

Original article

Predictors of extracapsular extension and positive margins in African American and White men[☆]

Edmond L. Paquette, M.D.^{a,b}, Roger R. Connelly, M.S.^b, Leon Sun, M.D.^b,
Laurence R. Paquette, Ph.D.^b, Judd W. Moul, M.D.^{b,c,*}

^a Urology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, DC 20307, USA

^b Center for Prostate Disease Research, 1530 East Jefferson Street, Rockville, MD 20852, USA

^c Uniformed Services, University of the Health Sciences, Department of Surgery, Bethesda, MD 20814, USA

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Abstract

Objective: Radical retropubic prostatectomy (RRP) pathology from African American (AA) and White men from 1988 to 1999 was examined to determine if the pre-treatment factors PSA, clinical stage, biopsy grade, age at surgery, and year of surgery (YOS) were predictive of extracapsular extension (ECE) and positive margins for each ethnic group. **Methods:** Clinical and pathologic data was collected on 179 AA and 548 white men undergoing RRP from 1988 to 1999 at a tertiary military medical facility. Logistic regression with multivariate analysis was used to determine which pre-operative data-points were predictive of pathologic ECE and positive margins for each ethnic group. **Results:** PSA, biopsy grade, age, and YOS (more recent years had better surgical pathology) were predictive of ECE for AA and white men. PSA, biopsy grade, and YOS were predictive of positive margins for AA men, while PSA and YOS were predictive of positive margins for white men. PSA continues to be a strong predictor of ECE and positive margins for both AA and white men. However, we describe for the first time, YOS being predictive of ECE and positive margins for both AA and White men, using multivariate regression analysis. **Conclusion:** This is thought to be reflective of the improving public awareness of prostate cancer that has occurred during the PSA-era, resulting in patients participating in screening programs and being diagnosed earlier. Close follow-up of these patients is warranted to determine if the improved pathologic stage of those patients treated more recently translates into improved disease-specific mortality. © 2003 Elsevier Science Inc. All rights reserved.

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1. Introduction

African American (AA) men have historically presented with more advanced clinical stages, and have experienced increased rates of recurrence and mortality, and exhibited a shorter disease-specific survival from prostate cancer, as compared with other ethnic groups [1–6]. Some recent studies indicate that the rates of ECE, recurrence and survival may be equilibrating between AA and white men,

which may be secondary to more active screening and more aggressive treatment of the AA population [7–9]. Despite these recent findings others have demonstrated that AA race continues to be an independent predictor of positive margins [10]. Furthermore, AA men with positive margins have decreased disease specific survival as compared to white men [11]. It is in this context, that we seek to delineate the pre-operative predictors of ECE and positive margins for AA and white men undergoing radical prostatectomy. Attention is focused on whether year of surgery is a significant predictor in order to determine if during the PSA-era, improvements in pathologic stage have occurred for either AA or white men. Despite the fact that population-based screening efficacy has yet to be proven, it is hoped that documenting an improved intermediate endpoint will have public health implications for the high-risk AA population.

[☆] The opinions and assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the US Army or the Department of Defense.

* Corresponding author. Tel.: +1-240-453-8930; Fax: +1-240-453-8912.

E-mail address: Jmoul@cpdr.org (J.W. Moul).

2. Methods

The Center for Prostate Disease Research (CPDR) is a congressionally mandated, department of defense funded, prospective program that registers and follows men with prostate cancer treated in the military health care system. All patients sign an informed consent allowing the CPDR to collect this data and proactively follow participants. The study began at Walter Reed Army Medical Center (WRAMC) in 1994, and 9 additional military sites were added between 1997 and 1998. Because the data is most mature and complete at WRAMC, this site was selected for the study.

Between 1988 and 1999, 799 consecutive patients that underwent radical retropubic prostatectomy (RRP) for the treatment of prostate cancer were registered in the database at WRAMC, in Washington, DC. Two of the patients received salvage prostatectomy following radiation therapy and were excluded. The varied ethnic backgrounds for these remaining 797 men included 195 AA, 587 white, 7 Hispanic, 3 Asian and 5 other. Because of the low number of men that were non-AA or non-whites, they were excluded from the study, leaving 782 men included for analysis. Fifty-five of 782 patients had neo-adjuvant hormone therapy with either gonadotropin-releasing hormone agonist (GnRH), anti-androgen or both. These patients were excluded, leaving 727 patients (179 AA, and 548 white) included in the study.

Patients diagnosed between 1988 and 1993 were retrospectively registered and patients diagnosed between 1994 and 1999 were prospectively registered.

The following variables were analyzed in this study: date of surgery, age at surgery, ethnicity, pre-treatment PSA, clinical stage, the worst (highest) biopsy Gleason sum, the worst biopsy tumor grade, and pathologic stage and margin status [12–16].

There were 196 patients that did not have a biopsy Gleason sum, because our institution did not begin using the Gleason scoring system regularly until 1992. There were 213 patients without a biopsy tumor grade, because once Gleason scoring was instituted, biopsy tumor grade was not consistently reported. However, there were only nine patients where the biopsy Gleason sum and the biopsy tumor grade, were not recorded. Because of this we converted tumor grade to Gleason scoring, with well differentiated tumors considered Gleason sum 2–4, moderately differentiated tumors assigned Gleason sum 5–7, and poorly differentiated tumors being Gleason sum 8–10. This reflection of biopsy result is referred to as “biopsy grade” in the tables and in the text. The nine patients with missing biopsy results were not included in the multivariate logistic regression model.

The pre-treatment PSA was not recorded for 15 of 727 patients. There were 14 missing values for 1988–1989, and one missing value in 1990. Prior to 1990 PSA level was determined by radioimmunoassay. In 1989 WRAMC

changed to the Abbott immunoassay^R, and over the last several years have utilized the Hybritec^R monoclonal antibody immunoassay, as well as the Elecys^R system, which uses electrochemiluminescent technology. The patients with missing PSA values were excluded from the logistic regression model for prediction of pathologic stage and margin status.

Since 1993, 452 men have had whole mount pathologic assessment at the Armed Forces Institute of Pathology. The prostate and seminal vesicles were fixed in 10 buffered formalin for at least 48 h. The outer surface of the left side of the prostate and the left adnexa were inked in red, and the right side and the right adnexa were inked in green. Specimens were step sectioned in 2.25 mm intervals perpendicular to the long axis of the prostate. The entire prostate was embedded. Prior to 1993 standard pathologic assessment was done at the pathology department at Walter Reed Army Medical Center by inking the specimen with a different color for each respective section of the prostate: right and left anterior, right and left posterior, etc. The specimen was then breadloafed, and each section was submitted in 3 to 4 cassettes, depending on the size of the section. Each block (cassette) was given a number (1, 2, 3 etc.) with a site and side designation, and each slide was then examined by a board certified pathologist to determine pathologic stage.

ECE was defined as tumor extending beyond the capsule of the prostate, either with or without seminal vesical involvement. A positive margin was defined as tumor extending to the inked margin of the specimen. A pathologic specimen in which the inked border of the tumor was disrupted, in which a definitive assessment of ECE or margin status could not be determined, was classified as pathologic stage Tx (pTx). There were 49 patients since 1993 who were classified as having pTx, 12 were AA, and 37 were white. In clinical practice, pTx is usually classified as pT3, and it is categorized as such in this study, assigning pTx tumors as having ECE and positive margins.

Logistic regression with backward elimination was performed with the following variables: biopsy grade, PSA level, age, year of diagnosis and clinical stage, and was used to determine which pretreatment factors were significant predictors of ECE, and positive margins for the AA and the white population. PSA with sigmoid transformation ($10/1 + e^{6.8704 - 9815 * \text{PSA}}$) was used in the logarithmic models in order to incorporate the patients with outlier PSA values [17–18].

3. Results

Table 1 displays the rates of ECE, positive margins, and the ranges of age, biopsy grades and clinical stages for AA and white men over the twelve years of the study. Note that there is no significant difference in the rates of ECE or positive margins between these two groups when analyzing

Table 1
Distribution of demographic, clinical, and pathological variables among 179 African American, and 548 white radical prostatectomy patients

Variable	African-American		White		P-value ^a
	No.	%	No.	%	
Total patients	179	100.0	548	100.0	
Year of surgery					0.039
1988–1989	5	2.8	51	9.3	
1990–1991	17	9.5	68	12.4	
1992–1993	44	24.6	111	20.3	
1994–1995	36	20.1	104	19.0	
1996–1997	31	17.3	103	18.8	
1998–1999	46	25.7	111	20.3	
PSA					0.012
0–4.0	26	14.6	116	21.7	
4.1–10.0	91	51.1	292	54.7	
10.1–20.0	50	28.1	94	17.6	
>20.0	11	6.2	32	6.0	
Unknown	1		14		
Biopsy grade					0.154
2–4	53	30.1	205	37.8	
5–7	114	64.8	317	58.5	
8–10	9	5.1	20	3.7	
Unknown	3		6		
Age					0.112
<59	47	26.3	136	24.8	
60–64	45	25.1	129	23.5	
65–69	59	33.0	151	27.6	
>69	28	15.6	132	24.1	
Clinical stage					0.297
T1a+b	3	1.7	22	4.0	
T1c	83	46.4	229	41.9	
T2	90	50.3	290	53.1	
T3 + T4	3	1.7	5	0.9	
Unknown			2		
ECE					0.569
Positive	90	50.3	289	52.7	
Negative	89	49.7	259	47.3	
Margins					0.560
Positive	70	39.1	201	36.7	
Negative	109	60.9	347	63.3	

^a P-value for the chi-square test is of no association between ethnicity and the variable.

data over the entire length of the study: 50.3 ECE for AA, and 52.7 for white men ($P = 0.569$), and 39.1 positive margins for AA, and 36.7 for white men ($P = 0.560$).

Tables 2 and 3 display the significant predictors of ECE and positive margins for AA and white men. PSA, biopsy grade, age, and YOS were predictive of ECE for AA and white men. PSA, biopsy grade, and YOS were predictive of positive margins for AA men, while just PSA and YOS were predictive of positive margins for white men.

Tables 4 and 5 reflect the strength of PSA in predicting ECE and positive margins for both the AA and white men. The rates of ECE for AA men with PSA values between 0–4.0 and 4.1–10.0 ng/dl are 30.8 and 39.6 respectively. These compare similarly to the rates for white men (29.3 and 53.1) for the same PSA ranges. Likewise, the rates of positive margins for AA men are 15.4 and 29.7, and for the

Table 2
Logistic regression for predictors of extracapsular extension for African-American (AA) and White (W) Men

Variable	DF	Chi square (AA)	P value (AA)	Chi square (W)	P value (W)
PSA	1	8.32	0.004*	31.57	<.001*
Biopsy Grade	2	9.81	0.007*	8.44	0.015*
Year	1	8.02	0.005*	1.83	0.176**
Age	1	3.45	0.063*	7.57	0.006*
Clinical stage	1	0.12	0.743	0.70	0.402

DF = Degrees of Freedom.

* Remained significant after backward elimination of insignificant variables.

^a After backward elimination of clinical stage, p value is 0.093, which is significant.

White men are 16.4 and 36.3 for the ranges of PSA of 0–4.0 and 4.1–10.0 ng/dl, respectively. Also, as the PSA rose to higher than 10.0 ng/dl, the rates of ECE and positive margins increased dramatically, for both AA and white men. Clinical stage was not a significant predictor of pathologic stage or margin status for AA or white men.

4. Discussion

There were two new, and important, findings of this study: First, YOS is a positive predictor of ECE and positive margins for both AA and white men. Second, there are strikingly similar rates of ECE and positive margins for each range of PSA values for AA and white men. The first finding has important public health implications, while the second sheds further light on the relationship between ethnic differences, tumor aggressiveness, and PSA values.

4.1. Year of surgery as a predictor of ECE and margin status

YOS was found to be a predictor of ECE and margin status in a multivariate logistic regression model for both AA and white men. Specifically, the more recent a patient had surgery, the less likely that patient would have ECE or

Table 3
Logistic regression for predictors of positive margins for African-American (AA) and White (W) Men

Variable	DF	Chi square (AA)	P value (AA)	Chi square (W)	P value (W)
PSA	1	11.74	<0.001*	26.70	<0.001*
Biopsy grade	2	5.38	0.068*	2.66	0.265
Year	1	7.48	0.006*	3.58	0.059*
Age	1	0.67	0.414	1.37	0.240
Clinical stage	1	1.00	0.317	0.081	0.776

DF = Degrees of Freedom.

* Remained significant after backward elimination of insignificant variables.

Table 4
PSA ranges and chance of ECE and positive margins for AA Men

PSA ranges	# Patients	# ECE	% ECE	# (+) Mar.	% Pos. Mar.
0–4.0	26	8	30.8	4	15.4
4.1–10.0	91	36	39.6	27	29.7
10.1–20.0	50	36	72.0	29	58.0
>20.1	11	9	81.8	9	81.8

positive margins. We suspect that as the PSA era evolved, the increasing public awareness (which we believe is reflected by the YOS) of prostate cancer was responsible for recruiting more men into screening programs, with subsequent earlier diagnosis, and improved pathologic stage migration in predominately white populations. The first by Jhaveri et al. [23], describes a decrease in ECE from 81% to 36% from 1987 to 1997. They included only T1c tumors and patients with PSA values greater than 4.0 ng/dl. The second, by Stamey et al. [24], demonstrated a decrease in the rate of ECE from 60% to 25% from 1988 to 1996. They included clinical stage T1c and T2 tumors as well as all ranges of PSA. Similarly, other investigators have demonstrated that the rate of positive margins has decreased with time, which is likely indicative of improved techniques of surgery, as well as probably reflecting surgery being performed on patients with less locally advanced tumors [25–28]. None of these studies commented on the pathologic trends of AA men during the PSA era. We have recently described a pathologic stage migration for AA men treated in our institution during the PSA era [29]. However, we believed this is the first report of YOS being predictive of both ECE and positive margins for AA and white men.

ECE and positive margins on surgical pathology have each been shown to increase the chance of disease recurrence. Powell et al. [11] have recently shown that there was no difference in disease-free survival (DFS) between AA and white men with organ confined disease. However, in patients with ECE, both AA race, and elevated PSA levels were predictive of shorter DFS. In an earlier study, Powell et al. [10] demonstrated that PSA, race, clinical stage, and Gleason score were predictive of positive margins. The rates of positive margins were 58% for AAs and 40% for whites, a statistically significant difference. They did not investigate whether year of surgery was predictive of positive margins.

Table 5
PSA ranges and chance of ECE and positive margins for White Men

PSA ranges	# Patients	# ECE	% ECE	# (+) Mar.	% Pos. Mar.
0–4.0	116	34	29.3	19	16.4
4.1–10.0	292	155	53.1	106	36.3
10.1–20.0	94	66	70.2	49	52.1
>20.1	32	26	81.2	22	68.8

Table 6
Comparison of contemporary studies of percent positive margins and ECE, grouped by race and PSA

PSA level	AA % (+) Margin ^a	Caucasian % (+) Margin ^a	Mixed Race % ECE ^b
<4.0	38.5	3.0	36.5
4.0–9.9	35.1	30.1	49.7
10.0–19.9	65.2	51.7	65.5
>20.0	81.5	68.1	83.8

^a Powell, I.J. et al. Urology 49:726, 1997.

^b Partin, A.W. et al. JAMA 277:1445, 1997.

However, in an equal-access health care system (as is our system) Witte et al. [8] has recently shown that race is not an independent predictor of margin status.

Despite historically poorer outcomes from prostate cancer, several investigators have reported equal rates of ECE, positive margins and survival between AA and white populations in recent years [7–9,30]. This agrees with the findings from our study and may suggest that the reason AA men have historically poorer outcomes is due primarily to a lack of access to care and screening programs as well as inadequate treatment, rather than a genetic predisposition to more aggressive tumors [31–34].

4.2. PSA as a predictor of ECE and margin status

PSA level is the strongest predictor of ECE and positive margins in our logistic regression model for AA and white men. A lower PSA lessens the chance of extracapsular extension. Catalona et al. [35] has shown that patients who are serially screened with PSA, are more likely to have organ confined disease, as compared to patients screened only with a DRE. Carter et al. has recently demonstrated that PSA, as well as age, was predictive of finding “curable cancer” on pathologic examination, which was defined as organ confined, or capsular penetration of low grade with negative margins [36]. Similarly, pre-operative PSA level has been shown to be predictive of ECE, as well as seminal vesicle involvement, lymph node metastasis and positive margins [37–43]. All of these studies involved examining AA and white men in the same cohort.

Powell et al. [10] has examined the positive margin rates for AA and white men for varying ranges of PSA. The rates are displayed in Table 6. The most striking is the positive margin rate of 38.5% in AA men with a PSA of less than 4.0. This is much higher than our series, (15.4%) and much higher than the 3.0% positive margin rate for white men in their study. This higher percentage could be affected by the smaller number of patients in this category (13 patients), and is also unusual in that it was higher than the rate (35.1%) of positive margins for AA men with PSA values between 4.0 and 9.9 ng/ml. Comparing the remaining data for Powell’s group, with ours, reveals a slightly higher rate of positive margins for each of the ranges of PSA values in

the Powell data, but overall they are quite similar. Partin et al. [43] also stratified rates of ECE for PSA values and their results are also shown on Table 6. They had a mixture of AA and white men in their study and when comparing their values to ours they are also quite similar.

Moul et al. [44] previously demonstrated a statistically significant difference in pre-treatment PSA values between AA and white men, which persisted after multivariate analysis, adjusting for 3-D tumor volume, benign gland volume, age, stage and Gleason sum. This leads one to believe that AA men with prostate cancer may inherently have higher PSA values after correcting for other variables. Conversely, Abdalla et al. [45] has shown that after multivariate analysis, race was not a significant factor in predicting PSA or PSAD (prostate specific antigen density). They suggested that sociological, not biological reasons were the reasons for higher PSA and PSAD levels in AA men. This may indicate that if AA men are screened appropriately and treated aggressively at similar values of PSA as that of white men, their rates of ECE and positive margins would be comparable to white men. Lowering the threshold of PSA testing to 2.0 or 2.5 ng/dl in younger men may further improve pathologic stage, but must await further study.

4.3. Age as a predictor of ECE and margin status

Age at the time of surgery was shown to be predictive of ECE for AA and white men. This implies that diagnosing and treating AA men at a younger age may result in a better surgical outcome. This is in accordance with the American Urologic Association's recommendations of screening AA men at a younger age than white men [46]. The impact of age predicting pathologic stage is somewhat mixed in the literature, with some studies demonstrating that age was not predictive of pathologic stage or positive margins [37,47] while others have shown that operating on younger patients improves the chance of cure [36]. None of these studies commented on race and its effect on whether age at surgery influenced the final pathology. Interestingly, age was not predictive of margin status for either AA or white men in this study.

4.4. Biopsy score as a predictor of ECE and margin status

The lack of Gleason scoring on 196 of our biopsy specimens necessitated conversion of tumor grades to Gleason scoring, which has been done in previous papers, but is less than an ideal method of depicting biopsy pathology [48–50]. This “biopsy grade” is meant to be reflective of the general histology of the tumor, and not to infer that all Gleason 6 tumors are moderately differentiated, or all Gleason 4 tumors are well differentiated.

As expected, the biopsy scores were predictive of ECE for AA and white men. However biopsy score was only

marginally significant ($P = 0.068$) for predicting positive margins for AA, and did not predict positive margins for white men. The reason for this may be secondary to our conversion of biopsy pathology, surgical technique, or other unknown factors. Biopsy Gleason sum or tumor grade has been shown in many studies to be predictive of capsular penetration [38,40–42,51] as well as positive margins [10,37] in populations of mixed race. Of these investigators, only Powell [10] examined by race, and found grade to be a predictor of positive margins for AA men.

Pre-operative PSA level and YOS were predictors of both ECE and positive margins for both AA and white men. Also for each range of PSA values, there were very similar rates of ECE and positive margins between the two ethnic groups possibly indicating that absolute PSA values, regardless of race, may be most predictive of ECE and positive margins. The significance of patients treated more recently having better pathologic results indicates that during the PSA era valuable ground may have been gained in the surgical treatment of men with prostate cancer. Hopefully, the improved pathologic staging will translate into improved survival and decreased disease-specific mortality in the coming years. The delineation of significant pre-operative predictors of pathologic status of men of different ethnic backgrounds undergoing radical prostatectomy may help clinicians counsel patients in the future regarding the appropriateness of surgical therapy.

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