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Short-course preoperative radiotherapy increases pelvic fracture risk in rectal cancer

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ABSTRACT

Introduction: Pelvic insufficiency fractures (PIFs) are adverse events associated with chemoradiotherapy (CRT) administered preoperatively in rectal cancer, with incidences of 0–33.6% reported in the literature. Data on PIFs after 5 × 5 Gy fractionated short-course radiotherapy (SCRT) using highly conformal radiotherapy techniques such as volumetric modulated arc therapy (VMAT) is limited.

Methods: The Turku University Hospital colorectal cancer database was searched for patients operated on for stage I–III rectal cancer during the years 2014–2018. The hospital's routine follow-up includes a 2-year computed tomography (CT) scan, which was systemically re-evaluated to detect PIFs. Only radiotherapy delivered using VMAT and image-guided approaches was included. Baseline demographics, tumor data, and dose-volume data were collected to identify risk factors for PIFs.

Results: Median time to CT scan was 24 months. Among the 164 patients analyzed, the 2-year PIF incidence was 22.2% for SCRT (n = 12/54, OR 9.1 (CI95% 1.9–42.9), p = 0.004), 9.1% for CRT (n = 4/44, OR 3.2 (CI95% 0.6–18.3), p = 0.13) and 3.0% (n = 2/66, reference) for those operated on without radiotherapy. The PIF incidence was not explained by differences in dose-volume data in either the SCRT or CRT groups. Fracture risk was higher in women, up to 50% after SCRT.

Conclusions: Every fifth patient treated with SCRT and rectal surgery presented with a PIF. Critical bony structures to be avoided during radiotherapy contouring could not be identified. Clinicians, especially those involved with the follow-up of rectal cancer, should be aware of this potentially debilitating and surprisingly common adverse event.

1. Introduction

Radical surgery with total mesorectal excision is the current mainstay of curative-intent rectal cancer treatment [1,2]. Preoperative chemoradiotherapy (CRT) and short-course radiotherapy (SCRT) may be utilized in locally advanced rectal cancer, or when intermediate-risk features are present, to reduce the risk of local recurrence [1,3,4,5]. In the case of tumors with a threatened margin, i.e. involved mesorectal fascia, CRT has resulted in better surgical outcomes than long-course radiotherapy alone [6]. The recently introduced total neoadjuvant treatment approach may increase the use of SCRT in the near future [7].

The commonest late adverse effects following preoperative radiotherapy include gastrointestinal, urinary, and sexual dysfunction [8,9,10]. CRT results more often in these problems than SCRT [11]. A less common late adverse effect is pelvic insufficiency fracture (PIF). In previous studies, the PIF incidence after CRT has been 3.1–7.1%

Abbreviations: PIF, pelvic insufficiency fracture; RT, radiotherapy; CRT, chemoradiotherapy; SCRT, short-course radiotherapy; VMAT, volumetric modulated arc therapy; CT, computed tomography; SI, sacroiliac; DVH, Dose-volume histogram; ECOG, Eastern Cooperative Oncology Group; PTV, planning target volume; IMRT, intensity-modulated radiation therapy; MRI, magnetic resonance imaging; GTV, gross tumor volume; CTV, clinical target volume.

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[10,12,13], except for a single study that reported no PIFs at all [11] and two studies that reached a rather exceptional incidence of 33–33.6% with their MRI-based imaging [14,15]. For SCRT, the literature reports a PIF incidence of 1–5.3% [16,17,18,19]. Of these studies, only two have systematically reviewed the follow-up images [13,14], and only one has primarily used the modern volumetric modulated arc therapy (VMAT) technique [15]. Independent risk factors for PIFs in previous studies have been older age, female sex, and osteoporosis [12,13,14].

Our aim was to determine the PIF rate in rectal cancer patients treated with modern VMAT-based SCRT or CRT. Theoretically, larger radiation fractions delivered during SCRT than during CRT might result in a higher PIF incidence [20], and therefore we explored possible differences in the dose-volume distribution between fractured and non-fractured patients.

2. Material and Methods

2.1 Ethics

This study is based on our previous retrospective cohort of colorectal cancer patients [21], covering the years 2014–2018 when VMAT had become routine practice in our institution. The study was approved by the Institutional Review Board of Turku University Hospital, Turku, Finland (T176/2019). In Finland, a register-based study does not require informed consent from the study subjects.

2.2 Patients

All patients with non-metastatic stage I–III rectal cancer (n = 217) at the time of diagnosis were initially screened from our database [21]. Our hospital's follow-up protocol includes a single diagnostic routine CT scan at roughly 2 years postoperatively for all CRT patients and all SCRT patients who have received postoperative adjuvant chemotherapy. Frail and co-morbid patients are not included in the intense follow-up. To extend the study population, all CT examinations from approximately 1.5 to 2.5 years after surgery, also in the metachronous metastatic setting, were included. Exclusion criteria were: not allocated in the intense follow-up (n = 39), non-VMAT patients (n = 2), and follow-up elsewhere (n = 6).

The patients (n = 170) were designated into three cohorts: those who received preoperative SCRT, those who received preoperative CRT, and those who underwent surgery only without any preoperative radiotherapy. In Finland, SCRT followed by immediate surgery is recommended in rectal tumors with intermediate risk factors, namely clinical staging of T3c/d, extramural venous invasion, cN2-status, or extranodal lymphatic extension. CRT with a 7–11 weeks' delay to surgery is recommended when the mesorectal fascia is compromised or there are lymph node metastases outside the mesorectal fascia [22].

2.3 Radiotherapy

CRT was administered with 45 Gy to the elective pelvic nodal area in 25 fractions followed by a 5.4 Gy boost dose to the primary tumor volume in 3 fractions. All CRT patients received capecitabine 1650 mg/m^2 daily during the radiotherapy. Surgery was performed 5–8 weeks after radiotherapy. SCRT was administered with 25 Gy in 5 fractions to the tumor and the elective nodal area, followed by immediate surgery. The mesorectal, pelvic presacral, and internal iliac lymph nodes were invariably included in the radiation field, whereas the inclusion of the abdominal presacral, obturator, external iliac, and inguinal lymph nodes was dependent on the extent of the disease, identically for both SCRT and CRT. The only exception was the involvement of the inguinal nodal areas, which obliged the selection of CRT.

Plan optimization criteria varied between patients as they were treated over five years' period. Bones were not delineated pre-treatment, except for femoral heads, which were used to minimize the dose to the joints. Treatment planning for each patient was performed with two 6 MV VMAT arcs (three plans with three VMAT arcs) using the Eclipse treatment planning system (v11.0 and v13.6, Varian Medical Systems Finland Oy, Helsinki, Finland). Treatments were performed with Varian linear accelerators (Varian Medical Systems, Palo Alto, CA). Both CRT and SCRT were given with daily image guidance using kV X-ray imaging.

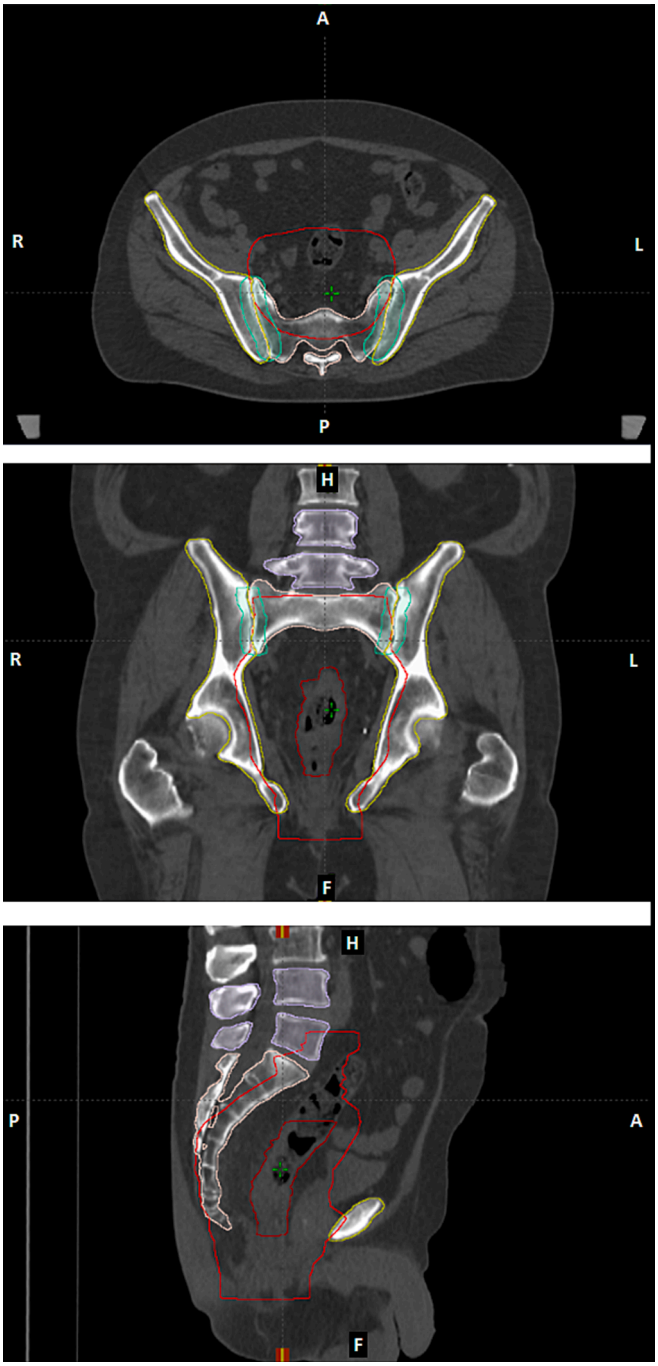

Fig. 1. Contouring of bony structures. From the top: Axial, coronal, and sagittal view of a treatment planning CT scan. Bone structures contoured as described in the dose evaluation section: sacrum (light brown), iliac bone (yellow), L4–L5 vertebrae (purple) and sacroiliac joint (light green). Also PTV (red) and GTV (dark red) are visualized. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

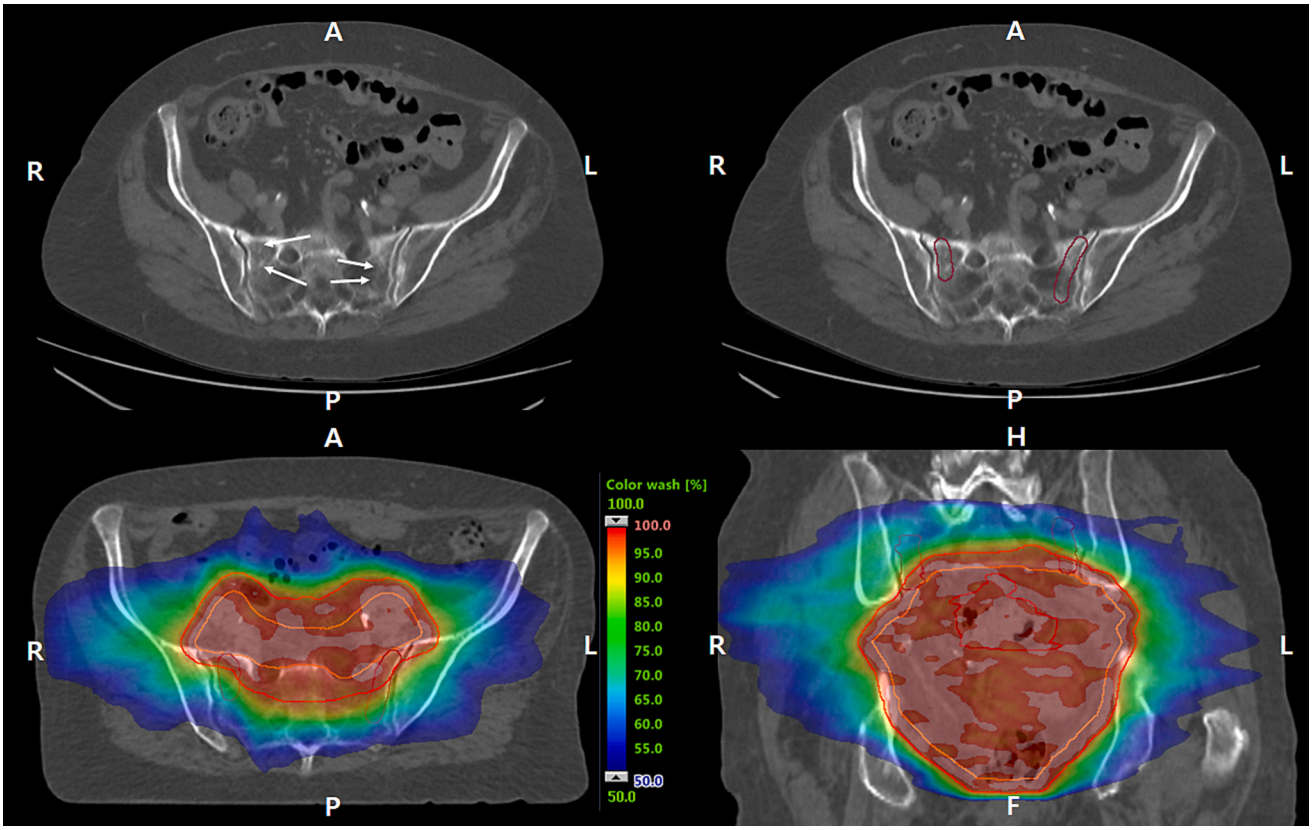

Fig. 2. Example of a pelvic insufficiency fracture. Top left: axial view of a 2-year control CT scan. The fractures appear as slightly sclerotic lines (arrows). Top right: fracture regions contoured with a 1 cm brush (dark red contour). Bottom left: corresponding axial slice from a planning CT scan. The dose is shown in color wash. The contoured fracture (dark red) has been copied to the planning scan with bony registration. CTV and PTV are also presented (orange and red contour, respectively). Bottom right: corresponding coronal planning CT slice with identical features, additionally displaying GTV contour (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.4 Screening for fractures in follow-up CTs

Multi-detector CT with intravenous contrast enhancement is part of our hospital's post-treatment follow-up protocol for rectal cancer patients with a high risk of relapse. The scan is performed roughly at the 2-year time point after surgery. CT images were systematically analyzed by the musculoskeletal radiologist (IK) of the study group. A PIF was defined as a radiolucent fracture line with or without endosteal callus, endosteal callus formation only, or cortical disruption [23]. A soft tissue mass does not belong to a PIF [24]. The bony pelvis was divided into four regions for fracture localization: sacrum, iliac bone, pubic rami, and L4/L5 vertebrae. Due to the ring-like structure of the pelvis and the consequent predisposion to multiple simultaneous fractures, fractures in different regions were considered as one PIF, with the exception of the vertebrae.

2.5 Dose-volume histogram analysis

Pelvic bone structures were delineated retrospectively on the treatment planning CT scans. Automatic segmentation software (MVision AI, Helsinki, Finland) was initially used for contouring the sacrum, iliac bone, and L4–L5 vertebrae. All contours were manually reviewed. In addition, sacroiliac (SI) joints were manually contoured using a 2 cm diameter brush, including the joint space between the sacral and iliac bones (Fig. 1).

For patients with a PIF, fracture regions were manually contoured on the 2-year follow-up CT scan using a two-dimensional 1 cm diameter brush along the fracture line (Fig. 2). The musculoskeletal radiologist (IK) of the study group reviewed all fracture contours. The control CT was registered with the planning CT using Eclipse bony registration and the fracture contouring was copied on the planning CT for dose evaluation.

Dose-volume histograms (DVH) were re-calculated for the following structures: total bone (including sacrum and iliac bone), SI joints, sacrum, iliac bone, L4–L5 (only included if the treatment field extended to vertebra level), and fracture region.

Dose-volume relationships were evaluated for both groups (CRT and SCRT) and compared between patients with and without PIFs. For the CRT group, V20Gy, V30Gy, and V45Gy were chosen to represent low, mid, and high dose ranges as described by Kronborg et al. [15]. Using the linear-quadratic model and the bone α/β value of 2.3 Gy for late bone damage [25,26], we calculated dose regions for SCRT group with different dose per fractions, 2.5 Gy, 3.5 Gy and 4.9 Gy, so that the equivalent dose in 2 Gy fractions (EQD2) for low, mid and high dose ranges was equal in both groups. This resulted in V12.5 Gy, V17.5 Gy, and V24.5 Gy representing low, mid, and high dose ranges, respectively.

2.6 Statistics

Due to the limited number of patients and events, the 2-year fracture rate was tested with the 2-sided Fisher's exact test. Comparison between explanatory variables was performed either with a Chi-square test or ANOVA with SPSS-integrated Bonferroni corrections when multiple testing was performed. Relapse-free survival was calculated with the Kaplan–Meier log-rank method. SPSS ver. 27 (IBM) was used for statistical analyses.

Table 1
Patient and disease characteristics of the three study groups.

Patient characteristics	No RT n = 66	SCRT n = 54	CRT n = 44	p
Women n (%)	22 (33)	18 (33)	18 (41)	0.67
Age median (IQR), y	71 (63–79)	66 (60–72)	68 (59–77)	NA
Age mean (range), y	69 (42–91)	66 (49–87)	63 (37–78)	0.02
BMI mean (range), kg/m^2	27.3 (19–49)	26.1 (16–33)	26.5 (18–40)	0.41
ECOG performance status 0 n (%)	12 (18)	7 (13)	8 (18)	0.51
ECOG performance status 1 n (%)	40 (61)	44 (81)	32 (73)	
ECOG performance status 2–3 n (%)	2 (3)	2 (4)	4 (9)	
ECOG unknown n (%)	12 (18)	1 (2)	0 (0)	NA
Charlson comorbidity index 0 n (%)	47 (71)	40 (74)	33 (75)	0.46
Charlson comorbidity index > 0 n (%)	19 (29)	14 (26)	11 (25)	
Current smoker n (%)	7 (11)	13 (24)	6 (14)	0.10
Former smoker n (%)	14 (21)	10 (19)	16 (36)	
Never smoker n (%)	36 (55)	26 (48)	19 (43)	
Smoking status unknown n (%)	9 (14)	5 (9)	3 (7)	NA
Disease characteristics				
Operated R0 n (%)	59 (89)	46 (85)	33 (75)	0.38
pStage I n (%)	5 (8)	10 (19)	10 (23)	0.03
pStage II n (%)	24 (36)	14 (26)	19 (43)	
pStage III n (%)	37 (56)	30 (56)	13 (30)*	
Adjuvant chemotherapy n (%)	42 (64)	37 (69)	31 (70)	0.73
Local recurrence prior/at 2-y CT n (%)	5 (8)	2 (4)	5 (11)	0.35
Metastatic disease prior/at 2-y CT n (%)	15 (23)	16 (30)	14 (32)	0.53

Abbreviations: RT: radiotherapy; SCRT: short-course radiotherapy; CRT: chemoradiotherapy; IQR: interquartile range; NA: not applicable; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; pStage: pathological stage; CT: computed tomography.
*Two patients in the CRT group are not included in stages I–III; one pStage IV patient (two intraoperatively observed peritoneal metastatic nodules that were resected along with the primary tumor) and one patient with an unknown pStage (patient refused surgery after CRT).

Table 2
Patient and disease characteristics of patients who received preoperative radiotherapy (SCRT or CRT) and either did or did not present with a PIF at follow-up.

Patient characteristics	PIF present n = 16	PIF absent n = 82	p
Women n (%)	12 (75)	24 (29)	0.001
Age median (IQR), y	72 (67–77)	66 (57–71)	NA
Age mean (range), y	69 (38–80)	64 (37–87)	0.11
BMI mean (range), kg/m^2	24.7 (18–33)	26.6 (16–39)	0.09
ECOG performance status 0 n (%)	2 (13)	13 (16)	0.13
ECOG performance status 1 n (%)	11 (69)	65 (79)	
ECOG performance status 2–3 n (%)	2 (13)	4 (5)	
ECOG unknown n (%)	1 (6)	0 (0)	NA
Charlson comorbidity index 0 n (%)	11 (69)	62 (76)	0.18
Charlson comorbidity index > 0 n (%)	5 (31)	20 (24)	
Current smoker n (%)	3 (19)	16 (20)	0.16
Former smoker n (%)	1 (6)	25 (30)	
Never smoker n (%)	11 (69)	34 (41)	
Smoking status unknown n (%)	1 (6)	7 (9)	NA
Disease characteristics			
Operated R0 n (%)	13 (81)	66 (80)	0.90
SCRT n (%)	12 (75)	42 (51)	NA
CRT n (%)	4 (25)	40 (49)	NA
pStage I n (%)	6 (38)	14 (17)	0.13
pStage II n (%)	2 (13)	31 (38)	
pStage III n (%)	8 (50)	35 (43)*	
Adjuvant chemotherapy n (%)	8 (50)	60 (73)	0.08
Local recurrence prior/at 2-y CT n (%)	1 (6.3)	6 (7.3)	1.0
Metastatic disease prior/at 2-y CT n (%)	7 (44)	23 (28)	0.24

Abbreviations: SCRT: short-course radiotherapy; CRT: chemoradiotherapy; PIF: pelvic insufficiency fracture; IQR: interquartile range; NA: not applicable; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; pStage: pathological stage; CT: computed tomography.
*Two patients in the PFI absent group are not included in stages I-III; one pStage IV patient (two intraoperatively observed peritoneal metastatic nodules that were resected along with the primary tumor) and one patient with an unknown pStage (patient refused surgery after CRT).

3. Results

During follow-up 4 patients died and 2 presented with pelvic bone metastases prior to the 2-year CT scan, and were censored, resulting in 54 SCRT, 44 CRT, and 66 non-radiotherapy (control) patients for analysis (Table 1). Median time to the 2-year CT scan was 24.2 months (IQR 22.8–25.4 months). Control group patients were on average 4 years older. pStage I was the most frequent in the CRT group, probably reflecting the downstaging effect of CRT. No differences in sex, BMI, Eastern Cooperative Oncology Group (ECOG) performance status, smoking status, comorbidities, or 2-year cancer recurrence rate were observed. The 5-year relapse-free survival of CRT, SCRT, and surgery-only groups was 61%, 65%, and 71%, respectively, with no statistically significant difference ($p = 0.0589$, Supplementary Fig. 1).

A total of 18 PIFs were observed in 18 patients, 12 in the SCRT group, 4 in the CRT group, and 2 in the control group, resulting in a 2-year PIF incidence of 22.2% (OR 9.1 (95CI 1.9–42.9), $p = 0.004$) in the SCRT group, 9.1% (OR 3.2 (95CI 0.6–18.3), $p = 0.13$) in the CRT group, and 3.0% in the non-radiotherapy group (reference). Table 2 outlines the patient characteristics between patients with and without PIF who had received radiotherapy, where the majority of patients with PIFs were women ($p = 0.001$). Fracture rate for women was 9/18 (50%) after SCRT, 3/18 (17%) after CRT and 1/22 (5%) in the control group. For men, respective numbers were 3/36 (8%), 1/26 (4%) and 1/44 (2%). No patients with PIF after radiotherapy had osteoporosis, rheumatic diseases or excessive alcohol consumption as fracture predisposing conditions. Only 7 out of the 18 PIFs (39 %) were noted in the original radiologist's report, leaving 11 to be observed in the present study for the first time. The observed locations of PIFs were sacrum (SCRT 10, CRT 4, no radiotherapy 2), pubic bone (SCRT 3, CRT 0, no radiotherapy 1), and L4-5 vertebrae (SCRT 1, CRT and no radiotherapy 0).

No CT scans were performed due to pelvic pain. Of the 18 patients with PIFs, 7 were imaged as part of the routine 2-year follow-up time point, 3 were imaged during follow-up but earlier due to rise in carcinoembryonic antigen or new susceptible symptoms, and 8 were imaged in a metastatic setting for response evaluation or follow-up in case of no current antineoplastic treatment.

The DVH analysis revealed no differences between the patients with and without PIF in terms of distribution of different dose levels into various bony structures within the treatment field or planning target volume (PTV) (Table 3). The dose-volume data of the delineated fracture sites is gathered in Table 4. 22 patients were treated in the prone and 76 in the supine position. 6 patients received a slightly variant radiation dosing in the CRT group (Supplementary Table 1). 13 SCRT patients were treated up to L5 level; 15 CRT patients were treated up to L5 level and 2 up to L4 level.

4. Discussion

To our knowledge, this is the first study to examine the incidence of PIFs after SCRT administered exclusively with the modern VMAT technique. Furthermore, only two studies have systematically explored the PIF incidence after CRT [13,14], and only one previous study has analyzed DVHs to identify possible associations between dose distribution and PIFs after CRT [15]. We reviewed the imaging examinations

Table 3
Treatment and dose-volume characteristics of CRT and SCRT patients.

		CRT				SCRT			
		All patients (n = 44)	PIF absent (n = 40)	PIF present (n = 4)	p-value	All patients (n = 54)	PIF absent (n = 42)	PIF present (n = 12)	p-value
	PTV 1, ccm (median, IQR)	1853 (1655–2407)	1846 (1655–2407)	2243 (1940–2533)	0.73	1741 (1392–1999)	1741 (1357–2002)	1772 (1591–1967)	0.56
	PTV 2, ccm (median, IQR)	626 (461–910)	626 (461–910)	667 (551–953)	0.46	–	–	–	
Mean dose, Gy	Pelvic bones* (median, IQR)	31.6 (29.1–34.4)	30.9 (29.1–34.4)	34.1 (31.5–34.8)	0.79	15.7 (14.6–16.8)	15.7 (14.5–16.8)	15.9 (15.5–16.7)	0.54
	SI joint (median, IQR)	34.3 (31–39.4)	34.1 (31–39.5)	37 (34.5–38.3)	0.86	18.2 (16.5–20.1)	18.2 (16.1–20.1)	17.7 (17.4–20)	0.97
	Sacrum (median, IQR)	38.4 (35.7–42)	38.2 (35.7–42.1)	40.9 (38.8–41.5)	0.89	20.3 (18.5–21.9)	20.4 (18.3–22)	20.2 (18.5–20.6)	0.61
	Iliac bone (median, IQR)	28.8 (26.7–32.1)	28.6 (26.7–32.1)	31.8 (28.8–32.6)	0.80	15.2 (13.2–15.3)	15.5 (13–15.3)	15.1 (14.1–15.1)	0.54
	L4-L5** (median, IQR)	16.7 (11.3–20.5)	16.7 (11.6–23.2)	14 (12.6–15.3)	0.78	6.1 (4.8–10.6)	5.5 (4.5–10.1)	6.3 (6.1–8.8)	0.89
Low dose, %	Pelvic bones* (median, IQR)	80 (74.7–84)	79.8 (74.7–84.1)	81.4 (76–83)	0.62	69.8 (65.2–75.4)	69.4 (63.3–77)	70.9 (67.8–75.3)	0.46
	SI joint (median, IQR)	91.2 (79.5–99.4)	88.7 (79.5–99.4)	98.6 (91.3–99.8)	0.45	84.7 (73.2–91.3)	85.7 (68.4–92.3)	84.1 (78.9–88.7)	0.41
	Sacrum (median, IQR)	93.5 (88.5–98.6)	93.1 (88.5–98.1)	97.5 (92.2–98.7)	0.63	87.6 (74.9–93.3)	88.2 (75.1–93.3)	85.6 (76.6–90.1)	0.69
	Iliac bone (median, IQR)	76.2 (70–79.3)	76.2 (70–79.6)	75.9 (70.1–77.8)	0.38	64.4 (58.9–71.2)	64.2 (57–72.4)	66.9 (63.4–70.4)	0.29
	L4-L5** (median, IQR)	32.3 (18.6–47)	32.3 (18.6–56.7)	28.2 (23.4–32.9)	0.87	15.2 (11.4–38.2)	15 (10.9–35.1)	15.4 (14.8–28.6)	0.97
Mid dose, %	Pelvic bones* (median, IQR)	59.8 (50.8–66.6)	59.1 (50.8–65.2)	67.5 (60.4–70)	0.53	44.4 (37.2–50)	42.6 (36.9–49.8)	46.1 (43–49.6)	0.41
	SI joint (median, IQR)	69.8 (55.7–88.8)	68.3 (55.5–89.1)	76 (68.4–83)	0.61	59.1 (42.1–69.9)	56.7 (40.2–69.9)	62.6 (45.1–72.3)	0.51
	Sacrum (median, IQR)	80.4 (71.9–91.7)	80.1 (71.4–91.7)	90.6 (85.1–92.2)	0.44	72.7 (62–83.7)	75.8 (60.4–85.9)	70.4 (65–77.8)	0.63
	Iliac bone (median, IQR)	52.2 (43.6–60.2)	50.7 (43.6–59.7)	58.5 (51.6–61.5)	0.82	35.4 (30.3–40.4)	33.5 (30–40.3)	37.7 (34.6–40.5)	0.49
	L4-L5** (median, IQR)	22.9 (12.7–38.5)	23.4 (14.4–42.4)	17.8 (15.3–20.4)	0.78	10.7 (8.2–24.9)	9.1 (7.8–28.1)	12.2 (10.6–18)	0.88
High dose, %	Pelvic bones* (median, IQR)	18.8 (12–25.9)	18.2 (12–23.6)	25.9 (22.3–26.7)	0.66	11.9 (8.7–17.5)	11.1 (8.7–17.6)	12.5 (9.8–16.5)	0.96
	SI joint (median, IQR)	18.7 (13–37.1)	17.7 (12.7–37.2)	23.5 (20.6–26)	0.67	17.4 (10–26.3)	14.7 (9.6–26.3)	19.3 (13.4–27.9)	0.59
	Sacrum (median, IQR)	39.3 (27.7–50.5)	36.5 (26.4–51.1)	40.3 (36.6–41.3)	0.70	30 (21–46.5)	28.5 (21–47.9)	35 (24.3–44.9)	0.83
	Iliac bone (median, IQR)	11.5 (7.9–18.9)	11.1 (7.9–17.7)	20.1 (16.2–21.9)	0.25	5.3 (3.9–7.4)	6 (4–8.2)	4.7 (4–5.5)	0.30
	L4-L5** (median, IQR)	5.5 (3.8–8.7)	5.7 (3.9–10.7)	3.8 (3.7–4)	0.66	4.2 (2.5–8.6)	4.9 (2.5–11.5)	2.8 (2.2–5.4)	0.65

Low, mid and high dose ranges for CRT were V20Gy, V30Gy and V45Gy, and for SCRT V12.5 Gy, V17.5 Gy, and V24.5 Gy.
*Includes sacrum and iliac bone.
**Only included if the treatment field extended to the L4-L5 level.
Abbreviations: CRT: chemoradiotherapy; SCRT: short-course radiotherapy; IQR: interquartile range.

Table 4
Fracture dose-volume characteristics. Low, mid and high dose ranges for CRT were V20Gy, V30Gy and V45Gy and for SCRT V12.5 Gy, V17.5 Gy and V24.5 Gy, respectively.

	All fractions (n = 16)	CRT (n = 4)	SCRT (n = 12)
Volume, ccm (median, IQR)	26 (16–37)	21 (14–29)	27 (18–38)
Mean dose, Gy (median, IQR)	22.4 (20.4–27.9)	40.1 (37.8–43.2)	21 (19.8–23.4)
Low dose, % (median, IQR)	99.3 (92.3–100)	99.7 (97.8–100)	98.6 (88.8–99.7)
Mid dose, % (median, IQR)	82.6 (72–97.4)	91 (81.2–97.9)	78.3 (71.8–95.5)
High dose, % (median, IQR)	41.7 (24–61.7)	42.5 (37.9–51.3)	36.8 (17.5–61.7)

Abbreviations: CRT: chemoradiotherapy; SCRT: short-course radiotherapy; IQR: interquartile range.

systematically to minimize fracture incidence underestimation. A remarkably high PIF incidence after SCRT was observed, in nearly every fifth patient, while the PIF incidence after CRT was close to the average of previous studies [10,11,12,13,14,15]. While CRT outperforms SCRT in local control among locally advanced rectal cancer, the forthcoming total neoadjuvant treatment, e.g. according to the RAPIDO trial protocol [7], is likely to increase the use of SCRT. Thus, the fracture issue may become even more important in the future.

Kim et al. reported that only 19 of the 35 fractures (54%) were mentioned in the routine radiologist's reports [13], which is quite close to our 39%. Thus, around half of the fractures seem to be missed without a systematic review. Many of the previous studies giving an estimate of PIF incidence after preoperative radiotherapy have collected a broad spectrum of late toxicities and do not specifically focus on fracture incidence [3,8,10,11,16,17,18,19]. Compared to fracture-focused studies, the estimates inevitably are somewhat rough. Even among the fracture-oriented studies, only Kim et al. and Jørgensen et al. conducted a systematic review of radiological examinations, leading to PIF incidences of 7.1% and 33.6%, respectively [13,14].

Most earlier studies have utilized the traditional 3D conformal radiotherapy [3,10,11,12,13,16,17,18,19], which results in more late toxicity, arguably including PIFs, compared to more modern intensity-modulated radiation therapy (IMRT) and VMAT techniques [27]. Two studies do not specify the radiotherapy technique used [8,28]. Only Jørgensen et al. and Vitzthum et al. have used primarily IMRT [14,29], while the study by Kronborg et al. is the only study with a mainly arc-based technique [15]. Since IMRT and VMAT are mainly used nowadays, much of the previous fracture incidence data cannot be applied directly.

Two previous studies have directly compared long- and short-course radiotherapy in terms of PIF risk. Bujko et al. collected a large selection of late toxicities during a clinical trial, without focusing on fractures. In the study population of 312 patients, they found only one fracture in a patient treated with SCRT and none in patients treated with CRT [3], which probably reflects a low PIF diagnosis sensitivity in that study. Kang et al. focused solely on pelvic fractures, picking the relevant ICD-9 codes from a large national database of over 30,000 Taiwanese patients. In their multivariable Cox regression analysis, the difference in PIF incidence between long-course and short-course radiotherapy was not significant [28].

The patient characteristics of our three cohorts were well balanced (Table 1), with only a modest difference in age. Comparing radiotherapy-treated patients who presented with a PIF with those who did not, female sex seemed to be the only clinical characteristic associated with an increased fracture risk. This is no surprise, since female sex has earlier proven to be one of the few independent risk factors for post-radiotherapy PIFs [12,13,14]. The indications for CT scans were identical between the groups: PIF patients had no additional CT scans due to pelvic pain, which could have caused enrichment in the PIF population.

Until recently, dosimetry studies defining protective skeletal dose limits were non-existent albeit called for [30]. Kronborg et al. analyzed the DVH of 27 patients receiving CRT, with a special effort to retrospectively make alternative treatment plans to minimize radiation to bone, but they were not able to suggest any thresholds or protective restrictions for radiotherapy planning [15]. Our study analyzed the DVHs of 98 radiotherapy-treated patients, 54 after SCRT and 44 after CRT. The dose parameters were meticulously compared between the fractured and non-fractured patients, separately for each treatment type. Despite a larger cohort, neither we could demonstrate a statistically significant difference in any dose parameter.

The limitations of our study include a single follow-up time point, considering that the median time for a PIF to develop has been 1.4–3.8 years in previous studies [12,13,28]. Our imaging time point of roughly 2 years postoperatively was not decided by the investigators but is part of the clinical routine follow-up. To expand the coverage, we accepted CT examinations from approximately 1.5 to 2.5 years after surgery, including the ones done in a metastatic setting, pelvic bone metastases excluded. Furthermore, magnetic resonance imaging (MRI) appears to be a more sensitive modality to detect PIFs than the CT which we utilized [23], as suggested by the relatively high PIF incidence of 33.6% observed by Jørgensen et al. [14]. Due to the retrospective nature of our study, however, we could not choose the imaging modality. Also, allocation to intense follow-up causes selection bias, which can be seen in the relatively long RFS in all three study cohorts. On the other hand, no differences apart from age were seen in patient characteristics between the cohorts, making them quite comparable. Systematic clinical staging data was not available retrospectively, and probably patients treated with CRT had more severe initial clinical stages than SCRT-treated patients. The more pronounced downsizing effect of CRT then resulted in comparable pathological stages between the treatment cohorts. Many of the previous PIF studies analyzed patients included in a randomized clinical trial [3,8,11,14,15,16,17], making them not substantially less selective than our study. Additional risk factors for insufficiency fractures like bone mineral densitometry or vitamin D concentrations of the study subjects were unavailable.

5. Conclusion

This study demonstrated a high incidence of PIFs after modern VMAT-delivered preoperative SCRT, every fifth patient presenting with a fracture, and up to 50% among women. An elevated PIF incidence was also confirmed in patients treated with CRT compared to those treated with surgery only. For SCRT/CRT planning, no dose-volume thresholds to diminish PIF risk could be found.

Declaration of Competing Interest

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Appendix A. Supplementary data

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