Nanotechnology Perceptions
ISSN 1660-6795
www.nano-ntp.com

A Comprehensive Analysis On The Association Between The KI 67 And P 53 Markers And Different Types Of Brain Tumors

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Gliomas are characterized by mutations in the p53 tumor suppressor gene. The cell proliferation marker Ki-67 is frequently employed in the context of gliomas. The survival rates of individuals with brain tumors exhibit considerable variation, with treatment trials heavily relying on prognostic markers. The utilization of digital pathology and improved immune-histochemical diagnostics allowed for a more accurate assessment of the true significance of the Ki-67 labeling index (LIpredictive) in glioblastomas by eliminating the presence of proliferating non-tumor cells during research. Among these markers, MIB1 (Ki67) stands out as the most popular and practical option. Consequently, the Ki-67 Labeling Index (LI) may possess prognostic and therapeutic implications for patients. The p53 tumor gene (TP53) is the gene that is not frequently altered in various malignancies and is also absent in a variety of different types of brain tumors. The identification of the molecular mechanisms through which p53 mutations cause cancer forms the basis for the development of new treatment strategies. Obtaining more conclusive results could be facilitated by reviewing studies that involve a larger number of patients across multiple centers and have a planned prospective follow-up of longer duration. In future research, it might be feasible to explore whether the incorporation of surgical, histological, and imaging indications could result in a more accurate method for predicting recurrence.

Keywords: Brain tumor, gene markers, KI 67, P 53, cancer

Introduction

As the global population's average age rises, cancer has become a more serious threat to health. Less than 2% of all cancers in humans are malignant primary brain tumors. The most common solid tumours are malignant brain tumours. Glioblastoma is the most common primary malignant brain tumour in adults (GB) (Tobias & Hayward 2018). Gliomas account for 40% of all tumours and 78% of cancers. Grade I tumours are those that do not exhibit any of these features. The WHO categorization, which takes into account the presence of aberrant cells, mitosis, endothelium growth, and necrosis, categorises individuals with just one of these qualities, commonly atypical cells, as grade II. The four different grade I glioma types that are

most frequentlyinclude pleomorphic xanthoastrocytomas, gangliomas, and pilocytic astrocytomas. Astrocytomas, oligodendrogliomas, and oligoastrocytomas are uncommon. a member of the grade II group They account for 20% to 30% of all children malignancies, making them the main contributor to cancer-related deaths in this age range (Litofsky et al., 2020). The most prevalent types of juvenile brain tumours are gliomas, pineal tumours, craniopharyngiomas, teratomas, granulomas, and primitive neuroectodermal tumours (PNETs, primarily medulloblastoma).While the majority of adult brain tumours form in the supratentorial region, approximately 60% of paediatric brain tumours form below the tentorium. Meningiomas, for example, are non-glial intracranial tumours that grow slowly. They can occasionally become invasive and persist for an extended period of time. Meningiomas, which originate from arachnoid meningothelial cells, are primary malignancies of the neurological system (CNS). 15 different meningioma variations are classified into three classes by the WHO. Grades I, II, and III are the least harmful (malignant). They are responsible for 36.8% of all intracranial primary tumours (Raghavan et al., 2019). Astrocytomas, oligodendrogliomas, and oligoastrocytomas, on the other hand,the most prevalent primary brain cancers in children's populations. Ependymomas, medulloblastomas, craniopharyngiomas, choroid plexus neoplasms, and other neoplasms are examples of neoplasms. 70% of these paediatric brain tumours originate in the posterior fossa. The most common tumours in the infratentorial region are medulloblastoma, pilocytic astrocytoma, brain stem glioma, and ependymoma. Based on histopathological characteristics, astrocytomas are classified into four malignant groups: Grade 1 astrocytomas, which have the greatest prognosis for patients and the least effective course of advancement; Grade II astrocytomas, which progress more quickly and have a worse prognosis for patients; third-grade astrocytomas,also known as anaplastic astrocytomas (AA), Grade IV astrocytomas, which have a generally unfavourable prognosis for the patient.CNS astrocyte tumours Pilocytic astrocytomas of high grade,The most prevalent gliomas in children, known as grades III and IV, account for 10% of all cases (Alkhaibary et al., 2019). The majority of cerebellar astrocytomas are benign. Brain tumour pathogenesis is extremely variable. Both p53 and Ki67 have been linked to adult gliomagenesis. Gliomagenesis in children, on the other hand, appears to follow different molecular pathways than in adults. Not only are studies on paediatric brain tumours rare, but they are also diverse.

According to an increasing number of researchers, Ki67 immunohistochemistry staining is critical for classifying various tumour types. A key tumour suppressor, The phosphoprotein p53 in the cell mainly influences the cell cycle to affect aberrant cells' demise, which helps with DNA maintenance and repair. Due to the lack of p53 function brought on by the mutation, DNA mutations accumulate, the cell cycle is disrupted, and apoptosis is initiated. A high proportion of mutant p53 protein-containing cells indicates that the tumour is aggressive. A common characteristic of the development of many human malignancies is the loss of p53 suppressive activity, which increases genomic instability and spreading potential (Jaaskelainen 1986).

Ki67 as a prognostic factor of brain tumor

According to recent studies Ki67 immuno-histochemical labeling is vital for differentiating between exceptional tumor types. The proliferative potential of a tumor is determined through

the marker known as Ki67 LI, which is additionally correlated with the histological grade and recurrence. The rate of quantity growth and the Ki-67 proliferation index carefully correspond, and normally, cell proliferation will increase proportionately to grade. According to a wide variety of studies, a higher Ki-67 index is associated with a greater probability of recurrence. Moreover, the Ki67 labeling index has validated its efficacy in exactly detecting high-grade cancers (LI). The proliferative index is a beneficial marker for B cells due to its advantages over traditional markers (Abry et al., 2010). The excessive Ki-67 cell density suggests an aggressive neoplasm. Glioma tumors in teenagers have distinctive genetic profiles. The majority of juvenile glioblastomas look like Ki-67. Further lookup is wanted given that it demonstrates that the tissue in GBM is polymorphous. Compared to different sorts of brain cancer, glioblastomas have comparatively excessive Ki-67 levels. With the exception of the resting stage, it is lively for the duration of the entire most cancerous telephone cycle. Many studies have tried to gauge expressiveness, with various degrees of success.

In paediatric GBM, however, Ki67 expression tiers have been appreciably higher than those of grown-up patients'. The proliferation and malignancy of glioma cells might also be indicated by their expression. The majority of Ki-67+ glioma sufferers in the current lookup had high-grade tumors, which were once associated with a quick usual survival time (OS). Nevertheless, the univariate evaluation, no longer the multivariate evaluation, recognized Ki-67+ as a single prognostic factor. Even though Ki-67 may additionally recommend a bad outlook, it would possibly no longer be dependable to use in glioma patients, only the Ki-67 is used to predict survival. Nevertheless, each univariate and multivariate study, one after the other, evaluated the predictive value of Ki-67 and p53 double positivity (Ki-67+/p53+) for OS (Tao et al., 2012). The terrible normal survival (OS) prognosis for glioma sufferers has indicated the desire to prioritize glioma sufferers in accordance with the molecular situation of their tumors using grade II-IV gliomas that have Ki-67+/p53+ gliomas, which may additionally be used as a prognostic indicator and to verify the effectiveness of therapy. It was formerly necessary to establish a prognostic marker that might help with treatment planning and forecast cancer behaviour and prognosis, and Ki-67 LI was developed more than 20 years ago as a marker of tumour growth.

The complex radioresistance mechanism may potentially include a phase in which apoptosis is inhibited. Proliferating cells are supposedly more radiosensitive than non-proliferating cells, despite other research's findings indicating the opposite. Given that a higher Ki-67 LI probably indicates extra proliferative tumors, patients with higher Ki-67 indices are also likely to be more radiosensitive. The protein known as Ki-67 is generated by vertebrate animals and is used as a marker for cells that proliferate too quickly. According to previous research, acute Ki-67 deficiency causes a prolongation at the G1/S border of the cell cycle; alternatively, this prolongation calls for the activation of the checkpoint protein p21 (Kolles et al., 1995). Mitotic cells exhibit this damage, albeit to a far greater degree than cells in the S phase. Cells are sufficiently protected from this harm by the chromatin-binding region of Ki-67's C-terminus. Most cancer cells without checkpoint systems and cells that proliferate quickly often have short G1 phases. KI-67 is crucial for maintaining a variety of chromosomal structural integrity parameters as well as for accurately localizing heterochromatin to the nucleolar periphery. Moreover, it alters localized accumulation, a crucial component of tumor development and

metastasis. The preservation of spatially specific chromosomal fingers and the clustering of chromosomes prior to nuclear envelope reconstruction both depend on the protein Ki-67, which is fundamental to the rule of mobile phone form. In the nucleolus during interphase, ribolabeling and typically proliferating nucleoprotein complexes are present, and throughout mitosis, they regulate the progression of the cell cycle by stopping it at the G1/m stage in checkpoint-proficient cells. The activation inhibitor and cyclin-dependent kinase inhibitor are used in conjunction with this (Roser et al., 2014). These findings suggest the existence of a genome prevention molecule and that it has a specific role in chromosomal arm maintenance. The Ki-67 gene, which guards against chromosomal degradation during mitosis, is linked to the low average survival rate in glioma and glioblastoma patients.

Ki-67 is a condition that is connected with OS, and the effects that depend on whether they were determined using automatic digital quantification, which may also be more reliable than semi-quantitative pathologists' grading, or through the use of observer-based scoring, which is more susceptible to intra- and inter-observer variance, can also vary. The average proliferative activity and Ki-67 labelling may also be impacted by the presence of Ki-67 tumour non-neoplastic cells in tumour tissue. Yet, other investigations havethat meningiomas with a 3% Ki67 recurrence charge had a higher recurrence rate. Since that Ki-67 was previously solely associated with progression or regrowth in this study, The increase of grade I meningiomas could be impacted by this, it's probable.The normal limit for Ki67 in grade I meningiomas, which is between 1 and 4%, per the literature.substantial variation in the amount of positive depending on the kind of meningioma (Ho et al., 2012).

3% Ki67 cut-off values for grade I meningiomas may potentially be a possible sign of the likelihood of meningioma recurrence in terminal meningiomas with histological signs of malignancy. There have been several immunomarkers proposed as indicators of recurrence. Despite this, the Ki-67 test is the only one that is often used in medicine. No immunomarker had a significant effect on the price of recurrences. Ki67 typically ranged from 0% to 10%, with distinct tumors making up 3.34 0.4% and recurring tumors making up 10%. In contrast to our study, these results were no more highly significant, and according to Pavelin et al., 2013only a high degree of tumor excision and a protracted follow-up time were shown to be causally linked to the probability of recurrence. There are no known associations between expression and sex, age, calcifications inside the tumor, tumor size, peritumoral edoema, p53, Ki67, or between primary and common meningiomas. The biological makeup of Grade I meningiomas disqualifies them from benign status and indicates that they're likely to return. Recurrence was observed in 32.7% of meningiomas and 25.4% of grade I tumors in a study of 162 meningiomas that had undergone complete resection, with the exception of those with convexity, with a follow-up of 2–5 years (average of 3 years), a finding higher than that in study (Bruna et al., 2017).

Ki-67 LI is the most vital element for distinguishing between WHO grade I tumors and anaplastic meningiomas, which had an implied Ki-67 LI of 11% and 0.7%, respectively. One of the most frequent problems in the therapy of meningiomas is recurrence after an interestingly complete resection. One meningioma recurrence was once observed in our dataset out of 38 meningioma patients. A papillary meningioma used to be the first classification. The affected person had radiation after the mass was definitely removed, in

accordance with the tumor grade. A Ki-67 LI of 25.32% used to be detected in the unique tumor after retrospective examination. During the next two years, the tumor in the lower back underwent post-radiotherapy changes and developed an unclassifiable meningioma as its presentation. An excessively excessive end result (> 70%) for IHC staining with Ki-67 used to be observed. A robust tumor proliferation pattern and recurrence may additionally be precisely anticipated by way of Ki67 LI tiers over 4.2% (Ramesh et al., 2016).

Ki67, which measures mobile proliferation, has been established as a superb indicator of recurrence or regrowth in grade I meningiomas, and it is the sole marker used in scientific practice on a normal basis. Due to the tumor's heterogeneity, the selection of the block to be immunostained may also have some effect on Ki67 PI. The tumor's actual proliferative potential can be underestimated as a result of this. This overlap between tumor grades might possibly reduce the benefits of Ki-67 PI in the grade of meningiomas in a limited percentage of cases, especially when a lower Ki-67 PI is observed. Thus, prior to evaluation, Ki67 PI should be compared to scientific and radiological data. Ki67 PI is a helpful addition to histomorphology for determining the analysis of meningiomas. Ki67 PI 4%, on the other hand, denotes an extra-superior tumor grade, whereas values above 4% are associated with sluggish behavior. The threshold proportion of stained cells for Ki67 PI in the Abry et al. investigation used to be 3%. When Ki67 used to be evaluated in accordance with the number of histological subtypes of meningiomas, there had been considerable adjustments after attaining this cutoff threshold. Transitional (32.1%) and mesenchymal (80.0%) meningiomas have been more frequent amongst meningiomas that tested effective for the protein Ki-67, respectively (Horbinski et al., 2010).

Ki67-negative Even though we employed the identical cut-off value, we had been unable to become aware of a distinction between the histological subtypes and the Ki67 PI in our analysis. For numerous other tumor types, no longer has a Ki67 cut-off rate been defined As there is no widely accepted consensus about what defines an excess or low proliferative index in tumor cells, special discoveries may also be made when establishing a cut-off point. Because of this, future research should focus on identifying the ideal cut-off rate for evaluating the immune-histo-chemical expression of a cell growth marker. In a meta-analysis looking at Ki67 rising in grade I meningiomas, the authors found a suggested cost for Ki67 PI in common tumors of around 3%. A modest connection between tumor measurement and Ki67 PI was once observed. In line with the literature, we located that grade II tumors had increased Ki67 PI levels. Nevertheless, no affiliation between gender, histological subtype, or tumor region and Ki67 PI in meningiomas used to be discovered. Ki-67, a nuclear antigen for cellphone proliferation, may additionally serve as an indicator of the increase and aggressiveness of tumor cells. In glioma patients, greater Ki-67 expression has been observed to positively correlate with a growing grade of malignancy and a terrible prognosis. In line with prior investigations, the cutting-edge effects confirmed that a giant upward jostle in Ki-67 expression was once related to a greater tumor grade, indicating that Ki-67 expression is a dependable indicator of glioma malignancy. Ki-67 is additionally a vital marker for figuring out benign from malignant cancers. Overexpression of Ki-67 causes an increase in proliferation and invasiveness, which leads to tumor recurrence and malignant alterations (Suri et al., 2019).

Ki67 IHC expression will rise in proportion to the meningioma's degree of histopathology. The predicted Ki67 expression in grade 1 used to be 1.01%. Anaplastic meningiomas used to have the highest level of Ki67 expression, 16.6% (Kraus et al., 2012). Meningothelial meningioma used to no longer show Ki67. In grade III, the best expression had an inferred rate of 14.8% and a high score of 53%. Olivier et al., 2019 evaluated found that the grade I common labeling index (round off values) was previously estimated to be 3%, with a typical value range of 1–16%. Historically, the average cost for grade II tumors was 8%, with values often falling between 22% and 30%. Meningiomas in grade III had an average cost of 17% and a typical value range of 7–32%. 9 The information acquired by Ramesh et al. demonstrated excellent Ki-67 results in all cases of papillary, irregular, and metaplastic meningiomas as well as anaplastic meningiomas. The expressions of Ki-67 were excellent at 100% in grade 3 (100%), 76.7% in grade II meningiomas, and extremely low in grade I (Labreche et al., 2018). The symptom-free interval in meningioma sufferers may additionally be more precisely predicted with the use of a quantitative method that combines Ki-67 and the mitotic index. Three corporations of tumor sufferers have been created: crew A, which had a Ki67 of much less than 1% and no mitotic activity; crew B, which had a Ki67 of more than 5% and no mitotic activity; and team C, which had a Ki67 of greater than 5% and mitotic activity. For the patient's consequence evaluation, the top restriction for Ki67 used to be between 1 and 5%.

According to the mentioned research, Ki67 activity may be employed as a proliferation indicator in small biopsy specimen samples that are difficult to determine the mitotic index for. In part-resected meningiomas, excessive Ki67 index ranges are linked to an accelerated boom and doubling time. An excessive Ki67 index shows aberrant proliferation, which, in general, shows how aggressive a tumor is. Yet, the statistics regarding the affiliation between the Ki67 index and the diploma of peritumoral edema surrounding meningiomas, as well as different variables, can be used to decide if there may be a correlation between Ki67 index readings and these variables. Between benign, atypical, and anaplastic meningiomas, the expression stage of Ki-67 is thought to differ considerably. According to Abry et al., (2010) the common suggestive labeling indices for grade I–III meningiomas were 3%, 8%, and 17% respectively.

p53 as a genome guardian of cancer

Nuclear phosphoprotein p53, a key tumour suppressor, works primarily on the cell cycle to influence the death of mutant cells, which helps maintain and repair DNA. The lack of mutation-induced p53 function therefore results in the accumulation of Gene mutations, breakdown of a cell cycle, and induction of death. A high percentage of mutated p53 protein-containing cells indicates a more aggressive tumour. A typical condition in the evolution of various humanmalignancies is loss of p53 suppressive activity, which increases genomic instability and spreading potential. The most common disease-related cause of mortality in children and adolescents is cancer. Brain tumors make up about 40% to 50% of all pediatric solid tumors, making them the most prevalent kind of juvenile cancer. One of the most often targeted genes for genetic changes in human cancer is the p53 gene, a tumor suppressor gene that is found on chromosome 17 short arm (17p13). Changes in p53 function are closely related to the development of cancer (Pardo et al., 2014).
High-grade astrocytic gliomas have an expanded region of chromosome 12q that encodes

murine double minute 2 (MDM2) and cyclin-dependent kinase 4 (CDK4). The potential of many of these alterations as prognostic indicators has been investigated. Most of these commonly changed GBM genes, however, are not universally agreed upon in terms of their prognostic importance. For instance, Gliomas with a p53 mutated gene or immunopositivity, as some researchers have observed, are more likely to spread (a marker of abnormalities in the p53 pathway)are associated with a shorter survival time, whilst other researchers have not observed a statistically significant correlation. There is disagreement over the importance of EGFR as a prognostic factor, just like there is with p53. There is disagreement over the prognostic significance of EGFR growth or overexpression in glioblastoma; some studies claim there is no relationship between this abnormality and survival while others claim it is a poor prognostic predictor. Prior research suggested that P53 expression might be a possible indicator of OS in glioma patients, however other investigations found the opposite. Our research showed that patients' prognoses were worse for those whose positive p53 expression showed a higher association with poorer prognosis than for those whose p53 expression was negative.

The p53 immunopositivity and tumour suppressor gene mutation are linked to meningioma prognosis and serve as warning signs for the return of meningiomas. Many theories, p53 may serve as a poor independent predictive marker for the pathological or clinical characteristics of gliomas. This variation might be due to the different techniques utilised to identify p53 expression in glioblastoma samples from distinct patient groups. The p53 variation in the different tumor grades appears to be influenced by the ethnicity of glioma patients. Also, it has been shown that human astrocytic gliomas' alterations in p53 overexpression are typically linked to secondary glioblastomas rather than original ones (Kumar et al., 2014). A tumour suppressor gene called p53 also has a significant impact on how cells react to diverse stimuli. It has been suggested that p53 may be a good target for glioma-targeted treatment since it also shifts cells with a normal copy of the p53 gene into tumour cells, making them more susceptible to chemotherapy and/or radiation and encouraging tumour cell death.

Diagnosis

Results showed that there were more calcifications and more severe peritumoral edema in grade I meningiomas that were bigger findings differ from those published by Lin et al. (2015) in terms of calcifications and tumor size. Findings support those in the literature with regard to peritumoral edema and tumor growth. The percentage obtained here was comparable to that reported by previous researchers, who estimated a 20% chance of grade I meningioma recurrence, mainly in tumors displaying a stronger positive for Ki-67. Nevertheless, recurrence or regrowth were not linked with tumor size. The meningiomas in our range have different locations, some of which are comparable to others. 6.6% in the tentorial area, and 9.3% in the posterior fossa (Faria et al., 2012).

On a multivariate analysis, proton treatment, the degree of surgical resection, and the grade were predictive factors for both PFS and OS. The degree of surgical resection, grading, and location of the tumors were predictive factors for both PFS and OS also, the existence of mutations, which are frequently tested in other malignancies and may be therapeutic targets, as well as the production of chemicals that may affect the development and survival of

cancerous cells, The primary driver of tumor angiogenesis is thought to be hypoxia-driven VEGF expression. In line with a smaller series, we observed a high frequency of VEGF expression. Moreover, numerous malignancies have been linked to mTOR activation. It was found that at least one of the three mTOR antibodies under investigation was expressed in 56% to 91% of tumors, and that 46% of chordomas from 35 patients showed the three markers, indicating constitutive and cell-specific activation of the two primary mTOR pathways (S6 and p4EBP1), supporting earlier findings (Burger & Green 2012). In cancer cell lines that are resistant to chemotherapy, STAT3 pathway inhibitors enhance the rate of necrosis while inhibiting chordoma cell line proliferation. STAT3 may be a possible therapeutic target for chordomas because they are chemotherapy-resistant tumors. EGFR is involved in the proliferation, differentiation, and monitoring of cancer cells. Results from immunolabeling are quite inconsistent and depend on the antibody used.

Grading of tumors

According to the World Health Organization's classification from 2016, (WHO), there are 15 different meningioma types that are divided into three grades: I (benign), II (intermediate), and III (malignant). According to WHO recommendations, gliomas are classified into grades I through IV based on the histological criteria of cytological atypia, mitotic activity, cellularity, microvascular proliferation, and/or necrosis, according to WHO recommendations. The predictive value of EGFR was observed to differ between older and younger individuals. So, we sought to isolate a sample of situations in which the particular markers were related to survival.

IDH/KI 67, irrespective of WHO grade, might define unique prognostic groupings. There is a lack of consistency in the prognosis of astrocytic neoplasms of multiple grades (GBM) because of differences in the distribution of ages. However, only in cases where p53 was not detected immune-histochemically were higher levels of EGFR substantially related to poorer survival. The EGFR status of younger patients with malignancies that are p53-negative has been demonstrated to be a poor prognostic indicator for survival by WHO researchers.

Elevated MIB-1 was linked to lower survival in pediatric patients, while older patients also tended to experience worse survival. GBMs are the most fatal primary brain tumours and are distinguished with low rates of IDH and 1p/19q mutation in the primary tumour and frequency range of MGMT and TERT promoter alterations. Certain GBMs lack well-established genetic indicators, making it difficult to divide them into molecular subgroups and predict patients' overall survival (OS). According to earlier research, 7 Glioblastomas that were IDH-wt/TERTp/TERTRp-wt, 1 of which had a 1p+19q-codel, 3 of which were triple-negative, and the other cases were quadruple-negative. Nevertheless, several GBMs lack well-established genetic indicators, making it challenging to Kim et al., (1991) divide them into molecular subgroups and predict patients' OS. According to the study. The results indicate that classification via IDH mutation status allows for the differentiation of glioma subtypes.

Patients with grade III anaplastic astrocytoma and mutant IDH showed superior results than those of wild-type IDHand glioblastoma. Growing Ki67 expression is regarded as the final stage of glioma development and is a prognostic indicator. It is not surprising that recent

research suggests that classification by IDH mutation status allows for the separation of different glioma subtypes. IDH/KI 67, irrespective of WHO grade, might define unique prognostic groupings. Patients in Group 2 who had high levels of Ki67 expression and IDH1/2 mutant gliomas had a poorer clinical prognosis. We hypothesize that Group 2's thriving cellular proliferative activity had a role in its worse prognosis. Meningioma recurrence rates range from 7 to 25%. The rates for atypical and anaplastic forms are 29–52% and 50–94%, respectively. Depending on the degree of resection, malignant histological characteristics are also linked to a lower survival time. Grading has been mentioned as a crucial tool for choosing how to manage patients. In grade II-III gliomas and secondary glioblastoma, DH1/2 mutations were initially reported. Groups B (mitotic of 1-4) and C (mitotic of more then 4), which had shorter symptom-free intervals, saw recurrence rates of 87% and 90%, respectively, over the course of five years (43 and 16 months, on average) (Rasheed et al., 2014).

Grading from I to III, meningiomas are slow-growing tumours. In this study, there were 10 to 16 meningiomas, with one WHO grade III, two WHO grade II, and thirteen WHO grades I. Gangliogliomas are comprised of cancerous glial cells with a Ki67 LI of 1.1-2.7%, according to research byother authors. Hemangioblastomas, which manifest as cystic lesions with mural nodules in the cerebellum of older individuals, are classified as WHO Grade I tumours.

Meningiomas have a complicated biological makeup. These tumours might be entirely benign, exhibit unusual characteristics with a higher risk of progression or manifestly malignant tumours having high recurrence, metastasis, and mortality rates.

It has been suggested that grading is an important tool for deciding how to work with patients. Grade II and III malignancies are treated by surgery, radiation therapy, and chemotherapy depending on their size and atypia, whereas grade I tumours are referred to as benign and are solely treated with surgery. It can be linked to the prognosis and aid in determining the likelihood of recurrence. All varieties in the same grade do not necessarily display the same behavior, though. Moreover, crucial elements like invasion and recurrence cannot be anticipated only on the basis of clinical and histomorphological characteristics. In the most current 2016 WHO classification of CNS cancers, the grading of meningiomas was changed, and we have classified the tumors using the new grading method. In research including 600 meningiomas that was reported by Sneed et al., (2017), 91% of the patients were WHO grading I meningiomas, 7% was group 2 meningiomas, and 2% are grade III meningiomas, according to histological grading. These numbers matched those from several other studies. Grade I was the most prevalent in our series, with a result that was practically identical (79.2%). Nonetheless, grade III tumors occurred more frequently (13.2%) than tumours of grade II (7.9%) (Salmon et al., 2019).

Grading from I to III, meningiomas are slow-growing tumors. There are 13 WHO grading I, 2 WHO grading II, and 1 WHO grading III entriesmeningioma were examined in this study. With grade, cellular multiplication rises correspondingly. According to research by Perry et al., (@@@) meningiomas with The probability of recurrence was greater when Ki67 LI was >4%. and had mortality rates of >20%. An increased chance of recurrence and aggression were present in six of the 16 meningiomas with LIs of >4%. According to Gawlitza et al., (2016)

the MIB1 ranges for benign, typical, and anaplastic meningiomas are 0.7–2.2%, 2.1–9.3%, and 11–16.3%, respectively. According to this study, the prevalence of benign meningiomas is 2.22%, atypical meningiomas are 5.85%, and anaplastic meningiomas are 30%. This is equivalent. Nevertheless, there weren't enough participants to establish a threshold for LIs.

One male patient in his middle years had choroid plexus cancer. According to Sanai et al., (2010) Ki67 LIs for choroid plexus cancer ranged from 4.1% to 60%, and the LI performed in this instance was 60%. According to other investigations, gangliogliomas are WHO-graded Iglioneuronal neoplasms made upcomprises malignant glial cells with a Ki67 LI of 1.1-2.7% and dysplastic ganglion cells. A higher LI of 0.79% was applied to our instance. A four-month-old baby boy who had a hypothalamic tumour and a seizure disorder was seen.developed a glioneuronal tumor that was made up of round cells, presumably neurocytes, and astroglial cells. The stated Ki67 LI is at 3%, and in our situation, there was no discernible Ki67 positive. Both of the adenomas in this investigation were made up completely of Schwann cells that had undergone well-differentiation and had Antoni A and Antoni B regions. 20% has been found to be the threshold for malignancy by Pekmezci et al. Ki-67 LI was 5.3%, with a tolerance of 2.3% (Nanda et al., 2016).

Treatment

In the current data, only seven patients (four of whom had a Ki-67 of 27%) and one patient (over 60 years old) had a survival time of greater than 36 months. The original tumor site and affected lobe do not affect survival as much as gender or other demographic factors. Age of diagnosis and application of adjuvant chemotherapy and radiation in combination were the factors that determined this method's survival. A hazard ratio of 23.36 existed between patients with GB who received adjuvant therapy compared to those who did not. Those who had combination radiation and chemotherapy had a median survival of 99 months, giving them a 12-month rate of survival of 72% as compared to 15% for patients who chose to not get adjuvant therapy. Chemotherapy, radiation, and surgery are the available treatment methods for LGGs, and the choice of treatment is based on age, function, tumour site, histological diagnosis, proliferation markers, gene mutations, and individual preferences of the patient. In randomized clinical trials, the five-year OS and PFS rates to be 58-72% and 37-55%, respectively (Roser et al., 2014). Studies on the correlation between tumour grade, proliferation, and gene alterations for the epidermal growth factor receptor (EGFR), Isocitrate dehydrogenase, phosphatase and tensin homolog (PTEN), protein 53 (TP53), and cyclin dependant kinase inhibitor 2A (CDKN2A) have lately increased (IDH).

The higher advantage of total excision is still evident despite the fact that this variation was not statistically significant. The scheduling, estimation determining the optimal dose and achieving a benefit-harm balanceare the three most crucial elements in the planning of radiotherapy (RT) in order to ascertain the solitary effect on overall survival in LGGs. There is little information on the efficacy and safety of stereotactic radiosurgery in the treatment of LGGs, despite its development to retain control over discrete areas in recurring malignant gliomas. RT is frequently advised for patients who have a high mitotic index or recurrence in their follow-up neuroimaging. Postoperative RT was to increase five-year overall survival and delay tumour recurrence in individuals who were limited to subtotal excision due to localization (Ho et al., 2012).

It is not known which factor—tumor grade or postoperative radiotherapy—has a greater impact on survival in LGGs. Chemotherapy works better on bigger, more serious tumours, and genetic studies must be taken into consideration while making chemotherapy decisions. Procarbazine, lomustine, vincristine, the PCV regimen, and temozolomide treatment are all available as forms of chemotherapy. Gene therapy, monoclonal antibodies, immunotoxins, signal transduction inhibitors, and inhibitors of angiogenesis are among the other new agents being researched. Just seven patients in the current data were long-term survivors—those who survived for more than 36 months. One of these individuals was older than 60, and four of them had a Ki-67 of 27% (Tao et al., 2012).

Those who did not receive adjuvant treatment had a median survival of two months.but the median survival for individuals who only had radiation was 23 months. In reality, patients with GB who received both chemotherapy and radiation had a survival rate of 99 months, showing the significant positive impact of the mixed adjuvant therapy on survival rates, which led to a 12-month cure rate of 72% comparison to 15% of those who did not receive adjuvant therapy (Sanai et al., 2010).

Chemotherapy, radiation, and surgery are the available treatment methods for LGGs, and the choice of treatment is based on the age of the patient, functional characteristics, tumour site, histological diagnosis, proliferative markers, gene mutations, and preferences. There is still debate on the best course of action. In randomised trials, 58-72% and 37-55%, respectively, were determined to represent the five-year OS and PFS rates. It is now known that these tumours tend to progress to high grades and have a characteristic of continuous growth. As a result, research into the associations between tumour grade, proliferation, and gene alterations for the epidermal growth factor receptor (EGFR), Recent years have seen a rise in the expression of isocitrate dehydrogenase, phosphatase and tensin homolog (PTEN), tumour protein 53 (TP53), and cyclin dependent kinase inhibitor 2A (CDKN2A) (IDH) (Salmon et al., 2019).

This difference shows the better advantage of full excision, even if it is not statistically significant. It is challenging to isolate the single radiation (RT) influence on LGG survival times. The scheduling of RT, figuring out the drug concentration, and balancing the benefits and risks are the three most crucial considerations. There is no information on the usefulness and safety of stereotactic radiosurgery for the treatment of LGGs. It was created to retain control over tiny portions of recurring malignant gliomas. RT is often advised for patients who have a high mitotic index or progress in their follow-up imaging tests. Postoperative RT has been shown to increase five-year survival rates and delay tumour recurrence in individuals whose tumours could only be removed partially due to their site. It is not known which factor—tumor grade or postoperative radiotherapy—has a greater impact on survival in LGGs. Moreover, in the majority of LGGs, due to its propensity to cause lifelong brain damage, RT can be delayed, particularly among infants and small children, until the completion of chemotherapy or, as is the case with oligodendrogliomas, until the tumour advances. Chemotherapy is a possibility for patients who show progress after surgeries and RT or those who are at increased risk after surgery. Chemotherapeutic decisions must take into account the results of genetic studies. Chemosensitive glial tumors with prolonged PFS and OS durations were shown to be associated with the deletion of chromosomes 1p and 1p19q. Larger and more serious tumors are often thought to react better to treatment. Because of their less aggressive tumor behavior and lack of chemotherapy, individuals in our research who were better

candidates for surgery also had longer OS durations. Options for chemotherapy include temozolomide treatment and the PCV regimen, which includes procarbazine, lomustine, and vincristine (Kolles et al., 2012). Throughout the 10–24 months of follow-up, both treatments are linked to comparable response periods, although temozolomide was shown to be more tolerable. Monoclonal antibodies, immunotoxins, signalling pathway inhibitors, gene therapy, and inhibitors of angiogenesis are further treatments under investigation.

Future aspects

The longest running continuous series on this subject. We have a strong suspicion that the site and the association with matter are significant despite the fact that the current categorization of GBM divides patients into prognostic categories according to their genetic status. To strengthen the finding that GB contact with the LV is an independent predictor of survival, it would be interesting to do various histological investigations also on tumor-infiltrating SVZ and the rest of it in a larger cohort of patients with future diagnoses. It was discovered that the peritumoral zone has various prediction capacities at various ranges. The model's prediction accuracy for Ki-67 markers was observed to steadily rise with the peritumoral regions' enlargement. indicating that the peritumoral zone has textural characteristics that are associated with Ki-67 expression. These findings suggest that, while developing a glioma model, the peritumoral regions should be taken into account. Gliomas' peritumoral region exhibits distinct perfusion alterations from metastatic tumors, according to research on the peritumoral zone. Although research frequently describes ROI via solid, necrosis, and edema zones, other studies have demonstrated that tumor cell infiltration may be identified in the peritumoral regions without affecting the results of conventional MRI. The peritumoral regions were defined and analyzed in the current study using the technique of extending the tumor edge outward with a fixed width, which showed that a useful model may also be produced. In analyzing the texture of gliomas, the current investigation of glioma texture may benefit from further consideration of the peritumoral regions without alterations in conventional MRI in addition to ROI identification by tumor imaging. It may be possible to learn more about the radiological features of gliomas by paying attention to alterations in the peritumoral zone. There are a number of potential limitations to the current results. The accuracy of the prediction model may be subpar due to the sample size being quite small and hence inadequate. To evaluate the radiomics model's capacity for universalization, a future large multicenter investigation is required. More investigations are being undertaken in this area to address these issues because some patients in the data did not have contrast-enhanced T1-weighted pictures, diffusion-weighted images, or actual diffusion coefficient sequence checks.

Conclusion

Reviewing a detailed and systematic analysis of the literature. Both Ki67 and p53 have potential diagnostic and prognostic differentiation of uses in the diagnosis and differentiating various grades of tumor. To assess the existing conventional prognostic indicators The expression of p53 affects the tumor's response to therapy and the course of the patient's condition, making it a helpful prognostic tool in light of the significance of the TP53 gene in the genesis and development of CNS malignancies. Traditional treatment techniques, particularly for high-grade tumors like glioblastomas, make it challenging to treat CNS cancers

using chemotherapy and radiation. The prognosis for these individuals is anticipated to improve in the coming years as a consequence of the adoption of molecular medicines that might more effectively regulate the advancement of the disease. The advancement of molecular biology technologies has made it possible to conduct an extensive study on the role of p53 in the emergence of cancer. In present study the anatomical interaction of the lesion as a major indicator of poor oncologic prognosis in GB patients. The P53 score is "significantly positively correlated" with male gender but not with the patient's age. Ki-67 LI is "significantly positively correlated" with increasing grade of astrocytoma and patients age, but not with gender. Both the p53 and Ki-67 labeling indices are "significantly positively correlated" in relation to the grade of astrocytoma and to each other.

References

1. Tobias J, Hayward RD. Brain and spinal cord tumors in children. In: Thomas DG, editor. Neuro-oncology: Primary malignant brain tumors. Baltimore: The Johns Hopkins University Press; 2018. p. 164-92
2. Litofsky NS, Hinton D, Raffel C. The lack of a role for Sengupta, Pediatric brain tumors Indian Journal of Medical and Paediatric Oncology | Jan-Mar 2012 | Vol 33 | Issue 1 31 p53 in astrocytomas in pediatric patients. Neurosurgery 2020;34:967-73.
3. Raghavan R, Steart PV, Weller RO. Cell proliferation patterns in the diagnosis of astrocytomas, anaplastic astrocytomas and glioblastoma multiforme: a Ki-67 study. Neuropathol Appl Neurobiol 2019;16(2):123–33.
4. Alkhaibary, A.; Alassiri, A.H.; AlSufiani, F.; Alharbi, M.A. Ki-67 labeling index in glioblastoma; does it really matter? Hematol. Stem Cell Ther. 2019, 12, 82–88.
5. Jaaskelainen J. Seemingly complete removal of histologically benign intracranial meningioma: Late recurrence rate and factors predisposing recurrence in 657 patients: A multivariate analysis. Surg Neurol. 1986;26:461–469.
6. Abry E, Thomassen IO, Salvesen OO, The significance of Ki-67/ MIB-1 labeling index in human meningiomas: a literature study. Pathol Res Pract 2010;206:810–5.
7. Tao Y, Liang G, Li Z, Wang Y, Wu A, Wang H, Clinical features and immunohistochemical expression levels of androgen, estrogen, progesterone and Ki-67 receptors in relationship with gross-total resected meningiomas relapse. Br J Neurosurg. (2012) 26:700–4. doi: 10.3109/02688697.2012.6 85780
8. Kolles H, Niedermayer C. Schmitt W. Henn R. Feld WI, Steudel, Triple approach for diagnosis and grading of meningiomas: Histology, morphometry of Ki-67/feulgen stainings, and cytogenetics. Acta Neurochirurgica, 1995;137(3-4):174-81.
9. Roser F, Samii M, Ostertag H, Bellinzona M. The Ki-67 proliferation antigen in meningiomas. Experiencein 600 cases. Acta Neurochir (Wien). 2014;146:137–144
10. Ho D, Hsu CY, Ting LT, Chiang H. Histopathology and MIB1 labeling index predicted recurrence of meningiomas. Cancer. 2012;94:1538–1547
11. Pavelin S, Becic K, Forempoher G, Mrklic I, Pogorelic Z, Titlic M, Expression of Ki-67 and p53 in meningiomas. Neoplasma 60 : 480- 485, 2013
12. Bruna J, Brell M, Ferrer I, Gimenez-Bonafe P, Tortosa A. Ki-67 proliferative index predicts clinical outcome in patients with atypical or anaplastic meningioma. Neuropathol. 2017;27(2):114-20.
13. Ramesh BT, Amit KC, Nandya LR, Rashmi Patnayak, Bobbi DP, et al. Histopathological and Immunohistochemical Evaluation of Meningiomas with Reference to Proliferative Markers p53 and Ki67, J Clin Diagnostic Research. 2016;10(1);5-19.

14. Horbinski C, Oakley GJ, Cieply K, et al. The prognostic value of Ki-67, p53, epidermal growth factor receptor, 1p36, 9p21, 10q23, and 17p13 in skull base chordomas. Arch Pathol Lab Med 2010;134:1170–6
15. Suri V, Das P, P, Jain A, Sharma MC, Borkar SA, Pediatric glioblastomas: A histopathological and molecular genetic study. Neuro Oncol 2019;11:274-80.
16. Kraus JA, Felsberg J, Tonn JC, Reifenberger G, Pietsch T. Molecular genetic analysis of the TP53, PTEN, CDKN2A, EGFR, CDK4 and MDM2 tumour associated genes in supratentorial primitive neuroectodermal tumours and glioblastomas of childhood. Neuropathology and Applied Neurobiology 2012; 28(4):325-33.
17. Olivier M, Taniere P. Somatic mutations in cancer prognosis and prediction: lessons from TP53 and EGFR genes. Current Opinion in Oncology 2019; 23(1):88-92.
18. Labreche K, Kinnersley B, Berzero G, Diffuse gliomas classified by 1p/19q co-deletion, TERT promoter and IDH mutation status are associated with specific genetic risk loci. Acta Neuropathol. 2018;135(5):743–755.
19. Pardo FS, Hsu DW, Zeheb R, Efird JT, Okunieff PG and Malkin DM: Mutant, wild type, or overall p53 expression: freedom from clinical progression in tumours of astrocytic lineage. Br J Cancer 91: 1678-1686, 2014.
20. Kumar S, Kakkar A, Suri V, Kumar A, Bhagat U, Sharma MC, et al. : Evaluation of 1p and 14q status, MIB-1 labeling index and progesterone receptor immunoexpression in meningiomas: adjuncts to histopathological grading and predictors of aggressive behavior. Neurol India 62 : 376-382, 2014
21. Lin T, Chao C, Saito S, Mazur SJ, Murphy ME, Appella E, Xu Y. p53 induces di ff erentiation of mouse embryonic stem cells by suppressing Nanog expression. Nature Cell Biology 2015; 7(2):165-71
22. Faria MH, Neves Filho EH, Alves MK, Burbano RM, de Moraes Filho MO, Raben- horst SH. TP53 mutations in astrocytic gliomas: an association with histological grade, TP53 codon 72 polymorphism and p53 expression. APMIS 2012; 120(11):882-9.
23. Burger, P. C., and Green, S. B. Patient age, histologic features, and length of survival in patients with glioblastoma multiforme. Cancer (Phila.), 59: 1617–1625, 2012.
24. Kim, T. S., Halliday, A. L., Hedley-Whyte, E. T., and Convery, K. Correlates of survival and the Daumas-Duport grading system for astrocytomas. J. Neurosurg., 74: 27–37, 1991.
25. Rasheed, B. K., McLendon, R. E., Herndon, J. E., Friedman, H. S., Friedman, A. H., Bigner, D. D., and Bigner, S. H. Alterations of the TP53 gene in human gliomas. Cancer Res., 54: 1324–1330, 2014.
26. Sneed, P. K., Prados, M. D., McDermott, M. W., Larson, D. A., Malec, M. K., Lamborn, K. R., Davis, R. L., Weaver, K. A., Wara, W. M., Phillips, T. L., and Gutin, M. D. Large effect of age on the survival of patients with glioblastoma treated with radiotherapy and brachytherapy boost. Neurosurgery, 36: 898–903, Discussion 903– 904, 2017.
27. Salmon, I., Dewitte, O., Pasteels, J. L., Flament-Durand, J., Brotchi, J., Vereerstraeten, P., and Kiss, R. Prognostic scoring in adult astrocytic tumors using patient age, histopathological grade, and DNA histogram type. J. Neurosurg., 80: 877–883, 2019
28. Gawlitza, M., Fiedler, E., Schob, S., Hoffmann, K. and Surov, A. (2016) Peritumoral Brain Edema in Meningiomas Depends on Aquaporin-4 Expression and Not on Tumor Grade, Tumor Volume, Cell Count, or Ki-67 Labeling Index. Molecular Imaging and Biology, 19, 298-304. https://doi.org/10.1007/s11307-016-1000-7
29. Sanai, N. and McDermott, M.W. (2010) A Modified Far-Lateral Approach for Large or Giant Meningiomas of the Posterior Fossa. Journal of Neurosurgery, 112, 907-912. https://doi.org/10.3171/2009.6.JNS09120

30. Nanda A, Bir SC, Konar S, et al. Outcome of resection of WHO Grade II meningioma and correlation of pathological and radiological predictive factors for recurrence. J Clin Neurosci 2016;31:112–21.