Incorporating genomic signatures into surgical and medical decision-making for elderly glioblastoma patients

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Glioblastoma (GBM) is the most common type of malignant primary brain tumor in adults. It is a uniformly fatal disease (median overall survival 16 months) even with aggressive resection and an adjuvant temozolomide-based chemoradiation regimen. Age remains an independent risk factor for a poor prognosis. Several factors contribute to the dismal outcomes in the elderly population with GBM, including poor baseline health status, differences in underlying genomic alterations, and variability in the surgical and medical management of this subpopulation. The latter arises from a lack of adequate representation of elderly patients in clinical trials, resulting in limited data on the response of this subpopulation to standard treatment. Results from retrospective and some prospective studies have indicated that resection of only contrast-enhancing lesions and administration of hypofractionated radiotherapy in combination with temozolomide are effective strategies for optimizing survival while maintaining baseline quality of life in elderly GBM patients; however, survival remains dismal relative to that in a younger cohort. Here, the authors present historical context for the current strategies used for the multimodal management (surgical and medical) of elderly patients with GBM. Furthermore, they provide insights into elderly GBM patient-specific genomic signatures such as isocitrate dehydrogenase 1/2 (*IDH1/2*) wildtype status, telomerase reverse transcriptase promoter (*TERTp*) mutations, and somatic copy number alterations including *CDK4/MDM2* coamplification, which are becoming better understood and could be utilized in a clinical trial design and patient stratification to guide the development of more effective adjuvant therapies specifically for elderly GBM patients.

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GLIOLASTOMA (GBM) is the most common and most aggressive primary brain tumor in adults.¹ Standard of care entails maximum safe resection followed by concurrent temozolomide (TMZ)-based chemotherapy and radiotherapy, a regimen associated with a median survival of 16 months.² Although GBM is uniformly fatal across all demographics, age remains an independent risk factor for a poor prognosis in newly diagnosed GBM cases, regardless of baseline function, tumor size, or administration of the standard treatment regimen.^{3,4}

From 1977 to 2000, the median age at GBM diagnosis was 63 years, with diagnosis increasing at a rate of 2.3% per year during that period.⁵ According to the Central Brain Tumor Registry of the United States (CBTRUS), the median age at diagnosis of GBM from 2005 to 2009 was 64 years and from 2011 to 2015 it was 65 years.^{6,7} Unfortunately, the management of GBM in the elderly (i.e., age ≥ 65 years) remains variable, with a tendency toward conservative approaches that are not evidence-based.⁸ Since elderly patients remain underrepresented in many GBM clinical trials, most current management strategies are ex-

ABBREVIATIONS BEV = bevacizumab; CNS = central nervous system; EOR = extent of resection; GBM = glioblastoma; GGN = German Glioma Network; GTR = gross-total resection; *IDH1/2* = isocitrate dehydrogenase 1/2; *MGMT* = [6]-methylguanine-DNA methyltransferase; OS = overall survival; PFS = progression-free survival; PR = partial resection; RT = radiation therapy; SCNA = somatic copy number alteration; SRS = stereotactic radiosurgery; STR = subtotal resection; SupTR = supratotal resection; *TERTp* = telomerase reverse transcriptase promoter; TMZ = temozolomide; VEGF = vascular endothelial growth factor.

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trapolations from results obtained from biologically distinct tumors in younger populations.⁷⁻⁹

In this review, we provide a historical perspective on the successes and failures of the multimodal management of GBM in the elderly. We also report how progress on the genomic front has impacted what constitutes a maximum safe extent of resection (EOR) in the elderly, the choice and timing of chemoradiation, and the development of targeted therapy based on the unique genomic profiles of elderly GBM patients.

Current Strategies for the Management of GBM in the Elderly Patient

Standard of care for newly diagnosed GBM remains maximum safe resection followed by concurrent TMZ (75 mg/m²/day for 6 weeks) and external beam radiation therapy (EBRT; 60 Gy in 30 fractions over 6 weeks), with subsequent maintenance cycles (n = 5) of TMZ (150–200 mg/m²/day for the first 5 days of a 28-day cycle).² The adjuvant chemoradiation protocol is based on a clinical trial in patients younger than 70 years old with end data extracted to fit the elderly population.² Few retrospective studies and prospective clinical trials have specifically addressed multimodal management of GBM in elderly cohorts (Table 1).⁹⁻²⁴ Despite this research, the survival of elderly patients remains poor (Fig. 1).

Some elderly patients present with frailty, which is defined as loss of reserve (energy or cognitive function) and accumulation of deficits.²⁵ Frailty has been shown to influence management decisions and predict surgical outcomes in elderly patients.²⁵ Objectively, frailty is assessed using scales such as the Canadian Study of Health and Aging 70-item Frailty Index (CSHA-FI), based on history and physical examination (including comorbidities such as seizures, diabetes, and congestive heart failure).²⁶ A simpler form of the CSHA-FI is the modified Frailty Index (mFI), including 11 items and shown to predict morbidity and mortality in elderly patients.²⁶ In neurosurgery, frail patients (higher mFI) or those with a poor Karnofsky Performance Status (KPS) have been less likely to undergo surgery (p = 0.0002, OR 0.15) versus biopsy and have decreased overall survival (OS; p = 0.0028).²⁵

Even with a matched KPS and tumor size, however, age (≥ 65 years) remains an independent risk factor for a poor prognosis.¹¹ This suggests that elderly patients may have underlying differences in tumor biology and could benefit from a different management approach that includes assessing and targeting differences in underlying biology compared with that in younger patients. Below, we discuss the historical context for both surgical and medical management of newly diagnosed and recurrent GBM as it pertains to elderly patients.

Surgery

In GBM, a more aggressive EOR, such as lobectomy or supratotal resection (SupTR; resection of areas with FLAIR signal abnormality), has been shown to be superior to gross-total resection (GTR) in two studies (median OS 20.7 vs 15.5 months, respectively, p = 0.001;²⁷ and median OS 44.1 vs 18.7 months, p = 0.040²⁸). Unfortunately, these

studies did not specifically address whether SupTR would benefit elderly patients by improving OS while maintaining baseline functional status. In the elderly, GTR and subtotal resection (STR) have been shown to be superior to partial resection (PR) or biopsy (median OS: GTR 17.7 vs STR 16.1 vs PR 11.4 vs biopsy 4 months).¹² However, the EOR maximizing OS in the elderly patient, while preserving baseline quality of life, remains undefined.

To develop a new roadmap for maximal safe resection across all demographics, some authors conducted a retrospective multicenter cohort study of 761 GBM patients to assess the association of EOR of contrast-enhancing and nonenhancing masses with molecular and clinical information, including age (≥ 18 years).²⁹ This research demonstrated that resection of both contrast- and noncontrast-enhancing masses (SupTR) in younger patients (age < 65 years) with isocitrate dehydrogenase 1/2 (*IDH1/2*)-wildtype tumors resulted in survival outcomes similar to those of patients with *IDH1/2*-mutant tumors (median OS 37.3 months). Interestingly, elderly patients (age > 65 years) with *IDH1/2*-wildtype tumors benefited the most from resection of only the contrast-enhancing mass (GTR, median OS 12.4 months). These findings suggest that in younger patients (regardless of *IDH1/2* status), a SupTR is needed to provide the best survival outcome possible, while elderly patients benefit most from GTR with the preservation of baseline quality of life.

In retrospective studies, the benefit of surgery for recurrent GBM remains controversial at any age.^{30,31} Therefore, until prospective randomized trials are performed, the decision to reoperate should be based on clinical status and focal disease, with stereotactic radiosurgery (SRS) as a salvage option in patients too frail to undergo surgery.³² Looking ahead, we anticipate that genomics-based patient stratification (such as *IDH1/2* status²⁹) will contribute to the standardization of surgical management across age demographics and that optimizing the postresection adjuvant treatment regimen (chemotherapy and radiation) in the elderly cohort will be critical for targeting residual microscopic tumor foci left behind following GTR.

Chemotherapy

Prior to TMZ-based chemotherapy for GBM, the relevance of adjuvant chemotherapy for GBM was extremely controversial given mixed results from clinical trials.^{2,33} Before TMZ-based chemotherapy became part of the GBM standard of care, we performed a meta-analysis of 16 randomized clinical trials (> 3000 patients) to compare the survival benefit of radiation therapy (RT) alone versus that with RT plus multiple chemotherapeutic agents for high-grade glioma.⁴ This meta-analysis demonstrated that chemotherapy provided a significant survival benefit when combined with radiation. Given the significant impact of age on survival, we also evaluated age as a potential confounder of the positive effect of chemotherapy on survival. The vast majority of studies (14/16) were balanced in terms of age distribution across treatment arms. Of the two studies reporting an age imbalance, one showed 62% of patients younger than 50 years in the chemotherapy arm and 34% of patients younger than 50 in the radiation arm.³⁴ The other study reported the opposite, with 48% of

TABLE 1. Studies including elderly patients with GBM

Authors & Year	Study Design	Publication Year	Age (yrs)	Arms	No. of Cases	Median OS (mos)
Surgery						
Vuorinen et al., 2003 ⁹	Prospective	2003	≥65	Biopsy Resection	16 14	2.8 5.6*
Iwamoto et al., 2009 ¹⁰	Retrospective	2009	≥65	GTR PR Biopsy	109 212 73	
Chaichana et al., 2011 ¹¹	Retrospective	2011	≥65	Resection Biopsy	40 40	5.7* 4.0
Oszvald et al., 2012 ¹²	Retrospective	2012	≥65	GTR STR PR Biopsy	19 26 35 66	17.7* 16.1* 11.4* 4
Chemotherapy						
Pérez-Larraya et al., 2011 ¹³	Prospective phase 2	2011	≥70	TMZ	70	6.2
Wick et al., 2013 ³⁸ (NOA-08)	Prospective phase 3	2012	>60	TMZ Standard RT	195 178	8.2 9.8
Malmström et al., 2012 ¹⁵ (NCBTSG)	Prospective phase 3	2012	>60	Standard RT Hypo-RT TMZ	100 123 119	6 7.5 8
RT						
Keime-Guibert et al., 2007 ¹⁶ (ANOCEF)	Prospective randomized	2007	≥70	RT + supp care Supp care alone	39 42	7.3 4.2
Scott et al., 2011 ¹⁷	Retrospective (registry)	2011	>70	RT No RT	1817 1019	
Hypo-RT vs standard RT						
Bauman et al., 1994 ¹⁸	Prospective	1994	≥65	Hypo-RT Supp care (historical) Standard RT (historical)	29	6* 1 10
Roa et al., 2004 ¹⁹	Randomized phase 2	2004	≥65	Standard RT Hypo-RT	51 49	5.1 5.6
Perry et al., 2017 ²⁰ (CCRTG CE.6/EORTC)	Prospective randomized	2017	≥65	Hypo-RT Hypo-RT w/ TMZ	281 281	7.6 9.3
Standard RT vs concurrent RT w/ TMZ						
Gerstein et al., 2010 ²¹	Retrospective	2010	≥65	Concurrent RT w/ TMZ	51	11.5
Minniti et al., 2012 ²²	Prospective	2012	≥70	Concurrent RT w/ TMZ	32	10.6
Concurrent hypo-RT w/ TMZ						
Minniti et al., 2008 ²³	Prospective	2008	≥70	Concurrent hypo-RT w/ TMZ	71	12.4
Cao et al., 2012 ²⁴	Retrospective	2012	≥60	Hypo-RT Concurrent hypo-RT w/ TMZ	57 55	6.9 9.3

hypo-RT = hypofractionated RT; supp = supportive.

* Statistically significant.

patients younger than 50 years in the chemotherapy arm compared with 57% of patients under the age of 50 in the radiation arm.³⁵ We performed the meta-analysis with and without both of these studies and found no effect on the overall analysis. Although no treatment-specific age data were reported in most of the studies reviewed, this meta-analysis corroborated the beneficial effect of chemotherapy independent of age.

Twelve years later, a prospective, randomized, multicenter phase 3 clinical trial was undertaken by the Euro-

pean Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group to assess the efficacy of RT with and without TMZ-based chemotherapy.² The study enrolled 573 patients aged 18–70 years and compared two groups: RT alone and RT with TMZ, an orally administered alkylating agent that readily crosses the blood-brain barrier (BBB), with a less toxic side effect profile relative to those of prior drugs in its class. In combination with RT, TMZ significantly extended the OS of GBM patients, par-

FIG. 1. Survival of patients with GBM based on age. Younger patients (age < 65 years, $n = 147$) with *IDH1/2*-wildtype tumors have better survival than elderly patients (age ≥ 65 years, $n = 109$) with *IDH1/2*-wildtype tumors. Data were obtained from The Cancer Genome Atlas (TCGA) and visualized on OncoScape.²⁵ Given the significant impact of the *IDH1/2* mutation on survival, this analysis excluded all *IDH1/2*-mutant patients ($n = 13$). *** $p < 0.003$ (Cox proportional hazards regression).

ticularly for those presenting with methylation of the gene encoding the DNA repair enzyme, [6]-methylguanine-DNA methyltransferase (*MGMT*; median OS 21.7 vs 15.3 months in unmethylated patients). A secondary endpoint analysis on health-related quality of life showed no detrimental effect following the addition of TMZ to RT. While some studies have shown a higher prevalence of *MGMT* promoter hypermethylation in the elderly cohort,^{36,37} others have shown no significant difference across age demographics.³⁸ Overall, these findings suggested that TMZ-based chemotherapy was well tolerated and had an efficacy in elderly patients with newly diagnosed GBM similar to that in younger patients.

The DIRECTOR trial (Dose-Intensified Rechallenge With Temozolomide, One Week On One Week Off Versus Three Weeks On One Week Off in Patients With Progressive or Recurrent Glioblastoma trial) evaluated the efficacy of rechallenge with TMZ following GBM recurrence in patients aged 18–80 years.³⁹ A multivariate analysis showed that *MGMT* promoter hypermethylation, but not age, predicted OS following treatment. Following TMZ reuse, the median time to treatment failure with *MGMT* promoter hypermethylated tumors was 3.2 months versus 1.8 months in *MGMT* promoter unmethylated tumors. Progression-free survival (PFS) rates at 6 months were 39.7% with *MGMT* promoter hypermethylation and 5.9% without. Since this study included elderly patients whose age was > 65 years, it suggests that TMZ rechallenge may also be effective and well tolerated by elderly patients with recurrent GBM.

Radiation Therapy

The relevance of RT for improving the OS of patients with GBM is well established based on randomized clinical trials.^{40,41} Elderly GBM patients (age > 70 years) who

undergo RT have improved OS compared to patients who do not undergo RT.¹⁷ Cognitive dysfunction and leukoencephalopathy, however, are significantly higher in elderly patients receiving standard RT courses.^{42,43} A prospective, phase 3 clinical trial (Nordic trial) randomized 291 patients 60 years of age or older to receive a standard 6-week course of RT (60 Gy administered in 2-Gy fractions over 6 weeks, $n = 100$), a shorter hypofractionated course of RT (34 Gy administered in 3.4-Gy fractions over 2 weeks, $n = 98$), or TMZ alone (200 mg/m² on days 1–5 of every 28 days for up to 6 cycles, $n = 93$).¹⁵ For patients with an age > 70 years, OS was increased with TMZ (9 months, $p < 0.0001$) and with hypofractionated RT (7 months, $p = 0.02$) compared to that with standard RT (5.2 months). Patient compliance was also worse in the group assigned to the standard RT course than in the hypofractionated RT group (72% vs 94.9% treatment completion rate).

Given these findings, a prospective, randomized, phase 3 clinical trial was performed in elderly patients (age ≥ 65 years) to assess the efficacy of a shorter course of RT (40 Gy in 15 fractions over 3 weeks) with or without concurrent TMZ (75 mg/m²/day for 21 days), followed by adjuvant TMZ (150–200 mg/m²/day for 5 consecutive days of a 28-day cycle for up to 12 cycles or until disease progression);²⁰ 562 patients underwent randomization, and the median age was 73 years. Relative to a shorter course of RT alone, a shorter course of RT combined with TMZ was associated with a longer median PFS (5.3 vs 3.9 months, $p < 0.001$) and median OS (9.3 vs 7.6 months, $p < 0.001$). The effect was more pronounced in *MGMT* promoter hypermethylated GBM, with a median OS of 13.5 months versus 7.7 months with a shorter course of RT alone ($p < 0.001$). These findings indicate that a shorter course of RT combined with TMZ leads to improved OS compared to that with a shorter course of RT alone in elderly GBM patients. Toxicity was slightly higher in the group receiving a shorter course of RT with TMZ than in the group receiving the shorter course of RT alone. A baseline quality-of-life assessment for symptoms and function was performed and found to be similar between the two groups. Only nausea, vomiting, and constipation were associated with the time to deterioration (defined as a 10-point decrease in the score in function or symptoms). As expected, the time to deterioration was shorter in the combination therapy group relative to that in the group with the shorter-course RT. There were no other clinically important differences in the trial groups, indicating that the survival advantage was achieved without a significant impact on quality of life.

Some studies have shown a survival benefit with SRS for recurrent GBM.⁴⁴ With an eye toward optimizing the response of recurrent GBM to SRS, we retrospectively evaluated the pattern of treatment failure (failure location, extent of failure, and time to failure) in patients with recurrent GBM undergoing SRS at our institution over a 10-year period.³² We found that elderly patients presented with a more remote or out-of-field treatment failure location relative to that in the younger cohort (mean age for remote failure 68.3 years vs in-field failure 52.1 years, $p = 0.035$). Since 72% of our cohort was placed on bevacizumab (BEV; anti-vascular endothelial growth factor

TABLE 2. Tumor genomic signatures of elderly GBM patients

Authors & Year	Genomic & Epigenomic Status	Proposed Impact on Prognosis	p Value*
Ferguson et al., 2016 ³⁶	<i>IDH1/2</i> -wildtype	Poor	0.0001
Eckel-Passow et al., 2015 ⁵⁷	<i>TERT</i> p mutation	Poor†	0.0001
Nghiempu et al., 2009 ⁵¹	VEGF-A mRNA upregulation	Poor	<0.01
Cimino et al., 2017 ⁷² & 2018 ⁴⁹	<i>CDK4/MDM2</i> coamplification	Poor	0.0121
Fukai et al., 2020 ⁶⁷			0.031‡
Ferguson et al., 2016 ³⁶	<i>PTEN</i> mutation	Poor	0.0258
Fukai et al., 2020 ⁶⁷			0.0404
Bozdag et al., 2013 ⁴⁸	Higher integrin-mediated cell migration signature (migration & invasiveness)	Poor	<0.03

* Difference between young and elderly GBM patients.

† In *IDH1/2*-wildtype patients.

‡ *CDK4* amplification only.

[VEGF] monoclonal antibody) following recurrence, we evaluated whether BEV use modified the effect of age on treatment failure location and found no significant effect (failure location OR 0.54, $p = 0.99$). There was also no significant association between age and extent of failure or time to failure. These findings indicate that elderly patients with focal recurrent GBM who are too frail to undergo resection may benefit from combining SRS with strategies that address microscopic disease, such as TMZ-based chemotherapy,³⁹ tumor-treating fields,⁴⁵ or immunotherapy.⁴⁶

Genomic Alterations and Adjuvant Treatment Options for the Elderly GBM Patient

Most classic GBM-associated genomic alterations, such as inactivating *TP53* mutations and *EGFR* amplification, are not over-represented in the elderly GBM cohort.⁴⁷ However, tumors in elderly patients possess unique molecular signatures, including different genetic profiles (*IDH1/2*-wildtype status, telomerase reverse transcriptase promoter [*TERT*p] mutation, *PTEN* mutation), expression patterns (VEGF mRNA expression, higher integrin-mediated cell migration), and somatic copy number alterations (SCNAs; *CDK4/MDM2* coamplification; Table 2).^{36,48–50} These biological differences provide opportunities for investigation of age-specific adjuvant treatment regimens.

Vascular Endothelial Growth Factor A and Bevacizumab

VEGF-A mRNA is upregulated in elderly patients with GBM.^{50,51} The clinical relevance of this expression pattern was highlighted following the addition of BEV to TMZ-based chemoradiation regimens in patients with primary GBM in two studies, AVAglio (A Study of Bevacizumab [Avastin] in Combination With Temozolomide

and Radiotherapy in Participants With Newly Diagnosed Glioblastoma) and RTOG 0825 (Temozolomide and Radiation Therapy With or Without Bevacizumab in Treating Patients With Newly Diagnosed Glioblastoma).^{52,53} Although this regimen did not prolong OS in study cohorts, initial reports demonstrated preferential benefit in elderly patients (age > 50 years vs younger patients with an age < 50 years, $p < 0.005$).⁵⁴ Therefore, a phase 2 randomized clinical trial (ARTE [Avastin Plus Radiotherapy in Elderly Patients With Glioblastoma]) was conducted to evaluate the efficacy of BEV (10 mg/kg for 14 days) plus hypofractionated RT (40 Gy in 15 fractions; arm A, $n = 50$) versus hypofractionated RT alone (arm B, $n = 25$) in elderly patients 65 years or older with GBM.⁵⁵ The median PFS was longer in arm A than in arm B (7.6 and 4.8 months, $p = 0.003$), but there was no significant difference in median OS between the two arms (12.1 and 12.2 months, respectively, $p = 0.77$). At the molecular level, prolonged PFS was restricted to tumors with receptor tyrosine kinase (RTK) I methylation subtype and a proneural gene expression profile.⁵⁶ These findings suggest that underlying genomic signatures may confer susceptibility to targeted therapy especially in the elderly population. Additional clinical trials including elderly patients stratified based on these genomic features are needed to explore this finding. Today, even though BEV is not indicated for patients with newly diagnosed GBM, it remains FDA-approved for the treatment of *MGMT* promoter unmethylated recurrent GBM and should be considered for elderly patients with tumor recurrence for the reduction of cerebral edema–associated symptoms and for its glucocorticoid-sparing effect.

Metabolism: *IDH1/2* Mutations

Regardless of tumor grade or histology, *IDH1/2* mutations are associated with significantly better OS and are prevalent in younger GBM patients but rare in elderly GBM patients.⁵⁷ Approximately two-thirds of lower-grade gliomas, including all oligodendrogliomas and about half of all diffuse astrocytic gliomas, typically possess *IDH1/2* mutations; however, most GBMs lack *IDH1/2* mutations.⁵⁸ In the 2016 WHO classification of central nervous system (CNS) tumors, *IDH1/2*-mutant and *IDH1/2*-wildtype tumors represent two distinct types of GBM.⁵⁹ This new designation is driven by the profoundly different biology and pathogenesis of *IDH1/2*-mutant compared to *IDH1/2*-wildtype GBM.⁶⁰ Given the unique biology and significantly worse outcomes in *IDH1/2*-wildtype GBM patients, the cIMPACT-NOW (Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) members have proposed that future WHO CNS tumor classification schemes reserve the specific diagnosis of “GBM” for only *IDH1/2*-wildtype diffuse astrocytomas with high-grade histological or molecular features (WHO grade IV).⁶⁰ These terminology changes, if incorporated into the upcoming CNS tumor classification, would have significant implications, as a GBM diagnosis will ultimately be more common in elderly patients purely based on the *IDH1/2*-wildtype status prevalence in this cohort.

Although the mechanism underlying survival differences between *IDH1/2*-wildtype and *IDH1/2*-mutant

FIG. 2. SCNAs in GBM. Distribution shift of SCNA subtypes by age within the *IDH1/2*-wildtype GBM cohort from the GGN ($n = 243$). Distribution shows poor-prognosis SCNA subtypes (combined W1 and W2) occurring predominantly in the elderly population, while better-prognosis SCNA subtype W3 occurs more frequently in the younger population. Dashed lines represent means for SCNA subtypes W1/W2 (pink) and SCNA subtype W3 (green). * $p = 0.0121$ (Mann-Whitney U-test, two-tailed).

GBMs is still being elucidated, biologically relevant differences in tumor genetics, metabolism, and immune microenvironment have been identified.^{61,62} While most studies have focused on targeting mutant *IDH1/2*, pre-clinical evidence suggests that inhibiting *IDH1/2*-wildtype activity in GBM could mimic the therapeutic response of *IDH1/2*-mutant tumors.^{63,64} Genetic and pharmacological inactivation of wildtype *IDH1* reduces levels of nicotinamide adenine dinucleotide phosphate (NADPH), which is critical for the biosynthesis of deoxynucleotides and antioxidants. This results in decreased cell growth, increases apoptosis following radiation-induced DNA damage, and prolongs the survival of mice bearing patient-derived xenografts.^{63,65} Human clinical trials are needed, but these findings suggest that targeting tumor metabolism by decreasing NADPH levels through wildtype *IDH1* inhibition may be a therapeutic option for *IDH1*-wildtype tumors, prevalent in the elderly GBM cohort.

Telomerase Activity: *TERTp* Mutations

TERT encodes for the catalytic subunit of telomerase. Telomerase activity is typically restricted in human somatic cells, in which there are a finite number of cellular divisions prior to senescence and death.⁶⁶ In tumor cells with unlimited replication potential, telomerase activity has been shown to be high.⁶⁶ In GBM, gain-of-function *TERTp* mutations are more prevalent within *IDH1/2*-wildtype tumors and elderly patients.^{57,67} In elderly patients, *TERTp* mutations have been associated with a significantly lower OS than that in patients with wildtype *TERTp* tumors (10.4 vs 18 months, $p = 0.01$).⁶⁸ These findings suggest that targeting mutant *TERTp* may provide another therapeutic approach for elderly GBM patients. An ongoing phase 1/2

human vaccine clinical trial (NCT04280848, Anticancer Therapeutic Vaccination Using Telomerase-Derived Universal Cancer Peptides in Glioblastoma [UCPVax-Glio]) is evaluating the safety and efficacy of telomerase-derived universal cancer peptides in GBM following standard GBM treatment.⁶⁹ Other ongoing strategies to target telomerase activity in GBM have shown some efficacy but remain in the preclinical stages of development, including small molecule-based inhibitors of telomerase activity such as ETP-47228, ETP-47037, and CRISPR-based editing of mutant *TERTp*.^{70,71}

Somatic Copy Number Alterations: *CDK4/MDM2* Coamplification

There is growing evidence that SCNAs, present at both the gene and chromosomal levels, may provide prognostic information for patients with GBM.^{49,72,73} Utilizing a large GBM series, the German Glioma Network (GGN), we have demonstrated that SCNA subgroups (determined by differential status of coamplification of *CDK4/MDM2*, gain of chromosome 1, and gain of chromosome 19) provide prognostic information^{49,72} and show an increased frequency of subtypes associated with a worse prognosis (specifically W1 and W2 with *CDK4/MDM2* amplification) in the elderly population (Fig. 2). Another recent study of a Japanese cohort (Kansai Molecular Diagnosis Network for CNS tumors) compared SCNAs between elderly and younger *IDH1/2*-wildtype GBM patients.⁶⁷ Consistent with our findings, there was a higher prevalence of *CDK4* amplification/gain in the elderly cohort. This suggests that these *IDH1/2*-wildtype GBM-associated SCNA signatures (*CDK4/MDM2* amplification) may contribute to less favorable outcomes in the elderly population.

Large GBM data sets, such as the GGN and The Cancer Genome Atlas (TCGA), provide information about SCNA subtype distribution across general populations but do not address the potential biases present in clinical trial populations, which are biased toward including younger patients and/or those with a better functional status. For example, the randomized phase 2 ARTE clinical trial, which was focused on newly diagnosed GBM in the elderly population,⁵⁵ showed that a majority of elderly patients enrolled in the study had a favorable SCNA signature, unlike the general GBM population, in which a majority of elderly patients have an unfavorable SCNA signature.⁴⁹ This has several implications for GBM clinical trials in the elderly, including the need to balance molecular signatures across trial arms or the desirability of trials tailored toward SCNA subtype-specific responses. Therefore, it may be prudent to perform SCNA profiling at the time of clinical trial enrollment to account for such potential biases, and to facilitate identification of SCNA subtype-specific responses for elderly patients with GBM.

Therapeutically, selective cyclin-dependent kinase (CDK) inhibition may be an option for elderly cohort-prevalent SCNA subtypes (W1 and W2) with *CD4/MDM2* coamplification. Selective CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib have been in clinical trials for other cancers including breast cancer, with ribociclib now used as first-line therapy for advanced hormone receptor-positive (HR+) breast cancer.⁷⁴ In GBM,

a phase 0 human clinical trial of ribociclib demonstrated excellent BBB penetration and distribution within tumors in patients, although there was limited clinical efficacy as monotherapy in recurrent GBM.⁷⁵ Therefore, additional clinical trials assessing the efficacy of ribociclib inhibitors as part of a combinatorial strategy with other therapies are indicated in GBM, particularly in the W1 and W2 SCNA subtype prevalent in the elderly cohort.

Conclusions

Elderly patients with GBM have a much poorer prognosis than younger patients with GBM. This difference in outcomes could be attributed to multiple factors, including a poorer baseline health status and age-related differences in underlying tumor biology. Currently, the best available evidence for the management of newly diagnosed GBM in elderly patients is resection of the contrast-enhancing lesion only²⁹ and a shorter hypofractionated course of RT (40 Gy in 15 fractions over 3 weeks) in combination with standard concurrent and maintenance TMZ chemotherapy.²⁰ This allows for higher treatment compliance and improves OS while maintaining a baseline quality of life.¹⁵ However, regardless of treatment (standard² or modified²⁰), survival outcomes in the elderly GBM cohort remain dismal. Major prognostic and biological differences driving the pathogenesis and natural history of GBM in the elderly compared with younger patients appear to be genomic. We propose that future surgical and medical clinical trials be agnostic to age and designed to stratify patients based on biological and clinically important genomic characteristics.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ene, Cimino. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ene. Study supervision: Fine, Holland.

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