Quantitation of Tissue Resection Using a Brain Tumor Model and 7-T Magnetic Resonance Imaging Technology

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BACKGROUND: Animal brain tumor models can be useful educational tools for the training of neurosurgical residents in risk-free environments. Magnetic resonance imaging (MRI) technologies have not used these models to quantify tumor, normal gray and white matter, and total tissue removal during complex neurosurgical procedures. This pilot study was carried out as a proof of concept to show the feasibility of using brain tumor models combined with 7-T MRI technology to quantitatively assess tissue removal during subpial tumor resection.

METHODS: Seven ex vivo calf brain hemispheres were used to develop the 7-T MRI segmentation methodology. Three brains were used to quantitate brain tissue removal using 7-T MRI segmentation methodology. Alginate artificial brain tumor was created in 4 calf brains to assess the ability of 7-T MRI segmentation methodology to quantitate tumor and gray and white matter along with total tissue volumes removal during a subpial tumor resection procedure.

RESULTS: Quantitative studies showed a correlation between removed brain tissue weights and volumes determined from segmented 7-T MRIs. Analysis of baseline and postresection alginate brain tumor segmented 7-T MRIs allowed quantification of tumor and gray and white matter along with total tissue volumes removed and detection of alterations in surrounding gray and white matter.

CONCLUSIONS: This pilot study showed that the use of animal tumor models in combination with 7-T MRI technology provides an opportunity to increase the granularity of data obtained from operative procedures and to improve the assessment and training of learners.

INTRODUCTION

Surgical technical skills education is evolving from a time-focused apprenticeship toward a quantifiable competency-based model.¹ Competency in bimanual psychomotor performance in neurosurgery may be considered to have been achieved when the trainee can safely and efficiently perform a variety of procedures using appropriate surgical techniques.² The subpial resection procedure allows neurosurgeons to resect brain tumors and epileptic foci that border on important cortical structures and to minimize injury to adjacent pial-lined gyral tissues and hemorrhage from subpial vascular structures.³,⁴ Maintaining pial layer integrity is associated with better postsurgical patient outcomes and is an important bimanual technical skill for surgical trainees to master.³ Studies on virtual reality neurosurgical simulators with haptic feedback highlight the importance of quantitating performance of simulated subpial resection skills. Normal gray and white matter tissue along with tumor volume resection associated with subpial...
resection, force application, tool acceleration, bimanual dexterity, and impact of stress have all been used to assess level of expertise on these simulators. Linking neurosurgical psychomotor bimanual skill performance in virtual reality simulator scenarios to resident specific training in operating room environments continues to be challenging. There is a need to outline models that can accurately quantitate both technical psychomotor skills and operative results in realistic operative settings with comparable virtual reality simulator resident evaluations of similar scenarios. These models need to possess both visual and tactile reality and be coupled with advanced quantitation magnetic resonance imaging (MRI) methodology. An animal model allowing quantitative assessment of surgical performance during the subpial resection for tumor procedures would be an important adjuvant in competency-based surgical education. Analytical MRI protocols based on the comparative analysis of baseline and postoperative images of patients are common but do not allow quantitative assessments of psychomotor performance during complex procedures such as subpial resection.

Although automatic methods exist to carry out these studies, manual segmentation delimitating abnormal tissue contours is also used and remains the gold standard. To make this method more efficient, semiautomatic tools exist that require decreased user input to perform these tasks. These magnetic resonance (MR) technologies have not been used in animal models to quantitate normal gray and white matter removal to improve access for tumor resection along with resultant tissue injury. We have developed a framework whereby neurosurgical performance and extent of resection can be accurately quantified in a controlled setting using an ex vivo calf brain artificial alginatum tumor model. This framework allows manual and semiautomatic brain segmentations on baseline and postresection MRIs. Images are acquired on a 7-T MRI scanner to optimize image registration and to carry out quantitative analysis of normal tissue and brain tumor resected volumes during the use of the subpial technique. The choice of 7-T MRI over 3-T MRI for its increased spatial resolution allowed for better resolution of subtle landmarks in brain tissue. High spatial resolution was critical in producing accurate segmentation of MRIs, thus increasing the accuracy of the subsequent MRI registration. This pilot study was carried out as a proof of concept to show the feasibility of using brain tumor models combined with 7-T MRI technology with the aim of verifying that the union of these methodologies is both a feasible and practical application in the quantitation and understanding of complex neurosurgical skills.

The aims of this pilot study aims were 1) to determine if the assessment of baseline images and postresection images acquired using a 7-T MRI scanner can accurately quantitate normal brain tissue removed in a calf brain model; 2) to assess if baseline and postresection 7-T MRI technology can quantitate alginatum brain tumor resected after subpial resection in a calf brain model; and 3) to outline if baseline and postresection 7-T MRI technology can quantitate gray matter, white matter, and total tissue resection after subtotal and total subpial resection of alginatum brain tumor in a calf brain model. To our knowledge, this is the first study to use a brain tumor model and 7-T MRI technology to gain insight into quantification of specific tissue resection during a complex neurosurgical procedure.

**METHODS**

**Ex Vivo Calf Brain Models**

Seven fresh ex vivo calf brain cortical hemispheres were used for these studies because they structurally resemble human brain, are low cost, and are small enough (about 150 g) to fit into the 7-T MRI coil (Figure 1A). The calf hemispheres were separated into 2 groups. Group 1 included 3 hemispheres that were used to assess if comparing baseline and postresection 7-T MRIs can quantitate normal brain tissue removed. Initial baseline scans were carried out before tissue resection (Figure 1C). Six brain segments of increasing sizes were resected from 3 calf hemispheres (Figure 1B). All resected brain segments were weighed (High Precision Scale [Smart Weight Ltd, Changanzhou, China]). Calf hemispheres with resected segments then underwent a postresection scan (Figure 1D). In group 2, the cortical gray matter gyri of 4 calf hemispheres were used to create alginatum artificial tumors of different sizes. Baseline 7-T scans were then carried out. After this scan, the neurosurgical resident operator was given specific instruction on how to perform a subpial resection of the overlying cortical gray matter tissue and tumor with minimal injury to underlying white matter tracts. After procedural completion, postresection scans were performed. Group 2 was used to assess if our pipeline of segmentation and registration of 7-T MRIs can quantitate percentage of alginatum brain tumor resection and quantitate gray and white matter removed and total tissue resected during the subpial procedure in the calf model. The McGill University Health Centre Research Ethics Board, Neurosciences-Psychiatry approved these studies.

**Image Acquisition Using a 7-T MRI Scanner**

Before baseline scans, three-dimensional (3D)-printed polyactic acid fiducials were inserted into all 3 calf hemispheres in group 1 and 1 of 4 calf brains in group 2 (Figure 2A and B). The fiducials were used to assess their usefulness during registration of baseline and postresection images. Calf hemispheres were placed in a cylindrical container and covered with an MR-invisible fluorinated solution, FC-40 (Sigma Aldrich, St. Louis, Missouri, USA).

In this study, hydrogen 1 MR scans at a resonance frequency of 300 MHz were performed using a Bruker Pharmascan 7-T MRI scanner with an AVANCE II radiofrequency amplifier system and a BFG-150/90-S gradient system (Bruker Biosciences, Billerica, Massachusetts, USA). The plastic tubes containing the brain hemispheres were imaged inside a cylindrical radiofrequency transceiver coil with an inner diameter of 6 cm. The sequences were run using the Bruker proprietary imaging software ParaVision 5.1. For each brain hemisphere, the same scanning protocol was performed to obtain baseline MRIs and postresection MRIs.

All 3 brains of group 1 were scanned using a 3D fast imaging with steady-state free precession sequence with, echo time, 5 milliseconds; repetition time, 10 milliseconds; scan repetition time, 4000 milliseconds; receiver bandwidth, 50 kHz; flip angle, 30°; axial field of view (FOV), 6 × 5.25 × 5.1 cm; voxel resolution,
200 μm; and matrix size, 300 × 255 × 255. Twenty-four averages were acquired, making for an anticipated total scan time of approximately 12 hours. Parameters were adjusted to determine the set of geometric parameters that represented the most optimal trade-off between spatial coverage and scan time. The parameters had to produce an FOV that encompassed the entire tumor in each brain and ensured that each scan did not exceed reasonable periods of time. All 4 brains of group 2 were scanned using a 3D fast imaging with steady-state free precession sequence with echo time of 5 milliseconds. The following parameters were common to all 4 brains of group 2: repetition time, 10 milliseconds; scan repetition time, 4000 milliseconds; receiver bandwidth, 50 kHz; and flip angle, 30°. The differences in protocol between the 4 brains included the FOV, matrix size, resolution, and antialiasing. The resolution for brains 1, 2, and 3 was 150 μm and the resolution for brain 4 was 200 μm: brain 1, axial FOV, 4.8 × 4.5 × 3.3 cm; matrix size, 320 × 300 × 220; brain 2, axial FOV, 5.25 × 5.25 × 3.3 cm; matrix size, 350 × 350 × 22; brain 3, sagittal FOV, 6 × 5.1 × 5.1 cm; matrix size, 300 × 255 × 255; brain 4, coronal FOV, 5.70 × 5.25 × 2.64 cm; matrix size, 380 × 350 × 176.

Calf Brain Tumor Model

The created artificial tumor consisted of a 2% weight by volume Alginate Alginate (KIMICA Corporation, Tokyo, Japan) and a calcium sulfate solution (final calcium concentration in the alginate 12 mM) along with a 10 times dilution of gadolinium solution, Gadobutrol (Bayer AG, Leverkusen, Germany) as previously described by Winkler-Schwartz et al.26 Alginate tumor stiffness was optimized based on data obtained from human tumor samples and food coloring (Club House [McCormick & Company, Inc., Hunt Valley, Maryland, USA]) was added to simulate realistic brain tumor color. The alginate, calcium, and gadolinium mixture was injected at a subcortical depth of 5–7 mm into the gray matter of a cortical gyrus to standardize tumor location.26 After baseline 7-T MR scan completion, the hemisphere was inserted into a plastic receptacle mimicking the shape of a human skull with surgical towels lining the surgical wound to replicate the human operating room environment. The gyrus region containing the tumor that was to be resected by the operator was outlined with black marker (Figure 2B). In an animal operative room, brain tumor resection was carried out using a subpial
technique using microscissors to incise the pia mater, a bipolar coagulator to lift the pia and a Sonopet ultrasonic aspirator (Stryker, Kalamazoo, Michigan, USA), to remove normal cortical gray matter overlying and surrounding the artificial brain tumor visualized through an OPMI Pico surgical microscope (Carl Zeiss Co., Oberkochen, Germany) (Figure 2C and D). A sample operation of the subpial resection technique can be viewed in Video 1 from Ref.26. After the operator judged that the tumor had been completely removed, the brain then underwent a postresection 7-T MR scan.

Segmentation Protocol
Each pair of baseline and postresection 7-T MRIs of each group was processed using the software 3D Slicer 4.10.2 (https://www.slicer.org/wiki/CitingSlicer). The N4ITK bias field correction filter was used to normalize the signal inhomogeneity in each volume, which was particularly necessary for volumes of group 2 because of gadolinium hyperintensity. This image-filtering process does not require previous tissue classification. After filtering, a combination of manual and semiautomatic segmentation methods was performed to assess the volumetric differences between baseline and postresection MRIs of calf hemispheres. Tissue types were defined as cerebral cortex, cerebral white matter, and artificial tumor; each tissue type was assigned a specific segment. Additional segments included fiducials and air. Each segment was assigned a specific color code, which was consistent across all MR volumes. The segmentation process was divided in 2 parts. First, white matter tracts were manually contoured by hand for improved accuracy. Image contrast was adjusted throughout the white matter segmentation process to highlight different sections of white matter tracts, such as borders between gray and white matter or white matter tracts directly adjacent to hyperintense tumor. Once white matter tracts were manually segmented, gray matter regions were segmented manually with level tracing around the white matter segment. Tumors were then automatically segmented
using the Otsu thresholding method.25 For each brain volume, 20—
30 slices were individually segmented, after which a semiautomatic
growing seed function14 was used to extend the segmentations to all
slices. Air and ventricles were then automatically segmented using
the Otsu thresholding method25 and removed from the final
segmentation. For greater anatomic accuracy, median smoothing
with a 0.50-mm kernel size (3 × 3 × 3 pixels) was applied for
white matter segments and gray matter segments.

Registration
Once segmentation was performed, postresection segmented
images were registered on to the matching baseline segmented
images to visualize the geographic location at which resection
occurred. This registration was performed using the 3D Slicer
extension “Segmentation registration.”32 The baseline
segmentation and image were kept fixed as the matching
postresection segmentation and image were displaced and
deformed such that relevant anatomic landmarks from these
brains matched their counterparts on the baseline brain. To
account for deformation, several baseline brains had fiducials
inserted to help in defining landmarks for registration.
Registration occurred in multiple steps. First, when present,
fiducials were registered using a rigid transformation of the
postresection images. Second, if necessary, the postresection
segmentation and image underwent another rigid transformation using white matter as the moving segments. If
the postresection shape of the brain was significantly different
from baseline on visual inspection, cerebral cortex underwent a
defformable transformation. For each of the segments previously
mentioned, registration was performed only once to reduce the
amount of deformation of the postresection segment. After
registration, a region of interest (ROI) was delimited around the
resected and operated regions to define the boundaries for the
extraction of volumetric information. ROI delineation varied
across brain hemispheres depending on the level of deformation of
each hemisphere. In group 1 hemispheres, the ROIs were
concentrated around the resection sites. In group 2 hemispheres, because the injection of the alginate artificial
tumor caused deformation of adjacent brain structures, the ROIs
were expanded to encompass the tumor and its immediate
surroundings. In brain 3 of group 2, the deformation was such that the ROI encompassed the entire section of the brain
containing the tumor.

Quantification of Normal Brain Tissue Removed
In the 3 group 1 hemispheres, predetermined segments of brain
tissue were removed after the baseline scan, which was followed
by a postresection scan. Quantitative information of each
segment was available in the form of tables containing the
segments statistics for each volume. Each table contained 2 sets
of information: the segment statistics for the entire volume and
the segment statistics for the region within the boundaries of the
ROI. These tissue volumes were reported in milliliters. Differences in tissue volume between baseline and postresection im-
ages were calculated based on the segment statistics for each
ROI. A linear model was created and used to predict the weight
(in grams) of the removed tissue based on the tissue volume
removed derived from the 7-T MRIs segmentation and regist-
tration results (Figure 3).

Quantification of Tumor and Gray and White Matter Tissue
Resected
All volumes are reported in milliliters. In a calf hemisphere
without the presence of a tumor after image segmentation and
registration, the total baseline volume (ROI) was composed of
total gray matter volume (Ng), and total white matter volume (Nw),
which may be represented as:

ROI = Ng + Nw

In group 2, after image segmentation and registration, an ROI
on the baseline scan containing the tumor was outlined
(Figure 4A). The total baseline ROI volume is composed of
total gray matter volume (Ng), total white matter volume (Nw),
and tumor volume (Nt). Therefore, the total ROI volume which
contains the tumor may be considered as:

ROI = Ng + Nw + Nt

The subpial removal for tumor involves resection of overlying
gray and surrounding white matter along with the tumor amount
removed. On the postresection images, the previously identified
ROI on the baseline scan is composed of residual gray matter
volume (Ng′), residual white matter volume (Nw′), residual tumor
volume (Nt), and total resected tissue volume (Nr), seen as empty
space:

ROI = Ng′ + Nw′ + Nt + Nr

The change in gray matter volume (ΔNg) between the baseline
and the postresection scan is the difference between the baseline
gray matter volume (Ng) minus the residual gray matter volume
(Ng′) after resection:

ΔNg = Ng − Ng′

The change in white matter volume (ΔNw), which is the total
volume of white matter resected, is the difference between the
baseline white matter volume (Nw) minus the residual white
matter volume (Nw′) after resection:

ΔNw = Nw − Nw′

The change in tumor volume (ΔNt), which is the total volume of
tumor resected, is the difference between the baseline tumor
volume (Nt) minus the residual tumor volume after resection (Nt):

ΔNt = Nt − Nt

The total resected tissue volume ( Nr) can be calculated from the
following equation:

Nr = ΔNg + ΔNw + ΔNt
Therefore, equation 7 allows for the calculation of the total resected tissue volume \( N_r \) during the procedure.

RESULTS

Quantification of Brain Tissue Removed

Six brain segments of increasing sizes were removed from the 3 calf hemispheres in group 1. Two small segments (0.17 and 0.54 g) could not be accurately identified on the postresection segmented images because of distortions associated with placing the postresection brain into the tube necessary for 7-T MRI. Four brain segments could be assessed (Table 1). Linear fitting of the data yielded a predictive model \( p(x) = 0.9373 x + 0.0576 \) was fitted and plotted. A correlation coefficient of 0.9987 and an \( R^2 \) of 0.9974 between recorded weights and predicted weights were found, suggesting good correlation between the 2 measures.

Quantification of Brain Tumor Removed

Four calf hemispheres were injected with alginate tumor ranging from 0.5 to 1.5 mL (Table 2). The alginate tumors were easily identified on the baseline coronal 7-T MRIs and segmented coronal images because of the presence of gadolinium (Figure 4). Postresection sagittal segmented images showed complete tumor removal in 3 of 4 tumors studied (Figure 5). The coronal and sagittal segmented images of the baseline scan show the presence of the injected alginate tumor in the gray matter gyrus (Figures 4 and 5). The area of tissue resection, involving gray matter, white matter, and tumor can be appreciated when comparing the detailed baseline and postresection coronal and sagittal segmentation images available. Injection of increased milliliters of alginate was associated with tumors of increased volume (Table 2). Baseline segmented sagittal images showed tumors of irregular form and different shapes (Figure 5A, C, E, and G). In brain 1, the tumor resection was subtotal; little gray matter overlying the tumor seemed to have been resected (Figure 5B). In postresection sagittal segmented images of brains 2 and 3, the overlying gray matter and a portion of white matter have been removed during the resection (Figure 5D and F). In the postresection image of brain 3 outlined in Figure 5F, the subpial gray matter resection seems incomplete, leaving irregular areas of gray matter in the resection cavity. In Figure 5H, the postresection cavity of brain 4 is severely compressed, leaving no resection cavity and thus preventing an

Figure 3. Recorded weights (grams) of resected brain segments versus their associated volumes (milliliters) determined from segmented images. Data points shown here are listed in Table 1. To show this quasi-linearity, a polynomial \( p(x) = 0.9373 x + 0.0576 \) was fitted and plotted. A correlation coefficient of 0.9987 and an \( R^2 \) of 0.9974 between recorded weights and predicted weights were found, suggesting good correlation between the 2 measures.
assessment of baseline gray ($N_g$) and white ($N_w$) matter removed tissue using our registration method. The ROI on a baseline coronal segmented image of a calf brain hemisphere containing an irregular tumor is delineated (Figure 6A). Both gray ($N_g$) and white ($N_w$) matter tissues are outlined in a detailed coronal segmented view of the ROI in which no tumor is present (Figure 6B). A baseline coronal segmented image of the ROI containing a complex irregular tumor is also shown (Figure 6C). Gray ($N_g$) and white matter ($N_w$) along with tumor ($N_t$) are outlined. On the postresection segmented coronal image, residual gray matter ($N_g^0$) and residual white matter ($N_w^0$) along with the residual tumor regions ($N_{t0}$) in the equivalent ROI location as on the postresection image can be identified (Figure 6D). An area of resected tissue can also be identified as
empty space along with what seems to be tissue injury to gray matter and white matter structures involving adjacent gyri.

**Calculation of Total Resected Tumor**

In 3 of 4 calf hemispheres containing tumors that were operated on, 100% of the tumor was removed because no residual tumor could be visualized on the postresection images (Table 2). In the experiment in which postresection residual tumor was seen (brain 1), equation 6 was used to calculate the change in tumor volume ($\Delta N_t$) between the baseline and after resection. This calculation was possible because the baseline and postresection ROI could be accurately aligned and the baseline tumor volume ($N_t$), residual tumor volume after resection ($N_t'$) and total volume of resected tumor ($\Delta N_t$) could be calculated (Table 2). These results show that 56.5% of the tumor was resected, with 43.5% of residual tumor still present after tumor resection on the postresection images (Table 2).

**Table 1. Removed Brain Tissue Weights of 6 Segments from 3 Calf Brain Hemispheres**

<table>
<thead>
<tr>
<th>Segments</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recorded weight (g)</td>
<td>0.17</td>
<td>0.27</td>
<td>0.54</td>
<td>0.66</td>
<td>0.86</td>
<td>1.9</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted weight (g)</td>
<td>—</td>
<td>0.214</td>
<td>—</td>
<td>0.696</td>
<td>0.821</td>
<td>1.963</td>
</tr>
<tr>
<td>Percent error</td>
<td>—</td>
<td>0.258</td>
<td>—</td>
<td>0.710</td>
<td>0.827</td>
<td>1.898</td>
</tr>
</tbody>
</table>

Volumes derived from analysis of segmented images (mL) and predicted weights (g) along with percent error were computed based on the polynomial model $p(x)$ as detailed in Figure 3.

**Table 2. Injected Alginate Tumor Volumes and Gray Matter, White Matter, and Tumor Volumes in Region of Interest from 4 Calf Brain Hemispheres**

<table>
<thead>
<tr>
<th>Calf Brain Hemisphere</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of injected alginate tumor (mL)</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Volume of alginate tumor $N_t$ inferred from 7-T magnetic resonance images (mL)</td>
<td>0.421</td>
<td>0.838</td>
<td>0.902</td>
<td>1.428</td>
</tr>
<tr>
<td>Tumor length (mm)</td>
<td>17.850</td>
<td>15.800</td>
<td>23.300</td>
<td>24.750</td>
</tr>
<tr>
<td>Baseline gray matter within ROI $N_{g}$ (mL)</td>
<td>14.634</td>
<td>18.535</td>
<td>25.300</td>
<td>—</td>
</tr>
<tr>
<td>Baseline white matter within ROI $N_{w}$ (mL)</td>
<td>7.848</td>
<td>6.037</td>
<td>14.049</td>
<td>—</td>
</tr>
<tr>
<td>Baseline ROI volume (mL)</td>
<td>22.903</td>
<td>25.410</td>
<td>40.251</td>
<td>—</td>
</tr>
<tr>
<td>Postresection tumor volume $N_t'$ (mL)</td>
<td>0.183</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resected tumor volume $\Delta N_t$ (mL)</td>
<td>0.238</td>
<td>0.838</td>
<td>0.902</td>
<td>1.428</td>
</tr>
<tr>
<td>Resected tumor volume (%)</td>
<td>56.5</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Residual tumor volume (%)</td>
<td>43.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resected gray matter volume $\Delta N_{g}$ (mL)</td>
<td>0.145</td>
<td>1.968</td>
<td>5.901</td>
<td>—</td>
</tr>
<tr>
<td>Resected white matter volume $\Delta N_{w}$ (mL)</td>
<td>0.141</td>
<td>0.478</td>
<td>0.534</td>
<td>—</td>
</tr>
<tr>
<td>Ratio of gray matter resected to white matter resected</td>
<td>1.03:1</td>
<td>4.12:1</td>
<td>11.05:1</td>
<td>—</td>
</tr>
<tr>
<td>Total resected tissue volume $N_r$ (mL)</td>
<td>0.524</td>
<td>3.284</td>
<td>7.337</td>
<td>—</td>
</tr>
</tbody>
</table>

Volumes in mL were derived from segmented baseline and postresection images. The baseline ROI volume in mL was composed of gray matter ($N_{g}$), white matter ($N_{w}$), and tumor ($N_t$). The postresection ROI volume was composed of residual gray matter ($N_{g}'$), residual white matter ($N_{w}'$), residual tumor ($N_t'$) and total resected tissue ($N_r$). The changes in gray matter ($\Delta N_{g}$), white matter ($\Delta N_{w}$), and tumor ($\Delta N_t$) volumes in mL were calculated between baseline and postresection segmented ROI images. Adding these values allowed the calculation of total resected tissue ($N_r$). Percentage tumor resected and residual tumor volumes, tumor lengths, and total gray/total white matter ratios were also calculated. Percentage tumor resected and residual tumor volumes were calculated based on the volume of injected alginate tumor inferred from 7-T magnetic resonance images.
Calculation of Total Gray and White Matter Resected
In 3 of 4 calf hemispheres with tumors, the baseline gray (\(N_g\)) and white matter volume (\(N_w\)) within their respective ROI could be calculated (Table 2). In these 3 tumors, it was possible to calculate residual gray (\(N_{gr}\)) and residual white matter (\(N_{wr}\)) present in the ROI of the postresection images (Table 2). In brain hemisphere 4, the baseline and postresection images could not be accurately aligned because the resection cavity was compressed (Figure 5G and H). The ability to accurately calculate residual gray (\(N_{gr}\)) and residual white matter (\(N_{wr}\)) volumes present on the postresection images for 3 tumors allowed for the calculation of change in gray (\(\Delta N_g\)) and white matter volume (\(\Delta N_w\)), and resected gray and white matter, respectively, on the postresection images (Table 2). It was the expectation that more gray than white matter would be removed during the subpial resection of tumors and the gray/white matter ratios seemed consistent with that expectation (Table 2).

Calculation of Total Tissue Resected
For 2 tumors studied in which the tumor was completely removed (\(\Delta N = 0\)) and for the incompletely resected tumor, the total tumor resected volume (\(\Delta N_t\)) was successfully calculated. Because it was also possible to calculate residual gray matter (\(N_{gr}\)), residual white matter, \(N_{wr}\), and residual tumor (\(\Delta N_{t}\)) volumes present on the postresection images, the total volume of tissue removed \((N_t)\) during the subpial resection could be calculated using equation 7. The total tissue resected ranged from 0.524 to 7.337 mL (Table 2).

Postresection Structural Integrity Analysis of Gray and White Matter Tracts
The registration process of the baseline and postresection 7-T MRIs provided structural information on the integrity of gray matter gyri and white matter tracts in the vicinity of the tumor before and after tumor resection. By matching each point on the postresection segmented image with its analog on the baseline segmented image using the Slicer extension "Segmentation registration," it was possible to evaluate the differences between both images after they were automatically registered by the software (Figure 5). On the baseline sagittal segmented images provided, the injected alginate resulted in irregular tumors within and covered by the overlying gray matter gyrus (Figure 5A, C, E, G). In some postresection segmented images, irregularities in the residual gray matter tissue can be visualized, which is consistent with incomplete resection of overlying gray matter and gray matter injury (Figure 5F and D). Residual tumor tissue in this model can be identified and easily quantitated on postresection images (Figures 5 and 6). Although fiducials were placed on only 1 brain in group 2, their presence improved baseline and postresection image alignment by acting as landmarks that could be easily recognized and registered. A video containing scrolling coronal baseline and postresection images is provided for brain 1 of group 2 and brain 3 of group 2 (Video 1). The video can be used to provide the learner with further information on surgical performance. Violation of the surgical pial boundaries and damage to the adjacent gyrus are
particularly apparent when both baseline and postresection segmented MRIs are put side by side for comparison.

**Baseline and Postresection 3D Reconstruction Views**

Using the information available on the segmented baseline and postresection images, it is possible to develop 3D reconstructions of the calf brain containing the tumor and postresection residual tumor (Figure 7). These images can provide further information related to the surface structure of the resection cavity and the 3D structure of the tumor within the calf brain both before and after resection; in the case of brain 1 of group 2, this sort of 3D view allowed the visualization of the residual tumor remaining after the subtotal resection (Figure 7).

**DISCUSSION**

**Summary**

This pilot study was carried out as a proof of concept that the combination of using a brain tumor resection model and segmented 7-T MRIs is feasible and has the potential to aid in understanding and evaluating neurosurgical performance. We were able to fulfill our aims of quantitating brain tissue removal, alginate brain tumor resected, and normal gray and white matter resected along with total tissue resected after subpial resection in a calf brain model.

**Quantification of Brain Tissue Removed**

The image analysis based on segmented 7-T MRIs used in this study can be used with the developed polynomial model to accurately predict small brain segment removals if brain deformation between baseline and postresection images is minimal. Significant deformation of anatomic structures in the baseline and postresection images prevents the registration of the 2 images, thus preventing the calculation of the difference in tissue volumes between the 2 images. Another limiting factor is the size of the removed piece of tissue. Smaller pieces cannot be accurately analyzed because they can easily be mistaken for brain surface deformation. The polynomial model can determine the brain tissue weights in grams when larger amounts of brain are removed. Further investigation needs to be performed to increase our ability to measure smaller quantities of brain tissue removed.

**Alginate Tumor Model and Quantitative Analysis of Tissue Resections**

Although attempts were made to provide the ex vivo alginate tumor model used with color and tumor stiffness characteristics
associated with human tumors, the model does not reproduce the multiple consistencies and bleeding associated with human glial tumors. Therefore, our studies are not able to assess the influence of these factors on resection technique. The alginate tumor hydrodissection injection into calf brain cortical gray matter resulted in a variety of tumor shapes, necessitating careful delineation of the ROI on the baseline and postresection images (Figure 5). The alginate tumor model and the segmentation and registration 7-Tesla MRI techniques utilized in this study allowed quantitative assessment of all 4 tumor volumes ($N_t$) and 3 out of 4 gray matter ($N_g$) and white matter ($N_w$) volumes within ROI outlined on baseline scans. The quantitation of residual gray matter ($N_g^r$) and residual white matter ($N_w^r$) along with the residual tumor ($N_t^r$) in the equivalent ROI location after resection is...
important to allow calculation of change in gray matter ($\Delta N_g$), change in white matter ($\Delta N_w$) and change in tumor ($\Delta N_t$). Using equation 7, the value for total resected tissue ($N_t$) can be obtained. This procedure is possible only if accurate alignment of baseline and postresection images can be achieved, which was accomplished in 3 of 4 tumors studied. Although only a small series, 4 of 7 calf hemispheres studied contained fiducials. There seemed to be an improvement in registration of baseline and postresection segmented images when fiducials were present. Accurate registration was not possible for the largest tumor in the series because of the infolding and collapse of the resection cavity during placement in the MRI coil (Figure 5). This situation suggested that larger resection cavities tend to be more compressible after being placed in the coil. Conceptually, filling the resection cavity after the completion of the procedure with an incompressible material that is not visible on MRI would result in lesser deformation, allow improved alignment, and increase the ability to find all 3 variables necessary to solve equation 7. Studies are ongoing to evaluate possible materials that could perform this function.

### Educational Opportunities: Combining Virtual Reality and Ex Vivo Models

Ex vivo models have been developed to aid in the assessment of neurosurgical technical skills. The ex vivo bovine model used in these studies is not an exact replicate for the human brain regarding size and convolutional surface appearance and should not be considered a substitute for the detailed anatomic studies involving cadaveric models. However, ex vivo models do provide new methods to quantitate trainees’ technical skills and different educational opportunities for learners. MRI has not been previously used to assess psychomotor bimanual performance in these model systems. Prerecession and postrecession imaging, whether MR or computed tomography, is available for patients undergoing operation for tumor resection but the ability to accurately quantify gray and white matter removal in these procedures is difficult. The ability to use this tumor model in combination with 7-T MRI provides an opportunity to increase the granularity of data obtainable from operative procedures.

Our group has used high-fidelity virtual reality simulators with haptic feedback to develop a model for bimanual psychomotor surgical performance and for quantitative assessment of expert performance. Present studies are focused on developing intelligent tutoring systems using machine learning and artificial neural networks for assessment and training of surgical performance along with the development of complex neurosurgical scenarios for use in these tutoring systems. The ability to compare expert performance on surgical virtual reality simulators to that in controlled operating room environments would advance both the understanding of surgical expertise and the ability to train learners to the mastery level using these intelligent tutoring systems. The combination of developing standardized alginate tumor and epilepsy models using the ex vivo calf brain model outlined in this communication along with segmentation and registration MRI technologies allows for future studies in skills transfer between virtual reality simulators and the operating room. These investigations would be able to focus not only on amount of tumor tissue resected but also on quantity of normal gray matter and white matter tracts resected, the method of resection, and the tissue injury to adjacent areas.

### Limitations

Although this is to our knowledge the first study that attempts to provide a quantitative method of analysis on an artificial tumor model obtained from a 7-T MRI scanner, there are limitations. First, the polynomial model developed using brain sections involving both gray and white matter was limited and needs to be expanded. Our polynomial model was based on 4 brain segments; further studies with different sizes of brain tissue removed must be carried out to increase the accuracy and predictive power of the model. Second, to quantitate residual gray and white matter in the postresection segmented images, methods to prevent infolding of the resection cavity need to be developed to avoid being unable to register prerecession and postresection segmented MRIs such as in the case of brain 4 (Figure 5H). Studies are under way to address this issue. Third, this model does not allow for an assessment of vascular injury but methods to perfuse the ex vivo calf brain hemispheres are being explored. Fourth, regarding segmentation, although manual segmentation remains the gold standard, it induces a range of variability in accuracy that may affect the quality of the segmentations. Variability may result from user factors and signal inhomogeneity of the volume despite the filtering process, particularly when same tissue types show residual noise. Manual segmentation requires a significantly higher amount of time compared with automatic methods, which may not be adapted to the clinical setting. Choosing the proper ROI after segmentation and registration is also time consuming and requires expertise. For instance, the processing of brain 4 was not possible not only because the postresection cavity collapsed on itself but also because only half of the brain was scanned, thus omitting important brain landmarks that could have been used to perform registration.

The choice of FOV for this brain was made with the idea that scanning the half of the brain that contains the tumor would be easier than scanning the whole brain. No atlas or database on calf brain exists, which makes the development of an automated segmentation pipeline difficult. The number of calf brain hemispheres used in this pilot study was small. However, these investigations functioned as a proof of concept and outlined important issues that need to be addressed to improve future studies. Only a few institutions have access to animal 7-T MRI units, limiting the number of research centers that can carry out these types of investigations. Studies using human 7-T MRI to quantitate operative performance may also find these studies useful.

### Conclusions

This pilot study was carried out as a proof of concept to show the feasibility of using brain tumor models combined with 7-T MRI technology to quantitate brain tumor resection along with normal gray matter, normal white matter, and total tissue resected after subpial resection procedures in a calf brain ex vivo tumor model.
The ability to use tumor models in combination with 7-T MRI provides an opportunity to increase the granularity of data obtained from operative procedures and improve the assessment and training of learners.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Dan Huy Tran: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. Alexander Winkler-Schwartz: Conceptualization, Methodology, Resources, Writing - review & editing, Funding acquisition. Marius Tuznik: Investigation, Data curation, Writing - review & editing. Houssem-Eddine Gueziri: Conceptualization, Methodology, Software, Investigation. David A. Rudko: Methodology, Investigation, Software, Resources, Writing - review & editing, Supervision. Aiden Reich: Conceptualization, Writing - review & editing. Recai Yilmaz: Conceptualization, Methodology. Bekir Karlik: Conceptualization, Methodology. D. Louis Collins: Methodology, Software, Writing - review & editing. Adrian Del Maestro: Methodology. Rolando Del Maestro: Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition.

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