



Kala Pohl. *Sunset Breeze* (detail). Acrylic on canvas, 12" × 12".

The development of more precise radiation planning and delivery methods has improved the ability to target radiation dose to the prostate, which has resulted in clinical benefit.

The Role of External-Beam Radiation Therapy in the Treatment of Clinically Localized Prostate Cancer

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Background: *The treatment of clinically localized prostate cancer is controversial. Options include radical prostatectomy, external-beam radiation therapy (EBRT), brachytherapy, cryotherapy, and watchful waiting.*

Methods: *The author reviews EBRT as treatment for clinically localized prostate cancer, with particular emphasis on the technological advances that have allowed dose escalation and fewer therapy-related side effects.*

Results: *Technological advances in the last two decades have significantly improved the delivery of EBRT to the prostate. This has resulted in an overall increase in the total dose that can be safely delivered to the prostate, which has led to modest improvements in biochemical outcome. An alternative approach of combining androgen suppression therapy and EBRT has also been successful in improving clinical outcomes. However, establishing the optimal therapy for prostate cancer remains controversial.*

Conclusions: *Recent progress has led to improvements in clinical outcomes in patients treated with EBRT for prostate cancer. It is hoped that the next decades will bring continued advances in the development of biologicals that will further improve current clinical outcomes.*

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Abbreviations used in this paper: EBRT = external-beam radiation therapy, BT = brachytherapy, AST = androgen suppression therapy, CRT = conformal radiotherapy, IMRT = intensity-modulated radiation therapy.

Introduction

In 2006, approximately 234,460 American men will be diagnosed with prostate cancer.¹ One of the first challenges they will face is the decision of how to treat their disease. A number of options are available to the vast majority of men with newly diagnosed prostate cancer, including surgery, external-beam radiation therapy (EBRT), brachytherapy (BT), cryotherapy, androgen suppression therapy (AST), expectant management, or some combination of these treatments. This review focuses on the role of EBRT in patients with clinically localized prostate cancer.

Technological Advancements in Radiation Dose Delivery: From Two-Dimensional Radiotherapy to Image-Guided Radiotherapy

In the last two decades, technological improvements in the delivery of EBRT have improved the ability of radiation oncologists to target radiation to the prostate while more efficiently sparing the surrounding normal tissue.² These improvements were initially achieved by integrating three-dimensional (3D) anatomical information into the radiation therapy planning process. Treatment planning utilizing 3D conformal radiotherapy (CRT) permitted the 3D visualization of both the target and the normal tissue, allowing for the planning of treatment techniques that conform the dose to the target while sparing the normal tissue. The next step came with the development of intensity-modulated radiation therapy (IMRT).³ With IMRT, further sparing of normal tissue is achieved by modulating the intensity of the beam across the different fields of radiation being delivered. Prior to IMRT, radiation oncologists chose and designed the treatment fields to be utilized in the treatment process.³ This resulted in a uniformity of the technique used for patients with a particular disease. For example, patients with prostate cancer were classically treated with a four-field technique combining four radiation ports that were delivered from the front, the back, and both sides of the patient. The development of CRT provided more options in terms of the field arrangements that would achieve the desired goals. Using CRT, both the target and normal tissue are contoured, which allows physicians to better customize treatment fields. However, in IMRT, the concept of inverse-treatment planning was introduced whereby the physician no longer chooses and designs the treatment fields. The responsibility of the radiation oncologist lies in contouring both the radiation therapy target volumes and the normal tissue that needs to be spared. The radiation oncologist also establishes a set of dose constraints for each target and normal tissue volume. A computer algorithm calculates the most effective way

to physically deliver the radiation and achieve the desired goals.³

As the ability to conform radiation dose to the prostate improved, many studies reported the clinical significance of prostate motion in the setting of 3D CRT.⁴ Movement occurs primarily in the anterior-posterior direction, although it also occurs in the superior-inferior and lateral directions.⁵⁻⁷ To address these concerns, a number of daily prostate localization techniques have been developed. A common technique utilizes a trans-abdominal ultrasound to daily localize the prostate during the delivery of a fractionated course of radiotherapy.⁸⁻¹⁰ Other approaches involve imaging implanted radio-opaque fiducial markers^{11,12} and using daily computed tomography (CT).¹³⁻¹⁵ The ability to image the position of the prostate on a daily basis has allowed the development of image-guided radiotherapy (IGRT), where imaging has helped to reduce set-up errors caused by organ motion and thus has improved the overall accuracy of treatment. The current development and integration of megavoltage cone beam CT technology into the design of linear accelerators will play a major role in IGRT.¹⁴⁻¹⁷

Clinical Benefits of Dose Escalation

Investigators at the M. D. Anderson Cancer Center were among the first to recognize the potential clinical benefits of increasing the radiation dose to the prostate. A principal rationale for increasing doses to the prostate stemmed from postradiation biopsy studies that showed a high incidence of positive prostate biopsies in patients treated with standard doses (70 Gy or less) of radiation therapy.¹⁸⁻²⁴ Pollack et al^{25,26} published the first prospective, randomized trial that supported a role for dose escalation in patients with clinically localized cancer (Table 1). They randomized 305 patients to receive either standard dose (70 Gy/35 fx) or high-dose (78 Gy/39 fx) EBRT. At a median follow-up of 60 months, there was an absolute benefit of 6% in improvement of 5-year biochemical failure-free survival. Further evi-

Table 1. — Randomized Trials of Dose Escalation in Prostate Cancer

Author	No. of Patients	Eligibility	Experimental Arm	Control Arm	Results
Pollack et al ²⁵	305	T1–T3 cancer	78 Gy	70 Gy	6-yr FFF 70% vs 64%, <i>P</i> = .03, favoring high-dose arm
Zietman et al ²⁷	393	T1b–T2b cancer, PSA < 15 ng/mL	79.2 Gy	70.2 Gy	5-yr bNED 80.4% vs 61.4%, <i>P</i> < .001, favoring high-dose arm
Sathya et al ²⁸	104	T2–T3 cancer	40 Gy EBRT + Ir-92 implant (35 Gy)	66 Gy	5-yr BFR 29% vs 61% favoring high-dose arm

PSA = prostate-specific antigen
 FFF = freedom from failure
 bNED = no evidence of biochemical disease
 BFR = biochemical failure rate

dence supporting the benefits of dose escalation was provided by a randomized phase III collaborative study²⁷ between Massachusetts General Hospital and Loma Linda University. In this study, protons were used to deliver a portion of the treatment in all patients. Patients randomized to the standard dose arm received a standard-dose equivalent to 70.2 Gy, while patients randomized to the experimental arm received a dose equivalent to 79.2 Gy. At 5.5 years of median follow-up, the patients who received 79.2 Gy had a superior biochemical failure-free survival rate (80.4%) compared with patients treated in the standard arm (61.4%, $P < .001$). A study by Sathya et al²⁸ has also shown a modest improvement in biochemical failure rates by dose escalation. In their approach, dose escalation was achieved by using a temporary interstitial iridium implant. In summary, all three studies showed a modest improvement in biochemical outcomes in clinically localized prostate cancer. However, none has shown an improvement in overall or disease-specific survival.

Dose Escalation: Is Brachytherapy Superior?

It could be argued that conceptually, brachytherapy (BT) provides the most “conformal” of all radiation delivery techniques.^{29,30} The placement of radioactive sources either permanently (iodine-125 or palladium-103) or temporarily (iridium-192) in the prostate allows the maximal sparing of the surrounding normal tissue while concentrating the dose on the target. As with EBRT, modern techniques of BT have been refined in the last 15 years with the introduction of transrectal ultrasound and template guidance as well as 3D volumetric treatment planning.^{29,31} Although no prospective, randomized study comparing BT to EBRT has been reported, most retrospective series suggest similar prostate cancer outcomes for both therapeutic approaches.³²⁻³⁵ Others have argued that BT in combination with supplemental pelvic radiotherapy may be the most effective approach when using BT. Several retrospective and mature series have been published showing excellent results for the combination approach.³⁶⁻³⁸

The belief that EBRT and BT have similar clinical outcomes has recently been questioned. Pickett et al³⁹ studied the effect of both EBRT and BT on normal prostate metabolism using magnetic resonance spectroscopy. Interestingly, these authors reported that patients treated with BT had a higher rate of complete metabolic atrophy than those treated with EBRT (60% vs 40%, respectively), suggesting that BT is biologically more efficient in abolishing normal prostate metabolism. Although their endpoint was not prostate cancer control, these intriguing observations strongly suggest that the biological effect of both techniques is different.

Table 2. — Risk Group Stratification (D’Amico) for Clinically Localized Prostate Cancer

Risk Group	Definition
Low risk	T1–T2b, Gleason score < 6, PSA < 10 ng/mL
Intermediate risk	T2b and/or Gleason score 7 and/or PSA 10 to 20 ng/mL
High risk	> T2c and/or Gleason score 8–10 and/or PSA > 20 ng/mL
PSA = prostate-specific antigen	

Whether this improved efficiency in abolishing metabolism will translate into better cancer control is currently being studied. However, it is important to note that in this study patients did not undergo daily prostate localization during the delivery of EBRT. Therefore, it could be argued that some of these patients could have been underdosed during EBRT as a consequence of the natural movement of the prostate. This is not an issue with BT because these patients underwent postimplant dosimetry to confirm coverage; it could be argued that low-dose regions in the EBRT patients could account for the difference in the complete metabolic atrophy rate.

AST in Low- and Intermediate-Risk Clinically Localized Prostate Cancer

For more than 60 years, AST has played a central role in the clinical management of prostate cancer. Although the role of AST in metastatic disease, as well as in high-risk patients with clinically localized disease, is well established,⁴⁰⁻⁴⁶ its role in patients with intermediate- and low-risk prostate cancer is more controversial. Table 2 presents the definitions of risk groups. Four prospective, randomized trials, all using standard doses of 70 Gy or less, have demonstrated that patients with high-risk clinically localized prostate cancer derive a clear clinical benefit from the use of long-term AST (at least 2 years) in conjunction with EBRT (Table 3).^{41,42,44,46} Several investigators have studied whether intermediate-risk prostate cancer patients also derive a benefit from the combination of AST and EBRT.⁴⁷⁻⁴⁹ A recent phase III prospective, randomized study by D’Amico et al⁴⁷ showed an improvement in 5-year survival rate in patients treated with complete AST for 6 months plus standard EBRT (70 Gy) when compared to patients treated with standard EBRT alone (88% vs 78%, respectively, $P = .04$). Eligible patients included patients with a prostate-specific antigen (PSA) of at least 10 ng/mL or a Gleason score of at least 7. Although the study was designed before the development of the risk stratification criteria, all of these patients would have been grouped in either the intermediate- or high-risk stratum. The only other trial examining EBRT alone vs EBRT plus AST showed an improvement in biochemical con-

Table 3. — AST and EBRT in High-Risk, Clinically Localized Prostate Cancer

Author	No. of Patients	Eligibility	Experimental Arm	Control Arm	Results
Pilepich et al ⁴¹	977	T3 or N1	EBRT (65–70 Gy) + AST indefinitely	EBRT alone	10-yr OS 49% vs 39%, <i>P</i> = .002
Pilepich et al ⁴²	456	“Bulky” T2–T4 cancer	EBRT (65–70 Gy) + AST 4 mos	EBRT alone	8-yr DFS 33% vs 21%, <i>P</i> = .004
Bolla et al ^{44,45}	415	T3–T4 cancer or T1–T2 WHO grade 3	EBRT (70 Gy) + AST 3 yrs	EBRT alone	5-yr OS 78% vs 62%, <i>P</i> = .0002
Hanks et al ⁴⁶	1,554	T2c–T4, PSA < 150 ng/mL	EBRT (65–70 Gy) + AST 28 mos	EBRT (65–70 Gy) + AST 4 mos	5-yr DFS 46.4% vs 28.1%, <i>P</i> < .0001

WHO = World Health Organization
 PSA = prostate-specific antigen
 OS = overall survival
 DFS = disease-free survival

rol (Table 4).⁴⁸ The other trials in this risk stratum addressed the length of AST as well as the sequence of AST and EBRT.^{48,50,51} Although the clinical benefit of AST in high-risk prostate cancer has been previously established, these trials suggest that AST in conjunction with EBRT may result in therapeutic benefit in intermediate-risk patients as well.

AST Plus EBRT or Dose Escalation in Intermediate- and Low-Risk Prostate Cancer

Determining the best therapeutic approach for patients with low-risk and intermediate-risk prostate cancer remains a subject of great debate among radiation oncologists. It is likely that no single approach is best for all

patients. The use of AST is associated with an increase in treatment morbidity, particularly sexual side effects.⁴⁰ Therefore, it is important that AST is used when treatment is more likely to influence cancer outcomes. Since there is no randomized trial in intermediate- or low-risk patients that has addressed whether dose escalation is equivalent or superior to short-term AST plus standard EBRT, this area will continue to be controversial. However, an analysis of the features of the dose-escalating trials as well as the D’Amico trial shows that there are some differences in both eligibility criteria and clinical outcome. In the trial by D’Amico et al,⁴⁷ 59% of patients showed a Gleason score of 7 compared to 33% and 15% in the trials by Pollack et al^{25,26} and Zietman et al,²⁷ respectively. Furthermore, the D’Amico trial included patients with a PSA level of up to 40 ng/mL. Therefore, the populations of these trials represent different overall

Table 4. — AST Plus EBRT in Intermediate-Risk Clinically Localized Prostate Cancer

Author	No. of Patients	Eligibility	Experimental Arm	Control Arm	Results
D’Amico et al ⁴⁷	206	PSA of at least 10 ng/mL or Gleason score at least 7	AST (6 mos) + EBRT (70 Gy)	EBRT alone (70 Gy)	5-yr OS, 88% vs 78%, <i>P</i> = .04
Laverdiere et al ⁴⁸	161	T2–T3 cancer	AST (3 mos) + EBRT (64 Gy) or AST (10 mos) + EBRT (64 Gy)	EBRT alone (64 Gy)	7-yr bNED 66% vs 69% vs 42%, <i>P</i> = .009
Laverdiere et al ⁴⁹	296	T2–T3 cancer	AST (10 mos) + EBRT (64 Gy)	AST (5 mos) + EBRT (64 Gy)	final analysis not reported
Crook et al ⁵⁰	378	T1c–T4 cancer	AST (8 mos) + EBRT (66 Gy)	AST (3 mos) + EBRT (66 Gy)	5-yr FFF 62% vs 61%, <i>P</i> = .36
Roach et al ⁵¹	1,323	T1–T4 cancer, PSA < 100 ng/mL, lymph node risk of 15%	NCAST (4 mos) + WPRT or NCAST (4 mos) + PORT or WPRT + adjuvant AST (4 mos) or adjuvant AST (4 mos) + PORT; total radiation dose in all arms = 70.2 Gy	Four arm study No actual control arm	5-yr CSS 59.6% vs 44.3% vs 48.9% vs 49.8%, <i>P</i> = .008

PSA = prostate-specific antigen
 bNED = no evidence of biochemical disease
 NCAST = neoadjuvant combined androgen suppression therapy
 WPRT = whole pelvic radiotherapy
 PORT = prostate only radiotherapy
 CSS = cancer-specific survival
 FFF = freedom from failure

risk groups in prostate cancer, with the Zietman and Pollack trials including patients who would have been classified mainly in the low-risk and intermediate-risk strata and the D'Amico trial with patients mainly in the intermediate- or high-risk strata. Furthermore, all dose escalation trials showed modest improvements in the biochemical control of the disease but no difference in disease-specific or overall survival. In contrast, the D'Amico trial showed an improvement in 5-year overall survival with the addition of 6 months of complete AST. This suggests that the effect of dose escalation and AST may be different. It could be speculated that dose escalation appears to be critical in patients with low risk for micrometastatic disease at the time of treatment. Since most of these patients would not die of prostate cancer in the first decade after diagnosis, one would not expect any therapeutic intervention to affect either disease-specific or overall survival. In contrast, in the D'Amico trial, AST was shown to affect overall survival at 5 years, suggesting that at least part of its effect is in altering the natural history of micrometastatic disease. Therefore, it could be argued that since a significant proportion of patients with intermediate-risk disease are also at risk of micrometastatic disease as well, short-term AST in conjunction with EBRT should be considered as an important option in their clinical management.

Conclusions and Future Directions

The previous two decades have brought great technological innovations in the field of radiation oncology. The development of more precise radiation planning and delivery methods has improved our ability of targeting radiation dose to the prostate, which has resulted in significant clinical benefit. Technological innovations will continue in the near future with the development of four-dimensional treatment planning systems that will allow further refinements in radiation delivery and planning techniques. However, some of the biggest strides in prostate cancer therapeutics will probably come from biological innovations that will allow more precise definitions of clinical risk groups through the use of genomics and proteomics technology. Furthermore, it is hoped that a better understanding of prostate cancer biology will lead to the development of better imaging modalities and to the development of biological modifiers of radiation response.

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