Doctoral Dissertation
Doctoral Program in Bioengineering and Medical-Surgical Sciences
(35th Cycle)

Bioengineered dermal matrix (Integra®) to reduce donor site morbidity in total phallic construction with radial artery forearm free-flap

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Mirko Preto

Turin, October 30, 2022

Summary

Background:

Genital reconstructive surgery, especially within the path of genital gender-confirming surgery (Female to Male) but also following trauma or genital amputations in cis-males, can involve the reconstruction of the penis and/or urethra. Different surgical techniques have been described for total phallic construction (TPC). The gold standard currently recognized for TPC is the radial artery forearm free-flap (RAFFF). [28,30] While RAFFF showed excellent results in terms of aesthetics, urinary and sexual function (after penile prosthesis implantation), on the other hand, it produced non-negligible donor-site morbidity because nearly two-thirds of the forearm circumference was harvested. Historically, donor site repair following RAFFF consisted of immediate skin grafting with either full (FTSG) or partial-thickness skin grafts (PTSG). Both of these techniques may result in specific complications including: tendon exposure, decreased sensation, functional disability (such as limited hand mobility and decreased strength), or poor cosmetics. Donor site morbidity also included graft failure requiring re-grafting in 2.7% of cases. More recently, the use of dermal matrix 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 post-traumatic or post-oncological defects, and such techniques now represent a tissue-engineered alternative. Integra is an acellular dermal substitute composed of crosslinked type-1 bovine collagen coated with a glycosaminoglycan (chondroitin-6-sulfate) organized in the three-dimensional pattern of normal dermal fibers. Integra acts as a tissue scaffold for dermal cellular ingrowth and remodeling without contraction and scarring. It was initially approved by the FDA in 2001 for the treatment of life-threatening third-degree burns then it has additionally been used for chronic non-healing wounds and for the reconstruction of deep cutaneous defects. Clinical and histological studies have demonstrated that Integra could provide a durable skin coverage similar to that of a FTSG with minimal donor-site morbidity. Dermal substitutes similar to Integra have demonstrated encouraging results with regard to functional and aesthetic outcomes when applied to a donor site. The aim of the present research project is to report surgical and functional outcomes after donor site reconstruction during RAFFF, and to provide a comparative analysis between FTSG and dermal matrix substitute

Materials and Methods:

All patients undergone TPC with RAFFF in the period 2016-2021 were enrolled. Data were extrapolated from medical and operating records. Donor site defect resurfacing with FTSG and Integra with STSG were the two evaluated techniques. The duration of the procedure, hospital stay, size of the donor-site defect, and postoperative complication rate (<90 days, according to Clavien-Dindo classification) were considered as surgical outcome measures. Functional outcomes were evaluated through validated tools and questionnaires: Vancouver scar scale, POSAS scale, Scar Pinch Test, and aROM. Patient-reported outcomes were inquired using a 3 items ad-hoc created questionnaire. Moreover, a sub-analysis was carried out according to the reconstructive technique performed (Group A: FTSG and Group B: single-layer dermal matrix (Integra) with STSG).

Results:

34 patients were included in the study. Group A included 18 (53%) patients, whereas 16 (47%) patients were assigned to group B. Mean follow-up was 24 months (IQR 11-40). Mean age was 33 years (IQR 27-45). Preoperatively, no significant differences among the groups were recorded. The median donor-site defect was 306 cc (IQR 302-323, p=0.21). No intraoperative complications were detected. Overall, early postoperative complications were described in 26.5% of cases. According to Clavien-Dindo classification, we recorded Grade 1 in 14.7%, Grade 2 in 5.8%, and Grade 3a and Grade 3b in a single case (2.9%) respectively. Mean graft take was 91%. A complete graft take was detected in 58.9% of the patients. Considering the two groups separately, a significant advantage for group B (93.8%) was recorded when compared to group A (27.8%) (p= 0.001). Furthermore, in Group B a significantly shorter operative time (310min vs 447min p= 0.001) and a reduced median hospital stay (8 days vs 10 days p= 0.001) were observed. From a functional point of view, in both groups the results were satisfactory, overall 80% were satisfied with the appearance of the arm, and 92% with the post-surgery functionality and the possibility of resuming the previous work activity. Considering the two groups separately, Group B reached a significantly higher satisfaction rate in terms of arm appearance compared to group A (94% vs 66% p = 0.048).

Conclusion:

FTSG or dermal matrix with STSG for donor-site reconstruction after RAFFF provides satisfactory surgical, functional, and aesthetic outcomes. Dermal matrix and STSG may guarantee higher surgical and functional results.

Acknowledgments

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Contents

1. Introduction:

1.1. Background

The radial artery forearm free-flap (RAFFF) for reconstructive purposes in different clinical conditions (such as head and neck oncological surgery or following trauma/loss of substance) was introduced in the early 1980s and then has spread in daily clinical practice. This wide diffusion is certainly due to the peculiar characteristics of the flap: thin and often hairless skin, pliability as well as a large and reliable pedicle. **[1]** Although there are no direct comparative studies with other described reconstructive techniques, RAFFF is currently recognized as the gold standard for total phallic construction (TPC). **[2-5]** TPC represents a challenge for genital reconstructive surgeons since patient functional requirements are very demanding. **[6]** The ideal technique for TPC should be safe, reproducible, and performed in the fewest number of surgical steps with minimal impact on the donor site and with no functional loss. It should provide a satisfactory aesthetic appearance of the phallus and allow patients to void while standing. Furthermore, the phallus should have its own tactile and erogenous sensitivity and allow penetrative sexual intercourse. **[3-8]**

Notwithstanding RAFFF showed excellent results in terms of aesthetics, urinary and sexual outcomes, on the other hand, donor-site morbidity is a non-negligible persisting problem since nearly two-thirds of the forearm circumference are harvested during the procedure. **[4, 7-10]**

1.2 Donor Site Management

Historically, donor site repair following RAFFF consisted of immediate skin grafting with either full (FTSG), partial (PTSG), or split-thickness skin grafts (STSG). All these techniques may result in specific and not negligible complications including graft loss, delayed healing, tendon exposure, sensory changes, functional disability (such as limited range of motion or decreased pinch and grip strength), or poor cosmesis (keloids, discoloration) widely described in scientific literature. **[8-9, 11-13]**

More recently, the safety and efficacy of acellular dermal matrix (ADM) in combination with skin grafts to cover deep cutaneous wounds associated with tendon, bone or joint exposure have been widely reported in several studies considering post-traumatic or post-oncological soft tissue defects, and now ADM represents a tissue-engineered alternative rather than traditional skin grafts or local flaps which are not always enough. **[14-15]**

ADM with its scaffolding properties acts like normal dermis restoring skin anatomy and physiologic function and facilitating the synthesis of the new dermis. **[16]** The use of ADM has proved to minimize scar contracture and to improve overall scar quality. **[17]**
Considered that, ADM could be useful in donor site management in order to reduce RAFFF forearm morbidity and improve surgical and functional outcomes.

1.3 Acellular dermal membrane

Integra (Life - Sciences Corp., Plainsboro, NJ, USA) is an acellular dermal substitute composed of crosslinked type-1 bovine collagen coated with a glycosaminoglycan (chondroitin-6-sulfate) organized in the three-dimensional pattern of normal dermal fibers. **[18]** Being a cell-free product and not reliant on immediate imbibition or inosculation for successful take, Integra, with its predetermined 3D structure and pore size acts as a tissue scaffold for dermal cellular ingrowth and remodeling without contraction and scarring. It was initially approved by the FDA in 2001 for the treatment of life-threatening third-degree burns then it has additionally been used for chronic non-healing wounds and for the reconstruction of deep cutaneous defects. **[19]**
Clinical and histological studies have demonstrated that Integra could provide a durable skin coverage similar to that of a FTSG with minimal donor-site morbidity. **[20-22]** AMD has demonstrated encouraging results with regard to functional and aesthetic outcomes when applied to a donor site. **[23-24]** In its first version, Intera is a bilaminate ADM that required two surgical steps to complete tissue repair. During the first step, ADM is placed on the soft tissue defect, and the outer silicone layer is fixed on the margins of the grafted area. Once the ADM engraftment process is completed, after about 2 weeks, the second surgical step is performed. The outer silicone membrane is removed and a STSG is harvested and placed over the neodermis to complete tissue repair. To allow a single-stage surgical procedure, a single-layer version is then developed while maintaining the same functional and aesthetic outcomes. **[21]**
Unlike during the physiological wound healing process where myofibroblasts align and contract to close the open wound, resulting in scarred tissue more prone to shrinking, the Integra 3D fibers pattern controls the cell recruitment process by inhibiting the activity of myofibroblasts and preventing contraction processes offering a stimulus for natural mechanisms of regeneration and reconstruction. **[25] (Figure 1A-B)**

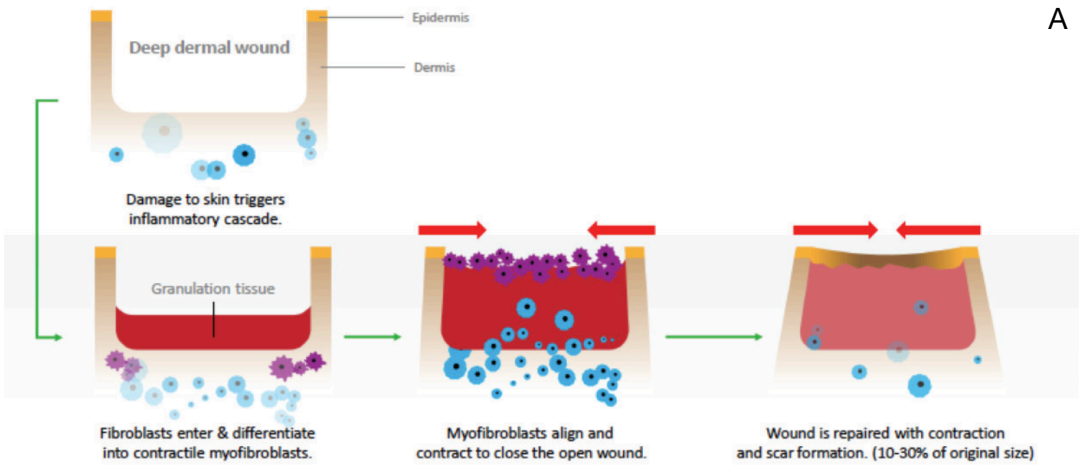


Figure 1A: Physiological wound healing process

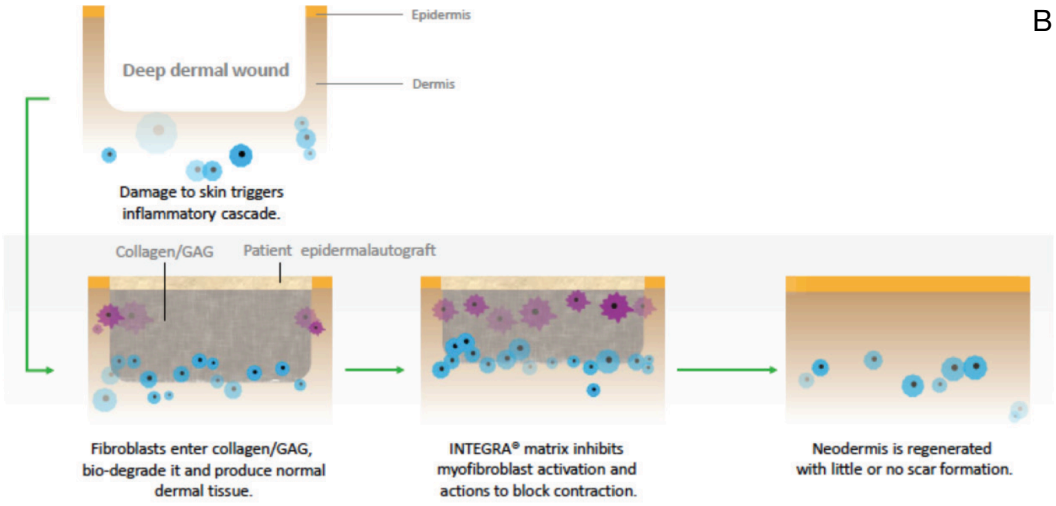


Figure 1B: Integra-guided healing proces

1.4 Aim of the research project:

The research project aims to report surgical and functional outcomes after donor site reconstruction during RAFFF providing a comparative analysis between the traditional FTSG and the ADM Integra and STSG to find out any significant difference.

2. Material and Methods:

2.1 Study Setting and Patients

From February 2016 to September 2021, all consecutive patients, who underwent TPC with RAFFF referred to our tertiary center, were enrolled in the present research project. All patients completed a written informed consent in order to undergo the procedure and to have their outcome data analyzed. Data were prospectively extrapolated from medical and operating records.

2.2 Surgical Technique and Management

2.2.1 Preoperative work-up

Typically, the radial artery flap was harvested from the non-dominant forearm. A preoperative Allen test or, when in doubt, a duplex ultrasonography was mandatory to evaluate the ulnar artery patency. **[25]** Furthermore, a laser-based air removal from the ulnar aspect of the forearm was recommended for patients to reduce the neourethra complication rate.

2.2.2 Radial artery flap elevation

RAFFF was elevated under tourniquet compression. The modified Gottlieb and Levine technique was performed. Generally, the flap was designed with a medial strip (17 x 4 cm) along the course of the radial artery and a lateral paddle (13x14cm). In order to allow neophallus closure, a 1cm-wide de-epithelialized strip of dermis is interposed between the two areas of the flap. All considered, about two-thirds of the forearm circumference were included in the flap. **[4, 6, 26] (Figure 2)**

From the vascular point of view, the RAFFF was supplied by the radial artery which was progressively isolated up to its origin from the brachial artery while the interosseous and ulnar arteries were spared. To provide the flap with the best venous drainage system and to reduce the risks of venous stasis and ischemia, as many veins as possible such as cephalic, basilic, venae comitantes, and lateral veins were included in the flap. As regards flap sensitivity, medial and lateral cutaneous nerves of the forearm were isolated and preserved. **(Figure 3)**

Applying the principle of tube-within-tube reconstruction, the medial strip was then tabularized over a 16F catheter, to create the neourethra while the lateral paddle was rolled around the neourethra to fashion the neophallus in a single-stage procedure. **(Figure 4)**

In the meantime, the recipient site was prepared by isolating the necessary anatomical structures. As regards the venous drainage, the great saphenous vein and accessory saphenous veins were isolated by an incision at the level of the inguinal fold. Through a pubic circular skin incision, subsequently extended along the lateral margin of the rectus muscle, the ilioinguinal and genital dorsal-bundle nerves were isolated to provide sensitivity to the flap, and the deep branch of the inferior epigastric artery was dissected for arterial supply.

Once the flap was transferred to the recipient site, a microsurgical anastomosis was carried out with the use of an optical microscope. The deep branch of the inferior epigastric artery was anastomosed with the radial artery in an end-to-end fashion. Similarly, the great saphenous vein was anastomosed with the forearm cephalic vein, while accessory flap veins (basilic or lateral flap) with the accessory saphenous veins or with the venae comitantes of the epigastric artery. Ilioinguinal and dorsal-bundle nerves were coapted to flap cutaneous nerves to provide tactile and erogenous sensation. **[4, 27]**

Postoperatively, low-molecular-weight heparin (sodic enoxaparin 4000UI/day) and antiplatelet therapy (acetylsalicylic acid 100mg/daily) were administered for 4 weeks.

2.2.3 Donor-site management

The donor site was managed in two different ways during the study period.

In both cases, once the RAFFF was transferred, the donor-site area was checked for hemostasis and, if necessary, the muscular plane edges were brought closer to provide a surface as regular as possible to ensure greater contact between the muscular bed and the graft used for resurfacing.

In the first part of the series, the donor site was directly covered by two FTSG harvested from patient' lower buttocks at the beginning of the procedure.

(Figure 5 - Group A)

The FTSGs were adequately defatted reaching the dermal plane and directly applied over the forearm defect, shaped and sutured along their margin with absorbable material, taking care to modulate the tension and adhesion to the underlying muscle plane in order to reduce the risk of hematoma/seroma formation in the following healing period. **(Figure 6)**

More recently, FTSGs were no longer used and were replaced by a bioengineered acellular dermal membrane (Integra). Once the traditional forearm management maneuvers were performed, Integra was applied to the defect area accordingly shaped. **(Figure 7)** Integra was then covered by STSGs (0.008–0.010 inch thick) taken from the inner aspect of patient's thighs through the use of an electric dermatome (Zimmer Air Dermatome; Zimmer Inc., Warsaw, Ind.,USA). STSGs were sutured with resorbable material with the same precautions used for the FTSGs. **(Figure 8 - Group B)**

Once donor site repair was completed, the forearm was dressed using non-adhesive, semi-occlusive, and absorbent material. The forearm was kept unloaded for the first postoperative 7 days.

Figure 2: Forearm flap design

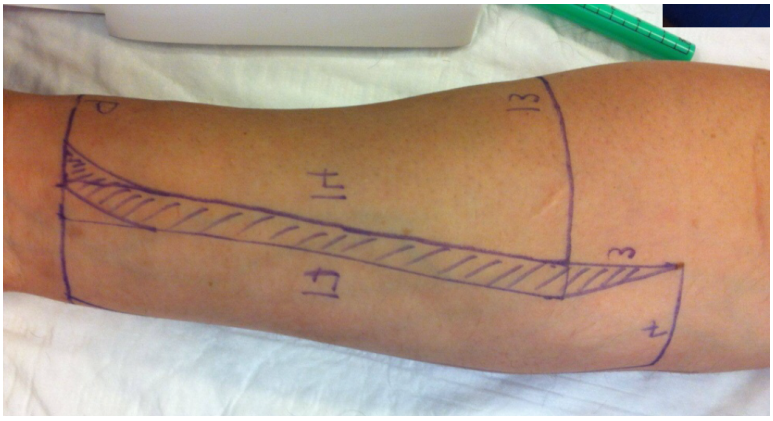


Figure 3: RAFFF dissected

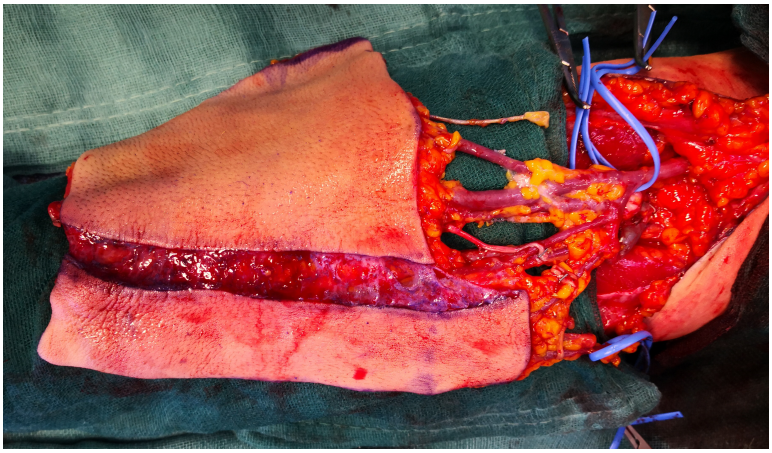


Figure 4: RAFFF tubularized

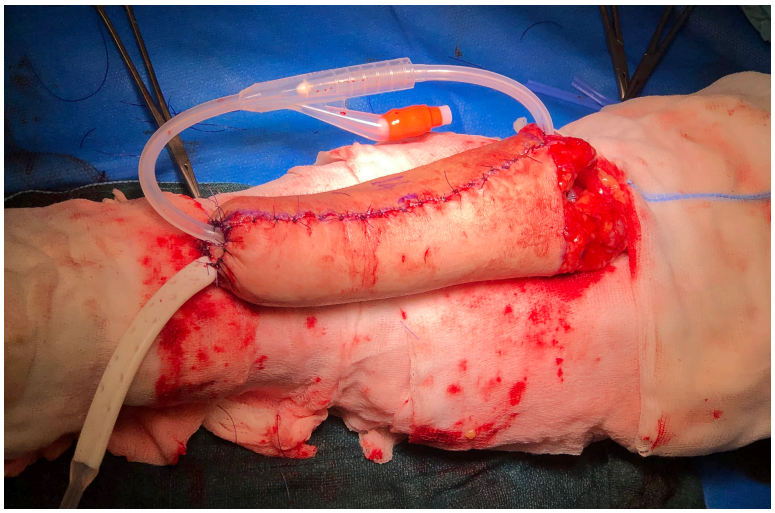


Figure 5: Lower buttocks harvesting

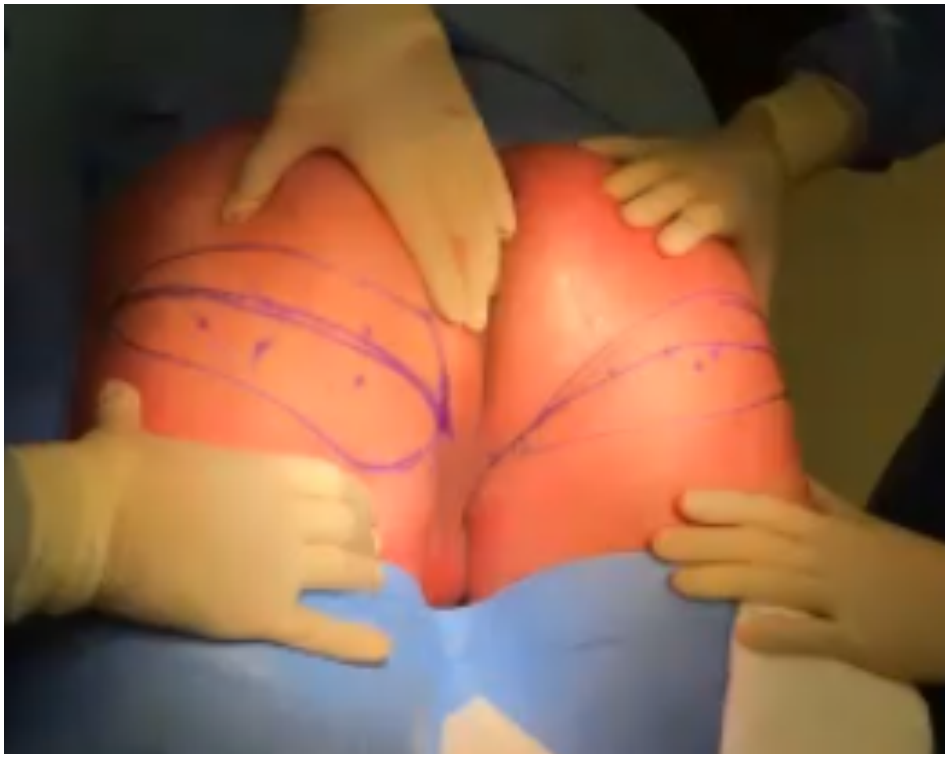


Figure 6: FTSG donor site resurfacing

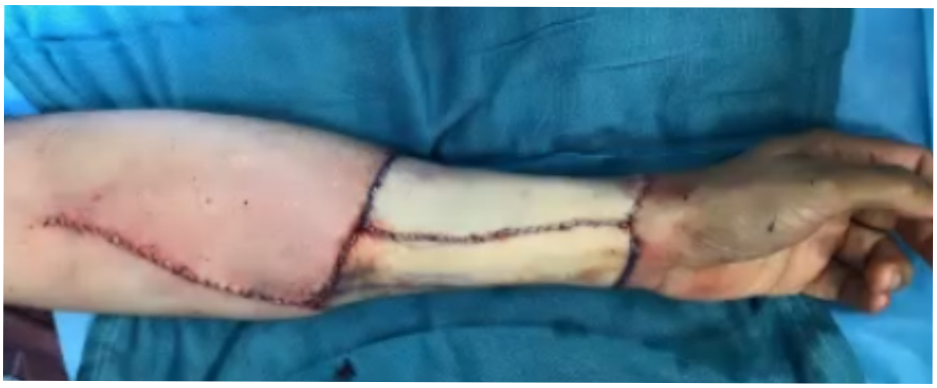


Figure 7: Integra applied on the forearm donor site

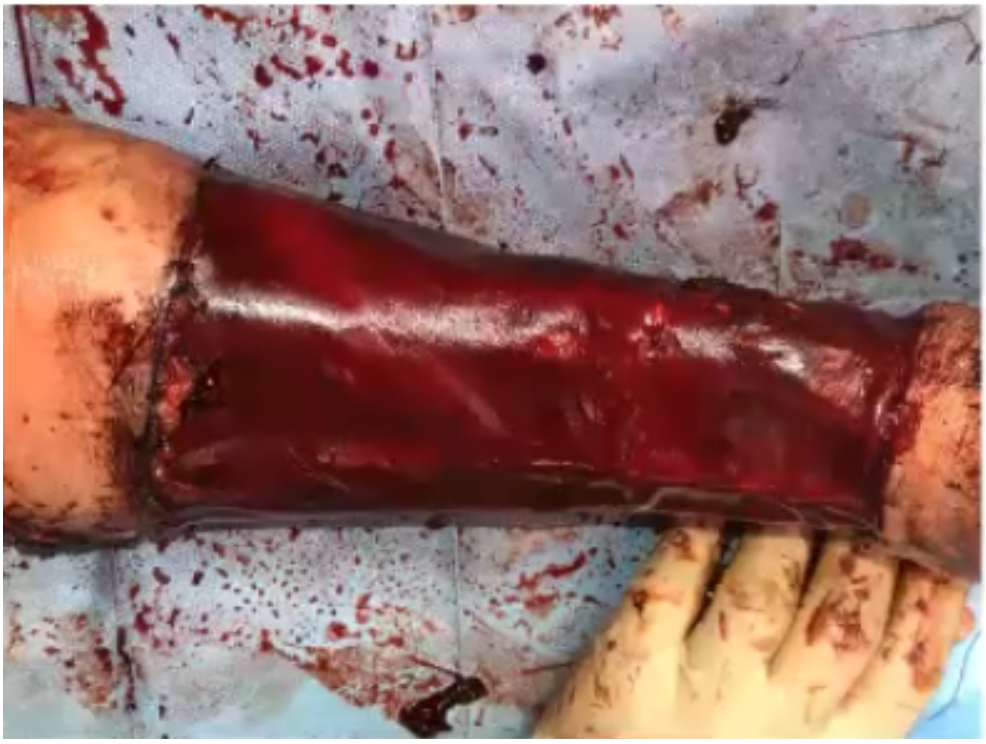
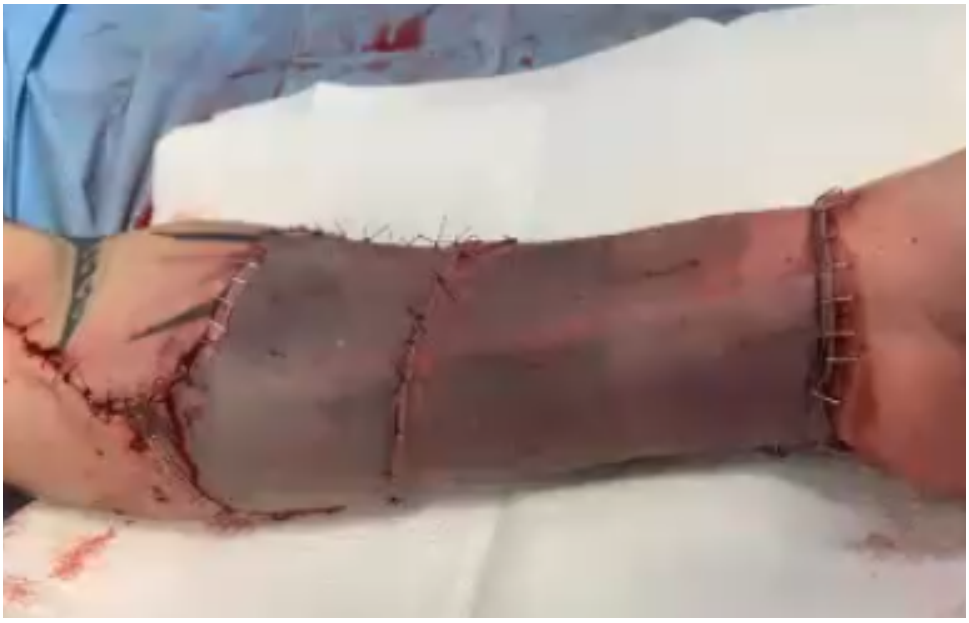


Figure 8: STSG applied over Integra



2.3 Outcome Measures

2.3.1 Surgical Outcomes

Operative time, hospital stay, size of the donor-site defect, postoperative complication rate (<90 days, according to Clavien-Dindo classification), and graft take or keloid formation at the donor site were considered as surgical outcome measures.

2.3.2 Functional Outcomes

Regarding functional outcomes, postoperative donor-site appearance, arm functionality, and the possibility of resuming normal daily and working activities were evaluated through the following validated tools and questionnaires at 6 months follow-up:

- The Vancouver scar scale (VSS) **[28]** was developed by Sullivan in 1990 and adopted to assess scars using a semi-quantitative approach. Scar vascularity, height, pliability, and pigmentation are included in VSS. A score is applied for each aspect to define the final score (0-13). **(Figure 9)**

- The Patient and Observer Scar Assessment Scale v2.0 (POSAS 2.0) which measures scar quality by evaluating vascularity, pigmentation, thickness, relief, pliability, and sensory characteristics of the scar from the perspective of the observer and patients. **[29] (Figure 10A-B)**

- Scar Pinch Test, which consists of a clinical evaluation of skin pliability where skin lifting is measured with respect to the underlying planes compared to normal skin on a comparable anatomic location.

- Active range of motion (aROM) to evaluate the full range of post-operative wrist movement **[30]**

- Medical Research Council Manual Muscle Testing scale is the most commonly accepted method of evaluating muscle strength. Specifically, it was used to assess post-surgery muscle capacity and strength according to a 0-5 score. **[31] (Figure 11)**

- Patient-reported outcomes (PROs) were inquired using a 3 items ad-hoc created questionnaire administered at 1-year follow-up. **(Figure 12)**

Moreover, a sub-analysis was conducted according to the reconstructive technique performed (Group A: FTSG and Group B: single-layer dermal matrix (Integra) with STSG) to find out any significant differences.

Figure 9: Vancouver Scar Scale

Scar characteristic	Score (Total 0-13)
Vascularity	
Normal	0
Pink	1
Red	2
Purple	3
Pigmentation	
Normal	0
Hypopigmentation	1
Hyperpigmentation	2
Pliability	
Normal	0
Supple	1
Yelding	2
Firm	3
Ropes	4
Contracture	5
Height (mm)	
Flat	0
<2	1
2-5	2
>5	3

Figure 10A: POSAS Observer scale

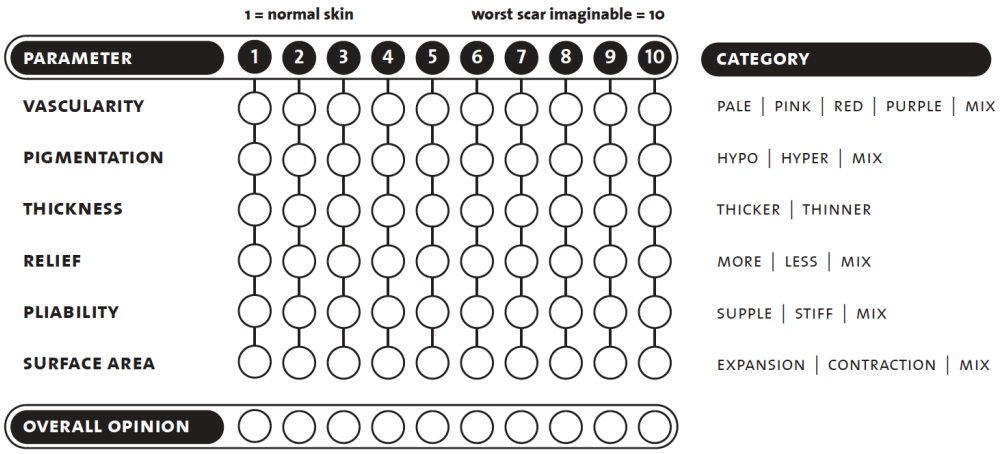


Figure 10B: POSAS Patient scale

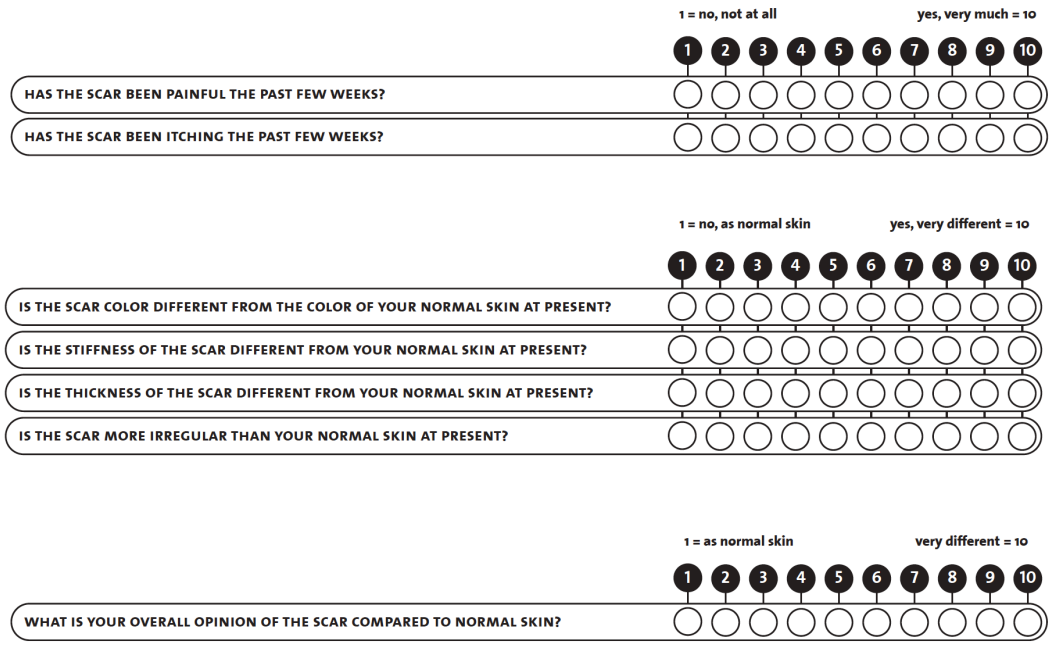


Figure 11: Medical Research Council Manual Muscle Testing scale

Clinical Condition	Score
No movement is observed	0
Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the muscle	1
Muscle can move only if the resistance of gravity is removed.	2
Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed.	3
Muscle strength is reduced but muscle contraction can still move join against resistance.	4
Muscle contracts normally against full resistance.	5

Figure 12: Ad hoc 3-items questionnaire to assess PROs

Question	Answer
Are you satisfied with the overall appearance of the arm?	Yes/No
Are you satisfied with the overall functioning of the arm?	Yes/No
Are you able to resume work?	Yes/No

2.4 Statistical Analysis

STATA software package (v.14, StataCorp LCC, College Station, TX) was used with a two-sided P value of <.05 being considered significant for carrying out statistical analysis. The normal distribution of variables was tested by the

Kolmogorov- Smirnov test. Categorical variables were described using frequency and percentage, while median and interquartile range (IQR) values were used for continuous variables. For evaluating and comparing surgical outcomes and functional questionnaire scores, a nonparametric Kruskal-Wallis, chi-square, test was performed.

3. Results:

3.1 Patients Cohort

Thirty-four consecutive patients were included in the study. Baseline descriptive features were listed in **Table 1**. The median age was 33 years (IQR 27-45). Donor site was managed with FTSG (Group A) in 18 cases (53%) whereas 16 (47%) with Integra and STSG (Group B). Median follow-up was 24 months (IQR 11-40). RAFFF was performed for TPC after penile amputation in 6 patients (17.6%) and for genital gender-confirming surgery in 28 cases (82.3%). The median donor-site defect was 306 cubic centimeters (IQR 302-323, p=0.21). Preoperatively, no significant differences among the groups were recorded, even with regard to recognized risk factors interfering with the engraftment and scarring process.

3.2 Surgical Outcomes

Surgical outcomes were reported in **Table 2**. No intraoperative complications were detected. The median operative time was 396 minutes (IQR 310-460), it is evident that in Group B a significantly shorter operative time (310min vs 447min p= 0.001) was observed. Similarly, a significantly reduced median hospital stay (8 days vs 10 days p= 0.001) was recorded for patients included in Group B compared to Group A. Overall, postoperative complications were described in 26.5% of cases. According to the Clavien-Dindo classification, we recorded Grade 1 in 14.7%, Grade 2 in 5.8%, and Grade 3a and Grade 3b in a single case (2.9%) respectively, no differences were identified in the sub-group analysis. Median graft take was 91%. Overall, regarding short-term results, a complete graft take was detected in 58.9% of cases while a partial loss of the graft (involving at least 30% of the grafted area) was recorded in 8.8% of patients. Considering the two groups separately, in terms of complete graft take. a significant advantage for group B (93.8%) compared to group A (27.8%) (p= 0.001) was recorded. As regards the surgical long-term results, a significantly higher rate of keloid formation was observed in group A compared to that managed with Integra and STSG (38.9% in Group A vs none in Group B, p=0.005).

3.3 Functional Outcomes

Overall, functional outcomes were satisfactory even in the separate analysis by surgical technique **(Table 3)**. Considering PROs, 91% of patients were satisfied with postoperative functionality and work activity recovery without significant differences between the groups. Although the overall satisfaction rate for forearm appearance was up to 80%, a significant difference between the two groups (66% Group A vs 94% Group B, p = 0.04) was identified. **(Figure 13)** Furthermore, analyzing the scores recorded in the different tests and questionnaires administered during the follow-up period, Group B showed significantly better scores in the POSAS observer questionnaire (p = 0.02) as well. On the other hand, there were no significant differences in terms of active mobility (aROM), muscle functioning (muscle testing scale), and grafted area pliability (scar pinch test) between the two groups.

Table 1: Patients' demographics

Variables	Total	Group A	Group B	p-value
Number of patients, n (%)	34 (100)	18 (53)	16 (47)	
Median age years, (IQR)	33 (27-45)	32 (23-51)	35 (28-44)	0.6
Follow-up months, (IQR)	24 (11-40)	33 (24-47)	10 (6-19)	**0.0001**
Risk factors and comorbidities:				
Smoke, n (%)	8 (24)	5 (28)	3 (19)	0.56
Diabetes, n (%)	0 (0)	0 (0)	0 (0)	-
Hypertension, n (%)	4 (12)	3 (17)	1 (6)	0.35
OSAS, n (%)	0 (0)	0 (0)	0 (0)	-

BMI value, (SD)	24 (2.5)	24 (2.3)	23 (2.6)	0.09
Defect volume, cc (IQR)	306 (302-323)	306 (299-323)	306 (305-325)	0.21

Table 2: Surgical Outcomes

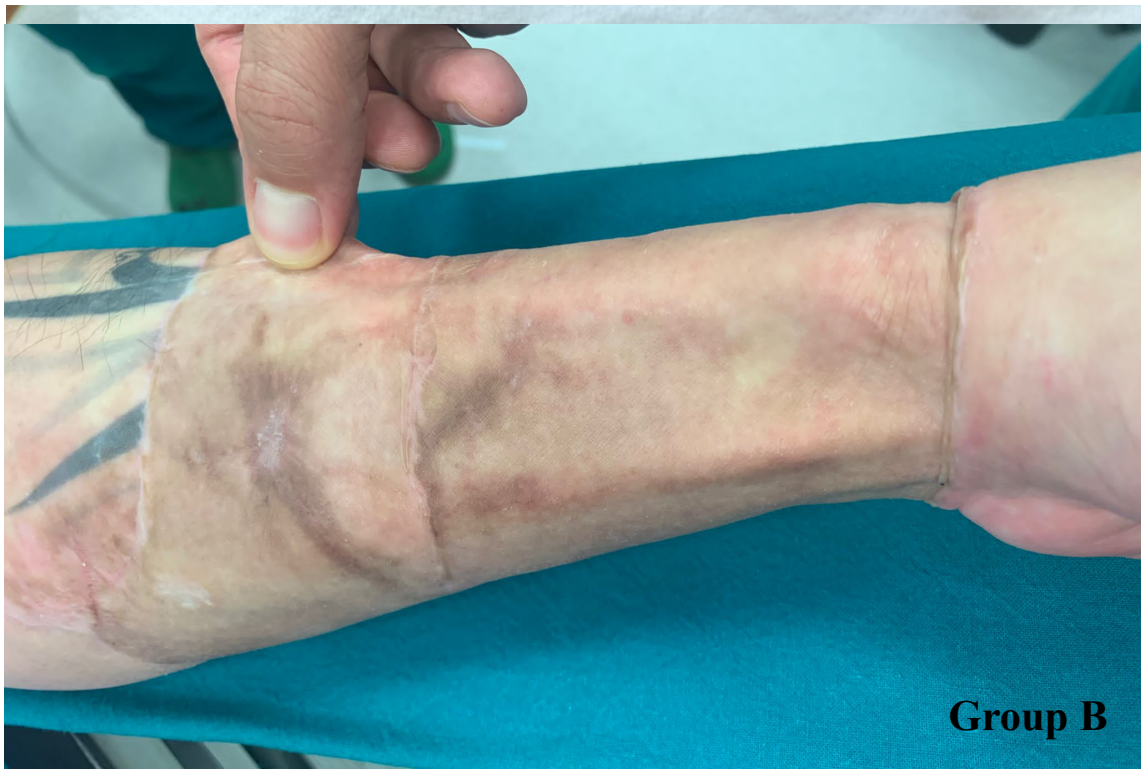
Variables	Total	Group A	Group B	P-value
Number of patients, n (%)	34 (100)	18 (53)	16 (47)	
Operative Time, min (IQR	396 (310-460	447 (405-480	310 (300-365	**0.001**
Hospital Stay, days (IQR)	9 (8-11)	10 (8-12)	8 (7-9)	-
Complications, n (%)	9 (26.5)	6 (33.3)	3 (18.7)	0.09
Grade 1	5	3	2	-
Grade 2	2	2	0	-
Grade 3a	1	1	0	-
Grade 3b	1	0	1	-
Partial Graft Loss, n (%)	3 (8.8)	2 (11.1)	1 (6.2)	0.6
Complete Graft Take, n (%	20 (58.9)	5 (27.8)	15 (93.8)	**0.001**
Cheloid formation, n (%)	7 (20.6)	7 (38.9)	0 (0)	**0.005**

Table 3: Functional Outcomes

Variables	Total	Group A	Group B	P-value
Number of patients, n (%)	34 (100)	18 (53)	16 (47)	
Vancouver Scar Scale (0-13)	4 (3-6)	4 (2-6)	5(4-6)	0.16
POSAS - Observer (6-60)	11 (14-18)	17 (12-20)	12 (10-15)	**0.02**

Overall POSAS Observer (1-10)	3 (2-4)	3 (2-4)	2 (2-3)	0.3
POSAS - Patient (6-60)	13 (10-19)	17 (8-28)	12 (10-15)	0.09
Overall POSAS Patient (1-10)	1 (1-4)	1 (1-5)	2 (1-3)	0.49
Positive Scar Pinch Test, n (%)	31 (91)	16 (89)	15 (94)	0.6
Physiological aROM, n (%)	33 (97)	17 (94)	16 (100)	0.34
Muscle Testing scale (0-5)	5 (4-5)	5 (4-5)	5 (4-5)	0.93
Overall Satisfaction				
Arm appearance, n (%)	27 (79.4)	12 (66.6)	15 (93.8)	**0.04**
Arm functioning, n (%)	31 (91)	15 (83.3)	16 (100)	0.09
Able to work, n (%)	31 (91)	15 (83.3)	16 (100)	0.09

Figure 13: Post-operative arm appearance Group A vs Group B



4. Discussion:

The introduction of microsurgical techniques and their application in TPC has made possible to transfer in a single stage the RAFFF, reconfigured as neophallus, from the donor to the recipient site in the pubic region. Over time, starting from the first description of this new frontier in reconstructive surgery **[6,32-33]**, changes and improvements in the technique have been made to optimize outcomes and reduce complications of the neophallus (especially for vascular and urethral ones). **[26, 34-35]** In the specific context of TPC, it seems that the attention to donor site surgical and functional drawbacks has been in some ways neglected. This aspect can be partly justified, as reported by some authors in the past, by the fact that TPC is often offered to patients in the context of genital gender-confirming surgery, and therefore at the end of a long and winding path, these patients are more inclined to accept forearm scarring and any functional limitations in order to reach the final goal of personal acceptance. **[13]** In other series, conversely, patients mostly complain of the scar on the forearm defining it as a stigma of their previous path and a reason for social discrimination. **[1]**
Ito et al. reported that up to 31% of patients were concerned about donor site color, depression, and sensation.**[11-12]**Therefore, it is not possible to manage the donor site as if it were a secondary aspect since the surgical, aesthetic and functional outcomes are of primary importance as well as the TPC as a whole for the overall satisfaction of the patient.

Generally, scar tissue is easily distinguished from healthy surrounding tissue in terms of color, texture, thickness, retraction and firmness. **[16]**
Considering surgical outcomes, donor site could be burdened with early and late complications. The former are characterized by hematoma, wound infection, skin graft failure, exposed tendons, neuroma formation, nerve compression, compartment syndrome, while the latter include hypertrophic scarring, lymphedema/swelling of the forearm, skin irregularity/contracture, local pain and itching scar. Overall, the reported complication rate is up to 8% of cases. **[9]**
Partial or total skin graft failure is the most frequently described complication (5% of cases), followed by forearm lymphedema in 3.9%. **[3, 13]**
Our series is in line with the literature with regard to graft failure, a partial graft loss has been described overall in 8.8% of cases and in 6% of cases if we consider only Group B (Integra + STSG), A donor site regrafting has been performed in a single case (2.9% - Clavien Dindo 3a in a patient of Group A) similarly, the literature reported regrafting in up to 3% of patients. **[1,9,13]**
Postoperative lymphedema is usually transient, Selvaggi et al reported how it resolved within 2-6 months after specific physical therapy. **[13]** Despite draining

physical treatment, two cases of persistent forearm edema (Clavien Dindo 1) at the 10-month follow-up have been described in our series, even if reduced compared to the initial condition and without hand mobility impact.
In some series, donor site infection has been described in terms of cellulitis with the need for antibiotic therapy in 16% of cases, we have recorded a donor site infection in only 5.8% of cases, always in the FTSG group. **[5,33,35]** Postoperative neuroma formation has not been described compared to the literature-reported rate (up to 10%). **[13]**

Regarding functional outcomes, the most frequent complaints after RAFFF elevation are decreased strength and altered sensation in the donor extremity (4.9%) followed by limited wrist ROM. **[5,9,35]**
Reduced sensitivity at the level of forearm radial dorsal aspect and wrist has been reported in 80% of patients due to injury or inclusion in the RAFFF of the lateral antebrachial cutaneous nerve and/or dorsal radial sensory nerve branch. **[9]**
Garaffa et al reported a reduced rate of wrist ROM in 1.5% of patients while in our series a limited ROM has not been recorded as also previously reported by other authors after Integra use in donor site repair. **[1, 16, 35, 36]**

As previously described, the donor site after RAFFF elevation requires defect repair using a skin graft, different types of skin grafts have been analyzed so far in several clinical settings from which it is possible to derive some useful information.
STSG, easily harvested from the thighs, could cover very large defects at the donor site but the color and texture of the graft are different compared to those of the forearm once healed. Theoretically, STSG could also be preferable for its ease of engraftment but, in case of graft loss, tendon exposure, incorrect and prolonged healing period could occur. In some series, the STSG loss rate has been reported to be as high as 28%. **[37]** Once healed, because of its thinness, STSG can furthermore determine the formation of adhesions with the underlying tendons leading to reduced ROM, functional impairment, and poor cosmesis. **[11,22, 38-39]**

Consequently, FTSG gained popularity as an alternative donor site grafting technique. A thicker graft was indeed thought to avoid at least some of the most common STSG complications. Davis et al. directly compared STSG and FTSG finding equal healing times with overall good satisfaction rates with both skin grafts. They described a more limited engraftment rate for FTSG (84-88%) compared to STSG (84-98%) probably justified by the different skin graft thickness. **[12,38-40]**

Hypertrophic scars and esthetic issues have been also complained by patients following FTSG for its limited take in addition to the greater invasiveness of its harvesting. **[22,38]**

Since optimal results have not been obtained even with the FTSG, bioengineered ADM has been considered for donor site repair. ADM application with its scaffolding action could restore skin anatomy, dermal physiologic function, and scar resistance to shear forces **[16-17]**
The application of Integra ADM on the donor site before STSG has already demonstrated its safety and efficacy by creating a gliding surface between the muscle-tendon structures and the STSG, recreating a sort of full-thickness graft. **[36]** Furthermore, ADM, stimulating the neodermis formation below the STSG, minimizes the depressive effect compared to the surrounding areas improving both the functional and cosmetic outcomes. **[1]** Moreover, after Integra application, easier engraftment and healing of the STSG with no tendons exposure or need for regrafting, compared to STSG alone, have been reported as well. No tendon adhesions, neither nerve irritations, local pain, or significant loss in wrist and hand aROM have also been reported. **[1, 16]** In the same way, in our series, higher engraftment and healing rates and minimal keloid formation have been reported in the group of patients served with Integra compared to the FTSG. In line with Shores et al. **[41]** and Wirthman et al. **[1]**, even in our experience no Integra infections or significant skin graft loss have been recorded.

The application of an ADM combined with a STSG in a single-stage procedure has already been described by Wester et al. using Alloderm comparing it with the STSG alone. As expected, the group treated with ADM achieved better cosmetic results with a lower complication rate than the STSG group. **[22,42]**
Subsequently, Demiri et al. reported an initial experience with Integra in a single-stage procedure in post-traumatic patients with satisfactory functional results, and an overall graft take up to 95–98% with no limitations in grip strength or wrist movement at the donor site. **[36]**
Our results confirm and further expand the indication for Integra combined with STSG with overlapping outcomes.

Definitely, the use of Integra represents an additional cost to be taken into account. In addition to determining better aesthetic results at the donor site, as already discussed, it can lead to reduced operative time and hospital stay as demonstrated in our series. These two aspects represent savings in all respects that can equal if not exceed the cost of the Integra itself. A better long-term outcome and a quicker recovery will reduce costs in long term. **[1,22]**

5. Conclusion:

Both the FTSG and Integra with STSG for the management of the donor site after RAFFF have proved to be safe and effective, providing satisfactory surgical, functional, and aesthetic outcomes. However, it resulted that Integra dermal matrix with STSG may guarantee higher surgical and functional results compared to FTSG.

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