



# Re-do craniotomy for recurrent glioblastoma



“Re-do craniotomy for selected patients can lead to significantly improved functional outcomes and survival. The morbidity of re-do craniotomy is acceptably low.”

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Glioblastoma multiforme (GBM) is a WHO grade IV astrocytoma and the most common type of primary brain tumor in adults. The incidence rate for glioblastoma is approximately 3–4/100,000 person years but varies to some extent in different regions of the world [1]. There has been little improvement in outcomes in spite of advances in adjuvant therapy over the past two decades, with the median duration of survival remaining at 12–15 months [2,3]. The current protocol in the treatment of newly diagnosed glioblastoma includes surgical resection or biopsy, followed by concomitant radiochemotherapy with temozolomide followed by 6 additional months of adjuvant temozolomide [3]. In newly diagnosed glioblastoma, methylation of the O6-methylguanine DNA methyltransferase promoter has been shown to predict response to alkylating agents such as temozolomide, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU; carmustine) and cyclophosphamide [4].

There is evidence that the extent of resection for the primary treatment of GBM can lead to significant improvement

in survival. Significantly, the threshold of greater than 78% resection based on volumetric assessment of enhancing tumor has been advocated with incremental improvements with increasing extent of resection. Many technological advances have been developed to improve the safety and completeness of resections, such as neuronavigation, functional mapping, intraoperative vital dyes and intraoperative imaging [5].

Despite optimal therapy, the estimated recurrence rate is in excess of 90% with no standard regimen and limited effective options for treatment. Whilst the role of initial aggressive resection is increasingly becoming standard practice, the role of re-do craniotomy for recurrent GBM is still highly controversial. A review of 31 studies investigating reoperation for recurrent high-grade glioma by Hervey-Jumper *et al.* found that 29 studies demonstrated a survival benefit of reoperation at recurrence [6].

With the improvement in surgical techniques and adjuvant treatment modalities, many patients are now surviving to

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- guidelines • progression
- recurrence • re-operation

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recurrence with good functional status. The indications for repeat surgery include individuals with new focal neurological deficit, tumor mass effect with altered consciousness or radiographic evidence of tumor progression without clinical deterioration. Surgery can also differentiate tumor recurrence from pseudo-progression or radiation necrosis. But with the absence evidence-based guidelines it is essential to determine treatment goals and the effect on survival and quality of life for the patient.

Age and Karnofsky performance status (KPS) are useful prognostic factors. Many studies have also suggested that tumor size is an independent predictor of outcome [7]. Other predictors of improved survival include longer interval between operations and histopathology as radiation necrosis at time of reoperation. Stark *et al.* [8] studied the effects of advanced patient age for primary and recurrent high-grade glioma and the multivariate analysis for patients more than 60 years of age revealed independent associations with patients receiving reoperation at recurrence, in addition to greater extent of resection and use of radiation therapy as predictors for better outcome. This suggests that reoperation should be considered in all patients with a favorable performance status regardless of age [8]. There have been efforts to establish a preoperative scale to predict survival after repeated surgery; one such scale is the National Institutes of Health Recurrent GBM Scale, which is based on factors such as tumor involvement of eloquent/critical brain regions, KPS and tumor volume [9]. Another scoring system had been introduced based on KPS and ependymal involvement of the tumor in the MR images at recurrence [10]. These scores have not been extensively validated and have not been widely adopted.

The role of extent of resection at recurrence is still questionable. Data from two recent published series [11,12] recommend extent of resection at recurrence as important predictor of overall survival and its importance at reoperation even with patients with initial subtotal resections [12].

With the advent of advancements in neurosurgical techniques, neuro-anesthesia and neurocritical care, the perioperative complications with repeated surgeries have decreased greatly. It has even been reported that there

is no significant difference in perioperative complications with initial craniotomy at diagnosis or repeat craniotomy at recurrence [13]. Implantation of biodegradable chemotherapy wafers (e.g., wafers with carmustine) at the time of repeat surgery may prolong survival; however, this practice remains highly controversial [14]. Preliminary evidence suggests that survival may be improved in patients with O6-methylguanine DNA methyltransferase promoter hypermethylation at recurrence [15], but may be adversely affected by postoperative complications such as bone marrow suppression, infection and poor wound healing [16]. With the widespread use of anti-angiogenic therapies, caution should be taken regarding wound healing complication when reoperating on any patient who has been treated with bevacizumab within 1 month of surgery [17].

In summary, while there is a paucity of definitive evidence supporting re-do craniotomy for recurrent glioblastoma, there is emerging data that subsets of patients can benefit significantly with improved functional outcomes and survival. There is also evidence to demonstrate that the morbidity of re-do craniotomy is acceptably low. It is recommended that patient selection for repeated surgery should be made according to individual circumstances guided with the available data in the literature and in consultation with the multidisciplinary team including neurosurgery, neuropathology, radiation oncology, neuro-oncology and allied health professions with comprehensive patient counseling.

With the present limitations and selection bias in the literature with regard to sample size and heterogeneity of treatment options at time of recurrence, the need for prospective large series data is crucial to establish more conclusive evidence for the role of re-do craniotomy for recurrent glioblastoma.

#### Financial & competing interests disclosure

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