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Reconstructive Science in Orthopedic Oncology

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Abstract

Limb salvage is widely practiced as standard of care in most cases of extremity bone sarcoma. Allograft and endoprosthesis reconstructions are the most widely utilized modalities for the reconstruction of large segment defects, however complication rates remain high. Aseptic loosening and infection remain the most common modes of failure. Implant integration, soft-tissue function, and infection prevention are crucial for implant longevity and function. Macro and micro alterations in implant design are reviewed in this manuscript. Tissue engineering principles using nanoparticles, cell-based, and biological augments have been utilized to develop implant coatings that improve osseointegration and decrease infection. Similar techniques have been used to improve the interaction between soft tissues and implants. Tissue engineered constructs (TEC) used in combination with, or in place of, traditional reconstructive techniques may represent the next major advancement in orthopaedic oncology reconstructive science, although preclinical results have yet to achieve durable translation to the bedside.

Keywords

Osseointegration; periprosthetic infection; biofilm; implant coatings; soft tissue attachments

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INTRODUCTION

The transition from amputation to limb salvage was a defining shift in the history of orthopaedic oncology. The advent of multi-agent chemotherapy regimens beginning in the 1970s dramatically decreased tumor size and increased survival in patients with primary bone tumors.[1-3] Coupled with advancements in imaging modalities and reconstructive techniques, orthopaedic oncologists were able to achieve complete tumor resection without requiring amputation.[4] Today, limb salvage has been adopted as the standard of care in most cases of extremity sarcoma. As the survivorship of sarcoma patients improves, so has the demand placed on reconstructed limbs. Unfortunately, orthopaedic oncologists and their patients have become well versed in the limitations of current reconstructive techniques. Failure rates in limb salvage procedures remain high, with rates recently reported from 24% to 42% depending on technique and location.[5-8] While each reconstructive technique offers its own advantages, none is free from common modes of failure such as fracture, infection, aseptic loosening, and joint instability.

Ideally, reconstructions of large bony defects restore anatomy, optimize function, and minimize the risk of implant failure and the need for revision. To optimize function, there must be i) stability at the osseo-implant interface and ii) soft tissue attachments required for limb function must be retained or re-created. A reconstruction that does not adequately restore skeletal stability or allow proper musculotendinous function will provide the patient with a sub-optimal outcome. Implant failure, however, is generally driven by loosening of the implant – septic or aseptic in etiology.[5] Therefore, to optimize longevity, the implant must remain free of infection and protect the host implant interface from osteoclastic-driven resorption. In this sense, protecting from infection and aseptic loosening prevent reconstructive failure, while solid osseointegration and optimized soft tissue attachments achieve reconstructive “success”.

Currently, large segment bony defects are primarily reconstructed using either metallic implants (endoprostheses) or bulk allograft. While autograft remains an important option for smaller defects, donor site morbidity precludes its use for reconstruction of large segments. Recent research has focused on optimizing the interactions of bone and soft tissue with metallic implants and osseous grafts, preventing infection on implanted materials, and expanding the reconstructive arsenal with tissue engineered grafts. Micro and macro alterations in implant design, specialized implant coatings, and biologic reconstructive techniques have already moved from the bench to the bedside. This review will focus on the current state of the field in these areas, as well as recent advancements and future directions.

ALLOGRAFT RECONSTRUCTION

Modern bone banking dates back to the establishment of the US Navy Tissue Bank in 1949.[9] Since that time, bulk allograft has been a mainstay in orthopaedic oncology. Despite challenges in procurement and processing, as well as the increasing use of endoprostheses and artificial bone substitutes, bulk allografts confer several reconstructive advantages when compared to metallic implants because they closely approximate host biology.

By more closely approximating host biology, bulk allograft confers several reconstructive advantages when compared to metallic implants. Osteoarticular grafts allow for anatomic reconstruction of joints and allograft reconstruction may maintain anatomic sites for tendon and soft tissue attachments thus improving stability and function. Such articulations and attachments are difficult to achieve with endoprostheses. In young patients, bulk allograft functions as an osteoconductive conduit for native bone tissue. Historically, bulk allograft supply has been limited and matching a graft to a patient's anatomy was imprecise. However, advancements in bone banking and processing have largely mitigated such concerns. Three-dimensional imaging modalities have allowed for precise allograft selection and recent development of automating algorithms may allow for improved selection from a larger stock of donor bone.[10, 11]

Despite these advantages, failure rates in allograft reconstruction remain high. Failure rates ranging from 23% in the upper extremity,[6] up to one third of allograft reconstructions of the proximal tibia have been reported.[7] The most common modes of failure are mechanical (fracture, aseptic loosening, nonunion, soft tissue failure) and infectious.[7] As such, current research in bulk allograft reconstruction has focused on developing stronger grafts by promoting bony ingrowth and union, and reducing the risk of infection.

Mechanical properties

Gamma-irradiation is a common method for sterilizing allograft. While highly effective against pathogens, this comes at the expense of mechanical strength and increased brittleness due to collagen fragmentation and change in chemical structure from radiation produced reactive oxygen species.[12] Treatment of allograft in a ribose solution, which acts as a free radical scavenger was shown to prevent gamma radiation-induced loss of mechanical strength and increased fragility.[13, 14] An important factor contributing to the reduced strength of bulk allograft compared to native bone is the lack of periosteum. While necessary to reduce possible immune reaction, stripping periosteum from bulk allograft during preparation reduces healing potential and integration. Some novel methods have been studied to form bio-engineered periosteum-mimetic scaffolds, which have been applied to bulk allograft to improve healing potential. Chitosan, a polysaccharide derived from the shells of crustaceans was evaluated in various forms as a biopolymer scaffold applied to bone allograft and was shown to support osteoprogenitor stem cells and possess the required physical properties to be of potential use in this application.[15] Similarly, chitosan has been shown to function as a suitable delivery substrate for growth factors in engineered bone graft substitute, a feature that could potentially be utilized on the surface of allograft to promote vascularity, osteoinduction and soft tissue attachment.[16] In a rabbit model of bulk allograft, Zhao et al showed that allograft treated with strontium significantly increased the rate and overall amount of new bone formation, while maintaining its mechanical strength compared to non-treated controls.[17] These studies did not demonstrate any cytotoxic effects or altered immune reaction to the treated allograft.

Resistance to infection

The porous structure and large surface area of freeze-dried bone allows it to be treated as an antibiotic eluting substrate. Coraca-Huber et al. compared antibiotic impregnated bone chips

to currently used antibiotic eluting PMMA beads and found no significant difference in antibiotic elution rates *in vitro*.[18] Hornyak et al. reported that coating antibiotic-impregnated allograft with various concentrations of calcium alginate dramatically enhances the duration of therapeutic levels of antibiotic elution.[19] Further *in vivo* studies are required to determine clinical viability.

ENDOPROSTHESIS RECONSTRUCTION

The development of customized and modular endoprostheses was a significant catalyst in the transition from amputation to limb salvage as the standard for extremity sarcoma. Reconstruction with endoprostheses confers several advantages when compared to allograft, chiefly early mobilization and mitigation of the risk of disease transmission from donor tissue. Furthermore, modular prostheses and growing prostheses allow increased versatility and adaptability when compared to allograft. However unlike bulk allograft, endoprosthesis reconstruction does not restore bone stock or provide anatomic locations for soft tissue attachments. Failure rates for endoprosthesis reconstruction remain high and do not appear to be significantly different than those of bulk allograft.[7, 20] In a recent meta-analysis, infection was the most common mode of failure for all endoprostheses used for tumor reconstruction, followed by aseptic loosening.[5] Current efforts to improve endoprosthesis reconstruction are largely focused on improving the interaction at the bone-metal interface to promote stability and infection prevention.

Osseointegration

Optimizing stability at the osseo-implant interface has long been a central tenant of orthopaedics. Historically this has been done with polymethylmethacralate (e.g. bone cement), but osseo-implant stability from ingrowth of bone into the implant, or osseointegration, is a theoretically advantageous, biological method of stabilization. Osseointegration is particularly important in orthopaedic oncology given the presence of short bone segments, frequent lack of soft tissue support, and the need to maximize implant lifespan. Advancements in implant design, as well as interventions manipulating the periprosthetic biologic environment have already yielded improvements in osseointegration, with many promising developments on the horizon.

Porous Metals

The effects of metal porosity on osseointegration were first examined by Weber and White in 1972.[21] Since that time, porous metals have become a staple of orthopaedic implants. Porous metals improve osseointegration and implant stability by increasing surface area, thereby enhancing friction and bone-metal contact to create an optimal environment for osteogenic cell ingrowth and new bone formation. Porous metals are most often applied as coatings to solid metal implants; fully porous implants often lack sufficient mechanical strength to be used for load-bearing.[22] However, fully porous implants are available for use in the acetabulum, spine, and shoulder.[23]

Titanium and tantalum are the most frequently used porous metals,[24] with titanium the most common. A lightweight metal with low Young’s modulus and high tensile strength, it most

closely mimics the physical properties of cortical bone. Titanium is easily alloyed with other metals (Nickel, Zirconium, Aluminum) to modulate its stiffness. While used less frequently than titanium, porous tantalum implant components have unique material properties that promote implant stability. Tantalum's protective oxide coating makes it highly biocompatible, thus minimizing interference in osseointegration by the host immune response.[24, 25] Furthermore, in vitro studies have suggested that tantalum itself forms a biological bond with bone.[22] Sintered cobalt-chromium (CoCr) or titanium beads are commonly used as porous coatings, although they are limited by low porosity and superficial osseointegration. Autopsy studies of these implants have shown limited bony ingrowth.[25] Plasma spray, metallic foams, and vapor deposition techniques may increase porosity of implant coatings and are commonly used with titanium or hydroxyapatite.

Compressive Osseointegration

Limited options for fixation of oncologic implants into short segments of bone as well as the untoward effects of stress shielding led to the design of the CompressCompliant Pre-Stress Device (Biomet Inc, Warsaw, IN, USA). By improving the fixation of implants into short segments of bone and loading those segments at the bone-implant interface with a compressive force, implants remain stable, stress shielding is prevented, and the bone maintains its integrity. Modifications of this implant to address early failures have led to an implant with excellent 10-year results.[26] Compressive osseointegration is one of the most significant recent advancements in reconstructive science in orthopaedic oncology.

Biologic And Cell-Based Implant Modification

Some metals used in implant coating primarily for their physical properties have also been shown to improve recruitment and adhesion of mesenchymal cells and promote osteogenesis via biological mechanisms.[27] When used in a porous configuration, tantalum and titanium were noted to promote differentiation of osteogenic cells from adipose-derived stem cells and were found to be a viable scaffold for human MSC proliferation.[28-30] *In vitro* use of a magnesium coating was shown to promote adhesion of mesenchymal cells and promote osteogenesis. Another possible advantage of using magnesium to improve osseointegration of implants is that it is biodegradable and can be resorbed and replaced with newly formed bone.[27]

Local delivery of growth factors and other biologically active compounds to the site of osseointegration or osteogenesis is a promising method to deliver a steady therapeutic dose of medication while minimizing systemic concentration and potential side effects. However, concerns regarding possible carcinogenic effects when used in oncological patients remain. Some of the substrates used to this end are hydrogels, biodegradable polymers, and peptide-linked medications.[31, 32] Substrate stability and resistance to clearing must be balanced against its ability to carry sufficient amounts of medication and elute it at the desired rate; it must also avoid eliciting an immune response. One currently investigated substrate is a hydrogel of sericin, a silk protein with strong adhesive properties, which has the ability to release bioactive compound in sustained manner and low immunogenicity.[33, 34]

SOFT TISSUE ATTACHMENTS

The interface between soft tissues and implanted prosthesis and grafts is an area of significant interest in orthopaedic oncology. The need for *en bloc* resection of tendons and/or their attachments often results in functional deficits, and current techniques for the attachment of soft tissue to implant and grafted bone are limited.

Preclinical models have recently focused on the use of biological augments such as bone graft, marrow contents, demineralized bone matrix (DBM), and stem cells to enhance soft tissue to implant interactions. These biologics are often combined with differing fixation techniques.[35-37]

Porous metals have been proposed as a means to improve tendon-to-implant and tendon-to-bone healing. Porous tantalum at the site of supraspinatus attachment as well as patellar tendon attachment showed near physiologic strength in two separate canine models.[36, 38] In a murine model of rotator cuff repair, porous titanium at the site of supraspinatus insertion showed superior mechanical properties when compared to repair to bone.[39] More recently, de-cellularized entheses have been proposed for use as a scaffold for biologic growth at the tendon-bone interface. The attachment of tendon to implants provides unique challenges, with previous studies focusing on both biological augments and novel reconstructive techniques. Ovine models for attachment of the patellar tendon to a metallic implant using a mesh with demineralized bone matrix (DBM)[37] and hydroxyappetite[40] augments suggest that mesh with biological augments are superior to mesh alone. Several biologics have been used to augment the healing of rotator cuff tendons to the humerus. A locally harvested periosteal augment was shown to enhance tendon-to-bone healing in a rabbit model.[41] The addition of stem cells directly to the tendon-bone interface has been studied at length and has shown promising preclinical results. Over a decade of *in vitro* and preclinical data on the biological enhancement of soft tissue attachments to bone and metal have shown promise, but effective translation to the clinical realm has been lacking.

Clinical data on novel soft tissue attachment techniques is relatively sparse. Utilization of (DBM) and synthetic mesh for tendon-to-implant repair has suggested enhanced soft tissue integration. Multiple small case series of extensor mechanism repair using mesh augments in the arthroplasty and oncology literature suggest improved outcomes when compared to non-augmented techniques.[42, 43] In small case series of nine patients, a synthetic tendon augment was used for repair of the patellar tendon to a proximal tibial prosthesis with one re-rupture and good functional outcomes at eighteen months.[44] Overall, the reconstruction of tendinous and other soft tissues to implants and grafts remains a major concern in orthopaedic oncology with a need for future research and advancement in this area.

STEM CELL AND BIOLOGICAL AUGMENTATION

Engineered bone augments and substitutes have long been viewed as the next major breakthrough in reconstructive science. Tissue engineered constructs (TEC) are viewed as a more biological reconstructive technique than implantation of isolated metal or allograft, and largely avoid issues of donor site morbidity associated with autograft. The creation TECs

generally entails the use of growth factors and stem cells to stimulate the regrowth of a patient's own tissues in an existing defect, or create *de novo* engineered tissues *in vitro* or ectopically for later implantation. In orthopaedics, the primary growth factor used for this purpose is bone morphogenic protein (BMP). Stem cells may be derived from a variety of sources, including autogenously harvested adipose tissue, bone marrow, and circulating cells.

In situ augmentation

Various protocols for defect reconstruction using TEC have been proposed. The simplest methods involve the use of growth factors and/or stem cells with standard graft material as an adjuvant to induce osteogenesis and enhance healing. In one series, autologous mesenchymal stem cells (MSC) were injected into the site of composite (allograft with associated endoprosthesis) reconstruction of primary malignant bone tumors. Ninety-two such cases were retrospectively reviewed, all of which went on to bony union. Rates of primary tumor recurrence and development of secondary cancers were not significantly different from historical controls at mean follow up of 15 years.[45] However, significant concerns regarding the possible pro-tumor effects of MSCs and growth factors in oncological patients remain pervasive in the orthopaedic oncology community. Few examples of this *in situ* technique used in oncological defects exist in the literature, likely due to these concerns. Advantages of the *in situ* technique include mitigating the need for staged surgery. These constructs may be best suited for small defects created from resection of benign tumors.

In vitro constructs

TECs may also be produced *in vitro* using stem cells and/or growth factors placed onto a scaffold to create a suitable graft outside of the body. Avoiding the use of growth factors at the site of reconstruction and allowing MSC to differentiate into osteogenic cell lines prior to implantation is thought to reduce the risk of pro-tumor effects. A wide variety of scaffolds have been proposed such as hydroxyapatite-augmented ceramics,[46] tricalcium phosphate,[47] decellularized matrix,[48] and 3D printed synthetic biomaterials.[49-51] Bhumiratana et al. describe the reconstruction of a complex mandibular defect in a porcine model by implanting autologous adipose-derived stem cells onto decellularized bovine bone custom fabricated using CT-guided micromilling. Grafts were placed in a bioreactor for three weeks prior to implantation. At six weeks after implantation, TECs showed increased bony integration and volumetric regeneration when compared to grafts without stem cells.[48] Morishita et al. expanded and grafted autologous MSCs from bone marrow aspirate onto hydroxyapatite ceramic scaffolds. These "cultured bone grafts" were then used to reconstruct bony defects in three patients undergoing curettage of benign cystic tumors. Postoperative CT showed new bone formation and osseointegration with no recurrence at two years. One graft was used in a periarticular defect and was pre-fabricated to match the patient's anatomy using preoperative CT scan.[46] Sandor et al. used autologous adipose derived stem cells and BMP cultured onto a tricalcium phosphate graft with a customized metallic mesh implant to reconstruct a mandibular defect in one procedure immediately after tumor resection. At three-year follow-up, there was histological evidence of osseointegration and no evidence of infection or recurrence.[47] Customized, 3D printed synthetic biomaterials

are increasingly seen as an appealing scaffold for TECs. Polycaprolactone (PCL) scaffolds have been proposed due to their similarity to cancellous bone and favorable biodegradable properties. PCL constructs have been used to successfully reconstruct calvarial defects in the clinical setting but have not been used in orthopeadic patients.[49] Reichert et al. showed that PCL scaffolds augmented with BMP were equivalent to autograft, and superior to PCL scaffold with MSCs when reconstructing segmental tibial defects in an ovine model.[51]

Endocultivation

The patient themselves may also be used as a bioreactor in a process known as endocultivation. First used to construct a congenital defect of the mandible, [52] Warnke et al. [53] were the first to demonstrate this technique in an oncological setting. A custom titanium cage was fabricated and exogenously filled with a bovine-derived bone substitute, infused with rhBMP and autogenous bone marrow, and implanted into the patient's latissimus dorsi. The graft was cultivated for seven weeks before it was harvested as a myo-osseous free flap and implanted in the mandible. While initial results were promising, the graft ultimately became infected and required revision.[54] There was no evidence of tumor recurrence at the time of the patient's death 13 months after implantation. Heliotis et al. used a similar technique for reconstruction of a resected mandibular tumor with failure of the graft at five months due to infection. After implantation in the rectus muscle for eight months, an endoculiviated maxillary graft was used to construct an oncological defect with good results at one year.[55, 56]

In orthopaedic oncology, the use of TECs has been met with trepidation. The use of BMP and stem cells is viewed with appropriate apprehension given concern for carcinogenic effects. However, this concern appears to be largely theoretical at this time rather than based on existing data. Autologous marrow-derived MSC have not been shown to increase cancer risk when used to treat orthopaedic maladies, either at the site on injection or systemically.[57] Similarly, MSCs injected at the site of primary malignancy of the bone have not demonstrated recurrence rates higher than controls.[45] More rigorous study of this question is required prior to the widespread use of BMP or stem cells in oncological patients. Furthermore, the clinical data on the use of TECs in oncological defects has shown mixed results, particularly when using the endocultivation technique (Table 1). Larger trials will be needed to compare the use of TECs to traditional reconstruction techniques.

INFECTION PREVENTION

Periprosthetic and graft infection are dreaded complication in orthopaedic surgery and have persisted as a major cause of reconstructive failure despite the use of perioperative antibiotic administration and advances in aseptic technique. Due to altered host defenses, large tissue defects, and iatrogenic immunosuppression, oncologic patients face a greater risk of infection than the general orthopaedic population and with the gravest possible consequences. Biofilm formation on implants remains a major hurdle in fighting periprosthetic infections. Various technologies are currently being investigated to prevent biofilm formation with the goal of establishing bone-implant integration before infection can take hold, a concept sometimes referred to as the "race to the surface".[58]

Biological adjuvants

The treatment of large bone defects in the setting of chronic infection is challenging and complicated by multiple factors. The inflammatory response alters normal cell signaling required for bone healing and scar tissue disturbs normal vascular function, reducing the supply of necessary nutrients and systemic antibiotics from reaching the area. Bioengineered tissues that are to be used in this setting must serve multiple functions: help treat the infection, improve bone healing and avoid becoming a nidus for further infection.[59] Various approaches are currently being investigated, including the combination of antibiotics, antibacterial nanoparticles, growth factors, and cultured mesenchymal stem cells. Wang et al. used a matrix composed of hydroxyapetite, fibronectin and alginate to hold cultured MSC that were treated to over-express WNT-11. When implanted in a rabbit model of osteomyelitis, these animals showed significant improvement in osteogenesis compared to controls.[60] While such techniques have been developed for reconstruction in an already infected bed, they are easily transferrable to primary reconstruction in a non-infected bed as a means of infection prevention.

Antimicrobial cement

The use of antibiotic impregnated polymethylmethacralate (PMMA) is widespread. Vancomycin, gentamycin and tobramycin are the most commonly used antibiotics in PMMA, due to their small size, reasonable broad-spectrum coverage, and limited heat sensitivity (allowing them to retain function in the exothermic hardening of the cement). Antibiotic impregnated PMMA showed a protective effect from infection in registry data;[61] however, a recent prospective randomized clinical trial of 3000 patients found no difference in the rate of infection with or without antibiotic-impregnanted cement.[62]

Antimicrobial coatings

Antibiotic and nanoparticle implant coatings have previously been used to prevent infection in the clinical setting. In two small case series in the trauma literature, tibial fractures treated with polylactic acid-gentamicin coated nails had no deep infections at one-year follow up.[63, 64] Nanoparticles such as silver and iodide, long known to have antimicrobial properties, have also been used to coat implants. The current clinical literature suggests that these coatings are safe and demonstrates a trend towards effectiveness.[65-68] In a prospective series of 51 silver-coated endoprosthesis implants in tumor patients, there was a trend towards decreased infection rates in coated implants compared to controls at five years (5.9% vs. 17.6%, p=0.062). None of the infected patients in the coated group underwent amputation, whereas 39% of infected controls required amputation.[66] In a retrospective meta-analysis of 68 tumor patients, silver-coated implants again showed a trend towards decreased infection at four years (7.9% vs. 16.7%).[69] In a subgroup analysis, silver-coated implants appeared to be more effective at preventing early infection (less than 6 months, 2.6% vs. 10%) than late infection (more than 6 months, 5.3% vs. 6.6%). Analysis of explanted prostheses suggested breakdown of the silver coating at 6 months, perhaps explaining this trend. However, given the small sample size, none of these findings were significant. Notably, no complications of systemic or local silver toxicity (agrygia) were reported in any of the above series. Small case series of iodine-coated endoprostheses have suggested similar efficacy and safety.[70]

While promising, more rigorous, large-scale trials are needed to prove that the efficacy of iodide and silver coated implants are worth the cost. At present, these coatings are not available in the United States, largely due to regulatory issues.

Recent research in preclinical models has focused predominantly on specialized implant coatings. Non-eluting (passive) coatings refer to those that use static surface modifications to prevent the adhesion of microbes to the implant surface, thereby prevention biofilm formation and chronic infection. These coatings must simultaneously allow osseointegration to maintain implant stability. Various compounds have been proposed for such coatings. In a sheep model of implant infection using locking compression plates (LCP), a hydrophobic cation paint effectively inhibited bacterial colonization and promoted fracture healing when compared to non-coated plates.[71] Prevention of bacterial adhesion and biofilm formation was also demonstrated on a subcutaneously implanted metallic disk coated with a Teflon-like material in a murine model, although this model did not evaluate the coatings effect on bony ingrowth and healing.[72]

Coatings that actively elute antimicrobial compounds into the periprosthetic environment provide the theoretical advantage of preventing soft tissue infection in addition to inhibiting biofilm formation on the implant surface. Local delivery of antibiotics may also reduce the risk of antibiotic resistance and systemic toxicity when compared to intravenous administration. While antibiotic coated implants are not novel and are already available in the clinical setting, current research is focused on optimizing release kinetics of eluted antibiotics. Ideally, such coatings will release antibiotics at levels above the minimum inhibitory concentration (MIC) for a defined period of time long enough to prevent implant infection and ceasing prior to the development of antibiotic resistance.[73] A wide variety of coating materials have been proposed to elute antibiotics in this manner including hydroxyapatite, phosphatidylcholine, polyethylene glycol, poly(lactic-co-glycolic acid) (PLGA), and chitosan.[74-78] More recently, “smart” coatings designed to elute antibiotics in the presence of infection have shown favorable release kinetics and *in vivo* efficacy at preventing implant infection in a murine model.[76]

Coatings designed without the use of traditional antibiotics have also been proposed as a means of avoiding antibiotic resistance. Nanoparticles such as electrospun polymer fibers and silver particles engineered for controlled release from implant surfaces have shown efficacy in preventing biofilm formation *in vitro* and *in vivo*.[79, 80] Bioactive compounds such as chitosan engrafted antimicrobial peptides have demonstrated promising antimicrobial characteristics, biocompatibility, and controlled release kinetics.[81]

Taken as a whole, the preclinical data for these next generation antimicrobial coatings suggest that translation to the bedside is imminent, possibly representing a breakthrough in the fight against implant infection. However, regulatory issues governing implanted materials and the cost of bulk fabrication of coated implants remain barriers to widespread use. Furthermore, the shelf life of many antibiotic coatings is unknown. In order to avoid such issues, coatings that are applied at the point-of-care have been developed and may avoid the pitfalls of regulation and cost.[75, 76]

SUMMARY

The reconstruction of large bony defects remains one of the central challenges in orthopaedic oncology. Endoprostheses and bulk allograft reconstruction are the primary modalities used to reconstruct such defects, although failure rates remain high. Advances in prosthetic design and the widespread use of perioperative prophylactic antibiotics are among the major breakthroughs in reconstructive science in the modern era, but similar durable advancements have been sparse. More recently, porous metals have improved osseointegration and compressive osseointegration has allowed durable fixation in short segments. Despite the promise of tissue engineered constructs and biological and cell based augments aimed at improving osseointegration and soft tissue/implant interactions, translation of these technologies to the clinical realm has fallen behind expectations. Antimicrobial implant modifications are increasingly common in the international community, but have yet to reach widespread use in the United States. Antimicrobial coatings, specifically those with active elution kinetics and point-of-care application capabilities, are perhaps the most promising imminent breakthrough in implant science.

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Table 1

clinical use of tissue engineered constructs (TEC) for reconstruction of osseous oncological defects.

Construct method	Author (year)	Demographics	Study design, level of evidence	Methods/TEC design	Clinical outcomes	Follow up (mean/minimum;years)
In situ	Herniguo et al. (2014)	N = 92, primary sarcoma of proximal femur	Retrospective cohort, level III	Autologous bone marrow derived MSC harvested at time of surgery, processed, and injected into site of composite allograft/prosthesis reconstruction	Bony union in all cases, 13/92 tumor recurrences compared to expected 15-20 recurrences in control cohorts, no functional outcomes	15.4/10
In vitro	Morishita (2006)	N = 3, cystic tumors of tibia/ femur (ABC, GCT, FD)	Case series, level IV	Autologous bone marrow derived MSC isolated and expanded (2 weeks), then cultured with HA ceramic scaffolds (2 weeks) prior to implant at time of tumor resection	Radiographic union at 3 weeks in all cases, no graft failure, no infection, no recurrence, no functional outcomes	3.1/2.4
	Sandor et al. (2013)	N = 1, recurrent ameloblastoma of mandible	Case report, level V	Autologous ASC isolated and expanded (3 weeks), cultured with TCP and rhBMP-2 (2 days) prior to implantation into custom titanium cage at time of resection	Histological and radiographic evidence of osseointegration, no graft failure, no infection, no recurrence, no functional outcomes	3
Endocultivation	Warnke et al. (2004, 2006)	N = 1, unspecified tumor of mandible	Case report, level V	Bovine bone mineral blocks, rhBMP-7, and whole bone marrow placed into custom titanium cage and implanted into latissumus dorsi (7 weeks), harvested with vascular pedicle and implanted in second procedure	Initial radiographic evidence of osseointegration and bone formation, infection requiring revision within one year, death of patient due to cardiac arrest, no recurrence	1.1
	Heliotis et al. (2006)	N = 1, SCC of mandible	Case report, level V	HA bone substitute, rhBMP-7 construct implanted into pectoralis major (6.5 months), harvested with vascular pedicle and implanted in second procedure	Initial radiographic and histological evidence of osseointegration and bone formation, infection and failure of graft at 5 months	0.4
	Mesimaki, 2009	N = 1, reccurent keratocyst of maxilla	Case report, level V	Autologous ASC isolated and expanded (2 weeks), cultured with TCP and rhBMP-2 (2 days) placed into custom titanium cage and implanted into rectus abdouminus (8 months), harvested with vascular pedicle and implanted in third procedure	Histological and radiographic evidence of osseointegration, no graft failure, no infection, no recurrence, no functional outcomes	1

MSC = mesenchymal stem cell, ABC = aneurysmal bone cyst, GCT = giant cell tumor, FD = fibrous dysplasia, HA = hydroxyapatite, ASC = adipose stem cell, TCP = tricalcium phosphate, rhBMP = recombinant human bone morphogenic protein, SCC = squamous cell carcinoma