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REVIEW ARTICLE

Precision medicine in neurosurgery: The evolving role of theranostics

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Abstract

Theranostics in neurosurgery is a rapidly advancing field of precision medicine that combines diagnostic and therapeutic modalities to optimize patient outcomes. This approach has the potential to provide real-time feedback during therapy and diagnose a condition while simultaneously providing treatment. One such form of theranostics is focused ultrasound, which has been found to be effective in inducing neuroablation and neuromodulation and improving the efficacy of chemotherapy drugs by disrupting the blood–brain barrier. Targeted radionuclide therapy, which pairs positron emission tomography tracers with therapeutic effects and imaging modalities, is another promising form of theranostics for neurosurgery. Automated pathology analysis is yet another form of theranostics that can provide real-time feedback during the surgical resection of tumors. Electrical stimulation has also shown promise in optimizing therapies for patients with cerebral palsy. Overall, theranostics is a cost-effective way to optimize medical care for patients in neurosurgery. It is a relatively new field, but the advancements made so far show great promise for improving patient outcomes.

Keywords: Focused ultrasound; Radiopharmaceuticals; Electrical stimulation; Cerebral palsy; Intraoperative consultation; Automated pathology analysis

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1. Introduction

Neurosurgery is a complex field of medicine where individual differences can significantly impact patient outcomes. Recent advances in technology and the development of novel therapies have paved the way for precision medicine, which aims to personalize clinical care using a scientific framework[1]. Precision medicine accounts for biopsychosocial differences among patients to optimize standardized clinical procedures for each patient's unique prognosis. One such approach within precision medicine is theranostics. The term "theranostics" is a combination of diagnostics and therapy. It was coined by John Funkhouser in 2002, but despite being a relatively new term, the concept has been applied and revisited over many years[2,3]. When a patient requires a neurological procedure, diagnostic imaging is typically conducted beforehand to assess the patient's diagnosis before proceeding with surgery. Theranostics aims to combine these two objectives together to improve the accessibility of neurosurgery, as well as patient outcomes. There are two types of theranostics within neurosurgery: (i) Combined treatment and diagnostics within the same medium or (ii)

separate therapeutic and diagnostic modalities to achieve theranostic capabilities.

First, theranostics can be a modality that combines diagnostic and therapeutic capabilities within the same medium. Delivering treatment while the patient's condition is being evaluated has countless implications for improving the accessibility and cost-effectiveness of neurosurgical procedures. If treatment and diagnosis can be completed at the same time, fewer hospital visits and less overall technology would be required to provide care, reducing the need for multiple treatment regimens, which can improve patient adherence over time. One such example is focused ultrasound (FUS), which has therapeutic effects, such as neuroablation, while simultaneously existing as a useful diagnostic tool[4]. In addition, using radiopharmaceuticals for molecular imaging can treat neurological disorders while they are being diagnosed[5]. In both procedures, the diagnostic medium can also be used for the treatment of a condition. Second, theranostics can combine a diagnostic tool with a separate therapeutic modality. This approach to theranostics strives to collect diagnostic biofeedback during therapy to improve the evaluation of clinical outcomes and the management of treatment toxicities. For instance, automated pathology analysis and intraoperative consultation (IOC) enhance the surgical resection process for brain tumors[6]. In addition, diagnostic tools for cerebral palsy (CP) can be used to inform electrical stimulation therapies to improve their accuracy and precision[7]. In these approaches, diagnostic techniques are used to enhance the treatment process.

Theranostics has many clear advantages, including the improved prediction of toxicities and a real-time evaluation of patient responses, as discussed through the various technologies used[3]. One limitation of theranostics is the relatively recent development of theranostic tools, which leads to a highly variable sensitivity and specificity and results in the unintended exclusion of patients who would have otherwise benefited from these technologies. In recent years, theranostics research has focused on oncology and immunology[8]. The current review will further investigate its applicability in neurosurgery through FUS, molecular imaging using radiopharmaceuticals, automated pathology analysis of brain tumors, and electrical stimulation in CP.

2. FUS

FUS in neurosurgery has transformed the treatment procedures available for various neurological diseases. This technology focuses beams of energy on a single location to provide critical diagnostic and therapeutic care without harming the surrounding tissue[9]. Research has shown that a promising benefit from this technology has emerged in its ability to disrupt the blood–brain barrier (BBB)[10], which is a dynamic membrane that encapsulates various cells, proteins, and molecules to protect the brain from harmful substances. The permeability of the BBB is maintained by tight endothelial junctions created between neuroendothelial cells, pericytes, microglia, and astrocytes[11]. These cells have different functions. For instance, microglia play a role in immune response, while astrocytes contribute to the structure of the BBB[10]. Contrastingly, the blood tumor barrier (BTB) that forms in the brain manipulates this barrier to become more "leaky" and permeable[11]. The BTB, however, is not leaky enough to promote enhanced permeability of various chemotherapy molecules or other therapeutic drugs. FUS is utilized for its ability to disrupt the BBB and temporarily create gaps to allow various therapeutic agents to transfuse and cross through the membrane.

FUS can improve the administration of specific chemotherapeutic agents by increasing the permeability of BTBs. For instance, drugs such as doxorubicin have displayed significant improvements in tumors *in vitro*, but they cannot cross the BTB[10]. Research on FUS in disrupting the BTB was previously restricted by the fear of permanent tissue damage, but FUS is now being increasingly studied for this ability. The interaction of FUS with tissue is frequency-dependent. FUS with lower frequencies provides a greater level of penetration but with a lower resolution. Higher frequencies achieve the opposite effect, with higher resolution and lower levels of penetration[12]. To protect the extraneous healthy soft tissue, lower frequencies with penetration depths restricted to 1 cm are used[13]. Further, a study by Hynynen *et al.* showed that when specific low frequencies of FUS are used, permanent cranial damage can be minimized[14]. One method for administering the low frequencies is through the use of microbubbles that span from 1 to 5 μm in diameter[10]. These bubbles contain lipid-enveloped gas molecules that are administered episodically, and dosage delivery to the BBB can be monitored and modified as necessary[15,16]. The various oscillations and concentrations of the microbubbles have the potential to create mechanical forces to open the BBB[10,13].

One team led by Liu *et al.* monitored the effectiveness of FUS in delivering therapeutic agents to the brain using magnetic resonance imaging (MRI)[17]. Their studies indicated that FUS can help provide an enhanced image monitoring system and dramatically increase the delivery of epirubicin, among other chemotherapeutic agents[17]. Another study analyzed pembrolizumab, which is a commonly used chemotherapy drug that targets the immune system and prevents specific T-cells from being

inhibited by tumor cells[18]. Utilizing the patient's own immune system against the tumor prevents many side effects that other foreign agents could cause. FUS-directed chemotherapy has drastically improved clinical outcomes for patients with glioblastoma[16,17]. Many studies have observed increased inflammation and cranial edema after repeated FUS use, but this finding is dependent on the parameters of FUS used. For instance, one study by Choi *et al.* evaluating an animal model found that 0.25 MPa of pressure led to no cellular or tissue damage, whereas a pressure of 0.42 MPa induced an inflammatory response[19]. For this reason, more research should be catered toward the prevention of adverse reactions when utilizing FUS.

2.1. Neuromodulation

Neuromodulation, another therapeutic tool, involves artificially firing neurons to stimulate a response within a patient's brain[20]. In particular, neuromodulation was found to provide relief from pain and discomfort for individuals with mobility disorders, such as Parkinson's disease (PD) or Tourette syndrome[21]. Its effect can be extended to brain tumors through the use of FUS. Since FUS is non-invasive, it allows for the proper charting and mapping of specific areas of the brain for neuromodulation without significantly exposing other regions[22]. Applying this pair of theranostic tools allows for cellular killing, discharge, and necrosis in selected tissue locations; this discharge can lead to the release of molecules that positively impact the prognosis of brain tumors[22]. One predominant side effect of neuromodulation is the unintended stimulation of both sides of the cortex in unilateral stimulation. A study by Guo *et al.* also found that after widespread use of FUS, there was overstimulation of auditory responses in patients[23]. The research team concluded that the administration of longer single pulses instead of multiple shorter pulses decreases this side effect[23].

2.2. Neuroablation

Similar to neuromodulation, neuroablation is an innovative treatment that kills suspected tumor cells by combining various mediums, such as toxic chemicals and extreme temperatures[24]. This technique is combined with FUS to minimize the killing of healthy neuronal cells. High-intensity FUS uses a high temperature that allows targeted tumor cells to undergo thermal ablation, which causes coagulative necrosis within brain structures and decreases tumor viability[25,26]. Similar to neuromodulation, neuroablation has unintended consequences, such as head and leg tremors[27]. More research will allow us to develop better techniques to guard nearby tissue while providing therapeutic interventions to patients, as depicted in Figure 1.

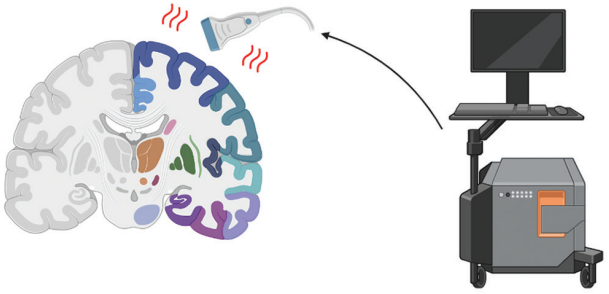


Figure 1. Guided neuroablation is a theranostic tool that combines the ability of focused ultrasound to visualize the various neurological fields while administering various substances, such as chemicals or heat, to destroy neurons. The guided probe provides specification while administering low-frequency ultrasound waves to minimize the killing of healthy tissue[28].

3. Radiopharmaceuticals and molecular imaging

Targeted radionuclide therapy (TRT) within neurosurgery is the theranostic application of radiopharmaceuticals[29]. This therapy involves the pairing of radioactive agents with imaging modalities, allowing for treatment decisions to be made while the condition is being diagnosed. The mechanism and action of radiopharmaceuticals are based on conjugating a radionuclide to carriers such as antibodies, peptides, or ligands. These carriers then enact a radiation effect on a tumor target or a specific tissue location. TRT emits energy signals in the form of β-particles or α-particles to effectively combat tumor progression or molecular pathologies[30]. Emitted when a neutron splits into an electron and proton, β-particles are energetic electrons that have negligible mass and carry a negative charge. They have a higher penetration power than α-particles. On the other hand, α-particles contain two protons and two neutrons, and they have a higher ionization power than β-particles. Nuclear imaging is used to monitor radioactive effects to ensure tissue specificity and minimal invasiveness in surrounding tissues. This duality that combines the diagnostic aspect of location selectivity and the therapeutic capability of radioactive particles provides a deep synergy that allows radionuclide therapy to be an effective theranostic tool, as shown in Figure 2[31]. TRT has been proven to be notably helpful in patients with other neurological comorbidities, where location specificity becomes a particularly relevant consequential factor when making treatment decisions.

3.1. Radiotracers in neuro-oncology

One example of TRT is the use of [^{68}Ga]Ga-DOTA-SSTR positron emission tomography (PET) tracers for their diagnostic and therapeutic capabilities in neuro-

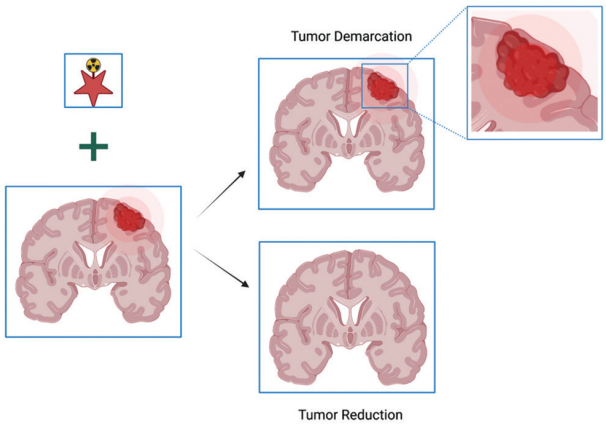


Figure 2. Targeted radionuclide therapy possesses both therapeutic and diagnostic capabilities in the form of size reduction and tumor demarcation, respectively. The incorporation of radiolabeled molecules safely allows for several routes of action as demonstrated.

oncology. A study by Palmisciano *et al.* found that [^{68}Ga]Ga-DOTA-SSTR PET tracers can provide accurate images for the clinical management of meningiomas and pituitary adenomas due to their strong binding to a pathological overexpression of somatostatin subtype receptors 2 (SSTR2)[32]. Accordingly, this tracer is employed in surgical resections to clearly demarcate tumor involvement and minimize damage to the surrounding tissue. Numerous studies have been conducted to assess the clinical applications of [^{68}Ga]Ga-DOTATOC-PET, which are outlined in Table 1. In one case report of a 68-year-old man with pituitary carcinoma, [^{68}Ga]Ga-DOTA-SSTR was combined with [^{177}Lu]Lu-DOTATATE and contributed to a decline in tumor progression over four years[33]. As [^{68}Ga]Ga-DOTA-SSTR imaged the tumor through its affinity for SSTR2, which was overexpressed in the pituitary gland by the tumor, [^{177}Lu]Lu-DOTATATE was able to exert its radioactive effects at binding sites to slow tumor progression[33]. Hence, diagnostic radiotracers, such as [^{177}Lu]Lu-DOTATATE, can be used to have a therapeutic effect on tumor progression, granting them excellent theranostic capabilities. Other forms of radionuclide therapy can be also used for the treatment of meningioma, such as ^{90}Y-DOTATOC. Studies evaluating the utility of this isotope are outlined in Table 2.

3.2. Radiotracers in neurodegenerative disorders

Radiopharmaceuticals can also be utilized to provide real-time feedback during neurosurgical interventions. For instance, [^{11}C]UCB-J in PET scans can be used to target synaptic vesicle protein A2 (SVA2) and subsequently measure synaptic density. SVA2 is a synaptic vesicle membrane protein involved in neurotransmitter release from neurons. Neurodegenerative disorders, such as PD or Alzheimer's disease (AD), are characterized by a decreased expression of SVA2 with a decreased synaptic density[42,43]. Various therapeutic modalities can be used to slow the progression of neurodegenerative disorders, such as electrical neural stimulation, and these forms of treatment can be paired with [^{11}C]UCB-J to provide active feedback while implementing therapeutic measures[44]. The measure of SVA2 by [^{11}C]UCB-J has a remarkable diagnostic capability in neurodegenerative diseases. It has long been and continues to be the standard radiotracer to diagnose different forms of dementia, as well as their severity and varying cognitive manifestations[42]. For instance, in one preclinical study by Bertoglio *et al.* using an animal model, PET scans were conducted for two groups of mice: One wild-type group and one group with AD[45]. Mice with AD showed a significantly lower uptake in the hippocampus. Similar studies were done in mouse models with PD and Huntington's disease, which showed diminished SV2A quantity on PET imaging, emphasizing that [^{11}C]UCB-J can be used to diagnose brain activity in different forms of dementia[45].

Decreased concentrations of the [^{11}C]UCB-J in mice with AD were recently corroborated in clinical trials, which further emphasized the diagnostic potential of [^{11}C]UCB-J. For instance, one study by Wilson *et al.* compared a group of 12 patients with PD to 16 control patients[46]. The study found significantly lower [^{11}C]UCB-J uptake volume on PET scans in various brain regions in patients with PD, but it also found correlations between SVA2 and the severity of patient symptoms. In doing so, it highlighted the correlation between synaptic density and subsequent brain and cognitive damage[46]. In another comparative study by Chen *et al.*, ten patients with AD were compared to 11 control patients. The study found a 41% reduction in hippocampal [^{11}C]UCB-J in patients with AD, and it expanded on this finding by linking [^{11}C]UCB-J to cognitive ability[47]. Hence, in neurosurgical procedures, [^{11}C]UCB-J can be used as a form of biofeedback for cognitive ability when paired with therapeutic modalities, including but not limited to electrical stimulation.

In addition, 18F-FDG is a glucose analog that can be utilized to monitor cerebral glucose metabolism. It has similar implications to [^{11}C]UCB-J in classifying neurodegenerative diseases by severity or cognitive impacts. Because patients with dementia have decreased cerebral glucose metabolism, 18F-FDG with PET scanning allows for the differentiation of AD from the other classifications of dementia by highlighting specific brain regions[48]. In recent years, 18F-FDG is being increasingly investigated to replace [^{11}C]UCB-J in imaging for patients with AD due to its longer half-life advantage[47].

Table 1. Summary of studies assessing the clinical application of [^{68}Ga] Ga-DOTATOC-PET as a diagnostic measure

Study	Participants enrolled	Outcome
Milker-Zabel *et al.*, 2006[34]	Twenty-six patients with meningioma diagnosed with [^{68}Ga] Ga-DOTATOC-PET	[^{68}Ga] Ga-DOTATOC-PET provided additional information about tumor extension that was otherwise not seen in imaging modalities, such as CT/MRI. It also identified a tumor in 1 patient that was otherwise not visible on CT/MRI. The researchers concluded that [^{68}Ga] Ga-DOTATOC-PET improves target definition for intracranial meningiomas
Gehler *et al.*, 2009[35]	Twenty-six patients with skull base meningioma diagnosed with [^{68}Ga] Ga-DOTATOC-PET	[^{68}Ga] Ga-DOTATOC-PET data provided additional information about the tumor in 17 patients. There were major changes observed in clinical target volume in 14 patients. The researchers concluded that [^{68}Ga] Ga-DOTATOC-PET strongly complements CT/MRI data in cases of complex meningioma
Kowalski *et al.*, 2021[36]	Nineteen patients with meningioma diagnosed with MRI and [^{68}Ga] Ga-DOTATOC-PET	Utilizing [^{68}Ga] Ga-DOTATOC-PET resulted in changes in clinical management for 3 patients. Maximum total lesion activity was better identified with [^{68}Ga] Ga-DOTATOC-PET, but meningioma volumes did not change significantly from what was detected by MRI

Abbreviations: CT/MRI: Computed tomography/magnetic resonance imaging; PET: Positron emission tomography.

Table 2. Summary of studies evaluating the utility of ^{90}Y-DOTATOC in meningioma treatment

Study	Patients enrolled	Outcome
Marincek *et al.*, 2015[37]	Thirty-four patients with progressive, unresectable meningioma treated with [^{177}Lu] Lu-DOTATATE and ^{90}Y-DOTATOC	Twenty-three patients achieved stable disease. Three patients experienced severe hematotoxicity, and one patient experienced severe renal toxicity. The study concluded that [^{177}Lu] Lu-DOTATATE and ^{90}Y-DOTATOC are promising tools for treating progressive, unresectable meningioma
Gerster-Gilliéron *et al.*, 2015[38]	Fifteen patients with recurrent or progressive meningioma treated with ^{90}Y-DOTATOC	^{90}Y-DOTATOC is a promising second- or third-line treatment for complex meningiomas
Bartolomei *et al.*, 2009[39]	Twenty-nine patients with recurrent meningioma resistant to treatment treated with ^{90}Y-DOTATOC; grade I (n=14), grade II (n=9), grade III (n=6)	Nineteen patients achieved disease stabilization after 3 months, and 10 experienced disease progression. Better results were seen in grade1 compared to higher grades, with a mean time to progression of 61 months compared to 13
Otte *et al.*, 1999[40]	Twenty-nine patients with advanced SSTR-positive tumors treated with ^{90}Y-DOTATOC	Twenty patients showed disease stabilization, with four showing a reduction of tumor mass and two showing partial remission. Three patients experienced disease progression. Five patients experienced severe renal and/or hematotoxicity from the treatment. The study concluded that ^{90}Y-DOTATOC is a promising therapy if issues of toxicity can be resolved
Seystahl *et al.*, 2016[41]	Twenty patients with progressive meningioma treated with [^{177}Lu] Lu-DOTATATE; grade I (n=5), grade II (n=7), grade III (n=8)	50% of patients reached stable disease after treatment with [^{177}Lu] Lu-DOTATATE. No statistically significant differences were observed between grades

4. Automated pathology diagnosis in neurosurgery

The role of pathology within surgery has held invariable significance over time. This is particularly accurate in neurosurgery with regard to the treatment of brain tumors[49]. The final objective of neuro-oncological procedures is typically dependent on the extent of tumorous tissue resection, which affects the level of cure that can be provided. The intricacies of neuro-oncology treatment following pathological analysis consist of several key events. To date, tumor resection for tissue analysis has followed a traditional pipeline: (i) intraoperatively, tissue samples are acquired and sent to pathologic analysis before proceeding with tissue resection. (ii) This is swiftly followed by the preparation of the sample for histological analysis. (iii) A pathological diagnosis is delivered to the operative team, including the neurosurgeon. (iv) Ultimately, this diagnosis guides the intraoperative, and consequently, the post-operative decisions of those involved in the patient's treatment. Treatment can exist in the form of chemotherapy, radiotherapy, or further surgical intervention following proper post-operative appraisal of the situation[50]. The pipeline described within surgical resection of neoplasms is often labeled as IOC, which is an indispensable step within the operative sequence and has granted theranostics a timely invitation.

Theranostics within the surgical resection of brain tumors primarily emphasizes a means to supplement surgical resection with the intraoperative diagnosis of tissue samples. Characteristics granting speed and accuracy have been increasingly explored within the field, paving the way for deep learning. Deep learning is a form of machine learning and artificial intelligence that is giving way to the development of more diagnostic technology within automated pathology for neurosurgical resections. Notably, a step within IOC pertains to the preparation of tissue samples, which lends itself to successful and accurate diagnoses. Conventionally, tissue samples have been processed as frozen sections and subjected to processing and labeling. Processing involves three steps to ensure the tissue is suitable for fixation within supportive molds. The steps are: (i) Dehydration with agents such as ethanol or isopropanol, among other alcohols; (ii) clearing, involving agents, such as xylene; and (iii) infiltration with a medium of choice, such as paraffin[51,52]. The invasiveness of these steps may carry downstream consequences for the visualization and analysis of slide samples[53]. These consequences can manifest as structural variations, including tissue shrinkage, protein denaturation, the resolution of macromolecules, and the intended degree of staining[54,55]. Conventionally, the processed specimen is labeled with hematoxylin and eosin (H&E) staining[56]. More recently, two techniques have been explored which include stimulated Raman histology (SRH) and third harmonic generation (THG) microscopy[57,58].

4.1. SRH

SRH, a modality that allows for the analysis of tissue through an unlabeled and unprocessed method for preparation and staining, contributes to the greater preservation of important molecular structures, which supports downstream analyses. Developed in 2008, SRH is an infrared microscopical technique that utilizes the vibrational frequencies within the chemical bonds of proteins, lipids, and DNA; it generates images highly reminiscent of H&E-produced imaging[59,60]. SRH has footholds within spontaneous Raman scattering, which is its original predecessor. This method, however, is multiphotonic and utilizes two lasers to generate the desired emission signal through stimulated rather than spontaneous excitation[59]. Overall, the potent variation within the hydrocarbon bonds of the sample creates ample contrast for quicker image resolution and generation.

The capabilities of machine learning in the form of deep convolutional neural networks (DCNNs) have also been explored in the context of SRH. DCNNs utilize trainable features based on histological patterns to allow for automated analysis of processed images. Depending on the specific disorder and pathology, the capacity to train will vary. For example, pathologies with a higher prevalence of pathognomonic features will lend themselves to greater ease in distinction[61]. In a non-inferiority randomized controlled trial, Hollon *et al.* assessed SRH paired DCNN to conventional H&E pathological analysis across 278 cases[61]. Sister samples were generated and designated to one arm of the trial. The overall diagnostic accuracy was 94.6% for the DCNN arm and 93.9% for the control, suggesting that accuracy is not sacrificed at the expense of augmented diagnostic speed. While IOC may consume approximately 20 min in duration, DCNN is implemented on a nearly real-time scale, as shown in Figure 3[62-64]. Further, its potential has been illustrated in other studies that coupled this modality to other forms of image preparation, namely, THG microscopy. Hence, the adoption of machine learning within IOC serves utility in the face of efficiency.

4.2. THG microscopy

As discussed, the processing stage plays a salient role in the diagnostic ability provided by machine learning and this subset of neurosurgical theranostics. Similar to SRH, THG is a multiphotonic technique that utilizes a label-free application. It uses three photons to produce a single photon with the sum of their energy in a process known as photoconversion[65]. The produced images rely on the inherent contrast of the visualized material to create high resolution, bypassing the detriments of certain procedures, such as photobleaching or reactive oxygen species (ROS) production[66,67]. A study of 45 samples assessing THG efficacy in distinguishing gliomas from non-tumorous tissue (n = 37 glioma and n = 8 normal) was described by Blokker *et al.*[68] According to the study, THG has an imaging capture speed that is 8 times faster than SRH, yielding significant advantages regarding speed. The researchers applied fully convolutional networks (FCN), which is a form of deep learning, based on a set of image-level features determined by three pathologists. This was applied to assess the binary diagnostic ability to distinguish between glioma and non-tumor. Overall, the accuracy was 79% with a mean average precision of 0.83. The results of this study in addition to those of the Hollon *et al.*[61] corroborate evidence for the diagnostic efficacy of machine learning and artificial intelligence within IOC while still granting a superior diagnostic speed. Nonetheless, development in this field remains relatively nascent. The latter of the two studies solely assessed the diagnosis of gliomas without other intracranial tumors. The success is extrapolatable to other forms of tumors, such as meningiomas and glioblastomas, based on the former

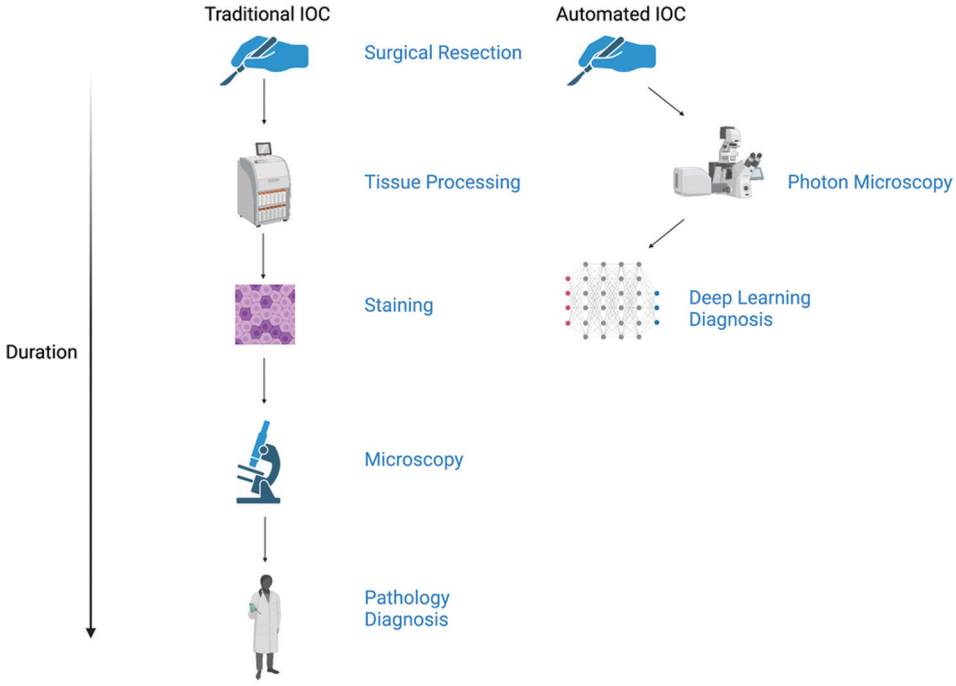


Figure 3. Intraoperative consultation pipeline for histological diagnosis in tumor resection.

study involving SRH and multiple forms of neoplasms, but few other studies have additionally assessed this.

4.3. Confocal laser endomicroscopy (CLE)

In a study by Izadyyazdanabadi *et al.*, CLE was assessed as a mode of imaging, similarly paired to DCNN[68]. The architecture of CLE involves a pen-sized device operated by the surgeon during a procedure requiring fluoroscopy for image generation[63]. This process occurs in real-time at a speed of 0.8 – 1.2 frames/s, as the surgeon navigates the nervous system. Further, these images can be adjusted in both depths without requiring resection, which is also controlled by the surgeon. There are two relevant disadvantages to using this imaging modality. First, as with any fluorophore dependency, there is a possibility of ROS production and damage to cellular structures[69,70]. Second, pertaining to CLE, the rapid generation of images creates a barrier in itself, as the interpretation and diagnosis of such images is a demanding task. Another limitation of CLE is its design – the motion in addition to blood flow and indiscernible tissue features ultimately produces images that are impractical for diagnosis. These images were described by Izadyyazdanabadi *et al.* as non-useful and occurred in nearly half of the 20,000 images generated in an *in vivo* application of CLE for intracranial neoplasms[71]. The DCNN model applied by Izadyyazdanabadi *et al.* displayed a tumoral diagnostic accuracy of 85% in comparison to a 75% and 67% accuracy, based on interpretations by two neurosurgeons, which still shows a significant benefit of utilization[68]. Overall, these recent advances suggest that machine learning within neurosurgery could play a significant role in theranostics and IOC.

5. Electrical stimulation in CP

CP is a group of neurological disorders that affect muscle tone, movement, and coordination; it is the most common cause of motor disability in children[72]. Historically, the diagnosis, prognosis, and management of CP have been challenging; however, with recent advances in technology, different treatments are becoming increasingly available. One such paradigm of treatment is through the use of electrical stimulation, which has emerged as a particularly effective mode of therapy for patients with CP, mirroring the success seen with other neuromuscular conditions. Within the scope of electrical stimulation, there are a few types that have predominated academic and clinical interest over the past decade, such as functional electrical stimulation (FES) and transcranial direct current stimulation (tDCS); both have shown efficacy in improving muscle function and movement. Along the theme of theranostic application, a notable benefit of utilizing electrical stimulation is its direct connection to the standard metric and methods used diagnostically to uncover and track the progression of neurological diseases, such as CP. This is congruent with the current drive within research to develop real-time biofeedback systems that can help patients during therapy,

which would automate and adapt treatment to the needs of each patient.

5.1. Functional electrical stimulation

Functional electrical stimulation is currently being studied in relation to its efficacy among patients with CP. Through this ongoing research, scientists and clinicians have found evidence of use-dependent muscle plasticity in patients with CP[73]. In many cases, this resulted in permanent improvements in voluntary ankle control after repetitive stimulation, implying a lasting therapeutic effect of FES, and providing a measurable metric of real-time efficacy. Trials conducted by Pool *et al.* have corroborated these findings by showing how FES can result in an increase in initial contact ankle angle, maximum dorsiflexion ankle angle in swing, normalized time in stance, and normalized step length in pediatric unilateral patients with CP[74]. Further, by combining adaptive ankle assistance with step-length biofeedback, lower-extremity gait mechanics in patients with CP can be monitored in real-time and immediately improved[75]. The expectation that this form of therapy will likely be beneficial is consistent with the understanding that an altered central drive to the ankle muscles and increased passive muscle stiffness may be the primary causes of foot drop and toe walking in patients with CP[76]. The feasibility and practical application of the mainstream application of this treatment are still being researched and established[77].

One specific form of FES, neuromuscular electrical stimulation (NMES), has shown particular promise in treating CP. When paired with electromyography or other acute, non-invasive measurements, NMES can act as a closed-loop system providing immediate feedback for therapeutic procedures. One specific example is the combination of NMES and robotic knee extension assistance as a theranostic modality. The combination of NMES and electromechanical feedback positively affects knee extension during stance with reliable, customized, and low-latency electrical stimulation[7]. Similarly, the knee-extension metric can be utilized as a prognostic metric to measure, recover, or diagnose the severity of CP symptoms. Continued work toward the use of diagnostics to synchronize NMES to gait cycles for improved effects is a current goal in the scope of rehabilitation medicine and medical research. Within that scope, the consideration of pathogenic physiology is still being explored[78].

5.2. Electromyography

Within neurosurgery, real-time biofeedback systems have garnered recent attention. Studies have shown that electromyography with high-quality biofeedback can encourage and support home-based therapy for pediatric patients with CP, particularly when coupled with some form of interactive medium such as a video game[79]. This mode of diagnostics provides a self-metric, which allows subjects and patients to adapt and adjust dynamically. In addition, motion in the upper extremities can be improved when robotic feedback therapy is utilized before conventional therapeutic methods; self-contained robotic systems are being developed to achieve this goal[80-82]. These cases highlight that modern therapies are not necessarily intended to replace conventional therapies, but instead to augment them or address special cases or gaps in previous methods. The current research has found that gait training is the most effective rehabilitation method for patients with CP, while strength training is negligible. Other methods, such as velocity training, electromyographic biofeedback training, and whole-body vibration, have appeared promising in individual cases, but further research is needed to prove that they are as effective as stand-alone therapies[83]. Gait training, among other methods, can be further optimized for each individual with CP using biofeedback.

5.3. Transcranial direct current stimulation

In a similar vein, trials are being conducted to establish the clinical utility of tDCS in treating CP[80,84,85]. Two such trials are currently evaluating the effects of combining tDCS with treadmill and mobility training on neuromuscular functionality in patients with CP[86,87]. In one of these studies, multiple non-invasive metrics were proposed for simultaneous tracking of the condition and visual feedback was provided to the subject through a gamified setup to allow for self-adjustment[87]. While this was not designed to generate an immediate closed loop, it should be noted that this form of feedback in training may be applicable to the general case of stimulation therapy. Ultimately, even in its current form, gait training was found to be more effective when using combined therapy. Scientific interest in tDCS seems to be leaning more toward hybrid applications than stand-alone therapy for CP. For instance, researchers are also currently investigating the combination of tDCS with hydrotherapy as a treatment for CP[88]. In this format, buoyancy would act as a form of instant adjustment and biofeedback in a corrective sense rather than a diagnostic sense. Conclusions on efficacy and function cannot yet be assumed, since this study is ongoing through December 2023, and there are no results as of yet. Safety standards will likely be discussed in the resulting paper.

Researchers have also found that anodal tDCS can result in an immediate improvement in the unimanual gross motor dexterity of the hemiplegic hand[89]. Under observation, this lasted for a minimum of 90 min,

Table 3. The post-operative effects of DBS on CP-based dystonia

Scale	Subscale	Pre-operative	3 months post-operative	6 months post- operative
Quality	Basal frequency (Hz)	192.11	212.77	219.38
	Jitter (%)	1.12	0.58	0.54
	Shimmer (dB)	4.948	3.39	2.988
	Noise-harmonic ratio	0.1822	0.114	0.0878
	Breath sound index	0.6	2.08	2.15
	Irregularity	1.72	1.4	0.81
	Maximum phonation time (s)	3.56	7.36	9.12
	DSI index	–0.2	0.8	2.9
Articulation	Jaw distance	550.73	535.92	508.96
	Tongue distance	1283.79	649.92	1783.17
	VSA	281914	278951	372958

Abbreviations: DBS: Deep brain stimulation; CP: Cerebral palsy; VSA: Vowel space area; DSI: Dysphonia severity index.

supporting its efficacy, even outside of the scope of gait correction. This conclusion, however, is not definitive. A literature review on tDCS interventions in pediatric motor disorders found that tDCS, while being a safe technique that likely improves gait measures and involuntary movements, has shown limited effectiveness in improving balance and upper extremity function overall[86]. Other studies have found that combining tDCS with bimanual training in children and young adults with unilateral CP showed inconsistent gains for objective measures of hand function[90]. The general and mechanistic effects of tDCS over the primary motor cortex, as well as when combined with functional training of the paretic limb, are currently under investigation[91]. Before considering the integration of tDCS into a brain-computer interface (BCI)-like loop or theranostic system, the mechanism must be isolated and defined.

5.4. Deep brain stimulation (DBS)

Along with FES and tDCS, DBS has rxxxecently been shown to be effective in treating CP-related pain and is currently being explored in terms of its capabilities to address motor symptoms[92]. In the clinic, stimulation of the superior cerebellar peduncles has shown efficacy in treating a subgroup of patients with CP-based dystonia and spasticity for whom stimulation of the dentate nuclei, which are deep cerebellar nuclei located within the white matter adjacent to the fourth ventricle, had been ineffective[93-95]. This finding coheres with other studies supporting the efficacy of DBS in improving motor symptoms in CP-based dystonia, as shown in Table 3[96]. Further research is still needed to determine the long-term effects of DBS on patients with CP, as DBS is still considered an experimental therapy for CP. Recent interest in developing a clinically viable bidirectional DBS-based neural interface projects a heavy implication that a real-time bidirectional form of DBS-based theranostic treatment may be just around the corner[97-99].

6. Conclusion

Theranostics in neurosurgery is an emerging field that combines diagnostic and therapeutic media in real-time to personalize medical care for each unique patient. FUS, radiopharmaceuticals, automated pathology analysis in tumor resection, and electrical stimulation for CP are four examples of innovative neurosurgical techniques within theranostics. Theranostics grants a new level of speed and accuracy to neurosurgical procedures, as seen in these techniques. Because these technologies are recent developments, more research is needed regarding their efficacy in different populations. Further, the accessibility of these technologies, particularly in rural areas, is largely unknown. These theranostic modalities are also likely applicable to many different neurological disorders, and future studies should focus on expanding their utility in various areas of neurosurgery. Despite these gaps in current research, theranostics permits a new level of precision medicine within neurosurgery, and its utility will only continue to increase as more research is conducted.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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