Scientific Article

Long-Term Risk of Hip Complications After Radiation Therapy for Prostate Cancer: A Dose-Response Study

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Abstract

Purpose: The aim of the present study was to analyze the long-term incidence of hip complications after external beam radiation therapy compared with age-matched controls from the general population. We also investigated whether there were any dose−response associations.

Methods and materials: A total of 349 patients with prostate cancer treated to curative dose with external beam radiation therapy between 1997 and 2002 were included in the study. Physical and fractionation-corrected dose-volume descriptors were derived for the femoral heads, pubic bone, and sacrum. Information on skeletal events was collected for the patients and 1661 matched controls through the Prostate Cancer database Sweden. Uni- and multivariable Cox proportional hazard regressions were used to analyze the time to event.

Results: Data from 346 patients were available for analysis. The median mean physical dose and corresponding equivalent 2-Gy/fraction dose (EQD2) to the femoral heads were 35.5 Gy and 28.7 Gy, respectively. The median follow-up time was 16.0 years. During the follow up, 12 hip fractures occurred. Hip osteoarthritis was diagnosed in 36 cases, with 29 cases leading to replacement surgery. No increased risk of hip fractures was found. Hip osteoarthritis was the only event for which a statistically significant difference was found between the irradiated cohort and the controls (cause-specific hazard ratio: 1.56; 95% confidence interval, 1.07-2.26; $P = .02$). The cumulative incidence of osteoarthritis at 10 years was 8.1% and 4.9% in the irradiated cohort and the controls, respectively. A significant relationship between osteoarthritis and the volume of the femoral head receiving $\geq$40 Gy (ie, EQD2) was found.

Conclusions: In this study of 346 patients treated with conventional radiation therapy, we found no increased risk of hip fracture but an increased risk of clinically relevant osteoarthritis at long-term follow up. Our results indicate a dose−response relationship between osteoarthritis and the volume of the femoral head receiving an EQD2 dose of $\geq$40 Gy.

Introduction

Hip injuries, such as femoral neck fractures, and hip osteoarthritis are common sources of pain and disability worldwide; however, the incidence varies considerable between countries. The age-standardized annual incidence of hip fractures in Northern Europe is high in both men

and women, has been reported at 200 to 500 of 100,000, and is related to osteoporosis and increasing with age. The incidence in men is approximately half of that in women.[1,2] The prevalence of hip osteoarthritis has been reported at 5.9 % in a large European study of individuals aged 65 to 85 years.[3]

Prostate cancer is the second most frequent form of cancer in men worldwide.[4] Many patients are treated with external beam radiation therapy (EBRT), which is associated with the risk of pelvic complications. Complications, such as pain, fractures, cortical bone thinning, and osteonecrosis, resulting from femoral head/neck toxicity, have been reported after radiation therapy to the pelvis.[5-7] Increased risks of pelvic insufficiency and hip fractures in women after pelvic irradiation have been reported,[8] but pelvic insufficiency fractures are more rare in men.[8,9] However, the association between pelvic radiation therapy in men and an increased risk of hip fractures has not been established, but Elliot et al reported a statistically significantly increased rate of hip fractures in patients treated with EBRT compared with those treated with prostatectomy.[10] Zelefsky et al reported a low incidence of long-term hip-related toxicity with no significant difference between treatment with EBRT and brachytherapy despite the lower radiation dose to the hip associated with brachytherapy.[11] Increased complication rates after total hip replacement of irradiated hips have been reported.[6,12]

Animal studies have shown that radiation therapy reduces bone formation and increases bone resorption resulting in a poorer function and strength of the bone. Effects on the vascular and nervous system may also contribute to complications, such as avascular necrosis.[8] Arthropathy resulting from irradiation is described as degenerative arthropathy associated with findings such as thin joint cartilage, fibrous and atrophic capsular lining, or as arthritis with inflammatory reaction and destruction.[13] Very few studies have been carried out on the effect of radiation on the pelvic bone and joints. Early radiation therapy studies reported that doses >30 Gy caused irreversible damage to bone tissue and joint arthropathy.[13,14] Emami et al suggested that doses of 52 Gy and 65 Gy to the femoral head were associated with 5% and 50% risk of osteonecrosis, respectively.[15] However, these recommendations come from clinical experience and the book *Radiation injury of bone* by Shimanovskaya and Shiman.[15,16]

The aim of the present study was to analyze the long-term incidence of hip complications, measured as fractures, replacements, infections, and osteoarthritis after EBRT compared with age-matched controls from the general population. We also investigated whether there were any dose−response associations in the treated patients. The study was approved by the Ethics Committee in Lund Sept. 6th, 2015.
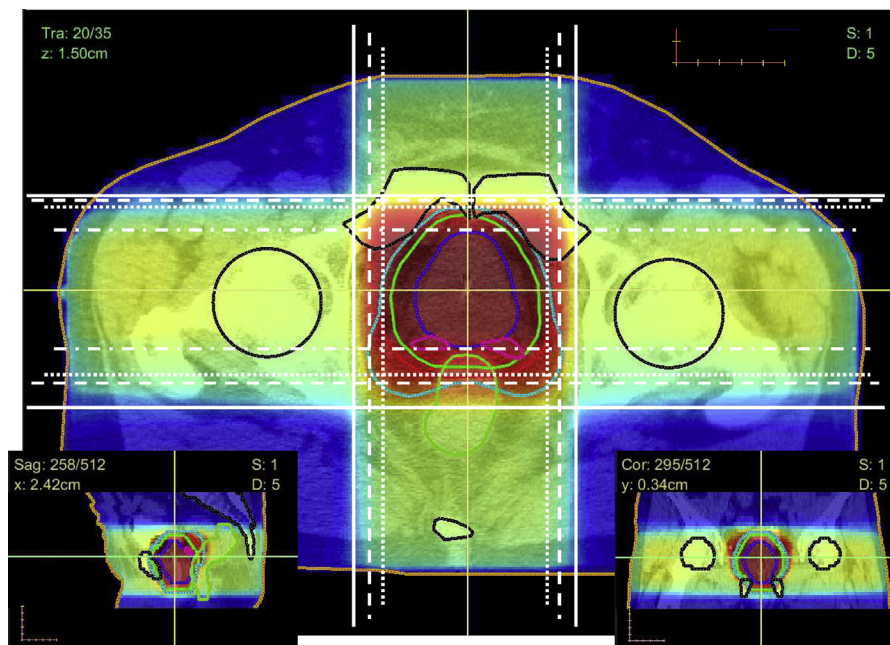

Figure 1   Example of shrinking 4-field box treatment planning technique + 2 lateral beams for delivery of a total prescribed dose of 78 Gy to the prostate. Structures shown are $CTV_{prostate}$ (dark blue), $CTV_{seminal\ vesicles}$ (pink), $PTV_{70\ Gy}$ (green), $PTV_{66\ Gy}$ (red), $PTV_{50\ Gy}$ (light blue), rectum (green), femoral heads (black), pubic bone (black), and sacrum (black). Treatment plans (prescribed doses): Phase 1 (50 Gy; solid white field borders), phase 2 (16 Gy; dashed), phase 3 (4 Gy; dotted), and phase 4 (lateral beams only; 8 Gy; dashed-dotted). Field borders are drawn without divergence for clarity. *Abbreviations:* CTV = clinical target volume; PTV = planning target volume. (A color version of this figure is available at https://doi.org/10.1016/j.adro.2020.09.011.)

Methods and materials

Patients with prostate cancer treated to a curative dose ($\geq$64 Gy) with EBRT were included in the study. The cohort consisted of all patients with retrievable data from the treatment planning system Helax-TMS (Nucletron B.V, Veenendaal, the Netherlands) at Umeå University Hospital, treated between1997 and 2002, and including 349 men. All patients were treated with 3-dimensional conformal radiation therapy (CRT), typically with a shrinking field box technique (Fig 1). A total of 1661 control patients (4-5 controls per case) matched for age and county were extracted from the Prostate Cancer database Sweden (PCBaSe).

Delineation of bone structures and derivation of dose-volume descriptors

The treatment planning computed tomography scans from Helax-TMS were imported into the treatment planning system at the Department of Oncology, Skåne University Hospital (Oncentra MasterPlan, Elekta, Stockholm, Sweden) for structure delineation. The femoral heads, pubic arch, and sacrum were delineated according to predefined descriptions as organs at risk (OARs) by the same senior radiation therapist who had many years of experience in treatment planning (Fig 1). The following physical dose-volume descriptors were derived for the OARs: mean dose (D_{mean}), median dose ($D_{50\%}$), maximum dose (D_{max}), near-maximum dose ($D_{2\%}$), and the fractional volume receiving at least dose D (V_D [%], where D = 10-40 Gy in 10 Gy steps). In addition, equivalent doses, converted, voxel by voxel, to 2 Gy with $\alpha/\beta = 3$ Gy (EQD2) were calculated. Because the treatment plans were symmetrical, the right and left femoral heads received similar dose distributions and were combined and analyzed as a single paired structure (Fig 1).

Prostate Cancer database Sweden

Information on diagnosed skeletal events was obtained from the PCBaSe, a national database for clinical epidemiologic research. PCBaSe is based on linkages between the National Prostate Cancer Register (NPCR) and other national demographic and health care registers, including the National Patient Register, Cause of Death Register, and Prescribed Drug Register.[17-19] PCBaSe includes, besides patients with prostate cancer, also control patients (5:1 from 1996) who lived in the same county and were born in the same year.

The NPCR was initiated in 1996 and includes >96% of all patients with biopsy-confirmed prostate cancer included in the Swedish Cancer Register, to which reporting of all new cases of cancer is mandatory according to Swedish law. The NPCR contains information on tumor characteristics, such as staging (TNM classification), Gleason score, and serum level of prostate-specific antigen at the time of diagnosis, and primary treatment delivered or decided within 6 months of diagnosis. The individually unique Swedish Personal Identity Number allows linkage to other population-based registers.[18] The National Patient Register covers in- and outpatient care at public and private hospitals in Sweden, and contains data on main diagnoses and up to 8 secondary diagnoses and surgical procedures, coded per the World Health Organization International Classification of Diseases, 9th and 10th revisions. The codes for inpatients have been collected in the National Patient Register since 1987, with a capture rate for somatic patient care of virtually 100%. Ambulatory surgery has been recorded since 1997 and all outpatient care since 2001.

The Prescribed Drug Register was initiated in July 2005 and contains data on pharmaceuticals dispensed to the entire population of Sweden on an individual basis, with the exception of drugs used in hospital and over-the-counter medication. All drugs are classified according to the Anatomic Therapeutic Chemical classification system.

Data collection from PCBaSe

Relevant International Classification of Diseases codes for bone-related diagnoses (Table E1) were selected after consulting an orthopedist, and sent to PCBaSe together with absorbed dose metrics for the irradiated patients. Deidentified information on patients with identified diagnoses was extracted from PCBaSe together with the same information for the controls.

Data collection was focused on conditions of the hip, fractures, replacements, infections, and osteoarthritis. In addition, a pooled variable called "any event" was created to include any of the 4 events mentioned, and used as a surrogate for any late skeletal-related injury. Fractures to the sacrum and pelvis were collected.

Information on androgen deprivation therapy (ADT) as adjuvant primary treatment was collected from the NPCR, and information on the prescription of ADT was collected from the Prescribed Drug Register using Anatomic Therapeutic Chemical code L02AE. Surgical orchiectomy was considered equivalent to ADT.

Statistical analyses

Cox proportional hazard regression was used to analyze the time to event in the irradiated cohort compared with the controls. Time to event was calculated from the date of completion of radiation therapy. Patients were censored at the time of death or diagnosis of bone metastases. In addition to cause-specific hazard ratios (HRs), subdistribution HRs were calculated with death (independent of cause) and bone metastases as competing events. Cumulative

Table 1   Baseline demographics, clinical characteristics, and absorbed dose metrics to organs at risk for the irradiated cohort (n = 346)

Age at the start of radiation therapy	67 (51-80)
Prostate-specific antigen, ng/mL	13 (0-527)
Gleason score	
≤ 6	102 (29%)
7	37 (11%)
≥ 8	17 (5%)
Missing	190 (55%)
Clinical T stage	
T1	121 (35%)
T2	155 (45%)
T3	64 (18%)
T4	3 (1%)
Tx	3 (1%)
Prescribed dose, Gy	76 (64-78)
Volume of clinical target volume, cm^3	46 (19-161)
Femoral head doses (paired structure)	
D_{mean}, Gy	35.5 (10.0-45.5)
$EQD2_{mean}$, Gy	28.7 (7.1-38.8)
$D_{50\%}$, Gy	38.0 (4.5-46.2)
$EQD2_{50\%}$, Gy	30.6 (2.8-39.4)
D_{max}, Gy	44.9 (33.4-63.8)
$EQD2_{max}$, Gy	38.4 (26.4-62.7)
$D_{2\%}$, Gy	43.6 (32.4-48.7)
$EQD2_{2\%}$, Gy	36.9 (25.5-42.3)
$V_{40\ Gy}$, %	31.7 (0-100)
$V_{EQD2\ 40\ Gy}$, %	0 (0-31.5)
Sacrum doses	
D_{mean}, Gy	8.0 (1.8-31.3)
$D_{2\%}$, Gy	41.7 (2.9-47.4)
Pubic bone doses	
D_{mean}, Gy	59.2 (39.0-71.8)
$D_{2\%}$, Gy	77.0 (64.3-81.2)

Abbreviations: $D_{2\%}$ = near-maximum dose; $D_{50\%}$ = median dose; D_{max} = maximum dose; D_{mean} = mean dose; EQD2 = equivalent 2-Gy/fraction dose; $EQD2_{50\%}$ = equivalent 2-Gy/fraction median dose; $EQD2_{max}$ = equivalent 2-Gy/fraction maximum dose; $V_{40\ Gy}$ = fractional volume receiving at least 40 Gy; $V_{EQD2\ 40\ Gy}$ = equivalent 2-Gy/fractional volume receiving at least 40 Gy.
Data are median (range) or n (%).

Table 2   Total number of bone related diagnoses according to the International Classification of Diseases, 9th and 10th editions, and reported use of ADT for irradiated cohort and control group

	Radiation therapy cohort (n = 346)	Control group (n = 1661)
	n (%)	n (%)
ADT at any time during follow up	97 (28)	101 (6)
ADT before hip fracture	1 (<1)	4 (<1)
Osteoporosis	2 (1)	21 (1)
Fracture, hip	12 (3)	94 (6)
Fracture, acetabulum	1 (<1)	6 (<1)
Osteoarthritis, hip	36 (10)	121 (7)
Hip replacement	33 (10)	128 (8)
Osteoarthritis and hip replacement	29 (8)	96 (6)
Hip infection surgery	3 (1)	5 (<1)
Fracture, sacrum	1 (<1)	4 (<1)
Fracture, pubic bone	6 (2)	13 (1)
Bone metastases	31 (9)	43 (3)

Abbreviation: ADT = androgen deprivation therapy.
ADT based on Anatomic Therapeutic Chemical code L02AE, International Classification of Diseases code KFC 10/15, or recorded as primary treatment in the National Prostate Cancer Register.

incidence functions of bone-related diagnoses, with metastases and death as competing events, were estimated and compared by means of Gray's test. Cox proportional hazard regression, unadjusted and adjusted for age, was also used for the analysis of the association between dose to the femoral heads and time to hip-related events.

The statistical analyses were performed using IBM SPSS Statistics, version 24, and R, version 3.4.3.

Results

Of the 349 patients included in the study, data were missing for 3 patients in the PCBaSe, leaving data from 346 patients for analysis. Baseline demographic information and clinical characteristics of the irradiated cohort are presented Table 1. The median follow-up time was 16.0 years. Overall survival at 10 years was 68% (95% confidence interval [CI], 63-73%) and 74% (95% CI, 72-76%) for the irradiated cohort and controls, respectively. During the follow-up period, 80 of 346 patients (23%) in the irradiated cohort died as a result of prostate cancer compared with 44 of 1661 men (3%) in the control group. The estimated prostate cancer-specific survival rate at 10 years was 83% (95% CI, 78-87%) in the irradiated cohort and 99% (95% CI, 98-99%) in the controls.

Absorbed dose metrics for the femoral head, pubic bone, and sacrum are also presented in Table 1. The median mean physical dose and corresponding equivalent 2-Gy/fraction dose (EQD2) to the femoral heads were 35.5 Gy and 28.7 Gy, respectively. The median near maximum doses were 43.6 Gy and 36.9 Gy, respectively. During the follow-up period, 20 fractures were reported: 12 hip, 6 pubic bone, 1 sacral, and 1 acetabulum fracture. Osteoarthritis of the hip was diagnosed in 36 cases, of which 29 led to hip replacement surgery. The total number of hip replacements was 33. Detailed information on the incidence of bone-related diagnoses in the irradiated cohort and the controls is presented in Table 2.

Table 3 HRs for hip fracture, hip osteoarthritis, hip replacement and any event* in 346 cases treated with external beam radiation therapy compared with 1661 controls without (cause-specific HR) and with (subdistribution HR) death and bone metastases as competing events

Event	Cause-specific HRs			Subdistribution HRs		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Hip fracture	0.69	0.38-1.25	.22	0.61	0.33-1.10	.10
Hip osteoarthritis	1.56	1.07-2.26	.020	1.44	0.99-2.09	.055
Hip replacement	1.36	0.93-2.00	.11	1.24	0.85-1.82	.26
Any event*	1.17	0.85-1.59	.34	1.06	0.77-1.45	.72

Abbreviations: CI = confidence interval; HR = hazard ratio.

  * Hip fracture, hip osteoarthritis, hip replacement, or hip infection surgery

No statistically significant increased risk of hip fractures was found in the irradiated cohort compared with the controls. Hip osteoarthritis was the only diagnosis that showed a statistically significant cause-specific HR (1.56; 95% CI, 1.07-2.26; P = .02) for the irradiated cohort versus the controls (Table 3). When analyzing the data using death and bone metastases as competing risks, the subdistribution HR was 1.44 (95% CI, 0.99-2.09; P = .055). The median time to hip osteoarthritis was 7.9 years (interquartile range, 4.2-9.1 years). The cumulative incidence of osteoarthrosis at 10 years was 8.1% (95% CI, 5.2-11.0%) and 4.9% (95% CI, 3.9-6.0%) in the irradiated cohort and the controls, respectively (Fig 2).

The results of the dose−response analyses are presented in Table 4. No statistically significant association was found between the absorbed dose to the femoral heads and hip fractures. However, a statistically significant relationship was found for hip osteoarthritis with one of the dose-volume descriptors (ie, $V_{EQD2\ 40Gy}$; unadjusted HR: 1.094; 95% CI, 1.041-1.149; P < .001). The

cutoff dose of EQD2 = 40 Gy is close to the maximum dose in the material; hence, a large fraction of the patients (77%) had maximum doses <40 Gy ($V_{EQD2\ 40Gy}$ = 0). A sensitivity analysis was performed, excluding the 8 patients with the highest $V_{EQD2\ 40Gy}$ values (>10%) 1-by-1, which resulted in a variation in the HRs of 1.09 to 1.11 (P = .0002-.01). When all patients with $V_{EQD2\ 40Gy}$ = 0 were excluded, leaving 81 patients in the analysis, an HR of 1.10 (95% CI, 1.031-1.17; P = .003) was obtained.

Discussion

Radiation therapy is a common curative treatment for men with prostate cancer, and because these patients have a long life expectancy, studying the long-term complications of this treatment, such as femoral neck fractures and osteoarthritis, is important. The aim of the present study was to analyze the long-term incidence of hip complications and investigate whether any dose−response associations could be found. The Emami tolerance data[15] for the femoral head (52 Gy and 65 Gy for 5% and 50% risk) are for the endpoint osteonecrosis. However, osteonecrosis is a rare complication, and other less severe hip complications will probably have greater effects on these patients.

We found no increased risk of hip fracture in the irradiated cohort compared with the matched controls after a median follow-up time of 16 years. This finding is in line with the study results by Zelefsky et al[11] who, even if not specifically hip fractures, reported a low incidence of long-term hip-related toxicity after a median follow-up period of 7 years. The researchers found no significant difference in hip-related toxicity between EBRT and brachytherapy using dose constraints limiting the maximum dose to the femoral heads to ≤68 Gy. In the study by Zelefsky et al,[11] 65% of patients were treated with intensity modulated radiation therapy and 35% with 3-dimensional CRT but in the present study, all patients were treated with 3-dimensional CRT. A previous Swedish register study of 76,000 patients with prostate
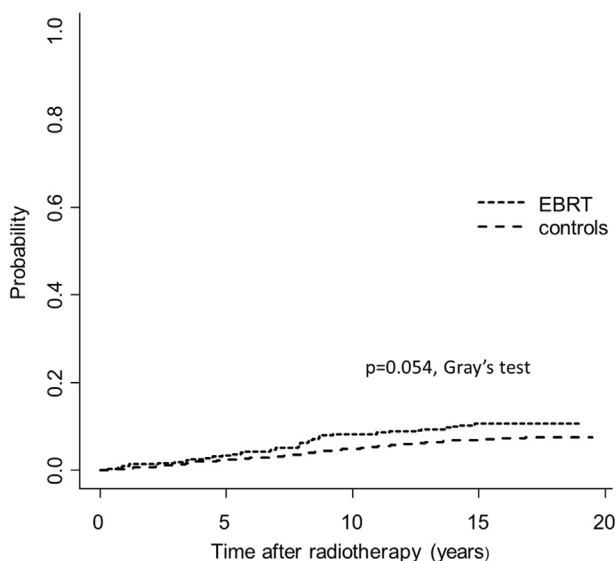

Figure 2 Cumulative incidence of osteoarthritis in the irradiated cohort versus the controls with bone metastases and death as competing events

Table 4   Results from Cox regression analyses of hip fracture, hip osteoarthritis, and any event[*] for different femoral head dose-volume covariates

	Unadjusted			Adjusted for age		
	HR	95% CI	P value	HR	95% CI	P value
Hip fracture						
$EQD2_{avg}$ (Gy)	0.991	0.899-1.094	.86	0.987	0.896-1.087	.80
$EQD2_{2\%}$ (Gy)	1.053	0.865-1.282	.60	1.035	0.849-1.262	.73
$V_{EQD2\ 40Gy}$ (%)	1.033	0.901-1.184	.64	1.022	0.891-1.173	.75
Hip osteoarthritis						
$EQD2_{avg}$ (Gy)	0.982	0.928-1.038	.52	0.981	0.927-1.037	.49
$EQD2_{2\%}$ (Gy)	1.075	0.957-1.208	.22	1.071	0.953-1.205	.25
$V_{EQD2\ 40Gy}$ (%)	1.094	1.041-1.149	<.001	1.092	1.039-1.148	.001
Any event[*]						
$EQD2_{avg}$ (Gy)	0.977	0.931-1.025	.34	0.975	0.930-1.023	.31
$EQD2_{2\%}$ (Gy)	1.049	0.951-1.158	.34	1.042	0.944-1.151	.42
$V_{EQD2\ 40Gy}$ (%)	1.079	1.027-1.134	.003	1.075	1.023-1.131	.004

Abbreviations: CI = confidence interval; $EQD2_{2\%}$ = equivalent 2-Gy/fraction near-maximum dose; $EQD2_{avg}$ = equivalent 2-Gy/fraction average dose; HR = hazard ratio; $V_{EQD2\ 40\ Gy}$ = equivalent 2-Gy/fractional volume receiving at least 40 Gy.

   * Hip fracture, hip osteoarthritis, hip replacement, or hip infection surgery.

cancer revealed no increased risk of hip fractures in men treated with radical prostatectomy or radiation therapy, but confirmed a previously shown increase in risk in men treated with orchiectomy or ADT.[20] However, the mean follow-up time of 4 years is short for the endpoint hip fracture.

The increased incidence of hip fracture 10 years after ERBT treatment for prostate cancer compared with prostatectomy, as reported by Elliot et al,[10] was not confirmed in the present study. Elliot et al[10] differentiated between patients treated with and without concomitant ADT, but did not report any absorbed doses. The discrepancy between their results and ours could be due to higher doses to the hip in their study. In addition, a remarkably large difference in survival was seen between the 2 groups studied by Elliot et al,[10] suggesting that the study may have been affected by selection bias.[10]

The only complication that was significantly worse in the irradiated cohort compared with the control group in our study was hip osteoarthritis. This finding is clinically relevant, because 80% of patients diagnosed with osteoarthritis required hip replacement. The median time to hip osteoarthritis was 7.9 years in the present study, which shows that hip osteoarthritis is a late side effect that can only be studied with long-term follow up.

The mean dose to the femoral heads was quite low in our study, with the median mean physical dose 35.5 Gy. Hip fracture after EBRT of different pelvic tumors has been reported to be rare after mean doses of <40 Gy to the femoral neck.[21,22] Our results support this finding but suggest an increased risk of hip joint arthropathy, which could be explained by the effects of radiation effect on tissues other than bone (eg, cartilage thinning, fibrosis in the capsule, and arterial changes).[13,23,24]

The only dose−response combination we found to be statistically significant was for $V_{EQD2\ 40Gy}$ and hip osteoarthritis, although with a wide CI. Thus, this dose−response relationship must be confirmed in other studies before recommended as a dose-volume objective in clinics. To the best of our knowledge, no dose-volume objectives have been published for the endpoint osteoarthritis. However, a dose level of 40 Gy to the femoral head may be associated with hip injury. In a study of 650 long-term gynecologic cancer survivors, a mean physical absorbed dose to the femoral head >37.5 Gy was found to be a significant predictor of hip pain.[25] Furthermore, a small study of patients with anal cancer showed that the volume of femoral neck receiving ≥40 Gy (V_{40Gy}) was predictive of clinically significant cortical thinning.[7] Hip fractures have been reported to be rare after a mean dose of <40 Gy.[21,22]

Hence, limiting the volume of the femoral head receiving >40 Gy, while ensuring dose coverage to the prostate and dose-volume constraints to OARs with a higher priority such as the rectum, seems plausible. Dose comparisons with other studies in the literature are hampered by the fact that the reported dose variables and whether fractionation effects have been considered is sometimes unclear.

Apart from the low absorbed doses to the hip as mentioned, other limitations of our study are associated with the information available in the various national registers. Information on diagnosed events was obtained from the National Patient Register covering in- and out-patients at hospitals, which means that osteoarthritis diagnosed only by a general practitioner was not included. On the other hand, cases identified in this study should be the most clinically relevant, because patients with severe

problems are expected to be referred to a specialist. Another limitation is that complete information on ADT was only available as of 2005 when the Prescribed Drug Register was set up. Before 2005, only limited information on ADT was available from planned initial treatments recorded in the NPCR. Thus, some patients possibly had ADT prescribed in the period before 2005 that we are not aware of. This is a weakness of the study, which would have been more serious if we had found an increased risk of fractures after radiation therapy because the association between ADT use and increased risk of fractures is well known. We found no indications of an increased risk of fractures after radiation therapy in the investigated dose range and to our knowledge, there is no reported association between ADT and osteoarthritis. Including the femoral neck in the delineation (as per the Radiation Therapy Oncology Group)[26] would have improved this study because this is the most common fracture site.

The patients in this study were treated with conventionally fractionated 3-dimensional CRT with 3 to 4 beams, usually with a 4-beam box technique. Today, most patients with prostate cancer are treated with (hypofractionated) volumetric modulated arc therapy, which may lead to higher doses to the femoral heads. In addition, pelvic lymph nodes are sometimes included, which affects the absorbed dose to the hip. Further studies should include patients treated with contemporary radiation therapy techniques to be able to recommend more reliable dose-volume objectives for use in clinics.

Conclusions

In this study of 346 patients treated with conventionally fractionated 3-dimensional CRT, we found no increased risk of hip fractures but an increased risk of clinically relevant osteoarthritis compared with age-matched controls. Our results indicate a dose−response association between osteoarthritis and the volume of the femoral head receiving an $EQD2_3$ dose of ≥ 40 Gy. These findings contribute to our knowledge on how radiation affects bone and hip joints several years after radiation therapy, and can be valuable in optimizing radiation therapy.

Acknowledgments

Supplementary Materials

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