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Letter to the Editor

The molecular evolution of glioblastoma treated by gross total resection alone

A better understanding of the biological evolution of gliomas and its modulation by therapeutic interventions has become a central topic.[1,2] However, little is known about the natural evolution of glioblastoma treated by surgery alone. Glioblastoma patients are almost always treated with radiotherapy or chemotherapy, and if not, rarely undergo second surgery.

Here, we report a series of 5 glioblastoma patients (pts), who did not undergo treatment beyond surgery, but had second surgery for recurrent disease after a median of 66 days (range, 36–128 days): 128 days (pt 1); 66 days (pt 2); 95 days (pt 3); 36 days (pt 4); 38 days (pt 5). Reasons included patient wish (pts 1, 2, 3) or early progression detected during radiotherapy planning (pts 4, 5). All patients had gross total resection at first surgery followed by another gross total (pts 1, 3, 4) or partial resection (<99%) (pts 2, 5) at recurrence. Median age at diagnosis was 63 years (range, 50–72 y). Three patients were included in a previous study.[2] This study was approved by the Ethics Committee of the Canton of Zurich.

All tumors were histologically classic glioblastomas, isocitrate dehydrogenase (IDH)-wildtype.[3] Fig. 1A shows representative histological features of primary and recurrent tumors, focusing on vital tumor areas with microvascular proliferation. There were no differences in cellularity, predominant cell types, and presence of necrosis or microvascular proliferation. Comparison of molecular profiles by gene panel sequencing[4] revealed few differences between primary and recurrent specimens (Fig. 1B). *MGMT* (O^6-methylguanine DNA methyltransferase) promoter methylation status did not change. DNA methylation profiling revealed IDH-wildtype glioblastoma methylation class family tumors of the receptor tyrosine kinase I (RTK I), RTK II, and mesenchymal (MES) subclasses.[5] Longitudinal methylation profiles were available from 2 patients, indicating a change in DNA methylation subclass in patient 1 from RTK II at initial surgery to RTK I at recurrence, while primary and recurrent tumors of patient 4 were both assigned to RTK II (Fig. 1B). Copy number variations (CNVs) slightly differed between primary and recurrent tumors in two patients with amplification of the cyclin-dependent kinase 4 (*CDK4*) gene at recurrence in patient 1, and homozygous deletion of cyclin-dependent kinase inhibitor 2 (*CDKN2A*) found only in the initial biopsy from patient 3. Finally, differences in single nucleotide variations were seen in the tumor from patient 4, where a mutation in the epidermal growth factor receptor (*EGFR*) gene was detected in the recurrence. In addition, tumor tissue from patient 5 showed a mutation in the neurofibromatosis 1 (*NF1*) gene at diagnosis but not recurrence (Fig. 1B). Except for these 2 cases, molecular profiles remained stable, as also exemplified in the CNV profiles in both the initial tumor and recurrence from patient 4 (Fig. 1C), which are typical for glioblastoma, IDH-wildtype. Representative neuroimaging scans from patient 4 at diagnosis and recurrence are shown in Fig. 1D.

Thus, histopathological features, DNA copy number profiles and driver gene alterations remain remarkably stable from primary to recurrent glioblastoma in patients treated by gross total resection alone. Overall, these findings differ from longitudinal studies of glioblastomas treated with cytotoxic therapy, which frequently reveal more pronounced molecular changes at tumor recurrence, including temozolomide-induced hypermutation in a subset.[1,2,6–8] Thus, therapy likely modulates the molecular evolution in glioblastoma. Admittedly, the time interval between surgeries in our series was short compared with other studies.[1,2,6–8] Still, a better understanding of molecular changes in response to specific treatments, including radiotherapy, alkylating chemotherapy and immunotherapy may aid clinical decision making by refining inclusion criteria for clinical trials at recurrence.

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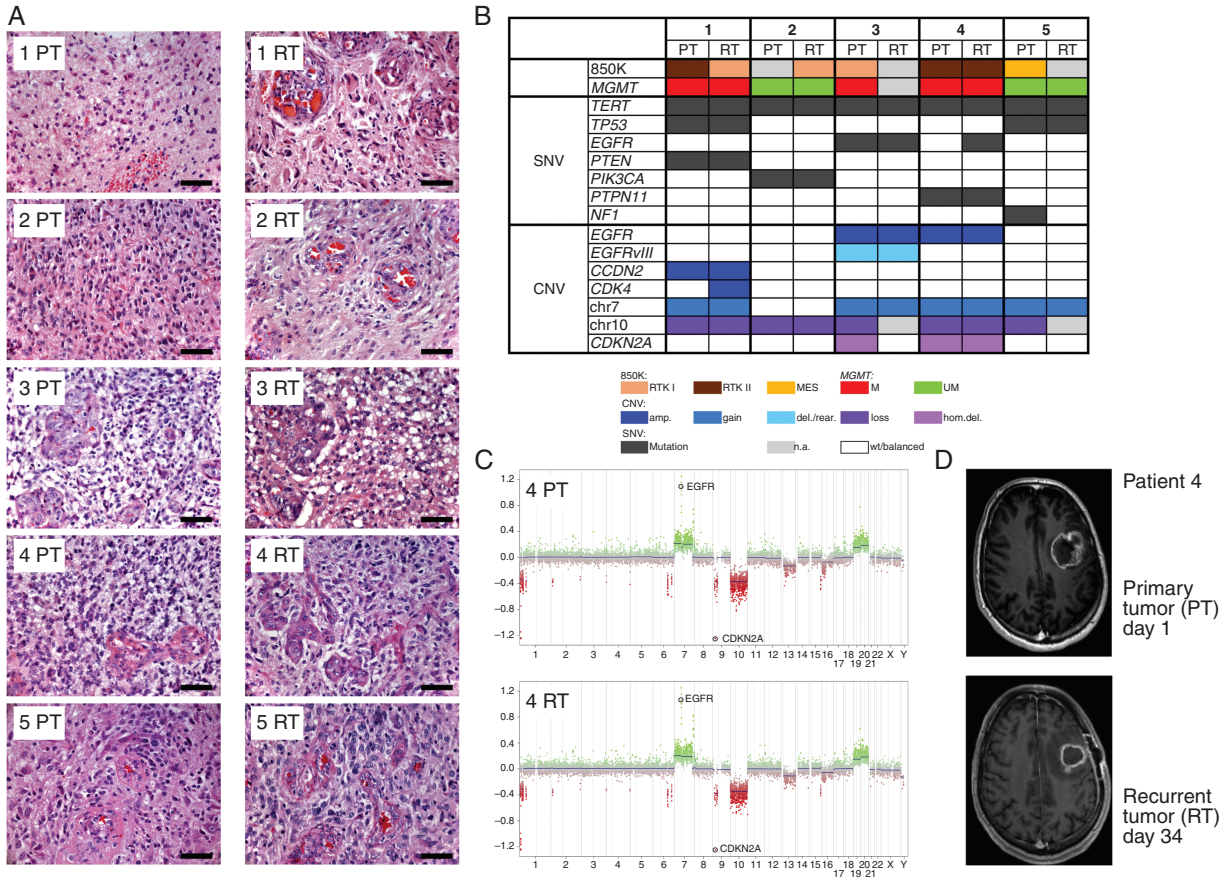

Fig. 1 Histopathological characteristics, DNA methylation subclasses and mutational profiles, and exemplary neuroimaging features of primary (PT) and recurrent tumors (RT) of the 5 glioblastoma patients (1–5). (A) Representative histological features in vital tumor areas of the 5 pairs of PT (left side) and RT (right side); scale bars, 50 µm. (B) Graphic representation of the results obtained by DNA methylation profiling and next generation sequencing of a glioma-associated gene panel. Assignments to molecular subgroups as well as absence or presence of the listed aberrations are indicated in color codes as illustrated below the figure. (C) Example of copy number plots calculated from DNA methylation array data of PT and RT of patient 4; results for chromosome 1–22, X and Y are shown with the p-arm (left) and the q-arm (right) separated by dotted lines; gains/amplifications represent positive (green), losses negative (red) deviations from the baseline. (D) Axial T1-weighted gadolinium- enhanced MRI scans of patient 4 with newly diagnosed tumor (day 1) and recurrent tumor (day 34) are shown; surgery was performed at day 2 and day 38; gross total resection after first surgery was confirmed with contrast-enhanced CT. Abbreviations: amp, amplification; *CCDN2*, cyclin D2; chr, chromosome; del. rear., deletion rearrangement; *EGFRvIII*, variant III of epidermal growth factor receptor (EGFR); hom.del., homozygous deletion; M, methylated; n.a., not available; *PIK3CA*, phosphoinositide-3-kinase; *PTEN*, phosphatase and tensin homolog; *PTPN11*, protein tyrosine phosphatase non-receptor type 11; SNV, single nucleotide variation; *TERT*, telomerase reverse transcriptase; *TP53*, tumor protein 53; UM, unmethylated; wt, wildtype.

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References

1. Barthel FP, Johnson KC, Varn FS, et al; GLASS Consortium. Longitudinal molecular trajectories of diffuse glioma in adults. *Nature*. 2019;576(7785):112–120.

2. Korber V, Yang J, Barah P, et al. Evolutionary trajectories of IDH(WT) glioblastomas reveal a common path of early tumorigenesis instigated years ahead of initial diagnosis. *Cancer Cell*. 2019;35(4):692–704 e612.
3. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803–820.
4. Zacher A, Kaulich K, Stepanow S, et al. Molecular diagnostics of gliomas using next generation sequencing of a glioma-tailored gene panel. *Brain Pathol*. 2017;27(2):146–159.
5. Capper D, Jones DTW, Sill M, et al. DNA methylation-based classification of central nervous system tumours. *Nature*. 2018;555(7697):469–474.
6. Draaisma K, Chatzipli A, Taphoorn M, et al. Molecular evolution of IDH wild-type glioblastomas treated with standard of care affects survival and design of precision medicine trials: a report from the EORTC 1542 study. *J Clin Oncol*. 2020;38(1):81–99.
7. Kim J, Lee IH, Cho HJ, et al. Spatiotemporal evolution of the primary glioblastoma genome. *Cancer Cell*. 2015;28(3):318–328.
8. Wang J, Cazzato E, Ladewig E, et al. Clonal evolution of glioblastoma under therapy. *Nat Genet*. 2016;48(7):768–776.