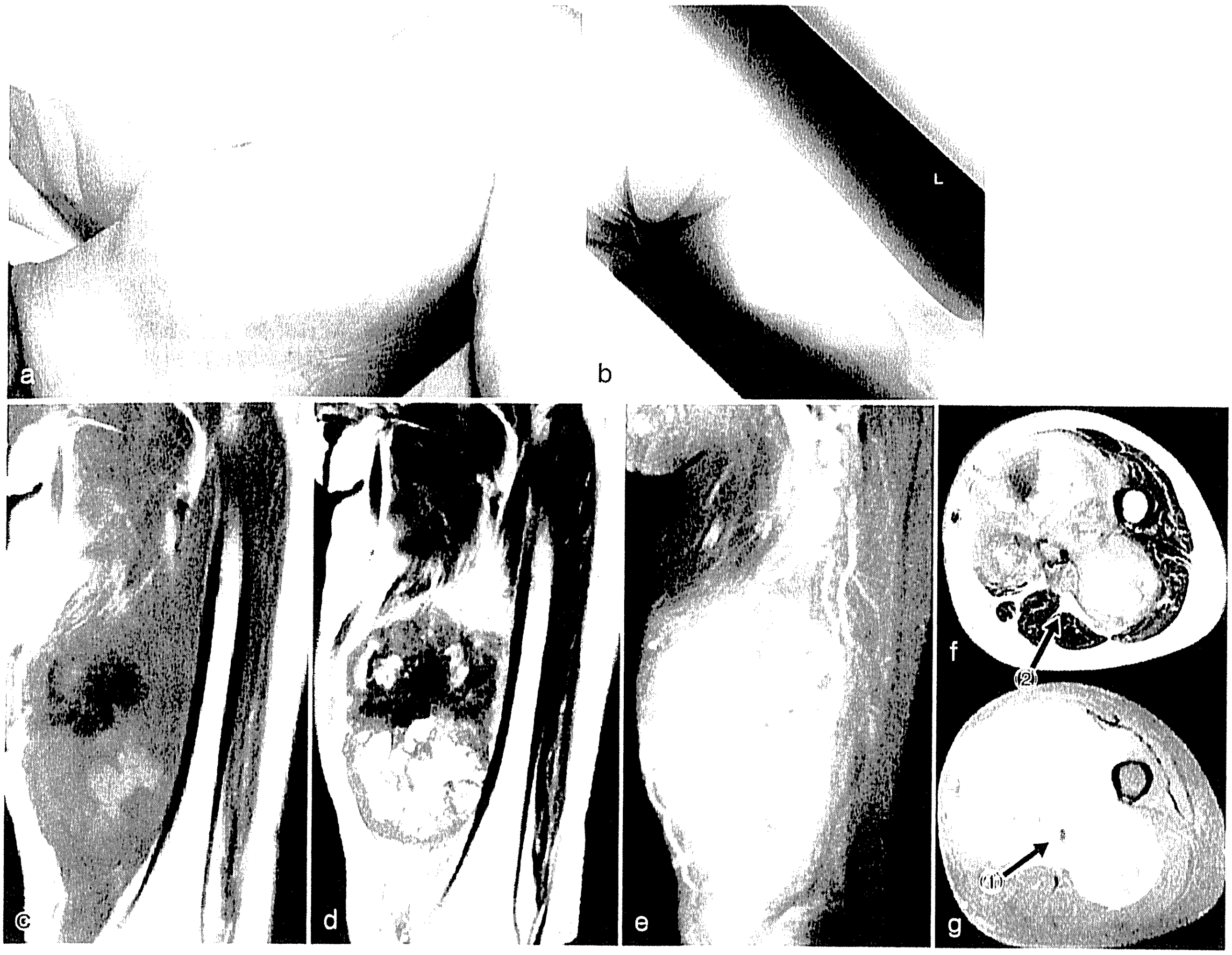

図 2　初診時左大腿肉眼的画像，単純 X 線像，および MRI

a：初診時の左大腿肉眼的画像　b：単純 X 線像　c〜g：MRI

c：T1 環状断像　d：T2 環状断像　e：T1 造影＋脂肪抑制環状断像　f：T2 水平断像　g：T1 造影＋脂肪抑制水平断画像 g の矢印①は腫瘍に浸潤された大腿動静脈を，f の矢印②は坐骨神経を示す．

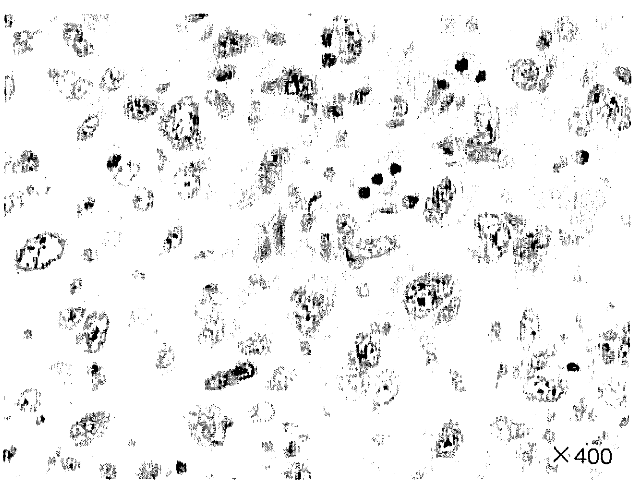

図 3　生検時病理組織像（HE 染色　前医標本）

前医病理標本を示す．

図 4　左大腿単純 X 線像および MRI 術前化学療法施行後

術前化学療法施行後の左大腿単純 X 線像（左）および MRI（右）を示す．MRI については T2 環状断像を示す．

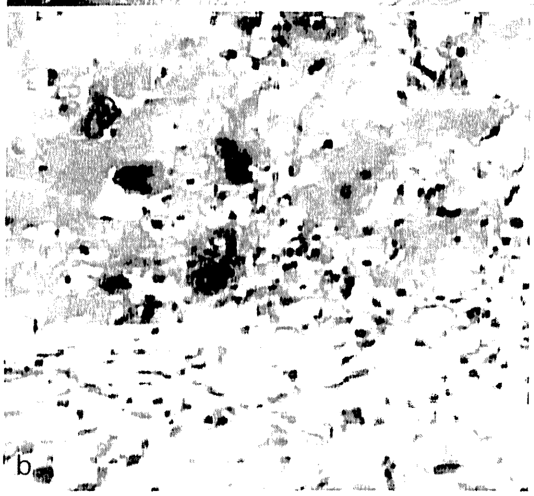

図5　手術時所見
a：手術時肉眼的所見
b：手術時病理組織像（HE染色）
a：手術時肉眼的所見の左図は腫瘍摘出後の左大腿部の画像である．人工血管でバイパスされている．また右図は摘出した腫瘍の画像である．
b：腫瘍壊死率は約90％であり，化学療法の効果ありと判断した．

3クールの計4クール施行した．術後3年2カ月の現在，局所再発や肺転移は認めておらず無病生存中である．

考察

骨外性骨肉腫は一般に高齢者に発症する極めて稀な疾患であり[7,8,10]，化学療法に対する有効性は明らかではない．しかし近年，骨外性骨肉腫に対しneoadjuvant化学療法を併用し予後の改善が認められたという報告が散見される[1,3,9]．骨外性骨肉腫に対し化学療法を積極的に行っていない報告では5年累積生存率は25～50％[2,4-6]，積極的に行っている報告では46～66％[1,3,9]とされており（表3），neoadjuvant化学療法を併用することにより，予後の改善傾向が認められる．今回，われわれの症例でもneoadjuvant化学療法を併用した系統的治療を行うことにより，5年累積生存率において有意に改善が認められた．また化学療法の併用だけに焦点を当て検討した場合でも，化学療法の併用により生存率が改善する傾向が認められた．系統的治療において化学療法の併用が生存率の改善に大きく影響していることが示唆された．またwide margin以上の手術を行った群でも有意に生存率の改善を認めた．系統的治療において，wide margin以上の手術も予後に大きく影響していることが示唆された．また病期に関しては，やはり早い段階のほうが治療成績が良く，早期発見・早期治療の重要性が示された．

一方で，化学療法の内容を検討すると各施設で統一されたプロトコールはない．また症例自体が稀であるため，単独の施設での治療成績の検討は難しい．よって多施設共同による統一したプロトコールによる治療を行い，その治療成績をprospectiveに検討する必要があると考える．

また，不適切な初回治療が予後に影響している可能性を先に述べた．われわれの研究では，前医で化骨性筋炎の診断で長期間経過観察されたために治療の開始が遅れた例や，病理組織像の診断確定までの長期化や診断の変更により，治療の開始が遅れた例が認められた．さらに病理診断を得ていない状態で不適切な外科的手術縁により，局所再発を来してから紹介されてくる症例も認められた．今後，そのような症例ができるだけ少なくな

表 3　骨外性骨肉腫の治療成績に関する報告例

報告者	症例数	化学療法併用例	局所再発率	転移率	5 年生存率
Bane BL, 1990 M.D.Anderson Cancer Center[2]	26	13	50%	61.5% (初診時 M1 の 5 例含む)	38%
Lee JSY, 1995 Mayo Clinic[5]	40	2	45%	65% (初診時 M1 の 3 例含む)	37%
Lidang JM, 1998 Center for Bone and Soft Tissue Tumors[4]	25	5	36%	60%	25%
McCarter MD, 2000 Memorial Sloan-Kettering Cancer Center[6]	15	3	7%	47%	50%
Ahmad SA, 2002 M.D.Anderson Cancer Center[1]	60	27	20% (n=6/30)	32% (初診時 M1 を除く)	46%
Goldstein-Jackson SY, 2005 COSS[3]	17	16	29% (n=4)	18%(n=3) (初診時 M1 の 2 例含む)	3 年　77%
Torigoe T, 2007 JMOG[9]	20	15	6% (n=3)	40%(n=8) (初診時 M1 の 2 例含む)	66%
自験例	17	12	29.4%	52.9% (初診時 M1 の 3 例含む)	41.2%(n=17) (初診時 M1 の 3 例を除くと 50.0%) 系統的治療例 54.6%(n=17)

骨外性骨肉腫の治療成績に関する報告例を示した．また最下段に自験例の結果を併記した．最上段より 4 つの報告は化学療法を積極的に併用していない報告群，それ以下が積極的に化学療法を併用した報告群とした．
JMOG：Japanese Musculoskeletal Oncology Group
COSS：Cooperative Osteosarcoma Study Group

るよう，一般の整形外科医，さらには他科医師に対しても，積極的に啓蒙活動を行っていく必要があろう．

結 語

骨外性骨肉腫の治療成績は，通常の骨原発骨肉腫に準じた neoadjuvant 化学療法と外科的広範切除を組み合わせた系統的治療を行うことで，予後改善できる可能性が高い．しかし非常に稀な疾患であるため症例数が十分ではなく，系統的治療の有用性を明らかにするためには，さらなる治療成績の集積やその検討が必要である．今後，治療成績を集積し，治療成績を改善するために，多施設共同による統一したプロトコールによる治療，並びにグループ研究の必要があると考える．

文 献

1) Ahmad SA, Patel SR, Ballo MT, et al: Extraosseous osteosarcoma: response to treatment and long-term outcome. J Clin Oncol **20**: 521-527, 2002
2) Bane BL, Evans HL, Ro JY, et al: Extraskeletal osteosarcoma: a clinicopathologic review of 26 cases. Cancer **65**: 2762-2770, 1990
3) Goldstein-Jackson SY, Gosheger G, Delling G, et al: Extraskeletal osteosarcoma has a favourable prognosis when treated like conventional osteosarcoma. J Cancer Res Clin Oncol **131**: 520-526, 2005
4) Lidang JM, Schumacher B, Myhre JO, et al: Extraskeletal osteosarcomas: A clinicopathologic study of 25 cases. Am J Surg Path **22**: 588-594, 1998
5) Lee JS, Fetsch JF, Wasdhal DA, et al: A review of 40 patients with extraskeletal osteosarcoma. Cancer **76**: 2253-2259, 1995
6) McCarter MD, Lewis JJ, Antonescu CR, et al: Extraskeletal osteosarcoma: analysis of outcome of a rare neoplasm. Sarcoma **4**: 119-123, 2000
7) 日本整形外科学会骨軟部腫瘍委員会(編)．全国軟部腫瘍登録一覧表(平成 20 年度)．pp19-65，2008
8) Roserberg AE, Helm S: Extraskeletal osteosarcoma. *In*: Fletcher CDM, Unni KK,

Mertens F (eds) : World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC Press, Lyon, pp182-183, 2002
9) Torigoe T, Yazawa Y, Takagi T, et al : Extraskeletal osteosarcoma in Japan : multiinstitutional study of 20 patients from the Japanese Musculoskeletal Oncology Group. J Orthop Sci **12** : 424-429, 2007
10) Weiss SW, Goldblum JR : Extraskeletal osteosarcoma. *In* : Enzinger and Weiss's Soft Tissue Tumors. 5th ed, Mosby-Elsevier, pp1051-1061, 2008

Asia-Pacific Journal of Clinical Oncology

Asia–Pacific Journal of Clinical Oncology 2011; 7: 15–16 doi:10.1111/j.1743-7563.2010.01373.x

LETTER TO THE EDITOR

Thenar muscle metastasis as recurrence of pulmonary squamous cell carcinoma

Dear Editor,
A 76-year-old man diagnosed with squamous cell carcinoma of the lung was referred to us in August 2008. The patient, a heavy smoker, was staged as having T4N2M0 disease and had a medical history of pulmonary emphysema. Physical examination revealed no remarkable change. Laboratory analysis revealed white blood cells of 6900 μL and evaluated C-reactive protein (4.4 mg/dL). Chest radiograph revealed a mass shadow in the right lower field of the lung. A computed tomography of the chest on admission revealed a heterogeneous mass with mediastinal lymphadenopathy. In September 2008, he had been treated with thoracic irradiation therapy up to 60 Gy. After thoracic irradiation therapy, there was no evidence of recurrence of lung cancer.

In February 2009, he complained of swelling and pain in the right thenar muscle. Physical examination revealed swelling of the right thenar (Fig. 1a). The rest of the chest examination was normal. Routine laboratory investigations showed no abnormalities, including tumor markers. Magnetic resonance imaging (MRI) revealed a well-defined enhanced mass in the right thenar muscle (Fig. 1b). A biopsy of the right thenar muscle showed extensive infiltration of the muscle with squamous cell carcinoma. This was found to be consistent with metastatic pulmonary squamous cell carcinoma with a possible lung primary. Further systemic evaluation revealed no evidence of recurrence, except for the right thenar muscle. Therefore, he was treated with palliative irradiation therapy for the right thenar muscle. He remains healthy at 9 months after the initial diagnosis.

Metastasis of carcinoma to the skeletal muscle is a rare event. The skeletal muscle is usually resistant to hematogenous metastases from epithelial neoplasms.[1,2] This in itself is quite peculiar because muscular mass accounts for approximately 50% of total body weight. It is thought that muscular contractile actions, local pH environment and the accumulation of lactic acid and other metabolites contribute to the rare occurrence of this phenomenon.[3] The most frequent sites of described clinical involvement are thigh, iliopsoas and paraspinous muscles.[4–7] However, the metastasis to the foot

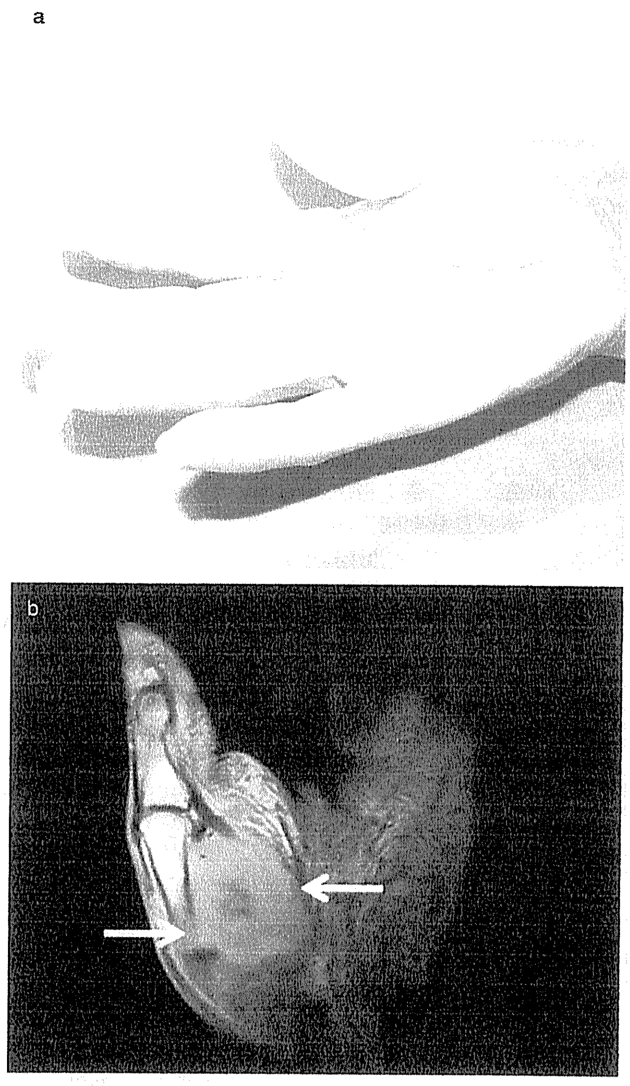

Figure 1 (a) Physical examination showing swelling in the right thenar. (b) Gd–DTPA-enhanced T1-weighted images on magnetic resonance imaging showing a well-defined enhanced mass with low signal area in the right thenar muscle.

and hand is extremely rare (0.007–0.3%), and metastatic hand lesions represent 0.1% of all osseous metastases, while metastases to muscles represent 0.8–16% incidence in autopsy series.[8,9] To our knowledge, the present case is the first report of thenar muscle metastasis resulting from lung cancer. Matsuno *et al.* also presented a case of thenar metastasis from lung cancer, but it was an unusual occurrence of skin metastasis to the thenar eminence, with a histological type of adenocarcinoma.[10] The present case was not an occurrence of skin metastasis, and the histology was different from their case.

The clinical manifestations and the MRI features of metastatic carcinoma to skeletal muscles closely resemble those of soft tissue sarcomas in many respects.[4–7] MRI is the technique of choice to characterize soft tissue lesions, but the metastatic lesions show non-specific characteristics: increased signal intensity relative to skeletal muscle on T2-weighted images, decreased signal intensity on T1-weighted images and heterogeneous enhancement after gadolinium administration.[11] The most frequent presentation of skeletal muscle metastasis is pain with or without swelling. In our case, thenar painful mass can also be confused with a soft tissue tumor by clinical features and radiographic imaging, although needle biopsy is mandatory for diagnosis. Physicians should be mindful that any painful soft tissue mass occurring in patients with a known history of carcinoma is highly suspicious for skeletal muscle metastasis.

Kyoichi KAIRA,[1] Eriko AYABE,[1]
Toshiaki TAKAHASHI,[1] Haruyasu MURAKAMI,[1]
Asuka TSUYA,[1] Yukiko NAKAMURA,[1]
Tateaki NAITO,[1] Masahiro ENDO,[2]
Mitsuru TAKAHASHI[3] and Nobuyuki YAMAMOTO[1]
Divisions of [1]Thoracic Oncology, [2]Diagnostic Radiology, and [3]Orthopaedic Oncology, Shizuoka Cancer Center, Sunto-gun, Shizuoka, Japan

REFERENCES

1 Ramanathan T. Bronchial carcinoma metastases presenting as gluteal abscess. *Br J Dis Chest* 1973; **67**: 167–8.
2 Di Giorgio A, Sammartino P, Cardini CL *et al.* Lung cancer and skeletal muscle metastases. *Ann Thorac Surg* 2004; **78**: 709–11.
3 Acinas Garcia O, Fernandez FA, Satue EG *et al.* Metastasis of malignant neoplasms to skeletal muscle. *Rev Exp Oncol* 1984; 34: 57–67.
4 Damron TA, Heiner J. Distant soft tissue metastases: a series of 30 new patients and 91 cases from the literature. *Ann Surg Oncol* 2000; 7: 526–34.
5 Plaza JA, Perez-Montiel D, Mayerson J *et al.* Metastases to soft tissue: a review of 118 cases over a 30-year period. *Cancer* 2008; **112**: 193–203.
6 Tsuya A, Kurata T, Tamura K *et al.* Skeletal metastases in non-small cell lung cancer: a retrospective study. *Lung Cancer* 2007; 57: 229–32.
7 Tuohei Y, Okada K, Osanai T *et al.* Skeletal muscle metastases of carcinoma: a clinicopathological study of 12 cases. *Jpn J Clin Oncol* 2004; 34: 210–4.
8 Vinod SU, Gay RM. Adenoid cystic carcinoma of the minor salivary glands metastatic to the hand. *South Med J* 1979; 72: 1483–5.
9 Maheshwari AV, Chiappetta G, Kugler CD *et al.* Metastatic skeletal disease of the foot: case report and literature review. *Foot Ankle Int* 2008; **29**: 699–710.
10 Matsuno Y, Watanabe K, Satoh H *et al.* Thenar metastasis from lung cancer. *Eur J Cancer Care* 2002; **11**: 61–2.
11 Williams JB, Youngberg RA, Mansfield LT *et al.* MR imaging of skeletal muscle metastases. *AJR Am J Roentgenol* 1997; **168**: 555–7.

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 208–213, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.10.056

CLINICAL INVESTIGATION **Metastases**

RADIOTHERAPY FOR PATIENTS WITH METASTASES TO THE SPINAL COLUMN: A REVIEW OF 603 PATIENTS AT SHIZUOKA CANCER CENTER HOSPITAL

MASASHI MIZUMOTO, M.D.,*‡ HIDEYUKI HARADA, M.D.,* HIROFUMI ASAKURA, M.D.,* TAKAYUKI HASHIMOTO, M.D.,*‡ KAZUHISA FURUTANI, M.D.,* HARUKO HASHII, M.D.,*‡ HIDEKI MURATA, M.D.,† TATSUYA TAKAGI, M.D.,† HIROHISA KATAGIRI, M.D.,† MITSURU TAKAHASHI, M.D.,† AND TETSUO NISHIMURA, M.D.*

From the Divisions of *Radiation Oncology and †Orthopaedic Oncology, Shizuoka Cancer Center Hospital, Nagaizumi-cho, Shizuoka, Japan; and ‡Division of Radiation Oncology, University of Tsukuba, Tsukuba, Ibaraki, Japan

Purpose: Long- and short-course radiotherapy have similar outcomes in the treatment of spinal metastases. Long-course radiotherapy is recommended for patients with good predicted survival to reduce the risk of in-field recurrence, whereas short-course radiotherapy is used for those with poor predicted survival. Therefore, prediction of prognosis and local control is required for selecting the optimal course of radiotherapy.
Methods and Materials: The subjects were 603 patients with spinal metastases who received radiotherapy at the Shizuoka Cancer Center Hospital between September 2002 and February 2007. Factors associated with survival and local control were retrospectively investigated by multivariate analyses. Local recurrence was defined as regrowth within the irradiated field or exacerbation of symptoms such as pain and motor deficits.
Results: Of the 603 patients, 555 (92%) were followed for 12 months or until death. The survival rates after 6, 12, and 24 months were 50%, 32%, and 19%, respectively, with a median survival of 6.2 months. The median survival periods after long- and short-course radiotherapy were 7.9 and 1.8 months, respectively. In multivariate analysis, primary tumor site, good performance status, absence of previous chemotherapy, absence of visceral metastasis, single bone metastasis, younger age, and nonhypercalcemia were associated with good survival. The local control rates after 6, 12, and 24 months were 91%, 79%, and 69%, respectively, and non–mass-type tumor, breast cancer, and absence of previous chemotherapy were predictors of good local control.
Conclusions: Identification of factors associated with good local control and survival may allow selection of an optimal radiotherapy schedule for patients with spinal metastases. © 2011 Elsevier Inc.

Radiotherapy, Prognostic factors, Local control, Survival, Spinal metastases.

INTRODUCTION

Bone metastasis is a common cause of cancer-related pain and neurologic disturbance. In recent years, several randomized trials have shown a similar outcome between long-course (30 Gy in 10 fractions or more) and short-course (8 Gy in one fraction, 20 Gy in five fractions) radiotherapy (1–9). For selection of optimal radiotherapy, we reported a new scoring system for survival using prognostic factors of age, tumor type, performance status, visceral metastasis, multiple bone metastases, previous chemotherapy, and hypercalcemia (10). Survival of patients with spinal metastases can also be predicted by prognostic scoring systems (11–13) using unfavorable tumor type, visceral metastases, multiple bone metastases, bad performance status, previous chemotherapy, interval from tumor diagnosis to metastatic spinal cord compression, and time to development of motor deficits before radiotherapy as prognostic factors.

Rades *et al.* suggested that choice of an optimal radiotherapy schedule is possible based on predicted survival (14), with a recommendation for short-course radiotherapy for patients with poor predicted survival based on the similar outcomes of short- and long-course radiotherapy. In contrast, long-course radiotherapy was recommended for patients with good predicted survival, because this reduces the risk of in-field recurrence and may improve survival. However, few clinical trials have shown the value of patient selection based on a scoring system. In our hospital, short-course radiotherapy is chosen for patients with poor predicted survival and long-course radiotherapy is chosen for those with good predicted survival or for reduction or prevention of paralysis.

Reprint requests to: Masashi Mizumoto, M.D., Division of Radiation Oncology, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki, 305-8575 Japan. Tel: +81-29-853-7100; Fax: +81-29-853-7102; E-mail: mizumoto1717@hotmail.com

Supported in part by a Grant-in-Aid for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government.

Conflict of interest: none

Received Aug 11, 2009, and in revised form Oct 2, 2009. Accepted for publication Oct 9, 2009.

Rades *et al.* also suggested that visceral metastases and the radiotherapy schedule are prognostic factors for local control (1), but limited data on local control are available compared with data for survival. Here, we examine whether an optimal radiotherapy schedule can be selected before radiotherapy, with a focus on prognostic factors for survival and predictive factors for local control after radiotherapy in patients with spinal metastases.

MATERIALS AND METHODS

Patients

A total of 603 patients with spinal metastases were treated by radiotherapy at our hospital between September 2002 and February 2007. The patients comprised 315 men and 288 women and had a median age of 63 years (range, 19–94 years). The primary sites were the lung ($n = 166$, 28%), breast ($n = 131$, 22%), gastrointestinal tract ($n = 101$, 17%), prostate ($n = 37$, 6%), liver ($n = 28$, 5%), and others ($n = 140$, 23%). Seventy-eight patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 158 were PS 1, 136 were PS 2, 148 were PS 3, and 83 were PS 4 (15). At the time of radiotherapy, 332 patients had visceral metastases and 539 patients had multiple bone metastases. Chemotherapy was performed before radiotherapy in 349 patients.

The purpose of radiotherapy was pain relief or prevention or improvement of paralytic symptoms in most patients. Of the 603 patients, 580 had pain at the time of radiotherapy: 64 did not require analgesics, 220 were taking nonnarcotic analgesics, and 296 were taking narcotic analgesics. Paralytic symptoms were present in 140 patients, with 86 able to walk with or without aid and 54 unable to walk because of spinal cord compression caused by spinal bone metastases.

Tumors were divided into two groups characterized by mass-type (111 patients) and non–mass-type (492 patients) metastases. A mass-type metastasis was defined as that with a clear boundary outside the vertebra. Most tumor characteristics were evaluated from three-dimensional computed tomography findings used in treatment planning. Local recurrence was defined as regrowth of the tumor within the irradiated field, as diagnosed by computed tomography or magnetic resonance imaging; or exacerbation of pain or motor deficits in a previously irradiated spinal region. Patients were followed until death from any cause. Informed consent was obtained from the patients regarding use of the data in the study.

Radiation therapy

Irradiation was performed with 4–18 MV photons from linear accelerators, and was mainly delivered through a single posterior field or parallel opposed fields. The radiation dose was focused on the center of the spinal cord in a radiation port using a three-dimensional treatment planning system. The treatment volume usually encompassed one normal vertebra above and below the metastatic lesion. In general, short-course radiotherapy was chosen for patients with poor predicted survival and long-course radiotherapy was selected for patients with good predicted survival or for improvement or prevention of paralysis. Different radiation schedules were compared using the equivalent dose in 2-Gy fractions (EQD2) (16), which take into account the total dose and the dose per fraction. EQD2 is calculated by the following equation, $EQD2 = D \times [(d + \alpha/\beta)/(2\ Gy + \alpha/\beta)$, where D is the total dose, d is the dose per fraction, α is the linear component of cell killing, β is the quadratic component of cell killing, and the α/β ratio an effect on the tumor is 10 Gy. The EQD2 values for short-course radiotherapy were 12 Gy (8 Gy in 1 fraction) and 23.3 Gy (20 Gy in 5 fractions), and those for long-course radiotherapy were 32.5 Gy (30 Gy in 10 fractions) and 40 Gy (40 Gy in 20 fractions). We defined 20 Gy in five fractions or less as short-course radiotherapy.

Statistical analyses

Rates for local control and survival were calculated using the Kaplan-Meier method. A log–rank test was used to examine the difference between survival curves for each factor (17, 18). Multivariate analyses were performed using a Cox proportional hazard model. The following patient characteristics were studied as potential prognostic factors for survival and local control: age, ECOG PS, primary sites, presence of visceral metastases, presence of multiple bone metastases, previous chemotherapy, and total serum calcium corrected for albumin level. We have previously shown the value of these parameters as prognostic factors for survival (10). In this study, we added tumor characteristics (mass-type or non–mass-type tumor) as a new potential prognostic factor, because empirically a mass-type tumor is known to be radioresistant. Regression coefficients, standard errors, p values, hazard ratios, and 95% confidence intervals were calculated. All statistical analyses were performed with SPSS v.11.0 (SPSS Inc., Chicago, IL).

RESULTS

Patients

The patient and tumor characteristics are summarized in Table 1. Of the 603 patients, 555 (92%) were followed for a minimum of 12 months or until death. During this time, 48 patients (8%) were lost to follow-up. The median duration of follow-up was 19.3 months (range, 0.2–67.6 months) for survivors. The overall survival and local control rates are shown in Fig. 1.

Table 1. Patient and tumor characteristics

Characteristics	Number	%
Age (y)	19-94 (range)	63 (median)
Gender		
Male	315	52
Female	288	48
ECOG performance status		
0	78	13
1	158	26
2	136	23
3	148	25
4	83	14
Distribution of primary tumor		
Lung	166	28
Breast	131	22
Gastrointestinal	101	17
Prostate	37	6
Liver	28	5
Others	140	23
Prognostic factors*		
Visceral metastases	332	55
Multiple bone metastases	539	89
Previous chemotherapy	349	58
Tumor characteristics		
Mass type	111	18
Non-mass type	492	82

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
* Number of patients with the risk factor.

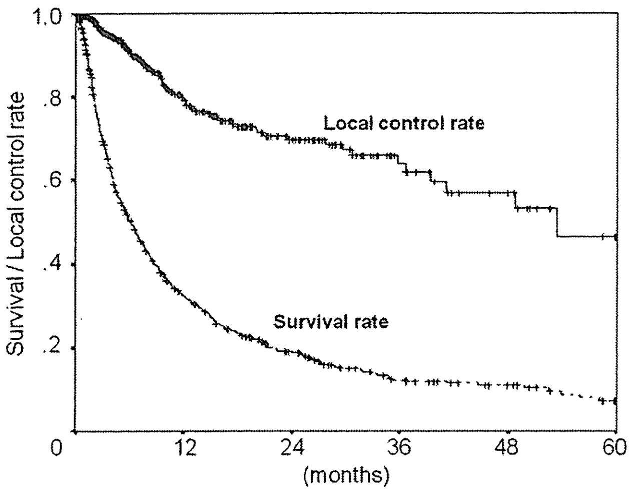

Fig. 1. Kaplan-Meier estimates of local control and overall survival.

Survival

The overall survival rates after 6, 12, and 24 months were 50% (95% CI, 46–54%), 32% (95% CI, 29–36%), and 19% (95% CI, 16–23%), respectively. The median overall survival period was 6.2 months (95% CI, 5.2 –7.2 months). Our previous scoring system for survival (10) included multiple prognostic factors (as described previously), but did not include the tumor type (mass-type vs. non–mass-type). Therefore, we performed a new multivariate analysis for survival with addition of tumor type as a prognostic factor. However, this analysis indicated that a mass-type tumor is not a prognostic factor for survival and the results (Table 2) were similar to those reported previously (10).

Local control

The local control rates after 6, 12, and 24 months were 91% (95% CI, 94–88%), 79% (95% CI, 84–74%), and 69% (95% CI, 76–63%), respectively. The following potential predictive factors were evaluated with respect to local control: age; ECOG PS, 0 to 2 vs. 3–4; primary site of tumor (breast, lung, gastrointestinal, other); presence of visceral metastases; presence of multiple bone metastases; presence of previous chemotherapy; and total serum calcium corrected for albumin level. These factors are also predictors of survival (10). The type of spine metastasis (mass-type vs. non–mass-type) and radiotherapy schedule (short-course vs. long-course) were also included in the evaluation. In univariate analysis, breast cancer, long-course radiotherapy, absence of previous chemotherapy, absence of visceral metastasis, and a non–mass-type tumor were associated with good local control. Multivariate analysis indicated that a non–mass-type tumor, breast cancer, and the absence of chemotherapy before radiotherapy were associated with good local control (Table 3).

Table 2. Multivariate analysis of potential prognostic factors for survival

Variable	No. of patients	MST (month)	1-y survival (%)	Standard error	*p* value	Hazard ratio	95% CI
Age (y)							
≤70	446	6.8	36.0	.109	0.025	1.28	1.03–1.58
>70	157	3.8	21.5				
Performance status							
0–2	372	9.1	41.3	.096	<0.001	1.99	1.65–2.40
3–4	231	2.9	17.7				
Primary tumor							
Favorable	195	15.2	55.7	.112	<0.001	2.85	2.29–3.55
Unfavorable	408	4.0	20.7				
Previous chemotherapy							
No	254	9.9	46.2	.103	<0.001	1.71	1.40–2.10
Yes	349	4.3	22.7				
Visceral metastases							
No	271	10.8	47.9	.103	<0.001	1.72	1.41–2.11
Yes	332	3.8	20.0				
Multiple bone metastases							
No	64	10.2	43.7	.165	0.001	1.72	1.25–2.38
Yes	539	5.7	31.1				
Serum calcium level							
Normal	542	6.8	34.6	.149	<0.001	2.31	1.72–3.09
Elevated	61	1.8	12.6				
Tumor characteristics							
Non-mass	492	6.2	33.1	.124	0.239	1.16	0.91– 1.48
Mass	111	5.7	29.5				

Abbreviation: MST = median survival time.

Table 3. Multivariate analysis of potential predictive factors for local control

Variable	No. of patients	1-year LCR (%)	2-year LCR (%)	Standard error	p value	Hazard ratio	95% CI
Age (y)							
≤70	446	79.4	69.7	.283	0.324	.76	0.43–1.32
>70	157	74.7	67.1				
Performance status							
0–2	372	79.5	69.6	.251	0.321	1.28	0.79–2.10
3–4	231	79.6	69.6				
Primary tumor							
Lung	166	81.1	68.8	.296	0.504	.82	0.46–1.47
Breast	131	91.5	86.0	.354	0.001	.32	0.16–0.64
Gastrointestinal	101	60.7	30.3	.360	0.422	1.36	0.66–2.70
Others	205	72.7	61.2				
Previous chemotherapy							
No	254	84.2	75.8	.255	0.005	2.05	1.24–3.37
Yes	349	74.5	61.8				
Visceral metastases							
No	271	82.0	74.7	.252	0.095	1.52	0.93–2.50
Yes	332	75.2	59.6				
Multiple bone metastases							
No	64	67.6	60.0	.291	0.788	.93	0.52–1.64
Yes	539	81.1	70.9				
Serum calcium level							
Normal	542	79.3	68.9	.521	0.951	1.03	0.37–2.87
Elevated	61	81.0	81.0				
Tumor characteristics							
Non-mass	492	86.3	75.9	.250	<0.001	3.03	1.86–4.95
Mass	111	45.7	38.9				
Radiotherapy schedule							
Long-course	511	79.9	70.4	.435	0.140	1.90	0.81–4.46
Short-course	92	70.7	47.1				

Abbreviation: LCR = local control rate.

Patient selection

Of the 603 patients, 92 (15%) with poor predicted survival were treated by short-course radiotherapy. The other 511 patients were treated by long-course radiotherapy because they had good predicted survival or a tumor located close to the vertebral canal. The overall survival rates for the two radiotherapy schedules are shown in Fig. 2. The median survival periods were 7.9 and 1.8 months for patients who underwent long- and short-course radiotherapy, respectively. The overall survival rates after 6, 12, and 24 months were 58% (95% CI: 54–62%), 38% (95% CI: 33–42%), and 23% (95% CI: 19–27%), respectively, for long-course radiotherapy; and 9% (95% CI: 3–15%), 3% (95% CI: 0–7%), and 0%, respectively, for short-course radiotherapy ($p < 0.001$). Eighty-nine of the 603 patients had local recurrence, 21 received reirradiation, 2 underwent surgery, 9 received systemic therapy such as chemotherapy, 53 required medical management such as an increased dose of analgesic drugs, and 4 showed recurrence on radiation diagnosis only. The pattern of in-field recurrence is shown in Table 4. Of the 21 reirradiation cases, 20 had received long-course radiotherapy (20/511; 4%) and 1 had received short-course radiotherapy (1/92; 1%).

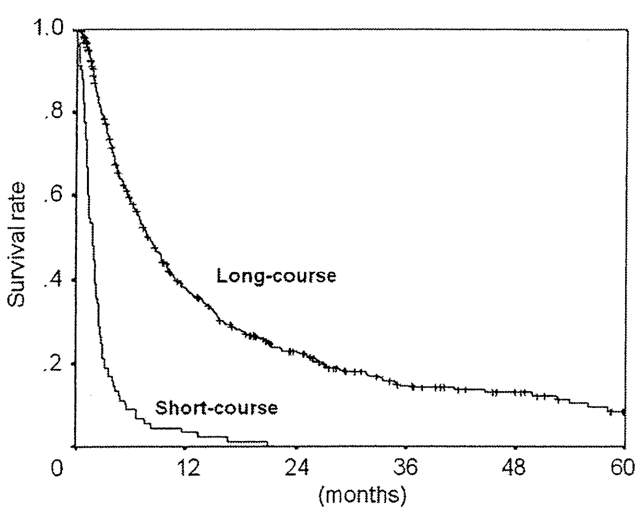

Fig. 2. Kaplan-Meier estimate of overall survival. The overall survival rates after 6, 12, and 24 months were 58%, 38%, and 23%, respectively, for long-course radiotherapy; and 9%, 3%, and 0%, respectively, for short-course radiotherapy ($p < 0.001$).

Table 4. Treatment for local failure after radiotherapy

Treatment	Number of patients
Reirradiation	21 (1)
Medical management	53 (5)
Systemic therapy	9 (1)
Only radiation for diagnosis	4 (0)
Surgery	2 (0)

Data in parentheses are the number of patients treated by short-course radiotherapy.

DISCUSSION

At Shizuoka Cancer Center Hospital, radiotherapy for spinal metastases is usually conducted using 30 Gy in 10 fractions or 40 Gy in 20 fractions, based on the tolerance of the spinal cord. Short-course radiotherapy is performed for patients with a poor prognosis based on the equivalence of the outcome of short- and long-course radiotherapy (1–9). Several predictive methods for prognosis have been proposed for selection of a radiation schedule (10–13). At our hospital, we determine this schedule by predicting prognosis using the scoring system proposed by Katagiri *et al.* (12). The schedule for individual patients is determined by their physician, but short-course radiotherapy is selected for patients with a poor prognosis, mainly for relief of pain. For cases in which a tumor is located close to the vertebral canal and those with neurologic symptoms such as paralysis and numbness, we use long-course radiotherapy in anticipation of an antitumor effect. Based on these criteria, 92 of 603 patients in the study were treated with short-course radiotherapy. Most of these patients had poor predicted survival, and their actual 1-year and 2-year survival rates were 4% and 0%, respectively, indicating a good prediction of prognosis prior to radiotherapy.

Rades *et al.* have described treatment of many cases with spinal metastases (19–21) and have discussed a predictive prognosis scoring system (11). An analysis of patients with a predicted good prognosis (1-year survival $\geq$70%) based on this system suggested that survival could be further prolonged by long-course radiotherapy through a significant decrease of in-field recurrence. In contrast, for patients with poor ($\leq$10%) or intermediate ($\leq$25%) predicted 1-year survival, there was no significant difference in survival time and treatment effect between long- and short-course radiotherapy. Based on these results, Rades *et al.* recommended long-course radiotherapy for patients with good predicted survival and short-course radiotherapy for other patients based on reduced costs and a shorter treatment period.

We selected long-course radiotherapy for patients with intermediate/good predicted survival or a spinal metastasis located near the spinal cord. Because only a few patients had poor predicted survival and a spinal metastasis distal to the spinal cord, only 92 of 603 patients underwent short-course radiotherapy. A randomized Phase III study has shown that short- and long-course radiotherapy have similar efficacy in patients with spinal metastases and spinal cord compression (1, 2). Therefore, patients with poor/intermediate predicted survival who received long-course radiotherapy from a tumor location close to the spinal cord should probably have been given short-course radiotherapy. In addition, patients with good predicted survival were given long-course radiotherapy to prevent in-field recurrence, but Rades *et al.* found that reirradiation is effective for in-field recurrence (22). These findings may enhance the clinical utility of short-course radiotherapy, and both the efficacy of the initial radiotherapy and that of reirradiation for in-field recurrence should be considered in developing criteria for selection of a radiation schedule.

We previously reported a scoring system for predicting survival (10) in which primary tumor site, PS, age, visceral metastases, multiple bone metastases, previous chemotherapy, and hypercalcemia were used as prognostic factors. In the current study, we added tumor type (mass-type vs. non–mass-type) as a potential new prognostic factor, but multivariate analysis indicated that tumor type was not associated with survival. In contrast, multivariate analysis of factors related to local control did show an association with a non–mass-type tumor, in addition to breast cancer and the absence of chemotherapy before radiotherapy. The strong association of a mass-type tumor with poor local control suggests that this type of tumor requires a higher radiotherapy dose than that for a non–mass-type tumor.

Rades *et al.* have reported that the radiotherapy schedule is also a predictive factor for local control (1), but in our patients the schedule was not predictive of local control. This may be because we selected short-course radiotherapy only for patients with poor predicted survival and the number of patients treated by short-course radiotherapy was small. Yamada *et al.* reported that high-dose single-fraction image-guided intensity-modulated radiotherapy achieved good local control for patients with spinal metastasis (23), and this technique may be especially effective for patients with a high risk of local recurrence (good predicted survival and a mass-type tumor).

In conclusion, prognostic factors for survival include primary tumor site, PS, age, visceral metastases, multiple bone metastases, previous chemotherapy, and hypercalcemia. These factors can be used to predict survival of patients with spinal metastases before radiotherapy, thereby allowing selection of an appropriate radiotherapy schedule. Predictive factors for local control include tumor type, previous chemotherapy, and primary tumor site; and a mass-type tumor has a particularly high risk of in-field recurrence. Based on these results, a prospective study is required to determine the optimal radiotherapy schedule for spinal metastases in patients with spinal metastases with similar backgrounds of survival and local control.

REFERENCES

1. Rades D, Fehlauer F, Schulte R, *et al.* Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *J Clin Oncol* 2006;24: 3388–3393.
2. Rades D, Stalpers LJ, Veninga T, *et al.* Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005;23:3366–3375.
3. Roos DE, Turner SL, O'Brien PC, *et al.* Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol* 2005;75: 54–63.
4. van den Hout WB, van der Linden YM, Steenland E, *et al.* Single- versus multiple-fraction radiotherapy in patients with

painful bone metastases: Cost-utility analysis based on a randomized trial. *J Natl Cancer Inst* 2003;95:222–229.
5. van der Linden YM, Steenland E, van Houwelingen HC, *et al.* Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: Results on survival in the Dutch Bone Metastasis Study. *Radiother Oncol* 2006; 78:245–253.
6. Foro Arnalot P, Fontanals AV, Galcerán JC, *et al.* Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. *Radiother Oncol* 2008;89:150–155.
7. Rades D, Lange M, Veninga T, *et al.* Preliminary results of spinal cord compression recurrence evaluation (score-1) study comparing short-course versus long-course radiotherapy for local control of malignant epidural spinal cord compression. *Int J Radiat Oncol Biol Phys* 2009;73:228–234.
8. Wu JS, Wong R, Johnston M, *et al.* Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003;55:594–605.
9. Chow E, Harris K, Fan G, *et al.* Palliative radiotherapy trials for bone metastases: A systematic review. *J Clin Oncol* 2007;25: 1423–1436.
10. Mizumoto M, Harada H, Asakura H, *et al.* Prognostic factors and a scoring system for survival after radiotherapy for metastases to the spinal column: A review of 544 patients at Shizuoka Cancer Center Hospital. *Cancer* 2008;113:2816–2822.
11. Rades D, Dunst J, Schild SE. The first score predicting overall survival in patients with metastatic spinal cord compression. *Cancer* 2008;112:157–161.
12. Katagiri H, Takahashi M, Wakai K, *et al.* Prognostic factors and a scoring system for patients with skeletal metastasis. *J Bone Joint Surg Br* 2005;87:698–703.
13. van der Linden YM, Dijkstra SP, Vonk EJ, *et al.* Prediction of survival in patients with metastases in the spinal column: Results based on a randomized trial of radiotherapy. *Cancer* 2005;103:320–328.
14. Rades D, Rudat V, Veninga T, *et al.* A score predicting post-treatment ambulatory status in patients irradiated for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2008;72: 905–908.
15. Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–655.
16. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Int J Radiat Oncol Biol Phys* 1982;8:1981–1997.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
18. Cox DR. Regression models and life-tables. *J Roy Stat Soc B* 1972;34:187–220.
19. Rades D, Veninga T, Stalpers LJ, *et al.* Outcome after radiotherapy alone for metastatic spinal cord compression in patients with oligometastases. *J Clin Oncol* 2007;25:50–56.
20. Rades D, Hoskin PJ, Karstens JH, *et al.* Radiotherapy of metastatic spinal cord compression in very elderly patients. *Int J Radiat Oncol Biol Phys* 2007;67:256–263.
21. Rades D, Karstens JH, Hoskin PJ, *et al.* Escalation of radiation dose beyond 30 Gy in 10 fractions for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2007; 67:525–531.
22. Rades D, Rudat V, Veninga T, *et al.* Prognostic factors for functional outcome and survival after reirradiation for in-field recurrences of metastatic spinal cord compression. *Cancer* 2008;113: 1090–1096.
23. Yamada Y, Bilsky MH, Lovelock DM, *et al.* High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys* 2008; 71:484–490.

ORIGINAL PAPER

Nagoya J. Med. Sci. **72**. 13 ~ 21, 2010

SURVIVAL AND AMBULATORY FUNCTION AFTER ENDOPROSTHETIC REPLACEMENT FOR METASTATIC BONE TUMOR OF THE PROXIMAL FEMUR

HIROATSU NAKASHIMA[1], HIROHISA KATAGIRI[2], MITSURU TAKAHASHI[2] and HIDESHI SUGIURA[3]

[1]*Department of Orthopedic Surgery, Aichi Hospital, Aichi Cancer Center*
[2]*Department of Orthopedic Surgery, Shizuoka Cancer Center Hospital*
[3]*Department of Orthopedic Surgery, Aichi Cancer Center Hospital*

ABSTRACT

The purpose of this study was to clarify the ambulatory functional and oncological outcomes of tumor excision and endoprosthetic reconstruction for a metastatic lesion of the proximal femur. Subjects comprised 40 patients (18 women, 22 men; average age 63.4 years). The mean follow-up periods were 15.2 months for patients dying of the disease, and 38.7 months for survivors. Seven patients were lost to follow-up for 1.9 to 13.1 months. Endoprosthesis was performed after intralesional aggressive curettage in 20 patients and following excision of the lesion with a clear margin, in another 20. Postoperative radiation therapy was carried out on 27 limbs (intralesional 13, marginal 6, wide 8). Chemotherapy was administered to 19 patients after discussion with the medical oncologist. The cumulative survival rates at 6 and 12 months were 60% and 35%, respectively, while the rates with ambulant status were 48% at 6 months and 34% at 12 months. An analgesic effect was achieved for all patients. Ambulatory function was restored in 34 patients with a mean ambulant period of 17.8 months; however, the other 6 patients remained non-ambulatory. The ambulant period expressed as a percentage of survival time averaged 75.9%. Though there was local recurrence in 4 of 40 patients, ambulant function was not affected. Postoperative ambulatory function was inferior in patients with a short life expectancy; those with moderate or long life expectancy are good candidates for endoprosthetic replacement after tumor excision and can regain ambulant function for as long as nearly 80% of the survival period.

Key Words: Metastatic bone tumor, Endoprosthetic replacement, Femur, Ambulatory function, Prognosis

INTRODUCTION

The aim of surgical treatment for metastatic bone tumors is not to cure the disease but rather to improve the quality of life by relieving pain and maintaining ambulatory function as long as possible in the remaining years. The proximal part of the femur is one of the most common sites for skeletal metastasis and the most frequent site for surgery.[1)] With advances in radiation therapy and chemotherapy, limb salvage became a viable option in the early 1980s, and the introduction of modular-type endoprostheses in the late 1980s permitted the reconstruction of a

Corresponding author: Hiroatsu Nakashima
Department Orthopedic Surgery, Aichi Hospital, Aichi Cancer Center,
18 Kuriyado, Kake-machi, Okazaki 444-0011, Japan
Phone: +81-564-21-6251, Fax: +81-564-21-6467, E-mail: hnakasima@acc-aichi.com

wide variety of skeletal defects after tumor resection.[2,3] Advances in cancer treatment have extended the survival period even for patients with skeletal metastasis, thus requiring reconstruction with long-term stability in some cases. Internal fixation with plates and screws or intramedullary rods using polymethylmethacrylate augmentation for metastatic bone lesions is well established, but internal fixation devices entail the risk of breakage in long-term survivors.[3,4] In contrast, endoprosthetic reconstruction is durable and implants are generally long-lasting. Until now, there have been no reports on the period of maintaining ambulatory function, the correlation between local recurrence and treatment as well as that between prognosis and postoperative function after endoprosthetic replacement for skeletal metastasis of the proximal femur. The purpose of this study is to assess the outcomes of tumor resection and endoprosthetic reconstruction for impending or pathological fractures from skeletal metastasis in the proximal femur, and to clarify the abovementioned issues.

PATIENTS AND METHODS

From 1993 to December 2006, 40 patients with a total of 41 metastatic lesions in the proximal part of the femur were treated surgically at our institutes. They included 18 women and 22 men with an average age of 63.4 years (range: 31 to 81 years). The mean postoperative follow-up period was 17 months (range: 1 to 92.5 months) for all patients, while for terminal patients and survivors it was 15.2 months (range: 1 to 92.5 months) and 38.7 months (range: 4.7 to 52.9 months), respectively. Seven were lost to follow-up from 1.9 to 13.1 months. The most common primary lesion was breast carcinoma, which was seen in 11 patients, including one with bilateral femoral lesions. Other primary lesions were lung carcinoma in 8, gastrointestinal tract carcinoma in 7, renal cell carcinoma in 4, thyroid carcinoma in 3, and in 1 patient each with hepatocellular carcinoma, cervical carcinoma, parotid carcinoma, bladder carcinoma, prostate carcinoma, malignant lymphoma, and multiple myeloma.

The indications for surgery were as follows: 1) a pathologic or impending fracture according to Harrington's criteria[5] requiring prophylactic treatment, i.e., a lytic zone of more than 2.5 cm in diameter, destruction of the cortex involving more than 50% of the bone, or a lesion for which radiation therapy had failed; 2) a sufficiently good general condition to survive an operation; and 3) a life expectancy of more than 2 months.[6]

Endoprosthetic replacement was performed after intralesional aggressive curettage in 20 patients and after excision of the lesion with a clear margin in another 20. If the lesion was localized in the femoral head and neck region, an endoprosthesis with an ordinary stem or a calcar-replacement femoral endoprosthesis (Zimmer, Warsaw, IN) was used. If the lesion extended from the femoral neck to the subtrochanteric region, a modular-type long-stem proximal femoral endoprosthesis (Japan Medical Materials, Osaka, Japan) was used. Polymethylmethacrylate (PMMA) was used in all cases to achieve immediate stability. Postoperative radiation therapy (20–40 Gy) was carried out on 27 limbs (intralesional 13, marginal 6, wide 8). Chemotherapy was administered to 19 patients following a discussion with the medical oncologist.

We retrospectively analyzed i) the correlation between local recurrence and treatment, ii) analgesic effect, iii) postoperative ambulatory function, iv) overall and ambulant function maintaining survival, and v) the correlation among survival, function and prognostic score.[7] The cumulative survival rate was determined using the method of Kaplan and Meier and was calculated from the date of the operation. The log-rank test was used to evaluate the significance of differences between groups, with p values less than 0.05 considered significant. Surgical procedures were evaluated according to the Enneking evaluation system[8] into radical, wide, marginal, and intralesional. Local recurrence was defined as radiographic expansion of an osteolytic lesion or tumor regrowth around the operated area. The analgesic effect was evaluated 2 to 4 weeks after surgery according to Suzuki's criteria,[9] in which postoperative analgesic effects are grouped into 4 categories: excellent (no pain whatsoever, no need for pain relievers), good (pain has mostly disappeared, but pain relievers are sometimes needed), fair (some pain alleviation, but periodic pain relievers are needed), and poor (no pain reduction). Postoperative functions of the lower extremity were also evaluated using Suzuki's criteria,[9] in which postoperative ambulatory functions are grouped into 4 categories: excellent (able to walk outdoors with or without an aid), good (able to walk only indoors with or without an aid), fair (unable to walk, but can use a wheelchair), and poor (bedridden).

RESULTS

Clinical data of the 40 patients with tumor resections and/or endoprosthetic replacements were shown in Table 1. Prognostic scores (Katagiri score) of point 0 was 4 patients, point 1 was 6, point 2 was 10, point 3 was 8, point 4 was 9, point 5 was 2 and point 6 was one.

Local recurrence

Wide, marginal and intralesional procedures were performed on 12, 9 and 20 limbs, respectively. Additional radiation therapy was performed on 8 out of 12 limbs with wide procedure, 6 out of 9 with marginal procedure, and 13 out of 20 with intralesional procedures. Local recurrence was found on plain radiographs in 4 patients, 2 of whom underwent an intralesional procedure and radiation therapy, 1 with a marginal procedure and radiation therapy, and 1 with marginal excision alone. However, no salvage operation was required in any recurrent cases, and none of their ambulant functions were affected by this local recurrence for their remaining lifespan. Local recurrence was not extensive and did not lead to failures including those of periprosthetic fracture and loosening.

Pain relief and ambulation

The analgesic effect was evaluated as excellent in 34 limbs and good in 7. Pain relief was good to excellent even in non-ambulatory patients. Twenty-nine patients achieved excellent results functionally, 5 were good, 3 were fair and 3 were poor. A total of 34 patients (85%) were able to regain or maintain ambulatory function, while 6 (15%) were not. The reasons for remaining non-ambulatory were as follows: 2 because of skeletal metastasis to other bone (ipsilateral acetabulum with contralateral femur in 1, and cervical spine in another), 2 due to their deteriorating general condition from cancer progression, 1 from dementia, and 1 from brain metastasis.

Overall and ambulant function maintaining survival

The overall survival rate of all patients was 60% at 6 months, 35% at 12 months and 21% at 24 months. The cumulative survival rate with ambulant status was 48% at 6 months, 34% at 12 months and 17% at 24 months (Fig. 1). The mean ambulant period was 17.8 months in the 34 patients with excellent or good functional results. The ambulant period expressed as a percentage of survival time averaged 75.9% (57 to 100%).

Correlation among survival, function, and prognostic score

The prognostic scoring system developed by Katagiri[7] is shown in Table 2. The score was calculated by adding scores for each prognostic factor, with possible scores ranging from 0 to 8.

Table 1 Clinical data in 40 patients with tumor resection and endoprosthetic replacement

Case	Gender	Age (year)	Primary tumor	Follow-up period (month)	Prog-nosis	Margin	Recur-rence	RT	CT	Analgesic effect	Ambulatory function	Ambula-tory period (month)	Katagiri score
1	F	66	GIT	7	DOD	I			Yes	Excellent	Excellent	7	3
2	F	56	Cervical	4.2	DOD	I		20 Gy	Yes	Excellent	Excellent	3	3
3	F	43	Breast	30.1	DOD	M		40 Gy	Yes	Excellent	Excellent	28	3
4	M	64	HCC	22	DOD	I		30 Gy		Excellent	Excellent	22	4
5	F	75	GIT	6.4	DOD	M	Yes	40 Gy	Yes	Good	Excellent	4	3
6	M	60	Lung	8	DOD	W			Yes	Good	Excellent	7	4
7	M	55	Lung	3.4	DOD	W		40 Gy		Excellent	Excellent	3	3
8	F	52	Lung	7.1	DOD	M	Yes		Yes	Good	Excellent	5	4
9	M	72	Prostate	6.8	DOD	W				Excellent	Excellent	6	0
10	F	45	Breast	92.5	DOD	W		20 Gy	Yes	Excellent	Excellent	90	1
11	F	68	Breast	9.8	DOD	W		40 Gy	Yes	Excellent	Excellent	9	2
12	M	60	Bladder	3.1	DOD	W				Excellent	Excellent	3	4
13	M	72	Lymphoma	2	Lost	I			Yes	Excellent	Good	2	1
14	M	81	Thyroid	1.9	Lost	M		40 Gy		Good	Excellent	2	0
15	F	58	Lung	2.1	Lost	M		29 Gy	Yes	Excellent	Excellent	1	4
16	F	82	GIT	13.1	Lost	I	Yes	40 Gy		Excellent	Excellent	13	2
17	F	79	Breast	4.7	AWD	W		40 Gy		Excellent	Good	4	0
18	F	46	Breast	72	AWD	I		40 Gy	Yes	Good	Excellent	72	2
				70		I		40 Gy		Good	Excellent		
19	M	68	RCC	40	DOD	M				Excellent	Excellent	38	2
20	M	78	Myeloma	19	DOD	I		40 Gy	Yes	Excellent	Good	19	1
21	F	58	Breast	64	DOD	M		36 Gy		Excellent	Excellent	64	1
22	F	35	Breast	13.6	DOD	I				Excellent	Excellent	14	0
23	M	31	Lung	4.2	DOD	I		30 Gy		Good	Poor	0	4
24	F	72	Breast	18	DOD	I	Yes	36 Gy		Excellent	Excellent	18	2
25	F	70	Breast	10.6	DOD	I			Yes	Excellent	Good	6	2
26	M	71	RCC	10.3	DOD	I				Excellent	Excellent	10	2
27	M	62	Lung	2.7	DOD	M		37.5 Gy	Yes	Excellent	Good	2	4
28	M	46	GIT	6.5	DOD	W			Yes	Excellent	Excellent	7	5
29	M	71	Lung	6.6	DOD	I		30 Gy	Yes	Excellent	Excellent	5	5
30	F	71	Breast	3.3	DOD	I				Excellent	Fair	0	2
31	M	40	GIT	1.3	DOD	I				Excellent	Poor	0	3
32	M	73	Parotid	1.8	Lost	I		39 Gy		Excellent	Fair	0	3
33	M	79	RCC	1	DOD	M				Excellent	Poor	0	4
34	M	75	RCC	52.9	AWD	W		20 Gy	Yes	Excellent	Excellent	53	3
35	F	55	Breast	2.5	Lost	I		30 Gy	Yes	Excellent	Good	3	4
36	M	71	GIT	3.6	Lost	I		20 Gy		Excellent	Excellent	4	2
37	M	73	GIT	23.5	DOD	W		40 Gy	Yes	Excellent	Excellent	17	2
38	M	66	Tyroid	42.4	AWD	W		20 Gy		Excellent	Excellent	42	1
39	M	65	Lung	1.5	DOD	I		30 Gy	Yes	Excellent	Fair	0	6
40	F	70	Tyroid	21.6	AWD	W		20 Gy		Excellent	Excellent	22	1

F: female; M: male
GIT: Gastrointestinal tract carcinoma; RCC: Renal cell carcinoma; HCC: Hepatocellular carcinoma
Lost: Lost to follow-up
I: Intra-lesional; M: Marginal; W: Wide
RT: Postoperative radiation therapy; CT: Chemotherapy

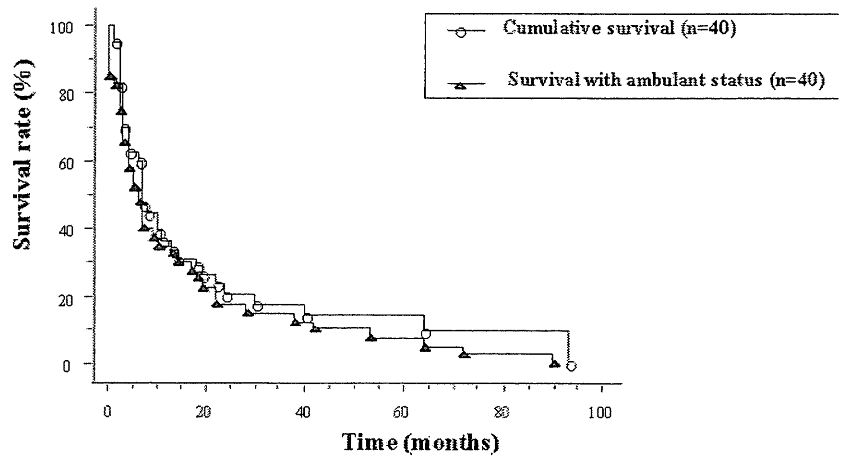

Fig. 1 Kaplan-Meier cumulative survival rate and survival with ambulant status.

Table 2 Prognostic scoring system according to Katagiri[7)]

Prognostic factor	Score
Primary lesion	
Hepatocellular carcinoma, gastric carcinoma, lung carcinoma	3
Breast carcinoma, prostate carcinoma, multiple myeloma, malignant lymphoma, thyroid carcinoma	0
Other carcinoma and sarcoma	2
Visceral or cerebral metastases	2
Performance status 3, 4	1
Previous chemotherapy	1
Multiple skeletal metastasis	1

The patients were divided into two groups with prognostic scores of 0 to 2 and ≥ 3, respectively. The survival rates in the respective groups were 77.4% and 40% at 6 months, and 56% and 13.7% at 12 months (Fig. 2, Table 3); these data showed a significant difference (log-rank test, $p = 0.004$). The survival rates with ambulant status in the respective groups were 65% and 22.5% at 6 months, and 51.7% and 13.3% at 12 months (Fig. 3, Table 3); again a significant difference was observed (log-rank test, $p = 0.01$). The mean survival periods with ambulant status in the respective groups were 22.6 months and 7.6 months, with a significant difference noted (t-test, $p = 0.025$).

Among patients with prognostic scores of 0 to 2, 19 (95%) were evaluated as excellent or good, and 1 (5%) as fair. In contrast, among patients with prognostic scores of ≥ 3, 15 (75%) were evaluated as excellent or good, and 5 (25%) as fair or poor. All patients showing either fair or poor functional results, had a postoperative survival period of less than 3 months.

The ambulant period, as mentioned above, averaged 75.9% of the survival period, but the reasons for those remaining non-ambulant patients were due either to their deteriorating general condition to skeletal metastasis to another site, rather than to problems with endoprosthesis.

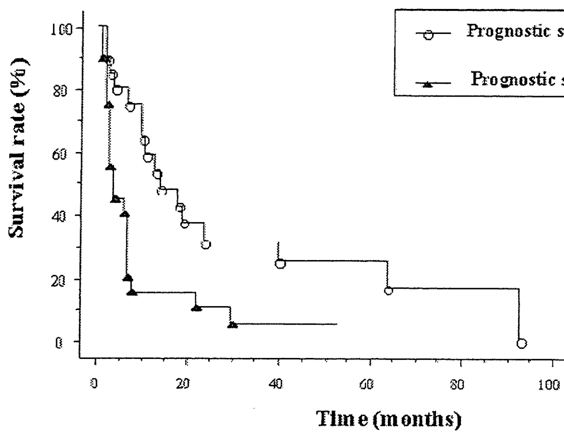

Fig. 2 Kaplan-Meier survival curves for patients with prognostic scores of 0 to 2 and more than 3. The rates of survival for the two groups are significantly different (log-rank test, p = 0.004).

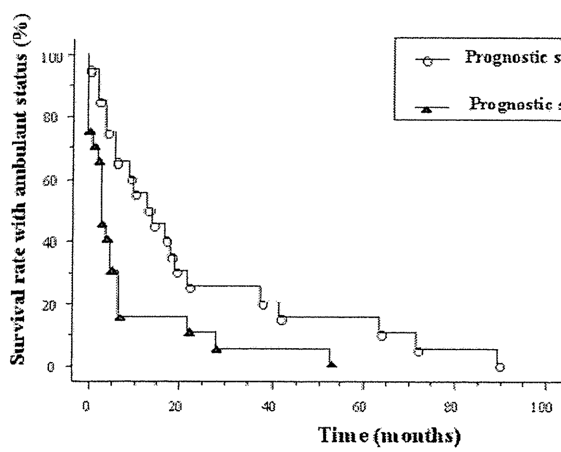

Fig. 3 Kaplan-Meier survival curves with ambulant status for patients with prognostic scores of 0 to 2 and more than 3. The rates of survival for the two groups are significantly different (log-rank test, p = 0.01).

Table 3 Prognostic score and survival rate, survival rate with ambulant status at three, 6, and 12 months

		Survival rate (months)		
Prognostic score[7]	Survival rate	3	6	12
0 to 2	OS	0.85	0.774	0.56
	SAS	0.8	0.65	0.517
≥ 3	OS	0.55	0.4	0.137
	SAS	0.45	0.225	0.133

OS, overall survival rate; SAS, survival rate with ambulant status

Complications

Complications included liver dysfunction in patient, deep infection in another, and central migration in a third. Deep infection in the second patient eventually healed after a debridement and intermittent daily wound irrigation. The patient with a central migration of the bipolar head was only monitored, but was able to walk with a cane.

DISCUSSION

For metastatic bone tumors of the proximal part of the femur, the aims of surgical treatment are pain relief and a restoration of the ambulatory function with immediate full-weight bearing and durability during the remainder of life. For metastatic lesions involving the femoral neck and head, conventional bipolar endoprosthetic replacement with a regular-length stem is the treatment of choice.[1] If an intralesional procedure is performed, adjuvant radiation therapy should be used to lessen the chance of metastatic lesion progression within the operative field.[1,4] However, when the metastatic lesion involves the intertrochanteric and subtrochanteric regions, the treatment of choice is either excisional surgery followed by reconstruction with a modular-type endoprosthesis or internal fixation with or without augmentation by polymethylmethacrylate (PMMA).[1,10] However, for long-term survivors, endoprosthetic reconstruction is preferred because of its lower risk of implant breakage.[4]

Although several reports have described endoprosthetic reconstruction for bone metastasis in the proximal femur,[3,10,11] most have focused on its utility and its complications, such as implant failure and infection. There have been very few detailed reports on clinical and functional outcomes after endoprosthetic replacement for bone metastasis in the proximal femur, and, to our knowledge, no reports on the ambulatory period following that replacement procedure.

Rompe *et al.*[11] have compared endoprosthetic replacement to plate osteosynthesis for patients with a metastatic lesion of the proximal femur, and have reported a local recurrence in 4 (44.4%) of 9 patients treated intralesionally and in 3 (18.8%) of 16 treated extralesionally with a prosthesis. However, the local recurrence rate in plate osteosynthesis was 48%. In our study, local recurrence was observed in only 4 (10%) of 40 patients, and neither affected their stability nor ambulatory function.

Wedin *et al.*[10] have also compared endoprosthetic reconstruction to osteosynthesis for pathologic fractures of a metastatic bone tumor of the proximal femur. They reported that the local failure rate was 16.2% in osteosynthesis, and 8.3% in endoprosthesis, and that, of 9 cases of prosthetic failure, 4 were due to periprosthetic fracture, 3 to technical error and 1 to loosening, with no failure due to local recurrence being observed. Rather than use reconstruction nails and other devices, they recommended endoprosthetic reconstruction for the treatment of metastatic lesions in the proximal third of the femur because of fewer local failures and a lower risk of the need for a second operation.

Rompe *et al.*[11] have demonstrated that the function of the hip joint based on measurements of active motion was better in patients who had undergone osteosynthesis than in those who had undergone endoprosthesis. However, they evaluated only the joint function at three months postoperatively, and their findings included neither ambulatory function nor the period of maintaining ambulatory function. Lane *et al.*[3] have reported a study of 163 patients treated with endoprosthetic replacement for pathologic or impending fractures of the hip. They found that 56 (72%) of 78 patients who were able to walk before their fracture regained ambulatory function, and that 40 (46%) of 85 patients who were non-ambulatory prior to fracture recovered ambulatory function.

In this study, we have shown that all patients obtained long-lasting pain relief, and that 34 (85%) of 40 had restored or regained ambulatory function over a mean ambulant period of 17.8 months. The ambulant period expressed as a percentage of survival time averaged 75.9%. Our results indicated that endoprosthetic replacement permitted patients with bone metastasis of the proximal femur to regain long-lasting ambulatory function.

An excisional procedure followed by reconstruction with endoprosthesis is more costly than a simple internal fixation or an internal fixation with PMMA augmentation, and a tumor resection followed by endoprosthetic reconstruction requires a larger and deeper incision than that needed for internal fixation with or without PMMA augmentation, with a higher risk of wound infection. Therefore, when deciding on the best treatment procedure, the patient's life expectancy must be taken into account.

Katagiri *et al.*[7] have identified five significant prognostic factors for survival: the site of the primary lesion; the performance status (Eastern Cooperative Oncology Group[12] status 3 or 4); the presence of visceral or cerebral metastases; any previous chemotherapy; and multiple skeletal metastases in patients with bone metastasis. We compared the survival of patients with prognostic scores of 0 to 2 with those of patients with scores of ≥ 3, and found a significantly longer survival period in the patients with lower scores. We also found that the survival rate with ambulatory status among patients with prognostic scores of 0 to 2 was better than that in patients with scores of ≥ 3. In addition, postoperative ambulatory function was found to be better in patients with prognostic scores of 0 to 2, suggesting that such patients may be expected to enjoy longer-term survival with better function by excision of their metastatic lesion followed by a prosthetic replacement. Even 13 of 17 patients with a score of only 3 or 4 regained ambulatory function. Therefore, if other skeletal and visceral metastases are not life-threatening, endoprosthetic replacement may be indicated. On the other hand, only 2 out of 3 patients with a prognostic score of 5 to 6 could achieve ambulatory status postoperatively.

Although this study is retrospective and the number of patients small, we concluded that patients with a long-life expectancy (Katagiri score 0–2) are good candidates for this resection using an endoprosthetic reconstruction procedure. We further concluded that patients with a score of 3 to 4 (moderate-life expectancy) treated using an intra-lesional or excisional procedure followed by an endoprosthetic replacement, also make promising candidates if other skeletal or visceral metastasis are not life-threatening. In those with a score of 5 or more, one should decide the indications for this procedure cautiously considering their age, general condition, and other site metastasis.

REFERENCES

1) Damron TA, Sim FH. Surgical treatment for metastatic disease of the pelvis and the proximal end of the femur. *Instr Course Lect,* 2000; 49: 461–470.
2) Eckardt JJ, Kabo JM, Kelly CM, Ward WG, Cannon CP. Endoprosthetic reconstructions for bone metastases. *Clin Orthop Relat Res*, 2003; 415: 254–262.
3) Lane JM, Sculco TP, Zolan S. Treatment of pathological fracture of the hip by endoprosthetic replacement. *J Bone Joint Surg Am*, 1980; 62: 954–959.
4) Yazawa Y, Frassica FJ, Chao EY, Pritchard DJ, Sim FH, Shives TC. Metastatic bone disease. *Clin Orthop Relat Res,* 1990; 251: 213–219.
5) Harrington KD. New trends in management of lower extremity metastases. *Clin Orthop Relat Res*, 1982; 169: 53–61.
6) Harrington KD, Sim FH, Enis JE, Johnston JO, Diok HM, Gristina AG. Methylmethacrylate as an adjunct in internal fixation of pathological fractures: experience with three hundred and seventy-five cases. *J Bone Joint Surg Am*, 1976; 58: 1047–1055.