In Reply We thank Dr Grasso and Drs Jabbour and Wion for their comments in response to our study and appreciate the opportunity to address the issues they raised.

In response to Grasso, the goal of our study was to determine the strength of the evidence supporting an association between extent of resection (EOR) and survival, and to provide the most precise estimate of this association possible. While many neurosurgeons acknowledge this relationship, no formal, quantitative analysis previously existed, and articles examining the relationship between EOR and survival continue to be published as recently as earlier this year. Armed with the results of our study, we can hopefully conclude the debate and authoritatively state the relationship between EOR and survival. As noted in our article, we agree with Grasso on the importance of the article by Lacroix et al; however, we were unable to include those authors’ data in our analysis because of how their data were presented. Fortunately, data from the patients in that study were included in an article published this year by the same group. Those data were captured in our analysis. Undoubtedly there are additional factors influencing the survival of patients with glioblastoma (GBM) beyond EOR; however, as Grasso points out, the consensus of nearly every article we identified, including the work of Lacroix et al, concluded that aggressive tumor resection independently confers enhanced survival to the entire population of patients with GBM. We did attempt to extract data regarding molecular characteristics of the tumor and performance status. Unfortunately, the state of the current literature precluded an analysis of the potential interaction of these factors with EOR. For these reasons, we advocate the establishment of a high-quality, international, prospective registry of patients with GBM that would collect this type of data and that would permit a rigorous analysis of these questions. We agree that surgical technique and technology have made greater EOR possible; however, both regression analysis and a subgroup meta-analysis of recent studies failed to show a difference in the relative risk of mortality based on date of study publication (eTable 2 in the Supplement). Additionally, although EOR was defined arbitrarily in the majority of studies included in our article, there was almost universal agreement that “gross total resection” required at least a 90% reduction in enhancement on postoperative magnetic resonance imaging, and many studies required no residual enhancement (100% reduction) (eTable 1 in the Supplement). We believe that this justifies combining these studies into a single meta-analysis.

We agree with Jabbour and Wion regarding the difficulty that the reverse migration phenomenon poses in the surgical and nonsurgical treatment of GBM. We have also studied this phenomenon and discussed the design of clinical trials targeting this aspect of GBM care previously. Perhaps the decreased progression-free survival and overall survival seen following subtotal resection compared with gross total resection is a consequence of GBM stem cell migration along persistent embryonic “scaffolding” to repopulate the margins of the resection cavity. We believe that this further strengthens the case for gross total resection, and suggests additional fascinating avenues for future clinical and basic research.

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