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Valor Preditivo do Primeiro Cancro Cutâneo Não-Melanoma: Estudo Retrospetivo

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RESUMO – **Introdução**: Os doentes com antecedentes pessoais de cancro cutâneo não melanoma têm um risco aumentado de desenvolver outro cancro cutâneo e alguns estudos sugerem que o tipo histológico do primeiro tumor pode ser preditor dos subsequentemente diagnosticados. O objetivo deste estudo foi avaliar a correlação entre o tipo histológico do primeiro cancro cutâneo não-melanoma e os subsequentemente diagnosticados no mesmo hospedeiro, em indivíduos imunocompetentes e com diferentes causas de imunodepressão. **Métodos**: Estudo retrospetivo em que foram incluídos todos os doentes sem antecedentes de cancro cutâneo, com o diagnóstico de dois ou mais cancros cutâneos não-melanoma entre 1 de Janeiro de 2008 e 31 de Dezembro de 2017. **Resultados**: Incluídos um total de 413 doentes, 51 (12,4%) dos quais imunodeprimidos. Verificou-se uma associação significativa entre o tipo histológico do primeiro e dos cancros cutâneos não-melanoma subsequentemente diagnosticados, quer em doentes imunocompetentes, quer em imunodeprimidos, com uma maior probabilidade de desenvolver um tumor do mesmo tipo histológico (p<0,001). Esta associação foi também significativa em doentes com uma neoplasia hematológica. O intervalo médio entre os dois diagnósticos foi de 30 meses (intervalo 7-111). Quarenta e três doentes (10,4%) apresentaram um tumor subsequente após mais de cinco anos de seguimento. **Conclusões**: O tipo histológico do primeiro cancro cutâneo não-melanoma foi preditor do risco de desenvolver um tumor do mesmo tipo. Pela primeira vez, esta correlação foi identificada em doentes com uma neoplasia hematológica. Os doentes de alto risco devem ter um seguimento prolongado de pelo menos dez anos.
PALAVRAS-CHAVE – Carcinoma Basocelular; Carcinoma de Células Escamosas; Imunossupressão; Neoplasias da Pele.

Predictive Value of the First Non-Melanoma Skin Cancer: A Retrospective Study

ABSTRACT – ***Introduction:*** *Patients with previous non-melanoma skin cancer have an increased risk of developing another skin cancer and some studies suggest that the histological type of the incident tumour can predict the one of the subsequently diagnosed. The aim of this study was to assess a correlation between the histological type of the first and the subsequent non-melanoma skin cancer diagnosed in immunocompetent patients and in different settings of immunosuppression.* ***Methods:*** *A retrospective study was conducted on all patients without previous skin cancer, with the diagnosis of two or more non-melanoma skin cancer between January 1st, 2008 and December 31th, 2017.* ***Results:*** *A total of 413 patients were included. Fifty-one individuals (12.4%) were immunosuppressed. There was a significative association between the histological type of the first and the subsequent non-melanoma skin cancer diagnosed both in immunocompetent and in immunosuppressed patients, with a higher probability of developing a tumour of the same histological type (p<0.001). This association was also significative in patients with the diagnosis of a hematologic malignancy. The mean interval between the two diagnoses was 30 months (range 7-111). Forty-three patients (10.4%) presented a subsequent tumour after more than five years of follow-up.* ***Conclusion:*** *The histological type of the incident non-melanoma skin cancer predicted the risk of developing another tumour of the same type. For the first*

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time, we showed this correlation in patients with a hematologic malignancy. High-risk individuals may benefit from a long-lasting follow-up of at least ten years.
KEYWORDS – *Carcinoma, Basal Cell; Carcinoma, Squamous Cell; Immunosuppression; Skin Neoplasms.*

INTRODUCTION

Non-melanoma skin cancer (NMSC) is the most common malignancy in fair-skinned people and its incidence is increasing worldwide.[1-3]

Patients with previous NMSC are at increased risk of developing another skin cancer and some studies suggest that the histological type of the incident tumour can predict the one of the subsequently diagnosed.[4,5] This association was reported not only in the general population, but also in solid organ transplant recipients (SOTR).[4-7]

However, the predictive value of the histological type of the NMSC diagnosed in immunosuppressed patients is seldom studied. Furthermore, the timing and risk factors for subsequent skin malignancies in these patients are also poorly characterized.

The aim of this study was to assess a possible correlation between the histological type of the first NMSC and of those subsequently diagnosed in immunocompetent patients and in different settings of immunosuppression, namely in SOTR, in human immunodeficiency virus (HIV) infection, in patients with the a hematologic malignancy and/or under immunosuppressive therapy.

MATERIAL & METHODS

A retrospective study was conducted on all patients without previous skin cancer, with the diagnosis of two or more non-synchronous NMSC between January 1st, 2008 and December 31th, 2017, at Hospital de Santa Maria, a tertiary teaching hospital in Lisbon, Portugal. All cases had histological confirmation. Data was obtained by reviewing dermatopathology registries and the clinical records of dermatology visits. We considered synchronous malignancies the ones that presented within the first six months following the diagnosis of the first NMSC. We excluded tumours situated on the genital area and those contiguous to a scar or at the site of a previous surgical procedure, which could represent a recurrence of a previous skin cancer. The information recorded for each patient included gender, age, causes of immunosuppression, the interval for the second diagnosis, number of tumours, anatomic location and histologic type of skin cancers.

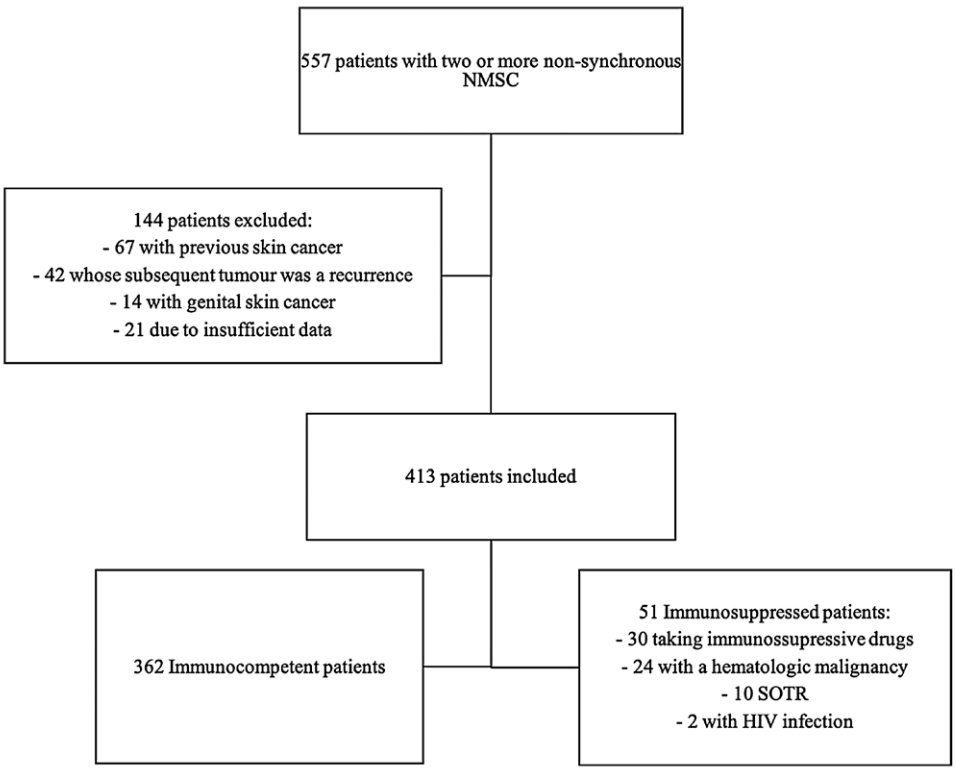

Figure 1 - Flowchart of study exclusions; Legend: HIV: Human immunodeficiency virus; NMSC: Non-melanoma skin cancer; SOTR: Solid organ transplant recipients.

Data was analysed using IBM SPSS Statistics® (Statistical Package for the Social Sciences, version 24, SPSS Inc, Chicago, IL, USA). Categorical variables were presented as frequencies and percentages and were compared with use of chi-square test or Fisher's exact test, when there were expected frequencies <5. Continuous variables were presented as means and standard deviations or medians and interquartile ranges, for variables with skewed distribution. These variables were compared with the use of Student's t-test. All reported P values are two-tailed, with a *P* value of 0.05 indicating statistical significance.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics review board (Comissão de Ética do Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte).

RESULTS

The sample included 577 patients who were diagnosed with two NMSC, but due to exclusion criteria (n=123) or insufficient data (n=21), 144 cases were excluded (Fig.1). A total of 413 patients without previous skin cancer developed two non-synchronous NMSC and were included. All patients were Caucasian. Patient demographical and clinical characteristics are shown in Table 1.

Fifty-one (12.4%) individuals were immunosuppressed (Table 2). Fifteen patients shared more than one cause of immunosuppression. The ten SOTR had immunosuppressive regimens composed of three drugs and five patients with the diagnosis of a haematologic malignancy also took immunosuppressive drugs.

Patients presented a total of 1000 NMSC, 508 incident and 492 metachronous tumours. Sixty-five patients (15.7%) had synchronous tumours at presentation. Pre-neoplastic dermatoses, in particular actinic keratosis, were found more frequently in patients who presented a squamous cell carcinoma (SCC) than in those with a basal cell carcinoma (BCC) (84.4% vs 52.0%; $p<0.001$).

Table 1 - Patient demographical and clinical characteristics.

			All patients (n=413)	Immunocompetent (n=362; 87.6%)	Immunosuppressed (n=51; 12.4%)
Age at first NMSC, mean (SD), y			73.6 (10.3)	74.1 (10.1)	70.2 (11.9)
Male gender, No. (%)			261 (63.2)	232 (64.1)	29 (56.9)
Incident NMSC	Number of tumours, No. (%)	Single	348 (84.3)	305 (84.3)	43 (84.3)
		Multiple	65 (15.7)	57 (15.8)	8 (15.7)
	Histologic type, No. (%)	BCC	323 (78.2)	289 (79.8)	34 (66.7)
		SCC	80 (19.4)	65 (18.0)	15 (29.4)
		Both	10 (2.4)	8 (2.2)	2 (3.9)
	Photoexposed area, No. (%)	Yes	295 (71.4)	254 (70.2)	41 (80.4)
		No	100 (24.2)	91 (25.1)	9 (17.7)
		Both	18 (4.4)	17 (4.7)	1 (2.0)
Subsequent NMSC	Number of tumours, No. (%)	Single	351 (85.0)	307 (84.8)	44 (86.3)
		Multiple	62 (15.0)	55 (15.2)	7 (13.7)
	Histologic type, No. (%)	BCC	314 (76.03)	282 (77.9)	32 (62.8)
		SCC	84 (20,3)	68 (18.8)	16 (31.4)
		Both	15 (4.8)	12 (3.3)	3 (5.9)
	Photoexposed area, No. (%)	Yes	278 (67.3)	242 (66.9)	36 (70.6)
		No	119 (28.8)	106 (29.3)	13 (25.59)
			16 (3.9)	14 (3.9)	2 (3.9)
Time between incident and subsequent NMSC, mean (SD), m			30.4 (21.4)	30.3 (21.2)	31.1 (22.7)

BCC; Basal cell carcinoma; NMSC: Non-melanoma skin cancer; SCC: Squamous cell carcinoma

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Table 2 - Immunosuppression causes.

Immunosuppressive therapy, No. (%)	**30 (7.3)**
Number of drugs, No. (%)	
One	15 (3.6)
Two	5 (1.2)
Three	10 (2.4)
Drug, No. (%)	
Corticosteroid	24 (5.8)
MMF	9 (2.2)
Cyclosporine	6 (1.5)
Azathioprine	5 (1.2)
Methotrexate	4 (1.0)
Tacrolimus	3 (0.7)
Sirolimus	1 (0.2)
Hematologic malignancy, No. (%)	**24 (5.8)**
Diagnosis, No. (%)	
Myeloproliferative syndrome	9 (2.2)
Non-Hodgkin lymphoma	7 (1.7)
Other leukaemia	3 (0.7)
Acute myeloid leukaemia / myelodysplastic syndrome	2 (0.5)
Multiple myeloma	2 (0.5)
Other	1 (0.2)
Solid organ transplant, No. (%)	**10 (2.4)**
Organ, No. (%)	
Kidney	9 (2.2)
Heart	1 (0.2)
HIV infection, No. (%)	**2 (0.5)**
HAART, No. (%)	2 (0.5)

HAART: highly active antiretroviral therapy; HIV: Human immunodeficiency virus; MMF: Mycophenolate mofetil

The anatomic distribution of the NMSC diagnosed is shown in Table 3. The most common body surface location was the head and/or neck. A total of 353 incident NMSC presented in this photoexposed area occurred in 303 patients (73.4%). Patients with incident NMSC in this anatomic location were in average older than the remainder (M=74.86 vs 70.30; $p<0.001$). Moreover, these patients were significantly more likely to present synchronous tumours ($p=0.003$) and a SCC as the first skin cancer diagnosed ($p=0.032$). Patients who presented an incident NMSC in the head and/or neck had a higher probability of developing a subsequent malignancy in the same body area ($p<0.001$).

The histological type of the incident NMSC was significantly associated with the same histological type in the subsequent cutaneous malignancies diagnosed, both in immunocompetent and in immunosuppressed patients, both with BCC and SCC as the incident tumour ($p<0.001$). This association was also significant in patients with the diagnosis of a haematologic malignancy, either those presenting with BCC ($p=0.004$) or SCC ($p=0.032$) as the first diagnosed NMSC.

The mean time between the diagnosis of the incident and the metachronous NMSC was 30 months (+/- 21.4). The interval between the two diagnoses ranged between 7 and 111 months. Forty-three patients (10.4%) developed a second tumour after a follow-up time longer than 60 months. The mean number of months was significantly lower in patients that presented a SCC than in those who presented a BCC as the incident NMSC (M=25.68 vs 31.49; $p=0.018$).

DISCUSSION

In this study, there was a significative association between the histological type of the incident NMSC and the subsequently diagnosed tumours, both in immunocompetent and in immunosuppressed patients. This correlation was previously reported in two meta-analysis and in a recently published retrospective study.[4-6] Although the histological type of the first NMSC diagnosed after solid organ transplant was identified as a strong predictor for the development of a subsequent skin cancer of the same type, this association is scarcely studied in other groups of immunosuppressed patients.[7-8] As far as we were able to search in the literature, this is the first study that identifies a correlation between the histological type of the first NMSC and of the subsequently diagnosed in individuals with a hematologic malignancy.

Skin carcinogenesis is a complex and multifactorial process, in which genetic factors interact with lifestyle habits.[5] Differences in sun exposure may contribute to the tendency of developing NMSC of the same histological type. Simultaneously, it is possible that patients develop a state of immunologic tolerance after the first NMSC, raising the risk of subsequent tumours of the same histological type.[8]

As with previous studies, the head and/or neck region was the most frequent anatomic location of NMSC.[6,9] Patients with an incident malignancy in this site were older, with multiple tumours at presentation and had higher probability of presenting a SCC. Moreover, these individuals had a higher risk of developing a subsequent tumour in the same body site. Altogether, these associations may put in evidence the mechanism of field cancerization, highlighting the critical role of chronic and cumulative sun exposure as the most important risk factor for the development of NMSC in this anatomic area.[10]

The correlation between follow-up times after the diagnosis of a NMSC and outcomes is scarcely studied and the duration of surveillance remains controversial.[5] Current guidelines recommend surveillance over a period of at least three to five years after the diagnosis and treatment of an incident NMSC, based on studies that reported a remarkable reduction of the risk of developing a subsequent tumour after this time.[4,5] However, a cohort study that prospectively followed up a large number of patients for more than ten years found a five-year probability of developing

Table 3 - Body surface distribution of diagnosed tumours.

		First NMSC		Subsequent NMSC	
	Histologic type	BCC	SCC	BCC	SCC
Body site, No.	Head and/or neck	271	82	256	85
	Face	194	52	188	60
	Ears	19	8	13	6
	Scalp	43	20	42	19
	Neck	15	2	13	0
	Chest and/or abdomen	49	1	27	3
	Back and/or buttocks	51	2	49	1
	Upper limbs	12	2	25	6
	Hands	0	10	0	8
	Lower limbs	25	3	21	8
	Feet	0	0	1	2
	Total	**408**	**100**	**379**	**113**

BCC: Basal cell carcinoma; NMSC: Non-melanoma skin cancer; SCC: Squamous cell carcinoma

a subsequent NMSC of 40.7%, value that increased to 59.6% at ten years.[11] In the present study, 10.4% of the patients only presented a subsequent NMSC after more than five years of follow-up. The significative risk of presenting a skin cancer after the currently recommended surveillance period might justify extending the follow-up of these patients for at least ten years after the diagnosis of a NMSC.

The main limitations of this study arise from the fact that this is a retrospective study. One of the main weaknesses is the small number of immunosuppressed patients included, that limited confident comparisons in some subgroups, namely those with HIV infection and SOTR. Moreover, the heterogeneity of drugs prescribed and the different degrees of immunosuppression, did not allowed us to rigorously assess patients taking immunosuppressive drugs. Data on specific skin type, sun exposure habits and the adoption of sun-protective measures after the incident NMSC were not available, but all the patients were Caucasian, the majority with a skin Fitzpatrick phototype II or III.

CONCLUSION

In the present study, the histological type of the incident NMSC predicted the risk of developing another tumour of the same type, confirming data from previous studies in the general population and in immunosuppressed patients. To the best of our knowledge, for the first time, we showed this correlation in individuals with a haematologic malignancy. This finding may contribute to improve risk stratification and surveillance after the diagnosis of a NMSC, particularly in immunosuppressed patients with SCC.

Current guidelines recommend lifelong intensive dermatologic surveillance to all SOTR with a history of NMSC. Also other therapeutically immunosuppressed and other high risk individuals, namely those with haematological malignancies, may benefit from a long-lasting follow-up of at least ten years, with shorter intervals between each evaluation in the first years.

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Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
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