Original Article

Effects of dose and dose-averaged linear energy transfer on pelvic insufficiency fractures after carbon-ion radiotherapy for uterine carcinoma

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\textbf{Abstract}

\textbf{Background and Purpose:} The correlation between dose-averaged linear energy transfer (LET\textsubscript{d}) and its therapeutic or adverse effects, especially in carbon-ion radiotherapy (CIRT), remains controversial. This study aimed to investigate the effects of LET\textsubscript{d} and dose on pelvic insufficiency fractures after CIRT.

\textbf{Material and Methods:} Among patients who underwent CIRT for uterine carcinoma, 101 who were followed up for > 6 months without any other therapy were retrospectively analyzed. The sacrum insufficiency fractures (SIFs) were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer toxicity criteria. The correlations between the relative biological effectiveness (RBE)-weighted dose, LET\textsubscript{d}, physical dose, clinical factors, and SIFs were evaluated. In addition, we analyzed the association of SIF with LET\textsubscript{d}, physical dose, and clinical factors in cases where the sacrum D\textsubscript{50\%} RBE-weighted dose was above the median dose.

\textbf{Results:} At the last follow-up, 19 patients developed SIFs. Receiver operating characteristic curve analysis revealed that the sacrum D\textsubscript{50\%} RBE-weighted dose was a valuable predictor of SIF. Univariate analyses suggested that LET\textsubscript{d} V10 keV/\textmu m, physical dose V5 Gy, and smoking status were associated with SIF. Cox regression analysis in patients over 50 years of age validated that current smoking habit was the sole risk factor for SIF. Therefore, LET\textsubscript{d} or physical dose parameters were not associated with SIF prediction.

\textbf{Conclusion:} The sacrum D\textsubscript{50\%} RBE-weighted dose was identified as a risk factor for SIF. Additionally, neither LET\textsubscript{d} nor physical dose parameters were associated with SIF prediction.

Radiation therapy (RT) is essential for treating cervical cancer. RT can deliver radical cure and symptom relief in all stages of cervical cancer, except stage IA [1]. Several studies have reported the clinical significance of carbon-ion radiotherapy (CIRT), a form of RT [2]. Clinical trials of carbon-ion beam therapy have been conducted for gynecological tumors, particularly cervical cancer [3–8]. In a systematic review, Wang et al. reported that CIRT for cervical cancer is safe and effective [9]. CIRT has shown good local control (LC) rates, especially in radioresistant tumors, such as cervical adenocarcinoma and gynecological melanoma [9]. Thus, CIRT is...
an effective treatment method for gynecological tumors. As with conventional RT, managing adverse events (AEs) after CIRT is considered vital.

Proctitis and cystitis are the most frequent late AEs after RT in the pelvic region [10]. Pelvic insufficiency fractures (PIFs) are also late AEs after RT and CIRT in the pelvic region [11,12]. RT for premenopausal women results in direct bone damage from radiation and indirect bone damage due to decreased ovarian function [13]. Pelvic injuries significantly decrease a patient’s quality of life and increase mortality [14]. Thus, PIF is a significant AE after RT. Regarding the risk analysis for PIF after conventional RT, Ramlov et al. reported that patients aged > 50 years and the dose irradiated to 50 % of the volume (D50%) of the sacrum were predictors of PIF [15]. However, given the differences in terms of biological effectiveness between photon beams and carbon-ion beams, these predictors are unlikely to be applied in CIRT. Linear energy transfer (LET) is the amount of energy an ionizing particle transfers to the material traversed per unit distance. CIRT originally possesses a high LET; therefore, it is highly effective against cancer cells because it induces complex deoxyribonucleic acid (DNA) double-strand breaks, dysfunction of the G2/M-phase checkpoint, and mitotic catastrophes at a high rate [16,17]. Therefore, the so-called “clinical dose” in CIRT is defined based on this biological effect, representing the relative biological effectiveness (RBE)-weighted dose [18–21].

Of note, LET has been suggested to be more critical than the RBE-weighted dose, Gray (Gy) (RBE), in the anti-tumor effect of CIRT. Hagiwara et al. reported that the minimum dose-averaged LET (LETd) within the tumor was significantly associated with LC in primary pancreatic cancers [22]. In addition, Matsumoto et al. reported that local recurrence was not observed when the effective minimum LETd value exceeded 40 keV/μm after CIRT for chondrosarcoma [23]. Meanwhile, our previous study found no correlations between severe rectal toxicities and LETd alone or physical dose per se after CIRT for uterine carcinoma [24]. In a study, Nie-mierko et al. reported that LET adjusted for dose was not associated with the risk of brain necrosis in proton beam therapy [25]. Thus, the correlation between LETd and its therapeutic effects along with AEs, especially in CIRT, is controversial. Therefore, the purpose of this study was to comprehensively investigate the effects of dose and LETd on PIFs following CIRT for uterine carcinoma.

Materials and methods

The present single-institution retrospective observational study commenced following institutional review board approval (QST 18–015). Owing to the retrospective nature of the study, the requirement for written informed consent was waived. A document establishing an opt-out policy was uploaded to the institution’s website, allowing patients and their families to opt-out of the study. The study adhered to the principles of the Declaration of Helsinki.

Patient eligibility criteria

Between June 1995 and January 2010, 134 patients with uterine carcinoma underwent definitive CIRT as part of four clinical trials [3–6]. None of the patients in this cohort received concurrent chemotherapy or brachytherapy because of the regulation of these clinical trials. Of the 134 patients, 102 who were followed up for > 6 months with no other external beam RT in the pelvic region were enrolled. We analyzed all patients except one whose LETd data could not be retrieved; therefore, we analyzed a total of 101 patients. The patient cohort was the same as that used in a previous study [12]. However, there was a longer follow-up period in this study.

Treatment outlines for carbon-ion radiotherapy

The modified microdosimetric kinetic model (MKM) was applied for CIRT RBE-weighted dose calculation at our institution, which was expressed in Gy (RBE) [18–20]. The RBE calculation based on MKM involves in vitro data on the 10 % survival rate of human salivary gland tumor cells under aerobic conditions and clinical experience with fast neutron beam therapy [26]. Details of CIRT for uterine carcinoma can be found in our previous studies [3–6]. In brief, the prescribed dose ranged from 52.8 to 74.4 Gy (RBE), which was determined due to the involvement of patients enrolled in dose-escalation clinical trials [3–6]. The patients received 20 or 24 fractions of CIRT for 5–6 weeks. The irradiation field size decreased in a stepwise manner from irradiating the whole pelvis to the tumor. All treatments were performed using passive beam irradiation, and no dose constraints were set for the pelvic bone of patients in this study. This study defined Gy (RBE) as the RBE-weighted dose to clarify definitions.

LETd distributions

The data acquisition method for the LETd distribution was similar to that in our previous study [24]. The RBE-weighted dose distributions based on modified MKM were calculated using the treatment planning system, XiO-N (Mitsubishi Electric, Tokyo), and the LETd was calculated from RBE and physical dose [27]. Additionally, primary carbon ions and secondary and tertiary projectile nuclear fragments were counted in the LETd using the Sihver model [28]. The LETd at location \( r \) was calculated as follows:

\[
L(r) = \frac{\sum |n_i \cdot D_i(r) \cdot L_i(r)|}{\sum |n_i \cdot D_i(r)|}
\]

where \( D_i(r) \) denotes the physical dose distribution for beam \( i \), \( n_i \) denotes the beam fraction, and \( L_i(r) \) denotes the LET distribution for beam \( i \). \( L_i \) in the equation is the LETd of the \( i \)-th beam at location \( r \). The LET for this study was defined by the following settings: unrestricted, LET for water, and no density normalization [29]. As illustrated in Fig. 1, the calculated LETd distribution was superimposed on planning computed tomography (CT).

Data acquisition

Our previous study examined the preferred PIF site after CIRT for gynecologic tumors and revealed that the sacrum insufficiency fracture (SIF) site was the most predominant one [12]. Therefore, we collected data on the RBE-weighted dose, LETd, and physical doses to the sacrum in this study. The contour of the sacrum was delineated on XiO-N. The outer line of the bone was defined as the outer edge of the sacrum, without distinguishing between the bony cortex and trabecular bone.

Next, dose parameters were determined using dose-volume histograms (DVHs) [30]. The RBE-weighted dose parameters, including \( V_{10–40} \), \( D_{50\%} \), \( D_{5cc} \), and \( D_{2cc} \), were obtained from DVHs using XiO-N. Vx Gy (RBE) in this context means the volume of the sacrum that received an RBE-weighted dose of \( \times \) Gy (RBE) or more. \( D_{RBE < cc} \) represents the minimum RBE-weighted dose to which a volume of \( \times \) cc has been irradiated. \( D_{RBE < 50\%} \) indicates the dose irradiated to 50 % of the volume of the sacrum. The D50% of the sacrum is a relative value that has been reported by Ramlov et al. as a significant risk factor for PIFs in photon beam therapy [15]. We subsequently obtained LETd parameters, including \( V_{1} 10–40 \) keV/μm, \( L_{50\%} \), \( L_{5cc} \), and \( L_{2cc} \) in keV/μm, as described previously [24]. \( V \times \) keV/μm in this context means the volume of
the sacrum that received an LETd of × keV/μm or more. Lx cc represents the minimum LETd value to which a volume of × cc has been exposed. L50% represents the LETd value exposed to 50% of the volume of the sacrum. The physical dose distributions were generated through the RBE-weighted dose calculation on XiO-N, and the parameters, including V5–15, D50%, D5cc, and D2cc in Gy, were also determined. VP × Gy in this context means the volume of the sacrum that received a physical dose of × Gy or more. DP × cc represents the minimum physical dose to which a volume of × cc has been irradiated. DP50% indicates the physical dose irradiated to 50% of the volume of the sacrum. These parameters and clinical factors, such as age, smoking history, alcohol consumption, and body mass index, were analyzed as risk predictors of SIF.

The diagnostic criteria of SIFs included findings of T1-hypointense and T2-hyperintense lesions on MRI and/or fracture lines or sclerotic changes without osteolytic lesions on CT images and no evidence of bone metastasis, similar to the previously reported findings [12].

Statistical analysis

Comparisons of RBE-weighted DVH parameters between patients with and without SIFs were performed by the Mann–Whitney U test. The optimal cut-off values for the RBE-weighted dose of SIFs were determined using receiver operating characteristic (ROC) curve analysis. Additionally, the area under the ROC curve (AUC) values were calculated. The log-rank test was used for univariate analyses. The factors with a p-value < 0.1 by univariate analysis were included in the Cox regression analysis. For multiple factors with p-value < 0.1 in each category, that is, LETd, physical dose, and clinical factors, a multivariate analysis was performed using factors with the lowest p-value from the univariate analysis to avoid confounding of factors. A correlation analysis was used to evaluate the correlation between the two values.

Firstly, we specifically identified the parameters for SIF based on the RBE-weighted dose using the Mann–Whitney U test. Thereafter, we validated the reliability of these parameters in predicting SIF by ROC analysis. We dichotomized the patient groups based on the RBE-weighted dose parameter(s) and determined whether LETd, physical dose, or clinical factors were associated with SIF in each group. Univariate and multivariate analyses were used for these validations. Additionally, we used 50 years as the cut-off age for multivariate analysis, as reported in a previous study on pelvic insufficiency fractures [15].

All test results were considered statistically significant at a two-sided p-value < 0.05. SPSS 27.0 (for Mac) was used for statistical analyses (Armonk, NY: IBM Corp, USA).

Results

Table 1 shows the patient and tumor characteristics in this study. The median follow-up time was 66 months (range, 8–297 months), and the median age at diagnosis was 58 years (range, 28–85 years). SIFs were observed in 19 patients during the last follow-up. Fig. 2A shows the DVH of each patient’s RBE-weighted dose to the sacrum in the groups with SIF and without SIF. The averaged DVHs in the groups with SIF and without SIF are shown in Fig. 2B.

Table 1 shows the patient and tumor characteristics of 101 patients.

| Characteristics (n = 101) | Number of patients (%) |
|--------------------------|------------------------|
| Follow-up period (months) | 66 (8–297) |
| Age at diagnosis (years)  | 58 (28–85)  |
| BMI (kg/m²)               | 11 (10.9)   |
| < 18.5                    | 89 (88.1)   |
| ≥ 18.5                    | 1 (1.0)     |
| Tobacco                   | 78 (77.2)   |
| Never smoker              | 7 (6.9)     |
| Past smoker               | 14 (13.9)   |
| Current smoker            | 2 (2.0)     |
| Alcohol per day (g)       | 71 (70.2)   |
| 0                         | 24 (23.8)   |
| 0 <, ≤ 20                 | 4 (4.0)     |
| 20 <, ≤ 40                | 2 (2.0)     |
| Sacrum insufficiency fracture | 19 (18.8) |
| Yes                       | 82 (81.2)   |

BMI, body mass index.
with and without SIFs, the patients with SIFs showed a statistically significant difference in V10 Gy (RBE), V20 Gy (RBE), V30 Gy (RBE), DRBE50%, DRBE5cc, and DRBE2cc compared to those of patients without SIF (Mann–Whitney U tests) (Table 2A). When dichotomized by the median of each parameter, the Mann–Whitney U test showed a statistically significant difference in the incidence of SIF for all parameters except DRBE5cc, which was particularly significant for DRBE50% and V20 Gy (RBE) (< 0.001, each) (Table 2B). ROC analyses showed that AUCs ranged from 0.682 to 0.755, and the AUCs of DRBE50% and V20 Gy (RBE) were particularly high for these factors (0.755 and 0.753, respectively), suggesting that they are valuable risk predictors for SIF (Fig. 2C). As shown in Table 2B, however, even in these groups with high DRBE50% or V20 Gy (RBE), there were cases with and without SIF. Therefore, univariate and multivariate analyses were performed to further examine the effects of physical dose, LETd, and clinical factors on SIF in the groups.

Next, we examined the factors influencing SIF in 51 patients whose DRBE50% was beyond the median. The characteristics of 51 patients are shown in Supplementary Table 1. Among these 51 patients, 17 developed SIF at the last follow-up. Table 3 shows the univariate analysis to assess the risk factors of SIF. The V10 keV/lm in LETd and the V5 Gy in physical dose showed significant differences according to log-rank tests, suggesting that they are

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**Table 2**

Comparisons of the histogram parameters of relative biological effectiveness-weighted dose-volume between patients with and without insufficiency fractures of the sacrum.

| Parameter | SIF - (n = 82) | SIF + (n = 19) | p-value |
|-----------|---------------|---------------|---------|
| V10 Gy (RBE) (mean ± SD, cc) | 132.9 ± 62.6 | 183.2 ± 45.6 | 0.003 |
| V20 Gy (RBE) (mean ± SD, cc) | 87.6 ± 59.7 | 143.9 ± 53.9 | 0.001 |
| V30 Gy (RBE) (mean ± SD, cc) | 22.3 ± 22.0 | 36.7 ± 26.1 | 0.016 |
| V40 Gy (RBE) (mean ± SD, cc) | 8.6 ± 17.4 | 15.4 ± 18.2 | 0.135 |
| DRBE50% (mean ± SD, Gy [RBE]) | 17.0 ± 8.0 | 23.9 ± 6.4 | 0.002 |
| DRBE5cc (mean ± SD, Gy [RBE]) | 37.5 ± 7.5 | 43.1 ± 8.6 | 0.006 |
| DRBE2cc (mean ± SD, Gy [RBE]) | 40.8 ± 8.1 | 46.7 ± 10.2 | 0.008 |

(B) Comparisons of dividing by median value.

| Parameter | Subgroup | Number of patients | Number of patient with SIF | p-value |
|-----------|----------|--------------------|---------------------------|---------|
| V10 Gy (RBE) (mean ± SD, cc) | < 159.1 | 50 / 51 | 4 / 15 | 0.008 |
| V20 Gy (RBE) (mean ± SD, cc) | < 92.1 | 50 / 51 | 2 / 17 | < 0.001 |
| V30 Gy (RBE) (mean ± SD, cc) | < 19.4 | 50 / 51 | 4 / 15 | 0.003 |
| V40 Gy (RBE) (mean ± SD, cc) | < 1.3 | 50 / 51 | 5 / 14 | 0.028 |
| DRBE50% (mean ± SD, Gy [RBE]) | < 19.9 | 50 / 51 | 2 / 17 | < 0.001 |
| DRBE5cc (mean ± SD, Gy [RBE]) | < 36.8 | 50 / 51 | 6 / 13 | 0.074 |
| DRBE2cc (mean ± SD, Gy [RBE]) | < 39.0 | 50 / 51 | 5 / 14 | 0.022 |

Analyzed by Mann–Whitney U tests.

RBE, relative biological effectiveness; SIF, sacrum insufficiency fracture; SD, standard deviation.
related to SIF. Moreover, Cox regression analysis of these two factors and smoking history, which had the lowest p-value (p = 0.093) among the patient factors, showed that current smoking habit is a likely risk factor for SIF, although it was not statistically significant (p = 0.068; hazard ratio [HR] = 2.913; 95 % confidence interval [CI]: 0.925–9.173) (Table 4A). Furthermore, the Cox regression analysis in patients over 50 years old showed current smoking habit to be the sole risk factor for SIF (p = 0.041; HR = 3.568; 95 % CI: 1.052–12.104) (Table 4B). Therefore, parameters of LETd or physical dose parameters were not found to be risk predictors of SIF.

To validate these findings, we performed univariate analyses to assess the risk factors for SIF in the 50 patients whose D_{RBE50%} was less than the median. None of the dose parameters or clinical factors showed a significant difference according to the log-rank test (Supplementary Table 2).

Table 3
Univariate analyses of risk factors for sacrum insufficiency fracture in 51 patients whose D_{RBE50%} was above the median in the relative biological effectiveness-weighted dose.

| Sacrum                      | Subgroup | Number of patients | Number of patient with SIF | p-value           |
|-----------------------------|----------|--------------------|----------------------------|-------------------|
| LETd                        |          |                    |                            |                   |
| V10 keV/μm (mean ± SD, cc)  | < 192.7  | 25 / 26            | 5 / 12                     | 0.034             |
| V20 keV/μm (mean ± SD, cc)  | < 161.3  | 25 / 26            | 6 / 11                     | 0.139             |
| V30 keV/μm (mean ± SD, cc)  | < 104.5  | 25 / 26            | 6 / 11                     | 0.415             |
| V40 keV/μm (mean ± SD, cc)  | < 29.5   | 25 / 26            | 6 / 11                     | 0.174             |
| L50% (mean ± SD, keV/μm)    | < 31.1   | 25 / 26            | 8 / 9                      | 0.808             |
| L5<sub>c</sub> (mean ± SD, keV/μm) | < 53.6 | 25 / 26            | 8 / 9                      | 0.868             |
| L2<sub>c</sub> (mean ± SD, keV/μm) | < 55.6 | 25 / 26            | 8 / 9                      | 0.828             |
| Physical dose               |          |                    |                            |                   |
| V5 Gy (mean ± SD, cc)       | < 188.8  | 25 / 26            | 5 / 12                     | 0.012             |
| V10 Gy (mean ± SD, cc)      | < 163.1  | 25 / 26            | 7 / 10                     | 0.123             |
| V15 Gy (mean ± SD, cc)      | < 20.6   | 25 / 26            | 6 / 11                     | 0.066             |
| D50% (mean ± SD, Gy)        | < 11.8   | 25 / 26            | 6 / 11                     | 0.097             |
| D5<sub>c</sub> (mean ± SD, Gy) | < 18.4 | 25 / 26            | 8 / 9                      | 0.462             |
| D5<sub>c</sub> (mean ± SD, Gy) | < 19.5 | 25 / 26            | 9 / 8                      | 0.552             |
| Patients’ factor            |          |                    |                            |                   |
| Age                         | < 50 years / ≥ 50 years | 10 / 41           | 2 / 15                     | 0.393             |
| Smoking history             | Never or past smoking | 39*               | 11*                        | 0.993             |
| Alcohol                     | Non-habitual drinking | 37*               | 12*                        | 0.544             |
| BMI                         | ≤ 18.5 / ≥ 18.5 | 7 / 44            | 4 / 13                     | 0.316             |

Table 4
Assessment of risk factors by multivariate analysis.

(A) Cox regression analysis in 51 patients whose D_{RBE50%} was above the median in the relative biological effectiveness-weighted dose.

| Factor                | SIF                   | p-value | HR (95% CI) |
|-----------------------|-----------------------|---------|-------------|
| V10 keV/μm in LETd(V10 keV/μm) | 0.186                | 1.012 (0.994–1.029) |
| V5 Gy in physical dose (V5 Gy)   | 0.345                | 1.068 (0.932–1.224) |
| Current smoking       | 0.068                | 2.913 (0.925–9.173) |

(B) Cox regression analysis in patients over 50 years old.

| Factor                | SIF                   | p-value | HR (95% CI) |
|-----------------------|-----------------------|---------|-------------|
| V10 keV/μm in LETd(V10 keV/μm) | 0.312                | 1.009 (0.992–1.026) |
| V5 Gy in physical dose (V5 Gy)   | 0.041                | 3.568 (1.052–12.104) |

As mentioned earlier, ROC analysis suggested that V20 Gy (RBE) was also a valuable predictor of SIF. Therefore, similar to the analysis based on D_{RBE50%}, we validated whether SIF was associated with LETd, physical dose, and clinical factors in patients with high V20 Gy (RBE). The characteristics of the 51 patients whose V20 Gy (RBE) was above the median are shown in Supplementary Table 3. Among these 51 patients, 17 developed SIF at the last follow-up. Supplementary Table 4 shows the results of univariate analyses of the risk factors for SIF; interestingly, neither LETd nor physical dose parameters showed significant differences with respect to SIF, suggesting that only smoking history was associated with SIF (p = 0.005). Cox regression analysis validated that current smoking habit was the sole risk factor for SIF (p = 0.006; HR = 5.188; 95 % CI: 1.593–16.900). Furthermore, the Cox regression analysis in the population over 50 years of age showed an even higher HR for current smoking habit with respect to SIF (p = 0.001; HR = 40.107; 95 % CI: 4.238–379.609) (Supplementary Table 5). Therefore, LETd or physical dose parameters were not found to be risk predictors of SIF, even with the analyses based on V20 Gy (RBE). The correlation analysis showed a high correlation between D_{RBE50%} and V20 Gy (RBE) (r = 0.891).

Discussion

To our knowledge, this is the first study to comprehensively examine the effects of the RBE-weighted dose, LETd, and physical dose on SIF development after CRT for uterine carcinoma. Firstly, this study revealed D_{RBE50%} to be a valuable risk predictor of SIF. The V20 Gy (RBE) was also suggested to be a significant risk predictor of SIF. The median D_{RBE50%} in this study was 19.9 Gy (RBE); the two variables, D_{RBE50%} and V20 Gy (RBE), were highly correlated. Ramlov et al. reported that the sacral D_{50%} was predictive of SIF in locally advanced cervical cancer patients over 50 years of age treated with radical chemoradiation using intensity-modulated RT [15]. Thus, our results support Ramlov’s findings [15]. Unlike the rectum and bladder, where small volumes in the high dose...
Effects of dose and LETd on pelvic bones

range are associated with late AEs [31], the medium dose for the entire sacrum resulted in the development of SIFs. Therefore, it seems reasonable to lower the D_{50\%} to < 19.9 Gy (RBE) to prevent SIFs in CIRT. However, as shown in Table 2A, in addition to D_{50\%}, the RBE-weighted dose parameters of V10–30 Gy (RBE), D_{50cc}, and D_{2cc} also correlated with SIF. In an in vivo experiment, Schreurs et al. reported that radiation decreased the bone mass of trabecular bones but not that of dense bones [32]. Although dense and trabecular bones were not distinguished in this study, DVH analysis considering the bone structure may be warranted in the future.

The multivariate analysis in this study revealed that LETd or physical dose per se were not significant predictors of SIF development. This result supports the validity of the model we used to calculate the biological dose [18–20]. This result also agrees with the findings of our previous study on late rectal AEs in CIRT [24]. Recently, in proton beam therapy, it has been reported that the RBE-weighted dose considering the LETd, rather than the LETd or the physical dose per se, was helpful in predicting late AEs in the brain and ribs [25,33–35]. Bahn et al. calculated the LETd distributions using the Monte Carlo method in patients treated with proton therapy for low-grade glioma and reported the degree of concordance of dose and LETd distribution with minor post-treatment brain necrosis [35]. Their study revealed that the dose distribution weighted by LETd correlated strongly with contrast-enhancing brain lesions, which was suggestive of minor brain necrosis, but not with the LETd distribution itself. Taken together, these results suggest that LETd per se may not be consistent with late normal tissue response in CIRT or proton beam therapy. However, in CIRT for primary pancreatic cancer and chondrosarcoma, low LETd in the tumor has been reported to be associated with local recurrence [22,23]. To date, there is no clear explanation for the discrepancy between the behavior of LETd in normal tissues and tumors. Therefore, further comprehensive analysis of the significance of LETd in other normal tissues and tumors is needed.

Regarding the mechanism of accelerated bone fragility after irradiation, Alwood et al. reported the effects of irradiation on bone and bone marrow cells of mice, using proton irradiation as low-LET radiation and iron ion radiation as high-LET radiation [36]. Their study revealed that 50 cGy proton irradiation did not cause significant changes in bone structure, but 50 cGy iron ion irradiation caused significant changes in bone structure, compared to the control. Additionally, gene expression in bone marrow cells after 200 cGy of iron ion irradiation showed an increase in the expression of Gadd45, which is involved in cell cycle arrest, and a decrease in the expression of Apli, which is an osteoblast differentiation gene. However, no such changes were observed after proton beam irradiation [36]. Thus, high-LET radiation may strongly affect bone cells or their gene expression. However, the effects in the dose range of several tens of Gy, such as those used in RT, have not been clarified. Additionally, it is difficult to extrapolate the results of in vivo study to those of humans, considering the differences in bone metabolism and external forces on bone due to differences in the skeletal structure between mice and humans. Considering the recent advancements in changing the LETd in the irradiation field by mixing multiple ion species [37,38], further studies on the effects of such high-LET radiation on the bone are critical to establishing a method for preventing fractures after CIRT.

In this study, age, smoking habit, alcohol consumption, and BMI as risk factors for SIF did not show significant differences in the univariate analysis of D_{50\%}. However, multivariate analysis in the group restricted to patients aged 50 years and older suggested that smoking was the only factor associated with SIF. In addition, the univariate analysis of V20 Gy (RBE) showed that only smoking history was associated with SIF. Smoking, including regular cigarettes or e-cigarettes, increases the risk of fractures and adversely affects fracture healing [39]. Furthermore, smoking worsens the overall survival of patients with locally advanced cervical cancer undergoing RT [40]. It also increases the incidence of malignancy and ischemic heart disease and increases the risk of mortality by a factor of 1.48 in women, compared to that in non-smokers [41]. Therefore, in addition to the negative health effects of smoking, smoking cessation guidance for patients undergoing CIRT is vital, as smoking can increase SIF risk.

This study had several limitations. First, the potential for bias, stemming from the retrospective nature and the limited sample size needs to be considered. Therefore, our findings need to be validated by other studies. Second, the effect of dose fractionation on CIRT has not been studied. All patients enrolled in this study had been enrolled in clinical trials for the dose-escalation study of CIRT; therefore, there was no room for dose fractionation adjustment. The fractionation effect in CIRT is likely to be small because the direct effect on DNA damage is more substantial than that in X-ray therapy [16]. However, further investigation into the effect of late AEs, including brittle bones, may be warranted. Third, a limitation due to the calculation model of CIRT was considered. This study applied a modified MKM for dose calculation [20]. Therefore, caution should be exercised in interpreting the results because the calculation method differs from that of the local effect model (LEM), which is mainly applied in European particle therapy facilities [42]. It would be worthwhile to validate the findings of this study with clinical data using LEM. Although the present study has these limitations, our results show that the risk factors in CIRT gynecologic tumors help prevent SIF and may contribute to the patient’s quality of life after CIRT treatment. Additionally, the fact that LETd does not affect SIF may support the feasibility of LET-modulated RT [43].

In conclusion, this study showed that the D_{50\%} was a risk factor for SIF. Neither LETd nor physical dose parameters were significant risk factors for SIF, and the current smoking habit was the only factor contributing to SIF when stratified by age > 50 years.

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Declaration of interest

Nobuyuki Kanematsu reports relationships with the Japan Society of Medical Physics (which includes board membership and travel reimbursement), Japan Radiology Congress (which includes board membership and travel reimbursement), Kanagawa Cancer Center (which includes consulting or advisory), Osaka International Cancer Treatment Foundation (which includes travel reimbursement), and the Association for Nuclear Technology in Medicine (which includes speaking and lecture fees). In addition, Nobuyuki Kanematsu has patents: #JP2020-044286A (pending), #JP6383429 (issued), #JP5954705 (with royalties paid), #JP5521225 (with royalties paid), and #JP4456045 (with royalties paid), all to the National Institutes for Quantum Science and Technology.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.10.008.

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