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Venous Thromboembolism in Patients with Cancer Receiving Specialist Palliative Care

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Abstract

Context: The prevalence of venous thromboembolism (VTE) in patients with cancer is particularly high at disease progression and during relapse. Patients cared for in specialized palliative care units (SPCU) are rarely included in VTE studies. Objective: We sought to study the prevalence, clinical characteristics, and survival of individuals with VTE in an SPCU setting.

Methods: We retrospectively included 2707 consecutive individuals with active cancer managed at a SPCU. Data were summarized using descriptive statistics and frequency for categorical variables. Overall survival was estimated by Kaplan-Meier and comparisons by log-rank test. Thrombotic events were confirmed by imaging.

Results: We studied 1984(73.3%) women and 723 (26.7%) men. The overall prevalence of thrombosis was 22.2% with only 6.2% occurring after initiating SPCU care, and was higher in women (24.6% vs 15.8%), particularly with gynecological tumors (cervical: 30.5%, ovarian: 29.2%). Median survival was slightly longer for patients without VTE (80 days [IQR21-334] and 69 days [IQR 25-235]; $p = 0.03$).

Conclusions: Prevalence of VTE was high and varied by tumor origin. VTE may impact survival. Though median survival is short, some patients are followed over months, suggesting that in the absence of high bleeding risk, treatment for thrombosis in an attempt to decrease the morbidity of re-thrombosis should be considered. On the other hand, few patients developed symptomatic VTE during SPCU care, making generalized primary prophylaxis probably unwarranted. Customizing anticoagulation for the risk of hemorrhage and physical performance is essential.

Keywords
cancer, thrombosis, palliative care

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Introduction

Venous thromboembolism (VTE) is most prevalent both during the initial months after cancer diagnosis and at the time of relapse, and is the cause of mortality in close to ten percent of individuals with solid tumors.[1,2] The incidence varies widely with frequently coexisting factors that either increase or decrease the risk of thrombosis, the main prothrombotic factor being metastatic disease.[1–4] Symptomatic thrombosis causes pain, often severe disability, deterioration of wellbeing, loss of independence, and anguish, all of which pose added burdens to both patients and their families particularly in the palliative care setting.[5,6] We sought to determine the prevalence and impact on survival of VTE in individuals with cancer seen in a Specialized Palliative Care Unit (SPCU), as well as the incidence of a first VTE event during the course of SPCU care. The populations of patients seen in oncology SPCU´s

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are by no means homogeneous with different tumor origins, diverse complications, comorbidities, bleeding risks, performance status, and personal as well as family views and expectations. Thrombosis and the need for treatment add to the morbidity in this stage of life, and defining its prevalence for different tumor types may help guide decisions on prevention and treatment of established thrombosis.

Material and Methods

We retrospectively studied consecutive patients with advanced stage active cancer seen at our SPCU between 2012−2020. Active cancer was defined as measurable, locally advanced or metastatic disease, corroborated by imaging studies. Demographic, clinical information, and tumor characteristics were obtained via retrospective medical record review. Patients with symptoms or signs suggestive of VTE are routinely sent for same day compression Doppler ultrasound or chest computed tomography (CT). When thrombosis is confirmed, patients are routinely cared for by the Cancer and Thrombosis Service and started on low molecular weight heparin for 5−10 days and acenocumarin for a target INR range of 2-3. Most patients as of 2020 have been changed to direct oral inhibitors (apixaban or rivaroxaban). Anticoagulation is routinely continued as long as there is persistence of risk factors for thrombosis, bleeding risk remains low, and there is no active bleeding. Anticoagulation is stopped during end-of-life care. For this study, imaging studies were reviewed for confirmation of venous thrombosis. Patients receive primary low molecular weight heparin prophylaxis only during periods of hospitalization, but not extended prophylaxis at discharge. Palliative care is given through hospital as well as home care visits by the Palliative Care Team; patients also have access to telephone contact through a call center. Information for all consultations is included in the hospital electronic chart.

Informed consent was waived for our ethics and research committee due to the retrospective nature of the study (Rev/007/20).

Statistics

Descriptive statistics were used to summarize patients´ characteristics, including medians, interquartile ranges (IQR), frequencies, and percentages. Overall survival was estimated by the Kaplan-Meier method, and statistical comparisons made via the log-rank test. Stata version 12 was used for analysis (StataCorp 2011 Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.).

Results

A total of 2707 patients were cared for over a nine-year period including 1984 (73.3%) women and 723 (26.7%) men, with an overall median age of 56 years (IQR 45−65). There was no difference in median age between patients with or without VTE. All but 22 patients were followed for at least one month in the SPCU. 468 patients were either lost to follow up or returned for care to their respective states outside of Mexico City. The sites of tumor origin by frequency were: breast (611, 22.6%), cervical (452, 16.7%), stomach (398, 14.7%), colorectal (385, 14.2%), ovarian (288, 10.6%), lung (246, 9.1%), sarcoma (224, 8.3%) and testicular (103, 3.8%). We found that 602 (22.2%) patients developed VTE at any time point after their initial diagnosis, with a higher prevalence in women 488 (24.6%) than men 114 (15.8%). Of the entire population, 8.4% and 7.6% had a history of VTE occurring more than three months or within three months prior to their first SPCU visit, respectively, and 6.2% of patients developed VTE during follow-up in palliative care (Table 1). VTE diagnosis was confirmed by Doppler ultrasound or CT scan in all patients with symptomatic VTE with 71.3% occurring in the lower extremities, 17.1% upper extremities, and 11.3% with vena cava thrombosis alone or in addition to VTE at other sites. The prevalence of VTE varied based on tumor origin and was particularly high for gynecological tumors (Figure 1).

Table 1. Characteristics of Venous Thromboembolic Events.

Clinical Characteristics	n	%
Time period of VTE[a] occurrence	602/2707	22.2
Historical VTE ≥ 3 months prior to SPCU care	229/2707	8.4
Acute VTE within 3 months prior to first SPCU[b] visit.	206/2707	7.6
Thrombosis during SPCU[b] follow up	167/2707	6.2
Site of VTE		
-Lower extremity	429/602	71.3
- Upper extremity	103/602	17.1
- Other	68/602	11.3
-Not available	2/602	0.3

[a]*VTE: Venous thromboembolism*
[b]*SPCU: Specialized Palliative Care Unit*

Median follow up was 1003 days (IQR 347−2795). Patients who developed thrombosis prior to starting care in the SPCU had a median survival of 69 days (25−235) as compared to those without VTE 80 days (21−334), ($p = 0.03$). The overall survival in patients without or with VTE at 3, 6, and 12 months was 48.2%, 34.2%, and 23.4%, compared to 42.6%, 25.1%, and 15%, respectively (Figure 2). When survival was studied based on the period of time when the patients developed VTE, the median survival in days was 76 (27−167) for those with ≥3 months from initiation of palliative care, 38 (12−103) days for patients developing VTE within the prior 3 months of the first SPCU visit, and 237 (96−420) when thrombosis occurred while patients were being followed in SPCU. Survival times varied according to tumor origin, and for most tumor types VTE was a marker of shorter survival as compared to individuals without VTE: breast (84 vs 76 days), colo-rectal (76 vs 108 days), cervical (69 vs 77 days), stomach (46 vs 47 days), ovary (39 vs 150 days), lung (39 vs 76 days) and sarcoma (46 vs 119 days) (Figure 3).

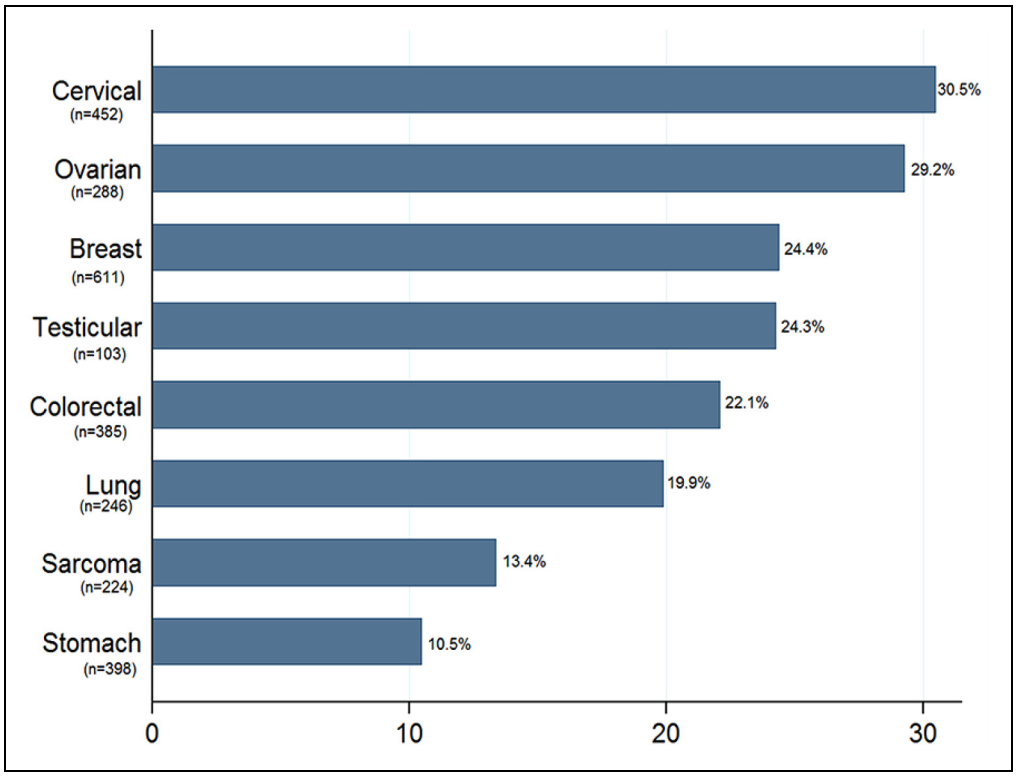

Figure 1. Prevalence of VTE according to oncological diagnosis. Estimated frequency of VTE in the National Cancer Institute: all patients are included

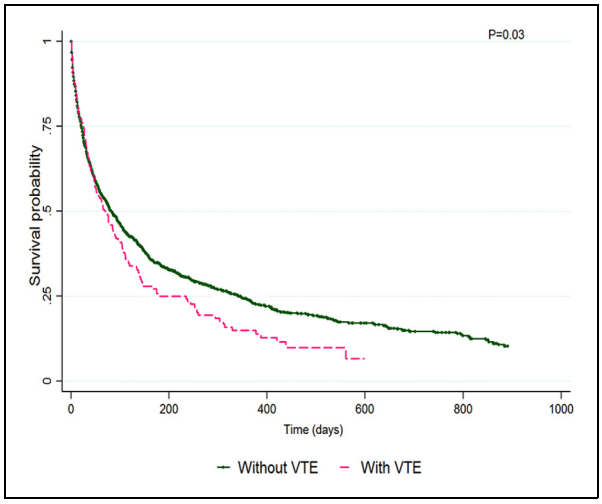

Figure 2. Overall survival effect of venous thromboembolism occurring at any time point after cancer diagnosis. Estimated survival evaluated from the first consultation in the National Cancer Institute: all patients with and without VTE are included independently of the time of VTE occurrence after the initial diagnosis of cancer.

Discussion

People with cancer who are treated in a palliative care setting do not represent a homogenous population in many respects, including history of VTE. Palliative care should be distinguished from end-of-life care, since the former may include individuals undergoing treatment with curative intent, some with month or year-long survivals with relatively good quality of life. Little is known about the prevalence of VTE according to tumor origin among patients with cancer who are receiving specialist palliative care services. We present retrospective data from 2707 consecutive individuals followed in a single center.

The prevalence of symptomatic VTE varied depending on tumor type and affected a high proportion of patients cared for in the SPCU. Large studies report a prevalence of VTE of 3.9% in a heterogeneous group of patients during the first 6 months from cancer diagnosis[7] with rates of VTE varying widely by tumor origin in different series.[8] Notably, the rates of VTE in our patients nearly triples that observed in patients undergoing initial treatment for tumors such as cervical cancer in whom we see a rate of thrombosis of 9.7% of 308 consecutive patients with locally advanced cervical cancer followed for a median of 9 months (unpublished results). The low rate of VTE during follow-up in palliative care suggests that generalized primary prophylaxis in our patients is probably not warranted. In addition, therapeutic anticoagulation during palliative care may cause bleeding, though the risk varies by type of anticoagulant and underlying disease.[9] In a recent prospective study of 22 SPCUs from France, the reported incidence of clinically relevant bleeding plus clinically relevant nonmajor bleeding at 3 months was 9.8% (95% CI 8.3−11.6).[10]

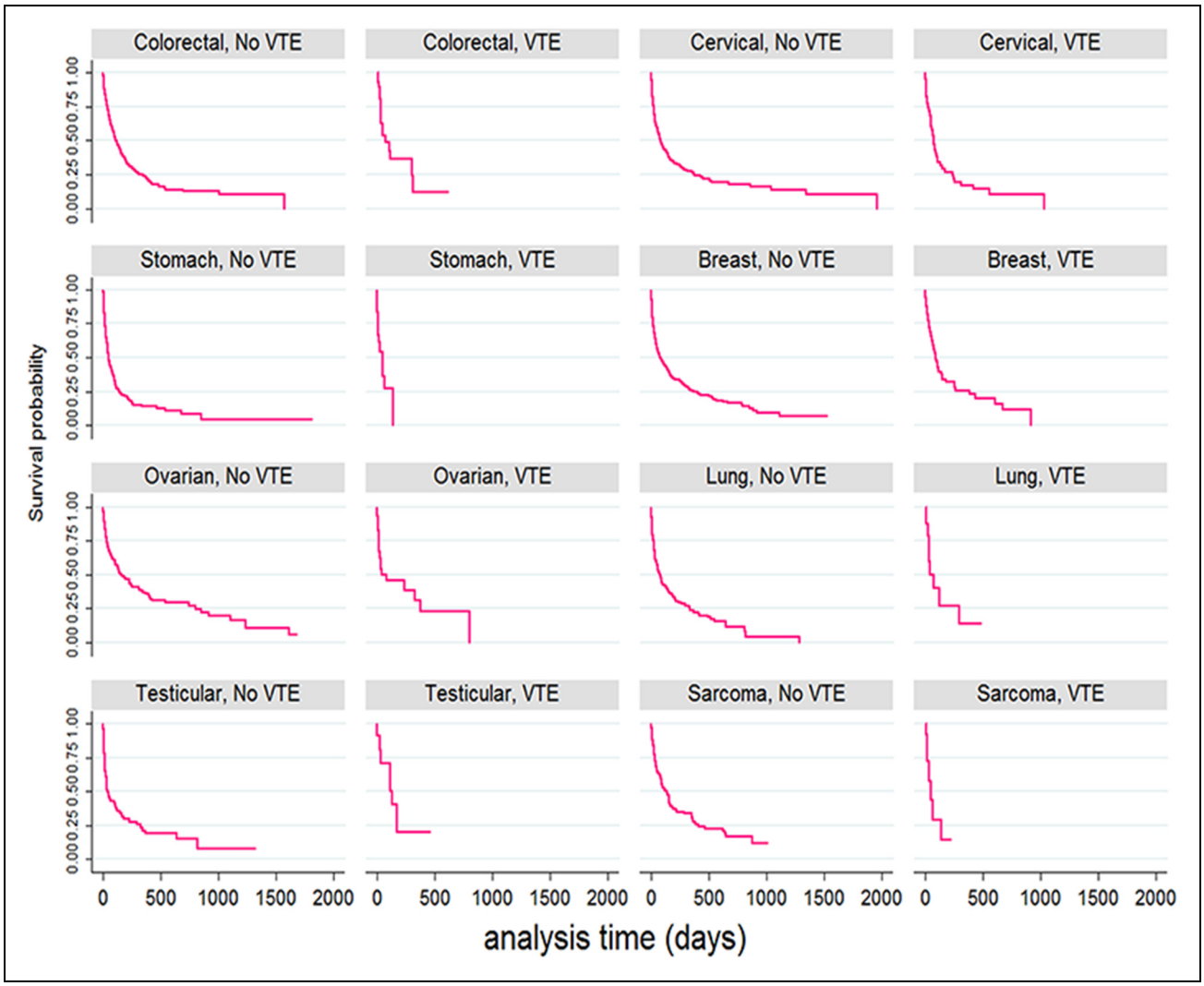

Figure 3. Overall Survival according to tumor origin. Survival was estimated from the first visit to the SPCU.

For patients receiving palliative care, expert opinion-based guidelines suggest considering pharmacological VTE prophylaxis with low-molecular-weight heparins (LMWH) taking into account conventional thrombotic and bleeding risk factors, life expectancy, and patient preferences.[11] We agree with reports showing that the use of injections poses an additional practical and economic burden in this setting, a fact that should be considered if parenteral anticoagulation is proposed.[10] We use therapeutic anticoagulation in patients with corroborated VTE who are in the SPCU, but not during terminal care, since as reported it is likely that treatment of established VTE, and prevention of recurrence, decreases symptoms[1] as shown in a prospective study in which all patients treated with LMWH for a new diagnosis of symptomatic DVT were noted to have symptomatic improvement.[12]

It is important to note that patients receiving specialist palliative care are frequently followed for several months, and in these patients, anticoagulation for established VTE should be considered. For patients with or without cancer having documented VTE anticoagulation is given in order to reduce mortality, morbidity, and recurrence, thus withholding treatment for documented VTE should only be considered in people with active bleeding or during end-of-life care.[13–15] We found decreased survival in patients with VTE which is consistent with other reports, highlighting VTE as a hallmark of poor prognosis in people with cancer.[16] However, the retrospective nature of our study, with evident heterogeneity between patients and diseases, may underestimate the rate of new or recurrent VTE as well as of relevant bleeding. Another limitation to the study is that only the most common sites of tumor origin were included, such as patients with pancreatic cancer in whom the risk of thrombosis is particularly high. The risks and benefits of treating patients in SPCU with direct oral anti-factor Xa anticoagulants, which have been recently accepted as front line treatment for patients with cancer, can only be determined in a prospective study.

Conclusions

The prevalence of symptomatic VTE in patients with cancer referred to SPCU is high, varying by tumor origin. However,

the risk of symptomatic thrombosis during SPCU care is low, suggesting that generalized prophylactic anticoagulation is not warranted. Up to a fourth of patients with VTE in PC are alive at 6 months, thus non-terminally ill patients should be evaluated and offered therapeutic anticoagulation to reduce the morbidity of recurrent thrombosis in the absence of an absolute contraindication.

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Data Research and Sharing

The database will be available upon request.

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Declaration of Conflicting Interests

T.W.L. reports the following disclosures from the past 24 months: personal fees for consulting or advisory boards from AbbVie, Agios, AstraZeneca, Amgen, Astellas, CareVive, BMS/Celgene, Daiichi-Sankyo, Heron, Flatiron, Pfizer, and Seattle Genetics; royalties from UpToDate; speakers bureau fees from Agios, AbbVie, and BMS/Celgene; grants and/or research contracts from the American Cancer Society, AstraZeneca, BMS, Jazz Pharmaceuticals, the NINR / NIH, and Seattle Genetics.

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Ethics and Patient Consent

Informed consent was waived for ethics and research committee due to the retrospective nature of our study (Rev/007/20).

Declaration of Conflicting Interests

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