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CLINICAL INVESTIGATION **Prostate**

DOES HORMONE THERAPY REDUCE DISEASE RECURRENCE IN PROSTATE CANCER PATIENTS RECEIVING DOSE-ESCALATED RADIATION THERAPY? AN ANALYSIS OF RADIATION THERAPY ONCOLOGY GROUP 94-06

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Purpose: The purpose of this study was to evaluate the effect on freedom from biochemical failure (bNED) or disease-free survival (DFS) by adding hormone therapy (HT) to dose-escalated radiation therapy (HDRT).
Methods and Materials: We used 883 analyzable prostate cancer patients who enrolled on Radiation Therapy Oncology Group (RTOG) 94-06, a Phase I/II dose escalation trial, and whose mean planning target volume dose exceeded 73.8 Gy (mean, 78.5 Gy; maximum, 84.3 Gy). We defined biochemical failure according to the Phoenix definition.
Results: A total of 259 men started HT 2 to 3 months before HDRT, but not longer than 6 months, and 66 men with high-risk prostate cancer received HT for a longer duration. At 5 years, the biochemical failure rates after HDRT alone were 12%, 18%, and 29% for low-, intermediate-, and high-risk patients, respectively ($p < 0.0001$). Cox proportional hazards regression analysis adjusted for covariates revealed that pretreatment PSA level was a significant factor, whereas risk group, Gleason score, T-stage, and age were not. When the patients were stratified by risk groups, the Cox proportion hazards regression model (after adjusting for pretreatment PSA, biopsy Gleason score, and T stage) did not reveal a significant effect on bNED or DFS by adding HT to HDRT.
Conclusion: The addition of HT did not significantly improve bNED survival or DFS in all prostate cancer patients receiving HDRT, but did approach significance in high-risk patient subgroup. The result of this study is hypothesis generating and requires testing in a prospective randomized trial. © **2011 Elsevier Inc.**

Prostate cancer, Hormone therapy, Radiation therapy, Dose escalation, Biochemical failure.

INTRODUCTION

Prostate cancer is a radio-responsive tumor. The 3 Dimensional Oncolgoy Group (3DOG)/Radiation Therapy Oncology Group (RTOG) 94-06 study was designed to identify the maximally tolerated radiation dose (MTD) (1, 2). This trial recently indicated improved efficacy for men with varying risk prostate cancer treated to doses as high as 79.2 Gy (3). In addition, several prospective randomized trials have demonstrated significant improvements in freedom from biochemical failure (bNED) and disease-free survival (DFS) with the use of dose-escalated radiation therapy (HDRT) as compared with conventional radiation doses (64–70 Gy) (4–7). Because of the potential disease control benefits of dose escalation, there has been a widespread implementation of intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and, more recently, particle beam facilities for the treatment of prostate cancer.

In addition, prostate cancer is a hormonally sensitive tumor. Multiple prospective randomized trials of hormone therapy (HT) and conventional doses of radiation therapy (RT) have demonstrated improved local tumor control, disease free-survival, cancer-specific survival, or overall survival (8–11). It is unclear whether the improvement of disease control also applies to patients who receive RT escalated to doses greater than 70 Gy.

However, it is reasonable to assume that the benefits of HT with RT derive from tumor volume reduction and the enhancement of tumor response by decreasing the number of

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Conflict of interest: none.

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viable clonogens (12). This hypothesis is supported by laboratory data (13). In LNCaP, Lim *et al*. showed a supra-additive interaction between androgen ablation and RT when androgen ablation precedes the single fraction radiation treatment by 3 days (13). These experimental data indicate that HDRT may offset the beneficial effects of androgen deprivation. To examine this hypothesis, we evaluated the bNED survival and DFS in men receiving HDRT of greater than 73.8 Gy on RTOG 94-06. This analysis was carried out by stratifying outcome into risk groups and HT use.

METHODS AND MATERIALS

Study protocol

RTOG 94-06 is a Phase I/II trial evaluating dose-escalated 3D CRT to treat men with clinically localized (T1–T3) prostate cancer (1). A detailed description of the clinical trial has been previously published (2, 3). Pertinent protocol guidelines will be given in this section as it relates to the subgroup analysis of the present study.

The primary objective of the protocol was to establish the MTD of RT that can be delivered safely to the prostate gland and surrounding tissue and to determine the toxicity rates. Because of the purported improved therapeutic ratio, local control, and DFS from the use of neoadjuvant (NHT) and/or adjuvant HT (AT), the study investigators opted to treat appropriately selected men with this combined approach.

Hormonal therapy began 2 to 6 months before registration and was allowed as long as a PSA was available before the initiation of HT. The PSA had to be obtained within 3 months of study entry, but no longer than 10 days after prostate biopsy. The inclusion of men receiving HDRT greater than 73.8 Gy makes it possible to study the independent effect of the addition of HT on toxicity and efficacy. The change in acute and late toxicities when HT was administered with HDRT has been previously reported (14). The current study focuses on the effect on biochemical control and DFS when HT is combined with HDRT.

Treatment planning

The standard nomenclature, as published by the International Commission on Radiation Units and Measurements (ICRU 50), was used (15).

In RTOG 94-06, men were originally stratified into three treatment groups according to their risk of seminal vesicle (SV) involvement (% SV risk = PSA + ([Gleason score – 6] × 10)) (20). Group 1 consisted of those men with T1 and T2 disease whose estimated risk of SV invasion was < 15%. Group 2 consisted of men with T1 and T2 tumors, but the risk of SV invasion of 15% or more. Group 3 consisted of men withT3 cancer and was only accrued to Dose Levels I and II. However, for the purpose of this subgroup analysis, men were broken down into three risk groups: low (prostate-specific antigen [PSA] ≤ 10 ng/ml or less, Gleason score 2–6, and T-stage ≤ T2b); intermediate (a group of patients who are not in the other two groups); and high (PSA ≥ 20 ng/ml, Gleason score > 7, or T stage > T2b).

3D treatment planning

Treatment was given to the PTV by using only 3D conformal fields shaped to minimize exposure of the bladder and rectum. The pelvic regional lymphatics were not treated electively. To reduce the rectal volume in the high-dose region on Level III, the minimum PTV dose (where overlap with the rectum was possible) was limited to 73.8 Gy, whereas the minimum GTV dose was prescribed to 79.2 Gy in 44 fractions. This was accomplished by prescribing 79.2 Gy to the isodose line encompassing the GTV only and by having the PTV enclosed by the lower isodose line that would deliver a minimum dose of 73.8 Gy. In this analysis, only patients receiving a minimum PTV dose of greater than 73.8 Gy were considered.

Table 1. Treatment according to risk group

Risk group	Treatment	*n* (%)
Low-risk	HDRT	242 (87%)
	NHT/HDRT	36 (13%)
Intermediate-risk	HDRT	217 (75%)
	NHT/HDRT	74 (25%)
High-risk	HDRT	99 (32%)
	NHT/HDRT	149 (47%)
	NHT+AHT/HDRT	66 (21%)

Abbreviations: HDRT = high-dose radiation therapy (planning target volume mean dose > 73.8 Gy); NHT = hormone therapy starting before HDRT but ≤6 months' duration; NHT+AHT = hormone therapy starting before HDRT but >6 months'duration.

Beam arrangements were determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient was based on an analysis of the volumetric dose, including dose–volume histogram analyses of the PTV and critical normal structures. Dose–volume histograms were generated for PTV, GTV, bladder, rectum, bilateral femora, and unspecified tissues. Because the treatment technique was left to the institutional principal investigator, a variety of field arrangements were planned. All treatment plans were of conventional ''forward'' type. Inverse treatment planning and intensity modulated radiation therapy were not used.

Follow-up

During treatment, the patients were seen weekly. The treating radiation oncologist saw men regularly thereafter. During the first year, they were seen in follow-up every 3 months. In the second year, they were seen every 4 months and then every 6 months until the fifth year. During follow-up evaluation, there was clinical assessment of the status of the disease and as well as measurement of the serum PSA level.

Statistical analysis

For each of the three risk groups, the distributions of pretreatment characteristics for patients with or without HT were compared using the Chi-squared test. The failure event for DFS was defined as the first event of either recurrences (local, distant, regional, second primary, or biochemical failure using the Phoenix definition) or death from any cause. Time to failure was measured from the date of study registration to the event date. Phoenix definition defines biochemical failure as occurring when PSA is greater than nadir + 2 ng/ml or any salvage hormone therapy after the end of radiation therapy (16). The date of failure was defined as the earlier of the date that PSA was greater than nadir + 2 ng/ml and the start date of salvage HT. Time to biochemical failure was measured from the date of study registration to the date of failure.

The Kaplan–Meier method was used to estimate the DFS, and the log-rank test was used to test the difference between the treatments or categories in the univariate analysis (17–19). The cumulative incidence method was used to estimate the biochemical failure rate (20), and Gray's test was used to test the difference between the treatments or categories in the univariate analysis (21). Cox proportional hazards regression (without adjusting for other covariates)