SCRIPTA MEDICA (BRNO) – 79 (5–6): 261–270, *December 2006*

HISTOLOGICAL TYPES OF BASAL CELL CARCINOMA

VANTUCHOVÁ Y.[1], ČUŘÍK R.[2]

[1] Department of Dermatology, University Hospital, Ostrava

[2] Department of Pathology, University Hospital, Ostrava

Received after revision November 2006

Abstract

Histological diagnostics and classification of basal cell carcinomas (BCCs) are essential for an assessment of the percentage proportions of particular histological groups, risk determination of the recurrence of this illness, and comparison of treatment results. There is no unified and generally accepted classification of BCCs. When classifying BCCs, most authors start from the growth pattern, which gives more information about bio-behaviour, and less often from the differentiation of tumours. All published works are in accord regarding their determination of the three basic groups of BCCs: nodular, superficial, and infiltrative, which present 80–90 % of all BCCs. Other BCC groups are defined by various authors in many different ways; the number of reported BCC groups can vary, too.

Information about the behaviour of a tumour classified as a BCC group into risk groups is very important for the clinical specialist to set up a further treatment plan and dispensing of the patient. Most authors agree with the fact that the nodular type belongs to the group of low risk, and infiltrative and superficial types belong to the group of high risk of local recurrence.

Key words

Basal cell carcinoma, Basalioma, Histology, Classification

INTRODUCTION

Basal cell carcinoma is a malignant skin tumour consisting of plugs and clusters of basal cells, with various clinical manifestations in accordance with the presence of various morphological features, which to a certain extent correspond with the histological types.

MATERIALS AND METHODS

Clinical picture

Clinical manifestations are various papulonodular lesions with a pearl transparent rim, destructive ulcerative lesions called ulcus rodens, pale foci with various degrees of induration, erythematous foci with obvious telangiectasia, or cystic nodules. Giant lesions with a diameter of more than 20 centimetres were also described, more rarely of linear and polypoid forms.

The manifestation of BCC is most frequently nodular, it consists of pearl papules or nodules with telangiectasias, sometimes with central ulcerations. The nodules may be pigmented in various extent and some of them may look like a cyst due to their clear colour and soft consistency. The second most frequent clinical manifestation is a superficial form creating relatively well circumscribed erythematous macular lesions with a fine filamentous pearl rim. A third clinical variant is the sclerosing or morphemic form, which is characterised by sclerosing, cicatricial, badly circumscribed lesions of white or yellow colour, which looks like scleroderma. These tumours are flat and their manifestation depends on the size of the fibrotic component. BCC lesions may sometimes be pigmented and, according to the degree of pigmentation, they may look like seborrheic keratosis or even malignant melanoma (*1,2*).

In most cases the clinical diagnosis is not difficult for an experienced clinician. There are cases, however, when the final diagnosis may be determined only on the basis of a histological examination of a completely removed tumour. In such unclear cases it is necessary to consider actinic keratosis, seborrheic dermatitis, seborrheic keratosis, pyogenic granuloma, Merkel tumour, psoriasis, Bowen's disease, non-pigmented melanocytic naevus, malignant melanoma, or squamous cell carcinoma.

Histopathological finding

BCC is an epithelial malignant tumour with a low malignant potential, consisting of cells which look like the basal epidermis layer (*3*). The diagnostic histological features, common for all types of the tumour, are basaloid cells with a thin pale cytoplasm surrounding round or oval nuclei with a rough granulated chromatin pattern. The peripheral borderline cell layers are characterised by palisade arrangement and the surrounding stroma is often separated by artificially created slits, whereas the internal arrangement of the cells is rather chaotic. Most tumours originate in the epidermis and invade the dermis in the form of solid or cystic nodules or streaky projections creating various growth patterns. Mitoses may be rare or multiple; often, especially in greater tumour nodules, there are central necroses (*3*). Intercellular bridges may also be present; these are less significant than in squamous cell carcinoma and cannot be evaluated in an examination by a light microscope (*1,2,4,5*).

Histopathological classifications

Up to now, there have been many histopathological types of BCC described by various authors. The highest number, twenty-six, was described by *Wade and Ackerman* (*6*) in 1978.

Most authors use two basic criteria in the creation of classifications of histological types, the histological growth pattern and histological differentiation. Most authors agree that the histological growth pattern is of the greatest biological significance. Classification based on the histological growth pattern is useful during the creation of the concept of low-risk and high-risk types of BCC (*2,7,8,9,10,11).* A greater probability of subclinical spread, aggressive local behaviour of the tumour with a more frequent occurrence of local recurrences and incomplete excision are characteristic of high-risk types (5,7,9,10). High-risk types include infiltrative (*Fig. 1, Fig. 2*) and superficial types (*Fig. 3*); a representative of the low-risk type of BCC is the nodular type (*Fig. 4*), in which many histological variants were described (*2,7,8,9,11,12*).

The criterion of cell differentiation obtained less support for classification. The significance of the squamous differentiation of BCC is controversial. There is no accord of views regarding the type of basosquamous carcinoma. This type is most frequently described as the simultaneous presence of basal cell and squamous cell carcinoma (*1,3,5,13,14*); some authors report further items, keratotic carcinoma (*3,5,14*) and metatypical carcinoma (*5,12*). Regardless of this unclear definition, some authors expressed the opinion that BCC associated with moderate or severe squamous cell atypia or malignity is associated with a higher occurrence of local recurrences and metastatic spread (*2,5,9,13,14*). In BCC with follicular differentiation there are usually less squamous cell atypias, however with no significance for the biological behaviour of the tumour (*9*). The classification by *Sexton* (*4*) and *Rippey* (*2*) does not include the variants with squamous cell differentiation as special types of BCC.

Classification of BCC						
Sloan 1977	**Sexton 1990**	**Rippey 1998**	**Weedon 2002**	**Rosai 2004**	**WHO 2006**	**Patterson 2006**
nodular	**Nodular**	**nodular,** including micronodular	**nodular**	**nodular**	**nodular**	**nodular**
superficial	**superficial**	**superficial**	**superficial**	**superficial**	**superficial**	**superficial**
infiltrating	**infiltrating**	**infiltrating** including sclerosing	**infiltrating**	**infiltrating**	**infiltrating**	**infiltrating**
nodular with infiltrative margin	micronodular		micronodular	micronodular	micronodular	
			fibroepithelial	fibroepithelial	fibroepithelial	fibroepithelial
			basosquamous	basosquamous (metatypical)	basosquamous	basosquamous
			keratotic	keratotic	keratotic	keratotic
			pigmented	pigmented		pigmented
			infundibulocystic	infundibulocystic	with adnexal differentiation	
			adenoid	adenoid		adenoid
			cystic	cystic		
	sclerosing		sklerosing	sklerosing		sklerosing
			metatypical	clear cell		metatypical
	mixed	**mixed**	**mixed**			basosebaceous

Table 1
Comparison of classification of BCC according to the various authors

The group defined according to cell differentiation, which usually has more aggressive behaviour, includes histological variants, which represent a certain degree of squamous cell differentiation. This is the keratotic BCC whose solid growth pattern contains central foci with pronounced squamous differentiation and keratinisation (*3,5,9,14*). Another controversial type of BCC included in this group is basosquamous carcinoma, which can be defined as basal cell carcinoma differentiated from squamous cell carcinoma. This variant consists of three groups of cells; basaloid cells, which are bigger, paler and rounder than in the solid type; also squamous cells with rich eosinophilic cytoplasm and intermediate cells (*5*). A fourth type of this group is the metatypical BCC, which is used by some authors as a synonym for basosquamous carcinoma (*3,13,14*) and set apart by others as a separate type (*5*). This variant contains nests of cells which lose the palisading arrangement and mature to bigger, paler cells.

Rippey et al. (*7,15,16*), in comparison with the classifications by *Sexton* (*4*), *Weedon* (*5*), *Rosai* (*14*) and the WHO classification (*3*), exclude micronodular BCC as a special type (*Table*). The authors believe that the micronodular type, after evaluation of the size of the tumour cell nests and the presence or absence of infiltration in the dermis, may be included in the nodular (*2,16*) or infiltrative types (*11*). The classification by *Rippey* (*12*) does not differentiate among other, less frequent variants. Secondary changes recognised in nodular BCC include the creation of cysts, ulceration, and pigmentation (*1,2,3,4,5,13,17*). We believe that, in accordance with other authors (*4,11*), these changes are insignificant for the determination of the biological behaviour of BCC and these terms should not be used. Nodulocystic, noduloulcerative, and nodulopigmented are attributes with no prognostic significance and secondary changes, especially the presence of pigment, may be found in all types of BCC, although they are most frequently described in the nodular and superficial type of BCC (*2,3,4,5,17*).

Pigmented BCC only contains functional melanocytes producing melanin; an admixture of a certain dominant growth type and their presence as well as the presence of melanophages in the dermis have no influence on the biological behaviour of the tumour (*4*).

The WHO classification (*3*) distinguishes among eight types; *Patterson* (*18*) reports eleven types, *Weedon* (*5*) and *Rosai* (*14*) report thirteen and fourteen types, respectively (*Table*).

These classifications contain the nodular, superficial, and infiltrative types; furthermore they set apart the micronodular, fibroepithelial, basosquamous, keratotic, and pigmented types. The WHO classification (3) has a category of BCC with adnexal differentiation, *Weedon* (*5*) and *Rosai* (*14*) differentiate among infundibulocystic, adenoid, and cystic types. Compared with the WHO classification (*3*), *Weedon* (*5*), *Rosai* (*14*), *Sexton* (*4*), and *Patterson* (18) separately describe a sclerosing type, which is part of the infiltrative type in most publications (*2,3,7,15*). *Weedon* (*5*) sets apart the metatypical type, which is considered to be basosquamous by *Rosai* (*14*). *Rosai* (*14*) is the only one to describe the type from clear cells. It is obvious that such a great number of histological types decreases the reproducibility of the morphological findings and disables the comparison of histological types with clinical findings and therapy results.

Furthermore, there are many other aspects that complicate the entire issue even more. Many BCC contain more histological types and there is no consent from what percentage of individual types the BCC should be determined as a new histological variant. Scant attention was paid to the evaluation of the growth pattern in the invading part of the tumour or in its border areas (*4,11*). There are no studies dealing with the reproducibility of the histological findings; there are only a few studies dealing with the description of the size of the protective rim of the excised tumour. The British Royal College of Pathologists (10) recommends description of the growth pattern in situations where it represents more than 50 % of the tumour or when the risky type is present in an invading part of the tumour or near the resection line of the tumour until such studies have been performed.

Histopathological classification should be well reproducible, should correspond to the clinical symptoms, biological behaviour of the tumour, and related therapeutic results.

The necessity to simplify histological classifications caused *Sexton* (*4*), who followed the previous work of *Sloan* (*11*), to set apart six histological types of BCC. Sexton's classification (*4*) defined the nodular, superficial, micronodular, infiltrative, sclerosing, and mixed types (*Table*). This classification, based mainly on evaluation of the growth pattern of the tumour, defines six histological types of BCC in accordance with the risk of the tumour and its biological behaviour. The risky histological group of the tumour is characterised by an increased probability of the subclinical spread of the tumour and the

higher probability of incomplete excision of the tumour, as well as locally aggressive invasive behaviour and more frequent recurrences of the tumour (*2,7,8,9,10,11*).

Sexton (*4*) includes the following among the risky types of BCC – the superficial, micronodular, infiltrative, non-sclerosing, and sclerosing types.

The risk potential of the superficial type of BCC, also referred to as the multicentric or multifocal type, is related to the subclinical spread of the tumour, its multifocality and the increased possibility of incomplete primary excision with a higher risk of local recurrence (*2,3,9,11,12,13,14*). The risk potential of infiltrative non-sclerosing and infiltrative sclerosing BCC is caused by the local invasive behaviour of irregular groups of tumour cells spreading in projections to the surrounding tissue (*5,7,8,9,11,12*). The risk of micronodular BCC is characterised by the increased tendency toward the subclinical spread of oval tumour islets, sized less than 0.15 mm (*2,9,12*).

The classification made by *Rippey* (*2*) is the most acceptable from the point of view of simplicity and good reproducibility. This classification further simplifies Sexton's classification (*4*), when the micronodular type is assigned to the nodular type and the sclerosing type to the infiltrative type.

Many authors report further histological types, calling into question the possibility of joining certain morphological features and their inclusion in one histological type.

During the histopathological description of BCC the classification, which defines the two risk groups of BCC and which uses the main and most frequent histological types, seems to be the most appropriate (*2*). The main classification should be performed on the basis of evaluation of the dominating growth pattern; the most risky should be selected in the case of several patterns present. The group with low risk includes, in accordance with most authors, the nodular type, the group with high risk includes the infiltrative and superficial types (*2,9, 11,12,13,15,16*). These basic histological types of BCC forming up to 90 % of all histological types are reported by all published studies and there is absolute agreement on these histological variations.

I. Nodular type (solid)

This histological type represents, according to various authors, 30 to 75 % of all BCC (*3, 4, 9, 14, 15, 19*). This wide range is influenced to a certain extent by the assignment or exclusion of similar growth types.

The nodular histological type (*Fig. 4*) consists of cell islets with a typical peripheral palisading of the cells and chaotic arrangement of the cells in the central region. It can achieve a cystic appearance in microscopy in the case of necrosis of centrally located cells, next to which an accumulation of mucin occurs. Sometimes the projections of the tumour cells produce a reticular formation. Some authors (*5,14*) set apart this cystic and adenoid pattern as special types, other authors (*2,3,4,11*) include these variants in the nodular variant due to the basic growth pattern. The fibroepithelial variant is also often included in the nodular type, in which cell nests interconnected with thin strands of cells are lost in the abundant stroma.

II. Superficial type (multicentric, multifocal)

This histological type, consisting of 10–15 % of BCC is most frequently described in younger age categories (*5*). It consists of frequent small islets of basaloid tumour cells (*Fig. 3*), well circumscribed against normal epithelia and in close contact but without apparent invasion; with papillary dermis. The nests are often surrounded by thin strands of fibrous stroma with lymphocyte infiltrate and thin-walled vessels. Multifocal development of this type is sometimes called into question by some authors since three-dimensional reconstruction studies have shown that the cell nests, no matter how distant they are from each other, are connected by tiny projections (*1,4,5*).

From this finding the authors conclude a single-centre development of this type of BCC; in spite of this the synonym multicentric is still being used for the superficial type (*1,2,3,5,11,12,13*).

III. Infiltrative type

This type, consisting of 10 % of all BCC, includes non-sclerosing (*Fig. 1*) and sclerosing (*Fig. 2*) histological variants with an infiltrating rather than expansible growth pattern, where long, thin strands of

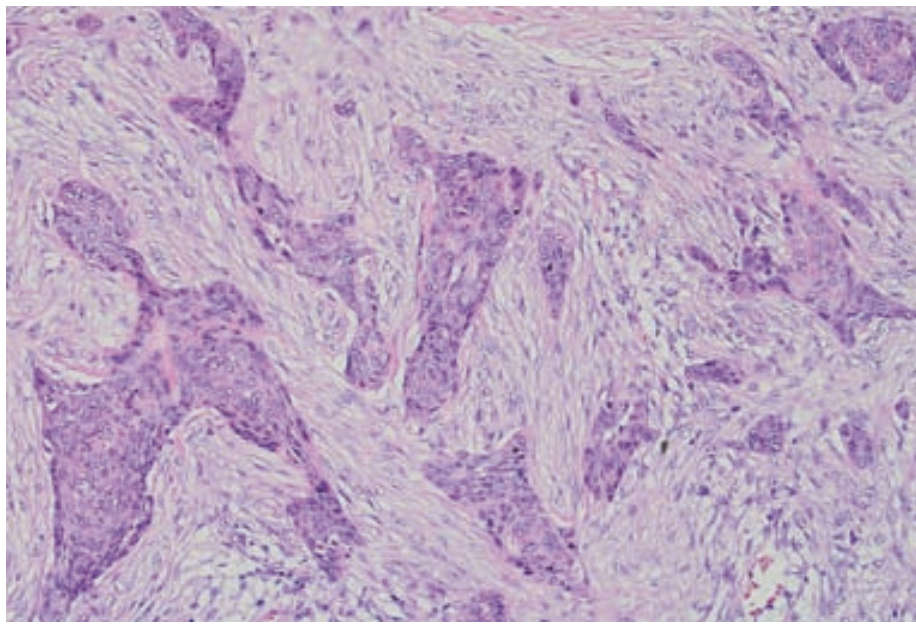

Fig. 1
Infiltrating non-sclerosing basal cell carcinoma (H&E, magnification x 200)

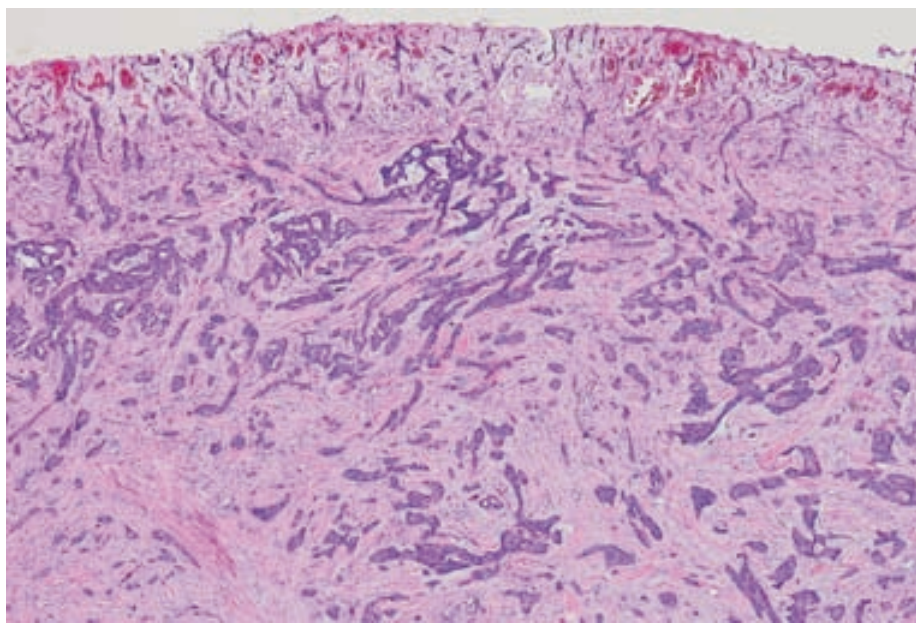

Fig. 2
Infiltrating sclerosing basal cell carcinoma (H&E, magnification x 20)

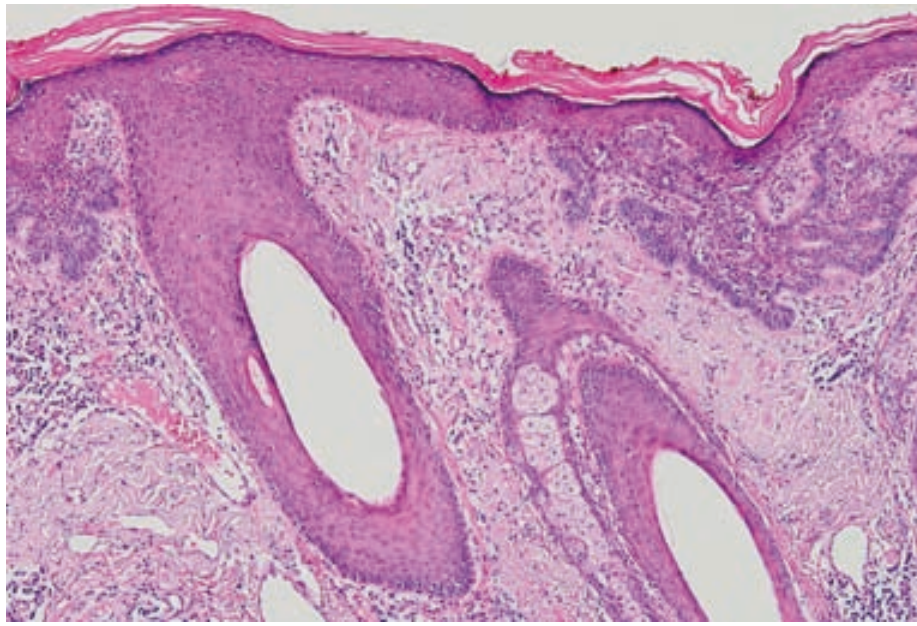

Fig. 3
Superficial basal cell carcinoma (H&E, magnification x 40)

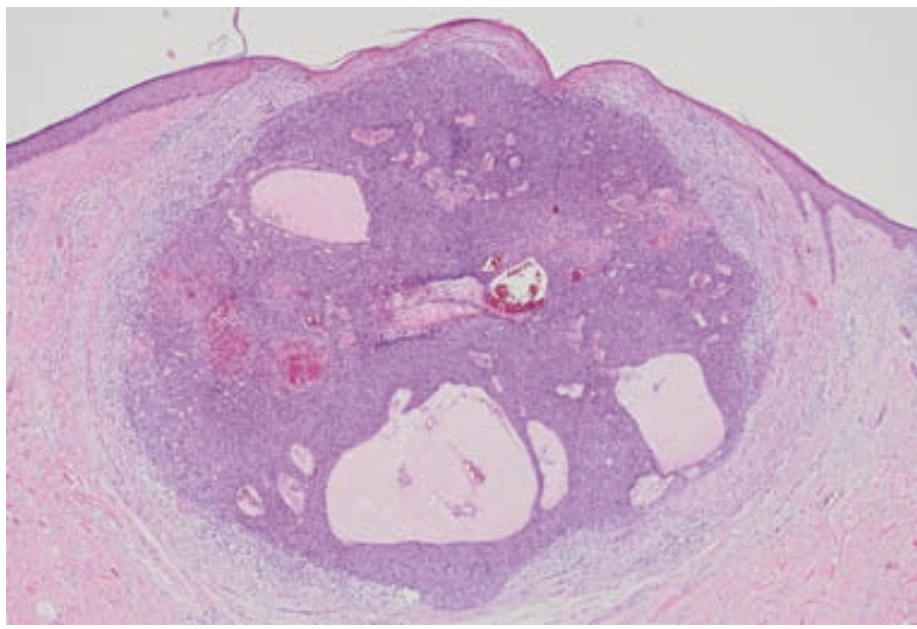

Fig. 4
Nodular basal cell carcinoma (H&E, magnification x 20)

tumour cells penetrate deeply among the collagen fascicles. The superficial layers of the tumour often have a solid growth pattern and the infiltrative type is present in the lower or peripheral layers of the tumour (*1,4,11*). If excision is not complete, this tumour can be included in the nodular type and the infiltrative type is detected only during re-excision.

The sclerosing (morpheic, fibrosing, cicatricial or desmoplastic) variant of infiltrative BCC is characteristic of an increased number of fibroblasts and the presence of fibrotic desmoplastic stroma, which gives the tumour a characteristic clinical picture of a morphea or keloid scar.

CONCLUSION

Histological diagnostics and classification of BCC are essential for the determination of the tumour type and its biological behaviour. There is no unique and generally accepted classification of BCC. BCC classification by most authors is based on the growth pattern of the tumour, which better reflects the biological behaviour of the tumour; less frequently on histological differentiation. Most authors agree that the group with low risk includes the nodular type and the group with high risk includes local recurrences, superficial and infiltrating types.

The request for simplicity and good reproducibility is best achieved by the Rippey classification, setting apart four histological variations based on the evaluation of the growth pattern, of which three histological types are basic and one type is mixed, consisting of a combination of several basic types. This classification enables the evaluation of the percentage of each histological type, age distribution, anatomic localisation, and malignant potential of the tumour.

Vantuchová Y., Čuřík R.

HISTOLOGICKÉ TYPY BAZOCELULÁRNÍHO KARCINOMU

S o u h r n

Histologická diagnostika a klasifikace bazocelulárních karcinomů (BCC) je zásadní pro vyhodnocení procentuálního zastoupení jednotlivých histologických typů, stanovení rizikovosti pro recidivu nemoci a porovnání léčebných výsledků. Neexistuje jednotná a všeobecně akceptovaná klasifikace BCC. Při klasifikaci BCC vychází většina autorů z růstového vzorce nádoru, který má větší výpovědní hodnotu pro biologické chování, méně často z diferenciace nádoru. Všechny publikované práce se shodují na stanovení tří základních typů BCC, typu nodulárního, superficiálního a infiltrujícího, které tvoří 80 až 90 % všech BCC. Ostatní typy BCC jsou různými autory definovány různě, různý je také počet uváděných typů BCC.

Informace o biologickém chování nádoru se zařazením typu BCC do rizikových skupin je pro klinika důležitá pro další léčebný plán a dispenzarizaci pacienta. Většina autorů se shoduje v tom, že do skupiny nízkého rizika patří typ nodulární a do skupiny s vysokým rizikem lokální recidivy typ infiltrující a superficiální.

REFERENCES

1. *Miller SJ, Moresi JM.* Actinic keratosis, basal cell carcinoma and squamous cell carcinoma. In: Bolognia JL, Jorizzo JL., Rapini RP, eds. Dermatology. London: Mosby, 2003: 1677–1696.
2. *Rippey JJ*. Why classify basal cell carcinomas? Histopathology 1998; 32: 393–398.
3. *LeBoit PE, Burg G, Weedon D, Sarasin A,* eds. World Health Organisation classification of tumors. Pathology and Genetics of Skin Tumors. Lyon: IARC Press, 2006: 10–33.
4. *Sexton M, Jones DB, Maloney ME*. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. J Am Acad Dermatol 1990; 23: 1118–1126.
5. *Weedon D, Strutton* G. *Skin pathology*. Edinburgh: Churchill Livingstone, 2002: 765–772.
6. *Wade TR, Ackerman AB*. The many faces of basal cell carcinoma. J Dermatol Surg Oncol 1978; 4: 23–28.
7. *Betti R, Inselvini E, Carducci M, et al.* Age and site prevalence of histologic subtypes of basal cell carcinomas. Int J Dermatol 1995; 34: 174–176.
8. *Boulinguez S, Grison-Tabone C, Lamant L, et al*. Histological evolution of recurrent basal cell carcinoma and therapeutic implications for incompletely excised lesions. Br J Dermatol 2004; 151: 623–626.
9. *Saldanha G, Fletcher A, Slater DN*. Basal cell carcinoma: a dermatopathological and molecular biological update. Br J Dermatol 2003; 148: 195–202.
10. *Slater DN, McKee PH*. Minimum dataset for the histopathological reporting of common skin cancers. London: The Royal College of Pathologists 2002: 1–22.
11. *Sloane JP.* The value of typing basal cell carcinomas in predicting recurrence after surgical excision. Br J Dermatol 1977; 96: 127–132.
12. *Lang PG Jr, Maize JC*. Histologic evolution of recurrent basal cell carcinomas and treatment implications. J Am Acad Dermatol 1986; 14: 186–196.
13. *Emett AJJ*. Surgical analysis and biological behaviour of 2277 basal cell carcinomas. Aust NZ J Surg 1990; 60: 855–63.
14. *Rosai J.* Rosai and Ackerman´s Surgical Pathology. Edinburgh: Mosby, 2004: 136–139.
15. *Breuninger H, Dietz K*. Prediction of subclinical tumor infiltration in basal cell carcinoma. J Dermatol Surg Oncol 1991; 17: 574–578.
16. *Scrivener Y, Grosshans E, Cribier B.* Variation of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol 2002; 147: 41–47.
17. *Kikushi A, Shimizu H, Nishikawa T.* Clinical and histopathological characteristics of basal cell carcinomas in Japanese patients. Arch Dermatol 1996; 132: 320–324.
18. *Patterson JW, Wick MR.* Nonmelanocytic tumors of the skin. In: Atlas of Tumor Pathology, Series 4, Fascicle 4. Washington DC: Armed Forces Institute of Pathology, 2006: 46–68.
19. *McCormack CJ, Kelly JW, Dorewitch AP*. Differences in age and body site distribution of histological subtypes of basal cell carcinoma. A possible indicator of different cause. Arch Dermatol 1997; 133: 593–596.