Location of metastasis and complications in patients with venous thromboembolism and cancer: systematic review

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ABSTRACT

According to current guidelines, patients with venous thromboembolism (VTE) and active cancer should receive prolonged anticoagulant treatment (>6 months). In patients with cancer-associated thrombosis (CAT), metastasis is a factor in recurrent VTE and bleeding; however, the function of metastasis location remains unclear. In order to assess the risk of complications (such as bleeding or recurrent VTE) based on the location of metastases in patients with CAT, we conducted a systematic review. The PubMed database search was used to perform a systematic review. MESH terms pertaining to metastasis, VTE, and neoplasms were employed. Patients with CAT who were at least eighteen years old and receiving therapeutic doses of anticoagulants were included, as were details regarding the locations of metastases and the availability of patients who had complications (bleeding or recurrent VTE). Among the 1,447 articles found by the search, 7 retrospective studies met all eligibility requirements and were added to the analysis. The majority of these studies addressed brain metastases. Studies found that intracranial hemorrhage occurred between 4% and 19% of the time. In the context of brain metastases and VTE, other studies examined the safety and effectiveness of direct oral anticoagulants in comparison to low-molecular-weight heparin. This systematic review draws attention to the paucity of data regarding the impact of metastasis location on complications in CAT patients. Further research is required to assess the effect of metastasis location on the risk of VTE complications in patients with CAT.

Introduction

Venous thromboembolism (VTE) that includes pulmonary embolism (PE) and deep vein thrombosis, is the second leading cause of death in cancer patients.[1] These patients have a 6 to 14-fold higher risk of developing VTE compared to patients without cancer,[2] and higher rates of recurrent VTE and bleeding complications during VTE treatment.[3]

Current clinical practice guidelines recommend at least 6 months of anticoagulant therapy in patients with cancer-associated thrombosis (CAT).[4-7] Beyond 6 months, the decision to discontinue or continue anticoagulation should be based on individual evaluation of the benefit-risk ratio, paying special attention to cancer activity (metastatic disease or oncological treatment).[4-7] Therefore, understanding the variables associated with complications in patients with CAT could be highly useful for decision-making in clinical practice.

The presence of metastasis has been described as a variable

associated with recurrent VTE and bleeding in patients with CAT. A systematic review of 10 studies (6 observational and 4 retrospectives), that included 4,791 patients with CAT, found a significantly higher risk of VTE recurrence in patients with metastasis [relative risk (RR): 1.4, 95% confidence interval (CI), 1.1-1.7; P=0.01].[8] In addition, the *post-hoc* analysis of the CLOT trial (comparison of low-molecular-weight-heparin *vs*. oral anticoagulant therapy for the prevention of recurrent venous thromboembolism in patients with cancer) observed that the risk of recurrent VTE was higher in patients with metastatic disease (P=0.018).[9,10] On the other hand, investigators of the *Registro Informatizado de la Enfermedad TromboEmbólica* (RIETE) registry performed a study that included 2,945 patients with CAT whom 1.0% had fatal bleeding during the first 3 months of anticoagulation therapy. Moreover, they observed that metastatic cancer was an independent risk factor for fatal bleeding [odds ratio (OR): 3.1, 95% CI, 1.4-7.1; P=0.006].[11] Furthermore, an analysis of the Caravaggio trial (Apixaban for the treatment of venous thromboembolism associated with cancer) that included 1,034 patients, showed that patients with metastatic cancer had numerically increased major bleedings compared to those with localized cancer [5.2%, hazard ratio (HR): 1.65, 95% CI, 0.7-3.8].[12]

Recent studies have shown that the rate of complications in patients with CAT varies based on the location of the primary tumor. However, the rates of recurrent VTE and bleeding according to the location of metastasis are unclear. Therefore, we performed a systematic review to evaluate the risk of complications (recurrent VTE or bleeding) according to the location of metastasis in patients with CAT.

Materials and Methods

To find an answer to the raised issue, we formulated the following PICO question: population (patients with CAT), intervention (anticoagulant treatment), comparison (patients with CAT without metastasis or with metastasis in other locations), and outcomes (bleeding and recurrent VTE). We performed a search in the PubMed database on 24th September 2023. The following MESH terms were used to search original articles, reviews, and guidelines: Neoplasms[mesh] OR neoplas*[tiab] OR cancer[tiab] OR malign*[tiab] OR tumor [tiab] OR tumour [tiab]) AND Venous Thromboembolism[Mesh] OR venous thromboem*[tiab] OR Venous Thrombosis[Mesh] OR venous thrombosis[tiab] OR deep vein thrombosis[tiab] OR deep venous thrombosis OR Pulmonary Embolism[Mesh] OR pulmonary embolism[tiab])) AND (Metastasis[mesh] OR metasas*[tiab] OR mestastatic*[tiab] (Table 1 shows the search strategy). There were no restrictions for year of publication or language. The references of the different articles included were examined to identify other articles of interest.

Two reviewers (MBH and VGG) independently assessed the eligibility of studies using a data extraction form. Study selection was initially performed by review of titles, subsequently, selected abstracts and finally full texts were reviewed. Discrepancies between reviewers were resolved by a third reviewer (LJP).

Study selection

Inclusion criteria were: i) patients aged ≥18 years with CAT that received anticoagulant treatment; ii) information about location of metastasis; iii) availability of the number of patients who experienced complications (recurrent VTE or bleeding). Case reports and case series with <3 patients and studies not involving humans were excluded.

Study objective

The objective of this systematic review was to evaluate the risk of complications (recurrent VTE or bleeding) according to the location of metastasis in patients with CAT. Active cancer was defined as any cancer diagnosed within the previous six months, recurrent, regionally advanced or metastatic cancer, cancer for which treatment had been administered within six months, or hematological cancer that is not in complete remission.[13] VTE was accepted as any objectively confirmed symptomatic or incidental thrombosis event, except superficial vein thrombosis. Complications were defined such as recurrent VTE or bleeding. Recurrent VTE was defined as objectively confirmed symptomatic or incidental VTE by imaging with evidence of thrombus progression or involvement of the thrombus in another region. Bleeding was evaluated according to the criteria of the International Society on Thrombosis and Hemostasis.[14]

Results

The PubMed database and manual search of references in included articles provided a total of 1,447 articles. After a review of titles, 1,396 articles were excluded because they did not meet the inclusion criteria. After reviewing 51 abstracts, 24 possible valid articles were identified. Finally, after a full-text assessment,

Table 1. Search strategy.

1	Neoplasms[mesh] OR neoplas*[tiab] OR cancer[tiab] OR malign*[tiab] OR tumor[tiab] OR tumour[tiab] (n=5,036,885)
2	Venous thromboembolism[Mesh] OR venous thromboem*[tiab] OR venous thrombosis[Mesh] OR venous thrombosis[tiab] OR deep vein thrombosis[tiab] OR deep venous thrombosis OR pulmonary embolism[Mesh] OR pulmonary embolism[tiab] (n=159,865)
3	Metastasis[mesh] OR metasas*[tiab] OR mestastatic*[tiab] (n=222,545)
4	"Infant"[Mesh] OR "infant"[MeSH Terms:noexp] OR "child"[MeSH Terms] OR "child"[MeSH Terms:noexp] OR infant, newborn[Mesh] OR child, preschool[Mesh] (n=2,806,435)
5	Animals[mh] NOT humans[mh] (n=5,174, 295)
6	4 OR 5
7	1 AND 2 AND 3 NOT 6 (n=1,440)

7 articles were included in the systematic review. All of them were retrospective studies. Figure 1 shows the study flow diagram. The characteristics of the studies included are specified in Table 2.

Schiff *et al*. observed that 7% of 51 patients with brain metastases and VTE developed symptomatic intracranial hemorrhage (ICH) and 7% an asymptomatic ICH.[15] Alvarado *et al*. found that the incidence of ICH in a cohort of 74 patients with melanoma with brain metastases and VTE who received anticoagulant treatment was 4%.[16] Moreover, they observed that the number of brain metastasis correlated with survival from VTE among the patients receiving systemic anticoagulation (2.6 months for 1-4 brain metastasis *vs*. 5.9 months for >4 brain metastases, P<0.0001).[16] In 2015, Donato *et al.*, matched 293 patients with VTE and brain metastasis (104 with enoxaparin at therapeutic doses and 189 controls) in a retrospective study.[17] The cumulative incidence of ICH at 1 year was 19% in the enoxaparin cohort and 21% in the control cohort (HR 1.02, 90% CI 0.66-1.59).[17] They concluded that patients with brain metastasis had a high incidence of spontaneous intracranial bleeding, and that this risk was not increased by anticoagulation. The risk for ICH was four-fold higher in patients with melanoma or renal cell carcinoma compared with those with lung cancer (adjusted HR 3.98, 90% CI 2.41-6.57; P<0.001).[17] In 2017, Chai-Adisaksopha *et al*. performed a retrospective study matching patients with primary brain tumor versus brain metastasis on low-molecular-weight heparin (LMWH) treatment for more than four weeks for VTE. The incidence rate of recurrent VTE was similar in both groups (11.0% in patients with brain tumors and 13.5% in brain metastasis). However, the incidence of major bleeding was 8.6% (95% CI, 4.8-14.7) in patients with primary brain tumor and 5.0% (95% CI 2.8-9.2) in patients with brain metastasis. In addition, rate of ICH was higher in brain tumor patients (4.4% *vs.* 0%, P=0.004).[18] In 2019, a retrospective study analyzed, in patients with brain tumors and venous thromboembolism (n=105), the cumulative incidence of ICH with direct oral anticoagulants (DOACs) compared with LMWH. Compared with LMWH, DOACs did not increase the risk of any ICH.[19] A retrospective study of 96 patients evaluated the incidence of ICH in patients with brain metastasis receiving DOACs (n=41) or LMWH (n=55) for VTE or atrial fibrillation, showed that the 12-month cumulative incidence of ICH in the DOAC group was 10.1% compared with 12.9% in LMWH group (HR: 0.77, 95% CI, 0.23-2.59).[20] Likewise, Lee *et al*. evaluated, in a retrospective study, the safety and efficacy of DOACs and LMWH for CAT in patients with primary brain tumor or brain metastasis.[21] In the brain metastasis cohort (n=85), the incidence of recurrent VTE events was 4.9% in DOAC group and 4.5% in LMWH group. However, the incidence of ICH was 4.9% and 2.3% with DOACs and LMWH, respectively.[21]

Discussion and future research

This systematic review shows that patients with brain metastasis and VTE present a high incidence of ICH during anticoagulant treatment. However, these studies did not evaluate the risk of ICH in patients with brain metastasis. Hunter *et al*. in a meta-analysis that included 4 of the 7 previously discussed studies, showed that there was no higher risk of ICH under anticoagula-

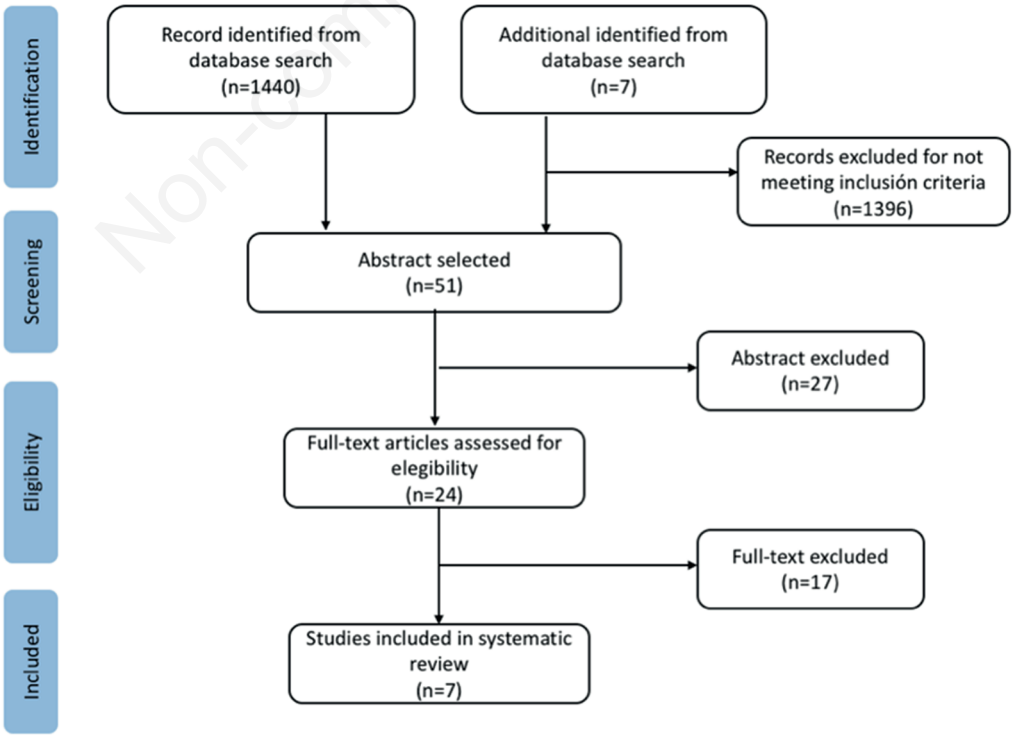

Figure 1. Flow diagram.

tion in patients with brain metastasis and VTE (OR 1.37, 95% CI, 0.86-2.1; P=0.18).[22] The meta-analysis by Zwicker *et al*. that evaluated whether therapeutic anticoagulation is associated with an increased risk of ICH in patients with brain tumors, observed that there was no statistically increased risk of ICH in patients with brain metastasis treated with anticoagulation compared with no anticoagulation (OR 1.07, 95% CI 0.61-1.88; P=0.81; I^2=0%).[23] A recent meta-analysis that evaluated ICH in primary or metastatic brain cancer patients with or without anticoagulant treatment, demonstrated that the risk of ICH was significantly higher in patients with metastatic brain cancer than in patients with primary brain cancer (RR 3.26, 95% CI 2.69-3.94; I^2=92.8%), although we need to be cautious with these findings due to quality of the studies and high heterogeneity.[24] On the other hand, in patients with metastatic brain cancer, anticoagulant therapy was not associated with an increased rate of ICH (RR 0.86, 95% CI 0.45-1.65; P=0.287).[24]

The presence of metastasis has been described as a variable associated with bleeding and recurrent VTE in patients with CAT. Cohen *et al*. provided a model to predict the risk of bleeding in patients with CAT and observed that the presence of metastasis was an independent predictor of significant bleeding.[25] Furthermore, an analysis of RIETE registry that included 2,945 patients with CAT in whom 1.0% had fatal bleeding during the first 3 months of anticoagulation therapy, showed that the presence of metastasis was an independent risk factor for fatal bleeding (OR 3.1, 95% CI 1.4-7.1; P=0.006).[11] Moreover, metastatic cancer was independently associated with an increased risk for fatal PE (OR 2.9; 95% CI 1.8-4.8; P<0.001).[11] On the other hand, a retrospective study that evaluated the risk factors of recurrent VTE after discontinuation of anticoagulation in 311 patients with CAT, found that the presence of metastasis was associated with a higher risk of recurrent VTE (sub-distribution hazard ratio: 3.8, 95% CI 1.54-

Table 2. Main clinical features of the studies included.

Author (year)	Study design	Sample size BM	Outcome	Complications	RR to complications (95% CI)
Schiff (1994)[17]	R	51	The efficacy and complications of IVC filters and anticoagulation in patients with brain metastases and VTE	IVC filter, ICH: 40% Anticoagulation: - Symptomatic ICH: 7% - Asymptomatic ICH: 7% - Global bleeding: 19%	NR
Alvarado (2012)[18]	R	74	The relative risk and benefits of systemic anticoagulation in patients with brain metastasis from melanoma and VTE	ICH: 4%	NR
Donato (2015)[19]	R	293	The risk for ICH associated with the administration of therapeutic doses of LMWH in patients with brain metastases	Cumulative incidence of ICH at 1 year: 19% LMWH	NR
Chai-Adisaksopha (2017)[20]	R	115	The effectiveness and safety of extended duration LMWH in adult patients with primary brain tumor *vs* metastatic intracranial tumors	- ICH=4.5% - Major bleeding: 8.6% (4.8-14.7%) - Clinically relevant bleeding: 12.4% (7.8-19.7%) - Recurrent VTE: 11% (6.7-17.9%)	NR
Carney (2019)[21]	R	105	The cumulative incidence of ICH in DOACs compared with LMWH in patients with brain metastases and VTE	12-month cumulative incidence ICH: - DOAC group: 27.8% - LMWH: 52.9%	NR
Leader (2020)[22]	R	96	The incidence of ICH in patients with brain metastases receiving DOACs (n=41) or LMWH (n=55) for VTE or AF	12-month cumulative incidence ICH: - DOAC group: 10.1% - LMWH: 12.9%	NR
Lee (2021)[23]	R	85	The safety and efficacy of DOACs in comparison with LMWH for cancer-associated VTE in patients with primary brain tumor or brain metastases	ICH: - DOAC group: 4.9% - LMWH: 2.3% Systemic bleeding: - DOAC group: 17.1% - LMWH: 20.4% Recurrent VTE: - DOAC group: 4.9% - LMWH: 4.5%	NR

RR, relative risk; CI, confidence interval; IVC, inferior vena cava; VTE, venous thromboembolism; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; DOACs, direct oral anticoagulants; AF, atrial fibrillation.

9.52; P=0.0039).[26] Likewise, a systematic review of 10 studies (6 observational and 4 retrospectives) that included 4,791 patients with CAT found a significantly higher risk of VTE recurrence in patients with metastasis (RR 1.4, 95% CI 1.1-1.7; P=0.01).[8]

This work has several limitations. First, the search was performed in a single database which increases the risk of excluding relevant studies that may be indexed in other databases. This may introduce a selection bias in the review process. However, previous studies conclude that searching only one database can be sufficient as searching other databases has no effect on the outcome.[27,28] Second, publication bias was not analyzed but we only found publications related to brain metastases and not in other locations, so we were unable to conduct such an analysis in our study. Third, all available studies were observational and retrospective. In addition, the sample sizes of these studies were limited, and may not be representative of the population. Finally, all included studies that collected information about metastasis location were focused on brain metastasis, without considering other locations.

Interestingly, there are previous studies that have evaluated the risk of VTE in cancer patients according to the location of the metastasis. In a cross-sectional analysis of data from the Nationwide Inpatients Sample database that included 850,570 patients with metastatic cancer, 6.6% developed a VTE.[29] Patients with metastasis to adrenal glands, liver, brain, lung and bone had an increased risk of developing VTE, while those with metastasis to genital organs and lymph nodes had a lower risk.[29] In addition, patients with multiple metastasis (≥2 locations) had a higher risk of VTE compared with patients with single metastasis (OR 1.09, 95% CI 1.05-1.13; P=0.001).[29] Nevertheless, these findings contrast with those observed in other works. Conteduca *et al*. performed a prospective biomarker analysis to evaluate the association between plasma tumor DNA fraction and risk of VTE in 180 patients with metastatic castration-resistant prostate cancer (mCRPC) and observed a cumulative incidence at 12 months of VTE of 17.1% (95% CI 10.3-23.9).[30] In the multivariable analysis, the presence of metastases in the liver (HR 2.22, 95% CI 0.25-19.28; P=0.470) and in the lung (HR 2.57, 95% CI 0.70-9.42; P=0.153) and number of metastasis (>7) (HR 0.73, 95% CI 0.24-2.22; P=0.584) were not associated with an increased risk of VTE.[30] However, the sample size of the study was small, and it included a group of highly selected patients that may not be representative of real clinical practice. Therefore, future studies are needed to evaluate the impact of metastasis location on the risk of VTE.

Conclusions

This systematic review highlights the lack of evidence on the role of metastasis location in complications in patients with CAT. Recent studies postulate that patients with brain metastases appear to have an elevated risk of ICH. Our work has identified a gap for future studies to analyze the risk of complications of VTE according to the location of the metastasis in patients with CAT. Future studies are needed to evaluate the impact of the location of metastasis on the risk of complications of VTE in patients with CAT. It may be relevant for the management of anticoagulant treatment in these patients.

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