Original paper

Time to failure after definitive therapy for prostate cancer: implications for importance of aggressive local treatment

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Abstract

Purpose: To explore patterns of time to failure in men receiving high doses of permanent seed brachytherapy with or without external beam radiation therapy as a function of risk status.

Material and methods: Two thousand two hundred and thirty four patients were treated with prostate brachytherapy with median follow up of 8.0 years. The population was 35% low risk, 49% intermediate risk, and 16% high risk (NCCN). Median day 0 implant D_{90} was 119% and V_{100} was 98%. Treatment failure was defined as PSA > 0.40 ng/mL after nadir. Rates of biochemical failure, distant metastases, and prostate cancer death were determined with non-prostate death as a competing risk.

Results: For all patients, the 10-year biochemical failure, distant metastases, and cause-specific mortality were 4.4%, 1.4%, and 1.3%, respectively. The biochemical failure rates were 1.3%, 4.8%, and 10.0% for men with low, intermediate, and high risk disease, respectively. Median time to failure was 2.8 years. In men who died from prostate cancer, the median time from treatment failure to death was 4.2 years. Overall, 83% of biochemical failures and 97% of metastases occurred within the first 4 years after treatment.

Conclusions: With the dose escalation achieved by high quality brachytherapy dosimetry, even high-risk prostate cancer patients have excellent long term biochemical outcomes. Treatment failures occur early, and one third become metastatic and progress rapidly to prostate cancer death. The low frequency and pattern of failures suggest the presence of micrometastatic disease prior to treatment is rare, even in high risk patients.

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Key words: biochemical survival, brachytherapy dose escalation, cause specific survival, metastases free survival, prostate cancer.

Purpose

There is emerging evidence that time to biochemical failure is a robust prognostic factor for prostate cancer mortality and overall mortality in men receiving definitive radiotherapy [1-3]. Interval to biochemical failure is also highly prognostic for prostate cancer mortality in men undergoing prostatectomy [4]. One cause of early biochemical failure is occult micrometastatic disease present at time of treatment. Regardless of efficacy of local treatment, individuals with occult metastases often have early recurrence with relatively poor prognosis, due to unappreciated stage IV disease at presentation. Early biochemical failure can also occur in men with strictly localized disease, if local therapy is inadequate to provide even short term local control. This can be due to radioresistant local disease, inadequate radiation dose delivered, inadequate surgical margin or deficient radiation targeting.

As with early failures, late failures can be caused either by more gradual progression of slow growing occult metastatic disease or gradual recurrence of partially treated local disease. In modern radiation therapy literature, there continues to be a relatively large number of late failures (> 4 years), even with dose escalation to 78 Gy or over 80 Gy [5,6]. The purpose of this paper is to explore whether further dose escalation would lead to a decrease in late failures. If so, particularly for high risk patients, this might suggest that the preponderance of late failures in recent studies may represent incomplete ability to eradicate local disease rather than high incidence of slow growing occult metastases at presentation.

In this paper, we examine a cohort of men who received high local radiation doses for clinically localized prostate

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cancer. Consistently, high implant D_{90}s with sizeable margins were utilized for all patients, and the majority of intermediate risk and almost all high risk patients received supplemental external beam radiation. Our goal was to explore patterns in time to failure in men receiving high local radiation doses to better understand the role of improved local control and the implications for long term prostate cancer outcomes. We also hope to provide some insight into the question of what portion of patients (particularly high risk patients) are potentially curable, in effect, without viable metastatic disease at presentation.

Material and methods

From March 1995 till July 2010, 2234 consecutive patients underwent definitive permanent interstitial brachytherapy by a single brachytherapist (GSM). All patients were treated more than three years prior to analysis. All biopsy samples were reviewed by a single pathologist (EA) to minimize inconsistencies in pathologic grading. Preplanning technique, intraoperative approach and dosimetric evaluation have been described in detail [7,8]. Categorized by National Comprehensive Cancer Network (NCCN) risk group, the cohort consisted of 785 men with low risk, 1098 with intermediate risk, and 351 men with high risk disease.

Of the 2234 patients, 1111 (50.3%) received supplemental external beam radiotherapy and 748 (33.5%) received androgen deprivation therapy. Supplemental external beam and androgen deprivation was utilized primarily for intermediate and high risk patients. Supplemental external beam was delivered to 69.6% and 96.3% of intermediate and high risk patients, respectively. Androgen deprivation therapy (ADT) was used in 27.4% and 71.8% of intermediate and high risk patients. When employed, supplemental external beam radiotherapy was generally used in a dose of 45-50.4 Gy covering prostate, seminal vesicles, and at-risk pelvic nodes. ADT, when utilized, was initiated 3 months prior to implantation, and consisted of a luteinizing hormone-releasing hormone (LHRH) agonist and an anti-androgen. The range of ADT duration was 3-36 months. Indications for ADT were prostate cytoreduction prior to implant and for men with higher risk disease.

For prostate implants, the target volume (PTV) was the prostate plus a periprostatic margin of 4-5 mm, except posteriorly to limit rectal dose. Median prostate volume was 32.0 cm^3, while the median planning volume was 60.6 cm^3. Also included in the brachytherapy PTV was the proximal 1.0 cm of seminal vesicles.

The primary radionuclide utilized was ^{103}Pd (Theragenics model 200), while the other radionuclide ^{125}I (Amersham model 6711 and its stranded form) was not implanted after 2003. Dosimetry was based on day zero computerized tomography (CT) studies. The overall population mean D_{90} (minimum dose received by 90% of the PTV) was 119.1% of prescription dose. The mean V_{100} for the study population was 96.6% of the PTV. These relatively large D_{90} and V_{100} values have been associated with improved treatment outcomes [9,10].

Biologically effective dose (BED) was calculated using the algorithm recommended by American Association of Physicist in Medicine (AAPM) Task Group 137 to provide consistency in radiobiological comparisons between institutions [11]. This consensus group recommends a uniform set of algorithms and radiobiological indices to facilitate consistency in routine outcome reporting. The Task Group values used in this work were: $\alpha = 0.15\ Gy^{-1}$, $\beta = 0.05\ Gy^{-2}$, $\alpha/\beta = 3.0$ Gy, $T_{pot} = 42$ days, and repair half-life = 16 min.

The brachytherapy BED was based on the day 0 D_{90}, and the total BED added any contribution from external beam radiation.

Patient demographics and treatment details are provided in Table 1, which is stratified by National Comprehensive Cancer Network (NCCN) risk groups. Patients were monitored by physical examination including digital rectal examination, and serum PSA determination at 3 and 6 months intervals. Patient survival was confirmed for all patients not only by PSA reports, but also by frequent quality of life surveys (QoL) (by telephone or occasionally mail) at least 25 times during the first five years following brachytherapy, and never less than twice per year thereafter. The primary outcome measures were time to biochemical failure, time to distant metastases, and time to prostate cancer death. We also assessed percent of men with biochemical failure who ultimately progressed to metastases or prostate cancer death, and the time from biochemical failure to those outcomes. Biochemical failure was defined as PSA > 0.40 ng/mL after nadir [12]. This definition has been shown to be particularly sensitive in detecting treatment failure [12]. Cause of death was determined for each deceased patient. Patients with metastatic prostate cancer or castrate resistant disease without obvious metastases who died of any cause were classified as dead of prostate cancer. All other deaths were attributed to the immediate cause of death. In our population, 40% of deaths were attributable to cardiovascular disease, 33% to non-prostate cancer deaths, 8% to respiratory disease, 4% to prostate cancer, and 15% to other causes.

Continuous clinical and treatment variables were compared across groups, using one-way analysis of variance (ANOVA). Categorical variables were compared using a chi-square analysis. Biochemical survival, metastases free survival, cause specific mortality, and all cause mortality were determined using cumulative incidence and cumulative survival curves. With the population stratified by low, intermediate, and high risk disease, biochemical failure rates were determined by competing risk analysis where non-prostate cancer death was the competitor. Significant predictors for prostate specific, biochemical progression free, and overall survival were first determined by univariate regression analysis, and those variables with $p < 0.010$ were included in multivariate analysis. Competing risk regression was employed for prostate specific and progression free survival analyses. All statistical analyses used Stata version 13.0 software (StataCorp, College Station, TX, USA), and statistical significance was defined a $p < 0.05$.

Results

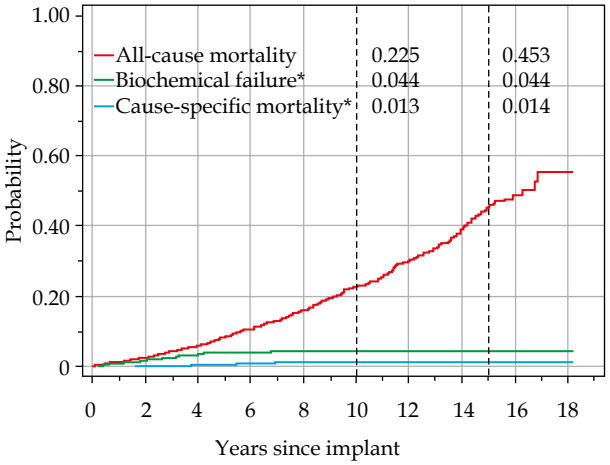
For the population, 10 year overall mortality and competing risk adjusted biochemical failure, and cause-spe-

Table 1. Clinical parameters of the study population, stratified by NCCN risk classification

Continuous variables		Low risk (n = 785)		Intermediate risk (n = 1098)		High risk (n = 351)		p^1	Total (n = 2234)	
		Med. (IQR)	Mean	Med. (IQR)	Mean	Med. (IQR)	Mean		Med. (IQR)	Mean
Age at implant		64 (11)	63.2	66 (10)	65.6	67 (11)	66.4	< 0.001	66 (11)	64.9
Follow-up (years)		8.0 (5.7)	8.4	8.2 (5.7)	8.5	7.6 (6.0)	8.1	0.280	8.0 (5.8)	8.4
PSA (ng/mL)		5.5 (2.2)	5.6	6.6 (4.5)	7.6	9.6 (14.4)	14.0	< 0.001	6.2 (3.9)	7.9
Gleason score		6.0 (0)	5.9	7.0 (0)	6.9	8.0 (1)	8.1	< 0.001	7.0 (1)	6.7
Percent positive biopsies		16.7 (20.8)	23.6	34.6 (27.8)	41.2	50.0 (38.1)	53.2	< 0.001	33.3 (33.3)	36.9
BMI (kg/m^2)		27.7 (5.2)	28.2	27.7 (5.5)	28.5	28.0 (5.4)	28.9	0.064	27.8 (5.4)	28.4
Prostate volume (cm^3)		34.0 (10.1)	34.5	31.9 (11.8)	32.4	26.4 (14.8)	28.2	< 0.001	32.0 (11.8)	32.5
Planning volume (cm^3)		63.4 (15.2)	63.7	60.4 (17.5)	60.2	52.0 (20.0)	53.8	< 0.001	60.6 (17.5)	60.4
V_{100} (% volume)		97.8 (3.3)	96.4	98.0 (3.1)	96.6	98.2 (3.1)	96.9	0.165	97.9 (3.2)	96.6
V_{150} (% volume)		69.3 (13.1)	66.6	71.4 (12.9)	68.7	73.2 (13.4)	70.4	< 0.001	71.0 (13.5)	68.2
V_{200} (% volume)		38.6 (13.6)	36.8	41.3 (12.8)	39.7	43.6 (12.7)	41.8	< 0.001	40.8 (13.3)	39.0
D_{90} (% prescribed dose)		118.0 (14.3)	117.6	119.5 (15.8)	119.5	121.2 (18.0)	121.1	< 0.001	119.2 (15.6)	119.1
Brachytherapy BED (Gy)		132.4 (20.1)	132.1	118.6 (36.5)	115.8	94.3 (20.6)	97.0	< 0.001	122.6 (36.6)	118.6
Total BED (Gy)		133.1 (20.3)	133.7	156.9 (27.0)	154.1	163.5 (17.6)	162.5	< 0.001	149.2 (31.5)	148.2
Most Recent PSA[§]		< 0.02 (0.02)	0.03	< 0.02 (0.02)	0.03	< 0.02 (0.01)	0.02	0.059	< 0.02 (0.01)	0.03
Categorical variables		**Count**	**(%)**	**Count**	**(%)**	**Count**	**(%)**	**p***	**Count**	**(%)**
Clinical stage:	T1b-T2a	785	(100)	942	(85.8)	235	(67.0)	< 0.001	1961	(87.8)
	T2b-T3c	0	(0.0)	156	(14.2)	116	(33.0)		273	(12.2)
Isotope:	^{103}Pd	604	(76.9)	1016	(92.5)	339	(96.6)	< 0.001	1959	(87.7)
	^{125}I	181	(23.1)	82	(7.5)	12	(3.4)		275	(12.3)
ADT:	None	590	(75.2)	797	(72.6)	99	(28.2)	< 0.001	1486	(66.5)
	≤ 6 months	187	(23.8)	207	(18.8)	49	(14.0)		443	(19.8)
	> 6 months	8	(1.0)	94	(8.6)	203	(57.8)		305	(13.7)
XRT:	No	764	(97.3)	334	(30.4)	13	(3.7)	< 0.001	1111	(49.7)
	Yes	21	(2.7)	764	(69.6)	338	(96.3)		1123	(50.3)
Hypertension:	No	410	(52.2)	543	(49.5)	156	(44.4)	0.052	1109	(49.6)
	Yes	375	(47.8)	555	(50.5)	195	(55.6)		1125	(50.4)
Diabetes:	No	711	(90.6)	958	(87.2)	305	(86.9)	0.055	1974	(88.4)
	Yes	74	(9.4)	140	(12.8)	46	(13.1)		260	(111.6)
Cardiovascular disease:	No	675	(86.0)	906	(82.5)	283	(80.6)	0.041	1864	(83.4)
	Yes	110	(14.0)	192	(17.5)	68	(19.4)		370	(16.6)
Testosterone[†]:	Lower tertile	352	(68.4)	473	(68.0)	144	(65.4)	0.425	969	(67.7)
	Middle tertile	130	(25.2)	160	(23.0)	56	(25.5)		346	(24.2)
	Upper tertile	33	(6.4)	63	(9.0)	20	(9.1)		116	(8.1)
Perineural invasion:	No	720	(91.7)	654	(59.6)	172	(49.0)	< 0.001	1546	(69.2)
	Yes	65	(8.3)	444	(40.4)	179	(51.0)		688	(30.8)

[1] *One-Way ANOVA*
[§] *PSA values only for non-biochemical failures, n = 2131*
* χ^2
[†] *Based on 1431 with testosterone values*
NCCN – National Comprehensive Cancer Network, IQR – inter quartile range, PSA – prostate specific antigen, BMI – body mass index, BED – biologically effective dose based on brachytherapy day zero D_{90} ± any external beam, ADT – androgen deprivation therapy, XRT – external beam radiation therapy

cific mortality were 22.5%, 4.4%, and 1.3%, respectively (Fig. 1). No metastases developed after 5 years, and the cumulative incidence of distant metastases at 5 years and beyond was 1.4%. The cumulative ten year competing risk adjusted biochemical failure rate for men with low, intermediate, and high risk disease was 1.3%, 4.8%, and 10.0%, respectively (Fig. 2). The median time to failure (TTF) was 2.8 years.



Cumulative incidence with non-prostate specific death as a competing risk

Fig. 1. Probabilities for all-cause mortality, biochemical failure, and cause-specific mortality are summarized at 10 years and 15 years post implant for the 2,234 patients in the population

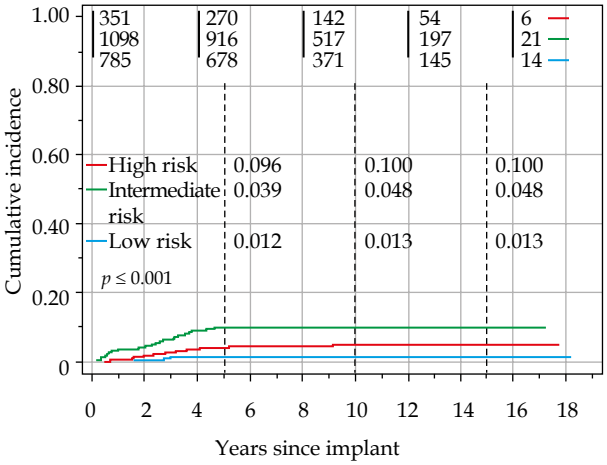


Fig. 2. Cumulative incidence of biochemical failure with non-prostate death as a competing risk, stratified by NCCN risk group, is summarized at 5, 10, and 15 years post implant. The number of patients remaining at risk in four year increments is listed at the top, stratified by risk group

Because completeness of follow up influences the validity of survival curves, Table 2 lists mean days since last contact of living patients for mortality and days since last PSA for biochemical failure. The mean elapsed days since last patient contact (64 ± 117 days), and last PSA (123 ± 164 days) were considerably greater than the medians (50 days and 99 days, respectively) because of a few outliers. For survival status, only 11 of 1713 living patients had not been contacted in the year preceding database closure. Nine of the eleven had either advanced dementia or were dying from a disease other than prostate cancer, and the patient or caregiver felt that further follow up and PSA testing were pointless. For biochemical survival follow up, PSA testing was more than one year delinquent in 57 of 1664 living, non-failed men. The most common reason for non-compliance was the inconvenience and expense of testing, followed by perceived futility among those dying from non-prostate causes.

There was no biochemical failure in any of the 745 patients followed for more than 9.2 years, out to the maximum PSA follow up of 18.2 years. The median TTF among the biochemical failures was 2.6 years, and there was no significant difference between risk groups (p = 0.077) where the mean TTF for low, intermediate, and high risk

Table 2. Time dependent outcomes stratified by NCCN risk group

Continuous variables	Low risk		Intermediate risk		High risk		p^1	Total	
	Med. (IQR)	*n*	Med. (IQR)	*n*	Med. (IQR)	*n*		Med. (IQR)	*n*
Age at death (years)	76.6 (10.7)	142	77.2 (8.4)	270	77.4 (7.3)	109	0.044	77.1 (8.7)	521
Years: implant to all-cause death	6.0 (6.3)	142	7.0 (4.3)	270	6.9 (6.5)	109	0.271	6.7 (5.7)	521
Years: implant to prostate death	4.3 (0)	1	7.3 (2.6)	9	5.7 (3.5)	12	0.141	6.5 (3.0)	22
Years: implant to metastases	3.3 (1.1)	2	2.3 (1.6)	11	1.9 (1.9)	17	0.278	2.3 (2.0)	30
Years: failure to prostate death	1.6 (0)	1	5.0 (3.3)	9	3.1 (3.0)	12	0.076	4.2 (3.8)	22
Years to biochemical failure	2.2 (1.9)	10	2.7 (2.1)	48	2.4 (2.5)	34	0.077	2.6 (2.0)	92
Days since last contact*	50 (62)	643	50 (62)	828	50 (63)	242	0.833	50 (62)	1713
Days since last PSA§	99 (95)	636	98.5 (96)	800	106 (109)	228	0.547	99 (99)	1664

[1]*One-Way ANOVA*
**Elapsed days from last patient contact to database closure on 25 Jul 2013 for all living patients (11 of 1713 living patients had not been contacted in the year prior to database closure)*
§*Elapsed days from last PSA to database closure on 25 Jul 2013 for all living, non-biochemical failures (57 of 1664 patients had not had a PSA determination in the year prior to database closure)*
NCCN – National Comprehensive Cancer Network, SD – standard deviation, PSA – prostate specific antigen

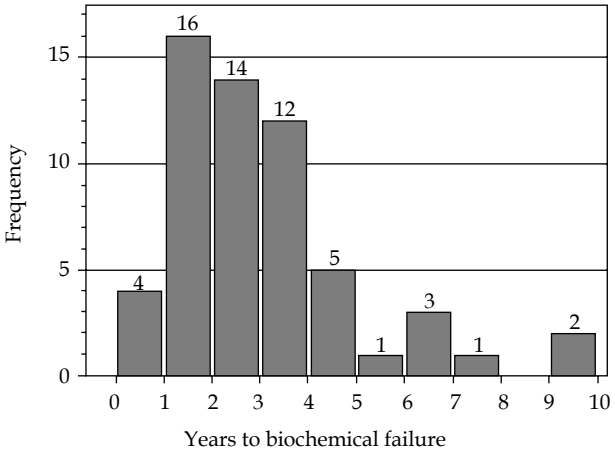


Fig. 3. Time to failure histogram for the 58 biochemical failures in low and intermediate risk patients

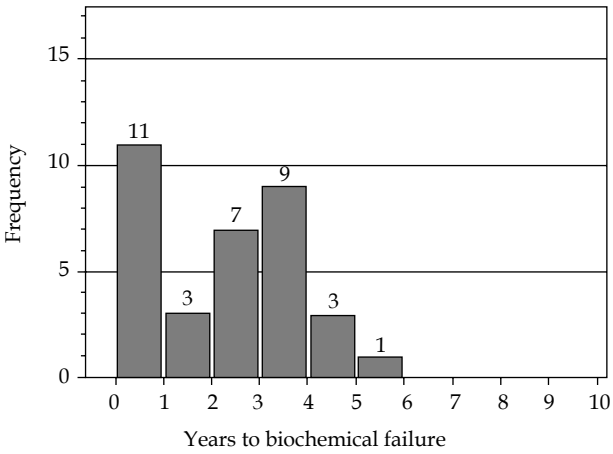


Fig. 4. Time to failure histogram for the 34 biochemical failures in high-risk patients

men was 2.5 ± 1.8, 3.2 ± 2.0, and 2.3 ± 1.5 years, respectively. Overall, 82.6% of biochemical failures occurred within the first four years after treatment. In men with low and intermediate risk disease (Fig. 3), 79.3% of biochemical failures occurred within the first four years, compared to 88.2% of failures in men with high risk disease (Fig. 4).

In men who died from prostate cancer, the median time from treatment failure to death was 4.2 years. Median time from treatment to development of metastases was 2.3 years. Overall, 96.7% of metastases occurred within the first 4 years.

Table 3 consists of univariate and multivariate analyses of cause-specific, biochemical progression free, and overall survival. Of the eight variables identified as significant predictors of biochemical progression free survival, six of them – PSA, Gleason score, clinical stage, percent positive biopsies, and ADT duration are strongly correlated with NCCN risk grouping. For overall survival, only two of the 15 variables included in the multivariate analysis were significant predictors: age at implant and tobacco use.

Discussion

Early failure after definitive prostate cancer treatment was significantly more common in the 1990s when lower radiation doses were employed. As an example, in the D'Amico *et al*. landmark 1998 paper comparing biochemical outcomes between prostatectomy, surgery and brachytherapy [13], the authors report on high risk men treated with 66 Gy of radiotherapy without ADT. Over 50% of men had failed therapy before 3 years. Likewise, Kestin *et al*. [14] reported in 1999 on William Beaumont patients, primarily Gleason ≤ 7, treated to a median dose of 66.6 Gy. They found a median time to failure of less than two years, with a failure rate approximating 50% at three years and relatively few failures after that time. These high rates of early local failure were likely due to both the more advanced disease common during that era, and to the inadequacy of 66 Gy to reliably eradicate local disease.

The increase in radiotherapy dose to 70 Gy with and without the addition of androgen deprivation, led to a decrease in early failures. In the milestone EORTC trial published by Bolla *et al*. [15], which demonstrated the survival advantage of androgen deprivation combined with 70 Gy radiotherapy, biochemical failures were relatively uncommon in either arm in the first three years. However, ultimate biochemical failure rates were high, with the significant majority of treatment failures occurring in the fourth year and later. At 3 years, biochemical failure was approximately 15-20% in both arms. However, by year 8, failure rates were approximately 50% in the ADT arm and 80% in the radiotherapy only arm.

As radiation doses have been increased, the overall rate of treatment failure has decreased, though the proportion of late treatment failures remains high. The M.D. Anderson dose escalation trial reported by Kuban *et al*. [5], compared men receiving 70 Gy to those receiving 78 Gy. With dose escalation, early treatment failures were uncommon; the overall number of treatment failures decreased; and the number of late failures decreased. However, the significant majority of treatment failures continued to occur after four years. The PROG dose escalation study [16] has shown similar results, with the significant majority of low and intermediate risk failures occurring in the fourth year or later in the high dose arm. Recently, Zelefsky *et al*. [6] reported on their prospective dose escalation, comparing men treated to < 81 Gy, with those treated up to 86.4 Gy. They found a modest decrease in treatment failures within the first four years, with a more prominent decrease in later failures. Nonetheless, even at doses > 81 Gy, the vast majority of failures occurred after four years, whether or not androgen deprivation was used. And overall treatment failure at ten years remained high at approximately 25% for intermediate risk patients and 45% for high risk patients. In high risk patients, the combination of moderate dose external beam radiation therapy, a brachytherapy boost and ADT decreases biochemical failure and prostate cancer deaths, when compared to patients treated with external beam and ADT [17].

These findings demonstrate that some early failures and many late failures can be eliminated with dose escalation to approximately 80 Gy, presumably because many of the failures at lower doses were related to inadequate

Table 3. Univariate and multivariate analysis of cause-specific, biochemical progression free, and overall survival in the study population of 2234 patients

Variable	Survival											
	Prostate-specific^{CR} (n = 22 PS deaths)				Biochemical progression free^{CR} (n = 92 failures)				Overall* (n = 521 deaths)			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	p	HR	p	HR	p	HR	p	HR	p	HR	p	HR
Age at implant	0.721				0.795				< 0.001	1.096	< 0.001	1.121
PSA	< 0.001	1.044	0.072		< 0.001	1.053	< 0.001	1.063	0.081	1.011	0.307	
Gleason score	< 0.001	3.015	< 0.001	3.405	< 0.001	1.863	< 0.001	2.016	< 0.001	1.229	0.355	
Clinical stage	< 0.001	1.981	0.215		< 0.001	1.792	0.003	1.370	< 0.001	1.167	0.092	
Percent positive biopsy	< 0.001	1.031	0.281		< 0.001	1.027	< 0.001	1.017	< 0.001	1.006	0.278	
Perineural invasion	0.050	2.309	0.985		< 0.001	2.180	0.453		0.085	1.176	0.307	
BMI	0.960				0.631				0.031	0.977	0.545	
Prostate volume	0.271				0.099	1.018	0.002	1.035	0.974			
V_{100}	0.697				0.076	0.975	0.882		0.640			
Brachytherapy BED	< 0.001	0.971	0.550		< 0.001	0.983	0.611		0.094	0.997	0.082	
Total BED	0.072	1.022	0.822		0.025	1.013	0.911		0.282			
ADT duration	0.002	1.055	0.056		0.016	1.030	< 0.001	0.926	0.050	1.012	0.534	
XRT (yes vs. no)	0.004	5.938	0.737		< 0.001	2.539	0.753		0.037	1.198	0.730	
Hypertension	0.003	0.163	0.010	0.181	0.388				0.034	1.205	0.860	
Hypercholesterolemia	0.045	0.224	0.353		< 0.001	0.355	0.043	0.544	0.655			
Diabetes	0.325				0.816				< 0.001	1.577	0.370	
Coronary artery disease	< 0.001	$7*10^{-20}$	< 0.001	$2*10^{-7}$	0.006	0.284	0.009	0.292	< 0.001	1.797	0.111	
Testosterone	0.158				0.808				0.059	1.115	0.347	
Tobacco (never vs. former vs. current)	0.796				0.501				< 0.001	1.497	< 0.001	1.952

^{CR} – competing risk regression
** – Cox regression*
HR – hazard ratio, PSA – prostate specific antigen, BMI – body mass index, BED – biologically effective dose, ADT – androgen deprivation therapy, XRT – external beam radiation therapy

local disease control. However, the preponderance of late failures even at dose levels of 78-86 Gy, leaves open the question as to whether men in those studies had occult metastases at presentation or were potentially curable with even further dose escalation.

With mean and median brachytherapy day 0 implant D_{90}s of 119%, generous margins with the prostate volume expanded by a factor of 1.9 to the planning volume, and extensive use of supplemental external beam radiotherapy, the patients in our implant population received relatively high dose escalation. Using the AAPM radiobiological formalism [11], 86.4 Gy of prostate external beam radiation has a BED of 131 Gy, while the mean total BED for our population ranged from 133 Gy for low risk men to 157 Gy, and 164 Gy in intermediate and high risk men, respectively (Table 1).

In patients with positive biopsies at the prostate base treated with brachytherapy monotherapy at M.D. Anderson, the 10-year biochemical progression free survival as 93.5%, and all failures occurred prior to 6 years [18]. A much larger population in a recent report by Morris *et al*. [19] on brachytherapy monotherapy in low and intermediate risk patients with median and maximum follow up of 7.5 years, and 13 years had 16% of failures occurring at < 3 years and 10% > 8 years. Using only ^{125}I seeds, their mean D_{90} was 151 Gy which translates to an AAPM BED of 116 Gy. In our low to intermediate risk cohort, 58.6% (34/58) of failures were within 3 years, while only 2 patients failed after 8 years.

Our rate of early treatment failures is roughly similar to the rates in the more recent external beam dose escalation studies. However, the rate of late treatment failures is much lower in our series than in those studies. The recent dose escalated external beam series have a high proportion of treatment failures five or more years after treatment; whereas 91% (84/92) of treatment failures in our series occurred within the first 5 years. This supports the hypothesis that in modern cohorts, even among men with high risk disease, the number of men who experience early failures and are "incurable" due to presence of occult metastases prior to treatment is quite small. As well, it would appear that most late treatment failures in current dose escalated external beam series are not the result of untreated

occult metastases; but more likely due to inadequate dose escalation. We view this optimistically, that with current combined modality dose escalation techniques, outcomes for high risk and intermediate risk patients can be significantly improved through a reduction of late failures. This builds on a line of reasoning dating back to Fuks *et al*. [20] in 1991, who found that even in men undergoing retropubic brachytherapy implants, durable local control led to a substantial reduction in development of metastases.

Limitations

The strengths of this work are that low, intermediate and high risk patients were treated with a consistent implant philosophy and pattern of dose escalation, that the dose escalation parameters were well documented, and that no patients were lost to follow up. In general, lower risk patients received high quality brachytherapy-alone with day 0 D_{90}s of approximately 120%. Higher risk patients received supplemental external beam radiotherapy, followed by equally high quality implants with day 0 D_{90}s of approximately 120%. One limitation is that this study was not a randomized trial comparing TTF between dose escalated brachytherapy with and without external beam radiotherapy versus dose escalated external beam radiotherapy alone. In addition, although the premise that early biochemical failures are due to subclinical distant metastases at diagnosis, this remains unproven due to the inability of current radiographic technologies to identify such early metastatic disease. Nevertheless, based on the results above, we feel comfortable with the conclusion that there is a low burden of micro-metastatic disease at presentation in modern day patient cohorts similar to ours; and that effective dose escalation with brachytherapy can lead to very successful treatment outcomes.

Conclusions

Aggressive radiation dose escalation provided by brachytherapy for men with low, intermediate, and high risk disease leads to low levels of late treatment failures. This supports the hypothesis that the great majority of prostate cancer patients, even those with high risk disease are without micro-metastatic disease on presentation, and therefore are potentially curable with adequate dose escalation.

Disclosure

Authors report no conflict of interest.

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