HEALTH TECHNOLOGY ASSESSMENT:
HIGH INTENSITY FOCUSED ULTRASOUND ABLATION FOR
PROSTATE CANCER TREATMENT

SUMMARY

Methods and description of the evidences used. The rapid assessment was based primarily on a basic systematic literature search in the following sources: • Cochrane Library database; • PubMed (Medline); • CRD database; • Hand searches including articles from the manufacturers.

The systematic literature search was conducted in March-May in 2015, with time limitation from 2011. Also, some information for the HIFU assessment was updated and used from the AGENAS (Agenzia nazionale per i servizi sanitari regionali, Italy) HTA report “HIFU for the treatment of prostate cancer”.

Relevant articles for the ‘Safety’ and ‘Clinical effectiveness’ domains were selected by the VASPVT (State Health Care Accreditation Agency under the Ministry of Health, Lithuania) and checked by the LBI-HTA (Ludwig Boltzmann Institute-Health Technology Assessment, Austria). References were included or excluded according to the PICO-scheme.

For assessing the quality of systematic reviews, the AMSTAR checklist for systematic reviews was used. The quality of case series was assessed using the IHE checklist for case series and the quality of randomized-controlled trials (RCT) was assessed using Consort 2010 checklist and the Cochrane risk of bias checklist for RCTs.

Substantiation for Health Technology Assessment. Prostate cancer often has no early symptoms and starts out as a pre-cancerous condition – changes in prostate gland cells that could be seen under the microscope. Prostatic cancerous cells form into malignant tumors or masses, which then overwhelm surrounding tissues or metastasize. However, advanced prostate cancer can cause frequent urination or a weaker flow of urine, but these symptoms can also be caused by benign prostate conditions. The main risk factors in the development of prostate cancer are race (ethnicity), family history and age. The impact of prostate cancer in an aging population is expected to increase, even if the incidence rate were to remain constant. There will also be an increased need for financial and human resources such as treatment facilities and trained specialists.

Target population for prostate cancer HIFU treatment includes men of all ages with diagnosed malignant prostate cancer. Prostate cancer is the most common cancer in Lithuanian men, nearly 3.000 men are newly diagnosed with prostate cancer and about 500 deaths occur from this disease annually.

High Intensity Focused Ultrasound Ablation (HIFU). According to scientific researches, HIFU is recommended for primary treatment of histologically proven localized prostate cancer (stage T1–T2N0M0, Gleason score ≤4+3) with undergone magnetic resonance imaging (or TRUS) and biopsies in patients who are not suitable for surgery because of age, co-morbidity, or patients refusal; for salvage prostate cancer treatment after biopsy-proven local recurrence when life expectancy is at least 10 yrs. and there is no evidence of metastatic disease on clinical and
radiographic evaluation. While HIFU therapy is considered as an experimental treatment by The European Association of Urology and The American Urological Association, patients with T3–T4 stages and combined treatment (e.g. chemotherapy, TURP, etc.) can be included into clinical studies.

The HIFU technique has been studied for 50 years, since the 1990s, HIFU has been investigated for the treatment of benign prostatic hyperplasia and prostate cancer and with recent technological developments in imaging technologies it allows to treat tumors of prostate, liver, kidneys, pancreas and other sites. However, HIFU is only useful to treat a single tumor or part of a large tumor and it cannot be used to treat metastasis. The major application of HIFU clinically is for the treatment of benign and malignant solid tumors, and there are different types of HIFU device models that are being used for different clinical indications around the world e.g., according to manufacturers JC/ JC200 (Chongqing Haifu Tech Ltd., China) models are being used for liver, kidney, breast, pancreas, bone, soft tissue cancer, uterine fibroids, uterine adenomyosis; Ablatherm (EDAP TMS S.A., France) for prostate gland cancer; Sonablate500 (Focus surgery Inc., USA) – prostate gland cancer and etc.

The key of HIFU treatment is to deliver the energy required to raise the tissue temperature to a cytotoxic level sufficiently fast such that the tissue vasculature does not have a significant effect on the extent of cell killing. HIFU uses precisely focused ultrasound waves which raise the temperature of the targeted prostate tissue to 80–98 °C in 2–3 seconds, causing the cancerous cells to be destroyed while leaving the healthy structures surrounding the prostate undamaged. The typical duration of treatment is 1.5–3 hours. The typical staff is composed by: urologist, anaesthetist and one or two nurses. HIFU procedure can be repeated over time and treatment involves a short operation in the operating room under general or spinal anesthesia and can be performed in day-surgery or outpatient settings in virtually all patients.

**Safety.**There is a suggestion that occurrence of adverse events could be related to experience of health professionals. Also, accurate patient selection is an essential pre-condition for achieving optimal cancer control with a focal therapy and selection process should exclude:

- Patients with subclinical, distant metastases;
- Previous rectal surgery preventing insertion of transrectal probe;
- Anal stenosis or any other condition that does not permit the introduction of the HIFU probe in the rectum;
- Intraprostatic calcifications making HIFU of focal areas of cancer difficult.

All adverse events related to HIFU treatment was divided into 4 major groups: urinary tract, rectum, sexual potency and pain. The most often reported adverse events concerning urinary tract are: haematuria (5.5–65%), different grades of urinary incontinence (0.7–35.9%), urinary debris (18–34%), dysuria (22–30%), urinary retention (2–24%), voiding difficulty (9.5–22%), urinary tract infection (0–17%); adverse event concerning rectum is rectourethral fistula (0.4–15.8%); adverse events related to sexual potency are such as not preserved potency (57.7%), erectile dysfunction (5–37%) and erection not sufficient for penetrative sex (11%). Pain related adverse events were not reported in any of case series published from 2011 and included in this assessment. It should be noticed that catheter after the HIFU treatment, mentioned almost in all of the studies was not considered as a complication; however, if there was no need for catheterization, the hospital stay after focal therapy was shorter.

There is no lifetime dose limit allowing HIFU to be repeated if necessary, but at the same time many studies reported higher rates of overall toxicity observed with salvage HIFU compared with its use in the primary setting. The most frequently reported complications associated with salvage HIFU treatment were urinary incontinence and rectourethral fistula. Also, some additional information about underlying factors that increase the rate of complications was found.

**Clinical effectiveness.** PSA level reduction after HIFU therapy is temporary – from the first there is a significant difference (p<0.05) in the reduction of PSA level, but 4-year biochemical recurrence-free rate (after Ablatherm salvage treatment) was 67%, 5-year (after Sonablate500 salvage and Ablatherm primary treatment, respectively) – 73.3–85%, 7-year (after Ablatherm
primary treatment) – 79%, 10-year (after Ablatherm primary treatment) – 60%, according to the Phoenix criteria (a rise by 2 ng/ml or more above the nadir PSA).

Negative biopsy rates after HIFU ranged from 63% to 95.5%; however, prostate cancer-free progression rates at 4-year (after Ablatherm salvage treatment) were 47.4–67%, at 5-year (after Ablatherm primary treatment) – 64%, at 7-years (after Ablatherm primary treatment) – 54%, at 10-year (after Ablatherm primary treatment) – 97%.

Reproductive functions were assessed by International Index of Erectile Function (IIEF-15 and IIEF-5) questionnaires. Almost all of the studies reported a significant reduction in IIEF-15 or IIEF-5 scores, which means the reduction of the proportion of men capable to have erectile function sufficient for penetration at the end of follow-up. Crouzet et al. reported that potency was preserved (IIEF ≥17) in the 42.3% of patients with a baseline IIEF score ≥17 without pharmacologic aid.

Investments and tools required to use the technology. The HIFU therapy is reimbursed by health insurance in some European countries. However, HIFU procedure has no specific code in DRG system; therefore, “Transurethral prostatectomy” was chosen close to the HIFU procedure, which is attributed to outpatient treatment. Medium-term transurethral prostatectomy with extremely severe complications (L05A) in Lithuania costs 1828.43 €, and without extremely severe complications (L05B) – 695.83 €.

The cost of HIFU device depends on HIFU model and manufacturer, e.g. Ablatherm (EDAP TMS S.A., France) costs 550,000 €, Sonablate500 (Focus surgery Inc., USA) – 300,000 €, and JC/JC200 (Chongqing Haifu Tech Ltd., China) – 1,650,000 €. Maintenance cost for the same HIFU devices are 45,000 €/ yr., 25,000 €/ yr. and 8,000 €/ yr., respectively. All main supplies needed to use HIFU technology come together with the HIFU device, except disposable accessories such as condoms, coupling fluid and etc.

Conclusions:
1. Three devices are presently available for the treatment of prostate cancer – Ablatherm (EDAP TMS S.A., France), Sonablate500 (Focus surgery Inc., USA) and Focal One (EDAP TMS S.A., France). Other HIFU device models (e.g. JC or JC200 (Chongqing Haifu Tech Ltd., China)) can be used for different clinical indications.
2. The cost of HIFU device depends on HIFU model and manufacturer, e.g. Ablatherm (EDAP TMS S.A., France) costs 550,000 €, Sonablate500 (Focus surgery Inc., USA) – 300,000 €, and JC/JC200 (Chongqing Haifu Tech Ltd., China) – 1,650,000 €. Maintenance cost for the same HIFU devices are 45,000 €/ yr., 25,000 €/ yr. and 8,000 €/ yr., respectively.
3. Adverse events related to the HIFU treatment could be divided into 4 major groups: urinary tract, rectum, sexual potency and pain. The most important and severe adverse events are incontinence and rectourethral fistula.
4. Urinary tract symptoms and the proportion of men capable to have erectile function sufficient for penetration are getting worse after HIFU treatment comparing preoperative values and those at the end of follow-up.
5. PSA level reduction after HIFU therapy is temporary – at the beginning there is a significant difference (p<0.05) in the reduction of PSA level, but 4–10-year biochemical recurrence-free rate varies from 60% to 85%.

Recommendations:
1. The results from case series require confirmation in well designed, prospective trials of sufficient size with appropriate end points and lengths of follow-up. Until data of this level becomes available, the use of HIFU should be restricted to clinical trials, and to patients for whom other local curative treatment options are not suitable.
2. When evidence will be available and support the use of the HIFU technology, we recommend defining strategies to gather all the related costs to calculate proper HIFU-specific reimbursement fees.