Duration of Short-Course Androgen Suppression Therapy and the Risk of Death As a Result of Prostate Cancer

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A B S T R A C T

Purpose

We evaluated whether the duration of androgen suppression therapy (AST) had an impact on the risk of prostate cancer–specific mortality (PCSM) in men with unfavorable-risk prostate cancer (PC) within established Gleason score (GS) categories.

Patients and Methods

Between February 2, 1996, and December 27, 2001, 761 men with unfavorable-risk PC were treated in Australia, New Zealand, Ireland, or the United States in a randomized trial with radiotherapy and 3, 4, or 6 months of AST (the study cohort). Competing risks regression was used to evaluate whether the duration of AST interacted with GS and was significantly associated with the risk of PCSM, adjusting for age, trial site, and PC prognostic factors.

Results

After a median follow-up of 10.9 years, 263 men died, 111 (42%) from PC. For all men, 6 versus 3 or 4 months of AST was associated with a reduced risk of PCSM (adjusted hazard ratio [AHR], 0.55; 95% CI, 0.36 to 0.82; $P = .004$). AHRs evaluating the impact of the duration of AST on the risk of PCSM were 0.67 (95% CI, 0.29 to 1.56; $P = .35$), 0.47 (95% CI, 0.25 to 0.85; $P = .01$), and 0.59 (95% CI, 0.30 to 1.19; $P = .14$) for men with GS ≤ 6 , 7, and 8 to 10 PC, respectively. Therefore, the strongest evidence for this benefit was in men with GS 7 PC.

Conclusion

AST durations of no less than 6 months should be considered when treating GS 7 PC with conventional dose RT.

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INTRODUCTION

Gleason score (GS)¹ remains an important determinant of the risk of death from prostate cancer (PC) following definitive treatment for men with localized or locally advanced PC. Although androgen suppression therapy (AST) is not typically used in conjunction with radiation therapy (RT) in the management of GS ≤ 6 PC, it is routinely used in the adjuvant setting for 2 to 3 years in conjunction with RT for men with localized or locally advanced PC and GS 8 to 10 PC on the basis of survival benefits documented from randomized controlled trials (RCTs).^{2,3}

However, the optimal duration of AST for men with GS 7 PC remains without consensus. The National Cancer Center Network (NCCN) guidelines⁴ specify that for men with GS 7 PC, initial treatment could include RT with 4 to 6 months of neoadjuvant, concurrent, and adjuvant

AST with or without a brachytherapy boost for men with localized disease, and RT and 2 to 3 years of adjuvant AST for men with locally advanced disease. The evidence for a PC-specific survival benefit of adding 6 months of AST to RT is derived from two RCTs^{5,6} in which a significant proportion of men had GS 7 PC. This proportion was 58% in the DFCI (Dana-Farber Cancer Institute) 95096 study⁵ in which all men had localized disease (American Joint Committee on Cancer [AJCC] tumor category [T] 1,2⁷) and 38% in the Trans-Tasman Radiation Oncology Group (TROG) 96.01 study⁶ in which 40% of men had locally advanced PC (AJCC T3,4). The evidence supporting a PC-specific survival benefit with as little as 4 months of AST was provided by two RCTs^{8,9} performed by the Radiation Therapy Oncology Group (RTOG). Of the total number of men in the RTOG 8610 study,⁸ 66% had locally advanced GS 7 PC; of the total number of men in the RTOG 9408 study,⁹ 27% had localized GS 7 PC.

The evidence for a PC-specific survival benefit from administering 3 years of adjuvant AST for men with locally advanced PC is provided by the European Organisation for Research and Treatment of Cancer (EORTC) randomized trial² of RT and 3 years versus 6 months of AST in which 30% of men had GS 7 PC. Although a minimum of 2 years of adjuvant AST is recommended in the NCCN guidelines for men with locally advanced PC, the subgroup analysis of the RTOG 9202 randomized study³ on which this recommendation is based evaluated RT and 28 months versus 4 months of AST for men with locally advanced PC and observed a survival benefit for long-term AST only in the subgroup of men with GS 8 to 10 PC. Therefore, the only data supporting long-term AST therapy in men with locally advanced GS 7 PC is from the EORTC trial² in which the overall and PC-specific survival benefit may have been driven by men with GS 8 to 10 PC, as suggested by the RTOG 9202 study.³

Although a reduction in prostate cancer-specific mortality (PCSM) has been consistently observed when at least 4 months of AST is added to RT for men with unfavorable-risk PC GS 7 to 10 or prostate-specific antigen (PSA) of more than 10 ng/mL or T2b or higher, it is unknown whether 6 months of AST reduces this risk specifically in men with GS 7 PC. In this study, by using individual patient data from three RCTs, we evaluated whether RT and the addition of 6 months of AST compared with 3 or 4 months of AST was associated with a reduction in the risk of PCSM in men with unfavorable-risk PC overall and within the specific GS strata of ≤ 6 , 7, and 8 to 10 adjusting for age, trial site, and PC prognostic factors.

PATIENTS AND METHODS

Patient Selection and Treatment

Between February 2, 1996, and December 27, 2001, 761 men with unfavorable-risk PC were treated with RT and 3, 4, or 6 months of AST and had a life expectancy of at least 10 years (the study cohort). Unfavorable-risk PC was defined as GS ≥ 7 , PSA more than 10 ng/mL, or 1992 AJCC⁷ clinical category T2b or higher based on digital rectal examination. Individual patient data from three RCTs^{5,6,10} were used to form the study cohort. Permission was obtained from each of the institutional review boards or ethics boards to perform this analysis. In all studies, AST included both a luteinizing hormone-releasing hormone (LHRH) agonist and flutamide 250 mg by mouth three times daily. All men were treated with three-dimensional conformal RT except for 3% of men in the Irish Clinical Oncology Research Group 97-01 (ICORG-97-01) study,¹⁰ and RT doses were 70 Gy in 1.8 to 2.0 Gy fractions in the DFCI 95096⁵ and ICORG-97-01¹⁰ studies and 66 Gy in 2.0 Gy fractions in the TROG 96.01 study.⁶

Follow-up and Determination of the Cause of Death

At each follow-up, a physical examination was performed that included a digital rectal examination, and a PSA level was obtained. Follow-up was performed every 3 months for men enrolled on the ICORG-97-01 study for the duration of the study,¹⁰ every 3 months for 2 years, every 4 to 6 months for 5 years, and annually thereafter on the DFCI 95096⁵ and TROG 96.01⁶ studies. Salvage AST following PSA failure used an LHRH agonist and was initiated at a median PSA of 9.6, 5.6, and 17.0 ng/mL for men on the DFCI 95096,⁵ ICORG-97-01,¹⁰ and TROG 96.01 studies,⁶ respectively. A patient who died needed to have documented castration-resistant and metastatic PC and an increasing PSA at the time of last follow-up for that death to be defined as a PC-specific death.

Statistical Methods

Descriptive statistics were used to characterize the distribution of clinical characteristics and risk group¹¹ of the study cohort at registration stratified by the duration of AST (6 v 3 or 4 months). A Mantel-Haenszel χ^2 metric¹² was

used to compare the distribution of baseline clinical characteristic categories across the cohorts defined by the AST duration. For continuous variables, medians and their distributions were compared by using a Wilcoxon two-sample test.¹³ The follow-up median and its distribution were compared by using a log-rank *P* value and calculated by using the Kaplan-Meier method¹⁴ for men who received 6 compared with 3 or 4 months of AST.

Competing Risks Analysis

A multivariable Fine and Gray's competing risks regression interaction model¹⁵ was used to evaluate whether the duration of AST (in months) interacted with GS and was significantly associated with the risk of PCSM, adjusting for age in years at random assignment (continuous), PSA level in ng/mL (continuous), 1992 AJCC category⁷ (T2c or higher v T2b or lower), and trial (United States^{5,11} or ICORG-97-01¹⁰ versus TROG 96.01.⁶) T and GS categories were selected on the basis of established risk groups.¹¹ A test for

Table 1. Comparison of the Distribution of Clinical Characteristics and Trial Site of the 761 Men in the Study Cohort at Random Assignment Stratified by the Duration of AST Received

Clinical Characteristic	AST Duration (months)				<i>P</i>
	3 or 4 (n = 392)		6 (n = 369)		
	No.	%	No.	%	
PSA, ng/mL					.01
Median	15.3		13.2		
IQR	9.0-27.8		8.4-21.1		
PSA level, ng/mL					.02
≤ 4	17	4	18	5	
> 4 to 10	103	26	106	29	
> 10 to 20	120	31	144	39	
> 20	152	39	101	27	
Age at randomization, years					.001
Median	67.7		69.7		
IQR	64.0-71.1		64.4-73.4		
≤ 60	45	11	36	10	<.001
61 to 70	224	57	158	43	
71 to 80	121	31	171	46	
> 80	2	1	4	1	
1992 AJCC T category ⁷					<.001
T2b or lower	114	29	170	46	
T2c or higher	278	71	199	54	
Gleason score*					.80
≤ 6	172	44	158	43	
7	151	39	155	42	
8 to 10	69	18	56	15	
Risk group ¹²					<.001
Intermediate†	59	15	119	32	
High†	333	85	250	68	
Trial site					.15
United States and Ireland	127	32	102	28	
Australasia	265	68	267	72	
Follow-up, years					.19
Median	10.8		11.0		
IQR	9.9 to 11.6		9.9 to 11.7		

NOTE. Percentages may not sum to 100% due to rounding.

Abbreviations: AJCC, American Joint Committee on Cancer; AST, androgen suppression therapy; IQR, interquartile range; PSA, prostate-specific antigen; T, tumor.

*Of the 330 men with Gleason score ≤ 6 , 128 men (39%) had Gleason score 5 prostate cancer.

†Intermediate risk includes Gleason score ≤ 7 and PSA > 10 to 20 ng/mL or T2b but no patient can have a PSA > 20 ng/mL or Gleason score of 8 to 10 or T2c or higher which constitutes high risk.

Table 2. Unadjusted and Adjusted HRs From the Competing Risks Regression Interaction Model¹⁵ Representing the Risk of PCSM by Duration of AST Received and for Trial Site, Age, and Prostate Cancer Prognostic Factors

Factor	No. of Men	No. of Events	Univariable Analysis			Multivariable Analysis		
			HR	95% CI	P	AHR	95% CI	P
Gleason score $\leq 6^*$								
6 Months AST	158	9	0.64	0.28 to 1.48	.30	0.67	0.29 to 1.56	.35
3 or 4 Months AST	172	15	1.0 (Ref)		—	1.0 (Ref)		—
Gleason score 7*								
6 Months AST	155	16	0.45	0.25 to 0.82	.009	0.47	0.25 to 0.85	.01
3 or 4 Months AST	151	33	1.0 (Ref)		—	1.0 (Ref)		—
Gleason score 8 to 10*								
6 Months AST	56	12	0.50	0.26 to 0.99	.046	0.59	0.30 to 1.19	.14
3 or 4 Months AST	69	26	1.0 (Ref)		—	1.0 (Ref)		—
AST duration $\times$ Gleason score	761	111	N/A		.79	N/A		.76
Age at randomization, years	761	111	0.98	0.95 to 1.01	.26	0.99	0.96 to 1.02	.59
PSA, ng/mL	761	111	1.009	1.004 to 1.014	< .001	1.007	1.002 to 1.013	.01
1992 AJCC T category ⁷								
$\geq$ T2c	477	89	2.34	1.47 to 3.72	< .001	1.97	1.21 to 3.23	.007
$\leq$ T2b	284	22	1.0 (Ref)		—	1.0 (Ref)		—
Trial Site								
Australasia	532	89	1.48	0.92 to 2.37	.11	1.30	0.79 to 2.14	.31
United States and Ireland	229	22	1.0 (Ref)		—	1.0 (Ref)		—

NOTE. After adjustment for all covariates listed, 4 v 3 months of androgen suppression therapy (AST) was not associated with a reduction in the risk of prostate cancer-specific mortality (PCSM; adjusted hazard ratio [AHR], 0.79; 95% CI, 0.45 to 1.40; $P = .43$). $P < .05/3$ or $< .017$ was considered significant.

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; N/A, not applicable; PSA, prostate-specific antigen; Ref, reference group for categorical covariate; T, tumor.

*After adjustment for all covariates listed, without the interaction between AST duration and Gleason score, 6 v 3 to 4 months of AST was associated with a reduction in the risk of PCSM (AHR, 0.55; 95% CI, 0.36 to 0.82; $P = .004$).

interaction between AST duration and three cohorts defined by GS ≤ 6 , 7, and 8 to 10 PC was also performed. The adjustment for trial (United States and ICORG-97-01 versus TROG 96.10) ensured that data containing 3 or 4 (TROG 96.01⁶ and ICORG97-01¹⁰) versus 6 months (TROG 96.01⁶ and United States¹¹) of AST were represented in each arm of the trial site covariate. This covariate also adjusted for the difference in the median PSA level at which salvage AST was initiated across trial sites. The same competing risks analysis¹⁵ was repeated for the end point of non-PCSM. Time 0 was defined as the date of random assignment. Unadjusted and adjusted hazard ratios (AHRs) for PCSM with associated 95% CIs and P values were calculated for each covariate from the Fine and Gray regression model.

Estimates of PCSM

The cumulative incidence method¹⁶ was used to estimate and characterize PCSM stratified by the duration of AST and also by GS. Comparisons of these estimates were performed by using a k-mean P value. A two-sided $P < .05$ was considered statistically significant, and a Bonferroni correction¹⁷ was used to adjust for multiple ($n = 3$) comparisons by GS. R version 2.12.1 software (R Foundation for Statistical Computing, Vienna, Austria) was used for all calculations pertaining to Gray's k-mean P value and Fine and Gray regression. SAS version 9.2 software (SAS Institute, Cary, NC) was used for all remaining analyses.

RESULTS

Comparison of the Distribution of Baseline Patient and Tumor Characteristics Stratified by the Duration of AST

As detailed in Table 1, men who received 6 as compared with 3 or 4 months of AST were older (median age, 69.7 v 67.7 years; $P = .001$), had a lower median PSA level (13.2 v 15.7 ng/mL; $P = .01$), and were less likely to have high-risk clinical T category (54% v 71%; $P < .001$). However, there was no significant difference in the distribution of GSs

($P = .80$), trial site ($P = .15$), or median follow-up (11.0 v 10.8 years; $P = .19$) among men who received 6 as compared with 3 or 4 months of AST.

Competing Risks Analysis

After a median follow-up of 10.9 years (interquartile range, 9.9 to 11.7 years), 263 men died, 111 (42%) as a result of PC. As listed in Table 2, for all men 6 versus 3 or 4 months of AST was associated with a reduced risk of PCSM (AHR, 0.55; 95% CI, 0.36 to 0.82; $P = .004$). AHRs evaluating the impact of the duration of AST on the risk of PCSM were 0.67 (95% CI, 0.29 to 1.56; $P = .35$), 0.47 (95% CI, 0.25 to 0.85; $P = .01$), and 0.59 (95% CI, 0.30 to 1.19; $P = .14$) for men with GS ≤ 6 , 7, and 8 to 10 PC, respectively, leading to a nonsignificant interaction ($P = .76$) between GS and AST duration because all the AHRs are less than 1.0. Within the subgroup of men with GS 7 PC, there was a reduction in the risk of PCSM among the 195 men with localized PC (AHR, 0.58; 95% CI, 0.23 to 1.43; $P = .24$) and 111 men with locally advanced PC (AHR, 0.41; 95% CI, 0.15 to 1.11; $P = .08$); however, by creating these subgroups within the GS 7 PC cohort, power was reduced and statistical significance could not be reached. For all men in the study and within each GS cohort, 6 versus 3 or 4 months of AST was not associated with an increase in the risk of non-PC-specific mortality ($P \geq .16$) on the adjusted analyses.

Estimates of PCSM

Among all 761 men with unfavorable-risk PC, cumulative incidence estimates of PCSM were significantly lower ($P < .001$) in men who received 6 months (10%; 95% CI, 7% to 14%) versus 3 or 4 months (17%; 95% CI, 14% to 22%) of AST and at 10 years following random assignment as shown in Figure 1. After adjusting for three

Fig 1. Cumulative incidence¹⁶ estimates of prostate cancer-specific mortality following random assignment for the 761 men in the study cohort stratified by the duration of androgen suppression therapy (AST) received in months; k-mean $P < .001$.

comparisons, cumulative incidence estimates of PCSM shown in Figure 2 were significantly lower in men with GS 7 PC undergoing 6 as compared with 3 or 4 months of AST ($P = .008$); however, these estimates were not significantly different for men with $GS \leq 6$ PC ($P = .30$) or GS 8 to 10 PC ($P = .04$).

DISCUSSION

In this study using individual patient data from the TROG 96.01,⁶ ICORG-97-01,¹⁰ and DFCI 95096⁵ RCTs, we found that the use of 6 versus 3 or 4 months of AST in addition to RT in men with unfavorable-risk PC was associated with a 45% reduction in the risk of PCSM and an absolute benefit of 7% at 10 years after a median follow-up of 10.9 years. The strongest evidence for this benefit was in men with GS 7 PC in which the P value (.01) measuring the impact of AST duration on the risk of PCSM was significant, unlike that for $GS \leq 6$ ($P = .35$) or GS 8 to 10 ($P = .14$). Given the nonsignificant interaction between GS and AST duration, it is possible that the risk of PCSM may be reduced with 6 as compared with 3 or 4 months of AST for all GS groups. The clinical significance of these findings is that for men with GS 7 PC (who make up approximately 30% of all men diagnosed with PC in the United States¹⁸), 6 versus 3 or 4 months of AST appears to result in a lower risk of PCSM. However, only a randomized trial could prove this association, and the trial would need approximately 600 men with GS 7 PC followed for 15 years to achieve 80% power and a 0.05 significance level.

Additional questions remain to be answered. First, every patient in this study received AST consisting of an LHRH agonist and an antiandrogen. Whether similar results would be achieved with an LHRH agonist only or whether the risk of PCSM would be decreased further with more prompt androgen suppression (as achieved with an LHRH antagonist¹⁹) or more complete androgen blockade by adding abiraterone acetate (a selective androgen biosynthesis inhibitor that blocks the action of CYP17) to the LHRH agonist remain unanswered. A postrandomization analysis²⁰ suggested a decreased risk of recur-

Fig 2. Cumulative incidence¹⁶ estimates of prostate cancer-specific mortality after random assignment for the 330, 306, and 125 men with Gleason score ≤ 6 (A), 7 (B), and 8 to 10 (C) prostate cancer, respectively, stratified by the duration of androgen suppression therapy (AST) received in months; k-mean $P = .30$, $P = .008$, and $P = .04$ for Gleason score ≤ 6 , 7, and 8 to 10, respectively. Significant $P < .017$ after adjustment¹⁷ for three comparisons.

rence in men who received both the LHRH agonist and abiraterone acetate (AA) for 6 months as compared with the LHRH agonist and the AA for less than 6 months, but a prospective RCT is needed to definitively answer this question. An RCT²¹ in men with metastatic, castration- and docetaxel-resistant PC produced a survival benefit when abiraterone acetate was given compared with placebo. Whether adding abiraterone acetate to an LHRH agonist will also prolong survival in men with nonmetastatic localized or locally advanced PC remains to be studied. Second, whether a further decrease in the risk of PCSM will be achieved when RT doses higher than 70 Gy to the entire prostate gland are used in combination with AST of 6 months duration also requires further study. The MRC RT01 RCT²² compared 74 to 64 Gy to the isocenter of the prostate in the setting of 3 or 6 months of AST and showed a decrease at 5 years in PSA failure-free survival. Further follow-up will be needed to determine whether PCSM is reduced in the higher-dose arm of that study. As detailed in Table 2, increasing PSA level was associated with an increased risk of PCSM. Additional study is needed in men with high-risk disease and a PSA of more than 20 ng/mL to assess the optimal duration of AST.

Several points require further consideration. First, the reduction in the risk of PCSM in men with GS 8 to 10 PC approached but did not reach significance ($P = .14$). One possible explanation for this finding is that this comparison may have been underpowered, given that only 125 (16%) of 761 men in this study had GS 8 to 10 PC. In addition, 6 as compared with 3 or 4 months of AST may be inadequate to further reduce the risk of PCSM for men with GS 8 to 10 and T3,4 disease, as suggested by two randomized trials (EORTC and RTOG 96.01).^{2,3} Specifically, although a survival benefit was observed for all men with clinical stage T3,4 PC by the EORTC RCT² with 36 months versus 6 months of AST, the RTOG 9202 study³ observed a survival benefit only in the subgroup of men with clinical stage T3,4 and GS 8 to 10 PC enrolled on an RCT of RT and 28 months versus 4 months of AST. Given the RTOG 9202 result,³ it is possible that the survival benefit in the EORTC study was driven by the GS 8 to 10 cohort. Since men with T3,4 made up a significant proportion or 46% (57 of 125) of the GS 8 to 10 cohort in this study, this could explain the marginally significant reduction in the risk of PCSM for men with GS 8 to 10 PC. Although evidence for a reduction in the risk of PCSM for 6 versus 3 to 4 months of AST was present but not significant in men with GS ≤ 6 , since a six-core biopsy was standard when the RCTs were performed, some men with GS ≤ 6 PC may have had GS 7 PC that was missed because of biopsy sampling error. Second, we combined the data on men who

received 3 or 4 months of AST because we could not measure a significant reduction in the risk of PCSM in men who received 4 months versus 3 months of AST ($P = .43$); however, the AHR for this comparison was 0.79 and, although the 95% CI includes 1.0, it is possible that with longer follow-up a significant difference may emerge. Third, all models in this study were age adjusted because although this study evaluated the risk of PCSM by duration of AST administered, it has been shown that testosterone suppression persists after withdrawal of AST, and the duration of this suppression increases with advancing age which, in turn, is associated with a decreasing risk of PCSM.²³ Finally, information on GS 4 + 3 as compared with GS 3 + 4 was not available for all men in the study cohort and, as a result, a future study will be needed to ascertain whether the reduction in the risk of PCSM for 6 versus 3 or 4 months of AST applies to all men with GS 7 PC or only to those with GS 4 + 3 or 3 + 4. However, given the way biopsy GS is now reported,²⁴ men in this study who were read as GS 5, 6, and 7 would likely be classified as GS 6, 3 + 4, and 4 + 3, respectively, by today's standards.

Despite these considerations, the evidence supporting a reduced risk of PCSM with conventional dose RT and 6 as compared with 3 or 4 months of AST in men with GS 7 PC and localized or locally advanced PC should prompt consideration for use of no less than 6 months of AST in these men.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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