Risk of recurrence and new malignant cutaneous neoplasms in Mexican subjects with basal cell carcinoma

Riesgo de recurrencia y de nuevas neoplasias cutáneas malignas en sujetos mexicanos con carcinoma basocelular

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Abstract

Introduction: Basal cell carcinoma (BCC) is the most common skin malignant neoplasm. **Objective:** Investigate the risk of recurrence and of new skin malignant neoplasms, after treatment of BCC. **Method:** Retrospective study. We examined the files of patients with histopathological diagnosis of primary BCC, between January 2007 and December 2009, and we investigate number of recurrences and their relationship with localization, treatment type, and histopathological variant, and the number of new skin malignant neoplasms. For analysis, we employed descriptive and inferential statistics; $p < 0.05$ was considered significant. **Results:** A total of 397 patients, with an average follow-up of 4 ± 1.5 years. Recurrences presented in 4%. Recurrences were related with longer time of evolution (36 vs. 32 months; $p = 0.04$) and treatment with destructive techniques (electrofulguration, cryosurgery or imiquimod; 31 vs. 4%; $p < 0.001$). There was no relationship with localization, or the histopathological variant. The risk of developing a new malignant neoplasm was 25%; 66% corresponded to a new BCC and 30% to squamous cell carcinoma. **Conclusions:** Follow-up of patients with BCC should be conducted independently of their localization and histopathological variant, especially in patients with greater evolution time, principally with surgical techniques.

KEY WORDS: Basal cell carcinoma. Recurrence. Skin cancer.

Resumen

Introducción: El carcinoma basocelular (CBC) es la neoplasia cutánea maligna más común. **Objetivo:** se investigó el riesgo de recurrencia y de nueva neoplasia cutánea maligna después del tratamiento de CBC. **Método:** Estudio retrospectivo. Fueron identificados los pacientes con diagnóstico histopatológico de CBC primario, de enero de 2007 a diciembre de 2009, y se revisaron los expedientes para investigar el número de recurrencias, la localización, el tipo de tratamiento y la variante histopatológica, determinando nuevas neoplasias cutáneas malignas. El análisis incluyó estadística descriptiva e inferencial, considerando significativa una $p < 0.05$. **Resultados:** Se incluyeron 397 pacientes, con un seguimiento promedio de 4 ± 1.5 años. La recurrencia se presentó en el 4% y se relacionó con un mayor tiempo de evolución (36 vs. 32 meses; $p = 0.04$) y haber sido tratado mediante técnicas destructivas (electrofulguración, criocirugía o imiquimod; 31 vs. 4%; $p = 0.0004$). No hubo relación con la localización ni con la variante histopatológica. El riesgo de desarrollar una nueva neoplasia maligna fue del 25%, y de ellas el 66% correspondió a un nuevo CBC y el 30% a carcinoma espinocelular. **Conclusiones:** Es importante el seguimiento de los pacientes con CBC para identificar tanto las recurrencias como las nuevas neoplasias malignas, independientemente de la localización y de la variante histopatológica del primario. El tratamiento con técnicas quirúrgicas condiciona una menor recaída que las técnicas destructivas.

PALABRAS CLAVE: Carcinoma basocelular. Recurrencia. Cáncer cutáneo.

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Introduction

Basal cell carcinoma (BCC) is the most commonly diagnosed malignant neoplasm in dermatological practice; it accounts for 65-74% of all skin tumors¹⁻⁴ and its incidence has increased over the years in different countries⁵⁻⁷. In Mexico, a prevalence of 3.9 per 1000 population is estimated^{2,8}. Although it has a low risk for producing metastasis, the risk of recurrence varies from 2 to 10%⁹⁻¹², and the risk for developing a new malignancy ranges from 10.4% to 21.2%^{13,14}. This depends on tumor clinical-histopathological characteristics, with location on the nose, eyelids, the temple, the helix or the neck, size larger than 10 mm, morpheiform histopathological pattern or recurrent BCC¹⁵ being factors of higher risk, as well as the type of treatment used, with recurrence rates being higher when destructive techniques such as electrofulguration¹⁶, cryosurgery (10%)¹² or imiquimod (20.6%) are employed¹⁷, while with excision with predetermined margins recurrence is lower (2%)^{10,11}. We did not find studies carried out in Mexico on the subject, and our goal was therefore to investigate, in patients diagnosed with BCC, which factors were associated with BCC recurrence and if said recurrence is related to patient clinical characteristics or of the tumor itself, as well as to determine the frequency of new malignant skin neoplasms.

Method

Retrospective study, where patients with primary BCC histopathological diagnosis recorded at Jalisco Dermatological Institute database from January 1, 2007 to December 31, of 2009, who had at least 2 years' follow-up after BCC treatment, were included. Electronic records were reviewed to investigate age, gender and evolution time, as well as to determine the number of recurrences (evidence of malignant tumor cells consistent with BCC on the previously-treated primary BCC scar or at 2 cm from it, and at least 2 months after treatment)⁹, and new malignant skin neoplasms (histopathologically confirmed; if it was a new BCC, it should be at least 2 cm apart from the previously-treated BCC scar or could be on the scar if the diagnosis was other than BCC)¹⁴. The relationship of the percentage of recurrences with the location, type of treatment and BCC histopathological variant was investigated. Records of patients whose histopathological diagnosis was obtained from a biopsy and

not from the result of tumor complete excision were excluded. For data analysis, averages and standard deviations were calculated. For the comparison of qualitative variables, the chi-square test or Fisher's exact test were used, as appropriate. For quantitative variables, Student's t-test was used. To estimate the relationship between the risk of recurrent BCC and clinical and histopathological characteristics, the odds ratio with a 95% confidence interval was calculated. Statistical significance was considered with a p-value < 0.05. For the processing of data, the Microsoft Excel 2013 and Epi Info™ (version 7.0) programs were used. This investigation was approved by the Ethics and Research Committee of the institution.

Results

General characteristics

During the study period, 397 patients with primary BCC diagnosis met the selection criteria. Average age was 65 ± 13 years (range: 16 to 98 years), and 156 subjects (39%) were males and 241 (61%) females. Average BCC evolution time at diagnosis was 33.5 ± 44 months (range: 1 month to 20 years). Average follow-up time was 4 ± 1.5 years (range: 2 to 10 years). The received treatment was grouped in two modalities: surgical (surgery with predetermined margins or Mohs micrographic surgery), which was used in 378 patients (95%), and destructive (electrofulguration, cryosurgery and imiquimod), which was employed in 19 patients (5%).

Recurrent BCC

Recurrent BCC was found in 16 patients (4%), with a median reappearance time of 24 months (range: 2 months to 4.8 years). Female gender predominated, with 10 cases (62.5%). Median age was 71 years (range: 47 to 98 years) and median primary BCC evolution time was 36 months (range: 4 months to 15 years).

Anatomical localization was as follows: H or high-risk zone (eyelids, eyebrows, periorbital region, nose, lips cutaneous and vermilion portions, chin, mandibular region, preauricular and retroauricular areas) in 8 cases (50%), and L or medium risk zone (scalp, forehead, cheeks and neck) in 8 cases (50%). No recurrences were observed in the M or low-risk zone (trunk and extremities). In 11 patients (69%) surgical techniques were used, whereas in 5 (31%), destructive techniques

Figure 1. Recurrent basal cell carcinoma (BCC) treatment.

Figure 2. Recurrent basal cell carcinoma (BCC) histopathological variants.

were used (Fig. 1). The low-risk histopathological pattern was present in 12 patients (75%), and the high-risk pattern in 4 (25%) (Fig. 2).

When the group of 16 patients with recurrent BCC and the group of 381 patients who had no recurrent BCC were compared, we found statistically significant differences in evolution time (36 vs. 32 months; $p = 0.04$), use of surgical techniques (69 vs. 96%; $p = 0.0004$) and the use of destructive techniques (31 vs. 4%; $p = 0.0004$). Table 1 shows the comparison between the variables of the cases with and without recurrent BCC.

New malignant skin neoplasms

Of the 397 patients diagnosed with primary BCC, 98 had a total of 147 new skin malignancies (25%): one new tumor in 70 patients (72%), two new tumors in 17 (17%) and three or more tumors in 11 (11%). Average onset time was 32 ± 45 months (range: 2 months to 15 years). Among these, BCC occurred in 97 cases (66%), while squamous cell carcinoma

developed in 44 (30%). Low risk BCC predominated, with 66 cases (68%), and out of them, the most common histopathological pattern was nodular in 48 (73%). Histopathological characteristics of the 147 new malignant skin neoplasms are shown in figure 3.

When the characteristics of the group of patients who developed a new malignant skin neoplasm were compared with those of the group of patients who did not, no statistically significant differences were found (Table 2).

Discussion

This study included 397 patients with primary BCC, a sample larger than that of Marghoob et al.¹⁴ of 260 patients⁴ and to that of McLoone et al.¹³ of 114 patients. Average age was 65 years, similar to the age of 62 reported in other Mexican studies^{2,8}. The female gender predominated, with 61% of cases, which differs from findings of others authors, who report a predominance of the male gender^{2,8,18}. BCC evolution time at diagnosis was, on average, 33.5 months,

Figure 3. New malignant skin neoplasms histopathological variants.

which is longer than the time intervals reported by other authors who refer that, in most cases, the diagnosis is made prior to 12 months of evolution¹⁹. Follow-up time after diagnosis was, on average, 4 years, which is less than that reported by Chren et al.⁹, which was 7.4 years on average, but longer than that referred by McLoone et al.¹³, who carried out a follow-up of 2 years, part of it through telephone calls and not through physical examination.

The risk of recurrent BCC was 4%, similar to the prevalence of 3.3% reported for a USA population in the aforementioned study by Chren, et al.⁹. In our study, recurrence occurred on average 25 months after the primary BCC diagnosis, but there were recurrences at up to 4.8 years, which is longer than the recurrence-free interval reported by Chren et al.⁹, which was 3.9 years. This finding is important, since in Mexico, according to the Clinical Practice Guidelines

for the Prevention, Diagnosis and Treatment of Basal Cell Carcinoma²⁰, the recommendation is a 3-year follow-up in high-risk patients; therefore, perhaps a longer follow-up would be desirable. We found a significantly longer evolution time in those patients with recurrence, which suggests that we should be especially careful with patients with long-evolving lesions.

Of the primary BCCs that recurred, 50% were found to be in high-risk areas, while other authors report this location in 81% of cases²¹. We did not find recurrences in tumors located at low-risk areas, which partially supports the recommendation of the British Association of Dermatologists of following only patients with tumors on high-risk anatomical sites or with aggressive histological type²².

The risk of recurrence was significantly higher with the use of destructive techniques than when surgical

Table 1. Comparison between recurrent and non-recurrent basal cell carcinomas

Variable	Recurrent BCC (n = 16)	Non-recurrent BCC (n = 381)	p	OR (95% CI)
Age in years ($\pm$ SD)	71*	65 $\pm$ 12	0.54 [†]	—
Female gender, n (%)	10 (62.5)	231 (61)	0.88 [‡]	1.08 (0.35-3.43)
Evolution, months ($\pm$ SD)	36*	32 $\pm$ 43	0.04 [†]	—
High-risk zone, n (%)	8 (50)	222 (58)	0.43 [‡]	0.72 (0.24-2.15)
Medium-risk zone, n (%)	8 (50)	123 (32)	0.13 [‡]	2.10 (0.70-6.31)
Low-risk zone, n (%)	0 (0)	36 (9)	0.38 [§]	—
Surgical technique, n (%)	11 (69)	367 (96)	0.0004 [§]	—
Predetermined margins, n (%)	9 (82)	355 (97)	0.05 [§]	—
Mohs surgery, n (%)	2 (18)	12 (3)	0.05 [§]	—
Destructive technique, n (%)	5 (31)	14 (4)	0.0004 [§]	—
High-risk histopathological pattern, n (%)	4 (25)	80 (21)	75 [§]	—
Low-risk histopathological pattern, n (%)	12 (75)	301 (79)	0.75 [§]	—

*Median.

[†]Mann-Whitney U-test.[‡]Chi-square test.[§]Two-tailed Fisher's exact test.

BCC: basal cell carcinoma; CI: confidence interval; OR: odds ratio; SD: standard deviation.

Table 2. Comparison between groups with and without new malignant skin neoplasms

Variable	BCC with new neoplasm (n = 98)	BCC without new neoplasm (n = 299)	p
Female gender, n (%)	53 (54)	188 (63)	0.12*
Age, years ($\pm$ SD)	70 $\pm$ 11	64 $\pm$ 13	2.9 [†]
Evolution, months ($\pm$ SD)	32 $\pm$ 41	34 $\pm$ 45	0.79 [†]
Follow-up, months ($\pm$ SD)	50 $\pm$ 19	49 $\pm$ 17	0.47 [†]

*Chi-square test.

[†]Student's t-test.

BCC: basal cell carcinoma; SD: standard deviation.

techniques were employed, which corroborates the fact that the former have a higher rate of treatment failure²³. The risk of recurrence in those patients treated with predetermined margins in our population was 2.5%, which is lower than that published by Mosterd et al.²¹ in Dutch patients: 4.1%.

As for the histopathological variant of the BCCs that recurred, the literature refers that the high-risk variant is a factor for the presence of recurrences¹⁵, but we found no significant difference with low-risk variants. Our result is similar to that published by Chren et al.⁹, who report that BCCs with low-risk histopathological variants also recurred more often than those with high-risk variants (3.8 vs. 1.6%).

With regard to the risk of new malignancies, in our study it was 25%, which is higher than the risk reported by McLoone et al.¹³ in Irish population, which was 17.5%. Average time at which new neoplasms appeared was 32 months, which is similar to the previously published time of 38.3 months¹⁴. There were also patients who presented with new neoplasms up to 15 years after the primary BCC diagnosis, and perhaps a longer follow-up time should be considered, and not only 3 years, as previously mentioned²⁰.

As for the number of new neoplasms per patient, only 11% had three or more. Conversely, Marghoob et al.¹⁴, in 260 US patients, reported that 21.2% had three or more tumors. This higher frequency may be due to the fact that they only included fair skinned patients, which have a higher predisposition for the development of cancer²⁴.

The most common new malignant skin neoplasm was BCC in 66% of cases, followed by squamous cell carcinoma in 30%. Both tumors are also referred by McLoone et al.¹³, although with lower frequencies of 16.7% and 2.6%, respectively. It is important to mention that in this last study, although the follow-up time was 2 years, 47% of subjects were only contacted by telephone and were not assessed by any doctor, which might explain these differences.

In new BCCs, the low-risk histopathological pattern prevailed, with 68% of cases, which is data that is not

specified in previously published series. When epidemiological characteristics of patients with a new malignant skin neoplasm, such as gender, age and evolution time or follow-up, were analyzed, we found no significant differences when comparing them with those of subjects who did not develop new skin malignancies.

Conflicts of interests

None to declare.

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