Glioblastoma: Is Survival Possible?

By
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Glioblastoma multiforme are among the most deadly neoplasms and continue to be regarded as incurable and universally fatal. This reputation seems well deserved, at least as based on population-based outcome data over a twenty-year period from the Alberta Brain Tumor registry. Of 689 glioblastoma patients, only 2% survived three years or longer, and of these 15 patients only 4 were still alive at the time of the report (1).

Case series reports from major individual treatment centers are somewhat more positive but still dismal, Of a series of 449 patients treated over a 16-year period at UCSF, 22 (5%) survived five years or longer (2). Of these, ten were still alive at the time of last follow-up, with six showing no sign of progression after initial therapy.

A case series of 213 GBM patients from George Washington University and surrounding treatment centers (3) reported that 33 (15%) survived three years or longer, but survival at the 5-year mark was not reported.

A series of 766 GBM cases receiving treatment at Duke University included 32 patients (4%) who survived five years or longer, but this number was reduced to 17 patients upon further histological review (4). The most frequent basis of the change in diagnosis was an initial diagnosis of a lower-grade glioma that transformed into GBM. Survival time after the detection of the change to higher-grade tumor was not reported.

A case series of 352 GBM patients from the Memorial Sloan-Kettering database included 39 patients (11%) who survived three or more years (5). Median survival for this selected group was 9.15 years, and 23 patients were still alive at last follow-up. Twelve patients remained in continuous remission after a median follow-up of over five years.

Given that the great majority of patients now receive the "Stupp protocol" (radiation + low-dose temozolomide, followed by monthly temozolomide) as initial treatment, the most relevant data for the current patient generation are the long-term survival outcomes from the landmark European clinical trial that resulted in temozolomide's FDA approval (6). Survival data for up to five years are now available (7). Of the 254 patients that received the now standard combined protocol, 16% were alive after three years, and 9.8% were still alive after five years.

The most recent follow-up report also included a survival analysis with respect to various prognostic variables. Five-year survival of patients under the age of 50 was 17%, compared to 6.4% for those over the age of 50. For patients with a methylated MGMT promoter gene, 5-year survival was 13.8%, compared to 8.3% for those with an unmethylated gene.

Although 5-year survival rate was approximately double that of previous patient series, Stupp et al. question whether a cure is really possible, because the survival curve showed no sign of a plateau, which suggests that the asymptotic level of survival will eventually reach zero.

A somewhat different perspective is provided by a Taiwanese study that examined the conditional probabilities of surviving an additional year given different lengths of prior survival time (8). The probabilities of surviving an additional year after 1, 2, 3, 4 and 5 years of prior survival were .65, .59, .86, .80,and .75. The increase in conditional survival rate after three years suggests that the probability of recurrence decreases the longer the survival. However, this patient series included only 69 patients. It is also important to recognize that a probability of .85 of surviving the next year implies that there is a .15 probability of death in the next year, which, when iterated over succeeding years, produces a cumulative probability of death that is increasingly high.

An additional conditional probability analysis of survival from a collection of six different clinical trials at UCSF (9) reported that the percentages of patients surviving one additional year after 1, 2, 3, 4, and 5 years of prior survival were 35, 49, 69, and 93%, respectively. The authors also noted that the data were better described by a Weibull probability function than by an exponential function.

The largest conditional probability analysis comes from the SEER database (10), which includes 28% of the population of the United States. Included were patients with a glioblastoma diagnosis from the years 1998 to 2008, a total of over 10,000 patients. The probabilities of surviving an additional year were 53% from the time of diagnosis, 38% after one year of prior survival, 55% after two years, 70% after three years, 82% after four years, and 78% after five years. They also noted that after five years of survival, the probability of surviving an additional five years was 45%. The percentage of patients surviving 5 years was 6.2%, which implies that the percentage surviving 10 years was approximately 3%.

A second very large data based came from all patients diagnosed with high-grade gliomas (Grades III and IV) from 1990 to 2000 in Los Angles County, California. (11). Collapsed over both tumor grades, median survival was only 6.6 months, and the probability of surviving at least one year was 31%, indicating much worse outcomes than those obtained when patients have participated in clinical trials. For GBM patients alone, the four-year survival rate was 3%. However, when a conditional probability analysis was performed, the probability of surviving one additional year (for GBM patients only) was .29, .55, .71, and .85, after one, two, three, four, and five years, respectively.

Of substantial interest from the conditional probability analysis is that variables that predict unconditional survival (tumor grade, patient age) lost their prognostic value after 3-4 years of prior survival.

The implication of these survival analyses is that a small percentage of patients survive at least 5-10 years, raising the possibility that at least some patients are genuinely cured. But

the further implication is that there continues to be a substantial rate of death even after extended survival, although the death rate substantially decreases the longer the prior survival.

Evidence that relapses frequently occur even for patients with extended long-term survival comes from a recent long-term follow-up of ten patients who had survived for five years at the time of their selection for further study (12). Survival analysis after a mean follow-up of 140 months revealed that only five of the original ten were alive, and one of these had a recurrence at 126 months and was still receiving treatment. Another had a relapse after 17 months and again after 28 months, but was still alive after 102 months. Two other patients had relapses after 118, and 124 months and were deceased. Of the three remaining patients with no relapse, ongoing survival time was 145, 134, and 123 months.

Although the late relapses seen in this study are consistent with the frequent statement that GBM is invariably fatal, the three patients with recurrence-free survival longer than ten years offer the possibility that at least a few patients are indeed true long-term survivors.

It is also important to recognize the possibility that some of the late "relapses" may not be recurrences of the original tumor but new disease induced by the radiation treatment. Experimental work with animal models supports the reality of this risk (13). Three-year-old normal rhesus monkeys were given whole brain radiation using a protocol similar to the common human radiation protocol and then followed for 2-9 years thereafter. A startling 82% of the monkeys developed glioblastoma tumors during that follow-up period.

Of major interest is whether long-term survival is due to the particular characteristics of the patients themselves or of the treatments they have received. The great majority of long-term survivors have had some form of systemic chemotherapy, although this may simply reflect the fact that chemotherapy has been part of the standard treatment. In fact

there is one report of three long-term survivors (11, 16, and 18 years) of 71 patients receiving only brachytherapy (14).

Patient characteristics most common among long-term survivors are young age at the time of diagnosis, higher Karnosky performance status, methylation of the MGMT promoter gene, and a complete surgical resection. However, there are long-term survivors who are exceptions to each of these generalizations. Several other characteristics have also occasionally been reported, including female gender, the presence of giant cell histology (15), and lower rates of mutations of p53 and PTEN (16).

The German Glioma Network has been reported a molecular analysis of patients from a very large database (301 patients) (17). Multivariate analysis showed younger age, higher KPS scores, and use of temozolomide chemotherapy predicted longer survival, but the only molecular markers predictive of LTS were MGMT promoter methylation and mutations of the gene for isocitrate dehydrogenase (IDH). There were no significant differences for p53 mutations, EGFR, and allelic losses on chromosome arms 1p, 9p, 10q, and 19q.

A second extensive genomic analysis focused on the differences between tumors of long-term survivors (LTS) (greater than 3 years) vs. those of short-term survivors (less than 1.5 years) matched in age to the LTS patients (18). Predictive of short-term survival was loss of 6q and 10q, and gains of 19p, 19q and 20q. Combinations involving two or more of these mutations were more strongly predictive of short survival than were any one mutation in isolation. Also, loss of 19q occurred only in the long-term survivors.

The most extensive report of the characteristics of long-term survivors comes from the German Glioma Network, which compared 69 patients who survived more than 36 months with 257 patients who survived less than 36 months (19). LTS patients were younger but not significantly different with respect to KPS. They were also only marginally more likely to have complete resection at the time of initial surgery, but were significantly more likely to have two or more surgical interventions. The analysis of

molecular markers showed that LTS patients were significantly more likely to have methylation of the MGMT promoter-gene, but less likely to have EGFR amplification. The difference in p53 mutations was not significant. The most consistent variable associated with LTS was IDH mutations, as 33% of LTS patients had the mutation, compared to only 4% for control patients. Presence of MGMT methylation and IDH mutations were highly correlated but still partially dissociable. Specifically, patients with IDH mutations but without MGMT methylation had the same prognosis as patients without IDH mutations. It is also noteworthy that there were a significant number of long-term survivors who had no IDH mutations.

Two case histories with very long survival have recently been reported. The first was a male patient diagnosed at the age of 25 with a tumor in the right frontal lobe, for which he received a subtotal resection (20). Following his participation in an 8-in-1 experimental chemotherapy protocol, he received standard focal fractionated radiotherapy with a 2-cm margin. The tumor recurred two years later, at which time he received a near total resection and the placement of gliadel wafers in the tumor bed. His condition remained stable for 18 years, at which time he suffered another recurrence involving two separate tumor masses, one of which was treated with a third resection and the other with stereotactic radiosurgery. He also received temozolomide chemotherapy. Soon after the 20-year anniversary of his diagnosis he suffered a multifocal recurrence that was rapidly progressive.

Molecular analysis of the tumor tissue taken at the time of the third surgery revealed that it was p53 positive, PTEN positive, and MGMT methylated. EGFR and protein kinase AKT were negative.

The second recent report (21) involved a male patient diagnosed at age 24 with an occipital lobe tumor, who received a gross total resection and then received localized radiation and chemotherapy with nimustine and interferon-beta. Surgery was repeated three months later to treat a local recurrence, and the patient remained tumor free for 19 years, at which time he developed a cavernous angioma, which upon removal was found

to be free of glioblastoma cells or radionecrosis. The patient remains tumor free two years later, 21 years after his initial diagnosis. Analysis of the initial tumor tissue showed it to be MGMT methylated.

The same report also described the case history of a third long-term survivor reported in a Turkish journal (22). This patient was diagnosed at age 16 with a tumor in his right frontal lobe. After a second surgery for an early recurrence, he was still alive at the time of the report twenty years after diagnosis. His tumor also was found to be MGMT methylated.

It is noteworthy but perhaps fortuitous that all three of these long-term survivors had early recurrences, for which they received a second resection, and then long periods of tumor remission.

The fact that some GBM patients live 10-20+ years after diagnosis implies that posing the issue in terms of whether the disease can be cured is not the right question. Everyone eventually dies, and it is likely that anyone who has received the surgery, radiation, and chemotherapy associated with a "terminal" cancer diagnosis will have a shortened life span quite apart from dying directly from the disease. Certainly late recurrences do happen. But a meaningful number of people also live a large chunk of their life expectancy after receiving a GBM diagnosis. It is an awful disease, but one that has responded to treatment in a significant number of patients. As of now, we have only a minimal basis for predicting which patients will receive a significant benefit of treatment, and even less basis for choosing treatments that will be most successful.

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