Does photodynamic therapy have the necessary attributes to become a future treatment for organ-confined prostate cancer?

CAROLINE M. MOORE*†, IVAN M. HOH*†, STEPHEN G. BOWN* and MARK EMBERTON†
*National Medical Laser Centre, and †Institute of Urology, University College London, London, UK

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INTRODUCTION

Most would agree that there are too many treatment options for men with early prostate cancer. The decision-making process is already complex and fraught with difficulties [1]. It seems logical therefore that any new treatment entering the arena must do so on the basis that it offers distinct advantages in terms of acceptability, side-effect profile or efficacy. We think that photodynamic therapy (PDT) offers promise in these three areas, and will argue this below.

Two interesting attributes of PDT that make it worth pursuing as an intervention in organ-confined prostate cancer relate to potential selectivity of tissue destruction. The first relates to the distribution of photosensitizer throughout the body. A photosensitizing agent administered intravenously will achieve different concentrations in adjacent organ systems at any given time. An understanding of tissue concentrations over time in the target organ and its adjacent structures mean that an optimum time and duration of light delivery can be sought.

The second relates to potential selectivity of effect. By this we mean that it may be possible that cancer cells and their supporting structures may sustain lethal injury at lower drug or light levels than comparable healthy tissue. The evidence for this will be reviewed.

MECHANISM OF ACTION

Before addressing the specific attributes of PDT for prostate cancer we outline how PDT works (Fig. 1). Three elements need to be present for a photodynamic effect to occur; photosensitizer, light and oxygen. The photosensitizer is administered in a stable form (ground state). It is then promoted to a higher energy state (singlet state) by light of a specific wavelength. The excited photosensitizer is then unstable and can release energy in one of three ways, i.e. emission of heat, emission of light, or conversion to an intermediate energy state (triplet state), before returning to stable ground state. In triplet state the photosensitizer can produce hydroxyl and superoxide radicals (type 1 reaction), or convert molecular tissue oxygen to form singlet oxygen (type 2 reaction). This singlet oxygen in turn reacts with proteins, lipids and nucleic acids in cells, causing functional and structural damage which leads to cell death. Hydroxyl and superoxide radicals are also directly responsible for cell death, although it is thought likely that type 2 reactions are more important for many of the photosensitizers [2]. It is likely that the immune response to PDT plays a part in its action, particularly in the long term. However, although this has been studied in animal models, it requires further study in the clinical setting [3].

PATIENT ACCEPTABILITY

Patients faced with a choice of treatments for organ-confined prostate cancer must balance the likely harms and benefits of each option. When the optimum treatment for cancer control is not clear, then the harms associated with each treatment tend to drive the decision-making process. One aspect of this is the reduction in quality of life whilst undergoing the treatment; this is influenced by the duration and bother of the treatment.

Radical prostatectomy involves a hospital stay of a few days, followed by a further period with a catheter, usually recuperating at home. External beam radiotherapy involves many outpatient visits. For PDT, older photosensitizers had a drug light interval of a few days, and patients would attend hospital once for drug administration and a second time for light delivery. Newer photosensitizers have drug-light intervals of a few minutes, so that PDT can be administered in a single session, on an outpatient basis.

After PDT there is rapid healing of affected tissues. PDT is not known to increase the cancer risk in surrounding tissues, or have any other form of cumulative toxicity. PDT can therefore be repeated if required. PDT is suitable for use after radiotherapy. A study in a canine model by Chen *et al.* [4] compared PDT after radiotherapy to that given to the treatment-naïve prostate. The lesion size at 1 week was comparable in each group, with a similar side-effect profile. The same photosensitizer is being studied as a primary and a salvage treatment, in the clinical setting.

SIDE-EFFECTS

Side-effects of prostate PDT are related to the photosensitizing drug and to the method used for light delivery, as well as the PDT effect itself. Traditionally, PDT has been associated with prolonged skin sensitivity which requires precautions against exposure to light for several weeks. Previously patients were required to wear close-weave clothes, protective glasses and hats. Some of the newer photosensitizers show very little skin accumulation, which is a significant advance.

The side-effects associated with placing many needles in the prostate (haematuria, infection, prostate oedema leading to urinary retention) are likely to be comparable for all similar techniques, such as low- and high-dose rate brachytherapy and cryotherapy.

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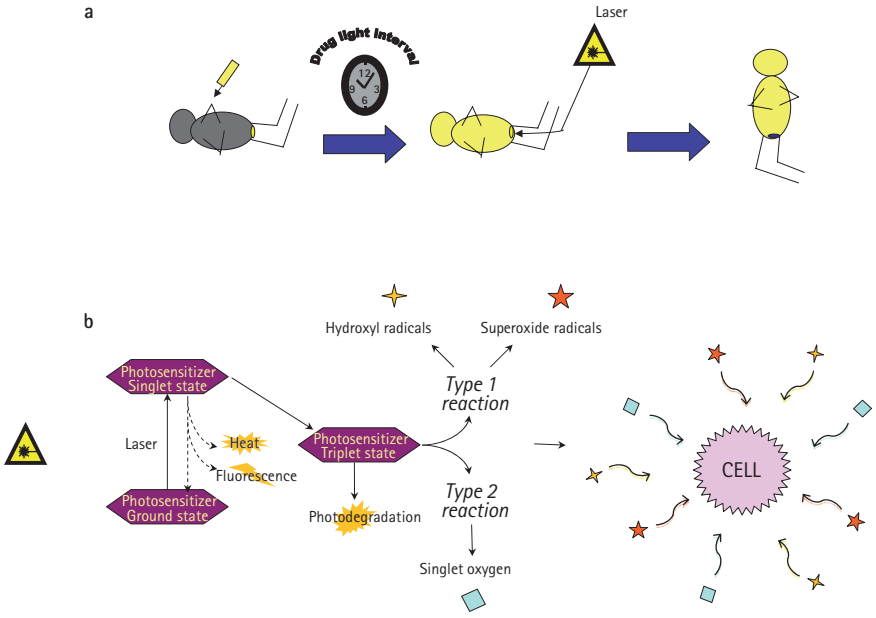
FIG. 1. ***a,*** *Mode of administration of PDT for prostate cancer. After systemic administration of a photosensitizer it is distributed throughout the body. The drug is activated in the prostate by light of a specific wavelength. The drug-light interval varies between different photosensitizers, and ranges from minutes to days. The laser light is directed into the prostate using optical fibres placed within hollow plastic needles. These needles are positioned using a perineal template and TRUS. After light exposure all fibres and needles are removed. The patient may have skin photosensitivity for some time after drug administration.* ***b,*** *The mechanism of action of PDT. The photosensitizer is administered in a stable ground state and is promoted to a higher energy state (singlet state) by light from a laser. The photosensitizer can then return to ground state by the emission of energy, either as heat or light (fluorescence). Alternatively, the photosensitizer can adopt an intermediate state (triplet state); it can then either undergo photodegradation, or a type 1 or type 2 reaction. In a type 1 reaction the photosensitizer reacts with the tissue to produce hydroxyl or superoxide radicals. In a type 2 reaction the photosensitizer reacts with molecular oxygen to produce highly reactive singlet oxygen. The hydroxyl or superoxide radicals, and singlet oxygen, all react directly with cells to cause necrosis.*



In the study of PDT after radiotherapy by Nathan *et al.* [5], two patients developed incontinence requiring surgical intervention, probably caused by direct sphincter necrosis, which could be avoided in future by improved light delivery techniques. Of seven patients who were potent before PDT four had erectile dysfunction afterward. It is possible that erectile function could be maximized by using a selective photosensitizer at a dose which affects glandular tissue more than nerves.

EFFICACY

Clinical work using PDT to treat several different cancers has shown that the PDT effect can be modulated to obtain excellent cancer control, both as a primary and a salvage treatment. Furthermore, it is established that PDT can cause necrosis in preclinical models of prostate cancer, and in the treatment-naïve and previously irradiated prostate in clinical studies. It is now necessary to establish the efficacy of PDT in treating the whole prostate, and to compare it with other treatments, discussed below.

PDT IN OTHER SPECIALITIES

PDT is used in a variety of specialities and for a range of diseases. It has been approved by the National Institute of Clinical Excellence (UK) for use in some cases of age-related macular degeneration [6]. It is approved in several countries for premalignant conditions, including Barrett's oesophagus, cervical dysplasia and actinic keratosis, and for cancers of the head and neck, oesophagus, lung and cervix. Many of the earlier uses of PDT were for treating superficial cancers, either cutaneous or subcutaneous. This was followed by the development of PDT for hollow-organ cancers. The use of PDT in solid-organ cancers (including pancreas, prostate, and head and neck) has been developed in more recent years, as light-delivery systems have been improved. Work at the National Medical Laser Centre in advanced head and neck cancer has shown PDT to be a valuable salvage treatment after the failure of surgery, chemotherapy and radiotherapy, as well as its use as a first-line treatment [7,8]. It is particularly suited to use in head and neck cancers, because of the need to avoid damage to nerves and blood vessels adjacent to the tumour, and to preserve function and cosmesis whenever possible. It is hoped that lessons learned in interstitial PDT in these other specialities will be applicable to the use of PDT in prostate cancer.

PRECLINICAL WORK USING PDT FOR PROSTATE CANCER

Initial work on PDT in prostate cancer cell lines transplanted into a rat model [9,10], established that prostate cancer cells are susceptible to killing by PDT, but further study was required in an anatomically relevant model. Studies were then carried out by several groups in the canine prostate [11–14]. Although this is a benign prostate model, it is the closest anatomical equivalent to the human prostate. Chang *et al.* [15,16] assessed several photosensitizers and concluded that meso-tetra-(m-hydroxyphenyl) chlorin (mTHPC) was the most effective photosensitizer available at the time for carrying out clinical studies.

Chen *et al.* [17] used WST-09 in a similar study, and produced lesions of >3 cm in diameter with a single interstitial fibre. The study was then repeated in dogs that had previously received prostate radiotherapy. There was no appreciable difference in either the volume of PDT necrosis or in side-effects [4].

The first report of PDT in clinical use for prostate cancer was in 1990, by Windahl *et al.* [18]. They found evidence of prostate cancer in chips from TURP, and 6 weeks later treated the TURP cavity with PDT using a haematoporphyrin derivative. Two patients were treated in a similar manner; one of them died from a previously undiagnosed lung cancer 6 months later, and at post mortem no

TABLE 1 Summary of clinical work on PDT for prostate cancer

Reference	Sensitizer	Patient group	Form of publication	Year of publication
Windahl *et al.* [18]	Haematoporphyrin derivative	After TURP (primary)	Letter	1990
Nathan *et al.* [5]	mTHPC	After radiotherapy	Paper	2002
Moore *et al.* [19]	mTHPC	Primary	Conference presentation	2003
Hahn *et al.* [20]	Motexafin lutetium	After radiotherapy	Conference presentation	2003
Zaak *et al.* [21]	Aminolaevulinic acid	Primary	Conference presentation	2003
Trachtenberg *et al.* [22]	TOOKAD	After radiotherapy	Conference presentation	2004

evidence of prostate cancer was found. However, Windahl *et al.* published no further work on prostate PDT.

The first formal clinical trial of PDT for prostate cancer was carried out at the Institute of Urology and the National Medical Laser Centre, University College London [5]. Fourteen patients who had recurrent prostate cancer after radiotherapy were assessed. The photosensitizer mTHPC (under the trade name Foscan™) was given intravenously, and 2–5 days later was activated in the prostate by light from a 652-nm laser. Optical fibres were inserted using a freehand transperineal technique within an open-access MRI scanner. The results were promising, with nine of the 14 patients showing a reduction in PSA level and evidence of necrosis on MRI and biopsy.

A smaller pilot study was carried out in patients, using PDT as a primary treatment [19]. Areas of cancer detected by biopsy, along with the adjacent peripheral zone, were treated, with four patients having a repeat treatment in the contralateral lobe. The same photosensitizer was used as in the group treated after radiotherapy, with similar light delivery techniques. The PSA level was reduced after eight of 10 treatments, with a mean reduction of 4 ng/mL per patient. TRUS-guided biopsy showed necrosis at 1 month after treatment, followed by fibrosis at 3 months. Other groups, using a variety of photosensitizers, are also carrying out clinical studies, some of which have been reported in abstract form (Table 1) [5,18–22].

It was clear that, whilst it was established that PDT could cause necrosis and reduce PSA levels in both the irradiated and previously untreated prostate, the treatment needed to be refined to treat 'the prostate, the whole prostate and nothing but the prostate'. There has been progress in several areas, with further areas awaiting translation of successful preclinical techniques into clinical work.

IMPROVEMENT IN TECHNIQUE

Previous studies used freehand placement of needles, with no continuous real-time imaging. Needle placement techniques developed for brachytherapy and cryotherapy, using a perineal template and real-time TRUS, are used in all the current clinical studies of prostate PDT.

Monitoring of light fluence in different areas of the prostate, urethra and rectum throughout treatment is used in current studies. This allows the light dose to be adjusted to obtain maximum light delivery to glandular tissue whilst minimizing light delivery to the urethra, rectum and urinary sphincter. It is likely that in the future computer software will be used to aid light dosimetry. This will take into account differences in individual light diffusers, and the range of optical properties seen in prostate tissue, to provide a personalized light-dose plan for each patient. Intraprostatic real-time drug and oxygen monitoring are also under development.

PDT has the potential to be selective in two ways. First, to affect the supporting structures, e.g. collagen, urethra and rectum, less than the prostate tissue. This could be achieved by a different initial response to treatment, or faster healing of normal tissue. Second, to affect malignant but not benign prostate tissue.

PDT has been shown in a canine model to have little effect on collagen at doses which ablate glandular tissue [15]. Thus, with appropriate drug and light doses, PDT could destroy prostate cancer whilst leaving the collagenous structure of the prostate gland intact.

There is evidence to suggest that PDT with some photosensitizers may be 'nerve-sparing'. Kubler *et al.* [23] studied the differential effect of PDT on nerves, blood vessels and surrounding tissue in a rabbit-groin model. They described complete necrosis of muscles, fat and connective tissue after mTHPC PDT, with no functional evidence of neurological damage despite up to 75% demyelinization. Clinical studies report similar findings, with preservation or restoration of nerve function after PDT of tumours compressing nerves [7,8,24]. Further work is underway in a preclinical setting to investigate whether this differential effect on nerves is seen with other photosensitizers, and which components of the PDT mechanism are responsible for it.

The selectivity of PDT for malignant rather than benign prostate tissue will depend on the photosensitizer being present in each tissue type in a different concentration, at the time of light delivery. Some photosensitizers are preferentially taken up by malignant tissue. This has led to the use of fluorescent photosensitizers in the detection of different superficial cancers and dysplasias, e.g. oral dysplasia, Barrett's oesophagus and superficial bladder cancer. It may be possible to exploit this property therapeutically, although this is seldom done at present.

Selectivity may be further improved by using specific targeting; two approaches to this are vascular targeting and molecular targeting. Vascular-targeted PDT is being developed with the photosensitizer palladium bacteriopheophorbide, or TOOKAD [25]. The photosensitizer is activated whilst in the vascular distribution stage, damaging tumour vasculature and causing subsequent necrosis. Vascular-targeted PDT is currently undergoing clinical trials in organ-confined

prostate cancer, both as a primary and a salvage treatment. Molecular targeting of PDT involves the use of a delivery system for the photosensitizer which leads to greater concentrations of drug in tumour tissue than in normal tissue. This is an area under current development [26].

WHY PDT MAY NOT BE SUITABLE FOR PROSTATE CANCER

Whilst at present the potential for PDT appears promising, there are reasons to be cautious at this stage. The first relates to the variable optical characteristics of the prostate [27,28]. Variability in light penetration seen in early studies was attributed to absorption by haemoglobin. However, later studies using longer wavelengths of light, which is not thought to be absorbed by haemoglobin, also indicate variability in optical properties. As the volume of PDT necrosis varies with light dose it may be possible to overcome an intrinsic variability of optical properties by using many light delivery fibres, using a smaller light dose per fibre.

The second relates to monitoring. It is not yet possible to monitor the effect of PDT during treatment. Because the PDT effect takes some time to develop it is necessary to develop systems which monitor indicators of the PDT effect, e.g. intraprostatic drug, oxygen and light levels. However, it appears that the interactions between these components may be complex. If this proves to be the case, it is likely that computer-assisted modelling will be required to predict the treatment effect. Such a model would take into account both optical properties and the vascularity of each treated prostate.

It is hoped that the development of newer photosensitizers with short drug-light intervals and minimal skin accumulation will improve the acceptability of PDT. However, the efficacy of these photosensitizers has yet to be confirmed in clinical studies.

COMPARISON OF PDT WITH OTHER MINIMALLY INVASIVE TREATMENTS

The two main competitors to PDT are high-intensity focused ultrasound (HIFU) and cryotherapy. Whilst each of these treatments has attributes that make them attractive options to patients, neither offer the potential for the two types of selectivity described above. If PDT is to have a place in the future treatment of prostate cancer it will need to be as well tolerated as HIFU, i.e. an outpatient treatment with no grade 2 or 3 urinary incontinence, preservation of erectile function in 50–70% of men, and at the same time offering 92% negative biopsy rates in low-risk patients after treatment [29,30], and freedom from biochemical progression of 95% in men with an initial PSA level of ≤10 ng/mL, at 72 months [31].

If PDT is to challenge cryotherapy it will have to be as effective as cryotherapy in high-risk disease, both in the primary and salvage setting [32]. In this setting, urinary incontinence rates of <5%, sloughing requiring intervention in 10% and high levels of erectile dysfunction are acceptable [33]. Currently, most would agree that the place for cryotherapy is in those men with the more aggressive (Gleason ≥8) or higher stage (T3) cancers. It is possible, given the attributes of PDT that we describe above, that both high-stage disease and high-grade cancer will be amenable to treatment with PDT.

CONCLUSIONS

We think that the future treatment of organ-confined prostate cancer will be based on a minimally invasive approach. PDT has the potential to be a selective, single-session treatment for use in the primary and salvage setting. Within the next 5 years several groups hope to complete large-scale clinical studies using different photosensitizers. It is expected that, after this time, the optimum treatment parameters of drug and light dose will be established, along with effective real-time monitoring systems to allow modulation of light dose depending on intraprostatic drug, light and oxygen levels. Once this work is complete, it will be possible to determine whether the potential benefits of PDT for early prostate cancer can be realized in clinical practice.

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CONFLICT OF INTEREST

C.M. and I.H. are clinical research fellows working on a clinical trial of PDT for organ-confined prostate cancer with TOOKAD. M.E. is the senior investigator for this trial. S.B. is a consultant to the company sponsoring this trial.

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Correspondence: Caroline M. Moore, National Medical Laser Centre, University College London, 1st Floor, Charles Bell House, 67–73 Riding House Street, London W1W 7EJ, UK.
e-mail: carolinemoore@doctors.org.uk

Abbreviations: **PDT**, photodynamic therapy; **mTHPC**, meso-tetra-(m-hydroxyphenyl) chlorin; **HIFU**, high-intensity focused ultrasound.