

Randomized Phase III controlled trials of therapy in malignant glioma: where are we after 40 years?



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Abstract

The objective of this study was to review the results of randomized Phase III controlled trials (RCTs) that involve initial treatments of malignant glioma and determine changes in median survival times (MST) over the last 40 years. An electronic database search identified RCTs for patients undergoing initial treatment for supratentorial high-grade malignant glioma. MSTs were analysed with respect to the date that patient accrual to the trial started, to identify the time course of changes in MST. Linear regression was used for statistical analysis. The review included 44 clinical trials that recruited patients between 1966 and 2004. Overall, there was a steady significant improvement in MST for the novel treatment cohorts over this period ($r^2 = 0.43$, $p < 0.001$), with MST increasing from around 8 to 15 months. There was also consistent improvement in the MST of the control cohorts, from around 7 months to 14 months, that reached statistical significance ($r^2 = 0.41$, $p < 0.001$). However, analysis including a quadratic term revealed a trend towards the rate of improvement in MST decreasing in the last two decades in the control, but not novel treatment, groups. The differences, either positive or negative, in MSTs between the control and novel treatment cohorts, and number of trials performed have all decreased with time. Subgroup analysis of the three most recent clinical trials report statistically significant better outcomes in MST after either >90% or 'complete' tumour resection. Despite tremendous advances in both the understanding of the biology of malignant gliomas and treatments in neuro-oncology, the prognosis for patients with malignant gliomas, although improved, remains very poor. The limitations of this type of analysis, including how trial design can bias outcomes and militate against comparison of trials are discussed.

Keywords: Malignant glioma; median survival time; randomized control trial