GLIOBLASTOMA, OLIGODENDROGLIOMA, MALIGNANT SCHWANNOMA: NOVEL APPROACHES

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ARISTOTLE (384 – 322 BC): WE CAN GATHER SOME WISDOM

ARISTOTLE (384 – 322 BC): AUTHOR OF THE NICOMACHEAN ETHICS

- A likely impossibility is always preferable to an unconvincing possibility.

- Character may almost be called the most effective means of persuasion.

ARISTOTLE (384 – 322 BC): AUTHOR OF THE NICOMACHEAN ETHICS

- It is the mark of an educated mind to be able to entertain a thought without accepting it.

- Education is an ornament in prosperity and a refuge in adversity.

CNS TUMOR TAXONOMY: WHO 2021 CNS TUMOR CLASSIFICATION, CNS WHO 5TH EDITION

LAYERED REPORT STRUCTURE:

1. **INTEGRATED DIAGNOSIS** (combined tissue-based histological and molecular diagnosis)

2. HISTOLOGICAL DIAGNOSIS

3. CNS WHO GRADE 1,2,3,4

4. MOLECULAR PROFILING / MOLECULAR PATHOGENESIS

CNS TUMOR TAXONOMY: WHO 2021 CNS TUMOR CLASSIFICATION, CNS WHO 5TH EDITION

CNS WHO Grades of Selected Types	
Astrocytoma, IDH-mutant	2, 3, 4
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	2, 3
Glioblastoma, IDH-wildtype	4
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	1
Polymorphous low-grade neuroepithelial tumor of the young	1
Diffuse hemispheric glioma, H3 G34-mutant	4
Pleomorphic xanthoastrocytoma	2, 3

CNS TUMOR TAXONOMY: WHO 2021 CNS TUMOR CLASSIFICATION, CNS WHO 5TH EDITION

Tumor Type	Genes/Molecular Profiles Characteristically Altered[a]
Astrocytoma, IDH-mutant	*IDH1*, *IDH2*, *ATRX*, *TP53*, *CDKN2A/B*
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	*IDH1*, *IDH2*, 1p/19q, *TERT* promoter, *CIC*, *FUBP1*, *NOTCH1*
Glioblastoma, IDH-wildtype	IDH-wildtype, *TERT* promoter, chromosomes 7/10, *EGFR*
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	*MYB*, *MYBL1*
Angiocentric glioma	*MYB*
Polymorphous low-grade neuroepithelial tumor of the young	*BRAF*, FGFR family
Diffuse low-grade glioma, MAPK pathway-altered	*FGFR1*, *BRAF*
Diffuse midline glioma, H3 K27-altered	H3 K27, *TP53*, *ACVR1*, *PDGFRA*, *EGFR*, *EZHIP*
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, *TP53*, *ATRX*

CNS TUMOR TAXONOMY: WHO 2021 CNS TUMOR CLASSIFICATION, CNS WHO 5TH EDITION

Cerebrum	
Integrated diagnosis	Diffuse low-grade glioma, MAPK pathway-altered *Subtype: Diffuse low-grade glioma, FGFR1 TKD-duplicated*
Histopathological classification	Oligodendroglioma
CNS WHO grade	Not assigned
Molecular information	Duplication of the *FGFR1* tyrosine kinase domain (next-generation sequencing)

GLIOBLASTOMA TREATMENT: NOVEL APPROACHES

- MAXIMAL SAFE SURGICAL RESECTIONS
- SUPRA – MAXIMAL SAFE SURGICAL RESECTIONS
- “CONNECTOME ATLAS / CONNECTOMICS”
- TRACTOGRAPHY / DIFFUSION TENSOR IMAGING
- CORTICAL MAPPING AND INTRA – OPERATIVE MRI
- GAMMA TILE IMPLANTATION
- LASER INTERSTITIAL THERMAL THERAPY / LITT

GLIOBLASTOMA TREATMENT: NOVEL APPROACHES

- PROTON BEAM RADIATION / PHOTON BASED RADIATION
- CLINICAL TRIALS ONGOING
- SYSTEMIC THERAPIES: TEMOZOLOMIDE, BEVACIZUMAB, BCNU IMPLANTABLE WAFERS, CCNU

GLIOBLASTOMA TREATMENT: NOVEL APPROACHES

- **NRG BN 001**
- **PHASE II**
- **Closed To Enrollment**
- **Randomized Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy Versus Conventional Photon Irradiation With Concomitant and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma**

GLIOBLASTOMA TREATMENT: NOVEL APPROACHES

- **NRG BN 002**
- **PHASE I**
- **Study of Ipilimumab, Nivolumab, and the Combination in Patients With Newly Diagnosed Glioblastoma**

GLIOBLASTOMA TREATMENT: NOVEL APPROACHES

- **NRG BN 007**
- **PHASE II / III**
- **A Randomized Phase II/III Open-Label Study of Ipilimumab and Nivolumab Versus Temozolomide In Patients With Newly Diagnosed MGMT (Tumor O-6-Methylguanine DNA Methyltransferase) Unmethylated Glioblastoma**

GLIOBLASTOMA TREATMENT: NOVEL APPROACHES

- NRG BN 010
- PHASE II
- A Safety Run-In and Phase II Study Evaluating the Efficacy, Safety, and Impact on the Tumor Microenvironment of the Combination of Tocilizumab, Atezolizumab, and Fractionated Stereotactic Radiotherapy in Recurrent Glioblastoma
- IL6 and PDL 1 Dual Targeting

GLIOBLASTOMA TREATMENT: NOVEL APPROACHES

- **NRG BN 011**
- **PHASE III**
- **A Phase III Trial of Lomustine-Temozolomide Combination Therapy Versus Standard Temozolomide in Patients with Methylated MGMT Promoter Glioblastoma**

OLIGODENDROGLIOMA TREATMENT: NOVEL APPROACHES

- CNS WHO GRADE 2 / 3
- 1P / 19Q CO DELETED
- IDH1 R132 H MUTATED
- MGMT HYPERMETHYLATED
- TRIPLE + / FAVORABLE GENOMICS
- PROGNOSTIC AND PREDICTIVE VALUE

OLIGODENDROGLIOMA TREATMENT: NOVEL APPROACHES

- Maximal Safe Surgical Resection
- Radiation Options (Photon Based IMRT versus Proton Based IMPT)
- Observation alone after Resection for CNS WHO Grade 2 Oligodendroglioma – Is this a viable strategy
- CNS WHO Grade 3 Anaplastic Oligodendroglioma – certainly post resection RT + Systemic Therapy is warranted

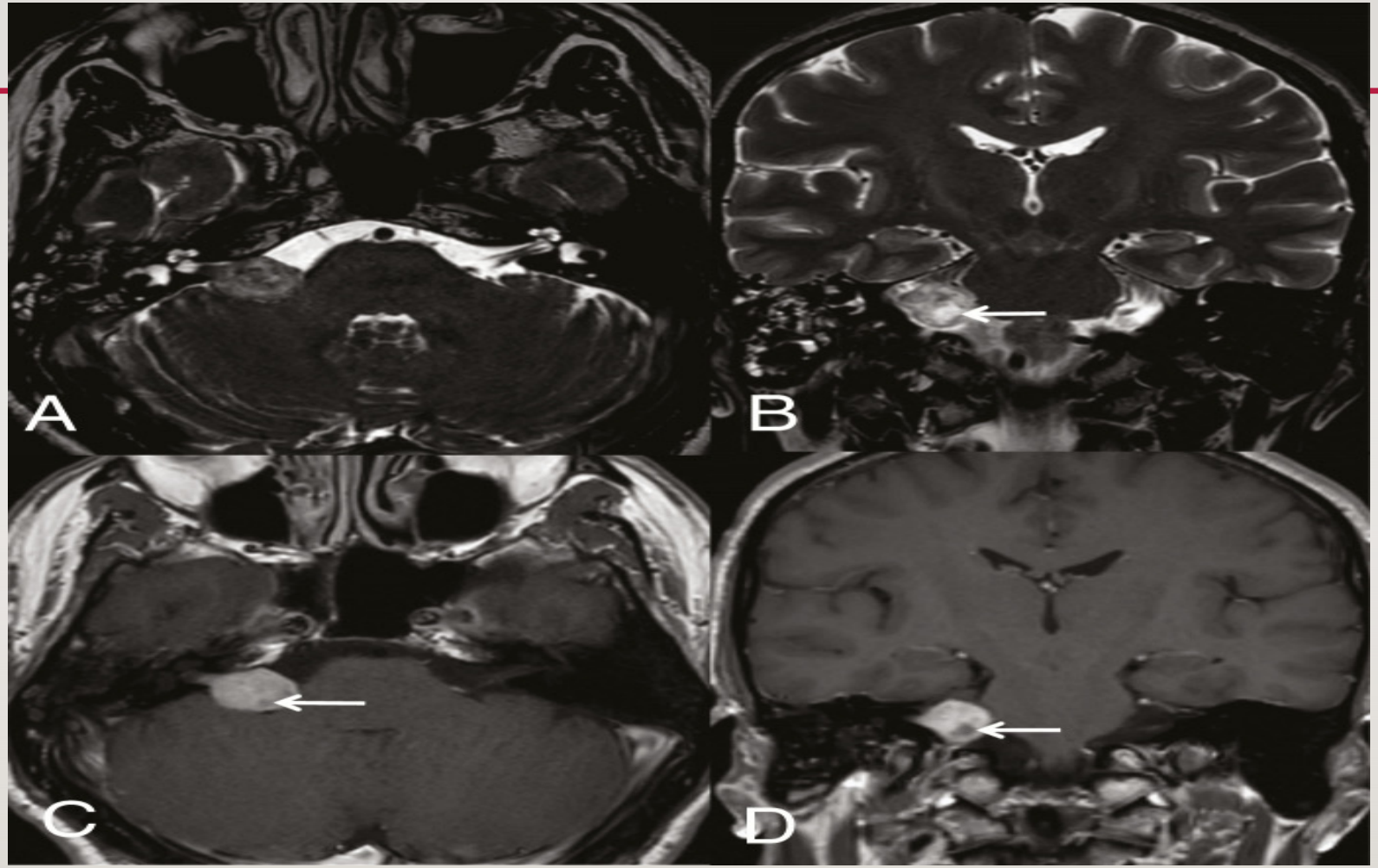
OLIGODENDROGLIOMA TREATMENT: NOVEL APPROACHES

- **ALLIANCE N0577 TRIAL**
- **PHASE III**
- **Phase III Intergroup Study of Radiotherapy With Concomitant and Adjuvant Temozolomide Versus Radiotherapy With Adjuvant PCV Chemotherapy in Patients With 1p/19q Co-deleted Anaplastic Glioma or Low Grade Glioma**

MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES

- **Inactivation of the *NF2* tumor suppressor gene is considered a major event in the tumorigenesis of conventional schwannoma**
- **Whole exome sequencing study demonstrated that 77% of VS show evidence of genomic inactivation of *NF2* via loss of chromosome 22q or *NF2* gene mutation.**

MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES



MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES

- MR Based Imaging preferred (with some special sequences)
- FIESTA (fast *imaging* employing steady-state acquisition), CISS (constructive interference in steady state), or DRIVE (driven equilibrium pulse)

MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES

- Histo – Pathological Features
- Vestibular schwannomas, formerly thought to originate from Schwann cells in the glial-Schwannian transitional zone of the vestibulocochlear nerve, do in fact arise anywhere along the eighth cranial nerve.
- In about 80% of cases they are found in the vestibular portion and in about 20% of cases in the cochlear portion.

MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES

- Four nonrandomized studies compared outcomes from observation and stereotactic radiosurgery (SRS) showing better tumor control after SRS (evidence class II, recommendation level B).
- Some studies reported less hearing loss in patients with SRS, whereas in others hearing outcome and complaints were not different

MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES

Koos Grade	Tumor Description
I	Small intracanalicular tumor
II	Small tumor with protrusion into the cerebellopontine angle; no contact with the brainstem
III	Tumor occupying the cerebellopontine cistern with no brainstem displacement
IV	Large tumor with brainstem and cranial nerve displacement

MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES

- **Surgical Treatment**

- **The suboccipital retrosigmoid (retromastoid) approach is favored by neurosurgeons and is particularly indicated for tumors located primarily in the cerebellopontine cistern or tumors with significant mass effect**
- **The translabyrinthine approach, usually performed by ENT surgeons, can be used to remove tumors of all sizes.**
- **A labyrinthectomy will result in complete loss of function of the inner ear**

MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES

- Radiation Options
- Stereotactic Radiosurgery (SRS)
- Fractionated – SRS
- Hypofractionated Stereotactic Radiotherapy (SRT)
- Photon or Proton Based IMRT / IMPT

MALIGNANT VESTIBULAR SCHWANNOMA: NOVEL APPROACHES

- Systemic Therapy Options
- Bevacizumab has been successfully used for patients with progressive VS associated with NF2
- EGFR Targeting with Erlotinib
- ERBB2 Targeting with Lapatinib
- MTOR / AKT / PI3K Targeting with Everolimus

ARISTOTLE (384 – 322 BC): AUTHOR OF THE NICOMACHEAN ETHICS

- **Knowing yourself** is the beginning of **all wisdom**
- **Educating the mind** without educating the heart is no education at all
- **Courage is the first of human qualities** because it is the quality which guarantees the others