Novel treatment (new drug/intervention; established drug/procedure in new situation)

Salvage radiotherapy after high intensity focused ultrasound for prostate cancer

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Summary

High-intensity focused ultrasound (HIFU) is a technique that has been used to treat localised prostate cancer. There is no standard treatment for patients who relapse with prostate cancer following primary treatment with HIFU; here we report the case of a patient who was successfully treated with external beam radiotherapy for disease relapse following HIFU. To date, our patient remains disease free with no toxicity from his treatment.

BACKGROUND

High-intensity focused ultrasound (HIFU) is a technique that uses focused ultrasound waves to generate heat, which then destroys areas of the target tissue. It has been used to treat localised prostate cancer and the non-invasive technique is performed under general or spinal anaesthesia. HIFU has been used as a primary treatment for localised prostate cancer; one study containing 803 patients who received primary treatment with HIFU found 5-year biochemical relapse-free survival rates of 83%, 72% and 68% in low-, intermediate- and high-risk patients, respectively.¹ Recognised complications following HIFU include retention of urine, impotence, urinary incontinence and recto-urethral fistula. A recent systematic review did not support the use of HIFU for the treatment of localised prostate cancer²; this conclusion was based on the fact that there are no randomised control trials comparing HIFU to standard treatment, the median length of follow-up in the case series is short, and the published case series do not contain exclusive groups of patients. The National Institute for Health and Clinical Excellence (NICE) has recently reviewed the lines of evidence available on the safety and efficacy of HIFU.³ NICE has commented that the clinical efficacy assessed by a reduction in prostate-specific antigen (PSA) levels and biopsy findings appears to be adequate for supporting the use of HIFU for the treatment of prostate cancer provided that the normal arrangements are in place for consent, audit and clinical governance. NICE has also recently reviewed the use of focal prostate therapy using HIFU.⁴ In addition, HIFU can also be used as a salvage treatment for local recurrence after the failure of primary external beam radiotherapy.

There is no defined treatment pathway for patients following local relapse of prostate cancer in patients who received HIFU as their primary treatment. Consideration must be given to offer radical treatment to patients with only local relapse, while taking into account cumulative toxicities of treatments in patients who have already received HIFU. Here we describe only the second reported

case outside of France, where salvage radiotherapy was successfully delivered to a patient with local relapse of prostate cancer following HIFU.

CASE PRESENTATION

The patient presented in 2007, aged 66, with lower urinary tract symptoms. The patient had ischaemic heart disease, hypertension, asthma and hypercholesterolaemia. He had no family history of prostate cancer.

INVESTIGATIONS

Examination revealed an abnormal feeling prostate, clinical stage T2 cancer and a PSA of 12.6 µg/l. A transrectal ultrasound-guided biopsy of the prostate was performed, which confirmed adenocarcinoma of the prostate in the right-sided biopsies, Gleason 4 + 3 = 7, in four out of five cores, involving 60% of the volume of the cores. The left-sided biopsies showed foci of high-grade prostate intraepithelial neoplasia but no evidence of invasive malignancy. A bone scan showed no evidence of bone metastases, and the MRI stage was T2N0M0. The prostatic volume was 46 cc.

TREATMENT

In order to reduce the prostatic volume prior to HIFU, the patient received 12 weeks of bicalutamide 150 mg daily, and had a transurethral resection of the prostate (TURP). The patient's PSA level was not rechecked following the commencement of hormones and prior to HIFU treatment. In August 2007, the patient received HIFU as the primary radical treatment for his prostate cancer. Following HIFU, the PSA fell to 0.1 µg/l. The patient had some postprocedure impotence which was treated with Levitra and medicated urethral suppository for erection (MUSE) urethral pellets. There was a slow rise in his PSA over a period of 3 years. In 2010, his PSA had risen to 4.4 µg/l and on clinical examination the prostate was small and fibrotic. A further transrectal ultrasound biopsy was performed which confirmed local relapse of his prostate cancer. Histology showed bilateral invasive

adenocarcinoma, Gleason 4 + 3 = 7 involving two of three cores and 40% of the core volume. The patient was unable to tolerate a further MRI; however, a CT scan showed a small prostate gland with no evidence of extra-prostatic disease. The patient was started again on bicalutamide 150 mg once daily. Following discussion with the urology multidisciplinary team, the patient was referred to a clinical oncologist for the consideration of prostate radiotherapy. The patient was then counselled about the advantages and disadvantages of radiotherapy, and following informed consent, the patient received radical external beam radiotherapy to the prostate and seminal vesicles. A radiation dose of 64 Gray in 32 fractions was administered over 6.5 weeks.

OUTCOME AND FOLLOW-UP

At the end of the course of radical radiotherapy, the patient had mild fatigue, Radiation Therapy Oncology Group (RTOG) grade 2 skin reaction and grade 1 bladder toxicity. Following radiotherapy, the patient's PSA fell to an unrecordable level ($<0.03 \mu\text{g/l}$). The acute radiation toxicity quickly resolved and, to date, the patient does not have any late radiation toxicity. Fluctuations in the patient's PSA over time are illustrated in figure 1. The patient remains in good health and in complete clinical and biochemical remission.

DISCUSSION

HIFU is not yet established as a primary treatment for localised prostate cancer. This may change in the future as more trials are performed and current data mature. The more common use of HIFU is as a salvage therapy for biochemical relapse following radical external beam radiotherapy. Previous work suggests that salvage HIFU can be a safe salvage therapy.⁵ In contrast, salvage radiotherapy for primary HIFU failure is an uncommon situation, particularly in the UK. Similarly to our own findings, Pasticier *et al*⁶ showed in a series of 45 patients that salvage radiotherapy after HIFU was feasible with no undue toxicity. Salvage surgery has been shown to be possible following the failure of primary HIFU; however, 6 out of 14 patients in this report had pT3a disease.⁷ In view of the high rate of positive margins, we suggest that

radical radiotherapy is a more appropriate salvage treatment following the failure of HIFU.

There are two published case series from France describing the use of salvage radiotherapy for biochemical failure following HIFU for localised prostate cancer.^{8,9} In the first study, Riviere *et al*⁸ found that of the patients treated with salvage radiotherapy alone, progression-free survival was 72.5% at 5 years. Ripert *et al*⁹ found that the disease-free survival was 83.3% at 36.5 months.

This case report suggests that radical radiotherapy can be delivered following HIFU with acceptable acute toxicity. Our patient has not developed any late toxicity following radiotherapy and he will require ongoing surveillance for this. The cumulative toxicity of HIFU and radiotherapy must be considered in such cases, in particular the risk of significant toxicities such as recto-urethral fistulae. In order to deliver radiotherapy safely, dose-volume histogram parameters must be respected.

To our knowledge, there is only one other reported case of salvage radical radiotherapy for biochemical relapse of prostate cancer after HIFU in the UK.¹⁰ This report is similar to our own in that the radical radiotherapy was well tolerated; however, a hypofractionated radiotherapy regimen was used and the PSA did not fall dramatically after radiotherapy as it did in this case report.

If the use of HIFU continues to increase, cases similar to the one described here will become more prevalent. Salvage prostate radiotherapy appears to achieve good biochemical control with acceptable acute toxicity. Patients with local relapse of prostate cancer following HIFU should be offered the option of external beam radiotherapy and such patients should be followed up carefully and assessed for unexpected late toxicity.

Learning points

- High-intensity focused ultrasound (HIFU) is a National Institute for Health and Clinical Excellence-accepted but less widely used primary therapy for localised prostate cancer. HIFU is being explored as a focal therapy for primary prostate cancer.
- Following biopsy-proven relapse of prostate cancer after HIFU, radical external beam radiotherapy can be delivered as a salvage therapy with acceptable acute toxicity.
- Salvage radiotherapy after HIFU can achieve good biochemical control of prostate cancer.

Competing interests None.

Patient consent Obtained.

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Figure 1 Fluctuations in prostate-specific antigen with time and following radical interventions.

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