Rajiv Gandhi Cancer Institute and Research Centre

NewsLetter

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EDITORIAL

HIROSHIMA AND NAGASAKI

Have we learnt anything from nuclear disasters?

A nuclear bomb dropped at 8:15 am on a clear August (1945) morning. Less than a minute later, a blinding flash was followed by a wave of destruction almost beyond human imagination. An estimated 80,000 people were killed instantly by the intense heat of the explosion.Thirteen square kilometres of a city that had been a bustling commercial, military and transportation hub was reduced to rubble. Immense firestorms swept through wood and paper houses. Thousands were dead and injured. A single bomb dropped from a B-29 bomber on the morning of 6 August 1945 had killed a third of Hiroshima's population and wiped 70% of the city off the face of the earth. Three days later, a second bomb fell on the city of Nagasaki, killing a further 40,000 people. The Atomic Age had arrived with a vengeance, and the world would never be the same again.

After the fires burned themselves out, Hiroshima was unrecognizable. The occasional ruin of a concrete building, and thousands of dead trees were all that remained standing in a vast wasteland of rubble. Those who survived the attack wandered the irradiated streets in a pitiful state, others lay buried under piles of rubble and others still lay stricken on the ground, too injured to walk. The city's rivers were clogged with the corpses. Radiation sickness and radiation poisoning began killing many who had survived the initial attack. Of Hiroshima's 28 hospitals, 26 had been destroyed and the vast majority of the city's doctors and nurses had been killed in the blast. Hideously wounded citizens, their eyeballs burned out of their skulls and their skin burned away, died in unimaginable agony. Help was quickly sent to care for the survivors, but there was little that could be done for so many, especially those suffering from severe radiation poisoning. Field hospitals were hastily set up and transportation of the injured to surrounding towns and cities was quickly arranged, but many more would die in the months after the bomb dropped. By the end of the year, the death toll stood at 130,000.

Those who survived the bombing were known as 'Hibakusha', which translates as 'explosion-affected people'. Their lives in the decades following the bombing would not be easy. An entirely false belief grew up that those who had been exposed to radiation carried illnesses they could pass on to others. As a result, many Hibakusha were shunned by society and faced severe financial hardships. For many Hibakusha, the physical and mental effects of the bombing lasted for the rest of their lives. Those who survived radiation sickness were plagued by recurring bouts of illness, often leading to their premature deaths.Leukemia – blood cancer –dogged the Hibakusha, as other forms of cancers, heart and liver problems and, in later life, cataracts. In Nagasaki an estimated 35,000-40,000 people died immediately with about 60,000 injured. The death toll climbed steadily over the following weeks and months as survivors succumbed to radiation poisoning and burns. Just 22.7% of Nagasaki's buildings were destroyed compared to the 92% of buildings either totally destroyed or badly damaged in Hiroshima The Japanese government formally surrendered on 15 August 1945, finally bringing an end to the Second World War.

The slow and inadequate treatment of victims probably contributed to the high casualty rates. Probably the number of deaths from the true blast effects, flame burns, or serious injuries from collapsing structures would not have been altered appreciably; generally speaking, these cases were killed outright. Probably the most significant results could have been achieved with the radiation cases. However, it is doubtful that 5 percent of all the deaths resulting from the atomic bombs could have been avoided with the best medical care.

Later on Hiroshima was designated as an international city of peace. In the case of Nagasaki, the government decided to designate it as an international city of culture. In 2016, Barack Obama became the first sitting US president to visit the city and the peace park. 'We have known the agony of war,' the president wrote in the visitors' book after visiting the peace museum. 'Let us now find the courage, together, to spread peace, and pursue a world without nuclear weapons.'Today, Hiroshima and Nagasaki are thriving, vibrant cities collectively home to over one and a half million people. But in the cities and memorial parks that arose from the ashes, the memory of those two terrible days in August will live on forever.

Yet another disaster hit Chernobyl, an accident in 1986 at the Chernobyl nuclear power station in the Soviet Union, the worst disaster in the history of nuclear power generation. The Chernobyl power station was situated at the settlement of Pryp'yat, 10 miles (16 km) northwest of the city of Chernobyl (Ukrainian: Chornobyl) and 65 miles (104 km) north of Kyiv, Ukraine. The station consisted of four reactors, each capable of producing 1,000 megawatts of electric power; Between 50 and 185 million curies of radionuclides (radioactive forms of chemical elements) escaped into the atmosphere—several times more radioactivity than that created by the atomic bombs dropped on Hiroshima and Nagasaki, Japan. This radioactivity was spread by the wind over Belarus, Russia, and Ukraine and soon reached as far west as France and Italy. Millions of acres of forest and farmland were contaminated, During the Russian invasion of Ukraine in 2022, Russian forces attacking from Belarus captured Chernobyl after a brief but pitched battle. Combat at the site of the world's worst nuclear disaster led to concerns about damage to the containment structure and the possibility of widespread radioactive contamination. Shortly after the Chernobyl accident it became evident that the main impacts of nuclear accidents are not radiological, but socio-economic and psychological. Stigmatisation of both exposed and evacuated populations following both accidents has strongly contributed to a significant rise in alcoholism, depression, anxiety, bullying and suicides.

On 11 March 2011, the strongest earthquake ever recorded in Japan triggered a massive tsunami along the Pacific Coast. The earthquake and the ensuing tsunami resulted in the death of 19,729 people (with 2559 still missing) and devastated communities up and down the country. Reactors close to the earthquake, including those operating at Fukushima were shut down. However, as a consequence of the flood caused by the tsunami, the backup generators at the Fukushima Daiichi plant, which were meant to pump cooling water through the reactor, were destroyed. As a result, three cores largely melted over the following three days and there were several hydrogen explosions, as well as the release of nuclear material into the environment.

Has the world learnt anything from Hiroshima, Nagasaki nuclear disasters? Has the world forgotten effects of radiation in Chernobyl Disaster (1986) and fukushima daiichi calamity. Have we become wise? Imagine the devastation that world occur with present day nuclear weapons. Imagine its impact on human and animal life and the environment. Are we waiting for action replay of 1945, 1986nuclear events? I hope and pray to God that wisdom prevails and no one uses destructive terrifying creations of their own.

Dr. A. K. Dewan
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GLIOMA UPDATE: CNS WHO 2021 AND BEYOND

Gliomas are the common primary central nervous system CNS (brain tumor) and require proper classification and grading. The classification of gliomas for the past century has been based largely on histogenesis and microscopic similarities. There has been a paradigm shift with the emergence of next generation sequencing (NGS) technique clarifying the genetic bases of tumor genesis and paving a way forward for classification of gliomas from a genetic standpoint. The 2016 World Health Organization classification of tumors of central nervous system encouraged "integrated diagnosis" and facilitated precise diagnoses of genetically defined entities. This also unraveled many tumors that did not fit into classification .The international society of neuropathology sponsored an initiative cIMPACT-NOW to propose changes in between two WHOs .The changes, entities thus recognized, along with many other modifications have been incorporated in the 2021 CNS WHO. The discovery of isocitrate dehdrogenase (IDH) mutations in gliomas lead to refinement in clinically relevant diagnostic schema of diffuse gliomas. The latter could be precisely classified into astrocytic or oligodendroglial tumors by using IDH, TP53, ATRXand 1p/19q codeletion studies.

Table 1 Grading within types

CNS WHO Grades	
Astrocytoma, IDH-mutant	2, 3, 4
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	2, 3
Glioblastoma, IDH wildtype	4

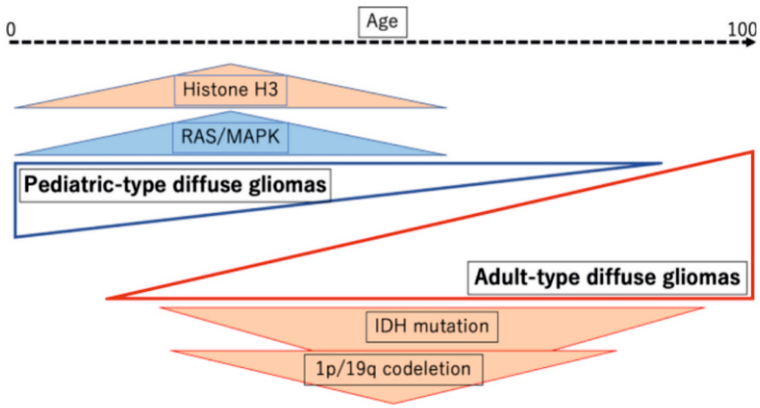
Table 2: Layered / structured reporting

Integrated diagnosis (combined tissue-based histological and molecular diagnosis)
Histological diagnosis
CNS WHO grade
Molecular Information (listed)

Specific Changes: Gliomas, Glioneuronal Tumors and Neuronal Tumors have been divided into 6 different families and fourteen newly recognized types have been added to the classification. Division of diffuse gliomas that primarily occur in adults (termed "adult type") and those occur primarily in children (termed "pediatric type").

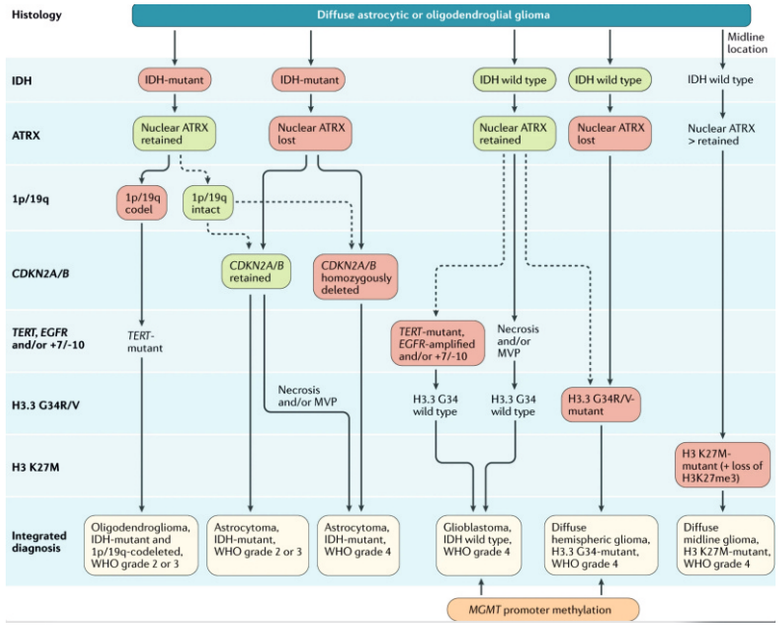
Figure 1: Schematic framework of pediatric- and adult-types difuse gliomas

(The orange high-grade tumors, blue one represents low-grade tumors)



{Komori, T. The molecular framework of pediatric-type diffuse gliomas: shifting toward the revision of the WHO classification of tumors of the central nervous system. Brain Tumor Pathol 38, 1–3 (2021)}

Figure 2: Diagnostic algorithm for classification of diffuse gliomas in adults



{Weller, M., van den Bent, M., Preusser, M. et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 18, 170–186 (2021). https://doi.org/10.1038/s41571-020-00447}

Adult type, diffuse astrocytic gliomas

In 2021 CNS WHO there has been an attempt for simplification of the classification of common, adult type, diffuse gliomas into only 3 types: Astrocytoma, IDH-mutant, Oligodendroglioma, IDH-mutant and 1p/19q codeleted; and Glioblastoma, IDH-wildtype.

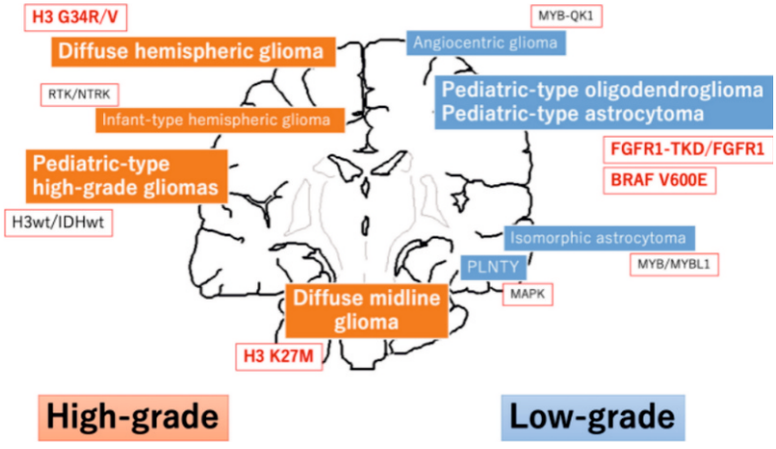
All IDH mutant, diffuse astrocytic tumors are considered a single type (Astrocytoma, IDH-mutant) and are then graded as CNS WHO grade 2, 3, 4. Moreover, grading is no longer entirely histological, since the presence of CDKN2A/B homozygous deletion with or without necrosis or microvascular proliferation results in a CNS WHO grade of 4.

For IDH –wildtype(wt) diffuse astrocytic tumors in adults, presence of 1 or more of 3 genetic parameters (TERT promoter mutation, EGFR gene amplification, combined gain of entire chromosome 7 and loss of entire chromosome 10 [+7/-10] is sufficient to assign the highest WHO grade i.e Glioblastoma, IDH wt .

Pediatric-type diffuse gliomas

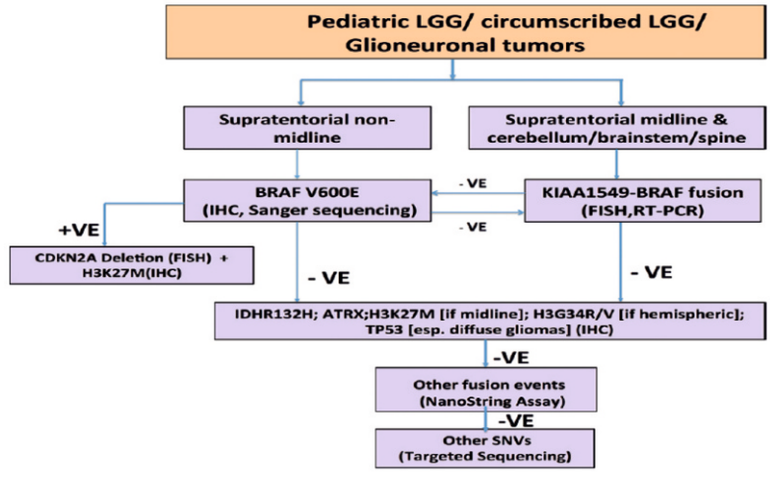
Majority of pediatric gliomas are low grade, slow growing lesions (Grade I or II) and account for 25%-30% of pediatric CNS tumors. The low-grade group includes 4 entities that feature diffuse growth in the brain but with sometimes overlapping and less specific histological features. A significant fraction of pediatric gliomas progress rapidly (WHO Grade III) and are designated pediatric high-grade gliomas (pHGGs) and comprise 8%-12% of all pediatric gliomas. The low-grade group includes 4 entities that feature diffuse growth in the brain but with sometimes overlapping and less specific histological features.

Figure: 3 Major histology and genetic alterations in pediatric-type diffuse gliomas



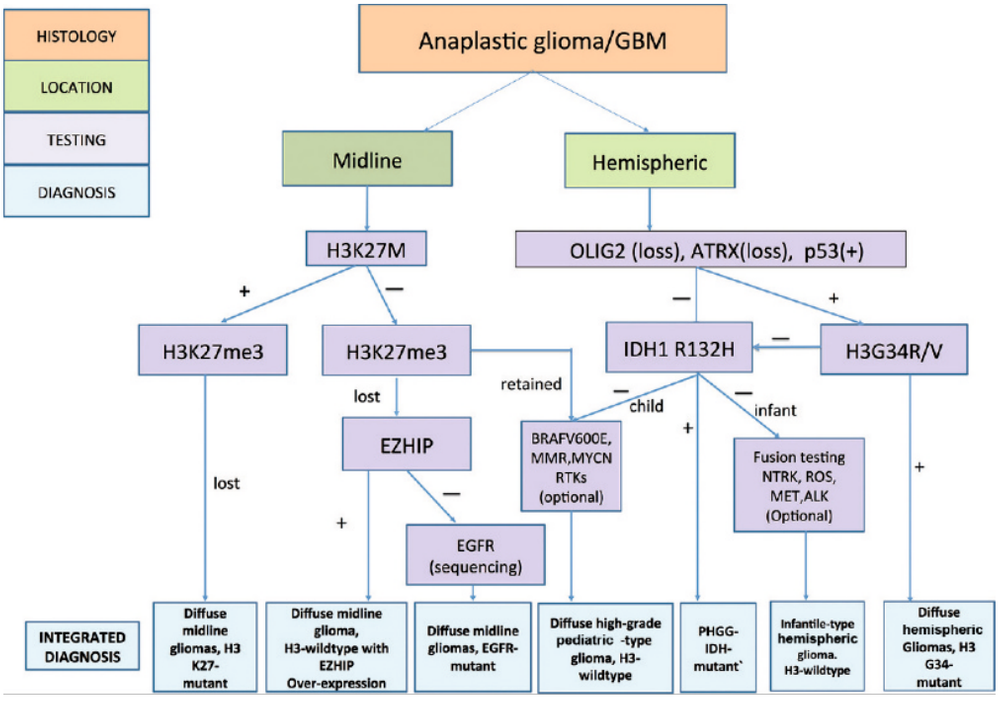
{Komori, T. The molecular framework of pediatric-type diffuse gliomas: shifting toward the revision of the WHO classification of tumors of the central nervous system. Brain Tumor Pathol 38, 1–3 (2021).}

Figure 4: Molecular testing decision tree for pediatric low grade gliomas



{Mahajan S, Sharma M C, Sarkar C, Suri V. Approach to integrating molecular markers for assessment of pediatric gliomas. Int J Neurooncol 2021; 4, Suppl S1:166-74}

Molecular landscape of pediatric high-grade gliomas



{Mahajan S, Sharma M C, Sarkar C, Suri V. Approach to integrating molecular markers for assessment of pediatric gliomas. Int J Neurooncol 2021; 4, Suppl S1:166-74}

Diffuse midline glioma(DMG), H3-K27M-altered

Diffuse midline gliomas, H3-K27M mutant was recognized as a new diagnostic entity in the updated 2016 WHO classification of CNS tumors unifying DIPGs and gliomas from the thalamus and spinal cord harboring a histone H3-K27M mutation.

Recently, studies identified a few cases of midline glial tumors that lacked H3-K27M mutation, has showed H3K27me3 loss along with wither enhancer of zest homologus inhibitory protein{EZHIP) overexpression or epidermal growth factor receptor (EGFR) mutation, thus extending the spectrum of DMG's beyond H3-K27M mutation.

Diffuse hemispheric glioma, H3G34-mutant

Mutations on H3F3A that substitutes glycine to arginine or valine at position 34 (G34R/V) have been identified in approximately 20% of the pHGG located in the cerebral hemispheres.

They occur predominantly within the age range of 11-30years.Patients harboring tumor with this mutation tend to have longer OS (median survival of 20 months) than DMG.

"Glioblastoma" is no longer used in the setting of a pediatric-type neoplasm.

Conclusion: Precise classification of gliomas,requires molecular characterization and the integration of histopathological and molecular information, in a tiered diagnostic format .Needless to say ,careful morphologic analysis of gliomas , judicious use of immunohistochemical stains, FISH and Sanger sequencing technologies can be used to obtain genetically rich and useful data essential for patient stratification in future clinical trials and to develop new efficient targeted therapies for gliomas.

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