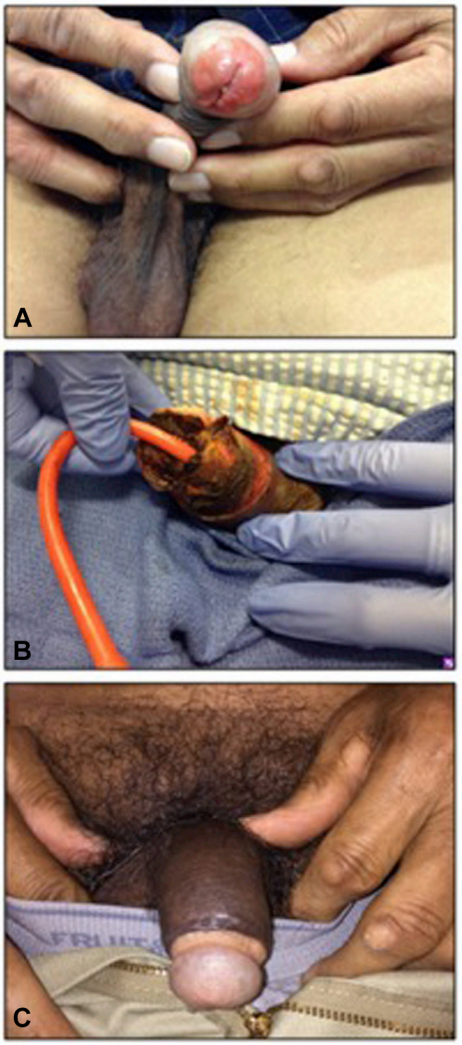

Fig 1. Penile squamous cell carcinoma in situ. **A**, 79-year-old man (patient 4) with superficial squamous cell carcinoma on the glans penis. **B**, After completed Mohs micrographic surgery and before urethral reconstruction. **C**, Four months after completed surgery; the patient is able to urinate standing and has normal sexual function.

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Basal cell carcinomas of the ear are more aggressive and have higher discordance rates between biopsy and Mohs histopathology

To the Editor: Although basal cell carcinomas (BCCs) have a low metastatic potential, aggressive variants have higher rates of incomplete excision, recurrence, and increased risk for perineural invasion. Treatment approaches vary based on histologic subtype, making accurate diagnosis critical for effective management. Studies demonstrated high variability in concordance rates (61%-82%) between diagnosis on biopsy and excision.[1,2] Ear BCCs are more

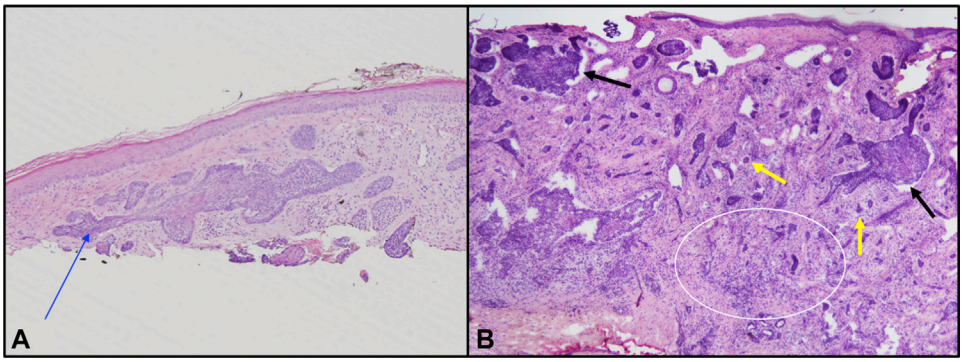

Fig 1. Basal cell carcinoma (BCC). Mohs histopathology identifies aggressive BCC subtypes not visualized on initial biopsy. **A**, Shave biopsy with nodular BCC. **B**, Mohs histology identified nodular (black arrow), micronodular (yellow arrow), and morpheaform (white circle) BCC subtypes.

aggressive, presenting with larger lesions and deeper subclinical extension.[3] We sought to evaluate ear and non-ear facial BCC subtype concordance between biopsy and Mohs histopathology.

We conducted a retrospective chart review of 92 BCCs of the ear and 40 BCCs of the face treated with Mohs micrographic surgery (MMS). The Cohen kappa statistic was used to evaluate the interrater agreement, and percentage of interrater agreement was compared by using the chi-square test. BCCs of the ear required significantly more stages for tumor clearance ($P = .04$) and had larger lesion and postoperative defect sizes ($P = .005$ and $P = .0005$, respectively). There was no statistically significant difference in the type of repair; however, there was a trend toward more advanced (nonprimary closure) repairs for defects on the ear.

BCCs of the ear had a 53% agreement, with 76% of the discordant cases found to be more locally aggressive by Mohs histopathology (Fig 1). Patients with non-ear BCCs had an 83% agreement, with 50% of discordant cases being more aggressive on Mohs histopathology. There was a statistically significant difference in proportion of agreement between ear and non-ear lesions ($P = .002$). Ear BCCs were 1.49 times ($P = .42$) and 5.86 times ($P < .0001$) more likely to be aggressive than non-ear lesions on the original biopsy and Mohs histopathology, respectively.

Among patients who presented with BCCs on the ear, those 65 years or older, as well as female patients, had higher discordance rates. Of patients 65 years or older, 82% of the discordant cases had a more aggressive subtype as detected by Mohs histopathology. Of the discordant cases of female patients with BCCs on the ear, 88% of the cases were more aggressive by Mohs histopathology. This analysis is limited by the small subgroup of tumors, and larger-scale studies are needed to assess the impact of these factors on discordance.

The high discordance rate for ear BCCs in this study suggests that biopsies may inaccurately characterize the histologic subtype and miss an aggressive subtype, which is likely due to small sample sizes of biopsies from architecturally complex anatomic site. This may result in treatment choices that lack adequate margin assessment, leading to higher recurrence rates, overall greater patient morbidity, and higher treatment costs. The high percentage of aggressive BCCs underdiagnosed on biopsy suggests that in higher-risk anatomic sites (such as the ear), the treating physician should be mindful of the possibility that a more aggressive subtype is present. Our data support the Mohs Appropriate Use Criteria,[4,5] which recommend the use of MMS in area H, which includes the ears. Our data give further credence to using MMS or complete circumferential peripheral and deep margin assessment for treatment of ear BCCs.

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A phase 2, multicenter, placebo-controlled study of single-dose squaric acid dibutyl ester to reduce frequency of outbreaks in patients with recurrent herpes labialis

To the Editor: Herpes labialis is a common condition with painful blisters or sores around the lips, and there are limited choices to prevent or reduce the severity of outbreaks.[1] It is caused by herpes simplex virus type 1 (HSV-1) and, less commonly, type 2 (HSV-2). Squaric acid dibutyl ester (SADBE) is a topical immunosensitizer to treat verruca vulgaris and alopecia areata.[2,3] Previously, a single topical dose of 2% SADBE dissolved in dimethyl sulfoxide (DMSO) applied to the arm skin significantly extended the time to the next outbreak.[4] In a separate study, a single topical dose of 2% SADBE in DMSO on the arm in patients with frequent outbreaks significantly improved immune response to HSV-1 in vitro 8 weeks later, with a significant increase in interferon gamma expression.[5] In this study, we explored whether a regimen with a second dose of topical 0.5% SADBE to the upper arm skin might be superior to a single dose of 2% SADBE to reduce the frequency or severity of herpes labialis.

After institutional review board approval and written informed consent, this study was conducted at 5 centers with patients with 4 or more herpes labialis episodes in the previous 12 months. Participants were randomly assigned to receive either (1) 1 dose of 2% SADBE on day 1, (2) 2% SADBE on day 1 and a second lower-dose (0.5%) booster on day 22, or (3) DMSO vehicle only on days 1 and 22. All participants were followed for 1 year.

Eligible individuals (N = 140) enrolled with a median number of outbreaks of 6 (mean, 7.8) in the prior 12 months. The 1-dose group had superior results versus the placebo group in time to next outbreak from day 43 to 121 ($P = .024$) (Fig 1), mean number of outbreaks in days 43 through 121 (0.231 ± 0.125 standard error in the 1-dose group vs 0.610 ± 0.068 in the placebo group; $P = .011$), and proportion of participants with an outbreak in days 43 through 121 (9/39 [23%] in the 1-dose group vs 19/41 [46%] in the placebo group; $P = .036$). The average number of moderate or severe outbreaks over days 43 through 121 was also reduced in patients receiving 1 dose of SADBE (0.128 ± 0.339) versus placebo (0.390 ± 0.703) ($P = .04$), as well as over days 1 through 365 in the 1-dose (0.641 ± 0.931) versus placebo group (1.341 ± 1.76) ($P = .04$).

Notably, the 2-dose group had superior results compared with the placebo group on these same measures, but not significantly so. Why the 1-dose may be superior to the 2-dose regimen remains to be investigated, but we hypothesize that the second dose at lower concentration may tolerize or downregulate the immune changes from the 2% SADBE in the first dose.

The largest improvements observed in the SADBE-treated groups occurred within days 43 through 121 of the study. One possible reason may be that SADBE takes about 6 weeks to exert maximal effect on the