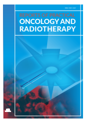

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RESEARCH PAPER

A prospective study of changes in bone health in adult cancer patients treated with pelvic radiotherapy

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ABSTRACT

Background: Cancer is a major health problem in today's world. Many patients of pelvic malignancies need treatment by radiation therapy. Post-treatment morbidity due to loss of bone health is less commonly studied. Our study aims at studying the impact of pelvic radiation therapy on bone health including bone mineral density and blood parameters and time of maximum change in Indian patients after pelvic radiotherapy.

Materials and methods: Patients suffering from histologically confirmed pelvic malignancies were included. Patients having metastasis, primary bone tumor or uncontrolled co-morbid conditions were excluded. Patients were treated with concomitant chemoradiation using conventional fractionation of external beam radiotherapy followed by brachytherapy where indicated. T score and Z score of bone mineral density, serum alkaline phosphatase, vitamin D3, phosphorus and calcium were measured before radiation therapy and 6 weeks, three months, and six months after completion of radiation therapy. A p-value ≤ 0.05 was considered statistically significant.

Results: We found that there was a significant decrease in mean Z score and a significant rise of mean serum alkaline phosphatase at three months post radiation therapy. This was associated with an insignificant changes of mean T score, vitamin D3, phosphorus and calcium after radiation therapy. No pelvic insufficiency fractures were detected.

Conclusion: In Indian patients, alkaline phosphatase rises, and Z score falls significantly after radiation therapy at three months after treatment. This suggests maximum bone turnover at three months after treatment. Pharmacological intervention, when necessary, may be considered by careful monitoring of patients by this time.

Key words: cancer; pelvis; chemoradiation

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Introduction

In today's world cancer is a major health problem. According to statistics by the World Health Organization in 2018, it is the second most common cause of death due to non-communicable diseases. Yearly, nine million deaths all over the world are attributable to cancer. Multimodality regimes of cancer treatment have improved cancer survivorship largely over the last four decades [1]. However, up to 30-50% of survivors have self-perceived unmet needs for supportive care [2]. With the advances of cancer management, many patients now survive a longer duration and experience long term skeletal side effects like osteomalacia, avascular necrosis and fractures. Early detection of treatment induced bone loss may help in reduction of these adverse events.

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Only a few studies, as discussed later, address the impact of pelvic radiation therapy on bone health including bone mineral density in patients suffering from pelvic malignancy. Risk factors and time of maximum change in bone mineral density and blood parameters which may lead to pelvic fractures after pelvic radiation therapy are less well understood. Our study aims at studying the impact of pelvic radiation therapy on bone health including bone mineral density in Indian adult cancer patients suffering from pelvic malignancy. This study attempted to determine the time of maximum change in bone mineral density and blood parameters after pelvic radiotherapy. The purpose of this study is to improve the understanding of changes in bone turnover kinetics related to pelvic radiotherapy and to determine the optimum time of necessary interventions.

Materials and methods

Our study is a prospective observational institutional study done at the Department of Radiotherapy at Institute of Postgraduate Medical Education and Research, Kolkata. Ethical approval was obtained from Institutional Ethics Committee. Patients suffering from histologically confirmed pelvic malignancies and registered between January 2020 and June 2020 were included in the study. Patients more than 18 years of age with a good Eastern Cooperative Oncology Group (ECOG) performance status (ECOG 0–2) without any history of prior radiation therapy, cytotoxic chemotherapy or surgery and having normal complete blood counts, liver function test, blood sugar, and electrolytes were included in our study. Patients having metastasis, primary bone tumor or associated uncontrolled co-morbid conditions were excluded. Patients suffering from osteoporosis or osteopenia or those on vitamin D supplements or bisphosphonates were also excluded. Patients were treated with concomitant chemoradiation using a conventional fractionation of external beam radiotherapy followed by brachytherapy in cases of carcinoma cervix.

Disease and patient characteristics including menopausal status of female patients, radiation dose received for both teletherapy and brachytherapy were recorded. T score (standard deviation from mean bone mass of 30-year-old healthy adult) and Z score (comparison of average bone density of people of same age and gender) of bone mineral density, serum alkaline phosphatase, vitamin D3, phosphorus and calcium were measured before radiation therapy and six weeks, three months, and six months after completion of radiation therapy. Bone scintigraphy, computerized tomography and/or magnetic resonance imaging (MRI) was used to exclude insufficiency fractures. The imaging studies were done at baseline and at three and six months after radiation therapy for all cases.

We used IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. for statistical analysis. One-way repeated measures ANOVA was used as the paired parametric test to analyze variance between the multiple data sets. Greenhouse-Geisser correction was done to exclude violation of sphericity. Partial eta squared values were considered to assess the effect size. Independent samples t-test was carried out to estimate effects of gender on test results. One-way ANOVA was used to assess if there was any effect of site of malignancy on test results p-value ≤ 0.05 was considered statistically significant.

Results and Analysis

Patients

Thirty patients were registered in our study. Mean age of patients was 52.7 years. Most (46.7%) of patients were of 51 to 60 years of age. Sixty percent of the patients were female. Seventeen of the eighteen female patients were menopausal. Majority of patients (56.7%) had a very good performance status (ECOG performance status one) (Tab. 1). Almost all of them had a normal body mass index (≥ 18.5 to < 23 kg/m^2).

Sites of malignancy

Colorectum (33.3%), cervix (30%) and urinary bladder (16.7%) were the most common primary sites of cancer. Other sites were vulva, endometrium, and anal canal (Tab. 1).

Treatment

All our patients were treated using conventional fractionation of radiation therapy using a telecobalt machine. Computerized planning by the four-field box technique was done with usage of shielding blocks to ensure target volume con-

Table 1. Patient and treatment characteristics

Patient groups	Number	Percentage
Age		
31–40 years	4	13.3%
41–50 years	6	20%
51–60 years	14	46.7%
61–70 years	6	20%
Sex		
Female	18	60.0%
Male	12	40.0%
Menopausal status of female patients		
Premenopausal	1	5.6%
Postmenopausal	17	94.4%
Body mass index		
Low (< 18.5 kg/m^2)	2	6.7%
Normal (≥ 18.5 to < 23 kg/m^2)	28	93.3%
High (≥ 23 kg/m^2)	0	0
Performance status		
ECOG 0	12	40.0%
ECOG 1	17	56.7%
ECOG 2	1	3.3%
Primary site of cancer		
Anal canal	1	3.3%
Urinary bladder	5	16.7%
Uterine cervix	9	30.0%
Colorectal	10	33.3%
Endometrium	2	6.7%
Vulva	3	10%
Radiation dose prescribed (teletherapy)		
50 Gy	15	50.0%
50.4 Gy	9	30.0%
54 Gy	1	3.3%
60 Gy	5	16.7%
Brachytherapy boost dose prescribed in cervical and endometrial cancer patients		
7 Gy per fraction, a total of three fractions	11	36.7%

ECOG — Eastern Cooperative Oncology Group

formity. Most of them received a dose of 50 Gy in conventional fractionation. All of them received concomitant chemotherapy with either weekly dose of cisplatin injection or daily oral capecitabine according to their primary site of the disease. Three fractions of intracavitary brachytherapy with a dose of 7 Gy per fraction for each of three fractions were performed for cervical and endometrial cancer patients as per institutional protocol.

This study revealed changes in scores of bone mineral density and serum biochemical changes after pelvic radiation therapy.

Bone mineral density

We found that there was a significant decrease in mean Z score at three months post radiation therapy ($p = 0.002$ after Greenhouse-Geisser correction) (Fig. 1). Effect size as determined by the partial eta squared value was 0.031. This was associated with insignificant changes of T score ($p = 0.853$) (Tab. 2).

Blood tests

There was a significant rise of mean serum alkaline phosphatase at three months post radiation therapy ($p < 0.001$) (Fig. 1). The effect size was large, partial eta squared value being 0.81. On the other hand, mean vitamin D3, phosphorus and calcium decreased six months after radiation therapy, although this was insignificant (Tab. 2). Only significant difference between two genders was revealed on serum alkaline phosphatase estimation, measured at six months ($p = 0.044$) where females recorded lower values [mean 134.06; standard deviation (SD) 12.12] than males (mean 143.17; SD 10.79). No impact of the primary site of disease occurrence on test results was observed ($p > 0.05$).

Insufficiency fractures

No case of insufficiency fracture was recorded in our study after bone scintigraphy, computerized tomography, or MRI.

Discussion

The structural integrity and metabolic role of the skeleton is related dynamically to physiological processes of the human body. Many extrinsic factors like weight carried, diet and exercise, exposure to sunlight and intrinsic factors like hormonal status and genetics play pivotal roles in skeletal homeostasis.

Pelvic insufficiency fractures are common complications of pelvic radiation therapy. Early diagnosis and treatment of these may improve quality of life after treatment for carcinoma cervix and decrease cost of medical treatment [3].

These fractures occur due to physiological stress on demineralized bone. The most common affect-

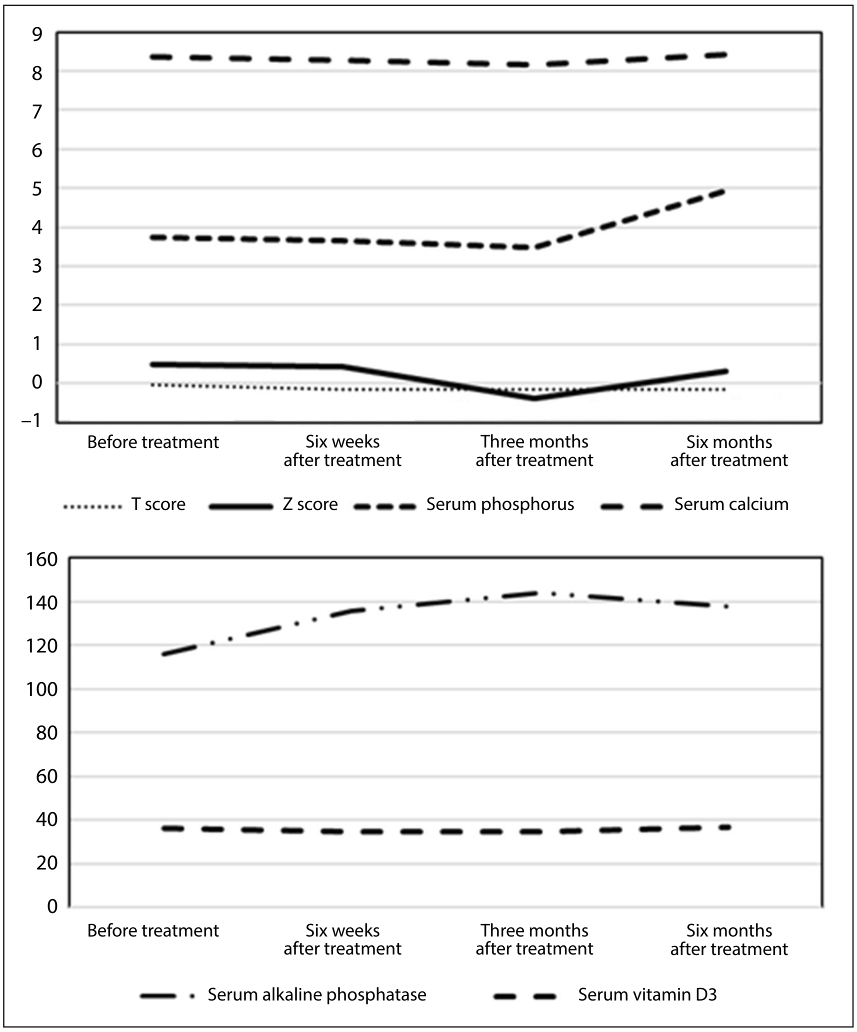

Figure 1. Line diagram to show the trend of changes in biochemical particulars, T score and Z score with time after radiotherapy (X-axis showing time and Y-axis showing respective units of measurements)

ed site is the lateral part of the sacrum. These fractures are differentiated from bone metastasis by the absence of soft tissue lesions and their typical locations like the sacrum [4].

Oh et al. [5] found that patients with age more than 55 years and body weight less than 55 kg were at high risk for developing pelvic insufficiency fractures. Postmenopausal women were also susceptible [6]. A study by Uezono et al. [7] associated lower CT density of bone and bone marrow in computerized tomographic scans with the development of these fractures.

Role of diet on skeletal homeostasis is immense, both in animals and humans. Patients suffering from cancer are often advised to have a high protein diet. Increased intestinal absorption of calcium due to a high protein diet causes increased renal excretion [8] but does not cause loss of bone mineral density. However, increased saturated fat consumption may lead to loss of bone mineral density (4.3% in men less than 50 years in femoral neck) [9]. Diet high in refined sugar causes increased calciuria [10] due to lowered calcium reabsorption in distal convoluted tubules of the kidney [11]. Animals are also susceptible to skeletal degradation after consuming a diet rich in refined carbohydrates. A study by Tjaderhane and Larmas [12] revealed that Wistar rats fed on a high sucrose diet are susceptible to skeletal degradation in both sexes but more in females. Study by Tsanzi at al. [13] showed that 13% glucose solution had profound negative effects on bone mass in rats when compared to fructose sweetened beverages. Study by Li et al. [14] showed that cancellous

Table 2. Changes in bone mineral density and blood parameters after pelvic radiation therapy

		Before treatment	6 weeks after treatment	3 months after treatment	6 months after treatment	p value	Effect size (partial eta squared value)
T score	Mean	–0.0467	–0.1533	–0.1667	–0.1433	0.853	–
	SD	1.568	1.499	1.474	1.455		
	Median	0.100	0.000	0.050	–0.100		
Z score	Mean	0.497	0.437	–0.377	0.320	0.002	Small (0.03)
	SD	1.444	1.467	1.493	1.408		
	Median	1.000	1.350	1.150	1.200		
Serum alkaline phosphatase [IU/L]	Mean	116	135.9	144.16	137.7	$p < 0.001$	Large (0.81)
	SD	17.156	13.805	13.953	12.284		
	Median	115.500	135.500	144.500	138.000		
Mean serum Vitamin D3 [ng/mL]	Mean	36.06	34.67	34.78	36.72	0.064	–
	SD	4.09	3.31	3.66	2.75		
	Median	37.00	34.500	35.000	36.500		
Mean serum phosphorus [mg/dL]	Mean	3.75	3.65	3.48	4.92	0.428	–
	SD	0.37	0.373	0.328	6.821		
	Median	3.800	3.60	3.50	3.75		
Mean serum calcium [mg/dl]	Mean	8.38	8.27	8.17	8.42	0.059	–
	SD	0.59	0.49	0.47	0.47		
	Median	8.20	8.10	8.10	8.40		

bones, like vertebrae, lose bone quality and tensile strength in animals fed on both high saturated fat and sucrose. A study by Ogur et al. [15] on young Sprague-Dawley rats revealed that cola consumption causes increased loss of calcium and iron as well as loss of lean body mass but increased fat deposition probably due to decreased consumption of milk and other fluid. Human study by Milne and Nielson [16] found that glucose rather than fructose has more deleterious effects on bone and mineral balance. Consumption of large amounts of sodium promotes calciuria since sodium and calcium compete for reabsorption in renal tubules. For every 2300 mg sodium excretion there is approximately 4250 mg loss of calcium [17].

Radiation therapy is identified as one of the risk factors for loss of bone mineral density in many studies. A study by Wu et al. [18] in cases of cervical cancer concluded that there is significant loss of bone mineral density in all lumbar vertebrae both in an out of field, following radiation therapy for cervical cancer. Hence, they suggested hormonal replacement therapy to improve bone mineral density recovery even in premenopausal women.

Study by Salcedo et al. [19] shows that significant loss of bone mineral density occurred after pelvic radiation therapy in a high proportion of women, with pelvic fracture diagnosed in 7.8% of cases. There was a significant risk of fracture in older women, in those having baseline osteoporosis or higher baseline alkaline phosphatase. Pharmacologic intervention was advisable in these women.

Okonogi et al. [20] found that systemic bone mineral density decreases in pre-menopausal women after pelvic radiation therapy. The study also revealed that loss of bone mineral density in the irradiated region occurred within 1 year irrespective of menopausal status. There was risk of insufficiency fractures even after adjuvant irradiation of stomach cancer [21].

Pelvic insufficiency fractures had been demonstrated after pelvic radiotherapy in some trials. Study by Tokumara et al. [22] demonstrated that pelvic insufficiency fractures may be as high as 36.9% in cervical cancer after radiation therapy. 89% of these fractures developed within one year of pelvic radiotherapy [23]. Park et al. [3] found that there is an increased risk of pelvic insufficiency fracture if the DEXA BMD T score was less than 3.5. Oh et al. [24] found that treatment of cervical and endometrial cancer results in increased bone loss in postmenopausal women.

Kronborg et al. [25] in their recent study found that treatment with volumetric arc therapy in rectal cancer resulted in increased incidence of pelvic insufficiency fracture after three years. Although a statistically significant causal relationship of dose threshold could not be established in their study, a high dose of V30 Gy to the sacroiliac joint was suggested for occurrence of these fractures.

Yamamoto et al. [26] found that radiation therapy in cervical cancer patients caused insufficiency fractures in radiated fields in 15.8% cases. Most of them (80%) developed fractures within 3 years after radiation completion. Median time was 14 months and the most fractured site was the sacral bone. Post-menopausal state and high dose rate intracavitary brachytherapy were significant predisposing factors according to multivariate analysis. A study by Kwon et al. [27] found that radiation therapy caused pelvic insufficiency fractures in femoral head, fifth lumbar vertebra and roof of acetabulum in addition to sacral alae.

This study attempted to elucidate the impact of pelvic radiation therapy on general bone health in Indian adult cancer patients suffering from pelvic malignancy. We also tried to find out the time of maximum change in bone mineral density and blood parameters after pelvic radiotherapy. We observed that in our group of Indian patients suffering from pelvic malignancy, alkaline phosphatase rose and Z score decreased significantly after radiation therapy at three months after treatment. This suggests maximum bone turnover at three months after treatment. Nonpharmacological (adequate intake of vitamin D and calcium, exercise and cessation of smoking and alcohol and caffeine consumption) and pharmacological interventions (antiresorptive medicine) may be considered by careful monitoring of patients at this time.

In contrast to some other studies, no case of insufficiency fracture was recorded in our study. Whether factors like diet, working habits or exposure to sunlight can be possible reasons behind this finding, needs to be corroborated by a larger study. Caveats of the study like time constraints and selection of patients with no osteopenia/osteoporosis may also be possible. Hence, this should be corroborated by a larger study with a longer period of follow up. In addition, analysis performed to assess relationships between radiation dose or menopausal status on biomarkers or bone density after radiation therapy may be performed in future studies.

Conclusion

Our study concludes that, in Indian patients, systemic effects on bone mineral density and other blood parameters of skeletal homeostasis are observed after pelvic radiation therapy. Significant rise of serum alkaline phosphatase (large effect size) accompanied by a significant fall of Z score are noted at three months of pelvic radiotherapy. This suggests that there is a significant bone turnover at three months after pelvic radiation treatment. Pharmacological intervention, when necessary, may therefore be considered after careful monitoring by this time.

In contrast to some other studies, no case of insufficiency fracture was recorded in our study. This may be due to their profession, dietary habit, climate, or other factors. A multicentric trial with a larger sample size and longer period of study (at least for one year and possibly more) needs to be conducted on Indian patients to get more elaborate data and understand the clinical significance of these biochemical changes or occurrence of insufficiency fractures later than six months. Effects of different concomitant chemotherapy regimens on bone turnover may also be studied.

Conflicts of interest

There are no conflicts of interest for any of the authors.

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