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Hip-related toxicity after prostate radiotherapy: Treatment related or coincidental?

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Abstract

Background and purpose—To evaluate the incidence and predictors of hip toxicity postradiotherapy for localized prostate cancer.

Methods and materials—4067 prostate cancer patients were treated with external beam radiotherapy (EBRT; $n = 2569$; 63%) or brachytherapy with or without supplemental EBRT ($n = 1508$; 27%). 43% ($n = 1738$) were treated with neo-adjuvant and concurrent ADT and 57% ($n = 2329$) with radiotherapy alone. Hip toxicity was defined as moderate or severe pain upon ambulation with or without the need for hip-revision surgery. Median follow-up was 7 years (range, 3–21 years).

Results—One hundred twenty-one (2.7%) patients developed moderate-to-severe hip pain after radiotherapy affecting ambulation. Of these, 73 (60%) required hip replacement secondary to persistent hip pain. Among patients with baseline degenerative joint disease (DJD) changes on scans, 10-year incidence of hip-related toxicity was 11% versus 3% for those without such changes ($P < .001$). The only variables on multivariate analysis associated with hip-related toxicity post-radiotherapy were baseline DJD on imaging ($P < .0001$) and prolonged ADT for salvage therapy ($P < .0001$).

Conclusions—Prostate EBRT or brachytherapy is associated with low incidence of long-term hip-related toxicity. The only variables identified associated with hip toxicity posttherapy was the presence of baseline DJD and prolonged salvage ADT posttreatment for patients developing recurrence.

Keywords

External beam radiotherapy; Brachytherapy; Hip replacement; Toxicity; Prostate cancer

While hip-related complications after radiotherapy for prostate cancer are unusual, there has been a paucity of reports specifically documenting the incidence of such toxicity after

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Conflict of interest statement

The authors have no conflicts of interest to report.

treatment [1,2]. Especially among elderly patients with pre-existing degenerative joint disease, the risk of hip fractures or pain requiring surgical intervention could possibly be increased, as higher radiation doses in the treatment of prostate cancer are now routinely employed. In addition, as the use of adjunctive androgen-deprivation therapy (ADT) has become a standard of care for intermediate- and high-risk disease, its effects could accentuate osteoporotic changes within the femoral heads, possibly leading to increased rates of hip-related toxicities in this patient population.

During the last 20 years at our institution, several thousand patients have been treated with radiotherapy for prostate cancer with various radiotherapeutic interventions at different dose levels, along with various durations of ADT. This large cohort treated with sundry approaches and radiation levels provides an opportunity to better understand the potential impact of such treatment-related variables on hip-related toxicities after radiotherapy. The 10-year incidence of hip pain and need for hip-revision surgery are described, as well as predictors for hip-related toxicity after prostate radiotherapy.

Material and methods

Between 1988 and 2009, 4067 patients with clinically localized prostate cancer were treated with external beam radiotherapy (EBRT; $n = 2559$; 63%) or brachytherapy with or without supplemental EBRT ($n = 1508$; 27%) at our institution. Among this cohort, 43% ($n = 1738$) were treated with neo-adjuvant and concurrent ADT and 57% ($n = 2329$) were treated with a radiation-therapy modality alone. The clinical characteristics of the entire cohort are shown in Table 1. The decision to select a particular treatment intervention was based upon the discretion of the physician and patient. In general, low-risk patients were treated with EBRT alone or brachytherapy used as monotherapy. In these patients, ADT would in general be used for prostate volume reduction prior to initiation of RT, and a short course of neo-adjuvant and concurrent ADT of 3–6 months' duration was routinely employed for that purpose. ADT consisted of neo-adjuvant and concurrent administration of a luteinizing hormone-releasing hormone agonist, typically combined with an anti-androgen for at least the first month of hormonal therapy. ADT was routinely discontinued after cessation of radiotherapy.

Intermediate-risk patients were treated with brachytherapy with or without supplemental EBRT or high-dose EBRT alone. In this cohort of patients, neo-adjuvant and concurrent ADT was used in 31.5% of patients and, in general for low-risk patients, ADT was discontinued after completion of the course of radiotherapy. High-risk patients were treated with high-dose EBRT with neo-adjuvant, concurrent, and adjuvant ADT, or brachytherapy combined with EBRT and ADT. The median duration of ADT in this latter cohort was 7 months. Risk groups were defined based on the National Comprehensive Cancer Network (www.NCCN.org) risk-stratification criteria. All patients underwent pretreatment evaluation for pelvic lymphadenopathy with computed tomography scanning or magnetic resonance imaging of the prostate and pelvis. Patients who developed evidence of relapsing disease were in general treated with salvage ADT and the median duration of this intervention was 53 months. Institutional review board approval was granted prior to data collection.

Treatment

The radiation techniques used have been previously described [3]. Briefly, for EBRT, dose levels ranged from 64.8 to 86.4 Gy in 1.8 Gy fractions using 15 MV photons. From 1988 to 2008, 894 patients (34.9%) were treated with three-dimensional conformal radiotherapy (3D-CRT) and the remaining 1665 patients (65.1%) were treated with intensity-modulated radiotherapy (IMRT) using a 5–7 field co-planar beam arrangement using 15 MV X rays. Image-guided IMRT was initiated in 2008 with fiducial marker placement, with daily correction of target position prior to the daily therapy. The radiation dose was prescribed to the isodose line encompassing the entire planning target volume, defined as the prostate and seminal vesicles with a 1 cm margin except at the anterior rectal wall, where the margin was 0.6 cm. During this study, patients did not receive elective radiation to the pelvic lymph nodes. In general, femoral head dose constraints limited the maximal dose to 68 Gy of the prescription dose delivered.

Baseline bone scans and/or computed tomography scans were available in all patients prior to the initiation of radiotherapy and retrospectively analyzed to determine if there was any radiographic evidence of degenerative joint disease (DJD) consistent with uptake in the hip-femoral regions. In general, as part of the initial evaluation patients were asked if they had any prior operations including prior hip surgery. All charts were also carefully reviewed to determine if the patient had baseline history of osteoarthritis or prior hip-related surgery for DJD. Baseline DJD or arthritis using these criteria was noted in 398 patients (9.8%). For this study, hip toxicity was defined as moderate or severe pain upon ambulation that the patient reported in the follow-up period with or without the need for a hip-revision surgery.

Follow-up and endpoints

Following radiotherapy, patients generally returned for follow-up visits with digital rectal exam and serum prostate-specific antigen levels every 3–6 months for the first 5 years, then yearly thereafter. The median follow-up was 7 years (range, 3–23 years).

Results

One hundred twenty-one (2.7%) patients developed moderate-to-severe hip pain after radiotherapy affecting ambulation at a median time of 72 months after completion of radiotherapy. Of these 121 patients, 73 (60%) required a hip replacement secondary to persistent hip pain. The 10-year actuarial incidence after treatment for moderate/severe hip pain was 4%. The 10-year likelihood of requiring a hip replacement was 1.9%.

No significant differences in hip toxicities were observed in the EBRT alone, combined brachytherapy with supplemental EBRT, or brachytherapy monotherapy treatment cohorts (Fig. 1), suggesting that the reduced dose to the hip-joint complex associated with brachytherapy (which is estimated to deliver <1% of its prescription dose to the hip-joint complex) did not impact the incidence of posttreatment hip-related complications. Significant differences, however, were observed when patients were stratified based on the presence of baseline DJD changes noted on pretreatment imaging studies. Among patients with baseline DJD changes on scans, the 10-year incidence of hip-related toxicity was 11%

versus 3% for the cohort without such baseline changes ($P < .001$). The use of neo-adjuvant ADT during the course of primary radiotherapy did not have an appreciable impact on post-treatment hip-related complications; however, among patients who received prolonged salvage ADT for post-treatment disease recurrence (whose median duration was 53 months), a greater incidence of hip toxicity was observed. Among patients who received postradiotherapy ADT ($n = 573$), 45 patients experienced subsequent hip toxicity (7.9%), compared with 2.2% among those who did not receive postradiotherapy hormonal therapy ($P < .0001$). A multivariable analysis was performed that included patient age, baseline DJD, type of radiation therapy (external radiotherapy versus brachytherapy), the use of short-course neo-adjuvant ADT, and salvage ADT in the model. This analysis revealed that the only variables associated with the development of hip-related toxicity after radiotherapy were the presence of baseline DJD on imaging studies ($P < .0001$) and the use of prolonged ADT when used in this population for salvage therapy ($P < .0001$).

Discussion

To our knowledge this is the largest single-institution report evaluating the incidence of hip-related toxicity after radiotherapy. Our initial hypothesis was that a potential contributor to this complication would be the radiotherapy technique employed or the radiation prescription dose level, which would impact the dose delivered to the femoral heads and the hip region. Yet we did not observe that the use of IMRT compared with 3D-CRT, lower prescription dose levels, or the use of brachytherapy (which is associated with $<1\%$ exposure to the femoral heads) were associated with a lower incidence of hip-related toxicity. Indeed there were no significant differences in the rates of hip toxicity among patients treated with brachytherapy (where the dose levels to the hip are negligible) compared with EBRT. These data would suggest that radiotherapy delivered with the techniques and dose constraints employed was not associated with hip-related complications.

In our report we did find that the use of prolonged salvage ADT for relapsing disease was associated with hip-related complications and likely related to the osteoporotic effects ADT is well known to cause. In these patients, the ADT in the salvage setting was administered indefinitely for the lifetime of the patient and the average duration was 4.5 years. Interestingly, we did not find that toxicity was more often observed among patients treated with short-course neo-adjuvant and concurrent ADT. We speculate that this could be explained by the shorter duration of exposure to ADT, which did not increase the risk of this complication. Our findings are in contrast to those reported by Elliot et al. [1], who reported a 76% increased risk of hip fractures among patients treated with 3D-CRT for prostate cancer. In that report, in 45,662 patients from the Surveillance, Epidemiology and End Results (SEER) Medicare who were diagnosed and treated between 1992 and 2004, the incidence of hip fracture was 3% among the patients who underwent radical prostatectomy and 8% among patients receiving EBRT or EBRT in conjunction with ADT. We speculate that the significantly higher incidence in this 3D-CRT patient population compared with our patients could possibly be attributed to the lack of dose constraints used for the femoral heads during planning in the Elliot et al. study [1]. Among our patients, dose constraints limiting the dose to the femoral heads to 70% or less of the prescription were routinely applied.

In our study we also observed that the risk of hip toxicity was increased among those with baseline DJD. It is possible that, in this subset of patients, radiation predisposed or increased the risk of this toxicity in this cohort of patients. In our study, the age of the patient did not play a significant role in the development of hip-related toxicity and this could possibly be explained by the fact that the majority of patients were 70–80 years of age and were at similar risk for hip-related toxicity. It is of course likely that patients in their 50s and those in their 80s possess different risks for the development of hip fracture, which could be associated as well with the presence of DJD.

Several reports have noted the incidence of hip fractures or hip-replacement surgery in the elderly population, citing incidences of 3–6% [4–8]. In one report [9], evaluating a population from Spain of older individuals ($n = 7577$) using a validated screening questionnaire, the estimated rate for hip replacement was 38% among men surveyed with osteoarthritis. In another report, from the United Kingdom [4], the overall risk in a random surveyed cohort of 7806 patients for elective total hip replacement was 5.3%, similar to the overall risk observed in our population. Davenport et al. [5] reported on the incidence of hip fractures in the Medicare population from 1992 to 1996. During this time period the incidence of hip fractures related to osteoporosis ranged from 4% to 5%. The incidence of hip fractures for the cohorts of patients 65–74 years, 75–84 years, and at least 85 years were 3%, 5%, and 15%, respectively. ADT has been shown to increase the risk of bone fractures. In a large study from the Karolinska University Hospital [7] consisting of 76,000 men with metastatic prostate cancer (but not restricted to those treated with radiotherapy), only those who were treated with gonadotropin-releasing hormone agonists or orchiectomy demonstrated an increased incidence of bone fractures requiring hospitalization. Patients treated with radiation or surgery did not have any increased incidence of fracture risk. Interestingly, patients treated with anti-androgen monotherapy did not have any excess risk in this patient population.

Based on this information, we suggest that the contribution of radiotherapy to the incidence of hip toxicity after treatment is uncertain and more likely explained by patient age and the presence of DJD. It would appear that prolonged ADT in this population potentially increased the risk of hip toxicity, possibly explained by the exacerbation of DJD. While radiotherapy has been reported to cause hip-related toxicity, especially using older techniques delivering higher doses to the femoral head, with current techniques using conformal and IMRT-based treatment delivery, the risk of hip toxicities that can be ascribed to the radiotherapy above the baseline risk that exists in this elderly population appears to be very low if not negligible. We recommend that dose to the femoral heads be restricted to maximum dose levels <68 Gy, as was done routinely for the patients treated in this study. As our patients were treated with tight constraints generally not exceeding this dose level, it is possible that higher prescription doses may impact hip-related toxicity.

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Fig. 1. Actuarial incidence of hip toxicity comparing external beam radiotherapy (EBRT), brachytherapy alone, and brachytherapy combined with supplemental EBRT (Combo), showing no significant differences between the treatment cohorts.

Table 1

Demographics.

	Brachytherapy						
	EBRT (n = 2559)			(n = 966)			
	EBRT (n = 2559)			Combo (n = 542)			
	n	%	n	%	n	%	
Age							
	<65	664	26%	401	42%	215	40%
	65	1895	74%	565	58%	327	60%
Prostate-specific antigen							
	<10	1448	57%	900	93%	438	81%
	10–20	659	26%	64	7%	90	17%
	>20	452	18%	2	0%	14	3%
Gleason score							
	<7	1175	46%	831	86%	135	25%
	7	953	37%	129	13%	337	62%
	>7	431	17%	6	1%	70	13%
T stage							
	T1c–T2a	1583	62%	930	96%	414	76%
	T2b–T2c	622	24%	34	4%	100	18%
	T3a	354	14%	2	0%	28	5%
Neo HT							
	No	1297	51%	691	72%	341	63%
	Yes	1262	49%	275	28%	201	37%
EBRT dose							
	<75.6 Gy	371	14%				
	75.6 Gy	2188	86%				
NCCN risk							
	Low	563	22%	754	78%	88	16%
	Intermediate	1102	43%	202	21%	360	66%
	High	894	35%	10	1%	94	17%

Abbreviations: EBRT, external beam radiotherapy; HT, hormonal therapy; NCCN, National Comprehensive Cancer Network.