CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S24

MEDICAL REVIEW(S)

Dunson

JUL 15 1998

NDA 19-726 SE1-024
NDA 20-578 SE1-003

Medical Officer's Review of Efficacy Supplement

Received: August 12, 1997
MOR draft complete: June 24, 1998
MOR final complete: July 15, 1998

Title: "Supplemental New Drug Application for ZOLADEX Plus an Antiandrogen as Adjunct Therapy in Early-Stage Prostate Cancer."

Sponsor: Zeneca Pharmaceuticals, Inc.
Wilmington, DE 19850-5437

Pharmacological Class: LHRH agonist
Drug: Zoladex® (goserelin acetate implant)
Dosage: 3.6 mg and 10.8 mg
Route of Administration: subcutaneous injection
Proposed Indication: For use in combination with flutamide or CASODEX® (bicalutamide) for the management of locally confined Stage T2b-T4 (Stage B2-C) carcinoma of the prostate. Treatment with Zoladex® and the antiandrogen should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy.

Background:

In December, 1989, Zeneca Pharmaceuticals received approval for ZOLADEX® (goserelin acetate implant) 3.6 mg Depot for the palliative treatment of advanced prostate cancer.

On January 11, 1996, Zeneca received approval for a 10.8 mg, 3-month depot formulation of ZOLADEX® for the same indication.

On June 21, 1996, the Division approved a supplemental new drug application for EULEXIN (flutamide) Capsules (Schering Corporation). This application (NDA 18-554 SE1-014) provided for the use of flutamide in combination with "LHRH agonists" for the management of locally confined Stage B2-C carcinoma of the prostate.

The study which supported this efficacy supplement was conducted by the Radiation Therapy Oncology Group (RTOG), under the sponsorship of the NCI (IND The protocol, RTOG 8610, was entitled, "Phase 3 Study of ZOLADEX® and FLUTAMIDE (EULEXIN®) Used as Cytoreductive Agents in Locally Advanced Carcinoma of the Prostate Treated with Definitive Radiotherapy."

On May 5, 1997, Zeneca met with the Division to discuss a plan for submission of a supplemental NDA for ZOLADEX® in combination with an antiandrogen for the same indication (e.g. management of locally-confined Stage B2-C [Stage T2b-T4] carcinoma of the prostate). The Division agreed to accept such an application accompanied by the literature publication of RTOG Protocol 8610, authored by Pilepich at al[1] (see Appendix 1).

---

[1] Pilepich, M.V., Krall, J.M., Al-Sarraf, M., John, M.J., Scotte Dogget, R.L., Sause, W.T., Lawton, C.A., Abrams, R.A., Rotman, M., Rubin, P., Shipley, W.U., Grignon, D., Caplan, R. and Cox, J.D.: Androgen

Summary of Study Design: The study was a randomized, multicenter trial. Patients with bulky, locally advanced prostate cancer confined to the pelvis (clinical stage B2 or C, primary tumor stage T2-T4) with or without pelvic lymph node involvement were eligible to participate. Following stratification for histologic grade and clinical stage, patients were randomized to one of 2 groups. The treatment group received flutamide + goserelin acetate for 8 weeks followed by flutamide + goserelin acetate + 65-70 Gy radiation for 8 weeks. The control group received 65-70 Gy radiation for 8 weeks.

The primary endpoint was **time to "loco-regional" failure**. The original protocol defined this endpoint as time from randomization to the earliest of one of the following events:

1. failure of the palpable primary tumor to clear within 2 years.
2. increase in tumor size by 50% or more as measured by palpation (product of length and width).
3. reappearance of palpable tumor after clearing.
4. biopsy revealing adenocarcinoma of the prostate at least 2 years after randomization.
5. clinical or radiographic evidence of tumor in the pelvis (**regional failure**).

The following were the secondary endpoints:

Time to distant metastases, defined as the time from randomization to the clinical or radiographic evidence of disease beyond the pelvis.

Disease-free survival, defined as the time from randomization to local failure, regional failure, distant metastases or death from any cause.

Overall survival, defined as time from randomization to death from any cause.

The sponsor conducted an additional analysis for disease-free survival which included PSA determinations. PSA determinations were not a mandatory part of the original protocol but were included following a July 1990 amendment. For this analysis, disease-free survival was defined as time from randomization to one of the following: local failure, regional failure, distant metastases, death from any cause, or an "elevated" PSA level (>4.0 ng/ml) beyond one year from randomization.

The actual sample size calculation of 150 patients per group was based on a 15% improvement in absolute survival at 5 years (from 50% to 65%), a one-sided alpha of 0.05, and a power of 80%.

Summary of Results:

A total of 471 patients (235 treated, 236 control) were enrolled and randomized at 64 centers over a 4-year period (April 15, 1987 through June 1, 1991). The intent-to-treat population consisted of 466 patients (231 treated, 235 control). Eleven (11) of these patients were excluded

---

Deprivation With Radiation Therapy Compared with Radiation Therapy Alone for Locally Advanced Prostatic Carcinoma: A Randomized Comparative Trial of the Radiation Therapy Oncology Group. Urology, 45: 616, 1995.

due to protocol violations. The treatment groups were comparable at baseline in terms of age, race, clinical stage, histologic grade, tumor area, and nodal status.

Local Failure:

Local failure was detected through digital rectal examinations of primary tumor as well as prostate biopsy. However, only a small percentage of patients were re-biopsied during the follow-up period; 23/225 treated patients (10%) and 27/230 control patients (12%).
The definition of local failure, as described in the original protocol, may be found in the preceding section.

In the safety update submitted on April 19, 1996, Schering Corporation re-analyzed local failure data in two ways. First, a revised, updated database was used. Second, the published revised efficacy definitions from Pilepich et al was used. Pilepich et al defined local progression as one of the following events:

1. a PSA level more than 4 ng/ml at 1 year or more from randomization.
2. additional hormonal therapy in the absence of metastatic disease.
3. an increase of more than 50% in tumor size (cross-sectional area).
4. recurrence of palpable tumor after initial clearance.
5. biopsy specimen revealing adenocarcinoma of the prostate 2 years or more after study entry.

Events #1 and 2 were new additions to the original definition of local progression.

The analysis of local failure from the original submission, from the safety update and from the Pilepich et al article, is depicted in Table 1:

Table 1. Analysis of local failure.

Source	Treated patients (#failed/N)	Treated patients: estimated cumulative incidence	Control patients (#failed/N)	Control patients: estimated cumulative incidence
NDA 18-554/ SE014	28/225	15.5* (4-year)	58/230	33.1%* (4-year)
NDA 18-554/ SE014/Safety Update-Updated Database	64/232		97/235	
NDA 18-554/ SE014/Safety Update-Pilepich definition	109/232		165/235	
Pilepich et al article	70/196	46.0% (5-year)$^{\nabla}$	125/200	71.0% (5-year)$^{\nabla}$

*Denotes information in the current EULEXIN label.
$^{\nabla}$Denotes information in the proposed ZOLADEX label.

In the Pilepich et al article only, a subset of the entire population was selected for analysis of local progression. This subset, consisting of patients with at least one PSA level recorded, totaled 396 patients (196 treated and 200 control patients).

Using the Pilepich et al definition and the described subgroup, the Pilepich et al article claims that 70/196 treated patients and 125/200 control patients had local progression, for an estimated

5-year cumulative incidence of local progression of **46%** in the treated group and **71%** in the control group. Using Gray's test, the difference in these incidence rates was significant ($P < 0.001$).

Reviewer comment:

1. **The definition of local failure in Pilepich et al is not the same as that from the original protocol and is not acceptable. The Pilepich definition included PSA level more than 4 ng/ml at 1 year or more after randomization as a criteria for local failure. This does not necessarily represent local failure; such a PSA level may represent occult distant metastases.**

2. **Use of the Pilepich et al data for labeling poses several clinical, statistical and regulatory concerns. First, the Pilepich et al article used unacceptable criteria to re-define local progression. Second, only a subset of the entire population was used for the analysis. Third, the raw data is unavailable for review. Therefore, the proposed ZOLADEX label should be revised to replicate the current EULEXIN label in terms of local progression.**

Distant metastases

Distant metastases were detected through bone scans and chest radiographs. These were not performed on a periodic basis, but rather "as clinically indicated". The definition of time to distant metastases may be found in the "Study Design" section. The analysis of distant metastases from the original submission, from the safety update and from the Pilepich et al article (all using the same definition) is depicted in Table 2:

Table 2. Analysis of distant metastases.

Source	Treated patients (#failed/N)	Treated patients: estimated cumulative incidence	Control patients (#failed/N)	Control patients: estimated cumulative incidence
NDA 18-554/ SE014	47/225	27.3%* (4-year)	62/230	36.4%* (4-year)
NDA 18-554/ SE014/Safety Update- Updated Database	68/232		89/235	
Pilepich et al article	59/226	34.0% (5-year)$^{\nabla}$	75/230	41.0% (5-year)$^{\nabla}$

*Denotes information in the current EULEXIN label.
$^{\nabla}$Denotes information in proposed ZOLADEX label.

In the Pilepich et al article, 59/226 treated patients and 75/230 control patients had distant metastases, for a cumulative 5-year incidence of 34% for treated patients and 41% for control patients. This difference did not reach statistical significance (P=0.09). It is notable that the benefit of hormonal treatment over placebo is diminished when estimated at 5-years (21% reduction) compared to 4 years (33% reduction).

Reviewer comment:

1. **In the Pilepich et al article, the estimated cumulative incidence of distant metastases was measured at 5 years from randomization, rather than 4 years. This represents a new analysis of the original data.**
2. **In the Pilepich et al article, there is an additional patient included in the analysis of treated patients (N=226).**
3. **The proposed ZOLADEX label should be revised to replicate the current EULEXIN label, in terms of distant metastases.**

Disease-free survival

The definition of disease-free survival as listed in the original protocol may be found in the "Study Design" section. In the original submission of the data (NDA 18-554 Efficacy supplement 014), the sponsor conducted two separate analyses of disease-free survival. One of these included PSA measurements as an endpoint for disease progression.

The analysis of disease-free survival from the original submission, from the safety update and from the Pilepich et al article (both with and without consideration of PSA levels) is depicted in Table 3:

Table 3. Analysis of disease-free survival.

Source	Treated patients: (# with event/N)	Treated patients: estimated incidence	Median disease-free survival (treated)	Control patients: (# with event/N)	Control patients: estimated incidence	Median disease-free survival (control)	
NDA 18-554/ SE014 (w/o PSA levels)	78/225	53.0 (4-year)	4.4 years*	109/230	41.0% (4-year)	2.6 years*	
NDA 18-554/ SE014 (w PSA levels)	82/172	36% (4-year)	2.7 years*	125/177	16.0% (4-year)	1.5 years*	
NDA 18-554/ SE014/Safety Update (w/o PSA levels)	125/232		4.0 years	159/235		2.6 years	
NDA 18-554/ SE014/Safety Update (w PSA levels)	143/232		3.2 years	194/235		1.8 years	
Pilepich et al article (including PSA)	98/196	36% (5-year)$^{\nabla}$		153/200	15.0% (5-year)$^{\nabla}$		

*Denotes information in the current EULEXIN label.
$^{\nabla}$Denotes information in proposed ZOLADEX label.

In the Pilepich et al article, again, a subset of the entire population was selected for the analysis of progression-free survival. This subset, consisting of patients with at least one PSA level recorded, included 396 patients (196 treated and 200 control patients). In this analysis, a total of 98/196 and 153/200 control patients had met an endpoint defining disease progression. The estimated incidence of disease-free survival at 5 years (by Kaplan-Meier estimates) was 36% for the treated group versus 15% for the control group. Using the log-rank statistic ($P < 0.001$), the difference in these incidences of progression-free survival was significant.

Reviewer comment:

1. **In the Pilepich article, the estimated incidence of progression-free survival was measured at 5 years from randomization, rather than 4 years. This represents a new analysis of the original data.**

2. **The total number of patients included in the analysis of progression-free survival by Pilepich et al is different than the total number analyzed in the original submission or safety update.**

3. **Progression-free survival data is presented as "estimated incidence" in the proposed ZOLADEX label but as "median disease-free survival" in the current EULEXIN label.**

4. **The proposed ZOLADEX label should be revised to replicate the current EULEXIN label, in terms of progression-free survival.**

Overall Survival

The analysis of overall survival from the original submission, from the safety update and from the Pilepich et al article is depicted in Table 4:

Table 4. Analysis of overall survival.

Source	Treated patients (#died/N)	Treated patients: estimated cumulative incidence	Control patients (#died/N)	Control patients: estimated cumulative incidence
NDA 18-554/ SE014	54/231	72.0 (4-year)	53/235	75.0% (4-year)
NDA 18-554/ SE014/Safety Update-Updated Database	65/232		78/235	
Pilepich et al article	55/226		51/230	

In the Pilepich et al article, 55 of 226 patients had died in the treated group and 51 of 230 patients had died in the control group. The difference was not significant.

Reviewer comment:

1. **In the Pilepich et al article, the total number of patients included in the analysis of survival was less than the total number analyzed in the original submission or safety update.**

2. **In the Pilepich et al article, the number of patients in the control group who died is less than the number that died in the original submission.**

3. **The proposed ZOLADEX label should be revised to replicate the current EULEXIN label, in terms of overall survival.**

Adverse events (AEs)

In Pilepich et al, the only data reported for adverse experiences is the incidence of withdrawals, the incidence of grade 3, 4 or 5 toxicity due to radiation therapy, the incidence of return of sexual potency and the incidence of the development of secondary malignancies.

Regarding **withdrawals**, of the 225 patients in the in the treated group with compliance information, 211 (94%) completed goserelin treatment and 188 (84%) completed flutamide treatment as planned. Pilepich et al claims that treatment was terminated in 23 patients for "flutamide toxicity", which included diarrhea (11 patients), liver function abnormalities (3), and various other reasons (rash, nausea and syncope). Two patients refuse goserelin.

Regarding **toxicity from radiation therapy** (RT), no patient was reported to have grade 4 or grade 5 toxicity from RT. Grade 3 toxicity was reported in 16 of 226 (7.1%) treated patients and 17 of 230 (7.4%) control patients.

Regarding the **return of sexual potency**, 81 of 102 treated patients who reported baseline potency had return of sexual function, while 74 of 102 control patients who reported baseline potency had return of sexual function.

Reviewer comment:

1. **The adverse event data, as presented by Pilepich et al, is insufficient for labeling. The proposed ZOLADEX label should present the most frequent AEs reported during the clinical trial for both the treated and control patients, in a manner identical to the current EULEXIN label.**

2. **It is not acceptable to assign specific adverse events to individual drugs used in combination. Therefore the reference to in the proposed ZOLADEX label should be removed.**

Labeling Implications:

Regulatory Actions: I recommend that these supplemental NDAs be approved. The recommended label revisions will be communicated to the sponsor by teleconference.

/S/

Mark S. Hirsch, MD
Medical Officer
Division of Reproductive and Urologic Drug Products
cc Orig NDA 19-726
Orig NDA 20-578
HFD-580/Division File
HFD-580/LRarick/MMann/DShames/ADunson

Appendix 1: Pilepich et. al.

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*

MILJENKO V. PILEPICH, M.D.
JOHN M. KRALL, PH.D.
MUHYI AL-SARRAF, M.D.
MADHU J. JOHN, M.D.
R.L. SCOTTE DOGGETT, M.D.
WILLIAM T. SAUSE, M.D
COLLEEN A. LAWTON, M.D
ROSS A. ABRAMS, M.D.
MARVIN ROTMAN, M.D.
PHILIP RUBIN, M.D.
WILLIAM U. SHIPLEY, M.D.
DAVID GRIGNON, M.D.
RICHARD CAPLAN, PH.D.
JAMES D. COX, M.D.

From the C. McAuley Health System, Ann Arbor, Mich; Radiation Therapy Oncology Group Statistical Unit, Philadelphia, Pa (now St. Luke's Hospital, Bethlehem, Pa); Wayne State University, Detroit, Mich; Kaweah Delta Cancer Care Center, Visalia, Calif; Radiation Oncology Center, Sacramento, Calif; LDS Hospital, Salt Lake City, Utah; Medical College of Wisconsin, Milwaukee, Wis; Johns Hopkins Oncology Center, Baltimore, Md; State University of New York Health Science Center, Brooklyn, NY; University of Rochester Medical Center, Rochester, NY; Massachusetts General Hospital, Boston, Mass; The University of Texas M.D. Anderson Cancer Center, Houston, Tex

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 ± 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.

*Supported by Public Health Service grants CA-21661 and CA-32115 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
Submitted (Rapid Communication): September 29, 1994, accepted (with revisions): January 5, 1995

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.[1] The probability of locoregional recurrence, however, increases with increasing size of the primary tumor as reflected in T stage.[2] 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).[3] More than 50% of patients in whom the product of tumor dimensions exceeded 25 cm^2 had locoregional failure by the sixth year after completion of treatment.[4]

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[5] 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[6] suggest that adjuvant androgen deprivation could enhance the cell killing of radiation therapy. Early RTOG studies of hormonal cytoreduction 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.[5,7] 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 cytoreductive 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.[8-12]

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)[13] 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^2 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[14] 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[15] 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 ± 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[16] 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[17] method. The cumulative incidence of local progression and metastasis was estimated.[18] 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.[19] 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

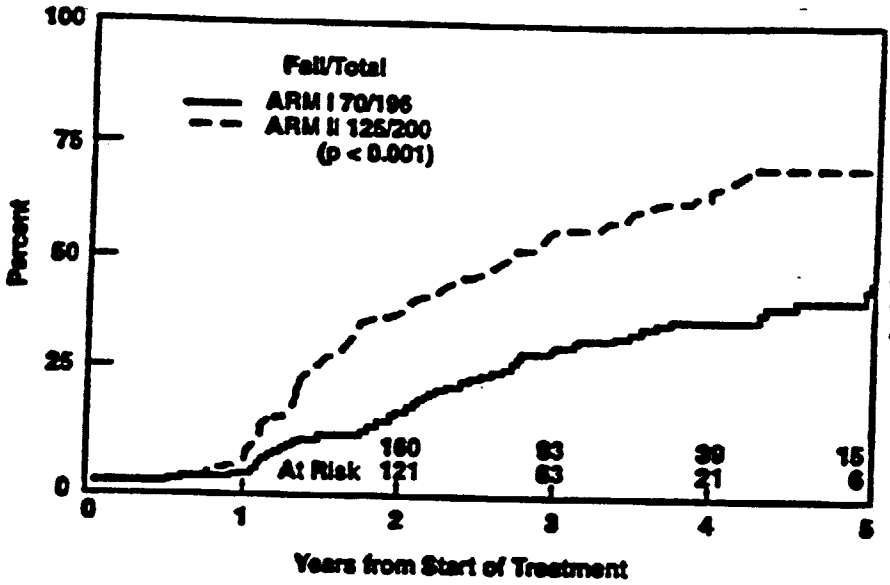

FIGURE 1. *Cumulative incidence of local progression by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.*

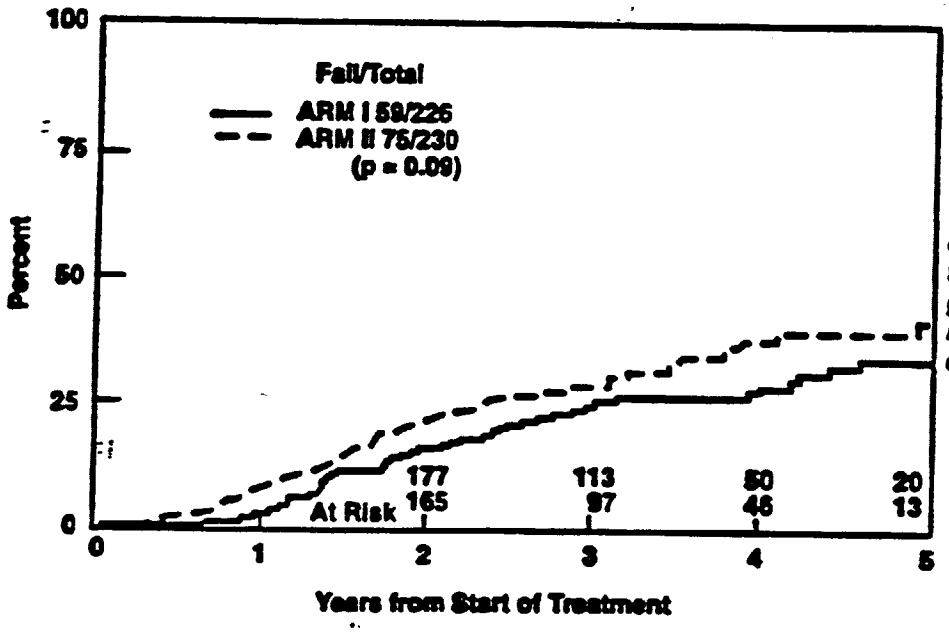

FIGURE 2. *Cumulative incidence of distant metastasis by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.*

(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

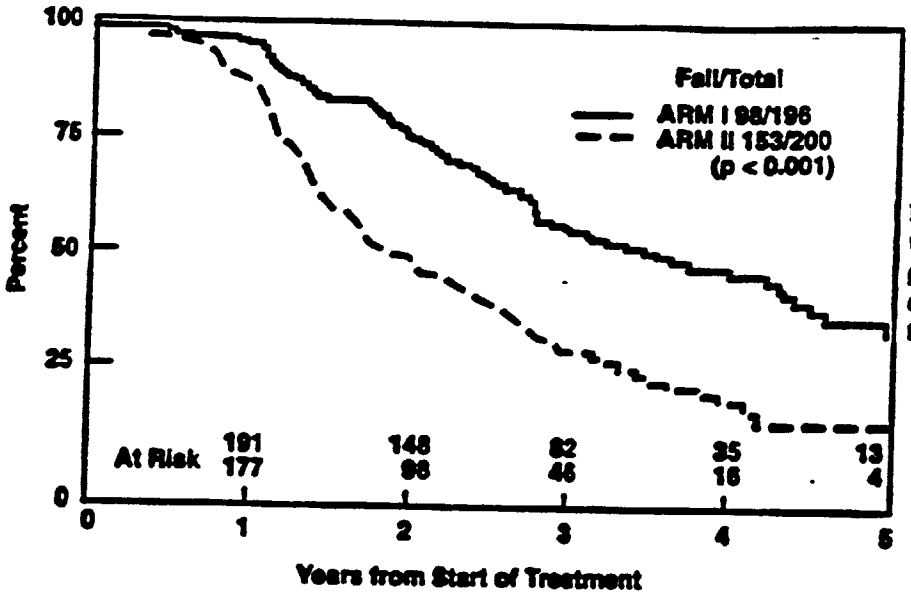

FIGURE 3. *Progression-free survival by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.*

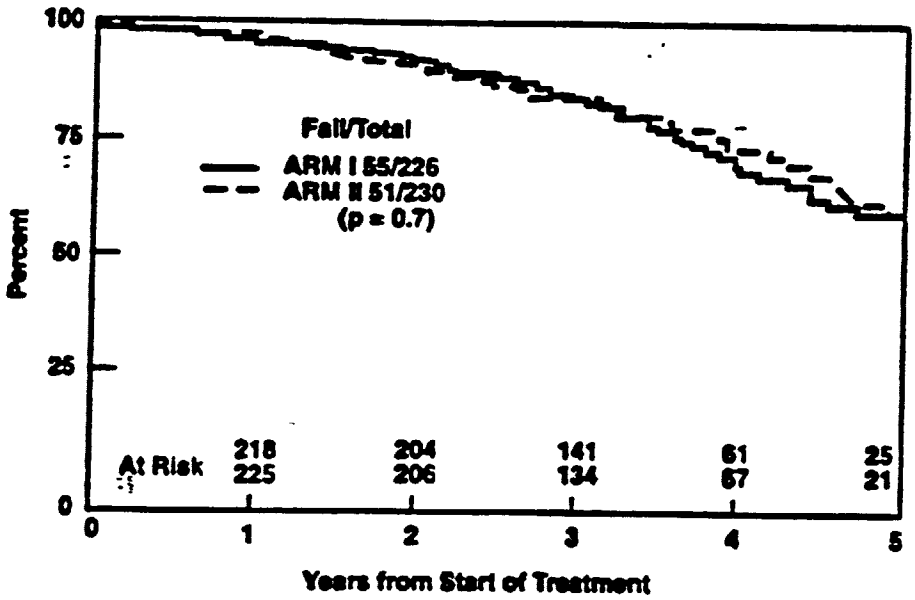

FIGURE 4. *Survival by treatment group. Arm I is goserelin and flutamide plus radiation therapy; Arm II is radiation therapy alone.*

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.[20-23] 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.[10,11,24] 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[10,21] and surgery[12] 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[25] and possibly by a second wave of metastases.[26]

Androgen dependence of human prostate carcinoma was first observed by Huggins and Hodges in 1941[27] with the cytotoxic effect of androgen suppression recently becoming understood as genetically controlled apoptosis.[6] 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.[28]

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)[29] 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.[26,30] 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 increased months and years free of new manifestations of prostate cancer.

Miljenko V. Pilepich, M.D.
C. McAuley Health System
P.O. Box 995
Ann Arbor, MI 48106

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, Zinninger 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, Zinninger 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 cytoreduction 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 cytoreduction 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 ^{125}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.

Mark S. Soloway, M.D.
Department of Urology
University of Miami Medical School
Miami, FL 33101