Incidence and Risk Factors for Pulmonary Embolism After Primary Musculoskeletal Tumor Surgery

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Abstract

Background Limited information is available regarding the incidence, risk factors, and optimal prophylaxis in orthopaedic oncology patients, although malignancy and major orthopaedic surgery are associated with an increased pulmonary embolism (PE) risk.

Questions/purposes We aimed to investigate the incidence of PE after musculoskeletal tumor surgery in Japanese patients and analyze the potential risk factors for PE.

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Methods We retrospectively identified 3750 patients (1981 males, 1769 females) who underwent musculoskeletal tumor surgery during 2007 to 2010 using the Japanese Diagnostic Procedure Combination administrative database. Data collected included sex, age, primary diagnosis, type of surgery, duration of anesthesia, and comorbidities that may affect PE incidence. Univariate logistic regression analyses were performed to examine the relationship of each factor with PE occurrence.

Results We identified 10 patients with PE during the survey period. A primary malignant bone tumor was associated with a significantly higher risk of PE than a primary malignant soft tissue tumor (odds ratio [OR], 5.58; 95% CI, 1.39–22.42). Bone tumor resection (OR, 7.94; 95% CI, 1.77–35.59) and prosthetic reconstruction (OR, 9.15; 95% CI, 1.52–55.07) were associated with a significantly higher risk of PE than soft tissue tumor resection.

Conclusions Malignant bone tumors and bone tumor resections have a higher risk of PE than malignant soft tissue neoplasms and soft tissue resections. Both populations might require PE prophylaxis as it is likely that the risk is greater than with other major orthopaedic surgery, but data accumulation should continue, and further investigation should be done to clarify details of the incidence, risk factors, and optimal prophylaxis for PE.

Level of Evidence Level II, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Postoperative pulmonary embolism (PE) is a potential major complication in patients who undergo orthopaedic surgery. PE is a severe sequella of venous thromboembolism (VTE);

most VTE occurs during the early postoperative period, usually within 2 weeks after surgery, and progression to PE is potentially life threatening.

It generally is recognized that patients with malignant disease are at increased risk of PE [3, 7, 12, 13, 26, 27]. This increased risk has been observed in many different types and stages of malignancies, but the PE risk in patients with musculoskeletal sarcoma remains unclear.

Considering that malignant disease and major orthopaedic surgery are independently associated with a high risk of VTE, patients undergoing musculoskeletal tumor surgery would be expected to have a particularly high risk of VTE. However, there is limited information available regarding the incidence, risk factors, and optimal prophylaxis for VTE in orthopaedic oncology patients, presumably because of the rarity of these diseases. The reported incidence of PE in these patients is between 0.6% and 11% [2, 13, 16, 27], but these data were based on small and heterogeneous patient cohorts at a single referral center. The wide range of reported incidences may result from the inclusion of patients with metastatic bone tumors who may have a higher risk of PE.

To our knowledge, no nationwide surveys of PE after musculoskeletal tumor surgery have been performed, and the factors affecting the incidence of PE in musculoskeletal tumor surgery remain unclear.

Therefore, as part of the research project investigating the nationwide surveys of PE in orthopaedic surgery [14, 19], we investigated the incidence of PE during the initial hospitalization following musculoskeletal tumor surgery in Japanese patients and analyzed the potential risk factors that might affect the incidence of PE using a nationally representative inpatient database, the Japanese Diagnostic Procedure Combination (DPC) administrative database.

Patients and Methods

The DPC is a case-mix patient classification system, which is similar to the diagnosis-related groups in Medicare in the United States. This system was launched in 2002 by the Ministry of Health, Labour, and Welfare of Japan and is linked to a lump-sum payment system. All 82 university teaching hospitals are obliged to adopt the DPC system, but adoption by community hospitals is voluntary. Data collection from the DPC hospitals is conducted between July 1 and December 31 each year by the DPC Research Group in collaboration with the Ministry of Health, Labour, and Welfare [10, 19, 28]. Administrative claims data and detailed patient data are collected for all inpatients discharged from the participating hospitals between July 1 and December 31. The survey started in 2003 with 82 teaching hospitals, and the number of participating hospitals has

increased steadily to 926 in 2007, 855 in 2008, 818 in 2009, and 952 in 2010. The numbers of patients included were 2.99, 2.86, 2.57, and 3.19 million in 2007, 2008, 2009, and 2010, respectively. The number of patients in 2010 (3.19 million) represented approximately 45% of all inpatient admissions to acute-care hospitals in Japan. All of the data for each patient were recorded at discharge. Data were compiled in the database server in the Department of Health Management and Policy at The University of Tokyo.

The database includes the following data for each patient: hospital location, age, sex, diagnoses, and comorbidities at admission and complications after admission recorded using text data in the Japanese language and the International Classification of Diseases, 10th Revision codes (ICD-10 codes), procedures coded with Japanese original codes, drugs and devices used, length of stay, and discharge status.

The DPC database partially corresponds to the Nationwide Inpatient Sample in the United States [21] but has several unique advantages. In the DPC database, complications that occurred after admission are clearly differentiated from comorbidities that were present at admission. To optimize the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts. The diagnoses and comorbidities are registered in the DPC database only at discharge. Medical clerks and licensed medical information managers accurately record the dates of all major and minor procedures and of drug administration and device use. Physicians and hospitals have a strong incentive for data compliance because compliance is mandatory to obtain the DPC-based reimbursement of medical fees.

Because of the anonymous nature of the data, informed consent was waived. Study approval was obtained from the institutional review board of The University of Tokyo.

We identified the records of all patients in the DPC database who underwent musculoskeletal tumor surgery during 2007 to 2010. For each patient, we extracted the sex, age, main diagnosis, type of surgery, duration of anesthesia, and comorbidities that may affect the incidence of PE (cardiac disease, cerebrovascular disease, chronic renal failure, chronic lung disease, and diabetes mellitus). Based on the protocol of Quan et al. [25], each ICD-10 code of a comorbidity was converted into a score, and the sum of the scores was used to calculate the patient's Charlson comorbidity index. The main diagnosis was classified into one of three groups: (1) primary malignant bone tumor of an extremity (ICD codes C40.x); (2) primary malignant bone tumor of another site (C41.x); and (3) primary malignant soft tissue tumor (C47.x, C48.x, C49.x). The type of surgery was classified into one of four groups: (1) bone tumor resection; (2) soft tissue tumor resection;

(3) amputation; and (4) bone or soft tissue tumor resection with prosthetic reconstruction. DPC data do not include operation time, but anesthesia time generally reflects operation time.

To identify patients with PE, we performed a search using the specific ICD-10 code for PE (I26).

Of 11.6 million inpatients included in the DPC database during 2007 to 2010, we identified 3750 eligible patients at 411 hospitals. These patients included 1981 males and 1769 females with an average ($\pm$ SD) age of 57.8 ± 19.7 years (range, 0–102 years). The main diagnosis was primary malignant bone tumor of an extremity in 286 patients, primary malignant bone tumor of another site in 301 patients, and primary malignant soft tissue tumor in 3163 patients. The type of surgery was bone tumor resection in 495 patients, soft tissue tumor resection in 2927 patients, amputation in 113 patients, and bone or soft tissue tumor resection with prosthetic reconstruction in 215 patients. The duration of anesthesia was 120 minutes or longer in the majority of patients, with an average duration of 253 ± 187 minutes. In the Charlson comorbidity index, “malignant tumor” is assigned a score of 2 and therefore approximately 75% of the patients were classified as having no comorbidities.

Univariate logistic regression analyses were performed to examine the relationship of each factor with the occurrence of PE. A *p* value less than 0.05 was considered to be statistically significant. Statistical analyses were performed using IBM SPSS Statistics software, version 19 (IBM SPSS, Armonk, NY, USA).

Results

We identified 10 patients with a diagnosis of PE during the survey period, which was an overall incidence of 0.3%. There was only one in-hospital death after PE among the 3750 patients (0.03%). The median (interquartile range) postoperative length of stay was 16 days (range, 9–31 days).

We identified three risk factors for PE in this population: primary malignancy of bone, bone tumor resection, and prosthetic reconstruction. Patients with a primary malignant bone tumor of an extremity had a 5.6-fold higher incidence of PE compared with patients with a primary soft tissue sarcoma (odds ratio [OR], 5.58; 95% CI, 1.39–22.42; *p* = 0.020) (Table 1). Patients who underwent bone tumor resection (OR, 7.94; 95% CI, 1.77–35.59; *p* = 0.007) and prosthetic reconstruction (OR, 9.15; 95% CI, 1.52–55.07; *p* = 0.016) also were more likely to have a PE. Sex, age, duration of anesthesia, Charlson comorbidity index, and all the extracted comorbidities were not significant predictive factors for PE.

Discussion

The incidence of PE in patients with musculoskeletal sarcoma has not been well described to date, and there is fairly limited information available regarding this topic (Table 2). The cited articles studied PE and VTE, unlike our study. The reported incidence of PE after musculoskeletal tumor surgery in earlier studies has varied widely, from 0.6% to 11% [2, 13, 16, 27]. This wide range presumably results from heterogeneity among study subjects, small sample sizes, and variations in surveying for PE and in prophylaxis. In addition, most of these reports included large numbers of patients with cancer metastasis or hematologic malignancy, which are risk factors for PE [2, 13, 27]. Mitchell et al. [16] reported that patients undergoing surgery for musculoskeletal sarcoma did not have a higher risk of PE than patients undergoing other routine orthopaedic procedures. By contrast, some physicians believe that because of the perceived increased risk of PE in this population, inferior vena cava filters should be used in all patients with sarcoma undergoing surgery [2, 27]. We used a large national database to try to estimate the frequency of this serious complication, and to determine what clinical parameters might be associated with an increased likelihood of a patient having a PE develop after musculoskeletal tumor surgery.

Our study has several limitations. First, this study was based on the review of an administrative database. Several differences might exist among hospitals in terms of PE detection and prophylaxis. If there was no routine investigation for PE using imaging (contrast-enhanced CT or ultrasonography) or serum D-dimer levels, detection of asymptomatic PE would not be possible. VTE prophylaxis also might differ among hospitals, and physicians may have administered anticoagulant therapy in high-risk patients. We did not look at specific VTE prophylaxis in this study. To resolve these questions, a prospective multicenter study should be conducted. Second, we were not able to determine the incidence of PE in the periods before surgery and after discharge. Previous reports have indicated that neoadjuvant chemotherapy and recent biopsy are risk factors for VTE in patients with musculoskeletal tumors [16, 18]. Therefore it is possible that some patients had a PE develop before surgery but were diagnosed afterward. Most patients with a postoperative PE would be included in our analysis, because the median postoperative hospital stay was 16 days, and the majority of postoperative PEs occur within the first 2 weeks [5]. Third, we were unable to determine any relationship between the risk of PE and the histologic type or clinical stage of the tumor. A previous study reported an increased risk of symptomatic VTE in patients with Ewing’s family of tumors [1]. This relationship may be attributable to the more aggressive

Table 1. Incidence of postoperative PE and univariate OR in each subgroup

Parameter	Number	PE (%)	OR	95% CI	p value
Total	3750	10 (0.27)			
Sex					
Male	1981	6 (0.30)	1.00		
Female	1769	4 (0.23)	0.75	0.21–2.65	0.650
Age (years)					
≤ 49	1085	2 (0.18)	1.00		
50–69	1417	5 (0.35)	1.92	0.37–9.90	0.440
≥ 70	1248	3 (0.24)	1.31	0.22–7.82	0.770
Diagnosis					
Primary malignant bone tumor (extremity)	286	3 (1.05)	5.58	1.39–22.42	0.020
Primary malignant bone tumor (other site)	301	1 (0.33)	1.75	0.21–14.62	0.600
Primary malignant soft tissue tumor	3163	6 (0.19)	1.00		
Type of surgery					
Bone tumor resection	495	4 (0.81)	7.94	1.77–35.59	0.007
Soft tissue tumor resection	2927	3 (0.10)	1.00		
Amputation	113	1 (0.88)	8.70	0.90–84.32	0.060
Prosthetic reconstruction	215	2 (0.93)	9.15	1.52–55.07	0.016
Duration of anesthesia (minutes)					
< 120	716	2 (0.28)	1.00		
120–240	1582	5 (0.32)	1.13	0.22–5.85	0.882
> 240	1445	3 (0.21)	0.74	0.12–4.46	0.745
Charlson comorbidity index					
≤ 2	2825	7 (0.25)	1.00		
3–4	579	2 (0.35)	1.40	0.29–6.73	0.680
≥ 5	346	1 (0.29)	1.17	0.14–9.51	0.890
Diabetes mellitus					
Yes	289	2 (0.69)	3.01	0.64–14.23	0.170
No	3461	8 (0.23)	1.00		
Cardiac disease					
Yes	108	1 (0.93)	3.77	0.47–30.04	0.210
No	3642	9 (0.25)	1.00		
Cerebrovascular disease					
Yes	13	0	Not performed		
No	3737	10 (0.27)			
Chronic renal failure					
Yes	26	0	Not performed		
No	3724	10 (0.27)			
Chronic lung disease					
Yes	58	0	Not performed		
No	3692	10 (0.27)			

PE = pulmonary embolism; OR = odds ratio.

nature of these tumors and their propensity for metastasis. Although advanced stage and metastasis also have been suggested as risk factors for VTE [23], we were unable to evaluate these factors in our series. These factors should be

evaluated in future prospective studies. In addition, the number of patients with PE in our study may have been too small for differences in some of the variables to reach statistical significance. The small number of patients with

Table 2. Summary of literature on VTE in musculoskeletal tumor surgery

Study	Year	Study sample	Number	Primary or metastasis (number)	Surveillance	DVT rate	PE rate	Risk factors for VTE
Damron et al. [4]	2011	Musculoskeletal sarcoma of the trunk or extremity or head/neck	171	P 171	Clinical	5/171 (2.9%)	3/171 (1.8%)	Chemotherapy
Morii et al. [18]	2010	Benign or malignant musculoskeletal tumor	299	Benign 195, P 73, M 31	D-dimer with/without enhanced CT	8/299 (2.7%), P 7/73 (9%)	4/299 (1.3%), P 3/73 (4%)	Malignancy, chemotherapy, plastic surgery, tumor size, elevated D-dimer
Patel et al. [22]	2010	Musculoskeletal tumor of the pelvis or lower extremity	348	P 195, M 153	Clinical	18/348 (5%), P 8/195 (4%), M 10/153 (7%)	4/348 (1.1%), P 0/195 (0%), M 4/153 (2.6%)	NA
Tuy et al. [27]	2009	Musculoskeletal tumor of the pelvis or lower extremity	81	P 46, M 35	Clinical	17/81 (21%)	2/81 (2%)	Concomitant skeletal reconstruction
Mitchell et al. [16]	2007	Musculoskeletal sarcoma of the trunk or extremity	252	P 252	Clinical	10/252 (4%)	3/252 (1.2%)	Tumor of hip/thigh/pelvis
Nathan et al. [20]	2006	Musculoskeletal tumor undergoing hip arthroplasty	87	P 21, M 66	Routine US	4/87 (4.6%)	1/87 (1.1%)	Tumor of pelvis, primary tumor
Benevenia et al. [2]	2004	Lower extremity pathologic fracture from metastasis	47	M 47	Routine US	8/47 (17%)	5/47 (10.6%)	NA
Lin et al. [13]	1998	Musculoskeletal tumor of the pelvis or lower extremity	169	P 50, M 119	Routine US	24/169 (4%)	1/169 (0.6%)	None
Current study		Musculoskeletal sarcoma of the trunk or extremity	3750	P 3750	NA	NA	10/3750 (0.3%)	Malignant bone tumor of an extremity, bone tumor resection, prosthetic reconstruction

VTE = venous thromboembolism; DVT = deep venous thrombosis; PE = pulmonary embolism; US = ultrasonography; NA = not available; P = primary tumor; M = metastatic bone tumor.

PE also prevented us from conducting multivariate logistic regression analyses. Further evaluation of a greater number of patients with PE should be done in future studies, as in a previous study that revealed the optimal prophylaxis and incidence and risk factors of PE in patients who had a joint arthroplasty [19]. Fourth, the ORs were compared with reference to soft tissue sarcoma surgery, not more familiar situations in orthopaedic surgery such as joint arthroplasty or spine surgery. Fifth, there is no way to determine the accuracy and completeness of the DPC database. However, for this reason, we focused on only PEs, a more critical end point.

In the current series, the overall PE rate during hospitalization was 0.3% (10 of 3750), which is relatively low compared with the rates in previous reports [2, 4, 13, 16, 18, 20, 22, 27]. One possible reason for this is the lower reported incidence of PE in Japanese patients compared with white patients [11]. The reported statistics from the DPC database indicate a PE rate of 0.45% in hip fracture surgery, 0.46% in THA, 0.68% in TKA, and 0.09% in spinal surgery [10]. Considering these figures for general orthopaedic procedures, musculoskeletal sarcoma may not be associated with an increased risk of PE, unlike other types of malignancies.

Several risk factors have been found to be associated with an increased risk of VTE in musculoskeletal tumor surgery (Table 2). In our study, two factors were identified as potential risk factors for PE in musculoskeletal tumor surgery: category of disease (primary malignant bone tumor of an extremity, 1.1%) and the type of surgery (bone tumor resection, 0.8%; prosthetic reconstruction, 0.9%). Among previous studies, only Tuy et al. [27] described an association between prosthetic reconstruction and an increased risk of postoperative PE. Primary malignant bone tumor has not been recognized previously as a risk factor for PE [4, 13, 16, 18, 27]. Surprisingly, known risk factors including older age, presence of various comorbidities, and longer duration of anesthesia were not identified as predictive factors for PE in our study, although, this may have been a function of the relatively few PEs detected in this population-based survey.

In patients undergoing major orthopaedic surgery, combined treatment with chemoprophylaxis, mechanical prophylaxis, and early mobilization reduces the risk of VTE [6, 15]. Most patients with musculoskeletal sarcoma are considered to be at high risk for VTE, and therefore receive mechanical prophylaxis, with or without anticoagulation therapy, to prevent postoperative VTE [4, 13, 16, 18, 22]. However, prophylaxis for VTE after musculoskeletal tumor surgery is not standardized in Japan. Postoperative anticoagulation therapy is controversial because patients with cancer who are treated with low-molecular-weight heparin have a 12% to 50%

greater risk of bleeding compared with patients without cancer [8, 17, 24]. Bleeding is of particular concern after musculoskeletal tumor surgery because of the large dead spaces and raw surfaces left after tumor resection.

Despite the study's limitations, we believe that the results are epidemiologically important, because they show the incidence of PE after musculoskeletal tumor surgery in the Japanese population. The DPC database population is representative of the population in Japan and includes the majority of patients undergoing musculoskeletal tumor surgery in Japan. The DPC data included approximately 45% of all the hospital admissions in Japan during 2010. According to data from the nationwide bone and soft tissue tumor registry in Japan [9], more than 80% of patients with primary musculoskeletal tumors underwent surgery in university hospitals or cancer treatment centers adopting the DPC system as a result of the rarity of the diseases and the specialized surgical procedures. To our knowledge, our study is the first to describe the nationwide incidence of PE in this population based on large-scale cross-sectional data. Future studies will be needed to clarify details of the incidence, risk factors, and optimal prophylaxis for PE.

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