



HAUTE AUTORITÉ DE SANTÉ

**High Intensity Focalized Ultrasound
for the treatment of localized prostate
cancer**

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Department of Medical and Surgical Procedures Assessment

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THE TEAM

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CONTENTS

| | |
|---------------------------|---|
| CONTEXT..... | 4 |
| INTRODUCTION | 5 |
| I Assessment method | 6 |
| II Results | 6 |
| III Conclusion | 7 |

SUMMARY

Introduction

High Intensity Focalized Ultrasound (HIFU) treatment of localized prostate cancer has been developed from the middle of the 90's onwards. In 2003, a first health technology assessment driven by the ANAES (HAS) concluded to the need of a further clinical research and a longer term follow-up. In 2009, the French Association of Urology (AFU) requested again the HAS for a new appraisal of this technology. AFU listed 2 indications regarding the HIFU treatment assessment: primary therapy of a prostate cancer at low or intermediate risk on one hand, and salvage therapy after local recurrence after radiotherapy failure on the other hand.

Prostate cancer is the most common cancer in men. In 2009, 71,000 new cases were registered in France. Prostate cancer risk is strongly related to age. Prevalence is probably more than 50% among men beyond the age of 70 years. However, prostate cancer is the main cause of death for 3% of men only, which occurs fairly late in life mostly after the age of 75. These data are closely related to the natural history of the disease: usually late in occurrence and slow growing cancer.

At the time of the diagnosis the median age is 70 years. Most often, diagnosis of prostate cancer is made at an early stage of the disease. The diagnosis is frequently oriented by an individual screening with prostatic specific antigen (PSA) in an asymptomatic man. Progression of the tumor, recurrence after treatment, and prostate-cancer related death risks are roughly estimated by gathering clinical (TNM staging), biochemical (PSA level), and histological (Gleason score) factors. This stratification of risk related to prostate cancer and the estimation of life expectancy related to age and co-morbidity are critical for the decision of treatment.

The optimal primary treatment of localized stages of prostate cancer remains unknown. Current options are radical prostatectomy, radical external beam (conformal) or internal (brachytherapy) radiotherapy. There is no strong evidence for the benefit of one treatment over another. The absolute decrease in 10-year cancer specific mortality associated with surgery compared to watchful waiting (see infra) has been estimated at 5% (which corresponds approximately to an increase of life expectancy by about 1 year for a 70-year old man). A wide range of complications and morbidity are associated with each of these options (incontinence after surgery, bowel dysfunction after radiotherapy, erectile dysfunction for all the options). Therefore, besides an immediate radical treatment, the possibility of differed treatment, notably active surveillance (i.e. observation with selective delayed intervention) and watchful waiting (observation with palliative treatment for symptomatic cancer progression) should be considered.

Recurrence of prostate cancer occurs in 10 to 60% of patients after radiotherapy, depending on the definition of biochemical relapse (with biopsy) and possible time to observe these events. Prostate cancer-related mortality is considerably increased in such situations. The expected benefit on survival of treatment is then important. Nevertheless, salvage treatment options, including radical prostatectomy, cryotherapy and brachytherapy are based on evidence from case series only. Radical prostatectomy as salvage is particularly difficult and carries a high risk of incontinence and rectal damage.

Opportunity of a new treatment of prostate cancer could then be related to an expected decrease of complications associated with primary radical treatment, feasibility and an expected effectiveness on survival in case of salvage therapy after radiotherapy failure.

HIFU treatment of localized prostate cancer

Two devices to deliver endo-rectally HIFU treatment are currently available: Ablatherm® (produced by EDAP-TMS, Lyon, France) and Sonablate® (produced by Focus Surgery, Indianapolis, In, USA). In France, Ablatherm® only is available.

HIFU therapy induces a prostate fibrosis after destroying the deep-seated target prostate cells by coagulating the tissue, while sparing the adjacent healthy tissues. High intensity ultrasound beams focus the target tumor achieving locally a temperature of 80 to 100°C. The entire prostate volume is treated step-by-step by consecutive prostate zones. The probe motion of the Ablatherm® device is robotized. The procedure is automated and controlled by the surgeon with real-time ultrasound imaging. A cooling balloon surrounding the probe protects the rectal mucosa. A strict immobility of the patient is required and closely monitored during the procedure (lasting around 2 hours). Regional or general anesthesia is administered preoperatively to the patient.

Primary therapy with HIFU is generally preceded by a transurethral resection of the prostate (TURP) to reduce the prostate volume (less than 40 ml can be treated) and decrease post operative urinary retention risk.

More than 22,000 patients have been treated in 250 centers all around the world with Ablatherm® device.

AFU proposed HIFU therapy in two indications :

- Primary therapy for low to intermediate risk localized prostate cancer (T1-2 NxM0), with PSA <15 ng.mL⁻¹ and a Gleason score ≤7 [3+4]. The target-patient is 70-year or older, with a life expectancy related to age and co-morbidity greater than 5 years.
- Salvage therapy of a localized prostate cancer recurrence after external beam radiotherapy failure.

The expected benefit of HIFU is a decrease in prostate-cancer specific mortality (when compared with watchful waiting) combined with reproducibility of the procedure and associated with a reduction of side effects (when compared to other treatment options).

Effectiveness criteria of judgment were defined as long term survival (-overall, -cancer-specific, -without metastasis, -without second treatment, - without biochemical or disease relapse) with at least 10 years follow-up, and long-term side effects of treatment and quality of life (according either to superiority or non inferiority hypothesis).

Safety criteria of judgment were operative and postoperative complications registered after HIFU therapy.

I. Assessment Method

The assessment method involved two steps: The first step consisted in a systematic review of the evidence (published or non-published literature until September 2010, in French or English languages) using checklists, and writing of a draft report. The second step consisted in consulting a multidisciplinary working group composed of health care professionals and patients to complete or revise the draft report when necessary.

The process, by which this report was produced, and the final version of this report were validated by the Committee for Assessment of Medical and Surgical Procedures, then approved by the HAS Board before publication.

II. Results

The evidence for the efficacy and safety of HIFU is solely based on case-series.

No HTA report or guidelines currently recommends HIFU in routine use.

Systematic reviews had concluded that long term follow-up studies are needed for further evaluation of cancer specific and overall survival rates.

At the moment, 2 controlled non-randomized studies are ongoing in United States, in which HIFU for low risk prostate cancer only is being compared (biochemical disease -free survival) to cryosurgery and brachytherapy respectively.

Case-series analysis :

- As primary therapy, 17 case-series were reported in 35 published studies (June 2010). Patients were described several times over time or in multicenter studies by 14 (European, Japanese, and North American) study groups. These studies were related to more than 2,000 selected patients (median age 70 years) treated by the 2 available devices Ablatherm® (10 case-series) or Sonablate® (7 case-series).

Localized prostate cancer was at low to intermediate risk in 90% of cases. Thirty to 40% of patients had received hormonal treatment before HIFU. Different devices of the same manufacturer over time were used in 5 case-series. Most of treated patients in these series were treated with the first commercially available device. At least 10 to 20% (in more recent series) of patients in series were treated by 2 sessions or more of HIFU. The maximum median follow-up was 6.4 years. A surrogate outcome (biochemical disease-free survival) measured according heterogeneous definitions among studies was most frequently used as the only efficacy criteria. Loss to follow-up rate was not reported in 80% of published studies.

With these limitations, post treatment 8-year prostate cancer-specific survival estimate was 98% CI 95 [82%; 99%]. Five-year biochemical disease-free survival estimate was between 66 and 77% according to the definition of biochemical relapse which was used. From 803 selected cases extracted from the AFU-@registry (including “published” cases) after exclusion of patients who received neo-adjuvant hormonal treatment, authors recently reported (July 2010) estimates of 8-year specific- and without metastasis- survival at 99% CI 95 [95% ; 99%] and 97% CI 95 [93% ; 99%] respectively.

Postoperative complications in case-series were urinary retention (10 to 20% of cases), urinary tract infection (2 to 10%), and recto-urethral fistula (1 to 2%). No postoperative death or major clinical event that could be related to treatment was reported.

Long term side effects after HIFU therapy were urinary incontinence (grade 2 or 3: 4 to 6%), and de novo erectile impotence (50%) in the more recent series.
- As salvage therapy after radiotherapy failure, 3 cases-series were reported in 5 studies (June 2010). Patients were described several times over time by 3 European study groups. These studies were related to 400 patients (mean age 68 years) treated by different Ablatherm® (2 case-series) or Sonablate® (1 case-series) devices over time. Fifty per cent of patients had a high risk prostate cancer before initial radiotherapy. Fifty per cent of patients received hormonal treatment when treated by HIFU as salvage therapy. The maximum median follow-up between series was 3.2 years. Loss-to-follow up rate was not reported in series.

Post treatment 5-year cancer-specific survival estimate was 90% CI 95 [80%; 96%]. Five-year biochemical disease-free survival estimate was 44% CI 95 [30%; 59%], and negatively correlated with the initial (before radiotherapy) cancer recurrence risk.

Postoperative complications were urinary retention (20 to 40% of cases), urinary tract infection (2 to 15%), and recto-urethral fistula (3 to 5%). No postoperative death or major clinical event that could be related to treatment was reported.

Long term side effects after salvage HIFU therapy were urinary incontinence (grade 2 or 3: 30%), rectal complications related to recto-urethral fistula, and impotence.

III. Conclusion

Based on these data, evidence is insufficient to determine net benefits or risks of HIFU therapy either as a primary treatment or as salvage therapy for prostate cancer.

It's unlikely that this conclusion would be change in the next future due to the lack of ongoing or planned studies (clinical trials or observational studies) comparing HIFU for the treatment of prostate Indications.