The outcomes of reconstruction using frozen autograft combined with iodine-coated implants for malignant bone tumors: Compared with non-coated implants

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The outcomes of reconstruction using frozen autograft combined with iodine-coated implants for malignant bone tumors: compared with non-coated implants

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Running title: Frozen autograft with iodine coated-implants

Abstract

Objective: We perform reconstruction using frozen tumor bone treated by liquid nitrogen after excision of malignant bone tumors. To prevent postoperative infection, we use iodine-coated implants that we developed. The purpose of this study is to compare the outcome of reconstruction using frozen autograft with non-coated implants (group N) and iodine-coated implants (group I).

Methods: Sixty-two patients were included in group N. The mean age was 31.9±2.3 years. A total of 20 patients died and two were lost to follow-up, averaging 20.0±2.9 months post-operatively, leaving 40 patients available for an assessment at a mean of 79.1±5.8 months post-operatively. There were 38 patients in group I. The mean age was 29.8±3.9 years. The mean follow-up period was 32.1±3.0 months. All patients were alive at the latest follow-up. Survival of frozen bone was determined by Kaplan-Meier analysis.

Results: In group N, survival of frozen bone was 80.7±6.0% and 57.4±10.2% at 5 and 10 years, respectively. Complications were encountered in 31 of 62 patients (50.0%), including deep infection in 10 (16.1%), fracture in 11 (17.7%), local soft-tissue recurrence in six (9.7%), and bone absorption in four (6.5%). In group I, survival of frozen bone was 86.7±6.3% at 5

years. Complications were encountered in 8 of 38 patients (21.1%), including deep infection in one (2.6%), fracture in four (10.5%), local soft-tissue recurrence in two (5.3%), and bone absorption in one (2.6%). There was a significantly lower infection rate in group I (P=0.032).

Conclusion: Reconstruction using frozen autograft combined with iodine coated-implants for patients with malignant bone tumor is very useful method in which good limb function can be gained with minimized risk of infection.

Mini-abstract

Reconstruction using frozen tumor bone treated by liquid nitrogen combined with iodine coated-implants for patients with malignant bone tumor is very useful method in which good limb function can be gained with minimized risk of infection.

Key words: frozen autograft, iodine-coated implants, postoperative infection, sarcoma

Introduction

Limb salvage surgery is a standard treatment for malignant musculoskeletal tumors with the development of a combined modality therapy (1,2). The reconstruction methods following tumor excision in limb salvage operation are tumor prosthesis (2), autograft (1,3), allograft (4), distraction osteogenesis (5), and vascularized fibular graft (6). Biological reconstruction by recycling the resected tumor-bearing bone is popular in Asian countries. Before re-implantation, the bone is subject to treatment including irradiation (1,7), pasteurization (8,9), or freezing with liquid nitrogen (3,10,11). In 1999, we developed and performed a re-implantation technique using frozen autografts treated with liquid nitrogen. The advantages of liquid nitrogen treatment include the following: simplicity, low cost, maintenance of osteoinductive and osteoconductive properties, perfect fit between graft and host bone, no disease transmission, no immunological rejection, preservation of the cartilage matrix, no need for a bone bank, no requirement of special equipment and strict thermal control, easy attachment of tendons and ligaments to bone, no harmful denatured substances, early revitalization and cryoimmunological effects (11).

Post-operative infection is one of the most serious complications for recycled autografts. We developed iodine-coated implants to prevent post-operative infection in 2005 (12). The anodic

oxide film was produced electrically, and use of a povidone-iodine electrolyte resulted in the formation of an adhesive porous anodic oxide with the antiseptic properties of iodine. The thickness of the anodic oxide film was between 5 and 10 μm, with more than 100,000 pores/mm^2 and capacity to support 10-12 μg/cm^2 iodine. The durability of the implants is not influenced, because it is just a coating. We have previously reported the clinical effects of iodine-coated implants (13,14,15).

The purpose of this study was to compare the outcomes of reconstruction using frozen autograft with non-coated implants (group N) and iodine-coated implants (group I).

Patients and methods

Between 1999 and 2008, we recruited 62 patients with bone tumors, who underwent reconstruction using frozen autografts with non-coated implants (group N). The mean age of the patients was 31.9 ± 2.3 years (range, 7 to 72). Thirty-nine patients were male and 23 were female. A total of 20 patients died and two were lost to follow-up, at a mean of 20.0 ± 2.9 months (range, 2 to 48) post-operatively. Therefore, 40 patients were available for assessment at a mean of 79.1 ± 5.8 months (range, 11 to 158) post-operatively. The diagnoses included 38

cases of osteosarcoma, seven of metastasis and chondrosarcoma, four of Ewing's sarcoma, two of malignant fibrous histiocytoma (MFH) and one case each of rhabdomyosarcoma, leiomyosarcoma, chordoma, and malignant hemangiopericytoma. The affected sites included 33 femur, 11 tibia, 10 pelvis, six humerus, and one radius and calcaneus. The following types of implants were used with frozen bone: 22 nails, 16 plates, 10 knee prostheses, eight hip prostheses, four screws, and two shoulder prostheses. Between 2008 and 2014, we included 38 patients, who underwent reconstruction using frozen autografts with iodine-coated implants (group I). The mean age of the patients was 29.8 ± 3.9 years (range, 6 to 79). Twenty-two patients were male and 16 were female. The mean follow-up period was 32.1 ± 3.0 months (range, 7 to 68). All patients were alive at the most recent follow-up. The diagnoses were 29 cases of osteosarcoma, three of metastasis, two of chondrosarcoma, and one each of Ewing's sarcoma (Fig. 1a-g), fibrosarcoma, MFH and adamantinoma. The affected sites included 19 femur, 12 tibia, three pelvis and humerus, and one radius. The following types of iodine-coated implants were used with frozen bone: 33 plates, 3 knee prostheses, and each one hip and shoulder prosthesis. The survival of frozen bone was determined by Kaplan-Meier analysis, and inter-group survival differences were determined using a log-rank test. The survival of frozen

bone was defined as the period until the surgical removal of the recycled bone. Post-operative complications during follow-up were evaluated in both groups. A Fisher's exact test was performed to examine post-operative complications such as infection, fracture, recurrence, and bone absorption. The function of the affected limbs of 46 patients in group N and 34 patients in group I, who were followed for at least one year, was evaluated with the Musculoskeletal Tumor Society (MSTS) functional scoring system (16). Functional outcomes in the two study groups were compared using a *t* test. Statistical analyses were performed using IBM SPSS Statistics software, version 19 (IBM SPSS, Armonk, NY, USA). A *P* value of less than 0.05 was considered significant.

Results

Between group N and group I, there was no significant difference with regard to the diagnosis and affected sites.

In group N, the survival rate of frozen bone was 80.7 ± 6.0% and 57.4 ± 10.2% at 5 and 10 years, respectively (Fig. 2). Complications were encountered in 31 of 62 patients (50.0%), including 10 cases of deep infection (16.1%), 11 of fracture (17.7%), six of local soft-tissue

recurrence (9.7%), and four of bone absorption (6.5%). Most infections had occurred within 6 months during postoperative chemotherapy. Frozen autografts were removed in 14 patients because of infection (6 cases), fracture (5 cases), tumor recurrence (2 cases), and bone absorption (1 case) (Table 1). The mean period of graft removal was 30.3 ± 10.2 months (range, 3.6 to 114.5).

In group I, survival of frozen bone was 86.7 ± 6.3% at 5 years (Fig. 2). Complications were encountered in 8 of 38 patients (21.1%) including one case of deep infection (2.6%), four of fracture (10.5%), two of local soft-tissue recurrence (5.3%), and one of bone absorption (2.6%). Frozen autografts were removed in four patients because of infection (1 case), fracture (2 cases), and tumor recurrence (1 case) (Table 1). The mean period of graft removal was 13.3 ± 4.1 months (range, 5.0 to 24.1). On Kaplan-Meier survival analysis, there was no significant difference (P=0.872) (Fig. 2). However, there was a significantly lower infection rate in group I (P=0.032) (Table I). The mean MSTS score was 85.2% in group N and 92.8% in group I. These differences were not statistically significant (P=0.12).

Discussion

The infection rate of group I was significantly lower for the reconstructions using frozen autografts, although there was no difference in the survival rate compared to previous recycled bone, such as allografts (17), irradiated autografts (18), pasteurized autografts (19), and frozen autografts (20) (Table 2). The results suggest that iodine-coated implants had antibacterial effects. Although the survival rate of the frozen bone was not significantly different using iodine-coated implants compared to frozen autografts alone, we expect that the survival rate may be improved by increasing the number of iodine-coated implant cases. The iodine coating is a revolutionary technology for implants because of its antibacterial efficacy. The iodine-coated implants make it possible for postoperative infection to be controlled. In 5 years, iodine-coated implants will be made available commercially in Japan.

In terms of functionality, the average MSTS scores were 90%, 62.6%, 78.7%, and 79.2% in allograft, irradiated autograft, pasteurized autograft and frozen autograft, respectively (18-21). In this study, the average of functional score was 85.2% and 92.8% for group N and group I, respectively. Therefore, functional outcomes for both groups were favorable compared to the other recycled bone techniques. Group I in particular displayed good functional tendencies,

although there was no significant difference in the MSTS scores between group N and group I (P=0.12).

There are a few limitations to note in this study. First, a relatively small number of patients limit the interpretation of our results. However, these numbers are comparable or greater than previous reports using recycled bone grafts. Second, group N represents our previous treatment method, whereas group I represents the treatment group after our development of iodine coating. In other words, the two groups may not be compared directly, and the historical nature of this study limits its level of evidence. Thirds, this study was retrospective and the study period included a relatively broad time frame. As such, patient selection between each group was not standardized. Fourth, the follow-up duration of group I was shorter than group N. More long-term follow-up is needed in group I.

In conclusion, the study showed that reconstruction using frozen autograft combined with iodine-coated implants for patients with malignant bone tumor is a very useful method in which good limb function can be gained with minimal risk of infection.

Conflict of interest statement

None declared.

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Legends

Figure 1: A 14 year-old boy with pelvic Ewing's sarcoma.

a: On initial MRI, there was a huge extraskeletal tumor mass (arrowhead).

b: On post-chemotherapeutic MRI, the extraskeletal mass had shrunk (arrowhead).

c: We performed reconstruction using a frozen autograft with iodine-coated implants after tumor excision.

d: The immediate post op computed tomography: osteotomy site was shown at sacrum (arrow)

e: Radiograph at 20 months after surgery.

f: Computed tomography showed excellent union between the host and frozen bone (arrow).

g: He is able to run normally at 20 months after surgery.

Figure 2: A Kaplan-Meier curve showing the survival rate of the frozen autografts according to the coating of implants.

Table 1: Complications and limb function according to the implant coating.

Table 2: Comparison with previous studies.

Figure1a

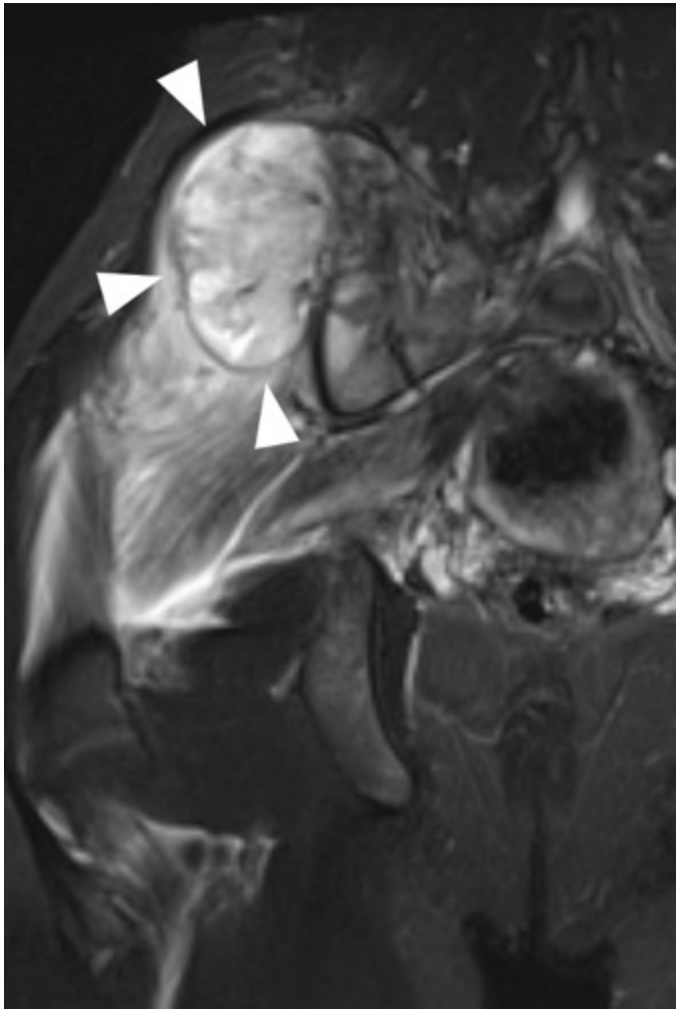

Figure1b

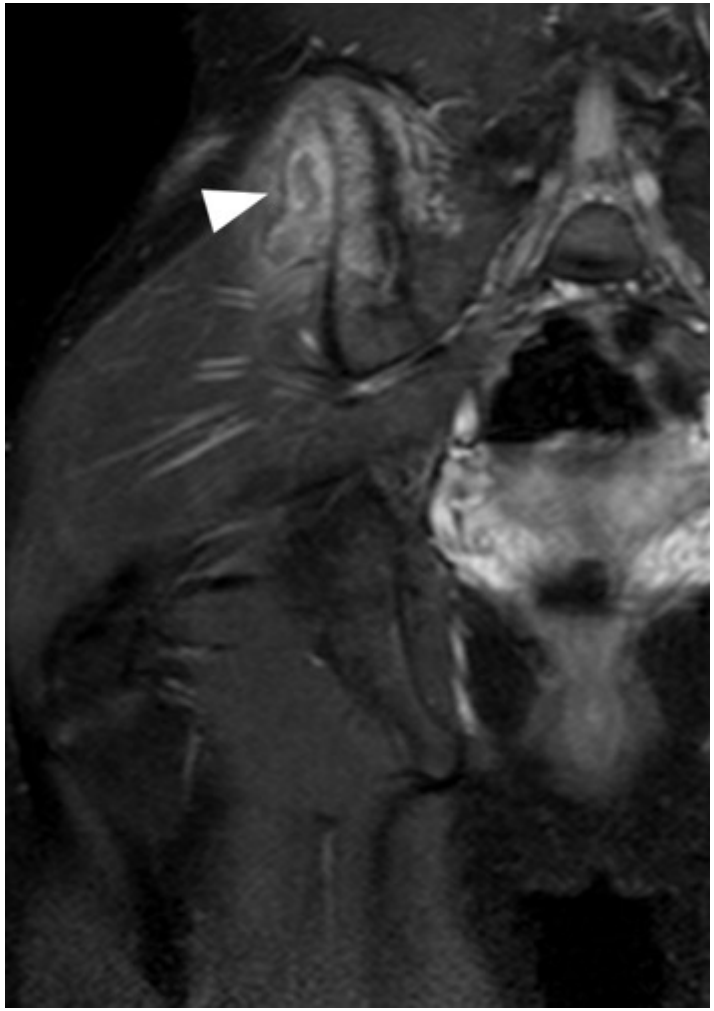

Figure1c

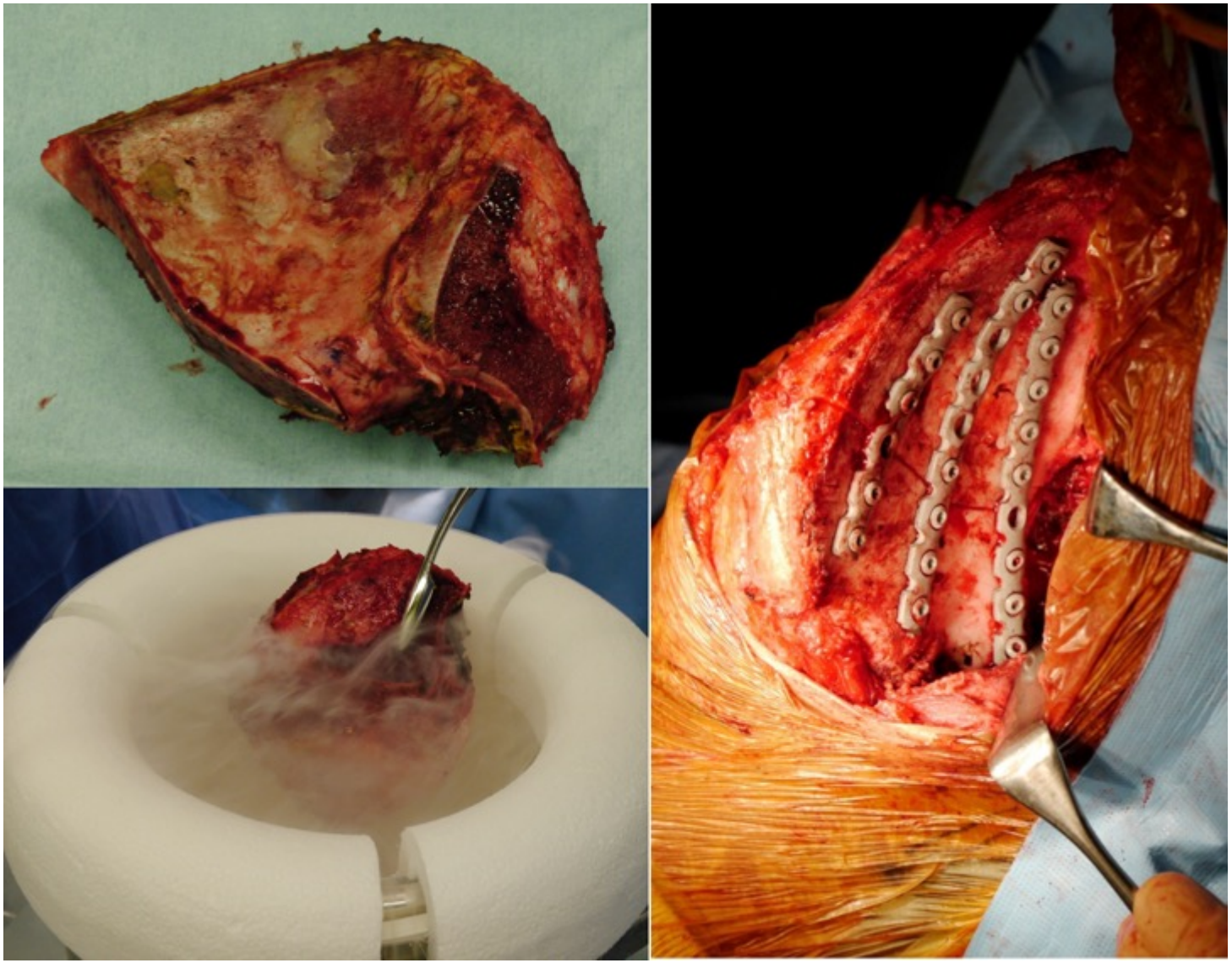

Figure1d

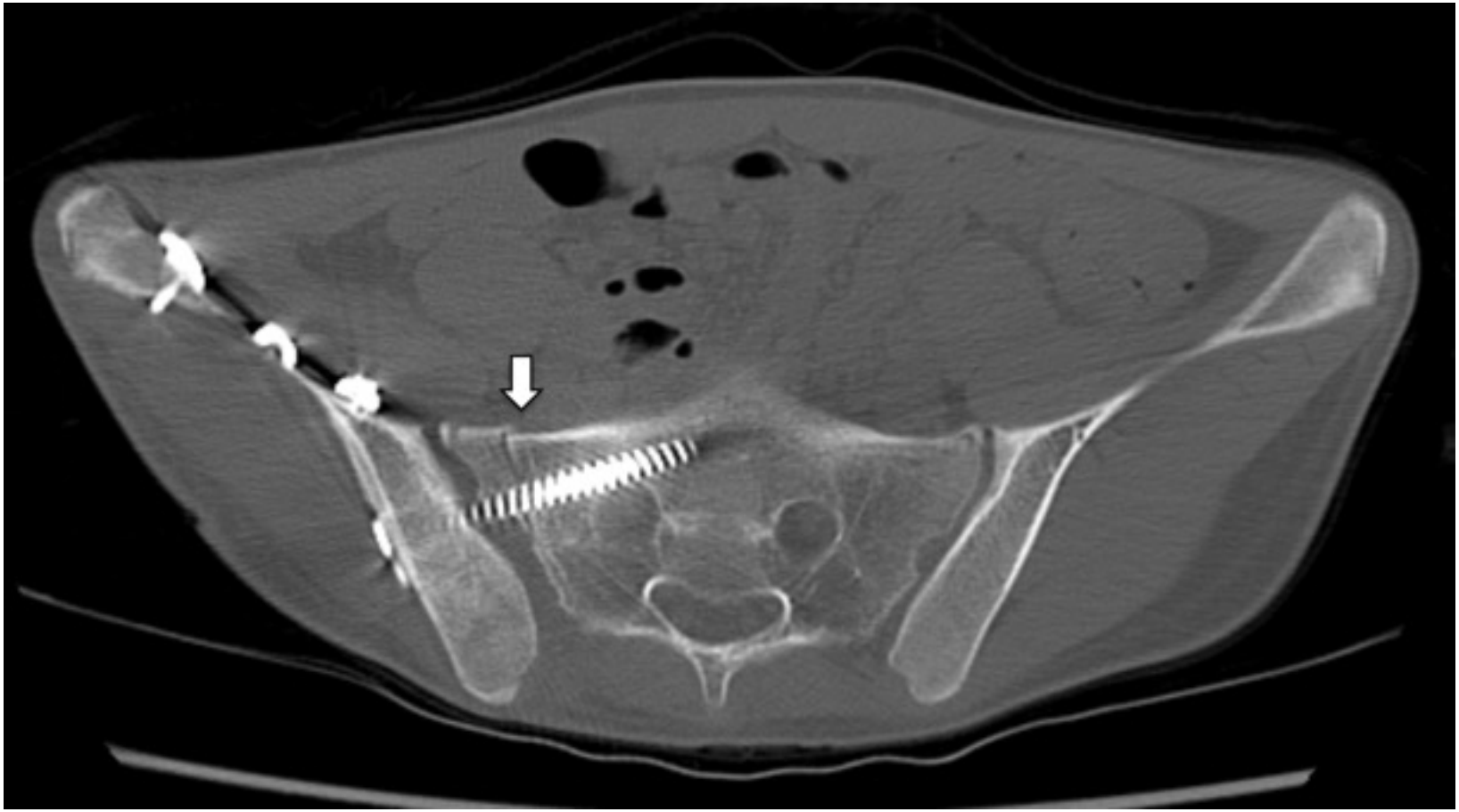

Figure1e

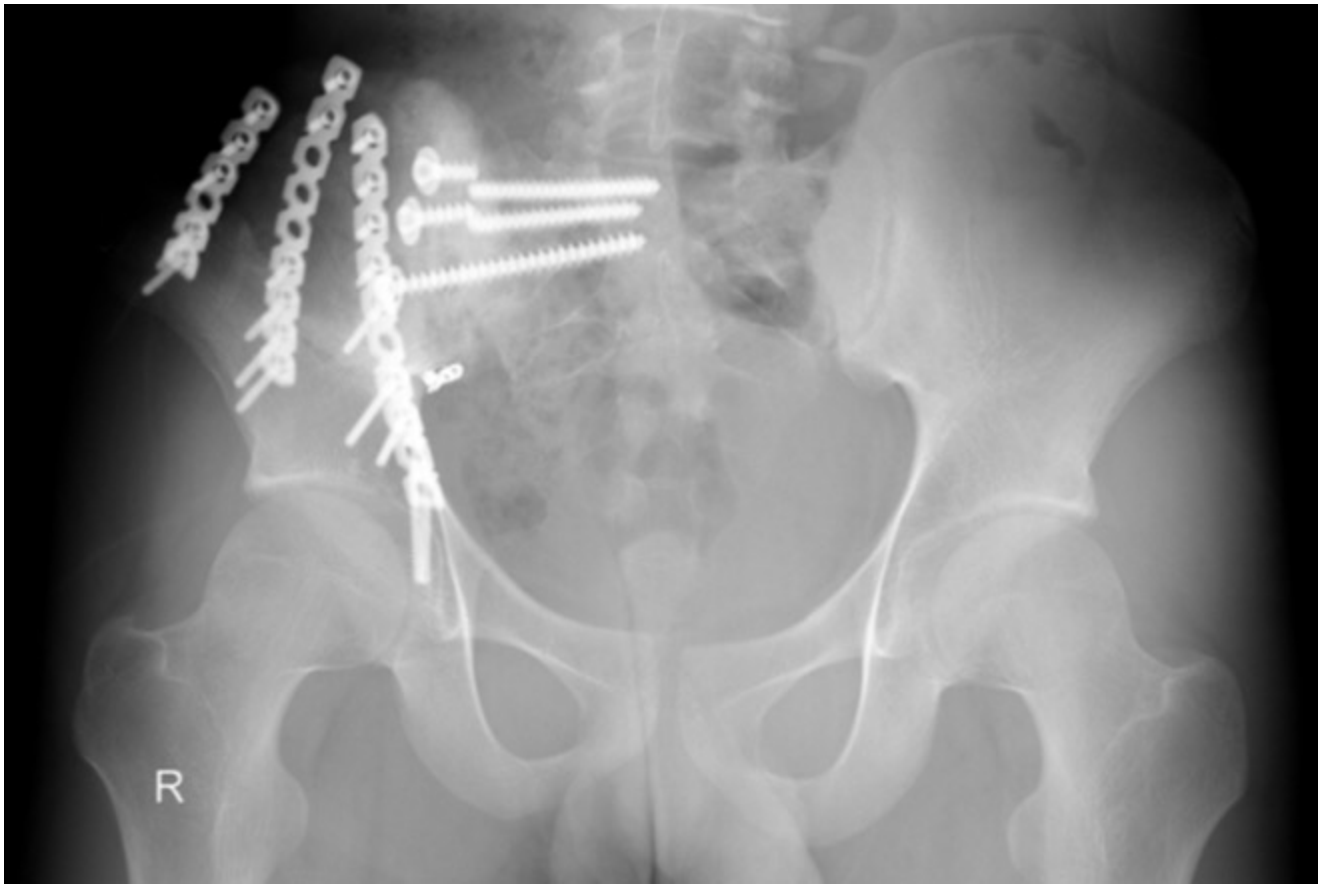

Figure1f

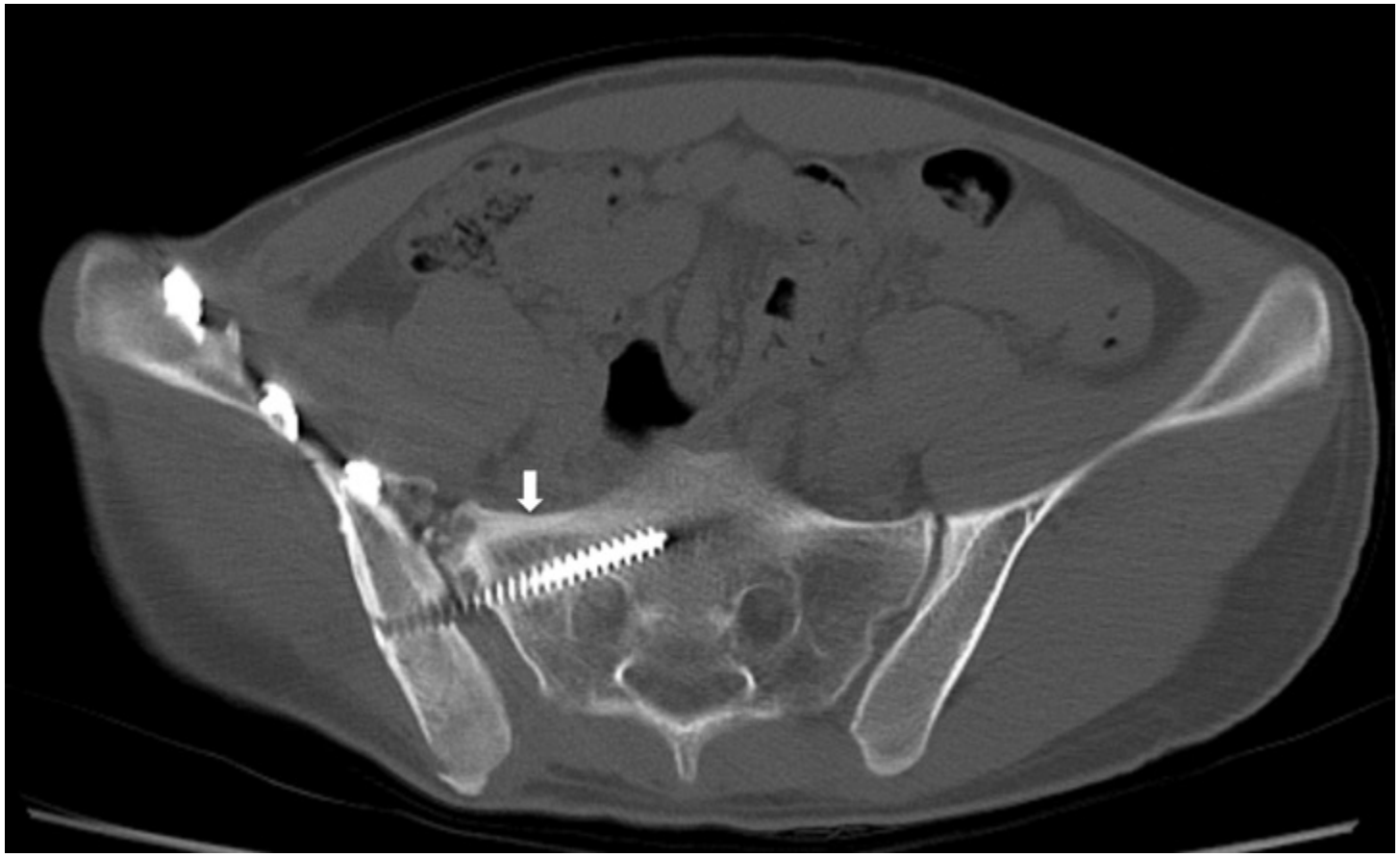

Figure1g

Figure 2

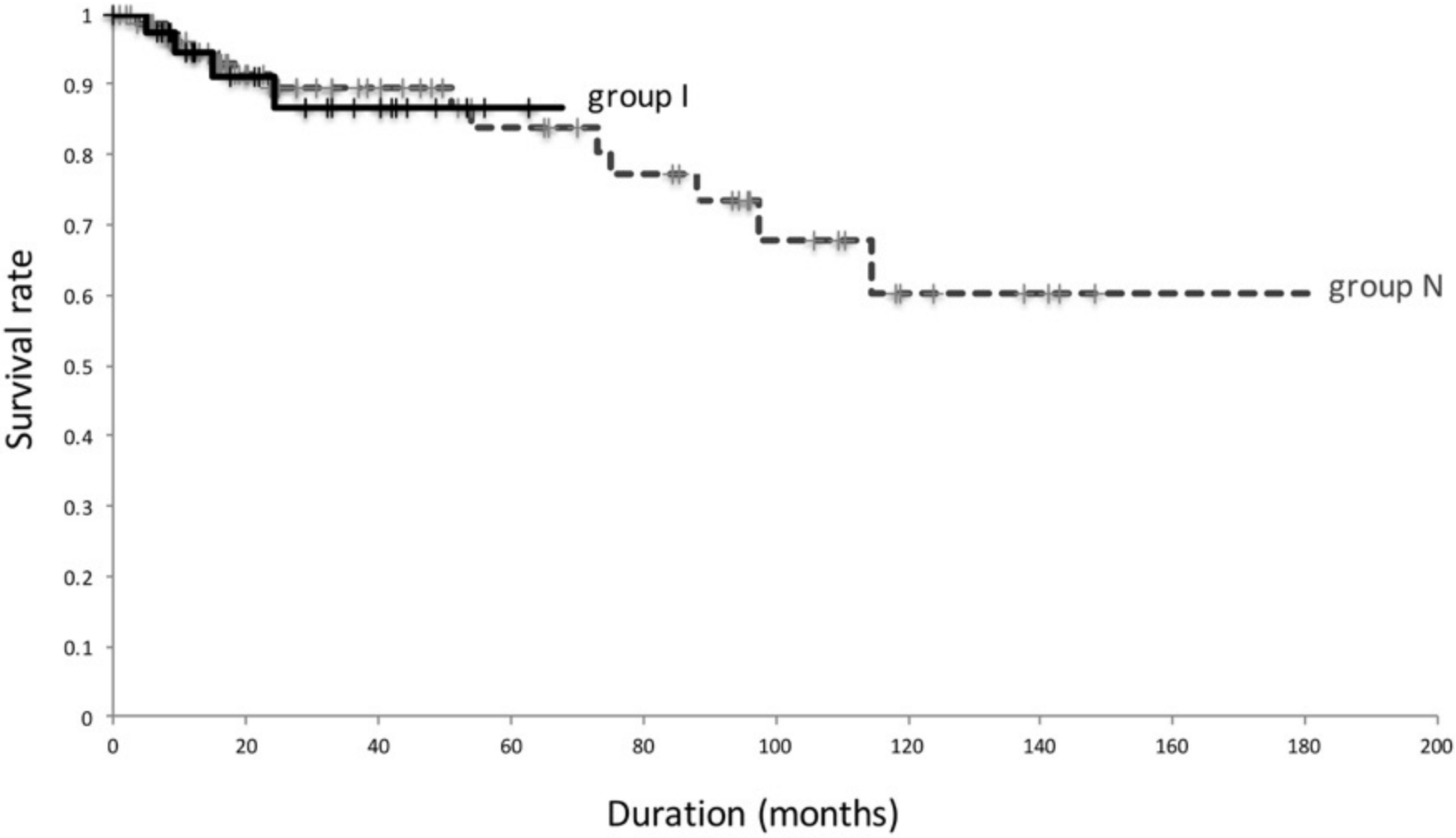
Survival rate
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
140
160
180
200
Duration (months)
group I
group N

Table 1

Variables	Non-coating	Coating	p-value
Infection			.032
yes	11	1	
no	52	37	
Fracture			.247
yes	11	4	
no	51	34	
Recurrence			.351
yes	6	2	
no	56	36	
Bone absorption			.368
yes	4	1	
no	58	37	
MSTS			
score	85.2 %	92.8 %	.123

Table 2

References	Type of reconstruction	Recycled bone survival		Complication rate	Infection rate	Fracture rate	Bone absorption rate	MSTS score
		5-year	10-year					
Biau et al[17)]	Allograft	68 %	33 %	73 %	23 %	27 %	23 %	90 %
Kim et al[18)]	Irradiated autograft	NA	43 %	87 %	22 %	9 %	NA	62.6 %
Jeon et al[19)]	Pasteurized autograft	77 %	NA	38 %	23 %	0 %	8 %	78.7 %
Paholpak et al[20)]	Frozen autograft	NA	NA	42 %	25 %	8 %	8 %	79.2 %
Current series	Group N	80.7%	57.4 %	50.0%	16.1 %	17.7 %	6.5 %	85.2 %
	Group I	86.7 %	NA	21.1 %	2.6 %	10.5 %	2.6 %	92.8 %

NA, not assessed