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Universitair Medisch Centrum Rotterdam

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brain tumor center

WHO CLASSIFICATION OF BRAIN TUMORS AND APPROACH TO LOWER GRADE GLIOMAS

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Disclosures

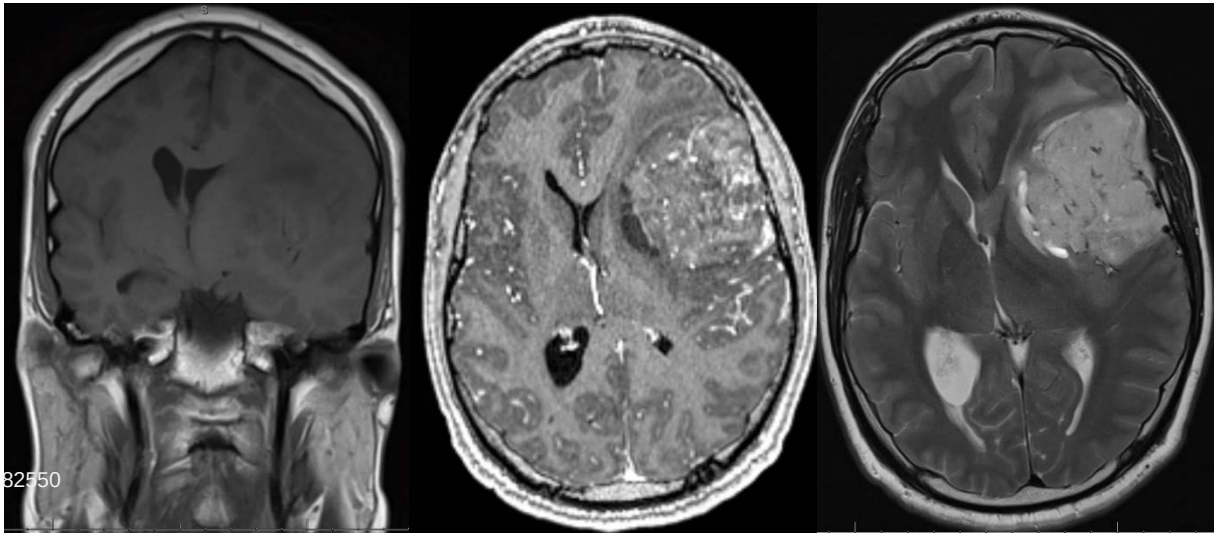
- Honoraria from Celgene, Bayer, Boehringer, Agios, BMS, Carthera

- Learning objectives:

- Understand the molecular basis of the 2016 WHO glioma classification
- Understand prognostic factors in IDH mutated glioma
- Understanding of the role of adjuvant chemotherapy in glioma

A 40 year old male with headache and difficulty walking

- 40 year old male with a short history headache and difficulty walking
- MRI: left frontal enhancing tumor; June 2016: partial resection
- Histopathology: glioblastoma
- Sequencing: IDH2 mutation, combined 1p/19q loss and deletion of chromosome 9
- Molecular diagnosis: anaplastic oligodendroglioma?
- Treated with RT/TMZ, 2 years later still doing well
- Diagnosis?



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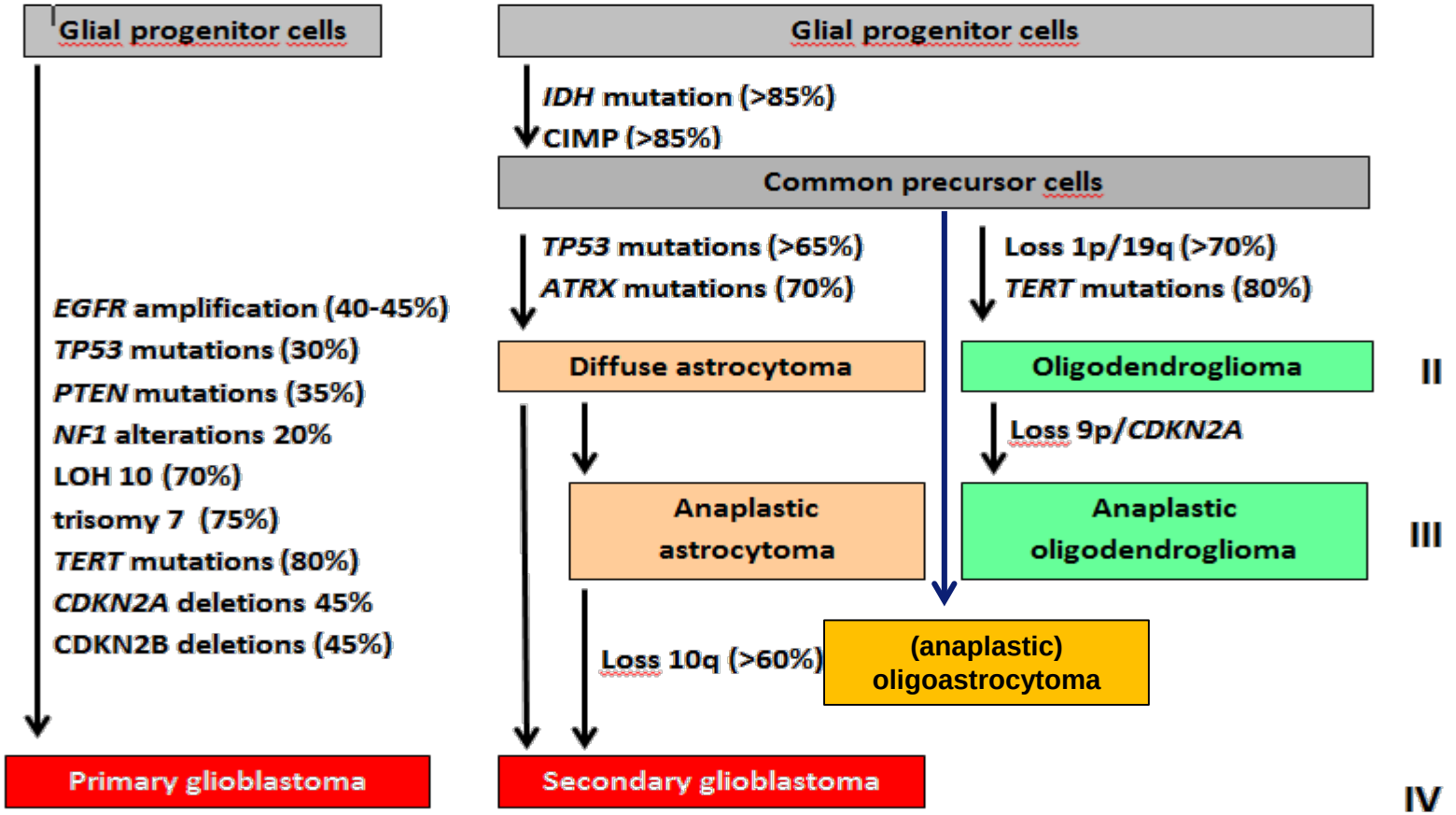
WHO 2007 – diffuse glioma (histology based)



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Shortcomings of the classical histopathological classification of gliomas

- Poor reproducibility of diagnosis in grade II and grade III tumors[1]
  - Both with respect to lineage and grade
  - 25-33% of cases
- Based on morphological resemblance and clinical outcome (prognosis)
  - Not a functional approach
  - Not correlated to outcome to specific treatments
- Data from studies conducted in 2013-2016 showed improved classification of diffuse glioma and demonstrated improved prognostication using few molecular markers:
  - IDH 1,2 mutations, codeletion 1p/19, TERT promoter mutations, combined trisomy 7/LOH10q

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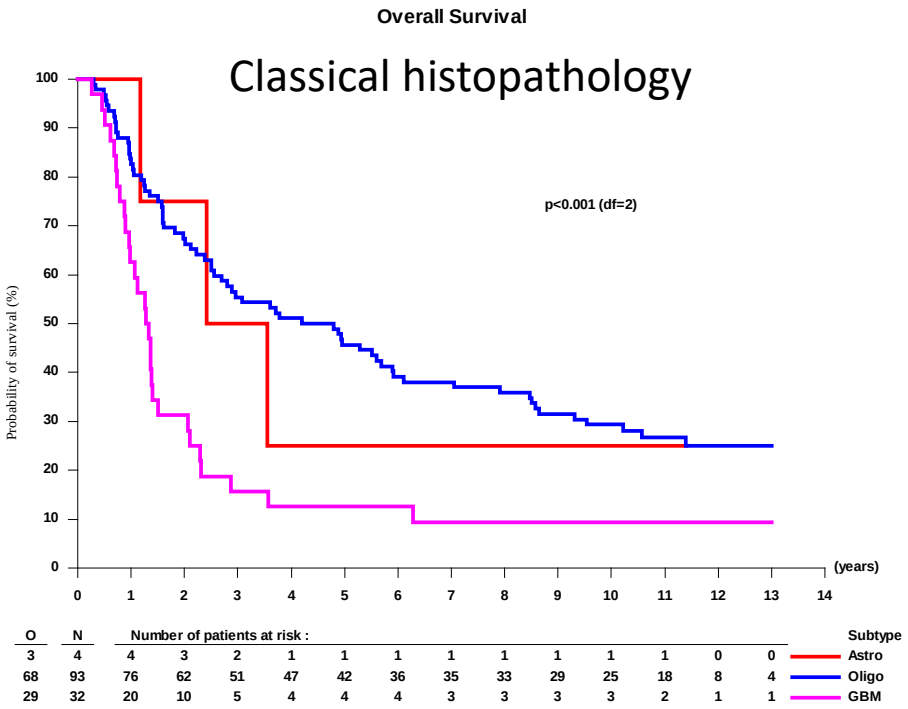
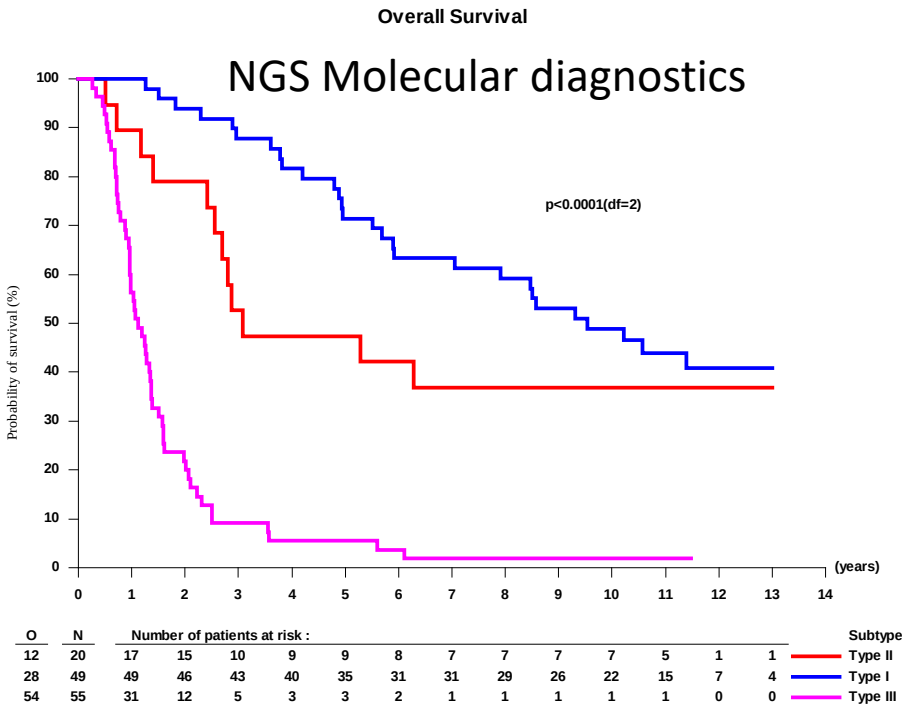
[1]van den Bent Acta Neuropathol (2010) 120:297–304

Dubbink et al, Neuro Oncol (2015) doi: 10.1093/neuonc/nov182

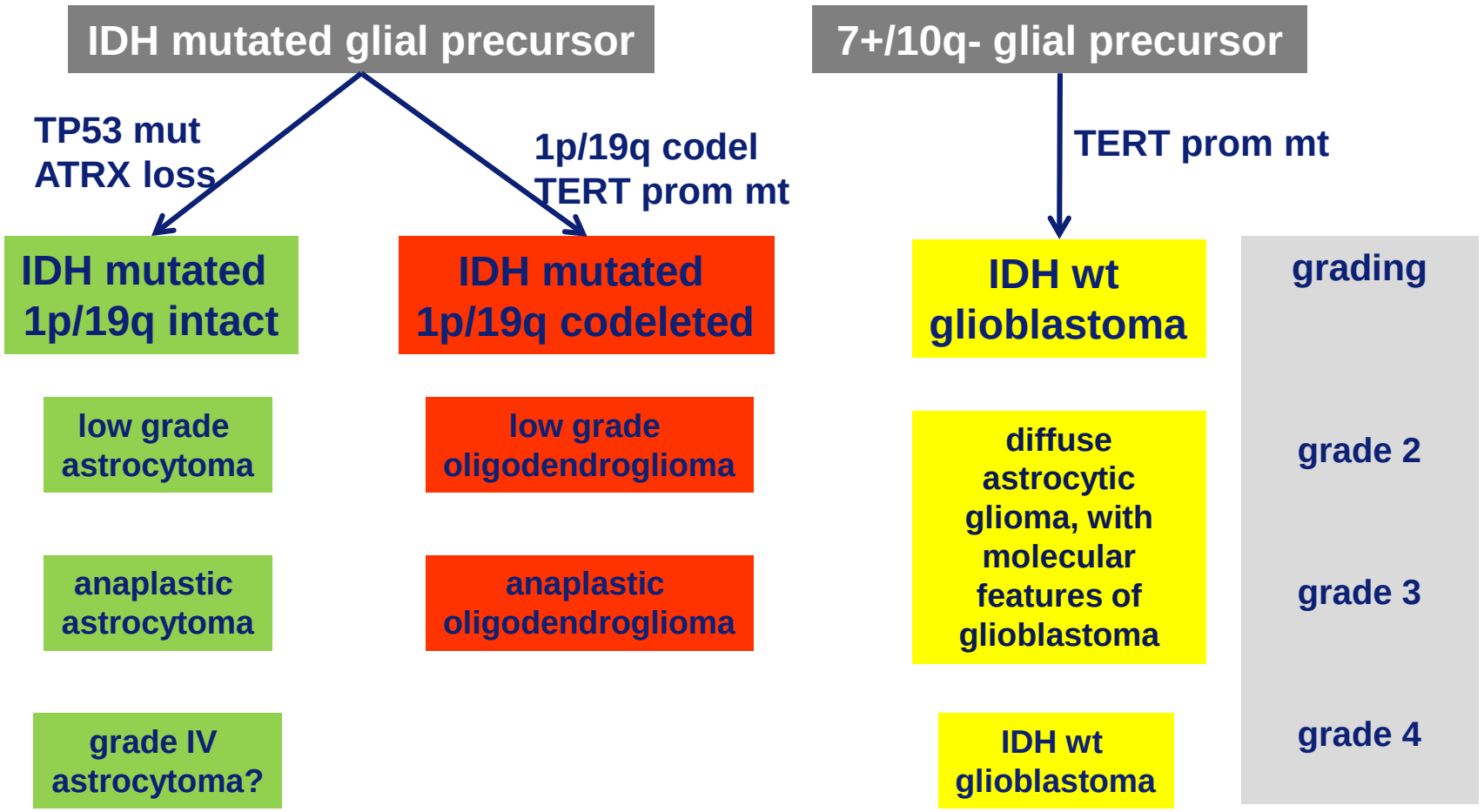
WHO 2016: Molecular diagnostics with NGS improves the classification of brain tumors





tumor	Molecular characteristics
oligodendroglioma	IDH mutated, 1p/19q loss
astrocytoma	IDH mutated
glioblastoma	LOH10q & trisomy 7, or TERT mutated but no 1p/19q loss

A modified WHO 2016 for diffuse glioma



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Key Points from the 2016 WHO Glioma Classifications and cIMPACT-NOW revisions

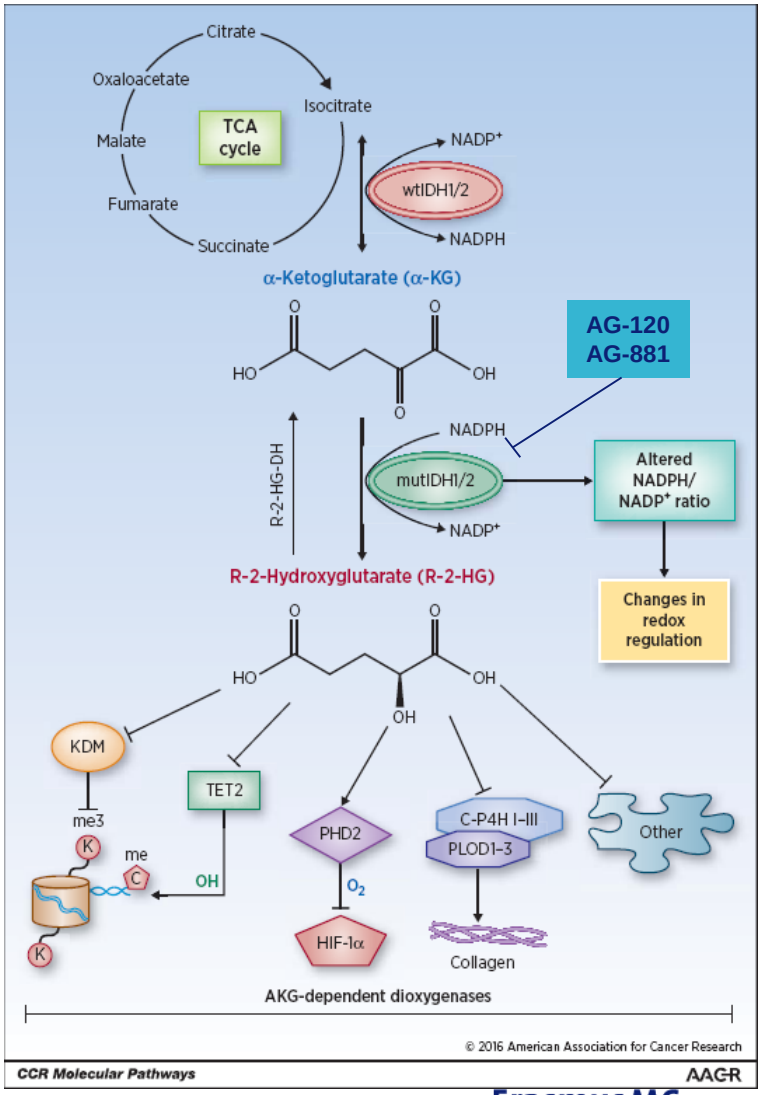
- Key role in the classification for IDH and 1p/19q[1]
- Not Otherwise Specified (NOS): intended for use for cases that could not be tested or in which testing was not successful[1]
- Oligoastrocytoma is only classified if NOS[1]
  - No clear molecular correlate: either *1p/19q co-deleted, IDH mt* or only *IDH mt*[1]
- Gliomatosis cerebri has disappeared as an entity[1]
- IDHwt low grade astrocytoma with molecular features of glioblastoma: perception of grade IV
- Changing name for glioblastoma, IDHmt?

1. Louis DN, *et al. Acta Neuropathol* 2016; **131:**803–820.

IDH mutation: a tumor driving mutation through altered enzym substrate affinity?

IDHmt onco-protein: decreased levels of α-ketoglutaraat, accumulation of 2-HG

- 2HG inhibits a wide range of α-KG dependent dioxygenases
- Epigenetic dysregulation via inhibition of αKG-dependent histone and DNA demethylases, resulting in CIMP, **MGMT methylation**
- Block of cellular differentiation
- Pathological self renewal of stem like progenitor cells?
- Upregulation of PI3K/mTOR signaling
- Contributes to the immosuppressive landscape of gliomas



Clark et al, Clin Canc Res 2016;22:1837-42

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Other molecular entities in the WHO classification

- Partial introduction of histone 3 mutations as a separate entity[1]
  - Limited to H3F3A-mutated only[1]
  - Diffuse mideline glioma with K27M mutation: very poor prognosis, MGMT not methylated (diffuse pontine glioma, thalamus glioma)
- Molecular subgroups of medulloblastoma with different outcome
- Ependymoma sublassification: RELA fusion hemisperic ependymoma

cIMPACT-NOW update 3

Acta Neuropathologica
https://doi.org/10.1007/s00401-018-1913-0

CORRESPONDENCE

cIMPACT-NOW update 3: recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV"

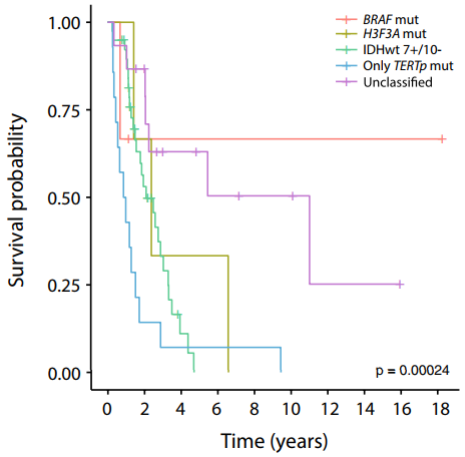
Daniel J. Brat[1] · Kenneth Aldape[2] · Howard Colman[3] · Eric C. Holland[4] · David N. Louis[5] · Robert B. Jenkins[6] · B. K. Kleinschmidt-DeMasters[7] · Arie Perry[8] · Guido Reifenberger[9,10] · Roger Stupp[11] · Andreas von Deimling[12,13] · Michael Weller[14]

- Criteria for **diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma**:
  - Histologically grade II, III astrocytoma, IDHwt, with
    - **EGFR amplification (high level)**

      or
    - **Combined whole chr 7 gain and whole chr 10 loss (+7/-10)**

      or
    - **TERT promoter mutation**

- Erasmus MC series:
  - 74 IDHwt: 39 7+/10q- (38 TERTp mt), 14 only
  - Prognosis even worse in TERTp mt only



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[2]Wijnenga et al, Acta Neuropathol 2017; DOI 10.1007/s00401-017-1781-z

OS in molecularly defined anaplastic glioma as reported in large phase III trials

study	histology	Molecular subtype	treatment	n	Median OS	Median PFS
RTOG 9802	Low grade glioma	IDH mutated (all) IDHwt	RT/PCV or RT RT/PCV or RT	71 42	13.1 yrs 5.1 years	
EORTC 26951	Anaplastic oligodendroglioma	1p/19q codeleted IDHmt 1p/19q intact 7+/10q-/TERTpmt	RT/PCV RT/PCV RT or RT/PCV	43 23 55	NR (>14 yrs) 8.3 yrs 1.13 yrs	147 4.2 yrs NS
RTOG 9402	Anaplastic oligodendroglioma	1p/19q IDHmt (all)	RT/PCV	59	14.7 yrs	8.4 yrs
RTOG 9804	Anaplastic astrocytoma	IDH mt (IHC) IDHwt	RT/chemo	49 54	7.9 yrs 2.8 yrs	
NOA4	Grade III	1p/19q codeleted IDHmt 1p/19q intact IDHwt	RT or chemo	66 83 58	NR 7.0-7.3 yrs 3.1 – 4.7 yrs	

Anaplastic glioma	Reported survival after RT/chemo
Oligodendroglioma, IDHmut & 1p/19q codeleted	> 14 years
Astrocytoma, IDH mutated	7 - 8 years
Astrocytoma IDH wt	1 – 4.7 yrs

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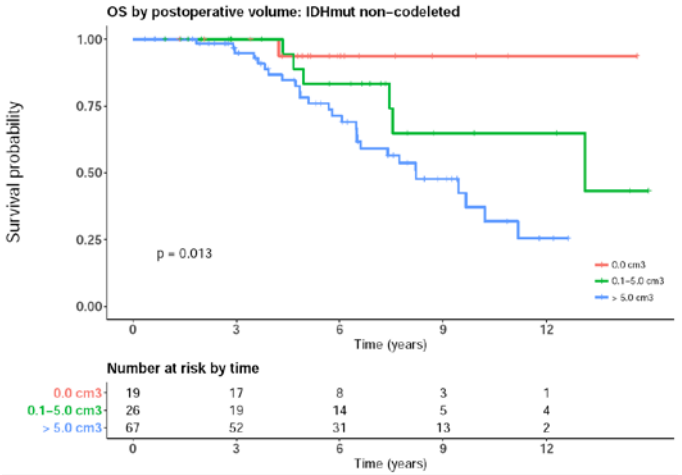
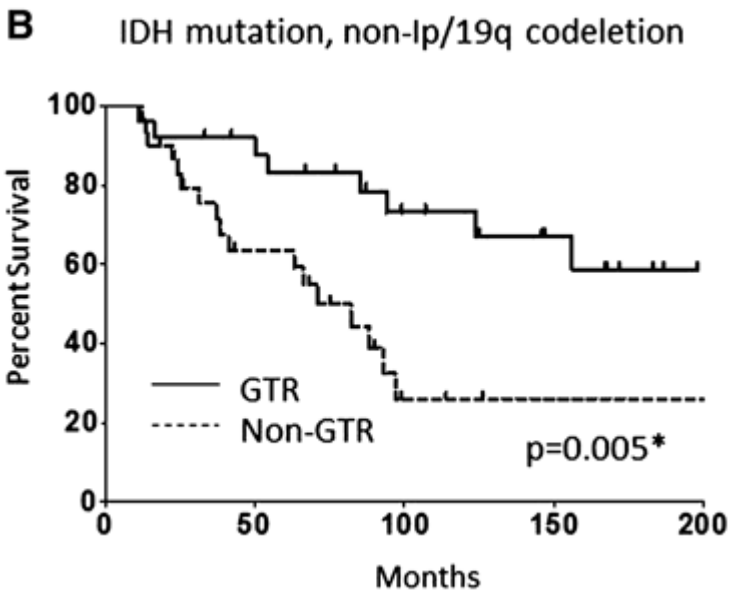
Extent of resection in IDHmt Astrocytoma

- Series on low grades, anaplastic IDHmt astrocytoma[1, 2]
- Both show early and significant effect from less than total resection on OS
- 2nd look surgery in case of less than complete resection?



- Bias remains: smaller tumors more likely to get extensively resected

- Less impact tumor residu in oligodendroglioma



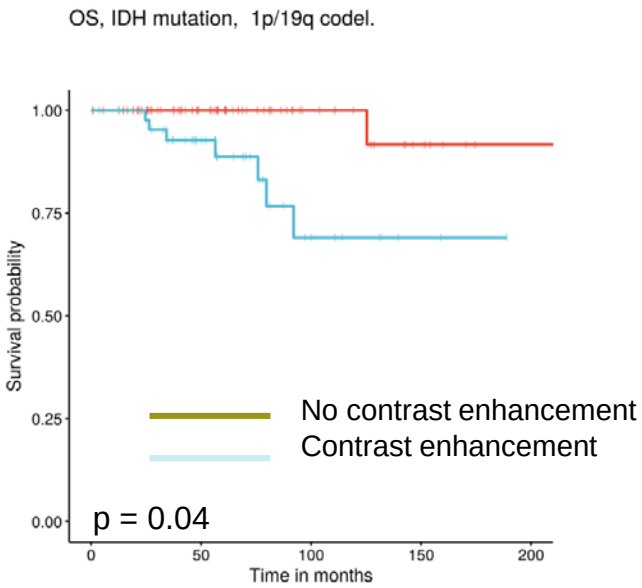
[1]Wijnenga et al Neurooncol 2017 doi:10.1093/neuonc/nox176
[2]Kawaguchi et al, J Neurooncol 2016;129:505-14

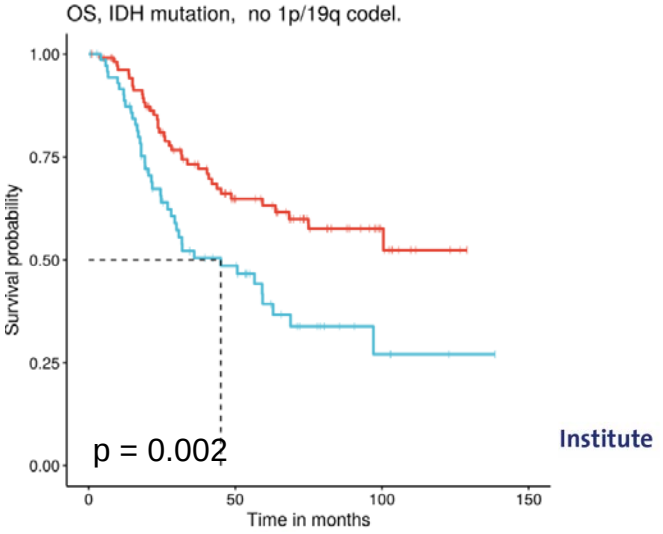
Prognosis in grade II, III glioma

- Depends on a combination of clinical and molecular factors
- Some clinical factors known
- Molecular factors within the WHO 2016 classification still to be unravelled

Contrast enhancement and outcome in IDHmt grade II and III tumors

- Series on 301 grade II and III glioma
  - 208 IDHmt
- Grade III tumors more likely to present with CE (60.8%) than WHO II tumors (26.5%, p<0.001).
- CE on initial MR imaging prognostic for survival in IDH mt tumors
  - No impact in IDHwt tumors
- With dependence on volume (p<0.05)
  - IDHmt: HR 0.31 (0.14 -0.69)
  - IDHmt 1p/19q codel: HR 0.08 (0.01 – 0.69)

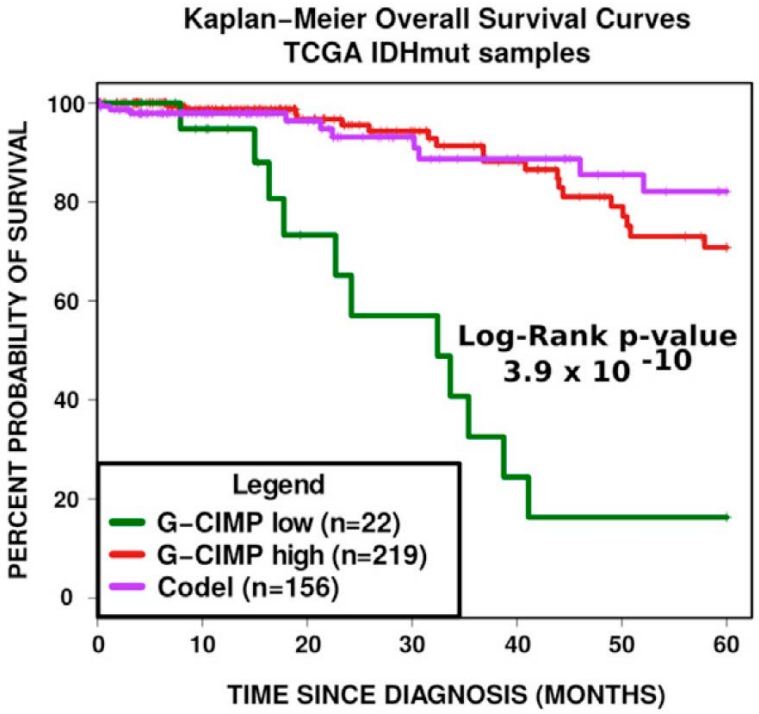


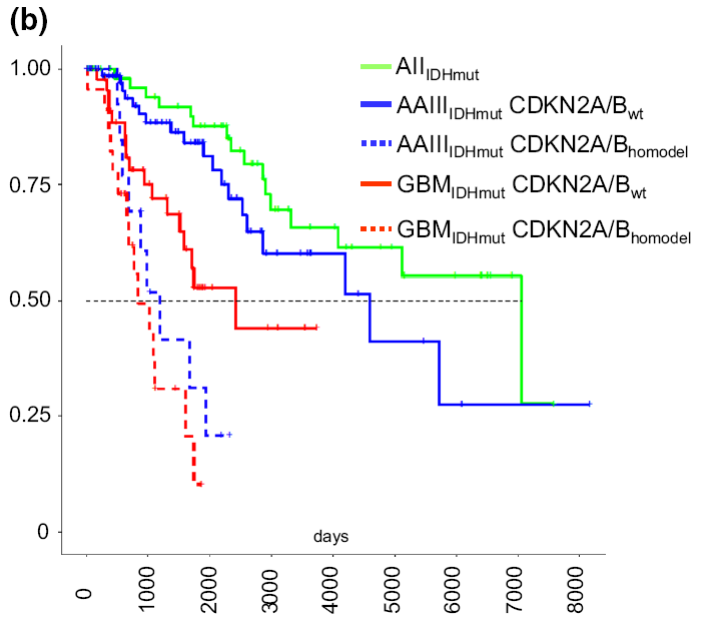


Suchorska et al, Eur J Canc 2019;107:15-27

Methylation, CIMP, IDH

- Most IDHmt tumors show CpG Island Methylated Phenotype (CIMP)
- In 95% includes MGMT promoter
- In astrocytoma, IDHmt reported worse outcome in
  - G-CIMP low
  - Necrosis and homozygous deletion CDKN2A/B
  - 7 hypomethylated CpG sites
  - Total CNA

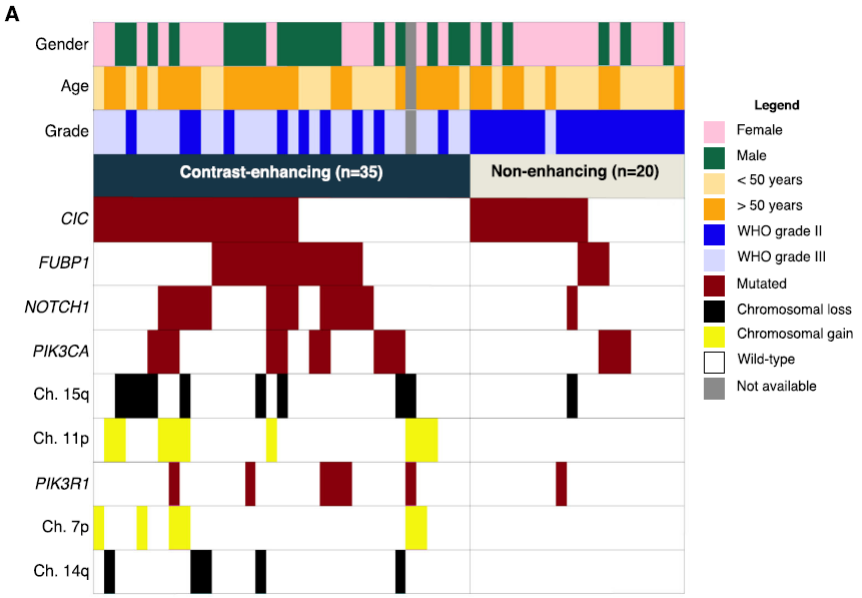


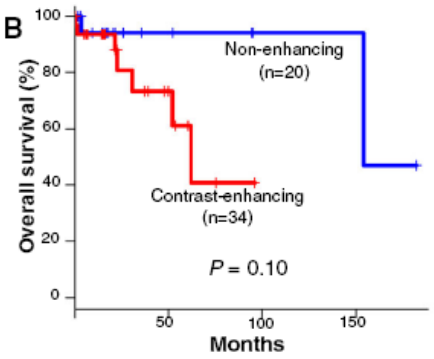


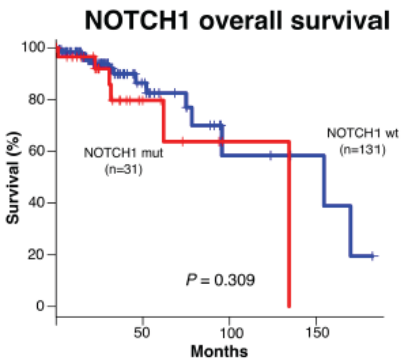
Shirahata et al, Acta Neuropathol 2018; Cecarelli et al, Cell 2016:164:550-63; Ferreira de Souza, Cell Reports 2018;23:637-51

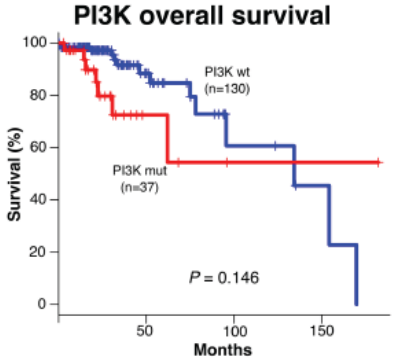
Multi-faceted computational assessment of risk and progression in oligodendroglioma implicates NOTCH and PI3K pathways

- CE+ tumors, high proliferation markers worse outcome
- Notch pathway inactivation and PI3K pathway activation associated with MRI and pathology findings of advanced disease and poor clinical outcome.
- However: NOTCH, PI3KC mutations in univariate analysis not informative









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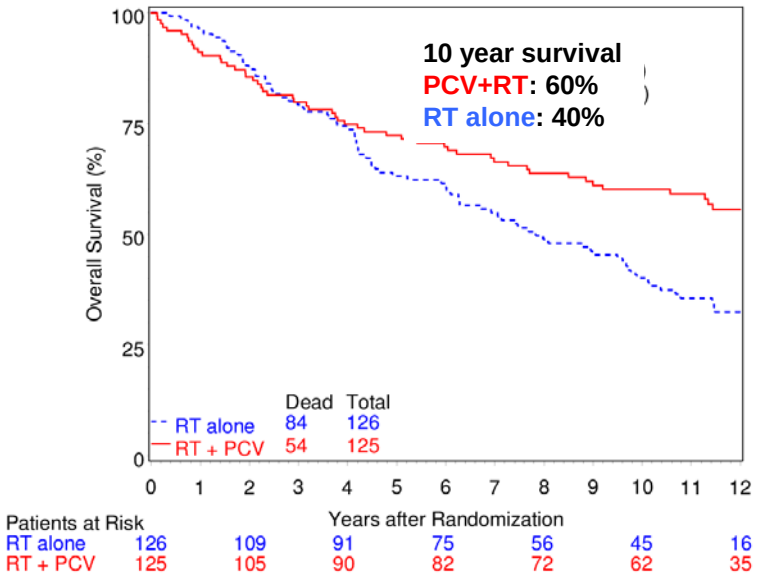
Halani et al, NPJ Precis Oncol 2018;2:24

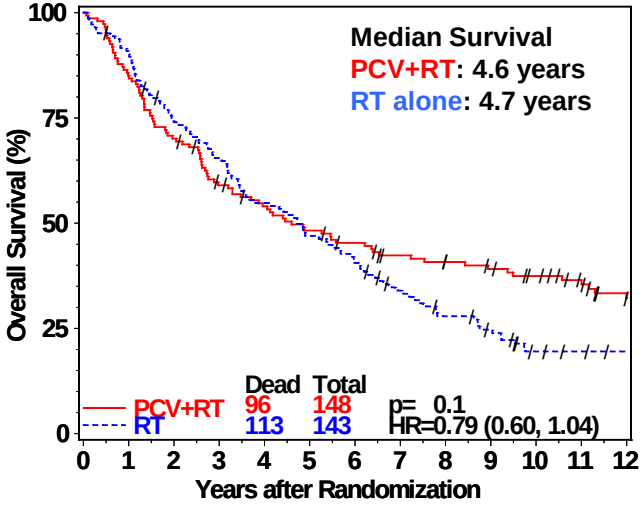
And chemo for all grade II and III glioma!

Four trials that changed the standard of care

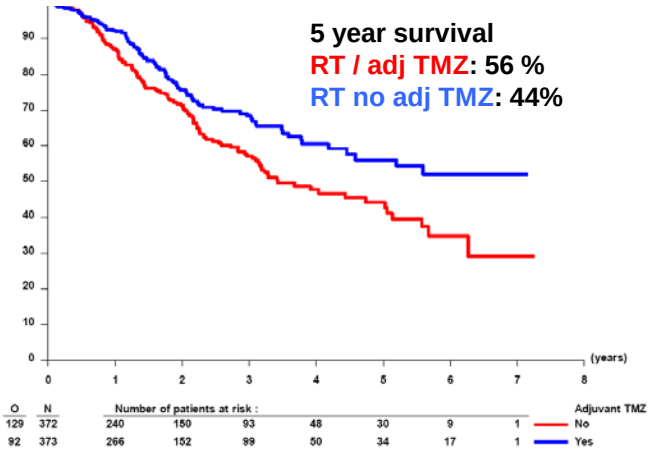
Low grade glioma: RTOG 9802



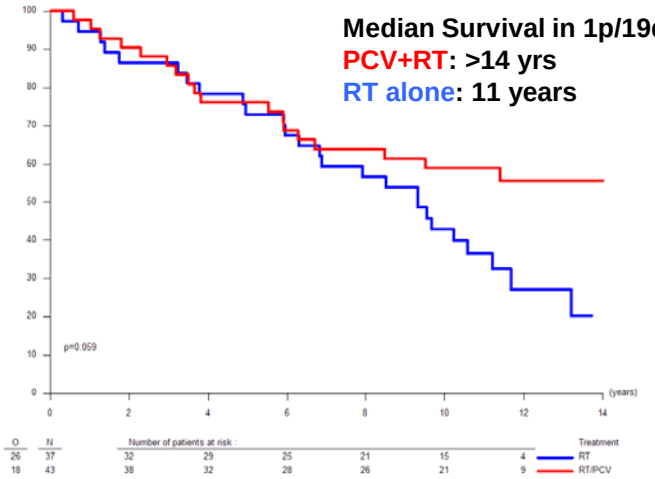
Anaplastic oligodendroglioma RTOG 9402



1p/19q intact anaplastic astrocytoma: the EORTC CATNON trial



1p/19q codeleted anaplastic oligodendroglioma: EORTC 26951



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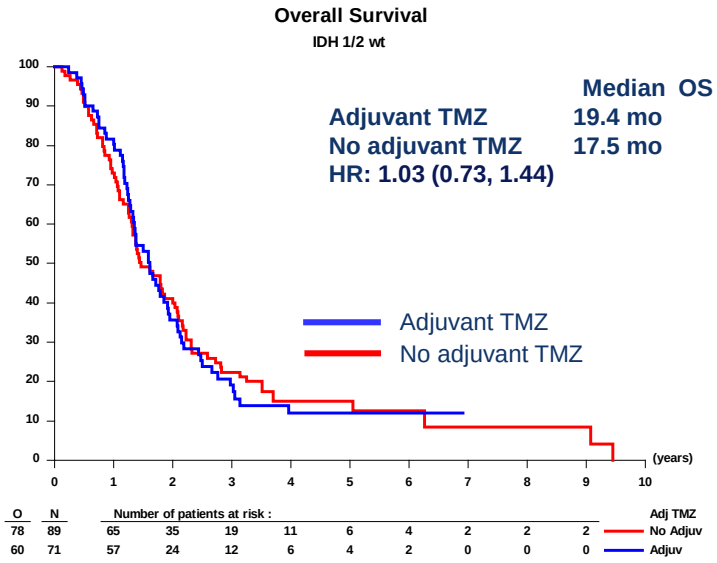
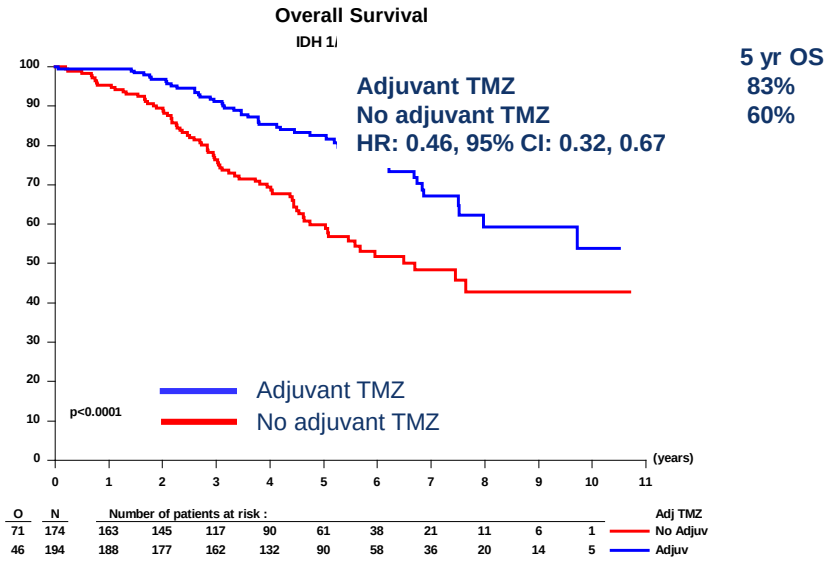
The CATNON trial: Adjuvant temozolomide in IDHwt and IDHmt anaplastic astrocytoma

IDH wild type



IDH mutant



- **Adjuvant temozolomide improves outcome in IDH mutant anaplastic astrocytoma**

EORTC

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EORTC 26951: Quality of Surival in a cohort with long term follow-up

Evaluation of cognitive functioning:

- Progression-free patients (n=27): highly variable
  - 44% no cognitive impairments
  - 30% severe cognitive impairments
- Treatment (small subgroups): additional PCV not associated with worse cognition
- 41% were employed and 81% could live independently
- Progressive disease (n=5): more cognitive impairments

- **Does this warrant postponement of RT?**

Habets et al, J Neurooncol 2014;116:161-8

EORTC IDHmut grade II/III Study: Wait Or Treat?

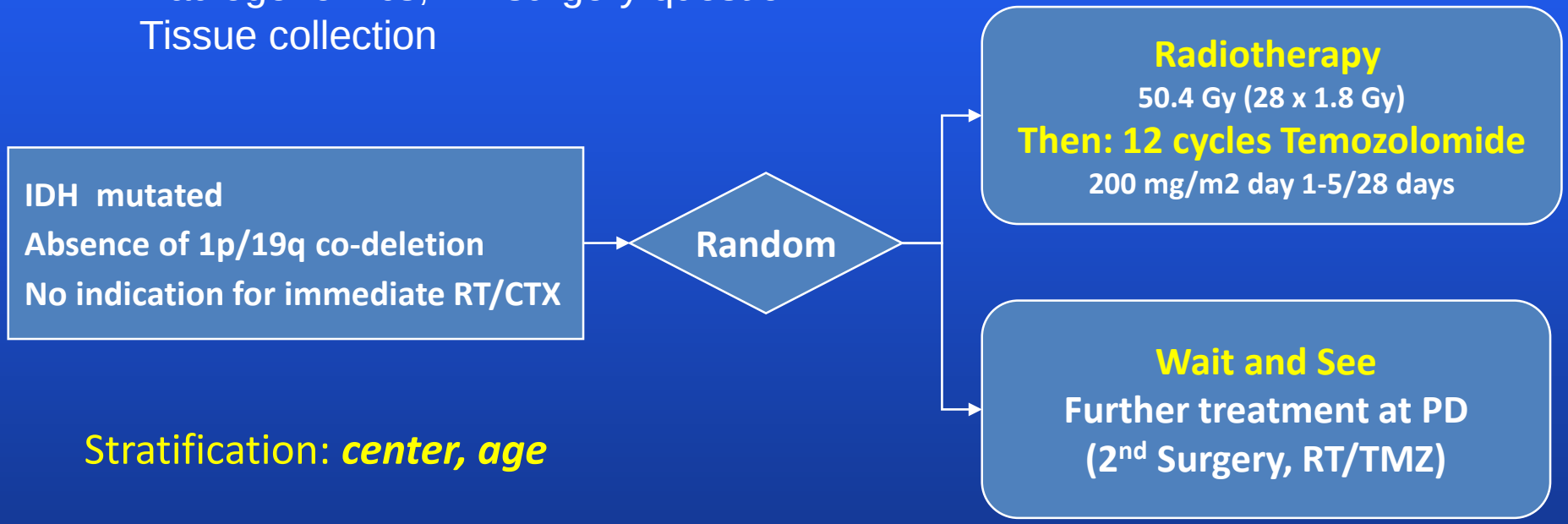
Primary endpoint: Next Intervention Free Survival

Secondary endpoints:

OS, QoL, Neurocognitive function

Radiogenomics, 2nd surgery question

Tissue collection



Stratification: ***center, age***

Some conclusions

- The WHO 2016 molecular based classification is more robust in terms of specificity and sensitity, with improved prognostication
  - Histology deceives…
- Currently based on mutational analysis and copy number alterations
- For all diffuse grade II, III astrocytoma, oligodendroglioma: standard of care radiotherapy with chemotherapy
  - Benefit in particular in IDHmt tumors
- Low grade tumors with molecular features of glioblastoma: to be considered as glioblastoma