Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 16, Issue 2, 2026, 65
https://doi.org/10.33263/BRIAC162.065

Brain Tumors and the Chemistry of Photodynamic Therapy

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Received: 25.12.2024; Accepted: 10.05.2025; Published: 15.04.2026

Abstract: Photodynamic therapy (PDT) offers a promising, minimally invasive treatment for central nervous system tumors, including glioblastoma and meningiomas. It works by activating photosensitizers with light, generating reactive oxygen species that selectively destroy tumor cells. Recent advancements in photosensitizers, nanomedicine, and combination therapies have improved efficacy and reduced side effects. Despite ongoing challenges in clinical implementation, PDT demonstrates significant potential in improving prognosis and quality of life in patients with aggressive brain tumors.

Keywords: brain tumor; glioblastoma; meningioma; photodynamic therapy; photosensitizers.

1. Introduction

The body's central nervous system (CNS) is composed of the brain and spinal cord. The brain is the center of thought, memory, and emotion. In addition, it controls the 5 senses (smell, touch, taste, hearing, vision) [1]. It also controls movement and basic bodily functions (heartbeat, circulation, breathing). The spinal cord consists of nerves that carry information back and forth between the body and the brain [2-4]. Brain tumors and other central nervous system (CNS) tumors, although rare, have significant mortality and morbidity in all age groups. Along with cardiovascular diseases, they are one of the most common causes of death. Despite years of research into the etiology of these tumors, no single risk factor has been identified for most cases. There are two main risk factors for the development of brain and other CNS tumors in children, adolescents, and adults that have been well established. These are inherited disorders of a single gene and ionizing radiation [5-9]. Primary brain tumors (BTs) account for about 1% of all newly diagnosed cancers in the United States and about 2% of cancer deaths [10,11]. Tumors of the CNS area are heterogeneous and include tumors of the brain, cranial nerves, spinal nerves, and meninges. There are well over 100 histological types, classifying them by cell origin and by other histopathological features [12,13].

Chemotherapy, radiotherapy, and surgery, as the basic methods of cancer treatment, are associated with adverse side effects, poor tolerance of chemotherapeutic drugs, or radioactive damage caused by radiotherapy, which significantly limit the therapeutic effects and reduce the quality of life of patients. A new way to alleviate these problems seems to be photodynamic therapy. PDT, as a non-invasive cancer treatment, is more target-specific and causes less damage to surrounding healthy tissues than its alternatives (Figure1). To achieve better therapeutic outcomes, combining PDT with conventional treatments may prove to be a good direction [14-16].

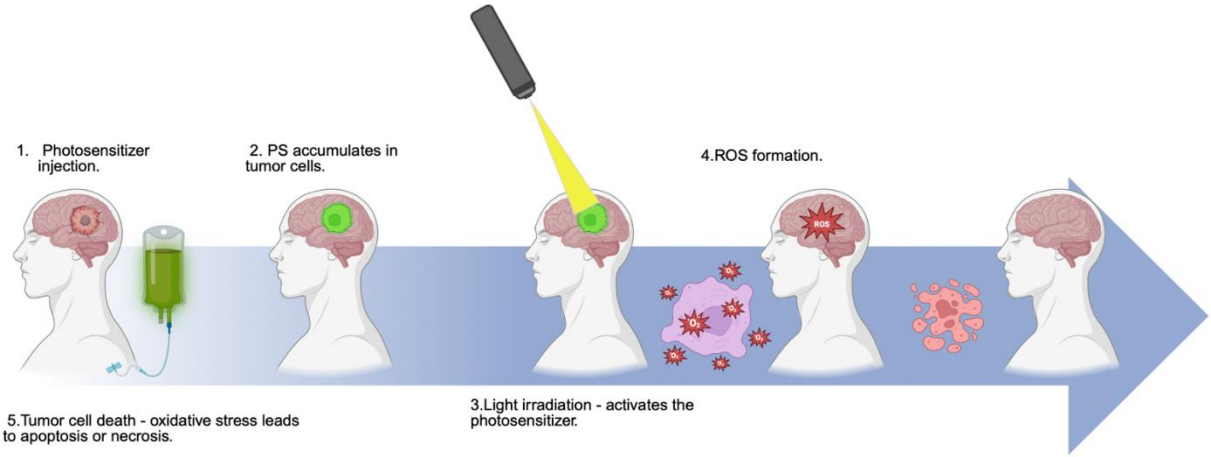


Figure 1. Photodynamic therapy in brain tumors. The mechanism of PDT in brain tumors involves three key components. PS is a light-sensitive molecule preferentially taken up by tumor cells. Light Source: Specific wavelength light activates the photosensitizer. Molecular oxygen present in tissues is converted into reactive oxygen species. The process proceeds through the following steps: 1. Photosensitizer uptake, the photosensitizer is administered and accumulates in tumor tissues due to enhanced permeability and retention (EPR) or specific targeting. 2. Irradiation, tumor tissue is exposed to light of an appropriate wavelength to excite the photosensitizer. 3. Energy transfer, the excited photosensitizer undergoes intersystem crossing to a triplet state and transfers energy to the surrounding molecular oxygen. 4. ROS generation, this interaction produces singlet oxygen and other ROS, which induce oxidative stress, damaging cellular components like membranes, proteins, and DNA. 5. Cell death, the damage triggers apoptosis, necrosis, or autophagy, which lead to tumor cell death.

PDT is mainly categorized according to the photosensitizers, light sources, and treatment methods employed. Since molecular oxygen serves as a substrate for the production of singlet oxygen and other reactive oxygen species, it is essential to the photochemical reactions of PDT [17]. The triplet state of molecular oxygen usually consists of two unpaired electrons with an electron spin of S=1. The electrons are paired when they are converted to the singlet state, which gives them an electron spin of S=0 [18]. Oxygen facilitates two primary kinds of reactions in PDT. A proton or electron is transferred to the substrate by the excited photosensitizer in type I reactions, creating radicals or radical ions that combine with oxygen to form oxidized products [19,20]. Singlet oxygen, the most harmful chemical produced during PDT, is produced in type II reactions when the photosensitizer directly transfers energy to oxygen [21]. Due to its high reactivity and relatively long lifetime, singlet oxygen is especially effective because it can permeate the cellular milieu over short distances. PDT involves exposing tumor tissues to non-ionizing light with a wavelength that corresponds to the photosensitizer's absorption spectrum [22]. In PDT, ROS plays a central role in achieving therapeutic effects. The generation of ROS in PDT relies on the interaction of light, a photosensitizer, and oxygen, leading to oxidative stress and cellular damage in targeted tissues [23,24]. A photosensitizer is administered to the patient and selectively accumulates in the target tissue (e.g., tumor cells) [25]. Upon exposure to light of a specific wavelength, the

photosensitizer absorbs energy and transitions to an excited singlet state (^{1}PS*). The excited singlet state of the photosensitizer can undergo intersystem crossing to a more stable triplet state (^{3}PS*). The triplet-state photosensitizer interacts with molecular oxygen (O_2) present in tissues, leading to two primary pathways for ROS generation [26]. Type I reaction is due to direct electron transfer between the photosensitizer and substrate, or oxygen generates superoxide anion (O_2^-), hydroxyl radical (·OH), and hydrogen peroxide (H_2O_2). Type II reaction occurs when energy is transferred from the triplet-state photosensitizer to molecular oxygen, producing singlet oxygen ($^1O_2$), a highly reactive form of oxygen [27,28]. Singlet oxygen ($^1O_2$) is the predominant ROS in PDT, responsible for most of the cytotoxic effects. It reacts with cellular components like lipids, proteins, and nucleic acids [29]. Superoxide anion (O_2^-) and hydroxyl radicals (OH) are formed through secondary reactions; these ROS amplify oxidative stress and contribute to cellular damage [30]. Hydrogen peroxide (H_2O_2) is less reactive than other ROS but can diffuse and cause damage in neighboring cells [31]. ROS generated during PDT have a localized and multifaceted impact on target tissues, like direct cytotoxic effects, vascular damage, and immune activation. ROS has a short half-life and limited diffusion range, ensuring selective damage to light-exposed areas [32].

X-ray photodynamic therapy (X-ray PDT) is an innovative approach combining radiotherapy with photodynamic therapy to treat tumors, including those in the central nervous system (CNS) [33,34]. It leverages X-rays to activate photosensitizers or scintillators, which generate reactive oxygen species (ROS) to induce tumor cell death. Unlike traditional PDT, which relies on visible light with limited tissue penetration, X-ray PDT uses the deeper tissue penetration capabilities of X-rays, making it suitable for treating deeply located CNS tumors [35,36]. In CNS tumors, X-ray PDT offers several advantages, such as improved precision in targeting malignant cells while sparing healthy tissue and the potential to overcome the blood-brain barrier limitations [37]. It holds promise for addressing therapy-resistant tumors like glioblastomas. However, clinical translation faces challenges, including optimizing photosensitizer delivery, minimizing off-target effects, and ensuring safe dose thresholds. Research is ongoing to refine this method for effective CNS tumor management.

The purpose of our review is to introduce the mechanisms of a variety of brain tumors and the importance of photodynamic therapy. In our narrative review, we introduced the reader to the chemistry of brain tumors, with a focus on photodynamic therapy as a potential treatment. Using databases such as Google Scholar and PubMed, we considered papers focusing on the keywords we wanted to present in the paper.

This study builds on recent findings in the application of PDT for the treatment of brain tumors, an area that continues to show significant promise. It offers a detailed examination of the developments, focusing on the fundamental mechanisms by which PDT exerts its therapeutic effects and how these mechanisms interact with the unique molecular and genetic landscapes of different brain tumor subtypes. The novelty of this review lies in its comprehensive synthesis, integrating current knowledge of tumor biology with advances in nanotechnology — such as targeted drug delivery systems, nanoparticle-mediated photosensitizer transport, and precision imaging techniques — that aim to overcome challenges such as limited light penetration, tumor heterogeneity, and treatment resistance. By bridging basic science with cutting-edge technological innovation, this review provides a forward-looking perspective on optimizing PDT strategies to improve clinical outcomes for patients with brain tumors.

2. Meningioma

Meningiomas account for approximately. 36% of cases and 53% of benign CNS tumors [38,39]. They are considered benign and are usually diagnosed incidentally [40]. As for their incidence, it increases significantly with age [41]. Their diagnosis is based on radiological examination, and when imaging studies accurately indicate a meningioma, a biopsy is not necessary [42]. Typically, tumor growth (asymptomatic meningiomas) is linear, with a rate of about 2-4 mm/year [43]. However, there are cases where it may not change in volume or may result in exponential growth [44].

The WHO distinguishes between meningiomas in different grades [45]. Grade I meningiomas typically present a range of differentiated histologic patterns that can mimic other types of tumors. Atypical meningiomas (grade II) are likely to have clear cell and choroidal histology. However, anaplastic or malignant meningiomas in grade III may have papillary or rhabdoid histology. Immunohistochemical markers for meningioma identification include epithelial membrane antigen, somatostatin receptor 2A, progesterone receptor, and estrogen receptor [46-48]. According to a genome-wide analysis, four mutually exclusive pathways have been identified that may contribute to meningioma development [49,50]. These are: increased hedgehog signaling (SMO, SUFU, or PRKAR1A mutation) - Smoothened class receptor (SMO) is the coding gene that is a smoothed homolog of the transmembrane receptor protein. It is responsible for transmitting signals from Hedgehog ligands towards cells, which leads to constitutive activation of SMO. According to research, SMO and mouse thymus virus oncogene AKT1 homolog 1 can lead to the activation of the PI3K - AKT - mTOR pathway. Additionally, it is quite common and is usually associated with meningiomas that are in the skull base [51,52]. Studies suggest that AKT1 mutations are closely associated with leptomeningeal tumors (grade I) located in the spine and skull base [51,53]. However, somatic mutations in codon 17 are associated with a higher risk of recurrence [53]; TRAF7 (KLF4 mutation, activation of the PI3K pathway) - TRAF7 mutations are observed in approximately 25% of grade I and II meningiomas. The most common change occurs in the WD40 domain, which is involved in the regulation of JUN N-terminal kinase (JNK) signaling and p38 mitogen-activated protein kinase (MAPK) [49,54,55]. According to the literature, it is possible that the TRAF7 mutation may be associated with changes in AKT1, Kruppel-like factor 4 (KFL4), or with a change in the catalytic alpha subunit of phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) [53]. Additionally, PIK3CA mutations are mutually exclusive with AKT1, SMO and NF2 and can rarely co-occur with TRAF7 mutations [53]; POLR2A mutations – mutations occur at two points in the A subunit of RNA polymerase II (POLR2A) and are closely related to the histology of the meninges [50]; other rarer mutations - knowledge about the molecular changes in grade III meningiomas is significantly limited because they occur rarely. In atypical meningiomas, increased expression of the EZH2 homolog enhancer is observed, interacting with epigenetic mechanisms [56,57]. It is probably a marker characterized by aggressiveness and a higher degree [58]. According to research, the Duchenne muscular dystrophy (DMD) gene, which encodes dystrophin, has also been found to be mutated in meningiomas [59]. Additionally, KDM5C, KDM6A mutations, or a mutation that is actin-dependent and associated with somatic SWI/SNF, as well as the regulation of proteins that belong to the B chromatin subfamily 1 (SMARCB1), are likely to lead to epigenetic modifications [51]. TERT promoter mutation has never been detected in atypical meningiomas de novo, although it is found in secondary atypical meningiomas [60,61]. Studies

illustrate the role of TERT promoter changes as a prognostic marker of relapse and survival. Its mutation in meningiomas is associated with a worse prognosis, with shorter overall survival, regardless of stage, according to the WHO [62-65]. Table 1 presents molecular changes.

Table 1. Molecular changes in meningioma [51-54,57, 66-79].

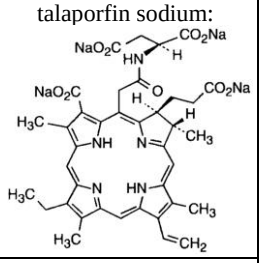
Gene	Molecular changes and pathway	Clinical significance
SMO	Leu412Phe and Trp535Leu mutations, Activation of the PI3K–AKT–mTOR pathway, Genome stability	Relatively common oc currence; Location – skull base
AKT1	p. Glu17Lys mutation, Activation of the PI3K–AKT–mTOR pathway, Genome stability	Relatively common. Location - spine, base of the skull
TRAF7	WD40 domain mutations, Signaling of N-terminal JUN kinase (JNK) and p38 mitogen-activated protein kinase (MAPK),	Up to max. 25% of grade I and II meningiomas. Location - anterior and middle skull base
KLF4	High cooccurrence rate with TRAF7 mutations, oncogenic activation, and tumor suppression,	Approximately half of the meningiomas are not mutated in the NF2 range; Location - medial and lateral skull base
POLR2A	Mutation p. Gln403Lys, p. Leu438_His439del,	Location - sellar tuberculosis
NF2	Deletion of chromosome 22q12, Genome instability	Location - hemispheres. Occurrence - often multiple
BAP1	There are many mutations	Early cancer recurrence
Epigenetic modificatio ns	Mutations in KDM5C, KDM6A, SMARCB1, EZH2	10% of meningiomas other than NF2. EZH2 mutation correlates with aggressiveness
CDKN2A	Somatic mutations and homozygous losses	Higher risk of recurrence

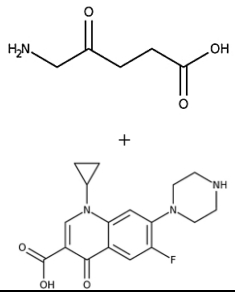
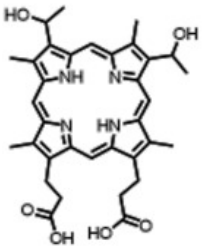
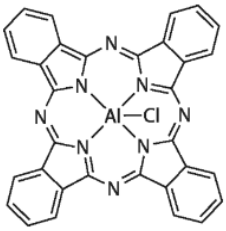
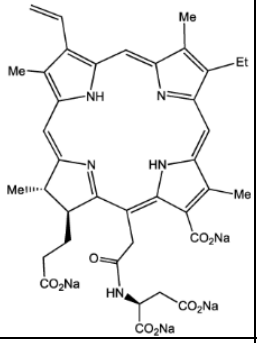
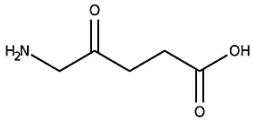
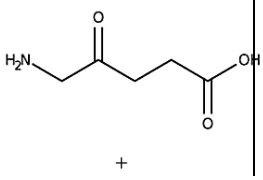
Studies show that the basic molecular change in meningiomas is the deletion of chromosome 22q12, encoding the tumor suppressor gene Merlin (neurofibromin 2, NF2). It is present in nearly half of all cancers studied [51,80]. The NF2 mutation has been found to contribute to the development of meningiomas and appears to be closely related to fibroblastic meningiomas [51,71]. In terms of NF2 inactivation, genomic instability of the tumor and characteristic multiple localization in the hemispheres are observed [54]. Currently, it has not been thoroughly investigated how the process of NF2 inactivation affects the development of meningiomas. However, hypotheses suggest that Merlin may exert a regulatory effect on cell proliferation [81]. Additionally, studies report that it can activate the mammalian target of rapamycin (mTOR) pathway during cancer development [82,83].

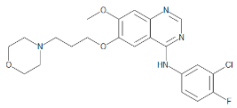
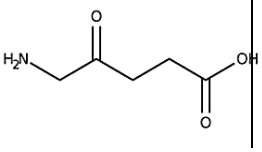
2.1. Meningiomas and photodynamic therapy

For the treatment of meningiomas, we can use PDT therapy. Below we present the currently available results (Table 2).

Table 2. PDT in meningiomas [84-91].

Authors	Year	In vitro/*in vivo*	Cell line	PS	Laser	Result
Ichikawa *et al*. [84]	2019	In vitro	human malignant meningioma cell line HKBMM	talaporfin sodium: 	3.4 mW/cm^2 and 1 J/cm^2	PDT NPe6 induced dose- and time-dependent apoptosis in human malignant meningioma HKBMM cells. At a high concentration of NPe6, however, it induced necrosis.
Cornelius *et al*. [85]	2014	In vitro	malignant human meningioma cell line (KT21-MG)	5-ALA (+ciprofloxacin)	635nm	Ciprofloxacin and longer ALA incubation time significantly increased the lethal

Authors	Year	In vitro/*in vivo*	Cell line	PS	Laser	Result
						effect of 5-ALA PDT on meningioma cells.
Kostron *et al*. [86]	1988	*In vivo* (2 patients)	one malignant meningioma, one melanoma metastasis	Hematoporophyrin derivative 	630nm	PDT of malignant gliomas indicates that PDT might be a valuable addition to our armament in the treatment of such tumors
Malham *et al*. [87]	1996	In vitro	human meningioma cells	aluminum phthalocyanine chloride, aluminum phthalocyanine disulphonate, aluminum phthalocyanine tetrasulphonate, and haematoporphyrin derivative 	broadband red light (5 muW/cm^2)	AlPc was found to be 400, 10,000, and 250 times more potent than AlS2Pc, AlS4Pc, and HpD, respectively, as an in vitro photosensitizing agent for meningioma cells.
Takahashi *et al*. [88]	2018	In vitro	KMY-J (rat MM)	Talaporfin 	664nm, 3.4 mW/cm^2	mRNA expression of heme oxygenase-1 was significantly increased by TS-PDT treatment
El-Khatib *et al*. [89]	2015	In vitro	primary meningioma cell lines	5-ALA 	635nm, 18.75 J/cm^2	Dose-dependent cytotoxic effects of 5-ALA-PDT on primary cell lines of meningiomas.
Sun *et al*. [90]	2013	In vitro	malignant meningioma cell line (IOMM-Lee)	5-ALA (+gefitinib 0.01-1.0 μM) 	635 nm	Gefitinib can inhibit ABCG2-mediated PpIX efflux from malignant brain tumor cells to increase the intracellular PpIX and thereby enhance the PDT effect.

Authors	Year	In vitro/*in vivo*	Cell line	PS	Laser	Result
						
Tsai *et al*. [91]	1999	In vitro	CH-157MN meningioma cells	5-ALA 	11 J/cm^2	ALA-PDT was more effective in killing U-105MG glioma cells than CH-157MN meningioma cells.

3. Tumors of the Sellar Region

Tumors of the sellar region are relatively rare, malformation tumors with low histological grade. There are five histological subtypes: adamantinomatous craniopharyngioma (ACP); papillary craniopharyngioma (PCP); pituitary cystoma, granular cell tumor of the sellar region, and spindle cell oncocytoma; pituitary adenoma/ PitNET, pituitary blastoma. They all differ in their genesis and age distribution. ACP is diagnosed at the bimodal peak of incidence (5–15 years and 45–60 years). PCP, on the other hand, is detected primarily in adults who are in the fifth or sixth decade of life. Tumors of the sellar region are usually located around brain structures that are very important for physical and mental development and are located along the pituitary-hypothalamic axis to the ventricle [92].

3.1. Adamantinomatous and papillary craniopharyngiomas.

Patients diagnosed with craniopharyngiomas experience symptoms closely related to the location of the tumor near the visual pathways, hypothalamus, and pituitary gland. These include intracranial pressure, endocrine deficiencies, and visual defects (Figure 2). The treatment of this cancer is not specific and does not always result in a cure; hence, the need for surgery and then radiotherapy. Recently, the use of targeted therapies has begun, primarily in PCPs, but also in ACPs. Research confirms the high survival of patients. However, the consequences of this cancer and its treatment can often lead to very serious comorbidities that affect, among others, the quality of life [93].

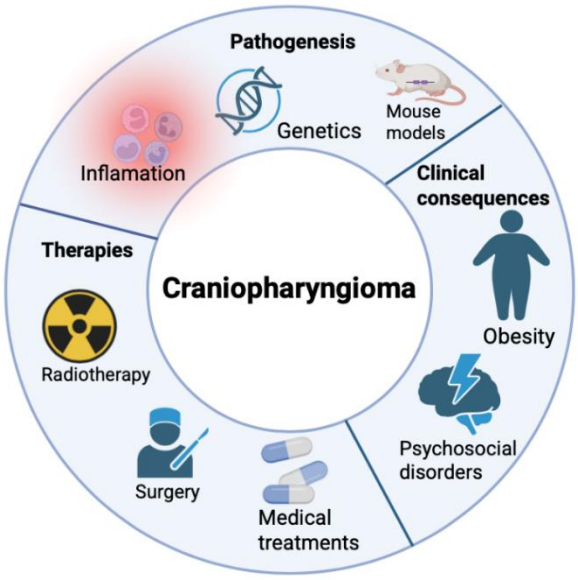


Figure 2. Characteristics of craniopharyngiomas.

CP subtypes have different pathogeneses, proven by genetic analyses. ACP has mutations in CTNNB1, encoding the regulator of the WNT signaling pathway, β-catenin [94-102]. Moreover, activating mutations in the exon 3 area lead to overexpression of β-catenin target genes (AXIN2, LEF1) [103]. In this case, beta-catenin is not phosphorylated by GSK3B, and unphosphorylated beta-catenin accumulates in the nucleus, disrupting the regulation of cell proliferation [104,105]. Many publications report CTNNB1 mutations in approximately 60% to 75% of ACPs, but more sensitive sequencing and analytical methods have shown CTNNB1 mutations in up to 100% of samples [94-97,102]. These methods are much more effective at identifying mutations with a low allelic fraction in samples with low tumor epithelium content. CTNNB1 mutations are clonal and have the status of driving events [97,99,102]. In the field of ACP from wild-type CTNNB1, mutations have been identified that inactivate the germline and somatic line in APC, which indicates that mutations in other components of the WNT signaling pathway may, in some situations, contribute to the pathogenesis of the AC subtype [106].

In the case of PCP, they do not show the CTNNB1 mutation, only the somatic BRAF V600E mutation [97]. It leads to activation of the MAPK signaling pathway, which, in turn, causes uncontrolled cell proliferation. Accordingly, the mutual exclusivity of the 2 CP variants makes them quite an important molecular diagnostic tool for histopathological differentiation. Recently, two cases of ACP have appeared in which the coexistence of both mutations was observed [97]. The presented insight into the molecular pathology of CP tumors determines the possibility of using targeted therapies. Based on studies of PCP patients with the BRAF V600E mutation, BRAF inhibitors have achieved very good results [108-112]. Another very promising pathway is the Sonic Hedgehog (SHH) pathway. It is involved in the regulation of cell differentiation and proliferation as well as in the proper development of organs [113,114]. The SHH pathway is involved in the initiation and growth of tumors across various cancer types [115]. In ACP, a significant increase in SHH levels is observed in human samples and mouse models, suggesting it may be a potential therapeutic target [98,116-119]. However, Carreno *et al*. demonstrated that inhibition of the SHH pathway using the inhibitor vismodegib led to a significant reduction in median survival in a murine model [120]. Therefore, they also observed inhibition of the SHH pathway, leading to increased cancer cell proliferation in cultures of human ACP explants. Currently, the use of SHH inhibitors in patients with ACP is considered contraindicated.

The latest discoveries in the field of genetic profiling of craniopharyngiomas allow the definition of new scenarios for developing targeted therapies based on entirely new biomolecular markers. However, the rarity of this type of tumor requires a multidisciplinary approach, including a team of experts, including endocrinologists, neurosurgeons, neuro-ophthalmologists, neuroradiologists, etc., to precisely define the impact on postoperative outcomes and long-term prognosis in this regard [120].

3.2. Pituitary adenoma/PitNET.

Pituitary adenomas (PA) are neuroendocrine tumors of the pituitary gland (PitNET). They constitute approximately 15% of all CNS tumors [121]. These are common intracranial tumors, characterized by different phenotypes. Many of them are rare and are not part of genetic diseases. Genetic tests have enabled the identification of somatic or germline mutations associated with pituitary tumors. This allowed us to deepen our knowledge of pituitary tumorigenesis. This type of testing can lead to early diagnosis, which will ultimately lead to

better outcomes. Additionally, molecular mechanisms will allow the introduction of new targeted therapies [122]. Most PitNET tumors are benign, i.e., they grow slowly and do not metastasize, which is why they are called adenomas. However, it sometimes happened that they attacked neighboring structures, leading to relapses. The 2022 WHO classification specifies that it is a neuroendocrine tumor of the pituitary gland, and this is consistent with the terminology used in the case of other types of neuroendocrine tumors. In turn, aggressive PitNETs are invasive and proliferative tumors with frequent recurrences. Additionally, they are resistant to conventional treatment. On the one hand, most tumors grow slowly and are benign, but on the other hand, a significant percentage of tumors are invasive or are characterized by a high recurrence rate, making treatment difficult [123]. To date, no morphological or histological marker has been identified to predict the aggressive behavior of this tumor type. Further multidisciplinary research is therefore necessary [124]. It should be noted that the term pituitary adenoma includes various types of tumors that originate in the anterior lobe of the pituitary gland. Their treatment is associated with high health care costs and may also lead to excessive or insufficient secretion of hormones, visual defects, and other types of disabilities [125,126]. According to research, these tumors are monoclonal, i.e., they result from the uncontrolled expansion of a single somatically mutated cell [127-131]. However, there are studies that show evidence of multiclonality in specific pituitary adenomas [132-134]. The exact cell of origin is currently unknown and may vary depending on the type of cancer [135,136]. There are suggestions that the cell of origin may be differentiated into anterior pituitary progenitor cells or pituitary stem cells [137-139]. An imbalance in pro- and anti-proliferative cell signaling is one of the hallmarks of cancer. This aberration is present in the signaling of pituitary adenoma cells and reveals decreased growth-suppressive signals and excess progression signaling. Researchers have shown that in most human pituitary adenomas, a reduction in the level of GADD45γ is observed, a protein that is involved in the cellular response to DNA damage and is also a negative regulator of cell growth [140,141]. Another type of tumor suppressor is MEG3, which is a gene encoding long non-coding RNA (lncRNA) [140,141]. MEG3 typically inhibits cancer cell growth, in part by upregulating p53 and p53-dependent processes [142]. p53 is an instrumental tumor suppressor that is rarely mutated in pituitary adenoma, but the p53 pathway is often dysregulated [134,143]. Another important aspect is the gene that transforms pituitary tumor (PTTG). It is identified as a proto-oncogene and plays a major role in the development of pituitary adenoma cancer. It was first isolated from pituitary tumor cells from a rat [144]. This is a type of human securin protein that stops the onset of anaphase and prevents the separation of sister chromatids until all chromosomes are properly assembled at the metaphase plate. Studies suggest that PTTG may contribute to tumor growth through SH3-mediated signaling pathways and by activating growth factors [145]. However, the detailed mechanism of action of PTTG is currently unknown. There are studies suggesting that hyperstimulation of the hypothalamus contributes to the development of pituitary adenomas. It is possible that excessive stimulation of the hypothalamus of the pituitary gland may lead to growth and, consequently, cancer [146], but Clayton *et al*. refuted the significance of this phenomenon [133]. Other sources, however, suggest that the imbalance in growth signaling may be caused by an excess of trophic and neurotrophic factors [147,148]. Wang *et al*. showed in their study that increased methylation of the LAMA2 gene promoter significantly reduces LAMA2 expression, thereby facilitating pituitary adenoma invasion, in a trial comparing invasive with non-invasive adenomas. LAMA2 is a component of laminin, an extracellular matrix protein. The study demonstrated that LAMA2 is mediated by the PTEN-

PI3K/AKT pathway, which may be significantly influenced by small molecule inhibitors. Additionally, researchers provided *in vivo* evidence of LAMA2 overexpression or demethylation, which largely inhibited tumor growth. They therefore determined the clinical potential of the gene as a prognostic marker [149]. In the study by Cheng *et al*., genes that were associated with invasion in the presence of genome-wide DNA methylation and RNA microarray analysis were identified in a series of 68 non-functioning adenomas. The entire series is divided by degree. Therefore, the results showed differential expression of 115 genes, with a quite strong, but negative, correlation between promoter methylation and other gene expression levels. 19 of them were involved in specific ontologies and gene pathways. More detailed analyses allowed the identification of several genes showing a strong but positive correlation between methylation and expression. It was found that many genes played an important role in oncogenesis. These genes were considered potential markers of tumor invasion and as targets for gene therapy [150]. Another study by Cheng et al. showed that caveolin-1, a protein involved in intracellular signaling and known to act as a tumor suppressor or oncogene in various types of cancer, is increased in invasive pituitary adenomas compared to the non-invasive control group [150]. A very interesting phenomenon was also observed during this study: knocking down the gene resulted in a significant reduction in cell migration and invasiveness, leading to Caveolin-1 being characterized as an oncogene in this specific subgroup and as a new therapeutic target. All innovations around genomics, epigenomics, and transcriptomics are currently the basis for therapeutic interventions against cancer. According to research, pituitary adenoma growth is primarily driven by processes such as unrestrained cell cycle progression, deregulation of growth pathways, proliferation, and abnormal epigenetic regulation of gene expression (Table 3). Many studies have attempted to establish links between gene mutations and cancer progression, but a precise understanding of the entire mechanism remains elusive now [151].

3.3. Photodynamic therapy in pituitary adenomas/PitNET.

Table 3. PDT in pituitary adenomas [152-156].

Authors	Year	In vitro/*in vivo*	Cell line	PS	Laser	Result
Neumann *et al*. [152]	2016	In vitro	immortalized rat pituitary adenoma cells (GH3) and human pituitary adenoma cell cultures	5-ALA	635nm, 625s, 18.75J/cm^2	Human pituitary adenoma cells could also be killed by 5-ALA PDT; however, this required higher 5-ALA concentrations.
Marks *et al*. [153]	2000	*In vivo*	12 patients with recurrent pituitary adenomas	Photofrin	630nm	The primary endpoints were visual, endocrine, and radiological improvement. The incidence of side effects was also monitored. The longest follow-up is 2 years. Most patients suffering from visual acuity or field defects have shown improvement when followed for 12 months or more.
Nemes *et al*. [154]	2016	In vitro	GH3 and AtT-20 cell lines	5-ALA	635nm, 25 J/cm^2	GH3 cells showed a heterogeneous uptake of 5-ALA in the flow cytometry profile, but not constant high concentrations; they might have a 5-ALA efflux mechanism, which still needs to be determined. In the case of AtT-20, the cells might need a longer time for the uptake due to their size or slow metabolism.

Authors	Year	In vitro/*in vivo*	Cell line	PS	Laser	Result
Cole *et al*. [155]	2008	In vitro	pituitary adenoma rat cell line, GH4C1	hypericin	600nm	The mean Photofrin level in pituitary adenoma tissue was 6.87 ng/mg (95% confidence interval [CI] 3.99-9.75).
Kirollos *et al*. [156]	1998	*In vivo*	Different subtypes of human pituitary adenoma cells were implanted subcutaneously into mice	polyhae matopor phyrin	630nm, 10 - 75 J/cm^2	Histopathological examination of the treated implants consistently showed tumour vascular changes with acute inflammatory reaction, interstitial haemorrhage, and evidence of cell death at higher doses of light.

4. Malignant Glioma - Subclassifications Based on Genetic Background

Gliomas are the most common primary tumors of the brain and spinal cord. They exhibit characteristics of normal glial cells, but whether these tumors originate from normal glial cells, glial precursors, neural stem cells, or other cell types remains under further investigation [157]. Until a certain point, gliomas were diagnosed and classified based on histopathology. The WHO's 2007 classification included the main groups of glial neoplasms, namely astrocytic tumors, oligodendroglial tumors, oligoastrocytic tumors, lining tumors, neuronal tumors, and mixed neuronal-glial tumors [158]. The above groups also included more limited grade I tumors (pilocytic stromal tumors, pleomorphic xanthoastrocytomas, and giant cell subcapsular stromal tumors) as well as the more common tumors, which include infiltrating gliomas, also including anaplastic scapulomas and anaplastic stromal tumors of grade II, anaplastic scapulomas, anaplastic stromal tumors, anaplastic scapulomas, anaplastic lining tumors and grade IV glioblastoma multiforme (GMB). The classification was established in 2007 as the basis for histological diagnosis and assessment of malignancy. Jenak had some shortcomings and limitations. One of them was the considerable variability between observers. There are several different incisions in this regard. Concordance among the group of individual neuropathologists who reviewed the case is about 52%, although differences of opinion relate to the classification of astrocytic tumors and sclerosing tumors, and to differences between observers in differentiating grade II and grade III tumors [159,160]. As a result, diagnostic criteria that distinguish stromal tumor from sclap granuloma work very well in prototypical cases; however, they can be inaccurate in most tumors that have a certain degree of mixed features [161].

In recent years, more time has been devoted to molecular alterations in gliomas, leading to improved diagnostic criteria, prognostic biomarkers, and the development of new capabilities applicable to therapies. WHO created the new 5th edition classification where gliomas, glioneuronal tumors, and neuronal tumors are divided into adult-type diffuse gliomas, pediatric-type diffuse low-grade gliomas, pediatric-type diffuse high-grade gliomas, circumscribed astrocytic gliomas, glioneuronal and neuronal tumors, and ependymal tumors [13].

One example of a molecular biomarker of glioma subtypes with prognostic, predictive, and clinical applications is MGMT (O6-methylguanine-DNA methyltransferase) promoter methylation. The methylation status of the MGMT promoter has become one of the most important determinants of prognosis and, additionally, a potential predictor of response to TMZ [162-164]. Temozolomide is thought to methylate purine bases (including the O6 and N7 sites on guanine or the N3 site on adenine). The induction of O6-methylguanine is the main cytotoxic event that leads to the insertion of thymine instead of cytosine during cell replication, which

consequently causes double-strand breaks, i.e., failure of DNA replication leading to cell death [165]. Thus, MGMT, as a mismatch repair enzyme, removes O6-methylguanine adducts induced by alkylator chemotherapy, and through this, it abolishes their cytotoxic effects. Thus, it has been suggested that higher levels of MGMT lead to resistance to temozolomide [165]. MGMT has not yet been used for treatment and is still under discussion [166]. Methods for assessing MGMT status known as of today are listed in Table 4 [162,166-170]. There is evidence of inconsistency between methylation status and protein expression levels, along with variable reports relating the correlation to patient outcomes [162,168,171-178].

Table 4. Methods for assessing MGMT status [162,166-170].

Parameter	Method	Description
Methylation of promoter	Non-quantitative methylation-specific polymerase chain reaction (MSP)	DNA is treated with bisulfite, resulting in the conversion of unmethylated cytosine to uracil, but without modifying 5-methylcytosine. Primers specific for either methylated or unmethylated sequences are used, and PCR is then performed. Analysis is performed using gel electrophoresis.
	Quantitative methylation-specific PCR (qMSP)	qMSP provides quantitative results when normalized to an unmethylated gene.
	Pyrosequencing	A method of DNA sequencing, following hydrogen-sulfur treatment and PCR, that yields a quantification of methylation for each CpG site sequenced.
	Ligation-dependent probe amplification (MS-MPLA)	Here, restriction enzymes that are sensitive to methylation are used to obtain semi-quantitative results of the methylation state.
	Infinium Methylation EPIC BeadChip Array	Methylation profiling of the entire genome, including the MGMT genomic region.
Expression of mRNA	Quantitative time-resolved polymerase chain reaction (qRT-PCR)	Measuring MGMT transcript expression
Protein expression	Immunohistochemistry	Tumor cells that have nuclear staining are treated as MGMT positive. The percentage of positive cells is assessed to define MGMT status.
Protein activity	Enzyme tests	The sample is incubated with 3H O6-methylguanine. The 3H methyl groups are then transferred to the MGMT protein.

The MGMT promoter region has a high frequency of CpG repeat sequences [179]. At CpG sites, hypermethylation mostly results in epigenetic silencing of MGMT transcripts. This results in a lack of MGMT-mediated DNA repair, which affects temozolomide sensitivity when MMR function is intact [164,176,180]. In addition, the unmethylated promoter typically results in high MGMT protein expression, enabling O6-MeG repair and further promoting TMZ resistance. A very important EORTC-NCIC clinical trial confirmed the association between MGMT promoter methylation and survival in patients with newly diagnosed glioblastoma multiforme treated with radiotherapy and TMZ. Despite the presence of TMZ in radiotherapy, patients diagnosed with MGMT-methylated glioblastoma multiforme showed a large improvement in survival. At the same time, this showed little benefit in patients with a non-methylated promoter [164,181]. Subsequent studies have confirmed the correlation between MGMT promoter methylation and patient outcomes, and thus MGMT promoter methylation has become a major marker for MGMT non-function to determine prognosis and potential response to chemotherapy [166,182]. However, it should be noted that the correlation between MGMT promoter methylation and mRNA or protein levels is not absolute [176,180]. According to the study, in terms of cancer cells, only about 50% of MGMT-negative cells are noted to exhibit promoter methylation [180].

According to Stupp *et al.*, in patients who received radiotherapy and temozolomide, MGMT promoter methylation was associated with improved median survival (about 21.7

months) compared with patients with unmethylated tumors (about 12.7 months) [182]. A large number of glioma cell lines have an unmethylated MGMT promoter and relatively low mRNA expression. The literature states that immunohistochemistry (IHC) results were not equivalent to those obtained with MSP [176]. Another study found no correlation between MGMT protein expression and methylation by MSP in 76 glioblastoma multiforme samples. Approximately 52.4% of unmethylated tumors recorded low MGMT expression, while 41.2% of methylated tumors recorded high MGMT expression [184].

The methylation status of the MGMT promoter helps predict the benefit of temozolomide in the treatment of glioblastoma multiforme (GBM). We sought a clinically optimized cutoff to select patients for treatment without temozolomide, while avoiding withholding it from those who could benefit. Low MGMT methylation (gray area) may confer some sensitivity to temozolomide, so a narrower safety margin should be considered when qualifying patients with unmethylated GBM for trials without temozolomide [185].

In addition, methylation is present in the MGMT gene. Methylation in terms of ecosan regions may lead to increased MGMT expression in specific patients. Therefore, this may in part explain the reasons for the differences in MGMT transcript levels compared to those expected based on promoter methylation status [186]. A study by Moen *et al*. evaluated the effect of gene body cytosine modification in glioblastoma multiforme [186]. It decreased MGMT expression in patients who had an unmethylated promoter, comparable to patients with a methylated promoter [187]. Gene body hypermethylation was associated with increased MGMT expression. The study also confirms that low expression of either the protein or the MGMT gene is closely associated with improved patient survival or with a treatment response, independent of MGMT promoter methylation. In addition, it is an independent marker of prognosis in patients with digitized glioblastoma multiforme [174,175,188-192].

An important element in classifying gliomas is the significance of IDH mutations. The genes that co-build isocitrate dehydrogenases (IDH1 and IDH2) are frequently mutated in many cancers. Mutations that specifically target IDH1 and IDH2 cause them to lose their normal catalytic activity, additionally produce α-ketoglutarate (α-KG), and acquire a new function, that of producing 2-hydroxyglutarate (2-HG). Thus, abnormal methylation of both histones and DNA is a common feature of cancers with IDH1 or IDH2 mutations, which can disrupt stem cell differentiation and lead to tumor formation. In line with the above, therapeutically, the unique features of IDH1 and IDH2 mutations make them good biomarkers [193].

IDH catalyzes the conversion of isocitrate to α-ketoglutarate in the conversion of nicotinamide adenine dinucleotide phosphate (NADP +) to reduced NADP + (NADPH) in the Kreb's cycle and in the cytoplasm. IDH1 and IDH2 are therefore present in a variety of cancers [193]. IDH1, as one of the three enzymes, contributes to the production of cytosolic NADPH in cells [194]. This has also been linked to the process of inhibiting apoptosis and increased cell survival or growth [195-197]. In addition, NADPH is required for glutathione synthesis, which protects cells from redox stress and increases resistance to apoptosis [195]. One recent study suggests that IDH1 and, in part, IDH2 provide abundant cellular NADPH for the processes, promoting autonomous survival with cell growth [197].

Another important consideration is chromosome 1p/19q. Information regarding the status of 1p/19q currently serves as a standard of therapeutic options in the treatment of tumors [198]. Since 1998, the codetermination of chromosome 1p/19q has been recognized as a diagnostic or prognostic marker for sclerosing tumors [199]. However, a study by Jankins *et*

al. showed that co-deletion of 2 arms of these chromosomes is caused by a balanced translocation between chromosomes 1 and 19, followed by loss of the other arms [200]. Consequently, the above mechanism explains why gliomas with a 1p or 19q deletion alone do not confer a similar survival advantage to tumors with co-deletions [201].

4.1. Neutrophils.

Neutrophils have various functions in diseases. They exert antimicrobial or inflammatory effects through phagocytosis, degranulation, and the release of neutrophil extracellular traps (NETs) [202,203]. In addition, they release decondensed DNA fibers and antimicrobial peptides, or NETs, and these net-like traps kill various bacteria, fungi, and parasites (Fig. 5) [204-207]. In recent years, there has been an increase in the importance and role of neutrophils in cancer [208]. Neutrophils have an oncogenic role, mainly through increased DNA damage, angiogenesis, and immunosuppression [209]. In addition, there are results that say there is a link between tumor initiation and progression and thrombosis, which is associated with cancer and NET (Figure 3) [210-213].

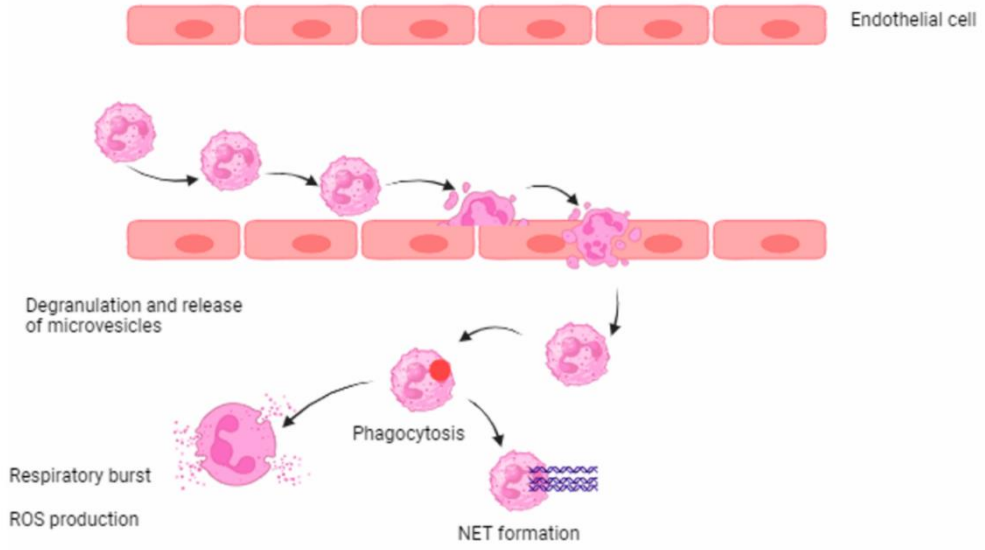


Figure 3. Inflammation and NET release.

Neutrophils are an important component of inflammation involved in cancer development and progression [214]. NLR, which is a marker of systemic cellular inflammation, is a non-invasive biomarker targeting patients with cancer. Tenpleton *et al*. calculated NLR as: NLR = neutrophil count/lymphocyte count [215]. Thus, NLR is a low-cost method, as it is very easy to determine the number of lymphocytes and neutrophils from the commonly used complete blood morphology [216]. Consequently, NLR is now a prognostic indicator of survival for many types of cancer, such as CRC, breast cancer, and gliomas [217-220]. In the field of gliomas, this NLR is often used as a parameter in both diagnosis and prediction of overall survival [221,222]. This approach has demonstrated diagnostic value in differentiating isocitrate dehydrogenase-mutant GBM (IDH-mt) from IDH wild-type GBM (IDH-wt) [223]. Auezova *et al*. found lower NLR values in patients with IDH-mt GBM [223]. Studies show that high NLR values were closely associated with significantly lower overall survival, while patients with high NLR values were more likely to have gliomas characterized by a high degree of malignancy [217]. In contrast, another study found that lower NLR levels were associated with longer overall survival during focal radiotherapy and concurrent temozolomide treatment

[225]. Balta *et al*. state that NLR can be influenced by bacterial or viral infections or by pharmacological treatments [226]. In addition, conditions such as hypertension, diabetes mellitus, metabolic syndrome, left ventricular dysfunction and hypertrophy, acute coronary syndromes, cardiovascular disease, abnormal thyroid function tests, renal or hepatic dysfunction, a history of infections, inflammatory diseases, and some medications can also affect NLR measurement [216]. Therefore, it is necessary to consider the potential effects of past or present other medical conditions or drug use when measuring NLR. Therefore, circulating neutrophils play a very important role in the diagnosis, prognosis, immunosuppression, and treatment resistance of patients with glioma [227].

4.2. Glioma stem cells.

Currently, cancer stem cells (CSCs) in gliomas, not only in this type of neoplasm, exemplify the extremely important intra-neoplastic heterogeneity. As mentioned earlier, it should be noted that in addition to providing insight into intra-neoplastic heterogeneity, it is the detailed genetic analysis of gliomas that is able to provide very important prognostic information, giving the possibility of determining the course of the disease already at the stage of diagnosis and then determining the exact help in choosing the best treatment options [164,183,199,228-231].

Gliomas, like other cancers, are composed of different cell types, including tumor cells, stromal cells, endothelial cells, and immune cells [232]. Tumor cells actively proliferate, accumulate mutations, and then form genetically differentiated clones, thereby increasing the diversity of these cells [233]. As a result of stimuli from the microenvironment, epigenetic changes are observed in certain cancer cells [234-236]. This results in a very high diversity of tumor cells, which are very specific for each individual patient or even tumor growth site [237-239]. This represents a practical aspect. It causes a difference in the clinical picture of the tumor in different patients. However, the prognosis of the disease depends on the presence or absence of drug-resistant or metastasis-giving tumor cells [240-243].

The presence of cancer stem cells (CSCs) in glioma has been confirmed by several studies [244-249]. Based on the hierarchical theory of oncogenesis, cancer originates from a mutant stem cell and has a hierarchical cell composition [251,252]. Thus, cancer stem cells occupy a place at the top of the hierarchy, while the remaining cancer cells undergo differentiation. The current view is that various transformed cells, including stem cells, progenitor cells, and differentiated cells, can serve as processing cells during tumor initiation [252,253]. Studies have used *in vivo* genetic barcoding [254] and lineage tracing via RNA sequencing analysis of single cells [255]. These studies have shown that a subpopulation of tumor cells (like a stalk) is composed of rare cells in a resting state and a large population (proliferating cells). A study by Lan *et al*. on the clonal evolution of barcode-positive glioma cells during serial xenotransplantation showed that proliferating stem cells give rise to more frequently dividing progenitor cells with maintenance potential and to non-proliferative cells. The results also revealed rare clones that significantly deviated from the proliferative hierarchy. As a result, the researchers showed that chemotherapy significantly enhances the expansion of pre-existing drug-resistant glioma stem cells [254].

Many transcription factors and structural proteins are required for the function of standard stem and progenitor cells. Glioma stem cell surface markers include CD133, CD15, integrin α6, CD44, L1CAM, CD24, EGFR, PDGFRA, A2B5 are divided in table 5.

Table 5. Molecular markers of glioma stem cells [256-268].

Cell type	Intracellular markers	Surface markers
Glioma stem cells	Sox2, Nanog, Olig2, Myc, Musashi1, Bmi1, Nestin, Oct4, Brn2, ID1	CD133, CD15 (SSEA-1), integryna α6, CD44, L1CAM, CD24, EGFR, PDGFRA, A2B5

The above approach, which is based on surface markers, is a convenient way to enrich the pool of cancer stem cells (CSCs) from the tumor mass using either flow cytometry or magnetic separation. However, studies show that not every marker is expressed in all glioma stem cells. It is possible that cells that do not express a particular glioma stem cell marker may be carcinogenic *in vivo*, but in addition, they may reproduce the initial heterogeneity of the tumor and give rise to cells that express a particular glioma stem cell marker [269-271]. Therefore, there is a need for additional functional assays to demonstrate stem cell properties and provide more precise evidence confirming that the cell belongs to the CSC subpopulation. Functional features of cancer stem cells include the formation of a specific tumor after xenotransplantation into immunodeficient animals and the ability to form spheroids in vitro [244,272]. However, isolated cells in a new microenvironment can change their state, regardless of the type of method used to enrich them. First, cell culture induces any changes in the expression of surface molecules and alters the biological state of glioma cells [273]. Studies confirm that each tumor contains distinct glioma stem cells from genetically distinct subclones, a key factor in the disagreement over glioma stem cell markers [274].

In addition, it should be noted that, in studies on intragenic cell heterogeneity, this most important information is currently provided by single-cell sequencing [275]. This type of technology includes a variety of methods to study the transcriptome, genome, methylome, and other chromatin modifications in the single-cell area [276-281]. This enables detection of cell populations and transcriptional activation of signaling pathways, but it does not provide an accurate picture of translational genomic or transcriptomic changes in the proteomic component. Therefore, it is essential to use high-throughput single-cell technologies, including imaging flow cytometry, flow cytometry, and mass cytometry, which can be combined with single-cell genetic analysis for research purposes [282-292].

Currently, there are innovative approaches that enable genetic and proteomic analysis of single cells, such as using oligonucleotide-typed antibodies that contain specific barcode sequences [293]. In addition, more complex multimodal omics approaches, which combine single-cell profiling of traits of epigenetic nature, DNA sequences, gene expression, proteome, etc., are also constantly being developed. Methods currently in use have limited efficiency and limited coverage of the epigenome, transcriptome, etc. [293].

Dirkse *et al*. showed that phenotypic heterogeneity that is based on cell membrane markers in the culture area of glioblastoma multiforme is really a dynamic process, characterized by reversible state changes [294]. The results showed that glioblastoma multiforme subpopulations possessed stem cell properties and had tumor-like effects. In addition, the researchers noted functional differences, namely differences in tumor growth in vivo, linked to the time required for subpopulations to reach the ultimate heterogeneity specified for a given environment. Wang *et al*., on the other hand, showed that gliomas, digitized in adult patients, contain a subpopulation of radial glial-like cells, with typical morphology and containing human fetal glial markers. The population studied consisted of transcriptionally dynamic clusters of cells in various resting and cyclic states. The results showed that radial glial cells can represent cells of origin or CSCs, which are at the top of the glioma cell hierarchy [295].

5. Brain Tumors and PDT – the Newest Studies from 2023 Onwards

GBM represents the most common and aggressive type of primary brain tumor originating from glial cells, with no curative treatment available for all patients [296,297]. Despite GBM's high frequency and rapid progression, physicians have achieved only limited therapeutic success [296,297]. Due to the limitations of surgery, radiotherapy, chemotherapy, and gene therapy, immunotherapy has emerged as a promising alternative, enhancing the immune system's ability to fight cancer [296,297]. However, the development of new drugs for GBM remains extremely challenging due to the need to overcome the BBB [298-300], which, together with the brain's natural immune restrictions, presents significant obstacles for therapeutic delivery. Innovative strategies include the use of exosomes as drug carriers, enabling targeted delivery of hydrophilic and hydrophobic drugs, stabilizing therapeutic compounds, and addressing multiple aspects of GBM pathology [301-303]. Furthermore, nanoparticle-based systems that deliver PD-1/PD-L1 blockade inhibitors have significantly improved anti-tumor immune responses [304,305]. Incorporating immune stimulators, such as CpG oligodeoxynucleotides or Toll-like receptor (TLR) agonists, into nanoparticles further activates immune cells, enhancing therapies for both cancer and infectious diseases [304-306]. In meningiomas, the use of 5-ALA has demonstrated benefits by increasing malignant tumor sensitivity during pediatric brain tumor PDT [307]. Additionally, the dual application of 68-Ga Dotatoc and 5-ALA fluorescence has been shown to be effective for detecting recurrent skull-base meningiomas after prior microsurgical resection and Gamma Knife radiosurgery [308]. In GBM treatment, the DOSINDYGO study, a multi-center phase II clinical trial and successor to the INDYGO project, aims to determine the maximum safe light dose for 5-ALA-mediated intraoperative PDT [309]. Another breakthrough involves the temporary opening of the BBB using microbubbles and focused ultrasound (FUS). Devices such as InSightec Ltd.'s ExAblate and CarThera's SonoCloud have demonstrated that FUS-mediated BBB disruption enables safe, localized delivery of chemotherapeutic agents, such as paclitaxel and carboplatin, in recurrent GBM patients [310,311]. In parallel, the pharmaceutical company Sonalasense is conducting the SONALA-001 Phase 0-I clinical trial (NCT04559685), investigating the safety and efficacy of sonodynamic therapy (SDT) using increasing concentrations of 5-ALA for treating high-grade gliomas [312].

6. Future Clinical Directions

Although photodynamic therapy was first introduced many years ago, its therapeutic use is still under research and in its early stages. Given the characteristics of an ideal PS, it is necessary to refine the second-generation photosensitizer to achieve the optimal effect of the substance. Ongoing research into Generation III PS could prove an effective solution, resulting in significant improvements in treatment standards for many diseases. Finding the right photosensitizer is crucial to improving PDT performance [313,314]. PDT has recently proven to be an effective treatment for solid tumors by oxidative modification, and the ECM may contribute to the cytotoxicity of photodynamic therapy. Shen *et al*. compared the liver-lacking ECM cells with the brain's ECM and observed a reduction in PDT cytotoxicity. In addition, by observing the reactive oxygen species produced by active indocyanine green in the near-infrared range, it was shown that ECM had no effect on reactive oxygen species production [315].

Accordingly, the brain's ECM can effectively increase glioma cells' adaptability to oxidative stress via signal regulation or protect biomolecules photodynamically from oxidation during PDT in the presence of indocyanine green and an 808 nm laser. In recent years, there has been a significant acceleration in the development of nanotechnology. The combination of photosensitizers with nanomaterials can enhance the effectiveness of photodynamic therapy while reducing its side effects. The future direction of scientific photodynamic therapy should be toward more accurate, individualized therapy, which can be improved not only through nanoparticles and conjugates but also through innovative light sources and better control of the photodynamic response [316,317]. The continuous development of nanomedicine provides various types of multifunctional means in the field of PDT. Although PDT has been extensively studied to find a treatment for oncology, it now goes far beyond this indication, which can be seen as a significant step toward a myriad of other applications [317]. It is necessary to conduct many studies to make it possible to introduce this method into standard treatment regimens for brain tumors and other CNS tumors or other diseases. One of the most recent studies focuses on polyethylene glycols (PEGs), which are used in nanomedicine formulations of prodrugs, among other applications. Pro-drug nanoparticles are sensitive to ROS in the combination of chemotherapy and PDT [318]. Self-organization of polyethylene glycol-conjugated doxorubicin using a thioketal linker has the potential to encapsulate hydrophobic PhA along with nanoparticles that release drugs via ROS in the tumor area. This action minimizes toxicity outside the indicated area. Consequently, the addition of an active grouping toward pro-drug systems has the potential to improve drug delivery to a specific site in the treatment of glioma. Lu and colleagues demonstrated that the chemotherapeutic camptothecin-PEG conjugate, through a disulfide bond, was modified with RGD peptide and then loaded with the photosensitizer IR780, effectively penetrated through the blood-brain barrier, and was additionally targeted specifically to glioma cells. This allowed an effective combination of chemotherapy and PDT [319]. Zhang and his team developed biomimetic lipid nanoparticles that have homology-like targeting and enhance PDT against glioma. The SLNP/ICG@M nanoparticles, together with NIR irradiation, induce the apoptosis pathway and activate the body's immune response. These studies reveal a new strategy for targeted PDT therapy of glioma. In addition, there is the possibility of using nanoplatforms that are coated with tumor cell membranes in immunotherapy [320]. Yakavets *et al*. investigated the efficacy of PDT with temoporfin. The study showed that nanoplatforms that were used in combination with temoporfin have the effect of increasing the efficiency AND penetration of treatment during PDT. This is a promising treatment option [321]. However, one of the challenges around using temoporfin in PDT is its low solubility in water. This suggests that the production of reactive oxygen species in this method is not sufficient [322]. At this point, there is not much research on the use of temoporfin to treat brain diseases. It is important to conduct thorough laboratory studies. Chlorin e6, which is one of the strongest photosensitizers used in PDT, may also be an interesting option. It is characterized by low toxicity and relatively fast dissolution, and in addition, it is quickly removed from the body. Chlorin e6 also exhibits strong properties of a fluorescent nature [323,324]. According to studies conducted to date, PDT, along with chlorine e6, has antibacterial, anti-inflammatory, and antimicrobial properties [325]. However, it has disadvantages, one of which is hydrophobicity. It correlates with poor biodistribution, which leads to its rapid removal from the body's circulatory system [326].

7. Future Perspectives of PDT

PDT holds significant promise as a treatment modality for brain tumors, particularly aggressive and recurrent forms like GBM. Despite its current limitations, ongoing advancements in technology, biology, and clinical strategies are paving the way for its broader adoption and improved outcomes. The development of next-generation photosensitizers with better tumor selectivity, deeper tissue penetration, and faster clearance from healthy tissues could reduce side effects and enhance efficacy. Nanoparticle-based photosensitizers offer potential for targeted delivery and controlled release, enabling more precise treatments. Advancements in fiber-optic and laser technologies, including interstitial light-delivery systems, could address the limited light penetration in deep-seated brain tumors. Image-guided PDT (e.g., using MRI or fluorescence imaging) could improve the therapy's real-time targeting and monitoring. PDT can be integrated with conventional therapies, such as surgery, radiation, and chemotherapy, to achieve synergistic effects. Immunotherapy in combination with PDT shows promise, as PDT-induced immune activation can complement immune checkpoint inhibitors and vaccine strategies. Strategies to overcome the hypoxic environment of glioblastomas, such as oxygen-releasing nanoparticles or combination treatments with oxygen carriers, are being explored to enhance ROS generation. Advances in genomics and proteomics could enable the customization of PDT protocols to the molecular characteristics of individual tumors, thereby improving therapeutic outcomes. The development of minimally invasive and non-invasive PDT techniques, such as the use of near-infrared (NIR) light, could make PDT more accessible and less burdensome for patients. Large-scale clinical trials are needed to validate PDT's efficacy and optimize protocols for brain tumors. Standardizing dosimetry, photosensitizer selection, and light delivery will ensure consistent outcomes across diverse patient populations. While photodynamic therapy for brain tumors is still evolving, it represents a promising, minimally invasive approach with the potential to improve outcomes for patients with difficult-to-treat brain tumors. As innovations continue to address current challenges, PDT is poised to become an integral component of multimodal therapies, offering hope of improved survival and quality of life for patients with malignant brain tumors.

8. Cost-Effectiveness and the Challenges of Implementation

PDT offers several advantages over traditional brain tumor treatments like surgery, radiotherapy, and chemotherapy, but also comes with limitations that affect its utility. While surgery remains the primary treatment for brain tumors, complete resection is often impossible due to the risk of damaging critical brain structures. PDT can serve as an adjunct to surgery, targeting residual tumor cells in areas that cannot be safely resected. However, it does not provide the debulking effect of surgery and is therefore not a standalone alternative. Radiotherapy is highly effective but carries risks of radiation-induced damage to surrounding healthy brain tissue and delayed cognitive deficits. PDT's spatial selectivity reduces off-target effects, making it a potentially safer option. However, its limited penetration depth (see earlier discussion) means it may not be as effective for large or deeply seated tumors. Chemotherapy often struggles with poor blood-brain barrier (BBB) penetration, limiting drug delivery to the tumor. PDT bypasses this barrier as light can be delivered directly to the tumor via optical fibers. Unlike chemotherapy, PDT does not cause systemic side effects, but its efficacy in treating diffuse infiltrative tumor cells, a hallmark of glioblastomas, remains uncertain. Innovations like tumor-treating fields (TTFs) and immunotherapy are gaining traction in neuro-

oncology. While PDT could complement these therapies by creating immunogenic cell death, it may struggle to compete as a monotherapy, given the complexity of brain tumor biology.

The cost-effectiveness of PDT in brain tumor treatment is influenced by its equipment, procedure, and potential to reduce the need for other treatments. PDT requires specialized lasers, photosensitizers, and expertise for precise light delivery. The upfront cost of equipment and training may be a barrier, particularly in resource-limited settings. By selectively targeting residual tumor cells, PDT could reduce recurrence rates and the need for additional surgeries or therapies, offsetting its initial costs. However, robust cost-effectiveness analyses comparing PDT to standard-of-care treatments are limited. PDT's minimally invasive nature could shorten hospital stays and reduce postoperative complications compared to extensive surgeries, potentially lowering overall treatment costs.

Bringing PDT into widespread clinical practice for brain tumors presents several logistical and technical hurdles. Delivering light to brain tumors requires invasive methods, such as interstitial fiber-optic placement, which requires neurosurgical expertise. Real-time imaging guidance (e.g., MRI) may help, but this increases procedural complexity and costs. Brain tumors are highly heterogeneous, with varying photosensitizer uptake and oxygenation levels. Standardizing PDT protocols across diverse tumor types and patient populations is challenging. Widespread adoption of PDT requires clear guidelines, regulatory approvals, and clinician training programs. These are still evolving in neuro-oncology. Clinical trials for PDT in brain tumors are relatively sparse, with limited long-term survival and quality-of-life data. This makes it difficult for clinicians to weigh PDT's benefits against its risks and compare it with established therapies. Brain tumors are typically treated with a combination of therapies. Defining PDT's role within this framework—whether as an adjunct, a salvage therapy, or part of standard care—is crucial for its clinical uptake.

From a clinical perspective, PDT's ability to precisely target tumor cells while sparing healthy tissue is appealing. Its minimal invasiveness and potential to address therapy-resistant tumor regions make it a valuable addition to the neuro-oncologist's toolkit. However, the logistical challenges and need for robust comparative evidence must be addressed to facilitate its adoption.

9. Limitations

One of the primary barriers to PDT is the restricted penetration depth of light into tissues. The light source, typically a laser or LED, is used to activate photosensitizers at specific wavelengths, but light penetration in biological tissues is limited by scattering, absorption, and tissue composition. Light in the near-infrared (NIR) region (650–900 nm) has better tissue penetration due to reduced scattering and absorption, compared to ultraviolet (UV) or visible light. However, many photosensitizers are activated by light outside this range, necessitating compromises in excitation efficiency or treatment depth. Dense tissues such as bone and pigmented regions absorb or scatter light more extensively, limiting the therapy's efficacy in these areas. For example, deep-seated tumors or organs shielded by layers of muscle or fat may be inaccessible with standard PDT methods. PDT relies on ROS generation to induce cytotoxic effects, which requires adequate molecular oxygen in the target tissue. Tumors often have regions with poor vascularization, leading to oxygen-depleted zones where PDT is less effective. These hypoxic areas can act as reservoirs for surviving cancer cells, facilitating recurrence and reducing therapeutic efficacy. The photochemical reactions in PDT consume local oxygen, potentially exacerbating hypoxia during treatment. This phenomenon, known as

the "oxygen flash effect," can lead to uneven therapeutic outcomes within the tumor. While PDT is lauded for its selectivity, light activation can sometimes affect adjacent healthy tissues, particularly in anatomically complex or sensitive areas such as the brain or retina. Prolonged photosensitivity caused by photosensitizers poses a risk of accidental light-induced damage to patients' skin and eyes, necessitating lifestyle adjustments for weeks or months post-treatment. Variations in photosensitizer accumulation across different tumor types or regions within a tumor can lead to incomplete treatment.

While PDT offers a targeted, minimally invasive treatment modality, its dependence on effective light delivery and adequate oxygenation poses critical challenges. Advances in nanotechnology, adaptive optics, and hypoxia-mitigating strategies hold promise for overcoming these barriers. However, further research and clinical optimization are required to enhance the efficacy and versatility of PDT for a broader range of cancers and other diseases.

10. Conclusions

In recent years, the surgical strategy used for CNS tumors, especially in younger patients, has significantly changed from a strategy of aggressive attempt at radical resection to a much more conservative and individualized approach, since a partial resection is planned, followed by adjuvant methods in the form of radiotherapy, or other methods, more innovative ones, such as PDT. Novel discoveries in the field of cancer genetic profiling open new possibilities for the development of targeted therapies based on entirely new biomolecular markers. Despite intensive treatment, based on standard therapy consisting of surgical resection followed by ionizing radiation with accompanying and complementary temozolomide therapy, it remains incurable. According to Gunaydin, there has been significant development in PDT; however, there are still impediments, including limitations related to the light source, PS properties, and tissue oxygenation. In addition, the mechanisms of action of PDT are still not well understood. PDT has the potential to induce apoptosis, necrosis, or autophagy. It is possible that these mechanisms may be activated simultaneously. Therefore, understanding the photobiological and photochemical mechanisms is necessary when designing new yet effective PDT strategies. There are unclear clinical studies. Therefore, it is necessary to develop strategies that will lead to solving the problems mentioned earlier. It is also worth focusing on new designs that will allow PDT to be more selective. There is also a high probability that strategies targeting cells or specific organelles will improve the efficacy of PDT. In addition, PDT that can be combined with other treatments (e.g., chemotherapy, immunotherapy) will yield much better results. Other studies confirm that PDT, which uses two-photon excitation, has shown significant properties, such as deep tissue penetration or remarkable therapeutic efficacy. This also confirms that in this area, as well, i.e., the application of nanomedicine in PDT, it is necessary to develop platform technologies for evaluation of a pharmacokinetic nature. Thus, advances in the development of high-power lasers will make it possible for a larger number of patients to benefit from this treatment option.

Author Contributions

Methodology, Investigation, Writing – original draft, Writing – review & editing: P.W., D.A., J.I., A.M., W.M., K.D., D.L., D.B.-A. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

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