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INSUFFICIENCY BONE FRACTURE AFTER PELVIC RADIOTHERAPY: RETROSPECTIVE EVALUATION OF RISK FACTORS AND DOSE-VOLUME RELATIONSHIP ANALYSIS.

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ABSTRACT

Introduction: Pelvic insufficiency fracture (PIF) is a possible but still underestimated complication of pelvic radiotherapy, defined as a non-physiological bone fracture related to demineralization and decreased elastic resistance. The aim of this retrospective study is to identify patients' characteristics and possible risk factors in order to prevent, correctly diagnose and treat future PIFs. **Methods:** Between 2008 and 2012, 264 patients with pelvic malignancies were treated with RT. Nine had symptoms suggestive for PIF. Median age was 66 years. All symptomatic patients were studied with Magnetic Resonance Imaging, 5 underwent Positron Emission Tomography and 2 patients had a bone scan. In 6 patients we retrospectively contoured the fracture site and we analyzed Dose-Volume Histograms data. Two different treatment plans were created for each patient, 3DCRT and IMRT, and compared in order to define possible differences in target and Organs at Risk coverage and dose. **Results:** PIFs were diagnosed after a median of 15 months after RT, with the sacrum as the most frequently involved site. Three out of nine patients had osteoporosis and eight out of nine received neoadjuvant/concomitant chemotherapy. The mean maximum dose and the mean dose on bone which developed PIF were 53,7 Gy and 34,1 Gy, respectively. IMRT plans, even without pelvic bones optimization, were superior to 3DCRT in reducing the dose to pelvic bones ($p<0,001$). **Conclusions:** As pelvic RT has become a curative treatment for many oncological patients, late toxicity effects such as PIF need more attention and accuracy in diagnosis and treatment. Possible risk factors could be osteoporosis and neoadjuvant/ concomitant chemotherapy. The use of IMRT and the study of bone status before beginning treatment could help to prevent PIFs, especially in high risk patients.

KEYWORDS: Insufficiency bone fractures, Pelvic Radiotherapy, Complication.

INTRODUCTION

Pelvic insufficiency fracture (PIF) is defined as a non-physiological bone fracture related to demineralization with decreased elastic resistance occurring after a normal bone stress.[1] It usually occurs in elderly subjects. The most common cause of PIF is post-menopausal or prolonged use of corticosteroid-induced osteoporosis[2]; furthermore PIF is a potential but quite rare complication in patients receiving pelvic radiation therapy (RT) for gynecological, rectal and anal cancer with reported incidence between 2,7% and 89%.[3] Other risk factors can be rheumatoid arthritis, renal failure, lower body weight, older age and mechanical changes after hip surgery.[4]

The wide range of incidence of PIF reflects the hetereogeneity of previous studies and probably these fractures are often underestimated. This can be due to many factors: fractures can be asymptomatic, radiological exams during follow-up may not be sensitive enough and, in cancer patients, PIF can even be misdiagnosed as bone metastasis.[2,3,5-7]

Even though they are rarely life-threatening, these fractures deserve attention as, being a source of functional disability, they can frequently lead to loss of independence in elderly, mostly female patients.[8]

The aim of this study was to perform a retrospective review of our medical records to identify patient characteristics and possible risk factors predisposing patients to develop PIFs in order to prevent, correctly diagnose and treat them. Furthermore, in order to evaluate the relationship between radiation doses and

bone toxicity and to identify the most appropriate radiation treatment in presence of risk factors, we contoured retrospectively the sites of PIF, analyzed Dose Volume Histograms (DVH) of original treatment plans and subsequently developed new plans with different techniques to be compared with previous ones.

MATERIALS AND METHODS

Between 2008 and 2012 a total of 264 patients with pelvic malignancies received external whole pelvic RT +/- endocavitary brachytherapy as a part of oncological treatment. There were 102 (38%) patients with cervical cancer, 76 (28%) with uterine cancer, 78 (30%) with rectal and 8 (3%) with anal canal cancer. Most patients with uterine cancer received adjuvant pelvic RT (96%) whereas most patients with cervical cancer were treated with primary pelvic RT alone or with concurrent chemotherapy (67%).

Whole pelvic irradiation was delivered with 4 field arrangement three-dimensional conformal radiotherapy (3DCRT) using 18 MV photon beams or five field arrangement intensity modulated radiation therapy (IMRT) sliding windows technique using 6 MV photon beams. The study population was treated with doses ranging between 50 and 66 Gy and all patients completed the planned course of RT.

Patients' clinical records included comorbidities, cancer and treatment details and potential risk factors for bone abnormalities, such as steroids and concurrent chemotherapy. All patients had regular follow-up after oncological treatment, according to specific cancer site guidelines, and diagnostic imaging was performed only in patients who developed bone symptoms.[9] Among 264 collected patients in our study, nine referred bone symptoms such as pain or mobility reduction.

Median age was 66 years (range 41-77) and median Body Mass Index (BMI) was 28 (range 21,2-36,5).

Patients and treatment details are reported in Table 1A and 1B.

Table 1 A Patients clinical characteristics

Pt	RT timing	CHT	RT Dose (Gy)	HDR Dose (Gy)	Energy (MV)	Technique
1	Neoadjuvant	concomitant	50,4	-	18	3DCRT
2	Adiuvant	neoadjuvant	50,4	15	18	3DCRT
3	Radical	concomitant	50,4	14	18	3DCRT
4	Radical	concomitant	50,4	21	18	3DCRT
5	Radical	concomitant	66	16	6	IMRT SIB
6	Adjuvant	neoadjuvant/ adjuvant	50,4	12	18	3DCRT
7	Neoadjuvant	-	55,8	-	18	3DCRT
8	Neoadjuvant	concomitant	50,4	-	18	3DCRT
9	Radical	concomitant	59,4	-	6/18	3DCRT

Table 1 B Patients clinical characteristics

Pt	RT timing	CHT	RT Dose (Gy)	HDR Dose (Gy)	Energy (MV)	Technique
1	Neoadjuvant	concomitant	50,4	-	18	3DCRT
2	Adiuvant	neoadjuvant	50,4	15	18	3DCRT
3	Radical	concomitant	50,4	14	18	3DCRT
4	Radical	concomitant	50,4	21	18	3DCRT
5	Radical	concomitant	66	16	6	IMRT SIB
6	Adjuvant	neoadjuvant/ adjuvant	50,4	12	18	3DCRT
7	Neoadjuvant	-	55,8	-	18	3DCRT
8	Neoadjuvant	concomitant	50,4	-	18	3DCRT
9	Radical	concomitant	59,4	-	6/18	3DCRT

CHT, chemotherapy; 3DCRT, 3 dimensional conformal radiotherapy; IMRT, intensity modulated radiation therapy; SIB, simultaneous integrated boost.

Magnetic Resonance Imaging (MRI) scan was performed only in symptomatic patients with a median time after the end of RT of 15 months (range 3-26). The standard pelvic protocols consisted of a coronal T1-weighted fast spin-echo sequence, a coronal short tau inversion recovery (STIR) sequence and fat-satured T2-weighted fast spin-echo sequence. 18F-Fluorodesossiglucose Positron Emission Tomography (PET) and technetium-99-methylene diphosphonate (99mTc-MDP) bone scan were performed in 5 and 2 patients, respectively. Pelvic MRI revealed T1-hypointense and T2-hyperintense lesions; 99mTc-MDP Bone scintigraphy and PET scan reports evidenced an increased activity in a bone segment. MRI study identified fractures in 5 patients (1 rectal cancer, 3 uterine cervix cancers, 1 pelvic lymph-node recurrence from cervical cancer), while in the other 4 patients (1 cervical, 2 rectal and 1 anal canal cancer)

images were defined as suggestive for PIF.

3DCRT and IMRT Simultaneous Integrated Boost (SIB) were performed in 8 and 1 patients, respectively.

The median prescribed dose to Planning Target Volume (PTV) was 50,4 Gy (range 50,4- 66,6Gy) delivered with conventional fractionation schedule of 1,8 Gy per fraction. One patient was treated with SIB technique, with PTV receiving 1.8, 2 and 2.2 Gy per fraction. In 5 gynecological cancer patients subsequent mean boost dose of 16,3 +/- 3,5 Gy was delivered in 3 fractions with Iridium-192 High Dose Rate (HDR) brachytherapy. Eight patients received neoadjuvant/concomitant chemotherapy.

Only for 6 out of 9 symptomatic patients MR studies were available at the time of this retrospective analysis. Characteristics and sites of PIF of these 6 patients are listed in Table 2.

Table 2. Patients with MR study available

Characteristics	
Number of patients	6 pts
Age - median (range)	66,5 (41-70)
Body Mass Index – median (range)	26,9 (21,2-37,2)
Concomitant chemotherapy	5 pts
Comorbidity	
Osteoporosis	2 pts
Sites of PIF	
Sacro-iliac joints	2 pts
Femoral heads	1 pts
Ilium-ischia-pubes	2 pts
Acetabula	1 pts
Sacrum	4 pts

Pts, patients.

In order to assess the relationship between bone toxicity and Dose-Volume Histograms (DVH), PIF sites were retrospectively contoured on MR images. Furthermore, in order to identify differences in target and Organs at Risk (OARs) coverage and dose distribution, two different treatment plans (3DCRT and IMRT) were generated and compared for each of these patients. Retrospectively, 5 field-IMRT plans (6 MV) with gantry angles of 36°, 100°, 180°, 260°, 324° (sliding window technique with and without optimization on pelvic bones) and 4 field-3DCRT plans (6 MV) were generated using a commercial Treatment Planning System (TPS) (Eclipse v. 8.6, Varian Medical Systems, Palo Alto, CA) and each DVH was compared for all patients. The Clinical Target Volume (CTV) consisted of the uterus and cervix, pelvic and presacral nodes, upper vagina and parametrial tissue. OARs included rectum, bladder, bowel (peritoneal cavity), pelvic bones (externally contoured as lumbosacral- LSB, iliac (IB) and lower pelvis (LPB), which were also used to evaluate the dose to pelvic bones (PB). In order to minimize hematological toxicity, V10, V20, V30 were optimized; D*mean*, V40 and V50 were used to reduce bone toxicity without compromising PTV coverage and other OARs sparing. Differences in dose distributions between the two sets of plans were analyzed using a paired τ-test.

HDR brachytherapy treatments were not considered in the dosimetric analysis because the dose received by pelvic bones, due to intrinsic characteristics of the technique, was so low that it could not induce any bone toxicity.

RESULTS

Pelvic insufficiency fractures were detected after a median time of 15 months (range, 2-22 months) after RT. PIF presentation sites are summarized in Table 3. The most common fracture site was sacrum (6 patients), followed by acetabula (1 patient), ilium-ischia-pubes (3 patients), femoral heads (with osteoradionecrosis in 1 patient), sacro-iliac joints (2 patients). All patients reported pelvic pain at diagnosis and pain intensity was assessed using VAS score, as reported in Table 3.

Table 3. PIFs presentation sites

Pt	**MRI (months after RT)**	**Bone scintigraphy (months after RT)**	**PET (months after RT)**	**PIF site**	**Radiological/ clinical timing of PIF (months after RT)**	**Pain (VAS Score)**
1	2-4-8	2	2	Sacrum/acetabula	2	8
2	6-8-11	8	-	Sacrum/Ilium-schia-pubes	8	8
3	7-14-22-23-33-45	-	24	Femoral heads	22	6

				(osteonecrosis)/ sacrum		
4	4-9-21	-	-	Sacrum	21	5
5	2-15	-	5	Sacrum/ sacro-iliac joints	15	5
6	26	-	24	Sacro-iliac joint	26	6
7	7	-	-	Ilium-ischia-pubes	7	6
8	20	-	-	Sacrum	20	9
9	3	-	3	Ilium-ischia-pubes	3	8

Pt: patient.

Among symptomatic patients, the most frequent comorbility was osteoporosis, which was reported in three out of nine symptomatic patients. Furthermore, eight out of nine symptomatic patients received neoadjuvant or concomitant chemotherapy.

The mean of maximum doses and the Dmean of bone which developed PIF were 53,7 Gy and 34,1 Gy, respectively. In the patient who had femoral head radio-necrosis, the maximum dose to PIF site was 65,5 Gy, taking into account that the patient received a parametrial boost of 16,2 Gy with 3D-CRT.

IMRT plan without pelvic bones optimization was superior to 3DCRT in reducing the dose to pelvic bones. Moreover, when we optimized the IMRT plan also for pelvic bones, we measured a further dose reduction between 3DCRT and optimized IMRT: V10 91.4 ± 3.5 vs 84.8 ± 1.9, V20 84.7 ± 4.7 vs 61.8 ± 3.1, V30 53,7 ± 5.6 vs 39.0 ± 4.8 for hematological toxicity, Dmean 33,3 ± 1.7 vs 25.9 ± 1.5 Gy, V40 32,6 ± 4.9 vs 19.0 ± 5.0, V50 16,1 ± 4.2 vs 3.3 ± 2.3 for bone toxicity sites (all with p<0,001). PTV coverage did not differ in both optimized and non-optimized IMRT plans. Dose volume comparison for all the pelvic bones and for three bone segment subsets performed in six patients analyzed are described in Table 4.

Table 4 - Dose-volume comparison for different treatment plans in 6 patients analyzed

Dose-Volume constraints	4-field 3DCRT	PB opt IMRT	PB no-opt IMRT	p value (PB opt IMRT vs 3DCRT)	p value (PB no-opt IMRT vs 3DCRT)
V10					
LSB	92.9±11.7	88.3±11.0	92.3±12.7	*ns*	*ns*
IB	84.9±3.1	84.1±8.1	86.4±7.4	*ns*	*ns*
LPB	92.8±4.8	81.8±6.7	87.3±6.3	*< 0.01*	*ns*
PB all	90.5±3.8	83.8±2.9	88.6±5.1	*< 0.01*	*ns*
V20					
LSB	89.8±13.4	70.1±5.9	88.5±13.4	*< 0.01*	*ns*
IB	75.3±4.4	59.7±4.8	62.0±4.9	*< 0.01*	*< 0.01*
LPB	86.0±6.5	62.0±4.9	72.3±9.8	*< 0.01*	*< 0.05*
PB all	83.9±4.6	63.0±4.0	73.8±4.0	*< 0.01*	*< 0.01*
V30					
LSB	55.3±6.4	50.3±4.4	57.7±6.5	*ns*	*Ns*
IB	50.3±13.6	36.6±8.6	38.0±10.3	*ns*	*Ns*
LPB	62.2±16.9	37.1±9.5	43.7±9.8	*< 0.01*	*< 0.05*
PB all	56.0±7.5	40.8±6.2	46.8±5.7	*< 0.01*	*< 0.05*
Dmean					
LSB	33.6±3.7	28.6±1.3	32.4±2.7	*< 0.01*	*Ns*
IB	30.2±1.9	24.4±1.8	25.1±2.2	*< 0.01*	*< 0.01*
LPB	35.5±3.8	25.9±3.6	28.4±3.8	*< 0.01*	*< 0.01*
PB all	33.4±1.6	26.3±1.6	28.6±1.8	*< 0.01*	*< 0.01*
V40					
LSB	33.3±4.1	24.9±3.9	28.2±3.2	*< 0.01*	*< 0.05*
IB	27.3±6.1	12.7±5.7	14.0±6.7	*< 0.01*	*< 0.01*
LPB	38.0±11.0	23.0±9.4	25.0±11.5	*< 0.05*	*Ns*
PB all	33.5±4.9	20.5±5.8	22.4±6.4	*< 0.01*	*< 0.01*
V50					
LSB	13.3±8.0	4.1±1.9	6.8±2.1	*< 0.05*	*Ns*
IB	14.8±5.0	1.9±1.7	1.9±1.7	*< 0.01*	*< 0.01*

LPB	20.0±12.2	5.3±3.4	5.4±3.5	*< 0.05*	*< 0.05*
PB all	16.8±4.1	3.9±2.6	4.3±2.6	*< 0.01*	*< 0.01*

LSB, lumbo-sacral bone; IB iliac bone; LPB, lower pelvis bone; PB, pelvic bones.

DISCUSSION

RT effect on normal bone tissue consists in both a direct effect on osteoblasts, osteoclasts and osteocytes that lead to a reduction in bone matrix production, and an indirect effect due to vascular damage, with microcirculation occlusions and further osteoblast function deficiency.[1,4,6]

The most frequent sites of bone stress fracture reported in literature, as observed in our study, are sacrum, sacro-iliac joints and ilium-ischia-pubes.[2,3,5-7,10]

Several recent studies showed that the incidence of post-RT insufficiency fractures has been underestimated, as the reported 5-year rate of PIF in literature, especially after pelvic RT in gynecological cancer patients, ranges from 8.2% to 17.9% or higher.[5] In our study the PIF rate was lower than literature data (3%, 9/264 patients), and this confirms that incidence of stress fractures is probably underestimated. The wide range of PIF incidence in literature can be related to different factors, such as heterogeneity of previous retrospective studies, non uniform recording of bone complications[4] and different radiation treatment characteristics. Some studies indeed reported that patients treated with radical intent had higher incidence of PIF (30.1%) compared with patients treated in adjuvant setting (11.1%), with a statistically significant threshold of 50.4 Gy as the dose beyond which PIF rate is higher: furthermore many authors reported higher PIF rates in patients treated with AP-PA fields than in patients treated with a 4-field box technique or other more conformed plans.[5-7, 10]

Dose constraints and dose-volume relationship between PIF/bone toxicity and dose to pelvic bone are not well established in literature. Furthermore, pelvic bones (in particular ilium and lumbosacral) significantly contribute to the production of blood component and more attention has recently been devoted to the relationship between low doses to the pelvic bones and hematological toxicity (V10 and V20 as best predictors).[11-14] In this study, IMRT plans optimized on pelvic bones provided better pelvic bones sparing than 4 field-3DCRT, both for low and high doses. Iliac, lumbar and sacral bones irradiation was reduced even though the plans were not optimized to spare pelvic bones. In particular, dose-volume comparison for "pelvic bones all" shows a statistically significant trend in all analyzed dose constraints. Therefore the IMRT technique could be used in order to minimize pelvic bones dose and thus fracture risk and hematological toxicity, by using the same OAR volume with different dose-volume constraints during the optimization procedure.

Furthermore literature data show that incidence of PIF is also correlated with patient risk factors. Patients with low BMI of about 22, as reported in studies from Asia (especially from Korea and Japan), developed higher rates of PIF compared with studies on occidental patients whose BMI is higher than 28.[2,4,5,15-17] Regarding other possible risk factors the most important is osteoporosis, which is the most frequent cause of insufficiency fractures in the general population, and therefore all the conditions leading to it such as post-menopausal status and the use of high dose of corticosteroid therapy.[18] Among the nine symptomatic patients osteoporosis was the most frequent comorbidity and this could confirm its possible correlation with the incidence of PIF, even if the analysis on such a small number of enrolled patients does not allow us to reach definitive conclusions. Moreover, even other comorbidities related to bone abnormality can be considered risk factors for PIFs, the most frequent being osteomalacia, Paget's disease, primary hyperparathyroidism, rheumatoid arthritis, hyperthyroidism and osteogenesis imperfect.[4, 18]

It is uncertain if concurrent chemotherapy could increase the risk of insufficiency fractures and literature data are discordant.[4,19,20] However the proportion of patients receiving concomitant chemotherapy ranged from 38 % to 90% and in most studies chemotherapy was not evaluated as an independent prognostic factor.[4] In our clinical records eight patients out of nine received neoadjuvant or concomitant chemotherapy and so such treatment could be a possible risk factor for insufficiency bone fractures.

PIF fracture symptomatology can vary: pain is the main presentation symptom and mobility reduction can also be very frequent.[18] Obviously the extent of the lesion may correlate with the severity of symptomatology.

Different imaging techniques can be used to detect PIFs. Previous studies reported low sensitivity of plain films for PIFs and pelvic fractures (20-38%) so they are not used in these patients.[21] Several investigations demonstrated high diagnostic accuracy for multidetector computed tomography (MDCT) in pelvic injury, detecting up to 50% of occult fractures missed at plain radiography.[22] It has been shown to be sensitive in detecting fractures lines and in the assessment of biomechanical stability.[8] However, there are some cases in which this technique is not sensitive enough, as when cortical bone is intact or in microfractures, and MRI is needed. In a study of Carrabus et al. where these two techniques were compared, overall sensitivity of MRI was demonstrated to be higher than CT in bone fracture.[8] In this imaging technique, sacral marrow oedema can be ill-defined and irregular, seen as hypointense in T1-weighted images or hyperintense in short T1 inversion–recovery (STIR) or T2-weighted images and fatty marrow can obscure fluid signal in fast

spin-echo T2-weighted images. The fracture line is usually visualized at between 3 weeks and 3 months and appears as an area of linear low signal intensity surrounded by enhancing marrow oedema in contrast-enhanced T1-weighted images.[23] Even other Authors have recently confirmed that MRI is a superior technique compared with other CT and even suggested it as the gold standard in cases of suspected insufficiency fractures.[24]

Bone scan is also considered one of the most sensitive examinations in detection of PIFs, with a sensitivity of 96%.[25] The pathognomonic sign of PIF is called "Honda" sign, but unfortunately it cannot always be seen.[25] Furthermore, in 2007 a study comparing planar bone scintigraphy, SPECT and SPECT/CT demonstrated that SPECT/TC was the best technique in characterizing focal bone lesions.[26]

In recent years, positron emission tomography and computed tomography (PET/TC) is widely used in cancer patients follow-up and it can detect PIF in patients who have undergone radiation therapy. PIF can be detected with the "H" shape 18F-Fluorodesossiglucose uptake, similar to what happens in bone scan, but standard uptake value of PIF is usually lower than in cancer lesions.[25]

Concerning treatment of PIF, many investigators reported that a conservative management with analgesics, rest and rehabilitation exercise could improve clinical status. Patients with mobility problems can be evaluated by the physiotherapist for appropriate therapy prescription.[18] Some serious cases may even need in-patient admission for pain control.[27] Vertebroplasty or sacroplasty could be a final option for persistent pain.

With a secondary prevention intent a recent study suggested treating PIF patients with a serum Vit D greater than 50 nmol/l, but there is no evidence that it can improve the outcome; the study further mentions bisphosphonate therapy, whose role has yet to be investigated referring to PIF.[18]

There were some limitations in our study. First, it is a retrospective analysis of a heterogeneous population of patients with different primary tumors, and toxicity data were often underreported and underrecorded. Second, the patients did not have the same imaging studies, and only symptomatic cases were studied to identify possible stress fractures. Third, only in 6 out of 9 patients replanning and dose calculation to PIF site were possible. Finally, dosimetric data of patients with PIF could not be compared with DVH analysis of patients who did not experience PIF and this comparison could have probably added important information.

CONCLUSIONS

In conclusion, symptomatic pelvic fractures have a great impact on quality of life in cancer patients. As pelvic RT has become a curative treatment for many oncological patients, with a lot of long term survivors among them, late RT toxicity such as PIF needs more attention and accuracy in prevention, diagnosis and treatment.

One of the suggested strategies to reduce radiation induced bone complication rate is the use of advanced steep dose gradient RT techniques (i.e. IMRT, Volumetric Modulated Arc Therapy-VMAT), that allows dosimetric advantages on OARs even without optimizing plans for pelvic bones sparing, especially when RT is performed with a radical intent. Furthermore, in order to identify patients and bone segments at risk of stress fracture, especially in those patients who present mentioned risk factors, it could be useful to assess bone status before the beginning of treatment, performing bone scan and bone mineral densitometry.

In conclusion, a proper knowledge and identification of risk factors and imaging patterns of bone complications could help the physician to avoid inappropriate treatment.

We declare that we have no conflict of interest.

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It is a retrospective study with analysis of radiotherapy treatment plans performed in the previous years in Our Institution.

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