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CLINICAL INVESTIGATION Prostate

RISK OF ALL-CAUSE AND PROSTATE CANCER–SPECIFIC MORTALITY AFTER BRACHYTHERAPY IN MEN WITH SMALL PROSTATE SIZE

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Background: Brachytherapy for prostate cancer can be technically challenging in men with small prostates (≤20 cc), but it is unknown whether their outcomes are different than those of men with larger prostates.

Methods and Materials: We studied 6,416 men treated with brachytherapy in one of 21 community-based practices. Cox regression and Fine and Gray's regression were used to determine whether volume ≤20 cc was associated with a higher risk of all-cause mortality (ACM) or prostate cancer–specific mortality (PCSM), respectively, after adjustment for other known prognostic factors.

Results: 443 patients (6.9%) had a prostate volume ≤20 cc. After a median follow-up of 2.91 years (interquartile range, 1.06–4.79), volume ≤20 cc was associated with a significantly higher risk of ACM (adjusted hazard ratio = 1.33 [95% CI 1.08–1.65], $p = 0.0085$) with 3-year estimates of ACM for ≤20 cc vs. >20 cc of 13.0% vs. 6.9% ($p = 0.028$). Only 23 men (0.36%) have died of prostate cancer, and no difference was seen in PCSM by volume ($p = 0.4$).

Conclusion: Men with small prostates at the time of implant had a 33% higher risk of ACM, and the underlying cause of this remains uncertain. No increase in PCSM was observed in men with volume ≤20cc, suggesting that a small prostate should not in itself be a contraindication for brachytherapy, but inasmuch as absolute rates of PCSM were small, further follow-up will be needed to confirm this finding. © 2011 Elsevier Inc.

Prostate cancer, Brachytherapy, Small volume, All-cause mortality, Prostate volume.

INTRODUCTION

Proper selection of patients for prostate brachytherapy is critical for optimizing long-term outcomes and minimizing morbidity. For example, patients with very large prostates (*e.g.,* larger than 60 cc) are generally considered suboptimal because of their higher risk for developing post-operative urinary retention (1, 2). They also have a higher potential for pubic arch interference, which can hinder efforts to provide adequate coverage of the whole gland (3).

Less attention has been paid to the issue of men with very small prostates (*e.g.,* ≤20 cc) because this is a less common occurrence, but small prostate size may also be considered a relative contraindication to prostate brachytherapy, mainly because of the perceived difficulty of performing a good implant in a small gland (4, 5). The technical challenge of a small gland is that there is less room for error, and there are fewer degrees of freedom, making it more difficult to create a plan that both provides adequate coverage and respects normal tissue tolerance. For this reason, some radiation oncologists are reluctant to implant glands ≤20 cc.

Some studies have explored the feasibility of performing technically adequate implants on small glands, but the clinical outcome after brachytherapy for men with small glands has not been extensively studied (4, 5). Even if implanting small glands is technically feasible, a finding of inferior outcomes for patients with small glands after brachytherapy might be a reason to choose an alternative treatment for them. Therefore, the purpose of this study was to compare both the prostate cancer–specific mortality (PCSM) and the all-cause mortality (ACM) in patients with small prostate

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volume (≤20 cc) vs. those with larger volumes at the time of prostate brachytherapy.

METHODS AND MATERIALS

Patient population and treatment

The study cohort was composed of 6,416 men (median age, 71.3 years; interquartile range, 66.3–73.4 years) with at least a 10-year life expectancy who were treated with brachytherapy for localized or locally advanced prostate cancer at the Chicago Prostate Cancer Center or in one of 20 community-based medical centers within the 21st Century Oncology group located in Florida, New York, and North Carolina. Men were treated between November 12, 1991, and September 23, 2007. Among the patients, 3,005 (46.8%) received supplement external beam radiation therapy (EBRT), and 2,886 (45.0%) had received neoadjuvant androgen deprivation therapy (ADT). Documented prostate volume at the time of implant was required for inclusion. The distribution of year and type of treatment was similar among centers.

The ADT consisted of a luteinizing hormone–releasing hormone agonist with or without an antiandrogen and was completed before brachytherapy. The EBRT was delivered using photons in 25 1.8-Gy fractions to the prostate and seminal vesicles for a total dose of 45 Gy, using computed tomography–based simulation and a three-dimensional conformal or intensity-modulated radiation therapy technique. The pelvic lymph nodes were not included in the EBRT volume. Brachytherapy was performed using a peripheral loading technique using preloaded iodine-125, palladium-103, or cesium-131 sources and preplanned dosimetry. The prescribed minimum peripheral doses used were consistent and accepted standards within the United States. Specifically, they were 144, 108, and 115 Gy, respectively, for iodine-125, palladium-103, and cesium-131 when used as monotherapy and 108, 90, and 100 Gy, respectively, when used in conjunction with 45 Gy of supplemental EBRT.

Implant volume analyzed in this study was the measured transrectal ultrasound measured prostate volume on the day of brachytherapy.

Prostate needle biopsy specimens underwent review by a pathologist with expertise in genitourinary pathology at each center. In accordance with federal and institutional guidelines, all research was conducted under an institutional review board–approved protocol permitting collection and analysis of de-identified patient data at baseline and follow-up. The data collection on the study patients was performed by a team of data managers and was overseen by a biostatistician at each facility.

Follow-up and determination of the cause of death

Follow-up started on the day of prostate brachytherapy and concluded on February 21, 2008, or the date of death, whichever came first. Patients were generally seen every 3 months for 1 year, every 6 months for an additional 4 years, and then annually thereafter. At each follow-up, a history and physical examination including a digital rectal examination was performed in addition to measurement of serum prostate-specific antigen (PSA) before the digital rectal examination. At the time of PSA failure, in addition to the routine follow-up assessment, a pelvic computed tomography or magnetic resonance imaging and a bone scan were also obtained. Salvage therapy used in men across all treatment groups was a luteinizing hormone–releasing hormone agonist, which was initiated within 1 year after PSA recurrence and always before symptomatic or radiographic progression. The attending oncologist or urologist who observed the patient until death determined the cause of death. All deaths resulting from prostate cancer were confirmed using either the National Death Index or attending report. It is presumed that to record a death resulting from prostate cancer, hormone-refractory metastatic prostate cancer was documented in the setting of an increasing PSA level despite the use of second-line hormonal maneuvers and cytotoxic chemotherapy before death.

Statistical methods

Comparison of the distribution of baseline patient and tumor characteristics across treatment modalities. Descriptive statistics were used to characterize the clinical characteristics of the study cohort at baseline and are shown in Table 1, stratified by prostate volume at the time of implant (≤20 cc vs. >20 cc). A chi-square metric was used to compare the distributions of baseline clinical characteristics across treatment modalities. For serum PSA levels and age, medians and their distributions were compared by prostate size using a Wilcoxon rank-sum test.

Predictors of ACM. Cox multivariable regression was used to evaluate whether the risk of ACM was significantly associated with prostate size, adjustment being made for age, year of brachytherapy, treatment with supplemental EBRT, treatment with neoadjuvant ADT, and known prostate cancer prognostic factors, including baseline PSA level, Gleason score, and clinical T category

Table 1. Baseline characteristics of 6416 men stratified by prostate volume

Characteristic	TOTAL n = 6416		Volume <=20cc n = 443		Volume >20 cc n = 5,973		p value
PSA (ng/mL)	n	%	n	%	n	%	
4 or less	598	9.32	64	14.5	534	8.9	
>4–10	4,397	68.53	289	65.2	408	68.8	
>10–20	1,131	17.63	77	17.4	1,054	7.7	
>20	290	4.52	13	2.9	277	4.6	<0.001
Gleason score							
6 or less	4,291	66.88	247	55.8	4,044	67.7	
7	1,637	25.51	152	34.3	1,485	24.9	
8–10	488	7.61	44	9.9	444	7.4	<0.001
T category							
T1	4,149	64.67	235	53.1	3,914	65.5	
T2	2,178	33.95	198	44.7	1,980	33.2	
T3	89	1.39	10	2.3	79	1.3	<0.001
ADT use	2,886	45.0%	216	48.8%	2,670	44.8%	0.098
Age (y) (median)			71.1		72.0		0.26

Abbreviation: ADT = androgen deprivation therapy.

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