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Surface-Registration Frameless Stereotactic Navigation Is Less Accurate During Prone Surgeries: Intraoperative Near-Infrared Visualization Using Second Window Indocyanine Green Offers an Adjunct

Steve S. Cho,^{1,2} Clare W. Teng,^{1,2} Ashwin Ramayya,¹ Love Buch,¹ Jasmin Hussain,¹ Jessica Harsch,¹ Steven Brem,¹ John Y.K. Lee¹

¹Department of Neurosurgery, The Hospital of the University of Pennsylvania, 801 Spruce Street, 8th Floor, Philadelphia, PA, 19107, USA ²Perelman School of Medicine, The University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA, 19104, USA

Abstract

Background: Frameless neuronavigation allows neurosurgeons to visualize and relate the position of surgical instruments to intracranial pathologies based on preoperative tomographic imaging. However, neuronavigation can often be inaccurate. Multiple factors have been proposed as potential causes, and new technologies are needed to overcome these challenges. *Objective:* To evaluate the accuracy of neuronavigation systems compared to near-infrared (NIR) fluorescence imaging using Second Window Indocyanine Green, a novel technique, and to determine factors that lead to neuronavigation errors.

Methods: A retrospective analysis was conducted on 56 patients who underwent primary resections of intracranial tumors. Patients received 5 mg/kg ICG approximately 24 h preoperatively. Intraoperatively, neuronavigation was used to plan craniotomies to place the tumors in the center. After craniotomy, NIR imaging visualized tumor-specific NIR signals. The accuracy of neuronavigation and NIR fluorescence imaging for delineating the tumor boundary prior to durotomy was compared.

Results: The neuronavigation centers and NIR centers were 23.0 ± 7.7 % and 2.6 ± 1.1 % deviated from the tumor centers, respectively, relative to the craniotomy sizes. In 12 cases, significant changes were made to the planned durotomy based on NIR imaging. Patient position was a significant predictor of neuronavigation inaccuracy on both univariate and multivariate analysis, with the prone position having significantly higher inaccuracy (29.2 ± 8.1 %) compared to the supine (16.2 ± 8.1 %, *p* value < 0.001) or the lateral (17.9 ± 5.1 %, *p* value = 0.003) positions.

Conclusion: Patient position significantly affects neuronavigation accuracy. Intraoperative NIR fluorescence imaging before durotomy offers an opportunity to readjust the neuronavigation image space to better align with the patient space.

Key words: Frameless neuronavigation, Intracranial tumors, Near-infrared fluorescence imaging, Second Window Indocyanine Green

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Correspondence to: John Lee; e-mail: leejohn@uphs.upenn.edu

Introduction

Completeness of surgical resection is a vital factor in the prognosis of intracranial tumors [1–3]. In order to achieve maximal safe resection, accurate localization of pathology in the intracranial space intraoperatively is crucial. While magnetic resonance imaging (MRI), computed tomography (CT), and angiography have guided surgical planning for decades, a reliable imaging system to help surgeons intraoperatively in real time has yet to be established. Among the recent adjuncts to neurosurgery, neuronavigation has become increasingly prevalent [4–6].

Neuronavigation, or frameless stereotactic navigation, was introduced in 1986 by Roberts and colleagues [7]. In contrast to its immediate, frame-based predecessor, neuronavigation is a "frameless" technique; conferring it increased adaptability and utility [8]. Neuronavigation relies on the spatial registration of anatomical landmarks in the physical "patient space" to the same structures in preoperatively acquired, virtual "image space" [9]. Despite its widespread adoption in neurosurgery, the benefits of neuronavigation remain controversial [10, 11]. One of the most discussed limitations of this technique is the brain shift phenomenon, in which the movement of the soft, pliable brain during surgery invalidates the initial patient-to-image registration. The causes of brain shift are multifold, including physical (i.e., gravity), surgical (i.e., fluid and tissue loss), and biological (*i.e.*, tumor type) factors [4, 12– 14]. While intraoperative MRI has been trialed to address these issues [15], its use is associated with high cost, low availability, and increased operative length [16, 17].

More recently, fluorescence-guided surgery (FGS) has emerged as a cost-effective alternative to visualize intracranial tumors in real time [18, 19]. In FGS, fluorophores are designed to selectively accumulate in neoplastic tissue, allowing surgeons to better visualize abnormal tissue intraoperatively to increase resection rates. For instance, in a randomized controlled trial, the use of delta-aminolevulinic acid (5-ALA), an FDA-approved visible spectrum fluorescent agent, led to an increased rate of gross total resection and progression-free survival in glioblastoma patients [20]. Our group has been studying indocyanine green (ICG), which fluoresces in the near-infrared (NIR) region (peak emission 805-820 nm), conferring it improved tissue penetration and reduced autofluorescence from the surrounding brain parenchyma compared to visible spectrum agents like 5-ALA [21, 22]. We have demonstrated that intravenous infusions of ICG at 2.5-5 mg/kg into patients 24 h preoperatively allows real-time visualization of gliomas, meningiomas, and brain metastases with high sensitivity (>85 %) [23-27]. This technique has previously been termed Second Window ICG (SWIG) or TumorGlowTM. Since NIR fluorescence penetrates through normal brain and dura (at least 1.5 cm, in prior studies), we have been able to detect SWIG signal from tumors prior to dura opening [23– 27]. The ability to accurately visualize the location and boundary of tumors prior to opening the dura allows surgeons to better plan safe and efficient approaches that can improve surgical results and patient outcomes.

In this retrospective study, we compare the accuracy of the surgeons' interpretation of neuronavigation systems to NIR fluorescence through the unopened dura. We then investigate factors that lead to neuronavigation errors. Based on prior experience, we hypothesized that patient positioning would significantly affect the accuracy of neuronavigation, with the prone position leading to greater inaccuracies. Furthermore, we hypothesized that the accuracy of NIR fluorescence imaging would not be affected by patient positioning or other intraoperative factors.

Methods

Study Population

All adult patients (>18 years) undergoing primary resection of central nervous system tumors were enrolled between October 2014 and January 2019 in a registered clinical trial that was approved by the institutional review board. Exclusion criteria were pregnancy and allergy to contrast dye, iodide, or shellfish. All patients gave informed consent for the research trial. For this retrospective analysis, additional criteria were designed to exclude patients in whom the craniotomy could not be centered over the tumor or those in whom NIR imaging would not be reliable: nonenhancing tumors, prior craniotomies, parasagittal tumors, tumors > 10 mm below the cortex, tumor diameter > 5 cm, irregular tumor shape, skull base tumors, surgery performed endoscopically, and any other surgeries in which the craniotomy was intentionally placed off-center for anatomic reasons. Thus, in the included patients, all craniotomies should have been centered over the tumor.

Near-Infrared Imaging

All patients were infused intravenously with either 2.5 mg/kg (after April 2018) or 5 mg/kg (before April 2018) ICG (C43H47N2O6S2.Na; Akorn Pharmaceuticals, IL, USA) approximately 24 h preoperatively at an outpatient infusion center. All cases were imaged using the FDA-approved, NIR-capable VisionSense Iridium[™] exoscope system (VisionSense, Philadelphia, PA) [25].

Stereotactic Neuronavigation Registration

All patients underwent preoperative 1 mm-slice MRI of the brain with intravenous gadolinium. In the operating room, "surface matching" was used to register the preoperative MRI to the stereotactic coordinate space by tracing several points on the face with a focus on surfaces that are difficult to deform (*e.g.*, nasal bridge, orbital ridge). Registration accuracy was confirmed by assessing whether the navigation

system correctly localized external landmarks (*e.g.*, external auditory canal, cranial sutures). For each case, one of the following commercially available neuronavigation devices was used: Stryker, Medtronic StealthStation, BrainLab, and BrainLab Curve. The registration was performed by residents prior to the surgery and confirmed by the senior surgeons prior to incision.

Study Procedure

After skin incision and skull exposure, neuronavigation was again used to outline the tumor. Craniotomy boundaries were planned to center the tumor within the craniotomy. Upon craniectomy, NIR signal was documented over the intact dura. In cases when neuronavigation and NIR imaging differed in tumor localization, NIR imaging was used to plan the dura opening.

Determination of Tumor Center, NIR Center, and Neuronavigation Center

Intraoperative videos were recorded and analyzed postoperatively by independent reviewers. By carefully visualizing the tumor boundary upon exposure and then resection of the mass, the tumor boundaries were determined (since these tumors were completely resected, the tumor boundaries were determined post-resection). These images were then transposed on the view over the intact dura to determine the tumor boundary on the dura. Then, the resulting white light image and the NIR images over the dura were exported into ImageJ (National Institute of Health, Bethesda, MD), and the centroid function (Analyze= > Set Measurements) was used to find the center of mass of tumor outlines using white light (tumor center) and NIR (NIR center) (Figs. 1 and 2). For the NIR imaging, areas of signal-to-background > 2 were used as the tumor boundary, based on our prior studies. Similarly, the center of mass and areas of the craniotomies were calculated (Neuronavigation Center). Then, the distance between the tumor centers and each of the NIR center and neuronavigation center was calculated and divided by the square root of the area of the craniotomy in order to arrive at the percent deviation factor, allowing each deviation to be assessed relative to the size of the craniotomy and controlling for differences in imaging distance. This was necessary, as actual size measurements were not performed at the time of surgery.

Clinical Data

For each patient, the following data were collected retrospectively from the electronic medical records: age, gender, ethnicity, post-graduate training year of the residents (both as number of years and <4 (junior) or \geq 4 (senior)), pathological diagnosis, location and side of the tumor, tumor depth (distance from cortex to the most superficial aspect of the tumor), neuronavigation device, and patient head position (supine, lateral, or prone).

Statistical Analysis

Statistical analyses were performed using STATA 10^{TM} (StataCorp LLC, College Station, TX). The Mann–Whitney test was used when comparing values. Each clinical variable was examined to assess their predictive capabilities for percent deviation using linear regression (age, tumor depth), analysis of variance (gender, ethnicity, pathology, tumor location, neuronavigation device, patient position), or Mann–Whitney test (gender, resident year). For the initial screening univariate analysis, a *p* value cutoff of 0.2 was used to determine variables for the multivariate analysis. An analysis of covariance was performed on the screened variables to assess for potential factors that could affect neuronavigation accuracy. A *p* value cutoff of <0.05 was used to determine statistical significance.

Results

Patient Recruitment

Between October 2014 and January 2019, 215 patients underwent craniotomy under the SWIG protocol for intracranial tumors. For this retrospective study, the following cases were excluded according to our exclusion criteria: 37 repeat craniotomies; 25 tumor-depth > 10 mm; 15 with low NIR signal; 57 parasagittal tumors (craniotomy could not be centered over the tumor with neuronavigation); and 25 poor visualization of craniotomy borders with NIR imaging (camera field of view too narrow). Fifty-six patients were included in the final analysis (22 metastases, 21 high-grade gliomas, 11 meningiomas, and 2 Other). Thirty-one patients were supine for the surgery, 12 were lateral decubitus, and 13 were prone. The clinical characteristics are summarized in Table 1.

Transdural Near-Infrared Fluorescence Imaging of Gross Tumor

In all 56 patients, the NIR fluorescence properly delineated the tumor boundary prior to opening the dura, with minimal deviations between the tumor center and the NIR center (mean 2.6 ± 1.1 % relative to craniotomy size; range 1.2– 4.4 %) regardless of patient positioning or tumor type (Figs. 1 and 2).

Transdural Neuronavigation of Gross Tumor

The Stryker neuronavigation system was used in 21 cases, followed by BrainLab (n = 17), BrainLab Curve (n = 14), and Medtronic Stealth (n = 4). Senior neurosurgery residents



Fig. 1. Example of a well-centered craniotomy using neuronavigation in a supine case. (A–C) preoperatively, T1 MRI was performed with and without gadolinium contrast agent at 1 mm resolution. The axial (A), sagittal (B), and coronal (C) images demonstrate a superficial, well-circumscribed, contrast-enhancing mass measuring 22 mm × 23 mm × 15 mm extending to the cortex, consistent with a metastasis. (D–G) Intraoperatively, the craniotomy borders were planned on the exposed skull using neuronavigation to center the tumor. After craniotomy (black, solid line), white- light imaging (D) does not visualize the tumor. However, based on white light imaging during and after resection, the tumor boundary was transposed onto the dura (white, solid line) and the tumor center is shown (black triangle). With near-infrared fluorescence imaging (E), the fluorescence from the tumor is clearly visible (black, dotted line) and the NIR center (black, dotted circle) closely approximates the tumor center (1.2 %). The neuronavigation center (black square) also aligns well with the tumor center, with 4.3 % deviation. The tumor is visible with white light after durotomy (F), and the location of near-infrared fluorescence is confirmed to be coming from the tumor (G).

(postgraduate year 4 or greater) performed 44/56 registrations, while junior residents performed 12/56. In order to assess neuronavigation reliability in this retrospective study, the accuracy of craniotomy placement was used as a surrogate. Compared to the tumor center, the Neuronavigation Center was, on average, 23.0 ± 7.7 % (range 4.3–47.6 %) deviated

relative to the size of the craniotomy. Deviations < 15 % (Fig. 1) were not largely noticeable intraoperatively; conversely, deviations > 15 % (Fig. 2) were easily recognized as such. In 12 cases of severe neuronavigation inaccuracies, dura opening was significantly altered based on NIR fluorescence.



Fig. 2. Example of a poorly centered craniotomy using neuronavigation in a supine case. (A-C) Preoperatively, T1 MRI was performed with and without gadolinium contrast agent at 1 mm resolution. The axial (a), sagittal (B), and coronal (C) images demonstrate a superficial, spherical mass measuring 19 mm × 15 mm × 20 mm in the right frontal lobe, consistent with a metastasis. (D–G) Intraoperatively, the craniotomy borders were planned on the exposed skull using neuronavigation to center the tumor. After craniotomy (black, solid line), white light imaging (D) does not visualize the tumor. However, based on white light imaging during and after resection, the tumor boundary was transposed onto the dura (white, solid line) and the tumor center is shown (black triangle). With near-infrared fluorescence imaging (E), the fluorescence from the tumor is clearly visible (black, dotted line) and the NIR center (black, dotted circle) closely approximates the tumor center (1.9 %). The neuronavigation center (black square), in contrast, aligns poorly with the tumor center, with 27.1 % deviation. The tumor is visible with white light after durotomy (F), and the location of near-infrared fluorescence is confirmed to be coming from the tumor (G). Prior to durotomy, the surgeon felt more confident in the fluorescence imaging results than in the neuronavigation, so durotomy was performed over the site of fluorescence rather than over the neuronavigation center.

Predictive Factors for Neuronavigation Deviation

The following potential factors that could contribute to neuronavigation inaccuracies were collected from patient charts: age, gender, ethnicity, tumor type, tumor location, tumor depth, patient position intraoperatively, neuronavigation device, and seniority of the resident performing the registration. From univariate analysis, tumor depth (p value = 0.17) and patient

 Table 1. Summary of clinical characteristics for patients included in the final analysis

Characteristic	Values
Total patients (n)	56
Age	61.4 ± 11.7
Males (n)	26
Metastases (n)	22
HGG (<i>n</i>)	21
Meningioma (n)	11
Other tumors (n)	2
Surgery supine (n)	31
Surgery lateral (<i>n</i>)	12
Surgery prone (n)	13
Tumor on right side	31
Registration performed by senior resident	44

position (*p* value = 0.0004) were selected for multivariate analysis (Table 2). These two variables were analyzed using analysis of covariance, which revealed only patient position to be significant (*p* value = 0.0083). The prone position was associated with significantly higher inaccuracies (29.2 ± 8.1 %) compared to the supine (16.2 ± 8.1 %, *p* value < 0.001) or the lateral (17.9 ± 5.1 %, *p* value = 0.003) positions (Fig. 3). Furthermore, using 15% deviation as the cutoff for clinically significant deviation, 12/13 (92.3 %) of prone cases were significantly deviated, *versus* 16/31 (52 %) for supine and 4/8 (50 %) for lateral cases (chi-2 *p* value = 0.036).

Discussion

Accurate localization within the intracranial space is vital to the safe and effective surgical treatment of patients with intracranial lesions. Thus, neurosurgeons have strived to enhance the precision of anatomical and functional localization within the cranium through various imaging modalities, such as CT and MRI. Stereotactic coordination using headframes further increased the accuracy for surgical targets [28]. More recently, frameless navigation systems have become widely adopted and have demonstrated potential for improving patient outcomes in tumor resections. However, it is well recognized that neuronavigation accuracy is affected by numerous factors. Wang and Song, in their review, classify potential causes of neuronavigation

 Table 2. Univariate and multivariate analysis to explore potential factors affecting neuronavigation accuracy

Factors	Univariate analysis <i>p</i> value	Multivariate analysis <i>p</i> value
Age	0.71	
Gender	0.99	
Ethnicity	0.35	
PGY year	0.22	
Tumor Dx	0.96	
Tumor side	0.54	
Tumor depth	0.17	0.83
Navigation device	0.56	
Patient position	0.0004	0.0083

errors into two groups, one caused by actual differences between the images and patients and the other caused by human errors in translating surgical tool position into the image space [13]. While some of these causes are easily addressable, such as properly positioning the tracking device or mitigating errors in fiducial registration, others, such as brain deformations during surgery, can be very difficult to correct. Due to these difficulties, the benefits of neuronavigation in increasing the extent of resection and prolonging patient survival have not been clearly defined [9– 11].

In 2015, we began enrolling our first patients in our clinical trial to investigate the utility of intraoperative NIR imaging with SWIG in real-time visualization of neoplastic tissue in intracranial tumors. Since NIR fluorescence penetrates through > 1 cm of brain parenchyma and dura, we observed NIR fluorescence signals from tumors immediately after craniotomy, prior to durotomy. During these cases, it was observed that neuronavigation was often inconsistent with the location of the NIR fluorescence and that the margin of error seemed to be exacerbated when the patients were prone. In order to better examine this trend, we designed this retrospective study to compare the accuracy of neuronavigation to NIR fluorescence and to determine the factors that affected neuronavigation accuracy. Due to the limited amount of neuronavigation data available retrospectively, we used the accuracy of neuronavigation-guided craniotomy placement as a surrogate for neuronavigation accuracy. Hence, we were able to compare the accuracy of neuronavigation and NIR fluorescence imaging in accurately delineating the tumor center. In an analysis of 9 potential variables, the patient position significantly affected neuronavigation accuracy, while NIR fluorescence imaging was not affected by any of the variables. This was consistent with a prior study by Asano et al., which demonstrated that the prone position led to larger inaccuracies using an optical neuronavigation system [29].

The inaccuracies associated with the prone position likely stems from multiple factors. Most current neuronavigation systems (including those used at our institution) rely on surface registration to align the image space to the patient space. When this registration is performed on the anterior surface of the face for prone cases, poor access to facial surface features can limit accurate registration. In addition, small errors from anterior registrations may propagate into larger errors over the increased distance between the registration surface and the posterior operative surface. Furthermore, preoperative images are performed with the patient supine, but when patients are placed prone, the skin and overall head shape changes due to gravity, which exacerbates the discrepancy between the image space and patient space. Finally, because the brain is relatively mobile compared to the skull, the prone position likely affects the degree and direction of brain shift differently than in the supine position. Although some neurosurgeons use point-topoint fiducial registration, skull screws, or intraoperative CT



Fig. 3. Distribution of neuronavigation deviation by patient position. Multivariate analysis revealed patient position to be the only significant factor affecting neuronavigation accuracy in our patient cohort. The supine and lateral positions demonstrated similar levels of deviations ($16.2 \pm 8.1 \%$, $17.9 \pm 5.1 \%$; *p* value = 0.99). The prone position, in contrast, demonstrated a significantly higher level of deviation ($29.2 \pm 8.1 \%$) compared to the supine (*p* value < 0.001) and lateral (*p* value = 0.003) positions.

to mitigate some of these factors and improve image-topatient registration, there remains a need for more accurate intraoperative, real-time navigation, especially in the prone position.

Even if perfect registration is achieved, neuronavigation loses accuracy intraoperatively. Opening the dura and draining cerebrospinal fluid, removal of tissue, and retracting the brain are all examples of unavoidable steps in surgery that change the intraoperative patient space that would not be reflected in the pre-acquired image space, no matter how well-registered. A potential approach to rectifying this issue is to readjust the image space to reflect changes in the patient space, which could be accomplished, for instance, by acquiring a new MRI scan intraoperatively. This could be done after the patient has been positioned to calibrate the neuronavigation system and could even be performed at the end of the case to assess for margins that could then be localized using neuronavigation [15, 30-32]. However, intraoperative MRI is expensive, time-consuming, cumbersome, and not widely available; furthermore, this approach still cannot account for intraoperative brain deformations that occur between scans. Repeatedly performing intraoperative MRI would prohibitively interfere with the surgical workflow and increase both surgical cost and time.

Alternatively, we propose FGS with NIR fluorescence as an adjunctive technique that may work synergistically with neuronavigation to help surgeons approach tumors more safely and to evaluate margins more accurately. In FGS, fluorophores are designed to accumulate in neoplastic tissue, such as through passive permeation (Second Window ICG), enzymatic conversion (5-ALA), or receptor targeting (ABY-029, OTL38) [20, 24, 33–37]. Since the fluorescence is directly detected from neoplastic areas, fluorescence imaging can account for changes in real time,

unlike neuronavigation. Furthermore, unlike visible spectrum fluorescence, NIR fluorescence can be detected through > 1 cm of normal tissue, allowing surgeons to detect neoplastic tissue that may be normally obscured from view. Since the dura is < 0.5 mm thick, NIR fluorescence imaging offers superb visualization of tissue that have accumulated fluorophores, before any opening is made in the dura. Based on our observations in this study, we believe that intraoperative NIR fluorescence imaging offers an opportunity to readjust the neuronavigation image space to better align with the patient space, improving neuronavigation accuracy. For instance, prior to durotomy, when the tumor is clearly visualized with NIR fluorescence, neuronavigation could be realigned using NIR fluorescence as the marker of tumor location. Unlike current techniques for updating registration data using known landmarks (bone or vasculature) that are indirectly related to the tumor location, using NIR fluorescence would allow direct registration to the tumor. With such readjustments at multiple intervals throughout the surgery, neuronavigation accuracy could improve even when the patient is prone or when tumor resection distorts the anatomy, since NIR fluorescence accurately reflects any changes in real time.

Furthermore, the addition of neuronavigation to FGS with SWIG has one major advantage over FGS-alone. We have previously demonstrated that SWIG leads to NIR fluorescence in gadolinium-enhancing tissue; conversely, nonenhancing tumors or non-enhancing portions of heterogeneously enhancing tumors do not demonstrate significant NIR fluorescence with SWIG, which is a major limitation of SWIG. In contrast, neuronavigation can visualize nonenhancing tissues, as well as T2 abnormalities and other signal changes. Thus, by combining SWIG and neuronavigation in resections of heterogeneously enhancing tumors, neurosurgeons could synergistically apply both technologies to enhance the detection of neoplastic tissue. Finally, novel techniques of visualizing fluorophores are currently under investigation that may offer superior visualization compared to simple optical imaging, which is the current standard in the operating room. Optical fluorescence imaging is limited by the 2-dimensional nature of the acquired images; although deep fluorescence can be detected as aforementioned, one cannot easily distinguish superficial from deep signals, since both would appear to be on the surface. In contrast, photoacoustic imaging and diffuse optical tomography both theoretically offer tomographic imaging in real time and have demonstrated the use of ICG as a contrast agent [38–40]. Such advances in fluorescence imaging can only improve the utility and applicability of FGS in the future.

A limitation of this study is that, as a retrospective study, we did not have direct data from the neuronavigation systems to compare to the fluorescence imaging. Instead, we used craniotomy placement as a surrogate, since our institutional policy is to plan the craniotomy using neuronavigation in such a way as to place the tumor in the center. However, we carefully designed our inclusion and exclusion criteria for the analysis to limit our study to tumors in which this craniotomy placement was feasible; thus, in this population, the craniotomy centers should not have deviated significantly from the tumor centers. Furthermore, at the time of surgery, we did not directly measure the size of the craniotomy, making it difficult to exactly quantify the extent of deviation; thus, we had to use the degree of deviation relative to the size of the craniotomy as a proxy. Even with this limited retrospective study, we were able to demonstrate that patient positioning significantly affects neuronavigation accuracy, and we offer an interesting, novel way to improve neuronavigation accuracy intraoperatively. Further studies to compare the two techniques during the resection and at the margins would be informative.

Conclusion

Accurate navigation within the intracranial space is crucial for neurosurgeons to better achieve safe maximal resection of intracranial tumors. Frameless stereotactic navigation, a ubiquitous technology now, relies on the registration of preoperatively acquired image space to the patient space in order to provide 3-dimensional guidance. However, it has been well documented that neuronavigation suffers from inaccuracies due to multiple factors that cannot easily be corrected. In this study, we used intraoperative near-infrared fluorescence imaging with Second Window ICG, a novel technique for fluorescence visualization of neoplastic tissue, to assess the accuracy of neuronavigation in 56 patients with intracranial tumors. Overall, we found that patient positioning in the operating room significantly affects neuronavigation accuracy, with the prone position being the significantly less accurate than the supine or lateral positions, while near-infrared imaging was not affected by positioning. Thus, we propose using near-infrared fluorescence imaging to provide real-time, intraoperative adjustments to neuronavigation to improve the accuracy of intracranial navigation.

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Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Disclosures

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