Incidence of 'Drop-Off' Cancer Development Within the Oral Cavity

Brynn Gwartzman[1], Elizabeth Philipone[1]*

[1] Columbia University College of Dental Medicine, [2] Department of Oral and Maxillofacial Pathology, Columbia University, [3]Department of Pathology, Columbia University Medical Center, *Elizabeth Philipone

Background

Histologically, oral squamous cell carcinoma can develop as a progression from severe dysplasia/carcinoma *in situ* or as an invasion from an epithelium that lacks severe or full thickness intraepithelial dysplasia. Thus, in the oral cavity, severe dysplasia/carcinoma *in situ* is not a prerequisite for development of an invasive squamous cell carcinoma. Such invasive carcinomas 'drop down' from the basal cell layer with the overlying mucosa showing little or in some cases, no evidence of dysplasia. This phenomenon is known amongst pathologists but is rarely reported in the literature. A search of scientific literature failed to reveal any studies reporting the incidence of 'drop-down' or 'drop-off' carcinoma within the oral cavity. We believe that it is critical for clinicians to be aware of this phenomena. Without awareness, clinicians may erroneously regard lesions without severe dysplasia as safe to monitor before providing definitive treatment.

Objectives

We seek to investigate the incidence of 'drop-off' or 'drop-down' cancer development within the oral cavity and bring clinical awareness to this phenomena as it is infrequently reported in scientific literature.

1) What is the incidence of 'drop-off' or 'drop-down' cancer development within the oral cavity?

2) Are there any descriptive statistics (i.e. site, sex, age, health history) that are statistically significant between 'drop-down' carcinomas and carcinomas arising from severe dysplasia/carcinoma *in situ*?

Materials & Methods

Columbia University Medical Center's Department of Pathology database was searched to identify cases of oral squamous cell carcinoma surgically treated by the department of ENT between January 1st, 2010 and June 1st, 2022. A random sample of 100 squamous cell carcinoma cases was selected to be analyzed as a part of this retrospective study. The histologic slides from both the diagnostic biopsy as well as the surgical resections for all available cases were retrieved and reviewed. The mucosa overlying and adjacent to the carcinoma was histologically evaluated to determine the dysplasia grade using the two-tier grading system (1). Those cases characterized by the presence of invasive carcinoma originating from dysplastic epithelium limited to the basal layer of the epithelium with the majority of surface epithelium lacking dysplasia fit the criteria of 'drop-off'/ 'drop-down' cancer development.

Below are examples of SCC associated with different grades of dysplasia demonstrating how the 100 samples were characterized.

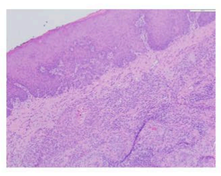

Figure 1

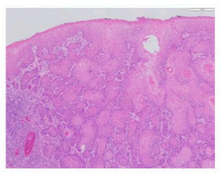

Figure 2a

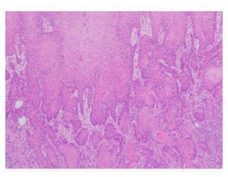

Figure 2b

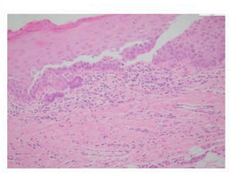

Figure 3

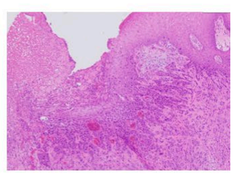

Figure 4

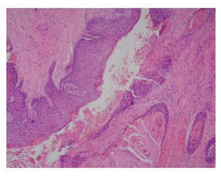

Figure 5a

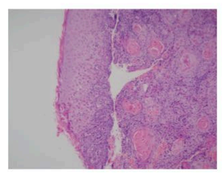

Figure 5b

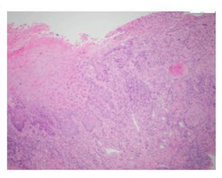

Figure 6

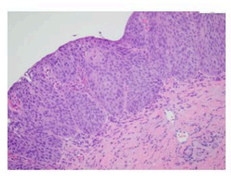

Figure 7

Figure 1 Low grade dysplasia associated with squamous cell carcinoma of the lateral tongue. Although there is no direct connection point between the cancer and the low grade dysplasia, it is presumed that the cancer invasion occurred by 'dropping-down' (Magnification 4x).
Figure 2a-2b Low grade dysplasia associated with squamous cell carcinoma of the buccal mucosa (Magnification 4x, 10x).
Figure 3 Low grade dysplasia associated with a superficial invasion of squamous cell carcinoma of the lateral tongue. Here, the epithelium appears to be "pinching off" which is the presumed method of 'drop-down' cancer invasion (Magnification 4x).
Figure 4 Adjacent low grade dysplasia associated with ulcerated epithelium overlying the presumed cancer invasion of the lateral tongue. Due to the presence of the ulcer, this sample was classified as 'indeterminate' (Magnification 10x).
Figure 5a- 5b High grade dysplasia associated with squamous cell carcinoma of the gingiva and lateral tongue respectively (Magnification 4x, 10x).
Figure 6 High grade dysplasia associated with squamous cell carcinoma of the lateral tongue with ulcerated epithelium. Enough of the full specimen contained high grade dysplasia epithelium associated with cancer invasion. Notable architectural changes include keratin pearls and dyskeratotic cells going past ⅔ of the epithelium (Magnification 4x).
Figure 7 High grade dysplasia (carcinoma *in situ*) of the lateral tongue (Magnification 10x).

Results

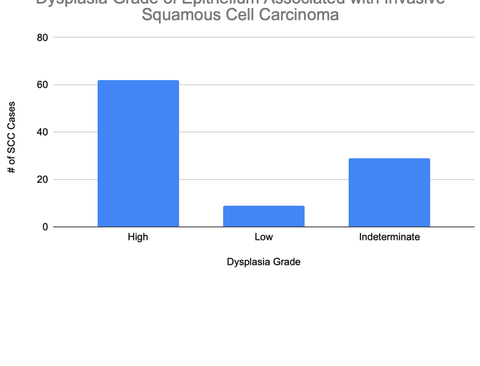

Figure 8 62 squamous cell carcinoma cases were associated with high grade dysplasia (62%), 9 low grade dysplasia (9%), and 29 indeterminate (29%). Of the cases that were marked indeterminate, 18 cases were associated with ulcer, although the adjacent epithelium appeared low grade. The other portion of the indeterminate cases did not have enough intact epithelium to correctly grade the presented dysplasia.

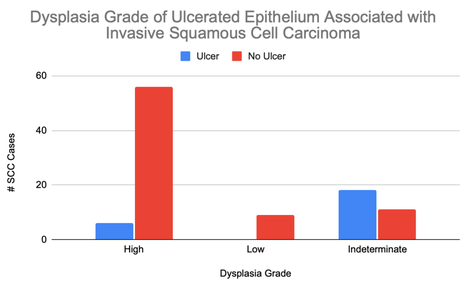

Figure 9 Of the high grade dysplasia cases, 6 were associated with ulcer. Of cases that were marked as indeterminate, 18 were associated with ulcer with adjacent epithelium being low grade, although no high grade dysplasia was seen in these cases they were categorized as indeterminate since it is possible that high grade dysplasia had been present in the segment that was ulcerated. The remaining indeterminate cases, though not ulcerated, lacked sufficient epithelium for thorough evaluation due to tissue orientation.

Results

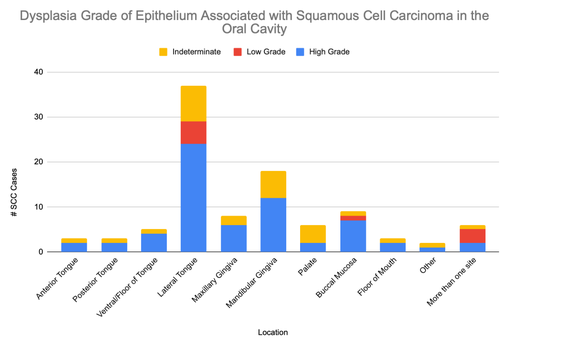

Figure 10 Both high and low grade dysplasia cases had the highest prevalence on the lateral tongue. The category labeled "more than one site" had the highest number of cases with low grade dysplasia associated with squamous cell carcinoma compared to other locations in the oral cavity. Low grade dysplasia cases associated with more than one site included the lip and floor of the mouth, mandibular gingiva and buccal mucosa, the floor of the mouth and buccal mucosa and mandible (bone). The category labeled "other" included two cases one of which was squamous cell carcinoma with high grade dysplasia of the skin of the lip and the other being indeterminate with squamous cell carcinoma of the maxillary bone.

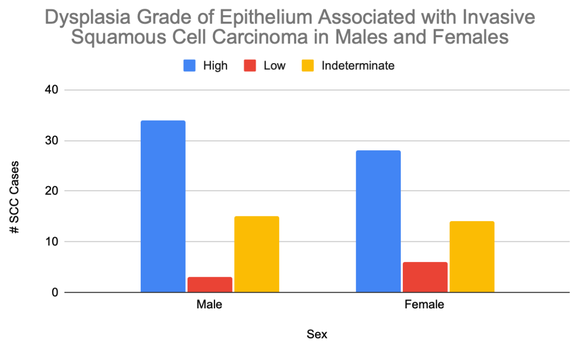

Figure 11 Majority of both male and female cases were associated with high grade dysplasia (34: male; 28: female). There were 6 female and 3 male cases associated with low grade dysplasia and 15 male and 14 female cases categorized as indeterminate.

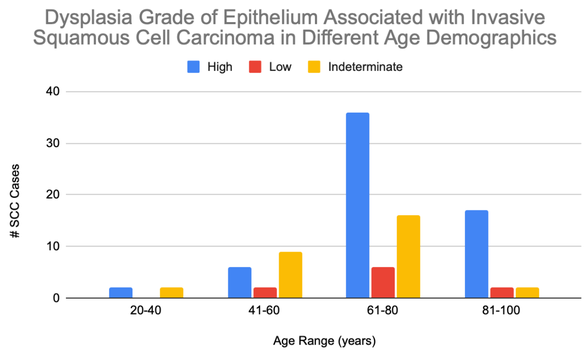

Figure 12 Age of diagnosis between 61-80 years was most prevalent in all three groups: low, high, and indeterminate.

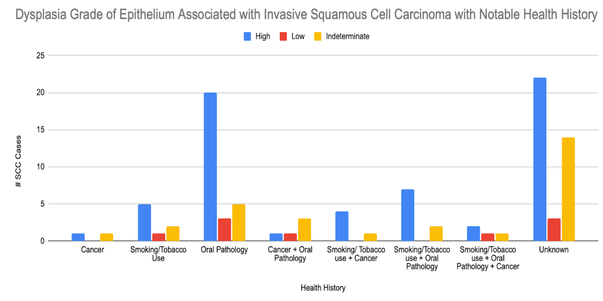

Figure 13 20 cases with a history of prior biopsy were associated with high grade dysplasia, 3 with low grade dysplasia, and 5 indeterminate. Unfortunately, given that the majority of the 100 cases studied did not have an adequate amount of health history provided, no definitive conclusions could be made about the relationship of squamous cell carcinoma with associated low grade dysplasia and health history.

Discussion

The historic model for grading epithelial dysplasia is based on the non-keratinizing form of dysplasia that occurs in the uterine cervix. In this model, there is a sequential progression of dysplasia from mild to moderate to severe to carcinoma *in situ* (CIS) before the development of carcinoma. However, in the oral cavity the dysplasia that presents is a keratinizing type. In the upper aerodigestive tract, which includes the oral cavity, severe dysplasia/carcinoma *in situ* is not a precondition for the development of an invasive squamous cell carcinoma. Such invasive carcinomas 'drop-off' or 'drop-down' from the basal layer with the overlying mucosa showing no evidence of severe dysplasia (Figure 3).

In our study, nine cases demonstrated squamous cell carcinoma arising from oral epithelium lacking high grade dysplasia or carcinoma *in situ.* A confounding factor arose in this study as many of the cases presented with ulcerated epithelium, which made proper evaluation of the entire epithelium challenging. If a case associated with ulcer demonstrated adjacent high grade dysplasia, it was reported as 'high grade'. However, if an ulcerated case only had low grade dysplasia adjacent to the ulcer as was seen in 18 cases, it was categorized as indeterminate since it is possible that high grade dysplasia had been present in the segment that was ulcerated.

Overall, the descriptive factors such as site, sex, age, and health history followed the expected risk factors for squamous cell carcinoma in the oral cavity and showed no significant differences between the 'drop-down' carcinomas and carcinomas arising from severe dysplasia/ carcinoma *in situ*. Further research with increased sample size is needed to confirm these findings and to better understand the relationship between squamous cell carcinoma and the 'drop-down' phenomenon. Examining if any molecular differences exist between cancers that arise with and without severe dysplasia could help establish targeted treatments and improve the clinical management of potentially malignant oral lesions and oral cancer outcomes. Unfortunately, as of now, there are no molecular biomarkers that specifically indicate the diagnosis of epithelial dysplasia. Although research has examined the role of p16 and Ki67 in diagnosing uterine cervical dysplasia, they proved to be of little diagnostic utility for upper aerodigestive epithelial dysplasia (1).

Conclusions

We found that out of the 100 cases of OSCC, 9 exhibited the 'drop-off' carcinoma phenomenon. The current risk factors associated with the malignant transformation of oral potentially malignant disorders namely: female sex, site predilection for the tongue, and age >50 years (2,3) were the same for both the 'drop-down' carcinomas and carcinomas arising from severe dysplasia/carcinoma *in situ* cases. However, due to the sample size, further investigation is needed to verify this finding. Awareness amongst clinicians that OSCC can develop without the prerequisite of severe dysplasia/carcinoma *in situ* is critical to ensure that patients with oral potentially premalignant lesions are managed properly.

References

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