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REVIEW

Photodynamic applications in brain tumors: A comprehensive review of the literature

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KEYWORDS
GBM;
Fluorescence image guided biopsy;
Surgery;
PDT

Summary
Introduction: GBM is the comment glioma. GBM-outcome had not changed much over two decades despite leaps in medical technology. Fewer than 25% survive 2 years. There is no jacket that fits all GBMs. This paper reviews the evidence for PDT in GBMs.
Rationale: Maximum safe resection is supported by level-II evidence. PDT-technology (PDTT) provides means to maximize safe resection. PDTT paints GBM red in contrast to brain because of selective uptake and retention of photosensitizers. Exposure to specific light wave produces cytotoxic singlet oxygen.
PDT-applications:

(1) Fluorescence image guided biopsy to sample high grade components of what looks like low grade glioma on MRI, 89% sensitive.
(2) Fluorescence image guided surgery for maximum safe surgical resection is >84% sensitive, achieves complete resection in >65% and prolongs tumor free survival (1 observational and 2 RCT, $p < 0.001$).
(3) Photodynamic treatment supported by several observational studies with combined total of >1000 patients and 3 RCT used PDT in GBMs. PDT was highly selective, safe, significantly improved good quality survival, and delayed tumor relapse ($p < 0.001$).

Safety: PDT had a very high safety track record, thromboemolism 2%, brain-oedema 1.3%, and skin photosensitivity complications 1—3%.
Conclusion: PDT in GBMs is safe, selective, and sensitive and leads to significant prolongation of good quality survival, delay in tumor relapse and significant reduction of further interventions. It would be impractical, impossible and probably unethical to randomize patients between PDT and placebo, in the same way it would be unethical to carry out a RCT to prove that the parachute saves lives.

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Contents

Introduction

Intracranial gliomas represent 38—40% of primary brain tumors and glioblastoma multiforme (GBM) is the most common glioma [1] GBMs are divided into: primary and secondary GBMs. Primary GBMs arise de novo, represent 60% of GBMs, and are diagnosed in over 50 years of age. Secondary GBMs represent 40% of GBMs, and are most common under the age of 45 years. Several research groups have studied GBMs extensively to assess their prognosis and factors associated with better survival. Three risk groups were identified [2]: low risk group consisted of young patients (under 40 years) with tumors located in the frontal lobe. Moderate risk group consisted of patients between 40 and 65 years of age, Karnofsky performance score (KPS) >70 and had surgical resection. High risk group included all patients >65 years of age and patients between 40 and 65 years who had KPS <80 or had biopsy only. Several recent studies assessed the impact of genetic mutations [3,4]. Loss of heterozygosity (LOH) on chromosome arm 10q is the most frequent gene alteration for both primary and secondary GBMs and is associated with poor survival. It occurs in 60—90% of GBMs. This mutation appears to be specific for GBMs and is found rarely in other tumor grades. Mutations in p53, a tumor suppressor gene, were among the first genetic alterations identified in astrocytic brain tumors and appear to be deleted or altered in approximately 25—40% of all GBMs particularly in secondary GBMs [5]. Epidermal growth factor receptor (EGFR) gene is involved in the control of cell proliferation. Multiple genetic mutations are apparent in this category, including both over expression of the receptor. Over expression or activation mutations in EGFR were more common in primary GBMs (40—50%). One such common variant, EGFRvIII, had shown promise as a target for kinase inhibitors, immunotoxins, and peptide vaccines [6]. Methylation of the promoter region of tumor suppressor genes (MDM2) may be associated with transcriptional silencing and tumor progression [7]. Amplification or over expression of MDM2 constituted an alternative mechanism to escape from p53-regulated control of cell growth by binding to p53 and blunting its activity. Over expression of MDM2 is the second most common gene mutation in GBMs and is observed in 10—15% of GBMs. Some studies showed that this mutation has been associated with poorer prognosis [8]. PTEN encodes a tyrosine phosphatase located at band 10q23.3. The function of PTEN as a cellular phosphatase, turning off signaling pathways, was consistent with possible tumor-suppression action. When phosphatase activity was lost because of genetic mutation, signaling pathways can become activated constitutively, resulting in aberrant proliferation. PTEN mutations have been found in as many as 30% of GBMs particularly primary GBM [9]. Platelet-derived growth factor-alpha (PDGF-alpha) gene acts as a major mitogen for glial cells by binding to the PDGF receptor (PDGFR). Amplification or over expression of PDGFR is typical (60%) in the pathway leading to secondary GBMs. Although progress has been made in the pathophysiology of GBMs, the survival of patients diagnosed with GBMs remained very poor and individual prediction of clinical outcome remained an elusive goal. Despite extensive clinical trials, the median survival remained about 12 months with fewer than 25% survived for 2 years and fewer than 10% survived for 5 years. In a series of 279 patients only 5 (1.8%) survived for 3 years [10]. Clearly, newer approaches for the management of GBMs are necessary and multimodality therapeutic approaches would be necessary to improve outcome of these tumors. The joint tumor section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) in 2008 produced guidelines for the management of newly diagnosed GBM [11]. The authors recommended maximum safe surgical resection of newly diagnosed GBM backed with type II scientific evidence, followed by 60 Grays of postoperative radiotherapy to the enhancing lesion (type I evidence) and for radiotherapy to include 2 cm cuff around the lesion (type II evidence). The guidelines also recommended concurrent and postoperative temazolamide in newly diagnosed GBM (type I evidence) and BCNU (carmustine wafers) in those who undergo craniotomy (type II evidence). This paper reviews the efficacy, efficiency and safety of photodynamic applications (PDA) in GBMs.

The rationale of PDA in GBMs

The role of surgical excision in GBM had been controversial for many years. There have been many attempts in the literature to resolve this issue (Table 1) with some success [12—27]. The majority of studies concluded maximal safe surgical excision was significant good prognostic factor. Most of the studies that supported surgical resection in GBMs had assessed the extent of post surgical resection by postoperative brain imaging. In total 2660 GBMs were surgically resected and in 61.5% postoperative imaging assessed the extent of resection. On the other hand studies that concluded surgery was not significant factor in outcome of GBMs were not powered enough to answer the question or had not assessed the extent of resection. Only 10% of patients in these studies had postoperative imaging to assess the extent of surgical resection (Table 1).

Table 1 Review of the role of surgical resection in GBM.

Authors	# of patients	Impact of surgery	Extent of resection assessed by postoperative imaging
Vecht et al. [12]	243	Significant	No
Curran et al. [13]	103	Not significant	No
Prados et al. [14]	357	Not significant	No
Lai et al. [15]	116	Significant	No
Kreth et al. [16]	225	Not significant	No
Albert et al. [17]	60	Significant	Yes
Nitta et al. [18]	101	Significant	No
Kiwit et al. [19]	274	Significant	Yes
Parker et al. [20]	301	Significant	Yes
Kowalczuk et al. [21]	75	Not significant	Yes
Keles et al. [22]	92	Significant	Yes
Lacriox et al. [23]	416	Significant	Yes
Laws et al. [24]	565	Significant	No
Kurimolo et al. [25]	76	Significant	Yes
Keles et al. [26]	101	Significant	Yes
Stark et al. [27]	345	Significant	Yes
Total number of GBMs in studies with surgery was significant	2660	Significant	Postoperative imaging was performed in 61.5%
Total number of patients in studies with surgery was not important factor	760	Insignificant	Postoperative imaging was performed in 10%

Studies that did not include postoperative evaluation of the extent of surgical resection can be disregarded as surgeons often over-estimate the extent of resection. For example Fig. 1A represents a typical intraoperative photograph at the end of surgical resection of GBM under the white light using image guidance. The surgeon thought that he made a total gross surgical resection of the tumor, however, when he switched to blue light, it was very obvious residual tumor was present (Fig. 1B).

Based on the published literature, maximum surgical resection of newly diagnosed GBM imparts better and longer survival [11]. The main hurdle of achieving maximum safe surgical resection of GBMs, is inability of surgeons to distinguish what is tumor and what is not [28,31]. Furthermore, over than 80% of recurrent GBMs are found within 2 cm of the resection margin (Fig. 2A and B). Therefore designing a way by which maximum surgical resection can be achieved safely and mobbing any residual tumor cells would undoubtedly prolong good quality life in these patients.

5-Aminolevulinic acid (ALA) is a naturally occurring compound and formed in all living mammalian cells from succinyle choline acetate and glycine within the mitochondria. ALA is then dehydrogenated in the cytoplasm producing porphobilinogen then to coproporphyrinogen III before returning to the mitochondria as protoporphyrin III. Protoporpyrin III is transformed within the mitochondria into protoporphyrin IX (PpIX). PpIX is then chelated by ferrocheletase into heme. Heme is required by each cell for energy production, but cancer cells are not dependant on the mitochondria for their energy supply leading to accumulation of PpIX within the mitochondria of cancer cells in large quantities (Fig. 3). PpIX is a photoactive compound that absorbs blue light (404 nm) and emits fluorescence in the red spectrum (635 nm). A recent study reported a PpIX-concentration of 1004.6 μg/g of wet GBM compared to 125.1 μg/g wet surrounding brain [32] (Fig. 4). If we can use this method to visualize tumor tissue during surgical resection, we can maximize safe surgical resection safely and without increasing morbidity or collateral damage.

Furthermore, PpIX and other photosensitizers such as Photofrin and temoporfin absorb light energy and produce singlet oxygen within the cells [29—31]. Each photosensitizer is activated by a specific light band (Table 2). Singlet oxygen is cytotoxic. In tumor cell experiments, glioma spheroids, GBM-tumor models and in clinical practice photodynamic therapy (PDT) had been shown to induce tumor cell-death, apoptosis and immune responses [29—31]. A recent study comparing the sensitivity of cancer cells and neurons reported that at 15 μg/ml of temoporfin PDT killed almost all of tumor cells compared to only 10% of neurons in the absence of blood brain barrier in 3D cell cultures [33]. Another clinical study examined the use of stereotactic PDT in 31 deep seated malignant gliomas with no additional treatment revealed complete resolution of the lesion in 64% on postoperative MRI, reduction of tumor volume by 50—90% in 26% and no change in 10% [34]. Therefore, the combination of photosensitizer selectivity in tumor cells and high concentration of photosensitizer in tumor cells and specificity of laser light to each photosensitizer makes PDT selective and potentially kills any residual tumor cells after maximum safe surgical resection. The limitation of PDT in brain is extent of light penetration within brain tissue (Table 2). Because of this limitation PDT may not impart the desired benefit if thickness of residual tumor was beyond laser light reach. It is therefore essential that maximum safe surgical resection is performed first (using photofluorescence) before PDT [35,36].

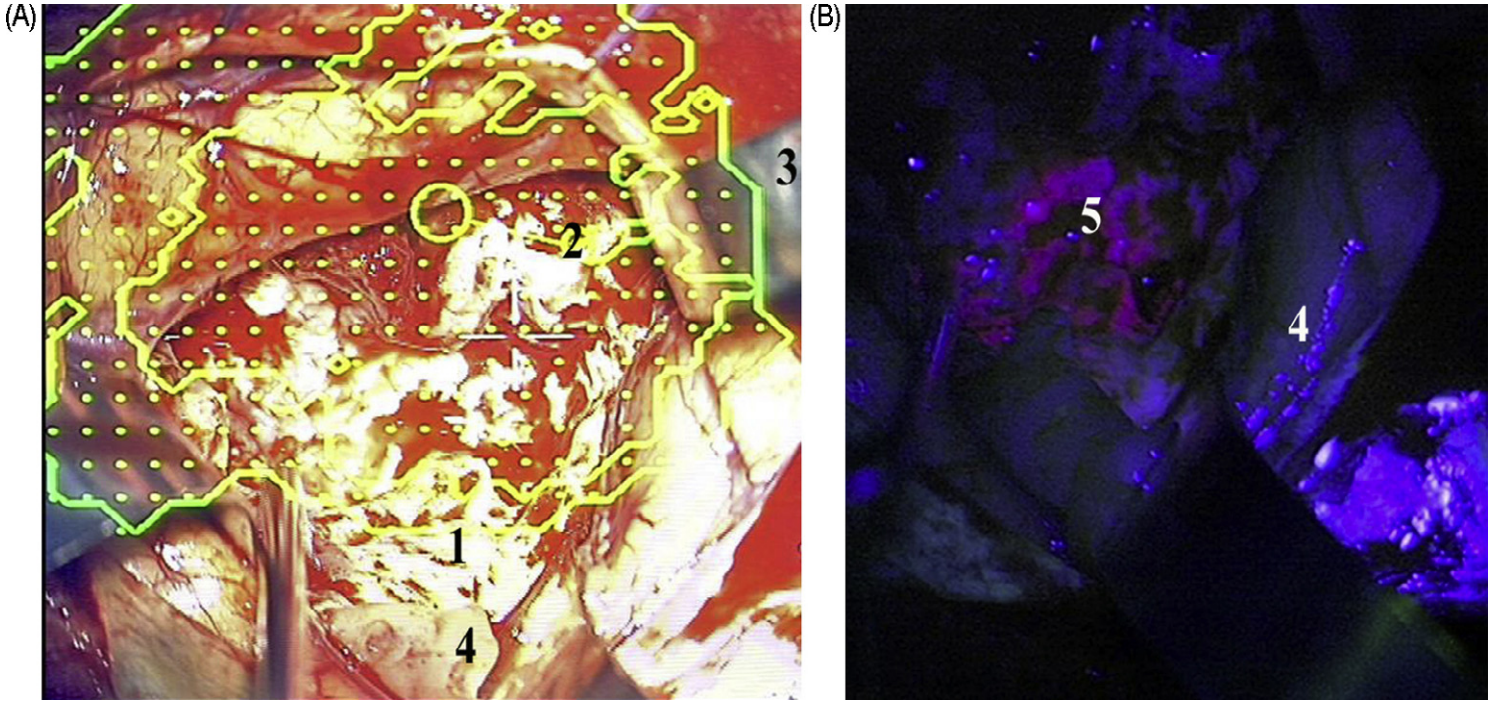

Figure 1 Intraoperative photograph during the final stages of GBM resection: (A) under the white light and image guidance (1 = resection cavity, 2 = head up display of image guidance, 3 = self-retaining retractor and 4 = surrounding brain); (B) the same scene under blue light after 5ALA administration 3 h before surgery (5 = fluorescing residual GBM).

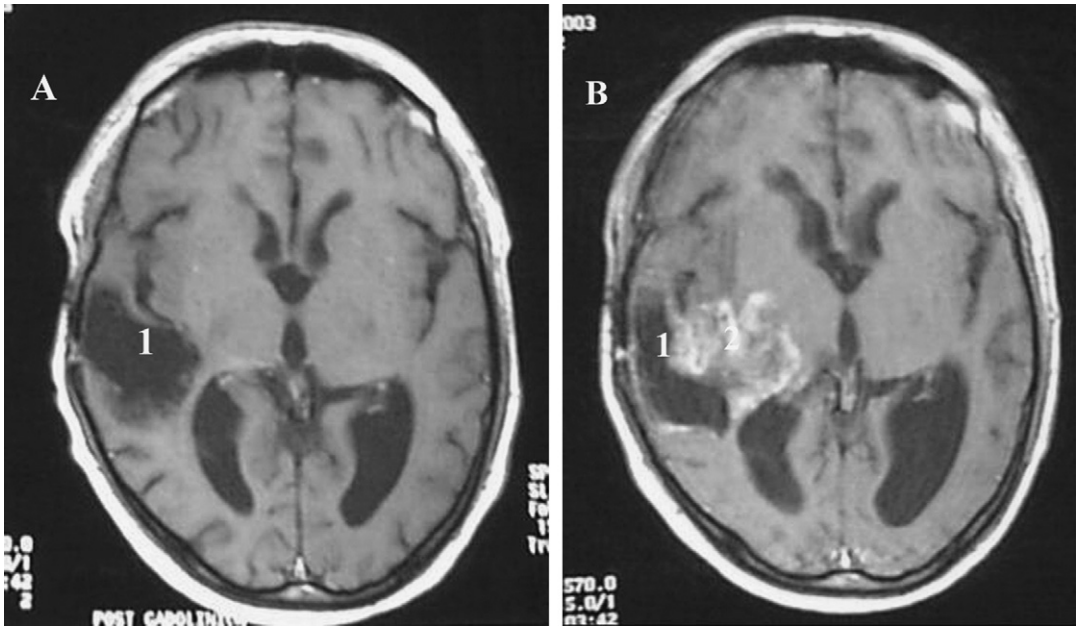

Figure 2 Post-surgical resection axial MRI scan of GBM in the right temporal lobe: (A) 3 months after surgery and (B) 6 months after surgery, 1 = post-resection cavity and 2 = recurrent GBM.

PDA in neurosurgery

Fluorescence image guided biopsy (FIGB)

Forty per cent of GBMs are secondary in nature and progress from lower grade astrocytomas. Therefore it is essential to grade these tumors correctly and identify a representative sample of higher grade component of what looked like low grade glioma on MRI. Using ALA guided biopsy identified 89% of grade III astrocytomas in patients who were classified as low grade glioma on MRI (Fig. 5) (personal communication).

Fluorescence image guided surgical resection (FIGS)

FIGS is PDA using ALA or temoporfin to guide surgical resection. FIGS is based on the selectivity of photosensitizers in GBMs and other high grade tumors within the brain including metastases [28,30,37,38]. FIGS involves administering 20 mg/kg body weight ALA three hours before anesthesia orally, removing the bulk of visible tumor and using the blue light and longpass filter to remove remaining residual tumor (Fig. 1B). Step by step explanation of FIGS technique had been published in Photodiagnosis and Photodynamic Therapy 2008 [28]. FIGS was first reported in a prospective observational study of 52 consecutive high grade gliomas [39]. The authors found FIGS to be selective (99.6%, only one fluorescing biopsy out of 223 fluorescing biopsies did not contain tumor cells), highly sensitive (81.6%, 222 biopsies of 272 fluorescent biopsies contained tumor) and resulted in complete resection of enhancing lesion in 63% of patients. Furthermore this study demonstrated that leaving more than 2 cm^3 tumor was an adverse prognostic factor. The ALA study group conducted a randomized controlled trial (RCT) in which 349 patients were randomized between white light and blue light arms [40]. 176 patients were randomized to the blue light arm. There were no significant differences between the study and control arms in age, gender, KPS, or location of tumor. Forty patients were excluded from the analysis

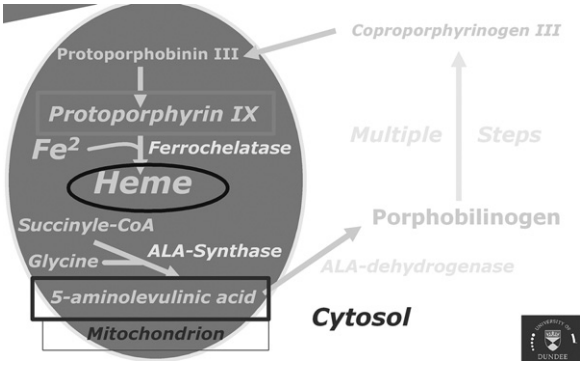

Figure 3 Schematic presentation of the heme synthesis pathways in mammalian cells.

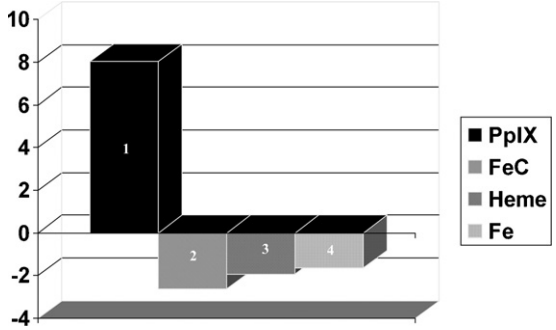

Figure 4 Diagram of PpIX, ferrous, ferrocheletase and heme concentrations in GBM compared to surrounding brain (bar 1 = PpIX 8 times more concentrated in GBM, bar 2 = ferrocheletase activity is 2.64 times less in GBM, bar 3 = heme concentration 1.93 times less in GBM and bar 4 = ferrous concentration is 1.65 times less in GBM).

Table 2 PDT grid to calculate light dose according to the size of the balloon diffuser and the laser fiber diffuser to give 100 J/cm^2 for Photofrin and ALA-PDT (for Foscan the dose 20 J/cm^2).

Balloon diffuser diameter to fit in the post-resection cavity (cm)	Laser fiber diffuser (cm)	Laser power (mW)	Irradiance (mW/cm^2)	PDT duration in seconds
0.5	1	400	509	196
0.75	1	400	226	442
1	1	400	127	785
1.25	1	400	81	1227
1.5	1.5	600	85	1178
1.75	1.5	600	62	1604
2	1.5	600	48	2094
2.25	1.5	600	38	2651
2.5	2.5	1000	51	1963
3	2.5	1000	35	2827

Photosensitizer	Photofrin	Temoporfrin	5-Aminolevulinic acid
Dose (mg/kg)	2	0.15	20
Time of administration	48 h	96 h	3 h
Route of administration	IV	IV	Oral
Light dose (J/cm^2)	100	20	100
Laser light wave (nm)	630	652	635
Light penetration in brain	7—12 mm	20—25 mm	15 mm
Photosensitivity (days)	90	16	1

because the underlying pathology was not high grade glioma (of which 15 were metastases, 7 low grade gliomas, and 14 benign lesions). Complete surgical excision of the enhancing lesion was achieved in 64% (112/176) under blue light compared to 38% (65/173) under white light ($p < 0.0001$). Tumor free survival was longer in patients who had FIGS (5.1 months vs 3.6 months, $p = 0.022$). Time to tumor progression was also significantly longer in patients within the blue arm ($p = 0.031$). Multivariate analysis of patients in this study and other similar studies had identified that KPS score of 70 or more, age less than 65 years and extent of surgical resection were independent good prognostic factors. Excision of 98% of the enhancing lesion extends live expectancy by at least 4.2 months compared to resections leaving more than 2% residual tumor. The median survival of GBM when complete resection was achieved was 16.7 months compared to 11.8 months in controls [41]. FIGS had the potential to excise much more than the enhancing lesion on MRI. High grade gliomas extend beyond gadolinium-enhancement. Fig. 6 demonstrates the size difference of a GBM in the temporal lobe. The GBM was excised by right temporal lobectomy. The temporal lobe was sectioned and the maximum diameter of the tumor was measured under the white light (35 mm) and the blue light (42 mm). The

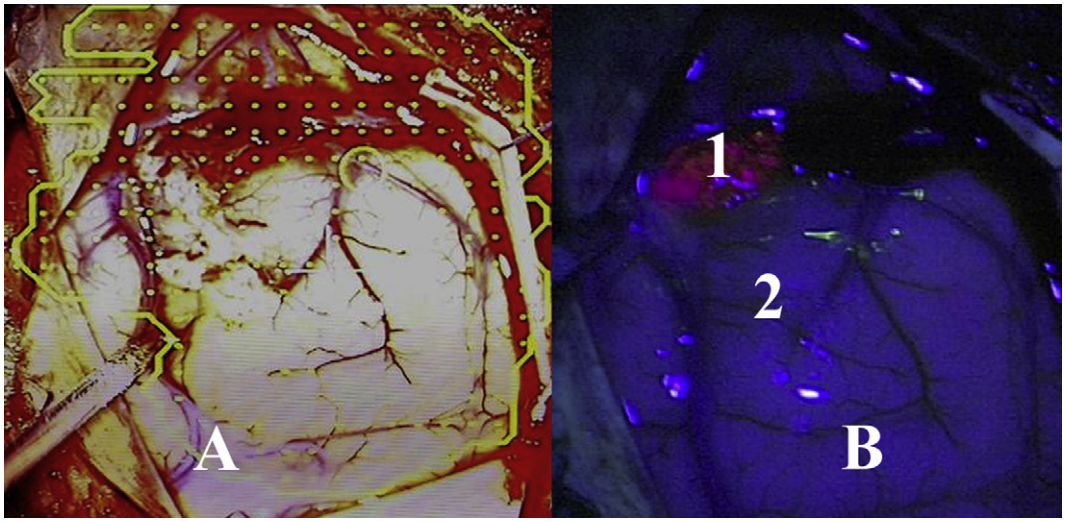

Figure 5 Photograph during open biopsy of diffuse grade II astrocytoma: (A) photograph under the white light; (B) under blue light and 5ALA identifying high grade component (1) and 2 is normal brain.

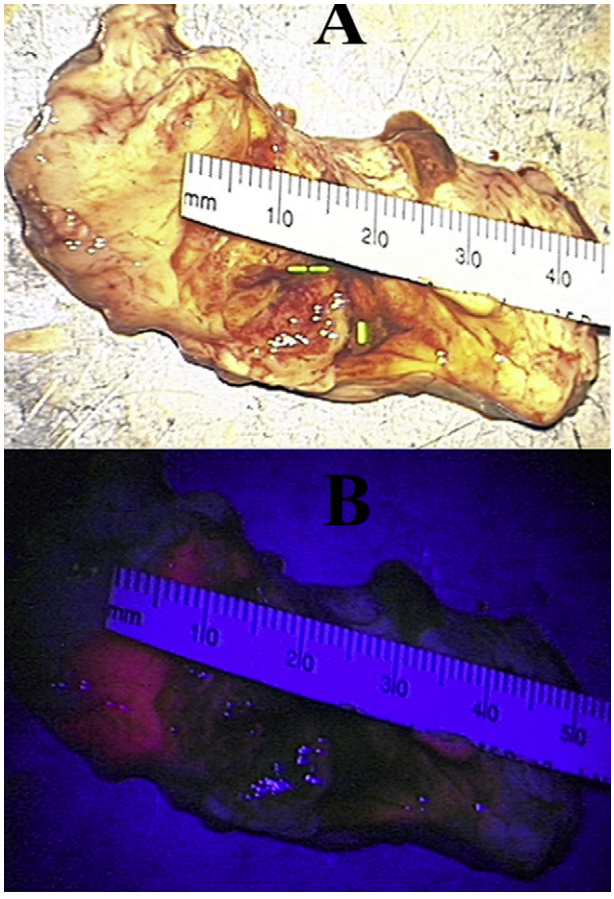

Figure 6 Photograph of resected GBM in the right temporal lobe: (A) under the white light using surgical microscope the maximum diameter was 35 mm; (B) the same lesion measured 42 mm under blue light.

maximum diameter of the tumor measured 37 mm on MRI. Kanako reported similar case in 2008 [42].

Photodynamic treatment (PDT)

PDT in brain is local selective therapy without systemic side-effects of chemotherapy and secondary effects on brain by radiotherapy or delayed cancers. It can be repeated as many times as patient and surgeon wished. It can be combined with surgery, FIGS and intraoperative identification of the tumor to maximize safe resection at the same sitting without delay or fear of wound breakdown. PDT has very low side-effects profile compared to its comparators, radiotherapy and chemotherapy. The concentration of the photosensitizers is high in GBM-cells compared to normal brain (normal brain to GBM is one to 3—400) [31]. Early studies of PDT in high grade gliomas demonstrated increased median survival and increased 2-year survival from 18% to 28% (Fig. 7) [29,41—43].

One of the largest experiences in PDT for GBM was from the Royal Melbourne Hospital, Australia [40]. A total of 350 patients were treated with hematoporphin derivative (HPD) and 230 J/cm^2 was used without balloon diffuser. 138 patients (78 GBMs and 58 AAs) were available for analysis with minimum follow up of 3 years. HPD 5 mg/kg was given IV 24 h before surgery and 70—240 J/cm^2 KTP laser.

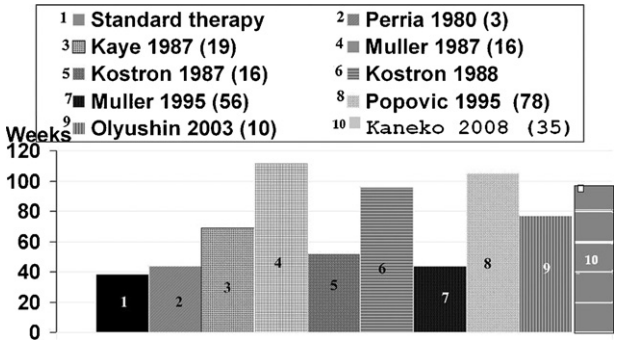

Figure 7 Diagram of early experience of PDT in high grade gliomas, the numbers between brackets are the total number of patients.

Twenty-nine per cent of these patients received chemotherapy. The median survival of newly diagnosed GBM was 14.3 months, for recurrent GBM 13.5 months and 2-year survival was 28%. The median survival of newly diagnosed anaplastic astrocytoma (AA) was 76.5 months, for recurrent AA was 66.6 years and 2-year survival was 37%. Older age at diagnosis was associated with worse prognosis (hazard ratio 1.25, 95% CI 1.05—1.49; $p = 0.010$). This was independent of tumor grade, and whether newly diagnosed or recurrent GBMs. Among patients with newly diagnosed GBMs, light dose $\geq$230 J/m^2 was associated with better prognosis (hazard ratio 0.502, 95% CI 0.27—0.94; $p = 0.033$). For recurrent GBMs there was no statistically significant association between survival and light dose. Tumor location ('frontal' or 'other') was not associated with better survival ($p = 0.540$). Neither was there any significant association with survival with regard to gender, or use of concomitant chemotherapy.

The cumulative experience from Innsbruck University, Austria, included 25 patients with newly diagnosed GBM treated with HPD-PDT with a median survival of 18 months and 67 patients with recurrent GBM with a median survival of 7 months [51]. It also included 22 patients with recurrent GBM treated with temoporin-PDT with a median survival of nine months. The Hokaido University (Japan) experience included 290 patients treated with ALA-FIGs and 35 patients treated with HPD-PDT [52]. The median survival of GBM was 20.5 months and for AA was 36 months. The North American experience (Toronto, Canada), using Photofrin-PDT included 96 high grade glioma patients (total number reported 112 patients, 11 metastases and one malignant meningioma). Photofrin 2 mg/kg was given IV 13—36 h before surgery and KTP laser intracavity. The median survival of GBMs was 10.5 months with 22% survived for 1 year and 2% survived for 2 years [53]. Metanlaysis of observational studies of PDT in high grade gliomas included more than 1000 patients with median survival of 16.1 months for newly diagnosed GBMs and 10.3 months for recurrent GBMs. These survival outcomes are better than standard therapy. However, advocates of evidence based medicine criticized these studies because they were observational in nature and are not double blind randomized placebo controlled crossover trials (DBRPCCT). DBRPCCT could not be applied to every intervention particularly in surgery because the surgical technique plays a bigger part and neither the patient nor the surgeon could

be blinded. DBRPCCT are not applicable to craft based specialties such as neurosurgery. Smith and Pell [54] reviewed the literature to find out if there were any DBRPCCT evaluated the use of parachutes before their adoption in airplanes and found no such trials. The authors concluded that ''As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomized controlled trials. Advocates of evidence based medicine have criticized the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organized and participated in a double blind, randomized, placebo controlled, crossover trial of the parachute''. However, PDT in high grade gliomas had been subjected to several prospective trails: a phase III multicentre randomized trail in North America using Photofrin 2 mg/kg PDT adjuvant to surgical resection compared to standard surgical resection [55], ALA-PDT randomized controlled trail in Germany [56], temoporfin-PDT with matched controls in Austria [55] and Photofrin 2 mg/kg PDT in conjunction with ALA-FIGS in Scotland [35]. The first RCT included 43 patients in the PDT-arm and 34 patients in the control arm [55]. The median survival of the PDT-arm was 11 months (95% CI, 6—14 months) compared to 8 months (95% CI, 3—10 months) in the control arm, an increase of 38% in median survival which was significant. However, the life curves crossed over at 15 months. There were multiple reasons of late failures. There was no information about extent of surgical resection in the two groups which is very important in such surgical trials, and there was no matching of post-recurrence therapies such as chemotherapy and further surgery as many of patients in the control arm had PDT on recurrence. Secondary treatments were likely to have cancelled earlier PDT-effect. The second RCT combined ALA guided FIGS and interstitial PDT [56]. The ALA dose was 20 mg/kg given orally 3 h before anesthesia and 200 J/cm^2 was used for PDT with 635 nm laser. The 6-month progression free survival was 41% in the study arm compared to 21% in the control group ($p < 0.001$). The Austrian trial recruited 26 patients and was matched by a similar group in the same institution [57]. This trial was not randomized but had a control group, it combined temoporfin guided FIGS and PDT at 0.15 mg/kg IV temoporfin and 20 J/cm^2 at 652 nm laser. The sensitivity and selectivity of FIGS in this study was 87.9% and 95.7%, respectively (172 biopsy samples) and a true prediction rate of 90.7%. Complete resection of enhancing lesion was achieved in 75% of study group compared to 52% in matched controls. The median survival was 9 months compared to 3.5 months in matched controls. The final trail recruited 42 patients [35]. Twenty-seven patients were eligible for analysis (14 were metastatic tumors on histology and one died of unrelated causes were excluded), thirteen were randomized to ALA + Photofrin FIGS and repetitive PDT and fourteen were randomized to standard therapy. The two groups were well matched for other prognostic factors such as age, and location. They were also matched for secondary therapies on relapse such chemotherapy and radiotherapy. The dose of PDT was 500 J/cm^2 fractionated into five sessions over 5 days. The relapse free survival of the study arm was 8.6 months compared to 4.8 months in the control group ($p < 0.01$). In the intent to treat analysis, the median survival was 52.8 (95% CI, 40—65) weeks in the study group compared to 24.2 (95% CI, 18—30) weeks in controls ($p < 0.001$). The median KPS scores were 70 and 80 before and after PDT in the study group compared to 80 and 70 before and after treatment in the control group. Although patient in the study group were worse off before surgery, their KPS scores improved to a much better scores postoperatively compared to controls (an absolute difference of 20 points).

Safety of PDA in brain

An adverse event (AE) is any adverse change in health or ''side-effect'' that occurs in a person who participates in a clinical trial while the patient is receiving the treatment (study medication, application of the study device, etc.) or within a pre-specified period of time after their treatment has been completed. AEs are classified as serious (SAE) or minor (MAE); expected (EAE) or unexpected (UAE); and study-related (SRAE), possibly study-related (PSRAE), or not study-related (NSRAE). Only SRAE and PSRAE that are unexpected that matters here. In PDT studies, skin and retinal photosensitivity are expected AEs. In our experience at the Scottish PDT centre we have carried out more than 365 treatments using ALA and Photofrin intracavity PDT with balloon diffuser and 630 nm diode laser in 150 patients in brain and encountered AE in seven patients: three (2%) patients developed deep venous thrombosis (DVT) (0.9% per Photofrin-PDT treatment, none in 5ALA mediated PDT), two (1.3%) patients developed skin photosensitivity because of non-adherence to light protection during summer months (0.6% per Photofrin-PDT treatment), two (1.3%) patients developed post-PDT brain swelling requiring treatment (0.6% per Photofrin-PDT treatment, no brain swelling was noted in newly diagnosed lesions after fives doses of PDT), one (0.1%) balloon diffuser fracture due to poor catheter fixation (0.03% per Photofrin-PDT treatment), and one (0.1%) patients developed skin necrosis and CSF leak of previously irradiated skin flap (0.03% per Photofrin-PDT treatment). These side-effects are not different from those encountered during standard therapy. Photofrin-PDT in 20 patients with recurrent GBM using escalating doses of Photofrin from 0.75 mg/kg to 2 mg/kg and three methods of light delivery was reported [58,59]. The authors reported no neurotoxicity by escalating the Photofrin dose and no neurotoxicity in intracavity 630 nm (LED or laser) with balloon diffuse. The authors reported neurotoxicity in two patients treated with interstitial PDT, one developed ataxia and one facial weakness. These SAEs were expected with any treatment of intrapaynchymal brain tumors without cytoreductive therapy. In fact this expected SAE of biopsy of such tumors and inserting multiple laser fibers in a brain tumor inevitably leads to SAEs in significant number of patients. In my opinion these two SAEs were the result of the interstitial insertion of the fibers rather than the PDT treatment. The authors concluded it was within the acceptable range of their practice in this area of neuro-oncology [58,59]. The authors had encountered no side-effects in their patients who had gliomas in the posterior cranial fossa and close to brain stem. Another earlier study of twenty patients treatment with HPD and 630 nm light reported five expected skin photosensitivity, none of which were SAEs [46]. Two of 136 HPD-PDT treated patients in Australia (2%) reported excessive sunburn related to skin photosensitization (expected

AE) [50]. In both cases they had failed to adhere to written instructions regarding sun-exposure, similar to our own experience. The Canadian early series [52] reported 2.7% mortality, 0.9% intracavity haemorrhage, 3.6% DVT, 3.6% wound infection, 0.9% CSF leak, 1.8% skin photosensitivity, and 5.7% worsening neurological deficit. All these AE are not specific to PDT and expected AE of cranial tumor surgery with the exception of skin photosensitivity. Skin photosensitivity is specific to PDT and is expected AE in patients who do not adhere to written and verbal light protection instructions. These rates of complications were unique to this study and were not replicated in any subsequent observational studies or any prospective RCT of PDT. These complications simply reflect the effect of three factors: interstitial insertion of KTP laser fibers in some patients, varied light dose, varied time to treatment and the steep learning curve. The same team had not reported any difference in the AEs profile in the RCT they carried out after their earlier experience [55]. Furthermore, our patients tolerated 500 J/cm^2 divided into five sessions. On the other hand interstitial and post-radiation PDT may be associated with higher complication rate. A study of eighteen patients with interstitial PDT reported no side-effects with a total dose of 1500—3700 J compared to two out of six patients received a total dose of 3700—4400 J and three out of six patients who received a total dose of 4400—5900 J [60]. This study is not powered enough or randomized to answer this question. It was superseded by RCT that did not demonstrate SAE [35,55—57]. In FIGS the AEs profile of the blue light arm (overall 42.8%) did not significantly differ from that of the white light arm (44.5%) [39]. Dysphasia (AE) was 3.5% versus 0.6% ($p = 0.07$, not significant), seizures was 6% versus 2.9% ($p = 0.21$, not significant), and hemiparesis was 4% versus 2.3% ($p = 0.4$, not significant).

Conclusions

(1) Photodynamic applications (PDA) in GBMs are very safe, selective and sensitive and did not increase the adverse events profile of surgical resection of these tumors.
(2) Fluorescence image guided surgical resections (FIGS) is associated with significant improvement of tumor free survival and significant increase in complete excision of enhancing GBMs.
(3) Photodynamic treatment of GBMs is associated with improved survival in both newly diagnosed and recurrent GBMs.
(4) Photodynamic treatment after maximum safe surgical excision using FIGS technology significantly improved tumor free survival, median overall survival and quality of life in patients with newly diagnosed GBMs.

These conclusions are based on the evidence discussed above, including large observational studies and RCTs, we do not need double blind controlled placebo crossover trials to prove that the parachute saves lives when jumping off airplanes, neither we need such trial to prove that seatbelts save lives in motor vehicle accidents. Such trials are prohibitive on ethical grounds, cost, variation in surgical techniques, inability to blind both surgeons and patients and the variability of treatment on tumor relapse. Due to aforementioned compelling reasons, the only primary outcomes that can be used in future studies of GBMs is tumor free survival, completeness of resection and quality of life postoperatively. These primary outcomes have already been proved in two RCT [34,39] and it would be unethical to deny such treatment if it was available to patients.

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