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Age Impact in Clinicopathologic Presentation and the Clinical Evolution of Prostate Cancer in Patients Submitted to Radical Prostatectomy

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ABSTRACT

Objective: To assess the influence of age in pathological findings and clinical evolution of prostate cancer in patients treated with radical prostatectomy.
Materials and Methods: Five hundred and fifty-six patients operated on between 1991 and 2000 were selected. Patients were divided into age groups of between 10 and 49 years, 50 to 59 years, 60 to 69 years and 70 to 83 years.
Results: Patients having less than 60 years of age presented clinical stage ($p = 0.001$), PSA ($p = 0.013$) and biopsy Gleason score ($p = 0.013$) more favorable than older patients. Age groups did not show any relationship between either postoperative Gleason score or pathological stage or risk of non-confined organ disease and involvement of seminal vesicles. After a mean follow-up of 58.3 months, 149 (27%) patients presented recurrence. Patients aged between 40 and 59 years presented a disease-free survival rate significantly higher when compared to patients aged between 60 and 83 years ($p = 0.022$). However, when controlled with clinical stage, PSA, Gleason score and percentage of positive fragments, there was no relationship between age and biochemical recurrence risk ($p = 0.426$).
Conclusions: Even though younger patients presented more favorable preoperative characteristics, postoperative pathological findings and biochemical recurrence rates did not differ between studied age groups.

Key words: prostatic neoplasms; age groups; recurrence; survival analysis
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INTRODUCTION

The ideal treatment for localized prostate cancer (PCa) is based on individual characteristics of each patient. Presently, clinical staging (1), Gleason score from the biopsy (2) and the serum prostate-specific antigen (PSA) are the prognostic indicators that are mostly used to prevent the risk of an organ-confined disease and tumor progression after treatment (3).

The patient's age also represents a fundamental aspect in the initial therapeutic decision. After the large scale use of PSA and the development of screening methods, more and more patients with PCa are diagnosed at earlier ages. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) show that during the 1970s, patients with less than 50 years of age represented only 1% of diagnosed cases; today this number has reached 4% (4).

The direct relationship between age and life expectancy and the different biological characteristics of cancer in younger men shows the need for improved knowledge of the behavior of tumors in those patients (4,5). We know that even though many cases present an inexpressive behavior during the first 10 to 15 years of evolution, progression-free, metastasis-free and specific disease-free survival rates are significantly reduced after this follow-up period (6). Because of this, the early institution of a more aggressive treatment could be the most appropriate approach in younger patients with life expectancies higher than 10 to 15 years (7), even though biological characteristics of PCa in younger patients are little understood (8,9). While previous studies point to a relationship between younger men and more advanced tumors, which suggests that those would not be ideal candidates for radical prostatectomy (RP) (10-12), more recent studies, show that younger individuals present a larger probability of organ-confined tumors and higher disease control rates when submitted to RP (4,8,9).

The objective of the present study is to assess the influence of age in pathological findings and the clinical evolution of prostate cancer in patients treated with RP.

MATERIALS AND METHODS

In the period from 1991 to 2000, 556 PCa patients treated with RP and bilateral pelvic lymphadenectomy at our institution were selected. All patients presented suspicion of organ-confined tumors because of elevation in the PSA or location of a palpable nodule during digital rectal examinations. They were diagnosed through a transrectal ultrasound-guided (TRUS) prostate biopsy. Surgical procedures were performed by the same surgeon and pathological analysis performed by the same pathologist.

During the staging period, patients were submitted to a clinical history of the disease and a physical exam, PSA, computerized tomography of the pelvis, bone scintigraphy and TRUS. Clinical staging was determined through the AJCC (American Joint Committee on Cancer, 1992) system (1), and the tumor grade was determined by the Gleason score system (2).

Pre- and postoperative characteristics of the 556 patients are listed in Table-1. The mean age was 63 years (40 to 83), and the mean PSA was 10.6 ng/mL (0.3 to 63.5). Seventy-nine percent of the patients presented Gleason score of 6 or less in the biopsy, and 53% presented clinical stage T2. After a pathological analysis of the surgical specimen, 75% of the patients were classified as bearers of a organ-confined

Table 1 – *Pre-and postoperative clinical and pathological characteristics in 556 patients.*

Age (years)	
Mean ± SD	63.0 ± 7.4
Interval	40 - 83
PSA (ng/mL)	
Mean ± SD	10.6 ± 7.7
Median	8.3
Interval	0.3 - 63.5
Gleason score in biopsy (%)	
2 – 6	439 (79.0)
7	80 (14.3)
8	37 (6.7)
Mean ± SD	5.5 ± 1.3
Median	6.0
Interval	2 - 8
Clinical stage (%)	
T1c	257 (46.2)
T2	297 (53.4)
T3	2 (0.4)
Gleason score in the surgical specimen (%)	
2 – 6	346 (62.2)
7	110 (19.8)
8 – 9	100 (18.0)
Mean ± SD	6.1 ± 1.3
Median	6
Interval	2 - 9
Pathological stage (%)	
T2	417 (75.0)
T3	139 (25.0)
Capsular penetration (%)	305 (54.9)
Apical invasion (%)	113 (20.3)
Bladder neck invasion (%)	8 (1.4)
Seminal vesicle invasion (%)	35 (6.3)
Extra-capsular extension (%)	122 (21.9)
Positive lymph nodes	-

tumor (pT2), with no patient presenting lymph nodes involvement.

During the postoperative period, patients were assessed every 2 months for a year, every 6 months for up to 5 years and annually thereafter. During each visit, a digital rectal examination and a PSA analysis were performed. The biochemical recurrence of the disease was defined as a PSA equal to or higher than 0.4 ng/mL (13).

Patients were divided into 4 groups according to age: group 1 – from 40 to 49 years of age (23 patients); group 2 – from 50 to 59 years of age (150 patients); group 3 –from 60 to 69 years of age (268 patients); and group 4 – from 70 to 83 years of age (115 patients). They were further analyzed according to pre-and postoperative clinical and pathological characteristics, as well as biochemical recurrence.

To analyze preoperative variables according to the age groups ANOVA, chi-square and likelihood ratio tests were utilized. The PSA was assessed as a continuous and categorical variable through logarithmic transformation. Clinical stage, Gleason scores and pathological stage were used as categorical variables. To analyze the prognostic value of age in the determination of the finding of a non organ-confined disease and the involvement of seminal vesicles, a model of logistic regression with adjusted proportional risks was utilized. In this case, age was analyzed as a continuous variable. The non organ-confined disease was defined as pT3 stage. An analysis of biochemical recurrence-free survival rates was performed through the Cox regression model. The Kaplan-Meier method was utilized to estimate survival rate curves, and to compare them the Breslow test was used. Statistical significance was considered as a $p \leq 0.05$.

RESULTS

Table-2 shows the main preoperative clinical and pathological characteristics in relation to age group. The majority of assessed patients belonged to the 60 to 69 year age group; only 4.1% of the patients assessed were in the 40 to 49 year age group. In relation to PSA, it was observed that no patient in the 40 to 49 year age group presented a PSA higher than 20 ng/mL. It was also observed that there was no significant change in PSA values in the distribution of patients from the 40 to 49 and 50 to 59 year age groups ($p = 0.724$). The same thing occurred between the 60 to 69 and 70 to 83 year age groups ($p = 0.729$). That is, the distribution of PSA values presented a statistically significant differences between the 40 to 59 and 60 to 83 year age groups ($p = 0.001$). As for Gleason score, we observed the same PSA behavior; i.e., statistically equal distributions between the 40 to 49 and 50 to 59 year age groups ($p = 0.288$), and between the 60 to 69 and 70 to 83 year age groups ($p = 0.695$). That is, the distribution of Gleason score presented a statistically significant difference between the 40 to 59 and 60 to 83 year age groups ($p = 0.007$). In relation to clinical stage, we once again observed behaviors similar to those reported previously; i.e., similar distributions for the 40 to 49 and 50 to 59 year age groups s ($p = 0.557$) and the 60 to 69 and 70 to 83 year age groups ($p = 0.065$). It is interesting to observe the apparent trend in the 70 to 83 year age group, which presents a higher percentage of patients with clinical stage T2 or T3 when compared to the 60 to 69 year age group; however this was only marginally significant ($p = 0.065$). In relation to postoperative pathological characteristics, we have observed that both Gleason score ($p = 0.582$) and pathological stage ($p = 0.180$) did not present associations to age groups.

In univariate logistic regression analysis, the age analyzed as a continuous variable showed to be statistically significant in determining the risk of the non organ-confined disease (pT3); however it failed in determining the risk of compromising seminal vesicles OR - 1.03; IC 95% [1.00 ; 1.06], $p = 0.032$ e OR - 1.03; IC 95% [0.979 ; 1.08], $p = 0.281$ respectively. However, when controlled by other preoperative variables, age did not appear to be capable of predicting those pathological findings.

With a median follow-up of 58.3 months (mean of 60.5 months, varying from 1 to 131), 149 patients (27%) presented recurrence. Figure-1 shows through the Breslow test that the 40 to 49 and 50 to 59 year age groups presented the same disease-free survival rates ($p = 0.497$). The same occurred for the 60 to 69 and 70 to 83 year age groups ($p = 0.606$). However, when compared to 60 to 83 year age group,

Table 2 – *Clinicopathologic characteristics according to age group.*

	Age Group (years)				
	40 to 49	**50 to 59**	**60 to 69**	**70 to 83**	**p Value**
N (%)	23 (4.1%)	150 (27.0%)	268 (48.2%)	115 (20.7%)	
PSA (ng/mL)*	8.2 ± 4.3	9.2 ± 7.0	11.1 ± 7.6	11.8 ± 8.8	0.002**
PSA					0.013***
0 to 4.0	4 (17.4%)	20 (13.3%)	21 (7.8%)	10 (8.7%)	
4.1 to 10.0	14 (60.9%)	92 (62.3%)	142 (53.0%)	54 (57.0%)	
10.1 to 20.0	5 (21.7%)	31 (20.7%)	77 (28.7%)	36 (31.3%)	
> 20.0	-	7 (4.7%)	28 (10.4%)	15 (13.0%)	
Gleason					0.040***
2 to 6	18 (78.3%)	131 (87.3%)	206 (76.9%)	84 (73.0%)	
7	3 (13.0%)	16 (10.7%)	40 (14.9%)	21 (18.3%)	
8 to 10	2 (8.7%)	3 (2.0%)	22 (8.2%)	10 (8.7%)	
Clinical stage					
T1C	12 (52.2%)	88 (58.7%)	118 (44.0%)	39 (33.9%)	< 0.001****
T2 or T3	11 (47.8%)	62 (41.3%)	150 (56.0%)	76 (66.1%)	
Post Gleason					0.582***
2 to 6	15 (65.2%)	103 (68.7%)	162 (60.4%)	66 (57.4%)	
7	4 (17.4%)	26 (17.3%)	56 (20.9%)	24 (20.9%)	
8 to 10	4 (17.4%)	21 (14.0%)	50 (18.7%)	25 (21.7%)	
Pathological stage					0.180***
T2a	5 (21.7%)	46 (30.7%)	81 (30.2%)	30 (26.1%)	
T2b	7 (30.4%)	39 (26.0%)	71 (26.5%)	28 (24.3%)	
T2c	7 (30.4%)	36 (24.0%)	44 (16.4%)	23 (20.0%)	
T3a	4 (17.4%)	20 (13.3%)	45 (16.8%)	28 (24.3%)	
T3b	-	1 (0.7%)	6 (2.2%)	-	
T3c	-	8 (5.3%)	21 (7.8%)	6 (5.2%)	

** Mean ± standard deviation; ** ANOVA; *** likelihood ratio test; **** chi-square test.*

the 40 to 59 year age group presented a higher disease-free survival rate (p = 0.039). When we analyzed the risk of biochemical recurrence through the Cox regression model (Table-3), we once again found statistical significance only when we divided the age groups into categories of 40 to 59 and 60 to 83 years

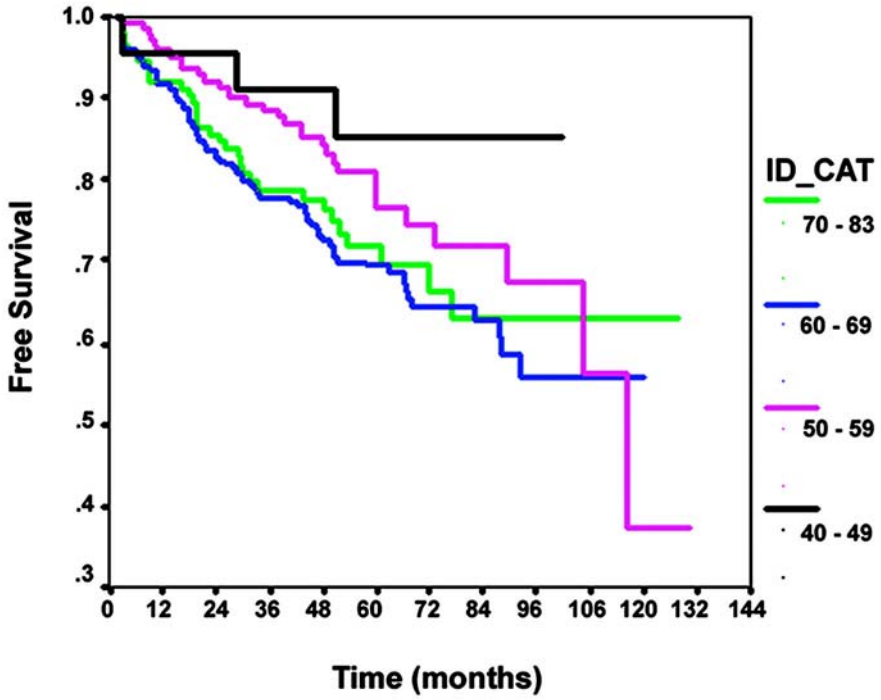

Figure 1 – *Disease-free survival rates according to age groups (Breslow test: p = 0.039).*

of age (HR - 1.56; IC - 1.07:2.27; p = 0.022). However, when the age group was controlled by PSA, clinical stage, Gleason score and percentage of positive fragments in the biopsy, these did not appear to be more capable of preventing biochemical recurrence risks (p = 0.426).

COMMENTS

In the present study we detected that patients with PCa submitted to PR with less than 60 years presented more favorable preoperative clinical and pathological characteristics when compared to patients having 60 years or more. However, these findings were not reflected in postoperative characteristics, for the Gleason score of the surgical specimen and pathological stage did not show any association with age groups. When we analyzed disease-free survival rates, even though patients having less than 60 years showed survival rates statistically superior compared to patients having 60 years or more in univariate analysis, when controlled by other preoperative variables age group of patients was not more determinant than the biochemical recurrence risk.

PCa has always been considered a disease that typically affects older men, and occurs rarely in men under 50 years of age (14). Historically, various studies report a higher incidence of more aggressive tumors among younger patients, leading us to suggest that they would not be ideal candidates for RP (10-12). Later, other researchers did not find any differences in histological characteristics of tumors when analyzed in patients of different age groups (15). Similarly, comparing patients with prostate cancer that had less than 60 years of age with patients aged between 65 and 74 years, Harrinson (16) did not find statistical differences in the survival rate curve between these groups. With the large use of PSA, we started to detect PCa cases in more early stages, as well as in younger men (4). This is how the knowledge of PCA characteristics in these individuals became more and more important.

Table 3 – *Analysis of biochemical recurrence risk through Cox regression model.*

	Hazards Ratio	95% CI	p Value
Univariate analysis			
Age	1.02	[0.99 ; 1.04]	0.159
Age group			0.106
50-59/40-49	1.72	[0.53 ; 5.62]	0.369
60-69/40-49	2.61	[0.83 ; 8.30]	0.102
70-83/40-49	2.31	[0.70 ; 7.55]	0.168
Age group			
(60-83/40-59)	1.56	[1.07 ; 2.27]	0.022
PSA	1.04	[1.03 ; 1.06]	< 0.001
Clinical stage			
(T2 or T3 / T1C)	2.07	[1.46 ; 2.93]	< 0.001
Gleason score			0.018
7 / 2 to 6	1.74	[1.14 - 2.67]	0.010
8 / 2 to 6	1.65	[0.93 - 2.93]	0.090
% Fragments +	5.13	[2.86 ; 9.21]	< 0.001
Multivariate analysis			
Age			
(60-83/40-59)	1.17	[0.79 ; 1.73]	0.426
PSA	1.04	[1.02 ; 1.06]	< 0.001
Clinical stage			
(T2 or T3 / T1C)	1.79	[1.25 ; 2.57]	0.001
Gleason score			0.025
7 / 2 to 6	1.60	[1.04 ; 2.45]	0.031
8 / 2 to 6	1.80	[1.00 ; 3.23]	0.049
% Fragments +	3.34	[1.82 ; 6.13]	< 0.001

Some findings of this research analysis agree with contemporary studies that analyze the influence of age in the control of PCa in patients submitted to RP. Obek et al. (5) compared men having 70 years of age or less to men older than 70 years of age. Even though no differences were found in Gleason scores or in pathological findings between both groups, which was different from our study, the first group presented a disease-free survival rate significantly higher than the older patients did. In comparing men having 50 years of age or less to men aged between 51 and 69 years of age, Smith et al. (17) found higher rates of organ-confined disease (pT1 e pT2) in younger patients; however the involvement of surgical margins and seminal vesicles were similar between both groups, with recurrence rates significantly lower among the younger. Khan et al. (4) also compared men having less than 50 years of age to patients of more advanced age groups than the ones treated with RP. They observed that when patients were 60 years of age or more, they presented higher pathological stages and a higher number of positive surgical margins when compared to patients of less than 50 years of age; however, only patients having 70 or more years of age presented disease-free survival rates significantly lower in comparison. Freedland et al. (9) observed that younger patients presented smaller prostates, less high-degree tumors in the biopsy and less lymph nodes metastasis; however they presented a higher percentage of fragments with cancer in the

biopsy. In multivariate analysis, patients aged 50 years or less presented lower recurrence rates than older patients did. Herold et al. (8) have documented the correlation between advanced age and distant metastasis in patients that have received radical radiotherapy for the treatment of PCa. According to those authors, age was a predictive factor for metastasis in uni- and multi-variate analysis; specifically that men having more than 65 years presented a risk of developing distant metastasis 3 times higher when compared to younger patients.

Some characteristics of PCa screening in young patients were studied by Ruska et al. (14). In analyzing 87 patients having less than 40 years of age submitted to prostatic biopsy, they found 23 (26%) cases of cancer and defined that the main predictive factors of this diagnostic were age, PSA and family history. In this sample, an altered digital rectal examination was not a cancer predictive factor in the biopsy. After surgery, 56% were classified as T2, 44% as T3 and 12% presented lymph node metastasis.

As demonstrated above, even though there are disagreements in relation to the postoperative pathological findings for the different age groups, there seems to be a trend to a more favorable evolution among younger patients when treated by RP. The exact mechanisms responsible for this behavior of prostate tumors in younger patients in contemporary series are not well known. In the Freedland et al. (9) series, younger patients (less than 60 years of age) presented lower Gleason score in comparison to older ones, suggesting that the latter can present tumors that are biologically more aggressive. These findings, however, were not reproduced in the present study, or in others (5,15). Another possible explanation for finding more advanced tumors among older patients (4,9) could be the closer relationship between advanced age and prostate benign hyperplasia. This could make diagnosis more difficult in cancers that must grow more before they are clinically detected (18).

Contrary to the majority of recent studies that assess the influence of age in disease-free survival rates, in this study lower recurrence rates among younger patients were not demonstrated. This data suggest that younger patients diagnosed with PCa should be treated in a similar way to older ones since biochemical recurrence rates between both groups were similar. We believe that the small group of patients having less than 50 years of age (23 cases) may have harmed the comparison with other age groups. Finally, in the present study we have concluded that even though younger patients submitted to RP present tumors with more favorable preoperative characteristics than older patients, age did not show to be a determinant factor of postoperative pathological characteristics.

CONFLICT OF INTEREST

None declared.

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