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ORIGINAL ARTICLE

Clinical factors predictive for histological aggressiveness of basal cell carcinoma: A prospective study of 2274 cases

Facteurs cliniques prédictifs de l'agressivité histologique : étude prospective de 2274 cas

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KEYWORDS
Basal cell carcinoma;
Dermatological surgery;

Summary
Introduction. — Since surgery is the first-line treatment for basal cell carcinomas (BCC), the histological aggressiveness of the disease must be clinically predicted in order to apply optimal safety margins that ensure a high rate of complete resection while minimising the risk of recurrence.

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Histological subtype;
Skin cancer;
Dermatopathology

Objectives. — To evaluate clinical predictive factors of histological aggressiveness of BCC, we conducted a national prospective multi-centre study.
Methods. — All consecutive patients presenting for BCC surgery were included, and standardised clinical data collected, and slides were submitted for review. Trabecular, micronodular and morpheaform BCCs were classified as aggressive.
Results. — Of the 2710 cases included, 2274 were histologically confirmed. Clinical subtyping was correct in 49.9% of superficial BCCs, 86.2% of nodular BCCs and only 22% of aggressive BCCs. By multivariate analysis, aggressive BCCs were more frequently ulcerated (45%), indurated (70%), showed adherence (8.6%), and were associated with high-risk anatomical zones (50.3%, $P < 0.0001$). These predictive clinical features may be helpful for decision making.

MOTS CLÉS
Carcinome basocellulaire ;
Chirurgie dermatologique ;
Sous-type histologique ;
Cancer cutané ;
Dermatopathologie

Résumé
Introduction. — La chirurgie est le traitement de première intention des carcinomes basocellulaires (CBC). Leur agressivité histologique doit être estimée cliniquement afin d'appliquer des marges de sécurité optimales permettant un taux élevé de résection complète et minimisant le risque de récidive.
Objectifs. — Cette étude prospective multicentrique nationale avait pour but d'évaluer les facteurs cliniques prédictifs de l'agressivité histologique des CBC.
Méthodes. — Tous les patients vus consécutivement pour une chirurgie d'une tumeur suspecte de CBC ont été inclus. Des données cliniques standardisées ont été recueillies et les lames ont été envoyées pour relecture centralisée après 1re lecture.
Résultats. — Les CBC trabéculaires, micronodulaires et sclérodermiformes ont été classés comme agressifs. Parmi les 2710 cas inclus, 2274 ont été confirmés histologiquement. Le sous-type clinique était concordant avec l'histologie dans 49,9 % des CBC superficiels, 86,2 % des CBC nodulaires et seulement 22 % des CBC agressifs. En analyse multivariée, les CBC agressifs étaient plus fréquemment ulcérés (45 %), indurés (70 %), présentaient une adhérence (8,6 %) et étaient localisés dans des zones anatomiques à risque élevé (50,3 %, $p < 0,0001$). De telles caractéristiques cliniques prédictives d'agressivité histologique peuvent être utiles pour la prise de décision chirurgicale.

Basal cell carcinoma (BCC) incidence continues to rise in many countries as the population ages [1,2]. The economic burden of BCC on health-care systems is high, mainly owing its high incidence, but also due to local aggressiveness and overall recurrence rates [3—5]. Clinical BCC subtypes are still classified using terms related to their histopathological aspect (superficial, nodular, trabecular, morpheaform) that reflect their prognosis, i.e. propensity to recur [6,7]. Among pathological subtypes, micronodular, infiltrative and morpheaform BCCs have higher recurrence rates and more frequent positive margins than nodular and superficial subtypes [8,9]. In addition, French, European and American guidelines include clinical criteria (size, location and recurrence) to help in decision-making [5,6,9,10].

In order to establish adequate margins for excision, clinicopathological evaluation is therefore critical. This means that in practice, dermatologists anticipate the histological subtype based on clinical examination. To date, no prospective large studies have evaluated the agreement between the clinical and histopathological features of BCCs. For this reason, we conducted a national, prospective study by examining the level of agreement between clinical subtyping and final histopathology result. The main objective was to determine whether any clinical features are associated with histological aggressiveness.

Patients and methods

Study design and ethics

This study was a prospective, cross-sectional, multi-centre study conducted in France between March and December 2015 in 38 centres by private and hospital-based dermatologists (41 investigators). We obtained approval from the ethics committee of the Bordeaux University Hospital (CPP DC 2014/106) and the CNIL (Commission nationale de l'informatique et des libertés, AR15818), the French national data protection agency. Informed written consent was obtained from all patients. A group of

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experts incorporating dermatologists, dermatopathologists and methodologists designed questionnaires detailing clinical and pathological data.

Inclusion criteria, clinical and histological data

Investigators were asked to include all consecutive patients who presented for BCC surgery. Inclusion criteria were as follows: aged 18 years or more; without any history of genodermatosis or BCC-predisposing condition; untreated, clinically suspected BCC (previous biopsy optional). Data were collected using a standardised questionnaire and comprised: year of birth; sex; previous biopsy; duration, location and diameter of lesion; clinically suspected subtype of BCC (superficial, nodular or morpheaform clinical subtype according to French and European guidelines [6,7]), ulceration, induration, adherence, well-defined borders or borders apparent only after palpation (stretching); type of surgery, lateral excision margins and depth of excision margins (both in millimetres). Surgery was performed according to the routine practice of each investigator.

After routine analysis by the local pathologist, all slides were sent to one of the three expert dermatopathologists (BC, BV and MB). The results from the clinical evaluation were compared to those of the final histopathological examination. The BCC subtype and pathological features were evaluated using a standardised form designed for the study and were blinded regarding both the clinical data and the first routine analysis. BCCs were classified into one of the following histopathological subtypes: superficial, nodular, micronodular, infiltrative trabecular or morpheaform, based on the predominant microscopic subtype. Micronodular, morpheaform and infiltrative trabecular subtypes were grouped together as ''aggressive subtypes''. The mean maximum thickness of BCC was measured from the upper stratum granulosum to the lowest malignant cells, as routinely performed when determining the Breslow index.

Statistical analysis

Descriptive characteristics by histological subtype of BCC (aggressive vs. non-aggressive) were first determined. Categorical variables were expressed as percentages with continuous variables given as means. Distribution was evaluated using the Shapiro—Wilk procedure. Next, all clinical variables considered as important were selected and analysed to identify factors associated with aggressive vs. non-aggressive BCC patterns. Groups were compared using univariate and multivariate unconditional logistic regression procedures. All potential predictors of aggressiveness were first assessed individually, and odds ratios (ORs), corresponding 95% CIs, and P values were computed. The OR significance was determined by Wald Chi^2 test or Fischer's exact test as appropriate and predictors with $P < 0.10$ were subsequently assessed using multivariate analysis with a forward stepwise selection procedure. Because of multiple testing and to avoid false positives, we applied a false discovery rate (FDR) and set the significance level at $P = 0.035$. In addition, we isolated BCCs considered as superficial by physicians and subsequently classified as aggressive patterns by the histologist. To compare the clinical features associated with one of these two groups (''misdiagnosed superficial BCC'' and ''true superficial BCCs''), we used a Chi^2 test or Fisher's exact test, as appropriate.

Results

Patients and histopathological features

Among the 2710 samples, BCC was confirmed in 2274 cases. The other cases consisted mainly of other tumors ($n = 242$) and absence of residual tumor after initial biopsy ($n = 91$) (Fig. 1).

The 2274 BCC occurred in 1126 males and 940 females, aged 24 to 103 years (mean age ± SD: 74 ± 12.6 years). Table 1 gives further details of the characteristics of BCCs according to initial clinical subtyping. A description of BCC histopathological subtypes is presented in supplementary material S1. An inflammatory infiltrate at the tumour infiltration edge was present in 50% ($n = 409$) of aggressive subtypes vs. 20.2% ($n = 290$) of superficial and nodular subtypes ($P < 0.0001$). Perineural involvement was present only in aggressive subtypes (4.8%, $n = 40$). The mean maximum thickness was 1.76 ± 1.03 mm (range 1—9.5). Median maximum thickness was significantly higher for aggressive subtypes than for nodular and superficial subtypes (2.01 vs. 1.59 mm; $P < 0.0001$).

Clinicopathological subtyping agreement

Clinicopathological subtyping agreement is detailed in Table 2. Final histological diagnosis was in accordance with clinical subtyping in 56.7% of cases. Clinical subtyping was correct in 49.9% of superficial BCCs, 86.2% of nodular BCCs and only 22% of aggressive BCCs. Among the 817 aggressive BCC, as assessed by final histopathological review, clinical subtyping was superficial in 5.5% ($n = 45$), nodular in 71.8% ($n = 587$) and morpheaform in 22% of cases ($n = 180$).

We analysed each clinical criterion by univariate and multivariate procedures according to histopathological subtypes, as detailed in Table 3. High-risk (HR) anatomical areas (facial periorificial areas) were significantly associated with aggressive BCCs: OR = 2.43 [95%CI: 1.77—3.32] ($P < 0.0001$). Supplementary materials (S2—S3) show the anatomical distribution of BCC subtypes.

Clinical criteria associated with histological aggressive subtypes

As shown in Table 3, aggressive BCCs were significantly more often ulcerated (45.3%), indurated (70.5%) and showed adherence (8.6%) vs. 17.4%, 48.1% and 2.2% respectively in the two other groups (superficial and nodular) taken together as the ''non-aggressive BCCs''. Poorly defined limits were observed in 36.9% of histological aggressive BCCs vs. 24.4% for nodular and superficial subtypes ($P < 0.0001$). Borders were well defined after palpation combined with pressure and stretching in 83.5% of the aggressive subtypes vs. 87.9% for nodular and superficial subtypes ($P = 0.003$). Multivariate analysis showed that ulceration (OR = 2.71; [95%CI: 2.13—3.44]), HR localization (OR = 2.42; [95%CI: 1.77—3.31]), induration (OR = 1.91; [95%CI: 1.51—2.40]) and

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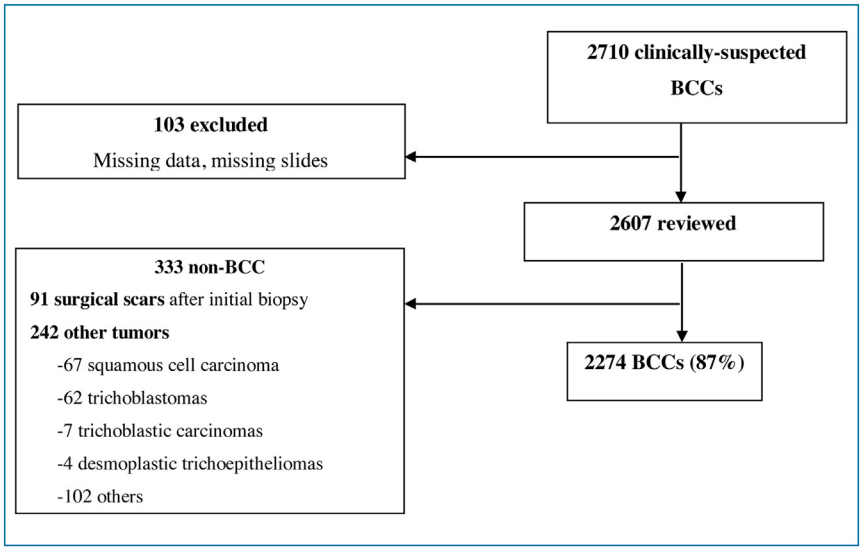

Figure 1. Flow-chart of the study.

Table 1 Characteristics of the clinical subtypes of 2274 basal cell carcinomas.

BCC[a] *n* = 2274	Superficial *n* = 286	Nodular *n* = 1694	Morpheaform *n* = 276
Previous biopsy	81 (28.3)	476 (28.1)	100 (36.2)
Duration (months)	18 ± 29 [1–360]	17 ± 19 [1–240]	18 ± 18.4 [1–126]
Largest diameter (mm)	12.4 ± 6 [2–37]	10.7 ± 6.2 [1–60]	14 ± 7.9 [3–50]
Smallest diameter (mm)	8.8 ± 4 [2–21]	8.3 ± 4.4 [1–40]	10.8 ± 6.1 [3–50]
Clinical ulceration	21 (7.3)	480 (28.3)	116 (42)
Induration	28 (10)	1013 (60)	229 (83)
Adherence	3 (1)	73 (4.3)	29 (10.5)
Well-defined borders	201 (70.2)	1313 (77.5)	91 (33)
Borders apparent only after palpation	243 (90)	1472 (86.9)	230 (83.3)
Type of surgery			
Standard excision[b]	285 (99.7)	1669 (98.5)	261 (94.6)
Surgical lateral margin[c] (mm)	3.6 ± 0.7 [1–5]	3.8 ± 0.8 [1–10]	4.3 ± 0.9 [2–12]
Deep plan of surgical excision			
Dermis	1 (0.3)	10 (0.6)	1 (0.4)
Subcutis	253 (88.5)	1189 (70.2)	148 (53.6)
Aponeurosis	26 (9.1)	382 (22.6)	66 (24)
Muscle	6 (2.1)	104 (0.6)	57 (20.7)
Cartilage	0 (0)	5 (0.3)	2 (0.7)
Fascia	0 (0)	1 (0.01)	1 (0.4)
Not specified	0 (0)	3 (0.2)	1 (0.4)

[a] 18 clinical subtypes were not determined; results are expressed as *n* (%) or mean ± SD [range].
[b] The other type of surgery was Mohs surgery.
[c] Surgical margins were only considered for standard excision.

adherence (OR = 2.51; [95%CI: 1.43–4.41]) were significantly associated with aggressive BCCs.

Clinical induration was correlated with level of invasion, i.e. the deeper the microscopic invasion, the higher the percentage of clinical induration (regression procedure: $P < 0.0001$). Thus, BCC was clinically indurated in 23.7% of cases where the papillary dermis was involved vs. 69.9% and 78.8% where the entire dermis and the entire subcutis respectively were involved.

Table 4 compares the 45 histologically aggressive BCC clinically diagnosed as superficial BCCs with adequately clinically subtyped BCC. Aggressive BCCs were more often

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Table 2 Clinicopathological agreement for BCC subtypes: comparison between final histological diagnosis and clinical suspicion.

BCC $n = 2274$[a]	Histopathological subtypes				
	Superficial $n = 347$	Nodular $n = 1087$	Aggressive $n = 817$		
			Trabecular $n = 765$	Micronodular $n = 36$	Morpheaform $n = 16$
Clinical subtype					
Superficial $n = 286$	173 (49.9%)	67 (6.2%)	43 (5.6%)	1 (2.8%)	1 (6.3%)
Nodular $n = 1694$	150 (43.2%)	937 (86.2%)	554 (72.4%)	29 (80.6%)	4 (25%)
Morpheaform $n = 276$	17 (4.9%)	77 (7.1%)	164 (21.4%)	5 (13.9%)	11 (68.8%)
Missing data	7	6	4	1	0

[a] The subtypes of the other 23 cases were Pinkus (9), basosquamous (6), and not determined (8). Results are expressed as *n* (%).

Table 3 Univariate and multivariate logistic procedures for patient characteristics according to BCC subtype (aggressive vs. non-aggressive).

Clinical features	Histopathological subtype[a]		Univariate analysis	Multivariate analysis	
	Non-aggressive $n = 1431$[b]	Aggressive $n = 817$	*P* value	Odds ratio [95%CI]	*P* value
Sex (male)	754 (54.6)	413 (54.4)	0.949		
Age (mean ± SD)	70.98 ± 12.6	73.58 ± 12.6	0.001		
Localisation[c]			< 0.0001	2.42 [1.77—3.31]	< 0.0001
High-risk	540 (37.9)	410 (50.3)			
Intermediate	413 (28.9)	268 (32.8)			
Low risk	473 (33.2)	138 (16.9)			
Size (larger diameter)	10.11	13.3	< 0.0001	0.95 [0.92—0.98]	0.002
Duration (months)	17.38	17.04	0.218		
Clinical ulceration	246 (17.4)	366 (45.3)	< 0.00001	2.71 [2.13—3.44]	< 0.0001
Induration	682 (48.1)	570 (70.5)	< 0.00001	1.91 [1.51—2.40]	< 0.0001
Adherence	32 (2.2)	70 (8.6)	< 0.0001	2.51 [1.43—4.41]	0.001
Well-defined borders	1071 (75.6)	512 (63.1)	< 0.0001	0.72 [0.57—0.92]	0.009
Borders apparent only after palpation combined with pressure and stretching	1243 (87.9)	678 (83.5)	0.003	0.66 [0.48—0.89]	0.007

Results are expressed as *n* (%).
[a] The subtypes of the other 23 cases were Pinkus (9), basosquamous (6), and not determined (8).
[b] Nodular BCC localised on perinea excluded.
[c] Low-risk area: trunk and limbs: intermediate-risk area: forehead, cheek, chin, scalp and neck; high-risk area: nose and periorificial, areas on the head and neck [6,7].

localized in intermediate and HR areas, and more often ulcerated and indurated.

Discussion

We report the initial results of the first multi centre, prospective, clinicopathological, large cohort study of BCCs analysing the level of concordance between clinical assessment and histopathological patterns. Clinical evaluation of subtyping is poor, especially in aggressive subtypes. This was also reported in the series by Christensen et al., where 7 of the 10 aggressive BCCs were misdiagnosed based on clinical evaluation only [11]. This attests the need to take into consideration clinical criteria such as location, size, borders and induration. Certain cases of nodular BCC, or even aggressive subtypes, may be relatively flat on the surface but extend downward. On the other hand, superficial BCC may present with surface changes or inflammation, resulting in overdiagnosis of nodular BCC [12]. Focusing on aggressive BCCs

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Table 4 Clinical factors associated with misdiagnosis of aggressive BCCs as clinically superficial in comparison with superficial BCCs adequately clinically subtyped.

	Final histological diagnosis		*P* value*
	Aggressive BCCS *n* = 45	Superficial BCCs *n* = 173	
Localisation[a]			< 0.0001
High-risk	10 (22)	14 (8)	
Intermediate	19 (42)	29 (17)	
Low-risk	16 (36)	130 (75)	
Clinical ulceration	8 (18)	6 (4)	0.002
Induration	11 (24)	11 (6)	0.001
Adherence	1 (2)	2 (1)	0.5
Well-defined borders	32 (71)	123 (71)	0.7
Borders apparent only after palpation combined with pressure and stretching	39 (87)	147 (85)	0.4

Results are expressed as *n* (%).
* Low-risk area: trunk and limbs; intermediate-risk area: forehead, cheek, chin, scalp and neck; high-risk area: nose and periorificial, areas on the head and neck [6,7].

misdiagnosed as superficial, we would emphasize that high and intermediate risk localisation, ulceration and induration are critical factors and that dermatologists should be very cautious when making a diagnosis of superficial BCC for the periorificial areas.

This was also demonstrated by multivariate analysis in the whole cohort, with induration, ulceration and adherence being a good indication of aggressive types. Moreover, clinical induration is correlated with maximum tumour thickness. Both morpheaform and infiltrative trabecular BCCs frequently presented an inflammatory infiltrate at the invasive tumour edge. This doubtelss contributes to clinical induration.

Christensen et al. found that the thickness of superficial BCCs was over-estimated by clinical evaluation, while that of nodular and aggressive BCCs was under-estimated [12]. Skin biopsy before surgical excision may therefore improve detection of BCC subtypes [13]. However, biopsy does not always correlate with histology on final excision [14,15].

Few studies have attempted to identify the factors influencing the depth of invasion of BCCs. Takenouchi et al. identified male sex, larger tumour diameter and histopathological subtypes (infiltrative, morpheaform and micronodular) related to depth of invasion [16]. Welsch et al. showed a significant correlation between histopathological subtypes and depth of invasion as micronodular and infiltrative BCCs tend to be deeper than nodular and superficial [17]. BCCs occurring on the middle of the face may invade deeply and have high recurrence rates [18]. However, Armstrong et al. did not find BCCs arising in embryologic fusion planes to be more invasive; the strongest factor affecting recurrence was the excision margin rather than the site, but the authors did not analyse the impact of histological subtype [19]. We found that the aggressive BCC subtype was significantly associated with localisation in an HR area.

In our study, we analysed the association of several clinical criteria with aggressive histological subtypes to facilitate clinical decision-making. Ulceration, induration and adherence were all highly associated with aggressive patterns and induration was correlated with the level of invasion. Visible borders, whether visible spontaneously or after stretching, and a larger diameter were significantly associated with non-aggressive BCCs.

The fact that the investigators of this study were trained expert oncodermatological surgeons may constitute a potential bias. This could have led to better clinical performance and over-representation of the aggressive subtype than in real-life BCCs, which might account for the fact only 15% of the BCC seen in this study were of the superficial subtype. However, the strength of our study resides in its use of a large cohort and a prospective method that included consecutive cases, together with two decisive strengths: inclusion by dermatologists, experts in surgery, thereby ensuring the homogeneity and quality of the data, and centralised pathological review.

Conclusion and implications

Although clinical diagnosis of BCC appeared very efficient overall, this was not the case for clinical BCC subtyping. We showed a significant association between the aggressive subtypes of BCC and HR facial areas, adherence, ulceration and induration. A significant correlation between clinical induration and level of invasion was demonstrated. Ongoing follow-up will try to better delineate the most relevant clinical features for risk of recurrence. We have thus provided data that will enable better clinical prediction of the potentially aggressive behaviour of BCC, hence facilitating decision-making.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.annder.2019.10.028.

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