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Longitudinal assessment of bone loss from diagnostic CT scans in gynecologic cancer patients treated with chemotherapy and radiation

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Abstract

Objective(s)—To measure volumetric bone mineral density (vBMD) using diagnostic CT scans in gynecologic oncology patients.

Study Design—In a retrospective study, spine and femoral neck (FN) vBMD was measured for one year in 40 patients receiving chemotherapy or radiation.

Results—There is significant bone loss after chemotherapy, radiation and combination of radiation and chemotherapy ($p=0.0211$). In one year, the percent reduction in vBMD ($\pm$ SE) at L1/L2 spine and the FN was a 15.9 % (± 5.67) and 10.4 % (± 4.06) in chemotherapy; was 11% (± 5.68) and 15.8 % (± 2.56) in radiation; and was 21.0 % (± 7.03) and 3.6 % ($\pm 3.3.7$) in combined therapy group. Bone loss was evident immediately after treatment and persisted or worsened in most women.

Conclusion—Gynecologic cancer patients treated with chemotherapy or radiation experience immediate and prolonged bone loss; thus, pre- and post-treatment monitoring of bone loss is important in these patients.

Keywords

Bone loss; chemotherapy; radiation; quantitative computed tomography

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Introduction

There is increasing interest in the impact of cancer therapy on bone loss and fracture risk. Epidemiological studies show a high incidence of hip fracture in cervical and anal cancer [1, 2]. Fracture is a long-term effect of radiation or chemotherapy. Reduction in bone mineral density (BMD) correlates to an increased risk of fracture [3,4]. Thus bone density is measured in an attempt to establish the risk of fracture and to provide a potential basis for treating osteoporosis.

Although fracture studies support the necessity of monitoring bone health, there is very limited information on the relationship between treatment and changes in bone mineral density in the gynecologic oncology patient population. Many of these patients receive combined treatment modalities (surgery, including oophorectomy, radiation and chemotherapy). It may be challenging to identify the risk of bone loss from individual components of any woman's treatment. Douchi et al [5] reported decrease in spine BMD by 12.6 % after chemotherapy in pre-menopausal ovarian cancer patients. Pre and post-menopausal women with ovarian, endometrial, and cervical cancer, treated with chemotherapy or radiation therapy may be at high risk for bone loss. To date the effects of individual and combined modalities on bone loss have not been well studied in these women.

Cancer patients undergo routine CT or PET/CT of the chest, abdomen, and pelvis as part of staging, assessment of treatment response and surveillance. We have exploited CT scans used to evaluate gynecologic oncology patients to monitor longitudinal changes in bone mineral density by quantitative computed tomography (QCT). Advantages of QCT over Dual energy X-ray absorptiometry (DXA) is that it provides true volumetric density (size independent) separately in trabecular and cortical bone and is free of the inaccuracies caused in spinal DXA by extra-osseous calcification and hyperostosis [6]. QCT has not been studied in gynecologic oncology patients. CT scans used for diagnosis and surveillance may be a useful to define the effects of cancer therapy on bone health.

Our objective is to investigate the longitudinal impact of chemotherapy and radiation on the vBMD in ovarian, endometrial and cervical cancer patients and to compare differences in each modality's impact on regional vBMD.

Materials and Methods

We retrospectively identified 40 gynecologic-oncology patients who had pre- and post-treatment CT scans in our database from 2005 to 2009. This study is approved by the University of Minnesota Institutional Review Board (IRB). Subjects with baseline CT scan performed prior to treatment and additional post treatment scans performed at the University of Minnesota Medical Center, were included for this study. This was approximately one year following up from start of the treatment. The time of first CT scans and second CT scans were not controlled. They were measured within 2-3 months. Details are summarized in Table 1.

Ovarian cancer patients who had an initial CT scan at the time of diagnosis, but before any surgery or chemotherapy and at least two additional scans after their initial course of platinum and taxane based chemotherapy were included in the study. The primary regimen for 11 of the women was carboplatin (AUC=6) with paclitaxel, 175 mg/m² IV over 3 hours, given every 21 days for at least 6 cycles. Because of toxicity, one patient received her last 4 treatments with single agent Carboplatin; and another received her final 6 cycles (of 8 total) with carboplatin and docetaxel. One patient received 6 cycles of carboplatin and paclitaxel in the neo-adjuvant setting and then received 3 cycles of IV cisplatin (75 mg/m²) and IP cisplatin and paclitaxel. One ovarian cancer patient was taking alendronate prior to her diagnosis and throughout the

series of CT scans. Five women experienced a recurrence of their disease and may have been on salvage chemotherapy at the time of the 12 month CT scan (or last follow-up) in this study.

The majority of endometrial cancer patients received external beam pelvic radiation therapy (EBRT) with a median dose of 45-50 cGy (in 25-28 fractions) and 5-18 Gy additional radiation dose at the vaginal surface using high dose rate (HDR) brachytherapy. Cervical cancer patients received radiation sensitizing chemotherapy with 40 mg/m² of cisplatin given once weekly during their external beam radiation. They received extended field EBRT with a median dose of 45-50 cGy (in 25-28 fractions) and 1-2 implants low dose rate (LDR) brachytherapy (20-40 Gy). The EBRT field and radiation doses were individualized according to tumor size, lymph node involvement, and the patient performance status. Figure 1 is a schematic representation of the EBRT field in anterior-posterior direction used for endometrial and cervical cancer treatment. In general, for endometrial cancer patients (without lymph node metastasis, stage I and II) the upper border extended up to lumbosacral joint (S1-L5) as shown in green boundary. For most cervical cancer patients, the superior border was extended up superiorly to L5 to L3. The inferior border was at the bottom of the obturator foramen. The lateral borders were approximately 1.5–2 cm lateral to the inner bony margins of the true pelvis. For the lateral fields, the anterior border included the anterior one third of the symphysis pubis, and the posterior border.

CT scans for this study were acquired using a standard, clinical CT protocol without a CT calibration standard to facilitate QCT analysis. Instead images were calibrated by scanning a CT calibration phantom and QA phantom (Mindways Software, Inc., Austin, TX), and the CT calibration equations derived from the phantom study were assumed to apply to all patient studies. The CT scanner was maintained in accordance with the CT manufacture's specifications over the time period of this study. No anomalies in CT scanner performance were found in the CT records. Images from picture archiving and communication systems (PACS) were transferred to a computer for QCT analysis. Images were analyzed using the QCT PRO software (version 4.2, Mindways Software, Inc., Austin, TX). Calibration equations were derived from the analysis of the QA phantom and CT phantom imaged simultaneously. The CT calibration equations were used in turn to estimate vBMD when analyzing patient data. We analyzed vBMD (mg/cm³) from trabecular regions (L1-L5) of spine and from the femoral neck (FN) region [Figure 2]. L1 and L2 trabecular vBMD was averaged to measure L1L2 vBMD; L3 and L4 trabecular vBMD was averaged to measure L3L4 vBMD; L5 vBMD was from L5 trabecular bone only; FN vBMD was calculated from integrated vBMD of trabecular and cortical bone at the femoral neck region of hip.

Statistical Methods

Patients were categorized into three treatment groups: chemotherapy (ovarian cancer patients), EBRT + HDR (endometrial cancer patients), and combination of radiation (EBRT+LDR) and chemotherapy (cervical cancer patients). We compared vBMD from CT scans performed at baseline (prior to any surgery, chemotherapy or radiation) and at two time points after completion of treatment. For each subject the BMD level at L1/L2, L3/L4, L5, and the FN was measured on each scan. The percent change in vBMD was computed. Descriptive statistics including mean, standard deviation and range of the absolute vBMD and percent reduction in vBMD were calculated. For each scan region, a patient's percent reduction in vBMD on each of two post-treatment scans was evaluated using paired t test or Wilcoxon's signed-rank test. In addition, general linear models for longitudinal data were used to evaluate the effects of age, treatment, scan time, scan region, and their interaction terms on percentage reduction of BMD. The variance-covariance structure was the first-order autoregression, and variance parameters were estimated using restricted maximum likelihood method with Satterthwaite approximation. The final model was determined by a backward selection and the least squares

means for percentage reduction of vBMD were calculated. The p-values reported for multiple comparisons were unadjusted. SAS V9.1 (The SAS Institute Inc., USA) was used. A p-value of less than 0.05 indicated statistical significance.

Results

Table 1 summarizes the demographic characteristics of our study population. The mean interval from the baseline CT scan to the first and second follow up scan was 7.5 months (± 3.6) and 12.5 months (± 3.9). Table 2 shows the descriptive statistics of absolute vBMD by treatment, months since completion of therapy and anatomic region. Figure 3 shows percent change in vBMD (gm/cm^3) at the femoral neck (FN) and L1/L2 after chemotherapy, radiation (pelvic EBRT+HDR), and combination of chemotherapy radiation (EBRT +LDR treatment). Overall, a subject's vBMD significantly decreased from baseline to the first and second post treatment scan at each anatomic region (L1-L2, L3-L4, L5 and FN, $p < 0.05$).

Treatment modality ($p=0.0059$), anatomic region ($p<0.0001$) and the interaction of treatment and anatomic region ($p<<0.0001$) were each associated with vBMD and were included in the final model to identify predictors of bone loss.

There were significant differences in mean percent reduction of vBMD between the three treatment groups ($p=0.0059$): The combined treatment group (radiation and chemotherapy) had the highest reduction (23.9%) while chemotherapy (15.2%) and HDR (11.0%) group had much lower reductions. There are significant differences in mean vBMD loss in the different anatomic regions ($p<0.0001$): L5 (26.2%) had the greatest bone loss followed by L3/L4 (17.0%), L1/L2 (12.4%) and the femoral neck (11.3%). As shown in Figure 4, the reduction in vBMD among the 3 treatment groups varied by anatomic region. At region L1/L2 and L3/L4, the combined treatment had a greater impact on bone loss than chemotherapy, and chemotherapy had a greater impact than radiation therapy. Similarly at L5 combined treatment had the greatest impact on bone loss, but radiation therapy had a greater impact than chemotherapy. At the femoral neck, radiation therapy had the greatest impact, followed by combination therapy and chemotherapy.

Comment

This pilot study emphasizes the importance of monitoring treatment related bone loss in gynecologic oncology patients. Chemotherapy, radiation and the combination of both modalities induces rapid bone loss in gynecologic oncology patients.

In pre-menopausal ovarian cancer patients, Douchi et al [5] reported bone loss after chemotherapy. Major bone loss was thought to be due to cessation of ovarian function and hence studies were focused mainly in pre-menopausal women [7,8]. Douchi's work may suggest that the chemotherapy has a direct and substantial effect on bone loss, though there could be a synergistic enhancement effect of oophorectomy and chemotherapy. Postmenopausal patients are most suitable since they are good candidates to verify the direct effect of chemotherapy on bone loss without (or minimum) interference from ovarian function, and more importantly the majority of ovarian cancer reported are postmenopausal with an average age of 60 in our cohort. Our study (Figure 3) indicates that the postmenopausal ovarian cancer patients are at high risk for bone loss and major loss was observed within the first 8 months after treatment. Bone loss was apparent in both spine and hip regions, suggesting that the effect of chemotherapy is systematic.

There is very limited information on the relationship between radiation and changes in bone mineral density [9]. Radiation was shown to cause rapid bone loss within 6 months (Figure 3). This observation is significant because it suggests that bone loss due to radiation is fast process,

similar to chemotherapy. Bone loss was evident at the irradiated femoral neck region, suggesting the radiation effect is regional. The implication of this finding is that the FN vBMD measurement, instead of standard spine vBMD, should be followed in these women.

Our study indicates that the total reduction in bone loss is much greater in patients undergoing chemotherapy compared to patients undergoing radiation therapy. Whether the total vBMD loss in whole body would have a greater adverse effect by weakening skeletal strength in general compared to vBMD loss in local areas is unknown. Fracture risk is greatest in the hip and spine. In order to investigate specific regional effects of therapy on bone loss, we performed multiple comparisons of treatment modality and anatomic region as shown in Figure 4. There is a strong correlation between treatment modality and regional bone loss (Figure 4). Integrated FN vBMD loss is significant without significant differences between treatment groups. The relative effect of chemotherapy and radiation was evident in spine trabecular bone regions. The patterns of percent vBMD reduction are roughly similar between endometrial (radiation), ovarian (chemotherapy), and cervical (radiation and chemotherapy) patients. Integrated vBMD (trabecular and cortical) at FN may be one reason for lower change in FN vBMD compared to spine trabecular vBMD. Trabecular bone is metabolically active and sensitive to metabolic disease such as osteoporosis [10]. Trends in spine bone loss in cervical cancer patients show a cumulative effect of radiation and chemotherapy. Increased vBMD loss in L5 (and L3/L4) is due to the fact that a majority of these patients have extended radiation fields to cover the para aortic field as shown in Figure 1.

There are certain limitations to this retrospective study: (1) time of first CT scans and second CT scans were not controlled. Therefore, cross-sectional comparison should be done with caution. (2) Radiation dose and extension of the field varied. Similarly there are variation in chemotherapy dose and the duration of treatment. Absolute quantification and correlation with bone loss needs to be established in subjects with controlled treatment conditions. (3) This retrospective analysis is performed without QCT phantom. So the precision accuracy is mainly based on morning quality assurance (QA). Multi-detector CT scans are shown to be stable for years, (4) There is no age matched healthy control. In this study, the goal was to measure pre and post treatment BMD for the same patient population. (5) Sample size was limited. Healthy control may help to identify the relative risk of bone loss in different treatment groups and healthy subjects. In future, a prospective longitudinal study is necessary to investigate the rapid bone loss and its impact on long-term bone loss and whether difference in bone loss caused by anticancer therapy persist for longer time period. Long-term studies follow up of bone health will also be helpful to understand whether there is a natural recovery process from skeletal damage for different treatment modalities, a signature that is perhaps present in the radiation treatment group. Such a study would likely need to be done as a multi-institution clinical trial. This is feasible since the inexpensive QCT Software can be installed on computers and applied to images outside of the Radiology Department. The QCT software does not require installation on the same computers that are used for primary CT imaging. Our companion paper showed that the presence of the QCT phantom during the CT scan will not increase dose to patients [11]. Oncologists, radiologists, specialists in osteoporosis care, research associates and technicians can be trained to use the software.

We have shown that chemotherapy and radiation therapy for gynecologic cancers result in substantial declines in BMD. Our findings suggest that measuring vBMD in this setting may improve patient outcomes. Further, these findings illustrate the need for future studies that validate qualitative CT assessment of vBMD in cancer patients. Large population studies are necessary to identify important risk factors within this population and to design intervention trials to prevent bone loss. As the number of gynecologic cancer survivors and women cancer survivors increases the need to monitor these effects will also increase. Traditional DXA scans are not a part of the routine management of cancer patients and the addition of DXA scans

would not only add to the cost of patient management it does not offer the flexibility to measure those areas which may have the greatest mineral loss such as the pelvis and cannot provide precise localization of cortical or medullary calcium loss. Having the ability to measure bone density of as part of the routine management of patients with no added cost, time or radiation dose will allow for the prospective evaluation of bone mineral changes. We believe that this ability will not only allow for the detection of abnormal bone loss, it will lead to better management of this loss and thus reduce the complications and associated morbidity in these cancer survivors.

Key messages

Application of diagnostic CT scans to study the effect of anti-cancer therapy on bone loss in patients with gynecologic cancer

Acknowledgments

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REFERENCES

1. Baxter N, Habermann E, Tepper J, Durham S, Virnig B. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA* 2005;294(20):2587. [PubMed: 16304072]
2. Schmeler K, Jhingran A, Iyer R, Sun C, Eifel P, Soliman P, Ramirez P, Frumovitz M, Bodurka D, Sood A. Pelvic fractures following radiation therapy for cervical cancer: Implications for survivors. *Gynecologic Oncology* 2008;111(2):382–382.
3. Cummings S, Black D, Nevitt M, Browner W, Cauley J, Ensrud K, Genant H, Palermo L, Scott J, Vogt T. Bone density at various sites for prediction of hip fractures. *Lancet(British edition)* 1993;341(8837):72–75.
4. Ross P, Genant H, Davis J, Miller P, Wasnich R. Predicting vertebral fracture incidence from prevalent fractures and bone density among non-black, osteoporotic women. *Osteoporosis International* 1993;3(3):120–126. [PubMed: 8481587]
5. Douchi T, Kosha S, Kan R, Nakamura S, Oki T, Nagata Y. Predictors of bone mineral loss in patients with ovarian cancer treated with anticancer agents. *OBSTETRICS AND GYNECOLOGY-NEW YORK-* 1997;90:12–15.
6. Adams J, Alsop C, Harrison E, Lernbass I, Davies M, Cann C, Selby P. Quantitative Computed Tomography (QCT): The Forgotten Gold Standard? *Journal of Bone and Mineral Research* 2000;15:1122–1122.
7. Vehmanen, L.; Antola, M.; Teppo, A.; Hilmola, OP.; Szekely, B.; Skrifvars, M.; Lukkarinen, J.; Hirsjärvi, S.; Gross, A.; Fordell, T. Effects of chemotherapy-induced ovarian failure on bone and lipid metabolism in premenopausal breast cancer patients: Impact of adjuvant clodronate and tamoxifen.
8. Walshe JM, Denduluri N, Swain SM. Amenorrhea in Premenopausal Women After Adjuvant Chemotherapy for Breast Cancer. *Journal of Clinical Oncology* 2006;24(36):5769. [PubMed: 17130515]
9. Hopewell JW. Radiation-therapy effects on bone density. *Medical and Pediatric Oncology* 2003;41(3):208–211. [PubMed: 12868120]
10. Genant HK, Cann CE, Ettinger B, Gordan GS. Quantitative Computed Tomography of Vertebral Spongiosa: A Sensitive Method for Detecting Early Bone Loss After Oophorectomy. *Clinical Orthopaedics and Related Research* 2000;372:3. [PubMed: 10738409]

11. Hui Susanta K, Weir Victor J, Brown Keenan, Froelich Jerry. Assessing the clinical utility of quantitative computed tomography (QCT) with a routinely used diagnostic CT scanner in a cancer center. *Journal of Clinical Densitometry*. 2010 In press.

Figure 1. shows schematic representation of radiation fields for pelvic irradiation up to S1-L5 junction (inside green boundary) and extended irradiation field up to L2-L3 junction (inside green and brown boundary).

Figure 2.
Shows locations of QCT measurements. Left - shows trabecular region of L spine where BMD was measured; Right - shows femoral neck selection for BMD measurement

Figure 3. shows % change in vBMD (gm/cm^3) at the femoral neck (FN) and L1L2 after chemotherapy, pelvic radiation, and chemotherapy + pelvic and extended filed radiation treatment. [Extended field is shown in Figure 1]

Figure 4. show the patterns of least squares mean % change in vBMD under different treatment and region combinations ($\pm$ SE)

Table 1

summarizes demographic characteristics of our patient population.

Variables	Treatment modalities (cancer type)		
	Chemotherapy (Ovarian)	EBRT + HDR (Endometrial)	Extended field EBRT +LDR with concomitant chemotherapy (Cervical)
Total number	12	10	18
Age ($\pm$ SD)	60.8 $\pm$ 11.7	55.9 $\pm$ 8.6	47.3 $\pm$ 10.8
Average weight ($\pm$ SD) in Lbs	173.10 $\pm$ 32.66	204.3 $\pm$ 77.8	167.95 $\pm$ 48.20
Average BMI ($\pm$ SD)	29.81 $\pm$ 4.46	30.0 $\pm$ 3.4	29.25 $\pm$ 7.23
1 st CT scan follow up ($\pm$ SD) after baseline CT scan in months	7.2 $\pm$ 2.3	7.4 $\pm$ 4.7	7.7 $\pm$ 3.7
2 nd CT follow up ($\pm$ SD) after baseline CT scan In months	11.8 $\pm$ 2.7	12.5 $\pm$ 5.4	13.6 $\pm$ 5.0

Table 2
shows the descriptive statistics of absolute BMD level by treatment, scan time and regions

Cancer Type/ Treatment	CT Scan	Region	N	Mean	SD
Ovarian Cancer (chemotherapy)	Baseline	L1L2	12	119.4	40.7
		L3L4	12	114.7	42.4
		L5	12	118.6	47.9
		FN	12	240.9	64.1
	First follow up	L1L2	12	104.1	38.7
		L3L4	12	96.2	42.9
		L5	12	98.4	47.8
		FN	12	218.3	67.5
	Second follow up	L1L2	12	99.5	36.4
		L3L4	12	95.2	36.4
		L5	12	96.2	44.0
		FN	12	216.6	70.2
Endometrial cancer (EBRT + HDR)	Baseline	L1L2	10	127.4	34.1
		L3L4	10	128.6	37.4
		L5	10	152.1	56.5
		FN	9	232.0	47.8
	First follow up	L1L2	10	121.6	29.5
		L3L4	10	129.1	45.8
		L5	10	127.6	47.4
		FN	10	205.5	42.9
	Second follow up	L1L2	4	121.7	11.1
		L3L4	4	112.5	17.5
		L5	4	107.0	35.1
		FN	5	192.3	43.4
Cervical cancer (Extended field EBRT +LDR with concomitant chemotherapy)	Baseline	L1L2	18	137.8	37.5
		L3L4	18	141.6	51.4
		L5	18	145.5	44.7

Cancer Type/ Treatment	CT Scan	Region	N	Mean	SD
		FN	18	241.0	51.2
		L1L2	18	117.1	30.9
		L3L4	18	101.0	43.4
		L5	18	87.4	45.5
		FN	18	219.1	62.1
	First follow up	L1L2	8	97.4	19.4
		L3L4	8	85.5	31.7
		L5	8	81.8	40.4
		FN	8	221.2	54.8