Thesis

Ten Rules Guided Planning Versus Manual Planning for Stereotactic Brain Biopsy: A Retrospective Comparative Study

Submitted by

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Declaration of Academic Integrity

I solemnly declare that I have written the present work independently and without external assistance, have not used any sources other than those specified, and have clearly identified passages that have been taken verbatim or in essence from the sources used.

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Graz, 16.05.2025 Aashish Pariyar m.p.

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Zusammenfassung

Hintergrund: Derzeit stellt die stereotaktische Biopsie des Gehirns eines der am häufigsten durchgeführten Verfahren zur Identifizierung von Malignität bei Hirntumoren dar. Um eine optimale Trajektorie planen zu können, ist es unerlässlich, die folgenden von Prof. Stefan Wolfsberger beschriebenen Punkte zu berücksichtigen: 1) Länge minimieren 2) Senkrecht am Eintrittspunkt 3) Senkrecht zum Zielbereich 4) Anwenden von transgyraler Kortikotomie 5) Vermeiden von eloquentem Kortex 6) Vermeiden von eloquentem Trakt 7) Sulci/Fissuren/Ventrikel/Zisternen vermeiden 8) Abstand zu Gefäßen maximieren 9) Nebenhöhlen meiden 10) Meiden des Gesichtsbereichs.

Ziel der Arbeit: Die vorliegende Studie zielt darauf ab, die Durchführbarkeit und diagnostische Aussagekraft der an der "Ten Rules" orientierten Trajektorienplanung mit der manuellen Planung zu vergleichen, um potenzielle Optimierungspotenziale zu identifizieren und die Entwicklung semi-automatisierter Planungssoftware in Zukunft zu fördern.

Methoden: Im Rahmen einer retrospektiven Datenbankrecherche wurden alle erwachsenen Patient*innen, die zwischen 2013 und 2023 am Universitätsklinikum für Neurochirurgie in Graz einer SBB unterzogen wurden, identifiziert. Von jedem Fall standen prä- und postoperative MRT- oder CT-Bilder zur Verfügung und es wurden zwei unterschiedliche Trajektorien generiert. Die erste wurde von einem Studenten mit der Ten-Rules-Methode erstellt, während die zweite von einem erfahrenen Neurochirurgen manuell erstellt wurde. Anschließend wurden die Mittelwerts- und Medianunterschiede zwischen Zielpunkten in Tumoren und Eintrittspunkten auf dem Schädel verglichen. Zusätzlich wurde die Trajektorie des Studenten als „akzeptabel für OP“ und „nicht akzeptabel“ eingestuft.

Ergebnisse: Die Anwendung der „Ten Rules“ gesteuerten Planung war bei allen Patient*innen möglich. Für Trajektorien beträgt die mediane Differenz am Eintrittspunkt 11,9mm und 2,6mm am Zielbereich, wobei Mittelwert Differenz beträgt, 16,6mm am EP und 2,6mm am TP. Von 19 TGPs waren insgesamt 16 Trajektorien akzeptabel.

Conclusio: Für die stereotaktische Hirnbiopsie erscheint die auf „Ten Rules“ basierte Planung vielversprechend und machbar zu sein. In einigen Fällen kann sie sogar sicherer als MPs sein und die diagnostische Ausbeute steigern.

Schlüsselwörter: Neurochirurgie, Stereotaktische Hirnbiopsie, Trajektorien Planung, Zehn Regeln Gesteuerte Planung, Manuelle Planung.

Abstract

Background: Stereotactic brain biopsy represents one of the most frequently performed neurological procedures for the identification of malignancy in brain tumours. In order to plan optimal trajectories, it is essential to consider the following ten features, as described by Prof. Stefan Wolfsberger: 1) Minimize length 2) Perpendicular at the entry point 3) Perpendicular of the target area 4) Use transgyral corticotomy 5) Avoid eloquent cortex 6) Avoid eloquent tracts 7) Avoid sulci/fissures/ventricles/cisternae 8) Maximize distance to vessels 9) Avoid sinuses 10) Avoid facial areas.

Objective: The objective of this study is to compare the feasibility and diagnostic yield of Ten Rules-guided trajectory planning with manual planning to identify potential areas for improvement and to develop semi-automated planning software in the future.

Methods: A database search was conducted retrospectively between June and August 2023 to identify all adult patients who had undergone SBB at the University Hospital of Neurosurgery, Graz between 2013 and 2023. For each patient, pre- and post-operative images in the form of MRI or CT scans were available. Two patients were excluded from the study due to the unavailability of MRI images. In each case, two different trajectories were generated: the first one was created by a student using the Ten Rules method, while the second was performed manually by a senior neurosurgeon using the *Stealth Platform (Medtronic*). The mean and median differences between target points in tumours and entry points on the skull were then compared.

Results: The implementation of the Ten Rules was feasible in all patients. For trajectories, the median difference was 11.9 mm at the entry point and 2.6 mm at the target point, whereas the mean difference was 16.6 mm at the entry point and 3.3 mm at the target point. Of the 19 TGPs, 16 trajectories were accepted by the neurosurgeon.

Conclusion: The application of ten rules-guided planning in the context of stereotactic brain biopsy appears to offer a promising and feasible approach that may enhance safety and increase diagnostic yield.

KEYWORDS: Neurosurgery, Stereotactic Brain Biopsy, Trajectory Planning, Ten Rules Guided Planning, Manual Plan

Table of Contents

Abbreviations

ABTR Austrian Brain Tumour Registry

AI Artificial Intelligence

CAP Computer-Assisted Planning

Cm Centimetre

CSF Cerebrospinal fluid

CT Computed Tomography

Diff. Difference

e.g., exempli gratia ‘for example’

EP Entry Point

FBS Frame-based stereotactic

FLS Frameless stereotactic

GBM Glioblastoma

ICH Intracranial Haemorrhage

ICP Intracranial Pressure

mm Millimetre

MP Manual Plan

MRI Magnetic Resonance Imaging

NA Not-Accepted

SBB Stereotactic Brain Biopsy

TGP Ten Rules Guided Plan

TP Target Point

TRP Trajectory Planning

WHO World Health Organization

List of Figures

List of Tables

Introduction

1. A Brief History of Stereotactic Biopsy

The term `stereotaxy` is composed of two Greek words, stereon and taxis. Stereon was used as a technical term for geometrical solids in Greek mathematics; this term gives the meaning of 'spatial' or '3-Dimensional'. Taxis means 'to position'. In 1961, the leaders in the field of Stereotaxy founded the *International Society for Research* in Stereoencephalotomy in Philadelphia. This Society changed its name to the Society for Stereotactic and Functional Neurosurgery because the word 'stereotaxic' was substituted by the word 'Stereotactic'. The ending of the term 'Stereotactic' derives from Latin which means to touch. However, the stereotaxic procedure speaks much in favour of positioning rather than touching. Horsley and Clarke spoke also of stereotaxis and of a stereotaxic rather than a stereotactic apparatus. (1)

The first historical sign of a development leading to the stereotactic frame was the work of Carl Dittmar (1844-1920). He published a paper in 1873 titled, *On the Location of the so-called vasomotor centre in the medulla oblongata*. For this experiment, he invented a device to avoid unnecessary movements of the rabbit´s head and of the operator`s hand, to insert the knife in medulla oblongata with higher accuracy. This device was not based on the cartesian coordinate system. It can be considered as a supportive arm that we know from stereotactic intervention in brain today. (2,3)

Further pioneering work was done by Zernov, Professor of Anatomy at Moscow University, who designed the first prototype of a stereotaxic instrument in 1889 called Zernov's encephalometer. This apparatus consisted of a basal ring, an equator and a meridian. It was based on the polar coordinate system, which helped to determine the exact position of both deep and superficial structures of the human brain.(3,4) Zernov´s student N. Valtukhov assisted him by developing encephalometric maps for different age groups and mapped the brain sulci and basal ganglia. Their collaboration aimed to determine the basal ganglia's spatial localisation, its projections and dimensions. Physicians based in Moscow were inspired after their success to use the encephalometer. (3)

Horsley and Clarke, their contribution represents a milestone in stereotactic neurosurgery. The first use of the terms stereotaxy and stereotaxic apparatus was noticed in their publication in the brain in 1908.They invented a new method to investigate the structure and function of the cerebellum. Horsley wanted to insert an electrode in the dentate nucleus. To make this fulfilled, he was joined by Clark. The first Clarke instrument was built by James Swift in 1906. This Horsley- Clarke apparatus was the first animal stereotactic apparatus built with a baseline for a three-dimensional cartesian coordinate system: the midline, the intraaxial plane and the canthomeatal plane. (5,6) Horsley-Clarke device was reproduced by Aubrey Museen. Due to his keen interest in stereotactic methods, he built his own stereotactic apparatus for human use around 1918. But he couldn't convince a neurosurgeon to use his device. (6)

A huge milestone in the field of human stereotactic surgery was made by Spiegel and Wycis in 1947. They invented the Spiegel-Wycis-Apparatus. It was connected to an X-ray that made it possible to take films in the operating room and develop them rapidly. It

helped to locate the deep brain structure and decreased the time duration needed for invasive procedure. They introduced the term `Pneumoencephalography`. This system was based on encephalitic measurement to visualize the internal cerebral structure. They used this device for psychosurgery, treatment of Chorea Huntington, and pain with lesions in the mesencephalon and thalamus. Further applications of this device were done in 1950 to treat seizures with stereotactic lesions and choreoathetosis using pallidotomy. Much of the procedure, that we do today in the field of human stereotactic surgery, is based on the principles they developed. (7,8)

In the early 1940s, the most common causes of death during neurological surgical procedures were poor outcomes, difficulty with anaesthesia, and blood loss during surgery. (9) Leksell assumed that the improvement of poorly designed surgical equipment could reduce the mortality rate. The Sweden-based renowned neurosurgeon in Europe was Lars Leksell, who went to Philadelphia in 1947 and built the Leksell Instrument. This Instrument was inspired by the principles of Spiegel and Wycis and was called a type II stereotactic instrument. It helped the Neurosurgeon to approach any brain target easily because it consisted of a semi-circular arc that can be fastened to the head and equipped with an X-ray device. The primary aim of his device was not for biopsies, but rather for functional surgery like for the treatment of Morbus Parkinson. (5) In the last few decades, many advancements have made this device more applicable for diverse frame-based neurological surgical procedures. Currently, the Leksell Vantage Stereotactic System and the Leksell Stereotactic System produced by Elekta are available in the market. (10) This device is still in evolving process.

1.1.1 Leksell Stereotactic System

Leksell Stereotactic System is currently in use at more than 1,400 sites globally. It is based on the arc-centred principle**.** His device comprised a semicircular arc with an adjustable probe carrier. The arc of the device is attached to the patient's head in such a way that its centre can be in tune with the selected target area in the brain. It is possible to approach the site of the target from any convenient point of entrance on the skull because the arc can be rotated around the axis rods in connection with the lateral adjustment of the electrode carrier (figure 1). This principle enables the planning of limitless trajectories and entry points to be used. (9)

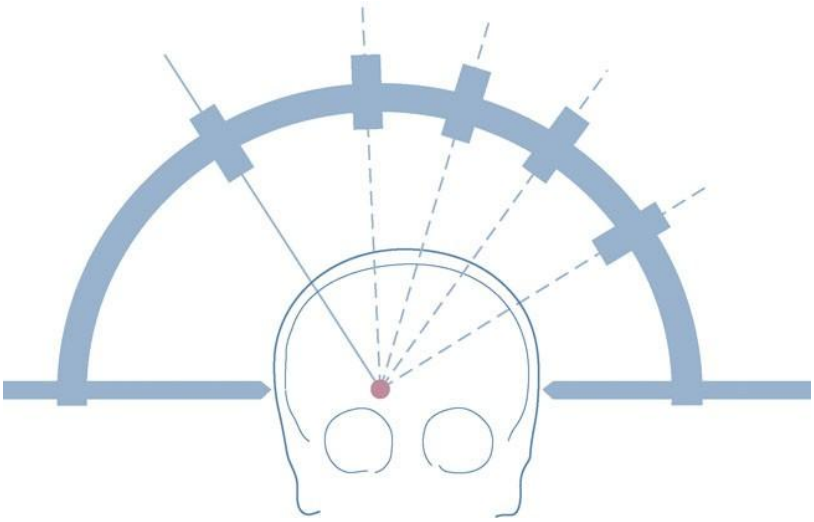

Figure 1. The Leksell arc-centered design with adjustable carrier. (9)

The model G instrument is currently available on the market and is widely used in different stereotactic procedures with all imaging modalities. (9)The frame has a rectangular base ring 190 X 210 mm (figure 2). The X-coordinate is set on the arc, which rotates around the Z rings (figure 3.). The y-coordinates are fixed by the supports attached to the Y-axes. The X, Y, and Z axes of the coordinate system match with the X, Y, and Z nomenclature of CT, MRI, and PET scans. (9,10) This system serves as a secure platform that ensures accuracy-requirement for the surgical procedure. The most common applications are listed below. (10)

- Biopsies, brain lesions
- Positioning and implantations of electrodes
- Catheter insertions, injections, and aspirations

Figure 2. G-Base Frame (10)

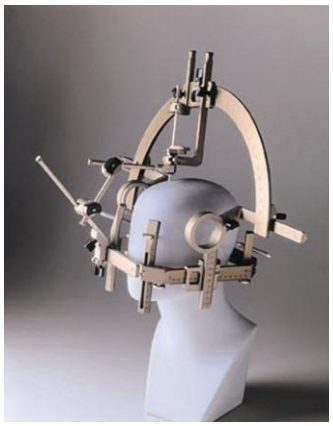

Figure 3. G-Base Frame with arc (55)

1.1.2 Stereotactic Brain Biopsy

Stereotactic brain biopsy is a well-defined minimal invasive procedure in neurosurgery, which assists in getting the histological diagnosis of patients with cerebral lesions and neurological diseases. (11,12) Various surgical methods can be used to perform a brain biopsy. The most common type of brain biopsy is an image-guided stereotactic frame-based biopsy which is delineated as a time-efficient and minimally invasive procedure. (12) Furthermore, studies have shown that frame-based systems are more precise modalities than frameless systems. (13) After its introduction in the field of neurosurgery, many papers were published regarding its safety. The accuracy of stereotactic biopsy has been covered in diverse studies, aiming for a high diagnostic yield of >90%. Moreover, a larger number of publications in the literature show an estimated morbidity of 1-10.8% and mortality of 0-2.3%. (14) However, it has been addressed in a few studies from Asian countries some of the possible risks of this procedure e.g., haemorrhage, seizure, and infection. Despite the proven safety, it is recommended reasonable attempt to undertake to detect a cerebral lesion. (15)

Generally, we can divide the procedure of brain biopsy into two categories. In an open biopsy, a tissue sample will be taken out during surgery after the exposition of the tumour through a craniotomy. A closed biopsy will be performed via a burr-hole or twist-drill craniotomy, as per the preference of the surgeon. (16) It is necessary to mark the burr hole and coagulate dura margins to open the underlying pia. While opening the pia, avoidance of cerebrospinal fluid egress assists in preventing brain shift. (17) Then a calibrated needle is inserted to take out a sample of tissue. Computer-assisted planning system with the help of CT and MRI is used, to provide precise information about the tumour's location. The procedure of brain biopsy consists of three phases: the preoperative phase(imaging), path planning of the needle, and assembly of the stereotactic equipment (Stereotactic Setup). (16,18)

Preoperative phase

In this phase, a CT- scan and an MRI of the patient's head are acquired. To precise the location of deep brain structures and generate their coordinates, a stereotactic frame is attached to the patient's head with the MRI localizer box (figure 1). (19) It helps as well to project the 3D visualization of the patient's head possible (figure 4).

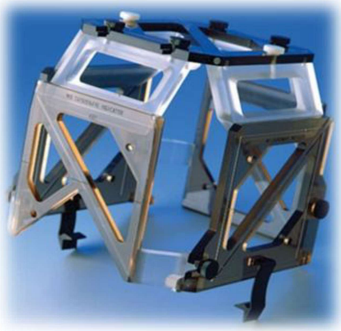

Figure 4. MRI localiser Box (56)

Figure 5. 3D Visualization of the patient's head (18)

Trajectory Planning

After 3D reconstruction of the patients, a neurosurgeon plans the trajectory carefully to avoid injuries of critical and deep-seated structures of the brain. The trajectory planning is done with the help of software like *Stealth Station S8 Surgical Navigation* from *Medtronic*, which allows surgeons to choose a target point in the tumour area and an entry point on the scalp. Moreover, it also allows one to plan more than one trajectory for the same tumour.

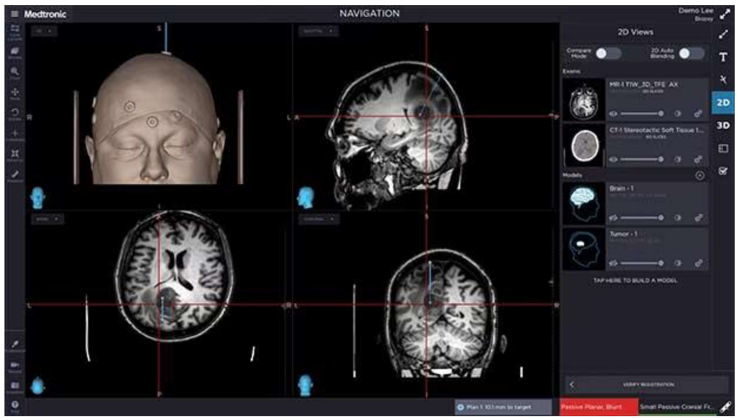

Figure 6 - Trajectory Planning (18)

Stereotactic Setup

After the arrival of the patient in the operating room, general anaesthesia is administered. In case of an awake procedure, a scalp block is preferred. A scalp block is regional anaesthesia of scalp nerves, using analgesia for a certain period. (17,20) The stereotactic head frame is fixed using skeletal pins at multiple points to avoid movements that may occur during a biopsy. After that, arc shaped device with a needle's holder is attached to the frame. With this stereotactic device, it is possible to adjust the needle with the desired orientation defined during the trajectory's planning by sliding the needle's holder through the arc. Once the needle is in the correct orientation each degree of freedom of the stereotactic device is locked to maintain the needle in the desired orientation during all biopsies. To date, FBS is regarded as the 'Gold Standard 'in functional neurosurgery. However, some neurosurgeons and patients find this procedure vexatious because of its wide range of system requirements such as reference frame and imaging after frame placement. Due to rapid progress in the field of technological innovation, SBB has developed from a frame-based to a frame-less setup through the development of a navigation system. An instrument holder and a trajectory guide have already been developed. Recently, a system for FLS with a lockable arm has been launched by Brain Lab, Germany. (21,22) Both frameless and frame-based setups are illustrated in Figure 7.

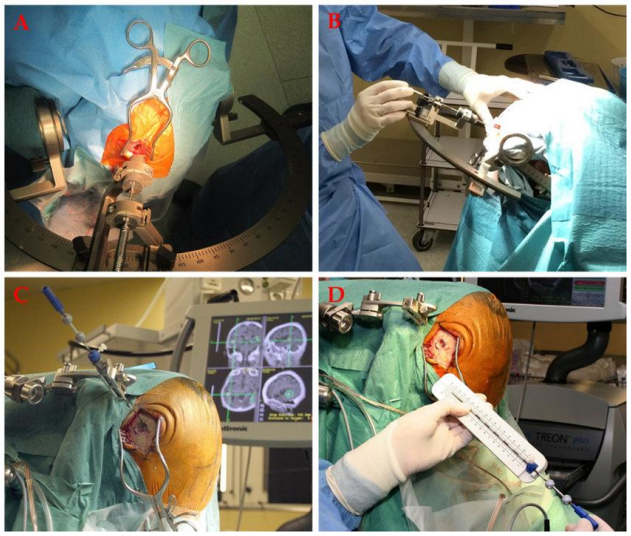

Figure 7. A u. B= FBS, C u. D= FLS biopsy for deep-seated brain lesions (22)

1.1.3 Neuronavigation assisted Brain Biopsy

Neuronavigation employs pre-operative imaging data and trajectories for biopsy guidance. (23) There is no requirement for a stereotactic frame and MRI localizer box. The setup in the operating room comprises a Mayfield frame (Figure 8), a Pointer System (figure 9) that navigates the position of the head, and surgical tools and a computer console. The

Mayfield *Frame* acts as a reference frame during the whole surgery, whereas the face pointer attached with an infrared sensor helps to recognize the points on the skull of the patient. To localize the target point, a surgeon inserts the needle with two infrared reflective markers. Neuronavigation system can easily detect the marker and estimate the path planning. (24)

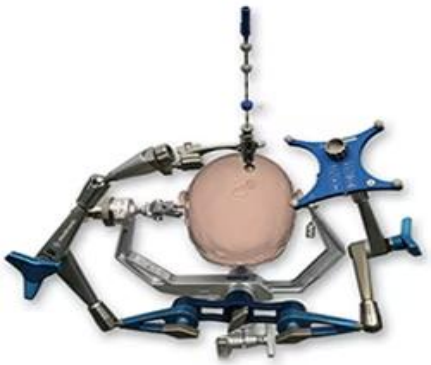

Figure 8. Mayfield Frame (18)

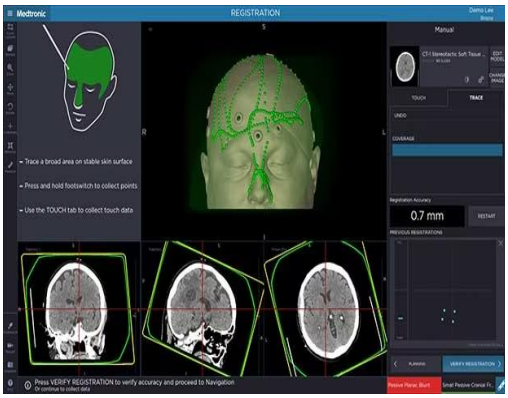

Figure 9. Pointer System (18)

Different steps of neuronavigation are demonstrated in Figure 10.

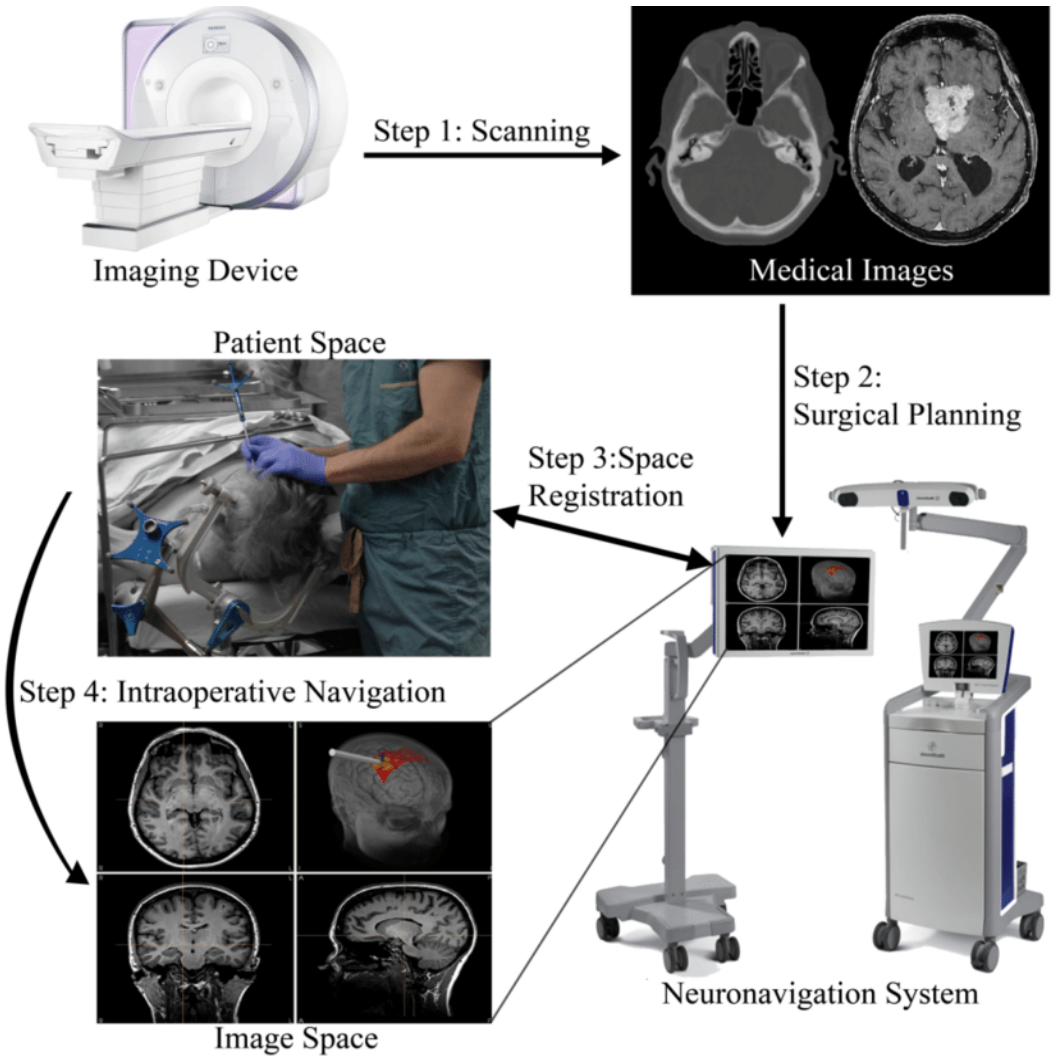

Figure 10. Workflow of Neuronavigation (24)

1.1.4 Brain Shift

Brain shift is defined as the brain displacement during brain surgery. After drilling a hole in the skull, the intracranial pressure decreases, causing the brain to move out of its original place. It was described for the first time in 1986 by Kelly et al. while performing volumetric stereotaxy. During this procedure, they saw the displacement of a steel ball in the surgical area. Various methods are used to recognize this process, e.g. neuronavigation, intraoperative ultrasound imaging, and scanning of surgical territory. (25,26) Brain shifting is associated with various causes, which can be categorized into three groups: surgical procedure, pathophysiological responses, and metabolic transformations. (26) All these causes interreact with each other. Their interrelation is illustrated below.

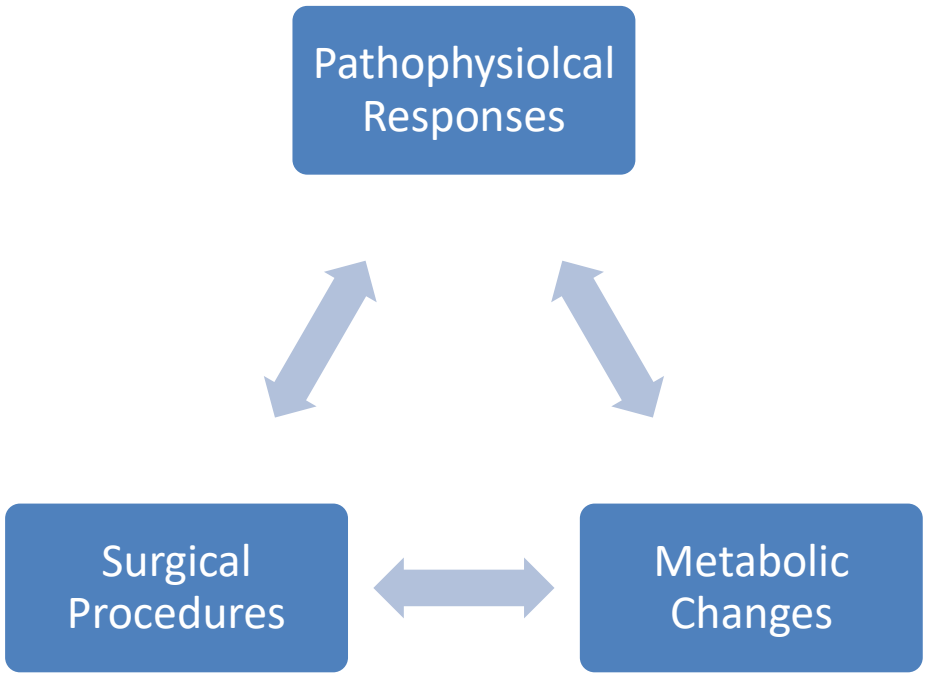

Figure 11. Interrelation of Causes (26)

The surgical procedure comprises the patient's head positioning, CSF loss, brain retraction, and removal of tissue. Pathophysiological responses e.g., alteration in ICP, ventricular deformation, and cerebral edema may directly or indirectly affect the intraoperative nature of the cortex. Metabolic modulation in the brain occurs due to anaesthetic, diuretics, fluid, and electrolyte imbalance. (23,25,26) Brain shift may vary from 0 to 24 mm depending on the volume of the tumour which needs to be taken into consideration. It is one of the most common complications that can occur during SBB which may alter the target point in the brain. Diverse approaches are currently being evaluated, to overcome the problem of brain shift. These include surgical techniques, intraoperative imaging, and mathematical models. (25,26) Among these approaches, mathematical models are unable to predict the brain shift because the intraoperative deformation of the brain can go in variable ways rather than in a

unidirectional course. As stated by M.I. Miga et al, the most promising method for correcting brain shift is intraoperative image guidance. It is therefore necessary, for intraoperative imaging and monitoring to be part of routine management in the SBB. (26,27)

1.1.5 Indications

The stereotactic brain biopsy is recommended for patients in whom standard craniotomy might carry a high risk of morbidity and complication or who are too old to undergo conventional neurosurgery. This biopsy is also very useful for the histological diagnosis of diffuse, infiltrative, or multiple lesions, in which cytoreductive surgery cannot be applied. It plays a vital role in further treatment of patients, for whom general anaesthesia may be harmful. In the case of cystic lesions, for both decompression and histological diagnosis, a brain biopsy can be performed. In addition to these, lesions with significant radiosensitivity e.g., lymphomas and germinoma. (28,29) Some of the other significant indications are listed below. (29)

- An undiagnosed intra-axial mass lesion.
- Invasive lesions without significant mass effect.
- In case of lesions that could be poorly detected by imaging techniques.
- Differentiating inflammatory and infectious lesions from neoplastic lesions.
- In case of multiple lesions medical therapy would play vital role than surgical procedure.

1.1.5 Complications

There are already numerous publications that discuss the complications after stereotactic brain biopsy. SBB has many notable benefits compared to open brain surgery such as shorter length of hospitalization, less trauma, and better cosmetic. However, the most common complications of SBB are haemorrhages, with a probability ranging from 0.9 % to 59.8%. (30) Other complications such as lowering of consciousness, brain edema, neurological deficit, seizure, and infection are often observed. Diverse studies suggest that the most common complication after SBB is intracranial haemorrhages. (20,31)

Haemorrhages

Various risk factors exert influence on bleeding associated with stereotactic brain biopsies such as an advanced age (>70), gender (male), hypertension, diabetes, location of the lesion, malignant glioma, antiplatelet medications and biopsies undertaken under

anaesthesia. Yoshifumi et.al described the correlation between postoperative haemorrhages and prothrombin time which shows its significance during a biopsy procedure. Hence, it is important to consider this correlation during SBB. (27) In addition to this, Yoshifumi et al revealed that the surgical risk is not higher for deep-seated lesions compared to lesions on a brain surface.

Based on location, haemorrhage can be categorized into an intralesional haemorrhage, intraparenchymal extralesional haemorrhage, intraventricular haemorrhage (IVH), subarachnoid haemorrhage (SAH), subdural haemorrhage (SDH), and epidural haemorrhage (EDH). (15,32) Intracranial haemorrhage is defined as bleeding within the intracranial area, including the brain parenchyma and surrounding meningeal regions. (31) ICHs have a high possibility of causing severe neurological consequences, that may change the clinical results. The range of rates of ICH after SBB varies from 7% to 10%. Haemorrhagic complications can be classified into symptomatic and asymptomatic/silent. Most of the studies suggested that only half (3.4-5.2) % of the distinguished haemorrhages were symptomatic. Symptomatic complications can cause neurological deficit that leads to a longer hospital stay, whereas asymptomatic are often seen on postoperative CT scans that may not be life-threatening. (15,32,33) Furthermore, it can be classified into intratumoral haemorrhage (biopsy-related) and haemorrhage along the needle track (trajectory-related). Some of the recommendations suggested by Ahmed et al to avoid post-operative haemorrhage are listed below. (15)

- Maintaining normal coagulation state and blood pressure during and after stereotactic procedure.
- Selecting the best trajectory, that avoids arterial/ venous structure can be obtained by using multiplanar reconstruction software.
- Use of phantom base to verify the target coordinates.
- Avoiding the area of neovascularization and abnormal blood vessels in malignant tumours while planning the trajectory.
- A CT scan of the brain after 4 hours to detect any post-biopsy clot and to figure out its size.

In case of finding haemorrhage in post-biopsy CT scans, admission to the inpatient department for further treatment is necessary. Otherwise, a patient with normal neurological status without haemorrhage can be discharged on the same operative day.

1.2 Most common types of Brain Tumour

This chapter will describe the most common types of brain tumours and the stereotactic biopsy that is done to identify them. A brain tumour is defined as an abnormal growth of brain cells which multiplies without control of mechanisms that control normal cells. It represents the second most frequent cause of mortality among neurological diseases. In

2005 registered ABTR an age-adjusted incidence rate of 18.1/100,000 person-years. The incidence rate in females (18.6/100,000) was higher than in males (17.8/100,000). (34) More than 150 different types of brain tumours have been registered. However, the main two groups of brain tumours are primary and metastatic.

1.2.1 Primary Brain Tumour

Primary brain tumours develop from brain cells, nerve cells, meninges and glands, such as the pituitary gland and pineal gland. It can be benign or malignant. Their size can vary from tiny to very large. Tumours can develop in different parts of the brain. Some of them are in the active and some are in a less active part of the brain. In the case of the less active part of the brain, symptoms may develop later. This can cause a bigger size of tumour at the time of detection. (28,29,35) Most malignant cancers are classified based on TNM (tumour size, lymph nodes and metastasis)-system, whereas tumours originating from the central nervous system are divided into four grades by the World Health Organization (WHO).

WHO Grade	Description	Examples
Grade I	Well circumscribed, slow growing and low proliferative potential, non-malignant, cure possible after surgical removal of the tumour	Pilocytic Astrocytoma Craniopharyngioma
Grade II	Slow growing, Infiltrative in nature, nuclear atypia,	Diffuse Astrocytoma Oligodendroglioma
Grade III	The quick growth of the tumour, Infiltrative in nature nuclear atypia, Mitotic activity	Anaplastic Astrocytoma Anaplastic Oligodendroglioma
Grade IV	The quick growth of the tumour, microvascular proliferation, Necrosis, mitotically active, Rapid disease evolution	Glioblastoma Medulloblastoma

Table 2. WHO Classification of Tumours of the Central Nervous System. Revised 4th Ed. International Agency for Research on Cancer; 2016 (36,37)

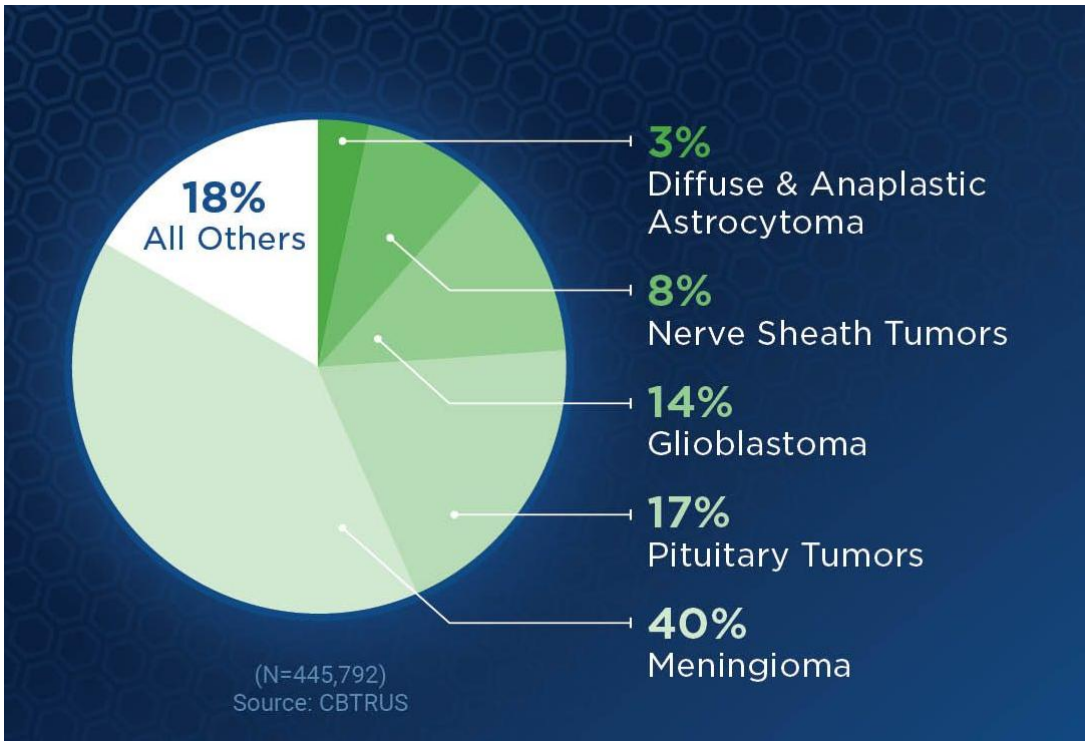

Figure 12. Distribution of all primary brain and other CNS Tumours (38)

Risk Factors

There have been several hypotheses introduced and evaluated to find out the appropriate risk factors that may cause primary brain tumours. However, most of the risk factors are still lacking scientific evidence. In general, genetics and environmental factors play significant roles in the development of primary brain tumours. There is a trend worldwide toward an increase in the incidence of environmental factors. Most of the common risk factors are illustrated below. (39,40)

Genetic	Cowden disease, Gorlin syndrome, Li-Fraumeni syndrome, Neurofibromatosis Typ I and II, Tuberous sclerosis complex, Turcot syndrome, Von Hippel- Lindau disease
Environmental	High dose ionizing radiation exposure, Alcohol use, Cellular telephone use, Chemical agents (e.g., hair dyes, solvents), electromagnetic fields, infections (e.g., viruses, Toxoplasma gondii), occupational exposure (e.g., vinyl chloride)

Clinical features of brain tumours rely on the localization of the tumour and include symptom complexes like progressive headache, seizure, educational or behavioural problems, aphasia, focal weakness, abnormalities of growth including weight loss or gain, sensory abnormalities, reduced level of consciousness, long tract signs and cerebellar signs. (41,42) These signs can occur alone or in combination with other symptoms. Headaches are a common presenting symptom in children. (41)

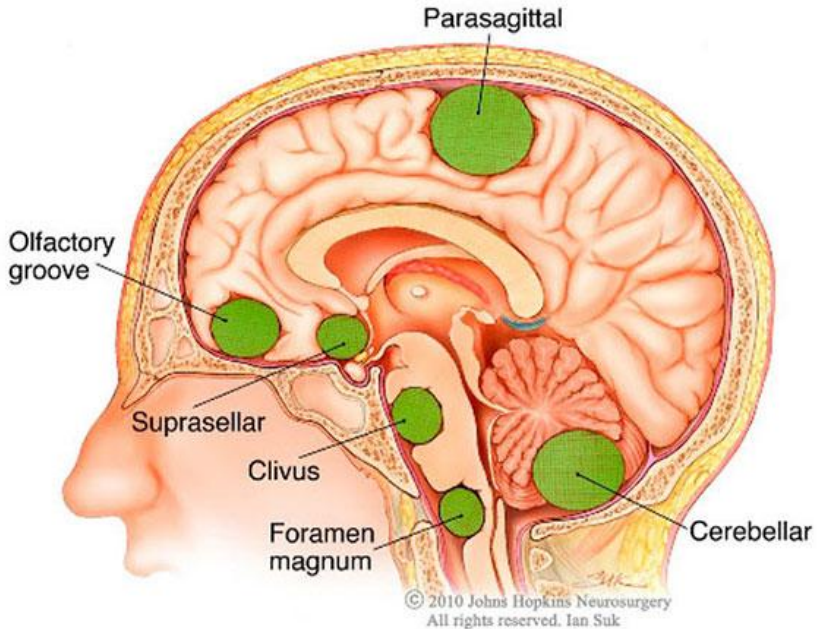

Figure 13. Different localization of Brain Tumours (43)

Glioblastoma

Glioblastoma is the most prevalent and aggressive malignant tumour in the central nervous system. It accounts for approximately 14% of all CNS neoplasms. According to WHO criteria, glioma can be histologically classified into Grades I-IV. Glioblastoma comes under the most malignant grade, WHO-Grad IV. The incidence of GBM varies from 3.19 to 4.17 per 100,000 person-years. Glioblastoma can develop in patients of any age, but more frequently between 75 and 84 years. It is reported a 2.97 times higher incidence of GBM in Caucasians compared to Asians and a 1.99 times higher incidence in Caucasians compared to African Americans. There is a male predominance, accounts 1.6:1 in the United States. (38,44–47)

Classification of GBM

According to the fourth WHO classification of gliomas from 2016, they can be distinguished into four types listed below. (45,46,48,49)

- Glioblastoma, isocitrate dehydrogenase (IDH) wildtype: Primary GBM developing de novo at about 60 years of age, accounts for 90% of GBM.

- Glioblastoma, IDH -mutant, secondary GBM: Secondary GBM developing from gliomas of WHO grades I-III, accounts for 10% of GBM, carries a better prognosis than wildtype IDH, and develops usually in younger patients.

- Glioblastoma not otherwise specified (NOS): It is not possible to determine IDH mutation status due to lack of material for testing.

- Not -Elsewhere -Classified (NEC) Glioblastoma: This fourth category has been distinguished in recent years. It has been made a required decision to classify NEC tumour, but the results did not allow the criteria of the tumour to any of the categories of the 2016 WHO classification. It may be possible that there is an unknown combination of features of glioblastoma subgroups that have not yet been classified by the WHO.

The latest criteria and nomenclature introduced by the WHO in 2021 show the significant role of molecular genetics in the diagnosis of GBM. IDH-mutant tumours that could previously be classified as diffuse astrocytoma, anaplastic astrocytoma, or glioblastoma are currently considered a single type of IDH-mutant astrocytoma graded II, III, or IV. (46,49)

Neuroimaging

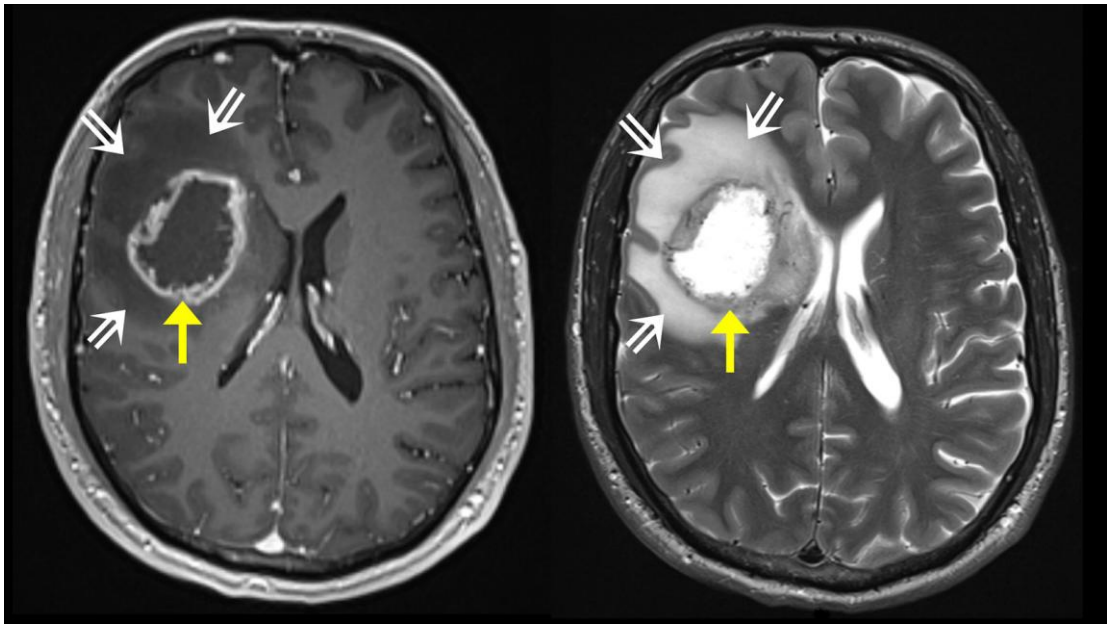

Figure 14. MRI images of Glioblastoma. Axial T1- sequence with contrast(left) and T2-sequence(right). White arrows show cerebral Edema whereas yellow arrow shows tumour areas. (50)

The MRI finding of glioblastoma is an irregularly shaped, ring-enhancing lesion with a central dark area of necrosis with significant perilesional edema. Almost all glioblastoma always enhances except in some cases of anaplastic astrocytoma. In addition, typical features of GBMs are necrosis, haemorrhage and garland pattern of enhancement. (46, 50,51) In some cases, a tumour may extend across the corpus callosum into the opposite hemisphere, forming a butterfly lesion. Occasionally, the tumour may be seen as multiple separate foci of contrast enhancement, although these areas are often connected histologically. Radiation necrosis ("pseudo-progression") presents similar imaging features in glioblastoma patients who have received radiation, which makes diagnosis challenging clinically. Localization of glioblastoma is often a subcortical white matter of the cerebral hemispheres, including the frontal, temporal, parietal and less frequently, occipital lobes. (44)

Histology

Histological features of Glioblastoma are listed below. (44)

- Glioblastoma show irregular hyperchromatic nuclei and elongated fibrillary processes.
- On histological sections, the cytoplasm is often invisible, and the tumour cells are mostly present as "naked nuclei" in a dense fibrillary background.
- The cellularity is usually very high in mitotic activity.
- Most tumours show significant nuclear pleomorphism with variable multinucleated giant cells, while some tumours have relatively uniform tumour cells (e.g., small cells).
- The other diagnostic hallmarks of glioblastoma are microvascular proliferation and necrosis. Microvascular/ Endothelial proliferation refers to the multi-layered appearance of the vessel. It occurs often in the areas next to necrosis or in the infiltrating edge of glioblastoma. Necrosis in glioblastoma has two forms: palisading necrosis (densely packed tumour cells form palisades around a necrotic centre) and geographic necrosis.

- In some tumours, endothelial cells proliferate to form multiple lumens like renal glomeruli, they are called "glomeruloid."

Clinical Presentation and Prognosis

The most common clinical presentations are seizures, behavioural changes, focal neurological deficits and signs of increased intracranial pressure. (44) Clinical symptoms may differ based on the location of the tumour. Glioblastomas have an infiltrative nature. Due to this feature, they cannot be completely resected, and they almost invariably recur

and progress. (52) The median survival after diagnosis is about 14 months. Established good prognostic factors are young age, high Karnofsky Performance Status (KPS), high mini-mental status examination score, O6-methylguanine methyltransferase promoter methylation, and resection of > 98% of the tumour. (53)

2. Objective of the study

Stereotactic Brain Biopsy has evolved as a powerful and safe procedure that allows a neurosurgeon to diagnose a brain lesion with minimal disruption of the normal functioning brain**.** This procedure needs trajectory planning with imaging like CT or MRI. These images help to reveal the location of lesions. To recommend treatment, a doctor may require a brain biopsy to obtain a sample that a pathologist can diagnose art of lesion. Neurosurgeon prefers to use stereotactic equipment to localize the most suitable site for the biopsy. This helps the neurosurgeon to map the brain in a three-dimensional coordinate system and select the suitable target coordinates for guiding the biopsy needle.

Generally, trajectory planning is done by a neurosurgeon manually without any rigid guideline rules. Prof. Wolfsberger describes ten rules for straightforward planning.

1. Minimize length
2. Perpendicular at entry point
3. Perpendicular to target area
4. Use transgyral corticotomy
5. Avoid eloquent cortex
6. Avoid eloquent tracts
7. Avoid sulci/fissures/ventricles/cisternae
8. Maximize distance to vessels
9. Avoid sinuses
10. Avoid facial areas

The main aim of the study was to compare Ten Rules Guided trajectory planning and Manual Planning to find out the feasibility and diagnostic yield of TGP, with the vision of innovating semi-automated planning software in the future.

3. Material and Methods

3.1 Study Design and Ethics

The study design was a retrospective comparative pilot study. The *Stealth* platform of *Medtronic Software* was used to generate Ten rules-guided trajectory plannings (TGPs), and these were compared to manual plans (MPs) to determine the feasibility and safety. The senior neurosurgeon evaluated the TGSs into "acceptable" and "not acceptable" trajectory regardless of the difference to the MPs. This Study is approved by the ethics committee of the Medical University of Graz.

3.2 Setting and Participants

The study was organised at the University Neurosurgery Hospital of Graz which acts as a centre for brain tumours for the 1.5 million population of Austria. All consecutive cases were recorded retrospectively as a database. The database was searched between June and August 2023, to identify the cases, who had undergone stereotactic brain biopsy in Neurosurgery Hospital of Graz and for whom pre- and post-operative images MRI/ CT were available. 21 cases were selected who had undergone SBB in Neurosurgery Hospital of Graz between 2013 and 2023. Of 21 cases, two cases were excluded, for whom MRI images were not available. The age range of patients was 18-75 years. The distances between TPs and EPs were compared in 3D reconstruction.

3.2.1 Ten-Rules Guided Planning

The trajectories were generated in accordance with ten rules suggested by Prof. Wolfsberger utilizing *Stealth Platform (Medtronic*) by one of the students. The identification of lesions involved preoperative CT/MRI scans. Entry and target points were fixed using the axial, coronal, and sagittal planes, and the trajectory was controlled with the help of the probe's eye reconstruction. Ten rules are outlined below.

1. Minimize length
2. Perpendicular at entry point
3. Perpendicular to target area
4. Use transgyral corticotomy
5. Avoid eloquent cortex
6. Avoid eloquent tracts
7. Avoid sulci/fissures/ventricles/cisternae
8. Maximize distance to vessels
9. Avoid sinuses
10. Avoid facial areas

3.2.2 Manual Guided Planning

The MPs of trajectories were done without any rigid guidelines using a *Stealth Platform (Medtronic*) by one of the senior neurosurgeons. The identification of the lesions and fixation of the TPs and EPs were carried out using same procedural framework as applied in the TGP.

4. Results

All patients' differences in EPs and TPs are detailed in Table 1. Collected data revealed median differences in EPs and TPs of 11.9 and 2.6 respectively. The mean differences in EPs and TPs are 16.6 and 3.3 respectively.

Case	EP-Difference(mm)	TP-Difference(mm)
1	6	4
2	10.8	1.5
3	5.8	1.5
4	3.2	1.7
5	4.4	2.2
6	10.5	4.4
7	18.9	4.1
8	7.8	2.6
9	13.7	2.1
10	6	6
11	12.3	6.8
12	23.5	3.3
13	25	2
14	42.7	3.9
15	60	0
16	7.1	1.9
17	12.3	5.2
18	33.9	7.8
19	11.9	1.8
Mean Diff.	**16.6**	**3.3**
Median Diff.	**11.9**	**2.6**

TABLE 1. Differences in Entry points and Target points of Trajectories in mm.

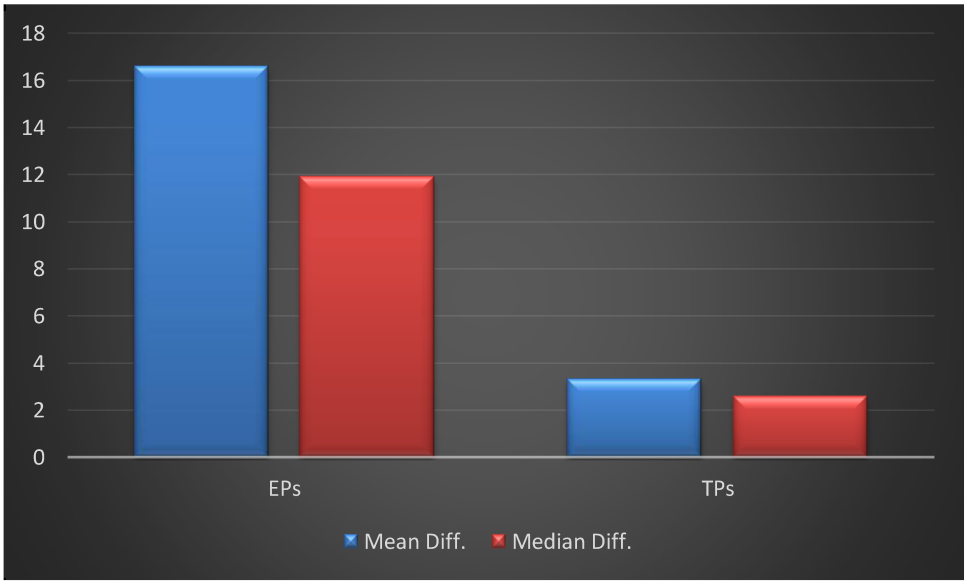

Figure 16: Graph comparing mean and median differences in TPs and EPs

The mean difference for EPs is considerably higher than the median difference, showing the presence of outliers. On the other hand, the mean and median differences for TPs are smaller, which shows the dataset is more evenly distributed.

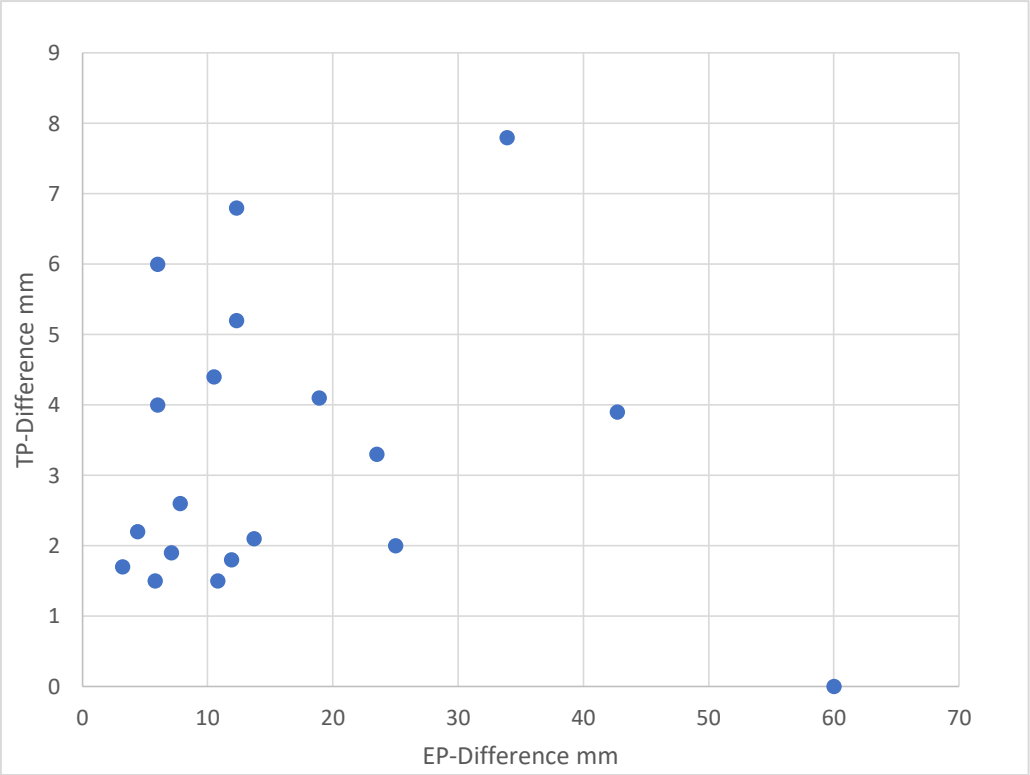

Figure 18: Scatterplot showing TPs and EPs.

The scatter plot illustrates that smaller EP-Differences are more common. However, a few outliers with significantly higher EP-Differences show sporadic extreme variations. The TP-Differences show some variability, but no clear linear correlation with EP-Differences.

Accepted TRPs	16
NA TRPs	3

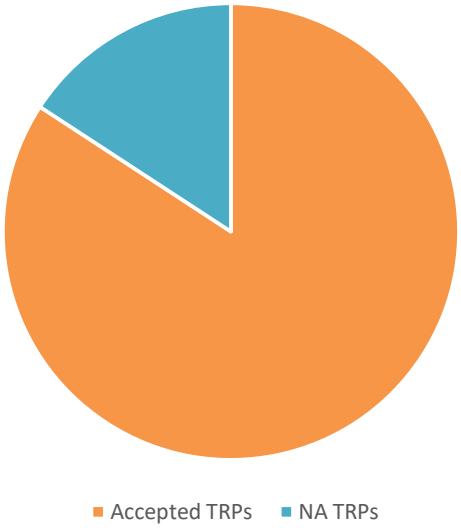

Figure 19: Pie chart showing the distribution of accepted and not-accepted TPs**.**

Of 19 Patients, 16 patients were accepted. NA-TRPs are illustrated below.

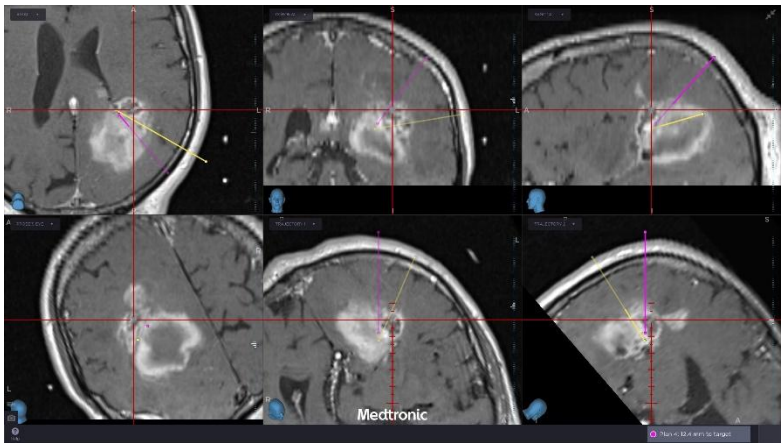

Figure 20: Case 14 trajectory planning (Violet-MP, Yellow-TGP)

In this case, TGP is located at the furthest point from contrast contrast-enhancing necrotic area, indicating a potential risk of bleeding in the necrotic area due to its positioning.

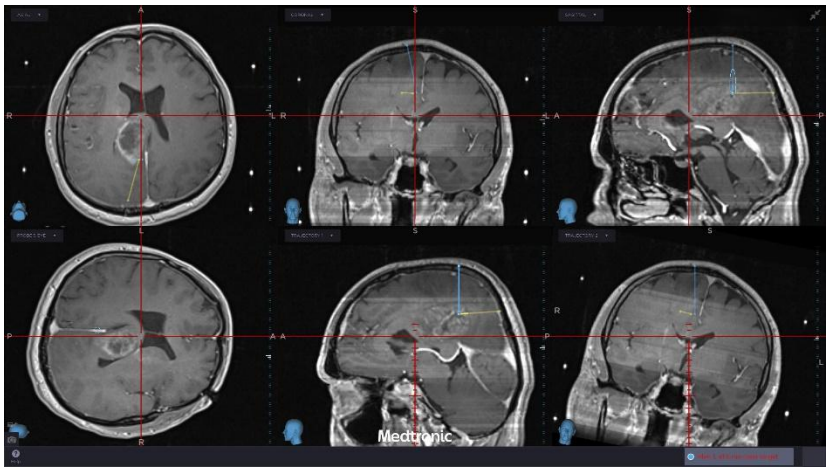

Figure 21: Case 15 trajectory planning (Blue-TGP and Yellow-MP)

In this case, the TGP- trajectory is close to the sinus(<20mm), with the risk of potential damage.

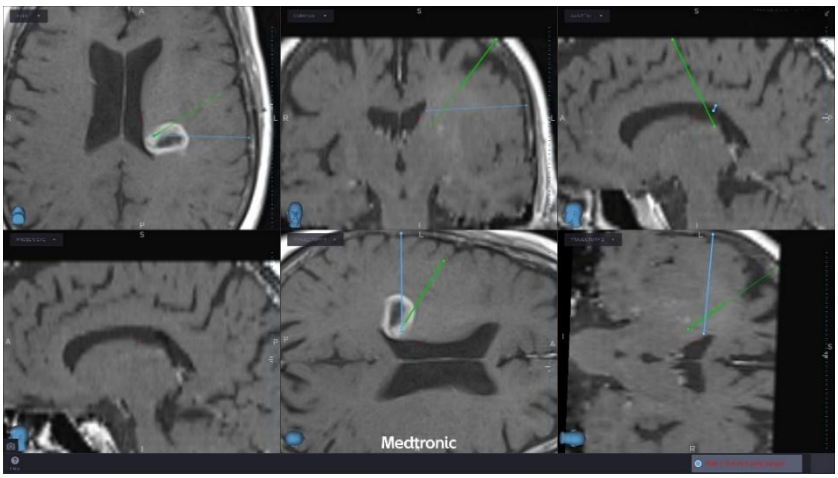

Figure 22: Case 18 trajectory planning (Blue-TGP and Green-MP)

The TGP trajectory has a shorter length within the tumour area than MP, indicating less opportunity to obtain multiple biopsy samples.

5. Discussion

Principle findings in our study indicate that TGP was feasible and mostly accepted, with an acceptance rate of 84%. The median differences noted were 11.9 mm for entry points (EP) and 2.6 mm for target points (TP), whereas the mean difference was 16.6 mm at the entry point and 3.3 mm at the target point, demonstrating the feasibility of TGP. The reasons behind not-accepted trajectories included the trajectory's position relative to the contrast-enhancing necrotic area, a shorter distance to the sinus (<20 mm), and shorter length of trajectory within the tumour area. These factors were not precisely described in TGP.

The objective of the study was to analyse the feasibility of Ten Rules Guided Planning (TGP) in comparison to manual planning (MP), to develop semi-automated trajectory planning software. In contrast, Marcus et al. evaluated computer-assisted planning with *SurgiNav* against manual planning to find out the feasibility of CAP. This study was conducted at University College London with 15 patients. It emphasizes the comparison between computer-assisted planning (CAP) and manual planning (MP), specifically analysing trajectory length, angle, and risk scores, while our study shows mean and median-differences on TPs and EPs. In terms of methodology, our study involved a student performing TGP-based planning, while an experienced neurosurgeon conducted the manual planning. The study compared mean and median differences in entry points (EPs) and target points (TPs), utilizing *Stealth Platform (Medtronic*) for planning.16 out of 19 TGPs were accepted. Conversely, Marcus et.al involved senior neurosurgeons performing manual planning using *Stealth Platform (Medtronic*), while computer-assisted planning employed *SurgiNav*, an automatic generator for entry and target points. Trajectory angle from orthogonal, trajectory length, and risk score were compared between CAP and MP. CAP demonstrated superior results in terms of safety and feasibility. (54)

To optimize TGPs, the neurosurgeon has established a new set of guidelines.
These guidelines are categorized into two prioritized groups:

Primary Rules (1-6):

1. Avoid sinus.
2. Avoid eloquent cortex.
3. Avoid sulci/fissures/ventricles/cisternae.
4. Use transgyral corticotomy.
5. Maximize distance to vessels (at least 25 mm).
6. Avoid eloquent tracts.

Secondary Rules (6-10):

7. Avoid facial areas.
8. Avoid necrosis.
9. Perpendicular at entry point and target point.
10. Minimize length.

These carefully structured guidelines ensure that the procedure is conducted safely and effectively while minimizing potential damage to critical areas of the brain. Additionally, the following key recommendations are outlined:

Lesion Selection: When multiple contrast-enhancing lesions are present in the brain, a single lesion should be carefully chosen before planning the procedure.

Trajectory Consideration: The distance from the sinus to the planned trajectory should be at least 2 cm to reduce risks.

Necrosis Avoidance: Biopsy samples should be taken from viable tumour tissue, avoiding necrotic areas to ensure diagnostic accuracy.

Optimal Trajectory Length: The trajectory length within the tumour plays a crucial role, allowing neurosurgeons to collect tissue samples from different tumour regions. This approach enhances the precision of the biopsy and improves pathological analysis.

Limitation

It was a single-centre study, which indicates the findings may not be universal. The TGP was performed by a student, which could introduce potential bias in the results due to the lack of experience.

Conclusion

The results of our study appear highly promising and feasible, paving the way for the potential development of semi-automated trajectory. Prioritizing the ten rules is crucial for improving trajectories, especially in complex cases.

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