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Interstitial brachytherapy in localised prostate cancer¹

Executive Summary

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Research question

The aim of this review was the evaluation of benefits and harms of low-dose-rate permanent interstitial brachytherapy in localised prostate cancer compared with standard surgical procedures, percutaneous radiotherapy, and watchful waiting. The focus of the evaluation was on patient-relevant therapy goals. Moreover, substantially different types of brachytherapy were to be compared with each other.

Methods

The evaluation was to include randomised controlled trials (RCTs). In addition, non-randomised intervention studies and observational studies with concurrent controls were also to be considered, as long as an adequate control for confounders had taken place.

The endpoints selected were outcomes that enabled an assessment of patient-relevant therapy goals, such as overall survival, disease-free survival, disease-related symptoms, disease-specific and health-related quality of life, adverse events, as well as number and duration of hospital stays.

The systematic literature search was performed in 7 electronic databases (including Medline, Embase, and Cochrane Central) and covered the period up to June 2006. Furthermore, a search was performed in reference lists of primary and relevant secondary publications, such as systematic reviews, HTA reports, evidence-based guidelines as well as in comments on the Federal Joint Committee's list of questions. The manufacturers of the relevant medicinal products and technologies were also asked to provide information.

The literature screening was performed by at least 2 reviewers independently of each other. After a quality assessment of the relevant studies to be included in the report (also performed by 2 reviewers independently of each other), the results of the single studies were organised according to treatment comparisons and therapy goals. The preliminary evaluation conducted by IQWiG (preliminary report) was published on the Internet and comments were invited. Substantial comments were discussed within the framework of an oral scientific debate. Subsequently, the final report was produced.

Results

This review is based on the results of studies that compared low-dose-rate permanent interstitial brachytherapy as monotherapy in localised prostate cancer, either with radical prostatectomy or with percutaneous radiotherapy. In total, 21 studies that initially fulfilled the inclusion and exclusion criteria of the underlying report plan were identified in the various

steps of the literature search. Of these studies, 11 (including a total of 10 900 patients) were included in the evaluation. None of these studies compared brachytherapy with a watchful waiting approach. Moreover, no study fulfilling the inclusion criteria investigated a combination of brachytherapy and additive treatment versus additive treatment alone. Likewise, no studies were identified that assessed different types of brachytherapy compared with each other. The data pool only included non-randomised studies, and only 4 of the 11 studies were described as being prospective. The preplanned quantitative summary of results by means of meta-analysis of the single outcomes was not appropriate due to the methodological problems of the individual studies. Nor were the data suitable for subgroup or sensitivity analyses.

Besides being non-randomised, all 11 studies included in the evaluation showed major quality deficits; 6 studies were of such poor quality that one must assume that their overall conclusion might have been different if these deficits had not existed. The quality deficits primarily refer to the lack of control for confounders and the insufficient description of missing data. No attempts were made in any study to conduct any type of blinding (e.g. blinded evaluation of outcomes). The interpretation of the findings is limited by further imponderables: For example, the brachytherapy techniques applied varied between studies, which may be due to advances in technology. Different isotopes with different activities were used as radiation sources, and were combined with various additive therapies. The latter were often not described, or not clearly described. In order to evaluate the issue of the equivalence of therapies with regard to tumour control, the studies lack sufficiently long observation periods and/or a correspondingly large sample size, despite the known low event rate. None of the studies was recognisably designed as a non-inferiority or equivalence study.

Overall survival

None of the studies included in the evaluation explicitly investigated overall survival or disease-specific mortality. Only one study reported survival data for a subgroup. In 3 further studies (2 of them broken down according to treatment groups) the occurrence of fatalities was reported. Ultimately, no conclusions on an advantage or disadvantage of therapy options in respect of overall survival or disease-specific mortality can be drawn from these data. However, neither can equivalence in this regard be inferred.

Disease-free survival

In 5 of 6 studies on treatment efficacy, this outcome was solely investigated by means of the biomarker PSA. In each case, the time to PSA recurrence, which was defined differently in the studies, was recorded. The median follow-up time was between 24 (in one arm of a study) to 56 months. The results did not show a clear difference between brachytherapy and radical prostatectomy or percutaneous radiotherapy at any time. An equivalence of brachytherapy to these therapy options cannot, however, be inferred for methodological reasons.

In 3 of the studies, the results were analysed separately according to risk groups. From a follow-up period of 5 years onwards, 2 studies showed statistically significant differences

between treatment options in high-risk groups to the disadvantage of brachytherapy (once compared with radical prostatectomy and twice compared with percutaneous radiotherapy).

It should be noted that the comparability of results is on the one hand impaired by methodological problems, and on the other, by statistical inaccuracies in data analysis and reporting. A fundamentally different definition of “recurrence” within the framework of surgical procedures on the one hand and radiotherapy on the other, as well as the different measurement of the time period up to the recurrence event, suggest a tendency in favour of radiotherapy. In contrast, bias to the disadvantage of radiotherapy may be caused by the fact that under radiotherapy, a short-term re-increase of PSA levels may occur (e.g. due to inflammation) and lead to an overestimation of the PSA recurrence rate. It ultimately remains unclear in which direction results may potentially be altered. The lack or unclear description of missing data arising during the course of a study further affects the uncertainty of results. Patients receiving brachytherapy also more frequently had more favourable prognostic characteristics (lower PSA baseline values, Gleason Score, clinical tumour stage) than patients receiving the two alternative therapies. They were also consistently older than patients who underwent prostatectomy. However, these potential sources of bias were not consistently considered in the further analysis.

Due to these limitations and the resulting difficulties in interpretation, no indication can be inferred from the results with regard to an (additional) benefit or harm of brachytherapy for the outcome “prolongation of disease-free survival”; this also applies to the potential equivalence to both control interventions.

Disease-related symptoms

This outcome was not explicitly investigated in the studies included. However, partial aspects are reflected in connection with results on disease-free survival (e.g. formation of metastases) and quality of life.

Health-related quality of life

Five of the studies had the aim of assessing the impact of disease and treatment on the quality of life of affected patients. All 3 treatment options were investigated in the studies. However, comparisons between brachytherapy and percutaneous therapy that are interpretable (with caution) were only available in 2 studies. Various assessment instruments were used, and we summarised the results in 3 categories: *general health-related quality of life*, *disease-specific quality of life* as well as *symptoms and functional restrictions*.

Overall, the studies only provide indications of an advantage of brachytherapy versus radical prostatectomy for the quality of life categories “sexuality” and “urinary incontinence”. For all other categories, no clear and consistent differences were noticeable. This also applies to the comparison with percutaneous radiotherapy (possibly with the exception of the category “rectal function”). However, for methodological reasons, this cannot be interpreted as equivalence. It should also be noted that the studies only provided interpretable data (and

moreover, only to a limited extent) for a short period between about 1 and 2 years. Baseline data on quality of life before the start of therapy were only provided in 2 of 5 studies. Even though important prognostic characteristics for quality of life were unevenly distributed between treatment groups, this was not consistently considered in the data analysis. However, it is not noticeable from the results that there is a direct association with this unequal distribution of confounders. The partially missing or incomplete documentation of missing data (drop outs, lost to follow-up etc.) negatively affects the results, particularly after a longer follow-up period.

Adverse events

Only limited data on adverse events were available. One study mentioned, and another explicitly investigated adverse events. Compared with radical prostatectomy, the overall adverse event rate was higher in patients receiving brachytherapy. However, the rate of serious adverse events was lower. A comparison of both radiotherapies showed that adverse events occurred later with brachytherapy and were more common in the urinary tract. A clear advantage or disadvantage of brachytherapy compared with the 2 treatment alternatives cannot be inferred, as insufficient data were available (or reporting of results was inadequate). However, it should be noted that the possible advantages of brachytherapy compared with radical prostatectomy described for the quality of life categories “sexuality” and “urinary incontinence” may ultimately be assessed as a manifestation of therapy-related complications occurring with radical prostatectomy.

Number and duration of hospital stays

None of the studies included provided data on this outcome.

Necessity and duration of catheterisation

For brachytherapy vs. radical prostatectomy, data on the duration of catheterisation as well as on the need for recatheterisation due to the adverse effects of therapy were not available for any studies. Only one study provided the relevant data for brachytherapy vs. percutaneous radiotherapy. No robust conclusions are possible on the basis of this information.

Frequency of necessary follow-up consultations regarding sexual function, urinary and rectal function

None of the studies included provided data on these outcomes.

Conclusion

In patients with localised prostate cancer, indications exist (based on data from non-randomised observational studies) of an advantage of brachytherapy vs. radical prostatectomy

concerning impairment of sexual function and urinary incontinence. With regard to rectal function, this also applies to the comparison between brachytherapy and percutaneous radiotherapy.

In respect of overall survival, as well as disease-specific and disease-free survival, no evidence is available to demonstrate a superiority or equivalence of brachytherapy versus prostatectomy or radiotherapy.

Therefore, the potential advantages of brachytherapy with regard to organ function and quality of life in patients with localised prostate cancer as the only evidence of a benefit are insufficient to apply this therapeutic procedure, as potential harm regarding survival and disease-related symptoms cannot be excluded with sufficient certainty. We therefore urgently recommend the conduct of sound clinical studies in order to define the relevance of brachytherapy compared with other treatment options.

Key words

Low-dose-rate permanent interstitial brachytherapy, seed implantation, percutaneous external radiotherapy, radical prostatectomy, watchful waiting, localised prostate cancer, systematic review.