Recurrent basal cell carcinoma: A clinicopathological study and evaluation of histomorphological findings in primary and recurrent lesions

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KEY WORDS

basal cell carcinoma, recurrence, aggressive and indolent variants

SUMMARY

Background. Basal cell carcinoma (BCC) of the skin is now the most common malignancy in the human population. One of the most negative features of this disease is frequent tumor recurrence. Unfortunately, all of the traditional diagnostic criteria have failed to definitively predict which patients should be considered at high risk of recurrence.

Objective. The aim of this study was to evaluate the prevalence, topographical localization, and histomorphological features of recurrent BCCs.

Methods. Biopsy samples and clinical data from 30 consecutive patients (15 women and 15 men) with 31 recurrent BCCs diagnosed from January 2007 to September 2010 were analyzed retrospectively. The mean age of the individuals at the time of diagnosis of recurrence was 68.2 years (range 32 to 97 years). Histological types and other pathological findings of original and relapsing BCCs, as well as the time between them, were able to be compared in 24 cases.

Results. Recurrent carcinomas represented 4.9% of all diagnosed cases during the observed period. Recurrence time varied from 4 to 105 months with a mean time of 31.2 months. The majority of recurrences occurred within 3 years after the primary treatment. The topographic localization of tumors was as follows: auricles (n = 5), cheeks (n = 4), medial canthus (n = 4), periauricular regions (n = 3), temporal areas (n = 3), paranasal regions (n = 3), nose (n = 3), forehead (n = 1), lower eyelid (n = 1), mandible (n = 1), chin (n = 1), neck (n = 1), and back (n = 1). Histologically, 50% of primary and 54.8% of recurrent BCCs demonstrated at least partial aggressive-growth features. Comparing primary and corresponding relapsing BCCs, 50% of them showed an identical type, in 16.7% the recurrent tumor had developed a more aggressive histological picture, and in 20.8% the histomorphology had became more benign. Of all primary tumors previously removed by total extirpation, 54.5% were resected completely and 45.5% incompletely.

Conclusions. BCC recurrences may vary considerably with respect to various tumor- and host-related factors, and so it is impossible to predict them precisely. Although aggressive histological types and positive excision margins are considered the strongest predictors, we demonstrated that

half of the primary cancers had shown an indolent character, and that more than half of them had appeared to be completely resected. We can conclude that all patients that have had BCCs removed should be re-examined regularly even after microscopically adequate excisions, or lesions with an indolent histomorphology. Careful monitoring must be undertaken for at least 3 years; however, the most appropriate course is a lifetime of regular follow-up.

Introduction

Basal cell carcinoma (BCC) constitutes approximately 70 to 80% of all malignant skin tumors and is the most common malignancy in the human population today. It has diverse clinical appearances, histomorphology, and biological behavior (1–3). Although it is usually a slow-growing tumor with only minimal metastatic potential, some types can grow aggressively from the start and infiltrate surrounding tissue and deeper structure in a fashion that may not be obvious on visual inspection (1, 2, 4). Thus, the clinical course of individual BCCs is largely unpredictable. Many therapeutic alternatives are available for this cancer, but total surgical excision is still considered the "gold standard." Almost all BCCs are curable if diagnosed and treated promptly. However, if left untreated for a long time, or not treated correctly, they can cause extensive destruction of tissue, particularly on the face, and may have a negative impact on patients' health status. In addition, many patients often suffer cosmetic and functional changes resulting from treatment (5, 6).

One of the most negative characteristics of this disease is frequent tumor recurrence. Relapsing cancers may clinically manifest as areas of erythema, induration, ulceration, or bleeding at a prior operative site for a known primary lesion (1). So far, limited demographic, clinical, and histological predictors for BCC recurrence have been identified (5). In particular, all of the traditional diagnostic criteria have failed to definitively predict which BCC patients should be considered at high risk of recurrence. Even the exact incidence of relapsing BCCs cannot be estimated objectively because recurrence risk depends on several factors that must be taken into consideration in the overall assessment. The most important are the tumor's topographic localization, the surgical margin status of excised lesions, and the histological type of BCC. Other important risk factors include the number of lesions, age at first presentation, tumor size, pathological stage, gender, skin type, immunological status, individual treatment strategy, and postoperative management (7, 8). This is why the reported rates of recurrent BCCs vary widely in the range of 0.5 to 38% according to various researchers (5, 9–14). Some differences are also reported with respect to the histomorphological features of primary and corresponding relapsing tumors (15, 16). The role of the pathologist is irreplaceable in the diagnostic process because, in addition to giving the correct diagnosis, he also describes important morphological parameters of the tumor, some of which are of valuable prognostic significance. The aim of this study was to evaluate the

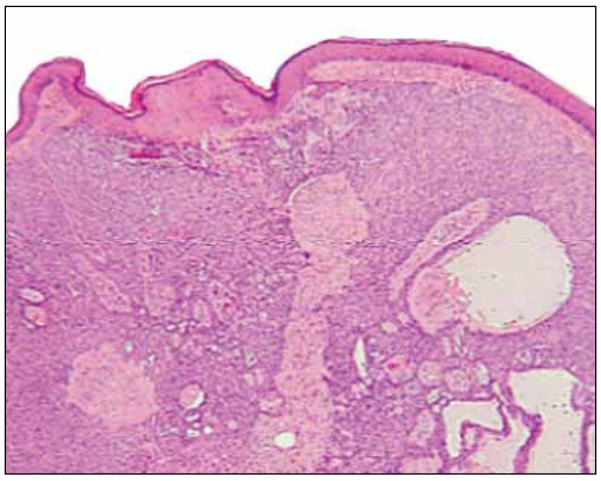

Figure 1. Nodular BCC is typically characterized by well-demarcated large nodular nests of basaloid tumor cells localized in the dermis. Cystic degeneration is often present (H&E, 400×).

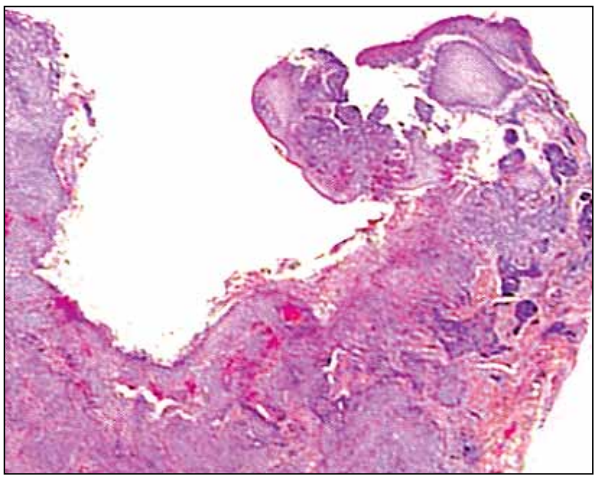

Figure 2. Ulcerative nodular BCC with infiltrative-growth features at the periphery. Note that the sample has not been entirely removed, because small nests of cancer are present in the lateral surgical margin (right; H&E, 200×).

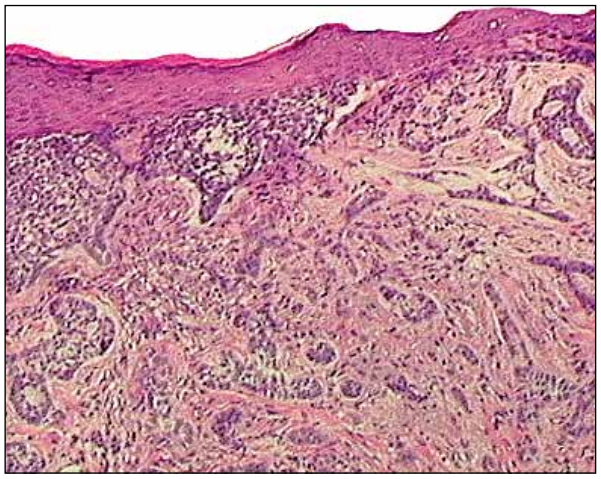

Figure 3. Infiltrative BCC types comprise irregularly-sized and -shaped nests of tumor cells showing widespread invasion from the epidermis into the corium and deeper structure (H&E, 400×).

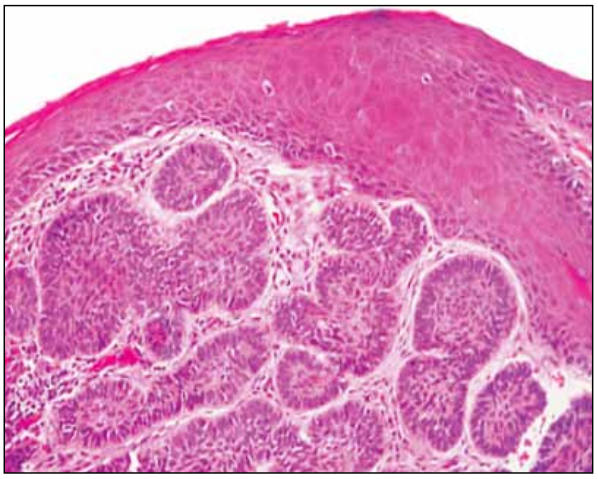

Figure 4. BCC with adnexal differentiation. Multiple small nests of basaloid tumor cells in the dermis have a trichoepithelioma-like appearance (H&E, 400×).

prevalence, topographical localization, and histomorphological findings of recurrent BCCs diagnosed at the Department of Pathology in the Faculty Hospital in Žilina.

Patients and methods

Pathology specimens and clinical data from 30 consecutive patients (15 women, 15 men) with 31 recurrent BCCs diagnosed from January 2007 to September 2010 were analyzed retrospectively. The mean age of the individuals at the time of diagnosis of recurrence was 68.2 years (range 32 to 97 years), with no significant difference between males (68.8 years) and females (67.5 years). The clinical data and samples from the primary tumors required for the study were available only in 24 cases. Histomorphological types and other pathological features of original (not cured previously) and relapsing BCCs were compared each other, as well as the time intervals between them. We did not register the primary cancers of the remaining seven patients in our database because their tumors had been treated in another hospital or medical institution, and categorization of recurrence was based only on clinical records that described them developing at the site of previously treated BCC. In such cases, we did not count the reported time interval after the surgical excision of the primary lesion and recurrence in the overall assessment. Two women exhibited two relapses of the same tumor, and one man had two separate relapsing cancers on the face. Individual lesions were excised in several clinical departments (i.e., departments of surgery, dermatology, ophthalmology, and otorhinolaryngology). Both primary and relapsing cancers were obtained by total or partial (probatory) surgical extirpation. Out of twenty-four primary cancers, 22 were removed by total excision and two by partial excision. Among recurrent (including re-recurrent) lesions, 25 samples were obtained by total resection and 8 by partial resection. In cases of excisional biopsies, none of the incompletely removed tumor was immediately re-excised. The adjuvant postoperative therapeutic modality (local radiotherapy, photodynamic therapy, Imiquimod, or Efudix application) were applied when required according to the clinicians' individual decisions. Biopsy material was fixed in buffered formalin, embedded in paraffin blocks, stained with hematoxylin and eosin, and the slides were reviewed by pathologists under a light microscope. In certain cases, in addition to standard hematoxylin and eosin staining, we used also some special histochemical methods (Masson, Gömöri, van Gieson staining) for better microscopic evaluation of tumor tissue. BCC histological types were categorized into aggressive-growth and indolent (non-aggressive) growth variants according to conventional classification reported in the literature (1, 4). Aggressive-growth variants included the infiltrative type (morpheic), micronodular, and metatypical carcinoma, whereas indolent-growth variants comprised superficial, nodular, and BCC with adnexal differentiation. Trichoepithelial features were considered as a form of adnexal differentiation. Information on patients was received from the hospital clinical records, or by consultations with the clinicians. None of the patients suffered from Gorlin-Goltz syndrome (nevoid basal cell carcinoma syndrome).

Results

Prevalence of recurrent BCCs and recurrence time interval

A total of 625 BCCs of the skin from 483 patients were excised and histologically verified in our institution from January 2007 to September 2010. In brief, recurrent carcinomas represented 4.9% of all diagnosed cases. The interval between the original and subsequent secondary excision of the lesion (generally considered "recurrence time") varied from 4 to 105 months (8.7 years) with a mean time of 31.2 months (2.6 years). This time was shorter in women (26.0 months) than in men (35.5 months). The majority of recurrences (70.8%) occurred within 3 years of the primary treatment. Two cases of re-recurrences manifested 8 and 36 months after the first relapse, respectively.

Topographical localization of tumors

As expected, recurrent BCCs predominated on the head, and parts of the face were especially affected. The topographic localization of tumors was as follows: five on the auricles (16.1%), four on the cheeks (12.9%), four on medial canthus (12.9%), three on the periauricular regions (9.7%), three on the temporal areas (9.7%), three on the paranasal regions including nasolabial grooves (9.7%), three on the nose (9.7%), one on the forehead (3.2%), one on the lower eyelid (3.2%), one on the mandible (3.2%), one on the chin (3.2%), one on the neck (3.2%), and one on the back (3.2%). The right and left sides of the face were equally affected (13:13). Considering the topographical classification of nonmelanoma skin cancers into the high-, intermediate-, and low-risk sites of the body (10), 58.1% of BCCs were localized on high-risk sites, 35.5% on intermediate sites, and 6.4% on low-risk sites (Table 1).

Histomorphological characteristics of the primary and recurrent BCCs

Both primary and recurrent BCCs exhibited varied histomorphology, harboring either homogeneous or mixed growth patterns. The histological types of all 31 recurrent BCCs (in two patients with repeated recurrences only the first relapse was included) were the following: nine were nodular (29.0%; Figure 1), nine nodular with focal infiltrative-growth features (29.0%; Figure 2), three infiltrative (9.7%; Figure 3), one micronodular (3.2%), three morpheic (9.7%), two superficial (6.5%), two trichoepithelial (6.5%; Figure 4), one nodular combined with trichoepithelial features (3.2%), and one metatypical carcinoma (3.2%). In summary, 54.8% of all recurrent BCCs demonstrated at least partial aggressive growth in the histological picture (Table 2). The retrospective evaluation of 24

Table 1. Topographical distribution and percentage of 31 recurrent BCCs (M = males, F = females).

Topography	M	F	*n* (%)
A. High-risk sites			
Auricle (right)	2	0	2 (6.45)
Auricle (left)	0	3	3 (9.67)
Nose	1	2	3 (9.67)
Paranasal region (right)	0	1	1 (3.22)
Paranasal region (left)	1	1	2 (6.45)
Medial canthus (right)	2	1	3 (9.67)
Medial canthus (left)	1	0	1 (3.22)
Lower eyelid (left)	0	1	1 (3.22)
Mandible (right side)	1	0	1 (3.22)
Chin (left side)	0	1	1 (3.22)
B. Intermediate-risk sites			
Preauricular region (right)	1	1	2 (6.45)
Retroauricular region (right)	1	0	1 (3.22)
Temporal region (right)	0	1	1 (3.22)
Temporal region (left)	2	0	2 (6.45)
Cheek (right)	1	1	2 (6.45)
Cheek (left)	0	2	2 (6.45)
Forehead	1	0	1 (3.22)
C. Low-risk sites			
Neck (left side)	1	0	1 (3.22)
Back	1	0	1 (3.22)

Table 2. Histological types and percentage of 31 recurrent BCCs.

Recurrent BCC (histological type)	*n* (%)
Aggressive-growth feature BCCs (at least focal)	
Infiltrative	3 (9.67)
Morpheic	3 (9.67)
Metatypical	1 (3.22)
Nodular-infiltrative	9 (29.0)
Micronodular	1 (3.22)
Indolent-growth BCCs	
Nodular	9 (29.0)
Superficial	2 (6.45)
Nodular-trichoepithelial	1 (3.22)
Trichoepithelial	2 (6.45)

previously resected primary cancers registered in our database revealed seven nodular BCCs (29.2%), six nodular with focal infiltrative-growth features (25%), four infiltrative (16.7%), two morpheic (8.3%), two nodular with trichoepithelial differentiation (8.3%), two trichoepithelial (8.3%), and one superficial BCC (4.2%). Like recurrent carcinomas, 50.0% of primary BCCs microscopically demonstrated aggressive-growth features of varying degree. In addition, both groups exhibited nearly the same proportion of homogeneous and mixed histological growth phenotype. Comparing primary tumors with the corresponding relapsing BCCs (in two patients with repeated recurrences only the first recurrence was included) we summarized, 12 cases (50%) showed an identical type, in four cases (16.7%) the recurrent tumor had developed a more aggressive histologic picture, and in five patients (20.8%) the histomorphology had became more

Table 3. Comparison of the primary and subsequent recurrent BCCs in 23 patients (TE = total excision, PE = partial (probatory) excision, SM = surgical margins, (+) = positive surgical margins, (–) = negative surgical margins, RT = recurrence time (in months), SO = surgical operation, pT = pathological TNM classification, x = not possible to assess.

	Primary BCC (histological type)	SO	SM	pT	Recurrent BCC (histological type)	SO	SM	RT
1	Trichoepithelial	TE	(+)	x	Trichoepithelial	TE	(–)	23
2	Nodular-trichoepithelial	TE	(–)	T1	Nodular	TE	(–)	46
3	Nodular-infiltrative	TE	(–)	T1	Nodular	TE	(–)	5
4	Nodular-infiltrative	TE	(+)	x	Infiltrative	PE	x	36
5	Infiltrative	TE	(+)	x	Infiltrative	PE	x	41
6	Morpheic	TE	(–)	T4	Metatypical	TE	(+)	49
7	Nodular	TE	(+)	x	Nodular	TE	(–)	11
8	Nodular	TE	(–)	T1	Morpheic	PE	x	105
9	Infiltrative	TE	(–)	T1	Infiltrative	TE	(–)	34
10	Superficial	TE	(–)	T1	Superficial	PE	x	33
11	Infiltrative	TE	(–)	T1	Nodular-infiltrative	PE	x	57
12	Infiltrative	TE	(–)	T1	Nodular-infiltrative	PE	x	15
13	Trichoepithelial	TE	(+)	x	Trichoepithelial	TE	(–)	30
14	Nodular-infiltrative	TE	(+)	x	Nodular	TE	(–)	4
15	Nodular-infiltrative	PE	x	x	Nodular-infiltrative	PE	x	28
16	Nodular	PE	x	x	Nodular	TE	(–)	7
17	Nodular-infiltrative	TE	(+)	x	Nodular	TE	(+)	7
18	Nodular	TE	(–)	T1	Superficial	TE	(–)	11
19	Nodular-trichoepithelial	TE	(+)	x	Nodular-infiltrative	TE	(+)	87
20	Nodular	TE	(+)	x	Nodular-infiltrative	TE	(–)	10
21	Nodular	TE	(–)	T1	Nodular	TE	(–)	21
22	Nodular	TE	(–)	T1	Nodular	TE	(–)	21
23	Nodular-infiltrative	TE	(+)	x	1. Nodular-infiltrative 2. Nodular-infiltrative	TE TE	(+) (+)	7 8
24	Morpheic	TE	(–)	T1	1. Morpheic 2. Morpheic	TE PE	(+) x	60 36

benign than before. Of the remaining three patients the histological phenotype was not identical, but it showed the same growth variant (two indolent and one aggressive-growth variant). Both women with a repeated tumor recurrence (localized on the left auricle and left paranasal region, respectively) had an identical histological type in the first, second, and third biopsies, and all showed an aggressive-growth component (Table 3).

Rather unexpectedly, of all the primary tumors removed by total extirpation, 12 (54.5%) were resected completely and 10 (45.5%) incompletely (defined by a presence of tumor cells at the margins or the base of the samples in paraffin-embedded sections). Among adequately excised original cancers, 10 lesions were classified as pathological stage pT1 and one as stage pT4. The horizontal and vertical diameters of these tumors ranged from 0.1 to 11 mm (mean 5.7 mm) and 0.1 to 5 mm (mean 1.7 mm), respectively. The high-stage BCC (localized on the right auricle) was histologically characterized by tumor infiltration of the hyaline cartilage, which was present in both the primary and recurrent lesions. It was not possible to assess tumor size and depth of infiltration in partial and incomplete excisions and so it can be hypothesized that at least some of them may have corresponded with higher pathological stages. None of the carcinomas showed perineural or vascular tumor invasion. Relapsing cancers usually showed regressive and reparative changes in the tissue, accompanied by ulceration, fibrosis, peritumoral lymphocytic infiltration, sporadic focal giant cell reactions, and solar dermatosis in the surrounding corium.

Discussion

BCC recurrences represent a serious therapeutic problem in the practice of several medical disciplines. Most of them occur within 3 years following the original surgical treatment (14, 17, 18), but approximately 20% come between 6 and 10 years after the surgical excision (19). We found similar results in our study, in which over 70% had manifested themselves during the first 3 years. It is worth noting, however, that the actual recurrence interval is somewhat shorter because all tumors grow for some time before removal. Thus, a precise evaluation of this period is not possible because it is based mostly on individual patients' perceptions, something that may be rather subjective, especially in older persons. We think this is the main reason that our study demonstrated a shorter recurrence time in females than in males, because women have a greater tendency to notice a postoperative skin wound. Although reliable prediction of BCC recurrences is difficult on the basis of routine clinicopathological parameters, some of them may indicate an increased probability of their development in the future. The presence or absence of these risk factors must be taken into account when choosing therapeutic options. Based on the topographical location, the vast majority arise on high- and intermediate-risk areas of the body (10, 16). High-risk anatomical sites include the nose and paranasal regions, nasolabial grooves, ears, chin, mandibular parts, and perioral and periocular areas. Intermediate-risk sites are the scalp, forehead, pre- and postauricular regions, and malar areas (10). The prognosis of cancers in these locations is worse, primarily due to the difficulty of complete removal of the lesion partly caused by extensive subclinical spread of the tumor (20). It is believed that the presence of hair follicles makes it less amenable to complete excision, thus increasing the likelihood for recurrence (3). Mohs micrographic surgery is the best treatment modality for such lesions if possible. Conversely, relapses become much less frequent on the low-risk anatomical areas (neck, trunk, and extremities) of the body (10). These data are in full compliance with our observations, which showed almost all recurrent BCCs being localized on the head. In general, the larger the tumor size and higher the pathological stage of disease, the more difficult is its removal and the higher the risk of recurrence. Bogelund et al. (8) described pT2 and pT3 tumors as having 2- and 3-fold increased relapse rates, respectively, compared with pT1 BCCs. It should be mentioned that the evaluation of this relationship is limited in clinical practice because the larger lesions usually cannot be removed completely and staging assessment is not possible in such cases.

Histologically, BCC recurrences are mostly associated with aggressive-growth variants (5, 18, 21, 22). Sexton et al. (23) described an overall recurrence rate in infiltrative types of 26%, but in nodular and superficial types only 6.4% and 3.6%, respectively. Zagrodnik et al. (17) demonstrated a similar rate in the sclerosing (infiltrative) type (27.7%) and nodular type (8.2%) but, surprisingly, in the superficial type it reached 26.1%. However, according to some researchers (24) no definite correlation could be established between BCC subtype and recurrence, and histopathological criteria for prognosis are limited. A better understanding of the pathogenesis and histological evolution of BCC recurrence can be gained by observations comparing the individual morphological features and biological characteristics of primary and subsequent relapsing lesions. There are only a few such relevant studies to date (15, 16). Boulingues et al. (16) compared 33 primary and corresponding recurrent BCCs and concluded that 20 original tumors had had microscopic features of non-aggressive tumors, and 13 of aggressive tumors. Upon recurrence, 20% of originally non-aggressive cancers became histo-

logically aggressive, and 31% of originally aggressive BCCs showed an even more aggressive component. Accordingly, in an earlier study by Lang and Maize (15) 65% of all primary BCCs demonstrated an aggressive picture microscopically. The subsequent recurrent tumors developed a more aggressive histologic feature in 23.5% of cases, but in 13.7% the histomorphology became more indolent. In our group, upon recurrence 16.7% of tumors developed more aggressive features, and one-fifth became more indolent. These results are very compatible with the previous studies and confirm the fact that primary and subsequent relapsing tumors may not always manifest the same histomorphology, and can also exhibit different biological behavior and clinical outcomes. It should be emphasized that precise microscopic evaluation of relapsing BCCs is very difficult for the pathologist because the tumor structure is significantly modified by scar formation and overproduction of fibrous tissue, which alters the original morphology as well as the character of tissue infiltration (1).

Currently, surgical treatment using postoperative histological assessment of the lesion is considered the most optimal therapy for BCC of the skin and is routinely practiced worldwide. However, whereas completely resected BCCs confirmed histologically by clear margins show recurrence in 2 to 5% during the following 5-year period, in cases of incompletely excised lesions the risk increases to 32 to 38% (10, 13, 18). The most critical are aggressive-growth histological variants having poorly circumscribed contours whose actual margins are usually more extensive than is grossly apparent (4). Several decades ago Burg et al. (25) showed that a clinically visible BCC surface may only represent one-fifth of its local microscopic invasion. Histographic analysis of BCCs later confirmed (26) that their peripheral margins had very irregular microarchitecture composed of a large number of small finger-like spreading outgrowths that remain in contact with the central tumoral mass. This is why a complete surgical tumor extirpation (especially of infiltrative types) is difficult in most cases, and the term "clear margins of the sample" in the pathology report cannot fully guarantee that the postoperative wound is definitively free of cancer (24). With the exception of Mohs micrographic surgery, it is not possible to be certain that total removal of cancer has been achieved (27). Our results supported these data because approximately half of the completely resected primary lesions had recurred. However, the main limitation of our study was the lack of precise data on previous treatment modalities for the primary BCCs after incomplete or only partial (probatory) excisions. Because reliable prediction of the recurrence risk of the incompletely resected BCCs is practically impossible, when physicians receive a pathology report indicating an inadequate tumor extirpation, they face the issue of further management. Management of such lesions still remains a matter of debate, mainly a question of immediate re-excision. According to some authors (16, 28), initially indolent variants of incompletely excised BCCs do not require re-excision except if they are located in high-risk parts with a poor prognosis. In fact, BCC remnants retained in situ after extirpation do have the tendency to spontaneously regress to some extent. Residual tumor cells have been found in 25 to 55% of all re-excised samples (16, 27, 29), indicating that they had been destroyed during the postoperative reparative and inflammatory mechanisms of the skin. This is why a large number of the incompletely resected BCCs never recur. On the other hand, other authorities (30–32) have suggested that spontaneous regression of BCC at the margins of an inadequate excision does not occur. Spencer et al. (31) and Nouri et al. (32) showed that the inflammatory process and wound healing do not significantly contribute to the eradication of BCC remnants following curettage and electrodesiccation in a few months after surgery. It is likely that this "disappearance phenomenon" develops only in cases in which the number of residual elements is too small to resist the physiological wound-healing tissue mechanism (16). Another question remains regarding why BCCs can also recur after a very long time, and what the initial impulse is to "reactivate" carcinogenesis after many years within the location of the original lesion. From a prognostic point of view, it must be taken into account that recurrent BCCs are more difficult to cure, and they have a more adverse response to most therapeutic modalities as well as higher frequency of further recurrences (8, 9, 14, 22, 33). This is partly due to the fact that scar tissue can cover residual tumor fields or because the appearance of tumor cells in recurrent BCCs is often infiltrative, which may be easily missed in scar tissue (33). In study by Silverman et al. (11) surgically excised relapsing BCCs were accompanied by recurrence almost 2.5 times more often. The risk of their extensive subclinical spread is 3 to 4 times higher compared with primary nodular BCC (20), which is a cause of more frequent positive surgical margins in re-excisions (16, 26). Thus, all recurrent BCCs should be treated as high-risk lesions, and require wider peripheral surgical margins. Although 5 to 10 mm margins have been suggested (6), it is usually not possible to perform such a large excision, especially on regions of the head.

Conclusion

BCC recurrences vary considerably with respect to various tumor- and host-related factors, and so it is

impossible to predict them precisely in routine clinical practice. Although the most recent study (5) reported that the strongest predictors were aggressive histological types and positive excision margins, we found that half of the primary cancers had showed an indolent character, and more than half of them appeared to be completely resected. Thus, all patients that have had BCCs removed should be re-examined regularly even after microscopically adequate excisions, or lesions with an indolent histomorphology. Careful monitoring must be undertaken for at least three years; however, the most appropriate course is a lifetime of regular follow-up.

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