U.PORTO

FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2020/2021

João Pedro Borges Catela Dos Reis Sousa

Long-term survivors of Glioblastoma: Clinical and radiological profile of a portuguese cohort

Abril, 2021

U.PORTO

FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

João Pedro Borges Catela Dos Reis Sousa

Long-term survivors of Glioblastoma: Clinical and radiological profile of a portuguese cohort

Mestrado Integrado em Medicina

Área: Neurociências Clínicas e Saúde Mental

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Dr. Bruno Miguel Fernandes Carvalho

E sob a Coorientação de:

Doutor António Luís do Carmo Cerejo

Trabalho organizado de acordo com as normas da revista:

Journal of Neuro-Oncology

Abril, 2021

FMUP

Índice

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

Eu, João Pedro Borges Catela Dos Reis Sousa, abaixo assinado, nº mecanográfico 200601896, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 02/04/2021

Assinatura conforme cartão de identificação:

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

UC Dissertação/Projeto (6º Ano) – DECLARAÇÃO DE REPRODUÇÃO

NOME

João Pedro Borges Catela Dos Reis Sousa

NÚMERO DE ESTUDANTE	E-MAIL
200601896	Joaobcatela@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Neurociências Clínicas e Saúde Mental

TÍTULO DISSERTAÇÃO

Long-term survivors of Glioblastoma:
Clinical and radiological profile of a portuguese cohort

ORIENTADOR

Dr. Bruno Miguel Fernandes Carvalho

COORIENTADOR (se aplicável)

Doutor António Luís do Carmo Cerejo

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	X
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 02/04/2021.

Assinatura conforme cartão de identificação:

Agradecimentos

À minha esposa Catarina,

Por me ter acompanhado e apoiado incondicionalmente ao longo de todo este percurso académico.

Aos meus pais,

Pela sua presença e apoio constante.

Ao Dr. Bruno Carvalho,

Por todo o apoio e orientação incansáveis na realização deste trabalho.

Abstract

Purpose: Glioblastoma (GBM) is the most common primary malignant brain tumor and entails a grim prognosis. The aim of the present study is to provide an in-depth analysis of clinical, analytical and radiological features of a cohort of GBM long-term survivors (LTS) treated at a major tertiary referral Hospital in Portugal and perform a matched cohort comparison to patients surviving less than 2 years in order to identify distinctive prognostic factors.

Methods: A study population was identified by analyzing a pathological database of GBM patients operated between 2010 and 2018 at Centro Hospitalar Universitário São João. LTS were identified if they had an overall survival (OS) of at least 36 months. A matching cohort for age, gender and performance status with less than 24 months OS was identified through binary logistic regression. Clinical and radiological data were obtained and statistically significant differences identified.

Results: Out of 436 adult GBM patients, 27 met inclusion criteria. Tumor's mass effect was identified more often in the matched cohort versus the LTS cohort ($p=0.006$), subventricular proximity was significantly different between cohorts, with subventricular zone involvement (group I/II) more frequent in the matched cohort ($p=0.039$). Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were significantly lower in the LTS cohort compared to the matched cohort ($p < 0.001$).

Conclusions: In our group of GBM long-term survivors, the absence of mass effect, low serum inflammatory markers and low frequency of subventricular zone involvement stand out as variables with prognostic impact when compared to non-long-term survivors.

Introduction:

Glioblastoma (GBM) is the most common primary malignant brain tumor and portends one of the most malevolent clinical prognoses. Median overall survival (OS) of patients with GBM in population-based studies is approximately 10 to 12 months [1,2], rising to 15-16 months for those receiving standard of care surgery and adjuvant chemoradiation [3,4]. However, only 3-5% of the patients survive for more than 3 years and are referred to as long-term survivors. Nevertheless, GBM exhibits a substantial degree of heterogeneity in both clinical and molecular profiles. The clinical and molecular factors that contribute to long-term survival are still incompletely defined [5]. For instance, contrary to what was thought, long-term survival does not require IDH mutation and therefore, IDH1 status is not the only player responsible for long-term survivorship in the temozolomide era [6]. Additionally, long-term survival is not dictated by a single transcriptional subclass [7].

Few studies have focused on features that predict long-term survival. These patients exhibit a disease course that is qualitatively different from the vast majority of GBM patients. For example, half of patients who have survived four years will survive four more [8]. Do these patients simply exhibit all the features associated with good prognosis or is it related to a different set of features of the disease? Answering this question would allow improvement of prognostic scales, but also indicate therapeutic strategies to convert more patients into extreme long-term survivors [9].

The present study aims to provide an in-depth analysis of clinical, analytical and radiological features of a cohort of GBM long-term survivors treated at a major tertiary referral Hospital in Portugal. Taking a relatively sized cohort of patients diagnosed and treated over a period of 8 years, we provide some insight into the clinical, analytical, radiological and therapeutic features of patients deemed long-term survivors (OS $\geq$ 3 years). Additionally, we perform a matched cohort comparison to patients surviving less than 2 years and identify predictive prognostic factors.

Materials and methods

Study population

The study population was identified by analyzing a pathological database comprising patients operated at Centro Hospitalar Universitário São João between 2010 and 2018. 1708 cases of CNS neoplasia were identified, of which 436 were adult GBM's. Out of that pool of patients the inclusion criteria were subsequently applied, as layed out in Figure 1. A final cohort was obtained, consisting of 27 adult patients with histologically confirmed *de* novo GBM with an OS of at least 36 months. All histopathological specimens were centrally reviewed by a neuropathologist, confirming the diagnosis of GBM.

Clinical and radiological data were obtained and reviewed. Variables included: gender, age, comorbidities (Charlson Comorbidity Index), ECOG (Eastern Cooperative Oncology Group) performance status at admission, motor deficits at presentation and the number of surgeries performed. MRI´s were reviewed to obtain information regarding localization, volume, largest diameter, focality, laterality, mass effect, subventricular zone proximity (SVZ score) and tumor resection rate. Haematological counts of the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were obtained. Adjuvant radiotherapy and chemotherapy treatments for each patient were fully reviewed.

Statistical Methods

Descriptive statistics were used to describe patient demographic and clinical characteristics. Categorical variables are presented as observed counts and weighted percentages, and continuous variables as median with the corresponding range. The Kaplan-Meier estimation method was used to obtain median survival times and survival probabilities for all patients. A matching cohort with less than 24 months of OS was identified through binary logistic regression, using age, gender and ECOG performance status as matching covariates. Differences between groups were analyzed using Chi-square, Fisher's exact test or Mann–Whitney U test as appropriate. A p value 0.05 was considered to be statistically significant. All statistical analyses were conducted in IBM SPSS Statistics 26.

Ethics approval

This study was approved by the Local Ethical Committee of Centro Hospitalar Universitário de São João, (Porto, Portugal) and was conducted according to the National Ethical Guidelines.

Results

Patient characteristics

The study population of GBM long-term survivors consisted of 27 patients, that presented at the time of diagnosis a median age of 54 years (range 30 – 76 years), with 12 male and 15 female patients. ECOG performance status was 0 for most patients (70%), with 4 patients presenting an ECOG of 2 or above (15%). Relating to comorbidities, as assessed by the Charlson Comorbidity Index, results were more scattered, ranging from 2 to 6, the more frequent indices being 3 (33%) and 2 (30%). At the time of diagnosis 10 patients presented with motor deficits (37%).

Haematological variables of interest were assessed, namely the NLR and the PLR, which presented a median of 1.21 (range 0.16 – 18.80) and 24.7 (range 8.13 – 353.16) respectively.

Furthermore, eight patients that were still alive at the time this study was conducted were contacted and asked to provide quality of life assessments through EORTC QLQ-30 and QLQ-BN20 surveys. Four completed surveys were obtained, showing that the patient's self-assessment of their health over the preceding week had a mean score of 5 out of 7 (range 4 to 7) and their assessment of their global quality of life over the same period also had a mean score of 5 out of 7 (range 4 to 7). Regarding the QLQ-BN20 assessments, the most frequent complaints were headaches, difficulty reading and difficulty in remaining up once standing, and concerns were also common regarding the future and changes in family dynamics.

Tumor characteristics

Tumor localization varied and had a frontal lobe distribution in 7 patients (26%). Fifteen were right-sided (56%), 8 were left-sided (30%) and 1 was bilateral. Nineteen patients (70%) presented unifocal disease while 5 patients (18.5%) presented multifocal tumors. Out of the assessed tumors, 13 (48%) presented mass effect.

Assessment was also performed regarding the tumor's proximity to subventricular and cortical zones, with most patients (41%) having cortical lesions without subventricular contact (group III), while 2 patients (7%) presented neither cortical nor subventricular contact (group IV), 7 (26%) presented cortical and subventricular contact (group I) and 4 (15%) only subventricular contact (group II).

Full clinical and tumor characteristics are depicted in Table 1.

Tumor volumes were assessed pre-operatively, with a mean of 34mm^3 (ranging from 6mm^3 to 126mm^3). The tumor's largest diameter was also assessed and presented a mean of 4 cm (ranging between 3 cm – 8 cm).

Unfortunately, MGMT (5 patients) and IDH status (12 patients) were not consistently available to draw further conclusions.

Treatment data

Out of the 27 patients assessed, one single resective surgery was performed in 21 patients (78%), while 4 patients (15%) underwent two surgeries and 2 patients (7.4%) had only biopsy performed. Surgical resection was assessed in post-operative MRI, with complete surgical resection achieved in 14 patients (52%) as valued by no contrast-enhancing residual tumor, subtotal resection in 7 patients (26%), and only partial resection in 3 patients (11.1%).

After surgery all patients underwent treatment with radiotherapy, with 23 patients (85%) undergoing a total dose of 60 Gy, 1 patient (4%) having 52 Gy, 2 patients (7%) having 40,05 Gy.

Regarding chemotherapy, all 27 patients had first line temozolomide. Further protocols varied and second-line chemotherapy was applied to 20 patients (74%). Third-line chemotherapy was applied to 11 patients (41%).

Fourth-line chemotherapy was applied to 4 patients (15%). Fifth-line chemotherapy was applied to a single patient, with 2 months progression-free survival period. The chemotherapy regimens used at different time points are described in Table 2.

Survival data

The group's median OS was 63 months (95% CI 38.6 – 87.4 months). Median progression-free survival (PFS-1) was 17 months (95% CI 0.038 – 33.96 months). Second median progression-free survival (PFS-2) was 8 months (95% CI 0.16 – 15.84). Third median progression-free survival (PFS-3) was 3 months (95% CI 2.05 – 3.95). Figure 2 illustrates Kaplan-Meier's survival curves of LTS.

Matching cohort

The group consisted of 27 patients with surgically resected *de novo* GBM matched for the demographic and clinical variables previously described, with a median OS of 12 months (95% CI 11.2 – 12.8), all having received temozolomide as a first-line chemotherapy and achieving a median progression-free survival of 6 months (95% CI 3.5 – 8.5 months) and 26 (96%) receiving 60 Gy of radiotherapy. Motor deficits at presentation were identified in 13 patients (48%), and 21 patients (78%) underwent single surgery, while 5 (19%) had two surgeries and a single patient had four surgeries. Comorbidity indices varied from 2 to 5, with the more frequent being 3 (41%) and 2 (30%). Frontal tumors were identified in 11 patients (41%), right sided were more frequent, seen in 15 patients (56%) and focal tumors accounted for the majority, identified in 24 patients (89%). Complete tumor resection was achieved in 15 patients (56%), subtotal in 6 (22%) and partial resection in the remaining 6 patients (22%).

Statistically significant differences were detected between the groups in several characteristics. Tumor's mass effect was identified in 24 patients (89%) in the matching group versus 13 patients (54.2%) in the long-term survival group ($p = 0.006$, Chi-Square test). Subventricular proximity was also significantly different between groups with 20 patients (74.1%) having SVZ group I or II in the matching cohort versus 11 patients (45.8%) in the long-term survival group ($p = 0.039$, Chi-Square test). Regarding haematological parameters, NLR was assessed using a cut-off of 4, and statistically significant differences were observed, with the matching cohort having significantly less patients with NLR < 4 (3 patients, 11.1%) compared to the long-term survival group (26 patients, 96.3%) ($p < 0.001$, Chi-Square test). Regarding PLR, matching cohort patients had significantly less patients with PLR <= 175 (8 patients, 29.6%) compared to long-term survival group (26 patients, 96.3%) ($p < 0.001$, Chi-Square test). The comparison of means of absolute values of NLR and PLR also disclosed statistical significance (Mann-Whitney U test, 39.00, $p < 0.001$). A full analysis of the differences identified between the matching cohort and the study population can be reviewed in Table 3. Kaplan-Meier curves according to mass effect, NLR and PLR are shown in Figure 3.

Discussion

In our study, the prevalence of LTS was found to be 6.2% (27 out of 436 patients) of the overall *de novo* GBM diagnosed in the study period, which is within the range of prevalence reported in the literature (2.2% to 14,6%) [10, 11, 12, 13, 14, 15]. An OS of at least 36 months is generally accepted as the cut-off to define a long-term survivor, although such definition is not consensual, as exemplified by several studies who define long-term survival as 24 months [16, 17, 18] while others define it as 60 months [19, 20, 21], and others yet combine a 36- and 60-month period [22, 23]. In the present study, 36 months was deemed the most reasonable option, given the literature available and the composition of our cohort. The available evidence from studies carried out using an OS of 36 months was assessed to compare for variables such as age at diagnosis, sex, median OS and presentation. Age at presentation was generally slightly lower than our cohort, with a minimum of 47 years in one study [10], and only one study presenting a comparable age at presentation of 55 years [11]. Interestingly, regarding sex distribution in the analyzed cohorts, all exhibited males as the majority of patients, which does not hold true in our study, where 55.6% of patients are female. Regarding motor deficits at presentation, one study reported it as present in 13% of patients [12] and another reported 33% [13], the former having a larger cohort and the latter a smaller and more similar cohort to our study, which reports motor deficits at presentation in 37% of patients. Tumor localization in the frontal lobe was also assessed in the literature, and values ranged from 25% to 52% [11, 12, 24, 14, 25], while our study reports 26% frontal tumors, being of note that Zreik *et al* report, in the largest cohort analyzed in the literature, a similar value of 31%, with 8757 patients in their group [11]. Finally, median OS was generally lower in the reviewed studies, ranging from 41 to 110 months, with only two studies reporting longer median OS [12, 13], while most reported lower median OS than the present study [10, 11, 24, 14, 26, 25]. Interestingly, although our matching cohort was matched for age, gender and performance status, the type of surgery and tumor characteristics (diameter, volume and EOR) were also fairly equivalent between groups. Numerous variables were analyzed and compared, and the available results point to significant differences between our study population and the matched cohort, namely in mass effect, NLR, PLR and involvement of subventricular zone.

Mass effect is a sign that is generally accepted as being associated with poorer outcomes, whether it originates from trauma, stroke or a tumor, so it is not a surprising find that in our study the identification of mass effect on pre-operative MRI has been associated with shorter OS. This was found in 48.1% (n = 13) of patients in the study population versus 88.9% (n = 24) of the patients in the matched cohort for comparison, which proved to be a statistically significant difference ($p = 0.006$). As Steed *et al* point out, the clinical estimation by measuring midline shift, apart from the inter-operator variability in the assessment, constitutes a variable that lacks exact quantification, thus having the potential to underestimate the mass effect of tumors located in areas where the mass effect vector would be in an anterior/posterior or superior/inferior direction [27]. On the other hand, the existence of a tumor creating a mass effect can lead to raised intracranial pressure, which can cause neurological symptoms, prompting an earlier patient assessment and diagnosis, which can in turn favor a better prognosis [28]. Another recent area of interest that warrants further investigation is tumor infiltration through white matter tracts, rather than purely mass effect identification on imaging, as the means to identify patients that might have poor prognosis [29].

NLR and PLR are systemic inflammatory markers which have been studied as possible markers of prognostic outcome in GBM patients, as means to identify high risk patients and target more aggressive therapies to this

subgroup [30, 31]. Lei *et al*, in a recent systematic review using the same cut-off point of 4 concluded that a high NLR is related to poor survival [32], as is confirmed by the present study, which found a median NLR of 1.21 in the study group versus a median of 7.67 in the matching cohort ($p < 0.0001$). Although such difference in the NLR between the two groups correlates with current knowledge in the literature, further investigation would be welcomed to assess the dynamics of NLR during treatment, and its possible association with different treatment modalities, as is stated by Mason *et al*, that suggest that these dynamic changes in NLR during focal radiotherapy and concomitant TMZ could yield stronger prognostic information [33]. PLR is another inflammatory marker that was analyzed, and which yielded statistically significant differences between the study group and the matching cohort, suggesting a lower PLR is associated with a longer OS ($p < 0.0001$). Although this fact has been reported in several studies [34, 35, 36], such conclusions are not overall accepted as true, since some studies have found this relationship to be either non-existent to the extent that it constitutes a viable prognostic marker or that it does exist but is of a lesser value than the NLR as a prognostic marker [37, 38]. Given the fact that such differences still exist, further investigation would be warranted to clarify the role of PLR as a prognostic marker.

The subventricular zone is an area that stands out as a prominent neural stem cell niche, which has led investigation into the possibility of it being related to the origin and biological behavior of GBM's, as well as its implications in OS and tumor progression [39, 40]. In the present study, pre-operative MRI's were analyzed and the tumor proximity to the SVZ was classified in four groups, as previously laid out. Subsequently, such classification was compared with the matching cohort, which yielded statistically significant differences ($p = 0.049$), suggesting that proximity to the SVZ (groups I and II) was more associated with the short-survival group, an outcome previously observed in other studies [41, 42, 15]. Although our study validates the findings of previous authors regarding the relationship between the tumor proximity to the SVZ and a decreased OS, further investigation is warranted to assess how this information can translate into effective targeted therapies.

Although reports from QoL questionnaires are too few to draw any legitimate conclusions, it is our understanding that a tendency towards a preserved quality of life can be seen from both tools applied (EORTC QLQ-30 and QLQ-BN20). However, this is an area that would warrant further investigation to enable potential conclusions to be drawn.

The present study has limitations, namely the fact that it is retrospective in nature, so prospective studies would be a welcomed addition to substantiate our findings. Another area we identify as a limitation in this study is the lack of complete molecular data, which could prove instrumental in understanding the biological behavior of these tumors, as well as possibly provide new insight into markers that could have a prognostic role or influence the overall prognosis of these patients in ways we are yet to uncover.

Conclusion

In our study, we identified a cohort of patients diagnosed with *de novo* GMB which reached a survival of at least 3 years, accounting for 6.2% of all diagnosed GBM in the study period. The absence of mass effect, low serum inflammatory markers and low frequency of subventricular zone involvement were significantly more prevalent in long-term survivors than in non-long-term survivors.

References

1. Ostrom, Q. T., Gittleman, H., Xu, J., Kromer, C., Wolinsky, Y., Kruchko, C., & Barnholtz-Sloan, J. S. (2016). CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009–2013. *Neuro-Oncology*, *18*(suppl_5), v1–v75. https://doi.org/10.1093/neuonc/now207
2. Korja, M., Raj, R., Seppä, K., Luostarinen, T., Malila, N., Seppälä, M., Mäenpää, H., & Pitkäniemi, J. (2018). Glioblastoma survival is improving despite increasing incidence rates: a nationwide study between 2000 and 2013 in Finland. *Neuro-Oncology*, *21*(3), 370–379. https://doi.org/10.1093/neuonc/noy164
3. Gilbert, M. R., Dignam, J. J., Armstrong, T. S., Wefel, J. S., Blumenthal, D. T., Vogelbaum, M. A., Colman, H., Chakravarti, A., Pugh, S., Won, M., Jeraj, R., Brown, P. D., Jaeckle, K. A., Schiff, D., Stieber, V. W., Brachman, D. G., Werner-Wasik, M., Tremont-Lukats, I. W., Sulman, E. P., . . . Mehta, M. P. (2014). A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma. *New England Journal of Medicine*, *370*(8), 699–708. https://doi.org/10.1056/nejmoa1308573
4. Chinot, O. L., Wick, W., Mason, W., Henriksson, R., Saran, F., Nishikawa, R., Carpentier, A. F., Hoang-Xuan, K., Kavan, P., Cernea, D., Brandes, A. A., Hilton, M., Abrey, L., & Cloughesy, T. (2014). Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma. *New England Journal of Medicine*, *370*(8), 709–722. https://doi.org/10.1056/nejmoa1308345
5. Krex, D., Klink, B., Hartmann, C., von Deimling, A., Pietsch, T., Simon, M., Sabel, M., Steinbach, J. P., Heese, O., Reifenberger, G., Weller, M., & Schackert, G. (2007b). Long-term survival with glioblastoma multiforme. *Brain*, *130*(10), 2596–2606. https://doi.org/10.1093/brain/awm204
6. Sarmiento, J., Mukherjee, D., Black, K., Fan, X., Hu, J., Nuno, M., & Patil, C. (2016). Do Long-Term Survivor Primary Glioblastoma Patients Harbor IDH1 Mutations? *Journal of Neurological Surgery Part A: Central European Neurosurgery*, *77*(03), 195–200. https://doi.org/10.1055/s-0035-1566121
7. Gerber, N. K., Goenka, A., Turcan, S., Reyngold, M., Makarov, V., Kannan, K., Beal, K., Omuro, A., Yamada, Y., Gutin, P., Brennan, C. W., Huse, J. T., & Chan, T. A. (2014). Transcriptional diversity of long-term glioblastoma survivors. *Neuro-Oncology*, *16*(9), 1186–1195. https://doi.org/10.1093/neuonc/nou043
8. Johnson, D. R., Ma, D. J., Buckner, J. C., & Hammack, J. E. (2012). Conditional probability of long-term survival in glioblastoma. *Cancer*, *118*(22), 5608–5613. https://doi.org/10.1002/cncr.27590
9. Bi, W. L., & Beroukhim, R. (2014). Beating the odds: extreme long-term survival with glioblastoma. *Neuro-Oncology*, *16*(9), 1159–1160. https://doi.org/10.1093/neuonc/nou166
10. Sonoda, Y., Kumabe, T., Watanabe, M., Nakazato, Y., Inoue, T., Kanamori, M., & Tominaga, T. (2009). Long-term survivors of glioblastoma: clinical features and molecular analysis. *Acta Neurochirurgica*, *151*(11), 1349–1358. https://doi.org/10.1007/s00701-009-0387-1
11. Zreik, J., Moinuddin, F. M., Yolcu, Y. U., Alvi, M. A., Chaichana, K. L., Quinones-Hinojosa, A., & Bydon, M. (2020). Improved 3-year survival rates for glioblastoma multiforme are associated with trends in treatment: analysis of the national cancer database from 2004 to 2013. *Journal of Neuro-Oncology*, *148*(1), 69–79. https://doi.org/10.1007/s11060-020-03469-w

12. Hottinger, A. F., Yoon, H., DeAngelis, L. M., & Abrey, L. E. (2009). Neurological outcome of long-term glioblastoma survivors. *Journal of Neuro-Oncology*, *95*(3), 301–305. https://doi.org/10.1007/s11060-009-9946-9
13. Scott JN, Rewcastle NB, Brasher PM, Fulton D, MacKinnon JA, Hamilton M, Cairncross JG, Forsyth P. Which glioblastoma multiforme patient will become a long-term survivor? A population-based study. Ann Neurol. 1999 Aug;46(2):183-8. PMID: 10443883.
14. Zhang, G. B., Cui, X. L., Sui, D. L., Ren, X. H., Zhang, Z., Wang, Z. C., & Lin, S. (2013). Differential molecular genetic analysis in glioblastoma multiforme of long- and short-term survivors: a clinical study in Chinese patients. *Journal of Neuro-Oncology*, *113*(2), 251–258. https://doi.org/10.1007/s11060-013-1102-x
15. Adeberg, S., Bostel, T., König, L., Welzel, T., Debus, J., & Combs, S. E. (2014). A comparison of long-term survivors and short-term survivors with glioblastoma, subventricular zone involvement: a predictive factor for survival? *Radiation Oncology*, *9*(1), 1–6. https://doi.org/10.1186/1748-717x-9-95
16. Mazaris, P., Hong, X., Altshuler, D., Schultz, L., Poisson, L. M., Jain, R., Mikkelsen, T., Rosenblum, M., & Kalkanis, S. (2014). Key determinants of short-term and long-term glioblastoma survival: A 14-year retrospective study of patients from the Hermelin Brain Tumor Center at Henry Ford Hospital. *Clinical Neurology and Neurosurgery*, *120*, 103–112. https://doi.org/10.1016/j.clineuro.2014.03.001
17. Gately, L., McLachlan, S. A., Philip, J., Ruben, J., & Dowling, A. (2017). Long-term survivors of glioblastoma: a closer look. *Journal of Neuro-Oncology*, *136*(1), 155–162. https://doi.org/10.1007/s11060-017-2635-1
18. Field, K. M., Rosenthal, M. A., Yilmaz, M., Tacey, M., & Drummond, K. (2013). Comparison between poor and long-term survivors with glioblastoma: Review of an Australian dataset. *Asia-Pacific Journal of Clinical Oncology*, *10*(2), 153–161. https://doi.org/10.1111/ajco.12076
19. McLendon, R. E., & Halperin, E. C. (2003). Is the long-term survival of patients with intracranial glioblastoma multiforme overstated? *Cancer*, *98*(8), 1745–1748. https://doi.org/10.1002/cncr.11666
20. Burgenske, D. M., Yang, J., Decker, P. A., Kollmeyer, T. M., Kosel, M. L., Mladek, A. C., Caron, A. A., Vaubel, R. A., Gupta, S. K., Kitange, G. J., Sicotte, H., Youland, R. S., Remonde, D., Voss, J. S., Fritcher, E. G. B., Kolsky, K. L., Ida, C. M., Meyer, F. B., Lachance, D. H., . . . Sarkaria, J. N. (2019). Molecular profiling of long-term IDH-wildtype glioblastoma survivors. *Neuro-Oncology*, *21*(11), 1458–1469. https://doi.org/10.1093/neuonc/noz129
21. Cantrell, J. N., Waddle, M. R., Rotman, M., Peterson, J. L., Ruiz-Garcia, H., Heckman, M. G., Quiñones-Hinojosa, A., Rosenfeld, S. S., Brown, P. D., & Trifiletti, D. M. (2019). Progress Toward Long-Term Survivors of Glioblastoma. *Mayo Clinic Proceedings*, *94*(7), 1278–1286. https://doi.org/10.1016/j.mayocp.2018.11.031
22. Millward, C. P., Brodbelt, A. R., Haylock, B., Zakaria, R., Baborie, A., Crooks, D., Husband, D., Shenoy, A., Wong, H., & Jenkinson, M. D. (2016). The impact of MGMT methylation and IDH-1 mutation on long-term outcome for glioblastoma treated with chemoradiotherapy. *Acta Neurochirurgica*, *158*(10), 1943–1953. https://doi.org/10.1007/s00701-016-2928-8
23. Nakagawa, Y., Sasaki, H., Ohara, K., Ezaki, T., Toda, M., Ohira, T., Kawase, T., & Yoshida, K. (2017). Clinical and Molecular Prognostic Factors for Long-Term Survival of Patients with Glioblastomas in

Single-Institutional Consecutive Cohort. *World Neurosurgery*, *106*, 165–173. https://doi.org/10.1016/j.wneu.2017.06.126

24. Hartmann, C., Hentschel, B., Simon, M., Westphal, M., Schackert, G., Tonn, J. C., Loeffler, M., Reifenberger, G., Pietsch, T., von Deimling, A., & Weller, M. (2013). Long-Term Survival in Primary Glioblastoma With Versus Without Isocitrate Dehydrogenase Mutations. *Clinical Cancer Research*, *19*(18), 5146–5157. https://doi.org/10.1158/1078-0432.ccr-13-0017
25. Krex, D., Klink, B., Hartmann, C., von Deimling, A., Pietsch, T., Simon, M., Sabel, M., Steinbach, J. P., Heese, O., Reifenberger, G., Weller, M., & Schackert, G. (2007). Long-term survival with glioblastoma multiforme. *Brain*, *130*(10), 2596–2606. https://doi.org/10.1093/brain/awm204
26. Das, P., Puri, T., Jha, P., Pathak, P., Joshi, N., Suri, V., Sharma, M. C., Sharma, B. S., Mahapatra, A., Suri, A., & Sarkar, C. (2011). A clinicopathological and molecular analysis of glioblastoma multiforme with long-term survival. *Journal of Clinical Neuroscience*, *18*(1), 66–70. https://doi.org/10.1016/j.jocn.2010.04.050
27. Steed, T. C., Treiber, J. M., Brandel, M. G., Patel, K. S., Dale, A. M., Carter, B. S., & Chen, C. C. (2018). Quantification of glioblastoma mass effect by lateral ventricle displacement. *Scientific Reports*, *8*(1), 1–8. https://doi.org/10.1038/s41598-018-21147-w
28. Stark, A. M., van de Bergh, J., Hedderich, J., Mehdorn, H. M., & Nabavi, A. (2012). Glioblastoma: Clinical characteristics, prognostic factors and survival in 492 patients. *Clinical Neurology and Neurosurgery*, *114*(7), 840–845. https://doi.org/10.1016/j.clineuro.2012.01.026
29. Drumm, M. R., Dixit, K. S., Grimm, S., Kumthekar, P., Lukas, R. V., Raizer, J. J., Stupp, R., Chheda, M. G., Kam, K.-L., McCord, M., Sachdev, S., Kruser, T., Steffens, A., Javier, R., McCortney, K., & Horbinski, C. (2019). Extensive brainstem infiltration, not mass effect, is a common feature of end-stage cerebral glioblastomas. *Neuro-Oncology*, *22*(4), 470–479. https://doi.org/10.1093/neuonc/noz216
30. Lopes, M., Carvalho, B., Vaz, R., & Linhares, P. (2017). Influence of neutrophil–lymphocyte ratio in prognosis of glioblastoma multiforme. *Journal of Neuro-Oncology*, *136*(1), 173–180. https://doi.org/10.1007/s11060-017-2641-3
31. Linhares, P., Ferreira, A., & Vaz, R. (2019). The importance of the neutrophil-to-lymphocyte ratio in the prognosis of glioma and its subtypes. *CNS Neuroscience & Therapeutics*, *26*(3), 394–395. https://doi.org/10.1111/cns.13270
32. Lei, Y.-, Li, Y.-, Hu, Q.-, Wang, J., & Sui, A.-. (2019). Prognostic impact of neutrophil-to-lymphocyte ratio in gliomas: a systematic review and meta-analysis. *World Journal of Surgical Oncology*, *17*(1), 1–8. https://doi.org/10.1186/s12957-019-1686-5
33. Mason, M., Maurice, C., McNamara, M. G., Tieu, M. T., Lwin, Z., Millar, B.-A., Menard, C., Laperriere, N., Milosevic, M., Atenafu, E. G., Mason, W., & Chung, C. (2017). Neutrophil–lymphocyte ratio dynamics during concurrent chemo-radiotherapy for glioblastoma is an independent predictor for overall survival. *Journal of Neuro-Oncology*, *132*(3), 463–471. https://doi.org/10.1007/s11060-017-2395-y
34. Zheng, S.-, Huang, J.-, Chen, M., Wang, B.-, Ou, Q.-, & Huang, S.-. (2018). Diagnostic value of preoperative inflammatory markers in patients with glioma: a multicenter cohort study. *Journal of Neurosurgery*, *129*(3), 583–592. https://doi.org/10.3171/2017.3.jns161648

35. Lv, Y., Zhang, S., Liu, Z., Tian, Y., Liang, N., & Zhang, J. (2019). Prognostic value of preoperative neutrophil to lymphocyte ratio is superior to systemic immune inflammation index for survival in patients with Glioblastoma. *Clinical Neurology and Neurosurgery*, *181*, 24–27. https://doi.org/10.1016/j.clineuro.2019.03.017
36. Wang, P.-F., Song, H.-W., Cai, H.-Q., Kong, L.-W., Yao, K., Jiang, T., Li, S.-W., & Yan, C.-X. (2017). Preoperative inflammation markers and IDH mutation status predict glioblastoma patient survival. *Oncotarget*, *8*(30), 50117–50123. https://doi.org/10.18632/oncotarget.15235
37. Kaya, V., Yildirim, M., Yazıcı, G., Yalçın, A. Y., Orhan, N., & Güzel, A. (2017). The prognostic role of indicators of systemic inflammatory response in patients with glioblastoma. *Annals of Oncology*, *28*, v118. https://doi.org/10.1093/annonc/mdx366.026
38. Yersal, Ozlem., Odabaşi, E., Ozdemir, Ozge., & Kemal, Y. (2018). Prognostic significance of pre-treatment neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with glioblastoma. *Molecular and Clinical Oncology*, 453–458. https://doi.org/10.3892/mco.2018.1695
39. van Dijken, B. R. J., Jan van Laar, P., Li, C., Yan, J.-L., Boonzaier, N. R., Price, S. J., & van der Hoorn, A. (2019). Ventricle contact is associated with lower survival and increased peritumoral perfusion in glioblastoma. *Journal of Neurosurgery*, *131*(3), 717–723. https://doi.org/10.3171/2018.5.jns18340
40. Berendsen, S., van Bodegraven, E., Seute, T., Spliet, W. G. M., Geurts, M., Hendrikse, J., Schoysman, L., Huiszoon, W. B., Varkila, M., Rouss, S., Bell, E. H., Kroonen, J., Chakravarti, A., Bours, V., Snijders, T. J., & Robe, P. A. (2019). Adverse prognosis of glioblastoma contacting the subventricular zone: Biological correlates. *PLOS ONE*, *14*(10), e0222717. https://doi.org/10.1371/journal.pone.0222717
41. Jafri, N. F., Clarke, J. L., Weinberg, V., Barani, I. J., & Cha, S. (2012). Relationship of glioblastoma multiforme to the subventricular zone is associated with survival. *Neuro-Oncology*, *15*(1), 91–96. https://doi.org/10.1093/neuonc/nos268
42. Woo, P., Ho, J., Lam, S., Ma, E., Chan, D., Wong, W.-K., Mak, C., Lee, M., Wong, S.-T., Chan, K.-Y., & Poon, W.-S. (2018). A Comparative Analysis of the Usefulness of Survival Prediction Models for Patients with Glioblastoma in the Temozolomide Era: The Importance of Methylguanine Methyltransferase Promoter Methylation, Extent of Resection, and Subventricular Zone Location. *World Neurosurgery*, *115*, e375–e385. https://doi.org/10.1016/j.wneu.2018.04.059

Anexos

Table 1: Clinical and tumor characteristics of study population

	N (%)
Sex	
Female	15 (55.6)
Male	12 (44.4)
Age (years), median	54
range	30 - 76
ECOG	
0	19 (70.4)
1	4 (14.8)
2	1 (3.7)
3	1 (3.7)
4	2 (7.4)
Charlson Comorbidity Index	
0	-
1	-
2	8 (29.6)
3	9 (33.3)
4	4 (14.8)
5	5 (18.5)
6	1 (3.7)
Motor deficits at presentation	
Yes	10 (37)
No	17 (63)
NLR, median	1.21
range	0.16 - 18.8
PLR, median	24.7
range	8.13 - 353.16
Median **OS**, months	63
95% CI	38.6 - 87.4
Median **PFS 1**, months	17
95% CI	0.038 - 33.96
Median **PFS 2**, months	8
95% CI	0.16 - 15.84
Median **PFS 3**, months	3
95% CI	2.05 - 3.95
Median **PFS 4**, months	2
95% CI	-
Median **PFS 5**, months	2
95% CI	-

Table 1: Continued

	N (%)
Tumor localization	
Frontal	7 (25.9)
Non-frontal	17 (63)
Unknown	3 (11.1)
Tumor laterality	
Right	15 (55.6)
Left	8 (29.6)
Bilateral	1 (3.7)
Unknown	3 (11.1)
Tumor focality	
Unifocal	19 (70.4)
Multifocal	5 (18.5)
Unknown	3 (11.1)
Tumor mass effect	
Yes	13 (48.1)
No	11 (40.7)
Unknown	3 (11.1)
SVZ group	
I	7 (25.9)
II	4 (14.8)
III	11 (40.7)
IV	2 (7.4)
Unknown	3 (11.1)
Tumor volume (cc), mean	33.97
range	5.89 - 125.54
Largest diameter (cm), mean	4.40
range	2.63 - 7-45

ECOG: Eastern Cooperative Oncology Group performance status; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; OS: Overall survival; PFS: Progression-free survival; SVZ: Subventricular zone

Table 2: Treatment data of study population

	N (%)
First line CT	
TMZ	27 (100)
Second line CT	
BEV-based therapy	11 (40.7)
Lomustine	1 (3.7)
PCV	1 (3.7)
TMZ	7 (25.9)
Third line CT	
BEV-based therapy	3 (11.1)
Lomustine	2 (7.4)
PCV	3 (11.1)
TMZ	3 (11.1)
Fourth line CT	
Lomustine	1 (3.7)
TMZ	1 (3.7)
Fifth line CT	
PCV	1 (3.7)
Radiotherapy	
40.05 Gy	2 (7.4)
52 Gy	1 (3.7)
60 Gy	23 (85.2)
Unknown	1 (3.7)
Surgeries	
1	23 (85.2)
2	4 (14.8)
Type of surgery	
Total	14 (51.9)
Subtotal	7 (25.9)
Partial	3 (11.1)
Biopsy	2 (7.4)
Unknown	1 (3.7)

CT: Chemotherapy; TMZ: Temozolomide; BEV: Bevacizumab; PCV: Procarbazine, lomustine, vincristine

Table 3: Characteristics of long-term survival group versus matching cohort (age, gender and performance status matched) at baseline

	LTS (>36 months)	**Matching cohort (<24 months)**	p
	N (%)	N (%)	0.690
Age (years), median range	54 30-76	54 26-77	
Gender			0.276
Female	15 (55.6)	11 (40.7)	
Male	12 (44.4)	16 (59.3)	
ECOG			0.669
0	19 (70.4)	21 (77.8)	
1	4 (14.8)	4 (14.8)	
2	1 (3.7)	1 (3.7)	
3	1 (3.7)	1 (3.7)	
4	2 (7,4)	-	
Tumor focality			0.451
Unifocal	19 (70.4)	24 (88.9)	
Multifocal	5 (18.5)	3 (11.1)	
Unknown	3 (11.1)	-	
Type of surgery			0.788
Total	14 (51.9)	15 (55.6)	
Subtotal	7 (25.9)	6 (22.2)	
Partial	3 (11.1)	6 (22.2)	
Biopsy	2 (7.4)	-	
Unknown	1 (3.7)	-	
SVZ group			0.039*
I	7 (25.9)	11 (40.7)	
II	4 (14.8)	9 (33.3)	
III	11(40.7)	7 (25.9)	
IV	2 (7.4)	-	
Unknown	3 (11.1)	-	
Mass effect Yes No	 13 (48.1) 11 (40.7)	 24 (88.9) 3 (11.1)	0.006*
Largest diameter (cm), mean	4.4	4.98	0.167
Tumor volume (cc)**,** mean	33.9	39.7	0.293
EOR (%), mean	90.5	88.9	0.187
Residual tumor volume (cc)**,** mean	2.29	3.96	0.434
NLR	1.21	7.67	<0.0001*
PLR	24.7	204.55	<0.0001*
Second-line CT			
BEV-based therapy	11 (40.7)	16 (59.2)	
Lomustine	1 (3.7)	-	
PCV	1 (3.7)	-	
TMZ	7 (25.9)	1 (3.7)	
Third-line CT			
BEV-based therapy	3 (11.1)	-	
Lomustine	2 (7.4)	3 (11.1)	
PCV	3 (11.1)	4 (14.8)	
TMZ	3 (11.1)	3 (11.1)	
median **OS**, months 95% CI	63 38.6-87.4	12 11.2-12.8	
median **PFS**, months 95% CI	17 0.04-33.96	6 3.5-8.5	

LTS: Long-term survival; ECOG: Eastern Cooperative Oncology Group performance status; SVZ: Subventricular zone; EOR: Extent of resection; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio. BEV: Bevacizumab; PCV: Procarbazine, lomustine, vincristine; TMZ: Temozolomide; CT: Chemotherapy; OS: Overall survival; PFS: Progression-free survival

*$p<0.05$ deemed significant

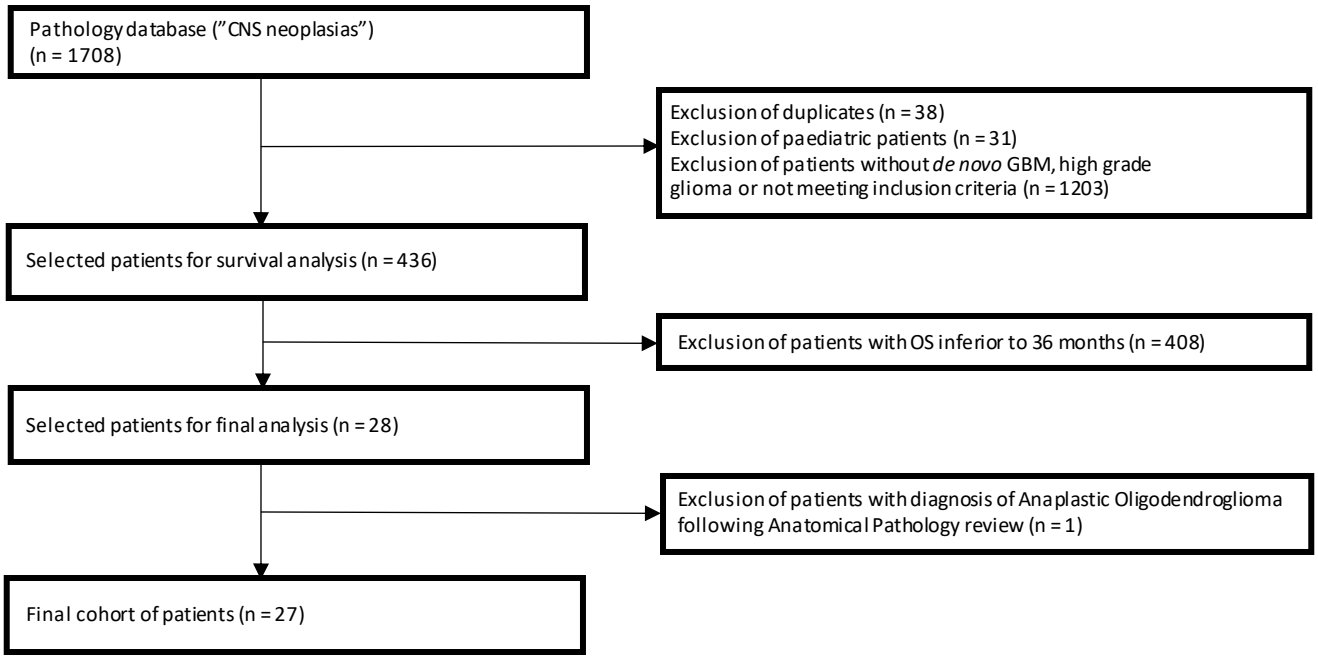

Figure 1: Flowchart of patient selection

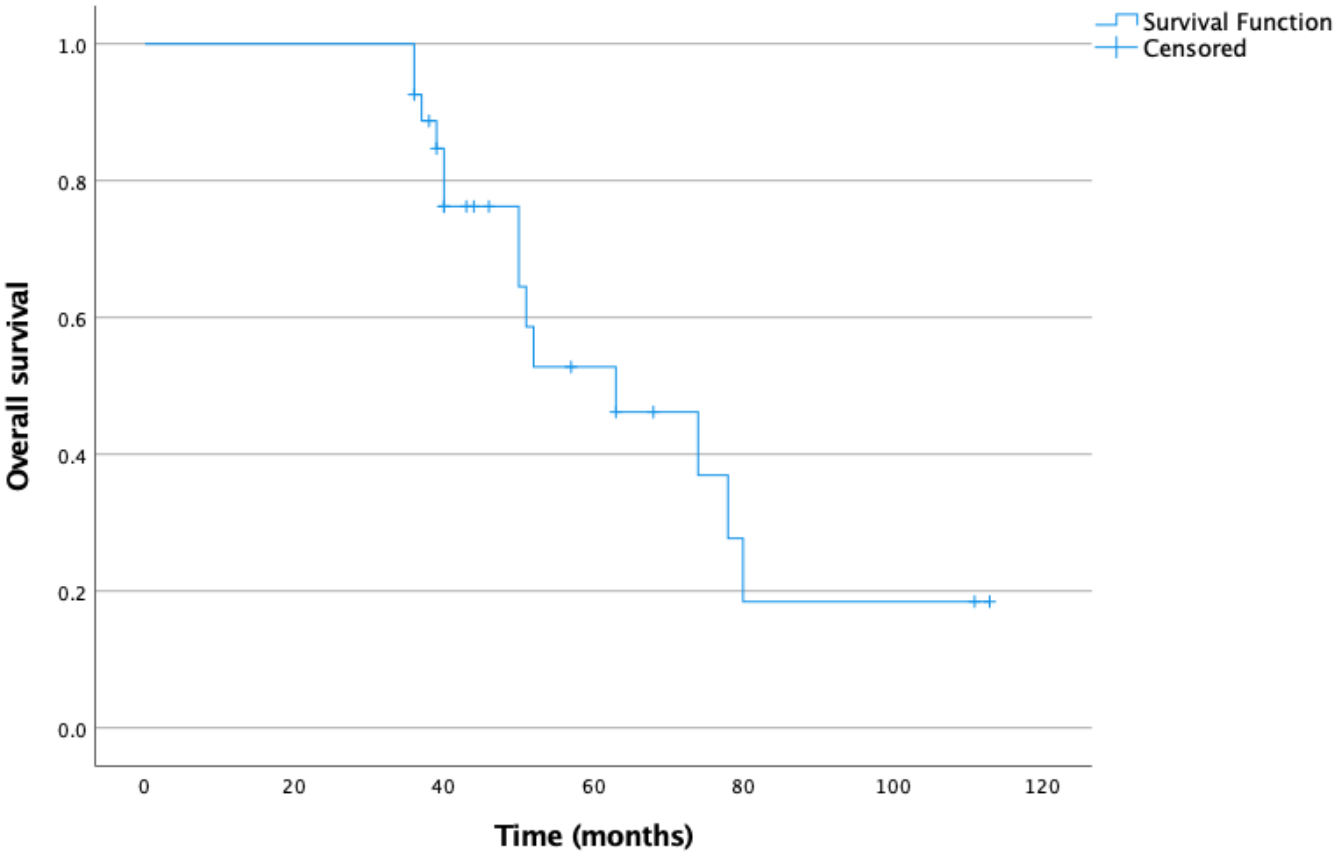

Figure 2: Kaplan-Meier survival curve of long-term survivors

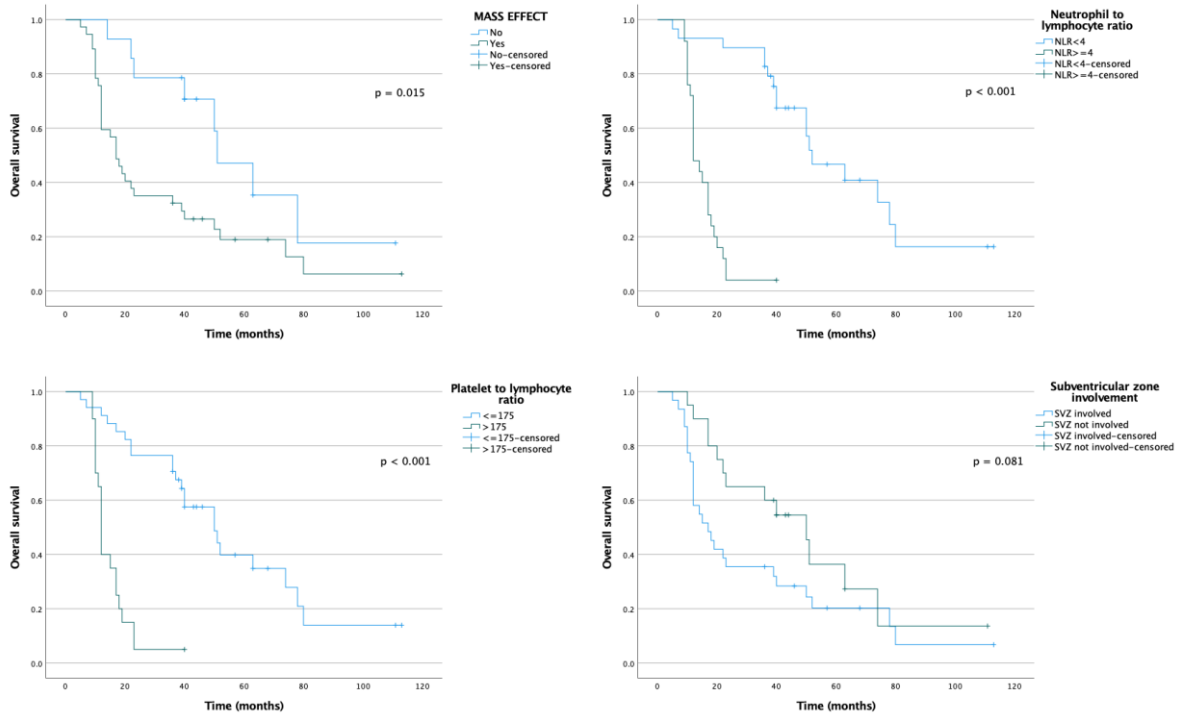

Figure 3: Kaplan-Meier survival curves according to mass effect, NLR, PLR and SVZ involvement

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Pag No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	11
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	11
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	12
Objectives	3	State specific objectives, including any prespecified hypotheses	12
Methods			
Study design	4	Present key elements of study design early in the paper	13
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	13
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	13
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	13
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	13
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	30
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	13
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	30
		(b) Give reasons for non-participation at each stage	30
		(c) Consider use of a flow diagram	30
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	25, 26
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	31

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	28, 29 27-31 NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	30-31
Discussion			
Key results	18	Summarise key results with reference to study objectives	14, 15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16, 17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16, 17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.