

# ANDROGEN DEPRIVATION WITH RADIATION THERAPY COMPARED WITH RADIATION THERAPY ALONE FOR LOCALLY ADVANCED PROSTATIC CARCINOMA: A RANDOMIZED COMPARATIVE TRIAL OF THE RADIATION THERAPY ONCOLOGY GROUP\*

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**ABSTRACT—Objectives.** Androgen deprivation therapy before and during radiation therapy could, by reducing tumor volume, increase local tumor control, disease-free survival, and overall survival in patients with locally advanced adenocarcinomas of the prostate.

**Methods.** In a randomized controlled clinical trial, patients with large T2, T3, and T4 prostate tumors, but no evidence of osseous metastasis, were randomized to receive goserelin 3.6 mg subcutaneously every 4 weeks and flutamide 250 mg orally three times daily 2 months before and during the radiation therapy course (Arm I) compared with radiation therapy alone (Arm II). Pelvic irradiation was administered with 1.8 to 2.0 Gy per day to a total dose of  $45 \pm 1$  Gy followed by a boost to the prostate target volume to a total dose of 65 to 70 Gy.

**Results.** Of 471 randomized patients, 456 were evaluable, 226 on Arm I and 230 on Arm II. With a median potential follow-up of 4.5 years, the cumulative incidence of local progression at 5 years was 46% in Arm I and 71% in Arm II ( $P < 0.001$ ). The 5-year incidence of distant metastasis on Arms I and II was 34% and 41%, respectively ( $P = 0.09$ ). Progression-free survival rates including normal prostate-specific antigen (PSA) levels for 396 patients with at least one PSA recorded were 36% in Arm I and 15% in Arm II at 5 years ( $P < 0.001$ ). At this time, no significant difference in overall survival could be detected ( $P = 0.7$ ).

**Conclusions.** Short-term androgen deprivation with radiation therapy results in a marked increase in local control and disease-free survival compared with pelvic irradiation alone in patients with locally advanced carcinoma of the prostate. Long-term surveillance is required to assess effects on overall survival.

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Radiation therapy is a well-established modality in the curative management of carcinoma of the prostate. In patients with small tumors and no evidence of spread beyond the pelvis, external beam irradiation has been associated with high locoregional

control rates and long-term survival rates comparable to those achieved with radical surgery.<sup>1</sup> The probability of locoregional recurrence, however, increases with increasing size of the primary tumor as reflected in T stage.<sup>2</sup> Despite the subjectivity and lesser accuracy than transrectal ultrasonography, large tumor size defined by the product of palpable tumor dimensions in centimeters at digital rectal examination, correlated strongly, even within stage, with locoregional failure in patients treated on prior studies of the Radiation Therapy Oncology Group (RTOG).<sup>3</sup> More than 50% of patients in whom the product of tumor dimensions exceeded 25 cm<sup>2</sup> had locoregional failure by the sixth year after completion of treatment.<sup>4</sup>

Androgen deprivation therapy in patients with disseminated carcinoma of the prostate is associated with a high response rate. The traditional methods of androgen deprivation include orchiectomy and estrogen administration. Newer approaches consist of administration of luteinizing hormone-releasing hormone (LHRH) agonists and androgen receptor blockers.

Investigators of the RTOG have studied the potential value of androgen deprivation therapy as an adjuvant to definitive radiation therapy since the early 1980s. One of the tested treatment regimens<sup>5</sup> used androgen deprivation therapy prior to and during irradiation, based on the hypothesis that reduction in the tumor volume prior to radiation therapy could lead to increased control of the primary tumor at a specific level of radiation dose. Current concepts of apoptotic regressions associated with reductions of dihydrotestosterone<sup>6</sup> suggest that adjuvant androgen deprivation could enhance the cell killing of radiation therapy. Early RTOG studies of hormonal cyto-reduction via androgen deprivation established the tolerance of short-term hormonal alterations in regard to acute reactions from pelvic irradiation and the preservation of potency postirradiation.<sup>5,7</sup> A Phase III trial was developed to compare standard radiation therapy alone with short-term use of an LHRH analogue plus an androgen receptor blocking agent before and during radiation therapy.

## MATERIAL AND METHODS

The study was designed to test the potential value of a combination of goserelin acetate, an LHRH analogue, and flutamide, an antiandrogen, used as cyto-reductive agents prior to and during radiation therapy in locally advanced (bulky) carcinoma of the prostate without radionuclide evidence of osseous metastasis. Patients on the control arm received radiation therapy only.

The endpoints of the study included local control rates, progression-free survival, and survival. The primary endpoint was the local control rate. Although the study was designed before prostate-specific antigen (PSA) determinations were available, their widespread use for determining outcome mandated their consideration in the analysis.<sup>8-12</sup>

## ELIGIBILITY AND STUDY DESIGN

The criterion for enrollment was histologic evidence of adenocarcinoma of the prostate, either confined to the prostate (clinical Stage T2b, T2c, or B2)<sup>13</sup> or extending beyond the capsule (clinical Stage T3, T4, or C), with no evidence of dissemination beyond regional lymph nodes. The tumors were required to be 25 cm<sup>2</sup> or more as measured by the surface area palpable by digital rectal examination. Patients with regional lymph nodes were eligible provided the involved nodes were below the common iliac chain. Patients with involved common iliac or periaortic lymph node involvement were not eligible. The lymph node evaluation was carried out by either computed tomography (CT), lymphography, or lymphadenectomy. Karnofsky performance status<sup>14</sup> had to be equal to or greater than 60. Pretreatment evaluation included medical history, including sexual function, and physical examination. The required studies included chest roentgenograms and radionuclide bone scans, complete blood count (CBC), serum aspartate transaminase, and alanine transaminase (only on patients who were to receive goserelin and flutamide). Serum prostatic acid phosphatase (PAP) and testosterone levels were mandatory for all patients. During the early years of the study, PSA was not available, but the protocol was later revised to include PSA determinations.

The study protocol was approved by the National Institutes of Health, the review boards of the RTOG, and all the participating institutions. All the patients gave informed written consent before they were enrolled.

The randomization scheme described by Zelen<sup>15</sup> was used to achieve balance among the institutions, with two stratification variables: clinical Stage (T2, T3-4) and histopathologic differentiation (well, moderate, poor).

## TECHNIQUES OF TREATMENT

### RADIATION THERAPY

Megavoltage radiation therapy units were used with a minimal distance of 80 cm from the source to the axis of treatment. Patients with no evidence of tumor spread to the pelvic lymphatic system were treated to a target volume that extended up

to L5-S1 interspace. In patients with evidence of pelvic lymph node involvement, the superior border was extended to include the lower para-aortic lymph nodes to the level of the L2-L3 interspace. The inferior margin of the field was at or immediately above the ischial tuberosity. The lateral margins were 1 cm lateral to the maximum width of the bony pelvis. A "boost" target volume included the prostate with margins sufficiently wide to encompass all of the tumor extensions into the surrounding tissues. Multiple fields were used to limit the total dose to the surrounding normal tissues. The large field, including the regional lymphatics, received a minimum total dose of  $45 \pm 1$  Gy. The small boost volume received an additional 20 to 25 Gy, bringing the minimum total dose to the tumor-containing volume from 65 to 70 Gy. The daily doses were 1.8 to 2.0 Gy, 5 days per week.

#### HORMONE THERAPY

Goserelin acetate (Zoladex), 3.6 mg, was administered subcutaneously every 4 weeks starting 2 months prior to initiation of radiotherapy. It was continued during radiation therapy for a total of four injections. Flutamide (Eulexin), 250 mg orally three times daily was also started 2 months prior to initiation of radiotherapy and was continued throughout the radiotherapy course.

A central review of the radiation therapy delivered for each case was performed by the study chair. The calibration of every machine on which a patient was treated was obtained from the Radiologic Physics Center at The University of Texas M.D. Anderson Cancer Center. Individual treatment parameters, such as total dose, field borders, and elapsed treatment days, were reviewed relative to protocol specifications. Report forms for compliance with drug administration were reviewed by headquarters staff and the study chair.

Radiation-induced effects on normal tissue<sup>16</sup> were assessed as either acute or late phenomena. Toxicity related to treatment was considered to be acute if it occurred within the first 90 days from the start of treatment. Toxicity was considered to be late if it occurred after 90 days or an acute toxicity persisted beyond day 90. The toxicities were scored from 0 (none) to 5 (fatal), with grades 3, 4, and 5 considered as major.

Central review of materials on which the diagnosis was based was performed for consistency in assigning degree of differentiation and Gleason scores. If central review data were not available, interpretations by the institutional pathologist were used.

#### DATA COLLECTION AND STATISTICAL ANALYSIS

Local progression was defined as a PSA level more than 4 at 1 year or more from randomization or additional hormonal therapy in the absence of metastatic disease, an increase of more than 50% in tumor size (cross-sectional area), recurrence of a palpable tumor after initial clearance, or biopsy specimen revealing adenocarcinoma of the prostate 2 years or more after study entry. Regional metastasis was defined as clinical or radiographic evidence of tumor in the pelvis with or without palpable tumor in the prostate by digital rectal examination. Distant metastasis was defined as clinical or radiographic evidence of disease beyond the pelvis. A failure in progression-free survival is defined as a failure in either survival, local progression, or regional or distant metastasis.

Survival was measured from the date of randomization to the date of death or the most recent follow-up. Time to a distant metastasis or a local progression (after reported tumor clearance by palpation) was measured from the date of randomization to the occurrence of either event or to the date of the most recent follow-up. Progression-free survival was measured from the date of randomization to the earliest occurrence of either death, local progression, or metastasis or to the date of the most recent follow-up. Estimates of survival and progression-free survival were derived by the Kaplan-Meier<sup>17</sup> method. The cumulative incidence of local progression and metastasis was estimated.<sup>18</sup> Statistical comparisons for survival and progression-free survival were made by the log-rank statistic in the case of censored data or by the proportional-hazards analysis to control for prognostic factors. Statistical comparisons for the cumulative incidence of local progression or distant metastases were made using Gray's test.<sup>19</sup> All the statistical comparisons were made with two-tailed tests. Assessment of sexual functions was based on patients' answers to the question, "Able to have an erection? No, Yes, or Unknown," which was ascertained at baseline and at every follow-up visit.

#### RESULTS

From April 15, 1987, through June 1, 1991, when the study was closed, 471 patients were enrolled. Central pathology review was completed for 98% (461 of 471) of the patients. Fifteen patients were excluded, leaving 456 analyzable patients, 226 on the treatment and 230 on the control arm. The reasons for exclusion were no follow-up (4), tumor too small (5), refused all treatment and follow-up (3), lung primary (1),

TABLE I. Pretreatment characteristics

	All Patients		Patients With One or More PSA Reading	
	Goserelin + Flutamide + Radiation Therapy (n = 226)	Radiation Therapy Alone (n = 230)	Goserelin + Flutamide + Radiation Therapy (n = 196)	Radiation Therapy Alone (n = 200)
Age				
Median	70	71	70	71
Range	50-88	49-84	53-88	49-84
Performance status (KPS)				
100	87 (38%)	96 (42%)		
90	121 (54%)	124 (54%)		
80	15 (7%)	10 (4%)		
70	2 (1%)	0 (0%)		
60	1 (<1%)	0 (0%)		
Differentiation				
Grade 1	34 (15%)	35 (15%)	31 (16%)	30 (15%)
Grade 2	84 (37%)	80 (35%)	75 (38%)	70 (35%)
Grade 3	63 (28%)	78 (34%)	55 (28%)	69 (35%)
Grade 4	29 (13%)	20 (9%)	21 (11%)	16 (8%)
Unknown/missing	16 (7%)	17 (7%)	14 (7%)	15 (8%)
Gleason score				
2-5	33 (15%)	34 (15%)	31 (16%)	30 (15%)
6-7	131 (58%)	123 (53%)	112 (57%)	109 (55%)
8-10	59 (26%)	69 (30%)	51 (26%)	57 (29%)
Missing	3 (1%)	4 (2%)	2 (1%)	4 (2%)
Nodal status				
Positive	16 (7%)	21 (9%)	14 (7%)	19 (10%)
Negative	207 (92%)	209 (91%)	179 (91%)	181 (91%)
Missing	3 (1%)	0 (0%)	3 (2%)	0 (0%)
Serum acid phosphatase				
Normal	130 (58%)	126 (55%)	115 (59%)	105 (53%)
Abnormal	87 (38%)	87 (38%)	74 (38%)	81 (41%)
Unknown	9 (4%)	17 (7%)	7 (4%)	14 (7%)
Clinical stage				
T2 (B2)	67 (30%)	70 (30%)	61 (31%)	59 (30%)
T3-4 (C)	159 (70%)	160 (70%)	135 (69%)	141 (71%)

bone metastasis (1), and benign disease (1). As of April, 1994, the median potential follow-up was 4.5 years and the median period of observation was 3.3 years (mean, 3.4 years).

Pretreatment prognostic factors are well-balanced between the two groups (Table I). Of the 37 (8.1%) patients considered to have pelvic lymph node metastasis, 23 had histologic confirmation and 14 had abnormal CT scans. There was no interaction between treatments and any of the prognostic factors, that is, treatment effect was similar in each of these subgroups: grade, Gleason score, stage, and initial PAP level. Of the 225 patients in Arm I with compliance information, 211 (94%) completed goserelin treatment and 188 (84%) completed flutamide treatment as planned. Treatment was terminated for flutamide toxicity in 23 patients. Reasons for termination were diarrhea (11), hot

flushes (3), liver function abnormalities (3), and other various reasons (rash, nausea, syncope). Two patients refused goserelin, 1 of whom also refused flutamide, but they are included in analyses. Thus, 186 patients completed both goserelin and flutamide treatment as planned.

No patient was reported to have acute grade 4 or 5 toxicities from radiation therapy. Three patients were reported with grade 4 toxicities in follow-up, 1 with hematuria in Arm I and 1 each with hematuria and hematochezia in Arm II. Grade 3 toxicities were reported in 7.1% (16/226) and 7.4% (17/230) of patients in Arms I and II, respectively.

There was no difference in frequency or time of return of sexual potency in the treatment groups; 81 of 102 of the radiation therapy plus hormone group and 74 of 102 of the radiation therapy alone group reported return of sexual function

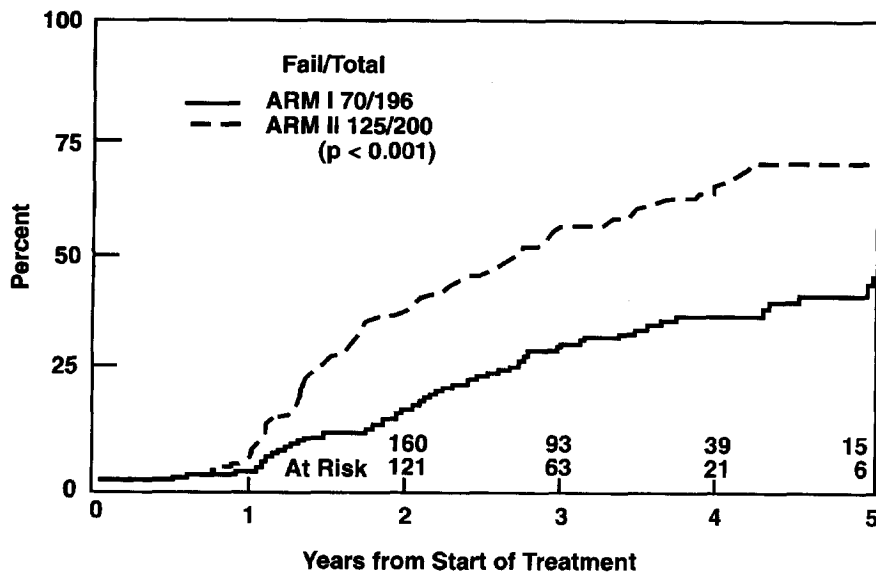


FIGURE 1. Cumulative incidence of local progression by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.

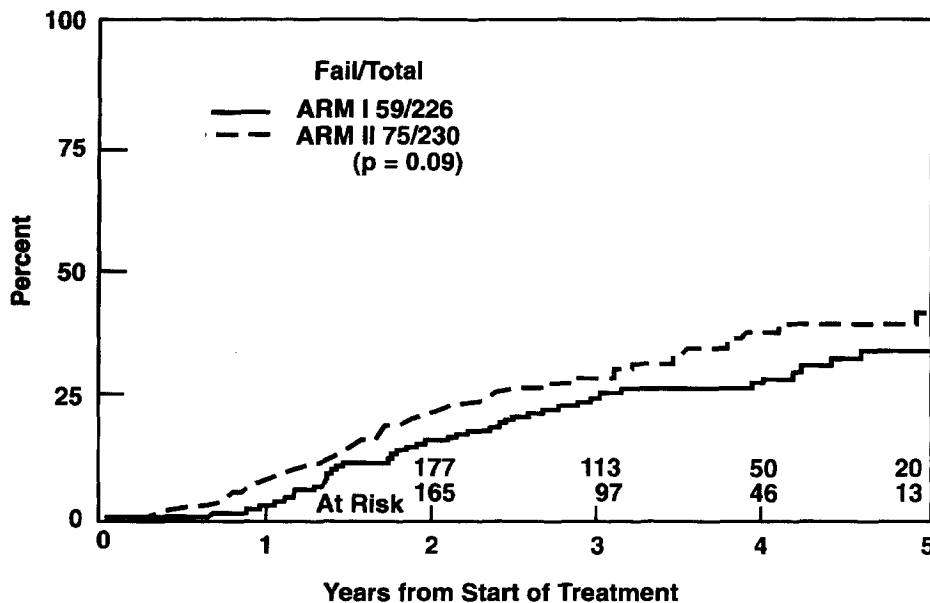


FIGURE 2. Cumulative incidence of distant metastasis by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.

(denominator in each group was number of patients reporting potency at time of enrollment). There was no difference between the treatment groups in respect to development of second primary malignant tumors; 9 of the radiation therapy plus hormone treatment group and 11 of the radiation therapy alone developed second primaries.

Biopsy result alone was the only evidence of failure in 1 patient; all other patients with positive biopsy results either had rising PSA or clinical progression. Of the patients who had biopsies taken more than 2 years, 8 of 19 (42%) in the radiation therapy plus hormone group and 11 of 19 (58%) in the radiation therapy alone group had positive biopsy results.

A subset of the study cohort was used for the analysis of progression-free survival and local progression consisting of patients with at least one PSA level recorded. The total subset size was 396, with 196 and 200 patients in Arm I and Arm II, respectively. Among patients included in the analysis of progression, the median time from the end of radiation therapy to the first PSA measurement was 9.6 months. After the first PSA measurement, patients had an average of 2.1 PSA determinations per year until progression, death, or last event-free follow-up visit.

There was a significant decrease in local progression for patients in Arm I (Fig. 1) ( $P < 0.001$ ): 70 treated patients versus 125 control patients

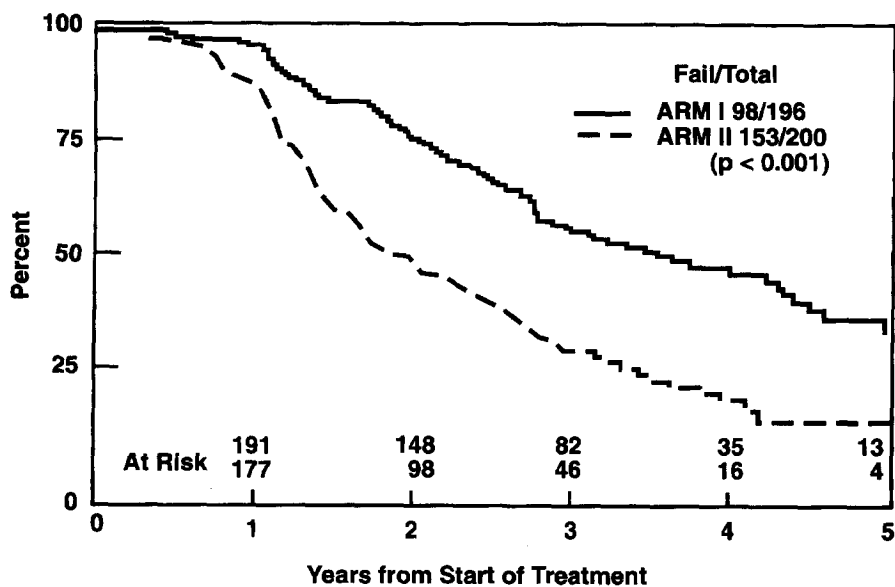


FIGURE 3. Progression-free survival by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.

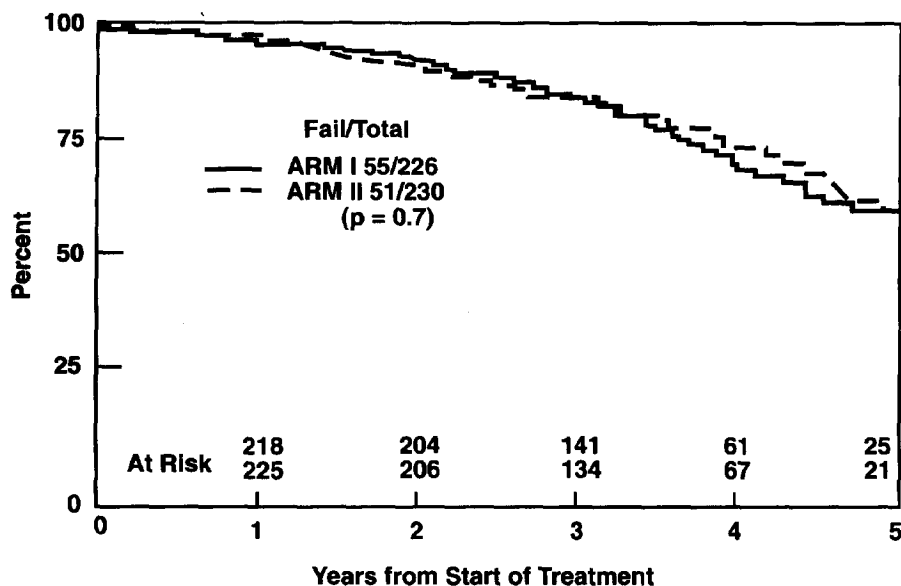


FIGURE 4. Survival by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.

had local progression. The 5-year cumulative incidence of local progression was 46% on Arm I and 71% on Arm II, respectively. A decrease in the incidence of metastasis was observed for patients in Arm I (Fig. 2) ( $P = 0.09$ ): 59 treated patients developed metastasis compared with 75 control patients. The 5-year incidence of metastasis was 34% in Arm I and 41% in Arm II. There was a significant improvement in progression-free survival for patients in Arm I (Fig. 3) ( $P < 0.001$ ) (5-year rates of 36% for Arm I, 15% for Arm II). There was no significant difference in survival between the two treatment groups ( $P = 0.7$ ) (Fig. 4).

#### COMMENT

Radiation therapy has for 3 decades been considered one of the gold standards of treatment for both early and locally advanced prostatic carcinoma. In recent years, the long-term success of

both radiation therapy and radical surgery has come under significant challenge with the use of more stringent criteria for local control and for relapse-free existence. For instance, a number of series have been published in which a biopsy of the prostate glands was redone 18 months or more following irradiation.<sup>20-23</sup> Although in none of these series was it clear that the patients selected to have a re-biopsy were in any way representative of the entire irradiated population, it is disquieting that in these series from 18% to 90% of re-biopsy specimens showed viable tumor.

The likelihood of obtaining a positive re-biopsy is low when the serum PSA is low, but it is more than 80% when PSA is elevated following treatment. This is consistent with the now wide use of serum PSA to detect persistent or recurrent disease.<sup>10,11,24</sup> These data show that recurrence-free survival figures are approximately 20% worse

when using an abnormal serum PSA as a definition of recurrence compared with those obtained historically using purely clinical endpoints. With the use of these two new yardsticks, pathologic local control and a serum PSA in the normal range as tumor control endpoints, it is evident that both radiation therapy<sup>10,21</sup> and surgery<sup>12</sup> are considerably less effective than was previously presumed.

The RTOG randomized trial that is reported here has tested one of the important strategies available to oncologists in urologic cancer to improve local control, namely, an attempt to reduce the tumor volume prior to irradiation, which, if it is accompanied by a decrease in the number of tumor clonogens, should improve local cure. This strategy has the advantage of not requiring radiation dose escalation with the attendant risks of morbidity. The goal is to reduce safely local recurrence, which is accompanied by substantial local morbidity<sup>25</sup> and possibly by a second wave of metastases.<sup>26</sup>

Androgen dependence of human prostate carcinoma was first observed by Huggins and Hodges in 1941<sup>27</sup> with the cytotoxic effect of androgen suppression recently becoming understood as genetically controlled apoptosis.<sup>6</sup> The possible long-term benefits of androgen deprivation by both an LHRH analogue and an androgen receptor blocker that we report here have recently been shown to be of survival benefit in men with minimal bony metastatic disease.<sup>28</sup>

The patients enrolled in this study had the most advanced carcinoma of the prostate still treated with curative intent: 70% were classified as T3 or T4 and could extend from one pelvic side wall to the other. Even the 30% with T2b-c tumors had a minimum size by palpation of 5 by 5 cm. Approximately 40% of the patients had elevated PAP levels. In the group treated with radiation alone, almost two thirds of the patients are estimated to be alive at 5 years. A 4-month course of goserelin and flutamide (costing \$2168 to the pharmacist)<sup>29</sup> before and during radiation therapy, markedly reduced the incidence of treatment failures with no increase in major toxicity. A relationship has been shown between control of the tumor in the prostate by radiation therapy and a decreased risk of metastasis.<sup>26,30</sup> If this is confirmed in long-term observations of the men included in this study, an eventual survival benefit would be expected. It may take several additional years of observation to assess the effect of this brief hormonal treatment on overall survival. In the interim, the individual patient and his physician will have to weigh the cost of the treatment with the potential for in-

creased months and years free of new manifestations of prostate cancer.

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#### REFERENCES

1. Hanks GE, Asbell S, Krall JM, Perez CA, Doggett S, Rubin P, Sause W, and Pilepich MV: Outcome for lymph node dissection negative T-1b, T-2 (A-2,B prostate cancer treated with external beam radiation therapy in RTOG 77-06. *Int J Radiat Oncol Biol Phys* 21: 1099-1103, 1991.
2. Hanks GE, Leibel SA, Krall JM, and Kramer S: Patterns of care studies: dose-response observations for local control of adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 11: 153-157, 1985.
3. Pilepich MV, Krall JM, Johnson RJ, Sause WT, Perez CA, Zininger M, and Martz K: Extended field (periaortic) irradiation in carcinoma of the prostate—analysis of RTOG 75-06. *Int J Radiat Oncol Biol Phys* 12: 345-351, 1986.
4. Pilepich MV, Krall JM, Sause WT, Johnson RJ, Russ HH, Hanks GE, Perez CA, Zininger M, and Martz KL: Prognostic factors in carcinoma of the prostate—analysis of RTOG study 75-06. *Int J Radiat Oncol Biol Phys* 13: 339-349, 1987.
5. Pilepich MV, Al-Sarraf M, John MJ, McGowan D, Hwang YS, and Perez CA: Phase II Radiation Therapy Oncology Group study of hormonal cyto-reduction with flutamide and Zoladex in locally advanced carcinoma of the prostate treated with definitive radiotherapy. *Am J Clin Oncol* 13: 461-464, 1990.
6. Akakura K, Bruchovsky N, Goldenberg SL, Rennie PS, Buckley AR, and Sullivan LD: Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. *Cancer* 71: 2782-2790, 1993.
7. Pilepich MV, Krall JM, John MJ, Rubin P, Porter AT, Marcial VA, and Martz KL: Hormonal cyto-reduction in locally advanced carcinoma of the prostate treated with definitive radiotherapy: preliminary results of RTOG 83-07. *Int J Radiat Oncol Biol Phys* 16: 813-817, 1989.
8. Zagars GK, and von Eschenbach AC: Prostate-specific antigen: an important marker for prostate cancer treated by external beam radiation therapy. *Cancer* 72: 538-548, 1993.
9. Catalona WJ, Smith DS, Ratliff TL, Dodds KM, Coplen DE, Yuan JJ, Petros JA, and Andriole GL: Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *N Engl J Med* 324: 1156-1161, 1991.
10. Ritter MA, Messing EM, Shanahan TG, Potts S, Chappell RJ, and Kinsella TJ: Prostate-specific antigen as a predictor of radiotherapy response and pattern of failure in localized prostate cancer. *J Clin Oncol* 10: 1208-1217, 1992.
11. Kaplan ID, Cox RS, and Bagshaw MA: Prostate specific antigen after external beam radiotherapy for prostatic cancer: followup. *J Urol* 149: 519-522, 1993.
12. Frazier HA, Robertson JE, Humphrey PA, and Paulsen DF: Is prostate specific antigen of clinical importance in evaluation outcome after radical prostatectomy? *J Urol* 149: 516-518, 1993.
13. American Joint Committee on Cancer. *Manual for Staging of Cancer*, 3rd ed. Philadelphia, JB Lippincott, 1988.

14. Karnofsky DA, and Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer, in Macleod CM, (Ed): *Evaluation of Chemotherapeutic Agents: Symposium, Microbiology Section, New York Academy of Medicine*. New York, Columbia University Press, 1949, pp 191-205.
15. Zelen M: The randomization and stratification of patients to clinical trials. *J Chron Dis* 27: 365-375, 1974.
16. Winchester DP, and Cox JD: Standards for breast-conservation treatment. *CA Cancer J Clin* 242: 134-162, 1992.
17. Kaplan EL, and Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53: 457-481, 1958.
18. Kalbfleish JD, and Prentice RL: *The Statistical Analysis of Failure Time Data*. New York, John Wiley & Sons, 1980, pp 167-169.
19. Gray RL: A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 16: 1141-1154, 1988.
20. Cox JD, and Stoffell TJ: The significance of needle biopsy after irradiation for stage C adenocarcinoma of the prostate. *Cancer* 40: 156-160, 1977.
21. Scardino P, Frankel J, Wheeler TM, Meacham RB, Hoffman GS, Seale C, Wilbanks JH, Easley J, and Carlton CE Jr: The prognostic significance of postirradiation biopsy results in patients with prostatic carcinoma. *J Urol* 135: 510-516, 1986.
22. Kabalin JN, Hodge KK, McNeal JE, Freiha FS, and Stamey TA: Identification of residual cancer in prostate following radiation therapy: role of transrectal ultrasound guided biopsy and prostate specific antigen. *J Urol* 142 (2 pt 1): 326-331, 1989.
23. Dugan TC, Shipley WU, Young RH, Verhey LJ, Althausen AF, Heney NM, McManus PL, and Abraham EH: Biopsy after external beam radiation therapy for adenocarcinoma of the prostate: correlation with original histological grade and current prostate specific antigen levels. *J Urol* 146: 1313-1316, 1991.
24. Stamey T, Yang N, Hay A, McNeal JE, Freiha FS, and Redwine E: Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 317: 909-916, 1987.
25. Holtzman M, Carlton CE, and Scardino PT: The frequency and morbidity of local recurrence after definitive radiotherapy for stage T3 prostate cancer. *J Urol* 146: 1578-1582, 1991.
26. Fuks Z, Leibel SA, Wallner KE, Bigg CB, Fair WR, Anderson LL, Hilaris BS, and Whitmore WF: The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with <sup>125</sup>I implantation. *Int J Radiat Oncol Biol Phys* 21: 537-547, 1991.
27. Huggins C, and Hodges CV: Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. *Cancer Res* 1: 293-297, 1941.
28. Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA, Blumenstein BA, Davis MA, and Goodman PJ: A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 321: 419-424, 1989.
29. 1993 Drug Topics Red Book. Montvale, NJ 1993, Medical Economics Data, pp 243, 629.
30. Kuban DA, el-Mahdi AM, and Schellhammer PF: The effect of local tumor control on distant metastasis and survival in prostatic adenocarcinoma. *Urology* 30: 420-426, 1987.

#### EDITORIAL COMMENT

I am pleased that the RTOG chose to publish the results of this prospective randomized trial in *Urology* for several reasons. First, urologists, in general, have the perception that radiation therapy is of limited value in the treatment of Stages T1-T3 prostate cancer. Second, we realize the importance of performing a properly conducted trial to answer therapeutic questions and, I believe, are likely to adopt the conclusions of such a study.

Realizing the relatively poor progression-free survival with radiation therapy alone in clinical T2b-T4 prostate cancer, the RTOG embarked on a study to evaluate the efficacy of the luteinizing hormone-releasing hormone analogue goserelin in combination with flutamide for 2 months before and 2 months during radiation therapy in an attempt to improve local control and both progression-free as well as overall survival. At a median potential follow-up of 4.5 years, patients not receiving androgen deprivation had a significantly greater incidence of local progression (71% versus 46%) and a lower progression-free survival (15% versus 36%). Importantly, the definition of progression-free survival included a PSA level of 4 or less.

Was the study perfect? Of course not. A few concerns are:

1. All patients did not have a PSA performed, since its importance as an indicator of tumor control was not fully appreciated in 1987 when the study was initiated.
2. A PSA level of 4 is probably too high to use as the upper limit of normal following radiation therapy.
3. Few patients had a biopsy done and thus the rectal examination (and PSA) were the primary criteria for local control. We know all too well how inaccurate the digital rectal examination is after radiation therapy.

Despite these and other limitations, the group should be complimented on designing and completing a prospective randomized trial in locally advanced prostate cancer. The study indicates that 3 months of androgen deprivation is beneficial in men with T2b-T4 prostate cancer who receive external beam radiation therapy. It is likely that the mechanism has something to do with an increase in tumor cell death before and during radiation, since the benefit is evident many months following the discontinuation of androgen deprivation. Unfortunately, the relapse rate is still above 50%, indicating substantial room for improvement.

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