J Orthop Sci (2003) 8:116–124

Journal of
Orthopaedic Science

Instructional lecture

Distraction osteogenesis for treatment of bone loss in the lower extremity

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Abstract Distraction osteogenesis has been widely utilized to treat leg length discrepancy, deformity, nonunion, osteomyelitis, and bone loss. It has been found that most difficult conditions can be resolved with this method. This paper introduces the usefulness of distraction osteogenesis for the treatment of nonunion and bone loss after tumor excision. The procedure was found to be extremely effective for the treatment of nonunion accompanied by bone loss and infected nonunion. In particular, the Ilizarov method offers a simultaneous solution for several problems related to nonunion, such as instability, infection, deformity, bone loss, joint contracture, limb length discrepancy, and skin defects. In addition, distraction osteogenesis is safe, useful, and efficient for the treatment of bone loss even after tumor excision. Joint preservation and reconstruction by means of distraction osteogenesis is the most conservative limb-saving surgery available at present. Furthermore, distraction osteogenesis can provide natural limb regeneration.

Key words Distraction osteogenesis · Bone defects · Bone tumor · Nonunion

Introduction

Skeletal defects related to bone tumor, trauma, or infection have been treated so far with free autografts, vascularized bone transfers, allografts, heat-treated autografts, artificial bone substitutes, spacers, or prostheses. In the case of skeletal reconstruction, however, bone defects are ideally repaired with living bone reconstruction. Recently, distraction osteogenesis with a ring fixator developed by Ilizarov and callotasis with a unilateral fixator by de Bastiani have been widely adopted for the treatment of several orthopedic problems, such as leg length discrepancy, deformity, nonunion, osteomyelitis, and congenital or acquired skeletal defects.[6,9–11] The main advantage of distraction osteogenesis is that it can achieve regeneration of living bone with the same strength and width as that of the native bone. Peripheral nerves, vessels, muscles, tendons, ligaments, and skin are also gradually lengthened in proportion to the lengthening bone. This paper introduces treatment of nonunion and reconstruction after tumor resection by means of distraction osteogenesis.

Distraction osteogenesis technique

Ilizarov initially generated bone with distraction physiolysis, by which the growth plate is mechanically distracted without osteotomy, resulting in bone formation. Subsequently, Ilizarov developed distraction osteogenesis, which features de novo bone formation between vascular bone surfaces created by osteotomy and gradual distraction.[9–11] We prefer to use four basic methods: simple lengthening, bone transport, shortening-distraction, and lengthening combined with intramedullary nailing. Intramedullary nailing is helpful for reducing the external fixation time. Lengthening is performed over an intramedullary nail with either proximal or distal locking screws when primary intramedullary nailing is feasible before distraction (primary nailing). Screws are placed on the unlocked side after distraction is complete as the external fixator keeps the length of distraction. In some cases intramedullary nailing is performed after the completion of distraction (delayed nailing) when primary nailing is difficult to apply[26,28] (Fig. 1).

The steps involved in distraction osteogenesis include bone division; stable fixation of the fragments; a phase consisting of latency, distraction, and consolidation; regeneration assessment; and removal of the frame.

Offprint requests to: H. Tsuchiya
Presented at the 75th Annual Meeting of the Japanese Orthopaedic Association, Okayama, Japan, May 2002
Received: June 24, 2002

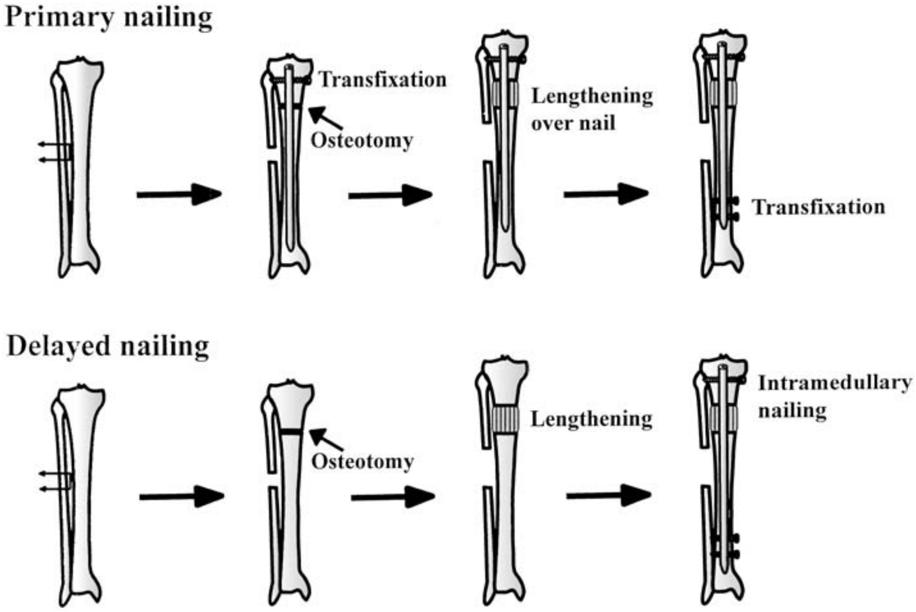


Fig. 1. Distraction osteogenesis combined with intramedullary nailing

Distraction is started 7–14 days after osteotomy at 0.5 mm twice daily or 0.25 mm four times daily. This is later reduced to zero when the callus formation is delayed or impaired or is increased to 1.5 mm per day if the callus formation is likely to consolidate prematurely. The external fixator is removed when sufficient consolidation is obtained (at least three cortices observed on frontal and lateral radiographs). When callus formation is poor, distraction is delayed or compression and distraction of a moving segment (accordion maneuver) is applied. Usually, consolidation takes one and a half to two times longer than distraction.

Three indices are used to assess the clinical results: the external fixation index (EFI), obtained by dividing the entire duration of external fixation by the length of bone regeneration; the distraction index, obtained by dividing the duration of distraction by the length of bone regeneration; and the maturation index, calculated by dividing the duration of external fixation (measured from the completion of distraction to removal of external fixation) by the length of bone regeneration.[26] Ideally, when comparing the maturation and external fixation indices among patients or studies, the length of the distraction must be taken into consideration.[21]

Table 1. Classification of nonunion

Type I: aseptic nonunion
A: lax (atrophic/hypotrophic) nonunion ± deformity
B: stiff (hypertrophic) nonunion ± deformity
C: nonunion with bone loss ± shortening
Type II: infected nonunion

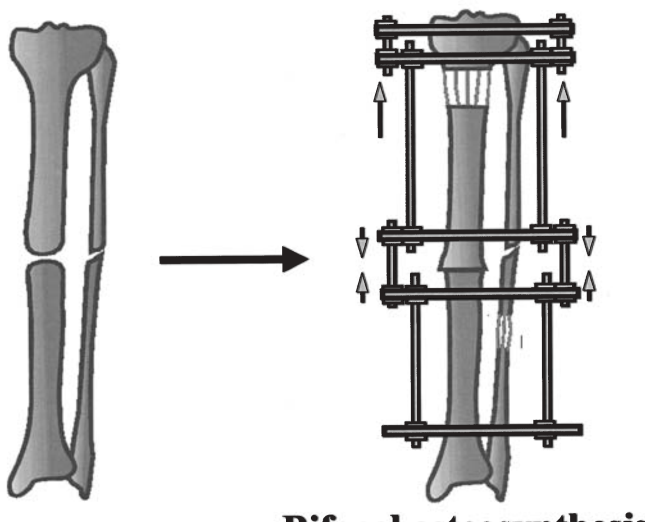
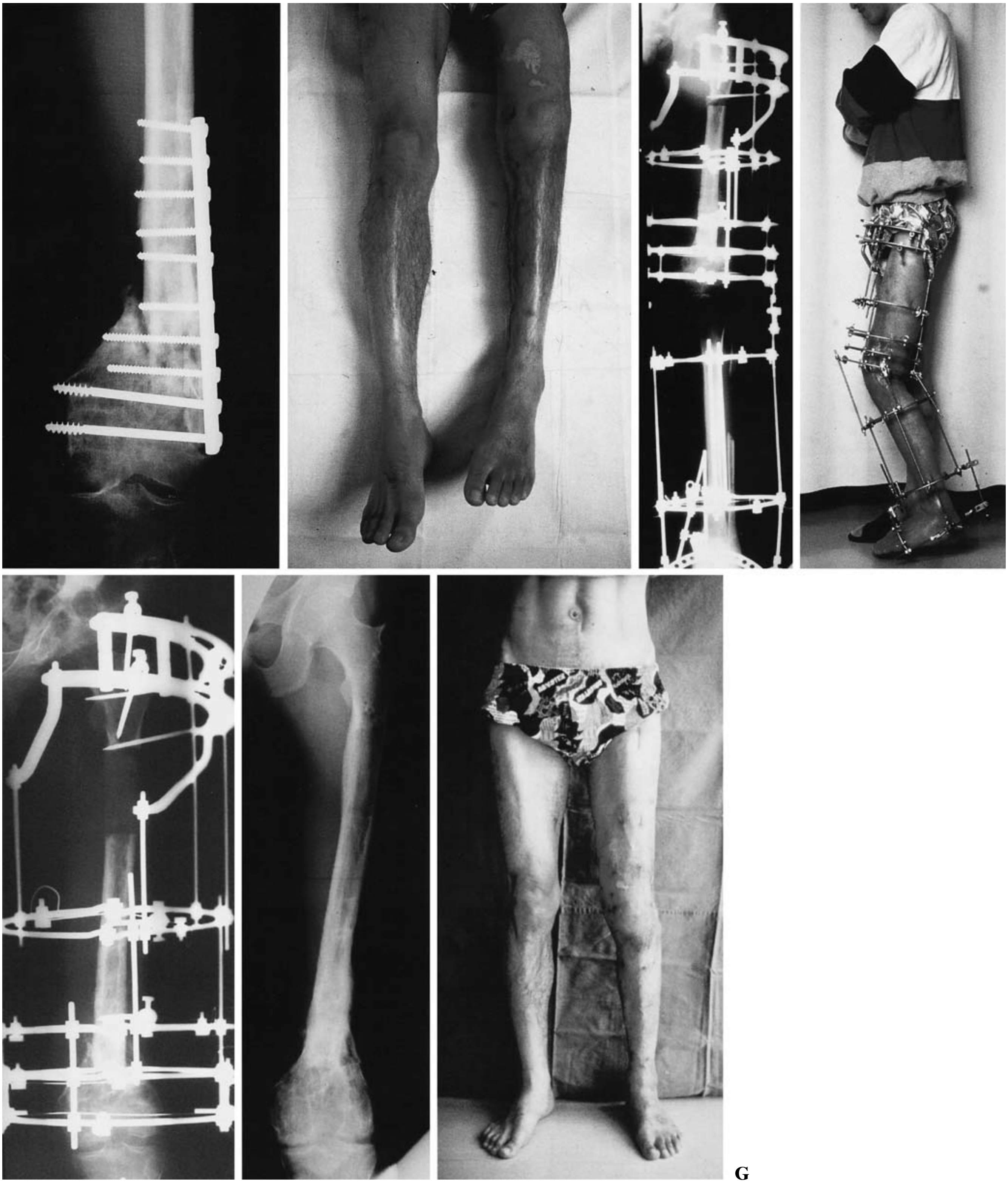


Fig. 2. Bifocal osteosynthesis for type IA lax (hypotrophic/atrophic) nonunion

Treatment of nonunion

Nonunion is classified as type I (aseptic nonunion) or type II (infected nonunion). Type I is further divided into three subgroups: type IA represents lax (hypotrophic or atrophic) nonunion with or without deformity; type IB is stiff (hypertrophic) nonunion with or without deformity; and type IC is nonunion with bone loss with or without shortening (Table 1).

Type IA (lax nonunion) is usually treated with rigid fixation and biological stimulation, such as bone



A,B C,D E,F G

Fig. 3A,B. A 27-year-old man with type IC nonunion accompanied by 7 cm shortening and deformity. **C** Resection of nonunion site and shortening-distraction. **D** Knee and ankle joint mobilization with the Ilizarov hinge system was carried out simultaneously. **E,F,G** The femur was lengthened by 9 cm, and the external fixation index (EFI) was 37 cm/day grafting, dynamization, and distraction osteogenesis to promote bone formation. Realignment is necessary for treatment of a deformity. Bifocal osteosynthesis using compression following resection of the nonunion site and bone lengthening at another osteotomy can be used for atrophic nonunion (Fig. 2). Atrophic nonunions, with thin, nonreactive bone ends, are treated initially with compression and then with distraction.[19] Type IB (stiff nonunion) is usually treated with rigid fixation alone because the hypertrophic nonunion site may unite spontaneously. Hypertrophic nonunions are mostly caused by instability of the fracture site even though the vascularization of the fracture site is well preserved. Hypertrophic nonunions have a vital blood supply from each bone end and a dense collagenous interface. For these reasons, bone formation can be stimulated by primary distraction.[3] Realignment should also be used when necessary. Type IC (nonunion with bone loss) is basically treated with bone transport or shortening-distraction (Fig. 3). When there is enough space, trifocal osteosynthesis (double segment transport) at two osteotomies is possible (Fig. 4).

Treatment for type II (infected nonunion) involves two steps. The first is resection of the focus of infection, and the second is reconstruction of the bone defect.[4] Bone transport or shortening-distraction can be applied to treat the bone defect. Local irrigation with physiological saline containing antibiotics or antibiotic-impregnated cement beads may be indicated when infection causes active discharge (Fig. 5). At the time of resection of the infectious focus, it is advisable to resect all necrotic and poorly vascularized tissue (Fig. 6). As for bone transport, the bone segment must have an adequate blood supply to promote bone formation at its trailing end and healing at its leading end, which is compressed against the host bone.[1] Supplementation with autogenous bone graft after operative débridement of the docking site accelerates and facilitates healing.[5,25,26] In children, cancellous allografts would be helpful for obtaining fusion at the docking site.

Several investigators have compared bone transport with the use of bone graft, antibiotic beads, and vascularized grafts for the treatment of segmental bone defects with or without infection.[5,8,13] Most have reported similar rates of healing, duration of treatment, final deformity, complications rates, and total number of operative procedures among these treatment modalities. However, limb length discrepancy was decreased by means of bone transport. Cierny and Zorn concluded that the advantages of the Ilizarov method include fewer complications, decreased cost of treatment, and a shorter duration of disability.[5]

The Ilizarov ring fixator is extremely useful for solving several problems related to nonunion, such as instability, infection, deformity, bone defect, joint contracture, limb length discrepancy, and soft-tissue damage. The Ilizarov frame can deal simultaneously with these problems because its multiple functions deal with fixation, deformity correction, bone lengthening, joint mobilization, and skin elongation. The Ilizarov method is thus highly effective for complicated nonunions, that is, type IC (nonunion with bone loss) and type II (infected nonunion). Type IA (lax nonunion) and type IB (stiff nonunion) can be treated with conventional procedures such as decortication or a bone graft combined with internal or external fixation.

Relative blood flow of the distraction area was measured under various conditions. An increase in the relative blood flow during treatment was considered beneficial for bone formation and was measured by means of technetium-99m angiography.[16,25] Rectangular regions of interest (ROI) were established in the bone-

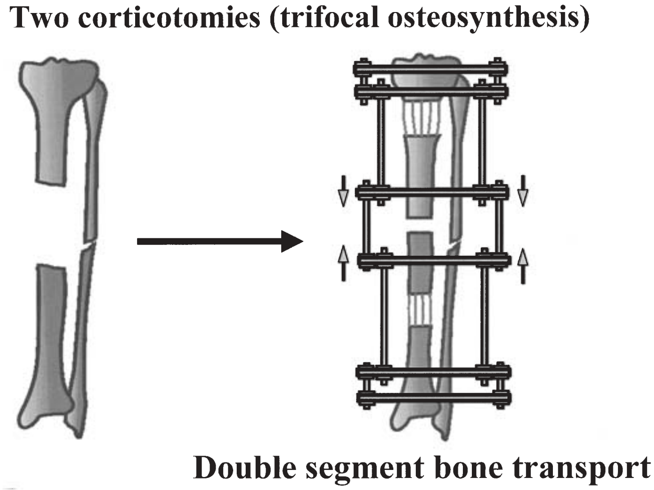


Fig. 4. Double segment bone transport (trifocal osteosynthesis) for type IC nonunion with bone loss

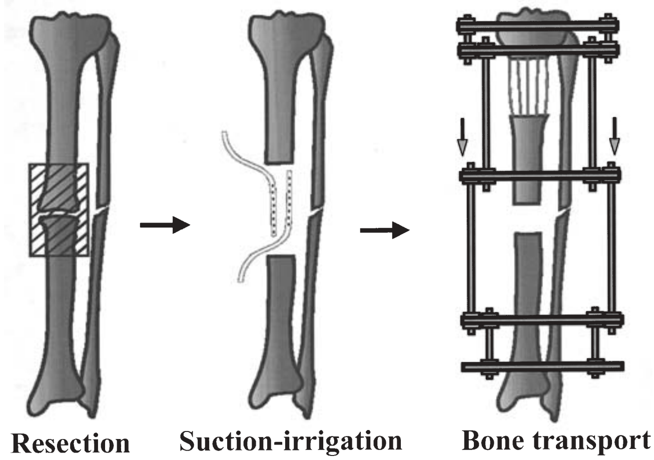
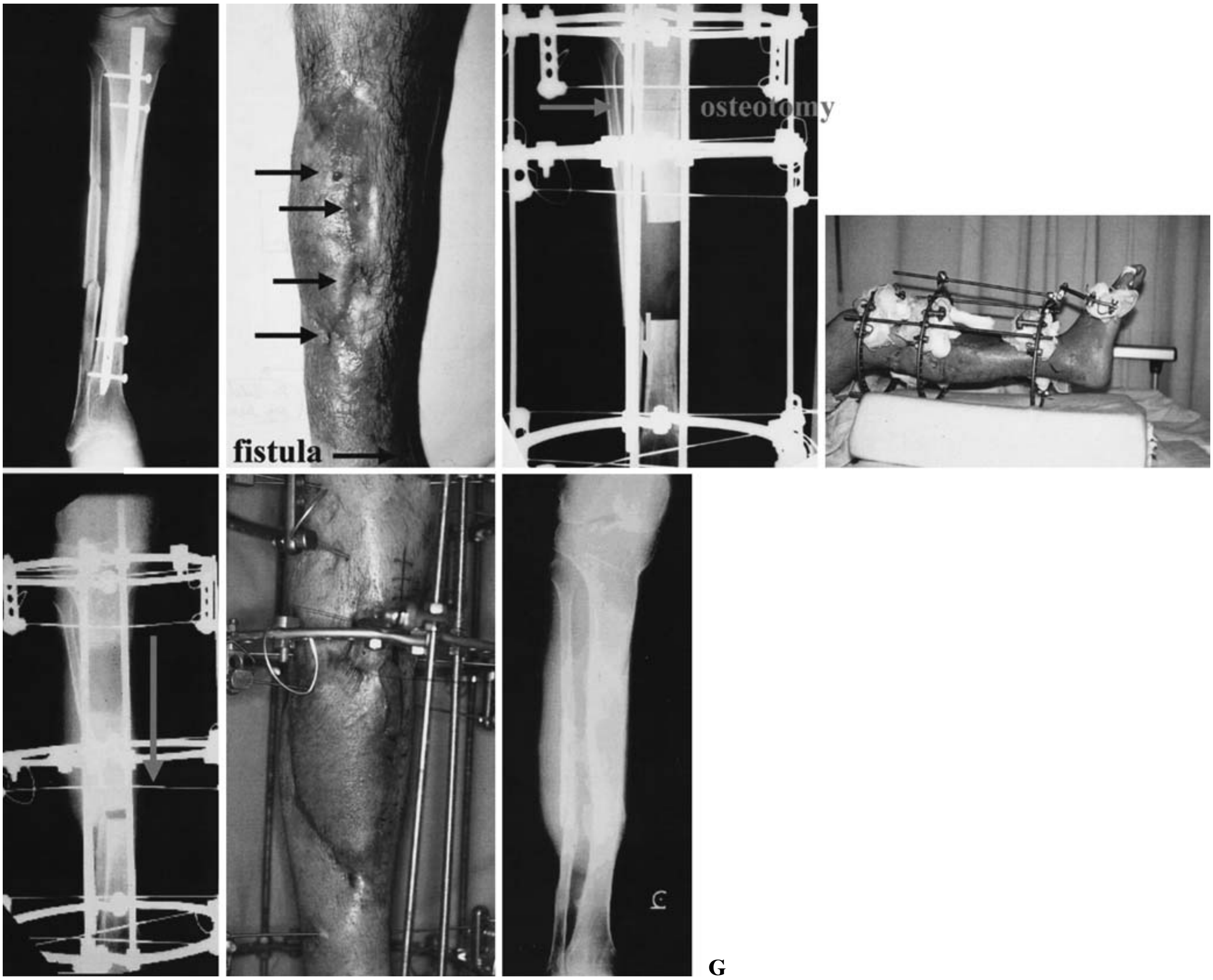


Fig. 5. Treatment of infected nonunion



A,B C,D E,F G

Fig. 6. A,B A 20-year-old man with infected nonunion who was primarily treated with intramedullary nailing and a free myocutaneous latissimus dorsi flap. **C** The infected focus was excised en bloc, and bone transport was applied with the Ilizarov frame. **D** Ankle joint mobilization was performed simultaneously. **E,F** During bone transport good bone regeneration was observed while the skin fistulas were healing. **G** EFI was 36 days/cm

lengthening area and on the opposite leg at the same level, as well as over the entire bone and soft tissue on both sides. A time-activity curve for each ROI was generated and the blood flow index determined by dividing the peak count of the arterial phase of the lesion by that on the control side (Fig. 7A).

Thirty-eight patients were divided into four groups. Group A comprised patients with a tumor who underwent chemotherapy during distraction osteogenesis, group B patients with a tumor who did not undergo chemotherapy, group C patients with trauma, and group D patients with congenital disorders. The mean increase in the relative blood flow on the healthy opposite site was 1.63-fold for group A, 2.10-fold for group B, 2.25-fold for group C, and 1.56-fold for group D (Fig. 7B). These increases in the relative blood flow during distraction osteogenesis are likely to have a positive effect on bone formation, suppression of infection, and delivery of antibiotics.

Reconstruction after tumor resection

A recent subject of interest regarding limb-saving surgery is the improvement of limb function without endangering patients' lives.[27] Several modalities are available for the treatment of bone loss, such as autografts, heat-treated bone, allografts, biomaterials, prostheses, and distraction osteogenesis. Prosthetic replacement is a simple procedure that provides excellent early results. However, late complications

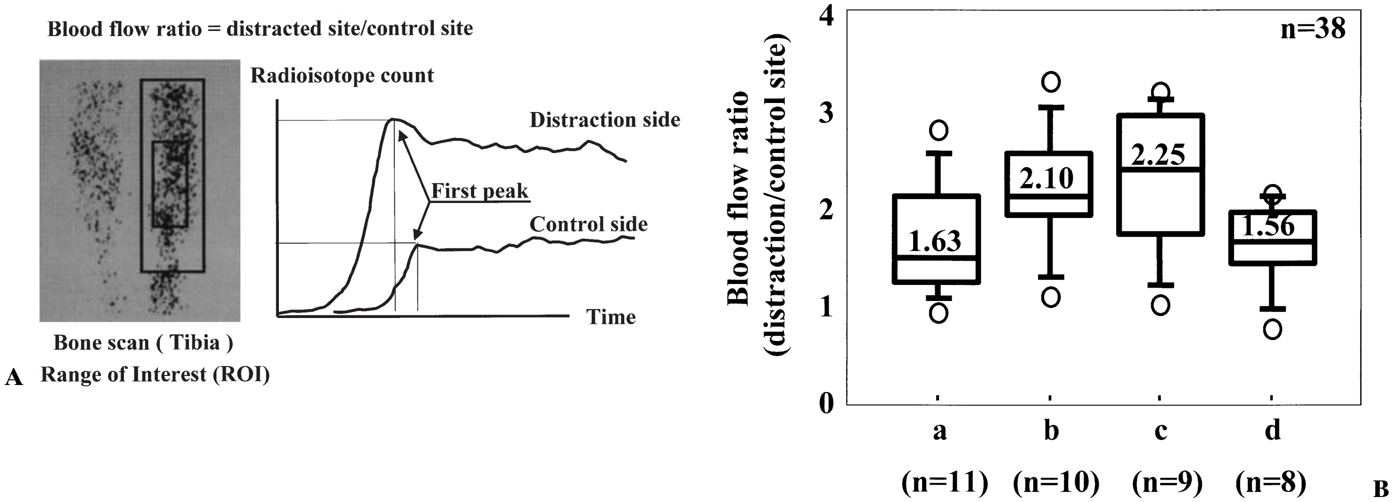


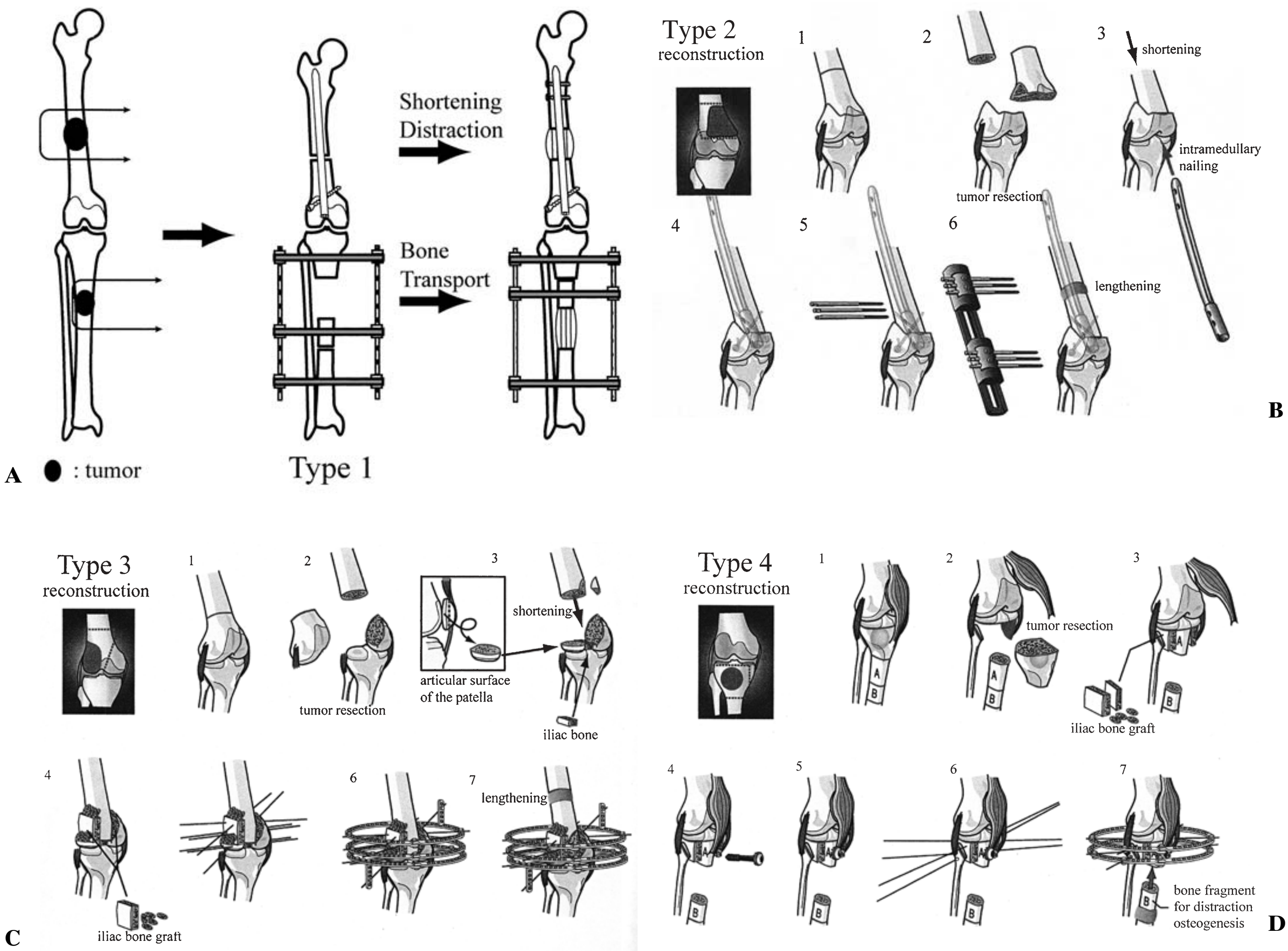
Fig. 7. A Method for relative blood flow measurement. **B** Relative blood flow in 38 patients with various diseases. *a*, patients with a tumor who underwent chemotherapy during distraction osteogenesis; *b*, patients with a tumor who underwent no chemotherapy; *c*, patients with trauma; *d*, patients with a congenital disorder

such as infection, loosening, and breakage are common and troublesome. The allograft is a form of biological reconstruction with a rather high rate of complications because an allograft uses dead bone. Vascularized fibular graft is also biological and uses living bone, but size and strength are limited and fracture and deformity frequently occur later. During the late 1980s our institute started searching for a procedure that would improve limb-saving surgery. We attended a lecture by Dr. Ilizarov in Davos, Switzerland in 1989 and were highly impressed by the excellent results obtained with osteomyelitis treatment. The linkage between distraction osteogenesis and primary reconstruction after massive tumor resection was thus established in our institute. Recently, several investigators have reported the advantages and disadvantages of distraction osteogenesis for tumor surgery.[2,7,12,15,18,20,23,25,26,28]

Ideal bone reconstruction should feature resistance to infection, durability, long-lasting stability, biological affinity, and eventually good limb function.[26] A characteristic of distraction osteogenesis is the regeneration of living bone together with muscles, tendons, nerves, and skin. Distraction osteogenesis has been used since 1990 to generate native bone for patients with malignant bone tumors. Tumor reconstruction by means of distraction osteogenesis consists of several steps: preconstruction of a frame, adequate tumor excision, osteotomy, and distraction with or without chemotherapy. The distraction procedure is the same as that used for trauma or congenital cases. In 1997 we reported a reconstruction classification based on the location of the bone defect after tumor excision[26]; comprising of five types: Type 1 is diaphyseal reconstruction, type 2 metaphyseal reconstruction, type 3 epiphyseal reconstruction, type 4 subarticular reconstruction, and type 5 arthrodesis (Fig. 8). After adequate tumor excision, a preconstructed Ilizarov frame or unilateral fixator is used. Distraction (0.5–1.0 mm/day) is initiated 7–14 days after osteotomy. A regular course of postoperative chemotherapy is usually given to patients with high-grade tumors. As for postoperative rehabilitation, weight-bearing while using crutches and motion exercises of the knee joint are initiated after subsidence of bleeding and wound pain, or 3 weeks after surgery when the patella tendon is reattached to the original place with a spike washer.

Benign bone tumors such as giant cell tumor, juvenile adamantinoma, and fibrous dysplasia are treated with curettage or marginal excision without loss of healthy soft tissue, so good bone formation following distraction osteogenesis can be expected. Distraction osteogenesis for late limb length discrepancy and failure after limb-saving surgery appears to be similar to that for benign conditions, as chemotherapy and irradiation have little effect. Limb lengthening is beneficial for growing children who suffer from leg shortening as a result of excision or radiation of the epiphyseal plate. Arthrodesis using distraction osteogenesis is also effective for the treatment of infected tumor prostheses.

Low-grade malignant tumors such as parosteal osteosarcoma, low-grade central osteosarcoma, chondrosarcoma, and adamantinoma are usually treated with wide or marginal excision. Sometimes healthy soft tissue must be sacrificed for tumor excision, and such loss may lead to a poor blood supply for regeneration.



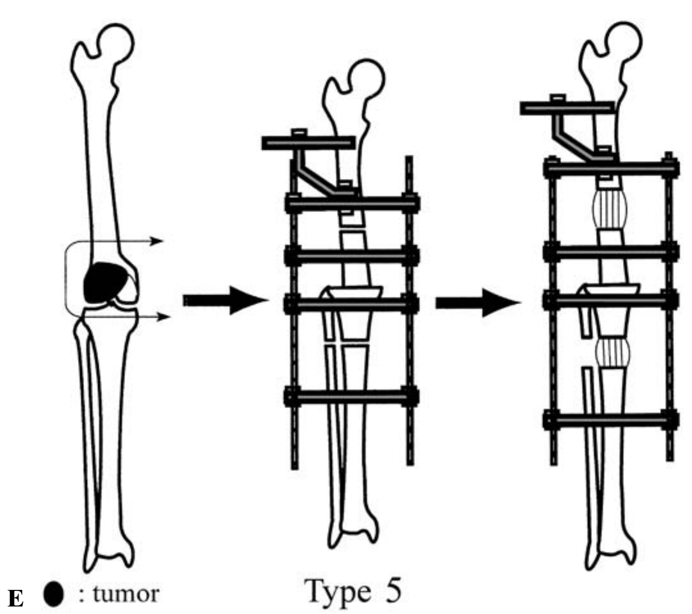
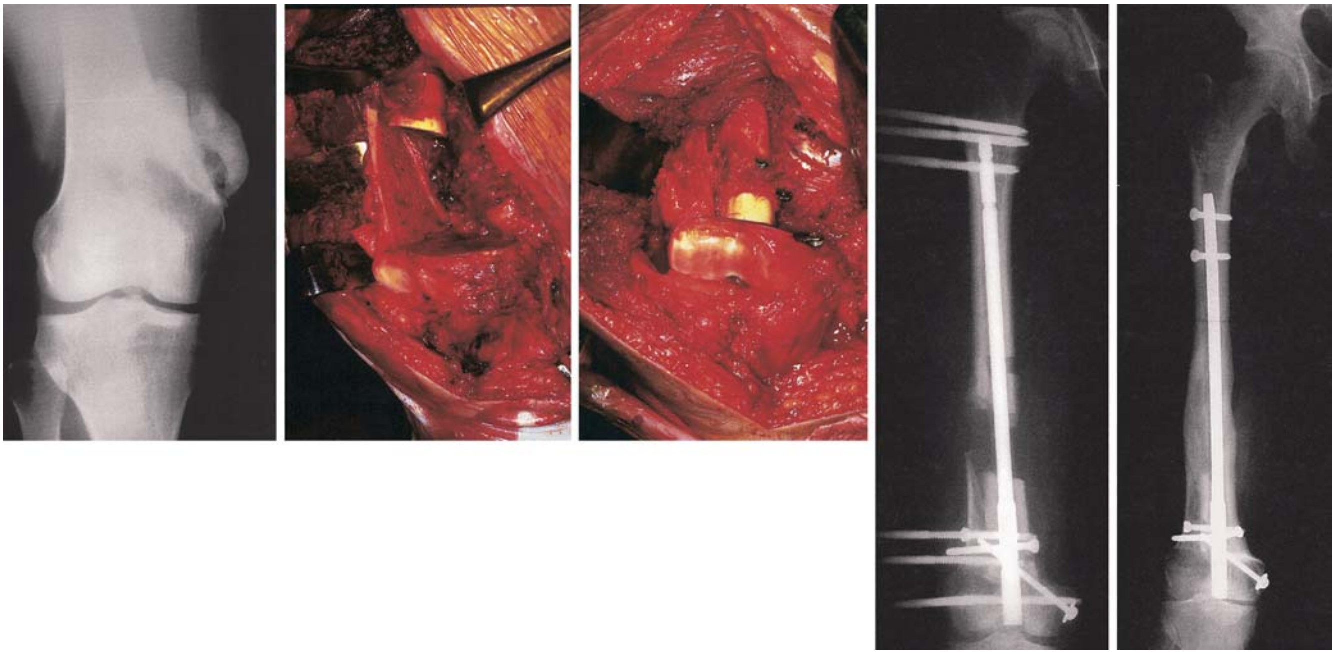


Fig. 8. Reconstruction types after tumor excision. **A** Type 1, diaphyseal reconstruction. **B** Type 2, metaphyseal reconstruction. **C** Type 3, epiphyseal reconstruction. **D** Type 4, subarticular reconstruction. **E** Type 5, arthrodesis



A,B,C

D,E

Fig. 9. **A** A 34-year-old woman with parosteal osteosarcoma in the distal femur. **B–D** After tumor excision the defect was shortened, and diaphyseal distraction at another osteotomy combined with intramedullary nailing was performed. **E** EFI was 17 days/cm. Remodeling of the distal femur was completed 8 months after operation

The case of a 34-year-old woman with a parosteal osteosarcoma in the distal femur is shown in Fig. 9. The epiphysis was preserved, and after tumor excision the defect was reconstructed with distraction osteogenesis over an intramedullary nail. A normal knee joint was restored in this case.

High-grade malignant tumors, such as osteosarcoma, Ewing's sarcoma, and malignant fibrous histiocytoma, are usually treated with wide or radical resection accompanied by loss of healthy soft tissue. In most cases chemotherapy is performed pre- and postoperatively, sometimes in conjunction with radiotherapy. The clinical effects of chemotherapy and irradiation on bone formation are still unclear but those of chemotherapy may well be negative. With the support of caffeine-assisted chemotherapy, a maximum amount of healthy soft tissue can be preserved in our series for good bone formation by means of an intentional marginal procedure. In addition, important structures such as the epiphysis and ligaments for joint stability can be preserved.[27]

Up to now, 31 patients have undergone this reconstruction. There were 11 patients with benign, 7 with low-grade, and 13 with high-grade tumors. For the benign tumor group, the mean size of the defect was 5.4 cm, the mean external fixation time was 244 days, and the mean external fixation index (EFI) was 38.8 days/cm. The corresponding values were 6.8, 220, and 34.4 for the low-grade tumor group and 10.1, 318, and 32.9 for the high-grade tumor group. There was no significant difference in the EFIs. Fifteen complications (delayed consolidation, fracture, deep infection, pes equinus, and skin invagination in two patients each and nerve palsy, skin necrosis, deformity, premature consolidation, and fibular subluxation in one patient each) were observed in 31 patients. Eight of these complications were successfully treated with additional surgery, and seven were treated conservatively. At present, it is not possible to avoid complications to some extent during limb-saving tumor surgery no matter what type of reconstructive method is used. However, reconstruction is more likely to be successful with distraction osteogenesis even when complications occur because living bone is easier to handle than dead bone or prostheses.

Distraction osteogenesis is safe and useful for bone reconstruction after tumor resection. The main advantage of distraction osteogenesis is living bone regeneration; the disadvantage is the mental burden and complications resulting from long-term external fixation. The Ilizarov fixator is mainly used for juxtaarticular reconstruction and a unilateral fixator for diaphyseal reconstruction or arthrodesis.[26,28] Epiphyseal preservation and reconstruction by means of distraction osteogenesis can provide excellent outcomes in selected cases, resulting in sturdy reconstruction and reproduction of the native limb. Tumor surgery has changed from amputation to limb-saving surgery and then to joint-saving surgery.[28] Reconstruction involves some difficulties, such as an extensive defect, loss of healthy soft tissue, and the need for chemotherapy. It is easier to manage benign and low-grade tumors because expertise and experience are needed for the treatment of high-grade tumors. For the latter, accurate timing of antibiotic administration, dressing changes, and adjusting the lengthening rate is essential.

Finally, we emphasize that use of the natural limb is always preferable. Joint preservation and bone regeneration by means of distraction osteogenesis constitute a highly conservative limb-saving surgery. The most important consideration for the use of this procedure is the indication. Patients with a defect of less than 15 cm, a large amount of preserved healthy tissue, and a good prognosis are good candidates for this method. Treatment time can be shortened by using intramedullary nailing for patients with a defect of more than 15 cm.

Future prospects

Acceleration of bone formation can be expected to reduce treatment time and make distraction osteogenesis even more attractive. As for biological stimulation, the effects of basic fibroblast growth factor, transforming growth factor-β, bone morphogenetic protein, insulin-like growth factor, bone marrow, stem cells, osteoblasts, and periosteal cells are being investigated.[17,24] The effects of ultrasound and a direct electrical current for physical stimulation are also under investigation.[14,22] Some of these concerns, as well as progress in bioengineering techniques and gene therapy, can be expected to become clinically applicable and useful in the not too distant future.

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