RETROSPECTIVE EVALUATION OF MRI PATTERN OF GLIOBLASTOMA IN A TERTIARY HOSPITAL IN NIGERIA

G.I. Ogbole[1], O.A.Ogunleye[1], M.C. Nweke[2], J.A. Akinmoladun[1]

1. Department of Radiology, College of Medicine, University of Ibadan and University College Hospital, Ibadan.
2. Department of Pathology, University College Hospital, Ibadan.

Corresponding:
Dr. J.A. Akinmoladun
Department of Radiology, University College Hospital, Ibadan.
jaakinmoladun@yahoo.com

Submission Date: 22nd July, 2021
Date of Acceptance: 30th Oct., 2023
Publication Date: 1st Nov., 2023

ABSTRACT

Introduction: **Malignant gliomas, especially glioblastomas, are among the most aggressive and devastating of cancers, commonly producing profound progressive disability and leading to death in most cases. Conventional magnetic resonance (MR) imaging with gadolinium-based contrast agents is the most widely established and most useful tool in the characterization of cerebral tumors including Glioblastomas. This study aims to describe the imaging characteristics of Glioblastoma in African patients using conventional MR imaging.**

Methodology: **This was a retrospective cross-sectional study carried out at a Nigerian tertiary hospital. The demographic data, MR images and reports of patients with imaging and histological diagnosis of Glioblastoma between January 2003 and September 2017 were retrieved and reviewed. All the recorded data were analyzed using simple proportion and descriptive statistics with the Statistical Package for Social Sciences (SPSS) version 20.0 software for Windows.**

Results: **One hundred and twenty-two (122) patients had brain tumors during the review period, out of which 14 (11.5%) had histologically confirmed glioblastoma. The male- to -female ratio was 2.5 to 1.0. The age ranged between 14 and 72 years with a mean age of 49.6 years SD ±16.3. Twelve (85.7%) patients had solitary tumors and 2 (14.3%) had multiple tumors. Six (42.9%) were found on the right hemisphere only, 5 (35.7%) were found on the left hemisphere while 3 (21.4%) traversed both hemispheres. All tumors showed inhomogeneous enhancement and significant midline shift to the contra-lateral side of greater than 3mm. Only 1 (7.1%) tumor showed evidence of intra-tumoral bleed detected on T2* sequence.**

Conclusion: **Glioblastoma is a known aggressive brain tumor with unique MR imaging characteristics. While midline shift is typical, intra-tumoral bleeding may be an uncommon finding at presentation in our center.**

Keywords: Glioblastoma, Magnetic resonance imaging, Brain, Tumor, Pattern.

INTRODUCTION

Malignant gliomas are considered to be the most aggressive and devastating of cancers, commonly producing substantial and progressive disability leading to death in most cases.[1] They present some of the greatest challenges in the management of cancer patients worldwide and are the most common malignant primary brain tumors in adults with an annual incidence of 4 to 5 in 100,000 people.[2–5] Glioblastomas account for approximately 60 to 70% of malignant gliomas. Gliomas are categorized by the World Health Organization (WHO) into four grades: grades I – IV, based on histological characteristics, which carry prognostic and survival correlates. Glioblastoma is a diffuse WHO grade IV glioma, which is the most malignant grade. Some gliomas of lower WHO grade have been known to recur, progress, or transform into Glioblastoma.[3] Glioblastomas arising de novo are termed primary while those arising from a previously documented lower grade glioma have been termed secondary. The demographic, molecular and survival characteristics of these two types are very varied. The mean age of primary glioblastoma patients is about 55years, while the mean age of secondary Glioblastoma patients is much lower- around 40years.[6] Primary Glioblastomas occur more frequently in males than in females (M:F ratio = 3:1),[3,7–10] while the secondary Glioblastomas occur more frequently in females (M:F ratio = 2:3).[7] Glioblastoma is also known to be commoner in Caucasians than Blacks and Asians.[2,5,11–13] with the white to black ratio being put at 2:1.[2,5] The reason for this increased prevalence in whites is not known. The overall survival in secondary Glioblastoma is better than in primary Glioblastoma which usually runs a shorter clinical course.

The cause of Glioblastoma is however unknown. A known risk factor includes exposure to ionizing radiation.[2,3,14] Evidence of associations with head injury, foods containing N-nitroso compounds, occupational risk factors, and exposure to electromagnetic fields remain inconclusive.[2,14,15] There have been previous concerns about the increased risk of Glioblastoma with the use of cellphones[16] however several larger studies have failed to demonstrate this.[3,14,17,18]

Approximately 5% of patients with malignant gliomas have a family history of gliomas with some of these familial cases associated with rare genetic syndromes, such as neurofibromatosis types 1 and 2, the Li-Fraumeni syndrome (germ-line p53 mutations associated with increased risk of several cancers), Turcot's syndrome (intestinal polyposis and brain tumors), and Cowden's disease.[2,15,19,20] Gene polymorphisms that affect detoxification, DNA repair, and cell-cycle regulation have also been suspected to be involved in the development of gliomas.[2,14]

Patients usually present with non-specific symptoms such as progressive headache, confusion, memory loss, focal neurologic deficits and seizures. Rarely, in less than 2% of cases, patients may present acutely with stroke-like symptoms and signs.[21]

Conventional magnetic resonance (MR) imaging with gadolinium-based contrast agents is the most widely established and most useful tool in the characterization of cerebral tumors.[22-25] With optimal technique and sequences, modern MR systems provide excellent anatomic or morphologic imaging of gliomas. MR imaging also provides information regarding contrast enhancement, peripheral edema, distant tumor foci, hemorrhage, necrosis and mass effect. More than 90% of all GBMs will show at least some enhancement, usually in an irregular, occasionally nodular, ring-like pattern.

Advanced MR imaging techniques such as timed perfusion MR imaging and proton MR spectroscopy have increased utility in demonstrating tumor cellular activity to correlate reliably with histologic findings for appropriate grading.[26-31]

Glioblastoma majorly occurs as a unifocal disease but can be multifocal having multiple lesions in the brain, mimicking brain metastases or other ring enhancing lesions.

The overall survival in GBMs is still averagely between 6 months and two years. Prognosis is poor and negative prognostic factors include deep location (e.g. thalamus), increased age and a low pre-diagnosis functional status.[21]

In this report, we describe the imaging characteristics and tumor pattern of Glioblastoma seen among native Africans in a tertiary hospital in Nigeria using a low-field MR system.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at the Radiology department of University College Hospital, Ibadan, Nigeria. utilizing data from patients diagnosed with Glioblastoma between January 2003 and September 2017. The study involved the review of demographic data, MR images, and reports of these patients. The MR images were acquired using a Siemens Magneto Concerto 0.2 Tesla system.

The data collected included the age, sex, and clinical information of the patients. The archived MR images were carefully reviewed, focusing on the preoperative scans, which included T1-weighted (T1-W), T2-weighted (T2-W), and contrast-enhanced T1-weighted sequences. Several parameters were extracted from the images, including the tumor's location, size, number, volume, enhancement pattern, and the presence of midline shift.

To ensure accuracy and reliability, the imaging data were independently analyzed by two experienced radiologists who were blinded to the patients' clinical information. Simple proportions and descriptive statistics were used to analyze the recorded data, employing the Statistical Package for Social Sciences (SPSS) version 20.0 software for Windows.

RESULTS

One hundred and twenty-two (122) patients had brain tumors detected on MR imaging during the study period. Fourteen (11.5%) had imaging features of glioblastoma which were confirmed on histology, and these included 10 males and 4 females giving M: F ratio of 2.5: 1.

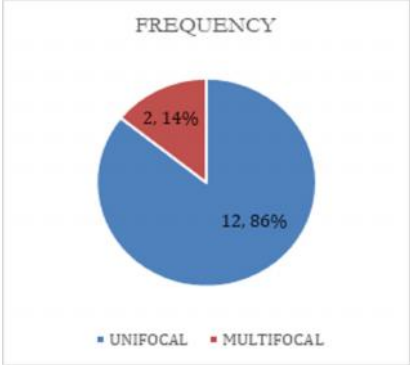

Figure 1: A pie chart showing the distribution of multifocal and unifocal GBM

The mean age of the patients with GBM was 49.6 years SD ±16.3 while the modal age was 72 years. No imaging features of Glioblastoma were found in patients younger than 14 years of age.

Twelve (12, 85.7%) patients had solitary tumours while 2 (14.3%) had multiple tumours and all multiple tumours were multi-focal in nature (figure 1). Six (42.9%) of the glioblastomas were found in the right hemisphere only, 5 (35.7%) were found in the left hemisphere only while 3 (21.4%) traversed both hemispheres (figure 2).

Table 1: A table showing the extension of the tumor within the different parts of the brain

	Frequency (n)	Percentage (%)
Parietal	13	92.9
Frontal	4	28.6
Temporal	6	42.9
Occipital	7	50.0
Mid brain	1	7.1
Basal ganglia	4	28.6
Corpus callosum	3	21.4

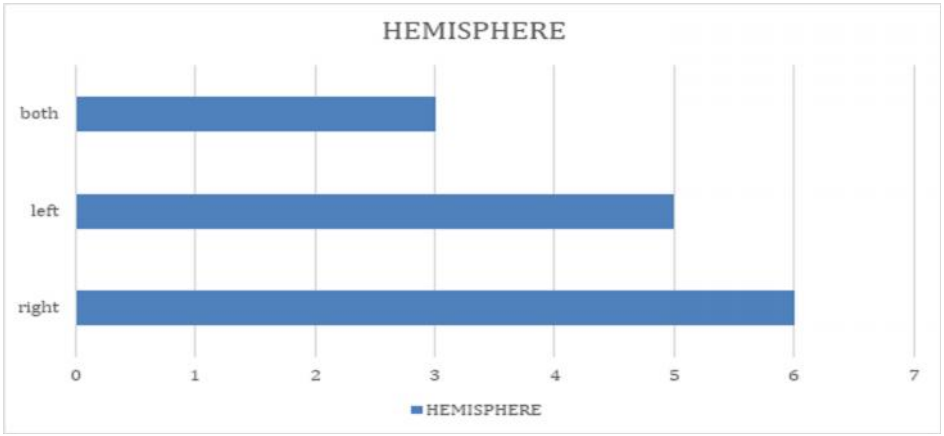

Figure 2: A bar chart showing the hemispheric distribution of the tumors

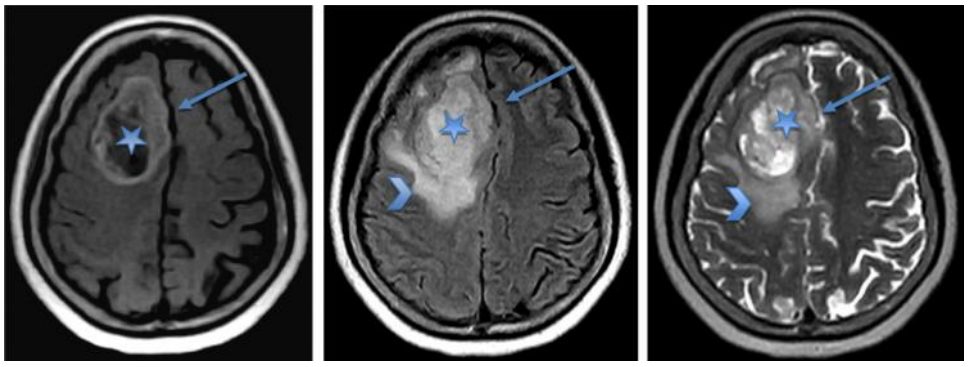

Figure 3: Post-contrast T1W, FLAIR and T2W images of a known GBM patient showing an oval-shaped mass (star) with cystic and solid components in the right parietal lobe. There is heterogeneous enhancement of the solid portion, mass effect- evidenced by shift of the midline(arrow) and peri-lesional edema (arrowhead).

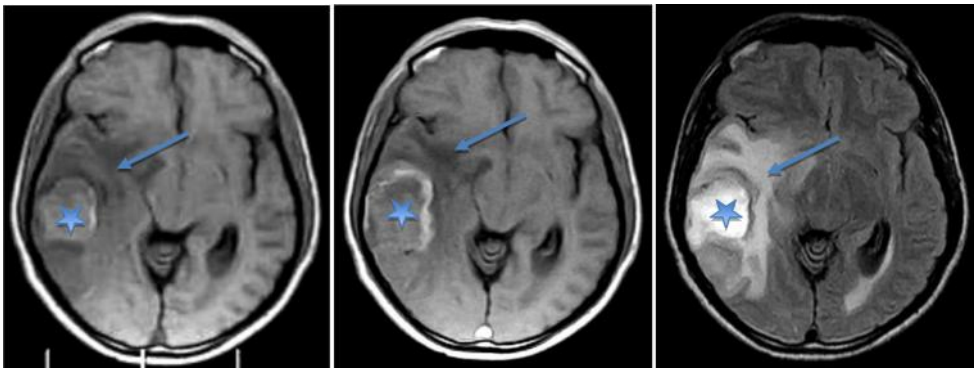

Figure 4: Precontrast, post-contrast T1W and FLAIR axial images of a known GBM patient showing a slightly hyperintense mass in the right temporal lobe(star), showing rim enhancement and extensive perilesional edema(arrow).

Thirteen (92.9%) of the tumours involved the parietal lobes, 4 (28.6%) were seen in the frontal lobes, 6 (42.9%) in the temporal lobes, 7 (50.0%) in the occipital lobes and 1 (7.1%) in the midbrain, 4 cases involved the basal ganglia (28.6%) whereas 3 cases (21.4%) involved the corpus callosum (Table 1).

The volumetric tumor sizes varied and ranged between 16.5mls and 262.4mls with a mean volume of 89.0mls ±SD81.2. Seven cases (50.0%) had cystic components with the size of the cysts ranging between 0.99 and 176.0mls, with a mean volume of 15.3mls ±SD 46.5.

All tumors displayed classic MR findings of prominent heterogeneous signal intensity, irregular border, finger-like perilesional edema and heterogeneous contrast enhancement (figures 3 and 4)

Significant midline shifts to the contra-lateral side was also demonstrated in all the patients with the minimum midline shift observed being 3.6mm and the maximum being 17.5mm (figures 3 and 4).

Only 1 (7.1%) of tumors showed evidence of intra-tumoral bleed detected on a T2* weighted sequence seen as a blooming artifact.

All the patients had histological diagnosis of GBM and the findings were marked cellular pleomorphism, palisading necrosis and microvascular proliferation (figure 5)

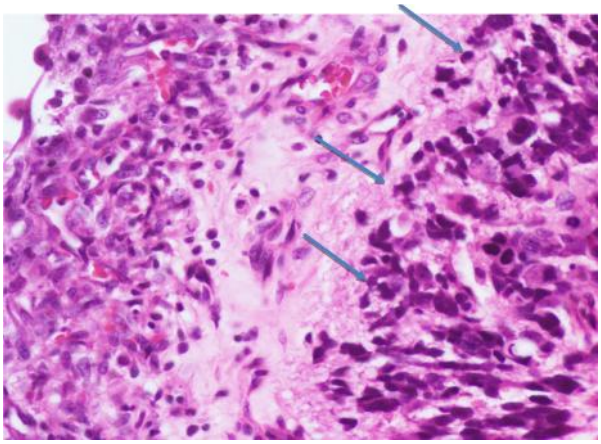

Figure 5: Photomicrograph showing a glioblastoma x400. Note the marked cellular pleomorphism, palisading necrosis and the microvascular proliferation (arrows)

DISCUSSION

Glioblastoma multiformes (GBM), a grade IV astrocytoma according to WHO, is the most common primary brain malignancy and it accounts for 12%–17% of all intracranial neoplasms. Some studies done in the United States reported that it accounts for about 15% of all intracranial tumors.[21,32]. In our study, glioblastomas accounted for 11.5% of all the reviewed intracranial tumors, which falls within the reported incidence.

A higher percentage of GBM has been reported to be found in men compared with women in some literature, with a mean male to female ratio ranging from 1.0 to 1.9. Some researchers also concluded that males are 60% more likely to develop glioblastoma overall than females[33-35]. There is also evidence that women tend to respond better than men to standard therapy for this disease. These differences are frequently linked to sex hormones, such as testosterone or estrogen, which contribute to many biological differences between men and women. Nevertheless, the gender differences are obvious and may have genetic implications. There may also be genetic differences that result in some relative protection of the female [3,7,34-36].

Li *et al.*[34] in their study observed a high frequency of estrogen receptor methylation GBMs, indicating that estrogen protects patients from GBM while Yu *et al.*[36] found that androgen receptor signaling could promote tumorigenesis of GBM in adult men by inhibiting TGF-β (transforming growth factor -β) receptor signaling. These findings corroborate our study in which we found more GBM in males than in females with a male to female ratio of 2.5 to 1. This finding was similar to those reported by Adamson *et al.* and Oghaki *et al.*[3,7] in their studies.

Glioblastoma is also known to be commoner in Caucasians than Blacks and Asians.[2,5,11–13] Our study was confined to our geographic localization and carried out among black persons only due to the homogeneity of our population. A white to black ratio therefore could not be determined. We also could not report the different incidences for primary and secondary glioma due to inability to properly follow up patients. Glioblastoma multiformes occurs most frequently in adults between 45 and 70 years of age and when it occurs, it is deadly with extremely poor prognosis.[6,37] Patients usually have a median survival of approximately 14 to 15 months from diagnosis.[37-39] The mean age in this study was 49.6 years which is very close to that reported by Altman *et al.*[6] which was put at 55 years.

GBM is however rare in children with fewer than 10% of cases occurring in them and when it occurs in them, it is associated with better prognosis than adults[40-42]. In an 18 years' retrospective study by Ansari *et al.*[41], only twenty cases of GBM were reported and the mean age was 15.2 years, with no occurrence in children less

than 10 years. There are also reports of congenital GBM, which are even associated with better prognosis than those seen in older children and spontaneous resolution have been recorded in some children.[43] Only one child was affected in this study was 14 years of age accounting for 7.1% of the cases.

The most frequent location for GBM is cerebral hemispheres; with 95% arising in the supratentorial region, while only few percent of tumors occur in the cerebellum, brainstem and spinal cord.[44] This is contrary to findings in children where the brainstem is affected more commonly than in adults.[43,44] All the tumors in our study were found in the supratentorial regions with none occurring infratentorial. This finding may be because about 90% of our patients were adults. GBM usually presents on imaging as a single peripherally or heterogeneously enhancing lesion mostly located in the frontal and temporal lobes.[45,46] Finding from this study was contrary with the right Parietal lobe being the most affected followed by the occipital lobe. Also, multiple enhancing lesions are rare in GBM with a reported incidence of 2–20%. These lesions are termed either multifocal lesions if there are connections between enhancing lesions, or multicentric lesions when no communication is demonstrated. Multiple lesions are associated with a worse prognosis compared with solitary lesion.[46-48] Solitary lesions were more than multifocal lesions in this study accounting for 85.7% and this is similar to the findings in a study by Patil *et al.*[45] where solitary tumors accounted for 87.2%.

The main causes of morbidity and mortality in patients with GBM is the induction of severe cerebral edema and necrosis, which lead to brain herniation in up to 60% of patients. Studies have shown that Patients with minimal perilesional edema and minimal midline shifts exhibited longer survival compared with patients with major edema[49,50]. All the patients in this study had significant perilesional edema, however they were not followed up in order to determine if the edema was associated with the prognosis.

Intra-tumoral bleeding is an uncommon finding in GBM and it is seen in less than 2% of patients.[21] *Haemorrhage* is best detected with T2* weighted sequences, such as susceptibility-weighted imaging (SWI) and gradient-echo (GRE because of their magnetic susceptibility effects.[51] Only 1 (7.1%) patient in our study showed evidence of intra-tumoral hemorrhage on T2* weighted sequence.

The major limitations of this study are the small sample size and the retrospective nature. This can be attributed to the number of patients lost to follow-up especially pre-operatively as a large proportion of patients do not consent to surgery as a treatment option.

CONCLUSION

Glioblastoma is an aggressive and malignant brain tumor that exhibits distinct MR imaging characteristics and can affect individuals from diverse ethnic backgrounds, including Africans. While the imaging features of glioblastoma are generally similar across populations, there may be individual variations. Our findings align with existing literature, emphasizing important traits such as occurrence in any brain region, infiltrative boundaries, increased water content within the tumor, variable contrast enhancement, significant peritumoral edema, regions of necrosis, and noticeable mass effect. It is worth noting that while midline shift is commonly observed as part of the mass effect, intra-tumoral bleeding may be a less common presentation in African patients.

REFERENCES

1. **Stewart LA.** Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. The Lancet 2002; 359: 1011-1018.
2. **Wen PY,** Kesari S: Malignant gliomas in adults. N Engl J Med 2008; 359;492-507.
3. **Adamson C,** Kanu O, Mehta A. *et al.* Glioblastoma multiforme: a review of where we have been and where we are going. Expert Opin Investig Drugs 2009;18(8):1061–1083.
4. **Wen P,** Macdonald D, Reardon D. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010; 28 (11): 1963–1972.
5. Central Brain Tumor Registry of the United States: Statistical report: Primary brain tumors in the United States, 2000-2004. http://www.cbtrus.org/reports/2007-2008/2007report.pdf.
6. **Altman DA,** Atkinson DS, Brat DJ. Glioblastoma Multiforme. RadioGraphics. 2007; 27(3) :883–888.
7. **Ohgaki H,** Dessen P, Jourde B, *et al.* Genetic pathways to glioblastoma: a population-based study. Cancer Res 2004;64(19):6892-6899.
8. **Godard S,** Getz G, Delorenzi M, *et al.* Classification of human astrocytic gliomas on the basis of gene expression: a correlated group of genes with angiogenic activity emerges as a strong predictor of subtypes. Cancer Res 2003;63 (20): 6613-6625.
9. **Xie D,** Zeng YX, Wang HJ, *et al.* Expression of cytoplasmic and nuclear Survin in primary and secondary human glioblastoma. Br J Cancer 2006; 94(1):108-114.

10. **Schrock E,** du Manoir S, Veldman T, *et al.* Multicolor spectral karyotyping of human chromosomes. Science 1996;273(5274):494-497.
11. **Parkin DM,** Muir CS. Cancer incidence in five continents. Comparability and quality of data. IARC SciPubl 1992; 120:45-173.
12. **Shinojima N,** Tada K, Shiraishi S, et al. Prognostic value of epidermal growth factor receptor in patients with glioblastoma multiforme. Cancer Res 2003;63(20):6962-6970.
13. **Ohgaki H.** Genetic pathways to glioblastomas. Neuropathology 2005;25(1):1-7.
14. **Fisher JL,** Schwartzbaum JA, Wrensch M, Wiemels JL. Epidemiology of brain tumors. NeurolClin 2007; 25:867-890.
15. **Kanu O.,** Mehta A., Di C, *et al.* Glioblastoma multiforme: a review of therapeutic targets. Expert OpinTher Targets. 2009;13(6):701–718.
16. **Hardell L,** Carlberg M, Soderqvist F, *et al.* Long-term use of cellular phones and brain tumours: increased risk associated with use for > or =10 years. Occup Environ Med 2007; 64:626-632.
17. **Lahkola A,** Auvinen A, Raitanen J, *et al.* Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer 2007; 120:1769-1775.
18. **Inskip PD,** Tarone RE, Hatch EE, *et al.* Cellular-telephone use and brain tumors. N Engl J Med 2001; 344:79-86.
19. **Farrell CJ,** Plotkin SR. Genetic causes of brain tumors: neurofibromatosis, tuberous sclerosis, von Hippel-Lindau, and other syndromes. Neurol Clin 2007;25: 925-946.
20. **Wrensch M,** *et al.* Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. Am J Epidemiol 1997;145(7):581-593.
21. **Gaillard F.** Glioblastoma Radiology Reference Article | Radiopaedia.org [Internet]. Radiopaedia. [cited 2021 March 24]. Available from: https://radiopaedia.org/articles/glioblas toma.
22. **Brant-Zawadzki M,** Berry I, Osaki L, *et al.* Gd-DTPA in clinical MR of the brain: I. Intraaxial lesions. Am J Roentgenol 1986; 147:1223–1230.
23. **Brant-Zawadzki M,** Badami JP, Mills CM, *et al.* Primary intracranial tumor imaging: a comparison of magnetic resonance and CT. Radiology 1984; 150:435–440.
24. **Bydder GM,** Steiner RE, Young IR, et al. Clinical NMR imaging of the brain: 140 cases. Am J Roentgenol 1982; 139:215–236.
25. **Just M,** Thelen M. Tissue characterization with T1, T2, and proton density values: results in 160 patients with brain tumors. Radiology 1988; 169:779–785.
26. **Wong ET,** Jackson EF, Hess KR, *et al.* Correlation between dynamic MRI and outcome in patients with malignant gliomas. Neurology 1998; 50:777–781.
27. **Bruening R,** Kwong KK, Vevea MJ, *et al.* Echo-planar MR determination of relative cerebral blood volume in human brain tumors: T1 versus T2 weighting. Am J Neuroradiol 1996; 17:831–840.
28. **Sugahara T,** Korogi Y, Kochi M, *et al.* Correlation of MR imaging determined cerebral blood volume maps with histologic and angiographic determination of vascularity of gliomas. Am J Roentgenol 1998; 171:1479–1486.
29. **Sugahara T,** Korogi Y, Shigematsu Y, *et al.* Value of dynamic susceptibility contrast magnetic resonance imaging in the evaluation of intracranial tumors. Top Magn Reson Imaging 1999; 10:114–124.
30. **Knopp EA,** Cha S, Johnson G, *et al.* Glial neoplasms: dynamic contrast-enhanced T2*-weighted MR imaging. Radiology 1999;211: 791–798.
31. **Aronen HJ,** Gazit IE, Louis DN, *et al.* Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. Radiology 1994; 191:41–51.
32. Central Brain Tumor Registry of the United States (CBTRUS). CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004- 2007. Available at: www.cbtrus.org/2011-npcr-seer/web-0407-report- 3-3-2011.pdf.
33. **Yang W,** Warrington NM, Taylor SJ, *et al.* Sex differences in GBM revealed by analysis of patient imaging, transcriptome, and survival data. *Sci Transl Med.* 2019;11(473): eaao5253
34. **Li Q,** Jedlicka A., Ahuja N, *et al.* Concordant methylation of the ER and N33 genes in glioblastoma multiforme. Oncogene 1998:16; 3197–3202
35. Glioblastoma Study Highlights Sex Differences in Brain Cancer was originally published by the National Cancer Institute." Available from https: www:ncbi.nim.nih.Gov/pmc/articles/pmc5819173.
36. **Yu X,** Jiang Y, Wei W, *et al.* Androgen receptor signaling regulates growth of glioblastoma multiforme in men. Tumour Biol. 2015;36, 967–972.
37. **Halani S.H.,** R. Babu, and D.C. Adamson, Management of Glioblastoma Multiforme in Elderly Patients: A Review of the Literature. World Neurosurg, 2017. 105: 53-62.

38. **Ma X,** Lv Y, Liu J. *et al.* Survival analysis of 205 patients with glioblastoma multiforme: clinical characteristics, treatment, and prognosis in China. J. Clin. Neurosci. 2009:16; 1595–1598.
39. **McGirt MJ,** Mukherjee D, Chaichana KL, *et al.* Association of surgically acquired motor and language deficits on overall survival after resection of glioblastoma multiforme. Neurosurgery 2009; 65, 463–469.
40. **Louis D.N.,** Ohgaki H., Wiestler O.D. *et al.* The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007; 114:97–109
41. **Ansari M,** Nasrolahi H, Kani AA, *et al.* Pediatric glioblastoma multiforme: A single-institution experience. Indian J Med Paediatr Oncol. 2012; 33(3):155–160.
42. **Winters JL,** Wilson D, Davis DG. Congenital glioblastoma multiforme: a report of three cases and a review of the literature. J Neurol Sci. 2001; 188(1–2):13–19
43. **Davis T,** Doyle H, Tobias V, *et al.* Case Report of Spontaneous Resolution of a Congenital Glioblastoma. Pediatrics. 2016;137(4): e20151241
44. **Nakada M,** Kita D, Watanabe T, *et al.* Aberrant signaling pathways in glioma. Cancers 2011; 3: 3242-3278.
45. **Patil CG,** Yi A, Elramsisy A, *et al.* Prognosis of patients with multifocal glioblastoma: a case-control study. J Neurol Surg 2012; 117: 4: 705-711.
46. **Lasocki A,** Gaillard F, Tacey M, *et al.* Multifocal and multicentric glioblastoma: Improved characterisation with FLAIR imaging and prognostic implication, 2016; 31: 92-98.
47. **Pérez-Beteta J,** Molina-García D, Villena M, *et al.* Morphologic Features on MR Imaging Classify Multifocal Glioblastomas in Different Prognostic Groups. American Journal of Neuroradiology 2019; 40(4):634-640.
48. **Singh G,** Mehrotra A, Sardhara J, *et al.* Multiple glioblastomas: are they different from their solitary counterparts? *Asian J Neurosurg* 2015: 10*;* 266–71.
49. **Liao C,** Chen Y, Xiao F. Brain Midline Shift Measurement and Its Automation: A Review of Techniques and Algorithms. International Journal of Biomedical Imaging 2018, Article ID 4303161, 1-13.
50. **Wu C,** Lin G, Lin Z, *et al.* Peritumoral edema shown by MRI predicts poor clinical outcome in glioblastoma. World Journal of Surgical Oncology 2015: 13:97-105.
51. **Lin DD,** Filippi CG, Steever AB, Zimmerman RD. Detection of intracranial hemorrhage: comparison between gradient-echo images and b(0) images obtained from diffusion-weighted echo-planar sequences. Am J Neuroradiol. 2001 Aug;22(7):1275-1281.