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Original Article

Proliferation Index Predicts Survival after Second Craniotomy within 6 Months of Adjuvant Radiotherapy for High-grade Glioma

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Abstract

Aims: To determine pathological features that predict survival in patients having repeat craniotomy within 6 months of radiotherapy for high-grade glioma (HGG).

Materials and methods: HGG patients (World Health Organization grade 3/4) managed with repeat craniotomy within 6 months of completing radiotherapy between 2008 and 2012 were included. Based on the presence of residual tumour cells, the pathology was reported as pathological progression or pathological pseudoprogression. The proliferation index (Ki67) was reported and compared with initial pathology as a percentage change. Tumour necrosis was estimated as a percentage of the specimen. Overall survival was calculated in months.

Results: Of 327 patients managed with HGG, 27 patients underwent repeat craniotomy within 6 months of radiotherapy. The median survival after reoperation was 11 months (95% confidence interval 1–22). Ki67 at reoperation of 0%, 1–9% and >10% was associated with survival with a median survival of 13, 13 and 3 months, respectively ($P = 0.007$). Change in Ki67 was also associated with median survival, with <50% reduction median survival 3 months, 50–80% median survival 7 months and >80% reduction median survival 13 months, $P = 0.02$. Widespread treatment-related necrosis improved outcome, with >80% necrosis having a median survival of 13 months versus 3 months in those with <80% necrosis ($P = 0.003$).

Conclusion: The presence of residual tumour at repeat craniotomy within 6 months of radiotherapy is not an independent indicator of prognosis. Patients with residual tumour that had a low Ki67 had a similar median survival as those with only treatment necrosis. Reduced proliferation of residual tumour cells and widespread necrosis may be more important indicators for future outcome.

Key words: GBM; glioblastoma; glioma; pseudoprogression; repeat craniotomy

Introduction

The introduction of concurrent temozolomide (TMZ) with radiotherapy has improved the median and 5 year survival in patients with glioblastoma multiforme (GBM) [1]. However, the intensification of adjuvant therapy has increased the incidence of post-treatment inflammatory changes that mimic tumour progression on magnetic resonance imaging (MRI) [2–8]. This phenomenon of pseudoprogression was originally described by Brandsma *et al.* [9] as a radiological diagnosis of an increase in size of contrast-enhancing lesion(s) or new areas of contrast enhancement immediately after radiotherapy, with subsequent improvement without any further treatment.

If these radiological changes are prolonged and associated with steroid-dependency then surgical intervention may be offered to patients to obtain a pathological diagnosis and relieve pressure effects. The presence of residual tumour cells may then be interpreted as progressive tumour and adjuvant TMZ may be ceased, or the treatment intention may change to best supportive care. In other tumour sites, such as prostate cancer or nasopharyngeal cancer, surgical biopsy of residual mass lesions in the 6 months after radiotherapy may show residual tumour cells that never lead to progression [10,11]. These non-viable

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cells appear as intact tumour cells on histochemical staining, but are reduced in number, have lower cellular proliferation and may be surrounded by treatment-related necrosis.

This study examined the pathological features on repeat craniotomy within 6 months of radiotherapy for high-grade glioma (HGG) that are associated with improved survival, with the aim to distinguish features of pseudoprogression pathologically from true residual refractory glioma.

Materials and Methods

All patients with HGG (World Health Organization grade 3 or 4) [12] managed with radiotherapy at the Northern Sydney Cancer Centre were identified. Eligible patients were those receiving a second craniotomy within 6 months of the completion of radiotherapy (40–60 Gy) with or without the addition of TMZ between June 2008 and December 2012. All patients had consented to have their medical information collected on an ethics approved prospective database before radiotherapy. A minimum follow-up of 12 months for surviving patients was required for inclusion.

Baseline Characteristics

Initial patient and tumour details were recorded. Specifically, patient age, pathological grade and initial Ki67 proliferation index (Ki67%) were documented. Initial treatment was detailed, including extent of surgical resection, radiotherapy dose and timing of TMZ chemotherapy. With respect to the extent of the initial surgical resection, based on both the operative report and the presence of residual tumour on postoperative MRI, the surgery was defined as biopsy only, subtotal resection or near total resection (>90%).

Radiotherapy Details

All patients were managed with megavoltage intensity-modulated radiotherapy or three-dimensional conformal radiotherapy to a dose of 59.4–60 Gy over 6–7 weeks or 40 Gy in 15 fractions over 3 weeks. The dose of radiotherapy was determined by grade (grade III were treated to 59.4 Gy, grade IV were treated to 40 Gy or 60 Gy) and fitness with respect to the grade IV patients. Age, performance status and comorbidities, as well as social supports were all factors in determining radiotherapy dose of 40 versus 60 Gy with or without the addition of TMZ.

Indications for Second Craniotomy

Patients proceeded to a second craniotomy for the following indications, increase in MRI T1 contrast enhancement suspicious for recurrence and in a location amenable to surgery, or symptomatic increase in T1 contrast enhancement not adequately controlled with steroids. Maximum safe resection was the intent of reoperation in all cases. When surgical resection was not possible, a stereotactic biopsy was carried out targeting the area of enlarging T1 contrast enhancement.

Pathological Review

A histopathological analysis was carried out on initial surgical resections and post-radiotherapy resections in all patients. Standardised reporting was used for all patients with macroscopic and microscopic descriptions of the specimens as well as immunohistochemistry including: Ki67%, p53, IDH1 and GFAP on all initial surgical specimens. For the purpose of this study, pathology at reoperation devoid of any persistent tumour cells was classified as pathological pseudoprogression (pPsP) and the presence of any tumour cells was classified as pathological progression (pPROG). Ki67 index was assessed by immunohistochemistry on histological sections (MIB-1 clone; DAKO) and was reported for all patients and compared with initial pathology as a percentage change. Estimation of the percentage of tumour cells versus necrotic changes was determined in each case on the basis of haematoxylin and eosin staining. All specimens were reported by the original pathologist at the treating centre, except where Ki67 or the percentage of tumour cells versus necrotic changes was not reported on repeat craniotomy specimen. In those cases, the slides were reviewed by a single pathologist and an additional report issued.

A molecular analysis was only carried out in selected patients and has not been included in the results or discussion as it did not add additional information.

Statistical Considerations

The primary end point was the survival time in months calculated from the time of repeat craniotomy. Survival curves were generated using the Kaplan–Meier method. Univariate predictors of survival duration were evaluated using Log-rank comparisons. All reported P values are two-tailed. Statistical significance was defined as $P \leq 0.05$ in all cases. STATA version12 (StataCorp, Texas, USA) was used for statistical analysis.

Results

In total, 327 patients diagnosed with HGG and managed with radiotherapy were identified from January 2008 to December 2012. Twenty-seven patients underwent repeat craniotomy within 6 months of completing radiotherapy and were included in this study. Patient characteristics and treatment details are shown in Table 1.

The median age at diagnosis was 59 years (range 41–74 years). Of the 27 patients, 22 had a histological diagnosis of GBM, four had anaplastic astrocytoma and one had anaplastic oligodendroglioma. Thirteen patients had bulky residual disease after initial craniotomy, four of whom were managed with biopsy only, and nine with subtotal resection. With respect to the addition of TMZ, 21 patients

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