Abstract

Men with non-metastatic prostate cancer have many treatment options. For over 35 years, radiation therapy has been a mainstay of treatment for this disease. With improvements in technology and better use of pretreatment prognostic factors, such as prostate specific antigen level and Gleason score, biochemical and clinical results have steadily improved.

This article reviews the current status of radiation therapy in the treatment of prostate cancer. Results of treatment utilizing three-dimensional conformal and conventional techniques are compared and contrasted. The appropriate use of adjuvant hormones and particle beam therapy in the management of this disease is also discussed. Finally, the toxicity and future directions of radiation therapy in the treatment of prostate cancer are addressed. (CA Cancer J Clin 2000;50:349-375.)

Introduction

The American Cancer Society estimates that 180,400 new cases of prostate cancer will be diagnosed in the US in 2000. For patients with non-metastatic prostate cancer, there are many treatment options, including observation, surgery, external beam radiation therapy, brachytherapy, or hormonal manipulation with or without radiation therapy. During the past 35 years, external beam radiation therapy (RT) has been a mainstay in the management of prostate cancer and continues to be used in the treatment of almost one third of all patients receiving definitive therapy. Throughout the past decade, increasing numbers of patients receiving radiation have been treated with three-dimensional (3D) conformal rather than with conventional techniques.

PROSTATE SPECIFIC ANTIGEN

The development of the prostate specific antigen (PSA) test and its utilization as a screening tool, therapeutic measure, and prognostic indicator, have increased the number of patients diagnosed and subsequently treated for non-metastatic disease. More importantly, pretreatment PSA level has been shown to be the strongest independent predictor of treatment outcome (especially PSA control) after both surgery and radiation. BIOCHEMICAL DISEASE-FREE SURVIVAL [bNED—biochemical no evidence disease—control] is defined by a non-rising post-treatment PSA level, while a rising post-treatment PSA level now predicts failure many years before disease becomes clinically detectable. Appropriate use of pretreatment disease classification and serial post-treatment PSA levels allow accurate and meaningful assessments of various treatment modalities.

Routine use of PSA measurement entered clinical practice in the late 1980s.
 Initially, there was no standard definition of bNED control; biochemical cure after RT was variably defined and correlated with clinical progression and outcome. In a large series of patients treated with conventional doses of radiation, Horwitz et al demonstrated that by merely changing the definition of biochemical control, statistically significant differences in outcome could be obtained. A conference was convened by a committee of the Board of Directors of the American Society of Therapeutic Radiology and Oncology (ASTRO) in an effort to develop a unified definition of PSA cure for reporting successes or failures following irradiation. The definition selected by the committee was to be applicable in clinical practice as well as in research trials, avoid the issue of the amount of baseline serum PSA that might be produced in the prostate gland following RT, be valid for comparing different methods of radiation delivery, and avoid requiring a specific single value for post-treatment nadir PSA, which is a notion fraught with statistical peril.

Since the publication of the Consensus Statement in March 1997, the radiation community has adopted this definition, namely three consecutive increases in post-treatment PSA after achieving a nadir, and the majority of series published in the radiation literature now utilize this definition of bNED failure, thereby making comparisons of treatment efficacy easier.

The development and clinical testing of new technologies including three-dimensional conformal radiation therapy (3DCRT) and particle beam therapy have demonstrated that in certain groups of patients, these technologies result in improved outcomes compared with conventional radiation techniques. This article reviews the current results of treating non-metastatic prostate cancer with external beam RT and discusses the roles of newer technologies (see page 380 for a discussion of brachytherapy) and adjuvant therapies including 3DCRT, particle beams, and hormones compared with conventional techniques.

### Radiation Treatment Techniques

#### THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY

The process whereby a radiation dose is planned and delivered so that the high-dose volume conforms to an accurately defined target volume is called “three-dimensional conformal radiation therapy” or 3DCRT. This process minimizes the volume of normal tissue receiving a clinically significant radiation dose and reduces the probability of complications in surrounding normal tissue. This result is achieved by better delineation and immobilization of the target (prostate), allowing decreased treatment margins. The technique is associated with an improved therapeutic index due to increased tumor control with reduced normal tissue complications.

**Technique**

3DCRT is administered in several steps. First, patients are immobilized in the treatment position with a posterior body cast to reduce day-to-day patient motion and positioning error. Next, the prostate (target) is reconstructed in three dimensions by the treatment planning computer from a computed tomographic (CT) scan imaged while the patient is in the treatment cast during the radiation planning (simulation). Third, the multiple beams, which are directed at the target, are shaped to conform to the contours of the target from each “beam’s eye view” (BEV—the view from the perspective of an observer at the radiation source looking out along the radiation axis at the target and normal tissues included in that particular radiation portal). Treatment planning computers with dosimetric algorithms are used to calculate the dose in three dimensions. Electronic portal imaging devices, ultrasound, and other
techniques may be employed, which allow daily confirmation of treatment portal locations.\textsuperscript{25,26} Dose-volume histograms (DVHs)—which are visual representations of the amount of radiation dose that the volume of a target or normal tissue organ receives—are used to aid in the quantitative analysis of 3DCRT treatment plans. Finally, multileaf collimation or specific cerrobend blocks can be used to shape the treatment portal.\textsuperscript{27-29} The target is treated with a beam that conforms to the target shape, which is the prostate in this case (Figs. 1 and 2). As illustrated in Figures 1 and 2, multiple non-coplanar beams have been chosen to reduce the radiation dose to the bladder and rectum.

Traditional radiation planning methods involve choosing the number, direction, and arrangement of radiation beams and determining the resultant dose distribution. The plan, which provides the best dose coverage to the target while minimizing dose to the surrounding normal tissues, is chosen. As conformal plans become increasingly complex, new techniques are required.

Intensity modulated RT is an investigational technique that can achieve tightly conformal dose distributions through the use of nonuniform radiation beams. Each beam is divided into multiple segments to modulate the dose. In contrast to the traditional method of radiation planning, intensity modulated RT works backward by choosing the desired dose distribution first and then determining the required number of beams and intensities that will achieve that dose distribution. The target volume and critical normal organs are defined, and the upper and lower dose limits for the target and normal structures are selected. This is known as inverse planning. Intensity modulated RT remains investigational at this time, although as the technique improves, its use in clinical practice will become more common.\textsuperscript{30-32}

CONVENTIONAL RADIATION THERAPY Technique

In contrast to the complexity of the 3D technique, planning involved in conventional techniques is more straightforward. Patients undergo simulation and treatment in the supine position, and custom immobilization devices are not commonly used. Rectal and bladder contrast and retrograde urethromgrams, to aid in the localization of the prostate, are not mandatory during the simulation. Custom blocking is not commonly utilized and treatment fields are shaped with corner blocks only. CT-based treatment planning is not used, and treatment field edges are usually based on bony landmarks rather than target volumes.

For large field treatment, the superior border of the pelvic field is usually set at the level of the mid-sacroiliac joints, the inferior border at the bottom of the ischial tuberosities. Lateral borders on the anterior/posterior and posterior/anterior fields are set 1.5 to 2.0 cm lateral to the pelvic brim, the posterior border at the S2/S3 interspace. Anteriorly, the
field edge is at the front edge of the pubic symphysis.

The field edges for the conedown and small pelvic field treatment extend superiorly to the top of the acetabulum, and laterally include two-thirds of the obturator foramen. Dose distributions for conventional treatment are typically generated in a single plane and the dose is prescribed at the isocenter and normalized at the 100% isodose line. Conventional anterior/posterior and lateral treatment portals are shown in Figure 3.

3DCRT: Variations in Technique

The Fox Chase Cancer Center 3DCRT technique has previously been described. In summary, the patient first undergoes a treatment planning CT while immobilized in a half-body alpha cradle from the waist to the knees. CT slices 3 mm thick are obtained from the top of the sacroiliac joints through the bottom of the obturator foramen. Radiation target volumes are defined according to the International Commission on Radiation Units and Measurements #50 report. The Gross Tumor Volume (GTV) is defined as all known disease indicated by the planning CT or any other information. The Clinical Target Volume (CTV) is defined as the GTV and any areas considered to potentially contain microscopic disease. In prostate cancer, the entire prostate is considered the CTV. Finally, the Planning Target Volume (PTV) is the CTV plus a surrounding margin to account for the variability of treatment setup and internal organ motion.

The seminal vesicles and periprostatic, obturator, internal, and external iliac lymph nodes are also contoured. Treatment field size and dose guidelines at Fox Chase depend on pretreatment PSA level, Gleason score, and palpation T stage. A contour 1.2 cm superior to the apex of the urethrogram contrast defines the inferior-most portion of the prostate. PTV is defined as the prostate plus 1.0 to 1.5 cm in all directions. Conformal blocks are placed around the PTV in all directions using BEV visualization. Doses range from 68 to 82 Gy. Since 1993, lateral blocking has been added during the final 10 Gy to reduce the dose to the anterior rectal wall.

Conventional Radiation Therapy: Results

Multiple studies using serial post-treatment serum PSA levels to assess treat-
ment outcomes in patients treated with conventional doses of radiation have reported bNED control rates in patients with non-metastatic prostate cancer.\textsuperscript{8,11,18,37} Table 1 shows bNED control rates stratified by pretreatment PSA levels for patients treated with conventional doses of external beam RT at several institutions. Direct comparison of results for older series, i.e., those conducted prior to the adoption of the consensus definition, is difficult due to different definitions of bNED control, unequal distribution of critical prognostic factors between series, and varying lengths of follow-up. In general, however, as pretreatment PSA levels increase, rates of bNED control consistently decrease for patients treated at institutions using conventional doses of RT.

Zietman et al reported outcomes on 1,044 men with stage T1 to T4 prostate cancer treated at Massachusetts General Hospital. Of 504 men with T1/T2 disease, rates of bNED control were 60% and 40% at five and 10 years, respectively. For the 540 men with stage T3/T4 disease treated with conventional doses of radiation, rates of bNED control at five and 10 years were 32% and 10%, respectively.\textsuperscript{16} Similar results were reported by Horwitz et al for 480 patients treated with conventional doses of radiation. The five-year rate of bNED control ranged from approximately 80% for T1 disease to 25% for patients with T3 disease. Identical trends in outcomes were observed when patients were stratified by pretreatment PSA level and Gleason score. As pretreatment PSA level and
Gleason score increased, bNED control decreased.⁸

At M.D. Anderson Cancer Center, bNED control at six years was 66% and 37% for the patients with T1/T2 and T3/T4 disease, respectively. As with other series, bNED control decreased as pretreatment PSA level increased (84%, 66%, 49%, and 11%, respectively, for patients with pretreatment PSA levels of 4 ng/ml or less, 4 to 10, 10 to 20, and greater than 20 ng/ml).¹¹

Keyser et al reported results for a group of patients with T1/T2 disease treated with external beam RT or prostatectomy at the Cleveland Clinic. The 607 patients in this series all had pretreatment PSA levels of 10 ng/ml or less and T1/T2 disease. For the 253 patients treated with conventional doses of radiation, bNED control rates stratified by pretreatment PSA levels less than 4 or between 4 and 10 ng/ml were 100% and 65%, respectively. No significant differences in rate of bNED control were observed between the radiation and surgery groups.³⁷

**3DCRT: Results**

Results of treatment with 3DCRT with long-term (more than five years) PSA follow-up are becoming available and

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**Table 1**

Rates of Biochemical Disease-free Survival According to Pretreatment PSA Levels (Conventional Radiation Therapy Series)

| PSA (ng/ml) | Cleveland Clinic²⁷ | EVMS²² | Mayo Clinic²³ | MDACC¹¹ | MGH²⁵ | Stanford¹⁸ | WBH⁸ |
|------------|---------------------|--------|---------------|---------|-------|-----------|------|
| < 4        | 100%                | 69%    | 84%           | 82%     | 90%   |           |      |
| 4-10       | 65%                 | 57%    | 66%           | 44%     | 54%   |           |      |
| < 10       |                     |        |               |         |       | 65%       |      |
| < 13       |                     |        |               |         |       | 92%       |      |
| > 13       |                     |        |               |         |       | 58%       |      |
| 10-20      | 56%                 | 49%    | 30%           | 72%     | 27%   |           |      |
| > 20       | 20%                 | 11%    |               |         |       | 14%       |      |
| 10-30      |                     |        |               |         |       |           |      |
| > 30       |                     |        |               |         |       |           |      |
| 20-50      |                     |        |               | 8%      | 28%   |           |      |
| > 50       |                     |        |               | 0%      | 17%   |           |      |

**EVMS:** Eastern Virginia Medical School  
**MGH:** Massachusetts General Hospital  
**MDACC:** M.D. Anderson Cancer Center  
**WBH:** William Beaumont Hospital
demonstrate superior bNED control rates. Because higher doses of radiation can be delivered to the prostate (without substantially higher rates of normal tissue complications) using 3DCRT, evidence indicates that bNED control rates are significantly improved.

Five-to-seven-year data from institutions including Fox Chase Cancer Center, Memorial Sloan-Kettering Cancer Center, the University of Michigan, and the University of California, San Francisco, show increased rates of bNED control, especially for patients with pretreatment PSA levels greater than 10 ng/ml—the group that benefits most from higher radiation doses. For patients with pretreatment PSA levels between 10 and 20 ng/ml, the advantage of 3DCRT was evident, with an almost 30% difference in bNED control compared with conventional RT at five years.38,39

The update from Fox Chase Cancer Center describing five-year results for our dose escalation study was reported.38 Two hundred thirty-two patients were treated with 3DCRT between June 1989 and October 1992, with
median follow-up of 60 months. During this time, radiation dose to the prostate increased from 63 to 79 Gy. Dose responses were demonstrated for patients with pretreatment PSA values between 10 and 20 ng/ml and greater than 20 ng/ml (Figs. 4 and 5). bNED control for patients with pretreatment PSA levels between 10 and 20 ng/ml treated at 70 Gy was 35% versus bNED control rates of 75% for the patients treated at 76 Gy (p = 0.02). bNED control was 10% at 70 Gy for the patients with pretreatment PSA levels greater than 20 ng/ml, but at 76 Gy, bNED control was 32% for the same strata of patients (p = 0.02).

Multivariate analysis revealed that increasing palpation T stage was associated with decreased rates of cause-specific (p = 0.002) and distant-metastases-free survival (p = 0.0004). Toxicity to normal surrounding tissue becomes potentially more significant as radiation dose increases. Five-year rates of grades 2 and 3/4 gastrointestinal toxicity were 33% and 8%, respectively, at doses of 75 to 76 Gy. When anterior rectal wall shielding was used to keep the dose to this structure lower than 72 Gy, the five-year rates of grade 2 and 3/4 gastroin-

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**Figure 5**

*Biochemical Disease-free Survival (bNED) by Dose Group for Patients with Pretreatment PSA Levels Greater Than 20 ng/ml Treated with 3DCRT at Fox Chase Cancer Center*

bNED: biochemical no evidence of disease
3DCRT: three-dimensional conformal radiation therapy

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intestinal toxicity were reduced to 11% and 2%, respectively.\textsuperscript{38}

Fukunaga-Johnson et al reported the University of Michigan experience treating patients with clinically localized prostate cancer using 3DCRT.\textsuperscript{40} Patients in this series were treated with RT alone. Dose in this study ranged from 49 to 80 Gy, although few patients received greater than 72 Gy. No patient received hormones before, during, or after treatment unless biochemical or clinical failure was documented.

bNED control was defined as two consecutive PSA increases of 2 ng/ml or more if the nadir PSA was 2 ng/ml or less, two consecutive PSA increases greater than 2 ng/ml if the PSA nadir was more than 2 ng/ml, or whenever hormonal therapy was initiated after RT. One criticism of this endpoint has been that it can overestimate the rate of bNED control.

The five-year actuarial rates of bNED were 88%, 72%, 43%, and 30%, respectively for patients with pretreatment PSA values less than 4, 4 to 10, 10 to 20, and greater than 20 ng/ml. Pretreatment PSA level, T stage, Gleason score, total dose, pelvic field treated, surgical status, and favorable grouping were all statistically significant on univariate analysis. However, only pretreatment PSA level, T stage, and Gleason score remained independent predictors on multivariate analysis. A radiation dose-response was not demonstrated, although few patients in this study received high doses. The authors concluded that additional therapy was warranted for this group of patients.

The update of the Memorial Sloan-Kettering Cancer Center dose comparison trial was reported by Zelefsky et al.\textsuperscript{39} Seven hundred forty-three patients were treated as part of a phase I study, and radiation dose increased from 64.8 to 81 Gy. Of all patients who received 75.6 or 81 Gy, 90% achieved a post-treatment PSA nadir of 1 ng/ml or less compared with 76% and 56% of patients who received 70.2 and 64.8 Gy, respectively. For patients with intermediate (defined as one of the following: T2c/T3 disease, pretreatment PSA more than 10 ng/ml, or Gleason score greater than 6) or high-risk (defined as more than one of the preceding indices) disease, overall five-year bNED control was 65% and 35%, respectively. Good-risk patients had five-year bNED control rates of 85%. These differences between groups were statistically significant (p = 0.001). Intermediate and poor prognosis patients treated with 75.6 Gy or more achieved improved bNED control rates.

Post-treatment nadir PSA levels were correlated with biopsy findings 2.5 years after treatment to evaluate response. Of all patients (good and poor grouping) receiving 81 Gy, 7% had a positive biopsy versus 45% at 70.2 Gy and 57% after 64.8 Gy (p < 0.05). Using multivariate analysis, pretreatment PSA level (< 10 ng/ml), T stage (< T2c), and radiation dose (<75.6 Gy) were independent predictors of achieving nadir PSA levels of 1 ng/ml or less for 530 patients not treated with neoadjuvant hormones.

Roach et al reported the University of California, San Francisco experience treating 50 patients with high-grade (Gleason score 8 to 10) prostate cancer using 3DCRT.\textsuperscript{41} The median dose delivered was 74 Gy (range, 63 to 80 Gy), and 27 patients had advanced T3/T4 disease. Patients treated with more than 71 Gy had four-year bNED control rates of 83% versus 0% for those patients treated with conventional doses of radiation (< 71 Gy). Ten patients received neoadjuvant hormones, but there was no difference in bNED control when outcome was stratified by hormone use.\textsuperscript{41} These data support the premise of a dose-response in the radiation treatment of prostate cancer and that more advanced disease requires more aggressive therapy.

Each of these studies reported data from a single institution. In an effort to examine the role of increasing dose in the
treatment of patients with high-risk prostate cancer, Fiveash et al reported pooled results on 180 patients from Fox Chase Cancer Center, the University of Michigan, and the University of California, San Francisco. As expected, in these 180 patients with stage T1-4 Nx-0M0, Gleason score 8 to 10 tumors, pretreatment PSA levels, T stage, adjuvant hormone use, and radiation dose (< 70 Gy versus > 70 Gy) were predictors of bNED control on univariate analysis. Using multivariate analysis, pretreatment PSA level and radiation dose were independent predictors of bNED control for patients with T1/T2 tumors. Patients treated with doses less than 70 Gy or with 70 to 75 Gy had five-year bNED control rates of 64.9% and 87.8%, respectively (p = 0.02). The median follow-up was three years for patients in this study; at this time, no statistically significant difference in clinical endpoints was observed using these known prognostic factors.

Dose-response data from Fox Chase Cancer Center and dose comparison data from Memorial Sloan-Kettering Cancer Center and M.D. Anderson Cancer Center demonstrate a dose response for patients treated with high doses (> 73 Gy) using 3DCRT most strongly in the subgroup of patients with pretreatment PSA levels between 10 and 20 ng/ml. However, evidence is now emerging that for all groups of patients, high-dose radiation with 3DCRT results in improved biochemical and clinical outcomes.

With the widespread use of PSA screening, larger numbers of patients with low PSA (≤ 10 ng/ml), early-stage disease are being diagnosed and treated. Pinover et al recently reported the Fox Chase experience treating patients with pretreatment PSA levels of 10 ng/ml or less. Patients were classified as good or poor risk based on palpation T stage, Gleason score, and the presence of perineural invasion; bNED control was calculated based on radiation dose received. bNED control was 91% at five years for good-risk patients treated with 71.5 Gy or more compared with 76% for those who received less than 71.5 Gy. The same trend was observed for the poor-risk patients (98% versus 79% versus 72%, respectively, for (74.5, 71.5 to 74.5, and < 71.5 Gy, respectively) (Fig. 6).

Multiple series treating patients with conventional and 3D-conformal techniques have reported results with radiation alone. The Education Committee of ASTRO sponsored a pooled analysis to determine bNED control for a large group of patients treated with both conventional and 3D-conformal techniques and compared it with results from single institutions.

Data from 1,765 patients with T1/T2 prostate cancer treated at Fox Chase Cancer Center, the University of Michigan, Massachusetts General Hospital, Washington University, Eastern Virginia Medical School, and Stanford University were combined and bNED control determined using the ASTRO Consensus Statement definition. Patients were treated from 1987 through 1995, and the median follow-up was four years. The five-year actuarial rate of bNED control for all patients was 65.8%.

When results were stratified by pretreatment PSA levels—< 4 ng/ml, 4 to 10 ng/ml, 10 to 20 ng/ml, and > 20 ng/ml—results at five years were 80%, 78%, 68%, and 41%, respectively. For patients with Gleason scores of 6 or less, bNED control was 71% compared with 52% for patients with Gleason scores of 7 or more at five years. The authors concluded that bNED control rates in this pooled analysis were equivalent to those reported by individual institutions.

**Adjuvant Hormones and Radiation Therapy**

One rationale for combining adjuvant hormones with definitive radiation is to decrease the volume of the prostate,
Figure 6
Biochemical Disease-free Survival (bNED) by Dose Group for Good- and Poor-Prognosis Patients with Pretreatment PSA Levels Less Than 10 ng/ml Treated with 3DCRT at Fox Chase Cancer Center

bNED: biochemical no evidence of disease
3DCRT: three-dimensional conformal radiation therapy
which decreases the size of the treatment fields, which, in turn, potentially decreases toxicity to adjacent normal tissues (rectum and bladder). Several authors have demonstrated the effect of neoadjuvant hormones on prostate volume and the subsequent effect on treatment volume.46-48 Forman et al determined the effect of three months of leuprolide prior to radiation therapy on the size of the prostate and the volume of bladder and rectum in a prospective study of 20 patients.46 The average prostate volume was reduced by 37%, while the volume of other organs receiving 40, 52, and 64 Gy was reduced as well, by 15%, 18%, and 20% for the bladder, and 13%, 20%, and 34% for the rectum.46

At Memorial Sloan-Kettering Cancer Center, Zelefsky et al47 reported the effect of neoadjuvant hormonal downstaging on 45 patients receiving 3DCRT. These patients underwent DVH analyses to evaluate the geometry of the target volume (i.e., the prostate). Pre- and post-hormone DVH calculations of the prostate, bladder, and rectum were compared, and the median reduction in the volume of the bladder and rectum receiving 95% of the dose was 46% and 18%, respectively.47

Yang et al demonstrated similar effects using DVH analysis with seven patients treated for three months with total androgen blockade.48 The mean volume of the prostate was reduced from 129 cm³ pre-hormones to 73 cm³ post-hormones (p = 0.0059). Similar changes in volume size were also observed for the normal structures (rectum and bladder). The volume of the rectum receiving 80% of the prescribed dose was reduced from 83.2 cm³ pre-hormones to 59.9 cm³ post-hormones (p = 0.045). Likewise, the volume of the bladder receiving 80% of the dose was reduced from 74.5 cm³ pre-hormones to 40.2 cm³ post-hormones (p = 0.098).48

All three series demonstrate the effect of neoadjuvant hormonal therapy on the target and normal organ volumes receiving clinically significant radiation doses. Complications from treatment are directly related to the radiation dose that the volume of a particular organ such as the rectum or bladder receives. These early studies support the possibility of decreasing complication rates with neoadjuvant hormonal downstaging, although no clinically significant reduction has been noted yet.

A second rationale for combining hormones and radiation is to improve the effectiveness of radiation. As the stage of disease increases, so too does the risk of systemic spread. Laboratory data reported by Zietman et al49,50 have shown neoadjuvant hormonal therapy can reduce the amount of radiation required to kill 50% of the tumors, from 89 Gy without hormones to 42.1 Gy after maximal volume regression. The effect was less pronounced if the radiation dose was given before maximal volume reduction had been achieved or if the androgen blockade was given after the radiation.49,50

Hypothesized mechanisms for these effects include reduction of the number of clonogens to be eradicated by the radiation; induction of apoptosis by both the hormonal ablation and radiation, resulting in additive cell killing; and the shifting of cells in the cell cycle from an active to resting phase resulting in a supra-additive killing effect.51-53 Any advantage conferred by hormone therapy, however, must be balanced by potential side effects including sexual dysfunction, bone density loss, and hepatic dysfunction.54

The original studies that combined hormones and radiation were initiated in the 1960s. A multi-institutional prospective study started in 1967 randomized patients with stage C tumors to RT alone or in combination with adjuvant estrogen, which was given at the completion of radiation.55,56

Zagars et al reported the results of long-term follow-up data from 78 of 82 patients randomized at M.D. Anderson Cancer Center.57 Forty patients were
treated with RT alone, while 38 patients received RT and adjuvant estrogen. At 15 years, disease-free survival was 63% for those in the RT-plus-hormones group versus 35% for those treated with RT alone. This difference was statistically significant ($p = 0.008$). No difference in overall survival was observed due to increased number of intercurrent deaths in the estrogen arm of the study.$^{57}$

**RTOG Trials**

Based on data accumulated from Radiation Therapy Oncology Group (RTOG) trials of the 1970s, which showed an association between tumor size and clinical outcome,$^{58}$ studies initiated in the 1980s combined definitive radiation with adjuvant hormones. Early studies investigated the efficacy and toxicity of various hormonal agents including megestrol and diethylstilbestrol (DES) as cytoreductive agents in combination with external beam RT. Differences in local control were observed between agents, but due to toxicities such as gynecomastia, fluid retention, and thromboembolic events noted especially in the DES arm, these agents were not selected for the later trials.$^{59}$

The RTOG developed follow-up trials based on these early studies that incorporated new hormonal agents with less cardiovascular toxicity. RTOG 85-31 randomized 977 patients (945 analyzable) (T1-2N1M0, T3N0-1M0, or pT3N0-1M0) to receive either 65 to 70 Gy external beam RT plus goserelin started during the last week of RT (arm I) and continuing indefinitely, or to RT alone with goserelin given at the time of relapse (arm II)$^{6}$ Lawton et al recently reported the eight-year update of this trial,$^{60}$ and significant differences between the two treatment arms remain for five-year bNED control (arm I: 54% versus arm II: 21%, $p < 0.0001$), distant metastases failure (arm I: 27% versus arm II: 37%, $p < 0.0001$), and local failure (arm I: 23% versus arm II: 37%, $p < 0.0001$). Although there were no statistically significant overall differences in cause-specific failure or overall survival, a subset analysis revealed significant differences in overall survival and cause-specific failure for patients with Gleason score tumors between 8 and 10, by central review. (Fig. 7).

The role of short-term total androgen blockade was examined in the companion study, RTOG 86-10.$^{61}$ Patients with locally advanced prostate cancer (T2b-4N0-1M0 and $T \geq 25 \text{ cm}^2$) in arm I received goserelin and flutamide two months before and during external beam RT (226 patients). In arm II, patients were treated with RT alone (230 patients; 65 to 70 Gy total dose).

As with the previous RTOG study, an eight-year update shows that a significant difference in local control between the two arms persists (arm I: 68% versus arm II: 57%, $p = 0.004$) as does an improvement in progression-free survival for arm I (29% versus 20%, $p = 0.0019$). With longer follow-up, a difference in the rate of distant metastases was also observed between the two groups (arm I: 35% versus arm II: 46%, $p = 0.04$), although no difference between the two arms was seen in overall survival. Subset analyses revealed that the increase in local control and decrease in distant metastases effected with neoadjuvant hormones was most beneficial for patients with Gleason scores 2 to 7.$^{61}$

**EORTC 22863**

The European Organization for Research and Treatment of Cancer (EORTC) completed the second major trial examining the role of adjuvant hormones. Bolla et al reported data on 415 patients randomized to receive either external beam RT alone (70 Gy) or external beam RT with goserelin starting the first day of treatment and continuing for three years post-treatment.$^{62}$ Cyproterone acetate was also given during the initial four weeks of goserelin therapy. Although T1/T2 patients with grade 3 disease were
Figure 7
Clinical Outcome for Patients Treated on the RTOG 85-31 Study of Radiation Therapy Alone Versus Radiation Therapy and Adjuvant Hormones (Centrally Reviewed Pathology: Gleason scores, 8 to 10)

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eligible and were included in this study, the majority (91%) of patients in both arms had T3/T4 disease.

An update with longer follow-up (median follow-up, 61 months)\(^{63}\) shows that the differences in clinical outcome persist between the two arms. Local control, disease-free survival, and overall survival were 97%, 75%, and 78%, respectively for the combined modality arm compared with 79%, 40%, and 62%, respectively for the RT-alone arm. These differences were all statistically significant (p < 0.001) (Fig. 8).\(^{62,63}\)

**A SWEDISH TRIAL: UMEÅ UNIVERSITY**

A final trial randomized surgically staged patients to RT alone (46 patients) or RT and orchiectomy (45 patients).\(^{64}\) All eligible patients with T1-4N0-3M0 disease participating in this phase III prospective trial from Umeå University in Sweden underwent bilateral staging pelvic lymph node dissections. With a median follow-up of 9.3 years, disease-free survival was 39% in the RT-alone arm compared with 69% in the RT-plus-hormone group (p = 0.005). Cause-specific survival was 56% versus 73% for the RT-alone group and RT-and-hormones group, respectively (p = 0.06). When results were stratified by lymph node status, no difference in survival was seen for the lymph-node-negative patients. The trial originally planned to accrue 500 patients; however, after an interim analysis revealed significant differences in survival, the study was halted prior to planned completion.\(^{64}\)

The significance of the findings in these trials, especially the difference between the two RTOG studies, lies in the differences between the use of short-term versus long-term adjuvant hormone therapy. The survival advantage seen when adjuvant hormones were combined with radiation was seen in the trials that utilized long-term adjuvant hormones.

**CURRENT RTOG TRIALS**

Current RTOG clinical trials are exploring issues including adjuvant hormones in good-prognosis prostate cancer patients, whole pelvis versus small field radiation, and neoadjuvant versus adjuvant hormones. Based on data from RTOG 86-10 and RTOG 85-31, the RTOG initiated a trial that combines both treatment strategies.

RTOG 92-02, which completed accruing 1,554 patients in April 1995, was a two-arm phase III randomized prospective trial that compared total androgen suppression two months prior to and during RT with total androgen suppression two months prior to and during RT, followed by two years of goserelin beginning after RT ends.

The first analysis of that trial was recently reported by Hanks et al. Statistically significant improvements in bNED control (46% versus 21%, p = 0.0001), freedom from distant metastasis (11% versus 17%, p = 0.001), local progression (6.2% versus 13%, p = 0.0001), and disease-free survival (54% versus 34%, p = 0.001) were observed for the patients receiving long-term versus short-term adjuvant hormones.\(^{65}\) Subset analyses of patients with T3/T4 disease, or with T2 and Gleason scores from 8 to 10, revealed statistically significant improvements in disease-specific survival for the patients receiving long-term adjuvant hormones (90% versus 86%, p = 0.03). For all patients with Gleason scores of 8 to 10, statistically significant improvements in disease-specific survival (90% versus 78%, p = 0.007) and overall survival (80% versus 69%, p = 0.02) were also seen in the group receiving long-term adjuvant hormones.

The use of adjuvant hormones has not been definitely established for early stage, clinically localized disease, although some ongoing investigations are seeking to address this issue. RTOG 94-08 is a phase III two-arm randomized prospective trial examining the role of short-term hormones in earlier stage prostate cancer. Patients with clinical
Figure 8
Clinical Outcome for Patients Treated on the EORTC Study of Radiation Therapy Alone Versus Radiation Therapy and Adjuvant Hormones

Kaplan-Meier Estimate of Overall Survival: The overall survival rate at five years was 79% (95% confidence interval, 72% to 86%) for the combined-treatment group and 62% (95% confidence interval, 52% to 72%) for the group treated only with radiotherapy.

Kaplan-Meier Estimate of the Disease-free Interval: This curve shows the proportion of surviving patients who were free of disease at each time point. The method takes the censoring process into account. The number of patients who are at risk for the event at each time point is the total number of patients minus the number in whom disease progressed or who were lost to follow-up.
stages T1b/T2b disease are randomized to receive pelvic RT with a prostate boost, with or without total androgen suppression (goserelin and flutamide) two months prior to and during RT.

RTOG 94-13 is a four-arm randomized prospective trial for patients with high-risk non-metastatic prostate cancer. This study is re-examining the issue of whole pelvic irradiation with a prostate boost compared with prostate-field irradiation only. Patients are also randomized to receive either neoadjuvant hormones (two months before and two months during RT) or adjuvant hormones (four months after RT).

**Particle Beam Therapy**

The theoretical advantage for using other subatomic particles in the treatment of prostate cancer rests with the physical characteristics of these particles compared with photons, which are used in conventional and 3D-CRT techniques. Investigators have used neutrons and protons to treat prostate cancer, mostly for stage III and IV disease. The original rationale for using neutrons was their lesser dependence on oxygen, which was thought to make them more effective for killing hypoxic tumors. However, more recent data have suggested that the real benefit of neutrons is seen in slowly proliferating tumors where the larger relative biologic effect of the particle is most effective compared with photons.

Protons are similar in size to neutrons, although they possess a charge. Their radiobiological properties are similar to those of photons. What makes protons unique is the physical characteristic of the beam. The majority of the energy is deposited at the end of a linear track known as a Bragg peak. Dose falls rapidly to zero beyond the Bragg peak. The advantage of protons is the ability to confine the high-dose region to the tumor volume while limiting the dose to the surrounding normal tissue.

**Neutrons**

Neutrons were first used to treat prostate cancer in a large national randomized prospective trial beginning in the 1970s, although they have been used in the treatment of cancer since the 1930s. RTOG 77-04 randomized 91 patients (78 analyzable) with T3-T4N0-N1M0 disease to photon alone versus mixed photon/neutron treatment.66 Clinical local control at 10 years was 58% for the photon-alone group versus 70% for the mixed photon/neutron treatment (p = 0.03). Overall survival was also significantly different between the two arms: At 10 years, overall survival was 29% for the photon-alone group compared with 46% for the mixed photon/neutron arm (p = 0.04).6

The Neutron Therapy Collaborative Working Group was established, based on the results of that RTOG study, to further test neutrons in the treatment of prostate cancer.67 One hundred seventy-eight patients (172 analyzable) with T3-T4N0-N1M0, as well as high-grade T2 disease, were randomized to receive either photon beam therapy alone (7,000-7,020 cGy) or neutron beam therapy alone (2,040 ncGy). At 10 years, local regional control was 53% for the photon arm versus 79% for the neutron arm (p = 0.0007).68 No statistically significant difference in survival between the two groups was noted at 10 years. Incidence of severe grade 3 and 4 late gastrointestinal complications was higher in the neutron arm at 10 years (11% versus 3%, p = 0.04).

Several clinical trials have been conducted at Wayne State University using an isocentric cyclotron equipped with multileaf collimation. One protocol treated 104 patients with earlier stage disease,68 while a second study treated 47 patients with locally advanced adenocarcinoma of the prostate defined as T3-T4N0-N1M0 and/or a Gleason score of 8 or higher.69 These patients were treated with 9 NGy (Neutron Gy) and 18 PhGy (Photon Gy) to the pelvis and an addi-
tional 15 NGy and 18 PhGy to the prostate. bNED control for patients in both groups was 92%, 85%, and 38% for patients with pretreatment PSA levels of less than 10 ng/ml, 10 to 20 ng/ml or more than 20 ng/ml, respectively. No acute grade 3 or 4 gastrointestinal or genitourinary toxicity was observed.

PROTONS
The proton is the other heavy particle with clinical significance in the treatment of prostate cancer. Investigators at Massachusetts General Hospital conducted a prospective trial in 202 patients (189 analyzable) with T3-T4N0-N2M0 who were randomized to either photons only (5,040 cGy to the pelvis with a 1,680 cGy photon boost to the prostate) or mixed photon/proton treatment (5,040 cGy to the pelvis with a 2,520 Cobalt Gray Equivalent [CGE] proton boost to the prostate). A statistically significant difference in clinical local control was observed between the two arms at eight years. Local control was 84% for the mixed photon/proton and 19% for the photon only arms (p = 0.0014). This statistically significant difference was seen in the high-grade (Gleason score 7 to 10) tumors only. No significant differences in overall, disease-free, and cause-specific survival were observed between treatment arms.

Slater et al reported the Loma Linda University Medical Center experience with protons. Between 1991 and 1995, 643 patients received mixed photon and conformal proton boost treatment; 106 of the patients with locally advanced disease participated in a phase I/II trial. Patients received 45 Gy to the pelvis with photons followed by a prostate boost of 30 CGE using 225-250 MeV protons. bNED control rates at five years for patients with pretreatment PSA levels of less than 4, 4 to 10, 10 to 20, and more than 20 ng/ml were 100%, 89%, 72%, and 53%, respectively. Grade 2 gastrointestinal toxicity was the most common complication, occurring in 21% of patients. Only 5% of patients experienced grade 2 genitourinary toxicity and two patients developed grade 3 toxicity. No grade 3-to-5 gastrointestinal toxicity was noted.

Although each series has shown a statistically significant improvement in local control using heavy particle therapy, a survival advantage was observed in only one study. The results from these studies have been promising. However, limited resources and facilities may restrict the widespread adoption of this technology.

Toxicity

CONVENTIONAL RT AND 3DCRT
Early data on 1,020 patients treated with conventional techniques and doses of radiation combined from RTOG studies 75-06 and 77-06 showed a 3.3% incidence of grade 3 or higher late gastrointestinal complications. Fewer than 1% of the patients experienced obstruction or perforation that required corrective surgery. Seventy-nine patients (7.7%) experienced grade 3 or higher late genitourinary complications and only 0.5% experienced toxicity that required major surgical intervention. Only total doses of more than 70 Gy significantly predicted late genitourinary complications. No factor significantly predicted late gastrointestinal complications.

Data from the early National Patterns of Care Study on 1,293 patients showed a 92% five-year actuarial rate free of complications. Sixty-eight patients experienced serious complications defined as those requiring hospitalization, and one third of these serious complica-
tions required surgical repair. Variables associated with a significant difference in major complications also included doses less than 70 Gy. Patients treated with a two-field technique tended to have increased complications compared with patients treated with four fields.

The acute morbidity of 3DCRT was assessed by the number of patients requiring medication for gastrointestinal or genitourinary symptoms during the course of radiation treatment. Figures 9 and 10 show grade 2 and higher rates of genitourinary and gastrointestinal morbidity for patients stratified by treatment technique and field size. Statistically significant differences were observed in morbidity rates between treatment techniques. The greatest difference was noted for gastrointestinal morbidity rates in patients treated with small-field 3DCRT (p < 0.001).

The late gastrointestinal and genitourinary complications following treatment with conventional or 3DCRT were recently reported by Schultheiss et al. Between 1986 and 1994, 712 patients treated with conventional (150 patients) or conformal (562 patients) techniques were analyzed for factors using a modified RTOG/SWOG scoring system that predicted late gastrointestinal (rectal bleeding requiring three or more procedures to correct, or proctitis) and genitourinary (cystitis or stricture) morbidity. One hundred-fifteen patients experienced grade 2 or higher gastrointestinal toxicity a mean of 13.7 months after treat-

Figure 9
Acute Genitourinary Morbidity Based on Treatment Technique and Field Size

3DCRT: three-dimensional conformal radiation therapy
Small Field: prostate only
Large Field: pelvis and prostate boost
Fifteen of these patients experienced grade 3 or 4 toxicity. Forty-three cases of grade 2 or higher late genitourinary toxicity were observed a mean of 22.7 months after treatment.

Only central axis dose (> 74 Gy isocenter) significantly predicted late grade 3 gastrointestinal toxicity on multivariate analysis. Central axis dose, use of increased rectal shielding, androgen deprivation therapy before RT, history of obstructive symptoms, and acute genitourinary symptoms significantly predicted late grade 2 genitourinary toxicity on multivariate analysis. After the presence of minor rectal bleeding was noted in 1993, techniques were developed to reduce the radiation dose to the anterior rectal wall. The necessity of multiple coagulations was reduced from 5% to 2% at 75 to 76 Gy.79

Results from other institutions treating patients with 3DCRT show reductions in morbidity at high doses of radiation similar to those achieved at Fox Chase when compared with patients treated with conventional techniques. Data from the Memorial Sloan-Kettering Cancer Center phase I dose escalation study of 743 patients with clinically localized prostate cancer have shown 6% grade 2 and 1% chronic genitourinary toxicity. No grade 4 toxicities were noted. Forty percent of patients experienced acute grade 2 genitourinary toxicity. The risks of chronic grades 2 and 3 gastrointestinal complications were 8% and 0.8%, respectively. One patient experi-

Figure 10
Acute Gastrointestinal Morbidity Based on Treatment Technique and Field Size

3DCRT: three-dimensional conformal radiation therapy
Small Field: prostate only
Large Field: pelvis and prostate boost

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enced a chronic grade 4 gastrointestinal complication.39

Sandler et al reviewed the University of Michigan experience and analyzed 712 patients treated with 3DCRT for late gastrointestinal effects.80 Doses in this study ranged from 59.5 to 80.4 Gy. Using the RTOG grading system, only 14 grade 3 or 4 complications were observed. Increasing dose was the only significant predictor of late gastrointestinal effects on univariate and multivariate analysis (including treatment technique, boost technique, age, and T stage). The actuarial risk of a grade 3 or 4 complication at five years was 3%.80

Michalski et al recently reported preliminary toxicity data from 3DOG/RTOG 94-06, an ongoing prospective phase I dose escalation trial determining the maximally tolerated radiation dose in men treated with 3DCRT in a multi-institutional setting. Between 1994 and 1997, 292 patients treated at the first two dose levels of 68.4 and 73.8 Gy were analyzed for rates of acute and chronic gastrointestinal and genitourinary toxicities. Acute and chronic grade 1 toxicity for both dose groups ranged from 30% to 46%; rates of acute grade 2 toxicity ranged from 34% to 45%; chronic grade 2 toxicity rates were 8% to 16%; acute grade 3 rates were between 1% and 3%; there were no acute grade 4 or 5, or chronic grade 3, 4, or 5 complications. Rates of chronic grades 1 to 5 gastrointestinal and genitourinary toxicities from Fox Chase Cancer Center, the University of Michigan, and Memorial Sloan-Kettering Cancer Center are summarized in Figure 11.

Discussion

External beam radiation remains a mainstay in the treatment of patients with prostate cancer. Current results of treatment with conventional doses of radiation (< 70 Gy) show similar rates of bNED control when patients are stratified by pretreatment PSA levels.8,18,82-85 However, as pretreatment PSA levels increase, rates of bNED control decrease. This trend is evident even in patients with pretreatment PSA levels less than 10 ng/ml.

The implementation of new technologies, including patient immobilization devices, CT treatment planning, BEV visualization and planning, dose calculation in three dimensions, multileaf collimation, and electronic portal imaging, have improved the radiotherapeutic management of prostate cancer resulting in increased radiation doses to the prostate. Simultaneously, these techniques have allowed the reduction in the volume of normal tissue that receives clinically significant doses of radiation, resulting in a reduction in complication rates.78

Prognostic Models

In addition to these new technologies, an improved understanding of tumor biology and prognostic factors, including pretreatment PSA level, Gleason score, and clinical T stage, has allowed for better patient selection among treatment modalities. Multiple studies in both the radiation and surgical literature have demonstrated that the pretreatment PSA level is the single most important independent prognostic variable for predicting and assessing treatment efficacy.3,8-11,86 Other series have demonstrated the importance of Gleason score, tumor stage, nadir PSA level, and presence of perineural invasion.87-90

Several authors have combined these various pretreatment prognostic variables to develop models that predict outcome.91-96 Pisansky et al evaluated the results of RT alone in 500 patients and reported that pretreatment PSA level, Gleason score, and clinical T stage used in combination provided the most accurate model to predict success or failure following definitive RT.91 Ben-Josef et al developed a predictive model that included pretreatment PSA levels, post-treatment PSA levels, PSA nadir, age, stage and
grade. The authors concluded that their model had an overall accuracy rate for predicting failure of 81.8%, and sensitivity, specificity, and false-negative rates of 87.2%, 79.6%, and 12.8%, respectively.92

Movsas et al evaluated several of these published models using patients from Fox Chase Cancer Center to determine the most accurate model. The authors analyzed six models using 421 patients treated with definitive RT. A stepwise Cox proportional hazards multivariate analysis was performed, and initially the model developed by Pisansky et al was most predictive. However, after a logarithmic transformation analysis was performed, each model was equally predictive of bNED outcome.97

Predictive models have been used and reported in the surgical, as well as the radiation, literature. Partin et al originally developed a nomogram based on the pretreatment PSA levels, clinical T stages and Gleason scores of 703 men who underwent radical prostatectomy at Johns Hopkins University Hospital to predict rates of organ-confined disease, established capsular penetration, seminal vesicle invasion, and positive pelvic lymph nodes.98 Because this nomogram was based on data from a single institution, Kattan et al successfully validated it with patients from the Baylor College of Medicine.95 Partin et al subsequently added additional patients from Johns Hopkins University Hospital and combined them
with patients from the University of Michigan and the Baylor College of Medicine (4,133 patients) increasing the predictive power of this nomogram. These independent prognostic variables can be used to select the most appropriate treatment modality (Table 2).

Results of treatment with 3DCRT with long-term (greater than five years) PSA follow-up are becoming available and show superior bNED control rates. Data from several institutions support the idea that when the volume of normal tissue receiving radiation is reduced, the total dose to the prostate can be safely increased, resulting in improved bNED control. Data from our institution demonstrate that this is particularly pronounced for patients with intermediate pretreatment PSA levels.33

Extensive long-term data on the gastrointestinal and genitourinary morbidity of external beam RT using conventional doses of radiation have been available for more than a decade. Data from several large national studies have shown consistently that the dose of radiation (> 70 Gy) and the technique used contribute significantly to normal tissue complication rates.73,74 New data becoming available from several institutions that treat patients with 3DCRT indicate that gastrointestinal and genitourinary morbidity is not significantly worsened despite the increased doses of radiation used.79,80

Because higher doses of radiation can be delivered to the prostate (without substantially higher rates of normal tissue complications) using 3DCRT, the available evidence clearly demonstrates that bNED control rates are significantly improved. Five-to-seven year actuarial data from several institutions, including Fox Chase and the University of Michigan, show increased rates of bNED control, especially for patients with pretreatment PSA levels greater than 10 ng/ml (a group that generally does not achieve durable bNED control rates with conventional RT). For patients with pretreatment PSA levels between 10 and 20 ng/ml, the advantage of 3DCRT was evident with an almost 30% difference in bNED control rates at five years.4,40 A major task for the radiation oncology community in the future is to expand the use of 3DCRT technology beyond the limited numbers of expert facilities currently utilizing this treatment program.

| Gleason Score | T1/T2 Pretreatment PSA | T3 Pretreatment PSA |
|---------------|------------------------|---------------------|
| 2-6           | < 10                   | 10-20               | > 20 |
|               | RP or RT               | RP or RT            | RT   |
| 7-10          | RP or RT               | RT                  | RT   |

Table 2
Selecting Treatment According to Pretreatment Prognostic Variables (PSA level, Gleason score, T stage)

RP: Radical Prostatectomy        RT: Radiation Therapy
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