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A review of high intensity focused ultrasound in relation to the treatment of renal tumours and other malignancies

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ABSTRACT

For 60 years, high-intensity focused ultrasound (HIFU) has been the subject of interest for medical research. HIFU causes tissue necrosis in a very well defined area, at a variable distance from the transducer, through heating or cavitation. Over the past two decades, the use of high-intensity focused ultrasound has been investigated in many clinical settings. This review summarises recent advances made in the field of renal cancer in particular, and gives an overview on the use of the extracorporeal machines in the treatment of other malignant tumours.

1. Introduction

Historically surgery has been the most effective local therapy for solid malignancies although the treatment will often include a combination of different approaches including chemotherapy, immunotherapy and radiotherapy. All of these treatments are associated with significant side effects and this has led to an ongoing quest for safer, better tolerated alternatives.

In recent years, there has been a notable shift away from open surgery towards less invasive techniques involving laparoscopic and robotic surgery, and from there to other methods for *in situ* tumour destruction often involving energy based destruction. These include embolisation, radiofrequency, microwave and laser ablation, cryoablation and HIFU. HIFU is the only one of these capable of completely non-invasive ablation. In contrast to ionising radiation, HIFU treatment can be given more than once as there is no upper limit of tissue tolerance to repeated ultrasound exposure. There are very few side effects of treatment, and serious adverse events are rare.

High-intensity focused ultrasound relies on the same principles as conventional ultrasound. It can propagate harmlessly through living tissue, but if the ultrasound beam carries sufficient energy and is brought into a tight focus, the energy within that focus can cause a local rise in temperature, which is sufficiently high to cause tissue necrosis (a 'lesion'). This occurs without damage to surrounding or overlying tissues. The ability to cause cell death in a volume of tissue distant from the ultrasound source makes HIFU an attractive option for development as a non-invasive surgical tool.

Ultrasound causes tissue damage through two mechanisms: heat and cavitation. As an ultrasound beam propagates through a tissue, some of its energy is deposited as heat, but in normal circumstances, this heat will dissipate rapidly. If the rate of heating exceeds the rate of cooling, the result will be a local temperature rise. Above a threshold of 56 °C, thermal toxicity occurs, with reproductive failure preceding irreversible cell death through coagulative necrosis. In the context of HIFU, the temperature at the focus can rise rapidly above 80 °C [1], which, even the shortest exposures should lead to effective cell killing [2]. There is a steep temperature gradient between the focus and neighbouring tissue, which is demonstrated by the sharp demarcation between the lesion and normal surrounding cells on histology. The cooling effect of perfusion, which limits the reliability of other forms of hyperthermia treatment, can be practically eliminated by keeping exposure times below three seconds [3].

Acoustic cavitation is complex, and unpredictable, but the end result is also cell necrosis through a combination of mechanical stresses and thermal injury. Ultrasound causes the tissues to vibrate, and the molecular structure is subjected to alternating compression and rarefaction. During rarefaction, gas can be drawn out of solution to form bubbles, which oscillate in size, or collapse rapidly, causing mechanical stresses and generating temperatures of up to 2000–5000 K in the microenvironment [4]. Cavitation is dependent, amongst other things, on pulse length, frequency and intensity [5], so is unlikely to occur with diagnostic ultrasound, but is a factor when using HIFU. The effect of heating is both

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repeatable and more predictable than cavitation [6], which makes it the preferred mode of action in most clinical applications of HIFU.

2. History of HIFU

The history of HIFU goes back more than a century to 1880 when Jacques and Pierre Curie reported the phenomenon of piezoelectricity [7]. In 1920 Langevin demonstrated the potential of piezoelectric materials as sources of ultrasound [8] and in 1927 Wood and Loomis first described the biological effects of high-intensity ultrasound [9]. In 1942 Lynn et al. [10], published the first paper which highlighted some of the possible applications of HIFU and in the next decade William Fry was able to produce lesions deep in the brains of cats and monkeys [11,12]. His brother Frank subsequently treated patients with Parkinson's disease and other neurological conditions [13].

The first suggestion that HIFU could be used for treating cancer came from Burov in 1956 [14], and in the following years several studies looked at the effects of ultrasound on tissues [15]. The specific properties of focused ultrasound conduction, and modes of destruction in normal tissues were investigated further during the 1970's and 1980's [16–18], and studies using HIFU to treat experimental tumours followed [19,20].

At the current time three main categories or HIFU device available for clinical use. Extracorporeal and transrectal machines have been available for a number of years and now phased array transducers that fit over the skull and are able to target focal areas in the brain are just coming into clinical use. Extracorporeal devices have been used to target many abdominal organs, and require a longer focal length. For this reason, they tend to employ transducers of larger dimensions, which operate at lower frequencies with higher intensities than their transrectal equivalent. Transrectal devices are used primarily to treat the prostate.

This review will look first at the work carried out on kidney and liver cancer and then review other applications for the treatment of malignant tumours.

3. Kidney

There have been many small animal studies in which benign and malignant tissue has been destroyed within the kidney [21–25], and also a number of studies in which the normal kidney tissue of large animals has been targeted [26,27,22]. Vallancien et al. treated four patients with renal cell carcinoma [28], but in all of these preliminary works, there were problems with skin damage, and wide variation in the extent of tissue ablation.

Susani et al. included two patients with a renal tumour in a phase I trial [29]. They claim accurate placement of lesion, but detail is sparse. In a more recent study, Daum et al. accurately created 7 lesions of $0.5 \times 0.5\ cm^2$ in the kidneys of two pigs *in vivo* [30]. In a human phase I trial, Koehrmann et al. targeted 24 kidneys and created lesions reliably enough to proceed to treat a patient with a single renal tumour. They caused coagulative necrosis, which was detectable on MRI at 17 days, and which had almost disappeared at nine months [31].

More recently an number of phase 1b and 2a trials have been carried out in Oxford looking at HIFU for renal tumours [32,33]. The first of these studies was designed to evaluate the safety and feasibility of the extracorporeal ultrasound-guided Model-JC Tumor Therapy System (Chongqing HAIFU™, China) in a Western population [32]. Eight patients with renal tumours underwent a single therapeutic HIFU session under general anaesthesia. Magnetic resonance imaging 12 days after treatment provided assessment of response. The patients were subdivided into those followed up with further imaging alone (three patients) or those undergoing surgical resection of their tumours (five patients), which enabled both radiological and histological assessment. HIFU exposure resulted in discrete zones of ablation in 67%. This first clinical study of HIFU for renal tumours demonstrated that the adverse event profile was favourable when compared to more invasive techniques. The next study carried out in Oxford by Richie et al. [33] investigated the use of HIFU for the management of small renal tumours over a three year period. This study comprised 17 patients with a mean tumour size of 2.5 cm with an initial radiological diagnosis of renal malignancy. The patients underwent extracorporeal HIFU using the same device under general anaesthetic. Patients were followed up with gadolinium enhanced MRI at 12 days and every six months for a mean of 36 months. Two of the 17 patients were abandoned due to intervening bowel precluding safe administration of HIFU and one patient had surgery due to persistent enhancement of the tumour. 14 patients were available for evaluation at six months and eight tumours had involuted. Four patients had other treatment due to irregular enhancement on subsequent imaging suggesting incomplete ablation of the tumour while the others maintained loss of enhancement and a mean decrease of 30% in the tumour area. This study showed that HIFU achieved stable lesions in two thirds of patients with minimal morbidity. A further study was then carried out in whereby patients with renal tumours less than 4 cm were initially treated with HIFU and then the tumours were resected surgically (by a partial nephrectomy) and the subsequent specimens examined histologically. This study showed similar findings to the previous study with variable degrees of ablation depending on other factors, mainly the degree of subcutaneous and perinephric fat and the position of the tumour in relation to the ribs. To investigate the first of these problems, ten patients undergoing renal cancer surgery had the perinephric fat examined separately to see the percentage output drop in energy as the thickness of the fat increased. The attenuation was significant and it decreased from 58% at 2 cm to 26% at 5 cm [34]. Thus high acoustic outputs are needed to compensate for this intensity loss which in turn will lead to an increased risk of pre-focal and surrounding tissue damage and subsequent loss of image quality due to the pre focal swelling. So it is important to take careful account of perinephric fat thickness when planning kidney HIFU and in due course there will be techniques developed to compensate for this.

Theoretically a patient with a renal transplant should be easier to treat as the kidney is placed in the iliac fossa with no overlying ribs, and the perinephric fat is removed before the transplant. Renal tumours in transplant kidneys are rare but do occur, and the standard management is transplant nephrectomy, although in some situations, especially for a small tumour, a partial nephrectomy is possible. Two renal transplant patients have been treated in Oxford with HIFU. The first was unsuccessful and the patient suffered skin burns due to technical problems from malpositioning of the water balloon between the transducer and the patient. The second patient [35] had a good technical result with lack of contrast uptake on the gadolinium enhanced MRI scan. A further biopsy of the lesion was taken and further malignant cells were seen, so a partial nephrectomy was performed. Histological review of the specimen demonstrated 90% ablation of the tumour with a small rim of viable tumour cells still present.

4. Liver

Primary and secondary liver tumours are amongst the most common malignancies in the world and hepatic metastases are the most common cause of death in cancer patients. Surgery still remains the key treatment as the response to other therapies