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COMBINING EXTERNAL BEAM RADIOTHERAPY WITH PROSTATE BRACHYTHERAPY: ISSUES AND RATIONALE

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The optimal treatment for clinically localized prostate cancer remains controversial. For patients with low-risk prostate cancer (Stage T1c-T2a, Gleason score less than 7, prostate-specific antigen [PSA] of 10.0 ng/mL), monotherapy with radical prostatectomy, three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated RT, or prostate brachytherapy results in similar biochemical relapse-free survival.[1–3] Patient and physician preferences usually influence the treatment selection, based on a critical assessment of the relative side-effect profiles and quality-of-life evaluations.

Although brachytherapy alone in patients with low-risk prostate cancer can yield excellent disease control and a reported 93% 5-year freedom from biochemical failure rate, brachytherapy as monotherapy in intermediate-risk and high-risk disease (Gleason score greater than 6 and/or PSA level greater than 10 ng/mL) is less than optimal.[3] In the late 1980s, Kuban *et al.*[4] reported greater rates of local recurrence in men with Stage B2 or C prostate cancer and tumors of moderate and poor differentiation treated with brachytherapy alone using the retropubic implant method. With the introduction and routine use of PSA follow-up, local control in intermediate-risk and high-risk patients has been much lower than previously reported. Even with modern brachytherapy techniques, intermediate-risk and high-risk patients fair poorly with brachytherapy alone. In a recent report by Kwok *et al.*,[5] the 5-year rate with iodine-125 prostate brachytherapy as monotherapy was a disappointing 63% and 24% for intermediate-risk and high-risk patients, respectively.

The combination of external beam RT (EBRT) in conjunction with a prostate brachytherapy boost has been used to improve outcomes in intermediate-risk and high-risk patients. The benefits of EBRT combined with prostate brachytherapy include delivery of a greater radiation dose to the prostate, inclusion of disease that has extended beyond the prostatic capsule, and coverage of pelvic lymph node metastasis, when indicated. The addition of EBRT to prostate brachytherapy can also provide a supplemental dose to the prostate when suboptimal implants have been performed. We outline the rationale and delivery techniques of combined-modality therapy, discuss optimal candidates for combined-modality therapy, and provide a review of the available data on treatment outcomes, biochemical disease-free survival (DFS), and toxicity profiles of combined EBRT and prostate brachytherapy.

RATIONALE FOR COMBINED-MODALITY THERAPY

Improved DFS, freedom from distant metastasis, and overall survival has been shown with delivery of greater radiation doses to the prostate.[6–8] Multiple approaches have been used to deliver dose escalation to the prostate, including intensity-modulated RT, high-energy neutrons, hyperfractionated RT, and prostate brachytherapy boosts in conjunction with EBRT.

The addition of EBRT provides a broader delivery of RT and the benefit of greater dose distribution and coverage of tumor that has extended beyond the prostatic capsule. Brachytherapy alone, however, may be limited in its ability to deliver adequate doses to disease extending beyond the prostate. By combining brachytherapy and 3D-CRT, one gains the benefit of greater dose delivery provided by brachytherapy along with coverage of disease that may extend outside of the prostate gland proper with the use of EBRT. Furthermore, if cancer cells have spread to the draining lymph nodes, brachytherapy will not address these areas of disease.

An additional benefit of combined brachytherapy and EBRT is in patients who have received suboptimal implants. A combined modality may be

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Submitted: February 19, 2004, accepted (with revisions): June 21, 2004

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justifiable in those patients who have received suboptimal implants and require supplemental radiation doses to compensate for underdosed areas of disease.

Achieving Higher Doses

The importance of treating patients to greater radiation doses has been established by multiple dose-response studies.[7–9] Both 3D-CRT and prostate brachytherapy data have supported a dose-response relationship in intermediate-risk and high-risk patients. The Radiation Therapy Oncology Group (RTOG) reported improved disease-specific and overall survival in patients with high Gleason scores who received higher doses of EBRT.[10] Stock *et al.*[11] reported their experience with permanent iodine-125 implants and found that the dose was the most statistically significant predictor of biochemical control. The benefit was greater for those patients presenting with PSA levels greater than 10 ng/mL. The 4-year freedom from biochemical failure (PSA level less than 1.0 ng/mL) rate was 51% and 100% in patients with a dose covering 90% of the prostate of less than 140 Gy versus one greater than 140 Gy, respectively ($P = 0.009$).

Treatment of Extraprostatic Extension

A second benefit of combining EBRT with brachytherapy is the added radiation doses to disease that has extended through the prostatic capsule and/or into the seminal vesicles. Both extracapsular extension (ECE) and seminal vesicle invasion (SVI) are adverse prognostic factors, and the risk of ECE and SVI can be estimated by the PSA level and Gleason score using the following equations derived from the Partin tables and described by Chen *et al.*,[12] Partin *et al.*,[13] and Roach[14]: ECE = 3/2 × PSA + [(Gleason score − 3) × 10] and SVI = PSA + [(Gleason score − 6) × 10].

The extent to which radioactive seeds placed within the prostate can adequately treat extracapsular disease has been debated. Patients at greater risk of ECE may benefit less from brachytherapy alone. Davis *et al.*[15] evaluated postprostatectomy patients and found that extraprostatic extension measured on average 0.8 mm (range 0.04 to 4.4). Current brachytherapy techniques typically encompass a distance of 3 to 5 mm beyond the prostate gland. However, available data on postprostatectomy measurements of ECE may not represent the in vivo distance of actual tumor spread. As the risk of ECE increases, the benefit of brachytherapy as monotherapy becomes less, and combined EBRT and brachytherapy or EBRT alone ought to be considered.

Treatment of Pelvic Lymph Nodes

With increasing T stage, PSA level, and tumor grade, men with prostate cancer are at greater risk of lymph node spread. The estimated risk of lymph node metastasis can be estimated from the formula devised by Roach[14]: positive lymph nodes = (2/3) PSA + [(Gleason score − 6) × 10].

Often, men with a greater than 15% risk of lymph node involvement are treated with whole pelvis EBRT. Clearly, if patients are at an increased risk of lymph nodal metastases that can be eradicated with RT, brachytherapy alone will not be adequate treatment. Thus, the addition of EBRT can address both extracapsular disease, as well as subclinical lymph node metastases. The results from the RTOG 9413 trial showed a statistically significant improvement in progression-free survival in men with prostate cancer treated with whole pelvis EBRT in conjunction with hormonal therapy compared with men treated with hormonal therapy and RT to the prostate only.[16] These data strongly suggest pelvic RT benefits patients with intermediate to high-risk disease and should be considered in this population.

Supplementation of Prostate Brachytherapy Dose

Adequate dose delivery with interstitial seed implantation is dependent on proper visualization of the prostate, dosimetric planning, correct placement of radioactive seeds, and, ultimately, physician expertise. Despite improvements in brachytherapy techniques and better visualization with transrectal ultrasonography, often the preplanned dosimetry does not match the actual doses delivered to the prostate at the postimplant evaluation. If on postimplant dosimetric analysis, subtherapeutic radiation doses have been delivered to the prostate, a patient may be considered for seed reimplantation or supplemental EBRT to provide adequate doses and avoid treatment failure.

POSTIMPLANT DOSIMETRIC ANALYSIS

The American Brachytherapy Society (ABS) recognizes the need for adequate postimplant dosimetry in delivering optimal patient care and has established guidelines for postimplant dosimetric analysis from an expert panel's review of published reports. The ABS recommends that computed tomography-based postimplant dosimetry be performed on all patients undergoing permanent prostate brachytherapy. The enlargement of the prostate owing to edema immediately after implantation can result in a 10% mean decrease in the dose delivered to the prostate compared with the dosimetry obtained 1 month after implantation.[17] Generally, imaging is obtained 1 month after implantation; however, the optimal timing of imaging remains unclear. The ABS recommends that postimplant dosimetry be performed at a consistent interval with documentation of the 50%, 80%,

90%, 100%, 150%, and 200% isodose lines, dose-volume histograms, and the minimal dose covering 90% of the prostate volume.[18] The percentage of volume of the prostate receiving at least 100% or 150% of the prescribed minimal peripheral dose are also recommended as parameters to be measured. The rectal and urethral doses should be reported and correlated with clinical outcome. Ultimately, the earlier the postimplant dosimetry is performed, the earlier an underdosed implant can be identified and additional treatment provided with either reimplantation or additional EBRT.

CANDIDATES FOR COMBINED-MODALITY THERAPY

As outlined by the ABS, brachytherapy is an option for patients with a life expectancy of 5 years or longer, who are without distant metastasis and without large transurethral resection of the prostate (TURP) defects.[19] In patients with a significant risk of disease outside the implant volume, the addition of EBRT or hormonal therapy is advised. The risk of lymph node and SVI, as well as the risk of ECE, should be calculated for each patient with the use of the Partin tables or other risk stratification models. The recommended brachytherapy doses when used in combination with EBRT are as follows: for iodine-125, a dose of 100 to 110 Gy should be combined with 40 to 50 Gy EBRT, and for palladium-103 implants, a dose between 80 and 90 Gy is recommended.[19]

TREATMENT OUTCOMES WITH COMBINED PERMANENT SEED IMPLANTATION AND EBRT

No randomized trials have been conducted to evaluate the benefit of combined brachytherapy and EBRT. The following section provides a review of the largest experiences using combined EBRT and brachytherapy.

Dattoli *et al.*[20] at the University Community Hospital in Tampa, reported the earliest data with combined EBRT and prostate brachytherapy. They studied 73 patients with T2a-T3 prostate cancer who had one or more of the following risk factors: Stage T2b or greater, Gleason score 7 to 10, PSA level greater than 15 ng/mL, or elevated prostatic acid phosphatase. These patients underwent palladium-103 implantation followed by EBRT. Ten patients also underwent 2 months of hormonal therapy before RT. With a median follow-up of 2 years, the actuarial freedom from biochemical failure (PSA less than 1.0 ng/mL) rate was 79% at 3 years.[20] Prostatic acid phosphatase was the only statistically significant predictor of biochemical failure ($P = 0.04$).

After poor results with iodine-125 interstitial implants alone, Critz *et al.*,[21] at the Radiotherapy Clinics of Georgia, began treating patients with combined brachytherapy and EBRT in the late 1970s. Their experience with "simultaneous" interstitial seed implantation and EBRT is the largest to date. More than 1000 men with Stage T1T2N0 low to high-risk adenocarcinoma of the prostate received iodine-125 implants followed 21 days later by EBRT, thus exposed "simultaneously" to both the radioactive seeds and EBRT.[21] Despite variable implant doses that were less than the current standard, excellent DFS was achieved. With a median follow-up of 3 years, the DFS rate, defined as achieving and maintaining a PSA nadir of 0.5 ng/mL or less, was 79% and 72% at 5 and 10 years, respectively. The median time to recurrence was 3.5 years. Patients who underwent retropubic iodine-125 implantation had a 73% 5-year DFS rate and those patients receiving ultrasound-guided transperineal implantation had a greater 5-year DFS rate of 92% ($P < 0.001$), emphasizing the importance of technique and the benefit of the more modern ultrasound-guided transperineal approach.

The second largest reported experience with combined permanent interstitial implantation and EBRT comes from Seattle, Washington. Ragde *et al.*[22] reported their updated results of 229 patients with Stage T1-T3 adenocarcinoma of the prostate treated with transrectal ultrasound-guided iodine-125 implantation with or without EBRT. Eighty-two men considered at high risk of ECE (Gleason score greater than 6 and/or Stage T2b or greater) received a mean peripheral dose of 120 Gy by implantation after EBRT. This prescribed implant dose was greater than that recommended by the ABS and American Association of Physicists in Medicine Task Group 43. Using the updated American Society for Therapeutic Radiology and Oncology definition of biochemical failure (three consecutive rises in serum PSA level measured 6 months apart), the observed 10-year biochemical freedom from disease rate for the monotherapy group was 66% and was 79% for the combination-therapy group. Four patients died of prostate cancer, yielding a disease-specific 10-year survival rate of 98%. The greater biochemical control rate observed in the combined-modality group, although not statistically significant, was nonetheless encouraging and further supports the notion that excellent disease control can be obtained in intermediate-risk and high-risk patients with combined-modality therapy.

The above updated results by Ragde *et al.*[23] are comparable to the earlier published data that used a PSA level of greater than 0.5 ng/mL as the definition of biochemical failure. In the earlier published data, a benefit in tumor control in the combined

TABLE I. ***Comparison of biochemical disease-free survival with combined brachytherapy and EBRT***

Investigators	Patients (n)	EBRT Dose (Gy)	Implant Dose (Gy), Source	Follow-up (mo)	Patients Receiving Hormones (%)	5-yr Biochemical DFS (%)	10-yr Biochemical DFS (%)	Definition of PSA Failure
Critz *et al.*[21]	1029	45	80, ^{125}I	45	0	79	72	PSA >0.5 ng/mL
Ragde *et al.*[22]	82	45	120, ^{125}I	122	0	—	79	ASTRO*
Dattoli *et al.*[20]	73	41	80, ^{103}Pd	24	13.7	79†	—	PSA >1.0 ng/mL
Grado *et al.*[25]	72	45	120, ^{125}I	46.9	13.9	72‡	—	Two successive rises in PSA
			100, ^{103}Pd			88§		
Merrick *et al.*[27]	66	45	90, ^{125}I 110, ^{103}Pd	53.7	14	80	—	ASTRO*
Singh *et al.*[26]	65	50.4	—, ^{103}Pd	36	86	87†	—	ASTRO*

KEY: EBRT = external beam radiotherapy; DFS = disease-free survival; PSA = prostate-specific antigen; ^{125}I = iodine-125; ^{103}Pd = palladium-103; ASTRO = American Society for Therapeutic Radiology and Oncology.

* *Three consecutive rises in serum PSA level measured 6 months apart.*

† *Three-year freedom from biochemical failure.*

‡ *Hormone-naive group.*

§ *Patients exposed to prior androgen deprivation.*

group was noted when a PSA endpoint of 0.4 ng/mL or less was used. The DFS rate was 74.5% in the combined modality group versus 63% in the implant alone group ($P = 0.046$).[23] The investigators suggested that combining EBRT with brachytherapy implantation might be the best modality for patients with clinically localized prostate cancer, with results comparable to prostatectomy. Although some physicians, such as Critz, have proposed combined implantation and EBRT for all locally confined prostate cancer, others, including Ragde *et al.*,[22] have used the following criteria for implant-alone therapy: PSA less than 10 ng/mL, clinical Stage T2a or less, and Gleason score less than 7.

Although the level of PSA nadir necessary for optimal treatment outcome is debated (less than 1.0 ng/mL or less than 0.5 ng/mL), a low post-treatment PSA nadir is a known predictor of DFS.[24,25] The 5-year DFS rate was 93% in patients with a PSA nadir of less than 0.5 ng/mL compared with 25% in patients with a PSA nadir between 0.5 and 1.0 ng/mL in men treated with combined EBRT and prostate implantation.[25] Critz *et al.*[24] showed that 77% of patients treated with combined EBRT and prostate implantation achieved a PSA level of 0.5 ng/mL or less at 60 months. The post-treatment PSA values decreased most rapidly within the first 3 months after implantation, and more gradually thereafter; by 24 months, 52% of patients had achieved a PSA nadir of 0.5 ng/mL or less. The rate of PSA decrease, however, was not a prognostic indicator.

Grado *et al.*[25] published results on actuarial DFS after prostate cancer brachytherapy using interactive techniques with biplane ultrasonography and fluoroscopic guidance. A total of 543 patients with T1-T3c prostate cancer (with no PSA, Gleason score, or hormonal therapy restriction) were treated with iodine-125 or palladium-103 seed implantation. Of the 543 patients, 490 patients were analyzable, of whom 72 had received 45 Gy adjuvant EBRT because of evidence of possible capsular involvement as determined by digital rectal examination, transrectal ultrasonography, or biopsy (n = 70) or because of a suboptimal implant dose (n = 2). Of the patients in the implant-alone group and combined-modality group, 26 and 10, respectively, received androgen deprivation therapy. No statistically significant difference in DFS was observed in patients treated by implant alone versus combined implantation and EBRT. For the hormone-naive group, the 5-year DFS rate was 80% for the implant-alone group and 72% for the combined-modality group; those patients receiving hormonal therapy had a 5-year DFS rate of 83% versus 88% for the implant-alone group and implant plus EBRT group, respectively.[25]

Singh *et al.*[26] reported early but favorable results with combination palladium-103 implantation and 3D-CRT in patients with intermediate-risk and unfavorable-risk prostate cancer treated at Memorial Sloan-Kettering Cancer Center. The PSA relapse-free survival rate at 3 years was 87%.[26] More recently, Merrick *et al.*[27] reported the outcomes on 66 hormone-naive patients with high-risk prostate cancer (Gleason score of 7 or greater, PSA level 10 ng/mL or greater, clinical Stage T2b or greater) treated with combined EBRT and permanent seed implantation. The 5-year biochemical DFS rate was 80%.[27] A summary of institutional experiences with combination EBRT and brachytherapy boost is provided in Table I.

TREATMENT-RELATED SIDE EFFECTS

Rectal and Urinary Toxicity

The morbidity from the combined approach appears to be comparable to high-dose 3D-CRT or surgery for similar-risk patients. The most commonly observed toxicity with combined 3D-CRT and brachytherapy boost is RTOG grade 1 and 2 rectal and urinary toxicity. In the study by Singh *et al.*,[26] 13% of patients experienced rectal bleeding and 8% experienced increased frequency of bowel movements, but no patient experienced grade 3 or 4 rectal toxicity.

The most commonly reported urinary side effects are symptoms of frequency, urgency, and nocturia, which are easily managed with alpha-blockers.[20,25] Less commonly observed are urinary obstructive symptoms requiring intervention. A 6% rate of temporary Foley catheterization was observed by Singh *et al.*,[26] and less than 3% of men required TURP after implantation for persistent urinary obstructive symptoms in the study by Dattoli *et al.*[20] Observed rates of stress incontinence have ranged from 1% to 5%.[20,21,26] One patient in the study by Dattoli *et al.*[20] developed complete urinary incontinence. Although complications of urinary incontinence, obstruction, and urethral stricture are rare with combined-modality therapy, they are more likely to be seen in men with a prior history of urinary obstructive symptoms and prior TURP.[20,21] In a study by Critz *et al.*,[21] all cases of urinary incontinence, urethral necrosis, and urethral stricture occurred in men with a prior history of TURP.

Similar to the urinary toxicity profile, rectal toxicity with combined-modality therapy is most likely to be RTOG grade 1 or 2. In the Memorial Sloan-Kettering Cancer Center experience, 13% of patients experienced rectal bleeding and 8% experienced increased frequency of bowel movements; no grade 3 or 4 rectal toxicities were observed.[26] Grado *et al.*[25] reported a rare 1% occurrence of rectal fistula.

Potency Preservation

Rates of potency preservation greater than 80% have been reported with brachytherapy as monotherapy.[28] Potency after EBRT, however, is less well preserved, with reported rates of only 50% at 6 years.[3] From the limited data available on the effects of combined prostate brachytherapy and EBRT on sexual function, the rates of sexual potency, not surprisingly, fall between those reported for either modality alone. Dattoli *et al.*[20] reported sexual potency rates of 82% and 77% at 1 and 3 years, respectively. Similar rates of potency were observed by Singh *et al.*,[26] with a reported 26% of sexually potent men developing erectile dysfunction after combined-modality treatment. No difference in the rate of erectile dysfunction was observed among those men receiving neoadjuvant androgen deprivation and those who did not.[26] Advanced age has been shown to play a role in the preservation of sexual function. Critz *et al.*[29] showed that men younger than 65 years old had an 85% rate of potency preservation, and men older than 65 had a 65% rate of potency ($P = 0.05$).

Future trials, including an ongoing RTOG Phase II study for patients with intermediate-risk prostate cancer receiving combined EBRT and prostate brachytherapy will provide additional data on treatment-related toxicity and the overall safety and efficacy of the combined approach.

HIGH-DOSE-RATE BRACHYTHERAPY BOOST

High-dose-rate (HDR) brachytherapy technology was developed in the mid-1980s. This remote afterloading technique enables treatment planning to take place after needles have been securely placed into the prostate. The dose delivered to the prostate is then calculated and controlled by the dwell time of the radiation source at specified locations within each needle. The advantages of HDR brachytherapy include improved implant dosimetry, shorter treatment time, no requirement for permanent seed implantation, and no risk of seed migration or radiation exposure to personnel. Several institutions have reviewed their experience with EBRT in combination with HDR brachytherapy for locally advanced prostate cancer. Mate *et al.*[30] reported their prospective results of 144 men with T1b-T3 clinically node-negative prostate cancer treated between 1986 and 1992 with whole pelvis EBRT combined with two fractions of HDR brachytherapy consisting of 15 Gy/Fx to the peripheral prostate and 9 Gy to the entire prostate. The overall survival and biochemical disease-free survival rate at 5 years was 80.4% and 74%, respectively.[30]

A matched-pair analysis was performed by Kestin *et al.*[31] to compare patients treated with EBRT alone and those treated with combined EBRT and an interstitial HDR brachytherapy boost. The 5-year biochemical control rate for EBRT plus HDR was statistically significantly greater than for EBRT alone (67% versus 44%, $P < 0.001$). The combined-modality group achieved a lower PSA nadir (0.4 ng/mL versus 1.1 ng/mL) and sustained longer intervals of PSA nadir (1.5 versus 1.0 years).[31] On multivariate analysis, Gleason score, T stage, and use of EBRT were significantly associated with freedom from biochemical failure. A correlation between biochemical control and cause-specific survival was also demonstrated.

ADDITION OF HORMONAL THERAPY

In addition to dose escalation, the use of hormonal therapy has been used to achieve better disease control in patients with intermediate-risk and high-risk prostate cancer. Although the addition of hormonal therapy to EBRT has shown a benefit in disease-specific and overall survival, the use of adjuvant hormonal therapy with brachytherapy has not been well established. Data supporting hormonal therapy in conjunction with brachytherapy are limited by the retrospective designs and small sample sizes.

Multiple prospective randomized trials have shown a benefit to the addition of androgen ablation to EBRT in patients with locally advanced prostate cancer. Both RTOG 86-10 and RTOG 85-31 showed a benefit in local control and DFS.[32,33] The European Organization for Research and Treatment of Cancer study showed improvement in overall survival in addition to DFS and local control with the addition of adjuvant hormonal therapy to EBRT.[34]

Neoadjuvant hormonal therapy (NHT) is routinely used for downsizing large prostate glands before brachytherapy, with the goal of shrinking the prostate and allowing greater ease of implantation and a better dose distribution. The ABS recognizes the use of hormonal therapy with brachytherapy and EBRT and recommends its use only in the context of downstaging large prostate glands (larger than 60 cm^3) before seed implantation.[18] Several institutions have reviewed their experiences with combined hormonal therapy and brachytherapy; however, no prospective randomized trials exist to date.

Stone *et al.*[35] reported their results with NHT and brachytherapy in 115 patients with intermediate-risk prostate cancer treated with leuprolide and flutamide for 3 months before implantation and an additional 3 months after implantation. A benefit in local control was suggested in high-risk patients (PSA level greater than 10 ng/mL, greater than Stage T2a, Gleason score greater than 6) who received NHT, with a rate of positive prostate biopsies at 2 years of 3.4% in the NHT group and 21.1% in the hormone-naive group ($P = 0.003$). Two additional retrospective studies, both limited by the number of patients and mean follow-up time, have evaluated the addition of androgen ablation to combined EBRT and brachytherapy seed implantation. Sylvester *et al.*[36] performed a matched-pair subset analysis of 98 patients with intermediate-risk to high-risk prostate cancer; 21 patients underwent combined implantation and EBRT plus androgen ablation. The overall rate of freedom from biochemical failure at 5 years was 77% in the hormonally treated group and 58% in the non-hormonally treated group ($P = 0.08$).

In the retrospective implant review of Grado *et al.*,[25] 36 of 490 patients with T1-T3c prostate cancer who underwent brachytherapy seed implantation had received prior androgen deprivation therapy for prebrachytherapy reduction of the prostate volume or by patient request. Of the 36 patients at risk of ECE, 10 underwent combined brachytherapy with EBRT. The 5-year DFS rate for the implant-alone group and the implant plus EBRT group was 83% and 88%, respectively.[25]

No strong evidence exists for the addition of adjuvant hormonal therapy or NHT to prostate brachytherapy and the potential benefit of hormonal therapy with brachytherapy requires further investigation. The studies published thus far have been limited in both patient size and duration of follow-up, and no consensus exists for the routine use of hormonal therapy with brachytherapy in intermediate-risk to high-risk patients.

CONCLUSIONS AND FUTURE DIRECTIONS

Prostate cancer remains the most common noncutaneous cancer diagnosed in men and the second leading cancer cause of death. With the widespread use of PSA testing, more men are detected with localized prostate cancer. The optimal therapy for organ-confined prostate cancer remains an ongoing dilemma.

Abundant evidence has shown the benefit of greater radiation doses in the treatment outcomes in men with intermediate-risk and high-risk features. Although patients with favorable-risk cancer have excellent outcomes with monotherapy, combined EBRT and brachytherapy is an excellent treatment option for men with intermediate-risk to high-risk prostate cancer. Combining 3D-CRT with a brachytherapy boost has been shown to be a safe and effective way of delivering high radiation doses to the prostate and can achieve results similar to those achieved for favorable-risk patients; however, we await the results of recently completed and future prospective randomized trials to verify these findings. Although the addition of hormonal therapy to EBRT has been proved beneficial, the potential benefit of hormonal therapy in combination with brachytherapy has not yet been thoroughly investigated, and no strong evidence exists for its routine use. Future prospective clinical trials will help to define better the role of combined EBRT and brachytherapy and the additional use of hormonal therapy.

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