Pelvic insufficiency fractures and bone pain after radiotherapy for anal cancer -Relation to pelvic bone dose volume parameters.

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Pelvic insufficiency fractures and bone pain after radiotherapy for anal cancer -
Relation to pelvic bone dose volume parameters.

Running title: Symptomatic PIFs after RT in anal cancer

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Trial information: (Regional Ethical Committee (1-10-72-79-16) and the Danish Data protection agency (2012-58-0005)
Pelvic insufficiency fractures and bone pain after radiotherapy for anal cancer - Relation to pelvic bone dose volume parameters.

Abstract:

Background and aim:

Chemoradiotherapy is the primary treatment for anal cancer. Radiotherapy (RT) can weaken the pelvic bone structure, but the risk of pelvic insufficiency fractures (PIF) and derived pain in anal cancer is not yet established.

We determined the frequency of symptomatic PIF after RT for anal cancer and related this to radiation dose to specific pelvic bone sub-structures.

Materials and methods:

In a prospective setting, patients treated with RT for anal cancer had an MRI one year after RT. PIFs were mapped to 17 different bone sites and we constructed a guideline for detailed delineation of pelvic bone sub-structures.

Patients were interviewed on pain and scored according to CTCAE. Dose volume relationships for specific pelvic bone sub-structures and PIFs was determined for V20-V40 Gy, mean and max doses.

Results:

Twenty-seven patients were included, and 51.9% had PIFs, primarily located in the alae of the sacral bone. Patients with PIF had significantly more pelvic pain (86% vs. 23%, p=0.001) and 43% had grade 2 bone pain.

Dose volume parameters for sacral bone and sacral alae were significantly higher in patients with PIFs, (p<0.05). V30 Gy (%) for sacral bone and alae implied AUC 0.764 and 0.758 in ROC analyses.

Conclusion:

We observed a high risk of PIFs in patients treated with RT for anal cancer one-year post-treatment. A significant proportion had pain in the sites where PIFs were most frequently found. Radiation dose to pelvic bone sub-structures revealed relation to risk of PIF and can be a used for plan optimization in future clinical trials.
Introduction:

Pelvic radiotherapy (RT) is associated to adverse effects from adjacent healthy tissues including pelvic pain, that can be caused by several mechanisms. Even though pelvic insufficiency fracture (PIF) is a well-known late complication to RT the effect of RT on bone has been less in focus. Acknowledging PIF as a possible cause of pelvic pain is important as it can affect physical function and quality of life and necessitate specific imaging [1, 2]. Chemoradiotherapy (CRT) is the primary treatment for anal cancer, but PIFs are solely described in small retrospective or registry studies after RT for anal cancer in 1.4-14% [3-5]. PIFs are more well described after RT for gynecological malignancies, but with varying frequency from 2%-89% [6-9].

Studies on PIFs after RT are heterogeneous in definition of PIF, imaging method and timing of imaging. Furthermore, studies are mainly retrospective and many with no clinical information [7-9]. Choice of imaging method is important, and for stress fractures in general magnetic resonance imaging (MRI) is estimated to have a sensitivity of 99-100 %, a specificity of 85 %, and specifically MRI is found to be better than CT (sensitivity 69%) in the pelvic area [10-12].

Across studies and cancer diagnoses, it has been documented that PIF are predominantly located in weight bearing areas, have a relation to higher radiation doses, with an increasing incidence with age and postmenopausal status [3, 4, 7, 8, 13, 14]. In gynecological malignancies two recent, large systematic reviews on PIF after RT found incidences of PIF of 9.4% and 14%, detected a median of 8-39 and 7.1-19 months after RT. The most frequently found risk factors for PIF included increasing age, postmenopausal status, low BMI and osteoporosis. Further, the most frequent localization was in the weight bearing areas sacral body/near sacroiliac joint (60-73.6%) followed by pubic bones (12-13%). There was an association to older RT treatment techniques and higher RT doses. The ratio of symptomatic patients differed, but was generally around 50-60% [7, 8]. Due to different chemotherapy, radiation dose and technique, data from gynecologic malignancies are not
directly comparable to anal cancer, but data corresponds to what has been found in anal cancer and 
other pelvic cancers [13, 15].

We have recently found a high incidence of PIF (around 30%) 3 years after radiotherapy for rectal 
cancer, and relation to radiation dose to pelvic bone sub-structures, but with limited information on 
symptoms Ref xx. The aim of this study was to determine the incidence of PIF on MRI with bone 
specific sequences one year after Chemoradiotherapy (CRT) for anal cancer, and to determine and 
grade symptomatic PIFs. Further to relate the radiation dose of pelvic bone sub-structures to the risk 
of PIF and provide guidelines for detailed delineation of pelvic bone sub-structures.

Materials and Methods:

Patients: Patients with anal cancer undergoing CRT were included in a prospective trial registering 
acute and late toxicity. An amendment was made to the protocol to conduct this sub-study including 
a bone-specific pelvic MRI and blood samples one year after CRT. Regional Ethical Committee 
(xx) and the xx Data protection agency (xx). At the one-year follow-up patients were offered 
participation in this sub-study. All patients gave written informed consent and were included 
between 2018 and 2021. Clinical data were collected prospectively, however pelvic bone sub-
structure delineation was done retrospectively and not included in the planning process.

Treatment: Planning PET-CT and MRI were acquired in treatment (supine) position. Gross tumor 
volume (GTV) was defined based on available imaging and clinical information. Clinical target 
volume (CTV) margins included a 5 mm margin to GTV and circumference of anal canal, a further 
5 mm isotropic margin (10 mm for margin tumors) and a 5 mm (8 cranio-caudally) planning target 
volume margin (PTV). Patients were treated with different radiotherapy and chemotherapy-
schedules: 54-64 Gy in 30-32 fractions (5 weekly) to tumor and pathological lymph nodes, and 48-
51.2 Gy in 30-32 fractions to elective nodal areas including pre sacral space, mesorectum, ischioanal space, bilateral internal and external iliac and bilateral inguinal regions (modifications to elective areas were allowed on individual basis) as described by Ng et al {Ng, 2012 #1}, but the ischiorectal fossa was only included fully if tumor growth through the levator muscles was seen on diagnostic MRI and the inferior boarder of the inguinal spaces was below the minor trochanter. Cisplatin was given either weekly (40 mg/m$^2$) (n=14) or on day 1 and 29 (70 mg/m$^2$) (n=5) together with flurouracil (3200 mg/m$^2$) (n=5) infusional over 96 hours day 1 and 29. Capecitabine (1700 mg/m$^2$, BID) was given as monotherapy in case of intolerance to cisplatin (n=3).

Rotational intensity modulated arc therapy was used for all patients, using 2-4 arcs. Dose coverage criteria were V95=100% and V95>99% for CTVs and PTVs respectively. Priority was as follows CTVs>PTVs>bowel>bladder>other OARs.

MRI: The bone-specific MRIs were performed on 1.5T platforms with a standardized scanning protocol including a 4 mm sagittal short-T1 inversion recovery (STIR) sequence and a 7 mm coronal T1 FSE of the bony pelvis and femoral heads. High signal intensity changes in the bone marrow at the STIR sequence, indicating bone marrow edema, with accompanying subtle linear, low signal intensity changes at T1 weighted images were defined as presence PIF. STIR is the most sensitive sequence for the detection of bone marrow edema while the T1 images ensured precise anatomical mapping and confirmation of subtle fracture lines. As most patients had multiple fractures, fractures were divided into following 17 sites: femoral heads (L/R), femoral neck (L/R), superior pubic ramus (L/R), inferior pubic ramus (L/R), pubic corpus (L/R), acetabulum (L/R), iliac bone near joint (L/R), alae of the sacrum (L/R), and midline of sacral bone.
All MRI examinations were evaluated by a consultant radiologist, with sub-specialization in pelvic MRI, blinded to all clinical and para-clinical data, with the exception of the pre-therapeutic MRI.

Blood tests: At the time of bone specific MRI, a blood sample was drawn and analyzed for factors potentially related to bone metabolism and risk of insufficiency fractures, including: plasma (p)-thyroid stimulating hormone (TSH), p-parathyroid hormone (PTH), p-glucose, p-calcium, p-phosphate, p-albumin, blood (b)-hemoglobin, p-Vitamin-D, b-leucocytes, b-thrombocytes, p-lactate dehydrogenase (LDH), p-bilirubin, p- alanine aminotransferase (ALAT), p-alkaline phosphatase, p-creatinine, p-c reactive protein (CRP), p-follicle stimulating hormone (FSH), p-testosterone.

Assessment of pain: In the outpatient clinic or during telephone consultation patients were firstly asked if they had pain in the pelvic area Y/N. Then, it was scored according to the CTCAE version 5.0, bone pain grade 0-III. Further, the patients were asked to characterize pelvic pain as 1: pain while resting, 2: pain with physical activity (i.e. walking) and 3: pain with provocation (i.e. applying pressure to the affected area) and to localize pain into following areas: 1: sacral area, 2: symphysis, or 3: hip area.

Delineation: The following pelvic bone structures were delineated: Pelvic bones (Total: including ileum, ischium, pubic and sacral bone, outer contour was delineated), femoral heads left/right (L/R) (from caput cranially including lesser trochanter caudally), Sacral bone (from s1 cranially to s5 caudally) outer contour including foramina when located in bone. Sacroiliac joints (L/R) delineated 1 cm to each side of the joint, where the sacrum and ilium bones forms the joint, the sacral alae (L/R) were delineated as the winged formation lateral to sacral body. The acetabulum (L/R) was delineated 15 mm cranially to the most cranial slice with femoral head and caudally to the fovea of
the femoral head. Pubic bones (L/R) were contoured with the most cranial slice meeting the acetabulum and caudally to a horizontal line through the obturator foramen (In the supplementary material we provide a more detailed description and depict bone sub-structure delineation). Delineations were done blinded to the clinical outcome.

Dose volume parameters:

We compared V20 Gy, V30 Gy, V40 Gy mean and max doses from the pelvic bone-substructures between patients with and without PIFs. V10 Gy was omitted as the rotational arc therapy gave all patients a similar low dose bath, V50 Gy was also not used as it was very close to the reported max doses.

Statistics:

Differences between patient groups with or without PIFs were evaluated by the Wilcoxon rank-sum test, Fischer´s exact test (dose volume parameters) or Chi2-test. P-values<0.05 were considered statistically significant.

Nonparametric Receiver operating characteristic (ROC) analyses were used to evaluate the dosimetric parameters for prediction of the risk of PIF, area under curve (AUC) was used to evaluate the best fit.

The STATA statistical software (ver. 17.0) was used for analyses.

Results:

We included 27 patients with a median age of 64 years (range 43-74), 81.5% were female. Baseline BMI was 26 (range 18.1-32.1) and all were in ECOG performance status (PS) 0 or 1. Tumor (T)-stages were T1: 25.9%, T2: 51.9%, T3: 3.7% and T4: 18.5% and 18.5% had lymph node N-positive disease. There were no significant differences in PS, T- or N-stage between patients with or without
PIF. Most patients (81.5%) received radiation doses between 60 and 64 Gy, and 5 patients (18.5%) did not receive chemotherapy. All of the patients were treated with 2, 3 or 4 arc rotational arc therapy technique and there were no differences between groups in chemotherapy, radiation dose or treatment technique. There were significantly more women in the PIF group compared to the no PIF group (p=0.01), otherwise baseline characteristics were equally distributed between the two groups. Baseline characteristics and differences between patients with and without PIF are listed in table 1. Fourteen patients (51.9%) had PIFs identified on the MRI. The MRIs were acquired a median of 482 days after initiation of radiotherapy (range 363-756 days). A total number of 44 fracture sites (on average 3.14 sites per patient) were identified with the alae of the sacral bone (L/R) being the most frequent site (n=20), followed by the acetabulum (L/R) (n=11), iliac bone, near joint (L/R) (n=4), pubic bones, all (n=4), femoral neck/heads (L/R) (n=4) and the body of the sacral bone (n=1). All but one patient had fractures in the sacral alae, uni- or bilaterally.

In the group of patients with no PIF, three patients had pain in the pelvic area (23%), whereas 12 (86%) of the patients with PIF had pain in the pelvic area, p=0.001. When grading according to CTCAE bone pain, we found that significantly more patients had grade 1 and 2 pain, p=0.015. Patients with PIF characterized pain as pain while resting, n=5, pain with exercise, n=8 and pain with provocation, n=6. Localizing pain, 9 had pain in sacral area, 7 in hip area and one in symphyseal area.

None of the blood tests (p-TSH, p-PTH, p-glucose, p-calcium, p-phosphate, p-albumin, b-hemoglobin, p-Vitamin-D, b-leucocytes, b-thrombocytes, p-LDH, p-bilirubin, p-ALAT, p-alkaline phosphatase, p-creatinine, p-CRP, p-FSH, p-testosterone) differed between patients with or without PIF.
Dose volume parameters for the delineated bone sub-structures were compared between patients with PIF and without PIF. The full data set of dose volume parameters can be seen in supplementary table 1. The largest differences were seen between the sacral bone/ sacral alae and as these were the primary sites for PIF (and all patient but one had PIFs in sacral alae), these sub-volumes were used for further analyses (Table 2). For sacral bone and sacral alae (mean dose L and R) all the evaluated dose volume parameters (Max dose (Gy), mean dose (Gy), V20 Gy(%), V30 Gy(%), and V40 Gy(%)) were significantly higher in patients who subsequently developed PIFs. In figure 1 this is exemplified by box plots for sacral bone V30Gy(%), sacral alae V30Gy(%), sacral bone V20Gy(%), and sacral alae V20Gy(%), p-values were 0.019, 0.022, 0.038, and 0.030 respectively. Looking at the ROC curves for sacral bone V30 Gy(%) and sacral alae (mean of L/R) V30 Gy(%) the AUC were similar, 0.764 and 0.758 respectively, figure 2a and 2b.

Discussion

In this prospective study we found a high frequency of MRI identified PIFs at a median of 14 months after RT for anal cancer. We found that a large fraction of patients had pain in the pelvic bones that could be related to the sites where PIFs were most frequently found.

We are the first to provide a detailed suggestion for pelvic bone substructure delineation, and relate radiotherapy dose volume parameters to these substructures and the risk of PIF.

Only a few studies have investigated PIF after RT for anal cancer either separately or combined with other pelvic tumors in larger registry studies. The frequency of PIF in anal cancer has been found in up to 14% in these studies. All are retrospective studies, with varying imaging modality or based on registries and with no coinciding information on symptoms [3-5, 13, 14, 16-20]
Pelvic pain is a well-known late effect after pelvic RT [21], and PIF might be overlooked if the correct imaging protocol is not applied.

We used MRI in a prospective setup, with sequences and extent that was intended to detect PIF, further a dedicated MR-radiologist reviewed all scans. This could explain, in part, why we found such a high frequency compared to previously published studies on anal cancer referenced above. It is however, in the range of what have been seen after radiotherapy for cervical cancer [7, 8]. MRI as compared to CT and bone scans has a higher both sensitivity and specificity for detecting insufficiency fractures in general [10, 11, 22] and specifically related to detection (higher incidence) of PIF radiotherapy for cervical cancer [9]. MRI should thus be the preferred imaging modality if insufficiency fractures are suspected [12]. The natural course for development and resolution of PIFs after radiotherapy for anal cancer is not known. A recent report on PIFs after RT for gynecological malignancies showed, that 93% of PIFs were detected within 1 year, and that only 16.3% resolved at varying time-points within the follow-up period (median 12 months, range 2-47 months) [23]. Two large reviews also in gynecological cancer showed median time to detection from 8-39 month and 7.1-19 month respectively [7, 8]. Thus we assume that the timeframe (1-2 years) used in our study reveals the majority of fractures.

More than 80% of patients with PIF had pelvic pain, and most were classified as grade 1 or 2 bone pain. Pelvic pain could be caused by other mechanisms, therefore a definitive relation between pain and PIFs cannot ensured. However, no patients had pelvic recurrence as a cause of pain, and PIFs were located in the areas, where PIF were most frequently seen. Across studies around 50-60% of patients with PIF had pain located in areas with high frequency of PIFs (lower back, hips groin or pelvis) [7, 8]. In this study the frequency was higher, which could be caused by bias of the patients having knowledge of PIFs in the recent scan, further that patients with pain could be more prone to accept participation in the study. On the other hand, and even though not quantified, the primary
response of some patients to "Do you have pain in the pelvic area?", was "no", but...."I cannot sleep on my left side due to pain", or "No, but I cannot sit on a normal chair", and these patients were classified as having pain, and only caught by interview, which indicate that the frequency of pain might be underestimated in other studies.

Localization of PIFs in weight bearing areas is in accordance with what has been found in other studies [2]. We found several radiation dose levels to be associated with increased risk of PIF for both sacral bone, alae of the sacral bone and a tendency for sacroiliac joints, with the most pronounced difference for V30 Gy. This corresponds well to what we have previously found in rectal cancer, where we reported that V30 Gy to the sacroiliac joint differed between patients with and without PIF (ref xx). In a study by Mir et al [23] on gynecological cancer patients, they found all PIFs in the alae of the sacral bone (median 2 per patient). They investigated sacral bone dose (V15-V60 Gy) and found especially V40Gy correlated to risk of PIFs. Also in gynecological patients a dose effect curve for PIFs showed that a reduction of radiation dose (D50% from 40 GyEQD2 to 35 GyEQD2) decreased risk of PIF from 45% to 22% [24]. Others have found higher doses (50.4 Gy) related to risk of PIF in gynecological cancers [2]. Pathophysiological studies also indicate changes in osteoblast function with doses around 30 Gy and cell death around 50 Gy [2]. A high radiation dose (up to 64 Gy to the primary tumor) has previously been standard at our institution [ref xx], and applied to a proportion of patients in this trial. However, the maximal dose given to the sacral bone was <55 Gy, corresponding to the elektive dose range, which is within the range of a standard radiation dose [26]. The extent of the elective irradiated volumes is also within the standard for anal cancer [27]. Studies on recurrences have suggested that the superior boarder of the elective volume can be lowered in low risk patients, which would decrease radiation dose to sacral bone and sacral alae and probably the risk of PIF [28]. Treatment technique could also impact
the risk of PIF. Studies have shown decreased risk of PIF with IMRT compared to older techniques [8]. Even though highly speculative, the rotational arc therapy, used in this study, results in a low dose bath to the pelvic bones that could affect bone structure more wide-spread impact risk of PIF negatively. Due to the limited number of patients included, and the fact that all but one patient had insufficiency fractures in the alae of the sacral bone, we chose to focus on the dose volume relationships in these sub-volumes, and we found that the AUC for the ala of the sacral bone was similar to that of the full sacral bone, implying that focus could be confined to these sub-structures in the treatment plan process and optimization. A limitation to this study is the low number of included patients, therefore statistical significance should be interpreted with caution. However, based on the high frequency of PIF and relation to specific dose volume parameters, we decided to initiate a prospective trial to explore the potential of bone-sparing, optimized RT for reducing the frequency of PIF in anal cancer patients. This phase 2 trial has incorporated constraints and priority to pelvic bone substructures in a two-step planning process, with one-year frequency of PIF as the primary end-point. We and others have already described, that bone sparing RT is possible when incorporated into the dose planning process in retrospective planning studies [29, xx], but until now it has not been implemented in prospective clinical studies. Here we provide a delineation guideline for pelvic bone sub-structures used in this study and illustrations to support this.

Conclusion.

A high proportion of patients treated with RT for anal cancer had radiologically confirmed PIFs approximately one year after treatment detected by MRI. A significant proportion of the patients had pelvic pain in the sites were PIFs were most frequently found.

Detailed delineation of pelvic bone sub-structures revealed relation of specific dose volume parameters to the risk of PIF and can be used for plan optimization in future clinical trials.
References


[25] xx


[30] xx

Figure captions:
Figure 1.
Figure 1. Box plots showing median, interquartile ranges, range and outliers for patients without and with PIF. Os sacrum V20 Gy(%) (green), os sacrum V30 Gy(%) (blue), Sacral alae V20 Gy(%) (orange), and sacral alae V30 Gy(%) (red) are shown. All are significantly higher in patients who developed PIF.
Figure 2. Receiver operating characteristic curves of all patients and A. V30 Gy(%) to the sacral bone as a predictor of PIF and (area under curve (AUC)= 0.7637) and B. V30 Gy(%) to the alae of the sacral bone (mean of left and right) as a predictor of PIF (AUC=0.7582).

<table>
<thead>
<tr>
<th></th>
<th>All patients n=27</th>
<th>Patients with PIF n=14</th>
<th>Patients w/o PIF N=13</th>
<th>p-values</th>
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</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>64 (43-74)</td>
<td>62 (43-72)</td>
<td>66 (45-74)</td>
<td>p=0.63</td>
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<tr>
<td>Gender, female (n,%)</td>
<td>22 (81.5%)</td>
<td>14 (100%)</td>
<td>8 (61.5%)</td>
<td>p=0.01</td>
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<tr>
<td>Baseline BMI (median, range)</td>
<td>26 (18.1 -32.1)</td>
<td>26.2 (19-29.5)</td>
<td>25.3 (18.1-32.1)</td>
<td>p=0.51</td>
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<td>Baseline PS</td>
<td>0</td>
<td>24 (96)</td>
<td>14 (100)</td>
<td>10 (91)</td>
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<td></td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Clinical T-stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>7 (25.9%)</td>
<td>4 (26.6%)</td>
<td>3 (23.1%)</td>
<td>p=0.73</td>
</tr>
<tr>
<td>T2</td>
<td>14 (51.9%)</td>
<td>7 (50.0%)</td>
<td>7 (53.9%)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1 (3.7%)</td>
<td>1 (7.1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>5 (18.5%)</td>
<td>2 (14.3%)</td>
<td>3 (23.1%)</td>
<td></td>
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<tr>
<td>Tumor size, cm (median, range)</td>
<td>2.9 (1-7)</td>
<td>2.55 (1-6)</td>
<td>3.0 (2-7)</td>
<td>P=0.34</td>
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<td>Clinical N-stage</td>
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<tr>
<td>N0</td>
<td>22 (81.5%)</td>
<td>11 (78.6%)</td>
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<tr>
<td>N1</td>
<td>4 (14.8%)</td>
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<tr>
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<td>64 Gy</td>
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<td>10 (71.4%)</td>
<td>7 (53.8%)</td>
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<td>2 (14.3%)</td>
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<tr>
<td>54 Gy</td>
<td>5 (18.5%)</td>
<td>2 (14.3%)</td>
<td>3 (23.1%)</td>
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<td>Chemotherapy</td>
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<tr>
<td>Cisplatin and/or 5 FU None</td>
<td>22 (81.5%)</td>
<td>13 (93%)</td>
<td>9 (69%)</td>
<td>P=0.11</td>
</tr>
<tr>
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<td>VMAT 2 arc</td>
<td>7 (26%)</td>
<td>6 (43%)</td>
<td>1 (8%)</td>
<td>p=0.11</td>
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<tr>
<td>VMAT 3 arc</td>
<td>17 (63%)</td>
<td>7 (50%)</td>
<td>10 (77%)</td>
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<tr>
<td>VMAT 4 arc</td>
<td>3 (11%)</td>
<td>1 (7%)</td>
<td>2 (15%)</td>
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<td>10 (77%)</td>
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<td>Grade 1</td>
<td>6 (22%)</td>
<td>5 (36%)</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>8 (30%)</td>
<td>6 (43%)</td>
<td>2 (15%)</td>
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</tr>
</tbody>
</table>

Table 1. Baseline and treatment characteristics.
<table>
<thead>
<tr>
<th></th>
<th>All patients n=27 median (IQR)</th>
<th>Patients with PIF n=14 median (IQR)</th>
<th>Patients w/o PIF n=13 median (IQR)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sacral bone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose (Gy)</td>
<td>52.8 (51.1-54.9)</td>
<td>54.2 (52.8-55.1)</td>
<td>51.8 (50.1-52.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>36.8 (34.5-40.9)</td>
<td>39.4 (36.1-41.7)</td>
<td>35.1 (31.6-37.4)</td>
<td>0.044</td>
</tr>
<tr>
<td>V20 Gy (%)</td>
<td>87.9 (77.7-91)</td>
<td>90 (84.1-96.3)</td>
<td>79.1 (74.6-88.6)</td>
<td>0.038</td>
</tr>
<tr>
<td>V30 Gy (%)</td>
<td>73.6 (68-82.7)</td>
<td>81.8 (73.5-84.1)</td>
<td>69.6 (60.9-73.6)</td>
<td>0.019</td>
</tr>
<tr>
<td>V40 Gy (%)</td>
<td>52.3 (46.5-61.4)</td>
<td>59.4 (49.9-64.4)</td>
<td>49.8 (35.9-58.5)</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Sacral alae (mean L/R)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose (Gy)</td>
<td>51.9 (50.3-53.1)</td>
<td>52.9 (50.9-53.8)</td>
<td>51.1 (49.8-51.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>36.3 (34-40)</td>
<td>38.4 (35.1-42.2)</td>
<td>34.5 (26.2-36.3)</td>
<td>0.026</td>
</tr>
<tr>
<td>V20 Gy (%)</td>
<td>87.9 (77-91.7)</td>
<td>90.6 (85.9-96.8)</td>
<td>78.7 (61-88.4)</td>
<td>0.030</td>
</tr>
<tr>
<td>V30 Gy (%)</td>
<td>75.5 (67-84.5)</td>
<td>81.2 (75-89.2)</td>
<td>68.6 (43.8-75.5)</td>
<td>0.022</td>
</tr>
<tr>
<td>V40 Gy (%)</td>
<td>50.3 (40.1-63.5)</td>
<td>52.2 (49.2-64.5)</td>
<td>44.2 (22.1-51.6)</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>SI-joints (mean L/R)</strong></td>
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</tr>
<tr>
<td>Max dose (Gy)</td>
<td>52.3 (49.9-53.5)</td>
<td>52.5 (50.1-53.6)</td>
<td>51.7 (49.8-52.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean dose (Gy)</td>
<td>32.1 (29.3-36)</td>
<td>32.5 (31.3-37.7)</td>
<td>29.9 (19.8-33.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>V20 Gy (%)</td>
<td>78.6 (68.8-88.6)</td>
<td>82.7 (74.5-95.3)</td>
<td>73.2 (42.9-87.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>V30 Gy (%)</td>
<td>60.8 (55-72.8)</td>
<td>61.0 (58.5-76.8)</td>
<td>60.4 (28.1-68.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>V40 Gy (%)</td>
<td>32.3 (23.3-42.7)</td>
<td>35.4 (30.9-43.7)</td>
<td>29.9 (10.9-34.1)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Table 2. Dose volume relationships for sacral bone and sub-structures.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: