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Prostate cancer

A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study

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ABSTRACT

Background and purpose: Patients treated with low radiotherapy dose or treated at young age are at a risk of developing local relapse.
Although data are preliminary, brachytherapy seems an attractive treatment option for recurrent prostate cancer after previous radiotherapy. Therefore, the UroGEC group of the GEC-ESTRO conducted a Delphi study, to explore expert opinion on the management of salvage prostate brachytherapy.
Material and methods: For this study, a series of digital questionnaires were sent, which enabled data collection from an international group of experienced participants. Consensus was defined as 80% agreement for each question.
Results: Eighteen experts completed all rounds of the Delphi study. After the final round consensus was reached on 17 out of 38 (45%) questions. Consensus was reached in 52% of questions about patient selection, in 50% of the questions about diagnostic tests and in 22% of the questions on performing salvage prostate brachytherapy.
Conclusions: The group was able to find consensus on less than half of the questions. Most consensus was reached on topics involving patient selection and diagnostic tests, where participants could build on their experience of daily practice. However, the way to perform the salvage treatment is less established and results in more disagreement between participants.
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With dose-escalated radiotherapy better biochemical control has been found, compared to the traditional 64–72 Gy delivered to the prostate. Patients treated with the lower radiotherapy dose are at a risk of developing biochemical relapse and many of them will have local relapse [1–3]. Also because of the increased prostate specific antigen (PSA) surveillance prostate cancer is detected at a relatively younger age. A part of these patients will receive treatment directly after diagnosis, but have a longer lifetime risk of developing a recurrence [4]. Less accurate brachytherapy treatment planning techniques of the past, with cold spots in the implant can also lead to local recurrence [5]. For these patients different salvage treatment methods are available. Based on the available experience brachytherapy seems an attractive treatment option for recurrent prostate cancer after previous radiotherapy [6].

Previous studies have treated the whole prostate gland as target volume. Recently, partial or focal prostate brachytherapy is gaining more interest [7]. For salvage treatment, partial treatment of the prostate might be a good option to further reduce the toxicity in re-irradiated tissue.

Only preliminary data exist on focal salvage brachytherapy of the prostate. Nguyen et al. [8] were able to retreat 25 patients with recurrent prostate cancer after previous radiotherapy, but had 30% grade 3 or 4 gastrointestinal or genitourinary toxicity. Peters et al. [9] re-treated 20 patients with focal LDR brachytherapy, resulting in 70% of the patients remaining biochemical recurrence-free at a median follow up time of 36 months. Although these data seem promising, no recommendations for treatment can be based on them.

A Delphi study is useful to learn from those who have experience with salvage treatment of the prostate in their clinical practice. The Delphi concept involves multiple rounds of questionnaires in which consensus between these experts is sought [10]. The outcome of a Delphi study is based on opinions and arguments of experts and is not always based on facts. An important aspect of a Delphi study is that it will provide an estimation of future developments, which is not available with contemporary data. Four elements characterize a Delphi study: anonymity, iteration, controlled feedback and statistical analysis. The anonymous data collection reduces the effect of dominant individuals on the outcome, provide an atmosphere in which individuals can express themselves freely, and increase the response rate. A moderator

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collects all the responses, summarizes and analyzes it and presents the results back to the panel as a controlled feedback. The questions are asked again in subsequent iterative rounds with a feedback of the previous rounds until stability in answers is reached. In certain cases questions are remodeled based on the answers or comments provided. After the final round statistical analysis can be performed and presenting the results in a descriptive way for frequency distribution, correlations, change trends between rounds, and the level of agreement between participants.

This study was initiated and conducted by the Uro-GEC working group of the Groupe Euopéen de Curiethérapie – European Society for Radiotherapy and Oncology (GEC-ESTRO). The aim of this Delphi study is to provide useful information to help in decision-making for salvage brachytherapy and design of trials in recurrent prostate cancer after radiotherapy.

Materials and methods

Literature search

The first questionnaire was based on a literature search undertaken between May and June 2014. The search involved the search terms *radiation-recurrent, radiation recurrent, radio-recurrent, radio-recurrent, relapse or recurrence* in combination with *prostatic neoplasms* and *salvage brachytherapy, salvage radiotherapy or salvage radiation therapy*, excluding *prostatectomy, cryotherapy and high-intensity focused ultrasound ablation*. Prostatic neoplasms, recurrence, prostatectomy, cryotherapy and high-intensity focused ultrasound ablation were entered as MeSH terms. The other search terms were entered as text words. The search was performed electronically using Pubmed database of the National Library of Medicine. In total 260 articles were retrieved. Articles were further selected by reading the title and abstract. This selection involved the following criteria: the article involves a clinical study, a treatment on salvage brachytherapy and involves patients with recurrent prostate cancer after previous radiotherapy. After this selection 33 articles remained useful for the purpose of our study [5,6,8,11–40].

Questionnaires

For this study, a series of digital questionnaires were sent, which enabled data collection from an international group within a limited time period. The questionnaires were built and sent with the Qualtrics Survey Suite (http://www.qualtrics.com/research-suite/). The outcome of a questionnaire and relevant comments were summarized and used for the next round, so participants were informed on the progress of the survey and feedback was given. The anonymous data representation reduced the effect of dominant individuals on the outcome [10,41].

The questionnaire comprised three different topics related to salvage therapy. The topics were (A) patient selection for prostate salvage brachytherapy, (B) diagnostic tests necessary for patient selection and (C) how to perform salvage prostate brachytherapy.

Every topic consisted of multiple-choice questions (Supplementary table A–C). Topic A contained 23 questions, topic B contained six questions, and topic C contained eight questions. For most questions, only a unique answer was possible and for some questions, there was the possibility for multiple answers. The first questionnaire contained one open question concerning the preferred dose schedule. In the second and third rounds, this question was converted to a multiple-choice question. For every question, there was the option to add comments to the question or the given answer.

Based on the answers to the questions and additional comments, some questions in the second and third rounds were adjusted. For every question consensus was defined as at least 80% agreement between participants. Questions that reached consensus were shown in the next questionnaire with the relevant comments, but were no longer open for answering.

Participants

The questionnaire was sent anonymously to a group of 33 radiation oncologists and urologists. The group of experts consists of the people mentioned as the corresponding authors of the articles found in the literature search and others closely involved with prostate salvage brachytherapy.

Analysis

For every question, frequencies were calculated using IBM SPSS Statistics version 19. To find out whether experience influences the final choices of the last round, the group was divided into a group with clinical experience in less than 25 patients and a group who has been treating more than 25 patients. The Cohen's kappa coefficient (κ) with the 95% confidence interval (95% CI) was calculated to understand agreement of participants between the different rounds. Comparison between groups was performed with the Chi-squared test or Fisher's-Exact test.

Results

Of the 33 participants, 19 (58%) responded in the first round and 18 (55%) completed the second and third questionnaires also. For every round two reminders were sent two weeks apart.

Five participants were involved with salvage prostate brachytherapy to 10 patients or less, five with the treatment of 11–25 patients, six with treatment of 26–50 patients, two with the treatment of 51–100 patients and one with the treatment of more than 100 patients. Experienced participants were defined as the 11 who have treated more than 25 patients. The other eight participants were considered as less experienced.

After the third round consensus was reached on 17 out of 38 questions (45% of the questions). In the stratified analysis according to experience consensus was found on four items in one of the subgroups, while there was no overall consensus. In Table 1 the questions where consensus was reached are given. The percentage agreement for all the questions per round is provided as a Supplementary Table available in Radiotherapy and Oncology online.

A. Patient selection

Consensus was reached in 52% of questions about patient selection.

Patient characteristics

Opinions were divided for age as a criterion for salvage brachytherapy of the prostate. In the first round the majority (60%) found that age should not be a criterion, but in the last round only 22% still had that opinion. With the measurement of agreement changed from fair (κ = 0.26; 95% CI 0–0.76) between the first and second rounds, to almost perfect (0.84; 95% CI 0.53–1) between the second and third rounds. All participants (100%) agreed in the first round already that minimum age is no criterion. However, in the first round 38% felt that 80 years should be the maximum age, while this was 75% in the final round.

In the first round 84% of the participants regarded life expectancy as a criterion. In the following round a new question was added including life expectancy more than 5 years or more than 10 years. No consensus was reached on the duration of life