April 30, 2021

PharmacologyOnLine

Special issue • 2021 • vol.1 • 47-58

ADVANCED IMAGING OF GLIOMAS

*Martina Mennella Md ,°Aniello Iacomino Md, PhD, *Gianluca Gatta Md

* Università della Campania "Luigi Vanvitelli" - Napoli, Italia
° Dipartimento di Scienze Umane, Università Guglielmo Marconi – Roma, Italia

martina.mennella@gmail.com

Abstract

Gliomas are the most common in primary malignant Central Nervous System tumors arising from glial cells in a global scenario where breast cancer is the highest-incidence cancer.
They represent a very heterogeneous group but astrocytomas have the biggest incidence among all.
Taking in account the newest standards in treatment, determining molecular and histopathological patterns is actually considered imperative to get the best management for pathology and its best outcome.
Imaging plays a key role in all the steps of the diagnostic pathway, from diagnosis to treatment and in follow-up, also being essential in defining prognosis.
Conventional gadolinium-enhanced Magnetic Resonance and particularly its new Advanced techniques (diffusion, perfusion, spectroscopy), definitely have been recognized to represent leading. Imaging modalities in both of initial patients' work-up and in follow-up, also if some limitation is present, such as a not completely and satisfying discrimination between high and low grade gliomas and/or between disease recurrences and physiological post-therapy changes and in fact MRI is today the most sensitive and accurate method of imaging in many fields of diagnostics.
Other novel hybrid Imaging modalities (PET/MRI) were found to be very interesting during patients follow-up, thanks to their high sensitivity and specificity in detecting any kind of post-treatment tissue change and also in evaluating prognosis.
Aim of this work is to highlight all the leading Imaging modalities that actually give the best chances in diagnostic pathways of gliomas, pointing out potentialities and limitations of any technique, also in the light of new frontiers that Artificial Intelligence offers.

Keywords: *Gliomas, Imaging, DWI, MRS, MRI/PET*

Introduction

Global Incidence of Central Nervous System tumors isn't actually completely known, but it estimated to be at least 45/100.000 patients a year.

CNS tumors are divided in a primary and a secondary type, with the last ones definitely representing the most common in adults.

Any kind of systemic cancer has the potential to spread malignant cells to brain but mostly, lung cancer, breast cancer, genito-urinary tract cancer, colorectal cancer and melanoma can cause CNS metastases in adults, while in children they are often seen due to sarcomas, lymphomas and leukemia.

On the other hand, talking about primary CNS tumors, it's important to take in consideration that WHO (World Health Organization) revisited their categorization in 2016 also including molecular criteria in addition to histopathologic features.

Primary brain tumors are classified into three different entity type: benign, malignant and borderline and their global incidence is actually reported to be 21/100.000 patients a year in USA, with meningiomas (36%) and gliomas (28%) representing the two commonest tumor types.

Gliomas are the most common in primary malignant Central Nervous System tumors arising from glial cells in a global scenario where breast cancer is the highest-incidence cancer [1]

Definitely, gliomas are one of the most heterogeneous group in all kind of neoplasms and most of them seem like to originate from transformation of pluripotential neural stem cells (NSCs).

In our work we'll mainly focus on astrocytomas, which account about three-quarters of all gliomas.

Astrocytomas are divided in four different histological grades: glioblastomas (grade 4) are the most common type among all the malignant forms of CNS tumors (53%), diffuse grade 2 (diffuse low grade) and grade 3 (anaplastic) gliomas represent about 30% with a median age of presentation at the diagnosis reported to be 64, 43 and 56 years respectively and grade 1 gliomas (mostly pilocytic astrocytomas) quite completely affecting pediatric population. [2]

In the common practice, grade 1 and grade 2 gliomas are also known as *low grade glioma* (LGG), while grade 3 and grade 4 gliomas are also known as *high grade glioma* (HGG), according to their malignancy status.

Imaging modalities in both of initial patients' work-up and in follow-up, also if some limitation is present, such as a not completely and satisfying discrimination between high and low grade gliomas and/or between disease recurrences and physiological post-therapy changes and in fact Magnetic Resonance Imaging (MRI) and Nuclear Medicine Imaging (NM) are today the most sensitive and accurate method of imaging in many fields of diagnostics. [3]

Mostly, our work will highlight LGG and HGG in adults, illustrating the key role of Imaging in their diagnostic pathways, from diagnosis to prognosis, in treatment and in follow-up, considering how the most appropriate diagnostic framework still remains a very challenging point to ensure the best compromise between a good outcome for pathology and an acceptable quality of life for patients.[4]

In this scenario, we'll describe why MRI and NM techniques play the major role both in diagnostic and in treatment, shortly reviewing potentials and new tools offered in all the different phases of diagnostic pathway.

Role of Imaging in Diagnosis

Most challenging points in the diagnostic pathway about a novel brain mass suspected for glioma have been mainly observed to be related with:

- determination of WHO grade (LGG or HGG);
- molecular characterization of the tumor, particularly related with isocitrate dehydrogenase (IDH)

genotype, loss of heterozygosity of the 1p/19q chromosome arms and/or O^{6-} methylguanine methyltransferase (MGMT) promoter methylation status. [5]

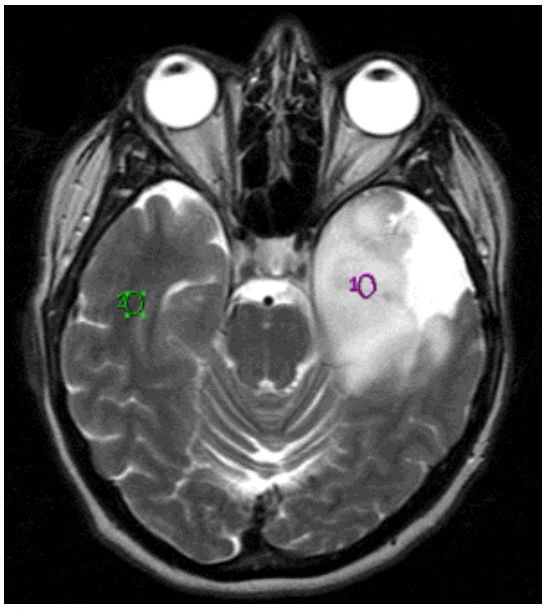

Fig. 1

At this point, Imaging gives chance to:

- obtain very thorough information about mass in a non-invasive way, often allowing to avoid tissue biopsies which are not so cost effective and above all, they can lead to very high biological implications for the patients;
- easily locate neoplasms target areas (highest grade area of the tumor) allowing to obtain a representative tissue sample for an accurate grade classification of glioma, that is considered to be essentially related with an early prognosis and an effective choice about the following therapeutic approaches. [6]

Definitely, MRI and NM modalities turn out to be the most powerful tools to reach these goals.

Among *Magnetic Resonance Imaging* techniques, conventional imaging features such as contrast- enhanced T1 images, are finally not demonstrated to be sufficient in discrimination between high- and low-grade samples. (Figure 1)

On the contrary, with the aim to identify the new molecular patterns, all the advanced Imaging techniques (diffusion, perfusion, permeability, spectroscopy) gave some excellent results, mostly related with their power in capability to improve predictive data over conventional imaging alone. [7]

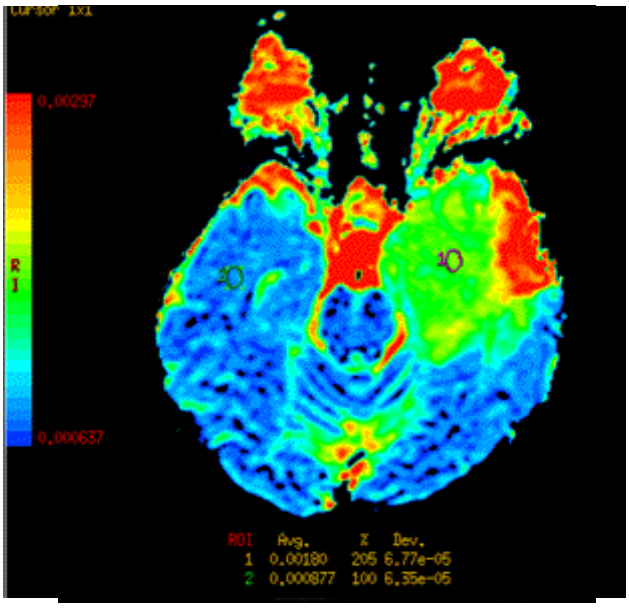

Fig. 2

A multiparametric approach has proven to give superior contribution in the clearest identification toward gliomas classification, mainly thanks to the high detailed information it furnish about microarchitectural structures and about functional tumor processes. (Figure 2)

At the best of our knowledge, Diffusion Weighted Imaging (DWI), Perfusion Weighted Imaging (PWI) and Magnetic Resonance Spectroscopy (MRS) are the leading sequences showing the most brilliant results in clinical practice.

Diffusion Weighted Imaging with the corresponding ADC maps, showed to give accurate measurements about restricted diffusivity of the protons in tissues, allowing to get a clear picture on the anisotropic diffusion of water through them, which is directly dependent to the total cellularity quota.

Overall, ADC values showed to be an excellent marker in gliomas grade determination (differential diagnosis between LGG and HGG) ; low ADC values showed to be greatly related with high grade foci of the neoplasms and because of this, they are definitely considered as a very good tool in precisely locate representative areas in the mass (solid portion of the anaplastic gliomas).

To clarify, it means gaining chance to precisely lead tissue biopsies and reducing global risks about underestimation of the neoplasm grade.

ADCs also showed having great sensitivity and specificity in capability to distinguish between HGGs an LGGs (lower ADCs were not seen in LGG); particularly, it revealed to be greatly useful in that kind of HGGs still not showing signs of central necrosis. [8][9]

Diffusion Weighted Imaging (DWI) and ADC maps also showed brilliant results in some other situations and particularly:

in early diagnosis of malignant gliomas lacking typical imaging features; it usually happens when a rapid nodular growth is present prior to the evolution of the central necrosis (non-enhancing tumors are about 4% of all GBMs showing no contrast- enhancement in their initial status); in this patients found with brain mass with restricted diffusivity (suggesting high tissue cellularity), a following biopsy should be strongly takes into account also if the mass not shows contrast- enhancement after contrast media injection;

in the precise identification of tumors borders despite normal surrounding white matter. [10]

Low ADCs were also proven to be strictly related with IDH-wild-type glioma (poorer prognosis despite IDH-mutant-type).

About Perfusion Weighted Imaging (PWI), most interesting results were reported about chances that this kind of modality also offers in the good characterization of neoplasm malignancy status. It's seen that data from PWI Imaging highly match with information about cancer progression and proliferation (giving chance to make a more accurate differential diagnosis between LGG and higher-grade tumors, also discriminating between the various tumors subtypes). (Figure 3)

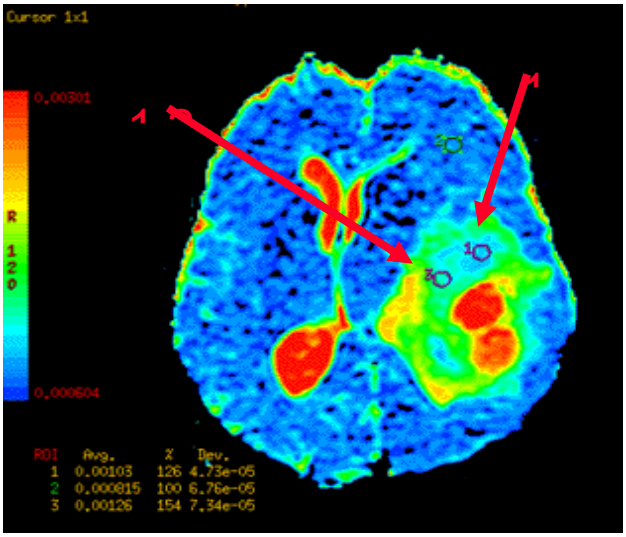

Fig. 3

Many studies strongly support that Perfusion MRI techniques also permit to acquire some excellent information about intra- tumoral heterogeneity, vascularity and about grade of neo-angiogenesis. [8]

Most of all, parameter of Relative Cerebral Blood Volume (rCBV) resulted to have the greater sensitivity and the higher positive predictive values in the most correct detection of gliomas grades (LGG vs HGG) despite conventional MRI techniques alone.

In fact, rCBVs have proven to be highly specific for LGG [8] and strictly related with gliomas mutational status; specifically, high rCBV values resulted to be significant both in prediction of IDH-wild-type glioma and in detection of 1p/19q co-deletion mutational

status among the oligodendroglial subtypes of diffuse LGG.

Arterial Spin Labelling (ASL) is another promising technique recently recognized in PW Imaging.

It permits to measure blood perfusion in encephalic tissues using as endogenous tracer the magnetically labeled arterial blood water. [10]

Representing a low/ non-invasive method, ASL has potentialities to be a powerful tool in the preoperative assessment of gliomas, but at the moment, some limitations are still present, such us the small confidence that radiologists have with the daily use of this method in clinical practice yet. [9]

Taking in account all the benefits of a multiparametric approach in gliomas diagnosis, Magnetic Resonance Spectroscopy (MRS) has been revealed another valuable technique offering brilliant chances in glioma Imaging, giving excellent results about metabolic processes in brain tumors that finally permit to increase the overall diagnostic impact. Furthermore, Spectroscopy is also considered to be greatly helpful in differentiation of gliomas grades. [10]

Particularly, among all the MRS parameters, Choline/Creatinine ratio was found to be the one mainly related to the grade of glioma; values are significantly different from the lower to the higher grades (II-IV); in fact, a persistent rise both in Choline peak and in Ch/Cr ratio, is usually observed in gliomas from grade II to grade IV. [11]

Lipids/Creatinine ratio also resulted to be helpful in the assessment of gliomas grading.

Its values allow to quantify lipidic concentration in the tumors core (highly related to the extent of necrotic component of the neoplasm) that means consequently, the entity of malignant status.

Moreover, being MRS widely available also in developed countries, it's considered to be a very suitable tool both in studying and in monitoring gliomas worldwide [8-10].

Tractography as a tool to enhance brain mapping. (Figure 4)

Tractography can be used to complement the information available from other brain-mapping techniques. In particular, the anatomical information provided by tractography reconstructions can be combined with the functional information provided by functional MRI

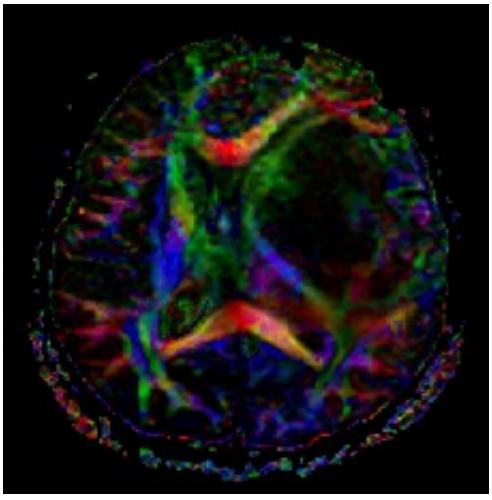

Fig. 4

Nuclear Medicine also plays a relevant role in the primary staging of gliomas.

Nuclear medicine imaging uses small amounts of radioactive material to diagnose, evaluate or treat a variety of diseases. [12-14] These include many types of cancers, heart disease, gastrointestinal, endocrine or neurological disorders and other abnormalities. [15-18] Radiotracers are molecules linked to, or "labeled" with, a small amount of radioactive material that can be detected on the PET scan. [19] The extent to which a radiopharmaceutical is absorbed, or "taken up," by a particular organ or tissue may indicate the level of function of the organ or tissue being studied. [20] Radiotracers accumulate in tumors or regions of inflammation. They can also bind to specific proteins in the body. [21] The most commonly

used radiotracer is F-18 fluorodeoxyglucose, or FDG, a molecule similar to glucose. [22] Cancer cells are more metabolically active and may absorb glucose at a higher rate. [23]

Behaving like an analogue of glucose, it can be taken up into cells by physiological glucose transporters and, once it passed, then it' is phosphorylated into [18F] FDG-6-phosphate. At this point, being this molecule far different from the real glucose, it cannot be metabolized by cells remaining trapped into them. This mechanism supports the high SUV levels of [18F] FDG in cancer cells despite that in healthy brain tissues.

At the moment, diagnostic use of [18F] FDG in detection of malignant brain mass still remains very challenging due to the high physiological uptake that is showed also in the normal brain matter.

Results can be however improved applying some preparation procedures before examination (for example, taking patients into rest) helping to reduce [18F] FDG uptake in normal tissues.

Rising levels of [18F] FDG intake resulted to be well related with worse histological gliomas grades and consequently, with a poorer prognosis.

Radioguided surgery allows a surgeon to identify lesions or tissues that have been preoperatively marked with a radioactive substance. [24] The intraoperative detection of these structures is performed using a gamma-probe, which leads to smaller and less traumatic excisions. [25] Radioguided neurosurgery, is a tech-nique derived from nuclear medicine, introduced in 1985 by Martin, used for intraoperative identification of brain tumors.

Above all, the new hybrid techniques such as PET/MRI, make it possible to obtain excellent information about neoplasms in order to planning the best possible treatment. [26]

In a single study that require a relatively short time, PET/MRI allows to create images with a high-resolution power that put together great information about both morphological and metabolic/physiologic aspects using different kind of labeled tracers.

Specifically to our interests, we're going to illustrate all the main benefits and disadvantages offered by the most frequent tracers used for diagnostic purposes in CNS tumors. [27,28]

Amino-acid PET tracers are also increasingly applied into diagnostic pathways of gliomas, basing their mechanism on the over-expression of amino-acid transporters on the surfaces of tumoral cells that depend on increased cellular metabolism and division rates in pathological tissues.

Major benefits with their use concern implications they have both on following biopsy and surgery planning.

Despite [^{18}F] FDG, amino-PET tracers show very low intake rates in normal tissues that in pathological areas, allowing a better contouring of the neoplasm.

Moreover, their uptake is not based on BBB permeability, and this allows to detect neoplasm areas whereas they're not enhanced by contrast media in MRI, when BBB would assume to be intact.

In particular, [^{11}C] Met, [^{18}F] FET and [^{11}C] DOPA are the most used amino-PET tracers, showing an excellent and specific uptake in the only tumor cells. This selectivity for neoplastic tissues allows to detect lesions with high sensitivity and specificity, showing all them similar predicting values in diagnostic power.

Determination of the hypoxic grade in a cerebral mass is another mechanism suitable by some other PET-tracers in clinical practice.

We know that states of massive hypoxia in neoplastic tissues is related to the high cellular division rates that rapidly exceed the needed blood supply in that areas.

Because of this, we know that assessment of the hypoxic status in a cerebral malignant mass

can be a crucial point of knowledge, being it related with poorer prognosis and lower rates in the global response to radiotherapy treatments.

[^{18}F] FMISO is among all the most widely studied and used tracer based on this mechanism, particularly due to its specific uptake in neoplastic cells (absent intake in normal brain parenchyma) and the good results showed in detection of differential diagnosis between LGG and HGG.

[^{11}C] Choline, [^{11}C] Acetate, [^{18}F] Fluorocholine and [^{18}F] Fluorothymidine ([^{18}F] FLT) represent other tracers belonging to this class but that are less routinely used; [^{18}F] FLT is the only one other actually considered having some potentialities in diagnostic use due to its probable but not confirmed role in an effective differential diagnosis between LGGs and HGGs. [29-31]

Doubts are related to the not completely proven correspondence between areas with high [^{18}F] FLT uptakes the same ones showing enhancement in MRI (suggesting dependency of the tracer on BBB disruption).

We surely confirm that PET Imaging and particularly *Hybrid Techniques* have a key role in diagnostic pathways of gliomas.

Another new interesting frontier in the use of NM, is actually represented by "Theranostic", a new branch allowing to guide drugs development and delivery studies to approach to pathology with a tailor-made strategy for every patient [32-33], improving quality in both of diagnostic and treatment of gliomas.

Role of Imaging in surgical treatment

Infiltrating behavior of gliomas causes many problems in surgical management.

At this point, major issues are related to the chance to planning the best possible surgical approach that is mainly related to the need of a precise identification of mass borders, also evaluating relations that neoplasm has with all the surrounding structures (evaluating if tumor infiltrates them and/or if is too close to eloquent and/or main encephalic areas) and to the need of the optimization of surgical resection, avoiding residual tumoral foci, neurological deficits and recurrence of pathology.

It's proven that many of the *Magnetic Resonance Advanced and Functional Imaging techniques* can improve quality in surgical management in gliomas, allowing to obtain brilliant and greatly accurate information about brain mapping.

Particularly, *DTI (Diffusion Tensor Imaging)* and *fMRI (Functional Magnetic Resonance Imaging)* are actually considered representing a gold standard to this goal.

Due to capability to assess physiological water direction and motion, DTI gives chance to obtain excellent data regarding CNS connectivity.

Non-invasively, it gives back a brilliant visualization about all the main tracts of white matter (main fiber pathways involved in speech, vision and motor activities) and, as well, relationships they entertain with lesions and other structures.

Being observed a high correspondence between images give back from Imaging and the real brain anatomy, this modality is actually considered a cornerstone in order to enable surgeons to choice the best surgical approach, that it is revealed to be such a precious tool particularly in eloquent areas. [34]

FA (Fractional Anisotropy) and MD (Mean Diffusivity) are the two main metrics used in DTI to provide images. [35]

fMRI is another tool providing an excellent assessment of brain mapping, being particularly able in detecting boarders of main cortical

areas, their role in human abilities and their specific relations with the mass. It allows surgeons to lead adequate decision making processes in surgical approach to preserve cortical brain functions and reducing the overall potential neurological deficits as well.

fMRI is based on a "task-based approach"; it mean that giving some different kind of tasks to patients, technique allows to precisely detect motor, sensory and speech areas with high sensitivity and specificity due to the increased cortical metabolism for every specific areas.

Mechanism is based on the increasing O_2 request in the tissues of activated areas (augmented local blood flow) causing a parallel increasement in deoxyhemoglobin local quota.

Changes that consequently happen in oxy: deoxy ratio are also known as *Blood Oxygen Level Dependent (BOLD)* and represent the main operating principle in fMRI.

Main limitations about the use of this technique are mainly related to the fact that areas around neoplasm may have some massive variation in BOLD signal being able to cause potential mistakes in detection of the surgical target areas, to the relatively high costs and the quite small diffusion that fMRI still has globally at the moment. [35]

Intraoperative MRI is another technique potentially suitable during surgery.

Excellent results are proven with its use in an excellent detection of potential residual foci around resection margins and/or in circumvention of lobar shift after dura has been opened, but the high costs of the technique don't make it very confident with a wide use in clinical practice.

IOUS (Intraoperative US) is on the contrary, a quite simple, confident and cheap Imaging technique with a great potential in application to gliomas resections.

It allows to detect any residual tumor foci around resection margins with high sensitivity and specificity. It's seen that identification of a hypoechoic rim around the neoplastic area that are major than 3 mm is strictly related to residual tumor.

Thus, we may consider IOUS as an helpful tool during surgery for gliomas, especially in detection of neoplasm margins, to reach an increased quality of the treatments in such an easy way to do.[36]

Role of Imaging in Follow-Up

To lead an attentive follow-up in patients after surgery is considered to be imperative to ensure the best outcome for pathology as well.

Last advices about standards of treatment in HGG give indication to add radiotherapy and adjuvant temozolomide-based therapy after surgical procedures because of the proven better survival rates.

In this scenario, issues are mostly related to the changes that therapy induces in tissues, that may lead to misunderstandings and mistakes in estimation of new Imaging findings and conditioning prognosis and follow-up management.

On one hand, main changes regard evidence of detection of new area showing tissue enhancement and/or identification of tissues edema mimic *Tumor Recurrence (TR)* and/or *Tumor Progression* that generally occurre from chemotherapy treatment in about 32-36 weeks.

On the other hand, *Radiation Necrosis (RN)* is the main troubled consequence usually occurring after radiotherapy treatment in 3-12 months. It consists on a new or increased contrast enhancement in tissues around surgical site that is caused by alterations in permeability of the BBB.

Pseudo-progression and *Pseudo-response* are the two other crucial entities occurring after therapies, critically needing to be recognized during follow-up.

Pseudo-progression occurs as an over-response to the effective radiotherapy

treatment, usually appearing in 10-30% of the patients within the first 3 months after.

On the contrary, *Pseudo-response* appears as a transient and rapid reduction both in the edema quota surrounding surgical site and in lesion enhancement after anti-angiogenetic treatment, due to the normalization of BBB; this process may mimic a good response to the treatment hiding the real and non-modified presence of the tumor or even worse its progression.

In this scenario, also if Advanced MRI modalities (PWI, DCS, DCE, ALS) continue to be considered as first line Imaging techniques in the assessment of gliomas follow-up, actually, the *Response Assessment in Neuro-Oncology Working Group*, strongly recommends PET using radio-labeled amino-acid tracers as additional tool in diagnostic evaluation of brain tumors at this point.

Differential diagnosis between Tumor Progression and Tumor Recurrence still remains a challenging point and no single technique provides a reliable detection of the real situation.

Main radio-tracers showing the best results for these purposes resulted to be [37]:

[^{18}F] FDG PET showing medium/ high levels of sensitivity (71%-86%) and specificity (62%-100%) when used in differential diagnosis between TR and RN.

Major limitations related to its use resulted to be mainly related to the high intake that it has also in healthy tissues, making difficult to well differentiate pathologic areas.

PET with ATTs and particularly using [^{11}C] Met showed high accuracy levels (66-91% sensitivity and 66-100% specificity) in differential diagnosis between TR and RN.

Such small new lesions also showed to be accurately detected using this kind of tracer.

Data obtained with [^{11}C]-Met was also recognized to have a remarkable relation with data given back from MRI.

[^{18}F] FET has particularly recognized to be very reliable in differential diagnosis between post- therapeutic benign tissues changes and TR.

[^{18}F] FDOPA has demonstrated to be ideal in to lead differential diagnosis between healthy and neoplastic tissues, showing a relative high uptake in pathologic tissues despite the low signal it has in the surrounding normal ones.

Thus, it also showed an improved diagnostic impact when compared with [^{18}F] FDG in differential diagnosis between TR and RN and other better results was shown by the tracer when it was compared with [^{18}F] FET in detection of TR.

Analog 3'-deoxy-3'-FLT has proven to be an excellent tool in discrimination of all different post-treatment entities in tissues after surgery. It showed high values both in sensitivity and specificity with also better results despite [^{18}F] FDG.

It works as a marker of cell proliferation being up taken in brain areas depending on BBB permeability (high tumor representation with low background signal).

Moreover FLT kinetic model, also gave precise data related to metabolic processes of the tumor, particularly related to DNA synthesis being very representative about the augmented proliferation rates in neoplastic areas.

Choline also works as a marker of cell proliferation being it related to phospholipids biosynthesis processes.

High diagnostic accuracy (sensitivity 87% specifity 82%) has been proven by recent studies for its use in differential diagnosis between TR and RN.

In each case, hybrid techniques such as PET/MRI have been showed achieving better diagnostic accuracy data than single techniques used alone. [38]

The main advantage is taken by chance to acquire both of morphological and functional information in one only study, achieving a higher globally impaction on the treatment management, particularly thanks to a timely and accurate identification of TR. [39]

Conclusions

Given the above, we want to highlight that all the actual applications of traditional Imaging in Machine Learning represent a new promising frontier in comprehension of pathologic processes, in their classification and their objective quantification, allowing to lead to a continuous path into diagnostic improvement and treatment management. [40,41]

Many of the parameters we described, are actually implemented by the latest generation of AI systems, allowing to get new references data that could carrying out the creation of new recognized and standardize protocols in treatment of brain tumors, with the common scope to improve quality in the global outcome for pathology. [42,43]

References

1. Ancona A., Capodieci M., Galiano A., Mangieri F., Lorusso V., Gatta G. – Vacuum-assisted biopsy diagnosis of atypical ductal hyperplasia and patient management (2011) Radiologia Medica, 116 (2) pp.276-291 doi 10.1007/s11547-011-0626-9
2. Osborn AG, Hedlund G, Salzman K, Osborn's Brain 2^Edition, Elselvier Books (2017), pages 509-512.
3. Regineli A., Di Grezia G., Gatta G., Iacobellis F., Rossi C., Giganti M., Coppolino F., Brunese L. Role of conventional radiology and MRI defecography of pelvic floor hernias (2013) BMC Surgery, 13 (Suppl.2) art. N. S53 doi 10.1186/1471-2482-13-s2-s53
4. Booth, TC, Williams M, Luis A, Machine learning and glioma imaging biomarkers Clinical Radiology 2019, pages 221-225 10.1007/s11060-006-9273-3
5. Lohmann P, Galldiks N, Kocher M et. al Radiomics in neuro-oncology: Basics, workflow, and applications, Methods (2020) Vol April 10.1016/j.ymeth.2020.06.003
6. Vamvakas A, Williams SC, Theodorou et al. Imaging biomarker analysis of advanced multiparametric MRI for glioma grading, Physica Medica (2019) 60C:188-198 10.1016/j.ejmp.2019.03.014
7. Gates E, Lin J, Weinberg J et al. Imaging-based algorithm for the local grading of glioma American Journal of Neuroradiology (2020) Vol 41 No 3 pages 400-407 10.3174/AJNR.A6405
8. Fouke SJ, Benzinger T, Gibson D et al. The role of imaging in the management of adults with diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline, J Neuroncology, (2015) Vol 123 No 3 pages 457-59 10.1007/s11060-015-1908-9
9. Baehring JM , Wenya LB, BannykhS, et al.Diffusion MRI in the early diagnosis of malignant glioma J Neurooncol (2007) 82:221–225 DOI 10.1007/s11060-006-9273-3
10. Kim M, Jung S, Park J et al. Diffusion- and perfusion-weighted MRI radiomics model may predict isocitrate dehydrogenase (IDH) mutation and tumor aggressiveness in diffuse lower grade glioma European Radiology 2020, Vol 30, No 4 10.1007/s00330-019-06548-3
11. Kang X, Xi Y, Liu T aet al. Grading of Glioma: combined diagnostic value of amide proton transfer weighted, arterial spin labeling and diffusion weighted magnetic resonance imaging, BMC Medical Imaging (2020) 20:50, 10.1186/s12880-020-00450-x
12. Briganti V, Cuccurullo V, Berti V, Di Stasio GD, Linguanti F, Mungai F, Mansi L. 99mTc-EDDA/HYNIC-TOC is a New Opportunity in Neuroendocrine Tumors of the Lung (and in other Malignant and Benign Pulmonary Diseases). Curr Radiopharm. 2020;13(3):166-176.

13. Cuccurullo V, Di Stasio GD, Mansi L. Physiopathological Premises to Nuclear Medicine Imaging of Pancreatic Neuroendocrine Tumours. Curr Radiopharm. 2019;12(2):98-106.

14. Briganti V, Cuccurullo V, Di Stasio GD, Mansi L. Gamma Emitters in Pancreatic Endocrine Tumors Imaging in the PET Era: Is there a Clinical Space for 99mTc-peptides? Curr Radiopharm. 2019;12(2):156-170.

15. Cuccurullo V, di Stasio GD, Evangelista L, Ciarmiello A, Mansi L. Will 68Ga PSMA-radioligands be the only choice for nuclear medicine in prostate cancer in the near future? A clinical update. Rev Esp Med Nucl Imagen Mol. 2018 Mar-Apr;37(2):103-109.

16. Cuccurullo V, Di Stasio GD, Mazzarella G, Cascini GL. Microvascular Invasion in HCC: The Molecular Imaging Perspective. Contrast Media Mol Imaging. 2018 Oct 4;2018:9487938. doi: 10.1155/2018/9487938. PMID: 30402046.

17. Cuccurullo V, Di Stasio GD, Prisco MR, Mansi L. Is there a clinical usefulness for radiolabeled somatostatin analogues beyond the consolidated role in NETs? Indian J Radiol Imaging. 2017 Oct-Dec;27(4):509-516.

18. Cuccurullo V, Prisco MR, Di Stasio GD, Mansi L. Nuclear Medicine in Patients with NET: Radiolabeled Somatostatin Analogues and their Brothers. Curr Radiopharm. 2017;10(2):74-84.

19. Cuccurullo V, Di Stasio GD, Cascini GL. PET/CT in thyroid cancer - the importance of BRAF mutations. Nucl Med Rev Cent East Eur. 2020;23(2):97-102.

20. Kitson SL, Cuccurullo V, Ciarmiello A, Mansi L. Targeted Therapy Towards Cancer-A Perspective. Anticancer Agents Med Chem. 2017;17(3):311-317.

21. Cuccurullo V, Di Stasio GD, Schillirò ML, Mansi L. Small-Animal Molecular Imaging for Preclinical Cancer Research: PET and SPECT. Curr Radiopharm. 2016;9(2):102-13.

22. Mansi L, Cuccurullo V. Diagnostic imaging in neuroendocrine tumors. J Nucl Med. 2014 Oct;55(10):1576-7.

23. Cuccurullo V, Faggiano A, Scialpi M, Cascini GL, Piunno A, Catalano O, et Al.Questions and answers: what can be said by diagnostic imaging in neuroendocrine tumors? Minerva Endocrinol. 2012 Dec;37(4):367-77.

24. Parmeggiani D, Gambardella C, Patrone R, Polistena A, De Falco M, Ruggiero R, et Al. Radioguided thyroidectomy for follicular tumors: Multicentric experience. Int J Surg. 2017 May;41 Suppl 1:S75-S81.

25. Cuccurullo V, Di Stasio GD, Mansi L. Radioguided surgery with radiolabeled somatostatin analogs: not only in GEP-NETs. Nucl Med Rev Cent East Eur. 2017;20(1):49-56.

26. Mansi, L., Ciarmiello, A. & Cuccurullo, V. PET/MRI and the revolution of the third eye. Eur J Nud Med Mol Imaging 39, 1519–1524 (2012). https://doi.org/10.1007/s00259-012-2185-x

27. Almansory K, Fraioli F, Combined PET/MRI in brain glioma imaging, British Journal of Hospital Medicine (2019) Vol 80 No 7 pages 380-386 0.12968/hmed.2019.80.7.380

28. Pruis I, van Dongen G, Veldhuijzen van Zanten S, The added value of diagnostic and theranostic PET imaging for the treatment of CNS tumors, International Journal of Molecular Sciences (2020) Vol 21 No 3 10.3390/ijms21031029

29. Cuccurullo V, Di Stasio GD, Evangelista L, Castoria G, Mansi L. Biochemical and Pathophysiological Premises to Positron Emission Tomography With Choline Radiotracers. J Cell Physiol. 2017 Feb;232(2):270-275.

30. Evangelista L, Cervino AR, Guttilla A, Zattoni F, Cuccurullo V, Mansi L. ^{18}F-fluoromethylcholine or ^{18}F-fluoroethylcholine pet for prostate cancer imaging: which is better? A literature revision. Nucl Med Biol. 2015 Apr;42(4):340-8.

31. Mansi L, Cuccurullo V, Evangelista L. Is radiocholine PET/CT already clinically useful in

patients with prostate cancer? J Nucl Med. 2014 Sep;55(9):1401-3.

32. Abdullah K, G.Lubelski D, Nucifora P et al. Use of diffusion tensor imaging in glioma resection, Neurosurgical Focus (2013) Vol. 34 No 4 pages 1-710.3171/2013.1.FOCUS12412

33. Brahimaj BC, Kochanski RB, Pearce JJ et al. Structural and Functional Imaging in Glioma Management, Neurosurgery 2021 Jan 13;88(2):211-221. doi: 10.1093/neuros/nyaa360.

34. Garzon-Mudvi T, Kut C, Li X et al. Intraoperative imaging techniques for glioma surgery, Future Oncol. 2017 Aug;13(19):1731-1745. doi: 10.2217/fon-2017-0092.

35. Soni N, Ora M, Mohindra N, et al. Diagnostic performance of PET and perfusion-weighted imaging in differentiating tumor recurrence or progression from radiation necrosis in posttreatment gliomas: A review of literature American Journal of Neuroradiology 2020 10.3174/ajnr.A6685

36. Zikou A, Sioka C, Alexiou GA et al. Radiation Necrosis, Pseudoprogression, Pseudoresponse, and Tumor Recurrence: Imaging Challenges for the Evaluation of Treated Gliomas, Contrast Media Mol Imaging. 2018; 2018: 6828396. doi: 10.1155/2018/6828396

37. Cuccurullo V, Di Stasio G, Cascini G. et al. The molecular effects of ionizing radiations on brain cells: Radiation necrosis vs. tumor recurrence, Diagnostics (2019) Vol 9 No 4 pages 1-15 10.3390/diagnostics9040127

38. Ciarmiello A, Giovannini E, Meniconi M, Cuccurullo V, Gaeta MC. Hybrid SPECT/CT imaging in neurology. Curr Radiopharm. 2014;7(1):5-11.

39. Cistaro A, Cuccurullo V, Quartuccio N, Pagani M, Valentini MC, Mansi L. Role of PET and SPECT in the study of amyotrophic lateral sclerosis. Biomed Res Int. 2014;2014:237437. doi: 10.1155/2014/237437.

40. Lu CF, Hsu FT, Hsieh KLC et al. Machine Learning-Based Radiomics for Molecular Subtyping of Gliomas, Clin Cancer Res, 2018 Sep 15;24(18):4429-4436 doi: 10.1158/1078-0432.CCR-17-3445.

41. Kocher M, Ruge M, Galldiks N et al. Applications of radiomics and machine learning for radiotherapy of malignant brain tumors Strahlentherapie und Onkologie (2020) Vol 196 No 10 pages 856-867 10.1007/s00066-020-01626-8

42. Lotan E, Jain R, Razavian N, et al. State of the Art: Machine Learning Applications in Glioma Imaging, Neuroradiology/Head and Neck Imaging (2019) Vol January pages 1-12 10.2214/AJR.18.2021

43. Robinson J, Xi K, Kumar R et al. Artificial intelligence in glioma imaging: Challenges and advances, Journal of Neural Engineering (2020) Vol 2 pages 0-31 2020