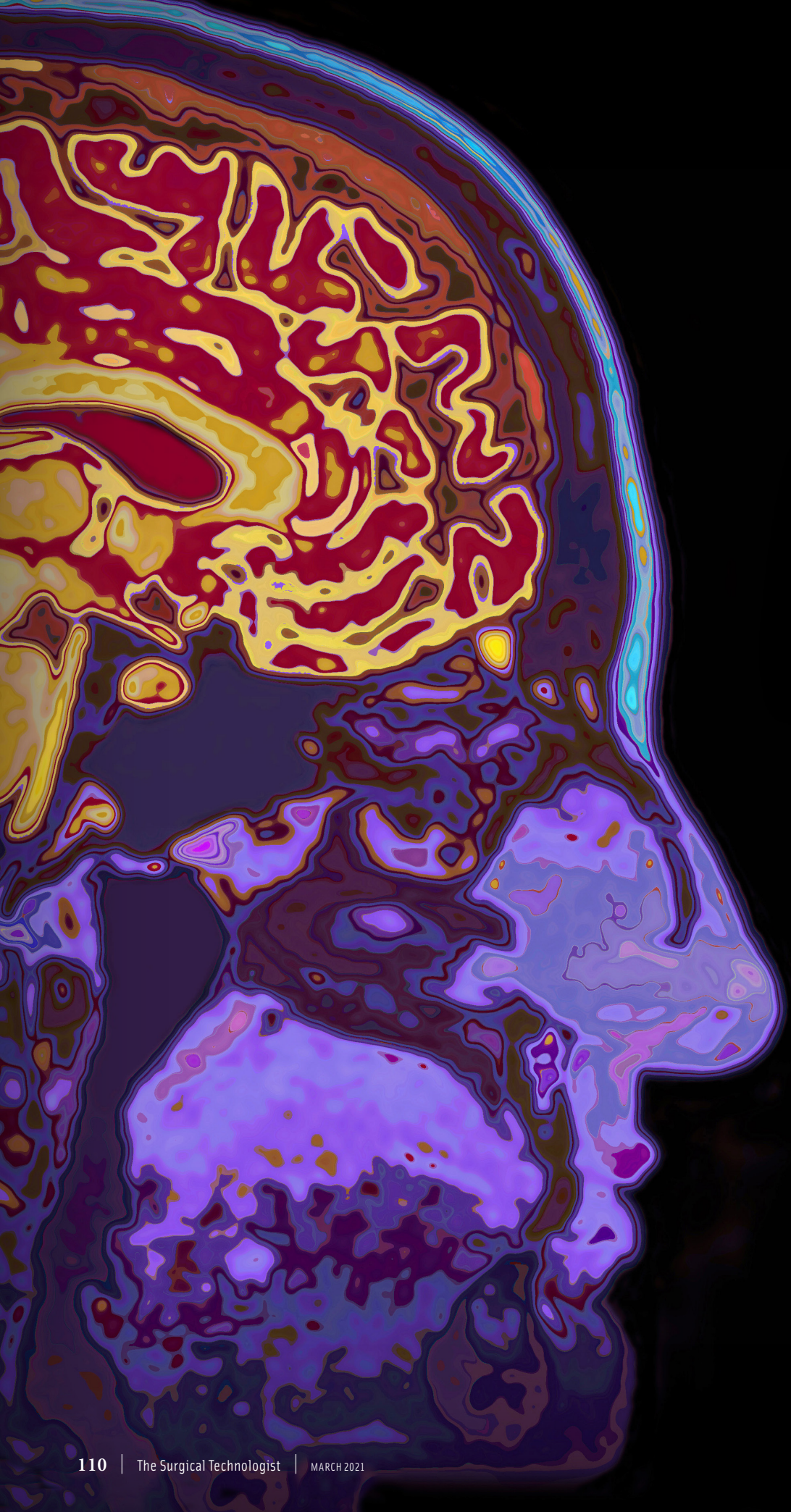

5-ALA Fluorescence-Guided Resection of Malignant Gliomas

Jeffrey Anderson, CST

One of the greatest challenges in the surgical treatment of malignant gliomas revolves around the visualization and subsequent resection of tumor margins. This is where fluorescence-guided surgery (FGS) using 5-aminolevulinic acid (5-ALA) oral solution comes into play.

This method utilizes tumor marking that permit the surgeon to have real-time intraoperative guidance and visualization of glioma tumor borders. The 5-ALA method can be independent of or work in tangent with stereotactic neuronavigation that allows direct real time visualization to differentiate the tumor from normal neural tissue.

5-ALA is delivered orally in a prepared solution to the patient approximately three hours prior to surgery. It is associated with unprecedented predictive ability for identifying malignant glioma tissue. Tumor dissection often utilizes white light microscopy, unlike the blue light microscopy used with 5-ALA. To this end, 5-ALA FGS has aided in achieving a significantly higher rate of complete resections in malignant gliomas cases. 5-ALA FGS has been found to be a reliable surgical technique and quickly has become the standard of care at many neurosurgical departments globally.[2]

Initially this method was introduced by Dr. Walter Stummer in 1998. Stummer and his team conducted a trail in Europe that demonstrated the efficacy of this technique. He was able to

LEARNING OBJECTIVES

- Learn about fluorescence-guided surgery for the treatment of malignant gliomas
- Evaluate the pathophysiology prompting surgical intervention for this procedure
- Identify the supplies and equipment used during this procedure
- Review the procedural steps required during a 5-ALA fluorescence-guided resection of malignant gliomas
- List the special considerations needed for this procedure

show that this technique resulted in much higher rates of gross total resection when compared to the control group of patients.[5] 5-ALA is a naturally occurring metabolite in the human body. It is produced within the metabolic pathway. The unique characteristic of this metabolite is that it easily crosses the blood brain barrier and consequently easily passes through the surgical capsule or tumor interface. Normal tissue can metabolize the drug to hemoglobin where cancer cells cannot, and therefore, the fluorescence accumulates within the tumor cells causing them to glow red under blue light.

Once 5-ALA is taken up by malignant glioma cells, it is metabolized into the fluorescent metabolite, protoporphyrin IX (PpIX). Elevated PpIX production within malignant brain tumor cells permits violet-red fluorescence visualization of malignant tumor tissue after excitation with 405 nm wavelength blue light. The preferential accumulation of 5-ALA within malignant glioma cells is felt to occur due to decreased levels of ferrochelatase (a heme production enzyme that produces heme with the addition of iron (Fe)) and selective uptake by an ATP-binding cassette transporter (ABCB6). Other factors that correlate with fluorescence induced by 5-ALA are cellular density, tumor cell proliferative activity, neovascularity of the tumor, and BBB permeability.[2]

5-ALA has offered tremendous advancement in the treatment of malignant gliomas. However, it is not without its drawbacks. There is a risk for false positive fluorescence. Some patients have experienced fluorescence in viable tissue areas surrounding the resected tumor site. It is noteworthy to state that the fluorescence usually will not be found in normal brain tissue distant from the original tumor site. Reactive astrocytes may be to blame in patients who do experience false positive fluorescence. In rare cases, a patient might experience what is called autofluorescence of normal brain tissue. Moreover, research has shown that in 313 patients operated on for suspected recurrent glioblastomas, about 3% turned out to have pathology consistent with radiation necrosis in tissues demonstrating fluorescence.[2]

Conversely, there are some occasions where 5-ALA does not properly mark the margins of the tumor. This usually occurs for specific reasons. Malignant gliomas are characterized by a disseminated in-growth pattern within normal brain tissue. To that end, cancer cells may be found centimeters away from the bulk of the tumor and will not be highlighted in the same way as more dense parts of the glioma would be. However, the success rate in identifying these less dense margins is increased with the use of spectrometry. Spectrometry is what aids in identifying fluorescence in regions of low-density cell infiltration too weak to be visualized directly with the microscope alone by causing the fluorescence to glow. Moreover, false negatives can occur due to structural barriers that interfere with the visualization of the fluorescence. This can occur due to photobleaching, blood and/or normal brain tissue obstructing the direct visualization of the resection cavity. Photobleaching occurs when the fluorescence breaks down due to prolonged light exposure. Thus, fluorescence cannot replace proper surgical technique and adequate visualization of the entire resection cavity. Additionally, timing is critically important when it comes to positive patient outcomes. Once 5-ALA is given it is rapidly absorbed into the bloodstream within one hour. However, protoporphyrin IX (PpIX) plasma levels peak four hours after oral administration of 5-ALA. Consequently, taking the patient to surgery too soon or too late will negatively impact the efficacy of the tumor fluorescence. Lastly, tumor necrosis may not demonstrate tumor fluorescence and could therefore be misidentified.[2]

> Tumor dissection often utilizes white light microscopy, unlike the blue light microscopy used with 5-ALA. To this end, 5-ALA FGS has aided in achieving a significantly higher rate of complete resections in malignant gliomas cases.

Fluorescence-guided surgery is a great and simple tool that allows for real-time intraoperative identification of residual glioma tissue. Despite its risks, research suggests this method will continue to be an important component to any neurosurgeon's armamentarium when it comes to the definitive treatment of malignant gliomas.

SUPPLIES

- Hemostatic scalpel clips (Raney) or Dandy scalp clamps
- Basic neuro pack
- Ray-Tec and laparotomy sponges
- Hemostatic agents and/or bone wax
- Bipolar cord
- Monopolar ESU
- Cottonoid patties in various sizes
- Hemostatic clips that are MRI compatible
- Cotton balls
- Drain
- Nerve stimulator
- Microscope drape
- Ultrasound wand
- Suture of surgeon's choice
  -Usually silk or neurolon for dura, polyglactin 910 for galeal closure and monofilament nylon or stainless steel clips for skin.

Medications and solutions

- Antibiotic irrigation
- Thrombin for gelfoam (hemostasis)
  -5-ALA
  *All supplies may be evaluated for use with non-magnetized options[1]

EQUIPMENT

- Operative ultrasound machine
- Frame-based or frameless stereotaxis system
- Cavitron Ultrasonic Aspirator (CUSA)
  -Uses ultrasonic waves to emulsify and aspirate tumors
- Body temperature regulation systems (warming blankets, temp monitors,etc.)
- Bipolar and monopolar ESUs
- Neuroendoscope, light source and monitor
- Fluid warmer
- Cell saver autotransfusion machine[1]
- Microscope with spectrometric capabilities

INSTRUMENTATION

Basic Neuro Tray to include (if traditional room is employed):

- Hudson brace with bits
- Gigli saw with handles
- Various rongeurs: Kerrisons, Leksell, Stille-Leur, Adson, Ferris-Smith
- Penfield dissectors
- Self-retaining retractors: Weitlaners, Adson-Beckman, Adson cerebellar, Leyla or Greenberg
- Manual retractors: Cushing, Meyerding, Taylor, Love or Scoville
- Malleable brain spoons: pituitary spoons, nerve hooks, dura hooks, dural elevators
- Neuro forceps: Bayonet, Cushing, Adson, Gerald with and without teeth and Dural forceps
- Periosteal elevators: Adson, Langenbeck, Freer, Cushing
- Curettes of various sizes and angles
- Gouges
- Osteotomes
- Suction tips of various size: Frazier, Adson or Fukushima
- Scalp clip applicators
- Dandy clamps
- Hemoclip applier
- Bipolar forceps: irrigating or plain

Microsurgical Instruments:

- Arachnoid knife
- Micro-forceps
- Curettes
- Micro-scissors
- Needle holders (Castroviejo)
- Micro-dissectors
- Micro-bipolar forceps

Powered Equipment:

- Midas rex, Anspach or TPS drill systems with attachments

* *Non-magnetized equipment and instrumentation necessary if MRI is used intraoperatively*[1]

Specimen Care:

- Fresh/frozen protocol for margin analysis
- Permanent in formalin for non-fresh/frozen specimens

PATHOPHYSIOLOGY PROMPTING SURGICAL INTERVENTION

Glial cells are essential for nerve cell function. They are found in surrounding neurons; however, they do not take part in the synaptic signaling that neurons do. Glia are more numerous than neurons. They are smaller and lack axons and dendrites. Glial cells function to maintain homeostasis by regulating the rate of nerve signal propagation and synaptic action by controlling the rate of neurotransmitters, providing scaffolding for neural development, and by aiding in the recovery of or preventing of neural injury. The three types of glial cells found in the central nervous system are microglial cells, oligodendrocytes and astrocytes.[4]

A glioma is a tumor that arises from glial cells. To that end, gliomas can be found in either the central or peripheral nervous systems. The types of glioma are defined by the types of glia from which they are derived. Astrocytoma can include astrocytoma, anaplastic astrocytoma and glioblastoma. Ependymomas include anaplastic ependymoma, myxopapillary ependymoma and subependymoma. Finally, oligodendrogliomas can include oligodendroglioma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma.[3]

Signs and symptoms of gliomas include:[3]

- Headache
- Nausea or vomiting
- Confusion or a decline in brain function
- Memory loss
- Personality changes or irritability
- Difficulty with balance
- Urinary incontinence
- Vision problems, such as blurred vision, double vision or loss of peripheral vision
- Speech difficulties
- Seizures, especially in someone without a history of seizures

Diagnostic interventions (preoperative):[1]

- Computerized Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Magnetic Resonance Spectroscopy (MRS)
- Positron Emission Tomography (PET)
- WADA test (lateralization of the brain)
- Stereotactic guided bx

PATIENT POSITION

Patient positioning will be dependent on the tumor site. Commonly, the patient will be placed in the supine positon and secured in a skull fixation system or accompanying stereotactic system. The supine position is commonly used because it allows access to the frontal, parietal and temporal lobes. However, the lateral or semi-lateral position may be utilized in the treatment of lesions found in the temporal lobe, occipital lobe, brain stem or cerebellum. A bean bag, pillow, tape, or chest rolls may be employed to stabilize the patient's body. The sitting position facilitates bilateral access to the occipital lobe, brain stem or cerebellum. Occasionally the prone position is used to access the occipital lobe, cerebellum or brain stem. Chest rolls or a Wilson-style frame may be used to facilitate respiration in this position.[1] Patient positioning devices will need to be evaluated for compatibility with hybrid or interventional radiology rooms.

SPECIAL CONSIDERATIONS

It is important to ensure that all scans, angiograms and plain films are available prior to the case start. Additionally, the surgical technologist needs to test all power equipment during the case set-up to ensure everything is working. The absorbable hemostat will need to be cut to the same size of the available cottonoids as they will be used in unison with thrombin added. A 10 ml slip tip syringe will be helpful when unclogging Frazier style suction tips. There most likely will be multiple small countables used during this type of procedure so organization and good count strategies are paramount. Also, bacitracin irrigation may induce seizures when introduced to neural tissue and needs to be avoided.[1]

PROCEDURAL STEPS

Standard neurosurgical methods often will be used in conjunction with stereotactic equipment to access the site of pathology. A U-shaped incision will be made followed by the application of Raney style scalp clips or Dandy scalp clamps. Next, the galea and periosteum will be incised with the ESU. The periosteal elevator will be used to aid in the freeing of the scalp flap exposing the cranium. Hemostasis will be achieved, and the scalp will be retracted.

Two burr holes will be made into the cranium with a perforator bit and craniotome or manually powered Hudson Brace. Irrigation will be used to cool the bit and flush out debris when perforating the bone. The holes will be curetted

out and the dura will be freed from the cranium with a #3 Penfield or Adson dissector. The perforations will be connected by using a side-cutting bit on a powered craniotome or manually with a Gigli saw. Once the flap has been freed, it will be peeled off the dura with the help of a periosteal elevator. The bone flap will be isolated and kept moist on the back table in a properly labeled basin.

> Fluorescence-guided surgery is a great and simple tool that allows for real-time intraoperative identification of residual glioma tissue.

Bone bleeding from the edges of the craniotomy will be attended to with bone wax. At this time, small holes may be drilled around the edge of the cranial defect to facilitate the tacking of the dura. The dura will be incised with a #11 or #15 blade, extended with Metzenbaum or dura scissors and tacked and/or retracted. Cottonoids soaked in thrombin will be used to aid in hemostasis and to protect the neural tissue underneath the dura. Brain spoons will be moistened and attached to the Layla system if indicated.[1]

It is at this point that the site of pathology is approached through careful dissection. As the neurosurgeon nears the radiographic or functional boundaries of the tumor, they will reference anatomical and visual cues, MRI-based neuronavigation, intraoperative stimulation mapping, and 5-ALA-based FGS using wide-field surgical microscopy. Once the margins are identified, the regions adjacent to the malignancy that are non-eloquent will be resected using more aggressive techniques.

Once the tumor has been debulked, the surgeon will continue the dissection to critical areas of tumor that may be near eloquent brain tissue. High-resolution spectrometric microscopy of the exposed tissue surfaces allows the surgeon to measure the microscopic PpIX expression that should correlate with the preoperative pathologic studies such as tumor burden and proliferative/mitotic index. It is the PpIX that highlights the glial cells of the tumor. Margins are often biopsied and sent to pathology using frozen-section protocols to confirm adequate resection. However, the addition of 5-ALA has offered a reliable alternative to frozen sectioning and offers a non-invasive and real-time alternative to traditional biopsies.

The dissection will be completed using conventional surgical methods such as ultrasonic aspiration and microscopic dissection techniques. Neuronavigation is frequently employed to track and identify or confirm the spatial coordinates of the pathology.[5] Once adequate margins have been confirmed, the surgeon will attain hemostasis with the use of warm irrigation, absorbable hemostat, thrombin-soaked absorbable gelatin powder, and bipolar cautery. Once irrigated, the dura is closed in an airtight fashion. The most frequently used suture used is a 4-0 braided nylon or silk suture.[1]

A drill is used to place several small holes in the edges of the cranial defect and the removed bone flap. The flap is then secured to the cranium with titanium screws and plates. The flap may also be wired in place with stainless steel wire.[1] A closed system drain is placed adjacent to the incision and secured with a non-absorbable suture. The wound is closed and in the usual layered fashion and dressings are applied.

The wound is classified as a Class 1: Clean/Sterile – Ideal.[1]

COMPLICATIONS/RISKS:

The common complications or risks to this procedure include the following:

- Infection
- Hemorrhage
- Blood clots
- Pneumonia
- Unstable blood pressure
- Seizures
- Muscle weakness
- Brain swelling
- Leakage of cerebrospinal fluid

Other complications are rare and generally relate to specific locations within the brain, so they may or may not be valid risks for certain individuals such as memory problems, speech difficulty, paralysis, abnormal balance or coordination, and coma.[3]

ABOUT THE AUTHOR

Jeffrey Anderson has been a Certified Surgical Technologist (CST) since 1998. He began his medical career as a Certified Nurse's Assistant, which taught him the people skills and empa-

thy needed to care for patients. He then progressed to a Certified Registered Medication Technician, which taught him the necessity of being organized in his practice. He eventually discovered surgical technology from a dear friend and immediately signed up to become a surgical technologist through the Maine Medical Center School of Surgical Technology which broadened his knowledge of anatomy, physiology, and aseptic technique. He received his associate degree in applied science degree in surgical technology from Southern Maine Community College and later graduated from the National Institute of First Assisting (NIFA), based in Colorado. He completed his undergraduate studies at St. Joseph's College of Maine in 2018 and was awarded a Bachelor of Science in general studies degree in education and training. He is currently working on a master's degree in healthcare education at the same institution. He is also an instructor at the Maine Medical Center's School of Surgical Technology in Portland, Maine where he has been teaching for the past 11 years and lectures out of the Southern Maine Community College campus in South Portland. He currently serves as the vice president of AST's Maine State Assembly.

Jeffrey was a traveling CST for several years early in his career, and clinically has worked in a variety of settings ranging from level one trauma centers to ambulatory surgery centers. Geographically, he has worked all across the country from Anchorage, Alaska to Yuma, Arizona. He aims to bring his life experiences and clinical skills acquired throughout his adventures to the classroom where he aspires to inspire the next generation of surgical technologists to embrace the motto "Aeger Primo." With this fast-paced and ever-changing career field, he views learning as a life-long endeavor and encourages students to continue to strive for excellence within their practice beyond the confines of the school's program. He hopes to advocate for this profession on a broader scale through his position and participation on the Maine State Assembly Board of Directors.

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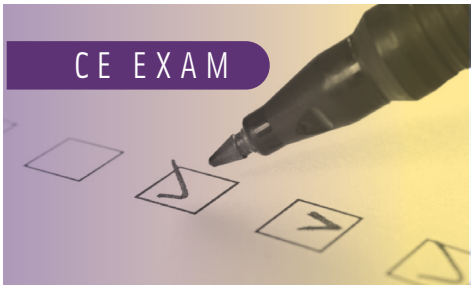

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5-ALA Fluorescence-Guided Resection of Malignant Gliomas

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1. **5-ALA is delivered orally in a prepared solution to the patient approximately ___ prior to surgery.**
a. 30 minutes
b. 3 hours
c. 6 hours
d. 1 day

2. **True or false: Tumor dissection often utilizes blue light microscopy, unlike the white light microscopy used with 5-ALA.**
a. True
b. False

3. **_____is what aids in identifying fluorescence in regions of low-density cell infiltration too weak to be visualized directly with the microscope alone.**
a. Photo bleaching
b. Light microscopy
c. Spectrometry
d. None of the above

4. **A glioma is a tumor that arises from:**
a. Glial cells
b. Glioma neurons
c. Bone cells
d. Endothelial cells

5. **What type of incision will be used to start the procedure?**
a. C-shaped
b. Lateral
c. Perpendicular
d. U-shaped

6. **Malignant gliomas are characterized by a disseminated ____ pattern within normal brain tissue.**
a. Lateral
b. In-growth
c. Infiltrative
d. Expansive

7. **Once 5-ALA is given it is rapidly absorbed into the bloodstream within:**
a. 10 minutes
b. 45 minutes
c. 1 hour
d. 3 hours

8. **True or false: Glia are more numerous than neurons.**
a. True
b. False

9. **For this procedure, which patient positioning is commonly used because it allows access to the frontal, parietal and temporal lobes?**
a. Lateral
b. Prone
c. Fowler's
d. Supine

10. **Since the cancer cells cannot metabolize 5-ALA, the fluorescence accumulates within the tumor cells causing them to glow ___ under blue light.**
a. Yellow
b. Red
c. White
d. Orange

5-ALA FLUORESCENCE-GUIDED RESECTION OF MALIGNANT GLIOMAS #447 MARCH 2021 1 CE CREDIT $6

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