ORIGINAL RESEARCH

Volumetric and dosimetric impact of post-surgical MRI-guided radiotherapy for glioblastoma: A pilot study

1MARCUS TYYGER, MSc, 1SUCHANDANA BHAUMIK, MBBS, MD, FRCR, 1MICHAEL NIX, PhD, 2STUART CURRIE, PhD, 1CHANDRAN NALLATHAMBI, FRCS, 1RICHARD SPEIGHT, PhD, 1BASHAR AL-QAISIEH, PhD and 1,3LOUISE MURRAY, MRCP, FRCR, PhD

1Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
2Department of Neuroradiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
3Radiotherapy Research Group, University of Leeds, Leeds, UK

Address correspondence to: Mr Marcus Tyyger
E-mail: marcus.tyyger@nhs.net

Objectives: Glioblastoma (GBM) radiotherapy (RT) target delineation requires MRI, ideally concurrent with CT simulation (pre-RT MRI). Due to limited MRI availability, <72 h post-surgery MRI is commonly used instead. Whilst previous investigations assessed volumetric differences between post-surgical and pre-RT delineations, dosimetric impact remains unknown. We quantify volumetric and dosimetric impact of using post-surgical MRI for GBM target delineation.

Methods: Gross tumour volumes (GTVs) for five GBM patients receiving chemo-RT with post-surgical and pre-RT MRIs were delineated by three independent observers. Planning target volumes (PTVs) and RT plans were generated for each GTV. Volumetric and dosimetric differences were assessed through: absolute volumes, volume-distance histograms and dose-volume histogram statistics.

Results: Post-surgical MRI delineations had significantly (p < 0.05) larger GTV and PTV volumes (median 16.7 and 64.4 cm³ respectively). Post-surgical RT plans, applied to pre-RT delineations, had significantly decreased (p < 0.01) median PTV doses (ΔD99% = -8.1 Gy and ΔD95% = -2.0 Gy). Median organ-at-risk (OAR) dose increases (brainstem ΔD5% = +0.8, normal brain mean dose =+2.9 and normal brain ΔD10% = 5.3 Gy) were observed.

Conclusion: Post-surgical MRI delineation significantly impacted RT planning, with larger normal-appearing tissue volumes irradiated and increased OAR doses, despite a reduced coverage of the pre-RT defined target.

Advances in knowledge: We believe this is the first investigation assessing the dosimetric impact of using post-surgical MRI for GBM target delineation. It highlights the potential of significantly degraded RT plans, showing the clinical need for dedicated MRI for GBM RT.

BACKGROUND

Glioblastoma (GBM) is the most common malignant primary brain tumour in adults.1 Their aggressive nature and treatment resistance lead to poor prognosis, with a median survival of 12–15 months.2 The current standard of care is maximal safe tumour resection followed by radiotherapy (RT) with concurrent and adjuvant temozolomide.3–5 Current RT treatments rely on accurate gross tumour volume (GTV) delineations as tumour infiltration cannot be directly observed on anatomical MRI. As a result, isotropic margins of 20–30 mm are added to GTVs to create clinical target volumes (CTV).3 Therefore, to accommodate infiltration whilst minimising the volume of normal-appearing tissue irradiated, uncertainties in GTV delineation should be reduced wherever possible.

Current clinical guidance3 recommends a dedicated MRI for RT target delineation at the time of CT-simulation (pre-RT MRI). However, for RT departments with limited MRI access, there may be difficulty in acquiring an RT dedicated MRI. In these situations, it is common practice to include additional sequences for RT delineation on the <72 h post-surgical MRI acquired to assess the completeness of tumour resection. However, post-surgical acquisitions can contain acute oedema or inflammation, blood products and vascular changes around the surgical cavity. In addition, tumour progression or anatomical adjustment can occur during the delay between surgery and commencement of RT.6–8 Whilst clinical guidance3 acknowledges the risk when delineating based on the post-surgical MRI, it does not evaluate the potential severity of delineation inaccuracy or its dosimetric impact.

Previous studies assessed differences in high-grade glioma delineation between post-surgical and pre-RT MRIs, although results were inconclusive. Pennington et al3 found...
a statistically significant GTV increase of 11.09 cm³ when delineating on pre-RT MRI, concluding that tumour progression was the root cause. Conversely, Champ et al.9 and Farace et al.10 found no statistically significant changes in GTVs between MRIs.

To our knowledge, there remains no investigation assessing dosimetric differences between RT plans generated by post-surgical and pre-RT GBM delineations. This pilot study aims to quantify differences between delineations and their dosimetric impact in the context of GBM RT.

METHODS
A cohort of six patients (Table 1) with primary GBM treated with chemo-RT were enrolled within a separate local pilot study between May 2018 and September 2019 (IRAS Project ID: XXXXXX). One patient was excluded due to a lack of post-surgical MRI. Post-surgical and pre-RT MRIs were acquired within 72 h of surgery and prior to RT commencement, respectively. The median times from surgery to pre-RT MRI and plan CT were 42 days (range: 33 to 45) and 31 days (range: 28 to 34), respectively.

Post-surgical MRIs were gadolinium contrast-enhanced T1W 2D spin echo sequences, acquired in the standard radiology position at 1.5 T (Aera, Siemens Healthineers, Erlangen, Germany) with: 2 mm contiguous slices, 1.2 × 1.0 mm in-plane resolution, 565 ms repetition time, 8.6 ms echo time and 250 Hz pixel⁻¹ bandwidth.

Pre-RT MRIs were gadolinium contrast-enhanced T1W 2D spin echo sequences, acquired at 3 T (Prisma, Siemens Healthineers, Erlangen, Germany) in the RT treatment position with: 4 mm slices with 1.2 mm gaps between slices, 1.0 × 1.0 mm in-plane resolution, 600 ms repetition time, 6.0 ms echo time and 250 Hz pixel⁻¹ bandwidth.

CT simulation (Brilliance Big Bore, Phillips Healthcare, Amsterdam, The Netherlands) was performed in the RT treatment position at 120 kVp with 1.17 × 1.17 mm in-plane resolution and 2 mm contiguous slices.

GTVs were independently delineated on post-surgery and pre-RT MRIs in RayStation (8B DTK, RaySearch Laboratories, Stockholm, Sweden), by a consultant neuroradiologist (CNR), a consultant oncologist (CCO) and a senior trainee oncologist (TCO). GTV was defined as the visible contrast-enhancing tumour and surgical cavity, following ESTRO-ACROP guidance.3 Observers were provided access to post-surgical radiology reports, and memory bias was accounted for by seven-day wait periods between delineations of individual patients. Clinical target volumes (CTVs) were generated from GTVs using 25 mm isotropic margins with manual adjustment for anatomical boundaries (e.g., bone, falx cerebri, tentorium). Planning target volumes (PTVs) were grown from CTVs using 5-mm isotropic margins, with volumes clipped 5 mm from patient external contours for treatment planning purposes. Planning PTV - 54 Gy OARs’ structures were created by subtracting brainstem, optic chiasm and optic nerves from PTVs. Organs at risk (OAR) were not specifically delineated for this study but instead the pre-existing clinical OAR delineations were used, previously contoured by the treating clinical oncologist and included: brainstem, cochleas, globes, lenses, lacrimal glands, optic chiasm, optic nerves and pituitary gland.

MRIs were rigidly registered to CT with registration quality assessed visually by a Clinical Scientist specialised in radiotherapy imaging. Target delineations were copied from MRI to CT. RT plans were generated in Monaco (v. 5.11.02, Elekta, Stockholm, Sweden) using the local glioma class solution. Treatment plans were optimised for individual target volumes from both MRI time points for each observer and patient. 60 Gy in 30 fractions 6 MV flattening filter free volumetric modulated arc therapy (VMAT) treatment plans were produced using a 180° coplanar arc and a 45° anterosuperior non-coplanar arc.

Dosimetric impact was assessed through differences in dose-volume histogram (DVH) statistics for the target and OAR constraints shown in Table 2 between post-surgical and pre-RT plans for each observer. PTV and ‘brain - PTV’ statistics for both post-surgical and pre-RT plans were determined using pre-RT MRI delineations (PTVpre-RT). These volumes were the closest available analogue to tumour and healthy brain tissue at the time of treatment, and were therefore used to represent ‘true’ tumour/normal tissue anatomy. Thus, the impact of the post-surgical plan on this ‘true’ anatomy could be assessed.

Volumetric changes were determined through differences in absolute volume, contour similarity metrics and volume-distance histograms between post-surgical and pre-RT delineations for each observer. Dice Similarity Coefficient (DSC), sensitivity and specificity (equations 1-3) were calculated using pre-RT delineations as the reference contour and post-surgical delineations.

Table 1. Patient demographics, patient one was excluded as no post-surgical MRI was acquired

| ID   | Sex | Age | Primary tumour location          | Days after surgery to… |
|------|-----|-----|----------------------------------|------------------------|
| Pt_2 | M   | 48  | (r)superior parietal lobe        | Post-surgical MRI      |
| Pt_3 | M   | 55  | (r)temporal lobe                 | CT-Simulation          |
| Pt_4 | F   | 66  | (r)anteromedial frontal lobe     | Pre-RT MRI            |
| Pt_5 | M   | 56  | (r)parietal lobe                 |                        |
| Pt_6 | F   | 68  | (l)posterior frontal lobe        |                        |

| ID   | Sex | Age | Primary tumour location          | Post-surgical MRI      | CT-Simulation | Pre-RT MRI |
|------|-----|-----|----------------------------------|------------------------|---------------|------------|
| Pt_2 | M   | 48  | (r)superior parietal lobe        | 1                      | 28            | 34         |
| Pt_3 | M   | 55  | (r)temporal lobe                 | 3                      | 32            | 45         |
| Pt_4 | F   | 66  | (r)anteromedial frontal lobe     | 2                      | 31            | 42         |
| Pt_5 | M   | 56  | (r)parietal lobe                 | 3                      | 30            | 33         |
| Pt_6 | F   | 68  | (l)posterior frontal lobe        | 3                      | 34            | 45         |

ID Sex Age Primary tumour location Post-surgical MRI CT-Simulation Pre-RT MRI
Pt_2 M 48 (r)superior parietal lobe 1 28 34
Pt_3 M 55 (r)temporal lobe 3 32 45
Pt_4 F 66 (r)anteromedial frontal lobe 2 31 42
Pt_5 M 56 (r)parietal lobe 3 30 33
Pt_6 F 68 (l)posterior frontal lobe 3 34 45
as the novel contour. DSC values ranged between 0 and 1, with values of 1 indicating the post-surgical and pre-RT delineations completely overlapped. Sensitivity values also ranged between 0 and 1, with a value of 1 meaning the pre-RT delineation was entirely contained within the post-surgical delineation. Specificity values ranged between \(-\infty\) and 1, with a value of 1 meaning the post-surgical delineation was entirely contained within the pre-RT delineation. Specificity values < 1 meant there were volumes of the post-surgical delineation outside the pre-RT delineation, and values < 0 meant these volumes were larger than the total pre-RT delineation volume.

\[
DSC = \frac{2 \cdot |\text{ROI}_{\text{reference}} \cap \text{ROI}_{\text{novel}}|}{|\text{ROI}_{\text{reference}}| + |\text{ROI}_{\text{novel}}|}
\]  
Eq. 1

\[
\text{Sensitivity} = \frac{|\text{ROI}_{\text{reference}} \cap \text{ROI}_{\text{novel}}|}{|\text{ROI}_{\text{reference}}|}
\]  
Eq. 2

\[
\text{Specificity} = 1 - \frac{|\text{ROI}_{\text{novel}} \setminus \text{ROI}_{\text{reference}}|}{|\text{ROI}_{\text{reference}}|}
\]  
Eq. 3

Volume-distance histograms (Figure 1), based on a methodology by Nelms et al.\(^{12}\) were generated to allow further assessment of volumetric differences between delineations. These were discretised into individual voxels and classified as either ‘union’, ‘extra’ or ‘missing’. Union voxels were contained within post-surgical and pre-RT delineations. Extra and missing voxels were only contained within the post-surgical or pre-RT delineations, respectively. Missing and extra volumes were calculated by summing the overall number of missing and extra voxels, respectively. For all extra and missing voxels, the minimum Euclidean distance to the other delineation was determined, with union voxel distances set as zero. Missing voxel distances were set as negative, as this allowed them to be distinguished from extra voxel distances. Volume-distance histograms were then generated using the Euclidean distances and number of voxels for GTVs and PTVs, per patient, per observer. Cohort-level histograms for each observer were generated by summing all individual patient histograms, which allowed systematic changes to be identified.

Volumetric and dosimetric differences were statistically analysed in R\(^{13}\) using a linear mixed effects models through the

### Table 2. Local dose volume histogram objectives for gliomas treated with 60 Gy in 30 fraction volumetric modulated arc therapy

| Targets (Gy) | Mandatory OARs (Gy) | Optimal OARs (Gy) |
|-------------|---------------------|-------------------|
| **PTV**     | D99% > 54           | Brainstem D5% < 54| Lenses D1% < 6   |
|             | D95% > 57           | Mean < 52         | Lacrimals D1% < 30 |
|             | 59 < D50%<61        | Optic Chiasm D1% < 54 | Cochleas D50% < 45 |
|             | D5% < 63            | Optic Nerves D1% < 54 | Brain - PTV D10% < 57 |
|             | D2% < 64            | Globes D1% < 45   | Mean < 24       |
| **PTV**     | D99% > 51.3         | Pituitary Max < 45 |
| **PTV - 54 Gy OARs** | D99% > 54          |                   |
|             | D95% > 57           |                   |

\(^a\)Additional planning target volume (PTV) objectives were used where the PTV overlapped the 54 Gy organs at risk (OARs): brainstem, optic chiasm, and optic nerves.
'lme4' package, with $\alpha = 0.05$ as the threshold for statistical significance. Analysis of variance was used to assess differences between a null model only employing observers and patients as random effects, and a full model which also used MRI time point as a fixed effect.

**RESULTS**

Figure 2 shows post-surgical and pre-RT GTV delineations for patients 4 and 6. Patient four had the largest difference in GTVs, with post-surgical GTVs being larger than pre-RT for all observers. Patient six was the only patient that showed signs of progression between MRI acquisitions, and post-surgical GTV delineations were smaller than pre-RT GTVs for: consultant clinical oncologist (CCO), trainee clinical oncologist (TCO), and consultant Neuroradiologist (CNR).

![Figure 2](image-url)

Figure 2. Axial slices of pre-RT MRIs for patients 4 and 6, with pre-RT (orange) and post-surgical (blue) delineations. Patient four showed the largest difference in GTVs, with post-surgical GTVs being larger than pre-RT for all observers. Patient six was the only patient that showed signs of progression between MRI acquisitions, and post-surgical GTV delineations were smaller than pre-RT GTVs for: consultant clinical oncologist (CCO), trainee clinical oncologist (TCO), and consultant Neuroradiologist (CNR).

Patient 4

Patient 6

RESULTS

Figure 2 shows post-surgical and pre-RT GTV delineations for patients 4 and 6. Patient four had the largest GTV reduction across observers on pre-RT MRI compared to post-surgical MRI. Patient six was the only patient to show signs of tumour progression between MRIs. Volumetric differences for GTVs and PTVs are shown in Figure 3. At a cohort level, across all observers, pre-RT delineations for GTVs and PTVs were smaller than post-surgical delineations by a median of 16.7 cm$^3$ (range: −44.8 to 31.9, p value < 0.01) and 64.4 cm$^3$ (range: −142.5 to 91.5, p value < 0.05), respectively. Patient six was the only patient to have larger delineations on pre-RT MRIs for all observers, with a median increase of 16.65 cm$^3$ and 67.70 cm$^3$ respectively.

Figure 3. Absolute volume differences (cc) between post-surgical and pre-RT delineations for gross tumour and planning target volumes. Positive values indicate larger volumes on post-surgical MRI. Patient six showed progression between planning scans. TCO’s planning target volume for patient three was larger on pre-RT MRI despite a smaller gross tumour volume; this was caused by a small distant blood vessel being included in the gross tumour volume delineation and the large isotropic growth margins caused a large volume of normal appearing brain tissue to be included in the planning target volume. See Supplementary Material 1 for example images.
Contour similarity metrics were calculated with median values across all patients and observers shown in Table 3. Poor agreement between post-surgical and pre-RT GTV delineations was found in terms of DSC, sensitivity and specificity values. Whilst PTVs showed greater agreement than GTVs, overall the agreement was still poor.

Volume-distance histograms were generated, with cohort-level histograms shown in Figure 4 and individual patient histograms in Supplementary Material 2. The median extra and missing volumes per patient for GTVs were 19.6 cm³ (range: 0.6 to 45) and 3.7 cm³ (range: 0.2 to 29.7), respectively. For PTVs these values were found to be 75.3 cm³ (range: 11.4 to 142.3) and 15.7 cm³ (range: 1.1 to 109.2), respectively.

RT plans were generated for all patients, including three patients who required compromised PTV coverage to achieve mandatory OAR constraints due to target volumes intersecting OARs. Figure 5 shows differences in DVH statistics between post-surgical and pre-RT plans for individual observers, based on the pre-RT delineations for PTV and ‘brain – PTV’ statistics, with positive values indicating a higher dose on post-surgical plans. At a cohort level OARs were found to have either a higher median dose on post-surgical MRI or a near zero difference with pre-RT MRI. These differences were not statistically significant except for ‘brain - PTV_{pre-RT}’ D10% (5.3 Gy; range: −7.1 to 11.8, p value:<0.005), ‘brain - PTV_{pre-RT}’ mean dose (2.9 Gy; range: −3.7 to 3.5, p value:<0.005), and brainstem D5% (0.8 Gy; range: −2.3 to 12.8, p value:<0.01). PTV_{pre-RT} D99% and D95% were found to be statistically significantly lower on post-surgical plans, with median values of −8.1 Gy (range: −30.0 to 0.4, p value:<0.01) and −2.0 (range: −4.5 to 0.3, p value:<0.01), respectively.

**DISCUSSION**

Dedicated planning MRI for RT target delineation is recommended in preference to the use of <72 h post-surgical MRI. MRI acquisitions shortly after surgery can contain oedema, ischaemia or inflammation around the surgical cavity, and the necessary delay between surgery and RT allows for post-surgical anatomical adjustment and tumour progression. However, for departments with limited MRI access, such as many of those within the UK, the resources required for a dedicated MRI scan may not be available. Previous studies into the impact of using post-surgical MRI for GBM delineation focused on volumetric differences and did not assess dosimetric impact. Here, we investigated the volumetric and dosimetric impact of RT target delineation on post-surgical MRI in a small cohort of primary GBM patients. Significant volumetric and dosimetric differences were found, showing degraded RT when delineating on post-surgical MRI.

Post-surgical MRI GTV and PTVs were larger than pre-RT MRI volumes across all observers, with median differences of 16.7 cm³ and 64.4 cm³ respectively. Only one patient had smaller volumes on post-surgical MRI, attributed to tumour progression. For observer TCO, their patient three post-surgical PTV was smaller median dose on post-surgical MRI or a near zero difference with pre-RT MRI. These differences were not statistically significant except for ‘brain - PTV_{pre-RT}’ D10% (5.3 Gy; range: −7.1 to 11.8, p value:<0.005), ‘brain - PTV_{pre-RT}’ mean dose (2.9 Gy; range: −3.7 to 3.5, p value:<0.005), and brainstem D5% (0.8 Gy; range: −2.3 to 12.8, p value:<0.01). PTV_{pre-RT} D99% and D95% were found to be statistically significantly lower on post-surgical plans, with median values of −8.1 Gy (range: −30.0 to 0.4, p value:<0.01) and −2.0 (range: −4.5 to 0.3, p value:<0.01), respectively.

**DISCUSSION**

Dedicated planning MRI for RT target delineation is recommended in preference to the use of <72 h post-surgical MRI. MRI acquisitions shortly after surgery can contain oedema, ischaemia or inflammation around the surgical cavity, and the necessary delay between surgery and RT allows for post-surgical anatomical adjustment and tumour progression. However, for departments with limited MRI access, such as many of those within the UK, the resources required for a dedicated MRI scan may not be available. Previous studies into the impact of using post-surgical MRI for GBM delineation focused on volumetric differences and did not assess dosimetric impact. Here, we investigated the volumetric and dosimetric impact of RT target delineation on post-surgical MRI in a small cohort of primary GBM patients. Significant volumetric and dosimetric differences were found, showing degraded RT when delineating on post-surgical MRI.

Post-surgical MRI GTV and PTVs were larger than pre-RT MRI volumes across all observers, with median differences of 16.7 cm³ and 64.4 cm³ respectively. Only one patient had smaller volumes on post-surgical MRI, attributed to tumour progression. For observer TCO, their patient three post-surgical PTV was smaller median dose on post-surgical MRI or a near zero difference with pre-RT MRI. These differences were not statistically significant except for ‘brain - PTV_{pre-RT}’ D10% (5.3 Gy; range: −7.1 to 11.8, p value:<0.005), ‘brain - PTV_{pre-RT}’ mean dose (2.9 Gy; range: −3.7 to 3.5, p value:<0.005), and brainstem D5% (0.8 Gy; range: −2.3 to 12.8, p value:<0.01). PTV_{pre-RT} D99% and D95% were found to be statistically significantly lower on post-surgical plans, with median values of −8.1 Gy (range: −30.0 to 0.4, p value:<0.01) and −2.0 (range: −4.5 to 0.3, p value:<0.01), respectively.
than their pre-RT PTV, despite the larger GTV on post-surgical MRI (Figure 3). This was caused by a small blood vessel far from the tumour bed being included in the pre-RT GTV, meaning the growth margins used caused a large volume of normal-appearing brain tissue to be included in the pre-RT PTV.

Volumetric results differ from previous investigations,\textsuperscript{6,8,9} which used larger patient cohorts. Pennington et al\textsuperscript{8} found post-surgical GTVs were smaller than pre-RT volumes due to tumour progression, whilst Champ et al\textsuperscript{9} and Farace et al\textsuperscript{6} found no statistically significant difference. The difference in results could be caused by the small cohort size paired with the heterogeneous nature of GBM or different timings between post-surgical and pre-RT MRI acquisitions. Recent investigations\textsuperscript{16,17} have identified potential GBM phenotypes with specific behaviours and characteristics. Therefore, a small cohort has potential to sample a smaller number of GBM phenotypes and not be representative of the full range of GBM behaviours and characteristics. It should be noted that Pirzkall et al\textsuperscript{7} found 53\% of patients showed signs of progression between acquisitions, whereas in this investigation only one of five patients showed signs of progression.

Volume-distance histograms found overall GTV extra and missing volumes of 19.6 cm\textsuperscript{3} and 3.7 cm\textsuperscript{3} respectively, across all observers. Thus, despite post-surgical delineations being significantly larger they did not entirely contain the pre-RT delineations. This result was also found through contour similarity metrics, where the median GTV sensitivity value was only 0.77. Whilst PTVs had a higher median sensitivity of 0.95 and a median DSC of 0.80, extra and missing volumes were still found (median 75.3 and 15.7 cm\textsuperscript{3} respectively). Therefore, for this cohort of patients, post-surgical delineations did not accurately represent pre-RT delineations. Given the expected correlation between irradiated brain volume and toxicity,\textsuperscript{10,11} the increased treatment volume of RT plan guided by post-surgical MRI has the potential to cause additional toxicity. This may impact negatively on quality of life in a patient population who already have a guarded prognosis, although non-tumour complication probability models that examine this are not well established.

Dosimetric differences were assessed through DVH statistics, as seen in Figure 5, with insignificant differences found for most OARs. However, statistically significant median increases of 5.3 Gy, 2.9 Gy, and 0.8 Gy were found on post-surgical MRI for ‘brain - PTV\textsubscript{pre-RT}’ D10\%, ‘brain - PTV\textsubscript{pre-RT}’ mean dose, and brainstem D5\%, respectively. As the ‘brain - PTV\textsubscript{pre-RT}’ volumes were generated using pre-RT delineations for both post-surgical and pre-RT DVH statistics, the increase in doses can be attributed to larger PTV volumes on post-surgical MRI. Traditional late radiation-induced toxicity endpoints such as radiation optic neuropathy and brainstem necrosis are rarely observed in clinical practice when OAR constraints are met, perhaps as a result of the poor prognosis in this patient group. As such, differences in doses to these OARs are unlikely to be of clinical significance.

PTV DVH statistics for post-surgical and pre-RT plans were generated using the pre-RT PTV delineations to allow an assessment of the post-surgical plan on the ‘true’ anatomy at the time of treatment. Statistically significant decreases were found for PTV\textsubscript{pre-RT} D95\% and PTV\textsubscript{pre-RT} D99\% on post-surgical RT plans, with a median reduction at a cohort level of 2.0 Gy and 8.1 Gy, respectively. Observer CNR had a 30.0 Gy decrease in PTV D99\% for patient two despite a small change in delineation volume. The large dosimetric change was due to the delineation difference being out-of-plane, meaning these regions were shielded by multi-leaf collimators and doses were actively minimised. Had this deviation been in-plane, it would not have been
actively shielded and doses would also have been higher due to beam entrance/exit doses.

The origin of decreases in PTV<sub>pre-RT</sub> D95% and D99% for post-surgical MRI RT plans was caused by regions of pre-RT target volumes not present in the post-surgical delineation; highlighting that despite larger treatment volumes on post-surgical MRI, RT treatments may not cover tumour extent at the time of RT.

Whilst we believe the cohort size is the main weakness of our investigation, other limitations should also be considered. Treatment planning was optimised for individual target volumes, meaning differing planning optimisation could have caused dosimetric differences. However, this effect was limited by using a single experienced clinical scientist to produce all plans, and optimised using the same priority order of mandatory OARs, target volumes and optional OARs.

As the pre-RT MRI sequence used thicker non-contiguous slices, there was potential for delineations to miss regions of tumour or to inaccurately represent the tumour tissue. However, as the delineation, volumes were large compared to the slice thickness the effect of interpolation should be small. We believe this effect could not be large enough to cause a median increase of approx.-imately 16 cm³ in absolute volume.

As pre-RT MRIs were acquired on a 3 T MRI scanner, they had a higher signal-to-noise ratio (SNR) than the post-surgical MRIs. An increased SNR could have resulted in greater contrast at the boundary of the tumour, meaning delineations were less likely to account for uncertainty in the tumour boundary. Additionally, whilst visual assessment did not find any chemical-shift artefacts in the MRIs, the increased field strength without an increase in bandwidth means there was greater chemical-shift artefact on pre-RT MRIs.

It should also be noted that this investigation used a low number of observers from two separate disciplines, and the results from all observers were given equal weight. CNR is not trained clinically to define target volumes for RT, and TCO would have their delineations checked by a consultant clinical oncologist when used clinically. Therefore, these differences in delineation techniques and experience could have impacted the results.

CONCLUSION
This pilot study assessed differences in target delineation and dosimetry between post-surgical MRI and pre-RT MRI in a small cohort of patients with GBM. Post-surgical GTVs and PTVs were found to be significantly larger than pre-RT delineations. Despite larger volumes, they did not necessarily contain the pre-RT delineations. Dosimetric analysis found insignificant changes for most OARs but significant increases for normal-appearing brain tissue and brainstem. Statistically significant dose decreases for PTV<sub>pre-RT</sub> on post-surgical RT plans were also found, implying potential undercoverage of the ‘true’ tumour volume at the time of treatment. This work shows that tumour delineation based on post-surgical MRI can significantly impact RT planning for GBM, with larger volumes of normal appearing tissue being irradiated and target doses being significantly reduced. These dosimetric changes could affect outcomes, treatment tolerance and treatment-related toxicities. These results support clinical guidance that a dedicated pre-RT MRI should be used for target delineation in preference to the post-surgical MRI.

FUNDING
Dr Richard Speight is supported by a Cancer Research UK Centres Network Accelerator Award Grant (A21993) to the ART-NET consortium. Dr Stuart Currie and Mr Marcus Tyyger are supported by funding received from Leeds Hospitals Charity. Mr Marcus Tyyger, Dr Michael Nix, and Dr Richard Speight acknowledge funding for this work received from The Sir John Fisher Foundation. Dr Louise Murray is a University Clinical Academic Fellow funded by Yorkshire Cancer Research (Award number L389LM).

REFERENCES
1. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: primary brain and central nervous system tumours diagnosed in the United States in 2006-2010. Neuro Oncol 2013; 15(suppl 2): ii:5–56. doi: https://doi.org/10.1093/neuonc/not151
2. Koshy M, Villano JL, Dolecek TA, Howard A, Mahmood U, Chmura SJ, et al. Improved survival time trends for glioblastoma using the SEER 17 population-based registries. J Neurooncol 2012; 107: 207–12. doi: https://doi.org/10.1007/s11060-011-0738-7
3. Niyazi M, Brada M, Chalmers AJ, Combs SE, Erridge SC, Fiorentino A, et al. ESTRO-ACROP guideline "target delineation of glioblastomas". Radiother Oncol 2016; 118: 35–42. doi: https://doi.org/10.1016/j.radonc.2015.12.003
4. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352: 987–96. doi: https://doi.org/10.1056/NEJMoa043330
5. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10: 459–66. doi: https://doi.org/10.1016/S1470-2045(09)70025-7
6. Farace P, Amelio D, Ricciardi GK, Zoccatelli G, Magon S, Pizzini F, et al. Early MRI changes in glioblastoma in the period between surgery and adjuvant therapy. J Neurooncol 2013; 111: 177–85. doi: https://doi.org/10.1007/s11060-012-0997-y
7. Pirzkall A, McGue C, Saraswathy S, Cha S, Liu R, Vandenberg S, et al. Tumor regrowth between surgery and initiation of adjuvant therapy in patients with newly diagnosed glioblastoma. Neuro Oncol 2009; 11: 842–52. doi: https://doi.org/10.1215/15288517-2009-005
8. Pennington C, Kilbride L, Grant R, Wardlaw JM. A pilot study of brain tumour growth between radiotherapy planning and delivery. Clin Oncol 2006; 18: 104–8. doi: https://doi.org/10.1016/j.clon.2005.09.004

9. Champ CE, Siglin J, Mishra MV, Shen X, Werner-Wasik M, Andrews DW, et al. Evaluating changes in radiation treatment volumes from post-operative to same-day planning MRI in high-grade gliomas. Radiat Oncol 2012; 7: 220. doi: https://doi.org/10.1186/1748-717X-7-220

10. Farace P, Giri MG, Meliadó G, Amelio D, Widesott L, Ricciardi GK, et al. Clinical target volume delineation in glioblastomas: pre-operative versus post-operative/pre-radiotherapy MRI. Br J Radiol 2011; 84: 271–8. doi: https://doi.org/10.1259/bjr/10315979

11. Udupa JK, Leblanc VR, Zhuge Y, Imielinska C, Schmidt H, Currie LM, et al. A framework for evaluating image segmentation algorithms. Comput Med Imaging Graph 2006; 30: 75–87. doi: https://doi.org/10.1016/j.compmedimag.2005.12.001

12. Nelm BE, Tomé WA, Robinson G, Wheeler J. Variations in the contouring of organs at risk: test case from a patient with oropharyngeal cancer. Int J Radiat Oncol Biol Phys 2012; 82: 368–78. doi: https://doi.org/10.1016/j.ijrobp.2010.10.019

13. R Core Team. R: A Language and Environment for Statistical Computing. Published online. 2019. Available from: https://www.r-project.org/.

14. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. J Stat Softw 2015; 67: 1–48. doi: https://doi.org/10.18637/jss.v067.i01

15. Speight R, Schmidt MA, Liney GP, Johnstone RI, Eccles CL, Dubec M, et al. IPEM topical report: a 2018 IPEM survey of MRI use for external beam radiotherapy treatment planning in the UK. Phys Med Biol 2019; 64: 175021. doi: https://doi.org/10.1088/1361-6560/ab2c7c

16. Rathore S, Akbari H, Rozycki M, Abdullah KG, Nasrallah MP, Binder ZA, et al. Radiomic MRI signature reveals three distinct subtypes of glioblastoma with different clinical and molecular characteristics, offering prognostic value beyond IDH1. Sci Rep 2018; 8: 1–12. doi: https://doi.org/10.1038/s41598-018-22739-2

17. Osman AFI. A multi-parametric MRI-based Radiomics signature and a practical ml model for Stratifying glioblastoma patients based on survival toward precision oncology. Front Comput Neurosci 2019; 13: 58. doi: https://doi.org/10.3389/fncom.2019.00058

18. Wilke C, Grosshans D, Duman J, Brown P, Li J. Radiation-induced cognitive toxicity: pathophysiology and interventions to reduce toxicity in adults. Neuro Oncol 2018; 20: 597–607. doi: https://doi.org/10.1093/neuonc/nox195