Application of Three-Dimensional Printed Tractography in Neurosurgical Planning: a systematic review

Review

Abranches GP, Silva ACF, Dering LM, Scremin LG, Pedro MKF, Leal AG - Application of Three-Dimensional Printed Tractography in Neurosurgical Planning: a systematic review

ABSTRACT

Background and purpose: White matter tractography (WMT) is a neuroimaging method that allows in vivo demonstration of the central nervous system pathways via diffusion magnetic resonance imaging that, recently, has been combined with three-dimensional (3D) printing. The tool presents a potential way to improve surgical treatment with better outcomes, and it has barely been explored in clinical practice. The present review summarizes the advantages, limitations, and potential clinical application of WMT 3D printed models. Methods: A search was performed at PubMed, Cochrane Library, and Google Scholar databases. Full-text, peer-reviewed journal publications were the selection criteria. No language, regional, or data restrictions were applied, and data extraction followed the PRISMA guidelines. Results: Among the 7 articles included in the systematic review, 6 were case series or case reports, and only 1 was a technical note, totaling 11 patients evaluated, all with brain tumors (4 frontal lobe tumors, 2 parietal lobe tumors, 3 temporal lobe tumors, 2 sellar tumors and 1 acoustic neuroma). The tumor and adjacent fiber pathways were printed in all studies, but only 3 cranial nerve fibers and 2 blood vessels were printed. All studies reported successful surgeries with total or subtotal tumor resection. All studies were case series, case reports, or technical reports. Conclusion: A review of the currently available literature showed that although promising, 3D printing models of WMT are still in its early stages, and further studies are needed before indicating the use outside the preoperative assistant modality context.

Keywords: Tractography; Three-dimensional printing; Neurosurgery

RESUMO

Introdução: A tractografia de substância branca (SB) é um método de neuroimagem que permite a demonstração in vivo de vias do sistema nervoso central através de ressonância magnética por difusão que, recentemente, foi combinada com impressão tridimensional (3D). A ferramenta apresenta um modo potencial de aperfeiçoar o tratamento cirúrgico com melhores resultados, e tem sido mal explorada na prática clínica. A presente revisão sistemática resume as vantagens, as limitações e a potencial aplicação clínica dos modelos impressos da tractografia de SB em 3D. Métodos: Uma pesquisa foi realizada nos bancos de dados PubMed, Cochrane Library e Google Scholar. As publicações em revistas com texto completo e revisadas por pares foram critérios de seleção. Não foram aplicadas

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Received Oct 8, 2022
Accepted Nov 6, 2022
Abranches GP, Silva ACF, Dering LM, Scremin LG, Pedro MKF, Leal AG - Application of Three-Dimensional Printed Tractography in Neurosurgical Planning: a systematic review

INTRODUCTION

White matter tractography (WMT) is a neuroimaging method that allows in vivo demonstration of the central nervous system pathways via diffusion magnetic resonance imaging. As the magnetic resonance-guided intraoperative neuronavigation, intraoperative electrophysiology, and fluorescence microscopy techniques, WMT aims to improve neurosurgical results by maximizing tumor resection margin with minimum or no damage to eloquent areas during neurosurgical procedures, with the advantage of being noninvasive and preoperative. Even though diffusion tensor imaging (DTI) has not been considered as effective as intraoperative stimulation (gold standard), WMT enriches surgical planning, allows safe extent of resection, increases overall survival and, potentially, Karnofsky Performance Scale (KPS) score.

Recently, WMT has been combined with three-dimensional (3D) print, a technology developed in 1981 and first used for surgical planning support in 1994. The applications in the neurosurgical field have been well documented and proved to be useful for neuro-oncology, cerebrovascular, functional, spine and endoscopic surgeries, although mostly in neurovascular approaches for brain aneurysms. The prototyping process requires an interface between structural and functional information obtained by Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), which are subsequently processed and submitted to segmentation and printing protocols. Obtaining a solid 3D printed model allows a better understanding of patient-specific anatomy and surgical simulation, ensuring more accurate surgical planning.

SYSTEMATIC REVIEW

This study identified all full-text, peer-reviewed publications of the applications of 3D printed tractography in neurosurgical planning. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement was adapted for the current review to increase certainty, comprehensiveness and transparency of reporting. Published studies pertaining to 3D printed tractography were found by utilizing a thorough search strategy of the PubMed, Google Scholar and Cochrane Library databases from inception to March 5th, 2022.

The selection process was adapted for each database and reproduced by all authors. In PubMed, the search was conducted for ‘tractography’ or ‘fiber tracking’ or ‘white matter tracts’ and ‘neurosurgery’ and ‘3D printing’ or ‘three-dimensional printed models’ with 9 results found. In Google Scholar, the search was conducted for ‘tractography’, ‘neurosurgery’, ‘3D printing’ and ‘white matter tracts’ and 58 results were found. In Cochrane Library, the search was conducted for ‘tractography’ or ‘fiber tracking’ or ‘white matter tracts’ and ‘neurosurgery’ and ‘3D printing’ or ‘three-dimensional printed models’, but no results

Palavras-Chave: Tractography; Impressão tridimensional; Neurocirurgia
were found. No language, regional or data restrictions were applied. The reference lists of chosen articles were searched to identify relevant articles further.

All authors performed data collection process, and each article was assessed for inclusion independently. Studies that had no description of 3D printed tractography were excluded. After removing duplicates, 60 articles remained for analysis, from which 59 were considered articles of interest by all authors (Figure 1).

The information extracted from each article were: author, year, level of evidence and study design, patient diagnosis, software used for the design of the 3D-model, 3D-model material, whether there was preoperative simulation or not, time of surgery, and patient outcome. All authors reviewed the data selection and collection processes two times to reduce the study risk of bias. All data were collected manually by the authors and tabulated for synthesis (Table 1).

RESULTS

After a detailed analysis of the 59 articles of interest, all authors excluded 49 for not presenting a 3D printed model of fiber pathways. Each author analyzed the 10 remaining articles twice, and 3 of them were banned. In the remaining 7 reports, 3D printing tractography models were used as a preoperative study tool. We summarized the selection process in Figure 1.

Among the 7 articles included in the systematic review, 6 were case reports or case series, and only 1 was a technical note, totaling 11 patients evaluated, all with brain tumors (4 frontal lobe tumors, 2 parietal lobe tumors, 3 temporal lobe tumors, 2 sellar tumors and 1 acoustic neuroma). The tumor and adjacent fiber pathways were printed in all studies, but only 3 printed cranial nerve fibers and 2 blood vessels.

All studies reported successful surgeries with total or subtotal tumor resection. Data from all included reports are detailed in Table 1.

Softwares and 3D printing model design

The rapid prototyping technique is based on three steps: (1) CT and MRI acquisition; (2) eloquent fiber tracts identification, obtained from DTI; (3) combination of anatomical and functional data (Figure 2). These steps requires specific software that may vary in quality and accuracy, providing different results, despite being based on the same reconstruction algorithm.

Gargiulo et al. pointed out this technical limitation describing the designing process of a 3D model of a young female with low-grade glioma. They used two different softwares for rapid prototyping, focused on five fiber tracts and then compared the models produced by the two programs. They noticed considerable differences in ending morphology and thickness between the two software platforms that may be important to ponder while evaluating pathological areas of interest. Regardless of this limitation, they selected the program considered more accurate, designed the model and used it to prepare the surgical operation with the support of neurosurgical navigation system.

Other well-known limitations are those regarding tractography. The limitations are due to use-dependent heterogeneity, difficulty...
Table 1. Articles included in systematic review with summarized results.

| Author            | Study design      | Patient diagnosis                                      | Software                                      | Printer                | Material(s)                  | Structure(s) printed | Outcome                                                                 |
|-------------------|-------------------|--------------------------------------------------------|-----------------------------------------------|------------------------|-----------------------------|----------------------|-------------------------------------------------------------------------|
| Gargiulo et al.   | Case Report       | Low-grade frontal lobe glioma                         | NordicBrainEx                                 | ProJet (3D systems, Rock Hill, USA) | VisiJet M3-X                | ARC, CC, left/right motor and sensory tracts; optic tracts; skull base | Neurosurgeons were better prepared and the operation was successful |
| Konakondla et al. | Technical Report  | Not specified                                          | Mimics Innovation Suite (Materialise, Leuven, Belgium) | Stratasys Objet 260 Connex 3 (polyjet, photo curable resin); 3D systems CJP460 Plus (binder jet, gypsum powder); Ultimaker’s 2 and 3 (fused deposition modeling, also known as FDM) | Several types of resin | Tumor; fiber tracts; fMRI data – all fused with the brain              | Improved understanding of disease, surgical planning, operating time and position of eloquent areas; decreased blood loss and surgical site infections |
| Thawani et al.    | Case series       | Patient A: right posterior frontal tumor Patient B: right parietal lobe tumor Patient C: right temporal / insular tumor | Solidworks (Dassault Systems SolidWorks Corporation, Waltham, Massachusetts); Meshmixer 10.9.297 (Autodesk, Berkeley, California) | ProJet 6000 3-D Printer (3-D Systems Corporation, Rock Hill, South Carolina) | Polycarbonate-like photoreactive polymer | Tumor, CC, ARC, CST (all cases)                         | Facilitated education of residents, operative teamwork, and patients understand their diagnosis and treatment indicated |
| Thawani et al.    | Case series       | Two cases of sellar region tumor and one case of acoustic neuroma | Mimics Research Version 17.0 (Materialise, Leuven, Belgium) | Connex3 Objet350 (Stratasys, Eden Prairie, Minnesota, USA) | VeroCyan; VeroMajenta; VeroYellow | Tumor, brain tissue, CNs, arteriovenous vessels | Improved pre-operative planning and prevents possible damage to cranial nerves |
| Lin et al.        | Case series       | Two cases of sellar region tumor and one case of acoustic neuroma | Mimics Research Version 17.0 (Materialise, Leuven, Belgium) | Connex3 Objet350 (Stratasys, Eden Prairie, Minnesota, USA) | VeroCyan; VeroMajenta; VeroYellow | Tumor, brain tissue, CNs, arteriovenous vessels | Improved pre-operative planning and prevents possible damage to cranial nerves |
| Romero-Garcia et al. | Single-center prospective cohort | Participant 1: right middle and inferior frontal gyrus tumor Participant 2: left anterior superior frontal gyrus tumor | FMRIB Software Library version 5.0; semiautomated pipelines (Unified Segmentation with Lesion toolbox); FreeSurfer (version 6.0 for Linux); MeshLab 2016 (IST-CNR) | Scaled and printed at Addenbrooke’s Media Studio (Addenbrooke’s Hospital, Cambridge, UK) for 3-dimensional (3D) printing (process: 3D ColorJet Printing Technology, machine specification: Projet 660 Pro [3D Systems, Rock Hill, South Carolina, USA]) | VisiJet PXL (plaster powder, 3D Systems) and ColorBond (cyanoacrylate) infiltrant (3D Systems) | Tumor, cortex, gyri and sulci, association fibers | Improved physical interaction, portability, cost-effectiveness and flexibility |

fMRI = functional magnetic resonance imaging; 3D = three-dimensional; ARC = Arcuate fasciculus; CC = Corpus callosum; CST = corticospinal tract; CNs = cranial nerves.
Table 1. Continued...

| Author                  | Study design | Patient diagnosis                                      | Software                         | Printer                          | Material(s)                      | Structure(s) printed                        | Outcome                                                                 |
|-------------------------|--------------|--------------------------------------------------------|-----------------------------------|----------------------------------|-----------------------------------|---------------------------------------------|--------------------------------------------------------------------------|
| Watanabe et al.         | Case Report  | Mass lesion in the right-sided temporal lobe           | GrabCAD Print (Stratasys Ltd., Eden Prairie, MN, USA) | J750 (Stratasys Ltd., Eden Prairie, MN, USA / Rehovot, Israel) | VeroMagenda-Vivid, VeroCyan-Vivid, Vero-Yellow-Vivid, Agilus30Clear, VeroPureWhite, VeroClear | Tumor, brain tissue, tentorium, optic radiations, arteriovenous vessels, lateral ventricle, venous sinus | Enable easy preoperative understanding of the anatomy, allowed visualization of surgery from another angle. |
| Gomez-Feria et al.      | Case series  | Patient A: right temporal – insular lesion Patient B: left frontal-parietal – insular DLGG | SimNIBS; Matlab toolbox MRICross toolbox; 3DSlicer; Autodesk Meshmixer 3.3.15 (Autodesk, Inc., Mills Valley, California, USA) | BQ Witbox 2 3D printer (BQ, Las Rozas de Madrid, Spain) | Rigid polylactic acid filament | Skull, tumor, gray matter, tracts and functional volumes | Low cost, better understanding of disease by surgeons and patients, improved knowledge on the tumor's location within the head and its relation with eloquent areas. |

fMRI = functional magnetic resonance imaging); 3D = three-dimensional; ARC = Arcuate fasciculus; CC = Corpus callosum; CST = corticospinal tract; CNs = cranial nerves.

Figure 2. Digital 3D reconstruction of a tractography at the Neurological Institute of Curitiba (INC).
in verify correlation between image and function, anatomical differences of fibers, displacement of fibers by injuries or edema and functional reorganization resulting from displacement, and the noise caused by false continuity or crossing fibers. It is even more challenging in children because of incomplete nervous system development and incomplete myelination at 12 months of age 14. False negatives (a fiber may be lost) or false positives may occur 25. In a study carried out with 250 patients with brain tumors, Treiber et al. 26 found that regions close to the paranasal sinuses – such as the temporal poles, orbitofrontal cortex and brainstem – are mostly affected by distortion. Those findings are in agreement with cases reported by Lin et al. 7, Romero-Garcia et al. 8 and Thawani et al. 29.

Additionally, there are still limitations regarding imaging acquisition methods. CT and MRI may present signal distortion or artifacts, directly affecting the ability to identify and delineate target volumes and critical structures. All radiation-generated medical images are reconstructed from information that undergoes statistical fluctuations and therefore has a predictable error. Moreover, there are several patient-dependent restrictions related to the performance of the exams, such as patient’s allergy to contrast, chronic kidney disease, cochlear implants, pacemakers and aneurysm clips performed before 1995 27.

Model material

As Martin-Nogueirol et al. 30 pointed out, there is a wide diversity of printing materials, which allows using different colors to facilitate delimitation of the structures and enables printing each structure with different physical characteristics and creating 3D-printed models even more identical to human tissue texture, stiffness and consistency.

These advantages were explored by Watanabe et al. 9 that printed a 3D model with adjustments in color, hardness, and transparency to perform reliable preoperative simulation. Despite the arbitrariness of adjustments, the authors considered that the final 3D model preserved the spatial arrangement of each structure while keeping a smooth and natural appearance.

Lin et al. 7 and Gomez-Feria et al. 24 also reported excellent results with surgery simulation on a 3D model printed with varying stiffness between the skull and brain tissue. In both cases, a soft texture was selected to print the tumor so the material could be easily cut and separated.

Applications in preoperative simulation

Lin et al. 7 performed simulation both virtually and on 3D model. Their 3D models were consistent with virtual surgery results, as they showed the surgical site and reflected directly in the displacement of adjacent structures by the tumor and the tumor invasion into the bones of the skull base. However, they noticed that the printed cranial nerve shape was not always consistent with the actual condition seen intraoperatively. They concluded that models are mainly useful for determining position and path of the fiber bundles, along with the degree of tumor displacement of adjacent structures.

Watanabe et al. 9 simulated in the 3D model the extent of the resection on the T1-weighted image with contrast. They established resection boundaries on previous imaging exams using the computer and then reproduced this intraoperative delimitation using two catheters as fence posts. They achieved total gross removal and agreed the 3D model helped to understand the degree of resection and the relationship between the tumor and essential structures, especially in deep regions, as it shows portions not visible during surgery. They also emphasize the importance of printing all structures in a single process since printing each one individually and then manually combining all results in anatomically inaccurate models, therefore, would be unsuitable for preoperative simulation.

Gomez-Feria et al. 24 proposed that eight experienced neurosurgeons tested the highly realistic 3D head models in the preoperative simulation of tumor resection in two patients. All surgeons agreed that the model aided surgical planning and training, intraoperative surgical guidance, and physician-patient communication. They emphasize that various cutting planes performed on the model helped quickly to identify brain areas of interest during the surgery.

Intraoperative advantages and patient outcome

Gargiulo et al. 7 demonstrated that previous patient studies with the 3D printed tractography improved the quality of surgical planning, as it improved the quality of diagnosis, reduced anesthesia time, blood loss and exposure to the surgical wound. Other works evidenced, additionally, major tumor resection and decreased postoperative deficits 28,29.

Lin et al. 7 highlighted 3D-printing technology as a way to assemble more accuracy to neurosurgical planning by allowing recognition and understanding of the patient’s anatomical details from an
entirely new perspective. Therefore, it is possible to formulate strategies to protect delicate structures, ensuring safer and faster surgical resection.

Konakondla et al. also recognized that 3D printing tractography improved operating time, decreased blood loss, and a downward trend in surgical site infections. There are also suggestions for improving postoperative morbidity considering the technology as a beneficial adjunct to achieving maximum safe surgical resection. Romero-Garcia et al. concluded that, despite limitations, the data provide valuable additional information to the neurosurgeon if properly interpreted.

Besides the reduction in intraoperative risks, reports reveal higher KPS scores at six-month evaluation besides fewer motor deficits postoperatively with preoperative DTI and tractography, along with higher probability of gross total resection in patients with HGG. Moreover, DTI capacity in predicting preoperative neurological impairment and postoperative outcomes showed significant value. DTI has a well-established role in both low- and high-grade gliomas, and also serves as an adjunct to radiation planning for stereotactic radiosurgery and awake craniotomy for tumor resection.

**Educational benefits**

Although validated as useful for anatomic studies when compared with traditional models, 3D printing applications as an educational tool for neurosurgery residents and supporting staff need to be explored. Brief surveys were performed by Konakondla et al., Lin et al., Thawani et al., and Gomez-Feria et al. in their respective services.

Thawani et al. evaluated the technique’s utility by offering 3D models and patient information to 4 faculty and 5 residents utilizing a Linkert scale (1 = definitely no, 2 = likely no, 3 = neutral, 4 = likely yes, 5 = definitely yes) to assess the utility. They obtained scores of 4.75 between faculty and 4.77 between residents (postgraduate years 3-6), which highlighted the model’s utility.

Konakondla et al. applied a questionnaire to the surgical staff and residents concerning to the patient positioning, fiber tract location, lesion location, surrounding structures, the importance of structures, case goals, and case preparedness. For each question, the participants were told to circle a number from 0-10 on scale (0 = strongly disagree, 5 = somewhat agree, 10 = strongly agree). Significant improvement in overall understanding was observed.

Lin et al. invited 16 neurosurgeons familiar with skull base surgical anatomy to evaluate, using a questionnaire, the 3D printed skull base tumor models after examining and manipulating the models. The questions covered three aspects (accuracy of the model, an overall evaluation and practicability), each item scored with a 5-point scale, the highest score being 5. The average scores of 3.94 ± 0.60, 4.14 ± 0.52, and 3.81 ± 0.52 indicate skull base tumor model has a great potential as neurosurgery training tool.

Gomez-Feria et al. performed a survey with 3 residents specializing in neurosurgery and 5 faculty neurosurgeons. All participants evaluated the 3D model after surgery through an 11-item questionnaire (nine 5-point Likert-type items and 2 questions on overall usefulness), obtaining > 95% acceptance, which supports the use of this model for surgical training and planning, intraoperative surgical guidance and doctor-patient communication.

Beyond that, there is still application in patient education. Gomez-Feria et al. and Konakondla et al. also highlighted the 3D model as useful for patients to improve comprehension of the procedure and disease process, engagement in surgical considerations and become more active participants in their treatment.

**DISCUSSION**

Although data regarding the impact of 3D printing on clinical outcomes of patients undergoing neurosurgery are scarce, all authors validated the technique as a helpful tool in providing patient-specific information that allowed better results by increasing surgical procedures safety with a reduction of surgical time and complications, which is encouraging. However, it is essential to consider that 3D printed tractography models absorb image acquisition limitations and DTI processing and prototyping software.

It is necessary to improve image acquisition techniques to ensure anatomically reliable and highly accurate models. Additionally, new impression materials are still needed, as they need to be more realistic and deformable to mimic in vivo brain tactility and appearance. It would be advantageous to improve preoperative simulations by better replicating the displacements suffered by the

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J Bras Neurocirur 33 (4): 463-471, 2022
https://doi.org/10.22290/jbnc.2022.330410
nervous tissue during craniotomy and consequent cerebrospinal fluid outflow.

Considering that impression materials fail to mimic human tissues and tractography has inherent inaccuracy due to its reconstruction algorithms, preoperative simulation with 3D-printed WMT models may become unnecessary for expert neurosurgeons who have already developed accurate anatomical comprehension. In addition, these flaws can hinder the use as a training instrument for residents in the anatomical aspect, presenting as more valuable for surgical technique practices. However, it may give surgeons a better idea of the access path’s difficulties or tumor resection.

Despite all limitations, this technique allows a better understanding of the disease by surgeons and patients, improves knowledge of tumor’s location within the head, evidence its relation to eloquent areas, and may give surgeons a better idea of the difficulties in the access path or tumor resection. The association with the surgical navigation system can attenuate the intrinsic limitations of the imaging acquisition techniques and enhance its use intraoperatively. Besides, printing all structures in the same process is essential to guarantee anatomical reliability.

Considering the limitations and advantages of printing 3D models of tractography, we propose that there is better performance in the fields of neurosurgical resident education (as a practice tool) and preoperative preparation (helping determine the surgical approach, traveling and position of fiber bundles, the degree of displacement of adjacent structures by the tumor and the resection performed). Its role is still insufficient to change the actions during the surgery itself. Still, with advances in imaging technology and 3D reconstruction software, there is great potential for accurate intraoperative application, especially in functional oncology.

**CONCLUSIONS**

Based on this critical review, although promising, 3D printing models of WMT are still in their early stages. The lack of good data makes it impossible to support the validity of the technique or the benefits for the patient. Further studies are needed before using the 3D-printing tractography outside the preoperative assistant modality context.
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Funding: nothing to disclose.  
Conflicts of interest: nothing to disclose.  
Institution: Neurological Institute of Curitiba.