# Residual Enhancing Disease after Surgery for Glioblastoma: Evaluation of Practice in the United Kingdom

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## Abstract

*Background*
Despite extensive research the prognosis for patients with glioblastoma (GB) remains poor. A growing body of clinical data highlights the prognostic importance of minimising post-operative residual enhancing disease (RED) following resection, underlining the importance of gross total resection (GTR). GTR is defined by the absence of RED on early post-operative MRI. The introduction of new surgical technologies and the advent of neurosurgical sub-specialisation offer an opportunity to target improved surgical resection of enhancing tumour as a means to improving patient outcomes. Here we report the results of a service evaluation of practice in the United Kingdom.

*Methods*
The study was in two parts: an electronic questionnaire sent to UK neuro-oncology surgeons to assess surgical practice followed by a 3-month prospective multi-centre observational study of current neurosurgical oncology practice. The questionnaire was completed in March 2016 and observational data collected between 01/05/2016 and 31/07/2016 through the British Neurosurgery Trainee Research Collaborative. Inclusion criteria included adult patients (age >18) with suspected GB on presenting magnetic resonance imaging (MRI) scan and multi-disciplinary meeting (MDT) decision that the tumour was suitable for GTR. Exclusion criteria included children (age <18) and subsequent histology that confirmed an alternative diagnosis.

*Results*
Twenty-seven surgeons representing 22 neurosurgical units completed the questionnaire. Prospective data was collected from 15 surgical units from 113 patients who were deemed suitable for GTR of glioblastoma. There was varying use of surgical adjuncts between differing neurosurgical units. Most patients (70.8%) had a postoperative MRI scan within 72 hours of surgery. GTR was deemed to be achieved at time of surgery in 82% (91/111) of cases, but in only 45% (36/80) on postoperative MRI. RED was deemed operable in 16.3% (13/80) of cases, however, no patient underwent early repeat surgery for RED. The most commonly cited reason (38.5%, 5/13) was perceived lack of clinical benefit.

*Conclusion*
There is a subset of patients in which GTR is thought possible, but not achieved at primary surgery. Residual disease may be amenable to early re-intervention and this may improve patient prognosis. There is a paucity of studies looking at the potential benefit of this early re-intervention. Further prospective surgical research is required to better define the prognostic implications of RED/GTR and explore the options for converting sub-total resection to GTR before commencing adjuvant treatment.

Key words: Residual Enhancing disease, Glioblastoma, Glioma, neurooncology, Glioma Surgery, Survival

## Introduction

Glioblastoma (GB) is the most common and most malignant primary brain tumour in adults, with over 20 years of life lost per patient [1]. Survival trends for patients with CNS malignancies have remained largely static [2]. Despite optimal treatment the median survival for such patients is still only 14-24 months with a two-year survival of 26.5% [3,4] and a five-year survival of approximately 10% [5] .The current gold standard of treatment involves gross total resection (GTR) followed by concurrent radiotherapy and chemotherapy with temozolomide and subsequent adjuvant temozolomide chemotherapy [4]. GTR is defined by complete resection of contrast enhancing tumour on a contrast-enhanced T1-weighted postoperative magnetic resonance imaging (MRI) scan performed within 72 hours of surgery [6].

GB is an intrinsic brain tumour, infiltrating normal brain tissue. Microscopically there is no distinct tumour/brain interface and radical resection risks causing permanent neurological deficit, worsening prognosis [7,8]. In fact, in some patients GTR is not possible, because of the eloquent location and multi-focal distribution of the tumour. Nevertheless, the importance of obtaining a gross total resection where possible is increasingly recognized [3,9–23] and is being incorporated into European guidelines for the management of patients with GB [24,25]. Some surgical studies suggest that there is a stepwise increase in survival with extent of resection (EoR) from a threshold of 78-80% [23,26] up to 95-100%. Other studies suggest that removal of all contrast enhancing disease is necessary [12,27] or that supra-maximal resection of GB may provide further survival benefit [10,28,29]. A recent meta-analysis of 37 studies (41117 patients with newly diagnosed GB) concluded that GTR "substantially improves overall and progression-free survival" but added that "the quality of the supporting evidence is moderate to low" [30].

The opportunity for awake tumour surgery to identify and preserve eloquent function, along with advances such as 5-ALA that accumulates in tumours, and intra-operative MRI, have improved the neurosurgeons ability to maximise the extent of surgical resection. Despite the use of operative adjuncts in cases where GTR is the expressed preoperative aim, there are circumstances where GTR is not achieved [31,32]. In some cases this may reflect changing surgical priorities, for example in the context of bleeding, but in other cases it may be unintentional. In these patients there may be prognostic benefit from re-operating on the residual enhancing disease (RED). This will also have risks, but there is some preliminary evidence to suggest that it is safe [33].

The study was conducted in two parts: (1) an electronic questionnaire to neuro-oncology surgeons and (2) a 3-month prospective multi-centre observational study of current neuro-oncological practice, both in the UK.

## Methods

*Study design – Questionnaire*

An electronic questionnaire was sent to UK neuro-oncology surgeons to assess surgical practice including the throughput of tumour patients and the numbers deemed suitable for GTR (supplementary file). There were also questions regarding access to surgical adjuncts such as 5-ALA, awake surgery, and attitudes towards contributing to a randomised control trial investigating early repeat operation.

*Study design – Prospective cohort study*
The second part of the study was a prospectively collected multi-centre observational study on current neuro-oncological practice.

*Patient Selection*
Patients with suspected GB that were scheduled to undergo GTR at first surgery following discussion at a multi-disciplinary meeting (MDT) between 01/05/2016 and 31/07/2016 were eligible for inclusion. Patients were identified prospectively at MDT meetings and data was collected prospectively during their subsequent inpatient stay. Inclusion criteria included adult patients (age >18) with suspected GB on presenting magnetic resonance imaging (MRI) scan and MDT decision that the tumour was suitable for GTR. Exclusion criteria included children (age <18) with subsequent histology that confirmed an alternative diagnosis. Patients with recurrent tumours were included in the study provided GTR was the aim at surgery.

*Data Collection*
Data on patient demographics, tumour location, surgical adjuncts, residual disease intraoperative/postoperative MRI as well as adjuvant treatment and complications (Supplementary data) was collected through the British Neurosurgery Trainees Research Collaborative (BNTRC). As with previous models of research performed by the BNTRC [34], each neurosurgical unit had a trainee principal investigator and a consultant principal investigator. Data was collected locally and then collated centrally after the end of the study period. Data was analysed in *Microsoft Excel* (2011).

## Results

*Surgical Practice*
There were responses from 27 neuro-oncology surgeons from 22/38 neurosurgical units in the UK, who estimated a total of ~3000 operations for newly diagnosed GB per year, of which roughly 1800 (60%) were amenable for GTR. 24/27 (88.9%) of responders said >90% of patients were discussed at MDT before surgery.

With regards to surgical adjuncts, 100% of surgeons had access to intraoperative neuro-navigation. 44.4% of surgeons said they had routine access to 5-ALA with a further 29.6% of surgeons having limited access for specific cases and 25.9% of surgeons having no access to 5-ALA. 17/27 (63%) of surgeons said they routinely used awake surgery with bipolar stimulation where indicated, with 16/27 (59.3%) using speech and language testing and 4/27 (14.8%) using electromyography recordings under general anaesthetic.

The majority of surgeons (24/27, 88.9%) were able to obtain a MRI within 72 hours of surgery routinely, with only 1 surgeon unable to obtain postoperative MRI imaging. Most surgeons estimated there to be 11-20 patients per annum who were deemed suitable for GTR, but who had RED on their post operative scan (9/27, 33.3%), followed by 5-10 patients in 6 (22.2%) of surgeons with 4 (14.8%) surgeons estimating over 20 cases per annum.

*Service Evaluation*

We prospectively collected data on 113 patients from 15 neurosurgical centres (range 1 – 26 patients per centre) with a mean age of 58.2 (range 28-85) and a male:female ratio of (73:40). Table 1 highlights the demographic information of the cohort of patients included in the study. Most patients were independently functioning at presentation with 91 patients (80.5%) classified as World Health Organisation (WHO) Performance Score (PS) 0 or 1 (table 1). 89 patients (78.7%) had at least once comorbidity (table 1). The most common presenting symptom/sign was headaches (44/113, 38.9%) followed by focal neurological deficit (40/113, 35.3%) (table 1). The intracerebral distribution of tumours can be seen in table 1.

There was varying practice in the use of intraoperative surgical adjuncts, illustrated in table 2. 5-ALA was the most commonly used adjunct, being used in 18 (15.9%) of cases followed by awake surgery (14, 12.4%) and intraoperative ultrasound (14, 12,4%). There was little use of iMRI (4, 3.5%), reflecting the small number of centres with access to this technology in the UK.

Postoperative complications were seen in 27 (23.6%) patients (table 2), of which the majority were medical complications (6/27) or miscellaneous (8/27). Other complications included worsening cognition, hydrocephalus, new focal neurological deficit, bowel perforation and rapid clinical decline.

In 91/111 (82.0%) cases the operating surgeon felt that GTR was achieved at the time of surgery. Reasons for residual disease were: tumour adherent to vessels (2.7%), eloquent brain (5.4%), cardiac instability (0.9%), unknown (7.2%).

After surgery 80 patients (70.8%) had a MRI scan within 72hours. In marked contrast to the operating surgeon's perception the imaging data confirmed 44 patients (55%) had RED on their postoperative scan. This RED was deemed operable in 13 cases (16.3%). However, no patient had a repeat debulking within 1 week of primary surgery. Reasons for non-operation include perceived lack of clinical benefit (5/13), medical comorbidities/poor PS (2/13) and disagreement between surgeon and radiologist about whether there was RED (2/13) and unknown (4/13).

**Discussion**

This study highlights varying practices amongst neurosurgical units in the UK in the approach to resection of suspected GB amenable to GTR. This likely represents the wide variety of surgical techniques available and a lack of consensus over the best surgical practice. In addition, financial restraints may restrict the access to investigations and equipment such as postoperative MRI scans within 72 hours of surgery and intraoperative surgical adjuncts. It is encouraging that over 70% of patients now receive a postoperative MRI as baseline for identification of residual disease in order to plan adjuvant therapy. Our survey also demonstrates that the utilisation of surgical adjuncts to maximise the extent of surgical resection is low. This may reflect cost pressures in the publically funded National Health Service, but the 15.9% of patients who had 5-ALA used in their surgery contrasts to the 44.4% of surgeons who reported routine access to 5-ALA in the questionnaire. Consistent with these observations we note that while 22 units responded to the questionnaire, only 15 units participated in the survey. So it is likely that our data under-represents

the true incidence of RED and may over-represent the extent to which advanced surgical adjuncts are used.

The lack of utilisation of surgical adjuncts is a concern when a significant proportion of patients have postoperative RED even where GTR was thought possible pre-operatively. Identifying the enhancing tumour margin intra-operatively with only microscopy and image guidance can be challenging, as evidenced by only 30-40% of operations achieving maximal resection when these traditional methods were used [6]. The failure to achieve GTR in our study cohort is underlined by the discrepancy between the perceived rate of GTR at the time of surgery and the actual rate of GTR on the postoperative scan (82% c.f. 55%), reflecting the difficulty identifying the tumour margins. This is not a new phenomenon, and reports demonstrate that surgeons ability to judge GTR at the time of surgery is only correct in approximately one third of cases [31,32]. Newer techniques, such as iMRI, 5-ALA and awake surgery are reported to facilitate surgeons in achieving doubling of GTR rates to over 65% in selected patients [6,11,16,35,36]. The failure to achieve GTR may also reflect a failure to correctly assess whether GTR was possible.

16.3% of patients in our study had RED that was thought amenable to early repeat resection before adjuvant therapy, but no patient went back to surgery. Early re-operation to remove RED in patients with GB before further treatment has been shown to be feasible without increased morbidity [33]. In that study only 6% of patients underwent early re-intervention.

GTR as a predictor of outcome does not necessarily imply that revision surgery would be of benefit. There is very little data looking at whether rapid reoperation to resect RED will improve clinical outcome to the same level as patients in whom GTR was achieved at first surgery. One worry about repeat surgery is that whilst it may offer a theoretical survival advantage by reducing the tumour load, the potential delay to radiotherapy may impact negatively on survival. There have been numerous studies looking at the relationship between timing of radiotherapy and survival, with some showing a beneficial effect of early radiotherapy[37], whilst others suggested no impact of timing as long as it is commenced within a 6 week window [38]. One study even showed a beneficial effect of waiting at least 4 weeks postoperatively [39]. Encouragingly, a recent meta-analysis of 8716 GB patients has found no difference in overall survival (OS) related to the time to radiotherapy [40]. If this is the case then that early reoperation may not negatively impact on survival through delay to radiotherapy. However, other risks of revision surgery including neurological dysfunction or infection may delay definitive treatment.

The most common reason UK surgeons gave for not undertaking this early surgery was a lack of perceived clinical benefit (38.4%) despite a growing body of evidence to suggest GTR is an independent positive prognostic factor (Watts & Sanai 2016 and Table 3). Maximally reductive surgery not only increases survival independently, but also increases the effectiveness of adjuvant therapies [41].

If the data favours maximal resection of tumours where possible, debate exists over the minimum EoR that is associated with maximal survival benefit. Studies have historically classified EoR into 3 or 4 categories: gross total resection (GTR), near

total resection (NTR), subtotal resection (STR) and partial resection (PR). Apart from GTR, which is classified as the complete removal of contrast enhancing disease on a postoperative MRI performed within 72 hours, the definition of the other categories is variable and subjective in nature, making it difficult to incorporate into clinical management protocols, or indeed to compare studies [17,20,22,42–44].

Quantification of residual tumour volumes can produce more accurate data on EoR and RED. Lacroix et al. published a volumetric series looking at patients undergoing resection for GB. They reported that a minimum EoR of 89% was required to achieve any benefit in survival from surgery with incremental benefit from further resection up to a maximum of 4.2 months with 98% resection [23]. This was followed by a study by Sanai et al. that found a survival difference in a dichotomised cohort with EoR values of 78% or above but a clinically meaningful survival difference of 3.8% only in patients EoR values at or above 95%. They conclude that "whereas the 78% threshold represents the minimum value at which a survival benefit is seen, [recursive partition analysis] selected 95% as the most significant predictor of survival in patients with GB, emphasizing the added value of a complete resection".[26]. A common interpretation of these data is that an EoR as low as 78% is sufficient to yield a clinically meaningful survival benefit. However, analysis of recent clinical data suggests that "complete" resection (defined as the absence of RED on post-operative MRI) provides optimal clinical benefit. For example in a trial of Enzasturin patients with GB who had GTR on their baseline post-op MRI had enhanced PFS-6 (progression-free survival at 6 months) [45]. In EORTC 26071-22072 (CENTRIC) GTR conveyed a 6.6 month survival advantage in the experimental arm (30.4 vs 24.8 month) and 10.7 month survival advantage in the control arm (34.3 vs 23.6 month).[46]. In the DIRECTOR trial (NCT00941460) complete resection of contrast-enhancing tumor volume was associated with improved survival in recurrent glioblastoma (Suchorska et al 2016).

*Conclusion and Future Directions*

This study is the first to prospectively evaluate the current surgical management of GB patients in the UK who were judged suitable for radical surgery by the SMDT. We show that there is wide variation in approaches to achieving GTR in the UK. Where RED occurs despite surgery there remains clinical doubt as to whether these patients would benefit from early revision surgery. Whilst there is a large volume of retrospective data to support the beneficial effects of maximal safe resection in patients with GB there is little prospective data. Consequently relatively little is known about the impact of GTR on prognosis, morbidity and quality of life for patients. In order to develop and optimise surgical management protocols further prospective research is required to determine the clinical impact of RED and early re-intervention to convert STR to GTR.

## Collaborators

The following are members of the BNTRC and acted as either local trainee/consultant principal investigators and as such are citable collaborators.

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