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Role of neurosurgery in brain metastases management

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by SOLTI

Brain metastases: current scenario

- About 30 % of neoplasms have brain metastases
- Nowadays systemic treatments are increasing survival
- Systemic treatments have difficulty crossing the blood brain barrier
- Total brain metastases resection can increase survival

The important role of surgery

EANO guidelines for brain metastases surgery (2017)

- Surgical resection should be considered in patients with a limited number (1 to 3) of newly diagnosed brain metastases, especially in case of lesions of >3 cm in diameter (symptomatic or not), lesions with necrotic or cystic appearance and edema/mass effect, lesions located in the posterior fossa with associated hydrocephalus, and lesions located in symptomatic eloquent areas

- Surgical resection is recommended when the systemic disease is absent/controlled and the KPS is 60 or more, as it can prolong survival (level A)

- Surgical resection can be an option when the systemic disease is active but effective systemic treatment options are available or when the primary tumor is relatively radioresistant (melanoma, renal carcinoma, colon carcinoma)

Soffietti R, Abacioglu U, Baumert B et al " Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuroncology (EANO), Neuro-Oncology, 2017, 19(2),162-174

What should and can offer surgery today?

Planning surgery

- Functional MRI
- DTI images *(tactography)*
- TMS *(transcranial magnetic stimulation)*
- Planning approaches for more than one metastases

Basic principles for M1 resecction

Surgical tumor visualization

Visualization of tumor extension

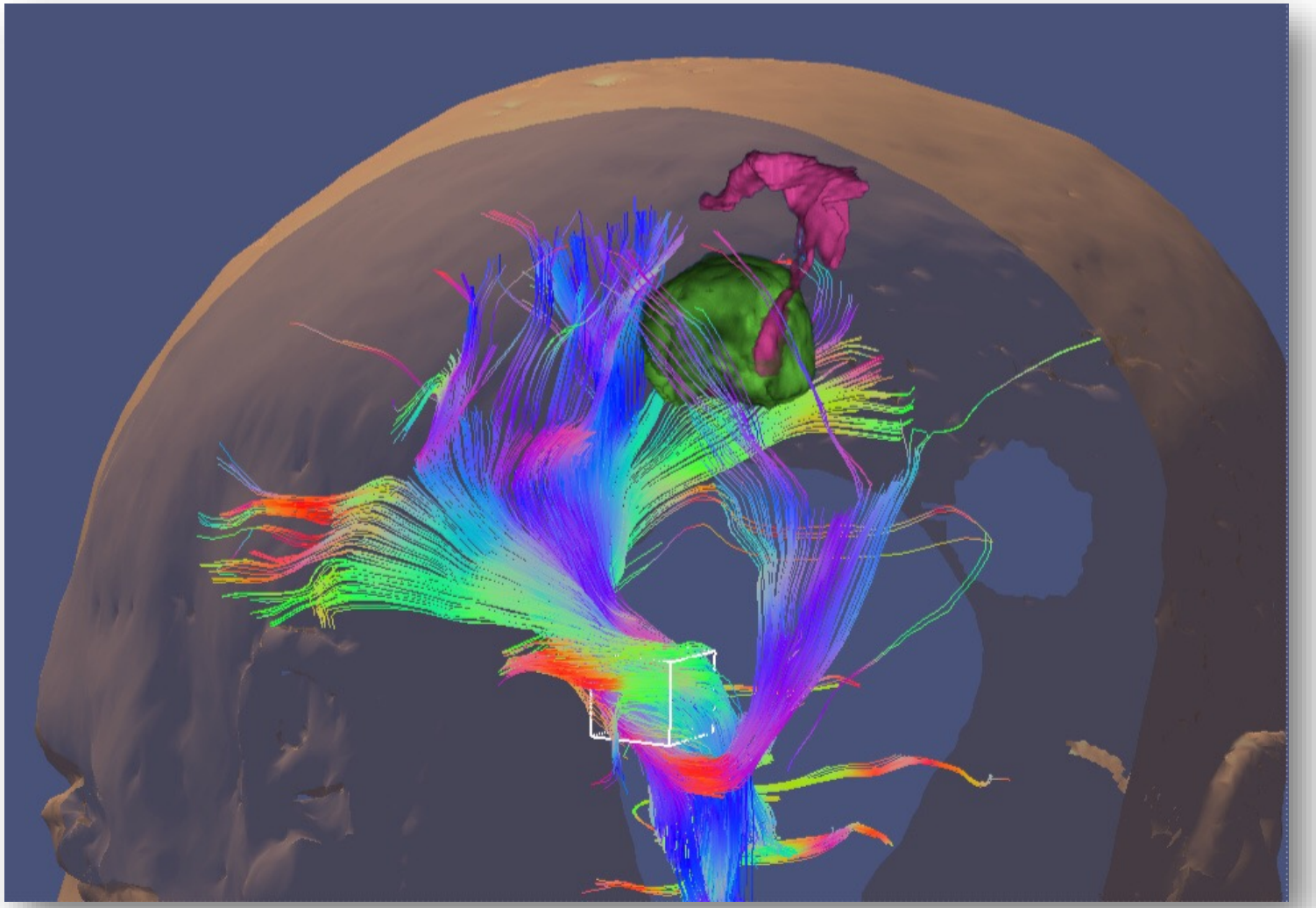
- Supramarginal and en bloc resection
- Intraoperative neurophysiological monitoring
- Intraop. MRI, intraop. ecography
- Intraoperative fluorescent dyes
- Confocal laser endoscomicroscopy (CLE)
- Raman spectroscopy

Other treatments beyond resection with neurosurgical collaboration

- Intraoperative radiotherapy
- Braquitherapy
- Gliadel
- LITT *(laser interstitial thermal therapy)*
- tcMRgFUS *(transc. MR guided focused ultrasound)*

Presentation index

1. Preoperative surgical image study



- The preoperative workup of brain metastases center on neuroimaging. If the metastasis is adjacent or near to an eloquent area (motor or language function) some image techniques are mandatory to can predict the risk of neurological complications.

- Sometimes, the metastasis is not adjacent to an eloquent area, but the surgical approach
- can be near an eloquent area.

- There are 3 kinds of image that can inform about the functional metastasis localization:

    - Functional MRI (motor or language). Motor function evaluated under functional MRI can offer an accurate localization of motor cortical area. Language function evaluated under functional MRI can offer a moderate accurate localization of language cortical area

    - Diffusion tensor image (DTI). It is an image technique of MRI that analyze neural networks. It is more accurate with pyramidal tract (motor function), but is less accurate with tracts for language function

    - Transcranial magnetic stimulation (TMS). It is a no invasive procedure that use magnetic field to stimulate brain cells. This technique allow to know motor or language areas round the tumor with a great accuracy (motor area with more accuracy than language)

All these techniques can predict the distance between the tumor and the motor or language area, but the gold standard, the technique with the most accuracy ,is the intraoperative mapping

1. Weng H, Noll K, Johnson J Radiology, vol 286, vol2 2018; 2. Wiwer BP, Moftakhar R, Hasan KM et al J Neurosurg 2002 97(3):568-75; 3. Krieg SM, Picht T, Sollmann N et al Front Oncol 2016;6;261; 4. Barajas RF, Cha S Neuroimaging Clin N Am. 2016;26(4):601-620; 5. Tan TC, Black PM "2007;61(1 Suppl):349–56; dis- cussion 356; 6. Lucas C, Tursunova I, Neuschmelting V Neyuroimage Clin 2017;13:297-309.

Image 1. Functional MRI (motor function). Tumor (dark grey) is adjacent to hand motor area (red)

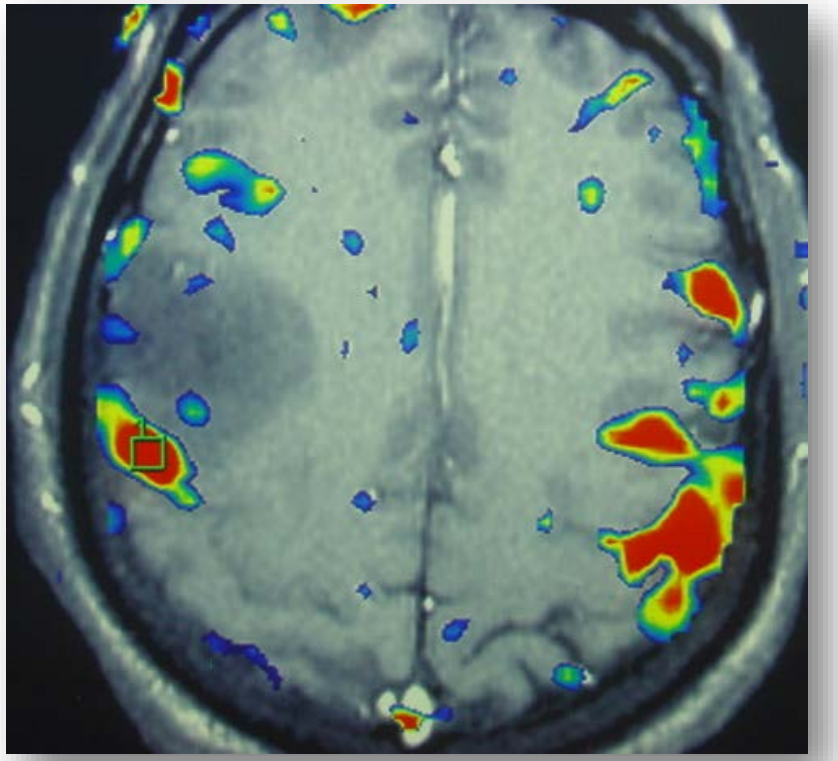
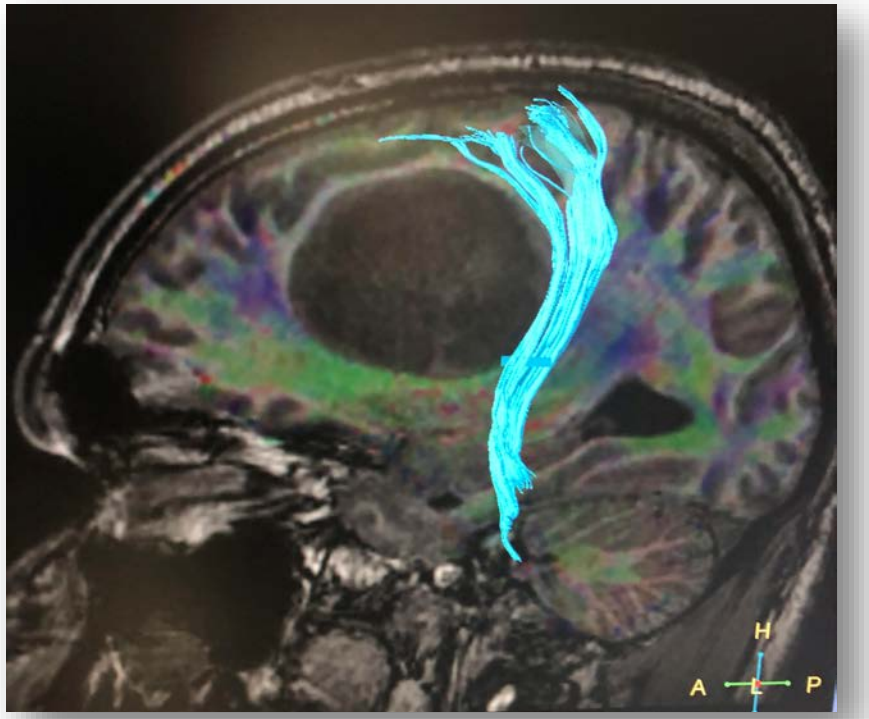


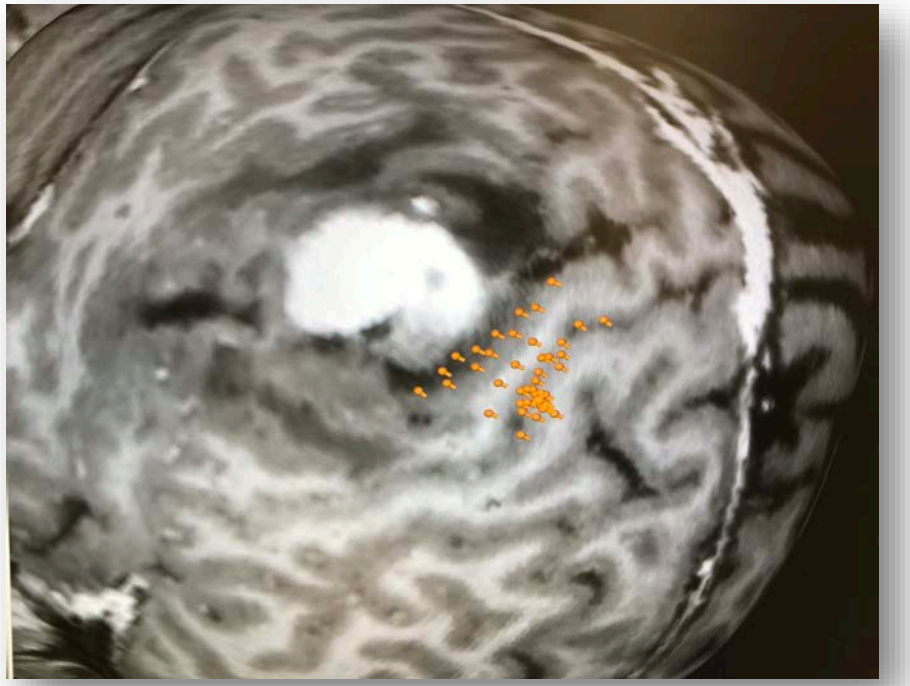
Image 2. DTI MRI , the blue tract represents the pyramidal tract. The metastasis is just anterior and adjacent to the motor area.



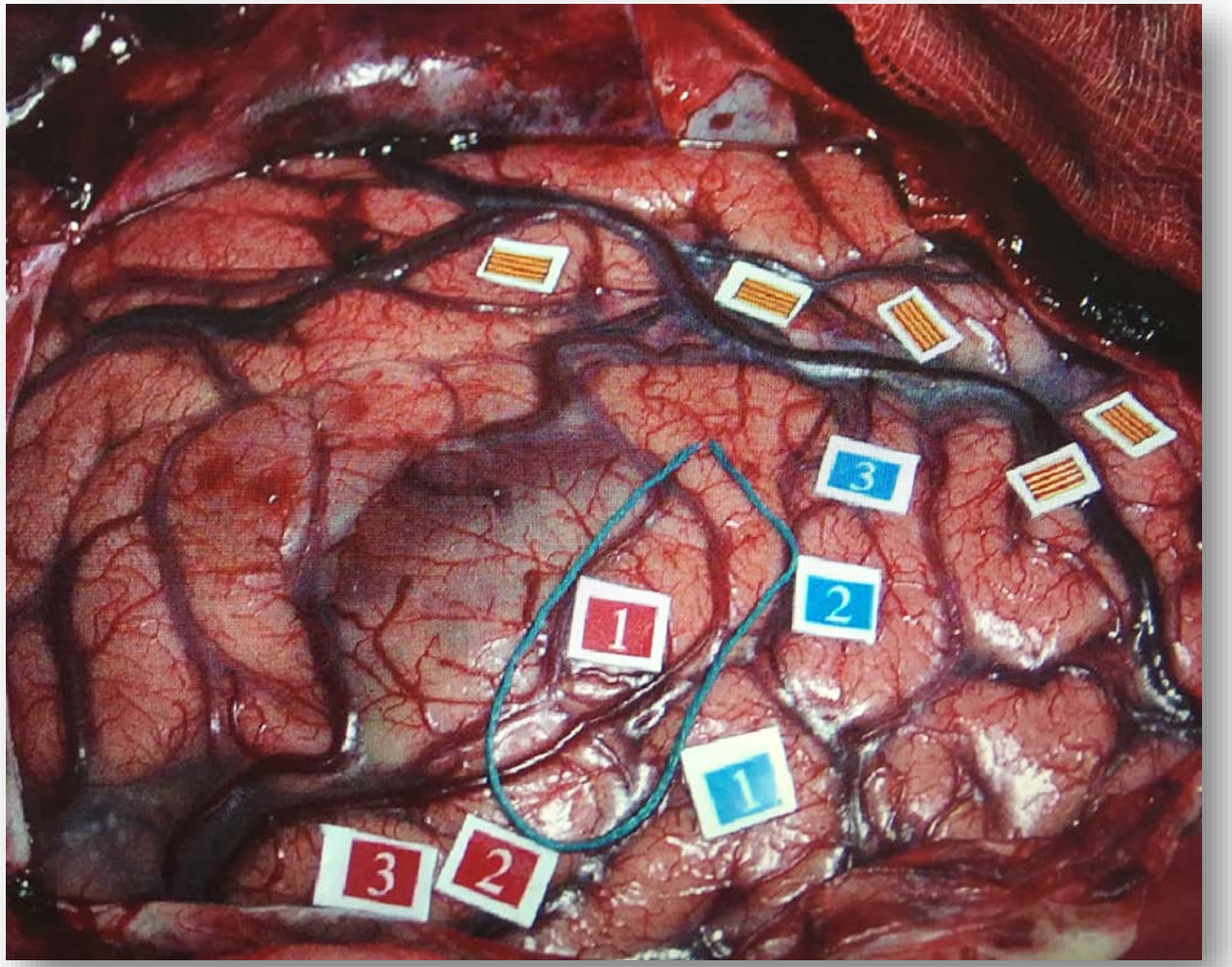
Transcranial magnetic stimulation (TMS)

Image 1. Patient performing TMS by neurophysiologist.

Image 2. Orange points show arm motor area adjacent to the metastases.



2. Intraoperative neurophysiological monitoring



- For metastases in eloquent brain areas, mapping of critical functions (motor or language) must be performed intraoperatively (gold standard)

- Neurophysiologic techniques for intraoperative motor monitoring use cortical responses to peripheral inputs and direct cortex stimulation with recording of the motor response peripherally.

- Motor evoked potentials (MEP) monitoring can be obtained:

    1. By the use of transcranial electrodes
    2. The use of cortical strips placed over motor area (Direct current stimulation)
    3. Cortical and subcortical direct stimulation with a stimulator

- Somatosensorial evoked potentials can be monitored through transcranial electrodes and with cortical strips

Transcranial electrodes stimulation offers the opportunity to record MEP from the beginning of the surgery to the end, and to monitor both hemispheres. Cortical strips over motor area , uses lower current intensities, and MEP are registered from dura opening to closure. The use of a stimulator allows a more precise answer, cortical and subcortically.
MEP monitoring is predictive of motor outcome. The occurrence of reversible of irreversible loss of MEP during the procedure is associated with a high chance (80%) of developing motor deficits and poor motor outcome.

- The use of motor mapping improves resection and outcomes in patients with tumors involving motor pathways.

About awake surgery for mapping motor or language function:

- For monitoring language functions, awake surgery is needed. Direct cortical or subcortical stimulation with a stimulator allows identify difficulties in language functions (anomia, paraphasia...). The participation of a neuropshychologist during language monitoring is preferred.
- Motor function can be mapping under awake or asleep surgery.
- Several groups posit that intraoperative monitoring and mapping using MEP under general anesthesia improves extent of resection, although MEP can have an associated false negative rate.
- Cortical stimulation has a risk or seizures during surgery. In awake patients a generalized seizure with the t head fixed by the craniostat and a opened duramater, can lead to some complications.
- . Numerous studies have demonstrated safety and feasibility of awake craniotomy for brain metastases located in motor or speech areas, with 76 % of patients showing improvement or stability of neurologic function immediately postoperatively. Of the 24 % with worsening postoperative neurologic symptoms, 96 % experienced long-term improvement.

- In the absence of high quality prospective data, selection of awake versus asleep craniotomies depends on surgeon preference, anesthesia familiarity, quality of preoperative and intraoperative mapping and monitoring, and individual patient selection.

- The great part of metastases are corticosubcortical, and the greatest use of monitoring is for mortor or language function. But in some cases the metastasis need a different neurophysiological monitoring:

    - Monitoring of cranial nerves is mandatory in metastases adjacent to cranial nerves (pontocerebellar localization, adjacent to the brain stem, skull base localization)

    - Monitoring of optic path is possible with visual evoked potential

1. Chua TH, See AAQ, Ang BT et al. World Neurosurg2018;120:e1128-35; 2. Sanmillan JL, 2016, J Neurosurg 2016:1-10; 3. Lee SJ, 2016 , Brain Tumor Res Treat, 4(2):70-76; 4. Kellogg RG,,2013, Surg Neurol Int, 17;4:66; 5. D´Andrea G, 2012, Neurosrug Rev, 35(3):401-412; 6. Wang J, Bradley Elder J Neurosrug Clin N Am 31,2020,527-536; 7. Groshev A, Padalia D, Patel S et al Clin Neurol Neurosurg 2017;157:25-30; 8. Berger MS, Ojemann Ga Stereotac Funct Neurosurg 1992;58(1-4): 153-61; 9. Obermueller T, Schaeffner M, Shiban E et al BMC Neurol 2015;15;211.

Image 1. Transcranial stimulation

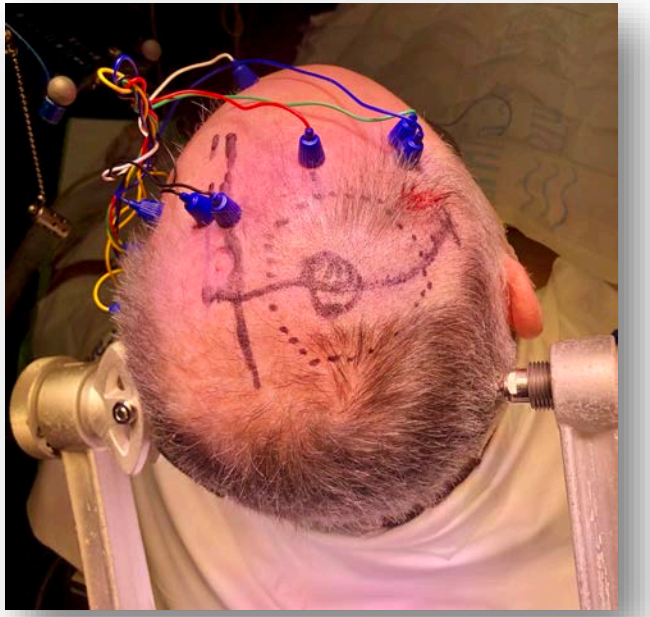


Image 2. Cortical stimulation with a strip grid

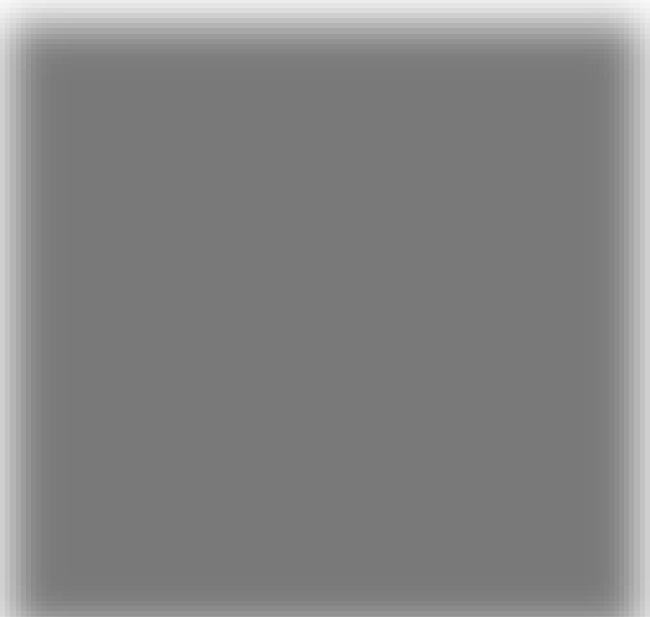
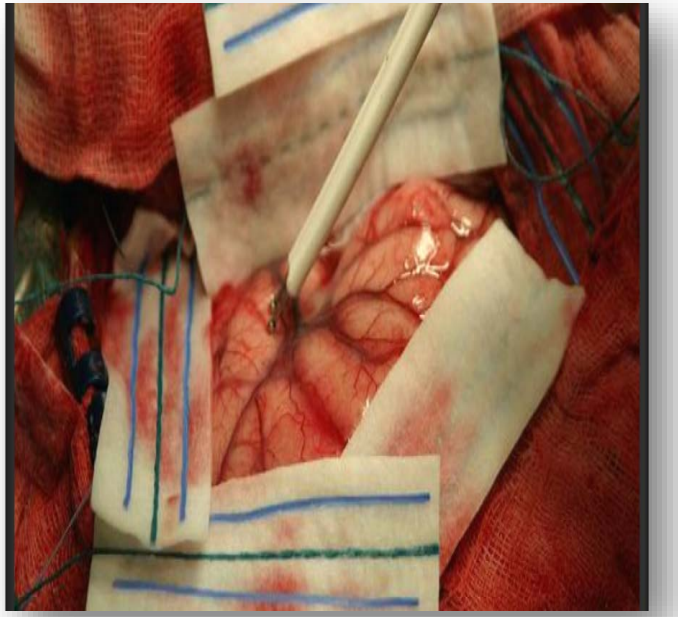
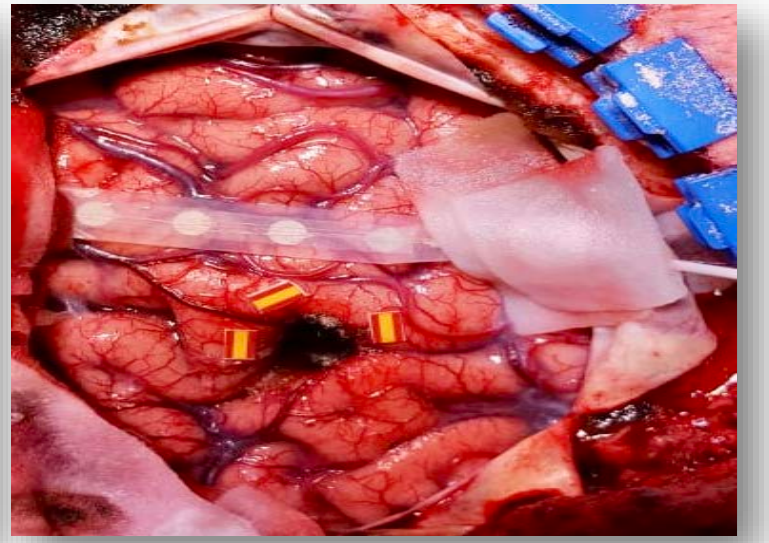
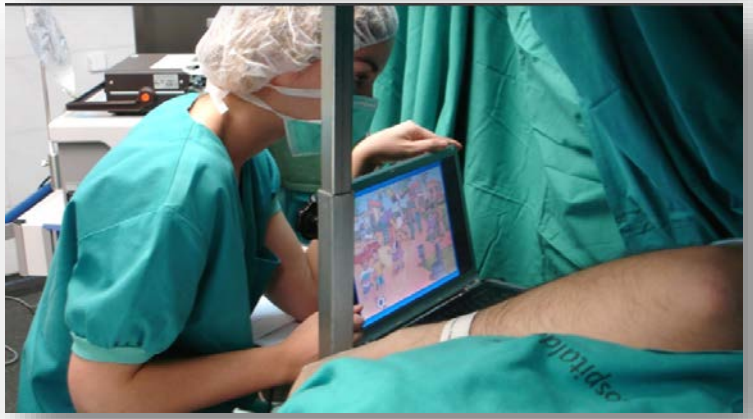


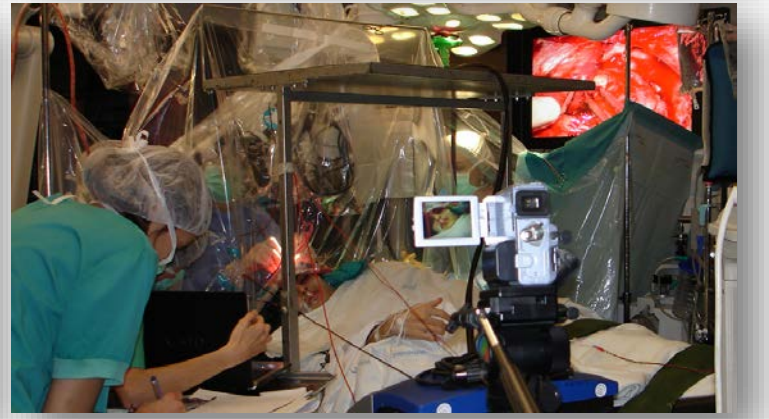
Image 2. Cortical stimulation with a stimulator



Images during awake surgery for a metastasis en Broca area







3. Supramarginal resection

- Tumor infiltration has been reported in the setting of brain metastases although metastases have a gliotic pseudocapsule.
- The depth of the infiltration is <5 mm.
- About 63 % of brain metastases in autopsies have a parenchyma infiltration.
- Supramarginal resection: Microscopic total resection.
- Gross total resection (GTR) is not the same that Supramarginal resection.
- Supramarginal resection is feasible in eloquent area (with intraoperative neurophysiological monitoring).
- When supramarginal resection: 23% local recurrence, if not supramarginal resection: 43% local recurrence.
- Some studies have shown that greater extent of surgical resection prolongs survival only in cohorts with controlled extracranial disease.

1. Baumert BG, 2006,Int J Radiat Oncol Biol Phys 66(1):187-194; 2. Kamp MA, 2012, Acta Neurochir 154(11):1981-1986; 3. Yoo H 2009, J Neurosurg 110(4):730-736;
4. Berghoff AS 2013, Neuro Oncol 15 (12):1664-1672; 5. Siam L, 2015, Oncotarget 6 (30):29254-29267; 6. Kamp MA, 2015, Acta Neurochir 157(6):905-910.

4. En bloc resection

- En bloc resection: no piecemeal fashion resection
- Continuous visualization of the tumor borders during resection and avoiding dispersion of tumor : No exposing surrounding cortex and/or white matter to malignant cells
- The center of the metastasis can be vascular, en bloc resection avoid bleeding that can darken the tumor boundaries
- No en bloc resection has 1,7 times more local recurrence versus en bloc resection
- Local recurrence: 5,7 % with en bloc resection versus 13,9 % with no en bloc resection
- En bloc resection is very important in posterior fossa metastases for the high risk of leptomeningeal dispersion
- Currently there are publications and studies underway on the application of preoperative radiotherapy instead of postoperative, with the intention of irradiating all tumor cells, before they can spread with surgery.
- A retrospective analysis of patients who underwent either preoperative radioteraphy or postoperative radiotherapy, finding a lower incidence of leptomeningeal disease with preoperative . Authors conclude that single fraction neoadjuvant radiotherapy confers excellent local control with very low risk of radio necrosis or leptomeningeal disease (4.8% and 4.3%, respectively, at 2 years). Given this favorable early data, multiple prospective trials investigating the utility of neoadjuvant radiotherapy (NCT01891318, NCT03163368, NCT03368625) are currently accruing

1. Patel AJ, 2010, J Neurosurg 113(2):181-189; 2. Suki D,2008, J Neurosrg 108 (2):1664-1672; 3. Salvati M, 2018, Neurological Sciences39(4):671-677; 4. Ahn JH, 2012, J Neurosurg 116(5):984-93; 5. Patel KR, Burri SH, Asher AL, et al. Neurosurgery. 2016;79(2):279-285; 6. Prabhu RS, Miller KR, Asher AL, et al. J Neurosurg. 2018;1-8.

5. Intraoperative image

- The utility of preoperative image for neuronavigation, however is diminished by the well characterized phenomenon of brain shift, in which the brain deforms intraoperatively as a result of craniotomy, swelling, gravity, tumor resection, cerebrospinal fluid drainage, and many other factors. As such, there is a need for updated intraoperative information that accurately reflects intraoperative conditions:

- **Intraoperative ultraosund.** Is widely used and is the least expensive and least complex option with rapid and repeatable use. Given a high density of tumor cells in comparison with normal brain tissue, brain metastases are often hyperechoic on ultrasound and easily distinguishable from the surrounding anatomy. *In multiple trials, use of intraoperative ultrasound increases extent of resection and postop. KPS.* It has false positives and negatives

- **Intraoperative MRI (iMRI).** Has become more widespread in their use but are still limited by cost. iMRI can update frameless navigation systems, assess extent of resection, and identify surgical complications. However, the additional workflow associated with iMRI is not as convenient as intraoperative ultrasound. Because most brain metastases are well circumscribe, the use of iMRI in neurosurgurgical oncology has usually focused on glioma. In a study of 163 patients, iMRI was associated *with increased extent of resection in all enhancing lesions, including gross total resection in 73 % of metastases.*

- **Intraoperative CT**. IT has workflow and applicability advantages over iMRI,but are limited by their soft tissue definition. As such, intraoperative CT is most useful for tumors invading the skull base.

1. G. E. Keles, Current Opinion in Neurology, vol. 17, no. 4, pp. 497–500, 2004; 2. F. Lindseth, J. H. Kaspersen, S. Ommedal et al., Computer Aided Surgery, vol. 8, no. 2, pp. 49–69, 2003; 3. Bayer S, Maier A, Ostermeier M International Journal of Biomedical Imaging Volume 2017, Article ID 6028645, 18 pages https://doi.org/10.1155/2017/6028645; 4. Rahul S, Wenya , Steve P J Neuroimaging. 2017 January ; 27(1): 5–15; 5. Livne O, Harel R, Hadani M et al World Neuyrosur 2014;82(5);770-6; 6. Lindner D, Trantakis C, Renner C et al Minim invasive Neurosurg 2006;49/4):197-202; 7. Schichor C, Terpolilli N, Thorsteindsdottir J et al Neurosurg Clin N Am 2017;28(4);595-602; 8. Garcia-Baizan A, Tomas-Biosca A, Bartolome Leal P et al Radiology 2018;60(2):136-42

6. Surgery for more than one brain metastases

- Between 30-50% of all brain metastases patients present with multiple lesions, depending on the primary cancer type
- In contrast to single brain metastasis, in with the beneficial role of surgical resection has been established by prospective trials, no class I evidence exists for the patient population with multiple brain metastases. Some studies have demonstrated that, if all lesions are removed, the survival outcome in patients with multiple brain metastases is no longer inferior to patients with single lesion
- In some studies the most prominent prognostic factor was the postsurgical KPS, regardless of the number of lesions
- Although no class I evidence is available, surgical resection in patients with multiple lesions can reduce neurological symptoms and improve functional independence
- The trend is to operate the lesion or the lesions (normally 2, rarely 3) with mass effect, and the other lesions are treated with radiotherapy
- In general, small craniotomies are preferred, and for multiple metastases surgery, the concept has more interest
- Minimally invasive approaches are refinements of conventional craniotomies and particularly useful for minimizing approach morbidity for deep seated tumors:

- *Keyholes*: studies have shown that keyhole approaches minimize soft tissue and bone trauma, decrease postoperative complications, and improve cosmetic results

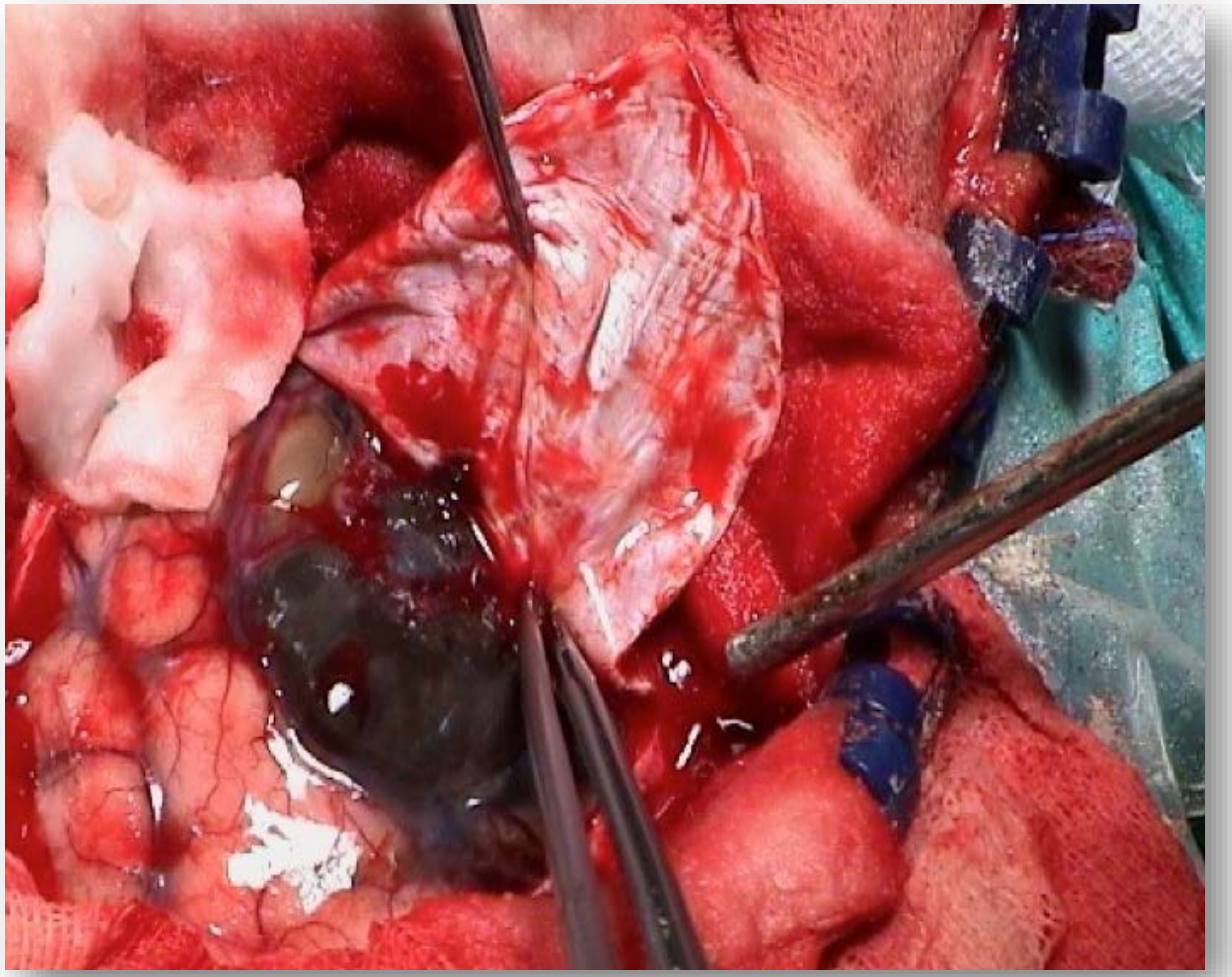
- *The supraorbital "eyebrow" craniotomy* is a variation of the standard pterional or orbitozy-gomatic craniotomies that provides access to the frontal pole and subfrontal , suprasellar, and retrosellar regions without frontal lobe retraction

- *Tubular retractors:* This kind of retractors allow dilation and maintenance of the operative corridor while minimizing retractor induced injury, to access deep seated lesions. Though most commonly used for subcortical and periventricular lesions, tubular retractors can also facilitate high efficacy, low morbidity resection of brain metastases in the posterior fossa

- The use of endoscopes and exoscopes can facilitate surgery in deep seated lesions with a small access

1. Baker C, Glenn C, Briggs R, World Neurosurgery,106;359-367, 2017; 2. Gazzeri R, Nalavenkata S, Teo C Clinical Neurology and Neurosurgery 2014, 123;117-126; 3. Bidal RK, Sawaya R, Leavens ME et al J Neurosurg 1993;70(2);210-6; 4. Iwadate Y, Namba H, YamauraA Anticancer Res 2000;20(1B):573-7; 5. RazaSM, Garzon-Muvdi T, Boaehene K et al 2010;53(1):1-8; 6. Gassie K, Alvarado-Estrada K, Bechtle P et al J Neurol Surg A Cent Euro Neurosurg 2019;80(3):198-204; 7. Salvati M, Tropeano MP, Maiola V, et al. Neurol Sci. 2018;39(4):671–677; 8. Reisch R, Stadie A, Kockro RA, Hopf N. World Neurosurg. 2013;79(2 Suppl):S17.e9–S17.13; 9. Zammar SG, Cappelli J, Zacharia BE. Cureus. 2019;11(3):e4272.

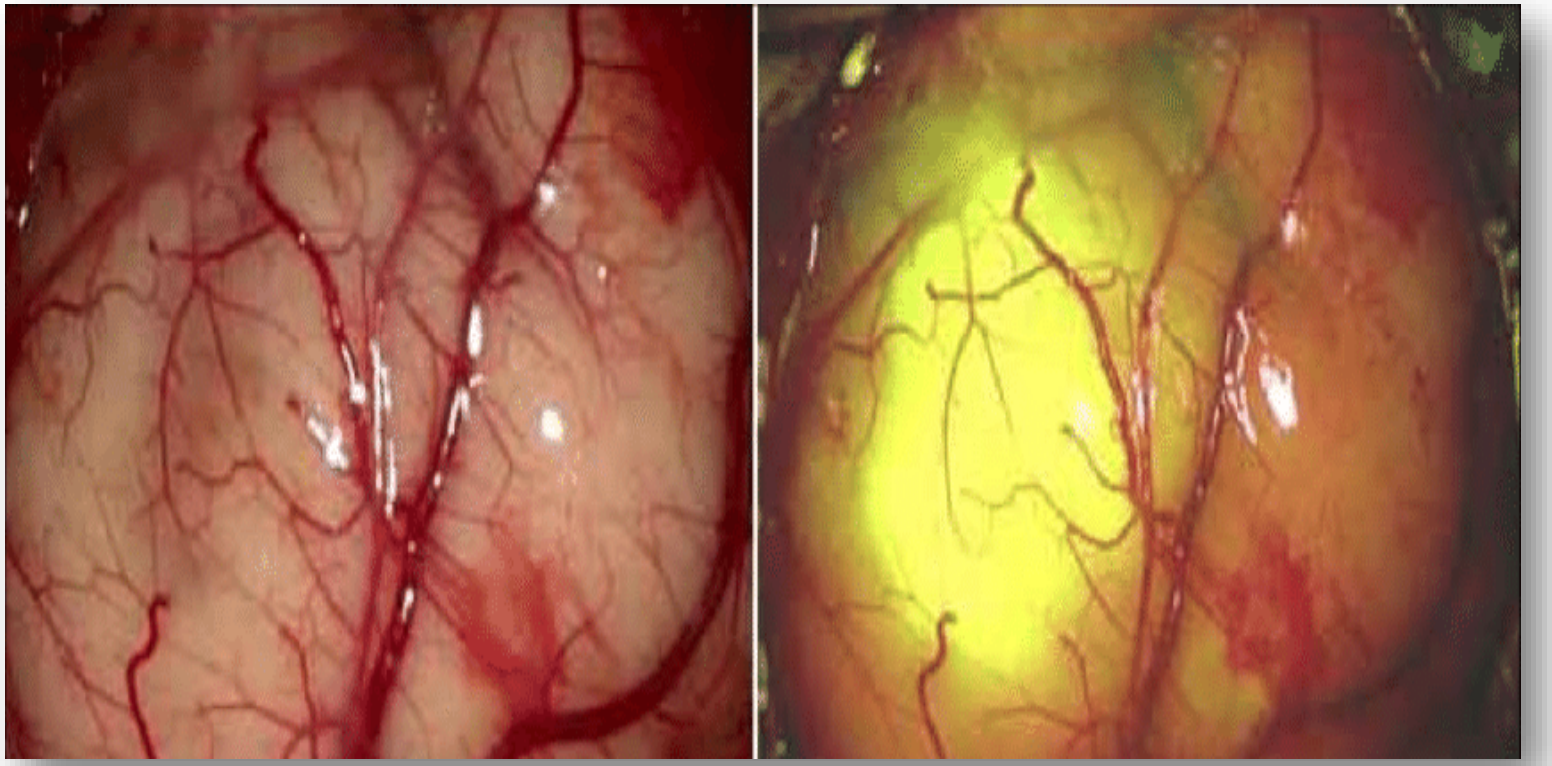
7. Surgery for recurrent metastases



- Decision for surgery in recurrence must consider : Time from first surgery, control of extra cranial disease, KPS, existence of neurological symptoms , expected complications and possible complications after surgery
- The risk of complications in recurrence surgery must compensate the survival and the quality of life after surgery, the same concepts as in first surgery
- The morbidity rates reported in available studies for recurrence surgery range from 31-0 % (compares with 2-10 % reported in first surgery), and mortality of 0-3 % (the same that reported in first surgery)

1. Bindal RK, Sawaya R, Leavens ME et al J Neurosur 1995;83(4):595-605; 2. Paek SH, Audu PB, Sperling MR, Cho J, Andrews DW Neurosurgery. 2005;56(5):1021–34; discussion 1021. 3. Patel, A.J.; Suki, D.; Hatiboglu, M.A.; Rao, V.Y.; Fox, B.D.; Sawaya, R. J. Neurosurg. 2015, 122, 1132–1143. 4. Stark AM, Tscheslog H, Buhl R, Held-Feindt J, Mehdorn HM Neurosurg Rev. 2005;28(2):115-119.

8. Intraoperative fluorescent dyes



Subcortical metastasis from breast cancer. Schebesch KM, TurlkNeurosurg 26(2), 185-194,2016

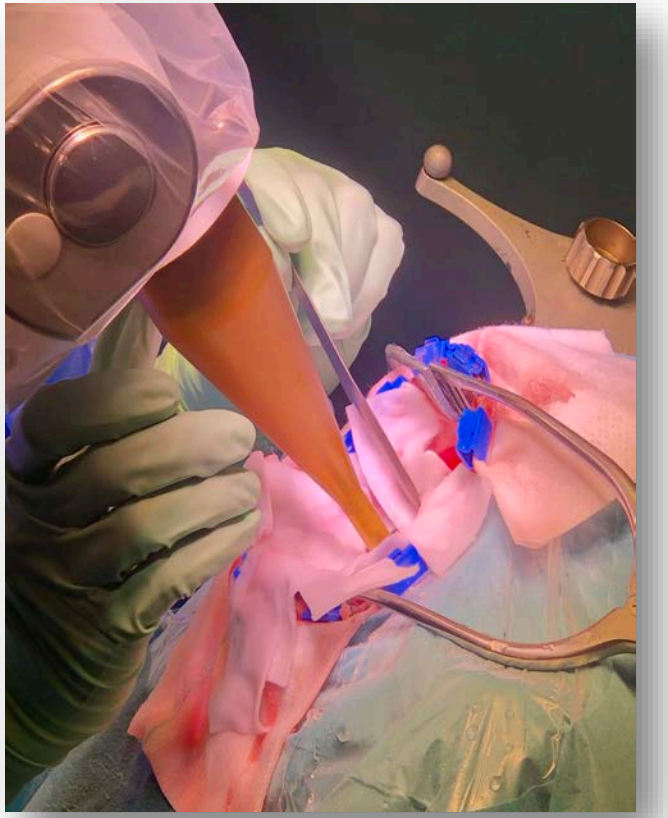
- It exists 2 types of fluorophores used on oncological fluorescence: 5-ALA (Gliolan) and sodium fluorescein
- 5-ALA has FDA and CE mark approval. It has low captation for metastases (60 % of fluorescence)
- Sodium fluorescein:
    - It is a water soluble organic dye that accumulates in areas with a disrupted blood-brain barrier.
    - For sodium fluorescein visualization a microscope filter (Yellow 560 filter) is needed.
    - 5 mg/Kg bodyweight endovenous in the moment of surgery
    - It is not FDA or CE mark approved for any malignant tumor
    - Some studies shows better fluorescence in metastases with sodium fluorescein that with 5-ALA
    - Across several retrospective cohorts, fluorescein visualization facilitated gross total resection in 83.3-100% of cases
    - Off label at the moment, some studies show that is safe and practical tool for metastases resection, but further prospective research is needed to confirm that this advanced technique will improve the quality of cerebral metastases resection

1. Kamp MA, Fischer I, Buhner J et al Oncolarget 2016;7(41):66776-89; 2. Hohne J, Hohenberger C, Proescholldt Acta Neurochir ,2017,159:363-367; 3. Manoharan R , Parkinson J Asian Journal of Neurosurgery | Volume 15 | Issue 1 | January-March 2020; 4. Schebesch KM, Hoehne J, Hohenberger C, et al. Acta Neurochir. 2015;157(6):899–904; 5. Okuda T, Kataoka K, Yabuuchi T, Yugami H, Kato A. J Clin Neurosci. 2010;17(1); 6. Schebesch KM, Proescholdt M, Höhne J, et al. Acta Neurochir (Wien). 2013;155(4):693–699.

Registered studies in www.clinicaltrials.gov

2	☐	Recruiting	Diagnostic Performance of **Fluorescein** as an Intraoperative **Brain** Tumor Biomarker	• **Brain** Cancer	• Drug: Fluorescein • Drug: Fluorescein + ALA	• Dartmouth Hitchcock Medical Center Lebanon, New Hampshire, United States
3	☐	Completed	Use of **Fluorescein** Dye for the Removal of **Brain** Tumors	• **Brain** Neoplasms	• Drug: Fluorescein	• UPMC Shadyside Hospital Pittsburgh, Pennsylvania, United States
4	☐	Terminated Has Results	Yellow 560 Microscope for Intraoperative Visualization of **Fluorescein** Stained Intracranial Lesions	• Adult Intracranial Neoplasm • Vascular: Intracranial	• Drug: Fluorescein Sodium	• Aaron Cohen-Gadol, MD Indianapolis, Indiana, United States • Sentara Norfolk General Hospital Norfolk, Virginia, United States
5	☐	Not yet recruiting	Comparison of **Fluorescein**-INtra-VItal Microscopy Versus Conventional Frozen Section Diagnosis for intraOperative Histopathological Evaluation	• Intracranial Tumor	• Drug: Alcon	
6	☐	Unknown †	Yellow 560 Microscope for Intraoperative Visualization of **Fluorescein** Stained Intracranial Lesions	• Cerebrovascular Disorders • Intracranial Neoplasms	• Drug: Fluorescein Sodium	• Florida Hospital Orlando, Florida, United States

9. Intraoperative radiotherapy (IORT)



- Adjuvant postoperative radiation treatment on the surgical cavity is the most appropriate treatment according to the brain metastases treatment guidelines. Currently ,all modalities of radiotherapy have certain drawbacks; whole brain radiotherapy can lower the risk of local recurrence but delays the systemic treatment and bears risks of leukoencephalopathy. Radiosurgery has the drawback of precisely delineating the irradiation area, and high doses cannot be reached in large cavities for risk of radionecrosis. There are no prospective randomized studies of fractional focal radiotherapy efficacy.

- Intraoperative radiotherapy (IORT) is a new alternative for local radiotherapy with the advantages of dose escalation, reduced overall treatment time, and be more comfortable for patient, however the degree of efficacy and wich is the most efficient dose is unknown.

- About 20-30 minutes is the time that IORT can prolong the anesthesia time

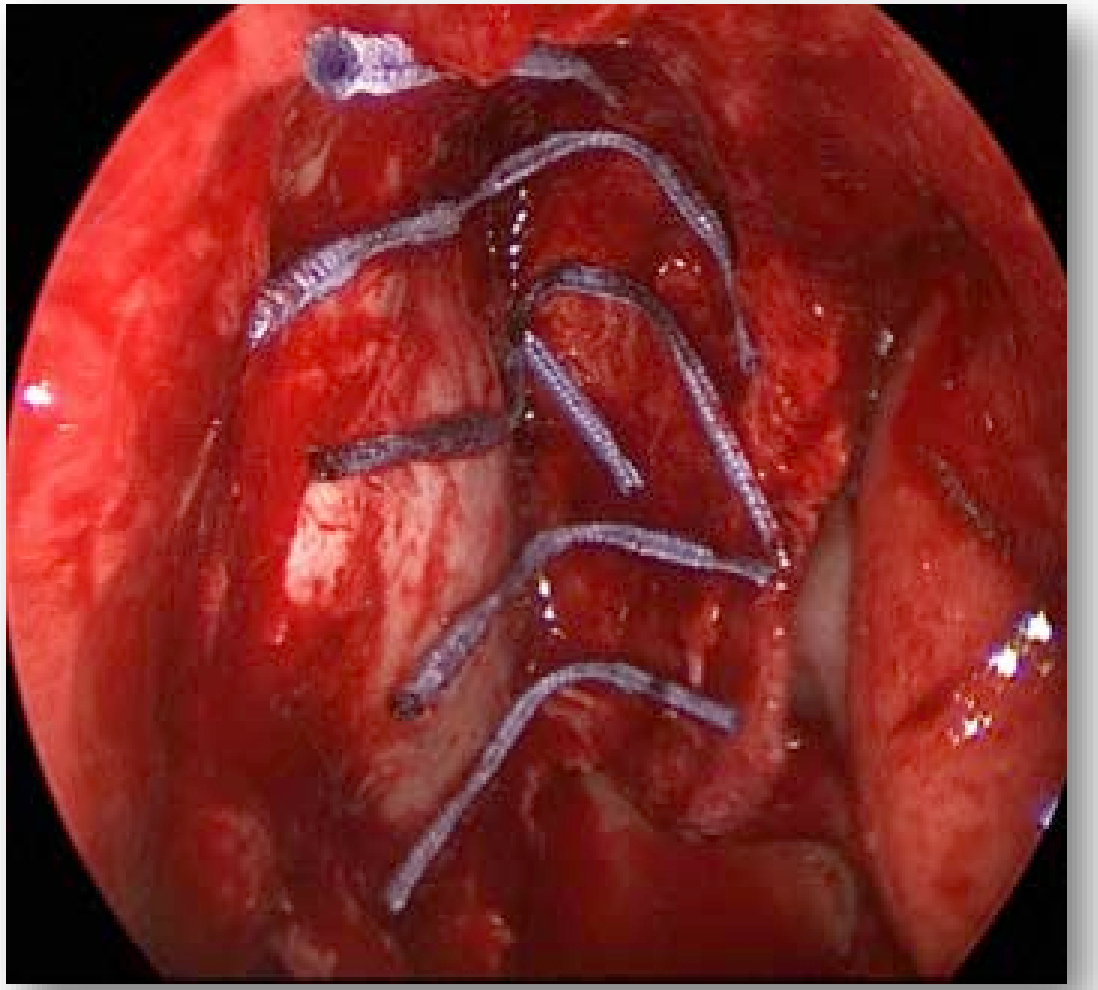
- To date, 3 publications have been collected where IORT is applied after resecction of brain metastases, showing safety and efficacy. Due to the paucity of publications, it is unknown if 30 Gy is more efficient than 20 or 14 Gy

1. Christopher Cifarelli, et al. Neurooncol Adv. 2019 Aug; 1(Suppl 1): i25. 2. Weill R, Mavinkirve G, Chao S et al. 2015 J Neurosurg 122; 3. John A. Vargo, Kristie M. J Neurooncol. 2018 Nov; 140(2): 413–420. Published online 2018 Aug 9.:825-832.

Registered studies in www.clinicaltrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	**Intraoperative Radiotherapy** After the Resection of **Brain Metastases**	• **Brain Metastases**	• **Radiation**: **Intraoperative Radiotherapy**	• Universitätsmedizin Mannheim Mannheim, Germany
2	☐	Recruiting	**Intraoperative Radiotherapy** in Patients With **Brain Metastases**	• **Brain Metastases**	• **Radiation**: **Intraoperative radiotherapy**	• Palmira Foro Arnalot Barcelona, Spain
3	☐	Recruiting	Study of **Intraoperative Radiotherapy** for Patients With Large **Brain Metastases** Treated With Neurosurgical Resection	• **Brain Metastases**	• Device: **intraoperative radiotherapy** (IORT)	• University of Louisville, James Graham Brown Cancer Center Louisville, Kentucky, United States
4	☐	Active, not recruiting	Focal **Intraoperative Radiotherapy** of **Brain Metastases**	• **Brain Metastases**, Adult • Central Nervous System **Metastases**	• **Radiation**: **Intraoperative Radiotherapy**	• AC Camargo Cancer Center São Paulo, SP, Brazil
5	☐	Recruiting	IORT After Surgical Resection of **Brain Metastases**	• **Brain** Neoplasms	• Device: **Intraoperative Radiotherapy** (IORT)	• Catalan Institute of Oncology Hospitalet de Llobregat, Barcelona, Spain
6	☐	Recruiting	Post-Surgical Stereotactic **Radiotherapy** (SRT) Versus GammaTile	• **Brain Metastases**	• Device: Gamma Tile-Surgically Targeted **Radiation** Therapy (STaRT) • **Radiation**: Stereotactic **Radiation** Therapy	• Piedmont Hospital Atlanta, Georgia, United States • The University of Texas M. D. Anderson Cancer Center Houston, Texas, United States
7	☐	Unknown †	**Radiation** Therapy in Treating Patients Who Are Undergoing Surgery to Remove a **Metastatic Brain Tumor**	• **Metastatic** Cancer	• Procedure: conventional surgery • **Radiation**: **intraoperative radiation therapy**	• Cleveland Clinic Taussig Cancer Center Cleveland, Ohio, United States

10. Brachitherapy



- Two modalities have been primarily studied for the treatment of brain metastases: iodine-125 (125I) and cesium-131 (131Cs) brachytherapy.

- Though 125I brachytherapy is the more widely studied and has been associated with local control and overall survival rates comparable to radiosurgery , clinical adoption has been limited by high rates of radiation necrosis (up to 30%). It has been attributed to the long half-life of 125I and shrinkage of the tumor cavity shifting the position of radioactive seeds.

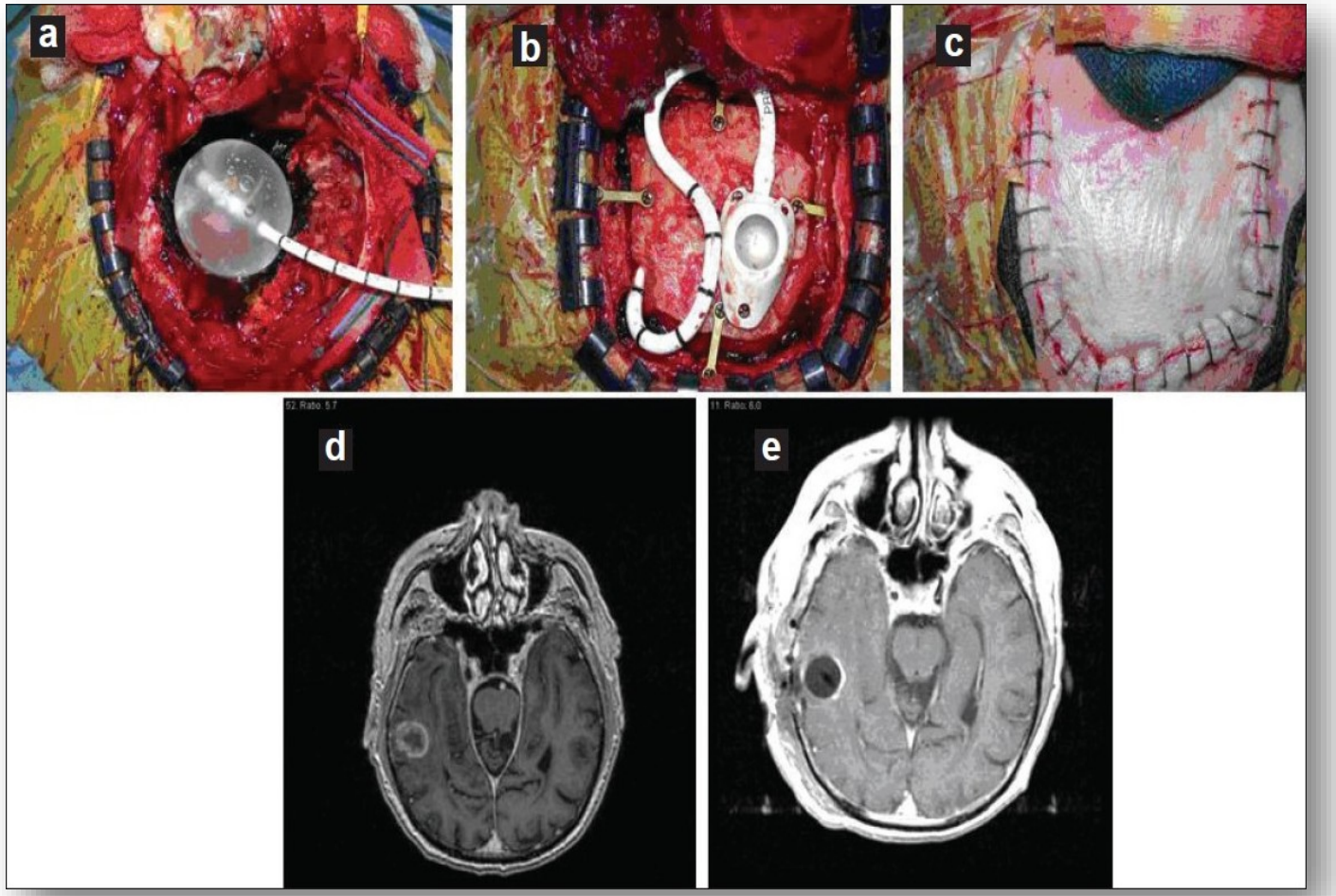
- Compared to 125I, 131Cs brachytherapy is a more promising modality with similarly high local control rates and a more favorable side effect profile. In a phase I/II study of surgical resection with 131Cs brachytherapy for newly diagnosed brain metastases, Wernicke et al demonstrated 100% local control, median overall survival of 9.9 months, and no cases of radiation necrosis.

- Adjuvant 131Cs brachytherapy has demonstrated promising benefits, especially with larger lesions, as well as significantly lower rates of radiation necrosis than 125I brachytherapy. A randomized controlled trial comparing postsurgical 131Cs brachytherapy vs. radiosurgery for newly diagnosed brain metastases is currently underway and will provide crucial data on the appropriate use cases of brachytherapy (NCT 04365374, Clinicaltrials.gov).

- For a variety of reasons including absence of physician expertise in brachytherapy, lack of pub- lished data on treatment outcomes, and rates of radiation necrosis, brachytherapy is not present as part of the standard paradigm treatment for brain metastases.

1. Julie DA, Lazow SP, Vanderbilt DB, et al. J Neurosurg. 2020;134(5):1447–1454; 2. Wernicke AG, Yondorf MZ, Peng L, et al. J Neurosurg. 2014;121(2):338–348; 3. Rogers LR, Rock JP, Sills AK, et al.; J Neurosurg. 2006;105(3):375–384.

(Image from: Bhargava BS, The role of brachyterapy in the managemente of brain metastases: a systematic review, Journal of contemporary brachyterapy,2020,vol12,n1)

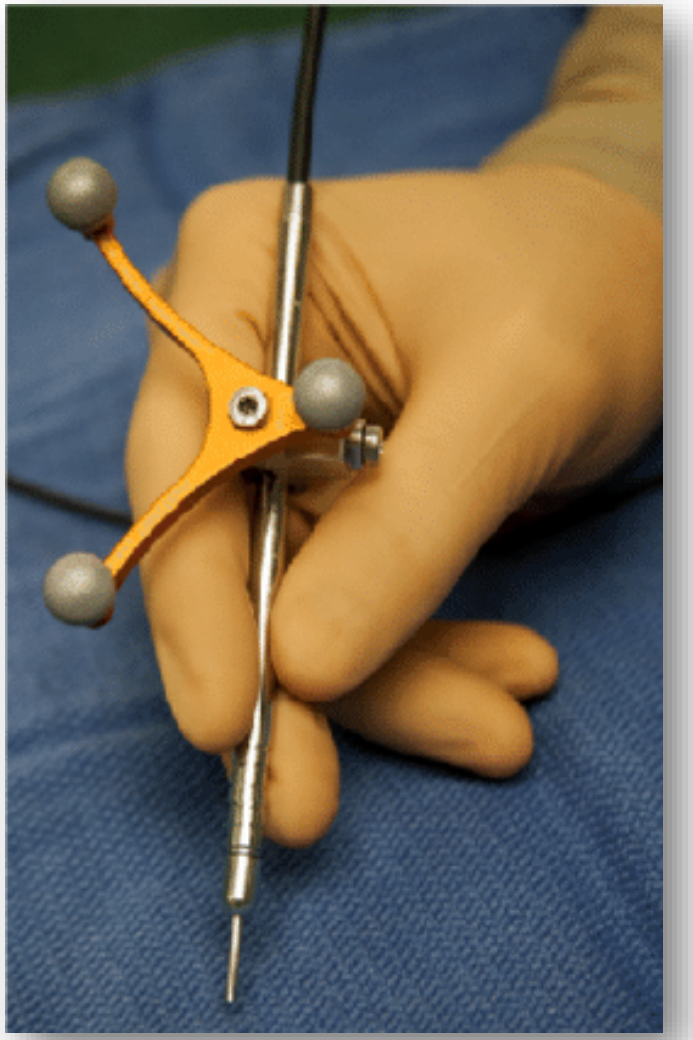


11. Confocal laser endomicroscopy

- Confocal laser endomicroscopy (CLE) is an established tool in basic research for tissue imaging at the level of microstructures. Refinement of the technology have made this modality available for operative imaging with a handheld device.
- It provides microscopic information of tissue in real time. Multiple optical biopsies intraoperatively with histological images.
- Up to know there are some publications with small series of patients.
- An intravenous fluorophore is needed to achieve a good image
- The pathologist receives the image at the same time that neurosurgeon maintains the CLE in the interesting place
- CLE has the potential to change intracranial tumor surgery. Exact sensibility, specificity and accuracy in identifying tumor cells and the real role that this technology may have in the near future in neurosurgery is still under deep investigation

1. Julie DA, Lazow SP, Vanderbilt DB, et al. J Neurosurg. 2020;134(5):1447–1454; 2. Wernicke AG, Yondorf MZ, Peng L, et al. J Neurosurg. 2014;121(2):338–348; 3. Rogers LR, Rock JP, Sills AK, et al.; J Neurosurg. 2006;105(3):375–384.

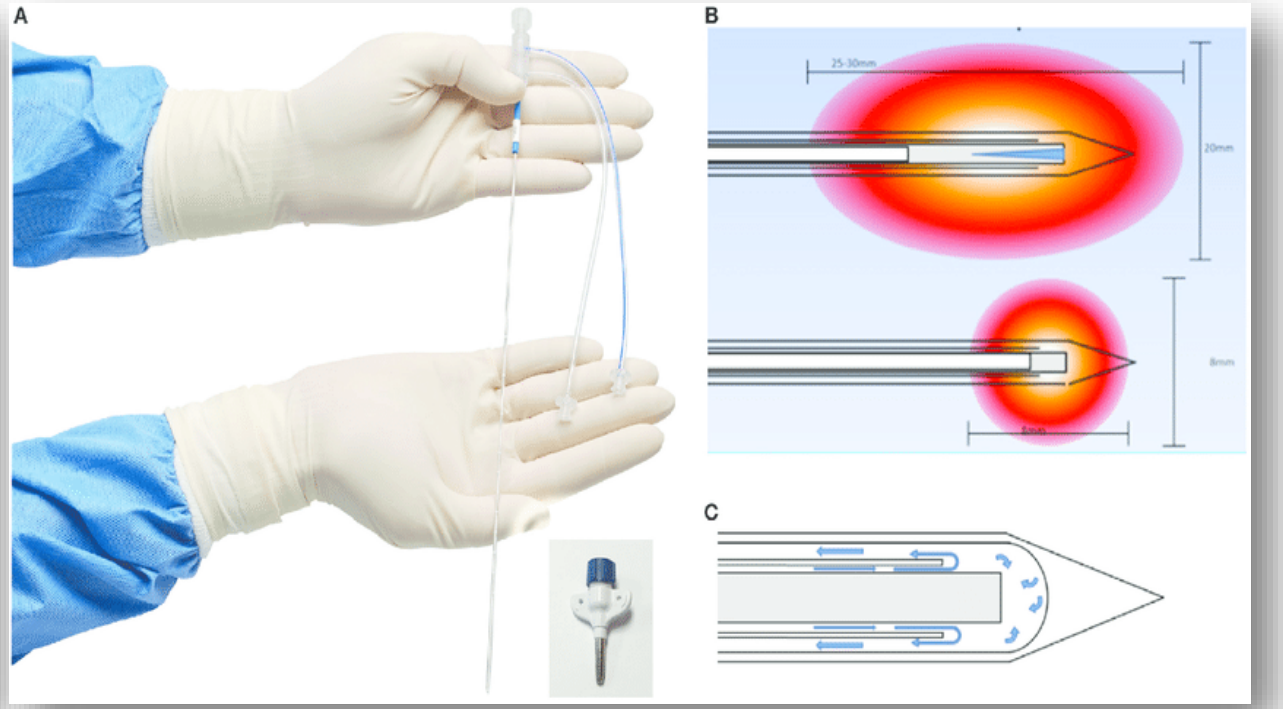
12. Raman spectroscopy



- Raman spectroscopy is a purely optical technique that allows label free analysis of brain tumor tissue. Real time in vivo Raman spectroscopy is a developing tool in brain tumor surgery with potential for integration into the neurosurgical workflow
- Can be performed within few minutes during the surgical routine, and that it allows the identification of tumor infiltration not visible under microscope.
- Up to know there are some publications with small series of patients.
- Exact sensibility, specificity and accuracy in identifying tumor cells and the real role that this technology may have in the near future in neurosurgery is still under deep investigation

1. Hollon Y, Lewis S, Freudiger C et al Neurosurg Focus. 2016 March ; 40(3): E9; 2. Kirsch M, Schackert G, Salzer R et al Anal Bioanal Chem. 2010; 398:1707–1713; 3 .Jermyn M, Mok K, Mercier K et al "Science translational medicine Vol 7 Issue 274ra19; 4. Galli R, Meinhardt M , Koch E et al Front Oncol. 2019; 9: 1165.

13. Laser interstitial thermal therapy (LITT)



- LITT (laser interstitial thermal therapy) is an ablative technique to treat a tumor or radionecrosis. It uses photons generated from a stereotactically implanted laser for thermally ablate.
- Induce coagulative necrosis and disrupting the peritumoral blood brain barrier that potentially increases efficacy of cytotoxic chemotherapy , immunotherapy and radiotherapy.
- Nowadays there are two kinds of LITT ; Neuroblate (Monteris) and Visualase (Medtronic), the basic principles are the same, but they use different thechnology.
- The main indication is for metastases that have no chance to surgery, that have been previously irradiated, no more than 3 cm in size, located no near from a vessell or important structure.
- Possible complications are: intracerebral hemorrhage, cerebral edema and transiently or permanent deficit
- There are some publications, with no more patients. Still many remaining questions regarding how this therapy is compared across different tumors types and to other treatment modalities.
- In one prospective multicenter trial in 42 patients treated with LITT, the local recurrence rate was 25 % in patients with complete ablation, in contrast to 62,5 % after incomplete ablation.
- Negative points: It is an expensive technique, and it need to transfer the patient from the operating room to the MRI room, where the ablation under MRI visualization is performed (the procedure can take hours).
- It could be a useful technology, provided that it is applied to the adequate patient and lesion.

1. Chaves D, Winberg J, Kumar V Cancer Lett.2020 Oct 1; 489;9-18; 2. Sujijantarat N, Hong C, Owusu K Journal of Neuro-oncology, 2020,148:641-649; 3. Ahluwalia M, Barnett GH, Deng D. J Neurosurg 2018;130:804-11; 4. Hong CS, Deng D, Vera A J Neurooncol 2019;142:309-17; 5. Carpentier A, McNichols RJ, Stafford RJ Laser Surg Med.2011;43:943-50; 6. Melnick K, Shin D, Dastmalchi F Curr Treat. Options in Oncol,2021,22:108; 7. Srinivasan E, Sankey E, Grabowski M, International Journal of hyperthermia,2020,vol 37,n2,27-34.

Registered studies in www.clinicaltrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed	MR Guided **Laser Interstitial Thermal Therapy** for the "Minimal Invasive" **Treatment** of **Brain Metastasis** and Primary **Brain** Tumors	• **Brain** Neoplasms • **Brain** Tumor • **Brain** Cancer • Recurrent **Brain** Tumor	• Device: MR-guided **Laser Interstitial Thermal Therapy** System	• Hospital Lariboisiere Paris, France
2	☐	Not yet recruiting	REMASTer: REcurrent **Brain Metastases** After SRS Trial	• **Brain Metastases** • Radiation Necrosis • Recurrent Tumor • Recurrent **Metastases**	• Procedure: Radiation **Therapy** • Drug: Steroid **Therapy** • Procedure: **Laser Interstitial Thermal Therapy**	
3	☐	Terminated	Magnetic Resonance Temperature Imaging & Imaging-Guided **Laser** Induced **Thermal Therapy** for **Treatment** of **Metastatic Brain Tumors**	• **Brain** Tumor	• Procedure: Visualase® **Thermal Therapy** System	• UT MD Anderson Cancer Center Houston, Texas, United States
4	☐	Not yet recruiting	Study of **Laser Interstitial Thermal Therapy** (LITT) **Treatment** Response Assessment With Fluciclovine PET MR	• **Brain Metastases** • Cancer • Gliomas • Glioblastoma	• Drug: F18 Fluciclovine • Other: Standard of Care	• M D Anderson Cancer Center Houston, Texas, United States
5	☐	Recruiting	MRI Following Stereotactic Radiosurgery (SRS) for **Brain Metastases**	• **Brain Metastases**	• Other: MRI	• Duke University Health System Durham, North Carolina, United States
6	☐	Unknown †	Magnetic Resonance Imaging-Guided **Laser** Induced **Thermal Therapy** for **Treatment** of **Metastatic Brain Tumors**	• **Brain** Neoplasms	• Device: MRI-Guided **Laser** Induced **Thermal Therapy**	• North Shore University Hospital Manhasset, New York, United States

14. Transcranial MR guided focused ultrasound (tcMRgFUS)

- Transcranial MR guided Focused ultrasound (tcMRgFUS) , also knowed as FUS, is a procedure that applied focused ultrasounds beam toward a specific therapeutic target through the intact skull.

- Extensive preclinical research has showed that tcMRgFUS is a promising physical method for targeted blood brain barrier /brain tumor barrier disruption. Increase the delivery of small chemotherapeutic agents, monoclonal antibodies and nanoparticle drug formulations.

- It is a non invasive procedure for ablative purposes with high frequencies (HIFUS). Using low frequencies (LIFUS) temporarily disrupts the blood brain barrier.

- Experiences are limited to small studies in patients with no surgical treatment possibility. While initial clinical implementation of FUS has demonstrated safe, reproducible, and repeatable opening of the blood brain barrier, heterogeneous procedural and technical parameters are collected, and the long-term effects of this modality need to be delineated

- The first successful treatment was performed in 2014. The procedure allowed physicians to ablate 10 % tumor volume. In the attempt to achieve a total ablation of lesions, come phase I trials are still ongoing (metastases and gliomas) (NCT00147056,NCT01698437)

- An external helmet system is placed over the head (shaved hair), all the procedure is performed into the MRI room. Nowadays, neurosurgeons are the responsible to directing the process

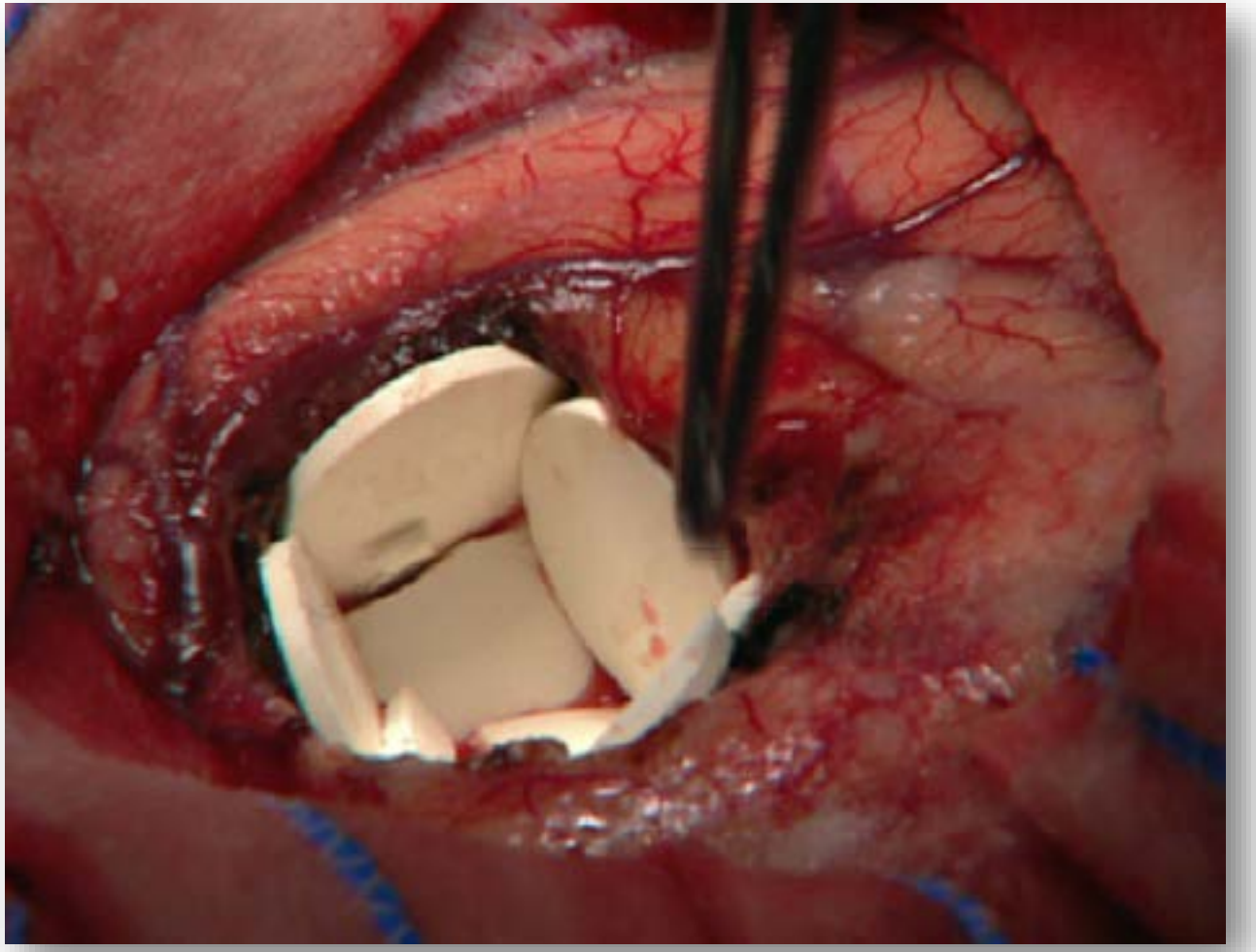
- It is expected that the use of FUS to deliver therapeutics across the blood brain barrier for brain tumors (and for neurological disease) will increase in the coming years

1. Arvanitis CD, Askoxylakis V, Guo Y Proc Natl Acad Sci U S A 2018;115(37):E8717–E8E26; 2. Arsiwala TA , Sprowls SA , Blethen KE Neoplasia Vol. 23, No. 7, 2021; 3. Abdolhosseinzadeh A, Mojra A, Ashra zadeh A.. J Therm Biol 2019;83:119–33; 4. Mainprize T, Lipsman N, Huang Y Sci Rep 2019;9(1):321; 5. Beisteiner R , Lozano A " Transcranial Ultrasound Innovations Ready for Broad ; clinical application " Adv. Sci. 2020, 7, 2002026; 6 McDannold, G. T. Clement, P. Black, F. Jolesz, K. Hynynen, Neuro- surgery 2010, 66, 323; 7. D. Coluccia, J. Fandino, L. Schwyzer, R. O'Gorman, L. Remonda, J. Anon, E. Martin, B. Werner, J. Ther. Ultrasound 2014, 2, 17; 8. Giammalva G, Gagliardo C, Marrone S Brain Sci,2021,11,84.

Registered studies in www.clinicaltrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Active, not recruiting	MRI-Guided **Focused Ultrasound** Feasibility Study for **Brain Tumors**	• **Brain Tumor**	• Device: ExAblate **transcranial** system	• Brigham and Women's Hospital Boston, Massachusetts, United States • Swedish Medical Center Seattle, Washington, United States
2	☐	Active, not recruiting	Blood-**Brain** Barrier Disruption Using **Transcranial** MRI-Guided **Focused Ultrasound**	• **Brain Tumor**	• Device: **Transcranial** ExABlate	• Sunnybrook Health Sciences Centre Toronto, Ontario, Canada
3	☐	Completed	Magnetic Resonance (MR) Guided **Focused Ultrasound** in the Treatment of **Brain Tumors**	• Malignant **Brain Tumors**	• Device: Non-invasive intervention with **focused ultrasound** (ExAblate 4000)	• MR-Center, University Children's Hospital Zurich, Switzerland
4	☐	Active, not recruiting	ExAblate (Magnetic Resonance-guided **Focused Ultrasound** Surgery) Treatment of **Brain Tumors**	• Glioma • Metastatic **Brain Cancer**	• Device: ExAblate **Transcranial** System	• Sunnybrook Health Sciences Centre Toronto, Ontario, Canada
5	☐	Completed	Magnetic Resonance (MR) Guided Functional **Ultrasound**-Neurosurgery for Movement Disorders	• Essential Tremor • Dystonia • Parkinson's Disease	• Device: Non-invasive intervention with **focused ultrasound** (ExAblate 4000)	• MR-Center, University Children's Hospital Zurich, Switzerland

15. GLIADEL



Kleinberg L. Polifeprosan 20, 3.85% carmustine slow release wafer in malignant glioma: patient selection and perspectives on a low-burden therapy. Patient Prefer Adherence. 2016;10:2397-2406

- Carmustine (BCNU) polymer wafer is the generic name for the trade name drug Gliadel.
- Nowadays is the only chemotherapy wafer that it is possible to put into the brain cavity after tumor resection.
- There are a long experience with Gliadel in high grade glioma, but litte experience in brain metastases. In high grade glioma, Gliadel appears to prolong 2-3 months the period until recurrence.
- In 2007, Ewend et al. reported their experience on the BCNU polymer wafer for treatment of solitary brain metastasis in conjunction with radiation therapy. In this report, 25 patients with solitary brain metastasis from various primary malignancies underwent craniotomy for tumor resection and placement of BCNU polymer wafers followed by whole-brain radiotherapy. This was a three-institutional feasibility study, and there was no comparison group. The median survival was 33 weeks with 33% of patients surviving past 1 year and 25% of patients surviving past 2 years. Interestingly, there was no local recurrence observed at a median follow-up period of over 36 weeks, but four patients did develop recurrence elsewhere in the brain.
- Other preliminary studies of the BCNU polymer wafer for brain metastases have been presented as abstracts at various meetings or are registered as ongoing clinical trial.

Ewend MG, Brem S, Gilbert M, et al. “Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control” Clin Cancer Res 2007;13:3637-41.

Registered studies in www.clinicaltrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed Has Results	Exploratory Study, Evaluating the Treatment Effect of Surgery Plus **GLIADEL®** Wafer in Patients With **Metastatic Brain Cancer**	• **Metastatic Brain Cancer**	• Drug: **GLIADEL**	• University of Arizona / University Medical Center Tucson, Arizona, United States • University of California, Los Angeles Los Angeles, California, United States • University of South Florida Tampa, Florida, United States • (and 14 more...)
2	☐	Completed	**Carmustine** Implants in Treating Patients With **Brain Metastases**	• **Metastatic** Cancer • Unspecified Adult Solid Tumor, Protocol Specific	• Drug: polifeprosan 20 with **carmustine** implant • Procedure: conventional surgery	• University of Alabama at Birmingham Comprehensive Cancer Center Birmingham, Alabama, United States • H. Lee Moffitt Cancer Center and Research Institute Tampa, Florida, United States • Emory University Hospital - Atlanta Atlanta, Georgia, United States • (and 8 more...)
3	☐	Unknown †	**Carmustine** Followed By Surgery in Treating Patients With Recurrent Supratentorial Malignant Glioma or **Metastatic Brain** Neoplasm	• **Brain** and Central Nervous System Tumors • **Metastatic** Cancer	• Drug: **carmustine** in ethanol • Procedure: conventional surgery	• UCSF Cancer Center and Cancer Research Institute San Francisco, California, United States • Massey Cancer Center Richmond, Virginia, United States
4	☐	Recruiting	A Study Comparing **GLIADEL** to Stereotactic Radiosurgery in **Metastatic Brain** Disease	• **Brain** Tumor - **Metastatic**	• Drug: **Carmustine** 7.7Mg Wafer	• University of Nebraska Medical Center Omaha, Nebraska, United States

Conclusions

- Systemic treatments are increasing survival in oncological patients, and consequently the probability to develop brain metastases is higher. Brain metastases are difficult to treat with systemic therapy , therefore surgical resection take an important role in the treatment.
- Advances in technology make surgical procedures safer and with more probability to achieve a total and supramarginal resection
- Some new technology could open the opportunity to treat no resecable metastases, or to facilitate the treatment with systemic agents into the brain
- Define what is the best practice and the necessary technology for brain metastases surgery or treatment is mandatory
- The best practice for brain metastases surgery , including technology, should be offered equally to all patients in the same city and in the same country.

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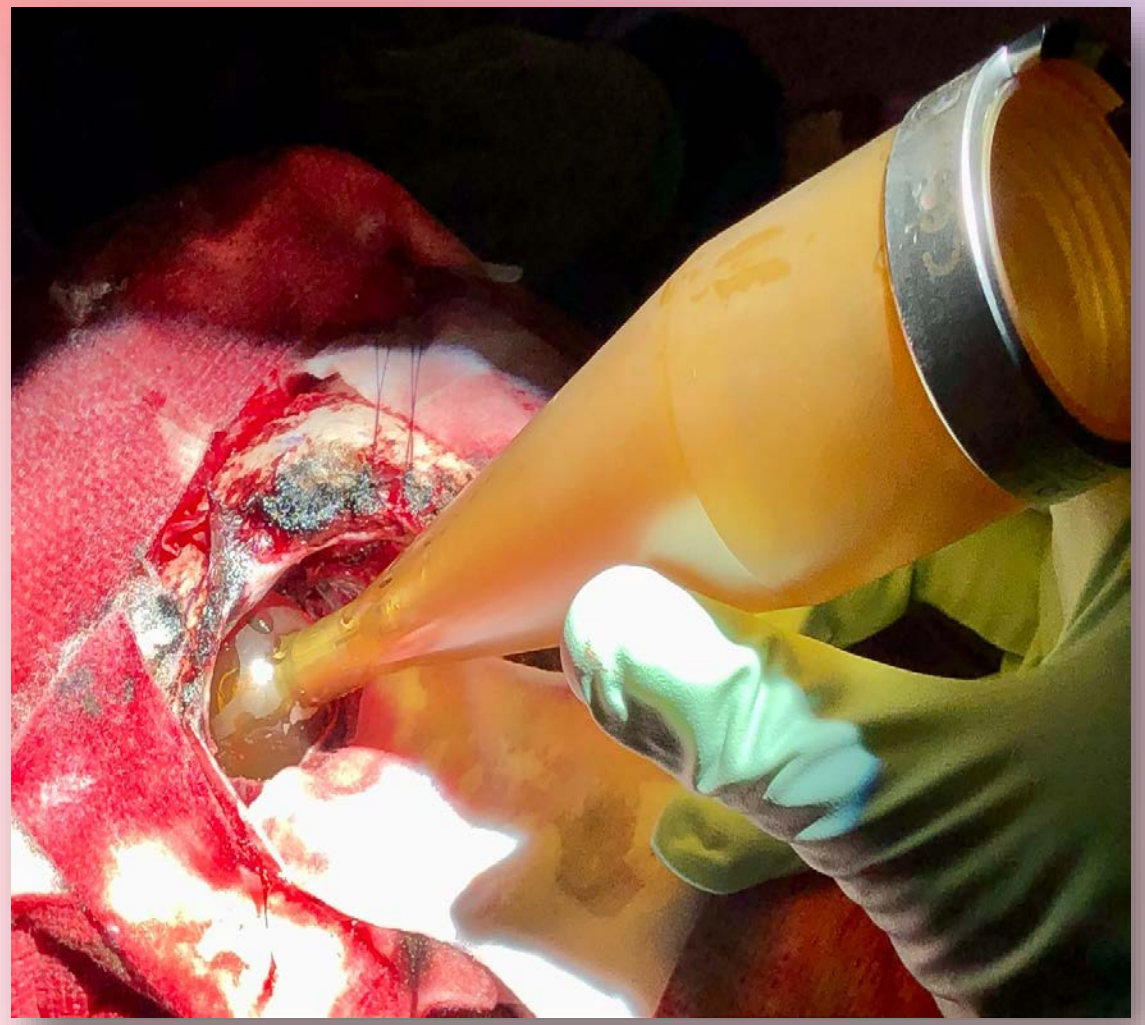

by SOLTI