Commentary

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Brachytherapy for prostate cancer: Effective, but …?

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The implantation of radioactive seeds into the prostate gland: Is it a new therapeutic approach to cure localized prostate cancer? In 1978 my esteemed professor of urology at Queen's University, an acknowledged international expert in prostate cancer, convinced a young naïve urology resident that brachytherapy was the best procedure to cure localized prostate cancer. We selected our patients carefully, staged their cancer as accurately as possible, even doing a pelvic lymph node dissection to rule out local metastases, and through an open and visual retropubic approach carefully inserted radioactive seeds using an acrylic plastic template for accuracy. Our early results[1] and those of the Memorial Sloan–Kettering Cancer Center in New York[2] indicated that brachytherapy was less invasive, quicker and associated with less morbidity and recovery time than radical prostatectomy, and it appeared to produce similar or better results than the surgery. Two years and hundreds of patients later, we abandoned the procedure. Post-treatment biopsies showed residual cancer in too many patients. Ten to 15 years later, local cancer progression rates and mortality data confirmed our impression.[1,2] Brachytherapy, as practised in the 1970s, was not that effective and was essentially abandoned by the urological community until it re-emerged in the 1990s in a modified form.

Here we go again. I only hope that this time around, with a better understanding of prostate cancer biology, better diagnostic and follow-up testing, advanced technology and critical evaluation, this brachytherapy story will be different. The prostate cancer patient of today is very different from the patient who presented for treatment in the 1970s and 1980s. With the introduction of widespread prostate-specific antigen (PSA) testing and an increased awareness of this particular cancer among the public, our patients are now younger, have less advanced disease and are much more educated about their treatment choices. We are now able to use serum PSA levels and imaging techniques such as transrectal ultrasonography and CT scanning to better stage the disease in patients with early prostate cancer. "Modern" brachytherapy incorporates a perineal approach, guided by transrectal ultrasonography for insertion of the radioactive seeds. This negates the need for an open surgical procedure and appears to allow for more accurate placement of the seeds. To the patient, and to many physicians, brachytherapy is an attractive alternative to surgery. In the United States, widespread acceptance of brachytherapy appears to be driven by patient preference and economic pressure rather than by long-term clinical results. It is only hoped that time and evidence will justify this enthusiasm.

In this issue of *CMAJ* (page 975) Crook and associates, with the Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative, report on their systematic review of the literature on brachytherapy in an attempt to provide an evidence-based approach for the use of "modern" brachytherapy in early prostate cancer.[3] The use of early surrogate endpoints such as serum PSA level and prostate biopsy findings to permit early evaluation of treatment efficacy is controversial. Although post-treatment biopsy results did predict the ultimate failure of the brachytherapy technique used in the 1970s, Crook and associates did not rely on this criterion, since post-implant biopsies were not used widely and case selection made the comparison of results difficult in the series that did report biopsy results.

The serum PSA level is the best surrogate for determining early treatment success, but many definitions of PSA failure were used in the studies evaluated, and early freedom from biochemical failure does not necessarily predict long-term results. Survival is the irrefutable measure of successful treatment of prostate cancer, and brachytherapy, like all other prostate cancer therapies, will ultimately be assessed by this most important criterion. With brachytherapy, rates of freedom from biochemical failure (bNED [biochemically no evidence of disease]) ranged from 63% to 93% within 5 years after implantation. Positive biopsy results were reported in 3% to 26% of cases within 2 to 3 years after implantation. There was a trend toward improved bNED rates when brachytherapy was combined with external beam radiotherapy, but positive biopsy results were reported in as many as 27% to 48% of cases. The authors could not (and really did not even try to) compare these data with results obtained with conventional radical prostatectomy or modern external beam radiotherapy.

It was distressingly clear that, with no randomized controlled trials and with only short-term results (for prostate cancer 4 to 5 years of data is short term) from uncontrolled clinical series, Crook and associates' task to provide an evidence-based approach for the use of modern brachytherapy in early prostate cancer was impossible. The authors conclude that "clinical experience indicates that permanent implantation of [iodine 125 or palladium 103] seeds under transrectal ultrasound guidance yields promising short- and

intermediate-term rates of freedom from biochemical failure among selected patients with early-stage prostate cancer." They can make no recommendations, but they state that brachytherapy may be indicated in selected patients with small prostate glands, stage T1c or T2a tumours, a Gleason score of 6 or lower and a serum PSA level of 10 μg/L or less. This carefully researched overview, critical analysis and consensus report is a breath of fresh air on a subject that is awash in unsubstantiated claims, testimonials and hyperbole. But the report is also sobering. Only a small minority of patients found to have prostate cancer meet the criteria for brachytherapy suggested by the authors.

Although freedom from biochemical failure is achievable in this selected cohort, many of these men with low-stage, low-grade, low-volume cancer would never die from their disease, even without therapy. And the morbidity is not inconsequential. The rates quoted by Crook and associates of irritative urinary symptoms in 46%–54% of cases, urinary retention in 1%–14%, proctitis in 1%–2%, incontinence in 5%–6% and impotence in 4%–14% are disturbing. The morbidity increases following transurethral resection of the prostate (incontinence in 13% of cases) and when brachytherapy is combined with external beam radiotherapy (persistent urinary retention in 21%, rectal pain or tenesmus in 55%, persistent perineal pain in 12%, severe persistent cystitis in 25%, hemorrhagic proctitis in 16% and rectovesical fistula in 6%). These adverse consequences, when they occur, significantly reduce quality of life. The morbidity reported from these large academic centres with exceptional clinical expertise in the procedure may be lower than what would be found in less experienced centres. It is also recognized that patients with low-stage, low-grade, small-volume prostate cancer also do very well with surgery, and the morbidity of radical prostatectomy in such selected patients has decreased dramatically over the last decade.[4,5]

Crook and associates could not recommend brachytherapy for patients with localized prostate cancer on a solid "evidence-based" basis. They recommend randomized controlled trials with adequate follow-up before real critical evaluation of brachytherapy is possible. These trials are feasible, but it would be at least 10 to 15 years after the last patient was enrolled (and it would take many years to organize and subsequently recruit enough patients) before a possible conclusion could be drawn regarding the most important outcome criterion, survival. But the authors have convinced me that, on a "best evidence-based" approach from the current literature, brachytherapy is a feasible alternative to surgery in selected patients with low-stage, low-volume and low-grade disease. It is likely that, for the foreseeable future, clinical experience and longer follow-up of clinical series, rather than properly designed and implemented randomized controlled trials, will unfortunately guide the profession and the public in decisions regarding brachytherapy for early prostate cancer.

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Competing interests: None declared.

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