Patient Selection for Prostate Brachytherapy

a report by
Gregory S Merrick, MD[1], Wayne M Butler, PhD[1] *and* **Kent E Wallner, MD[2]**

1. Schiffler Cancer Center and Wheeling Jesuit University, 2. Puget Sound Healthcare Corporation, Group Health Cooperative, and University of Washington, Seattle

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Introduction

Although the majority of permanent prostate brachytherapy studies have demonstrated biochemical control rates and morbidity profiles that compare favorably with radical prostatectomy (RP) and external beam radiation therapy (XRT),[1,2] it has become increasingly apparent that efficacy and morbidity are highly dependent on implant quality.[1–3] Sophisticated dosimetric analyses have demonstrated that cure rates and brachytherapy-related morbidity are related to specific source placement patterns and the subsequent dose gradients produced.[1,2,4] In addition, the need for supplemental XRT or androgen deprivation therapy (ADT) to optimize biochemical outcome is increasingly in doubt.[5,6] With high quality brachytherapy, the vast majority of patients can be successfully managed without such supplemental therapies.[5]

With the emergence of brachytherapy as a mainstream treatment for clinically localized prostate cancer, a rapidly expanding body of literature regarding patient selection and treatment approach has been reported.[1,2,7–11] Although not all patients are acceptable candidates for brachytherapy, a reliable set of pre-treatment criteria for predicting outcome has not been formulated. Fortunately, evidence-based factors are rapidly accumulating. The elucidation and widespread adoption of evidence-supported planning philosophies, intra-operative techniques, and medical management should further improve outcomes.

Prostate Size

Although no clear relationship exists between prostate size and a greater incidence of urinary morbidity,[12–15] large prostate size remains a relative contraindication to brachytherapy due to technical concerns and the perception that large prostate size increases the risk for acute and prolonged urinary morbidity.[16,17] In fact, patients with large prostate glands can be implanted with acceptable morbidity.[12–15] In a study using the patient-administered Expanded Prostate Cancer Index Composite (EPIC), long-term urinary function did not correlate with prostate size.[14] In the other extreme, favorable dosimetry with minimal urinary morbidity has been reported for patients with small glands (<20cm^3).[6,14,18]

Transition Zone

Unlike overall prostate size, transition zone volume has consistently correlated with brachytherapy-related urinary morbidity (see *Figure 1*).[19–21] Investigators at Harvard University reported that transition zone volume was the most important predictor of acute urinary retention following brachytherapy.[19] In patients receiving neoadjuvant ADT for cytoreduction, International Prostate Symptom Score (I-PSS) normalization, prolonged catheter dependency, and the need for post-brachytherapy transurethral resection (TURP) were best predicted by the per cent decrease in transition zone volume.[21]

In particular, prolonged urinary morbidity was unlikely in patients with greater than a 30% decrease in transition zone volume.[21] The currently available data suggest that the transition zone may have a greater predictive power for prediction of significant urinary dysfunction than any other single parameter.

Pubic Arch Interference

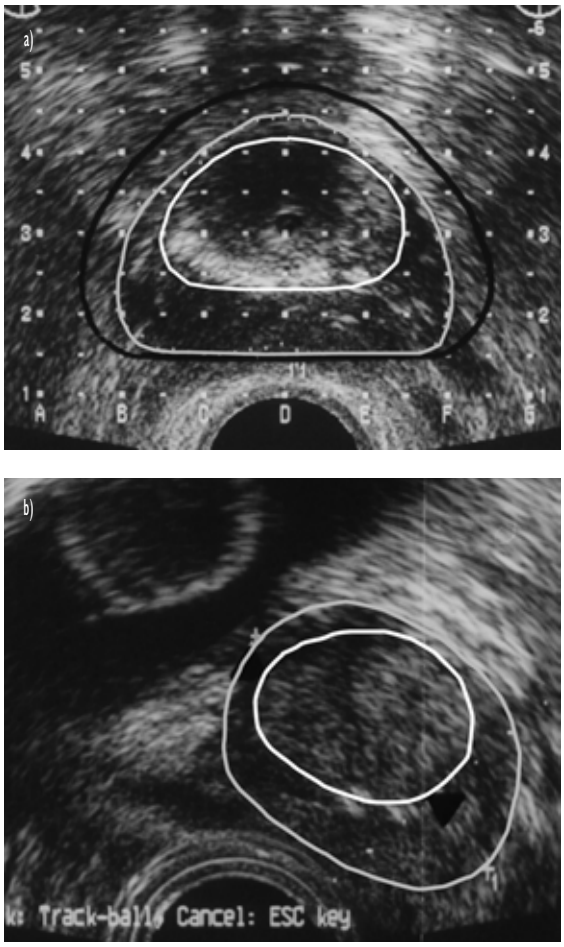
Pubic arch interference (the obstruction of anterior needle placement insertion by a narrow pubic arch) has long been considered a relative contraindication to brachytherapy. Surprisingly, prostate volume has proven to be a poor predictor of pubic arch interference.[22] With use of the extended lithotomy position and/or veering needles around the arch, almost all patients can be successfully implanted with favorable post-implant dosimetry regardless of the degree of pubic arch interference.[22,23]

Median Lobe Hyperplasia

Median lobe hyperplasia (the protrusion of hypertrophied prostate tissue into the bladder) is a

Gregory S Merrick, MD, is the Director of the Schiffler Cancer Center, Wheeling Hospital, and Associate Professor of Physics at Wheeling Jesuit University. He is a member of the board of directors of the American Brachytherapy Society, currently serving as Treasurer and Public Relations Chairman. He sits on the editorial board of the journal *Brachytherapy* and serves as a manuscript reviewer for numerous other peer-reviewed scientific oncologic and urologic journals. He has published 125 original scientific publications and 80 scientific abstracts, as well as contributing to and/or editing multiple medical textbooks. In conjunction with Kent E Wallner, MD, of the University of Washington, Dr Merrick has recently completed the only two large prospective randomized prostate brachytherapy trials ever conducted.

Figure 1



relative contraindication to brachytherapy due to concerns of an increased risk of post-implant urinary morbidity and/or technical difficulties of implanting intravesicle tissue.[17] In a small series, complete dosimetric coverage of the median lobe was reported in all patients.[24] However, a quarter of those patients developed prolonged post-implant urinary retention and others experienced prolonged I-PSS elevation. Although median lobe hypertrophy should not be considered an absolute contraindication to brachytherapy, such patients should be approached with caution. It is conceivable that pre-implant resection of the intravesicle component may reduce the incidence of brachytherapy-related morbidity.

International Prostate Symptom Score

The role of the I-PSS in predicting urinary morbidity (including urinary retention) has been studied extensively with conflicting conclusions.[9,12,14,16,17,25–28] Although almost all brachytherapy patients develop urinary irritative/obstructive symptoms, with up to 34% developing acute urinary retention,[12,19,25–27,29] fewer than 5% require a urinary catheter for more than one week.[12,30] Pre-implant I-PSS does correlate with the duration of post-implant obstructive symptomatology,[12,25,28] but does not predict for long-term urinary quality of life.[14]

In contrast to three recently-published patient selection guidelines,[9,16,17] prospective studies have demonstrated little correlation between pre-implant I-PSS, urodynamic studies, post-void residual urine volume, or pre-implant cystourethroscopy and acute or long-term urinary function.[26,31] The prophylactic and prolonged use of alpha blockers results in a return of I-PSS to baseline significantly faster than in patients not receiving alpha blockers or receiving them after substantial exacerbation of urinary symptoms.[12,30]

Transurethral Resection of the Prostate

In contemporary brachytherapy series, the risk of incontinence in patients with a pre-implant TURP has been reported to be 6% or less.[32,33] This is thought to be a result of the use of peripheral source loading and limitation of the radiation dose to the TURP defect to approximately 110% of prescription dose.[32,33] Using the EPIC instrument, patients with a pre-implant TURP have been found to have urinary quality of life approaching that of non-TURP brachytherapy patients.[34]

After brachytherapy, approximately 2% of patients develop prolonged urinary retention with the vast majority eventually spontaneously urinating.[34] If a post-implant TURP or transurethral incision of the prostate (TUIP) is necessary, it should be delayed for as long as possible. Significant urinary morbidity has been demonstrated in approximately 50% of patients undergoing a post-implant TURP. Patients requiring a pre- and post-implant TURP have an especially high risk of urinary incontinence.[34]

To minimize post-brachytherapy TURP-related incontinence, preservation of the bladder neck at the five and seven o'clock positions with minimal use of cautery to maintain sufficient prostatic urethral blood supply has been recommended.[35] Surgical intervention should be discouraged for at least the first 12 months following brachytherapy.

Prostatitis

Prostatitis remains a relative contraindication to brachytherapy. However, a recent study reported no relationship between the presence or severity of prostatitis and the incidence of urinary retention or prolonged I-PSS elevation following implantation.[36]

Age

Patient age alone should not influence treatment decisions. Patient age may be a stronger predictor of prostate cancer curability than differences in pre-implant prostate-specific antigen (PSA).[37] Older patients have been reported to be at increased risk for extracapsular extension, higher Gleason scores, and a greater propensity for distant metastases.[37,38] Contemporary RP series have demonstrated a greater incidence of organ-confined disease in younger patients.[37,39] In addition, outstanding biochemical outcomes (median PSA <0.1ng/ml) have been reported for hormone-naïve patients ≤62 years of age undergoing brachytherapy.[40] On the other hand, older patients tolerate brachytherapy as well as younger men.[12,14]

Obesity

Obesity presents substantial procedural difficulties for RP and XRT, but only relatively minor problems for brachytherapy.[41] Favorable biochemical and quality of life outcomes have been demonstrated for brachytherapy patients regardless of body mass index (BMI).[41,42]

Tobacco

Consistent with a correlation between cigarette smoking and aggressive prostate cancer and/or prostate cancer-related deaths, tobacco consumption correlated with a trend for poorer biochemical progression-free survival following brachytherapy.[43]

In addition, tobacco may exacerbate brachytherapy-related morbidity. Although the absolute differences were small, tobacco was the strongest predictor for adverse late urinary quality of life including adverse changes in EPIC and I-PSS.[14] Tobacco was also a statistically significant predictor for compromised late rectal function.[44] Accordingly, tobacco may be a weak contraindication to brachytherapy, but its role in treatment selection for RP or XRT has not been elucidated.

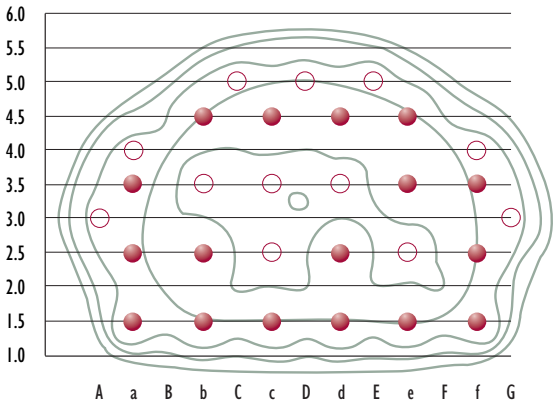
Inflammatory Bowel Disease

Inflammatory bowel disease, ulcerative colitis, and regional enteritis (Crohn's disease) have been considered relative contraindications to radiation therapy. However, following brachytherapy, a small series reported no increased risk of gastrointestinal morbidity.[45]

Adverse Pathologic Features

High Gleason score, perineural invasion, and per cent positive biopsies correlate with a greater likelihood of extracapsular extension, leading some to conclude that patients with high-risk features may not be adequately treated with brachytherapy.[8,9,11] In contrast, multiple brachytherapy studies have demonstrated favorable biochemical outcomes for hormone naïve patients at high risk of extraprostatic extension.[46–50] Pathologic evaluation of RP specimens has demonstrated that almost all cases of extraprostatic extension are limited to within 5mm of the prostate capsule.[51] As such, high quality brachytherapy with or without supplemental XRT should sterilize extraprostatic extension. These findings suggest that an aggressive loco-regional approach that includes generous peri-prostatic brachytherapy treatment margins and/or the addition of supplemental XRT can result in a high likelihood of cancercidal eradication (see *Figure 2*).[52] The relative resiliency of brachytherapy to adverse pathologic findings is likely a result of intra-prostatic dose escalation with therapeutic radiation dose delivery to the peri-prostatic region.[46,52]

Figure 2: A Mid-gland (2.0cm) Slice of a 34.6cm³ Prostate with the 75%, 100%, and 150% Isodose Lines Plotted, Progressing from Outside in



The prostate is the heavy black outline and the urethra the small dark circular object in the center. Seeds present on this slice are filled circles, and needle coordinates used in the implant are open circles on the dotted 0.5cm grid.

Prostatic Acid Phosphatase

Pre-treatment enzymatic prostatic acid phosphatase (PAP) is predictive of biochemical outcome and/or disease-specific survival following potentially curative local treatment modalities.[50,53] In contemporary RP series, enzymatic PAP did not predict organ-confined disease or lymph node status, but was an independent predictor of biochemical recurrence.[53] Similarly, PAP was the single strongest predictor of freedom from biochemical progression for intermediate and high-risk brachytherapy patients.[50] Although a substantial minority of brachytherapy patients with an elevated

pre-treatment PAP remain curable, it is conceivable that these patients should benefit from effective adjuvant systemic therapy.

Isotope

No definitive data supports the potential curative superiority of one isotope over another for any clinical stage, Gleason score or pre-treatment PSA;[54–56] however, a prospective randomized trial has suggested that Pd-103 may be more efficacious.[56]

Androgen Deprivation Therapy

Despite recent reports detailing favorable biochemical outcomes for hormone naïve brachytherapy patients with higher-risk features,[48–50] intermediate and high-risk brachytherapy patients often receive adjuvant ADT as an extrapolation from the conventional XRT dose (65–70Gy) literature.[58] The favorable interaction between conventional dose XRT and ADT likely results from the inability of conventional XRT doses to sterilize large bulky prostate cancers and as such may not be applicable to brachytherapy. In a large retrospective matched-pair analysis, no benefit for ADT with brachytherapy was discerned for any risk group, Gleason score, pre-treatment PSA, or clinical stage.[59] Although it is possible that subgroups of high-risk brachytherapy patients may benefit from adjuvant ADT, that patient population has not been definitively identified.

Most brachytherapy studies have demonstrated favorable biochemical outcomes with a morbidity profile that compares favorably with competing local modalities.

Supplemental Therapies

Both XRT and adjuvant ADT are commonly used as supplements to brachytherapy in patients with adverse pathologic and/or biochemical features. In contrast, contemporary series strongly suggest that with high quality brachytherapy dose distributions and generous peri-prostatic treatment margins, the vast majority of prostate brachytherapy patients can be managed with implant alone.

External Beam Radiation Therapy

The rationale for supplemental XRT combined with brachytherapy is to enhance the coverage of peri-prostatic tissue, escalate the dose to the intra-prostatic tumor, supplement inadequate radiation dose distributions and/or treat loco-regional disease. The American Brachytherapy Society (ABS) recommended monotherapy for patients with clinical stage T1–T2a, PSA ≤10ng/ml and Gleason score ≤6 with the addition of supplemental XRT for all other patients.[7] Recently, however, the utility of supple-mental XRT has been questioned by favorable biochemical outcomes following monotherapeutic brachytherapy in patients with higher PSAs and/or Gleason scores.[48] It is possible that high quality brachytherapy dose distributions with generous peri-prostatic margins may obviate the need for combined modality therapy for low, intermediate, and selected high-risk patients.[48,52] Supplemental XRT has also been demonstrated to exacerbate brachytherapy-related morbidity.[14,44,57]

ADT has been implicated in brachytherapy-related morbidity.[2,21,25] ADT of greater than a six-month duration resulted in deleterious changes in EPIC with a trend for poorer post-implant I-PSS.[14] In addition, conflicting results have been reported regarding the potential deleterious effect of neoadjuvant ADT on erectile function.[4]

Conclusions

Most brachytherapy studies have demonstrated favorable biochemical outcomes with a morbidity profile that compares favorably with competing local modalities. A reliable set of pre-treatment criteria for patient selection is lacking. Even in situations where patients present with alleged contraindications, brachytherapy may remain the best choice when compared with alternatives. Continued refinement in brachytherapy planning philosophies, intra-operative technique, and post-implant medical management should result in further improvements in biochemical outcome and a reduction in brachy-therapy-related morbidity. ■

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