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# High-Intensity Focused Ultrasound (HIFU) - An Alternative Choice in Prostate Cancer Treatment

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## 1. Introduction

Prostate cancer is considered one of the most discussed topics in male health with an important social impact on the quality of life.

In Europe, it is the most common solid neoplasm with an incidence rate of 214 cases per 100,000 men<sup>1</sup>. The increasing life expectancy and the more and more widespread use of Prostate Specific Antigen (PSA) are probably the two most important reasons why more patients are diagnosed with prostate cancer. In Europe, 2,6 million new cases of prostate cancer are yearly observed (11% of male cancer diagnosis), responsible for 9% of deaths for male cancer cases.

Radical surgery represents the treatment of choice in clinically localized prostate cancer and in > 10 year life expectancy prostate cancer. Nevertheless, radical surgery itself may be considered a high morbidity treatment<sup>2</sup>.

Mini-invasive procedure development, such as three-dimensional external radiotherapy, brachytherapy or cryotherapy, especially in elderly or anaesthetically high risk patients, represents a useful treatment in prostate cancer.

HIFU (High-Intensity Focused Ultrasound) is a new and alternative choice in localized and low or intermediate-risk prostate cancer treatment<sup>3-5</sup>.

For a variety of reasons, transrectal HIFU appears highly attractive as a minimally invasive treatment for localized prostate cancer. It is a method of delivering ultrasonic energy with resultant heat and tissue destruction to a discrete point without damaging intervening tissue or cells. HIFU has been used for the management of patients diagnosed with various types of cancer, including prostate, breast, liver, pancreas, kidney, bone, and soft tissue.

## 2. Experimental studies

It has been shown in canines and humans that HIFU is capable of ablating prostatic tissue both contact and irradiation free<sup>6,7</sup>.

One of the first investigators who experimented the application of the technique to human beings has been S. Madersbacher<sup>8</sup>.

Early studies considered focused ultrasound as a potential technique for neurosurgery (Lynn, 1942; Warwick and Pond, 1968). A significant development was the construction of precision apparatus suitable for human treatment by Fry et al. in 1958.

HIFU has also been used in other clinical fields including ophthalmology (Coleman, 1985), urology (by Foster and Gelet in 1993) and oncology (Chapelon in 1992 and Prat in 1995). To date, focused ultrasound has been used successfully in the management of many tumours, including prostate cancer, in which this technique represents a good treatment option. HIFU was also used by Madersbacher and colleagues as a treatment for Benign Prostatic Hyperplasia (BPH). To date, this technique is not still used to treat BPH, because of its side effects on bladder neck function.

### 3. Description of the procedure

HIFU is performed through a computerized surgical device equipped with a treatment table, an ultrasound treatment system connected to an endorectal probe, a safety infrared ray detector, a refrigeration system keeping the rectal mucosa temperature below 14°C and a monitor to set and control the treatment procedure through echographic screening (Fig. 1). For anatomical reasons, the transrectal approach appears ideally suited to ablate prostatic tissue because the proximity of HIFU transducer and target tissue facilitates HIFU treatment from the technical standpoint.

After introducing the rectal probe, anatomic landmarks must be echographically set (apex, bladder neck, rectal side, prostate capsule), in order to make the computer able to determine the correct subdivision in different prostate portions (generally four).

The probe is equipped with a transducer that gives out a beam of high-focused convergent ultrasounds. The HIFU transducer has an aperture of 37 cm and a focal distance of 25.5 cm.

The focus has a -6 dB beam width of 1.6 mm and axial length of 10 mm. In the ultrasound converging point (focal point), the ultrasound beam absorption generates an immediate growth of temperature (85-100°C), destroying prostate cells in the circumscribed area.



(Ablatherm®-Edap Technomed device).

Fig. 1. Overview of HIFU procedure. The bed with the High-intensity ultrasound probe can be clearly seen. On the right, the ultrasound screen and the screen to set the machine and follow the procedure

Adequately translating the focal point with a robotic and automatic device, the successive ultrasound emissions may destroy all prostate cells (Fig. 2).

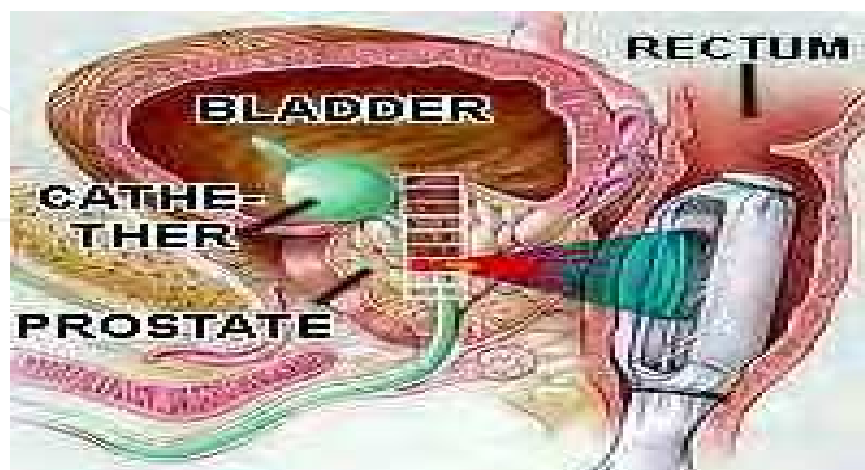


Fig. 2. Anatomical scheme of HIFU endorectal device

These lesions have a predictable size and shape, closely matching the focal region of the ultrasound source. As the lesion width is almost constant along their length, they can be placed side-by-side without leaving gaps (Fig. 3).

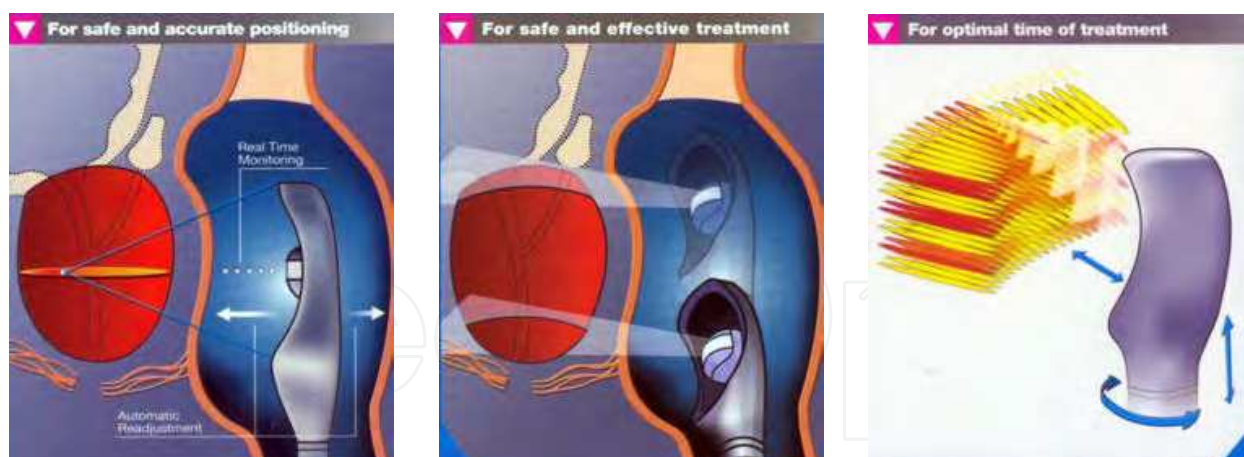


Fig. 3. HIFU mechanism scheme. On the left, ultrasound beam positioning; in the middle, the area to treat; on the right, an overall view of the sections treated by high-intensity ultrasound.

A standard procedure can be personalized in order to obtain ideal treatment settings: ultrasound frequency (standard 3 MHz), shot duration (standard 5 seconds) and waiting-time between shots (standard 5 seconds) may be modified (Fig. 4). Elementary lesion volume measures 19-24 mm and its diameter measures 1.7 mm





Fig. 4. On the screen, it is possible to follow the procedure and to change settings, such as ultrasound frequency and shot duration. Thus, a safe and optimal treatment can be performed.

#### 4. Management of the patient before and after the procedure

In order to safely perform the treatment, the surgeon is advised to follow some recommendations, in accordance with the European and American guidelines:

- Anti-trombotic prophylaxis with sodic Dalteparin 5.000 I.U. the day before the procedure. Other low molecular weight heparin (LMWH) can be administrated, according with local policies.
- Antibiotic prophylaxis should be given in order to prevent infection. A quinolone represents a good choice, but other antibiotic can be used, according with local policies.
- Careful intestinal toilet. This is an important key point in infection prevention. Also, it is fundamental to obtain a good view of the whole prostate on ultrasound, which is important in order to treat the target area properly. This will also prevent some side effects of the treatment, such as bladder neck irritation, reduces the risk of rectum fistulisation, and improves the erectile function outcome.

All patients undergo intra-spinal block with Chirocaine®.

Marcaine® can be used instead of Chirocaine.

If Marcaine is administrated, it is important to begin the procedure from the left lobe of the prostate, because this lobe is above due to the left decubitus of the patient on the device.

In order to make the procedure more bearable and to obtain the best cooperation from the patient, Midazolam 0,03 mg/kg administration during the procedure is recommended.

Other benzodiazepine can be used, according with their pharmacocynetic and pharmacodynamic features.

Reportedly, patients have no postoperative pain, except in case of complication. Just in the first two hours after the treatment the patient might complain of confusion and dazzling, but these are considered common consequences of the anaesthetic treatment.

The anaesthetist should be involved pre-operatively, intra-operatively and post-operatively, in order to manage the patient properly before and during the treatment and in order to relieve post-operative pain and anaesthetic side-effects and/or complications.

## 5. Mechanism

Conceptually, a piezoelectric transducer generates a high intensity converging ultrasound beam that destroys local tissues through three mechanisms:

1. Coagulative necrosis;
2. Cavitation;
3. Heat damage.

These three key-points are discussed below.

### 5.1 Coagulative necrosis

Coagulative necrosis, is due to hyperthermia (85-100°C) generated in the focal point.

Elementary lesion has ellipsoidal shape. The short length of the shot limits heat diffusion around the focal point. Shot by shot, it is possible to generate a plethora of elementary lesions until all prostate tissue is destroyed.

Coagulative necrosis is a non-reversible phenomenon (Fig. 5).

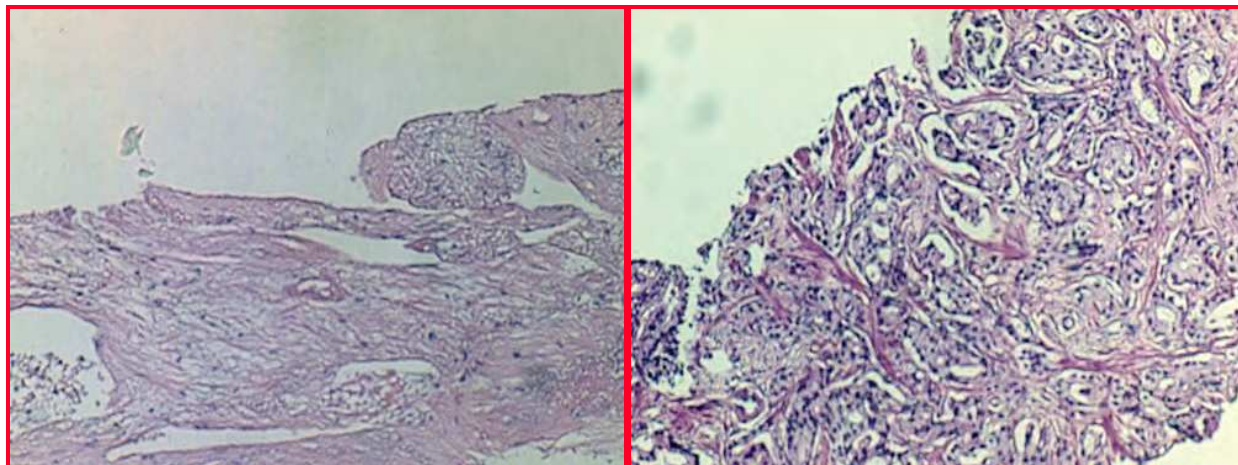


Fig. 5. On the left, pre-HIFU histology aspect; on the right, post-HIFU histology change

This kind of lesion can be clearly seen on optical microscopy. Its effectiveness in cancer treatment is demonstrated by the absence of cell functional structures, such as membranes, active nuclei, and organelles.

After the treatment, glandular structures cannot be seen any longer, thus demonstrating that the HIFU technique provides a lack of function in the treated prostate.

Also liquefactive necrosis and apoptotic necrosis are reported as a common consequence of HIFU treatment (see § 6.1), but these kinds of necrotic lesions do not affect the whole amount of necrotic areas.

## 5.2 Cavitation

Cavitation is due to the gas microbubble (bubble clouds) vibration dissolved in prostate tissue. Lindau and Lauterborn investigated the collapse and rebound of a cavitation bubble near a flat rigid wall using a high-speed camera<sup>9</sup>.

Due to the depression caused by the negative part of the ultrasound wave, intracellular water may enter the gaseous phase.

That would lead to the development of microbubbles.

When they reach the size of resonance, these bubbles suddenly collapse and produce high-pressure shock waves, destroying adjacent tissue.

In a study carried out by Chen H and colleagues<sup>10</sup>, the dynamics of cavitation bubble clouds generated at the tissue boundary in continuous HIFU fields has been experimentally investigated by a high-speed photography method.

The experimental results revealed that the cavitation bubble clouds organize into two shapes, which were named “cone-shape” bubble cloud structure and “crown-shape” bubble cloud structure.

The cavitation bubble cloud is visible at the tissue surface at 200  $\mu$ s; then a tiny tip becomes obvious at 600  $\mu$ s. The elongated tip leads to the formation of a cone-shape bubble cloud structure.

After 1.8 ms, the cone-shape bubble cloud attains a dynamically stable state.

The bubble cluster grows larger and develops a crown-like shape. Meanwhile, it moves forward and finally hits the tissue boundary forming the crown-shape cavitation bubble cloud structure.

Among the 171 image series recorded in the study carried out by Chen H et al, 85% showed the evolution of the cone-shape bubble cloud structure. Another 11% of the image series showed the dynamics of the crown-shape bubble cloud structure.

The remaining 4% exhibited the interchanging of these two structures.

## 5.3 Heat damage

The tissue ablation induced by high-intensity ultrasound results primarily from bulk heating, with possible contributions from boiling and acoustic cavitation. Bubbles, when present, may enhance local absorption (Fig. 6).

The position and shape of the heated region are determined by the intensity of the field near the focus, the attenuation and the effects of diffusion.

The rate of change of temperature at any point is proportional to the absorbed power density and hence to the incident beam power and attenuation<sup>11</sup>.

The irreversible changes in proteins associated with tissue denaturation and coagulation start at low temperature.

When temperatures of approximately 60°C are approached, the rate of denaturation becomes so great that irreversible changes can occur in seconds.

Temperature reached during HIFU treatment is clearly higher, as reported above: When lesioning occurs, the attenuation within the treated volume increases<sup>12</sup>, thus altering the absorbed power distribution, depending on the biologic feature of the prostate.

Consequently, the region in which heat is deposited may be expected to change during the heating process.

By a macroscopic point of view, we can say that heat growth is maximal in the middle of the treated volume and minimal in the external area of the treated volume.

This difference allows to surely set the treatment outlines and save the prostate apex, and the striated sphincter and vasculo-nervous bundles.

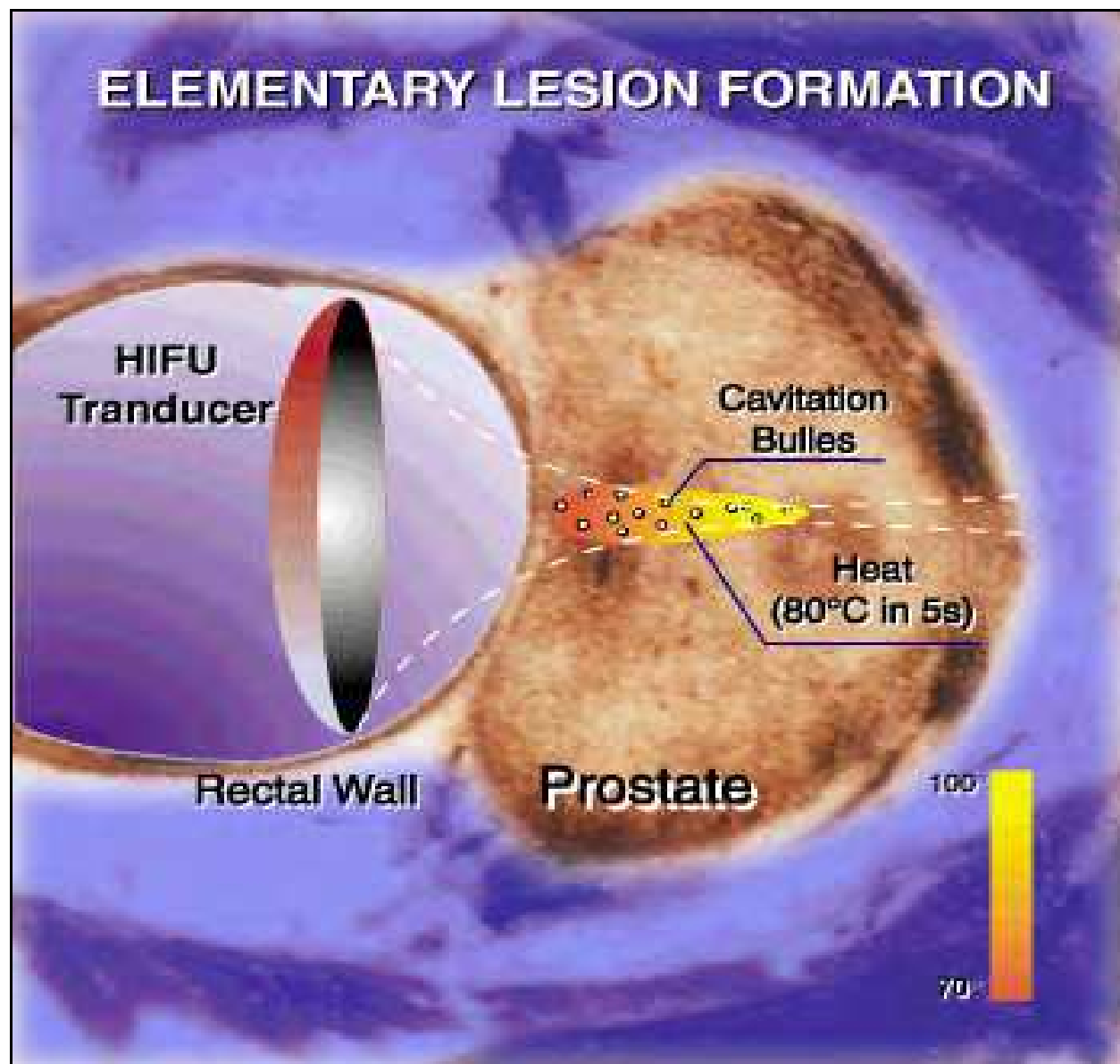


Fig. 6. Elementary lesion formation and its effects on prostate parenchyma, due to heat and mechanical damage.

## 6. HIFU-induced histopathological changes

HIFU-induced histopathological changes can be studied thanks to light microscopy, immunohistochemistry and electron microscopy.

### 6.1 Light microscopy

At light microscopy, we can say that the prostatic structure is completely disrupted and hardly recognizable. Three different types of cellular necrosis are generally found:



- a. liquefactive necrosis;
- b. coagulative necrosis;
- c. apoptotic necrosis.

Cell death is generally due to a mixture of the three with liquefactive necrosis being the least common and coagulative necrosis the most common.

Histological findings show consistent coagulative necrosis with precisely defined, sharp margins to normal tissue.

Lesion size and position correlates well with the assumed target zones, thus demonstrating that HIFU permits therapeutic tissue ablation.

Strictly speaking, HIFU treatment induces a spectrum of morphological changes ranging from apparent light microscopic necrosis to more subtle ultrastructural cell damage (see below).

Necrotic tissue in the coagulative necrosis areas consists of homogeneously stained eosinophilic fragments (Fig. 7a).

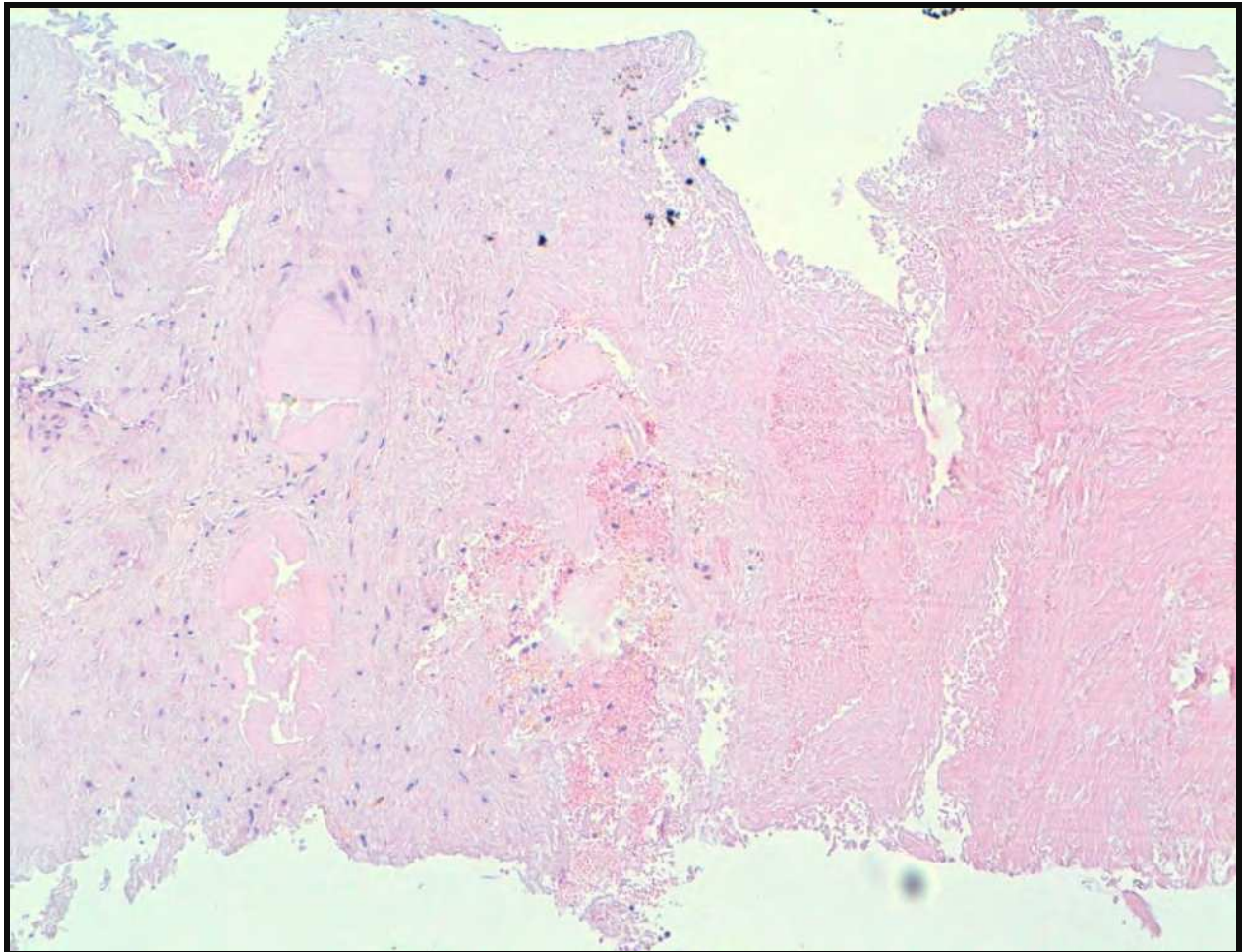


Fig. 7a. Areas of coagulative necrosis can be clearly seen, thus demonstrating the effectiveness of HIFU treatment.

Little structure is apparent aside from some faintly staining collagenous bands and rare indications of the former glandular epithelium. In some cases, necrotic tissue expelled from

the coagulative necrosis areas is visible in prostatic ductules of the margin area. Brightly staining blood droplets can be observed on the hematoxylin-eosin slide, of which most are concentrated in the coagulative necrosis area.

The nuclei of epithelial and stromal cells are either pyknotic or totally absent, corresponding to cell necrosis. The nuclei are of normal size with a fine chromatin structure and sporadically small nucleoli.

This epithelial cells also contain pale to eosinophilic cytoplasm, with few vacuoles. Although cell borders are not discernable in most of these cells, they can be identified locally.

Every so often, extended haemorrhagic areas are found (Fig. 7b).

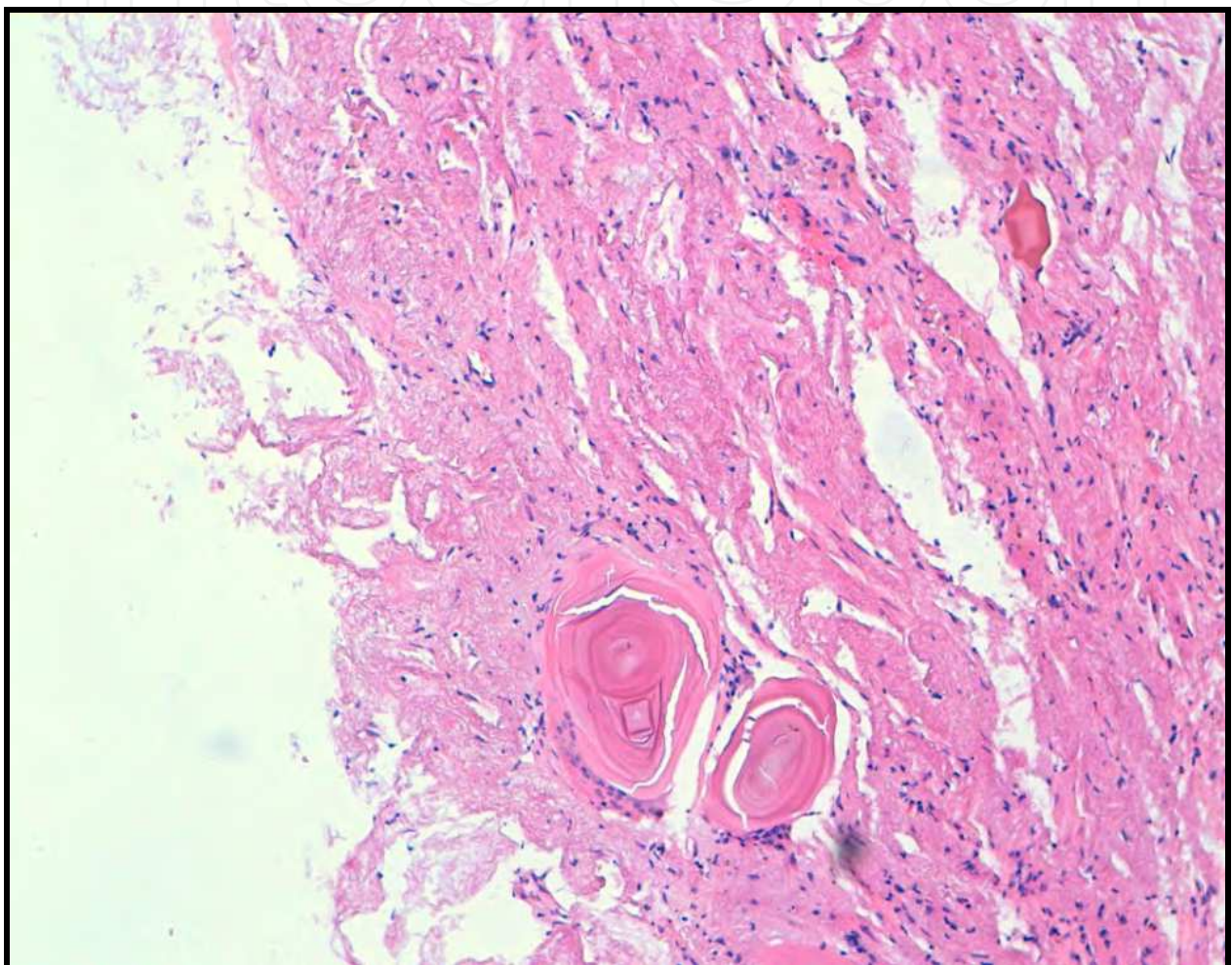


Fig. 7b. Areas of tissue damage, including haemorrhagic areas

Also, HIFU causes injuries to small vessels, with considerable oedema and swelling of endothelial cells in the margin between the treated and untreated areas. However, in the centre of treated tumor tissue, severely damaged tumor vessels show pyknotic nuclei and debris of nuclei, which indicated endothelial cell death.

Endothelial cells exhibited an irreversible cell death. Almost all of the endothelial cell nuclei disappear, cellular margins were not distinct and junctions between individual cells were disrupted.

The repair of lesions appears to have slow processes of damaged tissue absorption and granulation tissue replacement (Fig. 8).



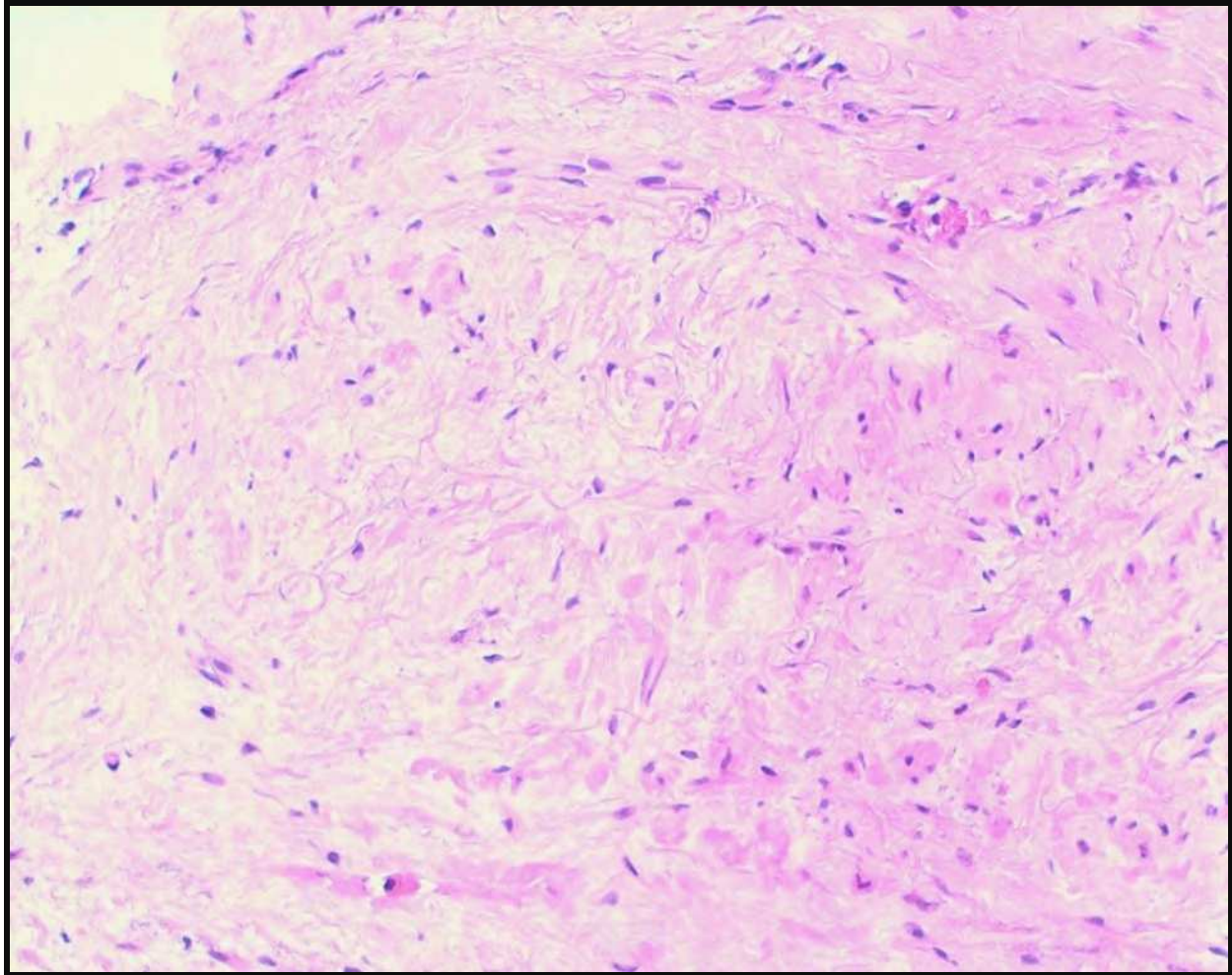


Fig. 8. Granulation tissue and fibrosis 6 months after HIFU treatment.

### 6.2 Immunohistochemistry

The expression of PSA, panCK, and Ki67 in non-treated regions of the prostate is marginally stronger than in the HIFU region. CK8 is strongly expressed in luminal cells of normal and malignant glands outside the HIFU lesion, but pre-existing and malignant epithelium within the HIFU lesion does not express CK8, regardless of the histomorphological changes in conventional light microscopy.

The hyperplastic epithelium at the periphery of the HIFU lesions reacts with the basal cell antibody 34 $\beta$ E12.

In summary, we can say that prostate glandular epithelium after HIFU treatment reacts with antibodies to pancytokeratin, prostate specific antigen (PSA), and Ki67, but does not express cytokeratin 8, which is indicative of severe cellular damage.

### 6.3 Electron microscopy

Ultrastructural examination after HIFU reveals disintegration of cellular membranes and cytoplasmic organelles consistent with cell necrosis.

Electron microscopy is not routinely performed. When performed, it confirms submicroscopical cellular damage in the centre of the HIFU lesion.

Electron microscopy is capable to demonstrate cell necrosis also in areas that show no apparent morphological cell necrosis by conventional light microscopy.

Treated areas lack nuclear membranes, but show a fine chromatin pattern that is clumped at the periphery of the nuclei, and conspicuous nucleoli.

The cytoplasm contain some vacuoles, but organelle structures and cell membranes are not generally identified.

## 7. Immunologic response after HIFU

T-lymphocytes appear in granulation tissue along the ablation margin in all HIFU-treated neoplasms, with no infiltration in those showing typical signs of coagulation necrosis.

The tumor-infiltrating lymphocytes are found mainly in granulation tissue along with immature fibroblasts, new capillaries, and other inflammatory cells.

This observation suggest that their infiltration occurs after HIFU ablation and that these tumor-infiltrating lymphocytes are new lymphocytes moving into the ablated neoplasms from peripheral blood.

As it has been reported by Hartveit and colleagues, this is a typical findings in all tissues treated with HIFU<sup>13</sup>.

HIFU treatment may definitively increase the local infiltration of tumor infiltrating lymphocytes in the ablation area, including activated cytotoxic T-Cells and Natural-Killer cells<sup>14</sup>.

## 8. The role of heat-shock proteins (HSP)

Heat shock proteins (HSPs) were first discovered in 1962 as a group of highly conserved proteins that are induced by hyperthermia and other kinds of cellular insults.

There are four principal HSP: HSP-90, HSP-70, HSP-60 and the subgroup of small HSPs including HSP27.

Benign and malignant human prostatic cells respond to heat by increased expression of HSP *in vitro* and *in vivo*.

To obtain a more detailed insight on the effect of heat on prostatic cells, heat shock protein expression of normal and malignant prostatic cells has been studied.

Transrectal HIFU therapy induces intraprostatic necrosis surrounded by a zone characterized by a massive up-regulation of HSP expression.

Recently, several molecular heat shock proteins have been reported to be involved in development and progression of hormone-refractory prostate cancer.

HSP27 and HSP70 are the most strongly induced heat shock proteins during cellular stress (Fig. 9).

HSPs are not all of prognostic value, however some have been demonstrated to have clinical utility as prognostic markers: among this group of heat shock proteins, the most important one is HSP-27, which particularly plays a role in many immunological processes and might stimulate immune defence responses against tumour cells<sup>15</sup>.

Accumulating evidence suggests that HSP27 levels correlate with both hormone-refractory prostate cancer and development of resistance to heat. Nevertheless, the functional significance of changes in HSP27 expression associated with heat-resistant prostate cancer remains undefined.



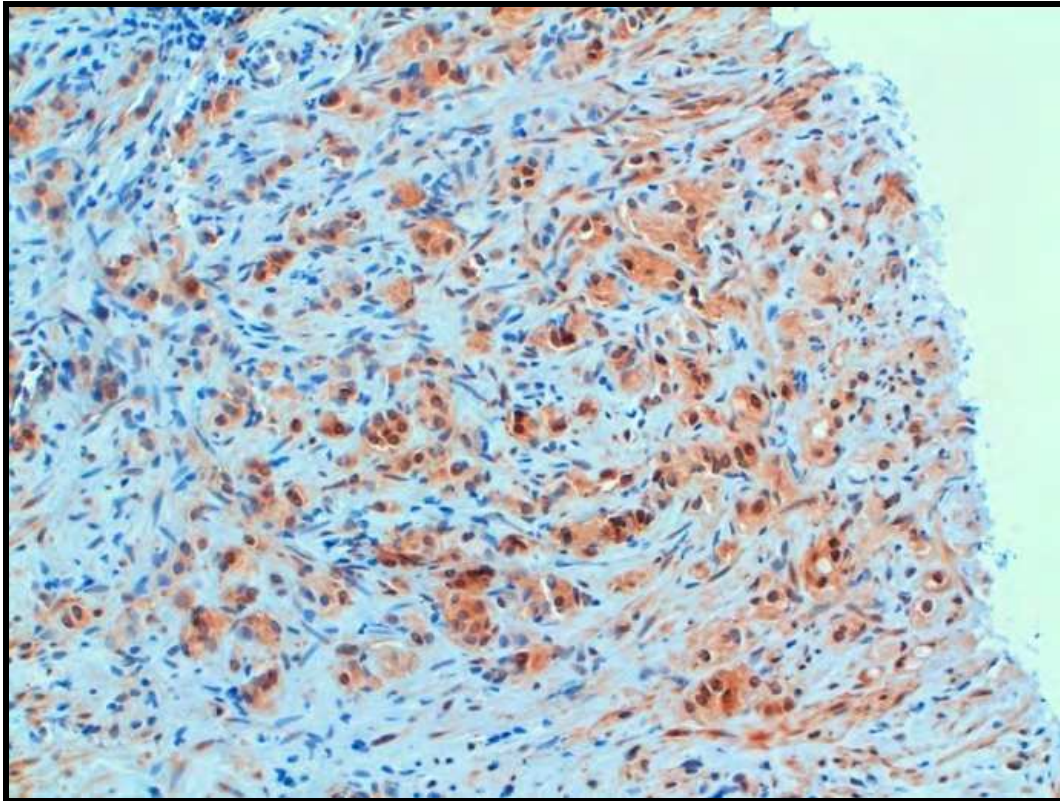


Fig. 9. HSP-70 expression in prostate tissue after HIFU treatment in a case of recurrence

### 9. Long-term results of HIFU treatment

Many authors have reported their series after HIFU treatment.

One of the most recent is the multicentric study carried out by Crouzet et al<sup>16</sup>, who reported a series of 803 patients with a mean follow-up of 43 months. The results of this study are excellent, showing that local control and disease-free survival rate achieved with HIFU were similar to those expected with conformal external-beam radiation therapy (EBRT).

The excellent cancer-specific survival rate reported in this study is also explained by the possibility to repeat HIFU and use salvage EBRT.

The first UK series was reported by Ahmed et al and published on the British Journal of Cancer. 172 men were treated with HIFU with excellent result: 92.4% of patients had no recurrence after a mean follow-up of 346 days<sup>17</sup>.

Blana et al published a series of 140 men treated with HIFU, reporting good oncological outcome in long-term follow-up (6.4 years), demonstrating the effective long-term cancer control achieved with HIFU in patients with low- or intermediate-risk localised prostate cancer<sup>18</sup>.

Finally, it is correct to cite the negative results reported by Challacombe et al, who interrupted the treatment because of the poor oncological outcome<sup>19</sup>.

From all the studies presented, there is clear evidence that the treatment could affect prostate cancer, as shown by both a substantial decrease in serum PSA and negative biopsies after therapy there is clear evidence that the treatment could affect prostate cancer.

The effect has also been demonstrated on radical prostatectomy specimens examined 2 weeks after HIFU.

There are no randomized controlled studies available to compare the outcome of these therapies with each other, other therapies, or watchful waiting.

The combination of a TURP performed just before an HIFU seems to reduce the complications but without affecting the oncologic outcome negatively.

As of today, it is not possible to compare the outcome of HIFU with other treatment modalities for localized prostate cancer.

## 10. Complications and side effects of HIFU treatment

HIFU is a minimally invasive treatment for prostate cancer, thus resulting in a low complication rate.

Sometimes, minor complications can occur, in the vast majority of cases related to lower urinary tract.

The first one is urinary retention, commonly treated with longer catheterism. The most common is urge incontinence, due to the irritative effect of high-focused ultrasound on the bladder neck. Generally, it disappears in a couple of months, and only in rare cases anticholinergic treatment is required.

Lower urinary tract symptoms, such as frequency, nocturia, weak urinary stream, and so on, are prevented by Trans-Urethral Resection of Prostate (TUR-P), that is recommended to be done 6-8 weeks before HIFU treatment. Anyway, the surgeon is advised to administer IPSS questionnaire (or equivalent) before the treatment and 3 months after the treatment, in order to assess persistent lower urinary tract symptoms, that should be treated pharmacologically or surgically, if needed.

Infection is another possible complication of this treatment. Antibiotic prophylaxis should prevent this complication, if administered in accordance with guidelines on infection prevention.

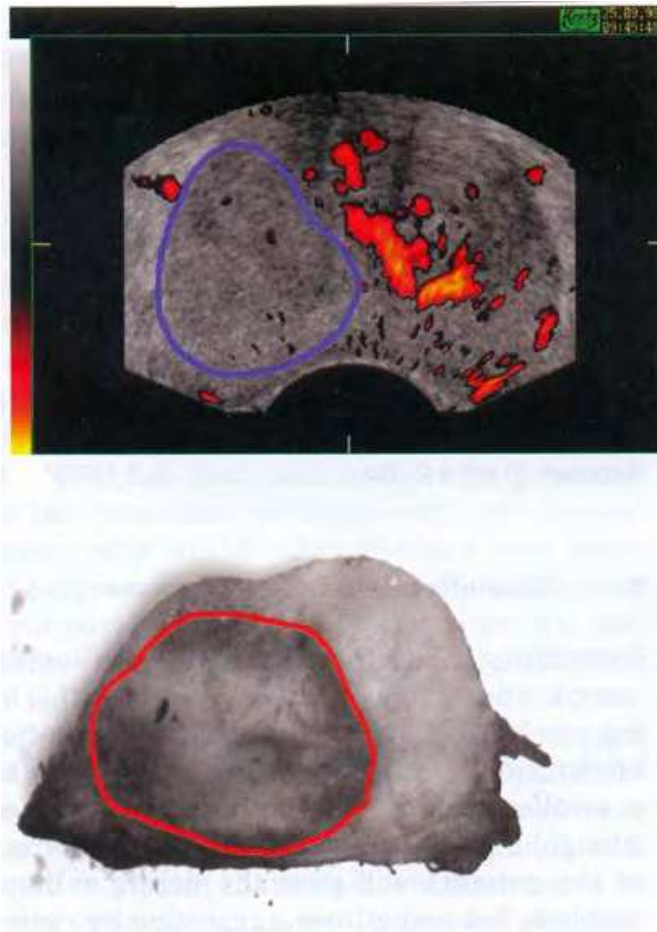
Among the major complications, the most important is recto-vesical or recto-urethral fistula. Only few cases are reported in literature. This complication can be initially treated with longer catheterization, but in some cases surgical repair is required. A common tip to avoid this complication is to safely set the target area on the ultrasound screen, as the slight wall of the rectum can easily lead to fistulization. Also, patients previously diagnosed with ulcerative recto-colitis must not be treated with high-intensity focused ultrasound.

The most important side-effect of HIFU treatment is erectile dysfunction and impotency, due to the effect of high intensity ultrasound on the neural bundle. This effect is well known and must be discussed with the patient before the treatment.

Color-doppler-combined technique is reported in literature in order to perform a sort of vessel-sparing procedure, thus resulting in a better outcome by the andrological point of view. However, there is not common agreement among the investigators about the effectiveness and the feasibility of this technique. For this reason, it cannot be recommended at the present time (Fig. 10).

The best management of the patient should include IIEF questionnaire (or equivalent) to be given before the treatment and 6 months after the treatment in order to assess the sexual outcome.

Patients who are keen on having sexual activity should receive a proper treatment.



not affected by tumor (red line).

Fig. 10. Color-doppler device for HIFU treatment. Thanks to this additional equipment, it is possible to perform a highly selective treatment (blue line). This can preserve vascular bundle or a portion of prostate

## 11. Summary

At the time of diagnosis, prostate cancer is organ-confined in 70% of the cases.

The choice of the appropriate treatment for localized prostate cancer is one of the most controversial issues in urologic oncology. Approximately, the most majority of these patients undergo local therapy: surgery or external beam radiation. The rest of the remaining patients do not fit this treatment and are scheduled for Androgen Depriving Therapy (ADT) or watchful waiting.

Besides these treatments, other mini-invasive procedures have emerged in the last few years, such as Brachytherapy, Cryosurgical Ablation, Radiofrequency Interstitial Tumour Ablation and High-Intensity Focused Ultrasound (HIFU).

HIFU represents an alternative choice in mini-invasive treatment of prostate cancer. The treatment is performed under regional anaesthesia and is generally preceded by limited Trans-Urethral Resection of Prostate (TUR-P).

It is a transrectal procedure: after introducing the rectal probe, anatomic limits must be echographically set (apex, bladder neck, rectal side, prostate capsule), in order to make the computer able to determine the correct subdivision in different prostate portions (generally four).

An absolute contraindication to the procedure is every rectal anatomic or pathologic condition that excludes the transrectal approach.

The technology of the device used to perform the treatment allows to exactly destroy a pre-selected area and to save all the tissues around it.

Conceptually, a piezoelectric transducer generates a high intensity converging ultrasound beam that destroys local tissues through three mechanisms:

1. *coagulative necrosis*, due to hyperthermia (85-100°C) generated in the focal point. Elementary lesion is ellipsoidal and the short length of the shot limits heat diffusion around the focal point. Shot by shot, it is possible to generate a plethora of elementary lesions until all prostate tissue is destroyed;
2. *cavitation*, due to the gas microbubble vibration dissolved in prostate tissue;
3. *heat growth*, maximal in the middle of the treated volume and minimal in the external area of the treated volume.

This difference allows to surely set the treatment outlines and save the prostate apex (and the striated sphincter) and vasculo-nervous bundles.

HIFU is a minimally invasive ablative technology for managing localized prostate cancer in both the primary and salvage setting. It is a single-session procedure with the possibility of a re-treatment if required.

The advantage of this technique are short hospital stay, reduced convalescence, low morbidity and preservation of continence and erectile function.

As reported in literature, HIFU demonstrated a good oncologic outcome.

The PSA nadir is a major predictive factor for HIFU success and it is generally reached within 6 months after the treatment in all patients.

The most recent results are reported in a study carried out by Crouzet et al. In this multicentric study the mean PSA nadir was  $1.0 \pm 2.8$  ng/mL with a median of 0.25 ng/mL. The 5-year and 7-year Disease Free Survival Rate (DFSr) for low, intermediate-, and high-risk patients (according to D'Amico risk stratification criteria) were, respectively, 83-75%, 72-63% and 68-62%.

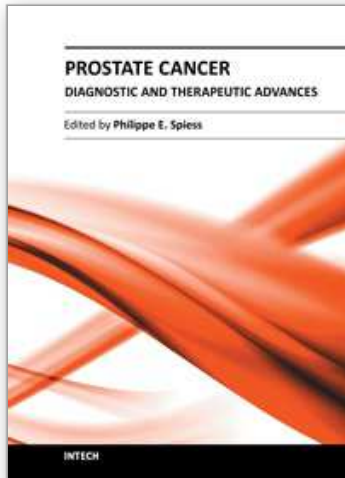
As expected by most investigators, the development of more sophisticated technologies should improve these results and lead to a widespread use of this technique. Focal treatment or doppler-combined devices for nerve- or vessel- sparing procedures will be available in the next years.

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In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book, readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade. This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.

### **How to reference**

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