Photodynamic Therapy Using Meso Tetra Hydroxy Phenyl Chlorin (mTHPC) in Early Prostate Cancer

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Background and Objectives: Prostate cancer is increasing in incidence, but current treatments including surgery and radiotherapy have significant side effects. This pilot study was designed to assess the potential of photodynamic therapy (PDT) using meso tetra hydroxy phenyl chlorin (mTHPC) for organ confined prostate cancer.

Study Design/Patients and Methods: Six men with organ confined prostate cancer were photosensitised with mTHPC (0.15 mg/kg). Between 2 and 5 days later, red light (652 nm) was delivered to areas of biopsy proven cancer via fibres inserted through transperineal needles (50–100 J per site).

Results: After 8 of 10 PDT sessions, the prostate specific antigen (PSA) fell by up to 67%. Early MRI scans showed oedema and patchy necrosis, which resolved over 2 months. Biopsies of treated areas revealed necrosis and fibrosis at 1–2 months.

Conclusions: PDT for primary prostate cancer appears safe and can reduce PSA levels. As this was a phase I study, no attempt was made to treat the whole prostate; this or targeted tumour ablation could be attempted in a phase II study with an increased number of fibres. This technique merits further investigation in early prostate cancer. Lasers Surg. Med. 38:356–363, 2006.

Key words: minimally invasive treatment

INTRODUCTION

Prostate cancer is the second most frequently diagnosed male cancer in the United Kingdom, and the second commonest cause of cancer related death in the USA [1,2]. Since the advent of prostate specific antigen (PSA) testing, cancers are being diagnosed at an earlier stage and in younger men. However, the optimum treatment for any particular individual is often uncertain because a significant proportion of those with organ confined disease will not gain a survival benefit from radical treatment, and risk side effects, including incontinence and erectile dysfunction [3–5].

If radical treatment does not offer a survival benefit, men with organ confined prostate cancer will seek treatment options which have less impact on quality of life. Minimally invasive treatments are being developed with this in mind. Photodynamic therapy (PDT) is one such option.

PDT uses a photosensitising drug, activated by low power light, usually from a laser, which then produces cytotoxic reactive oxygen species. The first report of its use in the management of prostate cancer was the description of two cases treated with the photosensitiser porfimer sodium and transurethral light delivery. This was done 6 weeks after a transurethral resection of the prostate (TURP) [6]. In a larger study published more recently using percutaneous, interstitial light delivery, 14 patients with locally recurrent disease following external beam radiotherapy were treated with PDT using meso tetra hydroxy phenyl chlorin (mTHPC) [7]. The results were encouraging with up to 91% necrosis of the prostate seen on post-treatment MRI scans and a reduction in PSA in 9 of 14 patients (2 to undetectable levels).

During the latter study undertaken in our centre, several newly diagnosed patients requested PDT as a primary treatment for prostate cancer. Our ethics committee approved this and the results are reported here.

PATIENTS AND METHODS

Patients were recruited from urology outpatients at the University College London Hospitals. All had histologically proven, untreated, organ confined, prostate cancer, as assessed by MRI and bone scan. Each patient was either unsuitable for, or declined alternative treatments and had requested PDT. All patients were sensitised with 0.15 mg/kg of mTHPC (Scotia Quanta Nova, Guildford, now produced by Biolitec, Edinburgh, UK) given intravenously.

As the time for maximal concentration of mTHPC in the untreated normal prostate and cancer areas was not

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known, drug light intervals of 2–5 days were used and quadrantic biopsies taken immediately prior to light delivery. These were dropped into isopropane cooled in liquid nitrogen and cryosections prepared for fluorescence microscopy, as described previously [8]. Fluorescence was excited using an epi-fluorescence microscope and the resulting image false colour coded. The level of mTHPC fluorescence was quantified in the normal and neoplastic prostatic epithelium and in the stroma for each drug light interval.

As this was a phase I/II study, no attempt was made to treat the whole gland. Treatment was limited to areas of cancer as detected by biopsy, along with the peripheral zone of the same lobe, from base to apex. Light was delivered under sedation with pethidine and midazolam and antibiotic prophylaxis (Gentamicin 120 mg, IV) using 4–8 MRI compatible 16G Kellet needles (William Cook, Denmark) inserted in a freehand manner through the perineal skin under transrectal ultrasound or open access MRI guidance. As in our study on post-radiotherapy patients, the transperineal route was used as the canine studies [9] and the case report [6] showed the transurethral route to be associated with considerable morbidity, particularly urethral sloughing and urinary retention. Laser light at 652 nm was delivered through the needles using two types of optical fibre and a four-way fibre splitter (Applied Optronics Corporation, South Plainfield, NJ). For bare tip fibres, the needle was pulled back after fibre insertion to leave 3 mm of fibre protruding into the tissue. For diffuser fibres (Rare Earth Medical, West Yarmouth, MA), clear plastic sheaths were introduced over the MRI compatible needles, then the needle removed and the fibre inserted through the sheath. The needle positions were checked using the open access MRI scanner. Some of the fibres were used in multiple positions (up to four), where a fibre was pulled back after the first treatment, to give a light dose closer to the prostatic apex along the same needle track. Areas close to the capsule, neurovascular bundles, external sphincter, and urethra were exposed to PDT in all patients, particularly during treatment of the prostatic apex.

The total light dose per lobe varied between patients and was dependent on the volume of tissue to be treated. Mid and basal prostate was treated with light doses of 100 J (bare fibre) or 100 J/cm (3 cm diffuser fibre), while areas near the prostatic apex received doses of 50 J or 50 J/cm, respectively. The laser power output was kept low (150 mW for a bare tip fibre and 100 mW/cm for the diffuser fibre) to avoid thermal effects or charring of the fibre tip and subsequent loss of light transmission. Both bare tip and diffuser fibres were used in order to assess the effect of each.

Rectal integrity was monitored by flexible sigmoidoscopy prior to PDT and 2–5 days after PDT. The prostate was assessed by contrast enhanced MRI prior to PDT, at 2–6 days and up to 2–3 months following PDT. Tumour response was assessed by monitoring PSA levels, and by TRUS guided sextant biopsies. Urinary and sexual function were monitored by questionnaires (AUA-7 and Barry et al.) [10,11]. Following drug administration, patients were advised to stay in reduced light conditions for up to 6 weeks, in order to avoid activation of the photosensitiser in the skin, and subsequent sunburn like reactions. The precautions included staying in a darkened room with a light bulb of 60 W or less, and keeping at least 2 m away from a television for the first 24 hours; to gradually increase light exposure over the next 7 days in order to help to eliminate the drug from the skin, whilst avoiding bright light by staying away from windows and doors, and covering skin with close weave clothing if outside. Protective glasses were given to all patients. During subsequent weeks, light exposure could be increased, although patients were warned that if they experienced any prickling or burning sensation in the skin or eyes they should go into a darkened room immediately.

Three months following PDT patients with evidence of locally persistent disease were offered further treatment, including repeat PDT.

RESULTS

A total of 10 treatments were undertaken on 6 patients (mean age 66 years, range 61–71, Gleason score 3+3 in all, PSA prior to treatment 1.9–15). Treatment details are shown in Table 1. Fluorescence microscopy showed the highest concentration of mTHPC in the epithelium and the highest epithelial:stromal concentration ratio with a drug light interval of 2 days, although the number of measurements available was insufficient to show statistically significant differences.

Four of the six patients had two treatments. Each patient was offered repeat treatment following the finding of persistent cancer on biopsy. One patient (F) chose to continue on a monitoring programme, and another chose to have external beam radiotherapy at this point.

Eight of the 10 PDT sessions resulted in a reduction in PSA (Fig. 1). The percentage reduction in PSA was calculated for each patient, and was found to vary from 67% reduction to an increase of 133%. This increase was in a man who had been on hormone therapy prior to PDT and whose pre-PDT PSA was 2.7 compared to a pre-hormone therapy level of 10.1. If the PSA readings relating to both of the treatments for this patient are excluded, the mean percentage reduction for the eight remaining treatments is 48.3% (range +2% to 67%; Table 1).

Biopsies of treated areas 1 month after PDT revealed necrosis and early fibrosis, along with areas of haemorrhage. Six cores were taken in all but one patient who underwent biopsy by a doctor unfamiliar with the protocol. At 2 months, areas of established fibrosis with increased vascularity were seen, consistent with healing after necrosis (Fig. 2). Some patients also showed evidence of a chronic inflammatory response at 2 months.

MRI changes 2–6 days after PDT were variable. In some cases, there were diffuse, patchy areas of reduced enhancement, although in others the zones of devascularisation (believed to indicate necrosis) were much better defined, with marked oedema in treated areas, sometimes extending into peri-prostatic areas. One month after treatment, healing was advanced and by 2–3 months, most oedema

TABLE 1.

Patient	Age	Cancer stage	Treatment no.	Fibre type (no. of fibres)	Drug light interval (days)	Total energy, Joules (no. of sites)	PSA (ng/ml) prior to treatment/ nadir (months post-PDT)	% PSA reduction per treatment (pre-PDT—nadir)/ pre-PDT)	Pre-PDT prostate volume (cm^3)	Post-PDT necrosis in first week (cm^3)[b]	Volume reduction (pre to >1/12 after last PDT)	No. of positive cores/ total cores pre-PDT	No. of positive cores/ total cores post-PDT	AUA pre-PDT/ 3 months post-PDT	Potency before/ after PDT
A	62	T2b	1	Bare	3	N/a	15.0/5.0 (3)	67	N/a	Patchy		3/4	3/4	N/a	+/+
			2	Bare (8)	3	1,350 (27)	5.0/5.1 (1)	+2	61	1.7	N/a	3/4	3/6	2/4	+/+
B	71	T2a	1	Diffuser + bare (5)	5	1,150 (13)	10.4/3.9 (2)	63	87	1.2		2/6	4/6	0/0	−/−
			2	Bare (4)	3	1,400 (16)	5.5/4.4 (1)	20	67	Patchy	36%	4/6	1/6	0/2	−/−
C	61	T2b	1	Diffuser (4)	2	1,800 (6)	2.7[a]/6.3 (10)	+133	57	4.6		2/8	1/6	3/3	−/−
			2	Diffuser (4)	3	1,800 (8)	7.2/4.7 (9)	35	58	Patchy	22%	1/6	2/6	3/11	−/−
D	70	T2c	1	Bare (4)	3	1,400 (16)	10.3/3.9 (3)	62	50	13.6	21%	4/6	2/6	18/10	+/+
E	62	T1c	1	Diffuser (4)	5	1,200 (4)	3.6/3.1 (5)	14	168	51.1		3/7	3/6	15/8	+/±
			2	Diffuser (6)	2	900 (6)	3.1/1.6 (2)	48	109	18.3	35%	3/6	4/6	8/8	+/±
F	70	T2c	1	Bare (4)	2	300 (8)	1.9/1.0 (2)	47	31	3.0	33%	4/6	1/6	18/11	−/−

All areas of reduced uptake had disappeared in scans taken more than 1 month after PDT.

N/a: data not available.

[a]PSA 4 months after stopping Zoladex and Casodex. PSA 10.1 prior to commencing hormonal treatment.

[b]The figures given indicate volumes of necrosis. In all cases, there were more extensive new areas of reduced uptake of contrast, which may have represented localised necrosis or ischaemia.

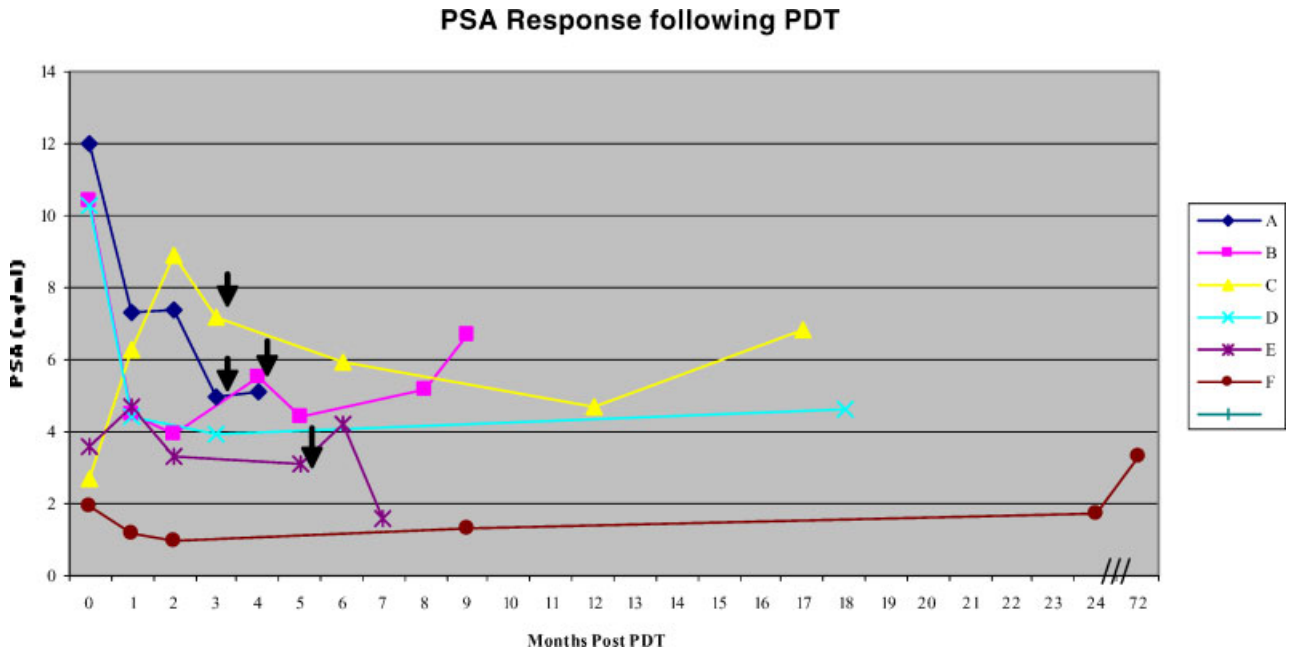

Fig. 1. PSA levels are shown prior to PDT (month 0) and until alternative treatment was commenced (in four patients) or until last recorded (Patient F has had no additional treatment and has a level of 3.3 ng/ml at 6 years after PDT). The arrows show the time of second PDT treatments. [Figure can be viewed in color online via www.interscience.wiley.com.]

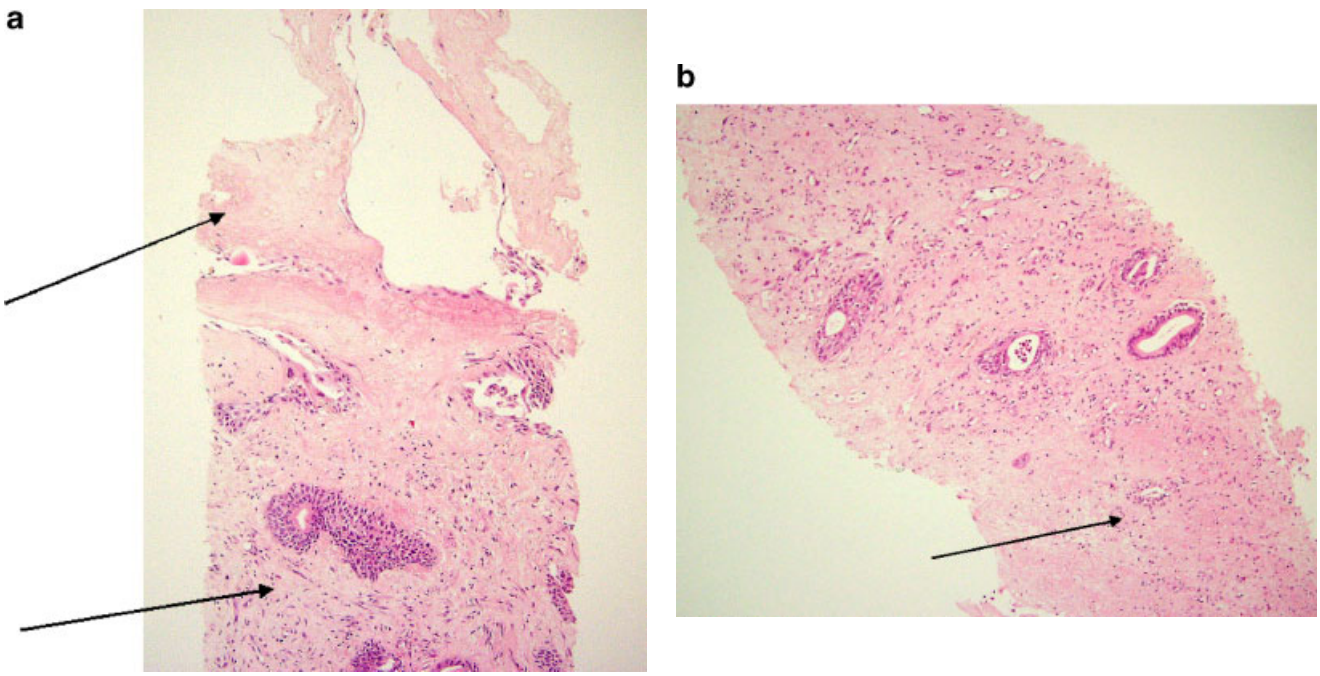

Fig. 2. Histological changes following PDT (**a**) biopsy 1 month post-PDT. The lower arrow shows unaffected tissue, and the upper arrow points to an area of necrosis. Magnification 10×. **b**: Biopsy 2 months post-PDT. The arrow shows vascular inflammation and fibrosis. Magnification 10×. [Figure can be viewed in color online via www.interscience.wiley.com.]

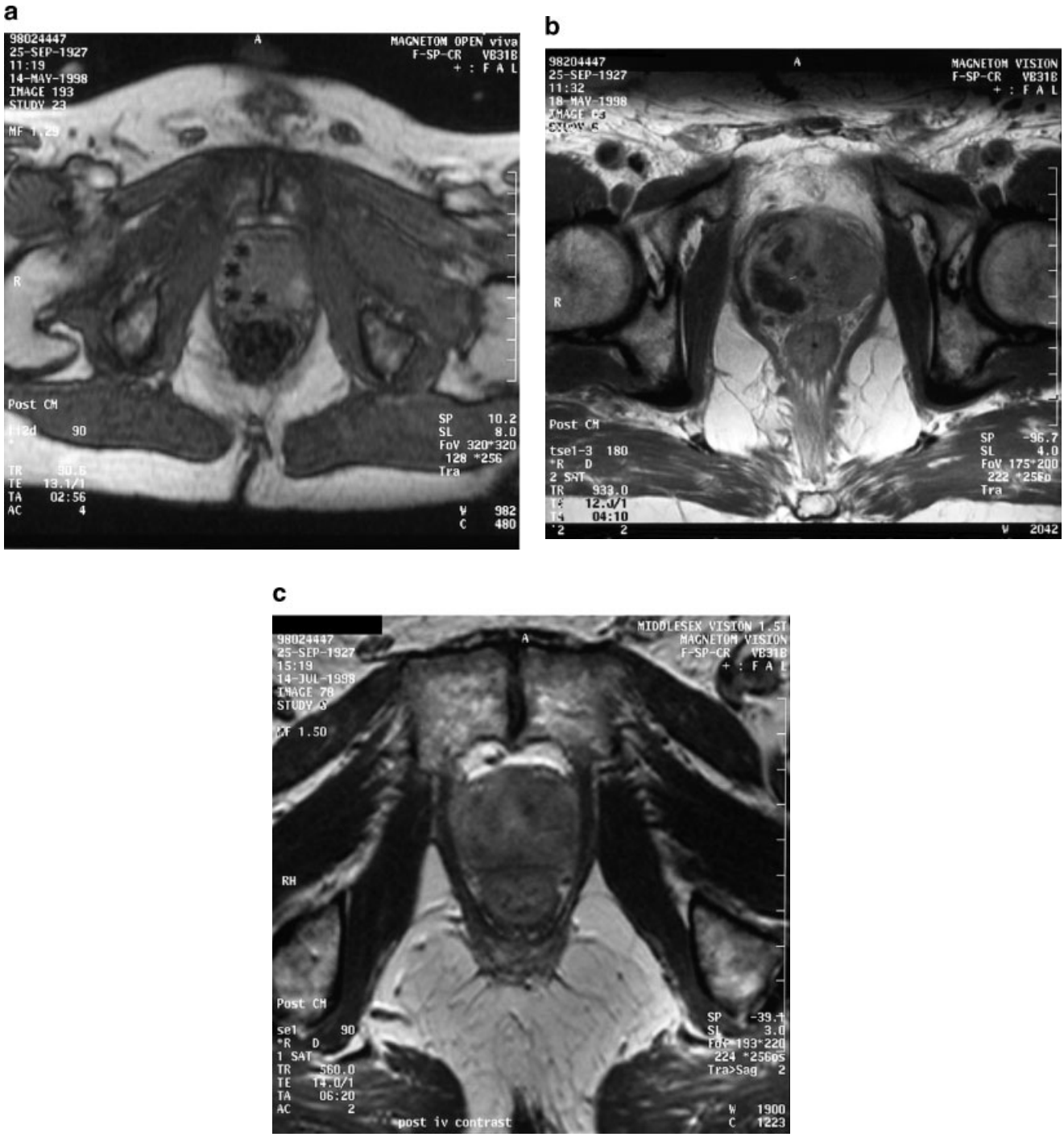

Fig. 3. Contrast enhanced MRI of Patient D, first treatment (**a**) four needles in right lobe of the prostate, just prior to light delivery. **b**: Four days after light delivery, the right lobe shows large areas of loss of enhancement, which indicate early necrosis. **c**: Two months after treatment the enhancement pattern is almost entirely returned to that prior to therapy, indicating resolution of necrosis. Histology suggests that healing is by fibrosis.

and necrosis had resolved (Fig. 3). In the first week after PDT, the prostate volume increased from that documented prior to PDT by a median of 28% (range 5%–62%), due to oedema and inflammation, but by 2–3 months there was an overall reduction in prostate volume below the pre-treatment size, ranging from 21% to 35% (Table 1).

Assessment of tumour volume was done in the knowledge that not all tumour is visible on MRI and that needle core

biopsies are susceptible to sampling error. The number of positive biopsies before and after PDT were recorded, as shown in Table 1. However, as the technique varied between pre- and post-PDT biopsies, it is difficult to relate this to changes in tumour volume.

Post-procedure perineal discomfort was well controlled with simple oral analgesics. The catheter inserted for the procedure was removed prior to hospital discharge (1–4 days post-treatment). All patients had irritative voiding symptoms for the first 2 weeks following treatment, but apart from this, four of the six patients had no more than very minor complications. The other two had more troublesome problems after their second PDT. Each required temporary re-catheterisation and one of these subsequently experienced mild stress and urge incontinence, which resolved spontaneously over 4 months. One of these patients developed a gram-negative sepsis the day after his first PDT, despite antibiotic prophylaxis, but this responded well to intravenous antibiotics and fluids.

From the questionnaire on sexual function, only one of the three patients with reasonable erectile function at presentation reported any deterioration after PDT, which he attributed to worsening angina and performance anxiety. This resolved after 5 months, but deteriorated again when he commenced hormone therapy, prior to radiotherapy. The questionnaire concerning urinary symptoms showed that only one patient had a markedly worse AUA-7 score 3 months after PDT than he had prior to treatment (Table 1). A paired t-test showed that there was no statistically significant difference between pre- and post-PDT AUA scores ($P = 0.55$).

Three patients had areas of erythema seen on flexible sigmoidoscopy after PDT, two of whom passed a few specks of blood, but these changes resolved completely within a month without intervention.

All patients had residual cancer in at least one biopsy taken after PDT. Four patients decided to undergo radiotherapy (three had external beam radiotherapy, and one had brachytherapy). One patient had cryotherapy 18 months after PDT, and the sixth patient remains well 6 years after PDT with a PSA of 3.3, and has had no further treatment.

DISCUSSION

Prostate cancer is a multi-focal disease and it is difficult to identify every focus of disease on pre-treatment imaging [12,13]. Thus the key to any new minimally invasive treatment for organ confined disease is to destroy as much as possible of the glandular tissue without any serious or persistent side effects. A major attraction of PDT is that as there is no change in tissue temperature, there is little effect on the structural connective tissue, like collagen, which allows the mechanical integrity of hollow organs to be maintained. It has been shown experimentally that PDT to the prostate can produce small areas of rectal mucosal necrosis. However, these areas heal by regeneration of normal mucosa and the submucosal collagen is unaffected, so minimising the risk of an urethro-rectal fistula [9]. Further PDT can be applied repeatedly to the same areas, even in previously irradiated tissue. It does not carry the cumulative toxicity associated with ionising radiation [7].

The other potential problems are with continence and erectile function. The irritative symptoms described by all patients early after PDT were most likely due to urethral inflammation and necrosis, but these resolved in a short time, as predicted from the canine studies [9]. Only one patient had a period of mild stress incontinence (4 months), but this resolved spontaneously. His MRI showed extensive PDT effects around the prostatic apex and distal urethral sphincter. This was similar to the effects seen previously in the post-radiotherapy patients, in whom stress incontinence after PDT resolved, although sometimes over a longer period [7]. These results support the contention that PDT induced damage to continence mechanisms is likely to be reversible, although of course it would be preferable for continence not to be affected at all.

In the patient who experienced a reduction in erectile function, the post-treatment MRI showed involvement of the right and left neurovascular bundles in the PDT affected areas. His performance returned to pre-treatment levels over 5 months. The other two patients who maintained erectile function after PDT had only unilateral neurovascular bundle effects on their post-PDT scans, which suggests that only bilateral neurovascular bundle involvement causes a transient reduction in potency. In the post-radiation patients, deterioration in potency after PDT was not reversible, and was most likely related to underlying damage from the radiotherapy [7].

The reduction in prostate volume of 21%–35% at 2–3 months post-treatment was unexpected. This was considerably larger than the 5% reduction typically seen in previously irradiated prostates at comparable times after PDT, although slightly larger reductions were seen at later follow up times in this group. PDT studies on the normal canine prostate showed necrosis of glandular tissue, but preservation of collagen with minimal changes in volume [9,14]. It has been suggested that PDT may have a role in the management of benign prostatic hyperplasia (BPH) [14], but this seems unlikely. The volume reductions are relatively small, the gland enlarges, due to oedema and inflammation, before it gets smaller and the limited shrinkage is not apparent until several weeks after treatment.

PDT was done following confirmation of cancer on routine biopsy. The number of cores taken ranged from four to eight, which was common in clinical practice at the time. This has now changed and the routine practice at our institution is to take eight cores at first transrectal biopsy. The ideal situation would be to do template guided transperineal histological mapping of the prostate both before and after PDT. This is being considered for future studies. Also, as the aim of this phase 1 study was to assess the extent of PDT effect, whilst minimising side effects, tumour volume reduction was not as extensive as would be anticipated in future studies.

Falls in PSA were documented in this study and in the previous one on post-radiotherapy patients, presumably

related to a reduction in the volume of viable cancer, normal prostate glandular tissue, and possibly any adenomatous tissue present. The significance of PSA reduction where there was no attempt to ablate the whole gland is uncertain. Both the absolute level of nadir PSA and the time to nadir are parameters that will be evaluated in further work on PDT for early prostate cancer.

A serious disadvantage of PDT with mTHPC is the prolonged period of skin photosensitivity. However, experimental and clinical studies with prostate cancer are currently under way with a new photosensitiser, WST09 (a palladium metalated bacteriopheophorbide, Tookad, Negma-Lerads, France). WST09 remains localised primarily to the vasculature and clears from the body within a few hours rather than several weeks. The optimum drug light interval is so short that light delivery can commence before a 20-minute infusion of the drug is complete. Experimental studies suggest that there is less urethral damage with WST09 than with mTHPC, although the volume of glandular necrosis that can be achieved around each fibre position is about the same [15,16]. The first phase I clinical study with WST09 in patients with local recurrence of prostate cancer after radiotherapy has shown that the technique is safe, that the PSA can be reduced, and that areas of necrosis can be documented on MRI scans [17].

Another photosensitiser that has been investigated for prostate PDT is 5 ALA-induced protoporphyrin IX (ALA). The advantage of ALA is that it has a much shorter drug light interval (6 hours) and much reduced skin photosensitivity compared to mTHPC. ALA has been assessed in the canine model by Chang et al. [18]; Johnson et al. [19], and Sroka et al. [20]. Chang produced lesions of 1–2 mm diameter at an ALA dose of 100 or 200 mg/kg with transperineal activation at doses of 360 J at 100 mW. A larger lesion was seen with a higher light dose of 1,080 J at 300 mW, but as this was almost identical to the lesion seen with the light only control, it was concluded that this was probably a thermal effect. In contrast to this, Johnson et al. using 100 mg/kg ALA activated by 1,755 J delivered tranurethrally at 650 mW, saw lesions of up to 10 mm depth; it is likely that at this power the effect could have also been thermal.

Sroka et al. used a smaller dose of 50 mg/kg in the canine model, with a light dose of 50 or 100 J/cm and a power of 200 mW using a cylindrical diffuser inserted interstitially following surgical exposure. A lesion size of 11 and 12 ± 2 mm was seen at each respective light dose.

In the present study, the areas of PDT induced necrosis seen on the MR scans seem relatively small compared with the percentage fall in PSA, especially when contrasted with the same measurements on the post-radiation patients, so the scans may not be identifying the full extent of PDT necrosis. This could only be clarified if patients who had undergone PDT with follow-up MR scans subsequently underwent a prostatectomy.

We did not attempt to ablate the entire prostate, but with improvements in the accuracy of needle placement and in drug and light dosimetry, it should be possible to destroy all the glandular tissue with no unacceptable effects in adjacent organs. The apex was given a reduced light dose in this pilot study in an attempt to limit the risk of incontinence due to damage to the urethral sphincter, which is adjacent to the prostate apex.

Transrectal ultrasound guided needle placement, using a perineal template, as used for high dose rate (HDR) prostate brachytherapy [21], will enable needle placement to be performed accurately and quickly, which will, in turn make treatment of the whole prostate feasible in one session. In this study, the effects documented in adjacent organs were relatively minor and reversible.

In future studies, with improved imaging of the prostate using MRI spectroscopy, and dynamic contrast enhanced MRI (DCE-MRI) it is hoped that it will be possible to target the tumour directly. It is anticipated that this will allow a targeted light dose to ablate tumour, whilst reducing the PDT effects outside the prostate, and hence reducing side effects. This will require the use of multiple cylindrical diffusers.

CONCLUSION

This pilot study demonstrates that PDT can produce necrosis in previously untreated prostate cancer, with a resulting reduction of PSA. PDT appears worthy of further study as a therapeutic option for newly diagnosed patients with prostate cancer who are unsuitable for or who decline other management options.

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