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Research Paper

Profile of Surgically-treated Metastatic Extremity Bone Tumours at a University Hospital in Hong Kong
在香港一所大學醫院用手術治療的轉移性肢端骨腫瘤的概況

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ABSTRACT

Background/Purpose: Metastatic deposits in bones increase overall morbidity in cancer patients. The orthopaedic oncologist aims at controlling the skeletal morbidity as a way of reducing the overall morbidity in the survival period of the cancer patient. This study investigated the characteristics of metastatic extremity bone tumours requiring surgical treatment, with a view to setting a template for a local database of extremity metastatic bone tumours in Hong Kong.
Methods: A retrospective review of metastatic extremity bone tumours treated surgically at a university hospital in Hong Kong, from January 2006 to December 2015, is presented.
Results: In total, 126 patients were studied. The lung (28.6%) was the most common source of metastasis to the extremity bones. The femur (70.1%) was most commonly involved. Pathological fractures (47.4%) were the most common indications for surgery. Intramedullary nailing (57.3%) was the most common surgical treatment. The overall postoperative complication rate was 8.7%. The mean duration of follow-up was 10.8 ± 4.1 months. Furthermore, 79.4% of the patients died within the study period, with mean duration of postoperative survival of 6.1 ± 1.1 months. Spinal compression ($p = 0.001$), indication for surgery ($p = 0.001$), age of the patient ($p = 0.001$), and option of surgical treatment ($p = 0.000319$) were found to have significantly affected the duration of postoperative survival.
Conclusion: The surgical management of extremity bone metastasis is a key consideration in averting potentially crippling morbidity. Options of treatment need be carefully chosen in appropriate patients for a good outcome.

中 文 摘 要

背景：腫瘤的骨轉移增加了癌症患者的病況。骨科腫瘤學家旨在控制骨骼的病況來降低癌症病人的總病態。這項研究調查需要手術治療的轉移性肢端骨腫瘤的特點，以便建立香港的轉移性肢端骨腫瘤的本地數據庫模板。
方法：回顧性研究由2006年1月至2015年12月在一所香港大學醫院手術治療的轉移性肢端骨腫瘤個案。
結果：共有126例患者進行了研究。肺部（28.6%）是最常見轉移到肢體骨骼的來源。股骨（70.1%）是最常見出現骨轉移的位置。病理性骨折（47.4%）是最常見的手術適應症。髓內釘（57.3%）是常見的手術治療方法。整體術後併發症發生率為8.7%。平均隨訪時間為10.8 ± 4.1個月。79.4%的患者在研究期內死亡，平均術後生存期為6.1 ± 1.1個月。脊柱壓迫（P值 = 0.001）、手術適應症（P值 = 0.001）、患者年齡（P值 = 0.001）、手術方法的選擇（P值 = 0.000319）都顯著影響術後生存期。
結論：手術治療肢體骨轉移是避免潛在的致殘發病率關鍵。要達到好的結果，需要為合適的病人仔細選擇治療的方法。

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Introduction

Opinion is divided in literature with respect to whether or not the skeleton is the most common site of metastatic disease ahead of the lung and the liver.[1–3] Whereas Teixeira et al[1] hold that bone is the third most common site for metastatic disease, after lung and liver, Utzschneider et al[2] and Coleman[3] have stated that the skeleton is the most common site affected by metastatic cancer. Metastatic lesions are the most common malignant tumours affecting the skeleton, representing a significant burden on the healthcare system in a place like the United States, where more than 280,000 adults had metastatic bone disease as at 2008.[4] The vulnerability of bone to metastasis is a consequence of the high blood flow under low pressure in the areas of red marrow, making the bone matrix a fertile ground for the implantation of tumour cells.[1] Although virtually any malignancy can metastasise to bone, about 80% of skeletal metastases originates from primary diseases in the breast, prostate, lung, kidney, and thyroid. The incidence is reportedly greatest for breast and prostate cancers.[5] A number of adhesion molecules have been found to play significant roles in tumour cell osteotropism.[6,7]

The appendicular skeleton, understandably, presents a large surface area for deposition of tumour metastasis. Metastatic deposits in these sites predispose to pain, mechanical instability, and fractures, all of which contribute to the overall morbidity and reduced survival in cancer patients. Managing bony metastatic disease can be challenging.[5] Lytic skeletal metastases, especially when located in the extremity bones, present the patient and the surgeon with the risk for impending pathologic fracture requiring a decision for surgical intervention. Large destructive lesions in the femur and hip areas are particularly worrisome.[5] Stabilisation of impending and pathologic fractures, restoration of mobility and gait, with resultant reduction in the overall morbidity during the survival period of the cancer patient, are the major objectives of orthopaedic surgical interventions in bone metastases. Surgery should, therefore, provide pain relief and improve the quality of life (QoL).[1,8,9]

There is paucity of literature, in Hong Kong, on metastatic bone diseases in general and metastatic extremity bone tumours in particular. To the best of our knowledge, there is no literature regarding such a study in tumour patients in this region. The aim of this study was to investigate the characteristics of metastatic extremity bone tumours that required surgical treatment at a university hospital in Hong Kong and to set a template for a local database of extremity metastatic bone tumours in Hong Kong.

Methods

This was a 10-year retrospective observational review of metastatic extremity bone tumours treated surgically from January 2006 to December 2015. The study was approved by the University/Hospital Authority Hong Kong West Cluster Institutional Review Board (Division of General Orthopaedics and Orthopaedic Oncology, Department of Orthopaedics and Traumatology, University of Hong Kong, Queen Mary Hospital, Pok Fu Lam Road, Hong Kong) (Reference Number UW 15-414). All patients gave informed consent prior to surgery.

The particulars of patients seen at the orthopaedic department of the hospital for metastatic bone disease in the given period were retrieved from the medical health records. With the help of patients' particulars, the electronic patients' record domiciled in the hospital's Clinical Management System (CMS) was accessed. Patients that were treated by surgical operative procedures for extremity metastases were isolated as the study population.

The inclusion criterion was extremity metastasis treated by surgical operation. Patients treated surgically for bony metastasis in the upper and lower limbs including the pelvic and pectoral girdles were included. The exclusion criteria were primary bone tumours, extremity soft tissue tumours, cases that did not have surgery to the extremity, cases treated conservatively, craniofacial metastasis, more than one primary site, cases outside the study period, incomplete entries into the CMS, and those whose hospital numbers were returned as invalid and could not be accessed.

The clinicopathological data of patients in the study population, as contained in the CMS, was studied with attention to the following: demographics, diagnosis and site of primary tumour, extremity bone affected by metastasis, indications for surgery, options of operative procedures, date of surgery, complications related to surgery, and date of discharge and of last follow-up. The use of postoperative adjuvant therapy and occurrence of skeletal-related events (SREs) were noted. Where applicable, the date of death was also noted. All patients signed informed consent prior to surgery and had physiotherapy as well as oncological follow-up in the postoperative period. Clinical diagnoses of metastatic bone tumour arising from pre-existing primary tumours were validated by radiological and histopathological examinations and reports. Histopathological reports of bone tissue biopsy specimens taken at the time of bone surgery were compared with those of primary tumours.

Data were analysed using the SPSS version 17 (SPSS Inc., Chicago, IL, USA). Frequency distributions were generated for all categorical variables. Numeric variables were assessed using Student *t* test, and categorical variables were assessed using Chi-square test. A p value < 0.05 was considered statistically significant.

Study limitations

A good number of patients are seen by oncology and other specialties and, therefore, orthopaedic referrals could either come late or not at all.

This was a retrospective study as stated in the methodology. Consequently, we did not have the opportunity of setting up and observing the known objective criteria for measuring the QoL in these patients at such designated periods as preoperative, immediate postoperative or 3 months postoperative, as would have been the case in a prospective study.

Results

In total, 280 patients were seen for bone metastases in the study period. Cancer patients from different specialties were followed-up at different departments of the hospital; therefore, the number of patients seen in the orthopaedic department for bone metastases depended on referrals from these sources. Of the 280 patients, 126 (45.0%) met the study criteria and were included in the analysis, covering the period of 2006–2015 (Figure 1). The remaining 154 patients that were excluded from the study did not meet the inclusion criteria despite having metastatic bone disease. They were

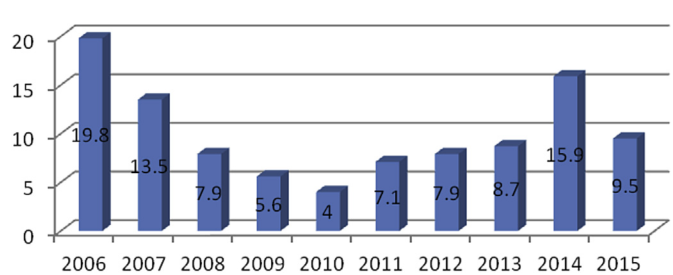

Figure 1. Percentage representation of patients seen according to year.

excluded based on criteria, such as not having been operated in the extremity (e.g., those operated in the spine), cases treated conservatively, craniofacial metastasis, more than one primary site, cases with incomplete entries into the CMS, and those whose hospital numbers were returned as invalid and could not be accessed in the CMS.

The highest number of patients needing surgery for extremity metastases was recorded in 2006, representing 25 (19.8%) patients of the study population. There were 70 (55.6%) female and 56 (44.4%) male patients, with a male to female ratio of 1:1.3. The age range was 14–96 years, with a modal range of 55–69 years (49.2%), and a mean age of 64.1 ± 6.0 years (Table 1).

The lung was the most common site of primary malignancy, accounting for 36 (28.6%) of the cases. This was followed by 22 (17.5%) from the breasts, 15 (11.9%) from the kidneys, 11 (8.7%) from the prostate, 10 (7.9%) from the liver, and eight (6.3%) from the gastrointestinal and colorectal areas, in that order. Furthermore, five (4.0%) were malignancies of unknown primaries (Table 2). The femur (70.1%) was the most commonly affected bone. This was followed by the humerus (18.2%) and the pelvis (5.8%). Other bones affected were tibia (2.9%), clavicle (1.5%), ulna (0.8%), and patella (0.8%). Distribution of metastatic deposits on the long bones showed a predilection for the proximal third (75.4%), followed by the middle third (14.8%), and then the distal third (6.6%). The neck of femur alone accounted for 3.3% of the sites of deposition of metastasis on the long bones. The entire proximal third of femur accounted for 78.7% of the metastatic sites.

A total of 135 surgical indications were recorded in 126 patients, namely 64 (47.4%) pathologic fractures, 59 (47.4%) impending pathologic fractures, and 12 (8.9%) solitary metastases. In total, 131 surgical procedures were performed in 126 patients. Intramedullary nailing was the commonest surgical procedure accounting for 75 (57.3%) of all procedures. Only 2 (2.7%) of the intramedullary nails required cement augmentation; 17 (13%) plate fixations, 15 (11.5%) hip hemiarthroplasty, eight (6.1%) tumour resections, among others were also commonly done. Four tumour resections were reconstructed with cemented tumour prostheses; two with cemented allografts and the remaining two (clavicle and iliac bone resections) did not need reconstruction. Additionally, 29.4% of plate fixations were augmented with bone cement (Table 3). Eight (6.1%) other less commonly done procedures for extremity metastases in this study were shoulder hemiarthroplasty (1), total elbow replacement (1), hip disarticulation (1), patellectomy (1), excision hip arthroplasty (2), above knee amputation (1), and cannulated screw fixation (1).

In total, 115 (91.3%) patients had postoperative adjuvant therapy, whereas 11 (8.7%) did not for reasons that included refusal of treatment and being lost to follow-up. Options of postoperative adjuvant treatment and frequency of use of the various modalities were radiotherapy (58.5%), chemotherapy (10.2%), bisphosphonate (20.5%), targeted therapy (8.5%), and hormonal therapy (2.3%). In the entire study, 11(8.7%) postoperative complications were observed. Of the study population, 115(91.3%) patients had no complications referable to the surgical treatment. Infection was the most common complication, and the overall infection rate in the entire study was 3.9%. Two (1.6%) patients had failed rehabilitation in physiotherapy and were confined to wheel chairs. Two (1.6%) cases of failed implant were recorded as a result of recurrence of tumour. At the time of this report, 100 (79.4%) patients were documented as dead and 13 (10.3%) as alive and still attending follow-up clinics. The postoperative survival status of another 13 (10.3%) patients could not be conclusively established from the available information in the clinical record. The mean duration of postoperative survival prior to death among the 100 patients was 6.1 ± 1.1 months. The duration of postoperative survival was measured from the date of surgery to the date the patient was certified dead by the attending medical personnel. The 13 surviving patients were noted to have so far survived an average period of 26.7 months, measured from the date of surgery to the date of documented last follow-up visit. The average duration of follow-up in the entire study population was 10.8 ± 4.1 months (range, 0.1–104.8 months).

A cross tabulation of the duration of postoperative survival prior to death against the site of primary tumour, age of the patients, indications for surgery, and surgical procedures performed is presented (Tables 4–8). The overall survival rate beyond 12 months for the entire study population was 23%. Renal cell carcinoma had the best individual survival rate of 41.7% beyond 12 months as well as the best mean duration of postoperative survival period of 8.2 months among the large group of commonly encountered malignancies in this study (Table 4). This was followed by gastrointestinal/colorectal cancers (25%), carcinomas of the breast (31.3%), and lung cancers (16.1%). This relationship as it applied to

Table 1
Age distribution (mean age = 64.1 ± 6.0 years)

Age range (y)	*n* (%)
10–24	1 (0.8)
25–39	6 (4.8)
40–54	16 (12.7)
55–69	62 (49.2)
70–84	33 (26.2)
85–99	8 (6.3)
Total	126 (100)

Table 2
Site of primary malignancy

Site of primary malignancy	*n* (%)
Breast	22 (17.5)
Thyroid	4 (3.2)
Liver	10 (7.9)
Prostate	11 (8.7)
Uterus/cervix/ovaries	2 (1.6)
Lung	36 (28.6)
Kidneys	15 (11.9)
Gastrointestinal	8 (6.3)
Lymphoproliferative tissue	4 (3.2)
Pancreas	3 (2.4)
Nasopharynx	2 (1.6)
Others	4 (3.2)
Unknown	5 (4.0)
Total	126 (100)

Table 3
Surgical procedures/options for treatment (131 surgical options in 126 patients)

Option of surgery	*n* (%)
Plate fixation	17 (13.0)
Intramedullary nailing	75 (57.3)
Hemiarthroplasty	15 (11.5)
Resection and reconstruction	8 (6.1)
Curettage and cementation	4 (3.1)
Total hip arthroplasty	4 (3.1)
AO screw fixation	1 (0.8)
Above knee amputation	1 (0.8)
Excision hip arthroplasty	2 (1.5)
Patellectomy	1 (0.8)
Hip disarticulation	1 (0.8)
Total elbow arthroplasty	1 (0.8)
Neer (Shoulder) hemiarthroplasty	1 (0.8)
Total	131 (100)

Table 4
Cross-tabulation of duration of survival according to site of primary tumour in 100 patients (duration of survival in months versus site of primary tumour)

Site of primary tumour	Survival period (mo)							
	0–2.0	2.1–4.0	4.1–6.0	6.1–8.0	8.1–10.0	10.1–12.0	>12.0	Total
Breast	2	7	1	1	—	—	5	16
Thyroid	—	1	—	—	—	—	—	1
Liver	2	3	1	—	—	—	1	7
Prostate	1	3	1	2	—	—	1	8
Uterus/cervix/ovaries	—	1	—	—	—	—	1	2
Lung	7	5	9	3	1	1	5	31
Kidney	2	1	1	2	1	—	5	12
Gastrointestinal/colorectal	1	3	2	—	—	—	2	8
Lympho-proliferative	1	—	—	—	1	—	—	2
Pancreas	1	—	1	—	—	—	—	2
Nasopharynx	—	—	—	—	—	1	1	2
Urinary bladder	—	—	—	—	—	—	1	1
Bone	—	—	—	—	—	1	—	1
Oesophagus	—	—	—	—	1	—	—	1
Melanoma	—	—	—	—	—	—	1	1
Unknown	3	1	—	1	—	—	—	5
Total	20	25	16	9	4	3	23	100

Chi-square test = 5.0519; $p = 0.28201$.

Table 5
Cross-tabulation of duration of survival according to age in 100 patients (duration of survival in months versus age of patients).

Age distribution (y)	Survival period (mo)							
	0–2.0	2.1–4.0	4.1–6.0	6.1–8.0	8.1–10.0	10.1–12.0	>12.0	Total
10–24	—	1	—	—	—	—	—	1
25–39	—	2	1	—	—	1	2	6
40–54	1	4	1	—	—	1	3	10
55–69	12	7	7	5	4	1	12	48
70–84	5	8	7	3	—	—	5	28
85–99	2	3	—	1	—	—	1	7
Total	20	25	16	9	4	3	23	100

Chi-square test = 19.0659; $p = 0.000763$.

Table 6
Cross-tabulation of duration of survival according to indications for surgery in 98 patients (duration of survival in months versus indications for surgery)

Indications for surgery	Survival period (mo)							
	0–2.0	2.1–4.0	4.1–6.0	6.1–8.0	8.1–10.0	10.1–12.0	>12.0	Total
Impending pathologic fracture	6	8	8	2	1	2	14	41
Pathologic fracture	12	14	8	6	3	1	8	53
Solitary metastasis	1	1	—	1	1	—	—	4
Total	19	23	17	9	5	3	22	98

Chi-square test = 13.6267; $p = 0.001099$.

Table 7
Cross-tabulation of duration of survival according to options of surgical treatment in 100 dead patients (duration of survival in months versus options of surgical treatment)

Options of surgical treatment	Survival period (mo)							
	0–2.0	2.1–4.0	4.1–6.0	6.1–8.0	8.1–10.0	10.1–12.0	>12.0	Total
Plate fixation	3	6	3	1	—	—	3	16
Intramedullary nailing	12	13	8	3	3	3	16	58
Hemiarthroplasty	2	5	2	3	—	—	1	13
Resection and reconstruction	1	—	—	2	—	—	2	5
Curettage and cementation	—	—	—	—	—	—	1	1
Total hip arthroplasty	1	—	2	—	—	—	—	3
Others	1	1	1	—	1	—	—	4
Total	20	25	16	9	4	3	23	100

Chi-square test = 20.9836; $p = 0.000319$.

the mean survival periods according to the major primary sites of breast, liver, prostate, lung, and kidney was, however, not found statistically significant at $p < 0.05$ (Chi-square test = 5.0519; $p = 0.282$).

The relationship between the duration of postoperative survival and age in 100 patients showed that the mean duration of postoperative survival (Table 5) decreased steadily with increasing age from 8.1 months in the age group of 25–39 years to 4.5 months in

Table 8
Skeletal-related events (SREs)

Type and total number of SREs in all patients	Distribution of SRE among the patients				
	No. of events	No. affected in the entire population	No. affected among the surviving patients	No. affected among the dead patients	Mean survival (mo) before death
Pathologic fracture 71 (34.3)	1	56 (44.4)	9 (69.2)	42 (42.0)	7.8
Spinal compression 7 (3.4)	2	61 (48.4)	4 (30.8)	50 (50.0)	8.4
Radiation or surgery to bone 120 (58.0)	3	8 (6.3)	—	7 (7.0)	12.2
Hypercalcaemia 9 (4.3)	4	1 (0.8)	—	1 (1.0)	2.3
Total 207 (100.0)	Total	126 (100.0)	13 (100.0)	100 (100.0)	

Data are presented as *n* (%).
Chi-square test = 3.4449; $p = 0.063446$.

the age group of 85–99 years (Chi-squared test = 19.0659; $p = 0.001$).

Two cases with multiple indications for surgery were excluded from cross-tabulation analysis of survival period against indications for surgery (Table 6). Prophylactic fixations or fixations for impending fractures were associated with postoperative survival rate of 34.1% beyond 12 months compared with fixations for actual pathological fractures which had postoperative survival rate of 15.1% beyond 12 months. The mean duration of postoperative survival after fixation for impending pathologic fractures was 7.3 months compared with 5.3 months after fixation for established pathologic fractures (Chi-squared test = 13.6267; $p = 0.001$).

Tumour resection and reconstruction as well as curettage and cementation procedures were associated with higher survival rates after 12 months than other modalities of surgery (Table 7). Moreover, 40% of patients that died after resection and reconstruction surgery survived beyond 12 months with a mean survival period of 8.2 months compared with 27.6% patients and 6.6 months in the intramedullary nailing group and 18.8% patients and 5.2 months in the plate fixation group (Chi-square test = 20.9836; $p = 0.000319$).

A total of 13 patients were still attending follow-up clinics at the time of preparing this paper. The average age of the long survivors was 67.2 years. There were seven male and six female patients, and the average duration of follow-up so far was 26.7 months. The sites of primary malignancies among the long survivors were prostate (3), kidneys (2), breasts (3), thyroid (2), lung (2), and liver (1). Five were operated for solitary metastases, four for impending pathologic fractures, and four for pathological fractures. Six had intramedullary nailing, two had curettage with cementation, one had total hip replacement, one had shoulder arthroplasty, and three had resection surgery. Out of the three resection surgeries, one (clavicular resection) did not require reconstruction, and the remaining two had allograft and modular endoprosthetic reconstructions, respectively.

A total of 207 SREs were recorded in 126 patients (Table 8). Radiation or surgery to the bone (58.0%) was the commonest SREs in the entire study population. Others were pathologic fracture (34.3%), spinal compression (3.4%), and hypercalcaemia (4.3%). Of the entire study population, 56 (44.4%) patients had only one SRE, whereas 70 (55.6%) patients had more than one SRE. Nine (69.2%) of the surviving patients had only one SRE, whereas four (30.8%) of them had more than one SRE. Furthermore, 42 (42.0%) patients that died within the study suffered only one SRE, whereas 58 (58.0%) suffered more than one SRE. The rate of mortality was noticed to be also directly proportional to the number of SREs, but this relationship was not found statistically significant at $p < 0.05$ (Chi-square test = 3.4449; $p = 0.063$). Also, the number of SREs did not have any consistent effect on the mean survival duration before death in 100 patients (Table 8).

Among the dead, 93 did not have spinal compression with evidence of neurological signs and were found to have a mean survival duration of 8.7 months compared with seven that had spinal compression and mean survival duration of 5.4 months (Chi-square test = 10.751; $p = 0.001$). This is shown in Table 9.

Discussion

As prolonged survival is recorded in more patients with primary malignancies following advances in oncological and surgical treatments, it is expected that the prevalence of metastatic bone diseases would also be on the increase.[1,8] This has been postulated to imply that the burden of the primary malignant diseases with the potentials of bone metastases would assume a chronic proportion.[8] Therefore, there is bound to be an increase in the need for stabilisation of impending and actual pathologic fractures, restoration of mobility and gait, as a means of contributing to the reduction in the overall morbidity during the survival period of cancer patients.[1,8,9]

This is a retrospective observational review of surgically-treated metastatic extremity bone tumours. The basic demographic data of patients in this study with respect to age parameters and sex distribution is in agreement with reports elsewhere of patients affected by bone metastases in general.[1,2,8,10] The slight preponderance of females over the males as well as the mean age of the patient population observed in our study is corroborated by these other reports. Such primary carcinomas as prostate, breast, kidney, lung, and thyroid cancers have been associated with high risks of metastatic bone diseases and are known to be responsible for 80% of all the metastases to the bone.[9,11] There is a variation in the relative individual contributions of these primary malignancies to the burden of bone metastases. According to Coleman,[3] 70% of patients dying of breast and prostate carcinomas have evidence of metastatic bone disease, whereas thyroid, kidney, and bronchogenic carcinomas produce bone metastases, with incidence of 30–40% at post mortem examinations. Gastrointestinal tract tumours are reported to be rarely (< 10%) involved in bone metastases,[3] and this seems to agree with our finding, in which gastrointestinal tract tumours contributed 6.3% to the sources of bone metastases encountered in our study. Other authors[1,8] have also written to strengthen the view that the breast is the most common source of metastasis to the bone. This does not agree with the finding in our study which shows that the lung (28.6%) is the most common source of bony metastases in Hong Kong. It is followed by the breast (17.5%) and kidneys (11.9%). The contribution of hepatocellular carcinoma (7.9%) to extremity metastases in our study is noteworthy. Some authors[12–14] believe that bone metastasis in hepatocellular carcinoma is an emerging issue as literature evidence shows that bone had long been regarded as an uncommon site of metastasis. Hepatocellular carcinoma skeletal involvement was rarely diagnosed until a few years ago, and this is thought to be responsible for the nature and characteristics of bone metastases in hepatocellular

Table 9
Effect of spinal cord compression on duration of survival before death among 100 patients

Subset	No.	Average survival period (mo)
Extremity metastasis with cord compression	7	5.4
Extremity metastasis without cord compression	93	8.7

Chi-square statistic = 10.751; $p = 0.001042$.

carcinoma not being fully explored in literature.[12] Advances in imaging techniques now make possible the early detection of osseous involvements by hepatocellular carcinoma. This includes the use of dual-tracer positron emission computerised tomography,[12,13] which is also employed in the assessment of cancer patients in our centre. A few larger series[15] have reported the incidence of bone metastasis from hepatocellular carcinoma as 8–23%, and this also seem in agreement with our finding. On the strength of their findings, Ho et al[13] concluded that bone is not a rare site of metastasis in hepatocellular carcinoma.

The biological mechanisms underlying metastasis and bone destruction by malignant cells have been documented.[7,16,17] Chemokine receptors, cell adhesion molecules, and cell surface receptors are factors produced by tumour cells which enable them to attach to and establish growth in the bone matrix.[16] Tumour cells attach to the basement membrane of the vessel wall in distant sites using proteolytic enzymes such as integrins and cadherins. They disrupt the receptor site basement membrane and subsequently migrate into the substance of the distal host tissue. By means of chemotactic factors as well as receptor activator of nuclear factor kappa-B ligand (RANK ligand), the tumour cells stimulate osteoclast activity, causing bone resorption and leading to the formation of lytic areas in the bone in which the tumour cells grow. The RANK ligand is a soluble transmembrane protein required for the formation, function, and survival of osteoclasts. Also, some tumours such as breast carcinomas and oat cell carcinomas are specifically known to express substances like parathyroid hormone-related peptide, which promote bone resorption.[7,17]

The femur is the most common site for metastatic bone disease requiring surgery. In the study by Yehuda et al,[10] the femur was the most common site of renal cell carcinoma metastasis requiring surgery. Also the work by Teixeira et al[1] showed that the femur accounted for 79.7% of metastatic sites requiring surgery in their patients. In both series, the proximal femur (hip) was the most common site of metastasis needing surgery. These findings are in consonance with ours, in which the femur accounted for 70.1% of all metastatic sites and the proximal femur (hip) 78.7% of the metastatic sites on the femur itself.

A key outcome measure in this study was the duration of patients' survival after surgical intervention. This was examined against such group characteristics as age of the patients, sites of primary malignancies, indications for surgery, and options of surgery offered among a total of 100 patients that were already dead within the study period. We found that the overall mean duration of postoperative survival among the 100 patients was 6.1 ± 1.1 months. Also, 78% of the patients died within the 1st year after surgical treatment. This is very similar to the report by Utzschneider et al,[2] who reported 78% death rate within the 1st year after surgical treatment among their patients treated for bone metastasis from lung cancers, with a mean duration of postoperative survival of 7.1 months. Similarly, in a series of 64 patients that underwent surgical treatment for bone metastases, Teixeira et al[1] recorded a mean survival of 9.20 ± 11.96 months (median, 6.6 months). Current guidelines suggest that surgical treatment for bone metastases be considered, when indicated, in patients with life expectancy of more than 3 months.[18,19] The estimation of life expectancy is within the domains of the oncologists, but the essence of the surgical intervention is to maximise the quality of remaining life.[8,9,18] Metastatic deposits predispose to pain, mechanical instability, and fractures, thus contributing to the overall morbidity in cancer patients. This is an important consideration in patients with extremity metastasis in whom ambulatory potentials can be seriously marred. Therefore, stabilisation of impending and pathologic fractures, restoration of mobility and gait, in carefully selected patients, reduce the overall morbidity in the survival period of the cancer patients. It is well understood that treatment of bone metastases is palliative and that surgery is probably one of the most important aspects of multimodal therapies available to these patients, which play together to improve prognosis.[2,9,20–22]

The relationship between the mean duration of postoperative survival and age of the patients was found significant in our study. The mean duration of postoperative survival (Table 5) decreased steadily with increasing age from 8.1 months in the age group of 25–39 years to 4.5 months in the age group of 85–99 years (Chi-square test = 19.0659; $p = 0.001$). Although this is significant at $p < 0.5$, we believe that it is still in order to think that medical co-morbidities may have also had a contributory effect. This, however, was not tested in this study, but medical co-morbidities were found to be a major concern among the elderly in our study population. It may well also be that the younger patients tolerated the entire burden of tumour, including the biochemical changes in tumour metastasis, better than the elderly. However, in a study of 58 patients with bone metastasis from lung cancer, Utzschneider et al[2] found that the patients' age did not influence the postoperative survival time.

It appeared that the mean duration of postoperative survival was better in relation to some primary sites of tumour, with the renal cell carcinoma group leading at 8.2 months among such other major primary sites as breast, prostate, lung, thyroid, and liver (Table 4). However, we did not find this relationship statistically significant (Chi-square test = 5.0519; $p = 0.282$). Although this may not be significant in this study, perhaps due to the limited size of our sample, renal cell carcinoma metastasis is reputed to be amenable to surgical interventions, especially resection surgeries.[9,23] Because of the expected survival associated with renal cell carcinoma, it is advocated that patients with metastatic renal cell carcinoma of bone be given the opportunity of the needed palliative orthopaedic procedures.[10,24] The oncological objective of excising metastatic renal cell carcinoma of bone is the achievement of local tumour control, which is the most appropriate criterion to evaluate the oncological adequacy of resection margins. In renal cell carcinoma, a significant percent of the patients live a few years after clinical presentation.[10]

Impending pathologic fracture was the most common indication for surgery recorded in this study (Table 6). The definition of impending pathologic fractures in this study was according to the Mirels[25] scoring system. In the literature, it is recommended that surgery be done in all cases where metastases posing risks of fractures are diagnosed, and this applies to lesions with Mirels score of > 7.[3] Such prophylactic surgeries for impending pathological fractures are believed to impact the QoL positively and perhaps the survival profile of patients with extremity metastasis.

Overall treatment results are better in cases where pathological fractures have not occurred.[8] The patient that had prophylactic fixations in this study had significantly higher postoperative duration of survival than the ones operated for actual pathological fractures. This finding is statistically significant at $p < 0.05$ (Chi-square test = 13.6267; $p = 0.001$). We think that it is difficult to measure the lag in time between metastasis detection and fracture and that much less complication is associated with prophylactic fixation. This supposition is, however, subject to proof. Otherwise, it may be argued that the higher postoperative duration of survival in those with prophylactic fixations than those with fixation for actual pathological fractures only reflects the natural history of the disease process, but not the effect of surgery.

Resection surgeries with curative intents are often indicated for solitary metastases. There is lower incidence of recurrence, and evidence shows that survival rates after resections are higher than after other standard treatments.[8] This corroborates the finding in this study, whereby patients who had surgical resections and reconstructions (Table 7) were found to have a higher mean postoperative survival period of 8.2 months in comparison with the ones who had intramedullary nailing or plate fixation. This finding is statistically significant at $p < 0.05$ (Chi-square test = 20.9836; $p = 0.000319$). If this finding can be further confirmed in subsequent large-scale studies, it would change our future indication for surgical treatment in this group of patients.

The indications for amputation due to cancer metastases are extremely rare.[8] Only one patient (0.8%) had an above the knee amputation in this study.

We noticed that the number of mortality was directly proportional to the number of SREs; however, this relationship was not found to be statistically significant at $p < 0.05$ (Chi-square test = 3.4449; $p = 0.063$). Also, the number of SREs did not have any consistent effect on the mean survival duration before death in 100 patients (Table 8). SREs have been defined as pathologic fractures, spinal cord compression, requirement for radiotherapy to treat bone pain or impending fracture, or hypercalcaemia. They are difficult to treat and also diminish patients' QoL.[26]

The presence of spinal compression with the evidence of neurological symptoms and signs in seven out of the 100 patients who died within the study was noted to significantly reduce the mean postoperative survival duration to 5.4 months (Table 9) compared to 8.7 months when there was no spinal compression (Chi-square test = 10.751; $p = 0.001$). This information can be useful in the management of extremity metastasis by motivating the surgical team to undertake prompt and necessary procedures in appropriate patients.

Another important outcome measure from this study is the relatively low overall postoperative complications of 8.7% in contrast to a much higher complication rate of 26.6% reported by Teixeira et al[1] in a sample size of 64 patients. In our study population, 91.3% patients had no postoperative complications. Avoiding postoperative complications in the circumstance of bone metastasis may depend on proper patients' selection, adequacy of operative techniques and planning, and strict adherence to the surgical principles of asepsis as well as avoidance of tumour contamination of surgical fields. These principles are rigidly applied in our tumour service centre and may explain the comparatively low rates of complications in our study. This may also explain why all our patients, except two (1.6%), were rehabilitated to ambulation. It might well be argued that any failure in rehabilitation is an indication of failure of the surgical effort. Among the few complications recorded in our study, postoperative wound infection was the most common with an overall rate of 3.9%. This compares closely with postoperative infection rates of 4.8% in the work by Teixeira et al[1] and 3.5% by Harrington et al.[27] Among another category of patients treated by arthroplasty, Thai et al[28] and Jacofsky et al[29] recorded postoperative wound infection rates of 8.6% and 10%, respectively. We suggest future study on the protocols for achieving infection rate of 0% for this group of tumour patients.

All our patients were followed-up in the physiotherapy and oncology clinics. It is important to consider the rehabilitation potentials of patients as a guide to predicting the outcome of rehabilitation measures in individual patients. With advances in oncological services and surgical techniques, it is anticipated that the overall prognosis of metastatic bone diseases will continue to improve.

Conclusion

The femur is the most common site for metastatic bone disease requiring surgery. There is paucity of literature on this subject in Hong Kong, and this study can become a template for further documentations on extremity bone metastasis in Hong Kong.

The surgical management of extremity bone metastasis is a key consideration in averting potentially crippling morbidity occasioned by mechanical instability arising from the deposition of cancer cells on skeleton. The duration of postoperative survival of patients with extremity bone metastasis can be affected by the age of the patient, indication for surgical operation, the type of surgical procedure offered the patient, and presence or absence of neurological deficits from concomitant spinal compression.

Extremity metastases do not represent the overall burden of bony disease from secondary tumours; therefore, a wider study designed to include the axial and craniofacial skeleton is advocated in order to have a comprehensive local reference database for metastatic bone disease in Hong Kong.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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