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Survival and low grade glioma: the emergence of genetic information

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Abstract

Significant gaps exist in our understanding of the causes and clinical management of glioma. One of the biggest gaps is how best to manage low grade (World Health Organization (WHO) grade II) glioma patients. Low grade glioma is a uniformly fatal disease of young adults (mean age 41 years) with survival averaging approximately 7 years. Although low grade glioma patients have better survival than patients with high grade (WHO grade III/IV) glioma, all low grade gliomas eventually progress to high grade glioma and death. Data from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute suggest that for the majority of low grade glioma patients, overall survival has not significantly improved over the past three decades, highlighting the need for intensified study of this tumor. Newly published research suggests that historically utilized clinical variables are not sufficient (and are likely inferior) prognostic and predictive indicators relative to information provided by recently discovered tumor markers (e.g..1p/19q deletion and IDH1/2 mutation status), tumor expression profiles (e.g. the Proneural Profile) and/or constitutive genotype (e.g. rs55705857 on 8q24.21). Discovery of such tumor and constitutive variation may identify variables needed to improve randomization in clinical trials as well as patients more sensitive to current treatments and targets for improved treatment in the future. This manuscript reports on survival trends for patients diagnosed with low

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grade glioma within the United States from 1973–2011 and reviews the emerging role of tumor and constitutive genetics in refining risk stratification, defining targeted therapy, and improving survival for this group of relatively young patients.

Keywords

glioma; low grade; survival; SEER; epidemiology; genes; GWAS; treatment

Introduction

Gliomas are classified as grades I to IV based on histology and clinical criteria.[45] Grade I tumors are generally benign and frequently curable with complete surgical resection, occur primarily in children and are believed to represent an entity separate from grade II-IV (seen primarily in adults). Adult grade II tumors (Low Grade Gliomas (LGG) include: 1) astrocytomas, 2) oligo-astrocytomas or mixed gliomas, and 3) oligodendrogliomas.[45] Astrocytomas and oligodendrogliomas consist of astrocytes or oligodendrocytes, respectively, while mixed gliomas contain a mixture of the two cell types. Essentially all Grade II lesions eventually progress to High Grade Glioma (grade III/IV or HGG).Grade IV tumors (aka glioblastoma (GBM)) that arise from LGG are termed “secondary GBM” to differentiate them from “primary” or “de-novo” GBM as the pathway leading to these two GBM types differs by a number of genetic abnormalities and clinical characteristics.[77] Most patients initially receive surgical resection/biopsy at time of diagnosis and then radiation therapy (XRT) and/or the single chemotherapeutic agent temozolamide (TMZ) at some point. However, many of these relatively uniformly treated patients advance more quickly than others to recurrence and death. Variation in the few known prognostic factors (most of which are themselves highly correlated), e.g. age, performance status, tumor size/location, extent of surgical resection, and histological subtype does not adequately explain the progression and survival differences in these patients. To date, the detection of treatment effect is limited. A surgical gross total resection appears associated with better survival for patients able to undergo such a procedure but has never been and is unlikely to be assessed in randomized clinical trials (RCT);[13,32,61] the improvement may be due to biases from differential tumor aggressiveness in non-resectable versus resectable portions of the brain and from clinician predictions of the patients likely to benefit most from resection. Randomized clinical trials suggest radiation therapy prolongs time to recurrence but not overall survival[3840,66,75] and may be associated with reduction in quality of life and cognition,[1,17,40,47] while the impact of the primary single chemotherapeutic agent temozolamide (TMZ) now used to treat LGG has shown benefit primarily in RCT of HGG but is not fully assessed in LGG.[4,6,39,52,56,73] For LGG no RCT have compared TMZ (which is associated with blood disorders and leukemia)[44] to other agents (trials are ongoing that compare TMZ to radiation therapy (XRT) as well as the combination of TMZ/XRT to XRT). A recently updated trial (RTOG 9802) comparing radiation therapy with or without procarbazine, CCNU and vincristine (PCV) reports improved progression-free as well as overall survival with addition of PCV, but ironically is infrequently used over the past decade to treat LGG.[7] No comprehensive clinical prognostic or predictive classification for LGG exists that combines information on histology, tumor markers and constitutive/tumor

genotype, and surgical treatment relative to outcome leading to confusion over how to best manage these patients. The goal of this review is to examine population-based survival rates for LGG within the United States by standard patient demographics and initial treatment and to then review emerging data on patient and tumor genotype relative to survival after a diagnosis of low grade glioma.

Methods

We examine data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute from 1973–2011[65] that includes 2825 patients diagnosed between the ages of 20–79 years with a histologically confirmed grade II supratentorial (Topography codes C71.0–71.4) glioma (Morphology codes: mixed glioma (ICD-0 9382), oligodendroglioma (ICD-0 9450) or astrocytoma (ICD-0 9400)). In an effort to examine a homogenous study population and to reduce the probability of including individuals with metastatic lesions, individuals with more than one primary cancer (i.e. a glioma and a cancer of another site) were excluded from these analyses, as were patients diagnosed at death (autopsy only).

In addition to topography and morphology, information on sex, race, age and year of diagnosis were available as was information regarding whether the patient had received surgical resection (yes/no), radiation therapy (yes/no), and chemotherapy (yes/no) as part of the first course of treatment. Treatment parameters after the first course are not available in these data nor are specifics of chemotherapy regimes. Race was defined according to SEER categories of white, black, and other due to small sample sizes in the non-black, non-white categories. Age was utilized as a continuous variable in the proportional hazards model. The primary outcome variable was time to death as measured in years.

Comparison of cases by descriptor variables was done using a chi-square or Fisher's exact test for discrete variables and a t-test for continuous variables. Estimates of survival probabilities (with 95% confidence intervals) were calculated using Kaplan-Meier product limit methodology and compared using a Wilcoxon log rank test. Hazard rates were computed using a Cox proportional hazards model.[19] All analyses were completed using the SAS statistical software package version 9.13.[63]

Results

Descriptive statistics for the sample are presented in Table 1. The majority (51.6%) of the cases are classified as astrocytoma with 33.5% and 14.9% classified as oligodendroglioma and mixed glioma, respectively. The reported distributions of these three tumor types has changed significantly over time ($p < 0.001$) with fewer cases being classified as astrocytoma and more being identified as either oligodendroglioma or mixed gliomas.[23] The majority of patients were male (58.9%) and white (89.1%). The mean age at diagnosis is 41.4 (SD 15.6) years and does not vary by sex, race or year of diagnosis. Persons with mixed glioma were diagnosed on average two years earlier than patients with other pathology. Treatment data, which includes only the first course, show the majority of LGG patients received only surgical resection at first course while only 3.7% received chemotherapy as part of the initial

treatment with use of radiation at first course declining over time. Initial treatment did not vary by sex or race but did differ by age with younger patients more likely to undergo surgical resection. Treatment differed by location of the lesion (which did not vary by sex or race). As would be expected, individuals with parietal lobe lesions were more likely to receive radiation therapy and less likely to receive surgical resection than were patients with lesions located elsewhere in the brain.

The median survival for patients with astrocytoma, mixed glioma, and oligodendroglioma was 5.2, 5.6, and 7.2 years, respectively, with younger age at onset associated with an improved prognosis and use of radiation therapy at initial treatment associated with a less favorable prognosis across all three histological subtypes. Approximately 20% of patients survived for at least two decades. Female sex was associated with improved prognosis for patients with astrocytoma but not for persons diagnosed with mixed glioma or oligodendroglioma. After controlling for race (white versus non-white), age at onset, gender and initial course of treatment (surgery yes/no, radiation yes/no) there was no improvement in overall survival over time (defined as year of diagnosis before year 2000 versus diagnosis on or after the year 2000) for patients diagnosed with oligodendroglioma (HR = 1.08, (95%CI: 0.85, 1.4)), astrocytoma (HR = 0.98, (95%CI: 0.83, 1.15)) or mixed glioma (HR = 0.76, (95%CI: 0.54, 1, 07)) (Figures 1–3). Interestingly, when the time cut point is placed at 2005 rather than at 2000, the results are similar for astrocytoma and oligodendroglioma but persons diagnosed with mixed glioma on or after 2005 show improved survival versus those diagnosed prior to 2005.

Discussion

The general lack of improvement in survival for LGG patients over the past three decades points to the need for an intensified focus on these tumors. As for HGG, several intriguing findings have emerged, many over just the past year or two, with respect to molecular tumor markers, gene expression and constitutive genotype.

Molecular Tumor Markers

A number of molecular tumor markers have been associated with LGG overall survival including 1) combined deletions of chromosomes 1p and 19q[30,33] 2) mutations in the Isocitrate dehydrogenase 1/2 (*IDH1/2*) genes[30,84] and 3) methylation of the O^6-methylguanine-DNA methyltransferase (*MGMT*) gene.[30] The high rate of *p53* mutation/deletion in some gliomas as well as the belief that this change represents an early step in glioma development has led investigators to examine this alteration in association with LGG survival with inconsistent results.[23,28,30]

Co-deletion of 1p/19q—Although present in all LGG subtypes, chromosomes 1p and 19q are deleted in 40% –90% of oligo II and are associated with increased survival as well as treatment sensitivity.[33,37] The mechanism by which 1p/19q loss affects outcome and response is unknown with no gene clearly defined at either location. Recent sequencing revealed mutations in two tumor suppressor genes (homolog of Drosophiliacapicua (*CIC*) on 19q and far-upstream binding protein 1 (*FUBP1*) on 1p in 38% and 14% of 21 oligo II (and 0/15 (0%) of astro II and 1/18 (6%) of mixed II).[36] Essentially all glioma with a *CIC* or

FUBP1 mutation in that study[36] also had an *IDH* gene mutation as well as co-deletion of 1p/19q. Jenkins et al[33] found most 1p and 19q deletions in oligo II were the result of an unbalanced translocation between the whole chromosomal arms of 1p and 19q and that translocation/deletion was associated with significantly improved overall survival.

IDH1/2—A recent notable finding is that mutations in the $NADP^+$ dependent isocitrate dehydrogenases encoded by *IDH1* and *IDH2* occur in the majority of grade II (all subtypes)[84] and III gliomas as well as secondary GBM but in only a minority of primary GBM.[53,84] *IDH1* is an enzyme that catalyzes the oxidative decarboxylation of isocitrate to alpha-ketoglutarate leading to NADPH production and is thought to play a role in cellular protection from oxidative stress. *IDH* mutations are associated with a glioma CpG island DNA hypermethylator phenotype (G-CIMP)[74] and are associated with improved LGG survival[84] as well as possible LGG response to treatment.[28,30] Such data suggest that *IDH* mutations are an early step in the development of LGG.[46]

MGMT—Methylation of *MGMT* (a DNA repair gene located on 10q) is a commonly observed change in LGG[28] that predicts HGG response to treatment as well as overall survival;[9,29] this change may confer chemo sensitivity in LGG[28,30] by causing an altered response to TMZ (the primary agent used to treat LGG) although efforts to examine this are limited by small sample size.[28,30]

TP53—There is evidence to suggest that a series of ordered genetic alterations occurs when progressing from LGG to HGG with TP53 mutation an early event.[84] *TP53* is the most frequently mutated gene in GBM and a common event in the TCGA Proneural GBM subtype (believed to include the majority of LGG that progressed to HGG). *TP53* mutation is found in all LGG subtypes[28] but is highly correlated with the proportion of tumor astrocytes. Interestingly, a recent study[36] examined mutations in the chromatin modifier Alpha Thalassemia/Mental Retardation Syndrome X-linked (*ATRX*) (as well as *CIC*, *FUBP1*, and *IDH1*) and noted almost complete correlation between the presence of *TP53* and *ATRX* mutations, regardless of LGG subtype.

The extent to which any of these markers are merely indicators of the natural progression of disease or of treatment sensitivity (or both) remains ill-defined. In some instances (i.e. 1p/19q co-deletion and oligodendroglioma histology) marker and subtype are correlated leading to confusion about whether it is the marker or the subtype (or both) that is associated with outcome.[28] Similarly, correlation exists between markers (i.e. *IDH1* mutation and 1p/19q deletion).[30] Adding to the confusion is the dynamic classification process of LGG subtype with changes in the relative reported proportions of these subtypes over time reflecting an increasing awareness of the subtleties of histopathological classification for this group of tumors.[14,45] Researchers have started to elucidate the relative roles of histology and the aforementioned markers both before (thus capturing factors associated with prognosis) and after treatment (capturing factors associated with prediction). Several small studies suggest that response to TMZ[41] and progression free survival (PFS)[24] is associated with 1p deletion[41] and low *MGMT* protein expression[24,41] but all have a sample size <70, primarily focus on oligo II, and do not examine overall survival (OS). Recently, several groups have presented results from larger case series: Using 271 LGG drawn from the Groupe

Hospitalier Pitie-Salpetriere in Paris, Houillier et al[30] tested whether *TP53* mutation, 1p/19q co-deletion, *MGMT* promoter methylation, and *IDH1* mutation predicted natural course of disease or response to treatment (alkylating agent/XRT) while controlling for extent of surgical resection. In multivariate analyses only performance status and surgical resection (but neither histology nor marker) was predictive of outcome in untreated patients (PFS). *IDH1* mutation and 1p/19q co-deletion was predictive of OS while *IDH1* mutation, 1p/19q deletion and *MGMT* promoter methylation were each associated in univariate analyses with response to TMZ but small sample size precluded a multivariate analysis including the three markers simultaneously. Hartmann et al[28] performed a similar analysis on139 LGG patients from the German Cancer Network. Again no marker was prognostic in patients who did not receive chemo/XRT. *IDH1* mutation and 1p/19q co-deletion were predictive of OS (and of PFS in persons receiving chemo/XRT at diagnosis). As noted by the authors of both studies, insufficient sample size did not allow for examination of these markers by histological subtype.

Tumor Gene Expression

Recent Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov) analyses of high grade glioma tumors use several different technology platforms, including mutation arrays, copy number arrays, expression arrays and methylation arrays.[10,54,77] Expression array data has identified molecular subtypes associated with grade and outcome and shown that expression profiles are better predictors of outcome than histological subtype.[10,15,54,77] The TCGA and others[10,26,54,77] have recently defined and validated four gene-expression-based classification profiles for grade IV glioma (GBM): Proneural (notable for PDGFRA alterations, IDH1 and TP53 mutations, as well as oligodendroglioma cell type), Neural (associated with a variety of neuron markers and closest to normal brain), Classical (EGFR amplification and CDKN2A alterations) and Mesenchymal (NF1 and MET alterations). Despite being constructed using only GBM tumors, intriguing findings relative to LGG are noted: 1) the Proneural profile included 3 of the 4 known secondary GBM, (believed to arise from LGG) and 2) as for LGG, the Proneural profile was notable for young age at onset as well as longer survival particularly when grade II and III gliomas from validation sets were added. The absence of LGG in the TCGA data led two groups[16,27] to examine the predictive value of the TCGA profiles for LGG. Both groups[16,27] utilized Affymetrix gene expression data for a small set of LGG (65 astro II, 4 mixed II, and 30 oligo II) from the Repository for Molecular Brain Neoplasia Data (Rembrandt) and reported similar findings with the TCGA profiles associated with prognostic value for LGG.[16] More recently, the TCGA analyzed 293 lower (II/III) grade gliomas. Despite using a wide range of sophisticated technology platforms, the final results suggested that lower grade tumors can be simply and better characterized solely by two tumor markers, IDH1/2 and 1p/19q deletion status, than by the traditionally used histology/grade.[78] The findings are considered paradigm-breaking and suggest that the decades-long classification system for glioma (focused on histology and grade) is likely inferior to a new more molecularly-based (but clinically simple and cost efficient) classification scheme. With respect to outcome, these molecular findings remain untested in a pure LGG cohort and uncorrected for an additional variable of clinical import, extent of surgical resection.[13,55]

Constitutive genetic polymorphisms

Glioma Risk—Genetic polymorphisms identified in association with glioma incidence are clearly of interest when considering genes associated with glioma survival.[2,3,8,11,18,20–22,31,49,50,57–59,64] An emerging theme in glioma research has been that the genes/pathways identified in linkage and tumor studies are also being identified in GWAS. This demonstrates that, in addition to the rare variation associated with Mendelian disorders, common genetic variation also contributes to glioma genesis. While rare heritable loss-of-function mutations in *TP53* and *p16* cause glioma-associated familial cancer syndromes, inherited SNPs near both these genes also appear to contribute to glioma genesis. In total, GWAS of glioma patients have identified 9 independently significant SNP associations located in 8 genes (Table 2).[34,35,62,68,71,79,81] The first two glioma GWAS.[68,82] one of which included only HGG (from UCSF/Mayo)[81] and the other (from the M.D. Anderson Center (MDA))[68] which included HGG and some LGG, confirmed glioma risk loci in or near *TERT* (5p15), *CDKN2A/B* (9p21) (a gene region harboring p16, a tumor suppressor gene often homozygously deleted in GBM), and *RTEL1* (20q13). The MDA GWAS[68] which included LGG cases identified two additional loci: *CCDC26* (8q24) and *PHLDB1* (11q23).The top 13 SNPs in these five regions were further investigated by tumor subtype in 1446 cases and 1134 controls from UCSF/Mayo (with 224 oligo (II/III), 166 mixed (II/III) and 103 astro (II only)).[34] As reported in the MDA GWAS[68] *CCDC26* (8q24) region loci were associated with oligo (II/III) (OR=2.05, $p=8.3\times10^{-11}$) but not GBM (Grade IV) risk with association with oligo II/III seen regardless of 1p/19q deletion status (although greatest risk was seen with co-deletion present). In contrast, *RTEL* region polymorphisms were most strongly associated with grade IV but less so with grade II/III glioma risk. The TERT region was associated with all grades and types of glioma. The *CDKN2A/B* region SNPs were also associated with Grade IV and grade II/III astrocytoms but not with oligo II/III. Insufficient data was available to draw conclusions about Grade II astrocytoma and Grade II oligodendroglioma independently of Grade III oligodendroglioma as well as Grade II versus Grade III mixed glioma). A similar analysis was performed in the German and French replication cohorts of the MDA GWAS again finding that *CCDC26* and *PHLDB1* loci were inversely and *RTEL1* and *TERT* loci were positively correlated with grade.[71] Data from a Chinese population agree as well.[11] A pooled analysis of the US/UK/German/French data confirmed these findings and found evidence of an additional independent association for glioma (regardless of grade) risk with rs11979158 and rs2252586, at 7p11.2 which encompasses the *EGFR* gene although interestingly this gene was not associated with survival.[62] The results listed above are remarkably confirmatory (in an era where GWAS results may vary widely) and strongly suggest distinct germline polymorphisms underlie different glioma subtypes (i.e. *CCDC26* and *PHLDB1* loci are consistently associated with LGG while other loci are either primarily associated with high grade glioma or with all glioma regardless of grade and histology. Jenkins et al[35] further examine the *CCDC26* (8q24) region and find strong association for a low frequency variant at 8q24.21 (rs55705857) associated with 1) oligo II/III regardless of IDH mutation status (OR=6.3, $p=2.2\times10^{-23}$), and 2) astro II-IV with mutated IDH1/IDH2 (OR=5.16–6.66, $p=4.7\times10^{-12}$ to 2.2×10^{-8}) but not astrocytic tumors with wild type IDH1/IDH2. Their LGG specific findings are remarkable with increasing risk associated with decreasing astrocyte involvement ($OR_{astroII}$=3.82 (95CI: 2.63, 5.54), $p=1.7\times10^{-12}$, $OR_{mixedII}$=5.01 (3.48, 7.21, $p=3.7\times10^{-18}$

and $OR_{oligoII}$=7.06 (5.10, 9.77), p=6.2×10^{-32}). Two[60,78] new reports are also of note; Using existing as well as new data from the UCSF/Mayo groups, Rice et al[560] show that the PHLDB1 SNP is associated strictly with IDH-mutant while Walsh et al[78] replicate the findings that CDKN2B SNPs are associated with low-grade astrocytomas. In summary, four of the above mentioned genes appear to contribute to development of all glioma grades and histologies (RTEL, *TERT*, *EGFR*, *TP53*), while the other 3 genes appear to contribute only to the development of certain glioma subtypes (Table 2). *CCDC26* variants increase risk for oligodendroglial tumors regardless of IDH-mutation status and also for IDH-mutated astrocytoma. SNPs near *CDKN2B/ANRIL* confer increased risk for astrocytic tumors of all grades, including glioblastomas, but are not associated with oligodendroglial tumors. The histologic specificity of these SNP associations remains an area of active research.

Glioma outcome—There are few studies of genetic polymorphism and survival after diagnosis of glioma; those that exist focus on HGG (no study includes more than 50 LGG patients) with examination of SNPs in genes involved in DNA repair, cell cycle regulation, and immune function as well as in tumor markers of note.[5,23,42,51,70,72,76,81,85]

GWAS: No data exist specific to LGG but several informative efforts have been undertaken relative to HGG by Dr. Wrensch's group which performed the first GBM GWAS survival analysis[83,84] in uniformly treated (surgery, XRT, and TMZ) patients and found that SSBP2 (a single-stranded DNA binding protein on 5q14.1) germline variants were associated with survival (discovery (UCSF) and validation (MAYO, Glioma SE, and TCGA) sets show a combined $HR_{rs7732320}$ = 1.64 (1.34, 2.00), p=1.3*10^{-6}) and that expression of SSBP2 in GBM tumors was significantly related to reduced survival (HR=1.22, (1.09, 1.36), p=5.3 × 10^{-4}).Interestingly, among TCGA and other GBM patients, SSBP2 expression was highest among patients with the Proneural signature, a group likely to include persons with secondary GBM (i.e. progressed from LGG) suggesting that SSBP2 germline variants and tumor expression (which were not linked to IDH mutation status) may be an important independent predictor of survival for LGG. Dr. Bondy also examined associations with GBM survival with the 100 top-ranking glioma susceptibility polymorphisms identified from the two glioma GWAS[68,82] and found that polymorphisms in the LIG4, HMGA2, BTBD2, and RTEL1 genes (all involved in the double-strand break repair pathway) were associated with GBM survival in the MDA GWAS cohort (although not confirmed in the validation set).[43] Preliminary analyses from the UCSF/Mayo study indicate that the variant at 8q24.21 (rs55705857) associated so strongly with glioma risk appears to also be associated with survival. The data used here to estimate survival are taken from the SEER program.[65] Although an important description of "real-world" LGG practice that includes persons of all ages, race and medical status, the data are limited by 1) a lack of a uniform histological review, 2) treatment data restricted to first course (hence data on XRT and chemotherapy are limited or absent) and not adjusted for clinical factors likely to influence treatment assignment and, 3) no information on constitutive/tumor genotype, tumor markers, or patient co-morbidities.

One important reason for the lack of knowledge concerning LGG is that these patients are generally only included as a convenience sub-sample in studies of HGG with results driven

by the much larger numbers of HGG in these studies.[10,12,34,62,68,69,82] Furthermore, the lack of effect in randomized clinical trials is likely also due in part to the unknowing inclusion of genetically dissimilar tumors into one study arm. In the future, clarification of the tumor markers/profiles known to be associated with outcome (both natural progression as well as response to treatment) and will be required to be measured in any planned RCT to preserve randomization. The import of such markers and profiles is already recognized by organizers of the HGG trials with tumor materials retrospectively being analyzed to assess randomization. As LGG represents the first step in a multistage disease process, the need to focus efforts at the start of the disease process is clear. Large sample cohorts which will likely require the development of consortia given the relatively small numbers of these tumors. As can be seen from the literature morphological and molecular sub typing is critical to cancer genetic epidemiology[35] and to date not explored specifically for LGG. Discovery of genes associated with poor outcomes will inform allow for improvement of randomization schemes in clinical trials of LGG as well as suggest novel biologic mechanisms for development of targeted therapy designed to improve survival. The time is right for researchers to take advantage of emerging genetic technology, statistical methodology and computing capability to create a new clinical paradigm for LGG.

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References

1. Aaronsen NK, Taphoorn MJ, Heimans JJ, Postma TJ, Gundy CM, Beute GN, et al. Compromised Health-Related Quality of Life in Patients With Low-Grade Glioma. J Clin Oncol. 2011; 29:4430–4435. [PubMed: 22010018]
2. Bethke L, Webb E, Murray A, Schoemaker M, Johansen C, Christensen C, et al. Comprehensive analysis of the role of DNA repair gene polymorphisms on risk of glioma. Hum Molecular Genet. 2008; 17:800–805.
3. Bethke L, Sullivan K, Webb E, Murray A, Schoemaker M, Auvinen A, et al. The common D302H variant of CASP8 is associated with risk of glioma. Cancer Epidemiol Biomarkers Prev. 2008; 17:987–989. [PubMed: 18398042]
4. Stege EM, Kros JM, de Brulin HG, Enting RH, van Heuvel I, Looijenga LH, et al. Successful treatment of low-grade oligodendroglial tumors with a chemotherapy regimen of procarbazine, lomustine, and vincristine. Cancer. 2005; 103:802–809. [PubMed: 15637687]
5. Bhowmick DA, Zhuang Z, Wait SD, Weil RJ. A functional polymorphism in the EGF gene is found with increased frequency in glioblastoma multiforme patients and is associated with more aggressive disease. Cancer Res. 2004; 64:1220–1223. [PubMed: 14973082]
6. Brada M, Viviers L, Abson C, Hines F, Britton J, Ashley S, et al. Phase II study of primary temozolamide chemotherapy in patients with WHO grade II gliomas. Ann Oncol. 2003; 14:1715–1721. [PubMed: 14630674]
7. Bruckner J. Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: RTOG 9802 with Alliance, ECOG, and SWOG. J Clin Oncol. 2014; 32:5s.
8. Caggana M, Kilgallen J, Conroy J, Wiencke J, Kelsey K, Miike R, Wrensch M. Associations between ERCC2 polymorphisms and gliomas. Cancer Epidemiol Biomarkers Prevention. 2001; 10:355–360.

9. Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, et al. Specific predictors of chemotherapeutic response and survival in patients with oligodendrogliomas. J Natl Cancer Inst. 1998; 90:1473–1479. [PubMed: 9776413]
10. Cancer Genome Atlas Research Network: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008; 455:1061–1068. [PubMed: 18772890]
11. Carpentier C, Laigle-Donadey F, Marie Y, Auger N, Benouaich-Amiel A, Lejeune J, et al. Polymorphism in Sp1 recognition site of the EGF receptor gene promoter and risk of glioblastoma. Neurology. 2006; 67:872–874. [PubMed: 16885506]
12. Chen H, Chen Y, Zhao Y, Fan W, Zhou K, Liu Y, et al. Association of sequence variants on chromosomes 20, 11, and 5 (20q13.33, 11q23.3, and 5p15.33) with glioma susceptibility in a Chinese population. Am J Epidemiol. 2011; 173:915–922. [PubMed: 21350045]
13. Claus EB, Horlacher A, Hsu L, Schwartz RB, Dello-Iacono D, Talos F, et al. Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. Cancer. 2005; 103:1227–1233. [PubMed: 15690327]
14. Claus EB, Black PM. Survival rates and patterns of care for patients diagnosed with supratentorial low grade gliomas: Data from the Surveillance, Epidemiology, and End Results (SEER) Program, 1973–2001. Cancer. 2006; 106:1358–1363. [PubMed: 16470608]
15. Colman H, Zhang L, Sulman EP, McDonald JM, Shooshtari NL, Rivera A, et al. A multigene predictor of outcome in glioblastoma. Neuro Oncol. 2010; 12:49–57. [PubMed: 20150367]
16. Cooper LA, Gutman DA, Long Q, Johnson BA, Cholleti SR, Kurc T, et al. The Proneural Molecular Signature is Enriched in Oligodendrogliomas and Predicts Improved Survival Among Diffuse Gliomas. PLoS One. 2010; 5:e12548. [PubMed: 20838435]
17. Correa DD, Shi W, Thaler HT, Cheung AM, DeAngelis LM, Abrey LE. Longitudinal cognitive follow-up in low grade gliomas. J Neurooncol. 2008; 86:321–327. [PubMed: 17926007]
18. Costa BM, Ferreira P, Costa S, Canedo P, Oliveira P, Silva A, et al. Association between functional EGF+61 polymorphism and glioma risk. Clin Cancer Res. 2007; 13:2621–2626. [PubMed: 17473192]
19. Cox DR. Regression models and life tables. J R Stat Soc [B]. 1972; 34:187–202.
20. De Roos AJ, Rothman N, Inskip PD, Linet MS, Shapiro WR, Selker RG, et al. Genetic polymorphisms in GSTM1,-P1,-T1, and CYP2E1 and the risk of adult brain tumors. Cancer Epidemiol Biomarkers Prevention. 2003; 12:14–22.
21. De Roos AJ, Rothman N, Brown M, Bell DA, Pittman GS, Shapiro WR, et al. Variation in genes relevant to aromatic hydrocarbon metabolism and the risk of adult brain tumors. Neuro Oncol. 2006; 8:145–155. [PubMed: 16598069]
22. Egan KM, Thompson RC, Nabors LB, Olson JJ, Brat DJ, Larocca RV, et al. Cancer susceptibility variants and the risk of adult glioma in a US case-control study. J Neurooncol. 2011; 104:535–542. [PubMed: 21203894]
23. Egan KM, Nabors LB, Olson JJ, Monteiro AN, Browning JE, Madden MH, et al. Rare TP53 genetic variant associated with glioma risk and outcome. J Med Genet. 2012; 49:420–421. [PubMed: 22706378]
24. Everhard S, Kaloshi G, Criniere E, Benouaich-Amiel A, Lejeune J, Marie Y, et al. MGMT methylation: a marker of response to temozolamide in low-grade gliomas. Ann Neurol. 2006; 60:740–743. [PubMed: 17192931]
25. Eyre HJ, Crowley JJ, Townsend JJ, Eltringham JR, Morantz RA, Schulman SF, et al. A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas. A Southwest Oncology Group study. Neurosurgery. 1993; 78:909–914.
26. Freije WA, Castro-Vargas FE, Fang Z, Horvath S, Cloughesy T, Liau LM, et al. Gene expression profiling of gliomas strongly predicts survival. Cancer Res. 2004; 64:6503–6510. [PubMed: 15374961]
27. Guan X, Chen Y, Barnholtz-Sloan J. Association between TCGA Gene-expression-based Glioblastoma Subtypes and Lower Grade Gliomas. http://cdn0.pathable.com/abstract/28/1308951897.?1308951897.

28. Hartmann C, Hentschel B, Tatagiba M, Schramm J, Schnell O, Seidel C, et al. Molecular Markers in Low-Grade Gliomas: Predictive or Prognostic? Clin Cancer Res. 2011; 17:4588–4599. [PubMed: 21558404]
29. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005; 352:997–1003. [PubMed: 15758010]
30. Houillier C, Wang X, Kaloshi G, Mokhtari K, Guillevin R, Laffaire J, et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology. 2010; 75:1560–1566. [PubMed: 20975057]
31. Idbaih A, Boisselier B, Marie Y, El Hallani S, Sanson M, Crinière E, et al. TP53 codon 72 polymorphism, p53 expression, and 1p/19q status in oligodendroglial tumors. Cancer Genet Cytogenet. 2007; 177:103–107. [PubMed: 17854663]
32. Jaloka AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgard G, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. J Amer Med Assoc. 2012; 308:1881–1888.
33. Jenkins RB, Blair H, Ballman KV, Giannini C, Arusell Rm, Law M, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis for patients with oligodendroglioma. Cancer Res. 2006; 66:9852–9861. [PubMed: 17047046]
34. Jenkins RB, Wrensch MR, Johnson D, Fridley BL, Decker PA, Xiao Y, et al. Distinct germ line polymorphisms underlie glioma morphologic heterogeneity. Cancer Genet. 2011; 204:13–18. [PubMed: 21356187]
35. Jenkins RB, Xiao Y, Sicotte H, Decker PA, Kollmeyer TM, Hansen, et al. A low-frequency variant at 8q24.21 is strongly associated with risk of oligodendroglial tumors and astrocytomas with IDH1 or IDH2 mutation. Nat Genet. 2012; 44:1122–1125. [PubMed: 22922872]
36. Jiao Y, Killela PJ, Reitman ZJ, Rasheed BA, Heaphy CM, de Wilde RF, et al. Frequent ATRX, CIC, FUBP1 and IDH mutations refine the classification of malignant gliomas. Oncotarget. 2012; 3:710–722.
37. Kaloshi G, Benouaich-Amiel A, Diakite F, Taillibert S, Lejeune J, Laigle-Donadey F, et al. Temozolamide for low-grade gliomas. Predictive impact of 1p/19q loss on response and outcome. Neurology. 2007; 68:1831–1836. [PubMed: 17515545]
38. Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys. 1996; 36:549–556. [PubMed: 8948338]
39. Kesari S, Schiff D, Drappatz J, LaFrankie D, Doherty L, Macklin EA, et al. Phase II study of protracted daily temozolomide for low-grade gliomas in adults. Clin Cancer Res. 2009; 15:330–337. [PubMed: 19118062]
40. Kiebert GM, Curran D, Aaronson NK, Bolla M, Menten J, Rutten EH, et al. Quality of life after radiation therapy of cerebral low-grade gliomas of the adult: results of a randomised phase III trial on dose response (EORTC trial 22844). Eur J Cancer. 1998; 34:1902–1909. [PubMed: 10023313]
41. Levin N, Lavon I, Zelikovitsh B, Fuchs D, Bokstein F, Fellig Y, et al. Progressive low-grade oligodendrogliomas. Response to temozolamide and correlation between genetic profile and O6-methylguanine-DNA methyltransferase protein expression. Cancer. 2006; 106:1759–1765. [PubMed: 16541434]
42. Lima-Ramos V, Pacheco-Figueiredo L, Costa S, Pardal F, Silva A, Amorim J, et al. TP53 codon 72 polymorphism in susceptibility, overall survival, and adjuvant therapy response of gliomas. Cancer Genet Cytogenet. 2008; 180:14–19. [PubMed: 18068527]
43. Liu Y, Shete S, Etzel CJ, Scheurer M, Alexiou G, Armstrong G, et al. Polymorphisms of LIG4, BTBD2, HMGA2, and RTEL1 genes involved in the double-strand break repair pathway predict glioblastoma survival. J Clin Oncol. 2010; 28:2467–2474. [PubMed: 20368557]
44. Liu R, Solheim K, Polley MY, Lamborn KR, Page M, Fedoroff A, et al. Quality of life in low-grade glioma patients receiving temozolomide. Neuro Oncol. 2009; 11:59–68. [PubMed: 18713953]

45. Louis DN, Ohgaki H, Wiestler OD, Cavanee WK, Burger PC, Jouvet A, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol. 2007; 114:97–109. [PubMed: 17618441]
46. Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature. 2012; 483:474–478. [PubMed: 22343901]
47. Mainio A, Tuunanen S, Hakko H, Niemela A, Koivukangas J, Rasanen P. Decreased quality of life and depression as predictors for shorter survival among patients with low-grade gliomas: a follow-up from 1990 to 2003. Eur Arch Psychiatr Clin Neurosci. 2006; 256:516–521.
48. Malmer B, Barnholtz-Sloan J, Bernstein J, Claus EB, Houlston R, Jenkins R, et al. Gliogene: An international effort for delineating the underlying causes of familial glioma. Cancer Epid Biomarkers Prev. 2007; 16:1730–1734.
49. Malmer B, Feychting M, Lonn S, Ahlbom A, Henriksson R. p53 Genotypes and risk of glioma and meningioma. Cancer Epidemiol Biomarkers Prev. 2005; 14:2220–2223. [PubMed: 16172235]
50. Malmer BS, Feychting M, Lonn S, Lindstrom S, Gronberg H, Ahlbom A, et al. Genetic variation in p53 and ATM haplotypes and risk of glioma and meningioma. J Neurooncol. 2007; 82:229–237. [PubMed: 17151932]
51. Nigro JM, Misra A, Zhang L, Smirnov I, Colman H, Griffin C, et al. Integrated array-comparative genomic hybridization and expression array profiles identify clinically relevant molecular subtypes of glioblastoma. Cancer Res. 2005; 65:1678–1686. [PubMed: 15753362]
52. Okcu MF, Selvan M, Wang LE, Stout L, Erana R, Airewele G, et al. Glutathione S-transferase polymorphisms and survival in primary malignant glioma. Clinical Cancer Research. 2004; 10:2618–2625. [PubMed: 15102663]
53. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. An Integrated Genomic Analysis of Human Glioblastoma Multiforme. Science. 2008; 321:1807–1812. [PubMed: 18772396]
54. Phillips HS, Kharbanda S, Chen R, Forrest WF, Soriano RH, Wu TD, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. Cancer Cell. 2006; 9:157–173. [PubMed: 16530701]
55. Pignatti F, et al. Prognostic factors for survival in adult patients in cerebral low grade glioma. J Clin Oncol. 2002; 20:2076–2084. [PubMed: 11956268]
56. Quinn JA, Reardon DA, Friedman AH, Rich JN, Sampson JH, Provenzale JM, et al. Phase II trial of temozolamide in patients with progressive low-grade glioma. J Clin Oncol. 2003; 21:646–651. [PubMed: 12586801]
57. Rajaraman P, Wang SW, Rothman N, Brown MM, Black PM, Fine HA, et al. Polymorphisms in apoptosis and cell cycle control genes and risk of brain tumors in adults. Cancer Epidemiol Biomarkers Prev. 2007; 16:1655–1661. [PubMed: 17684142]
58. Rajaraman P, Stewart PA, Samet JM, Schwartz BS, Linet MS, Zahm SH, et al. Lead, genetic susceptibility, and risk of adult brain tumors. Cancer Epidemiol Biomarkers Prev. 2006; 15:2514–2522. [PubMed: 17164378]
59. Rajaraman P, Hutchinson A, Wichner S, Black PM, Fine HA, Loeffler JS, et al. DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. Neuro Oncol. 2010; 12:37–48. [PubMed: 20150366]
60. Rice T, Zheng S, Decker PA, Walsh KM, Bracci P, Xiao Y, et al. Inherited variant on chromosome 11q23 increases susceptibility to IDH mutated but not IDH normal gliomas regardless of grade or histology. Neuro-Oncology. 2012 (in press).
61. Sanai N, Berger MS. Glioma Extent of Resection and Its Impact on Patient Outcome. Neurosurgery. 2008; 62:753–766. [PubMed: 18496181]
62. Sanson M, Hosking FJ, Shete S, Zelenika D, Dobbins SE, Ma Y, et al. Chromosome 7p11.2 (EGFR) variation influences glioma risk. Hum Mol Genet. 2011; 20:2897–2904. [PubMed: 21531791]
63. SAS Institute Inc.. SAS/STAT User's Guide. Vol. 1. Cary, NC: SAS Institute Inc.; 2006.
64. Schwartzbaum JA, Ahlbom A, Lonn S, Warholm M, Rannug A, Auvinen A, et al. An international case-control study of glutathione transferase and functionally related polymorphisms and risk of

primary adult brain tumors. Cancer Epidemiol Biomarkers Prev. 2007; 16:559–565. [PubMed: 17372252]

65. [based on the November 2013] Surveillance, Epidemiology, and End Results (SEER) Program(www.seer.cancer.gov) Research Data (1973–2011), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch. released April 2014, submission.
66. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol. 2002; 120:2267–2276. [PubMed: 11980997]
67. Shaw EG, Wang M, Coons SW, Brachman DG, Buckner JC, Stelzer KJ, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. J Clin Oncol. 2012; 30:3065–3070. [PubMed: 22851558]
68. Shete S, Hosking F, Robertson LB, Dobbins SE, Sanson M, Malmer B, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nature Genetics. 2009; 41:899–904. [PubMed: 19578367]
69. Shete S, Lau C, Houlston R, Claus EB, Barnholtz-Sloan J, Lai R, et al. A High-density SNP Genome-wide Linkage Search identifies Susceptibility Loci for Glioma: Results from the GLIOGENE Consortium. Cancer Res. 2011; 71:7568–7575. [PubMed: 22037877]
70. Simon M, Ludwig M, Fimmers R, Mahlberg R, Müller-Erkwoh A, Köster G, et al. Variant of the CHEK2 gene as a prognostic marker in glioblastoma multiforme. Neurosurgery. 2006; 59:1078–1085. [PubMed: 17016233]
71. Simon M, Hosking FJ, Marie Y, Gousias K, Boisselier B, Carpentier C, et al. Genetic risk profiles identify different molecular etiologies for glioma. Clin Cancer Res. 2010; 16:5252–5259. [PubMed: 20847058]
72. Tang J, Shao W, Dorak MT, Li Y, Miike R, Lobashevsky E, et al. Positive and negative associations of human leukocyte antigen variants with the onsent and prognosis of adult glioblastoma mulitforme. Cancer Epidemiol Biosmarkers Prev. 2005; 14:2040–2044.
73. Tosoni A, Franceschi E, Ermani M, Bertorelle R, Bonaldi L, Blatt V, et al. Temozolomide three weeks on and one week off as first line therapy for patients with recurrent or progressive low grade gliomas. J Neurooncol. 2008; 89:179–185. [PubMed: 18431544]
74. Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature. 2012; 483:479–483. [PubMed: 22343889]
75. van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, et al. EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet. 2005; 366:985–990. [PubMed: 16168780]
76. Vauleon E, Auger N, Benouaich-Amiel A, Laigle-Donadey F, Kaloshi G, Lejeune J, et al. The 61 A/G EGF polymorphism is functional but is neither a prognostic marker nor a risk factor for glioblastoma. Cancer Genet Cytogenet. 2007; 172:33–37. [PubMed: 17175377]
77. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010; 17:98–110. [PubMed: 20129251]
78. Verhaak, RGW., et al. San Diego: 2014. AACR 2014: Presentation Abstract: Comprehensive and Integrative Genomic Characterization of Diffuse Lower Grade Gliomas. (http://cancergenome.nih.gov/newsevents/events/AACR2014_Abstract_LGGs)
79. Walsh KM, Anderson E, Hansen HM, Decker PA, Kosel ML, Kollmeyer T, et al. Analysis of 60 reported glioma risk SNPs replicates published GWAS findings but fails to replicate associations from published candidate-gene studies. Genetic Epidemiology. 2012; 37:222–228. [PubMed: 23280628]

80. Walsh KM, Codd V, Smirnov IV, Rice T, Decker PA, Hansen HM, et al. Variants near TERT and TERC influencing telomere length are associated with high-grade glioma risk. Nat Genet. 2014; 46:731–735. [PubMed: 24908248]

81. Wiencke JK, Aldape K, McMillan A, Wiemels J, Maghadassi M, Miike R, et al. Molecular features of adult glioma associated with patient race/ethnicity, age, and a polymorphism in O6-methylguanine-DNA methyltransferase. Cancer Epidemiol Biomarkers Prev. 2005; 14:1774–1783. [PubMed: 16030116]

82. Wrensch M, Jenkins RB, Chang JS, Yeh R-F, Xiao Y, Decker PA, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. Nature Genetics. 2009; 41:905–908. [PubMed: 19578366]

83. Wrensch M, Wiencke JK, Wiemels J, Miike R, Patoka J, Moghadassi M, et al. Serum IgE, tumor epidermal growth factor receptor expression, and inherited polymorphisms associated with glioma survival. Cancer Res. 2006; 66:4531–4541. [PubMed: 16618782]

84. Wrensch M, McMillan A, Wiencke J, Wiemels J, Kelsey K, Patoka J, et al. Non synonymous coding single-nucleotide polymorphisms spanning the genome in relation to glioblastoma survival and age at diagnosis. Clin Cancer Res. 2007; 13:197–205. [PubMed: 17200355]

85. Xiao Y, Decker PA, Rice T, McCoy LS, Smirnov I, Patoka JS, et al. SSBP2 variants impact survival in glioblastoma patients. Clin Cancer Res. 2012; 18:3154–3162. [PubMed: 22472174]

86. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in Gliomas. N Engl J Med. 2009; 360:765–773. [PubMed: 19228619]

87. Yang P, Kollmeyer TM, Buckner K, Bamlet W, Ballman KV, Jenkins RB, et al. Polymorphisms in GLTSCR1 and ERCC2 are associated with the development of oligodendrogliomas. Cancer. 2005; 103:2363–2372. [PubMed: 15834925]

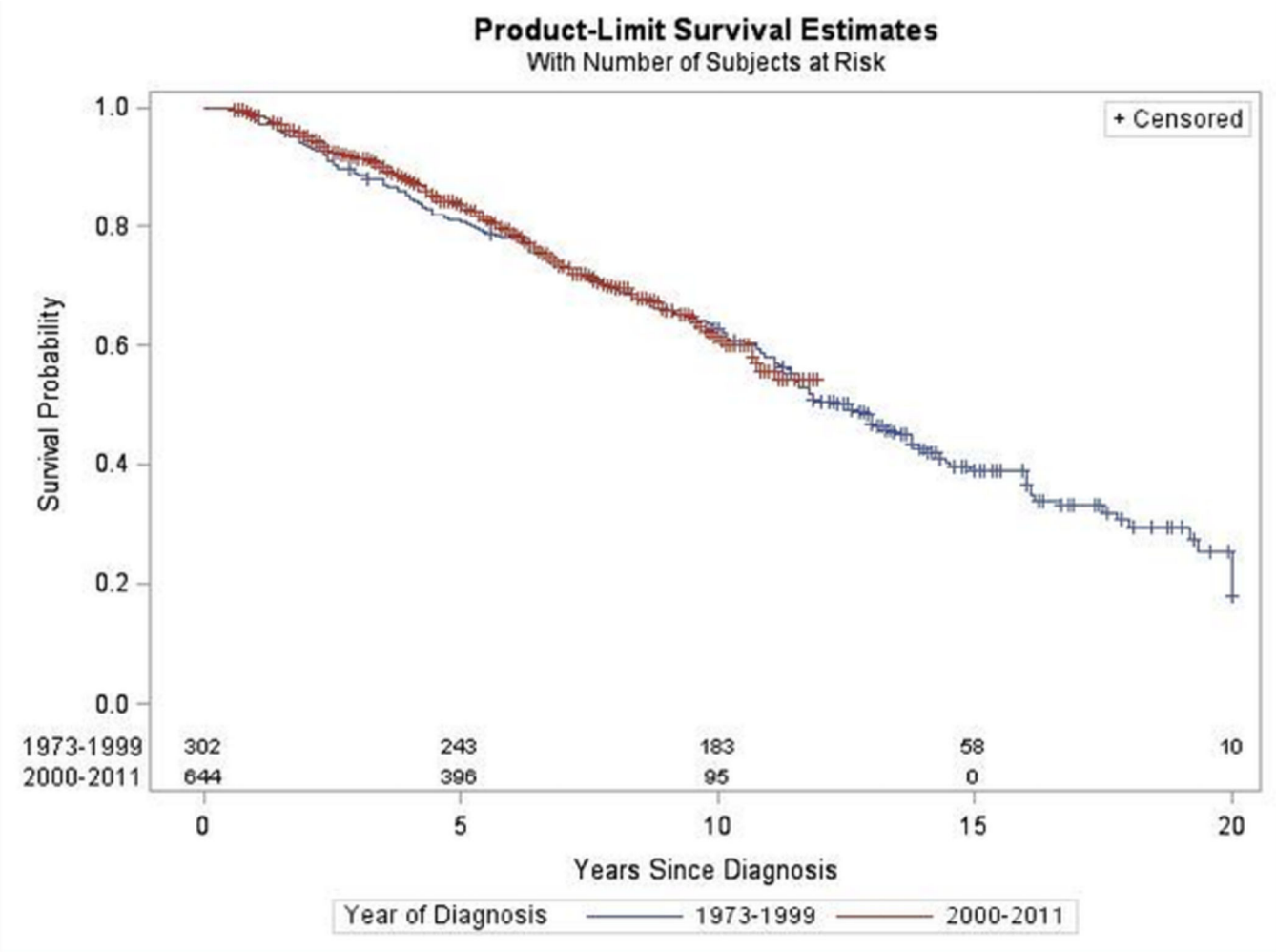

Figure 1.
Survival by Year of Diagnosis for Oligodendroglioma. SEER 1973–2011

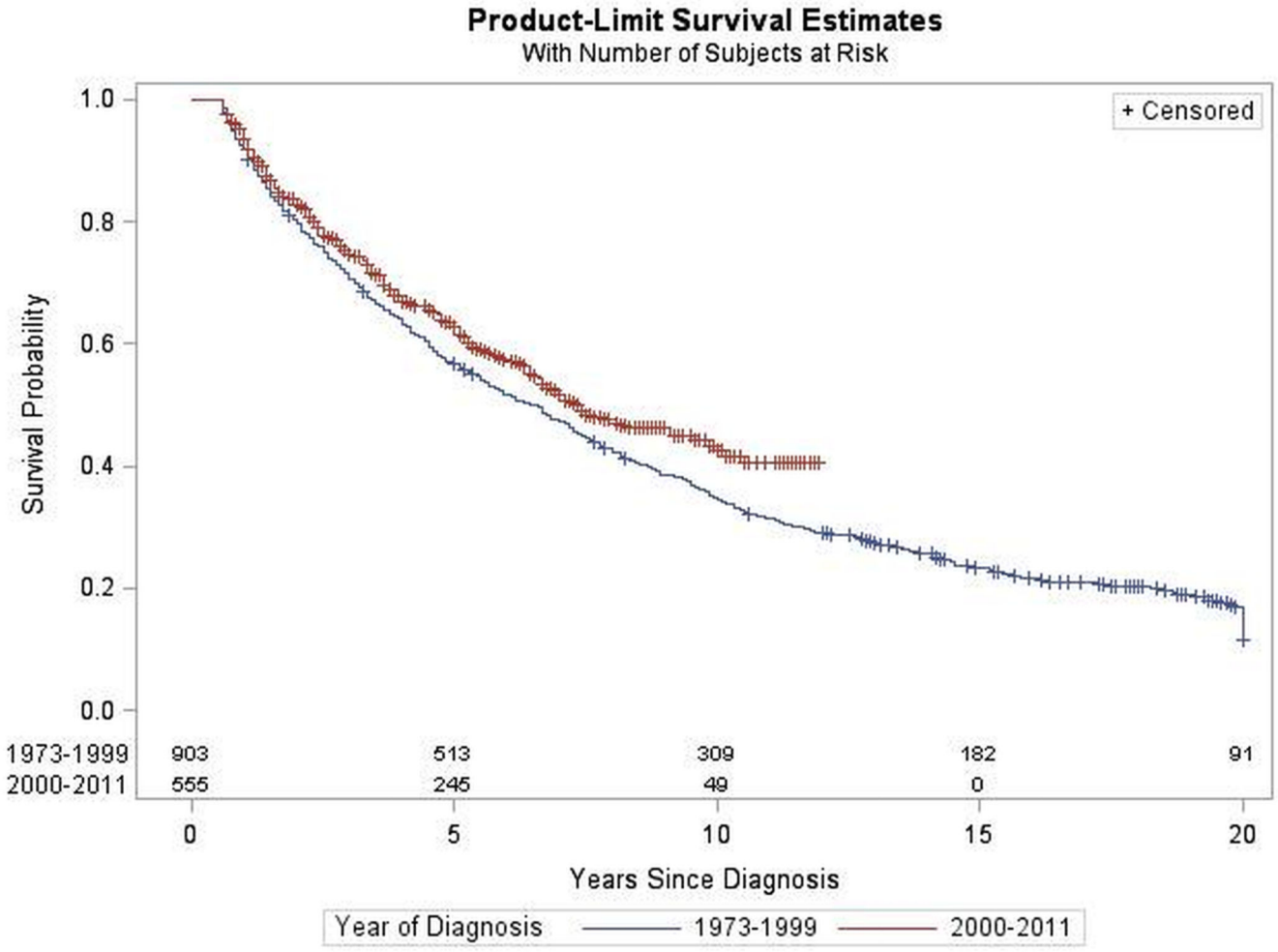

Figure 2.
Survival by Year of Diagnosis for Astrocytoma. SEER 1973–2011

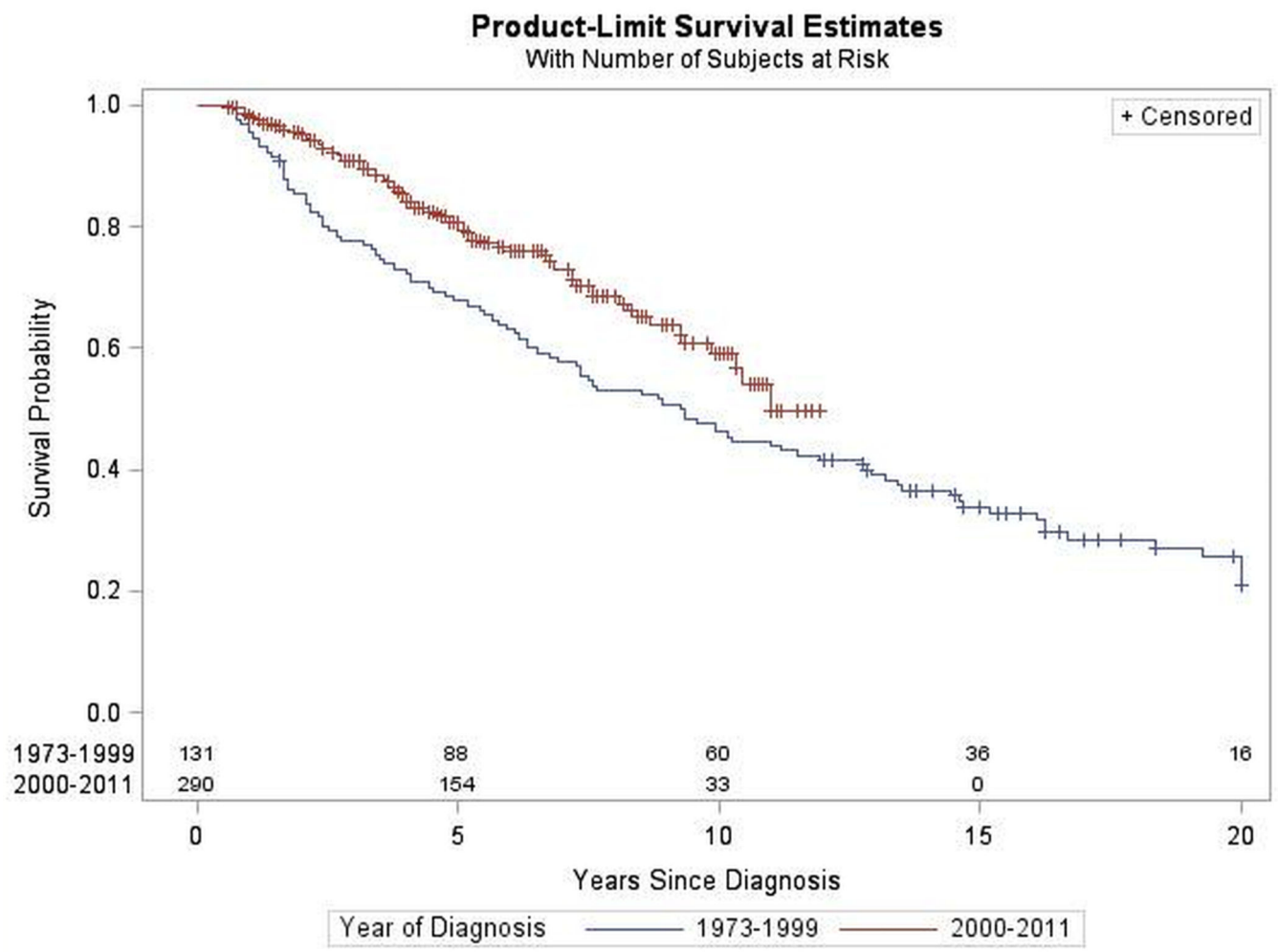

Figure 3.
Survival by Year of Diagnosis for Mixed Glioma. SEER 1973–2011

Table 1

Number of diagnoses (and deaths) for adult supratentorial low grade glioma by histologic subgroup, Surveillance, Epidemiology, and End Results (SEER) data, 1973–2011

		Astrocytoma	Oligodendroglioma	Mixed Glioma	Total
Age	20–39	732 (442)	445 (153)	229 (83)	1406 (678)
	40–59	538 (392)	421 (248)	161 (66)	1120 (616)
	60+	2188 (162)	80 (56)	31 (20)	299 (238)
Race	White	1295 (889)	849 (317)	374 (150)	2518 (1366)
	Black	92 (70)	32 (13)	18 (8)	142 (91)
	Other	71 (37)	65 (27)	29 (11)	165 (75)
Sex	Female	591 (391)	384 (131)	185 (69)	1160 (591)
	Male	867 (605)	562 (226)	236 (100)	1665 (931)
Year	Diagnosed				
	1973–1979	143 (133)	7 (7)	3 (3)	153 (143)
	1980–1989	414 (370)	28 (24)	36 (28)	478 (422)
	1990–1999	346 (252)	267 (154)	92 (64)	705 (470)
	2000–2009	520 (1237)	594 (171)	263 (74)	1377 (482)
	2010–2011	36 (4)	59 (1)	27 (0)	112 (5)

Table 2

Glioma-associated susceptibility variants detected by GWAS and fine-mapping

Candidate Gene (Chromosome Location)	Risk allele	Magnitude of Association[1]	Risk Allele Frequency[2]	Putative Functional Significance	Associated glioma subtypes
TERC (3q26.2)	rs1920116-G	+	0.72	Increased telomere length	High-grade glioma
TERT (5p15.33)	rs2736100-C	+	0.51	Increased telomere length	All glioma subtypes
EGFR (7p11.2)	rs2252586-A	+	0.27	Unknown	All glioma subtypes
EGFR (7p11.2)	rs11979158-A	+	0.82	Unknown	All glioma subtypes
CCDC26 (8q24.21)	rs55705857-G	+++	0.046	microRNA site	Oligodendroglial tumors and IDH-mutated astrocytic tumors
CDKN2B/ANRIL (9p21.3)	rs1412829-G	+	0.43	Unknown	Astrocytic tumors of all grades
PHLDB1 (11q23.3)	rs498872-A	+	0.31	Unknown	IDH-mutated gliomas
TP53 (17p13.1)	rs78378222-C	++	0.014	Alteration of polyadenylation signal impairs *TP53* mRNA processing	All glioma subtypes
RTEL1 (20q13.33)	rs6010620-G	+	0.76	Unknown	All glioma subtypes

[1] Magnitude of Association: +++ represents OR>=5.0, ++ represents 2.0<=OR<5.0, and + represents 1.0<OR<2.0

[2] Allele frequency in Caucasians, extracted from HapMap CEPH data where available.