Photodynamic Therapy: A New Approach to Prostate Cancer

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Current Urology Reports 2003, **4:**221–228
Current Science Inc. ISSN 1527-2737

Photodynamic therapy (PDT) is based on the concept that light irradiation can change an inert substance into an active one. In urology, hematoporphyrin derivative (HpD) and Photofrin (Axcan Scandipharm Inc., Birmingham, AL) are used most commonly as photosensitizing agents predominantly for the treatment of transitional cell carcinoma of the bladder. To investigate the basics for PDT of prostate cancer, several studies were performed on the optical characteristics of prostate tissue and prostate carcinoma tissue in vitro and in vivo and on the penetration depths of different laser wavelengths. Initial experimental studies to treat prostate cancer with PDT using HpD were done on Dunning tumors in rats. Combined with interstitial applicators, photodynamic therapy seems to have a great potential in the treatment of prostate carcinoma. However, it is an experimental treatment and even a preliminary evaluation will be possible only after the conclusion of clinical studies with the corresponding long-term results.

Introduction

Photodynamic therapy (PDT) is based on the relatively old concept that light irradiation can change an inert substance into an active one. Current PDT involves the interaction of a specific light-sensitive agent, the so-called photosensitizer, and light of a particular wavelength in an oxygenated environment. The light energy is absorbed by the photosensitive molecules and "activates" them. The activated molecule transfers an electron to an adjacent oxygen molecule and generates oxygen radicals or the energy is transferred from the activated photosensitive molecule to an oxygen molecule, generating an excited singlet oxygen molecule. These reactive oxygen species (ROS) have a very short lifetime, but are extremely reactive and usually induce a cytotoxic reaction or cell destruction, respectively. Other, more macroscopic effects (*eg,* vascular damage and possibly immunologic reactions) contribute to the final tissue damage, probably to a wide extent.

Although only relatively low, nonthermal power densities of light are required for PDT, the laser, combined with an appropriate application system, made it possible to apply PDT to hollow and parenchymatous organs.

To achieve an effective and safe tumor treatment, the photosensitizing agent should fulfill some requirements: it should be nontoxic when it is administered; selectively concentrating in malignant tumor cells; and cytotoxic after activation in the tumor, but not in other organs that are exposed to light naturally, such as the skin. The laser light must be transmitted to the tumor through optical fibers and the laser wavelength must be suitable to activate the particular photosensitizer and should penetrate as deeply as possible into the tissue for complete tumor illumination. The power density of the laser light can be (even needs to be) low to avoid unwanted thermal effects other than hyperthermia, which may contribute to the treatment. Activation of the photosensitizing agents usually is ideal at one of their absorption maxima; the laser wavelength needs to be chosen accordingly.

The first report of the use of PDT in urology was published in 1975 by Kelly *et al.* [1] who observed the destruction of urothelial tumors by light application into the bladder after systemic administration of hematoporphyrin derivative (HpD). HpD, which consists of a mixture of various porphyrins, needs to be administered intravenously. It concentrates relatively selectively in epithelial and, in particular, tumor tissue. The maximum absorption level for HpD is 630 nm. In clinical use, light of this wavelength usually was provided by an argon laser-pumped dye laser. Apart from the requirement of cumbersome technology, PDT using HpD has relevant treatment morbidity, such as potential allergic reactions and a significant and relatively long-lasting phototoxicity for the skin, which makes it necessary for patients to remain in shadow for up to several weeks [1–8].

Since the first report of PDT, several studies for the treatment of transitional cell carcinoma of the bladder, in particular for carcinoma in situ, have been published [2–8]. New developments included improved delivery and dosimetry systems [2–8].

New photosensitive agents also were tested. Recently, 5-aminolevulinic acid (ALA) was introduced as a new drug for PDT of bladder cancer [9] and to be used in a diagnostic procedure (photodynamic diagnosis [PDD] or ALA-induced fluorescence endoscopy, [AFE]) [10,11]. An advan-

Table 1. Optical parameters of prostate tissue with different wavelengths suitable for photodynamic therapy

Study	Material (in vivo)	Wavelength, *nm*	Effective weakening coefficient, mm^{-1}	Diffusing coefficient, cm^{-1}	Absorption coefficient, cm^{-1}	Penetration depth, *mm*
Arnfield *et al.* [13]	Rat, R3327H	630	0.8 ± 0.5	12.3 ± 3.2	0.9 ± .04	N/A
	Rat, R3327AT	630	0.57 ± 0.32	10.1 ± 3.5	0.9 ± .04	N/A
	Rat, R3327H	789	0.31 ± 0.14	6.7 ± 1.7	0.5 ± 0.3	N/A
	Rat, R3327AT	789	0.42 ± 0.12	5.3 ± 1.4	0.4 ± 0.2	N/A
Pantelides *et al.* [14]	Human*	633	0.43 ± 0.05	8.6 ± 0.5	0.7 ± 0.2	2.31 ± 0.3
Whitehurst *et al.* [15]	Human, benign	633	0.35 ± 0.02 (0.28–0.48)†	N/A	N/A	N/A
	Human, Ca.	633	0.36 ± 0.02	N/A	N/A	N/A
Lee *et al.* [16,17•]	Human, Ca.	633	0.39 ± 0.05	N/A	N/A	N/A
	Human, Ca.	665	0.32 ± 0.05 (0.24–0.42)†	N/A	N/A	N/A
Levy *et al.* [18]	Human, apex	650	N/A	7.61 ± 2.37	0.47 ± 0.14	3.8 ± 0.6
	Human, center	650	N/A	17.19 ± 5.49	0.192 ± 0.05	3.8 ± 0.5
	Human, apex	800	N/A	5.21 ± 1.17	0.413 ± 0.15	5.2 ± 1.2
	Human, center	800	N/A	10.84 ± 2.39	0.172 ± 0.03	5.1 ± 0.9

*In vitro.
†Interindividual fluctuation spectrum with 11 patients
N/A—not applicable.

tage of ALA is the possibility of topical administration [10]. ALA is an initial substrate of heme biosynthesis. In early animal experiments, an accumulation of fluorescent porphyrins in malignant tissues of epithelial origin could be demonstrated after exogenous administration of ALA [12]. It became apparent that, in the cells, ALA is converted into the photoactive component protoporphyrin IX (PPIX) as part of the biosynthesis of heme. In the tissue deep-penetrating red light spectrum, the relative absorption maximum of PPIX is 635 nm. To activate the photosensitizer, laser light of this wavelength is required.

Photodynamic Therapy of the Prostate

Optical parameters of prostatic tissue

Several authors performed studies on the optical characteristics of prostate tissue and prostate carcinoma tissue in vitro and in vivo to measure the penetration depths of different wavelengths [13–16,17•,18–20] (Table 1).

Using laser light with a wavelength of 633 nm applied interstitially through a 400 µm fiber, Pantelides *et al.* [14] observed a similar penetration depth in human prostate tissue in vitro (63% loss within an average of 2.31 ± 0.3 mm) to that in chicken thoracic muscles and a larger penetration depth than in liver tissue (4.3x). The penetration depth in the prostate decreased to as little as 0.55 mm with 612-, 594-, and 543-nm wavelengths, respectively. With surface irradiation of a slice of prostate tissue, Newman and Jaques [21] measured a penetration depth of approximately 2 mm for the argon laser (488 nm) and the KTP laser (532 nm), approximately 3 mm for the dye laser (630 nm), and approximately 5 mm for the Nd:YAG laser (1064 nm). McPhee [22], whose measurements were concerned with thermal tissue destruction, not with photodynamic, studied the penetration depth of Nd:YAG laser irradiation in Dunning R3327AT prostate tumors in rats and in potatoes and found very similar optical properties in both tissues, leading them to recommend the potato model. With a variation in the angle of impact of the laser beam, McPhee [22] noticed that the penetration depth and the necrotic area were smaller with an oblique angle of impact. On irradiation with 60 W for 4 seconds in air, the potato showed a penetration depth of 2.5 mm with a fiber with 36 ° beam divergence and vertical impact (90°) of 1.85 mm at 60° and of 1.45 mm at 30°. With 8° beam divergence of the fiber, the penetration depth at the 90° impact was 3.1 mm, 2.75 mm at 60°, and 2.2 mm at 30°. It would only be possible to achieve the desired thermal tissue necrosis of 3 to 4 mm with vertical beam application, which is something that, as the author noted, could not be attained in practice in the prostatic urethra [22].

Other authors reported on measurements on experimental prostate tumors in vivo [13] and on patients [14–16,17•,18] with prostate carcinoma (Table 1). Arnfield *et al.* [13] compared the penetration depth using 630 nm and 789 nm in Dunning R3327AT and R3327H tumors, respectively, in rats. The absorption coefficient of both tumors amounted to 0.9 cm^{-1} with 630 nm, 0.4 cm^{-1} with 789 nm

Table 2. Photodynamic therapy for the treatment of prostate cancer*

Year	Study	Applicator	Power	Energy	Experiment
1984	McPhee *et al.* [23]	One to four diffuser tips (1 cm)	150 mW	500 J	Dunning-R3327H and AT tumors in rats
1985	Camps *et al.* [25]	Bare fiber	500 mW/cm²	N/A	Dunning-R3327H tumors in rats
1986	Gonzalez *et al.* [24]	One to four diffuser tips (1 cm) plus cooling	300 mW	1200–2400 J	Dunning-R3327H and AT tumors in rats

*Initial experiments in rats using hematoporphyrin derivative as a photosensitizer.

in the quick-growing anaplastic R3327AT tumor, and 0.5 cm^{-1} in the well-differentiated R3327H tumor. The weakening factor for both tumors was greater with 630 nm by a factor of 1.9 than it was with 789 nm. For this reason, the authors recommended using photosensitizers with their favorite absorption maximum in longer wavelengths for future applications [13]. Whitehurst *et al.* [15] conducted measurements on 11 patients. The application fibers and the measuring fibers were inserted into the prostate interstitially. For 633 nm, there was an average weakening coefficient of 0.35 mm^{-1} (benign tissue) and 0.36 mm^{-1} (carcinoma tissue). However, the values measured on different patients showed considerable fluctuations, ranging from 0.28 to 0.48 mm^{-1}. The authors concluded that, with the necessary individual modification of the irradiation parameters, it would be possible to treat a volume of approximately 25 mL with four simultaneously inserted fibers. Lee *et al.* [16] compared 633 nm and 665 nm (optimum wavelength for the activation of the photosensitizer tin(II)etiopurpurin-dichloride) on 11 patients. With 665 nm, the authors discovered that the average penetration depth was 22% greater [16]. The weakening coefficient mounted to 0.39 mm^{-1} (633 nm) and 0.32 mm^{-1} (665 nm), with a fluctuation of 0.24 to 0.42 mm^{-1} with various patients. Levy *et al.* [18] studied wavelengths from 400 to 800 nm in six patients; usable results were acquired for the wavelength range of 650 to 800 nm. The average penetration depth ranged from 0.38 cm (650 nm) to 0.52 cm (800 nm); however, the absorption coefficient varied considerably in different areas of the prostate (0.47 cm^{-1} [apex, 650 nm], 0.413 cm^{-1} [apex, 800 nm], 0.192 cm^{-1} [center, 650 nm], and 0.172 cm^{-1} [center, 800 nm]). The authors were not able to find an explanation for this observation [18].

Chen and Hetzel [20] concluded that, because of the limited light penetration of the wavelengths required for most suitable photosensitizers, multiple fiber irradiation is necessary to treat the whole prostate gland.

Treatment Studies

Initial experimental studies on the use of PDT using hematoporphyrin derivatives (HPD) with prostate carcinoma were first described in 1984 by McPhee *et al.* [23] (Table 2). Dunning R3327H and Dunning R3327AT tumors in rats were used as a model. The laser fibers, with a cylindrically emitting tip over a section of 1 cm, were inserted into the tumors using trocar needles. In addition, temperature sensors were positioned to evaluate thermal effects.

The Dunning R3327H tumors were irradiated with a single fiber, with 500 J of laser energy being administered at a power level of 150 mW. It was only possible to demonstrate minor thermal effects with temperature increases of 1.5°C on the fiber. Therefore, the effects on tumor growth in the HPD and laser group compared with all of the control groups were interpreted as photodynamic effects. With the Dunning R3327AT tumors, four fibers were inserted simultaneously at a distance of 1 cm. Each fiber irradiated 150 mW of power using a beam splitter. The authors measured temperature increases of 20°C in the tumor close to the fibers and of 8°C at a distance of 1 cm from the fibers. They concluded that the effects on the tumor were primarily of a thermal nature [23].

In a further series of experiments [24], the subcutaneous Dunning R3327AT tumors were subjected to cooling. The temperatures during laser application in one series were maintained in the tumor at 40 to 41°C and at 44 to 45°C in a second series. The animals were subjected to PDT and four laser applicators were inserted into the tumor at distances of 0.7 cm from each other and used to administer 300 mW over 17, 30, and 33 minutes to a total energy level of 1224, 2160, and 2376 J, respectively. One group also was administered misonidazole as a potential effect amplifier. A delay in tumor growth was seen in all of the PDT groups and much more strongly when misonidazole was administered. The additional hyperthermia only had a minor effect; laser hyperthermia of 45°C on its own achieved no noticeable delay in growth. It was not possible to achieve the disappearance of the tumor with any of the combinations.

Camps *et al.* [25] were able to achieve the devitalization of cells in cell cultures from Dunning R3327AT prostate tumors by exclusively using laser irradiation with more than 500 mW/cm^2, which the authors interpreted as a hyperthermia effect. Regardless of the dosage, the PDT with HPD showed cytotoxic effects.

Further experiments concentrated on the optimization of irradiation parameters and new photosensitive substances. Since 1994, a number of authors conducted experimental photodynamic therapy on normal canine

Table 3. Photodynamic therapy for the treatment of prostate cancer*

Year	Study	Photosensitizer	Wavelength	Applicator	Lesion size
1994/1996	Selman *et al.* [26,27]	SnET2	660 nm	One diffuser tip (2 cm) in the urethra; two diffuser tips (3 cm)	4.3 cm^3
1995	Johnson *et al.* [33••,34]	ALA	630 nm	Diffuser tip in the urethra	1 cm radius
1996	Muschter *et al.* [35] and Sroka et al. [36••]	ALA	635 nm	Diffuser tip (1 cm)	0.9–1.6 cm in diameter
1996	Chang *et al.* [29••,30]	mTHPC AlS2Pc	650 nm	One to four diffuser tips	20 x 25 x 25 mm (up to 40 mm diameter with four fibers) 10 x 9 x 9 mm
1996	Shetty *et al.* [38]	Photofrin II (Axcan Scandipharm Inc., Birmingham, AL)	630 nm		0.41–0.63 cm in diameter
1997	Chang *et al.* [32••]	AlS2Pc ALA	Interstitial diffusor tips		12 mm in diameter 1–2 mm in diameter
1997	Lee *et al.* [39]	Photofrin II	630 nm	1 or 2 interstitial diffusor tips (2 cm)	5.3 ± 1.4 mm radius
2001	Hsi *et al.* [40••]	Lu-Tex (Pharmacyclics Inc., Sunnyvale, CA)	732 nm	Several cylindrical diffusing fibers, interstitial and/or transurethral	Entire prostate (combined or interstitial approach)
2002	Chen *et al.* [41••]	WST09	763 nm	Superficial (surgically exposed), interstitial	> 3 cm in diameter

*Canine experiments with various photosensitizing agents.
ALA—5-aminolevulinic acid; AlS2Pc—aluminum disulphonated phthalocyanine; mTHPC—meso-tetra-(m-hydroxyphenyl)chlorine; SnET2—tin(II)etiopurpurin-dichloride; Lu-Tex—lutetium texaphyrin; WST09—palladium-bacteriopheophorbide.

prostates using various photosensitizers (tin(II)etiopurpurin-dichloride [26,27,28••], meso-tetra-(m-hydroxyphenyl)chlorine [mTHPC] [29••,30], aluminium disulphonated phthalocyanine [AlS2Pc] [30,31,32••], ALA [32,33••,34,35,36••,37], Photofrin II (Axcan Scandipharm Inc., Birmingham, AL) [38,39], and motexafin lutetium) [40••] (Tables 3 and 4).

Selman and Keck [26] and Selman *et al.* [27,28••] conducted PDT pilot studies with the photosensitizer tin(II)etiopurpurin-dichloride (SnET2). Forty-eight hours after PDT and interstitial irradiation with 660 nm, the authors found extensive areas of hemorrhagic necrosis (on average 4.3 ± 1.0 cm^3), which accounted for as much as 47.3% of the prostate. After 3 to 6 weeks, there was a reduction in the size of the glands; histologically fibrotic tissue could be seen. In the first study [26], a 2-cm diffuser tip was placed in the prostatic urethra; the second stage followed irradiation with two transperineally applied interstitial laser fibers. Chang *et al.* [29••,30,31,32••] also irradiated the prostate transurethrally or interstitially through transperineally applied laser fibers. The photosensitizers mTHPC and AlS2Pc were tested. Using only one fiber, it was possible with mTHPC to achieve a lesion of 20 x 25 x 25 mm; AlS2Pc led to a hemorrhagic necrosis of 10 x 9 x 9 mm [30] and 12 mm in diameter, respectively [32••]. Four simultaneously placed fibers destroyed 85% of the gland. Atrophy of the glands in the treatment area, with otherwise intact structures, was recognizable after 4 weeks. Urethral lesions healed by 28 days without functional impairment. Shetty *et al.* [38] conducted PDT with Photofrin II and 630 nm laser light. Depending on the dosage, it was possible to create lesions with diameters ranging from 4.1 ± 0.9 mm (Photofrin II dosage: 1 mg/kg bodyweight) to 6.3 ± 0.9 mm (Photofrin II dosage: 5 mg/kg bodyweight). Another study using Photofrin (2 mg/kg bodyweight) as a photosensitizer for PDT on canine prostates was published by Lee *et al.* [39]. Using one or two 2-cm long diffuser tips, which were placed interstitially, a lesion with a radius of 5.3 ± 1.4 mm was achieved. The measured light penetration was 2.14 ± 0.2 mm. Hsi *et al.* [40••] investigated different dosages (2–6 mg/kg bodyweight) of motexafin lutetium for PDT in canine prostates. Laser light of 732 nm was administered interstitially or transurethrally through cylindrically diffusing fibers at 75 to 150 J/cm. Comprehensive treatment of the entire prostate could be achieved. However, complications such as urethral fistulae occurred at the highest dose level.

The intention of Johnson *et al.* [33••,34] was that of using PDT for the therapy of benign prostatic hyperpla-

Table 4. Photodynamic therapy for the treatment of prostate cancer*

Year	Study	Photosensitizer	Wavelength	Applicator	Patients, *n*
1990	Windahl *et al.* [48•]	Photofrin II (Axcan Scandipharm Inc., Birmingham, AL) (1.5/2.5 mg/kg)	628 nm	Transurethrally, ball-shaped diffusor tip; energy density = 15 J/cm²	2
2002	Nathan *et al.* [49••]	mTHPC (0.15 mg/kg)	652 nm	Interstitially, multiple bare fibers; power = 100–150 mW per fiber	14
2003	Zaak *et al.* [50••]	ALA (20 mg/kg)	633 nm	Interstitially, multiple 1-cm diffusor tips; 50 J/cm² per fiber (0.5 W for 500 s)	20 (5 therapeutic)

*Clinical studies with various photosensitizing agents.
ALA—5-aminolevulinic acid; mTHPC—meso-tetra-(m-hydroxyphenyl)chlorine.

sia (BPH). In accordance with this objective, they used laser diffuser tips urethrally after determining the pharmacokinetics of ALA. Irradiation was achieved with 630 nm with 650 mW for 45 minutes 8 hours after ALA administration; the authors determined this to be the time of ALA concentration maximum. Seven days after therapy, a hemorrhagic necrosis with a radius of 1 cm could be observed histopathologically. Muschter *et al.* [35] and Sroka *et al.* [36••,37] reported on experimental studies on canine prostates using ALA with the primary objective of therapy of prostate carcinoma. When determining the in vivo pharmacokinetics and the distribution of the ALA-induced PPIX (which is the active photosensitizing agent) in the prostate, the authors found a concentration maximum approximately 3 to 4 hours after intravenous ALA administration [35,36••,37]. The PPIX-induced fluorescence was strongly restricted to the epithelial tissue. With an interstitially placed 1-cm long laser diffuser tip and 635 nm dye laser irradiation with an irradiation of 50 J/cm^2 and 100 J/cm^2, it was possible to induce hemorrhagic lesions of as much as 13 mm in diameter in the normal prostate gland. There was no consequential increase in temperature. Another study using ALA-induced PPIX as the photosensitizing agent for PDT in the canine experiment was reported by Chang *et al.* [32••]. Laser light at 100 mW was delivered interstitially 3 hours after ALA administration. In contrast to the previous findings of other authors, the lesions obtained with ALA were only 1 to 2 mm in diameter [32••].

The photosensitizer most recently tested for PDT of prostate cancer is a pure and stable bacteriochlorophyll derivative named palladium-bacteriopheophorbide. In normal canine prostates, PDT was performed by irradiating the surgically exposed prostate superficially or interstitially, using a 763-nm laser source at a fluence of 100 J/cm^2 or 200 J/cm^2, respectively. With a single interstitial treatment, a maximum lesion size of more than 3 cm in diameter could be achieved. There was no damage to the bladder or rectum caused by scattered light [41••].

With gaining interest in PDT for the treatment of prostate cancer, more recent experiments were done on cell lines [42••,43,44••,45]. Using a 630-nm dye laser at 3 J/cm^{2,} Chakrabarti *et al.* [42••] could demonstrate the high cytotoxic potential of ALA-induced PDT on two different in vitro prostate cancer cell lines (LNCaP and PC-3) and a benign modified prostatic cell line (TP-2). However, the cell lines responded differently, suggesting a dependence on the intracellular production of PPIX and some characteristics of the cell mitochondria. Xue *et al.* [43] were able to identify some factors potentially protecting prostate cancer cells from apoptosis after PDT. Colasanti *et al.* [44••] also investigated PDT on LNCaP and PC-3 cell lines. They found hypericin photosensitization followed by dye laser irradiation at 599 nm, with a fluence of 11 J/cm^2 being very effective in both cell lines.

Further animal and dosimetry studies with PDT for prostate cancer were performed in the rat model. Momma *et al.* [46], who tested Photofrin II in rats in an orthotopic prostate cancer model (MatLyLu variant of Dunning 3327), stated a high cytotoxic efficacy, in particular in a combination with prostate resection. Although local control could be obtained by PDT alone, compared with the control groups, the number of distant lung metastases was significantly higher.

The effects of ALA-induced PDT on MatLyLu tumors in 39 Copenhagen rats were investigated by Zaak *et al.* [47]. PPIX concentration in the tumors was found to be (at maximum) approximately 2.5 to 3.5 hours after intravenous application of ALA (150 mg/kg bodyweight). Forty-eight hours after laser irradiation (diode laser, 633 nm) with 100 mW/cm^2, 70% to 100% of the tumor was found to be necrotic, compared with 0% to 8% in all of the control groups with no treatment, only ALA administration, or only laser irradiation.

Clinical Application

Windahl *et al.* [48•] had already used PDT clinically in 1990 for two patients with localized prostate carcinoma.

Analogously to thermal transurethral laser therapy, a maximum transurethral resection was initially performed in two sessions. Six weeks after the second transurethral resection of the prostate, 1.5 mg/kg bodyweight HpD (first case) and 2.5 mg/kg bodyweight Photofrin II (second case) were administered. Irradiation was performed within 48 to 72 hours with a laser wavelength of 628 nm (energy density, 15 J/cm^2) through a ball-shaped diffuser tip placed in the prostatic urethra. The first patient died 6 months later of causes unrelated to his disease; the prostate was found to be tumor-free. In the second patient, the prostate-specific antigen (PSA) had fallen 5 months after the treatment from 6 µg/L before the operation to 0.2 µg/L. Further reports on the follow-up were not given.

The largest series of patients treated with PDT in a phase I study was reported by Nathan *et al.* [49••] in 2002. All 14 patients had biopsy-confirmed local recurrence of prostate cancer after radiotherapy. The photosensitizer mTHPC was administered intraveneously (0.15 mg/kg bodyweight). Three days later, laser application of a wavelength of 652 nm was administered through bare fibers placed interstitially on the location of positive biopsies. Up to four fibers were operated simultaneously at 100 to 150 mW, each using a beam splitter. Regarding the phase I character of the study (no attempt was made to treat the entire gland), the results were good; nine patients had a relevant decrease of PSA, PSA was undetectable in two patients, and five patients had no viable cancer on post-treatment biopsies. Magnetic resonance imaging and a computed tomography scan, which were performed several days and 2 months, respectively, after PDT showed, after an initial marked inflammatory response with edema and volume increase by a median of 81% in the later phase, necrosis of up to 91% of the prostate cross section. Urinary stress incontinence developed in four patients and erectile function was impaired for four of seven men who were able to have intercourse before PDT. There were no rectal complications directly related to PDT, but one patient experienced a urethrorectal fistula after rectal biopsy.

In a similar phase I study published in 2003, ALA or ALA-induced PPIX was used as the photosensitizing agent in 20 patients with prostate cancer by Zaak *et al.* [50••]. In 14 patients, ALA (20 mg/kg bodyweight) was administered before scheduled radical prostatectomy to investigate the PPIX distribution. In fluorescence microscopic pathology, PPIX fluorescence was observed exclusively in cancer cells; however, normal epithelial cells and stromal tissue showed only autofluorescence. One patient underwent ALA-induced PDT. Laser application at 633 nm (irradiation 50 J/cm^2, irradiance 0.5 W for 500 s, light energy 250 J) was performed with three subsequent interstitial applications of a cylindrical 1-cm diffuser tip before radical retropubic prostatectomy. In the specimen, cell dissociation and necrosis within the tumor were found. A total of five patients were treated with ALA-induced PDT. In three patients, the interstitial fibers were placed transurethrally (5 to 10 subsequent applications); in two patients, they were placed perineally using transrectal ultrasonographic guidance (40 to 55 subsequent applications). Within 6 weeks, PSA showed an average decrease to approximately 55% of the pretreatment value.

A phase I trial of PDT in patients with recurrent prostate carcinoma who had failed radiotherapy was proposed [51]. The photosensitizing agent lutetium texaphyrin was chosen, which is administered intravenously. Delivery of 730 nm laser light was proposed to be achieved using laser fibers inserted interstitially into the prostate through a perineal template.

Conclusions

In combination with interstitial applicators, PDT seems to have great potential in the treatment of prostate carcinoma. However, a number of answers have to be found regarding the manner and dosage of the most suitable and least toxic photosensitizers and the resulting irradiation parameters.

Several studies in normal canine prostates, in prostate cancer cell lines and the rat model, and in humans have demonstrated the capability of several different photosensitizing agents to produce defined necrosis of prostate tissue or prostate cancer cells. However, some photosensitizers, such as Photofrin, come along with a relevant toxicity, such as skin photosensitization [48•]. The need for avoiding bright light after administration of such photosensitizers, for at least several days, reduces life quality and adds other problems. For example, if mTHPC is used as a photosensitizer, patients have to stay in reduced room lighting for as long as 3 days after mTHPC administration before the laser treatment can be performed and PDT is completed to prevent skin photosensitivity [49••]. Such problems regarding the preoperative logistics do not occur with photosensitizers with more favorable pharmacokinetics and much shorter incubation times, such as ALA or motexafin lutetium. Although mTHPC is a more potent photosensitizer than ALA-induced PPIX requiring a lower therapeutic light irradiation, there seems to be some advantages of ALA in clinical use [50••]. Regarding the oncologic results of the phase I studies, using mTHPC and ALA are comparable.

The analysis of the published studies shows that, at least for some photosensitizers, the optimal route of administration and dosage, the interval between drug administration and laser irradiation, and the laser wavelength and parameters (irradiation [J/cm^2], irradiance [W, irradiation time [s, energy [J]) seems to be known. However, some studies are lacking such data. The application system (*ie,* the laser fiber) is not standardized. The technique of laser application to the targeted tissue is even more problematic. Most laser wavelengths required for PDT do not penetrate deep enough to treat the entire prostate if the laser fiber is placed in the prostatic urethra.

Therefore, interstitial irradiation using (multiple) fibers placed percutaneously from the perineum will most likely be required. Modern diode laser technology and beam splitters should overcome wavelength and irradiation problems. Future PDT may involve transrectal ultrasonography guidance and a template, which is known from brachytherapy or cryotherapy.

In all events, a final evaluation will be possible only after the conclusion of clinical studies with the corresponding long-term results. However, the commencement of such studies should be possible in the near future.

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