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Chapter

Skin Substitutes and Biologic Agents for Wound Closures after Melanoma Resection

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Abstract

Wound healing is a highly complex process mediated by microscopic cellular interactions. An improved understanding of the physiology of wound healing has laid the groundwork for translational research to create biologic wound care technologies that have significantly impacted patient care. Biologic wound technologies have broad applications and have had a significant impact on the reconstructive ladder, as the reader will see throughout this chapter. Despite their frequent use, many surgeons are unfamiliar with the plethora of products on the market, as well as each product’s relative advantages and disadvantages. This chapter will go over oncologic reconstruction of the nose, scalp, lip, cheek, and extremities after wide local excision of melanomas in these areas, which is a significant challenge for plastic surgeons. Traditional methods for reconstructing these defects include primary closure techniques, skin grafts, local flaps, pedicled flaps, and free tissue transfer; however, the increased risk of metastasis associated with melanoma makes it difficult to use biologic wound healing agents like Integra and Cytal as alternative reconstructive options without causing additional donor site morbidity. In this chapter, we examine the use of biological agents in soft tissue reconstruction, including the surgical approaches, complications, and limitations of various reconstructive methods.

Keywords: plastic surgery, reconstruction, biocompatible materials, acellular dermis, wounds and injuries, lip, cheek, nose, scalp, extremity, melanoma, cutaneous malignancies

1. Introduction

The largest organ in the body, the integument, performs a variety of vital tasks like thermoregulation and defense against environmental microorganisms [1, 2]. Given these roles, injuries to the integument and underlying soft tissue can be anything from merely unsightly to, in the case of severe burns, potentially fatal. Independent of the deformity, the goals of reconstructive surgery are to optimally restore the patient’s shape and function. Although there are numerous methods for reconstructing these defects, there are clinical situations where their application is constrained [3]. Several biologic wound care products were created as a result of these challenging situations and developments in our understanding of the physiology of wound healing.
Biological wound agents have advanced the reconstructive ladder since they were originally created in the late 20th century and are now used to repair abnormalities in the skin, soft tissue, and bone [4–6]. The classification of biologic wound care products used in skin and soft tissue restoration, as well as benefits and drawbacks of their application, will be covered in this chapter.

Biologics, biomaterials, and bioconstructs are all names that can be used to refer to a large group of products created from human or animal tissue, or synthetic materials made from organic compounds. As a scaffold for cellular proliferation and differentiation, these substances can be incorporated into or used to replace host tissue as they stimulate wound repair on a cellular level [7–12].

The function, anatomical structure, cellular makeup, and material type are only a few of the features used to categorize biologics [8]. For convenience, we categorize these products based on whether they contain bioactive cells or are acellular in design. Dermoinductive, or cellular, products contain living cells that encourage the creation of extracellular matrix and the growth of new tissue. These cells are often fibroblasts or keratinocytes [13–16]. Products that are dermoconductive or acellular serve as regenerative scaffolds for cell migration, cell proliferation, and the production of extracellular matrix [10]. By enhancing the angiogenic qualities of cytokines generated by the product’s cells, dermoinductive wound agents are believed to better aid wound healing when compared to the other types of products [17, 18]. Integra (Integra LifeScience Corporation, Princeton, NJ) and other dermoconductive technologies are believed to be less immunogenic than dermoinductive ones, boosting the success of reconstructive procedures [17, 19]. Several randomized controlled trials comparing cellular and acellular wound agents are ongoing at the time this book was written, but preliminary results indicate that both types of agents are equally effective [17, 19]. In numerous trials, it has been demonstrated that both medicines offer comparable-to-superior results when compared to conventional wound treatment [20–32].

Patients and healthcare professionals have an alternative to conventional reconstructive techniques attributable to the use of biologic wound healing agents in head and neck soft tissue reconstruction [7]. Their effectiveness in challenging surgical situations has received significant acknowledgment [20, 22, 26, 33–36]. These synthetic dermal substitutes, which are useful in a variety of settings, can significantly affect the rates of tissue regeneration and scar development. Notably, they offer a practical answer for covering soft tissue abnormalities resulting from tumor removal.

The final treatment for melanoma resection surgery entails extirpation and thorough dissection to obtain clear margins. Unfortunately, patients may be left with major tissue abnormalities that disrupt the natural symmetry of their face, necessitating reconstructive surgery. Due to restrictions on the surrounding tissue envelope, the severity of the disease’s involvement, and cosmetic considerations, reconstructing soft tissue in these areas after melanoma removal presents a considerable challenge for plastic surgeons. Traditional methods for closing these defects include skin grafts, regional flaps, and pedicled flaps; however, developments in skin replacements over the past few decades have produced adaptable substitutes for patients and healthcare professionals [37]. In addition, the development of acellular dermal matrices like Integra (Integra LifeScience Corporation, Princeton, NJ) and Cytal/MicroMatrix (ACell Inc., Columbia, MD) provides solutions for denuded avascular structures. These materials can also be used in conjunction with skin grafting in a staged reconstruction for better skin-tone matching and improved cosmesis [38–41].
1.1 Applications

The surgeon must assess the location, size, and depth of the wound to decide whether the patient will benefit from the use of a biological agent before choosing the best one for them [42, 43]. The surgeon must also assess the defect to see if any underlying tissues, such as tendons, bones, or blood arteries, are exposed. The surgeon must then describe the condition and quality of the wound bed. Although their indications for use have substantially broadened, biologic wound treatments were traditionally used in burn and abdominal wall restoration [43]. Several dermoinductive and dermoconductive wound agents have currently been approved by the United States Food and Drug Association (FDA) for the purpose of soft tissue reconstruction; nevertheless, many reconstructive surgeons use them off-label to fix defects not explicitly permitted by the FDA [44].

2. Scalp reconstruction

The epidermis, dermis, galea aponeurotica, loose areolar tissue, and periosteum—overlying the calvarium—are the five tissue layers that make up the scalp [45]. The epidermis and dermis are composed primarily of fat, adnexal appendages, and hair follicles. The avascular barrier created by the subgaleal loose areolar tissue separates the periosteum’s outer layers from its highly vascularized center [45]. The superficial temporal, postauricular, occipital, supraorbital, and supratrochlear branches of the scalp’s vascularity are provided by the external and internal carotid arteries [45]. Blood flows inward through these branches to build an intricate network of anastomoses as it moves from the scalp’s edges into the center [45]. This offers the best foundation for grafting and the application of dermal substitutes.

Baseline considerations for scalp reconstruction should include the affected region of the scalp, the amenability of the scalp tissue to flap reconstruction, and the healing method. Galeal aponeurosis mobility is constrained by big defects due to its relative rigidity. Compared to the central scalp and vertex, the lateral regions of the galeal aponeurosis typically display more flexibility. Even with relatively bigger defects, the loose areolar tissue can frequently be mobilized to create a flap [45].

Our institution has focused on increasing the use of biologic wound-healing therapies for scalp reconstruction after oncologic resections more recently [46]. Biologic wound-healing agents provide constant, dependable results with high success rates and very few downsides when used in conjunction with color-matched split-thickness skin grafts. Dermal substitute placement is a reasonably simple surgery that can be completed in less than an hour with either local anesthetic or intravenous sedation, drastically reducing on overall operating time. Additionally, there is no additional scar burden because it does not require for the creation of additional incisions. Although there are many dermal substitute products available, Integra is the biologic we favor because it produces the most trustworthy outcomes. Integra was initially just applied to defects requiring bone burring of the calvarium to create deep margins. This restricted its usage in patients with minor defects or intact periosteum. The expanded approach for wound agents allowed us to apply Integra directly to unburred bone in defects less than 4 cm or on the wound beds for all patients with an intact periosteum. Our reasoning for bone burring was further broadened to cover any lesions with dispersed soft tissue, more than 4 cm of exposed bone, any past radiation history, and other questionable soft tissue vascularity.
3. Nasal reconstruction

Given its prominent physical position as the most central part of the face, the nose can significantly contribute to defining a person’s overall identity as well as their esthetic look [47, 48]. Therefore, it is crucial that surgeons take into account the delicate foundations of each reconstruction. This necessitates a full comprehension of the intricate nature of nasal anatomy, as well as the value of esthetics for the patient. The superficial fatty layer, fibromuscular layer, and deep fatty layer make up the nasal soft tissue structurally. The superficial musculoaponeurotic system, which is located under the nasal perichondrium and periosteum, serves as the division between the superficial and underlying tissues [49]. When considering the esthetic subunits of the nose: the lower third is made up of the soft triangles, columella, tip, and ala, while the upper two-thirds are confined by the dorsum and nasal sidewalls [50].

Our institution now uses a Depani et al. algorithm to direct the use of biological agents in nasal reconstruction [46]. The strength of these therapies is their capacity to expedite healing without requiring delayed full-thickness skin grafting, which is especially important for reconstructions. Wounds with a properly vascularized bed can be first temporized using Integra or an ACell construct rather than subjecting patients to additional risks including donor-site morbidity and poor color-matching. Then, if necessary, a delayed split- or full-thickness skin graft can be performed; alternatively, patients who are still viable can simply move on to secondary healing. An additional application of ACell to the wound bed can boost the overall effects of the product and raise the likelihood of successful healing. We have been able to considerably enhance outcomes in both upper and lower nasal restorations because of this approach. Our use of biological agents significantly decreased the necessity for distant flap reconstructions for procedures involving the upper nose. Additionally, the dorsum and sidewall’s structural characteristics make these agents favorable for satisfactory esthetic results.

The value of biologics was less significant in the lower third of the nose, but our understanding of how they can be used is continually changing. At first, our institution used very few ACell matrices for lower nose reconstructions. Early iterations of

Figure 1.
A 74-year-old female with skin malignancy. (A) Photograph was taken before excisional surgery of the lesion at the left alar groove. (B) Resultant defect involving the left ala and sidewall. (C) 12 days after ACell MicroMatrix and Cytal placement; (D) 30 days postoperatively; (E) 60 days postoperatively; and (F) 4 months postoperatively.
our technique did not believe the use of biologics was necessary; lower nose recon-
structions were nearly always closed with flaps due to the anatomic consequences
of these surgeries. The sole exceptions to this rule were two patients that were ruled
unfit for secondary procedures because the graft bed was not properly vascular-
ized. In these two patients, the necessary vascular basis was established using ACell
constructs, facilitating secondary full-thickness grafting (Figure 1). Applying an
ACell construct made of Cytal and MicroMatrix in these circumstances can lessen
the burden of undesirable scarring and eliminate the need for delayed full-thickness skin
grafting.

4. Lip reconstruction

The lips are one of the first facial features that people notice during interper-
sonal interactions, and the ordinary person can immediately detect tiny flaws and
distortions [51–53]. The patient can eat, drink, and speak clearly attributable to
the lips’ ability to control oral competency in addition to their cosmetic value [54].
Furthermore, because they are so important in the display of emotion, the lips
are also crucial parts of nonverbal communication. The architecture of the upper
lip differs from that of the lower lip in that it has several esthetically significant
subunits, such as the philtrum, white roll, and Cupid’s bow. The use of biological
wound treatments for lip reconstruction comes with a number of challenges. First,
because biologic wound agents need a wound bed to integrate with the patient’s
native tissue, they can only restore partial thickness deficits of the mucosal and
cutaneous lip. Second, both deliberate and involuntary motions of the lip can dis-
rupt the interaction between the wound bed and the wound agent. The importance
of biologic wound agents for lip reconstruction cannot be understated, despite these
drawbacks.

The senior author uses a specific technique to restore mucosal-only defects.
In essence, an acellular dermal matrix in sheet form called Cytal Wound
Matrix (ACell Inc., Columbia, MD) is sutured over the defect and packed with
MicroMatrix (ACell Inc., Columbia, MD), an acellular dermal matrix. After that,
patients are told to use Surgilube (HR Pharmaceuticals Inc., York, PA), a water-sol-
uble lubricating jelly, up to five times daily for 3–5 weeks. When compared to local
and regional flaps, the reconstructive surgeon can produce outstanding esthetic
results with this procedure with little to no lip distortion [55]. It should be noticed
that the lip will initially develop dark granulation tissue before it is replaced with
mucosa that looks natural. Other acellular dermal matrices have been used with
comparable esthetic results to reconstruct vermillion-only lesions [56, 57]. After
primary reconstruction, if minor variations still exist, further revisions can be
done using autologous fat grafting or fillers.

For reconstructing cutaneous deformities of the lip, biologic wound treatments
have a limited role. To prepare the wound bed for subsequent definitive reconstruc-
tion with a full-thickness skin graft, dermoconductive wound agents like Integra
Bilayer Wound Matrix (Integra LifeSciences, Princeton, NJ) may be employed. Use of
biologic wound treatments lowers the chance of scar contracture as compared to skin
grafting alone, lowering the danger of distorting nearby structures like the vermilion
or, in the case of the upper lip, the nose [58]. MicroMatrix and Cytal Wound Matrix
can be used as indicated in the preceding section in place of the Abbe flap when a
defect involves the white roll and vermilion.
5. Cheek reconstruction

The ability of the surgeon to reconstruct the defect without producing retraction of the lips, nose, or eyelids is a key factor in successful cheek reconstruction [59, 60]. The reconstructive strategy should take this into consideration because the eyelid, in particular, is more vulnerable to extrinsic stressors. The cheek is divided into three visual zones, each with its own esthetic and practical considerations [61]. Locoregional tissue transfer and skin grafting procedures are the main reconstructive approaches utilized to treat partial thickness defects, regardless of the zone(s) that are affected [62–64]. The reconstructive method for partial thickness cheek defects also includes biological wound agents, but only in specific clinical situations.

A key component of cheek soft tissue reconstruction is the cervicofacial advancement flap [65]. Patients who are unable to discontinue anticoagulant and antiplatelet drugs are not recommended for this surgery because it increases intraoperative complications. It is better to reconstruct the defect with a biologic wound agent with or without delayed skin grafting for patients who lack soft tissue flexibility, such as those who have previously undergone rhytidectomy or who cannot stop taking anticoagulants and antiplatelet treatment. Finally, patients whose surgical specimens are awaiting pathology examination may employ biologic wound agents as a temporary remedy, however this is rarely done in the long-term situation due to the exorbitant cost of these agents.

6. Extremity reconstruction

The most frequent cancers overall are cutaneous malignancies, with UV light being the main risk factor for their occurrence [66]. There is a significant incidence of carcinogenesis on the face, more notably in the H-zone. The lower extremities,
which are often in many locations less exposed to the sun, occur less frequently. Both non-melanoma and melanoma skin cancers have the potential to cause localized tissue damage, with the latter having a high chance of metastasizing [67, 68]. Additionally, certain melanomas skin cancers are known for appearing in places that are not exposed to the sun directly, such the soles and subungually [69–71] (Figure 2).

Extensive local excision is currently the gold standards of therapy for melanoma skin malignancies [72–74]. These resections produce defects that range in complexity and magnitude, and they frequently cause serious functional and psychological impairment in the people who are affected.

Given the lack of surrounding tissue available for reconstruction with local muscle and fasciocutaneous flaps, lesions of the legs and feet can be particularly challenging to reconstruct in comparison to those of the thigh. In addition, numerous lesions expose underlying tendon and bone, especially those that are present in the dorsal side of the foot and the distal third of the leg. Free tissue transfer is frequently regarded as the gold-standard reconstructive technique to address these defects, but if microvascular reconstruction is not an option, biologic wound treatments are a great option [75]. In this chapter, we discuss how soft tissue defects in the lower extremities can be repaired with biological wound treatments after melanoma resections.

The best functional and esthetically pleasing results after reconstructing leg and foot deformities depend on meticulous preoperative planning. The surgeon must take into account the soft tissue quality and laxity of the surrounding area in addition to the defect's location, size, and depth while assessing a defect. The surgeon must take a detailed medical and social history in addition to assessing the wound to find any medical issues or lifestyle choices that might have an adverse effect on the results of reconstructive surgery. Most significantly, people who smoke, have had radiation therapy in the past, or have peripheral artery disease are more likely to experience postoperative problems [76, 77].

Split-thickness skin grafting (STSG) can often be used to reconstruct superficial defects that preserve the underlying muscles, tendons, and bones with acceptable results [76]. However, adding biological wound agents before graft placement is typically beneficial for larger superficial lesions [78]. Biologics followed by STSG have been demonstrated to significantly reduce scar contracture over time, which is consistent with outcomes observed in the care of patients with third-degree burns [79].

On the other hand, defects that expose the underlying tendon or bone require more complicated management. Since the tendons are naturally poorly vascularized, they rely significantly on synovial fluid and the soft tissue that lies above them for hydration, lubrication, and defense against the outside environment [80]. Exposed tendons are more prone to dehydration, which lowers compliance and limits the ability of each muscular contraction and relaxation to move fluidly [81]. On the other hand, although strongly vascularized, bony structures are vulnerable to infection when they are unprotected by soft tissues [82]. Deeper defects that expose the paratenon or periosteum need to be covered surgically, and standard autologous skin grafts cannot be used in these situations.

For both the patient and the surgeon, biologic wound agents have several benefits. First, patients who are medically unfit for extensive microsurgical repair can receive soft tissue coverage in an outpatient environment by using biologic agents [75, 76]. The incidence of medical comorbidities that can lead to unfavorable surgical outcomes is much higher than it would be in the general population because numerous patients having oncoplastic repair of cutaneous malignancies are middle-aged or older [83]. In the event that the size of the soft tissue defect exceeds a certain threshold and
the size of the free flap required for reconstruction results in unacceptable levels of donor site morbidity, biologic wound agents may be used. Before final reconstruction with an STSG, small lesions can be easily reconstructed with biologic wound agents in regions where locoregional tissue transfer is challenging, such as the dorsum of the great toe. Acellular dermal matrix products can also be used as a temporary fix until the patient is cleared for permanent reconstruction if the surgical pathology evaluation results are incomplete.

7. Complications and limitations

7.1 Complications

Biologic wound agents are frequently used for wound reconstruction, with different degrees of success. Even though most of these wounds heal adequately after their initial application, problems do occasionally occur [13, 84]. Infection is the most frequent and preventable complication of using biological wound agents [84]. Infections can often be cured with antibiotics and negative pressure wound care early in their clinical course, avoiding the need for surgical intervention [85]. It should be noted that individuals receiving Integra for reconstruction frequently have a creamy exudate at the surgical site between weeks 3 and 5 [86]. Since this phenomenon is sometimes misinterpreted as a soft tissue infection, a thorough evaluation of the patient is necessary to spot any physiologic indications of an infection before beginning an aggressive antibiotic regimen.

Another complication that plastic surgeons face frequently is the biological wound agent detaching and delaminating from the wound bed. To reduce this possibility, it is essential to make sure the wound bed-wound agent interface is completely cleaned and closed with a bolstered dressing or vacuum-assisted closure. Patient education is essential to prevent shearing of the construct before ingrowth into the wound bed in places where these constructs are more challenging to hold [13].

Finally, seroma development is another regularly observed complication linked to the use of dermoconductive wound agents [87–90]. Given that thinner products are easier to incorporate than thicker ones and that seroma formation often results from extended engraftment, using thinner products may lower the likelihood of seroma formation [91].

7.2 Limitations

The effectiveness of biological wound treatments in specific clinical scenarios has been shown in numerous multicenter randomized controlled trials. Despite this, there is a lack of high-quality data for the off-label uses of many products, making it challenging for surgeons to explain their usefulness [78, 92]. Many biologic wound agents have a steep learning curve as compared to conventional skin grafting methods, which commonly causes new surgeons to have difficulties [19]. Lastly, there is little information available about how biologic wound agents affect the expenses associated with providing healthcare [93, 94]. Although these items are pricey, it is likely that, when compared to other reconstructive modalities, they will result in lower costs if they considerably cut the number of revisional surgeries needed after surgery. Furthermore, the use of biological wound agents has been severely constrained in low- and middle-income nations because of their expensive cost.
8. Conclusions

Through translational research, a better understanding of the physiology of wound healing has resulted in the creation of numerous biologic wound agents. Biologic wound agents have been successfully used in numerous therapeutic situations since they were originally used for burn surgery. While numerous studies including ones done at our institution have demonstrated the excellent efficacy of these products in reconstructing a variety of defects, many of their off-label applications have not undergone rigorous multi-institutional investigation. There is also little information contrasting dermoinductive and dermoconductive items. Moving forward, the authors anticipate that the refinement of present technologies, as well as the introduction of new products, will result in patients having better postoperative outcomes throughout time.

Conflict of interest

None to disclose.

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