in 10% ethylenediaminetetraacetic acid (EDTA) for 2 weeks. After embedding in paraffin, sections were stained with hematoxylin and eosin.

2.13. Tumor burden and number

Histomorphometric analyses of tumor burden in the metastatic tumors in the distal femoral and proximal tibial metaphyses of both hindlimbs were performed using longitudinal sections stained with hematoxylin and eosin. Tumors were measured in the intraosseous and extraosseous regions of the distal femur and proximal tibia on the central section of the tumor (largest tumor area). The measurement area in each bone was ~1.5 mm, beginning 100 μm below the growth plate, as described previously [14]. All measurements were made using NIH-Image 1.62b7 image analysis software. Tumor burden is shown as tumor area (%) per femur and tibia. The total number of tumor foci associated with metastases was recorded on each section for each hindlimb bone (femur and tibia) per mouse. Ten mice were included in each group, and the experiment was repeated twice.

2.14. Statistics

All numerical values are expressed as means ± standard error (SE). Statistical analysis was performed by one-way analysis of variance, followed by the unpaired Student's *t*-test. Differences between the treated mice and the untreated mice were examined by Fisher's exact test; $p < 0.05$ was considered statistically significant.

3. Results

3.1. Analysis of TNF-α expression and signaling

TNF-α mRNA and TNF-R1 mRNA were expressed in breast cancer cell lines (Supplementary data 1), but TNF-RII mRNA was not expressed in all cell lines (data not shown). TNF-α protein was produced especially in MDA-231 cells (6.73 ± 6.06 pg/ml). TNF-α protein production was not observed in MCF7 and ZR-75-1, because levels were below the sensitivity of the ELISA test (4.0 pg/ml).

Thus, we investigated whether TNF signaling can be suppressed by infliximab using MDA-231 cells. TNF-α is a well-known regulator of NFκB. In recent report, TNF-α regulate JNK phosphorylation [15]. On immunoblotting analysis, phospho-JNK as well as NFκB was suppressed by infliximab (Fig. 1A). These results suggest that infliximab suppresses TNF-α signaling in MDA-231 cells.

3.2. Effect of anti-TNF-α antibody on CXCR4 expression

Recent evidence suggests that the CXCR4 plays a critical role in the homing of cancer cells to specific metastatic sites [16]. Previous reports demonstrated that CXCR4 was expressed in MDA-231 cells [17]. In the present study, endogenous CXCR4 protein expression was found in MDA-231 cells on immunoblotting analysis, and treatment of MDA-231 cells with infliximab inhibited CXCR4 protein expression in a time-dependent (Fig. 1B) and a dose-dependent manner (Fig. 1C).

3.3. Effect of anti-TNF-α antibody on decorin expression

Decorin, the prototype of an expanding family of small leucine-rich proteoglycans, is involved in a number of cellular processes, including matrix assembly, fibrillogenesis, and the control of cell proliferation. We previously demonstrated a novel role for decorin in the reduction or prevention of tumor bone metastases in an animal model [14]. Previous studies have suggested that TNF-α interacts with decorin [18] and inhibits decorin gene expression [19]. This effect of infliximab on decorin expression was examined in MDA-231 cells. After treatment with infliximab at a dose of 10–100 μg/ml, decorin expression in MDA-231 cells was investigated by immunoblotting analysis. Interestingly, infliximab increased decorin expression in MDA-231 cells in a dose-dependent manner (Fig. 1D).

3.4. Cell growth, adhesion, migration, and invasion

Next, the effect of infliximab on the proliferation of MDA-231 cells was examined. Infliximab (⩽100 μg/ml) had no effect on tumor cell proliferation in vitro (Fig. 2A). Malignant cells exhibit the enhanced adhesiveness, motility, and invasive capacity indispensable for the metastatic process. Thus, whether TNF-α inhibitor could affect migration and invasion ability was tested. Specifically, the number of cells that had passed through a membrane was counted. Treatment with infliximab inhibited cell motility; 10 and 100 μg/ml infliximab suppressed cell migration ($p < 0.01$) (Fig. 2B), and 100 μg/ml infliximab suppressed cell invasion ($p < 0.05$) (Fig. 2C).

3.5. Radiographic analysis of the effect of TNF-α inhibitor on development of metastases in nude mice

To test whether infliximab directly affects the ability of MDA-231 cells to metastasize, MDA-231 cells were injected into the left ventricles of mice. On X-ray analysis 4 weeks after tumor inoculation, the number of osteolytic lesions was investigated. Osteolytic bone metastases appeared around the knee joints (Fig. 3A) in the mice without infliximab treatment. Untreated mice developed 9 metastases per mouse. In contrast, in mice treated with 10 mg/kg infliximab (Fig. 3B), there were 4 metastases per mouse ($p < 0.05$). Infliximab suppressed bone metastases significantly in the animal model (Table 1). The metastasis area (mm^2) per hindlimb bone was 4.48 ± 1.39 and 2.89 ± 1.19 (mm^2) in untreated and treated mice, respectively. Osteolytic lesions were decreased by infliximab, but not significantly.

3.6. Histomorphometric analysis of the effect of TNF-α inhibitor on development of osteolytic lesions

The effects of infliximab on bone metastases of MDA-231 cells in nude mice were then examined histologically. Histological examination of femurs and tibias with MDA-231 cells showed wide tumor burden with trabecular bone destruction (Fig. 3C). Radiographic analysis demonstrated that infliximab (10 mg/kg/week) decreased the number and area of osteolytic lesions. The metastases ratio (%) per hindlimb bone was 47.5 ± 6.9 and 19.4 ± 8.1 (%) in untreated and treated mice, respectively ($p < 0.05$). The metastases area (%) per hindlimb bone was 34.6 ± 6.8 and 13.3 ± 5.4 (%) in untreated and treated mice, respectively ($p < 0.05$). Histomorphometric analysis also showed that the metastases rate and the area of metastatic bone tumor was decreased significantly in infliximab (10 mg/kg/week)-treated mice (Table 1 and Fig. 3D).

4. Discussion

Breast cancer is a relatively common tumor, with an estimated incidence of 1.2 million new cases worldwide every year [20], and the outcome of patients mainly depends on the development of distant metastases [21]. Bone is the principal metastatic site in patients with mammary carcinomas [22]; approximately 20% of patients with significant bone metastases survive for more than

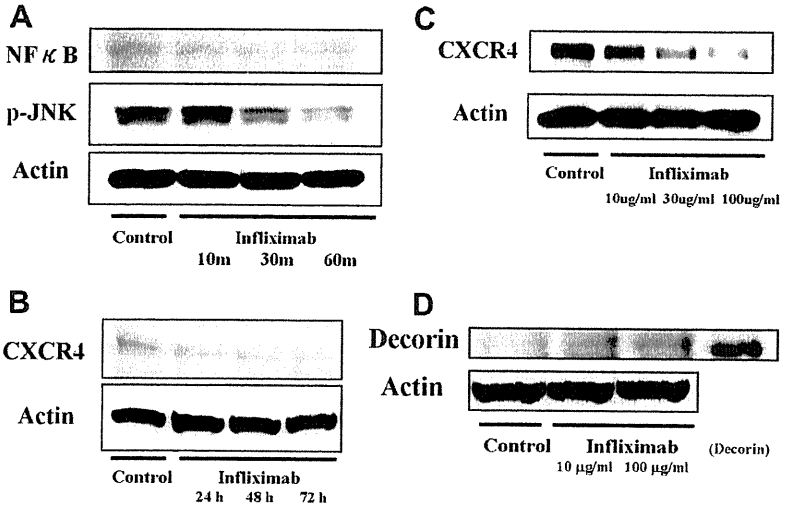

Fig. 1. Effect of anti-TNF α antibody on TNF-α signaling (A), CXCR4 expression (B, C) and decorin expression (D) in MDA-231 cells. Phospho-JNK is a MAPK activated by a variety of environmental stresses, including TNF-α. Phospho-JNK as well as NFκB in MDA-231 cells is suppressed with infliximab, likely the result of infliximab suppressing TNF-α signaling (A). CXCR4 expression was investigated by immunoblotting analysis in MDA-231 cells. Treatment with 100 μg/ml infliximab inhibits CXCR4 protein expression in a time-dependent manner (B). And infliximab inhibits CXCR4 protein expression in a dose-dependent manner (C). Infliximab, at doses of 10 and 100 μg/ml, increases decorin expression in MDA-231 cells in a dose-dependent manner (D). "(Decorin)" as positive control is extracts of MDA-DCN, which stably expresses human decorin.

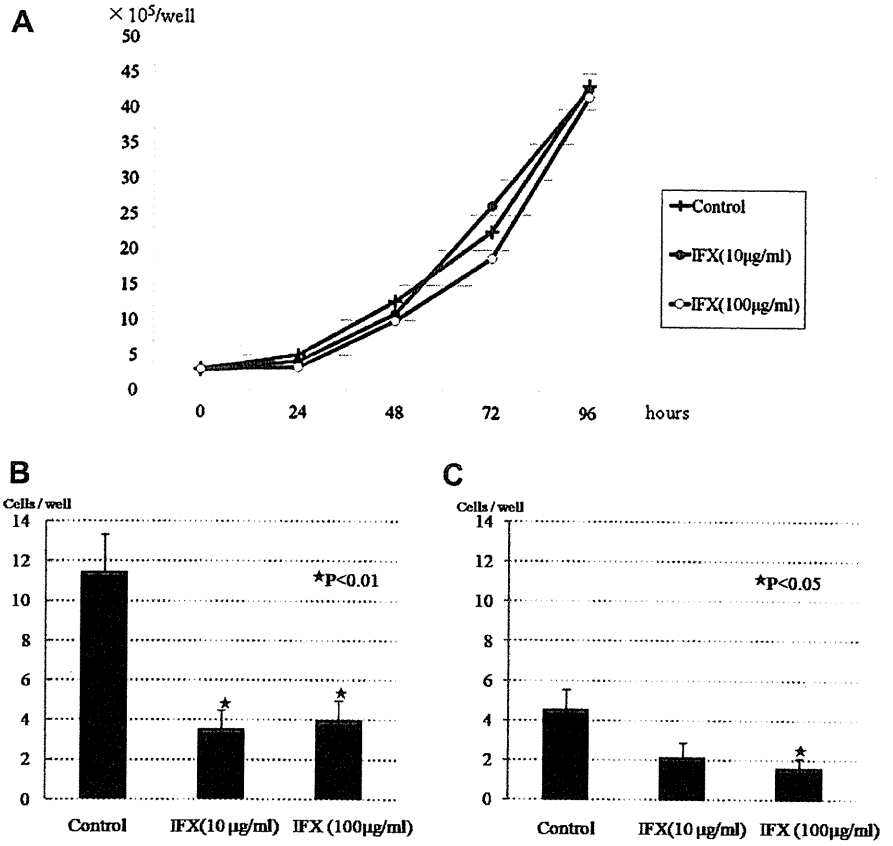

Fig. 2. Cell proliferation assay (A), migration assay (B) and invasion assay (C) in vitro. Infliximab (IFX; ⩽100 μg/ml) has no effect on tumor cell proliferation in MDA-231 cells. Migration assay and invasion assay were counted the number of cells that moved through a membrane. Both 10 and 100 μg/ml infliximab suppress cell migration ($p < 0.01$), and 100 μg/ml infliximab suppresses cell invasion ($p < 0.05$). Columns, mean; bars, SE.

5 years, whereas those with minor metastases in the bone can survive up to 10 years or more. Bone metastasis is clinically significant because of decreased patient mobility and concomitant deterioration of the patient's quality of life.

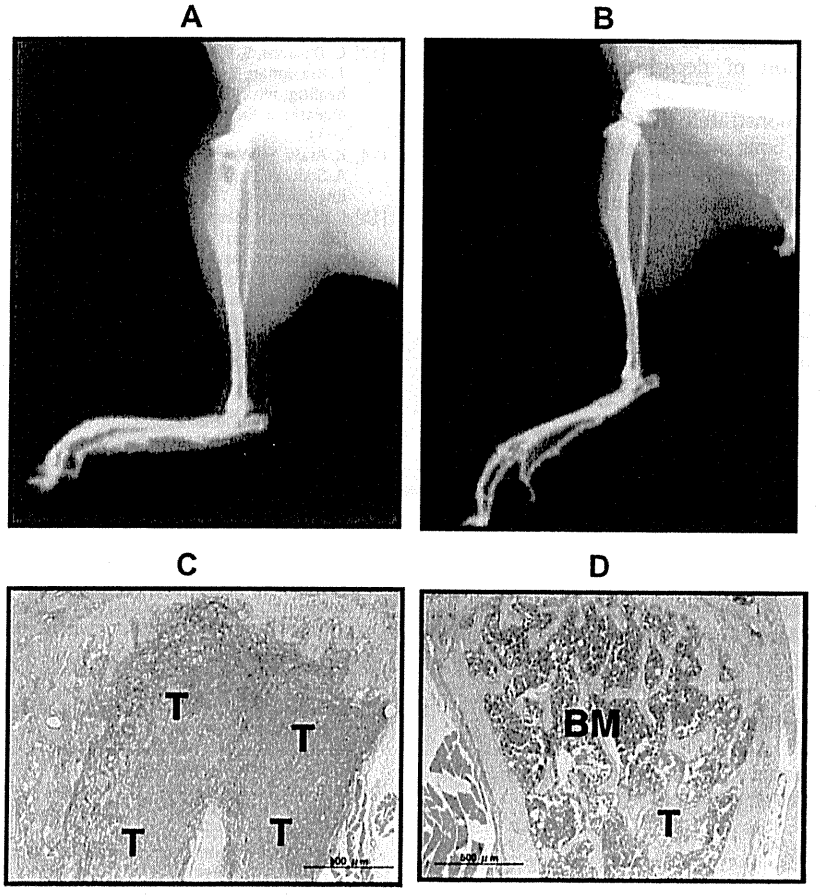

Fig. 3. Effects of infliximab on bone metastases of MDA-MB-231 human breast cancer cells. Representative radiographs of bone metastases treated without (A) or with infliximab (10 mg/kg/week) (B). Representative histological view of bone metastases treated without (C) or with infliximab (10 mg/kg/week) (D) is shown hematoxylin-eosin staining (T: tumor, BM: bone marrow, scale bar = 500 μm).

Table 1
Effects of infliximab on bone metastases of MDA-MB-231 human breast cancer cells. Representative histological view of bone metastases treated without or with infliximab were examined. Metastatic tumor burden in bone was assessed by histomorphometry as described in Section 2. Data are shown as rate and area of metastases/hindlimb.

	Rate (%)	Area (%)
Control	47.5 ± 6.9	34.3 ± 6.8
Infliximab	19.4 ± 8.1*	13.3 ± 5.4*

* Significantly different from control ($p < 0.05$).

Inflammatory processes can have quite diverse effects on cancer development. In many inflammatory scenarios, the cytokine TNF-α plays a central role. TNF-α actually has a bimodal role in cancer [4]. Local administration of high-dose TNF-α is antiangiogenic and has a powerful antitumor effect [5]. On the other hand, endogenous TNF-α chronically produced in the tumor microenvironment enhances tumor growth and invasion by inducing other cytokines/chemokines involved in cancer progression. Tumor cell-derived TNF-α plays a profound role in malignant tumors [23–26].

Animal models of bone metastasis using cancer cell lines derived from human carcinomas have been studied in order to understand the intrinsic pathological event. The most common tumor to cause osteolytic lesions is breast carcinoma; MDA-231 cells of human breast carcinoma selectively colonize the tibias and femurs of nude mice, including osteolytic metastases [14]. In this report, it was confirmed that the breast cancer cell line MDA-231 secreted TNF-α and expressed its receptor, TNF-R1.

Infliximab, an anti-TNF-α antibody, has been shown to bind and inhibit exclusively human and chimpanzee but not rodent TNF-α [10]. In this model, widespread skeletal metastases to femur and tibia were observed, while treatment with infliximab significantly reduced both the incidence and extent of bone metastases in vivo. This is the first report showing that anti-TNF therapy suppressed bone metastases. Inhibition of TNF-α with infliximab showed effects on cell migration and invasion in vitro, but not on cell proliferation. Supporting our results and in line with some reports [23,24], inhibition of TNF-α had no influence on tumor cell growth in vitro. The antitumor mechanism of action may be through modulation of the cytokine-dependent communication between cells in the tumor microenvironment rather than direct antibody-mediated cytotoxicity.

Tumor cell migration and invasion are chemokine-dependent. CXCR4 plays a critical role in the homing of cancer cells to specific metastatic sites [16]. The results of the present study show that treatment with infliximab suppressed CXCR4 expression in MDA231, suggesting that infliximab may suppress bone metastases by down-regulating the expression of CXCR4 in MDA231 cells.

Decorin expression in MDA-231 cells was examined as another possible mechanism. It is known that low levels of decorin in invasive breast carcinomas have been associated with larger tumor size, shortened time to progression, and worse outcome [27]. We previously reported that decorin suppressed lung metastases and bone metastases in an animal model [14,28]. In previous reports,

TNF-α inhibited decorin gene expression. Interestingly, infliximab increased decorin expression in MDA-231 cells. Our data suggest that the increased expression of decorin may inhibit bone metastases.

In this report, it was demonstrated that anti-TNF-α therapy using infliximab suppresses bone metastases of breast cancer. The results also suggest that TNF-α is a target in breast cancer. Clinical trials with anti-TNF-α therapy are currently under way in patients with solid cancers [29–32]. Indeed, preliminary results from phase II clinical trials in patients with breast cancer provide some evidence for this [29]. We believe that the information provided in this article may aid in the design of future clinical trials of TNF-α antagonists, suggest suitable combinations with other targeted therapies, and identify biomarkers for patient selection and monitoring response to treatment.

5. Conflict of interest

The authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2011.03.051.

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Clinical Outcomes of the KYOCERA Physio Hinge Total Knee System Type III After the Resection of a Bone and Soft Tissue Tumor of the Distal Part of the Femur

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Background and Objectives: The KYOCERA Physio Hinge Total Knee System Type III (PHKIII) was developed to reconstruct bony defects of the distal femur. The PHKIII is originative in that the metallic parts are fully made of titanium alloy, and this prosthesis has a unique semi-rotating hinge joint and was designed especially for people with the Asian physical body-type. The clinical outcomes of the PHKIII after the resection of musculoskeletal tumors of the distal femur were evaluated.

Methods: There were 41 males and 28 females with a median age of 48-years. The median duration of follow-up was 57 months.

Results: Eleven early complications and 37 late complications were observed, including 10 recurrences, 7 deep infections, 7 aseptic loosenings, 4 stem breakages, 4 displacements of shaft cap, and one wear of rotation sleeve. Twenty four prosthesis (35%) required a secondary operation because of complications. The five-year overall prosthetic survival rates, -prosthetic survival rate without aseptic loosening, and -limbs preservation rate were 85%, 90%, and 86%, respectively. The mean functional score according to the classification system of the Musculoskeletal Tumor Society was 20.5 points (68%).

Conclusions: Although continuous follow-up is required, reconstructions using PHKIII are considered to achieve more acceptable functional results.

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KEY WORDS: **limb salvage surgery; clinical outcomes; musculoskeletal tumors; distal femur**

INTRODUCTION

Because of advances in imaging, surgical techniques, radiation therapy and adjuvant chemotherapy protocols, there has been a considerable improvement in the prognosis for patients with musculoskeletal sarcoma over the past 25 years [1]. Limb salvage is considered to be the standard procedure for the majority of the patients with a sarcoma involving the extremities [1,2]. The distal femur is a common site for primary and metastatic bone tumors, and therefore, it is a frequent site in which limb salvage surgery is performed.

Various types of prostheses have been developed and applied for the reconstruction of bone defects after tumor resection [3]. The current model of the prostheses include a modular segment, a wrought stem, a kinetic rotating hinge, a circumferential porous coating around the prosthesis at the bone-prosthesis junction, and a loophole for soft tissue attachment. The advantages of the current modular prosthesis include their durability, intraoperative flexibility to fill the bony defects, and the immediate structural stability they provide to permit immediate weight bearing.

However, these prostheses are generally designed for the Caucasian physical body-type, and are frequently too large in size and too heavy in weight for Asian-pacific patients. Mensch and Amstutz measured the linear dimension of predominantly Caucasian cadaver knees and described that the width of the femur, depth of the lateral femoral condyle, width of the tibia, and depth of the medial tibial plateau were 75, 64.6, 74.9, and 48.9 mm, respectively [4]. In contrast, Miyake et al. examined these bones in Japanese cadaver knees and showed that they were 71.5, 60.9, 71.4, and 45.4 mm, respectively [5]. The average size of Japanese knees was found to be 5–10% smaller than that of Caucasians. Therefore, in 1997, the Japanese Muscloskeletal Oncology Group developed a new modular prosthesis, the KYOCERA Physio Hinge Total Knee System Type III (PHK III).

The PHKIII is originative in that the metallic parts of the prosthesis are fully made of titanium alloy, and this prosthesis has a unique semi-rotating hinge joint and was designed especially for people with the Asian physical body-type. The purpose of this study was to evaluate

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the clinical outcome of the treatment with the PHK III after the wide resection of a musculoskeletal tumor of the distal femur in 69 Japanese patients.

PATIENTS AND METHODS

Patients

Between April 1997 and May 2002, 108 patients with bone and soft tissue tumors of the distal femur were treated by surgeons of the JMOG, using the PHK III. The records of 80 of the 108 patients were collected using a questionnaire administered to the members of the JMOG. The collected data included the demographic details, histological diagnosis, tumor location, stage, grade, adjuvant therapy, surgical methods, size of the prosthesis components, complications, post-operative limb function, range of motion of knee joint, and oncological outcomes at the final follow-up. Since the PHK III was used for revision arthroplasty in 11 patients, these revision cases were excluded from the present study. Therefore, the performance of PHK III used for 69 patients was retrospectively reviewed and evaluated. There were 41 males and 28 females who ranged in age from 10 to 79 years (median, 48 years-old). The duration of the follow-up ranged from 6 to 134 months (mean, 57 months). There were 58 primary malignant bone tumors, 4 giant cell tumors, 5 metastatic bone tumors and 2 direct bone invasion of soft tissue sarcomas. The primary malignant bone tumors included 40 osteosarcomas, 8 chondrosarcomas, 8 malignant fibrous histiocytomas, one Ewing's sarcoma and one leiomyosarcoma of the bone. Staging according to Enneking's surgical staging system [6] was as follows: stage IA, 3 patients; stage IB, 2 patients; stage IIA, 5 patients; stage IIB 44 patients; stage IIIA 1 patient; stage IIIB, 10 patients; unknown, 4 patients. Chemotherapy was performed in 47 patients, and irradiation was administered in combination with the chemotherapy in 5 patients. Informed consent was obtained from all patients according to the guidelines of the each institutional ethics review board.

Prosthesis

PHK III is a full modular prosthetic system with a rotating-hinge joint, which was created in order to reconstruct distal femoral bone defects after a tumor resection, and designed for Asian patients, including the Japanese with the smaller anatomical architecture of the knee joint (Fig. 1a). The PHK III has a unique semi-rotating hinge joint which allows a maximal flexion of 142° and an internal/external-rotation of 5° (Fig. 1b and c). The metallic parts of the PHK III are made of light-weight and high-strength titanium alloy (Ti-6Al-4V) with good bio-compatibility and bio-stability and allow scanning by magnetic resonance imaging (MRI). As a result, the PHK III is extremely light in weight. When the PHK III is used for an 11 cm bony defect of the distal femur, the total weight is about 660 g, whereas reconstruction of a 12 cm bony defect using the HMRS reaches a weight of about 1200 g. The metallic surface of the hinge shaft and the rotator, which creates friction between high density polyethylene, is fabricated using a surface-hardening treatment by azote-ionic inpouring to increase the durability of the hinge joint. The rotation sleeve, plate and shaft sleeve are made of ultra high molecular weight polyethylene. The PHKIII requires the use of polymethylmethacrylate cement for the fixation of the femoral stem and tibia component (Fig. 1c).

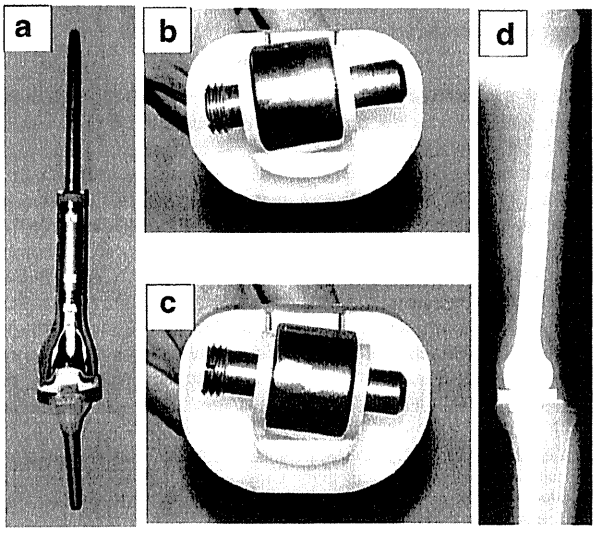

Fig. 1. The photographs showing (a) an overview of the PHK III and a unique semi-rotating hinge joint (b and c) which allows internal/external-rotation of 5°. (d): Radiography showing anterior–posterior view of PHK III used for the osteosarcoma patient.

Surgical Procedure and Postoperative Rehabilitation

All operations were performed under general anesthesia. All surgical interventions were performed by trained surgeons specialized for orthopedic oncology. All surgical resections followed the guidelines of the Japanese Orthopedic Association outlined by Enneking [6,7]. The length of the resected distal femoral bone were 9 cm in 4, 11 cm in 11, 13 cm in 16, 15 cm in 7, 17 cm in 11, 19 cm in 12, 21 cm in 7, and 23 cm in 1. The following surgical margins were provided: a wide margin in 60 patients, a marginal margin in 4, an intralesional margin in one and the margin was unknown in 4. Extra-capsular resections were performed in 16 patients, whereas intra-capsular resections were performed in 50. More than 2 segments of musculus quadriceps femoris were resected in 67 patients. The musculus quadriceps femoris was not totally resected in any of the patients. The prostheses were implanted using modern cementation techniques. A local musculocutaneous flap was required in 3 patients, and a free vascularized musculocutaneous flap was required in one patient to cover a defect of the skin after the resection of the tumor. All patients received intravenous antibiotics preoperatively and postoperatively. Deep drains were used routinely and antibiotics were given while the drains were in place. All patients were kept at bed rest, and immobilized with the extremity in 30° of flexion in a bulky dressing for the first 24 hr. Thereafter, the patients were started on a regimen of gentle passive range of motion (ROM) and isometric exercises such as straight leg raisings. The use of a machine which administered continuous passive motion and a knee brace were used, depending on the institution. Full weight bearing was permitted one week after the surgery.

Assessment and Statistical Analysis

The complications, overall prosthetic survival rate, prosthetic survival rate without aseptic loosening, limbs preservation rate and functional outcome were evaluated in the 69 patients.

The overall prosthetic survival was defined as the time from the surgical reconstruction using the PHK III to the date of revision or amputation due to prosthetic failure. Prosthetic failure was defined as replacement of the any of the prosthetic components including minor parts of the prosthesis or complete removal of the implant. Patients in whom the implant was removed for a local recurrence or deep infection were not considered prosthetic failures in the prosthetic survival analysis. The prosthetic survival rate without aseptic loosening was defined as the time from the surgical reconstruction to the date of aseptic loosening assessed by radiographic examination. The limb preservation rate was defined as the time from the surgical reconstruction to the date of amputation due to complications. When analyzing the survival rate, the death of the patients without any prosthesis-related event was

conducted as censoring at the date of patient's death. The relationships between various characteristics and prosthetic survival were assessed by a univariate analysis (Log-rank test). A P-value of <0.05 was considered to be significant. Analyses were performed using the StatView statistical software program (version 5.0; SAS Institute Inc. Cary, North Carolina).

The functional assessments were performed according to the scoring system of musculoskeletal tumor society (MSTS) [8].

RESULTS

Complications

Out of the 69 prosthetic surgical treatments, 11 early complications (16%) were found (Table I). Of the 7 patients with skin necrosis, 5 patients underwent minor surgery under local anesthesia and 2 patients with a relatively wide skin defect underwent a free vascularized flap. The peroneal nerve palsy improved within 3 months in all patients.

Thirty-seven late complications were found. Of the 10 patients with local recurrence, 8 patients required a wide resection of the recurrent tumor, and finally 4 patients underwent amputation of the affected limbs. Out of the 7 patients who had a deep infection, 4 patients required surgical debridement and partial exchange of the components, and 3 patients underwent an amputation of the affected limbs. Of the 7 patients with aseptic loosening of the femoral stem, 4 patients required revision surgery. Because the 4 of 15 femoral stems with a 10 mm diameter had broken, the stems were exchanged to those with an 11 m diameter during the revision surgery. Four patients with displacement of the shaft caps underwent an exchange to a new shaft cap. Three patients with a patellar tracking abnormality were treated conservatively using a brace. A patient with an undisplaced avulsion fracture of the tibia tuberculum was treated conservatively using a cast. A patient with wear of rotation sleeve was treated by the exchange of rotation sleeve.

TABLE I. Details of Complications after Reconstruction of Defect in the Distal Femur Using the PHKIII

Complication	No. of complication (%)	No. of re-operation (%)	No. of amputation (%)
Early complication			
Skin necrosis	7 (10%)	7 (10%)	0
Peroneal nerve palsy	4 (6%)	0	0
Total	11(16%)	7 (10%)	0
Late complication			
Recurrence	10 (14%)	8 (12%)	4 (6%)
Deep infection	7 (10%)	4 (6%)	3 (4%)
Aseptic loosening	7 (10%)	4 (6%)	0
Stem breakage	4 (6%)	4 (6%)	0
Displacement of shaft cap	4 (6%)	3 (4%)	0
Patellar tracking abnormality	3 (4%)	0	0
Fracture	1 (1%)	0	0
Wear of rotation sleeve	1 (1%)	1 (1%)	0
Total	37(54%)	24 (35%)	7(10%)

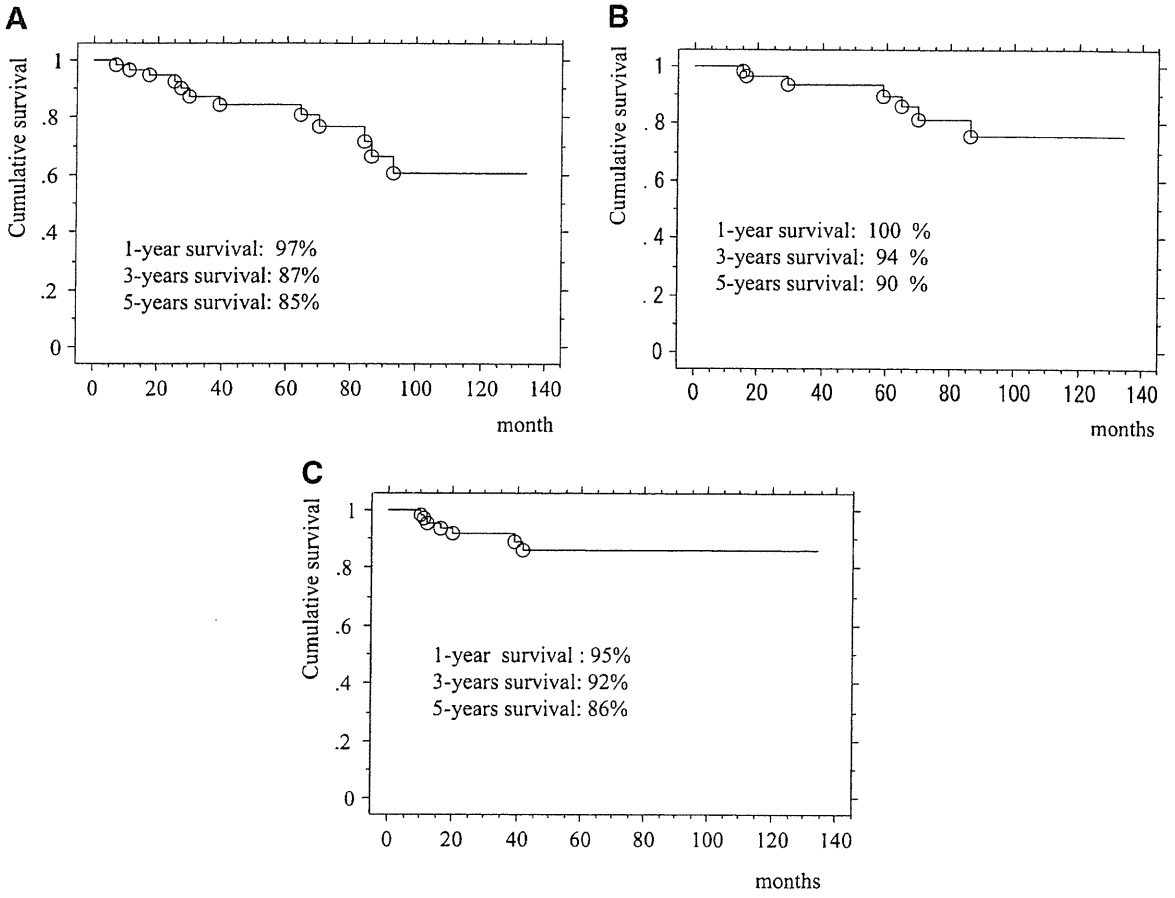

Fig. 2. Kaplan–Meier curve showing (a) the overall prosthetic survival of 69 prostheses, (b) the prosthetic survival without aseptic loosening after reconstruction using the PHK III, and (c) overall limb preservation rate.

Overall Prosthetic Survival Rate and the Factors which Affect the Prosthetic Survival

There were 22 prosthetic surgeries which required additional surgery. Excluding failure because of local tumor recurrence or deep infection, there were 12 prosthetic failures which required revision surgery. The reasons for prosthetic failures included 4 stem breakages, 4 aseptic loosening, 3 displacements of the shaft cap, and one wear of rotation sleeve (Table I). Based on Kaplan–Meier estimates, the 1-, 3-, and 5-years overall prosthetic survival rates were 97%, 87%, and 85%, respectively (Fig. 2a). When the factors which affect the overall prosthetic survivals were investigated, a univariate analysis showed better prosthetic survival in female gender ($P = 0.012$) (Table II).

Prosthetic Survival Rate Without Aseptic Loosening and Overall Limbs Preservation Rate

The prosthetic survival without aseptic loosening and the overall limb preservation rate were examined. 7 cases of aseptic loosening were observed between 15 months and 46 months postoperatively after prosthetic reconstruction. Thus, the 1-, 3-, 5-years prosthetic survival rates without aseptic loosening were 100%, 94%, and 90%, respectively (Fig. 2b). A total of 7 patients underwent a subsequent amputation (Table I). The time to amputation varied from 10 months to 42 months, with a mean of 21.4 months. Therefore, the 1-, 3-, 5-year overall limb preservation rate were 95%, 92%, and 86% (Fig. 2c).

TABLE II. The Relationships Between Various Factors and Prosthetic Survival

	No.of patients	3-yrs survival	5-yrs survival	*P*-value*
Gender				
Male	28	78	78	0.012†
Female	41	95	89	
Age				
<50	39	90	86	0.77
≧50	30	82	82	
BMI				
<25	56	88	84	0.99
≧25	9	83	83	
Femur resection				
<40	32	89	89	0.81
≧40	23	86	86	
Capusular resection				
Intracapsular	50	86	82	0.57
Extracapsular	16	92	92	
Irradiation				
Yes	5	100	—	Incomputable
No	64	87	84	
Chemotherapy				
Yes	47	89	85	0.94
No	22	81	81	
Diameter of stem				
10 mm	15	93	84	0.98
Except for 10 mm	53	85	85	
Length of stem				
130 mm	55	86	86	0.26
170 mm	13	92	77	
Replacement of patella				
Yes	28	90	90	0.74
No	41	86	81	

*Log-rank test.
†$P < 0.05$ significant.

TABLE III. Results of the Limb Function Evaluated with the MSTS Scoring System

	MSTS score						
Factor	5	4	3	2	1	0	Mean
Pain	44	10	9	1	1	1	4.4
Function	10	9	26	5	12	4	2.8
Acceptance	16	14	18	10	7	1	3.3
Supports	22	6	16	1	17	4	3.0
Walking ability	24	14	21	1	3	3	3.7
Gait	18	13	18	4	10	3	3.2
						Total	20.5 (68%)

Functional Outcome and the Factors Which Affect the Limb Function

At the most recent follow-up, the mean range of passive motion of the knee joint was: extension −0.6° (±2.6), flexion 90° (±26). In 6 patients, an extension lag was observed with a mean lag of 15° (±26°). At the latest follow-up examination, the functional score according to the classification system of the MSTS ranged from 3 to 30 points. The mean was 20.5 points, which represents function that is 68% of normal. When this was evaluated in detail, the score of pain seemed to show a relatively high score and function showed a relatively low score (Table III).

DISCUSSION

One of the unique properties of the PHKIII is that the metallic parts of the PHKIII are fully made of light-weight and high-strength titanium alloy (Ti-6Al-4V). Here has been, and is still, concern about the high elastic modules of the metallic alloys as compared to bone, and the variable fatigue resistance of the prosthesis, because both properties may eventually lead to prosthesis failure through loosening or breakage. Long and Rack indicated that the titanium alloy, Ti-6Al-4V, has acceptable strength levels as defined by either the percent elongation or the percent reduction of area in a standard tensile test [9]. The smooth fatigue strength of the titanium-alloy is as high as that of CoCrMO. The problems related to implant stiffness-related stress shielding of bone have resulted from the high elastic modulus of alloys. However, titanium alloy has a lower elastic modulus value closer to bone, approximately half that of CoCrMo alloy [9]. In addition, the titanium alloy has superior biocompatibility and corrosion resistance [9]. Furthermore, the titanium alloy allows scanning by MR imaging, which is an important diagnostic modality that can be used to detect the local recurrences of the tumor. Therefore, we considered that the titanium alloy is generally preferable to a cobalt-based alloy for the tumor prosthesis, and developed the PHK III.

Failure analysis allows the investigator to determine the causes of poor outcome and potentially to improve future outcomes. Out of the 37 late complications, local tumor recurrences were observed in 10 of the 69 patients (14%). This local recurrence rate seems to be slightly high compared to that of other previous reports [10–27]. The histological diagnoses of the 10 recurrent cases were osteosarcoma in 6, MFH of bone in one, high-grade soft tissue sarcoma in 2 and chondrosarcoma in one. Four of the 10 recurrent cases were in non-osteosarcoma patients. MFH of bone and soft tissue sarcomas generally exhibit poor prognosis with a high local recurrence rate, in comparison to osteosarcoma [1]. Therefore, these types of histological diagnoses seem to exert an influence on the high recurrence rate in the present study. In all of the 10 patients who had local recurrences, MRI was a useful diagnostic modality although minor distortions and halation of images were visible. Thus, the PHK III which is made of titanium alloy is considered to have a great advantage for the detection of local tumor recurrence.

TABLE IV. Summary of the Clinical Results of Prosthetic Reconstruction of the Distal Femur after Resection of a Muskuloslkeletal Tumor

			Prosthetic survival rate[‡]				Limb preservation rate[‡]			Complications							
Author	Prosthesis* (no.)	Hinge type[†]	1-yr	3- yrs	5- yrs	10- yrs	1- yr	3- yrs	5- yrs	Loosen-ing	Breakage of femoral component	Infect-ion	Recur-rence	Hinge trouble	% of amputation	Functional outcome (MSTS)	Follow-up (months)
Robert[21]	Stanmore(133)	F	93	87	72	—	99	90	89	6.0%	2%	7%	8%	—	10%	—	34
Capanna[20]	KMFTR/HMRS (95)	F	—	—	—	—	—	—	—	0%	6%	12%	5%	30%	6%	—	51
Unwin[23]	Stanmore(218)	F	—	91[‡]	82[‡]	68	—	—	—	5.0%	3%	2%	4%	—	—	—	58
Torbert [19]	Not clearly shown(57)	—	97[‡]	90	84	66	—	—	—	—	—	—	—	—	5%	—	56
Muschler[16]	Custom(37)	Semi-c	89	73[‡]	57	—	—	—	—	16.0%	3%	3%	14%	—	5%	—	49
Unwin[22]	Stanmore(493)	F	—	—	—	—	—	—	—	46.0%	10%	8%	30%	—	7%	—	46
Biau[25]	GUEPAR (56)	F	—	—	85	55	—	—	—	17.9%		7%	11%	—	—	—	62
Kawai[14]	HSS(40)	Semi-c	91[‡]	85	67	48	—	93	90	40.0%	3%	10%	—	5%	8%	80%	96
Ham[17]	Spherocentric(3) Endo (12)	Semi-c(3) R(12)	93[‡]	87[‡]	87[‡]	80[‡]	—	—	—	—	—	7%	13%	47%	13%	—	61
Kawai[13]	Finn(25)	R	91[‡]	88[‡]	88	—	—	—	—	—	—	—	—	—	—	—	—
Kawai[12]	HSS(51), Finn(31)	HSS: Semi-c, Finn: R	—	82	71	50	—	94	92	21.9%	1%	6%	4%	5%	9%	—	HSS:84 Finn: 38
Bickels[15]	Modular Prosthesis(73) Custom(27) Expandable(10)	R	—	—	93	88	—	—	96	5.4%	—	5%	5%	—	4%	—	—
Heisel [11]	MUTAS(50)	Semi-c	—	—	—	—	—	—	—	22.0%	0%	12%	6%	10%	—	72	46
Griffin [24]	KMFTR/HMRS(74)	F	96[‡]	84[‡]	77[‡]	—	97[‡]	92[‡]	92[‡]	2.0%	6%	10%	5%	—	—	—	73
Sharma [18]	KMFTR/HMRS(77)	R		—	84	79				0%	0%	8%	7%	4%	7%	56	52
Present series	PHKIII(69)	Semi-R	97	87	85	—	95	92	86	10%	6%	10%	14%	6%	10%	68%	57

*Stanmore, Stanmore prosthesis; KMFTR/HMRS, Kotz Modular Femur-Tibia Reconstruction System/Howmedica Modular Reconstruction System; GUEPAR, GUEPAR prosthesis; HSS, Hospital for Special Surgery-modular-linked system; Finn, Finn prosthesis; Spherocentric, spherocentric type of semiconstrained knee endoprosthesis(Howmedica); Endo, axial rotating Endo knee (Waldemar Link); PHKIII, KYOCERA Physio Hinge Total Knee System Type III.

[†]F, fixed hinge; Semi-c; semi-constrained hinge; R, rotating hinge; Semi-R, semi-rotating hinge.

[‡]Numerical character determined based on the Kaplan–Meier curve indicated in the figure.

Prosthetic replacement following excision of a bone tumor can be complicated by infection because patients often are subjected to extensive soft-tissue dissection and long surgical times and are immune-suppressed [24]. Prosthesis-associated infection rates are reported to be 2–12% [11,12,14–18,20–26] (Table IV). In the present series, a deep infection was observed in 7 patients (10%). Although the majority of patients were immunosuppressed at the time of surgery and for prolonged periods afterwards, this relative high rate of infection is still hardly acceptable. This appeared to be due to, in large part, the thinness of the soft tissue covering the prosthesis. The use of muscle rotation flaps or a vascularized musculocutaneous flap should be considered when only the rectus femoris muscle have been preserved [12].

Radiographic aseptic loosening of the prosthesis is the most common reason for prosthesis revision [11,12,14,22]. The rotating hinge mechanism theoretically provides a more congruent articulation, leading to a decrease in wear and transmitted interfacial stresses to the femoral bone. Thus, special attention was paid to determine the prosthetic survival rate without aseptic loosening. In the present study, seven prostheses (10%) were identified as radiographically loose, and four of the seven loose prostheses required revision surgery. Thus, the 1-, 3-, 5-years prosthetic survival rates without aseptic loosening were 100%, 94%, and 90%, respectively. Previous reports indicated that the incidence of aseptic loosening varied from 0 to 46% [4,12,14–16,18,20–23,25]. A recent large retrospective study demonstrated that the overall risk of revision for any reason fell by 52% when the rotating hinge implant was used [27]. At the present time, definitive advantage on aseptic loosening in PHKIII is not observed. However, a further long-term follow-up study is needed before any definitive conclusions can be drawn.

There were 4 incidents of breakage of the femoral stem. Breakages of the femoral stem could be attributed to the fact that all of the 4 broken stems were small sized stems (10 mm diameter). Four of 15 stems with a 10 mm diameter had broken at the base. Some reports also described an association between the increased risk of stem breakage and the smaller stem size [20,24]. After excluding the 10 mm stem component from the PHKIII system in May 2001, no breakage of the femoral stem was observed. But, further careful follow-up is needed for the remaining 11 prostheses with 10 mm stem.

There were 4 displacements of the shaft caps. Because they were apparently due to material fragility of the shaft cap, a more robust shaft cap was developed in September 1998. After reinforcement of the shaft cap, there have been no displacements of the shaft caps. Wear of rotation sleeve was observed in a patient leading to revision surgery. Further long-term follow-up is needed to deliver the judgment whether the semi-rotator hinge joint of PHK III itself is a durable design, or not.

There were 12 prosthetic failures which required revision surgery. Based on the Kaplan–Meier estimates, the 1-year, 3-years, and 5-years prosthetic survival rates were 97%, 87%, and 85%, respectively for all 69 prosthesis. Prosthetic 5-year survivals for distal femoral replacement in previous studies ranged 57%–93% [12–18,19,21,23–25] (Table IV). Direct comparison of survival results in the current series to other published reports is difficult due to the heterogeneity with respect to the patient population. However, the prosthetic survival rate in the present study is comparable to that reported in the previous literature.

A univariate analysis showed better prosthetic survival in female gender. The similar result is indicated in the other previous report [14]. I supposed that the loading to the prosthesis in female is less than that in male due to the lower activity in daily life. Some previous reports demonstrated that resection of more than 40% of the femur was found to be a significant negative prognostic factor for prosthetic survival [10,12–14,17]. However based on the Kaplan–Meier survival analysis, there was no statistically significant difference in failure rate based on the length of the resection. These results suggest that the PHKIII has a stable clinical performance which was rarely affected by the patients' characteristics and the surgical procedure.

Because prosthetic replacements are usually associated with a great risk of complications, there is significant risk of amputation following prosthetic replacement [26]. In the current study, the 1-, 3-, 5-year overall preservation of the limbs were 95%, 92%, and 86%. Although the overall risk of amputation in the current study is comparable to the other series [12,13,15–18,19–22] (Table IV), further long-term follow-up is required.

The final goal of prosthetic reconstruction after a resection of a distal femoral tumor is to obtain better limb function. In the current study, the mean functional score according to the classification system of the MSTS was 68% of normal, and which is comparable to that seen in the previous series [11,14,18]. This result suggest that the reconstruction using PHKIII promise the acceptable functional outcome for the patients with musculoskeletal tumor at the distal femur.

In summary, we developed new type of tumor prosthesis, PHK III for the people with the typical Asian physical body-type to reconstruct bony defects of the distal femur. Although more continuous follow-up is required to determine the clinical performance of the PHKIII, reconstructions using PHKIII are considered to achieve acceptable clinical outcome.

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The Symptom-To-Diagnosis Delay in Soft Tissue Sarcoma Influence the Overall Survival and the Development of Distant Metastasis

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Background: There are very few reports regarding the impact of the symptom that caused patients to consult a doctor and the symptom-to-diagnosis delay on survival for soft tissue sarcoma patients. The purpose of this study is to investigate whether symptom-treatment delay are associated with the presence of metastasis at diagnosis, overall survival and distant metastasis-free survival in primary soft tissue sarcomas.

Methods: This study retrospectively reviewed the medical records of 100 newly diagnosed patients with primary soft tissue sarcoma referred to our hospital.

Results: Eighteen of 100 sarcoma patients had distant metastases at diagnosis. A multivariate logistic regression analysis revealed that tumor size, tumor site, and the interval between the onset of the initial symptom and the first consultation to our hospital were all found to be significant predictors of distant metastases at diagnosis. The patients (n = 48) who were treated within the first 6 months from the onset of the initial symptom showed significantly better cumulative overall survival rate than those (n = 34) who were diagnosed more than 6 months (5-years: 77.0% vs. 59.7%).

Conclusion: These results suggest that a shorter delay may have a beneficial effect on treatment options and outcome, improving survival in some sarcoma patients.

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KEY WORDS: soft tissue sarcoma; delay; metastasis; survival

INTRODUCTION

Several relevant prognostic factors have been defined for soft tissue sarcoma. Factors predictive of survival included large tumor size, high histological grade, deep location, presentation with local recurrence, lung metastasis at diagnosis, and a positive surgical margin [1–3]. However, there are very few reports regarding the impact of the symptom that caused patients to consult a doctor and the symptom-to-diagnosis delay on survival for soft tissue sarcoma patients [4,5]. The possible influence of diagnostic delays on survival and the risk factors of the delay in cancer patients have been the subject of considerable interest and controversy for many years [6–9]. Some authors have found that a shorter diagnostic delay progressively decreases the degree of cancer invasion, while increasing the survival rate [7–8]. However, others have asserted that there is not necessarily any relationship among diagnostic delays, the extent of invasion, and mortality [9].

The purpose of this study is to investigate whether symptom-treatment delay are associated with the presence of metastasis at diagnosis, overall survival, and distant metastasis-free survival in primary soft tissue sarcomas.

MATERIALS AND METHODS

This study retrospectively reviewed the medical records of 100 newly diagnosed patients with primary soft tissue sarcoma referred to our hospital between January 2001 and December 2009. Well-differentiated liposarcomas and dermatofibrosarcoma protuberance were excluded from this study because there is extremely good prognosis in these histology. The cases that were referred for additional resection were also excluded. The histopathological diagnosis and tumor grade determined using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) system for all patients was reviewed and confirmed by independent pathologists. Informed consent has been obtained by all patients.

Follow-Up and Assessments

Treatment and follow-up were done by the orthopedic surgeons specialized in bone and soft tissue tumors (T.N, A.M, T.M, K.A). The follow-up protocol included routine physical examinations, laboratory tests, as well as computed tomography studies every 3–4 months.

The primary purpose of this study was to examine the risk factors associated with distant metastasis at diagnosis. The following factors were studied: patient age (>60 vs. ≤60), gender (male vs. female), first symptom (e.g., tumor progression, pain) which made the patients to consult the our hospital, the interval between the onset of the first symptom and diagnosis (>6 month vs. ≤6 months), primary tumor site (extremities vs. trunk), tumor size (≥8 cm vs. <8 cm), tumor depth (superficial vs. deep) at diagnosis.

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Each author certifies that his institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with the ethical principles of research.

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The secondary purpose of this study was to examine the prognostic factors associated with the patients' survival using univariate and multivariate analyses. The nine characteristics were investigated in terms of their relationships with the prognosis. Age, gender, and symptoms (mass progression, pain), which made the patients to consult the hospital were selected to represent individual clinical covariates. The interval between onset of the initial symptom and the start of treatment was included as a variable. The primary tumor site, tumor size, tumor depths, and tumor histological grade (high grade vs. low-intermediate) were also chosen as variables.

Statistical Analysis

The risk factor of metastasis at diagnosis was assessed by a univariate analysis using Fisher's extract test or the Chi-square test, and by a multivariate analysis using a logistic regression analysis (StatMate III, ATMS Co. Tokyo, Japan).

Survival was estimated by the Kaplan–Meier method. Cumulative overall survival rates and distant metastasis-free survival rates were compared with the log-rank test. The survival time was counted from the date of the initial treatment (surgery, chemotherapy, or radiation) for the primary tumor. The multivariate analysis was performed using Cox proportional hazard model. In all statistical analyses, $P < 0.05$ was considered to be significant.

RESULTS

Patient, Tumor, and Treatment Characteristics

The mean age at diagnosis was 57 years (range 0–89, median 61). There were 62 male and 38 female patients. The mean follow-up period from the date of the initial treatment was 34 months (range 1–97 months, median 29 months). The mean tumor size at diagnosis was 9.5 cm (range 3–25 cm, median 8 cm). Sixty-eight patients had high-grade sarcomas, and 32 patients were histologically classified as low-intermediate grade sarcomas. Histologically, 18 patients had malignant fibrous histiocytomas, 15 patients had myxoid liposarcomas, 14 patients had leiomyosarcomas, 11 patients had synovial sarcomas, 10 patients had myxofibrosarcomas, 10 patients had malignant peripheral nerve sheath tumors, 5 patients had extra-skeletal chondrosarcoma, and 17 patients had other tumors. The primary tumor site were extremities (n = 81) (lower extremity, 55; upper extremity, 17; buttock, 9) and trunk (n = 19). Eighteen of 100 patients first felt pain. The main symptoms, which made the patients consult our hospital were; increased mass size (n = 44), awareness of mass (n = 33), pain (n = 32). Nine patients had two clinical symptoms that caused them to consult our hospital.

The interval between the onset of the symptoms and first consultation with the primary doctor were 1–72 months with a median period of 3 months. Twenty-eight patients had a delay of more than 6 months from the onset of the first symptom to consulting the primary doctor.

The interval between the onset of the symptoms and histological diagnosis were 1–72 months with a median period of 6 months. In fourteen patients, it took more than 2 months before consultation from the first primary doctor to us. The most frequency reason for the delay was a misdiagnosis at the initial clinic, based only on a clinical examination without diagnostic imaging in 13 patients (93%) of 14, leading to no or inadequate follow-up. A biopsy was performed in only one of these 14 patients (7%), but unfortunately, the diagnosis of "hematoma" was given without histological examination because of its macroscopic finding.

The median interval between the onset of the symptoms and histological diagnosis in patients with high-grade sarcoma was 6 months. The median interval between the onset of the symptoms and histological diagnosis in patients with low-intermediate sarcoma was 3 months.

The median interval between diagnosis and start of treatment in 100 sarcoma patients was 2 weeks.

Ninety-four of 100 soft tissue sarcoma patients received surgery, and 6 patients received radiation therapy. Adjuvant chemotherapy was administered to 31 of 100 patients. Local recurrence was detected in 14 patients.

Risk Factors of Distant Metastases at Diagnosis

First, we examined the risk factors associated with distant metastasis at diagnosis. Eighteen of 100 sarcoma patients had distant metastases at diagnosis. A univariate analysis revealed that tumor depths, tumor size, and the interval between the onset of the initial symptom and diagnosis were found to be statistically significant predictors of distant metastases at diagnosis (Table I).

A multivariate logistic regression analysis revealed that tumor size and the interval between the onset of the initial symptom and the first consultation to our hospital were all found to be significant predictors of distant metastases at diagnosis (Table II). Tumor depths was excluded from the multivariate analysis because there were no patients with superficial tumor location with detectable metastatic disease at diagnosis.

Patient's Survival and Risk Factors Which Affect the Patient's Survival

Next, we examined patient's survival and risk factors, which affect the patient's survival. Fifty-seven of 100 patients were alive with continuous disease free (CDF) status as of March 2010, 2 had no evidence of disease (NED), 5 were alive with disease (AWD), 34 had died of disease (DOD), and 2 had died of other causes (DOOC). The overall 5-year survival rate was 54.4%.

TABLE I. Univariate Analysis for Predictable Factors for Presence of Metastasis at Diagnosis in 100 Patients With Sarcomas

Variables	Without metastasis at diagnosis	Metastasis at diagnosis	*P*-value
Age			
>60	46	10	0.99
≤60	36	8	
Gender			
Male	52	10	0.72
Female	30	8	
Pain			
Yes	27	5	0.78
No	55	13	
Tumor progression			
Yes	37	7	0.83
No	45	11	
Interval-1*			
>6 months	31	12	0.048
≤6 months	51	6	
Primary site			
Extremities	64	17	0.20
Trunk	18	1	
Tumor size			
≥8 cm	43	17	0.003
<8 cm	39	1	
Tumor depths			
Superficial	20	0	0.02
Deep	62	18	

Interval-1*, interval between onset of first symptom and diagnosis.

TABLE II. Multivariate Analysis for Predictable Factors for Presence of Metastasis at Diagnosis

Variables	Hazard ratio (95%CI)	*P*-value
Interval-1*		
>6 months	4.02 (1.2–13.1)	0.02
Primary site		
Trunk	0.18 (0.02–1.6)	0.13
Tumor size		
≥5 cm	20.9 (2.5–172)	0.01

Interval-1*, interval between onset of first symptom and diagnosis; 95% CI, 95% confidence interval.

Eighteen patients had distant metastases at diagnosis and the overall 5-year survival rate in this group was 5.9%. These patients were excluded from further survival analysis except where stated.

The overall 5-year survival rate in the 82 patients who had no distant metastases at diagnosis was 66.8%.

Gender, tumor size and the interval between the onset of the initial symptom and start of treatment were identified to be significant prognostic factors in the univariate analysis (Table III). The multivariate analysis found that the interval between the onset of the initial symptom and initiate treatment and tumor size were independent predictors of survival (Table IV). The overall 5-year survival rate in the 48 patients who were treated within the first 6 months from the onset of the initial symptom was 77.0%. The overall 5-year survival rate in the 34 patients who were treated more than 6 months from the onset of the initial symptom was 59.7% (Fig. 1).

TABLE III. Univariate Overall Survival Analysis in 82 Patients With Sarcomas

Variables	n	5-Y OS (%)	*P*-value
Age			
>60	46	60.8	0.22
≤60	36	71.1	
Gender			
Male	52	80.3	0.04
Female	30	43.4	
Pain			
Yes	27	61.9	0.79
No	55	69.6	
Tumor progression			
Yes	37	45.1	0.46
No	45	73.3	
Interval-2*			
>6 months	34	59.7	0.04
≤6 months	48	77.0	
Primary site			
Extremities	68	66.4	0.32
Trunk	18	67.8	
Tumor size			
≥8 cm	43	49.0	0.01
<8 cm	39	88.3	
Tumor depths			
Superficial	20	80.9	0.64
Deep	62	63.5	
Tumor histological grade			
3	50	59.3	0.11
1or 2	32	79.4	

Interval-2*, interval between onset of first symptom and start of treatment; 5-Y OS, 5-year overall survival after the treatment of primary tumor.

TABLE IV. Multivarate Overall Survival Analysis in 82 Patients With Sarcomas

Variables	Relative risk (95%CI)	*P*-value
Age		
>60	1.4 (0.51–3.83)	0.52
Gender		
Male	2.2 (0.82–6.0)	0.12
Tumor size		
<8 cm	0.17 (0.048–0.61)	0.01
Tumor grade		
1 or 2	0.62 (0.20–1.95)	0.26
Interval-2*		
>6 months	2.83 (1.08–7.45)	0.03

Interval-2*, interval between onset of first symptom and start of treatment; 95% CI, 95% confidence interval.

Risk Factors Which Affect the Appearance of Distant Metastasis During the Follow-Up

Distant metastasis was detected in 20 of 82 patients during the follow-up periods. The site of first distant metastases was the lung in all 20 patients. The 5-year distant metastasis-free survival was 70.6%. Clinical and tumor-related variables were analyzed as potential determinants of distant metastasis-free survival (Table V). Gender, tumor size, and the interval between the onset of the initial symptom and start of treatment were identified to be significant prognostic factors in the univariate analysis (Fig. 2). The multivariate analysis found that the interval between the onset of the initial symptom and start of treatment, gender, and tumor size were independent predictors of survival (Table VI).

DISCUSSION

Generally, it has been considered that earlier diagnosis of malignant tumors would lead to a better disease-free survival. In many types of cancer, the patients with small localized tumors have much better prognosis than patients with advanced or metastatic disease [6–8]. However, it has been much less clear whether the symptom-to-diagnosis delay, which might result in the late start of initial treatment has adverse effects on survivals of patients with soft tissue sarcoma. In the present study, we investigate the influence of

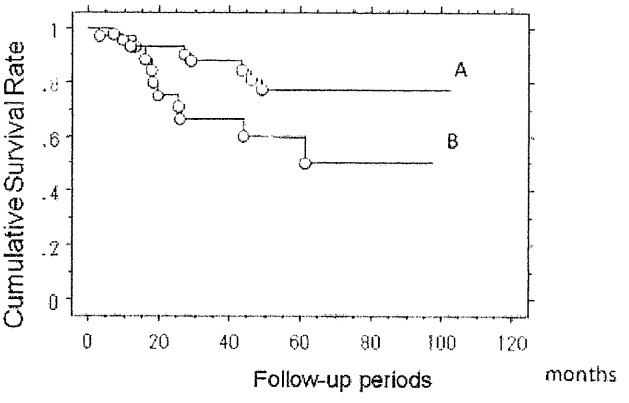

Fig. 1. Kaplan–Meier survival curve shows the overall survival of the 82 patients with soft tissue sarcoma. (**A**: patients with the delay within first 6 months (**B**) patients with the delay more than 6 months).

TABLE V. Univariate Analysis for Predictable Factors for Distant Metastasis Analysis in 82 Patients With Sarcomas

Variables	n	5-Y DMR(%)	*P*-value
Age			
>60	46	65.6	0.34
≤60	36	74.7	
Gender			
Male	52	79.3	0.02
Female	30	48.4	
Pain			
Yes	27	63.9	0.31
No	55	72.6	
Tumor progression			
Yes	37	67.5	0.49
No	45	72.9	
Interval-2*			
>6 months	34	38.8	0.04
≤6 months	48	76.5	
Primary site			
Extremities	68	69.4	0.93
Trunk	18	69.7	
Tumor size			
≥8 cm	43	54.6	0.02
<8 cm	39	87.6	
Tumor depths			
Superficial	20	73.8	0.71
Deep	62	68.2	
Tumor histological grade			
3	50	65.0	0.17
1–2	32	76.9	

Interval-2*, interval between onset of first symptom and start of treatment; 5-Y DMR, 5-year distant metastasis-free survival rate after the treatment of primary tumor.

symptom-to-diagnosis delay on survival in patients with soft tissue sarcoma.

Approximately 20% of the patients with sarcomas have isolated lung metastatic disease [10]. Several large series have defined a number of clinical prognostic factors that are associated with an increased risk of distant metastasis. The most significant of these factors appear to be the histological grade of the tumor, tumor size, and depth [11,12]. A multivariable analysis of the 100 soft tissue

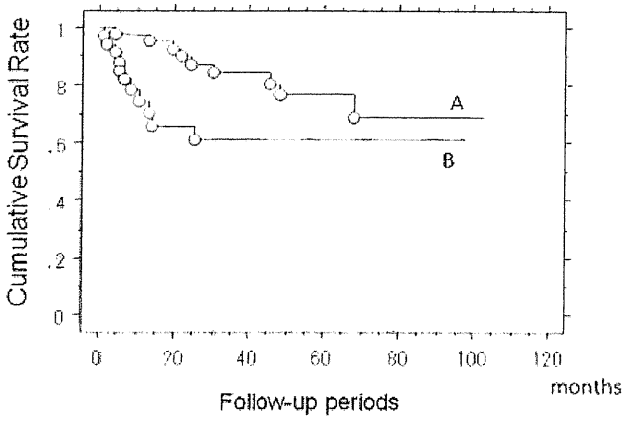

Fig. 2. Kaplan–Meier survival curve shows the distant relapse-free survival of the 82 patients with soft tissue sarcoma. (**A**: patients with the delay within first 6 months (**B**) patients with the delay more than 6 months).

TABLE VI. Multivarate Distant Metastasis Analysis in 82 Patients With Sarcomas

Variables	Relative risk (95%CI)	*P*-value
Gender		
Male	2.55 (1.03–6.29)	0.04
Tumor size		
<8 cm	0.27 (0.09–0.75)	0.01
Tumor grade		
1 or 2	0.74 (0.27–2.08)	0.57
Interval-2*		
>6 months	2.74 (1.09–6.72)	0.03

Interval-2*, interval between onset of first symptom and start of treatment; 95% CI, 95% confidence interval.

sarcoma patients in the current series found that tumor size, primary tumor depth, and the interval between the onset of the symptom and diagnosis were statistically significant predictors of the presence of metastases at diagnosis. In addition, all tumors of 18 patients with metastases at diagnosis developed in a deep location. These results suggest that deep-seated soft-tissue tumor would be difficult to impress that it may be "malignancy" on not only patients but also clinicians. Furthermore, these results indicate that longer delays between the onset of symptoms and diagnosis or treatment may account to be associated with worse survival in patients with soft tissue sarcoma.

The impact of symptom-to-diagnosis delay on survival cannot be studied in randomized controlled trials. Much of the literature focusing on symptom-to-diagnosis delay is limited to diseases with a social system of medical check for early diagnosis, such as breast and prostate cancer [7,8]. Head and neck squamous cell carcinomas show no correlation between duration of symptoms before the diagnosis and stage or survival [9]. Regarding sarcoma, Clark et al. [4] stated that the symptom-to-diagnosis delay is likely to have had a detrimental effect on treatment options and outcomes. Contrarily, Rougraff et al. [5] reported that the duration of symptoms did not predict the presence of metastatic disease at diagnosis and survival in patients with sarcoma.

The current study showed that the short interval between the onset of the initial symptoms and start of treatment has a significant association with an improved survival in patients with primary soft tissue sarcoma. A delay of more than 6 months to treat was identified as the worse prognostic factor in both the univariate and multivariate analyses.

The symptom-to-diagnosis delay can be attributed to several reasons. One is that the patients do not present the initial clinic in spite of awareness of the tumor-related symptom. The other is that the patients present the initial clinic, but unthinkingly followed-up without any imaging examination [4,13].

Twenty-eight patients in the current series had a delay of more than 6 months from the appearance of the first symptom to consulting the first doctor. The reason for this delay in soft tissue sarcomas may be the lack of specific and severe symptoms.

Fourteen patients had a delay of more than 2 months from the first doctor to us specialized to bone and soft tissue sarcoma. The rarity as well as the wide variability in clinical presentation of soft tissue sarcoma appears to be the cause of general doctor's delay in referral to a specialist. The delay in diagnosis of soft tissue sarcoma may be a problem, which can be resolved by the education for both doctors and general public. The continuous educational program for doctors and general public might be able to improve the patient's prognosis in soft tissue sarcoma.

There are some limitations in the current study. One of the limitations in this study is that it relies largely on clinical record, which

describes data, based on the patient recall. The other is that this study includes the various histological type of sarcoma. However, we believe that the study indicates the impact of delays in the diagnosis of soft tissue sarcoma.

CONCLUSION

The symptom-to-diagnosis delay was found to be significant predictors of distant metastases at diagnosis. The symptom-to-diagnosis delay was also associated with worse survival in patients with soft tissue sarcoma.

This suggests that a shorter delay may have a beneficial effect on treatment options and outcome, improving survival in some sarcoma patients. The educational program for both doctors and general public must be taken to reduce the symptom-to-diagnosis delay.

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RESEARCH PAPER

Clinical impact of the tumor volume doubling time on sarcoma patients with lung metastases

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Abstract The volume doubling time (VDT) is an accurate and reproducible method for the quantitation of the rate and pattern of tumor growth in individual patients. The purpose of this study is to investigate the tumor VDT using chest CT in individual sarcoma patients with lung metastasis and to determine whether VDT is associated with survival after lung metastasis in bone and soft tissue sarcomas. Forty patients had measurable lung metastases in at least two sequential chest CT images taken at least 14 days apart. The VDT was calculated using the method originally described by Schwartz. The median and mean VDT in all 40 patients was 21.5 and 53 days, respectively. Similarly, the median and average VDT in 29 soft tissue sarcoma patients was 26 and 57 days, respectively. The median and mean VDT in 11 bone sarcoma patients was 13 and 42 days, respectively. The current univariate analysis revealed significantly poorer predictive values for VDT in all 40 sarcoma patients and 29 soft tissue sarcoma patients. A multivariate analysis showed the VDT to be an independent predictor of survival in 29 soft tissue sarcoma patients. These results suggest that patients with a shorter VDT and consequently a more rapid rate of tumor growth have a significantly lower chance for long term survival especially in soft tissue sarcoma. The patients with lung metastasis that have a longer VDT should therefore be considered for aggressive treatment even if the lesions are multiple and/or bilateral.

Keywords Volume doubling time · Lung metastasis · Bone and soft tissue sarcoma · Prognosis · Computed tomography

Introduction

Several relevant prognostic factors have been defined for bone and soft tissue sarcomas after lung metastasis. Metastasectomy, histological tumor grade, age, number of lung nodules and disease free interval are predictive of survival [1–7]. The volume doubling time (VDT) is an accurate and reproducible method for the quantitation of the rate and pattern of tumor growth in individual patients [8–14]. The previous reports indicated that a shorter VDT evaluated using chest film radiography decreased the survival rate in sarcoma patients after lung metastasis [10–12]. Lung metastases are detected earlier and more accurately with computed tomography (CT) than with chest film radiography. However, there are no reports on the use of CT to measure the tumor VDT in sarcoma patients with lung metastasis.

The purpose of this study is to investigate the tumor VDT using chest CT in individual sarcoma patients with lung metastasis and to determine whether VDT is associated with survival after lung metastasis in bone and soft tissue sarcomas.

Materials and methods

Seventy-two patients with lung metastases from bone or soft tissue sarcomas were treated between 2001 and 2009.

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Each author certifies that his institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with the ethical principles of research.

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Chest CT images (X-Vigor or Aquilion, Toshiba, Tokyo, Japan) were used to identify patients with lung metastases. The scan parameters were from 2 to 5 mm collimation and from a 0.4 to 0.75 s scan time. Forty of these patients had measurable lung metastases in at least two sequential chest CT images taken at least 14 days apart. The remaining 32 patients were excluded from the study because only one CT scanning was examined. In 13 of 32 patients, only one CT scanning was examined due to rejection of further examination and treatment when lung metastases developed. Twelve of 32 patients had treatment just after initial CT scanning was examined. Four patients did not undergo the intimate follow-up CT at our institution because no measurable tumors were detected due to plural effusion and they died of rapid progression of metastases. The remaining three patients died of brain metastasis before follow-up CT scanning was examined.

No patients received chemotherapy during the period of measurement. Twelve of the 40 patients had lung metastases at presentation. One of the 40 patients had lung metastasis during postoperative chemotherapy. The remaining 27 patients had lung metastases during the follow-up. Seven of the 40 patients received chemotherapy before the measurement of metastases, and all seven of those patients had lung metastasis at presentation. The size of metastases was measured by two independent investigators (T.N and A.M). Only the largest nodule or mass was measured if a number of tumors appeared simultaneously on the scan. The VDT was calculated using the method originally described by Schwartz [9]. The tumor volume was calculated using the following equation, assuming the tumor to have a spheroidal shape:

$$V = 4/3 \times \pi \times (a/2)^3$$

where "a" indicates the maximum tumor diameter.

The VDT was calculated using the equation:

$$VDT = (T_2 - T_1) \times \log 2 / \log V_2 - \log V_1$$

where $T_2 - T_1$ indicates the length of time between two measurements and V_1 and V_2 denote the VDT at two points of measurement.

Patient, tumor, and treatment characteristics

The mean age of the patients at the time of lung metastasis was 52 years (range 12–86). There were 23 male and 17 female patients. The mean follow-up period from the date of the lung metastasis was 26 months (range, 2–95 months). The mean maximum diameter of lung metastasis at first metastasis was 9.5 mm (range, 2–26 mm). The mean number of lung metastasis was 5 (range, 1–20). Thirty-one patients had high grade sarcomas, and nine patients were histologically classified as low to intermediate grade sarcomas. Six patients had osteosarcomas (OS), five had malignant peripheral nerve sheath tumors (MPNST), five had malignant fibrous histiocytomas (MFH), four had extra-skeletal chondrosarcomas (ESCS), three had synovial sarcomas, two had chondrosarcomas, two had myxoid liposarcomas, three had other bone tumors (including 1 Ewing sarcoma), and five had other soft tissue tumors.

Twenty-eight of 40 sarcoma patients underwent metastasectomy or/and radiofrequency ablation (RFA) for lung metastasis. Chemotherapy for lung metastasis was administered to 15 of 40 patients.

The histopathological diagnosis and tumor grade for all patients were reviewed and confirmed by pathologists.

Follow-up and assessments

Treatment and follow-up were performed by orthopedic surgeons specialized to soft tissue and skeletal tumors (T.N, A.M, T.M, K.A). The follow-up protocol included routine physical examinations, laboratory tests, as well as radiography and/or CT scannings every 3 months. The mean interval between the two examinations was 68 days (range,15–645 days. median, 46 days).

The primary purpose of this study was to calculate tumor VDT in the individual patients.

The secondary purpose of this study was to examine the prognostic factors associated with the patients' survival from first lung metastasis using univariate and multivariate analyses. The valuables included nine characteristics. Age and gender were selected to represent individual clinical covariates. Regarding the primary sarcoma lesions, tumor type (bone tumor or soft tissue tumor) and local recurrence were chosen. The maximum metastatic tumor size at the time of initial detection, the number of lung metastases at the time of initial detection, lung metastasis at presentation, distribution (unilateral or bilateral), and VDT were also chosen as variables.

Statistical analysis

Survival was estimated by the Kaplan–Meier method. The cumulative survival rates after first lung metastasis were compared with the log-rank test. (StatMate III, ATMS Co. Tokyo, Japan). The survival time was counted from the date of the first lung metastasis. The event-free interval was defined as the period between the date of primary treatment and the date of local recurrence or distant metastasis. The multivariate analysis was performed using Cox proportional hazard model. Mann–Whitney *U*-test and Student's *t* test for quantitative data, and the chi square test or Fisher extract test for qualitative data was used respectively. A value of $P < 0.05$ was considered to be significant in all statistical analyses.

Results

Determination of tumor doubling time

Tumor VDT was first examined in individual patients. The VDTs according to tumor type are shown in the Fig. 1. The mean calculated diameter of lung metastasis at the first examination was 10.5 mm (range, 3.3–31 mm; median, 8.3 mm). The mean calculated diameter at the second examination was 16.6 mm (range, 5–60 mm; median, 13.9 mm). The median and mean (±standard deviation) VDT in all 40 patients was 21.5 days and 53 ± 79 days, respectively. The VDT varied between 7 and 410 days. Similarly, the median and average VDT in 29 soft tissue sarcoma patients was 26 and 57 ± 82 days, respectively. The median and mean VDT in 11 bone sarcoma patients was 13 and 42 ± 72 days, respectively. All six osteosarcoma patients had VDT of less than 14 days, which ranged from 7 to 13 days. The VDT in patients with MPNST, leiomyosarcoma or myxoid liposarcoma ranged from 10 to 38 days. Those with MFH ranged from 12 to 65 days. Those with synovial sarcoma, ESCS or chondrosarcoma ranged from 27 to 410 days. We examined the relationship between the VDT and their background in 40 patients with lung metastases, and found the VDT of patients presenting with high grade tumors to be significantly shorter than that of low grade tumors ($P = 0.02$) (Table 1).

Five of 15 patients who were treated with chemotherapy for lung metastases had measurable lung metastases in at least two sequential chest CT images taken at least 14 days apart after chemotherapy. Compared to the VDT before chemotherapy, the VDT after chemotherapy had not significantly changed ($P = 0.38$) (Table 2).

Table 1 Relationship between the VDT and background of 40 patients with lung metastases

	VDT > 21 days	VDT ≤ 21 days	*P* value
Age			
≤65	6	8	
>65	14	12	
Gender			
Male	11	12	0.99
Female	9	8	
Primary site			
Bone	4	7	0.48
Soft tissue	16	13	
Histological grade			
High	12	19	0.02
Low-intermediate	8	1	
Met. at presentation			
Yes	5	7	0.73
No	15	13	
Distribution at first lung met.			
Lateral	8	8	0.99
Bilateral	12	12	
Number of lung met. at first lung met.			
≤3	13	7	0.52
>3	10	10	
Size of lung met. at first lung met.			
≤10	16	12	0.3
>10	4	8	

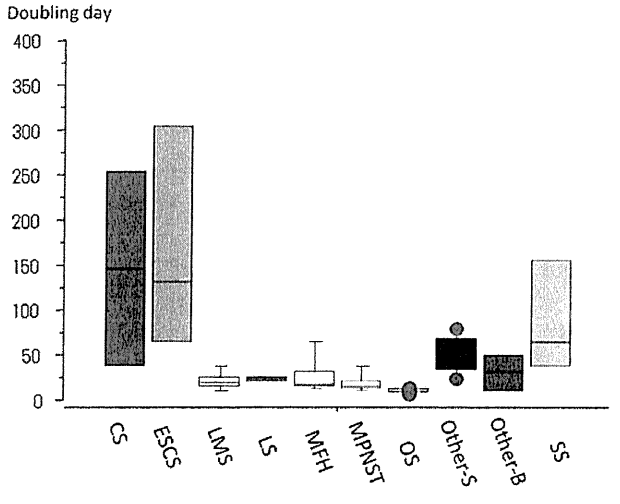

Fig. 1 Relationship between the tumor histologic type and VDT (*CS* Chondrosarcoma, *ESCS* extra-skeletal chondrosarcoma, *LMS* leiomyosarcoma, *LS* liposarcoma, *MFH* malignant fibrous histiocytoma, *MPNST* malignant peripheral nerve sheath tumor, *OS* osteosarcoma, *Others-S* other soft tissue sarcomas, *Others-B* other skeletal sarcomas, *SS* synovial sarcoma)

Patient survival after lung metastasis and risk factors which affect the patient's survival

Total patient' survival and risk factors which affect the patient's survival

Five of 40 patients had no evidence of disease (NED) at the final follow-up, three were alive with disease (AWD), 32 had died of disease (DOD). The 3- and 5-year survival rate after lung metastasis was 32 and 16.8%, respectively.

VDT was an only significant prognostic factor in the univariate analysis (Table 3). The 3-year survival rate after lung metastasis in the 20 patients with a VDT of within 21 days was 10.8%. The 3-year survival rate in the 20 patients with a VDT of more than 21 days was 52.8% (Fig. 2).

Table 2 Influence on VDT with the chemotherapy

Patients	Histology	VDT before Cx (days)	VDT after Cx (days)	Evaluation of Cx
21 y.o F	Osteosarcoma	9	16	PR
18 y.o M	Ewing sarcoma	11	14	PR
13 y.o F	Osteosarcoma	13	14	PD
23 y.o F	Fibrosarcoma	63	45	SD
38 y.o F	Extraskeletal chondrosarcoma	198	175	SD

F Female, *M* male, *VDT* volume doubling time, *Cx* chemotherapy, *PR* partial response, *SD* stable disease, *PD* Prgressive disease

Risk factors which affect the patient's survival in soft tissue sarcoma

Next, we examined the survival of 29 of 40 soft tissue sarcoma patients with lung metastasis. Three of the 29 patients had NED at the final follow-up, three were AWD, 23 had DOD. The 3- and 5-year survival rate after lung metastasis was 34.1 and 10.6%, respectively.

VDT was an only significant prognostic factor in the univariate analysis (Table 4). The multivariate analysis found that VDT and lung metastasis at presentation were independent predictors of survival (Table 5). The 3-year survival rate after lung metastasis in the 15 patients with a VDT of within 26 days was 14.8%. The 3-year survival rate in the 14 patients with a VDT of more than 26 days was 54.2% (Fig. 3). There was no significantly relationship between histological tumor grade (high vs. low-intermediate) and VDT ($P = 0.08$).

Risk factors which affect the patient's survival in bone sarcoma

Furthermore, we examined the survival of 11 bone sarcoma patients with lung metastasis. Two of 11 patients had NED at the final follow-up, 9 DOD. The 3- and 5-year survival rate after lung metastasis was 27.3 and 13.6%, respectively.

There was no significant prognostic factor in the univariate analysis (Table 6). The 3-year survival rate after lung metastasis in the seven patients with a VDT of within 13 days was 14.3%. The 3-year survival rate in the four patients with a VDT of more than 13 days was 50%.

Discussion

The concept of exponential growth rate of human solid tumors suggested by Collins et al. [8] in 1956 has been generally verified in primary and metastatic lung tumors. Schwaltz [9] proved the mathematical accuracy of this

Table 3 Clinical characteristics and univariate survival analysis in 40 sarcoma patients with lung metastasis

Characteristics	*n*	3-year survival (%)	*P* value
Age			
≧65	14	23.9	0.54
<65	26	34.6	
Gender			
Male	23	32.5	0.9
Female	17	31.5	
Tumor type			
Bone	11	27.3	0.98
Soft tissue	29	34.1	
Local recurrence			
Yes	18	46.7	0.36
No	22	22.7	
No. of lung met.			
>3	17	25.5	0.59
≦3	23	36.4	
Maximum tumor size of lung met.			
>10	12	37.5	0.24
≦10	28	30.1	
Lung met. at presentation			
Yes	12	16.7	0.21
No	28	39.2	
Distribution			
Lateral	16	23.4	0.32
Bilateral	24	37.4	
VDT			
>21 days	20	52.8	0.01
≦21 days	20	10.8	

VDT Volume doubling time

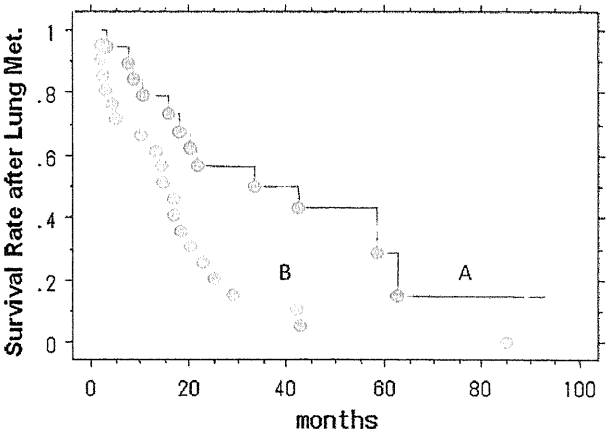

Fig. 2 Kaplan–Meier survival curve shows the survival after lung metastasis of the 40 patients with skeletal and soft tissue sarcomas. (**a** patients with a VDT of more than 21 days **b** patients with a VDT of within 21 days)