MRI-TRUS fusion focal cryotherapy of the prostate: a prospective development study

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ABSTRACT

Objectives

The use of software-based MR-TRUS fusion to deliver focal therapy may increase the precision of treatment. This is a prospective development study assessing the feasibility of MRI-TRUS fusion focal cryotherapy.

Methods and materials

Consecutive patients undergoing focal cryotherapy were included in an academic registry (Dec 2013-June 2014). MRI-TRUS fusion focal cryotherapy was offered to men with visible clinically significant prostate cancer (Galil SeedNet system). Eligibility was determined by multi-parametric MRI (mpMRI), and transperineal template mapping or targeted biopsies. A rigid fusion platform (Biojet) was used with the operator ensuring the ice-ball covered at least the lesion. Adverse events were scored using the NCICTC V4. Genito-urinary toxicity was assessed using patient-reported outcome measures (IPSS, IIEF-15 and UCLA-EPIC). Early contrast-enhanced MRI and mpMRI at 6-12 months were used to assess extent of lesion ablation.

Results

Of 23 patients scheduled, 5 did not have image-fusion due to surgeon preference. 18 undergoing image-fusion cryotherapy had median age 68 (IQR 65-73) years and median preoperative PSA 9.54 (5.65-16) ng/ml. 13 (72.2%) and 5 (27.8%) patients had intermediate and high-risk cancer, respectively. Ten adverse events were reported with one of these as serious (grade 3) due to admission for haematuria requiring wash-out only. There was no difference in the IIEF-15 between baseline and study end ($p=0.24$). The IPSS remained stable ($p=0.12$), while the UCLA-EPIC tended to improve ($p=0.065$). The PSA significantly decreased at 1.8 (1.04-2.93) ng/ml ($p<0.001$). Early and late mpMRI showed no residual disease in the treated area. In two men, radiological progression of known contralateral disease was observed; both underwent focal HIFU.

Conclusion

MRI-TRUS fusion focal cryotherapy is feasible in most patients and seems to accurately guide ablation demonstrated by post-treatment imaging. Additional studies are needed to determine efficacy using post-cryotherapy biopsy.

1. Introduction

The therapeutic ratio of current radical treatments for localised prostate cancer is being questioned by clinicians, authorities and lately by patients themselves. Recent randomised trials have questioned the exact benefit from radical treatments across all localised prostate cancer, but do point to survival advantages in men with clinically significant disease who have a good life expectancy [1-3]. Nonetheless, the genito-urinary toxicity of radical treatments can be significant with a rate of erectile dysfunction and urinary incontinence varying between 30-60% and 15-20%, respectively, and a high rate of serious complications in the long-term, especially in older patients [4, 5]. To re-balance the therapeutic ratio, one strategy that has been proposed is focal therapy [6].

This strategy aims to treat the area of the prostate harbouring the largest volume, highest grade (index) lesion with a margin, while preserving the rest of the gland and reducing collateral tissue damage [7]. Concern and enthusiasm both exist with regard to this novel approach [6, 8]. Despite the open debate, there is consensus that although further robust research is required, focal therapy is an attractive strategy for patients and health-care systems.

Focal therapy can be delivered using various sources of energy. A recent systematic review of the literature has shown variable results with urinary incontinence, erectile dysfunction and disease control (using histological outcome measures) ranging between 0-5%, 0-46% and 77-96.3%, respectively [9]. Focal therapy efficacy has been criticised in light of two issues: first, some novel sources of energy have not been tested in the clinical setting; therefore, treatment failure might be related to incomplete ablation, rather than failure of the focal strategy. Second, the inability of devices to deliver precise therapy in the area harbouring the index lesion.

In this study, we sought to assess the feasibility of focal cryotherapy delivered to the index lesion using software-based MRI-TRUS fusion.

2. Materials and Methods

2.1 Design

Consecutive patients undergoing software-based MRI-TRUS fusion focal cryotherapy were identified from a prospective academic registry (Dec 2013-June 2014). Signed informed consent was obtained. Internal Review Board approval was waived by the local Joint Research Office. This report is adherent to the recommendations of the Idea Development Evaluation Assessment and Long-term (IDEAL) guidelines for stage I-IIa prospective development studies assessing novel technologies in surgery[10].

2.2 Population

In our unit, men with primary localized prostate cancer as well as men with recurrent disease after initial radiation or ablative therapy underwent mpMRI. Images were acquired in a 1.5 or 3T scanner with a pelvic coil using a standard protocol including T2-weighted, diffusion-weighted and dynamic contrast enhanced sequences. Every scan was reported by an experienced radiologist reporting all zones with a Likert score between 3 (equivocal presence of clinically significant disease) and 5 (extremely likely presence of clinically significant disease) [11]. Histological characterisation of the radiological phenotype was obtained according to the mpMRI report. Transperineal targeted biopsy with no additional sampling to zones scoring </=2 were performed in men with a single lesion; template prostate mapping biopsies were offered to men with multiple lesions or diffuse equivocal findings (figure 1). Treatment-naïve men with Gleason pattern >/=4 and/or PSA >/=10ng/ml as well as all men with radiorecurrent disease also underwent a radioisotope bone-scan to rule-out metastases.

MRI-TRUS software-based fusion focal cryotherapy was offered to men with one or two MR-visible lesions confirmed to be clinically significant in whom a standard focal strategy was deemed to be able to achieve complete ablation (hemi-, quadrant, focal or bi-focal ablation).

2.3 Procedure

Before the procedure, the full 3mm thickness T2-weighted sequence was downloaded and imported onto the Biojet rigid image-fusion platform (D&K Technologies GmbH, Barum, Germany). The prostate as well as visible lesion(s) were contoured [12]. The cryotherapy procedure was carried out in the lithotomy position. Antibiotic prophylaxis was administered intravenously at induction of general anaesthesia. First, the prostate was scanned using a bi-plane transrectal ultrasound probe (Hitachi Preirus, Hitachi Aloka Medical America, Inc. Wallignford USA) positioned on a stepper fixed to the operation table by a flexible arm (D&K Technologies GmbH, Barum, Germany). Second, the Biojet computer was connected to the ultrasound probe via sensors located on the stepper, one for tracking longitudinal movements and one for rotation. MRI-TRUS fusion was obtained manually by aligning the contour of the prostate drawn on the MRI to the margins of the prostate visible on the TRUS by rigid registration. Third, cryotherapy needles were inserted transperineally via a brachytherapy grid in order to ensure a parallel position. The cryotherapy needles were placed using the Biojet platform for guidance in order to cover the area to ablate with a margin of 1cm (figure 2). We used the cryotherapy SeedNet® system (Galil Medical Inc. Arden Hills, MN 55122, USA) with 17 Gauge (1.5mm) needles. Two types of needle were chosen according to the dimensions of the lesion to ablate on the axial and the longitudinal MR/TRUS software. IceRod needles achieve a complete ablation of 41mm longitudinally, whereas IceSeeds achieve 19mm. Thermocouples were then placed within the ablation area, and in the Denovilliers' fascia in case of posterior or mid-gland lesions, or in the peripheral area in case of anterior lesions.

Fourth, a flexible cystoscopy was performed to rule out urethral perforation, and a urethral warmer was inserted. Finally, two freeze-thaw cycles were delivered to achieve a temperature below minus

40°C in the ablation area, as measured by thermocouples. A temperature above 0°C was maintained in the area of the posterior thermocouple. At the end of the procedure, a urethral catheter was left in place, and the patient was discharged the same day.

2.4 Follow up

The urethral catheter was removed at 7-10 days after the procedure, and an early contrast-enhanced MRI was carried between 7-21 days to evaluate ablation. Patients were reviewed in clinics at 3, 6, 9 and 12 months with PSA measurements. Validated questionnaires were posted to patients at baseline and every three months following the procedure: 15-item International Index of Erectile Function (IIEF-15), International Prostate Symptoms Score (IPSS), and University of California Los Angeles Expanded Prostate Cancer Index Composite (UCLA-EPIC) urinary function [13, 14]. Non- responders at baseline were not sent questionnaires after treatment. Late mpMRI was carried out between 6 to 12 months, and scored according to the likelihood of presence of significant residual disease from 1 (extremely unlikely) to 5 (extremely likely). Complications were scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.

2.5 Statistical Analysis

Continuous variables are displayed as median and interquartile range (IQR); categorical variables as frequencies and percentages. Variation over time of continuous variables is represented by box and whisker plots. Two-tailed Wilcoxon signed rank test was employed to evaluate variation of continuous variables between baseline and 12 months follow-up. A p-value </= 0.05 was considered statistically significant. Statistical analysis was carried out using SPSS® version 20.0 (IBM corporation, Armonk, NY, USA).

3. Results

3.1 Study population

Twenty-three patients were scheduled for MRI-TRUS fusion focal cryotherapy. Five of them were excluded as the registration system could not be used to plan the treatment. In three of these, the histological results showed the extent of the disease to be beyond the visible lesion; therefore, the MRI lesion alone could not be used for treatment planning. In two patients, MRI-TRUS registration was judged by the surgeon as lacking sufficient accuracy, and the procedure was performed using visual/cognitive estimation as per standard of care. Of note, both patients had recurrent disease, one after radiation therapy and one after focal High Intensity Focused Ultrasound (HIFU), which cause significant gland distortion.

Eighteen patients constitute the cohort of this analysis. Median age was 68 (IQR 65-73) years and median preoperative PSA 9.54 (5.65-16) ng/ml. 14 (77.8%) had primary disease and 4 (22.2%) had recurrent disease (table 1) with NCCN intermediate and high risk in 13 (72.2%) and 5 (27.8%), respectively.

3.2 Perioperative outcome

Uni-focal, bi-focal and hemi-ablation were performed in 12 (66.7%), 4 (22.2%), 2 (11.1%) patients, respectively. Median procedure time was 85 (74-100) minutes for an overall anaesthetic time at 120 (108-145) minutes. Median hospitalization time was 11 (9.5-22.5) hours. Catheter removal was performed after a median of 8 (7-9) days (table 2).

3.3 Adverse events

10 adverse events were recorded. 1 of 11 was a serious adverse event, scoring CTCAE grade 3. This patient was hospitalised the day of the procedure with continuous irrigation for haematuria with clots. He was discharged after two days, and the catheter was successfully removed 10 days later. Among the 10 CTCAE grade 1 and 2 adverse events, three had urinary infections, three failed first

trial without catheter, two had self-resolving urinary dribbling, one had a urethral stricture that required dilation under local anaesthetic, and one complained of temporary penile numbness.

3.4 Functional outcome

Thirteen (72.2%) replied to questionnaires at baseline and follow-up. In terms of erectile function, the IIEF-15 score decreased after three months from cryotherapy, while there was no statistically significant difference between baseline and last follow-up at 12 months (p=0.24) (supplementary figure 1). The number of patients using PDE-5 inhibitors increased from 2 (11.1%) at baseline to 5 (27.8%). In terms of urinary function, the IPSS remained stable over time with no difference between baseline and 12 months (p=0.12) (supplementary figure 2); the IPSS quality-of-life score significantly improved (p=0.026) (supplementary figure 3). The UCLA-EPIC urinary domain tended to improve but this did not reach statistical significance (p=0.065) (supplementary figure 4).

3.5 Ablation effect

The PSA significantly decreased from baseline to 12 months follow-up at 1.8 (1.04-2.93) ng/ml (p<0.001) (supplementary figure 5). Early MRI scan showed score 1 (highly unlikely), 2 (unlikely) and 4 (likely) with respect to presence of clinically significant residual disease in 14 (77.8%), 2 (11.1%) and 2 (11.1%) (figure 3). Late mpMRI showed score 1 (highly unlikely), 2 (unlikely), 3 (equivocal), 4 (likely) and 5 (highly likely) in 7 (38.9%), 6 (33.3%), 3 (16.7%), 1 (5.6%) and 1 (5.6%) patients. The two patients with score 4-5 had no radiological evidence of in-field residual disease (i.e., in the treated area), but presented with radiological progression of known out-of-field (i.e., non-treated tissue); both underwent focal-HIFU. No other patient underwent another form of focal or radical treatment; none died or developed distant disease.

4. Discussion

In summary, our study shows that MRI-TRUS fusion focal cryotherapy is feasible in most patients choosing to have focal cryotherapy, has low toxicity and low impact on genito-urinary function with encouraging early ablation based on post-treatment MRI.

Prior to discuss the implications of our study, we would like to acknowledge its limitations. First, the sample size is small although intentionally so due to the pilot nature of our study. Whilst selection bias is likely to be present and only well characterised men were included, we did not apply restrictive criteria. Only men scheduled for focal cryotherapy with visible disease were offered the procedure under MRI-TRUS fusion. This reflects real practice, and therefore should enhance external validity. Second, the study population was heterogeneous with most patients having primary disease but a number following other treatment failures. In this early stage of assessment, we did not aim to focus on a specific sub-group of men, but to explore the applicability of this procedure to the whole spectrum of men undergoing focal cryotherapy. Third, the lack of mandatory biopsy after treatment represents a limitation in the measurement of ablative effect, and we cannot derive robust oncological outcomes of this procedure based on this study. However, this was beyond the purpose of this early study.

We assessed the feasibility of an established ablative source of energy combined with MRI-TRUS fusion to deliver focal therapy in a more precise fashion. Cryotherapy effect in ablating prostate cancer areas has been well proven, with a number of studies showing good efficacy, both when delivered as a whole-gland or a focal treatment [15, 16]. One randomised controlled trial has shown that cryotherapy might also have better disease control than radiation therapy [17]; a match-paired controlled study showed similar local control between focal cryotherapy and surgery [18]. Therefore, cryotherapy can provide reliable tissue effects, which in turn can be employed to assess the utility of novel technologies to guide focal therapy.

The use of MRI-TRUS fusion to guide focal cryotherapy merits further reflection. The procedure was feasible in most cases, but as previously discussed, men presenting with recurrent disease might have tissue changes that can alter the imaging signal and cause distortion of the gland making rigid fusion difficult. Although we did not collect time spent for registration, in our experience, around

additional 10 minutes were needed for mpMRI interpretation and contouring before treatment, and approximately 2 to 5 minutes for intraoperative imaging alignment. It should be noted that the operators were experts in mpMRI reading and Biojet software in light of previous experience in the biopsy setting [12]. We felt the fusion was straight-forward and we did not encounter significant problems during the delivery of cryotherapy. In our experience, the use of MR/TRUS fusion was beneficial in determining the margins of treatment. This was true in all 3D-orientation as with the formation of the ice-ball the limits of the gland become poorly defined. For instance, for an anterior lesion like the one seen in figure 2, heterogeneity in the posterior extension with the basal extremity extending further towards the peripheral area, real-time visualization during ablation permitted us to set a predictable margin of treatment.

Although we demonstrated feasibility of guiding focal ablation and pilot data for a low rate of adverse events and good functional outcomes, without direct comparison against standard focal cryotherapy, we cannot determine the true utility of employing of a MRI-TRUS fusion device for treatment planning. In this stage I-IIa prospective development study adherent to the IDEAL guidelines, we focused on feasibility, technical success and assessment of toxicity using validated tools. The next stage of assessment might be a multi-centre study with careful assessment of medium term results using biopsy as the outcome of success, or a comparative study against focal cryotherapy without ~~no~~ use of software.

5. Conclusion

In conclusion, this study shows that MRI-TRUS fusion focal cryotherapy is feasible in most patients and seems to accurately guide ablation demonstrated by post-treatment imaging. Additional studies are needed to determine efficacy using post-cryotherapy biopsy.

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Conflict of Interest

M. Valerio has received funding for conference attendance from Geoscan Medical. M. Emberton and H.U. Ahmed receive funding from USHIFU, GSK, AngioDynamics and Advanced Medical Diagnostics for clinical trials. M. Emberton is a paid consultant to AngioDynamics, Steba Biotech and SonaCare Medical (previously called USHIFU). Both have previously received consultancy payments from Oncura/GE Healthcare and Steba Biotech. None of these sources had any input whatsoever into this article.

Legends

Figure 1

Preoperative multiparametric MRI showing a 4/5 score right anterior lesion (red arrow) slightly crossing the midline on the left with low T2 signal, marked restricted diffusion and mild enhancement (figure 1). A small equivocal lesion scoring 3/5 was also seen in the posterolateral left

apex. This patient underwent template prostate mapping biopsies confirming the right anterior lesion harbouring Gleason 3+4, maximum cancer core length 10mm. Biopsy in the rest of the gland showed no disease. This patient underwent MR/TRUS focal cryotherapy.

Figure 2

Step-by-step description of the utility of MR/TRUS fusion in focal cryotherapy. First, MR to TRUS fusion is performed at the beginning of the procedure. The needles are then placed under MR/TRUS fusion. Note that in this case the bottom cryotherapy needle was placed into the margin of the tumour (middle image). As the ablation area expands around, a 1cm margin is secured. Finally, real-time control of the ice-ball is possible also without fusion, but the continuous presence of the MR contour over the ultrasound allows to verify lesion coverage as well as adequate margins.

Figure 3

One week contrast enhanced MRI showing complete ablation in the treatment area (blue arrow). Follow mpMRI at 12 months shows right anterior gland distortion on T2 anatomical sequences with no residual restriction on DWI, and absence of suspicious enhancement on DCE (green arrow).

Supplementary figure 1

Box and whisker graph displaying sexual function variation after treatment, as measured by the IIEF-15 questionnaire.

Supplementary figure 2

Box and whisker graph displaying urinary function variation after treatment, as measured by the IPSS questionnaire.

Supplementary figure 3

Box and whisker graph displaying the variation of IPSS quality of life domain after treatment.

Supplementary figure 4

Box and whisker graph displaying continence function variation after treatment, as measured by the UCLA-EPIC incontinence questionnaire.

Supplementary figure 5

Box and whisker graph displaying the variation of PSA value after treatment.

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