Artigo Original

Risco de Recidiva a 5 Anos Após Excisão Convencional de um Carcinoma Basocelular

B Duarte[1], L Vieira[2], L Ribeiro[2], T Pessoa e Costa[1], A João[1], A Varandas[2], J Cabete[1]
[1]Dermatology and Venereology Department, Hospital de Santo António dos Capuchos, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal
[2]Plastic and Reconstructive Surgery Department, Hospital de São José, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal

RESUMO – **Introdução**: O tratamento dos carcinomas basocelulares é maioritariamente cirúrgico, sobretudo por cirurgia com avaliação histopatológica pós-operatória da margem (cirurgia convencional), mas os dados a longo-prazo relativos a recidiva de acordo com o resultado histológico da margem (excisão completa *versus* excisão incompleta, mantida em *follow-up*) são limitados. **Métodos**: Estudo coorte retrospetivo dos carcinomas basocelulares tratados por cirurgia convencional e por diferentes especialidades médico-cirúrgicas num centro terciário, entre 2008 e 2014. Realizou-se uma análise multivariada com uma regressão de Cox, estratificada pelo resultado da avaliação histológica da margem (excisão completa/incompleta) e ajustada a várias variáveis recolhidas. **Resultados**: Um total de 2876 carcinomas basocelulares foram identificados, dos quais 2306 [2100 primários, 206 recidivantes (primeira recidiva)] foram considerados elegíveis para análise. Nos 5 anos de *follow-up*, verificaram-se 80 (4%) recidivas entre os 1959 tumores completamente excisados (16/1000 casos-ano), contrastando com 83 (23,9%) recidivas em 347 excisões incompletas (100/1000 casos-ano). Foi realizada uma análise de sobrevida ajustada. No modelo final, ajustado, multivariado, foi identificada associação entre recidiva e intervenção cirúrgica a tumores recorrentes [*hazard ratio* (HR) ajustado 2,20 (Intervalo confiança (IC) 95%, 1,26-3,84), $p=0,006$], cirurgia com diagnóstico pré-operatório errado/ausência de realização de biópsia prévia [HR ajustado 2,75 (IC 95%, 1,68-4,5), $p<0,001$], tratamento prévio a 2012 [HR ajustado 1,47 (CI 95%, 1,06-2,05), $p<0,021$] e cirurgia em localização de alto-risco, de acordo com a classificação NCCN [HR ajustado 2,18 (IC 95%, 1,08-4,40), $p<0,030$]. Por localização anatómica específica, a probabilidade de recidiva a longo-prazo é especialmente elevada se a cirurgia for na pirâmide nasal [HR ajustado 3,18 (IC 95%, 1,71-5,87), $p<0,001$] ou nas pálpebras [HR ajustado 3,08 (CI 95%, 1,32-7,17), $p=0,009$]. Verificou-se também uma tendência para maior recidiva nos subtipos histológicos agressivos [HR ajustado 1,43 (IC 95%, 0,99-2,07), $p<0,058$]. **Conclusão**: Os carcinomas basocelulares recorrentes, independentemente da localização, e os carcinomas basocelulares primários em localizações de alto-risco da face, particularmente na pirâmide nasal e nas pálpebras, determinam um risco de recidiva superior e independente a longo-prazo, mesmo nas excisões "completas". Por outro lado, as estratégias *wait-and-see* nos carcinomas basocelulares incompletamente excisados devem ponderar o risco de recidiva aos 5 anos (1 in 10 lesões).

PALAVRAS-CHAVE – Carcinoma Basocelular; Neoplasias da Pele; Procedimentos Cirúrgicos Dermatológicos.

Five-Year Risk of Basal Cell Carcinoma Recurrence After a Conventional Surgical Excision

ABSTRACT – ***Introduction:*** *Basal cell carcinomas are mostly treated surgically, mostly by surgery with postoperative histopathologic margin evaluation ("conventional surgery"), but large long-term data regarding recurrence by completeness of excisions is limited.* ***Methods:*** *Retrospective cohort study of basal cell carcinomas treated by conventional surgery at different medical specialties in a large tertiary centre, between 2008 and 2014. Survival analysis with a Cox proportional-hazards was performed, stratified by completeness of excision (complete excision/incomplete excision) and adjusted to several potentially confounding covariates.* ***Results:*** *A total of 2876 basal cell carcinomas were identified, of which 2306 (2100 primary, 206 recurrent) were considered eligible for analysis. During the 5-years of follow-up, there were 80 (4%) recurrences among 1980 complete excisions*

Correspondência: Bruno Duarte
Dermatology and Venereology Department
Hospital de Santo António dos Capuchos
Centro Hospitalar Universitário de Lisboa Central
Alameda Santo António dos Capuchos
1169-050, Lisboa, Portugal
E-mail: brunoduarte@campus.ul.pt
DOI: https://dx.doi.org/10.29021/spdv.78.2.1174

Recebido/*Received* 2020/03/14 | **Aceite/*Accepted*** 2020/04/13 | **Publicado/*Published*** 2020/06/30

Artigo Original

(16/1000 cases-year) and 83 (23.9%) recurrences among 348 incomplete excisions (100/1000 cases-year). Survival analysis was performed with multivariable adjustment. In the final adjusted model, we identified an association between relapse and re-intervention on recurrent tumors [adjusted Hazard Ratio (HR) 2.20 (95% Confidence interval (IC), 1.26-3.84), p=0.006], a wrong preoperative clinical diagnosis/surgery devoid of preoperative biopsy [adjusted HR 2.75 (95% CI, 1.68-4.5), p<0.001], treatment prior to 2012 [adjusted HR 1.47 (95% IC, 1.06-2.05), p<0.021] and surgery on a high-risk location, accordingly to the NCCN stratification [adjusted HR 2.18 (95% CI, 1.08-4.40), p<0.030]. By specific anatomic location, the likelihood of recurrence was especially high in the nose [adjusted HR 3.18 (95% CI 1.71-5.87), p<0.001] and eyelids [adjusted HR 3.08 (95% CI, 1.32-7.17), p=0.009]. There was also a trend towards higher recurrence in aggressive histological subtypes [adjusted HR 1.43 (95% CI 0.99-2.07), p<0.058]. ***Conclusion:*** *Recurrent basal cell carcinomas, regardless of location, and primary basal cell carcinomas on high-risk locations of the face, especially on the eyelids and nose, should be considered to have a higher and independent likelihood of recurrence, even on "complete excisions" evaluated by histopathology. On the other hand, wait-and-see approaches in incompletely excised BCCs should be considered against a significant 5-year risk of relapse (1 in 10 lesions).*
KEYWORDS – *Carcinoma, Basal Cell; Dermatologic Surgical Procedures; Skin Neoplasms.*

INTRODUCTION

Basal cell carcinoma (BCC) is an exceedingly common malignancy worldwide.[1] In spite of being almost devoid of metastatic capacity, BCC behaves as a locally destructive tumor, ultimately causing functional and cosmetic impairment as well as significant economic burden.[2,3] At present, surgery remains the preferred treatment for most BCC, mostly performed with postoperative histopathological margin control ("conventional surgery"). Mohs micrographic surgery (MMS) is an alternative which is regarded as the optimal treatment for high-risk BCCs, allowing full margin control.[4] Nevertheless, it is time-consuming and requires facilities and trained personnel, which are not widespread in some countries. Thus judicious selection of the lesions with the highest risk of recurrence to be intervened by MMS is a reasonable use of the technique.

In conventional surgery, regardless of the completeness of excision, a significant proportion (5.9%) of tumors will still recur,[5] leading to unwarranted morbidity and costs. On the other hand, incomplete excisions is commonly regarded as a surrogate for recurrence, but some physicians advocate a careful long-term follow-up instead of immediate surgical re-intervention, due to a degree of uncertainty regarding recurrences in incompletely excised lesions.[6]

The aim of this study is to identify the rate and the risk factors that may preoperatively foresee recurrences for basal cell carcinomas treated with conventional surgery, in both complete and incomplete excisions.

METHODS

Study design and data retrieval

We performed a retrospective cohort study in one of the largest university-based tertiary medical institutions in Portugal. All electronic health records and pathology reports of surgically-treated BCCs between January 2008 and December 2014 were retrieved and collected through database searching tools hosted at the institution.

Study population

We included adult patients with at least one BCC subjected to surgery of curative intent with postoperative histopathological evaluation ("conventional surgery") in any surgical department of the hospital. Recorded variables included patient age (dichotomized into <80 and ≥80 years), gender, immune status, department of the treating physician (Dermatology, Plastic and Reconstructive Surgery (PRS), Other), year of surgical treatment (dichotomized into 2008-2011 and 2012-2014), tumor status (primary vs recurrent), tumour size (<1 cm, 1-3 cm, >3 cm), tumor location [evaluated by the specific anatomic location: forehead, nose, ears, lips, upper and lower eyelids, eyebrows, cheeks, jawline and chin, preauricular and temporal area and trunk and extremities; and by the latest National Comprehensive Cancer Network (NCCN) risk stratification framework (7): high-risk area (H area), medium-risk area (M area) and low-risk area (L area)], histopathological BCC subtype (nodular subtype, superficial/other non-aggressive subtypes, aggressive subtypes), completeness of excision (as defined by the absence of residual neoplastic tissue at the lateral or deep margins, while an incomplete excision is characterized by residual tumor in either of the margins; of note, incompletely excised tumors included only those which were chosen to follow-up instead of immediate re-excision or in which the re-excision did also not achieved clear margins), defect closure technique (primary closure, second intention, skin flap, full or split thickness skin graft) and time until recurrence or end of follow-up (60 months). Exclusion criteria included BCCs treated with non-surgical treatments (imiquimod, 5-fluorouracil) or minimally invasive techniques (curettage and electrodessication, laser therapy, photodynamic therapy). MMS is not currently performed in our institution. A flowchart of the selection process is presented in Fig. 1.

Statistical analysis

Baseline data were reported as n (%) and mean SD, or medians and interquartile range according to the distribution. We used a chi-square test to compare the baseline categorical variables between the recurrence and non-recurrence groups. To characterize the variables associated with local recurrence after a conventional surgical treatment, a univariate and adjusted Cox proportional-hazards model stratified by the completeness of excision (complete vs incomplete) was constructed for recurrences occurring for 60

months after surgery. Patients were censored at the date of histological confirmation of a recurrence or at the date of the last follow-up visit. Crude hazards ratio (HR) at a 95% Confidence Interval (95% CI) were calculated and reported. For all tumor characteristics, the category with higher representation was selected as reference. All covariates considered important according to their clinical or statistical significance were included in the multivariate analysis. A significance level of 0.05 and a confidence interval of 0.95 was considered significant. All statistical analyses were performed with StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.

RESULTS

Baseline characteristics and non-independent associations

A total of 2876 BCCs were identified in the electronic healthcare database, of which 2306 BCCs [2100 primary, 206 recurrent (first recurrence)] were eligible after complying with both the inclusion and exclusion criteria (see detailed flowchart in Fig. 1). The baseline clinical, histological and tumoral characteristics were collected and several, albeit not-independent, associations were observed (shown in Table 1). As incomplete excisions are often regarded as a surrogate for long-term recurrence, we stratified the lesions into two groups – completely excised and incompletely excised tumors (Table 2, and for visual comparison between crude recurrences in both groups, see Fig. 2). During the 60 months of follow-up (total person-years: 5871.4) there were 80 (4%) recurrences among the 1959 complete excisions (16 cases per 1000 patient-years), which compares with the 83 (23.9%) recurrences among the 347 incomplete excisions (100 cases per 1000 patient-years).

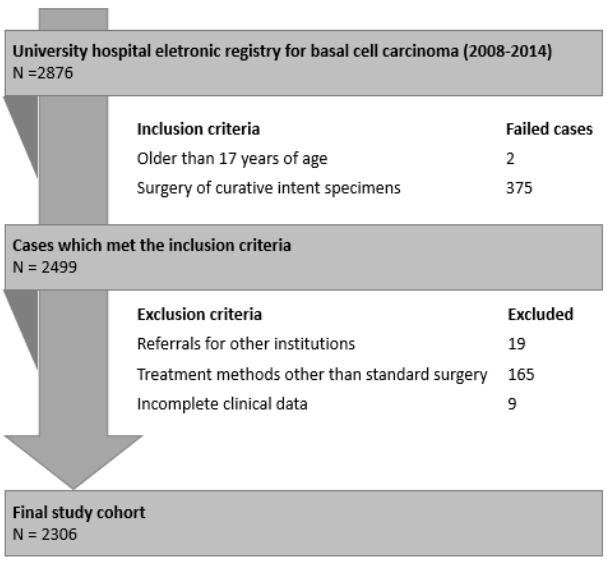

Figure 1 - Flowchart of patient selection.

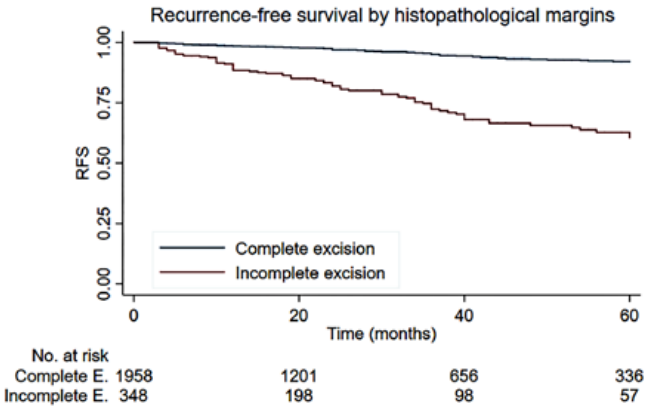

Figure 2 - Recurrence probabilities of basal cell carcinomas, according to the completeness of excision.

Survival analysis

In the crude analysis, recurrences were associated with the type of diagnosis, the treating department, the histological subtype, the NCCN and anatomic risk locations and closure with flaps. Neither age, gender, immune status, year of surgery or tumor size met statistical significance in the unadjusted analysis.

After multivariable adjustment, there was an association between relapse and recurrent tumors [adjusted HR 2.02 (1.40-2.93), $p=<0.001$. Fig. 3] tumors in which the diagnosis was made by excisional (therapeutic) biopsy without a preoperative biopsy [adjusted HR 1.75 (95% CI, 1.25-2.45), $p<0.001$], surgical treatment prior to 2012 [adjusted HR 1.47 (95% CI, 1.06-2.05), $p<0.021$] and surgery on a NCCN high-risk location [adjusted HR 2.74 (95% CI, 1.25-4.90), $p<0.001$]. After adjustment for specific anatomical regions (instead of the more general NCCN risk locations. Fig. 4), there was a strong association with recurrence after

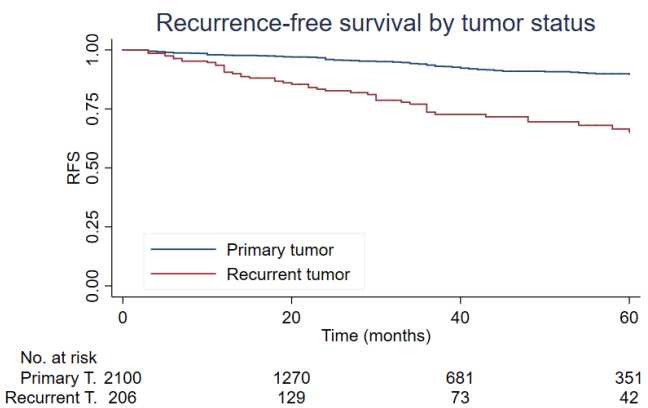

Figure 3 - Recurrence probabilities of basal cell carcinomas, according to the status of the tumor (primary or recurrent).

Artigo Original

Table 1 - Study groups baseline clinicopathological characteristics. Stratification by the excision status (complete vs incomplete under follow-up).

	N=1959	Completely excised BCCs			N= 347	Incompletely excised BCCs		
		Recurrence (N = 80, 4.10%)	No recurrence (N = 1879, 95.90%)	p-value		Yes (N= 83, 23.92%)	No (N=264, 76.08%)	p-value
Age at treatment								
< 80 years	1229	47 (2.40)	1182 (60.34)	0.452	217	60 (17.29)	157 (45.24)	0.035
≥ 80 years	730	33 (1.68)	697 (35.58)		130	23 (6.63)	107 (30.84)	
Gender								
Male	1078	52 (2.65)	1026 (52.37)	0.067	191	46 (13.26)	145 (41.79)	0.937
Female	881	28 (1.53)	853 (43.54)		156	37 (10.66)	119 (34.29)	
Immunosuppression								
No	1850	76 (3.88)	1774 (90.56)	0.822	332	74 (31.55)	258 (74.35)	0.001
Yes	109	4 (0.2)	105 (5.36)		15	6 (1.73)	9 (2.59)	
Year of surgery								
2008-2011	678	40 (2.04)	638 (32.57)	0.003	120	36 (10.37)	84 (24.21)	0.054
2012-2014	1281	40 (2.04)	1241 (63.35)		227	47 (13.54)	80 (51.87)	
Treating department								
Dermatology	1760	69 (3.52)	1691 (86.32)	0.391	292	71 (20.46)	221 (63.69)	0.304
PRS	165	10 (0.51)	155 (7.91)		45	8 (2.31)	37 (10.66)	
Other	34	1 (0.05)	33 (1.68)		10	4 (1.15)	6 (1.73)	
Type of diagnosis								
Clinical	1768	39 (1.99)	1486 (75.86)	<0.001	243	49 (14.12)	194 (55.91)	0.012
Histological	538	41 (2.09)	393 (20.06)		104	34 (9.80)	70 (20.17)	
Histological subtype								
Nodular	1564	60 (3.06)	1504 (76.77)	0.188	210	45 (12.97)	165 (47.55)	0.157
Superficial	154	5 (0.26)	149 (7.61)		28	5 (6.63)	23 (1.44)	
Aggressive	241	15 (0.77)	226 (11.54)		109	33 (9.51)	76 (21.90)	
NCCN risk locations								
H area	761	43(2.19)	718 (36.65)	0.007	200	55 (15.85)	145 (41.79)	0.002
M area	613	24 (1.23)	589 (30.07)		86	24 (6.92)	62 (17.87)	
L area	585	13 (0.66)	572 (29.20)		61	4 (1.15)	57 (16.43)	
Anatomic area								
Trunk and extremities	585	13 (0.66)	572 (29.20)	0.012	61	4 (1.15)	57 (16.43)	0.029
Nose	345	21 (16.24)	324 (1.07)		108	34 (9.80)	64 (21.33)	
Cheeks	192	7 (0.36)	185 (9.44)		34	11 (3.17)	23 (6.63)	
Forehead	147	7 (0.36)	140 (7.15)		26	8 (2.31)	18 (5.19)	
Preauricular	125	7 (0.36)	118 (6.02)		27	8 (2.31)	19 (5.48)	
Temple	126	6 (0.21)	120 (6.13)		10	2 (0.58)	8 (2.31)	
Eyelids	80	8 (0.41)	72 (3.62)		22	5 (4.90)	17 (1.44)	
Other	359	11 (0.56)	348 (17.76)		59	11 (3.17)	48 (13.84)	
Tumour size								
<1 cm	318	14 (0.71)	304 (15.52)	0.545	100	29 (8.46)	71 (20.46)	0.250
1-3 cm	1420	60 (3.06)	1360 (69.42)		223	47 (13.54)	176 (50.72)	
>3 cm	221	6 (0.31)	215 (10.97)		24	7 (2.02)	17 (4.90)	
Recurrent BCC								
No	1815	59 (3.01)	1756 (89.64)	<0.001	285	56 (16.14)	229 (65.99)	<0.001
Yes	144	21 (1.27)	123 (6.28)		62	27 (7.78)	35 (10.09)	
Defect closure technique								
Primary closure	1607	57 (2.91)	1550 (79.12)	<0.001	5	63 (18.16)	199 (57.35)	0.654
2nd healing intention	6	2 (0.10)	4 (0.20)		262	0 (0.00)	5 (1.44)	
Flap	196	13 (9.34)	183 (0.66)		44	11 (3.17)	33 (9.51)	
Skin graft	150	8 (0.41)	142 (7.25)		36	9 (2.59)	27 (7.28)	

Table 2 - Univariate and multivariate analysis of clinicopathological risk factors for recurrence. Stratification by the excision status (complete vs incomplete under follow-up).

	N= 2306	Univariate analysis		Multivariate analysis (by NCCN risk areas)		Multivariate analysis (by anatomic location)	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at treatment							
<80 years	1446	1 [Reference]	-	-	-	-	-
≥ 80 years	860	1.17 (0.84-1.61)	0.353	-	-	-	-
Gender							
Male	1037	1 [Reference]	-	-	-	-	-
Female	1269	1.07 (0.79-1.47)	0.634	-	-	-	-
Immunosuppression							
No	2182	1 [Reference]	-	-	-	-	-
Yes	124	.1.53 (0.86-2.74)	0.148	-	-	-	-
Year of surgery							
2008-2011	798	1.37 (0.99-1.86)	0.051	1.47 (1.06-2.05)	0.021	1.47 (1.07-2.04)	0.019
2012-2014	1508	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Treating department							
Dermatology	2052	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
PRS	210	2.46 (1.26-4.80)	0.008	1.31 (0.75- 2.78)	0.348	1.30 (0.74-2.51)	0.358
Other	44	1.36 (0.19-9.83)	0.760	2.43 (0.97-6.12)	0.059	2.32 (0.82-6.60)	0.113
Type of diagnosis							
Clinical	1768	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Histological	538	2.30 (1.69-3.14)	<0.001	1.75 (1.25-2.45)	0.001	1.78 (1.30-2.50)	0.001
Histological subtype							
Nodular	1774	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Superficial and other non-aggressive	182	1.37 (0.71-2.69)	0.340	1. 36 (0.66-2.80)	0.410	1. 38 (0.68-2.88)	0.377
Aggressive subtypes	350	2.44 (1.24-4.85)	0.010	1.43 (0.99-2.07)	0.058	1.45 (0.99-2.11)	0.052
NCCN risk locations							
High-risk area	961	2.57 (1.39-4.77)	0.003	2.74 (1.25-4.90)	0.001	-	-
Medium-risk area	699	1.66 (0.85-3.26)	0.141	2.39 (1.30-4.37)	0.005	-	-
Low-risk area	646	[Reference]	-	1 [Reference]		-	-
Anatomic area							
Trunk and extremities	646	1 [Reference]	-	-	-	1 [Reference]	-
Nose	453	3.47 (2.01-6.01)	<0.001	-	-	3.18 (1.71-5.87)	<0.001
Cheeks	226	2.67 (1.37-5.17)	0.004	-	-	2.99 (1.45-6.17)	0.003
Forehead	173	3.21 (1.60-6.44)	0.001	-	-	2.86 (1.37-6.00)	0.005
Preauricular	152	2.98 (0.93-5.81)	0.073	-	-	2.93 (1.39-6.16)	0.005
Temple	136	.2.16 (0.93-4.99)	0.074	-	-	2.01 (0.63-4.91)	0.122
Eyelids	102	4.07 (1.97-8.43)	<0.001	-	-	3.08 (1.32-7.17)	0.009
Other	418	1.78 (0.94-3.41)	0.079	-	-	1.65 (0.83-3.31)	0.156
Tumour size							
<1 cm	318	1.16 (0.81-1.66)	0.421	1.13 (0.68-1.54)	0.509	1.17 (0.81-1.70)	0.411
1-3 cm	1420	1 [Reference]	-	1 [Reference]		1 [Reference]	
>3 cm	221	1.03 (0.58-1.84)	0.908	1.03 (0.59-1.88)	0.931	1.14 (0.60-2.14)	0.688
Recurrent BCC							
No	2100	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Yes	206	2.84 (2.01-4.06)	<0.001	2.02 (1.40-2.93)	<0.001	1.99 (1.37-2.88)	<0.001
Defect closure technique							
Primary closure	1869	1 [Reference]	-	-	-	-	-
2nd healing intention	11	1.51 (0.37-6.15)	0.561	-	-	-	-
Flap	240	1.88 (1.21-2.92)	0.005	-	-	-	-
Skin graft	186	1.27 (0.76-2.12)	0.349	-	-	-	-

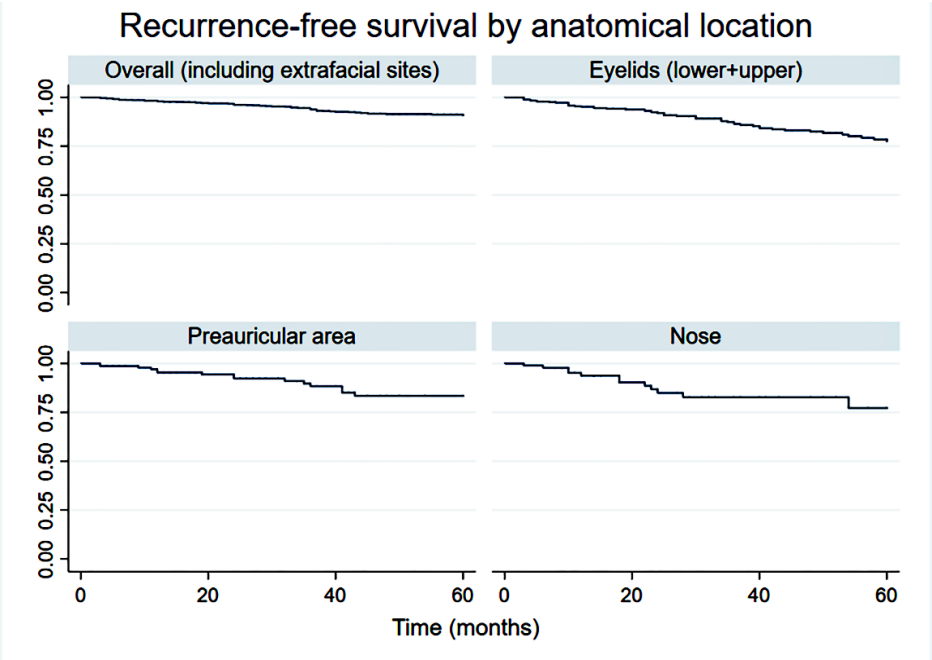

Figure 4 - Recurrence probabilities of basal cell carcinomas, according to their specific anatomic location.

excisions on the nose [adjusted HR 3.18 (95% CI 1.71-5.87), $p<0.001$] and the eyelids [adjusted HR 3.08 (95% CI, 1.32-7.17), $p=0.009$] followed by the cheeks [adjusted HR 2.99 (95% CI, 1.45-6.17), $p=0.003$] the preauricular region [adjusted HR 2.93 (95% CI, 1.37-6.00), $p=0.005$], and the forehead [adjusted HR 2.86 (95% CI, 0.92-4.47), $p=0.081$]. There was also a trend towards a higher risk of recurrence in aggressive histological subtypes [adjusted HR 1.43 (95% CI 0.99-2.07), $p<0.058$]. Neither the treating department or the type of defect closure achieved statistical significance in the final adjusted model.

DISCUSSION

To the best of our knowledge, we present one of the largest multidisciplinary real-world studies where predictive factors for BCC long-term recurrence were evaluated. This knowledge is of paramount importance to improve surgical planning and to provide evidence-based support to prioritize some tumors (of higher risk) to more radical and/or effective treatments, such as MMS, instead of others with lower long-term risk of relapse.

After adjusting for several confounders, we found a positive association between neoplastic recurrence and preoperative misdiagnosis, location in a NCCN high-risk area (especially the nose and eyelids), recurrent BCCs (re-operated by conventional surgery) and surgical treatment prior to 2012. Likewise, we observed a trend towards statistical significance in aggressive histologic subtypes (non-superficial and non-nodular). While the lack of statistical significance in the latter may be explained by the low caseload of aggressive subtypes, it may in fact portend a diminished effect in the long-term risk of recurrence determined by the histologic subtype after a "complete" excision when compared to the aforementioned covariates.

In our analysis, we found that tumors on the nose [adjusted HR 3.18 (95% CI 1.71-5.87), $p<0.001$], followed closely by the eyelids [adjusted HR 3.08 (95% CI, 1.32-7.17), $p=0.009$] had the higher likelihood of relapse in the long-term. To achieve easier defect closures in these are sensitive areas, surgeons are more likely to try to preserve lateral tissue compared with other anatomical areas where more tissue can be safely removed.[5] This probably contributes to explain the higher long-term risk of relapse, even after multivariate adjustment. It should be reminded that it is the reconstruction technique that should be tailored to the size of the excision defect, and not the contrary, as the main objective of the surgery is to remove the tumour and its subclinical spread completely.

The only randomized controlled trial with long-term follow-up comparing MMS and conventional surgery to manage high-risk facial BCC was few years ago published by van Loo *et al*.[8] As fewer recurrences were found with MMS, the authors suggested that high-risk facial primary and recurrent BCCs should be the main indications for this technique.[8] Our study is in complete agreement with these recommendations. Nevertheless, the decision to referral or intervention by standard (conventional) excision should rely on best judgement of experienced physicians in dermato-oncological care, which should take into account all of the patient's clinical and cutaneous malignancy characteristics.

For example, those with limited life expectancy or in poor health can probably be managed by conventional surgery or other minimally invasive procedures instead of MMS.[9] This may aid to relieve pressure on the awaiting lists of Mohs surgery facilities.

Larger (>3 cm) tumoral dimensions failed to be of prognostic significance to recurrence in the adjusted model. Several explanations could be gathered. First, larger BCCs are usually clinically easier to diagnose compared to smaller lesions. Secondly, they are more prone to be biopsied (to avoid unnecessary mutilating excisions) than smaller lesions amenable to primary closure. Lastly, "scarier" tumoral masses will instigate surgeons into more radical excisions (with larger peripheral margins).

A final remark is made on the controversy regarding recurrence risk after an incomplete excision. Although presence of residual tumour in the histopathological evaluation ("incomplete excision") is considered a surrogate for recurrence in most cancers, in BCC management this association is not clear-cut. In fact, not all incompletely excised tumors recur.[10] Additionally, residual neoplastic tissue is found in only 36%–54% of the immediate re-excision specimens.[6,11,12] Potential, albeit speculative, explanations are the clearance of residual neoplastic cells by the hyperinflammatory wound repair, as well as the unclear histopathological definitions of "incomplete" versus "close" or "tangential" excisions in some of the published papers. Most importantly, a significant number of physicians often perform an expectant approach rather than immediate re-intervention in the presence of an incompletely excised BCC. In spite of this preference, our results demonstrate a remarkable clinical and statistical difference regarding the recurrence rate, as 1 in every 10 incompletely excised tumors under follow-up will recur (5-year risk of 23.9%), contraposing to only 4% (80/1980) after a completely excised lesion. This outcome was similar to the recent Codazzi *et al* study.[5] Expectant "wait-and-see" approaches should thus be considered with the present risk in mind. When the patient is deemed unfit for a new surgery local radiotherapy might be a good alternative to maintain a low-risk of recurrence in the long term.

Our study demonstrates several strengths, such its large sample size and data comprising different, independent departments that perform cutaneous surgery at a large referral institution. Thus, our study best represents the BCCs real-life management in a tertiary setting. Nevertheless, it also has limitations. As in all observational studies, our retrospective design implies that some residual confounding, due to either unmeasured or poorly measured covariates, cannot be excluded. Some factors, such as tumoral border definition and surgeon dependent-outcomes (technical experience and expertise), were impossible to acquire and analyse and thus were not included as a covariate in the model. Lastly, the follow-up ended at 60 months, which is insufficient to capture ultra-late recurrences.[13]

In conclusion, in our large multidisciplinary single-centre study, recurrent BCCs and primary BCCs in high-risk locations, especially on the eyelids and nose, identify a higher risk cohort for long-term recurrence. On the other hand, wait-and-see approaches in incompletely excised BCCs should be considered against a significant 5-year risk of relapse (1 in 10 lesions).

Conflitos de interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
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.
Proveniência e revisão por pares: Não comissionado; revisão externa por pares.

Conflicts of interest: *The authors have no conflicts of interest to declare.*
Financing support: *This work has not received any contribution, grant or scholarship.*
Confidentiality of data: *The authors declare that they have followed the protocols of their work center on the publication of data from patients.*
Protection of human and animal subjects: *The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).*
Provenance and peer review: *Not commissioned; externally peer reviewed*

ORCID
Bruno Duarte
http://orcid.org/0000-0003-4757-0679
Luís Vieira
http://orcid.org/0000-0002-9353-2537

REFERENCES

1. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166:1069-80.
2. Kauvar ANB, Cronin T, Roenigk R, Hruza G, Bennett R; American Society for Dermatologic Surgery. Consensus for nonmelanoma skin cancer treatment : basal cell carcinoma , including a cost analysis of treatment methods. Dermatol Surg. 2015;41:550-71. doi: 10.1097/DSS.0000000000000296.
3. Cameron MC, Lee E, Hibler BP, Barker CA, Mori S, Cordova M, Nehal KS, Rossi AM. Basal cell carcinoma: Epidemiology; pathophysiology; clinical and histological subtypes; and disease associations. J Am Acad Dermatol. 2019;80:303-17. doi: 10.1016/j.jaad.2018.03.060.

Artigo Original

4. Otley CC, Salasch SJ. Mohs surgery: efficient and effective. Br J Ophthalmol. 2004;1:1223-9.
5. Codazzi D, Velden J Van Der, Carminati M, Bruschi S, Bocchiotti MA, Serio C Di, et al. Positive compared with negative margins in a single-centre retrospective study on 3957 consecutive excisions of basal cell carcinomas. Associated risk factors and preferred surgical management. J Plast Surg Hand Surg. 2014;48:38-43.
6. Patel SS, Cliff SH, Booth PW. Incomplete removal of basal cell carcinoma: what is the value of further surgery ? Oral Maxillofac Surg. 2013;17:115-8.
7. Andersen JS, Berg D, Bowen GM, Cheney RT, Daniels GA, Glass LF, et al. Basal Cell Skin Cancer, Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2016;14:574-97.
8. Loo E Van, Mosterd K, Krekels GA, Roozeboom MH, Ostertag JU, Dirksen CD, et al. Surgical excision versus Mohs' micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10 year follow--up q. Eur J Cancer. 2014;50:3011-20. doi:10.1016/j.ejca.2014.08.018.
9. Linos E, Parvataneni R, Stuart SE, Boscardin WJ, Landefeld CS, Chren M-M. Treatment of nonfatal conditions at the end of life: nonmelanoma skin cancer. JAMA Intern Med. 2017;173:1006-12. doi: 10.1001/jamainternmed.2013.639.
10. Lee Dellon A, De Silva S, Connoly M, Ross A. Prediction of recurrence in incompletely excised basal cell carcinoma. Plast Reconstr Surg. 1985;75:860-71.
11. Griffiths RW. Audit of histologically incompletely excised basal cell carcinomas: recommendations for management by re-excision. Br J Plast Surg. 1999;52:24-8.
12. Wilson AW, Howsam G, Santhanam V, Macpherson D, Grant J, Pratt CA, et al. Surgical management of incompletely excised basal cell carcinomas of the head and neck. Br J Oral Maxillofac Surg.2004;42:311-4.
13. Bichakjian C, Armstrong A, Eisen DB, Iyengar V, Lober C, Margolis DJ, et al. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol. 2018;78:540-59. doi: 10.1016/j.jaad.2017.10.006.