ELSEVIER

Urologic Oncology: Seminars and Original Investigations 23 (2005) 238–245

UROLOGIC ONCOLOGY

Original article

Relative importance of PSA in prostate cancer treatment

Henry A. Unger, M.D.[a], Richard D. Kane, M.D.[b], Kathleen M. Fox, Ph.D.[c,*], Sanjay Gandhi, Ph.D.[d], Carlos Alzola, M.S.[e], Lois Lamerato, Ph.D.[f], Don Newling, M.D.[g], Sanjaya Kumar, M.D.[e]

[a] *Cary Urology, Cary, NC, USA*
[b] *Wake Urological Associates, Raleigh, NC, USA*
[c] *Strategic Healthcare Solutions, Monkton, MD, USA*
[d] *AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA*
[e] *Quantros, Inc., Milpitas, CA, USA*
[f] *Henry Ford Health System, Detroit, MI, USA*
[g] *AstraZeneca, Macclesfield, UK*

Received 20 September 2004; received in revised form 21 February 2005; accepted 3 March 2005

Abstract

Methods and Materials: A retrospective study was conducted to (1) determine the relationship between baseline prostate-specific antigen (PSA) levels and initial treatment decisions for prostate cancer (surgery, hormone therapy, radiation, or watchful waiting) and (2) estimate the impact of PSA progression (doubling or three consecutive rises) on subsequent treatment decisions. Patient records ($n = 1116$) from three community urology practices and a large academic health system were reviewed. Multivariate models were fitted to assess the relationship between initial treatment and baseline PSA, Gleason score, race, number of comorbid conditions and age and between PSA progression and time to subsequent therapy (adjusted for other factors).

Results: Baseline PSA was a significant predictor of initial treatment among men with localized disease with the likelihood of hormone therapy increasing with higher PSA levels and the likelihood of surgery decreasing steadily with higher PSA levels. PSA was the strongest predictor of hormone therapy as first choice followed by age. Age followed by PSA was the strongest predictor of surgery as first treatment as well as radiation therapy. Initial PSA levels did not predict the choice of watchful waiting. Patients with PSA progression were eight times (95% CI: 5.3–12.1) more likely to initiate a subsequent therapy than patients who did not have PSA progression when controlling for other predictors.

Conclusions: In clinical practice, PSA significantly impacts the urologist's primary therapy choice and determines when they introduce subsequent treatments.

Keywords: PSA; Prostate cancer; PSA progression; Initial treatment

1. Introduction

Prostate cancer is the most common cancer among U.S. men with approximately 190,000 new cases diagnosed and approximately 32,000 men dying each year [1,2]. One in six American men are at lifetime risk of developing prostate cancer. Prostate cancer is different from most cancers in that a large percentage (>80%) of men present with asymptomatic disease that is frequently confined to the prostate gland and well differentiated [1,3].

The prostate-specific antigen (PSA) test is one of the most widely used screening tests for the detection of prostate cancer and it has been recommended that periodic PSA measurements be continued for life [4,5]. No tumor marker has had as great an impact on the diagnosis and management of a disease as has PSA levels in prostate cancer [6]. PSA not only has a role in screening and early detection, but also in assessing patient outcomes, monitoring disease progression, and evaluating the effectiveness of treatment [6]. Researchers have found that PSA levels indicate post-treatment tumor status because approximately 33% of men with prostate cancer developed biochemical failure with rising PSA during follow-up [7,8]. Despite the widespread use of PSA testing there is uncertainty and lack of consistency

* Corresponding author. Tel.: +1-443-690-2198; fax: +1-410-357-8018.
E-mail address: kathyfox@comcast.net (K.M. Fox).

1078-1439/05/$ – see front matter
doi:10.1016/j.urolonc.2005.03.019

about the significance of PSA levels in the choice of first treatment and significance of post-therapy changes in PSA for assessing tumor control and therapy effectiveness. Indeed, very little is known about the way urologists utilize PSA results in their treatment decisions.

Several recent investigations have examined biochemical recurrence of prostate cancer as characterized by detectable PSA levels after initial treatment. An increase in PSA almost always occurs before clinical evidence of disease progression [8]. PSA doubling time (PSADT) and three consecutive rises in PSA have been introduced as measures of disease progression [3,8,9]. However, to what level these findings have translated to the community urologists and impacted their patterns of care for prostate cancer is not completely clear.

Various nomograms have been developed to assist urologists and oncologists in predicting PSA progression and survival [10–13]. PSA levels have been a consistent predictor of patient outcomes in these nomograms. The degree to which urologists utilize PSA change to assess disease aggressiveness and guide changes in treatment has not been examined. This retrospective study was designed to examine the impact and importance of PSA levels in the care of prostate cancer patients.

2. Materials and methods

A retrospective chart review was conducted to determine the relationship between baseline PSA levels and initial treatment decision for prostate cancer and further to estimate the impact of PSA progression on subsequent treatment decisions.

2.1. Patients

The study population comprised prostate cancer patients from three community urology practices and one large health system in the Midwest. Two of the community urology practices were located in North Carolina (NC) and the third in California. These community-based practices see approximately 9,000 to 10,000 male patients per year with approximately 50 to 100 new prostate cancer patients each year. Patients with T1 or T2 stage prostate cancer were included in the analysis to assess the importance of PSA on treatment decisions in localized disease. There were 1116 with a confirmed diagnosis of localized prostate cancer between January 1, 1995 and March 1, 2001 included in the study. Males age 40 yr and older with two or more PSA tests within 1 yr of diagnosis were eligible for the study. Patients with multiple cancers were excluded. The medical records of these patients were abstracted by urology nurses or certified tumor registrars to obtain data on practice patterns and PSA progression.

Data were abstracted from the patient charts from the date of diagnosis to present time (January 2004) or until the patient died or was last seen in the urology practice. All eligible prostate cancer charts were abstracted except for one NC site that abstracted a random sample (45%) of their charts. Henry Ford Health System (HFHS), a large health system provided data from the HFHS tumor registry, administrative databases and electronic medical records. This healthcare system has an active patient population of over 850,000 persons from the Midwest with more than 2.5 million patient contacts annually.

The study protocol was approved by the Western Institutional Review Board and HFHS Institutional Review Board. The primary study objective was to estimate the impact of PSA levels on treatment decisions of urologists in the United States. Watchful waiting was defined as no treatment within 90 days from the date of diagnosis. PSA progression was defined as either PSA doubling [8,14,15] or three consecutive rises in PSA levels since initial therapy [16]. This definition of PSA progression was chosen because there is no consensus in the literature or in clinical practice for a standard of PSA progression.

2.2. Statistical analysis

To assess the relationship between initial treatment choice and baseline PSA and other tumor characteristics, four binary logistic regression models were fitted with the following covariates: age, race, baseline Gleason score, baseline PSA level, and number of comorbid conditions. The dependent variable in each regression model was a dichotomous outcome indicating whether hormone therapy, surgery, radiation therapy, or watchful waiting was the initial treatment to reflect the therapy decision of choosing one therapy versus all others.

Time to PSA progression was examined by using a Kaplan-Meier analysis stratified by initial therapy (surgery, radiation, hormone therapy, and watchful waiting). The effect of PSA progression on the time to change in treatment (initiation of second line of therapy) was evaluated by means of a Cox Proportional Hazards regression model. Covariates in all the models included patient age, race, baseline Gleason score, and number of comorbid conditions. All statistical models examined nonlinear effects of continuous variables by means of regression cubic splines [17].

For all models, the relative contribution of each factor (e.g., PSA, age) was ranked using the Akaike information criterion (AIC). The AIC is defined as the chi-square for the variable minus twice the degrees of freedom [17,18]. The AIC provides an estimate of the strength of the relationship between each characteristic and the response (treatment decision) accounting for the complexity with which the variable is modeled. The area under the ROC curve (AUC) is provided to demonstrate the discrimination of the models.

Approximately 6% of patients had a missing Gleason score and 13% had a missing baseline PSA level. Patients with missing data were deleted from the analysis since the