cream on AFXL-pretreated skin.[5] Since concentration of anesthetics was comparable for both formulations (AHES 4% vs lidocaine/prilocaine 5%), we proposed that a liquid solution may penetrate more easily into the AFXL ablation channels. Therefore, in the present study we aimed to compare AHES with a cream formulation containing a much higher concentration of anesthetics (AHES 4% vs LTC 14%), which may still not have sufficiently compensated for the possibly inferior vehicle. Despite the lack of comparability of the pharmacologic properties of both anesthetics (different anesthetics, presence of the potent vasoconstrictor epinephrine in AHES, which could enhance the sustained effect of the anesthetic), our finding that AHES still rendered more effective anesthesia than LTC might be considered as another indication for the superiority of a liquid vehicle.

In conclusion, both AHES and LTC give effective anesthesia when applied on AFXL-pretreated skin for ≥5 minutes. Maximum anesthesia is already achieved after 15 minutes for AHES. Despite the much lower concentration of anesthetic, AHES is superior to LTC in this setting. Additional research comparing different formulations containing the same anesthetic at a fixed concentration is needed to assess the exact role of the drug vehicle in AFXL-assisted topical anesthesia and drug delivery in general.

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Predominance of oral mucosal melanoma in areas of high mechanical stress

To the Editor: Melanoma uncommonly involves the oral cavity and pursues an aggressive course with poor prognosis in this anatomic location. The risk factors of primary oral mucosal melanoma (POMM) are unknown and, unlike cutaneous melanoma, do not include sun exposure. The prognosis of this melanoma variant is likely associated with late detection and inadequate screening. Previous POMM case reports have shown that the oral cavity is not uniformly affected but rather shows striking predilection for the hard palatal mucosa and maxillary gingiva.[1] In contrast, squamous cell carcinoma, comprising 90% of oral cavity malignancies, has a predilection for the ventrolateral aspect of the tongue, the floor of the mouth, and gingiva and rarely involves the hard palatal mucosa.[2,3] As with POMM pathogenesis, the reason for its unique predilection remains unclear. These questions prompted a systematic review of POMM cases to establish a comprehensive anatomic predilection that may educate dermatologists on the importance of screening areas of the oral cavity, provide insight into novel candidate risk factors for POMM, and raise awareness of this melanoma presentation to clinicians.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to search MEDLINE, Embase, and the Cochrane database for POMM cases with specific anatomic location stated. Twenty-one retrospective cohort studies and 4 case series totaling 549 POMM cases met the inclusion criteria. The maxillary gingiva and hard palatal mucosa were involved in 71.77% (394/549) of cases, with remaining cases involving the mandibular gingiva and the floor of mouth (12.39%), the labial mucosa/lips (6.19%), the buccal mucosa (4.92%), the

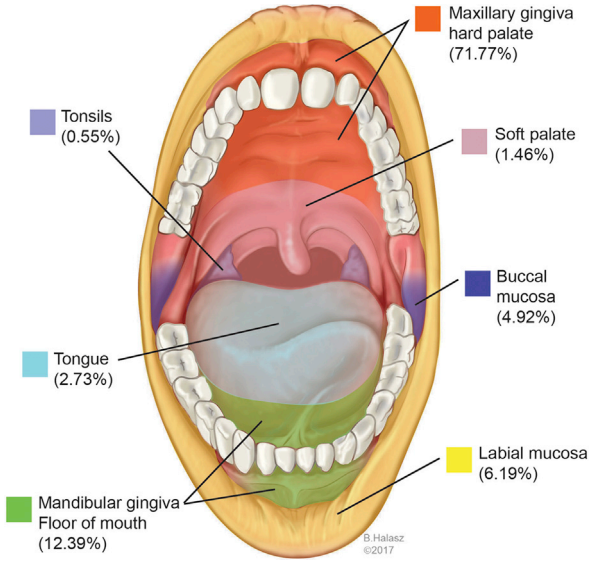

Fig 1. Distribution of 549 oral melanoma lesions.

tongue (2.73%), soft palatal mucosa (1.46%), and the tonsils (0.55%) (Fig 1). Palatal mucosa not otherwise specified was involved in 1.96% of cases. This systematic review confirms the propensity for oral melanoma involvement for the masticatory mucosa of the hard palate and maxillary gingiva.[1]

Investigations into oral melanoma pathogenesis may be revisited in light of recent publications associating mechanical stress with melanoma formation on plantar surfaces.[4,5] Mastication, occlusion, and deglutition convey stress patterns predominantly dispersed through the palatine processes of the maxilla and the maxillary alveolar bone, sites overlaid by mucosa preferentially involved by POMM.[6] Moreover, sinonasal mucosal melanoma (also of unknown pathogenesis) has a predilection for the mucosal surfaces at least partially lining these bony structures. In vitro mechanical stimulation of melanocytes has been shown to increase mitogen-activated protein kinase signaling, which is associated with increased cell proliferation, invasiveness, and metastatic potential.[7] We postulate that mechanical stress may be partially responsible for melanoma distribution in the oral cavity and previously described mitogen-activated protein kinase signaling alterations in POMM.[8] Future studies are needed to investigate the role of masticatory sheer stress on initiation of oral melanomas.

The poor prognosis for POMM (often secondary to late-stage diagnosis) can be attributed to several factors, including a frequently asymptomatic early disease course, occurrence in an anatomic location that is generally not amenable to self-examination, and delayed physician detection. Though POMM is rare, our findings show that careful attention should be given to visual inspection of the hard palatal mucosa and maxillary gingiva by dermatologists and dentists. Even with better insights into POMM pathogenesis and novel treatment modalities, early diagnosis remains crucial to optimal patient management.

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Trends in utilization of topical medications for treatment of rosacea in the United States (2005-2014): A cohort analysis

To the Editor: Rosacea is a common inflammatory skin disorder (prevalence, 1.3%-2.1%).[1] In addition to gentle skin care and sun protection, metronidazole or azelaic acid are considered first-line topical therapy for papulopustular rosacea and topical α-agonists are first-line topical therapy for erythrotelangiectatic rosacea.[2] The aim of this study was to evaluate real-world topical rosacea therapy utilization and costs.

We carried a retrospective cohort analysis of the MarketScan Commercial Claims and Encounters database (henceforth referred to as the database). The study was exempted by the Institutional Review Board at the Milton S. Hershey Medical Center. The validated database consists of reimbursed claims of approximately 50 million employees per year who are covered under private insurance plans across the United States. Uniquely, the database can track an individual across payers and geographic locations and it contains demographic data, dates, and costs for services, procedures, and pharmacy claims. Costs were adjusted for inflation and are reported in 2015 US dollars.

During the period from January 1, 2005, to December 31, 2014, a total of 72,173 adults were continuously enrolled with a diagnosis of rosacea, defined as 2 or more claims for treatment for *International Classification of Diseases, Ninth Revision*, code 695.3 by a dermatologist, primary care provider, and/or ophthalmologist over the course of 18 months (Table I).

Most patients (86% [n = 62,074]) were treated with topical agents; only 6% (n = 4463) were treated with oral therapy exclusively (a discussion of oral therapy in this cohort is presented elsewhere).[3] Single-agent topical therapy was used for 75.8% of patients (n = 47,035), whereas 24.2% (n = 15,039) received combination topical therapy. Metronidazole and azelaic acid comprised the most common combination regimen (Table II). More patients utilized branded topical medications than used

Table I. Topical treatments for rosacea 2005-2015: cohort characteristics

Characteristic	Value
Overall cohort size, N	72,173
Median age, y (interquartile range)	50, 13
Female-to-male ratio, n (%)	52,541:19,632 (72.80:27.20)
Ratio of those residing in a metropolitan area to those residing in a nonmetropolitan area, n (%)	63,553:8620 (88.06:11.94)
Rosacea treatment, n (%)	
Enrollees with no treatment claims	5636 (7.81)
Enrollees with only topical treatment claims	27,684 (38.36)
Enrollees with only oral treatment claims	4463 (6.18)
Enrollees with both oral and topical treatment claims	34,390 (47.65)
Median time between visits, d (interquartile range)	241; 476
Enrollees by geographic region, n (%)	NE, 12,267 (17.00); NC, 18,043 (25.00); S, 31,239 (43.28); W, 9997 (13.85)
Type of provider, n, (%)*	
Dermatologist	66,460 (92.08)
Ophthalmologist	4927 (6.83)
Other provider	786 (1.09)

NC, North Central (Illinois, Indiana, Iowa, Kansas Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin); *NE*, Northeast [Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania Rhode Island, and Vermont), *S*, South (Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia); *SD*, standard deviation, *W*, West (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming).
*Provider associated with claim for initial visit for rosacea.