Prospective Multicenter Phase II Study on Focal Therapy (Hemiablation) of the Prostate with High Intensity Focused Ultrasound

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Purpose: We evaluated focal therapy with high intensity focused ultrasound hemiablation in a prospective trial.

Materials and Methods: We performed a prospective, multicenter, single arm study in patients with unilateral low/intermediate risk prostate cancer who were treated from April 2013 through March 2016 in Germany in AUO (Arbeitsgemeinschaft Urologische Onkologie) Study Protocol AP 68/11. Unilateral prostate cancer was assessed by transrectal ultrasound guided biopsy and multiparametric magnetic resonance imaging. Hemiablation was done using the Ablatherm® or the Focal One® device. The oncologic outcome was assessed by the salvage treatment rate, multiparametric magnetic resonance imaging and rebiopsy at 12 months. Functional outcome, quality of life, anxiety and depression were measured by validated questionnaires at baseline and every 3 months.

Results: Of the 54 recruited patients 51 completed 12-month or greater visits. Mean ± SD followup was 17.4 ± 4.5 months. Mean prostate specific antigen decreased from 6.2 ± 2.0 to 2.9 ± 1.9 ng/ml at 12 months ($p < 0.001$). Biopsy at 12 months was positive for any prostate cancer and for clinically significant prostate cancer in 13 (26.5%) and 4 (8.2%) of the 49 patients, respectively. Posttreatment multiparametric magnetic resonance imaging had limited 25% sensitivity for clinically significant prostate cancer. Ten patients (19.6%) underwent salvage treatment. Potency was maintained in 21 of the 30 men who were potent preoperatively. There was no increase in incontinence. Quality of life, anxiety and depression did not change postoperatively. The study was limited by a short followup and the lack of a control arm.

Abbreviations and Acronyms

csPC = clinically significant PC

FT = focal therapy

HADS-D = Hospital and Anxiety and Depression Score, German version

HIFU = high intensity focused ultrasound

IIEF = International Index of Erectile Function

I-PSS = International Prostate Symptom Score

mpMRI = multiparametric MRI

MRI = magnetic resonance imaging

PC = prostate cancer

PI-RADS™ = Prostate Imaging Reporting and Data System

PSA = prostate specific antigen

TRUS = transrectal ultrasound

TUR-P = transurethral resection of prostate

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Conclusions: Focal therapy hemiablation is safe with little alteration of functional outcome. The oncologic outcome is acceptable on short-term followup. Followup multiparametric magnetic resonance imaging performed poorly and should not replace repeat biopsy. Focal therapy has no impact on posttreatment anxiety and depression.

Key Words: prostatic neoplasms, high-intensity focused ultrasound ablation, magnetic resonance imaging, quality of life, surveys and questionnaires

DESPITE technical improvements radical treatment options for PC are still associated with a considerable risk of genitourinary and rectal toxicity.[1] Evidence from recent studies has revealed that not all PC patient subgroups benefit from radical treatment.[2,3]

FT of PC has gained rising interest in recent years. The idea of FT is local cancer control and reducing side effects in select patients. However, the number of reviews exceeds published study results on this topic by far. Therefore, it is of paramount importance to generate evidence from well designed, prospective trials.

Hemiablation is a relatively simple treatment concept offering the advantage of a large safety margin while sparing important anatomical structures. However, more evidence is needed to assess the impact on morbidity and side effects as well as on the oncologic, functional and psychological outcomes of this experimental focal treatment option. We present the results of the HEMI study, a prospective, multicenter study of hemiablation with HIFU.

MATERIALS AND METHODS

This prospective multicenter trial, AUO (Arbeitsgemeinschaft Urologische Onkologie) Study Protocol AP 68/11, was performed at the departments of urology at 5 German centers, including University of Leipzig, University of Heidelberg, University of Magdeburg, University of Köln and Fürth Hospital. At all centers independent central monitoring was done by the Center for Clinical Studies, University of Leipzig. The study was approved by local ethical committees. Prior to inclusion all patients provided signed informed consent.

Eligibility Criteria

Patients with certain inclusion criteria were prospectively selected, including age 18 years or greater, clinical stage T1c-T2a, biopsy proven unilateral PC, 30% or fewer positive biopsies on systematic TRUS prostate 12-core biopsy with a Gleason score of $3 + 4 = 7$ or less, maximum cancer core length 5 mm (only for Gleason score $3 + 4 = 7$ cores) and PSA 10 ng/ml or less. Peripheral zone height was allowed to be 30 mm or less and 40 or less on TRUS in patients treated with Ablatherm® Integrated Imaging and the Focal One® device, respectively.

All patients underwent mpMRI of the prostate with a minimum 6-week interval after biopsy to minimize artefacts. Study exclusion criteria were evidence of significant cancer on the contralateral side on mpMRI as defined by a score of 4 or greater on PI-RADS™, version 1 or later version 2, previous prostatic and/or urethral surgery, and/or intake of 5α-reductase inhibitors 6 months or less in duration, and/or previous androgen deprivation therapy.

Treatment Procedure

Patients were treated with Ablatherm Integrated Imaging at University Hospital of Heidelberg and with the Focal One device at all other centers. Treatment was performed with the patient under general anesthesia in the right lateral position with an indwelling urethral catheter in place, which was removed on day 2 postoperatively. Nerve sparing was not attempted on the treated side. A contrast enhanced ultrasound control for Focal One procedures was not part of our study protocol.

Baseline Evaluation and Followup

At baseline and every 3 months patients were followed by digital rectal examination, PSA and TRUS. Functional parameters, quality of life, anxiety and depression were measured by the German versions of validated questionnaires, including ICS-male SF (International Continence Society-male Short Form) for continence, I-PSS for micturition and IIEF-5 for potency. Global health status and quality of life were determined by items 29 and 30 on EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30, version 3.0.[4] Changes in anxiety and psychological disorder were determined by HADS-D.[5] Safety, side effects and additional treatments were assessed by a self-administered questionnaire. Postoperative complications were assessed by the Clavien-Dindo classification.[6]

Repeat mpMRI and systematic 1-core biopsy were scheduled in all patients at 12 months or earlier in case of rising PSA or progression on digital rectal examination based on study physician assessment. In cases of pathological mpMRI, defined as PI-RADS 4 or greater, systematic biopsy was combined with MRI targeted biopsy using different MRI/TRUS fusion devices at the different study centers. On biopsy csPC was defined as Gleason score $3 + 4 = 7$ or greater, or $3 + 3 = 6$ and total cancer core length greater than 4 mm.[7]

Study End Points

The primary end point was no initiation of definitive treatment during the study period. Secondary end points were no evidence of tumor on followup biopsy at 12 months (treated and untreated lobes), and overall and PC specific survival. Further secondary end points were