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ORIGINAL ARTICLE

Single application of high-intensity focused ultrasound as primary therapy of localized prostate cancer: Treatment-related predictors of biochemical outcomes

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Abstract *Objective:* Recent reports on high-intensity focused ultrasound (HIFU) treatment of localized prostate cancer suggest that preoperative risk groups of tumor recurrence are strong predictors of oncological outcomes. The purpose of this study is to determine the prognostic significance of treatment-related factors in relation to patient characteristics for biochemical outcomes after HIFU.
Methods: This retrospective single-center study included patients treated from December 2002 to December 2010 for localized prostate cancer with two generations of Ablatherm® HIFU devices (A1 and A2). All the patients underwent single HIFU treatment session under the concept of whole-gland therapy. Prostate surgery was performed before HIFU to downsize enlarged glands. Androgen deprivation therapy (ADT) was discontinued before HIFU. Biochemical failure (BCF) was defined as prostate specific antigen (PSA) nadir + 1.2 ng/mL (Stuttgart definition). Predictors of BCF were determined using Cox regression models. As covariates, patient-related factors (age, tumor characteristics, ADT) were compared with treatment-related factors (prostate volume, HIFU device generation, conduct of therapy, prostate edema, patient movement, anesthetic modalities).
Results: Three hundred and twenty-three (98.8%) out of 327 consecutive patients were evaluable for BCF. Median (interquartile range) follow-up was 51.2 (36.6–80.4) months. The overall BCF-rate was 23.8%. In multivariate analyses, higher initial PSA-values (Hazard ratio [HR]: 1.03; $p < 0.001$) and higher D'Amico risk stages (HR: 3.45; $p < 0.001$) were patient-related predictors of BCF. Regarding treatment-related factors, the A2 HIFU device was associated with a decreased risk of BCF (HR: 0.51; $p = 0.007$), while prostate edema had an adverse effect

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(HR: 1.8; $p = 0.027$). Short follow-up and retrospective study design are the primary limitations.

Conclusion: Success in a single HIFU session depends not merely on tumor characteristics, but also on treatment-related factors. Ablation is more efficacious with the technically advanced A2 HIFU device. Heat-induced prostate edema might adversely affect the outcome.

1. Introduction

High-intensity focused ultrasound (HIFU) is a non-surgical, minimal invasive procedure that enables ablation of the prostate *in situ*. Extensive experience in treating clinically localized prostate cancer (PCa) has been gained using Ablatherm® HIFU devices (EDAP-TMS, Vaulx-en-Velin, France). The curative potential was already recognized in 1996 with the use of a prototype [1]. Since then, the oncologic efficacy has been evaluated with two commercially available devices. Recently, oncologic outcomes have been reported from large studies [2—4]. All reports demonstrate that the efficacy of HIFU treatment is associated with the risk stages of tumor recurrence [5], which illustrates the strong influence of preoperative tumor characteristics.

By contrast, the impact of treatment-related factors on cancer control is not well documented.

The principles of a complete prostate ablation (whole-gland therapy) as a prerequisite of complete tumor eradication have been delineated recently [6,7]. Whether the evolving HIFU technology is associated with improving outcomes in patients treated under these principles has still to be determined [2]. Moreover, variations in planning and conducting whole-gland therapy might affect the outcomes. In addition, intraoperative prostate edema or unintentional patient movements might interfere with the treatment plan and influence the results of therapy.

The present retrospective single-center study reports on biochemical outcomes after whole-gland treatment of localized PCa involving two generations of Ablatherm® HIFU devices. We focused on the efficacy of a single HIFU application and determined whether treatment-related factors (prostate volume, HIFU device generation, conduct of treatment, prostate edema, patient movement, anesthetic modalities) have prognostic significance as outcome predictors independent of preoperative patient characteristics.

2. Methods

2.1. Patients

The records of all patients with clinically localized PCa who underwent a single session of whole-gland HIFU treatment as a first-line therapy with curative intent between December 2002 and December 2010 were assessed retrospectively. All men were unsuitable candidates for radical prostatectomy because of age or comorbidity and were unwilling to undergo radiotherapy. Extracapsular tumor extension and lymph node status was assessed with pelvic CT or MRI. Staging included a bone scan in patients with prostate specific antigen (PSA) $\geq$10 ng/mL, and laparoscopic lymphadenectomy was recommended in patients with PSA >20 ng/mL. Androgen deprivation therapy (ADT) was discontinued at the time of HIFU therapy.

Excluded from the study were patients with nerve-sparing HIFU ablation (preserving the neurovascular bundles by sparing the lateral prostate regions [8]), and patients with nodal extension or metastatic disease.

2.2. HIFU technology

Treatment involved two generations of Ablatherm® devices, the Ablatherm Maxis® and Ablatherm Integrated Imaging® (after February 2006), hereafter addressed respectively as device A1 and A2. Both devices comprised a 3 MHz therapeutic and a 7.5 MHz imaging transducer. The treatment transducer generates a focused ultrasound field and creates spindle-shaped elementary lesions of 1.7 mm in diameter by heat (85—100 °C) and cavitation. By variable focusing, the focal length is adjustable (19—26 mm) together with the rectum distance length (3—8 mm). The maximum penetration depth in prostatic tissue is limited to 30 mm [3]. The treatment-head moves computer-driven and larger target volumes can be ablated through repeated shots in juxtapositions. With the more advanced A2 device a new electronic probe with optimized treatment parameters was introduced which allows direct visual control of the procedure via transrectal ultrasound (TRUS) [9]. Local movements of the applicator system were reduced, thus providing a more accurate targeting of the prostate [10].

2.3. Standard planning and conduct of treatment

The intention of whole-gland therapy is destruction of the prostate with a safety margin of 6 mm from the apex to preserve the urethral sphincter. The ablation technique should avoid leaving gaps of untreated tissue at prostate margins and within the gland [6]. In patients at risk of extracapsular tumor extension, the treatment can be extended by millimeters beyond the lateral organ boundaries [7]. A safety margin of at least 3 mm is maintained around the rectum. In patients with enlarged prostate glands, prostate surgery is performed prior to HIFU in order to ensure that the anterior prostate margins are within the limited spatial span of the ultrasound focus [3].