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Biological reconstruction after bone tumor resection

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Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto.

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Resumo

Introdução: Tumores musculoesqueléticos são neoplasias raras, mas capazes de causar perda de função significativa. A reconstrução biológica após remoção tumoral permite a preservação funcional dos membros e tem sido cada vez mais preferida em detrimento de próteses.

Objetivos: Esta revisão narrativa pretende reunir informação organizada sobre o atual estado da arte das várias técnicas de reconstrução biológica, com vista a realçar as suas vantagens e expor métodos para ultrapassar as suas limitações.

Métodos: A pesquisa para esta revisão foi efetuada através das plataformas PubMed e ScienceDirect e do motor de busca Google Scholar. Artigos entre 2010 e 2024 e escritos em língua inglesa ou portuguesa foram incluídos e avaliados com maior detalhe.

Conclusão: A sobrevida de doentes afetados por tumores musculoesqueléticos tem vindo a aumentar nas últimas décadas, proporcionando uma mudança notável nos protocolos de tratamento, com inclusão de mais procedimentos reconstrutivos. A reconstrução biológica proporciona vantagens como a sua longevidade, mas os riscos associados a estes procedimentos não são negligenciáveis.

Palavras-chave: Reconstrução biológica, Neoplasias ósseas, Tumores ósseos, Aloenxertos, Autoenxertos, Retalho peroneal, Técnica de Capanna, Distração osteogénica, Técnica de Masquelet.

Abstract

Introduction: Musculoskeletal tumors constitute a rare but potentially function-impairing group of neoplasms. Biological reconstruction following bone tumor resection constitutes a limb-sparing procedure that has been increasingly preferred over traditional treatment methods such as prosthesis.

Objectives: This narrative review aims to present organized information on the current state of the art of various biological reconstruction techniques, highlighting their advantages and exposing methods to surpass their limitations.

Methods: The research for this review was conducted through PubMed, ScienceDirect and Google Scholar. Articles between 2010 and 2024 and written in English or Portuguese were selected and further evaluated.

Conclusion: The survival of patients afflicted with musculoskeletal tumors has increased in the last few decades, prompting a notable shift in the treatment protocols, consisting in the incorporation of reconstructive procedures. Biological reconstruction offers potential life-long longevity, but the risks associated with these procedures are not negligible.

Keywords: Biological reconstruction, Bone neoplasms, Bone tumors, Allografts, Autografts, Fibular graft, Vascularized fibula, Capanna technique, Distraction osteogenesis, Induced membrane technique, Masquelet technique.

Abbreviation list

ADSC – Adipose-derived stem cell

APC – Allograft-prosthesis composite

BMP – Bone morphogenetic protein

CT – Computed tomography

DO – Distraction osteogenesis

ECRT – Extracorporeal radiation therapy

MRI – Magnetic resonance imaging

MSTS – Musculoskeletal Tumor Society

NVFG – Non-vascularized fibular graft

PMMA – Polymethylmethacrylate

VFG – Vascularized fibular graft

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Introduction

Primary malignant bone tumors correspond to 0.2% of all tumors[1,2]. The most common tumor is osteosarcoma, accounting for around 40% of malignant bone tumors, and it is more common in the pediatric population and in patients over 60 years old[3–5]. Other common primary bone cancers include chondrosarcoma (5.6-20%), more prevalent in adults (40-75 years old), and Ewing's sarcoma (1.9-13.5%), which manifests mainly in the second decade of life[1,3–13]. In the pediatric population, sarcomas account for 10% of all solid tumors and 5% of all malignant cancers[7,12].

As for the most common benign bone tumors, osteoid osteomas correspond to around 10% of benign bone tumors. Giant cell tumors, osteochondromas and chondroblastomas account for 4-16.7%, 9.1% and 1-3.1% of all bone tumors, respectively[13–17]. Bone tumors usually present with pain that is worse at night, localized oedema, pathological fractures and impaired functionality[6,16,18].

Metastatic bone tumors are much more common than primary tumors[16], representing 70% of all metastases[19]. The cancers that most often metastasize to the bone include prostate, breast, and lungs[2,20,21], and the main sites for these lesions are long bones, especially the proximal femur[22], and pelvis[13].

Owing to the advances in chemotherapy, many patients with bone tumors have a much higher life expectancy than ever before[7,23,24]. For this reason, it is of the utmost importance to maintain their quality of life by ensuring the restoration of their limb function. Contemporary progress in surgical procedures has allowed for the preservation of functionality through reconstructive procedures, which can be divided into biological and non-biological reconstructions.

Non-biological reconstruction involves the use of endoprosthesis, mainly for the treatment of bone tumors that affect joints, and it includes the use of expandable prosthesis and allograft-prosthesis composites (APC)[25]. This type of reconstruction is associated with complications such as infection, disease recurrence, aseptic loosening and prosthesis failure[26]. Moreover, prosthetic replacements are frequently subject to re-evaluation and substitution in a short-period of time, conditioning the longevity of these procedures.

Biological reconstruction englobes various diverse techniques, i.e. allografts, autografts, Masquelet technique, and distraction osteogenesis. Compared with prosthetic replacement, biological reconstruction requires a more prolonged recuperation period and is associated with more early complications, including nonunion, fracture, infection and limb-length discrepancy, but these aspects are outweighed by the longevity of these reconstructions[26–28]. It is estimated that

biological reconstruction is currently implemented in the treatment of around 80% of cases of primary malignant bone tumors[24,29].

Objectives

The principal objective of this narrative review is to direct collective attention to the importance of biological reconstruction in the preservation of limb function and improvement of quality of life of patients suffering with bone tumors. The purpose of this report is to summarize and compile every biological reconstruction technique that has been described until the present day, in order to facilitate access to information and reliable sources.

Through an extensive review of the current state of the literature, this paper aims to promote knowledge and comprehension of the various techniques and their respective advantages and weaknesses. Furthermore, this review intends to mention emerging technologies and advancements in the field, and, ultimately, provide insight into the importance of biological reconstruction in the orthopedic field.

Methods

This review was elaborated through the use of PubMed and Science Direct databases and the search engine Google Scholar. The preliminary search was carried out using the keywords “biological reconstruction”, “bone tumors”, “bone neoplasms”, “allografts”, “autografts”, “distraction osteogenesis”, “fibular graft”, “vascularized fibula”, “induced membrane technique”, “Masquelet technique”, and “Capanna technique”.

Articles between January 2010 and April 2024 and written in either English or Portuguese were included, and, upon reading of their title and abstract, a total of 296 articles were obtained. Upon integral perusal of the selection, articles pertaining to other themes such as biological reconstruction following trauma, osteonecrosis, congenital or development disorders and infections, as well as any article concerning non-musculoskeletal tumors, were excluded from this review. Furthermore, whenever necessary, a manual article search was carried out in order to obtain all of the essential information.

Ultimately, a total of 95 articles were considered pertinent to the elaboration of this narrative review.

Discussion

1. Biological reconstruction

Biological reconstruction is an expanding branch of musculoskeletal tumor treatment, and it consists in the use of biological materials in the limb-conserving treatment of bone defects[30]. There are several diverse techniques that are included in this approach: allografts, autografts (including fibular grafts and recycled grafts), induced membrane technique and distraction osteogenesis. The main objectives of this approach are maintaining limb function and improving the patients' quality of life, and its biggest advantages are the preservation of bone stock and its achievable lifetime durability[27,31].

Skeletally immature patients, who require the preservation of their growth plates, constitute a challenging demographic group for reconstructive surgeries[25]. The use of biological reconstruction, unlike prosthesis, allows for the conservation or even restoration of their bone stock[9,32,33] and for a normal biological development after tumor resection without hindering their limb function[34,35].

The biomaterials utilized in biological reconstruction can be divided into two classifications: viable and non-viable. Viable materials, which can also be described as vascularized or vitalized, comprise vascularized fibular autografts, induced membrane technique and distraction osteogenesis. These materials have their own blood supply and are more easily capable of withstanding an infection on their own[24,30,36].

On the other hand, non-viable, non-vascularized or devitalized materials comprise allografts, recycled autografts, and non-vascularized fibular autografts[30]. All of these materials go through a prolonged incorporation process named creeping substitution, in which the grafted bone is slowly replaced by newly developed, viable host bone, and it's dependent on the concomitant action of osteoblasts and osteoclasts. In the event that this process fails, it could lead to a case of nonunion at the junction site or fracture[36–38]. It appears that diaphyseal reconstructions require a longer period for complete graft union, defined as a clear bridging of the periosteal bone over the junction or no visible osteotomy line (evaluated through radiographs), than metaphyseal grafts[27,36,39]. In addition, these grafts all lack their native vascularization and cells, rendering them more susceptible to infections and fractures[31,40].

Tumor recurrence is a worrying complication of reconstructive procedures, in particular because recurrent disease usually entails a worse prognosis than the primary lesion due to their increased tumor aggressiveness and possible systemic metastization[41].

An additional complication that is uniquely associated with young growing patients is limb-length discrepancy, and it is especially prevalent in cases where it is impossible to preserve the growth plate. This can be rectified with insoles (if the discrepancy is < 5 cm) or through expandable prosthesis, distraction osteogenesis or even contralateral epiphysiodesis[9,25,42].

It is indispensable to ensure a strong sturdy fixation of any biological reconstruction method to guarantee their long-lasting durability. Many fixation methods have been studied, for instance, single steel plate, double steel plate and intramedullary nail. It has been shown that the individual use of any of these techniques is associated with many post-operative mechanical complications[27,36], therefore the combination of these techniques has been implemented. Moreover, additional treatments like chemo and radiotherapy compromise the organism's immunological responses and have been shown to hinder the consolidation process of these bones because of their indiscriminate ability to kill actively proliferating cells, whether they are cancerous or normal, leading to an increase in complication rates[25,30,31,36,41,43–45]. A distinctive complication associated with biological reconstructions is the resorption of the grafted bone, which can be influenced by several factors, namely poor vascularization, inadequate graft fixation and continuous unregulated stress on the grafted bone[36].

2. Non-viable materials

2.1. Allograft

Allografts are a simple, practical, and effective method of biological reconstruction, with a limb salvage rate of up to 97%[43] and an overall graft survival rate around 80%[27,39]. This technique has been used since 1910, when the first refrigerated bone transplantation was documented[32].

Fresh frozen allografts are the first choice in many bone tumor cases mainly due to their mechanical stability, and robust osteoconductive and osteoinductive nature[27,35,39]. Osteoinduction is in the basis of osteogenesis, and it consists in the process of recruiting osteoprogenitor cells and the stimulation of their differentiation, through which calcified bone matrix is produced[46]. These characteristics are particularly relevant when treating younger, skeletally immature patients.

There are some mandatory factors for the success of an allograft reconstruction: robust internal fixation, optimized soft tissue coverage, adequate surface contact area and appropriate bone size matching[27,40]. Maximizing the contact surfaces between the host and donor bones at the osteotomy junctions and ensuring an effective compression can expedite bone healing and mitigate bone resorption. Small breaches in the contact surface can overload certain parts, which can then lead to an uneven distribution of weight and stress, which can hinder the consolidation and healing of the graft. Moreover, to ensure the compatibility between the patients and the donors, it is essential to perform an extensive comparison of their bones through radiographs, CT scans and/or three-dimensional reconstruction of CT and MRI imaging[32].

Once the donor has been carefully selected, the preparation of the allograft should take place. This usually consists in soaking the graft in saline and/or hydrogen peroxide solutions, and, if deemed necessary, adding antibiotic prophylaxis[27,39]. Additionally, the use of 3D printing to create accurate osteotomy guides[40,47] based on the patient's imaging can be of great help to prepare a precisely fitting allograft.

Once a devitalized bone transplant has been concluded, the patient's organism will begin the graft's incorporation through creeping substitution[37]. However, although allografts allow for a restoration of limb function of over 90%[27], similar to endoprosthesis[43], they are associated with a relatively high rate of short-term complications (within two to four years following the initial procedure[35,43]. These could be explained by the initially avascular and acellular character of these grafts[28,31,48]. Such complications include nonunion, fracture and infection.

Nonunion rates typically vary largely in the literature, with documented rates beginning in 3% and up to 53%[43], with a mean rate of 34%[40]. Simple factors as a length of > 10 cm could contribute to an increase in these rates.

Graft fractures usually occur in around 20 to 45% of the cases and allograft infections (10-30%) are responsible for the majority of deaths following this procedure[27,32,40].

Additional complications comprise disease recurrence, in around 18% of cases[39], limb-length discrepancy in 38% of cases[9], infectious (mainly viral) disease transmission, and, similar to any other allogeneic transplant, immunological reactions culminating in graft rejection[10,35,49].

Although allografts have been used for a long time, their use can't be applied to every reconstruction case, namely due to the limited availability of donors and their demanding size-matching accuracy[39]. Additionally, socio-religious beliefs and the high cost of this procedure also limit the implementation of this technique, especially in some parts of Asia[35,50]. Moreover, considering that the main purpose of biological reconstruction is to restore limb function and improve the patients' quality of life, it's mainly indicated for patients whose life expectancy is long, those with resectable surgical margins and/or those who respond to neoadjuvant chemotherapy[27].

2.1.1. Intercalary allograft

When bone tumors are located in the diaphysis, it can be difficult to fully repair the defects by endoprosthetic reconstruction, requiring the need for amputation in many cases. The introduction of intercalary allograft surgeries has allowed for a proper function-preserving treatment[40].

In comparison to osteoarticular allografts, intercalary reconstruction is less demanding on a technical level, and it appears to be less associated with complications and more likely to progress into a long-term favorable outcome[27,35]. However, despite the 92% limb salvage rate[43], the mechanical complications (nonunion and fracture) are not negligible[32,36].

2.1.2. Osteoarticular allograft

Contrary to endoprosthetic joint reconstruction, that requires the sacrifice of the entire joint, osteoarticular allografts allow the preservation of most of its components. This method is more technically challenging and has a more limited lifespan than intercalary allografts due to their frequent mechanical deterioration[27].

Osteoarticular allografts targets lesions located in the metaphysis, reducing in the risk of fracture and nonunion. However, it is important to note that this risk is not insignificant[32], and it does not interfere with other mechanical complications such as joint instability (5 to 20%) and degenerative

joint disease (13 to 31%)[36,51]. Appropriate selection of donor bone and preservation of the host's articular and ligamental structures can diminish their incidence, and, if necessary, there is the possibility to convert it to APC or even endoprosthesis in case of graft failure or irreversible degenerative deterioration.

Ultimately, the unpreventable high rate of complications forestalls its routine use[52], and APC or even endoprosthesis are still preferred over this method.

2.2. Recycled tumor-bearing autograft

In some regions with very few bone donations[31,35], few financial resources or with allograft-usage limiting socio-religious beliefs[24,36], the search for new biological reconstruction techniques was carried out. Thus, autografts, in particular recycled autografts and fibular grafts, began to be implemented.

The application of recycled tumor-bearing autografts stands on the principle that every cancerous cell can be destroyed extracorporeally through various techniques. There are numerous methods of recycling these bones, such as autoclaving, pasteurization, irradiation, freezing-thawing with liquid nitrogen and alcohol inactivation, and they all entail similar effects in the eradication of tumor cells[24,53].

It is essential to properly select the patients for these procedures, and these factors must be taken into consideration: quality of the affected bone, ability to preserve or repair the soft tissue structures, tumor's sensibility to chemotherapy, and the patient's general health condition. Patients that present with massive tumors, invasion of the surrounding soft tissue or blood vessels, and insensitivity or reluctancy to chemotherapy must not be considered for these procedures[49,53].

As evident as it might seem, one of the main benefits of these procedures is that these resected segments are a perfect fit to the remaining host bone[8,31,35,37,54–56], which greatly contributes to the simple and cost-effective nature of these procedures[36,39,42,57,58].

The course of these surgeries is quite simple: (1) resect the tumor-bearing segment of the affected bone, (2) remove the tumor, (3) devitalize the remaining resected bone, and (4) reimplant it into the patient[54].

As previously described, the incorporation time of the devitalized grafts is prolonged[37], but they generally have a more favorable osteogenic activity and, therefore, a shorter healing time than allografts[36,39]. However, it is essential to note that these sterilization procedures can hinder the quality and structural integrity of these bones, which renders autografts' strength disadvantageous in relation to allografts[55]. However, unexpectedly, they are associated with similar complications as the latter. The rates of nonunion, infection, fracture and other complications will be presented below. Regarding local recurrences, it's speculated that one of the main mechanisms for this occurrence is the permanence of tumor cells in the devitalized segment after the recycling processes[10].

The main differentiating issue related to recycled autografts is the subsequent unavailability of histopathological material to be analyzed[8,31,54], thus difficulting the assessment of surgical margins and the effects of possible previous treatment cycles, in particular chemo and radiotherapy.

2.2.1. Autoclaving

Autoclaving sterilization was first described in 1986 and it consists in the heating of the tumor-bearing bone, which usually demands temperatures around 120ºC. Due to these high temperatures, there is irreversible damage to the bone proteins and structure and some of its native properties are lost, in particular its osteoinductive abilities. Even so, it allows the preservation of osteoconduction. This interferes with the incorporation of the autograft, making it more susceptible to complications.

The estimated rates of nonunion, fracture and infection are, respectively, 30%, 20% and 20 to 41.6%[24,35,54].

2.2.2. Pasteurization

Pasteurized autografts were first introduced into the medical field in 1991[24], in hopes of avoiding the drawbacks associated with autoclaving. This method consists in heating the graft for 30 to 60 minutes in temperatures around 60 to 70ºC[35,55,57,59]. It has been studied that temperatures over 70ºC are associated with the destruction of vital bone proteins involved in osteogenesis, named bone morphogenetic proteins (BMPs)[35,55,60]. Consequently, keeping the temperatures below 70ºC allows for the preservation of the osteoinductive nature and integral structure of the autograft.

The reported rates of nonunion, fracture and infection are around 23 to 42%, 9.5 to 23% and 15 to 20%, respectively[35,37,59].

2.2.3. Irradiation

Extracorporeal radiation therapy (ECRT) consists in the use of radiation, usually 50 Gy, to sterilize the resected bone, and its use was first reported in 1968[24,35,49,54]. It has been established that the use of higher doses of radiation could entail higher rates of complications due to destruction of the microscopic bone structure and its native properties.

The main complications associated with this method of devitalization are nonunion (7-16%), fracture (20%) and infection (0-17%)[24,54].

2.2.4. Freezing-thawing with liquid nitrogen

The use of liquid nitrogen to recycle tumor-bearing bones was first introduced in the 1960s[24,61], and, since then, it has been one of the most implemented recycling techniques, along with irradiated autografts[60].

Liquid nitrogen is extremely effective in destroying tumors cells without compromising the structure and biological properties, such as osteoinduction and osteoconduction, of the tumor-bearing bone[35,39,42,60–66]. This method consists in soaking the bone for 20 minutes in liquid nitrogen at around -196ºC, followed by thawing for 15 minutes at room temperature, and, lastly, rinsing for 15 minutes with distilled water[30,35,42,63,67].

The freezing process causes intracellular ice crystal formation, thus promoting pH level modification, rise in salt concentration, and dehydration of cancerous cells, that are more easily affected by low temperatures than normal cells[35,42,52,60,63,64,67,68]. The thawing part of the technique further damages the tumor cells by promoting ice recrystallization[60]. Moreover, thrombosis of the microcirculation induced by the liquid nitrogen is also a possible explanation for the death of tumor cells[35,64].

Two distinct freezing techniques have been implemented: free-freezing and pedicle-freezing. Free-freezing consists in resecting the tumor-bearing bone through two osteotomies or a hemicortical resection, and performing the sterilization with liquid nitrogen solely on that segment, whilst pedicle-freezing does not fully separate a segment from the bone. Instead, a single osteotomy site is created at one end of the tumor-bearing bone, and the host bone is rotated and mobilized to allow the submersion of the affected segment in liquid nitrogen[30,35,52]. If the tumor location allows, the second technique is preferred as it not only seems to be associated with less complications due to the single osteotomy site, but also allows for earlier weight-bearing and a faster recovery, owing to the continuity between the affected and the normal host bone[30,35,58]. Additionally, this continuity may also promote a faster revascularization of the grafted bone, contributing to a quicker bone union[58,67].

Furthermore, it has been speculated that the use of pedicle cryosurgery induces a systemic antitumor response that can lead to the spontaneous regression of metastatic lesions[52,61]. This could be explained by the release of tumor antigens after complete tumor cell destruction, which, in turn, activates a tumor-specific immune response that will specifically target similar tumor cells present in metastasis[64,69].

Tumor recurrence has been reported to happen in around 7.1 to 13.7% of cases, mainly in the surrounding soft tissues and not the treated bone, which is thought to be caused by inadequate

tumor resection[39,42,68]. Furthermore, it appears that the pedicle-freezing technique is more prone to progress into local recurrence than free-freezing[39]. A complication that is uniquely associated with this procedure is thermal skin necrosis due to the proximity of the skin to the liquid nitrogen, and it is especially prevalent in pedicle-freezing cases, occurring in around 25% of patients[67].

The ability to preserve the native osteogenic properties, including the majority of BMPs[52,61,63,67,69], of the recycled bone is crucial for the union between the graft and the host bone, and it has been shown that frozen autografts have an equivalent union rate (83.3-100%) to vascularized fibular graft (86-100%), and better union rates than allografts (57-94%), non-vascularized fibular grafts (76-89%), and the other recycling methods (autoclaving 70%, pasteurization 58-76%, irradiation 69-93%)[42,52,55,67]. Nonunion only arises in about 13-14.7% of cases, fracture rates are between 7.1 and 19.4%, and infection ranges from 5.9 to 12.1%[39,42,68].

2.2.5. Alcohol inactivation

Although alcohol inactivation has been around since 1983, it's still a fairly unestablished technique that hasn't been studied as much as the previous ones. This method consists in the soaking of the resected bone in 99% ethanol for 30 minutes and its subsequent washing with a saline solution[11,53]. It has been hypothesized that alcohol not only destroys the tumor cells, but also contributes to the preservation of the creeping substitution process[10,11]. However, its clinical application and outcomes have not been sufficiently studied.

As for the complication rates of this technique, they have been reported as follows: nonunion 17.3%, fracture 20-30%, infection 14.3%, local recurrence 14.3%[10,70,71]. Moreover, studies indicate that the 5-year survival rate of this method (71.4%) is inferior to those of irradiation (82.8%) and liquid nitrogen (84.4%)[10].

2.3. Non-vascularized fibular graft

Fibular grafts are a different type of autografts that are routinely applied in the treatment of bone defects after tumor removal and can be divided into two: vascularized and non-vascularized. There is a unique advantage to the application of these grafts, which is the possibility to transplant not only the fibula, but also its vascularization (vascularized fibular graft) and other surrounding tissues like skin, fascia, and muscle (both types of fibular graft)[7,68].

Fibular autografts can be used on their own, with a limb salvage rate of up to 89%, but they face some obstacles, specifically diameter size matching with some recipient sites, such as the femur or tibia, which can predispose to a higher complication rate[8,12,29,35,72]. There are different indications for each type of fibular graft, yet they have similar complications, complication rates and potential to restore functional abilities[16,29]. One particularity associated with this type of autograft is the donor site morbidity[42,72], including peroneal nerve damage, ankle instability and compartment syndrome[44].

Non-vascularized fibular grafts (NVFG), as the name suggests, don't retain their native blood supply, consequently making the procedure simpler and less tedious and leading to fewer complications at the recipient site, without compromising the functional outcome[16,73]. For this reason, they are better incorporated into the target site if the latter possesses sufficient soft tissue coverage and vascularization, e.g. pelvis. The use of NVFG is not recommended for bone defects ≥ 12 cm[14,29,44]. Although their incorporation involves a somewhat similar process to that of allografts and recycled autografts, since these bones retain all of their native biological characteristics, their incorporation is easier and faster than the latter's[29,39], but it still takes longer than vascularized fibular grafts.

There is a large scarcity of studies in this field compared to other methods, but it has been shown that NVFG causes less complications than the others, although they are not inexistent. Fracture is the most common complication following this procedure, and it corresponds to up to 45% of cases. Nonunion is said to occur in 6 to 14.8%, infection in 3.7% and local recurrence in 14.8%[29,39,44].

3. Viable materials

3.1. Vascularized fibular graft

Vascularized fibular grafts (VFG) constitute a technically challenging and time-consuming procedure that allows for the preservation of their native vascularization and surrounding structures[12,16,34,74,] and were first described in the 1970s[7,29,35,75].

The mechanism of incorporation of vascularized fibular grafts is completely different from the previously mentioned grafts: instead of creeping substitution, these vitalized grafts go through a process much similar to a regular fracture healing process[12,29,35,37,75]. When subjected to mechanical stress, the fibula goes through a prolonged process (over 3 years) that culminates in hypertrophy, rendering it sturdier and more stable[7,75]. Until this process is finished, it is more common for complications to occur. The rates of nonunion, fracture and infection when using VFG are reported to be 4-55%, 0-40% and 4-18%, respectively[9,12,29,35,72].

Vascularized fibular grafts have been regularly associated with other biological reconstruction techniques, namely allografts and devitalized autografts, in hopes to decrease their complication rates[7,29], which will be further discussed below.

Furthermore, VFG can also be used as a salvage procedure when other biological reconstruction methods culminate in failure (graft resorption, nonunion, fracture or infection), with consequent limb salvage rates over 66%[76].

3.2. Induced membrane technique

In 1986[77,78], Masquelet et al. developed, by accident, a new biological reconstruction technique. It comprises the use of a cement spacer, composed of polymethylmethacrylate (PMMA), immediately after resection of the tumor-bearing bone, and the posterior substitution of this spacer with a bone graft, usually autologous cancellous bone collected from the posterior iliac crest, 6-8 weeks after the first procedure[35,78–80]. Usually, the second procedure is postponed as much as possible, to ensure the completion of chemotherapy cycles, due to the patients' immune debility[8,80].

The use of PMMA induces an inflammatory response resulting in the formation of a pseudo-synovial[77,80] membrane that will later act as a periosteum for the grafted bone, providing it with vascularization, growth factors, osteoinductive factors and preventing its resorption[35,77,78].

The induced membrane technique is a simple procedure and can be chosen for both treatment of primary or metastatic bone tumors, or as a limb salvage procedure following failure of another reconstructive procedure[79]. It is associated with very few complications on the donor site, but it has some downsides: the prerequisite of two different surgeries[8,78,80] and the need for large amounts of autologous cancellous bone. The latter could be overcome with the implementation of spongy bone allografts or graft substitutes such as demineralized bone matrix. Infection is the main complication of this method, which lead to the idea of impregnating the spacers with antibiotics such as gentamicin or vancomycin[77].

3.3. Distraction osteogenesis

Distraction osteogenesis (DO) is a completely different approach to bone tumors, and it consists in precise and progressive traction of bone segments separated by osteotomy with the intention of biologically inducing new bone formation and surrounding soft tissue hyperplasia. The native bone and periosteum constitute a direct pathway for the new bone to form, which allows the latter to be identical in size, structure, and functional abilities to the former. The osteotomy gap obtained from this process is first occupied by type I collagen fibers arranged in parallel with the direction of the traction. To ensure the adequate ossification of these fibers, it is mandatory to ensure proper stability of the affected bone. This can be achieved through different methods: circular fixators, lateral fixators, and intramedullary nails[81]. Once this process is complete, it is necessary for the patients to begin adequate physical activity to promote a "functional remodeling" of the newly formed bone[82,83].

DO requires a very prolonged surgery and, many times, repeated follow-up surgeries[31,38,42], it requires the patients to be compliant and accommodating[35], and it demands the use of heavy and uncomfortable frames for a long period of time[36,54]. The rate of distraction is usually 1 mm per day and should begin 1 to 2 weeks after the procedure[35,84]. There should be regular monitoring through X-rays to ensure a satisfactory progress and promote the patient's collaboration.

This procedure is not recommended for bone defects > 15 cm or when it is impossible to preserve at least 0.5 cm of subchondral bone after resection[30,31,38,72,85], as these factors are associated with a higher complication frequency.

Furthermore, distraction osteogenesis is not free of complications: late ossification (32%), nonunion (20%), axis malalignment (18%), infection (5-20%), pin (4.6%) or wire (4.9%) site infection, soft tissue overstretching, contractures (14%), fracture (15 to 45%)[31,35,38,82,86–88], and skin invagination or infolding. The latter might occur due to the open space created by the traction, and it might require additional surgeries for correction. To reduce this gap, the use of an intramedullary nail is recommended[30,31,35].

4. Combining viable and non-viable materials

As previously mentioned, due to their high biological activity, VFG are used in addition to other methods, such as allograft and recycled autografts, to lower their mechanical complication rates and improve functional outcomes of the patients[6,37,74]. This association is based on the benefits of combining the structural stability of the devitalized bone with the blood supply of a VFG, which promotes the cellular activity and, therefore, healing and incorporation of the grafts, accelerates bone union and decreases fractures and infections[16,31,35,75,76,80]. Initially, the devitalized bone's mechanical strength allows for proper weight-bearing, consequently promoting fibular hypertrophy, which vastly reduces the fracture rate[9,24,35,75,80,89].

In the 1990s, Capanna et al. introduced the idea of combining allografts with vascularized grafts[75,76] and reported a graft survival rate of 93.3%[35,89]. This technique helps decrease the rates of nonunion from 3-53% to 0-33%, fracture from 20-45% to 0-44%, and infection from 28% to 17%[31,32,40,43]. Some studies have even noted that the overall complication rate decreased 30% with the use of the Capanna method[29].

This can be achieved through two different techniques: intramedullary and on-lay. The intramedullary technique, also known as "hot dog" method, is the preferred method, and consists in the insertion of the fibula through the allograft's cortex and at least 2 cm, on each end, into the host bone, and it's more commonly used for large bones like femur and tibia. The on-lay technique is opted for when the intramedullary method is not feasible (e.g. when the VFG doesn't fit into the allograft), or when there are just partial bone defects, where it is only necessary to perform the osteotomization of the fibula longitudinally[8,9,35].

Similar approaches were developed after the demonstrated success of the Capanna technique, such as the use of recycled autografts instead of allografts, and comparable results were obtained[89].

5. Prognosis

Most of the literature resorts to the Musculoskeletal Tumor Society (MSTS) functional score to evaluate the outcomes of patients suffering from musculoskeletal tumors. This score has been developed for both the upper and lower limbs and it is composed of six elements. Common evaluated elements between the two limbs include pain, limb function and emotional acceptance. For the upper limb, hand position, manual dexterity and lifting ability were assessed. For the low limb, walking, gait and the need for support were the additional evaluated parameters. Each one of these components is scored from 0 to 5, and the higher the score, the better the function. The maximum score is 30 and it corresponds to "no disability", and the minimum score is 0 and it corresponds to "total disability". Additionally, it is possible to convert these points into a 0 to 100 scale[54,90,91].

Better functional outcomes seem to be associated with the use of frozen recycled autografts, Capanna technique, distraction osteogenesis and VFG, with MSTS scores of up to 94.5%[89], 95.2%[75], 91.5%[38,87] and 98%[53], respectively. The MSTS functional scores for the other techniques are as follows: allograft 79-89.3%[27,43], autoclaved autograft 73.3%[92], pasteurized autograft 80%[22], irradiated autograft 87%[49], alcohol inactivated autograft 77%[10], NVFG 77%[44], and induced membrane technique 84%[78].

6. Emerging techniques and future prospects

Besides the established techniques that have been previously discussed in this review, many adjuvant methods for biological reconstruction are currently being investigated, in order to provide even better functional outcomes and faster recovery periods.

The use of platelet-rich plasma has been associated with the use of autologous spongy bone grafts, and it has been shown to improve bone incorporation and union. Additionally, the use of autologous bone marrow injections has also been implemented, especially in the treatment of complications such as nonunion. The use of biomaterials, such as hydroxyapatite and calcium silicate, associated with osteoprogenitor cells derived from autologous bone marrow has also been reported. Furthermore, bone tissue engineering resourcing to stem cells, in particular, adipose-derived stem cells (ADSCs), has been proven to adequately promote the revitalization of bone and soft tissues[30,46,93–95].

Conclusion

Recent advances in the medical field, particularly in chemotherapy, have significantly improved the survival rates of patients suffering from musculoskeletal tumors. This has come to establish a precedent for treatment decisions, with an increasing number of cases now deemed eligible for reconstructive surgeries.

Given the longevity provided by biological reconstructions, these procedures are mainly indicated for patients with a substantial life expectancy, with those under 18 usually constituting prime candidates for these reconstructive surgeries, due to their immature skeletal structure.

Nevertheless, it is vital to recognize their prevalent and potentially serious complications, that can have catastrophic consequences for patients. Consequently, it is indispensable to thoroughly weight the benefits and risks of biological reconstruction methods, in order to properly address each patient's individual needs without compromising their quality of life.

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