JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of the Duration of Adjuvant Hormonal Therapy in Patients With Locally Advanced Prostate Cancer Treated With Radiotherapy: A Secondary Analysis of RTOG 85-31

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ABSTRACT

Purpose
Radiation Therapy Oncology Group 85-31 was a randomized trial of androgen suppression for life for patients with locally advanced prostate cancer. However, not all patients continued on the protocol-mandated long-term hormonal therapy despite no evidence of recurrence. We correlated duration of adjuvant hormonal therapy and outcomes among patients who prematurely discontinued hormonal therapy.

Patients and Methods
The protocol mandated pelvic radiotherapy followed by goserelin given indefinitely or until disease progression. There were 189 analyzable patients. Patients were divided in groups based on the tertile of hormonal therapy duration (HTD) as follows: ≤ 1 year, more than 1 year and ≤ 5 years, and more than 5 years. Overall survival (OS), disease-free survival (DFS), cause-specific mortality, local failure (LF), and distant metastasis (DM) were studied. Kaplan-Meier estimation and Cox proportional hazards regression model were used for OS and DFS, and Fine and Gray's regression model was used for the other outcomes.

Results
The median follow-up for surviving patients is 9.6 years. The median duration of adjuvant hormonal therapy was 2.2 years. The HTD more than 5 years group is significantly associated with an improved survival and DFS and fewer DMs than other HTD groups. After adjustment for age, radical prostatectomy, nodal status, Gleason score, and stage variables, the HTD more than 5 years group remains significantly associated with better OS and DFS than other HTD groups.

Conclusion
In this hypothesis-generating analysis, prolonged HTD of more than 5 years seems significantly associated with improvements in most outcomes. Given these data, decreasing HTD to ≤ 5 years may have a detrimental effect on patients with locally advanced prostate cancer. Only a randomized trial will conclusively clarify this issue.

J Clin Oncol 27:2137-2143. © 2009 by American Society of Clinical Oncology

INTRODUCTION

For patients with locally advanced localized prostate cancer, randomized trials have shown an improvement in survival rates when adjuvant hormonal therapy is added to pelvic irradiation.[1-3] However, the optimal treatment duration for the adjuvant hormonal component has not been well established.

Radiation Therapy Oncology Group (RTOG) 85-31[4] was a randomized trial comparing radiotherapy (RT) alone versus RT plus adjuvant androgen suppression for life in locally advanced prognosis carcinoma of the prostate. Long-term results of this trial show a significantly improved absolute survival, lower local failure, and lower incidence of distant disease and disease-specific mortality favoring the combined treatment arm.[3] However, not all patients remained on the protocol-mandated long-term hormonal therapy, despite no evidence of recurrent disease.

This article reports on a secondary analysis performed on the RTOG 8531 study correlating duration of adjuvant hormonal therapy and outcomes among patients who prematurely discontinued long-term hormonal therapy.

PATIENTS AND METHODS

Patients Evaluation and Treatment
Details of RTOG 8531 have been published previously.[3,4] Briefly, eligible patients had a Karnofsky performance status greater than 60 and histopathologic

diagnosis of adenocarcinoma of the prostate with clinical stage T3 or documented involvement of the pelvic lymph nodes. Patients who have undergone a prostatectomy were eligible if pathologically staged as pT3. Pretreatment evaluation included a complete medical history, physical examination with performance status evaluation, chest x-ray, bone scan, complete blood cell counts, acid phosphatase, and serum testosterone. Lymph node assessment was mandatory and could be performed either by lymphangiogram, computed tomography scan, or lymphadenectomy. Prostate-specific antigen (PSA) was not mandatory at the start of the trial because it was not widely available. All institutional, state, and federal regulatory guidelines had to be followed and, before random assignment, all patients gave written informed consent.

Patients were randomly assigned to receive RT and adjuvant goserelin (3.6 mg) monthly (arm 1) or RT alone followed by goserelin at time of relapse (arm 2). For patients randomly assigned to arm 1, goserelin was to be started at the last week of RT and to be given for life or until evidence of disease

progression. A dose of 44 to 46 Gy (doses up to 50 Gy were acceptable) was delivered to the pelvic contents, and a prostatic target volume boost of 20 to 25 Gy brought the total dose delivered to the volume to 65 to 70 Gy. In postoperatively treated patients, the prostatic bed received 60 to 65 Gy. Patients were stratified by histologic differentiation, nodal status, acid phosphatase level, and prior radical prostatectomy.

Statistical Methods

Hormonal therapy duration (HTD) is defined from the start of protocol-specified hormone injection date to the earlier of the final hormone injection date. Patients were divided into three groups based on the tertile of HTD as follows: ≤ 1 year, more than 1 year and ≤ 5 years, and more than 5 years. The following outcomes were studied: overall survival (OS), disease-free survival (DFS), cause-specific mortality (CSM), local failure (LF), and distant metastasis (DM). The same definitions of event for outcomes used in the primary article[5] were used for this analysis. The failure events for LF were defined as the

	HTD ≤ 1 Years (n = 67)		HTD > 1 and ≤ 5 Years (n = 61)		HTD > 5 Years (n = 61)		Total (N = 189)		
Characteristic	No.	%	No.	%	No.	%	No.	%	P*
Age, years									
Median	70		71		70		70		
Range	50-84		57-81		55-80		50-84		
< 70	32	48	25	41	27	44	84	44	.74
≥ 70	35	52	36	59	34	56	105	56	
Histologic differentiation									
Well	19	29	17	28	19	31	55	29	.82
Moderately	37	55	33	54	28	46	98	52	
Poorly	11	16	11	18	14	23	36	19	
Nodal status									
None	52	78	45	74	44	72	141	75	.76
Present	15	22	16	26	17	28	48	25	
Acid phosphatase									
Not elevated	41	61	44	72	39	64	124	66	.41
Elevated	26	39	17	28	22	36	65	34	
Radical prostatectomy									
No	60	90	50	82	50	82	160	85	.38
Yes	7	10	11	18	11	18	29	15	
Stage									
A	1	1	2	3	2	3	5	3	.65†
B	15	22	15	25	17	28	47	25	
C	51	76	44	72	42	69	137	72	
Gleason score									
2-6	23	37	20	34	20	34	63	35	.77
7	27	44	21	36	25	42	73	41	
8-10	12	19	17	29	14	24	43	24	
Missing	5		3		2		10		
Follow-up time, years									
All patients									
Median	7.8		6.9		11.0		9.6		
Range	0.7-14.6		1.7-14.4		5.4-14.9		0.7-14.9		
Surviving patients									
No. of patients	25		21		35		81		
Median	11.1		11.0		11.9		11.3		
Range	0.9-14.6		4.2-14.4		8.1-14.9		0.9-14.9		
HTD, years									
Median	0.4		2.5		9.3		2.2		
Range	0.003-0.99		1.00-4.9		5.1-13.5		0.003-13.5		

Table 1. Pretreatment Characteristics by HTD Groups (N = 189)

Abbreviation: HTD, hormonal therapy duration.
*From χ^2 test statistics; the P value is computed by excluding missing patients.
†Comparing A/B versus C.

reappearance of palpable tumor after initial clearance, progression of palpable tumor at any time, persistence of palpable tumor beyond 24 months after study entry, and the biopsy-proven presence of carcinoma of the prostate 2 years after study entry. Persistence of palpable prostate tumor beyond 2 years was recorded as local recurrence as of day 1. The failure event for DM was defined as the clinical or radiographic evidence of disease beyond the pelvis. DFS was defined as survival in the absence of locoregional failure or DM. DFS was also computed using PSA as an end point (either 1.5 ng/mL or 4 ng/mL as the threshold). The failure event for CSM was defined as death from prostate cancer or protocol treatment. Patients who died with disease and for whom the cause of death was unknown were also considered to have failure at this end point. The failure event for OS was defined as death from any cause. Time to event was measured from the randomization date to date of failure event. The Kaplan-Meier method[6] was used to estimate the OS and DFS. The log-rank test[7,8] was used to test the survival difference between the hormone duration groups. The cumulative incidence method[9] was used to estimate the LF rate, DM rate, and CSM rate. Gray's test[10] was used to test the difference between the hormone groups. Cox proportional hazards regression[11] was used for OS and DFS to estimate the hazard ratios (HRs) with/without adjustment for other covariates using χ^2 test. Fine and Gray's proportional hazards regression[12] was used for LF, DM, and CSM to estimate the HRs with/without adjustment for other covariates. The following covariates were adjusted in the models: age (< 70 [reference level; RL] or ≥ 70 years), radical prostatectomy (yes [RL] or no), nodal status (negative [RL] or positive), centrally reviewed Gleason score (2 to 6 [RL] or 7 to 10), stage (A/B [RL] or C). Unadjusted and adjusted HRs were calculated for all covariates using the proportional hazards models with associated 95% CIs and P values. All two-sided testing was done at a significance level of .05. Bonferroni correction[13] was used in pairwise comparisons to keep the overall significance level of .05.

RESULTS

Patients were accrued from February 1987 to April 1992. Among the 477 eligible patients in arm 1 of RTOG 85-31, 446 received protocol-specified hormonal therapy (31 did not start or refused hormone therapy after random assignment). Three hundred twenty-two patients (72%) discontinued their hormone therapy among 446 patients, and 124 patients are still continuing their hormone therapy. Among those 322 patients, 133 patients (41%) discontinued their hormone therapy due to death, disease progression, or initiation of another hormone therapy and were excluded from the analysis. Therefore, a total of 189 patients (59%) who were randomly assigned to arm 1 were analyzable and comprised the study cohort. A summary of their pretreatment baseline characteristics is listed in Table 1. The median follow-up time for surviving patients was 11.3 years (range, 0.9 to 14.9 years). The median HTD was 2.2 years (range, 0.003 [day 1] to 13.5 years). The tertiles of HTD are 1 year (33% percentile) and 5 years (67% percentile). The HTDs were considered as a continuous variable, and a categoric variable (HTD ≤ 1 year v 1 < HTD ≤ 5 years v HTD > 5 years). Pretreatment characteristics by HTD groups were well balanced, and the follow-up time for surviving patients is similar among the three HTD groups (Table 1).

Outcomes

There are statistically significant differences in survival/failure rates among the three HTD groups in all outcomes without adjusting

Table 2. Survival/Failure Rates by HTD Group									
Survival/Failure Measure	HTD ≤ 1 Year		HTD > 1 and ≤ 5 Years		HTD > 5 Years		Total		P*
	5 Years	11 Years	5 Years	11 Years	5 Years	11 Years	5 Years	11 Years	
Overall survival									.0001
%	71.9	41.7	66.7	33.1	100	63.9	79.5	46.3	
95% CI	59.1 to 81.3	29.1 to 53.8	53.3 to 77.1	21.0 to 45.7		50.1 to 74.8	72.9 to 84.6	38.7 to 53.5	
No. of failures	42		40		26		108		
Total No. of patients	67		61		61		189		
Disease-free survival									< .0001
%	50.2	24.4	53.8	23.7	100	60.9	67.7	36.3	
95% CI	37.4 to 61.7	14.4 to 35.9	40.5 to 65.3	13.5 to 35.4		47.2 to 72.1	60.5 to 73.9	29.2 to 43.4	
No. of failures	50		47		30		127		
Total No. of patients	67		61		61		189		
Cause-specific mortality									.03
%	11.1	15.9	5.1	14.4	0	5.2	5.4	11.8	
95% CI	3.3 to 18.9	6.8 to 25.0	0 to 10.7	4.9 to 23.8		0 to 10.9	2.1 to 8.7	7.0 to 16.6	
No. of failures	13		9		3		25		
Total No. of patients	67		61		61		189		
Local failure									.02
%	27.9	31.4	11.5	25.5	0	6.7	13.4	21.3	
95% CI	16.8 to 39.0	19.8 to 43.0	3.4 to 19.6	14.1 to 36.9		0.3 to 13.1	8.5 to 18.3	15.3 to 27.2	
No. of failures	21		16		9		46		
Total No. of patients	67		61		61		189		
Distant metastasis									.006
%	15.7	24.4	8.3	20.9	0	6.6	8.1	17.2	
95% CI	6.6 to 24.7	13.4 to 35.4	1.3 to 15.3	10.2 to 31.7		0.3 to 12.8	4.2 to 12.0	11.7 to 22.8	
No. of failures	17		13		4		34		
Total No. of patients	67		61		61		189		

Abbreviation: HTD, hormonal therapy duration.
*Overall survival and disease-free survival were tested using log-rank test statistics; all others were tested using Gray's test statistics.

for other covariates. The 5- and 11-year overall survival rates for patients with HTD more than 5 years was 100% and 63.9%, as compared with 71.9% and 41.7% and 66.7% and 33.1% for those receiving HTD of $\leq$ 1 year and between 1 and $\leq$ 5 years, respectively (Table 2 and Fig 1A; $P = .0001$). Likewise, DFS rate is improved with HTD more than 5 years, as shown in Table 2 and Figure 1B. There are statistically significant differences in CSM rates favoring the HTD more than 5 years group (Table 2 and Fig 2A, $P = .03$). The incidence of LF and the development of DM are illustrated in Table 2 and Figures 2B and 2C. Despite unfavorable prognostic factors, the LF rate at 11 years is only 6.7%, and the DM rate at 11 years is also only 6.6% of patients who received hormonal therapy for more than 5 years. The pairwise comparisons show that there are statistically significant differences between the HTD more than 5 years group and the other two HTD groups in OS and DFS at the significance level of .017 ($P = .05$ and $P = .03$, respectively). There are statistically significant differences between HTD $\leq$ 1 year and HTD more than 5 years group in CSM, LF, and DM (data not shown).
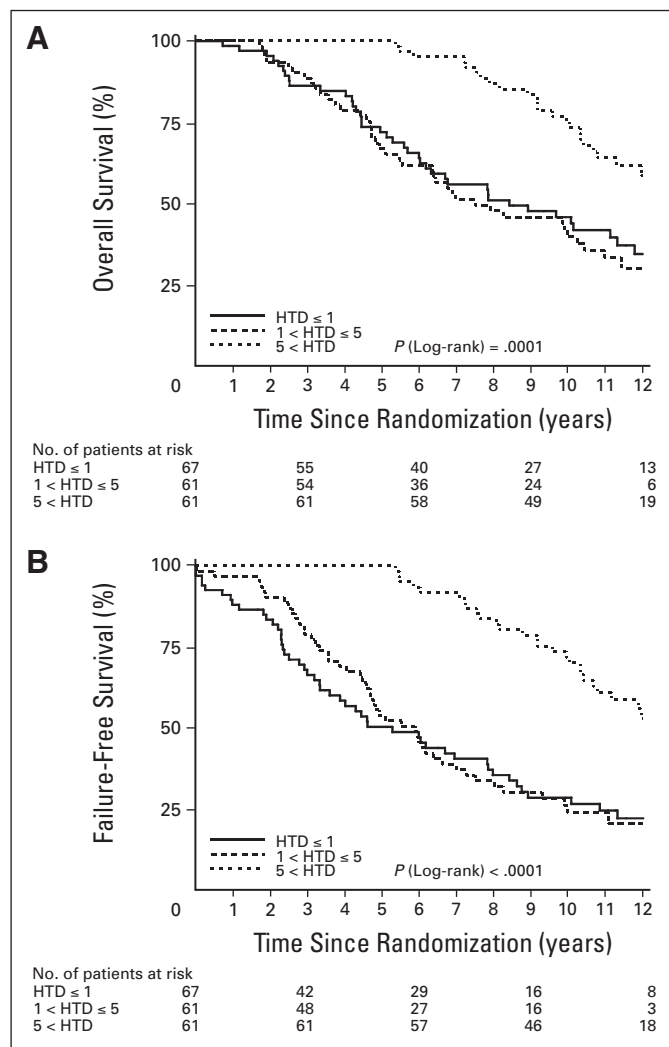

Fig 1. (A) Overall survival rates; (B) disease-free survival rates. HTD, hormone treatment duration.
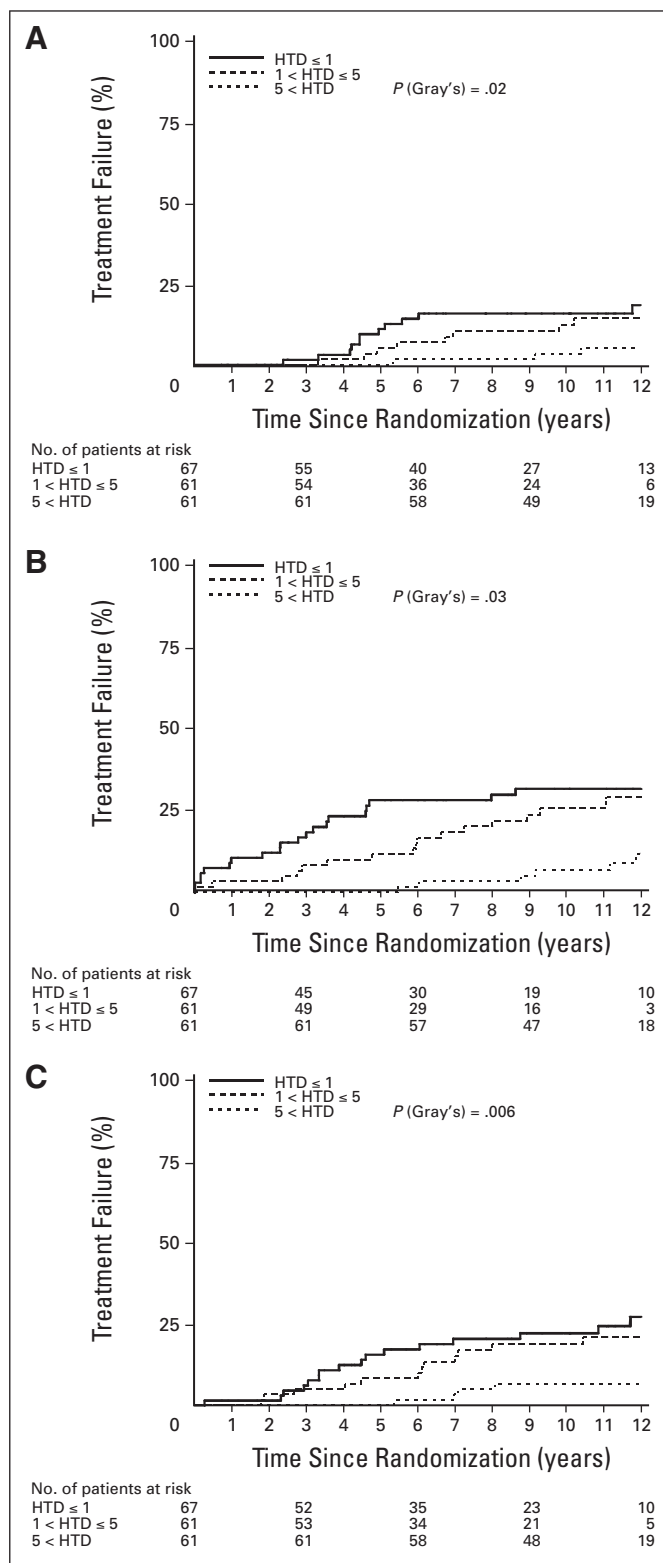

Fig 2. (A) Cause-specific mortality rates; (B) local failure rates; (C) distant metastases rates. HTD, hormone treatment duration.

Table 3 shows that patients in the HTD $\leq$ 1 year group have statistically significantly higher risk of having failure events in all outcomes without adjusting for other covariates. For the HTD more than 1 year and $\leq$ 5 years group, they also have statistically significantly

Table 3. Proportional Hazards Model by HTD Group

Comparison	Unadjusted			Adjusted*		
	HR	95% CI	P†	HR	95% CI	P†
Overall survival‡						
HTD ≤ 1 year	2.37	1.45 to 3.86	.0006	2.72	1.62 to 4.55	.0001
HTD > 1 and ≤ 5 years	2.65	1.61 to 4.36	.0001	2.98	1.77 to 5.03	< .0001
HTD > 5 years	RL			RL		
Disease-free survival‡						
HTD ≤ 1 year	3.18	2.01 to 5.03	< .0001	3.49	2.16 to 5.64	< .0001
HTD > 1 and ≤ 5 years	3.13	1.96 to 4.98	< .0001	3.59	2.20 to 5.86	< .0001
HTD > 5 years	RL			RL		
Cause-specific mortality§						
HTD ≤ 1 year	4.81	1.39 to 16.60	.01	—‖		—
HTD > 1 and ≤ 5 years	3.43	0.95 to 12.45	.06	—		—
HTD > 5 years	RL			RL		
Local failure§						
HTD ≤ 1 year	2.81	1.33 to 5.96	.007	—		—
HTD > 1 and ≤ 5 years	2.09	0.97 to 4.51	.06	—		—
HTD > 5 years	RL			RL		
Distant metastasis§						
HTD ≤ 1 year	4.86	1.66 to 14.28	.004	—		—
HTD > 1 and ≤ 5 years	3.80	1.26 to 11.47	.02	—		—
HTD > 5 years	RL			RL		

Abbreviations: HTD, hormonal therapy duration; HR, hazard ratio; RL, reference level.
*HR is adjusted for age (< 70 [RL] or ≥ 70 years), radical prostatectomy (yes [RL] or no), nodal status (negative [RL] or positive), centrally reviewed Gleason score (2 to 6 [RL] v 7 v 8 to 10), and stage (A/B [RL] or C).
†P value from χ^2 test.
‡Cox proportional hazards model was used.
§Fine and Gray's model was used.
‖The number events are too few to have stable estimates.

higher risk of having failure events in OS, DFS, and DM. However, the number of CSM events is too few to make a definite conclusion. After adjusting for age, radical prostatectomy, nodal status, centrally reviewed Gleason score, and stage variables, the HTD more than 5 years group remains statistically significantly associated with having fewer failure events in OS and DFS than other HTD groups at the significance level of .025. The number of events for other outcomes is too small to have a meaningful result in the multiple regression model (Table 3).

HTDs were considered as continuous variable and the results remained the same; risk of experiencing failure events, except LF, becomes lower as HTD increases by 1 year (Table 4).

Causes of Death

In Appendix Table A1 (online only), causes of death for each HTD group are shown. The rate of deaths from prostate cancer seems higher between the groups receiving fewer than 1 year of hormonal therapy compared with those patients receiving more than 5 years, but this is not statistically different (31% v 15%, P = .11).

DISCUSSION

The use of adjuvant hormonal therapy has been shown in randomized trials to improve outcomes in patients with high-risk prostate

Table 4. Proportional Hazards Model: Continuous Hormone Therapy Duration

Comparison	Unadjusted			Adjusted*		
	HR	95% CI	P†	HR	95% CI	P†
Overall survival‡	0.88	0.83 to 0.93	< .0001	0.86	0.81 to 0.91	< .0001
Disease-free survival‡	0.86	0.82 to 0.90	< .0001	0.85	0.80 to 0.89	< .0001
Cause-specific mortality§	0.81	0.70 to 0.94	.004	—‖		—
Local failure§	0.92	0.85 to 1.00	.052	—		—
Distant metastasis§	0.78	0.69 to 0.89	.0002	—		—

Abbreviation: HR, hazard ratio.
*HR is adjusted for age (< 70 [reference level] or ≥ 70 years), radical prostatectomy (yes [reference level] or no), nodal status (negative [reference level] or positive), centrally reviewed Gleason score (2 to 6 [reference level] v 7 v 8 to 10), and stage (A/B [reference level] or C).
†P value from χ^2 test.
‡Cox proportional hazards model was used.
§Fine and Gray's model was used.
‖The number events are too few to have stable estimates.

cancer[1-3] and is now considered standard of care for such patients. Three randomized trials comparing RT plus long-term adjuvant hormonal therapy with RT alone have demonstrated improved OS rates[1,3] or biochemical-free survival rate.[2] These trials differed in the duration of the hormonal treatment: RTOG 85-31[3,4] mandated the use of adjuvant analog of luteinizing-hormone releasing hormone (LHRH) agonists for life or until sign of disease progression with the drug starting during the last week of RT; the European Organization for Research and Treatment of Cancer (EORTC) 22863 randomized trial[1] initiated LHRH agonist therapy on the first day of RT and continued it for 36 months, and RTOG 92-02[2] administered LHRH agonist therapy 2 months before RT, during RT, and adjuvantly for another 24 months.

The prolonged use of LHRH agonist therapy results in secondary hypogonadism as a result of downregulation of the gonadotrophin receptors in the pituitary gland[14] and, particularly in older patients, may lead to several complications, including osteoporosis,[15] decline in bone density and muscle strength,[16,17] neurocognitive alterations,[18] and cardiac toxicity,[19] with a significant impact in patients' quality of life.[20,21] Thus investigating whether a shorter course of adjuvant LHRH agonists provides similar outcomes, minimizing toxicity, is a logical step in the management of localized high-risk prostate cancer.

In the current study, we assessed the possible impact hormonal duration could have in outcomes in a group of patients with locally advanced prostate cancer. After adjusting for known prognostic variables, the use of androgen suppression for more than 5 years proved to be significantly better in all end points studied, suggesting that a longer rather than a shorter course of hormonal therapy should be considered for these patients. This secondary analysis, however, has potential limitations and has to be viewed with some caution. First, this is a retrospective analysis from a mixed cohort of patients with prostate cancer, including postprostatectomy and node-positive patients. Second, the reason for the voluntary cessation of the hormonal therapy was not prospectively documented, and the possibility of selection bias has to be entertained. Early termination of hormonal therapy might also be associated with a comorbid condition (ie, obesity, diabetes, and so on) that may be exacerbated by hormonal therapy, leading to a worse survival and/or cancer outcomes. Finally, the trial was initiated before the PSA era, and it is quite possible that some of the patients had more advanced disease than originally thought.

D'Amico et al[22] recently evaluated survival outcome from the use of a prolonged compared with a short course of androgen suppression therapy in node-negative, high-risk prostate cancer. These authors carried out a pooled analysis of patients enrolled in three prospective randomized trials[1,23,24] and treated either with 36 or 6 months of androgen suppression and pelvic RT. They concluded that the longer use of hormonal therapy was not associated with increased survival.

Like our analysis, the D'Amico et al study[22] was not a randomized comparison. Recently, the EORTC reported on a randomized phase III trial[25] comparing 6 months versus 36 months of androgen deprivation for patients with locally advanced prostate cancer (EORTC 22961). In this study, 970 eligible patients received pelvic RT and either a short or a longer course of adjuvant LHRH agonist, with the study's end point being a noninferior survival, defined as a mortality HR of 1.35. At a median follow-up of 5.2 years, the 5-year overall survival rate was 85.3% on the longer duration LHRH agonist arm and 80.6% (HR = 1.43) on the short duration arm, with a 5-year biochemical PFS rate of 78.3% and 58.9% for the long and short duration arms, respec-

tively (HR = 2.29). The authors' conclusion was that a noninferior survival outcome could not be confirmed with 6 months of androgen suppression compared with 36 months.

Although not directly comparable to the prostate cancer population, in breast cancer, many randomized trials have evaluated the effect of 1, 2, or more years of adjuvant tamoxifen in localized disease and estrogen receptor–positive patients. These trials have consistently demonstrated a significant benefit in survival with the use of tamoxifen,[26] regardless of treatment duration. However, in randomized comparisons between 2 years versus 5 years,[27,28] the longer administration of tamoxifen has led to significant improvement in outcomes. Of interest is that further prolongation beyond 5 years was not associated with additional benefit from tamoxifen.[29]

In summary, in this hypothesis-generating exercise, our results from a secondary analysis of RTOG 85-31 protocol show that prolonged HTD with LHRH agonist for more than 5 years might be associated with improved outcomes in patients with locally advanced localized prostate cancer. Together with the recent results of the EORTC 22961 randomized trial, our data suggest that decreasing the duration of hormonal administration may have a detrimental effect in these patients. A recently completed randomized trial in Quebec, Canada, comparing 18 months versus 36 months of LHRH agonist therapy for high-risk patients (PCS IV Study, A. Nabid, MD, principal investigator) hopefully will help to shed further light on this intriguing question. Further studies are clearly warranted in this area, and only a properly designed randomized trial can conclude that more than 5 years of hormonal therapy is superior to the current standard of 2 to 3 years for men with locally advanced prostate cancer.

AUTHOR CONTRIBUTIONS

Conception and design: Luis Souhami, Kyounghwa Bae, Howard Sandler
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Final approval of manuscript: Luis Souhami, Kyounghwa Bae, Miljenko Pilepich, Howard Sandler

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