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Original Research Paper

Radiotherapy

IMPACT OF PELVIC IRRADIATION ON BONE MINERAL DENSITY IN CERVICAL CANCER PATIENTS- A PROSPECTIVE STUDY

Dr. Swapnil Govindrao More	Senior Resident of Radiation Oncology, Government Medical College & Cancer Hospital, Chhatrapati Sambhajinagar
Dr. Vijay Mahobia	Associate Professor of Radiation Oncology, Government Medical College & Hospital, Nagpur.
Dr. Ashok Kumar Diwan	Professor & Head of Radiation Oncology, Government Medical College & Hospital, Nagpur.
Dr. Priyanka Zumbar Pawar*	Junior Resident Of Radiation Oncology, Government Medical College & Hospital, Nagpur. *Corresponding Author

ABSTRACT **Background:** Cancer treatment induced bone loss has been retrospectively studied as a distinct entity in gynaecological cancers. Amongst gynaecological cancers, cervical cancer is the leading cause of mortality and morbidity, majorly in developing countries. Concurrent chemoradiation (CCRT) is considered as the standard of care in managing these patients. The present research was undertaken to study the impact of pelvic irradiation on bone mineral density (BMD) in cervical cancer patients visiting Radiation Oncology Department in tertiary care teaching hospital situated in the central India. **Method:** A total of 60 patients with histologically proven cervical cancer were studied over a period of 2 years from October 2020 to September 2022. **Results:** Most common histological type was squamous cell carcinoma (95.00%). Stage IIIB (33.33%) was the most frequently FIGO stage. Maximum patients received radical RT (91.67%) through 2-field technique (86.67%). At 3- and 6-months follow-up, none of the patients developed fracture. Overall, there was statistically significant decrease in BMD (T-Score) of lumbar spine and femur neck between baseline and 3- and 6-months follow up ($p<0.05$). The decrease in BMD reached statistically significant level in 41–50 years ($p=0.001$), and 51–60 years age groups ($p<0.0001$). Also, the decrease in BMD reached statistically significant level in BMI <18.5 kg/m2 ($p<0.0001$), 18.5–24.9 kg/m2 ($p=0.006$), and ≥ 25 kg/m2 ($p=0.033$). The decrease in BMD reached statistically significant level in patients with ($p<0.0001$), and without menopause ($p=0.004$). However, the decrease was greater in patients with menopause. **Conclusion:** Findings suggest that patients with cervical cancer undergoing RT have significant reduction in mean BMD. Proportion of patients with osteopenia and osteoporosis increases with time.

KEYWORDS : Cervical cancer; Bone mineral density; Squamous cell carcinoma; FIGO stage; Lumbar spine, Femur neck; Menopause

INTRODUCTION

Cervical cancer continues to be listed among the top gynecological cancers worldwide. According to current data, it is ranked fourteenth among all cancers and fourth-ranked cancer among women worldwide [1]. It is a major cause of cancer mortality in women, and more than a quarter of its global burden is contributed by developing countries [2]. As per 2020 GLOBOCAN, 604,100 new cases of cervical cancer were detected globally, and 341,831 deaths were attributed to this malignancy. Cervical cancer accounted for 9.4% of all cancers and 18.3% (123,907) of new cases in 2020 amongst the Indian population [3]. Although the age-standardized incidence rate of cervical cancer decreased substantially by 39.7% from 1990 to 2016, it is the second leading cause of cancer deaths for females in 12 Indian states [4].

Long-lasting human papillomavirus (HPV) infection causes almost all cervical cancers. But HPV 16 and 18 are the most commonly found HPV in invasive cervical cancer. Population-based HPV prevalence studies show that the greatest prevalence of high-risk HPV occurs in the young adult period before 25 years of life and cervical cancer death peaks in the middle age period of 40 to 50 years of life. Patient with cervical cancer is usually asymptomatic in the early stages [5, 6].

Definitive or adjuvant radiation therapy (RT) with concurrent chemotherapy have both become an essential component in the treatment of cervical cancer, especially in locally advanced cervical cancer, by reducing the recurrence of the disease and improving the overall survival rate for these patients [7]. Therefore, the quality of life of patients with cervical cancer after RT should be considered.

Pelvic RT can promote pelvic insufficiency fractures (PIFs) [8]. Moreover, Pelvic RT for gynecological malignancies has been shown to result in demineralization of bone matrix, with a pelvic fracture rate ranging from 1.7% to 89% [9]. Which leads to the belief that PIF are a rather common post-radiation complication and not as rare as previously thought. PIF are fractures caused by normal or physiological stress on bone with demineralization and decreased elastic resistance. The lateral mass of the sacrum is the most commonly affected site because of its weight-bearing function. Moreover, post-menopausal women, in particular, are at a higher risk for osteoporosis because of their rapid decrease in estrogen levels, which results in decreased BMD [7].

Irradiation to the pelvic region may cause direct damage to the bones and loss of ovarian function in premenopausal women. Hence, there is a possibility that the loss of ovarian function induced by RT may affect BMD in these women. India has substantial burden of cervical cancer and most of the patients present at an advanced stage. Based on these findings, evaluation of BMD is critical for these patient population [9]. Studies evaluating RT-induced change in BMD in Indian women are scarce. Therefore, in the present study, we aimed to measure the BMD of bones in the irradiated area which receives significant doses of radiation during treatment of cervical cancer at the start of chemoradiotherapy and again after 3 and 6 months of irradiation.

MATERIALS AND METHODS

After obtaining Institutional Ethical Committee (IEC) approval and written informed consent from all the patients, this prospective, observational, follow-up study was conducted in the Department of Radiation Oncology of a tertiary care teaching hospital situated in the Central India during a period

of 2 years from October 2020 to September 2022. All consecutive patients of aged 18 years or more with histologically proven squamous cell carcinoma and adenocarcinoma of ca cervix, with FIGO 2018 staging IIB to IIIC1, who receiving external beam radiotherapy to pelvic area, patients with normal KFT (i.e., serum creatinine), normal BMD, haemoglobin >8 gm% and Eastern Cooperative Oncology Group (ECOG) up to 2 were included in the study. Patient not willing/ not giving written consent, patients with early-stage cancer and operable disease, metastatic carcinoma cervix, bone diseases, patients with histologically proven ca cervix other than squamous cell and adeno-carcinoma, severe anaemia, abnormal KFT, abnormal BMD, patients with prior radiotherapy (RT), ECOG above 2, pregnant women, history of pelvic trauma, patients on hormone replacement or long-term corticosteroids, pelvic bone metastasis and patients below 18 years of age were excluded.

A total of 65 patients with histologically proven cervical cancer were initially screened for the study and were explained the study procedure in their native language. Of these, 3 patients did not give consent, and 2 had a history of already receiving RT. Excluding these 5 patients, those who were willing to participate and signed the informed consent document were enrolled in the study.

Following enrollment, a detailed history was taken with thorough clinical examination. They were further investigated with routine baseline blood investigation as per the standard guidelines. Following documentation of demographics, parameters relevant to the study, including menopausal status, serum vitamin D, phosphorus, calcium levels, histological type and FIGO stage of cervical cancer, type of radiotherapy treatment, and radiotherapy technique were noted in a specifically designed case report form.

Eastern Cooperative Oncology Group (ECOG) performance score is a standard criterion for measuring how cancer impacts a patient's daily living abilities. It describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). It was used as an eligibility criterion for enrolment of the patients. The ECOG performance score is depicted in Table 1.

Table 1: ECOG Performance Score.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Prior to RT, Dual-energy absorptiometry (DEXA) (Lunar Prodigy Advance Machine) was used to assess the BMD. T-scores in the lumbar spine (L1–L4) and femoral neck were assessed. BMD values were categorized into three groups, according to the World Health Organization criteria (normal, osteopenia and osteoporosis) [9].

Table 2: Interpretation of BMD [9]

T-score	Severity
< 1.5	Normal
1.5 – 2.5	Osteopenia
> 2.5	Osteoporosis

Patients were followed-up at 3-months,6 months and DEXA scan (Lunar Prodigy Advance Machine) was repeated, and BMD was compared to baseline. Moreover, during these 6-months, patients were assessed for the presence of fracture with its site. All these findings were recorded on a case report form.

Treatment

External beam radiotherapy (EBRT) was delivered to all patients using Cobalt Teletherapy Machine. Patients received 50 Gray (Gy) in 25 fractions (#), at 2 Gy per #, with anteroposterior-posteroanterior or 4 field box technique field for 5 # in a week, with total treatment duration of 5 weeks with injection cisplatin 40 mg/m^2 weekly. Cobalt-60 decay used in teletherapy units produces gamma rays with average energy of 1.25(1.37MV + 1.13MV) mega-voltage (MV).

Concurrent cisplatin administration to a dose of 40 mg per m^2 once weekly with adequate hydration, forced diuresis and anti-emetic prophylaxis. Patient were assessed weekly for biochemical assays [CBC, LFT, KFT, serum electrolyte, serum calcium, serum magnesium] followed by intracavitary brachytherapy 7Gy×3# (radical treatment) 1# per week and 7Gy×2# 1# per week (adjuvant treatment i.e., post-operative patients).

Figure 1: a) DEXA scan machine (Lunar Prodigy Advance Machine); b) Teletherapy cobalt unit (Theratron 780E); c) Brachytherapy Unit

Borders-

For AP-PA Field

Superior border-between L4 and L5 vertebrae
Inferior border- 2 cm below the lower extent of the clinical tumour or the inferior edge of obturator foramina

Lateral border-1.5 to 2 cm outside the bony pelvic side wall.

For 4 Field Box Technique

Superior Border-Same as AP-PA field
Inferior Border-Same as AP-PA field

Anterior border-Anterior to the pubic symphysis or through pubic symphysis

Posterior border-0.5 cm posterior to the anterior border of the S2/3 vertebral junction. May include the entire sacrum to cover the disease extent.

Figure 2: Localisation of X-Ray

Patients were followed up at 3-months and 6 months following RT. General clinical safety was monitored by vigilant follow-up of patients (i.e., volunteered by or by general direct question

from patient) for treatment emergent adverse events, if any and recorded in CRF. Rescue medications were available for managing adverse events. Reporting of adverse events was done asper National Pharmacovigilance Programme using suspected adverse drug reaction reporting form published by Indian Pharmacopeia Commission. Any adverse event occurring during the course of study were managed by clinicians.

Statistical Analyses

Data was collected and analyzed with SPSS (IBM, Armonk, NY, USA) version 23.0 for Windows. The categorical and continuous variables are represented as frequency (percentage) and mean (standard deviation, SD), respectively. Paired t test was used to assess the association between continuous variables. A two-tailed probability value of <0.05 was considered as statistically significant.

Observations and Results

During the study period, a total of 60 patients with histologically proven cervical cancer were studied. Patients predominantly belonged to the age group of 51–60 years (51.67%) and had a BMI of <18.5 kg/m2 (53.33%) as shown in table 3. The mean age of patients was 50.87±6.77 years, ranged from 32 to 60 years. However, the mean BMI was 20.69±3.69 kg/m2, ranging from 17.4 to 30.2 years. Of 60 patients, 37 (61.67%) had attained menopause, while the remaining did not (38.33%).

Table 3: Distribution of Patients According To Age and BMI

Parameters		Frequency (60)	Percentage
Age (years)	31 – 40	05	8.33
	41 – 50	24	40.00
	51 – 60	31	51.67
BMI (Kg/m2)	< 18.5	32	53.33
	18.5 – 24.9	19	31.67
	≥ 25	9	15.00

Table 4 depicts the distribution of patients according to laboratory parameters.

Table 4: Distribution Of Patients According To Laboratory Parameters

Laboratory parameters		No.	Percentage
Hemoglobin	< 10.5 gm%	47	78.33
	≥ 10.5 gm%	13	21.67
Serum calcium	< 8.5 mg/dL	14	23.33
	8.5 – 10.5 mg/dL	45	75.00
	> 10.5 mg/dL	1	1.67
Serum phosphorus	< 2.8 mg/dL	3	5.00
	2.8 – 4.5 mg/dL	45	75.00
	> 4.5 mg/dL	12	20.00
Serum vitamin D	< 20 ng/mL	42	70.00
	≥ 20 ng/mL	18	30.00

Most common histological type was squamous cell carcinoma (95.00%). Stage IIIB (33.33%) was the most frequently FIGO stage. Maximum patients received radical RT (91.67%) through 2-field technique (86.67%), (Table 5).

Table 5: Distribution Of Patients According To Histological Type And FIGO Stage Of Cervical Cancer, Treatment Type And Radiotherapy Technique

Laboratory parameters		No	Percentage
Histology of cervical cancer	Squamous cell carcinoma	57	95.00
	Adenocarcinoma	02	3.33
	Adenosquamous carcinoma	01	1.67
FIGO stage	Stage IIA	07	11.67
	Stage IIB	08	13.33
	Stage IIIA	14	23.33
	Stage IIIB	20	33.33
	Stage IIIC1	11	18.33
Treatment type	Adjuvant RT	05	8.33
	Radical RT	55	91.67
Radiotherapy technique	2 field	52	86.67
	4 field	08	13.33

At 3 and 6 months follow up, none of the patients developed fracture. There was no statistically significant difference in proportion of patients with normal and low BMD of femur neck (p=0.232) and lumbar spine (p=0.224) at 3- and 6-months as shown in table 6.

Table 6: Distribution Of Patients According To BMD Of Femur Neck And Lumbar Spine

BMD (T Score)		3-months, N (%)	6-months, N (%)	P value
Femur neck	Normal (< 1.5)	45 (75.0%)	39 (65.0%)	0.232
	Osteopenia (1.5 – 2.5)	15 (25.0%)	17 (28.3%)	
	Osteoporosis (> 2.5)	00 (%)	4.0 (6.67%)	
Lumbar spine	Normal (< 1.5)	46 (76.6%)	40 (66.6%)	0.224
	Osteopenia (1.5 – 2.5)	14 (23.3%)	17 (28.3%)	
	Osteoporosis (> 2.5)	0 (0.0%)	3.0 (5.00%)	

On repeated measures ANOVA, there was statistically significant decrease in BMD (T Score) of femur neck (p-value < 0.0001). On post-hoc-analysis by Bonferroni's test, there was statistically significant decrease in BMD (T Score) of femur neck between Baseline and 3-months, Baseline, and 6-months, and 3- and 6-months (all p-values <0.0001), (Figure 3).

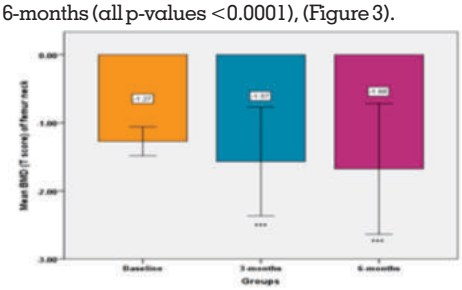

Figure 3: Comparison Of BMD (T Score) Of Femur Neck

On repeated measures ANOVA, there was statistically significant decrease in BMD (T Score) of lumbar spine (p-value < 0.0001). On post-hoc-analysis by Bonferroni's test, there was statistically significant decrease in BMD (T Score) of lumbar spine between Baseline and 3-months (p-value < 0.0001), Baseline and 6-months (p-value < 0.0001), and 3- and 6-months (p-value = 0.007), (Figure 4).

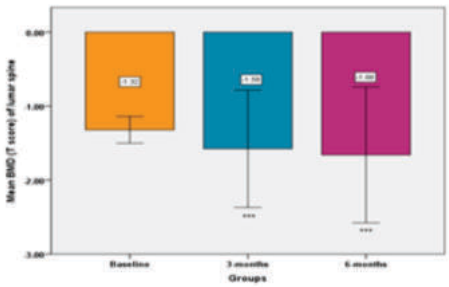

Figure 4: Comparison Of BMD (T Score) Of Lumbar Spine

The association of various factor including age groups, BMI, and menopausal status with average BMD scores are depicted in the Table 7 below.

Table 7: Association Of Various Factors With Average BMD Scores

Various factors		Baseline	6-months	p-value
Age (yrs) (BMD of lumbar spine)	31–40 (n=5)	-1.26 ± 0.11	-1.4 ± 0.0	0.052
	41–50 (n=24)	-1.34 ± 0.07	-1.43 ± 0.09	0.001
	51–60 (n=31)	-1.32 ± 0.09	-1.88 ± 0.55	< 0.0001
Age (yrs) BMD of femur neck	31–40 (n=5)	-1.28 ± 0.13	-1.4 ± 0.12	0.145
	41–50 (n=24)	-1.25 ± 0.11	-1.46 ± 0.28	0.001
	51–60 (n=31)	-1.28 ± 0.09	-1.89 ± 0.55	< 0.0001
BMI (kg/m2) BMD of lumbar spine	<18.5 (n=32)	-1.33 ± 0.09	-1.68 ± 0.49	< 0.0001
	18.5–24.9 (n=19)	-1.34 ± 0.09	-1.67 ± 0.44	0.006
	≥25 (n=9)	-1.26 ± 0.09	-1.57 ± 0.37	0.033
BMI (kg/m2) BMD of femur neck	<18.5 (n=32)	-1.27 ± 0.11	-1.7 ± 0.49	< 0.0001
	18.5–24.9 (n=19)	-1.25 ± 0.09	-1.64 ± 0.47	0.001
	≥25 (n=9)	-1.33 ± 0.1	-1.68 ± 0.49	0.077
Menopause status with BMD of lumbar spine	Yes (n=37)	-1.32 ± 0.09	-1.74 ± 0.52	< 0.0001
	No (n=23)	-1.32 ± 0.09	-1.54 ± 0.32	0.004
Menopause status with BMD of femur neck	Yes (n=37)	-1.27 ± 0.11	-1.75 ± 0.49	< 0.0001
	No (n=23)	-1.28 ± 0.11	-1.56 ± 0.43	0.006

DISCUSSION

Cervical cancer can develop in women of all ages, but it usually develops in women aged 35-55 years with the peak age of incidence varying among different population [10]. Age has a significant effect on the timing and frequency of cancer screening as demonstrated in a study by Sawaya et al [11]. In the present study, most of the patients belonged to the age group of 51–60 years (51.67%) followed by 41–50 years (40.00%). Thus, 91.67% patients were aged >40 years. The age of the patients ranged from 32 to 60 years with a mean of 50.87±6.77 years. This older age indicates a relative lack of awareness and access to adequate and equitable screening facilities for cervical cancer in our country [7] Various studies from India have reported similar findings [2, 12, 13]. Most of the patients had a BMI of <18.5 kg/m2 (53.33%) followed by 18.5 – 24.9 kg/m2 (31.67%). While the least number of patients had a BMI of ≥ 25 kg/m2 (15%). The BMI of the patients ranged from 17.4 to 30.2 kg/m2 with a mean of 20.69±3.69 kg/m2. These findings are correlated with the study done by Shrivastav et al [13] and Neha et al [14]. Some of the Indian study have reported that majority of the patients had normal BMI. The difference in BMI could be attributed to the fact that patients were mostly FIGO Stage I and II, while patients in the present study had more advance disease and belonged to poor socioeconomic status.

Recent studies suggest that older age, postmenopausal status, lower body weight or BMI, RT intensity (the larger volume irradiated, dose and the use of concurrent chemotherapy), and higher numbers of deliveries are risk factors for RT-induced pelvic insufficiency fractures [15]. In the current study, most of the patients attained menopause (61.67%), while remaining did not (38.33%) which is comparable with the study conducted by Okonogi et al [16] and O'Gorman et al [17]. Owing to diagnosis at advancing age, majority of the patients attained menopause.

In the present study, patients, 47 (78.33%) had hemoglobin <10.5 gm%, 14 (23.33%) had serum calcium <8.5 mg/dL, 3 (5.00%) had serum phosphorus <2.8 mg/dL, and 42 (70.00%) had serum vitamin D <20 ng/mL. The mean hemoglobin, serum calcium, phosphorus, and vitamin D were 9.95±0.78 gm%, 9.07±1.06 mg/dL, 3.99±0.68 mg/dL, and 18.87±5.05 ng/mL, respectively. Very few studies with similar study design have reported biochemical parameters in patients with cervical cancer. The findings observed in the present study are consistent with the existing literatures, with slight variation due to difference in study population [9,17,18].

Maximum i.e., 95% patients had squamous cell carcinoma (SCC), 3.33% had adenocarcinoma, and 1.67% had adeno-squamous carcinoma which is comparable with the previous studies [2, 10, 12, 13]. Also, these findings corroborate with the existing knowledge that SCC is the most common histological type and resulting in radiotherapy being the preferred mode of treatment. However, most of the patients had FIGO stage IIIB 20(33.33%) followed by stage IIIA14 (23.33%), stage IIIC1 11(18.33%), and stage IIB 8(13.33%). While the least number of patients had FIGO stage IIA 7(11.67%). Similar findings are reported in study conducted by Jain et al [12] and Thulaseedharan et al [19]. Some of the studies from India have reported lower stage at diagnosis [13, 14]. In developing countries, including India, the probable causes for late presentation and poor prognosis of cervical cancer among women are varied. They include lack of awareness among women, cultural factors, lack of centralized policies regarding cancer prevention, and HPV vaccination [20].

Majority of patients received radical RT (91.67%), while 8.33% received adjuvant RT which is in accordance with the study done by Schmeler et al [21]. Depending on stage and availability of resources, various studies have reported varying findings. However, most 52 (86.67%) received radiotherapy by 2 field technique, while 8 received radiotherapy by 4 field technique (13.33%). This finding is correlated with the study conducted by Salcedo et al [9], Okonogi et al [16] and Schmeler et al [21]. Thus, based on patient characteristics and hospital settings, various studies have used different techniques.

There are several predispositions for pelvic insufficiency fractures, the most notable being osteoporosis induced by post-menopausal changes in women. Pelvic insufficiency fractures following radiotherapy are not rare occurrences. In their study, Salcedo et al. followed the patients for a median duration of 13.7 months. The oneyear incidence of pelvic fractures was 3.6%. The two-year and three-year incidence of pelvic fractures were 12.7% and 15.7%, respectively [9]. In the present study, at 3- and 6-months follow-up, none of the patients developed fracture. In consensus with the present study, Okonogi et al [16] and Schmeler et al [21] reported no fractures in first 6-months of follow-up.

The measurement of BMD correlates with bone strength and predicts the risk of fracture [9]. Loss of BMD is a risk factor for developing fractures which can be both due direct effects of radiotherapy and induction of early menopause after chemotherapy [22]. In the present study, at baseline, all the patients had normal BMD of femur neck and lumbar spine. At 3- and 6-months, number of patients with normal BMD of femur neck decreased to 45 (75.00%) and 39 (65.00%), respectively. During similar time intervals, number of patients with normal BMD of lumbar spine decreased to 46 (76.67%) and 40 (66.67%), respectively. There was no statistically significant difference in proportion of patients with normal and low BMD of femur neck and lumbar spine at 3- and 6-months. Overall, there was statistically significant decrease in mean BMD (T Score) of femur neck and lumbar spine. At both the sites assessed, mean BMD (T Score) decreased significantly between Baseline and 3-months, Baseline and 6-

months, and 3- and 6-months. These findings are in accordance with the study done by Salcedo et al [9] and Okonogi et al [16].

We have analysed the association of various factor including age groups, BMI, and menopausal status with BMD. Compared to the baseline, BMD of lumbar spine and femur neck decreased in all the age groups at 6-months. On analysis with paired t-test, the decrease in BMD reached statistically significant level in 41–50 years (p-value=0.001), and 51–60 years age groups (p<0.0001). While the decrease was not statistically significant in 31–40 years age group (p-value = 0.052).

Compared to the baseline, BMD of lumbar spine decreased in all the BMI ranges. On analysis with paired t-test, the decrease in BMD reached statistically significant level in <18.5 kg/m^2 (p-value<0.0001), 18.5–24.9 kg/m^2 (p-value=0.006), and ≥25 kg/m^2 (p-value=0.033). Whereas compared to the baseline, BMD of femur neck decreased in all the BMI ranges at 6-months. On analysis with paired t-test, the decrease in BMD reached statistically significant level in <18.5 kg/m^2 (p-value=0.001), and 18.5–24.9 kg/m^2 (p-value<0.0001). While the decrease was not statistically significant in ≥25 kg/m^2 (p-value = 0.077).

Compared to the baseline, BMD of lumbar spine and femur neck decreased in patients with and without menopause. On analysis with paired t-test, the decrease in BMD reached statistically significant level in patients with menopause (p-value<0.0001), and without menopause (p-value = 0.004). However, the decrease was greater in patients with menopause.

Limitations

This study involved a relatively small number of patients registered in a single centre, so that future studies of larger sample size are required to confirm the findings. This was a single-centre study; hence, the results cannot be generalized to the community. Short follow-up period, and therefore the long-term morbidity associated with pelvic fractures and osteoporosis could not be reported.

CONCLUSION

Findings suggest that patients with cervical cancer undergoing RT have significant reduction in mean BMD. Proportion of patients with osteopenia and osteoporosis increases with time. However, further investigations with longer follow-up periods are required to determine the incidence of fractures in this cohort.

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