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Is interstitial photodynamic therapy for brain tumors ready for clinical practice? A systematic review

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ABSTRACT

Background: : Interstitial photodynamic therapy (iPDT), inserting optical fibers inside brain tumors, has been proposed for more than 30 years. While a promising therapeutic option, it is still an experimental treatment, with different ways of application, depending on the team performing the technique.
Objective: : In this systematic review, we reported the patient selection process, the treatment parameters, the potential adverse events and the oncological outcomes related to iPDT treatment applied to brain tumors.
Methods: : We performed a search in PubMed, Embase and Medline based on the following Mesh terms: "interstitial" AND "photodynamic therapy" AND "brain tumor" OR "glioma" OR glioblastoma" from January 1990 to April 2020. We screened 350 studies. Twelve matched all selection criteria.
Results: : 251 patients underwent iPDT. Tumors were mainly de novo or recurrent high-grade gliomas (171 (68%) of glioblastomas), located supratentorial, with a median volume of 12 cm^3. Hematoporphyrin derive agent (HpD) or protoporphyrin IX (PpIX) induced by 5-aminolevulinic acid (5-ALA) was used as a photosensitizer. Up to 6 optical fibers were introduced inside the tumor, delivering 200 mW/cm at a wavelength of 630 nm. Overall mortality was 1%. Transient and persistent morbidity were both 5%. No permanent deficit occurred using 5-ALA PDT. Tumor response rate after iPDT was 92% (IQR, 67; 99). Regarding glioblastomas, progression-free-survival was respectively 14.5 months (IQR, 13.8; 15.3) for de novo lesions and 14 months (IQR, 7; 30) for recurrent lesions, while overall survival was respectively 19 months (IQR, 14; 20) and 8 months (IQR, 6.3; 8.5). In patients harboring high-grade gliomas, 33 (13%) were considered long-term survivors (> 2 years) after iPDT.
Conclusion: : Regardless of heterogeneity in its application, iPDT appears safe and efficient to treat brain tumors, especially high-grade gliomas. Stand-alone iPDT (i.e., without combined craniotomy and intracavitary PDT) using 5-ALA appears to be the best option in terms of controlling side effects: it avoids the occurrence of permanent neurological deficits while reducing the risks of hemorrhage and sepsis.

1. Introduction

Photodynamic therapy (PDT) relies on the combination of a photosensitizer incorporated inside targeted cells, a specific wavelength light illumination and the presence of ground state oxygen. The synergy of the three above-mentioned elements leads to its therapeutic effect through the formation of reactive oxygen species and radicals that can induce cell death [1]. The selectivity of PDT depends in part on the photosensitizer used and its distribution in the living tissue. Some photosensitizers are diffusing in the whole body, others in the wall of the vessels and the more recent ones were developed to target more specific tissue. PDT emerged as a recommended treatment for many types of lesions, especially premalignant and malignant tumors [2,3]. It is now used in clinical practice for skin lesions such as actinic keratosis [4], prostatic lesions [5], thoracic tumors and mesothelioma [6] and for a variety of gastrointestinal dysplasia and cancers such as esophagus carcinoma [7, 8]. In the neurosurgical field, PDT still remains experimental [9]. In the case of brain tumors eligible to total resection, PDT can be performed inside the resection cavity at the end of tumor removal. It is called intracavitary PDT. In this configuration, the illumination is performed using a balloon filling the cavity. In front of non-surgical lesions, due to their critical location or in fragile patients, PDT can be performed

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without craniotomy, in a minimally invasive manner introducing optical fibers inside the lesion using stereotactic coordinates. The latter method is called interstitial PDT (iPDT). It has been applied to treat brain tumors in the late 1980's, thanks to the advent of better brain imaging, stereotactic instruments and laser devices. Through the years, several teams developed their own iPDT technique, treating a variety of brain lesions including gliomas, meningiomas or metastases, with various optical fiber devices and dosimetry schemes. In this systematic review, we focused on the clinical applications of iPDT to brain malignancies, excluding preclinical studies. We aimed at reporting the patient selection process, the treatment parameters with its dosimetry aspect, the potential adverse events and the oncological outcomes related to iPDT treatment applied to brain tumors.

2. Methods

This study was performed in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines [10]. We fulfilled a systematic database research, including in PubMed, Embase and Medline between January 1990 and April 2020, using the following Mesh terms: "interstitial" AND "photodynamic therapy" AND "brain tumor" OR "glioma" OR glioblastoma". Inclusion criteria required that each citation be a peer-reviewed original article, case series, case reports or congress proceedings (SPIE, international society for optics and photonics congress) of brain tumors treated with interstitial PDT. Preclinical studies were not included. Fig. 1 (Prisma Flow Diagram) illustrates the article selection.

We specifically collected data regarding patient characteristics, histology of treated tumors, physical and dosimetry treatment settings, post-treatment adverse events, and oncological outcomes (response rate to iPDT, progression-free survival (PFS), overall survival (OS)).

Were included 12 studies, as reported in Annex 1, understanding 251 treated patients.

2.1. Statistical analyses

This review reports descriptive data. Qualitative variables are expressed as numbers (percentage). Quantitative variables are expressed as the median (interquartile range (IQR)).

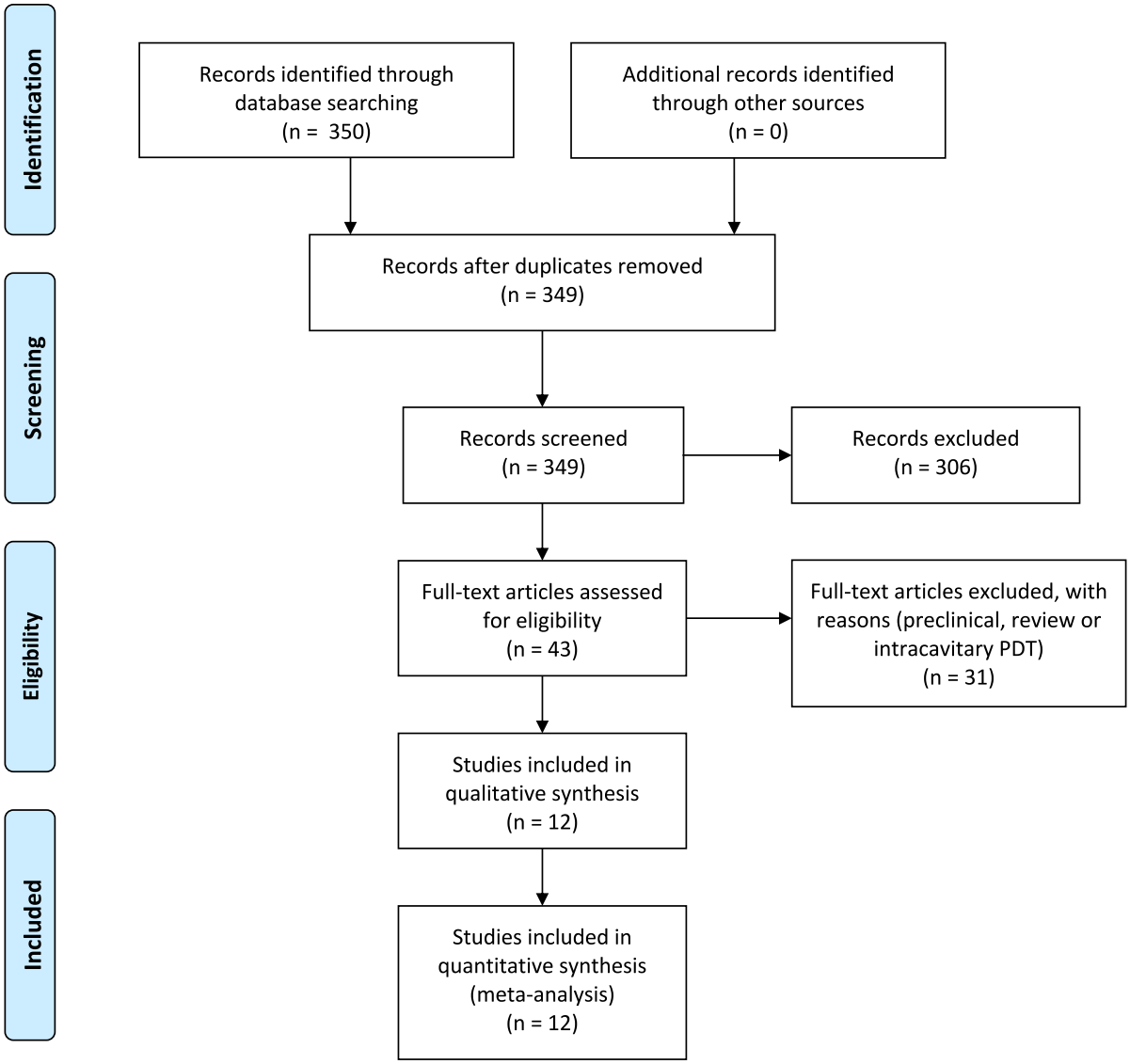

Fig. 1. Flow diagram for literature assessment (PRISMA 2009 guidelines). PDT: photodynamic therapy

3. Results

3.1. Patient population and tumor characteristics

Demographic and histologic data are summarized in Table 1. According to available literature, 251 patients underwent iPDT, alone or combined with intracavitary PDT. A vast majority, 224 (89%) were high-grade gliomas, with 171 (68%) glioblastoma WHO grade IV. Brain metastases were the second type of treated lesions, with 15 (6%) patients (primitive cancers were respectively melanoma and lung carcinoma). Interstitial PDT was performed equally for de novo (118 patients, 47%) or recurrent lesions (133 patients, 53%). All treated tumors were supratentorial, with a median volume of 12 cm^3 (IQR, 7; 41).

3.2. Treatment parameters

The type of photosensitizer agent, posology, modality of administration and dosimetry data are reported in Table 2. The majority of the studies included in this review involved diffusing optical fibers with a diffuser length varying between 2 and 3 cm [11,12]. The diffuser parts of the optical fibers were implanted inside the tumor. Up to 6 fibers were inserted, most of the time in a parallel manner to guarantee the safety of the light distribution and avoid intra parenchyma fiber collisions [11–13]. To check the fibers positioning, optical fibers harboring X-ray markers were used [11]. The laser generator delivered a median light power of 200 mW/cm for each fiber at a wavelength of 630 nm ± 5 nm (IQR, 630; 633). Fig. 2 illustrates the main treatment parameters.

3.3. Adverse events

The postoperative complications are depicted in Table 3. Three (1%) patients died in the early postoperative course. Two of them presented with compressive intracavitary hematoma [14]. For the third one, the cause of death was not reported, however, according to Muller et al. it was not related to the iPDT itself [15]. Of note, in these three previous cases, iPDT was performed in addition to tumor resection and intracavitary PDT. When PDT was performed strictly interstitially, no lethal complication was reported. The transient postoperative neurological morbidity was related to intracranial hypertension (13 (5%) patients). Post iPDT definitive neurological deficits occurred in 13 (5%) patients and consisted in: majored hemiparesis, loss of vision, quadranopsia and dysphasia. These patients harboring permanent deficits underwent iPDT using a non-selective photosensitizer (hematoporphyrin derivative agent). The above-mentioned persistent deficits were related to close peritumoral brain damages, correlated with significant post iPDT brain edema visible on early post-treatment imaging (CT scan or MRI) [13]. No permanent deficit was reported after 5-ALA iPDT. Infection was reported in 7 (3%) patients, whose underwent tumor resection with intracavitary illumination followed by iPDT [16].

Table 1
Demographics and tumors characteristics. (Karnofsky PS: Karnofsky performance status) PNET: primitive neuro-epithelial tumor. Values are presented as frequency (percentage) unless otherwise indicated.

Variables	Values
Population	n=251 (%)
Age (median, IQR)	51 (48; 54)
Sex ratio (m/f)	1.3
Initial Karnofsky PS (median, IQR)	84 (74; 89.5)
Tumor characteristics	
Supra tentorial	251 (100)
Posterior fossa	0
Volume (cm3) (median, IQR)	12 (7; 41)
Histology	
De novo	n=118 (%)
Glioblastoma	89 (75)
Astrocytoma III	19 (16)
Metastasis	7 (6)
Other	3 (3)
Recurrence	n=133 (%)
Glioblastoma	82 (62)
Astrocytoma III	33 (25)
Metastasis	8 (6)
Malignant meningioma	4 (3)
Malignant Ependymoma	3 (2)
Oligodendroglioma III	1 (1)
PNET	1 (1)
Gliosarcoma	1 (1)

Table 2
Treatment parameters. HpD: hematoporphyrin derivative agent, PpIX: protoporphyrin IX, ALA: aminolevulinic acid

Variables	Values
Photosensitizer agent (n=studies)	
HpD	8
PpIX induced by 5-ALA	4
Posology (mg/kg)	
HpD	2 (2; 2.75)
5-ALA	20
Drug light interval (h)	
HpD	30 (24; 45)
5-ALA	3 (2; 4.8)
Wavelength (nm)	630 (630; 633)
Light power (mW /cm)	200
Fluence (J/cm2)	215 (98; 480)
Total energy delivery (J)	3700 (1440, 7212)

3.4. Oncological outcomes

The oncological outcomes after iPDT, especially for gliomas, are reported in Table 4. The postoperative Karnofsky PS at discharge was 79 (77; 82), without statistical difference with the preoperative Karnofsky PS. The median response rate after iPDT for all types of tumors was 92% (IQR, 67; 99). Meningiomas and metastasis were less responsive to iPDT than primary glial tumors [14,17,18]. The median progression-free survival (PFS) was 14.5 months for de novo GBM and 14 months for recurrent GBM. The overall survival (OS) was 19 months for de novo GBM and 8 months for recurrent GBM. In an unexpected manner, PFS for recurrent GBM was superior to OS due to the reviewed series heterogeneity. Indeed, several studies reported very long PFS without OS data resulting in this data bias [12,19]. For WHO grade III astrocytomas, data are shown in Table 4. Regarding other histologic types of lesions, data were too sparse to analyze PFS or OS. We identified several criteria of prolonged survival (> 2 years) after iPDT in the reviewed studies (a majority of long survivors harbored GBM, and in a few cases WHO grade III gliomas). These criteria are listed below:

- Preoperative Karnofsky PS >70
- Complete response on early brain imaging
- Well limited /spherical lesion
- Tumor volume < 5 cm^3
- Strong tumor PpIX uptake

4. Discussion

Interstitial PDT has been applied to treat brain tumor for more than 30 years. Various surgical teams developed their own iPDT modality. This systematic review highlights the safety of iPDT applied to brain tumors as well as its effectiveness, especially in case of a de novo or recurrent glioblastoma WHO grade IV.

4.1. Patient population

In comparison with current neurosurgical practice, the median tumor volume treated with iPDT in the reviewed studies was smaller (12 cm^3 [IQR, 7; 41]). For instance, the median resected tumor volume in

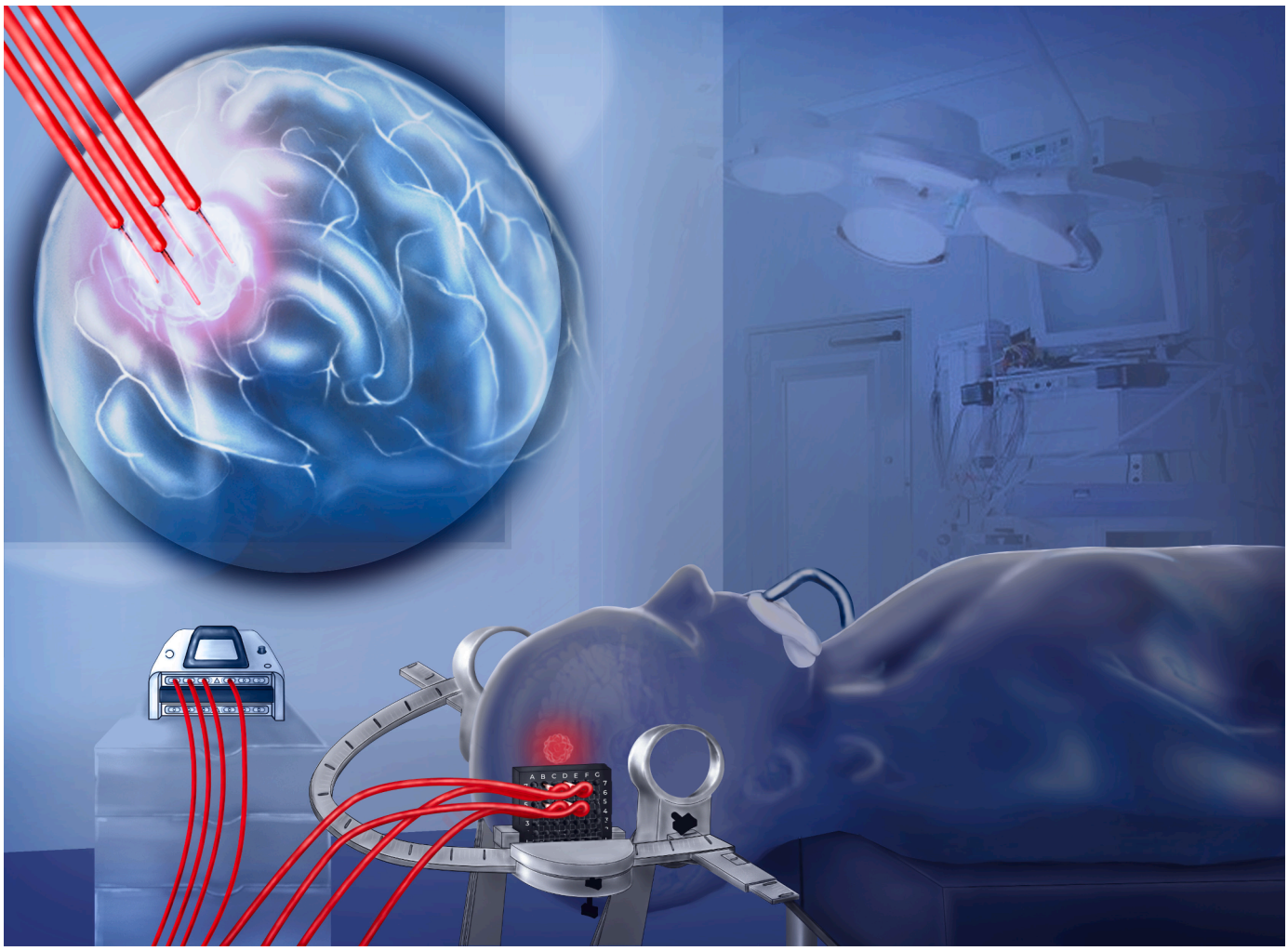

Fig. 2. Illustration of the interstitial PDT settings applied for brain tumor according to the reviewed literature. The treatment procedure is performed under general anesthesia in the operative room, with 100% O^2 ventilation to increase iPDT therapeutical effect. The targeted tumor is supratentorial, with a volume <10 cm^3, and a major axis between 3 to 5 cm. The photosensitizer used is protoporphyrin IX (PpIX) induced by 5-aminolevulinic acid (5-ALA) (20 mg/kg), delivered 3 to 5 h before illumination. 4 optical fibers are introduced inside the core of the tumor, in a parallel manner through a stereotactic grid. The diffusor length of the optical fibers can vary from 3 to 5 cm. The laser generator delivers 200 mW/cm to each diffusing fiber, at a wavelength of 633 ± 5 nm.

Table 3
Post iPDT adverse events, including patients treated with stand-alone iPDT or combined PDT (intracavitary and interstitial PDT), using all types of photosensitizers.

Variables	Stand-alone iPDT (n=159)	Combined PDT (n=92)
Mortality	0 (0%)	3 (3%)
Neurological morbidity		
Transient	7 (4%)	6 (6%)
Definitive	5 (3%)	8 (9%)
Other complications		
Hematoma	0 (0%)	2 (2%)
Infection	0 (0%)	7 (8%)
Thromboembolic event	1 (<1%)	4 (4%)
Skin sensitization	0 (0%)	2 (2%)

the Department of Neurosurgery of the Lille University Hospital, France, is 28.4 cm^3 (IQR, 11; 58)) [20]. One could assume that the targeted volumes with iPDT were smaller to reduce the risk of treatment side effects, such as brain swelling. *According to Kaneko et al., a tumor volume inferior to 5 cm3 was a criterion of total response after iPDT without persistent neurological deficits* [21]. In addition, larger high-grade gliomas are usually associated with inner necrosis which is not responsive to iPDT. The limit of 3 cm to 5 cm diameter was reported as the upper limit to treat brain tumors with iPDT [11,12,22]. *Larger tumors were associated with an increased rate of morbidity. In Krishnamurthy series, the median tumor volume was of 50 cm3, and the respective persistent neurological deficit rate was of 28%, which was the highest amongst the reviewed studies* [13]. In the reviewed series, iPDT was applied to monofocal lesions. Multifocal high-grade gliomas were excluded in order to avoid too much optical fiber insertions in different brain lobes. Moreover, such multifocal lesions clearly hamper the patient prognostic. In this review, all tumors were supratentorial. It reflects the predominance of supratentorial tumor location in adults. Treating with iPDT a lesion in the posterior fossa could increase the risk of related complications, such as brain herniation due to post-iPDT edema and the consequence of a cerebellar parenchyma hematoma. In the reviewed series, de novo and recurrent tumors were included in the same proportion. This illustrates the possibility of iPDT treatment at several stages of the disease, previously or concomitantly to surgery, radiotherapy or chemotherapy. Interstitial PDT could even improve local chemotherapy effectiveness by opening the blood-brain barrier [17].

4.2. Treatment parameters

In the 12 included studies, two types of photosensitizer agent were used: hematoporphyrin derivative (HpD) and protoporphyrin IX (PpIX)

Table 4
Post iPDT oncological outcomes. The Karnofsky PS was evaluated at discharge (few days after treatment). The response rate was evaluated with early postoperative imaging (CT scan or MRI), corresponding to contrast-enhancement reduction in the treatment area. Progression-free-survival and overall survival were respectively calculated from the date of iPDT treatment to recurrence and death (in months).

Variables	Values
Karnofsky PS (median, IQR)	79 (77; 82)
Response rate (%) (median, IQR)	92 (67; 99)
PFS (month) (median, IQR)	
De novo glioblastoma IV	14.5 (13.8; 15.3)
Recurrent glioblastoma IV	14 (7; 30)
Recurrent astrocytoma III	6
Survival	
1-year survival (%)	
Glioblastoma IV	47.5 (27.5; 60)
Astrocytoma III	44 (43.5; 72)
2 years survival (%)	
Glioblastoma IV	20 (0; 47.5)
Astrocytoma III	32 (31.5; 32.5)
Overall survival (month) (median, IQR)	
De novo glioblastoma IV	19 (14; 20)
Recurrent glioblastoma IV	8 (6.3; 8.5)
De novo astrocytoma III	12
Recurrent astrocytoma III	13.5 (12; 14.7)

induced by 5-aminolevulinic acid (5-ALA). HpD is a porfimer sodium excited when exposed to red light at 630 ± 5 nm. *Among the 12 reviewed studies, hematoporphyrin derivative agent (HpD) was mostly used before the advent of 5-ALA. When developing iPDT for brain tumors, the pioneers used HpD as it was already used for other types of cancers and its metabolism was well known. From 2007, except Kaneko et al., all clinical studies used protoporphyrin IX induced by 5-aminolevulinic acid mediated PDT. In comparison with 5-ALA, HpD is less selective with a ratio of 10/1 between the tumor and the healthy parenchyma (instead of 200/1 for 5-ALA)* [23]. *Furthermore, HpD is also present at a high concentration around the tumor which explains such post PDT edema after high intensity illumination.* In this review, the very majority of postoperative complications were reported after HpD use (three deaths, and most of transient symptoms related to intracranial hypertension). Moreover, due to HpD pharmacokinetics, the time to absorption was up to 24 h and expose the patient to skin sensitization problems. Gradually, HpD was supplanted by the use of 5-ALA. 5-ALA is used in clinical practice since 2007 in Europe and 2017 in the USA for intraoperative photo diagnostic application in glioma resection. It is a natural precursor to heme. It goes through a series of transformation in the cytosol before getting converted into PpIX in the mitochondria. Then PpIX chelates with iron in presence of ferrochelatase enzymes to produce heme. Cancer cells, including glioma, lack of ferrochelatase enzymes, which results in a selective accumulation of PpIX in tumors. Further exposure of cancer cells to red light at 630-635 nm, in presence of oxygen, induce selective tumor cell death through various metabolic processes, inducing free radicals and oxidative species formation. 5-ALA could be administered to the patient only few hours before the surgery and is quickly eliminated reducing the risk of skin sensitization. Its selectivity towards tumor cells decreases the risk of post-iPDT peritumoral edema. The PpIX concentration inside a tumor is correlated to its degree of malignancy, especially gliomas. A higher PpIX induced by 5-ALA concentration is a predictive factor of optimal response to PDT [12]. This explains why iPDT is particularly effective in high-grade gliomas. Another argument in favor of the use of 5-ALA is the absence of risk of overtreatment. Indeed, when illuminating with the optical fiber the PpIX fluorescent tissue, the fluorescence is converted into energy, in presence of oxygen, to get the therapeutical effect of PDT. If the tissue is over-illuminated, all the photosensitizer is consumed and there is no additional adverse effect, in particular no thermal effect with the dose prescribed in the reviewed studies [12].

In this review, two parameters were constant, the median wavelength of 630 ± 5 nm used for excitation of the photosensitizer and a light intensity of 200 mW/cm diffuser length. Using the above-mentioned wavelength, the light penetration is optimal and increases the potential therapeutic effect of iPDT (almost 1 cm diameter through the brain parenchyma). As an example, using a light intensity of 200 mW/cm, 1 W power is needed for an optical fiber with a 5 cm diffuser. According to authors, such a light power enabled a reliable and reproducible illumination through optical fibers, in a restricted time frame (less than one hour). It is important to mention that this light power was initially chosen because of the constraints related to the limited power of the first laser generators. Regarding the optical fibers, a consensus emerged from this review to use cylindrical optical fibers, with a diffuser part which could vary around 3 cm. Fibers with distal X-ray markers could be of interest to check their positioning more easily. Among the 12 studies, light delivery was performed in a continuous manner. In our laboratory, we reported the interest of light fractionation to let the targeted tissue reoxygenate itself between each illumination. We validated this light delivery scheme on a rodent model [24–26]. Light fractionation increased selective tumor cells death through the apoptotic way, reducing inflammatory response and minimizing post PDT necrosis. Our preliminary results are encouraging, and light fractionation could be of interest to increase iPDT effectiveness. In the current review, in most cases, the oxygen saturation was set to 100% intraoperatively to prevent from a lack of cellular oxygen during treatment [11].

Over the time, increased total energy was delivered, due to higher photodynamic agent selectivity towards tumor cells (PpIX induced by 5-ALA vs HpD). For instance, Muller et al. and Powers et al. who used HpD for iPDT, delivered a median total energy between 1240 and 1273 J [14,17,27]. Unlike the total fluence was low, they experienced a higher morbidity due to the HpD non-selectivity and to their more invasive approach, combining cavitary and interstitial PDT. At contrario, Beck et al. and Johansson et al. using 5-ALA, delivered a median total energy of 7200 and 8200 J, respectively, without significant adverse effect [11,12]. A higher delivered energy with a selective photosensitizer agent seems to be optimal for tumor control as we later discuss in the oncological outcomes section. Due to the 5-ALA metabolism, over treatment is not an issue. Theoretically, laser interstitial thermal therapy (LITT) could induce over treatment if improper calibration is performed due to his non-selective mechanism. With PpIX, in case of over exposition to red light, the only risk is to be inefficient because of total PpIX consumption during the photochemical reaction. Therefore, most recent studies stepped up the total energy delivery. Three studies reported the total fluence related to the treated volume (1000, 1405, 1200 J/cm^3) [11,17,19]. One could assume that taking into account the tumor volume to determine the total fluence would be relevant. It may enhance the conformity of the dosimetry and help select the appropriate number of optical fibers to deliver the adequate energy.

In most cases, the maximal number of intracerebral fibers was 6. They were introduced in a parallel manner, sometimes using a rigid grid to get the right trajectory [13]. This kind of rigid grid could help avoid fiber collision inside the brain and ensure a constant distance between the fibers, ensuring a more homogeneous light delivery in the treated volume. As reported by Beck et al., a distance of 9 mm should be respected between fibers to avoid thermal effect if the temperature rises above 42°C [11]. All diffusing fibers had a diffusing part ranging between 2 and 3 cm. Before optical fiber insertion into the brain, transparent sleeves were positioned according to the predefined coordinates to ensure that the flexible fibers would follow the right trajectory to the target [13]. In this review, most authors accomplished intratumoral fiber positioning. Krishnamurthy et al. added peripheral fibers in their series understanding 18 recurrent primitive brain tumors to enhance the field of treatment. However, it was associated with significant post iPDT morbidity with 28% of permanent neurological deficits. In this study, HpD was used, that could explain the higher complication rate. As glioma are infiltrative lesions, it could be of interest to add peripheral fibers to illuminate beyond the bulk of the tumor, with a selective

photosensitizer such as PpIX induced by 5-ALA. In addition to surgical tumor removal, iPDT applied beyond the resection borders could reduce the local tumor recurrence, which occurred in more than 80% in the 2 cm around the main core of the glioma [28]. The iPDT seems ideal to create a therapeutic halo of 5 to 8 mm around the lesion to reduce local recurrence.

Regarding potential additional costs, iPDT is not an expensive technique. In fact, it requires a standard laser generator able to deliver a power of 200 mW/cm, single-use optical fibers (up to 6 per patient) and appropriate photosensitizer available on the market (e.g., PpIX-5ALA induced PDT which is approved by EMA and FDA). Performing iPDT does not need an extensive hospital stay as it is a less invasive than classic craniotomy. For instance, in our neurosurgical unit, a patient undergoing brain tumor resection through craniotomy stays between 4 to 6 days. Concerning indication, iPDT could be discussed during multidisciplinary neuro oncological meetings as clinicians usually proceed for every brain tumor cases.

4.3. Adverse events

Every invasive treatment applied to the brain is likely to generate brain swelling. Such brain edema could be poorly tolerated and induce troubles of conscience even coma. For this reason, intracranial pressure (ICP) monitoring was performed in early published series [16]. No ICP elevation was reported during the monitoring period running from the surgical procedure to 72h later. In case of ICP elevation, it was planned to introduce corticosteroid. The hospital stay was not prolonged due to PDT. One could assume that iPDT could nowadays be performed during a short hospital stay of 3 to 4 days.

As reported in Table 3, the complication rates differ between stand-alone iPDT and combined PDT (intracavitary and iPDT in the same procedure). In the stand-alone iPDT group, no mortality was reported and morbidities were lower (no symptomatic hematoma, no infection). Regarding the neurological deficits after stand-alone iPDT, 7 patients harbored transient symptoms which dwindled under corticosteroid medication. All these patients belong to the Schwartz et al study and the complication could be explained by a higher total dose (12960 J) delivered to the tumors [22]. Five other patients in the Krishnamurthy series harbored permanent deficits occurring several days after treatment, linked to intracranial hypertension [13]. In the above-mentioned publication, iPDT was performed with HpD agent, which is not selective, and the total energy dose delivered in these patients were higher (>4400 J). The occurrence of neurological deficits was associated with the location of the lesion and the illuminated volume. The white fiber tracts in the neighbor of the illuminated volume could be impacted by edema, such as the arcuate fasciculus, optic radiation or the corticospinal tract. A preoperative deficit was noted as a predictive factor of neurological worsening after iPDT [13]. If we focus on iPDT using 5-ALA, no permanent deficit was reported.

Additional complications were reported when a concomitant craniotomy, tumor resection and intracavitary illumination were carried out (Table 3). Muller et al. performed the resection, intracavitary and iPDT during the same procedure [14,15]. They reported a mortality rate of 4-5% with a complication rate up to 26%. Muller et al. used HpD. It competed to the occurrence of postoperative edema and neurological deficit, in particular permanent deficits. The cases of infection were reported by Origitano et al. who performed cavitary PDT combined with iPDT [16]. Although skin sensitization is classically mentioned as a PDT adverse event, it occurred in only two (1%) patients after HpD iPDT, with no clinical sequelae (no reported cases with 5-ALA).

As a consequence, stand-alone iPDT appears to be safer than combined with intracavitary PDT. The use of a selective photosensitizer (5-ALA PpIX induced) avoided any permanent neurological deficit and should be recommended for cerebral treatment.

4.4. Oncological outcomes

Interstitial PDT for brain tumors is well tolerated, with a median Karnofsky PS of 79 at discharge (preoperative median Karnofsky PS was 84). The overall response rate (corresponding to the tumor shrinkage after treatment and the contrast intake regression) was 92%, with an even higher value in the glioma subgroup in comparison with other type of lesions.

Regarding high-grade glioma, the local control is all the most important to delay the disease recurrence which occurs in more than 85% in the 2 cm around the initial lesion [29]. *An early tumor relapse is often associated with a shorten life expectancy. Interstitial PDT helps improving patient prognosis as it is able to optimize local control, reaching the deep-seated tumor cells without damaging surrounding healthy parenchyma.* For de novo glioblastoma, in comparison with Stupp et al. landmark publication in 2005, iPDT allows an increase of progression-free-survival (PFS) from 6.9 months to 14.5 months [30]. More surprisingly, for recurrent glioblastoma, the PFS was also 14 months after iPDT whereas it is usually between 5 to 7 months [31]. Regarding the overall survival (OS), it seems also enhanced with iPDT. For de novo glioblastoma, the median OS in this review was 19 months, instead of 14.6 months in Stupp et al. No clinical statistical evidence can be deduced from this comparison (comparison of a random controlled study vs. observational series). Stupp et al. is a historical control cohort with a positive signal for PFS and OS when iPDT is applied. Further clinical trials are needed here. In the case of recurrent glioblastoma, the OS of 8 months did not differ from recent literature [32]. Surprisingly, the reported median PFS (14 months) was superior to the median OS (8 months) for recurrent GBM. This can be explained by several reasons. First, the median OS and the median PFS rely on different study data (PFS: Powers, Kostron, Stummer and Johansson, OS: Muller, Origitamo, Kostron, Krishnamurthy and Beck). Second, PFS were out of range in the Stummer and Johansson studies, reporting a higher percentage of long survivors (PFS Stummer: 57 months, Johansson: 21 months) [12,19]. At the same time, none of the two above-mentioned studies reported correspondent OS, which could probably have influenced the final median OS with an increasing trend.

Interstitial PDT should be pursued in high-grade glioma patients for several reasons. It represents an interesting option for non-surgical lesions (deep-seated, or located in eloquent area) as a first line treatment before the classic radiotherapy/chemotherapy scheme. In other cases, some could advocate for combined approach associating a safe surgical resection, letting in place a tumor remnant near risky areas, to treat it secondarily with iPDT. Thanks to the double effect of iPDT, 1) immediate tumor cells killing through apoptosis and necrosis 2) pro immune response, it opens the brain blood barrier [33] and could foster the efficacy of adjuvant oncological treatments, such as radiotherapy, chemotherapy and especially promising dedicated immunotherapy (e.g., CAR T cells). Regarding recurrent HGG, iPDT is all the more interesting as a salvage therapy which could be repeated depending on the evolution of the disease, especially since in these situations resection surgery brings disappointing results.

Regarding grade III gliomas, PFS and OS data are difficult to compare to actual literature due to the evolution of medical management of these lesions through the last 20 years [34]. Thirty-three patients with high-grade gliomas harbored prolonged OS, superior to 2 years, and could be qualified as long-term survivors. Among them, seven were still alive after three years of follow-up. In this review, were reported as positive predictive factor of prolonged OS: preoperative KPS > 70 [15], complete post iPDT response on brain imaging[14], spherical/well-limited lesions, small tumor volume (<5 ml) [21], strong PpIX uptake [12]. Interestingly, Krishnamurthy in his study scaled up the energy delivered from 1500 to 5900 J without oncological benefit [13].

On the other side, iPDT does not seem beneficial for lesions such as brain metastasis or malignant meningioma. In the case of metastasis, iPDT was applied as a salvage therapy, at a time when focal irradiation

was not so common. Nowadays treatment for the same metastatic lesions would rely on stereotactic radiosurgery.

Although iPDT shows interesting results in HGG treatment, for the following reasons it is not yet a widespread technique. 1) there is no phase III clinical trial reporting a definite interest in using PDT for HGG, 2) there is no consensus toward the most beneficial indication of iPDT (recurrence, or non-surgical de novo GBM), 3) each team performing iPDT has its own material which differs from center to center. The lack of industrial support in this area makes it difficult for new teams to begin with iPDT.

4.5. Limitations

In several series, iPDT was performed in addition to intracavitary PDT after tumor resection with conventional craniotomy [14,17]. This treatment combination makes it difficult to evaluate the proper iPDT effect as a stand-alone therapy, and could overestimate the associated treatment adverse events (especially due to surgical site infection or hematoma).

No information concerning the duration of the surgical procedures has been available in this review.

The amalgam of de novo and recurrent tumors in the reviewed studies, understanding primary brain lesions and also metastases, hampers the validity of post iPDT oncological outcomes, such as PFS and OS. Among the reviewed studies, no separated results for each respective histologic type of lesion were available.

Due to the studies/case reports heterogeneity, some presented results should be taken with caution (e.g. on recurrent GBM PFS 14.0 vs. OS 8.0).

The brain tumor management has changed dramatically during the last decades, including fluoroguided resection, intraoperative imaging, postoperative conformational radiotherapy, new chemotherapy and the advent of immunotherapy. For instance, adjuvant concomitant radiochemotherapy has become a standard of care for glioblastoma since 2005 [30]. Most of the reviewed series did not include such treatments. It should modify the potential iPDT indication of previous selected patients, and the synergy of iPDT with these above-mentioned treatments still has to be evaluated [35]. For instance, the oncological outcomes after iPDT applied to astrocytomas WHO grade III are no longer valid (Table 4). Indeed, we are now far more aggressive towards WHO grade III gliomas than in the 1990s, as nowadays this type of lesion systematically benefits from adjuvant radiotherapy and chemotherapy [34].

In the reviewed studies, none reported a control group in a randomized fashion. Well-designed clinical trials are required before using PDT in such oncological indications.

5. Conclusion

Interstitial PDT for brain tumors is now performed for more than thirty years, but still at the experimental level. Initial technical issues, such as improper stereotactic optical fiber guiding, unknown optimal dosimetry or non-selectivity of the photosensitizer did not allow a wide spreading of iPDT for brain tumors. Irrespective of the methodology used in the reviewed series, clinical and oncological outcomes are promising, justifying looking forward in this field. This review helps to better understand some key points about iPDT, especially patient selection, which pathology to treat, treatment planning of optical fiber implantation, dosimetry aspect and the clinical benefits for the patients. Performing stand-alone iPDT (i.e., without combined craniotomy and intracavitary PDT), using a selective photosensitizer such as PpIX induced by 5-ALA, appears to be the best option in terms of controlling side effects, notably by avoiding the occurrence of permanent neurological deficits but also by reducing the risks of hemorrhage and sepsis. Some questions still remained unanswered, such as the interest of light fractionation to enhance the iPDT effectiveness, the degree of lesion coverage to reach optimal therapeutic effect or the potential synergy of iPDT combined with new therapies, e.g., immunotherapy, or anti-vascular endothelial growth factor treatment. Real time monitoring and individualized dosimetry also have to be explored. Clinical trials evaluating iPDT in a prospective, randomized fashion are needed.

Author contributions

Database search was performed by H-A Leroy. Writing the article: H-A Leroy. L Guérin, and A-S Vignion contributed to copyediting of the manuscript. S Mordon, N Reyns, G Baert and F Lecomte drafted and/or critically revised the work. All authors have read and approved the final manuscript.

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Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethical approval

This study was approved by our institutional review board (CHU Lille). No. 791.

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Annex 1

1st Author	Year of publication	No of patient	Photosensitizer agent	Histology
Muller	1990	50	HpD	GBM:23, Astro III:18, Malignant ependymoma:2, PNET: 1, malignant mixed glioma: 1, malignant meningioma:1, metastasis: 5
Muller	1996	20	HpD	GBM: 11, Astro III: 9
Powers	1991	7	HpD	GBM: 1, Gliosarcoma: 1, Astro III: 4, Melanoma metastasis: 1

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(*continued*)

1st Author	Year of publication	No of patient	Photosensitizer agent	Histology
Origatamo	1993	15	HpD	GBM: 8, Astro III:6, Oligo III:1
Kaneko	1994	25	HpD	GBM: 16, Glioma III: 4, Metastasis: 5
Kostron	1996	58	HpD	GBM:50, melanoma metastasis:3, carcinoma metastasis:2, malignant meningioma:3
Krishnamurthy	2000	18	HpD	GBM: 12, Astro III: 5, malignant Ependymoma: 1
Beck	2007	10	PpIX 5-ALA	GBM: 10
Stummer	2007	1	PpIX 5-ALA	GBM
Kaneko	2011	27	HpD	GBM: 18, Astro III:6
Johansson	2013	5	PpIX 5-ALA	GBM:5
Schwartz	2015	15	PpIX 5-ALA	GBM: 15

Legends: GBM : glioblastoma, Astro : astrocytoma, Olig: oligodendroglioma, PNET: primitive neuro ectodermal tumor. Roman numerals correspond to the histology WHO classification grade. HpD: Hematoporphyrin derive agent. PpIX 5-ALA: protoporphyrin IX induced by 5-aminolevulinic acid.

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