Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
October 2015, Volume: 7, Issue: 6, Pages: 1330-1335, DOI: 10.14661/1330

Biochemical progression-free survival in localized prostate cancer patients treated with definitive external beam radiotherapy

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Type of article: Original

Abstract

Introduction: Prostate cancer is now the third most frequent noncutaneous malignancy in Iranian men and the fifth most common cancer worldwide. Measurement of total serum prostate specific antigens (PSAs) has been one of the strongest predictors of biochemical progression and overall survival in determining the efficacy of definitive external beam radiation therapy in patients with localized prostate cancer. The aim of this research was to identify the 5-year biochemical progression-free survival (BFS) and related prognostic and predictive factors of localized prostate cancer patients who were treated with definitive external beam radiotherapy.

Methods: This study analyzed 192 localized prostate cancer patients from stage T1aN0M0 to stage T3N0M0; they were treated with definitive radiation therapy and followed up in the radiation-oncology ward of Shohada-e-Tajrish Hospital in Tehran (Iran) between 2006 and 2013. The 5-year BFS was analyzed using the Kaplan-Meier estimate. For multivariate analysis, the Cox proportional hazards model was used to assess the strengths of various factors for 5-year BFS.

Results: The follow-up period was between 14-81 months, with a median of 31 months. The median cumulative prostate dose in our series was 64 Gray (Gy) (range 62 to 78 Gy). The 5-year BFS for all patients was 65.1%, and 5-year BFS in low-risk, intermediate-risk and high-risk groups were 100%, 86.5%, and 54.9% respectively. Multivariate analysis found statistically significant relation between 5-year BFS and initial PSA>20, Gleason score 8-10, high risk group, TNM stage≥T2cN0M0, radiotherapy dose<70 Gy, radiotherapy with 2D technique and hormonal therapy in high-risk group (p=0.003, p=0.032, p=0.014, p=0.001, p=0.035, p=0.035, p=0.022 respectively).

Conclusion: Our seven years' experience of follow-up with PSA showed that PSA was the strongest predictor of biochemical progression survival in patients with prostate cancer who were treated with definitive external beam radiation therapy.

Keywords: prostate cancer, progression-free survival, definitive radiotherapy, prostate specific antigen

1. Introduction

After gastric and lung cancer, prostate cancer is now the third most frequent visceral cancer in Iranian men and the fifth most common cancer worldwide. Although its incidence is much lower in Iran than in Western countries, the number has dramatically increased over the past ten years (1). Increased public health awareness in Iran of measuring total serum prostate specific antigens (PSAs) with the aim of screening and early detection of prostate cancer at earlier stages has resulted in increased early diagnoses of prostate cancer in recent years (2-4). These men with a clinically localized disease can be treated with radical prostatectomy, definitive external beam radiation therapy (EBRT) with or without brachytherapy, hormonal therapy and active surveillance.

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Received: June 23, 2015, Accepted: July 31, 2015, Published: October 19, 2015
iThenticate screening: July 27, 2015, English editing: August 08, 2015, Quality control: October 05, 2015

Choosing the best method of treatment for patients with prostate cancer depends on a number of factors such as initial total serum PSA, risk groups, Gleason grading score, clinical TNM staging and life expectancy (5). EBRT (with or without brachytherapy) and radical prostatectomy have similar curative and long-term efficacy in the treatment of clinically organ-confined prostate cancer (6-7). These types of treatment have acceptable long-term cure rates in clinically localized prostate cancer patients, but unfortunately 30% to 50% of these patients will show evidence of PSA failure ten years after treatment with definitive external beam radiation therapy (8). Because of the lack of randomized clinical follow-up trials in clinically organ- confined prostate cancer patients treated with brachytherapy, only EBRT has been included in this study. After about 24 months of EBRT, most patients might achieve a nadir of total serum PSA. Almost all clinically localized prostate cancer patients who have any type of disease recurrence present the first time with PSA elevation of 2 ng/mL above nadir PSA (9-11). This study aimed to describe the biochemical progression-free survival and related prognostic factors for localized prostate cancer treated with definitive EBRT in Iran.

2. Material and Methods

2.1 Research Design and Setting

This was a single-institutional retrospective-analytic study. Men diagnosed with pathologically localized prostate cancer from stage T1aN0M0 to stage T3N0M0 (clinical T staging was defined by MRI or transrectal ultrasound) were treated with definitive radiation therapy and followed up in the radiation-oncology ward of Shohada-e-Tajrish Hospital in Tehran, Iran between 2006 and 2013. The minimum follow-up period was 24 months. The medical records of the patients provided information such as age, initial PSA (pretreatment PSA), TNM stage, Gleason score, radiotherapy dose and technique, and type of radiotherapy machine. The risk groups were defined as low-risk (T1c- T2a, GS <7 and PSA ⩽10 ng/mL), intermediate-risk (T1b-T2b, GS 7, or PSA 11 – 20 ng/mL) and high-risk (T2c–T3, GS >7, or PSA >20 ng/mL), and further differentiated in terms of hormonal therapy (in the high-risk group) and time of biochemical (PSA) failure.

2.2. Eligibility criteria

We included all of the prostate cancer patients who met the inclusion criteria at our center from 2006 to 2013 in the study. The inclusion criteria were that they be men with a histopathology diagnosis of prostate cancer without lymph node or distant metastasis that were irradiated by definitive EBRT at our center. Patients were excluded from the study if they were without a histopathology diagnosis or without initial serum PSA, if they had been treated by radical prostatectomy, if they presented with lymph node or distant metastasis, if they had undergone adjuvant treatments such as radiation therapy or brachytherapy initiated by another radiation oncology center and if they were without follow-up.

2.3. Data collection

All patients had previously been treated with a linear accelerator (Linac) 9 MV or Cobalt 60 with 64-76 gray (Gy) in 32-38 fractions with 2 Gy per fraction. First, 44 to 46-Gy whole pelvic radiations were given to patients if they were at a higher risk of lymphatic spread, and then a 30-Gy boost dose was delivered to the prostatic fossa with or without seminal vesicle. Patients received a total dose of less than 70 Gy administered by two-dimensional (2D) treatment planning. Patients received a total radiation dose of 70 Gy or above administered by three-dimensional (3D) treatment planning such as three dimensional-conformal radiation therapy (3D-CRT). Radiation therapy was used 5 days a week from Saturday to Wednesday (with the exception of public holidays) with 2 Gy per fraction with 2D or 3D treatment planning. All patients were followed up according to standard guidelines and continuously, at least every three months for the first two years and at 6-month intervals thereafter. The follow-up procedure included disease-specific history and PSA monitoring. The 5-year BFS was determined per the definition of biochemical failure (BF) of PSA as rising by 2 ng/mL above the nadir after radiation therapy.

2.4. Ethical considerations

The ethical regulations dictated in the act provided by Shohada-e-Tajrish Hospital in Shahid Beheshti University of Medical Sciences (reference number of research ethics committee: 301/5375) were strictly observed. The data is preserved regardless of the patient`s names. All patients were followed-up by standard guidelines.

2.5. Statistical analyses

We used the Kaplan–Meier method to calculate 5-year BFS from the first day of radiotherapy and used pairwise log rank tests for comparisons of low-risk, intermediate-risk and high-risk groups. For multivariate analysis, the Cox

proportional hazards model was used to assess the strengths of various factors for 5-year BFS. The statistical analyses were performed using software SPSS version 21 (SPSS IBM).

3. Results

The study included 192 patients. The follow-up period was between 14-81 months, with a median of 31 months. Their median age was 67 years (range: 48 to 87 years). 131 patients (68.2%) were in stage<T2CN0M0, and 61 patients (31.8%) were in stage≥T2CN0M0. 124 patients (64.6%) had a combined Gleason score between 2-7, and 68 patients (35.4%) had a combined Gleason score between 8 and 10. According to the risk group, there were 3.6 % low-risk, 27.1% intermediate-risk, and 69.3% high-risk cases. Clinical T stages were 1% T1a, 17.7% T1b, 21.3% T1c, 21.9% T2a, 6.8 %T2b, 6.3 % T2c, and 25% T3 cases. The median pretreatment PSA was 22.8 ng/mL (range: 1.8 to 455 ng/mL). 53.1% of our patients had initial PSA>20 ng/mL, and 46.9% had initial PSA≤20 ng/mL.

The median cumulative prostate dosage in our series was 64 Gy with a range of 62 to 78 Gy). For subsequent analysis, radiation dosage was grouped into patients who received less than 70 Gy using two-dimensional radiation therapy (74.5%) and those who received 70 Gy or more using three- dimensional radiation therapy (24.5%). 44.3% of our patients were treated with Cobalt 60 and 55.7% were treated with Linac 9MV. Neoadjuvant hormonal therapy, concomitant hormonal therapy and adjuvant hormonal therapy were used in 81 of high-risk patients (60.9%). Biochemical failure was seen in 62 patients (32.3%). The patient and treatment characteristics are shown in Table 1.

Table 1. The patients and treatment characteristics of 192 prostate cancer patients

Characteristic		Value (%)
Age (years)	< 65	73 (38)
	≥ 65	119 (62)
Initial PSA group (ng/mL)	PSA≤20	90 (46.9)
	PSA>20	102 (53.1)
Risk group	Low risk	7 (3.6)
	Intermediate risk	52 (27.1)
	High risk	133 (69.3)
TNM stage	≤T2bN0M0	131 (68.7)
	≥ T2cN0M0	61 (31.3)
Gleason score group	2-7	124 (64.6)
	8-10	68 (35.4)
Radiotherapy dose group	<70 Gy	145 (75.5)
	≥70 Gy	47 (24.5)
Radiotherapy machine	Co60	85 (44.3)
	Linac 9MV	107 (55.7)
Radiotherapy technique	2D	145 (75.5)
	3D	47 (24.5)
Hormonal therapy (in high-risk group)	Yes	153 (79.7)
	No	39 (20.3)
Biochemical failure	Yes	62 (32.3)
	No	130 (67.7)
Total patients		192 (100)

The 5-year biochemical progression-free survival (BFS) for all patients was 65.1%, and 5-year BFS in the low-risk, intermediate-risk and high-risk groups were 100%, 86.5% and 54.9% respectively. According to the Kaplan-Meier analysis and pairwise 5-year BFS log-rank comparisons of low-risk to intermediate-risk p=0.311, low-risk compared to high-risk p=0.170, intermediate-risk compared to high-risk p=0.014, overall 5-year BFS comparisons p=0.018. Multivariate analysis found a significant correlation between 5-year BFS and initial PSA>20 (compared to initial PSA≤20) (p=0.003, HR=4.22, 95% CI=1.31-8.33), Gleason score 8-10 (compared to Gleason score 2-7) (p=0.032, HR=2.04, 95% CI=2.32-3.11), high-risk group (compared to intermediate-risk group) (p=0.014, HR=7.25, 95% CI=1.22-14.17), TNM stage≥T2cN0M0 (compared to TNM stage≤T2bN0M0) (p=0.001, HR=8.45, 95% CI=3.25-

17.55), radiotherapy dose<70 Gy (compared to radiotherapy dose≥70 Gy) (p=0.035, HR=3.22, 95% CI=1.24 - 5.35), Radiotherapy with 2D technique (compared to radiotherapy with 3D technique) (p=0.035, HR=3.22, 95% CI=1.24 -5.35), and hormonal therapy in high-risk group (compared to no hormonal therapy) (p=0.022, HR=2.55, 95% CI=1.72-4.04) (Table 2). There was no statistically significant relationship between 5-year BFS and age (p=0.425, HR=1.27, 95% CI=1.17-2.15), and type of radiotherapy machine (p=0.062, HR=1.76, 95% CI=0.52-3.22). The favorable prognostic factors in multivariate analysis were initial PSA≤20, Gleason score 2-7, intermediate-risk group, TNM stage≤T2bN0M0, radiotherapy dose≥70 Gy, radiotherapy with 3D technique and hormonal therapy (in high-risk group). Independent predictor factors for 5-year BFS are shown in Table 2.

Table 2. The 5-year biochemical progression-free survival according to multivariate analysis

Factor	Multivariate analysis	
	HR[a] (95% CI[b])	p-value
Age≥65/Age<65	1.27 (1.17-2.15)	0.425
Initial PSA[c]>20/Initial PSA≤20	4.22 (1.31-8.33)	0.003
High-risk group/Intermediate risk group	7.25 (1.22-14.17)	0.014
Gleason score 8-10/Gleason score 2-7	2.04 (2.32-3.11)	0.032
TNM stage≥T2cN0M0/TNM stage≤T2bN0M0	8.45 (3.25-17.55)	0.001
Radiotherapy dose<70 Gy/Radiotherapy dose≥70 Gy	3.22 (1.24-5.35)	0.035
Radiotherapy machine with Co60/ Radiotherapy machine with Linac[d] 9MV	1.76 (0.52-3.22)	0.062
Radiotherapy with 2D[e] technique/ Radiotherapy with 3D technique	3.22 (1.24-5.35)	0.035
Hormonal therapy/No hormonal therapy (in high-risk group)	2.55 (1.72-4.04)	0.022

[a]HR: hazard ratio; [b]CI: confidence interval; [c]PSA: prostate-specific antigen; [d]Linac: linear accelerator; [e]D: dimensional

4. Discussion

Measurement of total serum PSA has always been identified as one of the strongest predictors of biochemical progression and overall survival for more than twenty years to determine the efficacy of external beam radiation therapy in localized prostate cancer patients (9). It is clear that in the majority of prostate cancer patients, PSA decreases after definitive EBRT, but some prostate cancer patients will have an increasing serum PSA after definitive EBRT that indicates recurrence of the disease (10). Many reports have indicated that there is a clear relationship between the PSA nadir after definitive EBRT and the subsequent disease course (11). For example, Hanks et al. showed that based on information obtained from patients treated with RTOG protocols a level PSA of 1.5 ng/mL was the upper limit of normal (12). Other investigators found that prostate cancer patients with a PSA nadir of less than 1 ng/mL after definitive EBRT experienced favourable 5-year BFS. Independent of initial total serum PSA, combined Gleason grade and T stage, prostate cancer patients who were treated with EBRT with a PSA nadir of less than 1 ng/ml had a better 5-year BFS in multivariate analysis. In the present study the 5-year BFS was 65.1%, which is slightly lower than that in an earlier study of the meta-analysis of five large RTOG trials, which reported a 5-year BFS of 71.9% (13). There were several reasons for this difference: In our study, there were 69.3% of cases in the high-risk group with over 50% of them presented with initial PSA>20 ng/mL that was higher than in well-developed Western countries. More than 70% of our patients received a cumulative radiation dose of less than 70 Gy with 2D technique, while the RTOG trials used radiation doses exceeding 70 Gy that explained the high rate (32.3%) of BF in our study compared to 16.7% in their series. In our study, only 24.5% of patients received a cumulative radiation dose ≥70 Gy with 3D radiotherapy technique, while Zietman et al. conducted a long-term trial that compared the conventional 2D radiotherapy technique with modern radiotherapy techniques such as 3D-CRT and IMRT that can deliver higher doses >72 Gy, a significant decrease of 5-year BFS from 32.4% to 16.7% (14). In the multivariate analysis a few important predictors of 5-year BFS were identified (15). Independent predictors of unfavorable 5-year BFS in our study were initial PSA>20, Gleason score 8-10, high-risk group, TNM stage≥ T2cN0M0, radiotherapy dose<70 Gy, radiotherapy with 2D technique and no hormonal therapy (in high-risk group). There were some limitations in our study. First, our study was a retrospective-analytic study such as all those inherent in a retrospective analysis. Second, the median follow-up period was short (31 months). Third, the number of patients (192 patients) was considered small for accurate analysis of predictive factors.

5. Conclusions

In summary, in this retrospective-analytic study, initial PSA≤20, Gleason score 2-7, intermediate-risk group, TNM stage≤T2bN0M0, radiotherapy dose≥70 Gy, radiotherapy with 3D technique and hormonal therapy (in high-risk

group) were independent favorable prognostic factors for 5-year BFS in multivariate analysis. There was no statistically significant relationship between 5-year BFS and age and type of radiotherapy machine by multivariate analysis. Our seven years' experience of follow-up with PSA showed that PSA was the strongest predictor of biochemical progression survival in patients with prostate cancer who were treated with definitive EBRT.

Acknowledgments:
We thank the residents of radiation oncology, nursing staff, technicians, and physics unit of the Radiotherapy Department at Shohada-e-Tajrish Hospital for their contributions to the treatment and maintenance of our prostate cancer patients' records. We also thank Ms. Mohammadi for her contributions to our collection of data; this project would have been impossible without her.

Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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