Three-Dimensional Conformal External Beam Radiotherapy or Brachytherapy: Which is the “Best Alternative” to Radical Prostatectomy?

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In this issue of CA—A Cancer Journal for Clinicians, the reader finds two articles that make compelling arguments for defining the “best alternative” to a radical prostatectomy. Horwitz and Hanks1 eloquently describe the use and advantages of state-of-the-art three-dimensional conformal radiation therapy (3DCRT). Likewise, Ragde et al2 explain why there is so much excitement around the use of modern brachytherapy. Among radiation oncologists, there is no consensus as to which of these two options is best, although among patients, there is a growing belief that “getting seeds” is better than external beam radiotherapy.

Among urologists, neither radiation option is generally considered as good as surgery. This belief is changing, however, and in recent years there has been a surge in interest and enthusiasm for brachytherapy among urologists. As Dr. Ragde points out, some expect that this approach may one day surpass radical prostatectomy in popularity. Some argue that this trend is due to improved effectiveness of brachytherapy while others believe it simply represents an attempt by urologists to “hold on to their patients.”

Is there a rational way to resolve this controversy? As a prostate cancer researcher who has been studying and using both of these radiation approaches for more than 10 years, I have concluded that the answer is maybe.

“The Best Alternative?”

Before discussing the relative merits of each of these approaches, it is important to clarify that the phrase “Best Alternative” not be understood as implying that either is an inferior or second-choice therapy. Neither of these approaches should be considered a “back-up quarterback,” brought in only when “the starter goes down.” Rather, both of these approaches should be viewed as real options much the way ordering a good California Zinfandel is an option to ordering a good Oregon Pinot Noir. It is a matter of personal taste. The lack of consensus on the matter of surgery versus radiation suggests that “the jury is still out” and is likely to remain “hung” on this matter. For a growing number of patients, surgery is being viewed as an alternative to radiation!

Survival as the Real Endpoint

If either external beam radiation or brachytherapy were clearly the best alternative for all men with clinically organ-confined prostate cancer, I would not use both and I would certainly explain my rea-
sons to my patients. I view both approaches much the way an artist might view using oil, acrylics, or charcoal: Any of these media could be used to create a beautiful image. In a similar fashion, various forms of radiation can be used to generate desirable dose distributions. When high doses are placed in just the right places (where we believe the tumor is likely to be), disease control is much more likely. When placed appropriately, high-dose radiotherapy delivered by external or internal means can cure and not harm. On the other hand, when high doses are placed a little less precisely (0.5 cm or more away from where we would like them to be), they may cause great harm and not cure. Which medium to use depends on the artist and the eye of the beholder.

A more objective endpoint would be survival. Most analyses of the relative merits of these two local radiotherapy modalities to date have focused on the estimated risk of treatment failure, defined as “a rising” prostate specific antigen (PSA), but the true “gold standard” should always be survival. In the case of prostate cancer, I tend to favor disease-specific survival. This allows us to apply lessons learned from older men to younger men.

As screening and early detection efforts are increasingly implemented, and men are younger and younger at the time of diagnosis, competing causes of death become less relevant. The good news about either local radiotherapy modality is that based on the long-term studies reported by the Radiation Therapy Oncology Group, when matched by T-stage and Gleason scores, survival rates at five, 10, and 15 years appear to be comparable to those expected with radical prostatectomy. Firm conclusions about the relative merits of various treatment options are complicated by the fact that early detection of prostate cancer in men with very favorable disease means that we will have to wait a long time to use mortality as the major endpoint in contemporary patients. The early use of hormonal therapy is also likely to further compromise our ability to detect survival differences, if they exist.

**Factors Favoring 3DCRT**

Fewer patients are suitable candidates for brachytherapy than for 3DCRT due to factors such as prostate volume, pubic arch interference, large defects due to transurethral prostatic resection, and the presence of extra-capsular extension. Moreover, 3D technology is applicable to a wide variety of other cancer sites. Prospective randomized trials, as well as retrospective multi-institutional trials, demonstrate that use of this technology is feasible and associated with less toxicity than conventional radiotherapy.

According to data from a single institution, in low-risk patients, outcomes were similar with both radiation modalities, but urinary morbidity was worse for those who had undergone brachytherapy. Other investigators reported that while outcomes were similar in low-risk patients regardless of treatment option, those with intermediate or high-risk disease fared better with external beam radiotherapy. The arguments for 3DCRT are made even stronger by the fact that two studies demonstrated a better outcome with external beam radiotherapy, despite the use of conventional techniques and doses. Indeed, many of the retrospective studies outlined by Horwitz and Hanks in this issue of CA suggest that the results would even be better with high-dose 3DCRT. Only a prospective randomized trial will prove which of these approaches is superior.

**Factors Favoring Prostate Brachytherapy**

The proponents of 3DCRT argue that higher radiotherapy doses are better. None of the published series using
3DCRT deliver doses approaching those associated with prostate brachytherapy. With a target dose of 14,400 cGy, half of the prostate frequently receives 20,000 cGy or more. Thus, if it is true that in this case “more is better,” it follows that brachytherapy should be more effective.

Another argument in favor of prostate brachytherapy stems from the finding that the PSA nadirs tend to be lower after treatment with seed implantation. As numerous retrospective 3DCRT series suggest that a higher PSA nadir after treatment is a major predictor of subsequent biochemical failure, it would seem reasonable to assume that a therapy associated with lower nadirs may be more effective.

### Remaining Questions; Unresolved Issues

What about these arguments? None of the studies comparing prostate brachytherapy with external beam radiotherapy address the quality of the seed implants. None address the so-called PSA “blip”—a transient rise in PSA observed more frequently after brachytherapy—that occurs at six months to three years after treatment. Peak responses (nadirs) with external beam radiotherapy typically occur after 18 to 24 months, while brachytherapy nadirs tend to occur later (median, about 41 months). None of the comparisons of external beam radiotherapy and brachytherapy address this issue.

Although prostate brachytherapy may be more morbid if not well done, it is sometimes amazingly well tolerated. In my experience, my happiest patients have had seed implants and my most unhappy patients have had implants!

Some of the arguments that favor prostate brachytherapy are on “shaky ground.” First, we do not know the shape of the dose-response curve. Based on pooled data reported from the University of California, San Francisco and the University of Michigan, we believe the dose response after 3DCRT—as well as after Intensity Modulated Radiotherapy—may be flat above a maximum dose of 78 Gy. If this is the case with external beam radiotherapy, it may also apply in the brachytherapy setting. Thus, the higher doses of radiation delivered with brachytherapy may not be beneficial. Furthermore, the observation that PSA nadirs tend to decrease more after brachytherapy may simply reflect the death of more normal prostate tissue.

Earlier, I observed that treatment with external beam radiotherapy resulted in similar survival rates as radical prostatectomy. Neither of these radiation approaches yields undetectable PSA rates as often as radical prostatectomy does. Nevertheless, achieving an undetectable PSA does not change the fact that many such patients fail. Thus, delivering a higher radiation dose and obtaining a low PSA nadir do not prove that seed implantation is a better treatment.

### Practical Considerations

How do I choose which approach to use on a given patient? In most cases, I don’t. Patients frequently come to see me convinced that they know the “right thing” to do. Since I don’t know the right thing with any certainty, and the patient might be right, I don’t generally try to talk him out of it—unless he is not medically eligible for the type of treatment he prefers. If the patient does well, we are both happy. If he doesn’t, he can share the responsibility with me.

If the patient has no biases, I discuss the options with him and his family in detail and encourage them to decide together. If forced to make the decision for them, I generally favor more aggressive, albeit potentially toxic, therapy for the younger patient. My rationale is that I’m willing to take more risk in a patient who is more likely to survive other causes of
death. This usually involves seed implantation alone in the most favorable patients and a combination of brachytherapy with external beam radiotherapy for patients with high-risk features. For older, patients or those who are not comfortable with risk, I tend to avoid brachytherapy. I’d rather not put them at risk for a more serious complication if competing causes of death are likely to get them anyway.

**Conclusions**

I don’t know which radiotherapeutic approach is better—no one does. Even if a subset of patients might do better with one approach, a different subset might do better with the other approach. In other words, what is best for one patient may not be best for another. What is best in the hands of an expert might be worst in the hands of a novice.

Radiotherapy is an art form. By way of analogy, a crayon in the hands of a great artist can result in a great creation, but even the finest art supplier in the world cannot help someone lacking in artistic vision.

Both groups of investigators writing in this issue of *CA* (Horwitz and Hanks and Ragde et al) present compelling data suggesting that they can cure some men with prostate cancer. I am hopeful that some day the relative merits of each of these approaches will be more obvious to us all. In the meantime, as my father used to tell me, “Whatever you do, do it well.”

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