RISK FACTORS FOR VENOUS THROMBOEMBOLIC IN GLIOMA PATIENTS

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ABSTRACT

Background. Venous thromboembolic events are a frequent complication in patients with malignant tumors of the central nervous system and occupy the third place in the structure of causes of the death. **Objective.** To evaluate risk factors for VTE in patients with malignant glioma. **Design and methods.** The retrospective study included 337 patients with malignant glioma. The diagnosis of glial brain tumor was verified according to the morphological study of an intraoperative sample using the WHO classification. The analysis of risk factors for VTE was performed in two groups, depending on the presence of confirmed venous thrombosis. **Results.** The incidence of venous thromboembolic complications among patients with brain neoplasms was 6.2%. In patients with venous thrombosis in the postoperative period, recurrent glioblastoma and the tumor size exceeded 5 cm was more common: 33% (n = 7) versus 13% (n = 41); 85% (n = 18) versus 47% (n = 148) (p = 0.05 and p = 0.013, respectively). In patients with venous thromboembolic complications on admission, the platelet level was significantly lower than in patients from the other group: 189 ± 72 versus 240.8 ± 93.3 (p = 0.04). **Conclusion.** Thrombocytopenia, recurrent glioblastoma, tumor size more than 5 cm are the risk factors for venous thromboembolic.

Key words: cardio-oncology, deep vein thrombosis of the legs, glioblastoma, pulmonary embolism, thromboembolic complications.

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List of abbreviations: VTEC — venous thromboembolic complications, ICD — international classification of diseases, MRI — magnetic resonance imaging, PE — pulmonary embolism, CNS — central nervous system.

INTRODUCTION

The 2016 World Health Organization classification of tumors of the central nervous system (CNS) is based on histological and molecular criteria and includes malignant, benign and borderline tumors. Among malignant formations of the central nervous system, secondary tumors are leading, representing metastases of the main oncological process. It has been shown that a quarter of cancer patients develop intracranial metastases, while taking into account the increase in the attained age and the improvement of imaging diagnostic methods, the number of such patients increases every year [1]. Tumors of glial origin are the second most common among primary tumors of the central nervous system, while the most malignant variant of gliomas is glioblastoma, which occurs in 45.6 %of cases of all primary malignant brain tumors and with an extremely unfavorable prognosis. Thus, the median overall survival in the group of patients aged 18 to 40 years is 19.7 months, and among patients older than 70 years — only 4.5 months [2]. Venous thromboembolic events are a complication that frequently occur in patients with malignant CNS tumors and occupy the third place in the structure of causes of death after tumor progression and infectious complications. With metastatic brain lesion, venous thromboembolic complications (VTEC) occur in 20% of cases; in patients with glioblastoma, their incidence reaches 30% [3, 4]. One of the reasons for this high frequency of VTEC is the special pathogenetic mechanism of venous thrombosis, in which the tissue factor plays a key role. It has been shown that tumor cells release microparticles containing tissue factor into the bloodstream. High levels of these procoagulant microparticles are associated with increased risk of VTEC and reduced overall survival of patients [5, 6]. A number of authors demonstrated a high expression of tissue factor in gliomas, while the expression level correlated with the degree of tumor malignancy [7, 8]. Currently, much attention is also paid to the study of the mechanisms of platelet activation, which results in thrombocytopenia, which is characteristic of patients with malignant tumors of the CNS [9]. Prevention of VTEC in patients with brain formations is difficult given the lack of validated risk scales and high hemorrhagic risks. Current approaches to stratifying the risk of VTEC in patients with brain formations suggest individualizing factors associated with tumor and treatment, in addition to traditional risk factors associated with the patient (age, immobilization, history of VTEC, obesity), [10, 11]. The factors associated with the tumor include the degree of malignancy and the large size of the formation, thrombosis of the vessels sprouting the tumor according to imaging techniques, the absence of mutation in the IDH1 gene. Factors associated with treatment include tumor biopsy, subtotal tumor resection, the use of corticosteroids and chemotherapy. Among the laboratory data, it is proposed to pay attention to the level of D-dimer, platelets and leukocytes, since a number of studies have shown that the level of D-dimer is more than 1.66 mg/ml, leukocytosis is more than $11.5 \times 10^{9/l}$ and platelets less than $196 \times 10^{9/l}$ are associated with a high risk of VTEC [12, 13].

The purpose of this study was to retrospectively assess risk factors for VTEC and the incidence of venous thrombosis in the postoperative period in patients with malignant neoplasms of the brain treated at the Almazov National Medical Research Centre of the Ministry of Health of Russia in 2020, using the data of the medical information system.

MATERIALS AND METHODS

The retrospective study included 337 patients admitted to the neurosurgical departments of the Almazov National Medical Research Centre with a preliminary diagnosis of C71 — a malignant neoplasm of the brain according to the International Classification of Diseases, revision 10 (ICD-10). In routine practice, this diagnosis usually encodes malignant tumors of glial origin, a large proportion of which is glioblastoma. The data analysis was performed using the qMS medical information system. The diagnosis of glioblastoma was previously made according to magnetic resonance imaging, the type was clarified during a morphological examination of the intraoperative sample using WHO classifications. This classification is based on the detection of one of the following signs in the microscopic picture of a morphological preparation: nuclear atypism, mitosis, proliferation of vascular endothelium, necrosis. These signs are taken into account as follows: Grade I — none of these signs; Grade II — the presence of one of these signs (as a rule, nucleus atypia, but single mitoses are possible); Grade III — there are many mitotic figures in the tumor; Grade IV — pronounced proliferation of vascular endothelium, the presence of necrosis [14, 15].

The results were processed using the IBM SPSS Statistics 26 statistical program. All are presented as median and quartiles Q25-Q75. The analysis of the normality of the sample distribution was carried out using the Kolmogorov–Smirnov criterion. Comparison of quan-

titative parameters in the studied groups was carried out using the Student's criterion and the Mann-Whitney criterion. The Levene criterion of equality of variances was also used to assess the validity of the Student's criterion. The criterion of statistical reliability of the results obtained was considered to be the value of $p < 0,05$, generally accepted in medicine.

RESULTS

The study included 337 patients. The average age was 52 ± 14.5 years, 44.7% of patients were male, while 55.3% were female. Of the significant comorbidities, hypertension occurred in 23.1% of patients, coronary heart disease in 11.6% of patients, and type 2 diabetes mellitus also attracts attention, which was recorded in 10.6% of patients.

This study included patients with a preliminary diagnosis of malignant neoplasm of the central nervous system who were scheduled for surgical treatment. According to the morphological study, in 2.4% of patients (n = 8) from the studied population, secondary (more often metastatic) lesion of the central nervous system was verified. The data of a morphological study to determine the degree of malignancy are presented in Figure 1.

Several classic risk factors can be associated with the risk of venous thromboembolic events, such as previously performed chemotherapy (33.3%), radiation therapy (37.1%) and obesity, which was registered in 11.6% of patients. The Karnovsky index in the examined group was 74.5% [70; 80], indirectly reflecting the degree of immobilization of the patient, which is the most important risk factor for VTEC.

According to a retrospective study using a medical information system, it was not possible to objectively assess the frequency of paresis, which is due to the peculiarity of maintaining electronic medical records. In addition, it should be noted that the absence of such an important risk factor as previous venous thrombosis in the history of most patients is probably due to the lack of a special section in MIS and cannot fully reflect the true frequency of occurrence in the examined group.

Among the factors associated with treatment, corticosteroid therapy was used in 100% of cases, while tumor biopsy was performed in 3.4% of cases. The fact of complete or subtotal resection was not always reflected in the operation protocols and was difficult for retrospective evaluation.

Among the factors associated with the tumor, it is worth noting that the tumor size of more than 5 cm in one of the diameters was observed in 48.4% of patients, recurrent glioblastoma occurred in 13.6% of cases.

Postoperative venous thromboembolic events were diagnosed in 21 patients (6.2%). At the same time, in the case of deep vein thrombosis, which accounted for 61.9% of VTEC cases, the complication was verified by ultrasound examination of the veins of the lower extremities in symptomatic patients. Pulmonary embolism (PE) was a complication of deep vein thrombosis in 14.3% of cases. The frequency of registration of PE in the entire group of patients with VTEO was 23.8%.

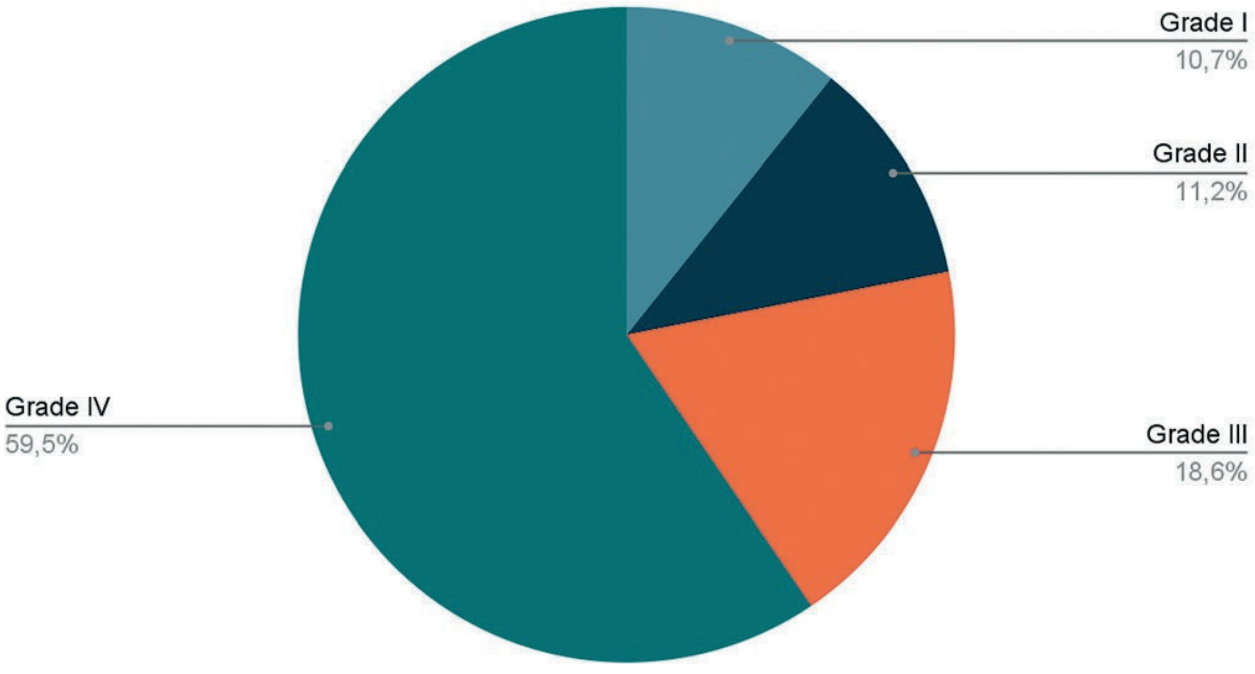

Fig. 1. Tumor distribution by degree of malignancy

Depending on the presence of venous thromboembolic events, patients were divided into two groups in order to analyze the presence of risk factors for VTEC, proposed in different scales. Patients with postoperative venous thrombosis were more likely to have recurrent glioblastoma and the tumor size exceeded 5 cm: 33% (n = 7) versus 13% (n = 41); 85% (n = 18) versus 47% (n = 148) (p = 0.05 and p = 0.013, respectively) (Table 1).

In patients with venous thromboembolic complications at admission, the platelet level was significantly lower than in patients from the other group: 189 ± 72 vs. 240.8 ± 93.3 (p = 0.04) (Table 2).

DISCUSSION

Glioblastoma is the most common variant among primary malignant neoplasms of the brain and is associated with an extremely high risk of both VTEC and hemorrhagic risks associated with anticoagulant therapy. The main directions of scientific and practical research in recent years in this area are to clarify the features of the pathogenesis of thrombosis in patients with CNS tumors and the development of specific VTEC risk stratification scales with the aim of a personalized approach to the choice of treatment tactics. This retrospective study was dedicated to the evaluation of routine management of patient data in a single center in order to plan further prospective research and optimize existing approaches to the prevention of VTEC.

Patients were included in the study in accordance with the code of the main diagnosis — C71, set by the neurosurgeon upon admission on the basis of the clinical picture and MRI data of the brain. Patients with histologically verified glioblastoma accounted for the majority of these patients — 59.5% (n = 201). At the same time, the frequency of VTEO was 6.2%, which is significantly lower than the data given in the literature. According to various authors, the incidence of thrombosis in the postoperative period varies from 3% to 20% and depends primarily on primary prevention and on the method of detection of VTEC [16, 17]. The low incidence of venous thrombosis in our study can be explained primarily by the limited observation period during the patient's hospitalization, while the maximum risk is noted in first 6 weeks after surgery, and during the first year of observation it is 7-28% [18, 19]. In addition, it should be noted that routine clinical practice does not regulate the targeted search for venous thromboembolic complications, while most of the deep vein thrombosis are asymptomatic [20].

Among the classic risk factors for venous thrombosis in the group of neurosurgical patients, noticeable is the

Table 1. Risk factors for venous thromboembolic events in patients depending on the presence of VTEC

Risk factors	Group 1 (n = 21),%	Group 2 (n =316),%	p
History of chemotherapy	40	28	0.341
History of radiotherapy	40	32	0.536
Glioblastoma recurrence	33	13	0.05
The tumor size is more than 5 cm	85	47	0.013
Tumor biopsy	7	3	0.537

Table 2 Characteristics of laboratory data in patients

Laboratory data	Group 1	Group 2	Group 3
Hemoglobin level	141,7 ± 16,3	140,6 ± 18,5	0.831
White blood cell level	9,7 ± 3,9	10,7 ± 4,4	0.492
Platelet level	189 ± 72	240,8 ± 93,3	0.04
Fibrinogen	2,5 ± 0,6	2,72 ± 0,6	0.492
Prothrombin time (Quick)	102,4 ± 11,5	97,4 ± 14	0.123

importance of the fact of immobilization of the patient, which is reflected in the degree of paresis of the lower extremities and the Karnovsky index, which in our study was 74.5%. It is noteworthy that moderate risk factors for VTEC, such as chemotherapy and radiation therapy, in the case of patients with glioblastoma, primarily indicate the progression of the tumor process, associated with a high prothrombotic risk. This statement is fully supported by the data of our study, according to which patients with relapse of glioblastoma were more common in the group with the presence of VTEC compared with the group without thrombotic complications.

In the analysis of risk factors directly associated with the tumor, in addition to the fact of progression, the size of the neoplasm was an extremely important indicator: in the group with VTEC glioblastomas exceeding 5 cm were more common, which fully complies with the data of other authors and ESMO recommendations for neurooncology [21]. Tumor typing by IDH1 mutation status and methylation of the MGMT (methyl-guanine-methyl-transferase) gene is important, as it has an important prognostic property in relation to the overall survival of patients and the risk of VTEC [22, 23].

Among laboratory markers associated with the risk of venous thrombosis in patients with glioblastoma, it is common to isolate thrombocytopenia, an increased level of soluble P-selectin as a reflection of activation platelets, leukocytosis and high D-dimer values [24]. According to our data, patients in the VTEC group had significantly lower platelet levels, which is consistent with the data of other authors. It has been shown that platelet activation plays a key role in the pathogenesis of venous thrombosis in patients with gliomas. At the same time, the role of podoplanin, neutrophils and extracellular vesicles in platelet activation is being actively studied [25, 26].

It is important to note that currently, when detecting VTEC in patients with brain tumors in the perioperative period, the question of the timing of the possible appointment of anticoagulants and the duration of this therapy still remains unsolved. This issue becomes especially relevant in the framework of preoperative preparation and in the early postoperative period. On the one hand, any neurosurgical intervention is accompanied by an extremely high risk of intracranial bleeding; on the other hand, a venous thromboembolic event itself can lead to fatal outcome. Speaking about the risk of bleeding, it is worth noting that in our population, in 54.5% of patients, background pathology was represented by hypertension and in 18.2% of patients — by gastrointestinal diseases associated with type 2 diabetes mellitus, which additionally increased the risk of bleeding and, of course, should be taken into account when prescribing anticoagulant therapy.

Different scales have been developed to assess hemorrhagic risk in patients with atrial fibrillation, which are mainly aimed at predicting bleeding from the gastrointestinal tract. Hankey et al. published a scale aimed at assessing the risk of intracranial hemorrhage in patients with atrial fibrillation [27]. The PANWARDS scale uses risk factors such as thrombocytopenia, hypoalbuminemia, history of congestive heart failure, warfarin use, advanced age, race, hypertension, stroke or a history of transient ischemic attack. Mantia C. et al. studied this scale on a population of patients with glioma and concluded that the use of this scale to identify the subgroup of patients with intracranial bleeding with anticoagulants is highly doubtful [28].

When prescribing anticoagulants in neurosurgical patients, the question of choosing a specific drug is particularly acute. There are publications comparing direct oral anticoagulants with low molecular weight heparins [29, 30]. These publications showed a greater risk of both bleeding and recurrent VTEC in patients with brain tumors, however subanalysis of this group was not presented and probably it wouldn't be reliable due to a small sample of patients with this type of oncology. There are publications highlighting the use of anticoagulant therapy in patients with brain tumors, according to which the risk of developing intracranial hemorrhages increased by 3 times with use of anticoagulants for the treatment of VTEC [31, 32]. However, the risk of fatal intracranial hemorrhages was less than 1%. It appears to be interesting that no increase was found in the incidence of intracerebral bleeding in patients with metastatic brain lesion when using anticoagulant therapy compared to the control group in which this therapy was not used.

According to modern concepts and recommendations, the prophylactic administration of anticoagulants is recommended for hospitalized patients with the purpose of surgical treatment of cancer in the perioperative period [33]. A separate issue is the prolongation of the intake of preventive doses of anticoagulants, taking into account the continued risk of remote VTECs. However, existing studies in patients with glioblastoma have not shown a reliable difference in the overall survival of patients with anticoagulant therapy and in the comparison group [34]. Thus, in order to clarify the indications, timing and duration of anticoagulant therapy both for the treatment of patients with VTEC and for the prevention of these conditions, further studies are needed to form a high-risk group for the development of VTEC. Randomized clinical trials to assess the risk-benefit ratio of the use of anticoagulants look promising, and so do fundamental studies clarifying thrombogenesis mechanisms in a group of patients with malignant brain neoplasms.

CONCLUSION

According to the results of our retrospective study, the incidence of venous thromboembolic complications among patients with brain neoplasms was 6.2%, however, it seems to us that the true prevalence of these events is higher. Among the tumor-associated VTEC factors, the tumor size exceeding 5 cm, the recurrent course of glioblastoma and thrombocytopenia are worth noting. Further studies aimed at clarifying the mechanisms of venous thrombosis and creating risk scales specific to this group of patients will help optimize treatment strategies.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Mantia C, Zwicker JI. Anticoagulation in the setting of primary and metastatic brain tumors. Cancer Treat Res. 2019;179:179–189.
2. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016 — PubMed [Internet]. https://pubmed.ncbi.nlm.nih.gov/31675094/ (29 Oct 2021).
3. Gerber DE, Grossman SA, Streiff MB; Management of venous thromboembolism in patients with primary and metastatic brain tumors. J Clin Oncol. 2006;24(8):1310–1318.
4. Weinstock MJ, Uhlmann EJ, Zwicker JI Intracranial hemorrhage in cancer patients treated with anticoagulation. Thromb Res. 2016;140(Suppl 1):S60–S65. DOI: 10.1016/S0049-3848(16)30100-1.
5. Bharthuar A, Khorana AA, Hutson A, et al. Circulating microparticle tissue factor, thromboembolism and survival in pancreaticobiliary cancers. Thromb Res. 2013 Aug;132(2):180-4. DOI: 10.1016/j.thromres.2013.06.026.
6. Sartori MT, Della Puppa A, Ballin A, et al. Circulating microparticles of glial origin and tissue factor bearing in high-grade glioma: a potential prothrombotic role. Thromb Haemost. 2013;110(2):378–385.
7. Hamada K, Kuratsu J, Saitoh Y, et al. Expression of tissue factor correlates with grade of malignancy in human glioma. Cancer. 1996;77(9):1877–1883.
8. Hamada K, Kuratsu J, Saitoh Y, et al. Expression of tissue factor in glioma. Noshuyo Byori. 1996;13(2):115–118.
9. Matthias Preusser, Michael Weller. Essentials for Clinicians: Neuro-Oncology. ESMO Press, European Society for Medical Oncology, 2017. P. 100.
10. Riedl J, Preusser M, Nazari PM, et al. Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. Blood. 2017;129(13):1831–1839.
11. Lavallée V-P, Chagraoui J, MacRae T, et al. Transcriptomic landscape of acute promyelocytic leukemia reveals aberrant surface expression of the platelet aggregation agonist Podoplanin. Leukemia. 2018;32(06):1349–1357.
12. Riedl J, Preusser M, Nazari PM, et al. Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. Blood. 2017;129(13):1831–1839.
13. Lavallée V-P, Chagraoui J, MacRae T, et al. Transcriptomic landscape of acute promyelocytic leukemia reveals aberrant surface expression of the platelet aggregation agonist Podoplanin. Leukemia 2018;32(06):1349–1357.
14. Kobiakov GL, Absaliamova OV, Poddubskiy AA, et al. The 2016 WHO classification of primary central nervous system tumors: a clinician's view. Zhurnal Voprosy Neirokhirurgii Imeni N.N. Burdenko. 2018;82(3):88-96. In Russian [Кобяков Г. Л., Абсалямова О. В., Поддубский А. А. и др. Классификация ВОЗ первичных опухолей центральной нервной системы 2016 г.: взгляд клинициста. Журнал «Вопросы нейрохирургии» имени Н.Н. Бурденко. 2018;82(3):88-96].
15. Louis DN, Ohgaki H, Wiestler OD, et al. WHO classification of tumours of the central nervous system, revised. 4th Ed. IARC (Lyon). 2016;408.
16. Perry J. Thromboembolic disease in patients with high-grade glioma. Neuro Oncol. 2012;14:iv73–80. DOI: 10.1093/neuonc/nos197.
17. Horsted F, West J, Grainge MJ. Risk of venous thromboembolismin patients with cancer: a systematic review and meta-analysis. PLoS Med. 2012;9(07):e1001275.
18. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. Cancer. 2000;89(03):640–646.
19. Walker AJ, West J, Card T, et al. Rate of venous thromboembolism by cancer type compared to the general population using multiple linked databases. Thrombosis Res. 2012;129(Suppl 1):S155–S156.
20. Russian clinical guidelines for the diagnosis, treatment and prevention of venous thromboembolic complications. 2015; 51. In Russian [Российские клинические рекомендации по диагностике, лечению и профилактике венозных тромбоэмболических осложнений. 2015;51].
21. Stupp R, Brada M, van den Bent MJ, et al. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25:iii93-iii101. DOI: 10.1093/annonc/mdu050.
22. Combs SE, Rieken S, Wick W, et al. Prognostic significance of IDH-1 and MGMt in patients with glioblastoma: one step forward, and one step back?

Radiat Oncol. 2011;6:115. DOI: 10.1186/1748-717X-6-115.

23. Hodges TR, Choi BD, Bigner DD, et al. Isocitrate dehydrogenase 1: what it means to the neurosurgeon: a review. J Neurosurg. 2013;118(6):1176-80. DOI: 10.3171/2013.3.JNS122282.

24. Riedl J, Ay C. Venous thromboembolism in brain tumors: Risk factors, molecular mechanisms, and clinical challenges. Semin Thromb Hemost. 2019;45:334–341. DOI: 10.1055/s-0039-1688493.

25. Demers M, Krause DS, Schatzberg D, et al. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. Proc Natl Acad Sci U S A. 2012;109(32):13076–13081.

26. Leal AC, Mizurini DM, Gomes T, et al. Tumor-derived exosomes induce the formation of neutrophil extracellular traps: implications for the establishment of cancer-associated thrombosis. Sci Rep. 2017;7(1):6438. DOI: 10.1038/s41598-017-06893-7.

27. Hankey GJ, Stevens SR, Piccini JP, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban. The rivaroxaban once daily, oral, direct factor Xa inhibition compared with Vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. Stroke. 2014;45(5):1304–1312.

28. Mantia C, Uhlmann EJ, Puligandla M, et al. Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin. Blood. 2017;129(25):3379–3385.

29. Raskob GE, van Es N, Verhamme P, et al. Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018;378(07):615–624.

30. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol. 2018;36(20):2017–2023.

31. Al Megren M, De Wit C, Al Qahtani M, et al. Management of venous thromboembolism in patients with glioma. Thromb Res. 2017;156:105–108.

32. Zwicker JI, Karp Leaf R, Carrier M. A meta-analysis of intracranial hemorrhage in patients with brain tumors receiving therapeutic anticoagulation. J Thromb Haemost. 2016;14(09):1736–1740.

33. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014. J Clin Oncol 2015;33(06):654–656.

34. Le Rhun E, Genbrugge E, Stupp R, et al. Associations of anticoagulant use with outcome in newly diagnosed glioblastoma. Eur J Cancer. 2018;101(101):95–104.

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