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Improved Overall Survival Trends of Men with Newly Diagnosed M1 Prostate Cancer: A SWOG Phase III Trial Experience (S8494, S8894 & S9346)

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Abstract

Purpose—Frequent PSA testing in screening and monitoring of prostate cancer has led to significant stage migration. We evaluated if overall survival (OS) in hormone naïve, metastatic prostate cancer patients has improved during the era of PSA use. We also assessed whether any subsets of patients benefited differentially during this period.

Materials and Methods—We compared OS in three sequential phase III trials of men with hormone naïve, metastatic prostate cancer receiving similar androgen deprivation therapy (n=3096): two conducted prior to the 'PSA era' (S8494 and S8894), and the other during this era (S9346). OS was adjusted for patient and disease risk factors in the latter two trials. Subgroups were evaluated by interactions of risk factors with trial.

Results—Median OS in S8494 was 30 months, 33 months in S8894; and 49 months in S9346. Adjusting for risk factors, there was a 22% lower risk of death in S9346 compared to S8894 (hazard ratio 0.78, 95% confidence interval 0.70, 0.87, p<0.001). The improvement in OS was greater in African Americans (AA) (p=0.008 for test of interaction). In both S8494 and S8894,

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median survival for AA was 27 months and 34 and 35 months for non-AA, respectively; this racial difference disappeared in S9346 (AA OS=48 months, non-AA OS=49 months).

Conclusions—Adjusting for risk factors, OS was significantly improved in the post-PSA era trial. However, attributing this solely to PSA monitoring cannot be concluded. AA men now have comparable OS to Caucasians. Current estimates of survival should be used for designing new trials in this population.

Introduction

Androgen deprivation therapy (ADT) has been the standard treatment for advanced prostate cancer since the observations by Huggins and Hodges in 1941[1]. Over the ensuing seven decades, several questions regarding the use and efficacy of ADT have been evaluated in phase III trials. These include the efficacy of medical vs. surgical castration, gonadal suppression vs. combined androgen deprivation, and intermittent vs. continuous ADT [2–6]. The majority of these trials accrued patients prior to the implementation of PSA use into clinical practice which generally began around 1990. The routine use of PSA in detection and monitoring of disease activity has led to a significant stage migration of prostate cancer [7]. Data from the CaPSURE database, including 2078 men with low-risk prostate cancer who were diagnosed between 1989 and 2001, demonstrated a significant increase in the proportion of patients with low-risk tumor characteristics from 29.8% in 1989–1992 to 45.3% in 1999–2001[8]. Most recent SEER data suggest a 5-year relative survival of 99% among men with prostate cancer diagnosed in 2000, a significant increase from 78% among men diagnosed in 1986. Some have argued that improvements in relative and cause-specific survival rates do not reflect true increases in life expectancy as survival rates among men diagnosed during the PSA era can be inflated by over-diagnosis and lead time[9]. An unanswered and important question is whether men with hormone-naive metastatic prostate cancer have experienced a similar improved survival during the PSA era.

An additional observation that has been made over the period from 1990 to 2006, is a fall in prostate cancer mortality by 39%[10]. This fall in mortality has been largely attributed to the widespread use of PSA screening yet two, large, prospective trials observed either a 20% reduction in prostate cancer mortality or no mortality reduction[11, 12]. It is possible that the observed fall in prostate cancer mortality is related to improved outcomes in men with locally-advanced or metastatic disease, disease stages which are responsible for the majority of prostate cancer deaths.

Over the past 3 decades SWOG has conducted a series of phase III trials: S8494 (enrolled 1985–1987) compared survival in patients randomized to leuprolide or leuprolide with flutamide[2] and S8894 (1989–1994) evaluated the impact of adding flutamide to bilateral orchiectomy[4], and S9346 (1995–2009) which evaluates whether intermittent ADT is non-inferior to continuous ADT[6]. These sequential trials with survival endpoints provide an opportunity to address the question of whether survival has changed since the advent of widespread PSA screening and follow-up testing. The patient populations and major eligibility criteria were comparable and were enrolled by cooperative groups with members from major cancer centers and community centers around the US. All patients received protocol-specified treatment, and were followed for disease progression and survival in a comparable way so differences in prognosis would be less likely due to access to health care.

We hypothesize that, during an era of increased PSA testing, there has been an improvement in survival for newly diagnosed patients with M1 prostate cancer.

Materials and Methods

SWOG coordinated three phase III trials in newly diagnosed Stage M1 prostate cancer since the mid 1980's. S8494 and S8894 represent the pre-PSA era. However, S8494 cannot be used for the multivariate risk analysis because PSA and Gleason score were not collected. S9346 represents the post-PSA era. Although a small fraction of men enrolled on S8894 may have been exposed to PSA screening or disease monitoring, the vast majority were not.

S8494 (enrolled 1985–1986) [PDQ Registry 10455554]

S8494 (intergroup study 0036) enrolled patients with metastatic adenocarcinoma of the prostate who were hormone-naïve, and with a SWOG PS of 0–3 and adequate renal and hematologic function. All patients received leuprolide and then were randomized to receive either flutamide (250 mg three times daily) or matching placebo. Patients were treated until progression and those randomized to placebo could cross-over to flutamide at progression. During the period from March 18, 1985 to April 2, 1986, a total of 617 patients were randomized.

S8894 (enrolled 1989–1994) [PDQ Registry 8656627]

Like S8494, S8894 (intergroup study INT-0105) enrolled hormone-naïve metastatic patients. Eligibility was nearly identical. All patients underwent bilateral orchiectomy and were subsequently randomized to receive either flutamide (250 mg three times daily) or a matching placebo. Cross-over at progression was allowed. The primary endpoint of the study was death from any cause. Patients underwent disease assessment at study entry and every six months for the first two years. After that, radiologic studies were done if the PSA level rose by more than 25 ng/ml during any 3-month period. Patients were treated until disease progression. All patients were followed until death. Gleason grading was performed through centralized pathologic review of the biopsy specimens obtained before entry into the study. When not centrally available, the local Gleason score was used.

During the period from December 15, 1989, to September 15, 1994, a total of 1387 patients were randomized. Two-thirds of the patients came from 99 SWOG institutions located in 30 states, and the other one-third came from ECOG institutions. 1286 were clinically eligible and evaluated for this analysis.

S9346 (accrued 1995–2009) [ClinicalTrials.gov identifier: NCT00002651]

S9346 is a Phase III intergroup trial (INT 0162) with participants from CALGB, ECOG, EORTC, and NCIC-CTG. Its primary objective is to determine if survival is non-inferior with intermittent ADT compared to continuous ADT in patients with newly diagnosed hormone sensitive metastatic prostate cancer. Key eligibility requirements include stage M1 prostate cancer, a minimum pretreatment PSA of 5 ng/mL, and a PS of 0–2.

Step 1 of treatment consists of a 7-month "induction" course with goserelin and bicalutamide. Patients could have started ADT within 6 months prior to registration if otherwise eligibles. Patients whose PSA level decreased to 4 ng/mL or below at months 6 and 7 were randomly assigned to intermittent or continuous ADT. Patients whose PSA level did not decrease to ≤4 ng/ml at the end of the induction were removed from protocol but followed for survival. Standard of care for these patients was continuation of hormonal therapy until progression. PSA levels were obtained at months 1, 4, 6, and 7 of the induction period, then monthly after randomization.

Final results of S9346 are expected in the summer of 2012. SWOG's DSMC has given permission for these results to be reported by pooled arms.

All eligible men from S8494 and S8894 and all eligible men from North America from S9346 were considered for this analysis. Only patients with complete risk factor information were included in the analysis. EORTC (Europe) patients were excluded from S9346 for this analysis because they do not report race.

Survival is defined for S8494 and S8894 from date of randomization to date of death due to any cause or censored at last contact date. For S9346, the survival interval started at treatment start date for those who started prior to enrollment, and at date of enrollement for those who had not yet started. A Cox regression model was used to assess the risk of death for S9346 compared to S8894, adjusting for other known risk factors. Extensive disease was defined exactly the same for all three trials as diffuse bone disease or visceral organ involvement. The methods of Kaplan-Meier were used to estimate survival curves. All analyses were conducted using SAS version 9.1, and a main effect or interaction test was considered statistically significant if the two-sided p-value was less than or equal to 0.05.

All patients from these three trials gave written IRB-approved informed consent prior to study entry.

Results

Table 1 provides the distribution of risk factors for each study. Eighteen percent of S9346 patients, 38% of men from S8894 and 16% of men from S8494 were excluded from these analyses due to missing risk factors, primarily due to missing PSA and Gleason scores for the two more recent trials leaving 509 men from S8494, 791 men from S8894 and 1796 men from S9346. There was more extensive disease, higher prevalence of bone pain, higher PSA values, more African Americans and fewer obese men in the earlier study, S8894 compared to S9346 in the multivariate analysis.

Figure 1 illustrates the survival curves stratified by clinical trial. The median survival in S8494 is 30 months, 33 months in S8894 and 49 months for S9346. The hazard ratio (HR) of 0.70 indicates a 30 percent reduced risk of death in the more recent S9346 compared to the older S8894 (95% CI 0.64, 0.77, $p < 0.001$). If all data from all eligible men from both trials are used regardless of completeness of risk factor information, the survival HR remains 0.70, suggesting that those with complete risk factor data are representative of both trials.

Table 2 provides the corresponding multivariate adjusted analysis of all-cause mortality. Factors associated with increased risk of death include extensive disease (versus minimal), presence of bone pain, older age, African American versus other race, BMI < 25, a performance status of 2 or 3, and a Gleason score of 8–10 (versus 2–6). PSA at study entry and a Gleason score of 7 (versus ≤6) were not significantly ($p<0.05$) associated with survival. After adjusting for these factors, S9346 has a lower risk of death compared to S8894 (HR=0.78; 95% CI 0.70, 0.87, $p < 0.001$). Adjustment for risk factors explained some of the difference in survival between the two trials, but not completely. There was still a 22 percent lower risk of death on S9346 compared to S8894.

The interaction of each risk factor with clinical trial was assessed. The interaction test evaluates whether the prognostic significance of a risk factor with survival is different for the two trials. Only the interaction with African American (AA) patient is statistically significant ($p=0.008$). AA patients have worse survival compared to non-AA patients in the S8894 trial after risk factor adjustment, but the disparity does not persist in S9346. Figure 2 provides the unadjusted survival curves stratified by clinical trial and African American status. Patterns of survival are similar for the two pre-PSA trials. Both racial groups show improvement over time when compared to S9346, but the AA group's survival improvement

is greater than non-AA (median increase of 21 months versus 14–15 months, respectively). For S9346 the AA and non-AA patients have survival curves that overlap, indicating that racial group is not a significant predictor of survival in patients with M1 prostate cancer in the post-PSA era trial. We chose to include the non-white, non-AA patients (n=2 S8494, n=14 S8894, n=68 S9346) in the non-AA category. When excluded from the analysis, the results remain unchanged.

Table 3 provides a comparison of patient and disease characteristics for AA patients in the three trials. There was a higher prevalence of extensive disease and bone pain in the earlier trials, and PSA values were also substantially higher in S8894 compared to S9346. Age was comparable, but there was more obesity in the more recent trial, S9346.

Discussion

The wide use of PSA in the detection and monitoring of disease activity has led to a significant stage migration of prostate cancer. Better local control and more detailed imaging may also have contributed to improved outcomes in the PSA era. We evaluated the potential change in survival in the setting of metastatic prostate cancer using three sequential phase III cooperative group trials with comparable eligibility criteria. Our analysis indicates an overall improvement in risk-adjusted survival for both non-AA and AA men. Of note is the resolution of the disparity in survival between the races in S9346. There are several possible explanations for the favorable survival observed in the latter trial. After adjusting for known risk factors such as PS, extent of disease, PSA and bone pain, the risk of death on S9346 is lower than S8894. This may be due to the model not containing precise enough risk factors to adequately model survival such as detailed enumeration and extent of bone lesions. There are no validated risk models in the setting of hormone sensitive disease. We did not have data on hemoglobin, LDH and alkaline phosphatase for these trials, possibly important measures as they were identified as prognostic factors in the Halabi nomogram which is based on castrate-resistant prostate cancer[13]. Additionally, assessment of PSA velocity in the period prior to the metastatic diagnosis or more detailed disease extent information might also explain some of the discrepancy between the trials[14, 15]. Unfortunately, this level of detail is not available for these trials. We employed the best disease predictors we could identify, but the multivariate model is likely incomplete.

Each trial used contemporary hormonal therapy. We do note that different anti-androgens (flutamide vs. bicalutimide) may have played some role in the different trial prognosis. Although half of S8894 patients were randomized to placebo after bilateral orchiectomy, the survival differences between trials cannot be explained by lack of anti-androgen use since, with long-term follow-up, there was no statistically significant survival difference between the two arms of S8894 (median survival 2.8 years for flutamide, and 2.5 years for placebo, logrank p=0.16). Additionally, we assessed the flutamide by race interaction (p=0.59).

S9346 was designed as a non-inferiority trial. Since the DSMC has let this trial continue to the final planned analysis, it is unlikely that either arm is substantially better than the other. Another potential contributor to the observed differences in survival is the overall improved health care for both non-prostate cancer and prostate cancer therapy including the introduction of docetaxel as a standard therapy for castration resistant prostate cancer. However, S9346 patients who were randomized before and after 2004 (when docetaxel received FDA approval) showed no difference in median survival (46.3 months prior to and 45.1 months after 2004).

Most gratifying is the improvement in outcomes of advanced prostate cancer overall and particularly that for AA men. Our previous analysis of S8894 found that these men

experienced worse outcomes from their disease even in the context of the carefully overseen therapy in a clinical trial[16]. When we evaluated zipcode summary information regarding income and education between the two trials (Table 4), there was no evidence of a shift in the SES over time. Also, the 5-year survival of AA and white patients in the SWOG trials are comparable to those reported by SEER for men with newly diagnosed metastatic prostate cancer, suggesting this is a fairly representative sample[17]. A strength of this analysis is that all patients received the same protocol-specified treatment and comparable follow-up and disease monitoring.

We, therefore, hypothesize that the survival improvement for all patients, particularly AA men, is based on a significant shift to less extensive disease. A similar finding of improved disease free survival was reported among AA men compared to white men diagnosed with clinically localized prostate cancer and treated with radical prostatectomy (1991 to 1995 versus 1996 to 1999)[18]. We would further hypothesize that this improvement is based on greater awareness of prostate cancer and improved health seeking behavior among AA men. The disappearance of this disparity is an important advance in the care of men with prostate cancer. However, AA men have a 2–3 fold greater incidence of newly diagnosed metastatic prostate cancer compared to White men ages 40 to 69 years from 1995 to 2007 which contributes to a similar increased mortality rate[17, 19]. A greater effort is needed to eliminate disparities in prostate cancer.

Conclusion

Based on SWOG trial data, men with newly diagnosed M1 prostate cancer who are hormone-naïve have significantly better survival in the PSA era after accounting for risk factors. AA men have greater absolute gains in survival compared to non-AA men. Current AA prognosis is similar to non-AA groups. These results suggest that these gains may be at least partially attributable to PSA monitoring.

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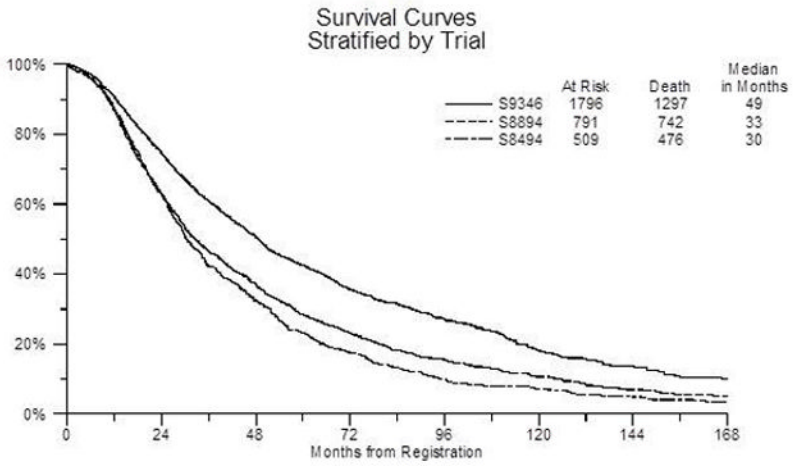

Figure 1.
Kaplan-Meier survival curves stratified by clinical trial

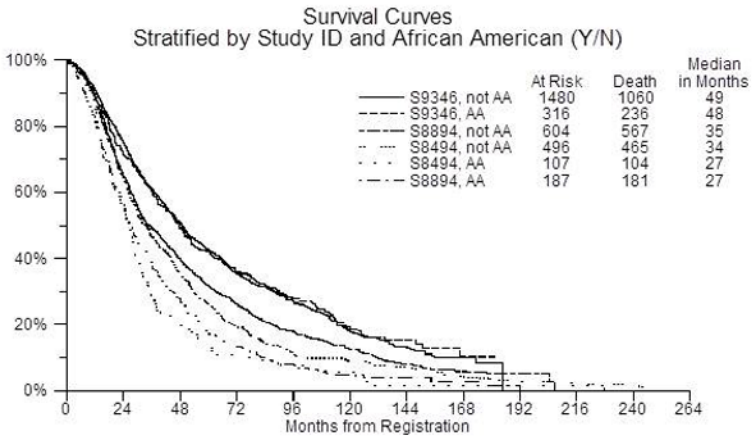

Figure 2.
Survival curves stratified by clinical trial and African American status

Table 1

Patient and Disease Factors for Eligible Patients with Complete Data from Each Trial

	S8494 (n=509)	S8894 (n=791)	S9346 (n=1796)
Years of Accrual	3/1985–4/1986	12/1989–9/1994	5/1995–9/2008
Extensive Disease vs. Minimal	439 (86%)	642 (81%)	1209 (67%)
Bone Pain Present	267 (52%)	46% (n=364)	36% (n=652)
Race			
African American	99 (19%)	187 (23.6%)	317 (17.7%)
White	409 (80%)	590 (74.6%)	1440 (79.0%)
Other	1 (0.2%)	14 (7.8%)	68 (3.7%)
Performance Status 2–3 vs. 0–1	79 (15.5%)	28 (3.5%)	115 (6.3%)
Gleason Score			
<=6	N/A	249 (32%)	313 (17%)
7	N/A	240 (30%)	614 (34%)
8–10	N/A	302 (38%)	896 (49%)
Age median (Q1, Q3)	68 (62, 74)	70 (64, 75)	68 (61, 75)
PSA median (Q1, Q3) ng/ml	N/A	126 (47, 516)	51 (17, 195)
% overweight (BMI ≥ 25)	287 (56%)	447 (57%)	1341 (74%)

Table 2

Results of Multivariate Proportional Hazards Modeling of Survival Adjustment for All Risk Factors (n=2587) for S8894 and S9346**

Covariate	Hazard Ratio	95% CI	p-value
Extensive vs. minimal	1.36	(1.22, 1.51)	<0.0001
Bone pain presence	1.70	(1.55, 1.87)	<0.0001
PSA in 50 ng/ml increments	1.00	(0.99, 1.000	0.22
Age in 5 yr. increments	1.04	(1.01, 1.06)	0.009
African American vs. Not	1.30	(1.10, 1.54)	0.003
Performance Status 2–3 vs. 0–1	1.67	(1.39, 2.01)	<0.0001
Gleason 7 vs. 2–6	1.10	(0.97, 1.24)	0.16
Gleason 8–10 vs. 2–6	1.55	(1.37, 1.75)	<0.0001
African American interaction with S9346*	0.74	(0.59, 0.93)	0.008
S9346 vs. S8894	0.78	(0.70, 0.87)	<0.0001

* all other interactions of risk factors (ie, extent of disease, PSA, age, performance status, Gleason score) with study cohort (S9346 vs. S8894) were non-significant; p>0.10

** S8494 is excluded because of no PSA or Gleason score information

Table 3

Distribution of Risk Factors among African Americans (AA) Stratified by Clinical Trial

	S8484	S8894	S9346
Risk Factor	**AA (n=99)**	**AA (n=187)**	**AA (n=317)**
Extensive Disease n (%)	90 (91%)	165 (88%)	219 (70%)
Bone Pain n (%)	65 (66%)	101 (54%)	110 (35%)
Performance Status 2–3 n (%)	26 (26%)	13 (7%)	33 (10%)
Gleason Grade 7 n (%)	N/A	60 (32%)	111 (35%)
8–10 n (%)	N/A	85 (45%)	162 (51%)
Overweight n (%)	49 (49%)	81 (43%)	202 (64%)
Age in yrs, median (25%, 75%)	67 (62, 72)	69 (63, 75)	66 (60, 73)
PSA ng/ml, median (25%, 75%)	N/A	268 (88, 1000)	117 (37, 526)
Percent of People with College Education in the Patient's Zip code, Median (25%, 75%)	N/A	15% (11%, 23%)	17% (12%, 26%)
Median Income in Thousands of Dollars in the Patient's Zip Code, Median (25%, 75%)	N/A	19.0 (14.2, 25.0)	21.7 (15.3, 30.1)