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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

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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):

$$V2 = K * \exp[\log(V1/K) * \exp(-\alpha t)] \quad (1)$$

where t is time, K is the upper limit of tumor size, α 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 μm, 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 T_1 MRI scans, including central necrosis. The tumor age for each patient in both

Table 1
Parameters used in growth model, K: upper limit of tumor size, α: growth parameter.

Parameter	Value
α	0.007545
K	158.04