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Clinical Investigation: Gynecologic Cancer

Changes in Bone Mineral Density in Uterine Cervical Cancer Patients After Radiation Therapy

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Summary

Pelvic radiation therapy (RT) may not only cause direct damage to the bones but can also cause the loss of ovarian function in women. This study investigated the changes in bone mineral densities (BMDs) after pelvic RT in patients with uterine cervical cancer, prospectively. A decrease in BMD in the irradiated region after RT was observed within 1 year, regardless of menopausal status. Furthermore, in premenopausal patients, pelvic RT caused a decrease in systemic BMD.

Purpose: To prospectively investigate the changes in bone mineral density (BMD) after pelvic radiation therapy in patients with uterine cervical cancer.

Methods and Materials: Of 52 cervical cancer patients who received pelvic RT in our university hospital between 2009 and 2011, 46 patients without recurrence and who were followed up for more than 12 months were included in the study. The BMD of the irradiated region and nonirradiated regions, serum estradiol, tartrate-resistant acid phosphatase-5b, and N-terminal cross-linking telopeptide of collagen 1 were measured before, at 3 months after, and at 12 months after RT. The patient cohort was divided into 2 groups according to estradiol level before RT, and the groups were defined as postmenopausal (<40 pg/mL) and premenopausal (≥40 pg/mL).

Results: The mean BMDs within the irradiation field (lumbar vertebra 5) in the postmenopausal and the premenopausal groups were 0.825 and 0.910 g/cm^2 before RT and 0.746 and 0.841 g/cm^2 12 months after RT, respectively. Significant decreases were observed in both groups ($P<.05$ and $P<.01$, respectively). In addition, in the premenopausal group the mean BMDs of the nonirradiated regions at thoracic vertebrae 9-12 and lumbar vertebrae 2-4 were 0.753 and 0.958 g/cm^2 before RT and were significantly decreased to 0.706 and 0.921 g/cm^2 12 months after RT ($P<.01$ and $P<.05$, respectively). Estradiol significantly decreased 3 months after RT, whereas tartrate-resistant acid phosphatase-5b and N-terminal cross-linking telopeptide of collagen 1 continued to increase over time in the premenopausal group.

Conclusions: A decrease in BMD in the irradiated region after RT was observed within 1 year, regardless of menopausal status. Furthermore, in premenopausal patients, pelvic RT caused a decrease in systemic BMD.

Introduction

Osteoporosis results in millions of fractures (1), more than 400,000 hospital admissions, and $13.8 billion in health care expenditures yearly in the United States alone (2). Postmenopausal women, in particular, are at a higher risk for osteoporosis because of their rapid decrease in estrogen levels, which results in decreased bone mineral density (BMD) (3).

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Uterine cervical cancer is the third most common cancer and the fourth leading cause of cancer death in women worldwide (4). Annually there are more than 520,000 cases and 270,000 deaths from cervical cancer globally (5). Notably, the number of cervical cancer cases diagnosed in young patients has been increasing (6). Radiation therapy (RT) is the standard treatment for all except the very early stages of cervical cancer (7-9). Previous studies regarding the use of RT for cervical cancer treatment have shown that it confers good survival (7-9). Therefore, the quality of life of patients with cervical cancer after RT should be considered.

Pelvic RT can promote pelvic insufficiency fractures (IFs) (10, 11). Baxter et al (10) reported that in cervical cancer patients who received pelvic RT, the 5-year cumulative occurrence rate of IFs in the irradiated region, as defined by the Medicare Provider Analysis and Review data, was approximately 8.2%. Recently, Tokumaru et al (11) reported that in cervical cancer patients who received pelvic RT, the cumulative 2-year rate of IFs diagnosed using magnetic resonance imaging (MRI) was 36.9%.

Irradiation to the pelvic region may cause not only direct damage to the bones but also the loss of ovarian function in women. Hence, there is a possibility that the loss of ovarian function induced by RT may affect BMD in these women. However, the specific effects of pelvic RT on the decrease of BMD are still unclear, including the extent of change in BMD, the changes in the levels of serum estrogen and bone metabolism markers, and the influence of estrogen level on the change in BMD.

Here we prospectively investigated the direct and systemic influence of RT by assessing the BMDs of the irradiated regions and the nonirradiated regions of cervical cancer patients. We also assessed the levels of estrogen and bone metabolism markers in these patients.

Methods and Materials

Patient characteristics

Between July 2009 and December 2011, 52 patients with newly diagnosed uterine cervical cancer met the following criteria for this study in our hospital: (*1*) patients with histologically proven cancer; (*2*) patients who would be treated with curative RT; and (*3*) patients without previous RT to any location. All patients were required to give their written informed consent for this study before treatment. In 52 of these patients we measured the BMDs of the irradiated and nonirradiated regions, as well as the levels of estrogen and bone metabolism markers before RT, 3 months after RT, and 12 months after RT. After excluding 6 patients who had disease recurrence, 46 patients were included in the final cohort for this study. Table 1 shows the study patients' characteristics. The median age was 60 years and ranged from 33 to 80 years. The patients were staged according to the International Federation of Gynecology and Obstetrics staging system; 8 patients were classified as stage 1B, 21 patients were classified as stage 2, and 17 patients were classified as stage 3. The median follow-up period was 30 months.

Table 1 Patient characteristics

Characteristic	n	%
Menopausal status		
Premenopause	18	39
Postmenopause	28	61
FIGO stage		
1B	8	17
2	21	46
3	17	37
Chemotherapy		
Yes	33	72
No	13	28
Histology		
Squamous	42	91
Adeno	4	9
Beam technique		
AP/PA	24	52
Box 4-field	22	48

Abbreviations: Adeno = adenocarcinoma; AP/PA = anteroposterior/posteroanterior field; FIGO = International Federation of Gynecology and Obstetrics; Squamous = squamous cell carcinoma.

Treatments

The treatment protocol for cervical cancer in our hospital has previously been described in detail (12, 13). The RT protocol consists of a combination of external beam RT and high-dose-rate intracavitary brachytherapy (HDR-ICBT), with or without chemotherapy. A total dose of 50 Gy of external beam RT was delivered in 25 fractions over 5 to 6 weeks. The early part of the therapy, comprising 20 Gy or 30 Gy, was delivered to the whole pelvis. Thereafter, the remaining 30 Gy or 20 Gy was administered to the same whole-pelvic field with central shielding. External beam RT was performed using the anteroposterior/posteroanterior field or box 4-field technique. The upper border of the pelvic field was the upper edge of lumbar vertebra 5 (L5), and the lower border was the transverse line below the obturator foramen. The lateral borders were 1 to 2 cm beyond the lateral margins of the bony pelvis. Along with central shielding, HDR-ICBT was started with a remote after-loading system using high-dose-rate ^{192}Ir sources. Four or 5 fractions of HDR-ICBT were administered once per week, with a total dose ranging from 20 to 36 Gy (median, 24 Gy) at point A. Twenty-four patients who had pelvic lymph node metastases received an additional irradiation boost of 6-10 Gy per 3-5 fractions. Ten patients received RT to the para-aortic lymph node region (including L1-L4) ranging from 38 to 56 Gy (median, 40 Gy), depending on the progression of the disease. Thirty-three patients, all younger than 75 years, with advanced-stage disease and with a bulky tumor (more than 4 cm), were given concurrent chemoradiotherapy, up to 5 courses of weekly 40 mg/m^2 cisplatin (median, 4; range, 3-5).

The actual delivered dose to the vertebral body was quantified using dose–volume histograms in an RT planning system (Xio; Elekta, Atlanta, GA). The dose of HDR-ICBT was not included.

Measurement of BMD

Bone mineral density was assessed by dual-energy x-ray absorptiometry using a detector device (HOLOGIC, Bedford, MA) that provided a bone density image and expressed the density as g/cm^2 with high sensitivity. The results obtained are expressed in *Z* scores. The *Z* score is defined to be the number of standard

deviations that a subject's BMD varied from the mean BMD of an age-, sex-, and race-matched population (14, 15). A low *Z* score means low BMD compared with the average BMD among the same race, sex, and age (14-16). To clarify the direct and the systemic influence of RT to bone on cervical cancer patients, we measured the BMD and *Z* score at several parts of the vertebral bodies, with L5 representing the irradiated region and thoracic vertebrae 9-12 (Th9-12) and L2-4 representing the nonirradiated regions.

Measurement of estrogen and bone metabolism markers in serum

Estradiol (E2) is the predominant estrogen during the reproductive years, both in terms of absolute serum levels as well as in terms of estrogenic activity. As such, in this study, the level of E2 was used for evaluating the menopausal status of the patients. Tartrate-resistant acid phosphatase (TRACP)-5b and serum N-terminal cross-linking telopeptide of collagen 1 (NTX) were measured as bone metabolism markers. Tartrate-resistant acid phosphatase-5b is a specific marker of osteoclasts that leaks into the blood when an osteoclast is absorbed by bone. Hence, TRACP-5b directly reflects the activity of osteoclasts (17). N-terminal cross-linking telopeptide of collagen 1 is a degradation product of type I collagen, which is a major constituent of bone matrix proteins. Thus, an increase in the level of NTX indicates the destruction of bone. These bone resorptive markers are helpful in the diagnosis of osteoporosis and bone diseases (18, 19). To avoid circadian variations, these bone markers and serum E2 were measured in the early morning.

Classification of menopausal status

All 46 patients were divided into 2 groups according to their E2 level before RT. In this study the premenopausal and postmenopausal groups comprised patients with E2 $\geq$40 pg/mL and $<$40 pg/mL, totaling 18 and 28 patients, respectively. Only1 patient was receiving hormone replacement therapy after RT.

Screening of IFs

All patients were also evaluated for the presence of IF. The diagnosis of IF was made when the patients had positive findings on computed tomography and MRI, without recurrent tumor lesions or traumatic histories. Computed tomography findings of IF were defined as fracture lines in the bones, and MRI findings of IF were defined as signal intensity changes in the bones on both T1- and T2-weighted images. All computed tomography and MRI images were evaluated by 2 investigators (N.O. and J.S.).

Statistical analyses

Linear regression analysis and Spearman's correlation analysis were used to analyze the relationships among variables. The cumulative occurrence rate of IF was calculated by the Kaplan-Meier method. The significance of differences was assessed by using the Wilcoxon signed-rank test and Welch's unpaired *t* test. Differences were considered statistically significant at $P<.05$. All statistical analyses were performed using SPSS 16.0 for Mac (SPSS, Chicago, IL).

Results

Changes in BMD of L5 (irradiated region)

The mean ($\pm$ standard error) actual delivered dose to L5 was 36.3 $\pm$ 10.2 Gy (range, 9.5-51.5 Gy). Four patients with IF of L5 were eliminated to avoid biases caused by stresses other than irradiation. Figure 1 shows the mean BMD and *Z* score of the premenopausal group (n = 15) and the postmenopausal group (n = 27). In both groups, the BMD of L5 decreased rapidly within 12 months after RT. The rates of decreased BMD at 12 months after RT were 7.5% and 9.6% in the premenopausal and postmenopausal groups, respectively. *Z* scores decreased from 0.13 to -0.54 and from 0.13 to -0.52 in the premenopausal and postmenopausal groups from before to 12 months after RT, respectively.

Because the Z score represents how far each subject's BMD differed from the mean BMD of an age-, sex-, and race-matched population, a decrease in the *Z* score in either group indicated that the decrease in BMD exceeded the influence of age-related BMD decline. The BMD of L5 in the premenopausal group was significantly decreased at both 3 months ($P = .016$) and 12 months after RT ($P = .009$). Similarly, the BMD in the postmenopausal group was significantly decreased 12 months after RT ($P = .037$).

Changes in BMD of L2-4 (nonirradiated and irradiated regions) and Th9-12 (nonirradiated regions)

To evaluate the influence of pelvic RT on nonirradiated regions, 10 patients who received RT to the para-aortic lymph node region (including L1-L4) were excluded when we analyzed the change in BMD in L2-4. Figure 2 shows the mean BMD and *Z* score in L2-4. There was no significant change in BMD over time in the postmenopausal group (n = 22). In contrast, in the premenopausal group (n = 14), the BMD was significantly decreased 12 months after RT ($P = .049$).

Similar patterns of BMD and *Z* score were found in Th9-12 (Fig. 3). There was no significant change in BMD in the postmenopausal group (n = 28). In contrast, in the premenopausal group (n = 18), BMD significantly decreased 12 months after RT ($P = .002$).

Among patients who received RT to the para-aortic lymph node region, the mean actual delivered dose to L2-4 was 46.2 $\pm$ 8.5 Gy (range, 36.1-54.2 Gy). Regarding the BMD in L2-4 of the 10 patients who received RT to the para-aortic lymph node region, the BMD of irradiated L2-4 was decreased at both 3 months ($P = .002$) and 12 months after RT ($P = .001$) (Supplementary Fig. e1, available online).

Effect of concurrent chemotherapy on BMD

The BMD of the concurrent chemotherapy group (n = 33) was higher than that of the radiation-alone group (n = 13) in the irradiated region as well as the nonirradiated regions. This could have been because the concurrent chemotherapy group contained younger patients. Thus, we analyzed the rates of decreased BMD at 12 months after RT in the concurrent chemotherapy group and radiation-alone group. There were no significant differences in

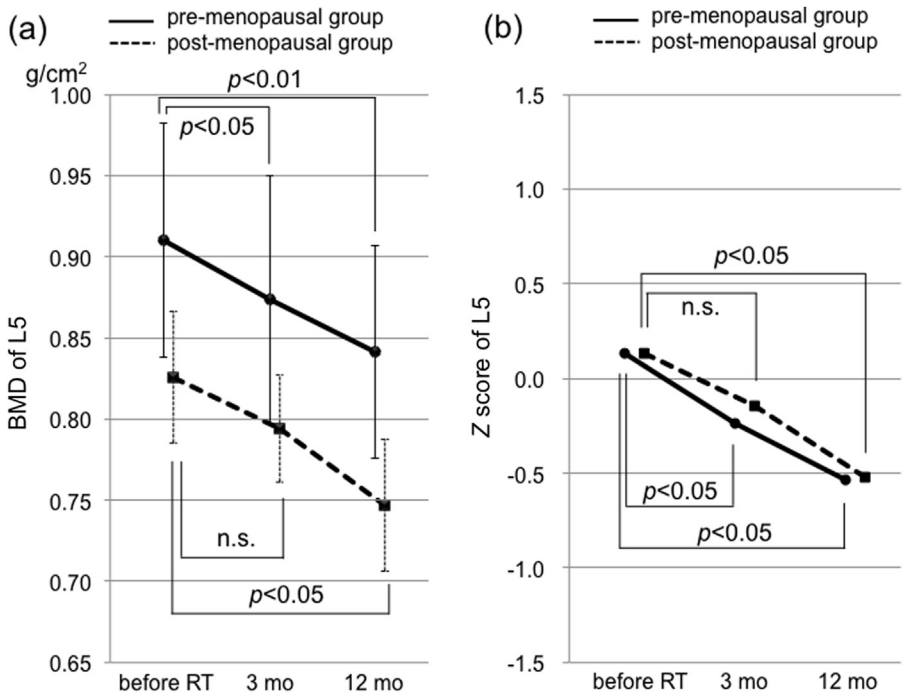

Fig. 1. Series of changes in (a) bone mineral density (BMD) and (b) *Z* score of L5 (irradiated region). The solid line shows the value of the premenopausal group (n = 15), and the dashed line shows the value of the postmenopausal group (n = 27). All values are presented as means ± standard error. n.s. = not significant; RT = radiation therapy.

rates of decreased BMD at 12 months after RT between the concurrent chemotherapy group and radiation-alone group in either the irradiated or nonirradiated regions.

Changes in E2, TRACP-5b, and NTX

All patients were included in this analysis. In the postmenopausal group (n = 28), the E2 level was not changed significantly at 3 months or 12 months after RT. In contrast, in the premenopausal group (n = 18), E2 was significantly decreased at both 3 months ($P = .013$) and 12 months after RT ($P = .009$) (Fig. 4a).

In the postmenopausal group (n = 28), TRACP-5b peaked 3 months after RT but fell off 12 months after RT. In contrast, in the premenopausal group (n = 18), TRACP-5b was significantly increased 3 months after RT ($P = .001$) and remained high 12 months after RT (Fig. 4b).

In the postmenopausal group (n = 28), the NTX level did not change significantly until 12 months after RT. Meanwhile, in the premenopausal group (n = 18), NTX continued to increase over time, and there was a statistically significant difference in the level of NTX between pre-RT and 12 months after RT ($P = .016$) (Fig. 4c).

Regression analysis showed that only E2 at 3 months after RT and TRACP-5b at 12 month after RT were significantly associated with the decrease of BMD in L2-4 (linear $r = 0.51$, $P = .048$ and $r = 0.49$, $P = .049$, respectively) and Th9-12 (linear $r = 0.67$, $P = .009$ and $r = 0.58$, $P = .023$, respectively).

Incidence of IFs

A total of 7 patients were diagnosed with IF after RT. Insufficiency fractures were observed at L5 in 4 patients (9, 10, 10, and 12 months after RT, respectively), at the sacroiliac joints in 2 patients (7 and 12 months after RT, respectively), and at L3 in 1 patient (8 months after RT). The patient with IF at L3 had received RT to the para-aortic lymph node region, including L3. All of the fracture sites were within the irradiated fields. The 2-year overall cumulative incidence of IF was 15.2% (Fig. 5). In the 4 patients who had IFs in L5, the BMD in L5 before treatment was significantly lower than in other patients ($P = .018$). However, there was no other relationship between the BMDs of other regions or between the serum markers and IF.

Discussion

Many studies regarding the adverse effects related to RT for cervical cancer, such as effects observed in the rectum, bladder, and small intestine, have been reported (20-22). Insufficiency fracture is another radiation-related adverse effect, and it occurs in the irradiated regions after RT (10, 11). However, the specific effects of pelvic RT on the decrease in BMD, including the extent of change in BMD, changes in the levels of serum estrogen and bone metabolism markers, and the influence of estrogen levels, are still unclear. Additionally, it is unclear whether RT has a systemic effect on IFs. Our study showed that in the premenopausal group, pelvic irradiation significantly decreased the BMD in the irradiated region after 3 months. In both the pre- and postmenopausal groups, the BMD was further decreased 12 months after RT. Strikingly, in the premenopausal group, pelvic irradiation also caused a decrease in BMD in the nonirradiated regions after 12 months. This systemic change in BMD outside the RT region indicates changes in bone metabolism.

Previous meta-analyses have shown that all estrogens, including E2, have a protective effect on BMD (23, 24). In contrast, ovarian

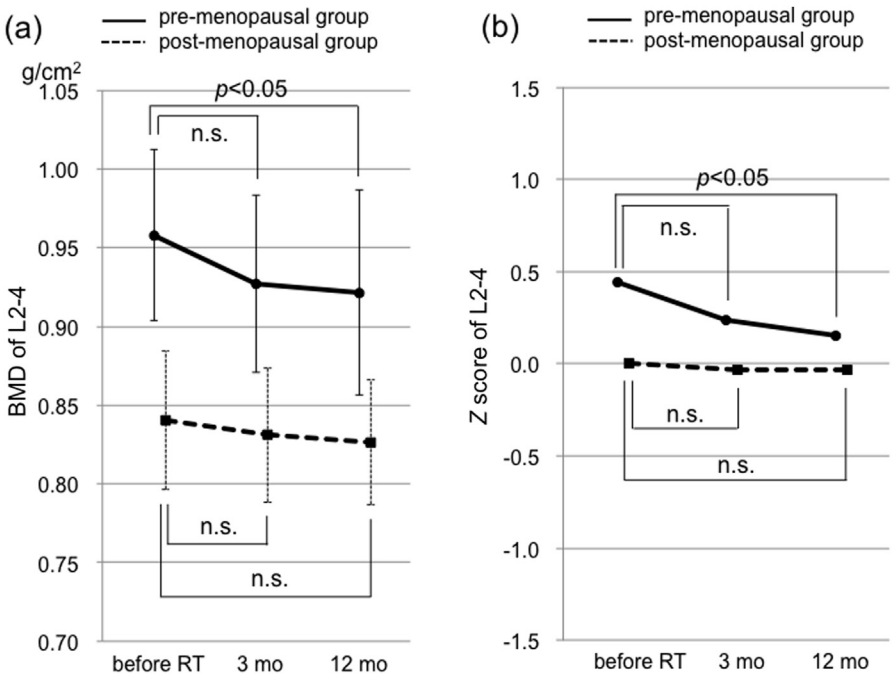

Fig. 2. Series of changes in (a) bone mineral density (BMD) and (b) *Z* score of L2-4 (nonirradiated region). The solid line shows the value of the premenopausal group (n = 14), and the dashed line shows the value of the postmenopausal group (n = 22). All values are presented as means ± standard error. n.s. = not significant; RT = radiation therapy.

dysfunction can result from pelvic irradiation that includes ovary exposure (25). Our study showed that 3 months after RT, E2 had decreased significantly. Additionally, the E2 level 3 months after RT was significantly associated with the decrease of BMD in L2-4 and Th9-12. Taken together, our findings suggest that pelvic irradiation may cause secondary decreases in systemic BMD in premenopausal patients within 12 months after RT, which may be mediated by a decrease in estrogens due to pelvic irradiation.

In the premenopausal group in this study, the bone metabolism markers in the serum were altered, reflecting a dramatic

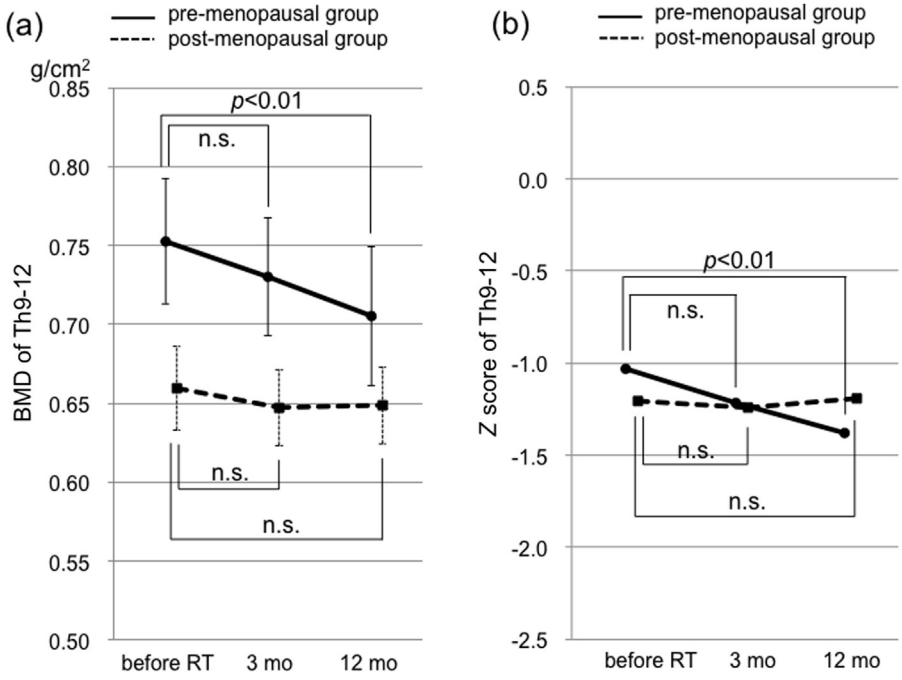

Fig. 3. Series of changes in (a) bone mineral density (BMD) and (b) *Z* score of Th9-12 (nonirradiated region). The solid line shows the value of the premenopausal group (n = 18), and the dashed line shows the value of the postmenopausal group (n = 28). All values are presented as means ± standard error. n.s. = not significant; RT = radiation therapy.

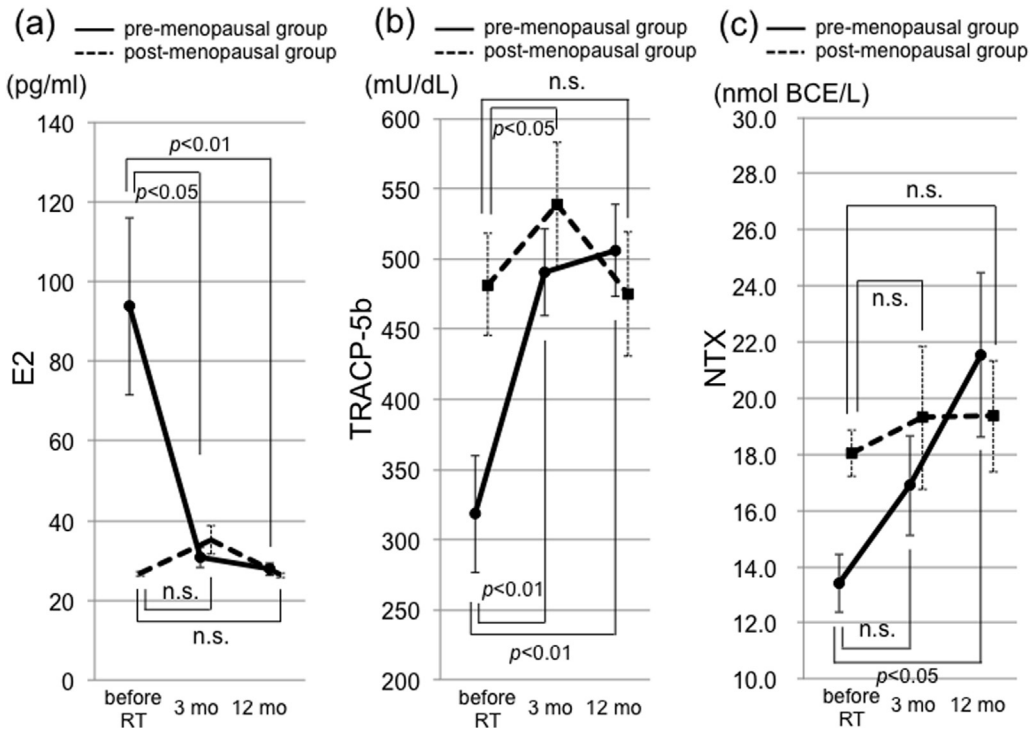

Fig. 4. Series of changes in (a) estradiol (E2), (b) tartrate-resistant acid phosphatase-5b (TRACP-5b), and (c) N-terminal cross-linking telopeptide of collagen 1 (NTX) levels. The solid line shows the value of the premenopausal group (n = 18), and the dashed line shows the value of the postmenopausal group (n = 28). All values are presented as means ± standard error. BCE = bone collagen equivalent; n.s. = not significant.

change in bone metabolism. In the premenopausal group, TRACP-5b was significantly increased 3 months after RT, and NTX continued to increase over time. N-terminal cross-linking telopeptide of collagen 1 is regarded as one of the most reliable biochemical markers of bone resorption (26). Tartrate-resistant acid phosphatase-5b is another reliable marker for monitoring bone resorption (17, 19) and can be measured with high sensitivity and specificity (27). In our study, there were positive correlations between the concentration of TRACP-5b at 12 months after RT and the decreases of BMD in Th9-12 and L2-4, although there was no correlation between NTX and BMD. Therefore, TRACP-5b may be useful as a predictor of radiation-induced osteoporosis.

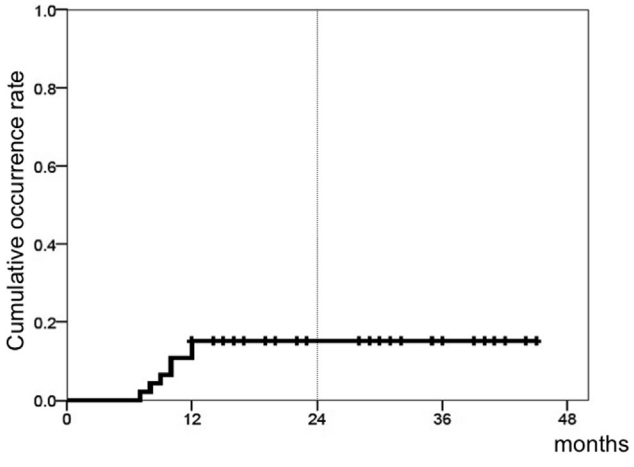

Fig. 5. Incidence of insufficiency fractures after pelvic radiation therapy for cervical cancer.

Hormone replacement therapy is an effective treatment option for postmenopausal patients with osteoporosis. A meta-analysis showed that all estrogens, irrespective of the mode of administration, are effective in maintaining BMD. Specifically, estrogen replacement therapy can be expected to prevent osteoporosis in women with menopausal symptoms (23). Thus, hormone replacement therapy should be considered in premenopausal patients who have received pelvic irradiation. Recently, selective estrogen receptor modulators have been developed and used to treat osteoporosis. Clinical trials have shown that selective estrogen receptor modulators prevent bone fracture and confer a lower risk for thrombosis and breast cancer (28-30). To date, few studies have validated the efficacy of these drugs in patients who have received pelvic irradiation. If pelvic irradiation causes a secondary decrease in systemic BMD that is mediated by the decrease in estrogens, these drugs may be effective, especially for premenopausal patients. Bisphosphonates are another treatment option for patients with osteoporosis. Bisphosphonates act by inhibiting bone resorption through their effects on osteoclast function (31). In patients with osteoporosis, bisphosphonates provide therapeutic benefits in preventing vertebral, nonvertebral, hip, and wrist fractures (32, 33). Further investigation is warranted to establish the efficacy of these drugs for treating radiation-induced osteoporosis.

In conclusion, decreased BMD in the irradiated region was found within 1 year after RT, regardless of the menopausal status of the patients. Furthermore, pelvic RT caused a decrease in systemic BMD within 1 year. This effect seems to be mediated by a decrease in estrogen levels due to the exposure of the ovary to

radiation. Further investigations with longer follow-up periods are required to determine the optimal treatment for the prevention of osteoporosis in female patients after pelvic RT.

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