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Whole-gland Ablation of Localized Prostate Cancer with High-intensity Focused Ultrasound: Oncologic Outcomes and Morbidity in 1002 Patients

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Abstract

Background: High-intensity focused ultrasound (HIFU) is a nonsurgical therapy for selected patients with localized prostate cancer (PCa).
Objective: The long-term oncologic and morbidity outcomes of primary HIFU therapy for localized PCa were evaluated in a prospective, single-arm, single-institution cohort study.
Design, setting, and participants: Participants were patients treated with HIFU for localized PCa from 1997 to 2009. Excluded were patients with local recurrence following radiotherapy. A second HIFU session was systematically performed in patients with biopsy-proven local recurrence.
Intervention: Whole-gland prostate ablation with transrectal HIFU.
Outcome measurements and statistical analysis: Incontinence was assessed using the Ingelman-Sundberg score, and potency was assessed using the five-item version of the International Index of Erectile Function (IIEF-5) scores. Primary outcomes were survival rates (biochemical-free, cancer-specific, metastasis-free, and overall survival). Secondary outcomes were morbidity rates. Median follow-up was 6.4 yr (range: 0.2–13.9). The Kaplan-Meier method was used to determine survival estimates, and multivariate analysis was used to determine predictive factors of biochemical progression.
Results and limitations: A total of 1002 patients were included. The median nadir prostate-specific antigen (PSA) was 0.14 ng/ml, with 63% of patients reaching a nadir PSA $\leq$0.3 ng/ml. Sixty percent of patients received one HIFU session, 38% received two sessions, and 2% received three sessions. The 8-yr biochemical-free survival rates (Phoenix definition) were 76%, 63%, and 57% for low-, intermediate-, and high-risk patients, respectively ($p < 0.001$). At 10 yr, the PCa-specific survival rate and metastasis-free survival rate (MFSR) were 97% and 94%, respectively. Salvage therapies included external-beam radiation therapy (EBRT) (13.8%), EBRT plus androgen-deprivation therapy (ADT) (9.7%), and ADT alone (12.1%). Severe incontinence and bladder outlet obstruction decreased with refinement in the technology, from 6.4% and 34.9% to 3.1% and 5.9%, respectively. Limitations included the fact that the study was a single-arm study without a comparison group, technological improvements, changes in surgical protocol during the study, and the use of ADT to downsize the prostate in 39% of patients.
Conclusions: HIFU is a potentially effective treatment of localized PCa, with a low PCa-specific mortality rate and a high MFSR at 10 yr as well as acceptable morbidity.

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1. Introduction

The objective of prostate cancer (PCa) treatment is the achievement of optimal cancer-specific survival rates with the lowest possible morbidity. High-intensity focused ultrasound (HIFU) is a nonsurgical treatment that uses nonionizing energy to induce irreversible damage to the malignant lesion through coagulation necrosis. Transrectal delivery of ultrasound under real-time monitoring forms the basis of HIFU. The thermal and cavitational effects can be repeated with subsequent treatment administration, and salvage external-beam radiation therapy (EBRT) is a therapeutic option in cases of local relapse following HIFU [1]. Since 1993, HIFU has been evaluated in our department as a minimally invasive option for the treatment of localized PCa in nonsurgical candidates [2]. Long-term oncologic results for HIFU are sparse in the literature, and HIFU is still considered investigational in the European Association of Urology guidelines [3,4]. The goals of the current study were to report the cancer control and morbidity outcomes for all patients treated with HIFU as primary therapy between January 1997 and December 2009 as well as to analyze factors that potentially influence treatment outcome.

2. Materials and methods

Following institutional review board approval, data from all treated patients were prospectively obtained and entered into a secure database (IRB: EB/MR92027/C, 200–032B, 2003–001B). Inclusion criteria were localized PCa, prostate-specific antigen (PSA) <30 ng/ml, clinical stage T1M0–T2M0, and no previous radical therapy for PCa. None of the patients were candidates for surgery because of age, comorbidity, or patient refusal. All patients were offered the treatment options of HIFU in a research protocol, EBRT, or active surveillance. Baseline and post-HIFU PSA measures were obtained for all patients.

2.1. Treatment protocol

All patients were treated with Ablatherm HIFU devices (EDAP-TMS, Vaulx-en-Velin, France), including prototype devices (1997–1999), Ablatherm Maxis (1999–2000), and Ablatherm Integrated Imaging (since 2005). Starting in 2000, transurethral resection of the prostate (TURP) was performed immediately prior to the HIFU session, under the same anesthesia, in patients with prostate volume <30 ml. In patients with prostate volume >30 ml, two strategies were used: androgen-deprivation therapy (ADT) before 2005 and TURP performed 6 wk prior to HIFU beginning in 2006. Pre-HIFU TURP avoids the adverse effects induced by hormonal therapy and dramatically reduces catheter time and rate of urinary tract infection [5]. The most recent treatment parameters for initial HIFU therapy involved a 3-MHz nominal frequency, 6-s treatment pulse, and 4-s shot interval. Five operators performed the procedures.

2.2. Follow-up

Before June 2007, all patients underwent post-HIFU biopsy at 6 mo regardless of PSA level. After June 2007, post-HIFU biopsy was performed only in patients with a nadir PSA >0.3 ng/ml, according to the Ganzer et al. publication [6]. Based on the small post-HIFU prostate volume, a minimum of six biopsy cores were obtained. Additional follow-up biopsies were performed in cases of biochemical failure (American Society for Therapeutic Radiology and Oncology/Phoenix definition). In cases of positive biopsy without evidence of metastasis, a second HIFU treatment was offered. Before 2005, some patients continuing to show positive biopsy who had little morbidity after the second session received a third HIFU session. Analysis of the initial repeat HIFU outcomes, including the elevated risk of rectourethral fistula, led to the introduction of specific parameters for HIFU retreatment in 2007.

2.3. Salvage treatment

Salvage therapy was performed after the last HIFU session in the event of biopsy-proven local recurrence and/or biochemical failure. ADT was used in patients without biopsy-proven local recurrence or with poor general health status, and salvage radiation therapy (SRT) alone or in combination with ADT was performed in patients with demonstrated local recurrence and long life expectancy.

2.4. Survival and morbidity evaluation

For disease-free rates, *biochemical failure* was defined using the Phoenix definition (nadir +2 ng/ml). All PCa-specific deaths were verified, and hormone-refractory metastatic PCa was documented by rising PSA level despite the use of second-line ADT and chemotherapy. Additional treatment–free survival was calculated by the initiation of salvage treatment as the date of failure. Palliative treatment–free survival was calculated by the initiation of definitive ADT. Incontinence was assessed using the Ingelman-Sundberg score [7], and potency was assessed using the five-item version of the International Index of Erectile Function (IIEF-5) scores between 12 and 24 mo after HIFU. All adverse effects, such as bladder outlet obstruction (BOO) (obstruction of the outflow of urine from necrotic debris or urethral stricture), were prospectively recorded. Only patients with complete data have been included in the final analysis (multivariate analysis, survival curves).

A statistical analysis was performed with SPSS v.20 (IBM Corp., Armonk, NY, USA). Survival curves were based on the Kaplan-Meier method, and the log-rank test was used for univariate comparisons. Actuarial survival rates were based on life table methods. For multivariable analysis, the Cox proportional hazards regression model was used.

3. Results

A total of 1002 patients met inclusion criteria. Patient demographics and baseline characteristics are summarized in Table 1. Median follow-up was 6.4 yr (0.2–13.9). HIFU was delivered by prototype model in 63 patients, Ablatherm Maxis in 652 patients, and Ablatherm Integrated Imaging in 287 patients. A total of 392 patients received pre-HIFU ADT for a median duration of 4.3 mo (range: 1–56) (n = 278 [71.0%] for ≤6 mo; n = 114 [29.0%] for >6 mo). ADT was stopped after HIFU in all recipients. As only 63 patients (6.3%) did not received pre-HIFU TURP, the effect of TURP on the oncologic results was not evaluable. The median number of HIFU sessions was one (range: one to three), with 596 patients (60%) receiving one session, 383 patients (38%) receiving two sessions, and 23 patients (2%) receiving three sessions. On average, 488 ± 122 shots were delivered, corresponding to a median treated volume of 30 ml (range: 3–60), which was 130% of the actual prostate volume size because of overlap in treatment zones.

Post-HIFU biopsies after the final HIFU treatment were available for 774 patients (77%). Results were negative in 485 patients (63%) and positive in 289 patients (37%).