Surgical treatment of nasal non-melanoma skin cancer using full-thickness skin graft: can antiplatelet therapy be related to a better result?

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Surgical treatment of nasal non-melanoma skin cancer using full-thickness skin graft: can antiplatelet therapy be related to a better result?

AIM: *The aim of this retrospective study is to evaluate if antiplatelet therapy in elderly patients undergoing surgical excision of nasal non-melanoma skin cancer and contemporary reconstruction with full-thickness skin graft can be related to a better vitality of the graft and consequently improved aesthetic result.*
MATERIALS AND METHODS: *Patients affected by BCC or SCC of the nose that underwent surgical excision and contemporary reconstruction with full-thickness skin graft were divided into two groups according to antiplatelet therapy. Medications were performed 7 and 15 days after surgery. To asses engraftment, we clinically evaluated the percentage of vital flap recognizing 3 different results: less than 20%, between 20% and 80%, and more than 80% of vital surface. Finally, patients were asked to express a subjective evaluation of the aesthetic result using a numeric scale ranging from 1 to 10. Statistical analyses were performed with SPSS 15.0 for Windows.*
RESULTS: *Twenty-four of the 36 eligible patients took antiplatelet therapy (Group 1). Statistical analysis was very close to demonstrate a significant difference between the two groups after the first evaluation (X^2= 3.6; p-value = 0.0578) and it showed a clear significant difference between the two groups after the second evaluation (X^2 = 13.5692 e p-value = 0.0002). The average value of the subjective evaluation conducted only on 32 of 36 patients, was 9.12. Any significant difference was observed between the two groups (p-value >0.1).*
CONCLUSIONS: *Our preliminary results seem to suggest that antiplatelet therapy in elderly patients with non-melanoma skin cancer of the nose treated with surgical excision and contemporary reconstruction with fill-thickness skin graft could favor the graft vitality with low risk of bleeding. Further studies will be useful to determinate if antiplatelet drugs can be prescribed in the perioperative period to selected patients presenting risk factors for wound healing to increase the chances of engraftment.*

KEY WORDS: Antiplatelet Therapy, Non Melanoma Skin Cancer, Skin Graft

Introduction

The term non-melanoma skin cancer (NMSC) refers to all types of cancer that occur in the skin and are not melanoma. The two major types are basal-cell carcinomas (BCC) and squamous-cell carcinomas (SCC) that represent about 80% and 20% of all NMSC respectively [1]. They belong to the most common human cancers with a rising incidence in many countries, a low mortality but a considerable high morbidity as most of lesions occur on visible areas such as the face [2]. More than 50% of NMSC is found in the head and neck region confirming that prolonged and intensive sun exposure is the most important risk factor in the development of skin cancer [3]. Due to its location on the face, the nose is

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the anatomical unit most affected by this neoplasm. Surgical excision of NMSC is one of the primary treatment modalities and several factors inherent to patients' surgical and oncological conditions can affect the reconstruction outcome.

Autologous full-thickness skin grafts (FTSG) are very simple to harvest, representing a viable option for nasal reconstruction instead of dermal substitute when primary closure or flap repair are deemed unsuitable, leading to satisfying results in case of defects on nasal tip, dorsum, ala, and sidewall [4-6]. Nevertheless, complete or partial graft failure mainly caused by hematoma, disruption of base-graft contact, infection, smoking or excessive intra-operative electrocoagulation can lead to poor aesthetical result [7]. The need for further grafting, healing by secondary intention or locoregional flap for the nose may result in addition scarring and nasal asymmetry [8]. Therefore, an effective post-operative blood perfusion and flow can be considered pivotal to ensure skin graft vitality and to reduce the possibility of failure.

Elderly patients are particularly exposed to NMSC of the face [9] and are generally afflicted by multiple diseases characterized by acceleration of the aging process, and a significative number of them undergo antiplatelet therapy for prevention or treatment of cardiovascular problems. The management of these patients represents a challenge for surgeons as they should carefully balance the risk of bleeding with the risk of thromboembolic complications resulting from the temporary interruption of therapy before and after invasive procedures. Surgical excision of NMSC of the nose is usually associated with a low risk of bleeding considering the potential for local control measures, therefore the interruption of therapy can be considered not necessary in this kind of surgery [10]. Moreover, the antiplatelet therapy could favor blood flow and FTSG vitality representing an advantage rather than a problem for both surgeon and patient.

The aim of this study is to evaluate if antiplatelet therapy in elderly patients with NMSC, promoting the revascularization of a FTSG in nasal reconstruction, may support its vitality reducing the possibility of graft necrosis and failure. A second goal is to study a relationship between antiplatelet therapy, graft viability and long-term aesthetic results. This study was conducted according to the declaration of Helsinki.

Materials and methods

We identified patients aged > 65 years that underwent surgical excision of nasal non-melanoma skin cancer and contemporary reconstruction with full-thickness skin graft for non-melanoma skin cancer at the "Fiorini" General Hospital of Terracina, Italy, between June 2020 and July 2021. All patients did not receive any previous surgery (comprising incisional biopsy) or treatment (radiotherapy, topical 5-FU) in the affected area, and presented a dermatoscopic diagnosis of BCC or SCC. According to antiplatelet drugs assumption, patients were divided into two groups. Regardless of the type of drug and the reasons for which they were taken, therapy had not to be interrupted or substituted before or after surgery. Patients taking double antithrombotic therapy, with persistent uncontrolled hyperglicemia or whitout adequate photographic documentation and those with close or positive margins after definitive histopathological examination were excluded from the study. Each surgery was performed by the same team (GP, VC and AS).

A dermatoscopic assessment of the margins of the lesion was performed by dermatologists and drawn on the patient's skin nose before surgery to ensure complete removal of the tumor surrounded by a border of healthy tissue. with the following surgical steps. Standard ASA monitoring was applied for each patient who laid in a supine position with the head as comfortable possible. All procedure were performed under local anesthesia.

Surgical technique

General disinfection was performed, and surgical drapes were placed on the face to leave only the nose and the donor site uncovered. The removal of the lesion was performed under local anesthesia using lidocaine HCL injection 2% 20 mg/ml for both recipient and donor sites. A border of healthy tissues was removed around the surgical wound and sent together with the tumor for histopathological analysis. Usually, a template of the surgical defect with foil from a suture packet was placed over the donor site to guide the graft design. The template was transferred to the postauricular region and outlined with a marking pen. In all cases the skin of the postauricular area was used as the donor site after verifying that it was suitable. The FTSG was harvested retaining dermis and epidermis, with the plane of dissection at the subcutaneous fat. This fat was then excised with scissors placing the graft on the index finger. The graft was placed into the surgical defect and sutured into position with simple interrupted sutures (non-absorbable 3-0 nylon).

A secure pressure dressing was placed and fixed over the graft to ensure a direct contact of the FTSG with the underlying wound bed. An interrupted 5-0 prolene suture is finally used to close the skin of the donor site. Postoperative complications such as infections of the surgical wounds or bleeding were analyzed. All patients underwent antibiotic therapy after treatment.

Pressure dressing were removed 3 days after surgery and then medication of both surgical wounds was performed. Sutures were removed 7-8 days after surgery and photo documentation was taken (first evaluation of graft vitality). A subsequent photo documentation was taken between 15 and 17 days after surgery when patients underwent a follow-up visit (second evaluation of graft

Fig 1: BCC of the right nasal sidewall before surgery (A), 7 days (B) and 18 days (C) after surgery.

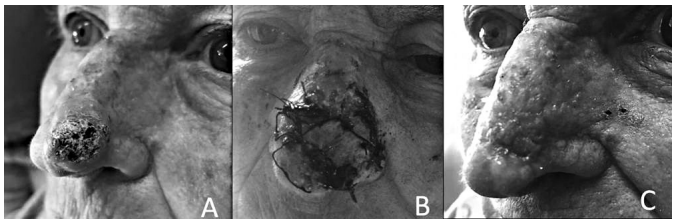

Fig 2: BCC of the left nasal sidewall and tip (A) before surgery and 7 days after surgery (B). Patient had wound bleeding about 6 hours after surgery surgically revised. Result 18 days after surgery is shown (C).

TABLE I - *Clinicopathological and demographic characteristics of patients enrolled.*

Age, Years	
Median Age	77.2
Range	68-88
Gender	
Male	20 (55.6%)
Female	16 (44.4%)
Antiplatelet Therapy	
Yes	24 (66.7%)
Not	12 (33.3%)
Tumors Site	
Sidewall	16 (44.4%)
Tip	11 (30.6%)
Dorsum	9 (25%)
Type of Cancer	
BCC	32 (88.9%)
SCC	4 (11.1%)
Tumor Size, mm	
Median Size	10.1
Range	5-18

vitality). Any significant local or systemic sign of infection, haematoma or seroma formation between the wound bed and the graft were recorded. The living and healthy percentage of the graft was assessed analyzing photographic documentation separately by three authors not involved in this kind of surgeries (AG, SM and VT) who divided our cases in three groups: patients with less than 20%, between 20% and 80%, and more than 80% of healthy surface respect to total (Fig 1). In case of disagreement, the evaluators met and gave a shared assessment. All patients with partial graft failure healed by secondary intention and changed dressings twice a week until wound healing.

At least 4 months after surgery, patients were interviewed by telephone and were asked to express their subjective satisfaction of the aesthetic result using a numeric scale ranging from 1 to 10, in which 1 corresponds to "absolutely not satisfied" and 10 to "completely satisfied".

Statistical analyses were performed with SPPS 15.0 for Windows. Qualitative and quantitative differences among the groups were analyzed using paired sample T-test. Differences were considered significant at $P < 0.05$.

Results

We identified 36 patients that respected inclusion criteria. Clinicopathological and demographic characteristics of patients enrolled are reported in (Table I). Group 1 comprises 24 patients taking antiplatelet drugs and group 2, 12 patients not taking therapy. A woman out of our 36 patients who belongs to the group 1 (taking antiplatelet drugs) experienced a significant bleeding of the nasal surgical wound about 6 hours after surgery and underwent a surgical revision for bleeding (Fig. 2).

Patients with viability of the graft greater than 80% at the first evaluation performed 7-8 days after surgery were 20 out of 36 patients (55.6%), 16 of them taking antiplatelet drugs. Any patient showed a graft viability lesser than 20%. Statistical analysis was very close to demonstrate a significant difference between the two groups (X^2= 3.6; p-value = 0.0578) as shown in (Table II).

In (Table III) we report our results collected during the second photographic evaluation of graft viability performed 15-17 days after surgery. Patients with graft viability greater than 80% were 26 out of 36 (72.6%), 22 of which taking antiplatelet drugs. Any patient had a graft viability lesser than 20% even at the second evaluation. Statistical analysis shown a significant different between the two groups (X^2 = 13.5692 e *p*-value = 0.0002).

Five out of 36 patients of our study were not available to be submitted to a telephonic interview for evaluation of aesthetic results. Statistical analysis was conducted on the remaining 32 patients, 21 patients who took antiplatelet drugs (group 1) and 11 patients who did not take antiplatelet (group 2). Telephonic interview was performed between 17 and 4 months after surgery (average: 9.72 months). The average value of the subjective evaluation was 9.12. Any significant difference was observed between the two groups (*p*-value >0.1).

Discussion

Due to the increase of life expectancy, the periprocedural management of patients receiving oral anticoagu-

TABLE II - *First evaluation of graft viability performed 7-8 days after surgery for two groups (group1: patients who took antiplatelet drugs; group 2: patients who did not take antiplatelet drugs). Statistical analysis shows a value close to a significant difference between the two groups (X^2= 3.6; p-value = 0.0578).*

	Healthy surface of the graft			
Group	**>80%**	**80%-20%**	**<20%**	**Tot**
1	22 (61.1%)	2 (5.6%)	0 (0%)	24 (66.7%)
2	4 (11.1%)	8 (22.2%)	0 (0%)	12 (33.3%)
Tot	26 (72.2%)	10 (27.8%)	0 (0%)	36 (100%)

TABLE III - *Second evaluation of graft viability performed 15-17 days after surgery for two groups (group1: patients who took antiplatelet drugs; group 2: patients who did not take antiplatelet drugs). Statistical analysis shows a significant difference between the two groups (X^2 = 13.5692 e p-value = 0.0002).*

	Healthy surface of the graft			
Group	**>80%**	**80%-20%**	**<20%**	**Tot**
1	16 (44.4%)	8 (22.2%)	0 (0%)	24 (66.7%)
2	4 (11.1%)	8 (22.2%)	0 (0%)	12 (33.3%)
Tot	20 (55.6%)	16 (44.4%)	0 (0%)	36 (100%)

lant or antiplatelet therapy for the primary or secondary prevention of cardiovascular disease is an increasingly common clinical problem [11]. A balance between reducing the risk of thromboembolism and preventing excessive bleeding must be reached for each patient considering the type of surgery to be performed. Thromboembolism and bleeding risks indeed should be carefully estimated considering both patients behaviors and type of procedures, and a decision can be made about whether the anticoagulant or antiplatelet should be eventually interrupted or substituted [12].

Surgical excision of cutaneous lesions are generally consistent with low risk of bleeding so the in most cases interruption of therapy is not necessary [13]. As a general guideline, in agreement with several authors [14], we do not require the interruption of therapy for excision of NMSC of the nose and contemporary reconstruction with FTSG, even in those patients who are taking antiplatelets drugs for preventive purpose, considering the effectiveness of measures to contain bleeding. Only one patient of 24 of our cases taking antiplatelet therapy, a 83 years old woman with a 16 mm nasal BCC and several comorbidity, had a postprocedural bleeding that was promptly resolved about 6 hours after surgery (Fig. 2). Furthermore, some reconstructive surgeons suggested that antiplatelet therapy are useful to improve flap survival, although it is less effective than heparin, preventing microvascular thrombosis when taken in the perioperative period [15]. Although there still no international consensus about routinely used prophylactic antithrombotic agents in microvascular surgery, antiplatelet seems to be less effective than heparin in preventing clot formation at the site of vessel anastomosis [16-19]. To the best of our knowledge, any similar experience has been previously published regarding the nasal skin graft. Full-thickness skin graft however takes an adequate vascular supply from the recipient site and, obviously, not from vascular anastomosis, as demonstrated in vivo by by Capla et al [20] using transgenic mouse model. They found that skin graft revascularization is an ordered process of vascular ingrowth, regression, and reconnection. On day 0 after grafting, the vascular networks of the graft and recipient are separate with no circulation in the graft vasculature. Over the course of 7 to 14 days, blood vessels from the recipient invade the graft edges along previously patterned vascular channels in the direction of the ischemic stimulus, whereas the native graft vasculature begins to regress. In addiction, within this period, reconnection occurs, restoring blood flow to the graft microcirculation as more vascular connections are made. By day 21, complete blood flow in the graft vasculature has been established, reoxygenating the graft tissue. We asked if antiplatelet therapy, decreasing the ability of blood clots to form by interfering with the platelet activation, can favor this process of revascularization or at least reduce the risk of thrombosis. Our study suggests that antiplatelet therapy in elderly patients undergoing FTNG after nasal NMSC excision is safe and could be considered useful to prevent graft necrosis.

We clinically evaluated graft viability considering the rate of its healthy surface dividing our cases in patients whose graft is for the most part viable (more than 80%), patients with partial failure (between 20 and 80%) and complete failure (less than 20% viable). In this study no patient reported a complete failure of the graft confirming the effectiveness and resistance of FTSG for the

closure of this kind of defects. Our results suggest that FTSG of patients taking antiplatelet therapy has minor risk of graft failure, but no significant difference was found between the two groups regarding the aesthetic results. Main limitation of this study is the limited sample and the impossibility to perform a multivariate statistical analysis, even if patients presenting on medical history factors related to poor healing such as radiotherapy, topical treatment with 5-FU, previous surgery or persisting hyperglycemia have been excluded. In our paper we decided to consider patients taking antiplatelet drugs only. This type of therapy is often taken by elderly especially for prevention of cardiovascular disease. We have considered the possibility of recommending in the future the use of antiplatelet even to healthy and younger patients in the perioperative period to prevent graft skin necrosis. Further experiences will be needed to clarify adequately this aspect and which type of antiplatelet drug is most suitable among those currently available.

The current COVID-19 pandemic has limited the possibility for elderly of moving to regional referral oncologic centers from peripheral areas. A great number of patients went to our hospital with the need to be promptly and effectively treated [21]. To perform a complete excision of the nasal tumour in elderly patients, who would have undergone Mohs micrographic surgery in the pre-pandemic period, not available in our hospital, we removed a border of healthy tissues around the surgical wound after tumor excision and sent together with the tumor for definitive histological diagnosis. A further surgical resection guided by histological evaluation of margins would have been performed in case of positive margins. It is our opinion, based on personal experience and not confirmed by specific studies, that, in case of positive margins, a reoperation would have been more effective and easier after FTGR respect to healing by secondary intention or closure using local flaps. A direct correlation between localization of the donor site and quality of the results has not been demonstrated [22]. We prefer to harvest the graft from postauricular region considering that it is a not sun exposed area, scars remain inconspicuous for the most part, and it can be considered satisfying in terms of tissue quality, color, texture, and thickness.

Our cases were telephonically interviewed at least 4 months after surgery, to grade the aesthetic result on a 1-10 scale. An unexpectedly high average result was observed (9.12). It is likely that several factors influenced this optimistic result as well as the overall good aesthetic outcomes. An elderly population indeed can be considered not very pretentious in evaluating an aesthetic result. Furthermore, the empathy between patient and healthcare professionals can affect the value expressed by patients who can be led to say a high value more on the professionalism of physicians than on real aesthetic results. The aim of the subjective evaluation of outcomes was to analyze if patients with partial failure of FTSG which do not assume antiplatelet, have a worse esthetic outcome than healthy graft patients taking therapy. Any significant difference was observed between the two groups of patients taking and not therapy.

Conclusions

Nasal defects are challenging problems for both patients and surgeons considering the aesthetic needs of the face. FTSG is one of the most common reconstructive procedures and is an effective tool to achieve wound coverage. Our experience, although preliminary and on a limited number of patients, seems to suggest that antiplatelet therapy can favor the engraftment at least in elderly patients even if it does not seem to affect the long-term aesthetic results. Further studies will be useful to evaluate whether to understand if selected patients presenting risk factors for wound healing should benefit from perioperative antiplatelet therapy.

Riassunto

Scopo: Lo scopo di questo studio retrospettivo è valutare se la terapia antipiastrinica in pazienti anziani sottoposti ad escissione chirurgica di carcinoma cutaneo nasale e contemporanea ricostruzione con innesto cutaneo a tutto spessore possa essere correlata ad una migliore vitalità dell'innesto e di conseguenza ad un migliore risultato estetico.

Materiali e metodi: I pazienti affetti da BCC o SCC del naso sottoposti a escissione chirurgica e contemporanea ricostruzione con innesto cutaneo a tutto spessore sono stati divisi in due gruppi in base alla terapia antipiastrinica. I farmaci sono stati eseguiti 7 e 15 giorni dopo l'intervento. Per giudicare l'attecchimento, abbiamo valutato clinicamente la percentuale di lembo vitale riconoscendo 3 diversi risultati: meno del 20%, tra il 20% e l'80%, e più dell'80% della superficie vitale. Infine, ai pazienti è stato chiesto di esprimere una valutazione soggettiva del risultato estetico utilizzando una scala numerica che va da 1 a 10. Le analisi statistiche sono state effettuate con SPSS 15.0 per Windows.

Risultati: Ventiquattro dei 36 pazienti eleggibili hanno assunto la terapia antipiastrinica (Gruppo 1). L'analisi statistica è stata molto vicina a dimostrare una differenza significativa tra i due gruppi dopo la prima valutazione (X2= 3,6; p-value = 0,0578) e ha mostrato una chiara differenza significativa tra i due gruppi dopo la seconda valutazione (X2 = 13,5692 e p-valore = 0,0002). Il valore medio della valutazione soggettiva condotta solo su 32 pazienti su 36, è stato di 9,12. Qualsiasi differenza significativa è stata osservata tra i due gruppi (p-value >0,1).

Conclusioni: I nostri risultati preliminari sembrano suggerire che la terapia antipiastrinica in pazienti anziani

con carcinoma cutaneo del naso trattato con escissione chirurgica e contemporanea ricostruzione con innesto cutaneo a spessore potrebbe favorire la vitalità dell'innesto con basso rischio di sanguinamento. Ulteriori studi saranno utili per determinare se i farmaci antipiastrinici possono essere prescritti nel periodo perioperatorio a pazienti selezionati che presentano fattori di rischio per la guarigione della ferita per aumentare le possibilità di attecchimento.

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