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Letter to the Editor

Long-term survivors of glioblastoma are a unique group of patients lacking universal characteristic features

Recent reports edged closer to the secret of long-term survival in patients with glioblastoma (GBM) by analyzing comprehensive genomic and epigenomic characteristics.[1–3] It is generally accepted that there is a subset of GBM patients who live longer than 3 years and are classified as long-term survivors (LTS), and 5% to 13% survive an exceptional 5 years.[3,4] There have been many efforts to define this unusual population, combining not only various clinical and molecular features but also recent genetic and epigenetic profiles. However, no single biomarker or subclinical signature failed to predict GBM LTS perfectly, including classic genetic prognostic factors such as O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase (IDH) mutation.[5–7]

Among 600 patients with newly diagnosed GBM at Seoul National University Hospital between 2005 and 2015, 108 patients (18.0%) and 49 patients (8.2%) survived 3 and 5 years or more, respectively. The histological diagnoses were reviewed and confirmed according to the WHO 2016 classification when IDH information was available. Key information on the 108 GBM LTS is highlighted in Figure 1. Comparing GBM LTS with the other 492 patients who survived less than 3 years (GBM STS), GBM LTS had a significantly younger average age at diagnosis (mean 46.8 ± 13.8 vs 55.4 ± 13.4 years, $P < .001$). However, there was a broad range in age (from 20 to 81 y) among the GBM LTS patients. Similarly, there was a higher complete resection rate (71.3% vs 45.5%) and a lower biopsy rate (5.6% vs 28.2%) in the GBM LTS group compared with the GBM STS group. However, as many as 31 patients with incomplete resection or biopsy lived longer than 3 years, including two patients with biopsy who survived longer than 5 years. No differences in treatment protocol ($P = .284$) or sex distribution ($P = .161$) were identified between the GBM LTS and GBM STS groups.

The classic prognostic factors, such as *MGMT* promoter methylation and *IDH* mutation, were found to be significantly more prevalent in the GBM LTS group than in the GBM STS group (*MGMT* promoter methylation rate: 66.7% vs 38.2% [$P < .001$] and *IDH1/2* mutation rate: 15.7% vs 6.9% [$P = .001$]). However, there were still 18 GBM LTS patients who harbored both an unmethylated *MGMT* promoter and wild-type *IDH*. No difference in the distribution of *EGFR* amplification between the GBM LTS and STS groups was observed ($P = .288$).

Considering all these data profiles of GBM LTS and the pooled evidence from the literature, it is still difficult to simply define this extremely favorable prognostic group. The consideration of *MGMT* promoter methylation and *IDH* mutation in studying LTS GBM may have a limited role because those prognostic factors are not fully responsible for predicting this unique prognosis. Identification of the characteristics common to all GBM LTS is a great help to overcome this devastating disease. However, there is no universal characteristic feature that can explain the entire group of GBM LTS as of now. A new approach that has not been tried to investigate the topic is expected to unveil the secret explaining the unique group of GBM LTS.

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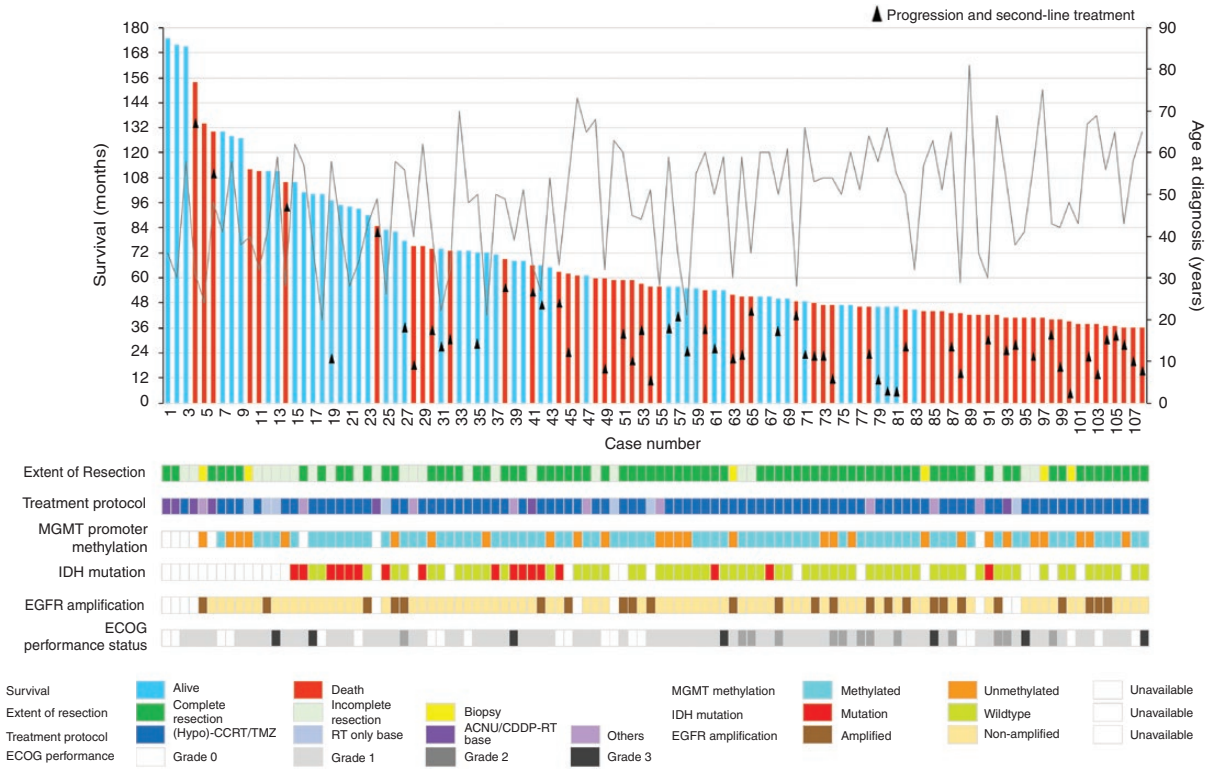

Figure 1. The clinical and genetic information of 108 long-term survivor glioblastoma patients who lived 3 years or more after initial diagnosis. Bars and lines indicate survival period and age at initial diagnosis, respectively. Status of variables is arrayed matching case by case below the graph. Postsurgical performance status is expressed in Eastern Cooperative Oncology Group (ECOG) Performance Status. Scale (https://ecog-acrin.org/resources/ecog-performance-status). Disease progression periods are marked by a filled triangle if they are available. Cases without filled triangle have no objective evidence of disease progression.