

Reconstruction of Full-thickness Soft Tissue Defects with Integra: Risk Factors and Treatment Algorithm

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Background: Despite the fact that dermal substitutes are widely used in reconstructive surgery, there have been no studies focused on predictors of complications or delayed matrix take. We propose an algorithm for management of soft tissue reconstruction with Integra dermal matrix, based on our 5-year-long clinical experience.

Methods: An estimated 111 patients who underwent Integra reconstruction of full-thickness soft tissue defects of different anatomical sites and etiology were enrolled, and dichotomized in two groups according to complications. Participants were further studied according to the wound healing strategy: healing by secondary intention, skin graft (STSG), and flap surgery. A regression analysis was conducted in the whole sample to identify possible predictors of complications.

Results: No significant differences according to complications were observed. The between-group statistical analysis showed significant differences in age, comorbidities, defect area, diagnosis, and defect site. The regression analysis revealed that the timing of split-thickness skin graft (STSG) was not influenced by age, comorbidities, body mass index (BMI), defect area, site, wound etiology, and risk factors in the subjects who underwent a two-step reconstruction. Healing by secondary intention is recommended for small post-oncological defects of the head, especially in elderly and multimorbid patients. Variables that may interfere with dermal substitutes' incorporation are independent of the timing of STSG placement; therefore, no predictors of complications or delayed matrix take were identified.

Conclusions: Our findings showed that Integra can be used in a wide range of patients regardless of their general features, thus acting as a useful alternative to conventional reconstructive techniques in selected cases. (*Plast Reconstr Surg Glob Open* 2020;8:e3099; doi: [10.1097/GOX.0000000000003099](https://doi.org/10.1097/GOX.0000000000003099); Published online 24 September 2020.)

INTRODUCTION

The use of dermal templates in combination with skin grafts to cover deep cutaneous wounds associated with tendon, bone or joint exposure has been widely reported throughout the literature. Several studies have revealed the efficacy of dermal substitutes in reconstructing posttraumatic or post oncological defects, and such techniques now represent a tissue-engineered alternative to flap surgery, especially in medically compromised

individuals because they reduce surgical morbidity.^{1,2} Moreover, dermal substitutes have been investigated even from a functional perspective, and several reports have shown that they might represent a safe and reliable tool for the reconstruction of challenging areas such as joints or weight-bearing surfaces.³⁻⁵

Among the available dermal matrices, most clinical data have focused on the Integra Dermal Regeneration Template (INT),⁶ and long-term analyses have shown significant improvements in patient-assessed mobility, softness, and appearance.⁷ Clinical and histological studies have demonstrated that INT could provide a durable skin coverage similar to that of a full-thickness skin graft with minimal donor-site morbidity, through a regeneration process involving 4 phases.⁸ Despite several studies focusing on dermal substitutes for soft tissue reconstruction have already been described, there are no available research works that analyze predictors of complications or delayed matrix take, nor their possible correlations with general features of the patients who underwent Integra

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reconstruction. Based on these observations, we reviewed the experience developed by our center in the use of INT for the reconstruction of soft tissue defects not amenable to direct skin grafting over a period of 5 years.

Objectives

The main objective of the study was to investigate whether the final outcome of Integra reconstruction might be affected by patient demographics and clinical features, specifically in terms of selected risk factors or comorbidities, and/or specific wound characteristics. Furthermore, a treatment algorithm for the weighted management of Integra-based reconstruction has been proposed.

MATERIALS AND METHODS

Study Design

The research was designed as a retrospective cohort study. Figure 1 shows the flow diagram of the study. This study was reported according to the STROBE guidelines and conducted in accordance with Good Clinical Practice requirements and with the principles of the 1975 Declaration of Helsinki.

Participants

An institutional board (Comitato Etico Regione Marche, CERM) approved a retrospective chart review of

patients with full-thickness soft tissue defects of different origin that were surgically treated with INT over a 5-year period. Patients suffering from defects involving the skin with exposed tendon, bone or cartilage/joint (thus considered as not amenable to direct skin grafting) who underwent a surgical reconstruction using INT between 2014 and 2018 were enrolled, regardless of age, sex, ethnicity, mental or physical condition, wound etiology, defect area, or anatomical site. Patients with superficial defects without exposure of deeper structures such as tendons, cartilages, joints, bones, or defects not involving the skin; patients who underwent reconstruction using skin substitutes different from INT; patients treated with a combined procedure with flap reconstruction and dermal matrix as a temporary dressing were excluded from this study. Dermal substitutes different from Integra were excluded to minimize any potential source of bias; in fact, although most commonly used dermal substitutes are employed for similar purposes, they usually have a different structural composition, which leads to a potentially different biological behavior and various clinical outcomes.

Study Variables

Independent Variables

The following demographics and clinical data were collected from the electronic medical records of our

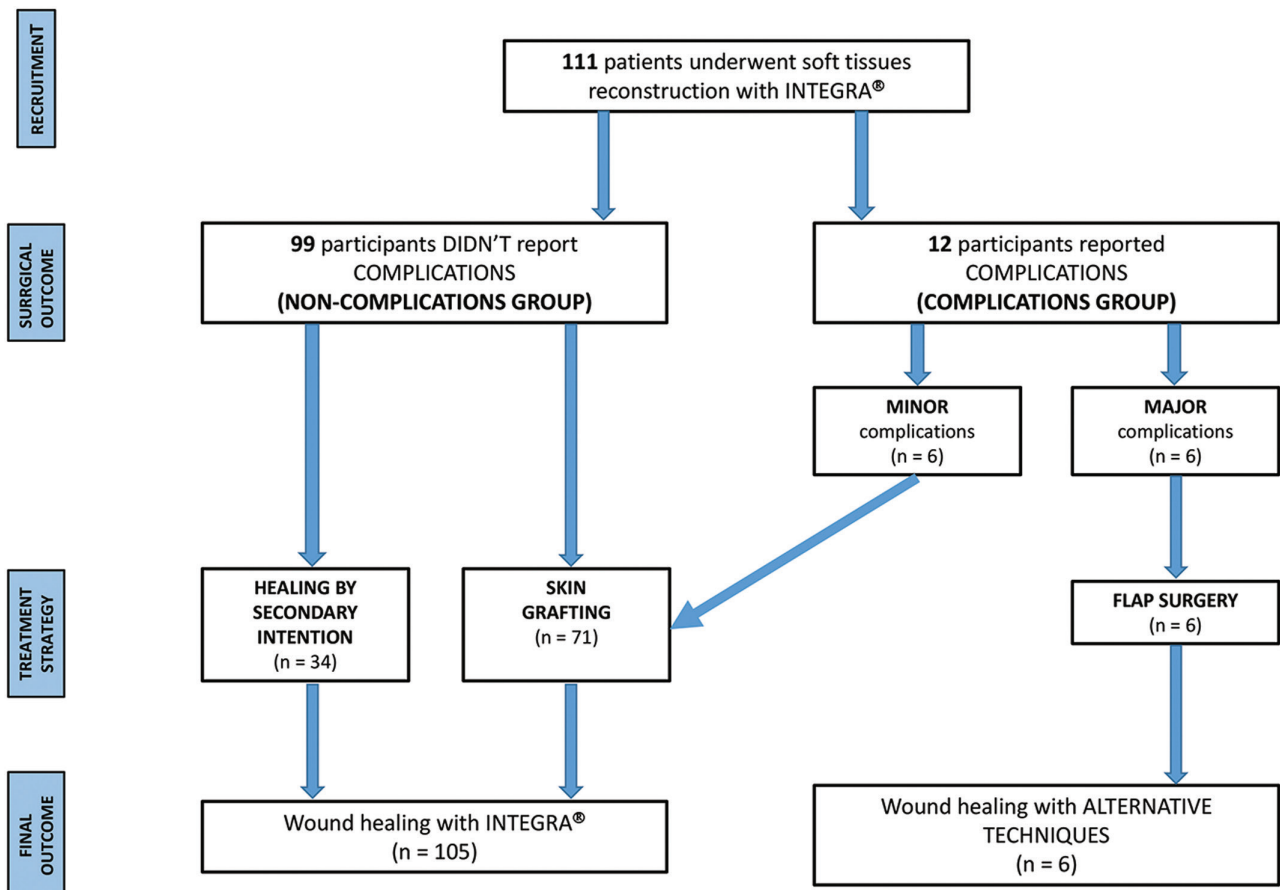


Fig. 1. Flow diagram of the study.

hospital: age, sex, kind of comorbidity, comorbidity burden, risk factors and BMI. Comorbidity burden was evaluated by means of Cumulative Illness Rating Scale Severity Index (CIRS-SI) and Comorbidity Index (CIRS-CI), which are used for measuring the chronic medical illness burden while taking into account the severity of chronic diseases.⁹ We defined those conditions such as smoking, diabetes, radiation, obesity, or peripheral arterial disease, which may predispose to impaired wound healing and inadequate take of the dermal matrix as “risk factors”.

The surgical characteristics of tissue defects such as defect site, wound etiology, defect area, kind of surgical procedure and anesthesia, timing of second surgical reconstruction, time laps from INT application to split-thickness skin grafting (STSG) and short-term postoperative complications were also recorded.

Dependent Variables

Complications that required a reoperation with an alternative reconstructive technique were classified as major, while complications that did not preclude the second reconstructive step with STSG were classified as minor. Major complications included total resorption of INT or an INT take $\leq 50\%$, while partial take of the matrix (51%–99%) that led to a complete coverage of the underlying structures such as bone or tendons was considered as a minor complication. Only a complete coverage of the entire wound bed was classified as the total INT take (100%). Data regarding long-term complications such as STSG take, scarring, STSG retraction or ulceration were not collected, as they were not considered as the main objective of our study.

Surgical Procedure

All patients received the same surgical and postsurgical management protocols. For posttraumatic wounds, after a first wound debridement in the emergency operating room to remove devitalized tissues, conservative management with negative pressure wound therapy was used. Alternatively, a serial delayed excision was performed to gradually evaluate the vascularity and viability of injured tissues. This staged management was continued until the wound bed was debrided. Only patients with a positive wound culture were administered an antibiogram-guided antimicrobial intravenous therapy. For all other soft tissue defects, such as post-oncological wounds, an immediate reconstruction using INT was performed.

Therefore, all patients underwent soft tissue reconstruction using a bilayer dermal matrix (INT) that was tightly anchored by suturing or stapling along the wound edges; the superficial silicone layer was meshed to prevent accumulation of fluid. The matrix was then circumferentially covered with a compressive polyurethane foam dressing to make sure the graft adhered firmly to the underlying structures. Dressings were then changed every 4 days to inspect step by step the matrix take. Once a well vascularized wound bed was observed under the silicone sheet, matrix take was assessed and the second surgical step consisting of the definitive coverage of the regenerated dermis with STSG was finally performed (Figs. 2–5).

The choice to proceed with skin grafting or move forward with an alternative reconstructive technique was solely dictated by clinical judgment; once the granulation tissue completely covered the exposed deep structures, the wound bed was judged amenable to skin grafting. We defined those wounds in which structures not amenable to direct skin grafting were completely covered by the growth of the granulation tissue, thus allowing for an ideal STSG take, as well-vascularized dermal templates.

In those cases with small defects, patients either unsuitable for or refusing a second operation, a wound healing by secondary intention after INT application was attempted, thus avoiding a second surgical step with skin grafting (Fig. 6). In cases with major complications leading to total/subtotal matrix loss with permanent exposure of structures that were not amenable to direct skin grafting, an alternative reconstruction using flap coverage was considered.

Statistical Analysis

The distribution of clinical and demographic variables was studied using descriptive statistics. All variables that resulted normally distributed were described in terms of mean and standard deviation (SD). The others were treated as non-parametric variables and described using median, range, and Interquartile Range (IQR) and analyzed using tools for non-parametric data: Mann–Whitney U test (complications group versus non-complications group) or Kruskal–Wallis test (non-complications group versus minor complications versus major complications; healing by secondary intention, skin grafting and flap surgery groups) for between-group comparisons. Category variables were described as percentages and compared using a χ^2 test. Regression analysis was used to estimate the relationships among variables (complications and timing of second surgical reconstruction as dependent variables; and age, sex, CIRS, BMI, defect area, defect site, wound etiology, risk factors, comorbidities as independent variables). The significance level was set at $P \leq 0.05$. Statistical analysis was performed using the StatView, version 5.0.

RESULTS

A total of 118 patients were enrolled. Seven patients were excluded because they underwent reconstruction using a non-Integra dermal matrix (Pelnac, 4 cases; MatriDerm, 2 cases; Nevelia, 1 case).

Of the 111 patients, 71 were men, with a mean age of 70.95 years (SD, 17.53 years). The descriptive analysis of the sample is summarized in Tables 1 and 2, which show defect features, clinical characteristics of patients, and surgical outcomes.

The most common cause of tissue defect was tumor resection (65.8%), followed by trauma (13.5%); no significant difference was found in initial diagnosis distribution between patients who developed complications and patients with no complications, as well as no significant differences were found between patients with major or minor complications. Miscellaneous diagnoses included inflammatory reaction to foreign materials such as siliconoma and paraffinoma, wound dehiscence, rhinophyma, and



Fig. 2. Surgical reconstruction of a large scalp defect. Preoperative picture showing a large metastatic scalp lesion of an occult melanoma in a 73-year-old woman (A) who underwent a wide local full-thickness excision with 2-cm margins, with a selective left neck dissection. Reconstruction was performed using a bilayer dermal matrix (B), which was fully vascularized after 28 days (C), followed by STSG after 32 days. The one-year follow-up visit showed no recurrences (D).

flap donor site coverage. The mean time between the first and second surgical reconstruction using skin-grafting was 40.7 days (range, 19–96 days).

Of the 111 tissue defects included, 55.9% were located in the head/neck, 31.5% were located in the lower limb, followed by the upper limb and trunk (6.3%). The most common surgical procedure conducted was tumor resection (71.2%), while surgical debridement was performed in 27% of cases. No significant differences were found in terms of defect location and surgical procedure between the two groups. The most frequent type of anesthesia used was local

anesthesia (60% of patients), followed by regional blocks (17%), while general anesthesia was used for less than 10% of patients.

The overall complication rate was 10.8%, and included 5.4% minor complications and 5.4% major complications. A comparison between groups in terms of complications (complications group versus non-complications group) revealed no significant differences in age, sex, CIRS-SI, CIRS-CI, kind of comorbidity, risk factors, or BMI. No significant differences were found between non-complications group, minor complications group, and major complications groups.

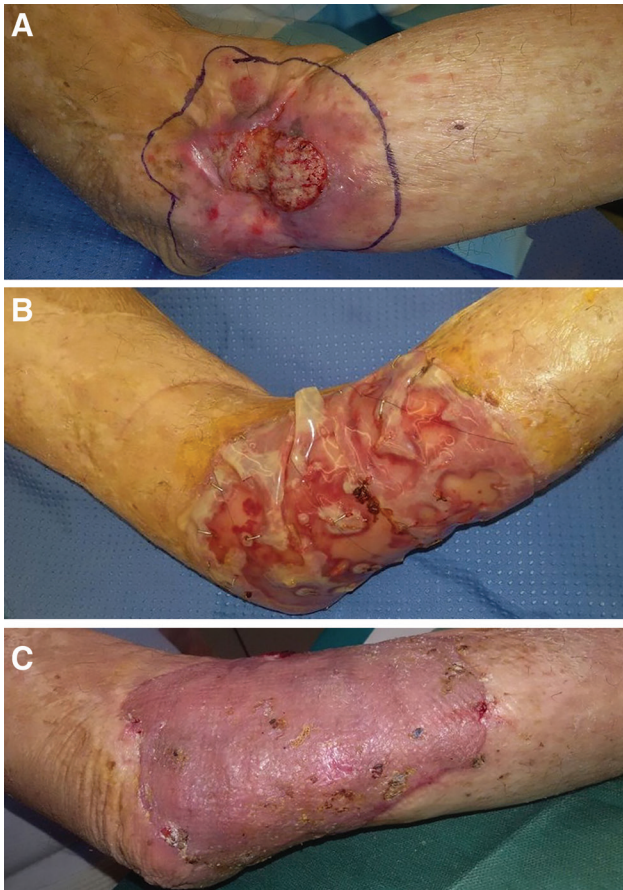


Fig. 3. Integra reconstruction of the upper limb. A burn-scar-related squamous cell carcinoma of the right elbow in a 62-year-old man who underwent a wide local excision with 1-cm margins (A) and surgical reconstruction using Integra (B). The one-month follow-up visit after STSG placement showed an over functional improvement and complete skin coverage of the defect area (C).

The between-group analysis according to treatment strategy after INT placement (healing by secondary intention, skin grafting and flap surgery groups) revealed differences in age, CIRS-SI, CIRS-CI, defect area, diagnosis, and defect site, while no differences with regard to sex and risk factors were found. In fact, in our sample, healing by secondary intention after INT reconstruction was more frequent in elderly patients ($P = 0.01$, $H = 8.7$, $DF = 2$). Also, CIRS-CI and CIRS-SI were higher in this group ($P = 0.006$, $H = 10.37$ and $P = 0.008$, $H = 9.6$, respectively). In the flap surgery group, the defect area was significantly wider, followed by the skin grafting group ($P = 0.0005$, $H = 15.2$). With regard to diagnosis, 86.7% of traumatic wounds underwent subsequent skin grafting, while only 58% of post oncological defects had the same course ($P = 0.027$, $\chi^2 = 10.96$). Finally, differences related to the defect site were observed: the most frequent sites of skin grafting reconstruction were upper and lower limb (85.7% and 80%, respectively), while head/neck was the least frequent one (52.9%; $P = 0.005$, $\chi^2 = 18.4$). The within-group analysis related to the skin grafting group revealed no differences between patients with minor complications and those without complications.

The regression analysis performed in the whole sample showed no predictors of complications. The regression analysis performed within the skin grafting group revealed no relationships between independent variables (age, sex, CIRS, BMI, defect area, defect site, wound etiology, and risk factors) and timing of second surgical reconstruction (time laps from INT application to STSG).

DISCUSSION

INT was approved for use in patients with extensive burns with insufficient donor tissue for coverage by the

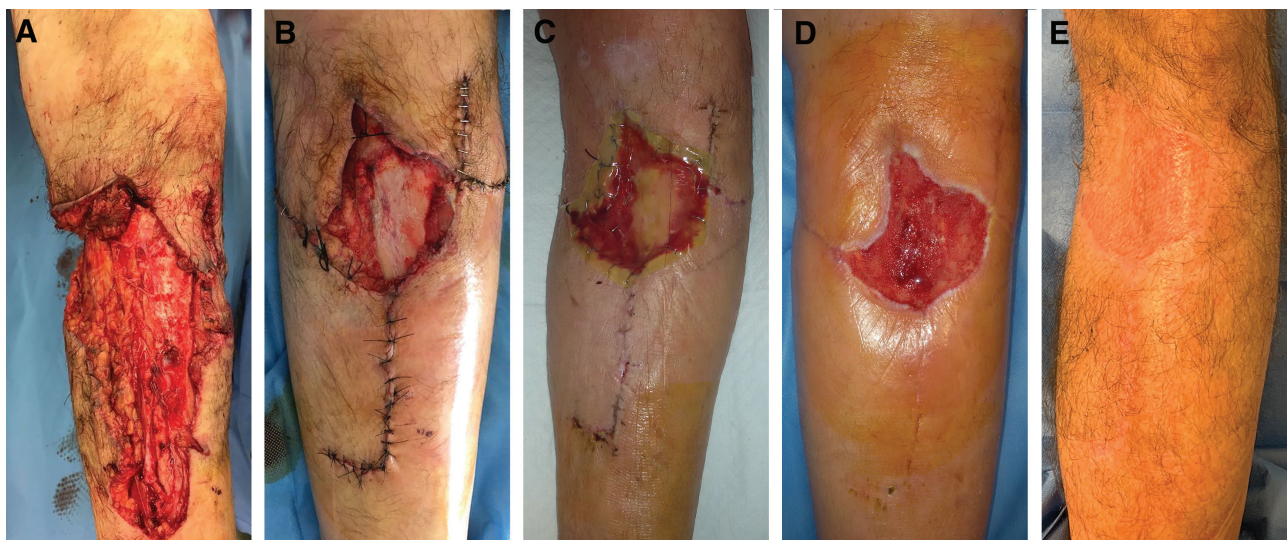


Fig. 4. Reconstruction of a complex wound of the lower limb. Posttraumatic full-thickness wound of the left leg with massive soft tissues deglovement and bone exposure after a work accident in a 54-year-old man (A). Wound bed preparation after surgical debridement and negative pressure wound therapy for 7 days (B). A bilayer dermal matrix applied over the exposed tibial bone (C), which was fully vascularized after 35 days (D). The one-year follow-up visit after STSG placement (E).

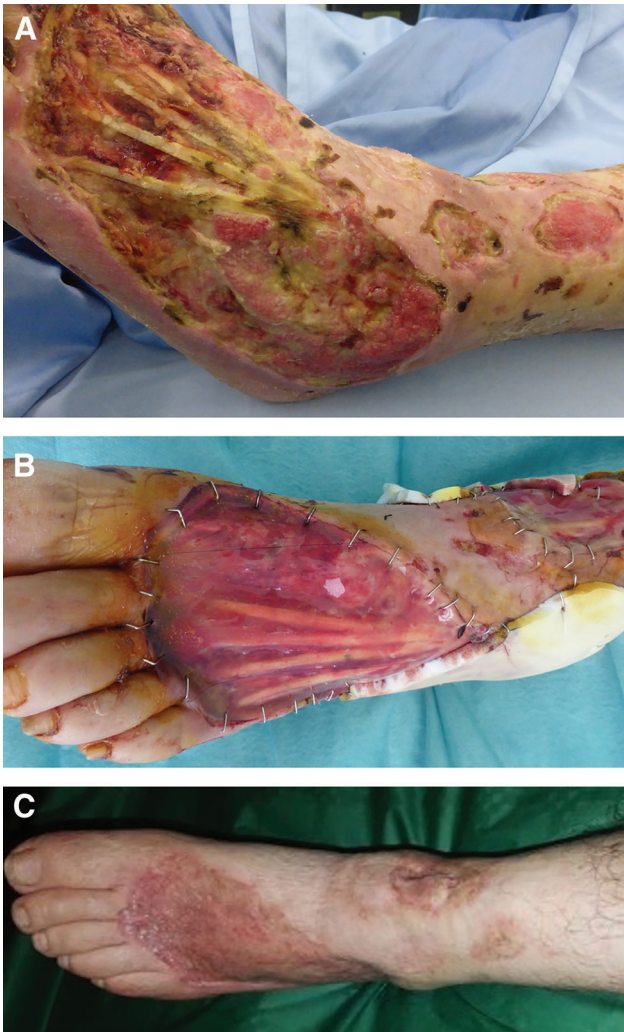


Fig. 5. Foot reconstruction with Integra. Posttraumatic wound of the left foot after first surgical debridement, with exposure of extensor hallucis longus, extensor digitorum longus to all digits, and anterior tibial tendons without covering paratenon (A). Surgical reconstruction using Integra after second surgical debridement (B). The one-year follow-up visit after STSG placement (C).

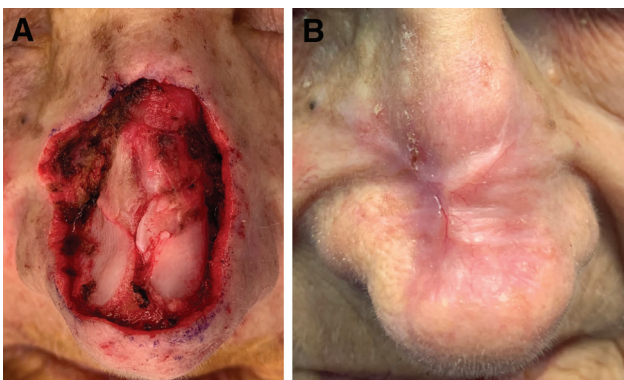


Fig. 6. Reconstruction of a full-thickness defect of the nose. Post-oncological reconstruction in a 89-year-old patient with infiltrating basal cell carcinoma (BCC) of the nasal dorsum. Intraoperative view after a wide surgical resection of BCC until the nasal cartilage (A), and the one-year follow-up visit after Integra reconstruction and healing by secondary intention (B).

Federal Drug Administration in 1996. However, its clinical application has broadened significantly, now including coverage of different wounds that are not amenable to direct skin grafting. Currently, INT is used for the reconstruction of several anatomical sites, ranging from the scalp to the lower extremity, for both post oncological and posttraumatic defects.¹⁰

Although its use is quite standardized and its important role from a reconstructive perspective has been widely elucidated, there are some aspects regarding the surgical outcomes of soft tissue reconstruction using dermal substitutes that need to be pointed out. A correct knowledge of complications and those factors that may preclude a successful reconstruction using dermal substitutes are mandatory to optimize their use. Common complications of dermal substitutes are infection, hematoma, graft failure, need for multiple procedures¹¹ or unpredictable matrix thinning with unpleasant aesthetic results in challenging facial defects.¹²

Our results showed an overall complication rate of 10.8%. The sample was divided into two main groups: patients with complications (complications group) and patients without complications (non-complications group). The comparison between these two groups revealed that complications related to INT in our sample are independent of age, sex, comorbidity burden (CIRS-CI and CIRS-SI), kind of comorbidity, BMI, defect area, wound etiology, defect site, and risk factors. These data were confirmed by the regression analysis performed in the whole sample, which showed no predictors of complications.

These results are quite encouraging and pose some important considerations. Features such as age, comorbidities, BMI, defect site, and risk factors for vascular disease (such as smoking or diabetes) make flap surgery (especially microsurgical tissue transfer) hazardous but should not be considered as absolute contraindications.¹³ A retrospective review demonstrates that age alone is not an independent variable for increased risk in microvascular reconstruction; however, operative time, ASA risk score, and location of the reconstruction site are more associated with the overall success of free tissue transfers.¹⁴ From this point of view, our results suggested that dermal substitutes can be used in a wide range of patients regardless of their general characteristics, as the final outcome is not influenced by the factors analyzed in our sample.

The statistical analysis revealed no significant differences among non-complications group, minor complications group, and major complications groups; these findings confirmed that both the overall surgical outcome and severity of complications are not influenced by the variables analyzed.

After the first surgical reconstruction using INT, all participants were divided into 3 different groups according to the treatment strategy used for the final wound healing (healing by secondary intention, STSG, or flap surgery). The between-group statistical analysis revealed significant differences in age, CIRS-SI, CIRS-CI, defect area, diagnosis, and defect site, while no differences were found in terms of sex and risk factors. Our data showed

Table 1. Demographics and Clinical Data (Continuous Variables) of the Patients

	Mean	SD	Range	Median	IQR
Age (years)	70.95	17.53	11–99	77	24
Defect area (cm ²)	36.18	40.03	1–304	24	33
BMI median	25.47	3.22	19.5–35.9	25.4	3.8
Timing II surgical step (d)	40.71	15.95	19–96	37	20
CIRS-CI	1.81	1.51	0–7	1	2
CIRS-SI	0.31	0.26	0–1.23	0.23	0.31

Table 2. Clinical Data According to the 2 Complications Groups

	Whole Population Count (%)	Complications Group Count (%)	Non-Complications Group Count (%)	P
Complications				
Total	12 (10.8)			
• Minor	6 (5.4)			
• Major	6 (5.4)			
Gender				0.7
Male	79 (71.2)	8 (66.7)	71 (71.7)	
Female	32 (28.8)	4 (33.3)	28 (28.3)	
Diagnosis				0.2
Tumor	73 (65.8)	6 (50)	67 (67.7)	
Trauma	15 (13.5)	2 (16.7)	13 (13.1)	
Ulcer	9 (8.1)	3 (25)	6 (6.1)	
Miscellaneous	7 (6.3)	0 (0)	7 (7.1)	
Necrotizing fasciitis	4 (3.6)	1 (8.3)	3 (3)	
Scar	3 (2.7)	0 (0)	3 (3)	
Defect Site				0.8
Head/neck	62 (55.8)	5 (41.7)	57 (57.6)	
Lower limb	35 (31.5)	5 (41.7)	30 (30.3)	
Upper limb	7 (6.3)	1 (8.3)	6 (6.1)	
Trunk	7 (6.3)	1 (8.3)	6 (6.1)	
1 st Surgical Procedure				0.4
Skin resection	79 (71.2)	7 (58.3)	72 (72.7)	
Debridement	30 (27)	5 (41.7)	25 (25.3)	
Flap donor site coverage	2 (1.8)	0 (0)	2 (2)	
2 nd Surgical Procedure				<0.0001
Skin grafting	71 (64)	6 (50)	65 (65.7)	
Spontaneous healing	34 (30.6)	0 (0)	34 (34.3)	
Flap surgery	6 (5.4)	6 (50)	0 (0)	
Risk Factors				
Total	48 (43.2)			
• Smoke	28 (25.2)	1 (8.3)	27 (27.3)	0.2
• PAD	1 (0.9)	0 (0)	1 (1)	0.7
• Diabetes	20 (18)	1 (8.3)	19 (19.2)	0.4
• Obesity	11 (9.9)	1 (8.3)	10 (10.1)	0.8
• Radiation	1 (0.9)	0 (0)	1 (1)	0.7
Comorbidities				
Total	96 (86.5)	11 (91.7)	85 (85.9)	0.6
• Dyslipidemia	20 (18)	2 (16.7)	18 (18.2)	0.9
• Heart disease	34 (30.6)	2 (16.7)	32 (32.3)	0.3
• Renal failure	18 (16.2)	2 (16.7)	16 (16.2)	0.96
• COPD	12 (10.8)	2 (16.7)	10 (10.1)	0.5
• Hypertension	60 (54.1)	6 (50)	54 (54.5)	0.8
• Anemia	4 (3.6)	0 (0)	4 (4)	0.5
Anesthesia				
Local	67 (60.4)			
Regional block	19 (17.1)			
Spinal anesthesia	14 (12.6)			
General	11 (9.9)			

PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease.

that healing by secondary intention was significantly higher in elderly patients ($P = 0.01$). Also CIRS-CI and CIRS-SI were higher in this group ($P = 0.006$ and 0.008 , respectively). Elderly multimorbid patients are frequently unsuitable for multistep procedures, due to a higher anesthetic risk and an overall low compliance. To overcome these problems, a one-step reconstructive procedure using INT in combination with STSG has been proposed by several authors.^{15–17} Despite encouraging results have been reported throughout literature, no consensus exists

on the reliability of the one-step procedure, and comparative randomized trials are scarce.¹⁸ A single-step procedure may preclude the engraftment of STSG, especially in wider and deeper wounds, thus putting the entire reconstructive procedure at risk. In our study, patients treated with conservative management with advanced dressings reported satisfactory outcomes from a functional and aesthetic perspective. Despite the prolonged healing time compared with the STSG group, healing by secondary intention help us avoid additional surgery, further surgical scarring, and

the postoperative care of the skin graft donor site, which could have delayed wound healing, thus requiring prolonged wound care too. Furthermore, secondary intention may be considered as a “tissue-sparing” alternative, especially in those patients who are prone to develop multiple skin cancers.

In our opinion, healing by secondary intention is particularly recommended for small post oncological defects located in the head and neck. In fact, the between-group statistical analysis showed that with regard to diagnosis, 86.7% of traumatic wounds underwent subsequent skin grafting, while only 58% of post oncological defects did ($P = 0.027$, $\chi^2 = 10.96$). Moreover, differences regarding defect site were observed; the most frequent sites of skin grafting reconstruction were upper and lower limb (85.7% and 80%, respectively), while head/neck was the least frequent one (52.9%; $P = 0.005$, $\chi^2 = 18.4$). We obtained excellent results in patients with scalp or nasal defects healed by secondary intention, and we believe that even if more immediate postoperative care is needed, the long-term cosmetic results are uniformly acceptable. On the other hand, because of the large amount of injured tissues, we believe that a two-step reconstruction is still more suitable for posttraumatic defects involving upper or lower extremities.

Finally, the statistical regression analysis performed within the group that underwent a two-step reconstruction using STSG revealed that time lapse from INT application to STSG is not influenced by independent variables such as age, CIRS, comorbidities, BMI, defect area, defect site, wound etiology, and risk factors. Inappropriate timing of secondary STSG can lead to a partial-thickness necrosis, requiring additional intervention and increasing patient morbidity. Four distinct phases of dermal regeneration have been histologically demonstrated: imbibition, fibroblast migration, neovascularization, and final remodeling and maturation. Usually, a full vascularization of the neodermis occurs within 4 weeks.⁸ The timing of STSG placement is meant to coincide with the neovascularization phase of matrix incorporation, allowing for the blood flow necessary for graft survival. To confirm ideal STSG timing, several methods have been proposed such as laser Doppler imaging and laser-assisted indocyanine green dye angiography.^{19,20} However, there are no studies focused on identifying those factors that may delay this optimal timing. Preoperative risk factors or predictors of complications have already been investigated for skin grafts, free flap surgery or lower extremity surgery^{21–24}; nevertheless, there is no available literature on predictors of matrix failure or delayed skin grafting after reconstruction using dermal substitutes.

In our study, the regression analysis showed no predictors of complications, and those independent variables that, for different reasons, may interfere with INT incorporation and normal wound healing revealed no relationships with timing of STSG placement. In our opinion, these findings represent an additional reassurance on the reliability and versatility of dermal substitutes for soft tissue reconstruction. However, randomized control trials

with flap reconstructions or systematic reviews would be necessary to elucidate these aspects.

CONCLUSIONS

Our findings showed that dermal substitutes can be used in a wide range of patients regardless of their general characteristics, and no predictors of complications or delayed matrix take were identified in our study. Healing by secondary intention after Integra reconstruction is recommended for covering small post-oncological defects in the head and neck, particularly in elderly patients with multiple comorbidities who are not candidates for a multi-step procedure. However, this conservative treatment strategy should be designated in selected and adequately counseled patients.

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REFERENCES

- Milcheski DA, Chang AA, Lobato RC, et al. Coverage of deep cutaneous wounds using dermal template in combination with negative-pressure therapy and subsequent skin graft. *Plast Reconstr Surg Glob Open*. 2014;2:e170.
- Menn ZK, Lee E, Klebuc MJ. Acellular dermal matrix and negative pressure wound therapy: a tissue-engineered alternative to free tissue transfer in the compromised host. *J Reconstr Microsurg*. 2012;28:139–144.
- Hur GY, Seo DK, Lee JW. Contracture of skin graft in human burns: effect of artificial dermis. *Burns*. 2014;40:1497–1503.
- Grassetti L, Torresetti M, Scalise A, et al. Acellular dermal matrices and paraffinoma: a modern tool for a nearly obsolete disease. *Arch Plast Surg*. 2017;44:234–237.
- Scalise A, Torresetti M, Verdini F, et al. Acellular dermal matrix and heel reconstruction: a new prospective. *J Appl Biomater Funct Mater*. 2017;15:e376–e381.
- Iorio ML, Shuck J, Attinger CE. Wound healing in the upper and lower extremities: a systematic review on the use of acellular dermal matrices. *Plast Reconstr Surg*. 2012;130(5 Suppl 2):232S–241S.
- Moiemen N, Yarrow J, Hodgson E, et al. Long-term clinical and histological analysis of Integra dermal regeneration template. *Plast Reconstr Surg*. 2011;127:1149–1154.
- Moiemen NS, Vlachou E, Staiano JJ, et al. Reconstructive surgery with Integra dermal regeneration template: histologic study, clinical evaluation, and current practice. *Plast Reconstr Surg*. 2006;117(7 Suppl):160S–174S.
- Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc*. 2008;56:1926–1931.
- Chang DK, Louis MR, Gimenez A, et al. The basics of Integra dermal regeneration template and its expanding clinical applications. *Semin Plast Surg*. 2019;33:185–189.
- Rehim SA, Singhal M, Chung KC. Dermal skin substitutes for upper limb reconstruction: current status, indications, and contraindications. *Hand Clin*. 2014;30:239–252, vii.
- Torresetti M, Scalise A, Di Benedetto G. Acellular dermal matrix for rhinophyma: Is it worth it? A new case report and review of literature. *Int J Surg Case Rep*. 2019;59:120–123.

13. Sanati-Mehrziy P, Massenbourg BB, Rozehnal JM, et al. Risk factors leading to free flap failure: analysis from the national surgical quality improvement program database. *J Craniofac Surg.* 2016;27:1956–1964.
14. Saçak B, Akdeniz ZD, Certel F, et al. Risk assessment for free tissue transfers: is old age a determining factor? *J Craniofac Surg.* 2015;26:856–859.
15. Koenen W, Felcht M, Vockenroth K, et al. One-stage reconstruction of deep facial defects with a single layer dermal regeneration template. *J Eur Acad Dermatol Venereol.* 2011;25:788–793.
16. Demiri E, Papaconstantinou A, Dionysiou D, et al. Reconstruction of skin avulsion injuries of the upper extremity with Integra dermal regeneration template and skin grafts in a single-stage procedure. *Arch Orthop Trauma Surg.* 2013;133:1521–1526.
17. Böttcher-Haberzeth S, Biedermann T, Schiestl C, et al. Matriderm 1 mm versus Integra Single Layer 1.3 mm for one-step closure of full thickness skin defects: a comparative experimental study in rats. *Pediatr Surg Int.* 2012;28:171–177.
18. Munster AM, Smith-Meek M, Shalom A. Acellular allograft dermal matrix: immediate or delayed epidermal coverage? *Burns.* 2001;27:150–153.
19. Morimoto N, Takemoto S, Kawai K, et al. Immediate evaluation of neovascularization in a grafted bilayered artificial dermis using laser Doppler imaging. *Ann Plast Surg.* 2014;72:84–88.
20. Fourman MS, Phillips BT, Fritz JR, et al. Laser-assisted indocyanine green dye angiography accurately predicts the split-thickness graft timing of Integra artificial dermis. *Ann Plast Surg.* 2014;73:150–155.
21. Stankiewicz M, Coyer F, Webster J, et al. Incidence and predictors of lower limb split-skin graft failure and primary closure dehiscence in day-case surgical patients. *Dermatol Surg.* 2015;41:775–783.
22. Zhao EH, Nishimori K, Brady J, et al. Analysis of risk factors for unplanned reoperation following free flap surgery of the head and neck. *Laryngoscope.* 2018;128:2790–2795.
23. Timmermans FW, Westland PB, Hummelink S, et al. A retrospective investigation of abdominal visceral fat, body mass index (BMI), and active smoking as risk factors for donor site wound healing complications after free DIEP flap breast reconstructions. *J Plast Reconstr Aesthet Surg.* 2018;71:827–832.
24. Arnaoutakis DJ, Scully RE, Sharma G, et al. Impact of body mass index and gender on wound complications after lower extremity arterial surgery. *J Vasc Surg.* 2017;65:1713–1718.e1.