Systematic review of the role of high intensity focused ultrasound (HIFU) in treating cancerous lesions of the hepatobiliary system

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Abstract

Aims:
High intensity focused ultrasound (HIFU) is an emerging non-invasive, targeted treatment of malignancy. This review aims to explore the efficacy, safety and optimal technical parameters of HIFU to treat cancerous lesions of the hepatobiliary system.

Methods:
A systematic search of the English literature was performed until March 2020, interrogating Pubmed, Embase and Cochrane Library databases. The following key-words were input in various combinations: 'HIFU', 'High intensity focussed ultrasound', 'Hepatobiliary', 'Liver', 'Cancer' and 'Carcinoma'. Extracted content included: Application type, Exposure parameters, Patient demographics, and Treatment outcomes.

Results:
Twenty-four articles reported on the clinical use of HIFU in 940 individuals to treat cancerous liver lesions. Twenty-one series detailed the use of HIFU to treat hepatocellular carcinoma. Mean tumour size was 5.1cm. Across all studies, HIFU resulted in complete tumour ablation in 55.32%. Data on technical parameters and the procedural structure was very heterogeneous. Ten studies (n=537) described the use of HIFU alongside other modalities including TACE, RFA and PEI; 66.11% of which resulted in complete tumour ablation. Most common complications were skin burns(15.42%), local pain(5.00%) and fever(1.60%).

Conclusions:
HIFU has demonstrated benefit as a treatment modality for cancerous lesions of the hepatobiliary system. Combining HIFU with other ablative therapies, particularly TACE, increases the efficacy without increasing complications. Future human clinical studies are required to determine the optimal treatment parameters, better define outcomes and explore the risks and benefits of combination therapies.

Introduction

High-intensity focussed ultrasound (HIFU) is a non-invasive therapeutic modality that relies on the biophysical effects of ultrasound propagation to bring about change to cellular micro- and macro-environments. HIFU has been used in many and varied disease processes. It has been widely used as a cancer therapy in prostate, hepatobiliary and breast tumours. However it can also be used in the treatment of benign disease such as uterine fibroids and neurological disorders including neuropathic pain and parkinsonian tremor.

The technology uses ultrasound waves typically in the frequency range 0.5 to 2 megahertz(MHz). As the ultrasound waves propagate through tissue they are partly absorbed and converted to thermal energy, HIFU exploits this bioeffect in order to heat millimetric volumes of tissue and induce coagulative necrosis. The extent of tissue damage is dependent on both the temperature reached and exposure time. Typically, the temperature of the target tissue will be raised to above 55°C and maintained for at least 1 second(1). Upon repeated sonication the focal volume can be thermally ablated, whilst leaving surrounding tissues intact. This is an attractive feature of HIFU for the treatment of cancerous tumours and benign conditions.

Focusing of the ultrasound beam is employed in order to obtain localised and sharply defined ablation of tissue. This can be achieved by using high output power, single-element piezo-electric materials with an acoustic lens. These lenses work analogously to a magnifying glass to create a convergent beam(2). Moreover, electronic steering of the acoustic beam and the treatment of clinically relevant volumes can be accomplished through the use of phased array technology. Phased arrays employ multiple transducers allowing for a variable focal length and beam steering in different directions. Since acoustic waves are more readily absorbed at higher frequencies, varying the ultrasound frequency and acoustic lens properties, allows for adjustment in the depth targeted. Frequencies as low as 0.5 MHz can be used for deep targets, whilst frequencies above 1 MHz are optimal for shallower ones(3).

The potential applications for HIFU treatment have significantly increased with the advent of modern imaging modalities; ultrasound and MRI are both used to guide and monitor HIFU beams. The ability of HIFU to target deep seated tumours has made it particularly attractive in cancer treatment, specifically in hepatobiliary tumours where it has been used to ablate hepatocellular carcinomas.

HIFU offers a number of benefits over alternative cancer treatment methods. Firstly HIFU is highly focused and spatially confined, hence minimising damage to surrounding tissues. Treatments are usually carried out in a single session, often as a day case so patients avoid prolonged stays in hospital. HIFU can be performed under general or epidural anaesthesia depending on tumour size, location and patient preference.. HIFU presents many advantages over surgery; it can target hard to reach areas, reduce risks of bleeding and infection, and there is reduced post-operative scarring and/or pain. HIFU is also trackless, compared to other ablative therapies, meaning it does not require an applicator onto the target area directly(2). Therefore, it does not carry the risk of cancer spread via seeding along the needle track associated with percutaneous ablation techniques.

This systematic review aims to detail the published literature on current HIFU modalities used in hepato-biliary cancer treatment and the outcomes achieved. We will provide discussion on the most effective parameters, and whether HIFU has the potential to be an efficacious treatment modality; both alone and in conjunction with other existing therapies.

Materials and methods

This study was completed following the Preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (www.prisma-statement.org/)(4).

Search strategy

A systematic search of the English literature was performed until March 2020, interrogating the Pubmed, Embase and Cochrane Library databases. The following key-words were input in various combinations during the search: 'HIFU', 'High intensity focussed ultrasound', 'Hepatobiliary', 'Liver', 'Pancreas', 'Gallbladder', 'Cancer' and 'Carcinoma'. Results were limited to English language articles and published within the last 11 years only. An example of the Medical Subject Headings (MeSH terms) used to search the PubMed database is shown in *box 1*.

***Box 1*: Search strategy in PubMed database**
1) ((((HIFU) OR High intensity focused ultrasound) AND "last 10 years"[PDat] AND Humans[Mesh] AND English[lang])) AND (((((Hepatobiliary) OR Liver) OR Pancreas) OR Gallbladder) AND "last 10 years"[PDat] AND Humans[Mesh] AND English[lang])
2) ((((HIFU) OR High intensity focused ultrasound) AND "last 10 years"[PDat] AND Humans[Mesh] AND English[lang])) AND (((Cancer) OR Carcinoma) AND "last 10 years"[PDat] AND Humans[Mesh] AND English[lang])
3) 1 AND 2

Study selection

Two reviewers (AS and SF) independently completed database searches to identify potentially relevant articles. The collated articles were screened initially by title and abstract, which were compared hierarchically to the predefined inclusion and exclusion criteria listed below. Pertinent full text articles were obtained and then reviewed for eligibility. Any disagreement between the reviewers was resolved through discussion. HIFU was occasionally used in conjunction with other treatment modalities, studies using either HIFU alone or with other systems were both included. Reported cases in any age group were included, hence there are some paediatric cases included below.

Exclusion criteria: (I) Not relevant to HIFU, (II) Not relevant to Hepatobiliary system, (III) Not Human clinical studies, (IV) Missing important data (e.g. Parameters of HIFU, patient demographics, outcomes), (V) letters/case-reports/editorials/reviews, (VI) Non-English texts, (VII) Older than 11 years.

Data extraction

Data was extracted from located articles based on a predefined electronic data extraction form (Microsoft Excel 365 ProPlus). Extracted content included: First author, Publication year, Type of application of HIFU, Exposure parameters (treatment dose), Patient demographics, and Outcomes of treatment.

Results

Study selection

The initial literature search yielded 2061 total records, across the different search platforms (Pubmed n=1393, Embase n=19, Cochrane library n=649) . After Initial screening and duplicate removal 1176 remained. Following manual abstract screening 1111 records were excluded; leaving 65 pertinent articles. The full text copies of the remaining 65 articles were obtained and scrutinized according the previously listed exclusion criteria. At this stage, n=31 were not relevant to liver/hepatobiliary cancers, n=1 was an animal study, n=6 was non-clinical (technical) study, n=1 was an ongoing trial with insufficient data, and n=2 did not have English full texts. Thus a total of twenty-four articles were identified and included for data extraction, as summarised in *figure 1*.

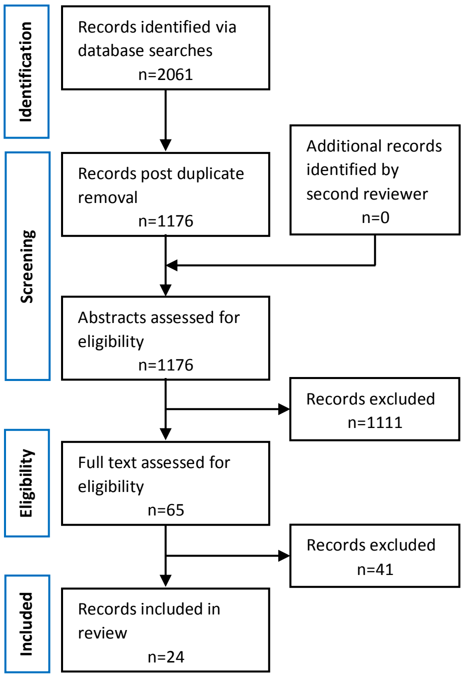

Figure 1: Study selection flow diagram according to PRISMA statement

Twenty-four articles reported on the clinical use of HIFU ablation to treat cancerous liver lesions(5-28), covering a total of 940 cases. However the total number of patients treated using HIFU for liver lesions is much larger, as this review only covers articles published between 2008-2020 and also excluded non-English texts. Twenty-one studies were on HIFU treatment of hepatocellular carcinoma (HCC) only, whilst three covered other hepatobiliary cancers or combined treatments(23, 25, 26); hepatoblastoma, HCC and cholangiocarcinoma, and HCC and hypersplenism respectively.

Demographic data

The mean age of patients treated was 56.78 years with a majority having Child-Pugh class A pathology (74.51%). All cases of Child-Pugh class B or C pathology were in patients with HCC. However there was still great diversity in the 940 patients' data was collected about; with ages ranging from 0.25-84 years, this includes 12 paediatric cases of hepatoblastoma. Tumour size was equally variable spanning 0.8-18cm in diameter, with a mean size of 5.10cm. Complete demographic data from all twenty-two articles is summarised in *table 1*.

Table 1: Demographic data

Characteristics	Overall	Hepatocellular Carcinoma	Hepatoblastoma	Cholangiocarcinoma
Patients, n	940	924	12	4
Age (years), mean (range)	56.78 (0.25-84.00)	57.50 (23.00-84.00)	1.70 (0.25-4.17)	n/a

Tumour size (cm), mean (range)	5.10 (0.80-18.00)	4.98 (0.8-18.00)	11.70 (6.50-14.70)	n/a
Child Pugh score, A/B/C (%A/%B/%C)	603/169/41 (74.51/20.60/4.82)	603/169/41 (74.51/20.60/4.82)	n/a	n/a

Procedural structure

Although most studies looked at the use of HIFU alone as an end treatment for HCC, there were some variations on this structure and other components of the study design which we will describe here. Five studies looked at the use of HIFU together with TACE (Transcatheter arterial chemoembolization) (15, 18, 23, 27, 28), in all instances HIFU treatment was performed 1-4 weeks after TACE procedure. One study looked at sequential treatment with TACE followed by 3D-CRT(three-dimensional conformational radiotherapy), and then HIFU (20). In four studies HIFU treatment took place after other treatments including RFA(radiofrequency ablation), PEI (percutaneous ethanol injection), hepatectomy or TACE (5, 6, 16, 24). HIFU was also studied for its use as a bridging therapy, whilst patients waited for liver transplant (6, 9, 14).

The HIFU ablation procedure was performed most often under general anaesthesia (n=748 cases) across eighteen studies(5-10, 14, 17-24, 26-28), whilst two studies used only epidural anaesthesia (n=25 cases)(11, 12). Four studies used either general or epidural anaesthesia (n=167 cases)(13, 15, 16, 25). To maximise the transmission of HIFU waves and reduce complications namely burns, a number of techniques were employed. Artificial right pleural effusion was created via injection of 6-800ml of saline into the right thoracic cavity in 101 patients (18, 19, 23, 24, 26, 27). Whilst partial rib resection, approximately two weeks before HIFU treatment, was reported in 53 cases (13, 15). Two studies reported using artificial pleural effusion or ascites in certain cases, without detailing the number of patients (5, 7). Assessment of ablation post HIFU treatment was done via MRI alone in nineteen studies (n=728 cases)(5, 6, 8-10, 12-15, 17-20, 22, 24-28), CT alone in one study (n=14 cases)(11) or either of the two modalities in four studies (n=198 cases)(7, 16, 21, 23).

HIFU technical and exposure parameters

In all of the twenty-four articles studied, guidance and monitoring of ablation was completed using ultrasound. The diagnostic ultrasound probe, usually operating at 3.5MHz, provided a grey-scale image of the lesion and surrounding tissue. Changes in the image were used to assess whether ablation had taken place. One study(12) also used colour Doppler alongside B-mode ultrasound, and concluded that this was useful in determining the original location of tumours, if multi-reflections or the appearance of a hyperecho resulted in poor visualisation. No clinical CT or MRI-guided procedures were reported on.

HIFU exposure parameters, i.e., frequency (MHz), exposure time (s), Transducer aperture (mm), focal length(mm), Acoustic power (W), were highly variable depending on the study, even when considering groups of homogenous patients. Choice of exposure parameters across all the studies focussed on: desired focal depth, sufficient power to thermally ablate the given lesion, and location of acoustic window such that the amount of bone or fat between the source and target is minimal to limit local adverse effects. One commonality across the articles collected was the HIFU system; Haifu Model-JC Focused Ultrasound Tumor Therapeutic System, Chongqing HIFU Technology Co Ltd. This model is able to deliver an acoustic power of up to 300W which, although variable, results in a focal peak intensity of approximately 20,000W/cm^2. A common parameter amongst most studies was the frequency of ultrasound waves used, sixteen studies (66.67%) operated at 0.8MHz frequency, with all studies operating HIFU at 0.8-1.8 MHz. Other variables such as exposure time (s), transducer aperture (mm), focal length (mm) and acoustic power (W) varied significantly or were not reported on in enough detail. Exposure parameters used in all the studies are summarised in *table 2*.

Table 2a: HIFU exposure parameters

Study	Frequency (MHz)	Mean Total Exposure time (s)	Exposure time range (s)	Transducer aperture (mm)	Focal Length (mm)	Acoustic Power (W), median (Range)
Chan2013 (5)	0.8				100-160	230-466
Cheung2012 (6)	0.8	2864			120	391
Cheung2013 (7)	0.8				120	
Cheung2014 (8)	0.8	2606	338-7302		120	
Chok2014 (9)	0.8	1560	180-7440		150	376 (155-473)
Numata2009 (10)	1	833	401-1225			300-450
Fukuda2012 (11)	1					
Fukuda2013 (12)	1			200	150	300-450
Zhu2008 (13)	0.8	10080	4260-22680	150	150	160-250
TCheung2013 (14)	0.8				120	
Jin2010 (15)	0.8		3480-14520	120	135-155	160-350
Zhang2008 (16)	0.8			150	150	160-250
Leslie2012 (17)	0.84 / 1.8	1260	12-2640		135/122	140-350
Kim2012 (18)	0.8	3660	1380-16320	150	135	100-400
ng2011 (19)	0.8	1560	180-7440	120	120	376 (155-473)
ni2012 (20)	0.8			120	150	
TCheung2012 (21)	0.8	1478	135-7487		120	371 (120-473)
wang2010 (22)	0.9	720	360-1260	200	120	200-400
Wang 2013 (23)	0.8		1800-12120	120	135-155	181-256
Xu2011 (24)	0.8 / 1.6	4680	2700-9000		100-135	160-240
Zhu2013 (26)	0.8	1985	611-4182	120	135 / 155	250-400
QZhang2019(27)	0.96					
Luo2019(28)	0.8		4946-16223		150	

Table 2b: Average HIFU technical parameters

Mode Frequency (MHz)	Mean Total Exposure time (min)	Mode Transducer aperture (mm)	Mode Focal Length (mm)	Mean Acoustic Power (W)
0.8	**49.3**	**120**	**120**	**323.45**

Outcomes

Tumour ablation rates for each study, as assessed by post-procedure imaging (MRI and/or CT), are presented in *table 3*. There was great variability in tumour ablation rates, coupled with the inhomogeneous treatment protocols, HIFU technical parameters and patient characteristics no clear relationships could be established. Of all HIFU treatment procedures 55.32% resulted in complete tumour ablation, and 44.67% did not achieve complete tumour ablation.

Data on the survival of patients post-procedure, both overall survival and disease-free survival, was only provided by some of the studies researched. Overall survival data, as a percentage of all patients treated with HIFU, was provided by eleven studies reporting on 480 cases and is presented in *table 4*. Mode follow up was three years, however four studies followed up patients for 5 years. Survival data is difficult to compare across the cohort, as we cannot take into account, stage, grade, size and position of tumour as well as comorbidities or patient demographic. Nonetheless we can see that overall survival at years one, three and five was 79.3%, 55.3% and 21.6% respectively.

In many of the studies HIFU was used as an adjuvant or secondary treatment(5, 6, 15, 16, 18, 20, 23, 24, 27, 28) and in a few studies as a bridging therapy(6, 9, 14). However there were some studies which directly compared HIFU with RFA or TACE treatment. HIFU treatment alone has been compared with TACE by Cheung et al (8, 14), In both of these studies there was a higher rate of complete tumour ablation and increased survival in the HIFU group. Chan et al (5), performed a prospective clinical trial which directly compared HIFU against RFA in the treatment of recurrent HCC. This study highlighted similar efficacy with both approaches, with slightly reduced side effects in the HIFU treatment group. Both Luo et al(28) and Zhang et al(27) demonstrated that HIFU combined with TACE has superior ablation outcomes than TACE alone and the later showed improved five year survival rates

There is some evidence to suggest that the combination of HIFU with other ablative therapies, particularly TACE, is more effective than any alone. In combination studies, HIFU in conjunction with TACE, RFA or PEI, complete tumour ablation rate was higher at 66.11% (n=537).

Table 3: HIFU treatment outcomes

Study	Total Number Treated	Complete Tumour Ablation 100% (n)	Incomplete tumour Ablation <100% (n)
Chan2013 (5)	27	23	4
Cheung2012 (6)	1	1	0
Cheung2013 (7)	47	41	6
Cheung2014 (8)	26	13	13
Chok2014 (9)	21	7	14
Numata2009 (10)	21	18	3
Fukuda2012 (11)	14	11	3
Zhu2008 (13)	16	16	0
TCheung2013 (14)	10	9	1
Jin2010 (15)	73	33	40
Zhang2008 (16)	39	21	18
Leslie2012 (17)	31	28	3
Kim2012 (18)	25	5	20
Ng2011 (19)	49	39	10
Ni2012 (20)	120	0	120
TCheung2012 (21)	100	76	24
wang2010 (22)	9	9	0
Wang 2013 (23)	12	10	2
Xu2011 (24)	145	34	111
Zhang2011 (25)	39	28	11
Zhu2013 (26)	9	9	0
QZhang2019(27)	50	45	5
Luo2019(28)	45	38	7
Total	**929**	**514** (55.32%)	**415** (44.67%)

Table 4: HIFU treatment overall five year survival

Study	Overall Survival % (number of surviving patients)				
	1 year	2 years	3 years	4 years	5 years
Chan2013 (5)	96.3 (26)	76.1 (21)	64.2 (17)		

Cheung2013 (7)	97.4 (46)		81.2 (38)		
Cheung2014 (8)	84.6 (22)		49.2 (13)		32.3 (8)
Chok2014 (9)	100 (21)	100 (21)			
Zhu2008 (13)	100 (16)	83.3 (13)	69.4 (11)	55.6 (9)	55.6 (9)
Jin2010 (15)	49.1 (36)	18.8 (14)	8.4 (6)		
Zhang2008 (16)	75.8 (30)	63.6 (25)	49.8 (19)	31.8 (12)	
Ng2011 (19)	87.7 (43)		62.4 (31)		
Ni2012 (20)	75 (90)		35 (42)		15 (18)
Mean	**80.56 (377)**	**60.17 (136)**	**47.88 (214)**	**48.57 (51)**	**39.15 (83)**

Complications

Post-HIFU complications were reported in sixteen(5, 7, 8, 13, 15-21, 23, 24, 26-28) of the twenty-four studies. There were no reported procedure-related deaths. The most common complications were those at the application site; skin burns (15.42%), local pain (5.00%) and fever (1.60%). Post-HIFU pain was a common complication, but was not reported systematically in a quantitative manner across the identified articles, furthermore some articles did not consider 'mild' pain as a complication or did not report on pain at all. Post-procedure pain was generally described as mild in severity and transient in nature. Cheung et al (21), completed a study looking into post-HIFU complications specifically, and provides the most comprehensive coverage of complications in the identified literature. Cheung et al(21) determined that patient age is the only factor found to be significant in HIFU intolerance, and that overall HIFU is a well-tolerated modality. As such patients previously thought to be untreatable surgically due to Child-Pugh B or C disease now have an alternative approach. All data gathered on complications is summarised in *table 5*. How complications were treated was not reported well across the studies, some of the common measures taken have been described in 'procedural structures'.

Table 5: HIFU treatment related complications

Complication	Number of reports
Skin burn at application site (total)	145
1st degree	81
2nd degree	53
3rd degree	7
Unspecified	4
Blistering at application site	3
Bruising at application site	6
Skin oedema at application site	6
Local pain	47
Fever	15
Pleural effusion	8
Pneumothorax	4
Vertebral injury	3
Rib fracture	2
Ascites	2
Acute cholecystitis	2
Liver abscess	2
Variceal bleeding	2
Renal impairment	2

MI	1
Hyperbilirubinemia	1
Chest infection	1

Discussion

HIFU is an emerging technology that offers a new line of treatment for hepatobiliary tumours. Although, more needs to be done to understand the biological effect of the energy source, it has found a place in more advanced liver tumours that may not be suitable for other modalities of treatment. Current modality of choice for unresectable tumours is radiofrequency ablation (RFA) (29-32) with good survival profile following its application (Figure 2). Although HIFU is a new modality, it does offer comparable survival benefit for patients with HCC when compared to RFA therapy. There is room for improvement both to achieve better toumour ablation and to improve overall survival profile. Parametrisation of the HIFU and adjusting it for the tissue ablation seems to be an important factor amongst other known limitations of the device.

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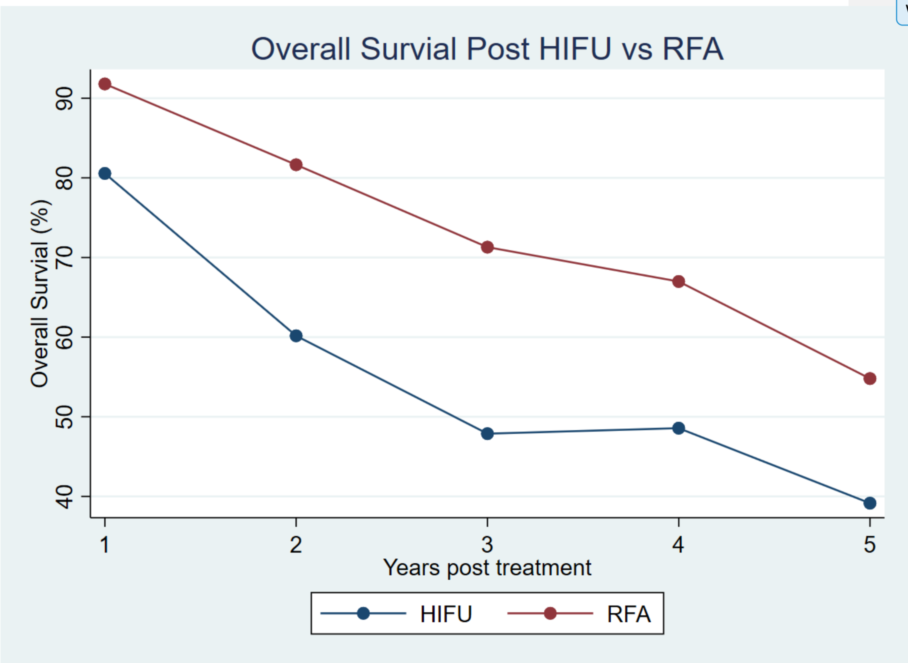

Figure 2 – Comparison of overall survival post HIFU and Radiofrequency ablation (RFA) treatment. RFA is currently considered as an alternative therapy for those unresectable tumours that offers the advantage of relatively low risk and it’s a minimally invasive approach.

Of the searched exposure parameters, three areas showed most concordance; frequency (MHz), Transducer aperture (mm) and Focal Length (mm). The mode frequency was 0.8MHz, mode transducer aperture was 120mm and mode focal length was 120mm. These settings were seen commonly across all of the studies, but more so in those trials with a high percentage of complete tumour ablation(7, 14, 17, 19, 21, 28). The aforementioned studies achieved complete tumour ablation in 71.01% in the 276 cases reported by them. This is significantly higher than the 55.32% complete tumour ablation across all 929 cases where data was provided. This may point to the discovery of clinically effective parameters in three domains; frequency, transducer aperture and focal length. However, the result may be an artefact of the fact that the same HIFU delivery system was used in all of the studies. Moreover all of the other seventeen articles studied had similar settings in the same domains but did not present as high levels of complete tumour ablation.

Exposure time (s) and Acoustic power (W) together give a picture of the treatment dose. These were much more variable across all studies. These are the parameters most likely to be changed depending on each tumour and patient and so are more pertinent in finding optimal HIFU exposure parameters, in a clinical setting. Furthermore details of the settings used per case i.e. tumour size, tumour position, patient comorbidities, were not given. So it is very difficult to comment on the settings which achieved the best outcomes for a particular case. The mean exposure time (s) and median and/or range acoustic power (W) was given by most studies. But these vary greatly and without specific details about each case and the settings used for each case, cannot be compared.

The search for the optimal combination of HIFU set-up and exposure parameters is particularly challenging. The absorption of ultrasound energy depends on the ultrasound excitation frequency and varies amongst different types of tissues. Higher ultrasound frequencies are more readily absorbed by tissue, which results in faster heating of the focal volume but also decreases the ultrasound focal depth. On the other hand, lower frequencies allow for a greater penetration depth but result in lower heat deposition rates(33). Furthermore, ultrasound exposures can be either continuous or pulsed. Different delivery modes of acoustic energy might render different temperature profiles, even if the same amount of acoustic energy is delivered over the same period of time. Likewise, repetition of the same sonication protocol in different organs/locations might also result in different temperature profiles. This can depend on the proximity of the focus to blood vessels, which act as a heat sink by cooling down the focal region, the thermal/acoustic properties of the tissues between the ultrasound source and the focal target, and the status of the background liver. This makes the optimal choice of ultrasound parameters and exposure conditions application dependent(2).

In terms of technical success HIFU is effective with the majority of cases (55.32%) achieving complete tumour ablation. Of the remaining 44.67% a significant portion will have had more than 50% of the tumour ablated. The efficacy of HIFU, particularly in cases where other treatments are suboptimal, has already been affirmed. Here we will discuss two studies with particularly high rates of complete ablation in fairly large numbers of patients. Both studies were conducted by Cheung et al (7, 21) and reported completed ablation rates of 87.23% in 47 cases and 76.00% in 100 cases respectively. Both of these studies are part of the six discussed in the previous section, and so share the same frequency, transducer aperture and focal length. But another similarity between the two studies was the size of HCC targeted Cheung2013(7) had median tumour size of 1.5cm (0.8-2.7) and TCheung2012(21) had median tumour size of 2.2cm (0.9-8.0). Thus both targeted smaller tumours than the average across all studies, 5.10cm (0.80-18.00). This indicates an increased technical success rate in the use of HIFU to treat small hepatocellular carcinomas compared to larger lesions (>3cm).

There is some evidence for increased efficacy of HIFU in combination with other ablative therapies such as RFA, PEI and TACE over its use alone. In particular the use of HIFU alongside TACE has been shown to result in higher rates of complete tumour ablation than either alone in various studies, as highlighted predominantly by Kim et al(18) and Zhang et al(27). Kim et al conducted a randomised control trial comparing TACE alone vs TACE + HIFU, and these results showed an improved disease control rate and a significant survival benefit in those receiving combination therapy. Disease control rate, calculated via the RECIST criteria, was 48% in the HIFU+TACE group compared to 47% in the TACE only group. Median survival time for the HIFU+TACE group was 57 months and only 36 months in the TACE group. Similarly, Zhang et al(27) presents the most recent randomised control trial comparing HIFU+TACE to HIFU alone (n=100), they showed that the HIFU+TACE group had 90% total effective rate (calculated by mRECIST criteria) compared to 60% in TACE alone. Additionally recent meta-analyses(34, 35) on the use of TACE alongside other treatments including HIFU reported in a higher survival compared to TACE alone. There are several theories as to how TACE alongside HIFU improves efficacy, one suggests that TACE reduces arterial flow to the cancerous lesion which in turn reduces heat loss during thermal ablation(36). Another theory suggests that there is an enhanced effect of HIFU on tissues retaining the lipiodol used for TACE(37). However, well-organized randomised control trials are required to confirm these findings, and then elucidate why two treatments in conjunction are more effective than either alone.

The complications occurring due to HIFU were most often due to local effects of heating e.g. skin burns, bruising or pain at the site of delivery. It is thought that this is most likely due to reflection of HIFU waves by the ribs or gas cavity of the right lung, the absorption or reflection of these rays also results in reduced ablative effect at the underlying lesion. Currently the two most common methods of combatting these problems are to surgically remove the rib, and to use an artificial pleural effusion. Both methods are effective and generally safe(21). However the development of newer methods may reduce complications further and increase efficacy of HIFU procedures. One proposed solution is to intermittently have the patient undergo ventilator-controlled breath holding, this can only be completed under general anaesthesia. Another is to use either MR of US-based motion tracking to steer the HIFU beams whilst the patient breathes(38, 39).

The major limitation of this review is the inhomogeneous nature of the articles studied, in terms of exposure parameters, procedural structure and reporting, this makes quantitative analysis and comparison difficult. The reporting of HIFU technical settings was lowest; with only five(13, 18, 19, 22, 26) of twenty-four studies providing all the information sought by our data extraction form, based on the article by Dewhirst et al(1). Hence providing any commentary on the optimum settings for HIFU treatment is very difficult. Furthermore the nature of HIFU, in that the settings have to be adjusted for each case, means that current clinical reporting of averages in diverse patient groups is insufficient to determine which parameters are achieving the best outcomes.

To improve and standardise future analysis of HIFU therapy for liver lesions we propose that future clinical trials should report at least the following: frequency (MHz), exposure time (s), transducer aperture (mm), focal length (mm), acoustic power (W), Intensity (Wcm^2). Moreover, the aforementioned details should be provided for each case if the tumour and patient characteristics are inhomogeneous. Aubry et al proposed a pivotal three-arm clinical trial which would compare TACE alone, HIFU alone and TACE+HIFU(40). This randomised control trial would include patients who are currently not eligible for surgical treatment. This could include those with large lesions (>5cm), more than three lesions, lesions close to major blood vessels or other structures that make resection or RFA difficult, or those with ascites. The trial would report on the above mentioned exposure parameters for each case, on any procedure related complications, and disease control rate calculated using the RECIST criteria. Ablative outcome and any recurrence would be measured using serial imaging (CT or MRI).

Conclusion

HIFU is considered a safe emerging technology with discernible benefits that can be applied to treating cancerous lesions of the hepatobiliary system, particularly in the treatment of HCC. Although the degree of tumour ablation is variable, achieving complete tumour destruction is very much dependent on the HIFU parameters, size and location of tumour ablated. Some benefits over TACE therapy and similar results to RFA have been shown in the literature. But greatest promise lies in the combination of HIFU with other ablative therapies, which has been shown to be more effective than any alone. However further human clinical studies are required to select the optimal technical parameters, as well as better reporting of currently used settings. Alongside this, improvement on the design of the technology and betters modes of delivery of HIFU would improve the complication profile. The clinical application of HIFU is expanding and further research is required to understand the biophysical properties of the technology.

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References

1. Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2003;19(3):267-94.
2. Haar GT, Coussios C. High intensity focused ultrasound: physical principles and devices. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2007;23(2):89-104.
3. Hill CR. Optimum acoustic frequency for focused ultrasound surgery. Ultrasound in medicine & biology. 1994;20(3):271-7.
4. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009;339:b2700.
5. Chan AC, Cheung TT, Fan ST, Chok KS, Chan SC, Poon RT, et al. Survival analysis of high-intensity focused ultrasound therapy versus radiofrequency ablation in the treatment of recurrent hepatocellular carcinoma. Annals of surgery. 2013;257(4):686-92.
6. Cheung TT, Chok KS, Lo RC, Sharr WW, Chan SC, Poon RT, et al. High-intensity focused ultrasound ablation as a bridging therapy for hepatocellular carcinoma patients awaiting liver transplantation. Hepatobiliary & pancreatic diseases international : HBPD INT. 2012;11(5):542-4.
7. Cheung TT, Fan ST, Chu FS, Jenkins CR, Chok KS, Tsang SH, et al. Survival analysis of high-intensity focused ultrasound ablation in patients with small hepatocellular carcinoma. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2013;15(8):567-73.
8. Cheung TT, Poon RT, Jenkins CR, Chu FS, Chok KS, Chan AC, et al. Survival analysis of high-intensity focused ultrasound therapy vs. transarterial chemoembolization for unresectable hepatocellular carcinomas. Liver international : official journal of the International Association for the Study of the Liver. 2014;34(6):e136-43.
9. Chok KS, Cheung TT, Lo RC, Chu FS, Tsang SH, Chan AC, et al. Pilot study of high-intensity focused ultrasound ablation as a bridging therapy for hepatocellular carcinoma patients wait-listed for liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2014;20(8):912-21.
10. Numata K, Fukuda H, Ohto M, Itou R, Nozaki A, Kondou M, et al. Evaluation of the therapeutic efficacy of high-intensity focused ultrasound ablation of hepatocellular carcinoma by three-dimensional sonography with a perflubutane-based contrast agent. European journal of radiology. 2010;75(2):e67-75.
11. Fukuda H, Numata K, Nozaki A, Morimoto M, Kondo M, Tanaka K, et al. Findings of multidetector row computed tomography of HCCs treated by HIFU ablation. European journal of radiology. 2012;81(3):e239-43.
12. Fukuda H, Numata K, Nozaki A, Kondo M, Morimoto M, Maeda S, et al. High-intensity focused ultrasound ablation assisted using color Doppler imaging for the treatment of hepatocellular carcinomas. Abdominal imaging. 2013;38(6):1263-8.
13. Zhu H, Zhou K, Zhang L, Jin C, Peng S, Yang W, et al. High intensity focused ultrasound (HIFU) therapy for local treatment of hepatocellular carcinoma: role of partial rib resection. European journal of radiology. 2009;72(1):160-6.
14. Cheung TT, Fan ST, Chan SC, Chok KS, Chu FS, Jenkins CR, et al. High-intensity focused ultrasound ablation: an effective bridging therapy for hepatocellular carcinoma patients. World journal of gastroenterology. 2013;19(20):3083-9.
15. Jin C, Zhu H, Wang Z, Wu F, Chen W, Li K, et al. High-intensity focused ultrasound combined with transarterial chemoembolization for unresectable hepatocellular carcinoma: long-term follow-up and clinical analysis. European journal of radiology. 2011;80(3):662-9.

16. Zhang L, Zhu H, Jin C, Zhou K, Li K, Su H, et al. High-intensity focused ultrasound (HIFU): effective and safe therapy for hepatocellular carcinoma adjacent to major hepatic veins. European radiology. 2009;19(2):437-45.
17. Leslie T, Ritchie R, Illing R, Ter Haar G, Phillips R, Middleton M, et al. High-intensity focused ultrasound treatment of liver tumours: post-treatment MRI correlates well with intra-operative estimates of treatment volume. The British journal of radiology. 2012;85(1018):1363-70.
18. Kim J, Chung DJ, Jung SE, Cho SH, Hahn ST, Lee JM. Therapeutic effect of high-intensity focused ultrasound combined with transarterial chemoembolisation for hepatocellular carcinoma <5 cm: comparison with transarterial chemoembolisation monotherapy--preliminary observations. The British journal of radiology. 2012;85(1018):e940-6.
19. Ng KK, Poon RT, Chan SC, Chok KS, Cheung TT, Tung H, et al. High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience. Annals of surgery. 2011;253(5):981-7.
20. Ni S, Liu L, Shu Y. Sequential transcatheter arterial chemoembolization, three-dimensional conformal radiotherapy, and high-intensity focused ultrasound treatment for unresectable hepatocellular carcinoma patients. J Biomed Res. 2012;26(4):260-7.
21. Cheung TT, Chu FS, Jenkins CR, Tsang DS, Chok KS, Chan AC, et al. Tolerance of high-intensity focused ultrasound ablation in patients with hepatocellular carcinoma. World journal of surgery. 2012;36(10):2420-7.
22. Wang Y, Wang W, Tang J. Ultrasound-guided high-intensity focused ultrasound treatment for needle-track seeding of hepatocellular carcinoma: preliminary results. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2010;26(5):441-7.
23. Wang S, Yang C, Zhang J, Kong XR, Zhu H, Wu F, et al. First experience of high-intensity focused ultrasound combined with transcatheter arterial embolization as local control for hepatoblastoma. Hepatology (Baltimore, Md). 2014;59(1):170-7.
24. Xu G, Luo G, He L, Li J, Shan H, Zhang R, et al. Follow-up of high-intensity focused ultrasound treatment for patients with hepatocellular carcinoma. Ultrasound in medicine & biology. 2011;37(12):1993-9.
25. Zhang Y, Zhao J, Guo D, Zhong W, Ran L. Evaluation of short-term response of high intensity focused ultrasound ablation for primary hepatic carcinoma: utility of contrast-enhanced MRI and diffusion-weighted imaging. European journal of radiology. 2011;79(3):347-52.
26. Zhu J, Zhu H, Mei Z, Jin C, Ran L, Zhou K, et al. High-intensity focused ultrasound ablation for treatment of hepatocellular carcinoma and hypersplenism: preliminary study. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2013;32(10):1855-62.
27. Zhang Q, Bian SQ, Lv W, Kou D, Hu HL, Guo SS, et al. Observation of efficacy of TACE combined with HIFU on patients with middle-advanced liver cancer. Eur Rev Med Pharmacol Sci. 2019;23(3 Suppl):239-46.
28. Luo Y, Jiang Y. Comparison of Efficiency of TACE plus HIFU and TACE alone on Patients with Primary Liver Cancer. J Coll Physicians Surg Pak. 2019;29(5):414-7.
29. Chen M-S, Li J-Q, Zheng Y, Guo R-P, Liang H-H, Zhang Y-Q, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Annals of surgery. 2006;243(3):321-8.
30. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A Randomized Trial Comparing Radiofrequency Ablation and Surgical Resection for HCC Conforming to the Milan Criteria. Annals of surgery. 2010;252(6):903-12.
31. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57(4):794-802.

32. Fang Y, Chen W, Liang X, Li D, Lou H, Chen R, et al. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. Journal of Gastroenterology and Hepatology. 2014;29(1):193-200.
33. Hill C, Bamber J. Physical Principles of Medical Ultrasonics: John Wiley & Sons, Ltd; 2004.
34. Liao M, Huang J, Zhang T, Wu H. Transarterial chemoembolization in combination with local therapies for hepatocellular carcinoma: a meta-analysis. PloS one. 2013;8(7):e68453.
35. Li L, Tian J, Liu P, Wang X, Zhu Z. Transarterial chemoembolization combination therapy vs monotherapy in unresectable hepatocellular carcinoma: a meta-analysis. Tumori. 2016;2016(3):301-10.
36. Pacella CM, Bizzarri G, Cecconi P, Caspani B, Magnolfi F, Bianchini A, et al. Hepatocellular carcinoma: long-term results of combined treatment with laser thermal ablation and transcatheter arterial chemoembolization. Radiology. 2001;219(3):669-78.
37. Cheng SQ, Zhou XD, Tang ZY, Yu Y, Bao SS, Qian DC. Iodized oil enhances the thermal effect of high-intensity focused ultrasound on ablating experimental liver cancer. J Cancer Res Clin Oncol. 1997;123(11-12):639-44.
38. Hsu A, Miller NR, Evans PM, Bamber JC, Webb S. Feasibility of using ultrasound for real-time tracking during radiotherapy. Med Phys. 2005;32(6):1500-12.
39. Ries M, de Senneville BD, Roujol S, Berber Y, Quesson B, Moonen C. Real-time 3D target tracking in MRI guided focused ultrasound ablations in moving tissues. Magn Reson Med. 2010;64(6):1704-12.
40. Aubry JF, Pauly KB, Moonen C, Haar G, Ries M, Salomir R, et al. The road to clinical use of high-intensity focused ultrasound for liver cancer: technical and clinical consensus. J Ther Ultrasound. 2013;1:13.