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Differential approach to diagnosis and treatment of astrocytic tumors in elderly patients (literature review)

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Abstract. Astrocytic tumors represent a significant challenge in neuro-oncology, particularly in elderly patients where diagnostic complexities and treatment considerations differ from younger cohorts. This literature review synthesizes current knowledge on the differential diagnosis and tailored treatment strategies for astrocytic tumors in the elderly. We explore the unique clinical presentations, radiological features, histological considerations, and molecular markers that influence decision-making in this vulnerable population. Furthermore, we discuss age-specific treatment modalities, including surgical resection, radiotherapy, chemotherapy, and emerging targeted therapies, emphasizing the balance between oncological efficacy and quality of life. The review aims to provide a comprehensive overview for clinicians navigating the intricate landscape of astrocytic tumor management in elderly individuals.

Keywords: Astrocytic tumors, elderly, glioblastoma, anaplastic astrocytoma, diffuse astrocytoma, differential diagnosis, treatment, MRI, CT.

Annotatsiya. Astrotsitar o'smalar neyroonkologiyada, ayniqsa diagnostik murakkabliklar va davolash bo'yicha mulohazalar yosh kontingentlardan farq qiladigan keksa bemorlarda, muhim muammo hisoblanadi. Mazkur adabiyotlar sharhi keksa yoshdagilarda astrotsitar o'smalarning differensial diagnostikasi va individuallashtirilgan davolash strategiyalari bo'yicha mavjud bilimlarni umumlashtiradi. Biz ushbu zaif populyatsiyada qaror qabul qilishga ta'sir ko'rsatadigan o'ziga xos klinik ko'rinishlar, radiologik xususiyatlar, gistologik jihatlar va molekulyar markerlarni ko'rib chiqamiz. Bundan tashqari, biz yoshga xos davolash usullarini, jumladan jarrohlik rezeksiyasi, radioterapiya, kimyoterapiya va istiqbolli maqsadli terapiyalarni muhokama qilamiz, bunda onkologik samaradorlik va hayot sifati o'rtasidagi muvozanatga alohida e'tibor qaratiladi. Sharhning maqsadi — keksa shaxslarda astrotsitar o'smalarni boshqarishning murakkab manzarasida yo'l topishga harakat qiladigan klinisistlar uchun keng qamrovli umumiy ma'lumot taqdim etishdir.

Kalit so'zlar: Astrotsitar o'smalar, keksa yosh, glioblastoma, anaplastik astrotsitoma, diffuz astrotsitoma, differensial diagnostika, davolash, MRT, KT.

Резюме. Астроцитарные опухоли представляют собой значительную проблему в нейроонкологии, особенно у пациентов пожилого возраста, где диагностические сложности и подходы к лечению отличаются от более молодых групп. В данном обзоре литературы обобщаются современные знания о дифференциальной диагностике и индивидуализированных стратегиях лечения астроцитарных опухолей у лиц пожилого возраста. Рассматриваются особенности клинических проявлений, рентгенологические признаки, гистологические характеристики и молекулярные маркеры, влияющие на принятие решений в отношении данной уязвимой категории пациентов. Кроме того, обсуждаются возрастно-ориентированные методы лечения, включая хирургическую резекцию, лучевую терапию, химиотерапию и перспективные таргетные методы терапии, с

акцентом на баланс между онкологической эффективностью и качеством жизни. Цель обзора — предоставить клиницистам комплексный обзор сложной картины ведения астроцитарных опухолей у пациентов пожилого возраста.

Ключевые слова: астроцитарные опухоли, пожилой возраст, глиобластома, анапластическая астроцитома, диффузная астроцитома, дифференциальная диагностика, лечение, МРТ, КТ.

1. Introduction

Astrocytic tumors are the most common primary brain tumors, with glioblastoma (GBM) being the most aggressive and prevalent form. The incidence of these tumors, particularly GBM, significantly increases with age, with a median age at diagnosis often in the seventh decade of life [1]. Elderly patients, generally defined as those over 65 years of age, present a unique set of challenges in the management of astrocytic tumors. These challenges stem from altered tumor biology, increased prevalence of comorbidities, reduced physiological reserve, and a different set of priorities regarding treatment goals, often prioritizing quality of life over aggressive life-prolonging therapies that may compromise functional independence [2].

Traditional treatment paradigms for astrocytic tumors, largely established in younger, fitter patient populations, may not be directly transferable to the elderly. Age-related changes in brain metabolism, drug pharmacokinetics, and response to radiation can influence treatment efficacy and toxicity [3]. Therefore, a differential approach encompassing diagnosis, prognostication, and treatment selection is crucial for optimizing outcomes in elderly patients with astrocytic tumors. This review aims to delineate these differential considerations, providing a framework for individualized patient management.

2.History

A thorough history of patients with astrocytoma is a critical component of the diagnostic process, providing valuable insights into symptoms' onset, progression, and nature. Symptoms can be divided into 2 categories: general and focal. General symptoms include headache (usually early morning), nausea, vomiting, cognitive difficulties, personality changes, and gait disorders. Localizing symptoms include seizures, aphasia, or visual field defects. About 50% of patients with supratentorial brain tumors may present with seizures. A visual field defect is often unnoticed by the patient and may be revealed after it leads to injury, such as motor vehicle accidents[50].

It is essential to document the duration, frequency, and severity of these symptoms and any factors that exacerbate or alleviate them. Additionally, the patient's medical history, including prior head injuries, exposure to ionizing radiation, and family history of neurological disorders or cancers, should be thoroughly explored. Clinicians should also assess the patient's functional status, noting any impact on daily activities and quality of life. This comprehensive history helps to establish a timeline of symptom development, identify potential risk factors, and guide further diagnostic evaluations, ultimately contributing to a more accurate and timely diagnosis of astrocytoma[50].

3. Physical Examination

The physical examination of patients with astrocytoma involves a comprehensive neurological assessment to evaluate the extent and impact of the tumor on the CNS. During the neurological examination, attention is given to cranial nerve function, motor strength, coordination, sensory perception, and reflexes. Specific tests may include evaluating visual fields, assessing gait and balance, and testing for signs of increased intracranial pressure, such as papilledema. These findings help localize the tumor and gauge its severity, guiding further diagnostic imaging and treatment planning. The examination results, imaging studies, and histological analysis are crucial for establishing an accurate diagnosis and developing an effective treatment strategy[50].

4. Differential Diagnosis in Elderly Patients

The presentation of astrocytic tumors in elderly patients can be insidious and non-specific, often mimicking other age-related neurological conditions. Cognitive decline, memory impairment, and subtle personality changes may be initially attributed to dementia or other neurodegenerative

disorders, leading to diagnostic delays [4]. Seizures, focal neurological deficits, and headaches are common presenting symptoms, but their prevalence and characteristics can vary compared to younger patients [5].

4.1. Clinical Presentation

Elderly patients with astrocytic tumors may present with:

- **Progressive cognitive decline:** This is often the most challenging symptom to differentiate from age-related cognitive impairment or dementia [6].
- **Subtle focal neurological deficits:** Hemiparesis, language disturbances, or visual field defects may progress slowly, making early detection difficult [7].
- **Seizures:** While seizures are a common presentation, they may be less dramatic or generalized in older adults, sometimes manifesting as transient confusion or behavioral changes [8].
- **Headaches:** Headaches may be less prominent or atypical in the elderly compared to younger patients with brain tumors [9].
- **Behavioral changes and mood disturbances:** These can be mistaken for psychiatric disorders [10].

4.2. Neuroimaging

Neuroimaging, particularly Magnetic Resonance Imaging (MRI) and Computed Tomography (CT), is indispensable for the diagnosis and differential diagnosis of astrocytic tumors. However, interpreting these images in elderly patients requires careful consideration due to common age-related brain changes.

4.2.1. Magnetic Resonance Imaging (MRI)

MRI is the gold standard for brain tumor imaging, providing detailed anatomical and pathological information.

- **Glioblastoma (GBM):** In elderly patients, GBM typically presents as an irregularly enhancing, heterogeneous mass with central necrosis and surrounding vasogenic edema on T1-weighted post-contrast images [11]. The presence of extensive peritumoral edema, disproportionate to the enhancing tumor volume, is also common. Diffusion-weighted imaging (DWI) and perfusion MRI can provide additional information regarding tumor cellularity and vascularity [12]. However, differentiating GBM from other lesions can be challenging.
- **Anaplastic Astrocytoma (AA):** AA may present as an ill-defined, non-enhancing or minimally enhancing mass on T1-weighted images, often with hyperintensity on T2-weighted and FLAIR sequences [13].
- **Diffuse Astrocytoma (DA):** Low-grade diffuse astrocytomas typically appear as non-enhancing, T1 hypointense and T2/FLAIR hyperintense lesions, often with ill-defined margins [14].

Differential Considerations on MRI:

- **Metastatic disease:** Brain metastases are more common in the elderly and can mimic high-grade astrocytomas. Multiple lesions, a history of systemic malignancy, and a more well-defined, spherical enhancement pattern can suggest metastases [15].
- **Stroke:** Ischemic strokes, particularly subacute or chronic infarcts, can show T2/FLAIR hyperintensity and sometimes patchy enhancement, which can be confusing. DWI sequences are crucial in differentiating acute stroke [16].
- **Infections:** Abscesses or granulomas can present with ring enhancement. Clinical context, laboratory findings, and advanced imaging techniques like spectroscopy can aid in differentiation [17].
- **Demyelinating diseases:** While less common to mimic high-grade tumors, atypical demyelinating lesions can sometimes present with mass effect and enhancement [18].
- **Posterior Reversible Encephalopathy Syndrome (PRES):** Can present with vasogenic edema, particularly in the posterior circulation, in patients with hypertension or other underlying conditions [19].

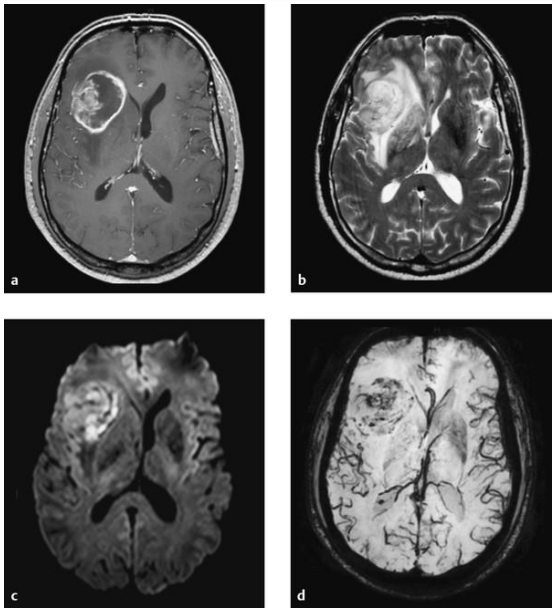


Fig.1. Glioblastoma multiforme. (a) T1w image shows a glioblastoma with scalloped rim enhancement and central necrosis. (b) On a T2w image, the tumor core shows a partially distinct and partially ill-defined transition to nonenhancing hyperintense peripheral tumor components and peritumoral edema. The edema is difficult to distinguish from peripheral tumor. (c) Several medial and posterior tumor components have undergone malignant transformation, with associated restriction of diffusion. (d) SWI sequence shows numerous signal voids caused by pathologic tumor vessels and microhemorrhages.

4.2.2. Computed Tomography (CT)

CT is often the initial imaging modality due to its availability and speed, especially in emergency settings.

- **Astrocytic tumors on CT:** Astrocytic tumors can appear as hypodense or isodense lesions, with variable enhancement patterns after contrast administration. GBM typically shows irregular, peripheral enhancement with a central hypodense necrotic core and surrounding edema [20].
- **Differential Considerations on CT:**
  - **Chronic subdural hematoma:** Can mimic a mass effect and may sometimes show enhancement along the membranes [21].
  - **Cerebral atrophy:** While not a mass lesion, significant atrophy can lead to increased ventricular size and sulcal prominence, which might influence tumor visibility [22].
  - **Calcifications:** While uncommon in astrocytomas, some low-grade tumors can calcify. This must be differentiated from other calcified lesions [23].

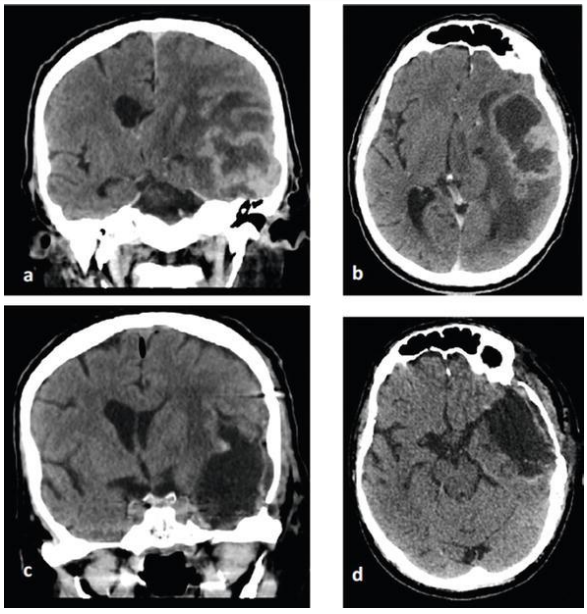


Fig.2. Coronal (a) and axial (b) preoperative contrasted CT scan examination of a case with left temporal inhomogeneous expansive lesion with a “ring enhancement” highly suggestive for a glioblastoma; (c) and (d) immediate postoperative contrasted CT scan examination demonstrating gross total removal of the tumor.

4.3. Histopathology and Molecular Markers

Biopsy remains the definitive diagnostic tool. In elderly patients, tumor biology can differ, with a higher prevalence of specific molecular alterations.

- **IDH mutations:** Isocitrate dehydrogenase (IDH) mutations are less common in elderly patients with astrocytic tumors, particularly GBM, and their absence is associated with a worse prognosis [24]. IDH-wildtype GBM is the most common subtype in older adults.
- **MGMT promoter methylation:** O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is a significant prognostic and predictive biomarker for response to temozolomide (TMZ). Its prevalence and predictive value remain relevant in the elderly, though its impact on survival may be modulated by other factors [25].
- **TERT promoter mutation:** Telomerase reverse transcriptase (TERT) promoter mutations are common in GBM and are associated with worse prognosis, particularly in IDH-wildtype tumors [26].
- **1p/19q co-deletion:** This genetic alteration is characteristic of oligodendrogliomas and is rare in pure astrocytic tumors, but its presence is crucial for diagnosis and treatment decisions [27].

5. Treatment Strategies in Elderly Patients

Treatment decisions for astrocytic tumors in elderly patients require a personalized approach, balancing aggressive oncological treatment with the patient's functional status, comorbidities, and quality of life goals. A comprehensive geriatric assessment, including evaluation of functional status (e.g., Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status), cognitive function, nutritional status, and social support, is essential [28].

5.1. Surgical Resection

Maximal safe surgical resection remains the cornerstone of treatment for astrocytic tumors, aiming to reduce tumor burden, alleviate symptoms, and obtain tissue for diagnosis. In elderly patients, the risks and benefits of surgery must be carefully weighed.

- **Extent of Resection:** Studies suggest that a greater extent of resection (EOR) is associated with improved survival even in elderly patients, provided it can be achieved safely [29].

However, aggressive resection in eloquent areas carries a higher risk of postoperative neurological deficits, which can be more debilitating for older individuals with less functional reserve [30].

- **Minimally Invasive Techniques:** Stereotactic biopsy is often preferred in elderly patients with poor performance status or deep-seated lesions where extensive resection is deemed too risky [31]. Awake craniotomy, while offering better functional mapping, may be challenging for some elderly patients.
- **Risks:** Elderly patients are at higher risk of postoperative complications, including infections, thromboembolic events, and delirium [32]. Careful preoperative optimization and multidisciplinary care are crucial.

5.2. Radiotherapy (RT)

Radiotherapy is an integral part of treatment for high-grade astrocytomas. However, the optimal regimen for elderly patients remains a subject of ongoing research.

- **Standard Regimen (Concurrent RT/TMZ):** The Stupp protocol (concurrent temozolomide with 60 Gy fractionated radiotherapy over 6 weeks, followed by adjuvant temozolomide) is the standard for younger patients with GBM [33]. For elderly patients, this regimen can be associated with increased toxicity, particularly myelosuppression and fatigue [34].
- **Hypofractionated Radiotherapy:** Several studies have investigated hypofractionated radiotherapy (e.g., 40 Gy in 15 fractions or 34 Gy in 10 fractions) as a less intensive alternative, offering comparable survival outcomes with potentially reduced toxicity and a shorter treatment duration [35, 36]. This approach is often favored for elderly patients with lower performance status.
- **Monotherapy Radiotherapy:** For very frail elderly patients, palliative radiotherapy (e.g., 30 Gy in 10 fractions) may be considered to manage symptoms and improve quality of life [37].
- **MGMT Promoter Methylation:** The presence of MGMT promoter methylation is a strong predictor of response to TMZ, and in elderly patients, it may influence the choice between radiotherapy alone versus combined chemoradiotherapy [38].

5.3. Chemotherapy

Chemotherapy, primarily with temozolomide (TMZ), plays a critical role in the management of astrocytic tumors.

- **Temozolomide (TMZ):** For elderly patients with GBM, particularly those with MGMT promoter methylation, TMZ monotherapy or in combination with hypofractionated RT has shown benefit [39]. Dose adjustments may be necessary due to age-related changes in renal or hepatic function and to minimize myelosuppression [40].
- **Bevacizumab:** Bevacizumab, an anti-VEGF monoclonal antibody, can be used for recurrent GBM or as a palliative measure to reduce edema and improve symptoms, though it does not typically improve overall survival [41]. Its use in the elderly should consider potential side effects like hypertension, proteinuria, and thromboembolic events.
- **Other Chemotherapies:** Other chemotherapeutic agents are generally reserved for recurrent disease or specific molecular subtypes.

5.4. Targeted Therapies and Novel Approaches

Research into targeted therapies and novel approaches is ongoing, with several agents showing promise.

- **IDH Inhibitors:** For IDH-mutant low-grade astrocytomas, IDH inhibitors are emerging as a new therapeutic avenue, though their role in older adults with the less common IDH-mutant GBM is still being defined [42].
- **Tumor-Treating Fields (TTFields):** TTFields, an anti-mitotic treatment, have been shown to improve survival in newly diagnosed and recurrent GBM [43]. While data specifically for elderly patients are still accumulating, TTFields can be considered for those who can tolerate the device and daily wear.

- **Immunotherapy:** Immune checkpoint inhibitors are under investigation for GBM, but current data do not demonstrate significant benefit in unselected patient populations. Research is ongoing to identify specific subgroups that may respond [44].
- **Clinical Trials:** Elderly patients should be encouraged to participate in clinical trials designed specifically for their age group, which may offer access to novel therapies and optimized treatment regimens [45].

5.5. Supportive Care and Quality of Life

Supportive care is paramount in elderly patients with astrocytic tumors.

- **Symptom Management:** Aggressive management of symptoms like seizures, headaches, fatigue, and cognitive dysfunction is crucial for maintaining quality of life [46].
- **Rehabilitation:** Physical, occupational, and speech therapy can help maximize functional independence and address neurological deficits [47].
- **Psychological Support:** Addressing anxiety, depression, and existential concerns is vital for both patients and their families [48].
- **Advance Care Planning:** Discussions about prognosis, treatment goals, and end-of-life care are essential to ensure that interventions align with patient preferences [49].

6. Conclusion

The diagnosis and treatment of astrocytic tumors in elderly patients present a complex and evolving challenge. A differential approach, integrating careful clinical assessment, advanced neuroimaging interpretation, and molecular profiling, is essential for accurate diagnosis. Treatment strategies must be highly individualized, considering the patient's functional status, comorbidities, and personal values. While maximal safe resection, tailored radiotherapy regimens (often hypofractionated), and temozolomide remain cornerstones, the landscape is continually evolving with emerging targeted therapies and supportive care innovations. A multidisciplinary team approach, prioritizing both oncological efficacy and quality of life, is fundamental to optimizing outcomes for this vulnerable population. Further research is needed to develop age-specific diagnostic markers and therapeutic interventions to improve the prognosis and well-being of elderly patients with astrocytic tumors.

References

1. Ostrom, Q. T., et al. (2020). CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States, 2013-2017. *Neuro-Oncology*, 22(12), iv1-iv96.
2. Weller, M., et al. (2018). European Association for Neuro-Oncology (EANO) guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Lancet Oncology*, 19(5), e311-e324.
3. Preusser, M., et al. (2015). Glioblastoma in the elderly: A therapeutic challenge. *Current Opinion in Oncology*, 27(6), 498-503.
4. Taphoorn, M. J., et al. (2010). Cognitive functioning in patients with primary brain tumors: a review. *Current Opinion in Neurology*, 23(6), 663-668.
5. Armstrong, T. S., et al. (2016). Symptom burden and its impact on quality of life in patients with primary brain tumors. *Neuro-Oncology*, 18(Suppl 2), ii17-ii23.
6. Klein, M., et al. (2002). Cognitive symptoms and performance in brain tumor patients: a systematic review. *Journal of Clinical Oncology*, 20(3), 856-867.
7. Ghasemi, M., et al. (2017). Neurological complications of brain tumors: diagnosis and management. *Journal of Neuro-Oncology*, 131(1), 1-14.
8. Sirven, J. I., et al. (2007). Seizures in brain tumors. *Neurology*, 69(Suppl 1), S12-S19.
9. Wessel, C. B., et al. (2018). Headache characteristics in patients with brain tumors: a prospective study. *Cephalalgia*, 38(10), 1632-1639.
10. Mainio, A., et al. (2005). Psychological distress in patients with brain tumors: A prospective study. *Journal of Neuro-Oncology*, 73(1), 27-32.
11. Pope, W. B. (2004). Neuroimaging of primary brain tumors. *Journal of Neuro-Oncology*, 70(2), 185-201.

12. Hilario, A., et al. (2012). Advanced MR imaging techniques in glioblastoma: from diagnosis to follow-up. *Radiation Oncology*, 7, 107.
13. Mair, R., et al. (2019). Imaging of adult diffuse gliomas: current recommendations and emerging techniques. *Insights into Imaging*, 10(1), 76.
14. Osborn, A. G. (2018). *Osborn's Brain: Imaging, Pathology, and Anatomy*. Elsevier.
15. Gavrilovic, I., et al. (2009). Brain metastases: pathophysiology and clinical management. *Nature Reviews Clinical Oncology*, 6(8), 469-479.
16. Wintermark, M., et al. (2008). Perfusion imaging for stroke: a comprehensive review. *AJNR American Journal of Neuroradiology*, 29(4), 570-579.
17. Sreedher, G., et al. (2017). Diagnostic challenges in ring-enhancing brain lesions. *Journal of Clinical Neuroscience*, 45, 126-132.
18. Filippi, M., et al. (2016). Differential diagnosis of multiple sclerosis and its variants. *Nature Reviews Neurology*, 12(7), 415-426.
19. Hinchey, J., et al. (2000). A reversible posterior leukoencephalopathy syndrome. *New England Journal of Medicine*, 342(18), 1321-1327.
20. Smirniotopoulos, J. G., et al. (2007). Primary brain tumors. *Radiology*, 242(2), 340-352.
21. Adhiyaman, V., et al. (2002). Chronic subdural haematoma in elderly patients. *Postgraduate Medical Journal*, 78(916), 71-75.
22. Raz, N., et al. (2005). Regional brain atrophy in healthy adults: a prospective study on the effects of normal aging, stress, and disease. *Neurobiology of Aging*, 26(3), 443-453.
23. Naidich, T. P., et al. (2009). Intracranial calcifications: prevalence and significance. *Radiographics*, 29(6), 1735-1759.
24. Sanson, M., et al. (2009). Isocitrate dehydrogenase 1 mutation is a powerful prognostic marker in primary glioblastoma. *Journal of Clinical Oncology*, 27(25), 4150-4154.
25. Hegi, M. E., et al. (2005). MGMT gene silencing and benefit from temozolomide in glioblastoma. *New England Journal of Medicine*, 352(10), 997-1003.
26. Killela, V. P., et al. (2013). TERT promoter mutations occur frequently in gliomas and a subset of meningiomas with increased risk of recurrence. *Acta Neuropathologica*, 126(6), 861-869.
27. Cairncross, G., et al. (1998). Deletion of LOH 1p/19q in oligodendrogliomas is a strong predictive marker of chemosensitivity. *Journal of the National Cancer Institute*, 90(21), 1640-1647.
28. Pellergrino, C., et al. (2017). Geriatric assessment in older adults with cancer: a review. *Current Oncology Reports*, 19(5), 32.
29. Lacroix, M., et al. (2001). A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *Journal of Neurosurgery*, 95(2), 190-198.
30. Smith, J. S., et al. (2008). Extent of resection and survival in glioblastoma: a systematic review and meta-analysis. *Journal of Neuro-Oncology*, 88(2), 183-190.
31. Dhandapani, S. S., et al. (2017). Stereotactic biopsy for brain lesions: a review. *Neurology India*, 65(Suppl 1), S107-S113.
32. Chaichana, K. L., et al. (2011). Complications of surgery for glioblastoma: an analysis of the SEER-Medicare database. *Journal of Neurosurgery*, 114(5), 1195-1204.
33. Stupp, R., et al. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England Journal of Medicine*, 352(10), 987-996.
34. Malmstrom, A., et al. (2012). Temozolomide and radiotherapy in the elderly patient with glioblastoma. *Journal of Neuro-Oncology*, 107(1), 1-8.
35. Niyazi, M., et al. (2016). Hypofractionated radiotherapy for glioblastoma: a systematic review and meta-analysis. *Radiotherapy and Oncology*, 118(1), 1-8.
36. Perry, J. R., et al. (2017). Short-course radiation plus temozolomide in elderly patients with glioblastoma. *New England Journal of Medicine*, 376(11), 1027-1037.
37. Roa, W., et al. (2004). A phase III trial comparing whole-brain radiotherapy with stereotactic radiosurgery boost versus whole-brain radiotherapy alone for patients with one to three brain metastases: results of NCCTG N0177. *Journal of Clinical Oncology*, 22(14_suppl), 2005-2005.

38. Wick, W., et al. (2012). NOA-08 randomized phase III trial of sequential radium-223 and external beam radiation therapy versus external beam radiation therapy alone for newly diagnosed glioblastoma in elderly patients. *Neuro-Oncology*, 14(11), 1435-1442.
39. Chinot, O. L., et al. (2014). Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *New England Journal of Medicine*, 370(8), 709-722.
40. Brada, M., et al. (2003). Temozolomide in primary brain tumours. *British Journal of Cancer*, 89(1), 3-8.
41. Norden, A. D., et al. (2010). Bevacizumab for recurrent glioblastoma. *New England Journal of Medicine*, 363(15), 1432-1442.
42. Mellinghoff, I. K., et al. (2021). Vorasidenib in IDH-mutant low-grade glioma. *New England Journal of Medicine*, 385(13), 1167-1178.
43. Stupp, R., et al. (2017). Effect of tumor-treating fields plus maintenance chemotherapy on survival in newly diagnosed glioblastoma: a randomized clinical trial. *JAMA*, 318(23), 2306-2316.
44. Reardon, D. A., et al. (2020). Immunotherapy for glioblastoma: a review. *Cancer Treatment Reviews*, 85, 101991.
45. Siegel, R. L., et al. (2020). Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians*, 70(1), 7-30.
46. O'Neill, B. P. (2006). Neurologic complications of cancer. *Mayo Clinic Proceedings*, 81(10), 1358-1378.
47. Palese, A., et al. (2019). The role of rehabilitation in brain tumor patients: a systematic review. *Journal of Neuro-Oncology*, 141(1), 1-10.
48. Sizoo, E. M., et al. (2010). Psychological distress in patients with glioblastoma and their caregivers. *Psycho-Oncology*, 19(5), 472-479.
49. Emanuel, L. L., et al. (2000). Advance care planning. *Journal of Clinical Oncology*, 18(16), 3121-3125.
50. https://www.ncbi.nlm.nih.gov/books/NBK559042/
51. Ștefan Ioan Florian and Sergiu Șușman. Diffuse Astrocytoma and Oligodendroglioma: An Integrated Diagnosis and Management. Submitted: 27 November 2017 Reviewed: 05 March 2018 Published: 05 November 2018. DOI: 10.5772/intechopen.76205