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ONCOLOGY

Prevalence of primary malignant tumours, rates of pathological fracture, and mortality in the setting of metastatic bone disease

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Aims

The modern prevalence of primary tumours causing metastatic bone disease is ill-defined in the oncological literature. Therefore, the purpose of this study is to identify the prevalence of primary tumours in the setting of metastatic bone disease, as well as reported rates of pathological fracture, postoperative complications, 90-day mortality, and 360-day mortality for each primary tumour subtype.

Methods

The Premier Healthcare Database was queried to identify all patients who were diagnosed with metastatic bone disease from January 2015 to December 2020. The prevalence of all primary tumour subtypes was tabulated. Rates of long bone pathological fracture, 90-day mortality, and 360-day mortality following surgical treatment of pathological fracture were assessed for each primary tumour subtype. Patient characteristics and postoperative outcomes were analyzed based upon whether patients had impending fractures treated prophylactically versus treated completed fractures.

Results

In total, 407,893 unique patients with metastatic bone disease were identified. Of the 14 primary tumours assessed, metastatic bone disease most frequently originated from lung (24.8%), prostatic (19.4%), breast (19.3%), gastrointestinal (9.4%), and urological (6.5%) malignancies. The top five malignant tumours resulting in long bone pathological fracture were renal (5.8%), myeloma (3.4%), female reproductive (3.2%), lung (2.8%), and breast (2.7%). Following treatment of pathological fractures of long bones, 90-day mortality rates were greatest for lung (12.1%), central nervous system (10.5%), lymphoma (10.4%), gastrointestinal (10.1%), and non-renal urinary (10.0%) malignancies. Finally, our study demonstrates improved 90-day and 360-day survival in patients treated for impending pathological fracture compared to completed fracture, as well as significantly lower rates of deep vein thrombosis, pulmonary embolism, urinary tract infection, and blood transfusion.

Conclusion

This study defines the contemporary characteristics of primary malignancies resulting in metastatic bone disease. These data should be considered by surgeons when prognosticating patient outcomes during treatment of their metastatic bone disease.

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Introduction

Despite advances in medical and surgical oncology, malignancy remains one of the leading causes of mortality worldwide.[1] In 2020 alone, there were approximately ten million deaths worldwide due to cancer.[1] One of the most frequent complications associated with advanced malignancy is metastatic disease, particularly to bone.[2] Though the exact incidence is unknown, approximately

Table I. Prevalence of primary tumours with subtypes.

Primary tumour	n (%)
Total	407,893
Oropharyngeal	5,720 (1.4)
Gastrointestinal	38,155 (9.4)
Upper GI	8,736 (22.9)
Central GI	6,308 (16.5)
Lower GI	15,039 (39.4)
Hepatobiliary	8,125 (21.3)
Lung	101,279 (24.8)
Upper respiratory	1,657 (1.6)
Lower respiratory	98,846 (97.5)
Other	776 (0.8)
Bone sarcoma	3,083 (0.8)
Skin	8,572 (2.1)
Melanoma	5,372 (62.7)
Non-melanoma	3,232 (37.7)
Mesothelial	4,356 (1.1)
Breast	78,658 (19.3)
Female reproductive	9,059 (2.2)
Endometrial	6,215 (68.6)
Other	2,997 (33.1)
Male reproductive	78,991 (19.4)
Prostate	78,304 (99.1)
Non-prostate	718 (0.9)
Urinary	26,493 (6.5)
Renal	16,379 (61.8)
Non-renal	10,355 (39.1)
Central nervous system	2,603 (0.6)
Endocrine	3,843 (0.9)
Thyroid	2,762 (71.9)
Non-thyroid	1,083 (28.2)
Hematogenous	19,481 (4.8)
Myeloma	10,203 (52.4)
Lymphoma	9,435 (48.4)
Neuroendocrine	4,262 (1.0)
Uncategorized	23,338 (5.7)

210,00 to 400,000 new cases of metastatic bone disease are diagnosed annually, and roughly 350,000 people die annually with bone metastasis in the USA.[2,3] Additionally, bone metastases can cause skeletal related events (SREs), such as pathological fractures, severe pain, compression of nearby neurovascular structures, and decreased mobility, which may negatively impact overall patient quality of life or require surgical intervention.[4]

Despite the significant impact of bone metastases on patient morbidity and mortality, their incidence by primary tumour and surgical outcomes remains poorly defined in contemporary oncological literature. Currently, it is estimated that up to 70% of all bone metastases are a result of metastatic breast and prostate cancer, with lung, kidney, and thyroid tumours following in frequency.[5,6] The most common locations of bone metastasis are thought to be the spine, ribs, and pelvic bones.[7] These estimates, however, may be skewed due to the paucity of comprehensive population-wide studies.[8] Furthermore, modern advances in cancer treatment may not be reflected in these historic approximations.[9] Recent investigations suggest the incidence of bone metastases from specific primary tumours may be evolving over time.[10]

In addition, postoperative survival and complication rates following surgical intervention for bone metastases remain difficult to assess. In a systematic review of studies examining surgical treatment of bone metastasis, Wood et al[11] found a 17% complication rate and a 4% overall mortality rate for patients treated surgically for metastatic bone disease.[11] These figures were limited by heterogeneity of primary tumour, differences in fixation method, and quality of evidence between studies.[11] Prognostic factors have been proposed for postoperative survival, including preoperative anaemia and hypoalbuminemia and predictive scores such as the New England Spinal Metastasis Score, which attempt to characterize postoperative morbidity and mortality for specific sites of metastasis.[12,13] While the clinical support tool PATHFx (Prognostics AB, Sweden) has made significant advancements in predicting postoperative survival in these patients, there is still work to be done in externally validating outcomes data across all patient populations.[14]

Therefore, the primary aim of this study is to identify the prevalence of various primary tumour subtypes in a population of patients with bone metastases. The secondary aim is to investigate whether rates of pathological fracture and mortality following surgical intervention for bone metastases vary depending on primary tumour subtype. Finally, this study describes differences in patient characteristics and postoperative outcomes for patients who underwent surgical intervention for an impending fracture versus those with a completed fracture.

Methods

A retrospective review was performed by querying all unique patients who were diagnosed with metastatic bone disease from 2015 to 2020 using the Premier Healthcare Database (PHD). PHD is a hospital administrative payer database in the USA that comprises inpatient and outpatient health information from diverse health systems across the country. The PHD contains granular, patient-level data regarding patient demographic details, hospital factors, insurance status, International Classification of Disease (ICD) diagnosis codes, ICD procedural codes, Current Procedural Terminology (CPT) codes, medication administration, and services rendered in the inpatient setting. The PHD is a nationally representative database that includes patients from over 1,000 hospitals and hospital systems across the USA. Patients with a diagnosis of metastatic disease of the bone were identified using ICD Tenth Revision (ICD-10)[15] diagnosis code

Table II. Demographic details by primary tumour.

Variable	Mean age, yrs (SD)	Sex, n (%)		Race, n (%)					
		Female	Male	Asian	Black	Other	Unknown	Caucasian	Hispanic
Total		175,029	209,758	8,393	48,652	23,933	6,493	296,791	21,860
Oropharyngeal	63.6 (12.4)	1,496 (0.9)	4,222 (2.0)	177 (2.1)	612 (1.3)	425 (1.8)	116 (1.8)	4,390 (1.5)	305 (1.4)
Gastrointestinal	65.2 (12.0)	13,588 (7.8)	24,561 (11.7)	1,107 (13.2)	5,030 (10.3)	2,814 (11.8)	707 (10.9)	28,497 (9.6)	2,764 (12.6)
Lung	67.7 (10.6)	46,652 (26.7)	54,591 (26.0)	2,527 (30.1)	11,017 (22.6)	5,368 (22.4)	1,465 (22.6)	80,902 (27.3)	4,092 (18.7)
Breast	63.9 (13.2)	77,620 (44.3)	1,020 (0.5)	1,728 (20.6)	10,209 (21.0)	5,067 (21.2)	1,340 (20.7)	60,314 (20.3)	4,917 (22.5)
Bone	58.7 (20.3)	1,347 (0.8)	1,707 (0.8)	81 (1.0)	307 (0.6)	245 (1.0)	63 (1.0)	2,387 (0.8)	300 (1.4)
Skin	67.8 (13.7)	2,819 (1.6)	5,752 (2.7)	57 (0.7)	210 (0.4)	370 (1.5)	80 (1.2)	7,855 (2.6)	328 (1.5)
Mesothelial	60.2 (18.6)	1,944 (1.1)	2,410 (1.1)	100 (1.2)	588 (1.2)	342 (1.4)	83 (1.3)	3,243 (1.1)	360 (1.6)
Female reproductive	62.4 (13.2)	9,059 (5.2)	0 (0.0)	222 (2.6)	1,314 (2.7)	676 (2.8)	188 (2.9)	6,659 (2.2)	752 (3.4)
Prostate	74.1 (9.7)	8 (0.01)	78,925 (37.6)	1,343 (16.0)	12,986 (26.7)	4,974 (20.8)	1,484 (22.9)	57,517 (19.4)	4,318 (19.4)
Renal	66.6 (11.6)	4,928 (2.8)	11,444 (5.5)	285 (3.4)	1,394 (2.9)	1,050 (4.4)	247 (3.8)	13,403 (4.5)	1,196 (5.5)
Non-renal urological	71.6 (10.7)	2,225 (1.3)	8,129 (3.9)	169 (2.0)	852 (1.8)	543 (2.3)	146 (2.2)	8,645 (2.9)	511 (2.3)
Central nervous system	57.5 (19.9)	1,363 (0.8)	1,240 (0.6)	69 (0.8)	239 (0.5)	267 (1.1)	55 (0.8)	1,973 (0.7)	214 (1.0)
Endocrine	60 (20.4)	2,025 (1.2)	1,816 (0.9)	143 (1.7)	495 (1.0)	326 (1.4)	93 (1.4)	2,786 (0.9)	354 (1.6)
Myeloma	68.6 (11.1)	4,388 (2.5)	5,814 (2.8)	173 (2.1)	1,979 (4.1)	695 (2.9)	201 (3.1)	7,155 (2.4)	659 (3.0)
Lymphoma	68.7 (14.3)	3,707 (2.1)	5,727 (2.7)	133 (1.6)	919 (1.9)	541 (2.3)	163 (2.5)	7,679 (2.6)	570 (2.6)
Neuroendocrine	65.6 (11.8)	1,860 (1.1)	2,400 (1.1)	79 (0.9)	501 (1.0)	221 (0.9)	59 (0.9)	3,402 (1.1)	220 (1.0)

SD, standard deviation.

Table III. Complications by primary tumour.

Variable	Total, n	Pathological fracture, n (%)	Surgery, n (%)	90-day mortality, n (%)	1-year mortality, n (%)
Oropharyngeal	5,720	103 (1.8)	87 (1.5)	5 (5.8)	5 (5.8)
Gastrointestinal	38,155	842 (2.2)	607 (1.6)	61 (10.1)	70 (11.5)
Lung	101,279	2,855 (2.8)	2,396 (2.4)	289 (12.1)	333 (13.9)
Breast	78,685	2,085 (2.7)	1,883 (2.4)	107 (5.7)	132 (7.0)
Bone	3,083	78 (2.5)	64 (2.1)	3 (4.7)	3 (4.7)
Skin	8,572	162 (1.9)	121 (1.4)	11 (9.1)	15 (12.4)
Mesothelial	4,356	101 (2.3)	64 (1.5)	1 (1.6)	1 (1.6)
Female reproductive	9,059	285 (3.2)	124 (1.4)	11 (8.9)	15 (12.1)
Prostate	78,304	1,249 (1.6)	1,187 (1.5)	59 (5.0)	76 (6.4)
Renal	16,379	951 (5.8)	689 (4.2)	47 (6.8)	57 (8.3)
Non-renal urological	10,355	269 (2.6)	150 (1.5)	15 (10.0)	18 (12.0)
Central nervous system	2,603	22 (0.9)	19 (0.7)	2 (10.5)	2 (10.5)
Endocrine	3,843	105 (2.7)	80 (2.1)	5 (6.3)	8 (10.0)
Myeloma	10,203	347 (3.4)	308 (3.0)	18 (5.8)	23 (7.5)
Lymphoma	9,435	222 (2.4)	164 (1.7)	17 (10.4)	18 (11.0)
Neuroendocrine	4,262	47 (1.1)	44 (1.0)	4 (9.1)	5 (11.4)

for secondary malignant neoplasm of the bone (C79.51). Only unique patients were included in this analysis, excluding repeat admissions under the same PHD-specific patient identifier.

This study was exempt from institutional review board review as all patient information was anonymized in accordance with the Health Insurance Portability and Accountability Act.

Identification of study cohorts. The overall cohort of patients was further categorized on the basis of their primary malignancy. All primary malignancies encoded by the ICD-10 diagnosis coding system were assessed, including oropharyngeal, gastrointestinal, lung, primary bone, skin, mesothelial, breast, prostatic, female reproductive, urinary, nervous system, endocrine, neuroendocrine, and haematogenous. These categories were further divided into malignancies of specific organs/organ systems based on clinical relevance.

Primary and secondary outcomes. The primary outcome investigated in this study was the prevalence of primary malignancies among the cohort of patients with secondary bone metastases. This was calculated by identifying the proportion of all patients with a secondary bone malignancy who had a concurrent ICD-10 diagnosis code for

Table IV. Impending and completed fracture demographics.

Variable	Impending	Completed	p-value
Total	6,007	4,871	
Mean age, yrs (SD)	68.6 (12.1)	66.9 (11.6)	< 0.001*
Mean LOS, days (SD)	6.6	8.1	< 0.001*
Total cost, USD (SD)	24,860.26 (22,867.15)	29,228.49 (25,267.16)	< 0.001*
Male, n (%)	2,715 (45.2)	2,069 (42.5)	0.004†
Race, n (%)			
Asian	81 (1.4)	86 (1.8)	< 0.001†
Black	520 (8.7)	512 (10.5)	
Other	373 (6.2)	370 (7.6)	
Unknown	73 (1.2)	79 (1.6)	
Caucasian	4,960 (82.6)	3,824 (78.5)	
Hispanic	283 (4.7)	279 (5.7)	0.025†
Payer category, n (%)			
Managed care organization	998 (16.6)	852 (17.5)	< 0.001†
Medicare	3,949 (65.7)	2,960 (60.8)	
Medicaid	466 (7.8)	508 (10.4)	
Other	594 (9.9)	551 (11.3)	
Marital status, n (%)			
Married	2,924 (48.7)	2,306 (47.3)	0.127†
Other	577 (9.6)	463 (9.5)	
Single	2,490 (41.5)	2,078 (42.7)	
Bed size, n (%)			
< 100	209 (3.5)	170 (3.5)	< 0.001†
100 to 199	606 (10.1)	398 (8.2)	
200 to 299	880 (14.7)	605 (12.4)	
399 to 399	895 (14.9)	685 (14.1)	
400 to 499	792 (13.2)	565 (11.6)	
> 500	2,625 (43.7)	2,448 (50.3)	
Urban vs rural, n (%)			
Rural	601 (10)	496 (10.2)	0.760†
Urban	5,406 (90)	4,375 (89.8)	
Teaching status, n (%)			
No	2,550 (42.5)	1,910 (39.2)	0.001†
Yes	3,457 (57.6)	2,961 (60.8)	
Region, n (%)			< 0.001†
Midwest	1,439 (24)	984 (20.2)	
Northeast	1,073 (17.9)	1,048 (21.5)	
South	2,606 (43.4)	2,181 (44.8)	
West	889 (14.8)	658 (13.5)	

*Independent-samples *t*-test.
†Chi-squared test.
LOS, length of stay; SD, standard deviation.

Table V. Impending and completed fracture comorbidities.

Variable	Impending, n (%)	Completed, n (%)	p-value*
Total	6,007	4,871	
AKI/CKD	885 (14.7)	703 (14.4)	0.659
Alcohol abuse	137 (2.3)	120 (2.5)	0.532
Blood loss anaemia	106 (1.8)	78 (1.6)	0.511
CHF	624 (10.6)	445 (9.1)	0.014
Chronic PUD	27 (0.5)	27 (0.6)	0.439
Coagulopathy	555 (9.2)	462 (9.5)	0.662
COPD	1,392 (23.2)	1,080 (22.2)	0.215
Iron deficiency anaemia	291 (4.8)	274 (5.6)	0.068
Depression	902 (15.0)	723 (14.8)	0.801
DM without complications	707 (11.8)	635 (13)	0.046
DM with complications	665 (11.1)	587 (12.1)	0.111
Drug abuse	166 (2.8)	186 (3.8)	0.002
Fluid imbalance	1,706 (28.4)	1,596 (32.8)	< 0.001
HIV/AIDS	0 (0.2)	11 (0.2)	0.358
Hypertension	2,746 (45.7)	2,236 (45.9)	0.842
Hypothyroidism	949 (15.8)	759 (15.6)	0.758
Liver disease	269 (4.5)	215 (4.4)	0.872
Lymphoma	220 (3.7)	181 (3.7)	0.883
Obesity	824 (13.7)	775 (15.9)	0.001
Other neurological disorder	489 (8.1)	365 (7.5)	0.212
Paralysis	72 (1.2)	78 (1.6)	0.073
Peripheral vascular disease	374 (6.2)	263 (5.4)	0.068
Psychosis	38 (0.6)	35 (0.7)	0.585
Pulmonary circulation disorder	295 (4.9)	261 (5.4)	0.292
Rheumatoid arthritis	112 (1.9)	71 (1.5)	0.101
Valve disease	59 (1.0)	34 (0.7)	0.109
Weight loss	785 (13.1)	750 (15.4)	0.001

*Chi-squared test.
AKI, acute kidney injury; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; PUD, peptic ulcer disease.

any of the aforementioned primary malignancies. These proportions were aggregated across all study years. The secondary outcomes included rates of pathological long bone fracture as well as 90-day and 360-day mortality rates following surgical treatment related to metastatic bone disease. Surgical treatment was defined as either treatment of an impending pathological long bone fracture or treatment of a completed pathological long bone fracture.

A subanalysis was performed to assess patient demographics, hospital factors, rates of medical comorbidities, 90-day risks, and 360-day risks of postoperative outcomes for patients who underwent surgery for impending pathological fractures compared to those who underwent surgery after completed pathological fractures. These two cohorts were identified depending on whether a ICD-10 diagnosis code for pathological fracture was present at the time of their admission.

Statistical analysis. All patient demographic details, hospital factors, comorbidities, rates of postoperative outcomes, and prevalence of primary tumours were presented using descriptive statistics. Chi-squared and

Table VI. Impending and completed fracture complications.

			Univariate analysis		Multivariate analysis	
Variable	**Impending, n (%)**	**Completed, n (%)**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Total	6,007	4,871				
SSI	19 (0.3)	20 (0.4)	1.3 (0.69 to 2.44)	0.415	1.36 (0.72 to 2.57)	0.340
Sepsis	407 (6.8)	344 (7.1)	1.05 (0.90 to 1.21)	0.557	0.97 (0.83 to 1.13)	0.700
PE	187 (3.1)	206 (4.2)	1.37 (1.12 to 1.68)	0.002	1.31 (1.07 to 1.60)	0.010
DVT	184 (3.1)	211 (4.3)	1.43 (1.17 to 1.75)	< 0.001	1.36 (1.11 to 1.67)	0.003
Wound dehiscence	28 (0.5)	25 (0.5)	1.1 (0.64 to 1.89)	0.726	0.96 (0.55 to 1.66)	0.879
Seroma	7 (0.1)	4 (0.1)	0.7 (0.21 to 2.41)	0.576	0.68 (0.20 to 2.35)	0.542
Stroke	84 (1.4)	67 (1.4)	0.98 (0.71 to 1.36)	0.919	0.97 (0.70 to 1.34)	0.850
Pneumonia	324 (5.4)	304 (6.2)	1.17 (0.99 to 1.37)	0.05	1.12 (0.95 to 1.32)	0.182
Respiratory failure	553 (9.2)	457 (9.4)	1.02 (0.90 to 1.16)	0.753	0.99 (0.86 to 1.13)	0.887
MI	61 (1.0)	50 (1.0)	1.01 (0.69 to 1.47)	0.955	1.15 (0.78 to 1.69)	0.487
AKI	737 (12.3)	650 (13.3)	1.1 (0.98 to 1.23)	0.095	1.09 (0.96 to 1.23)	0.172
UTI	517 (8.6)	478 (9.8)	1.16 (1.01 to 1.32)	0.03	1.16 (1.01 to 1.32)	0.036
Transfusion	1,044 (17.4)	1,033 (21.2)	1.28 (1.16 to 1.41)	< 0.001	1.19 (1.08 to 1.32)	0.001
Acute blood loss anaemia	1,708 (28.4)	1,424 (29.2)	1.04 (0.96 to 1.13)	0.359	1.03 (0.95 to 1.13)	0.443
Haematoma	23 (0.4)	22 (0.5)	1.18 (0.66 to 2.12)	0.579	1.09 (0.60 to 1.97)	0.776
Haemorrhage	13 (0.2)	12 (0.3)	1.14 (0.51 to 2.50)	0.746	1.05 (0.47 to 2.33)	0.912
90-day mortality	397 (6.6)	384 (7.9)	1.21 (1.05 to 1.40)	0.011	1.14 (1.01 to 1.33)	0.045
360-day mortality	485 (8.1)	463 (9.5)	1.2 (1.05 to 1.37)	0.009	1.13 (1.02 to 1.30)	0.042
90-day readmission	690 (11.5)	634 (13.0)	1.15 (1.03 to 1.29)	0.015	1.1 (0.98 to 1.24)	0.098

AKI, acute kidney injury; aOR, adjusted odds ratio; CI, confidence interval; DVT, deep vein thrombosis; DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; SSI, surgical site infection; UTI, urinary tract infection.

independent-samples *t*-tests were used for categorical and continuous variables, respectively, to assess differences between patients treated for impending pathological fractures and those with completed fractures. Univariate regression analyses were performed to assess the 90-day risk of postoperative outcomes following surgery for the impending pathological fracture and completed fracture subanalysis. A multivariate model was designed to assess for potential confounders, including patient demographics, hospital factors, and medical comorbidities that approached a significant difference between cohorts ($p < 0.100$). Significance was defined as $p < 0.05$. All analyses were performed using STATA v. 16.1 (StataCorp).

Results

Primary cancer type. From 2015 to 2020, 407,893 unique patients with metastatic bone disease were identified and 14 primary tumour categories were assessed. The top five primary tumours were lung (24.8%), prostatic (19.4%), breast (19.3%), gastrointestinal (9.4%), and urological (6.5%) malignancies. (Table I) Uncategorized primary tumours comprised 5.7% of bone metastases (Table I).

Of the primary tumour subtypes, prostatic malignant tumours were associated with the oldest patients (mean 73.9 years (standard deviation (SD) 10.2) while central nervous system cancers were associated with the youngest patients (mean 57.5 years (SD 19.9)) (Table II). Excluding prostatic malignancies (37.6%), lung (26.0%), gastrointestinal (11.7%), renal (5.5%), and non-renal urinary (3.9%) tumours were the four most common malignant tumours occurring in male patients. Excluding breast tumours (44.3%), lung (26.7%), gastrointestinal (7.8%), female reproductive (5.2%), and renal (2.8%) tumours were the top four in female patients. The most common tumour subtypes by race were: lung in Asian patients (30.1%), prostatic in Black patients (26.7%), lung in Caucasian patients (27.3%), and breast in Hispanic patients (22.5%) (Table II).

Primary tumour locations. The top five tumours with the highest rates of long bone pathological fracture were renal (5.8%), myeloma (3.4%), female reproductive (3.2%), lung (2.8%), and breast (2.7%) (Table III). Renal (4.2%), myeloma (3.0%), breast (2.4%), lung (2.4%), and bone (2.1%) malignancies required surgery for metastatic bone disease most frequently (Table III).

The 90-day mortality rates following treatment of pathological fracture of the long bones were greatest in lung (12.1%), central nervous system (10.5%), lymphoma (10.4%), gastrointestinal (10.1%), skin (9.1%), and neuroendocrine (9.1%) malignancies (Table III). Lung (13.9%), skin (12.4%), female reproductive system (12.1%), non-renal urinary (12.0%), and gastrointestinal (11.5%) tumours were the five primary tumours most likely to result in one-year mortality following treatment of pathological fracture of the long bones.

Timing of surgery. Of the 407,893 patients with bony metastases, 10,878 (3.7%) required surgery for an impending or completed pathological fracture. Fixation

of impending pathological fractures was performed in 6,007 patients, while fixation for completed fractures was performed in 4,871. Patients in the impending fracture cohort were older (68.6 years (SD 12.1) vs 66.9 years (SD 11.6); p < 0.001, independent-samples *t*-test), more likely to be male (45.2% vs 42.5%; p = 0.004, chi-squared test), and had shorter postoperative length of stay (6.6 years (SD 7.4) vs 8.1 years (SD 8.1); p < 0.001, independent-samples *t*-test) than those in the completed group (Table IV). Impending fracture patients were more likely to be Caucasian (82.6% vs 78.5%; p < 0.001, chi-squared test) and more likely than those with completed fractures to be insured by Medicare (65.7% vs 60.8%; p < 0.001, chi-squared test). Patients with completed fractures were more likely than those with impending fractures to get treated at a teaching hospital and large hospitals with more than 500 beds (p < 0.001, chi-squared test).

Comorbidities based on surgery timing. Of the 27 comorbidities examined, statistically significant but quantitatively unremarkable differences in six were identified. Impending fracture patients had higher prevalence of congestive heart failure (10.6% vs 9.1%; p = 0.014, chi-squared test) than completed fracture fixation patients (Table V). Completed fracture fixation patients had higher prevalence of diabetes mellitus without complications (13.0% vs 11.8%; p = 0.046), drug abuse (3.8% vs 2.8%; p = 0.002), fluid imbalance (32.8% vs 28.4%; p < 0.001), obesity (15.9% vs 13.7%; p = 0.001), and weight loss (15.4% vs 13.1%; p = 0.001, all chi-squared test) than impending fracture patients (Table V).

Complications based on surgery timing. After accounting for potentially confounding factors, patients who underwent completed fracture fixation had increased risk for pulmonary embolism (PE) (adjusted odds ratio (aOR) 1.31 (95% confidence interval (CI) 1.1 to 1.6); p = 0.010), deep vein thrombosis (DVT) (aOR 1.4 (95% CI 1.1 to 1.7); p = 0.003), urinary tract infection (UTI) (aOR 1.16 (95% CI 1.0 to 1.3); p = 0.004), transfusion (aOR 1.2 (95% CI 1.1 to 1.3) p = 0.001), 90-day mortality (aOR 1.2 (95% CI 1.0 to 1.3); p = 0.045), and 360-day mortality (aOR 1.1 (95% CI 1.0 to 1.3); p = 0.042, all multivariate analysis) compared to patients who underwent prophylactic surgery (Table VI).

Discussion

Bone is a common location for metastatic disease, and symptomatic bone metastases complicate the disease course of up to 40% of patients with the most common malignancies.[6] In patients with breast and prostate cancer, bone metastases can be found in up to 70% of patients on post-mortem analysis.[5] Skeletal metastases are associated with pathological fractures, hypercalcemia, spinal cord injury, and exacerbation of cancer-related pain, and can complicate the treatment course of the primary disease.[16] Appropriate management of skeletal metastases requires multidisciplinary management, which includes an understanding of the primary tumour, disease course, potential for pathological fracture, and survival following surgical treatment.[17] Studies prior to the widespread introduction of targeted therapy and immunotherapy consistently identified breast, kidney, lung, prostate, and thyroid malignancies to be the major contributors to metastatic disease of the skeleton.[18–20] Our study demonstrates the primary tumours of contemporary patients with metastatic bone disease are most commonly lung, prostate, breast, gastrointestinal, and urinary malignancies. This shift, especially in the rise of gastrointestinal cancers metastatic to bone, is likely due, in part, to increased survival in this cohort thanks to immunotherapy and targeted therapy. As the number of patients with less common cancers metastatic to bone continues to rise, it is imperative that orthopaedic surgeons understand their survival profile and risk of pathological fracture, so as to best choose appropriate treatment options for these patients.[21]

Predicting survival following treatment of impending or completed pathological fracture has been historically challenging. Certain histologies, such as lung, have been associated with poorer survival, while others, such as breast, have longer life expectancy after treatment for skeletal metastases.[22,23] However, these generalizations may not accurately predict disease trajectory for individual patients. There has been significant interest over the last decade in improving our predictive abilities, as this may help determine the most appropriate surgical treatment for each patient. Bayesian belief network models have been developed to determine survival after treatment of impending or completed pathological fracture and validated across multiple datasets in a number of countries.[24–28] These networks, including the online clinical tool PATHFx, have since been applied to patients treated non-surgically for skeletal metastases as well.[14] More recently, machine learning has been applied to this problem in a dataset of 1,090 patients with promising results.[29] While not as individualized as these other methods, our cohort of over 400,000 patients and over 10,000 pathological fractures provides 90-day and 360-day mortality following pathological fracture treatment for 14 primary tumour categories. Of the 10,878 fractures analyzed, the impending fracture cohort included 6,007 patients and the completed fracture cohort included 4,871 patients, allowing for greater generalizability than any previous study. These data can be used to help prognosticate risk of pathological fracture and subsequent patient survival for each of these histological groups, and tailor appropriate surgical timing to the patient's needs.

The advantage of prophylactic treatment of impending pathological fractures has been debated. Early studies demonstrated no difference in outcomes between

impending and completed pathological fractures, both in terms of complications and survival.[30] A modern cohort of 270 matched impending versus completed pathological fractures demonstrated no difference in 90-day survival or 30-day postoperative complications, despite higher intraoperative blood loss, anaesthesia time, and transfusions in the completed fracture cohort.[31] Our study demonstrates improved 90- and 360-day survival in patients treated for impending pathological fracture compared to completed fracture, as well as significantly lower rates of DVT, PE, UTI, and blood transfusion, in a cohort ten times the size. Interestingly, 30-day postoperative complications after surgery for metastatic long bone disease has been associated with higher one-year mortality, making the avoidance of complications in this patient population even more important.[32] In light of these findings, surgeons may feel more empowered to recommend prophylactic fixation for their patients with symptomatic metastatic bone disease, especially considering that this has also been demonstrated to be cost-effective.[33]

This study has multiple limitations that should be discussed. As with any large dataset, our data may be subject to coding errors, both in general and as a problem specifically identified in metastatic bone disease.[34] Given the retrospective nature of these data, there may be unaccounted selection bias as to which patients received prophylactic fixation. This dataset does not have the ability to capture the patients' outpatient therapy regimens, so no conclusions can be drawn as to whether certain complications could be related to common medical treatments for specific diseases. Additionally, disease burden to other organ systems could not be quantified. While this would affect survival, it is less likely to influence the treatment of pathological long bone fractures, except in the sickest cohort of patients at the very end of life. Finally, neoadjuvant or adjuvant radiation therapy could not be assessed, which is a mainstay of treatment for metastatic disease.

Despite these limitations, there are multiple strengths to this study. With a cohort size of over 400,000 patients and 10,878 pathological fractures, this is the largest study examining this clinical entity. Our large sample size allowed us to perform a robust analysis of all possible primary malignancies encoded by the ICD-10 coding system, and demonstrate a shift in the most common types of primary tumours seen in metastatic bone disease compared to historical series. Such data are important as clinicians assess disease type and trajectory, and help make decisions regarding metastatic disease care. This study was also able to retrospectively assess whether patients underwent prophylactic fixation of an impending fracture or surgery for a completed pathological fracture in a large patient population, which allowed for a robust assessment of postoperative outcomes. Finally, the PHD provides us the ability to examine mortality data of each tumour subtype on a granular scale. The use of this large-scale database to identify relative complication profiles and mortality among different tumour histologies will provide surgeons with an improved understanding of patient outcomes in those with impending fractures or completed fractures due to primary bone metastases.

This study defines the contemporary demographics of primary malignancies resulting in metastatic bone disease. It is important to understand the survival profile and risk for pathological fracture associated with each tumour subtype. Furthermore, patients with completed pathological fractures are more likely to experience postoperative complications, including 90-day and 360-day mortality. Physicians should consider these data when determining whether to choose prophylactic fixation of an impending fracture, and to prognosticate patient outcomes during treatment of their metastatic bone disease.

Take home message

- This is the largest modern cohort of patients with metastatic disease to bone.
- With increases in survival and treatment options, the primary sites of disease are shifting.
- Patients who are surgically stabilized for impending pathological fractures have lower complication rates and improved survival, compared to patients treated for completed pathological fractures.

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