Brachytherapy Boost Techniques for Locally Advanced Prostate Cancer

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Brachytherapy boosts in combination with external-beam radiation therapy allow a highly conformal dose of radiation to be delivered to the prostate in a safe, efficient manner. Several types of brachytherapy boost

Introduction

The management of patients with locally advanced prostate cancer remains a significant therapeutic challenge.[1-13] Although radiation therapy has been the traditional curative treatment option for these patients for the past 2 decades, the ability of standard doses of external-beam radiation alone to cure patients has recently been questioned. Prior to the use of post-radiation prostate-specific antigen (PSA) testing, most studies of radiation therapy for locally advanced prostate cancer reported clinical local control rates in the range of 75% at 10 years.[14] However, recent studies employing PSA monitoring, ultrasound-guided follow-up biopsies, and longer follow-up have made it clear that only 10% to 20% of patients treated with external-beam radiation doses of 65 to 70 Gy are free of recurrence at 5 years.[15,16]

Multiple factors are responsible for the suboptimal control rates reported in the past for locally advanced prostate cancer, but two factors are most important. First, locally advanced cancers are generally bulky tumors that have a statistically lower likelihood for cure with conventional doses of radiation. This is clearly exemplified by studies employing post-treatment biopsies, in which 75% to 80% of patients with increasing PSA levels had persistent disease in their prostate.[17] The inability to cure all of these cancers with conventional external-beam radiation therapy may be related, in part, to regions of hypoxia in these higher-grade, bulkier tumors or, possibly, their inherent radioresistance.

Second, although patients with locally advanced prostate cancer may be judged, both clinically and radiographically to have only locoregional disease, the probability that occult micrometastatic disease exists at the time of diagnosis has been clearly shown in multiple studies.[18,19] As a result, several ongoing trials are investigating whether some of these patients should be treated with systemic therapy (in the form of androgen deprivation) in combination with local treatment.[16,20-25] Already, substantial preliminary data suggest that combined-modality therapy may provide significant improvements not only in local, regional, and biochemical control but also in disease-free and overall survival (Table 1).

Irrespective of the impact androgen deprivation may have on improving various outcome measures, local disease control within the gland still remains a fundamental therapeutic goal. Data from the experience with iodine-125 implants at Memorial Sloan-Kettering Cancer Center indicates that persistent local cancer can lead to dissemination or death in patients whose disease would otherwise have been controlled.[26-28] In recognition of this fact, a series of clinical trials employing several radiotherapeutic techniques have been initiated to address this issue (see below). Central to all of these strategies is the premise that there is a direct relationship between the delivered radiation dose and the probability of tumor control. Both older and more recent data clearly support this concept.

Recent investigations of conformal external-beam radiation therapy,[12,29-34] high-energy neutrons,[7,35,36] hyperfractionated radiation therapy,[37] particle beam therapy,[38,39] and interstitial implants[28,40,41] have all suggested a dose-response relationship of radiation in this malignancy. The challenge facing today’s clinicians is to determine which of these strategies is most applicable when efficacy, cost, convenience, and quality of life are taken into consideration. This review will focus on the various brachytherapy boost approaches that have been developed to treat patients with locally advanced prostate cancer in an attempt to clarify their role in the overall management of this malignancy.
Definition of Locally Advanced Disease

Central to any discussion of the treatment of locally advanced prostate cancer is the issue of what constitutes advanced disease. Unfortunately, no consistent definition has yet been adopted in the literature.[13] This stems, in part, from the recognition that there are multiple critical prognostic factors. In the past, only patients with stage T3 or T4 disease were considered to have locally advanced cancer. Currently, patients with Gleason scores of 7 or higher,[42,43] perineural invasion, or those with serum PSA levels > 10 to 15 ng/mL have also been included in the locally advanced category.[44]

Although less frequently discussed, larger tumor volume (as represented by the number or percentage of biopsy cores with tumor involvement or the number of hypoechoic nodules on ultrasonography) also appears to be a factor that may need to be included in the locally advanced category.[45] All of these factors are considered to be part of the locally advanced spectrum due to poorer outcomes of standard treatment in patients with any of these findings.

Brachytherapy Techniques

Brachytherapy boost techniques can be broadly divided into two categories. The first is the open retropubic technique, which literally involves placing either radioactive sources or afterloading devices into the prostate gland via an open lower abdominal incision under direct visualization. The second technique consists of placing the same sources or afterloading devices transperineally under ultrasound guidance. Regardless of the technique used, sources can either be implanted permanently or temporarily at low- or high-dose rates.

Open Retropubic Technique

The concept that tumor control probability increases with the delivered dose has long been central to the practice of both older and modern brachytherapy techniques. To this end, the open retropubic placement of radioactive seeds was developed with the goal of significantly increasing the central prostatic dose while sparing adjacent normal tissues.

As unimodality therapy, the open retropubic approach did not prove to be highly successful. This was mainly due to the technical shortcomings inherent to the technique, which resulted in the inability to deliver a homogeneous dose of radiation therapy to the gland.[28] However, in combination with external-beam radiation therapy to a larger prostate field, the open retropubic approach has resulted in biochemical control rates that appear to be as good as or better than other forms of therapy in similarly staged patients.[46]

Permanent Implant

The traditional retropubic implant technique pioneered by Whitmore and colleagues at Memorial Sloan-Kettering Cancer Center consisted of a formal retropubic exploration through an extraperitoneal lower abdominal incision, pelvic lymph node sampling, opening of the endopelvic fascia, and mobilization of the prostate from surrounding tissues to allow for easy access of large-gauge trocars.[47] In order to produce a proper dose distribution of radiation, the trocars were placed as parallel as possible throughout the implanted volume so that the sources (radioactive seeds) were homogeneously distributed throughout the prostate gland. Radioactive seeds were then deposited into the trocars using a number of devices specifically designed for this function. The freehand nature of this retropubic implant technique, as well as the rich venous plexus of Santorini, led to imprecise, irregular source placement. The desired target dose was obtained by measuring the prostate intraoperatively and then determining the appropriate spacing of the sources and trocars by the use of a nomogram. Dose was calculated based on the concept of the matched peripheral dose, which is the dose delivered to an ellipsoid volume with the same average dimensions as the prostate. Unfortunately, this concept was inaccurate, since it did not account for the location of the prostate volume relative to the delivered dose. Although the open retropubic approach had relatively low morbidity, poor local control and disease-free survival rates diminished enthusiasm for the technique as unimodality therapy.

Several researchers have continued to use the open retropubic approach, but they combine it with external-beam radiation therapy and employ lower doses (Table 2).[48-54] The impetus to continue this technique was the belief that even though the implant might produce an inhomogeneous dose throughout the prostate, it still was capable of delivering a highly conformal boost dose to most of the gland. By adding external-beam radiation therapy to the implant, periprostatic and intraprostatic doses were increased homogeneously.

Unfortunately, many institutions abandoned these procedures due to morbidity and disappointing clinical results. Although recent publications by Critz et al have shown significantly better outcomes,
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The technique is only in use at a few centers across the country.[40,48]

**Temporary Implant Boost** [A modification of the open retropubic technique has been used by several groups (Table 2).[55-58] In this modified approach, afterloading guides are implanted into the gland via a transperineal approach (with a template) while the gland is directly visualized and palpated through the abdominal incision. The implant is designed to cover the entire gland, along with any local disease extension. After appropriate dosimetric treatment planning (generally using computed tomographic (CT) scans), low-dose-rate (LDR) radiation is delivered as a boost to the gland. This is followed by external-beam radiation therapy. Initially high morbidity and the subsequent introduction of ultrasound guidance have led most centers to abandon this technique in favor of the TRUS-guided approaches discussed below.[56]

**Ultrasound-Guided Transperineal Technique**

Major improvements in the efficacy of prostate brachytherapy occurred as a direct result of technologic advances in TRUS imaging.[59] This technique allows the physician to visualize needle and source placement during surgery. This real-time visualization not only improves accuracy but also enables the operator to identify and correct for potential sources of error. The improved imaging and a shift to the perineal route for needle placement eliminated the need for a laparotomy (with its associated surgical morbidity) and permitted the procedure to be performed on a cost-effective outpatient basis.

**Permanent Implant Boost** [Although combined with external-beam radiation therapy, the basic TRUS-guided transperineal permanent implant is performed in a manner analogous to its use as unimodality therapy. Before the implant is performed, prostate ultrasound images are obtained from the base to apex of the prostate at 0.5-cm increments, and the adjacent rectum, urethra, and bladder neck are identified. Following imaging, the appropriate distribution of needles and sources is determined using computerized treatment planning software, so that the desired dose of radiation is delivered to the prostate while ensuring that neither the urethra nor rectum receive an excessive dose. Seeds are then deposited into the gland during a separate procedure according to the idealized preplan. (The technique can also be performed using intraoperative, real-time dosimetric calculations for optimal seed placement).

It should be noted that different institutions have significantly different philosophies regarding radiation source and dose distribution. A comprehensive discussion of this topic is beyond the scope of this review. Common to all techniques and philosophies, however, is the conformal calculation of implant dosimetry based on the actual anatomy of the individual prostate.

Implant doses in this setting have ranged from 80 to 160 Gy, depending on the isotope used and the dose of external-beam radiation therapy planned (Table 3).[40,46,60-63] Although the implant is believed to provide a more effective radiobiological dose if given prior to external-beam radiation therapy, the sequencing of implantation and external-beam radiation therapy has varied from institution to institution.

Technical problems with the TRUS boost technique are similar to those experienced when implants are used as unimodality therapy. These include incomplete information on the impact of edema on the dosimetric quality of the implant,[64] problems stemming from seed placement error,[65] nonstandardized methods of assessing dosimetry and reporting implant quality,[66] and substantially different philosophies on optimal seed and dose distribution patterns.[59]

**Temporary Implant Boost** [A second TRUS-guided technique in current use is the placement of temporary afterloading needles into the prostate for LDR or HDR brachytherapy. Although technically similar to their permanent seed implant counterparts, these temporary implants take advantage of the improved dosimetric coverage of the gland that HDR brachytherapy offers.

Basically, afterloading needles or catheters are placed into the gland under TRUS guidance in a pattern predetermined either by computerized planning or physician preference. Depending on the institution where the implant is performed, the relationship of these needles to the gland, rectum, and urethra is recorded, and a dosimetric plan is developed.[67-74] A remote afterloading unit then transfers a single high-activity radioactive source into each needle at predetermined points. Since the single source can be kept at a desired position along the needle for a specified amount of time (dwell time), the radiation dose can be optimized to conform to the gland and to avoid excessive overdosage or underdosage to adjacent normal tissues. An additional advantage of this temporary implant system is that the prostate is essentially immobilized by the needles during the 8- to 12-minute treatment delivery time, thereby reducing the risk of a marginal miss.

Although the temporary HDR implant systems in current use permit a more homogeneous dose to be delivered to the gland (due to optimization after needle placement), further improvement in implant
quality is limited since needles cannot be adjusted once in position. However, Martinez et al.[75] have developed a novel, intraoperative, real-time implant procedure that continuously updates the physician on the dosimetric quality of the implant being performed. Not only does the software program provide the physician with ideal needle positions to construct an optimal implant, it also gives the physician the ability to adjust needles intraoperatively as needed to achieve the desired coverage.[67] In effect, since real-time adjustments of the implant can be performed, a truly conformal dose of radiation can be delivered to the gland.

Recent data by Kini et al clearly demonstrate this point.[76] Using three-dimensional radiation therapy evaluation tools, the authors showed that their real-time interactive HDR system resulted in excellent coverage of the gland in 20 randomly selected implants from their institution. On average, 92% of the target volume received the prescribed dose (range, 75% to 99%) with a mean homogeneity index of 0.8. These results compare quite favorably with both permanent implants (an average of 85% of the target volume receives the prescribed dose) and three-dimensional conformal radiation therapy.

Doses used in this setting have been quite variable due to the inherent problems encountered in determining the radiobiological equivalence of LDR and HDR radiation. In addition, some of the studies in Table 4 are dose-escalating studies.[67-74] Regardless of the institution, efficacy appears to be quite good. This approach is among those that have evoked great interest.

Results

Treatment Efficacy

Despite the numerous techniques and studies outlined above, the optimal boost treatment method for locally advanced prostate cancer remains undefined. Many factors account for this uncertainty; these include inconsistencies in defining treatment success, significant differences in follow-up among studies, unequal distribution of critical prognostic factors in most reports, incomplete reporting of complications in some studies, and inconsistent quality assurance guidelines.

Results from most studies, although preliminary, report biochemical control rates in the range of 70% to 85% at 5 years (Table 5).[46,48,60-62,67,69-73] These results compare quite favorably to those of other forms of therapy, such as three-dimensional conformal external-beam radiation therapy, external-beam radiation therapy combined with androgen deprivation, or radical retropubic prostatectomy (Table 6).[9,16,20,30,33,34,41,46,67,70,77]

Despite the inconclusiveness of these results, the technologic advantages of ultrasound-guided transperineal implants (both permanent and temporary) clearly suggest that this implantation method will be the focus of most implant boost programs in the future. In addition, the significant dosimetric advantages of HDR brachytherapy also suggest that this form of boost treatment may allow the safest conformal radiation dose to be delivered to the gland.

Already, preliminary data comparing HDR boosts to conventional external-beam radiation therapy show dramatic improvements in the rate of biochemical control.[67] Similar to recent data using three-dimensional conformal external-beam radiation therapy, HDR boost brachytherapy appears to exhibit a dose-response relationship, and this boost method may be the most optimal means of achieving biochemical control. In addition, complication rates at these higher doses are as good as or better than those reported with lower-dose techniques.

Complications

The complications associated with brachytherapy boosts are very similar to those encountered with conventional external-beam radiation therapy, except for the potential added morbidity of a surgical procedure (in patients undergoing open retropubic implants) and the added effects of brachytherapy on the bladder and rectum. Unfortunately, complication data on brachytherapy boosts reported so far are limited, particularly with respect to the incidence of complications with different implantation techniques.

From a qualitative viewpoint, acute effects on the urethra and rectum are rather common and are generally limited to the radioactive half-life of the isotope (for permanent implants). Long-term effects are variable and difficult to contrast due to significant differences in the definitions used and the length of follow-up (Table 7). Fortunately, at institutions with significant experience using brachytherapy, the rate of incontinence is quite low (particularly in the absence of a previous transurethral resection of the prostate), rectal injuries requiring surgical correction are extremely uncommon, and the rate of potency remains relatively high. As additional quality assurance programs are implemented on a national level, the rate of late complications should continue to decline.
Conclusions

Several different types of brachytherapy boost techniques are currently being used clinically to treat locally advanced prostate cancer. Techniques based on TRUS guidance clearly provide the most accurate method of source placement with reduced toxicity. Afterloading systems using HDR brachytherapy offer the added advantage of further optimizing dose distribution after implant placement. Novel brachytherapy programs using real-time dosimetric analyses have also been developed and implemented, offering additional options for performing conformal dose escalation. Results with these newer techniques appear to be comparable or superior to results with other forms of therapy in comparably staged patients.

Until standardized methods of reporting treatment data are utilized and longer follow-up is obtained with other modalities, prostate brachytherapy boosts in combination with external-beam radiation therapy should be considered an acceptable option in the treatment of patients with locally advanced prostate cancer. The challenge facing oncologists treating this malignancy in the future will be to determine which treatment approach is optimal given a certain combination of critical prognostic factors. In addition, the role that adjuvant androgen deprivation plays in controlling this malignancy will be critical and awaits publication of the results of several recently initiated or completed randomized trials.

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