Management of surgical soft tissue defects of the lower extremities

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Abstract

Management of post-operative soft-tissue defects on the lower legs is challenging owing to arterial and venous insufficiency, poor skin quality including epidermal and dermal atrophy, insufficient tissue laxity, and increased risk of infection. This paper highlights the management of post-operative soft-tissue defects on the lower extremity that cannot be closed primarily or by reconstruction with a local flap. A systematic review of the literature was performed using the National Library of Medicine (NLM) PubMed online database. Articles were included if they reported the management of post-operative lower extremity soft-tissue defects with secondary intention healing, full-thickness skin graft, split-thickness skin grafts, or skin substitutes. Sixty-three articles were included for analysis. There are several options for managing surgical defects on the lower legs and the method chosen should depend on various factors, including the quality of the skin, vascularity and size of the defect, medical history of the patient, and the experience of the surgeon.

Keywords: cancer, lower extremity, reconstruction, soft-tissue defect

Introduction

The incidence of melanoma and keratinocyte carcinomas continues to increase annually. The annual rate of increase is 3% per year for both skin malignancies and the cost of treatment approaches 5 billion dollars annually [1,2]. Skin cancer commonly occurs on sun exposed sites including the lower legs. The legs are the most common site of melanoma occurrence in women [2]. Post-surgical wound repair on the lower legs is particularly challenging because of the inability to recruit lax skin and lymphovascular compromise [3-5]. In this review, we discuss the various methods available for managing post-operative soft-tissue defects on the lower extremity that cannot be closed primarily or by reconstruction with a local flap.

Discussion

Secondary intention healing (SIH)

The limited laxity of the skin on the lower legs combined with poor skin quality often precludes apposition of the wound edges (primary intention healing). In these settings, secondary intention healing (SIH) may be a desirable solution. Secondary intention healing occurs when the edges of the wound are not opposed. This occurs in several phases, which include 1) inflammation, 2) epithelialization, 3) vascularization, 4) contraction, 5) collagen synthesis, and 6) late remodeling [6]. Classically, wounds on concave surfaces are believed to heal with minimal scarring with SIH. A 2015 survey reported that physicians were more likely to employ SIH to deeper and larger wounds and non-traditional convex sites such as the scalp and pretibial area;

increasing experience was defined as years of practice following fellowship training [7]. The utility of SIH on plantar foot following excision of acral lentiginous melanoma has been reported [8,9] with one study showing superior outcomes in function and cosmesis compared to full-thickness skin grafting [8]. Furthermore, SIH can be augmented by negative pressure wound therapy with excellent and predictable results [3,8].

Bleeding and undue postoperative pain occur infrequently with SIH. The risk of deep infection is decreased compared to primary closure, flap reconstruction, or full thickness skin grafting [10,11]. The major complication of SIH is the risk of wound contraction, which may extend to the surrounding free structures and cause undesirable distortion. However, this complication has been found to occur rarely in lower extremity defects [12]. Other complications of SIH may include prolonged erythema, hypopigmentation, and hyperpigmentation [11]. One disadvantage of SIH on the lower extremity is the prolonged time to complete re-epithelialization compared to the head and neck; therefore, patients must be counseled about this long post-operative course [5].

Lastly, although SIH usually has a predictable outcome, there are instances of healing phase disruption. Physical and psychological comorbidities, medications, allergies, diet, wound care abilities, and caregiver support all effect the SIH process and outcome. A well-balanced diet that is rich in protein and supplemented with vitamin C and zinc is of particular importance during the lengthy healing process [13].

Skin grafting

Full thickness skin grafting

A full thickness skin graft (FTSG) involves the transplantation of the full thickness epidermis and dermis to a non-native location [12,14] compared to a split thickness skin graft (STSG), which involves the full thickness of epidermis but only partial thickness of the dermis. Graft selection for a given defect is dependent on clinical factors including location, depth, and size of the defect. Final expectation of the cosmetic outcome and the experience of the surgeon with each modality will also influence graft selection [15]. Distinct advantages of FTSG include immediate wound coverage, improved cosmesis, and the ability to grow with the patient, which is especially important when used for children [12,14,16,17].

Full thickness skin grafting comes with a few disadvantages. Compared to STSG, a FTSG has a higher nutritional demand and requires a robust vascular supply [12,15]. Factors that reduce the vascular supply to the lower extremities can diminish the survival rate of FTSG. These include obesity, past and present smoking history, uncontrolled diabetes mellitus, uncontrolled hypertension, peripheral vascular disease, genetic connective tissue diseases, hypercoagulable conditions, and chronic venous stasis [18].

When performing FTSG, the donor site is selected based on consideration of the color and texture match to the recipient site. Importantly, the donor site should be meticulously checked for worrisome skin lesions. Common locations for harvesting a FTSG for the lower extremity are the upper medial arm and the inguinal crease. Rarely, the supraclavicular area may be used depending on the patient's donor reservoir of skin. Clinical indication and the experience of the surgeon will largely determine the FTSG harvest site.

Split thickness skin grafts

As outlined above, STSGs are thinner than FTSGs and involve the whole epidermis and part of the dermis. Although a STSG typically has a higher survival rate than a FTSG, the one study that investigated the lower extremities specifically found no differences between the two [18]. One benefit of a STSG is that it can be applied to larger surface area than a FTSG, especially when the graft is fenestrated or meshed [15]. Notably, a STSG should be used to cover a large (usually greater than 5cm) and shallow defect [15]. Owing to the tendency of STSGs to contract more than FTSGs, STSGs are generally limited to areas distant from joints to avoid functional compromise [17]. Furthermore, because of the decreased anatomical thickness of the graft, innervation is usually restored earlier with a STSG compared to a FTSG, although overall re-innervation is more complete in FTSG.

Table 1. *Summary of bioengineered dermal substitutes.*

Product	Properties	Indications	Disadvantages/risk	Advantages
Biobrane®	- Acellular - Bilayer of silicone and nylon mesh	- Temporary coverage - Delayed reconstruction - MMS defects	- Infection	- Readily available - Reduces pain - Shorter hospital admissions
Alloderm®	- Acellular dermal matrix from cadaveric skin	- Skin cancer reconstruction - Many others	- No epidermal layer	- Natural medium - Enhanced cosmetic appearance compared to STSG
Integra®	- Bi-layer of silicone and bovine collagen	- Burns - Scar contractures - Skin graft donor sites - MMS defects	- Two-step operation - Risk of infection	- Impermeable to water - Good aesthetic result - Immediate coverage - Reduces hypertrophic scars
Oasis®	- Porcine extracellular matrix	- Post skin cancer removal - Partial and full-thickness wounds - Burns	- Religious contraindications	- Immediate availability - Can be stored at room temperature for many years
EZ Derm TM®	- Porcine acellular dermis	- MMS defects of upper chest, lip, scalp, and nose	- Religious contraindications	- Reduces pain - Cost-effective - Store at room temperature

MMS, Mohs micrographic surgery; STSG, split thickness skin graft.

Disadvantages of a STSG are the result of the intrinsic anatomic consequences of the graft. Though the fenestrations and mesh increase surface area and durability and help decrease serosanguinous accumulation under the graft, the STSG is particularly susceptible to shearing forces. The unassuming patient may inadvertently damage the graft while moving in bed or around the room, so meticulous care must be taken to avoid damaging an STSG after placement. Additionally, skin hyperpigmentation and color mismatch are common sequelae following placement of a STSG. For both FTSG and STSG, patients should be counselled about donor site morbidity, which may include prolonged healing time, pain, and discoloration with STSGs.

Bioengineered skin substitutes

Bioengineered skin substitutes are a complement or supplement to traditional skin grafting and can be used to augment SIH on the lower extremities. These products can be divided into three broad categories: dermal, epidermal, and composite (dermal and epidermal) substitutes [19].

Bioengineered dermal substitutes

Commercially available dermal substitutes include Biobrane®, AlloDerm®, Integra®, Oasis®, and Dermagraft® (**Table 1**). The two most utilized acellular dermal grafts are Biobrane® and AlloDerm®, which primarily function to prevent fluid loss and microbial contamination [19]. Biobrane®, which is composed of nylon and silicone components, may also be used as a temporary coverage for wounds [20,21]. Studies have depicted the utility of Biobrane® in dermatologic surgery, especially in the management of dermatologic defects following Mohs micrographic surgery (MMS), hidradenitis suppurativa resection, and epidermolysis bullosa [22,23]. The use of Biobrane® following MMS has been shown to improve "quality of life" due to reduced pain and time to complete epithelialization [23].

AlloDerm® is an acellular dermal matrix derived from human cadaveric skin. It has been used effectively in burns, abdominal wall and breast reconstruction, and on surgical defects following MMS [24-26]. One study found that the use of AlloDerm® in large MMS defects resulted in a cosmetic appearance that was superior to that of a STSG [26]. Deneve et al. recorded their experiences with AlloDerm® either as a temporary or definitive reconstructive option and found AlloDerm® to be particularly useful in the setting of positive margins when post-operative

radiation was required. In these patients, there was no further intervention required in 75% of patients who received AlloDerm® [27].

Another dermal substitute, Integra®, is a permanent dermal replacement matrix composed of an inner layer of complex fibers that are coated with a silicone membrane, which act as a scaffold for the regeneration of the dermis after application of a split or full thickness skin graft [28-30]. An alternative to the use of Integra® plus skin grafting is to allow SIH after the silicone membrane is removed. Integra® has been found to be useful in the management of large post-operative defects on the forehead and back, and deep defects on the scalp and lower extremities with exposed bone and tendons. Studies have shown that Integra® results in less wound contraction and hypertrophic scarring compared to a STSG [31-33]. One study found that the application of dermal grafts was associated with excellent cosmetic and functional outcomes while resulting in less donor site morbidity compared to free tissue transfer [34].

Bioengineered dermal substitutes made of porcine-derived tissue (xenografts) include brands like Oasis® and EZ Derm®. Oasis®, which is derived from porcine small intestine submucosa, has been successfully used in treatment of diabetic foot ulcers, venous ulcers, posttraumatic wounds, and chronic wounds. Application of Oasis® to acute surgical defects has also been associated with decreased pain, reduced healing time, and ease of wound care when compared to traditional SIH [35,36]. A 2011 case series investigated the use of porcine xenografts for management of MMS defects on the upper chest, lips, scalp, and ear. These grafts were found to be effective as an intermediate step to final reconstruction or when tumor margins were indeterminate, increasing the possibility of additional procedures [37]. EZ Derm® has an 18-month shelf life, does not need to be refrigerated, and is relatively inexpensive and easy to handle, making it another useful bioengineered dermal substitute [38,39].

Bioengineered epidermal substitutes

Bioengineered epidermal substitutes have shown utility in the management of burns, venous leg ulcers, and diabetic foot ulcers. However, there are sparse data on the use of these products in the management of post-operative soft-tissue defects [40-42]. Commercially available epidermal substitutes include Neox® and Biodegradable Polyurethane Microfibers (BPM), (**Table 2**). Neox® is composed of human amniotic membrane, predominately collagen and fibronectin and serves as a barrier to microorganisms and fluid and heat loss. Use of this product has been associated with reduction of pain in healing wounds [43]. A 10-patient pilot case series using BPM for free-flap donor-site repair demonstrated successful integration of a skin graft with favorable scars at one year [44].

Table 2. *Summary of bioengineered epidermal and composite (epidermal and dermal) substitutes.*

Product	Properties	Indications	Disadvantages/risk	Advantages
Neox®	- Human amniotic membrane	- Thermal injuries (preferred) - Leg ulcers	- Dressings need to be changed every 2 days	- Prevents heat and water loss - Reduces pain
EpiFix®	- Human amniotic membrane	- Thermal injuries (preferred) - Leg ulcers	- Dressings need to be changed every 2 days	- Prevents heat and water loss - Reduces pain
Biodegradable polyurethane microfibers®	- Biodegradable polyurethane microfibers	- Free flap donor site repair	- Infection	- Good cosmetic results - Reduces pain
Apligraf®	- Bilayer of bovine collagen with epidermis formed by neonatal keratinocytes	- MMS defects	- Repeated applications may be necessary	- Faster healing - Reduces pain

MMS, Mohs micrographic surgery.

Bioengineered composite (dermal and epidermal) substitutes

Commercially available composite substitutes include Apligraf® and Orcel® (**Table 2**). These products are both composed of a bilayer of epidermal components (made of human neonatal keratinocytes) and dermal components (made of neonatal fibroblasts within a bovine type I collagen matrix). Apligraf® has been shown to be more effective in treating refractory venous stasis ulcers when compared to compression therapy alone, yielding a greater percentage of healed wounds and a shorter median time to complete wound closure [45-47]. Similar results were found in treatment of diabetic and pressure ulcers [48]. Apligraf® has also been shown to speed healing and decrease pain in acute surgical defects [49]. Compared to SIH, Apligraf® has also been found to decrease pain and dressing change frequency [50,51]. Apligraf® has also been used successfully in post-MMS or excisional defects resulting in more pliable and fewer vascular scars [52-54].

Conclusion

There are several options for managing post-operative soft-tissue defects on the lower extremity that cannot be closed primarily or by reconstruction with a local flap. The method chosen should depend on various factors, including the quality of the skin, vascularity and size of the wound, medical history of the patient, and the experience of the surgeon. Regardless of the method chosen, patients should be educated that healing from these methods is slow and pigment changes are common.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the U.S. Population, 2012. *JAMA Dermatol*. 2015;151:1081-6. [PMID: 25928283].
2. Reddy BY, Miller DM, Tsao H. Somatic driver mutations in melanoma. *Cancer*. 2017;123:2104-17. [PMID: 28543693].
3. Oh BH, Lee SH, Nam KA, Lee HB, Chung KY. Comparison of negative pressure wound therapy and secondary intention healing after excision of acral lentiginous melanoma on the foot. *Br J Dermatol*. 2013;168:333-8. [PMID: 23362968].
4. Bieniek A, Matusiak Ł, Chlebicka I, Szepietowski JC. Secondary intention healing in skin surgery: our own experience and expanded indications in hidradenitis suppurativa, rhinophyma and non-melanoma skin cancers. *J Eur Acad Dermatol Venereol*. 2013;27:1015-21. [PMID: 22817107].
5. Beckett N, Lawson C, Cohen G. Electrosurgical excision of acne keloidalis nuchae with secondary intention healing. *J Clin Aesthet Dermatol*. 2011;4:36-9. [PMID: 21278897].
6. Hayes H. A review of modern concepts of healing of cutaneous wounds. *J Dermatol Surg Oncol*. 1977;3:188-93. [PMID: 864076].
7. Vedvyas C, Cummings PL, Geronemus RG, Brauer JA. Broader Practice Indications for Mohs Surgical Defect Healing by Secondary Intention: A Survey Study. *Dermatol Surg*. 2017;43:415-23. [PMID: 28060171].
8. Jung JY, Roh HJ, Lee SH, Nam K, Chung KY. Comparison of secondary intention healing and full-thickness skin graft after excision of acral lentiginous melanoma on foot. *Dermatol Surg*. 2011;37:1245-51. [PMID: 21615605].
9. Schoenfeld J, Wirth P, Helm T. Mohs micrographic surgery and secondary intention healing of a plantar melanoma in-situ. *Dermatol Online J*. 2017;23. [PMID: 28329499].
10. Lateo SA, Langtry JA. A prospective case series of secondary intention healing for surgical wounds on the dorsum of the hand. *Clin Exp Dermatol*. 2013;38:606-11. [PMID: 23758530].
11. Zitelli JA. Wound healing by secondary intention. A cosmetic appraisal. *J Am Acad Dermatol*. 1983;9:407-15. [PMID: 6630602].
12. Robson MC, Krizek TJ. Predicting skin graft survival. *J Trauma*. 1973;13:213-7. [PMID: 4571903].
13. Odland PB, Murakami CS. Healing by secondary intention. *Facial Flaps and Facial Reconstruction*. 1993;4:54-60.
14. Ratner D. Skin grafting. *Semin Cutan Med Surg*. 2003;22:295-305. [PMID: 14740962].
15. Ratner D. Skin grafting. From here to there. *Dermatol Clin*. 1998;16:75-90. [PMID: 9460579].
16. Gloster HM, Daoud MS, Roenigk RK. The use of full-thickness skin grafts for the repair of defects on the dorsal hand and digits. *Dermatol Surg*. 1995;21:953-9. [PMID: 7582833].
17. Harrison CA, MacNeil S. The mechanism of skin graft contraction: an update on current research and potential future therapies. *Burns*. 2008;34:153-63. [PMID: 18226455].
18. Reddy S, El-Haddawi F, Fancourt M, et al. The incidence and risk factors for lower limb skin graft failure. *Dermatol Res Pract*. 2014;2014:582080. [PMID: 25132847].
19. Chern PL, Baum CL, Arpey CJ. Biologic dressings: current applications and limitations in dermatologic surgery. *Dermatol Surg*. 2009;35:891-906. [PMID: 19397669].
20. Gerding RL, Emerman CL, Effron D, et al. Outpatient management of partial-thickness burns: Biobrane versus 1% silver sulfadiazine. *Ann Emerg Med*. 1990;19:121-4. [PMID: 2405749].
21. Demling RH. Use of Biobrane in management of scalds. *J Burn Care Rehabil*. 1995;16:329-30. [PMID: 7673318].
22. Melkun ET, Few JW. The use of biosynthetic skin substitute (Biobrane) for axillary reconstruction after surgical excision for hidradenitis suppurativa. *Plast Reconstr Surg*. 2005;115:1385-8.

[PMID: 15809603].
23. Gladsjo JA, Kim SS, Jiang SI. Review of the use of a semisynthetic bilaminar skin substitute in dermatology and a case series report of its utility in Mohs surgery. *J Drugs Dermatol*. 2014;13:537-41. [PMID: 24809876].
24. Kolenik SA, 3rd, Leffell DJ. The use of cryopreserved human skin allografts in wound healing following Mohs surgery. *Dermatol Surg*. 1995;21:615-20. [PMID: 7606373].
25. Carucci JA, Kolenik SA, 3rd, Leffell DJ. Human cadaveric allograft for repair of nasal defects after extirpation of Basal cell carcinoma by Mohs micrographic surgery. *Dermatol Surg*. 2002;28:340-3. [PMID: 11966793].
26. Kontos AP, Qian Z, Urato NS, Hassanein A, Proper SA. AlloDerm grafting for large wounds after Mohs micrographic surgery. *Dermatol Surg*. 2009;35:692-8. [PMID: 19415797].
27. Deneve JL, Turaga KK, Marzban SS, et al. Single-institution outcome experience using AlloDerm(R) as temporary coverage or definitive reconstruction for cutaneous and soft tissue malignancy defects. *Am Surg*. 2013;79:476-82. [PMID: 23635582].
28. Prystowsky JH, Siegel DM, Ascherman JA. Artificial skin for closure and healing of wounds created by skin cancer excisions. *Dermatol Surg*. 2001;27:648-53. [PMID: 11442617].
29. Chalmers RL, Smock E, Geh JL. Experience of Integra((R)) in cancer reconstructive surgery. *J Plast Reconstr Aesthet Surg*. 2010;63:2081-90. [PMID: 20335086].
30. Muller CS, Schiekofer C, Korner R, Pfohler C, Vogt T. Improved patient-centered care with effective use of Integra(R) in dermatologic reconstructive surgery. *J Dtsch Dermatol Ges*. 2013;11:537-48. [PMID: 23464728].
31. Yannas IV. Studies on the biological activity of the dermal regeneration template. *Wound Repair Regen*. 1998;6:518-23. [PMID: 9893171].
32. Heimbach D, Luterman A, Burke J, et al. Artificial dermis for major burns. A multi-center randomized clinical trial. *Ann Surg*. 1988;208:313-20. [PMID: 3048216].
33. Abai B, Thayer D, Glat PM. The use of a dermal regeneration template (Integra) for acute resurfacing and reconstruction of defects created by excision of giant hairy nevi. *Plast Reconstr Surg*. 2004;114:162-8. [PMID: 15220586].
34. Tufaro AP, Buck DW, Fischer AC. The use of artificial dermis in the reconstruction of oncologic surgical defects. *Plast Reconstr Surg*. 2007;120:638-46. [PMID: 17700115].
35. Cronin H, Goldstein G. Biologic skin substitutes and their applications in dermatology. *Dermatol Surg*. 2013;39:30-4. [PMID: 22928551].
36. Mostow EN, Haraway GD, Dalsing M, et al. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. *J Vasc Surg*. 2005;41:837-43. [PMID: 15886669].
37. Raimer DW, Group AR, Petitt MS, et al. Porcine xenograft biosynthetic wound dressings for the management of postoperative Mohs wounds. *Dermatol Online J*. 2011;17:1. [PMID: 21971266].
38. Nyame TT, Chiang HA, Leavitt T, Ozambela M, Orgill DP. Tissue-Engineered Skin Substitutes. *Plast Reconstr Surg*. 2015;136:1379-88. [PMID: 26595026].
39. Troy J, Karlnoski R, Downes K, et al. The Use of EZ Derm(R) in Partial-Thickness Burns: An Institutional Review of 157 Patients. *Eplasty*. 2013;13:e14. [PMID: 23573334].
40. Carsin H, Ainaud P, Le Bever H, et al. Cultured epithelial autografts in extensive burn coverage of severely traumatized patients: a five year single-center experience with 30 patients. *Burns*. 2000;26:379-87. [PMID: 10751706].
41. Tausche AK, Skaria M, Bohlen L, et al. An autologous epidermal equivalent tissue-engineered from follicular outer root sheath keratinocytes is as effective as split-thickness skin autograft in recalcitrant vascular leg ulcers. *Wound Repair Regen*. 2003;11:248-52. [PMID: 12846911].
42. Lazic T, Falanga V. Bioengineered skin constructs and their use in wound healing. *Plast Reconstr Surg*. 2011;127 Suppl 1:75S-90S. [PMID: 21200276].
43. Salehi SH, As'adi K, Mousavi SJ, Shoar S. Evaluation of Amniotic Membrane Effectiveness in Skin Graft Donor Site Dressing in Burn Patients. *Indian J Surg*. 2015;77:427-31. [PMID: 26730039].
44. Wagstaff MJ, Schmitt BJ, Coghlan P, et al. A biodegradable polyurethane dermal matrix in reconstruction of free flap donor sites: a pilot study. *Eplasty*. 2015;15:e13. [PMID: 25987938].
45. Falanga V, Sabolinski M. A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal venous ulcers. *Wound Repair Regen*. 1999;7:201-7. [PMID: 10781211].
46. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. *Arch Dermatol*. 1998;134:293-300. [PMID: 9521027].
47. Brem H, Balledux J, Sukkarieh T, Carson P, Falanga V. Healing of venous ulcers of long duration with a bilayered living skin substitute: results from a general surgery and dermatology department. *Dermatol Surg*. 2001;27:915-9. [PMID: 11737123].
48. Brem H, Balledux J, Bloom T, Kerstein MD, Hollier L. Healing of diabetic foot ulcers and pressure ulcers with human skin equivalent: a new paradigm in wound healing. *Arch Surg*. 2000;135:627-34. [PMID: 10843357].
49. Muhart M, McFalls S, Kirsner RS, et al. Behavior of tissue-engineered skin: a comparison of a living skin equivalent, autograft, and occlusive dressing in human donor sites. *Arch Dermatol*. 1999;135:913-8. [PMID: 10456339].
50. Eaglstein WH, Iriondo M, Laszlo K. A composite skin substitute (graftskin) for surgical wounds. A clinical experience. *Dermatol Surg*. 1995;21:839-43. [PMID: 7551738].
51. Kirsner RS. The use of Apligraf in acute wounds. *J Dermatol*. 1998;25(12):805-11. [PMID: 9990773].
52. Gohari S, Gambla C, Healey M, et al. Evaluation of tissue-engineered skin (human skin substitute) and secondary intention healing in the treatment of full thickness wounds after Mohs micrographic or excisional surgery. *Dermatol Surg*. 2002;28:1107-14. [PMID: 12472488].
53. Eaglstein WH, Alvarez OM, Auletta M, et al. Acute excisional wounds treated with a tissue-engineered skin (Apligraf). *Dermatol Surg*. 1999;25:195-201. [PMID: 10193966].
54. Tarlow MM, Nossa R, Spencer JM. Effective management of difficult surgical defects using tissue-engineered skin. *Dermatol Surg*. 2001;27:71-4. [PMID: 11231250].