

Brachytherapy for prostate cancer

ALERT | EARLY ASSESSMENT OF NEW HEALTH TECHNOLOGIES | WWW.SBU.SE



Published Jun 7, 2000
Version 1

Findings by SBU Alert

Brachytherapy is not widely used in Sweden to treat localized prostate cancer. This treatment method has been available for some time, but recent advancements in technology are leading to increased utilization. Findings from isolated, uncontrolled studies of high dose rate brachytherapy in combination with external beam radiotherapy suggest some improvement in treatment outcomes. However, prospective, controlled studies are not available, and the improved outcomes may be explained by use of the method to treat smaller tumors. The type and frequency of side effects are similar to those from external beam radiotherapy, but there may be a somewhat higher rate of serious problems as the method is being established.

Currently, there is poor* scientific evidence concerning the patient benefits, short-term effects, and risks of the method. There is no* scientific evidence regarding its cost-effectiveness and long-term effects.

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.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see "Grading of evidence".

Alert is a joint effort by the Swedish Council on Technology Assessment in Health Care (SBU), the Medical Products Agency, the National Board of Health and Welfare, and the Federation of Swedish County Councils.

Technology

Brachytherapy for localized prostate cancer involves placing radioactive material in the prostate gland. Two main forms of brachytherapy are used: (a) insertion of permanent low dose radioactive (low dose/time unit) implants (palladium-103 or iodine-125) and (b) temporary placement of a high dose radioactive source (high dose/time unit) in the prostate using hollow needles (iridium-192). Both techniques are used separately or in combination with external beam radiotherapy (XRT; high dose rate irradiation from linear accelerators outside of the body). The present report is focused on the iridium-192 technique in combination with XRT.

The method of inserting permanent implants has been available for over 20 years. Initially, the results were inferior to those from external beam radiotherapy. During the 1990s, brachytherapy techniques have improved. Advancements in ultrasound imaging have helped to improve needle placement in the prostate, dose planning, and treatment followup.

Target group

Annually, over 5500 men are diagnosed with prostate cancer in Sweden. Of these, approximately 35 percent have clinically localized prostate cancer, approximately 15 percent have local advanced cancer, approximately 25 percent have metastasis, and in the remaining cases the tumor stage has not been classified.

Current approaches to localized prostate cancer include surgery, external beam radiotherapy, brachytherapy, or no therapy. Of all patients with newly detected cancer in 1996, 7 percent had a localized tumor and were younger than 70 years of age. Of these, 72 percent had received curative treatment (National Prostate Cancer Registry, 1996). A large number of younger patients with clinically localized cancer has to a larger extent during later years been offered curatively intended treatment. Younger patients with smaller tumors were more frequently offered surgery, while older patients and patients with larger tumors (more locally advanced, higher PSA value) were treated more frequently by external beam radiotherapy. Given current knowledge, it is not possible to accurately project the size of the target group for brachytherapy.

Relation to other technology

Curative treatment for localized prostate cancer includes surgery (radical prostatectomy) or external beam radiotherapy. Studies of patients receiving the various treatments show the results to be similar, with an expected cancer-specific, 10-year survival of approximately 90 percent, with some variation depending on the stage, differentiation grade, lymph gland status, and PSA value at the start of treatment. However, there are no generally accepted, randomized, controlled studies (where the alternatives have been surgery or radiotherapy on one hand, and no treatment on the other) which have shown that treatment affects survival or quality of life. Nevertheless, urologist and oncologists in Sweden have used surgery or external beam radiotherapy for many years to treat localized prostate cancer. Large regional variations exist in the choice of treatment method used and the utilization rates (National Swedish Board of Health and Welfare; State-of-the-art document on prostate cancer; <http://www.sos.se/mars/>, in Swedish).

Brachytherapy and XRT should be viewed as an alternative to these more traditional treatment methods. Future assessments will determine whether it achieves better treatment results without increasing the side effects, eg, radiation necrosis. In studies, brachytherapy and XRT should be compared mainly with higher dose external beam radiotherapy (equal to or exceeding 76 Gy).

In relation to surgery, brachytherapy and XRT (as well as XRT alone) has better chances of preserving patients' sexual function, and generally demonstrates a different pattern of side effects.

Patient benefits

Published studies with the combination of brachytherapy (iridium-192) and XRT from Sweden describe the technology and data on 50 patients in Göteborg [1,2]. A published study from Uppsala describes

experiences during the 1990s involving permanent gold implants combined with external beam radiotherapy to treat approximately 100 patients. The literature also includes four studies [5–8] covering 392 patients, most of whom were treated during the late 1980s.

In these studies, brachytherapy (iridium-192) was used in combination with external beam radiotherapy. The findings after combined treatment confirmed that cancerlike cells remained (positive biopsies) in 4 percent to 34 percent of the patients. In treatment with external beam radiotherapy alone, earlier series have shown cancerlike cells in 20 percent to 60 percent of the cases. The superior outcomes from brachytherapy and XRT could be a result of delivering higher doses to the areas of the prostate where it was possible to confirm an increase in connective tissue following treatment, but could also be due to selection of study subjects with smaller tumors.

A recent comprehensive review of brachytherapy methods, where patient populations were standardized by PSA values prior to treatment and then compared, could not define an optimal brachytherapy technique [10]. Several of these studies suggest that outcomes are better when higher doses and refined techniques (equalized dose distribution) are used. Since these studies were open, patient selection may also explain the differences in results. There is no scientific evidence to show that better outcomes, defined as a lower prevalence of residual cancer (positive biopsy), result in better survival.

A study from the United States of patients who were matched by tumor stage (size), differentiation grade, and PSA value prior to treatment found no difference in relapse time (measured by elevated PSA levels) between patients who received surgery and those who received only external beam radiotherapy [3]. Low dose rate brachytherapy, as monotherapy, was less effective on larger tumors (eg, PSA higher than 10). Another study [9] showed that the combination of high dose rate brachytherapy and external beam radiotherapy had a lower percentage of patients who relapsed (elevated PSA value) than conventional radiotherapy (70 Gy). Similar results, ie, a lower percentage of patients who relapsed (elevated PSA-value), were reported in several studies with higher dose external beam radiotherapy (exceeding 76 Gy). A large study with matched patients groups showed better survival at higher external beam radiation doses [4].

Complications and side effects

All forms of radiotherapy of the prostate gland involve a risk for injury of the urinary tract and intestines. Reports from several hospitals that use brachytherapy and XRT show a high percentage of side effects during the initial phase, but the percentage later declines. Data from Göteborg suggest there may be a higher risk (at least before the staff are proficient in the method) for scar tissue formation in the urethra and isolated radiation necrosis, which may cause problems in urination and require complementary surgery.

Acute side effects such as diarrhea, urgency problems, and prostate swelling are common (40 percent to 70 percent). Nevertheless, healing has been good with 3 percent to 10 percent reporting substantial residual problems. The type and rate of side effects are similar to those appearing with external beam radiotherapy, possibly with somewhat more serious problems while establishing the method. With low dose rate irradiating implants which are left in the body, there is a reported increased risk for incontinence in patients who have undergone TUR-P (transurethral resection of the prostate) prior to brachytherapy.

Costs and cost effectiveness

Brachytherapy usually requires the involvement of urologists (who can perform ultrasound), oncologists, technicians (physicists), and anesthesiologists. Access to an operating suite is also required. Additional costs for performing high dose rate brachytherapy are approximately 60 000 SEK. If one uses permanent low dose irradiating implants, the material costs are 45 000 to 50 000 SEK. In addition, there are costs for operating suites and possibly for nursing care. If brachytherapy is combined with external beam radiotherapy, there are further costs of 30 000 SEK to 50 000 SEK. Cost-effectiveness comparisons with other curative methods are lacking.

Structure and organization of health services

Brachytherapy for prostate cancer requires participation from several disciplines: an anesthesiologist, an oncologist, a technician (physicist), and usually an urologist are all involved in the treatment episode. Temporary implants require treatment on two occasions separated by a 2-week interval. The time that the patient is in the operating suite under the care of an anesthesiologist, who delivers spinal anesthesia, is approximately 4 hours. Treatment places a relatively large demand on planning and coordination. Most oncology departments in Sweden have access to adequate radiation resources for high dose radiation brachytherapy, and only special dose planning systems must be acquired. These, however, can also be used for treating other types of cancer.

Ethical aspects

There is no scientific evidence that brachytherapy and XRT for localized prostate cancer is superior to other forms of treatment (external beam radiotherapy, surgery, or no therapy). Therefore, it is important for the patient to receive adequate information about the different methods prior to treatment and be informed about the lack of scientific evidence concerning patient benefit.

Diffusion in Sweden

Brachytherapy in combination with XRT is offered in Göteborg, Uppsala, Stockholm (Radiumhemmet), Linköping, and in Örebro since the autumn of 1998. Göteborg has the greatest experience with approximately 200 patients treated, and approximately 100 patients have been treated in Uppsala.

Current evaluation research

Two studies are underway which will hopefully provide some evidence within 5 to 7 years on whether treatment by surgery or external beam radiotherapy has effects on survival and quality of life. The so-called SPCG 4-study includes fewer than 700 patients and compares no treatment (deferred treatment) with radical prostatectomy. Another study, the so-called Umeå-1-study, compares no treatment with external beam radiotherapy (170 patients plus 50 patients in Denmark).

A randomized study that compares brachytherapy and XRT with radical prostatectomy has been started in Göteborg and in the Uppsala region. Clinicians from Stockholm, Linköping, and Örebro who perform brachytherapy have joined the study. Thus far, approximately 75 patients of a planned 360 patients have been recruited. The purpose of this study is to assess side effects of the two different forms of treatment. The Scandinavian Prostate Cancer Group (SPCG) and oncologists in the Nordic countries are conducting discussions about performing a Nordic randomized study comparing surgery with radiotherapy. Radiotherapy would include brachytherapy or external beam radiotherapy depending on the local oncology method.

Expert

Anders Widmark, Assoc Prof, Norrland's University Hospital in Umeå.

Reviewer

Scientific Advisory Committee in Urology of the National Swedish Board of Health and Welfare.

References

1. Borghede G, Hedelin H, Holmang S, Johansson KA, Aldenborg F, Pettersson S, et al. Combined treatment with temporary short-term high dose rate iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma. *Radiother Oncol* 1997;44(3):237-44.
2. Borghede G, Hedelin H, Holmang S, Johansson KA, Sernbo G, Mercke C. Irradiation of localized prostatic carcinoma with a combination of high dose rate iridium-192 brachytherapy and external beam radiotherapy with three target definitions and dose levels inside the prostate gland. *Radiother Oncol* 1997;44(3):245-50.
3. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer [see comments]. *JAMA* 1998;280(11):969-74.
4. Hanks GE, Hanlon AL, Pinover WH, Horwitz EM, Schultheiss TE. Survival advantage for prostate cancer patients treated with high-dose three-dimensional conformal radiotherapy [see comments]. *Cancer J Sci Am* 1999;5(3):152-8.
5. Mate TP, Gottesman JE, Hatton J, Gribble M, Van Hollebeke L. High dose-rate afterloading 192Iridium prostate brachytherapy: feasibility report. *Int J Radiat Oncol Biol Phys* 1998;41(3):525-33.
6. Paul R, Hofmann R, Schwarzer JU, Stepan R, Feldmann HJ, Kneschaurek P et al. Iridium 192 high-dose-rate brachytherapy--a useful alternative therapy for localized prostate cancer? *World J Urol* 1997;15(4):252-6.
7. Syed AM, Puthawala A, Austin P, Cherlow J, Perley J, Tansey L et al. Temporary iridium-192 implant in the management of carcinoma of the prostate. *Cancer* 1992;69(10):2515-24.
8. Stromberg J, Martinez A, Gonzalez J, Edmundson G, Ohanian N, Vicini F et al. Ultrasound-guided high dose rate conformal brachytherapy boost in prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. *Int J Radiat Oncol Biol Phys* 1995;33(1):161-71.
9. Stromberg JS, Martinez AA, Horwitz EM, Gustafson GS, Gonzalez JA, Spencer WF et al. Conformal high dose rate iridium-192 boost brachytherapy in locally advanced prostate cancer: superior prostate-specific antigen response compared with external beam treatment [see comments]. *Cancer J Sci Am* 1997;3(6):346-52.
10. Vicini FA, Kini VR, Edmundson G, Gustafson GS, Stromberg J, Martinez A. A comprehensive review of prostate cancer brachytherapy: defining an optimal technique. *Int J Radiat Oncol Biol Phys* 1999;44(3):483-91