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.

TABLE 2. *Univariate and multivariate Cox regression models predicting biochemical recurrence after radical prostatectomy*

Variable	Univariate HR (95% CI)	Univariate p Value	Multivariate HR (95% CI)	Multivariate p Value
Clinical stage (vs T1):		<0.001		
T2	2.1 (1.3–3.2)			
T3	9.7 (3.8–24.7)			
Prostatectomy Gleason score:		<0.001		<0.001
7 vs 6 or Less	8.6 (4.9–14.9)		4.3 (2.4–7.9)	
8–10 vs 6 or Less	26.2 (13.9–49.6)		7.0 (3.4–14.7)	
Pathological stage (vs organ confined):		<0.001		<0.001
Extraprostatic extension	7.3 (4.1–12.9)		2.9 (1.6–5.6)	
Seminal vesicle invasion	30.8 (15.5–61.2)		8.5 (3.9–18.4)	
Lymph node invasion	24.6 (11.1–54.2)		5.3 (2.2–12.9)	
Pos surgical margins	6.9 (4.4–10.7)	<0.001	2.4 (1.5–3.9)	<0.001
Preop PSA	1.06 (1.04–1.07)	<0.001	1.02 (1.00–1.04)	0.04
Surgery yr	0.9 (0.87–0.95)	<0.001		
Race (black vs white)	1.6 (0.9–2.9)	0.10		
Age:		0.40		
46–55 vs 45 or Younger	1.4 (0.7–2.6)			
56–65 vs 45 or Younger	1.6 (0.9–2.9)			
66 or Older vs 45 or younger	1.6 (0.8–3.0)			

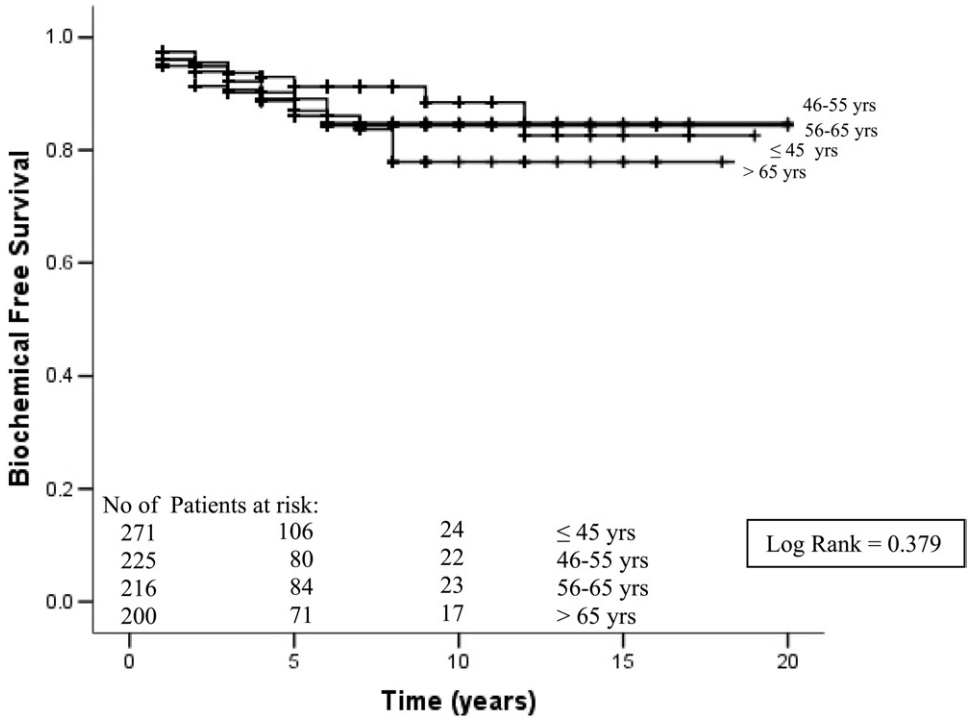
ciated with lymph node involvement (p = 0.85) or seminal vesicle invasion (p = 0.56).

Table 2 shows the association of preoperative and postoperative variables with biochemical recurrence. On univariate Cox regression analysis clinical tumor stage, prostatectomy Gleason score, pathological stage, positive surgical margins, preoperative PSA and year of surgery were predictive of biochemical recurrence following radical prostatectomy (each p <0.001). On multivariate analysis only prostatectomy Gleason score, pathological stage, positive surgical margins (each p <0.001) and preoperative PSA (p = 0.04) were predictive of biochemical recurrence following surgery.

Kaplan-Meier analysis demonstrated overall 5 and 10-year biochemical free survival rates of 91% and 85% for all patients in this study. On stratified analyses patients 45 years or younger, 46 to 55, 56 to 65 and 66 or older had 5 and 10-year biochemical-free survival rates of 93% and 89%, 89% and 85%, 89% and 84%, and 89% and 78%, respectively (see figure). On univariate log rank analyses no statistically significant differences were found in time to PSA recurrence following surgery in any age group (p = 0.38).

DISCUSSION

It is widely accepted that there has been a dramatic stage migration among men with prostate cancer since PSA testing was introduced in the late 1980s.[9–11] An increasing number of men are being diagnosed at a younger age with more favorable clinicopathological characteristics.[12,13] The



Kaplan-Meier actuarial likelihood of biochemical recurrence (PSA 0.2 ng/ml or greater) after radical prostatectomy in patients in 4 age groups.

importance of age as a predictor of biochemical recurrence following radical prostatectomy has been investigated by only a few groups with somewhat conflicting results. Table 3 lists the most important publications of the association of patient age with outcome following radical prostatectomy. In the pre-PSA era younger patient age was associated with less differentiated tumors and higher clinical stage, occasionally with widespread metastatic disease at presentation.[14,15] This led to the general conclusion that younger patient age was associated with a worse patient disease outcome. More recent studies in the context of serial PSA testing tended to show a worse prognosis for older patients with prostate cancer.[3,5]

The major limitation of many previous studies of the relationship of age and prostate cancer outcomes is that age cohorts were compared without adjusting for confounding variables, such as year of surgery, preoperative PSA and biopsy Gleason score. In a preliminary analysis of our patient cohort before propensity score matching we found a significant correlation between younger patient age and more recent year of surgery ($p < 0.001$, data not shown). This finding is in agreement with observations reported by Freedland et al.[5] An approach to overcome the limitation of prior studies is to match patients for preoperative variables across age cohorts to eliminate confounding factors known to be associated with patient age. The use of propensity scores to match patient cohorts has been used extensively in other disciplines to allow the correction of a large number of confounding covariates via logistic regression analyses. Furthermore, propensity score matching eliminates biases due to incomplete matching, which is a major limitation of conventional matching strategies.[16] To our knowledge this is the first study to use propensity score matching to investigate the relationship between patient age and biochemical recurrence outcomes following radical prostatectomy.

By successfully matching patients with prostate cancer across 4 age cohorts we observed that younger patients have significantly lower prostatectomy Gleason scores, lower rates of extraprostatic extension and lower rates of positive surgical margins than older men. These finding are consistent with the reports by Freedland[5] and Siddiqui[17] et al. Despite more favorable pathological features in younger men Kaplan-Meier analysis revealed no statistically significant differences in biochemical-free survival among the 4 age cohorts in our study. Cox regression analysis adjusting for multiple clinical variables also did not reveal any differences in postoperative outcomes among the 4 age cohorts. A recent study of the relationship between age and clinical outcomes following radical prostatectomy also showed that younger patients had more favorable pathological features but no difference in biochemical recurrence compared to older patients.[14] However, following adjustment for pathological features and preoperative PSA younger patients had worse outcomes with respect to disease progression. Few patients in this study were found to have metastatic disease, for example 1% to 2% had lymph node metastasis. This observation may be explained by lower PSA cutoffs used for younger patients and stricter biopsy algorithms for the subgroup of young patients to whom the other age cohorts were matched.

It remains challenging to compare previous studies of age as a predictor of biochemical recurrence following radical prostatectomy due to significant differences in study design. The age cutoff for young patients with prostate cancer varies widely in the literature from 40 to 65 years.[18,19] Our age cutoff of 45 years or younger was determined by the large sample size that we were able to maintain for each of the 4 age cohorts. A major limitation of our study was the relatively short followup with a median followup of 3 years for the entire cohort. The observation by Siddiqui et al that younger patients have worse biochemical progression-free survival following radical prostatectomy compared to older patients[17] may be attributed to the extended followup of 10 years or longer in their study. While the majority of early

TABLE 3. *Literature on impact of patient age on disease control following radical prostatectomy*

References	Total No. Pts/No. (age)	Results	Conclusions/Comments
Tjaden et al[14]	56/56 (younger than 50)	48/56 Pts (86%) inoperable, av survival 22.7 mos, 7/56 (12%) survived greater than 5 yrs	Occasionally young pts with prostate Ca have long-term survival. Multimodal treatment is indicated.
Smith et al[3]	477/79 (younger than 50), 398/(51–69)	Younger men had lower pathological stage + significantly better biochemical recurrence rates	Screening + aggressive treatment of young men may be effective to improve disease specific survival.
Khan et al[2]	2,897/341 (younger than 50), 2,556/(50 or older)	Age younger than 50 vs 50 or older: less extraprostatic extension, seminal vesicle invasion + pos surgical margins in younger pts. Age younger than 50 vs 69 or older: no significant difference in biochemical recurrence rates. Age younger than 50 vs 70 or older: older group had significantly worse biochemical recurrence rates.	Anatomical RRP yields excellent long-term results in men younger than 50. RRP was curative more often in men younger than 50.
Freedland et al[5]	1,753/88 (50 or younger), 473 (51–60), 990 (61–70), 202 (older than 70)	Younger men had lower grade + favorable pathology but greater % cores with Ca. Men 50 or younger had less biochemical recurrence.	Av age of men with RRP has decreased. Younger men have more favorable outcomes after RRP than older men.
Twiss et al[20]	790/66 (younger than 50), 724 (50 or older)	No differences in pathological stage, surgical margin rate or Gleason score. Erectile function was better in younger patients.	RRP yields good results in young patients. No comment on biochemical recurrence outcomes.
Siddiqui et al[17]	5,509/369 (younger than 55), 640 (55–59), 1,252/(60–64), 1,721 (65–69)	Younger patients had lower preoperative PSA, tumor grade + stage. No differences in Ca specific survival, biochemical recurrence or progession specific survival.	Younger men have survival outcomes following RRP similar to those in older men despite better clinicopathological features. Consider aggressive treatment for younger men.
Present series	1,740/435 (45 or younger), 435 (46–55), 435 (56–66), 435 (66 or older)	Younger patients had lower grade disease with less extraprostatic extension + fewer pos surgical margins. No significant differences in biochemical recurrence rates among age groups.	Age is not independent prognosticator of disease recurrence, but rather surrogate for known predictors of biochemical recurrence.

recurrences may be attributable to micrometastatic disease at surgery, late relapses among various age groups may be influenced by additional factors, including differences in tumor biology, genetics or the immune response.

CONCLUSIONS

In the last 2 decades the mean age of patients undergoing radical prostatectomy has progressively decreased due to widespread PSA testing. We used propensity scores to match patients according to preoperative variables to examine the relationship between age and clinicopathological outcomes following radical prostatectomy. Our data suggest that age is not associated with biochemical-free survival and, therefore, it should not be considered an independent prognosticator for disease recurrence following surgery. Instead, age should be considered a strong surrogate marker representing known predictors of outcome, as demonstrated in previously reported, unmatched studies. Thus, age alone should not be used to define or identify men at higher risk for biochemical failure following radical prostatectomy.

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Abbreviations and Acronyms

PSA = prostate specific antigen
RRP = radical retropubic prostatectomy

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EDITORIAL COMMENTS

These authors studied the impact of patient age on biochemical recurrence rates following radical prostatectomy in 1,740 patients. They conclude that increased age is not associated with worse biochemical outcomes after radical prostatectomy.

The question remains of why patient age should have an impact on biochemical recurrence. Local tumor bulk, and the number and percent of involved lymph nodes affect the survival rate significantly.[1] Moreover, wide positive surgical margins is a well-known factor for biochemical recurrence.

Table 3, which compares the current literature on this topic, shows different results. Freedland et al found that younger men have more favorable outcomes after RRP than older men in a study with 1,753 patients (reference 5 in article). Siddiqui et al observed that younger men had a similar survival outcome compared to older men following RRP in a study with 5,509 patients (reference 17 in article).

However, the crucial points are the number and percent of involved lymph nodes, and local tumor bulk as well as surgical margins. Patient age can only have a subordinate role.

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1. Daneshmand S, Quek ML, Stein JP, Lieskovsky G, Cai J, Pinski J et al: Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. J Urol 2004; **172:** 2252.

Briefly, these authors state that age is not an independent predictor for outcome after radical prostatectomy, but rather a parameter for known predictors of biochemical failure. This is an interesting observation for 2 reasons. 1) Alternate statistical approaches, such as propensity scores, are worth being applied to a data set to ensure that significant results are not created by such means. 2) The pathomechanics of prostate cancer in the elderly population are not well understood. With the new technologies in hand it is a challenge to seek different expression profiles with predictive value in the elderly population with respect to clinical information, as provided.

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