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Venous thromboembolism after surgical treatment of non-spinal skeletal metastases — An underdiagnosed complication

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ABSTRACT

Introduction and aim: Venous thromboembolism (VTE) is a severe complication associated both with major orthopaedic surgery and cancer. However, survival and postoperative complications of skeletal metastases despite their thrombogenic potential, have received little attention in both the clinical management and research setting. This single-centre observational cohort study aimed to evaluate the incidence and impact of VTE in association with cancer surgery targeted to the management of fractures secondary to skeletal metastases.
Methods: Data were collected retrospectively from the medical database. We included consecutive 306 patients operated for 343 non-spinal skeletal metastases during a 15-year period (1999–2014).
The incidence of VTE and its risk factors were assessed using binary logistic regression analysis. Kaplan–Meier and Cox regression analyses were used to evaluate variables affecting survival.
Results: The rate of symptomatic VTE was 10% (30/306) during the 3-month postoperative period, while 79% received thromboprophylaxis. Fatal pulmonary embolism (PE) rate was high, 3.3% (10/306) after surgery. Intraoperative oxygen saturation drop, pulmonary metastases and intramedullary nailing were independent risk factors for VTE. Indicators of decreased survival were lung cancer, intramedullary nailing, multiple skeletal and pulmonary metastases, anaemia, leukocytosis, and PE.
Conclusion: Relationship between fractures secondary to skeletal metastases and VTE needs further clinical attention. Whether the survival of patients with fractures secondary to skeletal metastases can be improved by targeted thromboprophylactic means should be studied further.

1. Introduction

Cancer is a well-known risk factor for venous thromboembolism (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism (PE). It is estimated that the overall risk of a VTE is increased seven-fold in patients with a malignancy compared with those without malignancy [1]. In patients with cancer, each of the three components of Virchow's triad (blood composition, vessel wall components and blood flow) represents abnormalities that predispose to thrombus formation. Additionally, abnormal angiogenesis is involved in tumour growth, resulting in a prothrombotic state [2]. Several other risk factors for VTE in cancer patients have been reported, including a history of VTE, female gender, older age, leukocytosis, and thrombocytosis [3,4]. Patients who are treated with chemotherapy or have metastatic disease have additional risks for VTE [1,2]. Patients with distant metastases and those undergoing chemotherapy are reported to have a two-fold increased risk compared with those without metastases or not undergoing chemotherapy [1]. One survey found that 5–10% of patients with breast cancer undergoing adjuvant chemotherapy and up to 15% of those with metastatic disease had VTE [5]. Different models for predicting chemotherapy-associated VTE have been developed. One model, the Khorana score, includes the following variables: site of cancer, platelet count, haemoglobin, leukocyte count, and BMI [6].

Trauma and orthopaedic surgery are also well-known risk factors for VTE [7,8]. However, the reported symptomatic VTEs have been few, as during the 90 days after the primary total hip arthroplasty symptomatic DVT occurs in 0.7% and PE in 0.3% of the patients. [9] In one large study including 199,952 patients with pelvic and lower-extremity fracture symptomatic PE was identified only in 0.5% of patients. [10] Cancer surgery seems to significantly increase the risk of postoperative VTE, as well as risk of fatal PE when compared to similar procedures in non-cancer patients (0.33% vs. 0.09%) [11]. Moreover, both cancer and trauma and their management may otherwise contribute to the prothrombotic state, including bed rest, infection, and certain chemotherapies.

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VTE is a severe complication in all hospitalized patients [4]. In a population-based study matched for type of cancer, sex, age, and the year of diagnosis, the 1-year survival of patients diagnosed with VTE and malignancy was 12% compared with those patients without VTE, whose survival rate was three-fold higher [12]. Mortality rates are three times higher in the first 6 months after VTE in patients with cancer than in those without cancer [13]. A necropsy study revealed that 10% (648 of 6197) of patients who died of cancer had PE [14]. After major surgery as much as 10–40% of the deaths were related to PE. [15].

Even though a number of studies have shown the importance of VTE after orthopaedic surgery and disseminated cancer, little attention has been given to the incidence of thrombosis in patients after pathological fractures secondary to skeletal metastases. Therefore, the aim of this observational study was to determine (1) the incidence and impact of symptomatic VTE postoperatively, (2) the risk factors for VTE, (3) whether the Khorana score itself or its haematological elements separately could predict VTE in this surgical patient cohort, and (4) risk factors for decreased survival after operation.

2. Patients and methods

Patients for this observational cohort study were identified from a prospectively maintained database in one referral centre. All consecutive patients, included in the study were treated surgically for non-spinal skeletal metastases, in the vast majority due to pathological fractures, between the 1st of April 1999 and the 31st of July 2014. The institutional ethical review board approved the study. Data were retrospectively collected from the medical records. All patients had metastatic stage IV cancer and all the patients were living independently before surgery. Patients whose survival was estimated to be less than four weeks were not operated. Surgical procedures included osteosynthesis with plate, intramedullary nailing with or without cementing, total arthroplasty, endoprosthetic replacement and Harrington procedure.

Symptomatic DVT was identified by ultrasound scan of lower extremities and PE was diagnosed with computer tomography or autopsy. Data regarding deaths were verified from death certificates or autopsy reports at our institution. Data of patients who died outside the hospital were obtained from Statistics Finland, which is the exclusive Finnish public authority holding data regarding causes of death and post mortem death certificates. Unfortunately, the mortality data are routinely updated 1 year later, thereby underestimating the true rate of occurrence towards the end of the study.

In year 2004 the national guidelines for postoperative thromboprophylaxis were introduced. After this recommendation all major orthopaedic patients had postoperative prophylaxis, enoxaparin 40 mg or dalteparin 5000 IU started 6–12 h postoperatively continuing on once daily basis, unless a bleeding complication or major bleeding risk ensued. No mechanical prophylaxis was used. Surgical techniques and operating times have remained stable in this 15-year period.

2.1. Statistical analysis

Univariate analysis was performed for risk factors of VTE. The chi-square test or Fisher's exact test in the case of proportions and by the *t*-test in the case of continuous variables was used. Using multivariable analysis with binary logistic regression we assessed independent risk factors for VTE and PE. Survival was assessed using the Kaplan-Meier method with a log-rank test for univariate analysis while Cox regression analysis was used to identify independent factors affecting patient survival. In survival analyses we censored patients still alive at the time of study and patients who died for other reasons than cancer. The following variables were evaluated: gender, age, primary diagnosis, number of skeletal metastases (solitary/multiple), metastatic load and sites (lung and liver), intraoperative haemorrhagic events, operation time, intraoperative oxygen saturation drop during application of nails or stems (no vs. minor drop of 5–15% and major drop >15%), fracture localisation (humerus, radius, ulna, scapula, pelvis, femur, or tibia), specific operation method (intramedullary nailing vs. others) and use of low-molecular-weight heparin (LMWH) (28-day period as cut off). The Khorana score as such and its separate haematological variables were analysed to investigate the prediction of VTEs and survival among these patients (6). The variables from the Khorana score are as follows: site of cancer (2 points for very high-risk site, including pancreas and stomach; 1 point for high-risk site, including lung, lymphoma, gynaecologic, and genitourinary organs, excluding the prostate), platelet count ≥350 $\times$ 10^9/L, haemoglobin <100 g/L and/or use of erythropoiesis-stimulating agents, leukocyte count >11 $\times$ 10^9/L, and BMI ≥35 kg/m^2 (1 point each). These variables were analysed both together and independently, in particular to focus on the haematological variables. Specifically, leukocyte count was analysed for different cut-off values (8, 9, 10, and 12 $\times$ 10^9/L). The laboratory parameters were measured preoperatively. *P*-value <0.05 indicated statistical significance. Analyses were conducted with statistical software package IBM SPSS Statistics version 21.0.

3. Results

A total of 343 orthopaedic procedures were performed in 306 patients; 171 females (55.9%) and 135 males (44.1%). The study population comprised several different primary tumours (Table 1). Breast cancer, myeloma and renal cancer were the most common. Patients had a mean age of 67.2 (range 23.4–94.7) years at the time of the operation. Demographics of identifiable risk factors for VTE are reported in Table 2. Altogether 55 patients did not receive thromboprophylaxis. 15 of them were encountered after year 2004, and 13 of them were operated because of upper extremity fracture, one patient had pelvic surgery but because massive intraoperative bleeding complication postoperative thromboprophylaxis was not used. Two patients; one after femoral nailing and one after tibia plating did not have thromboprophylaxis due to unknown reasons.

Symptomatic VTE was identified in 35 patients (11.4%), of which PE was identified in 26 patients (8.5%). In 3-month postoperative period the VTE rate was 10%. Ten out of 306 patients (3.3%) had the diagnosis of PE as the cause of death in post mortem death certificate, established by autopsy. From the 26 patients who had PE, primary tumours were lung cancer ($n = 7$), breast cancer ($n = 6$), renal cancer ($n = 4$), prostate cancer ($n = 3$), myeloma ($n = 2$), lymphoma ($n = 1$), HCC ($n = 1$), primary bone sarcoma ($n = 1$) and in one case tumour origin

Table 1
Distribution of the types of cancer among the study population.

Primary tumour	n	%
Breast cancer	97	31.7
Myeloma	50	16.3
Renal cancer	38	12.4
Prostate cancer	35	11.4
Lung cancer	33	10.8
Colon cancer	8	2.6
Lymphoma	8	2.6
Sarcoma	7	2.3
Unknown	6	2.0
Melanoma	4	1.3
Thyroid cancer	4	1.3
Bladder cancer	3	1.0
GIST	3	1.0
HCC	2	0.7
Squamous cell cancer	2	0.7
Parotid cancer	1	0.3
Merkel cell cancer	1	0.3
Pancreatic cancer	1	0.3
Ventricle cancer	1	0.3
Leukaemia	1	0.3
Chordoma	1	0.3

GIST = gastrointestinal stromal tumour, and HCC = hepatocellular cancer.

Table 2
Characteristics of patients with VTE.

Characteristics	Total/306 patients	Number of patients without VTE	Number of patients with VTE	*p*-Value*
BMI >30 kg/m^2	45 (15%)	43	2	0.13
Anaemia (Hgb < 100 g/L)	49 (16%)	45	4	0.62
Leukocytosis >9 × 10^9/L	197 (65%)	181	16	**0.01**
Operation method nailing	104 (34%)	98	6	**0.03**
Pelvic lesions	45 (15%)	38	7	0.32
Femoral lesions	155 (51%)	136	19	0.72
Pulmonary metastases	71(23%)	57	14	**0.02**
Lung cancer	33 (11%)	25	8	**0.04**
Multiple skeletal metastases	266 (87%)	236	30	0.79
Saturation drop	87 (28%)	69	18	**0.002**
LMWH prophylaxis	241 (79%)	213	28	0.09

VTE = venous thromboembolism, and LMWH = low molecular weight heparin.
Bolded P-values are statistically significant, p-values > 0.05.
* *p*-Values are calculated with univariate analysis comparing patients with or without VTE in different risk factors.

was unknown. DVT occurred in 11 patients (3.6%). The mean time interval for symptomatic PE was 14 days and for DVT 20 days in 3-months postoperative period. The overall number of VTE and PE events according to time of their occurrence is illustrated in Fig. 1.

In univariate analysis the risk factors for VTE were lung cancer, intramedullary nailing, intraoperative saturation drop, leukocytosis and pulmonary metastases (Table 2). In multivariable analysis the risk factors for VTE were pulmonary metastases, intramedullary nailing and intraoperative saturation drop, whereas the risk factors for PE alone were pulmonary metastases and intraoperative saturation drop (Table 3). Khorana score did not predict VTE in this patient cohort.

Overall survival was 42.9% at 1 year and 23.9% at 2 years, declining to only 16.1% at 3 years. According to the Kaplan-Meier analysis, decreased survival associated with intraoperative oxygen saturation drop, PE diagnosis, haemoglobin below 100 g/L, leukocyte count exceeding 9 × 10^9/L, the presence of pulmonary metastases, LMWH use of <28 days, lung cancer, intramedullary nailing and multiple skeletal metastases (Table 4). All significant variables from the Kaplan-Meier analysis were further subjected to analysis in a Cox regression model. Lung cancer, intramedullary nailing, multiple skeletal metastases, anaemia, leukocytosis, pulmonary metastases and PE turned out as risk factors for decreased survival (Table 5). There were no interactions between variables.

From the separately analysed haematological risk factors, we found that the leukocyte count above 9 × 10^9/L and haemoglobin below 100 g/dL were significant risk factors. Survival markedly declined in patients suffering from PE (Fig. 2). Twenty patients suffered PE, despite receiving postoperative LMWH thromboprophylaxis. Twelve of these utilized prophylaxis for 28 days (range 2–35). Six patients died within 24 h postoperatively, five of them had oxygen saturation drop four having PE. The intraoperative oxygen saturation drop was observed more frequently in patients with lung cancer (51.5%; 17/33) compared with those with the other primary cancers that usually cause skeletal metastases, such as breast cancer (25.8%; 25/97) and renal cell cancer (28.9%; 11/38).

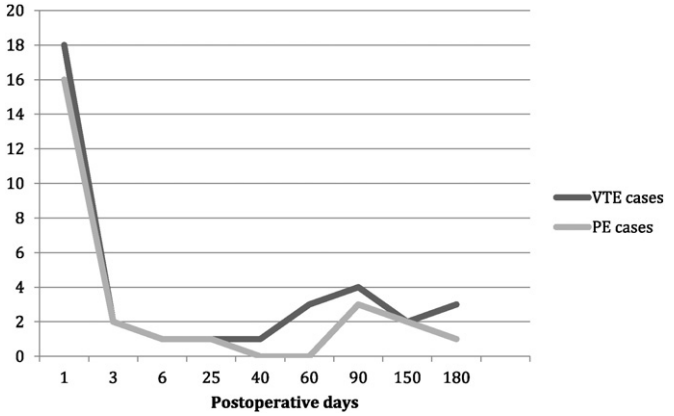

Fig. 1. Number of VTE and PE cases at the time of occurrence.

4. Discussion

During a 3-month postoperative period for cancer patients having undergone surgery for pathological fractures, we identified a striking occurrence of symptomatic VTE (10%), with an overall incidence of fatal PE of 3.3%. This is a relatively high incidence of VTE while 79% of patients had received postoperative thromboprophylaxis, albeit not of the recommended 4-week duration. This is the first study of its kind, with its focus on VTE and survival for 306 post-operative patients, surgically treated for pathologic fractures of non-spinal, skeletal metastases. In comparison to other studies of postoperative complications of skeletal metastases that found VTE complications to be uniformly low, or unstudied, we observed a high number of VTEs [16–19].

We identified several risk factors for VTE in univariate analyses, with multivariate analyses identifying intramedullary nailing, pulmonary metastases, and intraoperative saturation drop, as independent risk factors for VTE. Saturation drop during the cementing and nailing process was considered to be a significant risk factor, having ruled out other perioperative anesthesia-related causes (e.g. intraoperative bleeding). This finding agrees with the poor survival of patients who experience a reduction of intraoperative oxygen saturation, which correlates with the clinical severity of the embolism. [20,21].

In our study, symptomatic PE significantly contributed to premature death. The mean survival following PE was only 2 months, versus 10 months for patients who avoided this complication, who also benefited from a 5-fold greater overall survival. PE has been suggested to be one of the leading medical emergencies in clinical practice [22] with significant mortality [10]. Despite recognition of its severity, this topic has not received attention in survival studies for surgically treated skeletal metastases with pathologic fractures. The Khorana score is

Table 3
Multivariable logistic regression analysis of VTE and PE risk.

VTE			
Risk factor	OR	95 CI	*p*-Value
Pulmonary metastases	2.23	1.04–4.79	0.04
Intramedullary nailing	3.15	1.23–8.07	0.02
Saturation drop	3.28	1.56–6.88	0.002
PE			
Risk factor	OR	95 CI	*p*-Value
Pulmonary metastases	2.84	1.21–6.65	0.02
Intramedullary nailing	2.69	0.95–7.62	0.06
Saturation drop	4.03	1.72–9.41	0.001

Table 4
Kaplan-Meier survival analysis of the 306 operated skeletal metastases: prognostic factors, and median survival (months) with cumulative intervals and *p*-values.

Variable	n	Median	95 CI	*p*-Value
Pulmonary metastases				
Yes	71	5.2	3.4–6.9	0.001
No	235	11.4	8.2–14.5	
Primary disease				
Lung cancer	33	3.2	2.1–4.2	0
Other	273	10.7	7.9–13.6	
Number of skeletal metastases				
Solitary	38	17.3	7.0–27.5	0.002
Multiple	268	7.3	5.0–9.6	
Haemoglobin <100 g/L[a]				
Yes	254	11.4	8.9–13.9	0
No	49	2.7	0.3–5.1	
Leukocytosis $>9 \times 10^9$/L[a]				
Yes	106	4.0	2.8–5.3	0
No	197	12.9	10.8–14.9	
Operation method				
Intramedullary nailing	104	6.4	4.1–8.8	0.015
Other	202	10.5	7.1–14.0	
Intraoperative saturation drop				
Yes	86	4.1	2.1–6.2	0.009
No	220	11.4	8.4–14.4	
LMWH >27 days[b]				
Yes	155	14.3	10.8–17.8	0
No	84	5.8	1.4–6.1	
Pulmonary embolism				
Yes	26	2.0	0–4.3	0
No	280	9.7	6.9–12.6	

[a] Information missing in 3 patients.
[b] Information missing in 67 patients.

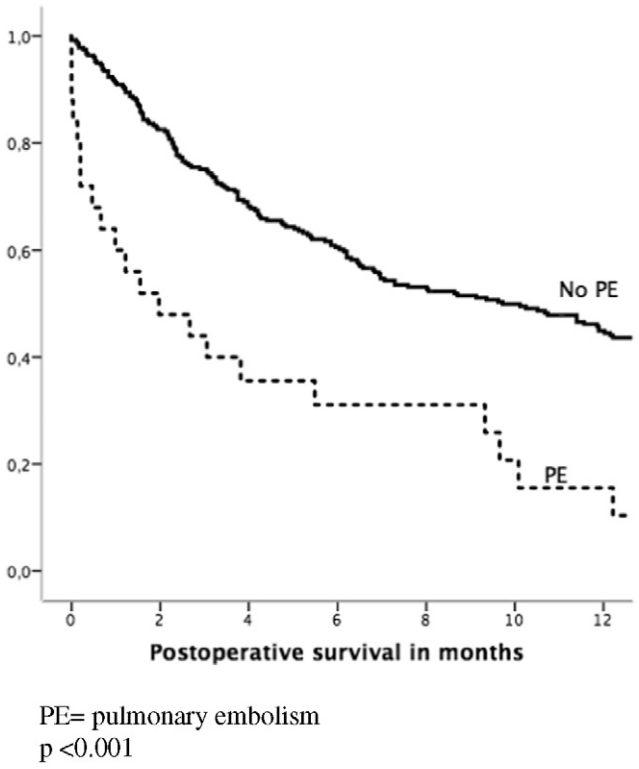

Fig. 2. Kaplan-Meier survival analysis showing the adverse effect of pulmonary embolism.

assumed to carry a predictive value for VTEs among cancer patients treated with chemotherapy. In our study with surgical management, we could find no correlation between high Khorana scores and VTE or survival. The predictive value of the Khorana score is most effective for patients with pancreatic or stomach cancers, or those with a high BMI. However, pancreatic and gastric cancers rarely metastasize to bone, and few patients suffering from disseminated cancer with skeletal metastases present with a high BMI. Therefore the total Khorana score is of little to no value for cancer patients with pathologic fractures.

In addition to PE, other significant variables associated with decreased survival were pulmonary metastases, lung cancer as primary disease, and multiple skeletal metastases, together with the haematological variants, i.e. leukocytosis and anaemia, as reported previously [23]. In addition, the operative nailing method was also associated with decreased survival. First, intramedullary nailing itself appears to carry a risk for VTE [24], thereby contributing to decreased survival. Second, when performing intramedullary nailing, the removal of a tumour with marginal resection cannot be achieved. Marginal resection of skeletal metastases has been shown to impair survival, at least for solitary skeletal metastases, as well as for metastases of renal cell carcinoma thereby contributing to decreased survival [25].

Interestingly, our study showed that lung cancer patients experienced the greatest number of intraoperative saturation drops and PE cases compared to patients with other primary cancers. The increased risk of VTE for lung cancer patients has already been described in the literature [24,26] as is their poor survival following surgery to remove skeletal metastases [27]. These adverse outcomes might reflect the strong association between thromboembolic events after surgical treatment of skeletal metastases. Interestingly, lung metastases were also a risk factor for PE in our study, suggesting that these two states may increase the risk for VTE by similar mechanisms, although it is acknowledged that the increased risk of VTE and decreased postoperative survival are multifactorial.

Table 5
Cox regression survival analysis: prognostic factors, risk ratios (RR), cumulative intervals and statistical analysis (*p*-values).

Factor	RR	95 CI	*p*-Value
Pulmonary metastases	1.49	1.09–2.04	0.013
Lung cancer	2.34	1.54–3.57	0
Multiple skeletal metastases	1.3	1.05–1.62	0.016
Anaemia (Hgb < 100 g/L)	2.7	1.91–3.81	0
Leukocytosis ($>9 \times 10^9$/L)	1.47	1.11–1.94	0.006
Intramedullary nailing	1.49	1.15–1.94	0.003
Pulmonary embolism	2.07	1.26–3.40	0.004

According to our study, a survival benefit was observed in univariate analyses following prophylactic use of LMWH for VTE for 28 days. However, it is noteworthy that 50% of patients (13/26 PE patients) still experienced PE despite this prophylaxis; additionally four patients developed PE despite warfarin use. Studies have shown that increasing DVT prophylaxis with LMWH for up to 30 days safely reduces the risk of postoperative thrombosis by 60% [28], especially in cancer patients [7]. The use of anticoagulants should be considered carefully when operating on patients with cancer, as they may be at high risk of bleeding complications because of their lowered blood cell count, chemotherapy, other drug interactions, renal impairment, and hepatic involvement with metastases [29].

This study has several limitations. First, our study design was observational, for which the most serious shortcoming is the selection bias [30]. However, in this observational study, as our cohort was derived from a single clinic and recruited consecutively, we feel that selection bias is an unlikely factor. Second, this study is retrospective, and lacks randomization. Additionally, there might be some bias in patient selection for surgery, although, as stated previously, patients were recruited consecutively. Despite its retrospective and observational nature, our study has its strengths. First, the patient information system is centralized, with all VTE events captured and registered, and standardized prophylaxis guidelines issued. Second, the total follow-up time was of considerable duration (15 years), and up to 1 year in most cases, which adds to the reliability of our findings. Third, Statistics Finland is the only Finnish public authority that gathers data regarding causes of death from its archive of death certificates. This facilitated

our comprehensive capture of data for patients who died of PE following discharge. Given that Statistics Finland updates "cause of death" data yearly, with the possibility that cancer related deaths could be coded as cancer rather than PE, we feel confident that, if anything, we are underestimating the true rate of VTE occurrence.

In conclusion, estimated VTE rates from autopsy studies differ from those analyzing postoperative complications of skeletal metastases treated surgically. Clinically diagnosed, symptomatic, and confirmed VTE rates are typically low. However, our study, focusing on postoperative VTE events, identified a much higher VTE rate of up to 10%. We provide evidence that VTE after surgery of skeletal metastases is under-diagnosed and adversely influences survival. A possible relationship between fractures associated with skeletal metastases and VTEs warrants further investigation. Collaborative efforts between hematologists and oncological orthopaedic surgeons are now needed to provide further insight into the pathophysiology, risk scoring, diagnosis, and treatment of VTE in patients suffering from this devastating disease. In the future, our aim is to prevent the excessive number of premature deaths currently caused by these under-documented thromboembolic events.

The authors state that they have no conflict of interest.

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