Radical Radiotherapy for Prostate Cancer Is the ‘Only Way To Go’

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In 2008, approximately 186,000 American men were diagnosed with prostate cancer, resulting in about 28,600 deaths.[1] It is the most commonly diagnosed cancer, and second only to lung cancer as the leading cause of cancer death in men.

ABSTRACT: Management options for localized prostate cancer include radical prostatectomy (RP), radiation therapy (external-beam radiation therapy [EBRT] or brachytherapy), with and without androgen-deprivation therapy (ADT), or active surveillance, also known as watchful waiting. Ultimately, the choice of treatment is determined by a variety of factors, including institutional preference, individual physician judgment, patient preference, and resource availability. In this editorial, we make the case for radiation therapy (EBRT or brachytherapy) as the management modality of choice for localized prostate cancer.

In 2008, approximately 186,000 American men were diagnosed with prostate cancer, resulting in about 28,600 deaths.[1] It is the most commonly diagnosed cancer, and second only to lung cancer as the leading cause of cancer death in men. The most effective therapy for a man with clinically organ-confined disease is not clear. In fact, it would be reasonable to hypothesize that standard local options for treatment are all equally effective at achieving local control. Management options include radical prostatectomy (RP), radiation therapy (external-beam radiation therapy [EBRT] or brachytherapy), both with and without androgen-deprivation therapy (ADT), or active surveillance, also termed watchful waiting. [Editor's Note: For a finer distinction between active surveillance and watchful waiting, see “Active Surveillance for Low-Risk Localized Prostate Cancer” by Drs. Michael Large and Scott Eggener in the October issue of ONCOLOGY.]

Many issues must be considered in choosing from among these treatments. The stage distribution and age at which men are diagnosed with the disease have changed over time. Perhaps as a result of widespread screening with prostate-specific antigen (PSA), prostate cancer is increasingly diagnosed in younger men and at an earlier disease stage, when the tumor is confined to the prostate and potentially curable.[2,3] As a result, there has been a marked increase in the number of men undergoing curative-intent local treatment for early-stage disease.[4,5] Whether this has been accompanied by improved survival is controversial.

Comparing Treatment Outcomes

In June 2004, the US House of Representatives adopted a resolution encouraging doctors to inform their prostate cancer patients of all of the proven treatment options available. According to the resolution, the Federal and State governments should ensure that health-care providers supply prostate cancer patients with appropriate information and any other tools necessary to receive readily understandable descriptions of the advantages, disadvantages, benefits, and risks of all medically efficacious treatments.[6]

Ultimately, the choice of treatment is determined by a variety of factors, including institutional preference, individual physician judgment, patient preference, and resource availability. In this editorial, we will make the case for radiation therapy (EBRT or brachytherapy) as the management modality of choice for localized prostate cancer. Modern PSA-based series suggest that outcomes are similar with RP and EBRT when men with clinically localized prostate cancer are stratified equally for pretreatment serum PSA, tumor (T) stage, and Gleason score, as long as adequate RT doses are administered.[7,8]

The two most common treatments for clinically localized prostate cancer are EBRT and RP. A randomized trial comparing these two approaches for men with clinically localized prostate cancer has not been performed in the modern era. Thus, published observational series provide the only available data comparing outcomes. However, these data are fraught with bias. Young, healthy men
are typically encouraged to undergo RP, whereas older patients tend to be steered toward RT or observation, thereby skewing study interpretation. Notably, guidelines from the American Urological Association (AUA) and National Comprehensive Cancer Network (NCCN) do not claim a cancer control superiority to either surgery or radiotherapy based on existing data and consensus.[12,13] As famed urologist Patrick Walsh has said, “patients with localized prostate cancer now clearly have two good options for treatment: surgery and radiotherapy.”[34]

**That was then... this is now**

Over the past decade, two concepts have emerged that have led to better outcomes in men undergoing RT for prostate cancer: dose escalation using newer higher conformal techniques (intensity-modulated radiation therapy, or IMRT), and combined-modality treatment with ADT. These and other technical advances in RT delivery, coupled with earlier diagnosis, have led to steadily improving outcomes with RT over the past 2 decades—with respect to both tumor control and morbidity.

**Impact of Dose**

RT techniques are now being used to increase the delivery of radiation to the target volume while sparing adjacent normal tissues. This has allowed escalation of the RT doses to the prostate gland above 72 Gy, compared to significantly lower doses used in earlier studies.[9,10] IMRT has had the most meaningful impact on dose escalation. IMRT allows higher doses to the prostate that are achievable with a reduced volume of irradiated normal bladder and rectum compared to three-dimensional conformal radiotherapy (3D-CRT). Because higher doses of radiation improve the oncologic outcome in men with both localized and locally advanced disease (see below), IMRT treatment planning is preferred over conventional EBRT.[11]

Data from retrospective analyses suggest that these technical improvements translate into decreased rates of local failure and distant metastases, as well as better overall survival.[14-16] One illustration of this was an analysis of 1,465 men treated in four randomized trials conducted by the Radiation Therapy Oncology Group (RTOG), in which one of the treatment arms was EBRT alone.[15] RT doses > 66 Gy were associated with a 29% lower relative risk of death from prostate cancer compared to lower doses. In addition, at least five randomized trials have directly addressed the issue of dose escalation, all of which demonstrated better clinical and/or biochemical failure-free survival with doses ≥ 70.2 Gy.[17-20]

None of these trials have established a survival benefit. However, RTOG 0126, a large randomized dose escalation trial that is powered to detect a small survival benefit, recently completed accrual. Given the recent positive trial of radiotherapy showing a survival benefit for men with high-risk localized disease, there is optimism about the benefit that may be seen in the intermediate-risk patients treated in the RTOG 0126 trial. Although it is feasible to administer doses in excess of 81 Gy using these techniques, whether doses above 78 to 79 Gy provide added benefit (particularly for men with low-risk disease) remains controversial.[21]

**Impact of Hormones**

A number of randomized trials have demonstrated that adding ADT to definitive RT improves outcomes. Most administered ADT before and/or during RT (neoadjuvant), but some gave it only upon completion of RT (adjuvant). One of the most important clinical trials that illustrated the benefit of ADT was RTOG 8610, where 471 men were randomly assigned to RT with or without goserelin (Zoladex) plus flutamide.[22] ADT was administered for 2 months before and 2 months during RT. At a median follow-up of 12.5 years, ADT significantly decreased the rates of disease-specific mortality, distant metastases, and biochemical failure (23% vs 36%, 35% vs 47%, and 65% vs 80% with and without ADT, respectively) while increasing the rate of disease-free survival (11% vs 3%).[23] Overall survival was improved at 10 years (43% vs 34%), although this difference was not statistically significant (P = .12). At 10 years, the increase in deaths from cardiovascular disease was not statistically significant (12.5% vs 9.1% without ADT, P = .32).

Although concerns have been raised about a possible increase in genitourinary and gastrointestinal toxicity due to neoadjuvant ADT, this was not supported by a combined analysis of 2,922 men with high-risk or locally advanced prostate cancer treated in three RTOG trials (85-31, 86-10, 92-02).[24] The addition of neoadjuvant ADT was associated with a decrease in the overall incidence of late grade 3 toxicities compared to RT alone (hazard ratio [HR] = 0.54, 95% confidence interval [CI] =
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0.39–0.74 for short-term ADT, and HR = 0.77, 95% CI = 0.62–1.01 with long-term ADT). The analysis showed no evidence of an increase in grade 3 or higher genitourinary, gastrointestinal, or other toxicity with either short- or long-term ADT.

The improvements in cancer-specific and overall survival seen with combined ADT plus RT represent an important step forward, and have led to the adoption of this approach rather than RT alone as the standard of care for men undergoing RT for cT3 disease. However, whether the results from ADT plus RT are better than can be achieved by RP is unclear; no contemporary multi-institutional randomized trials have been conducted.

Radiation Therapy vs Surgery

In retrospective series of men with clinically localized disease, cure rates with EBRT appear to be comparable to those after RP, at least for the first 5 to 8 years.[25-28] However, such comparisons are difficult because men undergoing EBRT tend to be older and less medically fit, and they are not typically pathologically staged. Furthermore, late recurrences can occur after EBRT, since the tumor may not be completely destroyed. As a result, some argue that 10 years or more after treatment, the outcome with EBRT may not be as favorable as with RP.[29]

However, the percentage of men with late recurrences after RT is small, and late recurrences can also occur after RP. In addition, the available data on this issue using modern RT techniques (sufficient doses, concomitant ADT) are limited. Thus, the issue of whether long-term results are inferior after RT as compared to surgery remains unresolved.

One of the more useful comparisons of the various modalities was published in 2004 by Kupelian and associates. This was a retrospective analysis of 2,991 men treated at three institutions for clinically localized disease. Men were treated with either RP, EBRT, or brachytherapy. The study concluded that biochemical relapse-free survival rates were similar with all treatments at both 5 and 7 years, as long as EBRT doses were ≥ 72 Gy. The results did not change when men with favorable (low-risk) or unfavorable (intermediate- or high-risk) tumors were considered separately.[30]

In addition, a systematic overview of 13 published case series and three cohort studies concluded that outcomes following brachytherapy were comparable to those after RP in men with favorable-risk tumors (clinical stage T1-T2, Gleason score ≤ 6, and serum PSA < 10 ng/mL).[31]

Comparing the Adverse Effects of RT and Surgery

Given that there are no data offering compelling survival advantages to either RT or surgery, perhaps the deciding factor in determining which modality is superior rests on comparisons of morbidities associated with therapy. In order to quantify treatment-related morbidity, the RTOG has developed physician report–based acute and late morbidity scales.[32] No randomized trials have compared the incidence and severity of complications from RT vs RP. However, several large prospective series of men treated with either modality for clinically localized disease provide valuable information regarding adverse effects.

Sanda and colleagues performed a quality-of-life analysis on 1,201 patients (as well as 625 spouses) at multiple centers before and after brachytherapy, RP, and EBRT. In this analysis, each of the three common therapies showed a unique pattern of changes in quality of life related to urinary symptoms, sexual function, bowel function, and vitality of hormone function. After 24 months of follow-up, it was evident that, relative to baseline status, EBRT and brachytherapy were associated with higher function scores than RP in all categories except bowel function, which had a slightly lower long-term average score. The authors also examined the relationship between quality-of-life changes in their partners and satisfaction with the overall outcome of treatment. Changes in each of the five quality-of-life domains were associated with overall outcome satisfaction among both patients and their partners, particularly with respect to sexual function.[33]

Conclusion

Radical radiotherapy, either alone or in combination with ADT, is the “only way to go” when managing early-stage prostate cancer. The main rationale for this approach is the relative therapeutic equivalence between this strategy and RP.

Considering that outcomes are equivalent, it makes sense to avoid an operation and its potential morbidities when an alternative is available. Historically, the outcomes associated with RT have been considered substandard to those of RP. But given that a very large proportion of patients who
underwent RT were deemed medically unfit for surgery and had a higher number of comorbidities—and given that technologic advances in the field of Radiation Oncology have drastically reduced the common toxicities—it is safe to assume that the information based on older data is fraught with bias, uncertainty, and selection. Having said that, the outcomes associated with RT have remained equivalent to those of RP and will only continue to improve. In light of this, radical radiotherapy is the way to go in the management of localized prostate cancer.

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References:

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