# Feasibility study of a system for combined light dosimetry and interstitial photodynamic treatment of massive tumors

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# Feasibility study of a system for combined light dosimetry and interstitial photodynamic treatment of massive tumors

Thomas Johansson, Marcelo Soto Thompson, Maria Stenberg, Claes af Klinteberg, Stefan Andersson-Engels, Sune Svanberg, and Katarina Svanberg

A system for the photodynamic laser treatment of massive tumors that employs multiple optical fibers to be inserted into the tumor mass is described. The light flux through the tumor can be assessed by use of the individual fibers both as transmitters and as receivers. With a computer model that describes the diffusive light propagation, optical dosimetry is under development. The system has been tested in an experimental animal tumor model in preparation for clinical work. Currently, delta-aminolevulinic acid is used as a sensitizer, activated by 635-nm radiation from a 2.0-W compact diode laser system. With the availability of future, highly selective drugs absorbing approximately 750 nm, larger tumor volumes should be treatable, and surrounding, sensitive normal tissue should be spared. 

*OCIS codes:* 170.5180, 170.3660, 170.1610, 300.2530, 060.2310.

## 1. Introduction

Despite extensive research and developmental activities regarding techniques for the abatement of cancer, the disease continues to take high tolls in human suffering and lives. Among the many new treatment modalities emerging, photodynamic therapy (PDT) offers potentially unique advantages in terms of selectivity and efficacy.[1–3] PDT relies on a preferential tumor retention of an administered photosensitizing agent, which is followed by a laser-mediated release of singlet oxygen in tumor cells. With the introduction of delta-aminolevulinic acid (ALA), a sensitizer precursor that induces protoporphyrin IX (PpIX) as a sensitizing agent, the clinical applications of PDT increased a great deal, especially with respect to skin tumors prepared with topically applied ALA cream.[4–9]

It is important in the development of more efficient PDT to have chemically well-defined sensitizers that exhibit a high contrast between tumor cells and normal tissue and that are nontoxic and swiftly cleared from the organism. Because light penetration of tissue under the influence of absorption and scattering increases toward the near infrared region, it is advantageous to have sensitizer absorption in that region rather than at 635 nm pertaining to PpIX. Further, the quantum yield in terms of singlet oxygen production should be as high as possible. Sensitizers such as mesotetra hydroxyphenylchlorine ($\lambda_{abs}$ = 652 nm), lutetium texaphyrin ($\lambda_{abs}$ = 732 nm), and bacteriochlorin ($\lambda_{abs}$ = 760 nm) are interesting in this context. Still, the tumor-eradication depth achievable in surface irradiation will be limited to 3–7 mm because of tissue absorption. Although the penetration is sufficient for treatment of most skin malignancies and lesions in hollow organs treated endoscopically, solid tumors remain outside the region of treatment. An adjunct PDT treatment can still be performed after surgical debulking of the tumor.

The system described here is developed for PDT of massive and potentially inoperable tumors by use of interstitial optical fibers for illumination of the tumor mass. Interstitial PDT has certainly been applied before (see, e.g., Refs. 10–13). What is new in the research presented here is the integration of optical dosimetry and diagnostics to permit an optimized

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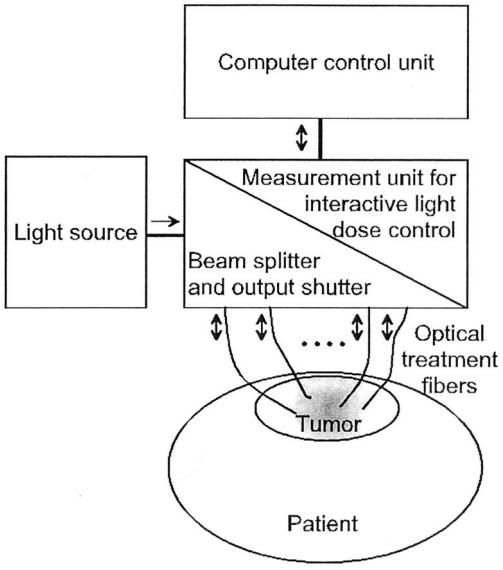


Fig. 1. Schematic view of a multifiber interstitial PDT system with optical feedback.

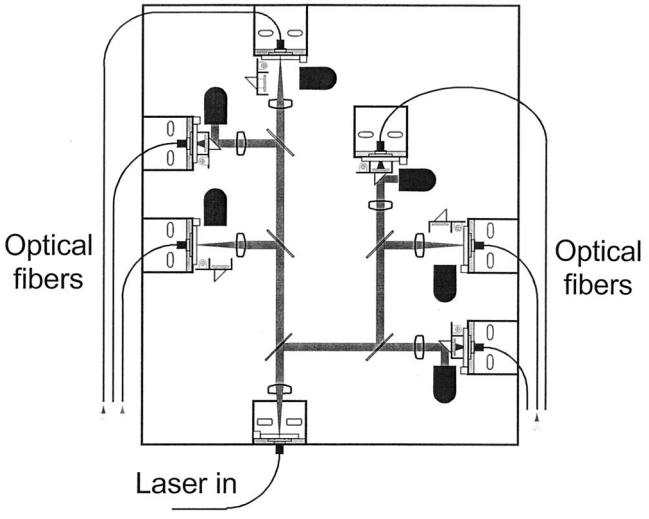


Fig. 2. Setup of the beam-splitting–light-flux-measuring unit.

treatment. The working principles of the system are illustrated in Fig. 1.[14] First, the optimal fiber positions, the fluence rate in the treated region, and the required treatment time are calculated. Continuous laser radiation of an appropriate wavelength is then divided into a number of individual optical fibers, which are inserted in the appropriate positions in the tumor mass while positioned in the lumen of syringe needles. Apart from being able to deliver light into the tumor, each fiber can also act as an antenna that receives light from the other fibers, thus allowing a measurement of the light flux. Each fiber can be quickly switched from a transmitter to a receiver mode of operation. The data from the measurements can be fed into the dosimetry model, which calculates the light distribution in the tumor to allow adjustments of the fiber-transmitted power to achieve an optimal treatment. During the treatment, the diagnostic light flux measurements are repeated a few times because it is known that tissue's optical properties are altered during the treatment.[15] The purpose is to ensure that each tumor cell is placed in a sufficiently effective photon bath for eradication. In the continued development of the system, the same fibers will be used for a number of other optical measurement tasks, which are important for optimizing the process. Parameters to be determined are oxygen concentration through the tumor, concentration of the sensitizer, and temperature at each of the fiber tips.

## 2. Description of the System for Interstitial Photodynamic Therapy

### A. Hardware Integration

The major parts of the optical layout of the interstitial treatment system are schematically shown in Fig. 2. The laser unit is a 2-W cw diode laser (Ceralas PDT 635, CeramOptec, Bonn, Germany) operating at 635 nm. The laser light is coupled into an optical fiber with a core diameter of 400 μm (KP-400L, ANDA, Livani, Latvia). This fiber is connected to a beam-splitting unit in which the light is divided into six different pathways. These six light beams are individually focused into six 400-μm fibers.

Beam splitters and lenses are used to divide the light and focus it into the output fibers. The components are placed on an aluminum plate of dimensions 300 mm × 250 mm × 8 mm, and the optical axis is at a height of 50 mm. The fiber from the laser is connected to the beam-splitting unit with an SMA connector (VERTX, Sweden). This fiber output end is at the focus of an $f$ = 12-mm lens (Melles Griot 01 LAG001/067) used to collimate the light. A 50:50 beam splitter divides the light into two equal parts. The optical components are the same for both beams, but the geometrical paths are slightly different to minimize the size of the beam-splitting unit. The next component is a 33:67 beam splitter in which the 33% light is focused into one of the treatment fibers with a lens of the same type as employed in the collimator. These treatment fibers are also connected with SMA connectors. The other part from the 33:67 beam splitter is again divided into two equal parts with a 50:50 beam splitter and focused with identical lenses into their individual treatment fibers.

The beam-splitting unit thus divides the treatment light into six optical fibers. However, the unit has also been adapted to allow measurement of the light fluence rate at the individual fiber tip locations for dosimetry purposes. When measurements are made, at least one of the fibers has to transmit light, so that the other fibers can be used to measure the fluence rate of the light from that fiber at the positions of the other fiber tips. To do this, six independent photodiodes, each with a detector surface of 16 $mm^2$, can be rotated into the light path of the incom-

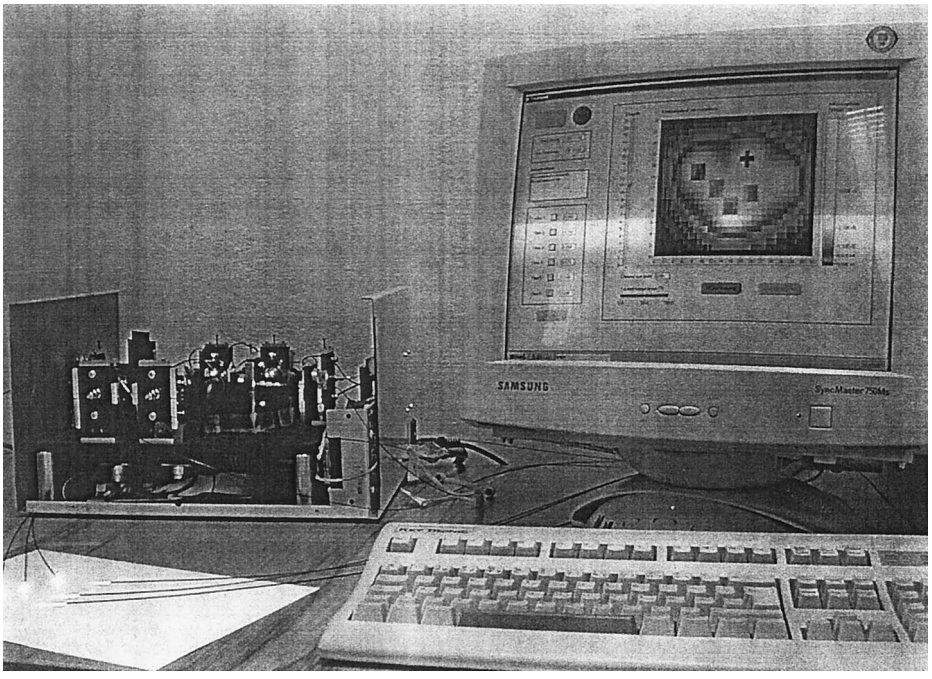


Fig. 3. Photograph of the system with six emitting fibers and a dosimetry chart displayed on the computer screen.

ing light from the treatment fibers; see Fig. 2. The signals measured by the diodes were calibrated by placement of the fibers into a large tank filled with an Intralipid (Fresenius, Kabi, Uppsala, Sweden)/ink mixture with optical properties determined by independent measurements by use of an integrating sphere setup. Direct current motors with appropriate gearboxes and friction clutches swing the gatelike mounts into position. Then the outgoing laser light is automatically blocked on the other side of the gate. The photodiodes are connected to a computer board with a multiplexed 10-bit analog-to-digital converter, measuring signals in the interval 0–5 V. A photograph of the system is shown in Fig. 3, with all six fibers transmitting light and a dosimetry chart displayed on the computer screen.

### B. Software for System Steering

A custom-made computer program was written for the dosimetry calculations to control the beam-splitting unit and to measure the light flux.[16] The development platforms used for this purpose were LabVIEW (National Instruments, Austin, Tex.) and C++ (Microsoft Corporation, Seattle, Washington). The program is divided into two parts. In the first part, the operator has to define absorption and scattering parameters for the tumor and the healthy surrounding tissue. The absorption coefficients used were 0.07 and 0.05 $mm^{-1}$ for tumor and muscle tissue, respectively, while a value of 1.6 $mm^{-1}$ was used for the reduced scattering coefficient for both types of tissue. Also, the shape and size of the tumor have to be defined. The operator can determine where to place the different fibers, or, alternatively, the computer can calculate the optimal positions. The criterion used is that the calculated light dose absorbed by the photosensitizer should exceed a predefined limit in the entire tumor, while the volume outside the tumor, for which this limit is exceeded, is minimized. The threshold used in this study was 15 $J/cm^3$. The system can now calculate the absorbed fluence rate in every part of the tissue because of the individual fibers. The calculations are performed by solution of the diffusion equation numerically by use of the finite element method.[17–19] The numerical method was tested for simple geometries in which an analytical solution is available and a good agreement was found.

The second part of the program is used during the treatment. The program guides the operator through different steps such as loading the right setup file, assigning a name for the output file, putting the fibers into position, and turning the laser on. After this, the operator can press the start button, and the treatment is initiated. The map that is calculated in the first step is now used to display the calculated absorbed dose. This map is frequently updated throughout the entire treatment so that the operator has a feeling of what is happening during the treatment. At regular time steps, the computer interrupts the treatment and initiates a series of measurements of the light. The measurements are done in two ways. The first measurement method is the use of one fiber as the transmitter and the other ones as receivers. Each fiber is used as a transmitter in sequence. The second measurement method is to use five fibers as transmitters and the last one as a receiver. Each fiber is also used sequentially as a receiver. All these data are saved to a file for later evaluation. The system will stop the treatment when the calculated time for full treatment is reached. This means that the different fibers suc-

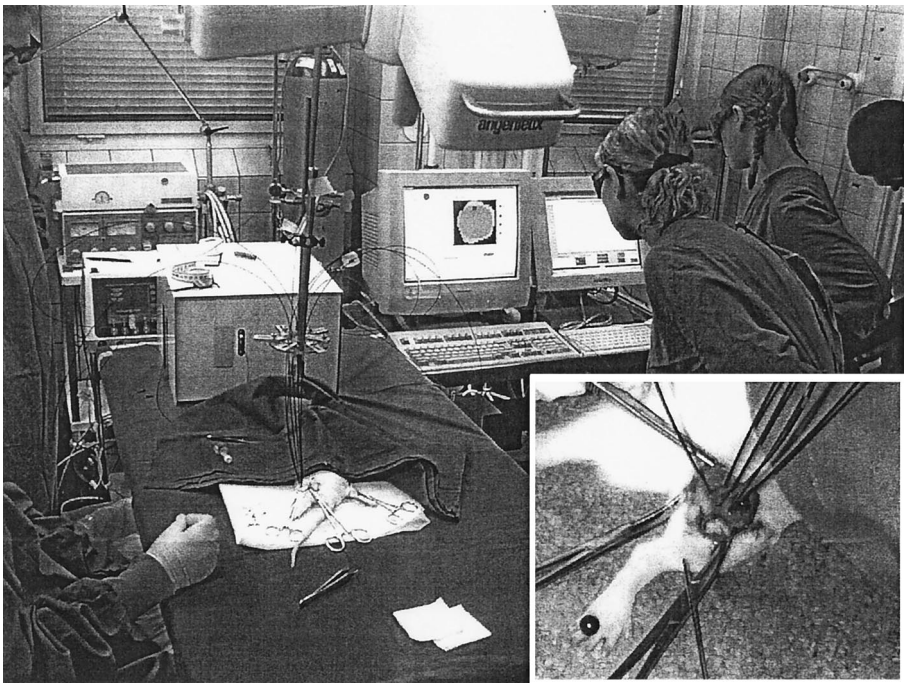

Fig. 4. Photograph of an animal treatment session.

cessively shut down their emission (when the motors swing in the detector that blocks the corresponding laser beam) when the individual tasks have been fulfilled.

### 3. Initial System Performance Studies

Interstitial photodynamic treatments of Wistar–Furth rats were performed in three campaigns, comprising three, four, and six animals, respectively. The rats, each weighing approximately 250 g, had been subcutaneously inoculated on both hind legs with cells from chemically induced adenocarcinoma.[20] Approximately one week after inoculation the tumors typically had diameters of 10–20 mm. Each rat was intraperitonially injected with ALA at a dose of 100 mg/kg body weight. Treatments were performed 1–2 h after the injection. In total, 13 tumors were treated in anesthetized animals. For 11 of the animals, the skin over both tumors was cut open, and the tumors and muscle surfaces were exposed. Three or six fibers were inserted into one of the tumors at predetermined locations. The tumor on the other leg served as an untreated control in the last two campaigns. In eight of the animals, six channels into the control tumor mass were made with the syringe in the same way as for the treated tumor. For the two last animals, the fibers and syringe needles were inserted into the tumor masses (treated and control) through the skin instead of first exposing the free surface by surgery. This procedure was found to work technically well with the additional advantage of perturbing the tumor area less. Frequently, an extra, diagnostic fiber was inserted into a position between the treatment fibers for assessing the PpIX accumulation and PDT-induced bleaching.[21] A fluorosensor, which has been fully described in Ref. 22, was used for those measurements. Optical measurements for assessing the light fluence rate through the tumor were made, and PDT treatment as described above was iteratively performed. For treated and control tumors the skin was closed with stitches after the procedure, and the rats were left with food and water *ad libitum* for three days before sacrifice and tumor extraction and preparation for histopathology. A photograph of the treatment scene is shown in Fig. 4. A primary evaluation was made by measurement of the tumor volume before the treatment and three days after. Two orthogonal dimensions were measured, and the corresponding ellipsoid volume was calculated. After the measurements of the size, the tumors were placed in 20% formaldehyde for subsequent routine histopathology.

### 4. Results

The output power from each individual treatment fiber depends somewhat on the fiber used. The power could easily decrease 20% if the fiber not was properly polished. The total throughput of the beam-splitting unit was 45%, with the light power reasonably uniformly distributed between the individual fibers. Curves of the measured signals as a function of distance from the emitter in the homogenous Intralipid/ink phantom used for calibration purposes are shown in Fig. 5. They gave a similar sensitivity for all diodes but one. The sensitivity was 0.055 $W/(cm^2\ V)$, yielding a measurement range of 0–275 $mW/cm^2$.

An illustration of how the treatment of a tumor utilizing six fibers progresses until the point at which the whole tumor has received the threshold light dose

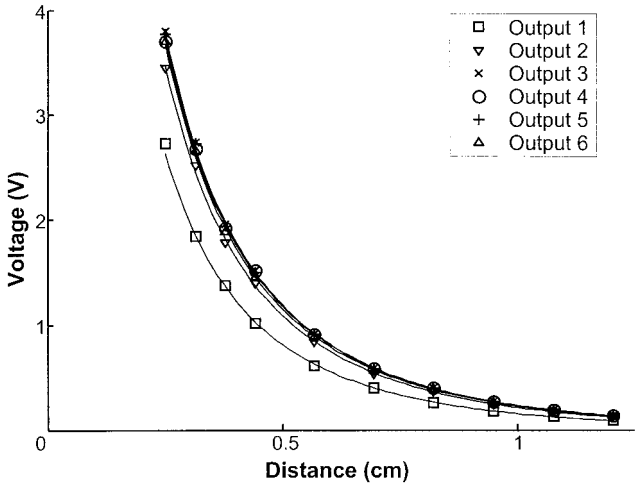


Fig. 5. Measured signals as a function of distance measured in an Intralipid/ink phantom. These curves were used to calibrate the detection sensitivity of the six fibers in the detection mode.

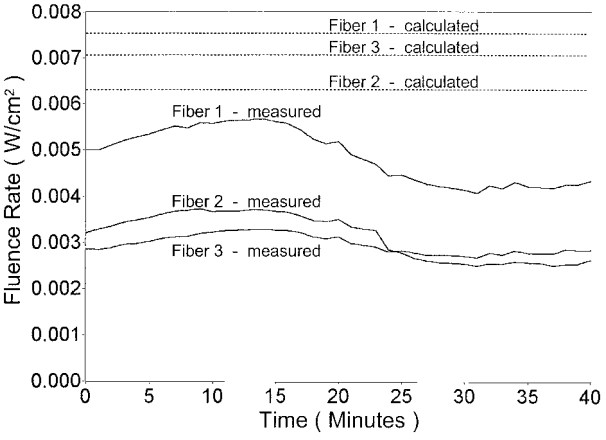


Fig. 7. An example of graphs of measured fluence rates during a treatment that used three treatment fibers. Each graph represents the measured fluence rate for that detection fiber when the other two fibers were transmitting treatment light. The predicted values calculated before the treatment started are also indicated.

is shown in Fig. 6. The figure illustrates the absorbed light dose in a plane through the tumor at four times during the treatment. An example of measured fluence rates during another treatment in which only three fibers were used is illustrated in Fig. 7.

The laser-induced tissue fluorescence level at a point 7 mm down from the surface of the tumor is shown in Fig. 8 before the start and during the course of the treatment. The bleaching of the PpIX can clearly be seen. The absorbed light dose can be assessed from either the absolute value of the 635-nm peak, the intensity of which is inversely proportional to the absorbed light dose, or from the relative intensity at 650 and 635 nm, which monitors the successive build-up of photodegradation products.[23] Figure 8 shows the changes in fluorescence intensity at the 635-nm peak during the treatment.

The temporal development results are shown for 13 tumors in Fig. 9. It was found that 11 out of 13 tumors (85%) reduced their size over the short period of three days following PDT. The average reduction

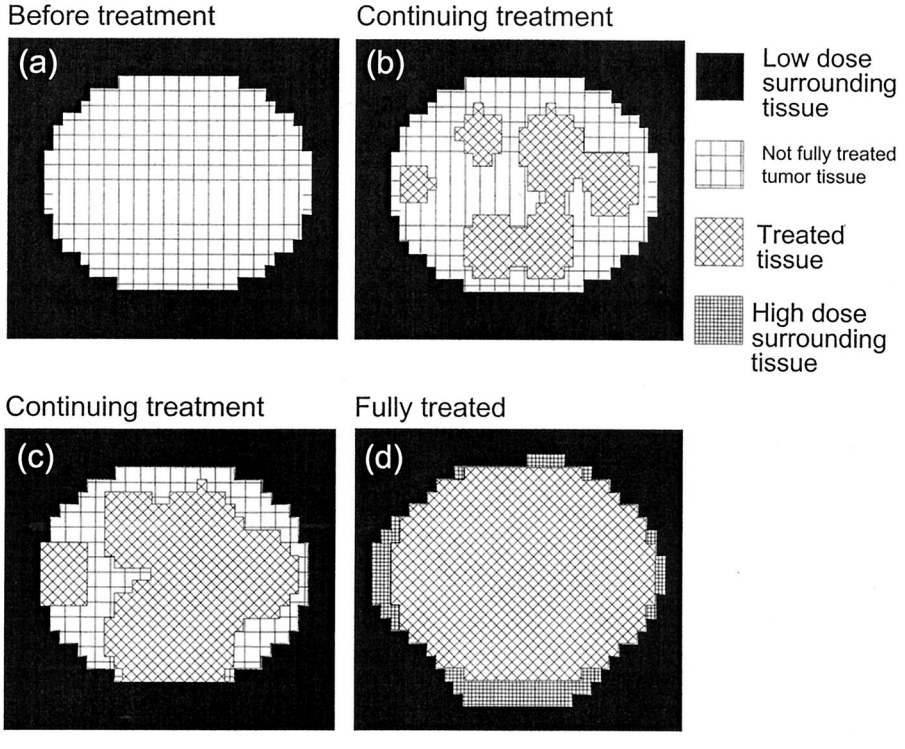


Fig. 6. Dosimetry modeling and temporal evolution of delivered light dose. The dose at distances very close to the source fibers, a region in which the diffusion approximation is not valid, was increased manually.

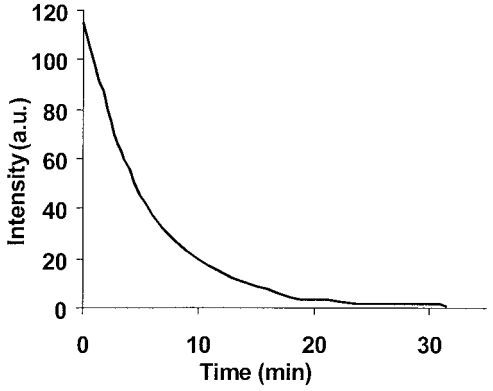


Fig. 8. Demonstration of bleaching of PpIX inside the tumor mass, owing to the flux of red photons through the tumor. The fluorescence intensity at 635 nm was recorded.

for the 13 tumors was 34%. For ten of the tumors, reference tumors of the other hind leg were prepared in a way similar to the treatment of the tumors, as discussed above. The results from the tumor intercomparison (treated versus nontreated) are shown in Fig. 10. Here it can be seen that six out of ten tumors (60%) were reduced compared with the controls. The average reduction for the ten tumors (with respect to their respective reference tumor) was 28%.

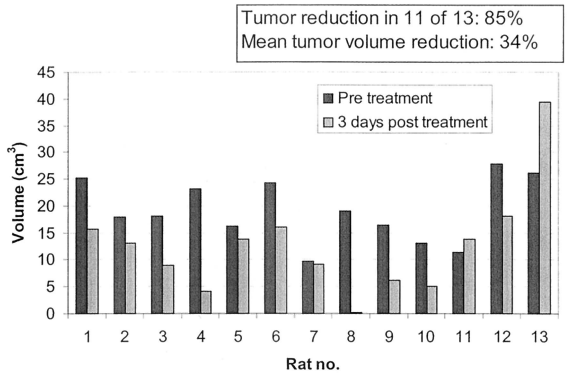


Fig. 9. Comparison of tumor volume before and three days after interstitial PDT in Wistar–Furth rats.

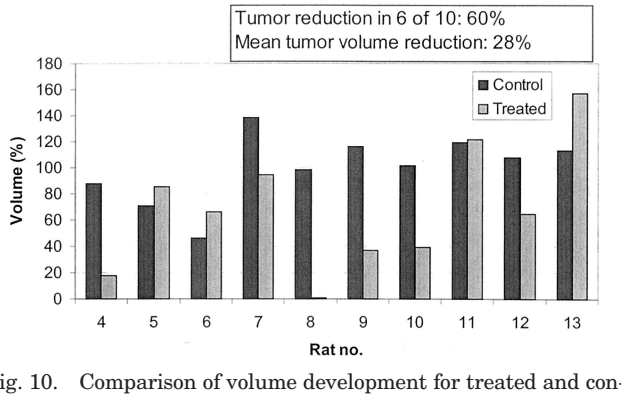


Fig. 10. Comparison of volume development for treated and control tumors during a three-day period starting just before the PDT and extending three days after.

It should be noted that the outcome is obscured by the fact that for two control tumors (in rats #5 and #6) a strong spontaneous reduction occurred.

The histopathological examinations visualized a large central necrosis in the treated tumors. Most treated tumors also had remaining vital regions with tumor cells close to the border to the muscle. Also, the control tumors showed regions of necrosis.

## 5. Discussion

A system for interstitial PDT of massive tumors, believed to be novel, has been developed and undergone an initial evaluation. It has proved to work reliably and to be useful for treating tumors that are not candidates for superficial illumination PDT owing to their size. The treatment outcome was, however, not fully satisfactory. Complete response was not obtained for most tumors, neither in the tumor-size measurements nor in the histopathological examination. Improvements are thus necessary. The threshold used for the absorbed light dose for killing the tumor cells may need to be increased. It would furthermore be of interest to know the oxygenation of the tissue, as it is important to have enough oxygen available for the PDT to be efficient. Also, three days is clearly an extremely short time for assessing the treatment outcome. Even though extensive parts of the tumors were killed, they did not reduce much in size after this short time. Still, using both size-evaluation methodologies presented in Figs. 9 and 10, we found that the interstitial treatment was effective in reducing the tumor mass. The evaluation time was chosen by taking practical considerations into account. The untreated tumors grew quickly, and a longer evaluation time would not have been good, as the general condition of the animals would have been much more affected. In addition, the spontaneous necrotic regions also developing in the control tumors made the evaluation uncertain. The model used for this initial evaluation was thus not ideal.

An extensive developmental plan for the system and treatment procedures now exists. We intend to use many of the procedures developed for other treatment modalities, for positioning the fibers. In most applications of brachytherapy, the radioactive-substance-loaded needles are positioned under visual inspection and palpation only. However, other applications may need more accurate positioning. The full clinical implementation of this system might thus require the integration of the new technology with stereotactic techniques, frequently used in the management of brain tumors. As a first step in future treatments, we plan to measure the tumor dimensions and guide the fiber positioning with ultrasound techniques.

The system will be improved in several ways. The data recorded on the flow of light through the tumor were so far not used as direct feedback for the ongoing treatment. The experience gained in animal and first clinical implementation will allow the setting of the parameters for an interactive feedback loop. We

also plan to integrate fluorescence measurements in each of the treatment–measurement fibers. This will allow an assessment of the distribution of the sensitizer concentration through the tumor mass. If the fiber tips are prepared with a suitably chosen rare-earth salt, melted into the quartz, it will be possible to measure sharp temperature-sensitive lines[24] superimposed on the broadband tissue fluorescence. This will allow determination of the temperature at the fiber locations. Possible synergism between photodynamic and thermal therapy might be exploited. It will be possible to see if coagulated blood makes the temperature rise at the fiber surface, blocking further light delivery. Because the availability of tissue oxygen is important for successful PDT, spectroscopic assessment of this parameter should be considered.

Clearly, the goal of the project is to progress to the state of clinical use as soon as possible. We are now convinced that the technique could be used to treat tumors not candidates for superficial PDT and that many clinical treatments would benefit from this modality. Those tumors are much better suited for this type of treatment than the ones treated in this initial study.

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### References

1. S. L. Marcus, "Photodynamic therapy of human cancer: clinical status, potential and needs," in *Future Directions and Applications in Photodynamic Therapy,* C. J. Gomer, ed., Proc. SPIE **IS-6,** 5–56 (1990).
2. L. I. Grossweiner, *The Science of Phototherapy* (CRC Press, Boca Raton, Fla., 1994).
3. T. J. Dougherty, C. J. Gomer, B. W. Henderson, G. Jori, D. Kessel, M. Korbelik, J. Moan, and Q. Peng, "Photodynamic therapy," J. Natl. Cancer Inst. **90,** 889–905 (1998).
4. J. C. Kennedy, R. H. Pottier, and D. C. Pross, "Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience," J. Photochem. Photobiol. B **6,** 143–148 (1990).
5. J. C. Kennedy and R. H. Pottier, "Endogenous protoporphyrin IX, a clinically useful photosensitizer for photodynamic therapy," J. Photochem. Photobiol. B **14,** 275–292 (1992).
6. K. Svanberg, T. Andersson, D. Killander, I. Wang, U. Stenram, S. Andersson-Engels, R. Berg, J. Johansson, and S. Svanberg, "Photodynamic therapy of non-melanoma malignant tumours of the skin using topical δ-amino levulinic acid sensitization and laser irradiation," Br. J. Dermatol. **130,** 743–751 (1994).
7. Q. Peng, T. Warloe, K. Berg, J. Moan, M. Kongshaug, K.-E. Giercksky, and J. M. Nesland, "5-aminolevulinic acid-based photodynamic therapy: clinical research and future challenges," Cancer **79,** 2282–2308 (1997).
8. I. Wang, B. Bauer, S. Andersson-Engels, S. Svanberg, and K. Svanberg, "Photodynamic therapy utilising topical δ-aminolevulinic acid in non-melanoma skin malignancies of the eyelid and the periocular skin," Acta Ophthalmol. Scand. **77,** 182–188 (1999).
9. I. Wang, N. Bendsoe, C. af Klinteberg, A. M. K. Enejder, S. Andersson-Engels, S. Svanberg, and K. Svanberg, "Photodynamic therapy versus cryosurgery of basal cell carcinomas: results of a phase III randomized clinical trial," Br. J. Dermatol. **144,** 832–840 (2000).
10. T. J. Dougherty, R. E. Thoma, D. G. Boyle, and K. R. Weishaupt, "Interstitial photoradiation therapy for primary solid tumors in pet cats and dogs," Cancer Res. **41,** 401–404 (1981).
11. J. P. A. Marijnissen, J. A. C. Versteeg, W. M. Star, and W. L. J. van Putten, "Tumor and normal response to interstitial photodynamic therapy of the rat R-1 rhabdomyosarcoma," Int. J. Radiat. Oncol. Biol. Phys. **22,** 963–972 (1992).
12. C. P. Lowdell, D. V. Ash, I. Driver, and S. B. Brown, "Interstitial photodynamic therapy. Clinical experience with diffusing fibres in the treatment of cutaneous and subcutaneous tumours," Br. J. Cancer **67,** 1398–1403 (1993).
13. S. F. Purkiss, R. Dean, J. T. Allardice, M. Grahn, and N. S. Williams, "An interstitial light delivery system for photodynamic therapy within the liver," Lasers Med. Sci. **8,** 253–257 (1993).
14. S. Svanberg, S. Andersson-Engels, R. Berg, J. Johansson, and K. Svanberg, "System for laser treatments of tumours," Swedish patent 503 408 (10 June 1996).
15. A. M. K. Nilsson, R. Berg, and S. Andersson-Engels, "Measurements of the optical properties of tissue in conjunction with photodynamic therapy," Appl. Opt. **34,** 4609–4619 (1995).
16. N. Ohlsson and O. Rylow, "Development of a multifibre system for interstitial photodynamic therapy of malignant tumours," MSc thesis (Lund Institute of Technology, Lund, Sweden, LRAP-240, 1998).
17. S. R. Arridge, M. Schweiger, M. Hiraoka, and D. T. Delpy, "A finite element approach for modeling photon transport in tissue," Med. Phys. **20,** 299–309 (1993).
18. N. S. Ottosen and H. Petersson, *Introduction to the Finite Element Method* (Prentice Hall International, London, 1992).
19. S. S. Rao, *The Finite Element Method in Engineering* (Pergamon, New York, 1989).
20. G. Hedlund and H. O. Sjögren, "Induction of transplantation immunity to rat colon carcinoma isografts by implantation of intact fetal colon tissue," Int. J. Cancer **26,** 71–73 (1980).
21. J. Johansson, R. Berg, K. Svanberg, and S. Svanberg, "Laser-induced fluorescence studies of normal and malignant tumour tissue of rat following intravenous injection of δ-amino levulinic acid," Lasers Surg. Med. **20,** 272–279 (1997).
22. C. af Klinteberg, M. Andreasson, O. Sandström, S. Andersson-Engels, and S. Svanberg are preparing a manuscript to be called "Compact medical fluorosensor for minimally invasive tissue characterization."
23. T. Andersson, R. Berg, J. Johansson, D. Killander, K. Svanberg, S. Svanberg, and Y. L. Yang, "Photodynamic therapy in interplay with fluorescence diagnostics in the treatment of human superficial malignancies," in *Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy,* T. J. Dougherty, ed., Proc. SPIE **1645,** pp. 187–199 (1992).
24. K. T. V. Grattan and Z. Y. Zhang, *Fiber Optic Fluorescence Thermometry* (Chapman & Hall, London, 1995).