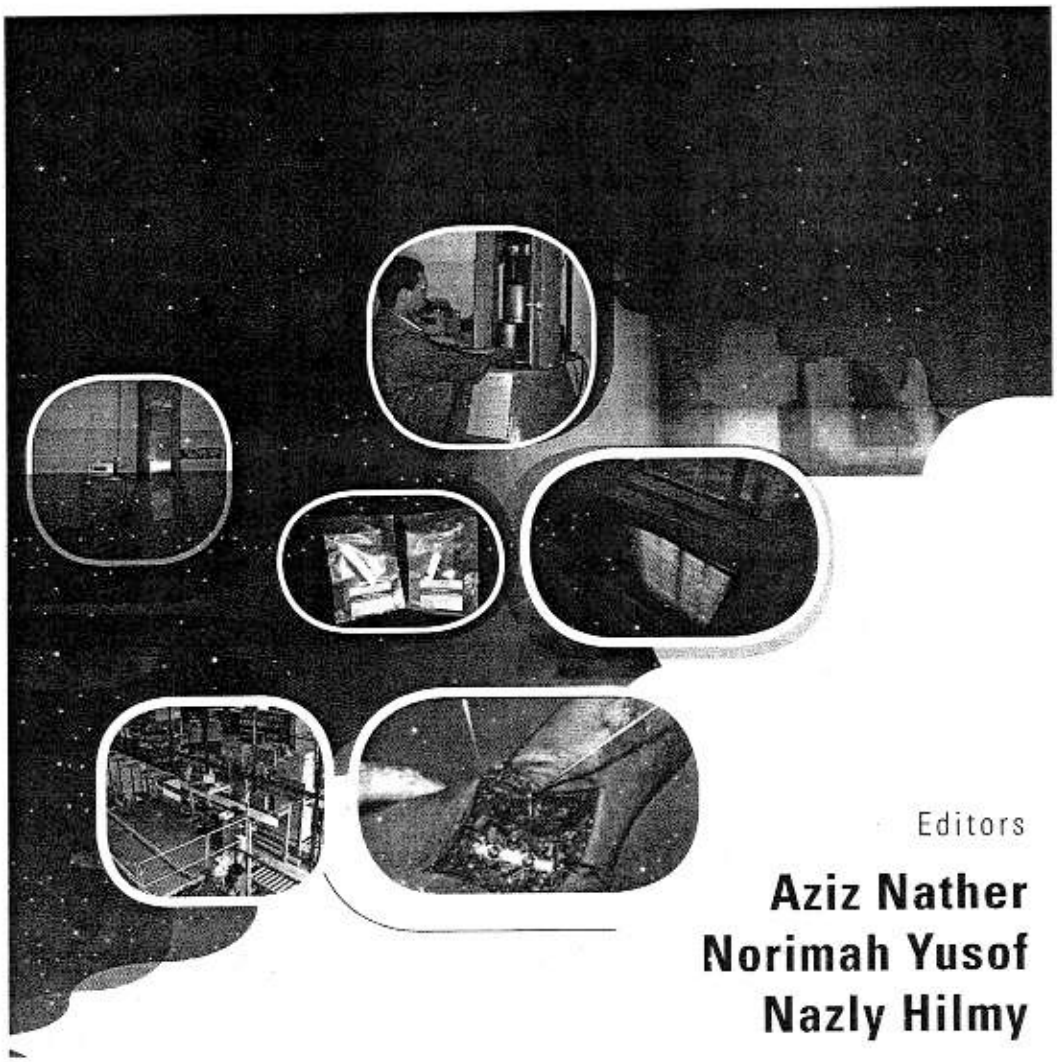

Editors

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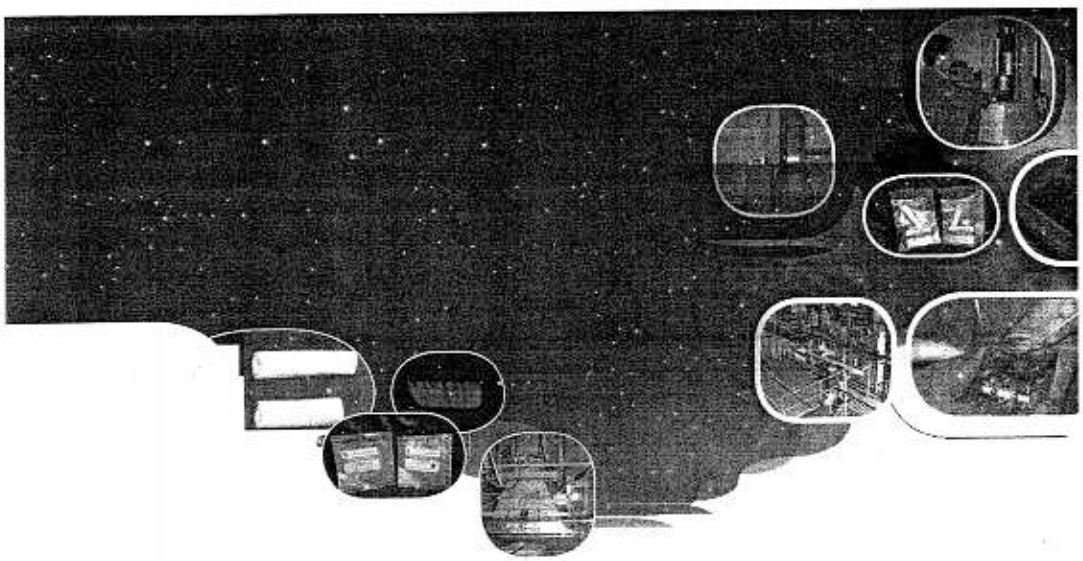
RADIATION IN TISSUE BANKING

Basic Science and Clinical Applications of Irradiated Tissue Allografts



RADIATION IN TISSUE BANKING

Basic Science and Clinical Applications of Irradiated Tissue Allografts

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Foreword from the Chairman of the National Nuclear Energy Agency of Indonesia (BATAN)

First, I would like to congratulate the authors and editors of this book for their excellent work in promoting the application of nuclear technology in tissue banking. I believe that this book will contribute significantly in meeting the need for relevant, qualified applications of irradiated tissue allografts in response to the increasing worldwide demand.

Increasing demands for surgical allografts such as bone, amnion, fascia, tendon, skin, and cardiovascular tissue have to be supported by the increasing quality and safety of these products for safe clinical use. The quality, sterility, and safety aspects of tissue bank products are analogous with the preparation of pharmaceuticals and medical devices in the manufacturing industry. The elimination of disease transmission from donor to recipient, especially the diseases caused by viruses, necessitates thorough donor screening, although (1) viruses at the window period and new emerging viruses may not be detected and (2) several diseases can still be transmitted through transplantation. These phenomena were reported by the Centers for Disease Control and Prevention (CDC) in the USA in 2003. The implementation of a quality system in tissue banking activities and the radiation sterilization of end products have been proven by several researchers around the world to be beneficial in overcoming these problems.

Radiation technology for the sterilization of healthcare products was first utilized in 1956 in the UK and Australia, and has since been followed by other countries such as the USA, Scandinavian countries, and other European countries. At present, more than 200 gamma irradiators of cobalt-60 and about 10 electron beam machines have been installed to sterilize around 40% of disposable healthcare products around the world.

In 1983, an Asia-Pacific regional project on the Radiation Sterilization of Tissue Grafts (RAS/7/003) was established by the International Atomic Energy Agency (IAEA), followed by a program on the Implementation of

Quality Systems in the Radiation Sterilization of Tissue Grafts for safe clinical use (RAS/7/008). Under the IAEA project (INT/6/052), two valuable standards were published: the IAEA International Standards for Tissue Banks (2002), and the IAEA Code of Practice for the Radiation Sterilization of Tissue Allografts (2004). May I take this opportunity to thank the IAEA for its efforts to establish several tissue banks in some countries in the Asia-Pacific region, as well as for carrying out training for potential users of tissue allografts and conducting diploma courses for tissue bankers that complete and enhance tissue banking activities in developing countries.

This book is certainly very useful to support one of the main pillars — the application of isotope and radiation technology — being developed by BATAN to enhance the contribution of nuclear techniques in health. I am confident that this book will also contribute to achieve one of the main millennium development goals, i.e. health, which is of paramount importance especially for countries in the Asia-Pacific region.

Professor Soedyartomo Soentono, MSc, PhD
Chairman
National Nuclear Energy Agency of Indonesia (BATAN)
Jakarta, Indonesia
December 2006

Foreword from the Director-General of the Malaysian Nuclear Agency (NM)

Radiation technology plays a vital role in the healthcare industry, with gamma irradiation used worldwide to sterilize more than 45% of all disposable medical products and devices. The radiation sterilization of tissue allografts — which was promoted by the International Atomic Energy Agency (IAEA) through regional and interregional programs from the 1990s to the early 2000s — highlights the peaceful use of nuclear technology in the health sector. In Malaysia, the Malaysian Nuclear Agency (or Nuclear Malaysia, NM) has played a big role in the establishment of the National Tissue Bank at the University of Science Malaysia and bone banks at several hospitals. NM also assists in radiation-sterilizing allografts processed by these banks as well as those from neighboring countries.

At a regional level, most of the tissue banks in the Asia-Pacific region have chosen gamma irradiation to sterilize their tissues. The supply of radiation-sterilized tissue allografts has met the expectations of end-users and clinicians. However, the sustainability of the supply of quality tissues is very much dependent on the availability of trained manpower to continue with the operation of tissue banks and ensure that the products are clinically safe. The availability of reading materials and textbooks is undoubtedly important in the training of manpower. Therefore, this publication is timely by helping readers keep abreast with the most recent developments in tissue banking. I hope that this book will serve as a useful reference, since it is authored by those who have been actively involved in tissue banking for many years.

May I congratulate the authors and editors for their dedicated effort in publishing this book. I am sure the book will not only be useful for

operators in tissue banking, but will also be a good and handy reference for young clinicians who intend to know more about the potential use of tissue grafts.

Daud Mohamad, PhD
Director-General
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December 2006

Preface

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At present, gamma irradiation has yet to be used in the processing of tissue allografts by all tissue banks. The Massachusetts General Hospital Tissue Bank in Boston — set up in 1990 by the pioneer Dr Henry J. Mankin — is still a surgical tissue bank employing sterile procurement and processing techniques, but not gamma irradiation (Mankin was succeeded by Dr William Tomford). Similarly, in Latin America, the Musculoskeletal Tissue Bank in Latin Hospital, Buenos Aires, Argentina, set up by another famous pioneer Dr Ottolenghi (now run by Dr Musculo), is also a surgical tissue bank. In Europe, the largest tissue bank, the DIZG Tissue Bank, set up by Dr von Versen, employs only chemical processing and does not use radiation.

In Singapore, Dr Nather started a surgical tissue bank at the National University Hospital (NUH) in 1988, and converted to using radiation in 1992 upon joining the International Atomic Energy Agency (IAEA) Program RAS 7/008: "Radiation Sterilization of Tissue Grafts". In the Asia-Pacific region, several tissue banks (e.g. in Korea and Japan) started likewise as surgical tissue banks, but were required to employ radiation as the end-processing sterilization step upon joining RAS 7/008. There is no doubt that the IAEA Program on Tissue Banking RAS 7/008 (1985–2004) has promoted the use of gamma irradiation in the Asia-Pacific region, and that its corresponding program in Latin America (ARCAL) has promoted the use of irradiation in Latin American tissue banks.

Today, the benefits of gamma irradiation are well recognized. There is now a move in the USA to use gamma irradiation; no tissue bank in the

USA has ever used irradiation before. In Australia, the Therapeutic Goods Administration Act lists gamma irradiation as compulsory. A move is being made from the traditional 25 kiloGrays (kGy) used for gamma irradiation to 15 kGy — a step that is made possible by the use of clean processing room facilities to reduce the bioburden of the tissues being processed.

Because of the many incidences of disease transmission (especially in the USA, a country that does not use gamma irradiation) and because of the growing professional awareness of the many benefits of gamma irradiation (including the fact that radiation guarantees product sterility, something a surgical tissue bank can never do), radiation is now becoming a necessity in the processing of tissue grafts. As the standards for tissue banking by the American Association of Tissue Banks (AATB), European Association of Tissue Banks (EATB), Asia Pacific Association of Surgical Tissue Banks (APASTB), Australian Tissue Bank Forum (ATBF), and Latin American Association of Tissue Banks (ALABAT) are continually being renewed and upgraded, radiation is expected to constitute an integral part of the standards in all regions in the near future.

This book addresses the controversies surrounding gamma irradiation and its role in tissue banking. The dosage required to be delivered to the tissues is itself an enigma. Why is 25 kGy advocated? What is the evidence for such a dose? Why does Dr Dziedzic-Goclowska, an eminent radiation biologist at the Central Tissue Bank, Warsaw, Poland, advocate the use of 35 kGy? Australia — a country with the best regulations as well as compulsory auditing and licensing — is now seeking to implement a much lower dose of 15 kGy. How is this possible? With 15 kGy, could we not now also irradiate soft tissues? Until today, soft tissues have never been irradiated for fear that the dose of 25 kGy is too large and could weaken the collagen structure of tendons and ligaments. These and many more issues important to transplantation surgeons and tissue bankers alike will be discussed in detail in this book.

The book begins in Part I with a description of the many types of terminal sterilization that can be used for the processing of tissue grafts, and then sets the stage for why gamma irradiation is the preferred method.

Part II deals with some of the basic issues in tissue banking. These include the developmental history of tissue banking in the Asia-Pacific region; ethical, religious, legal, and cultural issues relating to tissue donors in Asia-Pacific countries; the requirements of setting up a tissue bank; and the

training requirements needed for all tissue bank operators to provide good-quality control of tissue allografts for safe tissue transplantation practice.

Part III deals with the core issues of the basic science of radiation. How do tissues react to radiation, and what are the different types of radiation and irradiation facilities available? The radiation killing effects on bacteria and fungi are discussed. The effects of gamma irradiation on new emerging infectious diseases caused by viruses and prions, as well as on the biomechanical properties of bone and amnion, are also included.

Part IV deals with the processing and quality control of radiation. It covers dosimetry, requirements for process qualification, validation of the radiation dose delivered, and the importance of bioburden estimation. It discusses in great depth the various validation methods for the processing of freeze-dried bone grafts, amnion grafts, and femoral heads. It also includes dose setting and validation according to the IAEA Code of Practice (2004), as well as a quality system for the radiation sterilization of tissue grafts.

The clinical applications of irradiated bone grafts are described in Part V, and the applications of irradiated amnion grafts in Part VI.

This book includes three valuable sources of information in the Appendices: the Asia-Pacific Association of Surgical Tissue Banks (APASTB) Standards for Tissue Banking (January 2007), the IAEA Code of Practice for the Radiation Sterilization of Tissue Allografts (2004), and the IAEA Public Awareness Strategies for Tissue Banks (August 2002). The last appendix is particularly useful for tissue banks with a shortage of donors, as it provides a good guide on how to run public awareness campaigns.

This book is unique and very useful, as it provides a one-stop forum for tissue bankers who procure and process the grafts, radiation scientists who irradiate the grafts as the final processing step, and transplantation surgeons who use the irradiated products to learn about the latest developments in this multidisciplinary field of tissue banking and transplantation. The book is also a useful text for all tissue bankers, radiation scientists, and surgeons undergoing training in this field. This is especially so for participants of the National University of Singapore (NUS) distance learning Diploma Course in Tissue Banking, which is run by the IAEA/NUS International Training Centre in Singapore for the Asia-Pacific region, Latin America, Africa, and Europe; and also for participants of national training courses run by countries such as Korea.

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Chapter 22

Use of Freeze-Dried Irradiated Bones in Orthopedic Surgery

Ferdiansyah

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Introduction

The development of tissue banks in Indonesia began in around 1990. In 1986, the National Nuclear Energy Agency (BATAN) set up the country's first tissue bank in Jakarta, BATAN Research Tissue Bank (BRTB), and carried out research on the preservation of fresh amnion or fetal membranes by lyophilization and then by sterilization via gamma irradiation. In 1992, Dr Soetomo General Hospital, Surabaya, set up a bone bank producing frozen bones sterilized by ethylene oxide. In 2000, it was renamed the Biomaterial Center – "Dr Soetomo" Tissue Bank and started producing a variety of radiation-sterilized tissues, including fresh-frozen and freeze-dried bone, fresh-frozen and freeze-dried amniotic membrane, fresh-frozen and freeze-dried tendon, and fresh-frozen and freeze-dried fascia. There are currently five tissue banks in Indonesia: Dr Jamil Hospital, Padang; Sitanala Leprosy Hospital, Tangerang; Prof Dr Soeharso Orthopaedic Hospital, Solo; Dr Soetomo Tissue Bank; and BRTB.

Bone tissues can be sourced from both cadaveric and living donors. However, cadaveric donors are still limited in number because of cultural, religious, and ethical problems. Although the Indonesian Council of Ulamas

(MUI) issued guidance or fatwa on the recovery and transplantation of tissues, problems in obtaining donors still exist. The Biomaterial Center – "Dr Soetomo" Tissue Bank is developing a donation system for obtaining tissues; at present, it has secured donor candidates. Living donors are still the main source of bones, usually from orthopedic surgical procedures (head of femur bone from osteotomization) and primary traumatic amputations of the limb.

Before tissue banks were set up in Indonesia, orthopedic surgeons used commercial allograft or bone substitute products; unfortunately, the price was too high for most Indonesian people. This condition became a challenge for orthopedic surgeons and other scientists to develop tissue banks in Indonesia. However, following the development of tissue banks and campaigns by tissue bankers, the demand for both fresh-frozen and freeze-dried allografts has been high in recent years.

Procurement, Processing, and Radiation Sterilization

Procurement and processing

Bone from a living donor is taken from the hospital after the patient has signed the consent form and been screened (medical history, physical examination, and laboratory tests) by tissue bank staff. At the Dr Soetomo Tissue Bank, cadaveric bones are procured in sterile condition in the surgical room of the Forensic Department by tissue bank staff, and are then placed in a quarantine freezer in the tissue bank while waiting for the screening (laboratory) results.

Freeze-drying or lyophilization is the process of removing water from frozen samples via sublimation, i.e. the conversion of substances such as water from solid (crystalline) state to vapor state. The objective of freeze-drying is to obtain a chemically stable product at room temperature and to preserve the properties of the tissue, so that the tissue can be kept easily at room temperature and then distributed to the user after being sterilized. The freeze-drying procedure is usually divided into three stages: freezing of the tissue, primary drying by sublimation of the ice, and finally secondary drying by application of heat (IAEA/NUS 1997). The final product must not have a residual moisture content more than 7% of the dry weight. The method to determine the residual moisture is by gravimetry: after freeze-drying, the dried tissue is weighed daily on an analytical balance at 70°C until no further changes in weight are detected.

Packaging is done by wrapping the product in three layers of polyethylene plastic film in a laminar outflow cabinet and then sealing it in a vacuum sealer machine.

Radiation sterilization

At the BRTB, all freeze-dried tissue products (including bone grafts) are sterilized with gamma ray radiation using a radiation sterilization dose of 25 kGy (2.5 Mrad).

Properties of Freeze-Dried Bone

Biomechanical properties

Freeze-dried bone grafts are weaker than deep-frozen grafts. A comparison of the compression strength of freeze-dried gamma-irradiated dowel grafts from the iliac crest with identical dowel grafts obtained from fresh cadavers after reconstitution with normal saline showed that the compression strength of the former was only 50% of normal strength after 5 min of reconstitution and only 20% of normal strength after 8 min (Nather *et al.* 1987). Other research showed that the compressive strength of the bone is not modified after being freeze-dried (Bright and Burchardt 1983; Pelker *et al.* 1983), but freeze-dried cortical bone produces a significant deleterious reduction in the torsional strength of the long bone (Pelker *et al.* 1983) and in bending (Triantaphyllou *et al.* 1975). The combination of freeze-drying and irradiation causes an even more pronounced effect for compression, bending, and torsional strength, with the decrease varying from 10% to 70% (Komender 1976; Bright and Burchardt 1983; Pelker *et al.* 1983; Triantaphyllou *et al.* 1975). Consequently, freeze-dried bone grafts are rarely used as structural bone grafts; instead, they are mostly used as morselized bones to pack the cavities or gaps in the bone.

Biological properties

The biology of bone grafts and their substitutes can be appreciated from an understanding of the bone formation process as follows:

- Osteogenesis — the cellular elements within a donor graft that enable transplant survival and synthesization of the new bone at the recipient site.

- Osteoinduction — new bone realized through the active recruitment of host mesenchymal stem cells from the surrounding tissue that differentiate into bone-forming osteoblasts. This process is facilitated by the presence of growth factors within the graft, principally bone morphogenetic proteins (BMPs).
- Osteoconduction — the facilitation of blood-vessel incursion and new-bone formation into a defined passive trellis structure.

Freeze-dried bone grafts have osteoinductive, but not osteoconductive, properties. On the other hand, demineralized bone grafts have both osteoinductive and osteoconductive properties (Urist 1994; IAEA/NUS 1997; Delloye 1999; Strong and MacKenzie 1993; Reddi 2001; Yim 1999).

The sources of antigen in bone include noncellular antigens of the extracellular matrix (e.g. collagen together with noncollagenous proteins) as well as cells expressing the major histocompatibility antigens. The primary cause of the host immune response in bone allograft transplantation is the bone marrow cells, especially leukocytes. The reduction or removal of such cells by processing, freezing, freeze-drying, or irradiation reduces these cellular elements and thus lowers the likelihood of an immune response (IAEA/NUS 1997; Strong and MacKenzie 1993).

The comparative properties of bone grafts are shown in Table 1.

Table 1. Comparative properties of bone grafts (AAOS 2002).

Bone graft	Structural strength	Osteoconduction	Osteoinduction	Osteogenesis
Autograft				
• Cancellous	No	+++	+++	+++
• Cortical	+++	++	++	++
Cancellous allograft				
• Frozen	No	++	+	No
• Freeze-dried	No	++	+	No
Cortical allograft				
• Frozen	+++	+	No	No
• Freeze-dried	+	+	No	No
Demineralized freeze-dried allograft	No	+	++	No

Types of bone grafts

There are many types of bone products produced by tissue banks in Indonesia to fulfill the demand from surgeons. These include the following:

1. Human bone
   (a) Freeze-dried tissue
      i. Calvarial bone (bicortical)
      ii. Costae
      iii. Ilium (tricortical and bicortical)
      iv. Cortical strut graft (fibula and costae)
      v. Cortical chip
      vi. Cancellous chip
      vii. Bone powder
   (b) Demineralized tissue
      i. Cortical chip and powder
      ii. Cancellous chip and powder
2. Bovine bone
   (a) Cancellous chip
   (b) Bone powder
   (c) Eyeball

Clinical Application

Several indications for using freeze-dried bone allografts are to promote nonunion healing, promote spinal fusion, fill cavities after curettage of benign bone tumors, etc.

In tumor surgery, after curettage or resection of benign bone tumors (e.g. enchondroma, giant cell tumor, aneurysmal bone cyst, osteoblastoma, fibrous dysplasia, nonossifying fibroma), reconstruction can be done with freeze-dried bone allografts. In this case, allografts are mainly used to fill up cavities and maintain structural support (Gitelis and McDonald 1998; Wilkins 2002).

The Biomaterial Center – "Dr Soetomo" Tissue Bank serves about 42 hospitals in Indonesia (Fig. 1). Like other tissue banks in Indonesia, the center faces problems in donor supply, and so it also produces freeze-dried bovine bones as a bone substitute. The production of freeze-dried bovine

Fig. 1. Freeze-dried allografts packed with three layers of polyethylene plastic and sterilized by gamma ray irradiation at 25 kGy (Biomaterial Center, Dr Soetomo General Hospital, Surabaya, Indonesia).

bones is greater than that of freeze-dried human bones. The distribution of freeze-dried bone grafts for clinical application at Dr Soetomo General Hospital from 2002 to 2005 is shown in Table 2.

To achieve optimum results in bone tumor management, the window for curettage should be as large as possible so that the surgeon can see the full cavity. After removing the tumor tissue from the bone, intraoperative

Table 2. Distribution of freeze-dried human bone grafts for clinical application at Dr Soetomo General Hospital from 2002 to 2005.

	Cases	No. of cases
Benign bone tumors	Giant cell tumor	15
	Aneurysmal bone cyst	7
	Osteoblastoma	3
	Simple bone cyst	4
	Fibrous dysplasia	3
Trauma	Bone graft in fracture	67
	Delayed healing/Nonunion	29
Spinal fusion		4
Wedge osteotomy (valgus/varus) around knee		11
Total		143

adjuvant therapy — e.g. hydrogen peroxide (H_2O_2), phenol, liquid nitrogen, or thermal treatment — is needed to eliminate the rest of the tumor tissue. Then, the freeze-dried bone allograft is ready to be packed into the cavities (Figs. 2 and 3).

In spine surgery, the main purpose of freeze-dried bone allografts is to achieve a bony fusion between segments of vertebra. The indications include scoliosis, trauma, degenerative disease, and tumor. Spinal fusion can be performed with or without instrumentation (Fig. 4).

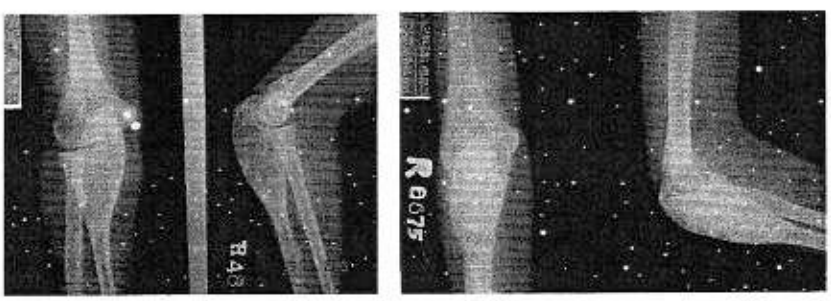

Fig. 2. X-rays of a 15-year-old boy suffering from osteoblastoma who underwent curettage and had the cavities packed with freeze-dried bone allografts. Left: preoperative X-ray; right: X-ray 1 year after curettage and bone graft surgery.

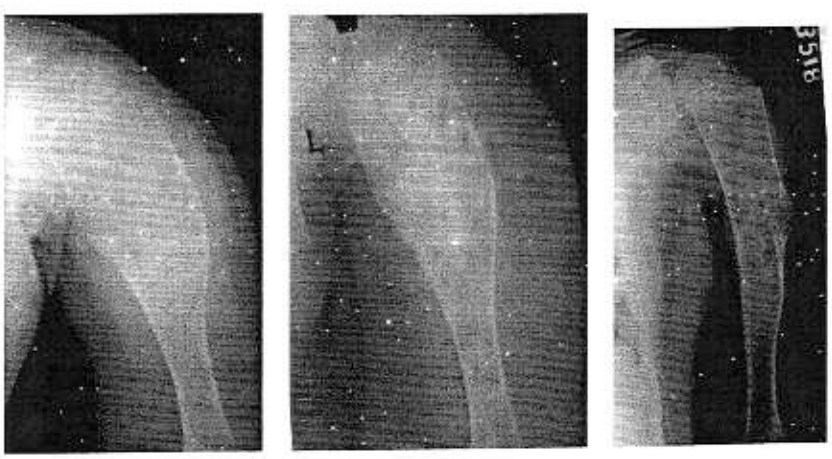

Fig. 3. X-rays of an 8-year-old boy suffering from simple bone cyst who underwent curettage and had the cavities packed with freeze-dried bone allografts. Left: preoperative X-ray; middle: immediate postoperative X-ray; right: 2-year postoperative X-ray.

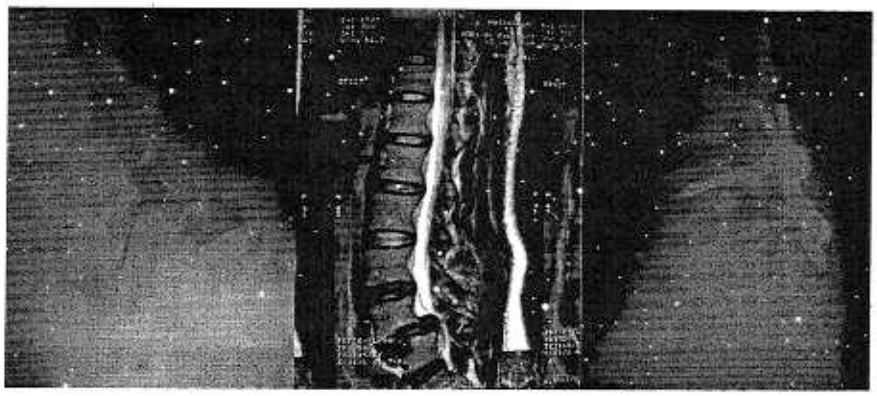

Fig. 4. X-rays of a 50-year-old woman suffering from canal stenosis (caused by spondylolisthesis vertebrae L5–S1) who underwent decompression, posterior stabilization, posterolateral fusion *in situ*, and then bone grafting with a mix of freeze-dried allograft and autograft from ilium.

Freeze-dried bone allografts can also be used for hip and knee surgery, nonunion, fractures, congenital anomaly, as well as oral maxillofacial and plastic reconstructive surgery (Figs. 5–7).

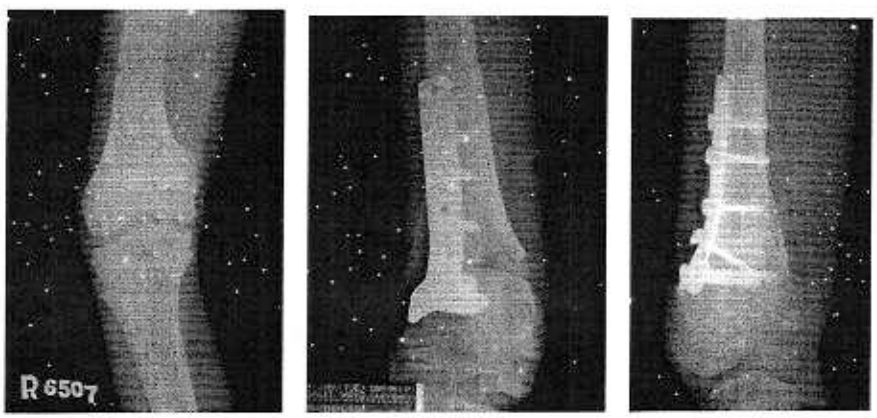

Fig. 5. X-rays of a 12-year-old boy suffering from varus deformity in his right knee (caused by disturbance of medial epiphyseal growth plate of distal right femur) who underwent valgus osteotomy of distal femur and then had freeze-dried bone allograft packed into the open wedge of the bone. Left: preoperative X-ray; middle: X-ray immediately after surgery; right: X-ray 6 months after surgery.

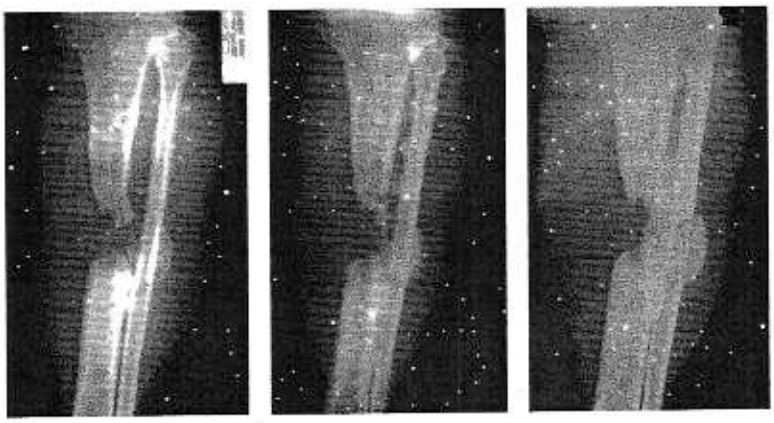

Fig. 6. X-rays of a 32-year-old man suffering from open fracture grade 3 and loose bone who underwent debridement and external fixation. After the infection subsided, he was given central bone grafting with a mix of freeze-dried bone and autograft from ilium. Left: preoperative X-ray; middle: X-ray 3 months after surgery; right: X-ray 8 months after surgery.

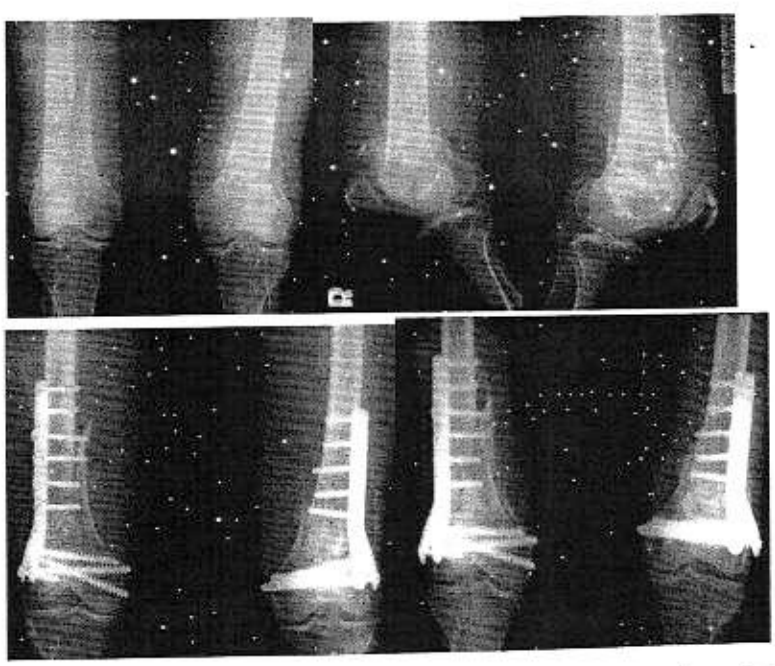

Fig. 7. X-rays of a 75-year-old woman suffering from pathologic fracture (porotic bone) of both supracondylar femurs with underlying thalassemia disease who underwent internal fixation and freeze-dried bone grafting. Top row: preoperative X-rays; below left: immediate postoperative X-ray; below right: X-ray 6 months after surgery.

Conclusion

The success rate of the application of freeze-dried allografts depends on several factors. In the author's experience, the application of freeze-dried allografts after curettage of benign bone tumors gives a satisfactory result. However, there are (sometimes recurrent) problems in applications on aggressive bone tumors such as giant cell tumor and aneurysmal bone cyst.

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