BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND BIOMEDICAL SCIENCES

Original article

Expenditures on the treatment of encephalon malignant neoplasia by the Brazilian public health system (2008-2017)

Carlos G. Garcia,[1]* Joice Nespoli[2]

Abstract

Introduction: Encephalon malignant neoplasia (EMN) is a harmful type of cancer and its most aggressive phenotypes lead to the demise of patients in 12-18 months despite the use of state-of-the-art therapies, which remain inefficient and expensive for patients, families and health systems. The aim of this work was to analyze the expenditures of the Brazilian Sistema Único de Saúde (SUS), the national public health system, on EMN patients compared to all neoplasia patients over a span of ten years (2008 to 2017). Methodology and resources: Monthly data were collected from the SUS data base DATASUS from 2008 to 2017 and analyzed with regard to EMN and general neoplasia for the following categories: value of total expenditures; number of hospitalizations; mean value of hospitalizations; mean of monthly permanence time and death rate. Results: More than 0.3% of SUS costs were directed to EMN patients, although they represented 0.1% of total hospitalizations. The mean value of hospitalization of EMN patients was almost 80% that of general neoplasia patients and hospitalization time was twice that of general neoplasia patients. Moreover, EMN patients had a death rate almost four times higher than that of general neoplasia patients. Discussion and conclusion: EMN therapies remained expensive and lacked efficacy in the time period under analysis, with a disproportionate share of SUS expenditure being dedicated to these patients. Improving the effectiveness of treatment requires drug repurposing and adjuvant chemotherapy—in addition to radiotherapy and the use of monoclonal antibodies.

Keywords: Encephalon malignant neoplasia; Cancer treatment costs; SUS.

1. Centro Universitário Anhanguera de Niterói, Biomedical sciences graduate course, Niterói, Rio de Janeiro, Brazil.
2. Centro Universitário Anhanguera de Niterói, Biomedical sciences graduate course, Niterói, Rio de Janeiro, Brazil.

***Correspondence address:**
Avenida Visconde do Rio Branco, 123
Niterói, RJ, Brazil.
CEP: 24020-005.
E-mail: cg_garcia@id.uff.br.
ORCID: https://orcid.org/0000-0002-1247-2967

BJHBS, Rio de Janeiro, 2022;21(1):39-46
DOI: 10.12957/bjhbs.2022.68180
Recebido em 15/07/2021. Aprovado em 25/04/2022.

Introduction

Primary central nervous system (CNS) tumors, such as encephalon malignant neoplasia (EMN), account for around 2% of all adult human neoplasia. They involve many types of tumor, such as astocytomas—the most common EMNs—, ependymomas, oligodendrogliomas, neuroblastomas and others.[1,2] Considering all EMNs, Ostrom and colleagues (2018) showed that the incidence of new cases in the USA varies from 5 (children) to 50 (elders above 60 years old)/100.000 habitants per year, with variations depending on the age group.[3,4] One of the most classic symptoms of EMNs are associated convulsions in peritumoral area.[5] It is well known in the literature that the most common adult EMN is grade IV astrocytoma, known as human multiform glioblastoma (GB). GB is a WHO-IV grade tumor that exhibits nuclear atypia and genetic heterogeneity; it can induce neoangiogenesis and exhibit large necrosis in central tumor areas.[3,6-8] In Brazil, Werneck de Carvalho and colleagues (2017) showed that neuroepithelial CNS tumors accounted for almost 50% of all CN-diagnosed tumors in the population of a certain region in the state of Pará, Brazil, from 1997 to 2014.[9] Another recent study[10] showed that the greatest incidence of these neuroepithelial CNS tumors in Brazil occurs in the 40-59 year-old age group with no distinction between the sexes.

EMN diagnosis is identified through magnetic resonance imaging (MRI) in order to evaluate the location of the tumoral mass inside the encephalon and is followed by neurosurgery for the removal of the largest possible area of the tumoral mass. With regard to GB, even after neurosurgery and radio/chemotherapy protocols using the DNA alkylating agent temozolomide (TMZ) for many sessions, tumoral recurrence transpires in the vast majority of the cases.[6,11,12] It is well known that the overall 5-year survival rate of GB patients is 5%, despite the use of all available therapeutic tools, due to the capacity of GB to deregulate diverse

signaling pathways, which makes the establishment of a therapeutic protocol extremely difficult.[4,13,14]

Even with this evident problem, significantly more than 700 clinical trials related to GB exist, using different therapeutic protocols and interventions in an attempt to enhance the overall survival rate of patients.[15] This fact calls into question current therapies for GB and highlights the need to find therapeutic alternatives for treatment of this type of tumor and other EMNs, such as neuroblastomas, oligodendrogliomas and even lower-level (II and III) astrocytomas. One of the explanations for this myriad of protocols is the attempt to act, mainly pharmacologically, on many deregulated signaling pathways in EMN cells. The literature highlights the fact that GB and neuroblastoma cells, for example, exhibit enhanced phosphoinositide 3-kinase/RAC-alpha serine-threonine protein kinase/mammalian target of Rapamycin (PI3 kinase/Akt/mTOR) activation as well as Rat sarcoma virus (Ras), epidermal/vascular endothelial growth factor (EGF/VEGF), glycogen synthase kinase 3 beta (GSK-3β) and protein kinase C (PKC) downstream pathway triggering.[13,16-19] Since many of these pathways interact in tumoral cells, it is clear that no simple therapeutic approach can be easily found.

The literature widely describes that diagnosing and treating EMNs, especially GBs, is a costly process that involves a significant amount of time and is also very expensive for patients and health systems around the globe, while leading to no significant results in its clinical management.[20-22] Considering these factors, the aim of this work was to evaluate how the Brazilian public health system (Sistema Único de Saúde, SUS) managed certain aspects related to EMN, especially treatment costs, hospitalization time and death rates, over a decade (2008-2017).

Materials and methods

Data collect and table generation: Data from the Brazilian "Banco de Dados do Sistema Único de Saúde" (DATASUS) (http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/niuf.def) were used for the 2008-2017 period, year by year, concerning: a) Total value per month, Total value for the ICD-10-Neoplasia category and Total value for EMN (Table 1); b) Number of hospitalizations per month, Number of hospitalizations for the ICD-10-Neoplasia category and Number of hospitalizations for EMN (Table 2); c) Mean value of hospitalizations per month, Mean value of hospitalization for the ICD-10-Neoplasia category and Mean value of hospitalizations for EMN (Table 3); d) Mean time of permanence per month, Mean time of permanence for the ICD-10-

Table 1. SUS expenditures percentage from 2008 to 2017

Year	A) SUS expenditures with all neoplasia (%)	B) SUS expenditures with EMN (%)	C) EMN expenditures/ all neoplasia expenditures (%)
2008	7.15	0.269514	3.76
2009	7.21632	0.282442	3.916286
2010	7.318336	0.26667	3.645068
2011	7.515978	0.28	3.787532
2012	7.907894	0.296386	3.748988
2013	10.13073	0.294075	2.922765
2014	10.83456	0.306753	2.833148
2015	11.2412	0.321342	2.859452
2016	11.51003	0.344574	2.995991
2017	11.59962	0.337538	2.9101
Mean ± SEM	9.24±1.97	0.30±0.02	3.34±0.46

Legend: SUS: Sistema Único de Saúde. EMN: Encephalon malignant neoplasia. Last line: mean ± standard error of the mean. Mean: Sistema Único de Saúde (SUS) total net expenditures (in Brazilian Real): 12,049,220,951.00.

Source: The authors (2022).

Table 2. SUS hospitalization percentage

Year	A) Hospitalizations due to general neoplasia (%)	B) Hospitalizations due to EMN (%)	C) EMN hospitalizations/ General neoplasia hospitalizations (%)
2008	5,05	0.09	1.841264
2009	5.166218	0.099831	1.934264
2010	5.323121	0.099351	1.867213
2011	5.531869	0.107138	1.93862
2012	5.949984	0.112836	1.897055
2013	6.199764	0.115381	1.861056
2014	6.410482	0.113681	1.773359
2015	6.640472	0.118143	1.779139
2016	7.382037	0.137936	1.868537
2017	6.933717	0.125973	1.816812
Mean ± SEM	6.06±0.79	0.11±0.01	1.86±0.05

Legend: SUS: Sistema Único de Saúde. EMN: Encephalon malignant neoplasia. Last line: mean ± standard error of the mean. Mean of total net hospitalizations/year: 11,041,635.00.

Source: The authors (2022).

Table 3. Mean hospitalization value percentage

Year	A) Mean hospitalization value for general neoplasia (%)	B) Mean hospitalization value for EMN (%)	C) Mean EMN value/ mean general neoplasia value (%)
2008	141.71	289.90	204.5576
2009	139.7482896	283.0601	202.5259
2010	137.5134631	268.2042	195.0322
2011	135.8815229	265.5436	195.4642
2012	132.9390426	262.8976	197.7258
2013	164.5797878	256.0027	155.5493
2014	169.0813648	269.8476	159.5963
2015	169.3457882	271.9947	160.6149
2016	169.2704299	271.1682	160.1982
2017	167.5050954	267.8203	159.8879
Mean± SEM	152.76±16.23	270.64±9.67	179.12±21.26

Legend: EMN: Encephalon malignant neoplasia. Last line: mean ± standard error of the mean. Mean: Sistema Único de Saúde (SUS) hospitalization values (Brazilian Real): 1070.29

Source: The authors (2022).

Neoplasia category per month and Mean time of permanence for EMN (Table 4); and e) Death rate for the ICD-10-Neoplasia category and Death rate for EMN (Table 5).

The data were then organized in tables and shown as a percentage of each given year's value/number. Mean values of the studied period regarding the following parameters were included in the captions of the respective

Table 4. Mean hospitalization time percentage

Year	A) Mean hospitalization time for general neoplasia (%SUS mean)	B)Mean hospitalization time for EMN ((%SUS mean)	C) Mean hospitalization time for EMN (% mean general neoplasia value)
2008	101.72	213.7931	210.1695
2009	101.7241	208.6207	205.0847
2010	100	208.7719	208.7719
2011	98.24561	207.0175	210.7143
2012	96.49123	205.2632	212.7273
2013	96.49123	207.0175	214.5455
2014	96.42857	201.7857	209.2593
2015	96.42857	201.7857	209.2593
2016	92.85714	196.4286	211.5385
2017	94.44444	194.4444	205.8824
Mean± SEM	97.48±2.93	204.49±5.92	209.80±2.87

Legend: EMN: Encephalon malignant neoplasia. Last line: mean ± standard error of the mean. Mean: Sistema Único de Saúde (SUS) hospitalization time (days): 5.66.
Source: The authors (2022).

Table 5. Death rate

Year	A) Death rate by general neoplasia	B) Death rate by EMN
2008	3.28	13.72
2009	3.48	13.63
2010	3.61	14.09
2011	3.71	13.82
2012	3.8	13.5
2013	3.94	13.4
2014	3.97	14.1
2015	4.18	13.67
2016	4.38	13.7
2017	4.29	13.59
Mean ± SEM	3.86±0.35	13.72±0.22

Legend: Last line: mean ± standard error of the mean.
Source: The authors (2022).

tables: Total value per month, Total hospitalizations per month, Mean value of hospitalization and Mean time of permanence per month.

Results

At first, we wanted to identify the overall sum of SUS expenditures—that is, including all ICD-10 identified pathologies—and the share of this sum dedicated to all neoplasia and to EMNs specifically. As shown in column A of Table 1, a mean of 9.24±1.97% of SUS expenses were allocated to neoplasia patients during the 10 years analyzed. Specifically verifying SUS expenditures on EMN patients during the same period, we found that 0.3±0.02% of overall disbursements were dedicated to them (Table 1, column B). Using a more specific comparison parameter, we found that only 3.34±0.46% of total SUS expenditures on neoplasia were allocated to EMN patients (Table 1, column C).

Following the initial identification of mean general expenditures, we decided to evaluate the percentage of SUS hospitalizations related to neoplasia (Table 2, column A) as well as to EMN (Table 2, column B). We observed that 6.06±0.79% of hospitalizations were due to neoplasia, but only 0.11±0.01% corresponded to EMN in the period. We also verified that these hospitalizations accounted for 1.86±0.05% of the total number of neoplasia hospitalizations. This highlights the low number of patients hospitalized in SUS due to EMN during the years under analysis.

Next, we decided to evaluate differences in the cost of hospitalization between neoplasia and EMN patients. Table 3 shows SUS outcomes per hospitalization for neoplasia (column A) and we verified that these were 52.76±16.23% higher than the mean overall cost of hospitalization. Specifically for EMN, we observed that these patients exhibit a higher mean cost of hospitalization compared to the same parameter (170.64±9.67%) (column B). Moreover, we observed that the value for EMN was 79.12±21.26% higher than that of neoplasia in general (column C). In summary, EMN patients generate more costs for the SUS than other neoplasia patients, even though they are fewer in number.

In light of the data presented, we wondered if the high cost of EMN patients could be justified by a reduction in their hospitalization time or else in their death rates. To study this hypothesis, Table 4 was generated and shows that neoplasia patients are hospitalized for roughly the same time as the general mean of the SUS (column A, 97.48±2.93%). On the other hand, EMN patients presented a doubled hospitalization time compared to neoplasia in general (column C, 209.8±2.87%) or the mean of the SUS (column B, 204.49±5.92%). Even after the costly treatment allocated to a very small number of SUS patients, EMN patients clearly remained hospitalized for a longer time.

Last, we sought to evaluate the death rate of EMN patients compared to neoplasia patients (Table 5). We observed that death rate for neoplasia is around 3.86±0.35%, while for EMN this rate is three times higher, reaching 13.72±0.22%. It is noteworthy that the EMN death rate showed only a small variation over the 10 years under analysis, while total neoplasia grew gradually during the same period. In summary, EMN patients spent more time hospitalized and exhibited a higher death rate.

Discussion

A study showed that annual cost for treatment of CNS tumors in the USA in 2010 was the highest among all tumor types evaluated in the study.[20] The same study projected that the total cost with the treatment of cerebral tumors in the USA would increase by more than 20% from 2010 to 2020.

Despite the small number of patients compared to other neoplasia types, the direct and indirect economic impacts caused by high EMN treatment costs and mortality are substantial.[22,23] As an example, Tykocki and Eltayeb[24] published a meta-analysis identifying the 10-year survival rate in GB-diagnosed groups involving more than 30 studies between 1950 and 2010. The authors observed that this percentage was less than 1% even after the use of the entire available therapeutic arsenal in the respective decades. In Brazil the reality is the same. Regarding patient mortality, a study by Monteiro and Koifman[21] revealed that, in Brazil, the mortality rate due to cerebral tumors, whether malignant or not, increased by almost 50% from 1980 to 1998, mainly in the adult and elderly population groups.

In the present study we observed that EMN treatment costs are high and directed to a small number of patients. Additionally, we evaluated that the death rates related to EMN were three times higher than those of other neoplasia in the decade under analysis, despite the use of the entire therapeutic arsenal.

Back in the 1990s, Silverstein and colleagues[25] published a work analyzing grade III astrocytoma or GB

patients between 1987 and 1992, which showed that the cost per patient at that time exceeded US$67,000, taking in account the entire therapeutic process. More recently, a study from the first decade of this century showed that each temozolomide (TMZ) cycle for recurrent glioma treatment cost more than €2,000/month per patient at that time. In a critical and elucidative review, Raizer and colleagues[23] compared direct medical costs and other encephalic neoplasia treatment-related factors among ten works in the literature. The authors confirmed that adjuvant therapies, such as the use of irinotecan and bevacizumab, increased the cost of treatment greatly. As an example, treatment with only bevacizumab cost up to US$240,000/year for a 70kg patient. Comparatively, our study showed that EMN patients exhibited almost double the costs for the SUS in comparison with other neoplasia patients—even though we were unable to compare numeric values from 2008 to 2017 because of variations in the exchange rate of the Brazilian real (currency) in relation to the euro and the dollar. The high effective cost for patients, families, or health care systems is, however, clear.

Clearly, a long and winding road that must be traveled until we reach more efficient therapeutic strategies. Bernard-Arnoux and colleagues[28] developed a model for calculating the cost-benefit of adding some therapies to the standard treatment for GBs. As a result, they observed that the increase in life expectancy barely surpassed 4 months with a total cost per patient greater than €180,000 until decease. Our study showed that death rates and mean hospitalization time did not vary during the decade under analysis in Brazil, as also observed in literature.

Nevertheless, the literature shows that new therapies are being used *in vitro, in vivo* and even in clinical trials for EMN with the objective of improving the effectiveness of treatments, enhancing patients' lifespan and reducing the death rate. A recent emerging and low-cost approach is drug repositioning—i.e. revisiting old drugs in order to find new therapeutic targets and reformulating their clinical indications, including cancer treatment. This strategy is appropriate for EMN and GB, being one of the most promising approaches nowadays due to its low cost and the wide variety of targets when a combination of drugs are used.[15,27] As an example, we can cite the use of sulfasalazine, a well-known anti-inflammatory drug used since the 1940s to treat chronic bowel inflammatory diseases and arthritis, and its discovered action in blocking the xC- transport system, the essential mechanism in GB for generating glutathione and recovering from oxidative stress.[11,29,30] Higher cost options can be considered as well for improving the overall survival rate of EMN patients, such as the use of adjuvant monoclonal antibodies—especially bevacizumab, a vascular endothelial growth factor-receptor (VEGF-R) targeted antibody.[31,32] Specifically, many clinical trials concerning GB treatments highlight that, following the pioneering work of Stupp and colleagues,[33] the use of a treatment combining alkylating agent temozolomide and radiotherapy increases the overall survival rate of patients—which can be increased even further if GB cells exhibit tumoral O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.[26,33-36]

Since EMNs are a genetically broad and heterogeneous group of tumors, it is clear to us that investment in basic and clinical studies that can unravel their biology, progression and pathogenesis is essential. With regard to genetic specificities, another practical approach is appropriate for EMNs. Precision medicine in cancer mainly looks for the variability of individual patient genetics for prevention, care and therapy, instead of a one-drug/one-dose/one-treatment-fits-all model, thereby helping to reach a better outcome for each patient.[37] Since 2016 we have identified genetically different GB subtypes (such as IDH gene mutant or wild-type), indicating that molecular subclassification is a useful tool for improving cancer treatments. In fact, precision medicine has already been pointed out as an excellent approach to achieve better results for EMN patients.[38-40]

Moreover, we can observe that EMN treatment in Brazil and worldwide is a high cost and low efficiency process with regard to decreasing the death rate of patients. However, new therapeutic approaches are now on the horizon and must be considered as adjuvant therapies for standard protocols. This study concluded that, from 2008 to 2017, SUS expenses with EMN patients surpassed mean expenditures per patient overall and on neoplasia in general, despite the small number of EMN patients. Even using state-of-the-art therapies, neither mean hospitalization time nor the death rate of EMN patients fell during the 10 years under analysis. Thus, these treatments still involve high costs that are not converted into significant increases in life expectancy, in concordance with other worldwide studies. Especially in the case of GB patients, palliative

care alternatives unfortunately still remain the only plausible solution despite all therapeutic protocols. Still, patients and families can have the option of advanced care planning (ACP) for decision-making, especially in the end-of-life phase.[41]

Acknowledgements

We thank FUNADESP for research funding through the Programa de Iniciação Científica-PIC/Anhanguera 2018/2019 (project number: 20180001).

References

1. McKinney PA. Brain tumours: incidence, survival, and aetiology. J Neurol Neurosurg & Psychiatry [Internet]. 2004 Jun 1;75(suppl 2):ii12 LP-ii17. Available from: https://doi.org/10.1136/jnnp.2004.040741
2. Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA [Internet]. 2013;310:1842–50. Available from: https://doi.org/10.1001/jama.2013.280319
3. Ostrom QT, Patil N, Cioffi G, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013–2017. Neuro Oncol [Internet]. 2020 Oct 30 [cited 2021 April 14]; 22(1):iv1–iv96. Available from: https://doi.org/10.1093/neuonc/noaa200
4. Undabeitia J, Torres-Bayona S, Samprón N, et al. Indirect costs associated with glioblastoma: Experience at one hospital. Neurol (English Ed.) [Internet]. 2018 July 20 [cited 2021 April 14];33(2):85–91. Available from: https://doi.org/10.1016/j.nrl.2016.05.003
5. Chen DY, Chen CC, Crawford Jr WSG. Tumor-related epilepsy: epidemiology, pathogenesis and management. J Neurooncol [Internet]. 2018 May 24 [cited 2021 April 14];139(1)13-21. Available from: https://doi.org/10.1007/s11060-018-2862-0
6. Schreck KC, Grossman S. Role of Temozolomide in the Treatment of Cancers Involving the Central Nervous System. Oncol (willist Park) [Internet]. 2018 November 15 [cited 2021 April 15];32(11):555–60. Available from: Available from: https://doi.org/10.1007/s11060-018-2862-0
7. Kaibara T, Tyson RL, Sutherland G. Human cerebral neoplasms studied using MR spectroscopy: a review. Biochem Cell Biol [Internet]. 1998 May 30 [cited 2021 April 13];76(2–3):477–86. Available from: https://doi.org//10.1139/o98-048
8. Davis ME. Epidemiology and Overview of Gliomas. Semin Oncol Nurs [Internet]. 2018 Dec 1 [cited 2021 April 17];34(5):420–9. Available from: https://doi.org/10.1016/j.soncn.2018.10.001
9. Werneck de Carvalho LE, Sarraf JS, Semblano AAP, et al. Central nervous system tumours profile at a referral center in the Brazilian Amazon region, 1997–2014. PLoS One [Internet]. 2017 Apr 3 [cited 2021 Apr 6];12(4):e0174439. Available from: https://doi.org/10.1371/journal.pone.0174439
10. Stoyanov GS, Sarraf JS, Matev BK, et al. A Comparative Review of Demographics, Incidence, and Epidemiology of Histologically Confirmed Intracranial Tumors in Brazil and Bulgaria. Cureus [Internet]. 2018 Feb 19 [cited 2021 April 21];10(2):e2203–e2203. Available from: https://doi.org/10.7759/cureus.2203
11. Garcia CG, Kahn SA, Geraldo LHM, et al. Combination Therapy with Sulfasalazine and Valproic Acid Promotes Human Glioblastoma Cell Death Through Imbalance of the Intracellular Oxidative Response. Mol Neurobiol [Internet]. 2018 Jan 19 [cited 2021 April 24]; 55: 6816-6833. Available from: https://doi.org/10.1007/s12035-018-0895-1
12. Lukas RV, Wainwright DA, Ladomersky E, et al. Newly Diagnosed Glioblastoma: A Review on Clinical Management. Oncology (Williston Park) [Internet]. 2019 Mar 13 [cited 2021 April 23];33(3):91–100. Available from: https://doi.org/10.1080/10463356.2018.1462031
13. Balça-Silva J, Matias D, Carmo A, et al. Cellular and molecular mechanisms of glioblastoma malignancy: Implications in resistance and therapeutic strategies. Semin Cancer Biol [Internet]. 2019 Sep 25 [cited 2021 April 29];58:130–41. Available from: https://doi.org/10.1016/j.semcancer.2018.09.007
14. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol [Internet]. 2020 Aug 17 [cited 2022 March 20]; 22(8): 1073-1113. Available from: https://doi.org/10.1093/neuonc/noaa106
15. Zanders ED, Svensson F, Bailey DS. Therapy for glioblastoma: is it working? Drug Discov Today [Internet]. 2019 Marcj 13 [cited 2021 May 4];24(5):1193–201. Available from: https://doi.org/10.1016/j.drudis.2019.03.008
15. Cagney DN, Alexander BM. The cost and value of glioblastoma therapy. Expert Rev Anticancer Ther [Internet]. 2017 Aug 3 [cited 2021 May 7];17(8):657–9. Available from: https://doi.org/10.1080/14737140.2017.1351355
16. Zuccarini M, Giuliani P, Ziberi S, et al. The Role of Wnt Signal in Glioblastoma Development and Progression: A Possible New Pharmacological Target for the Therapy of This Tumor. Genes (Basel) [Internet]. 2018 Feb 17 [cited 2022 March 20]; 9(2):105. Available from: https://doi.org/10.3390/genes9020105
17. Becker J, Wilting J. WNT signalling in neuroblastoma. Cancers (Basel) [Internet]. 2019 Jul 19 [cited 2022 March 20]; 11(7): 1013. Available from: https://doi.org/10.3390/cancers11071013
18. Zafar A, Wang W, Liu G, et al. Molecular targeting therapies for neuroblastoma: Progress and challenges. Med Res Rev [Internet]. 2021 March [cited 2022 March 20]; 41(2):961-1021. Available from: https://doi.org/10.1002/med.21750
19. Ney GM, McKay L, Koschmann C, et al. The emerging role of Ras pathway signaling in pediatric cancer. Cancer Res [Internet]. 2020 Dec 1 [cited 2020 March 20]; 80(23):5155-5163. Available from: https://doi.org/10.1158/0008-5472.CAN-20-0916
20. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst [Internet]. 2011 December 1 [cited 2021 May 9]19;103(2):117–28. Available from: https://doi.org/ 10.1093/jnci/djq495
21. Monteiro GTR, Koifman S. Mortalidade por tumores de cérebro no Brasil, 1980-1998 . Cadernos de Saúde Pública [Internet]. 2003 Sept 5 [cited 2021 May 4]; 19(4): 1139–51. Available from: https://doi.org/10.1590/S0102-311X2003000400035
22. Blomqvist P, Lycke J, Strang P, et al. Brain tumours in Sweden 1996: care and costs. J Neurol Neurosurg Psychiatry [Internet]. 2000 Jun 20 [cited 2021 May 13];69(6):792–8. Available from: https://doi.org/10.1136/jnnp.69.6.792

23. Raizer JJ, Fitzner KA, Jacobs DI, et al. Economics of Malignant Gliomas: A Critical Review. J Oncol Pract [Internet]. 2014 Dec 2 [cited 2021 May 21];11(1):59–65. Available from: https://doi.org/10.1200/JOP.2012.000560
24. Tykocki T, Eltayeb M. Ten-year survival in glioblastoma. A systematic review. J Clin Neurosci [Internet]. 2018 Aug 1 [cited 2021 May 12];54:7–13. Available from: https://doi.org/10.1016/j.jocn.2018.05.002
25. Silverstein MD, Cascino TL, Harmsen WS. High-Grade Astrocytomas: Resource Use, Clinical Outcomes, and Cost of Care. Mayo Clin Proc [Internet]. 1996 Oct 1 [cited 2021 May 11];71(10):936–44. Available from: https://doi.org/10.4065/71.10.936
26. Wasserfallen J-B, Ostermann S, Leyvraz S, et al. Cost of temozolomide therapy and global care for recurrent malignant gliomas followed until death. Neuro Oncol [Internet]. 2005 Apr 1 [cited 2021 May 11];7(2):189–95. Available from: https://doi.org/10.1215/S1152851704000687
27. Abbruzzese C, Matteoni S, Signore M, et al. Drug repurposing for the treatment of glioblastoma multiforme. J Exp Clin Cancer Res [Internet]. 2017 Nov 28 [cited 2021 May 13];36(1):169. Available from: https://doi.org/10.1186/s13046-017-0642-x
28. Bernard-Arnoux F , Lamure M, Ducray F, et al. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. Neuro-Oncology [Internet]. 2016 Aug 1 [cited 2021 May 12];18(8):1129–36. Available from: https://doi.org/10.1093/neuonc/now102
29. Chung WJ, Lyons SA, Nelson GM, et al. Inhibition of cystine uptake disrupts the growth of primary brain tumors. J Neurosci [Internet]. 2005 Aug 3 [cited 2022 March 20]; 25(31):7101-10. Available from: https://doi.org/10.1523/jneurosci.5258-04.2005
30. Lewerenz J, Hewett SJ, Huang Y, et al. The cystine/glutamate antiporter system xC- in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal [Internet]. 2013 Feb 10 [cited 2022 March 20]; 18(5):522-55. Available from: https://doi.org/10.1089/ars.2011.4391
31. Garcia J, Hurwitz HI, Sandler AB, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev [Internet]. 2020 June 01 [cited 2022 March 20]; 86: 1-18. Available from: https://doi.org/10.1016/j.ctrv.2020.102017
32. Sousa F, Moura RP, Moreira E, et al. Therapeutic monoclonal antibodies delivery for the glioblastoma treatment. Adv Protein Cher Struct Biol [Internet]. 2018 March 30 [cited 2022 March 20]; 112:61-80. Available from: https://doi.org/10.1016/bs.apcsb.2018.03.001
33. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. JAMA [Internet]. 2005 March 10 [cited 2022 March 20]; 352:987-96. Available from: https://doi.org/10.1056/NEJMoa043330
34. Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Onc [Internet]. 2012 May 10 [cited 2022 March 20]; 13:707-15. Available from: https://doi.org/10.1016/S1470-2045(12)70164-X
35. Braun K, Ahluwalia MS. Treatment of glioblastoma in older adults. Curr Oncol Rep [Internet]. 2017 Oct 26 [cited 2022 March 20]; 19:81. Available from: https://doi.org/10.1007/s11912-017-0644-z
36. Di Nunno V, Franceschi E, Tosoni A, et al. Treatment of recurrent glioblastoma: state-of-the-art and future perspectives. Exp Rev Antican Ther [Internet]. 2020 Sep 03 [cited 2020 March 20]; 20(9): 785-95. Available from: https://doi.org/10.1080/14737140.2020.1807949
37. Collins H, Calvo S, Greenberg K, et al. Information needs in the precision medicine era: how genetics home reference can help. Interact J Med Res [Internet]. 2016 Apr 27 [cited 2022 March 20]; 5(2):e13. Available from: https://doi.org/10.2196/ijmr.5199
38. Zhou Y, Wu W, Bi H, et al. Glioblastoma precision therapy: from the bench to the clinic. Cancer Lett [Internet]. 2020 Apr 10 [cited 2022 March 20]; 475: 79-91. Available from: https://doi.org/10.1016/j.canlet.2020.01.027
39. White K, Connor K, Clerkin J, et al. New hints towards a precision medicine strategy for IDH wild-type glioblastoma. Ann Oncol [Internet]. 2020 December [cited 2022 March 20]; 31(12):1679-92. Available from: https://doi.org./ 10.1016/j.annonc.2020.08.2336
40 Liu D, Yang T, Ma W, et al. Clinical strategies to manage adult glioblastoma patients without MGMT hypermethylation. J Cancer [Internet]. 2022 Jan 1 [cited 2022 March 20]; 13(1):354-363. Available from: https//doi.org/10.7150/jca.63595
41 Fritz L, Dirven L, Reijneveld JC, et al. Advance care planning in glioblastoma patients. Cancers (Basel) [Internet]. 2016 Nov 8 [cited 2022 March 20]; 8(11):102. Available from: https://doi.org/10.3390/cancers8110102