



Change in Neutrophil-to-Lymphocyte Ratio Following Glioma Resection

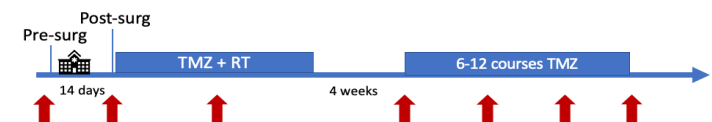
Yujia Shentu, MS¹; Jordan F. Isaacs, BA²; Carmen del Genio, BS²; Arti Gaur, PhD²;
¹ Geisel School of Medicine at Dartmouth College, Hanover, NH; ² Department of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, NH

Introduction

Glioma accounts for a third of all primary brain tumor. The interplay between glioma cells and the systemic immune response has been of great research interest. Previous studies have established correlation between neutrophilia and higher-grade glioma, whereas increased number of tumor-infiltrating lymphocytes indicates better survival prognosis. Combining the two hematological findings, neutrophil-to-lymphocyte ratio (NLR) is computed as a systemic inflammation marker. Previous studies have established NLR>4 as a prognostic marker for glioblastoma grading and survival. Specific genetic alterations such as IDH1 mutation and MGMT promoter hypermethylation are also associated with better glioma prognosis.

Methods

Data was collected as part of the ongoing NCT00887146 clinical trial. Patients with grade III-IV glioma were recruited through Norris Cotton Cancer Center and 4 other sites. Subjects underwent neurologic surgery on day 0. Surgically resected tumors were tested for IDH1 and MGMT mutation. On day 14, subjects start a 6-week combined temozolomide (TMZ) and radiation therapy (RT). Blood samples were collected pre-surgery, 14 days post-surgery, as well as at 5 other time points. Complete blood count reports were obtained for each blood sample.



Results

A total of thirteen patients were included in this analysis (61.5% female, mean age 59, 69% grade IV). The mean decrease in NLR from pre- to post-surgery was 12.91 (t (12) = 5.85, p < 0.001).

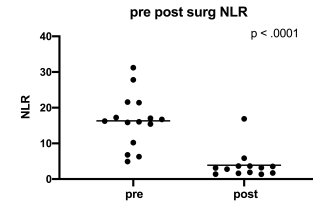
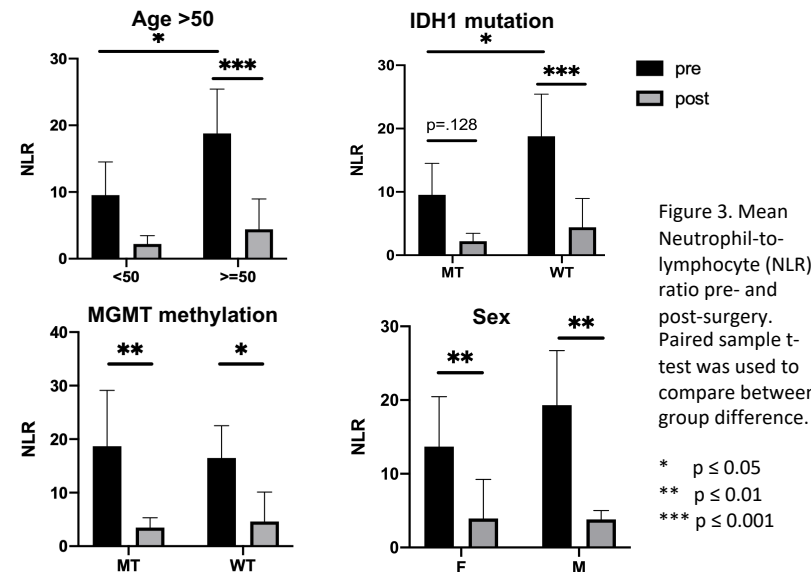


Figure 2. mean NLR pre- and post-surgery

Compared with patients under the age of 50, patients older than 50 had a significantly higher pre-surgery NLR (p < 0.05). Patients with IDH1 wild type had a statistically significant decrease in NLR from pre to post-surgery (p < 0.001), whereas IDH1 mutated group did not. No group differences in NLR change were found for MGMT mutation status, sex, or tumor grade.



Conclusion

NLR is a systemic marker for tumor burden and is drastically decreased following glioma surgical resection. Compared to wildtype IDH1 patients, patients with IDH1 mutation are generally younger and have lower pre-surgery NLR, and experience milder change in NLR after surgical resection. IDH1 mutated glioma cells produce a unique R-2-hydroxyglutarate metabolite, which differs from alpha ketoglutarate by one hydroxyl group. Such difference manifests as a reprogramming of cellular metabolism. The current study indicates such altered cellular metabolism might be associated with an underlying variation in immunological responses.

The team is currently analyzing plasma cytokines profile to better understand the shared pathway between altered cellular metabolism and systemic immune response. Limitation for this study is the limited subjects included.

References

- Bunse L, Pusch S, Bunse T, et al. Suppression of antitumor T cell immunity by the oncometabolite (R)-2-hydroxyglutarate. *Nature Medicine*. 2018;24(8):1192-1203. doi:10.1038/s41591-018-0095-6
- Fridlender ZG, Sun J, Kim S, et al. Polarization of Tumor-Associated Neutrophil Phenotype by TGF-β: "N1" versus "N2" TAN. *Cancer Cell*. 2009;16(3):183-194. doi:10.1016/j.ccr.2009.06.017
- Giese MA, Hind LE, Huttenlocher A. Neutrophil plasticity in the tumor microenvironment. *Blood*. 2019;133(20):2159-2167. doi:10.1182/blood-2018-11-844548
- Guthrie GJK, Charles KA, Roxburgh CSD, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: Experience in patients with cancer. *Critical Reviews in Oncology/Hematology*. 2013;88(1):218-230. doi:10.1016/j.critrevonc.2013.03.010
- Han S, Liu Y, Cai SJ, et al. IDH1 mutation in glioma: molecular mechanisms and potential therapeutic targets. *British Journal of Cancer*. 2020;122(11):1580-1589. doi:10.1038/s41416-020-0814-x
- Piccard H, Muschel RJ, Opendakker G. On the dual roles and polarized phenotypes of neutrophils in tumor development and progression. *Critical Reviews in Oncology/Hematology*. 2012;82(3):296-309. doi:10.1016/j.critrevonc.2011.06.004
- Shaul ME, Levy L, Sun J, et al. Tumor-associated neutrophils display a distinct N1 profile following TGFβ modulation: A transcriptomics analysis of pro- vs. antitumor TANs. *Oncotarget*. 2016;5(11). doi:10.1080/2162402X.2016.1232221
- Sippel TR, White J, Nag K, et al. Neutrophil Degranulation and Immunosuppression in Patients with GBM: Restoration of Cellular Immune Function by Targeting Arginase I. *Clin Cancer Res*. 2011;17(22):6992-7002. doi:10.1158/1078-0432.CCR-11-1107
- Survival Rates for Selected Adult Brain and Spinal Cord Tumors. Accessed July 23, 2020. <https://www.cancer.org/cancer/brain-spinal-cord-tumors-adults/detection-diagnosis-staging/survival-rates.html>
- Wang Z, Zhang C, Liu Y, Wang Z, Jiang T. Peripheral blood test provides a practical method for glioma evaluation and prognosis prediction. *CNS Neurosci Ther*. 2019;25(8):876-883. doi:10.1111/cns.13120
- Weng W, Chen X, Gong S, Guo L, Zhang X. Preoperative neutrophil-lymphocyte ratio correlated with glioma grading and glioblastoma survival. *Neurological Research*. 2018;40:1-6. doi:10.1080/01616412.2018.1497271
- Zhang J, Zhang S, Song Y, et al. Prognostic role of neutrophil lymphocyte ratio in patients with glioma. *Oncotarget*. 2017;8(35):59217-59224. doi:10.18632/oncotarget.19484
- Zadora P, Dabrowski W, Czarko K, et al. Preoperative neutrophil-lymphocyte count ratio helps predict the grade of glial tumor - A pilot study. *Neurologia i Neurochirurgia Polska*. 2015;49(1):41-44. doi:10.1016/j.pjnns.2014.12.006