Concomitant radio-fluorescence-guided surgery in high grade glioma. Cohorte study

Cirugía concomitante guiada por fluorescencia en glioma de alto grado. Estudio de cohortes

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Resumen

El glioblastoma multiforme es el tumor maligno primario del SNC primario en adultos. El metoxiisobutilisonitrilo (MIBI o sestamibi) tiene una gran disponibilidad de flujo de fotones lo que mejora la captación, sus propiedades físicas hacen que este radiotrazador sea de elección para la cirugía radioguiada. Por otro lado, la fluoresceína sódica (FS) es una sustancia colorante orgánica soluble en agua utilizada en el examen de circulación vascular del ojo y su uso en cirugías ha mostrado un rango aumentado de resección completa y una supervivencia de 6 meses. El objetivo principal de este estudio fue evaluar la utilidad de la cirugía guiada por radiofluorescencia (RFG) en pacientes con gliomas de alto grado utilizando MIBI como radiotrazador y FS. Estudiamos 11 casos con glioma de alto grado que fueron tratados con RFG. Los resultados mostraron que podemos lograr resecciones macroscópicas totales sin causar un nuevo déficit neurológico o aumentar el daño existente. La evaluación postoperatoria de los casos con déficit motor mostró una mejoría del 90%. La cirugía no agregó ningún déficit en el paciente. En el 81.8% de los casos, la lesión tumoral apareció en un área elocuente o cerca de un área elocuente, y ningún caso presentó daño de la región antes mencionada. **Conclusión:** La técnica RFG demostró utilidad en la resección tumoral total bruta, disminuyendo el tumor residual sin aumento de la complejidad de la cirugía y los tiempos quirúrgicos. En nuestro estudio no hay evidencia de efectos adversos para la administración de MIBI y FS.

Palabras clave: Cirugía guiada, fluoresceína, radiotrazador.

Abstract

Glioblastoma Multiformeis the most frequent primary malignant CNS tumor in adults. The gross total resection of glioma is directly proportional to the Increase of the survival. The methoxyisobutylisonitrile (MIBI or sestamibi) is a wide readiness to the rich flow of photons, which improves the detection of pathological uptake with gamma probe; these physical properties make the election of this radiotracer to Radio-Guided Surgery. On the other hand, the fluorescein sodium (FS) is a water-soluble organic coloring substance used in the vascular circulation exam of the eye and when it was used has shown an increased range of complete resection and a survival of 6 months. The main objective of this study was to evaluate the utility of Radio-Fluorescence-guided Surgery (RFG) in patients with high-grade gliomas using MIBI as radiotracer and FS. We carried out the report of eleven cases with high grade glioma which were treated with RFG. We can achieve gross total resections without bigger deficit. The postoperative evaluation of the cases with motor deficit showed an improvement of 90%. The surgery did not add any deficit in the patient. In 81.8% of the cases, the tumor lesion appeared in an eloquent area or near an eloquent area, and no case presented damage from the aforementioned region. **Conclusions**: The RFG technique demonstrated utility in the gross total tumor resection, diminishing the residual tumor without surgery increasing complexity and surgical times. In our study does not evidence of adverse effects for the administration of MIBI and FS.

Key words: Gamma probe, radio-fluorescenceguided surgery, radiotracer.

Introduction

In 1896 Becquerel discovers natural radioisotopes and De Hevesy invents the principle of "tracer" through his work with lead radiactivo. Radio-guided surgery (RGS) develops more less 60 years ago, today is used by surgeons to assess the degree of tumor resection and minimize the amount of healthy tissue to remover[1-4].

The MIBI (MIBI- 99mTc, methoxyisobutylisonitrile, MIBI or sestamibi) has a wide availability rich photon flux, which improves the detection of abnormal uptake by gamma probe, these physical properties make this radiotracer the choice for radioguided surgery, compared to other as thallium-201[5]. It was first described in 1980, to detect myocardial perfusion in coronarydisease[5, 6]. The radiotracer uptake by the neoplastic cell depends on various factors such as regional flow blood, plasma potential and mitochondrial membrane, angiogenesis, and tissue metabolism, about 90% of tracer activity is concentrated in the mitochondria. However physiological MIBI uptake by the choroid plexus is a disadvantage in the evaluation of deep lesions located in the paraventricular regions[6].

The lesion/bottom ratio is high with this tracer in tumors and suitable for technical purposes. In addition, the scar tissue has no active uptake, so it is useful to distinguish tumor tissue during surgery[7-14].

Brain tumors have a high degree of absorption of 99mTc-MIBI increased compared with that of the low-grade tumors, the Tc99m-MIBI absorption is related to the percentage of cells in S phase and level of tumor aneuploidy cerebral[9].

The impact of RFG in the updated treating cancer patients is offering an essential weapon in real time for surgeons in terms of determining the extent, location of the lesion, and the surgical margins. The technique is based on using a radiotracer preferentially taken up by the tumor to mark the cancerous tissue, from normal tissue, this radiopharmaceutical should be administered together before surgery[15].

With the passage of years to go looking for technical aids, pre and intraoperative images, making it possible to perform a complete as possible total tumor resection or infiltrative tumor lesions those applying neuronavigation, intraoperative MRI, intraoperative ultrasound, cortical stimulation and finally the use of dye 5-amino levulinicAcid (5-ALA) and Fluorescein Sodium(FS) the latter has shown an increased range of complete resection and 6 months sobrevida[16].

In 1948 Moore and Peyton described the use of FS for locating brain tumors, which was subsequently abandoned its use due to own adverse reactions FS substance[17].The FS is a water-soluble substance organic dye used in the examination of blood vessels eye[16].

GBM is the most common malignant primary tumor of adults that applying a multimodal therapy (surgery, chemotherapy, and radiotherapy) can achieve a median survival of 14 to 16 months, two years a 26-33% and less than 5% to five years[18].

There have been multiple studies in which direct relationship between the degree of tumor resection and prolonged survival is shown, which currently remains a point of contention between the neuro-oncologist[18-20]. Currently, it is widely accepted, which cannot be identified functional brain areas, especially language center, only based on anatomical landmarks, plus a maximum resection with minimal risks, it requires some functional single location pre and intraoperative. Radical resection of gliomas carries the risk of injuring the eloquent functional areas due to the infiltrative nature of the lesion. The main role of surgery is to remove the tumor and its macroscopic limits as completely as possible. Although it has been possible to demonstrate the presence of tumor cells imaging centimeters beyond the alleged margin hence the importance to functional studies (spectroscopy MRI, PET-CT, SPECT-CT) in planning and surgical guide.

There have been multiple attempts to intraoperative distinguish tumors from normal brain tissue: Using tissue photosensitizers (chloro-aluminum phthalocyanineTetrasulphonate) injection of dyes that cross the Blood-Brain Barrier (BBB) fluorescence-guided surgery (5-aminolevulinic acid) serial biopsies by freeze to discover the range, Doppler and intraoperative MRI guidance, most of these techniques lack the combination of ease of use and cost-efectividad[11].

Radioguided neurosurgery, is a technique derived from nuclear medicine, introduced in 1985 by Martin, used for intraoperative identification of brain tumors, due to emission by the same radiopharmaceutical, this can be done with a gamma probe or portable gamma camera[5].

This technique has already been used successfully in primary breast tumors, prostate, testicular, gastrointestinal, thyroid, parathyroid, melanoma and brain as well as in identifying sentinel nodes and metastases[13].

Studies published in 2012 and 2013 which combined the use of radiotracers and fluorescent substances for identification in the sentinel lymph node biopsy in patients with breast cancer, squamous cell carcinoma of oral cavity and in cases of head and neck melanoma[21,22].

It has designed a surgical trial comparing the results of Radio-Fluro Guided surgery with conventional surgery, aiming to demonstrate that the degree of resection of the tumor is greater with the RFG and with this progression free survival (PFS) and overall survival (OS). In this article we present the results of Phase II.

Material and Method

A cohort study is performed, controlled and prospective of 11 patients with diagnoses of high grade gliomas, selected according to the inclusion criteria, who underwent Radio-fluorescence guided surgery in the period from October 2014 to January 2015 to demonstrate that the practice of this approach is useful in our environment.

RFG candidates who met the defined inclusion criteria were considered.

Inclusion criteria

- Astrocytic tumors of high malignancy, AA anaplastic astrocytomas (grade III) or glioblastoma multiforme GBM (Grade IV) without previous surgery.
- Patients aged ≥ 18 years to 70 years.
- Life expectancy ≥ 12 weeks.
- Karnosfsky Index ≥ 70.
- Laboratory parameters within normal limits defined as:

a) Hematopoietic: Hemoglobin ≥ 9 g/L, total leukocyte count ≥ 4 x 109 cells/L, platelets ≥ 100 x 109/L.

b) Hepatic: liver function within normal limits and without liver disorders demonstrated by TGP, AST, GGT and alkaline phosphatase.

c) Renal function: Serum creatinine 132 mmol/L.
- Patients express written into the studio with his signature document voluntary informed consent.
- Tumor located in accessible areas to surgical resection.

Exclusion criteria
- Patients who are pregnant or breastfeeding.
- Patients at the time of inclusion present a chronic disease associated phase of descompensation (eg. Heart disease, diabetes, hypertension).
- Patients who have a history of bronchial asthma.
- Fevers.
- Severe septic processes.
- Acute allergic or gravity States.
- History of active malignant tumors elsewhere.
- Rejection by the patient.
- Special locations such as 1. Lesiones bilateral tumor.

2. Invasion of the Corpus Callosum.
3. Basal Ganglia.
4. Brain stem.

As neuroimaging study, simple and enhance image by magnetic resonance imaging (MRI) and single photon emission tomography (SPECT) brain, with both techniques confirmed the presence of uptake coincident with the lesion described in the contrasted MRI was used, these procedures preoperative were performed 72 hours after surgery (0.23-T Phillip MRI), can perform the calculation of tumor volume. The residual tumor would be defined as uptake area, provided it is greater than 0.175 cm^3, according to RANO criteria[14,23]. Tumor volume was calculated by the computerized planimetric method and formula for the volume of an ellipsoid V = 4/3 π (a) (b) (c), was performed using the dimensions of the MRI contrasting obtained preoperative and postoperative, the latter were obtained within the first 48-72 hours after the operation, defining the residual volume which presented enhancement by administering paramagnetic contrast.
This study allowed us to calculate the preoperative tumor volume as[15]:
- 35 cm^3 Large.
- $\leq$ 35 cm^3 Small.

For postoperative volumetric assess we use the following nominación[24].

Table 1 gives information about the degree of resection, the volume of tissue resected and the feature of the surgery.
Dye uptake (FS): To describe the uptake of dye used the nomination submitted by Bo Chenet al[17], (Table 2).
For a definition of eloquent area, defined as described by Sawaya[16] eloquent area (sensorimotor cortex, language center or visual, basal ganglia, hypothalamus, brainstem and corpus callosum) near eloquence (regions immediately adjacent to eloquent areas) and not eloquent (frontal lesions, temporopolar, right parietal-occipital, cerebellar hemisphere).
Fulfilling the standards of Good Medical Practice, before performing the procedure, the informedof consent was signed by patient and parent´s.
The cut in the patient follow-up was conducted in the first six months after surgery, with neurological and imaging evaluation, fulfilling the protocol according to the histological type in each case.
Phase III of the research are in progress.
Phase III: controlled, randomized, single-blind, where patients will be offered the Radio-fluorenceseguided surgery or conventional surgery, as methods of treatment for tumor pathology.
Phase IV: Follow-up study with cutting at 6 and 12 months after surgery, with neurologic examination and imaging protocol as the disease.

Protocol RFG
Brain SPECT with 20 mCi of Tc99m-MIBI, confirming the presence of coincident uptake (only) with the lesion described in contrasted MRI or CT, showing a high ratio injury / bottom (> 2).
In each patient subsequent to brain SPECT, the respective surgical procedure was scheduled. Two hours before surgery was given 14 mCi of Tc99m-MIBI intravenously and the surgical detection probe explored.

Proceed
The main sites of concentration of MIBI are; heart and liver, after anesthesia, the use of leaded vest about the patient was implemented to reduce radiation to medical personnel.
Intravenous injection of 14 mCi with 99m Tc-MIBI performed two hours before surgery. During anesthesia induction using fluorescein test with 200 mg of FS intradermally injection, it is expected 15 minutes, not allergic reaction, can proceed to the next step. Once craniotomy completed it proceeds to the administration of fluorescent substance, then using the gamma probe to guide the intracerebral approach, directed primarily to normal brain tissue (bottom), is taken as a benchmark, then the gamma probe is directed towards the tumor (lesion), the difference is recorded. Due to the use of this dye will be tinged with mild, moderate or

Table 1.
Data on surgery

Degree of resection	Volume	Feature
Total	$\leq$ 0.175 cm^3	Absence of residual mass or uptake ring in postoperative MRI
Subtotal	> 0.175 cm^3	Uptake residual tumor and measurable on postoperative MRI

Table 2.
Description of the dye uptake

Nomination	Feature
Intense yellow	When the tumor intense greenish yellow color evenly throughout the lesion is enhanced
Faint yellow	When the tumor uptake is clear and yellow portions that do not capture
No uptake	When there is no uptake

intense yellow color depending on the degree of disruption of the BBB. Once the resection of the lesion macroscopic fluorescence guided, the gamma probe to the tumor area is redirected, if activity tumor is detecting (lesion) higher than the bottom (2: 1) and still existed intensity yellowing, we proceeds to total resection.
Below check the decline in regional counting, to be equal to that of normal brain parenchyma in the gamma probe.

Results

In our study, the majority of our patients were male[7] and only four female patients, average age was 55 years, eight patients were diagnosed GBM, and the remaining two AA with Oligoastrocytoma grade III.
Table 3 shows the results of the RFG. The general data of the patients (diagnosis, age, sex), the Karnosfky record, the Sawaya scale, the motor deficit before and after the surgery, the pre and postoperative tumor volume, the clinical status, are described. the coloration, lesion before and after the surgery and the adjuvant therapy used.
The main sign of debut, was the motor deficit in 6 patients (54.5%), among them four patients had hemiparesis and two cases with hemiplegia, focal seizures occurred in three patients, although in two cases coincided deficit motor seizures, otherwise with lesion in the left parietal lobe shape debut left-right disorientation, dysgraphia, dyscalculia (Gerstmann syndrome) in a single case, the holocraneal headache was the only symptom debut.
The Figure 1 shows T1 weighted MRI simple skull and brains SPECT 99mTc-MIBI pre-surgery (Figure 1A) while Figure 1B shows a post-surgery image.
The Figure 2A evidence the early stage brain SPECTwith 99mTc-MIBI in pre-surgery moment skull and T1-weighted MRI were shown in Figure 2B . On the other hand, the Figure 3A shows the early stage brain SPECT with 99mTc-MIBI post-surgery and the Figure 3B skull and T1-weighted MRI.
The affected tissue is shown during intraoperative tumor resection (Figure 4). In conducting an assessment in the immediate postoperative cases with motor deficit improved by 90% and improved one part, maintaining a distal brachial

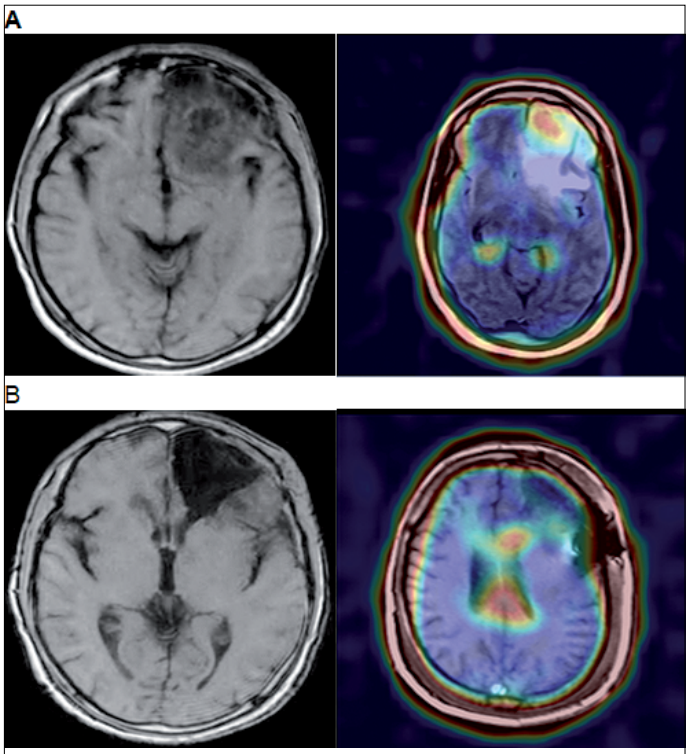

Figure 1. T1weighted MRI simple skull and brain SPECT 99mTc-MIBI. A. Pre-surgery. B. Post-surgery

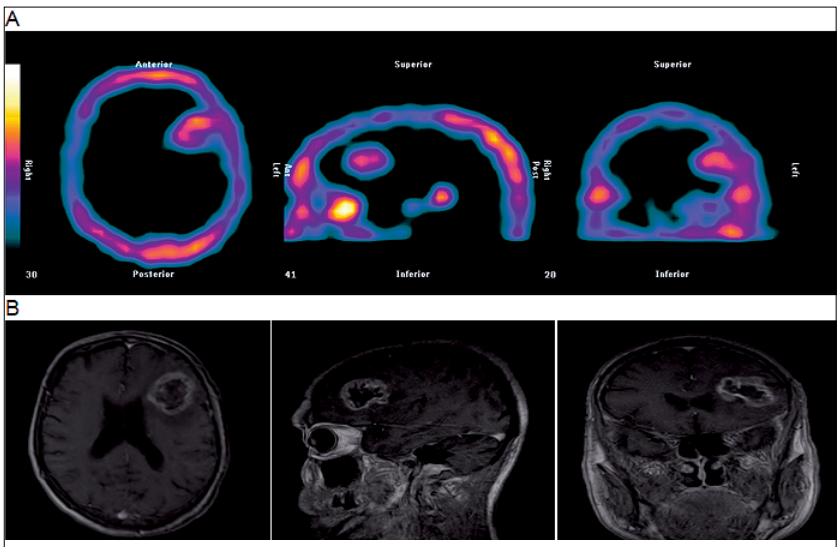

Figure 2. Pre-surgical early stage brain SPECT with 99mTc-MIBI (A) and skull and T1-weighted MRI (B).

monoplejía in those patients who had no preoperative motor deficit, no further deficit was added to the surgery. In 81.8% of cases the tumor lesion was presented in near eloquence[5] eloquent area[4] or, in any case there was damage to the functionality of the aforementioned region.
Regarding the degree of dye uptake in 90.9% of cases was severe (FI), in 100% of our patients received adjuvant radiotherapy (LINAC) and immunotherapy (nimotuzumab), chemotherapy alone was used in three patients. In

Table 3.
General Result of RFG

No	Diag-nosis	Age/ Sex	Kar-nosfky Score	Sawa-ya[1] Scale	Pre-op-Motor Deficit	Pre-op tumoral volumen	Post-op Motor Deficit	Clinical Status[2]	Colora-ción[3]	Lesion/ pottom-Pre-op	Lesion/ pottom Post-op	Post-op tumoral volumen	Adjuvant-Terapy[4]
1	GM	48/m	100	II	Yes	123 cm^3	No	DD	FI	> 2/1	< 2/1	63,5 cm^3	R, PCV, N
2	OA (gra-de) III	55/f	100	III	No	65 cm^3	No	PFS	FT	> 2/1	< 2/1	11,4 cm^3	R,N
3	GM	70/m	100	III	Yes	33 cm^3	No	PFS	FI	> 2/1	< 2/1	3,4 cm^3	R, PCV, N
4	AA	65/m	100	I	No	71 cm^3	No	PFS	FI	> 2/1	< 2/1	1,7 cm^3	R,N
5	GM	25/f	100	II	Yes	87 cm^3	No	PFS	FI	> 2/1	< 2/1	31,2 cm^3	R, PCV, N
6	GM	52/m	100	I	Yes	48 cm^3	No	PFS	FI	> 2/1	< 2/1	0,5 cm^3	R,N
7	GM	64/m	100	II	No	42 cm^3	No	PFS	FI	> 2/1	< 2/1	1 cm^3	R,N
8	GM	54/m	100	II	Yes	47 cm^3	Yes		FI	> 2/1	< 2/1	1,79 cm^3	R,T,N
9	AA	68/f	100	III	Yes	96 cm^3	No		FI	> 2/1	< 2/1	0,17 cm^3	R,T,N
10	GM	48/m	100	III	Yes	59 cm^3	No					2,87 cm^3	R,N
11	GM	67/f	100	II	No	43 cm^3	No					10,24 cm^3	R,N,T

Sawaya Scale (16):
I: Area not eloquent, II: Area close to eloquence, III: Eloquent.
State of the last follow-up:
DD: Died by the disease, DAC: Died for another cause, DP: Disease in progression, PFS: Progression free survival.
Degree of coloration:
IF: Intense fluorescent, FT: Fluorescence tenua, NF: no fluorescence.
Adjuvant therapy:
R: Radiation therapy, PCV: procarbazine cisplatin vincristine, T: temozolamide, N: nimotuzumab.
OA: Oligoastrocytoma.
GM: glioblastoma multiforma.
AA: anaplastic astrocytoma.

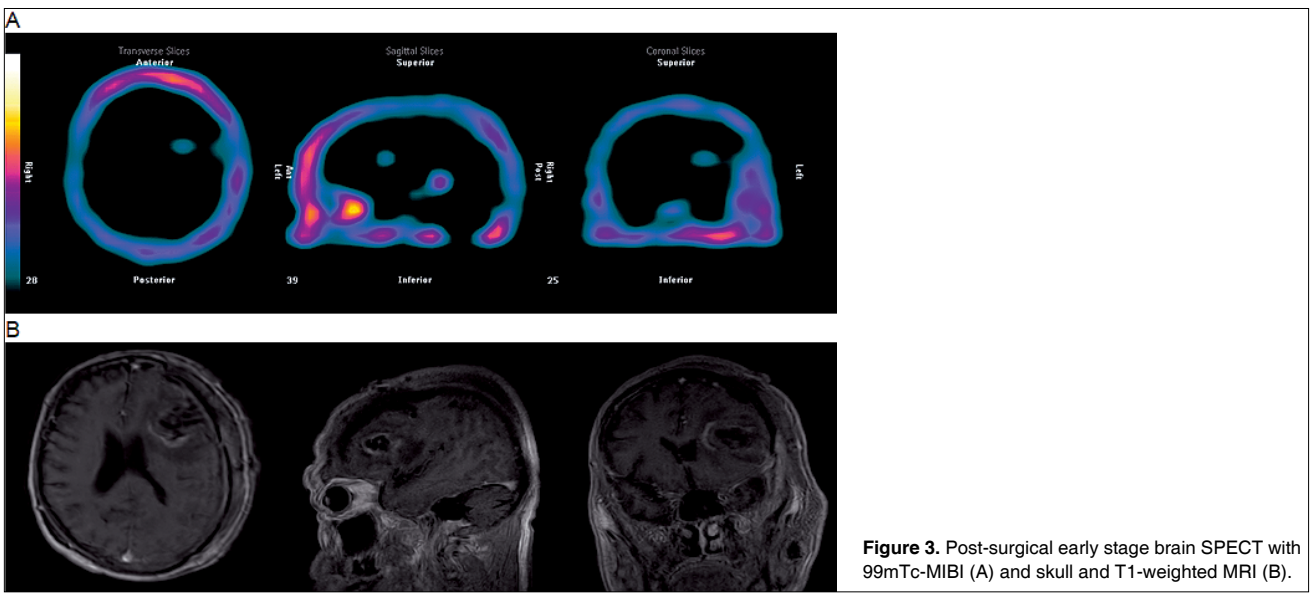

Figure 3. Post-surgical early stage brain SPECT with 99mTc-MIBI (A) and skull and T1-weighted MRI (B).

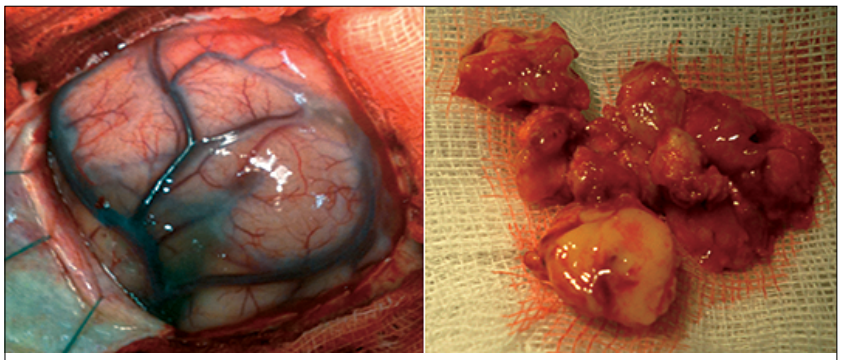

Figure 4. Pre and post intraoperative tumor resection image, notice the yellow colorationto the naked eye. (Visualrange (400-650 nm).

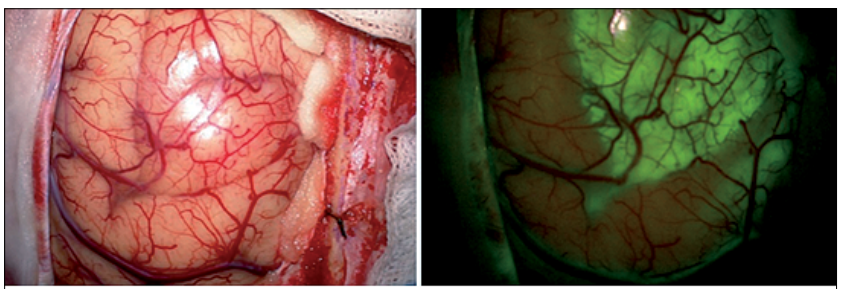

Figure 5. Intraoperative image with and without use of ultraviolet light, fluorescence contacting the injury.(750-1000 nm).

assessing preoperative tumor volume with postoperative tumor volume, they fell, with the lowest rates of postoperative residual volume of recent cases, which is related to the learning curve and have equipment reliability and the location not eloquent area. The background / preoperative injury ratio was in all cases and postoperative > 2 was always < 2, demonstrating that gets done the most complete resection of the lesion and possible to confirm intraoperative real time.

An example of an intraoperative image that shows how the injured tissue is observed with ultraviolet light is shown (Figure 5).

Discussion

The CRG using 99mTc-MIBI is not a common practice in neurosurgery, in our study, the concomitant use of FS, made the procedure had a greater degree of tumor resection. The first description of CRG using Tc99m methoxyisobutylisonitrile Filho Vilela was made in 2002[10], for resection of brain metastases in right parietal lobe, assisted with gamma probe, two years after Kojima et al. report the use of the radiotracer in 13 patients with primary or recurrentes[11] astrocytomas[16], in 2007, Bhanot et al, reported the use of Tc99m methoxyisobutylisonitrile, in a dose of 10 mCi (370 MBq) for assisted resection probe radius 13 patients with gliomas supratentoriales[6,13].

There are reports of other radiotracers como 111In- (DTPA) -D-Phe 1 pentetreotide and 201 Tl in meningioma CRG the first plate and the second in one case report of resection of astrocytoma of the right temporoparietal region[12,25].

In the vast majority of cases reported by different groups complete resection with the help of the gamma probe was performed with no adverse events or postsurgical complication, in the few cases of residual tumor after surgery confirmed by SPECT, the authors explain, the surgeon chose to leave remaining tumor although they indicated the probe due to the location in eloquent areas and little technical experience, which made them hesitate to continue the surgery[10,13].

The radiation exposure of operating staff 99m Tc-MIBI has been previously investigated[11]. The average whole body dose equivalent case was 25.8 and 27.9 14,9 μSv respectively for the surgeon, nurse and anesthesiology[12]. The United States Nuclear Regulatory Commission (USNRC) has set the annual occupational exposure limit for adults and total effective dose equivalent 50,000 μSv and The International Commission on Radiological Protection (ICRP) has set an occupational exposure limit annual total dose for adults 20,000 μSv effective by year[13].

The clinical trial from Schaafsma et al., evidenced that green indiocianina uses associated with Tc99m-nanocolloid in 32 patients with breast cancer, for detecting sentinel nodes, applying by local injection peri-areolar, concluding the accuracy for detecting pre and intraoperative lymph affected, just as the shown by Brouwer studies et al. and van den Berg et al. with 11 and 14 patients respectively[22,26], coinciding these studies in which the injection is local[21,22,26].

Using fluorescein sodium significantly increases the degree of tumor resection, Díez-Valle et al, found areas of vague color matching infiltrated by tumor cells, areas which are not displayed on the proven resonance[27], obviously resection of these areas are crucial as a way to prevent recurrence and malignant progression of these tumoraciones[15,17,18,23,24]. Some studies suggest that the use of high doses of sodium fluorescein is a useful agent intraoperative even without using equipment for visualización[28]. Shinoda et al., report on their study, that the degree of tumor resection total increase significantly with the use of FS at a dose of 20 mg / kg to 32 patients obtaining total resection in 27 of them to 84.4%, a significant difference when we compared with the level of total resection of the group control[29].

Koc et al, reported in their work a higher rate of complete resection with the use of guide FS in 47 patients in the control group, only 39 of them complete resection (83%) was achieved, compared to 18 patients (54.5%) in the control group[30].The study Chen Bo et al., in 2012 see light areas of contrast uptake around the tumor, which corresponded to areas adjacent edema, similar to that observed with the use of 5-ALA-Valle[17]. Díez et al., reports that these areas correspond to areas potentially infiltrated by tumor cells, this same mechanism

applies to the use of the FS and resection of these areas does not give the necessary safety margin to prevent and / or reduce recurrencias[27].

The fluorescent staining can be detected with high sensitivity, excitation of a fluorescent color is achieved by internal conversion in the emission of photons of different wavelength ranges, ondas[22,31-34]. Each color has its own fluorescent excitation and emission in wavelength fluorescent colors are emitted in the visual range (400 - 650 nm), which can be detected by the eye without special assistance (Figure 3) detection is generally more sensitive when using a camera with fluorescencia (Figure 4). Using dedicated systems, filters, lights the detection of fluorescent signals (photons) is similar to the rays gamma[35]. One of the drawbacks of the local use of substances such as sodium fluorescein dyes are detected, is that the depth that traverses the tissue is very limited, to increase the depth range, has set the use of near infrared dyes emission in the range (750 - 1,000 nm), with a tissue penetration of less than 1 cm, one of the most used is the Green Indiocianina, it is the most widely used dye for procedures of node biopsies in patients with breast cancer and melanoma vulvar[36].

Conclusions

RFG technique proves useful for total tumor resection without causing new neurological deficit or increase existing ones, this is not further increase in the complexity of the surgery, or surgical times. No adverse effects to the administration of the radiopharmaceutical was evident. The RFG is a new treatment modality that can be used as a tool in the procession of technical support tumor surgery, requiring future studies with evidence level IA, to validate its use as a standard technique.

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