D J Med Sci 2021;7(3):314-322
doi: 10.5606/fng.btd.2021.25074

Review

Current trends in Glioblastoma

Mihrican Koçak[1], Özüm Atasoy[2], Nilsu Çini[2], Oytun Erbaş[1]

[1]*Institute of Experimental Medicine, Kocaeli, Turkey*
[2]*Department of Radiation Oncology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Turkey*
[3]*Department of Physiology, Demiroglu Science University, Faculty of Medicine, Istanbul, Turkey*

ABSTRACT

Glioblastoma is the most aggressive primary malignant brain tumor, also known as isocitrate dehydrogenase (IDH) wild-type gliomas. Symptoms vary depending on where the tumor is located. It is often manifested by headaches, epileptic seizures, and personality changes. Glioblastoma constitutes 15% of primary brain tumors and the reasons for its formation are still unclear. Primary treatment is surgery, followed by chemoradiotherapy. Although maximal surgical resection is standard, it often recurs. The vast majority of patients die within two years of diagnosis. In this study, we aimed to examine glioblastoma in detail with the treatment possibilities available today.

Keywords: Glioblastoma, isocitrate dehydrogenase, O6-methylguanine-DNA methyltransferase.

A brain tumor is defined as an abnormally growing cluster of cells within the brain. Glioblastoma is a tumor in the malignant group that can develop in the brain and spinal cord, consisting of glia that supports nerve cells. Glioblastoma is mostly sporadic, except in rare cases, Turcot syndrome or Li-Fraumeni syndrome.[1] According to the 6th version classification made by the World Health Organization (WHO) in 2021,[2] glioblastomas are Grade IV diffuse astrocytic tumors with retained isocitrate dehydrogenase (IDH) wild-type and nuclear ATRX.

According to the old classification, glioblastoma was divided into primary and secondary according to its development. Primary glioblastoma arises directly (de novo) from glial precursor cells and is seen in the older population. It usually gives clinical symptoms in the first three months.[3,4] Glioblastoma is the most common primary brain malignant tumor in adults.[5,6] It characteristically has an amplification as well as overexpression of the epidermal growth factor receptor (EGFR) and ligand.[7] Secondary glioblastoma tumors are formed by the conversion of pre-existing lower grade astrocytomas to the more malignant grade of anaplasia.[4] Although patients with secondary glioblastoma can be considered younger, their average age is 45 years.[8]

NEW MOLECULAR CLASSIFICATION OF GLIOBLASTOMA

After the WHO 2021 classification of tumors of the central nervous system (CNS)[2] and cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy),[9] the definition of glioblastoma has changed. It now integrates into the glioma classification, histological tumor typing, and grading, as well as analyzes of molecular markers.

Tissue for histopathological diagnosis is first examined for isocitrate dehydrogenase 1 (IDH1) mutation and loss of nuclear ATRX. In patients >55 years of age without a previously known low-grade glioma, with a tumor located outside the midline, and with preserved nuclear ATRX

Received: December 28, 2021
Accepted: January 10, 2022
Published online: January 28, 2022

Correspondence: Mihrican Koçak.
e-mail: kocakmihrican3@gmail.com

Cite this article as:
Koçak M, Atasoy Ö, Çini N, Erbaş O. Current trends in Glioblastoma. D J Med Sci 2021;7(3):314-322.

expression, the presence of immunohistochemical negativity for IDH1 R132H is sufficient for classification as IDH wild-type. Patients with the histone H3.3 G34R/V mutation with IDH wild-type but the loss of nuclear ATRX are defined as Grade IV diffuse hemispheric glioma. To identify diffuse midline gliomas, it should be evaluated for histone H3 K27M mutations and loss of nuclear K27-trimethylated histone H3 (H3K27me3). IDH wild-type diffuse astrocytic gliomas without microvascular proliferation or necrosis should be tested for +7/-10 cytogenetic signature as EGFR amplification, TERT (telomerase reverse transcriptase) promoter mutation, and molecular features of IDH wild-type glioblastomas.[2,10]

Isocitrate dehydrogenase wild-type is essential for the diagnosis of glioblastoma. Although their histological appearance is similar in IDH-mutant and wild-type gliomas, they are no longer used to refer to as IDH-mutant astrocytic gliomas because their prognosis and biological features are different. IDH-mutant astrocytomas are now divided into three WHO grades: astrocytoma, IDH-mutant, WHO Grade 2; astrocytoma, IDH-mutant, WHO Grade 3 (instead of anaplastic astrocytoma, IDH-mutant, WHO Grade 3); and astrocytoma, IDH-mutant, WHO Grade 4 (old term glioblastoma, IDH-mutant.[9,10]

ISOCITRATE DEHYDROGENASE

Studies show that many genetic factors play a role in the development of glioblastoma. One of these genes is the IDH gene, which encodes the isocitrate dehydrogenase enzyme that plays a role in energy production and participates in the Krebs cycle.[11] The IDH enzyme family consists of three distinct proteins found in the cytoplasm and peroxisomes (IDH1) and mitochondria (IDH2 and IDH3), involved in many cellular processes such as mitochondrial oxidative phosphorylation, glutamine metabolism, lipogenesis, glucose sensing, and regulation of cellular redox state.[12-14] IDH3 is a heterotetrameric complex enzyme that catalyzes the conversion of isocitrate to alpha-ketoglutarate (α-KG) in the tricarboxylic acid cycle in a nicotinamide adenine dinucleotide (NAD+) dependent manner.[15] IDH1 and IDH2 are very similar homodimer enzymes that catalyze nicotinamide adenine dinucleotide phosphate (NADP+) dependent oxidative decarboxylation to α-KG.[15] It is also the main producer in the brain of NADPH, an important cellular reducing agent that plays a role in protection against reactive oxygen deoxyribonucleic acid (DNA) damage, which is required for detoxification through the reduction of IDH1, glutathione, and thioxins and activation of catalase.[15]

Somatic point mutations in IDH1/2 result in increased secretion and accumulation of D-2-hydroxyglutarate (D-2HG), an oncometabolite.[16] Overproduction of D-2HG inhibits α-KG-dependent dioxygenases, including histone and DNA methyls, leading to histone and DNA hypermethylation.[16] As a result, it enables tumor cells to maintain their biosynthetic precursor pools and suppress mitochondrial reactive oxygen species (ROS). Suppression of reactive species, even if oxygen metabolism is disrupted, blocking of DNA repair mechanism contributes to sustaining rapid proliferation rates, accelerating new vessel formation, thus contributing to oncogenesis.[11,16-18]

Isocitrate dehydrogenase wild-type glioblastoma is much more aggressive than IDH-mutant astrocytomas.[19] In addition, IDH1 mutation has been shown to be strongly associated with survival.[20] It has been confirmed in many studies that the survival of people with this mutation is longer.[19,21-22]

The results obtained in the studies show that the inhibition of mutant IDH1/2 enzymes reverses the differentiation by decreasing the D-2HG level in the cell.[16] Therefore, mutant IDH1/2 enzyme inhibitors represent a good group of drugs used in the treatment of patients with IDH/2 mutations.[16]

O^6-METHYLGUANINE-DNA METHYLTRANSFERASE (MGMT)

Another gene is the MGMT gene, which encodes the "O^6-methylguanine DNA methyltransferase" (MGMT) enzyme consisting of 207 amino acids. O^6-Methylguanine DNA methyltransferase is the most important of the DNA repair proteins that protect DNA from the mutagenic effects of alkylating agents.[23] Therefore, in the presence of MGMT in the cell, the toxicity of alkylating agents is reduced and they cannot manifest

their anticancer properties. This protein has a mechanism that creates resistance to drugs such as alkylating nitrosourea and temozolomide (TMZ) with its activity.[24] In this mechanism, while alkyl groups from the guanine O^6 location, which is one of the DNA alkylation sites, will be induced by chemotherapeutic agents, resistance to chemotherapeutic agents occurs due to their removal by MGMT.[25] It was determined that tumor cells with high MGMT enzyme levels were resistant to TMZ, and cells with low enzyme levels had high TMZ sensitivity.[26] Epigenetic silencing of MGMT by MGMT methylation will result in MGMT inactivation and reduced DNA repair activity.[25] Various studies have reported better responses to radiation therapy (RT) and chemotherapy (ChT) as a result of methylation.[19,22,27,28]

In addition, mutations in the gene of another molecule, TERT promoter, are associated with worse survival independent of other clinical and molecular factors.[29,30] The presence of TERT mutation in IDH wild-type astrocytomas alone is diagnostic for glioblastoma.[2]

The majority of glioblastoma patients are 65 years or older at the time of diagnosis.[31] Among the clinical factors affecting the prognosis of the disease, it has been seen in many studies that advanced age and poor performance status are associated with shorter survival.[31] The average survival of patients 65 years and older is approximately six months.[32,33] IDH mutations are becoming increasingly rare with age.[31] In addition, the most important prognostic factor in patients over 70 years of age is that methylated MGMT offers better survival than unmethylated MGMT.[34]

GLIOBLASTOMA DIAGNOSIS

At diagnosis, patients with glioblastoma include new-onset epilepsy, neurocognitive disorders, focal deficits, and signs and symptoms of increased intracranial pressure. Headache is among the most prominent complaints, but the pain is intermittent, more pronounced in the morning, moderate and very severe unilateral throbbing pain. This pain usually does not respond to medical treatment. Although seizure is usually the first sign in slow-growing superficial tumors, it can also be seen in high-grade tumors such as glioblastoma. Nausea and vomiting also occur following increased intracranial pressure. As a result of neuronal damage that the tumor may cause in the brain tissue, motor and sensory disorders may develop in the innervated region.[35]

The anamnesis taken during the physical examination of the patient is very important in establishing the diagnosis. Considerable attention should be paid to the neurological symptoms here. Hereditary diseases such as neurofibromatosis, Li-Fraumeni, Von Hippel-Lindau, Turcot syndrome should be questioned.[35] Additionally, the high number of deep vein thrombosis and pulmonary thromboembolism cases of malignant gliomas should not be ignored, and the findings related to these conditions should also be paid attention.[35]

The contrast-enhanced magnetic resonance imaging (MRI) technique is used in the diagnosis of glioblastoma. In contrast-enhanced MRI, the gadolinium used as a contrast agent carries minimal allergy risk. Gadolinium allows visualizing tumor formations by enhancing the contrast in areas where the blood-brain barrier is disrupted.[35] A pre-contrast, T1 (longitudinal relaxation) weighted image is taken to observe the anatomy of the brain. In addition, fluid-attenuation inversion recovery (FLAIR) or T2 (transverse relaxation) weighted images are required to detect edema, parenchyma, or corpus callosum invasion.[35]

Peripheral contrast enhancement with a central necrotic cavity in the middle, in the form of a ring with irregular borders, and the appearance of edematous lesions on T2 images around it are typical for glioblastoma.[35,36] 95% of the cases can be diagnosed with imaging techniques.[37]

Perfusion MRI and amino acid positron emission tomography (PET) can be helpful in tumor prediagnosis by identifying metabolic hotspots. It can be used in cases where tumor resection is difficult. Histopathological diagnosis is necessary to determine the prognosis and treatment of the disease. The tissue required for histopathological diagnosis is taken by surgical resection or stereotactic biopsy.[35]

Glioblastoma, which has intense mitosis, vascular proliferation, and necrosis features in its histopathology, has infiltrated the surrounding

tissues extensively and is usually located supratentorial.[38] Metastasis outside of the CNS is not a common condition. Although it is not a common situation, if metastasis is detected, this situation has occurred by hematogenous route or by direct spread of the tumor.

GLIOBLASTOMA TREATMENT

In glioblastoma treatment, following the widest possible surgical resection, simultaneous chemo-RT followed by adjuvant ChT is the main treatment.[38] In surgical treatment, safe maximal resection is aimed without damaging the normal tissues as much as possible. The maximum size of the tumor that can be resected may vary depending on its localization. It has been reported that as the percentage of the resected part of the tumor increases, survival is positively affected.[39]

Due to the invasive nature of glioblastoma, the tumor cannot be completely removed in most surgeries.[40] Even the microscopic size of the tumor that cannot be removed after surgery can cause recurrence. For this reason, RT and ChT constitute the basic treatment after surgery.[41,42]

In cases where the localization of the tumor is risky for the surgery, a stereotactic biopsy can be beneficial.[41] Could be used when the lesion is not suitable for resection, the tumor tissue cannot be removed in a meaningful way, or the general clinical condition of the patient is not suitable for surgery. In cases such as pons glioma, where biopsy is also life-threatening, radiological diagnosis is sufficient for treatment decision.

Under normal conditions and in glioblastoma that is not critically localized, it is sufficient to use a microscope during surgery. However, it can be difficult to distinguish tumors from a normal brain during surgery with conventional light microscopy. In cases where glioblastoma is localized in the speech center, in the control pathways of various limbs, or in the center of understanding; the use of neuronavigation, ultrasound, cortical stimulation, or fluorescein becomes mandatory. Tissue fluorescence after oral administration of 5-ALA (5-aminolevulinic acid) has high sensitivity, specificity, and positive predictive values for identifying malignant glioma tumor tissue.[43] Thus, it helps to reduce postoperative residual tumor volumes while protecting the risk of new tumors.

Unlike patients with meningioma, for whom awake surgery is recommended on the grounds that this high technology is not sufficient in some cases, this opportunity is not available for patients with glioblastoma. The reason for this is that the consciousness will not be clear during surgery because glioblastoma has made a lot of edema in the brain tissue.

Within 24-48 hours after the surgery, the extent of the surgery should be evaluated with MRI (or computed tomography [CT] if MRI is not possible), with and without contrast; it should also include diffusion-weighted arrays for the assessment of perioperative ischemia.[44]

After surgery, in patients with tumors that cannot be completely resected, the risk of progression within one year is reduced by 37%, and the risk of death by 45%.[45] It was determined that the average survival rate was 6.6 months in patients who underwent biopsy only, 10.4 months in partial resection, and 11.3 months incomplete resection.[46]

The purpose of adjuvant RT is to improve local control without inducing neurotoxicity and after surgery is to minimize the postoperative recurrence due to macroscopic or microscopic residues.[10] However, in cases where surgical resection cannot be performed, post-biopsy radiotherapy is the only treatment.

In glioblastoma, 50-60 Gy RT at a fraction dose of 1.8-2 Gy/day is applied for six weeks.[47] During the treatment, fractions are given on weekdays, and the patient is rested at the weekend to help restore normal cells.[47] No randomized data support that doses >60 Gy improve survival.[48] Hypofractionated radiotherapy with a higher dose per fraction and the lower total dose is appropriate in elderly patients and patients with poor performance status.[49]

Surgical bed area plus residual tumor area defined on T1-weighted, T2-weighted, and FLAIR MRI sequences is defined as gross tumor volume (GTV). For microscopic invasion, the clinical target volume (CTV) is established, which is usually modified to include edema on T2-weighted MRI and subtracted from anatomically normal tissues. GTV is given a margin of 1-2 cm. Finally, a margin planning target volume (PTV)

of 0.3-0.5 cm is established for motion or uncertainties during treatment.[50]

Adjuvant ChT is applied simultaneously with RT and afterward. Adjuvant ChT is administered for at least 6 months, once every 28 days for five days.[45,51]

O^6-Methylguanine DNA methyltransferase methylation in glioblastoma leads to DNA repair protein gene silence and loss of expression; it has been observed that this increases the benefit of ChT and has a positive effect on survival.[39] In glioblastoma patients under 70 years of age with MGMT methylation; adjuvant TMZ is recommended in the continuation of a treatment consisting of a combination of RT and TMZ.[41] In the recommended treatment, adjuvant TMZ has been shown to improve survival.[40,52] In addition, there is another alternative treatment created by adding lomustine to the RT and TMZ combination in young and resistant patients, but since it has been observed that it has higher toxicity in the observations, standard RT and TMZ combination therapy is considered more appropriate.[41] In glioblastoma patients without MGMT methylation, there was no statistically significant change in survival when the recommended treatment was applied.[41]

Temozolomide, which is used as a pill, modifies many regions of DNA and is an alkylating agent, is applied both simultaneously with RT and as monotherapy after RT.[46] Temozolomide is an oral alkylating agent dosed according to body surface area (BSA). During radiation, TMZ is given daily (seven days a week) at a dose of 75 mg/m^2.[41] Temozolomide is taken on an empty stomach at least two hours after the last meal. Temozolomide should be taken two hours before RT to maximize synergy with radiation.[39]

Bevacizumab, on the other hand, does not directly target tumor cells but targets the vessels that feed the tumor cells and are their oxygen source. Bevacizumab receives the vascular endothelial growth factor (VEGF) signal, which provides new vessel formation and growth, and blocks its formation. So, bevacizumab, a monoclonal antibody that binds to VEGF, is not recommended for routine use in patients with diagnosed glioblastoma.[53] Although bevacizumab has potent antiedema effects that can heal and reduce glucocorticoid requirements in selected patients with unresectable tumors to control refractory edema and mass effect that may occur during or shortly after RT, it has been reported that it does not improve overall survival and increases the risk of toxicity when used as part of initial therapy.[54] Bevacizumab also called a type of rescue therapy, is a chemotherapeutic that is usually administered when the expected success of treatment is not achieved or in relapses.

It is one of the cases reported that the application of RT, which is applied after surgery during the treatment, together with ChT, prolongs the survival by an average of two months.[55,56] According to another report, the survival rate up to two years is 10.4% with the application of RT alone, while this rate is 26.5% when ChT and RT are applied together.[55]

Alternative electric fields, also a method used in glioblastoma treatment; is a portable medical device that is applied to the scalp and produces Tumor Treating Fields (TTFields).[57,58] Monthly use of the device with TMZ in newly diagnosed glioblastoma patients has been shown to improve both progression-free and overall survival.[59,60] Although it is not a treatment that can be applied to every patient because it creates a potential load, it is applied to the shaved scalp in suitable patients with a four transducer array connected to a portable battery or a device working with a power source during the treatment.[41] The device should be applied continuously or for at least 18 hours a day, on the scalp that is kept shaved.[41] It has been reported experimentally that the treatment is a source of antimitotic action, in which alternating electric fields are generated that exert forces on the charged tubulin subunits, thereby interfering with the formation of the mitotic spindle.[61,62] Clinicians who will prescribe this treatment must be trained and certified.[1]

Scores from 0 to 100 on a criterion called the "Karnofsky Performance Scale" determine the patient's activity. According to this scale; patients with a score of 80-100 can continue their normal activities and do not need care, patients with a score of 50-70 can not work in their social life while they can fulfill most of their personal needs, patients with a score of 0-40 are completely in need of care and their diseases progress much faster. The prognostic factors are primarily affected by Karnofsky's performance status, age,

good mental status, and complete resection of the tumor at a rate of 98%.[63]

The treatment process in older adults may vary depending on factors such as comorbid disease, polypharmacy, increased susceptibility to side effects, and socioeconomic vulnerability.[31] In addition, maximal surgical resection compatible with the preservation of neurological function is recommended instead of biopsy in elderly patients.[31] In the study; A two- or three-month survival advantage was seen after subtotal resection adjusted for gross total resection, tumor size, location, and RT administration.[64] Simultaneous and adjuvant TMZ with RT is also recommended in older adults with good performance status and uneventful comorbidity.[31]

In general, there are no formal clinical studies that define the optimal frequency of follow-up in patients after treatment. The National Comprehensive Cancer Network (NCCN) guidelines recommend repeat MRI in glioblastoma patients approximately four weeks after completion of RT, then every four months for two to three years, and then less frequently.[65]

Despite the developing technology, the genetic structure and prognosis of glioblastoma, which is the most rapidly progressing and deadly known, still has not been fully determined. In addition, although a complete treatment is not possible yet, the patient's quality of life and survival could not be increased significantly. Even if recurrence is very common, there is currently no application that prevents this.

According to the studies so far, the best treatment is RT and ChT to be applied together after a large-scale resected surgery. In addition to MGMT methylation, young age, a good Karnofsky score, ChT, and RT performed together after surgery is important in terms of prolonging the survival and defining a better clinical prognosis of the patient diagnosed with glioblastoma.

According to the findings in our article, survival time is longer in patients with high Karnofsky scores than in patients with low scores. At the same time, it has been clearly seen that the maximum percentage of tumors resected by surgical operation and the survival time are directly proportional.

In general, no situation was encountered that affected the survival time depending on sex and tumor localization. It is among the findings that patients with MGMT methylation have a better prognosis than patients without MGMT methylation, regardless of treatment. And also, it is among the findings that patients without TERT gene mutation have a better prognosis than patients with TERT gene mutation.

In conclusion, glioblastoma is cytogenetically and genetically heterogeneous. Primary glioblastoma, which develops as de nova and is frequently observed in elderly individuals, has a worse prognosis than those with secondary structure seen in younger patients. Prominence and exacerbation of glioblastoma symptoms depend on the amount of local edema and intracranial pressure. They have a more favorable prognosis with short-term and mild symptoms. Despite treatment options, glioblastoma is still quite mortal. The best prognosis belongs to the tumor masses resected with the most extensive surgery. The fact that the studies up to the present period are not yet sufficient for a definitive treatment clearly reveals that many more studies are needed. Discovering the genetic structure of glioblastoma in detail will affect the treatment process in a very positive way.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Krex D, Klink B, Hartmann C, von Deimling A, Pietsch T, Simon M, et al. Long-term survival with glioblastoma multiforme. Brain 2007;130:2596-606.
2. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro Oncol 2021;23:1231-51.
3. Watanabe K, Tachibana O, Sata K, Yonekawa Y, Kleihues P, Ohgaki H. Overexpression of the EGF receptor and p53 mutations are mutually exclusive in the evolution of primary and secondary glioblastomas. Brain Pathol 1996;6:217-23.
4. Kleihues P, Ohgaki H. Primary and secondary glioblastomas: From concept to clinical diagnosis. Neuro Oncol 1999;1:44-51.

5. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, et al. Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev 2014;23:1985-96.
6. Ghosh M, Shubham S, Mandal K, Trivedi V, Chauhan R, Naseera S. Survival and prognostic factors for glioblastoma multiforme: Retrospective single-institutional study. Indian J Cancer 2017;54:362-7.
7. Vogel H, editor. Nervous System: Cambridge Illustrated Surgical Pathology. 1st ed. New York: Cambridge University Press; 2009.
8. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97-109.
9. Louis DN, Wesseling P, Aldape K, Brat DJ, Capper D, Cree IA, et al. cIMPACT-NOW update 6: New entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol 2020;30:844-56.
10. Weller M, van den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 2021;18:170-86.
11. Molenaar RJ, Maciejewski JP, Wilmink JW, van Noorden CJF. Wild-type and mutated IDH1/2 enzymes and therapy responses. Oncogene 2018;37:1949-60.
12. Yen KE, Bittinger MA, Su SM, Fantin VR. Cancer-associated IDH mutations: Biomarker and therapeutic opportunities. Oncogene 2010;29:6409-17.
13. Cairns RA, Mak TW. Oncogenic isocitrate dehydrogenase mutations: Mechanisms, models, and clinical opportunities. Cancer Discov 2013;3:730-41.
14. Reitman ZJ, Yan H. Isocitrate dehydrogenase 1 and 2 mutations in cancer: Alterations at a crossroads of cellular metabolism. J Natl Cancer Inst 2010;102:932-41.
15. Mondesir J, Willekens C, Touat M, de Botton S. IDH1 and IDH2 mutations as novel therapeutic targets: Current perspectives. J Blood Med 2016;7:171-80.
16. Ichimura K, Pearson DM, Kocialkowski S, Bäcklund LM, Chan R, Jones DT, et al. IDH1 mutations are present in the majority of common adult gliomas but rare in primary glioblastomas. Neuro Oncol 2009;11:341-7.
17. Icard P, Poulain L, Lincet H. Understanding the central role of citrate in the metabolism of cancer cells. Biochim Biophys Acta 2012;1825:111-6.
18. Hiller K, Metallo CM. Profiling metabolic networks to study cancer metabolism. Curr Opin Biotechnol 2013;24:60-8.
19. Labussiere M, Wang XW, Idbaih A, Ducray F, Sanson M. Prognostic markers in gliomas. Future Oncol 2010;6:733-9.
20. Rivera AL, Pelloski CE. Diagnostic and prognostic molecular markers in common adult gliomas. Expert Rev Mol Diagn 2010;10:637-49.
21. Kanu OO, Hughes B, Di C, Lin N, Fu J, Bigner DD, et al. Glioblastoma multiforme oncogenomics and signaling pathways. Clin Med Oncol 2009;3:39-52.
22. Ducray F, Idbaih A, Wang XW, Cheneau C, Labussiere M, Sanson M. Predictive and prognostic factors for gliomas. Expert Rev Anticancer Ther 2011;11:781-9.
23. Kaina B, Christmann M, Naumann S, Roos WP. MGMT: Key node in the battle against genotoxicity, carcinogenicity and apoptosis induced by alkylating agents. DNA Repair (Amst) 2007;6:1079-99.
24. Marchesi F, Turriziani M, Tortorelli G, Avvisati G, Torino F, De Vecchis L. Triazene compounds: Mechanism of action and related DNA repair systems. Pharmacol Res 2007;56:275-87.
25. Sabharwal A, Middleton MR. Exploiting the role of O6-methylguanine-DNA-methyltransferase (MGMT) in cancer therapy. Curr Opin Pharmacol 2006;6:355-63.
26. Agarwala SS, Kirkwood JM. Temozolomide, a novel alkylating agent with activity in the central nervous system, may improve the treatment of advanced metastatic melanoma. Oncologist 2000;5:144-51.
27. Weller M, Wick W, Hegi ME, Stupp R, Tabatabai G. Should biomarkers be used to design personalized medicine for the treatment of glioblastoma? Future Oncol 2010;6:1407-14.
28. Rivera AL, Pelloski CE, Gilbert MR, Colman H, De La Cruz C, Sulman EP, et al. MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma. Neuro Oncol 2010;12:116-21.
29. Simon M, Hosen I, Gousias K, Rachakonda S, Heidenreich B, Gessi M, et al. TERT promoter mutations: A novel independent prognostic factor in primary glioblastomas. Neuro Oncol 2015;17:45-52.
30. Labussière M, Boisselier B, Mokhtari K, Di Stefano AL, Rahimian A, Rossetto M, et al. Combined analysis of TERT, EGFR, and IDH status defines distinct prognostic glioblastoma classes. Neurology 2014;83:1200-6.
31. Batchelor T, Shih HA. Management of glioblastoma in older adults. UpToDate [Internet]. 2020 Nov 13. Available at: https://www.uptodate.com/contents/management-of-glioblastoma-in-older-adults?search=Management%20of%20glioblastoma%20in%20older%20adults&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 [Accessed: March 22, 2021].
32. Kita D, Ciernik IF, Vaccarella S, Franceschi S, Kleihues P, Lütolf UM, et al. Age as a predictive factor in glioblastomas: Population-based study. Neuroepidemiology 2009;33:17-22.
33. Amsbaugh MJ, Yusuf MB, Gaskins J, Burton EC, Woo SY. Patterns of care and predictors of adjuvant therapies in elderly patients with glioblastoma: An analysis of the National Cancer Data Base. Cancer 2017;123:3277-84.

34. Gerstner ER, Yip S, Wang DL, Louis DN, Iafrate AJ, Batchelor TT. MGMT methylation is a prognostic biomarker in elderly patients with newly diagnosed glioblastoma. Neurology 2009;73:1509-10.
35. Güler OC. Glioblastome multiforme tanısı ile temozolamid ve eş zamanlı konformal radyoterapi veya yoğunluk ayarlı radyoterapi tekniğiyle eş zamanlı entegre ek doz uygulanan ve uygulanmayan hastaların tedavi sonuçlarının karşılaştırılması. [Uzmanlık Tezi] Ankara: Başkent Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi Anabilim Dalı; 2015.
36. Öge E, Baykan B. Nöroloji. 2. Baskı. İstanbul: Nobel Tıp Kitabevleri; 2015.
37. Vougiouklakis T, Mitselou A, Agnantis NJ. Sudden death due to primary intracranial neoplasms. A forensic autopsy study. Anticancer Res 2006;26:2463-6.
38. Kelly KA, Kirkwood JM, Kapp DS. Glioblastoma multiforme: Pathology, natural history and treatment. Cancer Treat Rev 1984;11:1-26.
39. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997-1003.
40. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
41. Batchelor T. Initial treatment and prognosis of newly diagnosed glioblastoma in adults . UpToDate [Internet]. 2021 Jan 12. Available at: https://www.uptodate.com/contents/initial-treatment-and-prognosis-of-newly-diagnosed-glioblastoma-in-adults?search=Initial%20treatment%20and%20prognosis%20of%20newly%20diagnosed%20glioblastoma%20in%20adults&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 [Accessed: March 21, 2021].
42. Yıldız E, Atasoy Ö, Erbaş O. Glioblastoma drug treatments and animal models. JEB Med Sci 2020;1:140-6.
43. Hadjipanayis CG, Widhalm G, Stummer W. What is the surgical benefit of utilizing 5-aminolevulinic acid for fluorescence-guided surgery of malignant gliomas? Neurosurgery 2015;77:663-73.
44. Bette S, Gempt J, Huber T, Boeckh-Behrens T, Ringel F, Meyer B, et al. Patterns and time dependence of unspecific enhancement in postoperative magnetic resonance imaging after glioblastoma resection. World Neurosurg 2016;90:440-7.
45. Athanassiou H, Synodinou M, Maragoudakis E, Paraskevaidis M, Verigos C, Misailidou D, et al. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. J Clin Oncol 2005;23:2372-7.
46. Karachi A, Dastmalchi F, Mitchell DA, Rahman M. Temozolomide for immunomodulation in the treatment of glioblastoma. Neuro Oncol 2018;20:1566-72.
47. Smith KA, Ashby LS, Gonzalez LF, Brachman DG, Thomas T, Coons SW, et al. Prospective trial of gross-total resection with Gliadel wafers followed by early postoperative Gamma Knife radiosurgery and conformal fractionated radiotherapy as the initial treatment for patients with radiographically suspected, newly diagnosed glioblastoma multiforme. J Neurosurg 2008;109 Suppl:106-17.
48. Khan L, Soliman H, Sahgal A, Perry J, Xu W, Tsao MN. External beam radiation dose escalation for high grade glioma. Cochrane Database Syst Rev 2020;5:CD011475.
49. Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. J Clin Oncol 2004;22:1583-8.
50. Niyazi M, Brada M, Chalmers AJ, Combs SE, Erridge SC, Fiorentino A, et al. ESTRO-ACROP guideline "target delineation of glioblastomas". Radiother Oncol 2016;118:35-42.
51. Oh D, Prayson RA. Evaluation of epithelial and keratin markers in glioblastoma multiforme: An immunohistochemical study. Arch Pathol Lab Med 1999;123:917-20.
52. Stupp R, Hegi ME, Gilbert MR, Chakravarti A. Chemoradiotherapy in malignant glioma: Standard of care and future directions. J Clin Oncol 2007;25:4127-36.
53. Redjal N, Nahed BV, Dietrich J, Kalkanis SN, Olson JJ. Congress of neurological surgeons systematic review and evidence-based guidelines update on the role of chemotherapeutic management and antiangiogenic treatment of newly diagnosed glioblastoma in adults. J Neurooncol 2020;150:165-213.
54. Khasraw M, Ameratunga MS, Grant R, Wheeler H, Pavlakis N. Antiangiogenic therapy for high-grade glioma. Cochrane Database Syst Rev 2014;(9):CD008218.
55. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
56. Stewart LA. Chemotherapy in adult high-grade glioma: A systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet 2002;359:1011-8.
57. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. Eur J Cancer 2012;48:2192-202.
58. Uyanık A, Doğan EÖ, Ateş A, Erbaş O. Glioblastoma multiform tedavisinde alternatif elektrik tümör tedavi alanları: Gerekçe, preklinik ve klinik çalışmalar. FNG & Bilim Tıp Dergisi 2017;3:132-8.

59. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: A randomized clinical trial. JAMA 2015;314:2535-43.
60. Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical Trial. JAMA 2017;318:2306-16.
61. Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, et al. Disruption of cancer cell replication by alternating electric fields. Cancer Res 2004;64:3288-95.
62. Kirson ED, Dbalý V, Tovarys F, Vymazal J, Soustiel JF, Itzhaki A, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A 2007;104:10152-7.
63. Adamson C, Kanu OO, Mehta AI, Di C, Lin N, Mattox AK, et al. Glioblastoma multiforme: A review of where we have been and where we are going. Expert Opin Investig Drugs 2009;18:1061-83.
64. Noorbakhsh A, Tang JA, Marcus LP, McCutcheon B, Gonda DD, Schallhorn CS, et al. Gross-total resection outcomes in an elderly population with glioblastoma: A SEER-based analysis. J Neurosurg 2014;120:31-9.
65. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol 2012;137:516-42.