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Patient-reported Hip Symptoms following Treatment with Proton Therapy for Prostate Cancer

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Abstract

Purpose: We investigated patient-reported hip pain, stiffness, and physical function scores following proton therapy (PT) for prostate cancer.

Patients and Methods: Between April 2012 and August 2012, men treated ≥18 months earlier with PT for localized prostate cancer were asked to participate in an institutional review board-approved study by answering the Western Ontario and McMaster Index (WOMAC) questionnaire for scoring patient-perceived hip symptoms. The questionnaire was returned by 325 patients treated at our institution; 290 patients completed all 24 questions and are the subject of this study. A higher WOMAC score indicated more problems. Patients had received PT doses ranging from 70-72 Gy (relative biological effectiveness [RBE]) at 2.5 Gy (RBE)/fraction or 78-82 Gy (RBE) at 2 Gy (RBE)/fraction using passively scattered protons. Using a Wilcoxon signed rank test, the post-PT normative scores for hip pain, stiffness, and functional difficulty were compared with the averages from general population-based values.

Results: Median patient age was 67 (range, 50–90) years at the time of scoring their hip symptoms. Median follow-up was 36 (range, 18–66) months. The mean scores for hip pain, stiffness, and functional difficulty per the WOMAC questionnaire within the general population (age ≥50 years) were 1.48±0.18, 2.12±2.38, and 1.78±0.45, respectively. WOMAC scores from our 290 patients were significantly lower than those reported in the general public: pain 1.0±1.9 ($p<0.0001$), stiffness 1.5±2.2 ($p<0.0001$), and functional difficulty 1.1±1.8 ($p<0.0001$). In two subgroup analyses, WOMAC scores were not statistically different between patients who received 2.0 versus 2.5 Gy (RBE)/fraction, or 1 versus 2 PT fields per day.

Conclusions: Patient-reported hip symptoms following PT for prostate cancer per the WOMAC questionnaire did not exceed the scores of the general population of males >50 years. There were no differences in hip symptoms between fraction size or number(s) of PT fields per day.

Keywords: proton therapy; particle therapy; radiation therapy; Western Ontario and McMaster Index (WOMAC); outcomes; hip fracture

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Introduction

Prostate cancer is the most common noncutaneous cancer in men in the US [1]. Since the introduction of prostate-specific antigen (PSA) screening, more patients have been identified during the early stages of prostate cancer. These patients have various treatment options, including radiotherapy (RT) and surgery, which are expected to result in low rates of prostate cancer-specific death [2, 3]. Based on the excellent outcomes with these differing treatment options, treatment decisions are no longer guided as much by disease-specific outcomes (since they are quite similar) as by treatment side effects, which may impair quality of life.

Advancements in RT techniques, such as 3-dimensional conformal RT (3DCRT), intensity-modulated RT (IMRT), and image-guided RT (IGRT), have allowed for more precise and safe delivery of high doses of radiation, leading to improved biochemical outcomes [4–6]. Proton therapy (PT) is a highly conformal RT technique. Unlike other advanced x-ray-based therapies like IMRT, which achieves conformality by delivering radiation through multiple beams from multiple angles intersecting on the target, PT achieves conformality by modulating the intensity of the dose deposited along a single beam path. Because the entrance dose with PT is lower than the target dose and there is no exit dose, a two-field technique using opposed lateral beams is commonly applied to deliver a high dose of radiation to the target (such as the prostate with or without the seminal vesicles) with acceptably low radiation doses to the rectum [7, 8].

When treating prostate cancer patients with PT, two opposed lateral fields deliver a slightly higher radiation dose to the hip joint than multiple-field IMRT, which has led to speculations regarding whether PT increases hip joint symptoms after treatment [9, 10]. However, clinical data have not demonstrated any negative impact on the hip with proton therapy [9, 11]. The present study evaluates patient-reported hip joint symptoms in men treated at the University of Florida Proton Therapy Institute (UFPTI) with PT for localized prostate cancer.

Patients and Methods

Patients

The present study was approved by our Institutional Review Board (IRB) and included men who were treated with PT at UFPTI. According to our institutional treatment protocols, the patients received PT doses ranging from 70 to 72.5 Gy (relative biological effectiveness [RBE]) at 2.5 Gy (RBE) per fraction (if enrolled on the hypofractionated protocols) or 78 to 82 Gy (RBE) at 2 Gy (RBE) per fraction (if enrolled on the conventionally fractionated protocols) using passively scattered protons. Patients had a minimum of 18 months of follow-up. Patients who received pelvic nodal irradiation using photon RT or prior pelvic RT were excluded. A total of 325 patients with localized prostate cancer treated at UFPTI between April of 2012 and August of 2012 were recruited for this study.

Simulation, Planning, and Treatment

UFPTI's simulation, planning, and treatment guidelines for prostate cancer have previously been published [7]. For target delineation, the CTV included the prostate and when applicable, the proximal seminal vesicles. The planning target volume (PTV) expanded upon the CTV by 6 mm in the cranial and caudal direction and by 4 mm axially. The femoral heads of all patients were contoured before treatment planning; dose constraints to the femoral

head were as follows: for conventional fractionation, V55 Gy (RBE) $<$ 1 cm^3 (volume of the femoral head receiving 55 Gy [RBE] should be less than 1 cm^3) and V50 Gy (RBE) $<$10% (volume of the femoral head receiving 50 Gy (RBE) is less than 10%); for hypofractionation, V45 Gy (RBE) $<$ 1 cm^3.

Patient-reported Hip Joint Symptoms

The medical records of 290 men treated with PT for prostate cancer were reviewed to extract prospectively recorded medical events and interventions, including provider-assessed toxicity. Before treatment and at 6-month intervals after PT, nurses and physicians recorded interim medical events and interventions, and evaluated patients by using the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE) [12] to assess toxicities, including genitourinary (GU) events, gastrointestinal (GI) events, erectile function, and pain (including pain symptoms, pain location, pain scale, and medication use). Factors potentially associated with hip joint symptoms or bone integrity were recorded from each patient's initial consultation and completion notes, including androgen deprivation therapy, steroid use, testosterone level, body mass index (BMI), previous hip or pelvic trauma, smoking, excessive alcohol consumption, arthritis, osteoporosis, renal/liver disease, hyperparathyroidism, diabetes, and dosimetry details. The proton therapy start date and date of last physician assessment were obtained to calculate follow-up length.

Patient-perceived joint symptoms were scored using the Western Ontario and McMaster (WOMAC) Index [13]. The WOMAC Index is a disease-specific measure of health status widely used in arthritis research with demonstrated validity, reliability and responsiveness [14, 15]. It produces pain, stiffness and physical function subscale scores over 24 questionnaires. Among participants with hip joint symptoms, the total WOMAC score was used to classify severity of joint symptoms [16]. The higher the WOMAC score the more severe the joint symptoms. The questionnaire was returned by 325 patients; 290 patients completed all 24 questions and are the subject of the present study.

Statistics

JMP software was used for statistical calculations (SAS Institute, Cary, NC). The post-PT normative scores for pain, stiffness, and functional difficulty were compared with the averages from the general population-based values [17] using a univariate Wilcoxon signed-rank test. These same scores were also stratified by selected prognostic factors, and potential differences between levels of these factors were assessed with the Wilcoxon's signed rank test.

Results

Baseline characteristics for the 290 patients who completed the entire questionnaire are listed in Table 1. For the entire cohort of 290 patients, the mean pain score was 1.0 (standard deviation [SD]=1.9), the mean stiffness score was 1.5 (SD=2.2), and the mean difficulty score was 1.1 (SD=1.8). The distribution in score by age is listed in Table 2.

Previously reported national averages for similarly aged patients in the general public include a mean pain score of 1.48 (SD=2), a mean stiffness score of 2.12 (SD 2.38), and a mean difficulty score of 1.75 (SD=2.14). These scores were all significantly higher (worse hip problems) than those patients in the proton cohort ($P<0.0001$).

On univariate analysis evaluating for factors associated with worse pain, stiffness, or functional difficulty scores, only BMI $>$ 30 was associated with a higher (worse) pain score

Table 1. Patient characteristics

	Number of Pts. (N=290)	%
BMI		
<30	211	73%
≥30	79	37%
Prostate size		
< 60 grams	256	88%
≥60 grams	34	12%
Stage		
Low	128	44%
Intermediate	119	41%
High	41	14%
Recurrent	2	1%
Androgen deprivation therapy		
Yes	42	14%
No	248	86%
Proton therapy dose per fraction		
2 Gy	257	89%
2.5 Gy	33	11%
Fields treated per day		
One field	268	92%
Two fields	22	8%

BMI, body mass index

(p=0.0097), stiffness score (p=0.0551), and difficulty score (p=0.0060). Large prostate volume > 60 grams was associated with a higher functional difficulty score, but not associated with pain or stiffness scores.

Discussion

The present study is the first to evaluate patient-reported outcomes related to the hip following RT for prostate cancer by using the validated WOMAC tool for arthritis.

Table 2. Distribution of WOMAC score

		WOMAC score		
Age (year)	Number of Pts.	Pain	Stiffness	Functional difficulty
50–54	7	1.4 ± 2.4	0.6 ± 1.3	0.3 ± 0.8
55–59	29	0.6 ± 1.6	1.0 ± 2.1	0.5 ± 1.3
60–64	45	0.9 ± 1.8	1.4 ± 2.2	1.0 ± 1.9
65–69	75	1.4 ± 2.2	1.8 ± 2.5	1.4 ± 2.2
70–74	70	1.0 ± 1.8	1.5 ± 2.3	1.1 ± 1.9
75–79	43	1.1 ± 1.8	1.5 ± 2.0	1.1 ± 1.7
80+	21	0.6 ± 0.9	0.9 ± 1.2	0.6 ± 0.8
All Pts	290	1.0 ± 1.9	1.5 ± 2.2	1.1 ± 1.8
General population[a]				
≥ 50 yrs	2470	1.48 ± 2.0	2.12 ± 2.38	1.75 ± 2.14

[a]Data from "Population-Based Normative Values for the Western Ontario and McMaster (WOMAC)" Osteoarthirtis Index: Part I. Bellamy et al. *Semin Arthritis Rheum.* 2011; 41(2):139-48

Importantly, it demonstrates that WOMAC scores at least 18 months after PT were no worse than those found in the general public and, in fact, were significantly better (post-PT scores were lower). Furthermore, it confirmed no significant difference in hip function among patients treated with 1 field a day versus 2 fields a day or among patients treated on a hypofractionated protocol at 2.5 Gy (RBE) per fraction versus 2 Gy (RBE) per fraction.

Hip joint and bone integrity in patients with prostate cancer may be compromised by treatment and/or disease-related factors, such as androgen deprivation therapy, radiation therapy, or occult bone metastases [18–21]. PT has been used as an alternative RT modality to photon-based treatment for the management of many different cancers. Data support PT as an effective treatment with minimal side effects for men with prostate cancer [7, 8]. Nevertheless, some fear that the relatively higher radiation dose to the hip joint and bone with popular PT techniques, as compared to the dose with photon-based IMRT, could increase hip fractures or hip joint symptoms after treatment [9].

We recently reported that PT using opposed lateral fields for prostate cancer did not increase post-treatment hip fractures compared to expected rates in untreated men [22]. Using the WHO Fracture Risk Assessment Tool (FRAX), we generated the expected number of patients with hip fractures and the observed-to-expected ratio at a median follow-up of 4 years after PT. Per FRAX, 3.02 patients were expected to develop a hip fracture without PT; in actuality, 3 patients treated with PT developed fractures for a rate of 0.21 fractures per 100 person-years of follow-up, and an observed-to-expected ratio of 0.99 (p value not significant) [23].

Undoubtedly, hip joint-related symptoms after pelvic radiation have not been fully explored. In addition to hip fracture, radiation to the pelvis could cause an inflammatory response in the hip leading to hip joint arthritis, tendonitis, or bursitis that could present as an increase in hip joint-related symptoms, such as hip pain, stiffness, or functional difficulty after treatment.

Patient-reported symptoms measures are commonly used to assess joint symptoms. The WOMAC is a reliable, validated tool to evaluate symptoms in patients with hip and knee arthritis [13–15]. Using a comparison with WOMAC scores from the general population [17], this is the first study to explore the relationship between PT and patient-reported hip joint symptoms after PT in the management of localized prostate cancer. Importantly, the results demonstrate that WOMAC scores for pain, stiffness, and functionality were not worse (that is, scores were not higher) among patients treated with PT compared with the general population. In fact, the scores were actually statistically significantly lower than the general population, suggesting fewer hip joint problems among this cohort.

Our findings are not as surprising as one might think. The use of radiotherapy for osteoarthritis has been reported in the literature. In a study by Murley, 59 patients who were moderately or severely disabled from osteoarthritis were evaluated 1 year following irradiation of the hip to doses of 1000–2000 roentgens delivered as 6 doses over one week using a 150-kV apparatus [24]. Murley demonstrated that a quarter of the patients derived a subjective benefit from irradiation of their hip joint. Although the unintentional radiation from PT for the treatment of prostate cancer is higher than the intentional dose delivered in the osteoarthritis study, PT may have relieved some of the symptoms of mild osteoarthritis, thereby impacting patients' overall scores. Another explanation for the better scores in our cohort is that these patients do not represent the "general population" as they were well enough to travel to our proton center for the management of their prostate cancer. To control for this factor we would have to compare outcomes among men who chose active

surveillance and men who received PT. Alternatively, had we prospectively evaluated patients with the WOMAC instrument before and after treatment, we would have been able to observe improvements in patients' scores following treatment.

Another important finding from the present study is that there were no differences in patient-reported hip symptoms after PT regardless of differences in PT schedules, such as 1 versus 2 fields per day or 2.0 Gy (RBE) versus 2.5 Gy (RBE) per fraction. These are valid concerns since many proton centers choose to treat prostate cancer with 2 fields a day rather than alternate fields each day, and there is also a movement towards hypofractionated protocols for these patients in an effort to reduce costs and inconveniences of longer treatment courses with possible improvements in outcomes. At our institution, we usually treat prostate cancer patients with 1 field a day with the goal of decreasing intrafractional motion and improving patient flow via shorter daily treatments; however, in patients with narrow pelvises for whom either of the fields delivers 95% of the dose across the acetabulum, we use 2 fields a day based solely on institutional procedures and not because of clinical data. Demonstrating similarly good outcomes in hip functions among the patients treated with 1 versus 2 fields a day helps validate our current institutional practices. Additionally, similarly good outcomes among patients treated with 2 versus 2.5 Gy (RBE) per fraction also help confirm the safety of hypofractionated protocols with lateral fields by not noticeably increasing hip problems.

We observed that obese patients were more likely to have worse hip pain, stiffness, and physical function than non-obese patients following PT. Patient-reported hip joint symptoms in obese patients whose BMI equaled or surpassed 30 kg/m^2 as defined by the WHO were significantly higher in all three WOMAC scores than patients with a BMI below 30 kg/m^2. Our findings are in line with other population-based studies demonstrating that obesity is associated with an increased risk of arthritis [25]. In light of the rising obesity rates in many developed countries, the observed relationship between obesity and hip joint symptoms in patients with localized prostate cancer suggests the need for additional health counseling following PT and possibly IMRT.

Our study has some limitations. Most importantly, baseline WOMAC scores were never collected from these patients before PT. This cross-sectional cohort study comparing follow-up patients to the general public resulted from the urgent need to investigate the existence of any remarkable negative effects to the hip from PT that would require changes in our treatment design. A prospective study would require a much longer time period to collect patient information. Additionally, a portion of patients did not complete the entire form and their data was not tabulated, which could have potentially impacted the results if all of these patients happened to suffer from hip symptoms. Yet it is unlikely that this was the case and the average scores for each question were actually no different among the patients who completed the entire questionnaire and those who did not.

Conclusion

PT for patients with localized prostate cancer treated per a UFPTI protocol using opposed lateral or slightly oblique fields did not compromise hip joint symptoms after completing treatment compared to the general public. Longer follow-up and additional studies comparing prospectively collected WOMAC scores before and after PT are needed to confirm these findings.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflict of Interest: Bradford Hoppe has received an honorarium from Procure for lectures.

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