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Salvage ablative therapy in prostate cancer: International multidisciplinary consensus on trial design

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Abstract

Introduction: Salvage ablative therapy (SAT) has been developed as a form of localized treatment for localized recurrence of prostate cancers following radiation therapy. To better address the utility of SAT, prospective clinical trials must address the aspects of accepted standards in the initial evaluation, treatment, follow-up, and outcomes in the oncology community. We undertook this study to achieve consensus on uniform standardized trial design for SAT trials.

Methods: A literature search was performed and an international multidisciplinary group of experts was identified. A questionnaire was constructed and sent out to 71 participants in 3 consecutive rounds according to the Delphi method. The project was concluded with a face-to-face meeting in which the results were reviewed and conclusions were formulated.

Results: Patients with recurrent disease after radiation therapy were considered candidates for a SAT trial using any ablation scenario performed with cryotherapy or high-intensity focused ultrasound. It is feasible to compare different sources of energy or to compare with historical data on salvage radical prostatectomy outcomes. The primary objective should be to assess the efficacy of the treatment for negative biopsy rate at 12 months. Secondary objectives should include safety parameters and quality-of-life assessment. Exclusion criteria should include evidence of local or distant metastases. The optimal biopsy strategy is image-guided targeted biopsies. Follow-up includes multiparametric magnetic resonance imaging, prostate-specific antigen level, and quality of life for at least 5 years.

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Conclusions: A multidisciplinary board from international experts reached consensus on trial design for SAT in prostate cancer and provides a standard for designing a feasible SAT trial.

Keywords: Salvage ablative therapy; Trial design; Consensus

1. Introduction

Radiation is an effective treatment for prostate cancer (Pca) and approximately 25% of the patients with Pca receive radiation as primary treatment [1]. In up to 35% of the cases, biopsy-proven persistent or recurrent tumor tissue is identified during follow-up and approximately 60% of these patients eventually show clinically significant progression [2–4]. For selected patients with localized disease limited to the prostate gland, salvage therapies such as salvage radical prostatectomy (sRP) or brachytherapy are offered as treatment options with risks of associated toxicities caused by fibrosis and poor wound healing induced by the previous radiation [5]. The toxicities include bladder neck contracture (11%–41%), urinary retention (25.3%), urinary fistula (4.1%), abscess (3.2%), and rectal injuries (2%–10%) [5–7]. As an alternative, salvage ablative therapy (SAT) has been developed to provide local tumor control with limited side effects. The actual effectiveness of this approach concerning clinically relevant outcomes has been questioned. To date, literature on SAT is scarce and reported mainly retrospectively using different inclusion criteria and treatment objectives, which leads to incomparable and incomplete information. To generate an essential basis for the evaluation of scientific development, SAT trials should be performed using a uniform, systematic trial design representing well-defined pretreatment and posttreatment evaluation. The objective of this study is to establish consensus on standardized trial design for SAT trials to achieve a uniform basis to drive scientific progress.

2. Methods

The 4-staged consensus project is derived from the *Delphi Method* [8]. First, a literature study (Fig. 1) was performed, and among the authors of the studies in this search, an international multidisciplinary expert group was gathered. Subsequently, an online questionnaire (using www.surveymonkey.com; accessed June 15, 2014) was constructed and sent out to the 71 experts in 3 consecutive rounds (for details see Appendix A). The selection of the participants was based on publication record, academic interest, and current practice. Fig. 2 shows the 55 responding participants' experience with the different SATs. In each round, the participants had the opportunity to adapt, delete, or add questions. The results, including comments, were collected and reported back to the group. The process was iterated 3 times to obtain a convergence of the results in consensus. The project was concluded with a face-to-face meeting in which conclusions were formulated. This meeting was held on August 21, 2014, at the 7th International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer (Pasadena, CA; http://www.focaltherapy.org). All participants were invited to join the meeting. The meeting was attended by 16 panelists and 1 chairperson representing the specialties of urology [13], surgery [1], surgical oncology [1], radiology [1], and biomedical engineering and physics [1]. During this final consensus round, the results of the web-based questionnaires were presented. Consensus on a topic was defined as $\geq 75\%$ agreement on a question regarding this topic in the online questionnaire. The topics that did not reach consensus in the online questionnaire were discussed during the meeting. The panelists were given the opportunity to elaborate on these topics. Moreover, they were encouraged to provide feedback on the online comments as well as to discuss inconclusive results that were due to clinical discrepancy or misinterpretation.

3. Results

3.1. General

Patients with recurrent disease after any modality of radiation therapy were considered candidates for a SAT trial. All the noninvasive ablation scenarios (whole-gland, hemiablation and focal ablation) can be used if performed with cryotherapy or high-intensity focused ultrasound (HIFU). It is feasible to compare the different treatment scenarios, to compare both sources of energy, or to use the outcomes as comparison to sRP outcomes. Furthermore, the panel agreed that a randomized clinical trial should be conducted comparing 1 or 2 energy sources with sRP or comparing whole-gland SAT with focal SAT. As an entry biopsy strategy, consensus was reached to use image-guided targeted biopsy (>12 and <24 cores), preferably performed transrectal with magnetic resonance imaging (MRI)-transrectal ultrasound fusion guidance.

3.2. Objectives

The primary objective of a SAT trial should be to assess the efficacy of the treatment for negative biopsy rate at 12 months posttreatment. The secondary objectives include (1) assessment of quality of life (QoL); (2) treatment safety profile defined by adverse events and side effects; (3) 3-year and long-term biochemical disease-free survival (bDFS); and (4) progression-