Probabilistic MR Atlases of Biological and Interventional Phenotypes in Human Gliomas

Benjamin M Ellingson[1], Timothy F Cloughesy[2], Whitney B Pope[1], Taryar M Zaw[1], Phioanh L Nghiemphu[2], Kourosh M Naeini[1], Robert J Harris[1], and Albert Lai[2]
[1]Radiological Sciences, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, United States, [2]Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

Introduction

Glioblastoma is the most common and most aggressive form of malignant glioma for which there is no cure. Mean survival for patients with glioblastoma is approximately 11 months[1], regardless of treatment. Previous studies support tumor location as playing a role in prognosis[2,3], likely due to the genetic profile of tumor precursor cells and the stage in the development cycle that these cells transform (i.e. the glioma "cell of origin")[4]. However, identifying such glioma "cells of origin" is still a major issue challenging the field of neuro-oncology.[5] Examples of recently discovered "cells of origin" with significant prognostic importance include oligodendrogliomas[6], medulloblastomas[7,8], and ependymomas[9]. We hypothesize "probabilistic atlases" specifying pre-operative tumor locations on MR images and corresponding biological and interventional phenotypes may provide insight into the niche locations of such "cells of origin".

Methods

All patients participating in this study signed institutional review board-approved informed consent to have their information in our neuro-oncology database. A total of $n = 400$ patients with histology confirmed gliomas were enrolled in this retrospective study who met the following criteria: 1) pathology confirmed glioma, 2) pre-surgical T2/FLAIR images and/or post-contrast T1-weighted images, and 3) tissue available for testing biological phenotypes. All images were aligned to the MNI152 brain atlas. Contrast-enhancing regions on T1w images (including regions of central necrosis) and T2/FLAIR hyperintense regios were contoured on all images. Patients were then stratified by 1) Age, 2) O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, 3) isocitrate dehydrogenase 1 (IDH1) mutation status, 4) gene expression profile phenotype, and 5) overall survival independent of treatment. The total number of times a contoured tumor occurred within an image voxel divided by the total number of tumors were calculated for different sets of patient characteristics and biological phenotypes, resulting in probabilistic atlases for each phenotype.

Results

Probabilistic atlases revealed that large proportion of *de novo* glioblastomas contact the neural stem cell rich white matter regions adjacent to the subventricular zone (Fig. 1A,B). When stratified by age, probabilistic atlases suggested tumors tend to occur more posterior with increasing age (data not shown). MGMT promoter methylated tumors occurred in a high frequency within the left temporal lobe (Fig. 1C) compared with MGMT promoter unmethylated tumors (Fig. 1D). IDH1 mutant tumors occurred preferentially within the frontal lobe (Fig. 1F) when compared with IDH1 wild type tumors. Similarly, glioblastomas with the "proneural" gene profile were also more frontal lobe oriented (Fig. 1H) when compared with the more aggressive "mesenchymal" phenotype (Fig. 1G). When stratified by overall survival (OS), patients with right temporal lobe involvement tended to have a shorter survival (Fig. 1I), whereas patients with a longer survival tended to have tumor involvement in the left hemisphere (Fig. 1K).

Discussion

Germinal regions containing neural stem cells, including regions in the periventricular white matter near the subventricular zone (SVZ), have been proposed as a source for human gliomas[10]. Consistent with this hypothesis, our data shows a high frequency of T2/FLAIR hyperintense and contrast-enhancing lesions occur within the periventricular white matter regions adjacent to the SVZ. When examining MGMT promoter methylation, which is a favorable prognostic factor in patients treated with temozolomide (TMZ) and thought to occur as part of a genetic signature that develops from lower-grade gliomas[11] within glial cells predestined for specific locations[12], our results demonstrated a higher frequency of tumor occurrence in the left temporal lobe in tumors with MGMT promoter methylation compared to unmethylated tumors[13]. The atlas has also identified patients with IDH1 mutation as well as MGMT promoter methylation, a link only recently identified[14,15]. IDH1 mutant gliomas have recently been identified as being a genetic subtype of tumors with favorable survival[16]. We recently discovered plausible evidence of a distinct glioma "cell of origin" in IDH1 mutant tumors giving rise to their predominant localization within the frontal lobe regions early in development[14] based on genetic characteristics of IDH1 mutant tumors that appear consistent with oligodendroglioma precursor cells, and gene expression profiles suggestive of association with the "proneural" transcriptional subclass of glioma in The Cancer Genome Atlas (TCGA). Interestingly, a great deal of spatial overlap was observed in the frontal lobe between patients with the "proneural" signature and IDH1 mutation. A high degree of correlation has recently been observed between IDH1 mutant tumors and MGMT promoter methylated tumors[15], IDH1 mutant tumors and the proneural gene expression profile[17], and between IDH1 mutant tumors and 1p/19q co-deletion[18], suggesting these subclassifications may in fact be a distinct tumor phenotype consistent with a single cancer "cell of origin." Our results suggest this single cell of origin is likely located within the frontal lobe. In summary, our data clearly demonstrates the inherent power of large-scale probabilistic atlases in identifying regions of highest tumor incidence, which are useful in identifying niche locations for glioma "cells of origin."

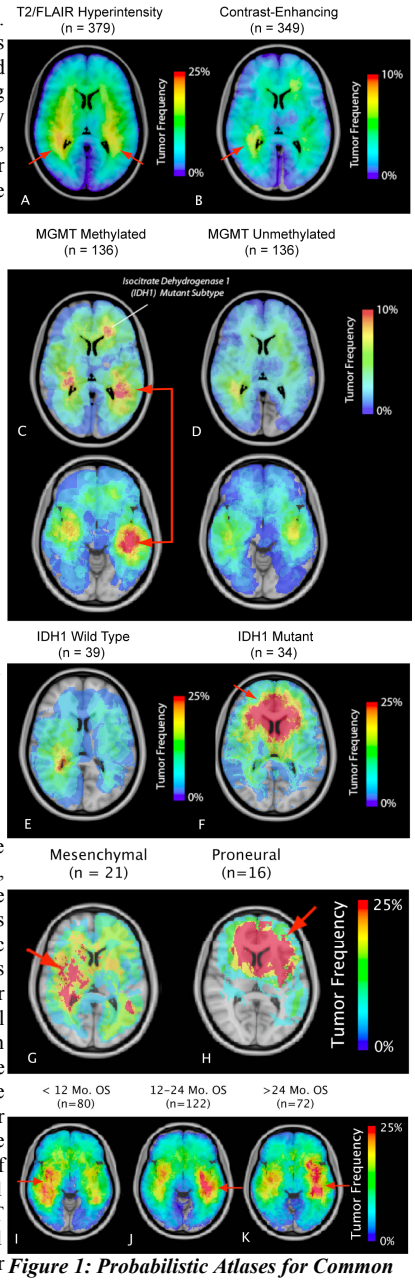

Figure 1: Probabilistic Atlases for Common Glioma Phenotypes *A) T2/FLAIR hyperintense lesions in GBM. B) Contrast-enhancing lesions in GBM. C) MGMT promoter methylated GBMs. D) MGMT promoter unmethylated GBMs.E) IDH1 wild type tumors in gliomas (WHO II-IV). F) IDH1 mutanttumors in gliomas (WHO II-IV). G) "Mesenchymal" gene expression subtype in GBM. H) "Proneural" gene expression subtype in GBM. I) OS < 12 mo.. J) OS 12-24 mo. K) OS > 24 mo.*

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