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Interstitial Photodynamic Therapy of Nonresectable Malignant Glioma Recurrences Using 5-Aminolevulinic Acid Induced Protoporphyrin IX

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Background and Objective: Limited knowledge of the light and temperature distribution within the target volume in combination with non-selective accumulation of the applied photosensitizers (PS) has hampered the clinical relevance of interstitial photodynamic therapy (iPDT) for treatment of malignant glioma patients. The current pilot study focused on the development and the clinical implementation of an accurate and reproducible irradiation scheme for iPDT using 5-aminolevulinic acid (5-ALA) induced protoporphyrin IX (PPIX) as a selectively working PS.

Study Design/Materials and Methods: Monte Carlo simulations of fluence rate and heat transport simulations were performed using the optical properties of normal brain tissue infiltrated by tumor cells (absorption coefficient $\mu_a = 0.2\ cm^{-1}$, reduced scattering coefficient: $\mu'_s = 20\ cm^{-1}$). A modified 3-D treatment-planning software was used to calculate both, the treatment-volume and the exact position of the light diffusers within the lesion. The feasibility and the risk of iPDT were tested in 10 patients with small and circumscribed recurrent malignant gliomas.

Results: The optimum distance between the implanted light diffusers was determined to be 9 mm with regard to both fluence rate and temperature distribution. For this distance a temperature increase above 42°C was not expected to occur. Up to six cylindrical light diffusers were stereotactically implanted to achieve a complete irradiation of the tumor volume, which was possible in every single patient (mean tumor volume: 5.9 cm^3). The total applied light fluence was between 4,320 J and 11,520 J. Side effectsof iPDT were not observed. Median survival was 15 months.

Conclusion: 5-ALA iPDT in combination with a 3-D treatment-planning (which was based on optical and thermal simulations) is a safe and feasible treatment modality. The clinical impact of these findings deserves further prospective evaluation. Lasers Surg. Med. 39:386–393, 2007. © 2007 Wiley-Liss, Inc.

Key words: neurosurgery; photodynamic therapy; stereotactic; interstitial; intratumoral; light application; brain tumor; glioblastoma; 5-aminolevulinic acid; protoporphyrin IX; cylindrical diffuser; dosimetry

INTRODUCTION

Glioblastoma multiforme is the most common and most malignant primary brain tumor in humans and the overall prognosis for patients continues to be dismal. The median survival after tumor resection, external beam irradiation, and various forms of chemotherapy still lies in the range of 12 months [1,2]. Taken into account that tumor recurrences usually occur locally at the margin of previously treated tumor volumes [3,4], the improvement and further development of local treatment concepts such as photodynamic therapy (PDT) remains a matter of utmost importance [5–10].

Treatment effects of PDT are based on the accumulation of photosensitizing drugs (PS) in malignant tissue, which exert tumor-toxic properties after activation by light of an appropriate wavelength. A possibly minimally invasive way to apply the light to the sensitized tumor is to place light guiding fibers directly within the treatment volume. This treatment modality is referred to as interstitial photodynamic therapy (iPDT). Its feasibility and effectiveness has been investigated in brain tumor models [11,12] and in first clinical applications with Photofrin [13–16]. Unfortunately, prolonged skin sensitization and damage to normal brain tissue due to the limited selectivity of the applied PS (Photofrin or Photofrin II) have obstructed the broad application of this potentially minimal invasive treatment concept.

5-aminolevulinic acid (5-ALA) induced protoporphyrin IX (PPIX) has proven its high potential as a PS for PDT in several experimental studies [17–20] and has recently gained interest in neurosurgery [21,22] due to a selective tumor uptake and only minimal skin sensitization [23–25].

The current pilot study focused on the development of an accurate and reproducible irradiation scheme for the

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5-ALA iPDT approach (e.g. optimal intratumoral fiber positioning and interfiber distance, applied fluence, fluence rate, and temperature distribution) and the feasibility of its clinical implementation. It was hypothesized that state of the art stereotactic techniques enabling both a 3-D-dosimetry and the optimal placement of the light guiding fibers in combination with a highly tumor selective PS such as 5-ALA induced PPIX would lead to controlled treatment effects and a significant reduction of the risk of the therapy. The feasibility and the risk of iPDT was analyzed in 10 patients with a circumscribed recurrence of a malignant glioma with a maximum diameter of 3 cm. The study protocol was approved by the institutional review board of the Ludwig-Maximilians-University, Klinikum Grosshadern, Munich.

MATERIALS AND METHODS

Technical Setup

The illumination was performed using a laser, a beam splitter, and light diffusers. The light source was a diode laser emitting light at a wavelength of $\lambda = 633$ nm with a maximum output power of 4 W (Ceralas PDT Diode Laser, biolitec AG, Jena, Germany). The laser light was coupled via a 400 μm fiber and a lens into a beam splitter with a variable number of output ports and variable output powers for each port. Up to six diffusers with variable diffuser lengths could be illuminated simultaneously with a constant power of 200 mW/cm.

Fiber-based cylindrical light diffusers were used as treatment fibers (CD403, CeramOptec GmbH, Bonn, Germany). The diffuser tips had an outer diameter of $d = 1.6$ mm and a radiation length of $l = 20$ mm or $l = 30$ mm (CD403-20 and CD403-30, respectively, Fig. 1). Depending on the tumor geometry, the 20 mm or 30 mm diffusers were used. The spatial light distribution of both diffuser lengths used is given in Figure 1. The light intensity distribution measured along the radiating zone was nearly homogeneous. X-ray markers on both ends of the radiating zone enable an X-ray controlled positioning.

Determination of the Irradiation Scheme

Pre-operatively, the temperature distribution was calculated with a commercial Monte Carlo-based simulation program using interfiber distances between 7 and 9 mm (LITCIT 32, LMTB GmbH, Berlin, Germany) [26]. In the LITCIT simulations, four cylindrical light diffusers were positioned at the edges of a square. The light power emitted from the diffusers was set to 200 mW/cm diffuser length, which had been already used for iPDT of malignant glioma by Powers et al. [13]. Optical tissue parameters for glioblastoma recurrences were not available. Instead, the optical properties of normal brain tissue infiltrated by tumor cells (BAT) were used [27], as a model for a multimodally treated malignant glioma. These parameters are similar to in-vivo measurements performed by Muller and Wilson [28,29]. The absorption coefficient μ_a was set to 0.2 cm^{-1} and the reduced scattering coefficient μ'_s to 20 cm^{-1}, resulting in an optical penetration depth (δ_{eff}) of

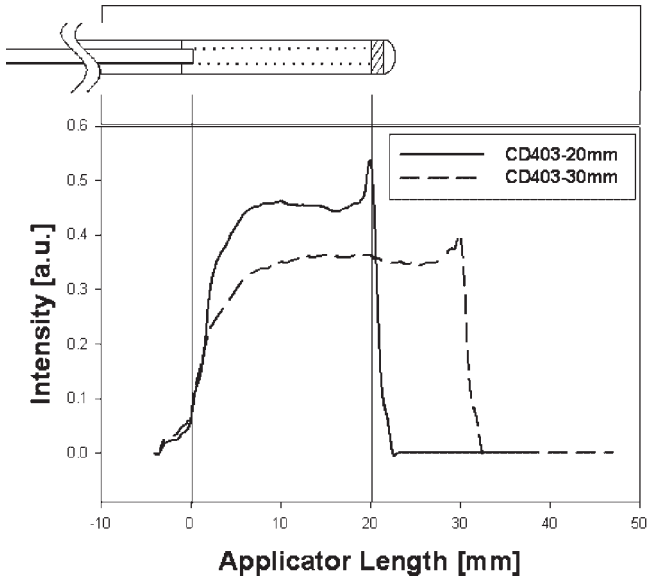

Fig. 1. Top: Cross section of the applicator CD403-20 including X-ray marker at the distal end. Bottom: Radiation profile of the two applicator types, l = 20 mm (—) and l = 30 mm (- - -).

3 mm ($\delta_{eff} = (3\mu_a(\mu_a+\mu'_s))^{-1/2}$). The relevant heat transport parameters were set as follows: initial tissue temperature: 37C, blood perfusion: 0.5 ml/(g · minute), water content: 75%, heat conductivity: 0.0048 W/(cm · K), heat capacity: 3.4882 J/(g · K), density: 1.075 g/cm^3 [26].

The fluence rate distribution was calculated with Monte Carlo simulations based on the algorithm of Prahl [30], using the optical parameters of BAT. Results were obtained by simulating 1,000,000 histories with a running time of some 30 minutes on an Intel Pentium M at 1400 MHz with 512 MB RAM. The fluence rate levels were simulated for one single diffuser. The fluence rate distribution in between two or more fibers could be deduced from these results by summing up the contributions of each single fiber.

Light Fluence

The threshold light fluence necessary to induce a significant phototoxic effect in malignant glioma tissue has still not been defined for the 5-ALA-iPDT approach. Clinical protocols for surface irradiation with 5-ALA-PDT usually operate with fluences in the range of 100 J/cm^2. Excessive photobleaching of the PS occurs at this fluence, and further irradiation should not be associated with a significant increase of phototoxicity. Therefore, the irradiation time was only limited with respect to the duration and invasiveness of the surgical procedure; side effects due to an excessive fluence were not expected. One hour was considered an appropriate irradiation time. The resulting total fluence and the fluence per tumor volume were calculated with the light power of 200 mW/cm diffuser length.

Patient Selection

Adult patients with a circumscribed recurrence of a malignant glioma with a maximum diameter of 3 cm (as defined by gadolinium enhanced T1 weighted magnetic

resonance imaging (MRI)) and a Karnofsky Score (KPS) of at least 70 were considered eligible for the study. A confirmatory stereotactic biopsy was required for all patients.

Stereotactic Treatment Planning

Treatment planning was based on multimodal imaging data: image fusion of the stereotactically localized computerized tomography (CT) scans (contrast enhanced scans, 2 mm slices), with additional MRI (T1 weighted gadolinium enhanced scans, 1 mm slices, T2-weighted scans, 2 mm slices), and FET-PET (*O*-(2-[18F]fluoroethyl)-L-tyrosine—positron emission tomography) scans were done for optimal visualization of the tumor and exact definition of the treatment volume (Image Fusion Software, BrainLAB AG, Heimstetten, Germany).

Irradiation planning was performed with the @target 1.19 software (BrainLAB AG). This program was originally designed for the planning of stereotactic biopsy trajectories and Iodine-125 seed implantation. An additional feature is the 3-D tumor demarcation and calculation of the tumor volume. It supports also the placement of treatment catheters within the tumor under full 3-D control of their position within the brain.

Stereotactic Surgery

One hour prior to surgery, patients received 20 mg/kg body weight 5-ALA (medac GmbH, Wedel, Germany) dissolved in 100 ml water orally. This dose is well tolerated and associated with strong fluorescence in malignant glioma [24]. All patients were treated under general anesthesia. Intraoperatively, the oxygen saturation was set to 100% in order to prevent a possible lack of cellular oxygen due to oxygen consumption during the treatment [31,32].

The output power of each diffuser was controlled with an integrating sphere. All fibers had an X-ray marker and the accuracy of the stereotactic implantation procedure was checked online during the operation with an orthogonal X-ray technique using a C-arm. The inserted fibers were fixed at the entry point with a fiber clip to avoid displacement.

Patient Evaluation

The first postoperative MRI investigation (T1/T2, with/without gadolinium) was done at day one after surgery for assessment of early treatment effects. Further clinical and neuroradiological follow-up was performed 1 month postoperatively and from then on at 3-month intervals at the outpatient clinic. Length of survival was calculated with the Kaplan–Meier-method.

RESULTS

Irradiation Scheme

Heat transport simulations were performed using interfiber distances between 7 and 9 mm. At an interfiber distance of 7 mm the temperature in the vicinity of a diffuser increased up to 42°C, whereas an interfiber distance of 9 mm resulted in a maximum temperature in the range of 41°C (Fig. 2). For this distance, further simulations with unfavorable parameter combinations (variations of absorption and scattering coefficients and heat transport parameters of up to 20%) were performed and did not result in a temperature increase above 42°C. Therefore, a distance of 9 mm seems to be sufficient in order to prevent unfavorable temperature increase within the irradiated tissue. Thus, further treatment planning was based on this interfiber distance.

The fluence rate levels around a single diffuser were calculated with a Monte Carlo program. Figure 3 shows the resulting iso-fluence rates when the applicator has a diffuser length of 2 cm and emits 200 mW/cm. The fluence rate at a distance of 4.5 mm from the applicator's surface is 260 mW/cm^2. Thus, in between two diffusers at an interfiber distance

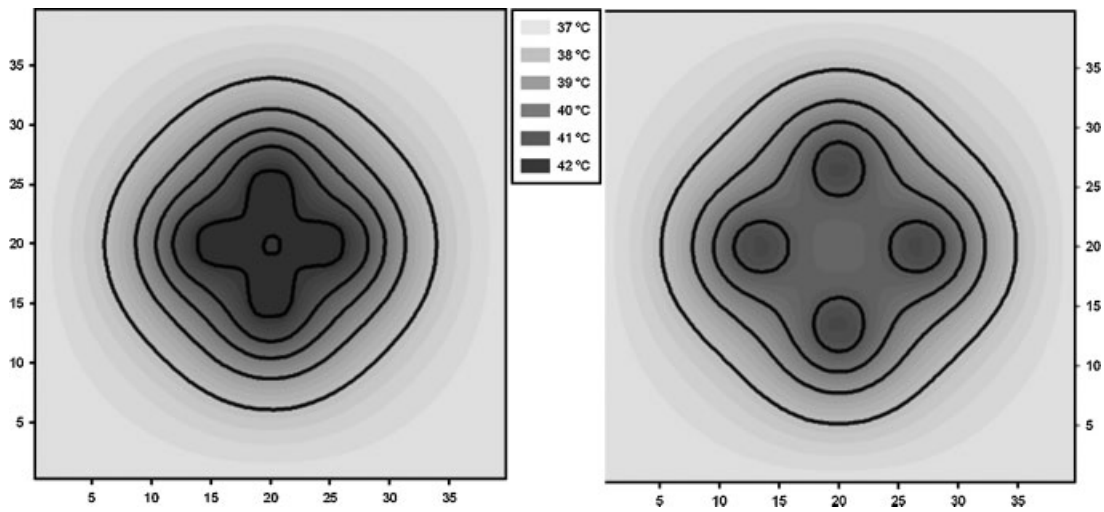

Fig. 2. Temperature distribution within the irradiated tissue according to LITCIT simulations at an interfiber distance of 7 mm (left) and 9 mm (right).

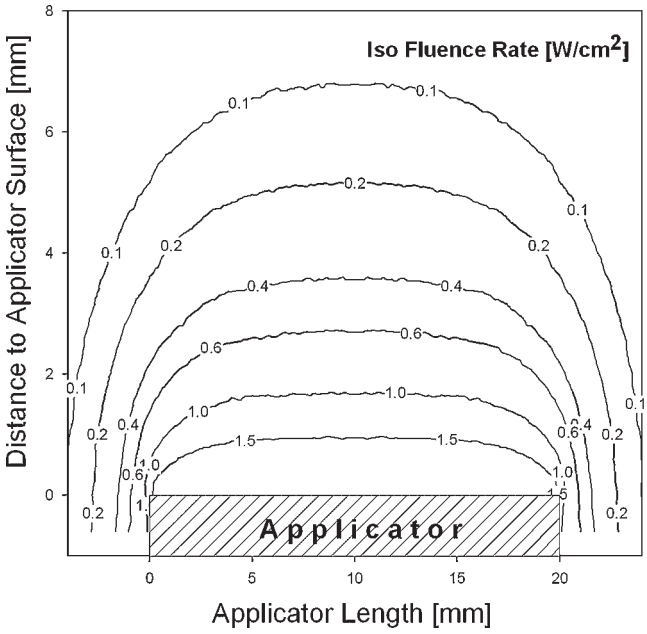

Fig. 3. Iso-fluence rates of a cylindrical light diffuser calculated by Monte-Carlo simulations.

of 9 mm, the fluence rates of both diffusers add to a total fluence rate of 520 mW/cm^2. This value was set to be the threshold value, which should also be obtained at the tumor margin, where, to a first approximation, only one light diffuser illuminates the tissue. As can be seen in Figure 3, 520 mW/cm^2 is obtained at a distance of about 3 mm from the applicator's surface. Accordingly, 3-D treatment planning is based on the maximum distance between the applicator's surface and the tumor margin. Due to the fast decrease of the fluence rate with increasing distance from the light diffuser (Fig. 3), an approximately 1.5 mm increased distance from the tumor border or interfiber distance reduces the available fluence rate by a factor of 2.

As the irradiation time was set to be 1 hour (as described above), a minimum fluence of 1,870 J/cm^2 was obtained at the tumor margin and in between the two diffusers. The light fluence per diffuser length was 720 J/cm. Irradiation parameters are listed in Table 1. The total applied light fluence depended on the number and length of the inserted light diffusers and was between 4,320 J and 11,520 J (mean: 7,212 J).

Treatment Implementation

The irradiation volume was estimated and visualized using the @target 1.19 software: A cylindrical irradiation volume with a diameter of 7.6 mm (radial distance from diffuser surface: 3 mm; diffuser diameter: 1.6 mm) was generated around each diffuser used and the corresponding iso-fluence was displayed in axial, sagittal, and coronar projections. It was aimed to overlap the entire treatment volume with these treatment cylinders. Taken into account the calculated optimal inter-fiber distance of 9 mm, only a minimal overlapping of the cylindrical irradiation volumes was allowed. Special care was taken that the stereotactically defined trajectories for fiber implantation run parallel to each other. In case of a complete irradiation of the treatment volume it could be expected that the fluence rate exceeded 520 mW/cm^2. A typical screen shot of the 3-D planning program is shown in Figure 4.

Feasibility and Risk of iPDT

During a 1-year period (October 2002–2003) 10 patients were included in the current pilot study. The median age was 54 years (range 31–72 years). Tumor volumes ranged between 2.1 and 10.2 cm^3 (mean: 5.9 cm^3) and the total volume light fluence ranged between 939 and 2,304 J/cm^3 (mean: 1,405 J/cm^3) (Table 1). A complete irradiation of the tumor volume was possible in all of these patients using four to six fibers per patient. The accuracy of the final fiber position (as compared to the original treatment plan) was in the range of 2 mm, as judged by X-ray control. Perioperative morbidity was not observed. A symptomatic early or delayed treatment induced edema did not occur during the follow-up period and steroid medication was only applied perioperatively (during the first 3 days after surgery).

TABLE 1. Patient Characteristics, Treatment Parameters, and Survival of the 10 Patients Included in the Pilot Study

Patient ID	Age	KPS pre-Op	Tumorlocation	Side	Tumor volume (ccm)	Total light fluence (J)	Volume light fluence (J/ccm)	Survival time (months)
1	31	100	Frontal	Left	6.9	7,200	1043	49
2	69	80	Parietal	Right	4.8	5,700	1188	4
3	72	90	Temporal	Right	4.5	7,500	1667	11
4	42	90	Fronto-temporal	Left	2.1	4,320	2057	32
5	54	90	Parietal	Right	6.3	6,600	1048	7
6	54	100	Frontal	Left	10.2	11,520	1129	5
7	56	80	Fronto-temporal	Left	9.9	10,080	1018	39
8	57	90	Parietal	Left	2.9	4,800	1655	27
9	32	80	Frontal	Left	9.2	8,640	939	17
10	50	90	Temporal	Right	2.5	5,760	2304	13

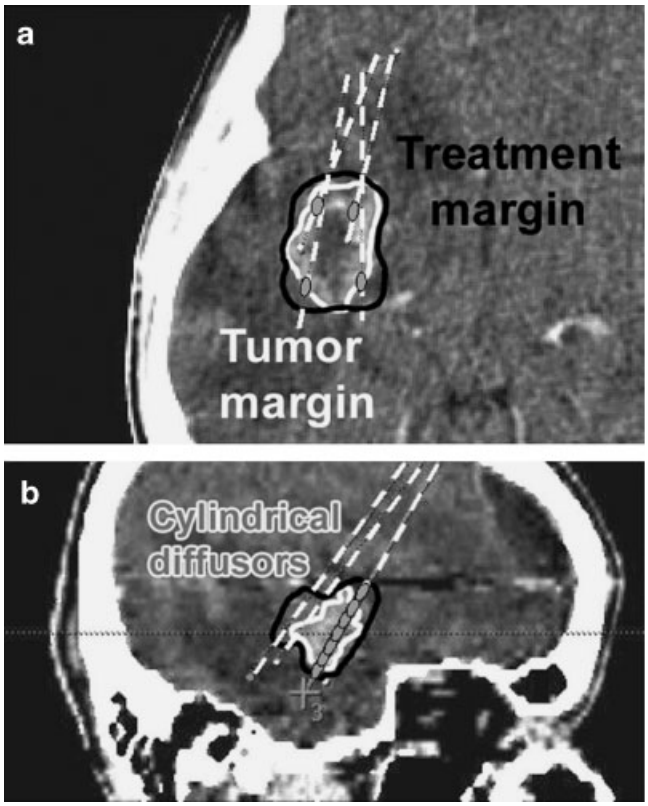

Fig. 4. Screen shot of the 3-D-planning showing excellent agreement between the estimated treatment margin (black line) and the tumor margin (white line). Axial plane (**a**) and sagittal plane (**b**).

MRI Follow-Up After iPDT

Early postoperative MRI (at day 1 after surgery) showed a complete resolution of the contrast enhancement of the treated lesion in seven patients and a partial resolution in the other three. Typically, transient contrast enhancement was seen again at day 7 after treatment at the boundary of the treatment volume. It was accompanied by a moderate increase of the peri-lesional edema, which slowly resolved spontaneously during the first 3 months after surgery. A representative example is given in Figure 5.

Survival

The 1-year-survival rate was 60% (median survival: 15 months). Four patients lived longer than 24 months and two of them are still alive (Fig. 6). Last follow-up evaluation revealed a high KPS of the survivors ($\geq$80).

DISCUSSION

A prerequisite for iPDT as a possible minimal invasive treatment option for selected patients with a circumscribed malignant glioma recurrence (after previously applied standard therapy) is the application of a PS with a selective tumor uptake and the availability of an accurate and reproducible irradiation scheme. In the current study an irradiation scheme was developed on the basis of theoretical models and the feasibility of its clinical implementation was tested thereafter. It was hypothesized that the combination of a new and selectively working PS (5-ALA induced PPIX) with stereotactic techniques enabling both a 3-D-dosimetry and optimal placement of the laser fibers thereafter would lead to controlled treatment effects.

Photosensitizer

Inefficient tumor control and severe side effects of the therapy have been described for iPDT if it is based on

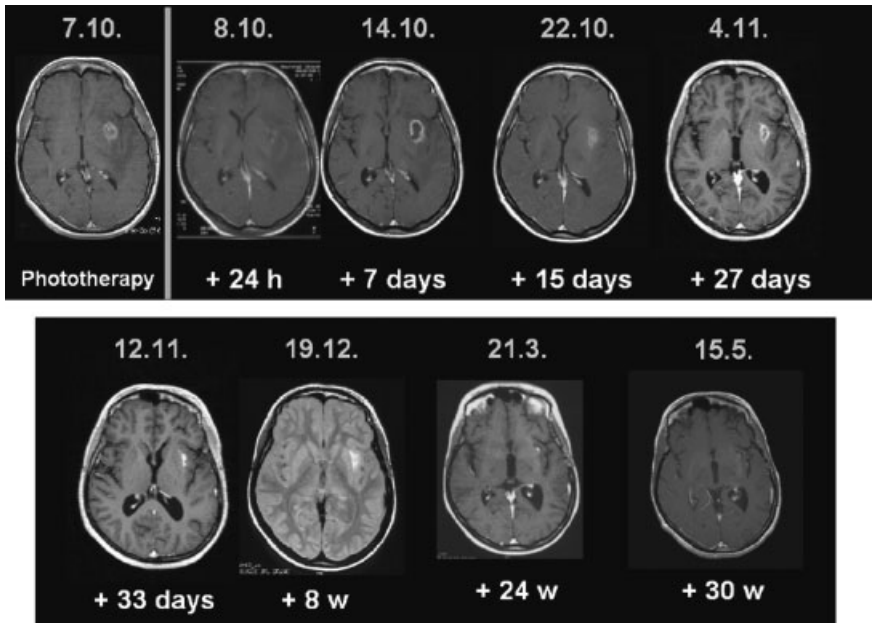

Fig. 5. Series of contrast-enhanced MRI-scans (T1 weighted) of a patient treated with iPDT.

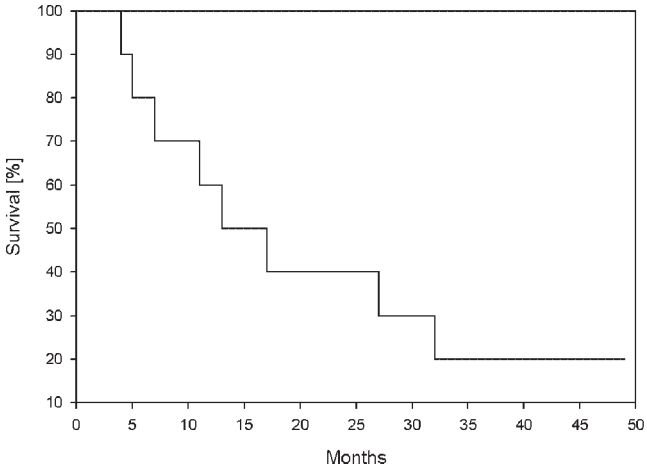

Fig. 6. Kaplan–Meier survival curve for survival post-iPDT calculated from date of surgery of the 10 patients included in the pilot-study.

synthetic porphyrins such as hematoporphyrin derivative (HpD) or Photofrin®. For example, five out of eight glioblastoma patients treated by Powers et al. [13] had a recurrence within two months after iPDT (using Photofrin®), while at the same time all patients suffered from treatment-induced edema and prolonged skin sensitization. Similar results have been reported by other groups [15,16].

Unselective effects of HpD and Photofrin® were also described in animal studies [12,33–37] and have been related to both the inhomogeneous distribution of the PS within the tumors and extensive leakage of the PS to the surrounding normal tissue (via peritumoral edema bulk flow). PDT by means of 5-ALA induced PPIX is expected to induce less often and less severe side effects for several reasons: (1) The drug applied systemically (5-ALA) is itself not phototoxic, (2) 5-ALA induced PPIX has been shown to accumulate selectively within the tumor, and (3) a significant redistribution of the PS by peritumoral edema bulk flow does not seem to occur. Olzowy et al. [17], for example, who investigated treatment effects of PDT by means of 5-ALA induced PPIX in an experimental glioma model, found selective phototoxic effects within the tumor (coagulative or hemorrhagic necrosis), whereas the damage to the normal or perifocal edematous tissue was negligible. Exactly these favorable characteristics of 5-ALA have led to a re-evaluation of iPDT as a potentially minimal invasive treatment modality and are an important prerequisite for accurate treatment planning.

Irradiation Scheme and Treatment Planning

A reproducible irradiation scheme for iPDT with 5-ALA induced PPIX has not been provided in the literature so far. Thus, uncertainties persist as to the temperature and light distribution within the treatment volume and the appropriate total light fluence.

In a first step, it was aimed to determine an interfiber distance that reliably excludes tissue heating beyond the 42°C level. Light dosimetry—in a second step—was mainly determined by clinical parameters such as the duration and invasiveness of the surgical procedure. A treatment time in the range of 1 hour was considered to be appropriate. Due to the selectivity of the applied PS and its photobleaching with fluences in the range of 100 J/cm^2,side effects due to an excessive fluence were not expected to occur and an upper limit for the applied fluence was therefore not considered necessary to define.

Temperature and light distributions during iPDT were analyzed by Monte-Carlo simulations and then indirectly validated by clinical data. Online measurements were not performed. The significance of such online measurements might be limited due to heterogeneous optical penetration depths within the tumor and the brain/tumor interface [28] and inaccurate position measurements of the implanted sensors. Moreover, the interstitial placements of sensors might be associated with an additional risk for the patient. Therefore, simulations were preferred in the current study. As optical parameters for malignant glioma recurrences are not available, the optical properties of BAT were used, which might be considered an adequate model for a mutimodally treated glioma; based on this model, different sets of input parameters were tested to check for the effects of a possible heterogeneity.

As expected, the LITCIT simulations showed that the degree of temperature increase within the treatment volume depended on the interfiber distance. An inter-fiber distance of 9 mm did not result in a temperature increase above 42°C even in the case of unfavorable input parameters and was therefore judged to be safe. A larger distance between the fibers is not advisable, as the steep decrease of the fluence rate from the fiber surface has to be compensated with much longer irradiation times.

With an interfiber distance of 9 mm, a distance from fibers to tumor margin of 3 mm, a light power of 200 mW/cm diffuser length, and a treatment time of 1 hour, the individually applied total fluence can be calculated depending on the number of diffusers. At the tumor margin, which is one penetration depth away from the light diffusers, a fluence of 1,870 J/cm^2 can be expected. This fluence may appear very high as compared to fluences commonly used in plane wave irradiation [10,38]. However, the fluence in cylindrical light diffuser irradiation decreases more rapidly to the periphery than in plane wave irradiation: The fluence at a distance of 6 mm (one penetration depth outside the treatment volume) from the applicator's surface decreases to a value of 400 J/cm^2 and equals the fluence obtained in 3 mm depth in plane wave irradiation using a fluence rate of 200 mW/cm^2 and a treatment time of 1,000 seconds. These estimations imply that high fluences must be expected to be applied to the adjacent normal brain tissue outside the treatment volume. However, due to the absence of a significant photosensitization of normal brain tissue as a consequence of a selectively working PS [23], significant side effects of the 5-ALA iPDT approach were not expected to occur.

To confirm the results of the Monte-Carlo simulations, online measurements of temperature, fluence rate, PS

concentration, and oxygenation would be helpful. Johansson et al. [39] presented such an online measurement system, which has been validated in animal studies. Thompson et al. [40] lately reported about a novel approach for a therapy system with combined on-line dosimetry, being able to monitor fluence rate, sensitizer fluorescence, and oxygenation. These combined systems seem to have a high potential for a reliable treatment dosimetry in iPDT. However, the fibers used in these systems were bare fibers and thus, the described computer model cannot be easily adapted to cylindrical diffusers used in the current study.

Clinical Implementation

An image-based computer-assisted protocol for iPDT of intracranial neoplasms has been already described by Origitano and Reichman [14]. Photoactivation was done intracavitarily or interstitially by inserting multiple fibers using the PS Photofrin-II. Even though the authors demonstrated the successful clinical implementation of their system within the framework of a phase I study, they did not provide data concerning the optimal interfiber distance, the corresponding temperature and light distributions, and the side effects of the applied therapy. In the present study, the customized 3-D planning software proved to be very useful for the determination of the exact fiber positions within the tumor volume. The accuracy of the final fiber position was always in the range of 2 mm and the treatment volume matched accurately the tumor volume in every single patient of this series. However, both the treatment-planning and stereotactic implantation procedure turned out to be complex and rather time consuming. The development of a computer-based optimization algorithm is therefore desirable and would help to simplify and standardize the planning procedure.

Imaging Changes After iPDT

The radiographic changes observed in the 10 treated patients were impressive with early MRI (within 24 hour) follow-up showing a complete resolution of the contrast-enhanced lesion in seven patients (a representative example is given in Fig. 5) and a partial response in the other three. This very early response might be explained by a treatment induced swelling of endothelial cells leading to a temporary "sealing" of the blood-brain-barrier (BBB). However, later MRI-scans (approximately after 1 week) showed a recurrent contrast enhancement at the boundary of the treatment volume indicating a transient leakage in the BBB, which was accompanied by moderate increase of the peri-lesional edema.

Median survival was 15 months in the current series and four patients lived longer than 24 months. Generally, a median survival in the range of 6–8 months is expected for patients with malignant glioma recurrences. Whether the encouraging survival data of this series should be related to effects of patient selection, treatment efficacy or both could not be resolved at this moment. Beyond direct phototoxic effects of iPDT (such as apoptosis and necrosis) activation of the immune response after PDT has been reported (e.g., increased expression of heat shock proteins), which deserves further experimental and clinical evaluation [41–43].

Risk of iPDT

The total applied light fluences in this study (4,320–11,520 J) are very high, yet there was no surgery or treatment-related morbidity or mortality in our patient series, whereas Krishnamurty [15] reported about increased risk of neurologic injury and permanent deficits at a total applied light dose above 4,000 J as compared to light doses between 3,700 and 4,000 J after administration of Photofrin®. In our patient series there was no enhanced treatment-induced brain edema and steroid medication was only applied for 3 days as routinely done in other stereotactic procedures in our institution. The absence of side effects supports the concept of a selectively working PS such as 5-ALA induced PPIX and the postulated implications of the applied irradiation scheme: Significant treatment-induced hyperthermia (42°C or more) and/or unwanted accumulation and activation of 5-ALA outside the tumor tissue apparently did not occur.

SUMMARY AND PERSPECTIVE

The intention of the present study was to establish an implementation concept for iPDT with 5-ALA-induced PPIX for minimally invasive treatment of patients with small malignant glioma recurrences. The development of a 3-D treatment-planning was based on optical and thermal simulations. A modus operandi was established to implant stereotactically up to six cylindrical light diffusers within the tumor in accordance with the created treatment plan. This treatment procedure ensured a minimum threshold light fluence within the entire tumor thereby avoiding significant hyperthermia (42°C or higher). Clinical implementation and outcome support the theoretical assumptions used for the determination of the irradiation and the postulated selective uptake of 5-ALA-induced PPIX: No side effects of the therapy were observed during the follow-up period. A further (prospective) clinical evaluation with a greater patient cohort is needed, which is the subject of an ongoing study at our institution.

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