Diffuse astrocytoma IDH Mutant outcome

The WHO classification for IDH-mutant grade II and grade III astrocytoma may not be as prognostically meaningful as expected.

Liu et al. aimed to develop a novel classification system based on the DNA damage response signature.

They developed the gene signature of DNA damage response with 115 samples from The Cancer Genome Atlas (TCGA) database. The dataset from Chinese Glioma Genome Atlas (CGGA) database with 41 samples was used as the validation set. Lasso Cox regression model was applied for selection of the best signature. Gene set enrichment analysis (GSEA) and gene ontology (GO) analysis were implemented to reveal its biological phenotype.

A two-gene DNA damage response signature (RAD18, MSH2) was developed using the lasso Cox regression model based on the TCGA dataset. Its prognostic efficiency was validated in the CGGA cohort. The result of the Cox regression analysis showed that the signature has better predictive accuracy than the WHO grade. The risk score was an independent prognostic factor for the overall survival of the IDH-mutant grade II and grade III astrocytoma. GSEA and GO analysis confirmed enhanced processes related to DNA damage response in high-risk group.

They developed a two-gene signature that can effectively predict the prognosis of patients with IDH-mutant grade II and grade III astrocytoma. It suggests a novel classification of astrocytoma with better prognostic accuracy based on the expression of DNA damage response genes [1].

A cohort with known IDH-mutations demonstrated a median survival of 10.9 years [2].

Pre-IDH era data showed worse prognosis with the following [3] (will now need to be validated with known IDH status):

1. age > 40 years (perhaps the most important unfavorable prognosticator)

2. astrocytoma histology

3. largest tumor diameter ≥ 6 cm

4. tumor crossing the midline

5. neurologic deficit prior to surgery

Dedifferentiation

These tumors are capable of malignant dedifferentiation, and the ultimate behavior of these tumors in adults is usually not benign, as 75% of adult tumors undergo anaplastic progression into IDH-mutant anaplastic astrocytoma and thence IDH-mutant glioblastoma, which is the major cause of morbidity, whereas pediatric diffuse astrocytomas (age<20) rarely undergo malignant degeneration [4].

WHO grade II astrocytomas tend to undergo malignant transformation more quickly when diagnosed after age 45 years. Once dedifferentiation occurs, median survival is 2–3 years beyond that event (pre-IDH era data [5]).

The UCSF preoperative grading system for WHO grade II astrocytomas [6] assigns 1 point for the presence of each of the 4 parameters shown:

Item	Yes/No
age > 50 years	Yes = 1, No = 0
KPS[b] ≤ 80	Yes = 1, No = 0
located in eloquent brain[c]	Yes = 1, No = 0
maximal diameter > 4 cm	Yes = 1, No = 0

[a] pre-IDH era data, tumors are therefore diffuse astroctyomas, NOS
[b] KPS = Karnofsky performance score (p. 1436)
[c] for this study, eloquent brain is defined as any of: primary sensory or motor cortex, Wernicke's or Broca's area,

The points are summed and the prognosis is

Sum	5-year survival	5-year progression-free survival
0–1	97%	76%
2	81%	49%
3–4	56%	18%

(this scale has been validated at other institutions, [7] but uses pre-IDH era data and will need to be updated).

1)
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