EDITORIAL

Surgical Resection and Glioblastoma: Molecular Profiling and Safety

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The article by Dea et al adds to the literature of information that suggests that the extent of removal of enhancing tumour in glioblastoma patients is associated with improved survival.[1]

In Recommendation 3 of the "Canadian recommendations for the treatment of glioblastoma pertaining to surgery", a consensus was reached that surgery was an integral component of the treatment plan for glioblastoma.[2] Surgery is critical in establishing the appropriate histopathological diagnosis. Since entry to all trials and present along with all future treatment paradigms determined by diagnosis, giving the pathologist adequate tissue is essential for both correct diagnosis and molecular genetic analysis. In an important subset of cases surgery may also improve clinical signs and symptoms. The type of surgery to be performed is not specified in these recommendations but the goal of surgery should be to achieve a safe (the important operative concept is safe) maximal and feasible resection with the primary surgical goal of performing a resection of all enhancing tissue. Stereotactic biopsy has limitations predominantly related to the heterogeneity of tumours like glioblastoma and usually does not provide the tissue necessary for multiple molecular genetic analyses. It is generally utilized when either the patient's condition and/or the location of the tumour preclude a more aggressive approach.

Dea et al's paper, like almost all others in the literature on this topic, has a number of limitations which have been outlined by its authors.[1] These issues include that it is retrospective, involving patients only from a single center, and patients received different treatments both after surgery and at the time of recurrence. However the major problem with almost all the prospective and the retrospective surgical trials in the literature is that they focused on the question of the importance of the extent of surgical resection and that they do not include genetic information that is known to have a critical impact on patient survival. The methylation of the promoter of the gene encoding O^6-methyguanine-DNA methyltransferase (MGMT) has been demonstrated in two large Phase III studies to be both prognostic and predictive of survival in patients diagnosed with glioblastoma.[3-5] The present standard of care for newly diagnosed glioblastoma patients is the Stupp Protocol consisting of concurrent radiation (60 Gy over six weeks) therapy and temozolomide (75 mg/m^2/day) for six weeks followed by at least six cycles of temozolomide (150-200 mg/m^2 for 5 of every 28 days).[2] In the Radiation Therapy Oncology Group 0525 trial, patients with MGMT promoter methylation had a median overall survival of 21.2 months compared to 14 months in patients without MGMT promoter methylation. ($p<0.0001$).[5] Since only 39 of 126 patients (31%) in the study by Dea et al were treated with the Stupp Protocol, this makes it difficult to assess the impact of surgical resection in this study to patients treated with the present standard of care.[1]

In the trial carried out by Stupp et al[3,6], surgeons were asked to comment on whether they carried out a biopsy, a partial or a complete resection. Unfortunately pre and post operative MR scans were not independently assessed; however, the results are enlightening since in this Phase III study patients were randomly assigned to radiotherapy only or what is now considered the Stupp Protocol group. Overall survival in patients treated with the Stupp Protocol was 18.8 months in the complete resection subgroup, and 13.5 months in the partial resection subgroup; both were statistically superior to the results with radiation alone (14.2 and 11.7 months respectively).[6]

Interestingly, there was no statistically significant improvement (9.4 months versus 7.8 months) in patients having only a biopsy when the Stupp Protocol patients were compared to the radiotherapy only group. This would suggest that the addition of concomitant radiotherapy and temozolomide followed by adjuvant temozolomide was more effective on residual tumour cells present after resection in situations in which the total tumour burden was reduced by cytoreductive surgery in patients with methylation of the MGMT promoter.

Ninety percent of glioblastoma recurrences occurred within 2 cm of the original tumour site and in the original radiation field on CT-based studies in patients treated with radiotherapy alone[7]. Recurrences in glioblastoma patients with MGMT promoter methylation treated with the Stupp Protocol are now seen more frequently (42%) outside the 2 cm radiation field[8] with a longer time before recurrence also suggesting improved control of postoperative residual tumour cells harboring MGMT promoter methylation. This concept is supported by other studies that also highlight the importance of MGMT promoter methylation. The impact of surgery in glioblastoma patients with MGMT promoter methylation has been assessed in a prospective cohort study in which all patients were treated with the Stupp Protocol[9]. Patients with a complete resection of enhancing tumour and MGMT promoter methylation had a mean survival of 27.3 months and although not significant a trend to improved survival was found in the patients having small residuals (≤ 1.5). In MGMT unmethylated patients the impact of complete or near complete resection was less evident. The exact extent of resection necessary to provide survival benefit in this selective MGMT subgroup of patients treated with the Stupp Protocol is not known. The data available would suggest that more than a biopsy is necessary to see a significant impact. I suspect the favorable impact of "partial" and "complete" resection of the enhancing mass on overall survival seen at 3.4 and 5 years after treatment[6] is predominantly seen in this MGMT promoter methylated subgroup. However, the operative resection should not result in prolonged increased patient morbidity[10] since patients suffering post operative deficit have decreased survival 11.5 months versus 14.7 months when compared to patients with no increased deficit.[11] Numerous techniques are presently available in the

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neurosurgical armamentarium to carry out safe resections of cerebral tumours and all should be considered in each case to decrease operative complications.

Testable Speculations

1. Is there a subset of MGMT promoter methylated initiating cells (derived from specific neural stem cells?) that result in glioblastoma tumours that occur in locations that are more accessible to surgical resection (frontal, temporal lobe vs. corpus callosum) in younger patients? Since these tumours respond better to radiation alone and the Stupp Protocol, are these tumours also more resectable and thus we would predict an increased impact of surgery predominantly in these patients?
2. A subgroup of primary glioblastoma patients (2-10%) have an IDH1 mutation which is frequently associated with MGMT promoter methylation and increased survival.[12] Are these patients a subgroup of the 10% of glioblastoma patients which are now surviving five years?

Summary

Rather than focusing on the percentage removal of glioblastoma, but as outlined in the Canadian recommendations, maximum achievable safe resection should be the goal of all operations for glioblastoma.[2]

Disclosure

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