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Impact of ultrahigh baseline PSA levels on biochemical and clinical outcomes in two Radiation Therapy Oncology Group prostate clinical trials

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Abstract

Purpose—To assess ultra-high (UH; PSA ≥ 50 ng/ml) patient outcomes compared to other high-risk patients and to identify outcome predictors.

Methods and Materials—PCP from two Phase III RTOG clinical trials (9202 and 9413) were divided into two groups; high-risk patients with and without UH baseline PSA level. Predictive variables included age, Gleason score, clinical T stage, KPS, and treatment arm. Outcomes included overall survival (OS), distant metastasis (DM), and biochemical failure (BF). Unadjusted and adjusted hazard ratios (HRs) were calculated using either the Cox or Fine and Gray's regression model with associated 95% confidence intervals (CI) and p-values.

Results—There were 401 in the UH PSA and 1792 in the non-UH PSA PCP out of 2193 high risk PCP. PCP with UH PSA was found to have inferior OS (HR 1.19, 95% CI 1.02-1.39, p-value=0.02), DM (HR 1.51, 95% CI 1.19-1.92, p-value=0.0006), and BF (HR 1.50, 95% CI

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1.29-1.73, p-value <0.0001) when compared to other high-risk PCP. In the UH cohort, PSA was found to be a significant factor for the risk of DM (HR 1.01, 95% CI 1.001-1.02) but not OS and BF. Gleason grade 8-10 was found to consistently predict for poor OS, DM, and BF outcomes (with HR estimates ranging from 1.41 to 2.36) in both the high-risk cohort and UH cohort multivariable analyses.

Conclusions—UH PSA levels at diagnosis are related with detrimental changes in OS, DM, and BF. All three outcomes can be modelled by various combinations all predictive variables tested.

Keywords

Prostate cancer; Prognostic Factors; External-Beam Radiation Therapy; Hormonal Therapy; Clinical Trials; Outcomes

INTRODUCTION

The management of high-risk prostate cancer routinely involves a combination of radiotherapy and hormonal therapy [1-3] with consideration of definitive radical prostatectomy for selective cases [4-6]. A variety of categorical schemes and statistical nomograms have been published to provide risk estimates of extracapsular/positive margin/seminal vesicle involvement, distant metastatic disease, as well as outcomes such as biochemical control, disease-specific survival and overall survival [7-8]. Although some heterogeneity between high-risk disease definitions exists, it is accepted that patients with any of Gleason 8-10 pathology, serum PSA >20 ng/ml, or non-localised (T3T4) disease populate the high-risk stratum [9]. Despite various pre-treatment staging investigations that can detect macroscopic disease with acceptable operating characteristics, the detection of micrometastatic disease still remains an elusive goal. This issue is particularly relevant in patients that present with pre-treatment PSA levels greater than or equal to 50 ng/ml [10]. Clinicians may have uncertainty regarding the clinical utility and outcomes of aggressive loco-regional treatment in the setting of ultrahigh pre-treatment PSA levels that are known to predict for inferior clinical outcome and higher risk of micrometastatic disease [11].

The primary objective of this study is to directly assess biochemical and clinical outcomes of this population of prostate cancer patients (PCP) with ultrahigh (UH) PSA (pre-treatment PSA ≥ 50 ng/ml) compared to other high-risk PCP in the context of two completed prospective multi-institutional Radiation Therapy Oncology Group (RTOG) phase III trials. Secondary objectives of this investigation include the characterisation of biochemical failure (BF), distant metastasis (DM) relapse, and overall survival (OS) rates as well as the identification of prognostic factors associated with these three outcomes in this ultrahigh PSA cohort. Our primary null hypothesis for this investigation is that the high-risk patients who have ultrahigh baseline PSA, defined as a baseline serum pretreatment PSA level ≥ 50 ng/ml (study cohort UH), have as good as biochemical, metastasis relapse, and overall survival outcomes as other high-risk patients who do not have ultrahigh PSA levels (study cohort non-UH).

MATERIALS AND METHODS

Patient Selection

In order to proceed with an investigation assessing an ultrahigh PSA patient cohort versus other high-risk prostate cancer patients, an *a priori* definition of high-risk prostate cancer needed to be adopted. For purposes of this statistical analysis, we have used a modification of the D'Amico risk stratification scheme [12] in which high-risk prostate cancer is defined as patients with pathologically confirmed adenocarcinoma of the prostate with serum

pretreatment PSA level of > 20 ng/ml OR Gleason Score 8-10 OR clinical T stage T3-T4N0M0 [9,13]. Once this definition of high-risk disease was adopted, a search for RTOG clinical trials with the following criteria was performed: high-risk population as part of the inclusion criteria, ultrahigh PSA ≥ 50 ng/ml not excluded from the clinical trial, biochemical and clinical outcome data available with mature follow-up. Two clinical trials, Radiation Therapy Oncology Group (RTOG) 9202 and 9413, were identified that contained data consistent with these criteria for inclusion into this analysis [14-17]. The analysis was performed using data from eligible patients have high risk features without distant metastasis at time of registration to RTOG 9202 and 9413.

Clinical Trials

RTOG 9202 was a phase III randomised clinical trial assessing an additional 2 years of adjuvant androgen deprivation after 4 months of neoadjuvant/concurrent hormonal cytoreduction with radiation therapy (9202 Arm 2) versus 4 months of neoadjuvant/concurrent hormonal cytoreduction (with no additional adjuvant androgen deprivation) with radiation therapy (9202 Arm 1) for locally advanced prostate cancer [17]. Patients with pathologically confirmed adenocarcinoma of the prostate with clinical stage T2c-T4NOMO, Karnofsky Performance status (KPS) ≥ 70, serum pretreatment PSA < 150 ng/ml were eligible for this clinical trial. This clinical trial found a statistically significant advantage in overall survival with the addition of long-term adjuvant androgen deprivation (5 year overall survival 81.0%) over no adjuvant androgen ablation (5 year overall survival 70.7%) in patients with Gleason 8-10 disease.

RTOG 9413 was a phase III randomised clinical trial assessing the additional effects of whole pelvis radiation therapy and adjuvant total androgen suppression (TAS) to standard neoadjuvant/concurrent TAS with prostate only radiotherapy in clinically localised prostate cancer [14-16]. A 2 × 2 factorial design was used to explore this research question (Arm 1 = whole pelvic RT with no adjuvant TAS, Arm 2 = no pelvic RT with no adjuvant TAS, Arm 3 = whole pelvic RT and adjuvant TAS, Arm 4 = no pelvic RT with adjuvant TAS). Patients with T1c-T4NOMO adenocarcinoma of the prostate, serum pretreatment PSA level ≤ 100 ng/ml, KPS ≥ 70, and an estimated pelvic lymph node risk of ≥ 15% by the Roach equation ((2/3)PSA + (Gleason Score − 6)) OR patients with T2c-T4 disease with Gleason score ≥ 6 that do not have ≥ 15% lymph node risk by the Roach equation. This trial demonstrated a difference in overall survival in the four clinical trial arms. Pairwise statistical comparisons demonstrated that Arm 1 > Arm 3, Arm 2 > Arm 3, and Arm 3 > Arm 4 was superior in terms of overall survival.

Outcomes

Overall survival (OS), distant metastasis (DM), and biochemical failure (BF) are the three outcomes of interest in the analysis. An OS event is defined as death due to any cause. A DM event is defined as clinical evidence of distant disease (non-prostate gland recurrence) by any clinical, pathological, or radiological method. A BF event is defined as either a serum PSA level > 2 ng/ml over the absolute nadir after completion of protocol treatment or initiation of salvage hormonal therapy [18].

Statistical Analysis Plan

A heterogeneity test was performed to assess the homogeneity of the data and to establish whether one estimate can be used to represent the metadata from two different trials. The Chi-square test was applied to assess heterogeneity among the stratifications at the significance level of 0.1 to take into account the difference among the trials such as the patient population baseline characteristics, treatment, and the period of accrual. The hazards

ratio (HR) was used as an estimator for time to event outcome with a pooled HR estimator [19] utilized to take into account the use of data from multiple clinical trials.

Chi-square test or t-test statistics were used to see if there was a difference with respect to the pretreatment characteristics and outcomes of patients with and without missing data. These test statistics were also used to compare pretreatment characteristics of patients. If there are no statistically significant differences between the two patient groups, then the missing at random (MAR) assumption is assumed. A multiple imputation (20 imputed datasets) with Markov chain Monte Carlo (MCMC) estimation was applied to impute missing data. The Kaplan-Meier method [20] was used to estimate the overall survival (OS), and the log-rank test [22] was used to test the difference between the treatments or categories.. The cumulative incidence method [22] was used to estimate the distant metastasis (DM) rate, biochemical failure (BF) rate and Gray's test [23] was used to test the difference between the treatments or categories. A Cox proportional hazards regression model [24] was used for OS, and Fine and Gray's regression model [25] was used for DM and BF to adjust for the defined prognostic covariates below. Unadjusted and adjusted hazard ratios (HRs) were calculated for all covariates using either the Cox proportional hazards model or Fine and Gray's regression model with associated 95% confidence intervals (C.I.s) and p-values. Prognostic covariates to be included in the statistical models include age (continuous), combined Gleason Score (2-6 [reference level; RL] vs. 7 vs. 8-10), T stage (T1-T2 [RL] vs. T3-T4), Karnofsky Performance Status (KPS, 70-90 [RL] vs. 100), Treatment Arm (9202 Arm 1 [RL] vs. 9202 Arm 2 vs. 9413 Arm 1 vs. 9413 Arm 2 vs. 9413 Arm 3 vs. 9413 Arm 4), and Baseline Serum Prostate Specific Antigen (PSA) Level (PSA < 50 ng/ml [RL] vs. PSA ≥ 50 ng/ml (UH), or continuous). All statistical tests were two-sided and a p-value <0.05 was considered statistically significant unless otherwise specified. Statistical Analysis System (©SAS Institute, Cary, NC) and R software were used for all statistical analyses.

RESULTS

Patient Characteristics

A total of 2796 patients (RTOG 9202: n=1521 and RTOG 9413: n=1275) that were enrolled in these two studies were potentially available for inclusion into this analysis. One-hundred patients (3.6%) have missing Gleason score data, all of whom were enrolled in the 9202 trial. This level of missing data was less than 5% of the data and the results of outcome analyses show that there are not statistically significantly differences between the two groups except distant metastasis (DM). Therefore, no imputation of data was carried out; therefore, 2696 patients who did not have any missing data were eligible and analysable for this analysis. Among those, 2193 (81%) patients are in the previously defined high risk group and 503 (19%) patients were in lower risk groups. Median age of the high risk group was 70 years (Table 1). Patients in this high risk group had 1 high risk factor (PSA >20ng/ml, T3T4, or Gleason 8-10) in 1194 (54%) cases, 2 high risk factors in 824 (38%) cases, and three high risk factors in 175 (8%) cases. Of the 2193 high risk patients, 401 (15%) patients had a baseline PSA level ≥ 50 ng/ml (UH group, median PSA 72.8 ng/ml) and 1792 (85%) patients are in high risk group but with a baseline PSA <50 ng/ml (non-UH group, median PSA 22.4 ng/ml). In a statistical comparison of the UH and non-UH groups, the UH group demonstrated statistically significant younger age, lower Gleason score, higher rates of T1/T2 disease, and lower KPS scores when compared to the non-UH group. A statistical difference in RTOG clinical trial treatment assignment was also observed between the two groups (Table 2).

The results of heterogeneity testing shows that the six study arms from the two trials were found to homogeneous with respect to the hazard ratios (HRs) of overall survival (OS),

distant metastasis (DM), and biochemical failure (BF), which indicated that the pooled HRs can be used.

Outcomes

Median follow-up for all (n=2696) and surviving (n=1485) patients was 7.3 and 8.1 years, respectively. Similarly, median follow-up for all (n=2193) and survival high risk patients was 7.2 and 8.0 years, respectively. In terms of overall survival in the high risk cohort, 1175 (54%) patients were alive at the time of analysis. Three hundred and ninety (18%) patients have had distant metastasis diagnosed and 1125 (51%) patients have had a biochemical failure.

Table 3 details the estimates for OS, DM, and BF 7-year failure rates for the UH and non-UH cohorts in their entirety and divided by RTOG study arm. The median time to OS, DM, and BF events in the non-UH cohort was 5.5 years, 3.6 years, and 2.9 years, respectively. Similarly, time to OS, DM, and BF events in the UH cohort was 5.1, 2.8, and 2.4 years, respectively. The 7 year OS rate for the UH patients and non-UH patients were similar (64.3 % vs. 68.0%), However, the UH patients have higher DM rates (21.3% vs. 13.7%) and BF rates (60.2 vs. 45.6%) than do non-UH patients. DM (p-value = 0.0004) and BF (p-value = <0.0001) show statistically a significant difference but not OS (p value =0.19) when comparing UH and non-UH cohorts. Figures 1 to 3 graphically illustrate the relative differences in OS, DM rate, and BF rate between the UH and non-UH cohorts by means of Kaplan-Meier curves.

In Table 4, The adjusted pooled HR of OS, DM, and BF all showed statistically significant differences in risk related to the UH versus non-UH cohort (OS pooled HR=1.21 (95% CI 1.03, 1.41), DM pooled HR=1.54 (95% CI 1.21, 1.96), and BF pooled HR=1.53 (95% CI 1.32, 1.77)).

Table 5 summarizes the proportional hazard regression analyses adjusted for other covariates relating the HR with 95% CI to time to failure for OS, DM, and BF for the entire high risk cohort as well as the UH cohort alone. In terms of the entire high risk patient group, PSA (PSA < 50 (RL) vs. PSA ≥ 50) is a statistically significant covariate in OS (p-value=0.02), DM (p-value<0.0001), and BF (p-value<0.0001) adjusted for other covariates, which is consistent with those from pooled HR. Other important covariates in the multivariable modeling of all high risk patients included age (OS/DM/BF), Gleason score (OS/DM/BF), T stage (DM), KPS (OS), and clinical trial study arm (improved OS for 9413 Arm 3 as well as DM/BF for multiple study arms).

In the proportional hazard regression analysis adjusted for other covariates of the UH cohort in which PSA is now considered to be a continuous variable, Gleason grade 8-10 was found to be a very significant predictor for inferior OS (HR 1.83, p-value=0.001), DM (HR 2.07, p-value=0.02), and BF (HR 1.41, p-value= 0.049) outcomes. Other important covariates included PSA level (DM), age (OS, BF), T stage (DM), KPS (OS), and clinical trial study arm (improved OS for 9413 Arm 3 and inferior BF for 9202 Arm 2) (data are not shown). Seven-year OS, DM, and BF rate estimates divided into important covariate groups are presented in table 6.

DISCUSSION

Multiple reports have demonstrated that the serum Prostate Specific Antigen level is correlated with prostate cancer disease burden. In addition, preoperative serum PSA can be used in conjunction with other independent prognostic factors such as clinical (TNM) stage and Gleason score to predict outcome in non-metastatic setting [26-27]. In the context of a

surgical series, Partin et al. have created tables relating serum baseline PSA level, TNM stage, and Gleason score to important post-surgical outcomes such as the risk of extra-capsular spread, seminal vesicle extension and lymph node involvement. Similarly other reports have demonstrated that patients diagnosed with localised prostate cancer and one or more high risk features such as PSA > 20 ng/ml, Gleason > 7 and clinical stage > T2c have inferior clinical and biochemical failure rates [28].

Given the known relationship of PSA > 20 ng/ml with inferior outcomes, the concern of occult micrometastatic disease is further intensified when PSA values are found to be extremely high at time of diagnosis [10,29,30]. In a report by Ou et al., patients that present with baseline serum PSA levels greater than 50 ng/ml were found to have higher rates of extracapsular disease and lymph node metastases, higher Gleason scores and tumor burden, and shorter freedom from PSA failure when compared to patients with PSA levels between 20.1-50 ng/ml [10]. Similarly, Roach et al., demonstrated that high risk prostate cancer patients treated with radiotherapy alone with no systemic therapy (e.g. hormonal therapy) with baseline serum PSA levels greater than 100 ng/ml had statistically and clinical significant deteriorations in overall survival [30].

In an initial attempt to investigate this issue and this patient population, a single institution retrospective chart review was completed and published in the medical literature [11]. In this cohort series of 48 non-metastatic prostate cancer patients presenting with serum PSA levels ≥ 50 ng/ml, the mean age of the study population was 66.6 years, median pretreatment PSA was 112.7 ng/ml (mean 108.2 ng/ml, range 51.23-668 ng/ml). Median Gleason score was 8 (range 6-10), and clinical T-stage was T1 6/48 (12.5%), T2 16/48 (33.3%), T3 19/48 (39.6%), T4 3/48 (6.25%) and Tx 4/48 (8.33%). On univariate analysis, clinical T-stage, Gleason score, primary RT, and PSA measurements including initial PSA, nadir PSA, change in PSA and respective log values were prognostic of biochemical failure. On multivariate analysis, log nadir PSA was prognostic of biochemical failure. No prognostic variables were significant for overall survival in this analysis. When this ultrahigh PSA cohort was compared to published Kaplan-Meier control curves, no apparent difference in overall survival was observed. However, the analysis of this cohort was limited by its sample size, lack of an appropriate control group, as well as the single institutional nature of the analysis. These study limitations impaired the statistical ability to draw robust conclusions regarding the true impact(s) of ultrahigh pretreatment PSA levels with respect to important clinical outcomes.

In the current analysis, utilising data from two RTOG clinical trials assessing issues of hormonal therapy and pelvic radiotherapy, we were able to determine that UH PSA levels do indeed confer inferior OS, DM, and BF outcomes. However, other covariates such as Gleason score and protocol treatment has effects on all three outcomes of the same or greater magnitude than the effect of UH PSA. Patient age was found to predict for all three outcomes, clinical T stage was found to be important in the prediction of DM failure and baseline KPS with OS. These prediction findings were also confirmed in the multivariable analysis of the UH cohort alone expect for protocol treatment which was likely due to lack of statistical power due to enlarging hazard ratio confidence intervals due to the analysis of 401 patients in six protocol treatment groups. The 7 year estimates for OS, DM, and BF that are presented in tables 3 and 6 can be used by clinicians to advise high risk prostate patients with UH PSA levels regarding expected outcomes of treatment. Additionally, based on these 7 year estimates of OS outcome from this study, we would argue that no high risk UH subcohort of patients was identified with such poor outcome that radical therapy should be withheld. This recommendation is consistent with the conclusion of previously published single institution cohort which was based on a UH PSA high risk cohort with a higher median PSA level and Gleason score.

A main limitation of this work relates to retrospective hypothesis testing that is inherent with the use of clinical trial data that was generated other purposes. The fact that this data was collected in an organised prospective fashion mitigates some of the biases involved with secondary clinical trial analyses. Another limitation relates to the fact that patients were not all treated with current standard of care radiotherapy and adjuvant hormonal therapy protocols that are routinely employed due to the randomised clinical trial nature of the data. This limitation was mitigated by an analysis of the heterogeneity of the hazard ratios of the various protocol study arms. Additionally, 7 year estimates of the various outcomes were able to be calculated; however, longer term OS survival data would be desirable given the long-term natural history of prostate cancer.

In conclusion, this study confirms that UH PSA levels can have a negative impact on OS, DM, and BF in patients treated on two RTOG randomised clinical trials assessing various combinations of radiotherapy and hormonal therapy. Other covariates such as age, KPS, T stage, protocol treatment and Gleason score can also have significant impacts on these three outcomes. Specifically, it appears that patients with high Gleason scores of 8-10 are at particularly high risk of negative outcomes. The relatively favorable outcomes observed even in patients with UH PSA values do not support the omission of radical therapy in any cohort of patients examined in this analysis with clinically localized prostate cancer. Therefore, good performance status patients with UH PSA high-risk prostate cancer with negative metastatic imaging should continue to be considered for standard of care radiotherapy and hormonal therapy as defined by previously published clinical trials.

Acknowledgments

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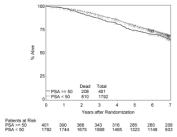

Figure 1.
Overall survival stratified by PSA group

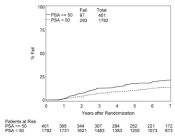

Figure 2.
Distant metastasis rate stratified by PSA group

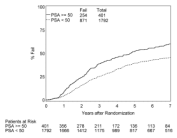

Figure 3.
Biochemical failure rate stratified by PSA group

Table 1
Pretreatment Characteristics By Risk Group (n=2696)

	Lower Risk Group†† (n=503)		High Risk Group†† (n=2193)	
Age				
Minimum	48		43	
25th Percentile	67		65	
Median	72		70	
75th Percentile	75		74	
Maximum	84		88	
	n	%	n	%
40-49	4	1	10	<1
50-59	25	5	153	7
60-69	159	32	865	39
70-79	297	59	1080	49
80+	18	4	85	4
PSA				
< 50	503	100	1792	82
≥ 50	0	0	401	18
Gleason				
2-6	251	50	671	31
7	252	50	792	36
8-10	0	0	730	33
T-Stage				
T1/T2	503	100	995	45
T3/T4	0	0	1198	55
KPS				
70-90	269	53	1166	53
100	234	47	1027	47
Study/Arm				
9202 Arm 1	147	29	558	25
9202 Arm 2	139	28	577	26
9413 Arm 1	57	11	263	12
9413 Arm 2	66	13	250	11
9413 Arm 3	47	9	272	12
9413 Arm 4	47	9	273	12

* p-value for continuous variables is from analysis of variance; for categorical variables it is from Chi-square test statistics.

† Not applicable due to insufficient cell counts

†† high risk; patients have any of following features; PSA>20, T-stage=T3 or T4, or Gleason score 8-10. lower risk: patients do not have any missing data are not in high risk group

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Table 2

Pretreatment Characteristics High Risk Patients (n=2193)

	PSA < 50 (n=1792)		**PSA ≥ 50 (n=401)**		**p-value***
Age					
Minimum	43		51		0.003
25th Percentile	66		64		
Median	70		69		
75th Percentile	74		73		
Maximum	88		86		
	n	%	n	%	
40-49	10	1	0	0	0.01
50-59	112	6	41	10	
60-69	698	39	167	42	
70-79	901	50	179	45	
80+	71	4	14	3	
Gleason					
2-6	545	30	126	31	0.04
7	630	35	162	40	
8-10	617	34	113	28	
T-Stage					
T1/T2	790	44	205	51	0.01
T3/T4	1002	56	196	49	
KPS					
70-90	932	52	234	58	0.02
100	860	48	167	42	
Study/Arm					
9202 Arm 1	441	25	117	29	0.005
9202 Arm 2	455	25	122	30	
9413 Arm 1	224	13	39	10	

	PSA < 50 (n=1792)		PSA ≥ 50 (n=401)		p-value*
9413 Arm 2	219	12	31	8	
9413 Arm 3	219	12	53	13	
9413 Arm 4	234	13	39	10	

* p-value for continuous variables is from analysis of variance; for categorical variables it is from Chi-square test statistics.

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Table 3

Outcome Estimates at 7 Years for High Risk Patients (n=2193)

		Ultra High PSA Group		Non-Ultra High PSA Group	
Endpoint	**Study / Arm**	**Failures/N**	**7-Year Survival/Failure Rate (95% CI)**	**Failures/N**	**7-Year Survival/Failure Rate (95% CI)**
Overall Survival	9202 / Arm 1	69/117	65.3% (55.8, 73.2)	255/441	67.7% (63.1, 71.9)
	9202 / Arm 2	67/122	69.3% (60.2, 76.7)	252/455	70.0% (65.5, 74.1)
	9413 / Arm 1	14/39	67.7% (49.9, 80.3)	73/224	66.9% (59.7, 73.2)
	9413 / Arm 2	9/31	NA*	69/219	69.6% (62.4, 75.7)
	9413 / Arm 3	29/53	51.8% (36.9, 64.9)	87/219	62.1% (54.7, 68.7)
	9413 / Arm 4	20/39	54.3% (36.4, 69.1)	74/234	68.7% (61.8, 74.7)
	Combined	208/401	64.3% (59.3, 68.9)	810/1792	68.0% (65.7, 70.2)
		p-value from log-rank test statistic†† = 0.19			
Distant Metastases	9202 / Arm 1	36/117	25.1% (17.1, 33.0)	112/441	19.8% (16.0, 23.5)
	9202 / Arm 2	32/122	20.6% (13.4, 27.9)	68/455	10.6% (7.7, 13.4)
	9413 / Arm 1	7/39	NA*	27/224	12.5% (8.0, 17.1)
	9413 / Arm 2	5/31	NA*	28/219	11.6% (7.1, 16.1)
	9413 / Arm 3	8/53	NA*	34/219	15.1% (10.1, 20.1)
	9413 / Arm 4	9/39	NA*	24/234	9.8% (5.9, 13.6)
	Combined	97/401	21.3% (17.2, 25.3)	293/1792	13.7% (12.1, 15.4)
		p-value from Fine Gray's test statistic = 0.0005‡			
Biochemical Failure	9202 / Arm 1	81/117	63.2% (54.4, 72.1)	271/441	55.1% (50.4, 59.8)
	9202 / Arm 2	72/122	53.0% (44.0, 62.0)	177/455	33.1% (28.7, 37.4)
	9413 / Arm 1	20/39	52.9% (36.3, 69.6)	102/224	45.1% (38.3, 51.8)
	9413 / Arm 2	23/31	69.9% (52.7, 87.1)	116/219	54.6% (47.5, 61.6)
	9413 / Arm 3	31/53	59.8% (46.1, 73.6)	109/219	48.7% (41.9, 55.6)
	9413 / Arm 4	27/39	73.3% (58.3, 88.3)	96/234	41.7% (35.1, 48.4)
	Combined	254/401	60.2% (55.4, 65.1)	871/1792	45.6% (43.3, 48.0)

Endpoint	Study / Arm	Ultra High PSA Group		Non-Ultra High PSA Group	
		Failures/N	7-Year Survival/Failure Rate (95% CI)	Failures/N	7-Year Survival/Failure Rate (95% CI)
		p-value from Fine Gray's test statistic < 0.0001[†]			

* Last failure < 7 years; estimate too unstable.

Table 4

Pooled Hazard Ratio using Proportional Hazards Regression Model High Risk Patients by PSA (n=2193)

	Adjusted Hazard Ratio** Overall Survival		Adjusted Hazard Ratio** Distant Metastasis		Adjusted Hazard Ratio** Biochemical Failure	
Stratification Variable : Arm	**Hazard Ratio (95% CI*)**	**p-value**	**Hazard Ratio (95% CI*)**	**p-value**	**Hazard Ratio (95% CI*)**	**p-value**
RTOG 9202: Arm 1						
PSA < 50	RL		RL		RL	
PSA ≥ 50	1.07 (0.82, 1.41)	0.61	1.29 (0.87, 1.93)	0.21	1.27 (0.98, 1.66)	0.07
RTOG 9202: Arm 2						
PSA < 50	RL		RL		RL	
PSA ≥ 50	1.00 (0.75, 1.31)	0.97	1.75 (1.12, 2.73)	0.01	1.63 (1.23, 2.15)	0.0006
RTOG 9413: Arm 1						
PSA < 50	RL		RL		RL	
PSA ≥ 50	1.11 (0.61, 2.00)	0.74	1.65 (0.70, 3.87)	0.25	1.18 (0.69, 2.00)	0.54
RTOG 9413: Arm 2						
PSA < 50	RL		RL		RL	
PSA ≥ 50	1.03 (0.51, 2.08)	0.94	1.18 (0.45, 3.07)	0.73	1.70 (1.05, 2.76)	0.03
RTOG 9413: Arm 3						
PSA < 50	RL		RL		RL	
PSA ≥ 50	2.26 (1.43, 3.59)	0.0005	1.28 (0.56, 2.95)	0.56	1.36 (0.90, 2.05)	0.14
RTOG 9413: Arm 4						
PSA < 50	RL		RL		RL	
PSA ≥ 50	1.82 (1.10, 2.98)	0.02	2.43 (1.17, 5.03)	0.02	2.56 (1.69, 3.89)	<0.0001
	Chi-Square T.S. (Q) = 12.6	p-value = 0.97	Chi-Square T.S. (Q) = 3.1	p-value = 0.31	Chi-Square T.S. (Q) = 9.3	p-value = 0.90
Pooled HR†						
PSA < 50	RL		RL		RL	
PSA ≥ 50	**1.21 (1.03, 1.41)**		**1.54 (1.21, 1.96)**		**1.53 (1.32, 1.77)**	

*CI = Confidence Interval; RL = Reference Level.

** Adjusted for age (continuous), Gleason (2-6 vs. 7 vs. 8-10), T-Stage (T1/T2 vs. T3/T4), and KPS (70-90 vs. 100).

Table 5

Proportional Hazards Regression Model High Risk Patients by PSA (n=2193)

Variable		All patients (n=2193)			UH PSA cohort † (n=401)		
		OS HR (95% CI)	DM HR (95% CI)	BF HR (95% CI)	OS HR (95% CI)	DM HR (95% CI)	BF HR (95% CI)
PSA	<50 ng/ml ≥50 ng/ml	RL 1.19 (1.02-1.39)	RL 1.51 (1.19-1.92)	RL 1.50 (1.29-1.73)	ns	1.01 (1.01-1.02)	ns
Age	Continuous	1.04 (1.03-1.05)	0.97 (0.96-0.99)	0.97 (0.96-0.98)	1.05 (1.02-1.07)	ns	0.97 (0.95-0.99)
Gleason Score	2-6 7 8-10	RL ns 1.49 (1.27-1.74)	RL 1.38 (1.05-1.82) 2.36 (1.82-3.07)	RL 1.30 (1.13-1.51) 1.51 (1.30-1.76)	RL ns 1.83 (1.27-2.62)	RL ns 2.07 (1.15-3.73)	RL ns 1.41 (1.002-1.99)
T Stage	T1/T2 T3/T4	RL ns	RL 1.49 (1.20-1.85)	RL ns	RL ns	RL 2.07 (1.33-3.20)	RL ns
KPS	70-90 100	RL 0.74 (0.65-0.84)	RL ns	RL ns	RL 0.70 (0.53-0.94)	RL ns	RL ns
Treatment arm	9202: Arm 1 9202: Arm 2 9413: Arm 1 9413: Arm 2 9413: Arm 3 9413: Arm 4	RL ns ns ns 1.32 (1.06-1.65) ns	RL 0.63 (0.49-0.81) 0.61 (0.42-0.89) 0.65 (0.44-0.95) ns 0.57 (0.39-0.84)	RL 0.53 (0.45-0.63) 0.69 (0.56-0.85) ns 0.77 (0.63-0.94) 0.70 (0.57-0.87)	RL ns ns ns 2.42 (1.51-3.88) ns	RL ns ns ns ns ns	RL 0.67 (0.48, 0.93) ns ns ns ns

† continuous PSA variable, OS=overall survival; DMFS=distant metastases; BF=biochemical failure; RL=reference level; ns=not significant; T=tumor; PSA=prostate specific antigen; KPS=Karnofsky performance status; HR= Hazard ratio; CI=Confidence interval; ns=statistically non-significant

Table 6
7-Year Estimates of OS, DM, and BF (n=401)

Variable	Group	7-Year OS Rate* (95% CI)	7-Year DM Rate* (95% CI)	7-Year BF Rate* (95% CI)
Age	<60	77.5% (61.1, 87.6)	32.1% (17.4, 46.7)	71.3% (56.9, 85.8)
	60-70	67.2% (59.9, 73.4)	18.3% (12.8, 23.8)	66.1% (59.3, 72.9)
	>70	57.5% (49.4, 64.8)	22.0% (15.5, 28.5)	50.3% (42.5, 58.1)
Gleason	2-6	71.1% (62.3, 78.3)	15.2% (8.9, 21.5)	52.3% (43.3, 61.1)
	7	63.4% (55.3, 70.5)	20.3% (13.9, 26.6)	61.9% (54.3, 69.6)
	8-10	57.3% (47.3, 66.2)	30.0% (21.2, 38.8)	66.9% (57.9, 75.8)
T-Stage	T1/T2	65.3% (58.1, 71.5)	14.3% (9.4, 19.2)	60.0% (52.7, 66.5)
	T3/T4	63.4% (56.1, 69.8)	28.4% (22.1, 34.8)	61.0% (54.0, 67.9)
KPS	70-90	61.3% (54.6, 67.3)	23.1% (17.7, 28.6)	60.5% (54.1, 66.8)
	100	68.5% (60.6, 75.2)	18.7% (12.6, 24.7)	59.9% (52.3, 67.5)
PSA	50-60	66.2% (55.8, 74.7)	15.3% (8.1, 22.5)	57.3% (47.4, 67.2)
	>60 – 72.5	61.0% (50.2, 70.1)	10.7% (4.4, 17.0)	59.5% (49.2, 69.7)
	>72.5 – 90	66.7% (56.4, 75.1)	26.5% (17.9, 35.2)	66.5% (57.3, 75.7)
	>90	62.9% (52.4, 71.6)	32.0% (22.6, 41.3)	57.6% (47.6, 67.5)