Interstitial Brachytherapy Should Be Standard of Care for Treatment of High-Risk Prostate Cancer

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Given the poor outcomes observed with radical prostatectomy (RP) and external-beam radiation therapy (EBRT), some in the urologic community contend that high-risk disease is not curable with currently available treatment strategies.[1,2] In fact, there is a growing contingent of clinicians who advocate the use of chemotherapy in conjunction with RP. With the established efficacy of brachytherapy, these efforts are likely excessive.

Long-term outcomes data now demonstrate excellent biochemical control rates among low- and intermediate-risk patients treated with interstitial brachytherapy.[3-6] Traditionally, there has been less enthusiasm for the use of brachytherapy in the setting of high-risk disease.[7] This relates in large part to historical data suggesting suboptimal outcomes among high-risk patients treated with brachytherapy.[8-10] These studies are limited by their inadequate reporting of implant dosimetry and lack of planned treatment margins. Indeed, most modern trials show exceptional biochemical control rates among high-risk patients treated with a regimen that includes brachytherapy.[11-16] Adverse pathologic features, which are characteristic of high-risk disease, correlate with a higher likelihood of extraprostatic extension and seminal vesicle involvement.[17] This has led to the perception that patients with high-risk features may not be adequately treated with brachytherapy.[7,18,19] On the contrary, modern implant technique allows for generous extracapsular margins and treatment of the proximal seminal vesicles, with the added benefit of intraprostatic dose escalation. For these reasons, brachytherapy offers a unique advantage over other local therapies and is actually ideally suited for patients with the most aggressive local biology. Several risk stratification systems have been developed. Nearly all are based on the premise that serum prostate-specific antigen (PSA), clinical T stage, and Gleason score are independent predictors of biochemical failure-free survival.[20-22] Perhaps most popular is the D'Amico system, which categorizes patients as low-risk (Gleason ≤ 6, PSA ≤ 10 ng/mL and stage T2a or less), intermediate-risk (Gleason 7, PSA 10–20 ng/mL, and/or stage T2b), or high-risk (Gleason 8–10, PSA > 20 ng/mL, and/or stage T2c or higher).[8] In recent years, percent positive biopsies has also been identified as an independent predictor of biochemical outcome.[23-26] Herein, we attempt to dispel some common misconceptions about prostate brachytherapy, and as a secondary objective, compare clinical outcomes with different treatment modalities. In doing so, we hope to convince the reader that brachytherapy is the best available local therapy and should be standard of care in the treatment of high-risk prostate cancer.

Risk of Extracapsular Extension

Early data published by D'Amico and others suggested better biochemical control rates among intermediate- and high-risk prostate cancer patients treated with RP or EBRT, as compared to those undergoing interstitial implant.[8-10] D'Amico's study, completed nearly a decade ago, continues to be cited as an argument against the use of brachytherapy in the setting of intermediate- and high-risk disease.

While this was undoubtedly an important study, it was completed in an era when optimization of implant dosimetry was in its fledgling stages. In particular, the importance of implant quality and treatment margins had not been fully appreciated.[27-30] Hence, the implant technique used in this particular analysis would be considered suboptimal by the standards of most modern
brachytherapists. It has been proposed that the poor brachytherapy outcomes observed in this early series are likely attributable in part to inadequate treatment margins.[31] Also of concern is the lack of reported implant dosimetry and low total implant activity. Numerous investigators have shown that D90 (the maximum dose covering 90% of the prostatic volume) and V100 (the percentage of the prostatic volume covered by the prescription dose) have a substantial impact on biochemical control rates.[27-29] Given the importance of these dosimetric parameters, it is imperative that these values be reported when evaluating the efficacy of brachytherapy. Collectively, these factors may explain the poor results observed by D'Amico and others.

**Promising Subsequent Results**

Most contemporary brachytherapy series show excellent biochemical control rates among intermediate- and high-risk patients (Figure 1).[3-6,11-16,32] These promising results can be explained in part by pioneering work done at the Mayo Clinic.[33,34] Davis and colleagues were the first to examine prostatectomy specimens with the intent of quantifying the average radial distance of extraprostatic extension (EPE). In this series, the median radial distance of EPE was only 0.5 mm (range: 0.04-4.4 mm).

Davis' early work has since been replicated by a number of other groups with reported median EPE distances ranging from 1.1 to 2.4 mm.[35-37] In nearly 99% of all cases, the radial extent of EPE is limited to ≤ 5 mm.[33,35] Several investigators have reported average postimplant treatment margins of 3 to 6 mm at the 100% isodose line, suggesting that adequate brachytherapy margins are easily obtainable and should be sufficient to eradicate extraprostatic disease (Figure 2).[38-40] Choi et al have confirmed the measurable impact of treatment margin on clinical outcome after prostate brachytherapy, showing that inadequate margins correlate with biochemical failure.[30] It should also be noted that most high-risk brachytherapy protocols have combined supplemental EBRT with interstitial implant to augment treatment margins, thereby increasing the likelihood of eradicating subclinical extraprostatic disease.[11-16]

**Predictive Models**

Future challenges in the treatment of prostate cancer will include the development of predictive models to accurately select those patients at risk for EPE beyond 5 mm. Schwartz and colleagues are making strides on this front, having formulated a predictive model for the extent of EPE according to pretreatment PSA, clinical T stage, and percentage of cancer in the biopsy specimen.[41] Tools such as this may enable the prostate brachytherapist to tailor treatment margins and perhaps gauge the necessity for supplemental EBRT. Even among the small subset of patients with estimated EPE greater than 5 mm, brachytherapy will likely remain a feasible treatment approach.

While somewhat of a contentious issue in the brachytherapy community, extraprostatic seeds can be placed to extend treatment margins. Hesitation over extraprostatic seed placement exists primarily due to concerns of seed migration within the pelvis or to distant sites such as the lung. Several investigators have demonstrated that seed loss is minimal with extracapsular seed placement.[42,43] Furthermore, there is no clear relationship between the number of seeds lost and proportion of seeds placed in the extracapsular regions of the prostate.[42] With extraprostatic spread estimated to be present to some degree in the majority of high-risk patients, it is crucial that local treatment modalities address this issue.[44] Based on the aforementioned data, it is evident that the likelihood of EPE should not in and of itself determine a patient's eligibility for brachytherapy. Instead, most data suggest that an aggressive locoregional approach that includes generous periprostatic brachtherapy treatment margins and supplemental EBRT, can result in a high likelihood of cancer eradication even among high-risk patients.[11-16]

**Patterns of Failure**

One common criticism of brachytherapy in the setting of high-risk prostate cancer is that it fails to address potential subclinical disease in the pelvic lymph nodes. While the utility of pelvic radiation therapy remains open to debate, the preponderance of data would suggest that the incremental benefit of prostatic dose escalation exceeds that of elective treatment to the pelvic lymph nodes.[45-48] Furthermore, the patterns of failure following standard treatments for high-risk prostate cancer reveal a large component of local recurrence. It is theorized that local recurrence remains a problem due to the inability of RP to adequately treat extracapsular spread, and the failure of EBRT to eradicate all known disease, primarily because of inadequate dose delivery.[11] From this standpoint, brachytherapy offers a clear therapeutic advantage over other local treatment modalities. Specifically, interstitial brachytherapy allows for both intraprostatic dose escalation and generous extracapsular margins. Additionally, interstitial implant should improve the tolerance of supplemental EBRT to the pelvis by reducing cumulative
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Cumulative Radiation Dose to the Prostate
In the EBRT literature, cumulative prostate dose has been shown to have a decisive impact on freedom from biochemical and/or clinical failure.[49,50] With long-term follow-up available, the M.D. Anderson dose-escalation study now demonstrates an absolute benefit of nearly 20% on freedom from failure with 78 vs 70 Gy. An even greater benefit was observed among patients with PSA > 10 ng/mL.[50]

Jacob and colleagues recently examined the role of prostate dose escalation in patients with a greater than 15% risk of pelvic lymph node involvement.[51] Their analysis revealed radiation dose to the prostate as the only statistically significant treatment-related factor predicting for freedom from biochemical failure on multivariate analysis. The authors of this study concluded that treatment of the primary tumor should take precedence over lymph node coverage and short-term androgen deprivation in the treatment of intermediate/high-risk prostate cancer. In a separate analysis, Jacob's group also showed a strong association between increasing prostate dose and reduced distant metastasis and overall mortality.[52]

Zelefsky et al have also reported on the relationship between cumulative prostate dose and likelihood of biochemical cure in their series of over 1,100 patients treated with intensity-modulated conformal radiotherapy.[53] In this series, 37% of high-risk patients had positive posttreatment biopsies at 2.5 years after treatment. This finding further underscores the importance of local recurrence as a pattern of failure among high-risk patients.

Evidence From Surgical Series
The importance of effective local treatment in high-risk prostate cancer is also highlighted in the surgical literature. Swanson et al recently evaluated the patterns of treatment failure in Southwest Oncology Group (SWOG) 8794, a cooperative study randomizing high-risk postprostatectomy patients to either immediate adjuvant radiation therapy to the prostatic fossa or no further therapy.[54] In this analysis, treatment failure occurred primarily in the prostatic fossa, with a relatively low incidence of metastatic failure. The authors concluded that optimization of local control appears to offer the best opportunity for cure in this patient population.

The European Organisation for Research and Treatment of Cancer (EORTC) 22911 trial, which used an identical schema to that of SWOG 8794, also demonstrated that the predominant form of failure was local in high-risk patients after prostatectomy.[55] Other surgical series have reported local recurrence rates of up to 44% among T3 patients treated with prostatectomy.[56,57]

Studies of Brachytherapy Plus EBRT
In contrast to other conventional treatment approaches, brachytherapy in combination with supplemental EBRT has been shown to be highly effective in eradicating local disease among high-risk patients. Stock and colleagues recently reported their outcomes data for high-risk patients treated with brachytherapy implant, supplemental EBRT, and 9 months of androgen deprivation therapy (ADT).[11] In Stock's study, the actuarial 7-year freedom from PSA failure and freedom from distant metastases were 83% and 89%, respectively. Posttreatment biopsy results were negative in 97% of cases, indicating excellent local disease control. These results compare favorably with the local control rates obtained with other treatment modalities.[53,56,57]

Merrick and colleagues have also reported excellent clinical outcomes among high-risk patients treated with brachytherapy and supplemental EBRT with or without ADT.[58] Their reported 11-year cause-specific survival and biochemical progression free survival rates were 90.1% and 88.5%, respectively. Interestingly, with the excellent cure rates observed in this study, the patterns of death emulated that of the general population, with cardiovascular disease being the main cause of mortality.

Summary
Collectively, the aforementioned data provide compelling evidence that delivery of cancericidal doses is paramount to curing localized, high-risk prostate cancer. The notion that high-risk patients are destined to experience treatment failure in draining lymph nodes or at distant sites is not supported by the literature. With the ability for local dose intensification and rapid radial dose fall-off, interstitial brachytherapy is ideally suited to addressing aggressive organ-confined disease.

Risk of Seminal Vesicle Involvement
Early cases of seminal vesicle (SV) invasion, limited to the confluence of the SV and vas deferens, are likely to receive a therapeutic dose with a typical interstitial implant. Extensive SV involvement, on the other hand, cannot be reliably treated with brachytherapy alone and is felt to be a poor
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The Seattle Prostate Institute (SPI) group has perhaps the longest published experience with interstitial brachytherapy in the setting of high-risk disease. Up to this point, we have sought to develop an argument for the role of brachytherapy among high-risk prostate cancer patients on the basis of dose distribution and patterns of failure. While this line of reasoning is intuitive, the most compelling evidence is the outcomes data published by several of the highest-volume prostate brachytherapy centers in the United States. For the remainder of this review, we shall focus on the biochemical control rates obtained with brachytherapy in the setting of high-risk disease.

Clinical Outcomes

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The Seattle Prostate Institute (SPI) group has perhaps the longest published experience with interstitial brachytherapy. With 15-years of follow-up, Sylvester and colleagues recently reported their biochemical outcomes stratified by risk group.[3] Between January 1987 and December 1993, a total of 232 patients were treated with neoadjuvant EBRT using a limited pelvic field (45 Gy) followed by interstitial brachytherapy using either palladium-103 (103Pd) at 90 Gy, or iodine-125 (125I) at 120 Gy. Among these patients, 114 (51%) were classified as high-risk according to the D'Amico stratification system. The 15-year biochemical relapse-free survival rate among this group of high-risk patients was 67.8%.

Although not commonly cited as a contraindication to interstitial prostate brachytherapy, SV involvement does present a formidable challenge. Stock and colleagues were the first to perform a dosimetric analysis revealing that the dose from an implanted prostate contributes little to the more distal SV.[60] They concluded that patients at highest risk for SV involvement may be undertreated with standard brachytherapy implant and supplemental EBRT.

Kestin et al performed a detailed pathologic analysis of 344 radical prostatectomy specimens with the intent of quantifying the incidence and median extent of SV involvement.[61] Among high-risk patients, 27% demonstrated SV positivity. The median SV length was 3.5 cm and median length of SV involvement was 1.0 cm. In the entire patient population, only 7% of patients had SV involvement beyond 1.0 cm. Similar analyses performed by other investigators have shown concordant findings.[62,63] While Kestin's work further promulgated the notion that SV involvement may not be adequately treated with standard implant, it also suggested that treatment of the entire seminal vesicle length may not be necessary.

From a technical standpoint, it is difficult to implant portions of the SV that extend cephalad from the base of the prostate. Seeds deposited in or near the more distal portions of the SV tend to bunch up or migrate. That being said, some groups have documented success implanting the proximal regions of the SV (Figure 3).[61,64] The Mount Sinai group reported on a series of 15 patients with positive SV biopsies treated with supplemental EBRT in combination with implantation of the prostate and proximal SV. They demonstrated that SV implantation is feasible and results in higher doses to the SV than that reported with implantation of the prostate alone. The authors concluded that although dose distribution with this technique was variable, these doses, in combination with supplemental EBRT, offer a reasonable likelihood of controlling SV disease. In a separate publication from the Mount Sinai group, Stock and colleagues reported a 7-year freedom from PSA failure of 67% among patients with biopsy-confirmed SV disease treated with the above-mentioned technique.[22]

Although these results are suboptimal in comparison to the general high-risk population treated with brachytherapy, they do compare favorably with other local treatment modalities. Swanson et al recently reported their outcomes among patients with SV involvement who underwent RP.[65] The 5-year rate of biochemical control ranged from 10% to 47%, depending on margin status and the presence of extracapsular extension. Swanson's group also identified SV involvement as the biggest single predictor of recurrence, with 73% of all patients with SV involvement exhibiting disease recurrence.

These high rates of failure with SV involvement are also observed at other centers of excellence. The reported 10-year failure rate in the Johns Hopkins surgical series was 70% and the 5-year failure rate in the M.D. Anderson series was 61%.[66,67] It is not routine for most radiation oncologists to biopsy the SV prior to commencing definitive therapy, and to our knowledge there are no published outcomes for biopsy-positive SV patients treated with EBRT and ADT. Based on the poor outcomes observed among high-risk patients treated in the large cooperative trials, it is unlikely that EBRT alone will cure SV-positive disease.[68-70] Further studies are needed to optimize the treatment strategy in this challenging subset of high-risk patients.
These results are particularly impressive when considering that the majority of implants were performed in an era where the optimization of implant dosimetry had not been fully realized. The eventual leveling of the Kaplan-Meier curves in the SPI series suggests durable disease control. This outcome is in contrast to contemporaneous trials using EBRT and ADT, where there is no plateau reached, suggesting delay in disease progression rather than cure.[68,70]

Modern brachytherapy trials continue to demonstrate excellent clinical outcomes. Dattoli et al recently reported their long-term biochemical control rates among 124 National Comprehensive Cancer Network (NCCN) high-risk patients treated with supplemental EBRT to the pelvis and interstitial brachytherapy (103Pd, 80–90 Gy) with or without ADT (median duration, 4 months). The 14-year freedom from biochemical progression among these patients was 72%.[15] As referenced earlier, the Mount Sinai group have reported a 7-year freedom from PSA failure of 83% with aggressive trimodality therapy consisting of brachytherapy implant, supplemental EBRT to the prostate/SV (median dose, 45 Gy), and 9 months of ADT.[11] Merrick and colleagues have previously reported their 5-year biochemical outcomes for high-risk patients treated with a multimodal approach.[16] With longer follow-up and larger numbers of patients, excellent biochemical control rates continue to be observed using a combination of brachytherapy implant and supplemental EBRT, with or without ADT.[14] The 10-year actuarial biochemical progression-free survival in this series was 86.6%.

Despite excellent biochemical control rates with brachytherapy, many continue to recommend EBRT with concurrent and adjuvant ADT as the standard of care for high-risk prostate cancer patients.[7] This prevalent recommendation is based on tradition rather than rigorous examination of the data. With varying definitions of both biochemical failure and high-risk disease, it is difficult to make direct comparisons between local treatment modalities. In fact, some would legitimately argue that the cooperative external-beam studies have included the most unfavorable subset of high-risk patients. Nevertheless, most modern data would suggest that a regimen of brachytherapy combined with supplemental EBRT offers a therapeutic advantage over EBRT alone (Table 1). In fact, the data would suggest that the 10-year biochemical control rates with brachytherapy are comparable and in some cases superior to the 5-year biochemical control rates obtained with EBRT. This likely relates to the high nominal doses attainable with interstitial implant as compared with EBRT. In addition, unlike EBRT, brachytherapy dose is not affected by prostatic motion.[73-75]

The divergence in biochemical outcome is even more pronounced when comparing outcomes between brachytherapy and prostatectomy (Tables 2 and 3, Figures 4 and 5). With few exceptions, the biochemical control rates among high-risk prostate cancer patients treated with RP are poor. These inferior control rates have led to the false understanding that high-risk patients are destined to fail after definitive local therapy and are the driving force behind many of the current chemotherapy-based trials.[1,2,84,85] Cancer treatment should undoubtedly involve a multidisciplinary approach, and any effort to improve therapeutic efficacy is laudable. That said, cytotoxic therapies are themselves destined for failure in the absence of effective locoregional therapy. This has been borne out in some of the published phase II trials using neoadjuvant taxane-based chemotherapy followed by prostatectomy. Among nonmetastatic, high-risk prostate cancer patients treated with this regimen, Prayer-Galetti et al reported 5-year PSA-recurrence free survival of only 40%, with over 90% of SV-positive patients failing biochemically.[86]

Given the excellent biochemical control rates obtainable with brachytherapy and supplemental EBRT, it is our opinion that future research efforts should be directed at optimization of local therapy. Indiscriminate treatment of all high-risk patients with neoadjuvant chemotherapy is likely of marginal benefit. Furthermore, such regimens subject patients to unnecessary levels of treatment-related toxicity. Clark et al report a 28% incidence of grade 3 toxicity among patients treated with a neoadjuvant regimen of estramustine (Emcyt) and etoposide.[87]

While brachytherapy results are encouraging, a number of important questions remain unanswered. Is supplemental EBRT necessary, and if so, should fields cover the prostate only or the whole pelvis? Does ADT offer benefit in combination with brachytherapy, and if so, what is the optimal duration of therapy? Future trials should be designed to answer these important questions. Indeed, some groups are already making strides in this direction.[14,88]

**Conclusions**

Despite strong evidence to suggest otherwise, many continue to maintain that high-risk prostate cancer is not curable with locoregional therapy, calling instead for more aggressive systemic therapies.[1,2,84-87] Presumably, this misconception stems largely from the suboptimal published outcomes with EBRT and RP.[50,53,68,70,76-79,82,83] Based on the aforementioned data, we
content that high-risk, localized prostate cancer is largely curable with an aggressive locoregional approach that incorporates interstitial brachytherapy as the cornerstone of treatment. Further studies are necessary to determine the optimal combination of brachytherapy with other adjunctive therapies such as external-beam radiation therapy and androgen deprivation therapy.

This article is reviewed here:

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Possible Selection Bias and Lack of Mortality Endpoints Prevent Conclusions About New Standards of Care
High-Risk Prostate Cancer: The Rationale for Brachytherapy

References:

43. Merrick G, Butler W, Dorsey A, et al: Seed fixity in the prostate/periprostatic region following...
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