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A comparison of early prostate-specific antigen decline between prostate brachytherapy and different fractionation of external beam radiation—Impact on biochemical failure

Daniel Taussky[1,2,*], Stéphane Bedwani[1,2], Nissan Meissner[1], Jean-Paul Bahary[1,2], Carole Lambert[1,2], Maroie Barkati[1,2], Marie-Claude Beauchemin[1], Cynthia Ménard[1,2], Guila Delouya[1,2]

[1]*Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Canada*
[2]*CRCHUM-Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, Canada*

ABSTRACT

PURPOSE: The aim of this study was to compare early prostate-specific antigen (PSA) decline patterns and PSA nadirs between low-dose-rate seed prostate brachytherapy (LDR-PB) and different fractionations of external beam radiotherapy (EBRT) and their predictive importance for biochemical failure (bF).

METHODS AND MATERIALS: Patients with D'Amico low- or intermediate-risk prostate cancer who underwent a single-modality treatment without androgen deprivation were included in this study. Three different treatment groups were compared: (*1*) normofractionation EBRT up to 70.2−79.2 Gy/1.8−2.0 Gy, (*2*) LDR-PB, and (*3*) EBRT with hypofractionation 60 Gy/3 Gy daily or 5−7.25 Gy once a week over 9−5 weeks, to a total dose of 45−36.25 Gy, respectively. The log-rank test, Cox regression analysis, and nonparametric tests were used.

RESULTS: We analyzed 892 patients: the median followup for patients without bF was 84 months (interquartile range 60−102 months), with 12% of patients experiencing bF. The PSA decline within the first 15 months was generally exponential. LDR-PB showed a faster early exponential decline compared with EBRT treatments, but whether decline was fast or slow had no influence on recurrence. The only factors that were positive predictive factors in univariate and multivariate analyses were the time to nadir >48 months (median), PSA nadir <0.5 ng/mL, and <0.2 ng/mL (all $p < 0.001$).

CONCLUSIONS: Although there are significant differences in early exponential PSA decline between different treatments, only the PSA nadir and longer time to nadir were predictive factors for bF.

Keywords: Prostate cancer; Radiotherapy; PSA decline; PSA nadir

Introduction

The best established method for predicting the effectiveness of prostate cancer treatment in terms of biochemical control after prostate radiotherapy is by measuring the patient's prostate-specific antigen (PSA) levels after treatment. The PSA nadir and the time until nadir is reached after radiotherapy are the two main factors used to predict biochemical cure of prostate cancer (1, 2).

As PSA can decline for several years after treatment, it is quite difficult to evaluate the success of the treatment especially in patients treated with radiation as compared with prostatectomy. Therefore, it would be helpful to be able to precipitously identify patients who have favorable PSA declines to reassure them and to allow for closer followup of those who have an unfavorable PSA decline. Our group has previously shown that patients with an early exponential PSA decline were a significant predictive factor of biochemical control, and this was independent of external beam radiotherapy (EBRT) dose (3).

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* Corresponding author. Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, 1560 Sherbrooke St. E., Montreal, Quebec H2L 4M1, Canada. Tel.: (514) 890-8254; fax: (514) 412-7537.

E-mail address: daniel.taussky.chum@ssss.gouv.qc.ca (D. Taussky).

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With the availability of different new treatment modalities, such as, hypofractionation, stereotactic radiotherapy, and low-dose-rate seed prostate brachytherapy (LDR-PB), as well as higher doses and image-guided radiotherapy, there is a need to reevaluate the importance of early PSA decline. In this present study, we compared early PSA declines and PSA nadirs between different treatment modalities and their predictive importance to predict for biochemical failure (bF).

Methods

All patients in our institutionalized database with either D'Amico low- or intermediate-risk prostate cancer who were treated with single-modality treatment from March 2003 to October 2013 were analyzed. Patients treated with a combination of brachytherapy and EBRT and all patients treated with neoadjuvant or adjuvant androgen deprivation therapy were excluded. This study received institutional ethical review board approval.

Biochemical failure was the primary endpoint: it was defined according to the Phoenix definition (nadir + 2 ng/mL) (4). To be included and to be able to observe an appropriate PSA nadir and time to nadir, patients without any bF needed a minimum followup of 48 months.

To obtain a long unbiased followup and uniform treatment delivery in the EBRT group, only patients who were treated in prospective Phase II or III studies were included. All patients were treated with image-guided radiotherapy. The normofractionation group was defined as those receiving 1.8−2.0 Gy per day in daily treatments. Patients included in this group were treated in the Radiation Therapy Oncology Group 0126 trial and randomized to 79.2 or 70.2 Gy in 1.8 Gy fractions (5). Others included in the normofractionation group were those treated to 78 Gy in 2 Gy fractions under the Prostate Fractionated Irradiation trial (6).

All the patients included in the hypofractionation arm were randomized from the Prostate Fractionated Irradiation Trial. (6) Patients received 60 Gy in 3 Gy daily fractions, five times a week, whereas the patients treated in a Phase II multicenter study (7) received a once-weekly fraction of 5 Gy over 9 weeks to a total of 45 Gy; patients treated in the followup Phase II trial received 36.25 Gy in five once-weekly fractions of 7.25 Gy (results not published yet).

In the LDR-PB group, we included all patients treated by two physicians at our institution. All patients were treated using the Fully Integrated Real-time Seed Treatment system (Nucletron, an Elekta Company, Columbia, MD) and had intraoperative planning of their iodine-125 seed implant. Median source activity was 0.59 mCi (0.32−0.68 mCi) (8). Patient data are entered into the database prospectively. Patients for whom no regular visits are scheduled are called regularly throughout the duration of a year as to obtain information on their PSA.

A total of 1154 patients were eligible for this study. Because of missing data or loss to followup, 12% of the patients treated with EBRT and 27% treated with LDR-PB were ineligible for analysis.

Statistical analysis

To analyze whether a fast or slow decay rate of PSA within the first eight or 15 months was predictive of bF, we calculated the slope of the natural logarithm of the available PSA values [ln(PSA)] measured at different times "x". The decay rate was calculated by linear regression, such as $\ln(\text{PSA}) = mx + b$, where m is the slope and b is the intercept (9). A coefficient of determination $R^2 = 1$ means that the PSA follows a perfect exponential relationship. The decay rate was only calculated when at least three PSA levels were available within the first 8−15 months after treatment.

Kaplan−Meier analysis (log-rank test) was used for survival analysis, and for multivariate analysis, Cox regression was used. Differences between groups were compared using the χ^2 and the Kruskal−Wallis tests when appropriate.

Statistical analysis was done using SPSS 23.0 for Windows (IBM SPSS, Chicago, IL).

Results

Pretreatment patients' characteristics are shown in Table 1 together with results of the univariate analysis for bF. For the 892 patients, the followup for patients without bF was 84 months (interquartile range [IQR] 60−102 months). A total of 108 patients (12%) experienced bF at a median of 59 months after treatment (IQR 35.3−78.0 months). Biochemical failure was experienced in 12%, 8%, and 27% of patients treated with hypofractionation, LDR-PB, and normofractionation, respectively. This significant difference ($p < 0.001$, log-rank test) can be explained by the fact that patients in the normofractionation group had Cancer of the Prostate Risk Assessment (CAPRA) scores of ≥3 more frequently than patients in the two other groups (Table 1). The CAPRA score was itself a prognostic factor ($p < 0.001$).

So far, 67 patients ($n = 7.5\%$) have died: six from prostate cancer. A median of 10 PSAs (IQR 7−14) was available per patient. Because of the small number of death from prostate cancer and since patients are referred to uro-oncologists once they have metastatic disease, we cannot make reliable predictions on these endpoints.

Importance of PSA decline after treatment

An early PSA decline could be addressed by a linear relationship, such as the percentage change from baseline at 1 month or 4 months after treatment. However, the observed PSA decline over a few months is rather exponential than linear. The decay rate of the PSA decline can thus be defined as the slope of the natural logarithm of the PSA measurements over a time period of 0−8 (or 15) months after treatment. This is illustrated in Fig 1, showing very similar PSAs within the first 15 months after treatment except for LDR-PB. Table 2 details the slope of the PSA