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The role of Lobectomy in Glioblastoma management: A Retrospective series

Christina K. Arvaniti [a,*], Alexandros G. Brotis [a], Jacob S. Young [b], Sivani Sivanrupan [c], Gracia Menna [b], Masahiro Nishide [b], Philippe Schucht [c], Mitchel Berger [b], Kostas N. Fountas [a,d]

[a] Department of Neurosurgery, University Hospital of Larissa, Larissa, 41110, Greece
[b] Department of Neurological Surgery, University of San Fransisco, San Fransisco, California, USA
[c] Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[d] Faculty of Medicine, School of Health Sciences, University of Thessaly, Biopolis, Larissa, 41110, Greece

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ABSTRACT

Introduction: Treatment choices for glioblastoma (GB) remain scarce. Multiple clinical studies have demonstrated the importance of supramaximal resection. Recently, it is emphasized the efficacy of lobectomy as treatment option in GB patients, achieving the maximum overall survival (OS) and progression free survival (PFS).
Research question: The primary aim of this study is to assess the OS and PFS of GB patients undergoing lobectomy, compared to those undergoing lesionectomy. Secondary aims include the identification of potential survival modifiers among clinical parameters.
Materials and methods: This retrospective analysis consists of a multicenter case series of GB patients who underwent lobectomy or lesionectomy between January 2015 and December 2022. Primary outcome included OS and PFS. Identification of potential survival modifiers and postoperative complications were also recorded. Kaplan-Meier survival curves were generated to assess overall survival. Multivariate analyses were performed to identify factors associated with survival.
Results: This study included 43 patients. There were 29 cases of lobectomy and 14 cases of lesionectomy. The median OS in lobectomy group was 34 months, compared to 15 months in the lesionectomy group. Multivariate regression analysis indicated that advanced age, tumor location, neurological deficits and the performance of lesionectomy were associated with poorer survival outcomes.
Discussion and conclusions: Lobectomy in GB cases is associated with increased OS, compared to lesionectomy. In our series, we demonstrated a significantly better survival with lobectomy than lesionectomy. However, there are complications associated with lobectomy. The identification of the subgroup of patients who would benefit from a lobectomy needs to be addressed.

1. Introduction

Glioblastoma (GB), the most common and aggressive primary tumor of the central nervous system in adults, is characterized by poor survival, while treatment choices remain scarce (Louis et al., 2016; Wach et al., 2023; Pessina et al., 2017; Eyüpoglu et al., 2016; Tripathi et al., 2021; De Bonis et al., 2012). Although the employment of radical resections in GBs has been debated over the years, a growing body of evidence supports the idea of supramaximal resection (Pessina et al., 2017; Eyüpoglu et al., 2016; Tripathi et al., 2021; Mampre et al., 2018; Glenn et al., 2018; Li et al., 2015; Vivas-Buitrago et al., 2021; Esquenazi et al., 2017; Otsuji et al., 2023; Tropeano et al., 2024; Laurent et al., 2019; Molinaro et al., 2020; Wen et al., 2020; Khalafallah et al., 2021; Mier-García et al., 2023; Karschnia et al., 2022). Indeed, it is yet well-known that among the factors extending the overall survival (OS) in GB patients, such as, the preoperative Karnofsky Performance Status (KPS) score, the tumor location, volume and molecular subtype, the only modifiable one is the extent of resection (EoR) (Pessina et al., 2017; Tripathi et al., 2021; Glenn et al., 2018; Li et al., 2015; Esquenazi et al., 2017; Baik et al., 2023; Figueroa et al., 2020).

Multiple clinical studies and cohorts have demonstrated that gross-

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* Corresponding author. Department of Neurosurgery Building A, 3rd Floor, University Hospital of Larissa, Larissa, 41110, Greece.
E-mail addresses: arvanitixristina@hotmail.com, arvanitixristina@hotmail.com (C.K. Arvaniti), alexgbrodis@yahoo.com (A.G. Brotis), jacob.young@ucsf.edu (J.S. Young), sivani.sivanrupan@insel.ch (S. Sivanrupan), grazia.menna01@icatt.it (G. Menna), mnis2743@uni.sydney.edu.au (M. Nishide), philippe.schucht@insel.ch (P. Schucht), Mitchel.berger@ucsf.edu (M. Berger), fountas@uth.gr (K.N. Fountas).

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Abbreviations

ALA	Amino-Levulinic-Acid
CI	Confidence Interval
EoR	Extent of Resection
GB	Glioblastoma
GTR	Gross Total Resection
HR	Hazard Rate
KPS	Karnofsky Performance Status
MCA	Middle Cerebral Artery
NaN	Not a Number
SMR	Supramaximal Resection
STR	Subtotal Resection
OS	Overall Survival
PFS	Progression Free Survival

total resection (GTR) is superior to a subtotal resection (STR) (Stummer et al., 2008; Ewelt et al., 2010; Kreth et al., 2013; Sharma et al., 2018) while supramarginal (SMR) resection is superior to gross-total resection (Pessina et al., 2017; Eyüpoglu et al., 2016; Tripathi et al., 2021; Mampre et al., 2018; Glenn et al., 2018; Vivas-Buitrago et al., 2021; Esquenazi et al., 2017; Otsuji et al., 2023; Tropeano et al., 2024). Moreover, it is recently emphasized the importance and efficacy of lobectomy in GB patients (Hamada and Abou-Zeid, 2016; Borger et al., 2021; Roh et al., 2019; Shah et al., 2020; Schneider et al., 2020; Hollerhage et al., 1991; Zheng et al., 2023; Arvaniti et al., 2024; Teyateeti et al., 2020). In particular, it is yet established in various studies that lobectomy in GB patients, when feasible, achieves maximum OS and Progression Free Survival (PFS) compared to all other surgical methods (Hamada and Abou-Zeid, 2016; Borger et al., 2021; Roh et al., 2019; Shah et al., 2020; Schneider et al., 2020; Hollerhage et al., 1991; Zheng et al., 2023; Arvaniti et al., 2024). In a recently published meta-analysis, the mean OS was 25 months for lobectomy, and 13.72 months for GTR group, while PFS in lobectomy and GTR was 16.13 months and 8.77 months, respectively (Arvaniti et al., 2024). However, the existing studies have been based on small size case-series, requiring thus further data for verifying these results.

The primary aim of our current study is to assess the OS and PFS of GB patients undergoing lobectomy, compared to a lesionectomy group. Secondary aims of our study included the identification of potential survival modifiers among several clinical parameters. The current article could be of interest to neurosurgeons specialized in neuro-oncology, neurologists, oncologists, and radiation-oncologists.

2. Methodology

The present study is a retrospective analysis of a multicenter case series of patients who underwent lobectomy to treat gliomas. This case series was compared to a second arm, comprised of patients undergoing lesionectomy. These patients were also retrospectively selected. Between January 2015 and December 2022, patients were identified from the medical records of the participating hospitals. Relevant clinical, radiological, and outcome data were collected and analyzed. The study was approved by the Ethics Committee of the participating institutions, and all enrolled patients provided written informed consent.

2.1. Eligibility criteria

Patients were included if they 1) underwent a lobectomy for the treatment of glioma, 2) had gross total resection on postoperative imaging, 3) had complete records for the extent of resection, radiation, chemotherapy, and demographic variables. Patients were excluded if they had missing data or if they underwent a biopsy or subtotal resection

Table 1
Baseline characteristics of our study groups.

Characteristic	Category	Lesionectomy	Lobectomy	p
n		14	29	
Age (mean (SD))		55.86 (12.18)	65.72 (8.50)	**0.004**
Sex	Male (%)	10 (71.4)	20 (69.0)	0.869
Seizures	Yes (%)	3 (21.4)	3 (10.3)	0.326
Headache	Yes (%)	1 (7.1)	2 (6.9)	0.976
Focal deficit	Yes (%)	8 (57.1)	4 (10.3)	**0.001**
Language/Memory	Yes (%)	4 (28.6)	7 (24.1)	0.755
Cognitive changes	Yes (%)	0 (0.0)	7 (24.1)	**0.045**
Increased ICP	Yes (%)	2 (14.3)	3 (10.3)	0.706
Incidental	Yes (%)	0 (0.0)	3 (10.3)	0.402
Other	Yes (%)	1 (7.1)	3 (10.3)	0.590
Dominant hemisphere	Left (%)	14 (100.0)	16 (59.3)	**0.020**
	NR		8 (29.6)	
	Right		3 (11.1)	
Tumor Location (Side)	Right (%)	7 (50.0)	17 (58.6)	0.594
Ipsi- vs. Contralateral to the dominant Side				**0.043**
	Contralateral		9 (31.0)	
	Ipsilateral (%)	7 (50.0)	10 (34.5)	
	Unclear		10 (34.5)	
Tumor Location (Lobe)				
Frontal	Yes (%)	3 (21.4)	10 (34.5)	0.382
Temporal	Yes (%)	4 (28.6)	20 (69.0)	**0.012**
Parietal	Yes (%)	7 (50.0)	0 (100.0)	**0.001**
Occipital	Yes (%)	1 (7.1)	29 (100.0)	0.145
Insula	Yes (%)	2 (14.3)	2 (6.9)	0.434
Other (2)	Yes (%)	1 (7.1)	1 (3.4)	0.590
Number of affected lobes				
	One	9 (64.3)	26 (89.7)	0.093
	Two	4 (28.6)	3 (10.3)	
	Three	1 (7.1)	(–)	
Extent of Resection				**0.001**
	Subtotal (%)	2 (14.3)	2 (6.9)	
	Gross Total	12 (85.7)	9 (31.0)	
	Supratotal	0	8 (29.6)	
	Missing	0	9 (31.0)	
Death	1 (%)	12 (85.7)	13 (44.8)	**0.011**
Time to Death (Months) (mean (SD))		16.46 (10.70)	16.28 (13.91)	
Progression	1 (%)	13 (92.9)	19 (65.5)	**0.054**
Time to Progression (Months) (mean (SD))		8.93 (7.62)	9.0 (9.55)	
Medical Complications	Yes (%)	1 (7.14)	3 (10.3)	
Language disorders	Yes (%)	3 (21.4)	2 (7)	
Motor Disorders	Yes (%)	4 (28.5)	3 (7)	
Intracranial hemorrhage	Yes (%)	0	1 (3.5)	
Hydrocephalus	Yes (%)	1 (7.14)	0	
Psychiatric	Yes (%)	2 (10.42)	0	
Acute Subdural Collection	Yes (%)	1 (7.14)	0	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Category	Lesionectomy	Lobectomy	p
Seizures	Yes (%)	4 (28.5)	4 (13.7)	
Cranial nerve palsy			1 (3.5)	
Wound infection			1 (3.5)	
KPS (Pre)		82.5 (20.6)	86.11 (15.01)	0.601*
KPS (Post)		74.14 (23.13)	85.56 (25.26)	0.215*
Methylation	Yes (%)	4 (28.5)	7 (24.13)	
	NR	7 (50)	13 (54.1)	

instead of a gross total resection. Our current study was approved by our Institutional Review Boards.

2.2. Interventions

29 of the patients underwent a lobectomy and 14 a lesionectomy based on the specific tumor's (dominant hemisphere, anatomic location, size, extension to another lobe) and patient's characteristics (neurological status, functional status, pre-operative modified frailty index, comorbidities). Hemispheric dominence was established, through meticulous medical history, clinical examination and the use of task-generated functional MRI. With the aid of neuronavigation, 5- Amino-Levulinic-Acid (5-ALA) fluorescent techniques, and intraoperative neuromonitoring, every effort was made to remove the tumor while preserving critical brain structures. The surgical technique has been described elsewhere (Arvaniti et al., 2024). In lesionectomy cases the surgical strategy focused on resecting all the contrast-enhancing lesion on T1 post-contrast MRI. Postoperative adjuvant therapies, such as radiation and chemotherapy as described in Stupp's protocol (Stupp et al., 2005), were routinely administered.

2.3. Outcomes

Primary outcome of this study were OS and mortality, along with recurrence and PFS. Identification of potential survival modifiers and postoperative complications along with hospital discharge and short-term survival rates, were also recorded. Gross total resection was defined as complete resection of any enhancing areas on post-operative, post-contrast T1-weighted images.

2.4. Data extraction

We observed patients and analyzed retrospective clinical data from the date of diagnosis until the date of death, or until May 30, 2025. We extracted the following data: patient demographics, tumor characteristics, details of surgical intervention, postoperative care, and survival outcomes.

2.5. Statistical analysis

Descriptive statistics were used to summarize patient characteristics and outcomes. Kaplan-Meier survival curves were generated to assess overall survival. Bivariate and multivariate analyses were performed using Cox proportional hazard regression models to identify factors associated with survival. The multivariate analysis took all potential risk factors into consideration and results are depicted in Figs. 2 and 4, using forest plots. All statistical analyses were carried out using R. The level of statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient sample description

This study involved 43 patients (Table 1). The majority were male (n = 30; 69,7 %), with a median age of 62.51 years (± 10,57 years, range: 37–78 years). The patients presented with focal neurological deficits (11, 26 %) or disturbances in language and memory (11, 26 %), and less commonly experienced seizures (6, 14 %), increased intracranial pressure (5, 12 %), and headaches (3, 7 %). The most frequently affected lobes were the temporal (24, 56 %) and frontal lobes (13, 30 %), followed by the parietal (7, 16 %) and occipital lobes (1, 2 %). The lesion was ipsilateral to the dominant hemisphere in 17 (39.5 %) cases, contralateral in 16 (37.2 %) cases, and remained unclear in 10 cases

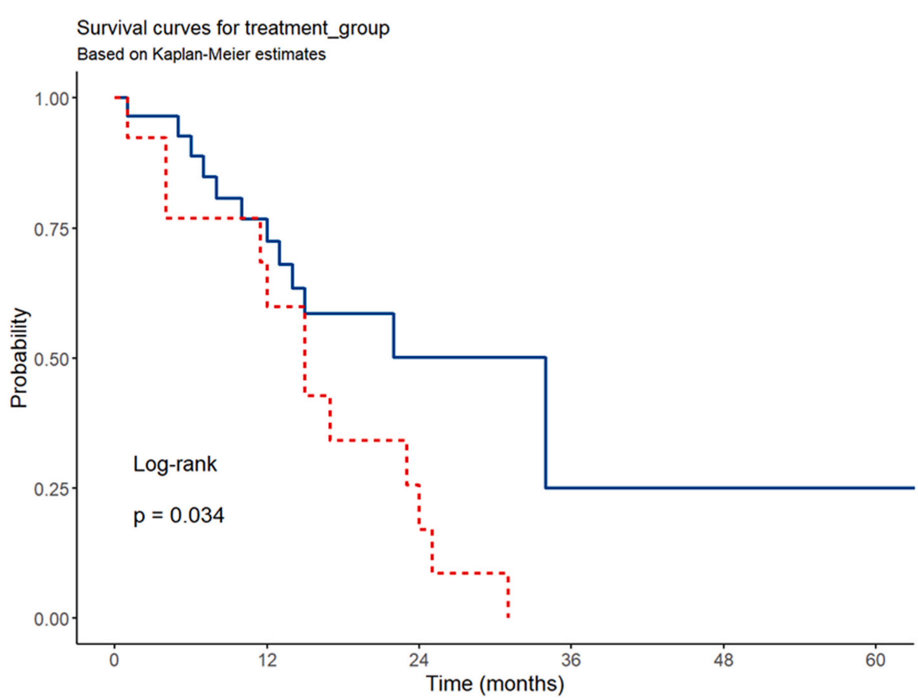

Fig. 1. The median OS time for lobectomy and lesionectomy groups was 34 months and 15 months respectively.

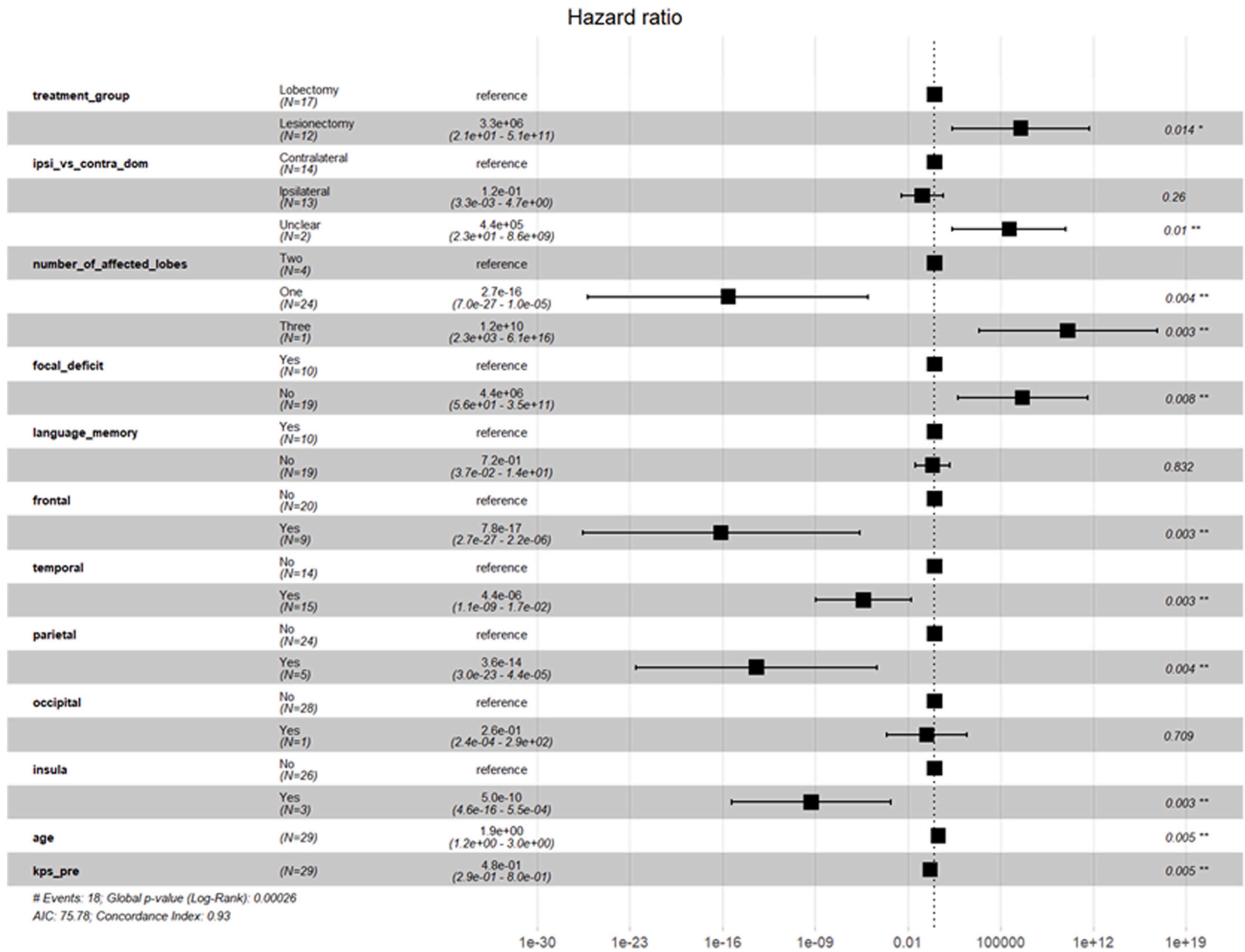

Fig. 2. The multivariate analysis demonstrated factors correlated with poor clinical outcome regarding OS.

(23.3 %). The KPS at presentation was 84.7 (±17).

3.2. *Surgery*

Of the 43 patients in our study sample, 29 (67 %) underwent lobectomy and 14 (33 %) underwent lesionectomy only. Lesionectomy resulted in gross total resection in 10 (85,7 %) cases and subtotal resection in 2 cases (14.3 %). On the other hand, lobectomy achieved gross total and supratotal resection in 9 (31 %) and 8 (29.6 %) cases, respectively.

3.3. *Mortality - overall survival*

A total of 25 deaths were recorded in our study sample, 13 (92.8 %) in the lobectomy group and 12 (41.3 %) in the lesionectomy group ($\chi2$ (1) = 6.486, p = 0.011). The 1-, 3-, and 5-year overall survival rates were 72 % (95 % CI, 57 %–92 %), 25 % (95 % CI, 6 %–7100 %), and 25 % (95 % CI, 6 %–7100 %), respectively. With lesionectomy, the 12-month survival was 60 % (95 % CI 38 %–94 %). The log-rank test showed a significantly better survival with lobectomy than lesionectomy (p = 0.034). The median OS in lobectomy group was 34 months (95 % CI 14 months -NA), compared to 15 months (95 % CI 12 months -NA) in the lesionectomy group (Fig. 1).

The multivariate regression analysis demonstrated that factors such as advanced age (p = 0.005), the involvement of more than three lobes by the neoplasm (p = 0.003), the presence of a focal neurological deficit at presentation (p = 0.008), a low Karnofsky Performance Status 14 (KPS) prior to surgical intervention (p = 0.005), and the execution of lesionectomy (p = 0.005) were significantly correlated with unfavorable clinical outcomes (Fig. 2).

3.4. *Progression free survival and recurrence*

We recorded 19 (42.4 %) and 13 (30.2 %) recurrences in the lobectomy and lesionectomy groups. The analysis revealed no statistically significant association between the type of surgery and recurrence ($\chi2$ (1) = 3.707, p = 0.054). The PFS with lobectomy is 9 months (95 % CI, 5 months -NA) and with lesionectomy is 8 months (95 % CI, 4 months - NA) (Fig. 3). The log-rank test showed that this difference was not significant (p = 0.44). The multivariate hazard regression analysis failed to identify any significant predictor of recurrence (Fig. 4).

3.5. *Complications*

One patient had o hospital acquired complication in the lesionectomy group (7.14 %) and 3 in the lobectomy group (10.3 %). There was one case of intracranial hemorrhage in the lobectomy group and one case of acute subdural hematoma in lesionectomy group. Language and motor disorders were interestingly more frequently observed in the lesionectomy group. Seizures were present postoperatively in 4 patients

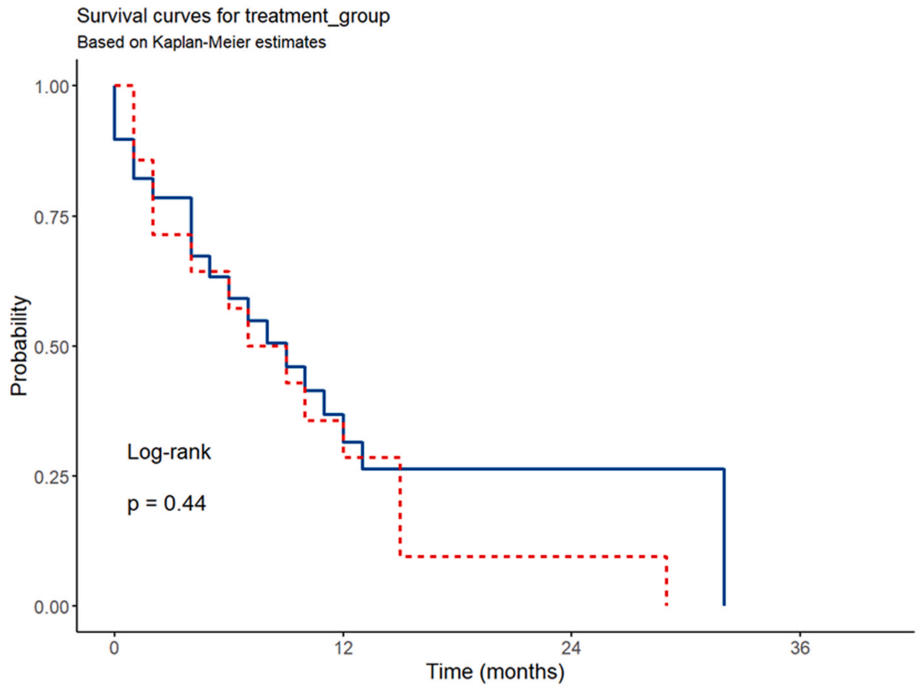

Fig. 3. The progression free survival for the lobectomy and lesionectomy groups was 9 and 8 months respectively.

that underwent lesionectomy (28.5 %) and in four patients (13.7 %) in the lobectomy group.

4. Discussion

The employment of supramaximal resection of GBs has been adequately identified in the literature (Pessina et al., 2017; Eyüpoglu et al., 2016; Tripathi et al., 2021; Mampre et al., 2018; Glenn et al., 2018; Vivas-Buitrago et al., 2021; Esquenazi et al., 2017; Otsuji et al., 2023; Tropeano et al., 2024). Moreover, the employment of lobectomy, in those GB cases that is possible, has been associated with increased OS and PFS in several, previously published series (Hamada and Abou-Zeid, 2016; Borger et al., 2021; Roh et al., 2019; Shah et al., 2020; Schneider et al., 2020; Hollerhage et al., 1991; Zheng et al., 2023; Arvaniti et al., 2024). Arvaniti et al. found in their meta-analysis that lobectomy demonstrated a significantly prolonged OS and PFS when compared to gross-total resection (Arvaniti et al., 2024). It is also important to emphasize, that even though supramaximal resection and lobectomy are the most radical resection strategies, constitute two very different surgical techniques. The significant cytoreduction accomplished by a lobectomy, and its potential beneficial role in the effect of post-surgical, adjuvant radio- and chemotherapy have also been properly outlined in the pertinent literature (Waqar et al., 2022; Knudsen et al., 2021; Yool and Ramesh, 2020; Youngblood et al., 2020). Indeed, our current results demonstrate extensive PFS and OS in our lobectomy patients. The 3-year OS was 25 % in the lobectomy series, which is higher than the average expected OS for GB patients, as this can be found in the pertinent literature (Pessina et al., 2017; Eyüpoglu et al., 2016; Li et al., 2015; Roh et al., 2019; Shah et al., 2020; Schneider et al., 2020; Zheng et al., 2023; Krigers et al., 2022). The median OS in lobectomy group was 34 months (95 % CI 14 months -NA), compared to 15 months (95 % CI 12 months -NA) in the lesionectomy group. There was no statistically significant association between the type of surgery and recurrence. The PFS with lobectomy is 9 months (95 % CI, 5 months -NA) and with lesionectomy is 8 months (95 % CI, 4 months - NA).

Furthermore, the complete resection of brain parenchyma accomplished via a lobectomy and the extensive resection of the highly epileptogenic, mesial temporal structures in cases of temporal lobe GBs may mitigate the incidence of any postoperative seizures (Esquenazi et al., 2017; Przybylowski et al., 2021; Hebb et al., 2011; Hussein et al., 2021). Unfortunately, our small number of cases and the retrospective character of our current study do not allow the drawing of any conclusions regarding the incidence of postoperative seizures, and the potential role of lobectomy in decreasing their incidence. However, Borger et al. have reported that lobectomy provided better seizure outcome in their patients (Borger et al., 2021). Moreover, the exact impact of these extensive resections on network level, in the residual tumor, if any, as well as on any induced intra-hemispheric and contralateral compensatory changes remain essentially unknown (Venkataramani et al., 2022). Likewise, such induced changes on cellular level remain unexplored, as well as its implications on the host immunologic and sprouting response remain unknown (Waqar et al., 2022; Knudsen et al., 2021; Venkataramani et al., 2022).

On the other hand, lobectomy has been associated with certain concerns. It may prolong the operative time, may be associated with increased intraoperative blood loss, and may predispose to the development of postoperative hematomas and/or hydrocephalus (Brotis et al., 2019; Popovic et al., 1995; Tebo et al., 2014; Georgiadis et al., 2013). Moreover, a temporary worsening of the pre-operative neurological condition may well be observed after a lobectomy (Brotis et al., 2019; Popovic et al., 1995; Tebo et al., 2014; Georgiadis et al., 2013; Helmstaedter and Witt, 2012; Braun et al., 1994; Goldstein et al., 1993; Suchy and Chelune, 2001; Jayalakshmi et al., 2015; Salanova et al., 2002; Engel, 2012; Lopez-Gonzalez et al., 2011; Wiebe et al., 2001; Sindou et al., 2005; Grivas et al., 2006; Ploesser et al., 2022). Indeed, in our series 17,2 % of our patients demonstrated post-operatively some neurological worsening, which was spontaneously resolved within four weeks. There was also one case of intracranial hematoma. This is a potential complication associated with lobectomy, due to the large resection cavity formed (Brotis et al., 2019). These potential complications need to be extensively discussed preoperatively with the patient. The potential role of advanced age in the development of a postoperative infarction due to atherosclerotic middle cerebral artery changes needs to be further explored. Additionally, there were no cases developing hydrocephalus. It has to be mentioned, however, that the incidence of postoperative hydrocephalus after temporal lobectomy in epilepsy cases

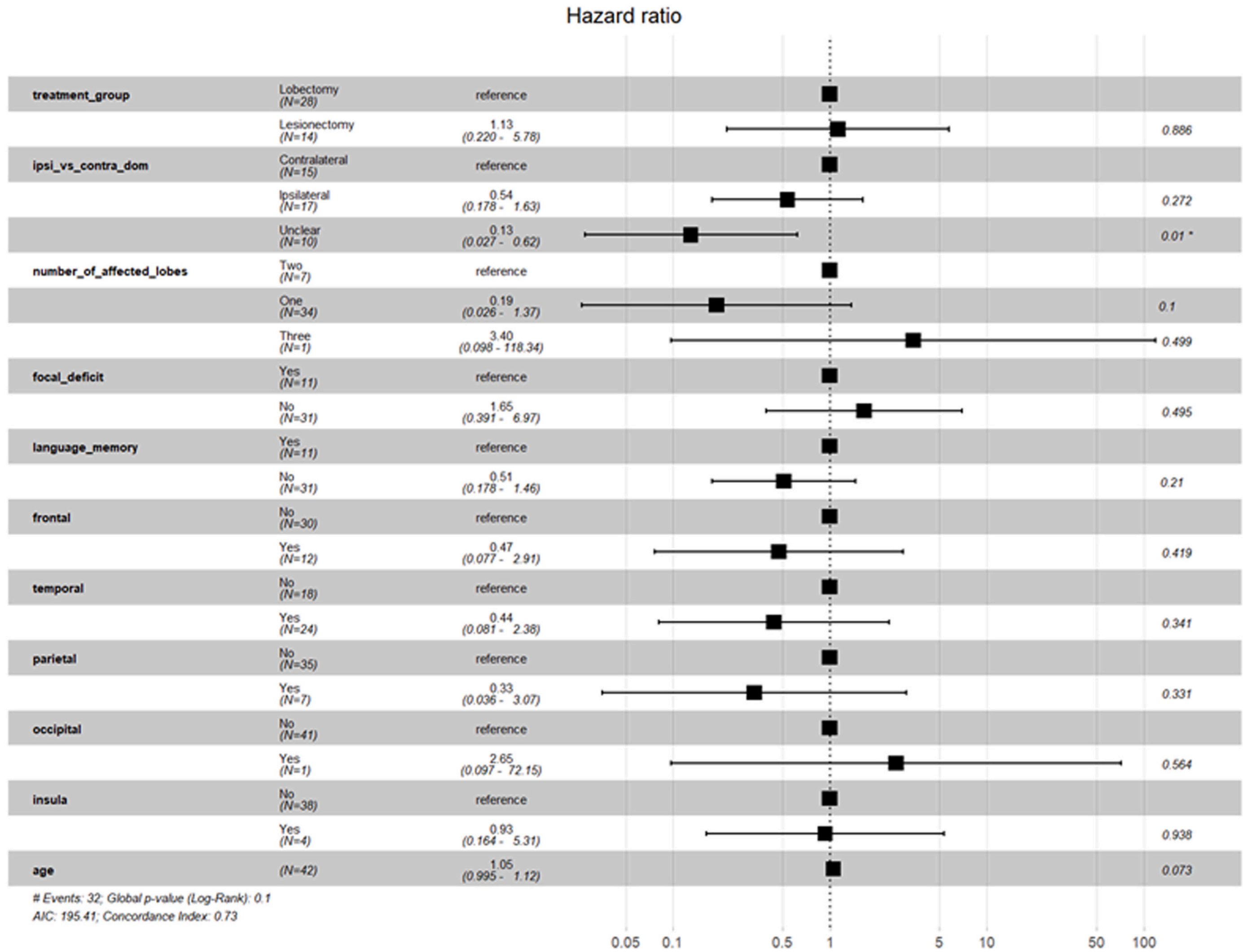

Fig. 4. The multivariate analysis demonstrated no prognostic factors regarding PFS.

has been reported to be between 2 and 7.1 % (Georgiadis et al., 2013). Furthermore, there is no doubt that lobectomy is a technically demanding procedure, requiring mastering of the surgical anatomy of the frontal and/or temporal lobes, as well as familiarity with the subpial resection/aspiration technique.

It is apparent that only patients with confined GBs of both frontal, or non-dominant temporal, or occipital lobes may be candidates for either a complete or a tailored lobectomy. In our current series, the vast majority of our patients (86 %) had temporal or frontal GBs. The extension of tumor to the adjacent lobe, was independent bad prognostic factors in our series. Even though all the authors agree that insular GB cases are the most challenging ones (Singh et al., 2020), in our multivariate analysis seem to be a positive prognostic factor regarding OS. However, we believe this to be a statistical paradox due to the limited number of patients. In addition, the potential role of the involvement of the dominant hemisphere cannot be explored in our current series, due to inconsistent registration of the hemispheric dominance among our participants. In cases where hemispheric dominence was verified, that occurred through meticulous medical history, clinical examination and the use of task-generated functional MRI. This needs to be explored in a prospective study, since it is anticipated that lesions in the non-dominant hemisphere allow for a more radical resection (Coluccia et al., 2018).

Undoubtedly, the selection of the ideal candidates for lobectomy constitutes a complicated and challenging process. Besides the tumor's anatomic location, other critical factors need to be also taken into consideration. For example, the patients' preoperative neurological condition, their functional status, their neurocognitive condition, and possibly their biological age have to be considered. The absence of any focal, preoperative neurological deficits has been used as a criterion in our series for performing a lobectomy. A good functional status, as this is reflected on a Karnofsky Performance Scale score higher than 70, is another criterion used in our practices. Likewise, a good preoperative neurocognitive testing and a good preoperative modified frailty index were also used in our current series. (Krenzlin et al., 2021; Jimenez et al., 2024; Katiyar et al., 2020).

Advanced age was a negative prognostic factor in our series. It has been demonstrated that older patients have worse outcome mainly due to their decreased ability to overcome any procedure induced, systematic complications (Tripathi et al., 2021; Molinaro et al., 2020; Roh et al., 2019; Krigers et al., 2022; Park et al., 2024). The establishment of an age safety cutoff for performing a lobectomy is of paramount importance, since the incidence of GB increases with age. Several concerns regarding the selection process and the establishment of precise cutoff values are significant limitations of our current study and need to be prospectively explored in the future. Additionally, the identification of a subgroup of patients based on the molecular characteristics of their tumors, who would benefit from a lobectomy needs to be addressed. It has been postulated that tumors with certain molecular characteristics benefit from such an extensive, beyond their imaging borders, resection.

Contrariwise, in other molecular subgroups of GBs, an extensive, supramarginal resection seems to provide no benefit (Tripathi et al., 2021; Otsuji et al., 2023; Tropeano et al., 2024; Molinaro et al., 2020; Mier-García et al., 2023; Karschnia et al., 2022; Roh et al., 2019; Shah et al., 2020; Park et al., 2024; Massaad et al., 2024).

4.1. Limitations

Our current non-randomized, retrospective study carries several weaknesses and limitations. Its retrospective character makes it carry all the limitations and the potential biases of all retrospective studies. Moreover, the number of our participants is quite low, and our data are collected in three different institutions, with some differences in the selection process, and also in the employed surgical technique. All these issues, along with the exact incidence of post-operative procedure associated complications, the impact of lobectomy on the neurocognitive outcome, and the post-operative quality of life of these patients need to be further studied in a prospective, large-scale clinical study. Data from molecular subtypes also need to be thoroughly examined in a prospective study, to provide us with useful information in the selection process of patients most suitable for lobectomy.

5. Conclusions

Lobectomy for GBs constitutes a promising, surgical strategy, which seems to improve OS and PFS, in a carefully selected subset of GB patients. However, data regarding the secondary outcome of lobectomy in GBs remain scarce. Further prospective, well-designed studies, analyzing parameters such as procedure duration, postoperative complications, neurocognitive outcome, and seizure incidence need to be addressed for defining the exact role of lobectomy in the management of GB patients.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: Christina K. Arvaniti, Alexandros G. Brotis, Philippe Schucht, Mitchel Berger, Kostas N. Fountas; data collection: Christina K. Arvaniti, Jacob S. Young, Sivani Sivanrupan, Gracia Menna, Masahiro Nishide; analysis and interpretation of results: Alexandros G. Brotis, Christina K. Arvaniti, Kostas N. Fountas; draft manuscript preparation: Christina K. Arvaniti, Alexandros G. Brotis, Kostas N. Fountas. All authors reviewed the results and approved the final version of the manuscript.

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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.

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