Reflectance confocal microscopy-guided carbon dioxide laser ablation of low-risk basal cell carcinomas: A prospective study

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Background: Basal cell carcinoma (BCC) treatment modalities can be stratified by tumor subtype and recurrence risk. The main limitation of nonsurgical treatment modalities is the lack of histopathologic confirmation. Reflectance confocal microscopy (RCM) is a noninvasive imaging device that provides quasihistologic images.

Objective: To evaluate the feasibility and efficacy of RCM-guided carbon dioxide (CO_2) laser ablation of low-risk BCCs.

Methods: Prospective study with biopsy specimen–proven low-risk BCCs imaged with RCM. RCM was performed on these sites before and after ablation. If residual tumor was found, a new series of laser passes were performed. The patients were then monitored for recurrence clinically and with RCM.

Results: Twenty-two tumor sites in 9 patients (5 men, 4 women) were imaged and treated. Median age was 59 ± 12.9 years (range, 30-74 years). Mean tumor size was 7.7 mm (range, 5-10 mm). Residual tumor was identified in 5 of 22 cases (22.7%) under RCM on immediate first-pass postablation sites, prompting additional laser passes. Median follow-up was 28.5 months (range, 22-32 months) with no recurrences found.

Conclusions: Addition of RCM to laser ablation workflow can detect subclinical persistent tumor after initial ablation and may serve as an aid to increase the efficacy of laser ablation. (J Am Acad Dermatol 2019;81:984-8.)

Key words: ablation; basal cell carcinoma; carbon dioxide laser; diagnosis; follow-up; laser; reflectance confocal microscopy; treatment.

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Conflicts of interest: Dr Rajadhyaksha is a former employee of and owns equity in Caliber I.D. (formerly, Lucid Inc), the company that manufactures and sells a reflectance confocal microscope (VivaScope). The VivaScope, for reflectance confocal microscopy imaging, is the commercial version of an original laboratory prototype that was developed by Dr Rajadhyaksha when he was at Massachusetts General Hospital, Harvard Medical School. Dr Rossi has no relevant conflicts of interest related to this manuscript. Dr Rossi has served on advisory board, as a consultant, or has given educational presentations for Allergan Inc, Galderma Inc, Evolus Inc, Elekta, Biofrontera, Quantia, Merz Inc, Dynamed, Skinuvia, Perf-Action, and LAM therapeutics. Drs Navarrete-Dechent, Cordova, Liopyris, Yélamos, Aleissa, Hibler, Sierra, Sahu, and Blank have no conflicts of interest to declare.

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According to the National Comprehensive Cancer Network (NCCN), basal cell carcinoma (BCC) treatment modality can be selected depending on tumor subtype and recurrence risk: low-risk BCCs are amenable to nonsurgical management.[1] Laser ablation is a localized treatment modality that can be used for managing low-risk BCC[2-4]; however, as with all nonsurgical treatments, it lacks histopathologic confirmation of clearance.

Reflectance confocal microscopy (RCM) can diagnose[5] and monitor treatment response of BCC.[6,7] Preliminary studies have evaluated the feasibility of RCM for monitoring low-risk BCCs with ablative lasers.[8-10] Our objective was to evaluate the feasibility and efficacy of RCM-guided carbon dioxide (CO_2) laser ablation of low-risk BCCs.[8]

CAPSULE SUMMARY

- In this prospective case series including 22 basal cell carcinomas, reflectance confocal microscopy found 22.7% of residual basal cell carcinomas immediately after first pass of carbon dioxide laser ablation. No recurrences were found after median of 28.5 months' follow-up.
- Reflectance confocal microscopy can better guide nonsurgical basal cell carcinoma treatment modalities, ultimately improving treatment efficacy.

PATIENTS AND METHODS

We prospectively included adult patients with a history of multiple BCCs (≥3 tumors) located on NCCN low-risk areas[1] who presented with biopsy specimen-proven BCCs between November 2014 and April 2018. This study was approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board (99-099), and all patients signed informed consent. Patient demographics and tumor data were recorded in a deidentified database.

RCM and laser ablation protocol

Baseline examination. The lesion site was delineated with specially designed paper rings[11] with a 4-mm normal skin margin. Preablation RCM was performed with a handheld device (VivaScope 3000; Caliber ID, Rochester, NY) scouting the entire area and margins to evaluate for the presence of BCC. We used previously described RCM criteria[12-14] to define "positive" or "negative" sites. All patients underwent laser ablation, irrespective of RCM residual status. RCM modified the lateral extension or number of laser passes, or both.

Laser ablation. After RCM mapping, laser ablation was performed under local anesthesia in the entirety of the paper ring–demarcated lesional area with a CO_2 laser (Lumenis UltraPulse 5000C; Lumenis Inc, San Jose, CA). The fluence was 300 to 350 mJ/cm^2, density of 100%, and a uniform spot size diameter of 2.25 mm. The number of passes was determined according our previous histologic study[8] and the RCM estimated tumor depth (RCM guided). Each laser pass removes approximately 20 to 30 μm.[15]

Immediate postlaser examination

Immediately after laser ablation, a new RCM evaluation was performed to scout for deep-seating residual BCC. We used topical aluminum chloride (35%) for 30 seconds as a contrast agent to enhance possible residual tumor via a mechanism of chromatin condensation (Fig 1).[16] Postablation RCM was performed with sterilized plastic caps and sterile gel applied directly to the wound. If residual BCC was identified on RCM, an additional series of passes based on the RCM-estimated depth was performed.

RCM follow-up

Patients were assessed at 3, 6, and 12 months and every 6 months thereafter. If BCC was suspected,

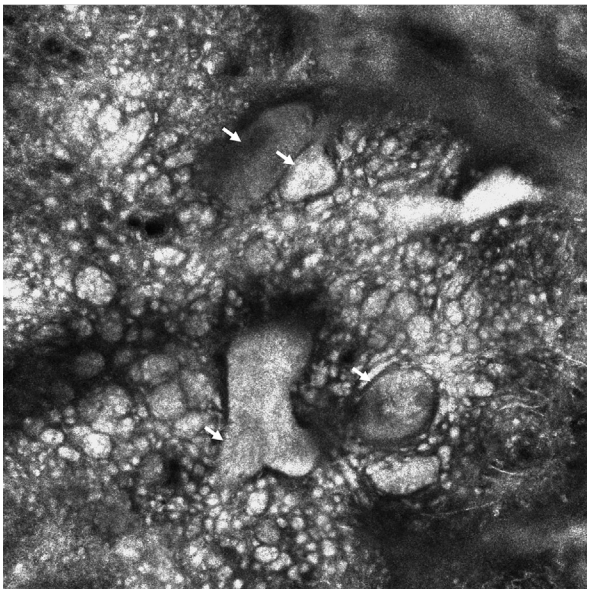

Fig 1. Reflectance confocal microscopy appearance of aluminium chloride–highlighted basal cell carcinoma tumor nodules (*white arrows*), immediately after the first pass of laser ablation (no epidermis present). A second pass of laser ablation in this patient showed no residual tumor under reflectance confocal microscopy (750 × 750 μm).

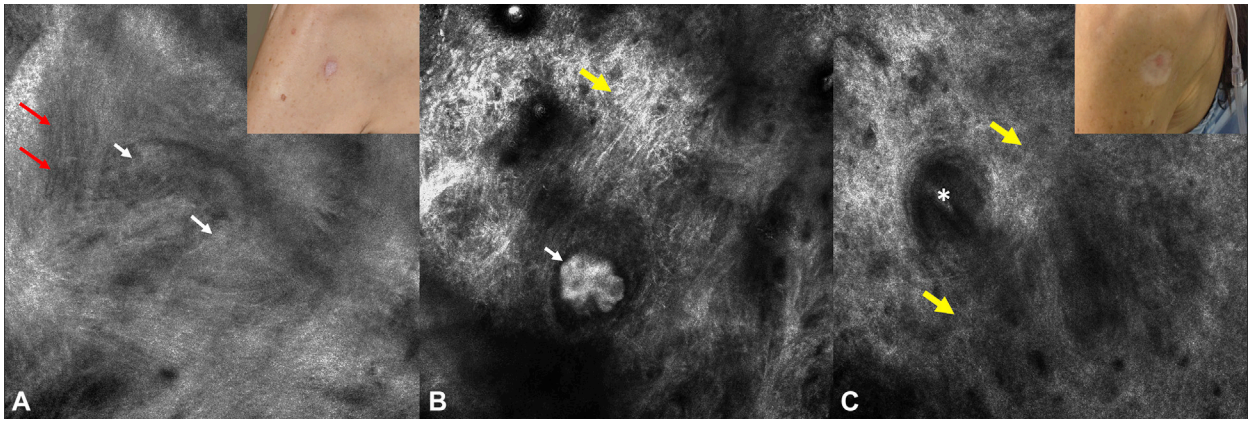

Fig 2. Superficial basal cell carcinoma on the posterior shoulder of a woman in her 50s with metastatic breast cancer. **A**, Preablation reflectance confocal microscopy (RCM) image shows suspicious cord-like structures/early tumor nodule with clefting (*white arrows*) and horizontal vessels (*red arrows*). The inset displays the preablation clinical appearance (750 × 750 μm). **B**, Immediate postablation RCM shows dermal tumor nodules after ablation of the epidermis. These tumor nodules were highlighted by aluminium chloride (*white arrow*). Reticulated collagen is also seen (*yellow arrow*). This patient underwent 3 subsequent passes. **C**, A 12-month RCM follow-up shows scar with dense collagen (*yellow arrows*); the *asterisk* corresponds to a hair follicle. Inset shows the appearance of the scar (750 × 750 μm).

biopsy was to be performed. After 12 months, patients continued their regular clinical and RCM follow-up as determined by the physician.

RESULTS

Included were 22 BCCs (mean size, 7.7 mm; range, 5-10 mm) in 9 patients (5 men, 4 women) who were a median age of 59 ± 12.9 years (range, 30-74 years). Two patients had history of radiation therapy during childhood. Twenty-one BCCs were superficial, and 1 BCC had a mixed type of superficial, nodular, and infiltrative.

Baseline, preablation, RCM examination of biopsy specimen–proven BCC sites identified residual tumor in 81.8% (18 of 22 lesions) (Fig 2, *A*; Table I). After imaging, the first laser ablation pass was performed.

Immediate, postablation RCM examination

Residual BCC was identified in 5 of 22 sites (22.7%) upon immediate postablation RCM examination (Figs 1 and 2, *B*; Table I). A second set of passes of the CO_2 laser was performed using the same parameters. In the repeated postlaser RCM group (n = 5), no BCC features were identified. Mean number of passes was 3.6 (range, 2-8).

RCM follow-up

At the 12-month follow-up, 3 patients (n = 5 lesions; 22%) were lost and excluded from the recurrence analysis. Six patients (17 lesions) completed at least 12 months of follow-up, and no clinical or RCM evidence of recurrence was identified (0 of 17) (Fig 2, *C*). Patients remained under clinical and RCM monitoring every 6 months, with no recurrences (median follow-up, 28.5 months; range, 22-32 months). Sites have healed well with good cosmetic outcomes.

DISCUSSION

The main limitation of nonsurgical treatments of BCC is lack of histologic clearance verification. Clinicians rely on visual appearance to assess whether a tumor has been completely removed or not.[8] The complementary use of RCM in different stages: preablation, immediately postablation, and during follow-up can guide BCC ablative treatments.[8-10,15]

The immediate postablation RCM examination identified nonclinically evident residual tumor in 22.7% of lesions. This guided further laser treatment, achieving probable complete removal of tumors. As a result, no recurrences have been identified after 28.5 months of follow-up. BCC recurrences may occur later, however, and longer follow-up is needed.[17]

Detection of residual BCC with immediate postablation RCM here of 22.7% is comparable to a study showing 21.2% of residual BCC on histopathology, 3 months after laser ablation.[3] Therefore, RCM-guided laser ablation could achieve a higher cure rate. Because RCM is limited to a depth of 200 to 250 μm, deep-seating residual tumor could have been missed on the initial RCM evaluation. Given

Table I. Reflectance confocal microscopy characteristics of basal cell carcinomas before (baseline) laser ablation, immediate after (postablation), and at 3, 6, and 12 months of follow-up

Confocal features	Baseline, % (No.) (n = 22)	Immediate postablation, % (No.) (n = 22)	3-month follow-up, % (No) (n = 17)	6-month follow-up, % (No.) (n = 17)	12-month follow-up, % (No.) (n = 17)
Atypical honeycomb	13.6 (3)	No epidermis	0	0	0
Ulceration	13.6 (3)	100 (22)	0	0	0
Streaming	63.6 (14)	No epidermis	0	0	0
Cobblestone pattern	13.6 (3)	No epidermis	0	0	0
Tumor nests	45.5 (10)	18.2 (4)	0	0	0
Palisading	50 (11)	18.2 (4)	0	0	0
Clefting	54.5 (12)	18.2 (4)	0	0	0
Cord-like structures	72.7 (16)	4.5 (1)	0	0	0
Dark silhouettes	4.5 (1)	0	0	0	0
Horizontal vessels	81.8 (18)	22.7 (5)	0	0	0
Bundled collagen	63.6 (14)	68.2 (15)	0	0	0
Plump cells	13.6 (3)	4.5 (1)	0	0	0
Inflammation	18.2 (4)	22.7 (5)	0	0	0
Reticulated collagen	0	81.8 (18)	0	0	0
Debris	0	81.8 (18)	0	0	0
Scar tissue	0	0	100 (17/17)	100 (17/17)	100 (17/17)

No., Number.

that epidermis was ablated with the initial laser treatment, we were able to evaluate deeper skin levels, allowing detection of deeper residual tumor that would be otherwise missed.

RCM can also be used to determine residual status of BCC after biopsy.[18] Here we found residual tumor in 82% of biopsy specimen–proven BCCs included. Use of RCM as a screening tool can potentially spare some unnecessary treatment in selected low-risk patients. A recent study showed that RCM is a useful tool to assess residual status in clinically negative BCC biopsy sites.[19]

Limitations

Limitations include a relatively small sample size and short follow-up time. An important inherent limitation of RCM is the maximum image depth of 200 to 250 μm. The use of multimodal imaging, such as RCM-optical coherence tomography, can potentially help overcome this by enabling evaluation of deeper tumoral components.[20-22] In addition, there was no histopathologic proof of clearance; nevertheless, correlation of RCM with final histopathologic status was demonstrated previously.[8] Finally, this study was performed in a tertiary cancer center with expertise in use of RCM.

CONCLUSION

RCM-guided laser ablation can detect subclinical BCC after initial ablation and potentially aid in increasing efficacy of laser treatments. RCM may emerge as a noninvasive tool to monitor different treatment modalities for BCC and other skin cancers.[23]

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