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

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Abstract

Glioblastoma Multiforme is the most frequent primary malignant CNS tumor in adult's. Multimodal therapy (surgery, radiotherapy, chemotherapy) achieved a median survival of 14 to 16 months, two years to the 26-33% and less than 5% to the five years. The gross total resection of glioma is directly proportional to the Increase of the survival. 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. The fluorescein sodium (FS) is a water-soluble organic coloring substance used in the vascular circulation exam of the eye. We carried out the report of eleven cases with high grade glioma to demonstrate the Radio-Fluro-guided Surgery utility (RFG). We can achieve gross total resections without bigger deficit. Conclusion. 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- fluoro guided surgery, radiotracer.

Resumen

El glioblastoma multiforme es el tumor maligno primario del SNC más frecuente en adultos. La terapia multimodal (cirugía, radioterapia, quimioterapia) logró una supervivencia media de 14 a 16 meses, A dos años el 26-33% y menos del 5% a los cinco años. La resección total bruta de glioma es directamente proporcional al aumento de la supervivencia. MIBI o sestamibi tiene una gran disposición para el rico flujo de fotones, lo que mejora la detección de captación patológica con sonda gamma; estas propiedades físicas hacen que la elección sea adecuada para este radiotrazador a la cirugía guiada por radio. La fluoresceína sódica (FS) es una sustancia colorante orgánica soluble en agua utilizada en el examen de circulación vascular del ojo. Se realiza el informe de once casos con glioma de alto grado para demostrar la utilidad de cirugía guiada por radio-fluoro (RFG). Podemos lograr resecciones totales brutas sin mayor déficit. Conclusión: La técnica de RFG demostró utilidad en la resección total del tumor, disminuyendo el tumor residual sin cirugía que aumente la complejidad y los tiempos quirúrgicos. En nuestro estudio no hay evidencia de efectos adversos para la administración de MIBI y FS.

Palabras clave: Sonda gamma, cirugia guíada por radio-flúor, radiotrazador.

Introduction

In 1896 Becquerel discovers natural radioisotopes and De Hevesy invents the principle of "tracer" through his work with lead radiactivo[1]. 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].

The MIBI (MIBI- 99mTc, methoxyisobutylisonitrite, 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, com-

pared to other as thallium-201[2]. It was first described in 1980, to detect myocardial perfusion in coronary disease[2, 3].
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 para-ventricular regions[3].
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[4-11].
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[6].
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[13].
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 levulinic Acid (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[15]. 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[17].
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[17-22]. 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 phthalocyanine Tetrasulphonate) 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[8].
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[2].
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[10].
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[23, 24, 25].
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.

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 may 2017 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 breast-feeding.
- 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.[11,12] Tumor volume was calculated by the computerized planimetric method and formula for the volume of an ellipsoid $V = 4/3\ \pi$ (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:[13]

- 35 cm^3 Large.
- $\leq$ 35 cm^3 Small.

For postoperative volumetric assess we use the following nominación[14].

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.

Dye uptake (FS): To describe the uptake of dye used the nomination submitted by Bo Chen[15] et al, in their publication *Gross Total Resection of Glioma with the Intraoperative Fluorescence guidance of Fluorescein Sodium* at 2012, where classified.: For a definition

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

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 informed of 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-fluro guided 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 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 pa-

N	Diagnóstico	Edad/ Sexo	Karnosfky	Sawaya[1]	Deficit motor Pre-op	Volumen tumoral Pre-op	Deficit motor Post-op	Estado[2]	Coloración[3]	Lesión/ fondo Pre-op	Lesión fondo Post-op	Volumen tumoral Post-op	Terapia adyuvante[4]
1	GBM	48/m	100	II	Si	123 cm^3	No	FE	FI	> 2/1	> 2/1	63,5 cm^3	R, PCV, N
2	OA grado III	55/f	100	III	No	65 cm^3	No	PFS	FI	> 2/1	> 2/1	11,4 cm^3	R, N
3	GBM	70/m	100	III	Si	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	GBM	25/f	100	II	Si	87 cm^3	No	PFS	FI	> 2/1	> 2/1	31,2 cm^3	R, PCV, N
6	GBM	52/m	100	I	Si	48 cm^3	No	PFS	FI	> 2/1	> 2/1	0,5 cm^3	R, N
7	GBM	64/m	100	II	No	42 cm^3	No	PFS	FI	> 2/1	> 2/1	1 cm^3	R, N
8	GBM	54/m	100	II	Si	47 cm^3	No		FI	> 2/1	> 2/1	1,79 cm^3	R, T, N
9	AA	68/f	100	III	Si	96 cm^3	Si		FI	> 2/1	> 2/1	0,17 cm^3	R, T, N
10	GBM	48/m	100	III	Si	59 cm^3	No		FI	> 2/1	> 2/1	2,87 cm^3	R, N
11	GBM	67/f	100	II	No	43cm^3	No		FI	> 2/1	> 2/1	10,24 cm^3	R, T, N

[1]Grado de localización funcional según Sawaya:
I Área no-elocuente
II Cercana a la elocuencia
III elocuente
[2]Estado al último seguimiento:
FE: fallecido por la enfermedad
FO: Fallecido por otra causa
EP: Enfermedad en progresión
SLP: sobrevida libre de progresión
[3]Grado de coloración:
Fluorescencia Intensa(FI)
Fluorescencia Tenue (FT)
No Fluorescencia
[4]Terapia Adjunta:
R: Radioterapia.
PCV: Procarbacina, Cisplatino, Vincristina.
T: Temozolamida
N: Nimotuzumab
OA: Oligoastrocitoma
GBM: Glioblastoma Multiforme
AA: Astrocitoma Anaplásico

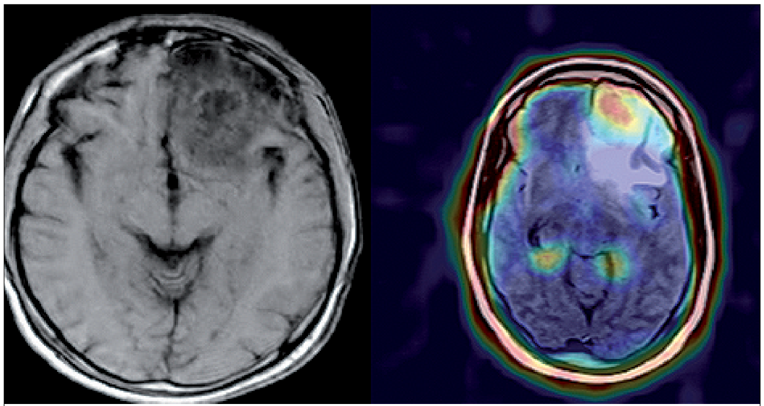

Figure 1. T1 weighted MRI simple skull and brain SPECT 99mTc-MIBI. Pre-operative.

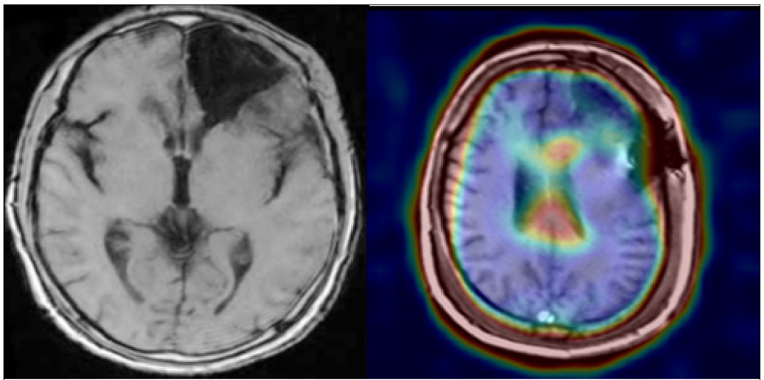

Figure 2. MRI T1 weighted skull and brain SPECT with 99m Tc-MIBI. Post-operative.

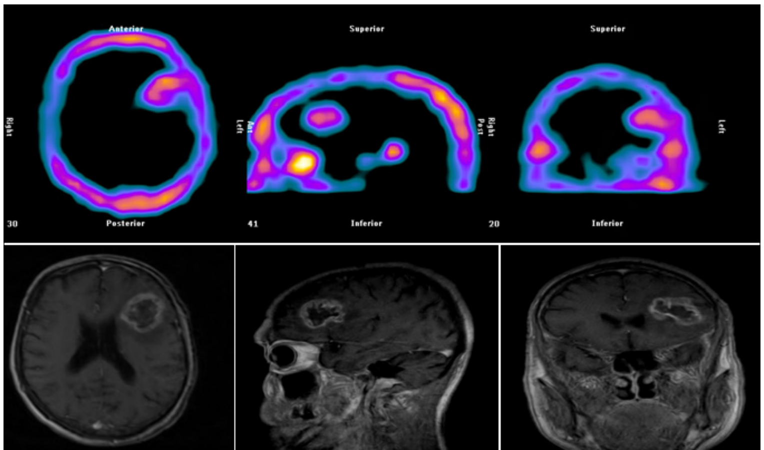

Figure 3. Early stage brain SPECT with 99mTc-MIBI. Pre-operative skull and T1-weighted MRI.

tients, average age was 55 years, eight patients were diagnosed GBM, and the remaining two AA with Oligoastrocytoma grade III.

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.

In conducting an assessment in the immediate postoperative cases with motor deficit improved by 90% and improved one part, maintaining a distal brachial 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 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.

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 methoxyisobutyl isonitrile Filho[7] Vilela was made in 2002, for resection of brain metastases in right parietal lobe, assisted with gamma probe, two years after Kojima[8] et al., report the use of the radiotracer in 13 patients with primary or recurrentes[8], astrocytomas[16], in 2007, Bhanot[3] et al reported the use of Tc99m methoxyisobutyl isonitrile, in a dose of 10 mCi (370MBq) for assisted resection probe radius 13 patients with gliomas supratentoriales[3,10].

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

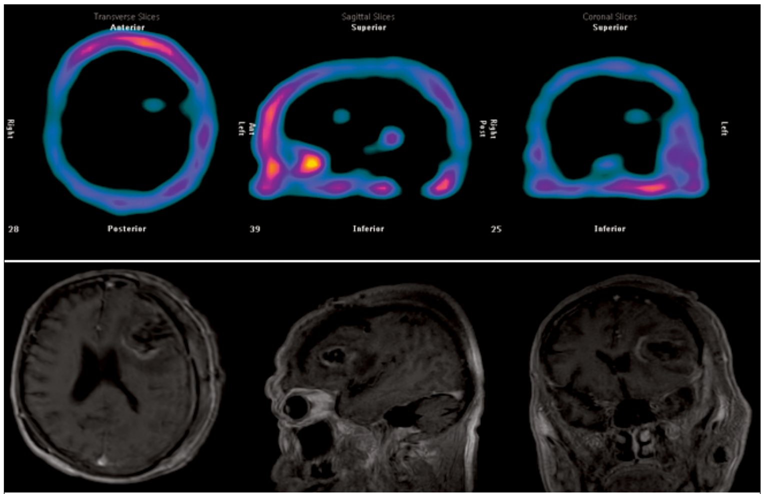

Figure 4. SPECT with 99m Tc-MIBI Post-operative skull and T1-weighted MRI.

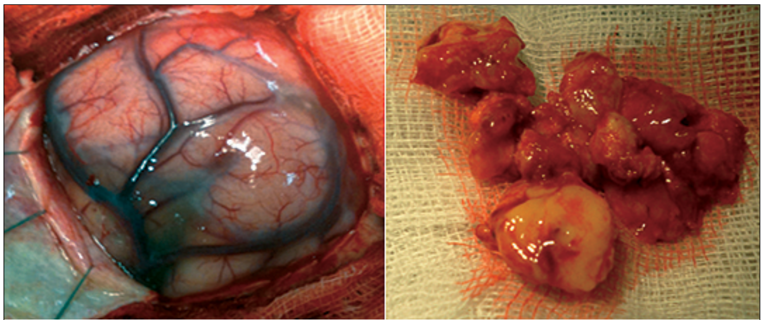

Figure 5. Pre and post intraoperative tumor resection image, notice the yellow coloration to the naked eye. (Visual range (400-650 nm).

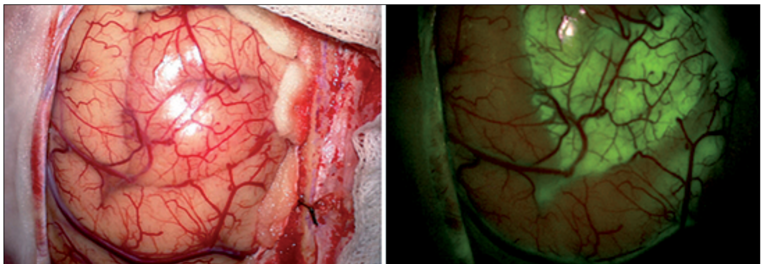

Figure 6. Intraoperative image with and without use of ultraviolet light, fluorescence contacting the injury. (750-1,000 nm).

of the right temporoparietal region[5,9].
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[7,10].
The radiation exposure of operating staff 99m Tc-MIBI has been previously investigated[8]. The average whole body dose equivalent case was 25.8 and 27.9 14,9 µSv respectively for the surgeon, nurse and anesthesiology[9]. 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[10].
The clinical trial Schaafsma[24] et al., 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[25] studies et al. and van den Berg[26] et al., with 11 and 14 patients respectively, coinciding these three studies in which the injection is local[24,25,26].
Using fluorescein sodium significantly increases the degree of tumor resection, Díez-Valle[27] 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[12-17]. 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[29] 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[23] 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[23]. The study Chen[15] Bo et al., in 2012 I 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[27] 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[16-29].
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[30,31,32]. 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 5) detection is generally more sensitive when using a camera with fluorescencia[30]. (Figure 6) Using dedicated systems, filters, lights the detection of fluorescent signals (photons) is similar to the rays gamma[30]. 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[33].

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.

Recommendations

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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