Oncological and functional outcomes of pathological fractures of lower extremities in patients with malignant bone tumors

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Abstract. As managing pathological fractures of the extremities can be difficult, the present study aimed to present a treatment algorithm for lower extremity bone malignancies. A total of 38 patients with impending and pathological fractures were treated at the Department of Orthopedic Surgery in Kindai University Hospital. Age, sex, fracture site, type of primary malignancy, number of metastases, pre-fracture Eastern Cooperative Oncology Group performance status (ECOG-PS) score, adjuvant therapy, treatment modality, operative time, blood loss, postoperative complications, Musculoskeletal Tumor Society (MSTS) score, outcomes, follow-up period and the MSTS scores and ECOG-PS were compared in cases of primary malignant tumors and those cases of metastatic malignant tumors were retrospectively surveyed. Post-treatment MSTS scores in cases of impending and pathological fractures were compared between intramedullary nail fixation and non-intramedullary nail fixation procedures. Disease sites included the sub-trochanteric femur in 10 patients, trochanteric femur in 8, femoral diaphysis in 7, femoral neck in 5, bilateral trochanteric femur in 3, proximal tibia in 3 and distal femur in 2 patients. A total of 10 patients had metastases between 3-20 sites. The median pre-fracture ECOG-PS score was 1. Adjuvant radiotherapy was administered to 5, chemotherapy to 8 and radiotherapy with chemotherapy to 10 patients. Surgical procedures included intramedullary nails in 18 patients, tumor arthroplasty in 4, plate fixation in 3, artificial head replacement in three, compression hip screw (CHS) in 3, conservative treatment in 2, bilateral intramedullary nail fixation in 2 and artificial bone stem with combined intramedullary nail and plate fixation, right-sided artificial head replacement and left-sided CHS in 1 patient each. The MSTS score was 19.9±8.95 for intramedullary nail fixation and 24.3±7.45 for other procedures, with a negative association between the MSTS score and pre-fracture ECOG-PS. The median follow-up period was 8 months. The outcomes were as follows: Alive with disease, 23 patients; continued disease-free, 1 patient; and dead due to disease, 14 patients. The 1-year postoperative overall survival rate was 60.5%. Moreover, the group with metastatic malignant tumors, which had significantly worse ECOG-PS, had significantly lower MSTS scores than the group with primary malignant tumors. The authors' treatment algorithm for malignant bone tumors of the lower extremity was shown to be useful.

Introduction

Primary bone tumors, whether benign or malignant, can cause pathological fractures (1,2). In particular, cystic bone tumors in the long bones of the extremities are prone to pathological fractures (3). By contrast, 10% of patients with primary malignancies develop metastases to the proximal femur. Most bone metastases originate from the breast, kidney, thyroid, prostate, or myeloma. In addition, these are either soluble or mixed; therefore, patients are at high risk of pathologic fractures (4). In 2001, Scorianz *et al* (5) published an algorithm for the treatment of long bone and pelvic metastases. The patients were divided into 4 classes: i) isolated lesions with a favorable prognosis; ii) pathologic fractures; iii) incisional fractures; and iv) other lesions. The most important factors for selecting the appropriate treatment for the long bones and pelvis include prognosis, disease type, visceral metastases, time taken to spread from the primary site, risk of pathologic fracture, sensitivity to chemotherapy, hormonal therapy and irradiation. Pathologic fractures also occur in 5-10% of patients with osteosarcoma, both at diagnosis and during chemotherapy (6,7). The role of orthopedic surgeons in the evaluation of patients with skeletal metastases is likely to increase over time, as improved treatment of patients with cancer increases survival (8). In addition, pathological fractures of the proximal femur are 3.5 times more likely to occur than pathological fractures of the proximal humerus (9). However, there is a lack of literature describing cases of pathological or impending fractures of the lower extremities in patients with primary and metastatic malignancies. Therefore, the present study aimed to provide a

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Abbreviations: CHS, compression hip screw; ECOG-PS, Eastern Cooperative Oncology Group performance status; MSTS, Musculoskeletal Tumor Society

Key words: pathological fractures, impending fractures, malignancy, bone tumor, surgical treatment

detailed description of the clinical characteristics of patients with pathological or impending fractures who underwent surgical treatment. In addition, the authors also aimed to examine the benefits and drawbacks of their treatment strategy.

Patients and methods

Patients. A total of 38 patients with impending and pathological fractures were treated in the Department of Orthopedic Surgery, Kindai University Hospital between March 2011 and November 2023 and were included in the present study. Cases in which the post-treatment course could be followed were included, and those in which the course could not be followed were excluded. Data on age, sex, pathology, number of metastases, pre-fracture Eastern Cooperative Oncology Group performance status (ECOG-PS) (10), adjuvant therapy, treatment modality, operative time, blood loss, postoperative complications, Musculoskeletal Tumor Society (MSTS) score (11), follow-up period and outcomes were retrospectively studied. Post-treatment MSTS scores in cases of impending and pathological fractures were compared. The MSTS scores were also compared between intramedullary nail fixation and surgical procedures other than intramedullary nail fixation. In addition, the 1-year overall survival of patients using the Kaplan-Meier method was investigated. All patients were treated using the algorithm shown in Fig. 1. The MSTS scores and ECOG-PS were compared using Student's t-test in 8 cases of primary malignant tumors and 30 cases of metastatic malignant tumors. In brief, the algorithm was as follows: First, patients were divided by their ECOG-PS (0-3 or 4). If 4, conservative treatment was chosen. Second, patients were then further divided by fracture site (proximal, distal or diaphyseal), followed by the focus (primary or metastasis), and number of metastases throughout the body (oligo or multiple). Finally, patients were divided by ECOG-PS (0, 2 or 3). The present study was approved by the Ethics Committee of Kinki University (approval no. 31-153; Osakasayama, Japan).

Statistical analysis. Variables are presented as the mean ± standard deviation (SD). The MSTS scores were compared using the unpaired Student's t-test for patients who underwent intramedullary nail surgery vs. other surgeries. ECOG-PS and MSTS scores were plotted to create a correlation diagram, and the coefficient of determination (R^2) was calculated by drawing a best-fit line to assess the correlation between ECOG-PS and MSTS scores. Pearson's correlation method was employed to determine these correlations. The strength of the correlation was classified according to Pearson's correlation coefficient (R) as follows: Very strong $1.0 \geq |R| \geq 0.7$, strong $0.7 \geq |R| \geq 0.5$, moderate $0.5 \geq |R| \geq 0.4$, medium $0.4 \geq |R| \geq 0.3$, weak $0.3 \geq |R| \geq 0.2$ and no correlation $0.2 \geq |R| \geq 0.0$. Overall postoperative survival was calculated using the Kaplan-Meier method.

$P<0.05$ was considered statistically significant for all analyses. All statistical analyses were performed using Stat Mate 5.05 (ATMS; (https://atms.shop-pro.jp/?pid=64906245).

Results

The present study included 19 men and 19 women (Table I). The median patient age was 68 years (range: 13-83 years).

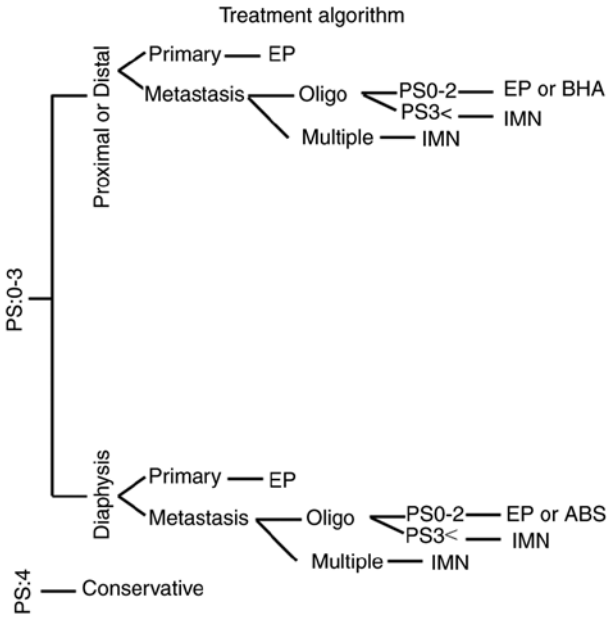

Figure 1. Tree diagram for treatment algorithm for lower leg malignancy. Patients were divided by Eastern Cooperative Oncology Group performance status, fracture site, focus (primary or metastasis) and number of metastases. ABS, artificial bone stem; BHA, bipolar head arthroplasty; EP, endoprosthesis; IMN, intermedullary nail; Multiple, multiple metastasis in whole body; Oligo, oligo metastasis in whole body; PS, performance status.

Cancer sites included the sub-trochanteric femur in 10 patients, the trochanteric femur in 8, the femoral diaphysis in 7, the femoral neck in 5, the bilateral trochanteric femur in 3, the tibia in 3, and the distal femur in 2 patients. Primary nodal pathology included lung cancer in 9 patients, breast cancer in 7, renal cancer in 3, multiple myeloma in 3, osteosarcoma in 3, liver cancer in 2, gastric cancer in 2, cancer of unknown primary origin in 2 and esophageal cancer, hemangiopericytoma, hemangiosarcoma, Paget's disease, neuroblastoma and chondrosarcoma in 1 patient each. Altogether, 10 patients had metastases between 3-20 sites. The median ECOG-PS score before the fracture was 1 (range 0-4: 0, 2 patients; 1, 18 patients; 2, 12 patients; 3, four patients; and 4, 2 patients). As adjuvant chemotherapy, radiotherapy was administered to 5, chemotherapy to 8 and radiotherapy and chemotherapy to 10 patients. Surgical procedures included intramedullary nail fixation in 18 patients, endoprosthesis in 4, plate fixation in 3, bipolar head arthroplasty in 3, compression hip screw (CHS) in 3, conservative treatment in 2, bilateral intramedullary nail fixation in 2 and artificial bone stem with combined intramedullary nail and plate fixation, right-sided artificial head replacement and left-sided CHS in one patient each. The operating time was 100±45.8 min and blood loss was 63±153.4 ml. The MSTS score was 19.9±8.95 for intramedullary nail fixation and 24.3±7.45 for procedures other than intramedullary nail fixation, with no significant difference (P=0.13) and a negative correlation between the MSTS score and pre-fracture ECOG-PS (r=-0.32; Fig. 2). Postoperative complications included implant failure after intramedullary nail fixation, which was replaced by tumor arthroplasty in 1 patient. The median observation period was 8 months (range: 1-150 months). The outcomes were as follows: Alive with disease, 23 patients; continued disease-free, 1 patient;

Table I. Characteristics of the study population.

Factor	Patients, n
Age (mean years)	68
≤70	22
>70	16
Sex	
Male	19
Female	19
Fracture site	
Femoral neck	5
Femoral diaphysis	7
Intertrochanteric	8
Subtrochanteric	10
Bilateral intertrochanteric	3
Proximal tibia	3
Distal femur	2
Type of cancer	
Lung	9
Breast	7
Kidney	3
Multiple Myeloma	3
Osteosarcoma	2
Liver	2
Gastric	2
Unknown	2
Esophageal	1
Hemangiopericytoma	1
Paget	1
Neuroblastoma	1
Chondrosarcoma	1
Number of metastasis	
Equal or less than 3	10
More than 3	20
ECOG-PS	
<2	20
2-3	16
>3	2
Adjuvant therapy	
Radiotherapy	5
Chemotherapy	8
Chemotherapy and radiotherapy	10
None	2
Treatment modality	
Intramedullary nail	18
Endoprosthesis	4
Fixation with plate	3
Bipolar head arthroplasty	3
Fixation with CHS	3
Bilateral intramedullary nail	2
Conservative	2
Artificial bone stem	1
Rt. Bipolar head arthroplasty, Lt. fixation with CHS	1
Operating time (min)	
0-100	18
>100	18
Blood loss	
0-60	17
>60	19
MSTS score	
0-10	9
11-20	7
21-30	22
Outcome	
CDF	1
AWD	23
DOD	14
Follow-up periods (months)	
Mean	8
Range	1-150

ECOG-PS, Eastern Cooperative Oncology Group performance status; CHS, compression hip screw; Rt, right side; Lt, left side; MSTS, Musculoskeletal Tumor Society; CDF, continuous disease-free; AWD, alive with disease; DOD, dead of disease.

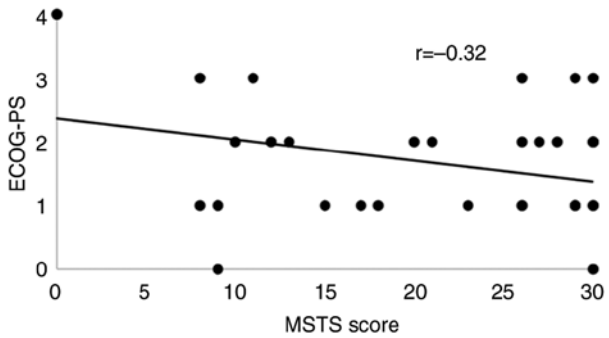

Figure 2. Negative correlation between MSTS score and ECOG-PS. r=-0.32. ECOG-PS, Eastern Cooperative Oncology Group performance status; MSTS, Musculoskeletal Tumor Society.

and dead due to disease, 14 patients. The 1-year postoperative survival rate was 60.5% (Fig. 3). The MSTS scores of metastatic malignant tumors (18.0±10.0) were significantly lower than the MSTS scores of primary malignant tumors (29.1±1.3) (average ± SD; P<0.01) (data not shown). In addition, the ECOG-PS of metastatic malignant tumors (1.7±1.0) was significantly worse than that of primary malignant tumors (0.87±0.35) (average ± SD; P<0.01) (data not shown).

Discussion

In this retrospective investigation of outcomes for malignant bone tumors of the lower extremities, the treatment outcomes according to the utilized treatment algorithm were favorable.

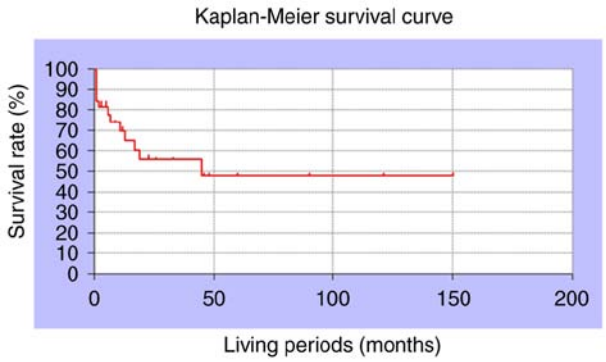

Figure 3. Kaplan-Meier curve showing survival rate. The 1-year survival rate was 60.5%.

The most commonly reported sites of pathological fractures are the femur, humerus, and tibia (12). The other reported sites of pathological fractures besides the lower extremities include the neck (50%), adductor region (30%) and sub-acetabulum (20%) (12). A different study reported 47.5% fractures in the femoral head and neck, 27.5% in the femoral metaphyseal area, and 25% in the region below the femoral metaphyseal area (13). In the present study, fractures were more common in the femoral and sub-trochanteric areas than in the femoral neck area.

In a previous study, the most common primary sites of pathological femoral fractures were breast cancer, myeloma, renal cancer, colorectal cancer, thyroid cancer and lung cancer (14). Breast, lung, myeloma, and kidney cancers are the most common primary lesions resulting in pathological fractures of the proximal femur (13). Lung cancer was relatively common in the current study, with reconstructive surgery with oncological arthroplasty, intramedullary nail fixation, or plate fixation as the most commonly adopted options (15-17).

The advantages of tumor arthroplasty include a quick return to stability, independent of the degree of fracture healing, and minimal risk of local progression or implant failure (18). The disadvantages include surgical invasiveness, bleeding, relative difficulty in muscle reconstruction and high costs (18). The advantages of intramedullary nail fixation include relatively low surgical invasion, the possibility of additional radiation therapy and the ability to load immediately after radiation (18). The disadvantages of plate fixation include the need for adequate bone stock, lack of stability in close proximity to the joint, risk of implant fracture, large incision, long surgical procedure, and lack of prophylactic fixation of the entire bone (18). The advantages of plate fixation include prevention of damage to the muscle cuff, strong fixation with locking screws, fixation of distal fractures and a relatively large operative field that allows visual resection of the tumor (18). Intramedullary nail fixation was used in the present study. The authors' department policy is to reconstruct pathological fractures of the femoral neck using either artificial head replacement or tumor arthroplasty; this choice is based on tumor spread, prognosis, invasiveness and the patient's ability to engage in rehabilitation including load-bearing. For pathological fractures of the femoral condyle and sub-trochanteric region, reconstruction using an intramedullary nail was performed in anticipation of postoperative radiotherapy. Impending fractures of the femoral neck or transverse condyle are treated with bipolar head arthroplasty or fixation using intramedullary nails or CHS plates. The selection of reconstruction was based on a comprehensive evaluation of postoperative radiotherapy, fixation stability and the amount of lesion removed. Functional prognosis was generally favorable for both types of fixation but was poor when rehabilitation did not proceed as expected owing to the patient's general condition.

Several studies have reported different outcomes and failure rates between the use of an intramedullary nail and endoprosthesis (19-22). Patients with malignancies are at the highest risk of thromboembolic complications and infections (14), with the rate of infectious complications ranging from 1.2-19.5%. Preoperative radiotherapy is one of the most important risk factors for radiotherapy (14); in addition, location in the proximal lower extremity has been reported as a risk factor for major wound complications such as infection (23).

Complications have been reported in 9-20% of patients who undergo intramedullary nail fixation, with primary complications including deep infection, myocardial infarction and stroke. Furthermore, 20% of the patients require revision surgery within 3 months. On the other hand, dislocation is reported to occur in 3-22% of the patients as a complication of tumor arthroplasty. The risk of periprosthetic failure has also been previously reported. In the present study, implant failure occurred in one patient who underwent intramedullary nail fixation, which was subsequently replaced by an oncological prosthesis. Previous studies have reported MSTS scores of 6.4-25.2 after implant have been used for pathological fractures (13,14,24). The results of the present study are comparable, and it is considered by the authors that their surgical indications (Fig. 1) are generally recommended.

Typically, treatment for this condition is individually tailored as these patients are in the terminal disease stage (25,26). In terms of overall patient survival, the 1-year survival rate reported in the literature ranges from 42-75% (21,27,28). Fractures are also associated with an increased mortality risk in patients with malignant bone disease (29). Until now, the Mirels' score has been used in surgical treatment algorithms for malignant metastatic bone tumors (30). According to this algorithm, surgery is not indicated unless the patient has a life expectancy of at least 6 weeks. Although the survival rate of patients with metastases remains low, medical advances have led to some differences related to tumor histology. In the present study, ECOG-PS and MSTS scores revealed a negative correlation. Based on these findings, it would be advisable to operate on patients with an ECOG-PS of 3 or higher to maintain ADLs until death, regardless of life expectancy. The authors consider the novelty of the algorithm is its focus on deciding whether or not to operate based on ECOG-PS, independent of life expectancy.

The present study is similar to a recent study by the authors (31). The novelty of the present study lies in the proposal of an algorithm for a larger cohort that includes primary tumors. Although primary and metastatic malignant tumors naturally exhibit different characteristics (32), it is considered that the algorithm proposed in the present study can be applied to both types. Cancer rehabilitation is strongly influenced by the local and systemic effects of the cancer itself, treatment side effects, and physical disabilities associated

with periods of bed rest and cachexia (a state of generalized weakness due to cancer progression) (33,34). In fact, the group with metastatic malignant tumors, which had significantly worse ECOG-PS, also had significantly lower MSTS scores compared with the group with primary malignant tumors. This observation ensures the validity of the algorithm proposed in the present study.

The current study has several limitations. First, the sample size was small, with few cases of primary malignancies. Comprehensive discussions have not been made. However, no problems were encountered during statistical analyses. Second, the study's retrospective design might have resulted in selection bias. Finally, the follow-up period was relatively short, which is unavoidable given the inclusion of cases with metastatic bone tumors and associated short postoperative survival. Despite these limitations, as numerous patients as possible were enrolled during the study period. Future research should aim to increase the number of cases and conduct a prospective randomized control study. Specifically, prospective randomized cohort studies are needed with a control group treated without the algorithm and a group treated with the algorithm.

In conclusion, the treatment of primary and metastatic malignant bone tumors should be based on a comprehensive assessment of the extent of malignant tumor resection, surgical invasiveness, and the patient's general condition and prognosis.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KH, SN, TI and KG conceptualized the study. KH, SN, TI, RK and KG contributed to the study's methodology. KH, RK and SN handled the software used. SN, TI, RK and KG validated the data. KH and SN confirm the authenticity of all the raw data. SN, TI and KG analyzed the data. KH, TI, RK, SN and KG curated the data, wrote the original draft, and reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval for the present study was obtained from the Ethics Committee of Kindai University Hospital (approval no. 31-153; Osakasayama, Japan), and it was conducted in line with the guidelines of The Declaration of Helsinki. Comprehensive consent for the current study was obtained. Written informed consent by individual signature was waived by the Ethics Committee of Kindai University Hospital.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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