PSA Response After Short-Term Hormonal Therapy Plus External Beam Radiotherapy and Outcome in Patients Treated on RTOG 9413

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Abstract

Purpose—Assess the impact of PSA-complete response (PSA-CR), measured at the end of external beam radiotherapy (EBRT) and short-term hormonal therapy (STHT), on treatment outcomes.

Design—The Phase III RTOG-9413 trial had as part of its original protocol the assessment of PSA-CR, i.e. PSA 0.3ng/ml, at the end of STHT as a secondary endpoint. STHT consisted of flutamide plus an LHRH-agonist for 4 months. Kaplan-Meier method was used to estimate overall survival (OS) and disease-free survival (DFS). Cumulative incidence was used to estimate biochemical failure (BF), distant metastasis (DM), and disease-specific survival (DSS). Univariate and multivariate analyses were performed to correlate PSA-CR after STHT with all endpoints, and the following variables were considered for analysis: PSA at baseline, Gleason score, treatment arm, age, and baseline testosterone. Phoenix-consensus was used to define PSA failure.

Results—For 1070 evaluable patients, the median PSA at the end of STHT was 0.2ng/mL. A total of 744 patients (70%) had PSA-CR. With median follow-up of 7.2 years, failure to obtain PSA-CR was significantly associated with worse DSS (p=0.0003; hazard ratio, 2.03[95%CI, 1.38–2.97]) and DFS (p=0.003; 1.28[1.09–1.50]), as well as with a higher incidence of DM (p=0.0002; 1.92[1.37–2.69]) and BF (p<0.0001; 1.57[1.29–1.91]). The other factors associated with worse DSS were Gleason score 8–10 (p=0.0002; 3.06[1.71–5.47]) and PSA>20ng/mL (p=0.04; 1.55[1.02–2.30]).

Conclusion—Failure to obtain a post STHT and EBRT PSA-CR (0.3ng/mL) appears to be an independent predictor of unfavorable outcomes, and may help identify patients who could benefit from the addition of long-term androgen ablation.

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INTRODUCTION

Androgen deprivation therapy (ADT) in combination with radiation therapy is frequently used in the treatment of patients with locally advanced prostate cancer[1]. ADT duration is usually predetermined based on tumor characteristics, mainly Gleason score, baseline prostatic specific antigen (PSA) and T stage (TNM staging system), on physicians' experience and also patients' characteristics (age, co-morbidities, life expectancy). Optimal ADT duration is unknown and patients are treated based on knowledge learned from clinical trials, most demonstrating that longer treatment duration for higher risk disease provides better treatment outcomes. ADT, however, is not innocuous and is associated with side effects in both the short- and long-term[2]. Therefore, the ideal balance between oncologic need and normal physiologic tolerance must be evaluated on an individual basis.

PSA and its various constructs, such as PSA doubling time, free PSA, PSA density, PSA nadir, time to PSA nadir, among others, are tools used for screening and post-treatment follow-up of prostate cancer, independent of the therapeutic option chosen[3,4]. However, most measurements of treatment efficacy are performed retrospectively and based on consecutive PSA measurements, not allowing for prospective interventions during treatment and, consequently, treatment individualization.

RTOG 9413[5] was a phase III randomized controlled trial that tested 2 different hypotheses in men with localized prostate cancer. First, whether total androgen suppression (TAS) plus whole pelvic radiation therapy improves outcomes when compared to TAS plus prostate only radiation therapy, and second, if neoadjuvant and concurrent TAS plus radiation therapy improves outcomes compared to adjuvant TAS plus radiation therapy. The original study protocol[6] had in its design a planned assessment of "PSA complete response" (PSA-CR), i.e. PSA 0.3 ng/mL, at the discontinuation of hormonal therapy, to measure treatment efficacy. For this specific purposed, the protocol required a blood test with serum PSA for all patients at completion of hormonal therapy. This information was acquired prospectively for patients enrolled in this trial. The objective of this study is to investigate the correlation between PSA 0.3 ng/mL with treatment outcomes considered as endpoints on RTOG 9413 study. The hypothesis of this analysis is that patients with PSA-CR at the end of hormonal therapy will have better treatment outcomes than those with a PSA nadir higher than 0.3 ng/mL at the same time point.

PATIENTS AND METHODS

RTOG 9413 trial accrued men with histologically confirmed adenocarcinoma of the prostate, who had an estimated risk of lymph node involvement higher than 15% but with negative nodes, and PSA 100 ng/ml. A total of 1279 patients were enrolled and treated between April, 1995 and June, 1999 and were randomized to one of four arms, receiving prostate only radiation therapy (PORT) or whole pelvis radiation therapy (WPRT), which was followed by a boost to the prostate only, in combination with neoadjuvant and concomitant hormonal therapy (NCHT) or adjuvant hormonal therapy (AHT). All patients were planned to receive a total dose of 70.2 Gy in 39 fractions, with the difference that patients receiving WPRT were treated with 2 plans, one for the whole pelvis to 50.4 Gy and a second to the prostate only reaching the total dose, while patients receiving PORT were treated with a single plan to the prostate and seminal vesicles. In regards to HT, all patients received total androgen suppression (TAS) for a total period of 4 months, which consisted of monthly leuprolide acetate 7.5 mg intramuscularly or goserelin acetate 3.6 mg subcutaneously, and fflutamide 250 mg tid orally. Patients receiving NCHT received their first LHRH-agonist injection 2 months before RT and continued HT for the duration of RT, while those receiving AHT were started on HT immediately after completion of RT.

Patients eligible for the current analysis were those treated on the RTOG 9413 protocol that had available baseline testosterone, end of hormonal therapy date and PSA data at the end of hormonal therapy, defined as a PSA evaluation done within 120 days following the completion of hormone therapy. Outcome parameters assessed on this study were biochemical failure (BF), local progression (LP), distant metastasis (DM), disease-free survival (DFS), disease specific survival (DSS) and overall survival (OS). RTOG-ASTRO Phoenix consensus definition[7] was used to characterize biochemical failure.

For endpoints OS and DFS, the Kaplan-Meier method[8] was used to estimate yearly survival rates. For all other endpoints BF, LP, DM and DSS, the cumulative incidence approach was used to estimate yearly incidence rates[9] and Gray's test[10] was used to test for differences. Univariate analysis was performed to correlate PSA-CR (PSA 0.3 ng/ml) after TAS with all endpoints, and the following variables were considered for multivariate analysis: PSA at baseline, Gleason score, treatment arm, age, and baseline testosterone. The Cox proportional hazards regression model[11] was used for univariate and multivariate analyses.

RESULTS

A total of 1279 patients were enrolled in the RTOG 9413 protocol, of which 1070 patients were eligible for the current study. Reasons for exclusion included a combination of absence of baseline testosterone (n=82), no end of hormonal therapy date (n=44) or no PSA data at the end of hormonal therapy (n=144). Patients' characteristics are summarized on Table 1. A balance in pre-treatment characteristics, including age, baseline PSA, T stage, Gleason score, baseline testosterone, between the 4 treatment arms is noticed after the exclusion of 209 patients non-eligible for the present study. Median PSA at the end of hormonal therapy for all patients was 0.2 ng/mL (range: 0 - 96.2). A total of 744 patients (70%) reached a PSA-CR at the end of hormonal therapy. The time to reach PSA nadir was 3.7 months, ranging from 0.8 to 8.2 months. With a median follow-up of 7.2 years, higher rates of BF (56% vs. 38%), LP (15% vs. 10%), DM (20% vs. 10%) and worse DFS (28% vs. 40%), DSS (85% vs. 93%) and OS (67% vs. 69%) were observed in those 326 patients who failed to achieve PSA-CR. Univariate analysis showed that 7-year BF, DFS, DM and DSS rates were statistically significant better for patients with end of HT PSA 0.3 ng/mL, while LP and OS rates were, not statistically significant between both groups (Table 2).

On multivariate analysis, shown on Table 3, failure to reach a PSA-CR at the end of ADT was an independent predictor for prediction of BF, DFS, DM and DSS. Other factors significantly and independently associated with worse DSS were baseline PSA > 20 ng/mL and Gleason score 8–10. The only factor associated with poorer OS was baseline PSA >20 ng/mL.

Assessing separately the 326 patients (30.4%) who failed to reach PSA-CR at the end of HT, it was observed that a total of 169 patients presented PSA-CR at a later time ("late responders"), while the remaining 157 patients *never* reached PSA nadir below 0.3 ng/mL ("non-responders"). The median time to reach PSA 0.3 ng/mL for late complete responders was 7.2 months. When late responders are compared to non-responders, significant lower DM (p=0.02) and better DSS (p= 0.002) and OS (p=0.0001) were observed in patients with "late" PSA-CR. However, when late responders are compared to those patients who achieved PSA-CR at the end of HT, early complete response confers significantly lower BF (p<0.0001) and higher DFS (p=0.002).

On a post-hoc analysis of all patients who reached PSA-CR 0.3 ng/dL, independent of time to response, univariate analysis showed that 7-year BF, DFS, DM, DSS and now OS rates were statistically significant better for patients with end of HT PSA 0.3 ng/mL.

During the follow-up period a total of 357 patients died, being 104 patients due to prostate cancer. Among them, 55 patients (53%) achieved PSA-CR at the end of HT. Among the 253 patients who died due to other causes and 712 patients who remain alive, PSA-CR at the end of HT was noticed in 75% and 70% of patients, respectively. In an attempt to identify a PSA value at the end of hormone therapy that would predict risk of death, regression analysis showed that PSA value above 1.0 ng/mL might be associated with worse overall and cause specific survival. For 103 patients, multivariate analysis showed that PSA 1.0 ng/mL at the end of HT (p<0.0001), PSA at baseline higher than 20 ng/mL (p=0.02) and Gleason score 8 or higher (p=0.0001) were associated with worse DSS, while PSA 1.0 ng/mL at the end of HT (p=0.0008), baseline PSA (p=0.04) and age (p<0.0001) were associated with worse OS.

DISCUSSION

Phase III trials including intermediate- and high-risk prostate cancer patients treated with EBRT combined with ADT have demonstrated lower rates of distant metastasis, with improved biochemical control, cause specific survival and overall survival[12–15]. Although optimal duration of hormonal therapy is constantly under investigation in clinical trials, ADT for 28 to 36 months is generally accepted as standard for patients with high-risk prostate cancer[14,15]. Given the significant morbidity with 2–3 years of ADT, it is of interest to determine if the same beneficial effect can be observed with shorter courses of ADT and which patient population would benefit from this potential shortening, given that high-risk prostate cancer is a broad group of cancers classed under the same risk stratification that may possibly need different treatment approaches, such as duration of hormonal therapy.

Many prognostic and predictive factors have been evaluated for disease control and survival after initial therapy for prostate cancer, including initial PSA and Gleason score[16], time to undetectable PSA[17], PSA nadir at specific time points[18–20] among others, but none has been tested by means of a clinical trial and translated to clinical practice. Currently, patients with prostate cancer have the duration of ADT pre-determined and based exclusively on baseline tumor characteristics, instead of individual responses to therapy. There are no means to differentiate patients who require shorter duration ADT from those who need longer periods of ADT, nor identify patients who have a higher chance to die from prostate cancer and could possibly benefit from more aggressive therapy.

A Canadian multicenter randomized trial designed to compare the effectiveness of two durations of neoadjuvant ADT before EBRT, 353 patients with prostate cancer of any risk group were randomized to receive 3- or 8-month ADT between 1995 and 2001[21]. At a median follow-up of 6.4 years, there was no significant difference in BF, DSS and OS between the study groups. On a post-hoc analysis[22], it was suggested that biochemical response measured at the end of ADT is more important than ADT duration before EBRT, when comparing patients whose PSA reached levels 0.1 ng/dL versus those who did not reach that level. For the entire cohort, biochemical response to levels 0.1 ng/dL was associated with a lower incidence of BF at 8 years; however, it failed to predict DSS or OS in any of the analysis performed for the entire cohort or subgroups; this is likely to be related to the relative short follow-up of this lower-risk prostate cancer population, and the small number of cancer-related deaths in this group of patients. Another possible contributing factor for the lack of predictive power is the threshold value (0.1 ng/dL) chosen for this post-hoc analysis.

Recently D'Amico et al.[23] used the Prentice criteria to demonstrate that PSA level higher than 0.5 ng/mL after 6 months of ADT and EBRT, and PSA nadir higher than 0.5 ng/mL, were surrogate endpoints for prostate cancer-specific mortality. This study was performed in a group of patients with intermediate- and high-risk prostate cancer from two different

clinical trials: the Dana Farber Cancer Institute, which randomized 206 patients to EBRT alone (70 Gy in 1.8 - 2.0 Gy fractions) or EBRT plus 6 months of ADT (EBRT during months 3 and 4 of ADT); and the Trans-Tasman Radiation Oncology Group Trial 96.01, in which 818 patients were randomized between EBRT alone (66 Gy in 2.0 Gy fractions), EBRT plus 3 months of ADT, or EBRT plus 6 months of ADT (ADT starting 2 months before EBRT in both arms). However, the group receiving 3 months of ADT in the TROG 96.01 trial was not included in the analysis, and a total of 734 patients were assessed: 371 patients treated with EBRT alone and 363 trated with EBRT plus ADT, and were followed for 8.2 years (median). This retrospective analysis shows results that are similar to ours, on a mixed group of patients with prostate cancer and adequate follow-up, but using a smaller number of patients enrolled in two different trials, and a higher PSA cutpoint.

In conclusion, failure to obtain PSA-CR of 0.3 ng/mL after short-term hormonal therapy and external beam radiotherapy appears to be an independent predictor of unfavorable outcomes. In an attempt to individualize therapy based on specific tumor needs, this hypothesis generating study suggests that complete responders (i.e., patients with a PSA 0.3 ng/dL after short-course ADT and EBRT) could stop ADT earlier than the usually recommended 2–3 years. Such important change in current practice must be investigated on a clinical trial.

Acknowledgments

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TABLE 1

Patients' characteristics.

	Hormones + RT Whole Pelvis+Boost(n=280)		Hormones + RT Prostate Alone(n=269)		RT Whole Pelvis+Boost + Hormones(n=260)		RT Prostate Alone + Hormones(n=261)	
Age (year)								
Median	70		70		70		70	
Range	46–83		44–87		50–84		45–85	
PSA (ng/mL)								
Median	23.1		22.9		22.1		23.9	
Range	2.9–97.6		4.1–95.1		3.0–98.0		4.1–98.2	
	n	%	n	%	n	%	n	%
T-Stage								
T1c,T2a	66	24	68	25	52	20	56	21
T1b,T2b	29	10	30	11	20	8	33	13
T2c-T4	185	66	171	64	188	72	172	66
Baseline PSA								
<30	190	68	183	68	169	65	179	69
30	90	32	86	32	91	35	82	31
20	116	41	116	43	113	43	111	43
>20	164	59	153	57	147	57	150	57
10	48	17	53	20	47	18	59	23
>10	232	83	216	80	213	82	202	77
Gleason (Institutional)								
2–6	71	25	74	28	70	27	69	26
7	130	46	124	46	111	43	108	41
8–10	79	28	71	26	79	30	84	32
Karnofsky status								
70	4	1	3	1	3	1	6	2
80	22	8	15	6	16	6	16	6
90	123	44	122	45	107	41	107	41
100	131	47	129	48	134	52	132	51
Race								

	Hormones + RT Whole Pelvis+Boost(n=280)	Hormones + RT Prostate Alone(n=269)	RT Whole Pelvis+Boost + Hormones(n=260)	RT Prostate Alone + Hormones(n=261)
White	202	191	193	183
African American	63	67	54	67
Hispanic or Latino	7	4	9	8
Other	7	4	4	2
Unknown	1	3	0	1
Baseline				
Testosterone Status				
Normal	236	215	214	204
Abnormal	44	54	46	57

	Hormones + RT Whole Pelvis+Boost(n=280)	Hormones + RT Prostate Alone(n=269)	RT Whole Pelvis+Boost + Hormones(n=260)	RT Prostate Alone + Hormones(n=261)
White	72	71	74	70
African American	23	25	21	26
Hispanic or Latino	3	1	3	3
Other	3	1	2	1
Unknown	<1	1	0	<1
Baseline				
Testosterone Status				
Normal	84	80	82	78
Abnormal	16	20	18	22

TABLE 2

Univariate analysis and survival rates at 7 years, comparing PSA 0.3 ng.mL with >0.3 mg/mL at the end of hormonal therapy.

Outcome	Variable	Rates (7 yr)	HR	p-value
PSA Failure	0.3 vs.	38.1% vs.	-	
	>0.3	56.4%	1.83 (1.51, 2.20)	<0.0001
Disease-Free	0.3 vs.	40.1% vs.	-	
Survival	>0.3	28.1%	1.44 (1.23, 1.69)	<0.0001
Local Progression	0.3 vs.	10.4% vs.	-	
	>0.3	14.7%	1.41 (0.99, 2.00)	0.06
Distant Metastasis	0.3 vs.	10.1% vs.	-	
	>0.3	19.6%	2.06 (1.49, 2.87)	<0.0001
Disease-Specific	0.3 vs.	93.1% vs.	-	
Survival	>0.3	85.4%	2.24 (1.53, 3.29)	<0.0001
Overall Survival	0.3 vs.	69.3% vs	-	
	>0.3	66.6%	1.08 (0.86, 1.35)	0.52

Table 3

Multivariate analysis of outcome parameters studied for all patients.

Stratified Variables	Variable Categories	PSA Failure (Phoenix)		Disease-Free Survival		Local Progression		Distant Progression		Disease-specific Survival		Overall Survival	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
PSA at End of HT	= 0.3 vs.	-		-		-		-		-		-	
	> 0.3	1.6 (1.3–1.9)	<0.001	1.3 (1.1–1.5)	0.003	1.3 (0.9–1.8)	0.20	1.9 (1.4–2.7)	<0.001	2.0 (1.4–3.0)	<0.001	1.1 (0.9–1.4)	0.43
PSA at Baseline	= 20 vs	-		-		-		-		-		-	
	.> 20	1.7 (1.4–2.1)	<0.001	1.5 (1.3–1.8)	<0.001	1.2 (0.9–1.8)	0.22	1.2 (0.8–1.7)	0.24	1.5 (1.0–2.3)	0.04	1.3 (1.1–1.6)	0.02
Gleason	2–6 vs.	-		-		-		-		-		-	
	7 vs.	1.5 (1.2–1.9)	<0.001	1.2 (1.0–1.5)	0.03	1.6 (1.0–2.6)	0.04	1.6 (1.0–2.6)	0.04	1.8 (0.9–3.2)	0.06	0.9 (0.7–1.2)	0.44
	8–10	1.8 (1.4–2.4)	<0.001	1.3 (1.0–1.6)	0.02	1.6 (0.9–2.6)	0.06	2.2 (1.3–3.6)	0.002	3.1 (1.7–5.5)	<0.001	1.2 (0.9–1.6)	0.18
Treatment Arm	Arm 1 vs.	-		-		-		-		-		-	
	Arm 2 vs.	1.4 (1.1–1.8)	0.01	1.3 (1.0–1.6)	0.03	0.9 (0.6–1.6)	0.95	1.2 (0.7–1.9)	0.53	1.2 (0.7–2.2)	0.46	0.9 (0.7–1.3)	0.80
	Arm 3 vs.	1.2 (0.9–1.6)	0.18	1.3 (1.1–1.6)	0.008	1.1 (0.7–1.8)	0.59	1.4 (0.8–2.2)	0.17	1.4 (0.8–2.4)	0.27	1.3 (0.9–1.7)	0.09
	Arm 4	1.1 (0.8–1.4)	0.56	1.0 (0.8–1.3)	0.73	0.8 (0.5–1.3)	0.37	1.1 (0.7–1.8)	0.59	1.2 (0.7–2.1)	0.57	1.0 (0.7–1.4)	0.81
Age	Cont.	0.9 (0.9–0.9)	<0.001	1.0 (0.9–1.1)	0.79	0.9 (0.9–0.9)	0.04	0.9 (0.9–1.0)	0.66	1.0 (0.9–1.1)	0.87	1.0 (1.0–1.1)	<0.001