AETNA BETTER HEALTH®

Clinical Policy Bulletin:
High Intensity Focused Ultrasound

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Policy

Aetna considers high intensity focused ultrasound (HIFU) for the treatment of prostate cancer (primary or salvage therapy) experimental and investigational because its long-term oncological effectiveness has not been established.

Aetna considers HIFU experimental and investigational for the following indications because of insufficient evidence of its effectiveness (not an all-inclusive list):

- Benign prostatic hypertrophy (see CPB 0079 - Benign Prostatic Hypertrophy (BPH) Treatments)
- Breast cancer
- Central nervous system diseases/disorders (e.g., brain cancer and stroke)
- Cesarean scar pregnancy
- Essential tremor
- Fractures
- Hepatocellular carcinoma
- Liver metastasis from colon and stomach cancer
- Osteosarcoma/bone tumors
- Pancreatic cancer
- Primary hyperparathyroidism
- Primary liver cancer
- Renal cancer
- Thyroid nodules
- Vulvar dystrophy.

For MRI-guided ultrasound ablation of uterine fibroids, see CPB 0304 - Fibroid Treatment.
Background

Prostate Cancer:

Prostate cancer, accounting for 33% of all male cancers, is the 2nd leading cause of cancer death in men, exceeded only by lung cancer. The disease is histologically evident in as many as 34% of men during their 5th decade of life and in up to 70% of men aged 80 years old and older.

Staging of prostate cancer entails the size of the tumor, if lymph nodes are affected, if the tumor has metastasized, and the appropriate course of treatment.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (A)</td>
<td>Prostate cancer can not be felt by digital rectal examination, causes no symptoms, and is only in the prostate, usually found incidentally in a prostatectomy specimen when surgery is done for benign prostatic hyperplasia.</td>
</tr>
<tr>
<td>Stage II (B)</td>
<td>Cancer confined to the prostate gland found by needle biopsy done for an elevated prostate-specific antigen (PSA) level or after rectal examination reveals a mass in the prostate.</td>
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<tr>
<td>Stage III (C)</td>
<td>Cancer cells have spread outside the capsule of the prostate to tissues around the prostate (e.g., seminal vesicles).</td>
</tr>
<tr>
<td>Stage IV (D)</td>
<td>Cancer cells have metastasized to lymph nodes or to organs and tissues (e.g., the bone, liver, or lungs).</td>
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Another staging system for prostate cancer is known as the TNM system, which separately evaluates the tumor (T), lymph nodes (N) and metastases (M).

**T (Tumor) Staging:**

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>The tumor is too small to be seen on scans or felt during examination of the prostate (it has been discovered by needle biopsy).</td>
</tr>
<tr>
<td>T2</td>
<td>The tumor is completely inside the prostate gland.</td>
</tr>
<tr>
<td>T3</td>
<td>The tumor has broken through the capsule of the prostate gland.</td>
</tr>
<tr>
<td>T4</td>
<td>The tumor has spread into other body organs</td>
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</tbody>
</table>

**N (Lymph Node) Staging:**

<table>
<thead>
<tr>
<th>Lymph Node Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No cancer cells found in any lymph nodes.</td>
</tr>
<tr>
<td>N1</td>
<td>One positive lymph node smaller than 2 cm across.</td>
</tr>
<tr>
<td>N2</td>
<td>More than 1 positive lymph node; or one that is between 2 cm and 5 cm across.</td>
</tr>
<tr>
<td>N3</td>
<td>Any positive lymph node that is bigger than 5 cm across.</td>
</tr>
</tbody>
</table>

**M (Metastases) Staging:**

<table>
<thead>
<tr>
<th>M0</th>
<th>No cancer spread outside the pelvis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Cancer has spread outside the pelvis.</td>
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</tbody>
</table>

The American Urological Association (AUA)'s Prostate Cancer Clinical Guideline Update Panel (Thompson et al, 2007) stated that standard options for the management of clinically localized prostate cancer include watchful waiting and active surveillance, interstitial prostate brachytherapy, external beam radio-therapy (EBRT), radical prostatectomy, as well as primary hormonal therapy. Other treatment modalities entailed cryotherapy, high-intensity focused ultrasound (HIFU), and combinations of treatments (e.g., EBRT and interstitial prostate brachytherapy). However, the Panel did not include the other treatment options in the analysis and recommendations because of a combination of factors (e.g., limited published experience and short-term follow-up).

Dubinsky and co-workers (2008) noted that although a great deal about HIFU physics is understood, its clinical applications are currently limited, and multiple trials are underway worldwide to determine its effectiveness. In this regard, HIFU has been studied for the treatment of patients with prostate cancer. This non-invasive approach destroys malignant cells by creating intense heat of 80 to 100°C with highly focused transrectal ultrasonic beams. Gardner and Koch (2005) stated that continued technological advances combined with well-designed clinical trials could allow HIFU to become part of the armamentarium against prostate cancer. Konstantinos (2005), in a review on prostate cancer in the elderly, noted that other treatment options under development include cryotherapy and HIFU.

Pickles et al (2005) performed an evidence-based review of published papers in the English language on the use of HIFU for prostate cancer. Only case series have been published; there were no randomized studies. These investigators stated that the quality of evidence was poor, with no reports having longer follow-up than a mean of 2 years, with median follow-ups substantially shorter. Effectiveness outcomes were thus premature and preclude assessment. Toxicity varied substantially with impotence rates 44 % to 61 %, grade 2 to 3 incontinence 0 % to 14 %, and rectal fistulae 0.7 % to 3.2 %. There were limited data on the use of HIFU as salvage therapy after radiation failure. There were no data on the toxicity of subsequent standard curative therapies after HIFU. The authors concluded that in view of the lack of effectiveness outcomes, and in the presence of significant toxicity, HIFU should only be offered within a research setting.

Uchida et al (2006) assessed the biochemical disease-free survival (DFS) rates, predictors of clinical outcome and morbidity in patients with localized prostate cancer treated with HIFU. A total of 181 consecutive patients underwent HIFU with the use of Sonablate (Focus Surgery, Indianapolis, IN). Biochemical recurrence was defined according to the criteria recommended by the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel. The median age and pre-treatment PSA level were 70 years (range of 44 to 88) and 9.76 ng/ml (range of 3.39 to 89.60). A total of 95 patients (52 %) were treated with neoadjuvant hormones. The median follow-up period for all patients was 18.0 months (range of 4 to 68). The biochemical DFS rates at 1, 3 and 5 years in all patients were 84 %, 80 % and 78 %, respectively. The biochemical DFS rates at 3 years for patients with pre-treatment
PSA less than 10 ng/ml, 10.01 to 20.0 ng/ml and more than 20.0 ng/ml were 94 %, 75 % and 35 %, respectively (p < 0.0001). Multi-variate analysis identified pre-treatment PSA (p < 0.0001) as an independent predictor of relapse. The authors concluded that HIFU therapy appeared to be a safe and effective minimally invasive therapy for patients with localized prostate cancer, especially those with a pre-treatment PSA level less than 20 ng/ml.

Eggener et al (2007) explained the rationale for and concerns about focal therapy for low-risk prostate cancer, and reviewed potential methods of delivery. The authors concluded that early detection of prostate cancer has led to concerns that while many cancers now diagnosed pose too little a threat for radical therapy, many men are reluctant to accept watchful waiting or active surveillance. Several emerging technologies seem capable of focal destruction of prostate tissue with minimal morbidity. The authors encouraged the investigation of focal therapy in select men with low-risk prostate cancer in prospective clinical trials that carefully document safety, functional outcomes and cancer control.

In a phase l/ll clinical trial, Koch et al (2007) examined the safety and potential effectiveness of transrectally delivered HIFU for the full gland ablation of previously untreated localized prostate cancer. A total of 20 patients underwent 1 to 3 HIFU treatments of the prostate. The primary outcome was safety and the secondary outcomes were PSA, prostate biopsy and quality of life (QOL) measures. A total of 19 patients had complete follow-up. Serious adverse events related to treatment were limited, with the most common adverse event being transient urinary retention of more than 30 days in only 10 % of patients. Rectal injury occurred in 1 patient. With 1 to 3 treatments, 42 % of the patients achieved PSA less than 0.5 ng/ml and a negative prostate biopsy. The authors concluded that HIFU in patients with previously untreated prostate cancer is generally well-tolerated and has the potential to completely ablate the prostate gland. With further refinement of the optimal treatment dose and technique, this technology has the potential to be an effective form of therapy for localized prostate cancer.

Illing and Chapman (2007) noted that transrectal HIFU for prostate cancer is a promising technique with medium-term oncological results broadly comparable to standard therapies. It is the only form of therapy which is non-invasive and does not utilize ionizing radiation. This is an exciting field undergoing rapid developments, both in the technology and the way in which prostate cancer is managed. Lynch and Loeb (2007) stated that HIFU has emerged in the past decade as a new addition to the arsenal of therapeutic options for prostate cancer. Clinical studies have investigated its use as a treatment for clinically localized disease and as salvage therapy in the setting of failure after EBRT. The authors stated that additional studies with long-term follow-up are needed to further evaluate cancer control and QOL outcomes of this new modality.

Huang and associates (2007) noted that for patients with biopsy-proven recurrent cancer confined to the prostate, local salvage therapy may be a potentially curative treatment option. Most men, however, do not undergo local salvage therapy owing to difficulties in diagnosis as well as concerns over treatment-related complications in the salvage setting. Recently, improvements in technique and technology have substantially reduced the morbidity associated with locally ablative therapies, resulting
in an increased interest in the use of minimally invasive therapies such as brachytherapy, cryotherapy, and HIFU in the salvage setting. Although these treatments are well-tolerated, concerns remain over incomplete and inadequate treatment with locally ablative therapies. The authors stated that more studies are needed to appropriately select candidates for salvage ablative therapies and to determine the long-term oncological effectiveness of these treatments.

Marberger (2007) stated that energy-based ablative techniques are of growing interest for today's heterogeneous spectrum of prostate cancer. At present, primary HIFU appears to be a valid alternative to active surveillance protocols in low-risk cancers; and to standard therapy in older patients. Morbidity is low, although post-operative impotence occurs frequently. Cryoablation has higher morbidity, even with third-generation conformal technology. With radio-recurrent cancer the potential radiation damage of the rectal wall renders transrectal HIFU more hazardous. Third-generation cryoablation seems to give better cancer control with lower morbidity in this situation. Unfortunately, long-term outcome data from controlled trials are not available. The author concluded that these minimally invasive techniques are not magic bullets, and patients must be informed accordingly. Focal ablation of the prostate segment with the index cancer would minimize morbidity and therefore appears highly appealing. Its success depends on correct localization of the lesion. Until this is achieved with sufficient reliability by appropriate biopsy or imaging techniques, focal ablation for the treatment of prostate cancer remains strictly experimental.

Lledo García et al (2007) assessed the current state of HIFU as therapeutical option of prostate cancer. These investigators noted that this technique is usually being indicated in Europe as treatment of many cases of either primary or relapsed prostate cancer following radiotherapy. Although some reports suggested that HIFU is very effective as treatment for low and medium risk localized prostate cancer, no randomized series comparing this technique with conventional therapies have been presented yet. They also found vast disparity in criteria to define DFS rendering interpretation of results difficult. The authors concluded that experience of some groups in HIFU is highly promising. Local tumor destruction is evident both in primary and relapsed cases of prostate cancer. However, randomized controlled studies with long-term follow-up are necessary to measure benefits in global survival and QOL. Comparisons must also be made with conventional techniques, and a uniform definition of DFS is necessary.

Barqawi and Crawford (2008) stated that the use of HIFU as a method for ablation of a localized tumor growth is not new. Several attempts have been made to apply the principles of HIFU to the treatment of pelvic, brain, and gastrointestinal tumors. However, only in the past decade has the understanding of the basic principles of HIFU allowed researchers to further exploit its application as a radical and truly non-invasive, intent-to-treat, ablative method for treating organ-confined prostate cancer. The authors stated that HIFU may play a crucial role in the search for a safe and effective primary treatment for localized prostate cancer. Its non-invasive and unlimited repeatability potential is appealing and unique; however, long-term results from controlled studies are needed. In addition, a better understanding of HIFU's clinical limitations is vital before this treatment modality can be recommended to patients who are not involved in well-designed clinical studies.

Rebillard et al (2008) discussed the safety and effectiveness of HIFU in patients with
prostate cancer. These investigators searched Medline and Embase for clinical studies evaluating the safety and effectiveness of HIFU in prostate cancer (July 2007). In addition, abstracts presented at the 2005 to 2007 annual meetings of the European Association of Urology and AUA were screened. In all, 37 articles and abstracts were selected. As the data on HIFU as salvage therapy were limited, the authors focused on HIFU as primary therapy. Studies consisted of case series only. Included patients were approximately 70 years old with T1-T2 N0M0 disease, Gleason Score less than or equal to 7, a PSA level of less than or equal to 28 ng/ml and a prostate volume of less than or equal to 40 ml. Negative biopsy rates with the Ablatherm device were 64% to 93%, and a PSA nadir of less than or equal to 0.5 ng/ml was achieved in 55% to 84% of patients. The 5-year actuarial DFS rates were 60% to 70%. The most common complications were stress urinary incontinence, urinary tract infection, urethral/bladder neck stenosis or strictures, and erectile dysfunction. For the Ablatherm device, the rate of complications has been significantly reduced over the years, due to technical improvements in the device as well as the use of transurethral resection of the prostate before HIFU. The authors concluded that HIFU as primary therapy for prostate cancer is indicated in older patients (greater than or equal to 70 years) with T1-T2 N0M0 disease, a Gleason score of less than 7, a PSA level of less than 15 ng/ml and a prostate volume of less than 40 ml. In these patients HIFU achieved short-term cancer control, as shown by a high percentage of negative biopsies and significantly reduced PSA levels. The median-term survival data also appeared promising, but long-term follow-up studies are needed to further evaluate cancer-specific and overall survival rates before the indications for primary therapy can be expanded.

Thüroff and Chaussy (2008) stated that reports describing results of HIFU for prostate cancer are mainly based on single-center, prospective, clinical trials. The latest published results suggest that HIFU is a valuable option for well-differentiated and moderately-differentiated tumors, as well as for local recurrence after EBRT. The authors noted that HIFU in locally recurrent cancer after surgery, as well as adjuvant HIFU for local debulking in locally advanced or metastatic disease, shows promising results for reducing local disease-induced morbidity and for delay of progression.

Poissonnier and colleagues (2008) ascertained the effectiveness and adverse effects of HIFU for the treatment of local recurrence of prostate cancer after exclusive EBRT. A total of 72 patients with histologically and biologically documented local recurrence after radiotherapy were treated by HIFU. The mean age was 68.27 +/- 5.93 years, and mean PSA was 6.64 +/- 7.26 ng/ml. A total of 30 patients were treated according to standard parameters and 42 according to specific parameters. The 2005 ASTRO criteria, specific for salvage therapy (Phoenix consensus), were used to define recurrence. Progression-free survival (PFS) was calculated by the Kaplan-Meier method. Mean follow-up was 39 +/- 28 months. The rate of negative biopsy was 80% and the median nadir PSA was 0.10 ng/ml. Specific survival was 94% at 3 years and 90% at 5 years, and PFS was 50% at 3 years and 44% at 5 years. The rate of urinary incontinence was 44% (grade 1: 12%, grade 2/3: 32%) and the rate of urethral stricture or bladder neck stenosis was 30%. The use of specific parameters reduced the incidence of severe incontinence (19% versus 50%, p = 0.005) and stenosis (24% versus 40%). The authors concluded that treatment with HIFU achieved a 5-year PFS of 44%, but patients must be clearly informed about the high rate of adverse effects.
Muto et al (2008) evaluated the feasibility and effectiveness of HIFU for localized prostate cancer. A total of 70 patients received HIFU using Sonablate(R) 500 were included in this study. In patients whose cancer was confined to only one lobe by multi-regional biopsies, total peripheral zone and a half portion of transitional zone were ablated (focal therapy). Otherwise, patients received whole organ ablation (whole therapy). Scheduled biopsies were performed at 6 and 12 months after treatment. Pre- and post-HIFU serum testosterone levels were measured. The 2-year biochemical DFS rates in patients at low-, intermediate- and high-risk were 85.9 %, 50.9 % and 0 %, respectively, (p = 0.0028). After 12 months, 81.6 % (40/49) of patients were biopsy negative; 84.4 % in patients who received whole therapy, whereas 76.5 % in those with focal therapy. The 2-year biochemical DFS rates for the patients at low- and intermediate-risk was 90.9 % and 49.9 %, respectively, in patients with whole therapy, whereas 83.3 % and 53.6 % in patients with focal therapy. In patients without neoadjuvant androgen deprivation, serum testosterone levels continuously decreased after whole therapy, whereas no changes were observed in those with focal therapy. Patients whose follow-up biopsies were positive tended to have significantly higher changes in PSA levels than biopsy-negative patients. The authors concluded that in patients with low-risk prostate cancer, HIFU monotherapy resulted in comparable immediate cancer control with other modalities. In particular, focal therapy might offer a feasible minimally invasive therapeutic option, which maintained serum testosterone level. To the authors' knowledge, this is the first report that whole, but not focal, therapy affects the serum testosterone level.

Zacharakis et al (2008) examined the use of HIFU as a salvage therapy in men with localized prostate cancer recurrence following EBRT. A review of 31 cases treated using the Sonablate(R) 500 HIFU device was carried out. All men had presumed organ-confined, histologically confirmed recurrent prostate cancer following EBRT. The mean (range) age was 65 (57 to 80) years with a mean pre-operative PSA level of 7.73 (0.20 to 20) ng/ml. Patients were followed for a mean (range) of 7.4 (3 to 24) months. Side effects included stricture or intervention for necrotic tissue in 11 of the 31 patients (36 %), urinary tract infection or dysuria syndrome in 8 (26 %), and urinary incontinence in 2 (7 %). Recto-urethral fistula occurred in 2 men, although 1 was due to patient movement as a consequence of inadequate anesthesia, so the "true" rate was 3 %. Half of the patients had PSA levels of less than 0.2 ng/ml at the last follow-up. Three patients had metastatic disease while another 2 had only local, histologically confirmed, failure. A further 4 patients had evidence of biochemical failure only. Overall, 71 % had no evidence of disease following salvage HIFU. The authors concluded that salvage HIFU is a minimally invasive day-case procedure that can achieve low PSA nadirs and good cancer control in the short-term, with comparable morbidity to other forms of salvage treatment. However, the issue of accurate staging at the time of recurrence is still problematic, as a proportion of these men will harbor microscopic metastases undetected by conventional staging investigations.

Sumitomo et al (2008) examined if combining short-term neoadjuvant androgen deprivation therapy (NADT) with HIFU had a significant benefit in a large population of men with non-metastatic prostate cancer. These researchers evaluated the records of 530 patients whose PSA level at diagnosis was 30 ng/ml or less and whose follow-up period was not less than 12 months, at 7 investigational sites. A total of 270 patients had received NADT (within 6 months), and 260 had not. The primary outcome
measure was DFS according to the combined criteria satisfying the Phoenix definition (less than nadir + 2), negative prostate biopsy, and no findings of distant metastasis after the last HIFU treatment. The significance of the differences of values or the distributions of each parameter between two groups was evaluated with a Mann-Whitney U test, unpaired t test, or chi-square test, and a multi-variate Cox proportional hazards model was used to evaluate the prognostic relevance of pre-operative parameters. Statistical analyses showed that the NADT group had worse disease (higher PSA and risk group) than the HIFU-only group. Variables shown by multi-variate analyses to be significant prognostic parameters were pre-treatment PSA level, clinical stage, and no use of NADT. Short-term NADT significantly improved the 3-year DFS rate of patients with intermediate-risk and high-risk prostate cancer. During follow-up the frequencies of complications did not differ significantly with or without NADT. The authors concluded that these findings suggested that combining short-term NADT with HIFU treatment is of significant clinical benefit to intermediate-risk and high-risk prostate cancer patients without increasing the likelihood of complications.

Misrai et al (2008) assessed the long-term oncological results of HIFU as a primary and single treatment for clinically localized prostate cancer. A total of 119 patients underwent HIFU as first-line treatment and were retrospectively reviewed. They were stratified according to risk groups proposed by D'Amico. No patient had undergone previous hormonal therapy. Patients' PSA level was monitored at 3, 6, 12, 18, 24 months and then yearly. According to the latest ASTRO criteria, failure was defined by a PSA rise of 2 ng/ml or more above the PSA nadir. The biochemical-free survival rate (BFSR) was calculated. Mean patient age was 68 +/- 7.8 years (46 to 83). Mean follow-up was 3.9 years (1 to 6.8). Overall, 52 patients (43.7%) experienced a biochemical recurrence which included 26, 23 and 3 patients in the low-, intermediate- and high-risk groups, respectively. In uni-variate and multi-variate analyses, there was a statistical association between pre-operative PSA value greater than 10, a nadir PSA value greater than 1 and the risk of biochemical recurrence (p < 0.05). The 5-year BFSR rate was 30% with no statistical difference between low- and intermediate-risk patients. None of the 119 patients died of prostate cancer. The authors concluded that HIFU therapy provides efficient oncological control only in patients with low-risk prostate cancer. However, these findings could be used to improve the selection of patients who are potential candidates for HIFU therapy.

Blana and colleagues (2008) evaluated the long-term effectiveness of HIFU therapy for patients with localized prostate cancer. Patients included in this multi-center analysis had T1-T2 N0M0 prostate cancer, a PSA of less than 15 ng/ml, and a Gleason score of less than or equal to 7, and were treated with prototypes or first-generation Ablatherm HIFU devices. The Phoenix definition of biochemical failure was used (PSA nadir + 2). Treatment failure was defined as: biochemical failure or positive biopsy. A total of 140 patients with a mean (SD) age 69.1 years (6.6) were included. Mean (SD) follow-up was 6.4 years (1.1). Control prostate biopsies were negative in 86.4% of patients. Median PSA nadir of 0.16 ng/ml (range of 0.0 to 9.1) was achieved at a mean (SD) of 4.9 months (5.2). A PSA nadir of less than or equal to 0.5 ng/ml was recorded in 68.4% of patients. The actuarial biochemical failure-free survival rates (SR) at 5 and 7 years were 77% and 69%, respectively. The actuarial disease-free SR at 5 and 7 years were 66% and 59%, respectively. The authors concluded that these findings demonstrated the effective long-term cancer control achieved with HIFU in patients with low- or intermediate-risk localized prostate cancer.
The American College of Radiology Expert Panel on Radiation Oncology-Prostate Work Group's guideline on locally advanced (high-risk) prostate cancer (Lee et al, 2006) did not mention the use of HIFU in the list of treatment options. Furthermore, National Comprehensive Cancer Network's guideline on prostate cancer does not include HIFU among the therapeutic options for localized prostate cancer (NCCN, 2008). The Agency for Healthcare Research and Quality's guideline on treatments for clinically localized prostate cancer (Wilt et al, 2008) does not cover some newer treatments (e.g., cryotherapy, HIFU, and laparoscopic or robotic-assisted prostatectomy) for which there is little research about comparative effectiveness. The American Urological Association lists active surveillance, radiotherapy as well as radical prostatectomy as options for the management of patients with clinically localized prostate cancer. It does not mention the use of HIFU (Dahm et al, 2008).

Guidelines on management of prostate cancer from the National Institute for Health and Clinical Excellence (NICE, 2008) state that HIFU for prostate cancer is "not recommended other than in the context of clinical trials." Guidelines on treatment of prostate cancer from the Spanish National Health Service (2008) conclude that HIFU is an experimental treatment for prostate cancer. Other systematic evidence reviews have reached similar conclusions about the experimental status of HIFU for prostate cancer (Pichon-Riviere et al, 2008; Dussault, 2008). Furthermore, HIFU for prostate cancer has not been approved for use in the United States.

Cordeiro et al (2012) provided an up-to-date review of the available literature on HIFU as a definitive treatment of prostate cancer. A systematic literature search was conducted using MEDLINE and EMBASE via Ovid databases (January 2000 to December 2011) to identify studies on HIFU for treatment of prostate cancer. Only English-language and human-based full manuscripts that reported on case series studies with more than 50 participants, patient characteristics, efficacy and safety data were included. No randomized controlled trials (RCTs) were identified by the literature search. These investigators identified 31 uncontrolled studies that examined the efficacy of HIFU as primary treatment and 2 studies that examined the efficacy of HIFU as salvage treatment. Most treated patients had localised prostate cancer (stage T1-T2); Gleason scores of 2 to 10 and mean prostate specific antigen (PSA) values of 4.6 to 12.7 ng/ml. The mean age range of the patients was 64.1 to 72 years. The mean follow-up ranged from 6.4 to 76.8 months. Negative biopsy rates ranged from 35 to 95 %; PSA nadirs ranged from 0.04 to 1.8 ng/ml. The 5-year DFS rates ranged from 61.2 to 95 %; 7- and 8-year DFS rates ranged from 69 to 84 %. The most common complications associated with the HIFU procedure as the primary treatment included: urinary retention (less than 1 to 20 %); urinary tract infections (1.8 to 47.9 %); stress or urinary incontinence (less than 1 to 34.3 %); and erectile dysfunction (20 to 81.6 %). Recto-urethral fistula was reported in less than 2 % of patients. Treatment-related morbidity appeared to be reduced by the combination of transurethral resection (TURP) of the prostate and HIFU. The authors concluded that novel therapeutic methods have emerged in recent years as "local" treatment alternatives, in which cancer foci could be eradicated by greatly reducing the associated side-effects of radical treatment. High-intensity focused ultrasound seems to result in short- to medium-term cancer control, with a low rate of complications comparable with those of established therapies. However, longer-term follow-up studies are needed to evaluate cancer-specific and overall survival. If available promising results on HIFU for definitive treatment of prostate cancer are confirmed in future prospective trials, focal therapy could start to challenge the current standard of care.
In a retrospective single-center study, Pfeiffer and colleagues (2012) reported cancer control results after a single application of HIFU in patients with localized prostate cancer (PCa), stratified by tumor recurrence risk according to D’Amico risk classification. These investigators analyzed the outcomes of patients with localized PCa who were treated with curative intent between December 2002 and October 2006 using an Ablatherm HIFU device. Transurethral resection of the prostate or adenomectomy were performed before HIFU to down-size large prostate glands. Oncological failure was determined by the occurrence of biochemical relapse, positive biopsy and/or metastasis. Biochemical relapse was defined as a PSA nadir +1.2 ng/ml (Stuttgart definition), or as a rise in PSA level to greater than or equal to 0.5 ng/ml if PSA doubling time was less than or equal to 6 months. Kaplan-Meier analysis was performed for survival estimates. A total of 191 consecutive patients were included in the study. The median (range) patient age was 69.7 (51 to 82) years, and 38, 34 and 28% of these patients were in the low-, intermediate- and high-risk groups, respectively. The median (range) follow-up was 52.8 (0.2 to 79.8) months. At 5 years, overall and cancer-specific survival rates were 86.3 % and 98.4 %, respectively. Stratified by risk group, negative biopsy rates were 84.2 %, 63.6 %, and 67.5 % (p = 0.032), 5-year biochemical-free survival rates were 84.8 %, 64.9 % and 54.9 % (p < 0.01), and 5-year DFS rates were 81.7 %, 53.2 % and 51.2 % (p < 0.01), respectively. The authors concluded that single-session HIFU is recommended as a curative approach in elderly patients with low-risk PCa. Patients at higher risk of tumor progression should be counseled regarding the likely need for salvage therapy, including repeat HIFU.

Komura et al (2012) evaluated the oncologic results of HIFU as treatment for clinically PCa. A total of 180 patients with clinically PCa underwent HIFU and were retrospectively reviewed. Of those 171 patients primarily treated with HIFU were included in the analysis. They were stratified by prostatic volume, neoadjuvant hormonal ablation (NHA), and post-treatment PSA nadir; PSA level was monitored every month during the first 6 months after the treatment and every 3 months thereafter. According to the latest Phoenix criteria, biochemical failure was defined by a PSA rise of 2 ng/ml or more above the PSA nadir. Seventy-six (44.4 %) patients were offered pre-operative NHA in median duration of 3 months (IQR: 3 to 5.75). Pre-operative TURP was performed in 56 (32.7 %) patients having the calcification within the prostate. Mean patient age was 68.3 +/- 7.0. The median follow-up time was 43 months (IQR: 30 to 55). According to D’Amico risk groups 52 (30.4 %) patients were identified with low-risk, 47 (27.5 %) patients with intermediate-risk, and 72 (42.1 %) with high-risk. The overall and cancer-specific survival rates at 5 years were 98.8 % and 100 %, respectively. The metastasis-free survival rate at 5 years was 99.4 %. No significant differences were seen in biochemical failure-free survival when stratified according to pre-operative prostatic volume and administration of pre-operative NHA (p = 0.931 and p = 0.712, respectively). Regardless of NHA administration, patients with smaller PSA nadir (0.2 ng/ml) achieved better biochemical failure-free survival ratio. The authors concluded that HIFU therapy provided sufficient oncologic control only in patients with low-risk prostate cancer. However, these data could be used to improve the selection of patients who are potential candidates for HIFU therapy.

Uddin et al (2012) described the use of the Sonablate 500 HIFU system in the salvage setting of PCa recurrence after EBRT. An evaluation was performed of a consecutive group of men with biochemical failure after EBRT with histologically proven local
recurrence and bone-scan and pelvic MRI to exclude macroscopic metastases, and who chose to have whole-gland salvage HIFU (Sonablate 500) at 2 centers (3 expert HIFU surgeons at each center). The modified Clavien system was used to categorize adverse events and validated questionnaires for functional outcomes. Progression following HIFU treatment was defined as ASTRO-Phoenix criteria (PSA greater than nadir+2 ng/ml) and/or a positive biopsy and/or start of hormone therapy. A total of 84 men underwent whole-gland salvage HIFU (2004 to 2009). Median age, pre-treatment serum PSA, and biopsy Gleason score was 68 years (range of 64 to 72 years), 4.3 ng/ml (range of 1.9 to 7.9 ng/ml), and 7 (range of 6 to 7), respectively. Mean follow-up was 19.8 months (range of 3.0 to 35.1 months). After salvage HIFU, 62 % of the men were pad-free and leak-free. Mean International Index of Erectile Function-5 point score fell from 8.8 to 4.7 (p < .001). International Prostate Symptoms Score and RAND-SF36 scores were not affected. Two men developed recto-urethral fistulae after 1 salvage procedure. A further 2 fistulae occurred in the 6 men undergoing a second salvage HIFU. Intervention for bladder outlet obstruction was needed in 20 % (17 of 84 patients). If PSA non-responders were included, 1- and 2-year PFS rates were 59 % (50 of 84 patients) and 43 % (36 of 84 patients), respectively. If PSA non-responders were excluded, 1- and 2-year PFS rates were 62 % (48 of 77 patients) and 48 % (37 of 77 patients), respectively. The authors concluded that salvage whole-gland HIFU is a high-risk procedure. Although its use in early cancer control is promising, strategies to better identify metastatic disease prior to salvage therapy and reduce local toxicity are needed to improve on this.

In a pilot study, Asimakopoulos et al (2012) examined HIFU as salvage first-line treatment for palpable, TRUS-evidenced, biopsy-proven locally recurrent prostate cancer (CaP) after radical prostatectomy (RP). A total of 19 patients with palpable, TRUS-evidenced, biopsy-proven local recurrence of CaP after RP, unwilling to undergo salvage radiotherapy (SRT), underwent HIFU as a single-session procedure. Pre-, intra-, and post-operative data including early and late complications, and oncologic outcomes (PSA nadir, biochemical recurrence (BCR)-free survival, and need of secondary adjuvant treatment) were prospectively evaluated. Success was defined as PSA nadir less than or equal to 0.1 ng/ml obtained within 3 months from HIFU. In case of PSA nadir greater than 0.1 ng/ml or PSA increase greater than or equal to 1 ng/ml above the PSA nadir, a biopsy of the treated lesion was performed, and if negative, maximum androgen blockade (MAB) was adopted. In case of positive biopsy, RT was performed. Failure was defined as use of secondary adjuvant treatment (MAB or RT). Median follow-up was 48 months. All cases were performed as overnight procedure. No case of urethra-rectal fistula or anastomotic stricture was observed. Two cases of acute urinary retention were resolved with prolonged urethral catheterization. Four cases of stress urinary incontinence were observed; 2 (mild incontinence) were resolved after pelvic floor exercises within 6 months, while 2 cases of severe incontinence required surgical minimally invasive treatment; 17/19 patients (89.5 %) were classified as success. Two patients failed to show a PSA nadir of less than 0.1 ng/ml. During follow-up, 8/17 patients (47 %) were classified as failure, with consequent total rate of failures 10/19 (52.6 %). A statistically significant difference was observed in pre-HIFU median PSA (2 versus 5.45 ng/ml, respectively, p = 0.013) and Gleason score of the RP specimen (p = 0.01) between the success and failure group. The authors concluded that salvage first-line HIFU for palpable, TRUS-evidenced, biopsy-proven local recurrence of CaP is a feasible, minimally invasive day-case procedure, with an acceptable morbidity profile. It seems to have a good cancer
control in the short- and mid-term. Patients with lower pre-HIFU PSA level and favorable pathologic Gleason score presented better oncologic outcomes. They stated that a prospective randomized trial with an adequate recruitment and follow-up is necessary to confirm these preliminary oncologic results.

An UpToDate review on “Initial approach to low-risk clinically localized prostate cancer” (Klein, 2013) states that “The role of ablation with cryotherapy or HIFU as an alternative to radical prostatectomy or RT remains uncertain. Potential advantages in men with localized disease include the ability to destroy cancer cells using a relatively noninvasive procedure. As such, these procedures are associated with minimal blood loss and pain. There is also a more rapid posttreatment convalescence. Whether the long-term outcomes are equivalent to those with definitive surgery or RT is uncertain however. Additional experience and longer follow-up are required to compare the rate of disease control and side effects profiles with other treatment modalities”.

Furthermore, the NCCN’s clinical practice guideline on “Prostate cancer” (Version 4.2013) states that “The panel feels similarly about other emerging focal therapies. High intensity focused ultrasound (HIFU) and vascular-targeted photodynamic (VTP) therapies, like cryotherapy, warrant further study”.

The National Institute for Health and Care Excellence’s clinical practice guideline on “Prostate cancer: Diagnosis and treatment” (NUCE, 2014) listed HIFU and cryotherapy (as part of clinical trials) as therapeutic options for the prostate cancer

Central Nervous System Diseases/Disorders:

Jagannathan and associates (2009) noted that the field of magnetic resonance imaging-guided HIFU surgery (MRgFUS) is a rapidly evolving one, with many potential applications in neurosurgery. These researchers discussed the historical development of the technology and its potential applications in modern neurosurgery. The evolution of MRgFUS has occurred in parallel with modern neurological surgery, and the two seemingly distinct disciplines share many of the same pioneering figures. Early studies on focused ultrasound treatment in the 1940s and 1950s demonstrated the ability to perform precise lesioning in the human brain, with a favorable risk-benefit profile. However, the need for a craniotomy, as well as the lack of sophisticated imaging technology, resulted in limited growth of HIFU for neurosurgery. More recently, technological advances have permitted the combination of HIFU along with magnetic resonance imaging guidance to provide an opportunity to effectively treat a variety of central nervous system disorders. Although challenges remain, HIFU-mediated neurosurgery may offer the ability to target and treat central nervous system conditions that were previously extremely difficult to address.

In a proof-of-concept study, Lipsman et al (2013) examined the effectiveness of MR-guided focused ultrasound for the management of essential tremor. This study was done in Toronto, Canada, between May, 2012, and January, 2013. A total of 4 patients with chronic and medication-resistant essential tremor were treated with MR-guided focused ultrasound to ablate tremor-mediating areas of the thalamus. Patients underwent tremor evaluation and neuroimaging at baseline and 1 month and 3 months after surgery. Outcome measures included tremor severity in the treated arm, as measured by the clinical rating scale for tremor, and treatment-related adverse events. Patients showed immediate and sustained improvements in tremor in the dominant hand. Mean reduction in tremor score of the treated hand was 89.4 % at 1 month and
81.3% at 3 months. This reduction was accompanied by functional benefits and improvements in writing and motor tasks. One patient had post-operative paraesthesia that persisted at 3 months. Another patient developed a deep vein thrombosis, potentially related to the length of the procedure. The authors concluded that MR-guided focused ultrasound might be a safe and effective approach to generation of focal intra-cranial lesions for the management of disabling, medication-resistant essential tremor. They stated that if larger trials validate the safety and ascertain the effectiveness and durability of this new approach, it might change the way that patients with essential tremor and potentially other disorders are treated.

In an open-label, uncontrolled, pilot study, Elias et al. (2013) investigated the use of transcranial MRI-guided focused ultrasound thalamotomy for the treatment of essential tremor. From February 2011 through December 2011, these researchers used transcranial MRI-guided focused ultrasound to target the unilateral ventral intermediate nucleus of the thalamus in 15 patients with severe, medication-refractory essential tremor. They recorded all safety data and measured the effectiveness of tremor suppression using the Clinical Rating Scale for Tremor to calculate the total score (ranging from 0 to 160), hand subscore (primary outcome, ranging from 0 to 32), and disability subscore (ranging from 0 to 32), with higher scores indicating worse tremor. These investigators assessed the patients' perceptions of treatment efficacy with the Quality of Life in Essential Tremor Questionnaire (ranging from 0 to 100%, with higher scores indicating greater perceived disability). Thermal ablation of the thalamic target occurred in all patients. Adverse effects of the procedure included transient sensory, cerebellar, motor, and speech abnormalities, with persistent paresthesia in 4 patients. Scores for hand tremor improved from 20.4 at baseline to 5.2 at 12 months (p = 0.001). Total tremor scores improved from 54.9 to 24.3 (p = 0.001). Disability scores improved from 18.2 to 2.8 (p = 0.001). Quality-of-life scores improved from 37% to 11% (p = 0.001). The authors concluded that in this pilot study, essential tremor improved in 15 patients treated with MRI-guided focused ultrasound thalamotomy. They stated that large, RCTs are needed to assess the procedure's safety and effectiveness.

Liver Cancer (Primary or Metastatic):

Park et al. (2009) ascertained the safety and effectiveness of HIFU in the treatment of liver metastasis from colon and stomach cancer. A total of 10 patients with liver metastasis from colon cancer and 3 from stomach cancer underwent HIFU under general anesthesia. Treatment was performed using an extra-corporeal, ultrasound-guided focused system. Complications during the study, extent of coagulative necrosis at 2-week follow-up, and evidence of tumor on further follow-up were analyzed. Patients were divided into 4 categories: (i) complete ablation with no evidence of recurrence on follow-up; (ii) apparent complete ablation of target mass with new foci of disease in the target organ or distant malignancy and no local tumor progression; (iii) local tumor progression after apparent complete ablation; and (iv) partial ablation. Mean follow-up period was 22 weeks in the colon cancer group and 58 weeks in the stomach cancer group. The sum of total lesion size was between 1.8 cm and 21.4 cm (mean of 8.4 cm +/- 6.7 cm) for the colon cancer group and between 1.7 and 16.3 cm (mean of 8.8 cm +/- 7.3 cm) for the stomach cancer group. In the colon cancer group, 1 patient was categorized as category (i), 1 as category (ii), 3 as category (iii) and the remaining 5 as category (iv). The stomach cancer group showed 2 patients as category (i), and 1 as category (ii). The authors concluded that for treating liver
metastasis from colon and stomach cancer, HIFU seems safe but its effectiveness is questionable. They stated that more research is needed.

An assessment of the evidence for HIFU for liver cancer from the Catalan Agency for Health Technology Assessment and Research (CAHTA) concluded: "Based on the scientific evidence available, there is not enough information on efficacy/effectiveness, safety and cost-effectiveness of HIFU treatment in patients with liver cancer (primary or metastatic). In fact, the design and scarcity of published studies hinder a correct assessment of HIFU treatment. Thus, interventions using high intensity focused ultrasound for liver cancer treatment should be tested in randomised clinical trials, of a sufficient sample size and adequate design" (Navarro, 2008).

Ng et al (2011) evaluated the outcome of patients with hepatocellular carcinoma (HCC) treated by HIFU in a single tertiary referral center. From October 2006 to December 2008, a total of 49 patients received HIFU for unresectable HCC. Each patient underwent a single session of HIFU with a curative intent. Treatment efficacy and survival outcome were evaluated. Clinicopathologic factors affecting the primary technique effectiveness and overall survival rates were investigated by uni-variate analysis. The median size of the treated tumors was 2.2 cm (range of 0.9 to 8 cm). The majority of patients had single tumors (n = 41, 83.6 %). Thirty-one patients (63.2 %) had artificial right pleural effusion during HIFU treatment to reduce damage to the lung and diaphragm. The hospital mortality rate was 2 % (n = 1) and the complication rate was 8.1 % (n = 4). The primary technique effectiveness rate was 79.5 % (39 of 49 patients). It increased from 66.6 % in the initial series to 89.2 % in the last 28 patients. Tumor size (greater than or equal to 3.0 cm) was the significant risk factor affecting the complete ablation rate. The 1- and 3-year overall survival rates were 87.7 % and 62.4 %, respectively. Child-Pugh liver function grading was the significant prognostic factor influencing the overall survival rate. The authors concluded that HIFU is an effective treatment modality for unresectable HCC with a high technique effectiveness rate and favorable survival outcome. The drawbacks of this study were its retrospective nature, short follow-up and small sample size. The authors stated that further studies are needed to compare the effectiveness of HIFU with other ablation modalities.

Chan and associates (2013) reported their preliminary experience of HIFU for the treatment of recurrent hepatocellular carcinoma (HCC). Clinico-pathological data of 27 patients who received HIFU ablation and 76 patients who received RFA for recurrent HCC from October 2006 to October 2009 were reviewed. Survival outcomes between the 2 groups were compared using the log-rank test. A value of p < 0.05 was considered significant. The median follow-up was 27.9 months. There was no difference in tumor size (HIFU, 1.7 cm; RFA, 1.8 cm; p = 0.28) between the 2 groups. Procedure-related morbidity rate was 7.4 % in the HIFU group and 6.5 % in the RFA group (p = 1.00). Skin burn and pleural effusion were the 2 morbidities associated with HIFU. There was no hospital mortality in the HIFU group, whereas 2 deaths occurred in the RFA group. The 1-, 2-, and 3-year DFS rates were 37.0 %, 25.9 %, and 18.5 %, respectively, for the HIFU group, and 48.6 %, 32.1 %, and 26.5 %, respectively for the RFA group (p = 0.61). The 1-, 2-, and 3-year overall survival rates were 96.3 %, 81.5 %, and 69.8 %, respectively, for the HIFU group, and 92.1 %, 76.1 %, and 64.2 %, respectively, for the RFA group (p = 0.19). The authors concluded that their preliminary experience in using HIFU for recurrent HCC is promising. They stated that further studies are needed to explore its treatment value for primary HCC.
Also, the NCCN’s clinical practice guideline on “Hepatobiliary cancers” (Version 2.2013) does not mention HIFU as a therapeutic option.

**Osteosarcoma/Bone Tumors:**

Li and co-workers (2009) prospectively evaluated the use of ultrasonographically guided HIFU in the salvage of limbs in patients with osteosarcoma. A total of 7 patients underwent HIFU ablation. Laboratory and radiological examinations were performed after intervention. Changes in symptoms and survival time were noted at follow-up. No severe complications were observed, and pre-existing severe pain disappeared in patients treated with HIFU. Alkaline phosphatase did not show statistically significant changes before and after HIFU treatment, although alkaline phosphatase did change 1 month and 2 months after HIFU. Complete response of the tumor was achieved in 3 patients with osteosarcoma. Partial response was achieved in another 3 patients treated with HIFU. Pulmonary metastasis was noted in only 1 patient 5 months after HIFU. The median survival time was 68 months. All patients were alive 3 years after HIFU treatment. Five patients were alive at follow-up visits after 5 years. One patient died from cachexia and infection after 4 years, another patient died of cardiac arrest attack after 4 years. Three patients died of lung dysfunction from pulmonary metastases after 5 years. The 5-year survival rate was 71.4%. The authors concluded that HIFU ablation was a safe and feasible method of treatment of osteosarcoma which salvages the limb, but they stated that large-scale randomized clinical trials are needed for confirmation.

Chen et al (2010) evaluated the long-term follow-up results of ultrasonographically (US)-guided HIFU ablation in patients with primary bone malignancy. A total of 80 patients with a primary bone malignancy -- 60 with stage IIb disease and 20 with stage III disease (Enneking staging system) -- were treated with US-guided HIFU ablation. High-intensity focused ultrasound ablation combined with chemotherapy was performed in 62 patients with osteosarcoma, 1 patient with periosteal osteosarcoma, and 3 patients with Ewing sarcoma. The remaining 14 patients had chondrosarcoma, giant cell bone cancer, periosteal sarcoma, or an unknown malignancy and were treated with HIFU ablation only. Magnetic resonance imaging (MRI) or computed tomography (CT), and single photon emission computed tomography (SPECT) were used to assess tumor response. Cumulative survival rates were calculated by using the Kaplan-Meier method. Adverse effects were recorded. High-intensity focused ultrasound ablation guided by real-time US was performed. Follow-up images demonstrated completely ablated malignant bone tumors in 69 patients and greater than 50% tumor ablation in the remaining 11 patients. Overall survival rates at 1, 2, 3, 4, and 5 years were 89.8%, 72.3%, 60.5%, 50.5%, and 50.5%, respectively. Survival rates at 1, 2, 3, 4, and 5 years were 93.3%, 82.4%, 75.0%, 63.7%, and 63.7%, respectively, in the patients with stage IIb cancer and 79.2%, 42.2%, 21.1%, 15.8%, and 15.8%, respectively, in those with stage III disease. Among the patients with stage IIb disease, long-term survival rates were substantially improved in the 30 patients who received the full treatment -- namely, complete HIFU and full cycles of chemotherapy -- compared with the survival rates for the 24 patients who did not finish the chemotherapy cycles and the 6 patients who underwent partial ablation only. Only 5 (7%) of the 69 patients who underwent complete ablation had local cancer recurrence during the follow-up period. A total of 40 adverse events were recorded, with 14 patients requiring surgical intervention. The authors concluded that US-guided
HIFU ablation of malignant bone tumors is feasible and effective and eventually may be a component of limb-sparing techniques for patients with these cancers.

Li et al (2010) evaluate 25 patients with malignant bone tumors before and after HIFU treatment. High-intensity focused ultrasound resulted in significant improvement in biochemical markers, and no severe complications were observed. Following HIFU treatment, 21 (87.5 %) patients were completely relieved of pain, and 24 (100 %) experienced significant relief. On the basis of MRI or PET-CT, HIFU was effective: For patients with primary bone tumors, 6 (46.2 %) had a complete response, 5 (38.4 %) had a partial response, 1 (7.8 %) had a moderate response, and 1 suffered progressive disease; the response rate was 84.6 %. For patients with metastatic bone tumors, 5 (41.7 %) had complete response, 4 (33.3 %) had partial response, 1 (8.3 %) had a moderate response, 1 (8.3 %) had stable disease, and 1 suffered progressive disease; the response rate was 75.0 %. The 1-, 2-, 3-, and 5-year survival rates were 100.0 %, 84.6 %, 69.2 %, and 38.5 %, respectively, for patients with primary bone tumors and 83.3 %, 16.7 %, 0 %, and 0 %, respectively, for patients with metastatic bone tumors. The survival rates for patients with primary bone tumors were significantly better than for those with metastatic tumors. The authors concluded that HIFU safely and non-invasively ablated malignant bone tumors and relieved pain. They stated that HIFU ablation should be further investigated in larger number of patients, as it appears to be successful in the treatment of primary malignant bone tumors.

In an editorial that accompanied the afore-mentioned study by Li et al (2010), Konski (2010) stated that caution needs to be exercised in interpreting these findings because the response rates were classified by MRI or PET-CT and not pathologically. Well-designed studies comparing HIFU to cryotherapy, radiofrequency ablation, and/or external beam radiotherapy are needed to ascertain the effectiveness of HIFU in the treatment of bone metastases. The editorialist noted that HIFU may provide another treatment option for patients with primary bone tumors who are not surgical candidates or who refuse surgery, but these data need to be confirmed.

Renal Cancer:

In a phase I clinical study, Klinger et al (2008) evaluated the feasibility of HIFU ablation of small renal tumours under laparoscopic control. A total of 10 kidneys with solitary renal tumors were treated with a newly developed 4.0 MHz laparoscopic HIFU probe. In the first 2 patients with 9-cm tumors, a defined marker lesion was placed before laparoscopic radical nephrectomy. In 8 patients with a mean tumor size of 22 mm (range of 11 to 40), the tumor was completely ablated as in curative intent, followed by laparoscopic partial nephrectomy in 7 tumors. One patient had post-HIFU biopsies and was followed radiologically. Specimens were studied by detailed and whole-mount histology, including NADH stains. Mean HIFU insonication time was 19 mins (range of 8 to 42), with a mean targeted volume of 10.2 cm3 (range of 9 to 23). At histological evaluation both marker lesions showed irreversible and homogeneous thermal damage within the targeted site. Of the 7 tumors treated and removed after HIFU, 4 showed complete ablation of the entire tumor. Two had a 1- to 3-mm rim of viable tissue immediately adjacent to where the HIFU probe was approximated, and 1 tumor showed a central area with about 20 % vital tissue. There were no intra- or post-operative complications related to HIFU. The authors concluded that the morbidity of laparoscopic partial nephrectomy mainly comes from the need to incise highly
vascularized parenchyma. Targeted laparoscopic HIFU ablation may render this unnecessary, but further studies are needed to refine the technique.

Klatte and Marberger (2009) reviewed the current status of HIFU for the treatment of renal tumors. Application of extra-corporeal HIFU for renal tumors is well-tolerated with no serious peri-operative complications. However, the techniques available do not permit sufficient tumor destruction that can be considered as an alternative to surgical extirpation. Laparoscopic HIFU avoids problems with respiratory movement and interphases and may achieve a greater rate of tumor destruction. The authors concluded that at the current time, HIFU of renal tumors has to be considered an experimental treatment approach; and prospective evaluation of laparoscopic HIFU is needed to assess its oncologic effectiveness.

Hernández Fernández et al (2009) reviewed the mechanisms of action of HIFU as well as both experimental and clinical work related to renal tumor treatment. While most currently available experience in urological tumors with HIFU has been obtained with prostate cancer, an increasing number of studies support the efficacy and safety of this procedure for renal tumor destruction. Together with cryotherapy and radiofrequency, HIFU completes the spectrum of minimally invasive surgery in renal cancer, intended to decrease surgical morbidity while achieving similar oncological control rates. The authors concluded that it is still early to recommend this procedure for daily clinical practice. They stated that while its safety and few side effects are known, many ongoing studies intended to confirm its mid-term and long-term oncological efficacy should be completed.

Caballero et al (2010) reviewed the development, physical principles, and current status of HIFU in the treatment of renal tumors. These investigators concluded that HIFU appears to be a new option among non-invasive therapies for renal cancer in selected cases. They stated that a low complication rate has been noted, but much longer follow-up times are needed for assessment of oncological results.

The European Association of Urology’s guidelines on “Renal cell carcinoma” (Ljungberg et al, 2013) stated that other image-guided percutaneous and minimally invasive techniques (e.g., microwave ablation, laser ablation, and HIFU ablation) are experimental and are recommended only in studies.

**Pancreatic Cancer:**

In a phase II clinical trial, Zhao et al (2010) evaluated the safety and effectiveness of concurrent gemcitabine and HIFU therapy in patients with locally advanced pancreatic cancer. Patients with localized unresectable pancreatic adenocarcinoma in the head or body of the pancreas received gemcitabine (1,000 mg/m) intravenously over 30 mins on days 1, 8, and 15, and concurrent HIFU therapy on days 1, 3, and 5. The treatment was given every 28 days. A total of 37 (94.9 %) of the 39 patients were assessable for response, and 2 cases of complete response and 15 cases of partial response were confirmed, giving an overall response rate of 43.6 % [95 % confidence interval (CI): 28.0 to 59.2 %]. The median follow-up period was 16.5 months (range of 8.0 to 28.5 months). The median time to progression and overall survival for all patients were 8.4 months (95 % CI: 5.4 to 11.2 months) and 12.6 months (95 % CI: 10.2 to 15.0 months), respectively. The estimates of overall survival at 12 and 24 months were 50.6 % (95 % CI: 36.7 to 64.5 %) and 17.1 % (95 % CI: 5.9 to 28.3 %), respectively. A total of 16.2 % of patients experienced grade 3/4 neutropenia. Grade
3 thrombocytopenia was documented in 2 (5.4%) patients. Grade 3 nausea/vomiting and diarrhea were observed in 3 (8.1%), and 2 (5.4%) patients, respectively. Grade 1 or 2 fever was detected in 70.3% of patients. Twenty-eight patients (71.8%) complained of abdominal pain consistent with tumor-related pain before HIFU therapy. Pain was relieved in 22 patients (78.6%). The authors concluded that concurrent gemcitabine and HIFU is a tolerated treatment modality with promising activity in patients with previously untreated locally advanced pancreatic cancer. Further investigation is needed to ascertain the role of HIFU in the treatment of pancreatic cancer.

**Vulvar Dystrophy:**

Ruan et al (2010) evaluated the effectiveness of HIFU in the treatment of patients with non-neoplastic epithelial disorders of the vulva. These researchers reviewed 41 cases of lichen sclerosus, 38 cases of squamous cell hyperplasia, and 17 mixed cases. Biopsy specimens were assessed with light microscopy before and after treatment. Pruritus and signs of vulvar lesions were dramatically improved after HIFU treatment, without severe complications, and 90.2% of the patients were cured or had their symptoms improved 6 months after treatment. On light microscopy, pigmentation and epithelial structures were recovered and dermal lymphocytic infiltration was reduced. The response rates were lower and complication rates higher among lichen sclerosus than among squamous cell hyperplasia cases (p < 0.05 for both). The authors concluded that treatment with HIFU may be safe and effective in cases of vulvar dystrophy. The findings of this trial need to be validated by well-designed studies with larger number of patients and longer follow-up periods.

**Thyroid Nodules:**

In an open, single-center, feasibility study, Esnault et al (2011) hypothesized that an optimized HIFU device could be safe and effective for ablating benign thyroid nodules without affecting neighboring structures. A total of 25 patients were treated with HIFU with real-time ultrasound imaging 2 weeks before a scheduled thyroidectomy for multinodular goiter. Thyroid ultrasonography imaging, thyroid function, were evaluated before and after treatment. Adverse events were carefully recorded. Each patient received HIFU for 1 thyroid nodule, solid or mixed, with mean diameter greater than or equal to 8 mm, and no suspicion of malignancy. The HIFU device was progressively adjusted with stepwise testing. One pathologist examined all removed thyroids. Three patients discontinued treatment due to pain or skin microblister. Among the remaining 22 patients, 16 showed significant changes by ultrasound. Macroscopic and histological examinations showed that all lesions were confined to the targeted nodule without affecting neighboring structures. At pathological analysis, the extent of nodule destruction ranged from 2% to 80%. Five out of 22 patients had over 20% pathological lesions unmistakably attributed to HIFU. Seventeen cases had putative lesions including non-specific necrosis, hemorrhage, nodule detachment, cavitations, and cysts. Among these 17 cases, 12 had both ultrasound changes and cavitation at histology that may be expected for an HIFU effect. In the last 3 patients ablated at the highest energy level, significant ultrasound changes and complete coagulative necrosis were observed in 80%, 78%, and 58% of the targeted area, respectively. There were no major complications of ablation. The authors concluded that these findings showed the potential efficacy of HIFU for human thyroid nodule ablation. Lesions were clearly visible by histology and ultrasound after high energy treatments.
and safety and tolerability were good. The authors identified a power threshold for optimal necrosis of the target thyroid tissue. They stated that further studies are ongoing to assess nodule changes at longer follow-up times.

Fractures:

In a Cochrane review, Griffin et al (2012) evaluated the effects of HIFU, low-intensity ultrasound (LIUS), and extra-corporeal shockwave therapies (ECSW) as part of the treatment of acute fractures in adults. These investigators searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (December 2011), the Cochrane Central Register of Controlled Trials (in The Cochrane Library 2011, Issue 4), MEDLINE (1950 to November week 3, 2011), EMBASE (1980 to 2011 week 49), trial registers and reference lists of articles. Randomized controlled trials evaluating ultrasound treatment in the management of acute fractures in adults were selected. Studies including participants over 18 years of age with acute fractures, reporting functional outcomes, time to union, non-union, secondary procedures such as for fixation or delayed or non-union, adverse effects, pain, costs or patient adherence were included. Two authors independently extracted data from the included studies. Treatment effects were assessed using mean differences or risk ratios and, where there was substantial heterogeneity, pooled using a random-effects model. Results from "worst case" analyses, which gave more conservative estimates of treatment effects for time to fracture union, are reported in preference to those from "as reported" analyses. A total of 12 studies, involving 622 participants with 648 fractures, were included. Eight studies were randomized placebo-controlled trials, 2 studies were RCTs without placebo controls, 1 study was a quasi-randomised placebo controlled trial and the remaining study was a quasi-RCT without placebo control. Eleven trials tested LIUS and 1 trial tested ECSW. Four trials included participants with conservatively treated upper limb complete fractures and 6 trials included participants with lower limb complete fractures; these were surgically fixed in 4 trials. The remaining 2 trials reported results for conservatively treated tibial stress fractures. Very limited data from 2 complete fracture studies showed no difference between ultrasound and placebo control in functional outcome. Pooled estimates from 2 studies found LIUS did not significantly affect the time to return to training or duty in soldiers or midshipmen with stress fractures (mean difference -8.55 days, 95% CI: -22.71 to 5.61). Based on a "worst case" analysis, which adjusted for incomplete data, pooled results from 8 heterogeneous studies showed no statistically significant reduction in time to union of complete fractures treated with LIUS (standardised mean difference -0.47, 95% CI: -1.14 to 0.20). This result could include a clinically important benefit or harm, and should be seen in the context of the highly significant statistical heterogeneity (I² = 90%). This heterogeneity was not explained by the a priori subgroup analyses (upper limb versus lower limb fracture, smoking status). An additional subgroup analysis comparing conservatively and operatively treated fractures raised the possibility that LIUS may be effective in reducing healing time in conservatively managed fractures, but the test for subgroup differences did not confirm a significant difference between the subgroups. Pooled results from 8 trials reporting proportion of delayed union or non-union showed no significant difference between LIUS and control. Adverse effects directly associated with LIUS and associated devices were found to be few and minor, and compliance with treatment was generally good. One study reporting on pain scores found no difference between groups at 8 weeks. One quasi-randomized study (59 fractures) found no significant difference between ECSW and no-placebo control groups in non-union at 12 months (risk ratio
0.56, 95% CI: 0.15 to 2.01). There was a clinically small but statistically significant difference in the visual analog scores for pain in favor of ECSW at 3-month follow-up. The only reported complication was infection, with no significant difference between the 2 groups. The authors concluded that while a potential benefit of ultrasound for the treatment of acute fractures in adults can not be ruled out, the currently available evidence from a set of clinically heterogeneous trials is insufficient to support the routine use of this intervention in clinical practice. They stated that future trials should record functional outcomes and follow-up all trial participants.

Miscellaneous Indications:

Yonetsuji and associates (2013) noted that HIFU is a promising technique for cancer treatment owing to its minimal invasiveness and safety. However, skin burn, long treatment time and incomplete ablation are main shortcomings of this method. These investigators presented a novel HIFU robotic system for breast cancer treatment. The robot has 4 rotational degrees of freedom with the workspace located in a water tank for HIFU beam imaging and ablation treatment. The HIFU transducer combined with a diagnostic 2D linear ultrasound probe was mounted on the robot end-effector, which was rotated around the HIFU focus when ablating the tumor. High intensity focused ultrasound beams were visualized by the 2D probe using beam imaging. Skin burn can be prevented or alleviated by avoiding long time insonification towards the same skin area. The time cost could be significantly reduced, as there is no need to interrupt the ablation procedure for cooling the skin. In addition, the authors stated that their proposed robot control strategies can avoid incomplete ablation. Experiments were carried out and the results showed the effectiveness of the proposed system. These preliminary findings need to be validated by well-designed studies.

Kovatcheva et al (2014) investigated the long-term safety and effectiveness of US-guided HIFU treatment in patients with primary hyperparathyroidism (PHPT). In this prospective study, 13 of 72 screened patients with PHPT were eligible for HIFU treatment, which was performed in 1 or 2 sessions. Parathyroid adenoma size and function were evaluated at baseline, 1, 3, 6, 9, and 12 months after the final HIFU session. In 11 females and 2 males, mean age of 55.2 ± 12.41 years, the mean applied energy was 15.2 ± 7.7 kJ. Parathyroid size and parathyroid hormone decreased significantly 1 month after HIFU therapy (p < 0.002 and p < 0.02, respectively). Calcium concentration decreased slowly to reach significant reduction 9 months later (p < 0.05). Complete remission was noted in 3 patients (23 %) after 1 year, good disease control was achieved in 9 (69 %), and procedure was unsuccessful in 1 patient (8 %). Number of sessions was significantly related to treatment success (p < 0.05). Transitory side effects were impaired vocal cord mobility in 3 patients (23.1 %), subcutaneous edema in 3 patients (23.1 %), and a combination of both in 2 patients (15.4 %). The authors concluded that HIFU is a promising non-invasive technique for PHPT treatment, which could serve as therapeutic alternative for selected patients.

In a preliminary study, Xiao and colleagues (2014) examined if ultrasound-guided (HIFU) can play a role in treating cesarean scar pregnancy (CSP). Between November 2011 and December 2012, a total of 16 patients with CSP were treated with ultrasound-guided HIFU ablation. Successful treatment was defined as disappearance of CSP mass, undetectable serum beta human chorionic gonadotropin (HCG), and no serious complications such as severe bleeding, uterine rupture, or hysterectomy. All patients
were successfully treated in the out-patient department and none required re-admission. After 2 to 5 treatment sessions, the mean time for achieving undetectable serum beta HCG was 4.94 ± 2.32 weeks, and the mean time for CSP mass disappearance was 6.69 ± 3.36 weeks. Three patients experienced moderate abdominal pain that subsided in 1 to 2 days, and 9 patients experienced mild vaginal bleeding (less than 30 ml) that resolved within 2 to 3 days. All 16 patients had recovered their normal menstruation function at follow-up. The authors concluded that these preliminary findings suggested that ultrasound-guided HIFU ablation is a non-invasive, feasible, and effective method for the treatment of CSP. These preliminary findings need to be validated by well-designed studies.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes not covered for indications listed in the CPB:

There are no specific codes for High Intensity Focused Ultrasound (HIFU):

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

151.0 - 151.9 Malignant neoplasm of stomach [liver metastasis from stomach cancer]

153.0 - 153.9 Malignant neoplasm of colon [liver metastasis from colon]

155.0 Malignant neoplasm of liver, primary [hepatocellular]

157.0 - 157.9 Malignant neoplasm of pancreas

170.0 - 170.9 Malignant neoplasm of bone and articular cartilage [osteosarcoma]

185 Malignant neoplasm of prostate [primary or salvage therapy]

189.0 - 189.9 Malignant neoplasm of kidney and other and unspecified urinary organs [renal cancer]

191.0 - 192.9 Malignant neoplasm of brain and other and unspecified parts or nervous system [central nervous system diseases/disorders]

197.7 Malignant neoplasm of liver, specified as secondary [liver metastasis from colon and stomach cancer]

198.82 Secondary malignant neoplasm of genital organs [primary or salvage therapy of prostate]

233.4 Carcinoma in situ of prostate [primary or salvage therapy]

241.0 - 241.9 Nontoxic nodular goiter

242.00 - 242.41 Toxic nodular goiter
320 - 389.9 Diseases of the nervous system and sense organs [central nervous system diseases/disorders]

430 - 438.9 Cerebrovascular disease [central nervous system diseases/disorders]

600.00 - 600.91 Hyperplasia of prostate [benign prostatic hypertrophy]

624.01 - 624.09 Dystrophy of vulva

720.0 - 724.9 Dorsopathies [central nervous system diseases/disorders]

800.00 â€“ 829.1 Fractures

997.02 Iatrogenic cerebrovascular infarction or hemorrhage [central nervous system diseases/disorders]

The above policy is based on the following references:


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