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ORIGINAL REPORT

Androgen Suppression Plus Radiation Versus Radiation Alone for Patients With Stage D_1/Pathologic Node-Positive Adenocarcinoma of the Prostate: Updated Results Based on National Prospective Randomized Trial Radiation Therapy Oncology Group 85-31

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ABSTRACT

Purpose
To update the effect of immediate androgen suppression in conjunction with standard external-beam irradiation versus radiation alone on a group of histologically lymph node-positive patients with adenocarcinoma of the prostate.

Materials and Methods
A national prospective randomized trial (Radiation Therapy Oncology Group 85-31) of standard external-beam irradiation plus immediate androgen suppression versus external-beam irradiation alone was initiated in 1985 for patients with locally advanced adenocarcinoma of the prostate. One hundred seventy-three patients in this trial had histologically involved lymph nodes. Ninety-eight patients received radiation plus immediate androgen suppression (luteinizing hormone–releasing hormone [LHRH] agonist), whereas 75 patients received radiation alone with hormonal manipulation instituted at the time of relapse.

Results
With a median follow-up of 6.5 years for all patients and 9.5 years for living patients, estimated progression-free survival with prostate-specific antigen (PSA) level less than 1.5 ng/mL at 5 and 9 years was 54% and 10%, respectively, for patients who received immediate LHRH agonist versus 33% and 4% for patients who received radiation alone with hormonal manipulation instituted at time of relapse ($P < .0001$). Multivariate analysis revealed radiation therapy and immediate hormonal manipulation as having a statistically significant impact on all end points analyzed: absolute survival, disease-specific failure, metastatic failure, and biochemical control with PSA less than 4 ng/mL and less than 1.5 ng/mL.

Conclusion
Pending the results of randomized trials, patients with adenocarcinoma of the prostate who have pathologically involved pelvic lymph nodes (pathologic node-positive or clinical stage D_1) should be considered for external-beam irradiation plus immediate hormonal manipulation rather than radiation alone with hormone manipulation at the time of relapse.

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INTRODUCTION

Prostatic carcinoma remains the second leading cause of cancer deaths in men in the United States and the most common non-skin malignancy diagnosed in American men. It is estimated that approximately 31,500 men in the United States will die this year as a result of prostate cancer.[1] Many of these deaths will be in patients who have positive regional lymph nodes at the time of diagnosis (pathologic node-positive disease [pN+]). The best form of treatment and the role of local therapy for these pN+ patients

remains controversial. Yet there are multiple single-institution series that suggest a survival advantage to local therapy (either surgery or radiation) plus hormonal therapy over hormone therapy alone.[2-4]

One recent report by Messing et al[3] favoring aggressive surgery and hormonal manipulation shows a survival advantage to the combination of radical prostatectomy and immediate androgen suppression over surgery alone. This represents some of the most promising data to date supporting local regional therapy in addition to hormonal manipulation for pN+ patients.

In trying to address this question with radiation therapy as the local-regional treating modality, the Radiation Therapy Oncology Group (RTOG) published a subset analysis of their phase III prospective randomized trial 85-31 evaluating the potential benefit of androgen suppression to radiation therapy for locally advanced disease.[5] This subset analysis included 173 patients with biopsy-proven pathologically involved lymph nodes (pN+) who were randomly assigned to receive either radiation alone (n = 75) or radiation plus immediate androgen suppression (luteinizing hormone–releasing hormone agonist; n = 98). The initial report of these patients (median follow-up, 4.9 years) showed a statistically significant difference in biochemical control, local control, and distant metastasis favoring the radiation plus immediate hormone arm, yet overall survival and disease-specific failure were not statistically different between the two arms.

Given the current median follow-up on this group of patients is 6.5 years for all patients and 9.5 years for living patients, an updated analysis was performed to determine whether radiation plus the immediate hormonal manipulation continues to show a benefit regarding local control, biochemical control, and distant metastasis. Finally, the question of a potential overall survival and/or disease-specific failure benefit was evaluated.

MATERIALS AND METHODS

Nine hundred seventy-seven patients were accrued on RTOG study 85-31, 488 patients on the immediate adjuvant goserelin arm (arm I) and 489 patients on the observation arm (arm II) who received radiation alone and goserelin at relapse.

Eligible patients include those with histologically confirmed adenocarcinoma of the prostate with regional lymphatic involvement or gross extension of the palpable primary tumor beyond the capsule (ie, clinical stage T_3/C). Patients with primary tumor confined to the prostate (clinical stage T_1/A and T_2/B) were eligible if there was either radiographic or histologic evidence of spread to regional lymph nodes. Patients who had undergone a prostatectomy were eligible if there was histologically documented penetration of the prostatic capsule to the margin of resection and/or

Table 1. RTOG 85-31: Patients With Pathologically Positive Nodes

	All Patients (N = 173)		Patients Without Prostatectomy (n = 131)		Patients With Prostatectomy (n = 42)	
	RT + Immediate Hormones (n = 98)	RT + Hormones at Relapse (n = 75)	RT + Immediate Hormones (n = 77)	RT + Hormones at Relapse (n = 54)	RT + Immediate Hormones (n = 21)	RT + Hormones at Relapse (n = 21)
Age, years						
Median	64	66	65	67	64	65
Range	44-79	50-77	44-79	50-77	53-72	53-75
Central Gleason score, n						
Not done	10	10	10	9	0	1
2-7	55	43	45	32	10	11
8-10	33	22	22	13	11	9
Stage, n						
T_1/A	3	6	2	5	1	1
T_2/B	68	53	52	37	16	16
T_3/C	27	16	23	12	4	4
Initial PSA						
Done, n	41	27	31	13	10	14
Median, ng/mL	30.1	10.1	44.5	22	8.75	1.3
Range, ng/mL	0-336	0.1-92.2	0-336	1.22-92.2	0-79	0.1-55.4
Follow-up, years (all)						
Median	4.66	4.59	4.87	4.85	4.25	4.30
Range	0.23-7.99	1.07-7.49	0.23-7.34	1.07-7.49	1.06-7.99	1.85-6.65
Alive, years						
Median	4.98	5.04	4.99	5.39	4.48	4.77
Range	1.97-7.99	1.61-7.49	1.97-7.34	1.61-7.49	3.45-7.99	2.26-6.55

Abbreviations: RTOG, Radiation Therapy Oncology Group; RT, radiation therapy; PSA, prostate-specific antigen.

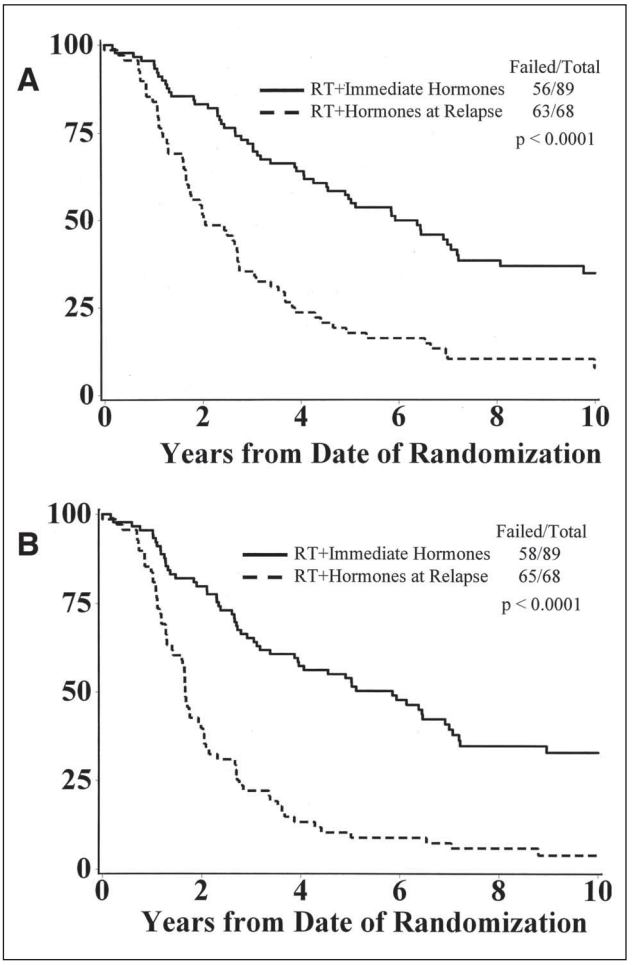

Fig 1. (A) Biochemical control by treatment type for prostate-specific antigen (PSA) less than 4 ng/mL for all patients with pathologic node-positive (pN+) disease; (B) biochemical control by treatment type for PSA less than 1.5 ng/mL for all patients with pN+ disease. RT, radiation therapy.

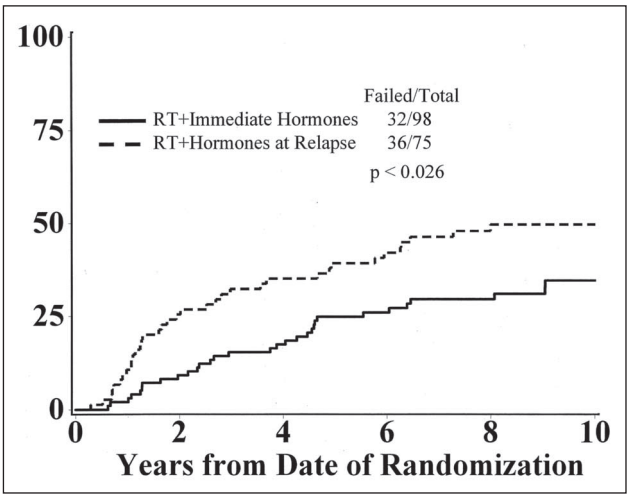

Fig 2. Incidence of development of metastatic disease for all patients with pathologic node-positive disease by treatment type. RT, radiation therapy.

seminal vesicle involvement. Karnofsky performance status had to be ≥ 60.

All institutional, state, and federal regulatory guidelines had to be followed. Patients must have signed an informed consent form before being placed on the study.

Pretreatment evaluation included a medical history, physical examination, and Karnofsky performance status evaluation. Chest x-ray and bone scan were required as well as laboratory tests, including serum acid phosphatase, CBC counts, serum testosterone, and, after July 1990, prostatic-specific antigen (PSA). PSA testing was not mandatory at the inception of the study because it was not widely available. Lymph node assessment was mandatory and could be performed by either lymphangiogram, computed tomography, or lymphadenectomy.

All patients gave informed consent before they could be randomly assigned. Patients were stratified before randomization by histologic differentiation (Gleason grade 2 to 5, or well, *v* Gleason grade 6 and 7, or moderate, *v* Gleason 8 to 10, or poor). Nodal status and extent of nodal involvement (none *v* below the common iliac *v* common iliac *v* periaortics), acid phosphatase status (nonelevated *v* elevated), and prior radical prostatectomy.

The randomization scheme described by Zelen[6] was used to achieve balance in the treatment assignment among the institutions within the four stratification variables.

Patients were randomly assigned to receive either radiotherapy and adjuvant goserelin (arm I) or radiotherapy alone followed by observation and then goserelin at the time of relapse (arm II). In patients assigned to adjuvant goserelin (arm I), the drug was to be started during the last week of the radiation therapy course and was to be continued indefinitely or until the sign of progression. Radiation therapy was delivered to all patients via megavoltage radiation therapy units with a minimum distance of 80 cm from source to the axis of treatment. For patients with evidence of tumor spread to the pelvic lymphatics (obturator, external, and internal iliac lymph nodes), the initial target volume included pelvic lymph nodes to the level of the L5-S1 interspace. The inferior margin was to be placed 5 to 6 cm below the superior margin of the symphysis pubis, and the lateral margins were 2-cm lateral to the pelvic brim. For those patients with evidence of spread to the common iliac lymph nodes, the initial target volume included not only pelvic, but also periaortic lymph nodes up to the level of L2/L3 interspace. In patients with evidence of spread to the periaortic area, the upper board of the initial target volume was extended to T11 vertebra.

The initial target volume was to receive a total of 44 to 46 Gy. Doses up to 50 Gy were acceptable. The prostatic boost volume included the prostate with margins wide enough to encompass all the tumor extensions into the surrounding tissues. This boost volume constituted 20 to 25 Gy, bringing the total prescribed dose to that volume of 65 to 70 Gy. Patients who received prostatectomy received a prostatic target volume dose of 60 to 65 Gy. Minimum dose to the prostatic target volume was 65 Gy in the definitively treated patients and 60 Gy in the postoperatively treated patients. These doses were delivered four to five times a week at a fraction size of 1.8 to 2 Gy.

Administration of goserelin (Zoladex; AstraZeneca Pharmaceuticals, Wilmington, DE) was started during the last week of radiotherapy for arm I and at the time of relapse for arm II. The drug was delivered indefinitely or until the sign of disease progression. Dosage of goserelin was 3.6 mg administered subcutaneously on a monthly basis in the anterior abdominal wall.

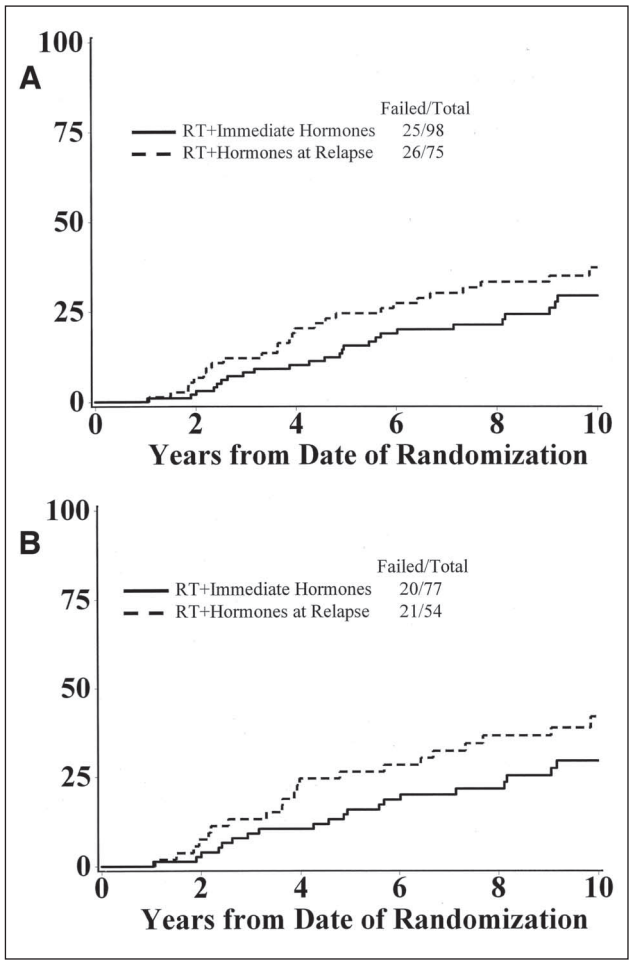

Fig 3. (A) Disease-specific failure by treatment type for all patients with pathologic node-positive (pN+) disease; (B) disease-specific failure by treatment type for all patients with pN+ disease with prostatectomy. RT, radiation therapy.

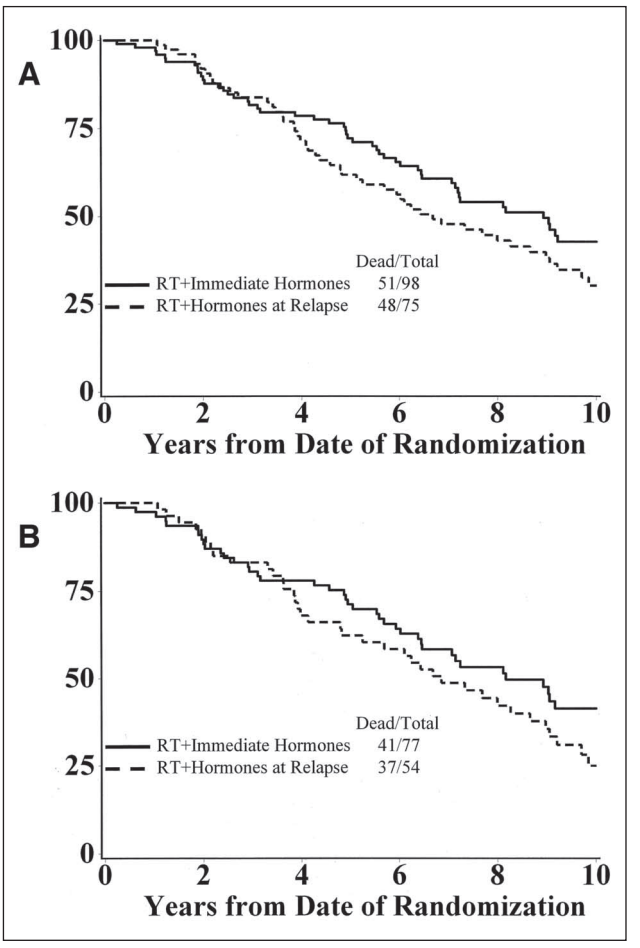

Fig 4. (A) Absolute survival by treatment type for all patients with pathologic node-positive (pN+) disease; (B) absolute survival by treatment type for all patients with pN+ disease without prostatectomy. RT, radiation therapy.

A central review of radiation therapy delivered, machine calibration for all machines on which a patient was treated, and review of materials on which the diagnosis was based was performed for each case as per the usual RTOG/National Cancer Institute requirements.

Definitions of end points are as follows: (1) local failure is the persistence of the palpable tumor beyond 24 months. After study entry, local failure is defined as reappearance of palpable tumor after initial clearance, progression of palpable tumor (at any time), or biopsy-proven presence of carcinoma of the prostate 2 years or more after study entry. (2) Regional failure is the clinical or radiographic evidence of tumor in the pelvis with or without palpable tumor in the prostate by digital examination. (3) Distant metastasis is defined as the clinical or radiographic evidence of disease beyond the pelvis. (4) Disease-free survival (no evidence of disease [NED] survival) is defined as survival in the absence of local or regional failure or distant metastasis. NED survival was also computed taking into account PSA failure (with either 1.5 ng/mL or 4.0 ng/mL as threshold). In these computations, only patients with PSA determination past 1 year were included in the analysis. (5) Absolute survival was measured from the date of randomization to the date of death or most recent follow-up. Disease-specific survival was similarly measured. Death from any cause was considered a failure for absolute survival, but only death attributed to prostate cancer or the treatment delivered was considered a failure for disease-specific survival.

Persistence of the palpable tumor in the prostate was counted as an immediate local recurrence as of day 1. Time to distant metastasis or local recurrence (after the complete regression of the palpable tumor of the prostate) was measured from the day of randomization to the occurrence of either event. The cumulative incidence approach was used to estimate time to local failure, time to distant metastasis, and disease-specific survival, because it specifically adjusts for the other competing risks of failure.[7] For example, the cumulative incidence for local failure adjusts for patients dying without it. The statistics developed by Gray[8] for comparing cumulative incidence rates were used. NED survival and absolute survival were estimated according to the Kaplan-Meier method.[9] The comparison for various survival end points was performed with the log-rank test.[10] All the statistical comparisons were made with two-tailed tests. Multivariant analysis was performed using a Cox regression model and the following variables: centrally reviewed Gleason score (2 to 7 *v* 8 to 10), treatment

Table 2. Multivariate Analysis: Absolute Survival

Covariate	Increased Survival	Decreased Survival	*P*	Relative Risk
Central Gleason score	2-7	8-10	.012	1.75
Treatment	RT + immediate hormone	RT + delayed hormone	.030	1.62
Age, years	< 70	≥ 70	.033	1.67
Acid	Not elevated	Elevated	.011	1.79

Abbreviation: RT, radiation therapy.

(radiation therapy plus immediate *v* delayed hormones), age (< 70 *v* ≥ 70 years), T stage (T1/2 *v* T3), prostatic acid phosphatase level (not elevated *v* elevated), and prostatectomy (yes *v* no).

RESULTS

From February 16, 1987, through April 17, 1992, when the study closed, 977 patients were entered, 488 patients on the adjuvant goserelin arm (arm I) and 489 patients on the observation arm (arm II). Results of the entire study are available.[11] One hundred seventy-three eligible patients on study had biopsy proven pathologically involved lymph nodes (pN+); 98 of these patients received radiation therapy plus immediate adjuvant goserelin, and 75 patients received radiation therapy and delayed hormonal manipulation at the time of failure. Of these lymph node–positive patients, 21 patients on each arm of the study also received prostatectomy. Thus 77 patients of the immediate goserelin group did not have prostatectomy and 54 patients in the radiation therapy–only group did not have prostatectomy. Ages ranged from 44 to 79 years for arm I patients, with a median of 64 years, and from 50 to 77 years for arm II patients, with a median of 66 years. Histologic grading by centrally reviewed Gleason score is shown in Table 1. There were no statistical differences in histologic grade by treatment arm. (Approximately 12% of the patients had no centrally reviewed Gleason score). Clinical stage is also shown in Table 1. There were no statistical differences in clinical stage by treatment arms.

Approximately 40% of patients had no initial PSA values. For those patients with initial PSA values, the medians are shown in Table 1. There is a statistically significant difference by pretreatment PSA values between the treatment arms, showing a greater frequency of higher pretreatment PSA values in the radiation plus immediate hormone group ($P = .01$).

Median follow-up was 6.5 years for all patients and 9.5 years for living patients. The location of positive lymph nodes by treatment type was previously reported,[5] and there was no significant difference in location of positive lymph nodes by treatment arm. Likewise, acid phosphatase levels were previously reported, and there was no statistical difference between the treatment arms.

Biochemical control by treatment arm as measured by PSA less than 4 ng/mL and less than 1.5 ng/mL is shown in Figures 1A and 1B, respectively. At 5 and 9 years, biochemical control by PSA less than 1.5 ng/mL was 54% and 10%, respectively, for arm I, and 33% and 4% for arm II. Patients who received immediate hormone therapy (arm I) had a statistically significant increase in PSA control compared with arm II ($P < .0001$). This statistical difference in biochemical control is present for patients both with and without prostatectomy.

The incidence of distant metastasis for all patients continues to be statistically better for patients receiving immediate hormonal manipulation (arm I; $P = .026$; Fig 2). This statistical difference was present for the subset of patients without prostatectomy but was not present for those patients with prostatectomy ($P = .025$ and $P = .16$, respectively).

Disease-specific failure is shown in Figures 3A and 3B for the entire pN+ group and for the no-prostatectomy group, respectively. There was no statistical difference in disease-specific survival between the groups of patients, regardless of prostatectomy status. Likewise, absolute survival by univariate analysis was not statistically effected by the use of immediate hormonal manipulation (Figs 4A and 4B). Five- and 9-year absolute survival rates were 72% and

Table 3. Multivariate Analysis: Cause-Specific Failure

Covariate	Decreased Failure	Increased Failure	*P*	Relative Risk
Central Gleason score	2-7	8-10	.0009	2.72
Treatment	RT + immediate hormone	RT + delayed hormone	.014	2.12
Acid	Not elevated	Elevated	.0078	2.27

Abbreviation: RT, radiation therapy.

Table 4. Multivariate Analysis: Metastatic Failure

Covariate	Decreased Failure	Increased Failure	*P*	Relative Risk
Central Gleason score	2-7	8-10	.0011	2.45
Treatment	RT + immediate hormone	RT + delayed hormone	.0005	2.54
Prostatectomy	Yes	No	.023	2.16

Abbreviation: RT, radiation therapy.

62%, respectively, for all patients in arm I, and 50% and 38%, respectively, for all patients in arm II ($P = .23$).

Multivariant analysis results are shown in Tables 2 through 6. This analysis identifies radiation therapy and immediate hormonal manipulation as having a statistically significant impact in all four end points analyzed: absolute survival ($P = .030$), disease-specific failure ($P = .014$), metastatic failure ($P = .0005$), and biochemical control with PSA less than 4 ng/mL and less than 1.5 ng/mL (both $P < .0001$). Other factors that statistically decreased absolute survival were an elevated acid phosphatase level, age ≥ 70 years, and Gleason score 8 to 10. Disease-specific failure was also negatively impacted by Gleason score 8 to 10 and elevated acid phosphatase level, but not age. Biochemical control likewise was decreased by Gleason score 8 to 10, elevated acid phosphatase, and no prostatectomy.

The fact that type of treatment was not statistically significant in regard to overall and disease-specific survival in the univariant analysis but was statistically significant in the multivariate analysis relates to the following. All patients (n = 173) were included in the univariant analysis, whereas only those patients who had central Gleason scores were included in the multivariate analysis (n = 153). Of the 20 patients not included in the multivariate analysis because of lack of central Gleason scores, 10 patients were from each treatment arm. Both groups of patients, the 153 patients included in the multivariate analysis and the 20 patients excluded from this analysis, are balanced across the treatment arms with respect to the their available prognostic factors included in the multivariate analysis.

With regard to the survival end point and the 20 patients excluded from the multivariate analysis, nine of 10 patients in arm I experienced treatment failure, whereas only six of 10 patients experienced treatment failure in arm II. Because there was already a smaller percentage of failures for arm I, taking out the group of 10 patients, nine of whom failed treatment, helped to increase the difference between the arms enough so that the treatment became a significant factor.

Protocol violations related to the radiation delivered were not statistically different between the two treatment arms.[5] Regarding the use of hormones on arm I, five of 98 patients discontinued hormones. Seventy-five percent of patients did describe hot flashes, with the next most common side effect of hormonal treatment for arm I patients being fluid retention (12%).

Both acute and late toxicity were evaluated by treatment arm using the RTOG schema.[11] There were four grade 4 toxicities in arm I. These included two bowel obstructions (one with perforation), one cystitis, and one hematuria. In evaluating grade 3 or higher toxicity, there was no statistical difference between the two arms ($P = .48$).

DISCUSSION

For patients with locally advanced or high-grade prostate cancer, the use of hormones in addition to radiation therapy has become a standard as a result of multiple randomized trials showing a benefit to the addition of hormonal manipulation to radiation treatments.[11-16] Patients with known positive regional lymph nodes (pN+ disease) are a subset of the above-mentioned patients who are particularly likely to succumb to their disease.[17] The potential benefit of aggressive local therapy in these patients has been a subject of much debate over the past several years.

However, there are data from both surgical and radiation series that suggest a benefit to local-regional therapy,

Table 5. Multivariate Analysis: No Evidence of Disease With Prostate-Specific Antigen < 4 ng/mL

Covariate	Increased Survival	Decreased Survival	*P*	Relative Risk
Central Gleason score	2-7	8-10	.0088	1.72
Treatment	RT + immediate hormone	RT + delayed hormone	< .0001	3.82
Acid	Not elevated	Elevated	.007	1.85
Prostatectomy	Yes	No	.0061	2.02

Abbreviation: RT, radiation therapy.

Table 6. Multivariate Analysis: No Evidence of Disease With Prostate-Specific Antigen < 1.5 ng/mL

Covariate	Increased Survival	Decreased Survival	*P*	Relative Risk
Central Gleason score	2-7	8-10	.046	1.50
Treatment	RT + immediate hormone	RT + delayed hormone	< .0001	4.74
Acid	Not elevated	Elevated	.02	1.69
Prostatectomy	Yes	No	.0046	2.03

Abbreviation: RT, radiation therapy.

albeit from single institutions.[2,3] The data from M.D. Anderson Cancer Center shows overall survival in 72 patients receiving radiation therapy and immediate hormonal manipulation that matches expected survival for a cohort of patients without prostate cancer.[2] This is in contrast to their 183 men who received early hormonal manipulation alone, where the overall survival declined dramatically after 5 years compared with the expected survival. Patients who received radiation therapy and immediate hormonal manipulation had an overall survival rate at 5 and 10 years of 92% and 67%, respectively, and a freedom from relapse or increasing PSA rate of 91% and 80% at 5 and 10 years, respectively.[2] The data from M.D. Anderson Cancer Center compares favorably with the data from this RTOG analysis, which shows an overall survival rate at 5 and 9 years of 72% and 62%, respectively. More importantly, the cause-specific survival in our data set was 84% and 76% at 5 and 9 years, respectively, indicating reasonable control of aggressive prostate cancer over a long period of time.

Pioneering surgical results for pN+ were reported by Messing et al.[3] These data revealed a benefit to immediate hormonal manipulation in addition to surgery for clinical T2 patients with positive lymph nodes.[3] One hundred patients were randomly assigned to immediate goserelin (3.6 mg administered subcutaneously every 28 days) indefinitely or bilateral orchiectomy versus delayed hormonal treatment when there were signs of clinical progression (other than detectable increasing PSA level).[3] With a median follow-up of 7.1 years, seven (15%) of 47 patients with immediate hormonal manipulation had died, versus 18 (35%) of 51 patients in the delayed treatment group ($P = .02$). The cause of death was prostate cancer in three (6%) of the 47 patients assigned to surgery and immediate hormonal manipulation and 16 (31%) of the 51 patients who received surgery alone ($P < .01$).[3]

The data from this RTOG trial are not directly comparable to the Messing data,[3] because 25% of our cases had clinical stage C (ie, T3) disease (these patients were excluded from the surgical trial) and only 14% of the surgical trial patients had Gleason score 8 to 10 disease, yet in the RTOG data reported here, 55 patients had Gleason score 8 to 10 disease, representing 32% of our 173 patients. Therefore, bulk and grade of disease were clearly greater in the cohort reported here compared with that of the Messing study. Yet the results at 5 and 9 years with respect to cause-specific failure are not terribly different, with prostate cancer–related death rates of 16% and 24% at 5 and 9 years, respectively, for the radiation and immediate hormonal manipulation arm.

The issue of the disparate results between the univariate versus multivariate analysis requires some discussion. One would expect the multivariate analysis to be the more accurate of the two in predicting statistically significant parameters of outcome. Yet given that the populations are not the same (ie, 10 patients in each arm did not have central Gleason review and therefore were not part of the multivariate analysis), one cannot make that assumption. In the univariate analysis, there was a trend toward improved absolute survival for arm I patients (72% *v* 50% at 5 years and 62% *v* 38% at 9 years), but the *P* value was .23. Cause-specific failure shows a similar result in that only 16% and 24% of arm I patients died of their disease at 5 and 9 years, versus 25% and 33% of patients at 5 and 9 years for arm II patients.

Finally this analysis documents a statistically significant difference in favor of immediate hormonal manipulation and radiation therapy for end points of distant metastasis ($P = .026$), NED survival ($P = .0009$), NED survival with PSA less than 4 ng/mL ($P < .0001$), NED survival with PSA less than 1.5 ng/mL ($P < .0001$), and a trend for local failure ($P = .059$). Given that patients with pN+ disease are being controlled statistically better with immediate hormonal manipulation and radiation therapy in regard to local disease, distant metastasis, and biochemical control, it seems plausible to believe the multivariate results that show that the treatment type is statistically significant regarding cause-specific survival.

This is a retrospective subset analysis of a phase III randomized trial. Only a prospective trial aimed at analyzing the potential benefit of radiation therapy and hormonal manipulation over radiation therapy alone for patients with pN+ disease will absolutely answer the question of potential benefit to hormonal manipulation. That type of trial was launched by the RTOG in the mid-1990s and, given poor accrual, was closed. So until such data are available, radiation therapy and immediate hormonal manipu-

lation clearly remain an effective means to control pN+ adenocarcinoma of the prostate in a significant cohort of men with such aggressive disease.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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