

Low-dose-rate brachytherapy for low-grade prostate cancer

BACKGROUND Prostate cancer is a radiosensitive type of cancer for which radiotherapy is used for both curative and palliative purposes. Low-dose-rate brachytherapy is an internal radiotherapy technique which allows high doses of radiation to be delivered to a tumour at short range and with a high degree of precision. We have conducted a systematic review of the evidence base for this treatment. The method is not established in Norway.

METHOD This review is based on systematic review articles and publications on treatment, outcomes, adverse effects and health economics considerations found by searching the databases Cochrane Library, Current Controlled Trials, Medline, Embase and NICE (National Institute of Clinical Excellence).

RESULTS Subsequent to long-term observations of the efficacy, adverse effects and costs presented in 43 selected studies, including one randomised, controlled trial, there is still uncertainty as to which of the three methods low-dose brachytherapy, external radiotherapy and radical prostatectomy is optimal. The reason for this is the methodological differences in patient selection and in endpoints such as biochemical disease-free interval and cause-specific survival. The evidence base appears to suggest that low-dose-rate brachytherapy causes more frequent grade 2 and 3 doctor-reported urogenital adverse effects than prostatectomy, but better patient-reported sexual functions and fewer patients with urinary incontinence than after surgery. Low-dose-rate brachytherapy appears to be socioeconomically cost-effective.

INTERPRETATION The evidence base with respect to therapeutic effect and toxicity in men with low-risk prostate cancer treated with low-dose brachytherapy is regarded as solidly documented. However, there are no good prospective randomised multi-centre trials with overall survival as an endpoint.

Prostate cancer is the most commonly occurring type of cancer in men in Norway, and 4 978 men received the diagnosis in 2011 (1). Prostatectomy and radiotherapy are the only two treatment modalities regarded internationally as having curative potential for localised disease. Despite improvements in both diagnosis and treatment, mortality in Norway has not been reduced accordingly (2). The prognosis is related to a number of clinical factors: extent of primary tumour (T-stage), prostate-specific antigen (PSA) and the degree of differentiation and aggressiveness of the tumour (Gleason score). These factors are used to classify patients into three prognostic risk categories: low, intermediate and high.

In patients with low-risk disease, the cancer develops very slowly as a rule, and there is little risk of spreading. Patients have favourable disease variables, classified as \leq T2a, PSA $<$ 10 μ g/l and Gleason score \leq 6. Because PSA screening is increasing, the incidence of prostate cancer with a low risk profile will increase in the years ahead. These patients do not necessarily require immediate treatment. Many may have stable, asymptomatic disease for many years, and can be included in a monitoring programme called «active surveillance». It

is assumed that approximately 30% of patients who are monitored will need treatment later (3). The indication for treatment tends to be a steadily rising PSA level and/or a more aggressive Gleason score.

However, some patients do not wish to be monitored without treatment when they have a cancer diagnosis, even if the disease is stable and without progression. If these patients are to be treated, the method should be effective and have the fewest possible adverse effects. Ultrasound-guided transperineal implantation of permanent radioactive iodine seeds (I-125) in the prostate gland (low-dose-rate brachytherapy – LDR-BT) is a method used in many countries for these patients (Fig. 1).

External beam radiotherapy (EBRT) is traditionally administered using multiple beams from an external source and daily 2 Gy fractions (Gy is the symbol for gray, the unit for absorbed radiation dose) five days a week for a total dose of 74–78 Gy over approximately eight weeks. Alternatively, open or robot-assisted radical surgery can be performed (PRECT).

Low-dose-rate brachytherapy, or internal radiation, is a high-technology therapeutic procedure which allows the deposition of very high cumulative short-range radiation

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MAIN POINTS

Long-term outcomes following low-dose-rate brachytherapy, with emphasis on biochemical disease-free interval and cause-specific survival, are equivalent to those following prostatectomy and external radiation.

Erectile dysfunction and patient-reported urine leakage appear to be less than with prostatectomy and external radiotherapy

The method appears to be cost-effective

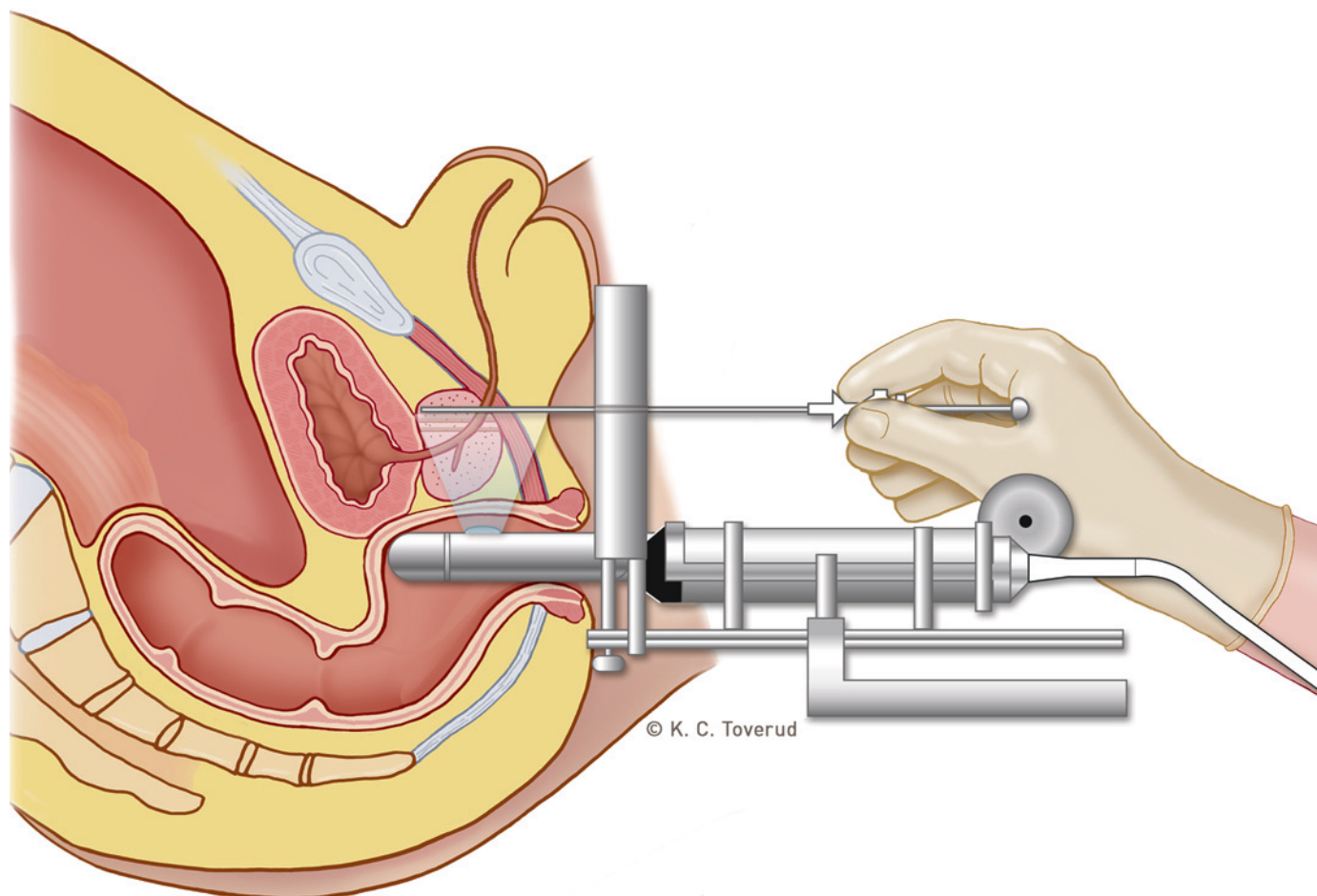


Figure 1 Low-dose-rate brachytherapy with transrectal ultrasound guidance. Transperineal implantation of radioactive iodine seeds ($I-125$) through a perforated template using a coordinate system for accurate deposition of the seeds in the prostate.

doses in the prostate ('brachy' is Greek for short), while the radiation dose that is deposited externally is considerably reduced. The radiation dose from the iodine seeds is gradually deposited in the prostate over a period of about two months (Fig. 2).

With high dose-rate brachytherapy (HDR-BT), which is used for patients with intermediate and high risk profile, hollow steel needles are implanted in the prostate gland. A radioactive source (^{192}Ir) is introduced temporarily into the gland through the needles (4).

There is over 25 years of experience internationally with low-dose-rate brachytherapy. Approximately a third of patients in the USA with low-risk disease, some 50 000, are treated using this method each year. Norway is the only country in Northern Europe where the method is not available. In this article, we review the efficacy, adverse effects and cost-effectiveness of this form of treatment.

Method

We searched for articles in English, German or Scandinavian languages published between

the beginning of January 2000 and mid-December 2013 in the following databases: the Cochrane Library, Current Controlled Trials, Medline, Embase and NICE. In the first two databases, a simple search was conducted for review articles and ongoing trials of prostate cancer with low-dose-rate brachytherapy.

In the Medline and Embase databases the following search strings were used: (prostate tumor AND brachytherapy AND (low-dose rate or LDR) combined with (survival analysis/or disease-free survival OR treatment outcome/or treatment failure OR survival OR brachytherapy/adverse effects OR radiation injuries OR quality of life). The Centre for Medical Method Evaluation (SMM), the NICE Institute and the Cochrane Library were used for input on health economics considerations.

Inclusion of trials

A total of 219 articles met the search criteria. Of this number, 176 articles dealing with low-dose-rate brachytherapy in combination with radical surgery or external radiotherapy

were excluded. This article is accordingly based on 43 articles concerning low-dose-rate brachytherapy as monotherapy: one randomised, controlled trial, 30 non-randomised observation studies, seven review articles based on various single studies and five health economics articles.

Table 1 (5–16) presents the long-term results of low-dose-rate brachytherapy in 12 trials that included more than 100 patients.

Trial evaluation

In order to judge the quality of the trials, we used a validation system recommended by the Norwegian Directorate of Public Health's Knowledge Centre. The national guidelines for treatment of prostate cancer were also used (17). We placed emphasis on endpoints such as biochemical disease-free interval (interval of time between therapy and evaluation time without a rise in PSA – BDFI), biochemical progression-free survival (percentage of patients alive without a rise in PSA at a given evaluation time – BPFS) and cause-specific survival (survival of prostate cancer patients as a percentage –

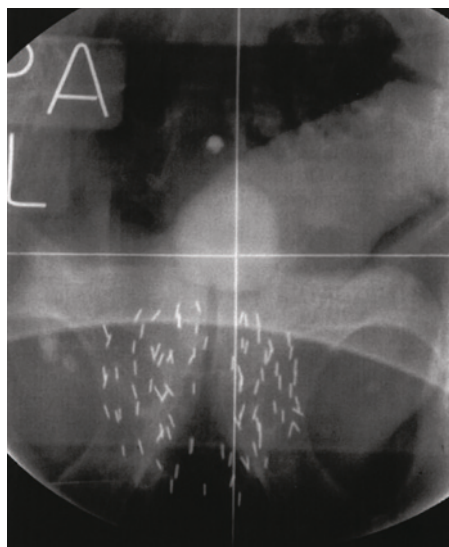


Figure 2 Radiological scan of the pelvis after low-dose-rate brachytherapy. Multiple radioactive iodine seeds are implanted permanently in the prostate gland. The patient is catheterised and the balloon in the bladder above the symphysis is clearly visible. Photo: Bereich Interdisziplinäre Brachytherapie, Universitätsklinikum Schleswig-Holstein, Campus Lübeck. Published with the permission of Dr György Kovács

CSS), overall survival (OS), adverse effects and health economics.

Low-dose-rate brachytherapy was also compared with published findings associated with radical surgery or external radiotherapy, which are established treatment modalities. Adverse effects were evaluated on the basis of doctor- or patient-reported information on gastrointestinal and/or urogenital functions and, if available, quality of life score.

Results

Outcomes

There is only one published randomised controlled trial with low-dose-rate brachytherapy. In it, 200 patients were randomised to either low-dose therapy or radical surgery (7). The primary endpoint was five years of BPFs survival (91% for surgery versus 91.7% for low-dose-rate brachytherapy). There was no difference in the relapse rate between the groups. In Cochrane's systematic review analysis, this trial was strongly criticised for methodological weaknesses. Peinemann et al. maintained that there was little to indicate that low-dose-rate brachytherapy offered therapeutic advantages compared with radical surgery and indicated a need for more randomised trials (18).

A number of treatment centres with long experience of low-dose-rate brachytherapy have published their long-term results (Table 1). Crook et al. have reported their ten years of experience with low-dose therapy for 1 111 patients at the Princess Margaret

Hospital (10), of whom 965 (86.9%) had low-risk disease. PSA relapses occurred in < 2% of the patients.

Taira et al. observed very good long-term results (biochemical disease-free interval) in their study of 1 656 patients after a median follow-up time of seven years (12). Biochemical progression-free survival in the low-risk group was 98.6% and cause-specific survival 99.8%.

Morris et al. published population-based results of a quality-assured brachytherapy programme involving 1 006 patients with both low (58%) and intermediate risk (42%) treated from 1997 at five different centres (16). After a median follow-up period of 7.5 years, estimated 10-year biochemical progression-free survival was 94.1%.

Zelesky et al. published a retrospective study of 448 low-risk prostate cancer patients where 7-year cause-specific survival was 95% for the group that received low-dose-rate brachytherapy, versus 89% for the group that received external radiotherapy with a total dose of 81 Gy ($p \leq 0.004$) (13).

Kupelian et al. reported in their comparative analysis of 950 patients that those who received low-dose-rate brachytherapy had BPFs of 83%, those who underwent radical surgery had a survival rate of 81% and those who received radiotherapy a survival rate of 81% ($p < 0.001$) (5).

A retrospective cohort study of 41 395 patients with the endpoints cause-specific survival and overall survival, in which those with low and intermediate risk profiles were analysed together, revealed no statistical difference, irrespective of age, between low-dose-rate brachytherapy and radical surgery (19). Nor do Kollmeier et al. find any difference between these two treatment modalities in their long-term results (15).

Adverse effects

Several studies report that there are few long-term adverse effects after low-dose-rate brachytherapy with respect to erectile function and urinary incontinence. In the study of Buron et al., which was based on patient-reported information from validated questionnaires, 88% of the patients who had undergone radical surgery had erectile dysfunction and 68.4% reported urine leakage six months after treatment. Of patients with low-dose-rate brachytherapy, 43.5% of whom had received neoadjuvant androgen deprivation therapy, 50.8% reported erectile dysfunction, whereas only 12.5% developed urine leakage (20).

In Stone and Stock's study, 75% of the patients had doctor-reported erectile function prior to implantation, compared with 50% in the follow-up time of at least five years. There was significant correlation between

age and retained erectile function. Urinary incontinence occurred in 1.2% (21).

In another report on long-term adverse effects five years after low-dose-rate brachytherapy, the patients' self-reported quality of life and sexual function were analysed. Grade 2 urinary tract and rectal complications occurred in 5% and 2.9%, respectively, while 37.1% had erectile dysfunction (22).

In an American retrospective study of 729 low-risk patients, it was found on the basis of doctor-reported adverse effects that treatment with low-dose-rate brachytherapy ($n = 448$) resulted in a higher incidence of grade 2 urinary tract and rectal problems (15.6% and 5.1%), but there were fewer with erectile dysfunction than after external radiotherapy (35% versus 44%) ($n = 281$) (13).

There are few long-term rectal problems after low-dose-rate brachytherapy, and they occur most commonly within the first two years in the form of bleeding in connection with defecation. Phan et al. report grade 2 bleeding in 3.7% and grade 3 in 0.4% (23).

A Dutch study has observed for up to 20 years 232 patients with prostate cancer who developed primary cancer of the urinary bladder and rectum subsequent to low-dose-rate brachytherapy or surgery. There was no difference in incidence between the two treatments or when compared with the incidence in the normal population (8).

Health economics

In 2007, a French group published health economics comparisons between radical surgery and low-dose-rate brachytherapy (20). No significant cost differences were found between the treatment methods. In its cost-benefit assessments of low-dose-rate brachytherapy, the NICE Institute regarded this method as economically on a par with radical surgery and external radiotherapy for low-risk patients with prostate cancer (24). However, Wilson et al. pointed out that the costs should be viewed in terms of expenses accruing after the interventions (25). A cost-benefit analysis found low-dose-rate brachytherapy to be equivalent to radical surgery.

The Norwegian Centre for Medical Methodological Assessment reports that low-dose-rate brachytherapy appears to have approximately the same cost level as the alternative treatment options radical surgery and external radiotherapy (26). However, the costs of sickness absence and transport expenses in connection with outpatient treatment do not appear to be included in the report.

Discussion

Our literature review shows that the long-term results following low-dose-rate brachytherapy are equivalent to the results following radical surgery and external radio-

Table 1 One randomised¹ and 11 non-randomised trials with more than 100 included patients treated with low-dose-rate brachytherapy

First author, year of publication [reference]	No. of patients	BPFS (%)	CSS (%)	Median follow-up time (months)	Evidence level
Kupelian P, 2004 [5]	950	75.0		56	3
Merrick G, 2005 [6]	119	96.1		82	3
Giberti C, 2009 [7] ¹	200	91.7		60	1b
Hinnen K, 2011 [8]	232	88.0	96.0	69	3
Prada P, 2010 [9]	734	92.0		55	3
Crook J, 2011 [10]	965	97.2	95.0	42	3
Sylvester J, 2011 [11]	128	85.9	80.4	139	3
Taira A, 2011 [12]	1 656	98.6	99.8	84	3
Zelevsky M, 2011 [13]	448	95.0		77	2b
Dickinson P, 2014 [14]	1 038	94.2		60	3
Kollmeier M, 2013 [15]	178	97.0		83	3
Morris W, 2013 [16]	1 006	94.1	99.1	89	3

therapy. At the NICE Institute, low-dose-rate brachytherapy is regarded as an established treatment, with results in line with those of the other two treatments for low-risk prostate cancer.

In 2011, the European Society of Radiation Oncologists (ESTRO), the European Organisation for Research and Treatment of Cancer (EORTC) and the European Association of Urology (EAU) issued clinical guidelines for low-dose-rate brachytherapy for prostate cancer patients with a low-risk profile, where extra-prostatic tumour extension was excluded (27). In the EAU guidelines for 2012, low-dose-rate brachytherapy is recommended for prostate cancer patients in the low-risk group (3). This is regarded as standard treatment in the countries where the method is used (28). The EAU judges the underlying data as evidence level 2b (knowledge based on at least one well-designed study without randomisation). In Norway, low-dose-rate brachytherapy is regarded as equivalent to radical surgery in the national action programme for treatment of prostate cancer (17).

The goals of low-dose-rate brachytherapy are local disease control, reduction in the risk of metastases and maintaining a good quality of life. Because of the good prognosis, the adverse effects and quality of life of the patients and their preferences are key aspects of the method (27, 28). Patients must be carefully selected to maintain a low morbidity profile.

In order to prevent overtreatment, there should be guidelines for the commencement of treatment, both at the time of diagnosis

and in connection with progression during active surveillance. However, the criteria for selecting and monitoring these patients are not clear. We have therefore concentrated on those wanting targeted primary treatment. There is also a risk of a primary tumour being underestimated and undertreated, as was demonstrated in a randomised study where patients under active surveillance had significantly reduced cause-specific survival compared with those who had had radical surgery (21).

In our literature search, we found that there were limited adverse effects after low-dose-rate brachytherapy. The treatment is not suitable for patients with obstructive urination problems – their symptoms will be exacerbated. They should be offered other curative treatment. The risk of secondary cancer of the rectum or urinary bladder is not higher than the risk in the normal population, so treatment of young patients does not appear to be contraindicated (8).

International randomised studies of low-dose-rate brachytherapy have not been conducted, and it is improbable that any will be (29, 30). This is due to the biology of prostate cancer. The frequency of recurrence in low-risk patients is low, and the probability of significant differences developing after 15–20 years of follow-up is limited. The patients' other treatment preferences may also make randomisation difficult (31).

Low-dose-rate brachytherapy is an attractive curative therapeutic option because of the few adverse effects. The method is standard treatment in Europe and the USA for organ-confined low-risk prostate cancer.

Cost-benefit assessments indicate that low-dose brachytherapy is comparable with radical surgery and external radiotherapy (9, 26), but sickness absence and the costs of patient transport do not appear to have been included in the calculations. The treatment takes about half an hour, average time spent in hospital is 12 hours, and the patient can usually start working again after 3–4 days. With external radiotherapy, patients receive outpatient treatment every day for about eight weeks, usually followed by eight weeks of sick leave. According to a recently published study, half of the patients are on sick leave for more than six weeks after radical surgery (32).

A number of uro-oncologists in Norway master the high-dose brachytherapy technique (33, 34). The implantation technique for high-dose-rate and low-dose-rate brachytherapy is virtually identical. In 2005, the treatment requirement for low-dose-rate brachytherapy in Norway was estimated at about 60–70 patients (internal report from expert group at the Radium Hospital). Because of increased attention to prostate cancer and increasing «wild» screening, the incidence of low-grade disease will also increase among younger men. This will probably lead to an increase in the future need for low-dose-rate brachytherapy.

From a medical point of view, the introduction of the method will be future-oriented. If sickness absence and patient transport are taken into account, we believe that low-dose-rate brachytherapy will yield socioeconomic savings compared with other treatment.

Conclusion

Low-dose-rate brachytherapy, or internal radiotherapy, is an effective and sure curative treatment option for patients with localized prostate cancer with a low risk profile. Our literature search reveals long-term results that are equivalent to those for prostatectomy and external radiotherapy, which means that the majority of patients can be spared long-term adverse effects.

However, no randomised trials with an endpoint of overall survival have been performed. The risk of urinary incontinence and erectile dysfunction is lower than that following external radiotherapy and prostatectomy. Because of the short treatment time, few adverse effects and short sick-leave period, the method appears to be cost-effective.

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