available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Jane M. Blazeby on pp. 1084–1085 of this issue

Focal Therapy in Prostate Cancer: International Multidisciplinary Consensus on Trial Design

Willemien van den Bos [a,], Berrend G. Muller [a], Hashim Ahmed [b], Chris H. Bangma [c], Eric Barret [d], Sebastien Crouzet [e], Scott E. Eggener [f], Inderbir S. Gill [g], Steven Joniau [h], Gyoergy Kovacs [i], Sascha Pahernik [j], Jean J. de la Rosette [a], Olivier Rouvière [k], Georg Salomon [l], John F. Ward [m], Peter T. Scardino [n]*

[a] *Department of Urology, AMC University Hospital, Amsterdam, The Netherlands;* [b] *Division of Surgery and Interventional Science, London, UK;* [c] *Department of Urology, Erasmus MC Rotterdam, The Netherlands;* [d] *Department of Urology, Institut Montsouris, Paris, France;* [e] *Hospices Civils de Lyon, Department of Urology, Edouard Herriot Hospital, Lyon, France;* [f] *Department of Urology, University of Chicago, Chicago, IL, USA;* [g] *Institute of Urology, Hillard and Roclyn Herzog Center for Prostate Cancer Focal Therapy, Keck School of Medicine, Los Angeles, CA, USA;* [h] *Department of Urology, University Hospitals Leuven, Belgium;* [i] *Interdisciplinary Brachytherapy Unit, University of Lübeck, Lübeck, Germany;* [j] *Department of Urology, University Clinic Heidelberg, Heidelberg, Germany;* [k] *Hospices Civils de Lyon, Department of Radiology, Hôpital E. Herriot, Université de Lyon, Lyon, France;* [l] *Department of Urology, University Medical Centre Hamburg, Hamburg, Germany;* [m] *Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [n] *Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

Article info

Article history:
Accepted January 2, 2014
Published online ahead of print on January 13, 2014

Keywords:
Focal therapy
Prostate cancer
Trial design

Abstract

Background: Focal therapy has been introduced for the treatment of localised prostate cancer (PCa). To provide the necessary data for consistent assessment, all focal therapy trials should be performed according to uniform, systematic pre- and post-treatment evaluation with well-defined end points and strict inclusion and exclusion criteria.
Objective: To obtain consensus on trial design for focal therapy in PCa.
Design, setting, and participants: A four-staged consensus project based on a modified Delphi process was conducted in which 48 experts in focal therapy of PCa participated. According to this formal consensus-building method, participants were asked to fill out an iterative sequence of questionnaires to collect data on trial design. Subsequently, a consensus meeting was held in which 13 panellists discussed acquired data, clarified the results, and defined the conclusions.
Outcome measurements and statistical analysis: A multidisciplinary board from oncologic centres worldwide reached consensus on patient selection, pretreatment assessment, evaluation of outcome, and follow-up.
Results and limitations: Inclusion criteria for candidates in focal therapy trials are patients with prostate-specific antigen <15 ng/ml, clinical stage T1c–T2a, Gleason score 3 + 3 or 3 + 4, life expectancy of >10 yr, and any prostate volume. The optimal biopsy strategy includes transrectal ultrasound-guided biopsies to be taken between 6 mo and 12 mo after treatment. The primary objective should be focal ablation of clinically significant disease with negative biopsies at 12 mo after treatment as the primary end point.
Conclusions: This consensus report provides a standard for designing a feasible focal therapy trial.
Patient summary: A variety of ablative technologies have been introduced and applied in a focal manner for the treatment of prostate cancer (PCa). In this consensus report, an international panel of experts in the field of PCa determined pre- and post-treatment work-up for focal therapy research.

* Corresponding author. Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel. +31 50 566 6465.
E-mail address: w.vandenbos@amc.uva.nl (W. van den Bos).

0302-2838/$ – see back matter
http://dx.doi.org/10.1016/j.eururo.2014.01.001

1. Introduction

Stage migration in localised prostate cancer (PCa) has led to a more significant potential role for focal therapy as a less invasive procedure in the management of the disease [1]. This increased detection rate is partially due to intensified prostate-specific antigen (PSA) testing, improved imaging technologies, and increased public awareness [2,3]. A variety of ablative energies have been introduced and applied in a focal manner for the treatment of PCa. These include cryotherapy, high-intensity focused ultrasound (HIFU), laser ablation therapy, radiofrequency ablation, irreversible electroporation, and photodynamic therapy. The first two modalities are mentioned by the European Association of Urology guidelines as true and experimental therapeutic options in patients with clinically localised PCa [4]. Although focal therapy is not yet the standard for organ-confined PCa, it is the therapeutic approach with the most important future potential [4]. Different approaches to focal therapy have emerged, with each using a variety of patient selection criteria, end points, and protocols for evaluation and follow-up. It is clear that intra- and intertechnology variability is wide [5,6]. There are conflicting recommendations and lack of consensus on the design of focal therapy trials, making it difficult to compare outcomes. Together with debate about what is meant by *focal therapy* and a divergent view of what is deemed a successful outcome, it is difficult to assess the current state of the field and to determine a clear path forward [7–9].

Focal therapy needs mature oncologic follow-up data and thus needs standardisation, clear definitions of eligibility criteria, and end points [10]. To provide the necessary basis for assessing scientific progress, focal therapy trials should be performed according to a uniform, systematic, pre- and post-treatment evaluation; well-defined end points; and strict inclusion and exclusion criteria. The objective of the present study was to develop consensus on focal therapy trial design in PCa. This report is, to our knowledge, the first from an expert consensus project to address the issue of focal therapy trial design in PCa.

2. Materials and methods

2.1. Consensus process

This four-stage consensus project is derived from the *Delphi method*, which was developed in the 1950s as an instrument to predict the future in political-military, technological, and economic topics [11]. Today, the Delphi approach is widely applied for evaluation of expert opinion on health and medical subjects [12,13]. It is a method for consensus building that uses a sequence of questionnaires to collect data from selected subjects [14]. The method generally involves multiple rounds of questionnaires in which answers are given anonymously. The results of the online questionnaire (using www.surveymonkey.com; accessed 28 April 2013), including participants' comments, were collected and reported back to the group. This feedback process allowed and encouraged the participants to reassess their initial judgments. Consequently, each participant was asked to complete the questionnaire again. For this study, the process was iterated three times to obtain a convergence of opinion on the subject.

2.2. Expert representation

A systematic literature search of the PubMed database was conducted through 10 April 2013 with prespecified English language and human studies restrictions. The search strategy was as follows: "PCa" OR "prostatic neoplasms" OR "PCa" OR "prostate carcinoma" AND "focal treatment" OR "focal therapy" OR "tissue-preserving/-preservation" OR "subtotal" OR "cryosurgery" OR "cryotherapy" OR "cryoablation" OR "high-intensity focused ultrasound ablation" OR "HIFU" OR "photodynamic therapy" OR "PDT" OR "laser therapy" OR "brachytherapy" OR "irreversible electroporation" OR "IRE". In addition, registered trials were retrieved from trial registries (ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number). The results of this search were used to construct the questionnaires.

After reviewing the literature and the trials, 48 experts in the field of focal therapy in PCa from Europe, the United States, and Asia were invited to participate in this consensus project. Selection was based on publication record, academic interest, and current practice in their respective fields. This group has overall experience performing >1500 PCa focal therapy procedures in total per year. All experts were asked to submit their protocols of future, currently ongoing, or completed focal therapy trials. In this consensus study, members of the following societies took part: the European Organisation for Research and Treatment of Cancer Genito-Urinary Group, the American Brachytherapy Society, the European Society of Therapeutic Radiology and Oncology, the European Association of Urology Section of Urotechnology, the European Association of Urology Section of Urological Imaging, the Society of Urological Oncology, and the Endourological Society. The experience of the experts by focal therapy is shown in Table 1. The affiliations and expertise of the contributors are described in Supplemental Table 1. The response rates for the questionnaires were 88%, 85%, and 96% in rounds 1, 2, and 3, respectively.

2.3. Consensus meeting design

As the final round of the Delphi process, a consensus meeting was planned for 29 May 2013, at the beginning of the 6th International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer (Amsterdam, The Netherlands; http://www.focaltherapy.org). Participants in the survey who were attending this meeting were invited to join the consensus meeting. The meeting was attended by 13 panellists representing the specialties of urology (12), surgery and interventional science (1), radiation therapy (1), radiology (1), and surgery (1) and was chaired by Dr. Peter Scardino.

During this final consensus meeting, all results of the Delphi study were presented and discussed. The panellists were given the opportunity to deliberate on the outcomes on the basis of the results of the literature search. There was the possibility of giving feedback on the group's responses and addressing inconclusive results due to clinical disagreement or eventual misinterpretation.

Table 1 – Experience of experts by focal therapy

Therapy	Experience, %
Cryotherapy	64
High-intensity focused ultrasound	60
Brachytherapy	43
Laser therapy	31
Photodynamic therapy	31
Radiofrequency ablation	12
Irreversible electroporation	17
Other	5