Females have the survival advantage in glioblastoma

Glioblastoma is the most common type of malignant brain tumor in the United States, with an average annual age-adjusted incidence rate (AAAIR) of 3.20/100,000.1 These tumors are 60% more incident in males (AAAIR = 3.99/100,000) than females (AAAIR = 2.52/100,000).1 Previous analyses have demonstrated a significant association between female sex and improved survival,2 but this has not been systematically assessed within population-based datasets.

This study was approved by the institutional review board at University Hospitals Cleveland Medical Center. Data were obtained from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program3 and from a multicenter study in Ohio (the Ohio Brain Tumor Study [OBTS])4 for glioblastoma cases in patients ≥18 years old and diagnosed in 2007 or later that received standard of care treatment (eg, surgery followed by concurrent chemoradiation). The SEER 18 includes 18 central cancer registries and represents ~28% of the US population. Ohio is not included within the SEER program. Thus, it is unlikely that individuals from Ohio would be included in both datasets. There were 5372 SEER cases and 228 OBTS cases. Analysis was performed using sex-specific Cox proportional hazards models adjusted for extent of resection (subtotal vs gross total), age at diagnosis, and Karnofsky performance status (KPS) (OBTS only). Postsurgical KPS was available for only 117 of 228 and was imputed using multivariate imputation by chained equations from the R package ‘mice.’

Overall median survival was 16 months (95% CI = 16–17) in SEER and 16.9 months (95% CI = 15.1–19.9) in OBTS. Sex was significantly associated with survival in both datasets. In SEER, median survival was 17 months (95% CI = 16–17) in females and 16 months (95% CI = 15–17, P = 0.0034) in males (Fig. 1A), and in OBTS median survival was 22.6 months (95% CI = 19.7–26.0) in females and 15.9 months in males (95% CI = 14.0–19.4, P = 0.0006) (Fig. 1B). The vast majority of glioblastomas are isocitrate dehydrogenase 1/2 (IDH1/2) wildtype (IDHwt, >95%), but IDH1/2 mutation is significantly associated with improved survival.5,6 Potential confounding between sex and molecular classification was assessed in OBTS IDHwt cases (these data were not available in SEER). Among IDHwt cases (N = 102, IDH1/2 status not available on all cases), a female survival advantage remained, with median survival of 25.5 months (95% CI = 18.1–43.2) in females and 15.0 months (95% CI = 13.6–21.4, P = 0.0082) in males (Fig. 1C).

![Fig. 1](A) Surveillance, Epidemiology, and End Results (SEER) 18 (2007–2014) and Ohio Brain Tumor Study (OBTS) (2007–2017); (B) all glioblastoma cases and (C) IDH1/2 wildtype cases only.
Methylation of the \( \text{O}^6\)-methylguanine-DNA methyltransferase (\( \text{MGMT} \)) promoter is associated with increased treatment response and overall survival in glioblastoma, and a prior study suggested that this effect may be sex specific.\(^7\) Information on \( \text{MGMT} \) methylation status is not routinely collected by SEER, and was available on only a minority of patients in the OBTS set (29 of 228, 12.7%). Of those with available \( \text{MGMT} \) methylation data, a larger proportion of females were positive for promoter methylation compared with males (7/11 [63.6%] compared with 10/18 [55.6%]). This is similar to the higher level of \( \text{MGMT} \) methylation observed in females by Schiffgens and colleagues (53% in females compared with 41% in males) and within the The Cancer Genome Atlas glioblastoma cohort (52% in females compared with 40.3% in males).\(^5,7\) Impact of \( \text{MGMT} \) promoter methylation on sex-specific survival could not be evaluated in the current study due to the low sample size within OBTS, but it is possible that sex-specific effects of \( \text{MGMT} \) promoter methylation could contribute to the observed survival difference.

The results of this analysis confirm a female survival advantage among glioblastoma patients who have received standard of care treatment, within samples collected via both the SEER national cancer registry system and a multicenter tertiary medical center network. Within an IDHwt subset, the female survival advantage remained. The results of this analysis suggest that female survival advantage in glioblastoma is independent of treatment, age, KPS, or \( \text{IDH1/2} \) mutation status. Further exploration of sex-specific features and outcomes is necessary to determine the cause of the observed female survival advantage.

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**References**


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