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Pride or prejudice: Does Phoenix flatter radiation therapy?

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ABSTRACT

PURPOSE: To compare disease-free survival (DFS) rates using a >0.4 ng/mL biochemical failure definition with the Phoenix (nadir+2 ng/mL) failure definition by analyzing a consecutive cohort of 1006 patients treated with low-dose-rate prostate brachytherapy (LDR-PB) monotherapy.

METHODS AND MATERIALS: Data for first 1006 consecutive LDR-PB implants (1998–2003) were extracted from a prospective database. Patients had low- (58%) or intermediate (42%)-risk disease. Three months neoadjuvant and 3 months concomitant androgen deprivation therapy were used in 65% of cases. The Phoenix definition was modified to "unfail" patients who had a benign prostate-specific antigen (PSA) bounce.

RESULTS: The median followup is 7.5 years. The median PSA at latest followup for disease-free patients was 0.04 ng/mL. The Phoenix definition yielded 5- and 10-year Kaplan–Meier DFS estimates of 96.5 ± 1.2% and 93.7 ± 2.0%, respectively. Applying the >0.4 ng/mL threshold reduced these estimates to 94.4 ± 1.6% and 88.8 ± 3.0% (log rank, $p = 0.015$).

CONCLUSIONS: Compared with Phoenix, applying a >0.4 ng/mL failure definition increased biochemical failure by ~2% at 5 years and ~5% at 10 years. These data show that Phoenix did not greatly exaggerate DFS estimates compared with a surgical-type threshold. However, this observation is a consequence of the exceptionally low residual PSA values characteristic of LDR-PB and cannot be generalized to other forms of radiation therapy.

Keywords: Prostate brachytherapy; Biochemical failure; Phoenix threshold; Biologic equivalent dose; Nadir PSA values

Introduction

Biochemical relapse is a surrogate for disease recurrence, and the Phoenix definition (nadir+2 ng/mL) provides a multiple validated end point that is correlated with diminished overall survival in both intermediate- and high-risk patients (1). However, critics of the Phoenix definition argue that it introduces a systematic bias favoring radiation therapy over radical prostatectomy (RP) by combining a relatively high (nadir+2 ng/mL) threshold with a lack of backdating to the start of an inevitable, but often slow, rise in prostate-specific antigen (PSA) that eventually crosses that threshold. This issue is greatly exacerbated in series with short followup and infrequent follow-up PSA measurements (2, 3).

In contrast to external beam radiation therapy (EBRT), practitioners of low-dose-rate prostate brachytherapy (LDR-PB) sometimes dispense with the Phoenix definition, preferring to report biochemical no evidence of disease results based on a fixed threshold of >0.2 or >0.4 ng/mL attained beyond a suitable posttreatment interval (typically 48–60 months) to define recurrence (4, 5). Because it is known that the risk of triggering the Phoenix threshold in long-term followup is correlated with the PSA level after LDR-PB or EBRT (6, 7), the residual posttreatment PSA value may provide an important independent measure of the relevant biologic effect of therapeutic radiation that is independent of the method of delivery.

In the current analysis, we have followed other authors in applying a PSA threshold (>0.4 ng/mL) to define biochemical recurrence and compared the results with those obtained using the nadir+2 ng/mL (Phoenix) definition.

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Methods

Patient population and treatment protocol

This analysis consists of all LDR-PB patients treated on or before October 23, 2003 ($N = 1006$). The treatment and followup protocol for the identical cohort were described in a recent publication (8). No patients received supplemental EBRT, but 65% received neoadjuvant and concomitant androgen deprivation therapy (ADT) as previously described (8).

Applying the Phoenix definition

The nadir+2 ng/mL threshold defined biochemical relapse. Patients with early rises in PSA that triggered the Phoenix definition were considered benign rises and later ''unfailed'' if subsequent PSA values declined to <0.5 ng/mL without intervention. This modification has been undertaken by several authors previously who feel, as we do, that it is inappropriate to score as a failure, a man whose PSA is near undetectable without additional intervention (9).

Applying the >0.4 ng/mL definition

In addition to the Phoenix definition, we applied a much lower threshold that defined biochemical failure as a PSA >0.4 ng/mL at any time ≥48 months after implant. The ≥48-month caveat exists because, in the first 4 years after implant, 20%–40% of implant recipients experience temporary benign increases in serum PSA; these are false positives and are not predictive of future biochemical relapse (10, 11). At times >48 months, benign fluctuations like these are rare, and the median PSA values converge near the detection limit.

Using the above criteria, biochemical failure using the >0.4 ng/mL threshold was determined as follows: All biochemical failures identified according to the Phoenix definition are, of course, automatically relapses according to the 0.4 ng/mL definition. Records for men that were disease free by the Phoenix definition and with PSA follow-up ≥48 months ($N = 745$) were examined for failure to maintain a PSA at ≤0.4 ng/mL and assigned accordingly. For men with PSA followup <48 months ($N = 212$), the Phoenix definition was used to signal biochemical recurrence. For all patients identified as having relapsed using the >0.4 ng/mL definition, the time to treatment failure was defined as the date of the first PSA value >0.4 ng/mL that was not followed by a decline (without intervention) to <0.4 ng/mL.

Defining disease-free survival

Disease-free survival (DFS) was defined as the absence of biochemical, clinical, histologic, or imaging evidence of recurrent or persistent prostate cancer and not having received any secondary treatment for prostate cancer at any time after the implant.

Statistical analysis

The rates of DFS and their respective 95% confidence intervals were estimated using the Kaplan–Meier (K-M) method. All statistics were done using SPSS (the Statistical Package for Social Sciences version 14.0.4, SPSS, Chicago, IL).

Results

Patient population

The patient's prognostic parameters and dose metrics are summarized in Table 1. As shown, 42% of patients had intermediate-risk disease using the criteria established by the National Comprehensive Cancer Network. Two-thirds of men in the cohort and 92% of the intermediate-risk patients received ADT by protocol (data not shown).

DFS

The K-M DFS outcomes using the nadir+2 ng/mL and the >0.4 ng/mL failure definitions are compared in Table 2 and Fig. 1. Using the 0.4 ng/mL definition increases

Table 1
Clinical characteristics, pretreatment risk factors, and dosimetry

Variable/subgroup	Entire cohort, $N = 1006$	ADT+, $N = 658$	Non-ADT, $N = 348$
Age (y)			
Median	66	67	65
Range	45–82	47–82	45–79
Pretreatment PSA (ng/mL)			
Median	6.4	7.1	5.1
Range	0.3–19	0.44–19	0.3–12
Gleason score			
≤6	766 (76)	419 (63)	347 (99)
7	239 (24)	239 (37)	1 (<1)
Clinical stage			
T1	450 (45)	292 (44)	158 (45)
T2	556 (55)	366 (56)	190 (55)
Risk group			
Low	586 (58)	272 (41)	314 (90)
Intermediate	419 (42)	386 (59)	34 (10)
Percent positive cores			
<50	640 (64)	389 (59)	251 (72)
≥50	269 (27)	195 (30)	78 (22)
Missing	97 (10)	74 (11)	1 (6)
D_{90} (Gy)			
Median	151	148	156
Mean ± SD	151.0 ± 19.0	148.7 ± 19.2	155.4 ± 18.0
V_{100} (%)			
Median	92	92	94
Mean ± SD	91.1 ± 6.1	90.3 ± 6.6	92.6 ± 5.0

ADT = androgen deprivation therapy; PSA = prostate-specific antigen; SD = standard deviation; D_{90} = the minimum dose received by 90% of the postimplant CT–based prostate volume; V_{100} = the percent of the postimplant CT–based prostate volume that receives at least 100% of the prescription dose.

Percentage values are given in parentheses.