Research Article

Supratentorial Mass Lesion Biopsy Using Frameless Stereotactic System; Diagnostic Yield, Surgical Morbidity, and Comparison With Freehand Biopsy

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Summary

Objective: The objective of this study is based on a comparison of freehand and stereotactic biopsy regarding diagnostic yield in terms of adequate tissue sample, morbidity in terms of postoperative complications like neurological deficit, bleeding, infection etc. and mortality.

Material and Methods: A randomized clinical study was carried out and included 70 patients (35 patients underwent freehand biopsy and 35 patients underwent stereotactic biopsy). The data was collected for variables including age, sex, location and size of tumor. The outcome was assessed by diagnostic yield in terms of adequate tissue sample, morbidity in terms of postoperative complications like neurological deficit, bleeding, infection etc. and mortality between the two groups was compared.

Results: Total 70 biopsies were excised and 35 (50%) of them underwent freehand biopsy while the rest of 35 (50%) underwent stereotactic biopsy. Freehand biopsy was associated with 5.71% morbidity, compared to 2.85% morbidity for stereotactic biopsy. Four freehand biopsies (11.42%) and two stereotactic biopsies (5.71%) were non-diagnostic. Statistical analysis showed no significant difference between morbidity in the two groups. The rate of diagnostic failure between two groups was not significantly different with a p-value of 0.673, but it was found significant clinically.

Conclusion: Stereotactic biopsy has provided us with a powerful and a safer tool to provide tissue diagnosis with minimal disruption of the normal-functioning studies, though with minimal morbidity. Our study is comparable to other international studies there is very little difference in the morbidity but significant difference in diagnostic yield.

Key words: Stereotactic biopsy, freehand biopsy, diagnostic yield, morbidity

Supra-tentorial Kitle Lezyonu Biyopsisinde Çerçevesiz Stereotaktik Sistem Kullanılması; Tanısal Sonuçlar, Cerrahi Morbidite, “Freehand” Biyopsi ile Karşılaştırılması

Özet

Amaç: Bu çalışmanın amacı serbest-el ve stereotaktik biyopsi sonuçlarının tanısal sonuçlar, uygun doku örneklemesi, nörolojik defisit, kanama, enfeksiyon gibi post-operatif morbiditeler ve mortalite açısından karşılaştırılması üzerine temellendirilmiştir.

Yöntem ve olgular: 70 hastaya kapsayan randomize bir çalışma yürütülmüştür (35 hastaya serbest el 35 hastaya ise stereotaktik biyopsi uygulanmıştır). Yaş, cinsiyet, tümörün lokalizasyonu ve büyükliğinin bilgileri toplanmıştır. Sonuçlar uygun doku örneklemesi, morbidity ve mortalite yönünden her iki grup arasında karşılaştırılmıştır.
Bulgular: 35 tanesi serbest-el 35 tanesi ise stereotaktik olmak üzere toplam olarak 70 biyopsi elde edilmiştir. Serbest-el yönteminde %5,71 stereotaktik yönteminde %2,58 morbidite ile karşılaşılmıştır. İstatistiksel yünden her iki grup arasında morbidite yönünden anlamlı fark bulunamamıştır. Her iki grup arasında tanısal başarısılık (p değeri 0,673) istatistiksel olarak anlamlı olmamakla beraber kliniksel olarak anlamlı bulunmuştur.

Sonuç: Stereotaktik biyopsi bizlere normal fonksiyon görmekte olan beyinde doku tanısal güçlü ve güvenli bir araç sunmaktadır. Çalışmamızın sonuçları diğer uluslararası çalışmalarıyla mukayese edilebilir düzeydedir; morbidite yönünden çok az fark olmakla birlikte tanısal sonuçlar açısından belirgin fark vardır.

Anahtar Kelimeler: Morbidite, serbest el biyopsi, stereotaktik biyopsi tanısal sonuçlar

INTRODUCTION

Primary intracranial tumors from the cells of or of the brain parenchyma or from its intracranial linings. Secondary intracranial tumors may arise in the skull or neighboring structures and extend through the skull or cranial foramina, or they may arise at distant sites and spread hematogenously to the brain or dura. Both primary and metastatic tumors may be intra-axial, extra-axial or both. Intra-axial tumors are located primarily within the brain parenchyma or ventricular system, whereas extra-axial tumors are located in the subarachnoid space or meninges. Unlike most systemic malignancies, primary brain tumors rarely metastasize to other regions of the body. Classification based on WHO-World Health Organization's schemes of brain tumors permit accurate predictions regarding natural history and the response to therapy. Intracranial tumors may arise either in the brain itself (neurons, glial cells, astrocytes, oligodendrocytes, ependymal cells), lymphatic tissue, blood vessels, in the cranial nerves (myelin-producing schwann cells), in the brain envelopes (meninges), skull, pituitary and pineal gland, or may be metastatic tumors. Regarding a radiologic diagnosis, imaging studies like computed tomography (CT) and magnetic resonance imaging (MRI) play an important role in the diagnosis of brain tumors.

Primary brain tumors are commonly located in the anterior two-thirds of the cerebral hemispheres in adults and in the posterior cranial fossa in children, although, they can affect any part of the brain. Astrocytoma is the most common, which accounts about 50-60 cases per year. Glioblastoma is the next which accounts 10-40 cases per year. Oligodendroglioma (OGD) averages about 10-15 cases per years. Metastatic brain disease incidence is about 5-7 cases per year, whereas, the pituitary tumors are about 5 cases per year. In the United States in the 2005, it was estimated that there were 43,800 new cases of brain tumors, which accounted for 1.4% of all cancers, 2.4% of all cancer deaths, and 20–25% of pediatric cancers. Further, according to a current report by American Brain Tumor Association (ABTA), U.S, it is mentioned that 70,000 new cases of primary brain tumor patients will be admitted and about 700,000 people with the brain tumor are living in U.S. Ultimately, it is estimated that there are 13,000 deaths per year in the United States alone as a result of brain tumors.

The most common presenting symptoms of Supratentorial tumors are due to increased intracranial pressure (ICP) from mass effect of the tumor and/or edema or from the leakage of cerebro-spinal fluid (CSF) drainage (hydrocephalus). The less common in Supratentorial tumors may occur, for example, with colloid cyst and entrapped lateral ventricle. There may be progressive focal deficits, including weakness and dysphasia, due to the destruction of brain parenchyma by tumor.
invasion or due to compression of brain parenchyma by mass and/or peritumoral edema and/or hemorrhage, or due to compression of cranial nerves. The patient may also present with headaches, seizures, mental status change, depression, lethargy, apathy or confusion. Brain tumors may present with the occlusion of vessel by tumor cells or hemorrhage into the tumor. There may be symptoms suggestive of transient ischemic attack (TIA) like transient hemiparesis, aphasia or sensory abnormalities, etc. In special cases of pituitary tumors, there may be symptoms due to endocrine disturbance, pituitary apoplexy or CSF leak. There is no specific clinical symptom or sign for brain tumors, however, slowly progressive focal neurologic signs and elevated intracranial pressure, as well as epilepsy in a patient with a negative history for epilepsy should raise the suspicion of a space occupying lesion (SOL) in the brain. However, a sudden onset of symptoms, such as an epileptic seizure in a patient with no prior history of epilepsy, sudden intracranial hypertension due to bleeding within the tumors, brain swelling or obstruction of CSF is also possible.

The definitive diagnosis of brain tumor can only be confirmed by histological examination of tumor tissue samples obtained either by means of brain biopsy or open surgery. The histological examination is essential for determining the appropriate treatment and the correct prognosis. In the past, freehand biopsy has been used after localizing the lesion by radiographic investigations, which were associated with a number of non-diagnostic tissue yields, and high morbidity and mortality. In a freehand biopsy, the surgeon guide himself by what he sees, his knowledge of anatomy and his interpretation of preoperative scans. Stereotactic surgery was used for surgery performed in humans, usually for thalamic lesioning to treat Parkinsonism where the target site to be lesioned was located. The first part of the procedure includes a CT scan, MRI, or occasionally angiography is performed with a localizing device attached to the patient's head. This allows the target to be precisely localized in space. Frameless systems use bony landmarks and sometimes reference markers to register the patient's skull relative to radiographic images. The second part of the procedure includes, a set of guides oriented to the same coordinated system to direct biopsy needles etc. to the target location. Stereotactic biopsy is used for deep-seated cerebral lesions, especially near the eloquent brain. Brainstem lesions may be approached through the cerebral hemisphere. Also, it can be used for multiple small lesions and in patients who are unable to tolerate general anesthesia for open biopsy. Stereotactic biopsy techniques have been widely utilized in the diagnosis of intracranial lesions for many decades. Few surgeons have evaluated this procedure, analyzed preoperative predictors of diagnostic yield, and morbidity rates of the frameless technique. Because, brain tumors frequently infiltrate the eloquent areas of the brain, it is important to have a technology that will identify and preserve functional brain.

Recent advances have allowed the introduction of frameless stereotactic systems. These allow intraoperative localization of fixed three-dimensional volumes defined with preoperative computerized images. The Neuronavigator uses a six-degrees-of-freedom arm to localize an intracranial point and correlate this point to a computerized image (either MRI or CT) displayed in the operating room. All these techniques suffer from the fact that the localization is based on a preoperative image that becomes obsolete as soon as the craniotomy is performed, brain or tumor removed, CSF drained etc. The clinical benefits associated with (IGS) have allowed the surgeons to perform less invasive surgery through smaller incisions and have been given direct access to specific targeted areas. These facts have given the image-guided techniques more
Neuronavigation adds an entirely new dimension to neurosurgery. In one study, a frameless stereotactic biopsy led to diagnostic yield of 89% with total permanent morbidity rate of 6% and mortality rate of 1%. Large lesions were five-fold more likely to yield diagnostic tissue. Deep-seated lesions were 2.7 fold less likely to yield diagnostic tissue compared with cortical lesions. For cortical lesions, more than one needle trajectory was required frequently to obtain diagnostic tissues with stereotactic biopsy, although this factor was not associated with morbidity. In another study, involving superficial lesions, freehand CT-guided biopsies were associated with less morbidity (5%) than stereotactic biopsy (6%). Freehand biopsy was also seen to be giving more yields, with only 9% non-diagnostic biopsies as compared to stereotactic biopsy with 18% negative biopsies. Since the frameless image-guided biopsy technique is a new development, there are no internationally accepted guidelines available for the selection of patients for IGS. Our study is also an effort to develop a criteria for the selection of patients in a clinical setting. All lesions smaller than 3 cm anywhere in the Supratentorial compartment and not deeper than 5 cm are included in our study. Also, all lesions of any size lying deeper than 3 cm but not deeper than 5 cm (thalamus) at the most superficial point are included in this study.

A tissue diagnosis of brain tumors is mandatory in order to treat them effectively. Previously a freehand biopsy has been used after localizing the lesion by radiographic investigations, which were associated with a number of non-diagnostic tissue yield, high morbidity and mortality. This has led to the repetition of the procedure and thus further increasing the risk of mortality and morbidity. During the recent years, stereotactic image-guided surgery (IGS) has revolutionized the outcome of biopsy yield and has significantly reduced the morbidity and mortality of this procedure. The hypothesis of this study was to determine whether the stereotactic image-guided biopsy has reduced the morbidity in terms of neurological deficit, bleeding, infection etc. and mortality and has it increased the diagnostic yield of the procedure in terms of an adequate tissue sample. Moreover, the hypothesis of this study was that the procedure is safer with less morbidity and better diagnostic yield.

The objective of this study was a comparison of freehand and stereotactic biopsy regarding: diagnostic yield in terms of adequate tissue sample, morbidity in terms of postoperative complications like neurological deficit, bleeding, infection etc. and mortality. During this study, two groups of patients having Supratentorial tumors were compared. One group underwent freehand biopsy after using computed tomograms (CT) and magnetic resonance imaging (MRI) for diagnosis of a space occupying lesion. The second group underwent stereotactic image-guided biopsy, using computed tomograms (CT) and magnetic resonance imaging (MRI), but this time with the help of the Stealth-Station for stereotactic localization of the lesion. Patient-specific three-dimensional (3-D) anatomy for preoperative planning and intraoperative navigation was obtained in order to assess the accuracy and safety of image-guided stereotactic biopsy. Both groups were then compared in terms of morbidity, mortality, diagnostic yield in terms of adequate tissue sampling and other aspects of procedure like time consumed, cost, etc. For all patients with brain tumors and surrounding edema a loading dose of dexamethasone 10 mg followed by 4 mg four times a day is given orally or intravenously.

As part of the operative management, most of the patients with brain tumors need one or more of the following approaches for excision/biopsy of the tumors. Burr-hole is made in order to do freehand, stereotactic or ultrasound guided biopsy. Cranietomy

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is done by doing a burr-hole and then removing the surrounding bone to extend the exposure. This method is done routinely to approach posterior fossa. Craniotomy is done by cutting and reflecting the bone flap, preferably by using frameless stereotaxy (image-guided system) for accurate lesion localization. Transphenoidal route for pituitary lesions are transoral routes to access anterior brainstem and upper cervical lesions. The goal of surgery is an important decision which make and depends on the nature, size and site of tumor, as well as, the presence of mass effect, increased intracranial pressure, general medical and neurological condition, stereotactic/freehand biopsy, partial removal, internal decompression or complete excision. If the tumor is infiltrative, a complete removal is seldom performed and treatment is restricted to either biopsy or tumor decompression. Generally, small deep lesions with minimal mass effect in a neurologically intact patient may require stereotactic biopsy only. Complete removal has good results with benign tumors such as meningioma or craniopharyngioma. If any part of the tumor is left behind, that results in recurrence of tumor. There are difficulties associated with stereotactic biopsy that include misdiagnosis, non-diagnosis, hemorrhage and neurological deficits. A biopsy is contraindicated in children with brainstem lesion because of risk of neurologic injury. Because of heterogeneity of gliomas, sampling error is a problem associated with stereotactic biopsy because tissue obtained with the help of small needle biopsy may not be representative of the true nature of tumor. Therefore, the accuracy of stereotactic biopsy ranges between 72-93% when compared with radical resection, while the risks of neurological complication are still significant at 3.7%. Therefore, the goal of surgery for most brain tumors is maximal resection of the tumor without producing new neurological deficits. Tailoring the operative approach and planning for each individual patient may achieve this goal. Debulking large tumors can also markedly improve neurological status, particularly for patients with large tumors in superficial locations. Studies have demonstrated that this improves survival. Radiotherapy is the primary adjuvant treatment after surgical resection of most gliomas. Success of radiotherapy is dependent on the nature of the tumor and the dose of radiation. It increases a long-term survival of patients with glioblastoma and anaplastic astrocytoma, especially patients with less than 65 years of age, regardless of extent of resection. Ependymomas are particularly sensitive to radiation and the survival duration depends upon the adequate dosage and delivery of radiation. Usefulness of radiotherapy for low-grade astrocytoma, oligodendroglioma and partially resected pilocytic astrocytomas is controversial because of younger patients and long-term side effects of radiation.

The role of chemotherapy in the management of brain tumors remains uncertain. The drugs most commonly used are nitrosoureas (BCNU, CCNU, methyl-CCNU), procarbazine, vincristine and methotrexate. Chemotherapy in combination with surgical resection and postoperative radiation is moderately effective in anaplastic astrocytoma (AA) and glioblastoma, and markedly effective in anaplastic oligodendroglioma (OGD). There are new approaches available where there is an inability to improve survival with chemotherapy and radiation. Over the past 20 years, there is an interest developed in other other therapeutic modalities such as differentiating agents, biological response modifiers (IFN, IL and TNF-alpha), gene therapy, antiangiogenesis factors and immunotherapy. Although exciting, due to exploitation of molecular differences between glioma cells and normal glial cells, none of these has yet proven to be
efficacious. The prognosis depends on the specific tumor type, location of tumor and age of the patient. The concept of minimally invasive surgery has long been ideal for modern medicine. This idea is of particular importance when it comes to treat disorders of central nervous system, because the brain is so delicate. Therefore, the primary idea is to excise/treat the diseased area while minimizing damage to the normal tissue. To attain this, the surgeon must be capable of navigating through the central nervous system with extreme precision. Between 1960-70, more than 40,000 stereotactic procedures were performed worldwide\(^{(32)}\).

Stereotactic surgery was performed for deep-seated lesions, tumor resection and stereotactic radiosurgery. Neuro-imaging like CT/MRI has dramatically improved the neurosurgeon's ability to target a lesion anywhere in the central nervous system. The introduction of three-dimensional anatomic and functional imaging has further the usefulness and safety of stereotactic surgery. Stereotactic radiosurgery began to be applied in a variety of neurological diseases with very encouraging results, as well as acceptance by the patients due to minimal invasiveness. The historical basis of stereotactic approach is based upon a stereotactic frame. The purposes of the frame are to establish a coordinate system in relation to the frame. This provides a means of co-registering physical coordinate space with atlases and imaging spaces. It provides a means of introducing surgical instruments within that coordinate system\(^{(36,22)}\).

The frames, which are rigidly fixed to the skull, ensure stability of the coordinate system in relation to the structures such as patient's skull. Before the fusion of ventriculography with stereotaxy by Spiegel and Wycis\(^{(45)}\), the frame placed on the patient's head provided reference with respect to extracranial landmarks. These were too crude and variable for human use. By employing intracranial landmarks, for example, foramen of monro and pineal gland, any intracranial point could be targeted with respect to these intracranial landmarks. Prior to the advent of CT and MRI, direct visualization of subcortical structures was not possible. Therefore, to target such structures would rely on indirect atlas-based measurements from known intracranial landmarks such as anterior and posterior commissures.

The improved user-friendliness and versatility of stereotactic systems have attracted their use for the procedures traditionally performed non-stereotactically. Several studies have demonstrated the efficacy and cost-effectiveness of stereotactic procedures\(^{(9,21,24,37)}\). Unpublished observations by many authors have also witnessed a significant rise in stereotactic operations at their respective institutions. This trend is expected to rise as the patients and surgeons are striving lesser and less invasive approaches to the treatment of neurosurgical disorders. One of the most common indications for morphological stereotactic surgery is stereotactic needle biopsy, especially of deep-seated lesions. It is now increasingly used for craniotomies for resection the lesions. The advantages of stereotactic surgery are:

Regarding new advances in stereotactic surgery/biopsy, stereotaxy has undoubtedly a bright future. With further improvement in technology used in stereotactic surgery, the surgical intervention will become less invasive and more precise in targeting deep-seated brain lesions. With functional imaging and its incorporation into stereotactic databases has improved its acceptance in general neurosurgical practice. Surgery in and around eloquent brain areas will become safer and more radical with affordable functional and anatomical imaging intraoperatively. With smaller and more powerful computers, micro or even nano-robotic devices will be
implanted intracranially to perform various tasks with greater precision.

Frameless robotically targeted stereotactic brain biopsy includes frameless stereotactic brain biopsy and is being used in many neurosurgical centers worldwide as an established procedure. Robotic modifications of image-guided frameless stereotactic procedure are promising in making these procedures safer, more effective and more efficient. In a retrospective study by Kimon Bekelis, et al. (2012), 41 patients underwent stereotactic frameless brain biopsy of lesions having a mean size of 2.9 cm for histopathological diagnosis. All of these patients underwent image-guided robotic biopsy using Surgi-Scope system in combination with scalp fiducial markers and with preoperatively selected target and trajectory. Procedures were performed in this study, which included 50 Supratentorial selected targets. Mean operative time for the robotic biopsy procedure was 44.6 minutes. Mean operative time decreased to 34.5 minutes from 54.7 minutes in the second half of study with a drop of 37% (p <0.025). There was a single non-diagnostic case in the second procedure with a diagnostic yield of 97.8%. Neurological deficit was noted in two cases, one was transient worsening of preoperative deficit (2%) while other deficit was permanent (2%). There were no infections. Robotic biopsy involving a preselected target and trajectory was safe, accurate, efficient and as compared to other procedures employing either frame-based stereotaxy or frameless, non-robotic stereotaxy. It permits biopsy in all patients, including those with small target lesions. Robotic biopsy planning facilitates careful preoperative study and optimization of the needle trajectory to avoid sulcal vessels, bridging veins, and ventricular penetration.

MATERIAL AND METHODS

It was focused on this research to ascertain whether IGS biopsy a better yield in terms of adequate sampling and less morbidity when compared to freehand biopsy of supratentorial mass lesions. Image-guided biopsy has better yield in terms of adequate sampling and less morbidity when compared to freehand biopsy of Supratentorial mass lesions.

**Study design and sampling associated criteria:**

It was a randomized clinical trial carried out in the Department of Neurosurgery, Shaikh Zayed Hospital-Postgraduate Medical Institute, Lahore Pakistan. The study conducted for one and half years. The sample size was estimated by using one tail technique with a 10% level of significance and 80% power of test by expecting 20% higher yield by stereotactic biopsy in comparison to freehand biopsy. The estimated sample size was 35 in each group. As part with the sampling technique, the patients were divided into two groups:

1. The patients with brain tumors who underwent freehand (FBH) biopsy.
2. The patients with brain tumors who underwent stereotactic biopsy.

The diagnostic yield in terms of adequate tissue sample and morbidity in terms of postoperative complications like neurological deficit, bleeding, infection etc. between the two groups was compared. All patients were worked up and investigated at the Shaikh Zayed Hospital, Lahore.

**Inclusion criteria:**

- Mass lesions lying in a depth not less than 3 cm and not more than 5 cm at the most superficial point.
- Mass lesions less than 3 cm in size, even if they are superficial.

**Exclusion criteria:**
• Patients with severe cardiovascular disease, not fit for general anesthesia (GA).
• Patients with bleeding diathesis.
• Patients/family not consenting for both the procedures, i.e., freehand/IGS biopsy.

• **Data collection:** The data of the patient under study was collected by a proforma designed.

• **Methodology:** Patients were admitted through outpatient door or the emergency room, worked up in the department with regards to inclusion and exclusion criteria. Written informed consent was obtained from the attendants of the patient in the presence of a senior medical practitioner. Patients and attendants were given time to consider if they want to be in the study. After the informed consent, randomization was done by using labeled envelopes with IGS and FBH. Preoperative work-up including CBC, PT, APTT, renal and liver profiles were done. Cardiovascular fitness for GA was assessed. Radiological investigations like CT and MRI (IGS protocol) were performed.

• **Image-guided stereotactic (IGS) biopsy group:** After preoperative work-up, the patients in this group were prepared for surgery. In operation theater, IGS protocol CT/MRI was fed to Stealth-Station. Figure 1 shows a pre-operative localization of the lesion, using a software on the images of the patient. After general anesthesia to the patient, a Mayfield three-point fixation device was used to fix the head. Registration was then performed using bony landmarks to register the patient's skull relative to radiographic images. Figure 2 shows the registration process during surgery. The area was then prepped and draped in the usual sterile fashion and burr-hole was made. Then, using probe and the frame of the Stealth-Station, biopsy of the lesion was performed and the sample sent for histopathological analysis. Figure 3 shows Preoperative active localization of lesion by the probe shown by green intersecting lines. Postoperatively, the patients were observed for postoperative complications.

![Image 1: Preoperative localization of the lesion, using software on the images of the patient. (Photograph taken in neurosurgery theater Sheikh Zayed Hospital, Lahore Pakistan).](image-url)
Freehand biopsy (FHB) group: After preoperative work-up, the patients in this group were prepared for surgery. In operation theater, after undergoing general anesthesia, the patient's head was fixed with Mayfield three-point fixation device. The area was then prepped and draped in the usual sterile fashion and burr-hole was made. Then, using CT/MRI brain, tumor site and depth, as well as, trajectory of brain cannula were assessed. Freehand biopsy of the lesion was performed and the sample sent for histopathological analysis. Postoperatively, the patients were observed for postoperative complications.

Qualitative variables: The patients were observed for 1-2 weeks and measurable
and comparable parameters for complications like hemorrhage, infection, neurological deficit were assessed. This included an assessment for deteriorating conscious level by observing patient's Glasgow Coma Scale (GCS), symptoms like fever, headache, vomiting, seizures and neurological deficit (aphasia, hemiparesis, etc.).

- **Quantitative variables:** The patient's mean age, depth and size of lesion were noted.

- **Data analysis:** Results were tabulated at the end of the study with SPSS 20.0. The age of patient, tumor size and depth were reported by using mean ± standard deviation. Comparison for these variables was made by using the t–test. The gender, site of tumor, size of tumor and yield and morbidity were described by using frequencies and percentages for both groups and comparison for these parameters was done by using Chi-square test. The p-value less than or equal to 0.05 was considered statistically significant.

### RESULTS

The study comprised of 70 patients, assigned at random to two groups, 35 belonging to each group. The patients were assigned to both groups at random by lottery method. One group (ISG) underwent stereotactic biopsy, while the other group (FHB) underwent freehand biopsy. Table 1 indicates the age distribution of the patients included. The age of patients in the IGS group was recorded 40.2±6.1 years, which was almost similar 38.1±5.1 years in FHB group and the difference was considered to be insignificant with p-value= 0.119 (Table 1). Table 2 shows the gender distribution of the patients. Both groups had also almost similar kind of gender distribution with overall male to female ratio of 1.6:1 and no difference for gender was observed for gender in two groups with p-value =0.806 (Table 2). The average tumor size recorded in all 70 cases was 2.7±0.45 cm as indicated in Table 3. When randomized in two groups, the tumors in IGS group were of average size 2.8±0.4 cm and 2.6±0.5 in FHB group. The difference was not significant with p –value =0.066 (Table 3).

#### Table 1: Age distribution of the patients (n=70)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean +SD</th>
<th>t-value</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Stereotactic biopsy (IGS)</td>
<td>40.2±6.1</td>
<td>1.56</td>
<td>0.119</td>
</tr>
<tr>
<td>Free-hand biopsy (FHB)</td>
<td>38.1±5.1</td>
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Table 2: Gender distribution of the patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Stereotactic biopsy Number (percent)</th>
<th>Freehand biopsy Number (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>22 (62.8)</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (37.14)</td>
<td>14 (40)</td>
</tr>
</tbody>
</table>

Chi-square = 0.060  p-value = 0.806

Table 3: Mean size of tumor in both groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean size (cm)</th>
<th>SD (standard-deviations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotactic biopsy</td>
<td>2.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Freehand biopsy</td>
<td>2.6</td>
<td>0.5</td>
</tr>
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</table>

t-value = 1.85  p-value = 0.066

The average depth of tumor after randomization in two groups is as follows: in IGS group, it was at an average depth of 4.1±1.0 cm and 4.4±0.8 in FHB group as indicated in Table 4. The difference between two groups was not significant with p-value 0.167. Table 5 shows the frequency of side tumor. When distribution of side involved was studied in two groups it was noticed that there were 20 (57.1%) cases of left-side in the IGS group while this number was 16 (45.7%) in FHB group and the difference was not significant with p-value = 0.473 (Table 5). Table 6 shows the comparison of adequate sample between two groups. In freehand biopsy group, 31 (88.57%) patients had positive biopsy and 4 (11.42%) patients had negative biopsy. In stereotactic biopsy group, 33 (94.28%) patients had positive biopsy and 2 (5.71) patients had negative biopsy. This difference could not be considered statistically significant with p-value = 0.673. Table 7 shows the comparison of complications between two groups. The only complication found in two groups was a neurological deficit, which was found 1 (2.85%) in ISG group and 2 (5.71%) cases in FHB group. The difference was not significant with p-value = 1.000.

Table 8 shows the comparison of location of tumor in two groups. In freehand group, 13 (37.1%) patients had tumor in frontal lobe, 4 (11.4%) patients had tumor in
temporal lobe, 12 (34.3%) patients had tumor in parietal lobe and 6 (17.1%) patients had tumor in the occipital lobe. In stereotactic group, tumor were found in these positions: 10 (28.6%), 4 (11.4%), 20 (57.1%) and 1 (2.9%) respectively. The distribution was not considered significant with p-value= 0.095. Table 9 shows the frequency of different types of tumor in study. When 70 cases of the study were studied for the final diagnosis, 22 (31.42%) patients had astrocytoma grade II, 12(17.14%) patients glioblastoma, 11(15.71%) patients had metastatic tumor, 6(8.57%) patients had grade II glioma, 6(8.57%) patients had low grade glioma, 5(7.14%) patients had ependymoma, 4 (5.71%) patients had oligodendroglioma and 4 (5.71%) patients had abscess.

| Table 4: Mean depth of tumor |
|-----------------------------|------------------|------|
| Groups                      | Mean depth (cm)  | SD   |
| Stereotactic biopsy          | 4.1              | 1.0  |
| Freehand biopsy              | 4.4              | 0.8  |
| t-value = 1.39              | p-value = 0.167 |

| Table 5: Frequency of side of tumor |
|------------------------------------|------------------|------------------|
| Tumor side                        | Stereotactic biopsy | Freehand biopsy |
| Right side                        | 15 (42.9)         | 19 (54.3)        |
| Left side                         | 20 (57.1)         | 16 (45.7)        |
| Chi-square = 0.515               | p-value = 0.473   |
### Table 6: Comparison of adequate sample between two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>No of positive biopsy/percentage</th>
<th>No of negative biopsy/percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotactic biopsy</td>
<td>33 (94.28)</td>
<td>2 (5.71)</td>
</tr>
<tr>
<td>Freehand biopsy</td>
<td>31 (88.57)</td>
<td>4 (11.42)</td>
</tr>
</tbody>
</table>

Chi-square = 0.729  
\text{p-value} = 0.673

### Table 7: Comparison of complications between two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Neurological deficit Number (percent)</th>
<th>Bleeding</th>
<th>Infection</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotactic biopsy</td>
<td>1 (2.85)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Free-hand biopsy</td>
<td>2 (5.71)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td>3 (4.28)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

\text{p-value} = 1.000
### Table 8: Comparison of location of tumor in two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Temporal</th>
<th>Occipital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
<td>Number (%)</td>
</tr>
<tr>
<td>Stereotactic biopsy</td>
<td>10(28.57)</td>
<td>20(71.42)</td>
<td>4(11.42)</td>
<td>1(2.85)</td>
</tr>
<tr>
<td>Free-hand biopsy</td>
<td>13(37.19)</td>
<td>12(22.8)</td>
<td>4(11.42)</td>
<td>6(14.28)</td>
</tr>
<tr>
<td>Total</td>
<td>23(28.57)</td>
<td>32(48.57)</td>
<td>8(11.42)</td>
<td>7(11.42)</td>
</tr>
</tbody>
</table>

Chi-square = 6.38  
*p-value = 0.095

### Table 9: Frequency of different types of tumor in study

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Number/Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma grade II</td>
<td>28(39.99)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>12(17.14)</td>
</tr>
<tr>
<td>Metastatic tumor</td>
<td>11(15.71)</td>
</tr>
<tr>
<td>Low-grade glioma</td>
<td>6(8.57)</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>5(7.14)</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>4 (5.71)</td>
</tr>
<tr>
<td>Abscess</td>
<td>4(5.71)</td>
</tr>
</tbody>
</table>
DISCUSSION

The goal of stereotactic surgery is to target a point or volume in space precisely via predefined minimally invasive trajectory. The target location is not absolute. It is always situated in reference to any other intra or extracranial sites. For example, center of frontal tumor may be 2 cm from the midline, 3 cm posterior to inner table and 1 cm dorsal to the base of anterior fossa. Similarly, that same tumor may be some three-dimensional distance from fiducial markers present on the skin surface or externally applied to head frame. Thus, all points within a given volume can be related to other sites within that same volume provided that there is a constant frame of reference\(^{36,22}\).

Establishment of frame of reference requires a minimal of one point per dimension. Operative space, therefore requires a minimum of three nonlinear points to establish the three-dimensional reference system. The majority of commercially available stereotactic systems requires a minimum of additional fourth point to estimate error of image co-registration. The process permits integration of patient specific imaging coordinate systems and atlases with the physical operating space defined by stereotactic coordinate system. This transforms not just points, but entire volumes. This has become extremely useful in surgical and radio-surgical treatment of tumors, AVMs (arteriovenous malformation) and other conditions where the target is to be defined a volume\(^{36,22}\).

Prior to the development of CT/MRI, invasive procedures like ventriculography, pneumoencephalography and angiography were used in stereotactic surgery by assembling frame of radiopaque material to localize a surgical point of interest such as anterior and posterior commissures. Once the operative target is determined, a radiation beam or instrument such as biopsy needle, lesioning probe or catheter can be directed to the target. Due to invasiveness, there was a risk of intracranial hemorrhage, headache, infection, nausea and vomiting. Before the availability of digital computers, it was time consuming, difficult to calculate and prone to human error. Development of CT and MRI has given the stereotactic surgery a new dimensions\(^{18}\). So rather than referring to the location of the anterior and posterior commissures based on ventricular anatomy, now it is possible to visualize structures directly. Stereotactic targeting accuracy of CT and MRI is comparable to ventriculography\(^{3,16}\). Therefore, there is no need for invasive procures like ventriculography or pneumoencephalography with their inherent risks. With CT and MRI, three-dimensional distances between structures can be easily calculated. Therefore, the location of intracranial structure with respect of stereotaxic frame can define and allowing for identification of multiple targets. With MRI, there are additional benefits of increased tissue contrast of the lesion/target, ability to visualize subcortical targets directly and ability to obtain non-formatted, multi-planar images. The disadvantage with MRI is that there is a potential for anatomic inaccuracy as a result of ferromagnetically induced inhomogeneities of magnetic field. Functional neuroimaging like electroencephalography (EEG), magnetoencephalography (MEG) directly measure neuronal activity, whereas positron emission tomography, single positron emission computed tomography, functional MRI and optical imaging to measure blood flow changes and deduce neuronal activity\(^{10,42,46,51}\). The results of Neuroimaging tell about regional blood flow and neuronal activity can be applied to determine the optimal surgical route and whether or the surgery should be undertaken. The information can be integrated into stereotactic database.
resulting infused functional-anatomic image-guided surgical procedure.

Image co-registration includes an anatomic imaging space is correlated physical stereotactic operative space to maximize image utility. Therefore, the preoperative images are aligned to patient's head during surgery for the surgeon to be able to decide what should be treated and what should be left alone. In addition to anatomic images, functional imaging modalities like PET, fMRI and MEG can be co-registered into stereotactic imaging database\textsuperscript{(5,20,29)}. This allows simultaneous visualization of pathological and functionally eloquent brain tissue. This minimizes risk and maximizes benefits. In the frame based systems, anatomic images used to co-registered to the stereotactic frame. Several reference plate used to place orthogonally at the periphery of frame base. Each reference plate contains fiducial rod in letter “N” arrangements. When images are obtained through any plane, cylindrical rods appear as a circle or oval. Some frames allow for the determination of x-y-z coordinates of intracranial point directly from CT or MRI computer image. Over the past few years, frameless system has gained popularity over the frame-based systems. These systems use fiducial markers, which are either fixed to skin temporarily or implanted into the outer table of the skull. These markers are visible on imaging modality being employed. By determining the physical location of the fiducial markers, corresponding points in the image can be aligned with physical operating space. This can also be done by digitizing surface contours of a portion of the patient's head and then aligning this surface with that from imaging studies\textsuperscript{(35)}.

Another method of doing this is by surface digitization performed by physically tracing the skin surface using a traceable pointer or by laser scanning of actual surface without any physical with the skin (e.g. Medtronic, BrainLab)\textsuperscript{(13,38)}. Accuracy is then confirmed by touching the point beneath the surface and visualize the corresponding point on the imaging studies. Figure 4 shows the registration process being done during surgery. By this method, there is no need to affix any skin marker prior to imaging acquisition, but is less accurate\textsuperscript{(1,38,40)}. According to the recent advances in computer imaging technology, image fusion across different modalities now can be performed by using software algorithm. Thus, MRI performed days to weeks before surgery can be fused with a stereotactic CT performed on the day of surgery. Prior to the development of these algorithms, the acquired images were co-registered to physical stereotactic operative space by using the physical fiducial localizer attached to the frame, applied fiducial markers or skin surface.

Stereotaxy is used for precise localization of a target. With recent trends towards minimally invasive surgery, stereotactic procedures have become more common. Many neurosurgical operations are performed using stereotactic methods. Overall, cost, time consumed, surgeon's comfort level and experience, size of lesion and location of the lesion are factors for surgeon's preference for the utilization of stereotactic surgery. The recent advances in frameless techniques are having a revolutionary impact on the use of stereotactic surgery in operation room. Four fundamental steps are involved in neuronavigation: (i) method for registering the image with physical space, (ii) an intraoperative localization device (ILD), (iii) computer video display of medical images and (iv) methods for real time intra-operative feedback.
A tissue diagnosis of brain tumors is the basis for making decision to further proceed with excision and/or radiotherapy and chemotherapy. Stereotactic biopsy has provided the neurosurgeons with the opportunity to do this in a safer way with the least chances of morbidity and mortality, yet high diagnostic tissue yield. Various studies conducted to verify the superiority of stereotactic biopsy/surgery as opposed to freehand biopsy have proven this fact. In our study, 70 patients were divided into two groups. 35 patients underwent freehand biopsy and 35 underwent stereotactic biopsy. The cases were selected by convenient sampling with randomized allocation after written consent. The data was collected by the proforma prepared for the study of variables including age, sex, location and size of tumor. The outcome was assessed by diagnostic yield in terms of adequate tissue sample, morbidity in terms of postoperative complications like neurological deficit, bleeding, infection etc., and mortality between the two groups was compared.

Mass lesions lying-in depth not less than 3 cm and not more than 5 cm at the most superficial point, were included in the study. Mass lesions less than 3 cm in size, even if they are superficial were also included in the study. The superficial lesions with less than 3 cm depth, more than 3 cm size and deep thalamic lesions with more than 5 cm were excluded from the study. Also, patients with severe cardiovascular disease, not fit for GA, patients with bleeding diathesis and patients/family not consenting for both the procedures, i.e., freehand/IGS biopsy were excluded from the study. The results of 35 freehand CT-guided biopsies were compared with those of 35 stereotactic biopsies performed with the help of Medtronic Stealth-Station Treon Plus Navigation System. Twenty-seven of the lesions in the stereotactic biopsy group measured less than or equal to 2 cm as compared to twenty of those in the freehand biopsy group. Four freehand biopsies (11.42%) and two stereotactic biopsies (5.71%) were non-diagnostic. So there was no statistically significant

**Figure 4:** Registration process being done during surgery. (Photograph taken in neurosurgery theater Sheikh Zayed Hospital, Lahore Pakistan.)
difference between two groups from a diagnostic point of view with a p-value = 0.673, but there was a clinically significant difference in the diagnostic yield of the stereotactic group as compared to the freehand group. There was no biopsy related to the death among the patients in either group. Freehand biopsy was associated with 2.85% morbidity compared with 2.85% morbidity with the stereotactic biopsy with a p-value = 1.000.

In a study performed at Department of Neurosurgery, University of Minnesota Hospital and Clinic, Minneapolis\(^{(49)}\), 154 patients underwent 167 CT-guided/stereotactic biopsy of the brain lesions. Of the stereotactic biopsy patients, 14 were having deep lesions while 12 of CT-guided biopsies were also found with deep lesions, therefore these were excluded from the study. Results of 66 stereotactic biopsies performed with the help of Brown-Roberts-Wells stereotactic system were compared with those of 75 patients who underwent freehand CT-guided biopsy of the superficial lesions. Twenty-five of the lesions in a stereotactic biopsy group measured less than or equal to 2 cm compared to 13 of freehand biopsy group. No biopsy related to death was noted in the freehand biopsy group. In patients who underwent stereotactic biopsy one death (1.5%) was noted. A morbidity of 5% was noted in freehand biopsy group whereas, stereotactic biopsy group had a morbidity of 6%. Nondiagnostic biopsy was noted in 7 (9%) of freehand CT-guided biopsy group, compared to 12 (18%) in the stereotactic biopsy group. No significant statistical difference was noted in morbidity/mortality between the two groups. But there was a statistically significant (p <0.05) difference in diagnostic failure between the two groups\(^{(49)}\).

Goldstein published an article in 1987 in which a comparison was made between freehand CT-guided biopsy and stereotactic biopsy of brain lesions\(^{(11)}\). Stereotactic biopsies performed with the help of Brown-Roberts-Wells system and 64 freehand CT-guided biopsy of superficial lesions was done and outcome was compared. There was no statistically significant difference in diagnostic yield, morbidity and mortality noted between the groups. It was concluded in this study that free-hand CT-guided brain biopsy was safe and effective in obtaining brain biopsy specimen for histopathological diagnosis. Also, it was less time consuming and less costly when compared with stereotactic brain lesion biopsy, yet provided correct histological diagnosis as often\(^{(12)}\). In another study performed by Greenblatt et al. (1993) conclusion was made that the stereotactic biopsy was superior to CT-guided freehand biopsy in lesions that are deep, small and located near the midline\(^{(14)}\). Analytical difficulties, however, were noted in making this comparison. As per the previous report, the success rate for stereotactic biopsy was in the range of 91-93%, but the success rate for CT-guided biopsy was about 85%. But, in CT-guided freehand biopsy, the majority of more superficial lesions were included. Hence, there was prejudice in reported success rate due to biased case selection criteria between the two groups. Krieger et al. (1988) described stereotactic brain lesion biopsy in his review article. According to him, the stereotactic brain lesion biopsy has evolved as a safe and powerful tool to get a correct histopathological diagnosis with minimal or no disruption of eloquent brain. He also concluded that the stereotactic system plays a significant role in the management of brain tumors where benefits of open surgery might not justify the attendant risks\(^{(26)}\).

**CONCLUSION**

Stereotactic biopsy is a powerful and safe tool to provide tissue diagnosis with minimal disruption of the normal-functioning brain, especially lesions near the eloquent areas of the brain with
minimal morbidity, thus providing the surgeon with confidence and comfort that was not possible in the absence of such technologically advanced equipment. It plays a significant role in the management of malignant brain tumors where the benefit of open surgery might not justify the concomitant risks. Stereotactic biopsy has some limitations like learning curve, the amount of time consumption, cost and the phenomenon of brain shift. During this study, as mentioned before, there was a significant difference in overall cost and time consumption with stereotactic biopsy as compared to freehand biopsy. Average time consumed with one stereotactic biopsy was about 2-3 hours, whereas the average time consumed with the freehand biopsy was less than one hour in performing one biopsy. Stereotactic biopsy was proven to be more expensive as compared to freehand biopsy, but the confidence of the surgeon and safety profile of the patients is very much satisfying.

Drawbacks of the study included subjective rather than a truly objective nature of the study and the relatively lesser number of patients. Also, learning curve seems to be an important factor that should be taken into account. We suggest conducting a larger, preferably multicenter study with randomization but the question of ethical approval would be a primary concern.

DECLARATION: The authors report no conflict of interest.

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