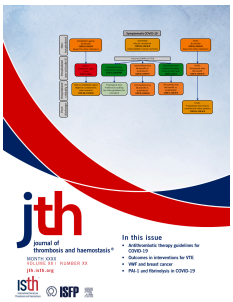

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Mechanisms and treatment of venous thromboembolism in patients with brain cancer: A narrative review

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Abstract

Malignant brain tumors, including both primary brain cancer (PBC) and metastatic brain cancer (MBC), are associated with a markedly increased risk of venous thromboembolism (VTE). Anticoagulation is challenging in this population, as these patients are not only at risk of thrombotic complications, but also at high risk of bleeding. In this review, we examine current knowledge on the incidence, risk factors, pathophysiology, and management of brain cancer-associated VTE. In primary brain cancer, particularly in glioblastoma, expression of the pro-coagulant proteins podoplanin and tissue factor by tumor cells was found to be an important pathophysiological driver of hypercoagulability. Expression of these prothrombotic factors was found to be dependent on the genetic profile of the brain tumor. Clinical data on the treatment of VTE in brain cancer are limited and mostly based on observational studies. The risk of intracranial hemorrhage during anticoagulation remains a key concern. Data from retrospective studies suggest that direct oral anticoagulants (DOACs) may be associated with a lower bleeding risk compared to low-molecular-weight heparins (LMWH). Pharmacological thromboprophylaxis in the ambulatory setting is not routinely recommended, largely due to the lack of trial data in this population. Future studies are needed to improve risk prediction, to clarify the underlying mechanisms of brain cancer-associated VTE, and to define safe and effective treatment strategies.

Keywords: brain neoplasms, glioblastoma, venous thromboembolism, anticoagulants, intracranial hemorrhages

Introduction

Brain cancer, including both primary and metastatic (secondary) malignant brain tumors, comprises a heterogeneous group of neoplasms with distinct clinical behaviors and outcomes. Glioblastoma is the most common and aggressive primary brain cancer (PBC) in adults, marked by rapid progression and poor prognosis, with a median survival time of only 14.6 months [1]. Patients with cancer in general are at a significantly increased risk of venous thromboembolism (VTE), and this risk is particularly elevated in those with brain cancer [2, 3]. VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent and serious complication that contributes to morbidity and mortality in this population [4, 5]. In patients with brain cancer, VTE is associated with poor outcomes and can impact overall survival [6]. However, anticoagulation for VTE in this group poses a clinical challenge due to a heightened risk of intracranial hemorrhage (ICH) [7]. Balancing the benefits of thromboprophylaxis and treatment with the potential bleeding risks remains a critical issue.

In this review, we discuss the risk, risk factors, mechanisms, and management strategies of VTE in patients with brain cancer, distinguishing between primary (PBC) and metastatic (secondary) brain cancer (MBC).

Incidence

Both patients with PBC and MBC carry a high risk of VTE. Depending on the study specifics, the reported incidences of VTE vary. In malignant glioma – the most common type of PBC – some studies report a relatively low incidence below 10% [6, 8] and other studies describe incidences between 10 and 30%, with the highest risk observed during the postoperative period [3, 7, 9]. Compared to gliomas, VTE in other types of PBC is only infrequently investigated. One study reports high postoperative DVT incidences in oligodendroglioma (12.5-20.0%), schwannoma (18.2%), lymphoma (29.6%), hemangiopericytoma (25.0%), and hemangioblastoma (22.2%) but only included few patients due to the rare types of disease [10]. Similarly, few studies on VTE epidemiology in MBC are available. The reported incidences range from 12 to 24% [10-12].

Risk factors

Risk factors for VTE have been investigated mostly in patients with PBC, whereas VTE risk in MBC is often investigated with the background of the underlying primary tumor. In these instances, the occurrence of MBC as a distant metastasis is often considered an additional VTE risk factor of the underlying tumor. Further investigations of potentially unique risk factors for VTE in patients with MBC are rare. Furthermore, patients with MBC only represent a fraction of the general population of patients with cancer [13].

This section focuses on the observational investigations of risk factors and biomarkers. The pathophysiological considerations of relevant risk factors will be discussed in the "Mechanisms" section.

Risk factors in PBC

In patients with PBC, several foundational studies from the past two decades have investigated risk factors for VTE. Factors that have been described in the general population, such as history of VTE, limb paralysis, and age, could also be confirmed in PBC, whereas non-O blood type was not associated with VTE risk [14]. Furthermore, risk factors specific to brain cancers were identified, such as higher-grade tumors, tumor size, podoplanin expression, and intratumoral thrombosis. Subtotal resection/biopsy vs. total resection and bevacizumab are treatment-related factors associated with VTE [14-18]. Lastly, analyses of biomarkers have indicated that lower platelet count, higher D-dimer, and higher soluble P-selectin (sP-selectin) are associated with brain cancer-associated VTE [19]. Especially the observation of **low** platelet counts being a risk factor for VTE in PBC is noticeable, as in other tumor entities a high platelet count was found as a risk factor for VTE [20].

More recent studies (Table 1) have largely confirmed these associations [21-24] but have also found contradictory results: Resection vs. biopsy was identified as a risk factor instead of a protective factor in one study [22], which included only gliomas of grade II and III. This might indicate that in such tumors, thrombosis could be driven by the surgery-associated immobilization to a larger degree than by the tumor biology. However, the study assessed only 16 VTEs in 124 patients and further confirmation of these results is needed. Furthermore, genetic

alterations of gliomas have been linked to the VTE risk. Most importantly tumor mutations in isocitrate dehydrogenase (IDH) 1 and 2 were found to be associated with a very low VTE risk in a number of studies [15, 16, 25-29], although some studies could not confirm this association [22, 23]. IDH mutations in gliomas are associated with less aggressive tumors and better overall survival and according to the latest World Health Organization (WHO) classification of tumors of the central nervous system, IDH mutated gliomas are defined as lower grade, while glioblastomas (WHO grade IV) are IDH wildtype [29]. The mechanistic aspects of IDH mutations regarding hypercoagulability are discussed below. Other recently described risk factors are male sex and long-course radiochemotherapy [2], whereas temozolomide treatment [30] was found to be protective. Worse patients´ performance status (higher Eastern Cooperative Oncology Group [ECOG] score) was associated with VTE in two large studies including patients with glioma (WHO grades 2 – 4, n=3,630) [2] and glioblastoma (n=967) [23], whereas contradictory results were found for pre- and post-operative performance status in one smaller study (n=293) [30]. Regarding novel biomarkers, cyclin-dependent kinase inhibitor 2A (CDKN2A) deletion [31], mitochondria count [32], and certain microRNAs (miRNAs) [33] were associated with VTE, but these findings are yet to be confirmed in larger studies.

Overall, the considerable heterogeneity in patient populations and methodology amongst studies on this topic requires careful interpretation of results (Table 1).

Risk assessment models for VTE in glioma

Risk assessment models (RAM) to quantify the risk of VTE have largely focused on the general population of patients with cancer rather than on specific tumors [34]. However, one glioma-specific RAM was recently developed and validated [28]. In this model, several specific and non-specific factors are used to predict VTE (Table 1), including factors that were previously not described, such as hypertension, asthma, and hypothyroidism. The resulting areas under the curves (AUC) ranged from 0.63 to 0.84 in the development and validation cohorts. This model also stands out for its pathophysiological investigations of tissue factor (TF) and IDH mutation. However, further studies in a competing risk framework and studies assessing the calibration of the model are required to further strengthen its clinical utility. Another recently developed RAM

[35] included the ECOG score, D-dimer, and epidermal growth factor receptor (EGFR) amplification to predict the risk of VTE but was not validated externally.

Risk factors in MBC

In patients with MBC, only one study was identified that reported risk factors for VTE. These included certain primary tumor sites (lung, renal cell, and unknown primary site), treatment with dexamethasone, chemotherapy, body mass index (BMI) >35 kg/m^2, and immobilization [12]. Based on this data, a risk assessment model (RAM) with good discrimination in a validation cohort was developed but no results on calibration of the model are reported. Further research is required to identify additional risk factors contributing to the risk of VTE in patients with MBC.

Mechanisms

Similar to risk factors, prothrombotic mechanisms have been investigated virtually exclusively in PBC and the specific role of MBC in thrombus formation is currently understudied. This section therefore reports results of research on prothrombotic mechanisms in PBC.PBCs, specifically higher-grade gliomas, create a profoundly prothrombotic microenvironment through multiple molecular mechanisms. One central driver of such prothrombotic alterations is tumor cell expression of procoagulant proteins. Current evidence suggests that the two most important proteins are podoplanin and TF. Their expression is influenced by the genetic subtype of the brain tumor. These mechanisms will be discussed in detail in the following and are illustrated schematically in Figure 1.

Podoplanin

Podoplanin is a transmembrane glycoprotein physiologically widely expressed in the lymphatic vasculature and on several other cell types, whereas it is not found in the blood vasculature [36]. Podoplanin is the ligand of the C-type lectin receptor type 2 (CLEC-2), which is highly expressed on platelets, and binding of podoplanin to CLEC-2 induces platelet activation and aggregation [37].

Several cancer types were found to ectopically express podoplanin on their tumor cell surface, including PBCs [38], and this expression seems to contribute to a prothrombotic cancer-

associated state. A study by our group investigated these mechanisms on tumor specimens of 213 patients with different types of primary malignant brain tumors in the Vienna Cancer and Thrombosis Study (Vienna CATS) [39]. First, we established the independent association of local tumor podoplanin expression with the risk of VTE. Specifically, the risk increased with higher podoplanin expression levels; the multivariable HR for VTE for high podoplanin expression vs. no podoplanin expression was 5.7 in a model adjusted for age, sex and tumor grade (WHO grade IV vs. others). The association of podoplanin expression and high VTE risk in patients with PBC has recently also been independently confirmed by other authors [40]. Furthermore, in our study, increasing podoplanin expression was associated with intravascular platelet aggregates in the tumor, with higher systemic D-dimer, and lower systemic platelet counts [39]. These results suggested an active role of podoplanin in thrombogenesis by activating platelets, causing platelet consumption and hypercoagulability. Lastly, we conducted in vitro experiments to confirm the thrombotic properties of podoplanin on a mechanistic level: Podoplanin-expressing glioblastoma cells induced platelet activation and aggregation, which could be inhibited by an antibody targeted against podoplanin. Several mechanistic studies by other authors confirmed this hypothesis: In a murine glioma model, expression of podoplanin on glioma cells was found to be the major driver for intratumoral platelet aggregate formation [41]. In another murine model of ovarian cancer, podoplanin expression by cancer cells and on extracellular vesicles (EVs) caused platelet aggregation and enhanced formation of venous thrombosis in a vena cava ligation model [42]. Moreover, in one study using glioblastoma cell-derived EVs that expressed podoplanin, injection of these EVs into mice led to platelet activation [43].

To the best of our knowledge no data exist on the association between podoplanin expressing EVs and risk of VTE in patients. In one study by Burdett et al., circulating podoplanin, measured by ELISA, could be detected in a subset of glioma patients (20 with high levels, 28 with low levels, 88 undetectable); however, no association with VTE risk was detected [40].

In summary, these studies suggest that podoplanin is a key driver of a local prothrombotic tumor microenvironment. Shedding podoplanin to the circulation might cause thrombosis in peripheral locations such as the deep veins of the legs. However, this mechanism linking the prothrombotic microenvironment to VTE is yet to be confirmed.

Tissue factor

TF is the primary physiological trigger of coagulation in vivo and is markedly overexpressed on the cancer cell surface by many cancer entities, including gliomas. Oncogenic signaling pathways have been identified that link increased TF expression to glioma aggressiveness, and it was suggested that these pathways have a role in promoting the thrombotic risk [44].

However, despite this mechanistic rationale, results from clinical studies are conflicting. Data from our own study, the Vienna CATS, did not indicate an association between levels of TF expression in brain tumor tissue and the risk of future VTE in 96 patients with gliomas (82 with high-grade gliomas) [45]. In contrast, other authors found an association between TF expression on tumor sections and an increased VTE risk in a cohort of patients with adult-type diffuse glioma [40]. These diverging results might be explained by the differences of the study populations regarding brain cancer subtype.

In human samples, conflicting data have been published on TF expressed on EVs (EV-TF) and its role in predicting VTE risk. In the study described above investigating patients included in Vienna CATS, no association between EV-TF activity with future risk of VTE in PBC patients (n=119) was observed [45]. However, in the more recent study by Burdett et al., high EV-TF activity predicted VTE risk in glioma patients (n=168) [40]. Differences between the study results might be due to brain cancer entities included, also considering the recently updated classification of glioma subtypes [29]. Furthermore, the timing of blood sampling differs between the studies. In the study by Thaler et al, blood was collected in most patients at least 2 weeks after first brain cancer surgery (resection or biopsy; but always before initiation of radio/chemotherapy), while in the more recent study by Burdett et al. blood sampling was performed directly before first brain cancer surgery.

In summary, although a biological rationale for the role of TF overexpression in driving the thrombotic risk in patients with brain cancer exists (procoagulant EVs shed from tumor cells), clinical data are inconsistent, and further research is required to clarify the role of TF in brain cancer-associated VTE.

Interestingly, one study suggested a synergistic effect of the co-expression of podoplanin and TF; as expression of both podoplanin and TF increased intratumoral microthrombosis formation in a mouse model of glioma, more than the expression of podoplanin or TF alone [43].

Tumor genetics

Genetic aberrations regulate the expression of proteins on the tumor cell surface and thereby the procoagulatory phenotype of brain cancer cells.

This pathophysiological link has been substantiated in several studies examining patients with brain tumors harboring IDH1 mutations**,** who consistently exhibited a markedly reduced risk of VTE (e.g., 26-30% in IDH1 wildtype vs. 0% in IDH1 mutant tumors in one study [46]) [27, 28]. In the Vienna CATS, IDH1 mutated primary brain tumors (n=42) showed either no or very low expression of podoplanin, and only one out of 42 patients with an IDH1 mutated glioma developed VTE, confirming the clinical association of IDH1 mutation and a very low VTE risk [47]. Mechanistic studies have demonstrated that IDH mutations trigger epigenetic changes—specifically promoter hypermethylation of the genes encoding podoplanin and TF—resulting in their downregulation and thereby contributing to the reduced risk of VTE. [46, 48].

One additional aspect was suggested, related to the oncometabolite D-2-hydroxyglutarate, which accumulates in IDH mutated tumors. This oncometabolite was shown to inhibit platelet aggregation via interfering with calcium signaling and a direct antithrombotic effect was suggested, leading to decreased platelet aggregation and thrombus formation in the tumor vasculature [46].

Beyond IDH mutations, other genetic aberrations have been identified that might be linked to thrombosis. One study investigated genetic aberrations in 324 IDH-wildtype glioblastoma specimens by targeted DNA sequencing of tumor tissue and found that CDKN2A deletion was associated with an increased VTE risk (HR for CDKN2A deletion vs. wildtype CDKN2A deletion: 2.53 (95% confidence interval [CI]: 1.12-5.73; p=0.026). Similarly to IDH, a connection to podoplanin and TF was subsequently identified; analyses of the Pan-Cancer Atlas showed that CDKN2A deletion was inversely correlated with podoplanin mRNA levels (p=0.009) and TF mRNA

levels (p=0.058) [49]. Furthermore, several other genetic aberrations commonly found in glioblastoma, such as alterations in the genes of *EGFR* or *PTEN*, were also shown to influence the expression of procoagulant proteins, such as TF and podoplanin, as recently reviewed by Kapteijn et al. [50].

Other mechanisms of coagulation activation in PBC

Neutrophil extracellular traps (NETs), decondensed chromatin fibers that are released from activated neutrophils, have been suggested to play a role in the prothrombotic state of cancer patients in general. However, data from our own study group investigating data from the Vienna CATS found no association between markers of NET formation and risk of VTE in the subgroup of patients with PBC [51].

Interestingly, one recent study found higher levels of circulating mitochondria and higher levels of cardiolipin antibodies in patients with glioblastoma who developed VTE, compared to glioblastoma patients without VTE. The authors also showed in a murine model of inferior vena cava stenosis that delivery of mitochondria induced increased rates of venous thrombi. They suggested that mitochondria, as sources of cardiolipin, induce the formation of cardiolipin antibodies, and thereby increase the VTE risk [32].

Circulating tumor cells (CTCs)

Although glioblastoma metastasizes only very rarely, circulating tumor cells (CTCs) are found in a substantial percentage of patients [52]; one recent study found such cells in 20% of 133 patients with glioblastoma [53].

A recent autopsy study found intrathrombotic cancer cells in venous thrombi in ~25% of patients with cancer-associated VTE. These cells frequently showed immunohistochemical expression of TF and/or podoplanin, suggesting a potential involvement of these cells in thrombus formation [54]. However, in this study only 4 out of 114 autopsy cases had tumors of the central nervous system, limiting applicability of this data to patients with brain cancer. Furthermore, in the study of 133 patients with glioblastoma, no association between detection of CTCs and risk of future VTE could be identified [53].

Further investigations are required to clarify the role of CTCs in brain cancer-associated VTE.

Treatment and prophylaxis

Although several guidelines for cancer-associated VTE have been published, only limited evidence and guidance specific to the treatment of VTE in brain cancers is available [4, 5, 55-58]. As intracerebral hemorrhage (ICH) during anticoagulation is the main safety concern, it has been investigated most rigorously.

Treatment

Anticoagulant treatment is generally recommended in patients with cancers who develop VTE (International Initiative on Thrombosis and Cancer [ITAC] 2022) [5, 58]. However, PBC and MBC are generally regarded as risk factors for bleeding [56], and only few guidelines give specific recommendations for the treatment of VTE in patients with PBC. One guideline recommends anticoagulant treatment with either LMWH or DOAC (ITAC 2022 [58]) but states that the risk of ICH should be considered. Differences in ICH rates between PBC and MBC are mentioned in another guideline but limitations in the available data are noted (ASCO 2019 + 2023 [56, 57]).

Bleeding risk with and without anticoagulation

MBC have a higher baseline risk of ICH than PBC, with spontaneous bleeding rates of 13.0% and 6.4%, respectively, [59] but during anticoagulation this relation seems to be turned around. Two meta-analyses [60, 61] have found an increased risk of ICH during anticoagulation for VTE in PBC (OR [95% CI] 3.66 [1.84-7.29] and OR 3.75 [1.42-9.95]). Conversely, in MBC, a meta-analysis [61] and one more recent retrospective study [62] (including patients anticoagulated for other reasons than VTE) have found only a small non-significant increased risk of ICH (OR 1.07 [0.61-1.88] and HR 1.31 [0.96-1.79]). All these studies compared anticoagulated to non-anticoagulated patients. Table 2 provides an overview of these studies.

Current guidelines partially mention these studies, but the final recommendations do not differentiate between patients with PBC and MBC [56-58]. However, significant safety concerns, such as recent ICH, urgent surgery, or low platelets should be considered before administering anticoagulation according to one consensus statement [7].

Bleeding risk and type of anticoagulation

Recent studies comparing bleeding risk in patients with brain cancer receiving different anticoagulant strategies are summarized in Table 2. Two recent meta-analyses [63, 64] have found evidence of a better safety profile regarding ICH of DOACs compared to LMWH but the decreased risk of ICH was only significant in PBC (RR 0.18 [0.06-0.50] and RR 0.35 [0.18-0.69]) but not in MBC (RR 0.65 [CI 0.37-1.14] and RR 1.05 [0.71-1.56]). Both meta-analyses have not only included patients that were treated for VTE but also for atrial fibrillation. In those studies that report ICH incidences in patients exclusively treated with anticoagulation for VTE, however, the risk of ICH was at least numerically also lower in those receiving DOACs (incidence of ICH with DAOCs: 0%-27.8% and with LWMH: 5.9%-52.9%) [65-67]. In an analysis of both PBC and MBC, the risk of major and fatal ICH was also decreased with DOACs compared to LMWH [63].

Two more recent observational studies have found similar results. One included a total of 153 patients with brain cancer (89% PBC) and reported a higher ICH risk with LMWH compared to DOAC (16% vs. 4%, p = 0.037) [68]. The other study included only patients with MBC (n=505) and found no difference between DOAC and LMWH (HR 0.84 [0.41-1.70]) [69]. Anticoagulation was also associated with a non-increased risk of ICH in patients with MBC treated with DOACs and non-DOACs in two earlier meta-analyses [59, 70]. These results are generally in line with the studies mentioned in the previous section that have found only an insignificantly increased bleeding risk in patients with MBC.

These results may indicate that DOACs are the safer anticoagulant treatment with regards to ICH in patients with PBC and are an appropriate alternative to LMWH in those with MBC. However, despite the availability of meta-analyses, which are generally regarded as high-level evidence, it should be kept in mind that the foundation of these analyses consists of overlapping observational studies potentially at risk of bias.

Apart from ICH, the evaluated studies show no signal towards decreased efficacy of DOAC (i.e., similar rates of recurrent VTE) and no evidence for an increased risk of other safety outcomes (i.e., overall bleeding and overall survival) [67, 71, 72]. One study even found a decreased risk for overall bleeding with DOACs [66]. In patients who were treated with anticoagulation for any

indication, results are similar [69, 73, 74] except for one study that found a higher rate of predominantly minor bleeds in patients treated with DOACs compared to LMWH [68].

In summary, DOACs seem to be an efficient and safe choice for the treatment of VTE in patients with brain cancers. We therefore conclude that patients with brain cancers and VTE should be treated according to the guidelines for cancer-associated VTE, i.e., anticoagulated for at least 6 months and for as long as the cancer is deemed active [4, 5, 55-58, 75]. Some authors, however, recommend applying a very cautious strategy, performing serial imaging studies to exclude ICH before and during anticoagulation, applying full-dose anticoagulation only in the absence of bleeding [76].

Anticoagulation after ICH

Data on the optimal management of patients after ICH during anticoagulant therapy is scarce. In one cohort of 79 patients with both PBC (26%) and MBC (74%) [77], a markedly decreased cumulative incidence of recurrent VTE upon restart of anticoagulation was found (8.1% vs. 35.3%, p=0.003). The incidence of recurrent ICH during anticoagulation was 6.1% vs. 4.2% without anticoagulation. Another study of patients with glioblastoma found that anticoagulation might be required to prevent recurrent VTE [56, 57]. A recent review on the management of VTE in the presence of ICH proposed an algorithm to make treatment decisions. Factors such as VTE site and ICH volume are incorporated to guide the use of anticoagulation and inferior vena cava filters [76]. More research – especially clinical trial data – is required to assess the balance between the risk of bleeding and VTE in patients with brain cancer.

Prophylaxis

Hospitalized setting

Current guidelines recommend the use of primary thromboprophylaxis for many patients of the general population with cancer in the hospitalized and perioperative setting [4, 5, 55, 56]. However, specifically in the setting of brain cancer, one guideline advises against the routine use of thromboprophylaxis for medical inpatients outside of neurosurgical procedures [58]. One meta-analysis that included mainly patients with brain cancer is available, which concludes that primary thromboprophylaxis decreases VTE risk but increases bleeding risk [78]. However, the

study data covers a period up to 2003 and the study population might therefore not be comparable to modern populations of patients with brain cancer. Several studies are available on primary thromboprophylaxis in general neurosurgery but these are non-specific to patients with brain cancers [79].

Ambulatory setting

In the general cancer population for patients in ambulatory care, primary pharmacological thromboprophylaxis is only recommended if the risk of VTE is high, defined by applying a risk assessment model (RAM) – the Khorana-Score – and scoring at least 2 points [58]. Brain cancers are usually regarded high risk cancers for VTE and their incorporation as such would prompt thromboprophylaxis if the decision is based on one of these models [13]. This recommendation is based on data of two randomized controlled trials [80, 81], which showed that low-dose DOACs reduce the VTE risk compared to placebo in ambulatory cancer patients [34]. However, patients with cancers of the brain were excluded from one of these two studies (CASSINI trial, investigating rivaroxaban [82]) and represented only 4% (n=24) of the population in the other trial (AVERT trial, investigating apixaban [80]). The only trial specifically investigating long-term thromboprophylaxis in patients with malignant gliomas was terminated early due to slow patient accrual and expiration of study medication [83] (PRODIGE trial). This study compared dalteparin with placebo for a duration of up to 12 months. In total, 186 patients were recruited before the study was terminated. There was a trend towards a reduced risk of VTE for dalteparin vs. placebo (9.1% vs. 15.0%), but also a trend towards an increased risk major bleeding (5.1% vs. 1.2%, all major bleedings were intracranial). One very small study with 10 participants has evaluated apixaban for up to 6 months as primary thromboprophylaxis in patients with malignant gliomas and attributed no adverse events to apixaban treatment [84].

In summary, with the high risk of ICH – one of the most detrimental types of bleeding – patients with brain cancers represent a population that would require high-quality evidence to guide treatment decisions, which is currently not available. Current guidelines therefore do not recommend primary pharmacological thromboprophylaxis in patients with brain cancer outside

of the surgical setting [58]. Specific studies, possibly focusing on patients at high risk of VTE are needed.

Conclusion and future prospects

Research of brain cancer-associated VTE has delivered important results regarding risk factors, mechanisms and treatment. However, many questions related to these topics remain still unanswered and future studies are needed to move the respective research fields forward.

Several general cancer-related risk factors apply to brain cancer, while tumor-specific factors such as podoplanin expression and IDH mutation status have been highlighted as particularly relevant. However, data on other potentially important variables—such as sex, type of surgery, and systemic therapy—are inconclusive and require validation in larger cohorts. Risk assessment in brain cancer remains underdeveloped; existing models are promising but need refinement and external validation.

Mechanistic studies have provided important insights into the prothrombotic phenotype of PBC, particularly the roles of podoplanin and TF in glioma. Podoplanin induces platelet activation via the platelet CLEC-2 receptor, while TF triggers the coagulation cascade, and both are subject to regulation by genetic alterations of the tumor. However, the precise pathophysiological link between localized tumor-driven coagulation activation and systemic thrombus formation remains incompletely understood. A deeper understanding of these mechanisms could enable the development of targeted therapeutic strategies.

Currently, factor XI inhibitors are in clinical investigation for cancer-associated thrombosis and show promise due to an improved safety profile but are yet to demonstrate sufficient efficacy [85]. Whether they are effective in counteracting the TF-driven coagulation observed in brain tumors remains to be determined. In addition, experimental studies targeting the CLEC-2 signaling pathway have demonstrated reduced venous thrombus formation without an increased risk of bleeding [86]. Although these results are so far limited to preclinical models, they appear highly promising and warrant further evaluation in clinical settings.

Therapeutic management of VTE in brain cancer remains particularly challenging due to the elevated risk of intracranial hemorrhage. Current treatment guidelines largely extrapolate from broader cancer populations and do not differentiate between primary and metastatic brain cancer. Observational data suggest that direct oral anticoagulants (DOACs) may offer a more favorable safety profile compared with low-molecular-weight heparins (LMWH), especially in patients with primary brain tumors; however, these observations have yet to be confirmed in randomized controlled trials.

Prospective studies—ideally randomized controlled trials—are needed to determine optimal strategies regarding treatment and prophylaxis of VTE, assess safety and efficacy of DOACs, and evaluate novel agents such as FXI inhibitors. Improved understanding of tumor-specific biology and risk stratification will be key to advancing individualized management of VTE in this high-risk population.

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Conflict of interest:

None declared.

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Tables

Table 1. Recently described risk factors for VTE in patients with primary brain cancers

Author (Ref)	Year	N / Design	Cancer Type	Risk Factors
Mandel [27]	2021	Retrospective cohort, n=282	Astrocytoma	Protective: IDH mutation
Osada [22]	2021	Retrospective cohort, n=124	Grade II/III astrocytomas	Not associated: IDH mutation Risk factor: Age, diffuse astrocytoma histology, resection
Eisele [24]	2022	Retrospective cohort, n=414	GBM, IDH wild-type	Risk factor: VTE history
Kaptein [23]	2022	Retrospective cohort, n=967	GBM	Protective: Resection (vs. biopsy) Not associated: Sex, IDH status Risk factors: Older age, and worse performance status
Burdett [28]	2023	Retrospective cohort, n=628	Adult-type diffuse glioma II-IV	Protective: IDH1/2, MGMT Risk factors: TF, PDPN, D-dimer RAM developed: 1) History of VTE; (2) hypertension; (3) asthma; (4) white blood cell count; (5) WHO tumor grade; (6) patient age; and (7) body mass index
Gonzalez-Delgado [32]	2023	Retrospective cohort, n=82	GBM	Risk factor: Mitochondria count in blood
Kapteijn [31]	2023	Retrospective cohort, n=324	GBM	Risk factor: CDKN2A
Kaye [30]	2023	Retrospective cohort, n=293	IDH wild-type GBM	Protective: KPS, Temozolomide treatment Not associated: EGFR (only in patients 60+), Length of stay
Erhart [33]	2024	Case-control, n=44	Grade IV glioma	Risk factors: Certain miRNAs
Hovman [2]	2024	Retrospective registry, n=3,630	Grade 2-4 gliomas	Not associated: Extent of surgery, Charlson Comorbidity Index Risk factors: Age, male sex, poor performance status, radiochemotherapy
Simakova [21]	2024	Retrospective cohort, n= 265	Glioma	Not associated: Many (including VTE history, BMI, and treatment factors) Risk factor: Leg paresis

BMI, body mass index; CDKN2A, cyclin-dependent kinase inhibitor 2A; EGFR, epidermal growth factor receptor; GBM, glioblastoma; IDH, Isocitrate dehydrogenase; KPS, Karnofsky performance status; MGMT, methylated-DNA–protein-cysteine methyltransferase; miRNA, microRNA; PDPN, podoplanin; RAM, risk assessment model; TF, tissue factor; VTE, venous thromboembolism; WHO, World Health Organization.

Table 2. Recent studies on bleeding risk in patients with brain cancer

Author (Ref)	Year	N / Design	Cancer Type	Indication	Treatment	ICH Risk
Anticoagulation vs. no anticoagulation						
Zwicker [61]	2016	Meta-analysis based on 8 retrospective studies, n=1,480	PBC & MBC	VTE	Any anticoagulation vs. none	PBC: OR 3.75 (1.42-9.95) MBC: OR 1.07 (0.61-1.88)
Porfidia [60]	2020	Meta-analysis based on 7 retrospective studies, n=1,291	PBC	VTE	LMWH/DOAC vs. none	PBC: OR 3.66 (1.84-7.29)
Wood [62]	2021	Retrospective cohort, n=291	MBC	Any	Any anticoagulation vs. none	MBC: HR 1.31 [0.96-1.79]
DOAC vs. LMWH						
Yang [63]	2023	Meta-analysis based on 6 retrospective studies, n=566	PBC & MBC	VTE & AF	DOAC vs. LMWH	PBC: RR 0.18 (0.06-0.50), MBC: RR 0.65 (0.37-1.14)
Abdelmessih[1] [68]	2024	Retrospective cohort, n=153	89% PBC	Any	DOAC vs. LMWH	4% vs. 16% (p=0.037)
Iyengar [64]	2024	Meta-analysis based on 10 retrospective studies, n=1,638	PBC & MBC	VTE & AF	DOAC vs. LMWH	PBC: RR 0.35 (0.18-0.69), MBC: RR 1.05 (0.71-1.56)
Hamulyák [69]	2025	Retrospective cohort, n=505	MBC	Any	DOAC vs. LMWH	HR 0.84 (0.41-1.70)

[1]VTE during anticoagulation was also assessed as an outcome in this study, yielding no significant differences (9% vs. 4%, p = 0.503).
AF, atrial fibrillarion; DOAC, direct oral anticoagulant; HR, hazard ratio; LMWH, low molecular weight heparin; OR, odds ratio; PBC, primary brain cancer; RR, risk ratio; MBC, metastatic brain cancer; VTE, venous thromboembolism.

Figure legends

Figure 1. Schematic illustration of proposed mechanisms underlying venous thromboembolism in primary brain cancer, particularly glioblastoma WHO grade IV. Depending on tumor genetics (IDH-wildtype, CDKN2A deletion) glioblastoma cells create a prothrombotic microenvironment by expressing podoplanin and tissue factor (TF) on their surface. Podoplanin activates platelets via CLEC-2, while TF triggers the coagulation cascade, promoting local thrombus formation within the tumor. Systemic thromboembolism (e.g., in the deep leg veins) may result from tumor-derived extracellular vesicles (EVs) or circulating tumor cells carrying podoplanin and TF.