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BRACHYTHERAPY AND PROSTATE CANCER

Report submitted to
the Minister of Research, Science
and Technology of Québec



Conseil d'évaluation des
technologies de la santé
du Québec

Information concerning this report or any other report published by the *Conseil d'évaluation des technologies de la santé* can be obtained by contacting the *Conseil*:

Conseil d'évaluation des technologies de la santé
201, boulevard Crémazie est, Bureau 1.03
Montréal (Québec) H2M 1L2

Telephone: (514) 873-2563

Fax: (514) 873-1369

E-mail: cets@msss.gouv.qc.ca

Web site address: <http://www.msss.gouv.qc.ca/cets/>

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MANDATE

To promote and support health technology assessment, disseminate the results of the assessments and encourage their use in decision making by all stakeholders involved in the diffusion of these technologies.

To advise the Minister on matters concerning the introduction, diffusion and use of health technologies and, to this end, give advice based on the assessment of their effectiveness, safety and cost, their impact on the health-care system, and their economic, ethical and social implications.

THE CONSEIL'S MEMBERS

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Epidemiologist

Denise Leclerc
Pharmacist

Jean-Marie Moutquin, MD
Obstetrician-gynecologist

Suzanne Nootens
Lawyer

Guy Rocher
Sociologist

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Jean-Marie R. Lance

BRACHYTHERAPY AND PROSTATE CANCER

Prostate cancer is an important health problem in North America, although recent data suggest that incidence is declining. In effect, prostate cancer management is improving due to improvements in treatments including watchful waiting, radical prostatectomy and external-beam radiation therapy. However, both surgery and radiotherapy have significant side effects, particularly incontinence and impotence.

In this context, many clinicians have suggested a revival of brachytherapy or interstitial therapy - therapeutic radiation of a tumour by radioactive sources implanted directly into the tumour - in contrast to external-beam radiotherapy where the radiation source is located outside the patient.

Given this interest and a request from the *Centre Hospitalier Universitaire de Québec (CHUQ)*, the *Conseil d'évaluation des technologies en santé (CETS)* decided to produce this evaluation report. This report summarises the evidence of brachytherapy's intended and unintended effects and compares these to treatments in current use. Cost and cost-effectiveness issues are also addressed and the report concludes with a statement on the status of brachytherapy in current practice.

The report concludes that the evidence is too weak to demonstrate either greater efficacy of brachytherapy compared to other treatments or better cost-effectiveness. However, complications appear to be much less frequent with brachytherapy. In sum, this technology remains experimental until data are available to confirm its efficacy, particularly among men with localised, well-differentiated early stage prostate cancer with low pre-treatment PSA levels.

In disseminating this report, CETS wishes to provide the best possible information to the many policy-makers at different levels in Quebec's health-care network.

Renaldo N. Battista
President

SUMMARY

INTRODUCTION

Prostate cancer is an important health problem in Quebec as in Canada and the United States, although recent data suggest that incidence is declining. Researchers suggest that this decline can be explained by better prostate cancer management or improved treatment modalities. For adenomas localised to the prostate, usual care ranges from watchful waiting through radical prostatectomy and external-beam radiation (EBRT). However, both of these last two are associated with substantial side effects, particularly incontinence and impotence.

In this context, many clinicians have suggested a revival of brachytherapy or interstitial therapy - therapeutic radiation of a tumour by radioactive sources, (typically iodine 125, palladium 103, or iridium 192), implanted directly into the tumour - in contrast to external-beam radiotherapy where the radiation source is located outside the patient. Implanted radiation sources, introduced locally, offer the theoretical advantage of concentrating radiation on the target tissue and diminishing dispersion of radiation and subsequent damage of adjoining, non-cancerous tissue.

Brachytherapy dates from the 1970s, but at that time implantation was done by freehand methods, limiting efficacy and the therapy was never widely adopted. During the 1980s, it returned to favour with advances in imaging (particularly transrectal ultrasound and computerised tomography (CT) scanning), and improvements in algorithms for dosage calculations. In addition, reorientation of health services to favour technologies that reduce hospital utilisation and free up EBRT resources has favoured a reintroduction of brachytherapy. Last, for the growing number of older men who will be diagnosed with prostate cancer, brachytherapy, particularly for early-stage cancer, may minimise side effects and enhance quality of life.

This report summarises the evidence of brachytherapy's intended and unintended effects and compares these to treatments in current use. Cost and cost-effectiveness issues are also addressed, and the report concludes with a statement on the status of brachytherapy in current practice.

EFFICACY OF BRACHYTHERAPY : THE EVIDENCE

Evaluation of the efficacy of brachytherapy is based on 33 articles published between 1972 and 1999 classified by the strength of the evidence and by the presence or absence of data on prostate specific antigen (PSA) levels pre- and post-treatment. None of the reviewed studies were randomised clinical trials and only three were comparative studies with PSA information, all the other reporting case series. It is important to highlight the substantial variation in patient characteristics and outcome definitions in this body of evidence.

Most of the studies defined clinical outcomes in terms of freedom from biochemical failure based on PSA measurements at various post-treatment intervals. Although this indicator is of interest and easy to measure and interpret, it cannot replace therapeutic outcomes defined in terms of disease progression (i.e. recurrence-free, metastatic disease, death attributable to prostate cancer).

In summary, although two of the three comparative studies suggest that brachytherapy is superior to radical prostatectomy in terms of non-progression of PSA levels at seven years or recurrence-free survival, methodological weaknesses render these inconclusive. In addition, the third comparative study reports no significant difference for low-risk patients and this also applies to comparisons with EBRT. Case series, a weaker level of evidence and generally consi-

Summary

dered less compelling, suggest that if outcome is defined in terms of freedom from biochemical failure or negative biopsy rates, brachytherapy may be efficacious. However, although these results suggest that certain well-defined groups of patients can benefit from brachytherapy, the data are insufficient to clearly define who will benefit.

SIDE EFFECTS OF BRACHYTHERAPY

The data on complications are also weakened by a lack of comparability due to minimal detail regarding the definitions of the various complications. However, based on the published reports, side-effects of brachytherapy are largely local and self-limited. The reported case series suggest that rates of post-treatment impotence are lower among brachytherapy-treated males compared to surgically-treated males. Reported rates of incontinence are no worse and, among men with no history of transurethral resection of the prostate, lower than among surgically-treated men.

ECONOMIC ASPECTS

No Quebec or Canadian data on brachytherapy costs are available. Sparse data from centres in the United States suggest vast centre-to-centre variation in how patients are selected and managed. As for information on human and financial resources for optimal brachytherapy care, only extremely limited data exist. Several treatment centres have argued that their experience with brachytherapy demonstrates cost savings in comparison with EBRT or radical prostatectomy and that it also frees EBRT resources for other uses. Caution is required in interpreting these limited and even contradictory data, implying that definitive conclusions regarding the cost-

effectiveness of brachytherapy are currently not possible.

CONCLUSION

Based on the three comparative studies and the case series literature, it is not possible to demonstrate an efficacy advantage of brachytherapy over existing treatments. Furthermore, it is also not possible to exclude the possibility that brachytherapy is less efficacious. However, reported adverse side effects, particularly impotence, are substantially less frequent with brachytherapy than either surgery or EBRT. No data on cost-effectiveness were located to substantiate claims by the promoters of brachytherapy that it is more cost-effective than EBRT.

Brachytherapy for prostate cancer is clearly not yet an accepted technology. Lacking direct evidence of its efficacy compared to watchful waiting or surgery or EBRT marks brachytherapy as an experimental therapy [2].

However, there is some agreement that brachytherapy might be of more benefit to men with early-stage, localised, well-differentiated prostate cancer and a low pre-treatment PSA level. Another promising avenue for brachytherapy is its use as a boost following moderate doses of EBRT for locally advanced disease. However, long-term results are still not available and randomised controlled trials are needed to confirm those different uses, to establish its comparative efficacy and to delineate the specific role of brachytherapy in prostate cancer management.

Evaluating brachytherapy's role in prostate cancer management will also require an evaluation of the settings and costs associated with delivering that treatment compared to the alternatives of surgery and EBRT.

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Véronique Benk	Radiologist, Department of Radiation Oncology, McGill University Health Centre, Montreal (Quebec);
Fred Saad	Urologist, Département of Uro-oncology, Centre hospitalier universitaire de Montréal, Clinical Associate Professor, Département of Surgery, Université de Montréal, Montreal (Quebec);
Padraig Warde	Radiologist, Department of Radiation Oncology, GU Oncology Site Group Leader, Princess Margaret Hospital and Associate Professor, Inter-Departmental Division of Oncology, University of Toronto, Toronto (Ontario).

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INTRODUCTION

Prostate cancer is a growing health problem for Quebec males as men live longer and increasing use of serum tests for prostate specific antigen (PSA) detects disease that would have remained clinically undetectable until autopsy. Promoted by advocates of early detection, PSA testing is increasingly used to “screen” for prostate cancer among healthy males. In August 1995, the *Conseil d'évaluation des technologies de la santé du Québec (CETS)* released an assessment of the benefits, health consequences and costs of prostate cancer screening, concluding that any health gains from population screening with PSA were at best uncertain and, even if realised, too small to justify a population screening program [10].

The 1995 report also noted that age-specific mortality attributed to prostate cancer had been rising by roughly 1.0% annually between 1970 and 1990 and that prostate cancer incidence was rising at 1.5% per year from 1984 to 1990. However, the situation is changing: according to a recent study by Quebec researchers [30], overall, age standardised rates declined by 23% in Quebec between 1991 and 1997 (that is from 33.1 to 25.4 per 100,000 person-years), and by 9.6% in Canada between 1991 and 1996 (from 31.2 to 28.2). Other preliminary Canadian data for 1999 confirm this downward trend [33], which parallels the situation in United States. According to the Quebec researchers, this phenomenon is more likely to be related to better prostate cancer management or improved treatment modalities. The decline in mortality rates occurred relatively early after the initiation of widespread screening with PSA, so that “it is unlikely that screening has as yet contributed in a major way to the decline [30]”.

Ninety-five per cent of prostate cancers are adenocarcinomas whose histology can be graded by the Gleason score. Gleason scores range from 2

to 10, increasing with decreasing differentiation of tumour cells, and are correlated with survival. Most prostate cancers are localised to the prostate gland at the time of diagnosis. Treatment for localised prostate cancer has generally involved surgery (i.e. radical prostatectomy), external-beam radiation therapy (EBRT), or watchful waiting. Both surgery and radiation therapy yield substantial side-effects, particularly incontinence and impotence. In this context, brachytherapy – a form of radiotherapy but localised – has sparked interest.

The 1995 report, noting the paucity of randomised trials comparing surgery and radiation therapy, examined case-fatality rates (CFR) and concluded that the difference between surgical and non-surgical management was less than 1% change in CFR [10, 61]. In the case of brachytherapy, direct comparisons with surgery or radiotherapy would be particularly valuable. Nevertheless, despite the absence of such comparative studies, the experience with brachytherapy's intended and adverse effects can be summarised and compared to that for alternatives. This is the intended objective of this brief report, which also discusses cost and cost-effectiveness issues and concludes with a statement on the status of this technology in current practice.

DESCRIPTION OF THE TECHNOLOGY

Brachytherapy or interstitial therapy refers to therapeutic radiation delivery from locally implanted sources in contrast to external-beam radiation where the source is outside the patient. Locally implanted sources offer the theoretical advantage of less radiation dissipation into interposed tissues and thus, less damage to adjacent non-cancerous tissues. As a result, higher doses

can be delivered to the prostate than would be possible with EBRT. Sources of radiation have expanded from the original iodine-125 (I-125) “seeds” to include other isotopes such as palladium-103, iridium-192 and gold-198. In addition, some investigators have published results of brachytherapy supplemented with EBRT.

The brachytherapy technique was first developed using I-125 seeds placed retropubically by a freehand method, typically at the time of pelvic node dissection [63]. In this approach, the surgeon literally “seeds” the prostate by inserting the radioactive material into the gland by hand, unguided by corroborating imaging information. This original freehand technique was initially heralded as a vast improvement over EBRT, but published case series from the 1970s reported high rates of local recurrence of disease and the therapy, never widely adopted, fell out of favour by the early 1980s [42].

During the mid-1980s, two technical factors combined to spark renewed interest in brachytherapy. The first of these is improved source placement using transrectal ultrasound (TRUS)-guided needles to place the seeds in the prostate [20]. Real-time, three-dimensional information about prostate volume and location increases the likelihood that the radioactive source is delivered into the optimal tumour location. The second is improved algorithms for measuring prostate volumes and for treatment planning to standardise radiation dosimetry, improving delivery of planned doses to the desired location.

Advances in imaging, particularly TRUS and the almost-ubiquitous availability of CT scanning, have not only had technical implications but have made the surgical approach required for freehand placement redundant. With less emphasis on surgical staging of prostate cancer, freehand placement today would require the patient to undergo an invasive surgical procedure merely

to have the seeds inserted. In addition to its role in non-surgical staging, CT scanning has also been used to validate seed placement.

BRACHYTHERAPY IN THE CONTEXT OF CHANGING HEALTH CARE SYSTEMS

Brachytherapy is then less a new technology than one which, when initially introduced, achieved little adoption due in part to low efficacy. Its recent renaissance is not due to changes in the technology itself but to advances in ancillary areas of imaging and treatment planning. Furthermore, its return to prominence is also driven by fundamental changes in health care delivery and demographics.

Both EBRT and prostate surgery require substantial infrastructure. For EBRT, this includes not only the radiation equipment but also the institutional setting for daily or weekly visits, often over a period of weeks to months. The English language brachytherapy literature is largely from U.S. centres. Many authors make reference to the markedly reduced number of hospital visits for brachytherapy compared to conventional EBRT. Since the “seeds” once implanted require no medical infrastructure, patients need not make the daily/weekly visits for EBRT. This literature is replete with vague but unsubstantiated claims about the cost-effectiveness of brachytherapy.

The demographic factor arises from rapid growth in the number of older males and the increasing proportion of them who are being diagnosed with prostate cancer by serum PSA testing. For example, in Quebec, the number of PSA tests has increased ten-fold since 1990. Particularly when used in asymptomatic males, this is likely to shift the distribution of stage of prostate cancer to earlier stages, stoking demand for treatment for early stage prostate cancer.

In this population of essentially well males, less invasive therapies requiring few visits to the physician or hospital are particularly important. Such therapies enable men to continue working and living their lives with minimal medicalization. For health care systems, this translates into the potential for more cost-effective care delivery. At the same time, the willingness of such essentially healthy males to accept treatments with substantial side effects is likely limited. As a result, brachytherapy has received a second look in part for technical reasons but importantly for reasons less connected with its efficacy than with the health care settings and patient populations where it is used.

EFFICACY

The brachytherapy literature, while growing, is marked by wide variation in admissibility criteria for patients, outcome definition, and follow-up. While brachytherapy was first reported in 1913 [34], the first significant case series dates to 1972. Thirty-three papers from 1972 through 1999 were reviewed for this project. The main sources of information were the Medline database and reference lists of identified papers. In order to appraise the literature not only in quantity terms but also in quality terms, Table 1 outlines a typology of evidence and the number of papers falling in each of the categories.

PSA information's influence in the ranking reflects the growing body of evidence indicating that PSA levels, pre- and post-treatment, are the most important predictor of treatment outcome. Reflecting this view, two reviews, one published in 1997 [53], and updated by the same authors in 1998 [54], limited their contributing studies to those in which both pre-treatment and post-treatment PSA levels were available. The 1998

review found only 8 articles meeting these criteria, four of which used brachytherapy alone and four using combinations of brachytherapy and EBRT. The 1997 review noted that only 5 of 30 brachytherapy papers met these criteria. While these articles represent the best available evidence, they remain level 5 evidence. Our own review includes more recent papers and less strict selection criteria.

No randomised studies comparing brachytherapy to other treatments were identified. The English language literature consists almost entirely of case series, level 5 and 6 evidence. Medline searches of abstracts from literature in languages other than English did not identify any level 1 or 2 studies. Three level 3 studies were identified. One compares a brachytherapy series from Washington State to a series of surgically-treated men from Baltimore [36]. The authors, based in Baltimore, noted that defining biochemical failure as a PSA level > 0.5 ng/mL was most compatible with the definition used in surgical series. Using this definition, the single comparative study, a relatively-weak, matched series design, where the matching methods were poorly described, reported seven-year freedom from progression of 79 % among men treated with brachytherapy compared to 97.8 % among men treated with surgery [36].

In a retrospective comparative study [43], patients having undergone a radical retropubic prostatectomy (all performed by the same surgeon) were matched for similar pre-treatment clinicopathological characteristics with men treated with I-125 brachytherapy as monotherapy for localised prostate cancer (data from another series [42]). The operated patients were sampled from a sub-group of men, having a Gleason score

Table 1 : Classification of Studies According to Level of Evidence

Strength of Evidence	Study description	Number of Studies Reviewed
Strong - Level 1	RCT with pre- and post-treatment PSA information	0
Level 2	RCT without PSA information	0
Level 3	Comparative study with pre- and post-treatment PSA information	3
Level 4	Comparative study without PSA information	0
Level 5	Case series with pre- and post-treatment PSA information	17
Weak - Level 6	Case series without PSA information	13

RCT : Randomised-controlled trial

6 or less on preoperative needle biopsy, a preoperative serum prostate specific antigen (PSA) value available and clinical stage T1 or T2 disease according to TNM (tumours, nodes, metastases) system.

To avoid a possible chance extreme result from one random sample, the authors estimated 7-year recurrence-free survival in five computer generated random samples of the study population. Mean 7-year recurrence-free survival was 84 % (95 % confidence intervals, 78-89 %) for the radical prostatectomy series compared to 79 % (confidence interval not provided) for the I-125 brachytherapy series. However, the authors pointed out that no definitive conclusions about the relative efficacy of one treatment modality over the other one can be made using this type of design and that “ comparisons are confounded by residual differences in clinicopathological features of tumours between groups and different treatment end points to determine outcomes ” [43].

The other level 3 study reports a three-group comparison among men treated surgically with EBRT or brachytherapy in which no statistically significant differences in relative risk of bio-

chemical failure were noted for low-risk men, (stage T1c/T2a and Gleason score < 7 and PSA ≤ 10 ng/mL) [13]. Men with intermediate, (stage T2b and Gleason score = 7 and PSA > 10 and ≤ 20 ng/mL) or high risk, (stage T2c or Gleason score > 7 or PSA > 20 ng/mL) had a statistically significant three-fold higher relative risk of biochemical failure if treated with brachytherapy rather than surgery or EBRT [13].

In addition, a paper presented at the October, 1998 American Society for Therapeutic Radiology and Oncology meetings reportedly found no difference in 5 year recurrence among a series of brachytherapy-treated men compared to an EBRT series of men [16].

Table 2, entitled “ Efficacy of Brachytherapy: The Evidence ” and appearing at the end of the report, details the evidence ranked in terms of strength. Assessing these studies is complicated by the wide variation in patient characteristics and outcomes. Even among the relatively few studies reporting pre- and post-treatment PSA information, outcome definition varies widely.

Most recent studies report some form of freedom from clinical or biochemical failure as the pri-

mary outcome, yet definitions of biochemical failure include serum PSA levels above various cut-off values, two or three consecutive increases in PSA levels, and various combinations of these definitions. The rationale for these biochemical measures arises in part from the low mortality among these men, meaning that mortality outcomes are too few for inference, and for comparison with surgical or EBRT series. In addition, biopsy results have also been used to classify patients as successfully treated or not [35, 38].

Based on the level 5 evidence, freedom from biochemical failure, however defined, at times from one to seven years, ranges from 74-98 % among men with low pre-treatment PSA to 33-80 % levels among men with high pre-treatment PSA levels. Negative biopsy rates range from 80 % to 55 % at one year. Biopsy-negative rates are likely to increase with time, and longer follow-up from the pre-PSA era indicates that as many as 97 % of patients with early-stage (A2) cancer will have negative biopsies at two years, but this figure should not be equated with the cure rate.

Care must be taken not to overestimate the depth of the data reported in the studies noted in Table 2. In several cases, brachytherapy centres have published papers that describe some part of previously published cohorts. In addition, the outcomes from centres with substantial experience are unlikely to be achieved in centres newly adopting this treatment. While the case series are important to appreciate the evolution of technique, the absence of comparative studies and of details about patient selection for these series, coupled with variable outcome definitions, weakens the value of this evidence for addressing the question of whether brachytherapy is an efficacious treatment for prostate cancer. With regard to outcomes, it must be pointed out that PSA-based measures do not replace the primary outcome of therapy, which remains clinical dis-

ease status, such as presence of metastases and death due to prostate cancer. Thus, the brachytherapy evidence is generally of poor quality. Taken together, the levels 5 and 6 case series evidence suggest that men with early-stage, localised, well-differentiated prostate cancer and a low pre-treatment PSA level have the best outcome defined in terms of freedom from biochemical failure. Some clinicians and researchers use those results to propose that optimal candidates for permanent seed implantation should be that selected group of men [13, 18, 37, 41]. However, there is insufficient evidence to make robust inferences about the relative efficacy of brachytherapy compared to other treatment modalities. There is also insufficient evidence to compare brachytherapy to watchful waiting.

SIDE-EFFECTS

Sidestepping efficacy, proponents of brachytherapy have made some of their strongest claims for its role in terms of reduced morbidity. Despite little agreement on what constitutes report-worthy impotence or incontinence, this claim is important as men with localised, well-differentiated, early-stage prostate cancer are persons with generally high pre-treatment functioning. Again, data on complications are plagued by a lack of comparability due to minimal detail regarding the definitions of the various complications.

For comparison, the 1995 CETS report noted that radical prostatectomy was associated with a 2 % risk of severe long-term urinary incontinence, a 57 % risk of impotence among previously potent men, and an intraoperative death rate of 1/300 [10]. Complications associated with radical prostatectomy may be reduced as the procedure is performed more often and wider use of the nerve-sparing operation should reduce impotence rates. However, a recent study found that postoperative sexual function is improved to a lesser extent than previously reported and that

the benefit of nerve preservation might be the result of patient selection and not of the technique per se [52]. Another study assessing health-related quality of life of prostate cancer patients treated with ERBT reported that impotence occurs in 50-70 % of men after treatment and that long term bowel damage causing symptoms of rectal urgency and diarrhea is not uncommon [27].

Table 3, entitled "Complications of Brachytherapy: The Evidence", and which is found at the end of the report, gives details about complication rates as reported in different studies.

Among the brachytherapy case series reporting rates of impotence, all are substantially lower than 57 %. Not all series include data on complications, but among those that do rates of impotence reported range from 0 to 34 %. This preservation of erectile function in the majority of patients is an important aspect of their quality of life after treatment [3]. Data on incontinence are similarly variable but reported incontinence risk is consistently on the order of 1 % among men with no previous transurethral resection of the prostate (TURP) and up to 12.5 % among men with previous TURP [6, 42].

Reported rates of proctitis are higher than in reported surgical series but lower than reported in conventional EBRT series, presumably due to the lower doses of radiation to adjacent tissue. A unique complication of brachytherapy is pulmonary embolization of the seeds, noted incidentally on chest x-rays and reported to be of no health consequence [32].

In sum, data on complications of brachytherapy has yet to be collected in a consistent manner. Based on the published reports, side-effects are largely local and self-limited. The reported case series suggest that rates of post-treatment impotence are lower among brachytherapy-treated males compared to surgically-treated males. Re-

ported rates of incontinence are no worse and, among men with no history of TURP, lower than among surgically-treated males.

SERVICE ORGANISATION AND COST-EFFECTIVENESS

Canadian or Quebec data on brachytherapy are essentially non-existent. The sparse data available from the U.S. suggest vast centre-to-centre variation in how patients are selected and managed. A 1997 survey of American urologists found that few referred patients for brachytherapy and that their staging practices varied widely, with 84% of urologists ordering bone scans as part of staging despite evidence of very low yields from these investigations [5].

The strongest evidence regarding service organisation comes from a 1998 survey of brachytherapy centres. Thirty-five of seventy American brachytherapists responded to the questionnaire. The data gathered from respondents indicated that there is wide variation in maximum Gleason scores and PSA levels used for patient selection for brachytherapy and wide variation in physics and dosimetry practice [39, 40]. The same authors reported that responding programs had a median of 2 radiation oncologists and three urologists involved at their institutions. Five programs reported no direct involvement of urologists and most reported some number of specially trained support staff including nurses, technologists and ultrasonographers in addition to the radiation support personnel. The mean number of personnel involved in the operative implant procedure was 3.6 [39].

From the extremely limited information available, no definitive conclusions about cost-effectiveness can be made. If brachytherapy is considered to be as efficacious as prostatectomy and EBRT, it is reasonable that there would be some reduction in direct costs of care. A 1998 proposal from the *Centre Hospitalier Universi-*

taire de Québec (CHUQ) based on charges, suggests that costs per case of brachytherapy are \$2986 with I-125 (seeds' cost is \$2000) or \$5486 with Pd-103 (seeds' cost is \$4500) in their centre compared to \$4560 for EBRT and \$6318 for prostatectomy (letter of Dr Jean Roy, Head of the Department of Radio-Oncology, to Dr Benoît Dumais, Director, Diagnostic, Clinical and Hospital Services, *Centre hospitalier universitaire de Québec*).

These figures should be interpreted with caution, however, as they appear to be based largely on physician and technical fees only and do not include overhead and equipment cost, and most other personnel and supplies. Other treatment centres also claim that the average cost of brachytherapy, as opposed to external beam radiation and radical prostatectomy, is significantly less, both in dollars, hospital time and recuperation time. Their argument is that this procedure is done in an outpatient setting with negligible intraoperative morbidity, avoids a hospital stay (compared to radical prostatectomy) and does not require repetitive treatments as for EBRT.

However, the situation might be different. According to a recent paper, the average total charges for brachytherapy (BT) are significantly higher than those for radical retropubic prostatectomy (RPP) [56]. Data were collected on 35 consecutive patients (RRP: 16 and BT: 19) and resulted in average total charges of US \$15,097 \pm 5,232 (including an average charge of \$1,897 for 3.8 days of hospital stay) for the RPP group and \$21,025 \pm 1,292 in the BT group (including an average hospital stay of 0.18 day for a mean charge of \$82). The \$5,928 difference was significant ($p < 0.0001$). The higher charges for BT came from dosimetry calculations, the seeds themselves (15 cases with P-103 for a cost of \$7,506 and 4 cases with I-125 for a cost for \$3,838) and the interstitial application complex. The authors mention that charges for complica-

tions are not adequately reported in both groups and that their data do not reflect the costs of recovery and loss of work time. These last two factors, which are expected to be higher in the prostatectomy group, might offset the higher charges for men treated with BT.

In addition, expansion of brachytherapy may lead to price increases for radioactive seeds in jurisdictions where only a single supplier exists, but the situation might be the opposite if more companies enter the market following an increase in the number of procedures done.

Data on costs of delivering brachytherapy, particularly in settings where EBRT treatment of early-stage prostate cancer uses substantial resources, are clearly needed. In a health care system committed to radiation treatment of early-stage prostate cancer, brachytherapy may be more cost-effective if its introduction frees EBRT resources for treating other tumours for which there are fewer therapeutic options. It must be stressed, however, that this is at best a hypothetical proposition and that, notwithstanding the claims of brachytherapy promoters, no evidence or evaluation of these claims is possible based on current information. In fact, if brachytherapy is also used in combination with EBRT for more advanced prostate cancers or for cases with high-risk of recurrence, very few EBRT resources will be freed.

CONCLUSION

Based on the three comparative studies and the case series literature, it is not possible to demonstrate an efficacy advantage of brachytherapy over existing treatments. Furthermore, it is also not possible to exclude the possibility that brachytherapy is less efficacious. However, reported adverse side effects, particularly impotence, are substantially less frequent with brachytherapy than either surgery or EBRT. No data on cost-effectiveness were located to sub-

stantiate claims by the promoters of brachytherapy that it is more cost-effective than EBRT.

Brachytherapy for prostate cancer is clearly not yet an accepted technology. Lacking direct evidence of its efficacy compared to watchful waiting or surgery or EBRT marks brachytherapy as an experimental therapy [2].

However, there is some agreement that brachytherapy might be of more benefit to men with early-stage, localised, well-differentiated prostate cancer and a low pre-treatment PSA level. Another promising avenue for brachytherapy is its use as a boost following moderate doses of EBRT for locally advanced disease [37]. However, long-term results are still not available and

randomised-controlled trials are needed to confirm those different uses, to establish its comparative efficacy and to delineate the specific role of brachytherapy in prostate cancer management.

An interesting additional feature is the extent to which innovation in care delivery has led to its renaissance, especially advances in imaging (transrectal ultrasound and CT scanning), which facilitate seed placement, and improved algorithms for dosimetry calculations. Evaluating brachytherapy's role in prostate cancer management will also require an evaluation of the settings and costs associated with delivering that treatment compared to the alternatives of surgery and EBRT [60].

Table 2 : Efficacy of Brachytherapy: The Evidence*

REF.	# Subjects & Follow-up	Patient Characteristics			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
<u>LEVEL 1 EVIDENCE: RCT WITH PRE- AND POST-TREATMENT PSA INFORMATION</u>							
No studies identified							
<u>LEVEL 2 EVIDENCE: RCT WITHOUT PSA INFORMATION</u>							
No studies identified							
LEVEL 3 Evidence: Comparative studies with pre- and post-treatment PSA information							
Polascik 1998 [36]	Matched series of 122 men treated with brachytherapy & 76 with surgery Mean F/U: 83.2 months	Surgical series had more T1b tumors and fewer T1c than radiation series			I-125 TRUS (n=122)	Freedom from PSA progression (PSA > 5 for radiation, > 0.2 for surgery) at 7 years	Surgery: 97.8% Rtx: 79%
D'Amico 1998 [13]	Series of 888 men treated with surgery, 218 with brachytherapy & 766 with EBRT Median F/U: 38-41 months	T1c: 256/222/72 T2a: 388/246/103 T2b: 93/141/12 T2c: 151/157/31 (surgery/EBRT/brachytherapy)	2-4: 164/109/16 5-6: 517/376/157 7: 133/192/39 8-10: 74/89/6	0-4: 85/77/21 4.1-10: 510/329/148 10.1-20: 210/198/40 > 20: 83/162/9	Pd-103 TRUS (n=152 also given adjuvant androgen therapy)	Actuarial freedom from 3 consecutive rising PSA values at least 3 months apart at 5 years	Low-risk: RR=1.1 for brachytherapy or EBRT compared to surgery Intermediate E RISK: RR=3.1 High risk: RR=3.0

* The table below summarises the evidence by the levels shown in Table 1. Two systems of staging are reported in the literature, the older A,B,C,D surgical staging and the currently used TNM (tumor, nodes, metastases) system. Under PSA level, the categories are those used by the authors of each study. There is, however, general agreement that PSA levels less than 4 are "normal". An explanation of abbreviations is presented at the end of the table.

Table 2 (Cont'd) : Efficacy of Brachytherapy: The Evidence

REF.	# Subjects & Follow-up	Patient Characteristics			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
Ramos 1999 [43]	Matched random sampled series of 299 men treated with surgery & 122 with brachytherapy [41] Mean age: 62 ±7 Mean F/U: 60 months	T1a: 9/5 T1b: 13/4 T1c: 64/19 T2a: 162/76 T2b: 48/17 T2c: 3/1	2: 22/10 3: 45/17 4: 81/34 5: 110/45 6: 40/16	0-4: 131/54 4.1-10: 101/42 > 10: 67/26	I-125 TRUS	Actuarial freedom from from PSA progression greater > 0.3 ng/ml, local recurrence or distant metastasis	Surgery: 84% (95% CI: 78 to 89) Rtx: 79% (CI not re- ported)
<u>LEVEL 4 Evidence: Comparative studies without PSA information</u>							
No studies identified							
<u>LEVEL 5 Evidence: case series with pre- and post-treatment PSA information</u>							
Ragde 1997 [47]	126 (data on 122) median age=70 mean F/U: 65.4 months	T1a: 5 T1b: 4 T1c: 19 T2a: 76 T2b: 17 T2c: 1	2: 10 3: 17 4: 34 5: 45 6: 16	0-4: 54 4.1-10: 42 10.1-20: 19 20.1-40: 6 > 40: 1	I-125 TRUS	Actuarial freedom from PSA > 1.0 @ 7 years (n=23 at risk)	87%
Beyer 1997 [6]	499 (data on 489) median age=74 median F/U: 34 months	T1a: 64 T2a: 260 T2b: 117 T2c: 48	2-4: 106 5-6: 306 7-10: 61 ND: 16	≤ 4: 20% > 4: 80%	I-125 TRUS	Biochemical disease-free survival (PSA ≤ 4), @ 5 years, by baseline PSA	≤ 4: 94% ≤ 10: 70% > 10: 39%
Prestidge 1997 [38]	402 of whom 201 had post- treatment biopsy	T1a: 8 T1b: 11 T1c: 88 T2a: 250 T2b: 40 T2c: 5	2-4: 158 5-6: 199 ≥ 7: 37 ND: 13	0.1-1.0: 6 1.1-4.0: 91 4.1-10.0: 208 > 10: 96 ND: 1	I-125 TRUS	Negative biopsy (no time given, some patients had multiple biopsies)	161/201 (80.1%)

Table 2 (Cont'd) : Efficacy of Brachytherapy: The Evidence

REF.	# Subjects & Follow-up	Patient Characteristics			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
Stokes 1997 [48]	142 mean age = 74 median F/U: 30 months	T1b: 13 T1c: 8 T2a: 63 T2b: 46 T2c: 12	all ≤ 7	Mean PSA = 10.6	I-125 TRUS	Disease-free survival @ 2 years (median f/u=30 months)	90%
Sharkey 1998 [45]	474 (data on 434) mean age = 73		2-4: 13.4% 5-6: 60.1% ≥ 7: 26.5%	< 10: 81%	Pd-103 TRUS & preoperative hormone therapy if Gleason > 7	PSA < 1.5 @ 1 year, by baseline PSA (brachytherapy only) **: results appear impenetrable without time course or clear description of method of analysis	0-4: 90% 4.1-10: 72% 10.1-20: 53% > 20: 33%
Mate 1998 [29]	104 mean age=68.6 median F/U: 45 months	T1b: 1 T1c: 31 T2a: 28 T2b: 24 T2c: 9 T3a: 8 T3c: 3		> 4: 90%	Ir-192 TRUS & EBRT	Freedom from 3 consecutive increases in PSA (variable testing intervals), by baseline PSA	< 10: 93% 10-20: 90% > 20: 60%
Zeitlin 1998 [64]	212 mean age=67 mean F/U: 33 months	T1b: 4 T1c: 107 T2a: 34 T2b: 30 T2c: 5 T3: 32	2-4: 49 5-6: 94 7: 49 8-10: 20	≤ 4: 11 4.1-10.0: 82 10.1-15.0: 44 15.1-20.0: 31 > 20: 44	Gleason 2-6: I-125 TRUS & EBRT Gleason 7-10: Pd-103 TRUS & EBRT	PSA ≤ 0.5 , by baseline PSA	> 20: 72% ≥ 20: 95%

Table 2 (Cont'd) : Efficacy of Brachytherapy: The Evidence

REF.	# Subjects & Follow-up	Patient Characteristics			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
Arterberry 1993 [4]	27 (data on 21) median age=67 mean F/U: 13 months	A: 1 B: 17 C: 1 D: 2		> 4: 17/18 stage A or B	I-125 TRUS	PSA < 4.0 @ 6 months	13/17
Dattoli 1996 [15]	73 median age=71	T2a: 2 T2b: 16 T2c: 19 T3: 36	4: 5 5: 9 6: 19 7: 26 8: 8 9: 6	< 15: 41 ≥ 15: 32	Pd-103 & EBRT	Actuarial freedom from PSA > 1.0 at 3 years	79%
Wallner 1994 [59]	62 median age=67 median F/U: 19 months	T1b: 2 T1c: 13 T2a: 25 T2b: 17 T2c: 5		≤ 4: 4 > 4: 56 ND: 2	I-125	Actuarial biochemical disease freedom @ 24 months by post-treatment PSA level	< 4: 94% < 2: 85% < 1: 74%
Kaye 1995 [23]	132 (data on 86) mean age=70 mean F/U: 26.1 months	T1b: 5 T2: 71 T3: 10	< 7: 64 ≥ 7: 22	≤ 4: 16 > 4: 70	I-125 (n=47) I-125 & EBRT (n=39) TRUS	PSA-progression-free survival (nadir PSA < 4, no increase > 2, and PSA< 4 after reaching nadir) @ 26.1 months	88%
						Negative biopsy at one year	55%
Kaye 1995 [22]	76 (note this is the T1 & T2 patients reported in [23] mean age=71 mean F/U: 26.3 months	T1: 5 T2: 71	< 7: 60 ≥ 7: 16	≤ 4: 16 > 4: 60	As in ref [23]	PSA < 4.0 post-treatment	97.7%

Table 2 (Cont'd) : Efficacy of Brachytherapy: The Evidence

REF.	# Subjects & Follow-up	PATIENT CHARACTERISTICS			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
Kaye 1995 [22] (cont'd)						Complete progression-free survival (PSA < 4.0, DRE negative, biopsy negative)	56.3%
Blasko 1995 [7]	197 mean age=70 median F/U: 3 years	T1b: 5 T1c: 33 T2a: 139 T2b: 21	2-4: 105 5-6: 87 ND: 5	Elevated: 138	I-125 TRUS	Actuarial freedom from biochemical failure (PSA > 4, two consecutive increasing values of PSA, PSA greater than baseline value in those where baseline < 4.0), by initial PSA	<4: 98% 4-10: 90% 10-20: 89% >20: 80%
Stromberg 1995 [51]	48 (data on 33) mean age=67 median F/U: 13 months	T2b: 9 T2c: 17 T3: 7	< 8: 8 ≥ 8: 25	≤ 4: 1 > 4: 32	Ir-192 TRUS & EBRT	PSA ≤ 4	29/32
Stock 1996 [46]	97 median age=69 median F/U: 18 months	T1b: 4 T1c: 9 T2a: 22 T2b: 52 T2c: 10	2-4: 31 5-6: 49 ≥ 7: 17	≤ 4: 12 4.1-10: 32 10.1-20: 29 > 20: 24	I-125 TRUS (Gleason < 7) Pd-103 TRUS (Gleason ≥ 7)	Biochemical failure at two years (two consecutive PSA increases from nadir or PSA >1 ng/mL for hormone-treated), by initial PSA	≤ 10: 83% 10.1-20: 82% > 20: 58%
Wallner 1996 [58]	92 median age=67 median F/U: 3 years	T1b: 2 T1c: 32 T2a: 33 T2b: 22 T2c: 3	2-4: 27 5-7: 64 ND: 1	0-4: 7 4-10: 43 10-20: 29 > 20: 12 ND: 1	I-125 TRUS	Actuarial freedom from biochemical failure (PSA > 1.0 ng/ml) by initial PSA @ 4 years	≤ 4: 100% 4-10: 80% > 10: 43%

Table 2 (Cont'd) Efficacy of Brachytherapy: The Evidence

REF.	# Subjects & Follow-up	PATIENT CHARACTERISTICS			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
Stone 1995 [49]	71 mean F/U: 2 years	T1b: 3 T1c: 5 T2a: 16 T2b: 42 T2c: 5	2-4: 27 5-6: 34 >6: 10	0-4: 8 4.1-10: 23 10.1-20: 22 > 20: 18	I-125 or Pd-103 TRUS (n=60)	Positive biopsy at varying times	6/36
LEVEL 6 Evidence: Case series without PSA information							
Paul 1997 [35]	40 mean F/U: 74 months	T1: 5 T2: 18 T3: 17			Ir-192 TRUS	Negative biopsy at 18 months	T1: 4/4 (100%) T2: 10/14 (71%) T3: 7/14 (50%)
						Proportion alive at median follow-up of 74 months	35/40 (87.5%)
						Actuarial freedom from PSA > 0.5 @ 7 years (n=23 at risk)	79%
						Actuarial freedom from biochemical progression (2 consecutive PSA increases) @ 7 years	89%
Vijverberg 1993 [55]	52 (data on 46) mean age=71	T0,pT1: 1 T2: 23 T2-T3: 21 T3: 1				Negative biopsy at 6, 12, 24, & 48 months	6 m: 22% 12 m: 33% 24 m: 40% 48 m: 50%
						Palpable residual tumor at 24 months	10%
						Persistent hypoechoic areas on TRUS	35%

Table 2 (Cont'd) Efficacy of Brachytherapy: The Evidence

REF.	# Subjects & Follow-up	Patient Characteristics			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
Zelevsky 1997 [66]	1078 median age=61 median F/U: 11 years Note: 403 of these patients were followed with serial PSA once the test became available in 1987	B1: 234 B2: 472 B3: 145 C: 227			I-125 & pelvic node dissection	recurrence-free survival @ 5 years	59% (+ nodes: 39%, - nodes: 69%)
						recurrence-free survival @ 10 years	36% (+ nodes: 20%, - nodes: 44%)
						Recurrence-free survival @ 15 years	15% (+ nodes: 14%, - nodes: 24%)
						Clinical disease-free survival @ 5 years	83%
						Disease-free survival @ 5 years (median f/u=30 months)	76%
						Recurrence (no time period given) by baseline PSA	≤ 4: 0/23 (0 %) 4-10: 9/63 (14.3%) 10.1-20: 8/39 (20.5%) >20.1: 7/13 (53.8%)
Critz 1996 [11]	538 (data on 536) median F/U: 40 months	T1a: 11 T1b: 46 T1c: 119 T2a: 150 T2b: 156 T2c: 54	2-4: 220 5-7: 253 8-10: 56		I-125 & EBRT	Disease-free survival @ 5 years, by lowest PSA nadir (uncorrected for number of PSA tests)	≤ 0.5: 95% 0.6-1.0: 29% >1.0: 0%
						PSA < 1.5 @ 4 years, by baseline PSA (brachytherapy only)	0-4: 90% 4.1-10: 76% 10.1-20: 50% >20: 100%

Table 2 (Cont'd) Efficacy of Brachytherapy: The Evidence

REF.	# Subjects & Follow-up	Patient Characteristics			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
Lannon 1993 [25]	180 mean age=67.1	A2: 38 B1: 38 B2: 87 C: 31			Au-198 & EBRT	Negative biopsy @ 2 years, by initial stage	A2: 97% B1: 94% B2: 77% C: 87%
						Actuarial 10 yr. Disease-free survival by stage	A2: 83% B1: 91% B2: 64% C: 51%
Stromberg 1993 [50]	57 mean age=63.3 median F/U: 72 months	B2: 5 C: 52	<7: 23 ≥ 7: 34		Ir-192 & EBRT & pelvic lymph node dissection	Actuarial 5 yr. survival by Gleason score	< 7: 96% ≥ 7: 77%
						Actuarial 5 yr. disease-free survival by Gleason score	< 7: 75% ≥ 7: 55%
Adolfsson 1994 [1]	37 median age=68 mean F/U: 62 months	T1: 1 T2: 16 T3: 19 ND: 1			I-125	Freedom from progression @ 5 years	57%
						Freedom from distant metastases @ 5 years	70%
Hochstetler 1995 [19]	177 (data on 157) median age=71 median F/U: 48 months	A2: 19 B1: 24 B2: 53 C: 60			Au-198 TRUS	Survival @ median follow-up of 48 months	78%
Loening 1993 [28]	31 (subset of ref. 38, comprising men with recurrence after EBRT)	A2: 2 B1: 3 B2: 9 C: 13 D1: 4			Au-198 TRUS	Negative biopsy at one year	6/15

Table 2 (Cont'd) Efficacy of Brachytherapy: The Evidence

REF.	# Subjects & Follow-up	Patient Characteristics			Isotope	Outcome	Result
		Stage	Gleason Score	PSA level			
Weyrich 1993 [62]	132	A2: 11 B1: 32 B2: 54 C1: 35			I-125 & pelvic lymph node dissection with EBRT for positive nodes	Disease-free (PSA < 4.0, negative DRE, negative biopsy) @ 5 years	59%
						Disease-free (PSA < 4.0, negative DRE, negative biopsy) @ 10 years	47%
Charyulu 1979 [9]	46 (data on 32)	B: 16 C: 16			I-125 & pelvic node dissection with EBRT (16) or no EBRT (16)	Survival after minimum 2 years follow-up among 17 patients with positive lymph nodes	8/17
D'Addressi 1995 [12]	63 mean age=65 mean F/U: 55 months	T1: 21 T2: 42			I-125 & pelvic node dissection	No evidence of disease (unclear definition) by stage @ 10 years	T1: 53% T2: 52%
						Overall survival by stage @ 10 years	T1: 71% T2: 57%
Roeleveld 1996 [44]	75 median F/U: 103 months	T0: 1 T1: 14 T2: 60			I-125 retropubically & pelvic node dissection	Survival @ 5 years	74%
						Survival @ 10 years	42%

Abbreviations:

CI: Confidence interval
 DRE: digital rectal examination
 EBRT: external-beam radiation therapy
 PSA: prostate-specific antigen
 RCT: randomised-controlled trial
 RR: relative risk
 TRUS: transrectal ultrasound
 Ir-192: iridium 192
 I-125: iodine 125
 Pd-103: palladium 103
 Au-198: gold 198
 ND: no data

Table 3 : Complications of Brachytherapy: The Evidence

REF.	# Subjects	Genitourinary Complications			Other complications
		Impotence	Incontinence	Other	
Ragde 1997 [42]	126		Previous TURP: 6/48 (12.5%) no TURP: 0/70	Urethral stricture: 17/118 (14.4%)	
Paul 1997 [35]	40	4/17 (23.5%)		Urethritis: 4 (10%)	Prostate necrosis: 4 (10%) Proctitis: 4 (10%)
Beyer 1997 [6]	489		7/489 (1.4%)	Prolonged obstructive or irritative symptoms: 21/489 (4.3%)	Chronic pelvic pain: 1 (0.2%) Proctitis: 3 (0.6%)
Nag 1997 [32]			Patient Characteristics		Pulmonary embolization of seeds: 19/107 (17.8%)
Zeleftsky 1997 [66]	1078			Chronic genitourinary related complications: 151 (14%)	Chronic GI-related complications including proctitis: 58 (5%)
Stokes 1997 [48]	142		7/142 (4.9%)		Proctitis requiring colostomy: 1 (0.7%)
Hu 1998 [21]	109				Rectal bleeding/ Proctitis: 19/109 (17.4%)
Sharkey 1998 [45]	434	“less than 15%”	“less than 5%” (all had previous TURP)		
Mate 1998 [29]	104			Urethral stricture: 7/104 (6.7%)	Proctitis: 2/104 (1.9%)
Zeitlin 1998 [64]	212	38%	2.8%		Proctitis: 47/212 (22.2%)
Lannon 1993 [25]	180	10%	3.3%	Urethral stricture: 9.4%	Proctitis: 24.4%
Dattoli 1996 [15]	73	23% @ 3 years (actuarial method)	1/73		
Kleinberg 1994 [24]	31	1/18	1/31		Rectal bleeding: actuarial incidence 31%, “persistent” in 5/9 patients

Table 3 (Cont'd) Complications of Brachytherapy: The Evidence

REF.	# Subjects	Genitourinary Complications			Other complications
		Impotence	Incontinence	Other	
Stock 1996 [47]	89	2.5% @ 1 year 6% at 2 years (actuarial method)			
Stromberg 1994 [50]	57	43%	18%	Urethral stricture: 18%	Proctitis: 12%
Wallner 1994 [59]	62	81% @ 3 years	0		
Adolfsson 1994 [1]	37	ND	ND		Proctitis: 6/37
Kaye 1995 [23]	86	73% @ 1 year	13/80	Urethral stricture: 2/80	Proctitis: 8/80
Kaye 1995 [22]	76 (as ref. 23)	75% @ 1 year	13/76	Urethral stricture: 2/76	Proctitis: 7/76
Nag 1995 [31]	32	ND	19%		Pulmonary migration of seeds: 6/30
Weyrich 1993 [62]	132	4%	1.6%		
Wallner 1997 [57]	19 (all had prior TURP)	0	6% @ 3 years (actuarial method)		
Glajchen 1996 [17]	73				Malpositioned seeds on CT scan: 10/73
Charyulu 1979 [9]	32		2/32		
Stromberg 1995 [51]	33		9%		
Chaikin 1996 [8]	27	45% @ 18 months			All patients reporting potency felt that erection quality had decreased after treatment

Table 3 (Cont'd) Complications of Brachytherapy: The Evidence

REF.	# Subjects	Genitourinary Complications			Other complications
		Impotence	Incontinence	Other	
Stock 1996 [46]	97	21% @ 2 years (actuarial method)	0	Major outlet obstruction requiring TURP: 2/97	Grade 2 proctitis: 1/97
D'Addressi 1995 [12]	63	2/63	0	Flow obstruction requiring TURP: 4/63	Proctitis: 5/63
Wallner 1996 [58]	92	14% @ 3 years	3/8 requiring TURP for outlet obstruction	TURP: 8/92	Rectal ulceration: 5/92, (risk 10% pre-1991, 2% thereafter)
Stone 1995 [49]	71	6%	0	Urinary retention: 4/71	Grade 2 proctitis: 3/71

Abbreviations:

TURP: Transurethral resection of the prostate

ND: No data

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