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Outcomes and Complications of Reconstruction Using Tumor-bearing Frozen Autografts in Patients with Metastatic Bone Tumors

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Abstract. *Background: Tumor-bearing frozen autografts have been used for reconstruction of bone defects after resection of bone tumors. In the present study, outcomes and complications of reconstruction using frozen autografts were assessed to determine indications for this procedure in patients with metastatic bone lesions. Patients and Methods: Twenty-two patients were treated with reconstruction using frozen autografts. The surgical technique involved excision of the bone lesion, curettage, freezing in liquid nitrogen, thawing and reconstruction. Results: Limb function was evaluated in 11 patients; wa found excellent in 10 patients and good in 1 patient. Five-year overall survival and disease-free survival rates were 46.7% and 26.3%, respectively. Five-year fracture-free survival and recurrence-free survival rates were 79.9% and 100%, respectively. Complications were observed in 6 patients and included fractures (4), deep infection (1) and osteoarthritis (1). Conclusion: Reconstruction using frozen autografts is a beneficial treatment option in patients with long expected survival or complete cure of the primary cancer.*

Advances in cancer treatment have improved the prognosis of patients with cancer. On the other hand, the incidence of bone metastases has increased due to prolonged survival of patients with cancer. Bisphosphonate, denosumab, irradiation and surgical treatment are widely performed as treatment for bone metastases (1, 2). Although bisphosphonate and denosumab can be used to inhibit systemic bone metastases, their effects are not curative. In patients with an impending pathological fracture, surgery is the only treatment that improves prognosis and quality of life (QOL). In patients with short expected survival, palliative surgeries using external fixation, intramedullary nails or plating are commonly performed. On the other hand, an impending fracture in patients with a long prognosis requires surgical treatment to prevent a pathological fracture during the expected survival period. In addition, solitary metastasis requires surgical treatment to achieve a complete cure of the cancer.

Megaprostheses, allografts and autografts are presently used for the reconstruction of limbs with large bone defects following tumor excision. The long-term durability of megaprostheses has been discussed due to reports of complications, such as loosening and breakage (3). Accordingly, long survival due to advances in cancer treatment makes it difficult to decide on the surgical method for metastatic bone lesions. In Asian countries, recycling of the tumor-bearing bone has been widely used because allografts are difficult to obtain for socioreligious reasons. Several methods have been developed for the re-use of the resected bone for reconstruction, including irradiation, pasteurisation and freezing in liquid nitrogen (1, 4). Since 1999, we have used tumor-bearing liquid nitrogen-treated autografts, which have a number of advantages for biological reconstruction (5, 6). The aim of the present study was to assess the oncological outcome and complications of reconstruction using frozen autografts to determine indications for this surgical procedure.

Patients and Methods

Patients. From March 1999 to December 2011, 22 patients with metastatic bone tumors in the extremities or pelvises underwent reconstruction using tumor-bearing frozen autografts. This study population comprised 11 males and 11 females, with a mean age of 64.8 years (range, 25-79). The mean follow-up period was 39.0 months (range, 3-168 months). Primary cancers in our study patients included kidney cancer (8 patients), lung cancer (4 patients), breast cancer (3 patients), liver cancer (1 patient), colon cancer (2 patients), gastric cancer (1 patient), vaginal cancer (1 patient), multiple myeloma (1 patient) and myxoid liposarcoma (1 patient). The surgical site was the femur in 14 cases, pelvis in 5 cases, humerus in 2 cases and tibia in 1 case. We obtained written informed consent from all patients and/or their families, with the approval of the institute's ethics

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committee. Reconstruction using frozen autografts was indicated in patients with single metastasis in the limb or pelvic bones and long expected survival (longer than 12 months) and for patients with impending pathologic fractures. Impending pathologic fractures were evaluated using the Mirels scoring system (7), with a score >8 indicating the need for surgical treatment.

Surgical technique. In principle, metastatic lesions were exposed in a manner similar to that used for primary bone tumors (5). Wide soft tissue margins were obtained, the shafts of long bones were transected at least 2 cm away from the margin of the disease as long as possible. Frozen tumor-bearing autografts were obtained by tumor excision and curettage. Tissues were then frozen in liquid nitrogen and used for reconstruction (Figures 1and 2); (a) Tumor excision: The tumor was excised with a surgical margin of safety; (b) Curettage: Soft tissues were removed from the excised tumor-bearing bone. After the cancellous bone was curetted, excess water in the bone was removed by suction to prevent bone damage due to ice expansion during freezing. The curetted cancellous bone and extraskeletal masses were evaluated histologically; (c) Freezing in liquid nitrogen: The tumor-bearing bone was frozen in liquid nitrogen for 20 min, thawed in air at room temperature for 15 min and thawed in distilled water for 10 min; (d) Reconstruction: Massive bone and osteochondral defects following resection were reconstructed using frozen tumor-bearing autografts and hardware including prostheses, intramedullary nails and plates.

Functional evaluation. In patients who were alive at the last follow-up, the function of the reconstructed limb was evaluated using the functional evaluation system of Enneking (8). Patients with mental disorders or functional disorders due to primary tumors or spinal metastases were excluded from this functional evaluation.

Oncological evaluation and local control. Overall survival, disease-free survival, fracture-free survival and recurrence-free survival rates were determined using the Kaplan–Meier method. Overall survival was defined as the time from reconstructive surgery to death from any cause. Disease-free survival was defined as the time from reconstructive surgery to death from the disease, recurrence of primary or metastatic tumors or metastasis to another site. Fracture-free survival and recurrence-free survival were defined as the time from reconstructive surgery to a pathological fracture and local recurrence at the reconstructed site, including soft tissues around the bone graft, respectively. Kaplan–Meier survival curves were made by the EZR software (Saitama Medical Center, Jichi Medical University).

Results

Nine bone specimens were treated by free freezing and 13 were treated by pedicle freezing (Figures 1-3) (Table I). After freezing of the tumor-bearing bone, plates were used in 10 patients, composite prosthetic replacements were performed in 6 patients and intramedullary nails were used in 6 cases (Table I). At the time of the last follow-up, 9 patients (40.9%) were alive and disease-free, 3 (13.6%) were alive with the disease and 10 (45.5%) had died of the disease. One-year, 3-year and 5-year overall survival rates were 81.8%, 46.6% and 46.6%, respectively (Figure 4a). One-year, 3-year and 5-year disease-free survival rates were 35.0%, 35.0% and 26.3%, respectively (Figure 4b).

Out of 22 patients, 11 were evaluated for functional outcomes. Limb function was excellent in 10 patients and good in 1 patient (Table II). No intraoperative complications were found (*e.g.* surrounding soft tissue damage or neurovascular injuries from freezing effects).

Although 1 patient (4.5%) with metastatic kidney cancer of the pelvis had local recurrence in soft tissues 65 months postoperatively, no recurrence was observed in the re-implanted tumor-bearing bone. At the time of the last follow-up, 21 patients (95.5%) were free from local recurrence of metastatic cancer. The 5-year recurrence-free survival rate was 100% (Figure 5).

Four patients (18.2%) experienced fractures of frozen bones at the mean follow-up period of 38.3 months (range=7-108 months). All 4 patients with postoperative fractures were treated with additional stabilisation. At the time of the last follow-up, 18 patients (81.8%) were free from fractures. One-year, 3-year and 5-year fracture-free survival rates were 88.9%, 79.9% and 79.9% (Figure 6). Patient 4 developed a deep infection 3 months postoperatively. Patient 8 developed osteoarthritis and received a prosthetic replacement.

Discussion

Treatment for metastatic bone lesions includes surgery, irradiation, chemotherapy and bisphosphonates. As well as indications, the choice of the treatment modality depends on many factors, including the patient's general condition, age, expected survival period, local control of the primary lesion, presence of metastasis to other organs, single or multiple metastasis, site of bone metastasis, destruction of metastatic bone and the risk of fracture and the risk of spinal paralysis in patients with spinal metastasis (1, 9). In patients with metastasis to limb bones appropriate local control has to be achieved during the expected survival period and the required surgical method, resection margin and supplementary treatment should be selected. Although metastatic lesions are presumed to be advanced-stage cancers, 5 of 22 (22.7%) patients in this study survived more than 5 years. Therefore, curative treatment, that achieves local control, affords good function and prevents a pathologic fracture, is required for patients with long expected survival. A life expectancy of at least 12 months is required for curative surgery (10, 11), which consists of excisional surgery followed by reconstruction using an implant to achieve long-lasting local tumor control and stabilisation. Implantation of a megaprosthesis for metastatic bone lesions is a relatively easy surgery that enables shorter rehabilitation and good outcomes have been reported (12). However, long-term outcomes for the use of megaprostheses are still unclear because no study on megaprostheses with a long follow-up period has been reported. Furthermore, revision hemi-arthroplasty and revision

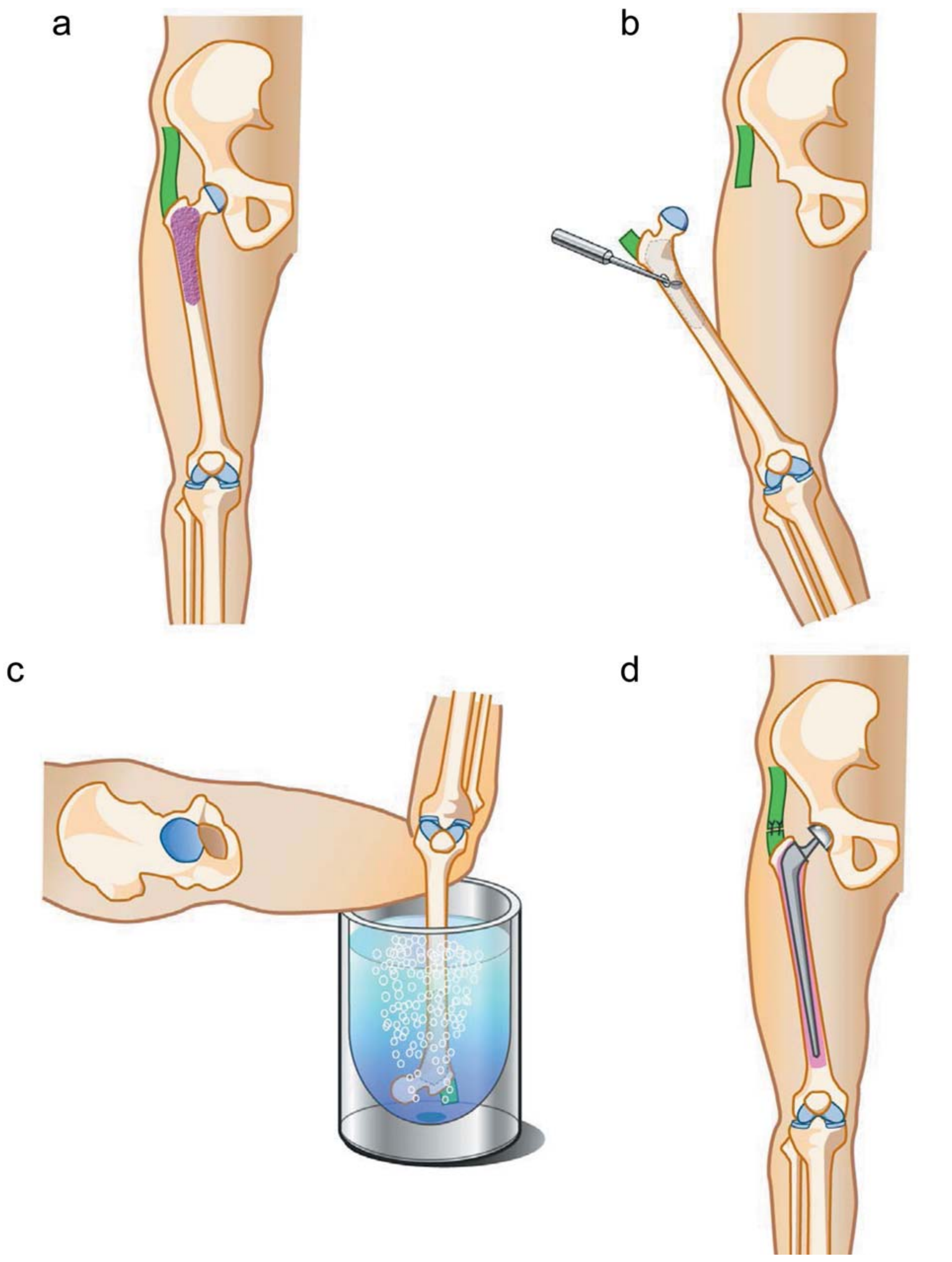

Figure 1. *Frozen autograft for reconstruction of femur. a. Metastatic bone tumor of femur. b. Joint dislocation and curettage of the lesion. c. Pedicle freezing in liquid nitrogen. d. Reconstruction using prosthesis.*

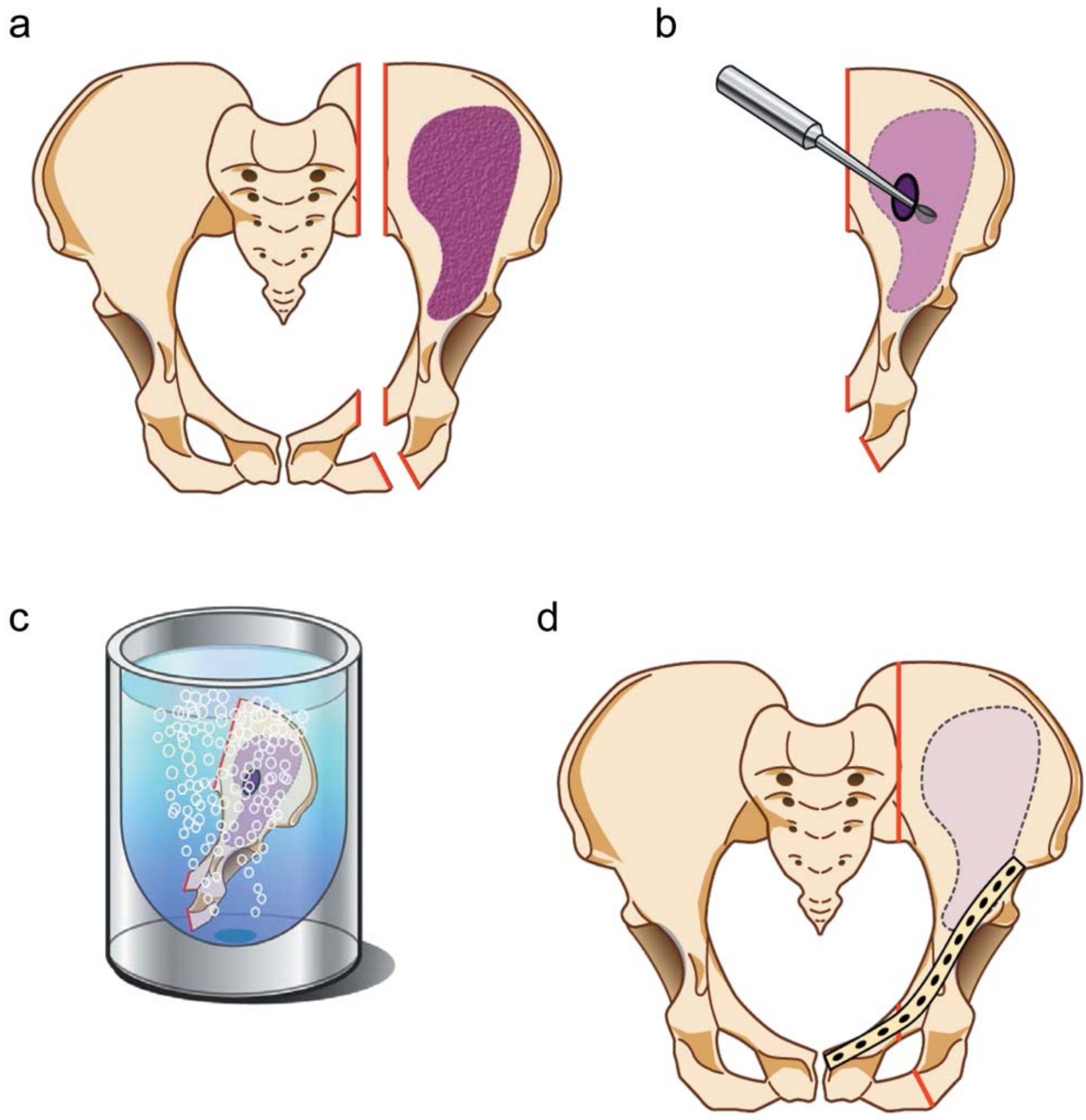

Figure 2. *Frozen autograft for reconstruction of pelvis. a. Excision of metastatic bone tumor of pelvis. b. Curettage of the lesion. c. Free freezing in liquid nitrogen. d. Reconstruction using plates with cement.*

total hip arthroplasty are difficult due to adhesions, bone loss and discrepancies between leg lengths. Biological reconstruction using various types of bone grafts is more beneficial for limb function than is reconstruction using megaprostheses (13). Allografts used for reconstruction of bone defects after resection of a tumor offer many advantages, including reconstruction of the joint and incorporation of the graft into the host bone. However, the high incidence of complications makes the outcome unpredictable (14). Tumor-bearing autografts are readily available, have no compatibility problems and circumvent the socioreligious issues surrounding allografts in Asian countries.

Before being used for reconstructive surgery, tumor-bearing bone grafts must undergo one of several pre-treatments, as

Figure 3. *Case 10, a 55-year-old man with myxoid liposarcoma (arrow) treated by pedicle freezing. a. Preoperative MRI scan. b. One-site osteotomy and exposure of the metastatic bone. c. Pedicle freezing in liquid nitrogen. d. Thawing of the tumor-bearing frozen autograft. e. Reconstruction using plate. f. Radiograph after the reconstruction.*

Table I. *Details of 22 patients receiving reconstruction using tumor-bearing frozen autografts.*

Case	Age	Gender	Primary tumor	Location	Mirels score	Margin	Freezing	Reconstruction
1	71	F	Kidney	Femur	9	W	Free	IM
2	69	M	Lung	Femur	8	W	Pedicle	Plate
3	49	F	Breast	Femur	10	W	Pedicle	Prosthesis
4	73	M	Liver	Femur	10	W	Pedicle	Prosthesis
5	75	F	Breast	Tibia	7	W	Free	Plate
6	54	F	Breast	Pelvis	9	W	Free	Plate
7	52	M	Lung	Femur	9	W	Free	IM
8	50	F	Vagina	Pelvis	8	W	Free	Plate
9	73	M	Lung	Femur	9	W	Pedicle	IM
10	55	M	Liposarcoma	Femur	8	W	Pedicle	Plate
11	60	M	Gastric	Femur	10	W	Pedicle	IM
12	76	F	Colon	Humerus	9	W	Pedicle	IM
13	52	M	Kidney	Pelvis	11	W	Free	Plate
14	69	F	Kidney	Femur	10	W	Free	Prosthesis
15	61	M	Lung	Femur	10	W	Pedicle	Prosthesis
16	60	F	Kidney	Femur	10	W	Pedicle	Plate
17	66	M	Kidney	Femur	10	W	Pedicle	Prosthesis
18	25	M	Kidney	Pelvis	9	W	Free	Plate
19	79	F	Colon	Femur	11	W	Pedicle	Prosthesis
20	79	F	Kidney	Femur	12	W	Pedicle	Plate
21	53	M	Kidney	Pelvis	10	W	Free	Plate
22	78	F	MM	Humerus	10	W	Pedicle	IM

MM, Multiple myeloma; W, wide excision; M, marginal excision; IM, intramedullary nail.

follows: pasteurisation, irradiation or freezing in liquid nitrogen (Table III) (1, 4-6, 15-17). The freezing method is particularly advantageous, as it affords simplicity, preservation of the cartilage matrix, perfect fit, sufficient biomechanical strength, no contagion, no requirement of a bone bank, easy attachment of tendons and ligaments and desirable bone and joint stock (5). In the present study, frozen autografts showed good local control, with the 5-year recurrence-free survival rate being 100%. Furthermore, freezing maintains tissue microstructure and tumor antigens, whereas pasteurisation and irradiation cause protein degradation (18). Certain reports have demonstrated spontaneous regression of metastases after cryosurgery (19, 20). In addition to complete cell death caused by freezing, cryoimmunology may contribute to preventing relapse of the disease.

Frozen bone has been reported to have strength equivalent to intact bone (21). However, in this study, 4 of 22 patients (18.2%) with metastasis to the femur experienced postoperative fractures in frozen autografts. Although we previously reported that 7.1-9.1% of patients with malignant bone tumors experienced fractures after reconstruction using frozen autografts (5, 6), the incidence of postoperative fractures in the present study was 18.2%. The higher incidence of postoperative fractures in the present study may be due to osteolytic lesions caused by metastatic tumors. Metastatic bone shows lytic, sclerotic or mixed lesions. Bone strength is particularly affected

Table II. *Outcomes and complications of reconstruction using tumor-bearing frozen autografts in patients with metastatic bone tumors.*

Case	Follow-up (months)	Outcome	Function	Complications
1	21	DOD	–	–
2	65	NED	Excellent	–
3	47	NED	Excellent	Fracture (12 m)
4	12	AWD	–	Infection (3 m)
5	21	NED	Excellent	–
6	32	DOD	–	–
7	168	NED	Excellent	Fracture (108 m)
8	117	NED	Excellent	Osteoarthritis (20 m)
9	4	DOD	–	–
10	9	DOD	–	–
11	27	NED	Excellent	Fracture (26 m)
12	17	DOD	–	–
13	67	AWD	Good	Recurrence (65 m)
14	3	DOD	–	–
15	36	NED	Excellent	–
16	67	AWD	Excellent	Fracture (7 m)
17	33	DOD	–	–
18	25	DOD	–	–
19	4	DOD	–	–
20	34	DOD	–	–
21	21	NED	Excellent	–
22	28	NED	Excellent	–

NED: No evidence of disease, AWD: alive with disease, DOD: died of disease.

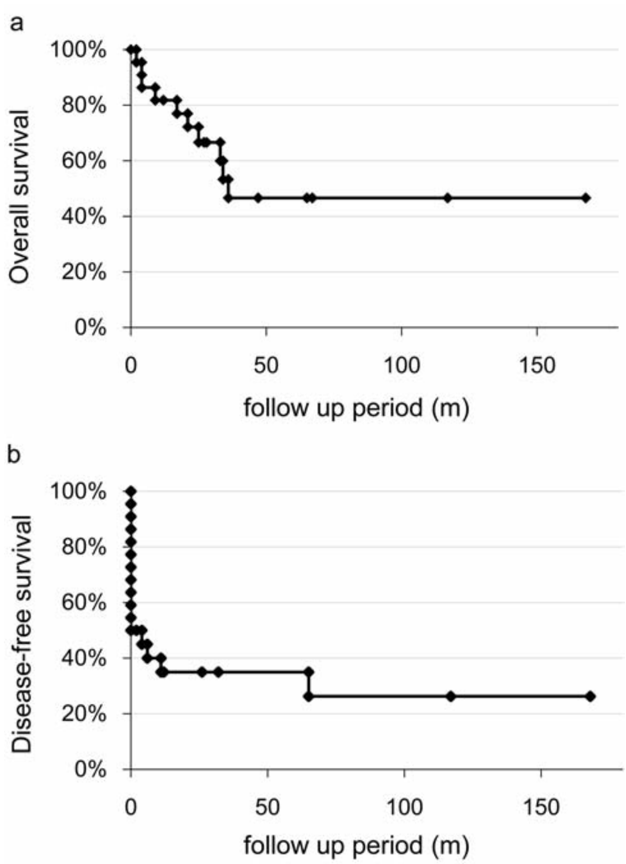

Figure 4. *Kaplan-Meier curve for overall survival and disease-free survival. a. Overall survival. b. Disease-free survival.*

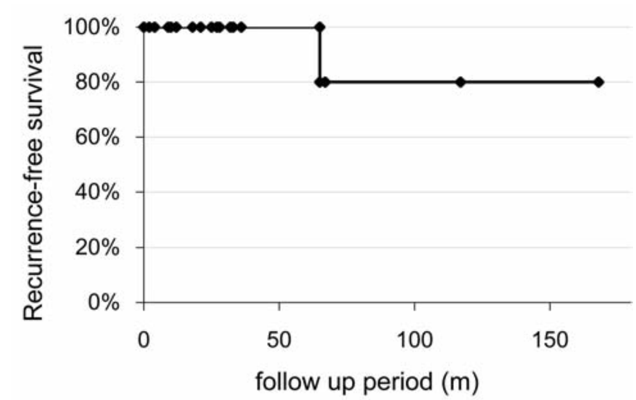

Figure 5. *Kaplan-Meier curve for recurrence-free survival.*

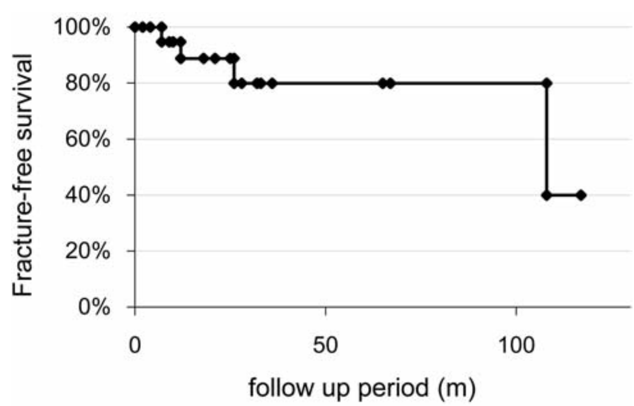

Figure 6. *Kaplan-Meier curve for fracture-free survival.*

by osteolytic lesions. Aside from a fraction of patients with prostate and breast cancer, most patients with bone metastases show lytic lesions. Therefore, the metastatic site and destruction of the bone cortex are important factors to consider when deciding indications for tumor-bearing autografts. Patients with severe destruction of cortex (>2/3 circumference) require additional stabilisation or megaprostheses.

Patients with pathological fractures or a high risk of fracture should be treated surgically, particularly if the metastasis is in the lower limbs. The pathologial fracture of a weight-bearing limb causes pain, gait disability and eventual decline in activities of living (ADL) and QOL. Surgical treatment including suitable reconstruction and prosthesis replacement can recover stability, thereby improving ADL and QOL.

Table III. *Outcomes of reconstruction using various bone grafts.*

Reference	This study	Tsuchiya *et al.* (5, 6)	Chen *et al.* (4)	Manabe *et al.* (1)	Chen *et al.* (4)
Bone graft	Frozen bone	Frozen bone	Irradiated bone	Pasteurized bone	Allograft
Fracture	18%	7-9%	20%	12%	14%
Infection	5%	11-12%	0%	20%	0%
Recurrence	5%	7-9%	7%	0%	5%
Function	Excellent 91%	Excellent 71-76%			
	Good 9%	Good 11-15%	96%	86%	80%
		Fair 9-11%			
		Poor 0-7%			

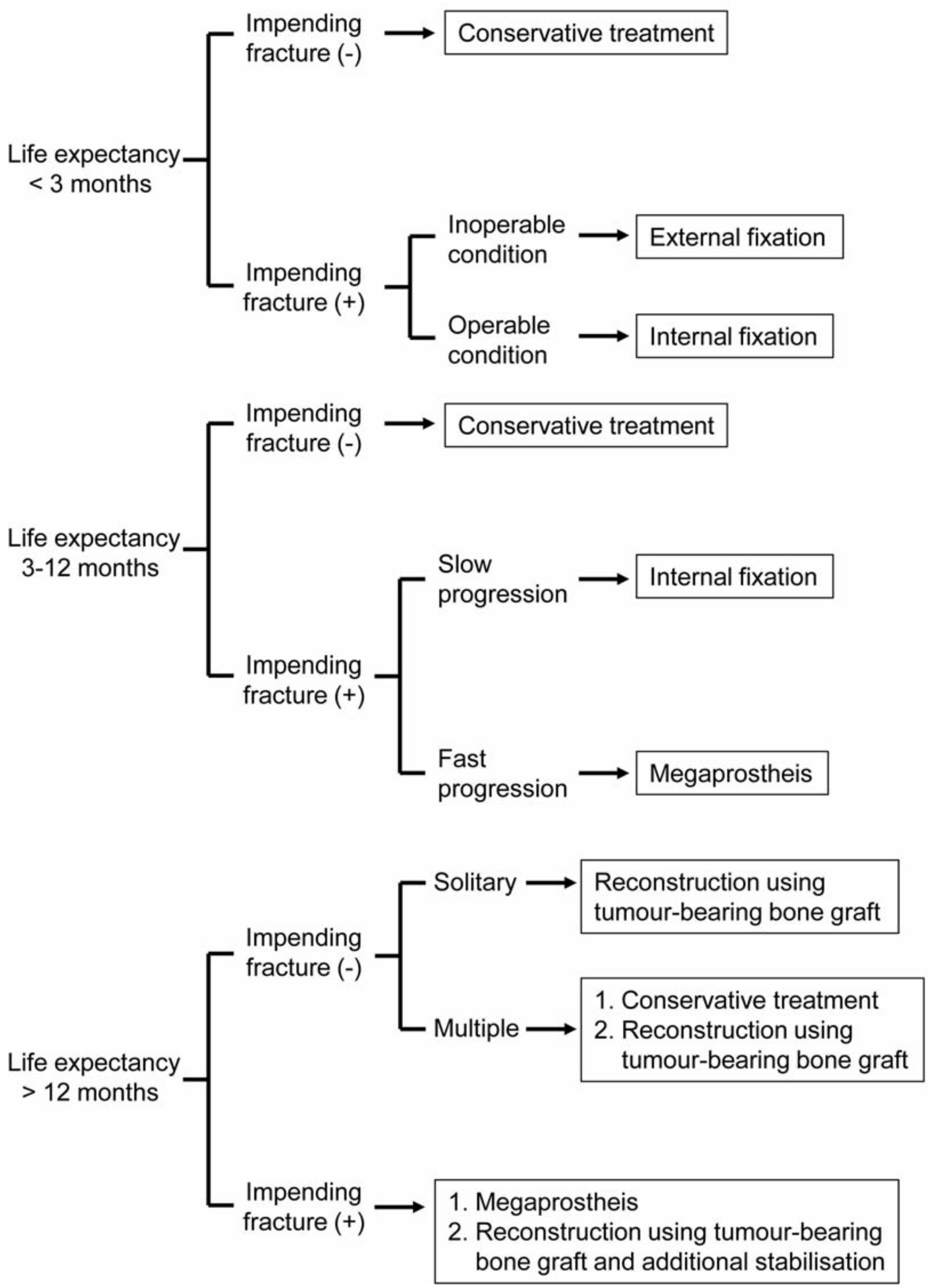

Figure 7. *Surgical strategy for bone metastasis.*

Because bone metastasis is a systemic disease, indications for surgical treatment are limited. Based on benefits and possible complications of each treatment option in patients with bone metastases, we developed a treatment strategy that includes indications for reconstruction using frozen autografts (Figure 7). In principle, conservative therapies take first priority in patients with short expected survival. Surgery is indicated in patients with a pathological fracture having any expected survival period, those with an impending fracture or those with solitary metastasis having long expected survival. In patients with severe destruction of the bone cortex having long expected survival, a megaprosthesis is indicated for reconstruction. It is reported that frozen autografts showed bone regeneration and were replaced by living bone (22). Therefore, reconstruction using frozen autografts is considered to be a beneficial treatment option in patients with long expected survival or complete cure of the primary cancer. Tumor-bearing frozen autografts can be used for reconstruction only in patients with slight destruction of the bone cortex. Although indications for frozen autografts require some degree of bone strength, reinforcement may enable reconstruction using frozen autografts in patients with severe destruction of metastatic bone.

Conflicts of Interest

The Authors declare no conflict of interest.

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