Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x-y 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, György 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, Hilliard 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 Center 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 panelists 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.

© 2014 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* 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 © 2014 European Association of Urology. Published by Elsevier B.V. All rights reserved.

http://dx.doi.org/10.1016/j.eururo.2014.01.001

Please cite this article in press as: van den Bos W, et al. Focal Therapy in Prostate Cancer: International Multidisciplinary Consensus on Trial Design. Eur Urol (2014), 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 therapy” 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 specialities 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      |
The panel recommended the inclusion and exclusion criteria for a focal therapy trial, as shown in Table 2, to be the minimum required. It is important to be aware that this consensus project on focal therapy trial design should be adjusted in the case of focal brachytherapy. Brachytherapy is a technique that requires different patient selection, as described by Langley et al. [18]. Agreement was reached not to include the following exclusion criteria: renal insufficiency, history of acute or chronic prostatitis, significant erectile dysfunction, and incontinence. Exclusion of individual patients should be based on good clinical judgment, being mindful of all comorbidities and performance status (eg, heart disease, concurrent cancers).

3.2. End points

The primary end point of focal therapy trials should be focal ablation of clinically significant disease (defined as...
prostates with a dominant tumour >0.5 ml) with negative biopsies evaluated at 12 mo after treatment as the primary end point. The clinical validity of MRI to analyse the presence of residual or recurrent cancer compared with histopathologic findings should be a secondary end point of the trial. Alterations on MRI itself are not a sufficient end point. In case of focal brachytherapy, a more prolonged schedule of follow-up should be accomplished [18].

The panel agreed that PSA levels should be monitored but should not be included as one of the end points because the utility of PSA kinetics in tissue preservation treatments has yet to be determined [6,19].

3.3. Pretreatment assessment

The panel agreed that a PSA measurement is essential, but testing of any PSA derivatives (e.g., velocity, doubling time, density) is not. The International Index of Erectile Function and the International Prostate Symptom Score are preferable questionnaires to assess patients' functional status. The experts were in agreement that quality of life should preferably be quantified by the Expanded Prostate Cancer Index Composite. In case of incontinence, the use of pads should be reported. Performing uroflowmetry is not essential but may provide additional data on outlet obstruction and postvoiding residual, which can (temporarily) worsen following focal therapy.

3.4. Biopsies and imaging

The literature states that performing systematic transrectal ultrasound (TRUS)-guided biopsy alone is insufficient for the purpose of selecting candidates and determining the exact location of the disease for focal therapy [20–25]. Subsequently, it was agreed that MRI/TRUS fusion-guided targeted biopsies should be performed in addition to systematic TRUS-guided biopsies. Moore et al. have made a notable effort to develop standards for reporting of MRI-targeted biopsy studies that are considered useful concerning the pretreatment assessment in focal therapy [26]. If MRI cannot be performed prior to the biopsies, it is recommended that an interval of at least 4–8 wk be allowed between biopsies and MRI scan to reduce image misinterpretation from biopsy-induced artefacts.

The panel recommended that an MRI scan be performed with the best MRI characteristics available, following the European Society of Urogenital Radiology guidelines and consensus recommendations as much as possible [27,28]. As the ultimate tool for detecting PCa is awaited, multi-parametric MRI (mp-MRI; T2 weighted image combined with at least two functional MRI techniques)—with its detection rate of up to 97%—is an accurate tool for identifying and quantifying intracapsular clinically significant tumour foci [29]. Because of the high negative predictive value (up to 95%) for clinically significant tumours, mp-MRI is a useful tool to detect aggressive tumours (e.g., high-volume Gleason 4 + 3 or higher), which should be excluded from trials (Table 2). Furthermore, mp-MRI can be used to distinguish which zones of the prostate do not require therapy [30,31].

3.5. Preplanning and preparation

It was agreed that the following MRI sequences are useful in the preplanning for focal therapy: T2 MRI for assessing the anatomy, diffusion-weighted imaging for specifying lesion characteristics, and dynamic contrast-enhanced MRI for increased cancer detection. Before commencing focal treatment, antibiotic prophylaxis should be administered combined with the placement of an indwelling urethral catheter. It was agreed that magnetic resonance spectroscopy, real-time or sheer wave elastography, contrast-enhanced ultrasound, and HistoScanning might be useful for preplanning because they may provide information about location, aggressiveness, and extent of the tumour [32–34].

3.6. Evaluation of outcome and follow-up

3.6.1. Oncologic outcomes

There was consensus that it is essential to measure PSA and to perform periodic biopsies during follow-up. Post-treatment PSA follow-up should be performed at 3-mo intervals during the first year, biannually in the second year, and annually in the third year. Thereafter, the frequency of checking PSA is at the discretion of the investigators. The panel was in agreement that the optimal biopsy strategy includes TRUS-guided systematic whole-prostate biopsies and additionally targeted biopsies to be taken between 6 mo and 12 mo after treatment. This interval allows resolution of inflammatory effects and formation of scar tissue. In case of clinical suspicion, it is advisable to perform biopsies in case of clinical suspicion only. Uro-oncologic experience is an agreed-upon requirement for any pathologist analysing prostate biopsies. All biopsy results should be reported in detail, including the number and location of cores taken and the number of positive cores as well as the amount per biopsy of the involved cancer (in millimetres). In case of in-field or out-of-field recurrent or residual disease, one-time retreatment within the trial is acceptable. MRI, preferably mp-MRI, should be performed before taking the biopsies (or at least 6–8 wk afterward) and should be assessed by trained uro-oncologic radiologists. However, this should be predetermined and described in the protocol.

3.6.2. Functional outcomes

It was agreed to measure functional status, quality of life, and adverse events as part of the follow-up. Although no consensus could be made about administering anxiety scores, it was considered interesting to measure anxiety in follow-up of focal treatment.

3.6.3. Treatment failure

In-field failure is defined as (1) cancer of higher Gleason grade, (2) persistent cancer of similar or lower grade after repeat focal therapy to the same area, or (3) the need for additional PCA treatment other than focal therapy because
of objective findings elsewhere in the gland (eg, high-grade cancer). Low-grade, low-volume tumour foci (<3 mm, Gleason 3 + 3) found out of field are not designated as failure. Moreover, out-of-field disease with tumour characteristics, as described in Table 2 (in inclusion criteria), was designated as selection failure. These latter groups are not to be excluded from further evaluation. The choice of retreatment after failed focal therapy depends on the stage and grade of the recurrent tumour.

The panel was in agreement that an accurate definition of biochemical failure cannot be made because of insufficient data.

Both phase 2 and phase 3 trials are currently under way in the focal therapy field. The favoured duration of future prospective phase 2 (single-arm) studies is 18–36 mo and 3–5 yr for prospective phase 3 (randomised) comparative studies. In randomised clinical trials, stratification should be based on PSA, stage and grade of the tumour, and amount of cancer in systematic and targeted needle biopsies.

4. Discussion

All recommendations were created by the Delphi method, which is based on expert opinions; therefore, this paper contains only level 5 evidence [15]. Because the contributors were selected for their expertise in focal therapy, they were possibly biased by their enthusiasm. Furthermore, the low number of participating panellists out of the large group of survey contributors is a potential limitation. However, the relatively high level of consensus (Supplemental Fig. 1) indicates that there was a preexisting notion about the design of focal therapy trials. This project evaluated these common grounds and extracted recommendations for future research. No consensus was determined on certain topics such as schedule, standardisation of functional status, quality of life scores, and adverse event reporting.

5. Conclusions

In conclusion, this paper describes a multistage Delphi process agreement on patient selection, pretreatment assessment, evaluation of outcome, and follow-up. This consensus report provides a standard for focal therapy trial design, which is considered important because clinical trials have been conducted with such different design characteristics that the outcomes are regarded as scarcely comparable. The recommendations were made in consultation with a multidisciplinary board from oncologic centres worldwide.

Author contributions: Willemien van den Bos had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: van den Bos, Muller, de la Rosette.

Acquisition of data: van den Bos.

Analysis and interpretation of data: van den Bos, Muller.

Drafting of the manuscript: van den Bos, Muller.

Critical revision of the manuscript for important intellectual content: Ahmed, Bangma, Barret, Crouzet, Eggener, Gill, Joniau, Kovacs, Pahernik, de la Rosette, Rouvière, Salomon, Ward, Scardino.

Statistical analysis: None.

Obtaining funding: de la Rosette.

Administrative, technical, or material support: van den Bos.

Supervision: de la Rosette, Scardino.

Other (specify): None.

Financial disclosures: Willemien van den Bos certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Van den Bos and Muller receive funding from Cure for Cancer Foundation. Ahmed receives funding for other research projects from the Wellcome Trust, National Institute of Health Research-Health Technology Assessment programme, the US National Institute of Health—National Cancer Institute, Prostate Action, Medical Research Council (UK), and Prostate Cancer Research Centre; he also receives funding from USHIFU, Focused Surgery, Misonix, Oncura and GE Healthcare for medical consultancy and is a consultant to Steba Biotech. De la Rosette is a consultant to AngioDynamics. Scardino is a consultant to Steba Biotech. The other authors have nothing to disclose.

Funding/support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.euro.2014.01.001.

References


