Neuro Oncol. 2023 Oct 11:noad197. doi: 10.1093/neuonc/noad197. Online ahead of print.

## Mean global DNA methylation serves as independent prognostic marker in IDH wild type glioblastoma

Alicia Eckhardt <sup>1</sup> <sup>2</sup> <sup>3</sup>, Richard Drexler <sup>4</sup>, Melanie Schoof <sup>2</sup> <sup>5</sup>, Nina Struve <sup>1</sup> <sup>6</sup>, David Capper <sup>7</sup>, Claudius Jelgersma <sup>8</sup>, Julia Onken <sup>8</sup> <sup>9</sup>, Patrick N Harter <sup>10</sup> <sup>11</sup> <sup>12</sup> <sup>13</sup>, Katharina J Weber <sup>10</sup> <sup>11</sup> <sup>12</sup> <sup>14</sup>, Iris Divé <sup>15</sup> <sup>14</sup>, Kai Rothkamm <sup>1</sup>, Konstantin Hoffer <sup>1</sup>, Lukas Klumpp <sup>16</sup>, Katrin Ganser <sup>16</sup>, Cordula Petersen <sup>1</sup>, Franz Ricklefs <sup>4</sup>, Malte Kriegs <sup>1</sup>, Ulrich Schüller <sup>2</sup> <sup>3</sup> <sup>5</sup>

Affiliations PMID: 37818983 DOI: 10.1093/neuonc/noad197

## Abstract

**Background:** The IDH wild type glioblastoma (GBM) patients have a devastating prognosis. Here, we analyzed the potential prognostic value of global DNA methylation of the tumors.

**Methods:** DNA methylation of 492 primary samples and 31 relapsed samples, each treated with combination therapy, and of 148 primary samples treated with radiation alone were compared with patient survival. We determined the mean methylation values and estimated the immune cell infiltration from the methylation data. Moreover, the mean global DNA methylation of 23 GBM cell lines was profiled and correlated to their cellular radiosensitivity as measured by colony formation assay.

**Results:** High mean DNA methylation levels correlated with improved survival, which was independent from known risk factors (MGMT promoter methylation, age, extent of resection; p=0.009) and methylation subgroups. Notably, this correlation was also independent of immune cell infiltration since higher number of immune cells indeed was associated with significantly better OS but lower mean methylation. Radiosensitive GBM cell lines had a significantly higher mean methylation than resistant lines (p=0.007), and improved OS of patients treated with radiotherapy alone was also associated with higher DNA methylation (p=0.002). Furthermore, specimens of relapsed GBM revealed a significantly lower mean DNA methylation compared to the matching primary tumor samples (p=0.041).

**Conclusions:** Our results indicate that mean global DNA methylation is independently associated with outcome in glioblastoma. The data also suggest that a higher DNA methylation is associated with better radiotherapy response and less aggressive phenotype, both of which presumably contribute to the observed correlation with OS.

Keywords: DNA methylation; glioblastoma; overall survival; radiotherapy response.

© The Author(s) 2023. Published by Oxford University Press on behalf of the Society for Neuro-Oncology. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

PubMed Disclaimer