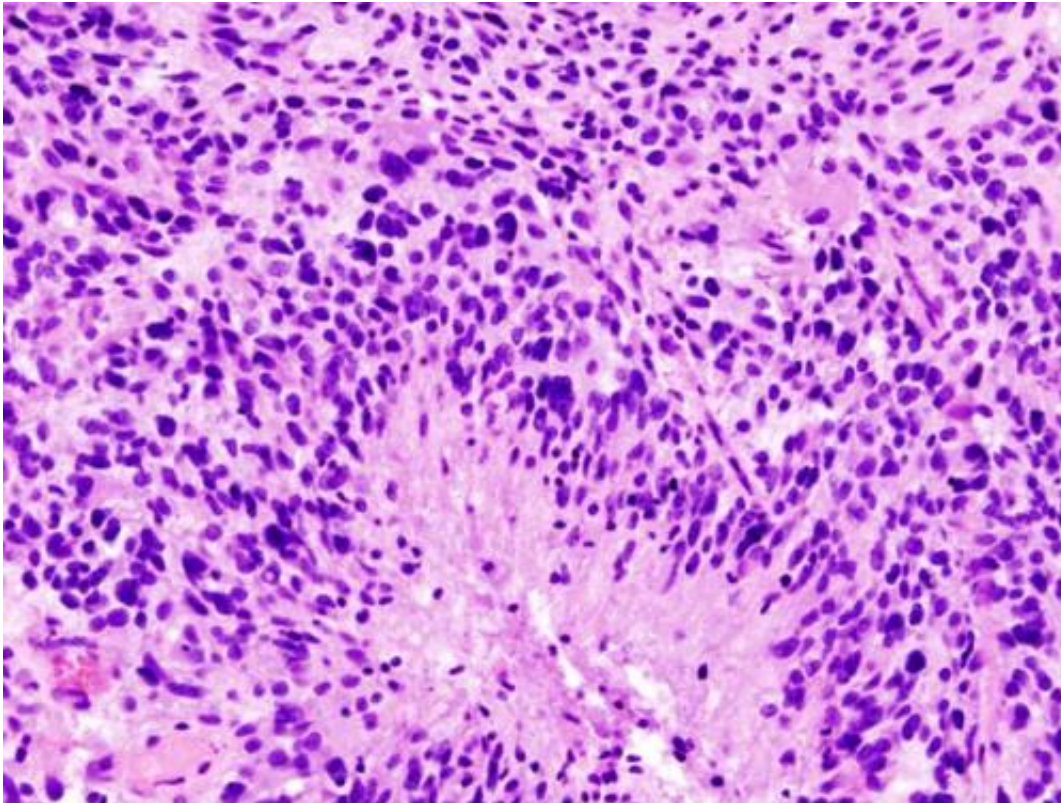


The evolution of brain tumors

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Glioblastoma (histology slide). Credit: Wikipedia/CC BY-SA 3.0

Scientists from the German Cancer Research Center found in a recent study that only three different genetic alterations drive the early development of malignant glioblastomas. At least one of these three cancer drivers was present in all tumors investigated. However, it is the activation of telomerase that leads to rapid growth. The tumors develop for up to seven years before they become noticeable as symptoms and

are diagnosed. However, in contrast to their early development, glioblastomas, which return after therapy, share virtually no concurrent genetic alterations.

Glioblastomas are the most common malignant brain tumors in adults. Since they invade diffusely into healthy brain tissue, surgeons rarely succeed in completely removing the [tumor](#). Therefore, glioblastomas often recur very quickly despite the radiation and chemotherapy following surgery and are then considered incurable according to current knowledge.

"There was a theory that certain [mutations](#) might enable [glioblastoma cells](#) to survive standard radiochemotherapy and then grow into resistant subclones of the tumor. Our question was: Does the therapy exert a selection pressure on the [tumor cells](#)?" said Peter Lichter from the German Cancer Research Center (DKFZ) explaining his current research project. For the development of new drugs that are also effective against relapsed tumors, it is crucial to identify genetic traits that enable [cancer cells](#) to evade therapy.

In order to answer this question, Lichter and systems biologist Thomas Hofer from the DKFZ investigated glioblastoma tissue samples from a total of 50 patients in which they were able to directly compare material from the primary tumor and recurrence. Based on a careful analysis of the tumor genome, the researchers were able to develop a mathematical model of tumor development. They used mutation rates and estimates of tumor cell count. "We simulated the evolutionary pathways of glioblastoma [cells](#) and the influence of their gene mutations during [tumor growth](#) on the computer," said Hofer describing the procedure.

The surprising results: At the time of diagnosis, a [glioblastoma](#) had already developed over a very long period of time, the researchers calculated up to seven years. "This is hardly conceivable in view of the

extremely rapid growth of glioblastomas," said Verena Koerber, the first author of the current publication. "However, we can explain this by the fact that many cancer cells die at the beginning, only at a certain moment does the rapid growth in size start.

The researchers have also discovered this decisive moment: During their [early development](#), all glioblastomas studied showed at least one of three characteristic genetic alterations (gain of chromosome 7, loss of chromosome 9p and 10). These chromosome losses or gains are associated with known, specific "driver mutations" that promote the development of cancer.

However the glioblastomas only start with their rapid growth and increase in size when an additional mutation permanently activates one of the promoters for the telomerase. The enzyme telomerase ensures that the cancer cells can now divide infinitely and do not reach their natural "limit" and die after a certain number of cell divisions. In healthy cells, the telomerase gene is therefore usually not active. During their exponential growth, numerous other mutations accumulate in the cancer cells.

In contrast to the common path of the early developing glioblastomas, the recurrent tumors did not share any characteristically corresponding mutations. They can develop from cancer cells with a variety of different mutation patterns. "This suggests that the current standard therapy does not exert any noticeable selective pressure on the [cancer](#) cells and therefore does not promote the development of resistant subclones. This shows that we basically need new forms of treatment in order to effectively treat glioblastomas," said Peter Lichter summarizing the current results.

More information: Evolutionary trajectories of IDH-wildtype glioblastomas reveal a common path of early tumorigenesis instigated

years ahead of initial diagnosis. *Cancer Cell* 2019, [DOI: 10.1016/j.ccell.2019.02.007](https://doi.org/10.1016/j.ccell.2019.02.007)

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