Counterpoint: Is there a need for supplemental XRT in intermediate-risk prostate cancer patients?

Nelson N. Stone1,2,*

1Department of Urology, Mount Sinai School of Medicine, New York, NY
2Department of Radiation Oncology, Mount Sinai School of Medicine, New York, NY

Introduction

Permanent brachytherapy has become an accepted modality for treating localized prostate cancer. Low-risk disease can be managed with seed implant monotherapy and high-risk disease with a combination of seeds and external beam radiotherapy (EBRT) with or without hormone therapy (HT). Treatment of the intermediate-risk group (IRG) remains controversial. Is monotherapy or combination treatment the best option? To make the case for monotherapy adequate radiation dose needs to be delivered. In addition to cancer control, differences between monotherapy and combination therapy in morbidity, secondary cancer (SC) risk, and costs also need to be addressed.

Disease extent

The current version (1.2013) of the NCCN guidelines defines an intermediate-risk prostate cancer as stage T2b-c or Gleason score 7 or a prostate specific antigen (PSA) 10–20 ng/mL (1). Furthermore, these guidelines recommend image-guided radiotherapy (IGRT) with or without brachytherapy. They do not recommend brachytherapy alone. The National Cancer Comprehensive Network (NCCN) IR grouping incorporates a diverse disease spectrum. Furthermore, it does not consider how radiation dose might influence outcomes. The Mount Sinai treatment stratification was developed for brachytherapy and was based on biochemical recurrence data (2). Patients were designated as intermediate risk if they had one intermediate-risk feature and high risk if they had two or more. Zelefsky’s classification is very similar (3). Based on this categorization, patients had been offered monotherapy if they had only one IRG feature and combination therapy if more than one. D’Amico also developed a similar classification based on radical prostatectomy and radiation data (D’Amico) (4). Given that these classification systems were developed over 15 years ago, treatment improvements may have made them obsolete. For example, the Mount Sinai system was described just when the first studies on dosing data became available and thus may or may not be applicable today where higher doses are more commonly delivered (5).

Dose response in intermediate-risk disease

Stock et al. (5) first described a dose response in permanent brachytherapy using CT-based dose–volume histogram data and demonstrated that a post-implant D90 of at least 140 Gy (I-125, TG43) increased PSA control. As techniques improved, implant D90 and V100 have risen, giving brachytherapists the opportunity to evaluate the effects of higher doses in all risk groups. For example, using the Mount Sinai treatment stratification in IRG prostate cancer, Kao et al. (6) reported a 5-year biochemical disease-free survival (ASTRO definition) of 92.8% when patients received an I-125 implant with a D90 of at least 180 Gy. Taira et al. (7) reported on 144 IRG patients defining this group as having only one of the following: Gleason score of 7, PSA level of 10.1–20.0 ng/mL, or clinical stage of T2c. Patients were treated with either Pd-103 (prescription 125 Gy) or I-125 (prescription 145 Gy) monotherapy. The 12-year bRFS (PSA ≤ 0.4 ng/mL after nadir) for IRG was 96.4%. The biochemical performance-free survival rate for patients with high-quality implants was 98.3% vs. 86.4% for those with less adequate implants (p < 0.01) (Table 1).

In 2006, Stock et al. (8) described the biologic effective dose (BED) as a means to compare outcomes when implant or implant plus EBRT was used. Using this methodology, Ho et al. (9) reported on freedom from biochemical failure (FFbF) in IRG patients. The actuarial FFbF at 10 years was 86%. Dose (BED <150 vs. ≥150 Gy2) was
the only significant predictor of FFbF ($p < 0.001$). None of the other variables (PSA, EBRT, Gleason score, treatment type, hormones, stage, and number of risk factors) was found to be a statistically significant predictor of 10-year FFbF. Patients receiving the lower dose had a 63% FFbF compared with 92% for the higher dose ($p < 0.001$). With similar BED calculations, Stone et al. (10) described the biochemical freedom from failure (bFFF) in multicenter investigation of brachytherapy outcomes. Using NCCN IRG classification, the 10-year Phoenix bFFF for IRG was 63.6%. Based on three dose groups, $<140$, $140–200$, and $>200$ Gy, bFFF was 52.9%, 74.1%, and, 94.3%, respectively ($p < 0.0001$). Both BED and EBRT (combination therapy) were the only significant variables in the proportion hazards model. The use of neoadjuvant HT did not influence the results (Table 2).

A recent update from the Mount Sinai Database identified 690 men categorized by the new NCCN criteria as IRG and followed a minimum of 2 years (median; 7.2; range, 2–19 years) (17). Of these 690, 500 had one IRG risk feature, 187 had two and, three had three features. Implant only was used in 310 and combination therapy in 380. HT was used in 478/690 (69.2%) for a median of 6 months. The 10-year bFFF (Phoenix) for the entire cohort was 88.3%. On log rank and cox proportion hazard rates, the use of HT, EBRT, and NCCN IRG sub-classifications (1–3 features) were not significant predictors of Phoenix failure. When dose data were dichotomized to $\leq 180$ vs. $>180$ Gy $bFFF$ was 80.8% vs. 91.6% ($p = 0.001$; hazard rate, 2.87; 95% confidence interval, 1.5–5.4).

### Morbidity

Patients who receive combination therapy may have a greater risk of complications compared with those IRG patients treated by monotherapy. The “trifecta” for brachytherapy patients should be freedom of biochemical relapse, sexual, and bowel dysfunction. Merrick analyzed 425 patients who underwent brachytherapy alone or in combination with EBRT (18). With a 6-year followup, 39% of patients maintained potency after prostate brachytherapy.

The preimplant potency score, use of supplemental EBRT, and diabetes had a negative impact on potency preservation. The addition of EBRT decreased potency from 52.0% to 26.4% ($p < 0.001$). Wu et al. (19) analyzed 2204 CaPSURE men who received treatment for prostate cancer. 246 patients received brachytherapy alone and 61 patients had brachytherapy with EBRT. At 20-month followup, sexual function was slightly worse with combination therapy. Snyder evaluated 1063 potent men with T1–T3 prostate cancer who were treated from 1990 to 2007 with seed implantation alone (69.6%) or combined modality treatment (30.4%). Patients were required to have a minimum of 2-year followup and to be off androgen deprivation therapy (ADT) for a minimum of 1 year (20). Erectile function was assessed before seed implantation and at each followup visit using the physician-assigned Mount Sinai Erectile Function Score. The 5-year and 10-year actuarial rate of potency preservation was 68.0% and 57.9%, respectively. Five-year potency was 76.4% for implant alone, 71.0% for implant with EBRT, 62.2% for implant with ADT, and 57.9% for implant with EBRT and ADT ($p < 0.001$).

The addition of EBRT to brachytherapy can increase the total radiation dose to the anterior rectal wall. Sarosdy reported on 177 consecutive patients who underwent either brachytherapy (56.5%) or combination therapy for clinical T1–T2 prostate carcinoma between July 1998 and July 2000. All the patients were analyzed with regard to disease characteristics, treatment details, and complications requiring unplanned interventions up to 48 months of followup (21). Colonoscopy with or without fulguration for rectal bleeding was performed in 37 men at a median of 17 months, including 15 patients after brachytherapy and 22 patients after combination therapy ($p = 0.002$). Combination therapy resulted in fecal diversion in 6.6% of patients ($p = 0.021$). Merrick mailed 189 prostate brachytherapy patients the Rectal Function Assessment Score (22,23). Patient perception of overall rectal quality of life was inversely related to the use of supplemental EBRT ($p = 0.007$). Tran determined rectal complications in 503 men randomized between 125I vs. 103Pd alone ($n = 290$) or to 103Pd with 20 vs. 44 Gy supplemental EBRT ($n = 213$). In a multivariate analysis, the rectal volume that received $>100\%$ of the dose was significantly

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Intermediate-risk group</th>
<th>PSA failure definition</th>
<th>Free of failure (%)/time (y)</th>
<th>Median followup (mo)</th>
<th>Median or mean $D_{90}$ (Gy)</th>
<th>bFFF dose dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelefsky et al. (11)</td>
<td>47</td>
<td>NCCN</td>
<td>ASTRO</td>
<td>89/5</td>
<td>63</td>
<td>173</td>
<td>No</td>
</tr>
<tr>
<td>Dallas et al. (12)</td>
<td>94</td>
<td>NCCN</td>
<td>Phoenix</td>
<td>97/NS</td>
<td>30</td>
<td>177</td>
<td>NS</td>
</tr>
<tr>
<td>Taira et al. (7)</td>
<td>144</td>
<td>NCCN</td>
<td>$\leq 0.4$</td>
<td>96.4/12</td>
<td>74</td>
<td>116.3$^a$</td>
<td>98.3/86.4%$^a$</td>
</tr>
<tr>
<td>Henry et al. (13)</td>
<td>430</td>
<td>MSKCC (4)</td>
<td>Phoenix</td>
<td>73.5/10</td>
<td>58</td>
<td>140</td>
<td>87/77%$^b$</td>
</tr>
<tr>
<td>Kao et al. (6)</td>
<td>113</td>
<td>NCCN</td>
<td>Phoenix</td>
<td>92/85</td>
<td>80</td>
<td>197</td>
<td>Minimum dose 180 Gy</td>
</tr>
</tbody>
</table>

MSKCC = Memorial Sloan Kettering Cancer Center; NS = Not Stated.

$^a$Prescription, I-125 145 Gy and Pd-103 125 Gy, greater or less than 116% prescription.

$^b$Dose dependence greater or less than 140 Gy, entire cohort of 1298 patients.
predictive of bleeding. Rectal fistulas occurred in two patients (0.4%), both of whom had received moderate rectal radiation doses and extensive intervention for rectal bleeding. In a long-term study of complications following brachytherapy, Stone also found that the incidence of late rectal bleeding was associated with greater prostate radiation doses \(p = 0.023\) (24).

Higher radiation doses can also affect urinary function, potentially increasing the risk of outlet obstruction and incontinence. Merrick et al. (25) did not find that the addition of EBRT increased dysuria. However, in a study where implant patients were compared with controls (no radiation), supplemental EBRT adversely affected function and incontinence (26). In a study of 1932 men who had the International Prostate Symptom Score assessed before implant and out to 10 years, the addition of EBRT was found to significantly increase the score \(p = 0.011\) within the first 2 years after implantation but not after that (27). Sarosdy (21) found an increased need for TURP, documenting the procedure in 14.5% of patients after combination vs. 5% for implant alone \(p = 0.029\). Postimplant transurethral resection of the prostate (TURP) greatly increases the risk of urinary incontinence. Kollmeier et al. (28) reported TURP in 38/2050 implant patients (2%) and found seven (38%) with incontinence. There was no significant correlation between incontinence risk based on the dose to 90% of prostate volume \(p = 0.32\) or the dose to 30% or 5 cm\(^2\) of urethral volume \(p = 0.30\).

**Secondary cancers**

Radiation therapy (RT) may be associated with a small increased risk of in field SCs. Inherently, the risk may be greater for combination therapy vs. monotherapy because of the larger volume treated. Abdel-Wahab et al. (29) reviewed the 1973–2002 Surveillance, Epidemiology, and End Results database and stratified patients into four groups. He identified 67,719 patients who had undergone RT only and 40,433 patients who had not undergone RT or surgery (Group 1, no RT, no surgery). EBRT (Group 2) was the most common RT modality and was given to 48,400 patients. Brachytherapy alone (Group 3) or in combination with EBRT (Group 4) was given to 10,223 and 9096 patients, respectively. The overall incidence of secondary primary cancers was 8.8% in patients who had received RT alone and in 7.9% patients who did not undergo RT. Among the RT groups, the greatest percentage (10.3%) of secondary primary cancers was seen in the EBRT (Group 2), followed by Group 4 (combination) at 5.7%. The lowest percentage was in the brachytherapy (Group 3) at 4.7%. All differences were statistically significant. On the other hand, Zelefsky et al. (30) found no increase in SC in 2658 patients treated with radical prostatectomy \(n = 1348\), EBRT \(n = 897\), or brachytherapy \(n = 413\).
 Costs

There is little controversy that EBRT (IMRT) is costlier than brachytherapy. Shah et al. (31) compared the costs of permanent brachytherapy, high dose radiotherapy, and IMRT and found reimbursement at $9938, $17,514, and $29,356, respectively. Nguyen et al. (32) assessed temporal trends in utilization and impact on national health care spending for the different treatments for prostate cancer from 2002 to 2005. For EBRT, IMRT utilization increased substantially (28.7% vs. 81.7%; p < 0.001), and for men receiving brachytherapy, supplemental IMRT increased significantly (8.5% vs. 31.1%; p < 0.001). The mean incremental cost of IMRT vs. 3D-CRT was $10,986 (in 2008 dollars); of brachytherapy plus IMRT vs. brachytherapy plus 3D-CRT was $10,789. Cooperberg et al. (33) performed a cost utility analysis for the different treatments. Direct medical and lifetime costs for brachytherapy compared with combination were $14,106 vs. $29,142 and $32,553 vs. $43,553 (p < 0.001).

 Conclusions

Brachytherapy alone seems to be as effective as combination therapy in treating intermediate-risk prostate cancer. While most data support the use of implant alone, delivered radiation doses should be >140 Gy (I-125). Long-term data suggest that BED may need to be greater than 180 Gy2 (I-125 O190 Gy). The addition of EBRT may increase rectal toxicity, erectile dysfunction, and risk of incontinence. The cost of treatment is markedly increased when combination therapy is used. Brachytherapists should consider implant alone as the preferred management option for intermediate-risk prostate cancer.

 References


