Chapter 1
History of Surgery for Limb Bone Tumors

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Abstract In this chapter, we take a look at the long history of developments in the treatments of bone tumors. Early in the twentieth century, only certain small, localized cancers that could be removed by surgery were curable. Then came radiation, which was used after surgery to control the growth of small tumors that could not be widely removed. The introduction of neoadjuvant and preoperative (induction) chemotherapy was the next big step forward. For some patients it was possible to combine treatments: adjuvant multi-agent chemotherapy, limb-salvage surgery and radiotherapy. Meanwhile, the development of new imaging techniques permitted better diagnosis and assessment of disease. As diagnostic and therapeutic techniques improve, patients with musculoskeletal sarcomas can expect increased survival, decreased complications and side effects, and an improved quality of life.

Keywords Bone tumors • Chemotherapy • Radiotherapy • Limb salvage – surgery

1.1 Introduction

The history of tumor treatment is a long story. Tumors were recognized back in the times of Hippocrates, who adopted the terms “carcinos” and “carcinoma”, based on the Greek word for a crab. Later, the Roman physician Celsus translated the term into “cancer”, and Galen used the word “oncos” (swelling, in Greek) to describe tumors. We can distinguish different phases of this history on the basis of discoveries and the introduction of new technologies. Early in the twentieth century, only small, localized cancers that could be removed by surgery were curable. At a second stage, radiation was used after surgery to control small tumor growths that could not be surgically removed. A big step then came with the introduction of chemotherapy

In memoriam of José Cañadell (1923–2014), a master and pioneer in the treatment of malignant bone tumors.

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agents; standard current treatment consists of multiagent therapy, with both neoadjuvant, preoperative or induction chemotherapy, and adjuvant chemotherapies associated with surgery and radiotherapy in some cases. The parallel development of new imaging techniques permitted better diagnosis and assessment of the disease.

The overall incidence of osteosarcoma is 1.5–2.5 per million persons per year, while for chondrosarcoma it is 1–1.2 per million per year, and for Ewing sarcoma 0.5–1 per million per year. For this reason, centers have been established that specialize in the interdisciplinary treatment of bone tumors, and research often involves multidisciplinary and multicenter studies. Large cooperative groups have successfully completed international clinical trials. The Vienna Bone Tumor Registry was founded in 1962 [167], while randomized protocols have been developed on the basis of the Cooperative Osteosarcoma Study COSS [6, 210] and the Cooperative Ewing Sarcoma Study CESS [102], or the Scandinavian Sarcoma Group (SSG), the European Osteosarcoma Intergroup (EOI) and the Children's Oncology Group (COG) in the USA [195].

1.1.1 Histological Classification

The nineteenth century saw the birth of scientific oncology, with the advent of the modern microscope and new histological techniques. Rudolf Virchow, the founder of cellular pathology, provided the scientific basis for modern cancer study, correlating microscopic pathology with disease. He analyzed the tissues that were resected during surgery and laid the foundations for modern practice, in which the pathologist has an essential role in determining both the diagnosis and the prognosis of cancerous disease. The first screening test for diagnosing tumors was that developed by George Papanicolau in 1923 for the early diagnosis of cervical cancer.

James Ewing (1866–1943) was the first person to describe the sarcoma which bears his name, a primary malignant bone tumor. He initially reported the sarcoma as a "bone endothelioma", in the belief that it derived from the blood vessels in the bone, but he later reclassified it as an "endothelial myeloma". He also described Ewing sarcoma of the soft tissues. He was the first professor of pathologic anatomy at Cornell University. In 1906, Ewing and his team published their findings about lymph sarcoma in dogs, showing how the disease could be transmitted from one animal to another during coitus. He was a co-founder, in 1907, of the American Association for the Control of Cancer. In 1913, he began to work in collaboration with James Douglas, an engineer interested in the therapeutic potential of radium. Ewing was the first Director of Research and President of the Medical Board of the General Memorial Hospital which would later become known as the Memorial Sloan Kettering Cancer Center, in New York. Under his leadership this center developed a new approach to treating cancer. His photograph was featured on the front cover of Time magazine in 1931, with the caption "Cancer Man Ewing" [93].

Another leading figure in the history of treatment for bone tumors was William Fischer Enneking (1926–2014) to whose team we owe much of our knowledge

about the natural history of orthopedic tumors. Whilst a doctor at the University of Florida, he started work with Howard Hatcher, a specialist interested in diagnosing and treating musculo-skeletal tumors and diseases. In the surgical field, he performed one of the first limb salvage operations and developed a course in musculoskeletal pathology. Enneking studied many whole-mount surgical specimens and was thereby able to determine the natural progression of bone tumors, which led to improved surgical procedures with better oncologic outcomes. High-grade sarcomas progress in a centripetal fashion. Bone sarcomas start either within the medullary space or near the surface of the bone. Surface tumors can be either periosteal or parosteal, originating from either the periosteum or the bone surface.

As malignant tumors progress, they do not respect natural barriers. They have a tendency to destroy the medullary cancellous bone and may extend up the medullary space involving marrow and generating apparent skip lesions [64]. During the process of tumor progression, the tumor outgrows its blood supply and spontaneous necrosis occurs. Such necrosis reflects aggressive tumor behavior, and it is important to note that it should not be confused with the necrosis that occurs as a chemotherapeutic response. The American Joint Committee on Staging End Results Classification System and their tumor Grades I, II or III are based on the number of mitoses per high-powered field [63, 66, 166]. The extent of necrosis is graded to the percentage of residual viable tumor [93, 94]. Wunden et al. [213] found that chemotherapy-induced tumor necrosis is also the most important indicator of event-free survival for patients who have had operative treatment of Ewing sarcoma. Spontaneous necrosis is slight in untreated bone tumors and rarely exceeds 25 % in osteosarcomas [167] and 20 % in Ewing sarcomas [51].

Progressively a malignant tumor grows within the medullary space, and the cortex is ultimately destroyed, frequently leading to soft tissue extension. An osteosarcoma or Ewing sarcoma involving the distal part of the long bones will initially respect the cartilaginous barriers, growth plate or articular cartilage; later, however, penetration through these structures occurs [184].

Enneking et al. [62, 63, 66] defined surgical margins by developing staging systems for both benign and malignant tumors. When the host is unable to contain a bone sarcoma, an inflammatory and vascular zone – typically an infiltrative margin and a pseudocapsule, that is, a zone that is contaminated by microscopic islands of tumor – develops in the margin between the normal tissue and tumor. Margins should be wide according to Enneking's definition, meaning that both the tumor and the biopsy scar surrounded by an unviolated cuff of healthy tissue must be removed en bloc [34, 62, 125, 148], marginal resections should be avoided, and intralesional or piecemeal surgery is clearly not sufficient. In addition, Enneking et al. [62–64, 66] formulated a means of classifying surgical procedures on the basis of the surgical plane of dissection in relation to the tumor and the method of accomplishing the removal, and gave surgeons a common language to distinguish between intralesional, marginal, intracompartmental or radical (extracompartmental) procedures.

In most cases where the osteosarcoma appears to be localized, tumor cells have already been disseminated without clinical or radiological manifestations [128, 153, 187, 193, 197]. Bone sarcomas can metastasize, and 80 % of osteosarcomas have

either micrometastatic or macrometastatic disease at the time of presentation [120], while about 20 % of patients with Ewing sarcoma present with clinically apparent primary metastases [147] and the bone itself is a potential metastatic site. This explains the high local failure rate: between 5 and 25 % [50, 59, 132, 180], when there is known microscopic tumor spread. Metastases confined to the lungs and or pleural space have been associated with a fair outcome, while involvement of bone or bone marrow is reported to imply an intermediate prognosis.

Until nearly the end of the twentieth century, diagnosing cancer often required exploratory surgery and pathological analysis of the resected tissue. Biopsy of musculoskeletal lesions should be carefully planned and performed after radiographic staging studies are completed [164]. Bone and soft tissue biopsy is challenging; core needle biopsy appears to be more accurate than fine needle aspiration, and incisional biopsy appears to be more accurate than either of these techniques. The advantages of a percutaneous technique compared with an incisional one are the low risk of contamination and the minimally invasive nature. However, if the result of a percutaneous biopsy is nondiagnostic, a small incisional biopsy should be performed. Incorporation of ultrasonography or computed tomography for guidance is easy and safe and can be useful for increasing the accuracy of the biopsy [196].

1.1.2 The Support of the Image Diagnosis

During the late 1970s and the 1980s, limb salvage surgery became a very popular technique. This was the result of several advances, one of the most important being that the imaging of bone and soft-tissue tumors improved as a result of the use of computed tomography (CT) scans, radioisotope scans, and magnetic resonance imaging (MRI). Tumors could be visualized precisely, and this allowed for adequate removal. Imaging tests such as ultrasound (sonography), computed tomography (CT scans), magnetic resonance imaging (MRI scans), and positron emission tomography (PET scans) have replaced many exploratory surgical procedures. CT scans and ultrasound can also be used to guide biopsy needles into tumors. With the use of CT and MRI, it is possible to evaluate the bone tumor size more precisely. The surgeon can then plan the resection preoperatively and decrease the need for removal of extensive amounts of normal tissue. In this way, by reducing the amount of normal tissue resected, functional outcomes are improving without sacrificing acceptable oncologic results.

Ernest Amory Codman (1869–1940) described, originally in the context of osteosarcoma, the eponymous triangular area that appears on radiographic images at the point where the periosteum, raised by a bone tumor, joins the bone cortex. A graduate of Harvard Medical School, Codman was a close friend of the neurosurgeon Harvey Cushing. After traveling around Europe and working in Vienna with Eduard Albert, he devoted his final year of training at the Massachusetts General Hospital, in Boston, to the use of the recently described Röntgen rays. He worked as a radiologist (“skiagrapher”) at the Boston Children’s Hospital, and in 1911 he

opened his own hospital, the Codman Hospital. He collected 148 cases of bone sarcoma which enabled him to establish 25 clinical, radiographic and histological criteria to define this kind of tumor. He was a pioneer in many areas of medicine, wrote the first atlas of normal skeletal radiography, the first articles on repair of the rotator cuff in the shoulder and the first book on shoulder pathology, but he is perhaps best remembered for his studies on the clinical and radiographic diagnosis of osteosarcoma and his pioneering evidence-based medical work. He created the first cancer register in the USA and was the first to describe the chondroblastoma: a primary tumor of cartilaginous origin which is known as Codman's tumor [22, 42].

Of imaging techniques, computed tomography (CT) has an important role in the local and extraskeletal staging of a bone tumor and in detecting pulmonary metastases. Magnetic resonance imaging (MRI) precisely outlines both the extra- and intraosseous extension of a tumor and reveals possible skip metastases. MRI has been proposed and tried as a non-invasive method for assessing the response of Ewing sarcoma to preoperative chemotherapy, but the changes identified by static imaging, with or without gadolinium enhancement, are not useful for determining the tumor response [70, 80, 90, 213]. MRI has been found to overestimate the extent of residual disease [213]. Later dynamic and angiographic MRI techniques may provide a more accurate estimate of the extent of tumor necrosis following chemotherapy [68, 113, 202]. Scintigraphy and dynamic contrast-enhanced MR images are useful in objective presurgical prediction of tumor response and regression to preoperative chemotherapy. Early detection of local recurrences and metastases is a further advantage of MRI and also of dynamic positron emission tomography (PET) with its high sensitivity.

1.2 The Hard Way of Radiotherapy

In 1896, the German physicist Wilhelm Conrad Röntgen presented his historic lecture entitled "*On a New Kind of Rays*". Röntgen named the ray the "X-ray", with "x" being the algebraic symbol for an unknown quantity. In 1901, his work was to earn him the first Nobel Prize ever awarded in physics. Within months, systems were being devised to use X-rays for diagnosis, and within 3 years radiation was being applied to treat cancer. Like X-rays, radium emits ionizing radiation, but of a shorter wavelength. Marie Curie, through the Curie Institute in Paris, publicized the potential of radium for treating and curing cancer. The public confused the two sources of radioactivity for a long time, since both are used medically. Radiation therapy began with radium and with relatively low-voltage diagnostic machines. A major breakthrough took place when it was discovered that daily doses of radiation over several weeks greatly improved the patient's chance of being cured. But at the same time it was discovered that radiation could cause cancer as well as cure it. Radium's reputation as a quasi-miracle elixir was promoted in the 1920s with an enthusiasm that is hard to recapture in the knowledge of the damage it inflicted on so many who worked with it, including Marie Curie herself. Many early radiologists

used the skin of their arms to test the strength of radiation from their radiotherapy machines, looking for a dose that would produce a "pink reaction" – an erythema – which looked like sunburn. They called this the "erythema dose," and this was considered an estimate of the proper daily fraction of radiation. It is no surprise that many of them developed leukemia from regularly exposing themselves to radiation.

The more rapid cell turnover is, the greater the effect of radiation is [38]. This is what enables postoperative radiation therapy to reduce the incidence of local recurrences of soft tissue sarcomas [138]. One of the main problems with radiotherapy is that ionizing radiation cannot differentiate between normal and pathologic tissue. With regard to bone, the growth plate has relatively high cell turnover, and radiation can decrease or stop bone growth [165].

Radiation therapy is generally used for patients who have refused definitive surgery, require palliation, or have lesions in axial locations. Radiotherapy takes on greater importance in the treatment of tumors of the axial skeleton and facial bones, and is more frequently used in Ewing sarcoma and peripheral primitive neuroectodermal tumors of the bone. In comparison with these, osteosarcoma is not a particularly radiosensitive tumor, although there was a time when the recommended management of this tumor was local radiotherapy to the primary tumor followed by amputation 6 months later, provided that the chest remained clear of metastasis and that the primary tumor remained under control. However, this approach made no difference to survival, though some patients who had developed lung metastases and in whom the primary tumor had remained under control were spared the loss of a limb. Sweetham et al. [193, 194] performed a retrospective survey of the cases of tibial and femoral osteosarcoma treated at major centers in the United Kingdom between 1952 and 1959 to assess the outcome of treatment by surgery and radiotherapy. Radiotherapy followed by amputation produced better results, in terms of survival, than amputation alone. For the largest age group, patients under 20 years, only 22 % survived 5 years. The survival rate of the group treated by radiotherapy alone was lower than that of the group treated by amputation or that of the group treated by a combination of radiotherapy and amputation.

The results of postoperative radiation therapy, described by Suit et al. [189, 190] and Lindberg [119], indicate that it effectively lowers the risk of local recurrence of sarcomas in the distal limb, but as Morton et al. [138] described, such treatment has not been as successful for more proximal lesions of the arm and thigh. Patients treated by operation and radiation therapy alone develop systemic metastases, particularly in the lungs [138]. Eilber et al. [60] reported than pre- and post- operative radiotherapy was highly effective at reducing the high recurrence rate in patients who did not undergo amputation surgery [189]: in patients who were treated with nonamputative excision of all gross tumor and postoperative radiation therapy, the expected local recurrence rate of 30–50 % was reduced to approximately 17 % [76, 189, 190]. A pilot study in 1976 of preoperative chemotherapy and radiation followed by surgical resection indicated that in most patients local tumor control and limb salvage could be accomplished with little morbidity and an even lower local

recurrence rate than 17 % [138]. Definitive local radiation for Ewing sarcoma is recognized as necessary, and such treatment has involved high doses of radiation [25, 67, 88, 104, 213]. Because of problems with high doses, operative treatment has been investigated as an alternative that could allow a reduction in the dose of, or obviate the need for, local radiation therapy.

Intra-operative radiation therapy (IORT) was first established as a treatment modality for locally advanced tumors, and its use in the treatment of osteosarcoma was described by Abe and Yamamuro [1]. IORT minimizes the amount of tissue that is exposed to radiation because normal tissues can be moved out of the way during surgery and shielded, allowing a higher dose of radiation to the tumor. Osteosarcoma is one of the most radioresistant tumors, but IORT uses high-dose single irradiation, and total necrosis of irradiated bone has been confirmed histologically [105, 145, 198]. The radiation can be given directly to the tumor or to the nearby tissues after tumor resection. IORT and brachytherapy are more commonly used in abdominal or pelvic cancers and in cancers that tend to recur, or to treat microscopic residual disease [28, 52].

Advances in radiation physics and computer technology during the last quarter of the twentieth century made it possible to focus radiation more precisely with the techniques of conformal radiation therapy (CRT) and intensity modulated radiation therapy (IMRT), both of which use CT images and computers to establish the location of a tumor on a very precise 3-D map [52]. Other approaches to improvement include the use of chemical modifiers or radiosensitizers, which are substances that make cancer more sensitive to radiation, and the search for substances that may help protect normal cells from radiation.

1.2.1 Immunotherapy

Von Haberer [18] began the quest for "nature's solutions" for cancer, but it was William Coley as a young surgeon at New York Memorial Hospital who, disillusioned with conventional approaches, first tried to stimulate the patient's own immune system as a cancer treatment. Serendipitously, he came across the case of an immigrant patient who presented on his left cheek a sarcoma that had been operated on twice, and which recurred below his left ear. The wound after surgery could not be closed, and the tumor progressed until a final operation was only partially able to remove the tumor. After the last operation the wound became severely infected with *Streptococcus pyogenes* and the patient developed a high fever. Surprisingly after each attack of fever the ulcer improved, the tumor shrank, and finally disappeared completely. Coley found the patient 7 years later in excellent health without any trace of cancer [91]. Coley suspected that the infection was responsable for the cure. He resolved to infect his next ten patients [43, 44]. Bloodgood [18] agreed that Coley's serum with the toxins of *Streptococcus* and *Bacillus prodigiosus* should be employed in all inoperable cases and also before and after the operation in operable sarcoma cases.

Coley's toxins [44] inspired researchers to start experimental immunological studies [157]. The dendritic cell therapy devised by Steinmann in 1973 yielded clinical applications in 1995 [55, 188]. Research continued into ways of treating tumors by boosting the immune system using biological agents, particularly monoclonal antibodies. The first agents of this kind were rituximab (Rituxan) and trastuzumab (Herceptin) for treating lymphomas and breast cancer, but growth factors like gefitinib (Iressa), imatinib (Gleevec) and cetuximab (Erbitux) and angiogenic factors like bevacizumab (Avastin) have also come into use. In the nineteenth century, before hormones were discovered, Thomas Beatson found that rabbit breasts stopped producing milk after ophrectomy and studied the use of this principle for treating breast cancer. His research laid the foundations for the hormone therapy currently used with breast cancer patients, such as tamoxifen and aromatase inhibitors.

1.2.2 The Big Change: Chemotherapy

During World War II, naval personnel who had been exposed to mustard gas were found to have undergone toxic changes in their bone marrow cells. During that same period, the US Army was studying a number of chemicals related to mustard gas to develop more effective agents for war and also develop protective measures. A compound called nitrogen mustard was studied and found to work against lymphoma. This agent was the first of a list of more effective agents, called alkylating agents, which killed rapidly growing cancer cells by damaging their DNA. Sidney Farber, in Boston, demonstrated that aminopterin, which blocked a critical chemical reaction needed for DNA replication**,** produced remissions in children with acute leukemia. Aminopterin was the predecessor of methotrexate, which heralded the era of chemotherapy.

Another major step forward was the discovery of the advantage of using multiple chemotherapy drugs. Doxorubicin, cisplatin, high-dose methotrexate and ifosfamide are considered the most active agents against osteosarcoma, and most successful protocols have been built around combinations of several of these drugs [15].

Metastatic cancer was first cured in 1956 when methotrexate was used to treat a rare tumor called choriocarcinoma. In the 1960s, chemotherapy drugs cured many patients with Hodgkin disease, childhood acute lymphoblastic leukemia and testicular cancer.

Chemotherapy was first introduced for malignant bone tumor treatment on a large scale in the 1970s, and now is the cornerstone treatment for this disease. Adriamycin (doxorubicin) was shown to have some activity [19], but the response rate varied greatly between studies. Gottlieb et al. combined Adriamycin with dacarbazine (DTIC) (ADIC), with DTIC and vincristine (VADIC), and with DTIC and vincristine and cyclophosphamide (CYVADIC), which resulted in a 59 % response rate if bone sarcomas were excluded [150, 151]. The 5-year survival rate

in the historical series presented before 1970 [50, 153, 193] was about 20–25 %; there was little difference between the survival rate of patients treated by immediate primary amputation and those treated by radiotherapy with amputation or those in whom radiotherapy was abandoned when early metastases occurred [27].

In 1976, in an attempt to increase the duration of response and to reduce toxicity, the EORTC Soft Tissue and Bone Sarcoma Group embarked on a randomized study comparing the efficacy of the four-drug CYVADIC combination [150]. Jaffe and Rosen with their co-workers [96, 99, 112, 158, 162], were the first to report satisfactory results in osteosarcomas that responded well to high-dose methotrexate and Adriamycin. With this treatment, the 5-year survival rate increased to 60 % in Ewing sarcoma and to 70–75 % in non-metastatic osteosarcoma, in contrast to 15 % and 20 % respectively, observed in the historical control groups. The first results combining chemotherapy showed an increase in the numbers of patients who remained free from metastases after surgery [45–47, 96, 152, 192]. Postoperative adjuvant therapy with high dose methotrexate and citrovorum rescue and/or Adriamycin reduced the incidence of pulmonary metastases from osteosarcomas [45–47, 96–99, 159–163].

The current standard consists of neoadjuvant and adjuvant chemotherapy. Neoadjuvant chemotherapy was introduced by Rosen et al. [163], and was found to induce necrosis in the primary tumor, facilitate surgical resection and eradicate micrometastases [5, 7, 15]. It has contributed to an improved prognosis in osteogenic sarcoma [44, 45, 96, 97, 99, 152, 159–163, 192] and also in Ewing tumors [12, 48]. Skeletal sarcomas seem to respond to preoperative continuous intra-arterial infusion of Adriamycin [54, 87]. In 1976, Morton et al. [138] showed that the effectiveness of intra-arterial Adriamycin was confirmed by the histologic evidence of tumor necrosis present in post-Adriamycin biopsies. Moreover, intra-arterial Adriamycin, followed by radiation therapy, resulted in dramatic tumor regression. Histologically, the degree of tumor necrosis was up to 88 %, and almost 40 % of the specimens contained no viable tumor cells.

The response to neoadjuvant chemotherapy is an important prognostic factor, and the drugs for adjuvant chemotherapy should be selected on the basis of the degree of tumor necrosis induced by neoadjuvant chemotherapy [10, 16, 102, 133, 148, 149, 160].

Eilber et al. [60] describe preoperative therapy before contamination of tissue planes by any type of surgery. They chose Adriamycin because of the high response rate obtained in bone tumors and also because of its known potential to sensitize the tissues to subsequent radiation therapy. Radiation of a tumor with an intact blood supply before surgical excision could possibly improve the radiation effect at the tumor margins and, therefore, improve the overall local recurrence rate. Campanacci and Laus [30] treated 248 high-grade central bone osteosarcomas by amputation or disarticulation; in 5.2 % the tumor recurred at the amputation site. In the view of Campanacci et al. [29], adjuvant chemotherapy does not have a significant effect on local recurrences, which should be treated by radical operation or, if this is not possible, by irradiation; chemotherapy may be used as an adjuvant. Bleyer et al. [17], in 41 consecutive patients with newly diagnosed osteogenic sarcoma between 1952

and 1977, found that the chemotherapy group had a significant increase in both survival and disease-free survival compared to the historical group who had not received chemotherapy. With adjunct chemotherapy only one of the seven patients had developed pulmonary metastases 9 months after diagnosis.

Today, research is necessary to improve the activity and reduce the side effects of chemotherapy with new drugs and new combinations of drugs. In addition, research is needed into new delivery techniques and novel approaches to targeting drugs more specifically at the cancer cells. Examples include the use of colony-stimulating factors, chemoprotective agents and approaches that reduce drug resistant clones. However, establishing treatment protocols has not been straightforward, and many failures have been reported, although published survival rates are now improving. Giving cisplatin intra-arterially did not improve results [71]. A controlled trial adding granulocyte colony stimulating factor (G-CSF) to doxorubicin and cisplatin, led by the European Osteosarcoma Intergroup, failed to achieve a survival advantage [116]. A French trial suggested that similar results may be obtained with ifosfamide instead of doxorubicin [114], and an American trial suggested that the addition of ifosfamide or liposomal muramyl tripeptide, an immunomodulator, to standard three-drug chemotherapy with doxorubicin, cisplatin, and high-dose methotrexate did not seem to confer any advantages.

1.2.3 Surgery in Malignant Tumors of the Limbs

Oncologic orthopedic surgery was long confined to amputation in order to remove malignant tissue and to avoid recurrence and metastases. However, specialists sought ways to preserve limbs and maintain satisfactory function, and thereby to avoid the psychological and cosmetic problems caused by amputation [5, 79]. Advances in imaging techniques and in biomedical engineering, an understanding of the optimal margins for resection determined by Enneking's tumor staging [62], and the use of chemotherapy, have led to a major shift away from amputation towards limb-salvage surgery [7, 15]. However, it should be noted that Jaffe et al. [97] reported that only 10 % of patients with osteosarcoma were cured exclusively with chemotherapy, and highlighted the significance of surgery in osteosarcoma treatment.

Billroth, in Germany, Handley, in London and Halsted, in Baltimore, were the first tumor surgeons. William Stewart Halsted, professor of surgery in Johns Hopkins, described radical breast amputation for breast cancer at the end of the nineteenth century. The work of such specialists led to "cancer operations" designed to remove the entire tumor along with the lymph nodes in the region where the tumor was located. Stephen Paget, in England, concluded that cancer cells spread by way of the bloodstream to all organs in the body but were able to grow only in a few organs. This understanding of metastasis became a key element in recognizing the limitations of cancer surgery. When anesthesia became available in 1846, surgery advanced so fast that the next 100 years became known as "the century of the

surgeon." During the final decades of the twentieth century, surgeons developed greater technical expertise in minimizing the amounts of normal tissue removed during cancer operations. Less invasive ways of destroying tumors without removing them are being studied, such as cryosurgery [129], which uses liquid nitrogen spray. Lasers can be used to cut through tissue or to vaporize cancers of the cervix, larynx, liver, rectum, skin, and other organs. Radiofrequency ablation transmits radio waves to a small antenna placed in the tumor to kill cancer cells by heating them.

1.2.3.1 Amputation

Amputation was the main, standard therapeutic option for patients with osteosarcoma before the 1970s, when non-amputative surgical procedures such as local excision or even the wider en bloc resection resulted in an unacceptable 60–90 % incidence of local tumor recurrence [21]. The 5-year survival in osteosarcoma in the first half of the twentieth century was less than 20 % [49], and most patients died of lung metastases [127, 128]. Extending the operative field to amputation of the limb one joint above the tumor was adopted, and this reduced the incidence of local recurrence to 5–25 % [50, 60, 69, 132, 146]. Amputation to achieve local tumor control of skeletal and soft tissue sarcomas was based on clinical experience using surgery as the primary treatment modality. Various complications are caused by amputations: wound necrosis, infection, overgrowth of bone in children, neuroma, stump pain and phantom limb pain [5].

Rotationplasty as a functional amputation procedure was first described in 1930 for treating shortening after tuberculous ankylosis of the knee joint [20], and was later popularized by Van Nes [203] for congenital defects of the femur. Rotationplasty was designed for the reconstruction of bone defects around the knee following above-knee amputation. The distal femur with tumor is removed and the distal part of lower leg and ankle are preserved. Then, the tibia and the foot are rotated 180° and attached to the femoral stump. The rotated ankle, at the appropriate height of the contralateral knee, acts as a functional knee joint, so that the patient can function with a below-knee artificial prosthesis [108, 215]. Good long term results were reported for survival, function and cosmetic and social acceptance [83, 89, 108], but the situation is, of course, cosmetically challenging. The technique is also available for tumors of the proximal femur [209] and, in the arm, for primary malignant tumors of the elbow or shoulder [208].

A special type of lower limb tumor is that which affects the pelvis. Hemipelvectomy is the only operation applicable in most malignant tumors of the pelvic girdle, and this is the operation which affords the best chance of curing malignant bone and soft tissue tumors of the upper thigh. The first attempt at hemipelvectomy was by Billroth; according to Ravitch and Wilson [155, 156] this failed attempt was casually reported by Savariaud in 1902 [175] whilst he was reporting his own unsuccessful attempt at hemipelvectomy. In 1895, Girard [77, 78] of Bern performed the first hemipelvectomy with survival of the patient [78]. By the time of his 1902 report, Savariaud was able to find 13 cases in all, one of them carried out by Salistcheff, of

Tomsk, in Russia, in 1900. Only four of these patients had survived the operation. Ransohoff [154], of Cincinnati, in 1909, performed a hemipelvectomy for tuberculosis of the hip, often called the first successful such operation in the USA. He lost "not more than a few ounces of blood" and was given an infusion of salt water. However, his patient died more than a month later of unrelieved sepsis. In the UK, Lee and Alt [115] presented their experience of seven operations, with no deaths. The largest individual experience was that of Sir Gordon Gordon-Taylor [81], with 102 pelvis amputations.

1.2.3.2 Limb Salvage Techniques

Limb-saving procedures in bone tumor patients involve resection of the bony lesion with a wide margin of soft tissue and reconstruction by cadaver allogenic grafts or prostheses [4, 23, 33, 35, 58, 111, 121, 138, 164, 170, 199, 200, 205, 216]. Some authors report attempted reimplantation of the affected bone after extracorporeal treatment, such as soaking in ethanol [191], autoclaving [8, 74], or irradiation [201].

Limb-sparing techniques were first devised during the early 1970s, but were developed in the 1990s for most malignant bone tumors. The modern tools of anesthesiology enable safe limb-saving intervention. These procedures can be offered to patients only when life expectancy is comparable with that of ablative surgery. Treatment results for 925 osteosarcoma patients in a COSS study, and 975 Ewing sarcoma patients in an EICESS study, justify limb-salvage surgery when the correct indications are present; 5-year survival rates are similar to or better than those for amputation [9, 130, 177]. Greenberg et al. [84] and Christ et al. [40], in separate studies, compared the functional and psychological assessment of osteosarcoma survivors treated by amputation and limb sparing. In general, most survivors were in good mental and physical health and the emotional disturbance among these patients was no different from that in the general population. On the other hand, patients with initial amputations had substantial difficulty maintaining an optimal level of limb function.

Early attempts, at the beginning of the twentieth century, at limb salvage in bone tumors were developed in lower leg tumors by Ferdinand Sauerbruch, in Germany [174]. In the same year, the inter-scapulo-thoracic resection of the shoulder girdle was developed by Tikhov in Tomsk, Russia. A similar method was described by Linberg (Smolensk, Russia) in 1928 [118]. Ernest Juvara (1870–1933), a Romanian doctor, developed a technique (which bears the name of Vittorio Putti) for arthrodesis in the treatment of malignant bone tumors, performed by resecting the tumor and performing arthrodesis in the affected joint.

There are two options for knee reconstruction after resection of the upper end of the tibia and lower end of the femur: arthrodesis and arthroplasty. There are several options for reconstruction after limb-sparing tumor resections in the limbs, and the choice is conditioned by the patient's age (adult or growing child) and the tumor site and size. During the procedure, various techniques may be used, some of which are

temporary and others definitive. Great care must be taken during surgery in order to avoid complications. Some techniques require one operation, while others involve a long process involving many different techniques. The development of these limb-sparing techniques has only been possible subsequent to finding the means to cure patients' diseases. The options for reconstruction after limb-salvage tumor resection include arthrodesis, endoprosthetic replacement, allografts, autografts, rotation-plasty or physeal distraction and bone distraction.

1.2.3.3 Graft Indications in Bone Tumor Surgery

In 1908 Lexer [117] reported his first four clinical bone tumor cases in which he used massive allografts derived from tissue procured from amputation. Methods of bone and cartilage preservation and storage were slowly adapted [26]. Bauer [11], in 1910, showed that bone could be preserved by refrigeration for as long as 3 weeks and then, in dogs, could be transplanted as allografts. At the same time, Kaush [103] established that boiled bone was far inferior to autogeneic bone. Albee and Gallie both used stored bone [3, 72], chilled or boiled, for clinical surgery. A hospital bone bank was organized by Inclan [95] in Havanna, Cuba, in 1942, who procured human bone at operation and preserved it in blood or saline solution at between 2 and 5 °C before implanting it [206]. Duthie [57] established the first bone bank in the UK, in Edinburgh, in 1953, while at the same time Sanchis-Olmos [173] founded the first Spanish tissue bank in Madrid. Merle d'Aubigné established the French equivalent in Hopital Cochin, Paris, in 1955. Three centers reported variable outcomes with the use of allografts for limb salvage following tumor resection: Ottolenghi from Argentina [144], Parrish [145] in the United States, and Volkov [204] in the Soviet Union. The use of allografts increased after a series of reports by Mankin et al. [122–124, 126, 183], and today bone banks have been established around the world in specialized bone tumor centers.

Autografts are performed using vascularized or nonvascularized fibula grafts to fill diaphyseal bone defects after wide tumor resection. The fibula is more suitable for reconstruction of the upper limbs than for that of the lower limbs. The vascularized fibula can be inserted into the allograft, such as the tibia, in order to reinforce its total bone grafting capacity [37]. A previous method for autografting was to remove the bone tumor from the resected bone and then sterilize the bone by autoclaving, irradiation [201] or pasteurization [136] before reimplantation.

Allografts have been used commonly since the 1970s for reconstruction of the remaining bone after limb-sparing tumor resection. Reconstructive options for such large defects include structural allograft transplantation [23, 36, 41, 61, 65, 92, 124, 139, 169, 214], endoprosthetic arthroplasty [14, 23, 85, 86, 134, 142, 200, 212], and composite reconstruction using allografts and metal prostheses [13, 56].

The most important late complications are graft collapse and instability, or osteoarthritis of the joint. Several studies have reported high rates of fracture, non-union, infection, and other major complications that often require removal or revision of

the allograft [53, 60, 61, 65, 75, 92, 126, 139, 172]. The majority of allograft complications occur within the first 2 years of therapy. Mankin et al. [126] reported on delayed union of the graft (32 %), a complication that can be partly explained by long-term chemotherapy, graft fracture (12–20 %) and infection (11 %).

1.2.3.4 Prostheses in Tumor Surgery

In the context of radical excision surgery, there has been development of special segmental bone and joint replacement systems, which are usually referred to as tumor endoprotheses or megaprotheses [79]. The term *megaprosthesis* seems to have been first used in the International Workshop on Design and Application of Tumor Prostheses, held at the Mayo Clinic in 1981. Endoprostheses are frequently considered to be the gold standard treatment after resection of tumors that involve a joint, particularly the knee and hip; but, even with the most modern devices, prosthetic survival without re-operation is still only 60 % at 5 years.

The first noteworthy report – it included a 2-year follow up study – on a metal hip joint was published in 1943 by Austin Moore and Harald Bohlman [135] in the United States. Total femur reconstruction was first described by Buchman [24] in the mid-twentieth century. The first tumor endoprostheses were mostly based on a custom made monoblock of cast steel alloys. There followed various developments in terms of the materials used: titanium and cobalt–chrome–molybdenum alloys; various acrylic polymers were subjected to trials and found to fail as a result of wear and were abandoned.

Prosthesis design has also evolved from a monoblock and fixed hinge model to modular endoprostheses and rotating platforms, with improved geometry to enhance fixation and stability [39, 178, 179]. Modular endoprostheses, which are currently standard and have predominated in surgical practice since 1980, consist of a number of different components in readily available sets. Various combinations of components can be assembled in the operating room in order to best address the specific bone defect of the patient.

In the former USSR, the first tumor prosthesis was implanted in 1967 by Sivash and Trapeznikov. By 1972 John Scales [176], in Stanmore, England, was using titanium endoprostheses for massive replacement after tumor surgery. Scales used intramedullary stem fixation with PMMA, and was also the first surgeon to introduce extending prostheses with a growing mechanism. The first custom-made knee prosthesis for tumors was implanted in 1975 in Vienna, followed by a total of 15 cases between 1976 and 1982 with different types of cementless stem fixation with two plates and a fixed hinge [106]. The design was then changed, and from this, in 1982, arose a modular system, which was published as the Kotz modular femur-tibia reconstruction system (KMFTR) [107]. In the United States, in 1977, Ralph Marcove used total femur and total knee replacement in osteosarcoma cases [127]. In Italy, Mario Campanacci published an account of the total resection of the distal femur or proximal tibia for bone tumors in 1979 [33]. Modular ceramic prostheses

for the humerus have been in use since 1972 [168]. More recently, the combination of allograft and prosthetic components (APC) has been advocated as an optional solution [13, 56].

Limb salvage surgery of the proximal tibia is one of the most demanding reconstructions owing to difficulties with soft tissue coverage [100, 181, 182], a high rate of infection (12–36 %) [13, 41, 56, 85, 100, 140], and the need to restore the knee extensor mechanism [14, 23, 85, 124, 139, 142], all of which lead to high failure rates (27–55 %) [41, 56, 92, 211]. As an alternative, the use of proximal tibia osteoarticular allografts after tumor resection may restore bone stock and help reconstruct the extensor mechanism [41, 92, 122, 139].

Relative to the use of allografts, prosthetic reconstruction offers some advantages, such as, maintenance of motion and immediate functional restoration [2, 14, 23, 134, 139, 140, 142, 200, 211]. Although high survival rates have been reported with current modular-type reconstruction [134, 140], the complication rate increases more rapidly with time compared with conventional endoprostheses, which is of great importance considering the young age of most osteo- and Ewing- sarcoma patients. In the large series published by Mittelmayer [134], aseptic loosening (27 %) and infection and fracture (54–54 %) of the implant were the most frequent complications leading to a need for intervention. Deep infection and aseptic loosening are the most frequent causes of failure [82].

For peri-acetabular tumors, Enneking and Dunham [63], Steel [186], Zatsepin [214] and Nilsonne et al. [143] preferred resection of the involved part of the pelvis and a reconstructive procedure in which the femur was put in contact with the remaining part of the pelvis [207]. The aim of the procedure was arthrodesis or prosthesis reconstruction, so that the results would be long-lasting and full weight-bearing would be possible. The disadvantage was, and is, the inevitable discrepancy in leg length, with a less than satisfactory functional and cosmetic result. Johnson [101] described a procedure in which the osseous gap was filled with cement in combination with a total hip replacement.

1.2.3.5 Malignant Bone Tumors in Growing Patients

The metaphysis is the predominant site of malignant bone tumors in children. For many years, when the adjacent metaphysis was involved in a malignant tumor, the physis was resected to obtain complete tumor excision with clear margins. This inevitably resulted in a discrepancy of limb length or dysfunction of the joint [73]. In some cases, preservation of the epiphyseal portion of the bone and the joint surface may be achieved by physeal distraction. However, this applies only to patients in whom the epiphysis is still open [31, 171]. Using Cañadell's technique, the epiphysis of the tumor-bearing bone can be preserved so that the function and growth capability of the involved joint are maintained. The indications for the Cañadell technique are that (1) the tumor should be localized in the metaphysis; (2) the growth plate should be open; and (3) the tumor should not affect the physis,

which should be confirmed by radiography, arteriography, CT or MRI preoperatively and pathological analysis of the resection after the operation [31]. MRI is considered to be the gold standard technique for determining the invasiveness of metaphyseal tumors [131, 171].

Skeletal reconstruction in skeletally immature children and adolescents is particularly challenging in that it must be dynamic in order to accommodate future growth. Expandable prostheses were developed in an effort to control the limb length discrepancy following limb-sparing surgery, but multiple surgical interventions were required to carry out the lengthening procedure [86, 109, 110]. Automatic modules were only used in distal femur locations. Noninvasive extendable lengthening devices, for instance those driven by an electromagnetic field from outside the body, are now available and broaden the indications for limb salvage in young patients [2, 86]. However, a conventional prosthesis can also be applied, followed by lengthening using an external fixator [32].

The use of osteosynthesis techniques (intermedullary pins and plates) is usual in tumor surgery, taking into consideration the special biomechanical characteristics of large bone defects and of the grafts used in limb sparing. The external fixator is of particular interest, usually being used as a temporary solution before tumor resection surgery (to prevent pathologic fractures), during resection surgery (to maintain bone length or perform physeal distraction) or after surgery to combat complications (infection, graft fracture) or correct deformities (dysmetry) [32, 35, 170].

1.3 Conclusion

History shows us that experience is our best teacher. Despite difficulties along the path of development, we have been able to find new ways of improving treatment and life expectancy. As diagnostic and therapeutic techniques improve, patients with musculoskeletal sarcomas can expect increased survival, decreased complications and side effects, and an improved quality of life. Much work remains to be done, and bone tumor surgeons need to keep pushing to better their patients' quality of life and to keep working to increase the survival rate with more accurate and convenient systems of diagnosis and treatment. We are now witnessing the introduction of targeted therapies including monoclonal antibodies and small signaling pathway inhibitors and drugs that act on specific immune checkpoints. Additionally, the search is on for new biomaterials to deliver drugs specifically and effectively into cancer cells. Moreover, research on expression profiling and proteomics can increasingly help us to distinguish more aggressive cancers from less aggressive ones, information that could also be useful for cancer screening. Further knowledge is needed about oncogenes and tumor suppressor genes. Finally, from the technical point of view, work is needed on systems that can remove tumors completely without surgical trauma.

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