

## OVERVIEW

### Brachytherapy

#### Introduction

Brachytherapy is derived from the Greek term *brachys*, or short, and relates to a form of radiotherapy in which the radioactive source is placed close to the target. While different methods of placement are employed based on the condition of interest, prostate brachytherapy refers to interstitial placement of radioactive seeds for clinically localized prostate cancer. There are two major forms of prostate brachytherapy currently in use today: permanent, low-dose rate (LDR) brachytherapy, in which seeds (typically iodine<sup>125</sup> or palladium<sup>103</sup>) are permanently implanted and emit a low dose of radiation over several months; and the newer temporary, high-dose rate (HDR) procedure, in which iridium<sup>192</sup> seeds are inserted through micro-catheters and removed after a short period (typically less than an hour). HDR brachytherapy is typically repeated 2-3 times over a 24-hour period, and is also typically supplemented by a “boost” course of external beam radiation (typically 30-50 Gray [Gy] units); androgen deprivation therapy (ADT) also may be used to aid in treatment planning and dose placement. The HDR procedure is also typically reserved for intermediate- or higher-risk patients, while the LDR procedure predominates in low-risk populations.

The use of prostate brachytherapy has grown exponentially in the last 25 years with the advent of transrectal ultrasound and other imaging guidance for seed implantation. It has been estimated that one-third of patients with prostate cancer in the U.S. who are referred for radiotherapy are treated with brachytherapy. As with other major forms of prostate cancer therapy, however, questions remain about the long-term effectiveness and adverse outcomes of this procedure relative to other treatment options such as three-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT). Specific areas of uncertainty, many of which this assessment seeks to address, include:

- 1) Impact of brachytherapy on local toxicity, recurrence, and development of secondary cancers
- 2) Variability in practice (e.g., timing/type of treatment planning, implantation, course of therapy) by individual clinicians and/or treatment centers
- 3) Differences in brachytherapy systems and delivery mechanisms (e.g., stranded vs. loose seed LDR implantation)
- 4) Clinical and cost-effectiveness of brachytherapy relative to other radiation therapy alternatives (3D-CRT and IMRT).

#### Professional Organizations and Agency Recommendations:

- National Comprehensive Cancer Network (2007): The NCCN/ACS Prostate Cancer Panel concludes that “permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, brachytherapy may be combined with external-beam RT (40-50 Gy) with or without neoadjuvant ADT.”

- European Organisation for Research and Treatment in Cancer (2000): The EORTC Radiotherapy Group, in conjunction with the European Society for Therapeutic Radiology and Oncology (ESTRO) and the European Urological Association (EAU), recommend that monotherapy with permanent brachytherapy be considered for patients with a PSA  $\leq 10$ , a Gleason score of 5-6, stage of T1c-T2a, and prostate volume  $< 40$ g. Brachytherapy with external radiation boost can be considered in those with a PSA 10-20, Gleason score of 7, stage T2b or T2c, and prostate volume 40-60g.
- American College of Radiology (2006): The ACR concluded that “in contemporary series, brachytherapy as a monotherapeutic approach for patients with low-risk features has resulted in high rates of biochemical control without further improvement following the addition of supplemental radiation therapy.” ACR appropriateness criteria suggest that, in patients with low-risk, clinically-localized disease, permanent interstitial brachytherapy monotherapy is considered one of the preferred approaches, along with external beam monotherapy and active surveillance (rating of 8 on a scale of 1-9).
- American Urological Association (2007): The AUA has concluded that interstitial brachytherapy is considered one of the viable monotherapy options for clinically-localized, low-risk prostate cancer, along with active surveillance, external beam radiotherapy, and radical prostatectomy, and that “study outcomes data do not provide clear-cut evidence for the superiority of any one treatment.”
- American Brachytherapy Society (2006): The ABS considers permanent LDR brachytherapy appropriate in patients with a life expectancy  $> 5$  years, clinical stage T1b-T2c (and selected T3), Gleason scores ranging from 2-10, and a PSA  $\leq 50$  ng/mL. Patients should also have no pathologic evidence of pelvic lymph node involvement or distant metastases.

### **Recent Technology Assessments**

- National Institute for Clinical Excellence (NICE, UK) (2005): Current evidence on the safety and efficacy of both LDR and HDR brachytherapy (the latter in combination with external beam radiation) appears adequate to support the use of these procedures.
- Medical Services Advisory Committee (MSAC, Australia) (2006): Subject to further evidence on the safety, effectiveness, and cost-effectiveness of brachytherapy, public funding for brachytherapy (only LDR was considered) should continue for patients at clinical stages T1 or T2, Gleason scores  $\leq 6$ , PSA  $\leq 10$  ng/ml, gland volume  $< 40$ cc, and life expectancy  $> 10$  years.
- Institute for Quality and Efficiency in Health Care (IQWiG, Germany) (2007): IQWiG concludes that the “potential advantages of brachytherapy (only LDR was assessed) with regard to organ function and quality of life...are insufficient to apply this therapeutic procedure” and states that sound clinical studies must be conducted before its relevance in comparison to other treatment options can be evaluated.

- Committee on Evaluation and Diffusion of Innovative Technologies (CEDIT, France) (2001): CEDIT’s opinion was that “there are too many reservations regarding brachytherapy as a treatment for early localized prostate cancer...”, and recommended that its application be reserved for use at one center with sufficient experience in the technique. There has been no further update to this opinion.
- Swedish Council on Technology Assessment in Health Care (SBU, Sweden) (2000): SBU concluded that “since there is no evidence to show that brachytherapy is superior to other treatment or no treatment in managing localized prostate cancer, the method should be used only within the framework of controlled clinical studies until further evidence becomes available.” The report has not been materially updated.

### **Coverage Policies**

- Medicare: There are no National Coverage Decisions on Brachytherapy. The majority of Local Coverage Decisions allow for coverage of both LDR and HDR brachytherapy, alone or in conjunction with surgery or external beam radiation, although at least one LCD recommends following ABS clinical criteria (see above) to determine medical necessity.
- United Healthcare: LDR brachytherapy is considered proven for the treatment of early stage, localized prostate cancer. HDR brachytherapy is only covered as an in-network benefit where LDR brachytherapy is unavailable.
- All other private health plans evaluated for this overview (including Humana, Aetna, and Cigna) consider both LDR and HDR brachytherapy medically necessary for the treatment of prostate cancer and do not distinguish between these techniques with regard to coverage levels.

### **Research in Progress**

The only randomized controlled trial involving brachytherapy as an explicit treatment arm is a small, multicenter Phase II trial of intensity-modulated radiation therapy (IMRT) vs. permanent interstitial brachytherapy sponsored by the British Columbia Cancer Agency; 50 men with low-risk disease are being enrolled and followed for up to 9 years. The primary endpoint is acute and late toxicity of the treatment alternatives; quality of life and disease-specific as well as overall survival will also be evaluated. The study was initiated in March 2007, and is expected to be completed in 2016.

Elsewhere, a large, multi-center, Phase III trial of active observation (i.e., “watchful waiting”) vs. radical treatment of prostate cancer co-sponsored by the National Cancer Institutes of the U.S. and Canada is currently recruiting over 2000 newly-diagnosed participants with favorable-risk prostate cancer. Patients will be randomized at the time of initial diagnosis; randomization will be stratified by treatment center, ECOG status, disease stage, baseline PSA, and age (<65 vs. 65+ years). The primary endpoint of interest is disease-specific survival. LDR and HDR brachytherapy are two of the radical treatment options available, along with radical

prostatectomy and external-beam radiotherapy. Initial results are expected to be available in May 2011.

Finally, the Radiation Therapy Oncology Group is conducting a large, multicenter, Phase III clinical trial of the use of external beam radiation with permanent interstitial brachytherapy vs. brachytherapy alone. A total of 1500 men with intermediate-risk prostate cancer will be randomized (in a stratified fashion by stage, Gleason score, PSA, and prior receipt of neoadjuvant hormonal therapy) will be followed for up to 5 years. The primary outcomes of interest are overall, disease-specific and disease-free survival, biochemical failure, local progression, and development of distant metastases; secondary outcomes of interest include morbidity and quality of life.

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