Cohort Study

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Impact of IDH mutation and adjuvant chemo(radio) therapy on survival outcome in grade II/III astrocytoma: a retrospective cohort study based on SEER database

Mohammad Hamad, MD[a], Mohamed Ahmed Ali, MD[b], Esraa Hamouda, MD[c], Heba Hamouda, MD[c], Nahla Ali, MD[d], Bushra Al-Shaikh, MD[e], Asmaa Ellaithy, MD[f]

Background: Astrocytoma is a primary brain tumor arising from specific glial cells called astrocytes. Isocitrate dehydrogenase (IDH) mutations represent an early oncogenic event in glioma evolution. The 2-hydroxyglutarate builds up and is produced in grade II/III astrocytoma. Adjuvant chemo(radio)therapy is the standard treatment. Optimal treatment strategies are controversial due to the risk-benefit ratio. This study aimed to assess the effect of IDH mutation on the survival outcome with different treatment modalities for better understanding of the disease.

Methods: Data were obtained from the SEER program for patients with diffuse and anaplastic astrocytoma diagnosed from 2018 to 2020. Patients were divided into wild-type (wIDH) and mutant-type (mIDH) groups and subclassified based on the received adjuvant therapy (chemotherapy, radiotherapy, chemoradiotherapy). All patients had surgery (tumor destruction, local excision, partial, radial, and total gross resection). SPSS 27 was used for statistical analysis, Kaplan–Meier curve, and Long-Rank test for survival analysis.

Results: Out of 811 patients, 486 (59.9%) had mIDH, and 325 (40.1%) had wIDH. The 2-year relative survival for mIDH was 95% and 51% for wIDH, $P < 0.001$. The highest 2-year relative survival among the mIDH group was for patients who received adjuvant chemotherapy (100%), compared to adjuvant chemoradiotherapy (95.3%) and adjuvant radiotherapy (81.2%), $P = 0.051$. The 2-year survival for wIDH who received adjuvant chemotherapy, combined adjuvant chemoradiotherapy, and adjuvant radiotherapy were 66%, 51%, and 42%, respectively; $P = 0.022$.

Conclusions: The mIDH had better 2-year relative survival compared to wIDH across all treatment modalities. Adjuvant chemotherapy had more than 20% survival benefit compared to radiotherapy in mIDH and wIDH. These results highlight adjuvant chemotherapy as the modality of choice for mIDH to improve the survival outcome and avoid radiotherapy's unfavorable side effects. The study was registered at Clinicaltrial.gov with identification number of NCT06620926.

Keywords: astrocytoma, chemotherapy, radiotherapy, survival, wild IDH

Introduction

Malignant brain tumors represent 1% of all invasive cancer cases in the United States. They are the leading cause of cancer death among males aged <40 years and females aged <20 years[1]. Being an extremely heterogeneous group of tumors, they comprise a diverse constellation of over 100 histologically distinct subtypes according to the World Health Organization (WHO) Classification of tumors of the Central Nervous System (CNS)[2].

Isocitrate dehydrogenase (IDH) enzymes catalyze the oxidative decarboxylation of isocitrate, playing an important role in the Krebs cycle and maintenance of stable conditions in the

HIGHLIGHTS

- Adjuvant chemotherapy was found to have a superior survival outcome in both wild-type and mutant-isocitrate dehydrogenase (IDH) patients.
- Race had an association with the survival outcome and African–Americans had better 2-year relative survival compared to American Indians and Alaskan natives.
- In mutant-IDH, adjuvant chemotherapy and adjuvant combined chemoradiotherapy had an improved 2-year cause-specific survival compared to adjuvant radiotherapy.
- There was no significant survival difference between different adjuvant therapies in the management of mutant-IDH group.

[a]Faculty of Medicine, The University of Jordan, Amman, Jordan, [b]Faculty of Medicine, South Valley University, Qena, Egypt, [c]Faculty of Medicine, Menoufia University, Menoufia, Egypt, [d]Faculty of Medicine, Alexandria University, Alexandria, Egypt, [e]Faculty of Medicine, Sana'a University, Sana'a, Yemen and [f]Faculty of Medicine, Suez Canal University, Ismailia, Egypt

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Corresponding author. Address: Faculty of Medicine, Sana'a University, Sana'a, Yemen. Tel.: +201024685762. E-mail: Bushra.Alshaikh.ye@gmail.com (B. Alshaikh).

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cell[3]. These mutations occur at a single amino acid residue of the IDH1/2 active site resulting in loss of the enzyme's ability to catalyze conversion of isocitrate to α-ketoglutarate[4]. Mutations in IDH can be seen in a range of human malignancies including astrocytoma.

According to the 2021 revision of the WHO classification of CNS tumors, astrocytoma and gliomas that arise from astrocytes specifically, are classified into two subtypes according to the IDH mutations: IDH-mutant (mIDH) and IDH-wild (wIDH)[5]. Astrocytoma, mIDH is graded, according to the level of anaplasia and mitotic activity, into CNS WHO grade II, III, IV. mIDH astrocytoma makes up the largest proportion of low-grade gliomas (80% of CNS WHO grade II–III), and a small proportion of high-grade gliomas (5% of CNS WHO grade IV gliomas)[6]. Compared to wIDH astrocytoma, mIDH astrocytoma is more common in the elderly with male predominance[5] with a better prognosis[7].

Clinicians still face a dilemma regarding the management of mIDH astrocytoma[8]. However, high-grade tumors require a more careful approach. Post-operative radiotherapy, despite its serious side effects on cognitive functions, is still offered to patients with high-grade tumors. Adjuvant/neoadjuvant chemotherapy shows the maximal effect in high-grade astrocytoma[9].

The cornerstone for the treatment of grade II and III diffuse astrocytoma is surgery. However, the patients should receive adjuvant chemo(radio)therapy[10]. The purpose of this study was to assess the impact of IDH mutation on the survival outcome with a comprehensive analysis of different treatment modalities to enhance treatment selection and expand our comprehension of mIDH astrocytoma.

Methods

Patients selection

patients with diffuse/anaplastic astrocytoma diagnosed from 2018 to 2020 were identified from the Surveillance, Epidemiology, and End Results (SEER) (www.seer.cancer.gov), which cover about 30% of the US population using SEER*Stat software. We used the Incidence – SEER Research Data, 17 Registries, Nov 2022 Sub (2000–2020) database – Linked to County Attributes – Time-Dependent (1990–2021) Income/Rurality, 1969–2021 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission." Ethical consent was not required in this study as the patients' data from the database were anonymous[11,12]. The study has been reported in line with the STROCSS criteria[13]. The study was registered at Clinicaltrial.gov with identification number of NCT06620926.

Patients were selected only if they had malignant behavior (defined according to SEER variable "Behavior code ICD-O-3 = Malignant"), a known age, and it was their first primary tumor with sequence 0 or 1. We excluded patients with unknown survival time, death certificate only, and autopsy only. Astrocytoma patients were identified using the variable "SEER brain and CNS record" in which "diffuse and anaplastic astrocytoma" was chosen. IDH status was determined by the variable "Site-Specific Data Items.Brain Molecular Markers (2018+)" and assigning the following codes "(9401/3)," "(9400/3)".

The clinicopathological data of patients, including the age, gender, race, IDH status (mutant/wild), astrocytoma type (diffuse/anaplastic), surgery (tumor destruction, Local excision, partial, radical, total gross resection, Surgery NOS), radiation (Beam radiation, Radioactive implants including brachytherapy, Radioisotopes, Combination of beam with implants or isotopes, Radiation, NOS method or source not specified), chemotherapy, vital status, and survival months, were extracted.

Eligible patients were categorized into two groups based on the IDH mutation (wild, mutant), and further subclassified based on treatment modalities, which included adjuvant chemotherapy, adjuvant radiotherapy, and combined adjuvant chemoradiotherapy. Adjuvant chemotherapy was defined as receiving chemotherapy with having one of the above-mentioned surgeries while adjuvant radiotherapy was defined as receiving radiotherapy with the surgical intervention, and adjuvant chemoradiotherapy means the patient had a surgical intervention with combined chemoradiotherapy.

Table 1.

Demographic and clinical characteristics of patients with wIDH or mIDH

Column 1	Total (*n*, %)	wIDH (*n*, %)	mIDH (*n*, %)
Total	811 (100%)	325 (40.1%)	486 (59.9%)
Sex			
Male	449 (55.4%)	178 (39.6%)	271 (60.4%)
Female	362 (44.6%)	147 (40.6%)	215 (59.4)
Race			
White	683 (85.2%)	277 (40.6%)	406 (59.4%)
Black	51 (6.4%)	21 (41.2%)	30 (58.8%)
Asian or Pacific Islander	64 (8%)	24 (37.5%)	40 (62.5%)
American Indian/Alaska Native	4 (0.5%)	1 (25%)	3 (75%)
Adjuvant therapy			
Chemoradiotherapy	731 (90.1%)	280 (38.3%)	451 (61.7%)
Radiotherapy	53 (6.5%)	34 (64.2%)	19 (35.8%)
Chemotherapy	27 (3.3%)	11 (40.7%)	16 (59.3%)
Astrocytoma type			
Diffuse	285 (35.1%)	103 (12.7%)	182 (22.4%)
Anaplastic	526 (64.9%)	222 (42.2%)	304 (57.8%)

Procedure

Cause-specific survival (CSS) was calculated using the SEER cause-specific death classification variable as an endpoint. Deaths that were attributed to cancer according to the defined SEER cause-specific death classification variable were treated as deaths caused by cancer and other causes were censored.

Table 2.

OS and CSS for various treatment patterns in mutant and Wild IDH astrocytoma

IDH	Adjuvant therapy following surgery	CSS		OS	
		1-year	2-year	1-year	2-year
Mutant	Chemoradiotherapy	98%	95%	98%	95%
	Chemotherapy	100%	100%	100%	100%
	Radiotherapy	89%	89%	89%	89%
Wild	Chemoradiotherapy	82%	54%	80%	50%
	Chemotherapy	81%	65%	81%	64%
	Radiotherapy	59%	48%	51%	42%

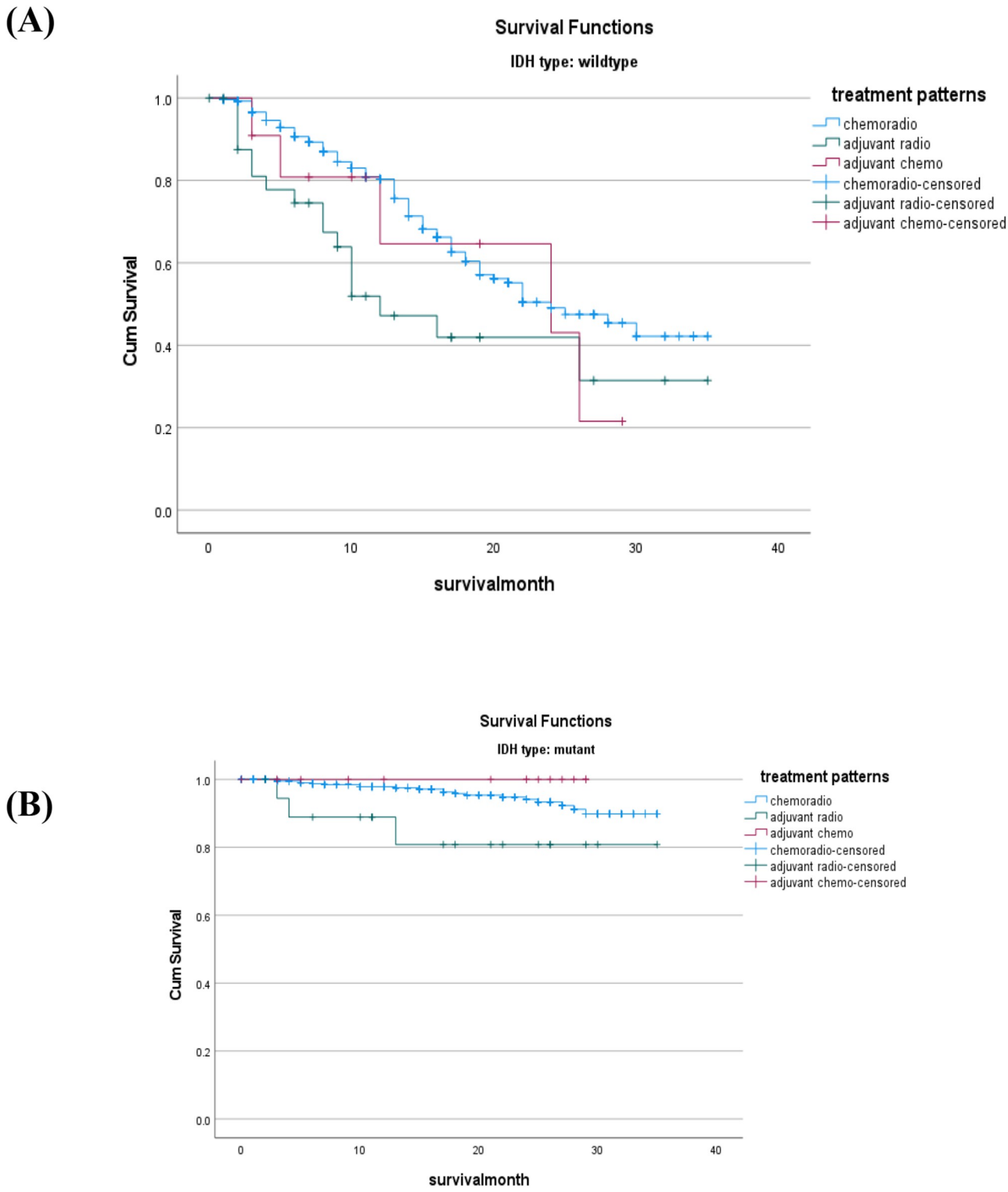

Figure 1. Kaplan–Meier curves show the association between different treatment modalities and the OS of wild-IDH (A) and mutant-IDH (B).

Survival was measured in months and patients were censored at the date of a patient being lost to follow-up. The overall survival (OS) was defined as the observed survival resulting from all causes of death. Relative survival was calculated with SEER as the ratio of observed survival to expected survival in cancer-free patients. Expected survival rates were calculated using the 1990 and 2000 US decennial life tables that were matched on age, sex, year of diagnosis, and race (White, Black, and Other).

Table 3.

The relative survival for gender and race among each IDH-type

IDH type	Variable	Relative survival		*P*-value
		1-year	2-year	
	Gender			
	Male	98%	94%	0.69
	Female	97%	96%	
Mutant	Race			
	White	97%	94%	
	Black	96%	92%	0.72
	Asian or PI	100%	NA	
	AI/AN	96%	96%	
	Astrocytoma type			
	Diffuse	97%	97%	0.28
	Anaplastic	97%	93%	
	Gender			
	Male	81%	52%	0.36
	Female	74%	49%	
	Race			
	White	77%	49%	
Wild	Black	95%	70%	0.04
	Asian or PI	NA	NA	
	AI/AN	73%	50%	
	Astrocytoma type			
	Diffuse	78%	51%	0.85
	Anaplastic	78%	51%	

PI, Pacific Islander; AI, American Indian; AN, Alaskan Native.

Data analysis

Edreer II method was used to calculate the expected survival. This method calculates expected survival rates for patients under observation at each point of follow-up, considering matched individuals to be at risk until the corresponding cancer patient dies or is censored. Survival rates were calculated using pre-calculated duration. The demographic and clinicopathological characteristics were assessed with chi-square test and *t*-test between groups. Multivariate COX-regression models were applied to calculate the hazard ratio (HR) with a 95% confidence interval (CI) and significance was achieved at 0.05. We used a stepwise selection process, incorporating both forward and backward selection methods, to determine the final set of confounders. We used the Kaplan–Meier curve and Log-Rank test for survival analysis. We used SPSS version 27 for data analysis.

Results

Patient characteristics

We identified 811 patients for this study according to our patient selection criteria. Their mean age was 44 years (SD = 16.3). About 59% had mIDH. The most prevalent race was the Caucasians (84.2%). Males represented 55.4% of the patients. Most of the patients had anaplastic astrocytoma (64.9%). The majority received chemoradiotherapy (90.1%). Detailed characteristics are mentioned in Table 1.

Survival analysis

In mIDH, adjuvant chemotherapy and adjuvant combined chemoradiotherapy had an improved 2-year CSS compared to adjuvant radiotherapy (100%, 95%, and 88%) While the 2-year OS for them was 100%, 94%, and 88%, respectively, (P = 0.051) (Fig. 1B). However, the 2-year CSS in wIDH was 65% for adjuvant chemotherapy, 54% for adjuvant combined chemoradiotherapy, and 48% for adjuvant radiotherapy with an OS of 54%, 50%, and 42% (P = 0.02) (Fig. 1A). For more details see Table 2.

Looking at other variables independently, in the wIDH group, both genders and astrocytoma types had no impact on the survival time (P > 0.05). However, Race had an association with the survival outcome and African–Americans had better 2-year relative survival (70.5%) compared to American Indians and Alaskan natives (50.1%, P = 0.04). See Table 3 and Fig. 2. However, among the mIDH group, no significant associations were found for the same variables (see Fig. 3).

Performing COX-regression model showed adjuvant radiotherapy had statistically significant worse odds of death (HR = 2.079, 95% CI: 1.269–3.406, P = 0.004). However, mIDH had better odds of death (OR = 0.18, 95% CI: 0.110–0.297, P < 0.00001). There was no significant difference in the odds of death for astrocytoma type, sex, and race (Table 4).

Discussion

Patients with mIDH astrocytoma generally have better survival outcomes compared to those with wIDH type. The 2-year relative survival was 95% for the mIDH and 51% for wIDH. These results are consistent with Cho *et al* study in which grade II and III IDH1/2-mutated astrocytic cases had a 5-year survival rate of 88% compared to 57% in IDH1/2-wildtype cases[14]. Another study highlighted that IDH1 mutant astrocytoma's, including anaplastic astrocytoma's and glioblastomas, showed substantially improved survival rates compared to IDH1 wild-type

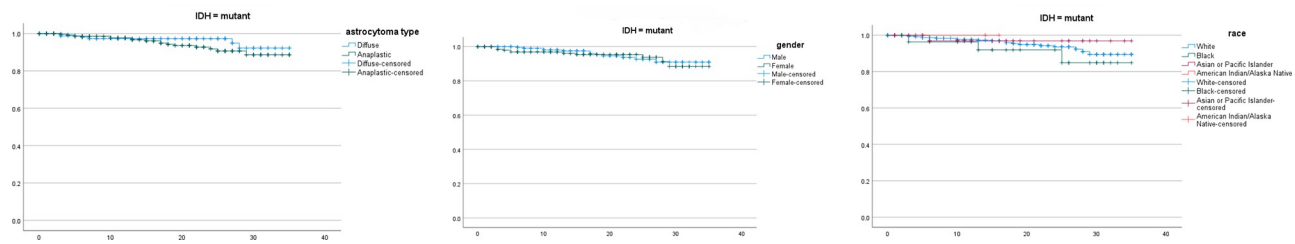

Figure 2. Kaplan–Meier curves show the association between the OS and astrocytoma type, race, and sex within IDH-mutant patients.

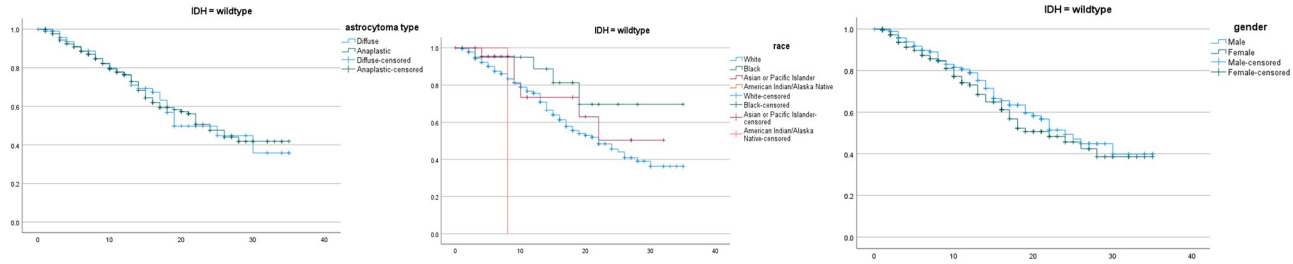

Figure 3. Kaplan–Meier curves show the association between the OS and astrocytoma type, race, and sex within IDH-wildtype patients.

tumors, with an estimated median survival of 163.4 months for IDH1 mutant[15].

This might be explained by the slower growth rate for mIDH astrocytoma compared to wIDH. The presence of IDH mutations is associated with alterations in the cellular metabolism, leading to the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG). This metabolite inhibits enzymes involved in cellular differentiation and promotes a less aggressive tumor phenotype leading to a slower tumor growth and less aggressiveness[16]. Tumor development process vary between mIDH and wIDH gliomas leading to variations in the molecular characteristics and vulnerabilities that influence their response to several treatment modalities[17].

Our results revealed that among the mIDH group, the majority (92%) received adjuvant chemoradiotherapy. In contrast, a smaller proportion of wIDH patients (86.1%) received adjuvant chemoradiotherapy, with a notable subset opting for adjuvant chemotherapy (3.4%) or adjuvant radiotherapy (10.5%). Among mIDH patients, the highest relative survival rate was observed in those who received adjuvant chemotherapy (100%) followed by adjuvant chemoradiotherapy (95.3%), and lastly, those who received adjuvant radiotherapy (81.2%). These findings suggest mIDH tumors may exhibit increased sensitivity to chemotherapy, potentially due to underlying molecular mechanisms associated with IDH mutation status.

Table 4.

Multivariate Cox-regression model shows the association of treatment patterns, histology, IDH type, gender, and race with the 2-year OS

	HR	95% CI	Sig.
Adjuvant therapy			
Chemoradiotherapy	Reference		0.013
Radiotherapy	2.079	1.269–3.406	0.004
Chemotherapy	0.906	0.360–2.281	0.835
Astrocytoma type			
Diffuse	Reference		0.915
Anaplastic	1.021	0.703–1.482	0.915
IDH type			
Wildtype	Reference		<0.001
Mutant	0.18	0.110–0.297	<0.001
Sex			
Male	Reference		0.486
Female	1.132	0.799–1.603	0.486
Race			
White	Reference		0.487
Black	0.768	0.355–1.661	0.503
Asian/Pacific islander	0.707	0.328–1.525	0.377
American-Indian/Alaska Native	3.056	0.422–22.155	0.269

Findings from the NOA-04 trial indicated that there was no significant difference in outcomes between using PCV (procarbazine, lomustine, vincristine) or temozolomide in combination with radiotherapy compared to radiotherapy alone for these patients[18]. However, The CATNON (EORTC26,053) trial demonstrated that administering radiotherapy followed by a maximum of 12 cycles of temozolomide extends the OS period in cases of mIDH tumors[19].

In contrast, survival outcomes among wIDH patients varied depending on the treatment modality. Notably, wIDH patients who received adjuvant chemotherapy had the highest survival rate (66%), indicating a potential benefit from systemic chemotherapy following surgical excision in this subgroup. However, patients receiving adjuvant chemoradiotherapy (51%) or adjuvant radiotherapy (42.6%) had worse survival outcome highlighting the need for alternative treatment strategies in this population.

While our study provides valuable insights into the association between IDH mutation status, treatment patterns, and survival outcomes in astrocytoma patients, there were some limitations: the retrospective nature of the study may introduce recall bias. SEER database lacks some data about confounding factors that could influence the interpretation of results such as smoking and associated other diseases. In addition, SEER does not provide any data regarding the types of chemotherapy. Although our patients were from the SEER data which represent 30% of the US population, the relatively small sample size may limit the generalizability of our findings to broader patient populations. However, this is the first retrospective study that handles the effect of IDH mutation in association with the treatment pattern to follow, which ultimately will lead to better management outcomes in patients and enhance the treatment-choosing process. Future prospective studies with larger cohorts and standardized treatment protocols are warranted to confirm the observation reported.

In conclusion, our study highlights the importance of molecular biomarkers, such as IDH mutation status, in guiding therapeutic decision-making and improving survival outcomes in astrocytoma patients. As, adjuvant chemotherapy was found to have a superior survival outcome in both wild-type and mutant-IDH patients. Tailored treatment approaches based on molecular profiling may hold promise for optimizing patient outcomes and advancing personalized medicine in the management of this challenging disease.

Ethical approval

Ethics approval was not required for this study as it was a retrospective SEER-based study and the data are anonymized and publicly available. However, the protocol was registered at Clinicaltrail.gov with identification number of NCT06620926.

Consent

Informed written consent was not required for this study as it was SEER based which concealed patients' personal data and the data were anonymous.

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Author's contribution

Conceptualization, data analysis, writing, study design, data extraction: M.H.; writing, figures, and tables creation: M.A.A.; interpreting findings, writing: E.H.; interpreting findings, writing: H.H.; writing, literature review: N.A.; writing: B.A.-S.; supervision, data extraction, editing: A.E. All authors approved the submitted version of the manuscript.

Conflict of interest disclosure

The authors have no relevant financial or non-financial interests to disclose.

Research registration unique identifying number (UIN)

The study was registered at Clinicaltrial.gov with identification number of NCT06620926. https://clinicaltrials.gov/study/NCT06620926.

Guarantor

Asmaa Ellaithy and Mohamed Ahmed.

Provenance and peer review

Not invited.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Presentations

The abstract was presented at ESMO targeted anticancer therapy congress 2024.

Assistance with the study

Not applicable.

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