Final Publishable JRP Summary Report for JRP HLT03 (DUTy) Dosimetry for Ultrasound Therapy

Overview

Ultrasound is currently used to treat a range of conditions. Over the last decade there has been a dramatic increase in the use of High Intensity Focused Ultrasound (HIFU) for treating cancer, stroke and bone repair. The main side effects of HIFU exposure to tissue are: ablation, caused by temperature increase and cavitation. Currently the techniques required to support the accurate application of a specific therapeutic dose to tissue do not exist, preventing manufacturers and clinicians from calculating the precise amount of ultrasound required for a particular therapy. This may result in over or under treatment of tissue and lead to patient harm, it also prevents the consistent implementation of new techniques and the creation of personalised treatment plans. This project has supported the development of appropriate dosimetry through the development of validated measurement techniques, reference standards and modelling methods for quantifying exposure to ultrasound and the dose to tissue. The new dosimetric framework will support treatments and allow health outcomes from different treatment centres to be correlated.

Need for the project

Ultrasound is the long established treatment of choice for kidney stones, many soft tissue injuries and a range of surgical applications including cataract surgery. The last decade has seen a substantial increase in the use of ultrasound as a surgical and therapeutic tool, many using very high power levels. New applications include High Intensity Focused Ultrasound (HIFU) for tissue ablation for treating prostate cancer without surgery or radiotherapy, stimulation of bone repair by low intensity ultrasound and ultrasound treatment of stroke in conjunction with clot-busting drugs. Other developments include the targeted delivery of drugs through the localised destruction of carrier particles by ultrasound, and the treatment of the condition essential tremor.

In order the exploit the potential of HIFU, there is a pressing need to develop the metrological framework to support well specified, traceable quantities for expressing exposure and dose. Having a traceable dosimetry framework will make it possible to determine dose-response curves and to arrive at robust, personalised treatment plans which maximise the benefits and reduce the undesirable side effects. These will improve patient treatment outcomes, benefit medical equipment manufacturers, giving healthcare providers optimised treatment planning methods.

Scientific and technical objectives

Objectives 1 and 2 set out to develop the metrological infrastructure (definitions, validated measurement and modelling methods) and reference materials (phantoms) to underpin the specification of dose for therapeutic ultrasound applications. Objectives 3 and 4 tested this infrastructure on commercial equipment, and looked at doses through bone and personalising treatment. The specific objectives were:

1. Development of a dose concept for therapeutic ultrasound;
2. Development of phantoms and measurement techniques for testing of dose concepts including the characterisation of measurement methods;
3. Development of test methods for the assessment of commercial machines and comparison of treatment effects and efficiency;

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4. Modelling and validation of linear and non-linear ultrasound propagation through phantoms and anatomical structures;
5. Development of methods to improve the accuracy of the individual treatment including use of anatomical data.

Results

Development of a dose concept for therapeutic ultrasound
A framework for exposure and dose has been developed and published. A common language and definitions for exposure and dose was established through direct consultation with academics, metrologists, regulators, clinicians and manufacturers, supported by a web survey. To develop a terminology for therapeutic ultrasound, different types of physical quantities were categorised: i) free-field (water) exposure quantities, ii) in situ exposure quantities, iii) instantaneous dose quantities, iv) cumulative dose quantities and v) effect quantities or changes in the tissue.

The primary dose quantities were related to the instantaneous quantity 'absorbed ultrasound dose rate' and the cumulative quantity 'absorbed ultrasound dose'.

A comparison of measurements of various potential dose quantities showed that those based on delivered ultrasonic energy could be readily compared; but that the thermal equivalent time (sometimes called thermal dose) is not a suitable quantity for a comparison.

Development of phantoms and measurement techniques for testing of dose concepts including the characterisation of measurement methods

Phantom materials are used instead of real human tissue, to study the effects of radiation, and they should closely mimic human tissue. A range of phantom materials were made and tested, and the use of zinc acetate dissolved in water was much more promising and reproducible as a reference material than phytagel materials. Two novel measurement systems were established for the measurement of Young's modulus and specific heat capacity.

A range of methods were developed to establish traceability for exposure and dose quantities. A single-element calibration source was developed with improved input voltage stability, leading to improved uncertainties in the delivered ultrasound waves. A multi-element phased array reference source has been developed, which can provide high power at multiple frequencies up to 10 MHz along with a calorimetric standard. Facilities for ultrasound field characterisation and heating measurements were established, as well as a system using an infrared camera for optical/geometrical observation of high intensity focused ultrasound (HIFU) lesion development.

Systems for non-invasive temperature measurement in phantoms have been established and tested with a measurement uncertainty of 10 % in the focal zone under laboratory conditions. Fast magnetic resonance imaging sequences were developed and tested.

Low density polyethylene (LDPE) was used as the reference medium for measuring absorbed ultrasonic dose and dose rate. The temperature increase at a point determined using a thin-film thermocouple during and after an ultrasound exposure. Following the general approach in radiotherapy, the dose in other media can be calculated by considering the relative properties of LDPE reference medium and the specific medium of interest.

The likelihood of generating cavitation in a particular medium depends not only on the acoustic pressure but on many other parameters such as drive voltage, burst length or burst period, so there is no single pressure threshold. The focused ultrasound source itself was used as the detector to collect acoustic backscatter which shows significant changes when cavitation occurs, so a threshold could be determined.

Together the dose concepts, measurements techniques and the phantoms provide the basis for the metrological infrastructure for dose for therapeutic ultrasound.

Development of test methods for the assessment of commercial machines and comparison of treatment effects and efficiency

This objective supported the testing of commercial clinical therapeutic ultrasound (commercial) systems. Infra-red thermal imaging has been developed as a dosimetry transfer standard. An IR camera was built into a housing to monitor the temperature distribution on the surface of a tissue mimicking target region. Testing was carried out on clinical magnetic resonance guided Philips Sonalleve focused ultrasound surgery system showing temperature equivalent noise of 0.02ºC, and temperature changes as low as 0.1ºC were easily observable, demonstrating that the dosimetry standard and measurement method are suitable for assessing commercial instrumentation

Modelling and validation of linear and non-linear ultrasound propagation through phantoms and anatomical structures

This work studies how large blood vessels can remove heat from treatment areas, therefore changing the expected medical outcomes. Treatments plans can be modified, by increasing exposure duration or power, so that the effects can be mitigated.

Theoretical and computer modelling procedures calculated acoustic and thermal dose quantities for 3D tissue-simulating media with well understood uncertainties. Linear acoustic holography has been established as the preferred method of providing acoustic input data for field and exposure modelling. An agreement between calculated and measured fields within approximately 2% for pressure magnitude was achieved.

A high performance workstation has been installed to take acoustic hologram data as the field input and use an operator-splitting approach to calculate the nonlinear field with an arbitrary number of harmonics. To model propagation in bone, UCL have developed a Kelvin-Voigt elastic wave model which has been released as part of their freely available k-wave toolbox for MATLAB.

It was shown that large blood vessels can remove heat from a treatment area, so treatments need to have increased exposure or power to be effective.

Development of methods to improve the accuracy of the individual treatment including use of anatomical data

The propagation of ultrasound is different in bone, compared with tissue, making treatment of cancers situated behind the ribcage particularly difficult. A 3D printed rib phantom was made and treatment planning software was tested against it. A more complex propagation model was developed to calculate scattering off the rib surfaces in order to calculate heating. Results indicated that a constrained optimisation approach was preferred over other strategies, or varying the most important of the many parameters that can affect the acoustic field.

To improve the understanding of the response of cells to high intensity ultrasound, a system for heating under continuous observation developed. This allowed thermal dose to be determined with an uncertainty of less than 20%. Cells were observed to shrink in area, becoming more rounded in shape.

The suitability of thermally equivalent time to describe HIFU treatments in cancer therapy was investigated through experiments on cancer cells grown in monolayers and in novel 3D collagen gel matrices. Results showed that cells heated rapidly to temperatures >55ºC were more resistant to heating than those heated slowly using the same thermally equivalent time, suggesting that current clinical levels of thermally equivalent time may underestimate the dose required to kill all cancer cells.

Actual and potential impact

Dissemination of results

Overall 49 scientific papers have been published or accepted for publication and with 69 conference presentations. A special session on ‘Field Characterization and Dosimetry for Therapeutic Ultrasound Applications’ was held at the Acoustical Society of America conference, a key international conference for ultrasound physicists. Workshops and symposia were also held with project partners presenting to 30 participants from the metrology, standards and regulatory communities. Two special issues of the International

Journal of Hyperthermia were published which included 8 papers authored by DUTy partners. Two books based on this work have been commissioned and will include chapters or be edited by project participants.

Impact on standardisation

The outputs from this project contributed to the development of a common language and a metrological infrastructure (basic definitions, validated measurement methods and validated modelling methods) for ultrasound dosimetry. These new capabilities have been disseminated widely to the instrumentation, clinical, standards and research communities, and are starting to be used to support the development and validation of ultrasound instrumentation and appropriate standardisation. During the lifetime of this project, there have been inputs to draft documentary standards IEC62556 & IEC62555 and published regulation IEC60601-2-37. There has been substantial impact on standardisation in IEC TC87 (Ultrasonics) and IEC SC62D (Electromedical therapeutic equipment). The UK and USA national committees have submitted two proposals related to therapeutic ultrasound to IEC TC87 (one on acoustic holography and field modelling; the other on high pressure field measurement). Another proposal on calibration of HITU hydrophones is currently under consideration.

Early impact

This project has enhanced the European measurement infrastructure for therapeutic ultrasound. The capabilities developed have been disseminated to the instrumentation, clinical, standards and research communities and are already starting to be used by the project participants and stakeholders to support the development and validation of ultrasound instrumentation and appropriate standardisation.

- NPL has established a measurement consultancy service for HIFU equipment which includes measurement of acoustic and electrical power, acoustic holography measurements to IEC62556, and modelling to support compliance with IEC60601-2-62. Measurements have been made for four European and international ultrasound equipment companies.
- PTB has developed a scheme to provide traceability to the German Primary Standard for hydrophones intended to be used for the measurement of very high intensity fields, typical of HIFU therapy systems;
- PTB is exploring the possibility of a collaboration on sensors for medical ultrasound with a manufacturer of cavitation sensors, and has had several requests from customers (mainly manufacturers of HIFU devices) concerning HIFU power measurements according to new IEC62555 Standard.
- HoMe has established a collaboration with an institute in Berlin to calibrate the output intensity of their new custom-designed system which uses ultrasound to stimulate nerve cells. These new capabilities will support the development of HIFU clinical applications and in particular provide confidence in applying defined and well-controlled acoustic exposures for treating a range of the clinical conditions, to the benefit of patients, clinicians and equipment manufacturers.

Long term impact

Manufacturers and regulators need measurement standards to allow them to bring new equipment to market and help to establish a more homogenous global regulatory and purchasing environment. This will give healthcare providers a greater range of reliable therapies available and allow more comparison of data and tailored treatment plans. It is anticipated that the measurement standards and methods developed will provide the basis for rigorous treatment planning of the emerging therapies, which in turn will lead to better, potentially cheaper, disease management, including less invasive treatments with fewer side-effects and shorter recovery times.

List of Publications (only publications that have been published are listed)

Papers in peer-reviewed publications

1. Haller J, Jenderka K-V, Seifert F, Klepsch T, Martin E, Shaw A, Durando G, Guglielmone C, Girard.F. A comparison of three different types of temperature measurement in HITU fields. Metrologia: 49 S279-281 (doi:10.1088/0026-1394/49/5/S279)
2. Jenderka K-V, Wilkens V. Measurement of time-averaged power in HITU fields - effects of duty cycle and target distance. Metrologia: Vol 49 (5), S275 - S278 (October 2012)
3. Gélat P, ter Haar G and Saffari N,The optimisation of acoustic fields for ablative therapies of tumours in the upper abdomen. Physics in Medicine and Biology: 57(24), 8471-8497 (December 2012)
4. Bessonova O, Wilkens V. Membrane hydrophone measurement and numerical simulation of HIFU fields up to developed shock regimes. IEEE Trans. Ultrason., Ferroelect., Freq. Contr: Vol 60(2), 290-300 (February 2013)
5. Shaw A and ter Haar G. Telling it like it is. Journal of Therapeutic Ultrasound: Volume 1, 2013
6. A Tokarczyk, IRivens, R Symonds-Tayler, E. van Bavel, G ter Haar. An experimental system for the study of ultrasound exposure of isolated blood vessels. Physics in Medicine and Biology: vol.58 pp2281-2304, 2013
7. Petr V Yuldashev, Svetlana M Shmeleva, Sergey A Ilyin,Oleg A Sapozhnikov, Leonid R Gavrilov and Vera A Khokhlova. The role of acoustic nonlinearity in tissue heating behind a rib cage using a high-intensity focused ultrasound phased array. Physics in Medicine and Biology: 58 (2013) 2537–2559
8. Khokhlova V, Shmeleeva S, Gavrilov L, Gelat PN, Martin EM and Shaw A. Infrared mapping of ultrasound fields generated by medical transducers: feasibility of determining absolute intensity levels. JASA: J. Acoust. Soc. Am. 134 (2), Pt. 2, pp1586–1597, August 2013
9. C. Perez, H. Chen, T.J. Matula, M.S. Karzova, V.A. Khokhlova. Acoustic field characterization of the Duolith: Measurements and modeling of a clinical shockwave therapy device. JASA: J. Acoust. Soc. Am., 2013, 134(2), Pt.2, pp. 1663-1674
10. Kreider, W., Yuldashev, P.V., Sapozhnikov, O.A., Farr, N., Partanen, A., Bailey, M.R., Khokhlova, V.A., Characterization of a Multi-element Clinical HIFU System using measurement and modeling. IEEE-UFFC: Vol60 (8), pp1683 - 1698, doi: 10.1109/TUFFC.2013.2750
11. John Civale, Hugh Morris, Ian Rivens, Gail ter Haar, Constantin Coussios, Peter Friend, Jeffrey Bamber. Calibration of Ultrasound Backscatter Temperature Imaging (BTI) for HIFU Treatment Planning. Ultrasound in Med. & Biol.,: Vol 39, No. 9, pp. 1596–1612
12. Gail ter Haar. Safety first: Progress in calibrating high-intensity focused ultrasound treatments. Imaging Med.: Vol 5 (6) pp. 567 - 575.
13. V.A. Khokhlova, L.A. Crum. Introduction to the special issue on therapeutic ultrasound. JASA: J. Acoust. Soc. Am., 2013, 134(2), Pt.2, pp. 1441.
14. Julian Haller, Volker Wilkens. Derivation of Continuous Wave Mode Output Power from Burst Mode Measurements in High-Intensity Ultrasound Applications. The Journal of the Acoustical Society of America - Express Letters: 135(3), EL123-EL127 (2014)
15. P Gélat, †, G ter Haar and N Saffari. A comparison of methods for focusing the field of a HIFU array transducer through human ribs. Physics in Medicine and Biology: 2014, 59, 3139 doi:10.1088/0031-9155/59/12/3139
16. Guangzhen Xing, Ping Yang, Wende Shou. Measure Low Level and High Frequency, Ultrasonic Power by Self-Reciprocity Technique. ACTA ACUSTICA: Vol. 100 (2014) 1 – 1
17. Ping Yang, Guangzhen Xing. Application of self-reciprocity in estimating ultrasonic power with a novel measurement method. Sensor Review: Sensor Review, Vol. 34 Iss: 4, pp.410 - 415.

18. Ping Yang, Guangzhen Xing. Experimental Research Between Calorimetry Method and the Radiation Force Balance Method for Measurement of Ultrasound Power. (In Chinese). ACTA METROLOGICA SINICA: 36, 1, 2015.

19. R. Cuccaro, C. Musacchio, P. A. Giuliano Albo, A. Troia, S. Lago. Acoustical characterization of polysaccharide polymers tissue-mimicking materials. Ultrasonics, 56, 210-9, 2015.

20. B. E. Treeby and B. T. Cox. Modeling power law absorption and dispersion in viscoelastic solids using a split-field and the fractional Laplacian. J. Acoust. Soc. Am., vol. 136, no. 4, pp. 1499-1510, 2014.

21. Mouratidis P., Rivens I. and Ter Haar G. A study of thermal dose induced autophagy, apoptosis and necroptosis in colon cancer cells. Int J Hyperthermia. 2015 Aug; 31 (5):476-88.

22. Shaw A, ter Haar G, Haller J, Wilkens V. Towards a dosimetric framework for therapeutic ultrasound. Int. J. Hyperthermia: Vol 31, Iss 2, pp. 182-192 (2015).

23. Alessandro Schiavi, Rugiada Cuccaro, Adriano Troia. Strain-rate and Temperature dependent material properties of agar and gellan gum used in biomedical applications. Journal of the mechanical behavior of biomedical materials 53 (2016) 119–130: Journal of the Mechanical Behavior of Biomedical Materials 53 (2016) 119–130

24. G. Durando, C. Guglielmone, J.Haller, O. Georg, A. Shaw, E. Martin, B. Karaböce. Towards Comparison of Ultrasound Dose Measurements - Current Capabilities and Open Challenges. 2015 Proceedings of ICU2015, Physics Procedia 70, 1114-1118 (2015).

25. Baki Karaböce, Hüseyin Okan Durmuş. Visual investigation of heating effect in liver and lung induced by a HIFU transducer. Elsevier Physics Procedia, 70, 2015, 1225-1228

26. D Sinden, G ter Haar. Dosimetry implications for correct ultrasound dose deposition: uncertainties in descriptors, planning and treatment delivery. Trans. Cancer Res: Sinden D, ter Haar G. Dosimetry implications for correct ultrasound dose deposition: uncertainties in descriptors, planning and treatment delivery. Transl Cancer Res 2014, 3 (5):459-471.

Conference Proceedings

1. Haller J, Jenderka K-V, Koch C, Seifert F, Klepsch T, Shaw A. A low-cost, easy-to-handle calibration phantom for MR thermometry in HIFU fields. AIP Conference Proceedings: Vol. 1481, 125-130 (October 2012)

2. Haller J, Wilkens V. On the reliability of voltage and power as input parameters for the characterization of high power ultrasound applications. AIP Conference Proceedings: Vol 1503, 276-281 (December 2012)

3. P Gélat, G ter Haar and N Saffari. HIFU scattering by the ribs: constrained optimisation with a complex surface impedance boundary condition. Proc 12th Anglo-French Physical Acoustics Conference 2013: J Phys Conf Series, 498, p36-46, 2014

4. Sapozhnikov O.A. Metrological aspects of studying ultrasound fields of therapeutic transducers. Proceedings of Metrology of hydroacoustic measurements (in Russian): 2013, v. 1, pp. 79 87

5. Tsysar S.A., Sapozhnikov O.A. Acoustic holography method for calibration of therapeutic ultrasound sources. Proceedings of Metrology of hydroacoustic measurements (in Russian): 2013, v. 1, pp. 251-57

6. B. E. Treeby and B. T. Cox. A computationally efficient elastic wave model for media with power-law absorption. IEEE International Ultrasonics Symposium: pp. 1037-1040, 2013

7. B. E. Treeby, J. Jaros, D. Rohrbach, and B. T. Cox. Modeling elastic wave propagation using the k-Wave MATLAB toolbox. IEEE International Ultrasonics Symposium, 2014.: IEEE International Ultrasonics Symposium, pp. 146-149, 2014

8. Baki Karaböce, Yakup Gülmez, Eyüp Bilgiç, Enver Sadıkoğlu, Ahmet T. İnce, Yani Skarlatos. Comparison of the Input Electrical Power Measurement Methods for HIFU Transducers. IEEE Xplore Conference Publications: DOI:10.1109/MeMeA.2014.6860141

9. P. Alberto Giuliano Albo, Simona Lago. Heat capacity measurements of novel tissue-mimicking materials. IEEE International Symposium on Medical Measurements and Application: Proceedings of MeMea2015, DOI: 10.1109/MeMeA.2015.7145183

10. Chiara Musacchio, Rugiada Cuccaro, P. Alberto Giuliano Albo, Simona Lago, Adriano Troia. Experimental apparatus for the measurement of the ultrasound attenuation coefficient. AIA-DAGA 2013 Merano: Proceeding AIA-DAGA 2013 Merano

11. Adriano Troia, Chiara Magnetto. Thermocromic Silica Gel as Tissue Mimicking Materials for Investigation of Temperature Rise Induced by HIFU Transducer. AIA-DAGA 2013 Merano: Proceeding AIA-DAGA 2013 Merano

12. Troia A., Magnetto C., Musacchio C., Cuccaro R., Pavese M. Thermochromic Tissue mimicking Materials for Investigation of Temperature Rise Induced by HIFU Transducers. ESS 14 Avignon: Proceeding of 14th Meeting of the European Society of Sonochemistry, ESS14, Avignon, June 2-6, 2014.

13. Baki Karaböce. Focused ultrasound temperature effect in tissue-mimicking material and sheep liver. IEEE Xplore Conference Publications: DOI:10.1109/MeMeA.2015.7145186

14. Francisco Chinchurreta, Rob Hekkenberg. Non-invasive temperature estimation on TMM based on the echo-shift method. Proceedings of the 46th Spanish Congress on Acoustics, 2015: pp1.609-1.616.

15. Francisco Chinchurreta, Rob Hekkenberg. Changes in field distribution for physiotherapy systems when in contact with skin mimics compared to the free-field distribution. Proceedings of the 46th Spanish Congress on Acoustics, 2015: pp1.609-1.616.

PhD and master theses

1. Tina Fuhrmann. Thermal Non-Invasive Laboratory Dosimetry for Therapeutic Ultrasound. Master's Thesis (Martin-Luther-University Halle-Wittenberg) Inst. of Physics 2014-06-12.

2. Pierre Gelat. Focusing the Field of a HIFU Array Transducer through Human Ribs. Ph.D Thesis (University College London) - 01/11/2014.

3. Baki Karaböce. Characterisation of Ultrasonic Transducers Used in Medical Applications and Investigation of Their Effects in Phantom Tissue. Ph.D Thesis (Istanbul Yeditepe University, Institute of Graduate Studies in Science and Engineering), 2014.

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