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SHORT COMMUNICATION

Subtyping Basal Cell Carcinoma by Clinical Diagnosis Versus Punch Biopsy

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International guidelines on the diagnosis and treatment of basal cell carcinoma (BCC) recommend a punch biopsy in the majority of clinically suspected BCC prior to treatment. This is to confirm diagnosis and to identify the histological subtype (superficial, nodular, aggressive), which is necessary to know for optimal treatment selection (1, 2). A punch biopsy can detect the most aggressive subtype in 84–92% of cases, but has the disadvantages of discomfort for the patient and costs for the health care system (3–5). In contrast, clinical diagnosis is a painless, and possibly money-saving procedure (6). However, the difference in diagnostic accuracy of BCC subtyping between punch biopsy and clinical diagnosis has never been evaluated. This study compares the diagnostic accuracy of clinical assessment and histological diagnosis by punch biopsy for subtyping of BCC. Furthermore, we evaluated the impact of omitting the punch biopsy on treatment recommendations.

MATERIALS AND METHODS

Eligible patients attending the outpatient department of Dermatology of the Maastricht University Medical Centre (MUMC) and the Erasmus Medical Centre Rotterdam (Erasmus MC), the Netherlands, were included between August 2011 and August 2012. Included were patients aged ≥ 18 years with a clinically suspected primary BCC that was histologically confirmed on surgical excision specimen. Exclusion criteria were: genetic skin cancer syndromes and use of immunosuppressive drugs. All patients gave written informed consent for participation. The trial was approved by the Medical Ethics and Scientific Committee of the Maastricht University Medical Centre.

Clinical diagnosis of the most aggressive BCC subtype was made by one of the dermatologists specialized in oncology (3 at MUMC, 2 at Erasmus MC), based on the criteria of Crowson (7). A distinction was made between superficial, nodular and aggressive BCC. Subsequently, a 3-mm punch biopsy was obtained from the clinically most aggressive tumour area. Superficial and nodular BCC were surgically excised with a 3-mm margin, aggressive BCC with a 5-mm margin. Incompletely excised BCC were re-excised and Mohs' micrographic surgery was performed in facial high-risk BCC (8).

All biopsy and excision specimens were haematoxylin and eosin stained. Biopsies were (partially) cut in serial sections of 150 µm. Four serial sections of 4–5 consecutive slices were made. Excision specimens were cut at 2 mm, completely imbedded and one slice per section was made. Histopathological slides were evaluated by 2 dermatopathologists, who were unaware of the diagnosis of the other pathologist and blinded to the clinical diagnosis. The most aggressive BCC subtype was recorded following histological criteria (7, 9). Aggressive BCC comprised infiltrative/morpheaform, micronodular and basosquamous BCC.

This study focused on the ability to discriminate clinically and histologically (by punch biopsy) between: (*i*) superficial BCC vs. nodular/aggressive BCC and; (*ii*) aggressive vs. nodular BCC. These distinctions were considered most relevant for optimal treatment selection, as superficial BCC can be treated non-invasively and aggressive BCC require a larger surgical margin than nodular BCC (10). The primary outcomes were sensitivity and specificity of clinical assessment and histological diagnosis by punch biopsy. The gold standard for BCC subtyping was the histological subtype on subsequent surgical excision. False-positive and false-negative results have an impact on treatment recommendations. False-positive results are associated with overstaging: clinical diagnosis or punch biopsy classified a BCC as more aggressive than the histological diagnosis on subsequent surgical excision. False-negative results are associated with understaging: clinical diagnosis or punch biopsy classified a BCC as less aggressive than the gold standard.

Diagnostic values with corresponding 95% confidence intervals were calculated for discrimination between (*i*) and (*ii*). Differences in proportions were tested using the McNemar test for paired proportions. p-values ≤ 0.05 were considered to indicate statistical significance. Statistical analyses were performed with SPSS-PC version 20.0 (SPSS, Chicago, IL, USA).

RESULTS

Biopsies were performed in 285 clinically suspected primary BCC. A total of 191 BCC were histologically confirmed, 152 of which where in the 116 patients who agreed to participate (64 men, 52 women). Mean age was 68 years (range 33–92 years). Prevalence of superficial, nodular and aggressive BCC on surgical excision were: 16.4%, 52.0% and 31.6%, respectively (Table SI[1]).

Table I shows the diagnostic parameters for discrimination between superficial vs. nodular/aggressive BCC. Sensitivity to detect nodular/aggressive BCC was similar for clinical diagnosis and punch biopsy (89.0% vs. 92.1%, $p = 0.38$), but punch biopsy was more specific than clinical diagnosis (88.0% vs. 64.0%, $p = 0.11$); i.e. the percentage of superficial BCC that was falsely diagnosed as nodular/aggressive decreased from 36% to 12%. Thus, omitting a punch biopsy would have resulted in overstaging in an extra 24% of superficial BCC.

Punch biopsy is more sensitive ($p = 0.002$) and more specific ($p = 0.29$) for discrimination between aggressive

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Table I. *Diagnostic parameters of clinical diagnosis and histological diagnosis by punch biopsy for detection of the most aggressive histological basal cell carcinoma (BCC) subtype on surgical excision*

	Sensitivity *n* (%) [95% CI]	Specificity *n* (%) [95% CI]	PPV *n* (%) [95% CI]	NPV *n* (%) [95% CI]	OR [95% CI]
Superficial vs. nodular/aggressive BCC					
Clinical diagnosis	89.0 (113/127) [0.85–0.92]	64.0 (16/25) [0.45–0.79]	92.6 (113/122) [0.89–0.96]	53.3 (16/30) [0.38–0.66]	14.4 [4.8–43.8]
Punch biopsy	92.1 (117/127) [0.89–0.94]	88.0 (22/25) [0.71–0.97]	97.5 (117/120) [0.94–0.99]	68.8 (22/32) [0.56–0.76]	85.8 [19.4–442.3]
Aggressive vs. nodular BCC					
Clinical diagnosis	56.3 (27/48) [0.45–0.67]	77.2 (61/79) [0.70–0.84]	60.0 (27/45) [0.47–0.71]	74.4 (61/82) [0.68–0.81]	4.4 [1.9–10.12]
Punch biopsy	85.4 (41/48) [0.75–0.93]	84.8 (67/79) [0.78–0.89]	77.4 (41/53) [0.68–0.84]	90.5 (67/74) [0.84–0.95]	32.7 [10.8–103.9]

PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval; OR: odds ratio.

and nodular BCC (Table I) than clinical diagnosis. The proportion of aggressive BCC that was understaged as nodular or superficial was 43.8% (21/48) after clinical diagnosis and 14.6% (7/48) after punch biopsy. Thus, omission of a punch biopsy would have resulted in understaging of aggressive BCC in an extra 29.2% of cases.

We repeated the analyses with restriction to BCC on the trunk and extremities. These analyses showed similar results.

DISCUSSION

These findings indicate that a punch biopsy is a better diagnostic tool than clinical diagnosis for detection of histological BCC subtype, i.e. essentially in line with current international guidelines (1, 2). However, some argue that omitting a biopsy might be acceptable or preferred in some cases (1, 2, 6). We show that, when a punch biopsy is omitted, there is a risk of overstaging superficial BCC as more aggressive in an extra 24% of cases. In such a case, the physician will probably advise surgical excision and deny the patient the choice of less invasive alternatives (photodynamic therapy, imiquimod or 5-fluorouracil). Superficial BCC comprises approximately 30% of the total BCC population (11). Thus, if treatment is based on clinical diagnosis, only a small minority (7%) of all patients with BCC would receive a more invasive therapy than is strictly required.

Another consequence of omitting a punch biopsy is a significantly increased risk of understaging an aggressive BCC as nodular BCC in approximately a quarter of cases. These patients run the risk of having their tumour excised with too small margins, resulting in a re-excision or recurrence (12).

Considering these findings, it may be justified that physicians choose to omit the punch biopsy if they have a high level of confidence in their diagnosis on the subtype of BCC, especially when using a dermascope (13). Histological confirmation by punch biopsy might then be reserved for diagnoses that are made with less confidence and also for BCC in the head/neck region because recurrences in this area are not retreated that easily and can cause great morbidity. Nevertheless, the consequences of omitting a punch biopsy need to be discussed with the patient.

A limitation of the study is that patients with superficial BCC who preferred non-invasive therapies did not participate. For this reason, the absolute estimates of sensitivity and specificity (for both clinical diagnosis and punch biopsy) may be subject to verification bias, which results in overestimation of sensitivity and underestimation of specificity (14). Secondly, some results lack statistical significance, probably due to the relatively small number of superficial BCC in this study. Thirdly, the level of confidence in the clinical diagnosis of BCC subtype was not recorded and, therefore, it was not possible to evaluate the level of over- and understaging in case of highly confident diagnoses.

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