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Pelvic insufficiency fractures after radiotherapy for cervical cancer: Analysis of risk factors and a new way to determine bone mineral density in planning CTs for radiotherapy

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Dedicated to my beloved parents

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List of abbreviations

AC	Adenocarcinoma
BMD	Bone mineral density
BMI	Body mass index
BSA	Body surface area
CIN	Cervical intraepithelial neoplasia
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Dmax	Maximum dose within the target volume
Dmean	Mean dose within the target volume
DVH	Dose-volume histogram
D50%	The dose 50% of the target volume received
DXA	Dual x-ray absorptiometry
EBRT	External beam radiation therapy
FIGO	International Federation of Gynaecology and Obstetrics
Gy	Gray
HDR-ICBT	High-dose-rate intracavitary brachytherapy
HPV	Human papilloma virus

HSIL	High grade squamous intraepithelial lesion
HU	Hounsfield units
IMRT	Intensity modulated radiation therapy
kVp	Kilovoltage Peak
LACC	Locally advanced cervical cancer
LN	Lymph nodes
LSIL	Low grade squamous intraepithelial lesion
MDCT	Multidetector-row computed tomography
mPIF	A contoured mirrored structure of the fracture on the planning CT
MRI	Magnetic resonance imaging
NECC	Neuroendocrine carcinoma of the cervix
OAR	Organs at risk
OS	Overall survival
OTH	Other patients, i.e. patients without a fracture
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PIF	Pelvic insufficiency fracture
PIF group	Patients with a fracture
PT	Primary tumor

PTV	Planning target volume
qCT	Quantitative computed tomography
ROI	Region of interest
RT	Radiotherapy
RCT	Radiochemotherapy
SB	Sequential boost
SIB	Simultaneous integrated boost
SCC	Squamous cell carcinoma
UICC	Union for international cancer control
V 30/40/50 Gy	The relative target volume that received 30/40/50 Gy

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1. Introduction

Radiotherapy (RT) plays a very important role in the treatment of cervical cancer. It is applied to the majority of patients, either through definitive/adjuvant external beam radiation therapy (EBRT) or brachytherapy.

Through advances in the treatment in recent decades, especially in radiotherapy, the late effects of the pelvic radiation have drawn more attention.

Pelvic insufficiency fractures (PIF) are a type of stress fracture, usually occurring after normal or physiological stress on bone with demineralization and loss of elastic resistance (Cooper, Beabout, & Swee, 1985). They can be a result of osteoporosis, but also a result of RT, as well as rheumatoid arthritis, prolonged corticosteroid therapy, and renal failure (Park, Kim, Lee, & Park, 2011). The massa lateralis of the sacrum is the most common affected site because of its weight-bearing function (Cooper et al., 1985).

Several studies investigating the incidence of PIF showed a wide range of incidence from 1.7% to 89% (Blomlie et al., 1996; Huh et al., 2002; Ramlov et al., 2017; Tokumaru et al., 2012), which leads to believe that PIF are a rather common post-radiation complication and not as rare as previously thought.

Risk factors for pelvic fractures after RT for cervical cancer are yet to be fully understood. Very few studies have been able to evaluate bone mineral density (BMD) as a risk factor for the occurrence of PIF. Osteoporosis, a disease in which bone weakening increases the risk of fracture, plays an important role in the development of PIF.

The BMD can predict osteoporotic vertebral fractures. Established methods of assessing BMD are associated with additional radiation to the patient. (Schwaiger et al., 2014)

There is no data on BMD measurements based on the planning CTs for radiation therapy up to date.

The aim of this study was to investigate whether bone mineral density – measured in planning CTs – is a risk factor for pelvic insufficiency fractures after radio(chemo)therapy (R(C)T) for cervical cancer.

1.1. Cervical cancer

Cervical cancer usually occurs in the squamo-columnar junction, called the transformation zone, where the squamous cell epithelium of the ectocervix and the columnar epithelium of the endocervix merge. In this transformation zone, the columnar cells are continuously being changed into squamous cells, particularly during puberty and child-bearing years. The development of cervical cancer is a long process that usually begins with an acute infection with human papillomavirus (HPV) infection, followed by viral persistence, which can lead to a precancerous lesion, from which then invasive cancer arises. (Schiffman et al., 2011)

1.1.1. Epidemiology

In the last decades, since the implementation of screening programs, there has been a notable reduction in the incidence of cervical cancer in Germany from the most common cancer in women (1971) to the 12th most common cancer with 2,1% of the incidence of all types of cancer in women. In 2011, 9,4 per 100 000 women were diagnosed with cervical cancer, with a mortality rate of 2,6 per 100 000 women. In 2016 the incidence rate was 8,7, the mortality rate 2,4 per 100 000 women. (RKI, 2015, 2019)

A total of 1562 women died from cervical cancer in 2016, when compared to the numbers from over 30 years ago, that is a decrease of more than 50%. The age distribution is between 40 and 59 years. The median age of 53 at diagnosis has had a decrease of 15 years compared to 25 years ago. (RKI, 2019; AWMF, 2021)

In 2016, the five-year relative survival rate was 67%, the ten-year relative survival rate was 63% (RKI, 2019).

Cervical cancer is the fourth most common cancer (with 528,000 new cases) and the fourth most common cause of death (266,000 deaths) in women worldwide. In 39 of 184 countries, it is the most common cancer among women, particularly in low-income countries, such as countries in the sub-Saharan Africa, parts of Asia, as well as central and south America. In western Europe, North America, Australia and New Zealand on the other hand, the incidence rates are among the lowest worldwide. (Stewart, Wild, International Agency for Research on Cancer, & World Health Organization, 2014)

This comes as a result of the implementation of screening programs as part of secondary prevention in high-income countries (Gelband, Jha, Sankaranarayanan, Horton, & World Bank, 2015).

The incidence of cervical cancer shows a wide range of variation. From 3,6 (Finland) to 45 (Colombia) per 100.000 women and year (AWMF, 2021). The incidence and mortality rates of cancer in women (2018) are shown in Figure 1.

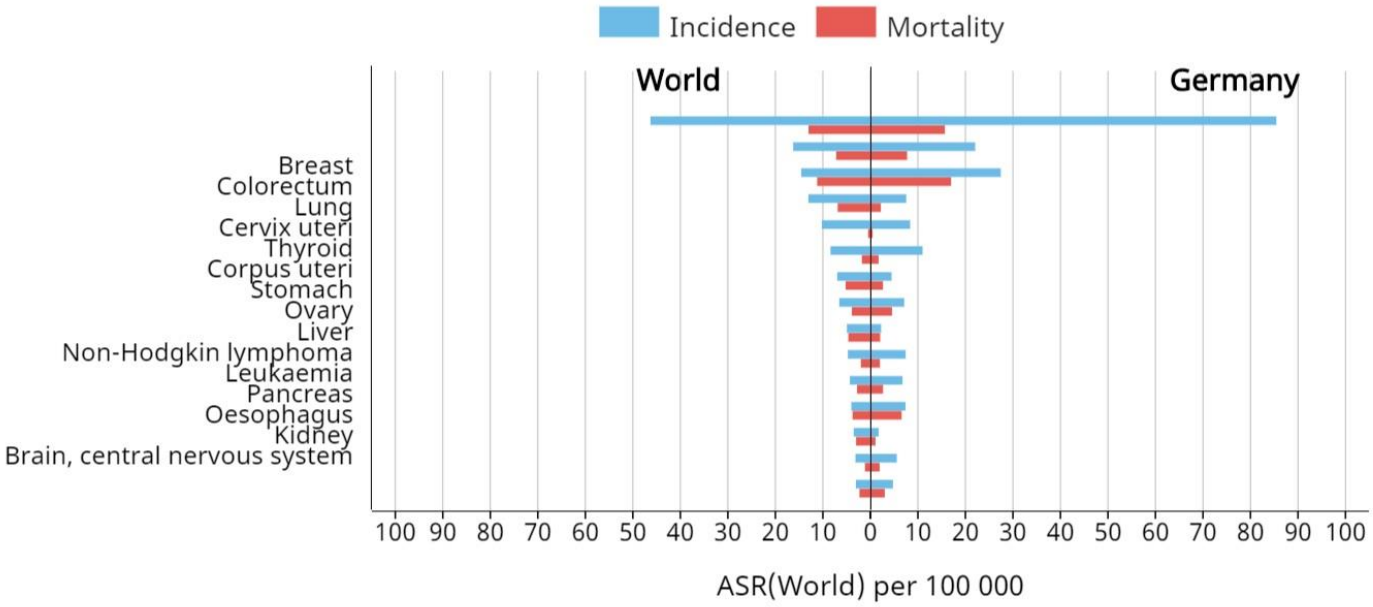


Figure 1. Incidence and mortality rates of cancer in women (2018). Estimated age-standardized incidence and mortality rates (ASR) per 100 000 women Worldwide (left) vs. Germany (right) in 2018, all ages. (GLOBOCAN 2018, Global cancer observatory) (Bray et al., 2018).

1.1.2. Etiology

HPV is known to be the main risk factor for cervical cancer. The infection with high-risk HPV-types can lead to cervical intraepithelial neoplasia (CIN), which over time can transform into cervical cancer. HPV infection is the most common sexually transmitted infection and affects most individuals at some point in their life. (Stewart et al., 2014)

The highest prevalence has been recorded in women <25 years (16,9%) (de Sanjose et al., 2007).

Half of new HPV infections regress over 6-12 Months, more than 90% within a few years (Rodriguez et al., 2008; Schiffman et al., 2011). Only 10% of all low-grade lesion progress into

high-grade lesions, with an average time of 10 years. Less than 2% of those low-grade lesions become invasive cancer. On the other hand, approximately 20% of high-grade lesions progress to invasive cancer. (Stewart et al., 2014)

There are several other risk factors that may contribute to the development of cervical cancer, such as smoking, immunosuppressed patients, early begin of sexual activity, other infectious diseases (genital herpes, chlamydia, gonorrhea), low-socioeconomic status, poor sexual hygiene, high number of births and long-term use of oral contraceptives (Castellsague, Bosch, & Munoz, 2002; International Collaboration of Epidemiological Studies of Cervical et al., 2007; Moreno et al., 2002).

Moreover, there are a number of genetic risk factors, that seem to affect the development of cervical cancer, such as FANCA, IFNG, EVER1/EVER2, TP 53, CCND1, etc. However, their influence is yet to be fully understood and is focus of current research. (AWMF, 2021)

1.1.3. Pathology

The most common types of cervical cancer are the squamous cell carcinoma (SCC) with 80% and the adenocarcinoma (AC) with 20%. In the last 25 years, the percentage of adenocarcinomas rose from 10% to 20%. One of the reasons for this increase in cases of adenocarcinoma could be the improvement of the histological classification, as well as the increased role of co-factors in the development of cervical cancer. Another reason for this shift in histological types could also be the HPV-vaccination, for it is too early to tell as it is still the subject of current research. (AWMF, 2021)

For the cervical histopathology of precancerous lesions, the classification that is commonly used is the cervical intraepithelial neoplasia (CIN), whereas for the cervical cytology of precancerous lesions the Bethesda system (low grade squamous intraepithelial lesion [LSIL] and high grade squamous intraepithelial lesion [HSIL]) (Waxman, Chelmow, Darragh, Lawson, & Moscicki, 2012).

The histological and cytological classification of squamous precancerous lesions are shown in Table 1.

Table 1. Histopathological (*cervical intraepithelial neoplasia, CIN) and cytological (Bethesda) classification of squamous precancerous lesions (Waxman et al., 2012).*

CIN classification	**Dysplasia**	**Bethesda system**
CIN 1	Mild dysplasia	LSIL
CIN 2	Moderate dysplasia	HSIL
CIN 3	Severe dysplasia Carcinoma in situ	HSIL

CIN = cervical intraepithelial neoplasia (used in the histopathological classification of squamous precancerous lesions)

LSIL = low grade squamous intraepithelial lesion (used in the cytological classifications of squamous precancerous lesions)

HSIL = high grade squamous intraepithelial lesion (used in the cytological classifications of squamous precancerous lesions)

1.1.4. Prevention

The prevention of cervical cancer is based on 2 main pillars: the nationwide screening programs and the prophylactic vaccines against HPV.

A massive reduction in the incidence and mortality of cervical cancer occurred in the last few decades due to the adequate nationwide screening programs. These programs used cytology based Papanicolaou (PAP) smears to identify precursors and remove them in order to prevent them from progressing into invasive cancer.

This way, up to 91 % of all invasive cervical cancers could be prevented in countries who were able to successfully undertake these nationwide screening programs. In low-/middle-income countries on the other hand, where they were not able to implement these screening programs due to the lack of funded health care systems, the incidence- and the mortality-rates of cervical cancer are still high, which is why it is still the second most common type of gynaecological cancer after breast cancer. (Gelband et al., 2015)

More than 95% of cervical carcinomas are HPV-positive. HPV16 is detectable in 50-60%, HPV18 in 10-20% of cervical cancer. (Klug et al., 2007; Plummer et al., 2003)

The currently prophylactic vaccines in use are against HPV 16 as a monovalent vaccine, against 16 and 18 (bivalent), and against 6,11,16,18 (quadrivalent).

Vaccines against HPV16 and HPV18 could prevent up to 75% of carcinomas and 60% of high-grad lesions (Stewart et al., 2014). The quadrivalent vaccine is 100% successful in preventing CIN or adenocarcinoma in situ in association with the vaccine-type HPV (Garland et al., 2007).

The HPV-vaccines cannot explain the reduction in incidence and mortality rate that occurred in the last few decades yet, as in Germany for example, they are recommended by the Ständige Impfkomission (STIKO) only since 2007. It is expected, however, to continue reducing the incidence and mortality rate in the future. (AWMF, 2021)

1.1.5. Diagnostics

Cervical cancer is one of the last types of carcinomas, whose classification is strictly clinical. The use of modern imaging modalities is yet to be included in the *International Federation of Gynaecology and Obstetrics* (FIGO) classification (the same goes for surgical staging). This

leads to the fact that imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) or gynaecological (vaginal) ultrasound are not taken into account by the TNM and FIGO classification. (AWMF, 2021)

It takes years or decades for abnormal cells to develop into cervical cancer. The abnormal cells are often harmless and cause few to no symptoms. If these cells develop into cancer, however, it can cause some symptoms that are often neglected by the patients or are misdiagnosed from health care professionals. Some of these symptoms are abnormal bleeding (i.e. after sexual contact, between periods or after the menopause), abnormal vaginal discharge with a possible unpleasant odor, pain in the abdomen and pelvis, pain when urinating, tiredness and weight loss. (Institute for Quality and Efficiency in Health Care (IQWiG); 2006)

It is known that by the time cervical cancer starts presenting these symptoms, it is very often already at an advanced stage, resulting in a rather poor prognosis of this disease.

The first diagnostic step in the screening guidelines is the gynaecological examination and cytology. If suspicious, additional steps such as HPV-Testing could be used. In case of higher-grade cytological abnormalities, a colposcopy with biopsy or if the lesion is well localized, a cervical conization or excision should be carried out. In cases of histologically proven cervical cancer, a staging should follow. (AWMF, 2021)

For determining the locoregional cancer-spread the vaginal ultrasound should be used. The use of vaginal ultrasound showed good validity, in particular on determining the tumor size of early-stage cervical cancer. (Epstein et al., 2013)

Moreover, a kidney ultrasound should follow, to see if the tumor has caused hydronephrosis or a non-functioning kidney by invading the ureter on either side (AWMF, 2021).

The term locally advanced cervical cancer (LACC) refers to FIGO IIb-IVa, as well as FIGO IB2-IIA2, when risk factors, such as lymph node involvement, are detected. In patients with histologically proven cervical cancer FIGO IB2-III, an MRI of the pelvis is preferred to determine the spread of the cancer. Alternatively, a CT of the pelvis can be used. (AWMF, 2021)

The data on if CT or MRI of the abdomen should be used in the diagnostics of cervical cancer is indecisive. The CT is more precise in the evaluation of the lateral structures - i.e. bone structures - up to the pelvic wall, whereas the MRI is superior in differentiating the primary tumor size and the invasion of the parametrial structures, as well as bladder, colon and lymph nodes. (Bipat et al., 2003; Thomeer et al., 2013)

The positron emission tomography-computed tomography (PET-CT) is yet to take an important role in the routine diagnostics of primary cervical cancer. Not being able to precisely differentiate invasive tumors from superinfections, as well as the lack of sensitivity and specificity in cases of micro metastasis of lymph nodes are arguments against the use of the PET-CT scan as a standard diagnostic tool in primary cervical cancer. (Gouy et al., 2013; Kang et al., 2010; Tsai et al., 2010)

In recent years, the surgical staging has gained a growing importance in the decision-making of treatment planning for cervical cancer. It is often carried out prior to a planned surgery to determine if lymph nodes are affected, as this is key to whether the patient will go through surgery or R(C)T as primary therapy. It allows the evaluation of lymph nodes, the peritoneum and the local tumor spread. This leads to a more precise staging and subsequently to a more precise treatment planning and thus reduces the impact of the treatment and the disease itself on morbidity and mortality. (AWMF, 2021)

1.2. Classification

Patients with cervical cancer should be staged according to the TNM, as well as the FIGO classification (Table 2).

Table 2. TNM (9th edition) and International Federation of Gynaecology and Obstetrics (FIGO, 2018) staging for cervical cancer (Bhatla et al., 2019; Cibula et al., 2018).

T	FIGO	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1	I	Cervical carcinoma confined to the uterus
T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5 mm
T1a1	IA1	Measured stromal invasion of <3 mm in depth
T1a2	IA2	Measured stromal invasion of ≥3 mm and <5 mm in depth
T1b	IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than IA), lesion limited to the cervix uteri[a]
T1b1	IB1	Invasive carcinoma ≥5mm depth of stromal invasion and clinically visible lesion <2 cm in greatest dimension
T1b2	IB2	Clinically visible lesion ≥2 cm and <4 cm in greatest dimension
T1b3	IB3	Clinically visible lesion ≥4 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to lower third of the vagina
T2a	IIA	Involvement limited to the upper two-thirds of the vagina without parametrial invasion
T2a1	IIA1	Invasive carcinoma ≤4 cm in greatest dimension
T2a2	IIA2	Invasive carcinoma >4 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion but not up to the pelvic wall
T3	III	Tumor extending to the pelvic sidewall and/or involving the lower third of the vagina and/or causing hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumor extending to the pelvic wall and/or causing hydronephrosis or non-functioning kidney

pN1 /pM1	IIIC	Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[b]
pN1	IIIC1	Pelvic lymph node metastasis only
pM1	IIIC2	Paraaortic lymph node metastasis
T4	IV	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis[c]
	IVA	Spread of the growth to adjacent organs
N		Regional lymph nodes
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis to pelvic lymph nodes only
N2		Regional lymph node metastasis to paraaortic lymph nodes, with or without positive pelvic lymph nodes
M		Distant metastasis
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis

[a]The lateral extent of the carcinoma is no longer considered distinguishing between FIGO Stage IA and IB carcinomas

[b]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage FIGO IIIC. For example: if imaging indicates pelvic lymph node metastasis, the stage allocation would be IIIC1r, and if confirmed by pathology, it would be IIIC1p. The type of imaging modality or pathology technique should always be documented.

[c]Bullous edema is not sufficient to classify a tumor as T4

1.3. Prognostic factors

The most important prognostic factors for cervical cancer are the tumor stage, tumor size, pelvic and/or para-aortic lymph node metastases and the resection margins (Ayhan et al., 2004; Baalbergen, Ewing-Graham, Hop, Struijk, & Helmerhorst, 2004; Endo et al., 2015; Ho et al., 2004; Kinney, Hodge, Egorshin, Ballard, & Podratz, 1995).

As for the histological type of cervical cancer and its relevance as a prognostic factor, it is important to mention that neuroendocrine carcinomas are related to a poor prognosis (Chan, Loizzi, Burger, Rutgers, & Monk, 2003; Cohen et al., 2010; Lee et al., 2010).

On the other hand, the distinction of AC and SCC seem to play an inferior role as a prognostic factor. While some authors evaluating the histological subtype as a prognostic factor have had inconclusive results (Singh & Arif, 2004), others have found no significant prognostic differences between the two most common histological types of cervical cancer (Ayhan et al., 2004).

Although there are studies (Chen et al., 2014) where AC showed to be more aggressive than SCC, with a worse 5-year progression-free survival (PFS), worse distant metastasis-free survival and worse overall survival (OS), it has had only an inferior prognostic relevance since the implementation of new therapy modalities, as there is no relevant difference in how each of the histological subtypes is treated. (AWMF, 2021)

1.4. Therapy

In most countries the therapy of cervical cancer complies with the FIGO classification, where clinical examinations, such as colposcopy, biopsy and conization determine the treatment plan. In high-income countries, such as Germany for example, imaging modalities and surgical staging play an important role in the decision-making for the treatment, by facilitating a more precise FIGO classification. The final decision should always be discussed in an

interdisciplinary tumor board, where gynaecological oncologists, radiation oncologists, pathologists, and radiologists come to an agreement on which treatment is most promising for the patient. Also, factors such as the patient's general condition, the stage of disease, menopausal status, as well as the patient's wish for children should be taken into account in the decision-making for the best possible therapy. (AWMF, 2021)

The definitive therapy consists of either surgery, concomitant RCT or RT alone. The trimodal therapy consisting of surgery + R(C)T doubles the ratio of long-term toxicities. Therefore, through precise selection of patients with the adequate diagnostic methods, the aim should be to choose between surgery alone or definitive RCT, in order to reduce the late toxicities to a minimum. (AWMF, 2021; Landoni et al., 1997; Marnitz et al., 2012)

1.4.1. Surgical therapy

In cervical cancer diagnosed in early stages (FIGO <IIA), without risk factors, such as lymph node metastasis or distant metastasis, surgery is the therapy of choice. In cases of pre-operative risk factors such as L1 (invasion into lymphatic vessels), Grading G3 (only when 2 further risk factors simultaneously present), neuroendocrine carcinoma, tumor size >4cm and tumor stage, a surgical staging should follow. Depending on the status of the intraoperative examined lymph nodes, a radical hysterectomy or definitive R(C)T should follow. If case of negative pelvic lymph nodes, the stage-related surgical therapy should be carried out. On the other hand, if pelvic lymph nodes are affected, surgical therapy should be canceled, and the patient should receive definitive R(C)T. (AWMF, 2021)

Until recently, para-aortic lymph node involvement was classified as distant metastasis, subsequently meaning the therapy should be planned individually and discussed in an intradisciplinary tumor board. There has been a notable change in the new FIGO classification. In the new version (2018) para-aortic lymph nodes are no longer classified as pM1 but are now rated as pN1. However, because of this rather recent modification, there are no available data from current studies that are based on the new FIGO classification yet. (AWMF, 2021)

1.4.2. Definitive radio(chemo)therapy

Radio(chemo)therapy plays an important role in the treatment of cervical cancer. It can be applied before surgery – i.e. neoadjuvant -, as definitive treatment, or after surgery - as adjuvant therapy.

German guidelines define that starting at stage FIGO IIB, definitive R(C)T after a surgical staging should be preferred. In some countries, definitive R(C)T is applied as early as FIGO IB2. (AWMF, 2021)

Definitive treatment consists of concomitant RCT and brachytherapy or external beam radiation therapy (EBRT) alone and brachytherapy. EBRT can be applied as concomitant RCT with a total dose of 45-50,4 Gray (Gy) (1,8 Gy per fraction) and single agent radio-sensitizing chemotherapy, preferably cisplatin. (AWMF, 2021)

The simultaneous use of chemotherapy throughout the radiation showed a significant higher OS and PFS, when compared to RT alone (Green et al., 2005; Wang et al., 2011). The preferred chemotherapeutic agent is cisplatin, with usually at least 5 doses of 40 mg/m^2 body surface area (BSA) on days 1, 8, 15, 22 and 29 of RT. In cases where cisplatin is contraindicated due to its side effects, for example if the patient's kidney function is impaired, carboplatin can be used as an adequate alternative chemotherapeutic agent. (AWMF, 2021)

Boost treatment for involved lymph nodes may be applied as simultaneous integrated boost (SIB) with the EBRT treatment or as sequential boost (SB). In large tumors brachytherapy should be delivered within 1-2 weeks toward the end or after R(C)T. In limited size tumors brachytherapy may start earlier during R(C)T. The aim should be to reach a total EBRT + brachytherapy dose of ≥ 85-90 Gy. (W. Small, Jr. et al., 2012; Viswanathan et al., 2012)

Brachytherapy is an integral component of the definitive R(C)T of cervical cancer. Is it useful to use MRI for the 3D image-based brachytherapy for cervical cancer, because of its better soft tissue image quality, ensuring the most favorable treatment planning and thus the best possible protection of organs at risk (OAR). (Dimopoulos et al., 2012)

1.4.3. Adjuvant radio(chemo)therapy

In accordance with the German S3 guidelines for cervical cancer, adjuvant therapy should follow in patients with the following postoperative risk factors:
histologically proven lymph node metastases, R1-resection margin or ≥3 risk factors (L1, V1, deep stromal invasion, tumor size >4cm), as well as Grading G3 (if two further risk factors are present simultaneously). In case of distant metastases RT may be indicated if uncontrolled bleeding occurs. (AWMF, 2021)

Also, if ≥3 pre-operative risk factors (for example L1, V1,G3) are found, a definitive R(C)T should be performed after surgical staging, in order to ensure a therapy with as little long-term complications as possible (AWMF, 2021).

Additional brachytherapy as part of the adjuvant treatment should only be considered, if a well-defined limited area is at high risk of local recurrence (i.e. vagina, parametrium) (AWMF, 2021). With the aim of optimal local control, a total therapy duration of no longer than 56 days is recommended (Song et al., 2013).

1.5. Risk factors for pelvic insufficiency fractures

In the last decades, several studies investigated risk factors for PIF.

There are studies who found that age ≥55 years and body weight <55kg are significant predisposing factors for developing PIF (Oh et al., 2008). In another study, postmenopausal status was also a significant risk factor (Schmeler et al., 2010).

Concomitant radiochemotherapy (RCT) as a possible risk factor was also evaluated in several studies (Gondi et al., 2012; Ramlov et al., 2017; Uezono et al., 2013). In the majority of those studies, however, it did not reach significance.

The impact of dose delivered through EBRT ± HDR-ICBT was also evaluated in a number of studies (Ramlov et al., 2017; Uezono et al., 2013), especially with the aid of dose-volume histogram (DVH) parameters, such as Dmean, Dmax, V55Gy and D50%. Nevertheless, no statistically significant correlation between DVH parameters and the occurrence of PIF has been found up to date.

These studies will be presented further in the discussion section.

One of the main risk factors for developing PIF seems to be bone mineral density (BMD).

1.6. Bone mineral density (BMD)

The BMD measures the amount of bone mineral per volume of bone tissue. It is broadly used for the diagnosis of osteoporosis (R. E. Small, 2005).

Osteoporosis, a disease in which bone weakening increases the risk of a fracture, plays an important role in the development of PIF. It is known to be one of the most common causes of insufficiency fractures. (Krestan & Hojreh, 2009)

The T-score is an important parameter when screening for osteoporosis. It gives us the BMD value compared to the mean value of a healthy young adult. Osteoporosis is defined as a T-score of -2.5 or lower, meaning a BMD two and a half standard deviations below the mean of a young healthy adult reference. (Sheu & Diamond, 2016)

The BMD can also predict osteoporotic vertebral fractures (Schwaiger et al., 2014).

Very few studies have been able to evaluate bone mineral density (BMD) as a risk factor for the occurrence of PIF.

A study by Uezono et al. was one of the few studies to associate lower CT density and the development of PIF (Uezono et al., 2013).

These studies will be presented further in the discussion section.

1.6.1. Standard methods of measuring bone mineral density

Usually, the BMD is assessed by using the dual-energy X-ray absorptiometry (DXA) or the quantitative computed tomography (qCT).

The DXA is the most common technique for measuring BMD. It assesses BMD in two dimensions, in trabecular and cortical bone, giving us the areal density in g/cm^2. The most common sites to measure BMD are the lumbar spine and the hip (Li et al., 2013).

The measurements made by DXA can be affected by a lot of factors. False elevations can be observed due to vertebral diseases and spinal degenerations, such as osteoarthritic spondylosis, scoliosis, osteophytes, vertebral fractures, or even artefacts from calcifications such as abdominal aortic calcifications (Sheu & Diamond, 2016). These shortcomings of DXA can be problematic, as it can lead to a mismatch between clinical findings that may indicate osteoporosis, and the results of DXA, where the BMD may still seem normal (Li et al., 2013).

The qCT makes use of a standard X-ray CT scanner with a calibration standard. It allows the assessment of trabecular bone density without the overlay of cortical bone and other tissues, giving us the results in true volumetric bone mineral density (mg/cm^3). The most common site to measure the BMD is the lumbar spine. (Li et al., 2013)

On occasion, results can be falsely low in a patient with normal T-scores on DXA. It is believed to be due to the increased bone marrow fat in patients of higher age, which affects the assessment of BMD on qCT. The qCT has its advantages, but also comes with its shortcomings. Higher doses of radiation, fewer standardized reference ranges and analysis protocols and less reproducibility are some of the limitations of qCT (Li et al., 2013).

1.6.2. New method of measuring bone mineral density

While we know the usual methods of assessment of BMD like the DXA and qCT to be well-established and to be mainly very accurate, we also know that the validity of a qCT depends on the experience of the technician performing the analysis (Schwaiger et al., 2014).

In recent years, a new method of measuring BMD has shown promising results by using converted BMD values from lumbar spine multidetector-row computed tomography (MDCT) scans. In a 2011 study, eight postmenopausal women received a qCT to assess the BMD of vertebrae L1-L3. Then, MDCT images of the same patients were used and apparent BMD of vertebrae L1-L3 were measured using the sagittal reformations. With the help of linear regression analysis, a MDCT-to-qCT conversion equation for BMD was calculated. The equation was then applied to vertebral BMD datasets (L1-L3) of 75 postmenopausal women. The correlation coefficient for the BMD values of MDCT and qCT Was r=0.94 ($p<0.05$). The short-term and long-term reproducibility errors for MDCT-BMD measurements were 2.09% and 7.70%, respectively. (Baum et al., 2011)

Similarly, Schwaiger et al. calculated mean BMD values for vertebrae scanned in qCT and mean Hounsfield units (HU) values from vertebrae scanned in MDCT. They calculated two different MDCT-to-qCT equations (for patients scanned with 120 kVp and 140 kVp tube voltage, respectively) by using a linear regression model. Then, the mean attenuation values (in HU) obtained from MDCT were converted into BMD by using the same equations. For their equations for 120 kVp and 140 kVp tube voltage, the correlation coefficient was $R^2 = 0.92$ ($P < .001$) and $R^2 = 0.81$ ($P < .001$), respectively. (Schwaiger et al., 2014)

Up until now, the above-mentioned method was used to differentiate patients with and without osteoporotic fractures (Baum et al., 2011; Baum et al., 2012), as well as predict incidental osteoporotic vertebral fractures and screw loosening after spondylodesis (Schwaiger et al., 2014).

2. Objectives, hypotheses and specific aims of the doctoral thesis

Our objective is:

- To investigate individual risk factors (bone mineral density, radiation dose, higher age) for the development of pelvic insufficiency fractures (PIF) after radiotherapy in patients treated for cervical cancer. This data will help predict the individual toxicity risk of a patient in future prospective studies.

Hypotheses:

- Planning CTs can be used for accurate measurement of bone mineral density (BMD).

- By using a MDCT-to-qCT conversion equation, we can obtain BMD values from existing planning CTs, consequently making the need of further imaging modalities and the associated additional radiation exposure, redundant.

- A lower BMD measured in the planning CT is associated with a higher risk of developing PIF after radiotherapy and should be taken into account as an individual risk factor.

Specific aims:

- To investigate risk factors (Bone mineral density, radiation dose, higher age) for PIF after radio(chemo)therapy (R(C)T) for cervical cancer.

- To present a new approach – BMD measurement in planning CTs for radiotherapy – which can help predict the risk for the development of PIF after radiotherapy in prospective studies.

3. Material and methods

3.1. Patients

Medical records of 62 patients with cervical cancer who received treatment between 2013 and 2017 at the Department of Radiation Oncology of Klinikum Rechts der Isar, Munich, Germany, were reviewed.

We acquired the patients' data by using their physical and the digital records. The obtained data includes: Age, TNM-Staging and -Grading, as well as data of the radiotherapy plans (for both EBRT and brachytherapy) and the chemotherapy used in each treatment plan. We also acquired the time of beginning and ending of the radiation-treatment. The exact date of the follow-up MRIs of the fracture group, in which PIF was diagnosed, was also obtained during the data collection.

The median age was 55 years (range, 32-81). Patients were treated with EBRT alone or EBRT and concurrent chemotherapy. Out of 62 patients, 33 (53,2%) were treated with definitive radiochemotherapy (RCT), 22 (35,5%) with adjuvant RCT, 5 (8,1%) with definitive radiotherapy (RT) and 2 (3,2%) patients were treated with adjuvant RT. Also, 31 (50%) patients received additional high-dose-rate intracavitary brachytherapy (HDR-ICBT).

Out of the 6 patients in the fracture group, 3 (50%) went through primary RCT, 2 (66,7%) through adjuvant RCT and only one (16,7%) received adjuvant RT.

Further details of the treatment, especially the applied dose, will be discussed in the results section.

The UICC (*Union for international cancer control)* TNM stages of our patients are described in Table 3.

Table 3. TNM-stage and grade distribution of our study group.

T n (%)	T1 19 (30,6)	T2 27 (43,5)	T3 11 (17,7)	T4 4 (6,5)	Tx 1 (1,6)
N n (%)	N0 17 (27,4)	N1 45 (72,6)			
M n (%)	M0 40 (64,5)	M1 19 (30,6)	Mx 3 (4,8)		
Grading n (%)	G1 1 (1,6)	G2 32 (51,6)	G3 28 (45,2)	Gx 1 (1,6)	
TNM-Stage and grade distribution of our study group in n (%) Tx = Main tumor cannot be assessed (i.e. due to lack of information) Mx = Metastasis cannot be assessed (i.e. due to lack of information) Gx = Grading cannot be assessed (i.e. due to lack of information)					

With special attention to our fracture group only, in the following section the TNM staging and grading in patients with PIF will be presented and are listed as follows: the most common size of the primary tumor was T2 (66,7%), meaning a tumor that invades beyond the uterus, but

not up to the pelvic wall or to the lower third of the vagina. The tumor of one patient (16,7%) was categorized as T3, meaning extending to the pelvic sidewall and/or involving the lower third of the vagina and/or causing hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes. In one patient the exact spread of the primary tumor could not be assessed (Tx) because of lack of available information. Half (50%) of the PIF group had metastases in the lymph nodes, additionally only one (16,7%) patient was diagnosed with distant metastases (in para-aortic lymph nodes, M1). The classification was based on the 9th edition of TNM and the International Federation of Gynaecology and Obstetrics (FIGO, 2018). Also, in our patient group, the majority (83,3%) had G2 grading, while one (16,7%) patients' tumor was described as G3 grading.

3.2. Imaging analysis

All patients underwent follow-up magnetic resonance imaging (MRI). The pelvic insufficiency fractures (PIF) were detected in the follow-up MRIs by experienced radiologists. In the MRI findings the PIF were defined as hypointense signal alterations on T1-(Figure 2) or hyperintense signal alterations on T2-weighted images (Figure 3).

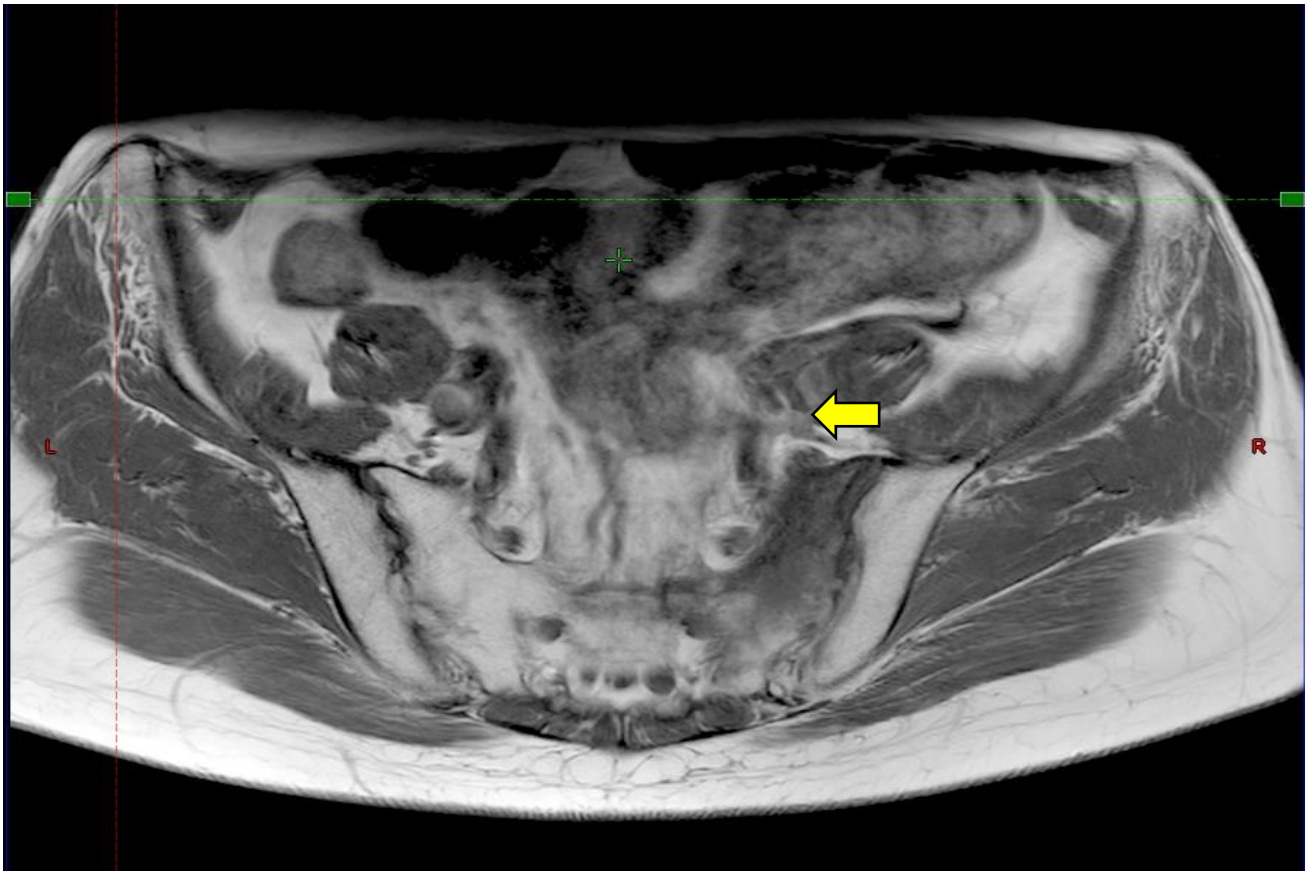


Figure 2. Pelvic insufficiency fracture (PIF) of the right massa lateralis (marked with an arrow) of the sacral bone on T1-weighted axial MRI images of a 61-year-old patient.

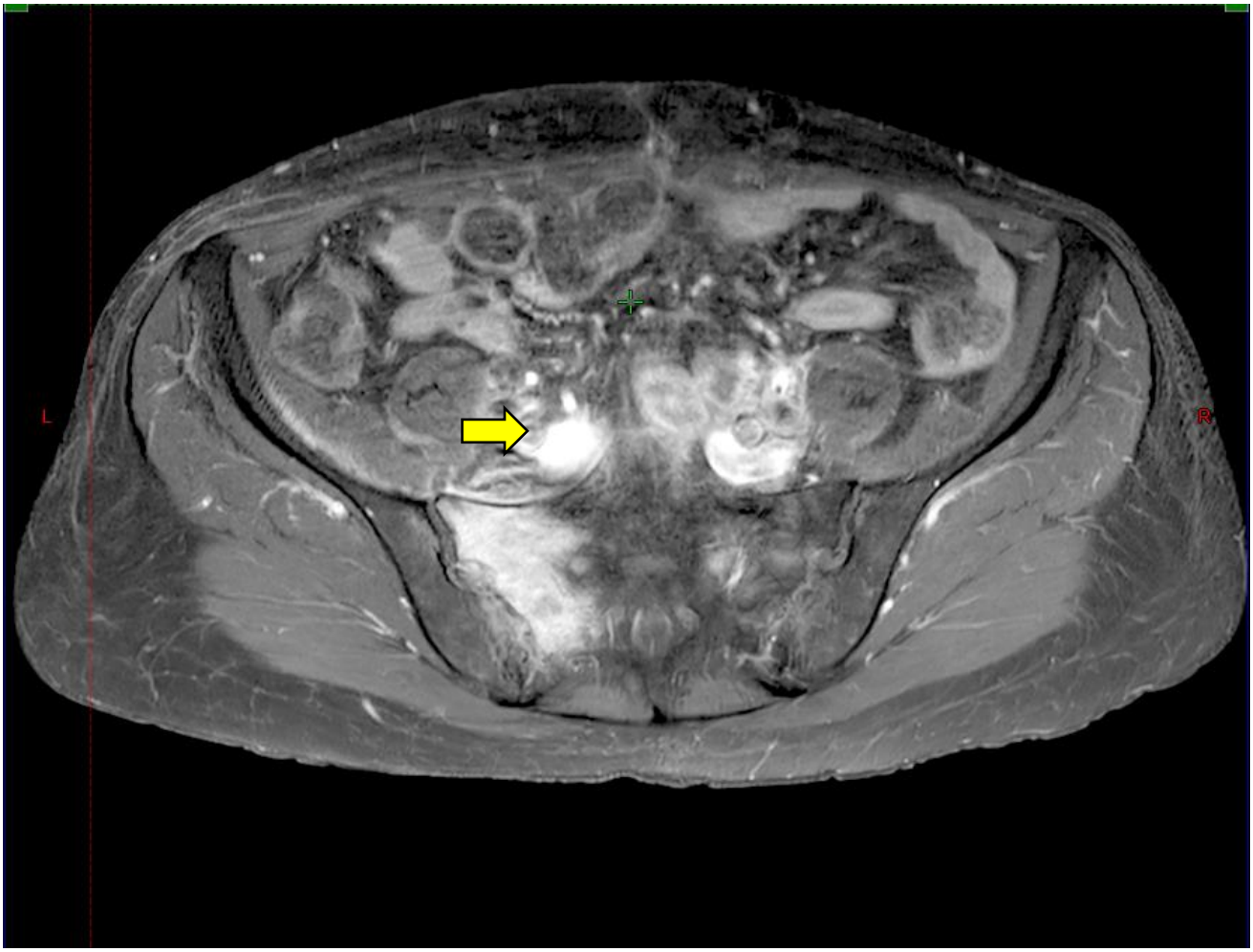


Figure 3. Pelvic insufficiency fracture (PIF) of the left massa lateralis (marked with an arrow) of the sacral bone on T2-weighted axial MRI images of a 67-year-old patient.

We registered the MRI of the patients in the PIF group into the planning CT scan and re-contoured the PIF region on the planning CT with MRI guidance using the ARIA Oncology Information System. Then, on the contralateral side of the fracture, a mirrored structure of the fracture (mPIF) was generated. We also manually contoured the sacrum for all patients.

We analyzed DVH parameters such as V30, V40 and V50Gy of the sacrum and the PIF for each patient. We used it to determine the relative volume that received the aforementioned doses. We also analyzed the D50%, which gives us the dose that 50% of the volume of the

sacrum/PIF received, as well as the Dmean and the Dmax, which provides information about the mean/maximum dose these structures were irradiated with.

A DVH with two examples of analyzed parameters (D50% and V40Gy) is shown in Figure 4.

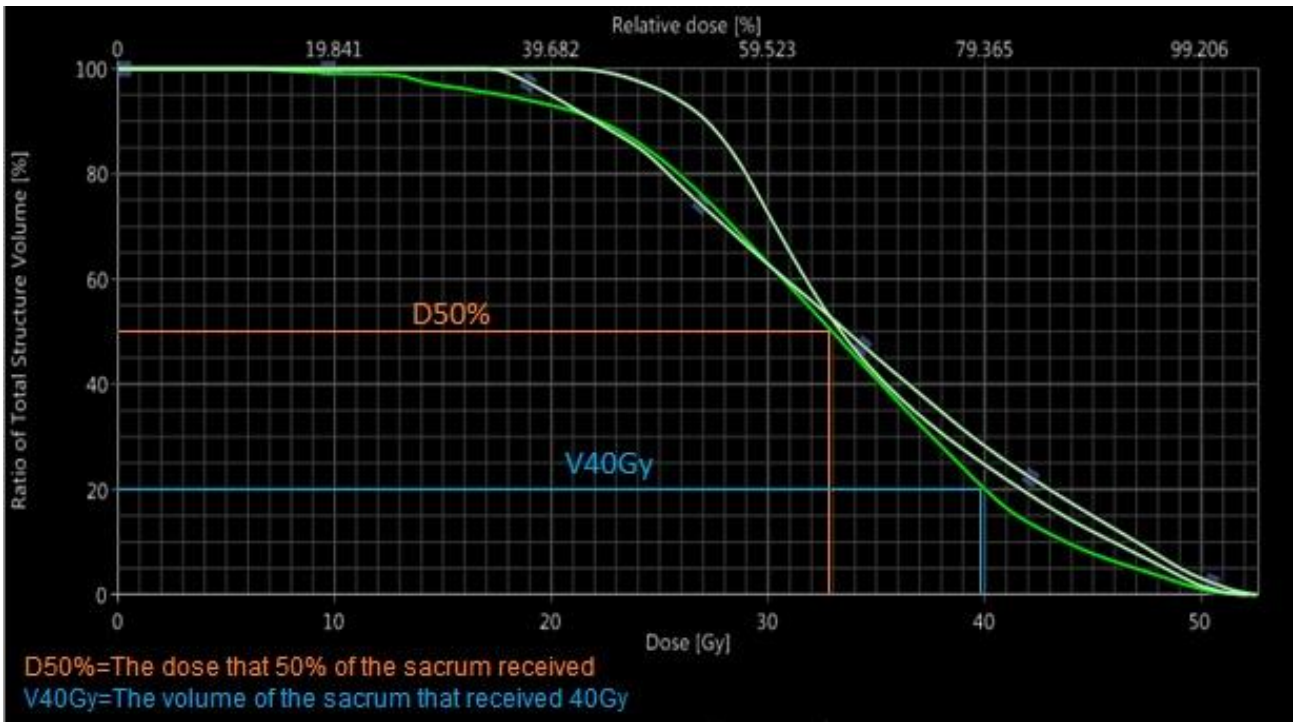
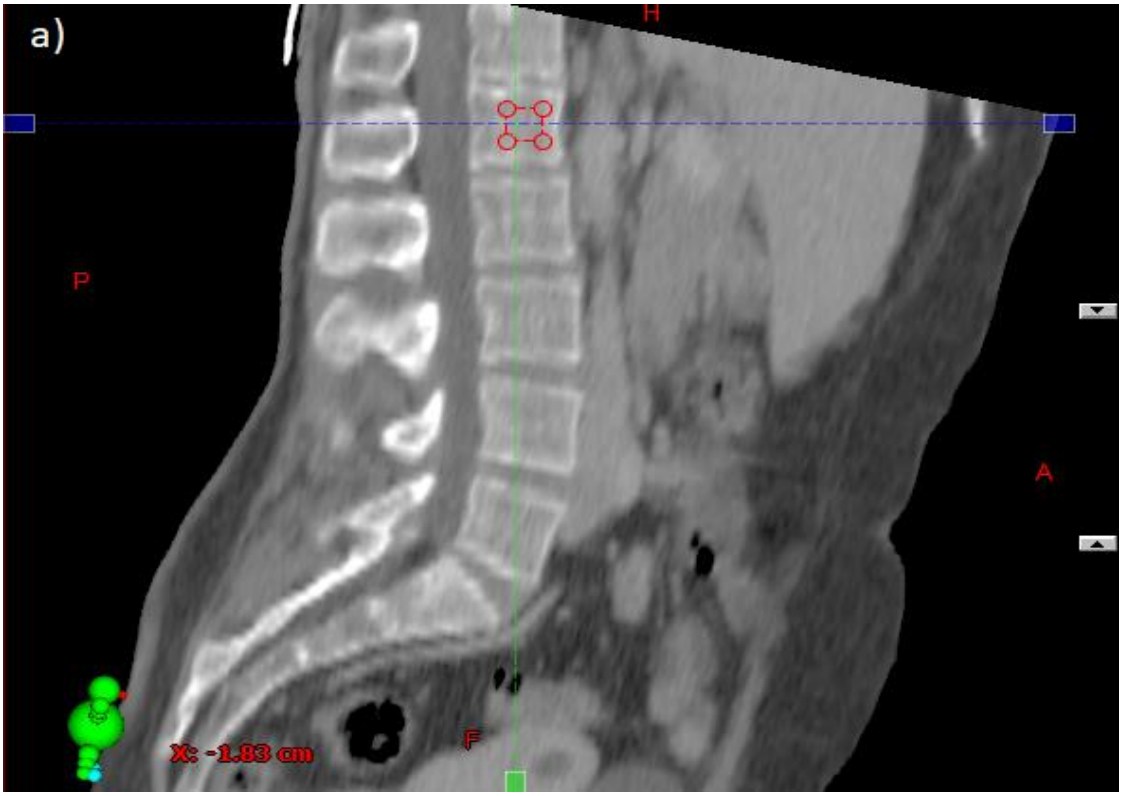


Figure 4. A Dose-volume histogram (DVH) with two exemplified analyzed parameters (D50%, V40Gy).

We also analyzed the BMD of three lumbar vertebrae, as well as the first and second sacral vertebrae for each patient, and compared the results of the patients with PIF, to those without. For the lumbar vertebrae we analyzed the 1st to the 3rd lumbar body, in the planning CT of patients where the 1st or the 2nd lumbar vertebra was not completely depicted, we analyzed the 2nd-4th and the 3rd-5th, respectively.

For this, in accordance with Schwaiger et al., we placed a square region of interest (ROI) half the height of the lumbar vertebrae in the sagittal plane of the planning CT for each patient (Schwaiger et al., 2014). The square was placed in the ventral half of the trabecular compartment of the vertebrae, as illustrated in Figure 5 (a), by tilting the CT image in order

for the trabecular compartment to be in a parallel position to the sides of the square ROI and was subsequently used to show mean attenuation values of the trabecular bone in HU, as seen in Figure 5 (b). Then, we used a MDCT-to-qCT equation (BMD = slope * HU + intercept; slope= 0,773549; intercept=-1,67321) to convert the acquired HU values from planning CTs into BMD (mg/cm^3). All patients had their planning CTs performed by the same CT Scanner (SIEMENS Emotion 16 - 2007).



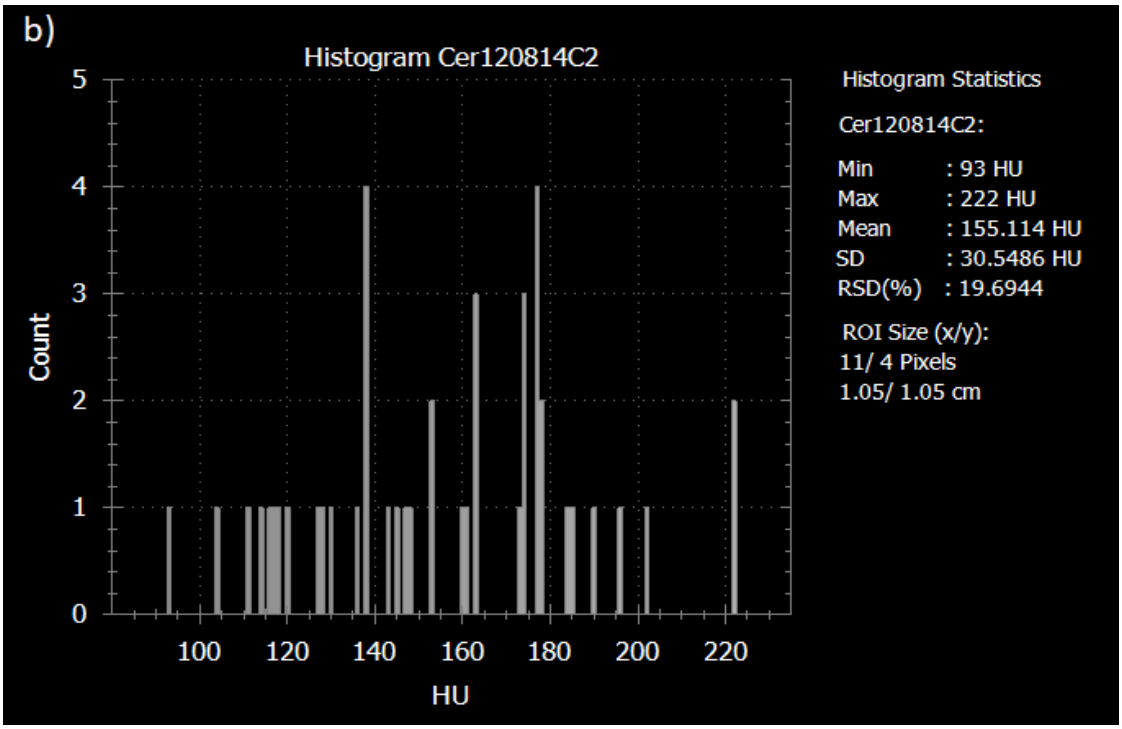


Figure 5. Region of interest (ROI) placement for the measurement of CT density (in HU) in the planning CT (a). In the sagittal plane of the planning CT, a square ROI (red) half the height of the lumbar vertebra was placed in the ventral half of the trabecular compartment of the 1st

lumbar body by tilting the CT image in order for the trabecular compartment to be parallel to the sides of the square ROI and was subsequently used to show mean attenuation values (in HU) of the trabecular bone (b).

3.3. Statistical analysis

The statistical analyses were performed with IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, IL, USA). Correlation between the BMD and PIF, as well as between the dose-volume histogram parameters and PIF were analyzed by *t*-test. A value of $p \leq 0.05$ was considered statistically significant. Association between age and BMD between the two groups was assessed using a linear regression model.

4. Results

Out of 62 patients, 6 (9,7%) had a fracture. All of them were detected in follow-up MRIs as PIF and all of them were located in the massa lateralis of the sacral bone. The median imaging follow-up was 16 months (range: 1,5-53 months). Two out of those six patients had a bilateral fracture with only one of them being symptomatic. The median age in the PIF group was significantly higher ($p<0.01$) with 62 years compared to 53 years in the other patients – i.e. without PIF - (OTH). In our study group, 43 (69,4%) patients received an EBRT boost to the primary tumor (PT) and/or the lymph nodes (LN), with 30 (69,8%) of them receiving a simultaneous integrated boost (SIB), 9 (20,9%) a sequential boost (SB) and amongst them, 4 (9,3%) patients went through both boost technique's (first SIB, then SB).

The median dose to the planning target volume (PTV) was 50,4 Gy (range, 36-50,4 Gy).

The median EBRT boost dose to the PT was 56 Gy (range, 42-70 Gy) and to the LN 58,8 Gy (range, 52-61,8 Gy). The median dose delivered through HDR-ICBT was 28 Gy (range: 5-28 Gy). Out of the 55 patients who went through concomitant chemotherapy, 52 (83,8%) patients received platin-based chemotherapy (cisplatin or carboplatin), while 3 (4,8%) patients were treated with vinorelbine. In our study group, 7 (11,3%) patients did not go through chemotherapy because of either medical contraindication or the patient's refusal.

The median time between the end of radiotherapy and the detected fracture was 7 months (range: 4,9-9,7 months).

The BMD of the sacral bone was significantly lower ($p<0.03$) in the PIF group with 127,8 mg/cm^3 compared to 173,1 mg/cm^3 in the OTH. There was a significant ($p\leq0.05$) difference of the mean BMD of the lumbar vertebrae in the PIF group (87,9 mg/cm^3) and the OTH (121,4 mg/cm^3) when comparing the two groups, as illustrated in form of a boxplot in Figure 6. However, the difference in the PIF compared to the mPIF and the first and second sacral bodies in the PIF group compared to the ones in the OTH, were both not significant ($p<0.49$ and $p<0.15$, respectively). (Kurrumeli et al., 2020)

Additionally, we measured the BMD of S1 and S2 by similar ROI placement as the BMD measurement in the lumbar vertebrae. There was no significant difference between the two groups.

Moreover, association between age and BMD between the two groups was assessed using a linear regression model, showing correlation between higher age and lower BMD (Figure 6).

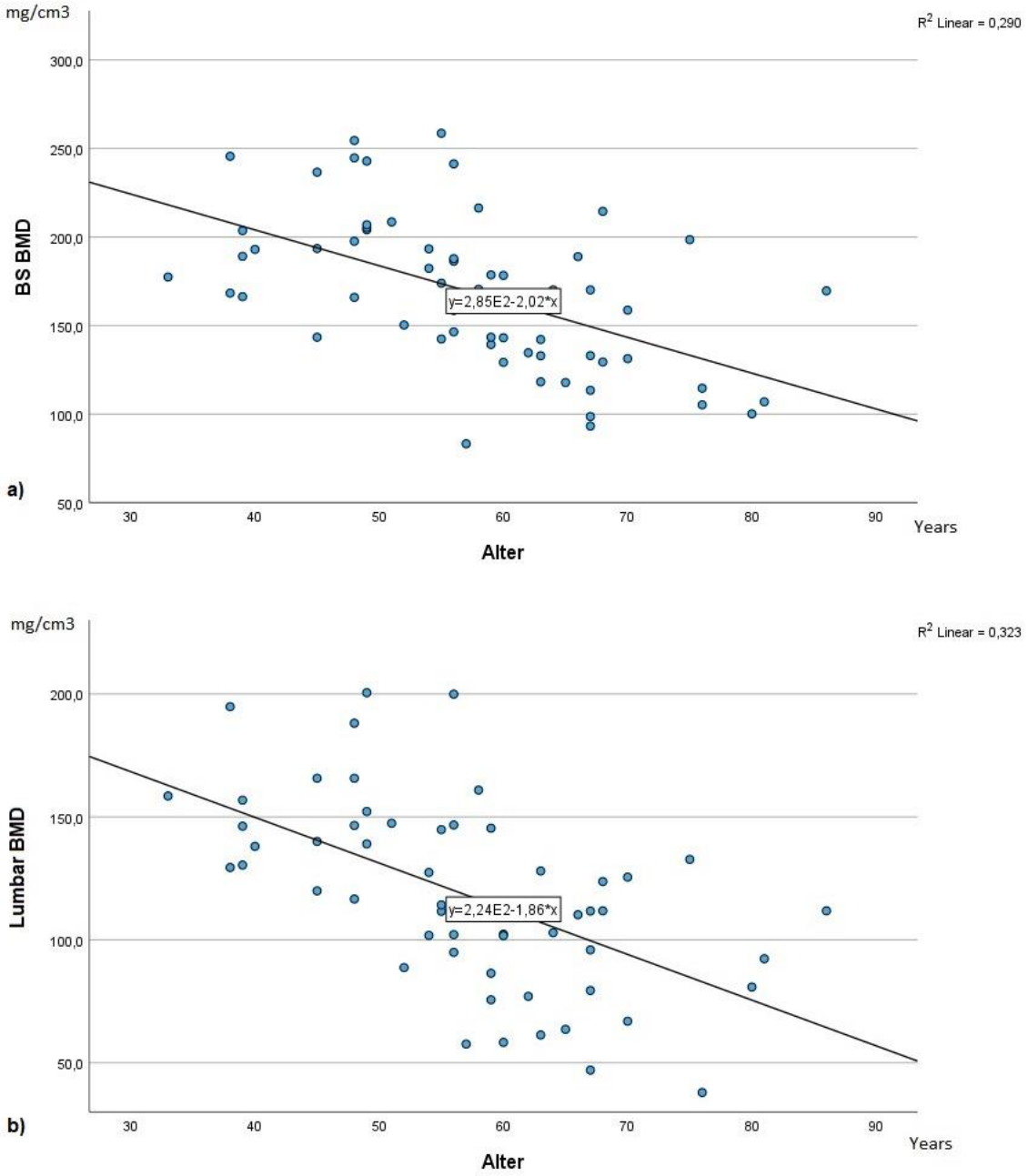


Figure 6. Linear regression model: Correlation between age and bone mineral density (BMD) of the sacrum (a) and the lumbar vertebrae (b).

The actual BMD of the fracture itself (PIF) might have been overestimated, as it is known that even BMD measured by CT is prone to falsely elevated BMD values when a fracture is present in the area to be measured.

The BMD association with PIF is shown in Table 4.

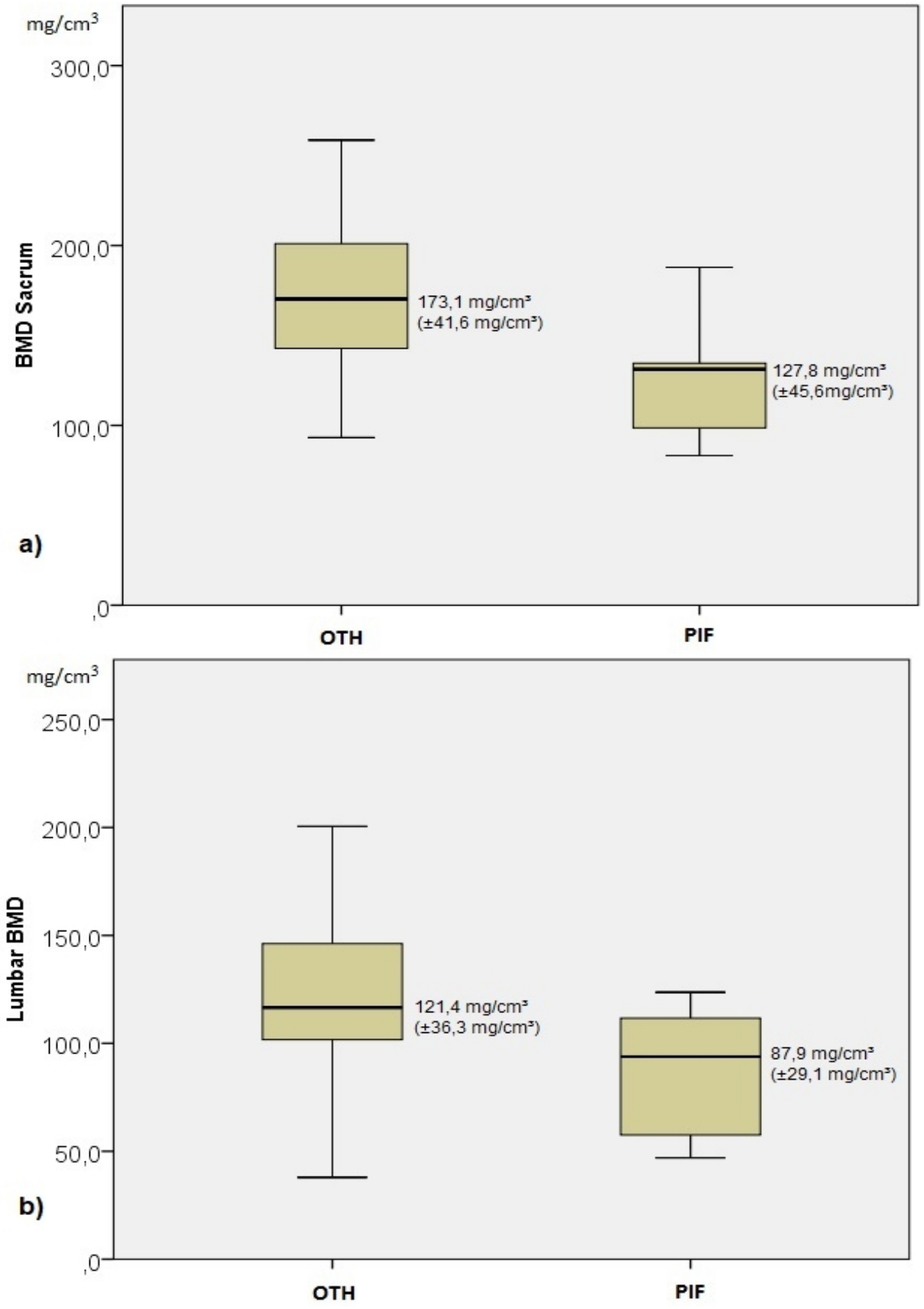


Figure 7. Boxplot depiction of the bone mineral density (BMD) - in mg/cm³ - of the sacrum (a) and lumbar vertebrae (b) in patients with a fracture (PIF) and in those without (OTH).

Table 4. Bone mineral density (BMD) association with pelvic insufficiency fractures (PIF).

	PIF group (n=6)	OTH (n=56)	P value
BMD_{sacrum}, mg/cm^3	127,8	173.1	0.03
$BMD_{lumbar,}$ ng/cm^3	87,9	121,4	0.05
$BMD_{S1,S2}$, mg/cm^3	79,3	107,8	0.15
$BMD_{PIF/mPIF}$, mg/cm^3	70,4/84,2		0.49

PIF group = patients with a fracture
OTH = patients without a fracture
BMD_{sacrum} = Bone mineral density (BMD) of the Os sacrum (in mg/cm^3)
BMD_{lumbar} = BMD of the lumbar vertebrae 1-3 (or 2-4 and 3-5, respectively, if vertebrae 1 and/or 2 were not depicted on the CT Scan, in mg/cm^3)
$BMD_{S1,S2}$ = BMD of sacral bodies 1 and 2 (in mg/cm^3)
$BMD_{PIF/mPIF}$ = BMD of the contoured fracture (PIF) and the mirrored structure (mPIF) of the fracture (in mg/cm^3)

The Dmean of the sacrum in the PIF group was 39,5 Gy and 39,7 Gy in the OTH. The Dmax of the sacrum in the PIF group was 55,1 Gy and 53,9 Gy in the OTH, showing no significant difference between groups.

The Dmean of the PIF, although higher than in the mPIF, did not reach significance ($p<0.20$). The Dmax of the PIF did also not reach significance when compared to the mPIF ($p<0.48$).

The D50% of the sacrum/PIF in our study group were both not significant ($p<0.89$ and $p<0.31$, respectively). Furthermore, there was no significant difference regarding the V30, V40 and V50Gy in our study group. (Kurrumeli et al., 2020)

The full list of analyzed DVH parameters are shown in Table 5 and 6.

Table 5. Dosimetric parameter association with pelvic insufficiency fractures (PIF).

	PIF group (n=6)	OTH (n=56)	P value
$Dmean_{sacrum}$, Gy	39,5	39,7	0.87
$Dmean_{PIF/mPIF}$, Gy	41,3/35		0.20
$Dmax_{sacrum}$, Gy	55,1	53,9	0.44
$Dmax_{PIF/mPIF}$, Gy	52,5/51,7		0.48
$D50\%_{sacrum}$, Gy	41,2	40,9	0.89
$D50\%_{PIF/mPIF}$, Gy	42,5/36		0.31

PIF group = patients with a fracture
OTH = patients without a fracture
$Dmean/Dmax_{sacrum}$ = Mean/Maximum dosis that the Os Sacrum received (in Gray (Gy))
$D50\%_{sacrum}$ = The dose that 50% of the sacrum has received (in Gy)
$Dmean/Dmax_{PIF/mPIF}$ = Mean/Maximum dosis of the contoured fracture (PIF) and the mirrored structure (mPIF) of the fracture (in Gy)
$D50\%_{PIF/mPIF}$ = The dose that 50% of the contoured fracture (PIF) and the mirrored structure of the fracture (mPIF) have received (in Gy)

Table 6. Volumetric parameter association with pelvic insufficiency fractures (PIF).

	PIF group (n=6)	OTH (n=56)	P value
$V30Gy_{sacrum}$, %	82,5	83,3	0.91
$V30Gy_{PIF/mPIF}$, %	83,7/66,6		0.36
$V40Gy_{sacrum}$, %	52,7	54,7	0.78
$V40Gy_{PIF/mPIF}$, %	60,6/37,6		0.24
$V50Gy_{sacrum}$, %	16,2	13,7	0.61
$V50Gy_{PIF/mPIF}$, %	25,2/7,8		0.11

PIF group = patients with a fracture

OTH = patients without a fracture

$V30/40/50Gy_{sacrum}$ = The relative volume of the sacrum that received 30/40/50Gy (in %)

$V30/40/50Gy_{PIF/mPIF}$ = The relative volume of the fracture (PIF)/mirrored structure (mPIF) of the fracture (in %)

5. Discussion

In our study, we found that approximately 10% of the cervical cancer patients will suffer a pelvic insufficiency fracture (PIF).

This study strengthens the assumption of recent studies that PIFs are not as rare of a complication after radiotherapy as previously thought and might have been underestimated in gynaecological patients. (Kurrumeli et al., 2020)

5.1. Incidence and symptomatic pelvic insufficiency fractures (PIF)

Several studies investigating the incidence of PIF showed a wide range of incidence from 1,7% to 89% (Blomlie et al., 1996; Huh et al., 2002; Oh et al., 2008; Ramlov et al., 2017; Schmeler et al., 2010; Tokumaru et al., 2012; Uezono et al., 2013).

In a study performed by Huh et al., 463 patients who received radiotherapy for uterine or cervical cancer were clinically examined. The median follow-up was 38 months. Eight patients were diagnosed with PIF after treatment and all of them complained of moderate to severe pelvic pain. (Huh et al., 2002)

Another study evaluated the clinical records and imaging studies of 557 patients with cervical cancer who received radiotherapy. Imaging studies included MRI, CT and bone scintigraphy. The 5-year cumulative incidence of PIF in this study was 19,7%. Pelvic pain was present in 57,8% of patients at the time of diagnosis. 13,3% had narcotics or even admission to the hospital because of severe pain. (Oh et al., 2008)

Schmeler et al. reviewed the records of 516 women who were treated with radiotherapy for cervical cancer. Imaging studies, such as MRI or CT, were available for 300 of the women. The median follow-up for all patients was 20,9 months. Out of 300 patients, 29 (9,7%) patients

were diagnosed with PIF and 13 (45%) of those had symptoms, with pain being the most common one. 72% of PIF were diagnosed by CT scans, 28% by MRI. (Schmeler et al., 2010)

To further investigate the incidence of PIF after radiotherapy for women treated with early-stage cervical cancer, Tokumaru et al. analyzed subjects in a prospective, multi-institutional study. They analyzed 59 patients. To find PIF, all patients received MRI and CT scans at 3, 6, 12, 18 and 24 months. PIF was diagnosed if patients had abnormalities in both CT and MRI scans. The two-year cumulative incidence was 36,9%. Out of 21 patients with PIF, 9 were symptomatic and complained of pain. All of them were successfully relieved of pain by rest and non-narcotic analgesic drugs. (Tokumaru et al., 2012)

In a 2006 study, the medical records of 158 patients with gynaecological malignancies who underwent radiotherapy were reviewed. The median follow up was 43 months. Out of 158 patients, 18 (11,4%) were diagnosed with PIF by CT and/or MRI. (Ikushima et al., 2006)

A study by Ramlov et al. reviewed the medical records and imaging studies of 101 patients treated with radiotherapy for LACC. MRI follow up scans were performed at 3 and 12 months after the end of radiotherapy or if indicated based on clinical signs. The median-follow up was 25 months. The MRI scans were evaluated by expert oncologic radiologists. In this study, 20% were diagnosed with PIF, with half of them being symptomatic. Some of them required no medication, while some needed narcotics for pain management. (Ramlov et al., 2017)

Uezono et al. reviewed medical records of 126 patients treated with radiotherapy for cervical cancer. Out of 126 patients, 99 had at least one CT or MRI scan during their follow-up at more than 6 months. The median follow-up was 21 months. The 2-year cumulative incidence was 32%. The 5-year cumulative incidence was 63%. Furthermore, the 2-year cumulative incidence of symptomatic PIF was 21% and the 5-year cumulative incidence was 32%. Most patients received nonsteroidal anti-inflammatory drugs for pain management, although 3 patients needed narcotics to achieve pain relief. One patient with femoral head necrosis needed hip replacement surgery due to uncontrollable pain with medication alone. The onset of PIF was defined as the date of diagnosis by imaging studies. (Uezono et al., 2013)

A 1996 study by Blomlie et al. performed a prospective study on 18 patients who were treated with radiotherapy for advanced cervical cancer. MRI scans were performed before, during,

and after radiation therapy. The scans were evaluated by two radiologists. They diagnosed PIF in 16 (89%) out of 18 patients. All fractures were confirmed by either CT scan or bone scintigraphy. The PIF were detected between 3 and 12 months after radiotherapy. Multiple fractures were detected at 24 months. During the observation period of 30 months in total, 21% of the pelvic fractures healed. (Blomlie et al., 1996)

As seen above, the more recent studies (Oh et al., 2008; Ramlov et al., 2017; Schmeler et al., 2010) generally described higher incidence rates compared to earlier studies. Blomlie et al. was an exception. Along with Tokumaru et al., the two prospective studies, recorded the highest incidence rates with 89% and 36,9%, respectively. (Blomlie et al., 1996; Tokumaru et al., 2012)

In a recent study, Sapienza et al. evaluated the incidence of PIF in a meta-analysis and meta-regression. Twenty-one studies with a total of 3929 patients were included. The overall PIF incidence was 14%. These studies had different approaches. Some studies evaluated the incidence of PIF in retrospective studies, while some of them performed prospective studies. Also, different imaging methods were used in different studies (MRT vs CT). Moreover, the frequency and timing of follow-up CT or MRI-scans had major differences between each study. (Sapienza et al., 2020)

Another reason for the low incidence rates in earlier studies may be that the imaging modalities to find PIF were mainly used on symptomatic patients. The reason of the overall higher incidence rate in recent studies may be the attention this post-radiation complication has received in recent years, as well as the improvement of follow-ups (i.e. the frequency, as well as the timing of the scans).

This is very similar to our data with approximately 10% PIF and low symptom burden due to PIF. Although generally not life-threatening and often few to no apparent symptoms, the relatively high number of PIF after radiotherapy should get special attention, making the timely diagnosis and management essential in regard to improving the quality of life (Park et al., 2011).

Furthermore, as it is often initially suspicious of metastatic bone lesions when a patient presents himself with lower back pain after radiotherapy for cervical or prostate cancer for

example, the knowledge of PIF is crucial to differentiate it from bone metastases and consequently prevent further unwarranted treatment (Igdem et al., 2010; Oh & Huh, 2014).

5.2. Common risk factors for pelvic insufficiency fractures (PIF) after radiotherapy

Several studies focused on risk factors for PIF. A series of clinical characteristics, such as lower BMI and postmenopausal status were investigated by a number of studies (Ramlov et al., 2017; Schmeler et al., 2010; Tokumaru et al., 2012; Uezono et al., 2013).

5.2.1. Body mass index (BMI) / Body weight

One of the risk factors for the development of PIF seems to be low BMI / body weight.

A study by Schmeler et al., who evaluated records of 516 women treated for cervical cancer, found that the BMI was significantly lower in women diagnosed with PIF compared to women without PIF after radiotherapy (26.0 kg/m^2 vs 28.0 kg/m^2) (Schmeler et al., 2010).

Lower body weight was described as a risk factor for developing PIF by a 2007 study by Tokumaru et al. In this study, PIF occurred significantly more often in patients with low body weight (<50kg). (Tokumaru et al., 2012)

Uezono et al. also investigated a lower BMI as a possible risk factor for the development of PIF. They compared patients with a BMI <21 and >21 kg/m^2. However, no significant difference between the two groups was observed. (Uezono et al., 2013)

A 2017 study by Ramlov et al. investigated lower BMI as a risk factor as well. They, too, did not find a statistically significant difference between patients with and without PIF. (Ramlov et al., 2017)

5.2.2. Postmenopausal status

Postmenopausal status was also discussed as a risk factor and evaluated in a series of studies.

Schmeler et al. found that 62% of the women who were diagnosed with PIF, were postmenopausal when the cancer got diagnosed, compared to 37% in the rest of their group of patients. (Schmeler et al., 2010)

The Ramlov et al. study found that the incidence of PIF was significantly higher in postmenopausal women. 17 out of 49 women who were postmenopausal (35%) developed a PIF, compared to 3 out of 52 premenopausal women (6%). (Ramlov et al., 2017)

Uezono et al. also found that postmenopausal state is significantly related to patients with diagnosed PIF. (Uezono et al., 2013)

5.2.3. Higher age

Higher age is one of the most common known risk factors for the development of PIF.

A 2017 study investigated risk factors for PIF in 101 patients receiving treatment for LACC. The median follow-up time was 25 months. They diagnosed PIF in 20 patients. They found that the incidence of PIF was significantly higher in patients aged >50 years (37%) compared to patients younger than 50 years of age (4%). (Ramlov et al., 2017)

Another study by Bazier et al. investigated the occurrence of PIF in 341 patients treated with radiotherapy for gynaecological or anal cancer. The imaging studies included CT and/or MRI scans. The median follow-up was 38 months. They found that the incidence of PIF after radiotherapy is low (4,4%) but is – similarly to Ramlov et al. (2017) - significantly higher in patients aged >50 years and in postmenopausal patients (Bazire et al., 2017; Ramlov et al., 2017). However, in this study, the osteoporosis status was available for only 9% of their patients, and pre-treatment bone density was not evaluated.

In a study by Schmeler et al. the median age at the time of cancer diagnosis was significantly higher in the group that developed a fracture when compared to patients without a fracture in the follow-up (56,5 vs 46,7 years) (Schmeler et al., 2010).

A series of further studies defined higher age as a risk factor for PIF (Oh et al., 2008; Tokumaru et al., 2012; Uezono et al., 2013).

The median age in patients with PIF was significantly higher ($p<0.01$) in our study (62 years compared to 53 years).

A summary of incidence and higher age as a risk factor for PIF in different studies is shown in Table 7.

Table 7. Summary of literature on pelvic insufficiency fractures (PIF) after radiotherapy (RT).

Reference	Patients (n)	PIF (%)	Age in patients with PIF (years)	Age in patients without PIF (years)	p-value	Time from completion of RT to PIF (months)
Blomlie et al. (1996)	18	89%	NA	NA	NA	Median: NA Range: 3-24
Huh et al. (2002)	463	1,7%	NA	NA	NA	Median: 12 Range: 7-19
Ikushima et al. (2006)	158	11,4%	69	59	P<0.01	Median: 6 Range: 3-51
Oh et al. (2008)	557	19,7%	NA	NA	NA	Median: 13 Range: 5-44
Schmeler et al. (2010)	300	9,7%	56,5	46,7	P<0.04	Median: 14 Range: 2-63
Tokumaru et al. (2012)	59	36,9%	NA	NA	NA	Median: 24 Range: NA
Uezono et al. (2013)	99	33%	NA	NA	NA	Median: 14 Range: 2-46
Ramlov et al. (2017)	101	20%	58	44	P<0.01	Median: NA Range: 3-12
Our study	62	9,7%	62	53	P<0.01	Median: 16 Range: 1,5-53

NA: not available.

A Summary of the following points on pelvic insufficiency fractures (PIF) after Radiotherapy (RT) from different studies:

-Incidence of PIF (in %)

-Median age of patients with/without PIF (in years)

-Median time from completion of RT to the diagnosis of PIF

5.2.4. Chemotherapy

In 2012, a study by Gondi et al. investigated the late toxicities following concomitant RCT compared to RT alone. The investigated the occurrence of vaginal, urologic or gastrointestinal toxicity using Common Terminology Criteria for Adverse Events version 4.0 (CTCAE), occurring $\geq$ 6 months after treatment completion. Additionally, they evaluated the occurrence of pelvic fractures in patients treated with RCT compared to RT alone. The study consisted of 480 patients who were treated with radio(chemo)therapy for cervical cancer. RT consisted of EBRT and brachytherapy. Out of the 480 patients, 106 were lost due to either relapse/death prior to 6 months or lost in the follow-up. Out of the remaining 374 patients, 195 patients received RT alone compared to 179 patients who received concomitant RCT. Cisplatin was the chemotherapeutic agent in 97% of those receiving concomitant RCT. The median follow-up was 35,5 months overall. The imaging studies were acquired only if patients complained of pain in the pelvic area. Twelve patients were diagnosed with a fracture, ten through MRI, two through CT scans. At 3 years, the probability for the occurrence of skeletal severe late toxicities (i.e. any pelvic fracture) was 1,6% in patients treated with RT compared to 7,5% in patients treated with concomitant RCT. (Gondi et al., 2012)

Various other studies investigating the same phenomenon were not able to show similar significant relations of PIF and patients receiving concomitant chemotherapy (Ramlov et al., 2017; Uezono et al., 2013).

The same was true for our study, as we were not able to find a significant correlation between concomitant RCT and the occurrence of PIF ($p<0.74$).

The Gondi et al. study (Gondi et al., 2012) has to be seen as an exception, as it is known that concomitant chemotherapy can improve the outcome in high-risk patients and is regarded as the standard treatment for LACC (Morris et al., 1999; Peters et al., 2000; Rose et al., 1999).

To underline the importance of chemotherapy as part of the treatment of cervical cancer, in the following section, two important studies - who delineate the importance of chemotherapy in patients treated for pelvic cancer - will be presented.

One of the studies investigating this matter, compared concomitant RCT with RT alone as adjuvant therapy after radical surgery in high-risk early-stage cervical cancer. The 243 patients included in their study were divided into a chemoradiotherapy group (CT+RT) and a radiotherapy group (RT). Patients who received CT+RT showed a statistically significant improvement in PFS. The projected 4-year PFS for the CT+RT group was 80%, compared to 63% for the RT group. The estimated 4-year OS were 81% in the CT+RT group, and 71% in the RT group. This shows that the addition of chemotherapy to the pelvic irradiation as adjuvant therapy after radical hysterectomy improves PFS and OS for high-risk, early-stage patients. (Peters et al., 2000)

Another study by Eifel et al. compared concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer. In this study, 403 patients with LACC were included and randomly assigned to receive either extended-field radiotherapy (EFRT) or concomitant chemoradiotherapy (CTRT). The median follow-up was 6,6 years. The overall survival rate for the CTRT arm was significantly higher than that of the EFRT arm (67% vs 41% at 8 years). The overall reduction in the risk of recurrence was 51% in the CTRT arm. The rate of serious late treatment-related side effects on the other hand, was not increased by adding chemotherapy to the pelvic irradiation. (Eifel et al., 2004)

5.2.5. Radiation dose

Several studies have also investigated the relation between the dose delivered to the sacrum and PIF.

A 2013 study evaluated the medical records of 126 patients who received R(C)T for cervical cancer. They included 99 patients who received at least one CT or MRI in the follow-up at >6 months after. The median follow-up was 21 months. They investigated a number of DVH parameters, such as V20, V30, V40, V50Gy, as well as the mean dose of the sacrum, the L5 vertebra, left and right pubis, and evaluated their relation to the occurrence of PIF. They evaluated patients in two groups, in patients who received EBRT doses of >43 Gy and in those who received ≤43 Gy. The 2-year incidence of the >43 Gy group was 7% vs 14% in the ≤43 Gy group, showing no statistically significant difference. They also compared patients who

received higher doses of HDR-ICBT (> 22Gy) to the ones receiving lower doses (≤22 Gy). The 2-year incidence in these groups were 16% vs 7%, respectively. However, no statistically significant correlation of DVH parameters to the incidence of PIF was observed. (Uezono et al., 2013)

Ramlov et al., although not in the whole patient cohort, did find a statistically significant correlation in the group of patients aged >50 years, according to which, a decrease in D50% sacrum dose from 40 Gy to 35 Gy decreases the risk of fracture by 23%, from 45% to 22%. Other DVH parameters, such as the V55Gy, did not reach significance in this particular study. (Ramlov et al., 2017)

In our study, we investigated a series of DVH parameters, such as V30, V40 and V50Gy, as well as D50%, Dmax and Dmean (Table 5 & 6). We did not observe a statistically significant correlation of these DVH parameters and the incidence of PIF.

A 2005 study by Baxter et al. investigated the occurrence of pelvic fractures in 6428 women aged 65 years or older treated for cervical, anal, or rectal cancer between 1986 and 1999. They found that women who received radiotherapy had a higher incidence of PIF compared to those who did not undergo radiotherapy. The time between the end of radiotherapy and the occurrence of the insufficiency fracture in this study was 7,1 to 19 months. The cumulative 5-year fracture rate was, 8,2% vs 5,9% in women with cervical cancer, 14% vs 7,5% in women with anal cancer, and 11,2% vs 8,7% in women with rectal cancer. The differences were statistically significant. They found that pelvic irradiation increases the risk of pelvic fractures, which is essential, as it is known that pelvic fractures play a significant role in morbidity and mortality in older women (Baxter, Habermann, Tepper, Durham, & Virnig, 2005).

Nevertheless, it is important to mention that the use of irradiation techniques, such as the IMRT, which is mostly used in the modern radiation oncology era, minimize the damaging effect of radiotherapy and come with a lower risk for PIF. Also, the group of patients evaluated by this particular study, was - due to the higher age - already at high risk for pelvic fractures. As called for by the authors of this study, posttreatment bone surveillance is essential in these patients, as a large group of patients are often asymptomatic by the time the PIF is diagnosed. (Sapienza et al., 2020)

In addition, we investigated BMD as a possible risk factor for PIF. Very few studies have been able to evaluate BMD and connect it to the occurrence of PIF.

5.3. The role of bone mineral density (BMD) as a risk factor for pelvic insufficiency fractures (PIF) and its measurement from planning CTs

The BMD is usually assessed by using DXA or the qCT. Baum et al. found an adequate method for acquiring qCT-equivalent BMD values from standard MDCT scans by using a MDCT-to-qCT equation. The converted BMD values could be used to differentiate patients with and without an osteoporotic vertebral fracture. (Baum et al., 2011)

Schwaiger et al. also used this method of acquiring converted BMD values from standard lumbar spine MDCT scans. They assessed the BMD of 106 vertebral bodies in 38 patients in qCT as a standard of reference and in sagittal reformations obtained from MDCT. Then, they calculated MDCT-to-qCT conversion equations and applied them to baseline MDCTs for another 62 patients. After a mean follow-up of 15±6 months, they re-assessed the patients for incidental fractures and screw loosening after spondylodesis. Patients who developed incidental fractures during follow-up showed significantly lower MDCT-BMD values than patients without incidental fractures (52,4 ± 10,5 vs 95,4 ± 28,4 mg/mL). Also, in this study group, patients with spondylodesis and signs of screw loosening had significantly lower baseline MDCT-BMD values than patients without screw loosening (77,3 ± 22,3 vs 110,1 ± 30,7 mg/mL). This study showed that converted BMD values can differentiate patients with or without osteoporotic fractures at baseline, as well as predict incidental fractures and screw loosening in patients with spondylodesis during follow-up. (Schwaiger et al., 2014)

A study by Uezono et al. had a different approach. They measured the pretreatment CT density (in HU) by selecting three different axial images showing visually the lowest bone-marrow density in the right and left sacrum. Then, circle ROIs on each side of the sacrum

were generated to measure the CT density of bone and bone marrow on each of the three different axial images. The obtained values of each of the three values (L5 vertebra, right and left sacrum), as well as the mean density of the three were analyzed and showed a significant correlation between low CT density and the occurrence of PIF. Although they evaluated imaging records of 99 patients who were treated at their institution between 2003 and 2009, they were only able to measure the pretreatment CT density of 59 (59,6%) of those patients, since a large number of the patients' HU values were not available. Those 59 patients' imaging data were acquired in or after 2006 and were therefore obtainable through their specific imaging viewer (Synapse) with the option of CT densitometry. Therefore, the other 40 (40,4%) patients' data acquired before 2006, were not available. (Uezono et al., 2013)

In our study, we were able to evaluate the BMD of every patient from the collected data from existing CT scans and converted the HU into mg/cm^3 with the help of a MDCT-to-qCT conversion equation, consequently making the need of a qCT, which brings along additional radiation exposure, redundant.

Furthermore, no osteoporosis screening was performed. In our study group, none of the patients had diagnosed osteoporosis as a pre-existing disease. Since most of our patients were comparatively young (with a median age of 55) and none of them have had any symptoms or complications that may have led to the diagnosis of osteoporosis, we did not find it necessary nor practicable to routinely screen every patient.

Based on our study, a lower BMD (measured by a MDCT-to-qCT conversion equation) is a significant predisposing factor for developing PIF after radiotherapy.

One strength of our study is that BMD assessment by a MDCT-to-qCT equation is predictive for bone health. The MDCT-to-qCT equation used in this study, like in the studies of Baum et al. & Schwaiger et al., is specific and limited to the CT scanner used for the planning CTs. Although, given a suitable comparison group, this method can get transferred into various clinical MDCT scanners. (Baum et al., 2011; Schwaiger et al., 2014)

The new approach presented herein (BMD measurement in the planning CT), enhances the radiation oncologists' armamentarium in predicting the individual toxicity risk of a patient.

This information can be used in clinical practice and should be used in future prospective studies by identifying the optimal cut-off vales for differentiation of groups and help predict osteoporosis and osteoporotic fractures after radiotherapy and implement countermeasures.

Subsequently, by identifying groups at risk of fracture, more follow up imaging techniques, especially MRI, could be performed in groups at risk, with special attention to PIF, in order to prevent the development of PIF or diagnose them early on and start countermeasures as soon as possible. Also, supportive or prophylactic therapy, such as substitution of vitamin D and calcium, as well as bisphosphonates if needed, should be used to lower the risk of developing PIF.

6. Limitations

A limitation to our study was the fact that this was a single-institution, retrospective study with a rather small number of patients. Also, due to the small number of PIF events, the likelihood of finding statistically significant correlations was low. In addition, follow-up imaging studies were not performed at specified intervals and were mainly targeted to the primary disease, which could have led to missed asymptomatic fractures outside the imaging interval.

7. Conclusion

PIF are a common complication after radiotherapy for patients with cervical cancer. In our study they were detected in 9,7% of the patients. In our group of patients, we did not find a statistically significant correlation between the dose and the incidence of PIF. Predisposing factors for developing post-radiation PIF seem to be older age and a lower BMD. Herein we report a new way to determine BMD in the planning CT for radiotherapy by using a MDCT-to-qCT equation without additional radiation exposure for the patient.

8. Summary

The aim of this study was to investigate the risk factors for pelvic insufficiency fractures (PIF) after radio(chemo)therapy (R(C)T) for cervical cancer.

RT plays a very important role in the treatment of cervical cancer. It is applied to the majority of patients either through definitive/adjuvant external beam radiation therapy (EBRT) or brachytherapy.

Cases of 62 women with cervical cancer who received definitive or adjuvant radio(chemo)therapy between 2013 and 2017 at the Department of Radiation Oncology of Klinikum Rechts der Isar, Munich, Germany, were reviewed. The median age was 55 years (range, 32-81 years).

Patients in our study group were treated with EBRT alone or EBRT with concurrent chemotherapy. The median dose to the planning target volume (PTV) was 50,4 Gy (range, 36-50,4 Gy). The median EBRT boost dose to the primary tumor (PT) was 56 Gy (range, 42-70 Gy) and to the lymph nodes (LN) 58,8 Gy (range, 52-61,8 Gy). The median dose delivered through high-dose-rate intracavitary brachytherapy (HDR-ICBT) was 28 Gy (range: 5-28 Gy).

All patients underwent follow-up magnetic resonance imaging (MRI). The pelvic insufficiency fractures (PIF) were detected in the follow-up MRIs by experienced radiologists.

We analyzed dose-volume histogram (DVH) parameters such as the V30, V40 and V50Gy of the sacrum and the PIF for each patient. We used it to determine the relative volume that received the aforementioned doses. We also analyzed the D50%, which gives us the dose that 50% of the volume of the sacrum/PIF received, as well as the Dmean and the Dmax, which provides information about the mean and maximum dose these structures were irradiated with. We did not observe a statistically significant correlation of these DVH parameters to the incidence of PIF.

In addition, we investigated bone mineral density (BMD) as a possible risk factor for PIF. Very few studies have been able to evaluate BMD and connect it to the occurrence of PIF.

We also analyzed the BMD of three lumbar vertebrae, as well as the first and second sacral vertebrae for each patient, and compared the results of the patients with PIF, to those without. For the lumbar vertebrae we analyzed the 1st to the 3rd lumbar body. In the planning CT of patients where the 1st or the 2nd lumbar vertebra was not completely depicted, we analyzed the 2nd-4th and the 3rd-5th, respectively.

For this, in accordance with the Schwaiger et al. study (Schwaiger et al., 2014) we placed a square region of interest (ROI) half the height of the lumbar vertebrae in the sagittal plane of the planning CT for each patient. The square was placed in the ventral half of the trabecular compartment of the vertebrae and Hounsfield units (HU) were obtained. Then, we used a multidetector row CT (MDCT)-to-qCT equation to convert the obtained HU values from planning CTs into BMD (mg/cm^3).

Correlation between the BMD and PIF, as well as between the DVH parameters and PIF were analyzed by *t*-test. Additionally, association between age and BMD between the two groups was assessed using a linear regression model, showing correlation between higher age and lower BMD.

Out of 62 patients, 6 (9,7%) had a fracture. All of them were detected in the follow-up MRI as PIF and all of them were located in the massa lateralis of the sacral bone. The median imaging follow-up was 16 months (range: 1,5-53 months). Two out of those six patients had a bilateral fracture with only one of them being symptomatic. The median age in the PIF group was significantly higher ($p<0.01$) with 62 years compared to 53 years in the other patients – i.e. without PIF - (OTH).

The BMD of the sacral bone was significantly lower ($p<0.03$) in the PIF group with 127,8 mg/cm^3 compared to 173,1 mg/cm^3 in the OTH. There was a significant ($p<0.05$) difference of the mean BMD of the lumbar vertebrae in the PIF group (87,9 mg/cm^3) and the OTH (121,4 mg/cm^3) when comparing the two groups.

The BMD is usually assessed by using the dual-energy X-ray absorptiometry (DXA) or the quantitative computed tomography (qCT). While we know these methods to be well-established and mostly very accurate, we also know that both methods have their shortcomings.

The measurements by DXA for example, can be affected by a lot of factors. False elevations can be observed due to vertebral diseases and spinal degenerations, or even artifacts from calcifications such as abdominal aortic calcifications. This may lead to a mismatch between clinical findings that may indicate osteoporosis and the results of DXA, where the BMD may still seem normal.

The results of a qCT can, on occasion, be falsely low in a patient with normal T-scores on DXA. It is believed to be due to the increased bone marrow fat in patients of higher age, which affects the assessment of BMD on qCT. Also, it is known that the validity of a qCT depends on the experience of the technician performing the analysis. Higher doses of radiation, fewer standardized reference ranges and analysis protocols, less reproducibility are also some of the shortcomings of this method.

With an incidence of approximately 10%, our study strengthens the assumption of recent studies that PIFs are not as rare of a complication after radiotherapy as previously thought and might have been underestimated in gynaecological patients.

Based on our study, a lower BMD is a significant predisposing factor for developing PIF after radiotherapy.

In our study, we were able to evaluate the BMD of every patient from the collected data from existing CT scans and converted the HU into mg/cm^3 with the help of a MDCT-to-qCT conversion equation (BMD = slope * HU + intercept; slope= 0,773549; intercept=-1,67321), consequently making the need of a qCT, which brings along additional radiation exposure, redundant.

Herein we report a new way to determine BMD in the planning CT for radiotherapy by using a MDCT-to-qCT equation without additional radiation exposure for the patient. This data will help predict the individual toxicity risk of a patient in future prospective studies.

This information can be used in clinical practice and should be used in future prospective studies by identifying the optimal cut-off values for differentiation of groups and help predict osteoporosis and osteoporotic fractures after radiotherapy and implement countermeasures.

The patients' data and parts of the herein presented results were published in October 2020 in form of a scientific article in the journal ''Strahlentherapie und Onkologie''. (Kurrumeli et al., 2020)

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