IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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# Interstitial brachytherapy in localized prostate cancer – Update[1]

# Executive Summary

[1] Translation of the executive summary of the rapid report "Interstitielle Brachytherapie beim lokal begrenzten Prostatakarzinom – Update" (Version 1.0; Status: 13.12.2010). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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## Research question

The aim of the present research is to answer the question as to whether the literature published on low-dose-rate interstitial brachytherapy (BT) in localized prostate cancer since the search conducted for the original final report N04-02 results in a change in the conclusions of the final report for the individual procedures to be analysed. (The search for and assessment of the new literature was to follow the same methodology used in the original report.)

This aim includes the aims stated in final report N04-02 (citation): the aim of the research is the comparative benefit assessment of low-dose-rate (permanent) interstitial BT in localized prostate cancer versus the surgical standard procedure (radical prostatectomy, RP), external beam radiotherapy (EBRT), and active surveillance / watchful waiting. The focus of the evaluation was on patient-relevant therapy goals. Moreover, substantially different types of low-dose-rate interstitial BT procedures were to be compared with each other.

## Methods

In principle, the same methodology was used in the present rapid report N10-01 as in commission N04-02. We therefore refer to section 4 of final report N04-02. As the criteria for the inclusion of studies in the analysis are particularly important for the assessment of study selection, they were additionally commented on. Minor deviations concerning the literature search and assessment of information are described in the corresponding sections of the rapid report. According to the methods of the Institute for Quality and Efficiency in Health Care (IQWiG), no commenting procedure is scheduled during the preparation phase of rapid reports, so that comments are not taken into consideration as a potential source of information. In contrast to final report N04-02, no requests for information were sent to manufacturers and professional societies.

The subdivision into *none*, *partial*, and *completely*, which was used in final report N04-02 for the assessment of statistical adjustment procedures, turned out to be of little informative value for the present rapid report, as in all studies considered here partial adjustment had been performed. The subdomain *comprehensive* consideration was defined for better differentiation of the extent of adjustment. The consideration of relevant influencing factors was classified as *comprehensive* if at least 3 of the following influencing factors classified as relevant a priori were taken into account: age, clinical stage according to the tumour-node metastasis (TNM) classification, prostate-specific antigen (PSA), Gleason Score, prostate size, and comorbidities. For quality-of-life outcomes, baseline values also had to be considered. For adverse effects, the consideration of at least one of the potential confounding factors age, prostate size and comorbidities was sufficient.

## Results

### Literature search

Of the 1252 hits from electronic bibliographic databases, 10.1% (126 of 1252 articles) were identified as potentially relevant articles for full text screening. A total of 15.9 % (20 of 126 full texts) were included in the benefit assessment. No further relevant primary studies were identified from the reference lists of systematic reviews, from electronic study registries, or from 183 articles cited in comments submitted to the Federal Joint Committee (G-BA). The total number of the studies considered in both reports was increased from 11 to 31 studies and, in contrast to final report N04-02, a randomized controlled trial (RCT) could be included for the first time. No studies on substantially different types of interstitial BT procedures were identified.

### Study and publication quality

The informative value of the results of the included studies should be generally classified as limited. This is due to the fact that besides only 1 RCT (with a high risk of bias) only non-randomized studies were available, of which 11 (58%) showed major deficiencies; therefore no proof was provided of a causal association between treatment and treatment result as a precondition for proof of benefit.

### Results on therapy outcomes

A summarizing overview of the state of the evidence regarding the investigated outcomes is presented in Table 33 of the rapid report.

#### *Overall survival (including disease-specific survival)*

In final report N04-02 no interpretable data on this outcome had been found, either. The only study containing data on this outcome and included in the present rapid report is not suitable to draw robust conclusions, due to the completely unclear composition of groups and consequently misinterpretable data. All in all, regarding overall or disease-specific survival, there is neither an indication nor proof of an advantage or disadvantage of BT versus other treatment options. However, this cannot be equated with an equivalence of treatment options.

*Disease-free survival*

No studies with data on disease-free survival were identified.

*PSA-based recurrence-free survival*

The results for PSA-based recurrence-free survival are summarized as follows: the data from 10 non-randomized studies (6 from the search update, 4 from final report N04-02) comparing

BT with EBRT showed great heterogeneity; 2 studies that were statistically significant in favour of BT were countered by 8 studies with no statistically significant effect and, in part, opposing numerical values. In an additional study from the search update no pairwise comparison was conducted for 4 treatment groups; merely a global test for the comparison of all observed treatment groups was reported. This test showed a statistically significant result. Further stratified analyses of this study provided no clear picture. The heterogeneity of these results can presumably be explained (at least partly) by dose differences and/or by the use of different radiation techniques (3-D conformal or intensity modulated) of the EBRT.

Relevant data from 7 studies (3 from the search update, one of which was an RCT; 4 from final report N04-02) were available for the comparison of BT with RP. The RCT showed no difference between treatment groups. Two of the 6 non-randomized studies showed a statistically significant effect in favour of BT; in 4 further studies practically no difference was noted.

PSA-based recurrence-free survival is a non-validated surrogate (a least for localized prostate cancer) and in particular is not designed as a surrogate for a comparison between different treatment groups. Due to the poor interpretability of results for the comparison between treatment groups (see section 5.2.1 of the rapid report), no sufficiently robust conclusions can be drawn regarding an advantage or disadvantage of BT versus other treatment options. However, this cannot be equated with an equivalence of treatment options.

*Adverse effects and complications of therapy*

The assessment is based on 7 studies from the search update and 2 studies from final report N04-02. No noteworthy differences between treatment groups for the comparison of BT and (active) surveillance / watchful waiting were observed (in 1 study). The results of the only randomized study comparing BT with RP did not show a clear picture. The risk of late urogenital toxicity (grade 2-3) was notably increased in 3 non-randomized studies in the BT group compared to the EBRT group. Although 2 of these studies showed major deficiencies, the effect in all 3 studies was extremely large, so that overall an indication is inferred of a disadvantage of BT versus EBRT. In an additional study the risk of developing an urethral stricture was also statistically significantly higher in the BT group than in the EBRT group.

For all further comparisons and outcomes investigated, neither an indication nor proof is available of an advantage or disadvantage of BT versus the other treatment options investigated.

*General health-related quality of life*

General quality of life was investigated in a total of 6 studies (3 from the search update, 3 from final report N04-02). However, the reported data were insufficient, so that overall,

neither an indication nor proof of an advantage or disadvantage of BT versus the other treatment options could be inferred regarding general health-related quality of life.

*Symptoms and impairment of functions as well as related bother*

After at least 6 months of follow-up, impairment of sexual function was statistically significantly better in the BT group than in the RP group in 3 out of 4 studies from the search update and in 1 study from final report N04-02 (in each case with minor deficits). An indication of an advantage of BT versus RP is available regarding impairment of sexual function.

In 2 of 3 studies with a follow-up period of at least 6 months, bother caused by impairment of urinary tract function was statistically significantly worse in the BT group than in the RP group; an indication of a disadvantage of BT versus RP is therefore available regarding this outcome. With respect to urinary incontinence, an indication of an advantage of BT versus RP is available.

Concerning impairment of bowel function, an indication of an advantage of BT versus EBRT is available.

With regard to all other comparisons and outcomes, neither an indication nor proof is available of an advantage or disadvantage of BT versus the other treatment options investigated.

**Conclusion**

The search update on low-dose-rate BT yielded one RCT with an insufficient sample size and 19 additional non-RCTs. The indications of advantages of low-dose-rate BT described in final report N04-02 in respect of certain aspects of quality of life and impairment of organ functions are, by and large, confirmed by the new studies and further supplemented. However, indications of disadvantages of low-dose-rate BT were also found.

The quality of the available studies and their poor interpretability are still insufficient to robustly describe the benefits or harms of low-dose-rate BT versus the other treatment options.

**Keywords:** low-dose-rate interstitial brachytherapy; localized prostate cancer; systematic review.