JBUON 2021; 26(5): 2146-2153
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Application of dermal regenerative template in reconstructing skin defects after plantar malignant melanoma excision

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Summary

Purpose: *The excision of plantar malignant melanoma frequently leads to wide skin defects on the plantar surface. This study aimed to investigate the advantages and feasibility of dermal regenerative template reconstructing plantar blemishes caused by malignant melanoma.*

Methods: *28 patients identified with plantar malignant melanoma were included in this retrospective article. Eighteen patients received immediate skin grafts after wide excision skin graft (SG) group), whereas the remaining 10 patients were treated with dermal regenerative template (DRT) (Lando ®, Shenzhen TsingCare Medical Co. Ltd) 14 days before skin grafts (DRT group) and the postoperative survival rate in the two groups was analyzed. During the 6-month follow-up, we compared the scar index, plantar pain, and recurrent skin graft ulcer incidence on the skin grafts area.*

Results: *Postoperative survival rate in the DRT group (91.75% ± 7.64%) was higher than in the SG group (80.51% ± 7.17%). The DRT group showed less scar formation on Vancouver scar scale (VSS index): 3.40 ± 1.07 than the SG group (VSS index: 6.33 ± 0.68). The dermal regenerative template alleviated plantar pain and decreased the incidence of ulcer on the skin grafts area.*

Conclusions: *The dermal regenerative template not only improves the survival rate of skin grafts but also alleviates scar condition, plantar pain and recurrent skin graft ulcer. This study provides a new reconstructive strategy in plantar skin defects after the excision of malignant melanoma.*

Key words: *plantar malignant melanoma, plantar reconstruction, dermal regenerative template, skin grafts*

Introduction

Excision with sufficient margin and depth to reduce the recurrence of plantar malignant melanoma remains the predominant therapeutic strategy in clinics [1,2]. Due to the plantar surface's structure and weight-bearing function, the reconstructive methods cause by excision operations are quite challenging for surgeons. Skin grafts and flaps are commonly used to cover plantar defects [3]. Skin graft is easy to be performed but limited by scar formation and wound contraction [4]. Although skin flap surgeries are performed to reconstruct the weight-bearing areas of plantar surfaces, these approaches consistently cause potential injuries to patients, such as: flap morbidity and damage on donor site [5,6]. Dermal regenerative template (DRT) has been widely used to promote wound recovery [7,8]. However, the reconstruction of plantar skin defects with DRT in cutaneous tumour is rarely explored. This retrospective review aimed to investigate the advantages and feasibility of DRT reconstructing weight-bearing part of plantar skin defects after malignant melanoma excision.

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Received: 13/06/2021; Accepted: 02/08/2021

Methods

Study objects

Thirty-five patients with plantar malignant melanoma were included from March 2017 to March 2020 at the Department of Plastic and Burn Surgery, The First Affiliated Hospital of Nanjing Medical University. The patients with diabetes or vascular morbidity of the lower extremity who could affect plantar skin graft condition were excluded. Finally, 28 patients who were treated with skin graft transplantation after wide excision were recruited in this retrospective study. Eighteen patients received immediate skin grafts (SG group) and 10 patients were treated with dermal regenerative template before skin grafts (DRT group) (Table 1). All of the patients studied signed the consent form for treatment and agreed to be followed after hospitalization. All the procedures were approved by local Ethics Committee of the First Affiliated Hospital with Nanjing Medical University.

Operation procedures

All of the patients underwent wide excision with a margin of 2cm and depth to deep fascia layer on primary location of plantar malignant melanoma. Eighteen patients in the SG group were subjected to immediate reconstruction of split-thickness skin grafts (STSGs), and the skin grafts areas were then treated with vacuum-associated closure (VAC) for 7 days.

The procedure of the patients in the DRT group were the following: (1) The DRTs were soaked by normal saline for 1 min and then were sliced into the shapes suitable for plantar wounds; (2) The DRTs were placed on the plantar skin defects after multiple holes for drainage were carved on the DRT surfaces; (3) The DRTs were sutured and then compressed to the plantar wound for 14 days; (4) The delayed STSGs were performed after 14-day therapy of DRT and the skin grafts areas were treated with VAC for an extra 7 days.

Evaluation of two groups

The evaluation included skin grafts survival rate, scar condition, skin grafts area ulcer incidence and plantar pain; 1: Skin grafts survival rate was evaluated by the ratio between the survival area and skin grafts area. The survival area was calculated 7 days after STSGs by photograph; 2: Scar condition was evaluated by Vancouver scar scale (modified Baryza version, MVSS) 6 months after skin grafts. The assessment index included pigmentation, vascularity, pliability, and height [9]; 3: Skin grafts area ulcer incidence was based on whether recurrent wound was observed in daily life; 4 Verbal Rating Scale (VRS) was used in analyzing plantar pain either walking or standing [10]. The plantar pain condition was divided into 4 levels (0-no pain, 1-mild pain, 2- moderate pain, 3-severe pain.)

Table 1. Patient demographics

	SG (n=18) *n (%)*	*DRT (n=10)* *n (%)*	*Total (n=28)* *n (%)*	*p value*
Age (y), (mean±SD)	65.05±12.62	70.90±13.73	67.14±13.9	>0.05
Sex				
Male	12 (67)	4 (40)	16 (57)	
Female	6 (33)	6 (60)	12 (43)	>0.05
Situ of plantar MM				
Right plantar skin	8 (44)	2 (20)	10 (36)	
Left plantar skin	10 (56)	8 (80)	18 (64)	>0.05
Location of plantar MM				
The ball of plantar	7 (39)	4 (40)	11 (39)	
The heel of plantar	10 (55)	2 (20)	12 (43)	
The literal arch of plantar	1 (6)	3 (30)	4 (14)	
The medial arch pf plantar	0 (0)	1 (10)	1 (4)	>0.05

The patient demographics were analyzed by Student's t-test, x^2 and Fisher's exact test. SG indicated the patients who received immediate skin grafts. DRT indicated the patients who were treated with dermal regenerative template before skin grafts. MM: malignant melanoma.

Table 2. The skin grafts condition in the two groups

	SG	*DRT*	*p value*
Skin graft area (cm^2)	17.48±4.81	16.98±4.66	>0.05
Survival area (cm^2)	13.68±3.91	16.02±4.75	>0.05
Survival rate (%)	80.51±7.17	91.75±7.64	<0.05*

The survival rate was analyzed by Student's t-test. *indicates statistically significant differences. SG indicates the patients who received immediate skin grafts. DRT indicates the patients who were treated with dermal regenerative template before skin grafts.

Statistics

Data were expressed as mean ± standard deviation, and analyzed by SPSS 25 (IBM, Armonk, NY, USA). Survival rate, total VSS index and total VRS scores were analyzed by Student's t-test. Chi square and Fisher's exact test were used to analyze recurrent skin grafts area ulcer and distribution of VSS. Wilcoxon rank sum test was used to analyze the distribution of VRS in the two groups. P<0.05 was considered statistically significant.

Results

Evaluation of the skin grafts condition of the two groups

Patients from each group were subjected to DRTs or immediate STSGs, respectively. The skin grafts survival rate in the DRT group was significantly higher than in the SG group (p<0.05; Table 2). In addition, the postoperative and follow-up condition of plantar skin grafts in the DRT group were generally better than in the SG group (Figures 1 and 2).

Scar evaluations of the two groups

The pigmentation of plantar skin graft in the SG group was severe compared to DRT group, and the scar texture of the patients treated with DRT was more pliable. In addition, the VSS index of plantar skin grafts in the SG group (ranging from 5 to 8) was significantly higher than in the DRT group (ranging from 3 to 5) (p<0.05; Table 3). However, there was no significant difference in terms of vascularity. It is possible that the scar in the plantar skin graft area had matured during the follow-up.

Skin grafts area ulcer incidence of the two groups

No recurrent skin grafts area ulcers in the DRT group were recorded, but 8 from SG group on the ball and heel of plantar surface (p<0.05; Table 4). It is possible that the DRT could reduce the ulcer incidence.

Plantar pain condition of the two groups

The plantar pain condition in the DRT group was mainly in no pain, while that in SG group was mainly 'mild pain'. Through comparison the total VRS scores in the two groups, the DRT could significantly reduce the plantar pain on the skin graft area (p<0.05; Table 5).

Discussion

Given the low incidence and unawareness on plantar malignant melanoma, Chinese people are more likely to develop severer local morbidity and larger skin defects [11]. Skin graft is easy to be performed, but the postoperative quality of life is usually affected by skin ulcer and scar condition. Skin flaps, such as medial plantar flaps or reverse sural neurocutaneous flaps, are used in covering defects on weight-bearing site of plantar surface [12-14]. However, the patients need to undertake more injuries and risks. DRTs are a kind of biological materials which play a prospective role in recovering skin defects [15,16] (Figure 3). Therefore, we investigated whether the DRTs could simplify reconstructive surgery and surpass the disadvantages mentioned above.

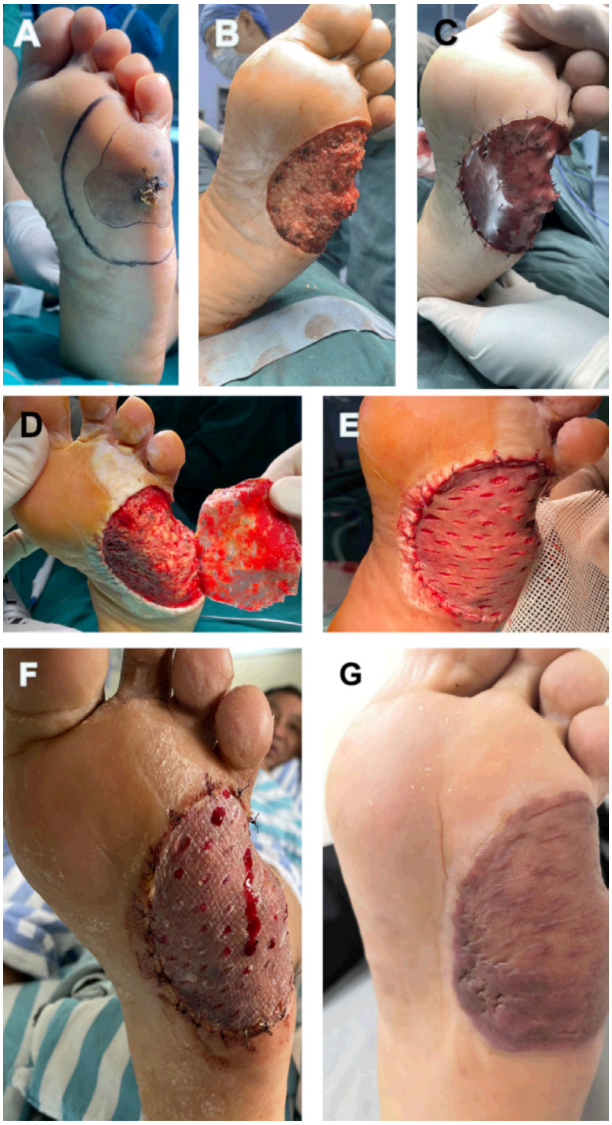

Figure 1. A-B: This patient with plantar malignant melanoma on the ball of left plantar surface was operated with wide excision surgery. **C:** Carved dermal regenerative template was directly applied to the plantar skin defect. **D:** Dermal regenerative template formed into abundant of granulation-like tissue after 14 days. **E:** Delayed split-thickness skin grafts was performed. **F:** Skin grafts survival condition. **G:** The skin grafts area condition.

Figure 2. A: This patient was subjected to wide excision of malignant melanoma on left plantar surface. **B:** The survival condition of skin grafts. **C/D:** The scar condition during follow-up and a recurrent ulcer occurred on the heel of the plantar surface.

Table 3. The MVSS scores in the two groups

The distribution of MVSS component scores in two groups(n=28)								
	Pigmentation n (%)		*Vascularity n (%)*		*Pliability n (%)*		*Height n (%)*	
	SG (n=18)	*DRT (n=10)*	*SG (n=18)*	*DRT (n=10)*	*SG (n=18)*	*DRT (n=10)*	*SG (n=18)*	*DRT (n=10)*
0	0 (0)	1 (10)	15 (83)	9 (90)	0 (0)	1 (10)	0 (0)	3 (30)
1	2 (11)	5 (50)	3 (17)	1 (10)	0 (0)	5 (50)	14 (78)	7 (70)
2	12 (67)	4 (40)	0 (0)	0 (0)	3 (17)	4 (40)	4 (22)	0 (0)
3	4 (22)	0 (0)	0 (0)	0 (0)	15 (83)	0 (0)	0 (0)	0 (0)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
P value	<0.05*		>0.05		<0.05*		<0.05*	

The comparison of total MVSS scores in the two groups			
	SG	*DRT*	*p value*
Total	6.33±0.68	3.40±1.07	<0.05*

Chi square and Fisher's exact test were used in the distribution of Pigmentation, Vascularity, Pliability and Height. Student's t-test was used in the comparison of total VSS scores. * indicates statistically significant differences. SG indicates the patients who received immediate skin grafts. DRT indicates the patients who were treated with dermal regenerative template before skin grafts.

Table 4. The recurrent skin grafts area ulcer incidence in the two groups

	SG (n=18)				*DRT (n=10)*			
	Heel n (%)	*Ball n (%)*	*Lateral arch n (%)*	*Medial arch n (%)*	*Heel n (%)*	*Ball n (%)*	*Lateral arch n (%)*	*Medial arch n (%)*
+	5(28)	3(17)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
-	5(28)	4(22)	1(5)	0(0)	2(20)	4(40)	3(30)	1(10)
P value	<0.05*							

The skin grafts ulcer incidence was analyzed by x^2 and Fisher's exact test. *indicates statistically significant difference. + indicates recurrent skin graft ulcers on plantar surface. - indicates no complaint about ulcers. SG indicates the patients who received immediate skin grafts. DRT indicates the patients who were treated with dermal regenerative template before skin grafts.

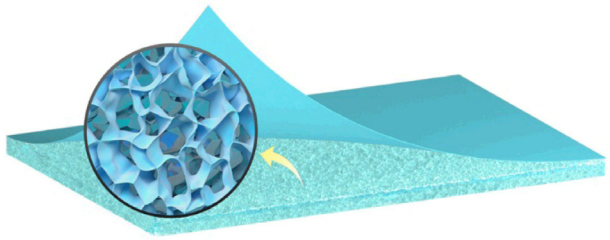

Figure 3. The structure and function of dermal regenerative template. The non-absorbable Silica membrane layer possesses the function of isolation from external environment. The 3D-scaffold collagen layer could benefit the recovery of skin defects and restore the function of skin.

Dermal regenerative template improves plantar blood supply

As a weight-bearing part of the body, the plantar plate is thick, with a large number of vertical fibers connected to the periosteum [17]. A hypovascular area (30-78%) is found along the length of the plantar plate, and even an avascular area exists around the plantar ball [18]. Only few blood vessels pass through the adipose tissue around the calcaneus [19]. We consider that the anatomic characteristics of these blood vessels and the subcutaneous fibrous bundle of plantar surface are the rea-

Table 5. The VRS scores in the two groups

The distribution of VRS scores in two groups (n=28)			
	SG (n=18)		*DRT (n=10)*
	n (%)		*n (%)*
0-no pain	2 (11)		8 (80)
1-mild pain	14 (78)		2 (20)
2-moderate pain	2 (11)		0 (0)
3-severe pain	0 (0)		0 (0)
P value	<0.05*		
The comparison of total VRS scores in the two groups			
	SG	*DRT*	*p value*
Total	1.0±0.48	0.20±0.42	<0.05*

The distribution of VRS scores was analyzed by Wilcoxon rank sum test. Student's t-test was used to analyze the comparison of total VRS scores. *indicates statistically significant differences. + indicates that the patients complained for plantar pain on skin grafts area, either standing or walking. - indicates no complains about plantar pain. SG indicates the patients who received immediate skin grafts. DRT indicates the patients who were treated with dermal regenerative template before skin grafts.

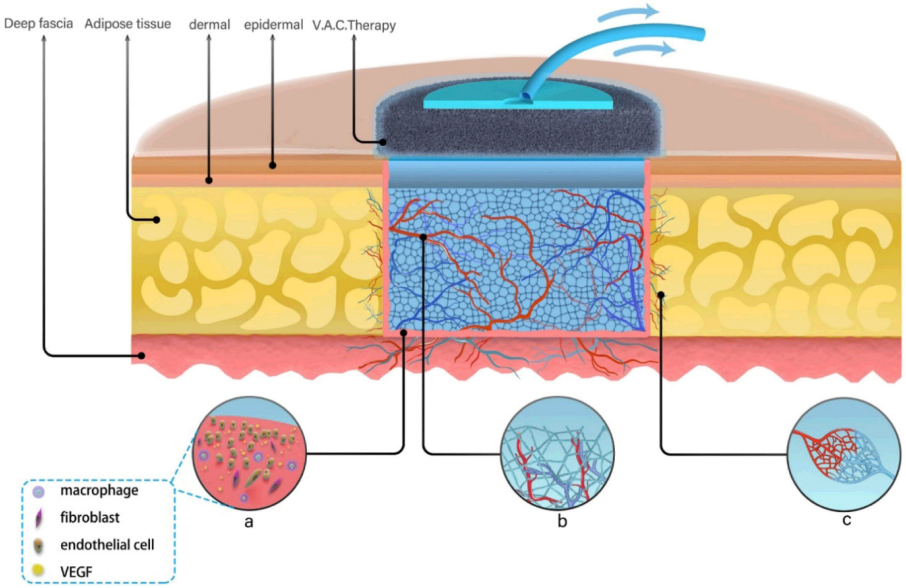

Figure 4. The mechanisms of dermal regenerative template promoting blood supply: **a:** The dermal regenerative template could improve the expression of VEGF, and induce infiltration and proliferation of intrinsic cells, such as macrophages, fibroblats and endothelial cells. **b:** The 3D-scaffolds of dermal regenerative template could act as the framework for the distribution of capillaries. **c:** The dermal regenerative template improves the blood supply and finally forms into abound-ant granulation-like tissue in the wound beds.

sons for the poor survival rates of immediate skin grafts. The collagen involved in DRT could induce the proliferation and distribution of intrinsic cells, and finally led to the regeneration of abundant capillaries in the skin wounds [20-23] (Figure 4). Based on these theories, we consider that the DRT can compensate for the poor blood supply on the plantar surface as indicated by the higher survival rates of the skin grafts in the DRT group.

Dermal regenerative template alleviates the scar condition of plantar skin grafts area

The excision operations lead to abundant extra-cellular matrix deposition in plantar skin defects. Histology has confirmed that the generation of scar tissues is due to the destruction of the original collagen and the replacement of disorderly-arranged fibers [24] (Figure 5). A bioengineering study demonstrated that the collagen structures involved in DRT are arranged regularly [25] (Figure 6). Our study indicated that the index of scar condition in the DRT group was significantly lower than in the SG group in terms of pigmentation, pliability and height. The DRT could improve the condition of plantar scar after excision surgery. In addition, we think that scar condition could be the etiological evidence for skin friction and plantar pain.

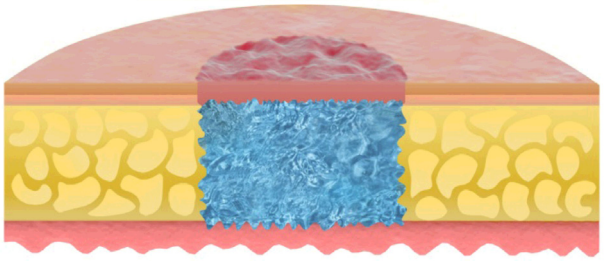

Figure 5. The mechanism of scar formation on plantar skin defects. With the destruction of the original dermal structure and subcutaneous adipose tissue, the fibroblasts are distributed disorderly, which leads to the accumulation of ECM on the wound bed of the plantar surface and uneven texture of skin graft. What's more, the collagen fibers in scar do not possess the function of dermal tissue.

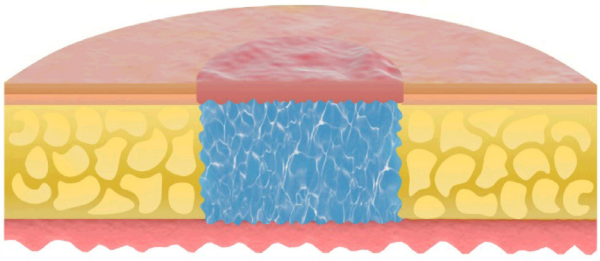

Figure 6. The mechanism of dermal regenerative template alleviating scar condition on plantar skin defects. The ultra-microporous scaffolds in dermal regenerative template could induce regular distribution of fibroblasts and uniform structure of ECM. Therefore, the skin grafts on theplantar surface are closer to ordinary skin, and dermal regenerative template induced fibers could mimic the function of dermal tissue.

Dermal regenerative template is more suitable for reconstructing plantar defects after malignant melanoma excision in reducing the incidence of skin grafts area ulcer

The structure of dermal layer sustains the integrity of epidermis and bears mechanical stimulation [26,27]. The vascular networks in dermal layer provide sufficient nutrition to maintain the function of the skin [28]. The scar tissues previously mentioned above do not possess this protective function, and the stiff textures could increase extra mechanical injury to the skin grafts. In addition, there are less capillary in scar tissue [29,30]. The impaired capillary density of lower extremities in elder people could also aggravate skin ulcer [31,32]. It was proved above that the DRT not only form into dermal-like tissue to restore skin structure, but also improve the micro-circulation on plantar wound [20-23,25]. Through the follow-up, we discovered that patients from the DRT group received no feedback of recurrent ulcers except 8 patients in the SG group. The DRT could solve the problem of skin grafts area ulcer.

Skin flaps operations, including medial plantar flaps, and toe flaps filleted reverse sural neurocutaneous flaps, are usually performed to reduce the incidence of skin friction and ulcers [13,14,33,34]. However, these operations cause severer injury to patients due to damage on the donor site. The preoperative design and intraoperative techniques are considerably challenging for surgeons. The malignant melanoma cells tend to occur on the weight-bearing parts of plantar surfaces [35]. Therefore, we considered that the application of DRT not only achieves the same therapeutic effects as skin flap operations, but also reduces the morbidity and operative difficulties.

Scaffolds involved in dermal regenerative template could alleviate plantar pain

The sensations of the plantar area are controlled by medial and lateral nerves, which typically travel under the deep fascia or surface of calcaneus. Especially for the superficial branch of lateral nerves in the plantar ball, the special anatomic location makes it easily contracted because it travels under the deep band of the lateral plantar aponeurosis [36]. These nerves are originally surrounded by plantar adipose tissue. However, exci-

sion operations normally result in the exposure of deep tissue and the damage to these protective adipose, which would be the main reason for plantar pain. Due to the structure of cross-linked scaffolds [37], the DRT could act as soft-tissue pad to protect plantar nerves and deep tissue. In addition, the firm textures of scar tissues could increase the pressure to plantar sensory nerves, while the resilient collagen scaffolds of DRT might reduce the compression.

Conclusions

DRT reconstructing plantar defects after wide excision of malignant melanoma improved the survival rate of skin grafts, alleviated the scar condition, plantar pain and reduced the incidence of recurrent skin graft area ulcers, which greatly enhance the quality of life of these patients. We will apply DRT to treat more patients with plantar defects caused by malignant melanoma wide excision in the future, and follow them for a longer period of time.

Author contributions

Xuanlong Zhang and Yute Sun contributed equally to this work. Prof. Gang Yao should be considered as the Co-corresponding author (Tel: +13951700640; E-mail: yaogang2005@hotmail.com). Conception or design of the work: Xuanlong Zhang, Yute Sun and Jian Tang; funding support: Jian Tang; interpretation of data for the work: Xuanlong Zhang, Yute Sun, Zuoqiong Hou; Drafting the work or revising it critically for important intellectual content: Xuanlong Zhang, Binlin Luo, Chujun Li, Keyu Jiang, Jinfang Liu and Gang Yao. All authors approved the final version of the manuscript.

Funding support

Natural Science Foundation of Jiangsu Province (Grant no. BK20171089).

Conflict of interests

The authors declare no conflict of interests.

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