Oncology
and Radiotherapy ©
16 (11) 2022: 023-028 • REVIEW

# Recurrent brain tumor versus radiation-induced necrosis: A review study

**Almusaedi Aseel[1], Peter McCarthy[2]**

[1]School of Medicine, Clinical Science Institute, National University of Ireland, Galway, Ireland
[2]Head of Department, School of Medicine, Clinical Science Institute, National University of Ireland, Galway, Ireland

ABSTRACT

Brain tumors account for less than 3% of all neoplasms. Post-radiation treatment necrosis is one of the most serious late sequels beyond radiotherapy. This review aimed to describe the recurrent brain tumor and radiation-induced necrosis. The MRSI is a safe, accurate, and informative tool for distinguishing between recurrent brain tumors and radiation-induced necrosis.

**Key words:** recurrent brain tumor, radiation-induced necrosis, pseudo-progression, high grade glioma, low grade glioma, astrocytoma

**Address for correspondence:**

Almusaedi Aseel, Kam, 45, Wemmel, Belgium, Email: asl.dhl1983@gmail.com, peter.mccarthy@nuigalway.ie

**Word count:** 4532 **Tables:** 01 **Figures:** 00 **References:** 61

**Received:** - 22-Oct-2022, Manuscript No. OAR-22-78074

**Editor assigned:-** 25-Oct-2022, PreQC No. OAR-22-78074 (PQ)

**Reviewed:-** 08-Nov-2022, QC No. OAR-22-78074 (Q)

**Revised:-** 12-Nov-2022, Manuscript No. OAR-22-78074 (R)

**Published:-** 15-Nov-2022, Invoice No. OAR-22-78074

## INTRODUCTION

Central Nervous System (CNS) tumours represent less than 3% of all malignancies. They have very specific anatomic, physiological, pharmacological, immunological, and functional characteristics, and pose challenges unique in all of the oncology [1]. The clinical manifestations are diffuse, varied, and highly dependent on anatomic location [1, 2].

Radiation-induced necrosis is one of the most serious late sequels of radiotherapy and appears from six months to years after the therapy it may be progressive and irreversible [3], due to destroyed of the white matter by vascular damage, demyelination, and necrosis. Post-radiation, the damage also involves injury to the endothelium which leads to aggregation of platelets and formation of thrombus, then the abnormal proliferation of endothelium and deposition of intraluminal collagen occur [4].

Pseudo progression without tumour recurrence is seen as a radiographic elevation in enhancement plus/minus oedema on the MRI. It is a transient elevation in enhancement that stabilizes or resolves and needs no changes in the treatment [5-9]. The incidence of post-radiation necrosis in Glioblastoma Multiform (GBM) lies between 14% and 50% [6, 9-13].

Up to date, dynamic MRI (dynamic susceptibility contrast) or perfusion MRI is the only imaging with a promise to reliably distinguish between pseudoprogression and progression.

This review illustrated the differentiation of recurrent brain tumours from radiation-induced necrosis and thereby identifying pseudo-progression.

## LITERATURE REVIEW

### Epidemiology

Globally, brain tumours whether benign or malignant rank in the 20$^{th}$ position in the list of incidences of new cases of cancer worldwide estimated by GLOBOCAN "Global Cancer Statistics Online Database 2020". They recorded 308,102 (1.6% of all cancer sites) new cases of CNS tumours, with 251,329 (2.5%) deaths in 2020 [14]. In the United States, approximately 23,130 low-grade gliomas and 68,000 new cases of high-grade gliomas are diagnosed annually [15]. Recently, gliomas accounted for more than 80% of malignant brain tumours. Glioblastoma (GBM) a

grade IV tumour is the most common primary malignant brain tumour. The rest are grade III tumours such as anaplastic tumours (astrocytoma, oligodendroglioma, and oligoastrocytoma). Males are more often diagnosed with glioma than females [16]. Different studies in the USA suggested that 14 per 100,000 individuals will be detected with a brain tumour [16, 17]. Children below 14 years of age and the elderly have an increasing incidence rate of brain tumours [18]. This increase in new cases is due to advancements in diagnostic neuroimaging such as MRI, more neurosurgeons and histopathologists, improvements in care for those age categories, and progression in the approaches to health care [16].

## Aetiology

In the USA, brain tumours are more often detected in Caucasians than in the African American population. Most risk factors are not related to any significant predisposition, yet the presence of hereditary syndromes is a significant risk factor for the development of CNS tumours [19]. Many of these hereditary syndromes are correlated with one or more types of CNS tumours, such as tuberous sclerosis with subependymal giant cell astrocytoma [16], neurofibromatosis types 1 and 2 with low-grade astrocytoma [20]. Nevoid basal cell carcinoma (BCC), Li-Fraumeni, and Turcot syndromes are found in 2–8% of all cases of CNS tumours. Ionizing radiation of the cranium is a potent risk factor even beyond the wide range of frequent exposures [16, 17, 21]. Other risk factors, shown by Newton, are a prior primary systemic malignancy, traumas, medication, viruses, ingestion of N-nitroso compounds, oxidants, and antioxidants, alcohol ingestion, smoking, and exposure to electromagnetic fields [22]. Other studies showed a correlation between cellular mobile phones and brain tumours or head and neck cancer. Authors from Denmark did a nationwide review including more than 420 thousand cell phones and estimated that the overall incidence of tumours was not increased compared to the control group [23]. Studies of molecular epidemiology in adult patients with HGG are promising for further publication [17]. In one study with 155 patients and 157 controls looked for a correlation between human leukocyte antigens (HLAs) and associated polymorphisms (HLA-A, -B, -C, -DRB1) and GBM, the two haplotypes were positively related with the occurrence of GBM ($p=0.01$, $p<0.001$, respectively) [24]. Another study revealed polymorphisms of ERCC1 and ERCC2 including 450 glioma patients and 500 controls [17]. A study, with 556 astrocytoma cases involved, looking for the p53 expression, murine double minute-2 (MDM2), epidermal growth factor receptor (EGFR), and O6-methylguanine-DNA-methyltransferase (MGMT) [25]. The data showed an inverse relationship between p53 mutation and MDM2 or EGFR. The p53 mutations were more often found in GBM among black people than among white ($p=0.004$) [17]. In addition, interleukin (IL)-4RA Ser478Pro TC, CC and IL-4RA Gln551Arg AG, AA was positively correlated to GBM, whereas IL-13-1,112 CT, TT had a negative correlation [22].

## Histopathological classification

According to the WHO classification, the gliomas are graded from I to IV according to the lesions. The grade I lesions are biologically indolent and grade IV is the most malignant lesions with poor prognosis [26]. The diffuse growing tumours are the most prevalent such as astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. These subtypes may be subject to malignant transformation and degenerate into the most aggressive and poorer form of glioma, the GBM [1]. The critical feature that shows the transformation from a grade II tumour to an anaplastic astrocytoma is the presence of harry mitotic activity, and in most cases of anaplastic gliomas, the Ki-67 indices range from 5% to 10%. The presence of microvascular proliferation and/or necrosis in a malignant astrocytoma upgrades the tumour to a GBM, which is accompanied by nuclear pseudo-palisading as a pathognomonic feature for GBM [27].

## Pathology

The appropriate therapeutic strategies depend on the appearance of the tumour or the tumour type. The classification and tumour grade direct the management decisions and define the prognosis [22]. Historically, LGGs have been considered a homogeneous group of tumours correlated with a more favourable prognosis [2]. LGGs are well-circumscribed, benign, and typically curable. The pilocytic astrocytomas are grade I brain astrocytomas. They tend to have a better prognosis and the transformation to HGG is rare [28]. The diffusely infiltrated LGGs classified as grade II (WHO), are the most prevalent and comprise astrocytoma, oligodendroglioma, and mixed oligoastrocytoma [2]. Whereas the anaplastic term refers to grade III tumours such as anaplastic astrocytomas, oligodendrogliomas, and oligoastrocytomas. The GBM is a grade IV glioma [27].

## Grading systems

There were several grading systems such as Kernohan, Ringertz, and St. Anne-Mayo systems in the past, which used abnormalities such as nuclear and endothelial proliferation, mitoses, and necrosis. The most widely used system is the WHO system [29]. WHO grade I gliomas are well circumscribed with low proliferative potential, and the cure post-surgical resection is high. Grade II gliomas are infiltrative, as a rule, recur, and may transform to high grades malignancy [1]. Grades II to IV is malignant gliomas characterized by a tendency to infiltrate neighbouring tissue. This diffuse infiltration makes complete resection of all brain tumour tissues impossible [27].

## Molecular biology

In the last three decades, the knowledge of brain tumour biology improved. The tumour proliferation is assessed by Ki-67/MIB-1 labelling. Increasing values of the Ki-67 index correlates with increments in the grade of brain tumours. This index differentiates diffuse astrocytoma II and oligodendrogliomas II from anaplastic gliomas III and GBM [30]. About 50-60% of gliomas have TP53 mutations, which may be higher in HGG [31]. In terms of molecular biology, low-grade oligodendrogliomas show a loss of 1p/19q, and the genotype is an unbalanced t (1;19) (p10; q10) with a peri-centromeric translocation. To some extent, this also occurs in GBM [32]. Recently, several studies showed in 70-80% of LGGs IDH1 mutations are related to an enzyme that participates in the cycle of citric acid [33]. Besides, the PI3K/mTOR pathway is activated in most LGGs, with methylation of the promoter area of the PTEN gene in 33% of patients [34]. MGMT promoter methylation is emerging as a potential but imperfect prognostic factor in the management of GBMs [27].

## Clinical manifestation

The low-grade gliomas generally occur in patients in their second, third, or fourth decades of age, with a mean of 37 years. They are more prevalent in males than in females by a ratio of 1.4:1. The most common symptom is a seizure, observed in two-thirds of the patients. Generalized tonic-clonic, simple partial, and complex partial seizures are recorded in respectively 43%, 23%, and 34% of the patients. Headache and paralysis occur in one-third of the patients. About half of affected patients have a normal neurologic examination [2]. Furthermore, several neurological signs may be present such as the sensory deficit, motor deficit, papilledema, aphasia, altered mental status, dysphasia, decreased memory, and altered consciousness (Table 1). The functions may be normal or moderately impaired in 25% of the population, and severe symptoms may occur in 12% [35]. There are no specific or pathognomonic symptoms of HGG. Generally, patients may show up with headaches, neurologic deficits, nausea, and vomiting [27].

## Management

Surgical resection is the common management approach for

**Tab. 1.** WHO Classification: Tumors of the Central Nervous System (CNS) [29]

| Tumours of Neuroepithelial Tissue | Astrocytic Tumors | | Embryonal Tumors | Tumours of the Meninges | Mesenchymal, Non-meningothelial Tumors | Primary Melanocytic Lesions |
|---|---|---|---|---|---|---|
| | Diffuse | LOCALIZED | | | | |
| Astrocytic tumours | Astrocytoma (WHO grade II) | Pilocytic astrocytoma | Medulloepithelioma | Meningothelial Cells (Meningiomas) | Lipoma | Diffuse melanocytosis |
| Oligodendroglia tumors | Fibrillary | Pleomorphic xanthoastrocytoma | Ependymoblastoma | Meningothelial | Angiolipoma | Melanocytoma |
| Ependymal tumours | Protoplasmic | Subependymal giant cell astrocytoma | Medulloblastoma | Fibrous (fibroblastic) | Hibernoma | Malignant melanoma |
| Mixed gliomas | Gametocytes | | Desmoplastic medulloblastoma | Transitional (mixed) | Liposarcoma (intracranial) | Meningeal melanocytosis |
| Choroid plexus tumours | Anaplastic astrocytoma (WHO grade III) | | Large cell medulloblastoma | Psammomata's | Solitary fibrous tumour | |
| Neuronal and mixed neuronal-glial tumours | Glioblastoma multiforme (WHO grade IV) | | Medullomyoblastoma | Angiomatous | Fibrosarcoma | |
| Pineal parenchymal tumours | Giant cell glioblastoma | | Melanotic medulloblastoma | Microcystic | Malignant fibrous histiocytoma | |
| Neuroepithelial tumours of uncertain origin | Gliosarcoma | | Supratentorial PNET | Secretory | Leiomyoma | |
| Embryonal tumours | | | Neuroblastoma | Lymphoplasmacytic rich | Leiomyosarcoma | |
| | | | Ganglioneuroblastoma | Metaplastic | Rhabdomyoma | |
| | | | Atypical teratoid/ rhabdoid tumour | Clear cell | Rhabdomyosarcoma | |
| | | | | Choroid | Chondroma | |
| | | | | Atypical | Chondrosarcoma | |
| | | | | Papillary | Osteoma | |
| | | | | Rhabdoid | Osteosarcoma | |
| | | | | Anaplastic | Osteochondroma | |
| | | | | | Hemangioma | |
| | | | | | Epithelioid hemangioendothelioma | |
| | | | | | Hemangiopericytoma | |
| | | | | | Angiosarcoma | |
| | | | | | Kaposi sarcoma | |

brain tumours and is the primary therapy for most. The surgery is indicated for reducing the size of the tumour, palliating the effects of the mass, for control of neurological deficit, and for confirmation of the histopathological diagnosis [22, 36, 37]. Complete removal of benign gliomas can be curative. Whereas for GBM, and AA, most surgeons apply a gross-total or sub-total resection, if possible. For diffusely infiltrative or multifocal tumours, stereotactic biopsies are more likely to elaborate neurological function deficits [22]. The accuracy of the size and location of the tumour is improved when the area is defined by contrast enhancement on MRI or MRSI or PET scan [2, 22].

External beam radiation therapy (EBRT) is an appropriate form of management for virtually all patients with HGG, as well as for selected LGGs that are surgically unresectable or have progressed beyond resection [38]. Advances in radiotherapy techniques over the recent decade have had a major impact on neuro-oncology. The majority of CNS cell populations have a low mitotic index and proliferate slowly, they are the prototypical "late-responding tissues" of conventional radiobiology [1]. Stereotactic radiosurgery, using a Cyberknife® or a Gamma Knife® to deliver a single high-dose radiation fraction is another method to boost radiation doses in the bed of the tumour, while sparing normal surrounding tissues [39, 40]. The success of local therapies, such as surgery and radiotherapy, is highly dependent on the accurate estimation of the extent of the CNS tumour. Moreover, the unusual phenomena of pseudoprogression, pseudo response, and therapeutically induced inflammatory changes, rarely seen outside the CNS region, pose frequent diagnostic conundrums [1, 2].

Chemotherapy is also used as an adjuvant protocol for malignant brain tumours (i.e., mostly GBM, and AA) and for some LGG which progress despite primary resection and radiation [41, 42]. Several studies have shown the efficacy of both temozolomide and PCV agents in newly diagnosed and progressing LGGs [43-46]. Many trials which investigated recurrent tumours, reported a high response rate in relapsing tumours [43, 44]. However, based on the data of two large phase III chemotherapy studies in newly detected LGGs, the role of chemotherapy is better referred to. One study was RTOG intergroup trial 98-02 [45-47], and the other study was the EORTC trial that evaluated the role of temozolomide in newly detected patients with high-risk LGGs [15].

## Recurrence of gliomas

The diffuse glioma at some stage is likely to show the progression of neurological signs and symptoms and is likely to recur. The majority of tumours progress at the tumour bed site but occasionally develop as a deep infiltration into dense tracts of white matter. In addition, leptomeningeal seeding is recorded. More than 70% of lesions have dedifferentiated or transformed into an HGG stage [48]. These are seen on the MRI scan through enhancement of damaged areas, which can appear after 6 -12 months, it shows a local volume increment of cerebral blood flow in the affected region. Generally, the survival of patients after tumour recurrence is very poor. Treatment modalities for the recurrence of gliomas include resection, re-irradiation, and second-line cytotoxic agents [1]. Pseudo-progression which confuses the interpretation of MRI imaging done in the first months after completion of RT has been described as early as 1979 [27]. In patients with disease progression immediately post-irradiation, nearly 50% were found to have improvement or at least stable disease on subsequent brain MRI imaging, and the incidence (of what? disease progression? Or disease improvement?) is reported to be as high as in patients with GBM [7, 49].

## Brain necrosis

Many radiation-induced side effects can occur in patients treated with radiotherapy, they range from cognitive sequels to necrosis [50]. The incidence of radiation necrosis in LGG is 3%, according to findings of NCCTG 86-72-51, in which the 2-year incidence of fatal radio-necrosis was 1% at a low dose and 5% at a high dose [47]. Brain necrosis is one of the serious and uncommon late toxic effects of radiotherapy treatment of gliomas [51]. Clinically and radiographically, radiation necrosis may seem the same as recurrent tumour through the reappearance and worsening of primary symptoms and neurologic deficits, and through the development of an irreversible, progressive, enhancing mass with associated oedema on imaging. However, PET, MSRI, and nuclear and dynamic CT scanning procedures may help to distinguish necrosis from recurrent tumours. Focal necrosis occurs because of radiotherapy alone, but massive diffuse leuko-encephalopathy is more commonly related to chemoradiation [3]. Radiation necrosis may manifest itself as high-tone hearing loss and vestibular damage, retinopathy or cataract formation, optic chiasm, and nerve damage as a decline in visual acuity, blindness, and hormone insufficiency. Whole cranium radiotherapy can lead to neuropsychological changes and neurocognitive dysfunction [52-57].

Classically, radiation toxicity has been explained by two theories, the vascular and the glial hypotheses. The vascular hypothesis states that radiation-induced vasculopathy results in ischemia and necrosis. The glial hypothesis proposes that radiation causes injury to oligodendrocytes and the precursors of cells [58].

## Differentiation of post-radiation necrosis from the recurrent tumour by MRSI

Longitudinal CNR ratios over time decline when there is necrosis and an elevation suggests a recurrence or residual tumour. MRSI has been observed to be of much more benefit when consistently applied with the meticulous acquisition of technical and post-processing standards and integrated with perfusion, diffusion, and anatomic imaging [59].

Multivoxel MRSI allows simultaneous sampling of the core of the necrosis, the margins of the lesion defined by Gd enhancement, and abnormal tissue outside the margins defined by hyper-intense on T2-weighted MRI. This may involve remote foci and/ or disease infiltration [60].

In post-radiation necrosis, the ipsilateral Cho/NAA ratio is abnormal, which may suggest recurrence, but in radiation necrosis, the Cho/Chocratio is below one. In this situation might arise the treatment-naïve tumour, either treated tumour or post-radiation necrosis had either a different spectral pattern or different admixtures of tissue types within the MRSI voxel itself (I do not understand what you want to say here) [60]. Thus, the spectral features of radiation-induced toxicities in normal and tumour tissue depend upon the time interval between the radiation and the MRSI application. Spectral features of delayed post-radiation necrosis show an overall decline in Cho, Cr, and NAA peaks, in addition to the presence of Lip-Lac [60, 61].

## CONCLUSIONS

The majority of the lesions were classified as HGG. The MRSI is a safe, accurate, and informative tool for distinguishing between the two diagnostic entities. A combination of advanced imaging technologies such as MRS, PET, DWI, SPECT, and MR perfusion assists in the differentiation of glioma recurrence versus post-radiation necrosis.

REFERENCES


1. Mehta MP, Kotecha RR. Clinical radiation oncology. Elsevier Health Sci. 2015;479-486.
2. Brown PD. Clinical radiation oncology. Elsevier Health Sci. 2015;461-465.
3. Halperin E, Perez C. Brady's principles and practice of radiation oncology. Fifth Lippincott Williams & Wilkins. 2008.
4. Chow BM, Li YQ, Wong CS. Radiation-induced apoptosis in the adult central nervous system is p53-dependent. Cell Death Differ. 2000;7:712-720.
5. De Wit MC, De Bruin HG, Eijkenboom W, Smitt PS, Van Den Bent MJ. Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. Neurology. 2004; 63:535-537.
6. Chamberlain MC, Glantz MJ, Chalmers L, Van Horn A, Sloan AE. Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma. J. Neuro-Oncol. 2007; 82:81-83.
7. Taal W, Brandsma D, de Bruin HG, Bromberg JE, Swaak-Kragten AT, et al. Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide. Cancer. 2008;113:405-410.
8. Brandes AA, Tosoni A, Spagnolli F, Frezza G, Leonardi M, et al. Disease progression or pseudoprogression after concomitant radiochemotherapy treatment: pitfalls in neurooncology. Neuro-Oncol. 2008;10:361-367.
9. Gunjur A, Lau E, Taouk Y, Ryan G. Early post-treatment pseudo-progression amongst glioblastoma multiforme patients treated with radiotherapy and temozolomide: a retrospective analysis. J Med Imaging Radiat Oncol. 2011; 55:603-610.
10. Roldán GB, Scott JN, McIntyre JB, Dharmawardene M, De Robles PA, et al. Population-based study of pseudoprogression after chemoradiotherapy in GBM. Can J Neurol Sci. 2009; 36:617-622.
11. Chaskis C, Neyns B, Michotte A, De Ridder M, Everaert H. Pseudoprogression after radiotherapy with concurrent temozolomide for high-grade glioma: clinical observations and working recommendations. Surg. Neurol. 2009; 72:423-428.
12. Sanghera P, Perry J, Sahgal A, Symons S, Aviv R, et al. Pseudoprogression following chemoradiotherapy for glioblastoma multiforme. Can J Neurol Sci. 2010; 37:36-42.
13. Young RJ, Gupta A, Shah AD, Graber JJ, et al. Potential utility of conventional MRI signs in diagnosing pseudoprogression in glioblastoma. Neurology. 2011; 76:1918-1924.
14. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J Clin.2021;71:209-249.
15. Baumert BG, Mason WP, Ryan G, Bromberg JE, Van den Bent MJ, et al. Temozolomide chemotherapy versus radiotherapy in molecularly characterized (1p loss) low-grade glioma: A randomized phase III intergroup study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033).
16. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, et al. The epidemiology of glioma in adults: a "state of the science" review. Neuro-Oncol. 2014; 16:896-913.
17. Wrensch M, Fisher JL, Schwartzbaum JA, Bondy M, Berger M, et al. The molecular epidemiology of gliomas in adults. Neurosurg. focus. 2005; 19:1-1.
18. Legler JM. Cancer surveillance series: brain and other central nervous system cancers: recent trends in incidence and mortality. J Natl Cancer Inst. 1999; 91:1382-1390
19. Osborne RH, Houben MP, Tijssen CC, Coebergh JW, Van Duijn CM. The genetic epidemiology of glioma. Neurology. 2001; 57:1751-1755.
20. Davis FG, McCarthy BJ. Current epidemiological trends and surveillance issues in brain tumors. Expert Rev Anticancer Ther. 2001; 1:395-401.
21. Hess KR, Broglio KR, Bondy ML. Adult glioma incidence trends in the United States, 1977–2000. Cancer: Interdiscip Int J Am Cancer Soc. 2004;101:2293-2299.
22. Newton HB, Tadipatri R, Fonkem E. Overview of brain tumour epidemiology. InHandb. neuro-oncol. Neuroimaging. 2022;3-8.
23. Johansen C, Boice Jr JD, McLaughlin JK, Olsen JH. Cellular telephones and cancer—a nationwide cohort study in Denmark. J. Natl. Cancer Inst.2001;93:203-207.
24. Tang J, Shao W, Dorak MT, Li Y, Miike R, et al. Positive and negative associations of human leukocyte antigen variants with the onset and prognosis of adult glioblastoma multiforme. Cancer Epidemiol. Biomark. Prev. 2005;14:2040-2044.
25. Wiencke JK, Aldape K, McMillan A, Wiemels J, Moghadassi M, et al. Molecular features of adult glioma associated with patient race/ethnicity, age, and a polymorphism in O 6-methylguanine-DNA-methyltransferase. Cancer Epidemiol. Biomark. Prev. 2005; 14:1774-1783.
26. Rodriguez FJ, Giannini C. Diagnostic neuropathology of tumors of the central nervous system. Handb. Clin. Neurol. 2012; 104:77-107.
27. Gunderson LL, Tepper JE. Clinical radiation oncology. Elsevier Health Sci; 2015.
28. Brown PD, Buckner JC, O'Fallon JR, Iturria NL, Brown CA, et al. Adult patients with supratentorial pilocytic astrocytomas: a prospective multicenter clinical trial. Int J Radiat Oncol * Biol* Phys. 2004; 58:1153-1160.
29. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, et al. The 2007 WHO classification of tumours of the central nervous system. Acta neuropathol. 2007; 114:97-109.
30. Johannessen AL, Torp SH. The clinical value of Ki-67/MIB-1 labeling index in human astrocytomas. Pathol Oncol Res. 2006;12:143-147.
31. Ständer M, Peraud A, Leroch B, Kreth FW. Prognostic impact of TP53 mutation status for adult patients with supratentorial World Health Organization Grade II astrocytoma or oligoastrocytoma: a long-term analysis. Cancer. 2004; 101:1028-1035.
32. Jenkins RB, Blair H, Ballman KV, Giannini C, Arusell RM, et al. A t (1; 19)(q10; p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer res. 2006;66:9852-9861.
33. Dubbink HJ, Taal W, van Marion R, Kros JM, van Heuvel I, et al. IDH1 mutations in low-grade astrocytomas predict survival but not response to temozolomide. Neurology. 2009;73:1792-1795.
34. McBride SM, Perez DA, Polley MY, Vandenberg SR, Smith JS, Zheng S, Lamborn KR, Wiencke JK, Chang SM, Prados MD, Berger MS. Activation of PI3K/mTOR pathway occurs in most adult low-grade gliomas and predicts patient survival. Journal of neuro-oncology. 2010; 97:33-40.
35. IR Whittle. The dilemma of low-grade glioma, J Neurol Neurosurg Psychiatry, 2004;75: 31-36
36. Dunn IF, Black PM. The neurosurgeon as local oncologist: cellular and molecular neurosurgery in malignant glioma therapy. Neurosurgery. 2003; 52:1411-1424.
37. IF Parney, MS Berger. Principles of brain tumour surgery', Handb. Clin. Neurol.2012; 104:187-213
38. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro-oncol. 2002;4:278-299.
39. Tomoyuki K, Nobuhito S. Efficacy and limitations of stereotactic radiosurgery in the treatment of glioblastoma. Neurol Clin Chir (Tokyo), 2012;52:548-552.
40. Elaimy AL, Mackay AR, Lamoreaux WT, Demakas JJ, Fairbanks RK, et al. Clinical outcomes of gamma knife radiosurgery in the salvage treatment of patients with recurrent high-grade glioma. World neurosurg. 2013; 80:872-878.
41. Viaccoz A, Lekoubou A, Ducray F. Chemotherapy in low-grade gliomas. Curr Opin Oncol. 2012;24:694-701.
42. Blakeley J, Grossman SA. Chemotherapy with cytotoxic and cytostatic agents in brain cancer. Handb. Clin. Neurol. 2012:229-54.
43. Pace A, Vidiri A, Galie E, Carosi M, Telera S, et al. Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. Ann. Oncol. 2003; 14:1722-1726.
44. JA Quinn. Phase II trial of Temozolomide in patients with progressive low-grade glioma. J Clin Oncol. 2003; 21:646-651.
45. Stege EM, Kros JM, de Bruin HG, Enting RH, van Heuvel I, et al. Successful treatment of low-grade oligodendroglial tumors with a chemotherapy regimen of procarbazine, lomustine, and vincristine. Cancer. 2005; 103:802-809.
46. Levin N, Lavon I, Zelikovitsh B, Fuchs D, Bokstein F, et al. Progressive low-grade oligodendrogliomas: response to temozolomide and correlation between genetic profile and O6-methylguanine DNA methyltransferase protein expression. Cancer: Interdiscip. Int J Am Cancer Soc. 2006; 106:1759-1765.
47. Shaw E, Arusell R, Scheithauer B, O'fallon J, O'neill B, et al. Prospective randomized trial of low-versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol. 2002;20:2267-2276.

48. MJ van den Bent, D Afra, Ode Witte, Ben Hassel, S Schraub, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomised trial. Lancet. 2006; 366:985-990.

49. Clarke JL, Iwamoto FM, Sul J, Panageas K, Lassman AB, DeAngelis LM, Hormigo A, Nolan CP, Gavrilovic I, Karimi S, Abrey LE. Randomized phase II trial of chemoradiotherapy followed by either dose-dense or metronomic temozolomide for newly diagnosed glioblastoma. J Clin Oncol. 2009 Aug 8;27(23):3861.

50. Laack NN, Brown PD. Cognitive sequelae of brain radiation in adults. InSeminars in oncology. 2004;31:702-713.

51. Gonzalez J, Kumar AJ, Conrad CA, Levin VA. Effect of bevacizumab on radiation necrosis of the brain. Int J Radiat Oncol * Biol* Phys.2007;67:323-326.

52. Peißner W, Kocher M, Treuer H, Gillardon F. Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. Mol Brain Res. 1999;71:61-68.

53. Lee AW, Kwong DL, Leung SF, Tung SY, Sze WM, et al. Factors affecting risk of symptomatic temporal lobe necrosis: significance of fractional dose and treatment time. Int J Radiat Oncol * Biol* Phys. 2002;53:75-85.

54. Monje ML, Palmer T. Radiation injury and neurogenesis. Curr Opin Neurol. 2003;16:129-134.

55. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol.2009;10:1037-1044.

56. Sun A, Bae K, Gore EM, Movsas B, Wong SJ, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non–small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol. 2011; 29:279.

57. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. Jama. 2016; 316:401-409.

58. Newton HB, editor. Handbook of neuro-oncology neuroimaging. Acad. Press; 2016.

59. Hlaihel C, Guilloton L, Guyotat J, Streichenberger N, Honnorat J, et al. Predictive value of multimodality MRI using conventional, perfusion, and spectroscopy MR in anaplastic transformation of low-grade oligodendrogliomas. J. Neuro-Oncol. 2010; 97:73-80.

60. Newton HB, editor. Handbook of neuro-oncology neuroimaging. Academic Press; 2016.

61. Rock JP, Scarpace L, Hearshen D, Gutierrez J, Fisher JL, et al. Associations among magnetic resonance spectroscopy, apparent diffusion coefficients, and image-guided histopathology with special attention to radiation necrosis. Neurosurgery. 2004;54:1111-1119.