Neuro-Oncology
20(9), 1150–1151, 2018 | doi:10.1093/neuonc/noy081 | Advance Access date 30 May 2018

Neurosurgeons still wanted

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See the article by Ellingson et al. pp. 1240–1250.

It is tempting to speculate that advances in molecularly targeted therapy might diminish the important role that surgeons have always played in the care of patients with glioblastoma (GBM). Maximum safe resection of at least the contrast-enhancing portion of the tumor mass is the desired starting point for treatment regimens in modern neuro-oncology. Surgical excision of >70% of the enhancing tumor volume significantly prolongs the overall survival of patients with GBM who are treated with the proven combination of external-beam radiation and temozolomide chemotherapy after initial diagnosis.[1–3] We do not know, however, whether the survival advantage associated with surgery observed in the radiation–temozolomide era of neuro-oncology will carry over into the future as highly selective anticancer drugs and immunotherapy agents emerge from the development pipeline and enter the clinic. The results of the study published by Ellingson and colleagues indicate that neurosurgeons will likely remain an effective strike force in the war on GBM even as medical treatment methods improve.[4]

The investigators measured the volume of contrast-enhancing tissue remaining on T1-weighted magnetic resonance images after surgery by using a digital subtraction method that corrects for tumor-mimicking blood products in the resection cavity. They then correlated overall survival time for 1511 GBM patients with the volume of residual contrast enhancement. As expected, there was a tight correlation between prolonged overall survival and smaller residual volumes of enhancing tumor in the 1054 patients treated postoperatively with radiation and temozolomide. Intriguingly, the authors then tested the effect of surgery on survival time in 457 patients enrolled in clinical trials of 2 molecularly targeted agents: bevacizumab, a monoclonal antibody that inhibits angiogenesis by neutralizing vascular endothelial growth factor A, and vorinostat (suberoylanilide hydroxamic acid), an inhibitor of histone deacetylase enzymes, which modify the transcription of various oncogenes. They found that more complete surgical resection remained a strong predictor of longer overall survival time even among patients treated with bevacizumab or vorinostat.

To be sure, this is welcome news to neurosurgeons, for whom better medical therapies for GBM might have an unsettling effect on their future job security. Nevertheless, we will not know the true impact of improved medical therapy on surgical efficacy until we have drugs that lengthen patient survival beyond that achieved by temozolomide. Addition of bevacizumab to temozolomide-based chemoradiation has not increased overall survival in patients with newly diagnosed GBM.[5,6] The jury is still out on vorinostat. The survival statistics for the vorinostat-treated patients came from a phase I/II trial (Alliance N0874/ATTC-0902), which has not been completed.

It seems improbable that even a blockbuster drug will eliminate the need for surgery in patients with GBM. Nevertheless, more effective antitumor agents will likely decrease the specific amount of tumor that surgeons must remove to affect outcome favorably. The study by Ellingson et al showed that the survival advantage of surgery was lost when surgeons left behind more than 12 mL of contrast-enhancing tumor tissue. Earlier studies, which quantified the percentage of enhancing tissue removed, have put the threshold for survival-extending surgery at >70%.[1–3] Conceivably, novel compounds that impede the molecular machinery of GBM might take the pressure off neurosurgeons to get a gross total resection. Relaxed standards for surgical aggressiveness will have the added benefit of reducing operative complications. In patients older than 75 years, surgical complications, especially those that lower Karnofsky performance scores, can eliminate the survival benefits gained by more complete tumor removal.[7]

When analyzing data across 4 large GBM trials, Ellingson and his coinvestigators made an observation that has important implications for clinical research. They found wide variation in postoperative tumor burden in all patient cohorts. This observation supports the authors' recommendation that future GBM trials should be designed with residual tumor volume balanced in the treatment arms.

The coming age of molecular medicine will find neuro-oncologists armed with more lethal weapons for the fight against GBM. No doubt, the new treatment armamentarium will still include the surgeon's scalpel.

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