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Residual enhancing disease after surgery for glioblastoma: evaluation of practice in the United Kingdom

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Abstract

Background: A growing body of clinical data highlights the prognostic importance of achieving gross total resection (GTR) in patients with glioblastoma. The aim of this study was to determine nationwide practice and attitudes towards achieving GTR and dealing with residual enhancing disease.

Methods: The study was in 2 parts: an electronic questionnaire sent to United Kingdom neuro-oncology surgeons to assess surgical practice followed by a 3-month prospective, multicenter observational study of current neurosurgical oncology practice.

Results: Twenty-seven surgeons representing 22 neurosurgical units completed the questionnaire. Prospective data were collected for 113 patients from 15 neurosurgical units. 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. Residual enhancing disease was deemed operable in 16.3% (13/80) of cases, however, no patient underwent early repeat surgery for residual enhancing disease. The most commonly cited reason (38.5%, 5/13) was perceived lack of clinical benefit.

Conclusion: There is a subset of patients for whom GTR is thought possible, but not achieved at surgery. For these patients, early repeat resection may improve overall survival. Further prospective surgical research is required to better define the prognostic implications of GTR for residual enhancing disease and examine the potential benefit of this early re-intervention.

Key words

glioblastoma | glioma surgery | neurooncology | residual enhancing disease | survival

Glioblastoma is the most common and most malignant primary brain tumor 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 to 24 months with a 2-year survival of 26.5%[3,4] and a 5-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 tumor on a contrast-enhanced, T1-weighted postoperative magnetic resonance imaging (MRI) scan performed within 72 hours of surgery.[6]

Glioblastoma is an intrinsic brain tumor, infiltrating normal brain tissue. Microscopically there is no distinct tumor–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 multifocal distribution of the tumor. Nevertheless, the importance of obtaining a GTR where possible is increasingly recognized[3,9–23] and is being incorporated into European guidelines for the management of patients with glioblastoma.[24,25] Some surgical studies suggest that there is a stepwise increase in survival with extent of resection, 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 supramaximal resection of glioblastoma may provide further survival benefit.[10,28,29] A recent meta-analysis of 37 studies (41 117 patients with newly diagnosed glioblastoma) 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 tumor surgery to identify and preserve eloquent function, along with advances such as 5-aminolevulinic acid (5-ALA) and intra-operative MRI, have improved the neurosurgeon's ability to maximize 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. This will also have risks, but there is some preliminary evidence to suggest that it is safe.[33]

The aim of this study was to determine nationwide practice and attitudes towards achieving GTR and dealing with residual enhancing disease in patients with suspected glioblastoma. We report the results of a service evaluation of practice in the United Kingdom (UK) to determine nationwide practice and attitudes towards achieving GTR and dealing with residual enhancing disease in patients deemed suitable for GTR. The study was conducted in 2 parts: (1) an electronic questionnaire to neuro-oncology surgeons and (2) a 3-month prospective, multicenter 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 tumor 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 randomized control trial investigating early repeat operation.

Study Design—Prospective Cohort Study

The second part of the study was a prospectively collected multicenter observational study on current neuro-oncological practice.

Patient Selection

Patients with suspected glioblastoma that were scheduled to undergo GTR at first surgery following discussion at a multidisciplinary meeting between May 1, 2016 and July 31, 2016 were eligible for inclusion. Patients were identified prospectively at multidisciplinary meetings and data were collected prospectively during their subsequent inpatient stay. Inclusion criteria included adult patients (age >18) with suspected glioblastoma on presenting MRI scan and multidisciplinary team decision that the tumor was suitable for GTR. Exclusion criteria included children (age <18) with subsequent histology that confirmed an alternative diagnosis. Patients with recurrent tumors were included in the study provided GTR was the aim at surgery.

Data Collection

Data on patient demographics, tumor location, surgical adjuncts, residual disease, intraoperative/postoperative MRI, as well as adjuvant treatment and complications (Supplementary data), were 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 were collected locally and then collated centrally after the end of the study period. Data were analyzed in Microsoft Excel (2011) and IBMSPSS Statistics® (version 24).

Ethics

This project was registered, approved, and recorded at each local unit by their local Research and Audit departments.

Results

Surgical Practice

There were responses from 27 neuro-oncology surgeons from 22 of 38 neurosurgical units in the UK. These respondents estimated a total of approximately 3000 operations for newly diagnosed glioblastoma per year, of which roughly 1800 (60%) were amenable for GTR. The majority of respondents (24/27, 88.9%) said that over 90% of patients

were discussed at multidisciplinary meetings before surgery.

With regard to surgical adjuncts, 100% of surgeons had access to intraoperative neuronavigation. Access to 5-ALA was variable: 44.4% of surgeons said they had routine access; 29.6% had limited access for specific cases; and 25.9% had no access. Seventeen of 27 surgeons (63%) said they routinely used awake surgery with bipolar stimulation where indicated, with 16 of 27 (59.3%) using speech and language testing and 4 of 27 (14.8%) using electromyography recordings under general anesthetic.

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. One-third of surgeons (9/27, 33.3%) estimated there to be between 11 and 20 patients per year who were deemed suitable for GTR, but who had residual enhancing disease on their postoperative scan; 6 surgeons (22.2%) estimated there to be between 5 and10 patients per year; and 4 surgeons (14.8%) estimated there to be over 20 patients per year.

Service Evaluation

We prospectively collected data on 113 patients from 15 neurosurgical centers (range, 1–26 patients per center) with a mean age of 58.2 years (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). Eighty-nine patients (78.7%) had at least one comorbidity (Table 1). The most common presenting symptom/sign was headache (44/113, 38.9%), followed by focal neurological deficit (40/113, 35.3%) (Table 1). The intracerebral distribution of tumors 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%) cases followed by awake surgery (14, 12.4%) and intraoperative ultrasound (14, 12,4%). There was little use of intraoperative MRI (4, 3.5%), reflecting the small number of centers with access to this technology in the UK.

Postoperative complications were seen in 27 (23.6%) patients (Table 2), the majority of which 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 at the time of surgery were: tumor adherent to vessels (2.7%), eloquent brain (5.4%), cardiac instability (0.9%), unknown (7.2%).

After surgery 80 patients (70.8%) had an MRI scan within 72 hours. In marked contrast to the operating surgeon's perception, the imaging data confirmed 44 patients (55%) had residual enhancing disease on their postoperative scan. This residual enhancing disease was deemed operable in 13 cases (16.3%). Surgeon estimation of GTR at time of surgery was similar whether 5-ALA (88.9% c.f. 80.6%, Fisher's exact test, $P = .52$) or any surgical adjunct (87.2% c.f. 78.1%, Fisher's exact test, $P = .32$) was used when compared to when the adjuncts were not used. However, the rate of GTR seen on postoperative MRI was trending towards significance when 5-ALA was used (76.5% c.f. 49.2%, Fisher's exact test, $P = .057$) and was significant when all adjuncts were taken into account (71.9% c.f. 43.8%, Fisher's exact test, $P = .021$). This would support the use of surgical adjuncts to increase GTR rates.

No patient had a repeat debulking within 1 week of primary surgery. Reasons included perceived lack of clinical benefit (5/13), medical comorbidities/poor PS (2/13), disagreement between surgeon and radiologist about whether there was residual enhancing disease (2/13), and unknown (4/13). In the 2 cases of disagreement, the surgeons perceived GTR at the time of surgery and the small amount of residual enhancing disease left was thought to not represent tumor but postsurgical changes possibly resulting from hemostatic agents used intraoperatively.

Table 1 Demographic information of patients included in study

Age, y, mean (range)	58.2 (28–85)
Sex	No. Patients
Male	73
Female	40
Presenting Symptom/Sign	
Focal Deficit	40
Headache	44
Seizure	33
Confusion	29
Altered Consciousness	7
Other	40
Comorbidites	
Smoking/Ex-smoker	8
Diabetes Mellitus	11
Hypertension	20
Previous Cancer	19
Other	32
WHO Performance Status	
PS 0	43
PS 1	48
PS 2	2
PS 3	3
PS 4	1
Tumor Location	
Frontal	51
Temporal	26
Parietal	28
Occipital	7
Cerebellar	1

WHO, World Health Organisation.

Table 2 Use of intraoperative surgical adjuncts for patients in the study and post-operative complications reported

Surgical Adjunct	No. Patients
iMRI	4
5-ALA	18
Awake mapping	14
fMRI	6
DTI	12
iUS	14
Other	0
Complication	**No. Patients**
Wound infection	1
Bone flap infection	0
Intracranial infection	1
Seizure	4
CSF leak	2
Hematoma	5
Medical	6
Other	8

5-ALA, 5-aminolevulinic acid; DTI, diffusion tensor imaging; fMRI, functional MRI; iMRI, intraoperative MRI; iUS, intraoperative ultrasound.

Discussion

This study highlights varying practices among neurosurgical units in the UK in the approach to resection of suspected glioblastoma 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 use of surgical adjuncts to maximize 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 residual enhancing disease and may over-represent the extent to which advanced surgical adjuncts are used.

The lack of utilization of surgical adjuncts is a concern when a significant proportion of patients have postoperative residual enhancing disease, even those for whom GTR was thought possible preoperatively. Identifying the enhancing tumor margin intraoperatively 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 tumor 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 intraoperative MRI, 5-ALA, and awake surgery are reported to increase 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.

In our study, 16.3% of patients had residual enhancing disease that was thought amenable to early repeat resection before adjuvant therapy, but no patient went back to surgery. Early reoperation to remove residual enhancing disease in patients with glioblastoma before further treatment has been shown to be feasible without increased morbidity.[33] However, in that study only a low proportion (6%) of patients underwent early re-intervention.

GTR as a predictor of outcome does not necessarily imply that early revision surgery would be of benefit. There is very little data on whether rapid reoperation to resect residual enhancing disease 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 while it may offer a theoretical survival advantage by reducing the tumor 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] and others suggesting 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 glioblastoma patients has found no difference in overall survival related to the time to radiotherapy.[40] If this is the case, then early reoperation may not negatively impact on survival through delay to radiotherapy. However, there are other factors that must be considered when deciding on early revision surgery. These include prolonged hospital stay and immobilization for a second operation, carrying inherent risk of venous thrombo-embolic disease and infection—both surgical and anesthesia-related. There are also psychological and social factors that become important when discussing a second large operation in a short space of time that patients and carers may not be prepared for. Although feasible on a small scale,[33] these factors need to be taken into account when upscaling this practice.

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 (Table 3).[8] Maximally reductive surgery not only increases survival independently, but also increases the effectiveness of adjuvant therapies.[41]

If the data favor maximal resection of tumors where possible, debate exists over the minimum extent of resection that is associated with maximal survival benefit. Studies have historically classified extent of resection into

Table 3 Summary of literature of extent of resection in GBM

New/ Recurrent GBM	Survival Benefit	Study	No. Patients	Maximum Survival Advantage	Volumetric Study	Minimum Resection Required
New	Yes	Brown et al 2016[30]*	20 769 20 699	16.1% 1-year survival 10.3% 2-year survival	No	GTR
		Chaichana et al 2014 (1)[18]	259	3.9 months	Yes	70% or < 5 cm^3 RTV
		Chaichana et al 2014 (2)[9]	292	4.7 months (EoR) 4.2 months (RTV)	Yes	95% or < 2 cm^3 RTV
		Grabowski et al[14]	128	4.5 months	Yes	98% or < 2 cm^3 RTV
		Hollerhage et al[42]	118		No	GTR
		Keles et al [43]	107	6.4 months	Yes	75%
		Kreth et al[22]	273	5.4 months	no	GTR
		Kuhnt et al[13]	88	5 months	yes	98%
		Lacroix et al[23]	416	4.2 months	yes	89%
		Li et al[10]	1229	5.4 months + 5.2 months extra for addition FLAIR resection	Yes	100% +/- 53.2% additional FLAIR resection
		Local data	285	4 months	No	GTR
		Marko et al[44]	721		Yes	Continuous relationship
		McGirt et al[17]	451	2 months (GTR vs NTR); 5 months (GTR vs STR)	No	GTR
		Nitta et al[45]	68	8 months	No	GTR
		Orringer et al[19]	46	44% 1-year survival	yes	90%
		Roder et al[11]	117	13% 6-month PFS	Yes	100%
		Salvati et al[20]	105	3.5 months	no	GTR
		Sanai et al[26]	500	3.8 months	Yes	78%
		Shibamoto et al[46]	135	4 months	No	STR
		Simpson et al[47]	645	0.9 months (GTR vs STR); 4.7 months (GTR vs biopsy)	No	GTR
		Stark et al[48]	267		No	GTR
		Stummer et al 2008[49]	243	4.9 months	no	GTR
		Stummer et al 2012[3]	143	> 7.1 months	No	Residual tumor diameter < 1.5 cm
		Ushio et al[50]	105	5.8 months	No	GTR
		Vecht et al[51]	177	1 month	No	Extensive surgery
	No	Coburger et al[16]	33	No difference	Yes	
		Kowalczuk et al[52]	52	No difference	No	
		Phillips et al[53]	173	No difference	No	
		Pope et al[54]	110	No difference	Yes	

Table 3 *Continued*

New/ Recurrent GBM	Survival Benefit	Study	No. Patients	Maximum Survival Advantage	Volumetric Study	Minimum Resection Required
Recurrent	Yes	Bloch et al[55]	107	3.4 months	Yes	95%
		McGirt et al[17]	294	2 months (GTR vs NTR); 6 months (GTR vs STR)	No	GTR
		Oppenlander et al[56]	170	10.8 months	Yes	80%
		Quick et al[57]	40	6.7 months	Yes	100%
		Ringel et al[58]	503	4.4 months	No	GTR
		Suchorska et al[12]	71	6.4 months	Yes	100%
		Yong et al[15]	97	7.5 months	Yes	< 3 cm^3 RTV

EoR, extent of resection; FLAIR, fluid attenuated inversion recovery; GBM, glioblastoma; GTR, gross total resection; NTR, near total resection; PFS, progression-free survival; RTV, residual tumour volume; STR, subtotal resection. Local data = unpublished data collected locally at Addenbrookes Hospital, Cambridge, UK.
*includes a meta-analysis.

4 categories: GTR, near total resection, subtotal resection, and partial resection. Apart from GTR, which is classified as the complete removal of contrast-enhancing disease on a postoperative MRI performed within 72 hours, the definitions of the other categories are variable and subjective in nature, making it difficult to incorporate them into clinical management protocols or to compare studies.[17,20,22,42,47,59]

Quantification of residual tumor volumes can produce more accurate data on extent of resection and residual enhancing disease. Lacroix et al published a volumetric series looking at patients undergoing resection for glioblastoma. They reported that a minimum extent of resection 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 dichotomized cohort with extent of resection values of 78% or above but a clinically meaningful survival difference of 3.8% only in patients extent of resection 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 glioblastoma, emphasizing the added value of a complete resection."[26] A common interpretation of these data is that an extent of resection 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 residual enhancing disease on postoperative MRI) provides optimal clinical benefit. For example, in a trial of enzastaurin, patients with glioblastoma who had GTR on their baseline postoperative MRI had enhanced progression-free survival at 6 months.[60] In EORTC 26071-22072 (CENTRIC), GTR conveyed a 6.6-month survival advantage in the experimental arm (30.4 vs 24.8 months) and 10.7-month survival advantage in the control arm (34.3 vs 23.6 months).[61] In the DIRECTOR trial (NCT00941460), complete resection of contrast-enhancing tumor volume was associated with improved survival in recurrent glioblastoma.[12]

As the present study did not assess resection volumes or, indeed, the volume or location of residual enhancing disease, the lack of early reoperation, of which 38.4% of cases were due to lack of perceived clinical benefit, must be interpreted with caution. Future studies should take into account the volume, location, and distribution of residual enhancing disease as these will likely have implications on the risk-benefit balance of early reoperation.

Conclusion and Future Directions

This study is the first to prospectively evaluate the current surgical management of glioblastoma patients in the UK who were judged suitable for radical surgery by a multidisciplinary team. We show that there is wide variation in approaches to achieving GTR in the UK. Where residual enhancing disease occurs despite surgery there remains clinical doubt as to whether these patients would benefit from early revision surgery. While there is a large volume of retrospective data to support the beneficial effects of maximal safe resection in patients with glioblastoma, there is

little prospective data and even fewer data on early reoperation to remove residual enhancing disease. Consequently relatively little is known about the impact of GTR on prognosis, morbidity, and quality of life for patients in this setting. In order to develop and optimize surgical management protocols further prospective research is required to determine the clinical impact of residual enhancing disease and early re-intervention to convert subtotal resection to GTR.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

Collaborators

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

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