Verrucous Carcinoma with Dysplasia or Minimal Invasion: A Variant of Verrucous Carcinoma with Extremely Favorable Prognosis

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Abstract Verrucous carcinomas (VC) recur locally but do not metastasize in the absence of an invasive squamous cell carcinoma (SCC) component. Although excluded from the definition of pure VC, some tumors harbor only dysplasia or minimal invasion, findings of unknown clinical significance. Surgically resected VC cases from two institutions were collected and categorized into three types: VC, VC with dysplasia or minimal invasion (VCDMI), defined as SCC less than or equal to 2 mm in depth, and SCC arising in VC (SCC-VC) where the SCC was greater than 2 mm in depth. Cases were also matched with conventional SCC based on location and T and N-stages, and clinical follow up was obtained. Of the 58 total cases, 18 were VC, 26 VCDMI, and 14 SCC-VC. Only 1 of 18 (5.6 %) VC and 5 of 26 (19.2 %) VCDMI cases recurred locally ($p = 0.37$) versus 7 of 14 (50 %) SCC-VC

($p = 0.01$). All VC and VCDMI cases were node negative at presentation whereas SCC-VC had nodal metastases in 2 of 14 (14.3 %) cases. No patients with VC or VCDMI died from disease, whereas 5 of 14 (35.7 %) patients with SCC-VC died from disease. T-stage matched conventional SCC cases from institutional databases had worse outcomes than VC and VCDMI, but not after they were matched for both T and N-stages. Our findings suggest that dysplasia and/or minimal invasive SCC do not adversely affect outcomes in tumors otherwise showing diagnostic features of VC.

Keywords Verrucous carcinoma · Dysplasia · Invasion · Hybrid · Squamous cell carcinoma · Survival

Introduction

Squamous cell carcinoma (SCC) of the head and neck has numerous histologic variants, many of which have substantial differences in pathophysiology and clinical behavior. Verrucous carcinoma (VC) is one of the most recognized variants given its unique morphology and major clinical significance. It has a warty, hyperkeratotic clinical appearance (Fig. 1a) and distinct histopathologic features such as large, pushing nests of bland, eosinophilic epithelium with abundant, “glassy” cytoplasm (Fig. 1b, c). This entity was first described by Dr. Lauren V. Ackerman in the late 1940s [1] and has thus been named “Ackerman’s tumor”. VC closely resembles verrucous hyperplasia clinically and histologically, however, the epithelium, including the rete pegs, in verrucous hyperplasia does not extend beneath the level of the adjacent normal mucosa. VC can recur locally but, in the absence of a conventional invasive SCC component, does not metastasize. It “invades” and destroys tissue only by slow, pushing expansion of the cells

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Fig. 1 Typical features of pure verrucous carcinoma. **a** Gross appearance of verrucous carcinoma of the oral cavity with a shaggy, white, polypoid appearing tumor of the anterior mandibular alveolar ridge. **b** Low power view showing thickened, “glassy” epithelium with hyperkeratosis piling up on itself and pushing down into the

stroma ($\times 1.5$ magnification). **c** Higher power view showing the rounded, pushing tongues of tumor cells with cells with abundant, eosinophilic cytoplasm, an inconspicuous basal layer, smooth interface with the stroma, and a characteristic, dense, chronic inflammatory infiltrate ($\times 10$ magnification)

as they pile up on each other within the expanded epithelial surfaces. In spite of being called a ‘carcinoma’, the strict definition of VC is that these tumors lack dysplastic cytologic features, and that there is no invasion by the tumor cells through the basement membrane. The 2005 World Health Organization Classification of Head and Neck Tumors, however, is a bit more open regarding the dysplasia issue in that it uses the wording that “the squamous epithelium (in VC) lacks cytologic features of malignancy [2].” While this position is more open, it is also more vague about what actually histologically constitutes VC and what does not. A minority of VCs have a component of conventional invasive SCC. Although most common in the oral cavity, VC also occurs at other head and neck sites such as the larynx [3], oropharynx, nasopharynx [4], and paranasal sinuses [5].

Pure VC is widely considered suitably treated by surgical resection of the primary tumor alone [6–8]. VC with a component of conventional invasive SCC is not well described in the literature so there is not much data to inform clinical management. However, based on our institutional experience, when any component of invasive SCC is present, tumors are treated clinically just as conventional SCC. These patients get surgical resection and, if indicated by overall pathologic stage, adjuvant radiation therapy. However, some VCs show dysplasia without any conventional invasive SCC or have just a minor component of invasive SCC. Currently, there is great difficulty in diagnosing tumors with these limited changes, and the terminology is widely variable. Pathologists use various descriptive terms such as ‘verrucous carcinoma with focal dysplasia and/or invasion’, ‘well differentiated squamous cell carcinoma with verrucous features’, ‘focus of squamous cell carcinoma arising within a verrucous carcinoma’, ‘verrucous squamous cell carcinoma’ [9], and ‘hybrid’ verrucous carcinoma [10]. There is a distinct lack

of standard nomenclature, and, although these “in between” type tumors are not uncommon, there are no robust studies assessing their clinical behavior.

We prefer the term ‘verrucous carcinoma with dysplasia or minimal invasion’ (VCDMI) for such tumors and, anecdotally in our clinical practice, patients with these tumors have appeared to have very favorable clinical outcomes. Thus, we speculated that their clinical behavior more closely matches pure VC than that of invasive SCC arising in VC or conventional SCC. This study analyzed a series of VC and related lesions, comparing VCDMI to pure VC and to SCC arising in VC, as well as to matched cohorts of conventional SCC, in order to characterize their clinical and pathologic features and patient outcomes.

Methods

This was a joint project between the Department of Pathology and Immunology at Washington University in St. Louis and Department of Pathology at Emory University School of Medicine. After appropriate approval from the institutional review boards for the conduct of the study and exchange of data, the surgical pathology files of Washington University were searched for the terms “verrucous” and “carcinoma” appearing anywhere in the report on head and neck cases from 1988 to 2012. Only cases that were surgically resected were included (biopsy only cases were excluded) in order to assure examination of all tumor tissue histologically. Hematoxylin and eosin stained slides from the resection specimens, as well as any prior biopsy specimens, were reviewed for classification. Patients meeting criteria for proliferative verrucous leukoplakia (based on clinical and pathologic features described in the literature) were excluded [11, 12]. Treatment and follow up information were gathered from the electronic medical

Fig. 2 Histologic features of verrucous carcinoma with dysplasia. **a** Low power view showing typical surface verrucous carcinoma features with papillomatosis and hyperkeratosis ($\times 1$ magnification). **b** Medium power view showing, at the tumor base, irregular nests of tumor with angulated edges, cells retaining abundant cytoplasm, and no obvious stromal desmoplastic reaction ($\times 4$ magnification). **c** High power view showing expansion of the dysplastic epithelium characterized by a basal layer having cells with higher nuclear to cytoplasmic ratios, nuclear hyperchromasia, and increased mitotic activity, including mitoses several layers above the basement membrane ($\times 15$ magnification)

cases were independently reviewed by four pathologists (KRP, JSL, RDC, SEM). The Emory University cases were searched from 2004 to 2009 and screened from the files of the Department of Pathology at Emory University School of Medicine with the same criteria. All Emory University cases were independently reviewed by three pathologists (SEM, KRP, JSL). Following classification (below), discrepant cases were resolved by consensus review.

The following criteria were used to classify tumors into Categories A, B, or C. Category A were pure VC cases showing the characteristic histopathologic features, such as thick, inward growing ribbons and nests with large epithelial cells having abundant glassy, eosinophilic cytoplasm, hyperkeratosis, broad pushing rete with or without chronic inflammation at the epithelial-stromal junction, and smooth stromal interface (Fig. 1). They specifically had to lack epithelial dysplasia, mitoses above the suprabasal layer (because these are known to be atypical), and frank stromal invasion. Category B or VCDMI were cases showing the above verrucous features but also showing either epithelial dysplasia (Fig. 2) or areas of conventional SCC, but where the conventional SCC component was minimal (specifically, invasive nests had to be less than or equal to 2 mm away from areas of VC) (Fig. 3). Epithelial dysplasia was defined in our cases as tumors having one or more of the following features: expansion of the basal layer by enlarged or hyperchromatic cells, cytologic atypia or pleomorphism, decreased maturation with enlarged or hyperchromatic nuclei above the basal layers, cells with high nuclear to cytoplasmic ratio above the suprabasal layer, or multiple or atypical mitoses above the basal or suprabasal layers. The cut off value of 2 mm was chosen somewhat arbitrarily based on published data on oral cavity SCC, where less than 2–4 mm of invasion means the likelihood of nodal metastases is quite low [13–15]. Depth of invasion was measured as the distance from the deepest point of invasion of the conventional invasive SCC component from the nearest focus of pure VC. Although it could be argued that invasion should utilize the distance of the conventional invasive SCC component from the level of the surrounding normal epithelium, this could not be clearly measured in most cases. Further, measuring from

records. Cases with less than 12 months of follow up were excluded due to insufficient follow up to reliably ascertain clinical outcome(s). All of the Washington University

Fig. 3 Verrucous carcinoma with minimal invasion. **a** Low power view again showing the typical verrucous carcinoma features ($\times 4$ magnification). **b** In addition, there are small nests detached from the basal aspect (*arrow*) that have irregular contours, more cytologic atypia, and focal stromal desmoplastic reaction ($\times 4$ magnification). **c** Higher power view of small detached, irregular nests, showing cells with abundant, eosinophilic cytoplasm, central keratin pearls, and eliciting a desmoplastic stromal reaction, features diagnostic of invasive tumor. The foci are < 2 mm from the nearest verrucous neoplastic area in the upper left portion of the field, thus diagnostic of verrucous carcinoma with minimal invasion ($\times 20$ magnification)

features of dysplasia, those utilized to diagnose dysplasia and/or invasion are those common to typical SCC. Prior to individual review and classification of the cases, the four reviewing pathologists did review select cases around a multi-headed microscope.

An attempt was made to further subdivide these tumors into categories Bd (only dysplasia, no conventional invasive SCC) and category Bi (conventional invasive SCC with < 2 mm of depth), although agreement among pathologists was poor in distinguishing Bd from Bi. Category C, or SCC-VC, were tumors with areas of VC and with a conventional SCC component which invaded more than 2 mm from the nearest focus of VC (Fig. 4). Tumors were T-staged based on overall amount of tumor rather than just on the conventional invasive SCC component for two reasons: (1) because these components frequently merged imperceptively together making subregion tumor area measurement very difficult and (2) because this is how such tumors would have to be clinically staged.

All cases were then manually matched with cases of conventional SCC (not associated with VC) with at least 24 months of follow up from large institutional research registries. These were matched in two separate ways: (1) by age, anatomic subsite, and T-stage and (2) by age, anatomic subsite, and T and N-stages. The first matching resulted in several more controls than the cases and the second type of matching was a paired match where each tumor of the case group was matched with a conventional SCC to form a control group. Statistical analysis was done using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla California USA). Fisher's exact and Chi square tests were used as appropriate for ordinal variables and descriptive statistics for continuous variables such as age. Interobserver variability in the assessment of classification of Bd versus Bi lesions among pathologists was calculated using Fleiss's kappa statistic.

Results

A total of 58 cases satisfied the criteria for inclusion in the study, 49 from Washington University (16 VC, 20 VCDML, 13 SCC-VC) and 9 from Emory University (2 VC, 6

the leading edge of the VC seemed to be a better assessment than measuring from actual surface because this does not combine the tumor burden from both the VC component and the conventional invasive SCC component for the overall depth of invasion. Although there was no formal system or criteria developed for the reviewers for the

VCDMI, 1 SCC-VC). The demographic and clinical features of the cases and controls are presented in Table 1 and clinical outcomes in Table 2. Among the VC group, patients were predominantly men with a mean age of 74 years. The follow up duration ranged from 12 to 145 months (mean 38.2; median 32) for the overall cohort, while for just the patients alive at last follow up, it ranged from 12 to 128 months (mean 46.3; median 41.5). The oral cavity and larynx were the most common anatomic sites across all three categories. Control cases consisted of 58 age, site, and T and N-stage matched conventional SCCs. Among these, most patients were men with a mean age of 63 years. The clinical follow up duration ranged from 21 to 134 months (mean 60.2; median 51).

None of the patients with VC or VCDMI presented with nodal metastases, and most patients (37/44; 84.1 %) had T1 or T2 tumors. There was no statistically significant difference in T-stage distribution between VC and VCDMI patients ($p = 0.68$). SCC-VC patients, however, showed a more uniform distribution across all T stages with fewer (8 of 14; 57.1 %) having T1 or T2 tumors. However, this difference was not statistically significant between VC and SCC-VC patients ($p = 0.096$) or between VCDMI and SCC-VC patients ($p = 0.15$). Two SCC-VC patients presented with nodal metastases while none of the VC or VCDMI patients had metastases. N-stage was statistically

significantly different between VC and SCC-VC and between VCDMI and SCC-VC, but not between VC and VCDMI. All but one patient was treated primarily with surgery. Further, 11 % of patients with pure VC (2 of 18), 15 % with VCDMI (4 of 26) and 43 % with SCC-VC (6 of 14) received adjuvant radiation. For the pure VC patients, radiation was given as the primary treatment modality after an excisional biopsy of the vocal cord cancer (one patient) and in the other patient the indication for adjuvant radiation post-surgery was not clear from the clinical records. The differences in radiation treatment rates between VC and VCDMI and between VCDMI and SCC-VC were not statistically significant ($p > 0.05$), but those for VC versus SCC-VC were significant ($p = 0.027$).

Tumor recurred locally in 1 of 18 (5.6 %) VC, 5 of 26 (19.2 %) VCDMI, and 7 of 14 (50 %) SCC-VC patients. Regional lymph node metastases developed in 1 of 18 (5.6 %) VC cases (upon recurrence of the tumor at a later date with development of conventional SCC), 2 of 26 (7.7 %) VCDMI cases, and 3 of 14 (21.4 %) SCC-VC cases. Taken together, disease recurrence, in any form, either local or in regional lymph nodes, occurred in 1 of 18 (5.6 %) VC cases, 5 of 26 (19.2 %) VCDMI cases, and 7 of 14 (50 %) SCC-VC cases. No patients in any of the three groups developed distant metastases. None of the patients with VC or VCDMI died from disease (all patients with local or

Fig. 4 Histologic features of established squamous cell carcinoma arising in verrucous carcinoma with a verrucous carcinoma component (*upper right*) also having a poorly differentiated squamous cell

carcinoma (*lower left*) that invades to a depth more than 2 mm beyond the verrucous component ($\times 2$ magnification)

Table 1 Demographic and clinical parameters of the cases and matched controls

Demographic and clinical parameters	Cases			Controls ^a		
	VC (n = 18)	VCDMI (n = 26)	SCC-VC (n = 14)	SCC matched to VC (n = 18)	SCC matched to VCDMI (n = 26)	SCC matched to SCC-VC (n = 14)
Age						
Range (mean)	48–96 (74)	33–101 (73.5)	56–98 (79)	44–91 (66)	41–86 (61.5)	52–82 (64)
Gender						
M:F	11:7	15:11	9:5	8:1	9:4	9:5
Follow up in months						
Range (Median)	12–113 (46)	12–128 (44.5)	12–145 (44)	29–120 (67)	21–134 (57)	24–132 (57)
Site						
Oral cavity (%)	11 (61.1)	15 (57.7)	9 (64.3)	11 (61.1)	15 (57.7)	9 (64.3)
Lip (%)	0 (0)	1 (3.8)	0	0 (0)	1 (3.8)	0
Larynx (%)	7 (38.9)	10 (38.5)	5 (35.7)	7 (38.9)	10 (38.5)	5 (35.7)
Radiation	2/18 (11.1)	4/26 (15.4)	6/14 (42.9)	1/18 (5.6)	11/26 (42.3)	9/14 (64.3)
T-stage (%)						
T1	14 (77.8)	12 (46.2)	4 (28.6)	14 (77.8)	12 (46.2)	4 (28.6)
T2	2 (11.1)	9 (34.6)	4 (28.6)	2 (11.1)	9 (34.6)	4 (28.6)
T3	2 (11.1)	3 (11.5)	2 (14.3)	2 (11.1)	3 (11.5)	2 (14.3)
T4	0	2 (6.1)	4 (28.6)	0	2 (6.1)	4 (28.6)
N-stage (%)						
N0	18 (100)	26 (100)	12 (85.7)	18 (100)	26 (100)	12 (85.7)
N1	0	0	1 (7.1)	0	0	1 (7.1)
N2	0	0	1 (7.1)	0	0	1 (7.1)
N3	0	0	0	0	0	0

Cat category, *SCC* squamous cell carcinoma, *SCC-VC* squamous cell carcinoma arising in verrucous carcinoma, *VC* verrucous carcinoma, *VCDMI* verrucous carcinoma with dysplasia or minimal invasion

^a Pair matching (each case paired with a single control case)

regional recurrence were salvaged successfully with surgery) whereas 5 of 14 (35.7 %) of SCC-VC patients died from recurrent disease. Disease recurrence rates were higher in the SCC-VC cases (50 %) compared with both the VC (5.6 %) and VCDMI cases (19.2 %). This was statistically significant for SCC-VC versus VC ($p = 0.01$) and, although not statistically significant, a trend was observed for SCC-VC versus VCDMI ($p = 0.07$).

As mentioned, an attempt was made to differentiate the VCDMI cases into those with just dysplasia and those with ≤ 2 mm stromal invasion. There was great variability among study pathologists in this distinction. Among the 26 VCDMI cases, all four study pathologists agreed on the same classification in only 14 (54 %) cases. The Kappa value for agreement for VCDMI tumors with only dysplasia versus with minimal invasion was only 0.158 (95 % CI 0.04–0.41), a result considered to be only slight agreement. By consensus review, the cases were divided to the extent possible into 13 cases with just dysplasia and 13 with invasive SCC of ≤ 2 mm. Similarities in the clinical outcomes were seen between the two groups and, moreover, between these groups and pure VC (see Supplemental

Table 1). When compared with SCC-VC patients (category C or invasive SCC component arising in VC), the VCDMI patients that had only dysplasia without any invasion (category Bd) showed significant differences in local recurrence ($p = 0.03$) and overall disease recurrence ($p = 0.03$). When such a comparison was done between patients of SCC-VC (Category C) and the VCDMI patients that showed focal invasion (Category Bi), patients with focal invasion showed lower rates of local, regional and overall disease recurrence, although this difference was not statistically significant. Only 4 of 13 (30.8 %) cases of Category Bi showed local recurrence as against 7 of 14 (50 %) in category C. Similarly, 2 of 13 (15.4 %) cases of Category Bi showed regional recurrence versus 3 of 14 cases (21.4 %) in Category C. Also, only 4 of 13 (30.8 %) cases of Category Bi showed overall disease recurrence versus 7 of 14 (50 %) cases of Category C.

Cases of VC, VCDMI, and SCC-VC were matched with conventional SCC (not associated with VC) for primary site (oral cavity or larynx) and for T-stage (Table 3). For the conventional SCC patients, nodal metastases were seen at presentation in 39 of 98 (39.8 %) T1 tumors, 99 of 153

Table 2 Differences in clinical presentation and outcomes amongst the major tumor categories

Clinical parameters	VC versus SCC-VC	VC versus VCDMI	VCDMI versus SCC-VC
Nodal metastases at presentation	0/18 (0 %) versus 2/14 (14.3 %) <i>p</i> = 0.001	0/18 versus 0/26 <i>p</i> = 1.0	0/26 versus 2/14 (14.3 %) <i>p</i> = 0.0002
Local recurrence	1/18 (5.6 %) versus 7/14 (50 %) <i>p</i> = 0.01	1/18 (5.6 %) versus 5/26 (19.2 %) <i>p</i> = 0.37	5/26 (19.2 %) versus 7/14 (50 %) <i>p</i> = 0.07
Regional (Nodal) recurrence	1/18 (5.6 %) versus 3/14 (21.4 %) <i>p</i> = 0.29	1/18 (5.6 %) versus 2/26 (7.7 %) <i>p</i> = 1.0	2/26 (7.7 %) versus 3/14 (21.4 %) <i>p</i> = 0.32
Any form of disease recurrence	1/18 (5.6 %) versus 7/14 (50 %) <i>p</i> = 0.01	1/18 (5.6 %) versus 5/26 (19.2 %) <i>p</i> = 0.37	5/26 (19.2 %) versus 7/14 (50 %) <i>p</i> = 0.07

p values calculated by Fisher's exact test; values in bold are statistically significant

SCC squamous cell carcinoma, SCC-VC squamous cell carcinoma arising in verrucous carcinoma, VC verrucous carcinoma, VCDMI verrucous carcinoma with dysplasia or minimal invasion

(64.7 %) T2 tumors, 61 of 100 (61.0 %) T3 tumors, and 88 of 149 (59.1 %) T4 tumors. Statistically significant differences were observed for nodal metastasis at presentation across all three VC categories versus the conventional SCC patients, particularly for the lower T-stage tumors (*p* = 0.002, 0.0076 and 0.03 for stage T1 VC, VCDMI, and SCC-VC, respectively). In other words, conventional SCC was significantly more likely to have nodal metastases at presentation than VC, VCDMI, and SCC-VC, particularly for lower T-stage tumors.

Cases of VC, VCDMI, and SCC-VC were then paired with conventional SCC not only for age, primary site (oral cavity or larynx), and T-stage, but also for N-stage (Table 4). The rates of local recurrence, regional (nodal) recurrence, or any type of disease recurrence were lower for VC and for VCDMI than for conventional SCC, but these differences were not statistically significant. For SCC-VC, however, recurrence rates were essentially comparable with conventional SCC.

Discussion

Pure VC, as classically described by Dr. Lauren Ackerman [1] is a tumor with no actual invasion by the tumor cells through the basement membrane. It has a much better

Table 3 Differences in rates of nodal metastasis at presentation when matched with all conventional SCCs for anatomic site and T-stage*

Tumor categories	Stage T1 39/98 (39.8 %)	Stage T2 99/153 (64.7 %)	Stage T3 61/100 (61.0 %)	Stage T4 88/149 (59.1 %)
VC (n = 18)	0/14 <i>p</i> = 0.002	0/2 <i>p</i> = 0.12	0/2 <i>p</i> = 0.15	–
VCDMI (n = 26)	0/12 <i>p</i> = 0.0076	0/9 <i>p</i> = 0.0001	0/3 <i>p</i> = 0.06	0/2 <i>p</i> = 0.17
SCC-VC (n = 14)	0/4 <i>p</i> = 0.03	0/4 <i>p</i> = 0.01	1/2 (50 %) <i>p</i> = 1.0	1/4 (25 %) <i>p</i> = 0.3

p values calculated by Fisher's exact test; values in bold are statistically significant

SCC squamous cell carcinoma, SCC-VC squamous cell carcinoma arising in verrucous carcinoma, VC verrucous carcinoma, VCDMI verrucous carcinoma with dysplasia or minimal invasion

* Group matching (each verrucous lesion matched to larger groups of SCC control cases)

Table 4 Differences in clinical outcomes between tumor categories and age, site, and stage (T and N) matched conventional SCCs

Clinical parameters	VC versus SCC	VCDMI versus SCC	SCC-VC versus SCC
Local recurrence	1/18 (5.6 %) versus 3/18 (16.7 %) <i>p</i> = 0.6	5/26 (19.2 %) versus 6/26 (23.1 %) <i>p</i> = 1.0	7/14 (50 %) versus 3/14 (21.4 %) <i>p</i> = 0.2
Regional (Nodal) recurrence	1/18 (5.6 %) versus 3/18 (16.7 %) <i>p</i> = 0.6	2/26 (7.7 %) versus 3/26 (11.3 %) <i>p</i> = 1.0	3/14 (21.4 %) versus 4/14 (28.6 %) <i>p</i> = 1.0
Any form of disease recurrence	1/18 (5.6 %) versus 5/18 (27.8 %) <i>p</i> = 0.2	5/26 (19.2 %) versus 7/26 (26.9 %) <i>p</i> = 0.7	7/14 (50 %) versus 5/14 (35.7 %) <i>p</i> = 0.7

Pair matching (each case paired with a single control case)

p values calculated by Fisher's exact test; values in bold are statistically significant

SCC squamous cell carcinoma, SCC-VC squamous cell carcinoma arising in verrucous carcinoma, VC verrucous carcinoma, VCDMI verrucous carcinoma with dysplasia or minimal invasion

prognosis than conventional SCC, even at advanced T stages [8]. Metastases do not occur unless there is an associated conventional SCC component where tumor cells have actually breached the basement membrane.

Surgical resection is the currently accepted treatment for VC of the head and neck [8]. Disease recurrence is infrequent and patient survival excellent. When disease recurs, it is almost exclusively local, so negative margins at the time of resection are important [16, 17]. In a study of 133

patients with oral cavity VC, Rekha et al. [18] reported a local recurrence rate of only 2.3 %. The vast majority of patients were treated with surgery alone. In another study of 38 patients with pure VC of the oral cavity, the majority of whom had T3 tumors (34.2 %), surgical excision alone (without neck dissection) was effective with no reported disease recurrence [19]. Another study involving 30 cases of laryngeal VC also showed that surgery is the optimal therapy but that radiation and even chemotherapy can be used as alternatives for inoperable cases [20]. Although the older literature raised the issue of radiotherapy-related anaplastic or malignant transformation in VC [3, 9, 21–25], this has clearly been refuted. Radiotherapy is now an accepted treatment modality for inoperable VC or for patients who are poor surgical candidates [26, 27]. VCs in locations other than the head and neck are treated similarly, with surgery being the first choice for resectable tumors and other modalities being used only for those not amenable to surgery [28, 29].

When it comes to cases of VC with dysplasia and/or focal invasion, there is little information in the literature about their diagnosis, terminology, or treatment at any of the anatomic sub-sites. The convention in common practice is that dysplasia and/or stromal invasion obviate the diagnosis of pure VC, essentially leaving such tumors to be regarded as conventional SCC. However, it is possible (and the previous literature [6, 30] suggests) that there is a pathologically discernible category of tumors that is biologically intermediate between pure VC and SCC arising from VC.

The limited literature addressing this question almost all utilizes the terms “hybrid verrucous carcinoma” or “verrucous squamous carcinoma”, the implication being that they are all SCC arising in VC. This is reported to occur in as many as 20 % of VC, either at primary presentation or upon recurrence. The lack of sub categorization suggests that VC with dysplasia, minimal invasion, or extensive invasion should be treated just as conventional SCC [6, 19, 24, 30–32]. One of the largest series of oral cavity VC involving 133 patients from India states that “some cases showed severe degrees of dysplasia and extension into the muscle layer”, however none of their patients showed histologically positive lymph nodes or distant metastases. Local recurrence was seen in only 3 of 133 patients [18]. Another study of 30 cases of laryngeal VC over 23 years showed surgery to be the primary treatment option with concomitant radio/chemotherapy as an alternative for voice preservation [20]. An additional study from the Mayo Clinic involving 53 patients of laryngeal VC over 30 years had six cases of “hybrid” VC. None of the cases had palpable neck nodes at presentation, and none developed distant metastases. There were a total of ten recurrences of which seven were local, one regional and two both. Of the ten recurrent tumors, only three were hybrid tumors. When the entire group of 53

patients (including six hybrid tumors) was compared with an age and sex matched cohort of conventional SCC patients, the survival curves did not show significant differences. In the most definitive study on VC with a component of conventional SCC, Medina et al. studied 104 VC and noted that 20 of them (19.2 %) “demonstrated foci of less-differentiated squamous carcinoma with the VC (hybrid tumors)”. Interestingly, after treatment, these latter tumors had a slightly higher rate of local recurrence, but none of the pure VC and none of the “hybrid” tumors had nodal or distant metastases [6]. All of these studies suggest that dysplasia and/or limited foci of conventional SCC in VC equate biologically more to VC rather than to pure conventional SCCs. However, many of the authors in these studies still have gone on to suggest that “hybrid” tumors should be treated as comparably staged conventional SCC [10].

In the current series of 58 patients, with clear definitions for the entity VCDMI, we found that although local recurrence in VCDMI was 2–3 times higher than for VC (5.6 vs 19.2 %, $p = 0.37$), all patients were successfully treated with additional surgery. None of them developed metastasis. This was different compared to SCC-VC (i.e. more extensive SCC arising in VC) (19.2 vs 50 %, $p = 0.07$) and compared to conventional SCC that was matched for T-stage but not for N-stage. Thus, although there appears to be a partial “spectrum” of clinical behavior from VC to VCDMI to SCC-VC, VCDMI behavior seems much closer to that of pure VC than to that of established SCC arising in VC or just conventional SCC. Hence, the data suggests that rather than grouping VCDMI with SCC arising in VC, an intermediate category between pure VC and SCC-VC may be warranted. Given the prior literature and these findings, one could suggest that treating VCDMI just as conventional SCC may result in overtreatment. Future studies could investigate if surgical therapy alone is sufficient treatment for VCDMI patients, as it is for VC.

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References

1. Ackerman LV. Verrucous carcinoma of the oral cavity. *Surgery*. 1948;23(4):670–8.
2. Johnson N, Francheschi S, Ferlay J, et al. Squamous cell carcinoma. In: Barnes L, editor. World Health Organization classification of tumours. Lyon: IARC Press; 2005. p. 168–75.
3. Kraus FT, Perezmesa C. Verrucous carcinoma. Clinical and pathologic study of 105 cases involving oral cavity, larynx and genitalia. *Cancer*. 1966;19(1):26–38.
4. Jahn AF, Walter JB, Farkashidy J. Verrucous carcinoma of the nasopharynx—a clinicopathologic case report. *J Otolaryngol*. 1980;9(1):84–9.

5. Durden FL, Moore CE, Muller S. Verrucous carcinoma of the paranasal sinuses: a case report. *Ear Nose Throat J.* 2010;89(7):E21–3.
6. Medina JE, Dichtel W, Luna MA. Verrucous-squamous carcinomas of the oral cavity. A clinicopathologic study of 104 cases. *Arch Otolaryngol.* 1984;110(7):437–40.
7. Oliveira DT, de Moraes RV, Fiamengui Filho JF, et al. Oral verrucous carcinoma: a retrospective study in Sao Paulo Region, Brazil. *Clin Oral Investig.* 2006;10(3):205–9.
8. Koch BB, Trask DK, Hoffman HT, et al. National survey of head and neck verrucous carcinoma: patterns of presentation, care, and outcome. *Cancer.* 2001;92(1):110–20.
9. Fonts EA, Greenlaw RH, Rush BF, et al. Verrucous squamous cell carcinoma of the oral cavity. *Cancer.* 1969;23(1):152–60.
10. Orvidas LJ, Olsen KD, Lewis JE, et al. Verrucous carcinoma of the larynx: a review of 53 patients. *Head Neck.* 1998;20(3):197–203.
11. Cerero-Lapiedra R, Balade-Martinez D, Moreno-Lopez LA, et al. Proliferative verrucous leukoplakia: a proposal for diagnostic criteria. *Med Oral Patol Oral Cir Bucal.* 2010;15(6):e839–45.
12. Batsakis JG, Suarez P, El-Naggar AK. Proliferative verrucous leukoplakia and its related lesions. *Oral Oncol.* 1999;35(4):354–9.
13. An S-Y, Jung E-J, Lee M, et al. Factors related to regional recurrence in early stage squamous cell carcinoma of the oral tongue. *Clin Exp Otorhinolaryngol.* 2008;1(3):166–70.
14. Chandler K, Vance C, Budnick S, et al. Muscle invasion in oral tongue squamous cell carcinoma as a predictor of nodal status and local recurrence: just as effective as depth of invasion? *Head Neck Pathol.* 2011;5(4):359–63.
15. Larsen S, Johansen J, Sorensen J, et al. The prognostic significance of histological features in oral squamous cell carcinoma. *J Oral Pathol Med.* 2009;38(8):657–62.
16. Sciubba JJ, Helman JJ. Current management strategies for verrucous hyperkeratosis and verrucous carcinoma. *Oral Maxillofac Surg Clin North Am.* 2013;25(1):77–82, vi.
17. Walvekar RR, Chaukar DA, Deshpande MS, et al. Verrucous carcinoma of the oral cavity: A clinical and pathological study of 101 cases. *Oral Oncol.* 2009;45(1):47–51.
18. Rekha KP, Angadi PV. Verrucous carcinoma of the oral cavity: a clinico-pathologic appraisal of 133 cases in Indians. *Oral Maxillofac Surg.* 2010;14(4):211–8.
19. Kang C-J, Chang JT-C, Chen T-M, et al. Surgical treatment of oral verrucous carcinoma. *Chang Gung Med J.* 2003;26(11):807–12.
20. Strojan P, Smid L, Cizmurevic B, et al. Verrucous carcinoma of the larynx: determining the best treatment option. *Eur J Surg Oncol.* 2006;32(9):984–8.
21. Perez CA, Kraus FT, Evans JC, et al. Anaplastic transformation in verrucous carcinoma of the oral cavity after radiation therapy. *Radiology.* 1966;86(1):108–15.
22. Demian SD, Bushkin FL, Echevarria RA. Perineural invasion and anaplastic transformation of verrucous carcinoma. *Cancer.* 1973;32(2):395–401.
23. McDonald JS, Crissman JD, Gluckman JL. Verrucous carcinoma of the oral cavity. *Head Neck Surg.* 1982;5(1):22–8.
24. Ferlito A, Rinaldo A, MannarÃ GM. Is primary radiotherapy an appropriate option for the treatment of verrucous carcinoma of the head and neck? *J Laryngol Otol.* 1998;112(2):132–9.
25. Ferlito A, Recher G. Ackerman's tumor (verrucous carcinoma) of the larynx: a clinicopathologic study of 77 cases. *Cancer.* 1980;46(7):1617–30.
26. Jyothirmayi R, Sankaranarayanan R, Varghese C, et al. Radiotherapy in the treatment of verrucous carcinoma of the oral cavity. *Oral Oncol.* 1997;33(2):124–8.
27. Vidyasagar MS, Fernandes DJ, Kasturi DP, et al. Radiotherapy and verrucous carcinoma of the oral cavity. A study of 107 cases. *Acta Oncol.* 1992;31(1):43–7.
28. Chuanyu S, Ke X, Jie Z, et al. Surgical treatment for 11 cases of penile verrucous carcinoma. *Ann Dermatol.* 2011;23(Suppl 3):S346–9.
29. Masih AS, Stoler MH, Farrow GM, et al. Penile verrucous carcinoma: a clinicopathologic, human papillomavirus typing and flow cytometric analysis. *Mod Pathol.* 1992;5(1):48–55.
30. Kolokythas A, Rogers TM, Miloro M. Hybrid verrucous squamous carcinoma of the oral cavity: treatment considerations based on a critical review of the literature. *J Oral Maxillofac Surg.* 2010;68(9):2320–4.
31. Yoshimura Y, Mishima K, Obara S, et al. Treatment modalities for oral verrucous carcinomas and their outcomes: contribution of radiotherapy and chemotherapy. *Int J Clin Oncol.* 2001;6(4):192–200.
32. Strojan P, Ferlito A, Wu CF, et al. Intraarterial chemotherapy: a valid option in the treatment of verrucous carcinoma? *Eur Arch Otorhinolaryngol.* 2010;267(6):835–7.