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Original Article

Isocitrate dehydrogenase-mutant astrocytoma in persons aged 55 years and older: Survival differences versus the young

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ABSTRACT

Isocitrate dehydrogenase (IDH)-mutant astrocytomas show a peak incidence in young and middle-aged adults and have relatively favorable outcomes. In patients with these tumors ≥55 years at diagnosis, clinical, histopathologic, and prognostic characteristics are less clear. Here, we compared histopathological, immunohistochemical, molecular, and overall survival of 34 patients aged ≥55 years with a group of 84 patients aged 19-54 years; all had IDH mutant astrocytomas. The older cohort had 14 World Health Organization (WHO) grade 2, 7 WHO grade 3, and 13 WHO grade 4 tumors versus 24, 32, and 28 WHO grade 2, 3, and 4 tumors in the younger group. Comparing equal-grade tumors in both cohorts, Kaplan-Meyer survival analysis revealed that patients ≥55 years of age showed worse prognosis despite receiving comparable treatment regimens (Stupp protocol). Roughly equal numbers of noncanonical IDH mutations were seen in both groups (11.76% in ≥55 vs 19.04% in <55). Older patients were more likely to show retention of nuclear protein alpha-thalassemia and mental retardation X-linked syndrome (ATRX) and/or absence of strong P53 staining by immunohistochemistry. Although patients ≥55 years of age with astrocytomas, IDH-mutant, had worse overall survival, many, particularly those with low-grade tumors, had 5 years or greater survival. Employing parallel treatment regimens with chemotherapy, radiation, and maximum safe resection may improve survival of older patients with IDH mutant gliomas.

KEYWORDS: astrocytoma; ATRX; brain tumor; IDH-mutant; molecular diagnostics; outcome

INTRODUCTION

Mutations in the isocitrate dehydrogenase (*IDH1/2*) genes are common genetic alterations in adult-type diffuse astrocytomas and have long been recognized as leading to better outcomes compared to identical World Health Organization (WHO) grade astrocytic tumors, IDH-wildtype.[1] Specifically, patients with astrocytoma, IDH-mutant, WHO grade 4, do significantly better than glioblastoma, IDH-wildtype, WHO grade 4. In addition, predilection for occurrence in different age ranges has long been recognized, with astrocytomas, IDH-mutant, manifesting peak occurrence in young- and middle-aged adults (median 38 years) versus 55 years of age or older in glioblastoma, IDH-wildtype.[2] However, astrocytomas, IDH-mutant, can sometimes be seen in persons aged 55 years and older. Few studies have detailed the clinical, histologic, molecular, and survival features in astrocytomas, IDH-mutant in those >age 55 years.[3–6]

A 2020 study from Cleveland Clinic assessing *IDH1/2* mutational status in 381 gliomas revealed that while mutation was more frequent in persons <55 years of age, 42 of their 381 patients were aged 55 years or older (11%). They identified noncanonical IDH1 mutations (ie, non-*IDH1* R132H) in a relatively high percentage of their older population.[4] This study also noted that the typical immunohistochemical (IHC) profile associated with astrocytoma, IDH-mutant, namely loss of nuclear protein alpha-thalassemia and mental retardation X-linked syndrome (ATRX) and strong diffuse P53 immunostaining, was often absent.[4]

A 2024 study from Memorial Sloan Kettering detailed the outcomes of patients ≥65 years of age who had undergone

resection or biopsy of astrocytoma, IDH-mutant, of which 52% were WHO grade 2, 32% WHO grade 3, and 16% WHO grade 4.[3] The authors found survival benefits associated with a gross total resection and a lower histologic grade. The study did not include a direct comparison group of younger patients at their institution.[3]

A 2019 study from the University of California San Francisco addressed the incidence of astrocytoma, IDH-mutant, in persons aged 60 years or older.[5] This group found that 19.2% of diffuse gliomas in this age group were astrocytomas, IDH-mutant. However, this study of 26 patients included 13 with oligodendroglioma, IDH-mutant and 1p/19q co-deleted and 5 with astrocytoma, IDH-mutant, the remainder having "diffuse astrocytoma, IDH-wildtype" or "mixed oligoastrocytoma."[5] This study concluded that *IDH* mutation was associated with better progression-free and overall survival even in older adults, mirroring the findings from the younger population.[7] Decreased residual tumor volume was associated with lower rates of malignant transformation and better overall survival, suggesting that maximum safe resection should be recommended for older patients with IDH mutations.[7]

Our group also has had a longstanding interest in brain tumors affecting older persons.[6,8,9] In our 2017 report in this journal, of 578 infiltrative gliomas at our institution tested for IDH1 R132H mutation by immunohistochemistry, 88 were astrocytomas, IDH-mutant, of which 11 had occurred in persons aged 55 or older.[6] Our prior work underscored that although infrequently, IDH-mutant astrocytomas can arise in older adults.[6] We and others concluded that IDH1 R132H IHC should be routinely conducted in all diffuse gliomas, regardless of patient age.[6] However, we did not have long-term clinical follow-up for our cohort at the time of our original publication.[6]

We now revisit and extend our 2017 study, specifically examining overall survival compared to a younger cohort at our institution.

METHODS

A search of the pathology databases for cases diagnosed with "astrocytoma, IDH-mutant" and "glioblastoma" was conducted from February 2014 to February 2024, inclusive. While different age cut-offs have been used in the literature for older patients with astrocytoma, IDH-mutant, we utilized a cut-off of 55 years and older to parallel our original work on this subject.[6] A cohort of younger adults 19-54 years, with astrocytoma, IDH-mutant, who were also diagnosed at our institution, was used for comparison ($n = 84$ patients).

The study was conducted in compliance with the guidelines of the University of Colorado Institutional Review Board (COMIRB#: 23-2104). Medical records were interrogated for the extent of resection, treatment modalities administered, date of death, or recurrence at the last follow-up. If no information was available in the medical records, death records or publicly available obituaries were consulted. Demographic information, diagnosis, and histological/immunohistochemical/molecular results, where performed, were provided within our departmental databases.

At the time of original diagnosis, tissue had been fixed in 10% formalin, embedded in paraffin, with sections cut at 4-6 μm and stained with Harris hematoxylin and eosin.[6] All cases were further assessed by IHC for ATRX, p53, glial fibrillary acidic protein, MIB-1, and IDH1 R132H.[6] In select cases where IDH1 R132H IHC was negative and histological, and the IHC profile prompted further testing; noncanonical *IDH1/2* mutational testing was performed using our in-house next-generation sequencing assay as published previously.[10] Earlier cases were tested with an assay that detected the presence of an IDH1/2 mutation but could not differentiate between the various mutations. These noncanonical cases were designated *IDH1* R132X. All cases that had been diagnosed before the WHO 2021 classification[11,12] were given diagnoses concordant with the new guidelines for this paper. Specifically, IDH-mutant gliomas originally diagnosed as glioblastoma, IDH-mutant, WHO grade 4 were reclassified as "astrocytoma, IDH-mutant, WHO grade 4." Similarly, cases with *CDKN2A/B* homozygous deletion were given a CNS WHO grade 4.

Survival was calculated from the date of surgery to death or the last known follow-up. The Kaplan-Meier methodology was used to graph survival. Curves were compared using the log-rank test using data limited to 5-year survival. Data were analyzed using the SAS software (Statistical Analysis System, SAS Institute).

RESULTS

Thirty-four patients were identified with astrocytoma, IDH-mutant, aged 55 years or older at the time of the diagnosis (Figure 1). Clinical follow-up was available for 29 of these 34 patients. The older patients represented approximately 10% of patients with astrocytoma, IDH-mutant, diagnosed in our hospital during the time period of study (2014-2024). The control group consisted of 84 patients aged 19-54 years with astrocytoma, IDH-mutant, diagnosed during the same period.

A mix of different grades was seen in the older age group, with 14 WHO grade 2 (40%), 7 WHO grade 3, and 13 WHO grade 4 tumors representing 40.2%, 20.6%, and 38% of the total tumors, respectively. Correspondingly, 24, 32, and 28 WHO grade 2, 3, and 4 tumors were present in the younger cohort. When equal grades were compared by Kaplan-Meyer survival analysis, those ≥55 years showed a worse prognosis (Figure 2). Chart review indicated similar treatment regimens for both cohorts with standard external beam radiotherapy and temozolomide (Stupp protocol). Thus, treatment differences were not apparent. In all cases in which death records were available, the cause of death was noted as a complication of their brain tumor. Five-year survival was better for younger patients across all grades, with 86% of grade 2, 96% of grade 3, and 64% of grade 4 patients surviving at 5 years. The corresponding 5-year survival for the older cohort was 70% for grade 2, 41% for grade 3, and 30% for grade 4. Data on 10-year survival were available for only a limited number of patients, making it difficult to draw meaningful conclusions (Figure 2). Univariate analysis also showed a significant effect

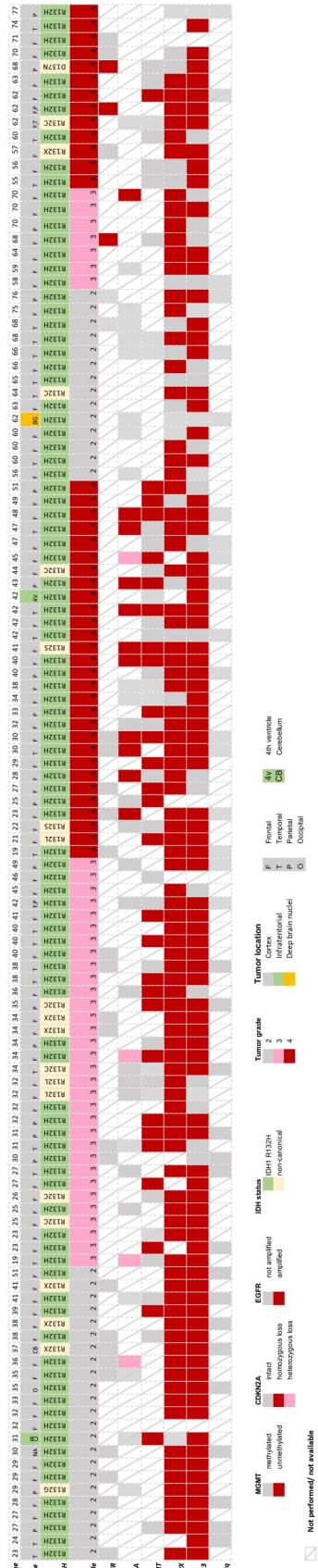

Figure 1. Histopathologic and molecular findings. An oncoplot showing isocitrate dehydrogenase mutation status, tumor grade, and immunohistochemical profile of the cohort.

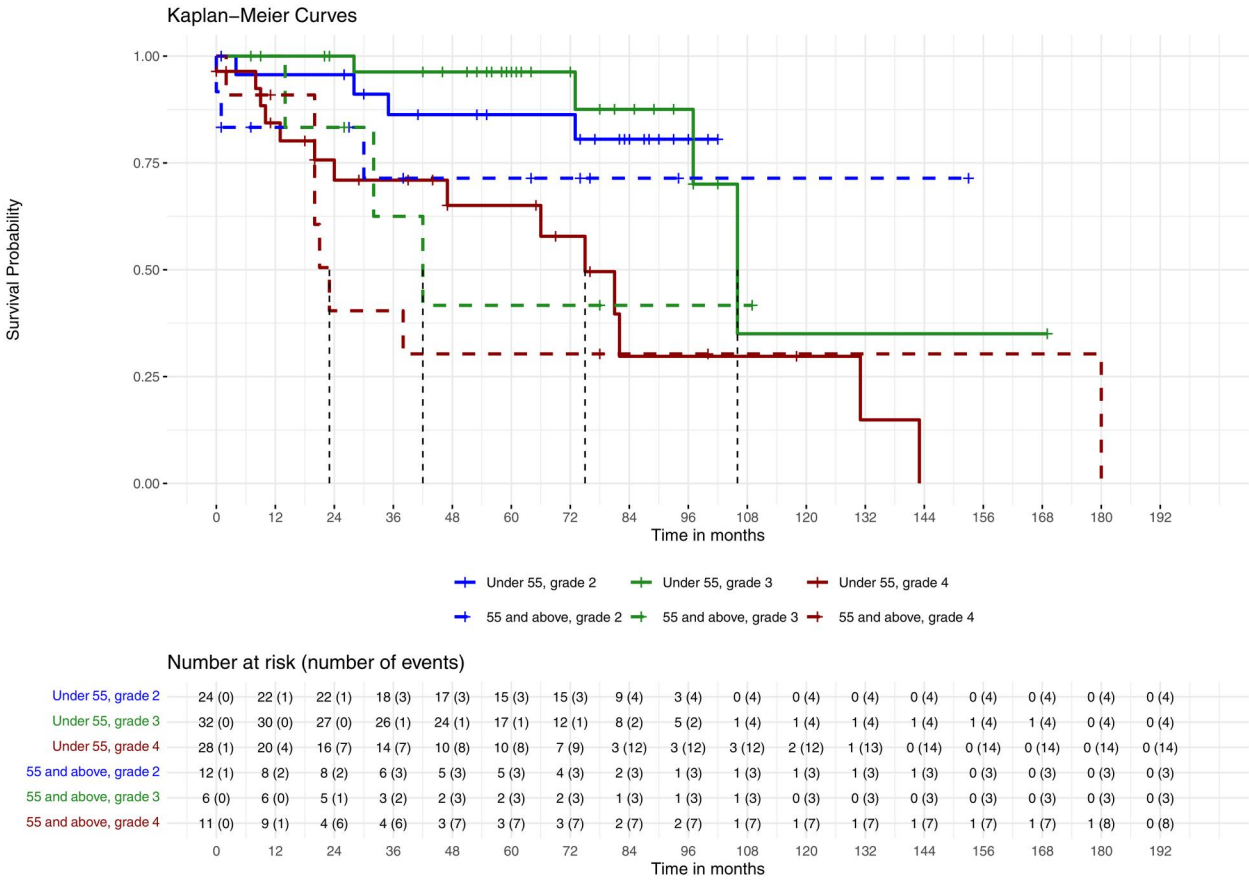

Figure 2. Prognostic differences in isocitrate dehydrogenase-mutant astrocytoma by age and histologic grade. Kaplan-Meier analysis of overall survival. Histologic grade and age category (<55 and ≥55 years) versus survival (log-rank for grade 2: $P = .2237$; grade 3, $P = .0003$; grade 4, $P = .1133$). Tick marks represent censored events.

of age on survival (hazard ratio = 4.153, 95% CI = 1.611-10.702, $P = .0032$).

The typical immunohistochemical pattern, including ATRX nuclear loss and strong diffuse P53 in >40% of tumor nuclei, was seen in roughly a third (37.5%; $n = 32$) of older patients with astrocytoma, IDH-mutant, as compared to patients in the younger age group, 80% ($n = 75$ patients) of which showed the typical pattern. Twelve out of 32 patients who are ≥55 years of age showed wildtype P53 immunostaining. Eight out of these 12 cases showed loss of ATRX staining. Cases with strong p53 immunostaining showed no classic histological features of oligodendroglioma, and, given the rarity of strong p53 expression in oligodendroglioma (WHO), these were considered bona fide astrocytoma, IDH-mutant. The remaining 4 cases with neither nuclear ATRX loss nor strong p53 immunoexpression also failed to manifest histologic features of oligodendroglioma. Three out of 4, where additional tissue was available, were additionally negative for co-deletion of 1p/19q by fluorescent in situ hybridization (FISH). Thus, for this study, we considered strong, diffuse P53 immunostaining, or absence of 1p/19q codeletion testing as excluding a diagnosis of oligodendroglioma. ATRX, P53, and 1p/19q codeletion status for individual cases is shown in Figure 1.

Roughly equal numbers of noncanonical *IDH1/2* mutations were seen in both older and younger aged cohort groups, with 4/34 (11.76%) of the older and 16/84 (19.04%) of the younger age cohorts exhibiting a non-R132H *IDH1* or an *IDH2* mutation (χ^2, $P = .3396$). Three cases with noncanonical IDH mutations in the older cohort showed the typical immunohistochemical profile with loss of ATRX and strong p53 staining. Only a single case with IDH1 R132H, positive with immunohistochemistry, showed preservation of nuclear ATRX and negative P53 staining. Thus, the unusual IHC profile did not correlate with a higher likelihood of noncanonical *IDH1* or *IDH2* mutation in our cohort. Atypical immunohistochemical pattern, noncanonical IDH status, or MGMT methylation status had no significant impact on survival in univariate analysis (χ^2, $P > .05$).

DISCUSSION

Isocitrate dehydrogenase-mutant gliomas are uncommon in older adults; consequently, only limited data on these patients' histopathologic, immunohistochemical, and overall survival are available. The literature suggests that older patients with gliomas tend to undergo lower rates of treatment with surgical resection and radiotherapy compared to younger cohorts of patients due to concern for high rates of treatment-related complications.[3] Our study suggests that when older patients with astrocytoma, IDH-mutant, can be treated parallel to

younger patients with the Stupp protocol, many of them can enjoy long-term survival, thus providing an additional incentive for full adjuvant therapy.

As detailed in the "Introduction" section, few studies have explored this patient population.[3–6] Ours is the largest study looking at outcomes in astrocytoma, IDH-mutant in older adults, acknowledging the slightly different criteria used for "older age" in all studies.[3–6] Giantini-Larsen et al[3] presented a series of 13 patients with oligodendroglioma and 12 patients with astrocytoma, IDH-mutant, all aged 65 or older at diagnosis. Unlike their study, we focused exclusively on astrocytoma, IDH-mutant, to extend our original 2017 study. We also included a comparison group of younger patients (aged 19-54 years) from our institution, treated similarly with the Stupp by the same clinicians. Similar to Morshed et al,[5] we show that the outcome of astrocytoma, IDH-mutant in older patients is relatively favorable. Despite CNS WHO 2021 noting "adverse prognosis in patients ≥55 years" with astrocytomas, IDH-mutant,[12] survival of 5 years or more was seen in a third of all patients ≥55 years in our cohort (Figure 2). Based on chart review, it appeared that a high percentage of the older patients at our institution received a full course of adjuvant chemoradiation, comparable in dose and type to that administered to young patients. While the cause of demise for our older patients was listed as their tumor, we cannot rule out the possibility that other comorbidities in older patients might further have contributed to their more adverse prognoses.

As shown previously, a larger percentage of astrocytomas, IDH-mutant, in the older age group do not show the typical IHC pattern of loss of nuclear ATRX and strong diffuse P53 staining.[4,5] Our findings, therefore, mirror that of the Andrews and Prayson study,[4] which showed a wild-type ATRX pattern in over 70% of patients over 55 years. The explanation for this is not apparent, but fortunately, the vast majority of older patients in both the study by Andrews and Prayson[4] and our study did show canonical mutation, as indicated by IDH1 R132H immunopositivity. Of note, in our study, IDH-mutant cases with unusual IHC profiles of retention of nuclear ATRX and absence of strong p53 immunostaining further lacked codeletion of 1p/19q, as assessed by FISH, eliminating oligodendroglioma as a diagnostic consideration.

We identified an almost equal proportion of noncanonical *IDH1/2* mutations in the younger and older age cohorts in our study. This contrasts with the study by Andrews and Prayson, which showed IDH1 R132H immunopositivity in less than a quarter of their cases. Whether atypical IHC profiles occurred preferentially in tumors with canonical IDH1 R132 immunopositivity or noncanonical cases was not specified.[4]

A limitation of this study is that few of our cases had had the molecular workup now recommended for astrocytoma, IDH-mutant, namely the presence of *CDKN2A/B* homozygous deletion.[12] We also acknowledge that we followed standard practices of many laboratories in not assessing glioblastoma, IDH-wildtype, WHO grade 4 by further molecular testing for *IDH1/2* in patients aged 55 years or older who had negative IDH1 R132H immunostaining and retention of nuclear ATRX. In fact, the current WHO criteria recommend that "absence of immunoreactivity for IDH1 p. R132H is sufficient (ie without further sequencing) to diagnose IDH-wildtype glioblastoma in a patient aged ≥ 55 years at diagnosis who has a histologically classic glioblastoma not located in midline structures and no history of a pre-existing lower-grade glioma." We cannot definitively rule out the possibility of missing noncanonical IDH mutant gliomas with wildtype P53 and ATRX immunostaining patterns, however. Further studies are needed to evaluate the prevalence of noncanonical IDH1/2 mutations in diffuse gliomas in the older population.

In conclusion, our study and those of the literature suggest that at least 10% of astrocytomas, IDH-mutant, occur in older aged adults (in our study defined as ≥55 years). Thus, they are uncommon but certainly not rare. Survival is still favorable in our study and the few previously in the literature.[3] While overall survival is decreased in persons aged 55 years or older with astrocytoma, IDH-mutant compared to the younger aged cohort, at least at our institution, a significant number enjoy long survival (>5 years) with receipt of adjuvant therapies.

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CONFLICTS OF INTEREST

None declared.

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