A new balloon catheter system used for PDT in the human urinary bladder, accuracy of light distribution

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ABSTRACT

Photodynamic therapy (PDT) may provide a new approach for treatment of patients with superficial transitional carcinoma and carcinoma in situ of the bladder. The light applicator for the bladder wall (Rüsch) is constructed as a balloon catheter with two concentric balloons. A new PDT applicator (Rüsch) was assessed for the homogenity and accuracy of irradiation during PDT.

In an in-vitro experiment with 17 freshly harvested porcine bladders the fluence rate was measured locally with isotropic detectors. The results were compared to the light fluence detected by the PDT applicator.

The increase of the fluence rate ß inside the bladders due to back scattering ranged between 5.3 and 7.0 with an average of 6.2. Local variations of the fluence rate in the sperical bladders were also smaller than 15%. Therefore it is concluded, that a homogeneous and accurate irradiation during PDT is possible.

Blood between the outer balloon and the bladder wall reduces the local fluence rate strongly and should to be avoided. Also larger air bubbles in the applicator can lead to an inhomogeneous light distribution.

In regular application the presented new catheter system provides accurate and easy light dosimetry during PDT of the bladder. Attention had to be paid to a continuous flushing of the space between balloon and bladder wall in order to prevent the accumulation of urine and blood.

To avoid a malfunction of the system and large errors in light dosimetry and application, it is advisable to monitor the measured light dosage and the shape of the balloon using ultrasonography during PDT.

Keywords: Photodynamic therapy, bladder cancer, intravesical therapy, balloon, light dosimetry

INTRODUCTION AND OBJECTIVES

Photodynamic therapy (PDT), in which hematoporphyrin derivative is activated by an externally applied red light, may provide a new approach for treatment of patients with superficial transitional carcinoma and carcinoma in situ of the bladder [1, 2]. The tendency of a reduced rate of recurrences in our clinic with PDT treated patients shows the importance to intensify the efforts in further investigations to improve this method. The effect is currently under investigation in phase III trials.

The effect of photodynamic therapy depends upon the concentration of photosensitizing drug and radiant exposure delivered to tissue. Therefore, for successful treatment a homogeneous and reproducible light dose is needed, otherwise insufficient treatment or severe damage to the bladder tissue may result. Due to the high backscattering at the wavelength used for treatment, the bladder acts as an integrating sphere. Therefore, depending on the reflectivity of the bladder wall, the light fluence varies considerably [3]. An accurate dosimetry is only possible, if the light fluence is determined for each patient individually [4,5]. We investigated a new PDT applicator (Rüsch), which provides in-situ measurement of the light fluence rate during PDT. The applicator was tested by in-vitro measurements of the local light fluence rate with isotropic detectors in porcine bladder. During the PDT treatment of humans, the shape of the applicator and the measured light fluence rate was monitored. The investigations were carried out to establish possible sources of error, which may result in patient-to-patient variation of the applied light dose.

MATERIAL AND METHODS

The light applicator for the bladder wall (Rüsch) is constructed as a balloon catheter with two concentric balloons [Fig. 1]. During treatment the outer balloon is positioned in the human urinary bladder, filled with 150- 250 ccm distilled water, depending on bladder capacity. The inner balloon is filled with a scattering fluid (4 ccm 0.5% Lipofundin®, Braun Melsungen). In the applicator one optical fiber is positioned in the center of the balloon to provide the light for the irradiation of the bladder wall. A second fiber is positioned outside of the inner balloon to detect light fluence rate. This fiber is connected to a PDT dosimeter (Ceram Optics, Bonn, Germany), which calculates the light dose (light fluence 150 J/cm^2 in human application).

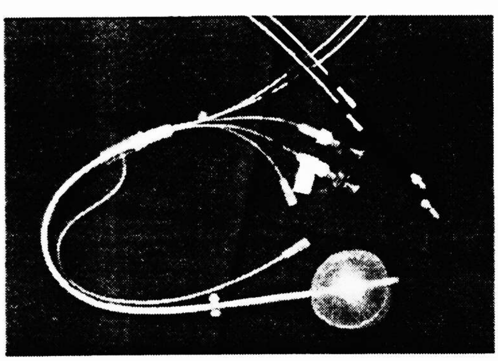

Fig. 1 The new PDT applicator (Rüsch)

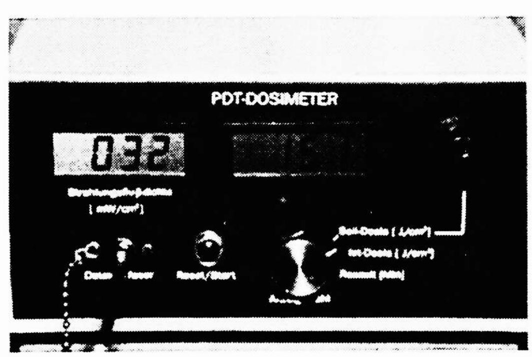

Fig. 2 PDT dosimeter

In vitro experiments:

For the in vitro investigations 17 freshly harvested porcine bladders were placed in a water bath, after inserting the applicator through the urethra in the minor cavity [Fig. 3]. The fluence rate was measured locally with isotropic detectors at 12 different positions, which were placed between the balloon and the bladder wall [Fig. 4/5].

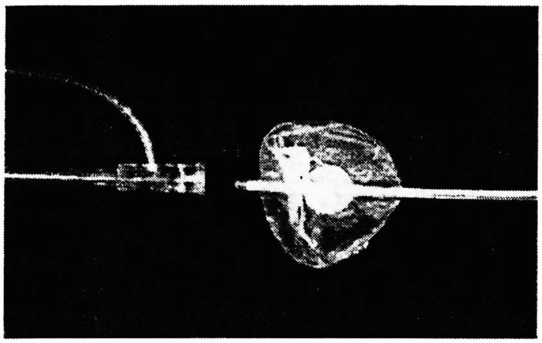

Fig 3. PDT catheter during insertion into the bladder catheter

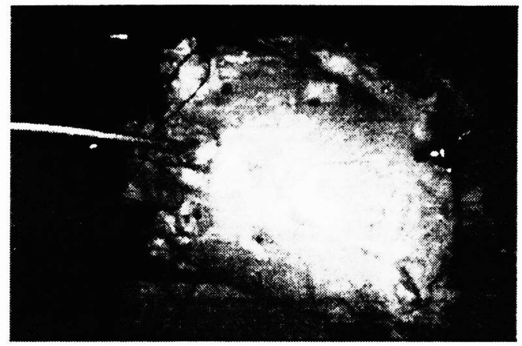

Fig.4 pig bladder during measiuring

The detectors were built from 200 μm fibers by melting one end of the fiber to form a sphere, which afterwards was coated with a highly scattering layer.

For the measurements, light from a dye laser, which was pumped to an argon laser (Spectra Physics 375B and 2035) was coupled in the irradiation fiber.

Local fluence rate was measured,

-at several fixed points of the bladder wall

-with different volumes of the catheter (150 - 300 ccm) and deformation of the bladder wall

-also adding blood between catheter and bladder wall

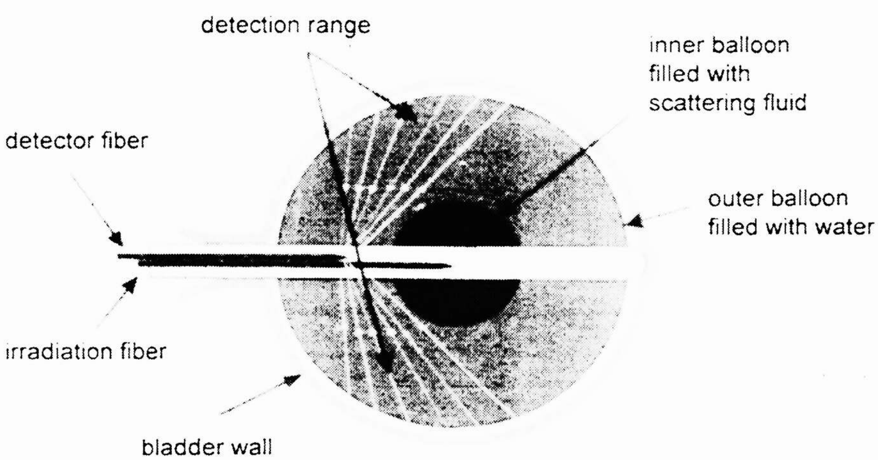

Fig. 5 Porcine bladder during light appl. for the bladderwall
The outer balloon is filled with 150-250 ccm distillated water,
the inner balloon with 4 ccm 0.5% Lipofundin® (Braun-Melsungen)

Additionally, the transmission of radiation through the wall was investigated by the isotropic detector.
The results were compared to the light fluence detected by the PDT applicator.

PDT of superficial bladder cancer:

In the clinical experimental approach the fluence rate was measured and documented during treatment in patients undergoing PDT.

Patients are admistered an intravenous injection of 1,5 mg/kg body weight Photofrin® II (Dihematoporphyinester, Quadra Logic Technologies) 48 hours before phototherapy. The light is supplied by a dye laser pumped by an argon laser (Lambda plus PDL® , Coherent, wavelength 630 nm, 1.5-2 W). Illumination times between 15 and 60 minutes depending on the output power size and reflectivity of the bladder were needed for the delivery of 150 J/cm^2. Symmetric expansion of the balloon in the bladder was checked by ultrasound and the light fluence rate measured by the dosimeter was monitored during PDT. From the output power of the laser and the size of the bladder an intervall of the light fluence rate was calculated which can occured at reasonable reflectivities of the bladder wall. Measured light fluence rate, which do not fall in this intervall, are indicative of an malfunction of the PDT catheter.

Additionally, after treatment each PDT applicator was carefully examined for damage.

RESULTS AND DISCUSSION

In a spherical bladder, the local fluence rate was quite homogeneous. Fig. 4 shows the locally measured fluence rate (Φ local) divided by the fluence rate measured by the dosimeter via the detector fiber (Φ integral).

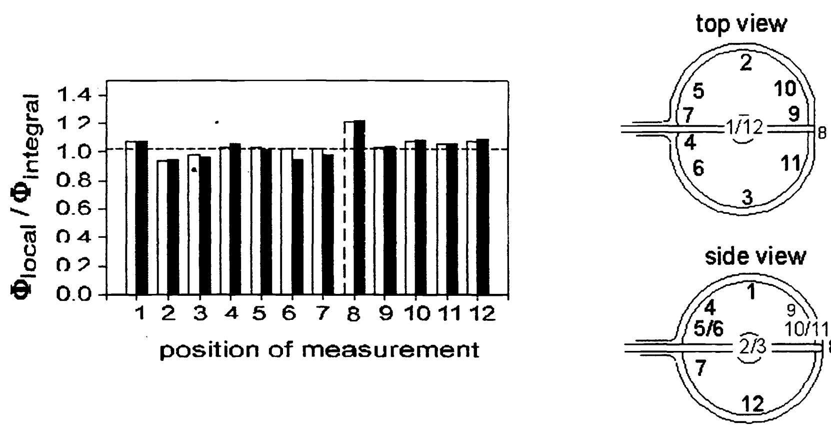

Fig. 6 Typ. results: local fluence rate measured ex vivo

Deformation of the bladder results in an inhomogeneous irradiation of the bladder. The light fluence rate at the parts of the wall, which are nearer to the center of the PDT applicator is higher than the fluence rate at parts of the bladder wall more distant from the center (Fig. 5/6/7). The ratio of fluence rates is approximately the ratio of distances from the center of the inner balloon. This is consistant with Monte-Carlo calculations [4, 5].

In the in vitro experiments, the increase of the fluence rate ß inside the bladders due to back scattering ranged between 5.3 and 7.0 with an average of 6.2. This is comparable to an average increase of 6 times, measured by Marignissen et al in vivo. Note that in their measurements of the fluence rate, the isotropic detectors were placed in a catheter filled with air. A correction factor of approximately 1.25 for the index of refraction of the different media was neglected in their calculations of ß [6]. With two exceptions the difference of the average of the local measurements at all site in the bladder and the fluence rate measured by the PDT applicator and dosimeter (Error of the average) was smaller than 15% [Tab.1]. Local variations of the fluence rate (average of the local error) in the sperical bladders were also smaller than 15%. Therefore it is concluded, that a homogeneous and accurate irradiation during PDT is possible. Blood between the outer balloon and the bladder wall reduces the local fluence rate strongly and should to be avoided. Also larger air bubbles in the applicator can lead to an inhomogeneous light distribution.

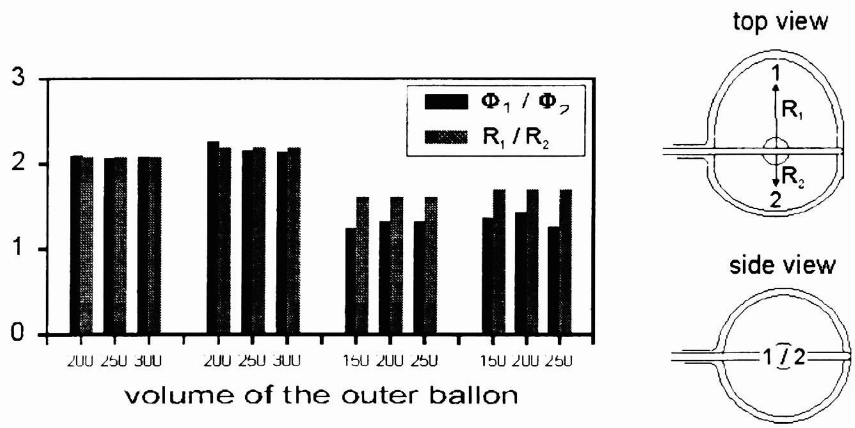

Fig. 7 Local fluence rate measured with excentrical outer balloon

bladder #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
ß	6,96	7,58		6,66		5,32		6,33	5,27	6,07	6,05	5,79	5,66	5,65	6,14	6,54	
error of the average %	15	15	22	30	16	4		2	2	-0,05	9	11	13	6	8	-5	3
average of the local error %	7	11	12	15	7	4		11	5	6	10	8	10	9	9	10	14

average ß	6,2
average error %	9 %
average local error %	9,3 %

Tab. 1 Summery of ex-vivo results

Therefore in clinical application of the PDT applicator attention has to be drawn to a correct filling of the balloons without air, a sperical inner and outer balloon and the absence of blood between balloon and bladder wall.

In connection with the Phase III trial 33 patients were treated with the new PDT applicator. In half of the treatments damage of the applicator, which could influence the dosimetry was observed. In 10 cases the outer balloon was asymetric (Ratio of the axises >2). In 7 cases damage of one of the balloons was observed.
In most cases the malfunction of the catheter was detected before irradiation by ultrasound or irregulations of the measured light fluence rate.
Damage of the balloon during PDT can also be detected by abnormalities of the measured fluence rate.

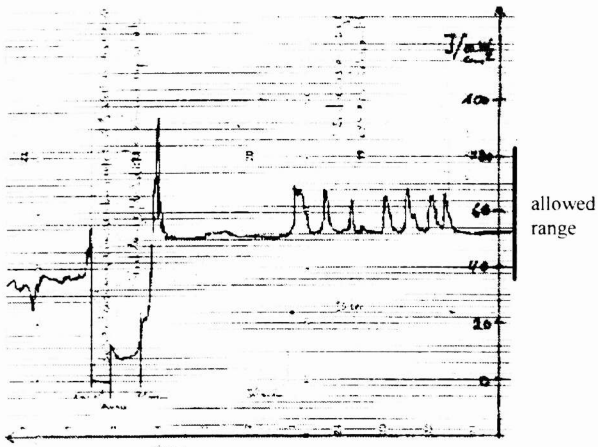

Fig. 8 light fluence during PDT

In Fig. 8 the light fluence decreases rapidly after destruction of the inner balloon; in such a case, ultrasound control shows a collapsed balloon and the catheter has to be changed [Fig. 9].
Attention had to be paid to a continuous flushing of the space between balloon and bladder wall in order to prevent the accumulation of urine and blood. Since the PDT applicator is inserted into the bladder through a 18 F rigid catheter care is needed not to damage the balloon at this occasion [Fig. 3].
During our clinic experiences no severe complications caused by the application system had to be managed; in case of catheter damage, the catheter system had to be changed.

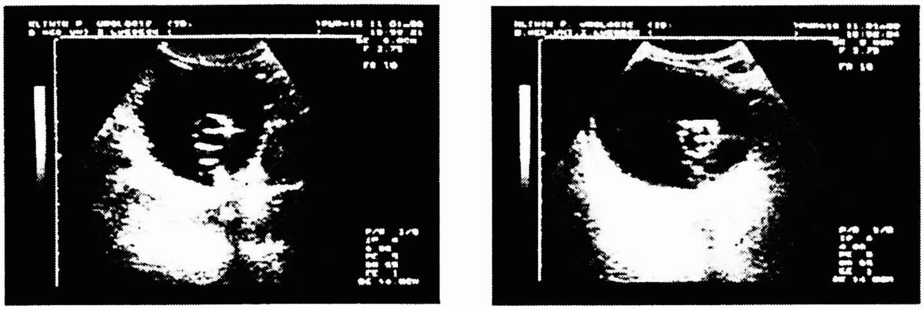

Fig. 9 Ultrasound control of the bladder

CONCLUSION

In regular application (blocking the inner and outer balloon without air, control of symmetric unfolding, excluding bleeding) the presented new PDT applicator provides accurate and easy light dosimetry during PDT of the bladder. Attention had to be paid to a continuous flushing of the space between balloon and bladder wall in order to prevent the accumulation of urine and blood.

To avoid a malfunction of the system and large errors in light dosimetry and application, it is advisable to monitor the measured light fluence rate and the shape of the balloon using ultrasonography during PDT.

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