Reflectance confocal microscopy confirms residual basal cell carcinoma on clinically negative biopsy sites before Mohs micrographic surgery: A prospective study

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Background: Biopsy specimens from patients with basal cell carcinoma (BCC) can present to surgery with no clinically residual tumor, complicating treatment decisions.

Objective: To evaluate reflectance confocal microscopy (RCM) for the assessment of residual BCC following biopsy.

Methods: Consecutive patients with biopsy-proven BCC and no clinical evidence of residual tumor who had been referred for Mohs micrographic surgery were included. Biopsy sites were imaged with a handheld RCM device. On the basis of RCM evaluation, cases were labeled RCM positive or RCM negative. Mohs micrographic surgery was performed in all cases; margins and 15-μm serial vertical sectioning were evaluated.

Results: A total of 61 patients were included (mean age, 61.7 years [standard deviation, 12.2 years]; range, 37-87 years); 60.7% were women. The mean lesion size was 5.1 mm (range, 3-12 mm); 73.8% of patients were positive on RCM, and 68.9% had residual BCC on histopathologic examination. The rates of RCM sensitivity, specificity, positive predictive value, and negative predictive value were 92.8%, 68.4%, 86.6%, and 81.2%, respectively. Three cases of BCC (high-risk, infiltrative, and basosquamous) were missed with use of RCM. When high-risk subtypes were excluded (n = 5), sensitivity and negative predictive value were both 100%.

Limitations: RCM can miss deep-seated residual tumor.

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Conclusion: RCM is a valuable tool for the evaluation of residual BCC following biopsy, with the potential to reduce unnecessary surgical procedures. (J Am Acad Dermatol 2019;81:417-26.)

Key words: basal cell carcinoma; biopsy; dermoscopy; Mohs micrographic surgery; reflectance confocal microscopy; residual; surgery.

Treatment of basal cell carcinoma (BCC) is usually guided by biopsy to confirm the diagnosis and determine histopathologic subtype.[1] After biopsy, patients may present to surgery with an inconspicuous scar and no clinical evidence of residual tumor, creating a dilemma as to whether there is a need for further operative management on account of the presence of residual BCC. In a previous study, of patients on whom a biopsy was performed and who appeared to be clinically disease-free, 67% had BCC identified in excised tissue.[2] Studies have also demonstrated poor accuracy of naked-eye examination for evaluation of persistence of skin cancer before surgery.[3] Improved identification of patients who are truly free of residual tumor following biopsy may decrease unnecessary invasive procedures and deliver cosmetic, functional, time, and economic benefits.

CAPSULE SUMMARY

- Of the basal cell carcinoma biopsy sites that appeared to be free of tumor clinically, 69% contained residual tumor on histopathologic analysis.
- Reflectance confocal microscopy may improve triage of patients with clinically negative biopsy sites, allowing selection of patients who should undergo surgery and those who can undergo observation only.

Reflectance confocal microscopy (RCM) is a noninvasive technique that allows for in vivo visualization of the skin with quasi-histologic resolution.[4] RCM has shown excellent sensitivity and specificity for diagnosing BCC.[5-7] However, its use on biopsy specimens of lesions has been evaluated only preliminarily, and no studies have focused on cases with no clinical evidence of disease.[8,9] The diagnostic accuracy of RCM on biopsy specimens of lesions has not been estimated, as it may be potentially affected by tissue scarring. In the present study we sought to assess the role of RCM in the evaluation of residual BCC tumors after biopsy and before Mohs micrographic surgery in patients with no clinical evidence of disease. As a secondary objective, we sought to evaluate the dermoscopic features present in this subgroup of lesions.

PATIENTS AND METHODS

This was a prospective case series comprising consecutive patients referred for Mohs micrographic surgery in the Dermatology Service at Memorial Sloan Kettering Cancer Center between October 2017 and September 2018. The institutional review board at Memorial Sloan Kettering Cancer Center approved the study (No. 99-099), and all patients gave written informed consent before imaging. All patients met the criteria for and underwent Mohs micrographic surgery in accordance with National Comprehensive Cancer Network guidelines.[1] RCM findings did not alter clinical management.

Inclusion criteria and exclusion criteria

Adult patients (age, ≥18 years) with a biopsy-proven BCC and no clinical evidence of residual tumor at the biopsy site when evaluated with naked-eye examination were included. We excluded patients with either clinically or dermoscopically persistent BCC, a biopsy site that had not healed (ie, presence of ulceration/erosion), and an anatomic location that precluded complete RCM evaluation (eg, nasal crease).

Clinical features

Demographic characteristics (age, sex) were recorded. Tumor characteristics (BCC predominant subtype and margin status, if available) were collected from the biopsy report. Location, size, biopsy site, and time from biopsy to RCM evaluation were also recorded. All biopsy specimens were evaluated by an expert dermatopathologist who confirmed the diagnosis and subtype of BCC.

Dermoscopic analysis

Clinical and dermoscopic images were taken with a digital camera coupled with a digital dermatoscope (VEOS DS3, Canfield Scientific, Parsippany, NJ). Dermoscopic images were retrospectively analyzed for consensus by 2 dermatologists (C.N-D. and A.A.M.) who were blinded to the final residual disease status. Images were analyzed for BCC dermoscopic criteria as previously described.[10,11]

Abbreviations used:

BCC: basal cell carcinoma
CI: confidence interval
RCM: reflectance confocal microscopy
SD: standard deviation

In addition, other dermoscopic criteria were evaluated as per the latest dermoscopic consensus[12] and for "porcelain white scars," which are defined as the presence of an homogeneous white pattern in an area on which a biopsy was previously performed. Finally, images were categorized by the investigators as positive for residual BCC versus negative for residual BCC on the basis of the aforementioned dermoscopic criteria.

RCM imaging technique and analysis

All biopsy sites were imaged with a handheld RCM device (Vivascope 3000, CaliberID, Rochester, NY) with the aid of paper rims as previously described.[13,14] RCM evaluations were performed in a systematic fashion: first, the center of the lesion was interrogated and then the lesion was circumferentially scouted with the probe at different levels to evaluate the extent of the lesion. Single images and image stacks of the most relevant features were taken. After RCM evaluation, findings were recorded in an Excel database (Microsoft Corporation, Redmond, WA) in real time by 2 investigators (C.N-D and M.C.). If BCC criteria were seen at any time during RCM evaluation of the biopsy sites, the case was labeled as RCM positive; if no BCC criteria were found under RCM evaluation, the case was labeled as RCM negative. The criteria used for the diagnosis of BCC were previously described.[15,16] In addition, on the basis of our experience, we included a new feature commonly observed under RCM on biopsy tissue termed *trapped epidermis*. This feature comprises well-defined hyper-reflective nodules composed of normal keratinocytes only, without palisading and clefting, which differentiates them from BCC nodules. Trapped epidermis is usually confounded with BCC tumor nodules on RCM examination of biopsy tissue.

Mohs tissue processing

Mohs micrographic surgery was performed as standard and was not modified by RCM findings. The first layer was taken with 1- to 2-mm margins, and the tissue samples were sent for Mohs sectioning (frozen section, hematoxylin-eosin staining). If residual BCC was found on Mohs layer margins, the case was labeled as frozen section—positive for residual BCC. If no BCC was observed on the first Mohs layer, 15-μm serial vertical sectioning was performed until the tissue was exhausted. If residual BCC was observed in any of the vertical sections, the case was also labeled as frozen section—positive. If the results of the margin analysis and serial sectioning were all negative, the case was labeled frozen section—negative.

Table I. Demographics and tumor characteristics.

Variable		*P* value
Age, years (mean [SD])	61.7 (12.2)	.97
Female (%)	37 (60.7%)	.25
Mean size (cm; mean size [SD])	5.1 (1.8)	.60
Time from biopsy to Mohs surgery (months)	1.7 (1.18)	**.07**
Location (n, %):		
Nose	21 (34%)	.40
Cheek	11 (18%)	
Forehead	7 (11.5%)	
Scalp	5 (8.2%)	
Periocular	4 (6.6%)	
Perioral	4 (6.6%)	
Lower extremity	3 (4.9%)	
Upper extremity	2 (3.3%)	
Trunk	2 (3.3%)	
Neck	1 (1.6%)	
Abdomen	1 (1.6%)	
Tumor subtype on biopsy (n, %):		
Nodular	22 (36.1%)	.75
Surface of a BCC	13 (21.3%)	
Superficial	10 (16.4%)	
Mixed BCC subtypes on histopathology	10 (16.4%)	
Basosquamous	3 (4.9%)	
Infiltrative	2 (3.3%)	
Nodulocystic	1 (1.6%)	

Boldface indicates statistical significance.
BCC, Basal cell carcinoma*; SD,* standard deviation.

Statistical analysis

Descriptive statistics, including means, medians, range, standard deviation (SD), and relative frequencies, were used to describe the study participants, the characteristics of the procedures, and the RCM and dermoscopic characteristics. The primary outcome variable was presence or absence of residual BCC observed on RCM evaluation and coded as a dichotomous variable. The distributions of study variables were assessed by residual BCC by using relative frequencies and chi-square statistics. The magnitude of the association was estimated by odds ratios and 95% confidence intervals (CIs). Measures of diagnostic accuracy along with exact 95% binomial CIs for overall RCM classification and

Table II. Dermoscopic and reflectance confocal microscopy characteristics

Characteristic	Frozen-section positive (N = 42)	Frozen-section negative (N = 19)	Total N (%)	*P* value
Dermoscopic features*				
Shiny white blotches and strands	15 (41.7%)	9 (52.9%)	24 (45.3%)	.55
Arborizing telangiectasia	7 (19.4%)	4 (23.5%)	11 (20.8%)	.73
Serpentine vessels	7 (19.4%)	2 (11.8%)	9 (17.0%)	.70
Porcelain white color	3 (8.3%)	4 (23.5%)	7 (13.2%)	.19
Scale	1 (2.8%)	3 (17.6%)	4 (7.6%)	.10
Polymorphous vessels	3 (8.3%)	1 (5.9%)	4 (7.6%)	1.0
Ecchymosis	2 (11.8%)	2 (5.6%)	4 (7.6%)	.58
Dotted vessels	3 (8.3%)	0 (0%)	3 (5.7%)	.54
Rainbow color	0 (0%)	1 (5.9%)	2 (3.8%)	.3
Shiny white lines	0 (0%)	1 (5.9%)	1 (1.9%)	.3
Reflectance confocal microscopy features†				
Horizontal vessels	37 (88.1%)	13 (68.4%)	50 (81.9%)	.081
Tumor nests	36 (85.7%)	6 (31.6%)	42 (68.9%)	**<.001**
Palisading	37 (88.1%)	4 (21.1%)	41 (67.2%)	**<.001**
Clefting	35 (83.3%)	5 (26.3%)	40 (65.6%)	**<.001**
Streaming	23 (54.8%)	7 (36.8%)	30 (49.2%)	.27
Bundled collagen	17 (40.5%)	5 (26.3%)	22 (36.1%)	.32
Cord-like structures	16 (38.1%)	2 (10.5%)	18 (29.5%)	**.036**
Trapped epidermis	8 (19%)	4 (21.1%)	12 (19.7%)	1.0
Dark silhouettes	10 (24.4%)	1 (5.3%)	11 (18.6%)	.14
Epidermal dendritic cells	3 (7.1%)	2 (10.5%)	5 (8.2%)	.64
Plump cells	2 (4.8%)	2 (10.5%)	4 (6.7%)	.62
Intratumoral dendritic cells	1 (2.4%)	0 (0%)	1 (1.7%)	1.0

Boldface indicates statistical significance.
*Data based on 53 patients with dermoscopic images available. Data do not add up to 100% because more than one feature was possible per patient.
†Data based on 61 patients. Data do not add up to 100% because more than one feature was possible per patient.

individual RCM features were estimated. The α level was 5% for all evaluations, and all tests were 2 sided. Analyses were performed by using Stata software (version 14.2, Stata Corporation, College Station, TX).

RESULTS

A total of 80 consecutive patients met the inclusion criteria; 19 were excluded (no surgery performed [n = 8]; the whole area could not be imaged [n = 4]; the patient opted for radiotherapy [n = 3]; residual BCC was clinically evident on consensus [n = 2]; and no serial sectioning was performed after Mohs layers [n = 2]). A total of 61 cases were included in the final analysis; the patients' mean age was 61.7 (SD, 12.2; range, 37-87 years); 60.7% were females. Most lesions were located on the head and neck (86.9%). All biopsies were performed by the shave technique, with diagnostic intention. The pathology reports included comments on biopsy margins status in 43 of 61 cases (70.5%); of these, 40 of 43 (93.02%) had margins involved. The mean size (healed biopsy site) was 5.1 mm (SD, 1.8; range, 3-12 mm). The mean time from diagnosis to Mohs micrographic surgery was 1.7 months (SD, 1.18; range, 0.7-7 months) (Tables I and II).

Clinical and demographic factors associated with positive status on histopathology

Residual BCC (frozen section—positive) was observed on histopathologic analysis in 42 of 61 cases (68.9%); BCC was identified in the first Mohs layer in 32 of these 61 cases (52.5%) and in vertical sectioning slides in 10 of the 61 (16.3%). No association was observed between residual tumor and age, sex, head and neck location, and margin status on biopsy (P = .97, .25, .24, and .29, respectively). Presence of residual tumor showed a statistical trend for association with time between initial biopsy and definitive treatment (1.5 months for frozen section—positive vs 2.3 months for frozen section—negative [P = .07]).

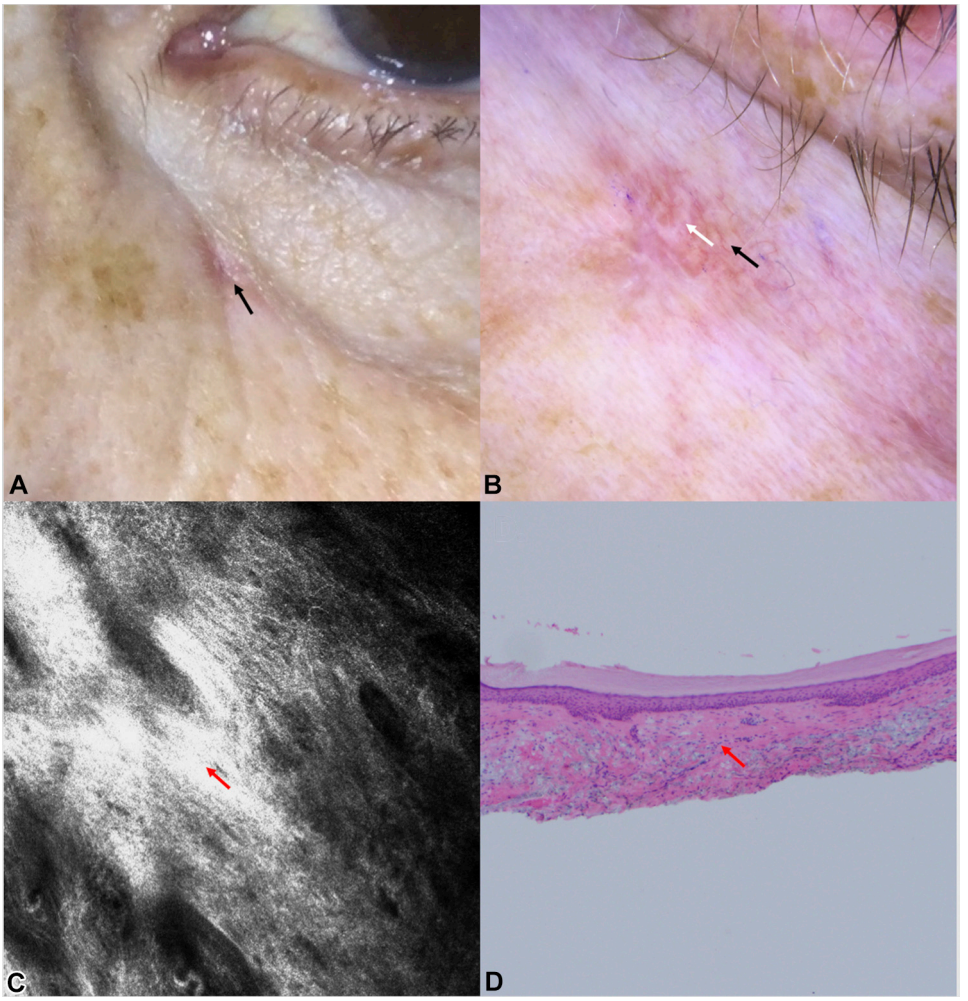

Fig 1. Nodular basal cell carcinoma on an H-site area with no histopathologic evidence of residual tumor. **A**, Clinical appearance of the biopsy site; no residual tumor is seen. **B**, Dermoscopic features showing serpentine vessels (*black arrow*) and shiny white blotches and strands (*white arrow*). **C**, Reflectance confocal microscopy image showing a scar with thickened collagen (*red arrow*) (750 × 750 μm). **D**, Serial sectioning of the Mohs debulking showing scar tissue (*red arrow*). The first Mohs layers were also negative in this case (not shown). (**B**, Polarized light dermoscopy; **D**, hematoxylin-eosin stain; original magnifications: **B** and **D**, ×10.)

Dermoscopic features

Dermoscopic images of biopsy sites were available for 53 cases; 26 of the 53 (49.1%) were classified as positive for residual BCC under dermoscopy. There was no agreement between the dermoscopic evaluation and the final histopathologic analysis; hence, no dermoscopic predictors were associated with the presence or absence of residual BCC in univariate analysis (Figs 1-3 and Table II). The sensitivity of dermoscopy was 58.3% (95% CI, 40.7%-74.5%), the specificity was 70.6% (95% CI, 44.04%-89.7%), the positive predictive value was 80.7% (95% CI, 65.7%-90.2%), and the negative predictive value was 44.4% (95% CI, 32.8%-56.7%).

RCM findings

Features suggestive of residual BCC were observed on RCM in 45 of 61 cases (73.8%). There was agreement between RCM positivity and final histopathologic status, with a sensitivity of 92.8% (95% CI, 80.5%-98.5%), specificity of 68.4% (95% CI, 43.4%-87.4%), positive predictive value of 86.6% (95% CI, 76.9%-92.6%), and negative predictive value of 81.2% (95% CI, 58.2%-93.1%) (Figs 1-4 and Table II). The odds ratio of finding residual BCC on histopathology when visualizing BCC-specific criteria on RCM was 28.1 (95% CI, 6.1−128.9). We found 39 true positives, 13 true negatives, and 6 false positives. There were 3 false-negative cases under

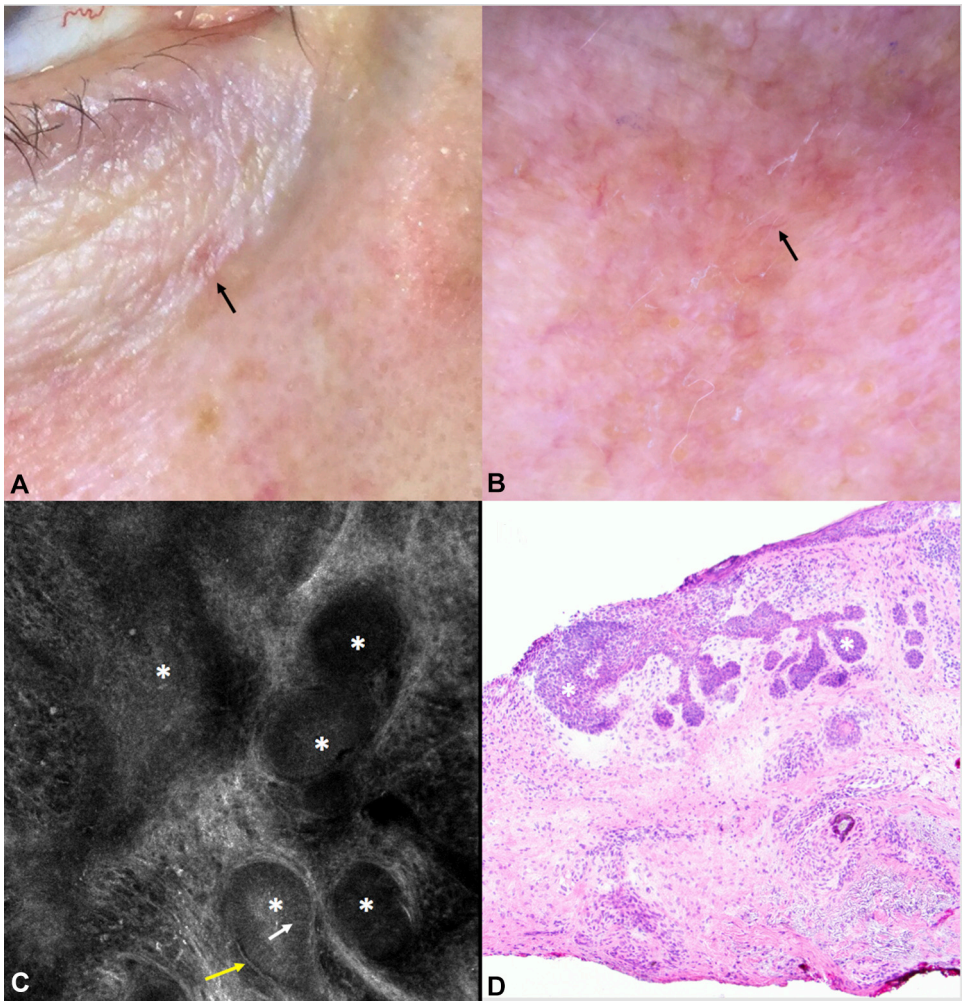

Fig 2. Nodular basal cell carcinoma on a H-site area with histopathologic evidence of residual tumor. **A**, Clinical appearance of the biopsy site; no residual tumor is seen. **B**, Dermoscopic features showing thin arborizing vessels (*black arrow*). **C**, Reflectance confocal microscopy image showing tumor nodules (white asterisks) with palisading (*white arrow*) and clefting (*yellow arrow*) (750 × 750 μm). **D**, Mohs first layer showing residual basal cell carcinoma, superficial and micronodular subtype (*white asterisks*). (**B**, Polarized light dermoscopy; **D**, hematoxylin-eosin stain; original magnifications: **B**, ×10; **D**, ×20.)

RCM (2 infiltrative and 1 basosquamous). When high-risk BCCs were excluded from our cohort (3 basosquamous and 2 infiltrative), RCM sensitivity increased to 100% (95% CI, 90.5%-100.0%), specificity remained unaffected, and negative predictive value increased to 100%.

Diagnostic accuracy measures were consistent across subsets of the study sample, with no differences observed by patient sex or age. The most relevant predictors were the presence of BCC-specific features, such as cord-like structures, tumor nests, palisading, and clefting (Table II). There were no differences in both RCM-positive and RCM-negative sites regarding the presence of streaming. Trapped epidermis was found in~20% of cases and was not associated with presence of residual BCC on histopathologic analysis (Fig 4).

DISCUSSION

RCM may help identify residual BCC at healed biopsy sites with no clinical evidence of residual tumor. In this study, we observed a strong association (odds ratio, 28.1) between in vivo RCM findings and histopathologic status (on frozen sections) of residual BCC in 61 patients showing no clinical evidence of residual tumor before Mohs micrographic surgery. We found an overall sensitivity of 92.8% and a specificity of 68.4%; when tumors determined by biopsy to be high-risk (ie, infiltrative and basosquamous) were excluded, the sensitivity

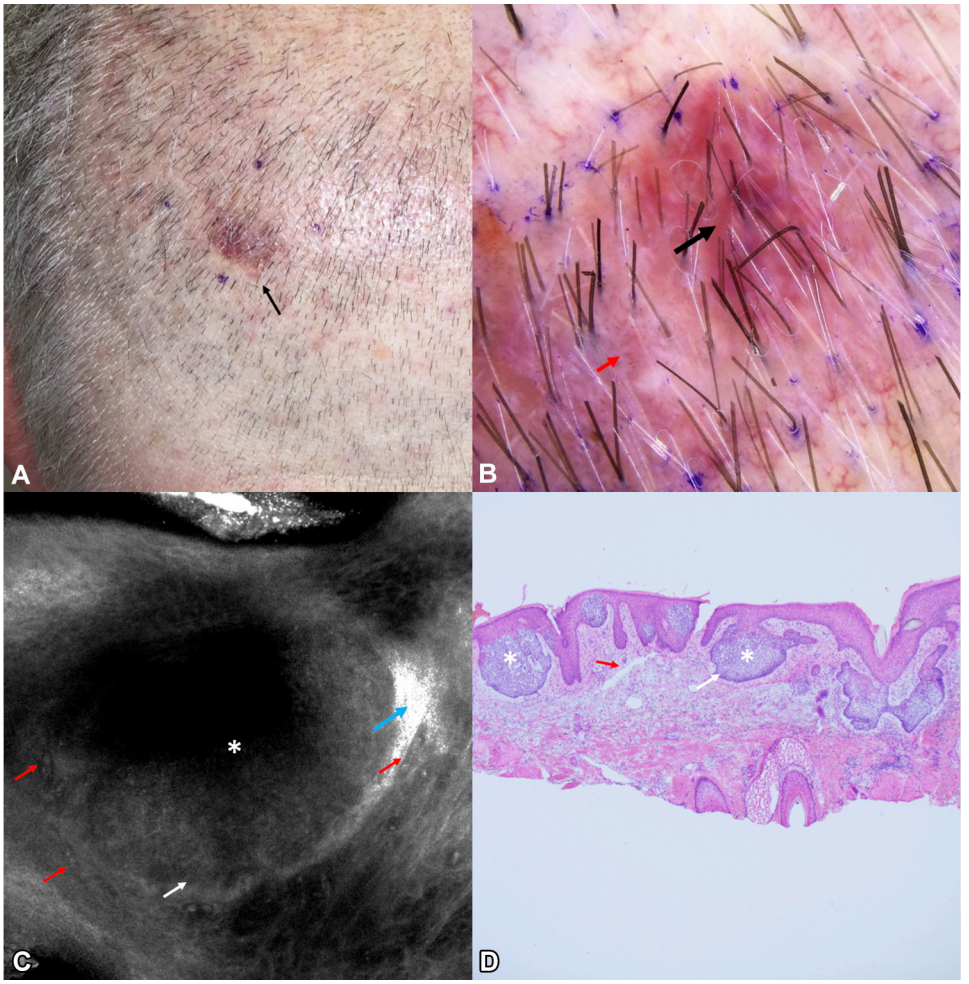

Fig 3. Nodular basal cell carcinoma (1.5 × 0.7 cm) on an M-site showing histopathologic evidence of residual tumor. **A**, Clinical appearance of the biopsy site; no evident residual tumor is seen. **B**, Dermoscopic features showing nonspecific erythema and ecchymosis (*black arrow*) and dotted vessels (*red arrow*). **C**, Reflectance confocal microscopy image showing a tumor nodule (*white asterisk*) with palisading (*white arrow*). Bundled collagen (*blue arrow*) and horizontal vessels (red arrows) are also seen (750 × 750 μm). **D**, Serial sectioning of the Mohs debulking showing residual basal cell carcinoma (*white asterisks*), superficial and early nodular subtypes. Blood vessels are also seen (*red arrows*). (**D**, hematoxylin-eosin stain; original magnification, ×10.)

and negative predictive value increased to 100%. In addition, we found no association between any dermoscopic predictor and either presence or absence of residual BCC on frozen sections (sensitivity, 58.3%; negative predictive value, 44.4%).

In a previous study, 67% of patients (28 of 42) with a biopsy specimen showing no clinical evidence of tumor were found to have residual BCC on histopathologic analysis.[2] Using the same methodology (Mohs excision with frozen section and serial vertical sectioning), we found a similar rate of positivity (68.9%), confirming the results of the landmark study of Holmkvist et al.[2] Naked-eye evaluation of scars for residual BCC has been investigated and found to have poor accuracy.[3] To the best of our knowledge, there have been no previous studies evaluating the role of dermoscopy in the evaluation of BCC biopsy sites. We found no association between BCC-specific criteria on dermoscopy and final histopathologic status.[10,11,17] Telangiectasias were present in 20.8% of our sample and were not associated with the presence of residual BCC on histopathology ($P = .73$). Shiny white blotches and strands have been described as a criterion of BCC;[10] they were present in 45.3% of cases but were not associated with residual BCC ($P = .55$). Therefore, telangiectasias and shiny white blotches and strands may lack validity as BCC-specific diagnostic criteria on lesions

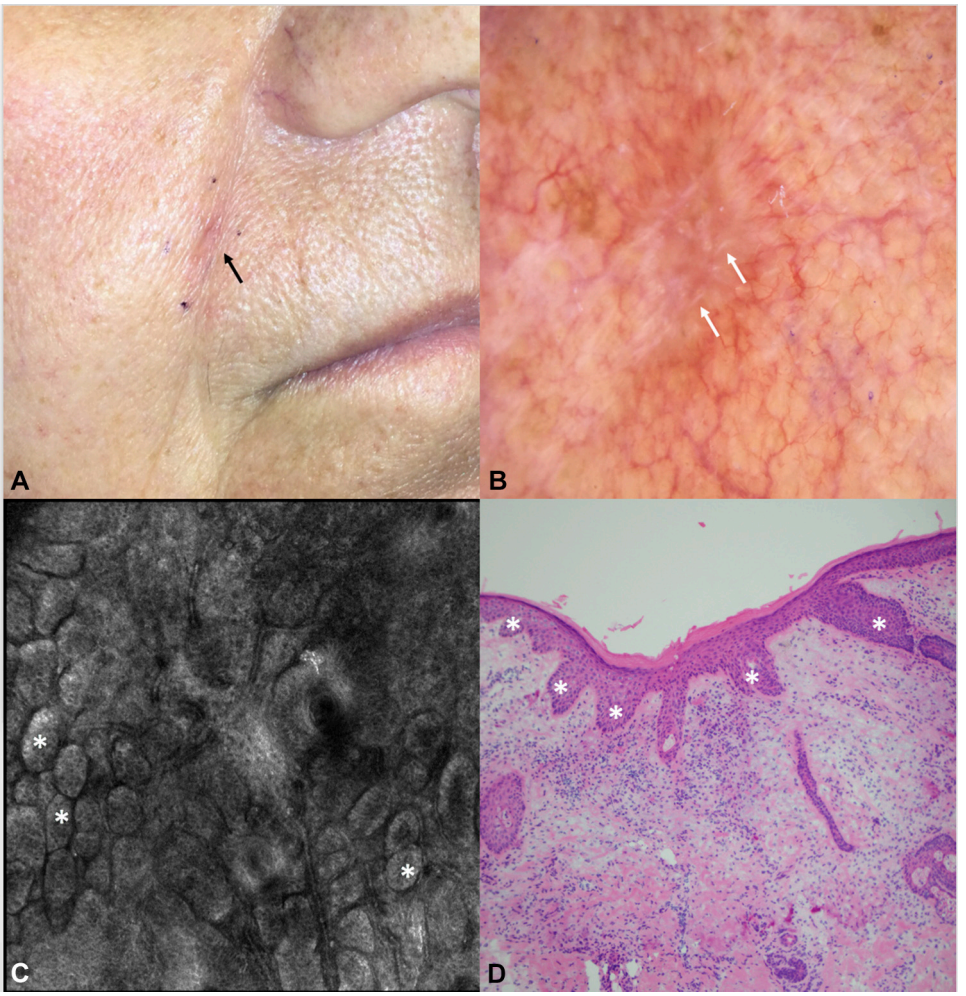

Fig 4. Micronodular basal cell carcinoma on an H-site showing no histopathologic evidence of residual tumor. **A**, Clinical appearance of the biopsy site; no residual tumor is seen. **B**, Dermoscopic features showing shiny white blotches and strands (*white arrows*). **C**, Reflectance confocal microscopy image showing multiple focus of trapped epidermis (*white asterisks*). This structure lacks palisading and clefting and includes a normal honeycomb pattern in the center (750 × 750 μm). **D**, Serial sectioning of the Mohs debulk showing multiple epidermal invaginations into the papillary dermis (*white asterisks*). The Mohs first layer was also negative (not shown). (**B**, Polarized light dermoscopy; **D**, hematoxylin-eosin stain; original magnifications: **B**, ×10; **D**, ×20.)

previously subjected to biopsy and thus should not be used alone when determining the presence of residual BCC after a biopsy. As patients with clinical or dermoscopic evidence of tumor were excluded from our study, other dermoscopic criteria were not analyzed.

Few studies have evaluated the role of RCM after biopsy to scout for residual BCC. Webber et al performed a prospective study on 8 patients with biopsy-proven superficial BCCs. All cases displayed cord-like structures under RCM; nevertheless, the authors did not comment on the presence of clinically evident disease.[8] Recently, Sahu et al studied the role of a combined RCM—optical coherence tomography probe to detect residual BCC on 25 tumors; whereas RCM showed BCC-specific features in 80% of cases, true residual tumor was found in only 40% of cases. They reported a sensitivity of 100% and a specificity of 23%; however, their study included patients with clinically evident disease at the moment of evaluation, which differs from our carefully selected group of patients.[9] We previously discussed the use of RCM to identify sites at which a biopsy was performed that were no longer clinically

evident.[18] The present study confirms the potential role of RCM in evaluating clinically negative sites for residual BCC following biopsy.

RCM evaluation of sites on which a biopsy was performed may have some potential pitfalls, such as the presence of trapped epidermis, which is a feature not previously described. Its recognition is important because it may lead to false-positives results when RCM is used to examine BCCs on which a biopsy had previously been performed (and perhaps on any other biopsy site). On the basis of histopathologic correlation, these areas were determined to correspond to epidermal invaginations over an inflamed and scarred dermis, with a tumor-like appearance. This feature occurred in 20% of our cases and was the primary reason for misdiagnosis of normal scars as residual BCC (false positives) (Fig 4). Scarring usually tends to create a flat epidermis; however, the healing process may proceed differently between patients and may present with this trapped epidermis feature. Streaming has also been described as a feature specific to BCCs examined by RCM[6]; however, we did not find an association between the presence of this feature and truly positive residual BCCs. Although streaming has been associated with superficial BCCs, in biopsy tissue it is more likely caused by traction of the dermis and epidermis by the scar, resulting in polarization of keratinocytes. Therefore, we do not recommend the use of streaming on RCM as the sole criterion for diagnosis of residual BCC following biopsy.

Limitations

The main limitation of the study is the inherent depth limitation of the RCM device (~200 μm), which was evident in the 3 improperly categorized cases. These cases corresponded to infiltrative and basosquamous subtypes, which often invade deep into the dermis. RCM might play a role in reducing unnecessary surgeries in a carefully selected subset of patients (ie, compliant patients with low-risk histopathology). The addition of multimodal imaging technology, such as the new RCM—optical coherence tomography device, may provide information from deeper layers and aid in diagnosing residual BCC in high-risk, deeper tumors.[9,19-21] Another limitation is the relatively small tumor size included. In the setting of larger tumors, we might not be able to confidentially scout the entire biopsy area; nonetheless, that scenario is not common because in larger tumors biopsies are more frequently incisional (with evident clinical residual tumor) than in smaller tumors, in which case excisional biopsies are more common.

Some cases had clear-cut RCM imaging compatible with residual BCC; however, on histopathologic examination, we did not find any tumor even after serial vertical sectioning with tissue exhaustion. These false positives are displayed as a relatively lower specificity of approximately 70% in this study. It is possible that some of these RCM findings were in fact correct and that histopathologic sectioning missed the target area with residual BCC owing to sectioning limitations.

Finally, the sensitivity and specificity achieved by RCM in our study may be biased because it was performed in a tertiary cancer center with expertise in this imaging technique. Accuracy of RCM interpretation may however vary depending on user experience.[22] We anticipate greater interest in, use of, and expertise in RCM now that RCM imaging of the skin has been granted category I Current Procedural Terminology reimbursement codes (granted in 2016).[23]

CONCLUSION

RCM may emerge as a useful tool for the evaluation of clinically negative biopsy sites, especially for low-risk BCCs. RCM may prove to be an effective modality for triaging compliant, low-risk patients. In carefully selected cases, it may also spare patients from unnecessary procedures, potentially reducing cost and morbidity. In patients with multiple BCCs, RCM may provide a window for better selecting lesions needing additional treatment after a biopsy. In elderly patients or in those with limited life expectancy, RCM detection of residual BCC may also help decide necessity of subsequent treatment.

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