

# Ultrasound & Therapy

by EDAP TMS



## Information on therapeutic ultrasound in the urology practice

### Enlight

### HIFU and Prostate Cancer

[www.pcaresearch.com](http://www.pcaresearch.com) / [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

## Ablatherm® HIFU clinical trial in the US

Dr John Rewcastle, Medical Director of EDAP TMS

EDAP TMS is conducting a clinical trial evaluating the safety and effectiveness of HIFU as a therapy for previously untreated prostate cancer. This is a comparative study with cryoablation.

The FDA has approved an Investigational Device Exemption entitled "Ablatherm Integrated Imaging High Intensity Focused Ultrasound for the Indication of Low Risk, Localized Prostate Cancer" and has allowed for the enrollment into the HIFU arm at up to 15 centers in the United States. There is also a site enrolling patients in Toronto, Canada. The inclusion and exclusion criteria include:

- Age ≥ 50 years old
- Gleason ≤ 6
- PSA ≤ 10
- Prostate volume ≤ 40 cc
- Anterior posterior height ≤ 25 mm
- No previous treatments for prostate cancer (including hormone therapy).

For the complete list of criteria,

visit the website [www.clinicaltrials.gov](http://www.clinicaltrials.gov). The anterior posterior size restriction is due to HIFU not being combined with a TURP. The study consists of pre-treatment assessments, treatment, and follow-up evaluations at a minimum of 24-months post treatment. The primary endpoint of the trial is attainment of a PSA nadir < 0.5 ng/ml with subsequent stability (according to the original ASTRO criteria) in absence of a positive biopsy 24 months following HIFU. Study participants will be evaluated before treatment, during treatment, and after treatment using clinical and laboratory tests, biopsy assessment, and subject self-assessment. Post-treatment follow-up will be conducted five days after the procedure and then at the following months after the procedure: 1, 3, 6, 9, 12, 15, 18, 21, and 24.

### Ablatherm® Robotic HIFU®



Sites participating in the Enlight trial enrolling patients into the HIFU arm include:

Duke University, Durham, NC	Hackensack UMC, Hackensack, NJ
Virginia Urology, Richmond, VA	Memorial Sloan Kettering, New York, NY
Florida Foundation for Health Research, Ocala FL	MD Anderson, Houston, TX
Thomas Jefferson, Philadelphia, PA	Medical College of Wisconsin, Milwaukee, WI
University of Colorado, Denver, CO	University of North Carolina, Chapel Hill, NC
Urology Associates of North Texas, Dallas, TX	Mc Master University, Toronto, Canada

### More information about Enlight clinical study ?

For patients:  
[www.pcaresearch.com](http://www.pcaresearch.com)/  
[www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
or please call 1-800-300-7252

For physicians:  
Contact our Medical Director:  
Dr. John Rewcastle  
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### Ablatherm® HIFU

Minimally-invasive treatment for localized prostate cancer

## Ablatherm® HIFU, the state-of-the-art robotic assistant

Ablatherm® HIFU is not yet FDA cleared

Ablatherm® HIFU, which was developed at the end of the 1980s in collaboration with Inserm, the French Institute of Medical Research, has been used to treat patients suffering from localized prostate cancer since 1993.



Currently, more than 19,000 treatments have been carried out in 28 countries demonstrating the growing worldwide acceptance of this minimally-invasive technique. The principle of Ablatherm® HIFU: HIFU (High Intensity Focused Ultrasound) induces a localized temperature elevation which creates a sharply demarcated volume of coagulative necrosis. The sharp demarcation allows for the effective ablation of targeted tissue while preserving the surrounding tissues at the same time.

Ablatherm® HIFU device consists of 2 modules: a treatment module and a computer console to control the treatment. The treatment module consists of a bed upon which the patient lies in the right lateral decubitus position and the Ablatherm® HIFU probe. The

Ablatherm® HIFU probe contains two ultrasound crystals; one designed for imaging (7.5 MHz) and one designed for treatment (3 MHz). The treatment is planned, controlled and observed by the physician sitting at the computer console.

### Treatment Planning

The probe is introduced into the patient's rectum in order to visualize the prostate, apex and rectal wall. After insertion of the probe all movements are completely robotic with 3 degrees of freedom. Based on imaged anatomy, the surgeon plans the treatment to completely ablate the prostate. The prostate is treated in one single passage due to the ability to treat the entire anterior posterior height of the prostate.

HIFU is flexible in application and the surgeon can choose to perform a full ablation, a focal treatment or a nerve-sparing strategy treatment.

### Three treatment modes

Tissue studies on the dissipation of heat demonstrated that prostate tissue does not always absorb HIFU in the same manner. Previous prostate cancer intervention is the most significant factor and for this reason EDAP TMS and Inserm developed 3 treatment modes:

- First-line treatment,
- HIFU re-treatment,
- Salvage HIFU for EBRT failure.

Continues on page 2 ...

## Interview with a HIFU expert

### John F. Ward, MD, FACS,

Department of Urology MD Anderson Cancer Center, University of Texas, Houston, Texas. John F. Ward is an investigator of the Enlight clinical trial.

### What made you interested in HIFU?

Prostate cancer is a rather unique cancer in having so many different forms all within one disease entity. Increasingly we are seeing more and more men diagnosed with prostate cancer when the disease is all still localized and small volume. Though our ability to diagnose this cancer earlier and earlier when it is increasingly amenable to cure, our tools to cure it had not progressed over the past 20+ years; radical surgery and radical radiation therapy remain the standard of care for all prostate cancer patients regardless of the disease risk. These "sledgehammers" remain very appropriate for the patient with high risk, high volume disease, but I increasingly felt that such methods were not necessary to achieve cure in the growing low risk, low volume patients. While surgery and radiation are certainly effective at eradicating the cancer effectively, the cost of such therapy in terms of physical stress, urinary and sexual function, and recovery can be high. Technological advancements such as HIFU now allow a very controlled energy to be applied to a very precise loca-

tion rather than the gross destruction of all tissue and vital structures. This type of therapy may offer equal cancer control for the properly chosen patient without the side-effects of more radical approaches to this common disease. While more prostate cancer therapies can make the treatment choice for patient and physician more complex, HIFU brings us the opportunity to individualize therapy.

### What do you foresee the diagnostic indications for HIFU being?

With the current technology of HIFU, the properly chosen patient will do very well with this therapy; but the patient must be properly chosen. The technology limits the size of the prostate which can be fully treated. This limits HIFU to men with smaller prostates and in all cases the cancer best treated by this ablative technology appears to be that which is organ confined which are usually also those which are low or intermediate grades. However, the technology is not limited by the grade and this is why it may also be useful in men who have failed primary external beam radiotherapy and now have a local recurrence. These men



In 2009, EDAP TMS (Nasdaq: EDAP) celebrates 30 years of success in developing and marketing innovative minimally-invasive therapies for urology.

Everyday EDAP TMS is focused on delivering technologies that guarantee positive and reproducible outcomes with low side effects and preserved quality of life. Based on its close basic science cooperation with Inserm (the French Institute of Medical Research), and clinical cooperation with university hospitals, EDAP TMS has established its leadership role in bringing innovative technical solutions for urological disorders. EDAP TMS has always been at the forefront of customer service. The Company offer a full range of options to facilitate high technology adoption at all types of medical institutions: device purchase, pay-per-procedure fee, top-level training and customer support. Consequently, EDAP TMS has a solid and faithful customer base that is constantly growing and securing the durability of the Company and its products portfolio with the 7<sup>th</sup> generation of Sonolith® lithotriptors and the 3<sup>rd</sup> generation of Ablatherm® HIFU for prostate cancer. Currently, the Company is seeking FDA clearance approval of its latest lithotripter and is present in the USA via the Enlight phase III clinical trial for Ablatherm® HIFU. It is with great pleasure that EDAP TMS will address you with semi-annual newsletters to keep you updated on latest HIFU and ESWL news.

usually have a smaller prostate because of the radiation therapy thereby making them excellent candidates if the disease remains localized to the prostate. In the future, I believe HIFU will be an outstanding therapy by which we can focus treatment just to the cancerous region of the prostate and not the entire gland. There are still some aspects of focal therapy which need to be worked out such as proper patient selection and imaging the cancer, but I believe that by the time HIFU receives a review by the FDA, many of these issues will be worked out by those of us exploring focal prostate cancer treatment.

### The concept of a non invasive treatment obviously resonates with patients. Do you think HIFU can meet the patient's expectations?

Thus far, my experience with HIFU would lead me to answer this with a resounding yes. Both patients and I have been amazed how little discomfort or "downtime" has been associated with this therapy. I look forward to continuing to refine and improve our HIFU technique to offer my patients even better outcomes.

John F. Ward, MD, FACS,  
Department of Urology MD Anderson Cancer Center, University of Texas, Houston, Texas

**Ablatherm® HIFU**

...continued from page 1  
These treatment modes use slightly different treatment energies and duty cycles to ensure different patients are treated safely and effectively.

**Robotic treatment**

After the treatment has been planned, the surgeon implements the treatment which is carried out automatically under robotic control. Unlike other prostate cancer treatment modalities that claim to be robotic the Ablatherm® HIFU truly is robotic and not a master slave system. It continuously images the prostate and surrounding tissue. The exact location of the rectal wall is determined prior to the creation of each elementary lesion to ensure safe treatment. At this point, the surgeon finds himself in a role akin to a pilot who has programmed his flight plan and will supervise the execution of the flight plan by the autopilot. Treatment of the entire prostate usually lasts between 1 1/2 hour and 2 1/2 hours.

**Safety features**

Protecting the rectal wall is crucial. During the entire treatment it is cooled using chilled fluid that circulates in a balloon surrounding the probe and the rectal wall temperature is constantly monitored by sensors. Additionally, an infrared movement detector is positioned on the patient's hip to detect any movements. If a movement does occur the surgeon double checks the accuracy of the treatment plan and adjusts the plan if necessary.

**European clinical experience**

**Long-term Ablatherm® HIFU outcomes from the @-Registry and literature review**

Dr François-Joseph Murat, Edouard Herriot Hospital, France

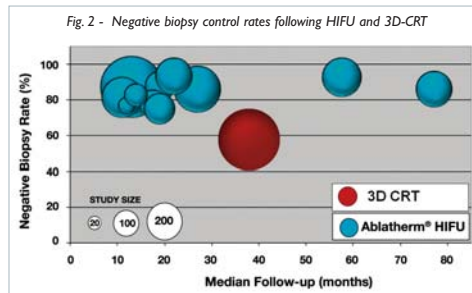
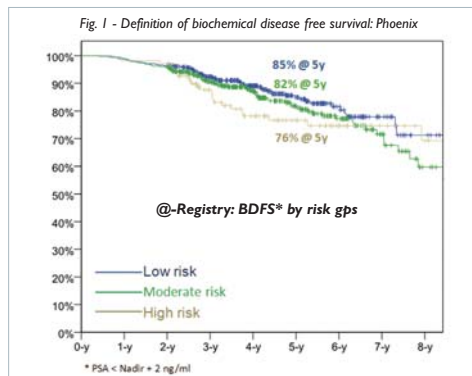
During the 2009 annual meeting of the European Association of Urology in Stockholm, the first long-term results on Ablatherm® HIFU treatment extracted from the @-Registry were presented by Dr. Murat.

Dr. Murat discussed in more detail the @-Registry, a database for Ablatherm HIFU outcomes that will be available for on-line use in the near future. It is intended that the @-Registry will be used by the urological community to improve the understanding of prostate HIFU outcomes and to report collectively the results of HIFU. For the individual urologist, it should provide real time statistical feedback regarding personal outcomes and to serve as an individual patient reporting system. To date, results from 2,872 treated patients from eight centres in France and Germany have been included in the @-Registry. Dr. Murat selected to report on 966 patients who fulfilled the criteria of T1-2, NX, M0 disease, who had undergone whole gland ablation and had a minimum follow-up of 2 years. Mean (SD) patients age was 69.3 (±6.2) years, mean (SD) PSA was 9.3 (±9.3) ng/ml and equal number of patients had T1 or T2 disease. In terms of D'Amico risk groups, 42%, 46% and 12% of patients were classified as low, intermediate and high risk, respectively. The mean (SD) follow-up was 55.2 (±23.8) months and the mean

(SD) PSA nadir was 0.45 (±1.0) ng/ml with time to nadir being 14.0 (±11.5) weeks. Of the 966 patients, 784 (78.7%) underwent control biopsies and of these biopsies, 85% were negative. Overall biochemical disease free survival (BDFS) survival was determined using the Phoenix definition of failure and showed a rate of BDFS of 82% at 5 years. The same applied when BDFS was determined according to risk group stratification (Fig. 1). It has been pointed out by Zelefsky that the strongest predictor of biochemical failure following 3-dimensional conformal radiotherapy for clinically localized prostate cancer was post-treatment biopsy status<sup>10</sup>. A review of the published literature on HIFU indicates that high negative biopsy rates of the order of 80-85% are achievable with HIFU. These rates compare with a 58% negative biopsy rate for hormone naive patients reported by Zelefsky following 3D-conformal radiotherapy at least 24 months after the RT<sup>10</sup>. (Fig. 2) Dr. Murat concluded that HIFU is a definitive treatment option for prostate cancer that should be considered by men diagnosed with localized disease. It can be considered as an alternative therapy to EBRT for low and intermediate risk prostate cancer, in that it results in higher negative biopsy rates, a similar BDFS rate, and a mild and acceptable morbidity profile. Unlike EBRT, however, HIFU can be repeated if necessary.

@-Registry, the global on-line outcomes management tool for Ablatherm® HIFU users

www.at-registry.com



Gele et al. J Endourol 2000;14(6):519-28; Gele et al. Eur Urol 2001;40(2):124-9; Pissoneiro et al. Prog Urol 2003;13(1):69-72; Poissonnier et al. Eur Urol 2007;51(2):381-7; Thurnoff et al. J Endourol 2003;17(8):673-7; Chaussy et al. Curr Urol Rep 2003;4(3):248-52; Zelefsky et al. J Clin Oncol 2004;22(29):5730-5; Ficarra et al. BJU Int 2006;98(6):1193-8; Prostate Cancer Prognostic Dts. 2006;9(4):439-43; Bana et al. European Urol 2008; 53: 1194-1203; Bana et al. Urology 2008;72:1329-33; Zelefsky MJ et al. J Urol 2008 ; 179 : 1368 - 1373; Zelefsky MJ et al. J Urol 2008 ; 179 : 1368 - 1373.

**ESWL**

**Extracorporeal Shockwave Lithotripsy**

www.edap-tms.com

**Electroconductive technology**

A new benchmark in ESWL

For the past 30 years, EDAP TMS has been developing and marketing Extracorporeal ShockWave Lithotripsy systems. This started with the development of the electrohydraulic "bathtub" Technomed systems in the early 1980s and then the first piezoelectric lithotripters.

Since 1994, EDAP TMS has been focusing its efforts on perfecting its patented Electroconductive Technology which equips its latest systems: the Sonolith® Praktis and the Sonolith® i-sys. Electrohydraulic shockwave generation was used in the first lithotripters introduced by Dornier more than 25 years ago. The shockwave is created with the well known spark gap technology: a high-voltage electrical current passes across a spark-gap electrode located within a water-filled container. The discharge of energy produces a vaporization bubble, which expands and immediately collapses, thus generating a high-energy pressure wave. Although fragmentation rates were high with this electrohydraulic technology (the Dornier HM3 has set a gold standard in this area), the lack of accuracy of the spark position created a varying focal spot location. EDAP TMS, together with INSERM, worked on a technology that would focus on the benefits of the electrohydraulic technology

(the high pressure of the shockwave generated, the size of the focal point of each individual shock as well as the high fragmentation rates) and compensate for the downsides (lack of accuracy of

electrode distance. The gap between anode and cathode has been reduced to 0,25 mm, the electrical discharge has therefore less distance to travel and can travel faster thanks to the conductive

**Electrohydraulic**  
Spark discharge

Figure 1 - Discharge formation between anode and cathode in electrohydraulic generator (1<sup>st</sup> shock)

**Electroconductive (EDAP TMS)**  
Spark discharge

Figure 2 - Discharge formation between anode and cathode in electroconductive generator (1<sup>st</sup> shock)

Figure 3 - Discharge formation between anode and cathode in electrohydraulic generator (2<sup>nd</sup> shock)

Figure 4 - Discharge formation between anode and cathode in electroconductive generator (2<sup>nd</sup> shock)

the focal spot from one shock to another, side effects, rapid aging of the electrode requiring a new electrode for each patient): With electroconductive technology, the electrode is filled with a highly conductive solution allowing an extremely accurate spark position thanks to a better conduction of electricity and a shorter inter-

electrode distance. The gap between anode and cathode has been reduced to 0,25 mm, the electrical discharge has therefore less distance to travel and can travel faster thanks to the conductive

draulic generator opposed to EDAP TMS Electroconductive generator: The electroconductive technology is used today in the whole EDAP TMS range of lithotripters: the Sonolith® Praktis and the Sonolith® i-sys.

• Revolutionary Stone Locking System: by simply pointing at the stone on the X-ray or Ultrasound image on the touch-screen, the system automatically knows where the stone is located and moves the patient table in order to bring the stone perfectly at the focus point of the shockwave



**The integrated lithotripter**

Sonolith® i-sys is EDAP TMS' latest lithotripter. This high-end integrated lithotripter brings exclusive features such as:

- Latest generation of electroconductive shockwave source with up to a 210mm penetration depth
- Double isocentric rotation high-power X-ray system
- Patented Automatic Ultrasound Positioning System
- Simultaneous dual imaging and treatment

**The modular lithotripter**

Introduced to the market in 1998, the Sonolith® Praktis is proven as the best in its category. Compact, modular and easy-to-use, it brings the efficacy and precision of the EDAP TMS patented Electroconductive technology. Sonolith® Praktis can be combined with any C-arm and Ultrasound system on the market in order to leverage previous imaging investments.

**Regulatory**

**Ablatherm® HIFU is not yet FDA cleared**  
Enlight clinical trial, in progress, more information on [www.pccaresearch.com](http://www.pccaresearch.com), [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

**Sonolith® i-sys is not yet FDA cleared**  
Sonolith® Praktis is FDA cleared (510k) and available for sale in the USA

**Imprint**

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