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ICH in patients with primary or metastatic brain cancer treated or not with anticoagulants: a systematic review and meta-analysis

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Abstract:
Anticoagulant treatment in patients with primary and metastatic brain cancer is a concern due to risk of intracranial hemorrhage (ICH). We performed a systematic review and meta-analysis to evaluate the risk of ICH in patients with primary or metastatic brain cancer treated or not with anticoagulants. Articles on ICH in patients with primary or metastatic brain cancer treated or not with anticoagulants published up to September 2021 were identified by searching PUBMED, EMBASE and CENTRAL.The primary outcome of this analysis was ICH. Thirty studies were included. Rate of ICH was 13.0% in 1,009 patients with metastatic and 6.4% in 2,353 patients with primary brain cancer [Relative risk (RR) 3.26, 95% CI 2.69-3.94; I^2 92.8%). In patients with primary brain cancer, ICH occurred in 12.5% and 4.4% of patients treated or not treated with anticoagulants, respectively [11 studies, 659 treated and 1,346 not treated patients, RR 2.63, 95% CI 1.48-4.67, I2 49.6%]. In patients with metastatic brain cancer, ICH occurred in 14.7% and 15.4%, respectively (5 studies, 265 treated and 301 not treated patients, RR 0.92, 95% CI 0.43-1.93, I2 0%). ICH occurred in 8.3% of 172 treated with direct oral anticoagulant (DOAC) and in 11.7% of 278 treated with low-molecular weight heparin (LMWH) (5 studies, RR 0.44, 95% CI 0.25-0.79, I2 0%). Patients with metastatic brain cancer have a particularly high risk of ICH. Patients with primary brain cancer have an increased risk of ICH during anticoagulation. DOACs are associated with a lower risk of ICH than LMWH.

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ICH in patients with primary or metastatic brain cancer treated or not with anticoagulants: a systematic review and meta-analysis

Running head: ICH in primary or metastatic brain cancer

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Abstract

Anticoagulant treatment in patients with primary and metastatic brain cancer is a concern due to risk of intracranial hemorrhage (ICH). We performed a systematic review and meta-analysis to evaluate the risk of ICH in patients with primary or metastatic brain cancer treated or not with anticoagulants. Articles on ICH in patients with primary or metastatic brain cancer treated or not with anticoagulants published up to September 2021 were identified by searching PUBMED, EMBASE and CENTRAL.The primary outcome of this analysis was ICH. Thirty studies were included. Rate of ICH was 13.0% in 1,009 patients with metastatic and 6.4% in 2,353 patients with primary brain cancer [Relative risk (RR) 3.26, 95% CI 2.69-3.94; I^2 92.8%). In patients with primary brain cancer, ICH occurred in 12.5% and 4.4% of patients treated or not treated with anticoagulants, respectively [11 studies, 659 treated and 1,346 not treated patients, RR 2.63, 95% CI 1.48-4.67, I^2 49.6%]. In patients with metastatic brain cancer, ICH occurred in 14.7% and 15.4%, respectively (5 studies, 265 treated and 301 not treated patients, RR 0.92, 95% CI 0.43-1.93, I^2 0%). ICH occurred in 8.3% of 172 treated with direct oral anticoagulant (DOAC) and in 11.7% of 278 treated with low-molecular weight heparin (LMWH) (5 studies, RR 0.44, 95% CI 0.25-0.79, I^2 0%). Patients with metastatic brain cancer have a particularly high risk of ICH. Patients with primary brain cancer have an increased risk of ICH during anticoagulation. DOACs are associated with a lower risk of ICH than LMWH.

Key Points

1. Anticoagulant therapy significantly increases the risk of ICH in patients with primary brain cancer but not in those with brain metastases.
2. The risk of ICH is significantly lower with direct oral anticoagulants compared to low-molecular weight heparins.

Keywords: brain tumors, brain metastasis, intracranial hemorrhage, anticoagulants, meta-analysis

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Introduction

It is estimated that 24,000 new cases of primary brain tumors and 200,000 new cases of brain metastatic cancers occurred in 2020 in United States (1). Up to 20-25% of metastases spreads to the central nervous system, with the highest incidence in patients with breast, melanoma, kidney and non-small cell lung cancer (1). Spontaneous ICH is a common complication in patients with primary brain cancer and brain metastases (2). The clinical presentation of ICH is extremely heterogeneous, ranging from asymptomatic deposition of hemosiderin within the tumor seen on neuroimaging to large bleeds that cause clinical symptoms either focal or related to intracranial hypertension (2, 3). The incidence of ICH in patients with primary brain cancer and brain metastases varies according to the imaging diagnostic criteria and the cancer histotype, with rates as high as 50% in patients with brain metastases from melanoma, thyroid carcinoma, renal cell carcinoma and choriocarcinoma (3-5).

When, for any reason, an anticoagulant treatment is required, in patients with primary brain cancer and brain metastases the conflict between the need of anticoagulation and the risk of bleeding is a challenge. In the context of a timely and debated medical issue, we report the results of a systematic review and meta-analysis in patients with primary brain cancer or brain metastases treated or not with anticoagulant therapy at therapeutic doses in order to provide summary estimates of ICH across studies, to evaluate these rates in patients with primary or metastatic brain cancer separately, and to investigate the impact of anticoagulation as well as of different anticoagulation strategies on ICH rates.

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Materials and Methods

This systematic review and meta-analysis was conducted according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" statement (6) (http://www.prisma-statement.org/). This meta-analysis has been registered in PROSPERO.

Search strategy

We performed an unrestricted search in PubMed, EMBASE and the Cochrane Library database from inception to September, 2021. We used the following search terms to search clinical trials, registers and databases: "glioma, glioblastoma, oligodendroglioma, astrocytoma, oligoastrocytoma, brain metastasis" and "anticoagulant, heparin, low-molecular-weight heparin, vitamin K antagonist, oral anticoagulant, direct oral anticoagulant " and "hemorrhage, haemorrhage". By hand searching of reference lists of the reviews and retrieved articles, additional studies were identified. Eligibility assessment was performed independently by two authors (G.P., M.G.), using a data extraction form, in an unblinded standardized approach. Study selection was initially performed by review of titles and candidate abstracts were then reviewed. A third reviewer (M.M.) resolved disagreements between reviewers and any differences in study selection.

Study selection

Inclusion criteria of this meta-analysis were: (1) randomized clinical trials or observational studies; (2) patients aged ≥ 18 years old with primary brain cancer and/or brain metastases treated or not with therapeutic doses of anticoagulants; (3) availability of number of patients who experienced ICH. No language, publication date, or publication status restrictions were imposed. Review articles not reporting original data, case reports and case series with less than 10 patients, abstracts, editorials/letters, studies not involving humans were excluded. Studies reporting on the rate of ICH in patients with primary brain cancer or brain metastases who received thromboprophylaxis for

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VTE were also excluded. The inter-reviewer agreement for study selection was assessed by the kappa statistic, which measures agreement beyond chance (7).

Study objectives and outcomes

The primary objective of this meta-analysis was to evaluate the overall incidence of ICH in patients with primary brain cancer or brain metastases treated or not with anticoagulants at therapeutic doses. The secondary objectives were to evaluate: 1) the rate of major and fatal ICH, 2) the rate of ICH in relationship to anticoagulant therapy, 3) the rate of ICH according to the type of anticoagulant treatment.

The primary outcome was ICH. Secondary outcomes were: 1) major ICH, 2) fatal ICH.

Major ICH was defined as symptomatic, requiring surgical intervention, with a volume equal or higher than 10 mL or as fatal (3, 4, 8-12). Any ICH was defined as the composite of major ICH and the other ICH categories that did not meet the major ICH criteria.

Data extraction

The following data were extracted from each included trial: 1) general data (study design, year of publication), 2) characteristics of trials participants (number, mean age, gender, site of cancer, cancer histotype), 3) type of anticoagulant (agent, dose, duration and daily dosing) and 4) study outcomes (primary outcome and secondary outcomes, length of follow-up). The quality of the studies was evaluated using the Newcastle-Ottawa quality assessment scale (NOS; range 1-9, with 1-3 indicating low quality, 4-6 indicating moderate quality, and 7-9 indicating high quality).

Statistical analysis

Pooled outcome event rates were calculated by using the logit transformed proportion and corresponding sampling variances. The rates of ICH were pooled using random effects models and

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presented with the corresponding 95% confidence interval (CI). Heterogeneity was assessed by the I^2 test. A I^2=0 was considered to indicate no heterogeneity; I^2 <25%, 25–75% and above 75% was considered to indicate low, moderate, and high degrees of heterogeneity, respectively (13). To evaluate publication bias both Egger's test and funnel plots of the logit transformed proportion versus standard error were computed. If the Egger's test confirmed asymmetry, we used the Duval and Tweedie's trim and-fill procedure to compute an unbiased estimate of the effect size. A mixed-effects meta-regression analysis was performed to test differences among sub-groups according to the median length of follow-up and to the median length of anticoagulation therapy. We also determined pooled relative risk (RR) and 95% CI using random-effects model for ICH in patients with primary brain cancer or brain metastases treated or not with anticoagulant therapy and according to the anticoagulant type. For studies presenting zero cells, 0.5 was added for a correct estimation of risk measures. The following pre-specified sensitivity analyses were performed: i) rate of ICH in primary brain cancer only; ii) rate of ICH in brain metastases only; iii) rate of major ICH in primary brain cancer or brain metastases; iv) rate of ICH according to the type of anticoagulant treatment; v) rate of fatal ICH; vi) rate of ICH in patients with VTE.

The statistical analyses, forest plots, and publication bias analyses were produced with Comprehensive Meta-Analysis, Version 3.0. P values < 0.05 were considered statistically significant.

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Results

The search of PubMed, EMBASE and Cochrane Library databases provided a total of 692 articles while 3 of them were identified through other sources. After removal of duplicates, and of additional 530 articles that did not meet the inclusion criteria at abstract review, the full text of the remaining 64 articles was examined in detail. Of these, 34 studies did not meet the inclusion criteria. Thus, 30 studies were included in the systematic review (3-5, 8-12, 14-35). No unpublished relevant studies were found. The flow diagram of literature search is shown in Figure 1S and the main features of the studies are reported in Tables 1,Table 1S and Table 3S. The inter-reviewer agreement for study selection was very good (kappa statistic 0.85).

The studies selected for the review included 3,893 patients (range for individual studies 16 to 364 patients) and were all retrospective. Fifteen studies included patients with primary brain cancer only (4, 9, 11, 12, 15, 17, 21, 22, 24, 28, 30, 31, 33-35), six studies included patients with brain metastases only (3, 5, 10, 16, 18, 27) and nine studies included both patients with primary brain cancer and patients with brain metastases (8, 14, 19, 20, 23, 25, 26, 29, 32). Overall, this analysis includes 2,353 patients with primary brain cancer and 1,009 with brain metastases. Seven studies (531 patients) did not report separately ICH occurring in primary cancer or brain metastases (17, 19, 23, 25, 26, 29, 32).

Mean age varied from 51 to 72 years, and men were slightly more represented than women. Seventeen studies (2,896 patients) included both patients treated (1,072 patients) and not treated (1,824 patients) with anticoagulants while 13 studies (997 patients) only those treated with anticoagulants. The main indication for anticoagulant treatment was acute VTE (25 studies, 3,313 patients), followed by atrial fibrillation (2 studies, 268 patients), cerebral vein thrombosis (2 studies, 187 patients) or any indication for anticoagulant treatment (1 study, 125 patients) (Table 1).

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The anticoagulant agent was heparin in 21 studies (1,338 patients) (3-5, 8-12, 14-25), warfarin in 13 studies (475 patients) (4, 5, 12, 17, 22-24, 30-35) and direct oral anticoagulants (DOACs) in 5 studies (172 patients) (8-10, 14, 16).

The median patient's observation was 125 days, ranging from to 27 days and 240 days. The median duration of anticoagulant treatment at the time of ICH was 8.1 months.

The quality of studies assessed by the NOS scale was poor in 22 studies and good in 8 studies. The quality assessment is reported in Table 2S.

Rates of ICH in primary or metastatic brain cancer

Overall, the weighted incidence rates in patients with primary brain cancer or brain metastases estimated by a random effect model was 7.7% (95% CI 5.1-11.5%, I^2 92.8%, 445 events in 3,893 patients) (Table 2). The Egger's tests revealed the presence of publication bias (t=5.90, p<0.001). After using Trim and Fill procedure, 5 studies were trimmed and the ICH adjusted rate was 9.1% (95% CI 6.2-13.2%). Bias assessment plots are reported in Figure 2S, panel A.

Rates of ICH in patients with primary brain cancer were reported in 18 studies and ranged from 1.1 to 25.4% (4, 9-12, 16, 18-21, 23, 27, 28, 30, 31, 33-35). The weighted incidence rate was 6.4% (95% CI 4.1-9.9%, I^2 84.4%, 156 events in 2,353 patients) (Figure 3S, panel A) and the risk of publication bias was significant (t=2.39, p=0.03) (Figure 2S, panel B). Adjusted value after Trim and Fill procedure was 7.5% (95% CI 4.9-11.3%).

Rate of ICH in patients with metastatic brain cancer was reported in 9 studies ranging from 2.7 to 47.6% (3, 5, 9, 12, 14-16, 18, 26). In these studies, the weighted incidence rate of ICH was 13.0% (95% CI 6.5-24.2%, I^2 93.7%, 218 events in 1,009 patients) (Figure 3S, panel B). The risk of publication bias was significant (t=5.10, p=0.001) and after Trim and Fill procedure, two studies were trimmed and adjusted rate of ICH was 17.5% (95% CI 9.6-29.8%) (Figure 2S, panel C).

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Risk of ICH was significantly higher in patients with metastatic brain cancer than patients with primary brain cancer (RR 3.26, 95% CI 2.69-3.94; I^2 92.8%) (Table 2).

At meta-regression analysis, the median length of patient's observation (p=0.99, I^2 87.7%) and the median length of anticoagulant therapy before ICH (p=0.763, I^2 92.4%) did not influence the rate of ICH.

With regard to patients with VTE, the overall weighted incidence rate of ICH was 7.1% (95% CI 4.4-11.5%, I^2 93.7%, 25 studies, 384 events in 3,313 patients) (3-5, 8, 9, 11, 12, 14, 15, 20-35) (Table 2). Specifically, the weighted incidence rate of ICH was 6.1% (95% CI 3.7-9.7%, I^2 85.3%, 17 studies) and 13.6% (95% CI 5.6-29.2%, I^2 94.1%, 6 studies) in patients with primary and metastatic brain cancer, respectively. Rates of major and fatal ICH in patients with primary or metastatic brain cancer are reported in Table 2.

Rates of ICH in patients treated or not with anticoagulant therapy

Overall, rates of ICH in patients treated with anticoagulants was 11.5% (95% CI 7.4-17.6%, I^2 83.7%, 152 events in 1,072 patients) and 6.0% in those not treated with anticoagulants (95% CI 3.0-11.5%, I^2 92.2%, 177 events in 1,824 patients) (RR 1.81, 95% CI 1.15-2.84, p=0.001, I^2 60.3%). No publication bias was observed (t=1.41, 0=0.17) (Table 3). In patients with primary brain cancer, anticoagulant therapy was associated with an increased risk of ICH and of major ICH (Figure 1, Table 3). In patients with metastatic brain cancer, anticoagulant therapy was not associated with increased rate of ICH (Figure 1, Table 3). Fatal ICH while on anticoagulant therapy was reported in 11 studies and the weighted incidence rate was 2.7% (95% CI 1.6-4.5, I^2 0%, 13 events in 764 patients) (4, 13, 14, 18, 21, 25, 26, 30, 32, 34, 35).

Rate of ICH according to the type of anticoagulant treatment

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In patients with primary brain cancer or brain metastases, DOACs were associated with a lower risk of ICH than low-molecular weight heparin (LMWH), (8.3% vs. 11.7%, RR 0.44, 95% CI 0.25-0.79, I^2 0%, 5 studies, 450 patients) (Figure 4S, panel A) (8-10, 14, 17). In patients with primary brain cancer, DOACs were associated with a reduced risk of ICH (RR 0.19, 95% CI 0.04-0.99, I^2 0%, 0 events in 69 DOACs-treated patients and 19 events in 95 LMWH-treated patients, 4 studies). In patients with brain metastases, 12 events were observed in 103 DOACs treated patients and 52 events in 183 LMWH-treated patients (RR 0.65, 95% CI 0.36-1.16, I^2 0%, 3 studies). When considering only studies in patients receiving anticoagulants for VTE, the RR for ICH was 0.36 (95% CI 0.18-0.71, I^2 0%, 4 studies) in patients treated with DOACs (8 events in 131 patients) compared to LMWH (64 events in 223 patients) (9, 11, 14, 16). Risk of ICH was not significantly different with LMWH versus warfarin (4 studies, 15 events in 211 LMWH treated patients vs 8 events in 198 warfarin treated patients) (RR 1.45, 95% CI 0.56-3.79, I^2 0%) (Figure 4S, panel B) (17, 22, 23, 27).

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Discussion

Our meta-analysis provides the following findings: 1) the rate of ICH and major ICH is higher in patients with metastatic brain cancer compared to those with primary brain cancer; 2) anticoagulant therapy is associated with an increase in ICH and major ICH in patients with primary brain cancer but not in those with brain metastases; 3) the risk of ICH is lower in patients with primary or metastatic brain cancer treated with DOACs compared to those treated with LMWH.

According to international guidelines, presence of an intracranial primary or metastatic brain cancer is not an absolute contraindication for anticoagulation (36). Nevertheless, limited data support the use of anticoagulant therapy in these patients. In this context of uncertainty, our results may be relevant and timely for clinical decision making and design of future clinical trials. Of potential clinical interest, our analysis provides data on brain cancer overall as well as separately in patients with primary or metastatic brain cancer. Data are also provided concerning the rate of ICH in patients treated or not with anticoagulants.

In our meta-analysis, the rates of ICH and major ICH were higher in patients with metastatic brain cancer than in patients with primary brain cancer. The safety profile of anticoagulant therapy appears to be different in patients with primary or metastatic brain cancer. Of clinical relevance, in patients with primary brain cancer, therapeutic anticoagulation was associated with an increased risk of ICH and major ICH. In contrast, in patients with metastatic brain cancer the administration of anticoagulant therapy was not associated with an increased rate of ICH. Although ICH from metastatic brain cancers is a relatively common clinical observation, its pathogenesis has not been fully elucidated. Several biomarkers involved in the neoangiogenetic process have been reported to contribute to vascular instability of brain metastases (37-39). Our meta-analysis is not able to elucidate the risk of bleedingassociated with specific tumour hystotypes. Future studies are needed in order to definitively establish rates of bleeding and the safety of anticoagulation in malignancies

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associated with high ICH rates including metastatic melanoma, choriocarcinoma and renal cell carcinoma.

Due to the high bleeding risk, patients with brain cancer should be, as a priority, the target for future studies with new potentially safer anticoagulant agents including the anti-XI inhibitors. These agents have been recently showed to be associated with a lower risk of bleeding than LMWH (40, 41) when given for thromboprophylaxis in patients who underwent major orthopedic surgery.

The data regarding the relative safety of anticoagulation in patients with brain metastases appear to be reassuring. This finding does not support anymore the exclusion of these patients from clinical trials on the treatment of cancer associated-venous thromboembolism with some remaining caution for patients with primary brain cancer. It should be recommended that patients with primary or metastatic cancer respectively should be subjected to a priori stratification before study randomization.

Interestingly, although the number of patients on DOACs in our analysis is relatively low, we found that treatment with DOACs was associated with a lower risk of ICH than treatment with LMWH in patients with primary or metastatic brain cancer, with no heterogeneity across studies. These results are in agreement with recent studies suggesting the safety profile of DOACs in terms of ICH rates in patients with brain cancer (42, 43) and make these agents an attractive strategy in particular for VTE treatment. Indeed, in our study, anticoagulants were mostly used for the treatment of VTE and DOACs were associated with a one third of the risk of ICH in comparison with LMWH.

The overall rates of ICH varied considerably, ranging from 1.4 to 47.6%. Specifically, among patients receiving anticoagulant therapy, rate of ICH in patients with primary and metastatic brain cancer ranged from 1.4 to 29.0% and from 2.7 to 47.6%, respectively. Several reasons can justify these large ranges: the retrospective design of the included studies, the heterogeneity in ICH

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monitoring, definition of ICH and utilized imaging modalities, cancer histotype and the type of the adopted anticoagulant therapeutic strategy.

We are aware of several limitations of our meta-analysis: none of the studies included in the analysis was prospective. Furthermore, for different subgroup analyses there was a significant heterogeneity due to differences in study target populations or targeted effects, protocol-scheduled imaging, types and duration of anticoagulant therapy, and/or analytical methods, including covariate adjustments. Moreover, the definition of major and non-major was not formally standardized although the same definition was consistently reported in different studies (3, 4, 8-12). Finally, due to the paucity of data, we were not able to distinguish rates of ICH in patients with brain cancer treated or not treated with chemo- or radiotherapy.

Nevertheless, our meta-analysis has several strengths including: 1) an extensive search of available data that makes this meta-analysis the most updated reported so far; 2) the punctual estimation of the rates of ICH and major ICH in large series of patients with primary or metastatic brain cancer; 3) the assessment of relative risks in patients with primary or metastatic brain cancer treated or not with anticoagulants.

In summary, our study confirms the not negligible risk of ICH in patients with primary brain cancer or brain metastases. Anticoagulation is associated with an increase in the risk of ICH and major ICH in patients with primary brain cancer. This increase in risk does not appear to occur in patients with brain metastases. DOACs seems to be associated with a lower risk of ICH than LMWHs. Prospective controlled studies on new anticoagulant strategies, potentially associated with a reduced risk of bleeding, are needed in patients with brain cancer with these patients and clinical settings as a priority in the unmet clinical need-based clinical research.

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Authorship contributions

Study conception and design: M.M., M.G.; Data acquisition: G.P., M.G, M.M.; Statistical analysis: M.G., C.B.; Interpretation of the data: All authors; Drafting of the manuscript: All authors; Critical revision of the manuscript for important intellectual content: All authors; Final approval of the manuscript: All authors.

Disclosure of Conflicts of Interest

M.G., G. P. and F.R have nothing to disclose, C.B. reports lectures' fees and consultancies for Bayer Health Care, Bristol Myers Squibb, Daiichi Sankyo outside the submitted paper, G.A. reports lecture fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb and Daiichi Sankyo outside the submitted paper, M.M. received honoraria for participation at advisory boards from Novartis, BMS, MSD, Pierre Fabre, Sanofi, reports lecture from Novartis, BMS, MSD, Pierre Fabre, Sanofi and reports grants from Roche, Novartis.

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Table 1. Main clinical features of the studies included according to PICO criteria

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Source and author	Study design	N° of pts	Participants	Intervention	Comparator	Median Follow-up	Primary outcome	Definition of major ICH
Lee [14] Thromb Res 2021	R	111	Pts with primary or secondary brain tumors who received either a DOAC or LMWH for treatment of VTE	DOAC (55 pts): Rivaroxaban (38) Apixaban (13) Edoxaban (3) Dabigatran (1)	LMWH (56 pts): Enoxaparin	6 months	Incidence of any intracranial hemorrhage within 6-months	NR
Jo [15] Neuro Oncol 2021	R	220	Pts with high-grade glioma and VTE on low molecular weight heparin	LMWH (88 pts)	No anticoagulation (22 pts)	12 months	Incidence of 1-year ICH	NR
Dubisnki [9] Neurosurgical Review 2021	R	46	Pts who underwent craniotomy for primary tumor resection and PE	DOACs (14 pts): Rivaroxaban (6) Edoxaban (8)	LMWH (32 pts)	15 months (DOACs) and 9 months (LMWH)	Clinical course, 6- and 12-months follow-up and survival	Any hemorrhage that was≥10 ml in volume, required surgical intervention, or was associated with clinical symptoms, such as nausea and vomiting, or focal neurologic deficit
Burth [16] J Neurooncol. 2021	R	172	pts with glioblastoma and pts with brain metastases with (cases)/without (controls) AF	Full anticoagulation (enoxaparin 40 mg, Phenprocoumon, DOAC or heparin) Vs. prophylactic anticoagulation/heparin	No anticoagulation	8.6 and 7.2 months	Incidence of ICH in pts with glioblastoma and brain metastases with/without AF.	NR
De Melo Junior [17] Clin Neurol Neurosurg. 2020	R	53	VTE pts on therapeutic anticoagulation started within the first 30 days after intracranial neurosurgical procedure (mostly primary neoplastic lesions)	Total 29: Warfarin	Total 21: DOAC (19 rivaroxaban and 2 apixaban) or 4 pts Enoxaparin 1 mg/Kg twice daily.	161 days .	Risk of ICH.	NR
Leader [10] Blood Adv. 2020	R	96	Pts with brain metastases and anticoagulation therapy prescribed at therapeutic doses for either VTE and AF	DOAC (41): apixaban (11), dabigatran (5), edoxaban (8), rivaroxaban (17)	LMWH (55): enoxaparin (34), nadroparin (15), tinzaparin (6).	136 days in DOAC and 175 days in LMWH	Major ICH during 12 months of follow-up.	ICH that measured ≥10 mL in volume, required surgical intervention or was associated with clinical symptoms, focal neurologic deficits or changes in cognitive function.
Horstman [18] Med Oncol. 2018	R	125	Pts with brain metastasis with or without history of long-term (> 1 month) anticoagulation therapy.	67 pts on anticoagulant therapy: once-daily enoxaparin (1.5 mg/Kg) or twice-daily enoxaparin (1 mg/Kg q12h).	58 patients: Not on anticoagulant therapy	NR	Incidence of ICH associated with anticoagulant use.	NR

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Carney [8] J Thromb Haemost. 2018	R	172	Pts with primary and secondary brain tumors on anticoagulation with a DOAC or LMWH for the treatment VTE.	- Primary brain tumors: total 67 20 with DOACs 47 with Enoxaparin - Brain metastases: total 105 21 with DOAC 84 with enoxaparin	Enoxaparin ≥1.5 mg $Kg^{-}1$, once daily.	NR	Major ICH within 12 months from start of anticoagulation.	ICH that measured ≥10 mL in volume, required surgical intervention or were associated with clinical symptoms, focal neurologic deficits or changes in cognitive function
Gessler [19] J Neurosurg. 2018	R	35	Pts with primary and secondary tumors who underwent craniotomy on anticoagulant treatment for cerebral vein thrombosis.	Full therapeutic anticoagulation (25 patients)	Intermediate dosing of LMWH (10 patients).	181 days	Investigate the occurrence, the risk factors and outcomes associated with the development of cerebral vein thrombosis after craniotomy.	NR
Chai-Adisaksopha [20] Thromb Haemost. 2017	R	364	Pts with primary or metastatic brain tumours with VTE (182) treated with anticoagulation and 182 controls (pts without brain tumors with VTE on anticoagulant treatment)	Therapeutic dose of LMWH. 5.9% pts received reduced dose LMWH.	162 of 182 pts in the control group received therapeutic dose LMWH. 3.6% pts received reduced dose LMWH.	6.7 months	The incidence of the first major bleeding after starting anticoagulant therapy.	
Mantia [11] Blood. 2017	R	133	Pts with primary brain tumors on therapeutic anticoagulation for VTE	Enoxaparin (50 pts) 1 mg/Kg, twice daily (76%) or enoxaparin at 1.5 mg/Kg (2 pts) or enoxaparin less than standard therapeutic dosing (8 patients)	No anticoagulation (83 pts).	NR	Major intracranial hemorrhage from time of diagnosis of primary brain tumor.	Any hemorrhage that was ≥ than 10 mL in volume, required surgical intervention or was associated with clinical symptoms such as nausea and vomiting, focal neurological deficit or change in cognitive function.
Al Megren [21] Thromb Res. 2017	R	152	Glioma patients with VTE or cerebral vein thrombosis	Full anticoagulation with/without IVC filter with LMWH or unfractioned heparin or fondaparinux (76 pts)	No anticoagulation: glioma pts without VTE (76 pts)	11 months	ICH defined ad any bleeding into the cranial vault over the follow-up period.	NR
Khoury [22] Neurooncol Pract. 2016	R	173	Pts with glioblastoma and VTE with/without anticoagulation.	Total 97 pts: LMWH (69 pts), Warfarin (26 pts), Heparin (2 pts)	No treatment: 76 pts	6.1 months	Incidence of ICH	NR
Donato [3] Blood. 2015	R	293	Pts with brain metastasis on therapeutic enoxaparin for the	Enoxaparin 1 mg/Kg twice daily (76 pts), 1.5 mg/Kg once daily (17	189 controls: no anticoagulation.	NR	Measurable (greater than 1 mL in volume) ICH from initial diagnosis of brain	Larger volume bleeds (>10 mL), the presence of new symptoms or the need for

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			treatment of VTE.	pts) and modified dose-reduced therapeutic dosing (11 pts).			metastases.	surgical intervention.
Smith [23] J Clin Neurosci. 2015	R	69	Pts who underwent surgical resection of primary or metastatic brain tumor.	Full anticoagulation with warfarin, enoxaparin, heparin, dalteparin	Prophylactic doses of heparin or enoxaparin	NR	Determine the risk factors for VTE in patients who underwent neurosurgical resection of brain tumors.	NR
Yust-Katz [24] J Neurooncol. 2015	R	64	Pts with glioblastoma who developed a VTE during the course of their disease.	Anticoagulation alone in 36 patients (8 patients with Coumadin and 28 with LMWH)	2 pts had IVC filter alone and 21 pts received both an IVC filter and anticoagulation	NR	Estimate the frequency of VTE in gliobastoma pts and identify potential risk factors for the development of VTE during adjuvant chemotherapy.	NR
Chaichana [25] Neurol Res. 2013	R	126	Pts who underwent surgery for primary or metastatic brain tumors.	Total: 109 81 treated with heparin, 28 with enoxaparin	Total: 17 patients who had vena cava filters placed	NR	The incidence of peri-operative VTE and of treatment-related complication.	NR
Aishima [26] Br J Neurosurg. 2013	R	23	Pts who underwent surgery for primary or metastatic brain tumors.	Screening cohort with serum D-dimer level.	Non-screening cohort.	NR	The effectiveness and safety of screening strategy for the detection and prevention of VTE	NR
Alvarado [27] Melanoma Res. 2012	R	74	Pts with melanoma with brain metastasis and VTE.	Total: 57 patients Anticoagulation alone in 26 pts, 31 also IVC filter placement.	No coagulation in 17 pts: 13 had IVC filter, 4 only supportive measures.	3.4 months	Risk and benefits of systemic anticoagulation in these patients.	NR
Norden [4] J Neurooncol. 2011	R	282	Pts with glioma treated with bevacizumab and anticoagulants for VTE.	Total 64: Enoxaparin (49 pts). Dalteparin (1 pt). Fondaparinux (1 pt). Warfarin (13 pts).	218 pts treated without anticoagulation	NR	Hemorrhagic risk of concurrent use of bevacizumab and anticoagulants in glioma pts.	Any hemorrhage of grade 3 or greater
Pan [28] Anticancer Res. 2009	R	39	Pts with glioblastoma with VTE or ICH	Total:25 pts. 14 pts with IVC filter and anticoagulation, 11 pts with anticoagulation without IVC filter	Total: 14 pts. Pts with IVC filter without anticoagulation	NR	Incidence of initial and recurrent compared with the incidence of ICH in pts with GB.	NR
Nghiemphu [12] Neuro Oncol. 2008	R	265	Pts with gliomas who were treated concurrently with bevacizumab and anticoagulation for VTE	Total: 21 patients 9 pts on LMWH and 12 on warfarin	Total: 244 pts No anticoagulation	184 days	Incidence of major ICH.	ICH with severe neurological deficits

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Ghanim [29] J Thromb Thrombolysis. 2007	R	175	Patients with VTE and primary or metastatic brain tumors and/or brain hemorrhage	Anticoagulants (total 39 pts): Prophylactic dose (7 pts) or therapeutic dose (32 pts).	Vena cava filter (136 patients)	92 days	Mortality risk for VTE between pts treated with IVF and anticoagulants.	NR
Schiff [5] Cancer. 1994	R	42	Pts with brain metastases who experienced VTE	Total: 42 29 pts on iv heparin followed by warfarin 2 on iv heparin 2 with warfarin alone 7 with iv heparin and subcutaneous heparin 2 pts with iv heparin, subcutaneous heparin and warfarin.	IVC filters	88 days	The efficacy and complications of filters and anticoagulation.	NR
Quevedo [30] Mayo Clin Proc. 1994	R	16	Pts with primary brain tumors	Heparin followed by warfarin sodium	No anticoagulation	NR	The associations between VTE and factors related to the risk of occurrence of VTE.	NR
Altschuler [31] Neurosurgery. 1990	R	23	Pts with malignant glioma treated with anticoagulant therapy for VTE	Continuous iv heparin and an oral dose of 10 mg of warfarin	NR	NR	Safety and effectiveness of anticoagulation treatment of VTE	NR
Olin [32] Arch Intern Med. 1987	R	49	Pts with primary and secondary brain tumors with VTE	Total 25 pts: Iv heparin sodium at continuos infusion of 500 U/Kg once daily or warfarin (17 pts)	Total: 24 pts treated with inferior vena cava filter	NR	The complications and mortality between pts treated with inferior vena cava filter and anticoagulants	NR
Choucair [33] J Neurosurg. 1987	R	36	Pts with malignant gliomas with a score of 60% or greater on the Karnofsky performance scale who underwent intracranial surgery.	Total: 22 pts Iv heparin for 7-10 days followed by subcutaneous heparin (5000-8000 U twice daily) for at least 3 months or oral warfarin.	Total: 14 pts No anticoagulation	NR	Risk of ICH in pts with malignant gliomas, treated with anticoagulant for late postoperative thromboembolism	NR
Ruff [34] Ann Neurol. 1983	R	266	Pts with malignant astrocytoma or glioblastoma multiforme.	Total: 95 pts Iv heparin for 7-14 days, followed by warfarin for 6 to 14 weeks.	Total: 171 pts No anticoagulant.	96 weeks and group 2 for 36 weeks.	Incidence, prevention and treatment of VTE	NR

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Ruff [35] Trans Am Neurol Assoc. 1981	R	375	Pts with malignant astrocytomas	Total: 103 pts heparin followed by warfarin for 6 to 14 weeks.	Total: 272 pts No anticoagulation	NR	Incidence of VTE and the risk of systemic anticoagulation	NR

Abbreviations: *R*, retrospective; *Pts*, patients; *ICH*, intracerebral hemorrhage; *AT*, atrial fibrillation; *VTE*, venous thromboembolism; *DOAC*, direct oral anticoagulant; *LMWH*, low molecular weight heparin; *IVC filter*, inferior vena cava filter; *IVCF*, inferior vena cava filters; *GB*, glioblastoma; *Vs*, versus; *Iv*, intravenous; *NR*, not reported.

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Table 2. Rates of ICH, major and fatal ICH in patients with primary brain cancer or brain metastases

Outcomes	N° of studies	N° of ICH/ N° of patients	Rate	95% CI	I squared
Overall ICH	30	445/3,893	7.7%	5.1-11.5	92.8%
Major ICH	7	117/1,287	6.2%	2.8-13.0	91.5%
Fatal ICH	11	13/764	2.9%	1.7-4.7	0%
ICH in PBC patients	18	156/2,353	6.4%	4.1-9.9	84.4%
ICH in MBC patients	9	218/1,009	13.0%	6.5-24.2	93.7%
Major ICH in PBC patients	4	30/793	3.9%	1.3-11.6	87.6%
Major ICH in MBC patients	3	87/494	15.4%	9.4-24.2	74.6%
ICH in pts with VTE	25	384/3,313	7.1%	4.4-11.5	93.7%

Legend

ICH=intracranial hemorrhage; VTE: venous thromboembolism; PBC: primary brain cancer; MBC: metastatic brain cancer

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Table 3. Rates of ICH in patients with primary brain cancer or brain metastases treated or not with anticoagulants.

	N° of studies	N° of ICH/ N° of patients treated	Anticoagulant therapy %	N° of ICH/ N° of patients not treated	No anticoagulant therapy %	RR	95% CI	P-value	I^2
Overall patients	17	152/1,072	11.5% (95% CI 7.4-17.6)	177/1,824	6.0% (95% CI 3.0-11.5)	1.81	1.15-2.84	0.001	60.3%
Patients with PBC	11	80/659	12.5% (95% CI 8.0-18.8)	50/1,346	4.4% (95% CI 2.5-7.7)	2.58	1.59-4.19	<0.001	45.5%
Patients with MBC	4	61/265	14.7% (95% CI 4.4-39.2)	81/301	15.4% (95% CI 5.3-37.2)	0.86	0.45-1.65	0.287	0%
Patients treated with DOACs vs LMWH	5	12/172	8.3% (95% CI 4.4-15.3)	71/278	11.7% (95% CI 2.9-37.0)	0.44	0.25-0.79	0.007	0%
Patients treated with LMWH vs warfarin	4	15/211	5.9% (95% CI 1.5-20.5)	8/198	5.4% (95% CI 1.5-17.3)	1.45	0.56-3.79	0.185	0%
Overall major ICH	4	33/239	10.4% (95% CI 4.0-24.5)	47/734	3.4% (95% CI 0.6-17.6)	1.93	0.79-4.73	0.001	38.7%
Major ICH in patients with PBC	3	9/135	6.3% (95% CI 1.7-20.3)	9/545	1.8% (95% CI 0.9-3.4)	3.75	1.6-4.5	0.003	0%

Legend
ICH: intracranial hemorrhage
CI: confidence interval
RR: relative risk
PBC: primary brain cancer; MBC: metastatic brain cancer

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Figures legend

Figure 1. Risk of ICH in patients with primary or metastatic brain cancer treated or not with anticoagulant therapy

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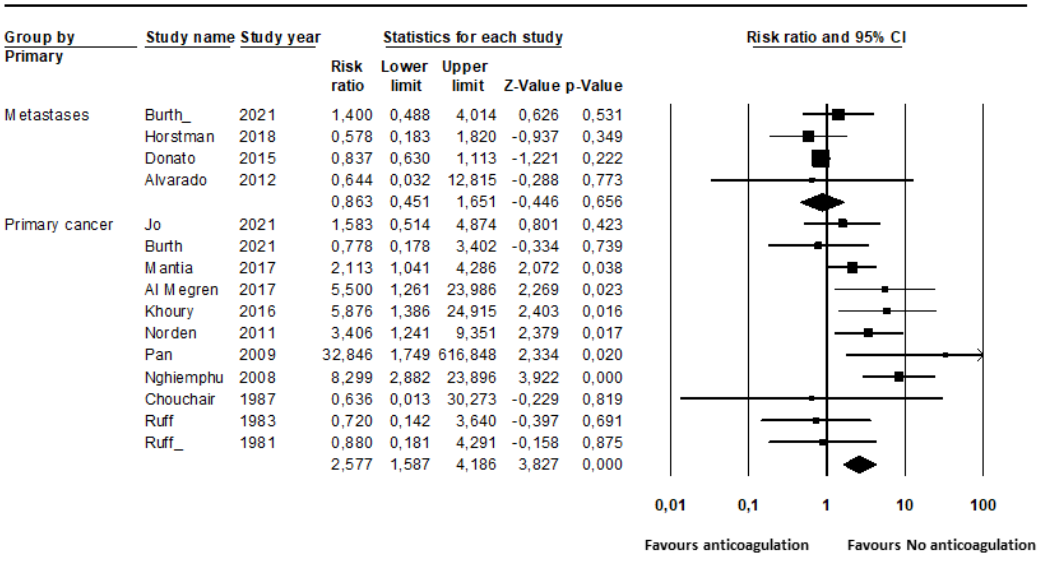
Figure 1



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