Impact of Patient Age on Biochemical Recurrence Rates Following Radical Prostatectomy

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Purpose: Increased age has been suggested to predict worse clinical outcomes in patients with prostate cancer. An explanation that was proposed for this observation is that it is due to inherent differences in the biological properties of prostate cancer in older men. Stage migration, prostate specific antigen and prostate biopsy pathology are variables that may confound the interpretation of age as an independent prognosticator of outcomes following radical prostatectomy.

Materials and Methods: Matched pairs analysis was performed comparing the 3 age cohorts 46 to 55, 56 to 65 and older than 65 years to a cohort of 435 patients who were 45 years or younger based on propensity scores calculated with all known preoperative variables. Postoperative clinical and pathological characteristics were compared among the 4 matched age cohorts. A Cox hazards model was used to compare time to prostate specific antigen recurrence across the different age cohorts and the actuarial risk of recurrence was calculated using Kaplan-Meier and log rank survivor analyses.

Results: Younger patients showed lower grade disease ($p < 0.001$), and lower rates of positive surgical margin rates ($p = 0.035$) and extraprostatic extension ($p < 0.001$) but they did not have higher rates of lymph node involvement ($p = 0.85$) or seminal vesicle invasion ($p = 0.56$). Kaplan-Meier analysis showed no significant differences in biochemical recurrence across the age cohorts (log rank 0.38). On multivariate analysis prostatectomy Gleason score, pathological stage, positive surgical margins (each $p < 0.001$) and preoperative prostate specific antigen ($p = 0.04$) were independently predictive of biochemical recurrence.

Conclusions: We report that increased age is not associated with worse biochemical outcomes following radical prostatectomy and it should not be considered an independent prognosticator for disease recurrence. Rather, age is a surrogate for known predictors of biochemical recurrence following surgery.

Key Words: prostate; prostatic neoplasms; age groups; prognosis; neoplasm recurrence, local

In the last 2 decades there has been a migration toward earlier stage disease at radical prostatectomy, resulting from advances in the screening and detection of prostate cancer.[1,2] Stage migration has been accompanied by a decrease in patient age, largely due to increased public awareness and implementation of prostate cancer testing via serial PSA measurements.[3,4] It was suggested that patients diagnosed with prostate cancer later in life have more aggressive disease and increased rates of biochemical recurrence following surgery.[5] It was proposed that this association is due to a direct link between increasing age and the biology of prostate cancer.[6] However, if age is unrelated to the intrinsic biological properties of prostate cancer, more severe disease and worse outcomes in older patients should be considered a result of factors other than age.

In previous retrospective studies of the influence of age on biochemical recurrence rates following radical prostatectomy a higher proportion of older patients underwent surgery during an earlier era. Older patients typically presented with higher PSA and worse clinical stage at surgery, and consequently they had worse biochemical recurrence-free outcomes.[5,6] Appropriate matching of patients among different age cohorts may lead to a better understanding of the true significance of age as a prognostic indicator for disease severity and outcomes following radical prostatectomy.

To our knowledge no studies to date have used propensity score matching of patients with prostate cancer to examine whether age is an independent prognostic variable for predicting postoperative tumor stage and biochemical outcomes following surgery. We investigated the importance of age as a predictor of biochemical recurrence in men undergoing radical prostatectomy using propensity score matching to account and adjust for multiple preoperative variables.

MATERIALS AND METHODS

Between 1984 and 2006 more than 14,800 men underwent radical prostatectomy with bilateral pelvic lymphadenectomy for clinically localized adenocarcinoma of the prostate at our institution. Standard lymph node dissection was routinely performed. We identified 476 patients who were 45 years or younger at surgery. The 21 patients treated with

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neoadjuvant hormonal therapy were excluded from the study, as were the 10 with incomplete clinicopathological data. No patient received neoadjuvant radiation. Thus, the patient cohort 45 years or younger comprised 435 men. Patients in the 3 age cohorts 46 to 55, 56 to 65 and older than 65 years were matched to the cohort of patients 45 years or younger based on propensity scores. Therefore, 1,740 men formed the overall study population. Data for this study were obtained and analyzed according to an approved institutional review board protocol. Tumor progression was defined as a postoperative serum PSA increase of 0.2 ng/ml or greater.

Propensity scores were used to match members of different groups based on a range of characteristics, as previously described.[7,8] Propensity scores were calculated for each patient using multivariate logistic regression based on certain covariates, including race, preoperative PSA, year of surgery, biopsy Gleason score and clinical tumor stage. This method is an approach to control for imbalances in confounding factors among discrete study cohorts. Continuous and categorical factors are combined to yield a propensity score for each individual in the study population. Individuals in each of the different study cohorts are then matched to those in the reference cohort based on their calculated propensity scores. The greatest advantage of implementing this method of matching is that variables are weighted by their relative importance, rather than being assigned equal weights. Furthermore, it was shown that cohort means and SDs related to covariates used for matching are equivalent when composite propensity scores are matched. Matching was performed with an SPSS® macro for propensity score matching (Dr. John Painter, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina) to select for the most similar propensity scores across each of the different age strata in a 1:1 ratio with respect to the reference group of patients who were 45 years or younger.

We compared the clinical and pathological characteristics of the different age cohorts using the chi-square test for categorical variables and 1-way ANOVA for continuous variables. Patient age, preoperative PSA and year of surgery were evaluated as continuous variables. Biopsy and prostatectomy Gleason score (6 or less, 7 and 8 to 10), and patient race (white or black) were considered categorical variables. Time to PSA recurrence was compared between groups using a Cox proportional hazards model with forward stepwise selection. The actuarial risk of PSA recurrence was calculated using the Kaplan-Meier method and compared across the 4 age cohorts using log rank survivor analysis. All statistical analyses were performed using SPSS, version 13.0.

RESULTS

Table 1 lists the clinical and pathological characteristics of the 4 matched study cohorts. There were no statistically significant differences with respect to the variables used for propensity score matching, including race ($p = 0.82$), preoperative PSA ($p = 0.46$), median year of surgery ($p = 0.93$), biopsy Gleason score ($p = 0.50$) and clinical tumor stage (0.20). Furthermore, no statistically significant differences were observed among the 4 matched age cohorts with respect to the duration of followup ($p = 0.41$). These results are consistent with 4 patient cohorts that are well matched based on the indicated preoperative variables and differ only with respect to age.

Examination of postoperative variables, including prostatectomy Gleason score, demonstrated significant differences across the age cohorts with younger patients showing higher rates of lower grade disease ($p = 0.001$). Younger patient age was also significantly associated with lower proportions of positive surgical margins ($p = 0.035$) and extraprostatic extension ($p < 0.001$). However, age was not asso-

TABLE 1. *Clinicopathological characteristics of patients with prostate cancer undergoing radical prostatectomy*

Characteristic	Age Group				p Value
	45 or Younger	46–55	56–65	66 or Older	
No. pts	435	435	435	435	
Median surgery yr:*	2000	2000	2000	2000	0.934 (ANOVA)
Race:*					0.823 (chi-square test)
White	392 (90)	393 (90)	386 (89)	387 (89)	
Black	43 (10)	42 (10)	49 (11)	48 (11)	
Followup (yrs):					0.406 (ANOVA)
Median	3	3	4	3	
Mean ± SD	4.4 ± 3.6	4.2 ± 3.6	4.5 ± 3.8	4.0 ± 3.6	
PSA (ng/ml):*					0.457 (ANOVA)
Median	5.2	5.1	5.4	5.6	
Mean ± SD	6.4 ± 5.6	6.2 ± 6.0	6.4 ± 6.3	6.7 ± 7.3	
No. clinical stage (%):*					0.201 (chi-square test)
cT1	282 (65)	288 (66)	285 (66)	301 (69)	
cT2	150 (35)	144 (33)	149 (34)	127 (29)	
cT3	3 (less than 1)	3 (less than 1)	1 (less than 1)	7 (2)	
No. biopsy Gleason score (%):*					0.502 (chi-square test)
2–6	369 (85)	365 (84)	364 (84)	372 (85)	
7	57 (13)	66 (15)	63 (14)	52 (12)	
8–10	9 (2)	4 (1)	8 (2)	11 (3)	
No. prostatectomy Gleason score (%):					0.001 (chi-square test)
6 or Less	338 (78)	310 (71)	276 (63)	265 (61)	
7	79 (18)	108 (25)	139 (32)	143 (33)	
8–10	18 (4)	17 (4)	20 (5)	27 (6)	
No. extraprostatic extension (%)	108 (25)	113 (26)	118 (27)	163 (37)	<0.001 (chi-square test)
No. pos surgical margin (%)	42 (10)	43 (10)	56 (13)	66 (15)	0.035 (chi-square test)
No. lymph node invasion (%)	5 (1)	7 (2)	6 (1)	8 (2)	0.854 (chi-square test)
No. seminal vesicle invasion (%)	15 (4)	15 (4)	16 (4)	22 (5)	0.556 (chi-square test)
No. disease progression/total No. (%)	19/272 (7)	23/227 (10)	24/217 (11)	22/202 (11)	

* Matched variables.