Photodynamic therapy (PDT) for malignant brain tumors — Where do we stand?

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KEYWORDS
Photodynamic therapy; Malignant brain tumors; PDT light penetration

Summary

Introduction: What is the current status of photodynamic therapy (PDT) with regard to treating malignant brain tumors? Despite several decades of effort, PDT has yet to achieve standard of care.

Purpose: The questions we wish to answer are: where are we clinically with PDT, why is it not standard of care, and what is being done in clinical trials to get us there.

Method: Rather than a meta-analysis or comprehensive review, our review focuses on who the major research groups are, what their approaches to the problem are, and how their results compare to standard of care. Secondary questions include what the effective depth of light penetration is, and how deep can we expect to kill tumor cells.

Current results: A measurable degree of necrosis is seen to a depth of about 5 mm. Cavitary PDT with hematoporphyrin derivative (HpD) results are encouraging, but need an adequate Phase III trial. Talaporfin with cavitory light application appears promising, although only a small case series has been reported. Foscan for fluorescence guided resection (FGR) plus intraoperative cavitory PDT results were improved over controls, but are poor compared to other groups. 5-Aminolevulinic acid-FGR plus postop cavitory HpD PDT show improvement over controls, but the comparison to standard of care is still poor.
Conclusion: Continued research in PDT will determine whether the advances shown will mitigate morbidity and mortality, but certainly the potential for this modality to revolutionize the treatment of brain tumors remains. The various uses for PDT in clinical practice should be pursued.

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Contents

Introduction ........................................................................................................................................ 531
Background ................................................................................................................................... 532
Technical considerations for PDT .................................................................................................. 533
Photosensitizers .............................................................................................................................. 533
Light delivery: dosimetric concepts ............................................................................................... 533
Light sources and light dispersion .................................................................................................. 534
Tumoral response to PDT .............................................................................................................. 534
Fluorescence guided resection ......................................................................................................... 536
Review of clinical trials .................................................................................................................. 536
Standard of care .............................................................................................................................. 538
Toronto .......................................................................................................................................... 538
Melbourne ..................................................................................................................................... 539
Milwaukee ....................................................................................................................................... 539
Japan ............................................................................................................................................... 539
Munich ............................................................................................................................................ 540
Innsbruck ......................................................................................................................................... 540
Dundee ............................................................................................................................................ 540
Infratentorial tumors ...................................................................................................................... 541
Discussion ....................................................................................................................................... 541
Conclusion ....................................................................................................................................... 541
Acknowledgements ......................................................................................................................... 542
References ........................................................................................................................................ 542

Introduction

Photodynamic therapy (PDT) and related techniques — where do we stand? Despite first being used over 35 years ago as an adjunctive measure in the treatment of cancer and its subsequent study in multiple clinical trials internationally, PDT and the related techniques of fluorescence guided resection (FGR) and photodiagnosis (PD) have yet to progress as a standard of care [1]. In general, PDT does not describe a single technique, rather a family of related protocols involving a photosensitizer (PS), that when excited by light irradiation, triggers an oxidative reaction. This in turn stimulates production of reactive oxygen species from molecular oxygen located within a cellular microenvironment (Fig. 1). Photosensitizers have been shown to preferentially accumulate within tumor cells, allowing for targeted, PDT-induced cytotoxicity of malignant cancer cells. Therefore, PDT may be a viable treatment option in treatment of brain tumors [2].

The interest in PDT as a treatment for high-grade gliomas stems from both the nature of tumor growth and limited effectiveness of modern therapies available to this patient population [3]. While surgical resection (SR) and fractionated radiation plus chemotherapy are mainstays of treatment for most of these tumors, invasive growth patterns, especially into eloquent regions of cerebrum [4], pose an obstacle to gross total resection. In addition, as gross total resection involves only the enhancing portion of the tumor as seen on MRI scans, we must realize that it is not likely that all occurrences of malignant material have been removed. Tumors recur possibly because of residual tumor left behind, either grossly viz. areas of function, or less obviously in areas not associated with function. Work here and other places suggest that there is a lot of potential for tumor activity in the unenhancing areas of diffusion abnormality. Possible concepts include residual distant tumor, migration, or transformation. Unlike surgery and radiation, PDT can treat areas of microinvasion and simultaneously spare sensitive brain regions. This advantage over current therapy may improve outcome in a patient population whose survival and incidence of iatrogenic injury is overall quite poor. There are many questions about PDT, however, which remain to be answered prior to investigating its utility as a standard adjuvant therapy.

First, the reported effects of PDT in clinical trials are confounded by an absence of standard treatment guidelines. The variables that exist across studies include: dose, irradiation light wavelength, method of light delivery, choice of PS, sensitivity of different tumor types, effectiveness on recurrent tumor, and adjuvant use with chemotherapy and radiation. Second, the analyses of PDT’s observed clinical effects in these trials have mostly been conducted in a retrospective fashion. Together, this has narrowed our understanding of PDT in clinical practice.
Given the challenges of treating high-grade gliomas, it is worthwhile to explore what has taken place in the field of PDT. In the long-term, it will be important to evaluate the role of adjuvant PDT therapy in treating malignant, intracranial tumors and also plan future steps needed to introduce PDT as a viable component of multimodal strategies.

Background

Annually, approximately 44,000 new primary brain tumors are diagnosed in the United States [5]. Malignant gliomas, which include anaplastic astrocytomas (AA, WHO Grade III), anaplastic oligodendrogliomas (AO, WHO Grade III), anaplastic oligoastrocytoma (AOA, WHO Grade III) and Glioblastoma (GBM, WHO Grade IV), are the second leading cause of cancer mortality in people under the age of 35 and the fourth leading cause in those under the age of 54, and account for approximately 13,000 deaths per year [5]. The most common malignant primary brain tumors in adults are GBMs, which are highly lethal [6,7]. GBMs account for 52% of all parenchymal brain tumor cases and 20% of all intracranial tumors [8,9]. These highly aggressive tumors are derived from the malignant transformation of either mature glial cells or neural stem cells [10,11]. In spite of recent advances in surgical techniques, adjuvant radiation therapy, chemotherapies, and other novel treatments targeting pathophysiological characteristics like neovascularization in GBM, the prognosis remains dismal. Local recurrence is the most common form of relapse affecting upwards of 80% of cases [12,13]. Though steps to optimize local control strategies are being coupled to invasive interventions such as gross total resection and adjuvant local irradiation, the current standard of care is associated with a median survival time of 14.6 months [14]. Simply, surgeons encounter difficulty in achieving complete resection of GBMs and other intracranial tumors because these cancer cells often arise proximal to and invade eloquent brain, which when injured can result in debilitating neurological impairment. From a pharmacological perspective, the blood—brain barrier (BBB) that protects...
the brain from foreign bodies such as bacteria also prevents many systemically delivered chemotherapeutic agents from ever reaching the target site of tumor. While novel drugs and combination therapies continue to be investigated, it appears that new therapies should aim to reconcile effectiveness with precision, so as to achieve localized tumor control that is especially necessary in cases of recurrence. In this regard, photodynamic therapy is a viable option to consider, as it aims at treating infiltrative tumor cells beyond the resection cavity while sparing normal functioning brain.

PDT is considered a paradigm shift from the treatment of tumors traditionally resected and targeted with systemic chemotherapy. The principle behind PDT is that cancer cell destruction is caused by light-induced activation of a photosensitizer that selectively accumulates within neoplastic tissue. In a study by Whelan et al. [15], the mechanism of selective localization of Photofrin was identified through radiolabeling of photosensitizer with Indium-111 (111In). It was reported that initial accumulation of the 111In-labeled Photofrin in the area of the brain tumor was due to passive diffusion through the BBB, which had been disrupted secondary to tumor growth. Interestingly, the concentration of the radiolabeled Photofrin in the tumor was found to be much higher than what was accountable by BBB breakdown alone [15]. While the exact mechanism of the selective uptake was not known, these findings demonstrated that Photofrin had selectivity for tumor cells. Owing to this fortuitous discovery, the production of singlet oxygen (1O2) and other reactive oxygen species (ROS) generated by PDT result in targeted cytotoxicity of tumor cells (Fig. 1) [16—20]. In summary, photosensitizer uptake and photoactivation are critical for PDT efficacy.

**Technical considerations for PDT**

**Photosensitizers**

Many different photosensitizers have been proposed and studied for treating brain tumors. The ideal compound would be non-toxic systemically, highly concentrated in malignant tissue, activated at light wavelengths needed to achieve deep brain tissue penetration, as well as minimal injury to surrounding normal tissue. Though no existing photosensitizer meets all of these criteria, agents which have been used include: hematoporphyrin, photofrin, boronated porphyrin, talaporfin sodium, meta-tetrahydroxyporphinylchlorin (mTHPC), and metabolic precursors of protoporphyrin such as 5-aminolevulinic acid [18]. As such, the search for improved agents continues.

**Light delivery: dosimetric concepts**

Mechanistically, PDT proceeds through the activation of a photosensitizer by light of a specific wavelength to produce the putative reactive oxygen species, singlet oxygen. This is the initial photochemical event that results in the destruction of photosensitizer bearing tissues [18]. Therefore one of the primary requirements when treating tumors using PDT is that a homogenous and dosimetrically sufficient dose of light is delivered to a tumor, which bears a therapeutic concentration of the administered photosensitizer [21]. This results in what has been referred to as the “photodynamic dose” and is defined as the area under the curve of sensitizer level plotted as a function of light dose [22]. In this way the efficacy of PDT as well as toxicity related to the therapy can be directly linked to the dose of light delivered [21]. The general range of wavelengths used for the broad applications of photosensitizer excitation in PDT procedures has been from approximately 405—900 nm. In this range there is a significant variance of depth of penetration into tissues. The use of this range of wavelengths is dependent on two important factors: (1) What is the depth of penetration one would like to achieve and (2) what are the wavelengths of absorption of the particular photosensitizer being administered. The photosensitizers may have more than one wavelength at which sufficient absorption will occur that would result in a likewise sufficient amount of singlet oxygen produced (quantum efficiency). The shorter wavelengths of light will have considerably shallower depths of penetration in most human tissues. The use then, of PDT, requires the appropriate matching of these factors.

One of the principal requirements for efficacious treatment of tumors in the brain is to achieve adequate light illumination throughout the targeted tissue volume. This would require various techniques to be employed delivering the total optical power for optimum penetration and the corresponding diffusion of the spatial distribution of that power with the size and shape of the illumination volume [23,24]. The light dose delivered and the method by which it is delivered is crucial to the success of treatment and the one major factor which can be controlled during PDT. The aforementioned “photodynamic dose” describes the amount of light necessary to achieve tumor eradication in a given application. This is different than the often quoted attenuation length [25]. The attenuation length is described as the distance into the tissue or media where the applied light is reduced to approximately 37%. This attenuation length is dependent on factors such as reflection, scattering, and absorption, and is analogous (using natural logs) to the path length needed for an absorbance unit of one in spectroscopy. Light attenuation can be modeled by a first-order decay type mechanism, and thus light attenuation can be calculated at other depths than those measured [25]. Further attenuation of the light occurs in cases of divergent sources, such as in spherical and cylindrical emitters where the inverse square law comes into play, so calculated attenuation would be further reduced by these geometries. This attenuation length, however, is not necessarily the equivalent of “photodynamic dose”. Other factors also impact the photodynamic dose, such as the concentration of oxygen radicals attacking the tumor cells, the extinction coefficient of the photosensitizer, the concentration of the photosensitizer achieved in the cell, the quantum yield for conversion of activated molecules into radicals, and local oxygen availability [26]. For wavelengths in the 625—640 region one attenuation length is described as approximately 3—5 mm. However the currently applied light dose, which is used in conventional PDT results in a therapeutic photodynamic dose effective at approximately 0.8—1.0 cm in depth at 630 nm [26]. Light applied will transmit through tissues at greater depths. The ultimate effective therapeutic dose can be manipulated by factors other than total light dose delivered, such as the
wavelength used, geometry of light delivery, and localization of illumination, such as spot irradiation or interstitial delivery. Other concepts being considered are pulsed rather than continuous light, and fractionated delivery throughout the post-op period. By increasing the total number of photons incident on the tissue one can effectively increase the number of photons at depth. Table 1 shows a selective review of light penetration values in a variety of tissues. The values reported in Table 1 are highly variable, representing both the wide variety of experimental protocols, and also indicative of large sample-to-sample variation. Most reported values for this parameter are in the range of 1-4 mm, with values as high as 1 cm [27] and 6.5 mm [28]. By comparing the calculated attenuation at various depths, it can be seen that most of the light energy is lost within the first 5 mm, with only small amounts reaching the 1 cm level. In most cases, essentially little or no light energy is expected to reach beyond 1 cm.

The effective therapeutic effect, that of actual depth of necrosis, is one that is more relevant clinically. Table 2 contains a review of data on depth of necrosis, as demonstrated by histological analysis of cells or tissue samples. Studies include both animal models and clinical specimens. Animal models include both normal tissue and tumor. Although necrosis of normal tissue can be seen, given large enough doses of light and PS, selective tumor kill normally results [28,33–35]. Depth of necrosis values reported in Table 2 are also highly variable. Typical range values from 2 to 7 mm, with isolated values as high as 2 cm [28] and 15 mm [36]. Given the high variability in tissue, tumor, and protocol selections, this variability is not unexpected. As in the penetration data, one can safely infer a measurable degree of necrosis to a depth of about 5 mm, with efficacy to about 1 cm not unreasonable. This is also the depth given in the official PDT website of the National Cancer Institute [37].

Light sources and light dispersion

Various delivery methods have been employed for emitting light into the brain. Initially, argon-dye laser and xenon arc light sources were commonly used. Diode lasers were officially introduced into the PDT field around the year 2000 and have been the latest technological development to gain approval for PDT. They have remained a mainstay for PDT since that time. More recently, light emitting diode (LED) arrays have been shown to be an effective and a less costly means of light delivery [44]. Developments in LED technology have provided higher power and narrower spectral characteristics making them a desirable alternative to lasers. Ensuring adequate dispersion of light to the area of desired treatment has also been dealt with through various strategies using fiber optic devices. Standard approved indications for PDT employ cylindrical diffusing fiber tips. These are particularly well adapted to the treatment of luminal disease such as encountered in pulmonary or esophageal tumors. They are also suited to interstitial PDT when implanted directly into the tumor mass. Interstitial PDT for brain tumors involves the stereotactic placement of fibers directly into the brain tissue. Illumination for intracavitary PDT can be achieved by placing the light emitting source in the space created by tumor resection [31]. The light source can be enclosed inside a balloon which is inflated by filling the balloon with a diluted liquid photodistributor such as intralipid, which evenly distributes light throughout the balloon. The balloon facilitates a spherical geometry coplanar to the resection cavity. A final strategy is to continuously irrigate the resection cavity with photodistributor, thereby tempering heat that may arise within the resection cavity as well as reducing blood accumulation, which would attenuate the light distribution during PDT treatment [45].

Tumoral response to PDT

There is considerable interest in the basic science arena to improve the tumoricidal effectiveness of PDT. Much of the pertinent investigation has been focused on understanding how nitric oxide (NO) signaling pathways in tumor cells respond to the stress of PDT-induced ROS-mediated damage. The nature and roles of these pathways in tumor cells has yet to be fully elucidated. It is apparent that NO can serve as either a pro- or anti-tumor mediator, depending on a number of complex variables [46]. Nitric oxide has been shown to play a cytoprotective and growth-stimulatory role in a variety of cancers such as melanoma, gastric, breast, colon, and head and neck carcinomas [47]. Researchers from our institution have published in vitro data indicating that breast cancer cell line exposed to 5-ALA based PDT therapy had significant upregulation of inducible nitric oxide synthase (iNOS). Additionally, tumoricidal activity was shown to be greatly enhanced through various methods of inhibition of the nitric oxide pathway [48,49]. Currently, no similar experiments reporting a PDT-induced iNOS/NO upregulation as a possible mechanism of cytoprotection in brain tumors exists. There is evidence, however, that glioma stem cells depend on upregulation of iNOS for growth and proliferation [50]. Therefore, it seems likely that gliomas would utilize the upregulation of NO production during times of stress, which would have clear relevance to PDT in the treatment of intracerebral gliomas. Several human trials using GW274150, an iNOS inhibitor, have been performed, evaluating its role as an anti-inflammatory agent in the setting of autoimmune disorders and migraine headaches [51,52]. Trials to evaluate the role of iNOS inhibitors in promoting PDT effectiveness may demonstrate that selective inhibition of this pathway serves to counteract the cytoprotective effects of iNOS. There are several other areas of research that show promise for improving the effectiveness of PDT. A recent study showed that the drug gefitinib, an EGFR inhibitor originally developed for use in breast and lung cancers, can enhance the photodynamic effect in brain tumor cells. The mechanism is due to gefitinib-mediated inhibition of the ATP-binding cassette transporter ABCG2. Inhibiting this transport mechanism prevented the efflux of photosensitizer from brain tumor cells and led to a more effective PDT effect [53]. Other strategies include the development of nanoparticles linked to photosensitizers with a goal of specifically targeting brain tumor. By targeting the nanoparticle-photosensitizers to tumor, this would limit the systemic drug exposure. This use of nanoparticles to improve the detection of tumors is being investigated [54].
Table 1  Selected depth of penetration data.

<table>
<thead>
<tr>
<th>Author</th>
<th>Photosensitizer (if used)</th>
<th>Dose (mg/kg)</th>
<th>Wavelength (nm)</th>
<th>Geometry</th>
<th>Model</th>
<th>Penetration deptha (mm)</th>
<th>% light remaining at depth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5 cm</td>
</tr>
<tr>
<td>Dougherty</td>
<td></td>
<td></td>
<td>600—700</td>
<td>Planar</td>
<td>Excised rat tumor</td>
<td>6.5b</td>
<td>46</td>
</tr>
<tr>
<td>Dougherty</td>
<td></td>
<td></td>
<td>630</td>
<td>Planar</td>
<td>In vivo animal tissues</td>
<td>1.7—4.4</td>
<td>5.3—32</td>
</tr>
<tr>
<td>Honda</td>
<td></td>
<td></td>
<td>632</td>
<td>Planar</td>
<td>Mouse subcutaneous carcinoma</td>
<td>1.4</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>664 690</td>
<td>Planar</td>
<td>Erythrocyte phantom</td>
<td>~10</td>
<td>61</td>
</tr>
<tr>
<td>Mitra</td>
<td></td>
<td></td>
<td>630</td>
<td>Planar</td>
<td>Intraoperative normal brain</td>
<td>1.0—2.1</td>
<td>0.7—9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intraoperative normal brain + tumor</td>
<td>0.8—4.9</td>
<td>0.2—36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intraoperative malignant brain tumor</td>
<td>1.5—4.1</td>
<td>3.6—30</td>
</tr>
<tr>
<td>Muller</td>
<td>Photofrin</td>
<td>2—2.5</td>
<td>630</td>
<td>Spherical</td>
<td>Normal rat brain</td>
<td>1.5</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal cadaver brain</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Svaasand</td>
<td>Hpd</td>
<td>10</td>
<td>633</td>
<td>Planar</td>
<td>Normal cadaver brain</td>
<td>1.0</td>
<td>1.2—1.7</td>
</tr>
</tbody>
</table>

aDefined as depth at which 37% of incident light remains.
bCalculated from 4—5% light remaining at 2 cm depth.
Table 2: Selected necrosis depth data.

<table>
<thead>
<tr>
<th>Author</th>
<th>Photosensitizer</th>
<th>Dose (mg/kg)</th>
<th>Wavelength (nm)</th>
<th>Fluence (J/cm²)</th>
<th>Geometry</th>
<th>Model</th>
<th>Necrosis depth (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dereski [38]</td>
<td>Photofrin II</td>
<td>12.5</td>
<td>632</td>
<td>140</td>
<td>Planar</td>
<td>In vivo normal rat brain</td>
<td>3.5</td>
</tr>
<tr>
<td>Dougherty [28]</td>
<td>HpD</td>
<td>5</td>
<td>600–700</td>
<td>120</td>
<td>Planar</td>
<td>Cutaneous and subcutaneous human tumors</td>
<td>Up to 20</td>
</tr>
<tr>
<td>Ferreira [39]</td>
<td>HPDs</td>
<td>2</td>
<td>630</td>
<td>200</td>
<td>Planar</td>
<td>Normal rat liver</td>
<td>1.9–3</td>
</tr>
<tr>
<td></td>
<td>Chlorines</td>
<td>1</td>
<td>660</td>
<td>200</td>
<td>Planar</td>
<td>Rat C₆ glioma</td>
<td>3.5–4.4</td>
</tr>
<tr>
<td></td>
<td>Foscan</td>
<td>0.3</td>
<td>660</td>
<td>30</td>
<td>Planar</td>
<td></td>
<td>3.4</td>
</tr>
<tr>
<td>Jacques [40]</td>
<td>Generic</td>
<td>5</td>
<td>630</td>
<td>240</td>
<td>Planar</td>
<td>Normal rat liver</td>
<td>7²</td>
</tr>
<tr>
<td>Kaye [33]</td>
<td>HpD</td>
<td>20–40</td>
<td>630</td>
<td>200–400</td>
<td>Planar</td>
<td>Rat C₆ glioma</td>
<td>4–7</td>
</tr>
<tr>
<td>Konaka [41]</td>
<td>HpD</td>
<td>5</td>
<td>630</td>
<td>43</td>
<td>Spherical</td>
<td>Human breast metastases</td>
<td>2–5</td>
</tr>
<tr>
<td>Madsen [42]</td>
<td>ALA</td>
<td>630</td>
<td>50</td>
<td>Spherical</td>
<td></td>
<td>In vitro glioma spheroids</td>
<td>0.9–1.2²</td>
</tr>
<tr>
<td>Olzowy [34]</td>
<td>ALA</td>
<td>100</td>
<td>635</td>
<td>200</td>
<td>Planar</td>
<td>Rat C₆ glioma</td>
<td>2.7</td>
</tr>
<tr>
<td>Perria [36]</td>
<td>HpD</td>
<td>5</td>
<td>633</td>
<td>9</td>
<td>Planar</td>
<td>Human brain tumor</td>
<td>15</td>
</tr>
<tr>
<td>Pottery [43]</td>
<td>Photofrin II</td>
<td>2</td>
<td>630</td>
<td>200</td>
<td>Planar</td>
<td>Breast tumor</td>
<td>3.5²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>180</td>
<td>Spherical</td>
<td>Coloctal cancer</td>
<td>2.5²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 J/cm²</td>
<td>Cylindrical</td>
<td>Melanotic melanoma</td>
<td>3.5²</td>
</tr>
<tr>
<td>Tudge [35]</td>
<td>HpD</td>
<td>1</td>
<td>630</td>
<td>800</td>
<td>Planar</td>
<td>Rat C₆ glioma</td>
<td>2.2</td>
</tr>
</tbody>
</table>

¹Necrosis depth calculated for generic photosensitizer using published light penetration and minimum photosensitizer dose data.
²Calculated necrosis depth from measured minimum light fluence for necrosis and published light penetration data.
³Necrosis depth calculated using published light penetration and minimum photosensitizer dose data.

Fluorescence guided resection

There is strong evidence to support that improved outcomes are associated with more complete surgical resections in patients with malignant brain tumors [55,56]. However, technical complexity of thorough tumor resection coupled with the risk of global harm from injury to eloquent brain severely limits neurosurgeons from achieving an "optimal" resection. In high-grade gliomas, the challenge becomes even greater, as tumor borders become less definable with invasion of malignant cells into normal brain tissue. In one study, complete resections occurred in less than half of high-grade glioma resections [57]. In order to address this disparity, a technique known as fluorescence-guided resection (FGR) was developed.

Intraoperatively, FGR can be used to improve tumor identification and allow for more complete resections. By reducing the remaining tumor burden as much as possible, subsequent tumor cell killing techniques will have that much greater chance to achieve their goals. Technically speaking, FGR shares similarities to PDT because it employs a hematoporphyrin derivative as the active compound, along with visualization by externally supplied light. In this manner, it is reasonable to consider these techniques together, one for visualization, and the other for tumor cell eradication. Indeed, FGR, along with photodiagnosis, is considered as a PDT-technology [62]. Most often, investigators have utilized 5-aminolevulinic acid (ALA, typical dose 20 mg/kg), which converts into the active fluorescent molecule protoporphyrin IX (PpIX). By exciting PpIX with blue light in the wavelength range 375–440 nm, red light emits in the visible spectrum, which in turn is recognized by light detectors that are built into instruments such as intraoperative microscopes. Through this technique, observers can visualize the malignant tissue bound by these fluorescent markers [58]. Many groups are now including these FGR techniques into their PDT protocols. It should be noted that any trial using FGR would, of necessity, also involve PDT to some degree, as singlet oxygen would be generated from the porphyrin compounds used to visualize tumor. Therefore, even in FGR-alone trials, overall results are attributable to both tumor resection and photosensitizer activation.

Review of clinical trials

Although there have been numerous clinical trials on the use of PDT in the treatment of malignant brain tumors, the majority of these are uncontrolled phase I/II studies (Table 3). Only one Phase III clinical trial for PDT, one for FGR alone, and one for PDT + FGR have been conducted to date. Further complicating the assessment of PDT efficacy is the
<table>
<thead>
<tr>
<th>Author</th>
<th>Approach</th>
<th>No. of Patients</th>
<th>GBM</th>
<th>AA</th>
<th>Other brain tumor</th>
<th>Photosensitizer</th>
<th>Dose</th>
<th>Light density</th>
<th>Median survival (months)</th>
<th>Progression free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stupp [14] Phase III</td>
<td>TMZ</td>
<td>573</td>
<td>Control 287</td>
<td>TMZ 286</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>Talaporfin sodium</td>
<td>40 mg/m³</td>
<td>27 J/cm²</td>
</tr>
<tr>
<td>Akimoto [77] case series</td>
<td>i/o cavity</td>
<td>14</td>
<td>10</td>
<td>4</td>
<td>i/o cavity spot</td>
<td>Talaporfin sodium</td>
<td>40 mg/m³</td>
<td>27 J/cm²</td>
<td>27.9</td>
<td>24.8</td>
</tr>
<tr>
<td>Muragaki [3] case series</td>
<td>i/o cavity spot</td>
<td>22</td>
<td>13</td>
<td>3</td>
<td>6</td>
<td>Talaporfin Sodium</td>
<td>5 mg/kg</td>
<td>70—240 J/cm²</td>
<td>GBM</td>
<td>14.3</td>
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<td>Styli [73] case series</td>
<td>i/o cavity</td>
<td>136</td>
<td>78</td>
<td>58</td>
<td>Talaporfin sodium</td>
<td>40 mg/m³</td>
<td>27 J/cm²</td>
<td>27.9</td>
<td>24.8</td>
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<tr>
<td>Rosenthal [75] Phase I</td>
<td>Intrapluid pool</td>
<td>28</td>
<td>16</td>
<td>8</td>
<td>Boronated porphyrin (BOPP)</td>
<td>0.25—8 mg/kg</td>
<td>25—100 J/cm²</td>
<td>AA</td>
<td>76.5</td>
<td>66.6</td>
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<tr>
<td>Schmidt [44] Phase I</td>
<td>Intrapluid pool</td>
<td>20</td>
<td>5</td>
<td>3</td>
<td>12</td>
<td>Photofrin</td>
<td>0.75—2.0 mg/kg</td>
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<td>Stummer [78] Phase III</td>
<td>FGR</td>
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<td>Control 115</td>
<td>FGR 122</td>
<td>10</td>
<td>12</td>
<td>5-ALA</td>
<td>20 mg/kg</td>
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<tr>
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<td>Interstitial</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>FGR 17</td>
<td>5-ALA</td>
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<td>Control</td>
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<td>Kostron [81] case series</td>
<td>i/o cavity superficial and interstitial</td>
<td>58</td>
<td>50</td>
<td>26</td>
<td>Foscan (mTHPC)</td>
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<td>20 J/cm²</td>
<td>Control</td>
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<td>52</td>
<td>Control 26</td>
<td>PDT 26</td>
<td>10</td>
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<td>5-ALA FGR</td>
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<td>Control</td>
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<tr>
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<td>Control 14</td>
<td>PDT 13</td>
<td>10</td>
<td>12</td>
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<td>ST 25</td>
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<td>77</td>
<td>Control 34</td>
<td>ST + PDT 13</td>
<td>10</td>
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<td>5-ALA FGR Photofrin PDT</td>
<td>20 mg/kg</td>
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<tr>
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<td>Balloon and fiber</td>
<td>96</td>
<td>PDT 43</td>
<td>49</td>
<td>24</td>
<td>26</td>
<td>Photofrin</td>
<td>2 mg/kg</td>
<td>120</td>
<td>Control</td>
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<tr>
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<td>Balloon and fiber</td>
<td>77</td>
<td>Control 34</td>
<td>ST + PDT 13</td>
<td>10</td>
<td>24</td>
<td>58 ± 17</td>
<td>Photofrin</td>
<td>2 mg/kg</td>
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PDT for malignant brain tumors.
heterogeneity of these studies’ methods, adjuvant therapy, and tumor subtypes.

Many excellent PDT review articles have been published over the years, and a number of them present summaries of clinical trials. Good examples have come from the pens of Styli [2,4], Kostron [59], Eljamel [60—62], and Bechet [1]. Typically, a table is presented, with text giving a very brief summary. As these trials are generally very different in design and execution, it is exceedingly difficult to come to an overall understanding of the state-of-the-art and to appreciate the direction the field is going in. As an alternative to this traditional summary method, we propose to organize the trials by research group or institution, in order to explore the approach to the problem each group is taking, and to detail their progress and direction for the future. These approaches may involve choice and dose of photosensitizer, choice and dose of light, method of light application, and use of additional techniques such as PD and FGR. Most recent results will be focused on, and groups that appear to no longer be active in the field will not be discussed.

In these summaries, we will try to focus on GBMs in particular, with lower grade gliomas included where studied. As GBMs have the worst prognosis, it seems reasonable to focus most attention in that area. If PDT is to have a future in regard to malignant brain tumors (MBT), it would seem that this is where it needs to prove itself the most. Many studies, however, present a mixture of diagnosis and histologies, and it is not always easy or even possible to separate out the relevant results.

In like manner, newly diagnosed and recurrent tumors may be stratified or mixed. Some studies focus on one or the other. Whenever possible, these results will be looked at separately. Recurrent GBMs in particular seem to have very poor survival; improvements here would be the most impressive.

There are a number of possible outcome measures, but the most common appear to be median overall survival (OS) and progression free survival (PFS). As OS reflects the effect of other factors and therapies beyond merely PDT and FGR, current thinking is that PFS is the preferred outcome measure; unfortunately it appears that, up to now, OS has been the more widely reported measure. These outcomes will be looked at in these summaries. Some trials may not report these however, and we may be forced to use some other measure of efficacy.

A word needs to be said regarding comparators. An ideal situation would of course be one with a control arm that is included in a random controlled trial (RCT). This situation is sadly rare, however. Most reports include no comparators, other than a perhaps vague bow to “historical controls”. Some will cite literature surveys or meta-analyses. Better yet, in case series studies, are closely matched local control series, or even a control arm that was not assigned randomly. In any case, a common problem is determining whether any efficacy has been demonstrated at all. In general, reported “normal” values for gliomas, especially for GBMs, seem to vary in the same range as “treatment” values where PDT has been used. Barring direct comparison to a judiciously determined control arm, it is nearly impossible to make a determination of efficacy, absent a very large and striking improvement in OS and PFS values.

A further issue is the case of an RCT that shows significant improvement over the control arm, but still falls short of or is similar to common “normal” values. While efficacy has been shown in that study and with that protocol, will this really translate to a benefit in the world at large? Was there something unique to the study group that invalidates translating these results outside, or was this just the result of the patient population, local conditions, etc.? We will not really know until we reach the stage of large, multi-center, Phase III trials.

Finally, we will attempt to compare these values with current standard-of-care. As the PDT field has been evolving since 1980, so too other treatment options have been improving. For PDT to be a viable choice, it will need to equal or exceed other options, or demonstrate an additional benefit when used in conjunction with the latest therapies.

### Standard of care

In 2005, Stupp [14] reported on a pivotal trial for use of temozolomide (TMZ) in conjunction with radiotherapy (RT) and surgical resection in treatment of GBM. This was a large, multi-center, Phase III trial comparing SR + RT against SR + RT + TMZ. The control arm contained 286 subjects, while the treatment arm contained 287. Median OS for the treatment arm was 14.6 months, vs. 12.1 for the control. PFS for the treatment arm was 6.9 months, vs. 5.0 for the control. These differences were significant. The use of concomitant and adjuvant TMZ has now become standard-of-care for newly-diagnosed primary GBM. As for recurrent GBM, there are few FDA approved modalities including Gliadel wafers (carmustine wafers), bevacizumab and NovoTTF-100A, also called tumor treatment fields (TTFields). While each is novel in its treatment approach, none have dramatically improved the outcome at the time of recurrence. Gliadel wafers provided a median survival advantage of 2 months compared to placebo [63]. Bevacizumab improves PFS but has no survival advantage [64,65]. Most recently, NovoTTF therapy has proven to be as effective as chemotherapy at the time of recurrence [66] and may actually improve OS to 9.6 months based on one retrospective study [67]. These values are now the standard by which any PDT results should be compared.

### Toronto

Muller and associates published a variety of cases series through the 1990s involving various mixtures of gliomas, light doses, and light application methods [66—73]. In general, they used Photofrin in low to moderate light doses, and intraoperative (i/o) cavitary balloon application with supplemental interstitial application in some cases. Results were modest, with OS values for newly-diagnosed GBM of 6—9 months, and recurrent GBM of 6—7 months. In 2006, they published a larger, updated, case series with 112 patients [45]. The photosensitiser was fixed at 2.0 mg/kg of Photofrin, but the light dose was varied, with an average of $58 \pm 17 \, J/cm^2$. Light application was by i/o cavitary balloon or bare fiber in Intralipid pool. Results were not improved from the earlier series, with OS for newly-diagnosed GBM of 7.6 months, and recurrent GBM of 6.7 months.
A Phase III trial with 150 newly-diagnosed and 120 recurrent gliomas was planned and listed in ClinicalTrials.gov (NCT00003788). It appears, however, that this trial was closed short of enrollment goals. A 2006 conference proceeding was reported [71], but no full report seems to have been published. Some details can be obtained from a review by Eljamel [62]. The photosensitizer was Photofrin at 2 mg/kg, and the light dose was 120 J/cm². Eljamel reports the light used were 532 nm, but it is more likely that it was 632 nm, consistent with previous trials and the recommended wavelength for use with Photofrin. The light application was not stated, but it could be assumed to be some form of i/o cavity, based on earlier studies. The OS for the treatment group was 11 months vs. 8 months for the control. The difference was stated to be significant, but the line-curves crossed at 15 months. Although there seems to be a significant 38% improvement over the control group, these results are still unimpressive compared to general experience with GBMs and standard-of-care. The light dose may have been insufficient, as many groups are moving toward increased doses; in particular Kaye and Whelan at 240 J/cm².

**Melbourne**

Kaye started out, in a publication from 1987, with HpD PDT in a Phase I trial and performed a light dose escalation study up to 230 J/cm² [72]. This protocol, with light doses up to 240 J/cm² was put into practice, and resulted in a large case series [73] published in 2005 that resulted in OS values of 14.3 months for newly-diagnosed, and 13.5 months for recurrent GBMs. The higher light doses were associated with better OS. The HpD used was manufactured in-house; the dose of 5.0 mg/kg would be equivalent to 2.5 mg/kg of the commercially available HpD Photofrin. Application was by i/o flat-cut laser fiber inserted in an Intralipid pool in the resection cavity. The result for the newly-diagnosed GBMs was higher than many of the typical non-PDT results of the time (OS of 8.5–14.2 months in various studies), and is comparable to current standard-of-care.

Kaye has also investigated a new PS, boronated porphyrin (BOPP). A 2003 report [74] presents the efficacy results for a 2001 safety study using this PS [75]. The approach was the same as with HpD, but the PS dose was escalated from 0.25 to 8 mg/kg, and the 630 nm light was escalated from 25 to 100 J/cm². OS results for newly-diagnosed GBMs were 5 months, and for recurrent GBMs 11 months. These results are for all doses pooled, so cannot be directly compared to other studies.

**Milwaukee**

The Whelan group reported in 2004 a phase I toxicity study, which enrolled 20 patients diagnosed with recurrent high-grade gliomas [44]. Patients received PDT treatment using a variety of light source and PS combinations. Photofrin was delivered in 18 subjects, receiving doses (0.75, 1.2, 1.6, 2.0 mg/kg) spanning an 18–24h period; 10 of these subjects received the maximum 2.0 mg/kg, while eight received lower than the maximum dose. Two patients received benzoporphyrin derivative (BPD, 0.25 mg/kg) in lieu of Photofrin, whose absorption peaks are 630 nm and 680 nm, respectively. Photoillumination was achieved by laser light, combined with either fiber-optic catheter or with laser fiber balloon adapter (intracavitary PDT), or LED light using a balloon adapter (LED-PDT) containing 144 LED chips. Both light sources were calibrated and adjusted to produce a total light dose of 100 J/cm². Though fiber-optic laser-induced photoillumination, and intracavitary PDT resulted in two separate complications, PDT exposure in sensory cortex, motor cortex, and visual cortex, especially by intracavitary PDT, did not result in additionally deficits. It appears that broader dispersion of light intensity mitigated heat exposure in tissue, so as to dampen power density achievable by this modality. Patients who underwent LED-PDT did not experience any signs of neurotoxicity or motor deficit, even when tumor extended into or arose adjacent to eloquent brain. The advantages of LED-PDT cited at the time included improved activation of photosensitizer deeper into brain tissue relative to laser-based PDT, afforded by a broader emission spectrum of LED (630–940 nm light) compared to laser-light, as well as improved temperature monitoring capabilities by the LED emitting instrument used. Finally, since the major absorbance peak of BPD is much closer to the major emission peak of LED, this combination of photosensitizer and light-source seemed to have been the best coupling, owing to more efficient energy transfer and decreased treatment time.

A Phase I clinical trial (NCT01682746) has been initiated to determine the safety and dose response of PDT in children. Using step-wise dose-escalation of Photofrin, we are aiming to determine the maximally safe dose for pediatric patients. At this time, three patients with infratentorial tumors have been enrolled and treated, using a dose of 0.5 mg/kg of Photofrin. Clinically, PDT has had no negative effects on these patients.

Another area of investigation is a phase II adult trial that is in development (NCT01966809). This trial will use the higher light doses described by the Melbourne group [73]. At present, there has not been a North American trial using PDT to this level of effectiveness. Initially, the study aims to reproduce the survival improvements reported and define the antitumor activity of Photofrin in a domestic (to the USA) setting. Beyond the clinical treatment arm of this trial, the plan is to further investigate the field of detection and utility of PDT as an adjuvant to other treatment paradigms, through high-resolution imaging and pre-clinical studies.

**Japan**

Kaneko reported in 2008 a very large case series involving 250 subjects with 5-ALA FGR and 63 subjects undergoing HpD PDT with a mixture of i/o cavitary and interstitial application [76]. No survival data was presented. In 2012, Akimoto reported a small case series of mixed gliomas, mostly grade IV, treated with talaporfin sodium and 664 nm light [77]. Application was i/o cavitary with optically guided spot irradiation of the walls of the resection cavity. The OS for newly-diagnosed gliomas was 26 months and the PFS was 23 months. For recurrent gliomas, OS was 9 months and PFS was 3 months.
Muragaki reported in 2013 a Phase II study using the same approach. Twenty-two malignant gliomas were included, 13 of which were GBM [3]. An unstated number were recurrent. For all 22 gliomas, OS was 27.9 months and PFS was 20 months. For the 13 GBMs, OS was 24.8 months and PFS was 12 months.

These results for newly-diagnosed GBM are intriguing and warrant further investigation, as they show substantial improvements over other reports, and substantially higher OS than current standard-of-care. Numbers were few, however, and MGMT methylation and other molecular marker status was not reported, so the involvement of these prognostic markers in the results cannot be ascertained. This protocol should be tested in the context of a Phase III RCT.

Munich

Stummer focused his attention in a 322-patient multi-center Phase III RCT (2006) on FGR using 5-ALA as a means to improve the completeness of surgical resection; PDT was not included [78]. Primary endpoints were number of subjects with residual tumor and 6-month progression-free survival. Compared to controls with conventional surgery, FGR gave more complete resections and better progression free survival. OS was not improved significantly (15.2 vs. 13.5 months), but a subsequent analysis of the same data showed that complete resection was associated with significantly better OS in RTOG-RPA classes IV (17.7 vs. 12.9 months) and V (13.7 vs. 10.4 months) [79]. These values are comparable to standard-of-care.

The assumption behind this approach is that better resection, obtained by FGR, will eventually give better OS, even if not seen in the current data when comparing FGR and control arms. FGR gives more complete resections, and complete resection is generally associated with better outcomes. In this case, FGR did not give better OS, but did give better six-month PFS. Stummer plans to add TMZ in future trials. Meanwhile, they have begun exploring interstitial PDT with 5-ALA (2007) and have determined that it is safe, and to require further trials would be unethically denying treatment to the placebo group.

In 2011 Lyons published a 73-patient case series using the above technique. His protocol involves a combination of PD, FGR, and post-operative PDT, and has been offered in Dundee since 2001 [83]. Photofrin 2 mg/kg is administered 48 h prior, with 5-ALA 20 mg/kg administered orally the day of surgery. PD is used at time of resection to confirm diagnosis, and white light resection is performed. This is followed by ALA-FGR, with PPIX spectroscopy of the resected tumor margin to confirm completeness. A balloon catheter is then repositioned, and allowed to remain for 5 days. Upon awakening, PDT at 100 J/cm² is administered, repeated every 24 h for a total of 5 treatments. Repetitive treatments are administered to allow the PS to be replenished from systemic stores after local bleaching during PDT. After 5 days, the catheter is removed. RT and CHT may be included after surgery [61]. Since 2005, intra-operative radiotherapy (IORT) has also been offered in conjunction with PDT [83].

This protocol is based on the following reasoning: case series studies indicate usefulness of PDT. One-shot applications appear to not be effective, likely due to residual tumor and insufficient light. The Stummer FGR RCT showed effectiveness at improving resection, but was insufficient at improving OS as invading tumor cells are still present macroscopically, regardless of resection completeness. Therefore, a combination of PD, FGR, and PPIX spectroscopy is used to maximize tumor resection, while PDT and IORT is used to kill all residual tumor cells. All steps are necessary, as PDT without complete resection leaves tumor areas that can regrow, while complete resection without PDT still leaves individual invading cells to regenerate tumor.

In 2008, a single-center Phase III RCT using the above protocol (no IORT) was published for primary GBM [84]. OS for the control group was 5.6 months, while the PDT group was 12.2 months. PFS for the control was 4.8 months, vs. 8.6 months for the PDT group. Although a significant survival and progression improvement was shown, it is not known if this is due to FGR or PDT separately, or together. These results are lower than typical values and are attributed to a much greater proportion of poor prognosis factors in the study population.

A larger multi-center Phase III trial was called for, but in a 2010 review Eljamel [62] claims that the case is proven, and to require further trials would be unethically denying treatment to the placebo group.

In 2011 Lyons published a 73-patient case series using the above PDT protocol for GBM with the addition of IORT [83]. No information was given whether these cases were newly diagnosed or recurrent. There were four groups: standard therapy (ST), ST + PDT, ST + IORT, and ST + PDT + IORT. OS for the combined PDT groups was 14.5 months, a significant improvement over ST alone, which was 4.6 months. OS for ST + PDT + IORT at 18.2 months was a non-significant improvement over ST + PDT at 9.2 months. PDT provided a statistically significant survival advantage, while the addition of IORT looks promising, but was not significant. Again, survival values are not impressive when compared to standard-of-care, while the control group in particular fared poorly than is typical.

Dundee

Eljamel has developed a rather different approach to the technique. His protocol involves a combination of PD, FGR, and post-operative PDT, and has been offered in Dundee since 2001 [83]. Photofrin 2 mg/kg is administered 48 h prior, with 5-ALA 20 mg/kg administered orally the day of surgery. PD is used at time of resection to confirm diagnosis, and white light resection is performed. This is followed by ALA-FGR, with PPIX spectroscopy of the resected tumor margin to confirm completeness. A balloon catheter is then repositioned, and allowed to remain for 5 days. Upon awakening, PDT at 100 J/cm² is administered, repeated every 24 h for a total of 5 treatments. Repetitive treatments are administered to allow the PS to be replenished from systemic stores after local bleaching during PDT. After 5 days, the catheter is removed. RT and CHT may be included after surgery [61]. Since 2005, intra-operative radiotherapy (IORT) has also been offered in conjunction with PDT [83].

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Infratentorial tumors

Though most studies of PDT have been restricted to treating neoplasms that arise above the tentorium cerebelli (supratentorial) away from functional cortex and the brain stem, PDT can be used to treat infratentorial malignancies. Due to the proximity of posterior fossa tumors to eloquent brainstem and other vital structures, most therapies pose threats immediately, or from long-term complication. Similarly, PDT may incite brainstem toxicity, but some evidence exists to defend its use in treating these tumors.

In pre-clinical studies using a canine animal model for infratentorial glioma, tissue from brain stem and other posterior fossa contents were analyzed to characterize the risks and adverse effects of PDT in this region. Effects from both high and low doses of photosensitizing agent were compared [85]. Events attributable to experimental intervention included neurotoxicity, which was defined as a decline in neurological function occurring within 1 week of PDT and persistent to 4 weeks post-PDT. Additionally, although high doses of Photofrin-II (2–4 mg/kg) incited severe neurotoxicity in these animals, lowered doses of Photofrin-II (0.75 mg/kg) resulted in significant tumor cell death with only "mild" neurotoxicity, according to Common Terminology Criteria for Adverse Events (CTCAE) [86].

Clinical application of PDT for treatment of infratentorial glioma includes the work by Laws et al. [87], which demonstrated no significant toxicity in 4 patients with posterior fossa neoplasm (2 medulloblastomas, 2 ependymomas). In another PDT trial conducted at our institution, IV Photofrin and 100 J/cm² of light were administered to 20 patients with recurrent brain tumors, which included four patients with infratentorial tumors either involving or immediately adjacent to brain stem [44]. We reported one adverse event in a single patient, which was attributed to high power density of a small spherical dispersion tip, and our results from this trial support the clinical application of PDT to treat malignant tumors located in or near the brain stem.

Discussion

There are four basic approaches used by the various research groups involved in the clinical trials reported here, with overlap between some. The first, seen in Toronto, Melbourne, and Milwaukee, involves (usually) a single cavitary balloon or fiber/Intralipid PDT application using HpD, or the more potent commercial version Photofrin. When sufficient PS and light doses are given, results are encouraging. The point has not been proven, however, with an adequate Phase III trial.

The second approach seen in Japan uses a newer PS, talaporfin sodium, and optically-guided cavitary spot light application. Results are the most promising of all so far, but only small case series are reported.

In a third approach taken in Innsbruck in a Phase II series with matched controls, FOSCAN was used both for FGR and 1/o cavitary PDT. While results were improved over controls, they are poor compared to other groups.

Finally, Eljamel has combined Stummer’s work on ALA-FGR with repetitive post-operative cavitary HpD PDT in a small Phase III trial. Again, while improvement over controls is seen, results compared to historical norms and standard-of-care is poor. An addition of IORT, while confirming the PDT results, does not give further improvement. Larger multicenter Phase III trials may sort out whether the poor results are purely a local phenomenon.

The use of photodynamic therapy in the treatment of brain tumors has produced exciting results in clinical trials over the past decade and yet it has failed to be established as a common adjuvant therapy with the exception of a few specialized international centers. The purpose of this article was to review the relevant data about this treatment and provide some insight into the future directions in the search to improve the outcomes for a patient population that has long been faced with a dismal prognosis. Future prospective clinical trials involving PDT are needed to determine its efficacy with current therapeutic regimens.

Moving forward, experimental designs of PDT studies may be better served by expounding upon the characteristics of the tumor populations that have benefited from this therapy. Since the clinical experience reported by Styli et al. [73], results from various prospective trials such as Stupp’s Phase III trial using adjunctive radiation and temozolomide have defended the use of chemoradiation for treating primary GBM [88]. While the results from the Australian-led PDT trial rival the survival outcomes achieved by today’s standard of care in adults, the post-PDT data unintentionally overlooks factors such as differential expression patterns within tumor cell populations (e.g. MGMT-methylation status, IDH-1 status). These are considered valid predictors of survival following administration of today’s standard of care [89]. While it is unclear if PDT efficacy will be limited by aberrant function that protects tumor cells against chemoradiotherapy, it is certain that further investigation of PDT’s penetration capacities and long-term survival will be needed to determine which properties hinder this intervention. Nevertheless, a clear advantage of PDT at the moment would appear to be its safety profile, evidenced by a low incidence of adverse effects compared to novel agents, such as those targeting VEGF, like Bevascizumab (Avastin). In addition to Avastin’s inability to improve overall survival for patients with recurrent GBM, the propensity of this novel inhibitory agent of VEGF to induce systemic deleterious effects also threatens the predilection for using this adjunct [89]. Having already demonstrated effectiveness at >230 J/cm² and improvement from the survival trends, especially for recurrent anaplastic astrocytomas, not to mention safe practice in infratentorially-based tumors, PDT may better serve vulnerable populations compared to other agents. Its use as an adjunct to gross-tumor resection and/or chemoradiotherapy treatment strategies seems to be a viable option in these situations and ongoing trials will help elucidate to what the extent it will improve the field of malignant glioma therapy.

Conclusion

Future questions to explore include whether PDT can be employed to treat less malignant tumors whose location makes resection impossible — "malignant by location." Also, the field of fluorescence-guided resection is creating the opportunity for combinations with PDT that may
prove synergistic in the treatment of brain tumors. Continued research in PDT will determine whether the advances shown in cancer research will mitigate morbidity and mortality from treating intracranial malignancies, but certainly the potential for this modality to revolutionize the treatment of brain tumors remains. The various uses for PDT in clinical practice should be thoughtfully pursued.

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