9-16-2015

Thromboembolism After Intramedullary Nailing for Metastatic Bone Lesions.

Brandon Shallop
Jefferson Medical College

Alexandria Starks
Jefferson Medical College

Simon Greenbaum
Albert Einstein Medical College

David S Geller
Montefiore Medical Center

Alan Lee
Brigham and Women's Hospital

See next page for additional authors

Thromboembolism After Intramedullary Nailing for Metastatic Bone Lesions

Brandon Shallop, MD, Alexandria Starks, MD, Simon Greenbaum, MD, David S. Geller, MD, Alan Lee, MD, John Ready, MD, Geno Merli, MD, Mitchell Maltenfort, PhD, and John A. Abraham, MD

Investigation performed at Thomas Jefferson University, Philadelphia, Pennsylvania

Background: The risk of venous thromboembolism (VTE) in patients undergoing intramedullary nailing for skeletal metastatic disease is currently undefined. The purpose of our study was to determine the risk of thromboembolic events, to define the risk factors for VTE, and to define the rate of wound complications in this population.

Methods: A retrospective review of surgical databases at three National Cancer Institute (NCI)-designated cancer centers identified 287 patients with a total of 336 impending or pathologic long-bone fractures that were stabilized with intramedullary nailing between February 2001 and April 2013. Statistical analysis was performed utilizing multivariable logistic regression and Fisher exact tests.

Results: The overall rate of VTE was twenty-four (7.1%) of the 336; thirteen (3.9%) were pulmonary embolism (PE), and eleven (3.3%), deep venous thrombosis (DVT). In two patients, adequate anticoagulation data were not available. We found no significant relationship between the type of anticoagulant used and VTE. There was a significant positive correlation found between lung-cancer histology and the development of VTE ($p < 0.001$) or PE ($p < 0.001$). The absence of radiation therapy approached significance ($p = 0.06$) with respect to decreased overall VTE risk. Wound complications were documented for 11 (3.3%) of the operations.

Conclusions: There is a high rate of VTE among those with skeletal metastatic disease who undergo intramedullary nailing, even while receiving postoperative thromboembolic prophylaxis. Current anticoagulation protocols may be inadequate. Wound-complication risk with anticoagulant use in this population is low and should not be a deterrent to adequate anticoagulant use for this population.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. It was also reviewed by an expert in methodology and statistics. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

Impending and pathologic fractures of long bones in patients with metastatic skeletal disease are generally treated with intramedullary nailing. The combination of neoplastic disease, loss of mechanical stability, vessel damage, and immobility would theoretically put these patients at substantial risk for the development of venous thromboembolism (VTE), which includes both deep venous thrombosis (DVT) and pulmonary embolism (PE).

There are many known risk factors for the development of VTE[1,2]. Virchow's original description of this problem proposed that VTE occurs as the result of a triad of factors: alterations in blood flow, vascular endothelial injury, and a hypercoagulable state[3]. The relatively high VTE risk of orthopaedic procedures[4] is related to intraoperative and postoperative factors. Estimated rates of inpatient DVT and PE among patients receiving prophylaxis following hip or knee arthroplasty are approximately 0.5% to 1%[5]. The risk of VTE is also increased in long-bone fractures[6-12]. Aggressive anticoagulation postoperatively, however, must be balanced with the risk of severe wound or bleeding complications[13,14].

Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. One or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

TABLE I Patient Demographics and Clinical and Disease-Specific Characteristics

Total patients *(no.)*	287
Total operations *(no.)*	336
Age* *(yr)*	60.5 (28-94)
Sex *(no. [%])*	
Male	114 (39.7)
Female	173 (60.3)
Bone *(no. [%])*	
Femur	264 (78.6)
Humerus	62 (18.4)
Tibia	10 (3.0)
Lesion *(no. [%])*	
Impending fracture	301 (89.6)
Pathologic fracture	35 (10.4)
Histology *(no. [%])*	
Lung	87 (25.9)
Breast	81 (24.1)
Multiple myeloma	50 (14.9)
Renal cell carcinoma	25 (7.4)
Metastatic sarcoma	13 (3.9)
Melanoma	10 (3.0)
Esophageal	9 (2.7)
Prostate	7 (2.1)
Hepatocellular carcinoma/ cholangiocarcinoma	7 (2.1)
Gynecological cancer (ovarian, cervical, endometrial, uterine)	7 (2.1)
Thyroid	6 (1.8)
Lymphoma	4 (1.2)
Colon/rectal	4 (1.2)
Bladder	3 (0.9)
Leukemia	3 (0.9)
Pancreatic	2 (0.6)
Other†	10 (3.0)
Unknown primary	8 (2.4)
Adjuvant therapy *(no. [%])*	
Radiation	
Yes	206 (61.3)
No	124 (36.9)
Unknown	6 (1.8)
Chemotherapy	
Yes	179 (53.3)
No	107 (31.8)
Unknown	50 (14.9)

*The values are presented as the median with the range in parentheses. †Other = stromal, parotid, neuroendocrine, squamous, gastrointestinal, adenoid, brain, and salivary.

The mechanisms for cancer-related hypercoagulability include cancer procoagulant, vascular compression or tumor invasion, prothrombotic chemotherapy, and radiation therapy[15,16]. VTE was found to occur in up to 11% of patients with cancer[17,18], and cancer patients undergoing orthopaedic surgery are presumably at very high risk[19,20]. Indeed, a recent study demonstrated a mildly increased risk of VTE in cancer patients undergoing routine joint arthroplasty when cancer was not present at the site of the operation (odds ratio [OR] = 1.2 to 1.6); the risk substantially increased when the arthroplasty was performed for an oncologic indication (OR = 6.6)[21]. The risk factors for VTE in patients with malignancy have been described in a number of large, population-based, case-control studies[22-28], but the risk in patients undergoing intramedullary nailing for prophylactic fixation related to skeletal metastases is unknown.

The purpose of the current study was to determine the risk of thromboembolic events in patients with metastatic long-bone cancer undergoing intramedullary nailing for skeletal metastatic disease, to define the risk factors for developing VTE in this group, and to define the rate of wound complications in this population.

Materials and Methods

Data Collection

After institutional review board approval, a retrospective review of surgical databases at three National Cancer Institute (NCI)-designated cancer centers identified 287 patients with a total of 336 impending or pathologic long-bone fractures that were stabilized with intramedullary nailing between February 2001 and April 2013. In all cases, the treating orthopaedic oncologist determined the postoperative anticoagulation protocol. These three institutions were chosen because of the variation in postoperative anticoagulation regimens, while maintaining identical surgical technique. Postoperatively, patients were generally allowed to bear full weight on the operatively treated limb immediately after surgery.

Data and Statistical Analysis

Adjuvant therapies recorded included any postoperative radiation specifically to the affected limb and any postoperative chemotherapy. Specific details of chemotherapeutic agents used were not obtained in all cases. Rates of documented VTE, divided into PE and DVT, and any postoperative anticoagulation details were recorded. Routine lower-extremity screening ultrasounds were not obtained in any of the centers studied, so it is likely that all DVTs identified were symptomatic because all patients with DVT did have ultrasound documentation. With the exception of one patient with renal cell carcinoma, who was diagnosed with use of a ventilation/perfusion (V/Q) scan, all patients with PE had documentation by a chest computed tomography (CT) scan. Wound complications, defined as requiring either reoperation or other modification of treatment (such as the initiation of antibiotic therapy), were recorded. Statistical analysis was performed by a statistician utilizing Fisher exact tests and multivariable logistic regression analysis. ORs and 95% confidence intervals (CIs) were calculated. A p value of <0.05 was considered significant.

Source of Funding

No external funding was received for this study.

Results

Patient Demographics

Patient demographics and clinical and disease-specific characteristics are shown in Table I. Of the 287 patients, the median age was 60.5 years (range, twenty-eight to ninety-four years). One hundred and fourteen (39.7%) of the patients were male, and 173 (60.3%) were female. Of the 336 operations, 264

TABLE II Anticoagulation, VTE, and Wound-Complication Data

	No. (%)
Anticoagulant	
Low-molecular-weight heparin	203 (60.4)
Enoxaparin	150 (44.6)
Dalteparin	53 (15.8)
Coumadin (warfarin)	56 (16.7)
Subcutaneous heparin	18 (5.4)
Aspirin	17 (5.1)
Arixtra (fondaparinux)	3 (0.9)
None	37 (11.0)
Unknown	2 (0.6)
VTE	24 (7.1)
DVT	11 (3.3)
PE	13 (3.9)
Infections and other wound complications	11 (3.3)
Hematoma	3 (0.9)
Infection requiring irrigation and debridement	2 (0.6)
Superficial cellulitis	2 (0.6)
Wound warmth and erythema	2 (0.6)
Wound breakdown	1 (0.3)
Septic shock	1 (0.3)
Both VTE and wound complication	0 (0.0)

(78.6%) involved the femur; 62 (18.4%), the humerus; and 10 (3.0%), the tibia. Eighteen major cancer diagnostic categories were identified (Table I).

Adjuvant Therapies

Any postoperative radiation therapy delivered to the affected limb commencing within a two-week time frame of surgery was recorded. Dosages ranged from 20 to 40 Gy. Details of the radiation field and non-VTE radiation-associated complications were not recorded. Because of the large variety of primary oncologic diseases and the corresponding large number of medical oncology physicians treating the patients in the study population, detailed records regarding the specifics of chemotherapy used could not be obtained in all cases. The distribution of adjuvant therapies is shown in Table I.

Anticoagulant Data

Low-molecular-weight heparin was the most frequently used anticoagulant and was documented for 203 (60.4%) of the 336 operations (enoxaparin, in 150 [44.6%]; and dalteparin, in fifty-three [15.8%]). With the exception of patients who required a treatment dose, or who had a history of thromboembolic disease, the general dosages used were thromboembolic prophylactic doses: for enoxaparin, 40 mg daily, and for dalteparin, 5000 IU daily. Warfarin (dosed to maintain an international normalized ratio [INR] goal of 2.0 to 2.5) was used for fifty-six (16.7%) of the operations; subcutaneous heparin (5000 units every twelve hours), eighteen (5.4%); aspirin (325 mg daily), seventeen (5.1%); and fondaparinux (10 mg daily), three (0.9%). In general, all centers utilized a protocol of two weeks of chemical anticoagulation postoperatively, but the exact duration of anticoagulation could not be confirmed for all cases. Neither patient compliance in the use of injectable anticoagulants (low-molecular-weight heparin, fondaparinux, and subcutaneous heparin) nor maintenance of the INR within the target range for the duration of warfarin administration could be verified for every case. For thirty-seven (11.0%) of the

TABLE III Demographic, Clinical, and Disease-Specific Characteristics of VTE Cases

VTE events *(no.)*	
Total	24
DVT	11
PE	13
No. (%) of patients	
Total	19 (6.6)
Male	4 (21.1)
Female	15 (78.9)
Age* *(yr)*	59 (43-81)
No. (%) of operations	21 (6.3)
Bone *(no. [%])*	
Femur	19 (90.5)
Humerus	2 (9.5)
Lesion *(no. [%])*	
Impending fracture	20 (95.2)
Pathologic fracture	1 (4.8)
Histology *(no. [%])*	
Lung	14 (66.7)
Breast	4 (19.0)
Multiple myeloma	1 (4.8)
Renal cell carcinoma	1 (4.8)
Melanoma	1 (4.8)
Adjuvant therapy *(no. [%])*	
Radiation	
Yes	9 (42.9)
No	12 (57.1)
Chemotherapy	
Yes	6 (28.6)
No	11 (52.4)
Unknown	4 (19.0)
Anticoagulant *(no. [%])*	
Low-molecular-weight heparin	16 (76.2)
Warfarin	3 (14.3)
Subcutaneous heparin	2 (9.5)

*The values are presented as the median, with the range in parentheses.

TABLE IV Patient Data for VTE Events

Sex	Age *(yr)*	Histology	Bone	Fracture Type	Radiation	Chemotherapy	Anticoagulant	DVT	PE	Postoperative Day
F	57	Multiple myeloma	Humerus	Pathologic	Yes	Yes	Enoxaparin	Yes	No	0
F	67	Lung	Femur	Impending	Yes	Unknown	Dalteparin	Yes	Yes	21
F	63	Breast	Femur	Impending	Yes	Unknown	Dalteparin	Yes	Yes	2
M	59	Lung	Femur	Impending	Yes	Unknown	Dalteparin	No	Yes	1
F	67	Lung	Femur	Impending	No	Unknown	Dalteparin	Yes	Yes	15
M	60	Lung	Femur	Impending	No	No	Warfarin	Yes	Yes	7
F	70	Renal cell carcinoma	Femur	Impending	Yes	Yes	Enoxaparin	No	Yes	48
F	61	Lung	Humerus and femur*	Impending	No	No	Enoxaparin	No	Yes	15
F	52	Lung	Femur and femur*	Impending	No	No	Heparin	No	Yes	0
F	64	Lung	Femur	Impending	No	No	Enoxaparin	No	Yes	4
F	57	Lung	Femur	Impending	No	No	Dalteparin	No	Yes	55
M	55	Lung	Femur	Impending	No	No	Enoxaparin	No	Yes	10
F	57	Lung	Femur	Impending	Yes	Yes	Dalteparin	No	Yes	3
F	43	Breast	Femur	Impending	No	Yes	Enoxaparin	Yes	Yes	53
F	48	Breast	Femur	Impending	Yes	Yes	Enoxaparin	Yes	No	2
M	70	Lung	Femur	Impending	No	No	Warfarin	Yes	No	7
F	59	Breast	Femur	Impending	No	No	Warfarin	Yes	No	7
F	48	Lung	Femur	Impending	Yes	Yes	Enoxaparin	Yes	No	31
F	81	Melanoma	Femur	Impending	Yes	No	Enoxaparin	Yes	No	38

*Fixation of two impending fractures.

operations, no form of chemical anticoagulant was given, and for two (0.6%), the anticoagulant could not be verified (Table II).

VTE Data

There were twenty-four documented VTE events: thirteen PE (3.9% of the operations) and eleven DVT (3.3%) (Table III).

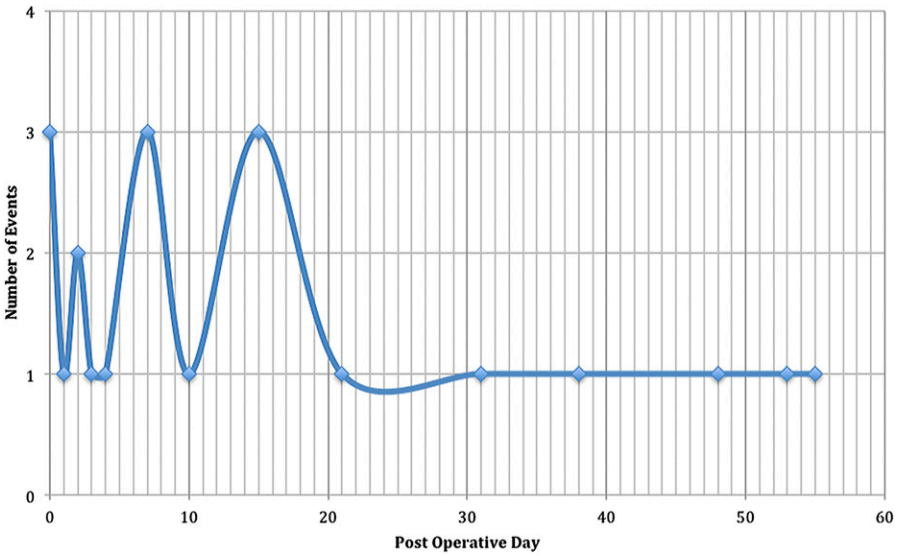

Fig. 1

The number of VTE events according to time of occurrence.

TABLE V Patient Data for Wound Complications and Infections

Sex	Age *(yr)*	Histology	Bone	Fracture Type	Radiation	Chemotherapy	Anticoagulant	VTE	Complication
F	59	Multiple myeloma	Femur	Impending	No	Yes	Warfarin	No	Thigh hematoma
F	67	Melanoma	Femur and femur*	Impending	No	Yes	Enoxaparin	No	Septic shock (died)
F	75	Hepatocellular carcinoma	Femur	Impending	No	Unknown	None	No	Hematoma
F	58	Breast	Femur	Impending	Yes	Yes	Enoxaparin	No	Wound erythema and warmth at incision
M	73	Renal cell carcinoma	Tibia	Impending	No	Yes	Aspirin	No	Wound erythema and warmth at incision
M	72	Renal cell carcinoma	Tibia	Impending	Yes	Yes	Warfarin	No	Infected nonunion requiring nail removal, staged irrigation and debridement
F	68	Breast	Femur	Impending	Yes	Yes	Enoxaparin	No	Wound breakdown
F	53	Breast	Femur	Impending	Yes	Yes	Warfarin	No	Wound infection requiring irrigation and debridement
M	34	Colon	Femur	Impending	No	Yes	Warfarin	No	Hematoma
F	72	Ovarian	Tibia	Impending	No	Yes	Enoxaparin	No	Superficial cellulitis
M	55	Lung	Femur	Impending	Yes	Yes	Warfarin	No	Superficial cellulitis

*Fixation of two impending fractures.

The twenty-four events occurred in nineteen (6.6%) of the patients (twenty-one [6.3%] of the nailing procedures). The patients (four [21.1%] male and fifteen [78.9%] female) had a median age of fifty-nine years (range, forty-three to eighty-one years). Lung cancer was the most common oncologic diagnosis. In nine (42.9%) of the twenty-one cases, adjuvant radiation was received, and in six (28.6%), adjuvant chemotherapy. Low-molecular-weight heparin was the most frequently used anticoagulant in the subset of patients who developed VTE. Table IV shows data recorded for each of the nineteen patients who developed VTE. The highest VTE incidence occurred during the first fifteen days following surgery, with the last event documented at fifty-five days after surgery (Fig. 1).

Infections and Other Wound Complications

Infections and other wound complications were documented for eleven (3.3%) of the operations (Table II). None of the patients with wound complications had VTEs. There were three hematomas (0.9% of the operations) requiring alteration in anticoagulation therapy or operative release, two (0.6%) major or deep infections requiring irrigation and debridement, two cases (0.6%) of culture-positive superficial cellulitis requiring

TABLE VI Multivariable Logistic Regression Analysis of VTE Risk

Variable	Odds Ratio	95% CI	P Value
Sex (male)	0.26	0.07-1.07	0.062
Age (per yr)	0.96	0.90-1.01	0.129
Histology			
Lung vs. others	7.49	1.56-36.07	0.012
Extremity			
Upper vs. lower	0.49	0.08-2.87	0.427
Location			
Proximal vs. distal	0.56	0.17-1.83	0.336
Pathologic fracture	1.64	0.16-16.84	0.679
Anticoagulant			
LMWH vs. others*	1.73	0.53-5.62	0.362
No radiation vs. radiation	0.35	0.10-1.20	0.096
Chemotherapy	0.43	0.11-1.63	0.215

*LMWH = low-molecular-weight heparin.

TABLE VII Multivariable Logistic Regression Analysis of PE Risk

Variable	Odds Ratio	95% CI	P Value
Sex (male)	0.28	0.05-1.63	0.155
Age (per yr)	0.93	0.85-1.01	0.083
Histology			
Lung vs. others	24.35	2.03-291.25	0.011
Extremity			
Upper vs. lower	0.35	0.02-4.81	0.429
Location			
Proximal vs. distal	0.47	0.10-2.35	0.361
Pathologic fracture	0.00	0.00-1060	0.900
Anticoagulant			
LMWH vs. others*	2.05	0.42-10.10	0.377
No radiation vs. radiation	0.10	0.01-0.73	0.023
Chemotherapy	0.61	0.09-3.94	0.599

*LMWH = low-molecular-weight heparin.

TABLE VIII Multivariable Logistic Regression Analysis of DVT Risk

Variable	Odds Ratio	95% CI	P Value
Sex (male)	0.78	0.12-5.21	0.797
Age (per yr)	0.98	0.92-1.05	0.545
Histology			
Lung vs. others	1.10	0.15-8.11	0.927
Extremity			
Upper vs. lower	0.51	0.05-5.38	0.573
Location			
Proximal vs. distal	0.48	0.09-2.39	0.367
Pathologic fracture	1.63	0.14-19.24	0.696
Anticoagulant			
LMWH vs. others*	1.07	0.23-4.96	0.929
No radiation vs. radiation	0.64	0.13-3.02	0.571
Chemotherapy	0.56	0.10-3.10	0.507

*LMWH = low-molecular-weight heparin.

antibiotic treatment, two cases (0.6%) of wound warmth and erythema (suspected to be cellulitis but without documented culture data) requiring antibiotic treatment, one case (0.3%) of wound breakdown requiring packing and dressing changes, and one case (0.3%) of septic shock in the setting of suspected wound infection with resultant death. There was no correlation between a specific anticoagulant and the rate of a wound complication (Table V).

Statistical Analysis

Univariable Analysis

Fisher exact tests were used to determine whether a significant relationship existed between the development of DVT or PE and cancer histology, use of anticoagulation, or use of radiation therapy. In the primary tumor analysis, we found a significantly increased risk of the development of PE in patients with lung-cancer histology (OR = 13.2 [95% CI = 3.45 to 74.94]; $p < 0.0001$) and also a relationship between lung-cancer histology and the development of VTE overall (OR = 6.7 [95% CI = 2.42 to 20.40]; $p < 0.0001$). However, we did not find a clear relationship between the development of DVT and lung-cancer histology (OR = 2.5 [95% CI = 0.59 to 10.13]; $p = 0.16$).

In the analysis of anticoagulant use, we did not identify a significant relationship between the use of any of the anticoagulants studied and the development of DVT, PE, or VTE ($p = 0.69$, $p = 0.27$, and $p = 0.32$, respectively).

There was a significant decrease in the risk of the development of PE in patients who did not receive radiation therapy (OR = 0.28 [95% CI = 0.7 to 0.94]; $p = 0.026$), but a relationship between the use of radiation therapy and DVT could not be shown (OR = 0.71 [95% CI = 0.18 to 3.00]; $p = 0.75$). We did find a slightly decreased risk, which approached significance, of the development of VTE overall in patients who did not receive radiation therapy (OR = 0.43 [95% CI = 0.15 to 1.14]; $p = 0.064$).

Multivariable Analysis

Multivariable logistic regression analysis was then performed to look at VTE risk overall as well as PE and DVT risk specifically. As demonstrated in the univariable analysis, we found a significantly increased risk of the development of VTE overall in patients with lung-cancer histology (OR = 7.49 [95% CI =1.56 to 36.07]; $p = 0.012$). The relationship between the absence of radiation therapy and the development of VTE approached significance (OR = 0.35 [95% CI = 0.10 to 1.20]; $p = 0.096$) (Table VI).

With respect to the development of PE, we found a significantly increased risk in patients with lung-cancer histology (OR = 24.35 [95% CI = 2.03 to 291.2]; $p = 0.011$) and a decreased risk in patients who did not receive radiation therapy (OR = 0.10 [95% CI = 0.01 to 0.73]; $p = 0.023$) (Table VII). With respect to DVT risk specifically (Table VIII), we found no significant correlation between the risk of the development of DVT and any of the variables tested.

Discussion

Patients undergoing intramedullary nailing for skeletal metastatic disease are at high risk for the development of a thromboembolic event postoperatively. Our goal was to investigate the risk of VTE and the rate of wound complications in this population, and our study included a series of 287 consecutive patients treated with intramedullary nailing for 336 metastatic long-bone lesions. We performed both univariable analysis and, using all variables presumed to be relevant to VTE, multivariable analysis.

Demographic data demonstrated a median age of 60.5 years (Table I). As expected, the femur was the most common site, followed by the humerus, and then the tibia. Although we suspected there may be a difference in risk of VTE on the basis of location—because lesions in the lower extremity have greater impact on patient mobility—this was not our finding. The fact that the location of the lesion did not confer additional risk for VTE, even in the case of pathologic fracture, may suggest that the effect of having skeletal metastatic disease alone outweighs the VTE risk imparted by immobility due to the presence of, or fracture through, a lesion.

The overall rate of thromboembolic events in this study population was 7.1% (twenty-four of 336), with eleven of the twenty-four being DVT, and thirteen of the twenty-four, PE. Interestingly, the development of VTE was not significantly related to the type of anticoagulant used. The study population was treated with a variety of postoperative anticoagulants, including low-molecular-weight heparin, Coumadin (warfarin), aspirin, fondaparinux, and heparin, or in some cases, no chemical anticoagulation at all. Given the relatively low numbers of thromboembolic events seen in this study, it is possible that the study was underpowered to detect a difference among these agents. However, given the high number of risk factors in this patient population, it is also possible that none of the current regimens of postoperative thromboembolic prophylaxis substantially decrease the risk of DVT or PE when compared with no anticoagulation. A study designed to specifically answer this question is required.

Regarding the timing of VTE in this population after surgery, we considered the ninety-day period after the operation to be the "postoperative period" in which the incidence of VTE was investigated. A *New England Journal of Medicine* study on abdominal cancer surgery, in which patients were randomized to placebo versus enoxaparin as a thromboembolic prophylactic agent, demonstrated a significant difference with respect to the development of thromboembolic events for three months[29]. The landmark "Million Women Study" found significantly increased risk of postoperative thromboembolism for twelve weeks in 1.3 million women with breast cancer undergoing surgical procedures for the cancer[30]. On the basis of this literature, we elected to include any VTE within a ninety-day period postoperatively as a "postoperative" event. As demonstrated in Figure 1, although half of the documented VTE events occurred within about two weeks after surgery, there were continued events noted as far as fifty-five days after surgery. This suggests that if there were an anticoagulant that could adequately prevent VTE, but it was used only for two weeks, it would have prevented only about half of the noted VTE events in this study. This potentially supports a longer duration of treatment, which is consistent with the findings of the Million Women Study[30]. Considering the high risk associated with this population, we believe this is likely warranted. Further investigation is needed to elucidate the precise ideal duration of anticoagulation postoperatively in this population.

Although we did not find a significant relationship between sex and VTE, multivariable logistic regression analysis showed a borderline significant relationship (OR = 0.26 [95% CI = 0.07 to 1.07]; p = 0.062) between male sex and decreased risk of VTE, and we observed that a high percentage (78.9%) of patients who developed VTE were female. There may be a relationship between female sex and development of VTE that we could not demonstrate because the study was underpowered. In studies of risk factors for VTE in the general (i.e., noncancer) population, females in childbearing years have a higher risk of DVT than do males, but this risk reverses after the age of fifty, when males are found to have a higher risk[31]. It is suspected that hormonal factors present in females during childbearing years, or other factors such as oral contraceptive use in the general population, may contribute to this increased risk. In the cancer population, alteration of the hormonal milieu could theoretically contribute to a sex-related risk. Although our study was not designed to investigate these specific concepts, the observation is interesting to note.

As expected, various primary histologies were seen in our patient population. When compared with other histologies, there was a significantly higher risk of developing VTE in patients with a primary tumor of the lung, which was demonstrated in both univariable and multivariable analyses. This is similar to other studies of thromboembolic events in patients with primary cancers that have shown that lung cancer is the most common primary cancer diagnosis at the time of a VTE event[28,32]. Possible reasons for this increased risk for lung cancer patients include a hypercoagulable state, substantial chemotherapy usage, circulating procoagulants, or other undescribed factors unique to lung cancer patients.

Adjuvant therapies used included both chemotherapy and radiation therapy. Although a significant decrease in VTE risk in patients who were not receiving radiation therapy could not be demonstrated, this relationship did approach significance in both univariable (OR = 0.43 [95% CI = 0.15 to 1.14]; p = 0.064) and multivariable analysis (OR = 0.35 [95% CI = 0.10 to 1.20]; p = 0.096). Patients who did not receive radiation therapy were found to be at decreased risk for PE in both univariable and multivariable analyses. A significant relationship between the use of radiation therapy and increased risk of DVT could not be shown in this study. This is likely due to the study being underpowered to detect these individual differences. Overall, these findings are in agreement with those of other studies, which suggest that radiation increases the risk of VTE[33].

The overall rate of wound complications was 3.3%. Although we did not find a relationship between the anticoagulant used and the development of wound complications, this is a relatively rare complication, and the numbers for each type of anticoagulant were low, so the study was very likely underpowered to detect a difference. In arthroplasty procedures, there is a well-documented increase in wound complications with increasing levels of anticoagulation[34]. As the incisions and dissection required for intramedullary nailing are much more limited than arthroplasty incisions, it is possible that the wound complication risk is less dependent on the anticoagulant used than it is in arthroplasty. In this study, only two patients (0.6% of the operations) required a repeat operation for deep wound infection, and only one of the patients required removal

of the hardware. This again is considerably different from findings for the arthroplasty population, in which a higher rate of implant removal is seen secondary to wound complications[35-37]. The use of intramedullary nailing in the setting of trauma also has been associated with a low risk of wound complication or infection requiring removal of the implant[38]. These results suggest, given the low risks of infection, wound complications, and hardware removal, that at least from a wound-risk standpoint, more aggressive anticoagulation could potentially be tolerated. Further study with a much larger population would be needed to determine if wound complication risk varies by anticoagulant.

Our study had several limitations. This was a retrospective study, and the limitations of this type of study design apply. Although it involved, to our knowledge, the largest series of its kind, the number of patients and thromboembolic events was still relatively small, which introduces the possibility that the study was underpowered to detect small differences and rare complications. Only symptomatic VTE was included in the study, which likely represents an underestimation of the true VTE occurrence in this population. This is a highly complex patient population, with multiple comorbidities and other disease-related factors, which could have had a confounding effect on our study.

On the basis of our results, several considerations are warranted. First, it is likely that the optimal postoperative anticoagulation protocol for this population has yet to be determined, and a clinical trial would be useful in elucidating the optimal postoperative management. Second, because the rate of wound complications seen in this study and in other studies is very low, and implant retention is the norm in the setting of wound complication, more aggressive anticoagulation may not introduce a notable patient morbidity specifically from the standpoint of wound risk. Third, anticoagulation protocols may need to be adjusted according to the patient's particular primary disease. Likewise, the optimal anticoagulation protocol should take into account the use of postoperative radiation therapy. The risk of thromboembolic events in the population of patients undergoing intramedullary nailing for metastatic disease involving long bones is clearly high, and the results presented here suggest that the current approach to anticoagulation therapy in this patient population is likely to be inadequate. ■

NOTE: The authors thank Marco Ferrone, MD, for his contribution of patients to this study.

Brandon Shallop, MD
Alexandria Starks, MD
Jefferson Medical College,
925 Chestnut Street,
Philadelphia, PA 19107.
E-mail address for B. Shallop: brandon.shallop@jefferson.edu.
E-mail address for A. Starks: alexandriaostarks@gmail.com

Simon Greenbaum, MD
Albert Einstein Medical College,
1300 Morris Park Avenue,
Bronx, NY 10461.
E-mail address: simon.greenbaum@med.einstein.yu.edu

David S. Geller, MD
Montefiore Medical Center,
111 East 210th Street,
New York, NY 10467.
E-mail address: DGELLER@montefiore.org

Alan Lee, MD
John Ready, MD
Brigham and Women's Hospital,
75 Francis Street,
Boston, MA 02115.
E-mail address for A. Lee: alee29@partners.org.
E-mail address for J. Ready: JREADY@partners.org

Geno Merli, MD
Thomas Jefferson University Hospital,
111 South 11th Street,
Philadelphia, PA 19107.
E-mail address: geno.merli@jefferson.edu

Mitchell Maltenfort, PhD
Rothman Institute,
Thomas Jefferson University,
125 South 9th Street,
Suite 1000,
Philadelphia, PA 19107.
E-mail address: mitchell.maltenfort@rothmaninstitute.com

John A. Abraham, MD
Rothman Institute,
Thomas Jefferson University,
925 Chestnut Street,
5th Floor,
Philadelphia, PA 19107.
Email address: John.Abraham@rothmaninstitute.com

References

1. Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis - current understanding from an epidemiological point of view. Br J Haematol. 2010 Jun;149(6):824-33. Epub 2010 Apr 29.

2. Goldhaber SZ. Risk factors for venous thromboembolism. J Am Coll Cardiol. 2010 Jun 29;56(1):1-7.

3. Virchow RLK. Thrombosis and emboli (1846-1856). Matzdorff AC, Bell WR, translators. Canton, OH: Science History Publications; 1998. p 5-11, 110.

4. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW; American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008 Jun;133(6)(Suppl):381S-453S.

5. Januel JM, Chen G, Ruffieux C, Quan H, Douketis JD, Crowther MA, Colin C, Ghali WA, Burnand B; IMECCHI Group. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review. JAMA. 2012 Jan 18;307(3):294-303.

6. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994 Dec 15;331(24):1601-6.

7. Montgomery KD, Geerts WH, Potter HG, Helfet DL. Thromboembolic complications in patients with pelvic trauma. Clin Orthop Relat Res. 1996 Aug;329:68-87.

8. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, Hamilton PA. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996 Sep 5;335(10):701-7.

9. McLaughlin DF, Wade CE, Champion HR, Salinas J, Holcomb JB. Thromboembolic complications following trauma. Transfusion. 2009 Dec;49(Suppl 5):256S-63S.

10. Owings JT, Gosselin R. Acquired antithrombin deficiency following severe traumatic injury: rationale for study of antithrombin supplementation. Semin Thromb Hemost. 1997;23(Suppl 1):17-24.

11. Planès A, Vochelle N, Fagola M. Total hip replacement and deep vein thrombosis. A venographic and necropsy study. J Bone Joint Surg Br. 1990 Jan;72(1):9-13.

12. Karadimas EJ, Papadimitriou G, Theodoratos G, Papanikolaou A, Maris J. The effectiveness of the antegrade reamed technique: the experience and complications from 415 traumatic femoral shaft fractures. Strategies Trauma Limb Reconstr. 2009 Dec;4(3):113-21. Epub 2009 Nov 21.

13. Torn M, Rosendaal FR. Oral anticoagulation in surgical procedures: risks and recommendations. Br J Haematol. 2003 Nov;123(4):676-82.

14. Burnett RS, Clohisy JC, Wright RW, McDonald DJ, Shively RA, Givens SA, Barrack RL. Failure of the American College of Chest Physicians-1A protocol for lovenox in clinical outcomes for thromboembolic prophylaxis. J Arthroplasty. 2007 Apr;22(3):317-24.

15. Dickson BC. Venous thrombosis: on the history of Virchow's triad. Univ Toronto Med J. 2004;81:166.

16. Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol. 2008 Oct;143(2):180-90. Epub 2008 Sep 6.

17. Sack GH Jr, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. Medicine (Baltimore). 1977 Jan;56(1):1-37.

18. Hedderich GS, O'Connor RJ, Reid EC, Mulder DS. Caval tumor thrombus complicating renal cell carcinoma: a surgical challenge. Surgery. 1987 Oct;102(4):614-21.

19. Behranwala KA, Williamson RC. Cancer-associated venous thrombosis in the surgical setting. Ann Surg. 2009 Mar;249(3):366-75.

20. Osborne NH, Wakefield TW, Henke PK. Venous thromboembolism in cancer patients undergoing major surgery. Ann Surg Oncol. 2008 Dec;15(12):3567-78. Epub 2008 Oct 8.

21. Karam JA, Huang RC, Abraham JA, Parvizi J. Total joint arthroplasty in cancer patients. J Arthroplasty. 2015 May;30(5):758-61. Epub 2014 Dec 18.

22. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005 Feb 9;293(6):715-22.

23. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006 Feb 27;166(4):458-64.

24. Alcalay A, Wun T, Khatri V, Chew HK, Harvey D, Zhou H, White RH. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol. 2006 Mar 1;24(7):1112-8.

25. Cronin-Fenton DP, Søndergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, Baron JA, Sørensen HT. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. Br J Cancer. 2010 Sep 28;103(7):947-53. Epub 2010 Sep 14.

26. Anderson LA, Moore SC, Gridley G, Stone BJ, Landgren O. Concomitant and antecedent deep venous thrombosis and cancer survival in male US veterans. Leuk Lymphoma. 2011 May;52(5):764-70. Epub 2011 Jan 27.

27. De Martino RR, Goodney PP, Spangler EL, Wallaert JB, Corriere MA, Rzucidlo EM, Walsh DB, Stone DH. Variation in thromboembolic complications among patients undergoing commonly performed cancer operations. J Vasc Surg. 2012 Apr;55(4):1035-1040.e4. Epub 2012 Mar 10.

28. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, Rimm AA. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore). 1999 Sep;78(5):285-91.

29. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, Dietrich-Neto F; ENOXACAN II Investigators. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002 Mar 28;346(13):975-80.

30. Sweetland S, Green J, Liu B, Berrington de González A, Canonico M, Reeves G, Beral V; Million Women Study Collaborators. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. BMJ. 2009;339:b4583. Epub 2009 Dec 3.

31. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998 Mar 23;158(6):585-93.

32. Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med. 2000 Dec 21;343(25):1846-50.

33. Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. Circulation. 2003 Jun 17;107(23)(Suppl 1):I17-21.

34. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R; American College of Chest Physicians. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2)(Suppl):e326S-50S.

35. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004 Oct 14; 351(16):1645-54.

36. Fink B, Grossmann A, Fuerst M, Schäfer P, Frommelt L. Two-stage cementless revision of infected hip endoprostheses. Clin Orthop Relat Res. 2009 Jul;467(7):1848-58. Epub 2008 Nov 11.

37. Haddad FS, Muirhead-Allwood SK, Manktelow AR, Bacarese-Hamilton I. Two-stage uncemented revision hip arthroplasty for infection. J Bone Joint Surg Br. 2000 Jul;82(5):689-94.

38. Farragos AF, Schemitsch EH, McKee MD. Complications of intramedullary nailing for fractures of the humeral shaft: a review. J Orthop Trauma. 1999 May;13(4):258-67.