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Abstract

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A novel tool to analyse MRI recurrence patterns in glioblastoma

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Running head: Recurrence pattern analysis

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ABSTRACT

At least 10% of glioblastoma relapses occur at distant and even contralateral locations. This disseminated growth limits surgical intervention and contributes to neurological morbidity. Preclinical data pointed towards a role for temozolomide in reducing radiotherapy-induced gliomas cell invasiveness. Our objective was to develop and validate a new analysis tool of magnetic resonance imaging (MRI) data to examine the clinical recurrence pattern of glioblastomas. MRICro software was used to map location and extent of initial preoperative and recurrent tumours on MRI of 63 patients of the EORTC 26981/22981/NCIC CE.3 study into the same stereotaxic space. This allowed us to examine changes of site and distance between the initial and the recurrent tumour on the group level. Thirty of the 63 patients were treated using radiotherapy while the other patients completed a radiotherapy-plus-temozolomide treatment. Baseline characteristics (median age, Karnofsky performance score) and outcome data (progression-free survival, overall survival) of the patients included in this analysis resemble those of the general study cohort. The patient groups did not differ in the promoter methylation status of methyl-guanyl-methly-transferase (MGMT). Overall frequency of distant recurrences was 20%. Analysis of recurrence pattern revealed no difference in the size of the recurrent tumour nor a differential effect on the distance of the recurrences from the preoperative tumour location between the groups. The data show the feasibility of group-wise recurrence pattern analysis. An effect of temozolomide treatment on the recurrence pattern in the EORTC 26981/22981/NCIC CE.3 study could not be demonstrated.

Key words: brain tumor, invasiveness, MRICro, relapse pattern, temozolomide
INTRODUCTION

Patients with malignant glioma face a poor prognosis, with current treatments offering limited benefits. However, recent preclinical and clinical studies have improved our understanding of gliomas. Longitudinal analyses of glioma patients revealed patterns of disease progression that resemble key stages in neurogenesis, implicating that the same signaling pathways that play a critical role in regulation of forebrain neurogenesis may be involved in the control of tumour aggressiveness.¹ Clinically, neurooncologists were limited to the assessment of overall survival or immediate response to therapy ² or to comparisons on a single case basis.³

A major challenge in the management of gliomas is their propensity to infiltrate healthy brain tissue. Infiltrating neoplastic cells escape surgery and develop resistance to radiation and/or chemotherapy. Further, as a consequence to treatment tumour cells may respond with increased migratory and invasive properties. Assessing tumour response based solely on anatomic representation of contrast enhancement on MRI by WHO criteria or even when taking into account the neurological function and performance status of the patient (Macdonald criteria) will miss any of these changes in tumour behavior.²

Novel imaging techniques and algorithms using perfusion MRI and MR spectroscopy allow the identification of areas with enhanced perfusion and metabolism within a morphologically homogeneous tumour.⁴ Diffusion-tensor imaging has helped to more precisely identify the association between tumour and anatomic fibre tracts and to correlate functions to the anatomical tumour location.⁵ However, these previous studies have focused on individual patients or on a single timepoint. Here we conduct a longitudinal study of a group of patients treated within a prospective clinical trial, allowing us also to examine whether the pattern of
recurrence was different after combined radiochemotherapy versus radiotherapy only.

To this aim we introduce a new tool based on MR imaging to analyze the efficacy of brain tumour treatments by measuring the size and location of tumour recurrences and allowing us to understand the typical pattern of tumour development after different treatment modalities. This method allows uncovering common and uncommon anatomical recurrence patterns in relation to the administered treatment. This may lead to better understanding of tumour progression, and provides a radiological tool for studying and quantifying the effect of novel therapeutic interventions, in particular with regards to glioma cell migration and invasiveness.

To validate this concept, we analyzed the MRI data from a randomized (EORTC 26981/22981/NCIC CE.3) trial comparing standard radiotherapy with radiotherapy with concomitant and adjuvant temozolomide chemotherapy in newly diagnosed glioblastoma. This cohort was ideal for validating our tool since there is preclinical evidence that irradiation enhances glioma cell dissemination and that temozolomide has specific anti-invasive properties in addition to its antiproliferative action. By comparing MR data on tumour location obtained prior to any therapy and at recurrence or progression of the tumour we asked (i) whether or not there are more local recurrences in patients with combined modality treatment because TMZ might antagonize the proinvasive properties of therapeutic irradiation, and (ii) whether or not there are more distant recurrences in patients with combined modality treatment because of the prolonged median time to progression in this arm.
MATERIALS AND METHODS

Patients and eligibility

Patients (N=112) from Lausanne, Rotterdam, Toronto, Tübingen, Utrecht, and Vienna were available for screening from the EORTC 26981/22981/NCIC CE.3 trial.6

Analysis of tumour location

All 63 patients had a glioblastoma affecting unilaterally either the right or the left hemisphere. The brain lesions were demonstrated by contrast-enhanced T1-weighted MRI sequences. The MR scans were oriented along the bicommissural plane. Mapping of lesions was performed by two experimenters (A.-C.B. & W.W.) blinded to the clinical features of the patients. The boundary of the tumour location at baseline and at follow-up was delineated using MRICro software ⁹ and mapped on the T1-template MRI from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/cgi/icbm_view) that is distributed with MRICro. The template scan provides various anatomical landmarks for precisely plotting localization of the tumour. Lesions were mapped onto the slices that correspond to MNI z-coordinates -37, -29, -21, -13, -4, 4, 13, 21, 30, 38, 47, 55, 64, and 72 mm by using the identical or the closest matching transversal slices of each individual. Tumours were mapped for each individual; with separate tumour maps generated for both the baseline and recurrence scan. By transforming each individual brain and lesion into the same stereotaxic space, the procedure allowed us to superimpose lesions of different individuals to find regions of mutual involvement and conduct subtraction analysis (Figure). These techniques are well established in stroke research ⁹,¹⁰ and were applied here to tumour lesions for the first time.

The logic of the analysis is straightforward. First, tumour lesions for a patient group at
baseline and lesions for this group at recurrence are defined on the same template image (see above). Next, the lesions at baseline are added together, creating an overlap image showing the regions of mutual involvement. The same is carried out for the lesions at recurrence. Finally, the overlap image of the lesions at recurrence are subtracted from the lesion overlap image at baseline. This method creates an image that shows regions that are commonly damaged in the patient group at recurrence but are typically spared in this group at baseline (coded as positive values), regions specifically damaged at baseline (coded as negative values) and regions that are damaged/spared in equal proportions between the two stages (values near zero). For example, a brain region that is affected by the tumour in all patients at recurrence (100%) and three quarters of patients at baseline (75%) would have a value of positive 25% (100%-75%) in the subtraction plot. The results can be graphically plotted on the same template image; we here used progressively brighter shades from red to white to highlight positive values and progressively brighter shades of blue to illustrate negative values. Regions with a value of zero (either where there were equal numbers of lesions at baseline and recurrence, or where none of the observed patients had a lesion) remain uncolored.

Further, by using MRIcon\textsuperscript{10} tumour volume and the location of the center-of-mass of the tumour for each individual were computed. The center-of-mass is the mean position for all tumour-affected voxels in each of the three spatial dimensions, resulting in a single cartesian coordinate (X,Y,Z position). In the case of a single spherical tumour, the center-of-mass thus will be located right in its center, while with e.g. a U-shaped configuration the center-of-mass may lie outside the tumour itself. Likewise this measure is influenced by satellites of the main tumour mass and thus sensitive to the development of satellites between baseline and recurrent images. Because all lesions were coded in the same stereotaxic space (see above), this
procedure allowed us to calculate the anatomical distance between the initial and the recurrent tumour on the group level.

For an additional case-by-case analysis a distant recurrence was defined as a recurrence with at least 50% of the tumour mass located outside the borders of the contrast enhancing tumour on T1-weighted images plus 2 cm margin.

**Ethics**

All participating centers obtained approval for the conduct of the study and further studies by their institutional review board according to local and national regulations. All patients provided written informed consent.

**Statistics**

A two-tailed t-test was conducted to determine if the two treatments influenced the size of recurrent tumours and/or the distance of the center-of-mass between the baseline and follow-up scan. A sample size of 30 per group would be sufficient to detect a 20% difference for the movement of the center-of-mass with a power of 80% that would be regarded clinically relevant.
RESULTS

Because of different imaging modalities at diagnosis and recurrence or because MRI was missing, 72 patients with localized focal contrast-enhancing disease were included in our analyses, all of whom exhibited primarily unilocular contrast-enhancing tumours. Nine patients had to be excluded as marked mass effect and midline shift did not allow the use of the MNI template for the present anatomical analysis. Thus, sixty-three patients with glioblastoma treated in the radiotherapy group (n=33) or in the radiotherapy-plus-temozolomide group with concomitant and adjuvant temozolomide (n=30) were analyzed. Clinical characteristics are summarized in the Table. Importantly, patients in both groups did not differ with respect to extent of resection or MGMT promoter methylation status. The median time between imaging used for the baseline MRI scanning and first histological diagnosis was 0.2 months in both groups. The median time between baseline MRI and the MRI demonstrating recurrence was 5.4 months in the radiotherapy group and 7.3 months in the radiotherapy-plus-temozolomide group, comparable to the whole study cohort.

Group-wise analysis of recurrence patterns

Group-wise analysis demonstrate wide spreading of tumour location at baseline and at recurrence in the two treatment groups. Tumours affected the temporal, parietal and frontal cortices in the left and right hemisphere without obvious preferred locations of tumour origin or growth. To investigate whether or not there were preferred directions of tumour growth or of tumour reduction after treatment in the radiotherapy versus the radiotherapy-plus-temozolomide group, the tumour locations at baseline were subtracted from the superimposed tumour locations after treatment in each treatment group (for details concerning the subtraction method see 11). For
both treatment groups we found no marked anatomical shift of tumour locations after
treatment. The overlap frequencies after subtraction did not exceed 40% of overlap at
any location indicating that the anatomical differences between baseline and follow-
up measurement were small and not directionally specific.

No change in the size or recurrence pattern of the recurrent tumours

Tumour volumes of the recurrent tumours measured in voxels on a per-patient basis
in both treatment arms were 1.32-fold (+/- 0.36) larger than the original tumours in
the radiotherapy and 1.29-fold (+/- 0.37) larger in the combined modality arm. Hence,
the sizes of the recurrent tumours did not differ according to treatment (p = .81). The
center-of-mass measure allowed us to examine whether treatment influences the
recurrence at distant sites. For each individual, the distance between baseline and
follow-up centroids was computed, providing a measure of whether the tumour
exhibited little movement (e.g. when changes primarily reflect growth or remission of
the initial tumour) or a large shift in location (e.g. when new satellite tumours have
developed). A t-test was conducted to determine if the two treatments influence
movement of the center-of-mass between the baseline and follow-up scan. A two-
tailed t-test revealed no significant difference t(62) = 0.869, p = .387, with a mean
movement of 11.67 mm (+/- 0.42) for the radiotherapy arm and 12.03 mm (+/- 0.39)
for the radiochemotherapy arm.

An additional comparison on a case-by-case basis suggested the same conclusion.
The frequency of distant recurrences was 23% in the radiotherapy and 18% in the
radiochemotherapy group (Chi²=1.18, p=0.056).
DISCUSSION

This study was conducted to implement a novel tool for the analysis of brain tumour studies by analyzing whether the anatomical recurrence pattern of glioblastoma in patients treated with combinational radiochemotherapy with temozolomide and adjuvant temozolomide in the EORTC 26981/22981/NCIC CE.3 study \(^6\) is altered compared to patients treated with radiotherapy alone. Although the analysis was technically feasible, the heterogeneity of imaging modalities (computed tomography and MRI) used in the original study, limited the number of eligible patients for this analysis since it depends on equal imaging modalities for comparison and required MRI scans during the entire follow-up.

Five-10% recurrent or progressive glioblastomas have been reported to be out of the primary tumour field defined by contrast enhancement.\(^{12,13}\) Our data using a pairwise comparison for the individual patient with a center-of-mass approach revealed an approximate incidence of out-of-field recurrences of 20%. This higher number could be due to methodological differences as the determination of distant recurrences in older studies did often not rely on MRI. Preclinical studies \(^8\) had suggested antiinvasive properties of temozolomide. In addition glioma growth patterns, more invasive or more angiogenic may correlate with molecular glioblastoma signatures, e.g. activation of the protein kinase-3/Akt or Notch pathways.\(^1\) However, our clinical data does not support the preclinical hypothesis that the improved outcome with combined temozolomide chemoradiotherapy is due to reduced tumour cell mobility. The pattern of recurrence, although delayed in TMZ treated patients, is comparable, and independent of the analyzed clinical and molecular factors (\textit{MGMT} promoter methylation according to \(^{14}\)). Similarly, one may have expected an increased frequency of distant (out of radiation field) recurrences due to the presumed radiosensitizing effect and the longer survival. Again, this has
not been observed when looking at the site first recurrence or progression. Our findings indicate that yet to be identified molecular and cellular determinants independent of current treatment is the main driver for tumour progression and pattern of recurrence.

New treatment approaches aiming at molecular targets of both tumour and stroma or vasculature (e.g. bevacizumab, cilengitide, enzastaurin or epidermal growth factor receptor inhibitors) may also alter the invasiveness of tumour cells, including the risk of an increasing cell motility during antiangiogenic treatment. Thus, systematic evaluation of recurrence pattern as in our study may be needed to identify changes in tumour behavior, and adequate prospective imaging surveillance should be implemented in future studies. This could also mean to perform the present analysis not only on post-contrast MRI but sequences likely to visualize infiltrative tumor, e.g. T2-weighted or fluid attenuated inversion recovery sequences, as well as metabolic imaging, e.g. aminoacid positron emission tomography.

In summary, the current study used tumour boundaries depicted on MRI sequences that are transposed onto the MNI template and analysed using MRICro. It allows detection of changes of site and distance between the initial and the recurrent tumour on the group level. We did not observe a difference in recurrence pattern between the patients treated with radiochemotherapy versus radiotherapy. This recurrence pattern analysis may aid the development of combinational therapies that counteract the putative pro-invasive adverse effects of therapeutic irradiation or antiangiogenic strategies.
REFERENCES


ACKNOWLEDGEMENTS

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LEGENDS

**Figure:** Overlay tumour location plots of a patient with local versus distant recurrence. Illustrated are the initial tumour locations in three transverse sections at diagnosis (D), at recurrence after treatment (R) and superimposed (S) for a prototypic local recurrence (left panels) as well as a prototypic distant recurrence (right panel). Colours encode additional tumour present at recurrence (yellow), tumour present at diagnosis but not at recurrence (blue) or tumour present at both time points (purple).
**TABLE**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radiotherapy (n=33)</th>
<th>Radiotherapy plus TMZ (n=30)</th>
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<tr>
<td></td>
<td>value (95% CI)</td>
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<tr>
<td>Median age [years]</td>
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<td>56</td>
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<td>Performance Status [n]</td>
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<td>70/80 (12)</td>
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<td></td>
<td>90/100 (20)</td>
<td>90/100 (18)</td>
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<td>Debulking Surgery [n]</td>
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<td>18</td>
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<tr>
<td>MGMT promotor*</td>
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<td>10/13</td>
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<tr>
<td>(methylated/unmethylated)</td>
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<td></td>
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<tr>
<td>PFS [months]</td>
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<td>7.1 (5.8-8.2)</td>
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<tr>
<td>Survival [months]</td>
<td>12 (11.2-13.2)</td>
<td>14.4 (13.4-16.8)</td>
</tr>
</tbody>
</table>

CI denotes confidence interval

*according to ¹³

Baseline characteristics of analysed patients.