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Survival of patients with clinically localized prostate cancer

ABSTRACT

OBJECTIVE: To assess survival rates and clinical (pretreatment) prognostic factors in patients with clinically localized adenocarcinoma of the prostate.

METHODS: Hospital cohort including 258 patients registered in the National Cancer Institute, in the city of Rio de Janeiro, Southeastern Brazil, from 1990 to 1999. Five- and ten-year survival functions were estimated using the Kaplan-Meier estimator from the histological diagnosis (initial time of follow-up) to death due to prostate cancer (events). Prognostic factors were assessed using hazard ratios (HR) with confidence intervals of 95%, following the Cox's proportional hazards model. The assumption of proportionality of risks was tested using Schoenfeld residuals and the impact of outliers in the model fitness was analyzed using martingale and score residuals.

RESULTS: Of 258 patients studied, 46 died during follow-up. The overall five-year and ten-year survival rates were 88% and 71%, respectively. A Gleason score higher than 6, PSA levels higher than 40 ng/mL, B2 stage, and white skin color were independent markers of poor prognosis.

CONCLUSIONS: Gleason score, digital rectal examination and PSA levels have great predictive power and must be used in pretreatment risk stratification of patients with localized prostate cancer.

DESCRIPTORS: Prostatic Neoplasms. Prognosis. Survival Rate. Cancer Care Facilities. Oncology Service, Hospital. Prostate-Specific Antigen. Neoplasm Staging.

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INTRODUCTION

Prostate cancer is the most common malignant neoplasm among Brazilian men, following non-melanoma skin cancer, with 52,350[a] new cases in 2010. Most of these tumors are confined to the prostate at diagnosis, accounting for 69.4% of prostate cancers diagnosed in public services of the *Sistema Único de Saúde* (National Health System) in the state of São Paulo.[17]

Many tumors clinically staged as localized are not actually localized, resulting in non-effective therapeutic indications.[9] Moreover, patients with clinically non-significant cancer are unnecessarily treated due to the limitations of current prognostic classification.[1]

Unclear definition of pretreatment prognosis of localized prostate cancer is a serious public health concern given high morbidity associated with common treatment options. For example, even five years after treatment, erectile sexual dysfunction affects 80% and 50% of patients undergoing radical prostatectomy and external beam radiation therapy, respectively.[10]

Given this limitation of clinical staging, new clinical prognostic factors have been thoroughly studied. Clinical prognostic factors are identified prior to treatment and guide the choice of the best therapeutic option for each patient.[11] The most important clinical prognostic markers currently available are pretreatment PSA (prostate-specific antigen) levels and the degree of histological differentiation according to Gleason score of tumor specimens collected through biopsy. There are many studies supporting these prognostic factors as valuable clinical tools.[4]

Despite their importance, both Gleason score and total PSA do not completely define the prognosis of patients with clinically localized cancer. It was found that even with a Gleason score ≤6, only 70% of patients have confirmed localized disease in the pathological staging. When the score is ≥7, this percentage falls to 34%.18 It is estimated that sensitivity of PSA to detect localized disease, with 100% specificity, is only 14%.[9]

To combine information from several prognostic factors that would allow more accurate and individualized predictions than the classical classification in risk groups, many researchers have developed nomograms based on results from multivariate models. In these models, discordant prognostic variables are incorporated in the estimate of the patient's individual risk.[5,7,12,21]

Biochemical recurrence and staging (after surgery) are commonly used outcomes in studies of clinical prognostic factors in prostate cancer. Major outcomes such as metastases and specific mortality are not widely used as they require long follow-up.[b]

The objective of the present study was to assess survival rates and pretreatment prognostic factors in patients with localized prostate cancer.

METHODS

Cohort study including all patients attended at a reference hospital for cancer treatment in the city of Rio de Janeiro, Southeastern Brazil, from 1990 to 1999. All patients had a confirmed histological diagnosis of adenocarcinoma of the prostate (ICD-O code: C61, 8140/3) confined within the prostate borders, i.e., in stages I or II of TNM classification or stages A1, A2, B1 or B2 of Jewett-Whitmore staging system.

Those patients without information on clinical staging of the tumor, those with date of first diagnosis before or after more than six months of the study entry and those who did not undergo the first treatment and follow-up in the study hospital were excluded.

Data sources used for selection of cases and collection of variables of interest included the hospital's cancer registry and medical records. Additional data on Gleason score and serum PSA levels were obtained from pathology and clinical pathology reports. Data from each patient were recorded on study forms and then entered on a questionnaire created in Epi Info software version 6.04.

Of 1,364 patients diagnosed with prostate cancer treated during the study period, 258 were eligible to participate in the study. Criteria of ineligibility were as follows: 718 patients did not complete the staging or treatment or did not undergo initial treatment in the study hospital; 81 had stage III (or stage C) and 275 had stage IV (or stage D) disease; and for 30 cases any information about the clinical stage could not be retrieved from the medical records, and two records were not found.

Information on the outcome, such as dates of death and cause of death, was collected from the sources mentioned above as well as from medical records of another affiliated hospital specialized in palliative care and from the archives. It was then searched the Mortality Information Database (SIM) of the State Health Department of Rio de Janeiro, which included information only on deaths occurring in the state of Rio de Janeiro from 1991 to 2006, when a field was filled out with a code for any cancer. Information was collected on the underlying cause of death. If the underlying cause of death was not specified, the researcher would classify it based on the following criteria: for all patients we tried to identify the origin of clinical events that led to the admission and/or death of the patient. Patients with unknown

[a] Brazilian Ministry of Health. National Cancer Institute. Estimativa 2010: incidência de câncer no Brasil. Rio de Janeiro; 2009.
[b] National Comprehensive Cancer Network.Clinical practice guidelines in Oncology: Prostate Cancer. 2005. Washington; 2006.

underlying cause of death, but who had information about the diagnosis of metastatic prostate cancer or who received palliative care at home and had no information on medical records of any other underlying disease were considered as death by prostate cancer.

For survival analysis, there were considered events deaths (date of death) due to prostate cancer or as a direct consequence of treatment. All surviving patients at the end of follow-up were censored at the last date recorded in the medical records. Patients lost to follow-up were analyzed up to the date of the last record. Patients who died from causes unrelated to prostate cancer or their treatment were censored at the date of death. The start time of observation for each individual (T0) was defined as the date of histopathological diagnosis of prostate adenocarcinoma. The limit date (start time of observation) for entry of new cases in the cohort was the last day of 1999. Patients were followed up until August 2007.

Figure 1 shows the entry of patients in the cohort, the number of patients lost to follow-up, censored cases, and events by time points. By the end of follow-up (n=258), 46 patients died, 27 were censored due to death by other causes (five of them of unknown causes) and 67 patients survived. There were 118 patients lost to follow-up, 107 of them with less than ten years of follow-up (41.5% of the study population). Among these 107 losses, 49 patients (45.8%) were followed up for more than four years. Since all patients were searched in the mortality database, the main assumptions for these losses are that these patients were alive by the end of 2006 or that they died in other states. Other possibilities that may explain these losses include missing information on cancer in death certificates (incomplete reporting error or due to clinically non-significant prostate cancer), or even errors in identification fields of the database.

Survival functions were calculated using the Kaplan-Meier method.[3] The log-rank test was applied for comparison of survival functions for each variable.[13]

The following variables were assessed as independent prognostic factors: age, skin color, schooling, treatment modality, year of first treatment, degree of cellular differentiation of the biopsied primary tumor (Gleason score), primary Gleason pattern (dominant histological pattern), clinical stage and pretreatment total PSA level. The variables were stratified by cut-off points (described in the literature) and the result of the log-rank test for Kaplan-Meier curves for each variable. For the assessment of prognostic factors associated with the outcome of interest, we estimated hazard ratios (HR) and 95% confidence intervals following the Cox proportional hazards model. Only those variables with statistically significant crude HR ($p<0.05$) were included in the model, except for tumor stage that was maintained because of its clinical relevance. Age was maintained in all models for adjustment. All other variables were added one by one according to their relevance according to the literature and only those with statistically significant effect remained in the model. A comparison of multivariate models was performed through the analysis of deviance for nested models and no missing values in any selected variable.[6] The adjusted model included the variables age, PSA, Gleason score, tumor stage and skin color.

The assumption of Cox's proportional hazards model was assessed by the analysis of Schoenfeld residues and the impact of outliers was analyzed using martingale and score residuals.[6] There was no violation of the assumption of Cox's proportional hazards model because none of the variables selected for the final model showed a characteristic pattern of association of its effect over time in the graphical analysis of Schoenfeld residuals using the rank time scale (sequence of events over time). The overall fit of the model was evaluated by the explanatory power (R^2 of the selected model / R^2 of the saturated model) and the graphical analysis of survival data by prognostic index.[6] The explanatory power of the fitted model was 26.7% (R2 = 0.221, maximum = 0.828), which is considered a good fit for survival models. All statistical analyses were performed using the R program, version 2.4.0.

The study followed the required standards of the Declaration of Helsinki and was approved by the Research Ethics Committee of the National Cancer Institute.

RESULTS

The median age of the study population was 66 years old, ranging from 50 to 87. The main modalities of initial treatment were external beam radiation therapy (132 patients) and radical retropubic prostatectomy (103), excluding those patients who underwent neoadjuvant and adjuvant hormone therapy (13). Six patients did not receive any initial treatment. No patient was treated with brachytherapy during the study period. The median age of patients treated with radiation therapy was 72 years old and of those treated with surgery was 63 years old.

The five-year and ten-year survival rates were 87.8% (95% CI: 83.3, 92.5) and 71.1% (95% CI: 63.2, 80.0), respectively. The median follow-up time was 6.4 years (maximum: 14.2 years).

The five-year survival for patients with pretreatment PSA <40 ng/mL was 91.2% and for patients with ≥40 ng/mL was 70.1% (Figure 2).

Throughout the follow-up, no deaths were seen among patients with a Gleason score between 2 and 4 (well-differentiated) (Table 1). For patients with a score of 5 or 6 (moderately differentiated), the five-year survival rate was 87.3% (Figure 3). The difference between the

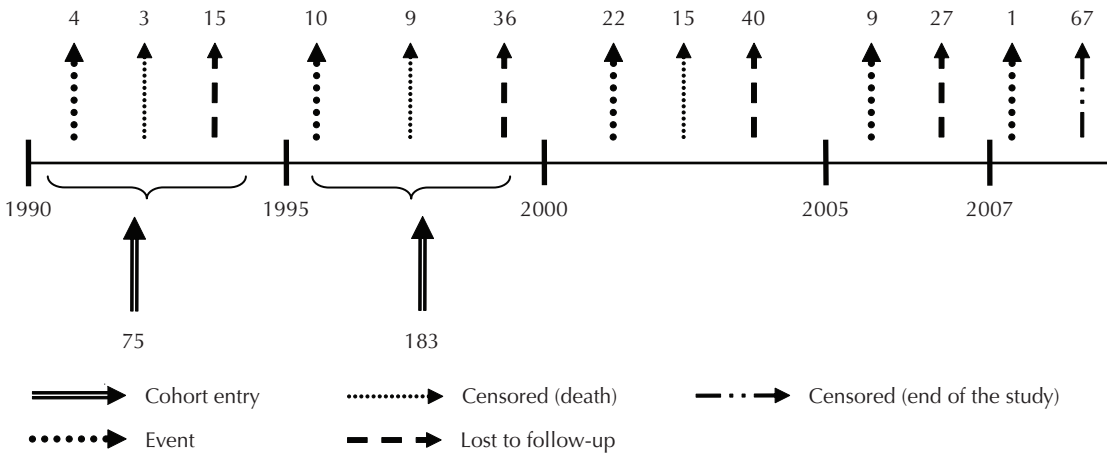

Figure 1. Schematic plan of patient follow-up in the cohort. Rio de Janeiro, Southeastern Brazil, 1990–2007.

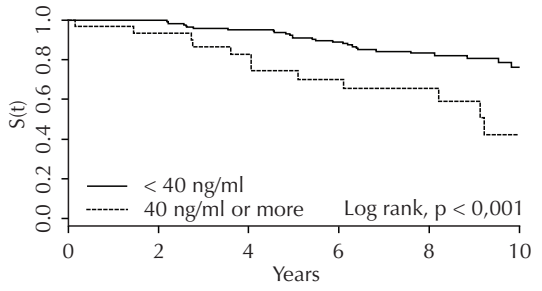

Figure 2. Survival curve stratified by pretreatment PSA level. Rio de Janeiro, Southeastern Brazil, 1990–2007.

survival curves stratified by primary Gleason score was significant (log-rank, p<0.05). Two out of four patients with stage A2 died: one in the middle of year four of follow-up and the other in the beginning of year six. The five-year survival of patients with tumor stage B1 and B2 was 98.1% and 81.7%, respectively.

Patients treated with radiation therapy had lower survival rates than those treated with radical prostatectomy, with five- and ten-year survival rates of 79.8% and 53.9%, respectively, compared with survival rates of 96.5% and 76.9%, respectively, for surgical patients (Figure 4).

With regard to skin color, the survival curves were significantly different (log-rank, p<0.05) with five-year survival of 96.1% among black and mixed skin color patients and 84.6% among white ones. Illiterate patients or those with incomplete elementary school were less likely to survive than those with higher schooling (log-rank, p<0.05). Among patients with black or mixed skin color, there was a higher proportion of illiteracy or incomplete elementary schooling (chi-square test: p=0.04). Survival curves stratified by year of initial treatment (1990–1994 and 1995–1999) showed no statistical differences in the log-rank test.

In the univariate analysis, patients with complete elementary and middle schooling or higher had a 50% lower risk (HR) of dying from prostate cancer for each year of follow-up (95% CI: 0.28, 0.96) compared to those illiterate patients or with incomplete elementary schooling. However, after adjusting for age, PSA level and Gleason score, this difference lost its statistical significance, i.e., schooling did not add information in predicting the prognosis.

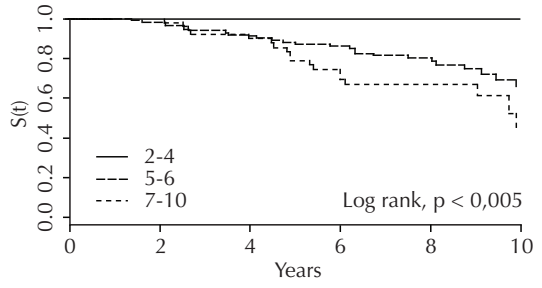

Figure 3. Survival curve stratified by pretreatment degree of histological differentiation (Gleason). Rio de Janeiro, Southeastern Brazil, 1990–2007.

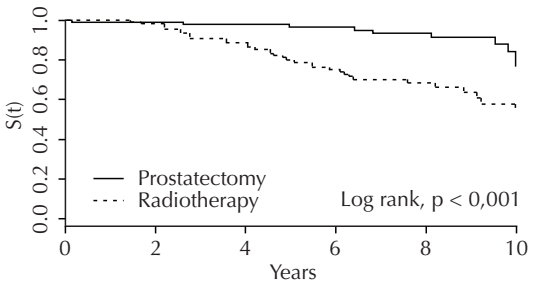

Figure 4. Survival curve stratified by modality of initial treatment. Rio de Janeiro, Southeastern Brazil, 1990-2007.

Table 1. General characteristics of patients in the cohort studied. Rio de Janeiro, Southeastern Brazil, 1990–2007.

Variable	n	%[a]	Death (n)[b]	%
Age group (years)				
50 to 59	40	15.5	4	8.7
60 to 69	125	48.4	20	43.5
70 to 79	80	31.0	19	41.3
80 or more	13	5.0	3	6.5
Skin color				
White	194	75.2	39	84.8
Black	16	6.2	1	2.2
Mixed	48	18.6	6	13.0
Nationality				
Brazilian	237	91.9	42	91.3
Portuguese	13	5.0	3	6.5
Other	8	3.1	1	2.2
City of residence				
Rio de Janeiro	149	57.8	26	56.5
Other	109	42.2	20	43.5
Schooling				
Illiterate	8	3.2	2	4.5
Incomplete elementary/middle school	101	40.2	26	59.1
Complete elementary/middle school	52	20.7	7	15.9
Complete high school	52	20.7	5	11.4
College education	38	15.1	4	9.1
PSA (ng/mL)				
4 or lower	24	9.8	3	7.0
4.1 to 10	80	32.5	12	27.9
10.1 to 20	69	28.0	9	20.9
20.1 to 40	40	16.3	6	14.0
Greater than 40	33	13.4	13	30.2
Clinical staging according to Jewett-Withmore classification				
A2	4	2.0	2	5.3
B1	76	38.6	10	26.3
B2	117	59.4	26	68.4
Degree of histological differentiation				
Well-differentiated	42	16.9	0	0.0
Moderately differentiated	144	58.1	26	59.1
Poorly differentiated	62	25.0	18	40.9
Primary Gleason pattern				
1 to 3	125	80.1	15	68.2
4 or 5	31	19.9	7	31.8
Modality of initial treatment				
External beam radiation therapy	132	51.2	34	73.9
Radical retropubic prostatectomy	103	39.9	10	21.7
Other	23	8.9	2	4.3
Year of initial treatment				
1990-1994	75	29.1	17	37.0
1995-1999	183	70.9	29	63.0

[a] Excluding patient with missing information for each variable
[b] Only deaths primarily due to prostate cancer
PSA: Prostate-specific antigen

Table 2. Hazard Ratios associated to prognostic factors included in the final model. Rio de Janeiro, Southeastern Brazil, 1990–2007.

Variable	HR[a]	95% CI	HR[b]	95% CI
PSA (ng/mL)				
Lower than 40	1		1	
Greater than or equal to 40	2.99	(1.56; 5.74)	3.75	(1.68;8.37)
Degree of histological differentiation				
Poorly differentiated (Gleason 7–10)	1		1	
Moderately differentiated (Gleason 5–6)	0.58	(0.32;1.07)	0.42	(0.19;0.92)
Well-differentiated (Gleason 2–4)[c]	0.73×10^{-8}	(0;Inf)	0.29×10^{-8}	(0;Inf)
Jewett-Withmore staging system				
B1	1		1	
B2	2.08	(1.00;4.31)	2.96	(1.27;6.89)
A2	4.28	(0.93;19.68)	2.35	(0.43;12.72)
Skin color				
White	1		1	
Black or mixed	0.44	(0.20;0.98)	0.4	(0.16;0.98)

[a] HR: Crude hazard ratio
[b] HR: Adjusted hazard ratio for all variables in the table and by age
[c] Category in which no events were seen during follow-up
PSA: Prostate-specific antigen

There were no deaths among patients aged 50 to 54. The poorest prognosis was seen among those aged 70 years or more who showed a risk of dying from cancer almost four times higher (95% CI: 1.24, 10.90) than that of patients aged 50 to 59 years.

Patients who underwent radiation therapy as initial treatment showed in the univariate analysis a risk almost four times higher of dying of prostate cancer for each year of follow-up (95% CI: 1.83, 7.64) when compared to those who have had surgery. However, this association lost significance after adjusting for age, PSA level, Gleason score, tumor stage, and skin color. The year of treatment (1990–1994 and 1995–1999) had no significant effect in the univariate analysis (95% CI: 0.40, 1.38).

Staging according to Jewett classification was not statistically significant in the univariate analysis due to the small number of patients classified as stage A2. However, in the multivariate analysis, the effect of stage B2 became significant, indicating a risk almost three times higher of dying from prostate cancer for each year of follow-up compared to that of patients with tumors classified as stage B1 (Table 2).

Other categories that had a statistically significant effect in the multivariate analysis were: black or mixed skin color, moderate degree of histological differentiation of the primary tumor, and pretreatment PSA of 40 ng/mL or more. Patients with black or mixed skin color had a 60% lower risk of dying from prostate cancer than white ones for each year of follow-up (Table 2). Patients with moderately differentiated tumors had a 58% lower risk of dying from prostate cancer than patients with poorly differentiated tumors. Patients with pretreatment PSA levels ≥40 ng/mL were almost four times more likely of dying than patients with lower PSA levels (Table 2).

DISCUSSION

The five- and ten-year prostate cancer-specific survival rates were 87.8% (95% CI: 83.3, 92.5) and 71.1% (95% CI: 63.2, 80.0). Pretreatment Gleason score greater than 6 (poorly differentiated tumors), PSA ≥40 ng/mL, stage B2 and white skin color were independent markers of poor prognosis. There were deaths throughout the follow-up among patients who had pretreatment well-differentiated tumors (Gleason 2-4).

The high number of losses, especially for ten-year survival, definitely produces inaccuracy in the estimates for longer follow-up times. However, in order to study the specific mortality of a disease with long survival that affects older individuals who very commonly have comorbidities and concurrent causes of death, we decided to use exclusively medical sources of information to prevent biased estimates due to misclassification of cause of death.

In a cohort study conducted in Sweden[11] in which all patients with palpable tumors at diagnosis were followed with an expectant management approach without receiving any initial treatment. The 15-year survival was 80.3%, which is higher than the ten-year survival of this cohort. As in our cohort only 17% of tumors were well-differentiated – a percentage similar

to that found in other national cohortl[2] – this difference may be explained by a higher prevalence of well-differentiated tumors at diagnosis in that cohort (66%). In the Swedish cohort the 15-year survival rates in patients with well-differentiated, moderately differentiated and poorly differentiated tumors were 88.9%, 64.5% and 28.6%, respectively. These results are similar to the ten-year survival rates according to histological grade found in our cohort: 100%, 66% and 44%, respectively. Studies of the US Surveillance, Epidemiology and End Results Program also showed a favorable survival among patients with well-differentiated tumors with a relative five-year survival rate of 100%.

In a study of patients with clinically localized cancer who underwent external radiation therapy in the US, specific ten-year survival rates were 100%, 94%, and 55% respectively, for low, medium and high-risk groups according to clinical prognostic factors.[7] In a study conducted in Uruguay with patients treated with salvage radiation therapy due to biochemical recurrence after prostatectomy, the specific five-year survival was 90%.[16] Another study, carried out at the same center, showed a specific nine-year survival of 88% in 560 patients with localized prostate cancer treated with conformal radiation therapy between 1993 and 2001.[15]

The findings of the present study do not support the theory that younger patients would have more aggressive cancers and poor survival, but they corroborate results of previous studies.[2,20] It is possible that this assumption was based on diagnostic bias among young people in the past when only symptomatic cases were diagnosed, which increased the risk of detection of more aggressive tumors.

The good distinction found in the prognosis of patients with stage B1 and B2 tumors shows the importance of digital rectal examination in the staging and management of patients with localized cancer. Although the small number of patients does not allow comparing the HR of patients with stage A2 tumors with that of other groups, the study provides strong evidence of the inadequacy of this classification as a marker of favorable prognosis. The very definition of stage A2, i.e., no palpable tumors with moderately or poorly differentiated cells in different parts of the prostate, indicates a flawed classification: it disregards the prognostic power of the degree of histological differentiation. The TNM classification – sixth edition by now includes the histological degree of moderately or poorly differentiated tumors as an exclusion criterion of the category of better prognosis (stage I). Thus, the best rule for the conversion of the Jewett-Whitmore into TNM classification would be to classify stage A2 tumors as "T1a N0 M0 G2, 3-4," or stage II.

We were not able to obtain an accurate estimate of HR for patients with well-differentiated tumors in the biopsy because there were no deaths from prostate cancer in this category. However, as there were 42 patients in this group, the non-occurrence of deaths is a strong indication of the excellent prognostic power of this classification. The relevance of this prognostic marker in our cohort is consistent with findings of other studies, which places it among the best available markers.[1,4,12,21]

While pretreatment PSA levels of 40 ng/mL proved a valuable predictor of prognosis, the levels of 4 ng/mL and 10 ng/mL used in several studies, including the development of the nomogram as proposed by Partin et al,[21] did not properly differentiate the groups in our cohort. A likely explanation would be the wide use of screening with PSA in the US, which would decrease mean levels of PSA at diagnosis. Lower cutoffs were also used in the cohort of patients treated with prostatectomy between 1988 and 2002 in São Paulo. This study found that stage T1c was the most common (almost 50% of cases) and only 7% of pretreatment PSA levels were higher than 20 ng/mL.[5]

The poorest prognosis among patients with lower socioeconomic status (schooling) may indicate more difficult access to care, as it is explained by pre-treatment clinical variables. The HR of the adjusted model for skin color suggests this variable is an independent predictor of specific survival for prostate cancer, in contrast to that reported in studies conducted in the US.[8,14,19] A possible explanation could be that white skin color individuals would have more aggressive tumors, although the highest proportion of well-differentiated tumors in black and mixed skin color patients (21% vs. 14% in whites) was not statistically significant (p=0.21).

The better prognosis of patients treated with radical prostatectomy compared to those treated with radiation therapy, as seen in the Kaplan-Meier curves and in the univariate model, lost significance after adjustment for other predictor variables. This result indicates that the difference attributed to treatment is in fact explained by differences in pretreatment prognostic factors and is probably due to a difference in the baseline risk of patients, which have been described in other studies.[10] The year of treatment showed no significant effect in the univariate analysis, suggesting that the advances in therapeutic procedures in the 1990s had no impact on survival in our cohort.

The Gleason score was shown to be essential in pretreatment evaluation, and should be focused in the training of pathologists. The digital rectal examination and PSA levels also have a significant predictive power and should be used in pretreatment risk stratification of patients with localized prostate cancer. Further studies are needed to investigate the differences in prognosis related to ethnicity and its potential causes, as well as to explore new morphological prognostic factors and validate prognostic classifications for the Brazilian population.

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