

Full running title:

Conduct of HIFU therapy for low to moderate risk, organ confined prostate cancer with the Sonablate® -500 System – results of consensus meeting.

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Consensus on conduct of HIFU therapy for prostate cancer.

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SUMMARY

Introduction: High Intensity Focused Ultrasound (HIFU) is now an established option for men with localised prostate cancer in Europe, Japan, Canada and parts of central and South America. Of the potentially curative options currently available, HIFU is the least invasive. It is at a relatively early phase in its diffusion into practice and, standardisation in the conduct of therapy is vital.

Methods: In order to help facilitate this challenging phase of technology diffusion a meeting was convened of experienced European users of the Sonablate® -500 (Focus Surgery, Indianapolis, IN, USA) HIFU system in order to define standards in the conduct of treatment through a process of discussion and consensus. The aims were to establish a likely contender for best practice (in the absence of long term evidence), to enable consistent teaching and training, to reduce variability in outcomes, and to help attribute outcome to changes in the conduct of treatment.

Results: A consensus of opinion on current best practice for HIFU therapy for low to moderate risk, organ confined prostate cancer with the Sonablate® -500 System was achieved. The four areas of consensus were patient selection, pre-operative preparation, techniques applied during treatment, and post operative management.

Discussion: The implications of this document are discussed in terms of treatment, training and outcome measures. The plans for future research and development for the consensus on conduct of therapy are outlined.

Introduction

Standardisation in the conduct of therapy is vital in the development of any new technology. As new technologies and procedures emerge, there will always be variation in the technique and patient selection. Indeed, there still remains around 50 methods for carrying out a total hip replacement(1, 2). If non standard conduct persists, it becomes very difficult to attribute outcomes to any single part of the treatment.

High Intensity Focused Ultrasound (HIFU) is now an established option for men with localised prostate cancer in Europe, Japan, Canada and parts of central and South America. Of the options currently available to men, HIFU is the least invasive and at a relatively early phase in its diffusion into practice(3). This has two consequences. The first is that the evidence base to support its use is relatively immature(4, 5). The second relates to a concentration of both experience and expertise into a few specialist centres, at a time when many other centres are wishing to introduce the technology into clinical practice.

In order to help facilitate this challenging phase of technology diffusion a meeting was convened of experienced users of the Sonablate® -500 HIFU system (Focus Surgery, Indianapolis, IN, USA & Misonix Inc., Farmingdale, NJ, USA) in order to define standards in the conduct of treatment through a process of discussion and consensus.

The benefits of establishing a standard technique in relation to HIFU therapy for localised prostate cancer are many. It will enable the fast growing group of surgeons using this technology to establish a likely contender for best practice. This is especially important in the early stages of the development of this technique as there remains little long term data or evidence for best practice. The dissemination of a new technique needs to be consistent. By a establishing a consensus of opinion on conduct of therapy, teaching and training of new users, and indeed the trainers themselves, should become consistent. This in turn allows outcomes between users to be comparable and, more importantly, maintains the high standards to which those using a new treatment must comply. The area where a standard therapy should provide the greatest benefit is in the reduction of variability in outcomes. By establishing a standard conduct of therapy, any data produced during a treatment is then comparable to other treatments. This standard will also enable users help attribute changes in outcome to changes in the conduct of treatment if it occurs.

In this document, we outline the consensus of opinion for the conduct of therapy using the Sonablate® -500 in the treatment of localised prostate cancer.

Methods

1. Scope of meeting

1.1. This meeting was designed to reach a consensus on the conduct of treatment of organ confined disease (T2c or less) and for low to moderate risk prostate cancer, as defined according to the D'Amico criteria of risk for prostate cancer (6, 7) ¹.

1.2. The meeting was also designed as a 'master-class' to encourage consistent dissemination of techniques required to effectively treat prostate cancer using the Sonablate® -500 throughout the urological community. It was held at the Royal College of Surgeons of London, Lincoln's Inn Field, London on the 9th June 2006.

2. Selection of participants

2.1. A European multicentre trial is currently underway assessing HIFU in the treatment of localised prostate cancer. The lead investigators and the

¹ Risk stratification is as follows:

Low risk –no risk factors
Medium risk- one risk factor
High risk- two or more risk factors

Risk factors include: presence of gleason pattern 4, T2c or higher stage, more than 50% cores positive, more than 50% of one core positive, PSA 10 or more.

surgeons carrying out the procedure, at each of the centres, were invited to attend this user group meeting. Ten surgeons attended the meeting.

3. Structure of the meeting

3.1. Live cases with interactive discussion

3.1.1. The HIFU treatment of a patient with organ confined prostate cancer was observed by the whole group. Throughout the treatment key points were analysed and alternative treatment procedures were assessed.

3.1.2. A patient with a post HIFU urethral stricture was treated and treatment methods were discussed.

3.2. Structured discussion

3.2.1. Following the live cases, a structured discussion was held. The agenda was as follows:

3.2.1.1. Data to date and future developments

3.2.1.2. Case selection

3.2.1.3. Strictures: how do we investigate them?

3.2.1.4. Erectile dysfunction: what are our rates?

3.2.1.5. Training Issues: theoretical and practical

4. Deriving consensus

4.1. A consensus was achieved by a show of hands regarding key points discussed during the day. A 100% majority was required for a significant change to any current practice.

5. Time limitation to recommendations

5.1. It was agreed that these recommendations should stand until the next user group meeting planned. At this time any amendments to the consensus opinion would be published.

Results

The following points are the results of the meeting and a consensus of opinion on current best practice for HIFU therapy for low to moderate risk, organ confined prostate cancer with the Sonablate® -500 System.

1. Patient selection

1.1. Factors relating to the cancer

1.1.1. There should be histological evidence of adenocarcinoma of the prostate.

1.1.2. Histological grade described as Gleason sum ≤ 7

1.1.3. PSA ≤ 15

1.1.4. No consensus was achieved on setting limits on tumour burden (number of cores positive) or estimated size of tumour (maximum cancer core length)

1.2. Factors relating to the prostate

1.2.1. Volume ≤ 40 cc as measured by transrectal ultrasound.

1.2.2. Maximum distance from rectal wall to anterior margin of the prostate at the widest point $\leq 4\text{cm}$ ⁱⁱ

1.2.3. Absence of confluent calcification of $> 1\text{cm}^3$. ⁱⁱⁱ

1.2.4. Absence of cysts $> 1\text{cm}^3$. ^{iv}

1.3. Factors related to coupling (contact of water balloon with rectal mucosa)

1.3.1. Absence of previous ano-rectal surgery, (excluding haemorrhoidectomy).

1.3.2. Absence of active inflammatory bowel disease in anorectal region

1.3.3. Absence of active ano-rectal sepsis

1.3.4. Absence of latex allergy

1.4. Factors relating to the patient

1.4.1. Patient should be fit for general anaesthesia

1.4.2. Status of exogenous androgen suppression prior to therapy should be recorded(8)^v.

ⁱⁱ The focal length of the transducer is maximally 4cm

ⁱⁱⁱ These should be avoided, as they may prevent reliable levels of acoustic energy to pass beyond them

^{iv} Cysts of this size may prevent reliable levels of acoustic energy to pass beyond them.

^v Pre-operative androgen suppression may be used either to cytoreduce the gland, or as a temporising measure if there was going to be a delay before treatment, as there seemed to be no adverse effect on outcome. The routine use of androgen suppression outside either of these indications was discouraged as it affects interpretation of PSA kinetics, thus making PSA nadir measurement invalid.

2. **Pre-operative preparation:**

2.1. Patient

2.1.1. Bowel preparation - phosphate enema 12-16 and 2 hours pre-op.

2.1.2. Prophylactic antibiotics – gentamicin 3mgkg^{-1} on induction.

2.1.3. DVT prophylaxis – TED stockings as a minimum.

2.2. Equipment

2.2.1. Degassed water should be prepared.

2.2.2. 2-3 luer-lock syringes 50 cc per patient

2.2.3. Ultrasound gel (approx. 100ml per patient)

2.2.4. Ample non-sterile gloves

2.2.5. The probe positioning system must be compatible with the operating room table.

2.2.6. Pre-operative software check completed

2.2.7. Careful application of the condom as smooth contact is essential and puncture requires replacement.

2.2.8. There must be no bubbles visible within the system. These may cause problems with application of the energy.

3. **Anaesthetic:**

3.1. The procedure can take as long as 5 hours so a **general anaesthetic** is advised.^{vi}

4. **Procedure:**

4.1. The patient should be placed in the lithotomy position.

4.2. The HIFU probe, covered with ample ultrasound gel, is placed in the rectum. Gentle anal dilatation may be required.

4.3. Under direct vision with a cystoscope, a **suprapubic catheter** (SPC) is inserted.^{vii}

4.4. A urethral catheter is passed for the first planning stage.

4.5. The prostate is imaged and the first sector is planned. The consensus amongst the user group is that each zone should be planned and treated **separately**. There may be as many as 6 or 7 treatment zones planned to cover the whole gland.

4.6. The urethral catheter is removed prior to commencing ablation and the suprapubic catheter remains in situ and on free drainage.

^{vi} This can be a day case procedure so a light, short acting agent is ideal, a recommend agent is remifentanyl. This is not only short acting but we have found that its opiate properties may reduce peristalsis peri-operatively thus reducing flatus and faeces obstructing the ultrasound images and improving safety.

^{vii} The flexible cystoscope can be used to assess key landmarks such as the bladder neck, verumontanum and external sphincter. This is especially important in repeat or salvage treatments.

4.7. The treatment must be observed **constantly** throughout ablation, only in this way will the treatment be optimal and side effects minimized.

4.8. At completion of treatment, the water is removed from the water balloon and the probe is withdrawn.

4.9. The suprapubic catheter remains in situ until the patient is voiding normally again, a minimum of 5 days.

5. **Techniques applied during treatment**

5.1. **Uchida changes** - grey scale changes seen within the treatment area on the real-time ultrasound imaging are used to set and adjust the appropriate power levels to treat the gland^{viii}. These are a useful indication for outcome and the consensus is that using these prompts as markers of treatment produce the best oncological results(9).

5.2. **Near-field changes** - It is important to pause the treatment if the greyscale changes start encroaching into the near-field^{ix}. These changes may prevent adequate energy reaching the target area.

5.3. **Water balloon** - Using the water balloon to adjust the point of focus dynamically allows optimal treatment^x.

^{viii} Illing et al. have shown that visually directed treatment can lead to better results than those achieved using a pre-defined treatment algorithm.

^{ix} This pause in treatment can be visualised with real-time ultrasound to assess resolution of the near-field changes, this can be as little as 5 minutes but can take much longer.

5.4. **Re-imaging** - towards the end of a planned treatment zone re-imaging allows re-assessment of gland swelling and the addition of extra treatment points to achieve complete coverage of the prostate gland.

5.5. **Flatus** - the optimal way of managing this is to pass a small soft Foley catheter per rectum parallel to the probe, this usually relieves the problem. A sweeping motion across the probe with the catheter can also help.

6. **Post operative management**

6.1. **Day-case procedure** – the patient should be mobilised as early as possible.

6.2. **SPC** - the patient should be aware that passing urine per urethra for the first 48 hours may be difficult, if not impossible. Once post void residuals are consistently less than 200mls, as measured by draining the bladder via the SPC, the SPC can be removed.

6.3. **Oral antibiotics** should be taken as long as the catheter is in situ. The recommendation is ciprofloxacin 500mg twice daily.

^x Using the water balloon is an important technique to improve treatment. When treating the posterior aspect of the gland maintaining close proximity to Denonvillier's Fascia without treating the fascia itself is difficult. This needs a second individual who can add or withdraw small amounts of water from the balloon to adjust the position of the focus and thus the whole gland can be covered.

6.4. **Anti-inflammatory**, such as diclofenac, is recommended until voiding is achieved per urethra.

6.5. Occasionally **bladder spasm** requires anticholinergics therapy to be prescribed.

6.6. **PSA** should be monitored at 6-12 weeks^{xi} (10).

6.7. **Erectile dysfunction** should be managed early with PDE5 inhibitors and therapy escalated if these agents fail.

6.8. **Dysuria** – the consensus is that a conservative approach is best. There will be at least 6 weeks of symptomatic prostatic sloughing.

6.9. **Urethral stricture** - has been reported as high as 25%(4), the consensus for management is gentle dilatation using a sound.

^{xi} The consensus of opinion is that in primary treatments a PSA nadir of 0.2 (without any androgen suppression) is strong predictor of a successful treatment. Uchida et al. in a recent analysis of 115 patients concluded that there was a clear and intuitive association between PSA nadir and the risk of treatment failure exists for HIFU

DISCUSSION

1. Summary of results.

1.1. This is the first attempt to standardise the conduct of care in treating low to moderate risk, organ confined prostate cancer with the Sonablate® - 500 HIFU System. Although over 500 treatments have been performed using this system in the last year, there remain variations in the conduct of therapy from user to user. This meeting has tried to establish some standard principles by which practitioners may perform procedures. The main area of consensus reached were:

1.1.1. **Patient selection.** A specific group of patients were identified who would most likely benefit. These patients are men with low to moderate risk, organ confined prostate cancer. They have small glands (<40cc) and a rectal wall to anterior surface of the prostate distance of <4cm. Specific exclusion factors were identified such as large areas of calcification or cysts, ano-rectal disease and latex allergy.

1.1.2. **Conduct of therapy.** A consensus on the techniques needed produce an optimal outcome was derived. The need to perform a visually directed treatment, using Uchida changes as markers to assess energy levels, was felt to be paramount. As a dynamic treatment, constant assessment and reassessment of the treatment

parameters using the software available, is vital. Using the water balloon to allow coverage of the entire gland has proven to be a useful technique. Other important factors in the conduct of therapy included: appropriate anaesthesia, having the correct equipment available, preparation of the patient with insertion of a suprapubic catheter under direct vision, and suitable bowel preparation minimises problems with flatus and rectal wall contact during therapy.

1.1.3. **Postoperative Management.** This is a day case procedure and patients need to be mobilised early and educated in the use of the SPC to allow this to occur. The major problem post-operatively is urinary morbidity and the consensus is that the use of an SPC, anti-inflammatories and anticholinergics can minimize this. Early use of PDE5 inhibitors is also recommended to optimize post procedure erectile function.

2. **Methodological limitations.**

2.1. The best way to characterise opinion is to use formal consensus methods.

2.2. Although this document does not use those formal methods, the format for this consensus document is based on the 'Delphi Process' of achieving consensus(11) Over a series of user-group meetings, culminating in the meeting at the Royal College of Surgeons, the various

statements and opinions stated in this document have been discussed and analysed. A formal ranking of the statements has not been garnered. However, the participants, all of whom are experts in the field, have freely given their opinion and have had input into the development of these statements.

2.3. No single individual has overtly taken the lead in developing these opinions. The meetings have been held at a number of centres throughout Europe and on each occasion there was a different chairperson and hosting team.

2.4. In terms of validity, the best that can be said is that the vast majority of surgeons using this technique have been involved in the user-group meetings, however testing the accuracy and reliability remains difficult.

3. Policy implications.

3.1. This document allows standardisation of the technique. This has implications in a number of areas:

3.1.1. **Treatment.** A standard treatment is essential and this document states the consensus of opinion for the conduct of therapy.

3.1.2. **Teaching.** With any new technology, dissemination of the technology can overtake the dissemination of the knowledge required to optimally use the technology. This document provides a standard technique for those undertaking the procedure for the first time and allows those teaching the method to set benchmarks by which all treatments must be taught and assessed.

3.1.3. **Outcomes.** A standard technique in the conduct of therapy allows outcomes to be comparable. Good outcomes are the end-goal of any treatment modality. New technologies are notoriously difficult to assess in comparison to established techniques. However, before being compared to other techniques there needs to be standardisation within the technology itself. By using the consensus of opinion discussed in this document oncological outcome and morbidity can be compared between surgeons, this should allow optimal clinical governance and lead to further improvements in all aspects of the treatment.

4. **Future research.**

4.1. **Multicentre European Trial Data.** The results of this trial will be based largely on data produced using this standardised technique. These

outcomes will allow further assessment of this technique. This trial is still recruiting.

4.2. Patient Registry. As discussed earlier, the dissemination of new technologies can be complex and often haphazard. To maintain a high standard of care and to collect as much data as possible, the European User group has proposed the establishment of a Sonablate® -500 patient registry. It is proposed that any patient treated with the device should be included in a data registry, with a minimum data set collected, and that this should be compulsory for all surgeons planning to use the device. The parent company Misonix Inc. are in full support of this and development of the registry is well underway. This system would be the first of its kind to collect data from practically the outset in the dissemination of a new treatment modality. It would provide an ever increasing pool of information to further develop and improve the technique.

CONCLUSION

In this article we present a standard, consensus-based approach to the conduct of HIFU therapy for prostate cancer with the Sonablate® -500 System. This technique has evolved considerably over the last 2 years and we hope by providing a standard basis for treatment that outcomes will continue to improve.

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APPENDIX

1. INFORMED CONSENT:

As with any procedure accurate informed consent is a key component in preparing the patient for theatre and managing their expectations of outcome.

Here we outline current evidence based advice for informed consent.

1.1. Oncological Outcome(4)

1.1.1. This does depend on a number of factors, but for those men who fulfil the previously mentioned criteria the current 5 year disease-free survival is in the region of 70-75%.

1.2. Urinary complications(4)

1.2.1. Following resolution of the immediate dysuria, incontinence rates are <2%.

1.2.2. Stricture rate is reported from as little as 1% but up to 25%. The experience of the group with respect to stricture rate is mixed and may well depend on catheter choice (urethral vs suprapubic).

1.2.3. Epidiymo-orchitis can occur in approximately 5% of cases.

1.2.4. Recto-urethral fistula is a serious complication but occurs in less than 1% of patients.^{xii}

^{xii} Within our group 3 recto-urethral fistulae have been reported in approximately 400 patients. Only one of these was in a primary treatment. As might be expected radiotherapy does increase the possibility of this complication

1.3. Erectile Dysfunction:

1.3.1. This is a difficult area to assess but impotence rates have been reported as low as 24%. But in general the consensus is that the erectile dysfunction in previously normal men is in the region of 40-50%.

1.4. Other complications:

1.4.1. Other expected complications are few. There is little discomfort, requiring only oral analgesia. Some men described perineal oedema, this resolves spontaneously and completely usually within 7 days.

Members of the User Group present at the Meeting held on 9th
June 2006 at the Royal College of Surgeons, London

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