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Risk factors for unintended discontinuation of tumor-specific treatment after tumor surgery in glioblastoma patients aged 70 or older

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ABSTRACT

Purpose: The most beneficial treatment option for newly diagnosed glioblastoma is maximum safe resection and adjuvant therapy. Elderly patients carry a higher perioperative risk for complications, thus, predictors of unfavorable surgical outcome must be evaluated more intensively. Consequently, we sought to evaluate surgery-related paradigms leading to discontinuation of adjuvant treatment after initial neurosurgical resection.

Methods: Patients receiving microsurgical tumor resection for newly diagnosed glioblastoma CNS WHO grade 4 were evaluated. Further inclusion criteria was age >70 years. Comorbidities were summarized using the Charlson Comorbidity Index (CCI), the 5 and 11 item modified frailty index (mFI-5 and mFI-11) and the CHA_2DS_2-VASc Score. Primary endpoint was discontinuation of tumor-specific before completion of adjuvant radiotherapy or radio-chemotherapy.

Results: 102 patients were included, mean age was 76.2 ± 4.2 years. The median extent of contrast-enhancing tumor volume was 99.1 ± 5.9 %. Surgical morbidity and mortality prohibited beginning of adjuvant treatment in 19 patients (18.6 %) and overall discontinuation of treatment before completion of radiotherapy was observed in 26/87 patients (29.9 %). Treatment failure was associated with increasing patient age ($p = 0.04$) and greater comorbidity scores. The mFI-5 and mFI-11 outperformed the CCI and the CHA_2DS_2-VASc Score. Two or more points in the 5- and 11-item mFI were significantly associated with increased risk of treatment failure ($p = 0.004$ and $p = 0.001$, respectively).

Conclusion: In Glioblastoma patients, advanced age and comorbidities are relevant confounders and put patients at risk for surgery-related morbidity. Nevertheless, it can be aimed at a maximum safe resection with acceptable surgical morbidity.

1. Introduction

The incidence of primary brain tumors is estimated at 7 cases per 100.000 individuals per year and Glioblastomas are the most common primary brain tumors (Schaff and Mellinghoff, 2023). Despite rapidly increasing research on intrinsic central nervous system (CNS) tumors, improving individual oncologic therapy, fluorescence-guided resection, intraoperative monitoring, non-invasive mapping, adjuvant radio-chemotherapy and tumor-treating-fields, the prognosis remains very limited (Schaff and Mellinghoff, 2023; Krieg et al., 2012; Schebesch et al., 2013; Stummer et al., 2006).

However, progression-free and overall survival of Glioblastoma patients can be improved by maximum safe resection and the admission of adjuvant therapy (Hart et al., 2013; Ahrens et al., 2022; Babu et al., 2016; Brown et al., 2016).

The standard therapy for adult Glioblastoma patients comprises microsurgical resection followed by adjuvant radiochemotherapy and tumor-treating fields (Stupp et al., 2005, 2017; Weller et al., 2017).

Due to the ageing population, the treatment of older patients with Glioblastoma is also becoming increasingly important, consequently. In this dedicated subset of patients several studies have shown that surgical resection can improve both progression-free and overall survival compared to conservative treatment or best supportive care (Stupp et al., 2017; Malmström et al., 2012; Schwartz et al., 2020; Straube et al., 2017; Hanna et al., 2020; Bauchet et al., 2014; Baumgarten et al., 2023; Perry et al., 2017; Glaser et al., 2017; Scott et al., 2011, 2012; Ewelt et al., 2011). Despite elaborated oncologic options, the patients' performance status is one key parameter both offering intensive treatment,

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quality of life and prolonged survival(Baumgarten et al., 2023; Scott et al., 2011, 2012; Sacko et al., 2015; Ening et al., 2015).

It is generally accepted that the initial performance status is a crucial factor to withstand intensified therapy, but data concerning concomitant confounders are sparse. In recent studies on elderly Glioblastoma patients, the number of patients not receiving adequate adjuvant treatment is up to 30 % (Schwartz et al., 2020; Baumgarten et al., 2023; Scott et al., 2011; Franceschi et al., 2016). Brain surgery in elderly patients is associated with high morbidity and mortality, regardless of the primary disease (Schwartz et al., 2020, 2024a, 2024b; Pöppe et al., 2023; Aghajanian et al., 2023; Hudelist et al., 2024; Huq et al., 2020, 2021; Roy et al., 2024). Consecutively, there is increased risk in the elderly that tumor-specific, adjuvant treatment cannot be continued since old patients bear an increased risk of significant postoperative deterioration in physical condition.

To the best of our knowledge, predictors of surgery-related morbidity prohibiting, or at least postponing consequent adjuvant treatment have not been evaluated sufficiently in elderly Glioblastoma patients, yet.

Hence, the aim of this study was to identify risk factors in patients >70 years, resulting in unintended and unexpected discontinuation of tumor-specific treatment after microsurgical resection and during adjuvant radiotherapy or radio-chemotherapy and, subsequently, the allocation to palliative care before completion of adjuvant treatment.

2. Methods

2.1. Ethical standard

The study design was approved by the Institutional Review Board (IRB-2024-09) and conducted in accordance with the declaration of Helsinki and its later amendments. No study-specific examinations were conducted. Informed consent was waived due to the study design and the use of routine data.

2.2. Study design and data collection

We conducted a retrospective monocentric study. Consecutive patients aged 70 or older with newly diagnosed Glioblastoma CNS WHO grade 4 between January 2013 and June 2024 were included into the study.

Patients with recurrent tumors and patients who previously underwent craniotomy for CNS WHO grade 2 or 3 tumors were excluded. Demographic data, clinical charts, surgical protocols and neuroimaging were reviewed. The Charlson Comorbidity Index (CCI)(Charlson et al., 1987), the 11- and 5-item modified frailty index (mFI-11 and mFI-5) (Velanovich et al., 2013) and the CHA_2DS_2-VASc Score (Lip et al., 2010) were calculated for each patient to evaluate comorbidities. The variables included in each score are displayed in Tables 1–3 in the supplementary file. Preoperative patient status was further dichotomized into good, independent status with Karnofsky Performance Scale (KPS) ≥70 % or dependent status with KPS <70 %.

Postoperative neurological status was assessed by neurosurgeons and a new neurological deficit was defined as a worsening in neurological status on discharge from the neurosurgical department. Apart from the primary endpoint, the failure to complete postoperative radiotherapy/radio-chemotherapy, we evaluated established comorbidity scores as a tool to predict the outcome of the patients in this cohort.

In the first part of the evaluation, surgical morbidity and mortality were analyzed to identify patients who are at risk for allocation to palliative care after tumor surgery due to reduced physical condition and limited overall status. The second analysis evaluates any treatment failure including discontinuation of treatment after surgery (i.e. results of the first part of the analysis) and during adjuvant radiotherapy.

For the second analysis, patients who refused to receive adjuvant treatment or who were lost to follow up were excluded.

2.3. Imaging analysis

Patients received preoperative contrast-enhanced MRI with 3D T1 gadolinium-enhanced sequences. Early postoperative MRI was performed within 48 h to document the extent of resection (EOR). A gross total resection was achieved, if the entire contrast-enhancing tumor tissue was removed on postoperative MRI. Imaging studies were reviewed by a neuro-radiologist. Pre- and postoperative tumor volumes were assessed volumetrically using inomed IPS 5 software (inomed GmbH, Emmendingen, Germany) and a semiautomatic segmentation algorithm.

2.4. Decision making and surgical approach

Patients were assigned to surgery according to the recommendations of the interdisciplinary tumor board, and maximum safe resection was the treatment of choice in all patients.

Microsurgical tumor resections were performed under general anesthesia, guided by neuronavigation and fluorescence induced by 5-aminolevulinic acid (5-ALA) or sodium fluoresceine (FL, since July 2023).

Postoperatively, patient cases were discussed within the interdisciplinary tumor board for the possibility to administer adjuvant treatment consisting of radiotherapy and Temozolomide chemotherapy. If postoperative patient status was too limited to start adjuvant treatment, best supportive care was recommended.

2.5. Statistical analysis

IBM SPSS Version 29.0 for Microsoft Windows was used for statistical analysis. Continuous variables are presented as mean ± standard deviation (SD) and categorial variables are presented as absolute numbers (n) and percentage (%). We applied Fisher-Exact and Fisher-Freeman-Halton Tests to compare distributions of categorial variables. Continuous variables were analyzed using Mann-Whitney-U-Tests and Kruskal-Wallis Tests. Comorbidity scores were tested for correlations among each other and with patient age using Spearman's correlation. The correlation coefficient Spearman's Rho r_s is reported in these cases. Comorbidity scores were further evaluated using receiver operating characteristics (ROC-curves). The area under the curve (AUC) is reported here. For significant scores in ROC-analyses, cut-offs were determined using the closest-top-left-method. Patient data were then divided according to the cut-off for that particular score and tested using Fisher Exact Tests.

A p-value <0.05 was considered significant in two-tailed testing.

3. Results

The patient population comprised 102 patients and 46 (45.1 %) were female. Mean age was 76.2 ± 4.2 years. Preoperatively, 27 (26.5 %) patients presented with motor deficits, 29 (28.4 %) had language disorders and 7 (6.9 %) had visual impairments. Eighty-four patients (82.4 %) had a KPS≥70 %, MGMT promoter methylation was positive in 55 cases (53.9 %). Baseline data are presented in Table 1.

Only age and CHA_2DS_2-VASc Score correlated well in the patient cohort and comorbidity scores were only partly associated with preoperative KPS≥70 % ($p = 0.31$ for CCI, $p = 0.53$ for CHA_2DS_2-VASc Score, $p < 0.001$ for mFI-11 and mFI-5). Please refer to Fig. 1 in the supplementary file.

4. Impact of surgical complications

Nineteen of 102 patients (18.6 %) did not receive or even start adjuvant treatment. Of those patients, 10 died during their inpatient stay. Reasons for death were postoperative hematoma in 5 cases, cerebral ischemia, sepsis and status epilepticus in 1 case each and

Table 1
Baseline data of the patient sample (IQR – interquartile range, CSF – cerebrospinal fluid).

Item	Mean	SD	N	%
Age (years)	76.2	4.2		
Female			46	45.1
Preoperative neurological deficits				
Motor deficit			27	26.5
Language deficit			29	28.4
Visual impairment			7	6.9
Preoperative Karnofsky Performance Status ≥70 %			84	82.4
Charlson Comorbidity Index	4.5	1.7		
CHA_2DS_2-VASc-Score	3.6	1.2		
5-item modified frailty index	1.3	0.9		
11-item modified frailty index	2.0	1.5		
Tumor volume (cm^3)	36.4	28.9		
Left-sided			42	41.2
Midline Shift (mm)	3.5	3.4		
Multifocal			19	18.6
Tumor location				
frontal			29	28.4
parietal			15	14.7
temporal			39	38.2
parietooccipital/occipital			8	7.8
temporal-parietal/temporal-occipital			9	8.8
cerebellar			2	2.0
MGMT-methylated			55	53.9
inconclusive			4	3.9
Median extent of resection (% contrast-enhancing tumor volume)	99.1	5.9 (IQR)		
New motor deficit/worsened motor status			23	22.5
New aphasia/worsened language function			9	8.8
Revision for hematoma			4	3.9
Revision for infection/CSF fistula			5	4.9
No adjuvant treatment due to morbidity and mortality			19	18.6
Adjuvant therapy			74	
Radiotherapy			74	100
Normofractioned			37	50
Hyperfractioned			15	20.3
Hypofractioned			4	5.4
Protocol unknown			18	25.7
Concomitant chemotherapy			49	66.2
Discontinued radiotherapy			1	1.4
Discontinued radiochemotherapy			3	4.1
Disdontinued chemotherapy			3	4.1
Missing			6	8.1
Refused adjuvant therapy			9	12.2
90-day mortality (n = 92)			23	22.5

cardiovascular reasons in 2 cases.

Reasons for unintended discontinuation of tumor-specific therapy after surgery of the remaining patients were:

One patient had a postoperative pneumonia and – as a consequence of the infection and tumor-burden - disturbance of consciousness and died within 30 days postoperatively. Two patients had a nosocomial pneumonia in combination with hemiparesis (new and worsened). One patient had a surgical site infection with a prolonged clinical course. One patient was hemiplegic postoperatively. Two patients were preoperatively hemiparetic and in very reduced overall status and remained unchanged postoperatively. Two patients deteriorated postoperatively in overall status, possibly due to tumor progression. Four of these patients had a preoperative KPS<70 %.

In the whole cohort, new motoric deficits occurred in 12 patients (11.8 %) whereas preoperative motor deficits aggravated postoperatively in 11 patients (10.8 %). Vice-versa, worsened postoperative language function was documented in 9 patients (8.8 %) with a preexisting aphasia in 6 cases. Postoperative new or worsened motor- or language status was not related to a discontinuation of treatment after surgery (p = 0.36 for each, new motor- and language deficit).

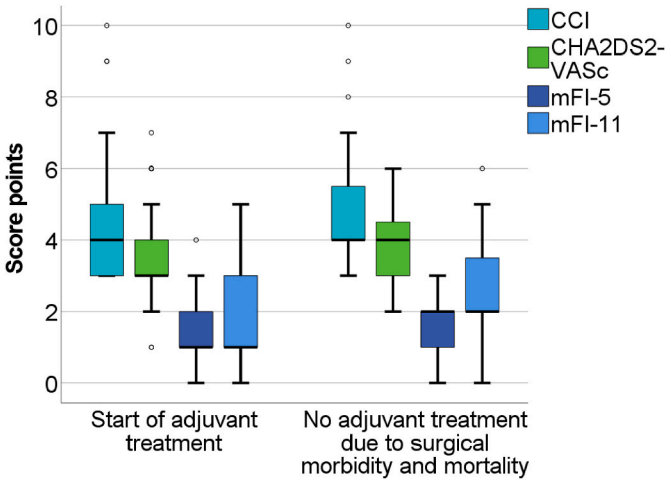

Fig. 1. Comparison of comorbidity scores in relation to surgical morbidity and mortality. The 5- and 11-item mFI were significant in this analysis (p = 0.23 for mFI-5 and p = 0.028 for mFI-11). The CCI (p = 0.11) and the CHA_2DS_2-VASc Score (p = 0.08) were not significant.

5. Impact of tumor-specific factors

Concerning tumor-specific factors, there was no relationship between tumor location (p = 0.61), tumor volume (p = 0.17) or preoperative midline shift (p = 0.21) and the allocation to palliative care for medical reasons. Residual tumor volume was greater in patients who did not start adjuvant treatment (p = 0.048)

6. Impact of age and comorbidities

The 5- and 11-item modified frailty scores showed significant differences in non-parametric testing to distinguish between good outcome and the primary endpoint, whereas the CCI and the CHA_2DS_2-VASc Score did not reach significance (Fig. 1). Additionally, patients were significantly older if they could not receive adjuvant treatment due to morbidity and mortality (p = 0.002). Preoperative KPS>70 % was not solely linked to a good postoperative outcome (p = 0.32).

The ROC-analyses confirmed the results of non-parametric testing (Fig. 2): the mFI-5 (AUC = 0.66, 95 %CI = 0.52–0.8, p = 0.022) and mFI-11 (AUC = 0.66, 95 %CI = 0.53–0.79, p = 0.017) were the most suitable scores to predict unintended discontinuation of tumor-specific therapy.

The CCI (AUC = 0.61, 95 %CI = 0.48–0.75, p = 0.1) and the CHA_2DS_2-VASc-Score (AUC = 0.62, 95 %CI = 0.5–0.75, p = 0.06) could not adequately discriminate between good and unfavorable outcome. Based upon the ROC-analyses, cut-offs for limited surgical outcome were defined ≥2 points in the mFI-5 (Sensitivity = 0.68, Specifity = 0.64, p = 0.019, Fisher Exact Test) and ≥2 points in the mFI-11 (Sensitivity = 0.79, Specifity = 0.51, p = 0.023, Fisher Exact Test).

7. Adjuvant treatment

Adjuvant treatment was recommended and patients were in appropriate status for adjuvant treatment in 83 cases. Nine patients (10.8 %) refused any adjuvant treatment (5 radiochemotherapy, 4 radiotherapy).

Concomitant Temozolomide chemotherapy was recommended in 49 patients (59 %) and no patient received adjuvant chemotherapy without radiation.

Adjuvant therapy was completed 61/74 cases (82.4 %), 1 patient died during radiotherapy, 3 patients discontinued radio-chemotherapy

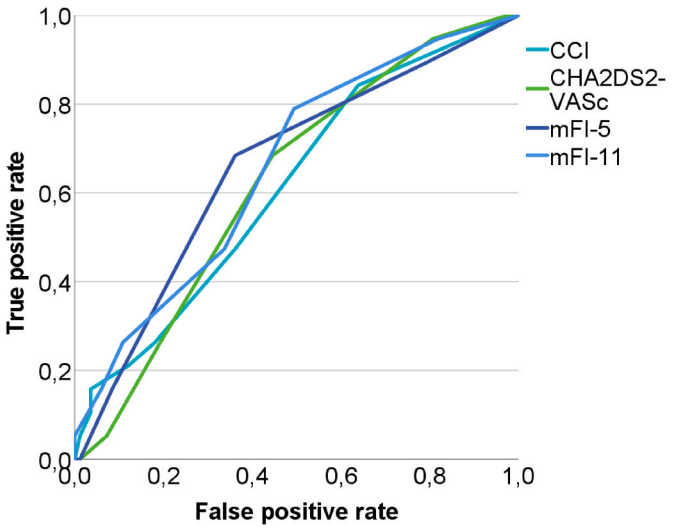

Fig. 2. ROC-analysis for comorbidity scores for treatment failure after surgery before adjuvant treatment. The mFI-5 (AUC = 0.66, 95 %CI = 0.52–0.8, p = 0.022) and mFI-11 (AUC = 0.66, 95 %CI = 0.53–0.79, p = 0.017) could discriminate between good and limited outcome.

(2 normofractionated protocol, 1 unknown protocol) and 3 additional patients discontinued chemotherapy during radiation. Six patients (8.1 %) were lost to follow up.

8. Risk factors for discontinuation of treatment (surgical and adjuvant)

Overall, 26/87 patients (29.9 %) discontinued tumor specific treatment either after surgery (n = 19) or during adjuvant radiotherapy (n = 7).

Patients who completed surgery and adjuvant treatment were younger (p = 0.04) and had lower comorbidity scores (Fig. 3, Table 2)

In the ROC-analyses, all comorbidity scores could discriminate between completion and failure of treatment. The mFI-5 and mFI-11 had the best model discrimination (mFI-5: AUC = 0.7, 95 %CI = 0.58–0.82, p = 0.001; mFI-11: AUC = 0.72, 95 %CI = 0.61–0.83, p = 0.001, respectively, Fig. 4).

The cut-off values of ≥2 points in the 5- and 11-item mFIs remained

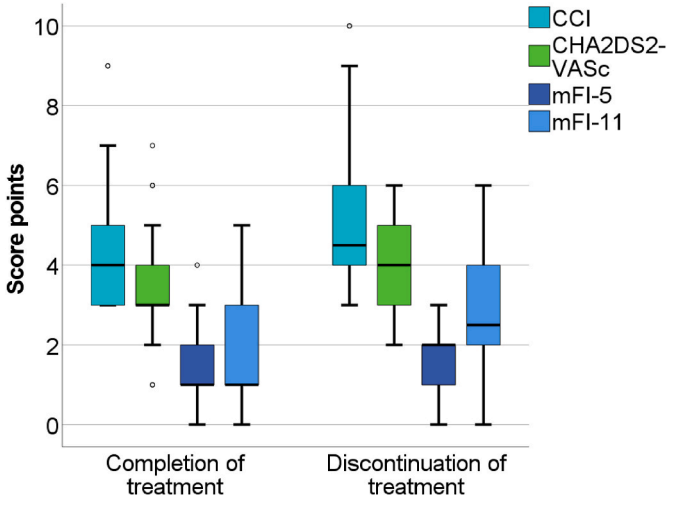

Fig. 3. Comparison of comorbidity scores in relation to discontinuation of treatment. The CCI (p = 0.036) and the CHA_2DS_2-VASc Score (p = 0.008) reached significance apart from the 5- and 11-item mFI in this analysis (p = 0.002 for mFI-5 and p = 0.001 for mFI-11).

significant (mFI-5: Sensitivity = 0.65, Specifity = 0.71, p = 0.004, Fisher Exact Test; mFI-11: Sensitivity = 0.81, Specifity = 0.59, p = 0.001, Fisher Exact Test).

Additionally, a CHA_2DS_2-VASc-Score of ≥4 (Sensitivity = 0.65, Specifity = 0.62, p = 0.021 Fisher Exact Test) could serve as a cut-off for discontinuation of treatment. However, model fit of mFI-5 and mFI-11 outperformed the CHA_2DS_2-VASc-Score.

In the subgroup of patients who discontinued only adjuvant therapy, solely a greater score of the mFI-11 remained a significant risk factor for failure of treatment (p = 0.02).

9. Discussion

Glioblastoma is a life-ending disease in most cases. Notwithstanding, especially for elderly and frail Glioblastoma patients the life-expectancy is very limited. Neurosurgeons should be aware that the highest goal in the treatment of Glioblastoma patients should be preserving function and quality of life (Baumgarten et al., 2023; Scott et al., 2011, 2012; Sacko et al., 2015; Ening et al., 2015). Especially performance status affect the prognosis of Glioblastoma patients despite extent of resection (Baumgarten et al., 2023; Scott et al., 2012; Sacko et al., 2015; Straube et al., 2020; Pirkkalainen et al., 2022). On the contrary, elderly patients are less likely to receive a comprehensive oncological treatment (Horowitz et al., 2024).

In our study, we established age and the score of the modified frailty indices as main factors for a limited outcome.

Complication rates were comparable to published literature (Schwartz et al., 2020), yet, revision surgery due to hemorrhage was associated with unfavorable patient outcome. Furthermore, a maximum safe resection was the surgical goal in all cases of the study and this could be achieved with an acceptable rate of surgery-associated complications, which is a clear indication for a maximum safe resection whenever feasible, even in the elderly. The extent of resection was comparable to other studies as well as the amount of patients receiving best supportive care after neurosurgical treatment (Schwartz et al., 2020; Scott et al., 2011; Straube et al., 2020).

Additionally, we could not find significant associations between neurologic sequelae after surgery and postoperative discontinuation of tumor-specific treatment. This indicates a willingness to receive a comprehensive treatment even in patients with surgery-related deficits. However, patients in reduced postoperative status had a limited prognosis in the study conducted by Straube et al. (2020)

In our study, we evaluated different scores for comorbidities and cardiovascular risk assessment. The 5- and 11-item modified frailty indices were significantly associated with postoperative unintended discontinuation of tumor-specific treatment. The meta-analysis conducted by Aghajanian et al. (2023) found clear relationships between inferior surgical outcome of Glioblastoma patients and increased frailty measured by these scores. These results are additionally reflected in several other published studies, indicating that frailty is a serious confounder for the prognosis of Glioblastoma patients. In the published literature, increasing frailty was associated with a higher risk of readmission and death within 30 days postoperatively as well as with decreased overall survival (Hudelist et al., 2024; Huq et al., 2020; Botros et al., 2022; Rmt et al., 2024; Bray et al., 2024; Cloney et al., 2016; Paiz et al., 2024; Schneider et al., 2020). In our study, frailer patients were less likely to be able to get allocated to adjuvant treatment and to complete adjuvant oncologic therapy. These results additionally underline the significance and the need for a standardized preoperative risk stratification, e.g. the usage of comorbidity scores. Therefore, neurosurgeons should be aware of their patients' comorbidities and frailty in the decision-making process concerning patient selection for microsurgical tumor resections.

The results of our study are supported by existing literature concerning patient-selection for comprehensive neurosurgical treatment even in patients aged >70 (Baumgarten et al., 2023; Pessina et al., 2018;

Table 2
Comparison of patients who completed adjuvant therapy and patients who could not complete adjuvant therapy.

	Completion of treatment (n = 61)				Discontinuation of treatment (n = 26)				
Item	Mean	SD	N	%	Mean	SD	N	%	p
Age (years)	75.6	4.0			77.9	4.7			0.04
Female			24	39.3			11	42.3	0.82
Preoperative neurological deficits									
Motor deficit			15	24.6			10	38.5	0.21
Language deficit			20	32.8			5	19.2	0.3
Visual impairment			5	8.2			1	3.8	0.66
Preoperative Karnofsky Performance Status ≥70 %			53	86.9			18	69.2	0.07
Charlson Comorbidity Index	4.3	1.5			5.2	2.1			0.036
CHA_2DS_2-VASc-Score	3.3	1.2			4.0	1.1			0.008
5-item modified frailty index	1.1	0.9			1.8	0.9			0.002
11-item modified frailty index	1.6	1.3			2.8	1.5			0.001
Tumor volume (cm^3)	32.5	25.9			43.3	34.3			0.23
Left-sided			28	45.9			9	34.6	0.47
Midline Shift (mm)	3.6	3.4			3.0	3.4			0.47
Tumor location									0.26
frontal			16	26.2			10	38.5	
parietal			8	13.1			4	15.4	
temporal			23	37.7			9	34.6	
parietooccipital/occipital			7	11.5			0	0	
temporal-parietal/temporal- occipital			7	11.5			2	7.7	
cerebellar			0	0			1	3.8	
MGMT-methylated			30/58	51.7			16/25	64	0.34
Median extent of resection (% contrast-enhancing tumor volume)	99.3	3.3 (IQR)			97.4	11.7 (IQR)			0.1
New motor deficit/worsened motor status			12	19.7			7	26.9	0.57
New aphasia/worsened language function			3	4.9			4	15.4	0.19
Revision for hematoma			1	1.6			3	11.5	0.08
Revision for infection/CSF fistula			3	4.9			2	7.7	0.63

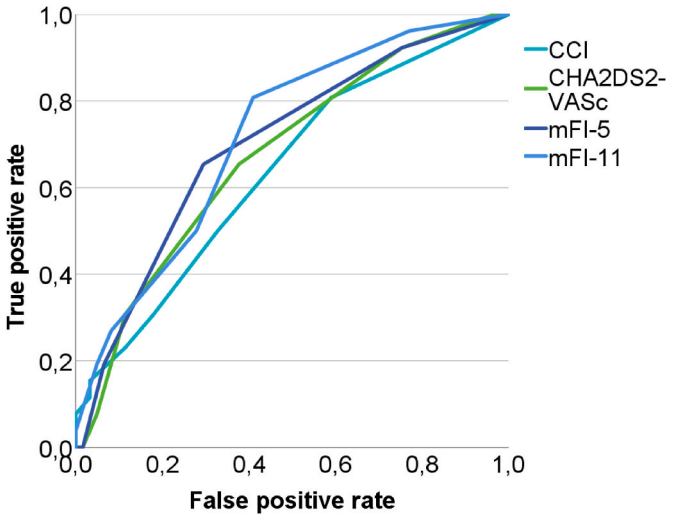

Fig. 4. ROC-analyses for the comorbidity scores. All scores had a AUC>0.6, but the mFI-5 and mFI-11 outperformed the CCI and the CHA_2DS_2-VASc-Score.

Niare et al., 2022; Laigle-Donadey et al., 2023). However, limited oncologic outcomes after resection in the very elderly are reported in recent literature and patient-selection for maximum safe microsurgical resection should be made carefully in the very elderly and frail patients (Connon et al., 2016).

Based upon the results of our study, the neurosurgical goal in elderly patients with Glioblastoma should be to make a patient-individual decision for an appropriate surgical treatment strategy. Patients who underwent resection have been reported to have increased survival and increased quality of life compared to patients who receive biopsy and therefore a maximum safe resection should be the neurosurgical option of choice whenever feasible (Babu et al., 2016; Baumgarten et al., 2023; Klingenschmid et al., 2022).

10. Strengths and limitations

Limitations of the study arise from the retrospective single-center design and a potential selection bias since the decision to perform tumor resection was made upon patient wish, patient status and tumor specific factors such as size and location in the institutional tumor conference. Additionally, some results may be underpowered with respect to the sample size of n = 102, especially the impact of the extent of resection. However, the patient sample represents a real life cohort and patient selection for a distinct treatment option is a problem which is faced every day in neurosurgical departments. The aim of the study was to provide data concerning those patients who will not be able to receive a comprehensive oncologic therapy and only best supportive care for medical reasons. Strengths arise from the detailed analysis of preoperative factors, comorbidities and the application of different scores to evaluate postoperative outcome and morbidity. Further prospective studies are mandatory to evaluate the impact of comorbidities in elderly patients with infiltrating brain tumors on progression-free and overall survival after neurosurgical tumor resection and comprehensive oncological treatment.

11. Conclusion

In our study of elderly patients with newly diagnosed Glioblastoma maximum safe resection did not result in higher surgery-associated treatment failure compared to a more defensive surgical strategy. Age and comorbidities measured by frailty scores were relevant factors which influenced the clinical course of the patients and put patients at risk for discontinuation of tumor-specific treatment after tumor

resection and during radiotherapy. These factors should be considered for treatment decisions in elderly patients undergoing surgery for Glioblastoma.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Thomas Eibl and Franziska Goschütz. The first draft of the manuscript was written by Thomas Eibl, Adrian Liebert and Leonard Ritter, editing and supervision by Karl-Michael Schebesch, Hans-Herbert Steiner and Markus Neher. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

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

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2025.104253.

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