Duration of Testosterone Suppression and the Risk of Death From Prostate Cancer in Men Treated Using Radiation and 6 Months of Hormone Therapy

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BACKGROUND. The authors evaluated whether the duration of androgen suppression (AS) after the completion of hormone therapy (HT) was associated with the risk of prostate cancer-specific mortality (PCSM) and all-cause mortality (ACM).

METHODS. The study cohort was comprised of 220 men who received radiation therapy (RT) and 6 months of HT for prostate cancer between 1996 and 2005. The duration of AS was defined as the time to return to the baseline testosterone level after the completion of HT. Grays and Cox regression analyses were used to evaluate whether the duration of AS after the completion of HT was associated with the time to PCSM and ACM, respectively, after adjusting for known prognostic factors.

RESULTS. An increasing duration of AS was associated with a decreased risk of PCSM (adjusted hazards ratio [HR], 0.89; \( P = .003 \)) and ACM (HR, 0.94; \( P = .007 \)). Men who had prostate cancer with Gleason scores from 8 to 10 had significantly lower cumulative incidence estimates of PCSM (\( P = .04 \)) if the duration of AS plus the length of HT administration was \( \geq 2 \) years compared with <2 years. After a median follow-up of 6.1 years, the respective 5-year estimates were 0% and 38%.

CONCLUSIONS. The duration of AS after 6 months of HT was associated with the risk of PCSM and ACM. This duration could be used to identify men who have prostate cancer with Gleason scores from 8 to 10 in whom 6 months of HT produces long-term testosterone suppression, which may provide the cancer-specific survival benefit observed with long-term HT. Cancer 2007;110:1723–8. © 2007 American Cancer Society.

KEYWORDS: baseline testosterone level, prostate cancer, mortality, androgen suppression therapy.

Randomized trials have documented a prolongation in the time to prostate cancer-specific mortality (PCSM)\(^1,2\) and all-cause mortality (ACM)\(^2\) when 6 months of hormone therapy (HT) and external-beam radiation therapy (RT), compared with RT alone, were used to treat men with higher risk prostate cancer based on a prostate-specific antigen (PSA) level > 10 ng/mL, Gleason score (7–10), and/or 2002 American Joint Commission of Cancer (AJCC)\(^3\) clinical T (tumor) category (T2b–T4). Therefore, the use of RT and 6 months of HT has become a treatment option for men with higher risk prostate cancer. For men who have prostate cancer with Gleason scores from 8 to 10, however, another standard of care is to administer 2 to 3 years of HT with RT based on the results of prospective randomized trials\(^4,5\) that compared long-term HT with no HT\(^4\) or to short-term HT\(^5\).
Prior investigators\textsuperscript{6–8} have reported longer times to return serum testosterone levels to noncastrate or normal levels after the discontinuation of HT in older men versus younger men, with the time to return to the baseline testosterone level (BTL) longer than the time to normalization of the testosterone level across all age groups.\textsuperscript{9} Moreover, the return to the BTL parallels the resolution of hypogonadal symptoms,\textsuperscript{7–9} suggesting that, until a man returns to his BTL, he is androgen-suppressed. What remains unknown is whether there is an association between the time to PCSM and ACM and the length of time that the testosterone level remains below the BTL after the completion of HT. Given the growing evidence regarding the metabolic side effects of HT with respect to endocrine,\textsuperscript{10} cardiac,\textsuperscript{11–13} and bone\textsuperscript{14} disorders, particularly in men of advanced age, this information would be of particular importance. Specifically, if the risk of PCSM decreases significantly as the duration of testosterone suppression increases, then the duration of testosterone suppression may be useful in identifying men who have prostate cancer with Gleason scores from 8 to 10, in whom a 6-month course of HT may provide the cancer-specific survival benefit associated with long-term HT.\textsuperscript{5} Therefore, the objective of the current study was to evaluate whether the duration of androgen suppression (AS) after the completion of HT is associated significantly with time to PCS and ACM in men who received RT and 6 months of HT for prostate cancer.

**MATERIALS AND METHODS**

**Patient Selection, Staging, and Treatment**

Between February 1996 and March 2005, BTLs and follow-up testosterone levels were collected on 220 men who received RT and 6 months of HT for prostate cancer with at least 1 higher risk feature at a main member or affiliate Harvard Hospital. The PSA and BTL were obtained within 14 days of the initiation of HT. A higher risk feature was defined as a PSA level > 10 ng/mL, or a Gleason score \(\geq 7\), or 2002 AJCC clinical T category\textsuperscript{3} \(\geq T2b\). All biopsy material underwent review by a single pathologist who had expertise in genitourinary cancers. Prior to study entry, men had a bone scan and a computerized tomographic or magnetic resonance imaging scan of the pelvis and were excluded if they were diagnosed as hypogonadal or had radiographic evidence of regional or distant metastatic disease. A summary of the pretreatment baseline characteristics of the 220 men who comprised the study cohort is listed in Table 1. All men read and signed an approved Internal Review Board consent form prior to study entry.

<table>
<thead>
<tr>
<th>Baseline patient characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of androgen suppression, mo</td>
<td>N = 220*</td>
</tr>
<tr>
<td>Median [IQR], mo</td>
<td>15 [7–24]</td>
</tr>
<tr>
<td>(\leq 6)</td>
<td>35 (16)</td>
</tr>
<tr>
<td>&gt;6 to 12</td>
<td>49 (22)</td>
</tr>
<tr>
<td>&gt;12 to 18</td>
<td>37 (17)</td>
</tr>
<tr>
<td>&gt;18 to 24</td>
<td>29 (13)</td>
</tr>
<tr>
<td>&gt;24 to 30</td>
<td>21 (10)</td>
</tr>
<tr>
<td>&gt;30 to 36</td>
<td>7 (3)</td>
</tr>
<tr>
<td>&gt;36</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Did not rebound T to the BTL</td>
<td>19 (9)</td>
</tr>
<tr>
<td>Age at end of hormone therapy, y</td>
<td>69 [64–73]</td>
</tr>
<tr>
<td>&lt;60</td>
<td>26 (12)</td>
</tr>
<tr>
<td>61–64</td>
<td>39 (18)</td>
</tr>
<tr>
<td>65–69</td>
<td>59 (27)</td>
</tr>
<tr>
<td>(\geq 70)</td>
<td>99 (44)</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
<td>8.3 [5.6–14]</td>
</tr>
<tr>
<td>Median [IQR], ng/mL</td>
<td>25 (11)</td>
</tr>
<tr>
<td>(\leq 4)</td>
<td>104 (47)</td>
</tr>
<tr>
<td>&gt;4 to 10</td>
<td>59 (27)</td>
</tr>
<tr>
<td>&gt;10 to 20</td>
<td>32 (15)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>51 (23)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>52 (24)</td>
</tr>
<tr>
<td>(\geq 6)</td>
<td>63 (29)</td>
</tr>
<tr>
<td>3 + 4</td>
<td>54 (25)</td>
</tr>
<tr>
<td>4 + 3</td>
<td>51 (23)</td>
</tr>
<tr>
<td>8–10</td>
<td>44 (20)</td>
</tr>
<tr>
<td>2002 AJCC clinical tumor category\textsuperscript{1}</td>
<td>41 (19)</td>
</tr>
<tr>
<td>T1c</td>
<td>97 (44)</td>
</tr>
<tr>
<td>T2a</td>
<td>11 (5)</td>
</tr>
<tr>
<td>T2b</td>
<td>8 (4)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; T, testosterone level; BTL, baseline testosterone level in ng/dL (median [IQR]: 437 [324–554]); PSA, prostate-specific antigen; AJCC, American Joint Committee on Cancer.

* Percentages may not sum to 100% because of rounding.

\textsuperscript{1} Greene, 2002.\textsuperscript{3}

The RT technique that was used in the current study has been described previously.\textsuperscript{2} HT consisted of 2 3-month injections of a luteinizing hormone-releasing hormone (LHRH) agonist (leuprolide acetate) or goserelin and a nonsteroidal antiandrogen (oral flutamide at a dose of 250 mg every 8 hours or oral casodex 50 mg once daily). Leuprolide acetate was delivered intramuscularly every 3 months at a dose of 22.5 mg. Goserelin was administered subcutaneously every three months at a dose of 10.8 mg. The nonsteroidal antiandrogen was discontinued on the 85th day after the administration of the second 3-month preparation of the LHRH agonist.
Follow-up and Determination of the Cause of Death
The median follow-up for the 220 men in the study cohort was 6.1 years (interquartile range [IQR], 3.8–7.7 years), and follow-up was initiated on the last day of HT and concluded on January 15, 2007 or the date of death, whichever came first. No patient was lost to follow-up. Follow-up occurred every 3 months for 2 years, every 6 months until 5 years, and annually thereafter. At baseline and within 1 week before to follow-up, a total serum testosterone level was obtained using the Bayer assay (Tarrytown, NY), which has a normal range for men aged ≥18 years from 280 ng/dL to 1100 ng/dL, in addition to a PSA level. HT consisted initially of an LHRH agonist, which was delivered for life when the PSA level reached 10 ng/mL in men who experienced PSA failure. The cause of death was determined by the attending physician who followed the patient from study entry until death. To record prostate cancer as the cause of death, there had to be documented, hormone-refractory, metastatic prostate cancer and evidence that the PSA level was rising at the time of the last follow-up visit despite the use of multiple second-line hormone maneuvers and cytotoxic chemotherapy before death. There were 25 deaths, and 12 of those deaths were from prostate cancer.

Statistical Methods
Calculation of the duration of AS
The duration of AS was defined as the difference in months between the date when the testosterone level reached or exceeded the BTL and the last day of the 6-month course of HT. The last day of the 6 months of HT corresponded to the 85th day after the administration of the second 3-month preparation of the LHRH agonist. The median and associated 95% confidence intervals (95% CIs) of the duration of AS were calculated within each predefined age strata. Men whose testosterone level did not reach the BTL were right censored on the date of last follow-up or death, whichever occurred first.

Association of the BTL and age with the duration of AS
Logistic regression was used to evaluate whether the covariates of the BTL and age at the end of HT were associated significantly with whether or not a man’s testosterone level returned to baseline. A Cox proportional-hazards model was used to assess whether the same covariates were associated with the duration of AS in men whose testosterone level returned to the BTL. Both covariates were considered as continuous variables for the purpose of the multivariable regression analyses. The adjusted odds ratio (AOR) and the hazards ratio (AHR) for return to the BTL and the duration of AS, respectively, with associated 95% CIs and \( P \) values were calculated for each covariate.

Association of the duration of AS with death from prostate cancer and death from any cause
For men whose serum testosterone level returned to the BTL, Gray regression and Cox regression analyses were used to evaluate whether the duration of AS was associated with the time to PCSM and ACM, respectively, adjusting for known prognostic factors. Time zero was defined as the date of return to the BTL. Prognostic factors included the PSA level, biopsy Gleason score, clinical tumor category, and (for the endpoint of ACM) age on the date that the testosterone level reached or exceeded the BTL. For the purposes of univariate and multivariate analyses, the duration of AS, PSA level, and age were considered as continuous variables. Gleason scores from 8 to 10, a Gleason score of 7, and the 2002 AJCC clinical T3 tumor category were evaluated as categorical variables, and the baseline groups were men with Gleason score ≤6 and a clinical T1 or T2 tumor category, respectively. For all categorical variables, the cut-off points selected were made prior to examining the data based on established strata.

For all regression analyses, the assumptions of the Cox and Gray models were tested and met. The unadjusted HR and the AHR for PCSM and ACM, with associated 95% CIs and \( P \) values, were calculated for each covariate. For the purpose of illustration, estimates of the time to PCSM and age-adjusted ACM estimates stratified at approximately an 18-month duration of AS were calculated and are displayed graphically. By selecting 18 months as the cut-off point for comparing survival estimates, men were stratified into those with ≥2 years of testosterone suppression (ie, 18 months of AS and 6 months of HT) versus <2 years of testosterone suppression. Justification for the 2-year cut-off point arises from 2 prospective randomized trials that established at least 2 years (ie, from 28 months to 3 years) of HT and RT as a standard of care for men with high-risk prostate cancer. A cumulative incidence and Kaplan-Meier (KM) methodology were used to calculate estimates for PCSM and ACM, respectively. K-sample and the log-rank test were used to compare the temporal distribution of these respective estimates. To ensure that the PSA and BTL followed a normal distribution, these values were log-transformed. R statistical software (version 2.1.1; R Foundation for Statistical Computing, Vienna, Austria) was used for all calculations pertaining to the Gray regression and cumulative incidence estimates. SAS
software (version 9.1.3; SAS Institute, Cary, NC) was used for all remaining statistical analyses.

RESULTS

Duration of AS

After 6 months, 12 months, 18 months, 24 months, and 36 months, we observed that 16%, 38%, 55%, 68%, and 81% of men, respectively, had a return of testosterone levels to the BTL with a median AS duration of 15 months (IQR, 7–24 months), as shown in Table 1. Of all men in the study, 19 men (9%) did not experience a return to the BTL after a median follow-up of 7.5 years (IQR, 6.2–8.4 years) and a minimum follow-up of 4.8 years after the completion of HT. Increasing age at the end of HT was associated significantly with a decreased rate of return to the BTL (AOR, 0.74; 95% CI 0.55–0.99; \( P = .04 \)) whereas a higher BTL was not associated with an increased rate of return (AOR, 2.2; 95% CI, 0.10–48.1; \( P = .04 \)). An increasing value of the BTL was not associated significantly (AHR, 1.2; 95% CI, 0.7–2; \( P = .45 \)) with the duration of AS; whereas advancing age at the completion of HT was associated with the duration of AS (AHR, 0.95; 95% CI, 0.92–0.98; \( P < .001 \)) with a median of 12 months (95% CI, 5–18 months), 14 months (95% CI, 9–18 months), and 16 months (95% CI, 12–18 months) for men ages \( \leq 60 \) years, 61 to 64 years, and \( \geq 65 \) years, respectively.

Association of the Duration of AS With Death From Prostate Cancer and Death From Any Cause

Table 2 illustrates a significant association between an increasing duration of AS and a decreased risk of PCSM (AHR, 0.89; 95% CI, 0.82–0.96; \( P = .003 \)) adjusting for the PSA level (AHR, 1.1; 95% CI, 0.5–2.4; \( P = .85 \)), for Gleason scores from 8 to 10 (AHR, 7.7; 95% CI, 1.2–48.4; \( P = .03 \)), for a Gleason score of 7 (AHR, 1.4; 95% CI, 0.1–14.4; \( P = .77 \)) and for clinical T3 disease (AHR, 0.94; 95% CI, 0.1–6.5; \( P = .95 \)). Similarly, after adjusting for these prognostic factors and age at the time of return to the BTL (AHR, 1.1; 95% CI, 1.02–1.2; \( P = .01 \)), the risk of ACM decreased significantly (AHR, 0.94; 95% CI, 0.89–0.98; \( P = .007 \)) as the duration of AS increased.

PCSM and ACM Estimates

Twelve men (5.5%) experienced PCSM, including 1 man with a Gleason score of 6, 3 men with a Gleason score of 7, and 8 men with Gleason scores from 8 to 10. Table 2 shows that only the covariates of duration of AS and prostate cancer with Gleason scores from 8 to 10 were associated significantly with the time to PCSM on multivariable analysis. The impact of these 2 covariates on the time to PCSM is illustrated in Figure 1. Specifically, significantly higher estimates of PCSM (\( P = .04 \)) were observed in men with Gleason scores from 8 to 10 who had a duration of testosterone suppression \( < 2 \) years (6 months of HT plus 18 months of AS) compared with men who had a duration of testosterone suppression \( \geq 2 \) years. For men with Gleason scores from 8 to 10, the 5-year cumulative incidence estimates of PCSM were 38% (95% CI, 17%–59%) versus 0% (95% CI, 0%–0%) if the effective duration of testosterone suppression was \( < 2 \) years compared with \( \geq 2 \) years, respectively.

Table 2 shows that only the covariates duration of AS and age were associated significantly with all-
cause survival in multivariable analysis. The impact of these 2 covariates on the time to ACM is illustrated in Figure 2. In particular, the age-adjusted K-M estimates of overall survival and the age-adjusted ACM estimates were significantly higher (P = .04) in men who had a duration of testosterone suppression <2 years compared with all others. At 5 years, these estimates were 19% (95% CI, 11–27%) and 7% (95% CI, 0–16%, respectively.

**DISCUSSION**

In the current study of 220 men who received RT and 6 months of HT for higher risk prostate cancer, a significant association was observed after adjusting for known prognostic factors between the duration of AS and the risk of PCSM and ACM. The current study also validated the previously described association between advancing age and a longer duration of AS after the discontinuation of HT.

The clinical significance of the current study is for men who have prostate cancer with Gleason scores from 8 to 10, for which the accepted standards of care are to administer from 6 months to 3 years of HT with RT based on the results of prospective randomized trials. The results of the current study provide evidence to support the use of the duration of AS after 6 months of HT as a way to identify men who have prostate cancer with Gleason scores from 8 to 10 who may achieve the cancer-specific survival benefit associated with longer term use of HT. Specifically, as illustrated in Figure 1, of the 51 men who had prostate cancer with Gleason score from 8 to 10, the 5-year estimates of PCSM were 0% in 19 men and 38% in 32 men if the duration of testosterone suppression (6 months of HT administration plus the duration of AS) was >2 years compared with ≤2 years, respectively. Therefore, what appears to be relevant when deciding how to manage an individual patient is the length of testosterone suppression and not simply the length of HT administration. Because it was observed that men of advancing age in this study and others experienced longer intervals of AS after a 6-month course of HT, and because older men are more likely to experience the metabolic side effects of HT, an opportunity to maximize the therapeutic ratio of HT may exist.

Several points require further discussion. First, the median duration of AS observed in this study was 15 months, which was longer than the 4 months (16.6 weeks) reported in a prior study in which 80 men received 6 months of HT. This difference may be explained by the older median age of the men (69 years vs 66 years) and use of the time to return.
(TTR) to the BTL, rather than the TTR to the lower limit of normal for testosterone, in the current study compared with the prior study,\(^9\) respectively. Second, in a prior report,\(^9\) men with a median age of 65 years had a median TTR to the BTL of 13.6 months after a single, 3-month administration of an LHRH agonist, similar to the results in the current study. Third, it is clear that an intermittent HT approach would be less costly and more likely to preserve quality of life.\(^{25}\)

However, it remains to be studied in the setting of a randomized trial whether this approach will produce an equivalent survival to continuous HT, especially in a man who rapidly returns his testosterone level to baseline after completing the initial 6 months of HT. Finally, in this study, we did not examine the association of duration of AS and PCSM and ACM in men who were hypogonadal at baseline. Further study is needed for this population of men.

In conclusion, the duration of AS after RT and 6 months of HT increases as men age and is associated with the risk of PCSM. This duration could be used to identify men who have prostate cancer with Gleason scores from 8 to 10, in whom 6 months of HT produces long-term testosterone suppression, which may provide the cancer-specific survival benefit observed with long-term HT.

REFERENCES


