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ORIGINAL ARTICLE

Complete high-intensity focused ultrasound in prostate cancer: outcome from the @-Registry

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BACKGROUND: To analyze data on patients with localized prostate cancer who were treated with complete high-intensity focused ultrasound (HIFU) prospectively captured within a voluntary HIFU user database (@-Registry).
METHODS: The @-Registry includes data from consecutive patients treated with Ablatherm (EDAP-TMS) HIFU at nine European Centres during the period 1994 and 2009. For this analysis, the data repository was reviewed for information on patients with localized prostate cancer (T1 – T2) treated with complete (whole-gland) HIFU on the basis of an anterior-posterior prostate height of $\leqslant$24 mm and a treated volume $>$120% of the prostate volume. Patients were regularly followed with PSA measurement and biopsy. Biochemical failure was defined for this study as PSA nadir $+2\,\mathrm{ng\,ml^{-1}}$ (Phoenix definition). Disease-free survival was based on a biopsy, retreatment and biochemical data. Patients were risk group-stratified using the D'Amico classification system.
RESULTS: The median follow-up was 2.8 years for the 356 patients included in the analysis. The majority could be classified as either low (44.9%) or intermediate risk (39.6%); 14.6% patients were classified as high risk. The median (mean, s.d.) PSA nadir was $0.11\,\mathrm{ng\,ml^{-1}}$ (0.78 and 3.6), achieved at a mean (s.d.) of 14.4 (11.6) weeks after HIFU. Follow-up biopsies on 226/356 (63.5%) patients revealed an overall negative biopsy rate of 80.5% (182/226); there was no statistically significant difference in positive biopsy rate by risk group-stratification. Actuarial freedom from biochemical recurrence at 5 and 7 years according to the Phoenix definition was 85% and 79%, respectively. Disease-free progression rates at 5 and 7 years were 64% and 54%, respectively.
CONCLUSIONS: Whole-gland prostate HIFU as primary monotherapy for localized prostate cancer achieves a recurrence-free survival in short-term analysis as assessed by prostate biopsy and serum PSA endpoints in a majority of patients.

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INTRODUCTION

High-intensity focused ultrasound (HIFU) is a versatile therapy for prostate cancer that is easily adapted to the individual patient. With little blood loss,[1] it has proven to be a safe method to treat patients who prefer to avoid radical prostatectomy or radiation therapy, as well as the patient who desires a single-day, curative treatment with little recovery time or disruption of daily life activities. The use of HIFU as a primary therapy for localized prostate cancer has increased and is recommended as an option for prostate cancer therapy by the Italian and French Urological Associations.[2,3] HIFU represents a trackless ablative sonic therapy that creates coagulative necrosis of the targeted tissue without collateral damage to the tissue through which the sound waves are propagated.[4,5]

Complete ablation (whole-gland HIFU therapy) of all prostatic tissue with the Ablatherm device (EDAP-TMS) is only possible if the anterior-posterior (AP) prostate height is $\leqslant$24 mm (in the range of the maximum height at which the Ablatherm device can treat). Calcifications, which can reflect the sound-wave transmission, should not be present in the treatment field. Whole-gland ablation with HIFU is usually achieved by treating the prostate in two to four zones from the apex to the base dependent on gland size and shape. For this complete gland-treatment concept, it is mandatory to overlap the treatment blocks in order to avoid leaving intervening untreated tissue. Therefore, the treated volume is $>$100% of the measured prostate volume if full gland ablation is performed.

The Ablatherm (EDAP-TMS) treatment registry (@-Registry) is a secure online voluntary database that consists of case-report forms specifically engineered to collect appropriate pre- and post-treatment information from multiple treatment centers for all patients entered, that is, consecutive patients who have undergone prostate HIFU utilizing the Ablatherm (EDAP-TMS) device. A review of a percentage of case is made at each centre to ensure the accuracy of information entered into the database. An expert committee meeting is held twice yearly to review the data in the registry. It represents the single largest multi-institutional repository of prospectively maintained information regarding the efficacy of prostate-cancer therapy with HIFU. We believe this is the first report of a large series of patients from the @-Registry and

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represents an analysis of patients who have undergone complete (whole-gland) HIFU without neoadjuvant or adjunctive hormone therapy.

MATERIALS AND METHODS

The @-Registry includes data from consecutively treated HIFU patients during the period February 1993 and October 2010. Data were reviewed on patients with localized disease (T1 – T2). In order to ensure that analysis was conducted strictly on those patients who had undergone complete HIFU, patients were selected from the database based on an AP prostate height of $\leqslant 24$ mm and a treated volume $>120\%$ of the prostate volume. Patients were excluded if they had undergone specific prior treatment for prostate cancer (non-steroidal antiandrogens, luteinizing hormone-releasing hormone agonist, radiation therapy or cryotherapy). Patients who underwent a TURP at the time of HIFU (within 2 days) are included in the analysis.

Following complete HIFU therapy, patients were followed with PSA measurement at 3 months and then every 6 months thereafter. Biopsy was recommended at 3 – 6 months post HIFU and/or if a PSA level was recorded that was considered clinically relevant by the treating physician. Secondary treatment was instituted based on the PSA level or positive biopsy according to the clinical judgment. Patients with a positive biopsy or who received adjunctive therapy (<90 days) or salvage therapy (>90 days) for prostate cancer were considered treatment failures on the date of biopsy or secondary therapy. The definition of biochemical failure used in this report was PSA nadir $+2\,\mathrm{ng\,ml^{-1}}$ (2006 Phoenix definition).[6]

Study patients were risk stratified according to the recommendations made by D'Amico *et al*.[7]: low risk: clinical stage T1c or T2a, GS $\leqslant 6$ and PSA $<10\,\mathrm{ng\,ml^{-1}}$; intermediate risk: clinical stage T2b or PSA $10-20\,\mathrm{ng\,ml^{-1}}$ or GS 7; and high risk: clinical stage $\geqslant$T2c or PSA $>20\,\mathrm{ng\,ml^{-1}}$ or GS 8 – 10.

Statistics

Statistical analyses were carried out with SPSS statistical software version 17 (SPSS, Chicago, IL, USA). Depending on the distributions, parametric and non-parametric tests were applied. Survival curves were based on Kaplan – Meier models and the log-rank test was used for univariate comparisons. Actuarial survival rates were based on life-table methods. All *P*-values <0.05 reflected statistically significant differences.

RESULTS

At the time of this analysis, 1975 patients with the following characteristics were in the registry: clinical stage T1/T2 and no previous prostate-cancer treatment. Of these patients, 75 had incomplete datasets and of the remaining 1900 patients, 356 (18%) were rated as complete HIFU patients based on the parameters set that is, treated volume $>120\%$ and AP diameter $\leqslant 24$ mm. The clinical characteristics at the time of treatment of the 356 patients are presented in Table 1. The majority of the patients could be classified as either low ($n=160$; 44.9%) or intermediate risk ($n=141$; 39.6%); 52 (14.6%) patients were classified as high risk and 3 (0.8%) patients were unclassified because of missing data. A total of 205 (57.6%) patients underwent TURP at the time of HIFU. The median follow-up at the time of this study analysis was 2.8 years. The median (mean, s.d.) PSA nadir was $0.11\,\mathrm{ng\,ml^{-1}}$ (0.78 and 3.6), achieved at a mean (s.d.) of 14.4 (11.6) weeks after HIFU.

Follow-up biopsy data are available on 226/356 (63.5%) patients; 100 (62.5%), 93 (66.0%) and 31 (59.6%) patients in the low-, intermediate- and high-risk groups, respectively. Negative biopsy was reported in 80.5% (182/226) patients overall; number of patients and rates for low-, intermediate- and high-risk groups were 86 (86.0%), 73 (78.5%) and 23 (74.2%), respectively. There was no statistically significant difference between the risk groups ($P=0.228$).

Table 1. Baseline characteristics of 356 patients treated with high-intensity focused ultrasound (HIFU)

Characteristic	*No. of patients (%) or mean (s.d.)*
Age (years)	69.6 (7.2)
Gleason score	
$\leqslant 6$	271 (76.1%)
7	80 (22.5%)
8 – 10	5 (1.4%)
Patients with clinical stage	
T1c	142 (39.9%)
T2a	83 (23.3%)
T2b	53 (14.9%)
T2c	37 (10.4%)
Patients in risk groups	
Low	160 (44.9%)
Intermediate	141 (39.6%)
High	52 (14.6%)
Not known	3 (0.8%)
PSA pre-HIFU (median (range) $\mathrm{ng\,ml^{-1}}$)	6.83 (0.12 – 58.0)
Prostate volume (ml)	18.0 (4.0 – 38.0)

Table 2. Biochemical survival in patients treated with whole-gland high-intensity focused ultrasound according to the Phoenix definition of biochemical failure

Risk group	*Freedom from biochemical recurrence at 5 years (no. of patients at risk)*	*Freedom from biochemical recurrence at 7 years (no. of patients at risk)*
All	85% (102)	79% (39)
Low	88% (49)	80% (22)
Intermediate	82% (40)	82% (14)
High	78% (11)	64% (3)

Actuarial biochemical disease-free survival rates (DFSR) and the number of patients at risk at 5 and 7 years according to the risk group-stratification are reported in Table 2. The differences between risk subgroups themselves were not significant. Kaplan – Meier biochemical DFSR curves according to the Phoenix definition is shown in Figure 1 for the overall populations and in Figure 2 for the risk subgroups.

The disease-free progression rates based on biopsy outcome, retreatment and the Phoenix definition of failure and the number of patients at risk at 5 and 7 years according to the risk group-stratification are shown in Table 3. Kaplan – Meier disease-free survival curves are shown in Figure 3 for the overall populations and in Figure 4 for the risk subgroups.

DISCUSSION

The current study is a retrospective analysis of data from patients who underwent whole-gland prostate ablation with HIFU and were tracked within the @-Registry. The focus of the paper is to determine if complete HIFU provides a good oncologic outcome. The morbidity of the procedure is currently being analyzed and will be the topic of another paper. Overall, the 5- and 7-year BDFRS rates reported using the Phoenix definition

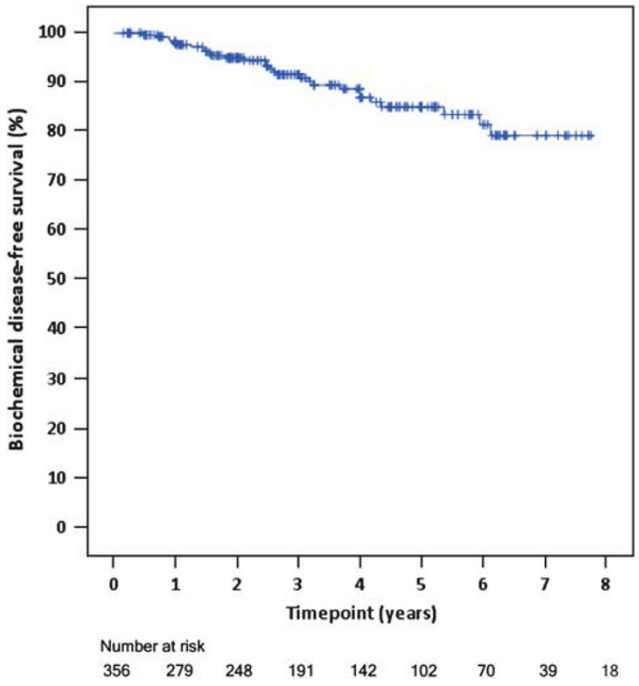

Figure 1. Biochemical disease-free survival rates for the overall population.

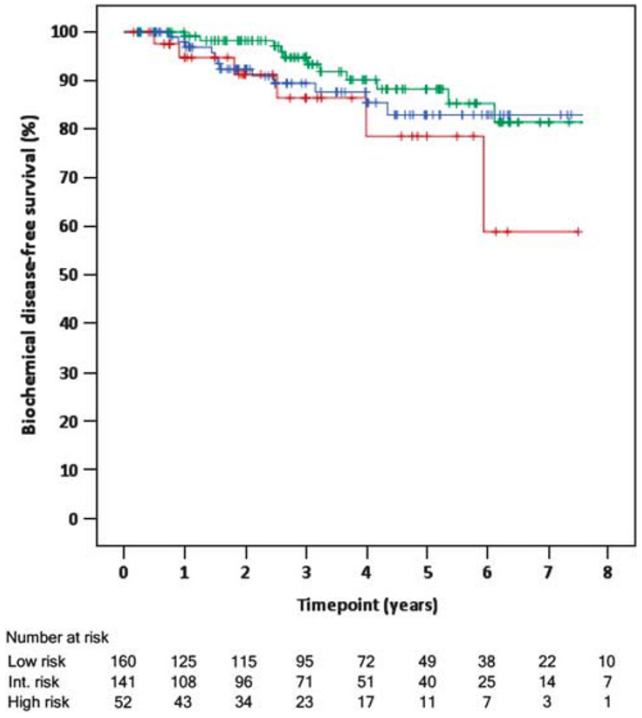

Figure 2. Biochemical disease-free survival rates stratified according to the risk group.

were 85% and 79%, respectively. BDFRS rates were higher in low-risk patients but the differences between risk groups were not statistically significant. Blana *et al.*[8] analyzed data on 285 patients treated with HIFU with a median (range) follow-up of 4.7 (2–10.9) years. It was shown that biochemical events that best predicted clinical failure were 'PSA nadir plus' values of 1.1–1.3 ng ml^{-1}, PSA

Table 3. Disease-free survival in patients treated with whole-gland high-intensity focused ultrasound according to biopsy outcome, retreatment and the Phoenix definition of biochemical failure

Risk group	*Disease-free survival at 5 years (no. of patients at risk)*	*Disease-free survival at 7 years (no. of patients at risk)*
All	64% (104)	54% (39)
Low	77% (50)	56% (11)
Intermediate	56% (40)	56% (7)
High	52% (12)	14% (1)

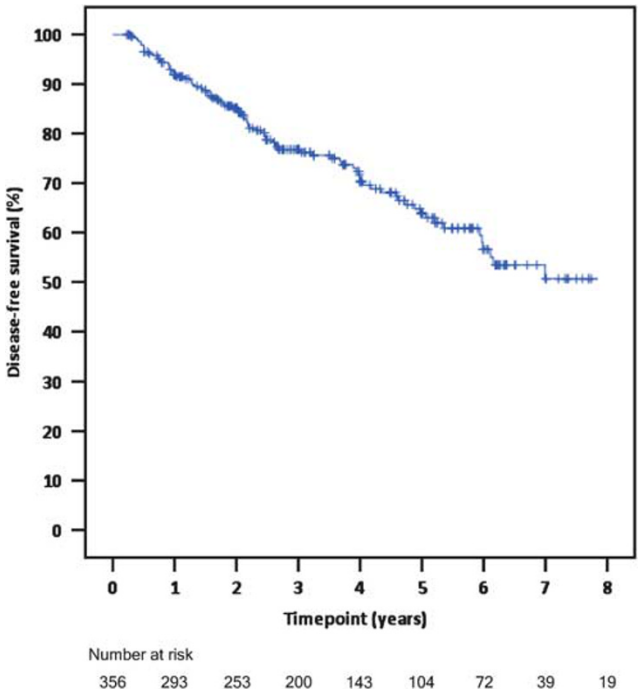

Figure 3. Disease-free survival rates for the overall population.

velocities of 0.3 ng ml^{-1} year^{-1} and PSA doubling times of 1.25–1.75 years.

A comparison can be made with other series of patients treated with HIFU. Uchida *et al.*[9] treated 181 patients with HIFU and reported a 5-year biochemical DFSR of 78% using the original American Society for Therapeutic Radiology and Oncology criteria (three consecutive rises in PSA with failure defined as the mid point between the nadir and first rise); 95 patients (52%) received neoadjuvant hormones in that study. More recently, Blana *et al.*[1] reported biochemical outcomes using the Phoenix definition applied to 140 patients at a mean follow-up of 6.4 years. The actuarial biochemical failure-free survival rates at 5 and 7 years were 77% and 69%, respectively.[1] Hormone therapy over a short period of time was given to 23 patients (16.4%) to effect downsizing to a treatable AP diameter. Poissonnier *et al.* reported on a study of 227 patients with T1-2 disease treated with HIFU with a mean follow-up of 27 months.[10] The actuarial 5-year DFSR based on a positive biopsy or a PSA >1 ng ml^{-1} with three consecutive rises was 66%. The 5-year DFSR rate in the current study based on a positive biopsy, retreatment or biochemical progression according to the Phoenix definition was comparable at 64%. This definition of DFS is unique for the HIFU literature and the results are always worse than the biochemical failure rates

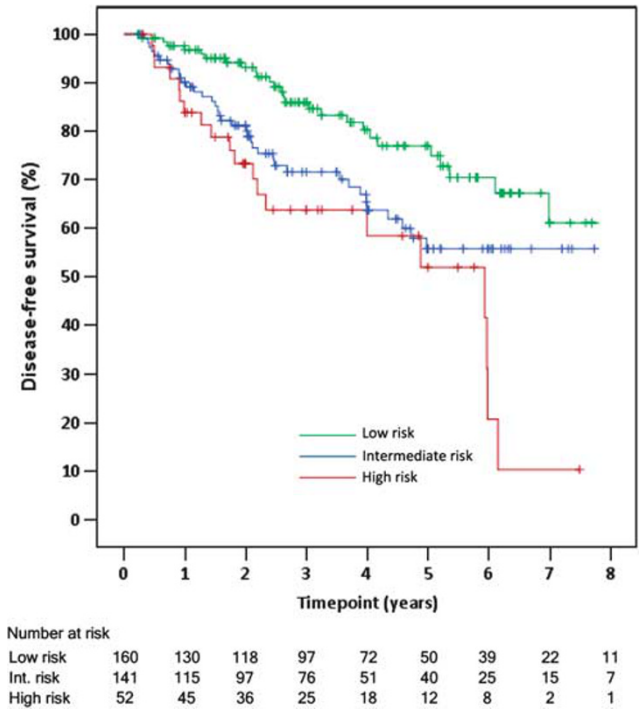

Figure 4. Disease-free survival rates stratified according to the risk group.

alone, but it gives an honest picture of what the patients might expect. In comparison with other treatment options, only biochemical failure rates should be applied.

The current study is distinct from these previously published reports of HIFU therapy of prostate cancer. All of these cited studies have in common the inclusion of patients not treated by complete ablation of the prostate. Some of the patients had an AP diameter in excess of 24 mm. As a consequence, anterior parts of the prostate were likely missed by the HIFU treatments. Another reason for incomplete treatment could have been a less aggressive approach by the physician. This could result from not overlapping the treatment blocks or by sparing the lateral borders of the prostate to protect the neurovascular bundles. Incomplete HIFU may not achieve the same result as residual prostate tissue may represent a source for PSA production, complicating endpoint Phoenix criterion interpretation.

There are limitations to this study. Registry data are voluntary and reflective of clinical practice variability by site. There are limitations to using such data; it can be subject to variations in clinical practice and is limited in its comparability to other single-site studies. It should also be noted that the definition of complete HIFU is a consensus definition for the purposes of this study and is not based on community standards agreed to by any specific HIFU-treating group or association. The AP diameter is dependent on the transrectal ultrasonography. Of note, transrectal ultrasonography measurements have been demonstrated to be more accurate in small glands <30 ml compared with those sized >50 ml.[11] The inclusion criteria of an AP diameter $\leqslant 24$ mm and a treated volume $>120\%$ of the prostate volume do not rule out that in the individual patient, parts of the prostate might have been missed. We still believe that these surrogate parameters represent the best method to define complete HIFU in a retrospective analysis. For future studies, especially when the concept of focal therapy is applied, prospective parameters of intended treatment areas will need to be defined before treatment planning.

CONCLUSIONS

Complete prostate-gland HIFU as primary monotherapy for localized prostate cancer is effective oncologically in a subset of patients with small prostate as measured by post-therapy prostate biopsy and serum PSA endpoints. In this study, HIFU is equally efficacious for all the grades of prostate cancer on short-term follow-up. Careful evaluation of long-term HIFU efficacy is needed and should be compared with established therapies with a complete HIFU approach to allow the most accurate evaluation of this promising and novel technology.

CONFLICT OF INTEREST

Dr Blana served as a paid consultant for EDAP TMS. The remaining authors declare no conflict of interest.

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