Is Age an Independent Factor for Prostate Cancer? A Paired Analysis

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Key Words
Age • Prognosis • Prostate cancer

Abstract
Introduction: Prostate cancer is the most prevalent malignant neoplasia among men worldwide. Several prognostic factors, including Gleason's score, the measurement of serum prostate-specific antigen (PSA) and the evaluation of the percentage of fragments affected by cancer on prostate biopsy, have already been established. Age alone, however, has yet to be studied as a prognostic factor independently from other known factors. The aim of the present study was to compare the characteristics and the evolution of prostate cancer in different age groups using a paired analysis for patients with equivalent known prognostic factors. In addition, we aimed to determine the true impact of age on the prognosis of prostate cancer.

Material and Methods: The data from 2,283 patients subjected to radical retropubic prostatectomy between 1998 and 2009 were reviewed. The patients were divided into three age groups: < 55 years old, between 56 and 65 and > 65 years old. Each patient was matched to another patient in the other groups who had the same PSA range (< 4.0, between 4.0 and 10.0 and > 10), Gleason score on the surgical specimen and prognostic range of positive fragments in the prostate biopsy (< 33%, between 34 and 50% and > 50%). After pairing, each group consisted of 215 patients, who were compared using the biochemical recurrence of the disease (PSA > 0.2), the interval for biochemical relapse, extra-capsular invasion and invasion of the seminal vesicles or the lymph nodes. RESULTS. No significant difference was observed between the groups regarding the frequency of relapses, interval of relapse, extra-capsular invasion and invasion of the seminal vesicles or lymph nodes.

Discussion: None of the studied factors were affected by the age of the patients. Therefore, patients of different ages had tumors with similar characteristics and behaviors. Conclusion: When assessed separately, without the effects of the main prognostic factors, age does not appear to be an independent prognostic factor for prostate cancer.
among others. As a result, few studies have assessed the effect of age isolated from other prognostic factors on prostate cancer [3].

The aim of the present study was to compare the characteristics and the evolution of prostate cancer in different age groups using a paired analysis. In addition, we aimed to assess age independent of other prognostic factors established in the literature, thus determining the true impact of age on the prognosis of prostate cancer in different age groups.

**Materials and Methods**

The data from 2,283 patients treated for prostate cancer between 1998 and 2009 by one of the authors (M.S.) at Hospital Sírio-Libanes and Hospital Alemão Oswaldo Cruz in São Paulo were assessed. All patients were submitted to radical retropubic prostatectomy and standard lymphadenectomy. The patients who needed hormonal treatment therapy were excluded. The patients were grouped into 3 categories (215 patients per group) according to age range: < 55 years, 56–65 years and > 65 years old. Each patient was paired with a patient in the other groups who had similar pretreatment serum PSA levels (< 4.0 ng/ml, 4.0–10.0 ng/ml and > 10.0 ng/ml), identical Gleason scores of the surgical specimen and the same risk range for the percentage of positive fragments on biopsy (< 34%, 34%–50% and > 50% of positive fragments) [4] (fig. 1). The pairing was performed independently by three people who searched for patients with similar characteristics. The choice of patients was made from the youngest of each group to the oldest. Once the pairing was completed, the groups were compared to minimize the errors and generate the final data, which were then analyzed.

Data on postoperative serum PSA levels were also collected during patient follow-up to determine the presence of biochemical relapse (PSA > 0.2 ng/ml after PSA had become undetectable). PSA dosing was performed 1 month after surgery, than trimonthly for the first year and every six months for subsequent years.

The data regarding presence of extra-capsular invasion and the invasion of the seminal vesicles or lymph nodes in the surgical specimen was also collected.

Tumor characteristics were noted for each age group. The existence of an association between each nominal characteristic and the groups was verified by generalized estimation equations (GEEs), with marginal distributions for the binomial responses and logit link functions [5].

GEEs were used to compare the intervals for biochemical relapses between the age groups, with a marginal Poisson distribution for the answers and identity link functions. A p-value of 5% was considered statistically significant.

**Results**

The means and standard deviations for preoperative characteristics, including age, preoperative PSA, Gleason score, the percentage of positive fragments on biopsy
and clinical staging, and the period of follow-up for each of the three groups in the paired analysis are described in table 1. The results obtained from the comparison between the three groups are shown in table 2. No statistical difference was noted regarding the biochemical relapse (p = 0.739) or the time interval for its occurrence (p = 0.796). The pathological characteristics regarding extracapsular, seminal vesicle and lymph node invasion were also similar among the groups (p = 0.436, p = 0.756 and p > 0.999, respectively).

### Discussion

The importance of age on the behavior and evolution of prostate cancer has been a matter of debate. Some studies have suggested that the onset of the disease at a younger age is correlated with a more aggressive tumor behavior and, consequently, a higher mortality rate. There is, however, no consensus regarding the age limit at which these tumors would be most aggressive or regarding the factors that would make these tumors more
aggressive in young individuals [6]. Contrary to these suggestions, subsequent studies have shown equivalent or even higher survival rates in younger patients compared with older patients [7, 8].

Advanced age is associated with higher Gleason scores, higher levels of PSA and more advanced local disease, which makes it difficult to assess whether age alone can alter the prognosis of prostate cancer [9, 10]. Recent studies have correlated advanced age with a worse prognosis for prostate cancer using univariate analyses; however, when performing a multivariate analysis using the Gleason score, clinical staging and PSA levels, age was not found to be a predictor of prostate cancer prognosis [10–13].

In the present study, we evaluated the data from different age groups using a direct paired analysis, and to the best of our knowledge, this is the first study to evaluate age independent of other prognosis factors. Although a paired analysis is more laborious and more prone to errors than a multivariate analysis, once the pairing is completed, this approach provides a clearer visualization of the characteristics between the groups [14]. To minimize the chances of errors during the pairing, we chose to have three individuals perform the pairing independently. We then compared their pairings in an attempt to reduce human error during processing.

Another difficulty of pairing is the requirement of a large cohort. In this study, the majority of our 2,283 patients had to be discarded because of the inability to incorporate them into the study using the pairing criteria. Each extra variable included in the pairing resulted in a considerable decrease in the sample size for each group. In addition, the number of groups limited the sample for analysis. Before reaching the model described in this study, we had chosen to divide the patients into four age groups and include the clinical staging of the patients in the pairings in addition to the PSA levels, Gleason scores and percentage of positive fragments on biopsy. This approach resulted in less than 30 cases per group, making the statistical analysis difficult. Thus, we chose to decrease the number of age groups to three and exclude clinical staging from the pairing. Using these criteria, each group achieved a sample size of 215 patients, thus eliminating 1,638 patients from the analysis.

Although clinical staging was not included in the analysis, its distribution was very similar among the groups, as the effects of three important independent prognostic factors (PSA levels, Gleason scores and the percentage of positive fragments) were removed from each group. The group of patients above 65 years of age appeared to have a slightly greater number of patients in stage T2b compared with the other two groups; however, staging should not have a greater prognostic implication because the major prognostic difference within stage T2 occurs between T2a and the latter stages (T2b and T2c) [15]. Nonetheless, the removal of clinical staging in the pairing remains a limitation of the current study.

Considering the cohort of the present study, no evidence was found to support age as an independent prognostic factor for prostate cancer as either a predictor of the risk of recurrence and interval for relapse or as a characteristic of the local invasion of the disease.

To our knowledge, only one other study has been performed using a paired analysis of age as a prognostic factor for prostate cancer. Magheli et al. [16] analyzed the impact of age in different age groups by pairing their cases through propensity scores generated by multivariate analysis. This method combines individuals from different groups and associates patient characteristics in order to simulate a manual pairing while giving each factor a specific weight. The greatest limitation of this method is the inability to verify the presence of confounding variables that are not included in the calculation of the propensity scores [17]. Regarding age, the conclusion reached by Magheli et al. [16], was that older patients had higher grades of disease and greater positive surgical margins according to a univariate analysis. With the multivariate analysis, however, age was not found to be an independent predictor of prognosis, as found herein. The main limitation of the Magheli et al. [16] study was the short follow-up period of the patients, which had an average of 3 years, whereas our study had an average follow-up time of over 5 years (69 months for patients < 55 years old, 70 months for patients 56–65 years old and 80 months for patients > 65 years old).

Finally, other limitations of the present study include the inability to sub-stratify the age groups and assimilate more prognostic factors into our pairing, which, as mentioned above, was limited by the size of our sample (n = 2,283) and the type of study we chose to conduct. Our study, however, is one of the few studies in the literature to assess age without the effect of the primary confounding variables. In addition, this is the first study to evaluate age through a direct paired analysis of the patients.

Conclusion

Several prognostic factors have been well established in literature, and several other possible factors have been investigated as well. According to our results and those
obtained from previous studies, age does not appear to be an independent predictor of prognosis in prostate cancer. In contrast, age appears to be entangled with other factors that become more frequent with age, such as higher PSA levels and elevated Gleason scores. Further studies are required for a better understanding of the interaction between age and other prognostic factors and for the identification of other unknown factors.

**Ethical Standard**

This patient study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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