



Effect of gynecological cancer and its treatment on bone mineral density and the risk of osteoporosis and osteoporotic fracture

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Objective

The purpose of this study was to evaluate the risk of osteopenia and osteoporosis by examining the bone mineral density (BMD) of the lumbar spine and femur in patients with gynecological cancer without bone metastasis and to evaluate the impact of treatment for different cancers on BMD.

Methods

This study retrospectively reviewed the medical records of 243 women with gynecological cancer and 240 controls between March 2010 and December 2016. Patients with cervical cancer (n=105), endometrial cancer (n=63), and ovarian cancer (n=75) were treated with total hysterectomy including bilateral salpingo-oophorectomy and/or chemotherapy and/or radiotherapy. For the control group, healthy post-menopausal women without gynecologic cancer were selected.

Results

Before anticancer treatment, the BMD of patients with cervical cancer and ovarian cancer was significantly lower than that of the controls, and the BMD of patients with endometrial cancer was not significantly different from that of the controls. However, the BMD of endometrial cancer significantly decreased after treatment. According to the treatment methods, there were significant differences in the BMD of L3, L4, and the femur neck. Changes in the BMD were lowest in patients who underwent surgical treatment only, and the highest bone loss was found in patients who underwent postoperative concurrent chemoradiotherapy.

Conclusion

Patients with cervical and ovarian cancer had lower BMD than those in the control group before treatment, and patients with endometrial cancer had decreased bone density after treatment. Therefore, during the treatment of gynecological cancer, strategies should be implemented to mitigate these risks.

Keywords: Bone density; Treatment-associated cancer; Osteoporosis

Introduction

Osteoporosis is the most common metabolic bone disease caused by reduced bone mineral density (BMD) and is associated with high risk of bone fractures. Fractures due to osteoporosis are closely related to the mortality rate of the elderly population, and there is an increased prevalence of osteoporosis due to increased life expectancy. Therefore, social and medical interest in the risk factors, diagnosis, and treatment methods of osteoporosis is increasing. Several systemic conditions and diseases may affect bone mineral density, includ-

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ing insufficient calcium intake, excessive sodium intake, lack of exercise, chronic kidney disease, parathyroid disease, hyperthyroidism, and gastrointestinal absorption disorder [1].

The mean BMD of women is lower than that of men, and bone mass accumulates between 20 and 30 years of age. The loss of bone density is most rapid after the age of 50, particularly 5 years after menopause in women [2,3]. A decrease in estrogen in postmenopausal women affects bone and lipid metabolism [4]. Estrogen plays an important role in the osteoclast-osteoblast balance related to maintenance of the BMD. It is known that BMD decreases when estrogen concentration decreases [5].

Previous studies have reported low BMD and high serum calcium levels in various types of cancer including prostate and breast cancer without bone metastasis [6-11]. The decrease in the BMD associated with cancer may be linked to the osteoclastic effect of the malignant cell itself as well as the cancer treatment-induced bone loss (CTIBL) caused by surgery, chemotherapy, and radiation therapy [12-14]. Gonadal dysfunction due to cancer treatment reduces hormone secretion, leading to decreased BMD.

The purpose of this study was to evaluate the risk of osteopenia and osteoporosis in patients with gynecological cancer according to the type of cancer and to analyze the BMD of the lumbar spine and femoral neck after various cancer treatments including surgery, chemotherapy, and radiation therapy.

Materials and methods

Between March 2010 and December 2016, a retrospective study was conducted by analyzing the medical records of women who were treated at Haeundae Paik Hospital Obstetrics and Gynecology. All subjects underwent physical examination, blood tests, ultrasonography, and bone mineral density measurements.

1. Study participants

A total 243 patients with gynecological cancer were selected for this study. Patients with cervical cancer (n=105), endometrial cancer (n=63), and ovarian cancer (n=75) were treated with total hysterectomy including bilateral salpingo-oophorectomy and/or chemotherapy and/or radiotherapy. Six patients with bone metastasis or those who did not undergo

surgery due to an advanced stage of cancer were excluded. For the control group, 240 healthy post-menopausal women who did not have menstruation for 1 year were selected. The BMD was measured before and 1 year after cancer treatment. In the control group, the BMD was measured again 1 year after the initial test.

Patients with thyroid disease, parathyroid disease, kidney stones, hyperprolactinemia, malabsorptive disorder, or previous pathologic fractures that may affect bone metabolism were excluded from the study. Patients who were prescribed medication that may affect the study outcomes, such as hormones, bisphosphonates, calcitonin, vitamin D, or calcium, were also excluded.

2. Methods

1) Bone mineral density measurement

The BMD of the 1st-4th lumbar spine and femoral neck was determined by measurement with dual-energy X-ray absorptiometry (DXA, Lunar Radiation Corp., Madison, WI, USA). According to the criteria of the World Health Organization, the diagnosis of osteopenia was made with a T-score in the range of -1.0 and -2.5 and that of osteoporosis with a T-score of -2.5 or below [15,16].

2) Cancer treatment

Gynecological cancer patients were treated with total hysterectomy including bilateral salpingo-oophorectomy and/or chemotherapy and/or radiotherapy. Eighty-five patients received only surgical treatment, and 92 patients were treated with surgery and an adjuvant or palliative chemotherapy. Eight patients received surgery and radiotherapy, and 58 patients received surgical treatment with concurrent chemoradiation therapy (CCRT). Forty-four cervical cancer patients underwent only total hysterectomy with bilateral salpingo-oophorectomy, and 48 patients underwent postoperative CCRT. Thirty-eight endometrial cancer patients (60.3%) underwent surgical treatment only. Most ovarian cancer patients (90.7%) were treated with chemotherapy after surgery (Table 1).

3) Research variable factors

Age, height, weight, body mass index (BMI), and obstetric history were included as common demographic characteristics. In gynecological cancer patients, the cancer stage ac-

According to the International Federation of Gynecology and Obstetrics (FIGO) classification, histological classification, and cancer treatment methods were included as research variables. Among them, the variables that showed a significant difference were set as covariates.

4) Statistical analysis

Statistical analysis was performed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) ver. 23.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set as $P < 0.05$. The independent t -test was used to compare continuous variables such as age, weight, and height, and the χ^2 test was used to compare the discrete variables such as obstetric history and prevalence of osteopenia and osteoporosis. According to cancer type, continuous variables were compared using analysis of variance. A multiple linear regression analysis was used to analyze the factors affecting BMD.

Results

1. Demographic characteristics

Table 1 shows demographic characteristics, cancer stage according to the FIGO classification, and cancer treatment methods of gynecological cancer patients. The mean age, height, weight, BMI, and obstetric history of patients with cervical cancer, endometrial cancer, and ovarian cancer were not significantly different between the groups. The body weight of the endometrial cancer group was greater than that of the other groups, and the BMI was slightly higher; however, there was no significant difference between the groups.

According to the FIGO classification, 25 (23.8%), 38 (36.2%), and 26 (24.8%) patients had cervical cancer at stages Ia, Ib, and IIb, respectively. Forty-five (71.4%) patients in the endometrial cancer group had stage Ia, and 24 (32.0%) and 19 (25.3%) patients in the ovarian cancer group had

Table 1. Demographic characteristics, cancer stage and treatment methods of patients with gynecologic cancer

| Characteristics | Cervical cancer (n=105) | Endometrial cancer (n=63) | Ovarian cancer (n=75) | P-value |
|----------------------------|----------------------------|------------------------------|--------------------------|---------|
| Age (yr) | 57.2±11.6 | 56.2±9.7 | 57.2±11.6 | 0.739 |
| Height (cm) | 156.1±5.3 | 157.2±5.7 | 156.4±6.2 | 0.488 |
| Weight (kg) | 56.9±8.1 | 59.2±11.3 | 57.7±8.3 | 0.065 |
| BMI (kg/m ²) | 23.4±3.3 | 24.2±4.2 | 23.7±3.6 | 0.066 |
| Parity | 2.1±1.1 | 1.9±1.1 | 1.9±1.2 | 0.332 |
| Cancer stage ^{a)} | | | | |
| Ia | 25 (23.8) | 45 (71.4) | 9 (12.0) | |
| Ib | 38 (36.2) | 5 (7.9) | 6 (8.0) | |
| Ic | - | | 9 (12.0) | |
| IIa | 10 (9.5) | 2 (3.2) | 4 (5.3) | |
| IIb | 26 (24.8) | 0 (0.0) | 4 (5.3) | |
| III | 3 (2.9) | 8 (12.7) | 24 (32.0) | |
| IV | 3 (2.9) | 3 (4.8) | 19 (25.3) | |
| Treatment methods | | | | |
| Surgery | 44 (41.9) | 38 (60.3) | 3 (4.0) | |
| Surgery + chemotherapy | 10 (9.5) | 14 (22.2) | 68 (90.7) | |
| Surgery + CCRT | 48 (45.7) | 6 (9.5) | 4 (5.3) | |
| Surgery + RT | 3 (2.9) | 5 (7.9) | 0 (0) | |

Continuous variables were compared by analysis of variance test and categorical variables by χ^2 tests. Values are presented as mean±standard deviation or number (%).

BMI, body mass index; CCRT, concurrent chemoradiation therapy; RT, radiation therapy; FIGO, International Federation of Gynecology and Obstetrics.

^{a)}The cancer stage follows the FIGO classification.

stages III and IV advanced stage, respectively.

2. Bone mineral density before and after cancer treatment according to cancer type

The BMD before and after cancer treatment in patients with cervical cancer, endometrial cancer, and ovarian cancer was compared with those of the control group (Table 2). There was no significant difference between the cancer type; however, the T-scores of ovarian cancer patients were lower than those of cervical cancer and endometrial cancer patients.

Before beginning cancer treatment, the BMD of cervical cancer patients was significantly lower in the 1st and 2nd lumbar spine and femoral neck than in the control group. Ovarian cancer patients showed significantly lower BMD

from L1 to L4, at each level. The average T-score with standard deviation of the lumbar spine was -0.9 ± 1.4 , and the T-scores from the 1st to 4th lumbar spine were -1.2 ± 1.4 , -1.1 ± 1.5 , -0.9 ± 1.5 , and -0.7 ± 1.5 , respectively, which was significantly lower than those of the control group. However, the T-scores of endometrial cancer patients were not significantly different from those of the control group.

Among 243 women with gynecological cancer, 96 (39.5%) were in the normal range, 114 (46.9%) were diagnosed with osteopenia, and 33 (13.6%) were diagnosed with osteoporosis according to the criteria of the World Health Organization. In 240 control subjects, 118 (49.2%), or approximately half were in the normal range, 100 (41.7%) were diagnosed with osteopenia and 22 (9.2%) were diagnosed with os-

Table 2. The T-scores of the lumbar spine and femur neck according to the type of cancer compared with the controls and the prevalence of osteopenia and osteoporosis before and after cancer treatment

| Variables | Cervical cancer (n=105) | P-value | Endometrial cancer (n=63) | P-value | Ovarian cancer (n=75) | P-value | Control (n=240) |
|-----------------------------|-------------------------|---------|---------------------------|---------|-----------------------|---------|-----------------|
| At baseline | | | | | | | |
| Lumbar spine BMD | -0.6 ± 1.5 | 0.056 | -0.5 ± 1.6 | 0.328 | -0.9 ± 1.4 | 0.001 | -0.3 ± 1.5 |
| L1 | -0.9 ± 1.4 | 0.013 | -0.8 ± 1.6 | 0.158 | -1.2 ± 1.4 | 0.000 | -0.6 ± 1.3 |
| L2 | -0.8 ± 1.5 | 0.029 | -0.7 ± 1.7 | 0.184 | -1.1 ± 1.5 | 0.001 | -0.6 ± 1.5 |
| L3 | -0.6 ± 1.7 | 0.179 | -0.5 ± 1.7 | 0.355 | -0.9 ± 1.5 | 0.007 | -0.4 ± 1.6 |
| L4 | -0.3 ± 1.6 | 0.209 | -0.1 ± 1.8 | 0.957 | -0.7 ± 1.5 | 0.004 | -0.2 ± 1.6 |
| Femur neck BMD | -0.9 ± 1.0 | 0.029 | -0.7 ± 1.2 | 0.643 | -0.9 ± 1.2 | 0.091 | -0.6 ± 1.1 |
| Prevalence | | | | | | | 0.079 |
| Normal (%) ^a | 44 (41.9) | | 24 (38.1) | | 28 (37.3) | | 118 (49.2) |
| Osteopenia (%) ^b | 47 (44.8) | | 32 (50.8) | | 35 (46.7) | | 100 (41.7) |
| Osteoporosis (%) | 14 (13.3) | | 7 (11.1) | | 12 (16.0) | | 22 (9.2) |
| After 1 years | | | | | | | |
| Lumbar spine BMD | -0.7 ± 1.4 | 0.047 | -0.9 ± 1.4 | 0.019 | -1.0 ± 1.4 | 0.013 | -0.3 ± 1.5 |
| L1 | -1.0 ± 1.4 | 0.028 | -1.3 ± 1.3 | 0.004 | -1.2 ± 1.4 | 0.010 | -0.6 ± 1.4 |
| L2 | -0.9 ± 1.5 | 0.046 | -1.1 ± 1.5 | 0.029 | -1.0 ± 1.5 | 0.046 | -0.5 ± 1.6 |
| L3 | -0.7 ± 1.7 | 0.110 | -1.0 ± 1.4 | 0.019 | -0.9 ± 1.5 | 0.044 | -0.3 ± 1.6 |
| L4 | -0.3 ± 1.6 | 0.189 | -0.3 ± 1.6 | 0.264 | -0.7 ± 1.5 | 0.016 | -0.0 ± 1.6 |
| Femur neck BMD | -1.0 ± 1.0 | 0.002 | -0.9 ± 1.2 | 0.129 | -1.0 ± 1.3 | 0.071 | -0.6 ± 1.1 |
| Prevalence | | | | | | | 0.167 |
| Normal (%) ^a | 37 (35.2) | | 19 (30.2) | | 23 (30.7) | | 90 (37.5) |
| Osteopenia (%) ^b | 51 (48.6) | | 35 (55.6) | | 37 (49.3) | | 122 (50.8) |
| Osteoporosis (%) | 17 (16.2) | | 9 (14.3) | | 15 (20.0) | | 28 (11.7) |

The T-scores are presented as mean±standard deviation, P-value by independent t-test.

BMD, bone mineral density; WHO, World Health Organization.

^aValues are presented as number (%), P-value by χ^2 test; ^bDiagnosed by T-scores of lumbar spine or femur neck according to WHO criteria.

teoporosis. There was no significant difference between the groups ($P=0.079$); however, the rates of osteopenia and osteoporosis were 5.2% and 4.4% higher in cancer patients than in the control group, respectively.

After 1 year of cancer treatment, the average T-score of the lumbar spine, the T-score of the 1st to 2nd lumbar spine, and femoral neck in cervical cancer patients was significantly lower than those in the control group. In the ovarian cancer group, the average T-scores of L1-L4 and the 1st to 4th level of the lumbar spine were significantly lower than those of the control group. In patients with endometrial cancer, the T-score of the 1st to 3rd level of the lumbar spine and the average T-score of L1-L4 was significantly lower than those of the control group.

Changes in the BMD before and after cancer treatment according to the type of gynecological cancer are shown in Fig. 1. In endometrial cancer patients, the BMD was significantly lower than that in cervical cancer and ovarian cancer

patients, and there was a significant difference in the lumbar spine ($P=0.024$).

3. Changes in bone mineral density according to treatment method

In 243 patients with gynecological cancer, changes in the BMD before and after cancer treatment were compared in relation to the different treatment methods (Table 3). The T-scores of the 3rd and 4th lumbar spine and the femoral neck were significantly different according to the treatment methods. The smallest change in the BMD was observed in 85 patients who had undergone only surgical treatment, including bilateral salpingo-oophorectomy. Conversely, the T-scores of the 58 patients who received surgical treatment with CCRT significantly decreased after treatment.

4. Factors associated with bone loss

The factors affecting the BMD in gynecological cancer pa-

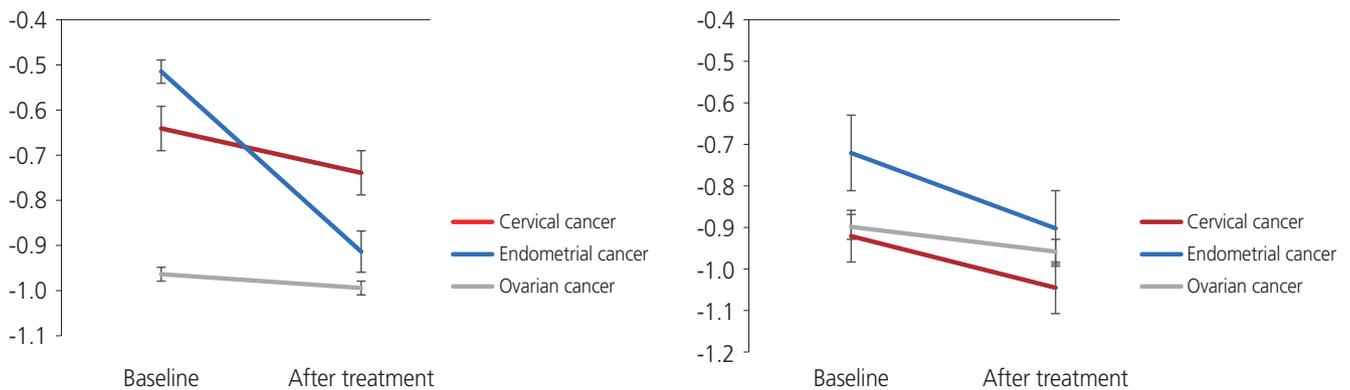


Fig. 1. The T-scores of the lumbar spine and femur neck in patients with gynecologic cancer before and after treatment. BMD, bone mineral density.

Table 3. The changes of bone mineral density in patients with gynecologic cancer according to treatment methods

| Variables | Surgery only (n=85) | Surgery + chemotherapy (n=92) | Surgery + RT (n=8) | Surgery + CCRT (n=58) | P-value |
|---|---------------------|-------------------------------|--------------------|-----------------------|---------|
| Lumbar spine BMD (g/cm ²) ^{a)} | 0.02±0.47 | -0.18±0.63 | -0.09±0.56 | -0.30±0.47 | 0.051 |
| L1 | -0.01±0.71 | -0.12±0.95 | -0.67±0.51 | -0.36±0.58 | 0.052 |
| L2 | 0.01±0.56 | -0.16±0.80 | -0.21±0.53 | -0.28±0.51 | 0.228 |
| L3 | -0.02±0.54 | -0.18±0.76 | 0.20±0.72 | -0.34±0.57 | 0.043 |
| L4 | 0.07±0.71 | -0.17±0.74 | 0.37±1.33 | -0.23±0.62 | 0.022 |
| Femur neck BMD (g/cm ²) | -0.04±0.24 | -0.03±0.26 | -0.19±0.26 | -0.27±0.30 | 0.026 |

Values are presented as mean±standard deviation, P-value by analysis of variance.

BMD, bone mineral density; CCRT, concurrent chemoradiation therapy; RT, radiation therapy

^{a)}Mean change of T-scores.

tients were analyzed by multiple linear regression analysis (Table 4). Age and BMI were found to affect the BMD in the lumbar spine and femur neck, and there was no significant relationship between height, weight, and obstetric history and the BMD. There was a negative correlation between age and the BMD, whereas there was a positive correlation between BMI and the BMD. According to the type of cancer, endometrial cancer showed a negative correlation with the BMD, but it was not a significant variable in other types of cancer. There was no significant difference when analyzing the influence of treatment methods and the stages of cancer.

Discussion

The life expectancy of gynecological cancer patients has improved due to the advances in medical technology for diagnosing and treating gynecological cancer. Quality of life is also important for patients with longer life expectancy, and osteoporosis can have a significant impact on quality of

life. Previous studies have reported a decrease in bone density and hypercalcemia in patients with other malignancies without bone metastasis [6-11]. Studies have shown that malignant tumor cells secrete serum growth factors that promote bone resorption and bone destruction. Prostaglandins [17,18], tumor growth factor [19], osteoclast activator [11], and parathyroid hormone analogue [20,21] are known to be involved in osteoclast activation [15].

The purpose of this study was to evaluate the risk of osteopenia and osteoporosis in patients diagnosed with gynecological cancer and to investigate the differences according to the type of cancer. Furthermore, we tried to identify the changes after cancer treatment. When the BMD before cancer treatment was compared according to the type of cancer, the BMD of cervical cancer patients was significantly lower in the 1st and 2nd lumbar spine and the femoral neck than that in the control group. Previous studies have reported a lower BMD of the lumbar spine in cervical cancer patients before cancer treatment [22-24]. Hung et al. [24] reported that premenopausal patients with cervical cancer had signifi-

Table 4. The factors associated with bone loss by a multiple linear regression analysis

| Variables | Lumbar spine T-score | | | | Femur neck T-score | | | |
|--------------------------|----------------------|--------------------|--------|---------|--------------------|--------------------|--------|---------|
| | β | Standardized error | t | P-value | β | Standardized error | t | P-value |
| Age (yr) | -0.050 | 0.003 | 2.055 | 0.041 | -0.042 | 0.002 | -1.904 | 0.058 |
| Height (cm) | -0.006 | 0.031 | 0.194 | 0.846 | 0.036 | 0.027 | 1.347 | 0.179 |
| Weight (kg) | 0.013 | 0.041 | -0.309 | 0.758 | -0.054 | 0.036 | -1.504 | 0.133 |
| BMI (kg/m ²) | 0.135 | 0.104 | 0.338 | 0.046 | 0.129 | 0.090 | 1.432 | 0.153 |
| Parity | -0.160 | 0.085 | -1.883 | 0.060 | -0.058 | 0.073 | -0.787 | 0.432 |
| Cancer type | | | | | | | | |
| Cervical cancer | 0.088 | 0.062 | 1.406 | 0.160 | 0.024 | 0.054 | 0.436 | 0.663 |
| Endometrial cancer | -0.311 | 0.078 | -3.989 | 0.000 | -0.104 | 0.067 | -1.568 | 0.118 |
| Ovarian cancer | -0.010 | 0.074 | -0.139 | 0.889 | -0.118 | 0.064 | -1.837 | 0.067 |
| Treatment methods | | | | | | | | |
| Surgery | -0.134 | 0.067 | -1.992 | 0.470 | -0.076 | 0.057 | -1.328 | 0.185 |
| Surgery + Chemotherapy | 0.237 | 0.100 | 2.375 | 0.180 | 0.148 | 0.087 | 1.694 | 0.091 |
| Surgery + CCRT | -0.056 | 0.118 | -0.476 | 0.063 | -0.070 | 0.103 | -0.679 | 0.059 |
| Surgery + RT | 0.204 | 0.189 | 1.077 | 0.282 | 0.067 | 0.165 | 0.408 | 0.684 |
| Cancer stage | | | | | | | | |
| Stage I | -0.069 | 0.051 | -1.341 | 0.181 | -0.072 | 0.049 | -1.480 | 0.140 |
| Stage II, III, IV | -0.152 | 0.087 | -1.742 | 0.082 | -0.041 | 0.056 | -0.732 | 0.465 |

β and standardized error are unstandardized coefficients.

BMI, body mass index; CCRT, concurrent chemoradiation therapy; RT, radiation therapy.

cantly lower BMD in L2-L4 spines than in the controls. Lee et al. [22] suggested that postmenopausal patients with cervical cancer had a lower BMD and higher risk of osteoporosis in the lumbar spine before cancer treatment than patients with endometrial cancer. Therefore, this study supports the results of previous reports.

In the present study, ovarian cancer patients had a lower BMD in the 1st to 4th lumbar spine and a lower average T score of L1-L4 than those of the control group before treatment. More than half (57.3%) of the ovarian cancer patients were in advanced stages of the disease, with stages III and IV according to the FIGO classification. The long period of exposure to estrogen deprivation due to ovarian failure presumably influenced the low BMD before treatment. However, when analyzing the stage of cancer as a variable through multiple linear regression analysis, no significant relationship was found.

The study analyzed bone loss after one year of cancer treatment. The BMD of cervical cancer patients was lower in the L1, L2 spines, for average T-scores of L1-L4, and in the femoral neck than those in the control group. Ovarian cancer patients showed a significantly lower BMD from L1 to L4, and the average T score of L1-L4, than the controls. However, as bone density was already lower in cervical and ovarian cancer patients than in controls before cancer treatment, it cannot be concluded that treatment had an effect on the reduction of BMD. Alternatively, the BMD of endometrial cancer patients was not significantly different when compared with the control group before treatment. The BMD of the 1st to 3rd lumbar spine, the average T-score of the lumbar spine, and the femoral neck were decreased after 1 year of treatment compared with that in the control group. Further, in multiple linear regression analysis, only endometrial cancer showed a negative correlation to bone loss when the type of cancer was set to variable, and other gynecological cancers showed no significant correlation.

In a previous study, endometrial cancer patients who had undergone bilateral oophorectomy, followed by chemotherapy or radiation therapy, showed significantly lower BMD than other gynecological cancer groups [25]. In estrogen-dependent endometrial cancer, high levels of estrogen protect bone mass from osteoclasts and stimulate osteoblasts to maintain bone density [26,27]. Similarly, in the present study, the BMD of endometrial cancer patients before treatment was higher than those of cervical cancer and ovarian cancer patients.

However, after cancer treatment, hypogonadism may cause a rapid decrease in estrogen levels, leading to abrupt changes in BMD in endometrial cancer patients. Previous studies have reported that cancer treatment-induced bone loss is associated with hypogonadism [12,13]. Conversely, persistent exposure to high levels of estrogen increases the accumulation of bone mass and lowers the risk of fractures. Previous studies verified low risk of endometrial cancer in patients with osteoporosis or osteoporotic fractures [28-30].

Several anticancer drugs used in chemotherapy have direct toxic effects on osteoblasts or can indirectly affect bone metabolism by inducing hypogonadism. In addition, immunosuppressive agents such as steroids and cyclosporine, used in combination with anticancer drugs, may increase the risk of osteoporosis [13,31]. When comparing the changes in the BMD according to the methods of cancer treatment, there was a significant difference in the BMD before and after treatment in the 3rd and 4th lumbar spine and the femoral neck (Table 3). The change in the BMD was lower in patients who underwent only surgical treatment including bilateral salpingo-oophorectomy, and the greatest decrease in the BMD was observed in patients who had undergone surgical treatment with CCRT. However, in the multiple linear regression analysis, no significant influence was found according to the treatment methods.

Previous studies have identified a decrease in bone density and an increase in bone turnover markers in cervical cancer patients treated with chemoradiotherapy [22,32-34]. In addition, cervical cancer has been found to reduce the BMD after radiotherapy and increase the incidence of osteoporotic fractures [35,36]. Radiation therapy leads directly to bone atrophy and indirectly to vascular changes of the bone, leading to destruction [13]. Radiotherapy of the pelvis is known as a risk factor for sacral fractures, and it has been reported that fractures of the femoral neck occur in approximately 2% of cervical cancer patients who underwent radiotherapy [14,35,36].

Hwang et al. [32] reported that the 4th lumbar spine and femoral bone density decreased in patients with cervical cancer after chemoradiotherapy. The 4th lumbar spine is an area affected by irradiation of the pelvis; thus, this area may experience a reduction in the BMD after irradiation. In the present study, patients who underwent chemotherapy with concurrent chemoradiation after surgical treatment had significant changes in their BMD, which is in line with the

results of previous studies. However, as a limitation of the study, the number of patients who underwent radiotherapy after surgery was small; therefore, this study cohort may not be truly representative of the population.

This study was a retrospective comparative analysis, with data extracted from patients' medical records. Through multiple linear regression analysis, the average age and BMI were found to affect the BMD in gynecological cancer patients. However, it was difficult to control all the factors that could affect the patients' bone metabolism, such as smoking, alcohol intake, nutrition, and physical exercise [1]. The study has limitations owing to the retrospective observational nature. Many types of covariates are expected to affect the dependent variable. Attempts to control these covariates would result in a reduced and insufficient number of subjects to represent the specific populations. Retrospective observational studies require a large population for reporting rare outcomes. In addition to the difficulty in controlling various factors, there are limitations related to various biases such as selection bias and information bias. Furthermore, we compared the changes in BMD before and after cancer treatment for 1 year in the study. However, the scale for detecting changes in the BMD was too small; therefore, the interpretation of the data was limited.

Nevertheless, this study has a large number of gynecological cancer patients and various analyses based on the type of cancer, cancer staging, and treatment methods. We tried to investigate the changes in the BMD before and after treatment and identify the risk of osteoporosis among gynecological cancer patients. In conclusion, the BMD of cervical and ovarian cancer patients before cancer treatment was significantly lower than that in the control group, and the BMD after cancer treatment was remarkably decreased in endometrial cancer patients.

The early diagnosis and treatment of cancer have improved the treatment rate and survival rate of gynecological cancer patients; however, osteoporotic fractures not only reduce the quality of life of long-lived patients but also increase their mortality. This study suggests that the risk of bone density loss and osteoporosis in gynecological cancer should be recognized, prevented, and diagnosed early to reduce the incidence of osteoporotic fractures. Proper calcium and vitamin intake, outdoor activity recommendations, and regular BMD measurements may improve the quality of life of gynecological cancer patients. In addition, larger scale prospective

studies should be carried out to investigate the factors that affect the long-term, as well as the short-term side effects of cancer treatment in gynecological cancer patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The study was approved by the Institutional Review Board of Haeundae Paik Hospital, Inje University (IRB No. 2018-04-019) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consents were obtained.

Patient consent

The patients signed written informed consent for the publication and the use of their images.

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