity was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme [25]. The tumor response was determined by comparing MRI and CT images taken before C-ion RT and 6 months later, and was assessed using Response Evaluation Criteria in Solid Tumors. The effect of the treatment was evaluated in terms of local control and overall survival. Local control was defined as the absence of tumor regrowth or recurrence in the treatment volume according to physical examination, CT, MRI and biopsy. Local control, progression-free survival, overall survival, and cause-specific survival rates were calculated by the Kaplan–Meier method and rounded off to no more than two significant figures.

**Statistical analysis**

One-tailed Fisher’s exact test was used for comparison in tumor responses and local control. All statistical analyses were performed using IBM SPSS Statistics for Macintosh ver. 23 (IBM Corp., Armonk, NY, USA).

**RESULTS**

**Acute and late toxicity**

All of the observed acute and late toxicities are listed in Table 2. All patients completed the scheduled therapy. Grade 2 late toxicity, rectal bleeding or hematuria, occurred in five patients, with two patients experiencing both GI and genitourinary toxicities. These patients improved with conservative therapy (e.g. oral drug administration). No patient developed Grade 3 or higher acute or late toxicity.

**Antitumor effect**

Tumor response is summarized in Table 3. Ten of the 14 patients achieved complete response (CR), three patients had partial response (PR), and one patient receiving 68.0 Gy (RBE) had stable disease (SD). Only two of six patients receiving 62.4–68.0 Gy (RBE) achieved CR, whereas all eight patients receiving 71.2–74.4 Gy (RBE) achieved CR. The difference in the rate of CR between the two groups was statistically significant (P = 0.015).

Two patients had local recurrence. Three patients had distant metastases, and one of them also had local recurrence. Two of three patients receiving 62.4–64.8 GY (RBE) had local recurrence, but none of 11 patients receiving 68.0 Gy (RBE) or higher dose had local recurrence (P = 0.033). Two of four patients in Stage III had local recurrence, and no patients in Stage I–II had local recurrence (P = 0.066). The 5-year local control, progression-free survival, overall survival, and cause-specific survival rates were 86% (95% CI: 67–100%), 64% (95% CI: 39–89%), 68% (95% CI: 41–94%) and 73% (95% CI: 47–100%), respectively (Fig. 2).

Figure 3 shows the tumor response of the patient of Fig. 1 with T2-weighted MRI images acquired before initiation of C-ion RT (A, B) and 25 months after C-ion RT (C, D). The tumor had invaded outside of the uterine corpus (red arrow) before C-ion RT. However, the tumor had shrunk and become unclear after C-ion RT. In addition, the patient has experienced no adverse effects up to 25 months after C-ion RT.

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![Fig. 1. Isodose curves of carbon-ion radiotherapy for endometrial carcinoma superimposed on axial and sagittal computed tomography images for the total irradiation plan. Highlighted are the contour of gross tumor volume (yellow), and 95% (red), 90% (orange), 70% (magenta), 50% (green) and 30% (blue) isodose curves.](image-url)
### Table 1. Patient characteristics and clinical outcomes

| No. | Age | PS | T   | N   | M   | Stage | MTD (cm) | TD [Gy (RBE)] | Failure patterns | OP (months) | Clinical outcome |
|-----|-----|----|-----|-----|-----|-------|----------|--------------|-----------------|-------------|-----------------|
| 1   | 75  | 1  | T2  | N0  | M0  | IIB   | 5.0      | 62.4         | CR None         | 167          | 167             | Death due to unknown cause |
| 2   | 67  | 0  | T3b | N0  | M0  | IIIB  | 8.0      | 62.4         | PR + 9         | None         | 218             | Alive |
| 3   | 77  | 0  | T3b | N1  | M0  | IIIC  | 9.0      | 64.8         | PR + 10        | Lymph node    | 12              | Cancer death |
| 4   | 73  | 1  | T3b | N1  | M0  | IIIC  | 8.0      | 68.0         | PR None 38     | None         | 40              | Cancer death |
| 5   | 76  | 0  | T2  | N0  | M0  | IIB   | 6.5      | 68.0         | CR None 116    | None         | 116             | Death due to other cause |
| 6   | 91  | 1  | T1  | N0  | M0  | I    | 3.8      | 68.0         | SD None 21     | None         | 26              | Cancer death |
| 7   | 73  | 1  | T2  | N0  | M0  | IIB   | 7.5      | 71.2         | CR None 13     | None         | 13              | Death due to other cause |
| 8   | 64  | 1  | T2  | N0  | M0  | IIB   | 6.5      | 71.2         | CR None 114    | None         | 114             | Alive |
| 9   | 45  | 0  | T2  | N0  | M0  | IIB   | 9.0      | 71.2         | CR None 137    | None         | 137             | Alive |
| 10  | 66  | 0  | T2  | N0  | M0  | IIB   | 4.8      | 74.4         | CR None 96     | None         | 96              | Alive |
| 11  | 35  | 1  | T2  | N0  | M0  | IIB   | 4.1      | 74.4         | CR None 60     | None         | 60              | Alive |
| 12  | 41  | 2  | T2  | N0  | M0  | IIB   | 13.8     | 74.4         | CR None 22     | None         | 22              | Alive |
| 13  | 58  | 1  | T3a | N0  | M0  | IIA   | 6.2      | 74.4         | CR None 25     | None         | 25              | Alive |
| 14  | 85  | 0  | T2  | N0  | M0  | IIB   | 5.5      | 74.4         | CR None 23     | None         | 23              | Alive |

Median 70

6.5 71.2 32 24 50

CR = complete response, DM = distant metastasis, LCI = local control interval, LR = local recurrence, LTR = local tumor response, MTD = maximum tumor diameter, OP = observation period, PALN = para-aortic lymph node, PFI = progression-free interval, PR = partial response, PS = performance status, RBE = relative biological effectiveness, RR = regional recurrence, SD = stable disease, TD = total dose. *Senile decay; cardiac insufficiency.

### Table 2. Acute and late toxicities

| Total dose [Gy (RBE)] | Acute GI toxicity | Acute GU toxicity | Late GI toxicity | Late GU toxicity |
|------------------------|-------------------|-------------------|-----------------|-----------------|
|                        | G0 | G1 | G2 | G3 | G4 | G0 | G1 | G2 | G3 | G4 | G0 | G1 | G2 | G3 | G4 | G0 | G1 | G2 | G3 | G4 |
| 62.4                   | 2  |1  | 1  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 2  | 0  | 0  | 0  | 0  | 2  | 0  | 0  | 0  | 0  |
| 64.8                   | 1  |1  | 0  | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 1  | 0  | 0  | 0  | 0  |
| 68.0                   | 3  |0  | 2  | 1  | 0  | 0  | 2  | 1  | 0  | 0  | 1  | 1  | 1  | 0  | 0  | 2  | 1  | 0  | 0  | 0  |
| 71.2                   | 3  |2  | 1  | 0  | 0  | 0  | 3  | 0  | 0  | 0  | 1  | 0  | 2  | 0  | 0  | 1  | 0  | 2  | 0  | 0  |
| 74.4                   | 5  |3  | 2  | 0  | 0  | 0  | 5  | 0  | 0  | 0  | 2  | 3  | 0  | 0  | 0  | 3  | 0  | 2  | 0  | 0  |
| Total                  | 14 |7  | 6  | 1  | 0  | 0  | 13 | 1  | 0  | 0  | 5  | 6  | 3  | 0  | 0  | 9  | 1  | 4  | 0  | 0  |

GI = gastrointestinal, GU = genitourinary, RBE = relative biological effectiveness.
To the best of our knowledge, the present study is the first to show the safety and efficacy of C-ion RT for endometrial carcinoma. We demonstrated that C-ion RT can be a safe and curative treatment modality without brachytherapy for inoperable endometrial carcinoma. There were no Grade 3 or worse acute or late complications at any dose applied in the present study, and all patients completed the scheduled therapy. In addition, despite 7 of the 14 patients in the present study being over 70 years of age, they did not develop any severe acute or late toxicities. According to previous conventional studies of photon radiotherapy with intracavitary brachytherapy for endometrial carcinoma, the incidence of Grade 3 or worse late complications was 0–21% [11–15]. Moderate complications of Grade 2 GI late toxicities were found in three patients receiving 68.0 or 71.2 Gy (RBE) in the present study. Using multivariate regression analysis models, Skwarchuk et al. reported that advanced age correlates with higher GI toxicity in conformal radiotherapy for prostate cancer [26]. In addition, the ages of the three patients with Grade 2 GI late toxicities in the present study were 64, 73 and 91 years. A careful approach would be required for implementing C-ion RT for endometrial carcinoma patients in old age.

Even though our cohort included patients with extensive and bulky tumors, the 5-year local control, progression-free survival, and cause-specific survival rates were 85.7%, 64.3% and 73.1%, respectively. The patients in the present study were treated with C-ion RT alone without intracavitary brachytherapy. To date, there are few reports assessing the efficacy of external body radiotherapy for endometrial carcinoma. Kemmerer et al. examined photon irradiation followed by stereotactic body radiotherapy without intracavitary brachytherapy for endometrial carcinoma patients [27]. In their study, 11 patients, median age 78 years, with Stage I–III endometrial carcinoma and who were not candidates for hysterectomy or intracavitary brachytherapy because of high comorbidities (91%) or refusal (9%) were analyzed. With a median follow-up of 10 months, estimated progression-free survival rates at 12 months and 18 months were 91% and 41%, respectively, which were poorer than the present results [27]. Thus, our present study suggests that C-ion RT could be more effective than external body radiotherapy with a photon beam for endometrial carcinoma.

Several studies have shown good results for definitive photon radiotherapy with intracavitary brachytherapy for endometrial carcinoma [11–15]. Coon et al. also reported that 3- and 5-year actuarial cause-specific survival rates for inoperable patients with Stage I–III endometrial carcinomas, consisting of 95.9% Stage I–II patients,

### Table 3. Tumor response at 6 months after carbon-ion radiotherapy

| Total dose [Gy (RBE)] | No. | Complete response | Partial response | Stable disease | Progressive disease |
|-----------------------|-----|-------------------|------------------|----------------|---------------------|
| 62.4                  | 2   | 1                 | 1                | 0              | 0                   |
| 64.8                  | 1   | 0                 | 1                | 0              | 0                   |
| 68.0                  | 3   | 1                 | 1                | 1              | 0                   |
| 71.2                  | 3   | 3                 | 0                | 0              | 0                   |
| 74.4                  | 5   | 5                 | 0                | 0              | 0                   |
| Total                 | 14  | 10                | 3                | 1              | 0                   |

RBE = relative biological effectiveness.

![Fig. 2. Local control (red), progression-free survival (green), overall survival (blue), and cause-specific survival (yellow) curves in all patients treated with carbon-ion radiotherapy.](image)

![Fig. 3. T2-weighted magnetic resonance images acquired before initiation of carbon-ion radiotherapy (A: axial, B: sagittal) and 25 months after carbon-ion radiotherapy (C: axial, D: sagittal) of the patient of Fig. 1. The red arrow indicates tumor invasion outside the uterine corpus.](image)
were 93% and 87%, respectively [11]. Knocke et al. reported a 5-year cause-specific survival rate for patients with Stage II disease of 68.6% [13]. In comparison with those results, the present study showed a similar cause-specific survival rate. Thus, C-ion RT for endometrial carcinoma could be considered an alternative treatment for inoperable patients with endometrial carcinoma.

The reason that the antitumor effect of C-ion RT was comparable with that of photon therapy with intracavitary brachytherapy may be attributed to the effective biological features of C-ion beams. Generally, a bulky tumor has a larger hypoxic component [28], and Suzuki et al. reported that hypoxic cervical tumors exhibit a poorer local control rate with conventional radiotherapy for uterine cervical cancer [29]. On the other hand, Nakano et al. reported favorable local control rates in both hypoxic and oxygenated tumors after C-ion RT for uterine cervical cancer [30]. Thus, the therapeutic effect observed in bulky tumors in our study indicates that C-ion RT is effective, at least, against the hypoxic component. In addition, C-ion RT is effective for tumor cells with mutated p53 cells and ample cancer stem cells [31–33]. Considering these observations, C-ion RT may be one of the favorable treatment options for advanced endometrial carcinoma.

A dose relationship of C-ion RT with the antitumor effect was seen in the present study. As Table 3 shows, four of six patients receiving 62.4–68.0 Gy (RBE) had PR or SD, while all of the eight patients receiving 71.2–74.4 Gy (RBE) achieved CR by 6 months after C-ion RT. Then, two patients who developed local recurrence had received a total dose of 62.4 or 64.8 Gy (RBE), and both these patients had Stage III disease, whereas no recurrence was observed in the patients receiving 68.0–74.4 Gy (RBE). These results suggest that a dose of 68.0 Gy (RBE) or higher in C-ion RT would be a prerequisite for the GTV of endometrial carcinoma, especially for Stage III disease. The dose to all GI tracts was strictly limited to <60 Gy (RBE), using the treatment technique that involves a two-step cone-down for the CTV in the present study.

There are some technical issues that need to be considered in radiotherapy for endometrial carcinoma, such as movement of the uterus and tumor shrinkage during the treatment period. Regarding movement of the uterus, we employed bladder infusion and laxatives to maintain consistency of the bladder and rectum volumes, which seem to affect uterus position [34–39]. In addition, the patients received vaginal packing to minimize uterus movement at each treatment session. These measures and set-up margin are the same as used in the previous study of C-ion RT for uterus carcinoma, as reported from our institution [21, 24, 40]. On the other hand, we acquired repetitive MRI and CT images for the patients just before initiation of each treatment session for CTV-1, 2 and 3 to take tumor shrinkage into account. Especially for the last four fractions, we carefully planned to achieve a dose for GI tracts of <60 Gy (RBE).

In conclusion, we demonstrated that C-ion RT can be a safe and curative treatment modality without brachytherapy for inoperable endometrial carcinoma. Although there is a limitation to our study, as the number of patients was small, thereby decreasing its statistical power, the results highlight the importance of continued investigation and analysis to confirm the therapeutic efficacy of this procedure.

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CONFLICT OF INTEREST
The authors state that they have no conflicts of interest to declare.

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REFERENCES
1. Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
2. Colombo N, Preti E, Landoni F et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vii33–8.
3. Group SGOCPECW, Burke WM, Orr J et al. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014;134:385–92.
4. Group SGOCPECW, Burke WM, Orr J et al. Endometrial cancer: a review and current management strategies: part II. Gynecol Oncol 2014;134:393–402.
5. Van den Bosch T, Coosemans A, Morina M et al. Screening for uterine tumours. Best Pract Res Clin Obstet Gynaecol 2012;26:257–66.
6. Kitchener HC, Trimble EL. Endometrial Cancer Working Group of the Gynecologic Cancer Intergroup. Endometrial cancer state of the science meeting. Int J Gynecol Cancer 2009;19:134–40.
7. Fishman DA, Roberts KB, Chambers JT et al. Radiation therapy as exclusive treatment for medically inoperable patients with stage I and II endometrioid carcinoma with endometrium. Gynecol Oncol 1996;61:189–96.
8. Niazi TM, Souhami L, Portelance L et al. Long-term results of high-dose-rate brachytherapy in the primary treatment of medically inoperable stage I–II endometrial carcinoma. Int J Radiat Oncol Biol Phys 2005;63:1108–13.
9. Rose PG, Baker S, Kern M et al. Primary radiation therapy for endometrial carcinoma: a case controlled study. Int J Radiat Oncol Biol Phys 1993;27:585–90.
10. Taghian A, Pernot M, Hoffstetter S et al. Radiation therapy alone for medically inoperable patients with adenocarcinoma of the endometrium. Int J Radiat Oncol Biol Phys 1988;15:1135–40.
11. Coon D, Beriwal S, Heron DE et al. High-dose-rate Rotte ‘Y’ applicator brachytherapy for definitive treatment of medically inoperable endometrial cancer: 10-year results. Int J Radiat Oncol Biol Phys 2008;71:779–83.
12. Dankulchai P, Petsuksin J, Chansipha Y et al. Image-guided high-dose-rate brachytherapy in inoperable endometrial cancer. Be J Radiol 2014;87:20140018.
13. Knocke TH, Kucera H, Weidinger B et al. Primary treatment of endometrial carcinoma with high-dose-rate brachytherapy: results of 12 years of experience with 280 patients. Int J Radiat Oncol Biol Phys 1997;37:359–65.
14. Okhuro Y, Kato S, Kiyohara H et al. Dose escalation study of carbon ion radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys 2000;47:103–13.
15. van der Steen-Banasik E. Primary brachytherapy as a radical treatment for endometrial carcinoma. Int J Radiat Oncol Biol Phys 2000;47:103–13.
16. Takahashi T, Fukawa T, Hirayama R et al. In vitro interaction of highLET heavy-ion irradiation and chemotherapeutic agents in two cell lines with different radiosensitivities and different p53 status. Anticancer Res 2010;30:1961–7.
17. Cui X, Oonishi K, Tsuji H et al. Effects of carbon ion beam on putative colon cancer stem cells and its comparison with X-rays. Cancer Res 2011;71:3676–87.
18. Oonishi K, Cui X, Hirakawa H et al. Different effects of carbon ion beams and X-rays on clonogenic survival and DNA repair in human pancreatic cancer stem-like cells. Radiother Oncol 2012;105:258–65.
19. Buchali AKS, Dinges S, Rosenthal P et al. Impact of the filling status of the bladder and rectum on their integral dose distribution and the movement of the uterus in the treatment planning of gynaecological cancer. Radiother Oncol 1999;52:29–34.
20. van de Bunt L, Jurgenleim-Schulz IM, de Kort GA et al. Motion and deformation of the target volumes during IMRT for cervical cancer: what margins do we need? Radiother Oncol 2008;88:233–40.
21. Taylor A, Powell ME. An assessment of interfractional uterine and cervical motion: implications for radiotherapy target volume definition in gynaecological cancer. Radiother Oncol 2008;88:250–7.
22. Chan P, Dinniwell R, Haider MA et al. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: a cinematic-MRI point-of-interest study. Int J Radiat Oncol Biol Phys 2008;70:1507–15.
23. Tyagi N, Lewis JH, Yashar CM et al. Daily online cone beam computed tomography to assess interfractional motion in patients with intact cervical cancer. Int J Radiat Oncol Biol Phys 2011;80:273–80.
24. Maemoto H, Toita T, Ariga T et al. Predictive factors of uterine movement during definitive radiotherapy for cervical cancer. J Radiat Res 2017;58:397–404.
25. Skwarchuk MW, Jackson A, Zelefsky MJ et al. Late rectal toxicity after conformal radiotherapy of prostate cancer (1): multi-variate analysis and dose–response. Int J Radiat Oncol Biol Phys 2000;47:103–13.