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REVIEW

Nanoprobe-Based Near-Infrared II Optical Imaging for Guiding Precision Glioma Therapy

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Abstract: Glioma is a heterogeneous primary and metastatic tumour of the central nervous system that is highly invasive and destructive, with a poor prognosis and low survival rate. Near-infrared II (NIR-II) fluorescence imaging has revealed significant potential for advancing glioma diagnosis because of its non-invasiveness, high spatiotemporal resolution, reasonable sensitivity, and deep penetration. These imaging techniques have been widely used to guide real-time glioma treatment with high accuracy and efficiency. This review summarised the applications and progress of NIR-II in guiding glioma surgery, targeted drug delivery, photoacoustic therapy, and multimodal therapy. We demonstrated the feasibility and practicality of integrating these technologies into glioma diagnosis and treatment. These technologies have great potential to improve patient prognosis further. Furthermore, this review highlights the challenges of using these technologies in future clinical studies.

Keywords: near-infrared II, glioma, surgery, multimodal therapy, phototherapy

Introduction

Glioblastoma (GBM) is the most common and aggressive malignant tumour of the central nervous system. It primarily affects the cerebral cortex and has an inferior prognosis and a high mortality rate. Little progress has been made in diagnosing and treating GBM in recent decades.[1,2] GBM exhibits infiltrative growth patterns and often infiltrates the surrounding brain parenchyma, preventing complete surgical removal.[3] Radiotherapy has the potential to cause toxicity and cognitive impairment in normal brain tissue. The blood-brain barrier (BBB) poses a significant challenge as it prevents almost 100% of large-molecule neurotherapeutic drugs and > 98% of small-molecule drugs from entering the brain. This greatly hinders the effective delivery of anticancer drugs to GBM.[4] Additionally, GBM treatment in neurosurgery is delicate because of the surgical and radiotherapy-related complications on normal brain tissue and the risk of tumour recurrence and treatment resistance.

Advances in molecular imaging technology are essential for achieving an accurate cancer diagnosis. Several imaging techniques, including magnetic resonance imaging (MRI), X-ray computed tomography (CT), and positron emission tomography (PET), have been widely used in clinical and preclinical imaging.[5–7] Although they provide deeper penetration, thus enabling whole-body imaging, they have some disadvantages. High-resolution MRI systems are expensive and slow for dynamic imaging; CT is unsuitable because of its limited ability to provide adequate functional information and soft tissue contrast, and it produces ionising radiation when used, making it unfit for frequent imaging.[8,9] Compared with traditional medical imaging techniques, near-infrared fluorescence (NIR) imaging technology can use different fluorescent probes under specific laser excitation to observe tumour sites and monitor tumour progression. It has attracted widespread attention due to its lack of radiation, higher sensitivity and resolution, and faster imaging speed. However, its penetration depth is still not as good as MRI/CT.[10–13] It is widely used as a complementary means in GBM diagnosis and treatment, providing a new solution for precise GBM treatment. We compared these commonly used GBM

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diagnostic methods in Table 1.[14,15] This study reviews the application and research progress of NIR-II optical imaging in GBM diagnosis and treatment.

Principles and Advantages of NIR-II Optical Imaging

Fluorescence imaging uses fluorescent probes to label imaging objects and detect specific components in biological molecules, cells, or tissues. This technique uses fluorescent dyes or proteins that specifically bind to target molecules. When these fluorescent molecules are excited by light of appropriate wavelengths, they absorb energy and emit light of longer wavelengths to produce fluorescence. The imaging system can capture this fluorescent signal, allowing researchers to observe and quantify specific molecules or cells in biological processes in real time and track molecular dynamics within cells and signalling between cells. Fluorescence imaging technology is widely used in biomedical research, clinical diagnosis, and treatment because it can provide high temporal and spatial resolution and non-invasive and in situ real-time imaging capabilities.[16–19]

During in vivo fluorescence imaging, photons lose intensity because of tissue absorption and scattering, which reduces the quality of optical imaging, including resolution and penetration depth. Traditional fluorescence is primarily located in the visible light (400–650 nm) and near-infrared I region (700–900 nm). In the NIR-I region, living tissues (including skin, blood, and fat) exhibit strong absorption and scattering effects on photons in this band, resulting in limitations such as shallow penetration depth, low spatial resolution, and insufficient signal-to-background ratio (SBR) during real-time imaging, which hinders deep tissue "visualization".[20,21] Consequently, more studies have focused on the second near-infrared window (NIR-II, 1000–1,700 nm) since 2009.[22–24] NIR-II fluorescence imaging leverages the optical advantages of longer wavelengths to significantly reduce photon scattering and absorption by biological tissues. This results in NIR-II imaging exhibiting approximately 1.7-fold greater penetration depth,[25,26] 2.1-fold higher resolution,[27,28] and 3.5-fold enhanced SBR compared to NIR-I imaging,[29,30] demonstrating significant potential for clinical translation.

The high-density characteristics of the skull greatly limit the resolution of MRI technology in deep brain structure imaging. However, Professor Xiao's research group developed the NIR-II dual-mode probe IR-32p to address this technological bottleneck, which achieved non-invasive and accurate imaging of the entire skull in the U87MG glioma animal model.[31] This innovative technology breaks through the physical limitations of traditional imaging and can clearly present the morphology of in situ gliomas without the need for craniotomy surgery, demonstrating superior translational potential. In addition, traditional imaging techniques have various limitations in GBM surgery: CT has cumulative radiation risks, while MRI is limited by intraoperative strong magnetic field interference and operational complexity, making it difficult to meet real-time navigation requirements. Based on this, Shi et al synthesized a NIR-II probe (64Cu DOTA-FA-ICG) by modifying Indocyanine Green (ICG). The probe can achieve high-sensitivity and accurate imaging during GBM surgery through NIR-II fluorescence real-time navigation, effectively solving the problem of traditional CT/MRI not being able to provide high-resolution images synchronously during surgery.[32] Therefore, It has obvious advantages in detecting early lesions in deep tissues and demonstrates excellent application potential in brain imaging (Figure 1).[33–35]

Application of NIR-II Fluorescence Imaging in Glioma Diagnosis and Treatment

Fluorescence Image-Guided Surgery

Surgery is the first-choice treatment for glioma. Thus, maximum safe resection is essential to improving patients' progression-free survival (PFS). However, the invasive nature of GBM makes it challenging to visualise and distinguish

Table 1 Comparison of Several Commonly Used GBM Diagnostic Methods

Diagnostic Method	Penetration Depth	Spatial Resolution	Radiation	Real-Time	References
MRI	High (whole brain penetration)	High resolution	No radiation	Low (scan time approximately 15–60 minutes)	8
CT	High (whole brain penetration)	Medium resolution	High (X-ray radiation)	Medium (quick scan takes about 1–5 minutes)	9
PET	High (whole brain penetration)	Low resolution	High (radioactive tracer)	Low (requiring radiopharmaceutical metabolism)	7
NIR-II	Low (5–15mm)	High resolution	No radiation	High (millisecond level dynamic monitoring)	15

Abbreviations: MRI, Magnetic Resonance Imaging; CT, Computed Tomography; PET, Positron Emission Tomography; NIR-II, Second Near-Infrared Window.

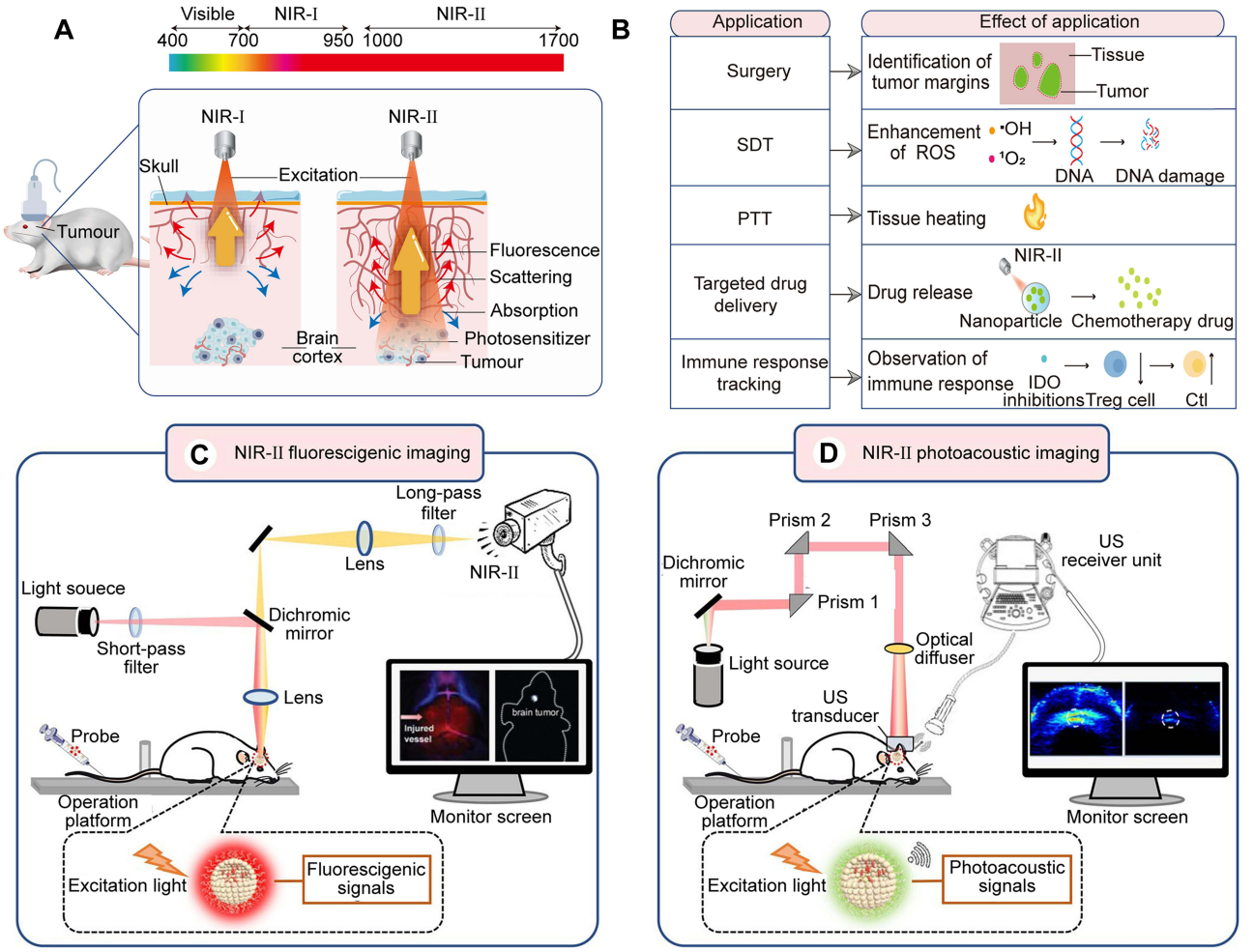

Figure 1 The Basic Principles and Applications of NIR-II Fluorescence Imaging. (**A**) Key bio-optical properties of light in the second near-infrared region (NIR-II) include lower levels of scattering in tissues compared to light in the visible and first near-infrared region (NIR-I), which provides higher imaging resolution, although due to the high absorption of these wavelengths by water, Imaging performance in the 1400–1500 nm subregion may be reduced. (**B**) Application of NIR-II fluorescence imaging in the diagnosis and treatment of glioma and its effect. SDT, sonodynamic therapy; PTT, photothermal therapy. (**C** and **D**) Schematic diagram of fluorescence and photoacoustic imaging of NIR-II. After the probe injection, the fluorescence or photoacoustic signals received by different filters with wavelengths less than 1000 nm dynamically reflect the cerebral blood vessel morphology in real-time. Part (**C** and **D**) reprinted with from Xie N, Hou Y, Wang S, et al. Second near-infrared (NIR-II) imaging: a novel diagnostic technique for brain diseases. Rev Neurosci. 2022;33(5):467–490. © 2021 Walter de Gruyter GmbH, Berlin/Boston.[35]

healthy brain tissue under white light, making precise resection almost impossible.[36] With the development of fluorescence imaging technology, neurosurgeons can further visualise the difference between tumours and normal tissues, minimising damage to the surrounding normal brain. The extent and margins of GBM are mapped using CT and MRI before surgery and incorporated into stereotactic navigation to guide surgery. However, due to gravity and intraoperative cerebrospinal fluid loss, brain tissue displacement may occur during surgery, reducing the accuracy of tumour positioning after craniotomy.[37] Additionally, the invasive growth characteristics of GBM make it difficult for neurosurgeons to identify tumour tissue under a microscope, resulting in non-radical removal or unnecessary resection of normal tissue.

Consequently, improving the real-time assessment of tumour margins during surgery directly maximises tumour resection and minimises typical tissue damage. Fluorescence-guided surgery (FGS) enables surgeons to enhance the visualisation of tumour tissue during surgery, especially in the neuro-oncology environment where invasive tumour margins persist. It can achieve precise tumour resection at the submillimeter scale and minimise the risk of damage to surrounding healthy brain tissue. It has excellent potential for improving surgical success and treatment outcomes (Figure 2A).[38,39]

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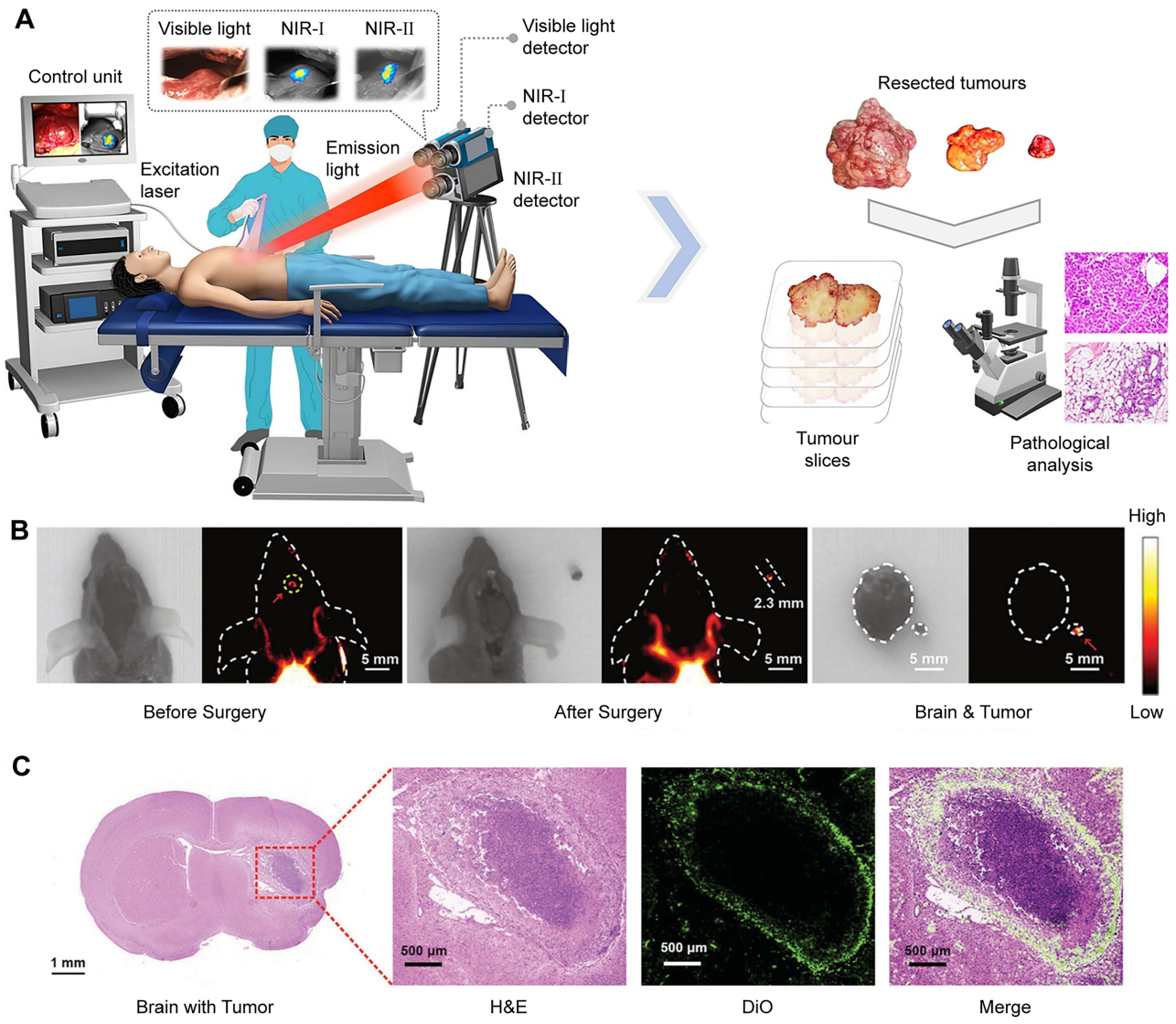

Figure 2 NIR-II fluorescence imaging-guided surgical treatment. (**A**) Surgery for human liver tumors under the guidance of visible and NIR-I/II window multispectral optical imaging. (**B**) Bright-field and NIR-II fluorescence images of glioma mice before and after surgery; (**C**) Whole brain H&E staining image of the tumor, H&E staining image of the tumor, and corresponding fluorescence microscope image. Label CC-LnNPs with DiO(green). Part (**A**) reprinted from Hu Z, Fang C, Li B, et al. First-in-human liver-tumour surgery guided by multispectral fluorescence imaging in the visible and near-infrared-I/II windows. Nat Biomed Eng. 2020;4(3):259–271. Copyright © 2019, The Author(s), under exclusive licence to Springer Nature Limited.[39] Part (**B** and **C**) reprinted from Wang Z, Zhang M, Chi S, Zhu M, Wang C, Liu Z. Brain tumor cell membrane-coated lanthanide-doped nanoparticles for NIR-IIb luminescence imaging and surgical navigation of glioma. Adv Healthc Mater. 2022;11(16):e2200521. © 2022 Wiley-VCH GmbH.[40]

Accurate Identification of Tumor Margins

The limitations of tissue penetration depth and the BBB make distinguishing brain tumours from the surrounding parenchyma boundary challenging, especially with high sensitivity and specificity during FGS.[41–43] Because of the high penetration ability of NIR-II light into deep tissues, higher spatiotemporal resolution can be obtained, making it easier for fluorescence imaging to detect gliomas in vivo and achieve high-contrast fluorescence imaging-guided surgery. Therefore, the development of probes for real-time fluorescence-guided surgery is essential to address the limitations of conventional surgical techniques. Researchers have designed NIR-II fluorescence imaging probes with excellent photostability and permeability to visualise the differences between tumours and normal tissue for better resection of gliomas. Li et al successfully synthesised the first dual-modal nanoprobe, Gd-DOTA-Ag_2S QDs, which combined MRI and NIR-II fluorescence imaging for preoperative diagnosis and intraoperative resection of U87MG brain tumours.[44] With the help of Gd-assisted T1 MRI, the mouse model brain tumour (U87MG) was depicted in situ, and after intravenous injection of

Gd-Ag2S nanoprobes, intraoperative tumour resection was accurately completed under the guidance of NIR-II fluorescence imaging of Ag_2S quantum dots. This probe will provide a visualisation strategy for potential clinical practice.

Kurbegovic et al developed a new targeted fluorescent probe (CH1055-4Glu-AE105) by coupling the fluorophore CH1055 and the uPAR-targeting peptide AE105 and performed dynamic imaging of GBM in situ in living animals.[45] The investigation revealed the outline of the GBM tumour in situ and achieved negative resection margins under the guidance of NIR-II fluorescence imaging. The probe has demonstrated promising preclinical results and is a potential tool for clinical transformation. Wang et al constructed a biomimetic nanoprobe (CC-LnNPs) for brain tumour imaging and surgical navigation using lanthanide-doped nanoparticles as the core and the brain tumour cell membrane as the shell.[40] The presence of the brain tumour cell membrane on the surface of the biomimetic nanoprobe allows for immune escape, BBB penetration, and homologous targeting, promoting its accumulation in brain tumours. Under the guidance of NIR-IIb fluorescence, the tumour margins were clearly outlined, and a brain glioma measuring 2.3 mm was precisely resected. This suggests that CC-LnNPs are reliable for accurate diagnosis and imaging-guided brain tumour surgery. These studies demonstrate their potential in NIR-II-guided glioma surgery (Figure 2BC).

Reduction of Intraoperative Bleeding

Visualisation of tumour blood vessels and brain vascular structures is of great significance for analysing the pathological state of brain diseases and tumour vascular abnormalities and improving tumour diagnosis. NIR-II FMI can enhance the visualisation of tumour blood vessels and potentially prevent iatrogenic damage. Because GBM is a highly vascularised tumour with invasive neovascularisation and abnormal vascular structure,[46,47] it is challenging to identify blood vessel distributions around the cancer accurately. Inadvertent severing of the blood vessels (arteries) can cause massive bleeding and increase the risk of ischemic stroke in patients.[48] Accordingly, ligating the arterial blood supply to the tumour and safeguarding critical drainage veins during surgery is essential.

The commonly used vascular imaging technologies in clinical practice include computed tomography angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA). Among them, CTA and MRA require a long scanning and reconstruction time to obtain imaging data, and microvascular changes' spatial resolution/contrast is limited.[49] At the same time, DSA provides a higher spatial resolution, it is limited by X-ray radiation and invasive examinations,[50] and its real-time guidance application in tumour resection is uncommonly used. NIR-II three-dimensional imaging can obtain more accurate vascular three-dimensional imaging information in real-time by converting NIR-II excitation light into acoustic signals. With a tissue depth of several millimetres and a spatial resolution of < 10 μm, this tool is ideal for fluorescence-guided glioma resection.[49]

Cao et al used ICG as a fluorescent probe to construct a multispectral FMI integrating NIR-IIa/IIb imaging and developed a corresponding image fusion method to guide GBM surgery.[51] The new imaging system simultaneously outlines the blood vessel distribution around the tumour and the surgical boundary. This can guide the surgeon in accurately ligating the blood vessels around the tumour. Compared with the control group, the average blood loss was reduced by 38%, and the operation time was significantly shortened. Although these studies are preliminary, NIR-II FMI has demonstrated significant performance in identifying essential structures, including microvessels, and has potential clinical application value (Figure 3).

Artificial Intelligence-Assisted Decision-Making

Glioma grading during surgery helps clinical treatment planning and prognosis; however, pathological examination of intraoperative frozen sections is limited by long processing duration and complex procedures. Artificial intelligence has excellent prospects for further improving image quality and integrating numerous physiological information.[52,53] In the past few years, artificial intelligence technologies, including deep convolutional neural networks, have been developed for classifying medical images and have demonstrated exceptional performance.[54] Artificial intelligence models can identify malignant lesions more accurately and effectively than traditional analysis tools during surgery. Existing data reveal that AI algorithms can extract various tumour features, including tumour grade and Ki-67 levels, from clinical ICG-based NIR-II images, helping neurosurgeons improve clinical decision-making.[55,56]

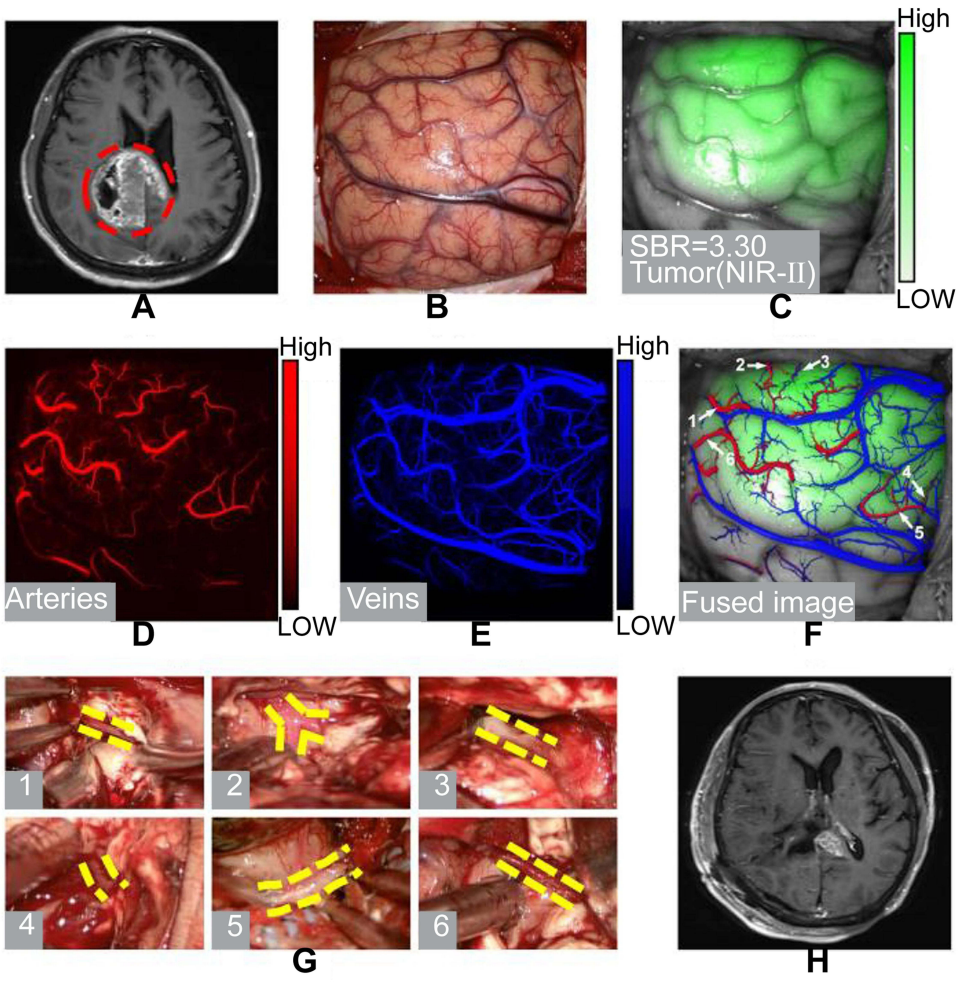

Figure 3 NIR-II image-guided feeding arteries blocking and tumor resection of a patient with GBM. (**A**) Preoperative enhanced MRI with red circles indicating lesions in the right parietal lobe. (**B**) Visible light images after opening the dural membrane. (**C**) In the NIR-II imaging of the tumor site, the tumor fluorescence is green, and the tumor SBR is 3.30. (**D**) Images of NIR-IIB of the supplying artery. (**E**) Intravenous NIR-IIB images 2min after ICG injection. (**F**) Fusion images of the tumor with arteries and veins are shown in green, red, and blue, respectively. The white arrows 1–6 correspond to the location of the arteries supplying the tumor. (**G**) The yellow dotted line indicates obstruction of the supplying artery during tumor resection. Figures 1–6 corresponds to the vessels labelled 1–6 in F. H. Post-operative enhanced MRI showed that the tumor had been removed to its maximum extent. Figure 3 reprinted from Cao C, Jin Z, Shi X, et al. First clinical investigation of near-infrared window IIa/IIb fluorescence imaging for precise surgical resection of gliomas. IEEE Trans Biomed Eng. 2022;69(8):2404–2413. © Copyright 2025 IEEE. Under a Creative Commons License.[51]

In another example, Shen et al combined convolutional neural networks (CNN) with NIR-II fluorescence imaging (termed FL-CNN) to provide real-time pathological diagnosis during surgery for patients with glioma.[54] They found that the developed FL-CNN exhibited a high area under the curve (AUC) of 0.945, a sensitivity of 93.8%, and a specificity of > 80% in capturing important information from NIR-II fluorescence images. Further experiments revealed that > 70% of the classification errors by neurosurgeons were corrected using FL-CNN, suggesting that this AI model could provide rapid and accurate intraoperative pathological diagnosis. Furthermore, FL-CNN rapidly predicted tumour specimens' grade and Ki-67 level during surgery (AUC 0.810 and 0.625). This is a promising approach to providing intraoperative pathological diagnosis, potentially assisting neurosurgeons in safely obtaining maximal resection.

Fluorescence Imaging-Guided Targeted Drug Delivery

Chemotherapy is essential in GBM treatment and can make up for the poor prognosis of surgery. Traditional chemotherapy primarily works by disrupting DNA synthesis and mitosis, leading to the death of rapidly proliferating cancer cells. However, systemic chemotherapy damages the bone marrow, affecting the number of resident immune cells and their activation state. Thus, precise local chemotherapy is crucial for brain tumours. Chemotherapy involving various

chemotherapeutic drugs is critical to clinical cancer treatment.[57,58] Currently, five FDA-approved drugs, including oral lomustine, intravenous carmustine, intraoperative carmustine chemotherapy wafer implant (Gliadel wafer), temozolomide (Temodar), and bevacizumab (Avastin), have been approved for brain tumour treatment.[59] However, since brain tumours have many unique characteristics relative to tumours growing in peripheral tissues, current brain tumour chemotherapy remains hampered by nonspecific drug distribution and severe side effects caused by drug overdose. This is one of the reasons for the poor prognosis and rapid recurrence of standard therapy. Researchers have been working to effectively deliver chemotherapy drugs to tumour areas and reduce unnecessary drug accumulation in the normal brain and surrounding tissues.

Fluorescent probes are modified with specific ligands and can recognise and bind to tumour tissues. They trigger drug release through NIR-II fluorescence irradiation, achieve controlled, targeted drug delivery, and produce precise antitumor effects (Figure 4). Fluorescent probe-mediated brain tumour-targeted drug delivery systems can achieve site-specific drug release, leading to higher tumour accumulation, and are a promising new approach for brain tumour treatment.[60] In addition, the fluorescent properties of the probes allow real-time tracking of drug distribution and release, which helps to optimise treatment plans and evaluate treatment effects.

Ding et al constructed a novel NIR-II diagnostic and therapeutic integrated nanoprobe PSY using FDA-approved material Pluronic F127 based on the co-assembly strategy of organic platinum (II) metal ring P1 and NIR-II molecular dye SY1030.[62] This design not only significantly improves the solubility stability and biosafety of the composite system through the encapsulation effect of the F127 matrix, but also achieves tumor-targeted delivery under NIR-II light control.

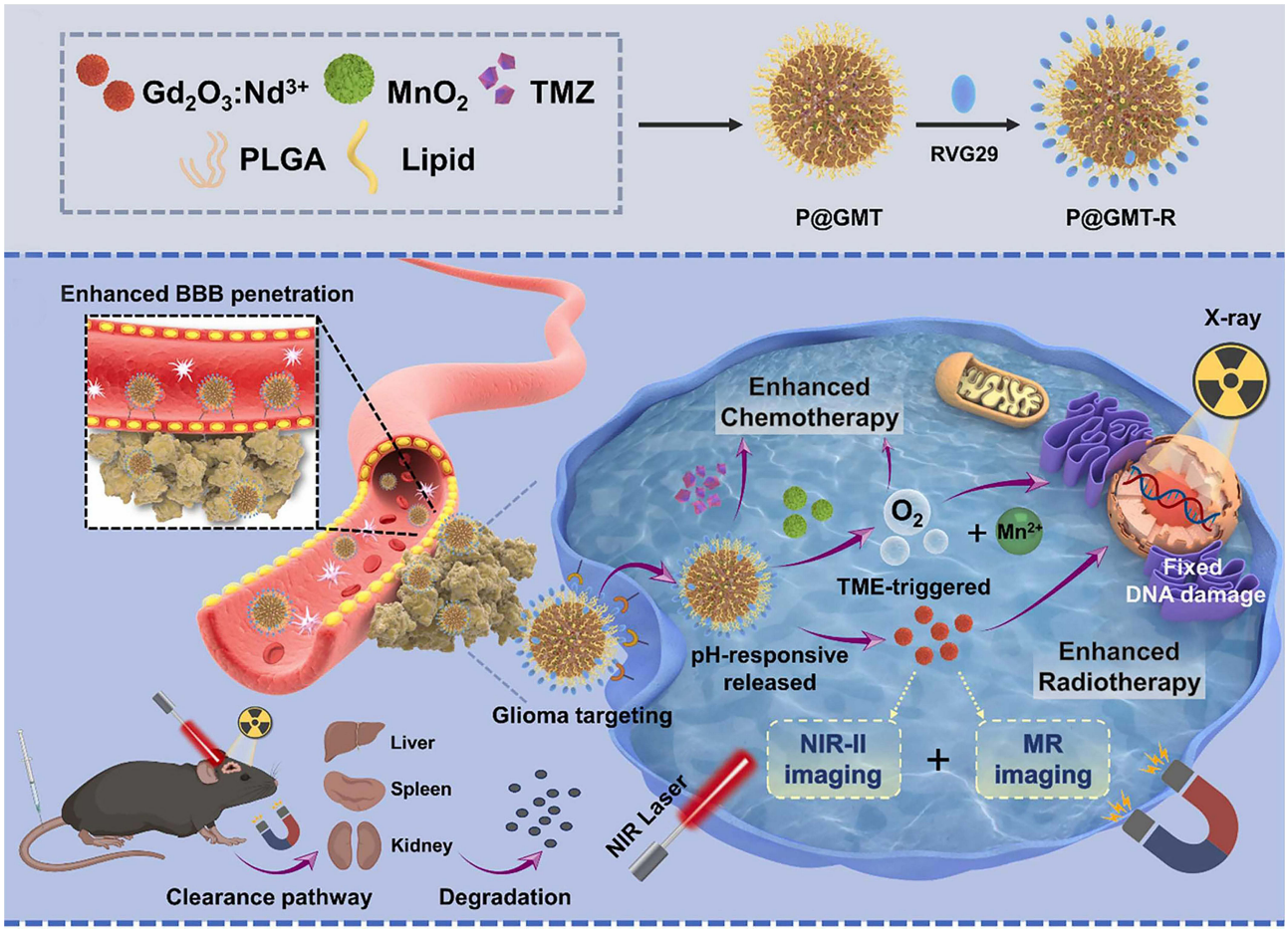

Figure 4 The synthetic route of P@GMT-R and their schematic diagram for enhancing Glioma chemotherapy under NIR-II guidance. Figure 4 reprinted From Yin N, Wang Y, Cao Y, et al. A biodegradable nanocapsule for through-skull NIR-II fluorescence imaging/magnetic resonance imaging and selectively enhanced radio-chemotherapy for orthotopic glioma. Nano Today. 2022;46:101619. © 2022 Elsevier Ltd. All rights reserved.[61]

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With the NIR-II fluorescence tracing function of SY1030, researchers can monitor the in vivo distribution, tumor accumulation, and metabolic clearance process of the probe in real-time, providing visual navigation for precise treatment. Experimental data shows that compared to traditional cisplatin formulations, PSY significantly increases the level of platinum enrichment at the tumor site. In the efficacy evaluation, the PSY treatment group showed the highest tumor suppression efficiency.

Carbon quantum dots (CQDs) have recently emerged as a promising class of imaging agents and drug carriers for various biomedical applications due to their outstanding biocompatibility, low toxicity, excellent optical properties, and drug-loading capacity.[63,64] The BBB has always been a significant obstacle for drug delivery to brain tumours. Large neutral amino acid transporter 1 (LAT1) is overexpressed in several tumours and the BBB and can be used for targeted delivery of therapeutic nanomedicines to brain tumours.[65,66] The edges of LAAM CQDs are functionalised with paired α-carboxyl and amino groups, triggering multivalent interactions with LAT1—Li et al designed large amino acids that mimic CQDs (LAAM CQDs). Since LAT1 is a carrier transporter overexpressed in cancer cells, the synthesised LAAM TC-CQDs can penetrate the BBB and deliver chemotherapeutic drugs to glioma cells with high specificity, avoiding systemic toxicity.[67] Additionally, LAAM TC-CQDs are capable of NIR fluorescence and photoacoustic imaging, making them an excellent NIR fluorescence imaging tool and drug delivery carrier.

Yin et al encapsulated Gd_2O_3: Nd^{3+} nanodots, manganese dioxide (MnO_2), and temozolomide (TMZ) in polylactic-co-glycolic acid (PLGA) and modified the surface with rabies virus glycoprotein (RVG29) to construct a new therapeutic nanoprobe (P@GMT-R) for NIR imaging and selectively enhanced chemoradiotherapy.[61] P@GMT-R nanocapsules have excellent NIR-II fluorescence and magnetic properties and can perform NIR-II FI/MRI through intact skulls and imaging-guided surgery with high sensitivity and spatial resolution. RVG29 has a strong interaction,[68] which enables the probe to cross the BBB and accumulate in deep gliomas. Simultaneously, the PLGA carrier can prolong the circulation time of TMZ in the brain to achieve controlled release at the tumour site triggered by the tumour microenvironment (TME), improve the efficient enrichment and utilisation of TMZ in the brain, and thus improve the utilisation rate of chemotherapeutic drugs.[69] Furthermore, the O_2 induced by MnO_2 can primarily alleviate intratumoral hypoxia and reduce the resistance of tumour cells to treatment.[70] All these findings indicate that P@GMT-R has the potential for efficient GBM diagnosis and treatment.

A fluorescent probe-mediated brain tumour-targeted drug delivery system is a promising approach for treating brain tumours. It will contribute to a better understanding of the relationship between brain tumours' physiological and pathological conditions and provide a basis for various targeted delivery systems. However, the nanoprobes for chemotherapy need to break through the BBB and consider safety issues, so the experimental design is difficult and technically complex, and there is still a long way to go until the clinical stage.

Real-Time Immune Response Tracking

Predictive monitoring of GBM immune status is critical for optimising patient care and advancing clinical outcomes. Photoacoustic imaging (PAI) is an emerging biomedical imaging technology that can selectively detect specific molecular markers, dynamically visualise regulatory T lymphocytes (Treg cells) in the TME, evaluate immune response status in situ, and provide timely feedback on treatment effects at micron-level resolution. It is a promising tool for tracking immune status (Figure 5).[71]

GBM is characterised by the accumulation of $CD25^+$ $CD4^+$ $FoxP3^+$ Treg cells, which promote tumour growth by suppressing immune responses. Previous studies have reported that highly immunosuppressive Treg cells can promote GBM development by inhibiting antitumor immune responses and establishing an immunosuppressive environment, thereby inhibiting the tumour rejection function of $CD8^+$ cytotoxic T lymphocytes (CTLs). At the same time, the expression of indoleamine-(2,3)-dioxygenase (IDO) increases the recruitment of Tregs and promotes tumour growth.[72,73] Consequently, indoleamine-(2,3)-dioxygenase (IDO) inhibitors can reduce the recruitment of Treg cells and promote the infiltration of CTLs, which is a promising immunotherapy method.

Zeng et al developed a new fluorescent probe (PEG/αCD25-Cy7/TMZ) by loading TMZ and the optical dye αCD25-Cy7 targeting Treg cells. The probe can accurately deliver TMZ for local chemotherapy and use IDO inhibitors for immunotherapy after chemotherapy, thereby reducing the infiltration of Treg cells by promoting immune responses and improving survival

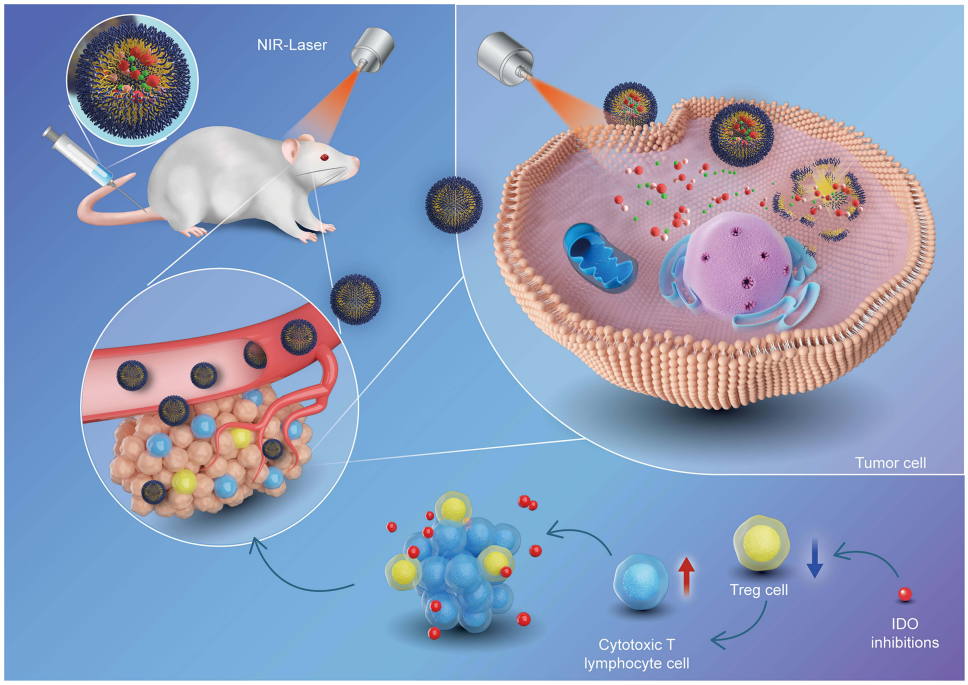

Figure 5 Schematic diagram of NIR-II fluorescence image-guided immune tracking.

rates.[74] Since CD25 is highly expressed in Treg cells, the probe can quickly observe Treg cells in situ, track the dynamic distribution of Treg cells to monitor immune response, and thus achieve accurate tumour chemoimmunotherapy. The results revealed that the targeting efficiency of the probe for Treg cells was as high as 92.3%. The fluorescent probe combined with PAI can accurately deliver chemotherapy drugs. It can observe the dynamic immune response process in real-time and non-invasively at the micrometre scale, which helps formulate personalised treatment plans.

Phototherapy

Phototherapy has attracted widespread attention due to its advantages, including high specificity, non-invasiveness, negligible drug resistance, and promising therapeutic effects.[75,76] It is primarily used to treat unresectable tumours or tumours that cannot be cured after other treatments. Researchers have found that many NIR-II fluorescent molecules have inherent NIR absorbance and have photothermal and photoacoustic therapeutic functions. They can be used together with other therapies to inhibit cancer through customised molecular design. Typically, NIR-II fluorescence generates heat energy, making cancer cells hyperthermic and inhibiting their growth.[77–80]

Photothermal Therapy

Photothermal therapy (PTT) is a treatment method that uses nanoparticles/quantum dots to convert light energy. It has the advantages of being non-invasive, offering high spatial resolution, and causing minimal side effects on normal tissues. This makes it a promising treatment method (Figure 6). Nanoprobes can convert NIR-II laser into thermal energy, achieving photothermal ablation of tumor cells. In addition, its local thermal effect can induce ferroptosis by regulating the ROS-GSH-GPX4 signaling axis, and synergize with mitochondrial membrane potential collapse to trigger apoptotic pathways, achieving a double-regulated cell death mechanism.[81,82] However, its development is hampered by the unique characteristics of GBM. First, photosensitisers must cross the BBB when administered to reach the tumour site at therapeutic concentrations.[4] Second, near-infrared light irradiating the head must pass through multiple barriers to reach the tumour site, causing deep local hyperthermia without causing damage to normal tissues, thereby achieving tumour destruction.[83] Some NIR-II fluorescent probes are intrinsic photothermal agents. By binding to specific receptors, they can cross the BBB, provide deeper tissue penetration, and effectively accumulate in tumour tissues. Heat is generated by

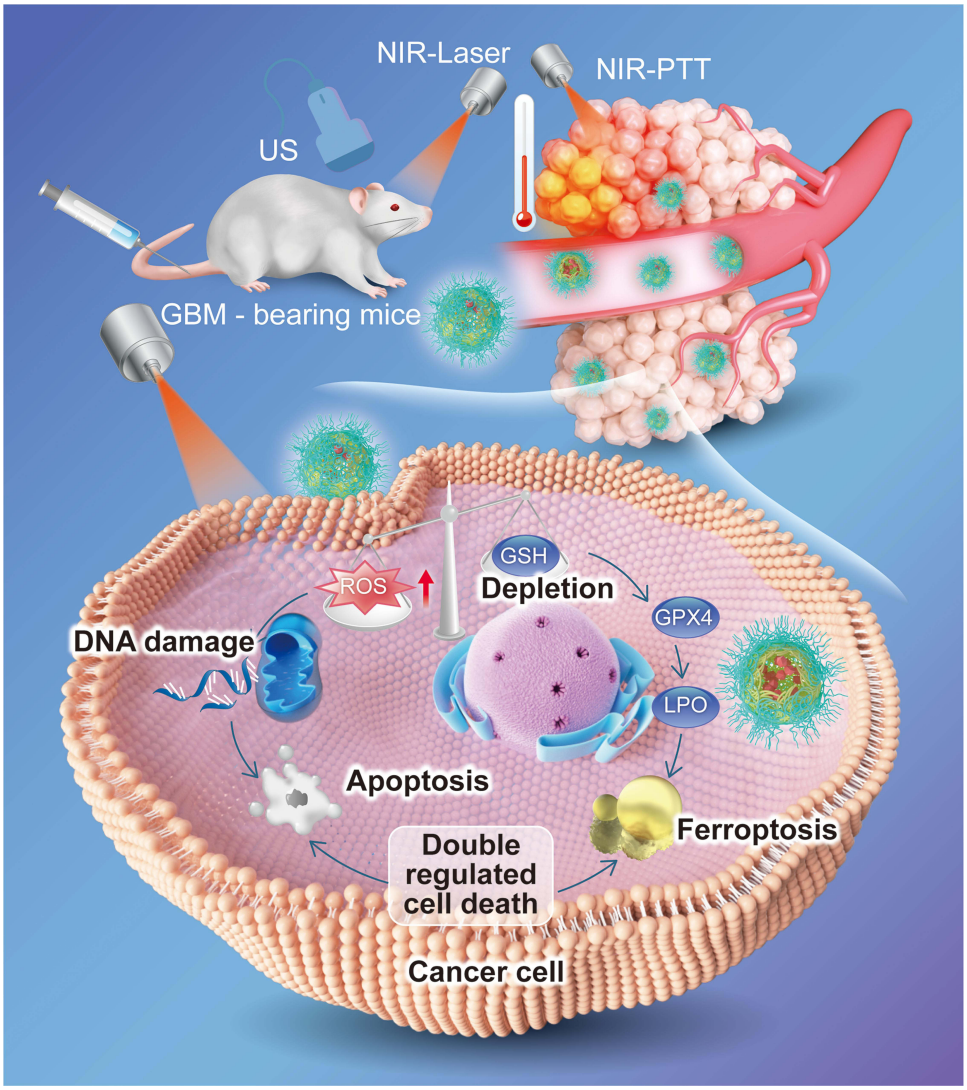

Figure 6 PTT and SDT can respectively trigger ferroptosis and apoptosis pathways by the thermal effect induced by NIR-II light excitation and the ROS burst induced by ultrasound, achieving precise and controllable temporal regulation of the dual cell death mechanism.

the excitation of NIR-II light sources, achieving precise treatment of tumours, which is significant for phototherapy of lethal brain tumours.

Wang et al proposed a new type of nitrogen-boron co-doped graphene quantum dots (NB-GQDs). The prepared NB-GQDs have an ultra-small structure with a diameter of approximately 5 nm and are highly stable when dispersed in serum.[84] Moreover, NB-GQDs can effectively absorb near-infrared light and convert it into heat for PTT. In vitro and in vivo experiments have confirmed its therapeutic efficacy. Tumor cells are effectively killed, and glioma growth is completely inhibited. The ApoE-Ph NPs designed by Professor Tang's research group with a 1500nm absorption peak have demonstrated outstanding advantages in GBM photothermal therapy.[85] The addition of brain targeted peptide ApoE increased BBB penetration rate and tumor specificity, The experimental results indicate that ApoE Ph NP has higher PTT efficiency and significantly improves the survival rate of mice carried in situ (Figure 7A–C). Guan et al first described a small organic molecule (N1) with NIR-II absorption. They used it as a photothermal and photoacoustic nanoagent to effectively treat brain tumours under the guidance of precise PA imaging.[86] N1 was nano-encapsulated with mpc-containing amphiphilic copolymers to form N1@2P nanoparticles with excellent BBB crossing efficiency by modifying the nanoparticle size and nanoparticle-based receptor-mediated endocytosis delivery strategy. The obtained N1@2P NPs have good photostability, biocompatibility, and a high photothermal conversion rate, allowing for high-quality real-time

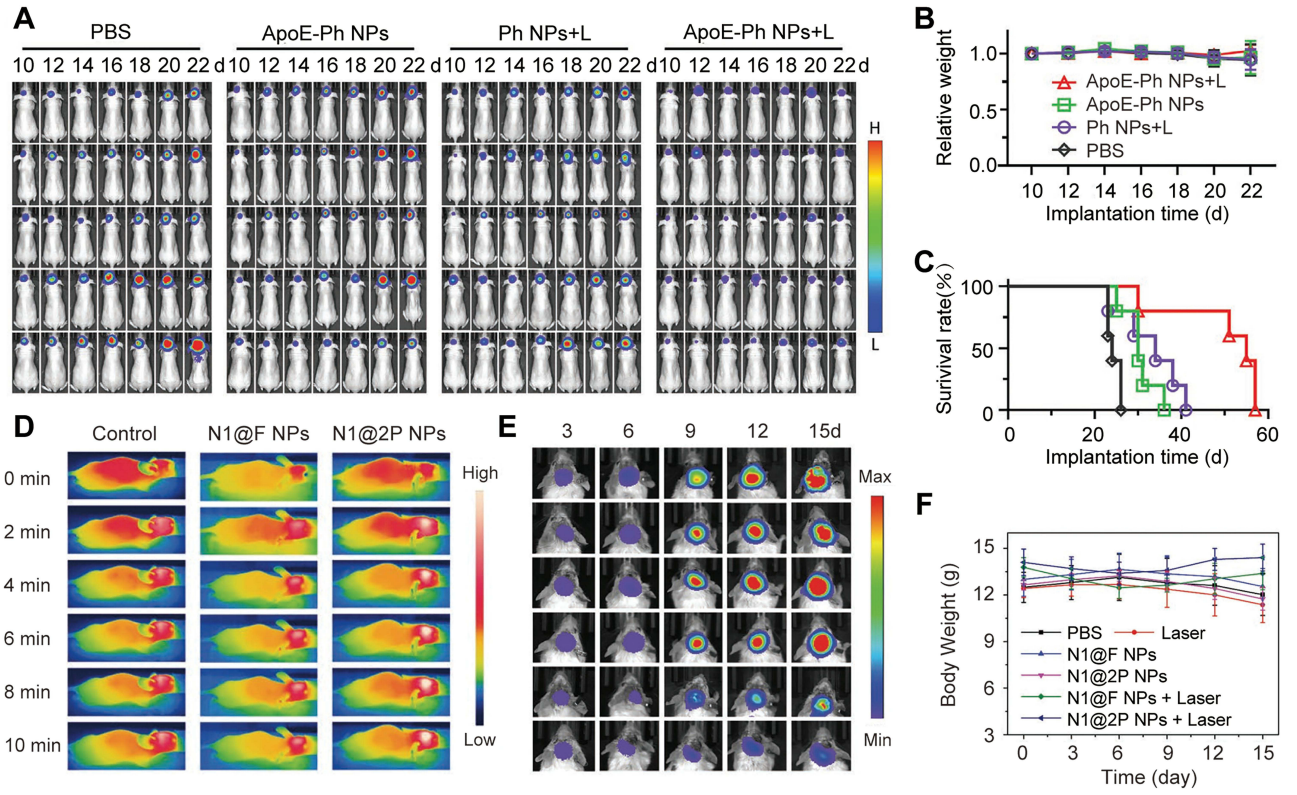

Figure 7 Growth and survival of mice after PTT guided by NIR-II fluorescence imaging. (**A**) Tumor growth in mice with in-situ GBM tumours was assessed by monitoring bioluminescence at different days after PBS, ApoE-Ph NPs, post-irradiation Ph NPs (+L), or ApoE-Ph NPs+L treatment (n = 5). (**B** and **C**) Relative weight changes and survival curves of mice treated with ApoE Ph NPs+L. (**D**) Infrared thermal images of U251-Luc tumor-bearing mice injected with PBS, N1@F Nps, and N1@2P NPs at different time points under a 1064 nm laser. (**E** and **F**) Bioluminescence images and body weight changes of U251 glioma-bearing mice after different treatments for 3, 6, 9, 12, and 15 days. Part (**A**, **B** and **C**) reprinted from Wang J, Liu Y, Morsch M, et al. Brain-targeted aggregation-induced-emission nanoparticles with near-infrared imaging at 1550 nm boosts orthotopic glioblastoma theranostics. Adv Mater. 2022;34(5):e2106082. © 2021 Wiley-VCH GmbH.[85] Part (**D**, **E** and **F**) reprinted from Guan J, Liu C, Ji C, et al. NIR-II perylene monoimide-based photothermal agent with strengthened donor-acceptor conjugation for deep orthotopic glioblastoma phototheranostics. Small. 2023;19(19):e2300203. © 2023 Wiley-VCH GmbH.[86]

PA imaging and significant PTT efficacy in deep orthotopic brain tumour models (Figure 7D–F). This provides new possibilities for new NIR-II PTA designs and practical deep-in situ GBM phototherapy.

Photoimmunotherapy

In addition to photothermal ablation of tumour cells, PTT triggers antitumor immunity and enhances antitumor effects by releasing relevant antigens and immunostimulatory molecules at the tumor site, activating immune responses, and recruiting tumor-infiltrating cytotoxic T lymphocytes (CTLs).[87] Li et al reported a dual-targeted nanotherapeutic agent for GBM photoimmunotherapy. A nanotherapeutic agent, TNP@JQ1/MRP nanoparticles, can cross the BBB and actively accumulate in the GBM through targeting by T7 peptide by synthesising the NIR-II fluorescent probe MRP and the reduction-activated prodrug (JPC) of JQ1 and modifying the T7 peptide (His-Ala-Ile -Tyr-Pro-Arg-His).[88] Under the guidance of NIR-II fluorescence imaging MRP, 808 nm laser irradiation can induce PTT, release antigens at the tumour site, and recruit CTL to initiate antitumor immune responses accurately. Simultaneously, PTT can trigger the release of JQ1 in tumour cells to circumvent IFN-γ-induced immune evasion. Combined immunotherapy with JQ1 and PTT significantly inhibited tumour growth and prolonged survival time in the subcutaneous G422 tumour model. Immunoanalysis revealed that TNP@JQ1/MRP treatment effectively enhanced antitumor immunogenicity and recruited CTL for tumour regression. Therefore, JPC-loaded TNP@JQ1/MRP prodrug nanoparticles cumulatively regressed GBM tumours by increasing antitumor immunogenicity and overcoming acquired immune resistance. In summary, NIR-II mediated phototherapy has emerged as a promising minimally invasive modality for cancer treatment, with a variety of photothermal agents exhibiting substantial

potential in preclinical investigations, but PTT and photoimmunotherapy for GBM have not yet entered clinical trials and are mainly in the animal model validation or early exploration stage.

Sound Dynamic Therapy

Ultrasound-triggered sonodynamic therapy (SDT) is a promising non-invasive cancer treatment with significant potential in glioma treatment due to its negligible side effects and excellent deep tissue penetration (up to 10 cm).[89–91] NIR-II imaging can provide real-time guidance for the localization of SDT treatment areas, accurately trigger ultrasound activation of sonosensitizers, and induce ferroptosis and apoptosis pathways. In addition, NIR-II imaging can dynamically monitor the spatiotemporal distribution of probes, optimize treatment parameters, and enhance treatment efficacy.[92–94] However, SDT is seriously hindered by the hypoxic TME, high ROS scavenger glutathione (GSH) levels, inefficient ROS production, and the inability to visualise gliomas in vivo for precise monitoring and treatment. Therefore, increasing the oxygen supply to the tumour is an excellent strategy to improve the efficacy of SDT. The introduction of imaging modalities can reveal the optimal treatment time to maximise drug accumulation and dynamically monitor the SDT process in situ and in vivo, which has broad application prospects.

Lv et al used YVO_4: Nd^{3+} particles as the core, MnO_2 nanosheets as the shell, and coupled the sonosensitizer hematoporphyrin monomethyl ether (HMME) and lactoferrin (LF) to construct a new type of nanoprobe (YVO_4: Nd^{3+} -HMME@MnO_2 -LF, labelled YHM), which has BBB penetration and specific targeting effects and can achieve NIR-II imaging/MRI bimodal imaging and MRI of brain tumours—High-efficiency SDT for orthotopic glioma.[95] Due to the overexpressed lactoferrin receptor in GBM cells, LF is further modified on its surface, endowing YHM with good BBB penetration ability and glioma targeting. The YVO_4:Nd^{3+} core exhibits good NIR-II fluorescence properties, enabling YHM to serve as a promising probe for NIR-II fluorescence imaging of orthotopic gliomas. The MnO_2 shell can catalyse H_2O_2 to provide O_2 in the TME, significantly improving the therapeutic effect of SDT; however, it releases Mn_2^+ for TME-responsive MRI. Effectively inhibits the growth of in situ GBM and exhibits significant sonodynamic effects.

In another study, Chen's research group developed a multifunctional nanoprobe named DFMSL by encapsulating luminescent down-shifting nanoparticles (DSNPs) and the chemotherapeutic drug sorafenib (SRF) into the shell of metal-organic frameworks (MOFs), which was further modified with LF ligands.[96] Under the guidance of NIR-II optical imaging, this probe enables targeted accumulation and imaging of nanodrugs in intracranial gliomas, while also facilitating dynamic monitoring of ROS during SDT. Upon ultrasound activation, DFMSL induces a cascade production of ROS, including •OH and $^1O_2$. The generated ROS further promote lysosomal escape of SRF and trigger GSH depletion by inhibiting the System Xc^-, thereby amplifying the destructive damage of ROS to tumor cells. Experimental results show that DFMSL combined with ultrasound irradiation significantly enhanced tumor ablation, with the tumor volume reduced to half of its original size and a survival rate of 80% 30 days post-treatment. These findings conclusively demonstrate the excellent anti-tumor efficacy of DFMSL nanoparticles under ultrasound irradiation. SDT therapy has shown clinical potential in the treatment of glioma, but it is still in the preclinical research stage.

Multimodal Treatment

Highly invasive and aggressive glioma cells blur the boundary between tumours and normal brain tissue, making them extremely difficult to diagnose and remove accurately.[97,98] With the increasing demands of modern medicine, single-modality imaging or treatment cannot obtain sufficient diagnostic information and satisfactory cure results. Brain glioma urgently needs to combine multimodal imaging with effective treatment to diagnose and guide surgery and treatment accurately.[99–101] We have summarized several commonly used multimodal treatment strategies for GBM in Table 2.

Surgery is one of the most commonly used treatment options in clinical practice; however, the complete surgical removal of tumours is hugely challenging. Fortunately, PTT can locally ablate the tumour area with minimal damage to non-laser treatment areas, which may be a good choice for inhibiting residual brain tumours after surgery. For example, Wang et al constructed a macrophage-captured nanotherapeutic agent (MFe_3O_4 Cy5.5) to achieve multimodal imaging-guided glioma treatment.[102] Due to the targeting effect of macrophages, MFe_3O_4 Cy5.5 crossed the BBB and

Table 2 Summary of NIR-II Guided Multimodal Treatment Strategies for GBM

Multimodal Treatment	Combined Treatment Mechanism	References
PTT + Surgery	Fluorescence navigation + Intraoperative photothermal ablation	102
PTT + Chemotherapy	Photothermal ablation + Drug controlled-release	101
PTT + SDT	Photothermal ablation + Oxidative damage enhancement	99
PTT + IT	Photothermal ablation releases tumor antigens	100

Abbreviations: PTT, Photothermal Therapy; SDT, Sonodynamic Therapy; IT, Immunotherapy.

accumulated in rat gliomas. MFe_3O_4 Cy5.5 has good detection depth and a high signal-to-noise ratio. It can perform trimodal FLI/MRI/PAI to distinguish brain tumours from surrounding normal tissues and accurately guide glioma resection. Simultaneously, MFe_3O_4 Cy5.5 can induce local PTT and inhibit the recurrence of gliomas after surgery. This new nano platform, which does not require complex modification, has excellent potential for accurately diagnosing and treating gliomas.

Furthermore, among various combination therapies, PTT/chemotherapy has been shown in several preclinical studies to achieve synergistic therapeutic effects and reduce side effects.[103,104] Li et al developed a functional nanomedicine by encapsulating the A1094 dye and TMZ in PLGA polymers, enabling precise guidance of chemotherapy and photothermal therapy via NIR-II photoacoustic imaging.[101] This approach was further enhanced by combining with anti-CD47 antibodies to relieve immune suppression, thereby amplifying the immune-mediated killing effect. In a recurrent GBM model, the combination of PA1094T and anti-CD47 antibodies significantly enhanced the phagocytosis of cancer cells and effectively remodeled the immunosuppressive microenvironment, leading to better therapeutic outcomes compared to conventional treatments.

Conclusion and Challenges

NIR-II fluorescence imaging is a revolutionary technology with great potential in glioma diagnosis and treatment. Providing more accurate and detailed disease information will pave the way for early diagnosis, surgical navigation, drug efficacy evaluation, and treatment effect monitoring of gliomas and offer new perspectives and tools for precision medicine. The application prospects of NIR-II fluorescence imaging in diagnosing and treating gliomas are becoming increasingly broad as science and technology advances, primarily through innovation in probe development, imaging equipment, and the integration of multimodal imaging technology. However, NIR-II nanoprobes are still in the early stages of development, and several challenges must be overcome for successful clinical translation:

Safety is the primary concern for clinical applications. Nanoprobes and nanotherapeutics are usually subjected to surface modification processes with various biocompatible polymers to reduce toxicity. However, potential toxicity caused by long-term retention and the release of toxic elements still exists, hindering their further application, and it is challenging to prepare probes that can achieve long-term imaging and low tissue accumulation. In addition, most animal experiments are conducted on mice, and the participation of large animal models (including primates) is urgently needed.

Unlike other tumors that grow in peripheral tissues, brain tumors have unique individual physiological structures that limit the entry of various fluorescent probes into brain tissues. Although peptides with targeting capabilities and FUS assistance (including RGD, lipoproteins, and ANG) have been widely used in diagnosing and treating gliomas, there remains a gap between clinical needs and technological development. Therefore, in the early stages of clinical translation, multidisciplinary efforts are necessary, and materials scientists and chemists should design and construct new and promising brain tumor-targeted therapeutic strategies. Simultaneously, the physicochemical properties of existing nanomedicines, including size, shape, surface charge, and coating ligands, are well adjusted to improve transport efficiency, thereby accelerating the transformation of technological advances into clinical benefits.

Under the guidance of near-infrared optical imaging, multimodal treatment is the mainstream trend in brain tumor treatment, which can significantly improve efficacy. More efforts should be made to investigate synergistic ways between various therapeutic functions rather than simply combining them. For example, PTT can induce a series of immunogenic cell deaths, leading to a synergistic tumor-specific immune response. The integration of PTT with emerging CDT, SDT,

and other methods offers the possibility of optimising cancer treatment through complementary mechanisms. Consequently, researchers should focus on preparing multifunctional NIR-II probes and pay more attention to multimodal therapies based on immunotherapy for GBM treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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