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Original article

Does family history of prostate cancer affect outcomes following radiotherapy?

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ABSTRACT

Objective: To examine family history (FH) as a prognostic factor following radiotherapy (RT).
Materials and methods: Between 1989 and 2007, 1711 men with clinically localized prostate cancer and complete family history who had received RT (median RT dose = 74 Gy) without androgen deprivation therapy were analyzed. FH was defined as any prostate cancer in a first degree relative. For the biochemical failure (BF) outcome, this sample size has 85% power to detect a hazard ratio of 1.56 for positive versus negative FH.
Results: With a median follow-up of 71 months, there was no significant difference in the distribution of Gleason score (GS) or prostate specific antigen (PSA) based on FH. A positive FH was not an independent predictor of BF, distant metastasis (DM), prostate cancer specific mortality (PCSM), or overall mortality (OM) in Cox proportional multivariable analysis. On further analysis in a Cox proportional multivariable analysis, men with two or more first degree relatives with prostate cancer had a significantly higher likelihood of BF and DM than those with no FH, although there was no difference in PCSM or OM. Men with a positive FH (23%) were more likely to be younger, have a lower PSA, and non-palpable disease. There was no interaction between a positive FH and neither race nor treatment era (pre-PSA vs. PSA era).
Conclusions: A positive FH is not a prognostic factor following RT and should not alter standard treatment recommendations. Patients with two or more first degree relatives with prostate cancer had a higher likelihood of BF and DM, but there was no effect on survival. There was no interaction between a positive FH and African American race or treatment era. A positive FH was however, associated with more favorable PSA values and T-stage that may be the result of earlier screening.
 Radiotherapy and Oncology xxx (2014) xxx–xxx

A positive family history (FH) of prostate cancer is feared to portend a poorer outcome following treatment. The traditional pretreatment risk factors used to establish prognosis are serum prostate specific antigen (PSA), Gleason score (GS), and tumor stage (T-stage). Combinations of these factors, as used in the American Joint Commission on Cancer (AJCC) [1] and National Comprehensive Cancer Network (NCCN) [2], group patients according to the risk of the recurrence, which in turn aids in providing treatment recommendations. A positive FH, however, may represent one or more unidentified negative prognostic factors not represented by PSA, GS, and T-stage.

There are few studies that examine the impact of a positive FH on prognosis following radiotherapy for prostate cancer and the results are conflicting [3–6]. The Cleveland Clinic was the first to report the detrimental effect of a positive family history of prostate cancer on recurrence following either surgery or RT [3]. These results however, were unconfirmed in other series [4–6]. Kupelian et al. later reported that the era of treatment might explain the conflicting results where a positive FH may have been important in the pre-PSA but these results have not be confirmed. Furthermore, there is a question as to whether African American race and positive family history might predict for worse outcome after definitive radiation therapy for prostate cancer [7]. Investigators from the University of Michigan observed combined African American race and positive family history was found to be a significant predictor of worse freedom from relapse rates [6].

More clinical data are needed to confirm or refute these conflicting findings. The importance of a family history on prognosis may impact an estimated 36,133 men with a familial inheritance pattern of prostate cancer in the United States during 2011 assuming a prevalence of 15% [8,9]. These men are at risk of receiving more aggressive therapy, such as combination radiotherapy and hormonal therapy, with the belief that a positive family history is detrimental without clear evidence that the prognosis is worse.

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The purpose of this study was to determine if a positive family history is a negative prognostic factor independent of PSA, GS and T-stage in the largest and most mature series of men treated with definitive RT. We also seek to determine the influence of treatment era (i.e. pre-PSA era vs. PSA era) and race (i.e. African American) on the prognostic importance of FH.

Materials and methods

Between 1989 and 2007, 1711 men with clinically localized prostate cancer with a complete family history received RT alone (no androgen deprivation therapy) at Fox Chase Cancer Center (Philadelphia, PA). Four hundred twenty-six men had been excluded due to missing family history data. All patients had information available regarding GS, T-stage, initial PSA (iPSA), RT dose, and family history. A positive first-degree FH was defined as prostate cancer in one or more first-degree relatives, consistent with prior studies [3–6]. To assess prostate cancer FH burden, FH was further defined as zero, one, or two or more first- degree relatives on the maternal or paternal side of the family. An expanded definition of FH, defined as prostate cancer in one or more first or second degree relatives was also considered. Race was defined as white, black/African American, and other/unknown. The impact of the pre PSA era was evaluated by adjustment for treatment from 1989–1992 compared to 1993–2007.

Radiotherapy

The techniques used for 3D-CRT and IMRT have been previously described [10,11]. Briefly, patients were immobilized supine in a thermoplastic cast and daily prostate localization was performed in all patients using either the B-type acquisition ultrasound, fiducial markers with electronic portal, computed tomography imaging, or radiofrequency beacons. The planning target volume included the prostate and 1 cm margin for 3D-CRT and 8 mm for IMRT, except posteriorly where the margin was less to enable better rectal sparing. The RT dose was prescribed such that 95% of the planning target volume received 100% of the prescribed dose. The median dose for patients treated with RT was 74 Gy (range: 70–80 Gy).

Patient evaluation and staging

All patients had a history and physical exam including digital rectal exam, pretreatment iPSA, and histologic confirmation of adenocarcinoma with a GS. Sixty eight percent of patients had computed tomography of the abdomen or pelvis while 81% had a bone scan to exclude metastasis. T-stage was established by palpation findings only, without upstaging using pathologic or radiographic information.

Statistical analysis

The Kaplan–Meier product limit method was used to estimate survival functions for each endpoint by FH (positive vs. negative), and differences in the curves were assessed using the log rank test. Cox proportional hazards methods were used for inferences about the relationship of time to endpoint with potential risk factors including FH, GS (2–6 vs. 7 vs. 8–10), T-stage (T1 vs. T2 vs. T3), iPSA (continuous), and RT dose (continuous). FH was modeled in three ways: positive vs. negative based on FDRs, positive vs. negative based on FDRs and SDRs, and to assess increased FH burden, as a categorical variable (0, 1 or 2+ FDRs). Endpoints included biochemical failure (BF, PSA nadir +2 ng/mL), distant metastasis (DM), prostate cancer specific mortality (PCSM), and overall mortality (OM). Men who did not have the endpoint were censored at their last PSA measurement (for BF) or their last available follow-up date.

Table 1
Demographic and treatment characteristics by family history of prostate cancer.

Characteristics	All (n = 1,711)		Positive FH (n = 386)		Negative FH (n = 1,325)		p-Value*
	N	Percent	*N*	Percent	*N*	Percent	
Age							
Median (range)	68.2 (40.7–87.3)		67.4 (46.9–87.3)		68.5 (40.7–86.7)		0.050
Race							
White	1483	86.7	312	80.8	1171	88.4	0.0006
Black	190	11.1	61	15.8	129	9.7	
Unknown or Other	38	2.2	13	3.4	25	1.9	
Gleason score							
2–6	1199	70.1	267	69.2	932	70.3	0.81
7	470	27.5	108	28.0	362	27.3	
8–10	42	2.5	11	2.9	31	2.3	
iPSA (ng/mL)							
Median (range)	6.3 (0.1–136)		6.0 (0.2–136)		6.4 (0.1–107)		0.041
<10 ng/mL	1315	76.9	305	79.0	1010	76.2	0.19
10–20 ng/mL	325	19.0	71	18.4	254	19.2	
>20 ng/mL	71	4.1	10	2.6	61	4.6	
T stage							
T1	1023	59.8	257	66.6	766	57.8	0.0035
T2	629	36.8	122	31.6	507	38.3	
T3/TX	59	3.4	7	1.8	52	3.9	
Technique							
Conformal	959	56.0	176	45.6	783	59.1	<0.0001
IMRT	752	44.0	210	54.4	542	40.9	
RT dose (cGy)							
Median (range)	7400 (7000–8000)		7600 (7000–8000)		7400 (7000–8000)		0.0002
Number of FDR with prostate cancer							
1			325	84.2			
2+			61	15.8			

Abbreviations: FH = family history; iPSA = initial pretreatment prostate specific antigen; IMRT = intensity modulated radiotherapy; RT = radiotherapy; FDR = first-degree relatives.

* p-Value from test comparing positive FH and no FH groups. Medians were compared using Wilcoxon rank sum tests, and Chi-square tests were used to compare categorical variables.

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