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FULL PAPER

Pelvic insufficiency fracture (PIF) incidence in patients treated with intensity-modulated radiation therapy (IMRT) for gynaecological or anal cancer: single-institution experience and review of the literature

LOUIS BAZIRE, MD, HAOPING XU, MD, JEAN-PHILIPPE FOY, MD, MALIKA AMESSIS, BSc, CAROLINE MALHAIRE, MD, KIM CAO, MD, ANNE DE LA ROCHEFORDIERE, MD and YOULIA M KIROVA, MD

Department of Radiation Oncology, Institut Curie, Paris, France

Address correspondence to: Dr Louis Bazire
E-mail: *louis.bazire@curie.fr*

Objective: To summarize the results of pelvic insufficiency fracture (PIF) incidence in patients with anal or gynaecological cancer treated by pelvic intensity-modulated radiation therapy (IMRT).
Methods: The clinical and morphological (CT and/or pelvic MRI) characteristics of patients treated by IMRT at our institution between 2007 and 2014 were analyzed. The global incidence of PIF after external beam radiotherapy and the impact of tumour site (gynaecological or anal cancer) were determined. A dosimetric study was then performed to compare patients with and without pelvic fracture.
Results: 341 patients were treated by IMRT for gynaecological or anal cancer between 2007 and 2014. 15 patients experienced at least 1 pelvic fracture after external beam radiotherapy, corresponding to an overall incidence of 4.4%. Age and menopausal status were correlated with an increased fracture risk ($p = 0.0274$ and $p < 0.0001$, respectively). The site of the primary tumour (gynaecological or anal canal) was not associated with an excess fracture risk. The median maximum dose received at the fracture site was 50.3 Gy (range: 40.8–68.4 Gy).
Conclusion: The incidence of pelvic fracture after IMRT is low, but is higher after the age of 50 and in patients who are postmenopausal. Pre-treatment evaluation of bone density by bone densitometry and phosphorus–calcium assessment could be useful prior to the management of these patients.
Advances in knowledge: Pelvic fractures are a frequent complication after radiotherapy. The influence of IMRT and clinical characteristics were evaluated in this study.

INTRODUCTION

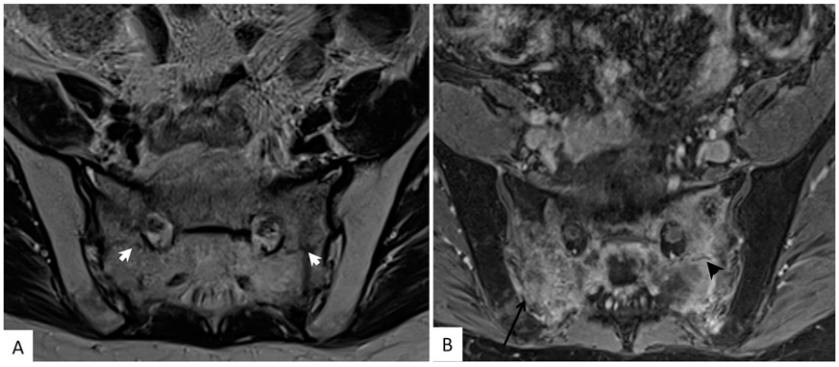
Pelvic radiotherapy is one of the standard treatments, together with surgery and chemotherapy, for the management of gynaecological and gastrointestinal tumours, as large or locally advanced cervical cancers, post-operative or locally advanced endometrial cancers, anal and middle and lower rectal cancers are commonly treated by neoadjuvant external beam radiotherapy, a technique that has been demonstrated to be beneficial in terms of local control and patient survival.[1–4]

Two types of post-radiotherapy complications may be observed: acute complications (occurring less than 6 months after radiotherapy) and late complications (occurring more than 6 months after radiotherapy).[5,6] Post-radiotherapy complications are mainly gastrointestinal, urinary tract and/or mucosal complications. There is also a probably underestimated risk of radiation-induced fracture.[7]

The estimated incidence of pelvic insufficiency fracture (PIF) is between 10% and 29%.[8–11] Physicians must be aware of this complication that can impair the patient quality of life and must be distinguished from bone metastasis.[12]

New techniques, such as intensity-modulated radiation therapy (IMRT), have been developed over recent years and allow optimization of the dose delivered to target lesions, while ensuring maximum sparing of healthy tissues. Several dosimetric and clinical studies have demonstrated the benefit of this technique, especially for the treatment of concave volumes, as in the case of pelvic tumours.[13–16] Gynaecological and gastrointestinal tumours

Figure 1. An MR axial image demonstrating a pelvic insufficiency fracture: turbo spin-echo T_2 weighted MR axial image (a) shows hypointense undisplaced fracture of the sacral ala with heterogeneous signal of the bone marrow (white arrows); fat-suppressed T_1 weighted contrast-enhanced axial image (B) depicts intense sacral enhancement indicating bone marrow oedema (black arrow) and hypointense fracture line (black arrowhead).



correspond to different treatment volumes and radiation doses, which may account for variations in the incidence of PIF.

The objective of this study was to retrospectively estimate the incidence and risk factors of PIF after IMRT for gynaecological or anal cancers.

METHODS AND MATERIALS

Study design

We analyzed clinical and morphological data of patients managed by IMRT for gynaecological cancer (cervix or endometrium) or anal cancer at our institution, Paris, from 2007 to 2014. Patient-reported symptoms, imaging study and imaging reports (pelvic CT and/or MRI) were systematically reviewed.

Male patients treated for anal cancer and female patients treated by three-dimensional conformal radiotherapy were excluded.

TREATMENT

Treatment indications for cervical cancer were based on a flowchart defined according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) classification and consisted of exclusive chemoradiotherapy for Stages IB2–IV or adjuvant chemoradiotherapy for Stages IA2 and IB1 in the case of external iliac vein and/or parametrial involvement and Stages IB2 and II in the case of lymph node (LN) involvement. The concomitant chemotherapy protocol consisted of cisplatin 40 mg m^{-2} delivered weekly for 5 weeks. The pelvis received a dose of 45 Gy in 1.8 Gy fractions per session, for five sessions per week, with the possibility, depending on the initial staging, of a boost dose up to 64.8 Gy to the iliac and 55 Gy to the paraaortic LNs. For locally advanced tumours, presacral nodes were routinely included. Radical hysterectomy was a possible treatment option, but was not performed systematically. Each brachytherapy procedure was performed under general anaesthesia. Depending on the length of the uterine cavity found during the brachytherapy procedure together with the topography of the vagina and cervix as clinically evaluated, the appropriate size and length of the uterovaginal applicator of Delouche type was used. The dose distribution was based on anatomic, clinical and implant parameters. Low-dose rate brachytherapy was realized in all cases using a Curithron machine with ^{137}Cs sources. Then, after machine replacement, we used pulse dose radiotherapy using ^{192}Ir source.

Treatment indications for endometrial cancer were also based on the 2009 FIGO classification and consisted of adjuvant external beam radiotherapy, possibly associated with complementary vaginal cuff pulse dose rate brachytherapy for FIGO Stages IB, II and IIIA and exclusive radiotherapy for Stages IIIB, IIIC and IV. The pelvis received a dose of 45 Gy in 1.8 Gy fractions per session, five sessions per week.

Treatment indications for anal cancer were based on the tumour-node-metastasis (TNM) classification and consisted of exclusive radiotherapy for small tumours with no LN involvement (T1N0M0 or T2 $<$ 2.5 cm) and chemoradiotherapy for large tumours and/or tumours with LN involvement. The pelvis (including bilateral inguinal nodes in all patients and presacral nodes in all patients treated with chemoradiotherapy) received a dose of 45 Gy in 1.8 Gy fractions per session, five sessions per week. A boost dose of 10–20 Gy was delivered to the tumour (2 Gy fractions per session for five sessions) and to any LNs initially involved. Concomitant chemotherapy, when indicated, consisted of two cycles of 5-fluorouracil 600 mg m^{-2} and cisplatin 20 mg m^{-2} at an interval of 4 weeks.

The following clinical characteristics were extracted from the patient medical charts: age at diagnosis, body mass index, smoking status, the presence of diabetes or hypertension, postmenopausal status, use of chemotherapy, history of hormone replacement therapy (HRT) and history of pre-existing documented osteoporosis.

Clinical follow-up consisted of physical examination every 3–4 months for 1 year, then every 6 months. Morphological follow-up was based on chest, abdomen and pelvis CT scan and pelvic MRI (± positron emission tomography-CT scan) every 6 months for 18 months, then annually. Pelvis CT and pelvic MRI reports were reviewed to identify PIF, described as hypointense line(s) surrounded by bone marrow oedema in any of the pelvic bone on T_2 or post-contrast T_1 weighted fat-

Table 1. Patient characteristics and pelvic insufficiency fracture outcome according to them

	Fracture(s)		*p*-value
	No (%)	Yes (%)	
Primary			
Cervix	170 (49.9)	6 (1.8)	0.1644
Endometrial cancer	107 (31.4)	4 (1.2)	
Anal	49 (14.4)	5 (1.5)	
Age (years)			
≤50	86 (25.2)	0 (0)	0.0151
>50	240 (70.4)	15 (4.4)	
BMI			
<18	8 (2.3)	1 (0.3)	0.9815
18–25	190 (55.7)	9 (2.6)	
≥25	128 (37.5)	5 (1.5)	
Diabetes			
Yes	11 (3.2)	0 (0)	1
No	314 (92.1)	15 (4.4)	
Unknown	1 (0.3)	0 (0)	
HT			
Yes	76 (22.3)	5 (1.5)	0.3631
No	249 (73.0)	10 (2.9)	
Unknown	1 (0.3)	0 (0)	
Postmenopausal			
Yes	243 (71.3)	15 (4.4)	0.0265
No	83 (24.3)	0 (0)	
Chemotherapy			
Yes	240 (70.4)	12 (3.5)	0.7674
No	86 (25.2)	3 (0.9)	
Hormonal substitute treatment			
Yes	63 (18.5)	5 (1.5)	0.3217
No	224 (65.7)	9 (2.6)	
Unknown	39 (11.4)	1 (0.3)	
Tobacco			
Yes	85 (24.9)	3 (0.9)	0.5598
No	168 (49.3)	11 (3.2)	
Unknown	73 (21.4)	1 (0.3)	
Osteoporosis			
Yes	10 (2.9)	1 (0.3)	1
No	18 (5.3)	1 (0.3)	
Unknown	298 (87.4)	13 (3.8)	

BMI, body mass index; HT, hypertension.

suppressed MRI sequences and as low density line(s), with or without surrounding bone sclerosis on CT images (Figure 1).

Statistical analysis

The overall incidence of pelvic fractures following external beam radiotherapy and the incidence of pelvic fractures by tumour site (gynaecological or anal canal) were calculated.

Retrospective and/or prospective (in the more recent patients) delineation of pelvic bones (right ilium and sacrum) was performed in all patients (femoral heads were delineated at the time of initial preparation). A dosimetric study was then performed to compare patients with pelvic fracture with patients without pelvic fracture. Data statistical analysis was performed using GraphPad Prism v. 6.00, (GraphPad software, Inc., San Diego, CA). The unpaired Mann–Whitney *U* test was performed to compare continuous values, and the Fisher's exact test allowed us to analyze contingency tables. All statistical tests were two sided, and *p*-values of 0.05 or less were considered to be statistically significant.

RESULTS

341 patients were included in this study, corresponding to 176 (52%) cases of cervical cancer, 111 (32%) cases of endometrial cancer and 54 (16%) cases of anal cancer. Median follow-up was 38 months (range: 1–109 months).

The patient clinical characteristics are summarized in Table 1. The median age was 61 years (range: 25–91 years). 257 (75%) patients were postmenopausal at the time of diagnosis. Osteoporosis status was available for only 30 (9%) patients, 12 of whom had documented osteoporosis. 81 (26%) patients were smokers. 68 (20%) patients had received HRT for menopause and 252 (74%) patients had received chemotherapy.

15 patients developed at least 1 PIF after external beam radiotherapy, corresponding to an overall incidence of 4.4%. The tumour and treatment characteristics of these patients are described in Table 2. A total of 20 fractures were reported in 15 patients: 13 fractures of the sacrum, 3 fractures of the left iliopubic ramus, 2 fractures of the left ischiopubic ramus, 1 fracture of the right iliopubic ramus and 1 fracture of the right ischiopubic ramus (Figure 2). The median time to fracture onset was 11 months (range: 3–66 months). Six of these patients were treated for cervical cancer, four patients were treated for an endometrial cancer and five patients were treated for anal cancer, corresponding to incidence rates of 3%, 4% and 9%, respectively. The incidence of pelvic fractures was not significantly higher in patients treated for anal cancer than in patients treated for gynaecological cancer ($p = 0.07$) (Figure 3). Age >50 years and postmenopausal status were significantly associated with a higher rate of pelvic fractures ($p = 0.0274$ and $p = 0.0268$, respectively). 11 patients had symptomatic fractures with intense mechanical sacral pain and 5 patients were referred to the pain clinic and received World Health Organization Step 3 analgesics.

Maximal doses at the site of the PIF for patients with a pelvic fracture are shown in Table 2, and mean, maximum and minimum doses delivered to pelvic bones are shown in Tables 3

Table 2. Patient characteristics in population of patients who experienced fractures

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age	57	73	68	64	69	87	75	76	65	62	67	63	86	66	55
Site of PIF	Cervical cancer	Cervical cancer	Cervical cancer	Cervical cancer	Cervical cancer	Cervical cancer	Endometrial cancer	Endometrial cancer	Endometrial cancer	Endometrial cancer	Anal canal	Anal canal	Anal canal	Anal canal	Anal canal
Histology of the primary tumour	SCC	SCC	SCC	SCC	SCC	SCC	ADK	ADK	ADK	ADK	SCC	SCC	SCC	SCC	SCC
Stage/FIGO/	IIIb	IV	IIb	III	IIb	II	II	IIIc	Ib	II	II	IIIa	IIIa	IIIb	IIIa
Latency period (months)	34	66	11	3	3	7	11	13	15	16	10	36	46	6	8
RT treatment modalities volume dose (Gy)	IMRT pelvis + LA : 45 Gy boost to T and pelvic LN 20 Gy (TD 65 Gy)	IMRT pelvis + LA: 45 Gy	IMRT pelvis + LA : 45 pelvic LN :57.6 brachytherapy 25 Gy PDR	IMRT pelvis 45 LN:59 T: 65 Gy	Pre-operative PDR brachytherapy 60 Gy IMRT pelvis 45 N 50 Gy	IMRT pelvis 45 T 65 Gy	IMRT pelvis 45 + curie 10 Gy HDR	IMRT pelvis 45 T 50	IMRT pelvis 45 + brachytherapy 10 Gy HDR	IMRT pelvis 45 T 50.4 brachytherapy 15 Gy PDR	IMRT pelvis 45 T 65	IMRT pelvis 45 T 65 LN 51	IMRT pelvis 45 T 65	IMRT pelvis 45 T 65	IMRT pelvis 45 T 65
Maximal dose at the site of the PIF (Gy)	68.4	47.3	58.5	57.1	50.3	58.3	45.5	40.8	45.5	45.2	52.6	48.8	46.4	62.3	65.1

ADK, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; HDR, high dose rate; IMRT, intensity-modulated radiation therapy; LA, lomboaortic; LN, lymph node; PDR, pulse dose rate; PIF, pelvic insufficiency fracture; SCC, squamous-cell carcinoma; T, tumour; TD, total dose.

Figure 2. Distribution of pelvic insufficiency fracture.

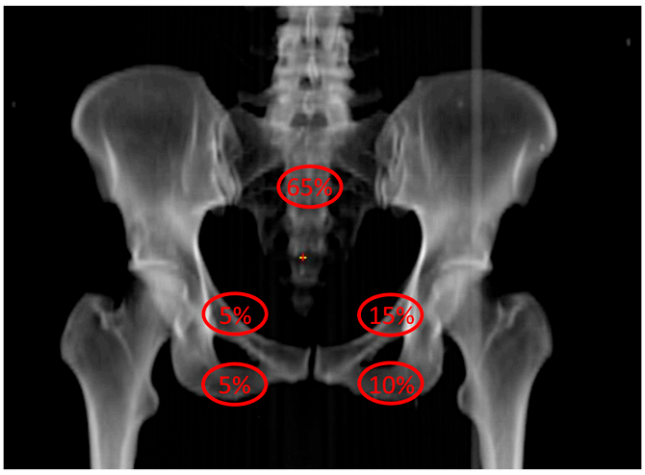
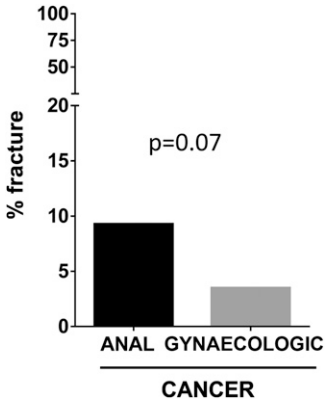


Figure 3. Pelvic insufficiency fracture rates by tumour location.



and 4 for patients who were fracture free. The maximum dose received by fracture sites in patients with a pelvic fracture was significantly higher than the maximum dose received by pelvic bones in patients who were fracture free ($p = 0.045$) (Figure 4).

DISCUSSION

In this retrospective study, with a median follow-up of 38 months, the incidence of radiation-induced pelvic fractures was 4.4%. 11 (73%) patients had symptomatic fractures and 4 (27%) patients had asymptomatic fractures (incidental finding on imaging). The median follow-up of 38 months is considerably longer than the median follow-up reported in other studies.[8–11,17–19] Age and postmenopausal status were associated with a significantly higher risk of radiation-induced fracture ($p = 0.0151$ and $p = 0.0265$, respectively). Other studies have demonstrated an association with HRT dose or low body mass index.[11,19,20]

In line with previous reports, the most commonly observed fracture site was the sacrum, corresponding to the site of transfer of forces from the vertebral column to the pelvis.[20,21] The morphology of stress fractures (either radiation induced or due to bone insufficiency) is characteristic, with a generally symmetrical (H-shaped) appearance, with no mass effect.[22] On MRI, stress fractures present an easily recognizable oedema signal in contrast to metastases that disorganize the bone and form a real replacement tissue. Finally, radiation-induced fractures are not associated with any invasion of adjacent soft tissues, which is commonly observed in the case of metastases. It is therefore essential to distinguish radiation-induced fractures from metastases, which may require biopsies and initiation of treatments such as chemotherapy. These two lesions can generally be distinguished by alternately performing pelvic CT and MRI follow-up.[9]

The incidence of pelvic fractures was not significantly higher in patients treated for anal cancer than in patients treated for gynaecological cancer ($p = 0.07$), while Baxter et al[7] reported a higher risk of radiation-induced fracture after treatment for anal cancer compared with gynaecological cancer.

Several articles have suggested a benefit of IMRT to spare bone and consequently decrease the risk of fractures and haematological toxicity.[17,23,24] In contrast, Shih et al[20] studied the incidence of fracture after external beam radiotherapy for a gynaecological cancer and did not observe any difference between patients treated with conventional radiotherapy (four-field pelvic technique) and those treated with IMRT (4.9% in both groups, $p = 0.3$).

In the present study, the maximum dose received by fracture sites in patients with a pelvic fracture was significantly higher than the maximum dose received by pelvic bones in patients who were fracture free ($p = 0.045$). It can be noted that despite a large population, the number of fractures reported is low. This comparison is therefore based on a small number of cases and must be confirmed on a larger number. To our knowledge, no dosimetric study has demonstrated a pelvic bone dose constraint that must be observed in order to significantly reduce the

Table 3. Dosimetric values of doses delivered to the pelvic bones in case of intensity-modulated radiation therapy (IMRT): IMRT for gynaecological cancers

Bone/dose (Gy)	Minimum	Maximum	Mean	Median
Right femoral head	0.76	44.39	12.87	9.9
Left femoral head	0.75	43.73	12.89	10.3
Right iliac bone	0.4	54.13	21.34	22.59
Left iliac bone	0.5	55.75	22.19	24.35
Sacrum	0.8	55.23	28.76	35.06

Table 4. Dosimetric values of doses delivered to the pelvic bones in case of intensity-modulated radiation therapy (IMRT): IMRT for cancers of the anal canal

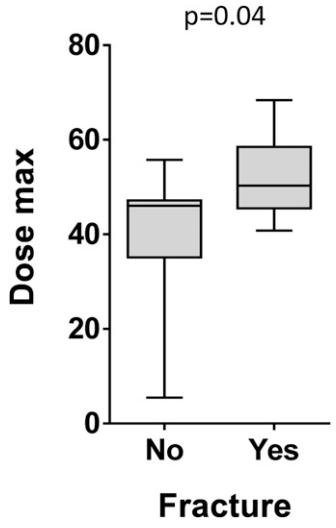
Bone/dose (Gy)	Minimum	Maximum	Mean	Median
Right femoral head	0.10	42.30	8.13	7.42
Left femoral head	0.10	40.55	8.19	7.57
Right iliac bone	0.02	46.95	13.93	19.06
Left iliac bone	0.02	46.46	14.07	18.86
Sacrum	0.025	47.38	18.33	31.66

fracture risk. In our centre, we have defined an internal margin of 3 mm that we have called "bone—3 mm", based on contouring of the pelvic bones. This margin can be used to impose a dose constraint to ensure that the planning target volume does not extend beyond with this "planning target volume—3 mm" contour. Other factors, such as total dose (TD), fractionation and duration of radiotherapy can also explain differences in radiation-induced fracture rates. Oh et al,[17] in a cohort of 557 patients treated for cervical cancer, reported a significant difference in the radiation-induced fracture risk between patients treated with a TD $<$50.4 Gy and those treated with a TD $\geq$50.4 Gy (2.1% *vs* 21.7%, respectively; $p = 0.005$).

The osteoporosis status was available for only 9% of patients, although osteoporosis constitutes the leading risk factor for bone insufficiency fractures.[25] Bone density can be estimated by performing Hounsfield unit measurements on CT scans.[26] Uezono et al[19] demonstrated a relationship between low bone density and increased fracture risk.

Diabetes has been reported to be possibly associated with an increased fracture risk, but such an association was not observed in our series.[27,28] Osteomalacia, hyperparathyroidism, chronic renal failure and long-term corticosteroid therapy are also major fracture risk factors, but were not assessed in the present series.[29]

Figure 4. Comparison of the maximum dose between patients with fractures and patients who are fracture free.



Similarly, the association between the occurrence of a fracture and smoking is not correlated in this study; but, smoking is a recognized factor for osteopenia.[30]

Although concomitant chemotherapy increases the toxicity of radiotherapy, its negative impact on pelvic fractures was not highlighted in this study.[31] Likewise, a study on 510 patients treated with pelvic radiotherapy for gynaecological cancer failed to demonstrate an excess fracture risk for patients who had also received chemotherapy.[9]

This study confirms that radiation-induced fractures can occur early (during the first months after treatment) or late (several years after treatment) and are difficult to predict.[32,33]

The effects of radiotherapy on bone tissues are both direct and indirect, mediated by vascular changes.[8,9,34] Following radiotherapy, the reduction of the number of osteoblasts induces a reduction of collagen production and decreased alkaline phosphatase activity, key mechanisms involved in bone mineralization. Radiation-induced occlusion of bone microvascularization also results in ischaemia, which participates in the formation of insufficiency fractures.[35]

Radiation-induced fractures generally require symptomatic management by Steps 1 (nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol) or 2 (weak opioids) analgesics and rest.[11,36–41] In some cases, pain control requires specialized management and/or hospitalization.[11,12]

The management of osteoporosis is particularly important in these patients who are postmenopausal treated with radiotherapy. Bone densitometry for the detection of osteopenia or osteoporosis prior to radiotherapy would be useful to prevent this excess fracture risk by initiating HRT. Phosphorus–calcium deficiency could also be systematically investigated and treated (vitamin D, calcium supplement) in these patients.

CONCLUSION

The incidence of pelvic fracture after IMRT is low, but is higher after the age of 50 and in patients who are postmenopausal. Pre-treatment evaluation of bone density by bone densitometry and phosphorus–calcium assessment could be useful prior to the management of these patients.

REFERENCES

1. Gibbons S, Martinez A, Schray M, Podratz K, Stanhope R, Garton G, et al. Adjuvant whole abdominopelvic irradiation for high risk endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 1991; **21**: 1019–25.
2. Myerson RJ, Karnell LH, Menck HR. The National Cancer Data Base report on carcinoma of the anus. *Cancer* 1997; **80**: 805–15.
3. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999; **340**: 1144–53. doi: https://doi.org/10.1056/NEJM199904153401502
4. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol* 2009; **27**: 5124–30.
5. Dörr W, Hendry JH. Consequential late effects in normal tissues. *Radiother Oncol* 2001; **61**: 223–31.
6. Dörr W. Radiobiology of tissue reactions. *Ann ICRP* 2015; **44**(Suppl. 1): 58–68. doi: https://doi.org/10.1177/0146645314560686
7. Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA* 2005; **294**: 2587–93. doi: https://doi.org/10.1001/jama.294.20.2587
8. Ikushima H, Osaki K, Furutani S, Yamashita K, Kishida Y, Kudoh T, et al. Pelvic bone complications following radiation therapy of gynecologic malignancies: clinical evaluation of radiation-induced pelvic insufficiency fractures. *Gynecol Oncol* 2006; **103**: 1100–4. doi: https://doi.org/10.1016/j.ygyno.2006.06.038
9. Kwon JW, Huh SJ, Yoon YC, Choi SH, Jung JY, Oh D, et al. Pelvic bone complications after radiation therapy of uterine cervical cancer: evaluation with MRI. *AJR Am J Roentgenol* 2008; **191**: 987–94. doi: https://doi.org/10.2214/AJR.07.3634
10. Schmeler KM, Jhingran A, Iyer RB, Sun CC, Eifel PJ, Soliman PT, et al. Pelvic fractures after radiotherapy for cervical cancer: implications for survivors. *Cancer* 2010; **116**: 625–30. doi: https://doi.org/10.1002/cncr.24811
11. Ogino I, Okamoto N, Ono Y, Kitamura T, Nakayama H. Pelvic insufficiency fractures in postmenopausal woman with advanced cervical cancer treated by radiotherapy. *Radiother Oncol* 2003; **68**: 61–7.
12. Gotis-Graham I, McGuigan L, Diamond T, Portek I, Quinn R, Sturgess A, et al. Sacral insufficiency fractures in the elderly. *J Bone Joint Surg Br* 1994; **76**: 882–6.
13. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 2013; **86**: 27–33. doi: https://doi.org/10.1016/j.ijrobp.2012.09.023
14. Lim K, Small W Jr, Portelance L, Creutzberg C, Jürgenliemk-Schulz IM, Mundt A, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. *Int J Radiat Oncol Biol Phys* 2011; **79**: 348–55. doi: https://doi.org/10.1016/j.ijrobp.2009.10.075
15. Klopp AH, Moughan J, Portelance L, Miller BE, Salehpour MR, Hildebrandt E, et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. *Int J Radiat Oncol Biol Phys* 2013; **86**: 83–90. doi: https://doi.org/10.1016/j.ijrobp.2013.01.017
16. McGuire SM, Menda Y, Ponto LLB, Gross B, Juweid M, Bayouth JE. A methodology for incorporating functional bone marrow sparing in IMRT planning for pelvic radiation therapy. *Radiother Oncol* 2011; **99**: 49–54. doi: https://doi.org/10.1016/j.radonc.2011.01.025
17. Oh D, Huh SJ, Nam H, Park W, Han Y, Lim DH, et al. Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1183–8.
18. Tai P, Hammond A, Dyk JV, Stitt L, Tonita J, Coad T, et al. Pelvic fractures following irradiation of endometrial and vaginal cancers-a case series and review of literature. *Radiother Oncol* 2000; **56**: 23–8.
19. Uezono H, Tsujino K, Moriki K, Nagano F, Ota Y, Sasaki R, et al. Pelvic insufficiency fracture after definitive radiotherapy for uterine cervical cancer: retrospective analysis of risk factors. *J Radiat Res* 2013; **54**: 1102–9. doi: https://doi.org/10.1093/jrr/rrt055
20. Shih KK, Folkert MR, Kollmeier MA, Abu-Rustum NR, Sonoda Y, Leitao MM Jr, et al. Pelvic insufficiency fractures in patients with cervical and endometrial cancer treated with postoperative pelvic radiation. *Gynecol Oncol* 2013; **128**: 540–3. doi: https://doi.org/10.1016/j.ygyno.2012.12.021
21. Leroux JL, Denat B, Thomas E, Blotman F, Bonnel F. Sacral insufficiency fractures presenting as acute low-back pain. Biomechanical aspects. *Spine (Phila Pa 1976)* 1993; **18**: 2502–6.
22. Schneider R, Yacovone J, Ghelman B. Unsuspected sacral fractures: detection by radionuclide bone scanning. *AJR Am J Roentgenol* 1985; **144**: 337–41. doi: https://doi.org/10.2214/ajr.144.2.337
23. Small W, Kachnic L. Postradiotherapy pelvic fractures: cause for concern or opportunity for future research?. *JAMA* 2005; **294**: 2635–7. doi: https://doi.org/10.1001/jama.294.20.2635
24. Mell LK, Kochanski JD, Roeske JC, Haslam JJ, Mehta N, Yamada SD, et al. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; **66**: 1356–65.
25. Krestan C, Hojreh A. Imaging of insufficiency fractures. *Eur J Radiol* 2009; **71**: 398–405. doi: https://doi.org/10.1016/j.ejrad.2008.04.059
26. Cann CE. Quantitative CT for determination of bone mineral density: a review. *Radiology* 1988; **166**: 509–22. doi: https://doi.org/10.1148/radiology.166.2.3275985
27. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. *Epidemiol Rev* 1985; **7**: 178–208.
28. Kathol MH, el-Khoury GY, Moore TE, Marsh JL. Calcaneal insufficiency avulsion fractures in patients with diabetes mellitus. *Radiology* 1991; **180**: 725–9.
29. Eastell R. Treatment of postmenopausal osteoporosis. *N Engl J Med* 1998; **338**: 736–46. doi: https://doi.org/10.1056/NEJM199803123381107
30. Cusano NE. Skeletal effects of smoking. *Curr Osteoporos Rep* 2015; **13**: 302–9. doi: https://doi.org/10.1007/s11914-015-0278-8
31. Jenkins PJ, Montefiore DJ, Arnott SJ. Hip complications following chemoradiotherapy. *Clin Oncol (R Coll Radiol)* 1995; **7**: 123–6.
32. Fu AL, Greven KM, Maruyama Y. Radiation osteitis and insufficiency fractures after pelvic irradiation for gynecologic malignancies. *Am J Clin Oncol* 1994; **17**: 248–54.
33. Lundin B, Björkholm E, Lundell M, Jacobsson H. Insufficiency fractures of the

sacrum after radiotherapy for gynaecological malignancy. *Acta Oncol* 1990; **29**: 211–5.
34. Howland WJ, Loeffler RK, Starchman DE, Johnson RG. Postirradiation atrophic changes of bone and related complications. *Radiology* 1975; **117**(3 Pt 1): 677–85.
35. Huh SJ, Kim B, Kang MK, Lee JE, Lim DH, Park W, et al. Pelvic insufficiency fracture after pelvic irradiation in uterine cervix cancer. *Gynecol Oncol* 2002; **86**: 264–8.
36. Casey D, Mirra J, Staple TW. Parasymphyseal insufficiency fractures of the os pubis. *AJR Am J Roentgenol* 1984; **142**: 581–6. doi: https://doi.org/10.2214/ajr.142.3.581
37. Cooper KL, Beabout JW, Swee RG. Insufficiency fractures of the sacrum. *Radiology* 1985; **156**: 15–20. doi: https://doi.org/10.1148/radiology.156.1.4001403
38. De Smet AA, Neff JR. Pubic and sacral insufficiency fractures: clinical course and radiologic findings. *AJR Am J Roentgenol* 1985; **145**: 601–6.
39. Grasland A, Pouchot J, Mathieu A, Paycha F, Vinceneux P. Sacral insufficiency fractures: an easily overlooked cause of back pain in elderly women. *Arch Intern Med* 1996; **156**: 668–74.
40. Moreno A, Clemente J, Crespo C, Martínez A, Navarro M, Fernández L, et al. Pelvic insufficiency fractures in patients with pelvic irradiation. *Int J Radiat Oncol Biol Phys* 1999; **44**: 61–6.
41. Peh WC, Khong PL, Yin Y, Ho WY, Evans NS, Gilula LA, et al. Imaging of pelvic insufficiency fractures. *Radiogr Rev Publ Radiol Soc N Am Inc* 1996; **16**: 335–48. doi: https://doi.org/10.1148/radiographics.16.2.8966291