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Duration of the anti-androgen in men undergoing six months of an LHRH agonist and radiation therapy for unfavorable-risk prostate cancer and the risk of death

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Abstract

Importance: Whether adding an anti-androgen (AA) to a luteinizing hormone-releasing hormone agonist in the radiotherapeutic management of unfavorable-risk prostate cancer (PC) reduces the risk of all cause and PC-specific mortality (ACM and PCSM) among men within differing comorbidity subgroups is unknown.

Objective: We evaluated whether the extent of AA received impacted the risk of ACM and PCSM within comorbidity subgroups.

Design, Setting and Participants: Randomized trial enrolling 206 men with localized unfavorable-risk PC between 1995 and 2001.

Intervention: Radiation with or without 6 months of androgen deprivation therapy (ADT) stratified by extent of AA received (Full: 6 versus Partial: < 6, median 4.2 months). Partial AA use was due to early discontinuation for elevated liver function tests or diarrhea.

Main Outcome Measures: Risk of PCSM and ACM within comorbidity subgroups.

Results: After a median follow-up of 16.62 years, 156 men died; 29 from PC (19%) of which 25 (86%) and 4 (14%) were among the 157 and 49 men with no or minimal versus moderate to severe comorbidity respectively. In men with moderate to severe comorbidity increasing death was observed as treatment transitioned from no to partial to full ADT ($p = 0.02$) with an increased ACM-risk with full versus partial AA use (adjusted hazard ratio (AHR), 2.25 [95% confidence interval (CI), 0.94–5.41]; $P = 0.07$); whereas only 1 and no PC deaths occurred in men receiving a partial versus full AA course respectively. Among men with no or minimal comorbidity there was no decrease in ACM (AHR, 0.97 [95% CI, 0.49–1.91]; $P = 0.92$) or PCSM-risk (AHR 0.39 [95% CI 0.07–52.18]; $P = 0.28$) for the comparison of full versus partial AA use.

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Conflicts of Interest: None

Conclusion and Relevance: Increasing AA use by 2 months does not appear to impact survival in men with localized unfavorable-risk PC and no or minimal comorbidity but may shorten survival in men with moderate to severe comorbidity raising concern regarding in whom and for how long the AA should be prescribed.

Keywords

prostate cancer; radiation therapy; mortality; androgen deprivation therapy

Introduction

Several prospective randomized trials have documented that the combination of radiation and androgen deprivation therapy (RT and ADT) is superior to RT alone in the treatment of intermediate and high risk prostate cancer (PC) (1–5) with respect to the endpoints of PC specific and overall survival (OS). However, it remains unknown if a combined ADT approach using both a luteinizing hormone-release hormone (LHRH) agonist and an anti-androgen (AA) confers an OS advantage as compared to an LHRH agonist alone. A single randomized study addressed this question and showed a significant prolongation in overall but not PC-specific survival and included men with locally advanced or metastatic PC treated with ADT without RT(6). Given the survival benefit in the absence of a reduction in death from PC and lack of RT use, the question regarding the optimal extent of ADT necessary to maximize OS and minimize death from PC in men managed with RT for non-metastatic and unfavorable-risk PC remains unanswered.

It has been recently shown that in men with no or minimal comorbidity using the Adult Comorbidity Evaluation (ACE)-27 comorbidity metric, the addition of 6 months of ADT to RT was associated with both an overall and PC-specific survival benefit in men with localized, unfavorable-risk PC (7). Conversely, among all men in the study, this improvement in overall survival was no longer significant in that ADT use was associated with a significant survival decrement in men with moderate to severe comorbidity due to an increased risk of fatal myocardial infarction. Therefore, the question remains as to whether the survival benefit or decrement observed would persist and in whom with respect to an individual's ACE-27 comorbidity score if treatment with 6 months of an LHRH agonist and < 6 months of the AA as compared to both an LHRH agonist and an AA for 6 months was utilized. We have previously shown that after a median follow-up of 8.2 years, the incidence of PSA recurrence was significantly increased in men who received less than 6 months of combined ADT due to early termination of the AA secondary to elevated liver function tests (LFTs) or diarrhea as compared to those who received the full six-month course of both the LHRH agonist and AA (8).

Therefore, using updated data with a median follow-up of 16.62 years from that prospective randomized trial of 206 men where baseline comorbidity measured using the ACE-27 comorbidity metric was available at study outset, we now report on the impact of full (i.e. 6 months) versus partial (i.e. < 6 months) AA use on the risk of all cause and prostate cancer specific mortality (ACM and PCSM) within ACE-27 defined comorbidity subgroups adjusting for age and PC prognostic factors.

Patients and Methods

Patient Population and Treatment

Two hundred and six men with 1992 American Joint Commission on Cancer (AJCC) clinical stage (9) T1b-T2bN0M0 unfavorable-risk were enrolled on a prospective randomized trials within academic and community based centers in Massachusetts between December 1, 1995 and April 15, 2001. Unfavorable risk factors included a PSA level > 10 ng/mL (maximum 40 ng/mL), biopsy Gleason score 7–10, or radiographic evidence of extracapsular extension and/or seminal vesicle invasion by using endorectal magnetic resonance imaging. Central review of prostate needle biopsy specimens was performed by a pathologist specializing in genitourinary pathology. Informed consent was signed by all participants prior to study entry. This trial has been registered on the National Institutes of Health Web site, <http://clinicaltrials.gov>, as NCT00116220. Details regarding this trial, including eligibility and exclusion criteria, randomization, stratification, treatment and quality assurance guidelines have been previously described (2).

Androgen Deprivation Therapy Usage and Modification

The protocol regarding ADT usage, toxicity and dose modification has previously been described (8). Briefly, ADT consisted of 6 months of an LHRH agonist (leuprolide or goserelin acetate) in combination with 6 months of the nonsteroidal AA flutamide. The prescription dose of flutamide was 250 mg three times a day. Liver function tests (LFTs) including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate and total bilirubin levels were obtained at regular intervals. Flutamide was discontinued if the ALT or AST level exceeded twice the upper limit of normal and then resumed once these levels normalized. If AST or ALT levels were elevated to twice the upper limit of normal again, flutamide was permanently discontinued. Flutamide was also held if the patient experienced gastrointestinal side effects including cramping, diarrhea, or uncontrolled nausea and was reintroduced once these symptoms resolved. If the patient could not tolerate the full dose of resumed flutamide, then a half dose was attempted. If the half dose could not be tolerated, then flutamide was discontinued permanently. The number of days each patient took flutamide was recorded. All patients received 6 months of LHRH antagonist. In the men receiving partial ADT, the median duration of flutamide was 4.2 months (interquartile range, 3.3 to 5.5 months).

The Adult Comorbidity Evaluation–27

Baseline information regarding patient health history was available prior to randomization permitting assignment of a comorbidity score using the ACE-27 metric, a validated comorbidity index designed for patients with cancer (10). The index was used to assign grades to conditions into one of four levels of comorbidity (none, minimal, moderate, severe). For the purpose of the current analysis, comorbidity subgroups were defined as no or minimal versus moderate or severe,

Follow-up and Determination of Cause of Death

Patients were seen in follow-up at three month intervals for the first two years, every 6 months for an additional 3 years, and annually thereafter. At each visit, a history and physical examination including a digital rectal examination (DRE) was performed. Prostate specific antigen (PSA) levels were obtained prior to DRE. At time of PSA failure, defined as PSA greater than 1.0 ng/mL and a PSA that increased by greater than 0.2 ng/mL at two consecutive visits after treatment, additional staging studies including pelvic computed tomography scan or magnetic resonance imaging scan and a bone scan were obtained. Salvage ADT was recommended when the PSA level reached 10 ng/mL. Patients' oncologists determined the cause of death, which was updated through February 21, 2015.

Statistical Methods

Comparison of the distribution of clinical characteristics at randomization stratified by receipt of combined, less than combined, or no ADT

Descriptive statistics were used to enumerate the distribution of clinical characteristics including median age, median follow up, median PSA, PSA by category (4 or less, >4 – 10, >10 – 20, >20 ng/ml), clinical T category (T2b vs. T2a vs. T1), ACE-27 comorbidity status (none/minimal vs. moderate/severe), biopsy Gleason score (9–10 vs. 8 or 4+3 vs. 3+4 or less), stratified by the extent of ADT received. For the continuous covariates, a Wilcoxon rank sum test (11) was used to evaluate the comparison of these distributions between patients receiving combined versus less than combined ADT whereas for categorical covariates, a Mantel-Haenszel chi square statistic (12) was used as the *P* value. For the comparison of median follow-up times and their distribution, the Kaplan Meier estimate (13) was used with a log rank *P* value. In addition, a trend *P* value was used to compare distribution across all three subgroups including no, partial or full ADT.

Competing risks and Cox regression analyses for PCSM and ACM

Univariate and multivariate Cox (14) and Fine and Gray's (15) regressions were used to assess whether the extent of ADT was associated with the risk of PCSM and ACM respectively, within comorbidity subgroups. This analysis was adjusted for PSA level, age, clinical T category, and biopsy Gleason score as categorized above. We included interaction terms (16) between comorbidity and treatment with full ADT or treatment with RT where treatment with partial ADT served as the reference group given the previously reported significant interaction between degree of comorbidity and extent of ADT (7). For the endpoint of PCSM, we included a single interaction term for comorbidity and any ADT due to no PC deaths in men with moderate or severe comorbidity who received full ADT. In order to more accurately estimate the adjusted hazard ratio (AHR) for the risk of PCSM for men who received full versus partial ADT in the Fine and Gray's model among men with no or minimal comorbidity, we performed a separate non-interaction multivariable model in these men. Ninety-five percent confidence intervals (CI) and associated *P* values were calculated for each clinical factor's AHR and HR and reported.

Estimates of ACM and PCSM

For the purpose of illustration, cumulative incidence estimates (17) of PCSM and 1-Kaplan-Meier estimates (13) of OS or ACM were calculated and graphically displayed for each comorbidity subgroup stratified by randomized treatment arm and extent of ADT received. For comparison of the estimates of ACM, the log rank *P* value was used, whereas for the comparison of PCSM estimates, a k-mean *P* value was reported. The ACM plots are covariate-adjusted to reflect the results in the multivariate model and the corresponding *p*-values are computed using the covariate-adjusted Log-Rank test (18). Ten-year point estimates and associated 95% confidence intervals were calculated and reported for each patient subset stratified by ADT treatment received and comorbidity subgroup for each endpoint. A two sided *P* value <0.05 was considered statistically significant. SAS version 9.4 was used for all calculations except for those involving competing risks regression and cumulative incidence in which case R was used.

Results

Comparison of the distribution of clinical characteristics at randomization stratified by receipt of combined, less than combined, or no ADT

As shown in Table 1, when assessing for trend from no ADT to partial ADT to full ADT, there were no statistically significant differences in follow-up and PC prognostic factors (age, PSA, Gleason score, clinical T stage, comorbidity) with the exception of category T1, which was found in 58.90%, 41.38% and 41.35% of men receiving full, partial and no ADT, respectively (*P* = 0.04). When comparing the distribution of clinical factors between men receiving partial versus full ADT, men who received partial ADT were statistically significantly more likely to have moderate or severe comorbidity (37.93% vs 17.81%; *P* = 0.03) when compared to men who received full ADT.

Competing risks and Cox regression analyses for ACM and PCSM

After a median follow-up of 16.62 years, 156 men died (76%); 29 deaths were from PC (19%) including 25 (86%) and 4 (14%) PC deaths occurring among the 157 and 49 men with no or minimal versus moderate to severe comorbidity respectively. In men with moderate to severe comorbidity, an increased ACM risk with full as opposed to partial AA use calculated from our interaction model that approached statistical significance was observed (adjusted hazard ratio (AHR), 2.25 [95% confidence interval (CI), 0.94–5.41]; *P* = 0.07); whereas only 1 and no PC deaths occurred in men receiving a partial versus a full AA course respectively. Among men with no or minimal comorbidity there was no decrease in ACM (AHR, 0.97 [95% CI, 0.49–1.91]; *P* = 0.92) or PCSM risk (AHR 0.39 [95% CI 0.07–2.18]; *P* = 0.28).

Estimates of ACM and PCSM

As shown in Figure 1A, men with no or minimal comorbidity had estimates of ACM which declined as the extent of ADT received increased from none to partial to full ADT (*P* for trend = 0.05). Conversely, in men with moderate to severe comorbidity, the reverse trend was observed (*P* for trend = 0.02) (Figure 1B). Specifically, the 10-year point estimates for men

with no or minimal comorbidity receiving no, partial or full ADT were 43.38% (95% CI, 33.19%–53.12%), 30.15% (95% CI, 13.10%–39.29%) and 18.90% (95% CI, 9.82%–30.23%). These respective values were 57.65% (95% CI, 37.42%–73.45%), 85.37% (95% CI, 0.00%–99.82%) and 77.04% (95% CI, 32.06%–94.19%) for men with moderate or severe comorbidity.

For men with no or minimal comorbidity, as shown in Figure 2A, the cumulative incidence estimates for PCSM were noted to decrease as the extent of ADT increased (P for trend = 0.003). In contradistinction, there was no significant trend noted in men with moderate or severe comorbidity with respect to estimate of PCSM by extent of ADT received (P for trend = 0.68) (Figure 1B). The 10-year point estimates for men with no or minimal comorbidity receiving no, partial or full ADT were 16.46% (95% CI 9.24%–25.48%), 11.11% (95% CI 1.71%–30.51%) and 1.67% (95% CI 0.13%–7.92%). For men with moderate or severe comorbidity, these respective values were 3.00% (95% CI 0.27%–17.40%), 9.09 (95% CI 0.40%–35.25) and 0% (95% CI 0%–0%).

Discussion

We observed that when comparing receipt of 6 months of both the LHRH agonist and AA versus 6 months of the LHRH agonist and a median of 4.2 months of the AA, in men with unfavorable-risk localized PC and moderate to severe comorbidity, a near significant increase in risk of ACM was observed (AHR 2.38, $P = 0.07$). Conversely, no reduction in ACM was noted in men with no or minimal comorbidity (AHR, 0.97, $P = 0.92$) for this comparison. Moreover a significant trend with increasing death was observed (Figure 1B) in men with moderate to severe comorbidity as treatment received transitioned from no to partial to full ADT ($p = 0.02$).

The clinical significance of these observations is that first, they raise the question as to whether men with moderate to severe comorbidity who opt for treatment with RT and ADT to manage their unfavorable-risk PC should be considered for less than 6 months of AA use. Also, for men with no or minimal comorbidity, it appears that the delivery of full versus partial ADT was not associated with prolonged survival (AHR = 0.97, $P = 0.92$) suggesting that supplementing the LHRH agonist therapy with an AA for approximately 4 rather than 6 months may be sufficient to minimize death from PC and prolong survival as compared to no ADT use.

Several points require further discussion. First, while it is not surprising that decreasing the AA duration by approximately two months did not lead to an increased risk of death in relatively healthy men, it is remarkable that adding these additional two months of the AA was associated with an increased risk of death in men with moderate to severe comorbidity. Moreover, the AA used in this study, flutamide, is less potent than currently employed AA agents such as bicalutamide or enzalutamide (19). Therefore, it is possible that the opposing effects on death of the additional 2 months of the AA in healthy versus unhealthy men may be more pronounced with modern agents. Nevertheless, our observation regarding the optimal extent of AA use within comorbidity subgroups is hypothesis generating and requires validation by other clinical trialists who may have similar data such as the Trans

Tasmanian Radiation Oncology Group (TROG) 9601 investigators. Their study randomized men to 6 versus 3 versus 0 months of combined ADT for intermediate or high risk PC treated with RT (20) and likely some men randomized to the 6 month ADT arm prematurely stopped the AA for elevated LFT's or gastrointestinal intolerance as occurred in our study. Second, when comparing full versus partial AA use with respect to the impact on the risk of death in men with no or minimal comorbidity, the reason there is no additional benefit with full ADT (AHR 0.97, $P=0.92$) can be explained by examining the AHRs for these two treatment groups compared to the RT only arm (AHR 0.63 and 0.65, respectively) where the point estimates for the reduction in the risk of ACM are nearly identical. Finally, a potential reason as to why the trend for men with no or minimal comorbidity, a decreasing risk in PCSM estimates ($P = 0.003$) as shown in Figure 2A did not translate to as large a trend for a decreasing risk in ACM estimates ($p = 0.05$) as shown in Figure 1A may be explained by competing risks. Specifically, 81% of deaths in this study were due to non-PC causes, thus any reduction in PCSM is diluted and will not translate in a 1:1 fashion into a decreased risk of all cause death. This highlights the important impact of competing risks on an individual patient's ability to derive an overall survival benefit from more aggressive PC therapy.

Not with standing these considerations, increasing AA use by 2 months does not appear to impact survival in men with localized unfavorable-risk PC and no or minimal comorbidity but may shorten survival in men with moderate to severe comorbidity PC raising concern regarding in whom and for how long the AA should be prescribed.

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Figure 1A

Figure 1B

Figure 1:
Kaplan Meier estimates (13) of all cause mortality stratified by receipt of full, partial or no androgen deprivation therapy amongst the 157 and 49 men with no or minimal (A) or moderate to severe (B) comorbidity respectively.

Figure 2A

Figure 2B

Figure 2:
Cumulative incidence estimates (17) of prostate cancer-specific mortality stratified by receipt of full, partial or no androgen deprivation therapy amongst the 157 and 49 men with no or minimal (A) or moderate to severe (B) comorbidity respectively.

Table 1:

Comparison of the distribution of clinical characteristics at randomization stratified by receipt of combined, less than combined, or no ADT

	Full ADT (N=73)		Partial ADT (N=29)		No ADT (N=104)		P Trend	P-value (Full ADT vs. Partial ADT)
Clinical characteristic	No. of patients	%	No. of patients	%	No. of patients	%		
Median Age at random assignment, (IQR, years)	71.97 [68.75, 75.38]		71.76 [70.17, 73.62]		73.21 [68.90, 76.30]		0.19	0.47
PSA, ng/mL								
Median (IQR)	11.0 [7.50, 14.84]		11.2 [7.85, 17.33]		11.0 [7.52, 16.35]		0.76	0.52
≤4	4	5.48%	4	13.79%	6	5.77%	0.52	0.77
>4–10	27	36.99%	9	31.03%	38	36.54%		
>10–20	36	49.32%	9	31.03%	43	41.35%		
>20	6	8.22%	7	24.14%	17	16.35%		
1992 AJCC clinical T category (9)								
T1	43	58.90%	12	41.38%	43	41.35%	0.04	0.09
T2a	13	17.81%	6	20.69%	26	25.00%		
T2b	17	23.29%	11	37.93%	35	33.65%		
Gleason Score								
9–10	4	5.48%	2	6.90%	11	10.58%	0.29	0.62
8 or 4+3	22	30.14%	6	20.69%	31	29.81%		
3+4 or less	47	64.38%	21	72.41%	62	59.62%		
ACE-27 Comorbidity Status (10)								
None	52	71.23%	15	51.72%	68	65.38%	0.42	0.03
Minimal	8	10.96%	3	10.34%	11	10.58%		
Moderate/severe	13	17.81%	11	37.93%	25	24.04		
Median follow up in years (IQR)	17.19 [15.42, 18.19]		16.68 [15.57, 17.69]		16.20 [15.13, 17.06]		0.17	0.54

Abbreviations: IQR, interquartile range; PSA, prostate specific antigen; AJCC, American Joint Commission on Cancer; T, tumor; ACE, Adult Comorbidity Evaluation

Mantel-Haenszel Chi-Square, Kruskal-Wallis Test, and Log-Rank test were used for testing trend.

Mantel-Haenszel Chi-Square, Wilcoxon Two-Sample Test, and Log-Rank test were used for comparing Full ADT and Partial ADT.

Table 2:

Unadjusted and Adjusted hazard ratios for each clinical characteristic from the competing risks and Cox regression analyses for PCSM and ACM respectively

Covariate	No of Men	All-cause mortality					Prostate-Cancer Specific Mortality				
		No of AC D	Univariate		Multivariate		No of PCD	Univariate		Multivariate	
			HR [95% CI]	P	AHR [95% CI]	P		HR [95% CI]	P	AHR [95% CI]	P
Age (years)	206	156	1.08 [1.05, 1.12]	<0.001	1.09 [1.05, 1.13]	<0.001	29	1.01 [0.96, 1.08]	0.64	1.02 [0.95, 1.10]	0.56
PSA, ng/mL											
>20	30	23	1.11 [0.69, 1.78]	0.67	0.92 [0.56, 1.52]	0.75	9	3.87 [1.48, 10.10]	0.006	2.07 [0.75, 5.69]	0.16
>4–10	74	52	0.90 [0.63, 1.29]	0.55	0.64 [0.43, 0.96]	0.03	8	1.19 [0.45, 3.15]	0.72	0.75 [0.25, 2.24]	0.64
≤4	14	11	0.95 [0.50, 1.79]	0.87	0.82 [0.41, 1.62]	0.75	4	3.54 [1.08, 11.65]	0.037	3.77 [1.05, 13.53]	0.04
>10–20	88	70	1 (Ref)	-	1 (Ref)	-	8	1 (Ref)	-	1 (Ref)	-
1992 AJCC clinical T category											
T1	98	76	1 (Ref)	-	1 (Ref)	-	9	1 (Ref)	-	1 (Ref)	-
T2a	45	31	0.90 [0.59, 1.37]	0.63	0.87 [0.55, 1.39]	0.56	4	0.98 [0.31, 3.13]	0.97	0.94 [0.27, 3.30]	0.92
T2b	63	49	1.08 [0.75, 1.56]	0.66	1.15 [0.78, 1.70]	0.49	16	3.06 [1.36, 6.91]	0.007	2.69 [0.95, 7.57]	0.06
Gleason Score											
9–10	17	16	2.65 [1.55, 4.54]	<0.001	2.12 [1.13, 3.96]	0.02	5	2.97 [1.06, 8.30]	0.038	1.90 [0.42, 8.51]	0.40
8 or 4+3	59	49	1.64 [1.15, 2.32]	0.006	1.71 [1.19, 2.46]	0.004	9	1.37 [0.60, 3.11]	0.45	1.38 [0.58, 3.31]	0.47
3+4 or less	130	91	1 (Ref)	-	1 (Ref)	-	15	1 (Ref)	-	1 (Ref)	-
Interaction Terms											
No/minimal comorbidity											
RT+Full ADT	60	42	1.03 [0.53, 2.01]	0.93	0.97 [0.49, 1.91]	0.92	3	0.35 [0.07, 1.62]	0.18	0.39 [0.07, 2.18]	0.28
RT	79	57	1.56 [0.81, 2.97]	0.18	1.54 [0.80, 2.98]	0.20	20	2.41 [0.70, 8.29]	0.16	3.08 [0.93, 10.21]	0.07
RT+Partial ADT	18	11	1 (Ref)	-	1 (Ref)	-	2	1 (Ref)	-	1 (Ref)	-
Moderate/severe comorbidity											
RT+Full ADT	13	13	2.55 [1.10, 5.87]	0.03	2.25 [0.94, 5.41]	0.07	0	NA *	NA *	NA *	NA *
RT	25	23	0.75 [0.36, 1.58]	0.45	0.50 [0.22, 1.10]	0.09	3	1.83 [0.16, 20.40]	0.62	1.41 [0.13, 14.81]	0.77
RT+Partial ADT	11	10	1 (Ref)	-	1 (Ref)	-	1	1 (Ref)	-	1 (Ref)	-
Full ADT × comorbidity	206	156	2.47 [0.85, 7.19]	0.10	2.33 [0.77, 7.02]	0.13	29	NA * 0.76 [0.07, 8.36]	NA * 0.82	NA * 2.19 [0.19, 25.08]	NA * 0.53
RT × comorbidity			0.48 [0.18, 1.30]	0.15	0.32 [0.11, 0.91]	0.03					

Abbreviations: PSA, prostate specific antigen; AJCC, American Joint Commission on Cancer; T, tumor; ADT, androgen deprivation therapy; AHR, adjusted hazard ratio

* The AHR comparing full vs. partial ADT was not estimable for men with moderate to severe comorbidity given no and 1 PC death amongst these men receiving partial and full ADT respectively.

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