When did the glioblastoma start growing, and how much time can be gained from surgical resection? A model based on the pattern of glioblastoma growth in vivo

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ABSTRACT

Objectives: Observational data on the natural course of tumor growth in humans is sparse, and mathematical models of tumor growth are often needed to answer questions related to growth. In this study, a theoretical model of glioblastoma growth was used to investigate two questions often asked by patients and clinicians. First, when did the tumor start growing? Second, how much survival time can be gained from various extents of surgical resection (EOR).

Patients and methods: A gompertzian growth curve was fitted from observational data of pre-treatment growth from 106 glioblastoma patients based on repeated volume segmentations. The curve was used to find the theoretical time since tumor initiation. In addition, as a proxy for the potential survival gain from surgery, the number of days until re-growth would reach the preoperative tumor volume were calculated for different extents of resection.

Results: The estimated age of the glioblastomas at diagnosis was median 330 days, but ranging from 156 days to 776 days, depending on the tumor volume at diagnosis. The median survival gains from 50%, 75%, 90%, 95% and 99% EOR were, 1.4, 2.5, 3.6, 4.3, and 5.6 months, respectively. However, survival benefit from surgery also depends on lesion volume. In theory, 100 days may be gained from 95% EOR in a 10 mL lesion or a 50% EOR in a 90 mL lesion.

Conclusion: In conclusion, we postulate that glioblastoma might originate median 330 days before the diagnosis, assuming the same growth pattern and biology from day one. The theoretical survival benefit of glioblastoma resection is much higher with higher EORs, suggesting that the last milliliters of resection matter the most. Our data also suggest that gain from resection is higher in larger lesions, suggesting that lesion volume may be taken into account in clinical decision-making.

1. Introduction

A common question from patients who are diagnosed with brain tumors is “for how long do you think I have had this tumor?” By raising this question, patients indirectly seek insight into the aggressiveness of the disease and its natural course. For both the patient and the surgeon, a subsequent question may be “what can be gained from surgical resection?” These questions are linked, since if no cure is possible, more time can usually be gained from cytoreductive surgery of slow-growing tumors than from resection of rapid growing cancers. However, these questions are difficult to answer, especially on an individual level.

Although there is level 2b evidence (Oxford Centre for Evidence-based Medicine) supporting that complete radiological resection improves survival of glioblastoma [1], the impact of lower grades of resection on survival is still much debated, and various extent of resection (EOR) thresholds with supposed impact on survival have been reported.
from observational data [1–4]. For later reoperations, it seems like only complete radiological resections have an impact on survival [5]. However, as pointed out earlier [6,7], this “threshold literature” has considerable weaknesses due to methodological limitations. It is by no means random if a surgeon obtains a 50% or a 98% EOR in a given case.

Surgical decision making in patients with glioblastoma can be difficult and is in many cases rather subjective, presumably leading to practice variations. Numerous factors including tumor location, patients’ functional level, co-morbidity, age, and expected EOR may be taken into account. In clinical practice some advocate primary resection in almost all patients, while others advocate resection only where gross total resection or resection above one of the published threshold levels seem realistic. However, the potential survival gain from a 90% EOR in a 150 mL tumor is also presumably different from the same EOR in a 20 mL tumor. Both the natural course if left untreated and the residual tumor volume (RTV) is clearly different in small and large tumors. It has been reported that RTV may be more closely linked to survival than EOR, and one paper reported that a statistical significant survival benefit was seen for RTVs of less than 2 mL in glioblastoma [8]. But does this mean that near total resections of small lesions offer greater benefit than near total resections of large lesions?

Clinically significant thresholds for EOR have so far not been much discussed or explored. How many days extra of survival are gained, and how many should be gained to justify the risk in individual patients? As randomized trials comparing various lower grades of resection (e.g. 70% vs. 80% EOR) are not feasible, we are left with either trusting observational data or constructing models based on knowledge about the natural course of the disease.

In a previous work, we assessed glioblastoma growth dynamics based on repeated pre-treatment imaging in a cohort of 106 untreated glioblastoma patients. We assumed that all glioblastomas follow the same growth pattern. Under this assumption, we found similar mathematical fit for two growth patterns, the linear radial growth, and the gompertzian growth pattern. Of these, we concluded that the most biologically plausible is the gompertzian growth pattern [9]. Following this growth pattern, the growth rate of the tumor is initially exponential before slowly declining as the tumor volume increases. By using observational data to estimate the gompertzian growth parameters, we developed a mean growth curve for glioblastomas. This curve can be used to estimate previous growth of the tumors, and to predict future growth.

In the current study, we used this theoretical model of glioblastoma growth to investigate two aims. First, we examined the theoretical starting point of each tumor. Second, we wanted to investigate the number of survival days gained by different theoretical extents of surgical resection. This could possibly serve as a useful framework for surgical decision making in patients with glioblastoma.

2. Material and methods

2.1. Patient cohort

The selection criteria and demographics of the patient cohort used for this study have previously been reported [9,10]. In brief, patients with confirmed glioblastoma were included if they had at least two preoperative magnetic resonance imaging (MRI) scans with at least a two week interval between the scans. A total of 106 patients were included. Of these, only two had IDH1 immunopositive tumors. The patients underwent gross total resections (n = 30), subtotal resections (n = 59) or biopsy only (n = 17). Eighty-three patients had received Temozolomide chemotherapy in the first six months after surgery, while 96 patients had received radiation therapy. The patients had a median overall survival of 12.6 months (95% CI 10.1–15.4 months) [10]. Median survival in patients undergoing gross total resection was 13.8 months (95% CI 10.5–18.7), while median survival in the biopsy-only group was 5.6 months (95% CI 4.1–11.8).

The study was approved by the Regional Ethics Committee (Central) as part of a larger project (references 2011/974 and 2013/1348) and adhered with the Declaration of Helsinki. Most patients had provided informed consent to be included in a related glioma outcome study (reference 2011/974), and the regional ethics committee waived informed consent for retrospective evaluation of patient data for the remaining patients.

2.2. Magnetic resonance imaging scans

Preoperative MRI scans had been obtained as part of the clinical routine for all patients. The first scan was from the time of diagnosis, while the second scan was obtained shortly before surgery to be used for intraoperative neuronavigation. About 40% of the diagnostic scans had been obtained using 2D sequences with thick slices, while the remaining diagnostic scans, and all preoperative scans had been obtained using 3D sequences with less than 2 mm slice thickness. Further information about scan parameters can be found in a previous publication [9].

2.3. Tumor segmentation

Tumor volumes on diagnostic and preoperative scans were semi-automatically segmented in the software BrainVoyager QX (Brain Innovation, Maastricht, the Netherlands). All segmentations were performed by one of the authors (A.L.S.) and verified by a neuroradiologist (E.M.B.). Measures of segmentation reproducibility can be found in [9]. Both the contrast-enhancing rim and the central non-enhancing tumor were included in the total tumor volume. Median tumor volume was 17.7 mL at the diagnostic scan, and 27.5 mL at the preoperative scan [9].

2.4. Mathematical growth models

In the previous study, the growth of these tumors were fitted to different growth patterns, using maximum likelihood estimations in R version 2.13.1. For this analysis, the tumors were assumed to follow the same growth pattern. Based on mathematical fit and biological knowledge, we concluded that the gompertzian growth model was the most plausible growth pattern for glioblastomas [9]. The gompertzian growth model is given by Eq. (1):

\[ V2 = K * \exp\left[\log\left(\frac{V1}{K}\right) * \exp\left(-\alpha t\right)\right] \]

where \( t \) is time, \( K \) is the upper limit of tumor size, \( \alpha \) is a growth parameter and \( V1 \) is the volume at \( t = 0 \) [11]. Using maximum likelihood estimations, the parameters of this growth model were estimated, as given in Table 1.

2.5. Calculation of tumor age

To calculate the age of the tumors at the time of diagnosis, the following assumptions were made: (1) all tumors exhibit a gompertzian pattern of growth, (2) the starting point of tumor growth was defined as one spherical cell, with a radius of 5 mm, corresponding to a volume of 5.24E-10 mL, (3) the volume of the tumor at the time of diagnosis was defined as the entire tumor depicted on contrast enhanced T1 MRI scans, including central necrosis. The tumor age for each patient in both

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>0.007545</td>
</tr>
<tr>
<td>( K )</td>
<td>158.04</td>
</tr>
</tbody>
</table>
growth patterns were calculated in Microsoft Excel 2016, using Eq. (2):

\[ t = \frac{\log (V2/K) - \log (V1/K)}{-\alpha} \]  

(2)

Summary measures were calculated in IBM SPSS version 24.

2.6. Investigation of different extent of resection thresholds

The same growth model was used to investigate the theoretical impact on patient survival of different extent of resection thresholds. Extent of resection was defined from the volume of the entire tumor on the preoperative MRI scan, and was set to 50%, 75%, 90%, 95%, 99% and 99.9%. The remaining tumor volume was calculated for all patients for each of these thresholds. Then, the estimated gompertzian growth curve was used to estimate the time the tumor would use to reach the preoperative tumor volume again. We assumed again that all tumors followed the same gompertzian growth pattern, and that the growth pattern remained unchanged after surgery. The time interval was calculated in Microsoft Excel 2016 using Eq. (2), with V1 representing tumor volume after surgery, and V2 representing tumor volume before surgery.

3. Results

3.1. Tumor age at diagnosis

The estimated age of the glioblastomas was median 330 days, but ranging from 156 days to 776 days depending on the tumor volume at diagnosis. For tumors with a known volume at diagnosis, the theoretical age of the tumor can be read from the curve in Fig. 1.

3.2. Impact of different extent of resection thresholds

The median survival time gained until the lesion grows back to the preoperative volume are shown for different extents of resection (Table 2). For this analysis, only 105 patients were included, as one tumor was larger than the estimated upper limit of gompertzian growth. The median gain when increasing resection from 75% to 99% was 92 days.

Estimated days gained from various EORs with different preoperative tumor volumes are shown in Fig. 2. As seen, more days are gained from extensive resections of larger lesions. In theory, 100 days may be gained from 95% EOR in a 10 mL lesion or a 50% EOR in a 90 mL lesion.

Fig. 1. Tumor volume at diagnosis with corresponding time since tumor initiation.

<table>
<thead>
<tr>
<th>Extent of resection</th>
<th>Residual tumor volume, mL (median, range)</th>
<th>Days gained (median, range)</th>
<th>Months gained (median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>13.1 (0.5–76.5)</td>
<td>43 (17–413)</td>
<td>1.4 (0.6–13.8)</td>
</tr>
<tr>
<td>75%</td>
<td>6.6 (0.2–38.3)</td>
<td>76 (32–502)</td>
<td>2.5 (1.1–16.7)</td>
</tr>
<tr>
<td>90%</td>
<td>2.6 (0.1–15.3)</td>
<td>109 (50–568)</td>
<td>3.6 (1.7–18.9)</td>
</tr>
<tr>
<td>95%</td>
<td>1.3 (0.0–7.7)</td>
<td>130 (61–602)</td>
<td>4.3 (2.0–20.1)</td>
</tr>
<tr>
<td>99%</td>
<td>0.3 (0.0–1.5)</td>
<td>168 (85–659)</td>
<td>5.6 (2.8–22.0)</td>
</tr>
<tr>
<td>99.9%</td>
<td>0.03 (0.0–0.15)</td>
<td>209 (114–712)</td>
<td>7.0 (3.8–23.7)</td>
</tr>
</tbody>
</table>

4. Discussion

In the present study, based on a theoretical model of glioblastoma growth, we postulate that glioblastomas might originate median 330 days before the diagnosis. Based on the growth dynamics data we constructed a resection grade model that may supplement the extent of resection threshold literature as a frame-work for decision-making in glioblastoma. As seen, the theoretical survival benefit of glioblastoma resection is much higher with higher EORs, suggesting that the last mL of resection matter the most. The survival gain of 99.9% EOR in number of days may be double the gain of 90% EOR. Our data also suggest that gain from resection is higher in larger lesions, suggesting that lesion volume may be taken into account in clinical decision-making.

4.1. Time from tumor initiation

In addition to the apparent biological interest and the curiosity in this matter often reported by patients and their relatives, knowledge about the length of the pre-diagnostic interval in glioblastoma may also have interest in medical legal settings. Examples of such include discussions concerning delayed diagnostics, and questions relating to potential pre-diagnostic carcinogenic exposure.

One previous study has estimated the time from tumor initiation to diagnosis for glioblastomas. This study used a proliferation-invasion growth model to estimate the time from tumor initiation to diagnosis, with a median tumor volume at diagnosis of 14 mL (spherically equivalent to a radius of 1.5 cm). In this model, the theoretical age of a tumor of 14 mL, with a proliferation rate of 15/y [12], would be around 17 months. This is more than the 10.5 months it would take for a tumor to reach 14 mL according to our growth model. Since malignancy of cancer presumably does not decrease over time, the estimated pre-diagnostic interval from mathematical models may be seen as minimum values.

4.2. Clinically relevant EOR thresholds

What is the importance of EOR versus tumor volume for obtaining a meaningful survival benefit from resection? Experimental data on this subject are not expected, so we are left with observational data or models. Attempts at identifying extent of resection thresholds in observational studies may be problematic for several reasons. Observational data are prone to bias due to differences at baseline. Post hoc attempts at adjusting for various skewed base-line factors may be insufficient, as several more unquantifiable confounders may be present. Still, it has been calculated that the EOR thresholds for improving survival may be 78% [4], 98% [3] or 100% [1] in patients with malignant gliomas. The reported thresholds have so far exclusively focused on statistical significance. In this context it should be remembered that any true difference, no matter how small, can be detected statistically given a large enough sample size. Given the same methods, larger studies will therefore most often identify lower EOR thresholds due to the higher statistical power. If the next EOR threshold study has 1000 or...
peripheral tumor cells are also more malignant and in a smaller residual tumor volume. However, some have speculated that milliliters of resection matter more. This increase is strictly an effect of increasing the resection from 75% to 90%. From this one can deduce that the last increasing the resection from 95% to 99%, than from increasing the residual tumor volume, including the central necrosis was used. It should be noted that it is this tumor volume that was fitted by a gompertzian growth pattern, and we make no assumptions about the growth pattern of the non-visible tumor burden, or the number of viable tumor cells. However, without measurements of each tumor from several time points it is not possible to obtain estimates of growth curves for individual tumors. It is thus difficult to know if the difference in growth rates observed is merely random, a result of differences in tumor volume, or if it truly reflects different tumor populations. Mehrara et al. suggested that a significant negative correlation between tumor growth rates and log tumor volume would indicate that “tumors probably follow the same growth curve and the difference in their growth rate is a result of difference in their volume” [18]. However, in their material, the only primary tumors to show such a correlation were benign meningiomas. In heterogeneous tumors such as glioblastomas, it is difficult to imagine that all the variation in growth rates could be explained only by differences in tumor volume. Nevertheless, we think that the current study is a useful theoretical exercise.

From growth rates, we estimated time until the tumor would reach its original tumor volume again after various EORs based on the aforementioned assumptions. However, although mostly local recurrences are seen, glioblastomas do not simply regrow into the surgical resection cavity but instead infiltrate the adjacent brain surrounding it. As it grows towards the same volume as before treatment, new brain regions will be involved. This infiltrative growth pattern will reduce the impact of surgery and is likely to lead to an overestimation of survival benefits from our crude model, but it does not necessarily affect the median survival of 13.8 months, compared to 5.6 months for biopsy-only patients. The theoretical survival time gained by 99.9% resection is therefore in line with the observed difference in survival between the two groups. However, as noted in Section 4.2, there may be considerable differences between patients receiving biopsy only and patients receiving gross total resections in clinical practice. In a population-based study from Spain, patients receiving biopsy only were older, had a worse post-operative KPS, and more often had multiple tumor locations, compared to patients receiving surgical treatment [17]. It is therefore not necessarily reasonable to directly compare the theoretical survival gain of different EOR thresholds, with data from observations studies.

4.6. Validity and limitations of assumptions

Like all model-based studies, the present also relies on several assumptions that may or may not be true.

For the analyses in this study, the volume of the contrast enhancing tumor volume, including the central necrosis was used. It should be noted that it is this tumor volume that was fitted by a gompertzian growth pattern, and we make no assumptions about the growth pattern of the non-visible tumor burden, or the number of viable tumor cells. It is quite clear from the data presented in our previous study that there is a wide variation in observed growth rates among glioblastomas. However, without measurements of each tumor from several time points it is not possible to obtain estimates of growth curves for individual tumors. It is thus difficult to know if the difference in growth rates observed is merely random, a result of differences in tumor volume, or if it truly reflects different tumor populations. Mehrara et al. suggested that a significant negative correlation between tumor growth rates and log tumor volume would indicate that “tumors probably follow the same growth curve and the difference in their growth rate is a result of difference in their volume” [18]. However, in their material, the only primary tumors to show such a correlation were benign meningiomas. In heterogeneous tumors such as glioblastomas, it is difficult to imagine that all the variation in growth rates could be explained only by differences in tumor volume. Nevertheless, we think that the current study is a useful theoretical exercise.

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relative benefit of various extents of resection as much. Also, in subtotal resections, mainly necrotic and less viable tumor cells are removed, perhaps leading to an overestimation of potential benefits of subtotal resections in our model. Further, residual tumor cells in the periphery of the tumor may as mentioned harbor a different biology than the more central tumor cells, and surgery might also alter tumor biology [19], adding to the uncertainty of our model. In addition, most patients are treated with concomitant radio- and chemotherapy, and this treatment could have a different impact depending on the size of the residual tumor [16]. It is likely that there is a synergistic effect between surgery and adjuvant therapy, and this might in turn accentuate the impact of EOR. However, in glioblastoma so-called complete resection is never biological radical since tumor infiltration reaches far beyond radiological tumor borders, and EOR still needs to be balanced against risks. For example, a survival difference was not confirmed in the 5-ALA study despite differences in complete resection and median residual tumor volume between groups, 65% vs. 36% and 0 ml vs. 0.7 ml respectively. However, more patients allocated to 5-ALA had deteriorated early (but not later) after surgery [20].

5. Conclusion

In conclusion, if assuming the same growth pattern and biology from day one, glioblastoma might originate median 330 days before the diagnosis. The theoretical survival benefit of glioblastoma resection is much higher with higher EORs, suggesting that the last milliliters of resection matter the most. Our data also suggest that gain from resection is higher in larger lesions, suggesting that lesion volume may also be taken into account in clinical decision-making.

Conflict of interest

The authors declare that they have no conflict of interest.

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