
The excursion to mount Olympus. First stop at St. Athanasios monastery
Radioguided surgery using gamma detection probe technology for resection of cerebral glioma


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Keywords: Gross total resection - Glioma - Gamma detection probe - Radioguided surgery

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Abstract

Objective: Using microsurgical procedures without intraoperative imaging, Gross Total Resection (GTR) has so far only been achieved in less than 30% of all cases. Radio-guided surgery was introduced in the clinical setting in 1985 in an attempt to facilitate intraoperative tumor detection. Because of few studies in literature about this subject, we decided to use gamma probe with the hypothesis that we could increase extent of tumor resection. Materials and Methods: From January 2013 till February 2014, 22 patients with cerebral glioma were randomized equally into two groups and evaluated. In the first group, 370MBq of Technetium-99m was injected. The microsurgical resection of the tumor was performed as much as possible, and then the tumoral bed was examined, if the signal was more than 2 times of the background signal, more tissue resection performed if feasible until the signal was diminished. In the control group, conventional resection of the tumor was performed. The extent of tumor resection was assessed by contrast magnetic resonance imaging (MRI) study. Results: Before surgery the patients in the first group had average tumor volume of 81.68±9.78. In the second group the average tumor volume before surgery was 82.63±10.06cc. There is no significant difference between preoperative tumor volumes in two groups. In the first group, in the post-operative MRI, the tumor volume was 5.04±2.69cc and in the second group it was 9.5±4.8cc. Eight patients (72.7%) in the radioguided group experienced radical resection (more than 95%), but in the control group radical resection was achieved in just 3 patients (27.2%), radical resection was significantly higher in radioguided group (P<0.001). Due to the usage of the gamma detection probe, time of finding the tumor in the radioguided group was significantly less than control group (P=0.02). However total operation time in the radioguided group, was not significantly more than the control group (P=0.88). Conclusions: Neuronavigation system increases the percentage of gross total resection, but it is expensive, increases duration of surgery is not considered a real-time assessment, and is not accurate in determining the borders of glioma due to brain shift. In contrast, radio-guided surgery is easy to use, real time, not expensive, and increases the extent of tumor resection.

Published on line: 12 December 2015

Introduction

The surgery of brain tumors is one of the major concerns in the field of neurosurgery. These tumors constitute approximately 2% of all adult tumors. Unfortunately, more than half of these tumors are high-grade gliomas that are highly aggressive with a great probability of recurrence that makes median survival time 1-3 years after diagnosis. Finally, 50% to 75% of patients suffering from low-grade glioma pass away because of the disease [1].

In the literature it is shown that extent of radical resection of malignant tumors is a predictor of survival; however, there is no randomized trial that compares simple debulking cytoreductive surgery with radical resection on survival [2-9]. Efficacy of radiotherapy and chemotherapy on these tumors are inversely related to the remaining of tumor after resection [10].

So, patients with extensive tumor resection, even with the same chemotherapy regimen, had significantly longer survival time than patients in whom just a biopsy was carried out [11]. On the other hand, aggressive resection also may increase the risk of neurological deficits which definitely affect on patient’s quality of life [12]. Obviously, the aim of surgery is to achieve maximum tumor resection with minimal neurosurgical complications.

The most important and basically therapeutic management of malignant gliomas is microsurgical resection. [8, 9] however complete resection of these tumors has been achieved in less than 30% of all the patients [2, 5]. Preoperative imaging like CT and MRI can help define the location of brain tumors, but estimation of the exact spatial location of an intracranial lesion during surgery is usually difficult [13].

One of the important challenges in complete resection of gliomas is the obscure plane between the tumor and normal brain tissue. Also, surgery near the eloquent areas is hazardous and prevents aggressive resection [14]. Several preoperative and intraoperative techniques have been developed to make resection of these tumors more accurate and feasible. These techniques can determine the tumors position anatomically and differ it with functional nearby brain
tissue. One of the innovative techniques in modern surgery is neuronavigation using image guided systems. This technique was used firstly by Robert et al. in 1986 [15].

In the late 20th century, neuronavigation system has been developed [16]. This technique is a frameless, image-guided system that is based on preoperative CT or MRI. It can increase the accuracy of the size and location of craniotomy and makes tailored tumor resection more feasible. Although neuronavigation shows the exact boundary of the tumor and other structure at the beginning of surgery, images were taken before the operation and don’t show changes in brain shape and location of its structure that would happen during surgery and so it is not considered as a real-time imaging procedure [16, 17].

Functional brain MRI is another modality that helps the surgeon to visualize eloquent areas of the brain. In this technique, active part of brain will be shown due to higher blood flow through them when the patients move their limbs or talk. MRI shows these parts in a different color.

However, it is not very accurate in assigning tumor position but surgeon can avoid functional regions during surgery. This imaging technique is not available in operation room, so it’s not a real-time imaging technique [18]. Fiber tracking using diffusion tensor imaging (DTI) shows exact location of the eloquent matter structures. Merged with neuronavigation data, the accuracy of surgery especially near the functional brain tissue is increased. This technique is not real-time too and it’s not available in most centers [18].

The functional brain tissues also can be determined intraoperatively with direct cortical stimulation. First time, Foerster reported “Direct Cortical Stimulation” and “Brain Mapping” technique in 1930, [19] and then Penfield et al. described it in details [20-22]. In this technique, after craniotomy with use of a bipolar or unipolar electrode touching the brain surface, motor responses will be recorded as MEP (motor evoked potentials) on limbs while the patient is just sedated without general anesthesia. The areas that caused MEP response will be marked with sterile papers to make a Brain Mapping in order to avoid during resection of tumor [8, 18].

Paramount benefit of this method is real-time detection of functional brain tissues, but it has some difficulties and complications. Anesthesia process is difficult and the operation time will increase [18]. On the other hand, operation on awake patient will cause some complications like respiratory dysfunction, hemodynamic instability (rising blood pressure and heart rate), seizure during surgery, neurological deficit, brain edema and hemorrhage, local anesthetizing drug toxicity, nausea and vomiting, aspiration, pulmonary emboli and even death [23].

Intraoperative imaging using ultrasonography is another technique for improving detection of tumors, especially in subcortical cystic glioma and adjacent ventricles and peritumoral vasculature with neuronavigation [24]. Koivukangas and Kelly introduced use of ultrasonography as an intraoperative imaging technique in 1986 [25]. The most important advantage of ultrasonography is the ability of real-time imaging during surgery. But it does not have adequate efficiency in non cystic tumors. Combination of ultrasonography with neuronavigation can increase the accuracy of glioma surgery [24, 26].

Another technique for improving resection of glioma is fluorescence-guided surgery that uses fluorescent tumor markers in order to distinguish tumor from natural brain tissues. In this technique, after administration of oral 5-aminolevulinic acid (5-ALA) that is nonfluorescent produrg, this substance will be metabolized to protoporphyrin IX (PpIX) in tumor tissue through heme biosynthesis pathway [27]. So PpIX accumulate in malignant glioma and it has fluorescent nature. In normal brain tissue, PpIX level is very low. In the view provided by the special microscope that emits blue light (400nm wavelength), the tumor tissue is shown as a reddish material and the normal brain as a bluish tissue [27-29]. It has been shown that fluorescence-guided surgery increases tumor resection with less morbidity. The reported side effects of oral administration of 5-ALA has been skin photo sensitivity [30, 31].

However, 5-ALA is not FDA approved yet. This method needs a special microscope that is limited to a few centers. 5-ALA is now commercially available but it is extremely expensive [29]. The other real-time intraoperative imaging procedure is intraoperative MRI that allows surgeons to take MRI during surgery in the operation room. The first 0.5 Tesla intraoperative MRI system was manufactured in Brigham’s Hospital in Boston in 1990 [32]. Sutherland et al. in 1999 used intraoperative MRI in neurosurgery field. They used this system to operate brain tumors and vascular lesions [33]. This technique is almost real-time and the surgeon can use it for maximum resection of glioma with minimum neurological deficit; [34] however, it needs specially equipped operation theatre without any magnetic material device in either surgery tools or anesthetic equipments that is so expensive and right now, it exists in just 100 centers all over the world [18]. It does not exist in Iran too. Moreover, this technique will lengthen the operation time and is technically demanding [35].

Radio-guided surgery has been developed about 60 years ago [36]. Using gamma detection probe technology, radio-guided surgery has revolutionized the surgical management of many malignancies such as breast cancer, colorectal cancer, melanoma and parathyroid disease [37, 38]. This technique provides critical and real-time information about size, location and invasion of the tumor into the adjacent tissues, so as to help find surgical resection margins accurately.

Moreover, this technique has enabled the surgeons to be able to perform maximal cytoreduction with fewer complications [38].

Morley and Jefferson used phosphorus-32 and a modified Geiger-Muller probe that detect beta radiation to map the tumor extent and locate the tumor to guide biopsy for the first time [39].

Dessiatnikov et al. used this technique with similar purposes in 1968 [40]. The first radio-guided brain tumor surgery with using a gamma probe was reported by Vilhel and Carneiro in 2002. They resect a metastatic renal cell carcinoma in the right parietal lobe of a 62 year old man with use of gamma probe after injection of Tc-99m [41]. Thereafter, just a few studies performed, using radioguided surgery. In 2004, Koima et al reported resection of primary or secondary brain tumors in 13 patients, using gamma probe. They used Tc-99m as a radionuclide agent [42]. Then Gay et al used In-111(DTPA)-D-Phe 1 pentetreotide (an analoge of somatostatin) as radionuclide to resect meningiomas in 10...
Materials and Methods

In this study all the patients who were diagnosed as cerebral glioma in our institute from January 2013 till February 2014 referred to our neurosurgical clinic were evaluated. They did not receive any brain surgery, chemo or radio therapy before. The inclusion criteria were patients aged between 18-60 years that their neuroimaging were consistent with cerebral glioma. After performing MRI (in postgadolinium T1-weighted images), only cases with the potential for complete tumor resection (non eloquent lesions and not deep seated) were selected. Our exclusion criteria were as follows: deep lesions, involvement of the eloquent areas, gliomatosis cerebri, pregnant or lactating women. All the selected cases were randomized into two groups.

Before the study, informed consent was obtained from all the patients and complete procedure of the study was explained to their family and themselves and our study was reviewed and accepted by Shahid Beheshti university ethical committee.

Functional metabolic imaging modalities can provide information about metabolic status of brain tumors. However it seems that positron emission tomography (PET) has more sensitivity than SPET (single-photon emission computed tomography), but SPET is considered as a valuable alternative because of lower cost and wider availability [49].

In the first group, before the procedures, Tc-99m MIBI SPET was performed. A brain SPET was performed 40 minutes after the injection of 111MBq of Tc-99m MIBI. Images were reported quantitatively and qualitatively. The patients who didn’t have enough uptakes in SPET were excluded from study. The others had acceptable uptake in SPET.

With using of the open-source image processing software “ImageJ” developed by the National Institutes of Health (http://rsb.info.nih.gov/ij/index.html) in slice with maximum lesion uptake, relative tracer concentration was calculated in ROI (region of interest) and a second mirror region on the contra lateral normal side of the brain in the same slice (as normal background uptake). By dividing average signal in the lesion ROI by those in the mirror regions, T/N (tumor/normal) ratios were achieved [49]. These T/N ratios are shown in Table 2.

A surgical gamma probe was used (SCINTIPROBE MR100) with the energy window manually ranged between 60 and 1800KeV, including the 2 main photo peaks of Tc-99m MIBI. Tip of our probe diameter was 15mm.

After all requisites had been fulfilled, an additional dose of 37MBq of Tc-99m MIBI chloride was injected at the same time as the craniotomy in the operating room. In the course of the surgery, the signal from skull, dura, cortex overlying the tumor and the tumoral bed after tumor resection was recorded with the use of hand held gamma probe and its related digital detector. The signal of the suspected tumoral area more than the index ratio of the background signal was considered significant. The time between the end of the bone flap resection and tumor identification were also determined in each case. Then surgical resection of the tumor was performed as much as possible considering the color and consistency and differentiation with surrounding tissue. Then the tumoral bed was examined, if the signal was more than T/N ratio of the background signal, more tissue resection performed (if feasible) until the signal was diminished. In the control group, conventional resection of the tumor was performed. After surgery, in all the cases, MRI with and without contrast were performed at first post-operative day and the tumor remnant was determined and compared with the preoperative MRI. The tumor volume was estimated using Cavalieri principle [50, 51]. The recorded variable were as follows: Age, sex, tumor location, pre op and post op tumor volume, the time between bone flap removal and tumor identification, and the signal recorded from skull, dura, cortex and tumoral bed. All the data were gathered in a data base using Excel software. For comparison of the data between the two groups we used Student T test and for the assessment of the intervening factors, Chi square test was performed.

Results

In this study all the patients who were diagnosed as cerebral glioma from January 2013 till February 2014 referred to our neurosurgical clinic were evaluated. According to our inclusion and exclusion criteria 22 patients were selected and randomized into two groups. The first group consisted of 11 patients who were considered for radio guided surgery. In this group 7 cases were male (63.7%) and 4 cases were female (36.3%). The average age of this group was 37.1y with the standard deviation of 10.9y. Maximum age was 54y and the minimum age was 32y with the median of 32y. The second group consisted of 11 patients who were considered as the control group. In this group 6 cases were male (54.5%) and 5 cases were female (45.5%). The average age of this group was 41.3y with the standard deviation of 5.2y. Maximum age was 52y and the minimum age was 36y with the median of 40y. There is no significant difference between ages of these groups. (P=0.099)

In 8 cases of the first group, the site of the tumor was in the right hemisphere (72.7%) and in 3 cases (27.3%) the tumor was located in the left hemisphere. The location of the tumor was in frontal lobe in 2 patients (18.2%), occipital lobe in 1 case (9%), temporal lobe in 7 cases (63.8%) and insula in 1 case (9%). The most common chief complaint of the
patients in this group was headache, 6 cases (54.5%). Seizure occurred in 4 cases (36.4%), hemiparesis in 3 patients (27.3%). The detected gamma probe signals were recorded by the detector in each step of the surgery. But in the second group, site of the tumor in 8 cases was in the right hemisphere (72.7%) and in 3 cases (27.3%) the tumor was located in the left hemisphere. The location of the tumor was in frontal lobe in 2 patients (18.2%), occipital lobe in 2 cases (18.2%), temporal lobe in 6 cases (54.6%) and insula in 1 case (9%). Comparing the location of tumor in two groups did not show significant differences. (P=0.76)

In the operative field, the average signal over the scalp was 28.9±8.5. The maximum signal was 42 and the min value was 15 and the median was 30. The average signal detected over the tumor site was 38.18±6.4. The mean signal in the second group it was 9.5±4.8cc.

In the operative field, the average signal over the scalp was 28.9±8.5. The maximum signal was 42 and the min value was 15 and the median was 30. The average signal detected over the tumor site was 38.18±6.4. The mean signal value after tumor resection was 13.6±5.8, maximum value was 25 and minimum signal was 6.

Details of gamma beam spectrometry are in Table 1.

Table 1. Data of gamma beam spectrometry

<table>
<thead>
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<th>Tumor</th>
<th>After Resection</th>
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<td>25</td>
<td>30</td>
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</table>

In the first group, the time interval between dural opening and tumor recognition was 7.5±3.5 min and the average duration of operation in the first group was 4.8±0.7h, maximum value was 6h, minimum time was 4h and the median was 5h. In the second group, the time interval between dural opening and tumor recognition was 13.5±2.44min and the average duration of operation in this group was 5±0.6h, maximum value was 6h, minimum time was 4h and the median was 5h.

Before surgery the patients in the first group had average tumor volume of 81.68±9.78. In the second group, the average tumor volume before surgery was 82.63±10.06cc. There is no significant difference between preoperative tumor volumes in two groups (P=0.71). In the first group, in the post-operative MRI, the tumor volume was 5.04±2.69cc and in the second group it was 9.5±4.8cc.

Table 2 shows pre and post operation tumor volume and operation time for the patients in details.

Table 2. Details of pre and post surgery tumor volume and resection extent in all cases

<table>
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<tr>
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<th>Tumor volume before surgery (cc)</th>
<th>Residual volume (cc)</th>
<th>Amount of resection (percentage)</th>
<th>Resection extent (Radical resection or not)</th>
<th>Surgery duration (hour)</th>
<th>T/N ratio (SPET)</th>
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* These patients had low grade glioma due to pathological examination after surgery.
After surgery the pathological report of the tumor were as follows: astrocyroma grade 2 in 1 case (9.1%), oligodendroglioma grade 2 in 2 patients, astrocytoma grade 3 in 2 cases and glioblastoma multiform 6 cases. In the second group, pathological report of the tumor were astrocyroma grade 2 in 1 case (9%), oligodendroglioma grade 2 in 2 patients (18.2%), astrocytoma grade 3 in 3 cases (27.3%) and glioblastoma multiform in 5 cases (45.4%). The difference between these two groups was not significant (P=0.88).

Discussion

In most centers from all over the world, common imaging techniques like neuronavigation system, MRI or CT-scan with contrast is not available in the operating room [32]. So lack of realtime imaging technique in the operating room is noticeable.

MRI but these imaging techniques are not usually available in the operating room and if they were, they would be so expensive.

Differentiation between brain tumors and natural brain tissue during an operation is so important, because we need to remove as much as possible of tumor with less damage to the normal and especially functional brain tissues. Maximum removal of the brain tumor and cytoreduction increases the efficacy of adjuvant therapies (i.e. radiotherapy or chemotherapy) [42].

In this study, the mean residual tumor volume was 5.04cc in radioguided group and 9.5cc in control group. There was a significant difference between residual volumes in the 2 groups (P=0.01).

In our study, 8 patients (72.7%) in the radioguided group experienced radical resection (more than 95%), but in the control group radical resection was achieved in just 3 patients (27.2%) that our control group is similar to other studies using microsurgery. Radical resection was significantly higher in radioguided group (P<0.001).

In our study, extending the amount of tumor resection in the cases demonstrating significant signal did not increase the rate of postoperative neurological deficit (18% in both groups). This may be due to the fact that we only included patients with total resectability potential.

Time of finding the tumor in the radioguided group was significantly less than control group (P=0.02). This reduction in finding tumor time is because of using gamma probe. However, total operation time in the radioguided group, was not significantly more than the control group (P=0.88).

The annual exposure limit of radionuclide was set by The International Commission on Radiological Protection (ICRP) as a total dose equivalent of 100000μSv per year in five years that it has to not exceed 50000μSv in a year [52, 53]. Radiation exposure from Tc-99m MIBI used for radioguided surgery of brain has been evaluated. The mean exposure time was 6.1 hours for all operation room personnel. The mean whole body exposure was 27.9μSv for surgeons, 25.8μSv for nurses and 14.9μSv for anesthetists [42].

According to existing data microsurgery without any intraoperative imaging, resulted in gross total resection (GTR) in 27% to 38.2% of patients [54-57].

Neuronavigation system increases the percentage of gross total resection, but it is expensive, increases duration of surgery and is not considered a real-time assessment, and is not accurate in determining the borders of glioma due to brain shift [2]. Kurimoto et al. reported that GTR can be achieved in 64.3% of cases using using neuronavigation system [57].

Our complication rate was 18%. In Kurimoto study the rate of complication after resection of cerebral glioma was 17.6% in microsurgery group (similar to our results) and just 9.5% in neuronavigation group [57]. Nimsky reported 10.2% complications after surgery using neuronavigation and just 2.9% in their patients operated with iMRI [56].

In a study performed by Enchev et al., they evaluated efficacy of intra-operative ultrasound combined with neuronavigation on operation of recurrent cystic glioma. Postoperation evaluation revealed 60% GTR, 20% near total resection and 20% subtotal resection of tumor.

Intraoperative ultrasonography is so useful in subcortical cystic tumors, it is real-time and economical; however it has not enough accuracy in operating solid tumors and interpretation of these tumors images need more experience [24].

In 2006, Muragaki reported that iMRI use in 96 cases with cerebral glioma, resulted in 0.025mL tumor residue whereas in the control group the average tumor remnant was 1.7mL. (P<0.001) [58]. They also reported that in patients with iMRI application, GTR achieved in 95% of their patients [58]. In Nimsky series, GTR was achieved in only 27% of their patients according to the results obtained by iMRI. After the iMRI evaluation, the overall GTR was achieved in 40% of the cases [54-56].

Currently, just about 100 centers in all over the world have special operation room and surgery device, adapted for intraoperative MRI and these facilities are very expensive [18]. It is not worldwide and there is no such an operation room in Iran. The overall cost of polestar N20 iMRI was over 3 million dollars that mentioned in Makary study and it has about 120,000$ running cost each year [59]. As claimed by American Hospital Association Health Data Management Group guidelines in 2008, this system’s economic life is only 5 years without any end-of-life salvages value [60].

As it was shown in the literature, iMRI elongates the operating time about 0.5 to 2 hours more than usual [61-63].

Stummer et al., in their series compared fluorescence-guided surgery using 5-ALA with microsurgery. In fluorescence-guided group 65% of patients showed GTR, but in microsurgery group just 36% of their patients showed GTR in post-operative MRI.31 Also in 2014, Piquer et al. reported 79.3% GTR in their series using fluorescence-guided [64]. This microscope is expensive and using 5-ALA is costly for each patient, however it is commercially available
worldwide, it is not available in Iran. Table 3 compares our study results with other studies with different methods.

<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging technique</th>
<th>Number of patients</th>
<th>Extent of resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurimoto (2004)</td>
<td>Neuronavigation</td>
<td>76</td>
<td>64.3% GTR with Neuronavigation, 38.2% GTR with Microsurgery</td>
</tr>
<tr>
<td>Nimski (2006)</td>
<td>iMRI</td>
<td>137</td>
<td>40% GTR</td>
</tr>
<tr>
<td>Enchev (2006)</td>
<td>Ultrasound + Neuronavigation</td>
<td>16</td>
<td>60% GTR</td>
</tr>
<tr>
<td>Stummer (2006)</td>
<td>Fluorescence-guided surgery</td>
<td>322</td>
<td>65% GTR with FGS, 36% GTR with white light</td>
</tr>
<tr>
<td>Muragaki (2006)</td>
<td>iMRI</td>
<td>96</td>
<td>91% GTR with microsurgery, 95% GTR with iMRI</td>
</tr>
<tr>
<td>Solheim (2010)</td>
<td>Ultrasound</td>
<td>156</td>
<td>37% GTR</td>
</tr>
<tr>
<td>Piquer (2014)</td>
<td>Fluorescence-guided surgery</td>
<td>38</td>
<td>79.3% GTR</td>
</tr>
<tr>
<td>Witt Hamer (2012)</td>
<td>ISM*</td>
<td>8091</td>
<td>75% GTR with ISM, 58% GTR without ISM</td>
</tr>
<tr>
<td>Kuhnt (2011)</td>
<td>iMRI</td>
<td>117</td>
<td>41.9% GTR</td>
</tr>
<tr>
<td>Our study</td>
<td>Radio-guided surgery</td>
<td>22</td>
<td>72.7% Radical resection with RGS, 27.2% Radical resection without RGS</td>
</tr>
</tbody>
</table>

*ISM: Intraoperative Stimulation Brain Mapping

Acknowledgment:

The authors want to express their deep gratitude to Mrs. Banoo Ashraf Saberi and Mr. Esmail Seddighi for their great collaboration in editing the manuscript and data collection.

The authors declare that they have no conflicts of interest.

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