ORIGINAL ARTICLE

Ultrasound as predictor of histologic subtypes linked to recurrence in basal cell carcinoma of the skin

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Abstract

Background Basal cell carcinoma (BCC) recurrences, especially in the facial region, represent a complex cosmetic problem. To date the possibility of predicting recurrence is supported solely by the histologic subtype.

Objective To evaluate the relationship between BCC histologic subtypes linked to high and low risk of recurrence and the presence of hyperechoic spots on sonography.

Methods Retrospective analysis of the pre-surgical ultrasound examinations of primary BCC tumours with visualization and counting of intra-tumoural hyperechoic spots. The data were then correlated with the corresponding histologic subtype.

Results Thirty one patients with histologically proven BCC were included in the study. Hyperechoic spots were detected in all cases and there was a positive, statistically significant association between hyperechoic spots count and high recurrence risk histologic subtypes. Higher hyperechoic spots count was found in the recurrence-prone micronodular, sclerosing variant and morpheiform BCC subtypes. Low risk and high risk of recurrence showed a significant difference on the mean hyperechoic spots count of 5.5 (range: 3–25) and 8 (4–81). A cut-off point ≥7 hyperechoic spots presented a sensitivity of 79% and specificity of 53% for predicting the high risk of recurrence subtypes.

Conclusion The presence and count of hyperechoic spots within BCC lesions may help predicting the high risk of recurrence histologic subtypes.

Received: 18 April 2014; Accepted: 25 June 2014

Conflicts of interest

None declared.

Funding sources

None.

Introduction

Non-melanoma skin cancer (NMSC) is not only the commonest cancer of white-skinned individuals, but its incidence has been increasing worldwide. Up to 90% of NMSC correspond to the low mortality basal cell carcinomas (BCC), a skin tumour that can be highly disfiguring through a predominant involvement of the face and neck in up to 85% of the patients.[1] Epidemiologic trends further suggest that both BCC incidence and morbidity may be increasing, while age of presentation may be decreasing.[2]

Tumour recurrence is another important morbidity factor in BCC, and it is estimated that its risk may be predicted from disease location, histologic type and extent of primary surgery. Thus, facial locations are associated with higher recurrence rates,

especially in areas where the skin is thin or 'H zone' such as the nose, eyelids, ears and lips.[3–5] As regards tumour histology, the risk is increased in the micronodular, sclerosing, infiltrating, morpheiform and metatypical BCCs subtypes; as well as in the presence of perineural invasion. In these settings the rate of recurrence can reach of up to 28%.[4–8] In contrast, tumours of the macronodular, superficial, adenoid cystic and Pinkus fibroepithelioma subtypes are considered less aggressive, with recurrence risks that do not exceed 6%.[4–7] Most BCC recurrences present within the first 3 years following primary surgical treatment, although 20% of recurrences may still appear as late as 6–10 years after tumour excision.[4] Lastly, when the surgical margins are positive for BCC, the rates of recurrence range from 15% to 67%, nevertheless, tumours with histologic free margins still connote a residual rate of up to 4%.[4,8,9]

Ultrasound is considered a first-line imaging technique for the evaluation of BCCs because of its high definition and penetration that provide sharply delineated images of the skin and deeper layers involvement.[10–13] There is, in fact, a high correlation between measurements of tumour depth by sonography and direct histologic assessment.[12]

Ultrasound studies on BCC have also identified tumoural hyperechoic spots (i.e. mini hyperechoic dots or lines) as a useful diagnostic imaging sign since, they have not been reported on sonographic imaging of the less common types of skin cancer such as squamous cell carcinoma and melanoma.[13] In our experience, these hyperechoic spots present diameters that range between 0.1 and 1.0 mm and usually do not present posterior acoustic shadowing. While the structure(s) or source(s) of hyperechoic spots is not yet clear, some of the postulated origins include calcifications, cornified cysts and/or cellular clusters undergoing parakeratosis, apoptosis or necrosis.[11,13] In the present work we evaluated the relationship between BCC histologic subtypes linked to low or high risk of recurrence and the sonographic presence and count of hyperechoic spots.

Material and methods

We reviewed our ultrasound data base for the period January 2007–December 2012, which consisted of a total of 18,334 ultrasound examinations of the skin. We then consecutively evaluated all the tests that had been performed pre-surgery in patients with histologic diagnosis of BCC (n = 373). The cases were further selected for inclusion if they were primary tumours (not recurrent cases), had been referred by a dermatologist, the surgery had been performed by the either of two dermatologists with extensive experience in oncologic surgery, and the biopsies had all been read by the same dermopathologist.

All sonographic examinations were performed by the same radiologist with extensive experience in ultrasound of the skin, and the ultrasound equipments were: the Logic E9 XD Clear (General Electric, Milwaukee, WI, USA) and HDI 5000 (Philips Medical Systems, Bothell, WA, USA) systems with probes of tunable, variable frequency of upper emission range 18 and 15 MHz respectively. The settings of the ultrasound machines were as follows: B-mode grey scale images, musculoskeletal superficial settings, gain 39, frame rate 23, Doppler frequency 12.5 MHz, wall filter low (112), pulse repetition frequency (PRF) 1.6. These settings are recorded in the machines therefore the operator does not need to change the settings from patient to patient.

A retrospective review of the BCC ultrasound cases was carried out. Hyperechoic spots detection and counting were performed on the ultrasound image that showed the tumour at its largest transverse diameter using a method already described for studying localized lesions of the skin (13). The technique for counting the hyperechoic spots followed four consecutive stages: detection, identification, segmentation and sum. Hence, at first stage, the tumour and its hyperechoic spots were detected; second, the borders of the lesion were identified and marked on a drawing (printed version of the image in high resolution), third the tumour was segmented in 3 to 15 regions according to the size and shape of the tumour for counting the spots. Lastly, the count went from right to left on the tumour (screen side) and the sum of all sections was considered as the final tumour count. The operator counted the most brilliant hyperechoic spots and leaved out of the analysis the mostly grey dots. (Fig. 1) Since the ultrasound examinations were performed before surgery, the radiologist did not know the histology of the tumour.

Haematoxylin-eosin stained histological samples obtained from the surgical specimens for determination of tumour type and subtype were analysed by the pathologist, who was blinded to the ultrasound report. The dermatopathologist also searched for, and classified categorically the presence of calcifications, cornified cysts and/or necrotic cysts, as present or absent. For this study, a high risk for BCC recurrence was assigned to the micronodular, sclerosing, morpheiform and metatypical histologic subtypes; conversely, a low risk of recurrence was assigned to the macronodular, superficial, adenoid cystic and fibroepithelioma of Pinkus subtypes. The study was approved by the Institutional Review Board at the place where the ultrasound examinations had been performed (Clinica Servet).

The histology report was considered the gold standard for the statistical analysis, which was descriptive for centrality and dispersion measures; the Fisher test was used for correlating qualitative variables (presence or absent); the Wilcoxon signed- rank and Kruskal–Wallis tests were applied for multiple comparisons. Factors presumed to be related to the presence of hyperechoic spots were tested with lineal bivariate and multivariate regression analyses; significance was assessed at $P < 0.05$ for linear bivariate analysis, and at $P = 20\%$ for multivariate analysis. When the variables were qualitative and present in more than one category, 'dummy variables' were generated. The software package used for the statistical analysis was the Stata V.12 with

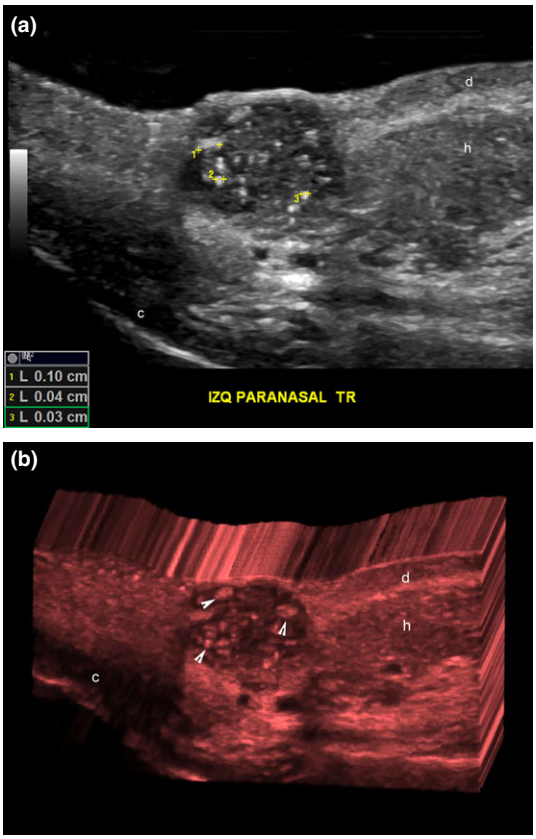

Figure 1 (a,b) Basal cell carcinoma ultrasound. (a): left nasal region (grey scale, transverse view) demonstrates multiple hyperechoic spots within the tumour (some marked and measured between 0.3 and 1.0 mm) and (b): left nasal region (transverse view, 3D reconstruction): multiple hyperechoic spots; some marked by arrowheads. c, nasal cartilage; d, dermis; h, hypodermis.

its subsequent updates (StataCorp. 2011. Stata: Release 12. StataCorp LP. College Station, TX, USA).

Results

The patient population meeting all the criteria for inclusion consisted of 31 patients of mean age 67 ± 14 years (range: 35–92), and 52% female. Of these, 94% (n = 29) of the lesions were located on the face (n: nasal=14; cheek=5; internal canthus=3, eyelid= 3, temple =2, frontal=1, upper lip=1), and the remaining 6% (n = 2) was located in the scalp (n = 1) and the leg (n = 1).

Hyperechoic spots within the lesions were detected in all lesions, (mean count ± SD = 13 ± 18; range = 3–81). Besides being determined by the presence of BCC, the hyperechoic spots count appeared to be related to the degree of malignancy, since it was significantly higher in lesions with histology of a high risk of recurrence subtype (mean: 8; range: 4–81), as compared with those associated with a low risk (mean: 5.5; range: 3–25); (Table 1, Figs. 1–3). Moreover, there was in fact a positive, statistically significant correlation (P = 0.023) between the hyperechoic spots presence and high recurrence risk BCC histologic subtypes.

Table 1 Hyperechoic spots on ultrasound and risk of recurrence in BCC

Histologic subtypes	Mean hyperechoic spots count (range)
Low risk of recurrence (n = 12)	5.5 (3–25)
High risk of recurrence (n = 19)	8 (4–81)*

*significant P value = 0.0178.

Other correlations, e.g. hyperechoic spots with patient gender and age were non-significant (P > 0.1) even after separation of the latter into four categories (≤68; 69–77; 78–86; ≥87 years).

On histology, the predominant subtypes were: macronodular 52% (n = 16); micronodular 26% (n = 8); morpheiform16% (n = 5); adenoid cystic 3% (n = 1) and sclerosing 3% (n = 1). Fifteen of the 31 lesions corresponded to a single subtype; whereas the remaining 16 lesions showed a mixed pattern of subtypes (15 comprising two subtypes, and one lesion with coexistence of three different subtypes). Of the 15 cases with a single histologic subtype, 67%(n = 10) had the macronodular variant; 13%(n = 2) had the micronodular form; 13% (n = 2) had the morpheiform subtype; and, 7% (n = 1) had the adenoid cystic histologic subtype.

When the histologic results were grouped into subtypes associated with high or low risk of recurrence, 18 of the 31 tumours (58%) showed at least one high-risk subtype. Of these 18 cases, four (22%) exhibited a high-risk variant as the only subtype, and another four cases (22%) had two or more high-risk subtypes coexisting in the same lesion. The last ten cases (56%) had a combination of high- and low-risk subtypes (mixed pattern).

Calcifications were detected in three cases (9.7%) and cornified cysts in 12 (39%) (Fig. 4); whereas areas of necrosis were seen in seven tumours (23%). The correlations between hyperechoic spots and either cornified cysts or necrosis statistical were not significant (P values= 0.2 and 0.5, respectively). While calcifications had an overall significant correlation with the presence of hyperechoic spots (P = 0.05), the same correlation restricted to the high risk of recurrence subtypes was non-significant (P = 0.62).

Overall, the micronodular subtype was associated with the largest number of hyperechoic spots (percentile 50 = 16), followed by the sclerosing (percentile 50 = 12), and morpheiform (percentile 50 = 7) BCC subtypes. The adenoid cystic subtype was associated with the lowest number of spots (percentile 50 = 5). Comparison of hyperechoic spots counts between the micro- and macronodular subtypes showed a significant difference (P < 0.01), with a higher number in the micronodular

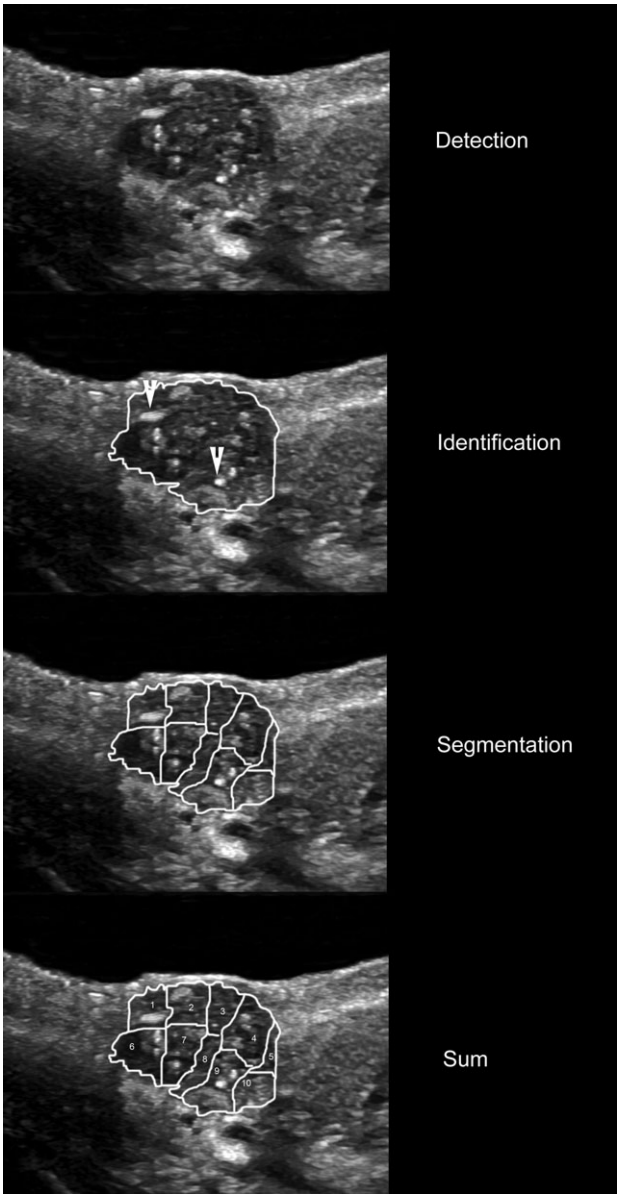

Figure 2 Ultrasound technique for counting the hyperechoic spots (composite image, transverse views) showing the four consecutive stages (detection, identification, segmentation and sum) from top to bottom as described in the text. In this case the final count of the tumour was 24 hyperechoic spots and the histology of the tumour demonstrated a micronodular subtype. Some hyperechoic spots are marked with arrowheads.

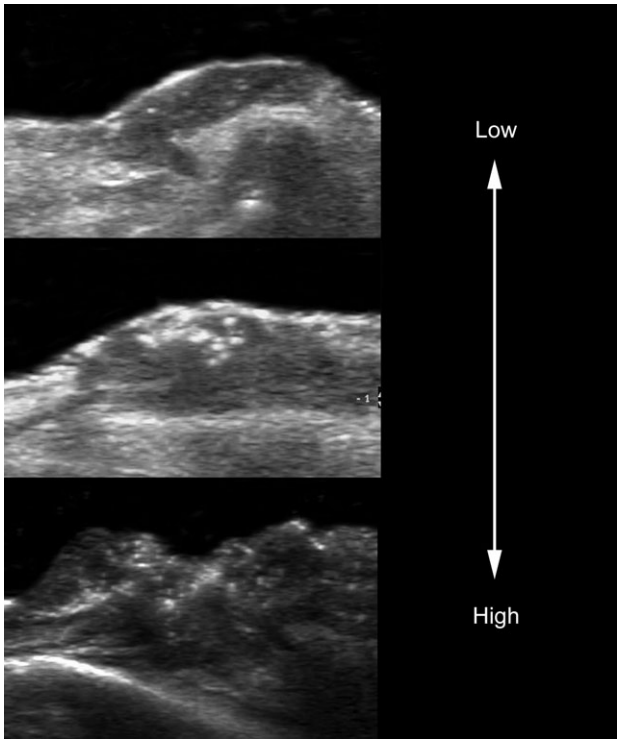

Figure 3 Basal cell carcinoma ultrasound (composite image, transverse views) with progressive increases in hyperechoic spots number of different BCC lesions. The cases correspond to (from top to bottom): macronodular, mixed micro and macronodular and mixed micronodular and morpheiform histologic subtypes, with respective hyperechoic spots counts of 5, 17 and 81 per lesion.

Table 2 Mean number of hyperechoic spots according to histologic subtype

Histologic subtype	Number of hyperechoic spots P50 (P25–P75)
AdenoidCystic	5 (5–5)
Sclerosing	12 (12–12)
Macronodular	6 (5–7.75)
Micronodular	16 (8–63.25)
Morpheiform	7 (5.5–9)

P, percentile.

group (Fig. 2, Table 2). In a multivariate model the presence of hyperechoic spots correlated significantly with the presence of the macronodular ($P = 0.013$) and morpheiform ($P = 0.003$) subtypes; and also, with the presence of calcifications ($P = 0.05$).

In a multivariate model the presence of hyperechoic spots correlated significantly with the presence of subtypes macronodular ($P = 0.013$), morpheiform ($P = 0.003$);and with the presence of calcifications ($P = 0.05$).

The hyperechoic spots also correlated positively and significantly with the presence of a mixed BCC histologic subtypes ($P = 0.007$). Overall, ultrasound-determined hyperechoic spots count had a level of exactness of 75% for discriminating pre-surgically low from high risk of recurrence subtypes (95% CI:57–93%). Optimal separation was observed with a cut-off point of ≥7 hyperechoic spots within the BCC lesions, with sensitivity of 79% and specificity of 53% (positive likelihood ratio 1.7, and negative likelihood ratio of 0.4; Fig. 5).

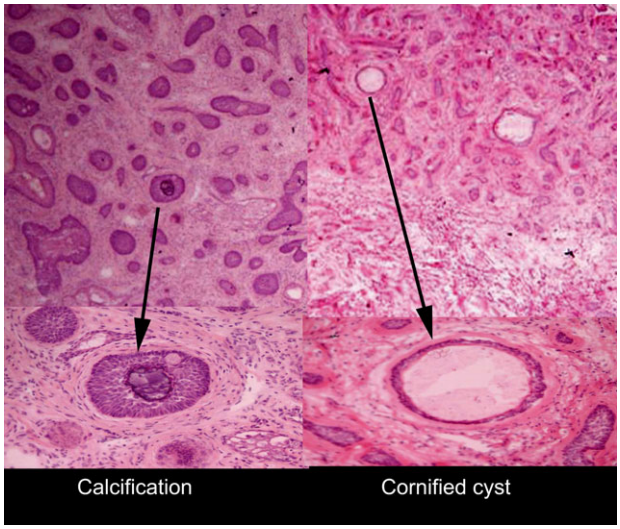

Figure 4 Basal cell carcinoma histology (H & E; magnification at top: × 4; magnification at bottom: × 20). On top left and right: small islets of tumoural BCC cells of mixed histologic subtype (micronodular and morpheiform). Bottom left: calcification within an islet of tumoural cells (arrow); bottom right: cornified cyst (arrow) within the lesion.

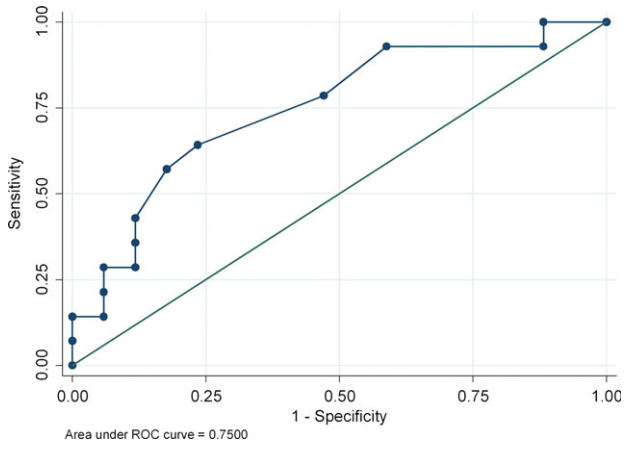

Figure 5 Basal cell carcinoma. Receiver operating characteristic curve (ROC) of BCC hyperechoic spots count on ultrasound at cut-off point ≥7 as discriminator of high recurrence risk subtype.

Discussion

In this large series of ultrasound examinations in histologically confirmed cases of BCC, we found that hyperechoic spots represent a robust sonographic sign highly suggestive, and likely pathognomonic of BCC. Moreover, the total number of hyperechoic spots also had predictive meaning, with elevated counts (≥7) supporting the possibility of a high recurrence risk histologic subtype.

It is important to note that the histologic features characteristic of a high-risk subtype lack clinical expression that would help decide the optimal therapy for lesions located predominantly in cosmetically important areas.[5–14] Thus, while the macro and micronodular subtypes present with similarly appearing lesions, the reported respective risks of recurrence are 6.4% and 18.6%.[4,14] In this regard the sonogram, by improving the prediction of potential BCC recurrence could help in the planning of a more customized surgical approach, including procedure type (standard or Mohs) and lesion-free margins size. Hence, the present work extends the usefulness of ultrasound beyond the description of BCC lesion anatomy and vascularity, to encompass prediction of high risk of recurrence histologic subtypes.[11,12,15–18]

The mechanism(s) for the generation of hyperechoic spots within BCC lesions is still unclear. We found that hyperechoic spots location do not exactly match the distribution of calcifications, cornified cysts or necrosis. In fact, calcifications were a rare event in this study, being detected in only three cases. Calcifications were found in the macronodular and morpheiform subtypes, but their low number makes the variable devoid of discriminatory power. Development of cornified cysts or necrosis was also sparse, leaving open a previously proposed possibility of multifactorial generation, i.e. a combination of abnormalities such as calcifications, cornified cysts or necrosis,[13] which also appears unlikely (Fig. 5).

As an alternative hypothesis, we postulate that hyperechoic spots could be due to increased acoustic transmission and the consequent hyperechoic posterior reinforcement artifact, which would develop by sound waves traversing extremely compact micronests of atypical hypercellular and hypermitotic basaloid cells or some other BCC-specific cytological signature that also calibrates the degree of malignancy. Of note, the presence of another hyperechoic artifact given by evident posterior acoustic reinforcement of anechoic or hypoechoic areas presumably due to tumour hypercellularity and not necrosis was previously described in melanoma nodal metastasis.[19] Regardless of mechanism(s) of production, it is apparent that hyperechoic spots represent an important by-product of the interaction between ultrasound waves and living cellular components, with potentially significant consequences for the management of BCC.

While a limitation of this work may appear to be the relatively low number of cases, it is also highly restrictive, while representing the first and largest series correlating BCC ultrasound images with histologic subtypes. Other limitation is that since this was a retrospective study and the tumours were surgically removed there was no possibility to assess the real percentage of recurrence according to histologic subtype. Moreover, the provision of the detailed anatomical data by the pre-surgical ultrasound study of the tumours, perhaps, per se may support a decrease of the recurrence rate, and in a

follow-up to date, all these cases are recurrence free. Most of our lesions (94%) were located on the face, which is a very critical location for cosmetic prognosis, however, further investigations should be performed to correlate the presence and count of hyperechoic spots with high risk of recurrence subtypes in different corporal locations. Other limitation would be the operator dependence for discriminating the hyperechoic spots, nevertheless, the selection of the brighter hyperechoic spots can make easier this process for a sonographer, and in our case this correlated well with histology. Lastly, while the capabilities of sonography are theoretically limited at < 0.1 mm for the detection of skin lesions, all the BCC tumours were ultrasound-detectable in this series.

Conclusion

Ultrasound examination of BCC tumours generates characteristic hyperechoic spots whose detection and total count measurement assist with the clinical characterization of the disease. Thus, the presence of the spots would not only confirm the diagnosis, but may also help in the prediction of high recurrence risk histologic subtypes. These findings enhance the value of ultrasound, as a powerful non-invasive imaging tool, in the management of dermatologic disorders.

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