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Biopsy Service

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THE IMPACT OF A PANDEMIC ON A MILITARY ORAL AND MAXILLOFACIAL
PATHOLOGY BIOPSY SERVICE

by

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A thesis submitted to the Faculty of the
Oral and Maxillofacial Pathology Graduate Program
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In partial fulfillment of the requirements for the degree of
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ABSTRACT

The Impact of a Pandemic on a Military Oral and Maxillofacial Pathology Biopsy Service

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Introduction: COVID-19, Coronavirus Disease – 2019, and the resulting societal reaction presented new challenges to the medical community by limiting patient access to care in 2020 and 2021. The Navy Postgraduate Dental School (NPDS) Oral and Maxillofacial Pathology (OMFP) biopsy service is dependent on patient-clinician interactions. Resultingly, NPDS policy makers and pathologists desired to understand the regulatory and societal impacts of COVID-19 restrictions on biopsy service submissions.

Objective: The aim of this study was to assess the impact of the COVID-19 pandemic on biopsy submission quantities and disease distribution.

Methods: All NPDS OMFP biopsy submissions from calendar years 2015-16 and 2019-21 were evaluated and patient demographics and biopsy diagnoses were recorded in a biopsy registry. Data collected included age, sex, biopsy site and diagnosis. Data from 2015, 2016, and 2019 were defined as pre-COVID and 2020 and 2021 as COVID. Biopsy reports for each year were organized in quarters. Diagnoses were categorized as malignant, pre-malignant, or benign.

Results: The study evaluated 9,351 biopsy submission reports. The annual pre-COVID count mean (\pm standard deviation) and yearly counts for 2020 and 2021 were 2063 ± 33.3 , 1,421, and 1,742, respectively. The mean (\pm standard deviation) percentage of diagnoses classified as malignant from pre-COVID, 2020, and 2021 were $2.46\% \pm 0.005\%$, 3.59%, and 3.04%, respectively. Case counts and representation as a percentage of all biopsy diagnoses for HPV-mediated squamous cell carcinoma increased significantly during COVID compared to pre-COVID years ($p < 0.05$).

Conclusion: Overall, reactive COVID-19 protocols led to a reduction in biopsy submission frequency, particularly during the second quarter (April to June) of 2020. However, case counts for malignant biopsies remained consistent between pre-COVID and COVID time intervals, suggesting that the identification and analysis of cases requiring definitive care were unaffected by COVID-19 protocols.

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LIST OF ABBREVIATIONS

CDC	Centers for Disease Control
COVID-19	Coronavirus Disease 2019
C-SCC	Conventional squamous cell carcinoma
DHA	Defense Health Agency
DoD	Department of Defense
HPV	Human papillomavirus
HPV-SSC	HPV-mediated squamous cell carcinoma
MD	Doctor of Medicine
NPDS	Naval Postgraduate Dental School
OMFP	Oral and Maxillofacial Pathology
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
US	United States

CHAPTER 1: Introduction

The pathway from oral pathology identification to treatment starts with a healthcare provider identifying abnormal clinical findings followed by the provisioning of a clinical differential diagnosis. If a definitive diagnosis is needed to guide treatment, a tissue biopsy is performed. The biopsied tissue is evaluated histologically, and a diagnosis is rendered to help guide treatment. Biopsy submissions serve a critical role in the differentiation of benign lesions from malignant mimickers and helps to ascertain a definitive diagnosis needed for appropriate and adequate treatment.

The timely acquisition of biopsies, and resultant guided treatment, is dependent on continuous and uninterrupted patient-provider interactions. In their absence, identification of oral disease and pathology can cause diagnostic delays, allowing for unmonitored disease progression and lowered treatment success odds. Common patient-provider interaction disruptions include personality conflicts, dental anxiety or phobia, burdensome treatment costs, changes to patient insurance plans or provider acceptance, dental practice or provider relocations or retirements, and changes in patient health status. Rare disrupters exist that have systemic effects of the frequency and quality of patient-provider interactions, to include national emergencies.

Spread of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2020 initiated the COVID-19 (coronavirus disease 2019) pandemic and resulting disease transmission prevention measures. Initial non-pharmacological interventions targeting community transmission of SARS-CoV-2 focused on social and physical distancing. In March 2020, following Centers for Disease Control (CDC) and Prevention and Defense Health Agency (DHA) public health guidance, military medical and dental treatment

facilities prioritized symptomatic problem focused exams over periodic evaluations or limited their practice to emergent care. Concurrently, many dental patients of record voluntarily delayed dental appointments, most people doing so for up to 3 months.¹ Consequently, DHA healthcare delivery and patient-provider interactions were severely restricted beginning in March 2020 and continued through 2021.²

Accordingly, questions arose in 2021 concerning COVID-19's impact on DHA biopsy services, a crucial and highly sensitive component of the identification to treatment pathway. Various studies indicated that private and public cancer services in 2020 and 2021 saw reductions in the frequency and quantity of cancer screenings, biopsies, patient evaluations and management visits, and treatment delivery.³⁻⁵ Another study indicated that COVID-19 related public health measures reduced the number of medical biopsy procedures performed, inhibited or delayed biopsy diagnosis, and consequentially delayed cancer diagnosis and/or treatment.⁶

Despite evidence indicating a negative correlation between COVID-19 mitigation strategies and cancer services utilization, no study has analyzed the effect of COVID-19 public health protocols and restrictions on an oral and maxillofacial biopsy service. Accordingly, the purpose of this study was to analyze the impact of COVID-19 mitigation strategies on a DHA oral and maxillofacial biopsy service at the Naval Postgraduate Dental School (NPDS). The primary objective was to quantify biopsy submissions by quarter and year, evaluate differences between years designated as pre-COVID-19 and by year and quarter and to analyze temporal changes in biopsy differences in biopsy submission and disease distribution

This was a seven-year retrospective analysis investigating how the COVID-19 pandemic affected oral diagnosis through the lens of NPDS's oral and maxillofacial pathology biopsy service.

CHAPTER 2: Materials and methods

STUDY DESIGN

This was a retrospective records review study analyzing reports of biopsies submitted to NPDS's Oral and Maxillofacial Pathology (OMFP) Biopsy Service from January 1, 2015 to December 31, 2021. Although the catchment area for submitted biopsies is any US Department of Defense (DoD) or Public Health Service treatment facility, most submitted biopsies are collected within the US National Capital Region and surrounding US states.

With approval from Walter Reed's Institutional Review Board, biopsy reports generated between 2015 and 2021 were queried from the DoD's Cerner CoPath digital pathology database. Biopsy reports stored in CoPath represented findings from a histological and pathological review by Oral and Maxillofacial specialists that received a definitive diagnosis. Queried results were filtered for completeness, diagnoses were verified by American Board of Oral and Maxillofacial Pathology Diplomates, and report data were transferred to a local study registry. Biopsy reports from 2017 and 2018 are currently undergoing review and not available for analysis at time of publication due to manpower constraints.

Collected data included patient age and sex, biopsy site, final diagnosis, pre-operative/differential diagnosis provided, referring provider type, referring provider source, and resection status. Biopsy sites were categorized as gingiva, mucosa, tongue, intraosseous-maxilla/mandible, salivary gland, oropharynx, sinonasal, neck, thyroid, larynx, or skin. Referring provider type categories were general dentist, periodontist, endodontist, oral surgeon, other dental specialist, otolaryngologist, other MD, and

unknown. Final diagnoses were recorded verbatim, assigned a generalized diagnosis (e.g. mucocele, mucus escape reaction, and mucus extravasation phenomenon were generalized as "mucocele"), and categorized as benign, pre-malignant, or malignant.

Years 2015 through 2019 were delineated as pre-COVID and years 2020 and 2021 as COVID. Categorical and continuous data were evaluated and presented as counts with percentages and means/medians with standard deviations, respectively. Cases were aggregated by quarter and year and assessed for temporal trends using linear regression analysis. Significant differences in proportions were assessed using χ^2 -analysis with type I error allowance set to 0.05. Statistical analyses were conducted using R v4.2.3.

CHAPTER 3: Results

DEMOGRAPHICS

A total of 9,351 pathology reports met inclusion criteria (**Table 1**). Majority of reports were from males (69.7%) with a mean age of 38.2 (sd = 17.3) years.

Approximately half of reports (45.3%, N = 4,233) did not list a referring provider type.

However, when listed, oral surgeons (27.6%, N = 2,592) and otolaryngologist (11.6%, N = 1,086) were the most common referring provider types. A small percentage of reports were generated from diagnosis of resections (1.0%, N = 96) and the majority of submitted cases were accompanied by a provider's preliminary differential (86.5%, N = 8,084).

ANNUAL SUBMISSION DISTRIBUTIONS

Annual pre-COVID case submissions for 2015, 2016, and 2019 were 2,071, 2,026, and 2,091, respectively, with a mean (standard deviation) annual case load of 2,063 (33.3). (**Figure 1**) Yearly counts from 2020 and 2021 were 1,421 and 1,742, respectively, and represented a 31.1% and 15.6% case submission decrease from mean pre-COVID counts. The greatest reduction in submission counts occurred in the second quarter (April to June) of 2020. Despite persistent case load reductions in 2021 from pre-COVID means, quarterly case submissions returned to pre-COVID distributions by October 2021.

COMMON DIAGNOSES AND SITE DISTRIBUTION

The most common diagnosis for all study years was fibroma with an annual mean count and proportion of total submissions of 206 (sd = 40.9) and 11.0% (sd = 1.02%).

(**Table 2**) Additionally, mucocele and periapical granuloma diagnoses and dentigerous cyst and hyperkeratosis/acanthosis diagnoses were in the top five diagnoses for all years

and three of five years, respectively. Majority of biopsies originated from the oral mucosa (N = 2,917, 29.2%) or intraosseously (N = 2,727, 29.2%). (**Table 3**) Case submissions of gingival origin as a percentage of all submissions decreased from 12.4% in pre-COVID years to 6.3% and 9.8% in 2020 and 2021, respectively. Conversely, submissions from oropharyngeal, sinonasal, and neck anatomical sites increased from 4.2%, 2.6%, and 0.3% to 6.9%, 4.0%, and 1.5%, respectively.

MALIGNANCIES AND PRE-MALIGNANCIES

The most frequent malignant diagnosis in 2015, 2016, and 2019 was conventional squamous cell carcinoma (C-SSC), averaging 29 (N = 86 total) diagnoses and 1.39% of all diagnoses per year. C-SSC diagnosis counts in 2020 decreased to 14 (51.7% reduction from the mean) and increased to 29 in 2021. Conversely, HPV-associated squamous cell carcinoma (HPV-SSC), pre-COVID mean of 3 (N = 10 total) diagnoses and 0.16% of all diagnoses per year, increased to 19 in 2020 (633% increase from the mean) and decreased to 8 in 2021. Total malignancy counts in 2020 and 2021 were 39 and 41, respectively, and were not significantly different from the mean total malignancy count of the pre-COVID group (mean N = 42). (**Table 4**) Pre-COVID, pre-malignant and malignant diagnoses represented 1.55% and 2.46% of all diagnoses, respectively. The contribution of pre-malignant diagnoses decreased to 1.20% and 0.80% in 2020 and 2021, respectively. Conversely, malignant diagnoses increased to 3.59% and 3.04% in 2020 and 2021, respectively. Linear regression models demonstrated that from 2015 to 2021, malignant diagnosis percentages increased 77% and pre-malignant diagnosis percentages decreased 14%. (**Figure 2**)

CHAPTER 4: Discussion

Between 2020 and 2021, the NPDS biopsy service experienced a significant reduction in biopsy submissions compared to pre-COVID years of 2015, 2016, and 2019. Reductions were most evident between March and June of 2020, but remained persistent through 2021. The distribution and rank ordering of benign lesions remained unaffected during COVID-19 years, however, the contribution of pre-malignant and malignant diagnoses significantly decreased and increased, respectively. Biopsy sites that anatomically overlapped with areas expressing COVID-19 symptomology saw significant increases in contributions to the total biopsy count.

Following CDC guidance, DHA medical and dental treatment facilities shifted in March 2020 to emergent or urgent only care. Although abnormal tissue biopsies were permitted due to their classification as emergent or urgent, the primary feeding source for abnormal tissue identification, periodic or comprehensive oral examinations with oral cancer screenings, were restricted. As patient-provider interactions declined, a concurrent drop in biopsy submissions occurred. Most notably, the second quarter of 2020 received 29.4%, 32.6%, and 37.8% of the biopsy submissions from 2015, 2016, or 2019, respectively.

Given the physical restrictions placed on routine or elective medical and dental care, it is not surprising that the biopsy service at NPDS experienced significant submission reductions in 2020. However, these reductions persisted through 2021; biopsy submissions in 2020 and 2021 were 68.9% and 84.5% of the mean submission counts between 2015 and 2019. The ebb and flow of biopsy submission counts in 2020 and 2021 demonstrated the link between external public health events to submission quantity. As

vaccines became available in the first quarter of 2021 and general restrictions were temporarily lifted, submission counts returned to normal levels (N = 510, 103.2% of pre-COVID levels). However, submission counts faltered in the second quarter of 2021 (N = 367, 72.0% of pre-COVID levels) as societal anxiety heightened over the failure of the COVID vaccines to prevent viral transmission.

Despite submission reductions in 2020 and 2021, not all types of biopsy submissions were equally affected. Biopsies diagnosed as benign lesions remained the predominant biopsy type pre-COVID and during COVID with fibromas, mucoceles, and periapical granulomas representing annually nearly 30% of all biopsies regardless of year. However, a general shift occurred in the contribution of pre-malignant and malignant diagnoses to the biopsy service. Pre-COVID, pre-malignant and malignant lesions represented 1.6% and 2.5% of all diagnoses, respectively. During COVID, pre-malignant and malignant lesion experienced diverging contributions with pre-malignant lesions accounting for 1.2% and 0.8% and malignant lesions for 3.6% and 3.0% of all diagnoses in 2020 and 2021, respectively. This increase in contribution to the whole among malignant lesions was a result of malignant submission quantities in 2020 and 2021 remaining consistent with pre-COVID quantities, whereas pre-malignant submissions declined. When viewed holistically, despite physical and psychological barriers to care during COVID, submissions that required definitive diagnosis were biopsied and evaluated at rates commiserate with pre-COVID levels.

Concurrent with the pre-malignant/malignant distribution shift in 2020 and 2021, a significant shift in biopsy site distribution occurred. Regardless of year, mucosal and intraosseous biopsies accounted for approximately 60% of biopsy sites. However, in

2020 we noticed a significant increase in the contribution of oropharyngeal, sinonasal, and neck submissions and a decrease in gingival submissions. Interestingly, sites that experienced increased contributions overlapped with anatomical locations expressly affected by an upper respiratory disease, such as COVID-19, and had historically been submitted by non-dentists. Pre-COVID, otolaryngologists submitted 71.3% (N = 311) of all oropharyngeal, sinonasal, and neck biopsies and during COVID they submitted 79.2% (N = 282). Additionally, a noticeable shift in type of squamous cell carcinoma (SCC) diagnosis occurred in 2020 where the contribution of HPV-mediated SCCs (commonly found in the palatine and lingual tonsils of the oropharynx) increased nearly ten-fold compared to pre-COVID. Based on our data we are unable to make declarative determinations concerning the link between referring provider type, anatomical location, malignant diagnosis, and COVID. However, we hypothesize that due to the heightened awareness of COVID symptomology, patients and clinicians were more acutely aware of or more likely to screen for abnormal tissue presentation in particular anatomical locations.

In general, the retrospective nature of this study, the reliance on biopsy reports and associated potential human clerical errors, date specificity limited to quarters, and missing data for calendar years 2017 and 2018 were limiting factors in the analysis the effect of COVID on NPDS's biopsy service. Of note is the absence of data from 2017 and 2018 and its effect on establishing pre-COVID norms. Data from this study were derived from and added to an initial study profiling a typical military biopsy service between 2015 and 2019. By 2020, data entry for 2015, 2016, and 2019 had been completed with plans to input 2017 and 2018 data. However, in mid-2020, study

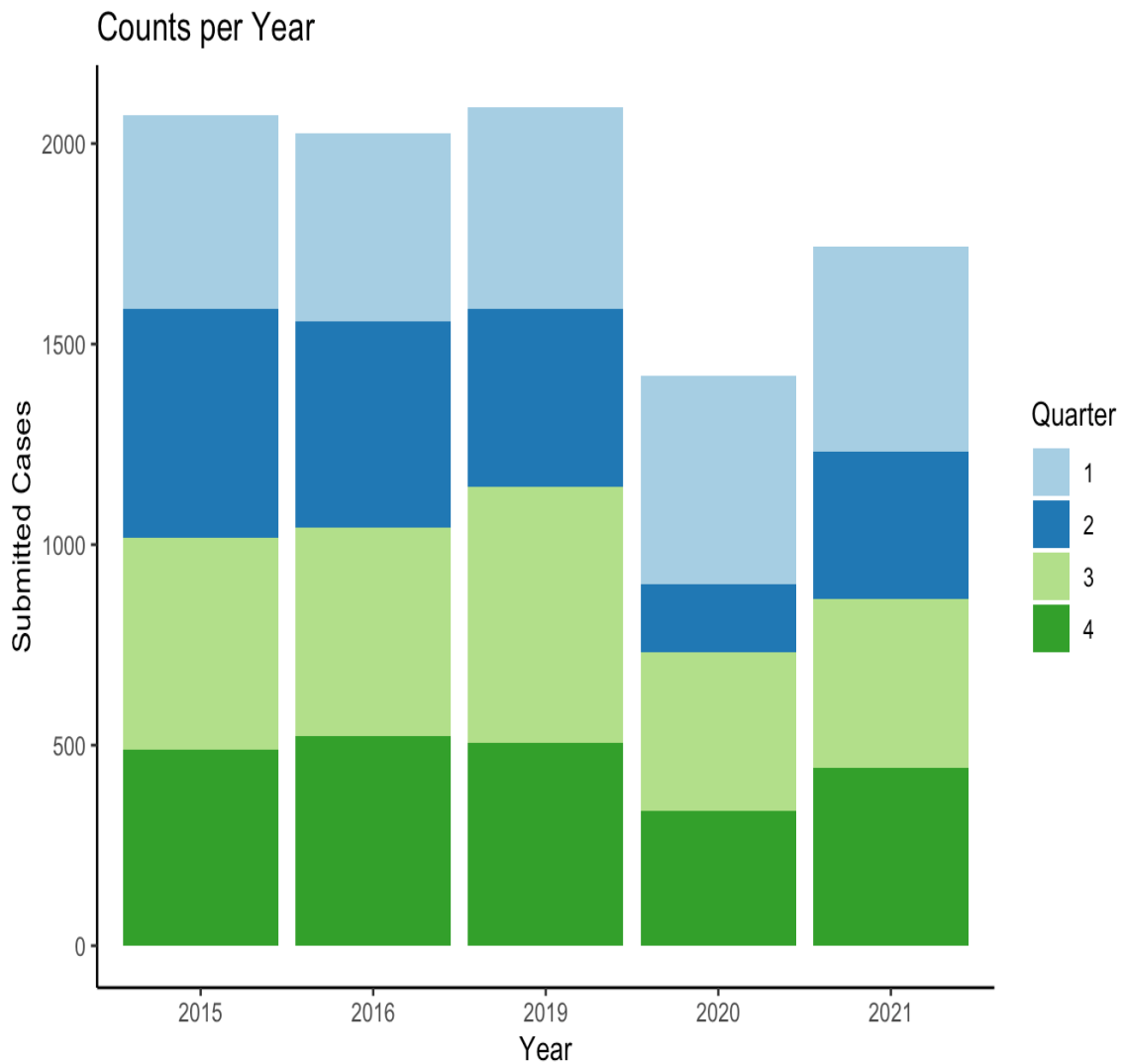
modifications were made to incorporate and prioritize 2020 and 2021 data input in order to evaluate the impact of COVID. Future research will incorporate 2017 and 2018 data in order to bolster our assessment of pre-COVID trends as well as add 2022 and 2023 data as a measurement of post-COVID trends.

CHAPTER 5: Conclusions

The NPDS biopsy service saw a significant reduction in biopsy submissions, increases in malignant diagnosis contributions, and biopsy site distribution changes during COVID compared to pre-COVID. Changes to the NPDS biopsy service profile were related temporally to structural restrictions and societal changes. Future research will seek to buttress the current limitations of this study by incorporating additional pre-COVID data and to add a post-COVID comparator time period.

Table 1. Biopsy Service Profile

	Overall (N = 9351)
Age	
Mean (SD)	38.2 (17.3)
Median [Min, Max]	35.0 [0, 89.0]
Missing	31 (0.3%)
Sex	
Female	2,829 (30.3%)
Male	6,521 (69.7%)
Missing	1 (0.0%)
Referring Provider Type	
Endodontist	259 (2.8%)
General Dentist	148 (1.6%)
General Pathologist	383 (4.1%)
Oral Pathologist	61 (0.7%)
Oral Surgeon	2,592 (27.7%)
Other Dental Specialist	5 (0.1%)
Other MD	70 (0.7%)
Otolaryngologist	1,086 (11.6%)
Periodontist	514 (5.5%)
Unknown	4,233 (45.3%)
Service Branch of Referring Provider	
Air Force	255 (2.7%)
Army	1,449 (15.5%)
Civilian	179 (1.9%)
Coast Guard	55 (0.6%)
Navy	2,551 (27.3%)
PH/HIS	656 (7.0%)
Unknown	4,206 (45.0%)
Resection Occurred	96 (1.0%)
Differential Provided by Referring Provider	8,084 (86.5%)



Year (Count, % of Yearly Total)					
Quarter	2015	2016	2019	2020	2021
1 (Jan – Mar)	484 (23.4%)	469 (23.1%)	502 (24.0%)	521 (36.7%)	510 (29.3%)
2 (Apr – Jun)	571 (27.6%)	515 (25.4%)	444 (21.2%)	168 (11.8%)	367 (21.1%)
3 (Jul – Sep)	526 (25.4%)	518 (25.6%)	638 (30.5%)	396 (27.9%)	421 (24.2%)
4 (Oct – Dec)	490 (23.7%)	524 (25.9%)	507 (24.2%)	336 (23.6%)	444 (25.5%)
Total	2,071	2,026	2,091	1,421	1,742

Figure 1. Biopsy Submissions by Year and Quarter.

The graph represents the total number of submitted cases categorized by year and further compartmentalized by quarter with colored designation. The counts per year are consistent until year 2020 where there is a substantial reduction in submitted cases predominantly occurring in the second quarter. Submissions partially rebound in year 2021 but do not fully recapture pre-COVID values.

Table 2. Top 5 Diagnoses by Year

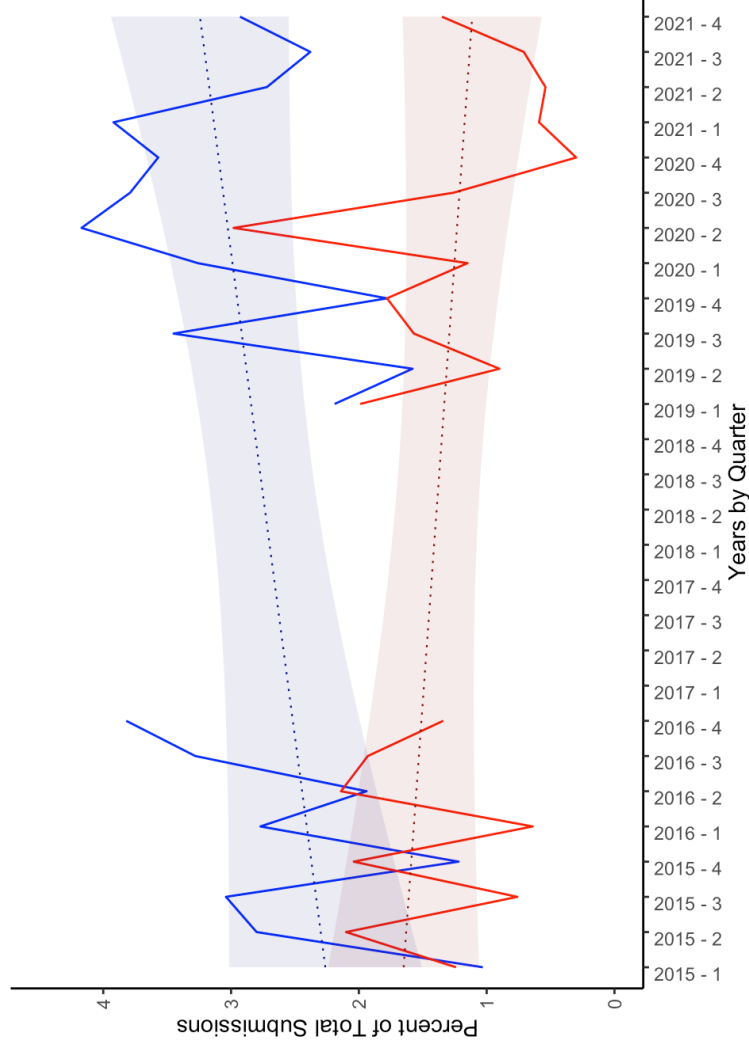
<i>Prior to COVID-19 Patient-Provider Interaction Restrictions (pre-COVID)</i>					
2015		2016		2019	
Diagnosis	N (%)	Diagnosis	N (%)	Diagnosis	N (%)
Fibroma	232 (11.2%)	Fibroma	241 (11.9%)	Fibroma	212 (10.1%)
Mucocele	209 (10.1%)	Mucocele	184 (9.0%)	Periapical Granuloma	166 (7.9%)
Periapical Granuloma	175 (8.5%)	Dentigerous Cyst	157 (7.8%)	Normal Tissue	164 (7.8%)
Dentigerous Cyst	156 (7.5%)	Periapical Granuloma	156 (7.7%)	Mucocele	156 (7.5%)
Hyperplastic Dental Follicle	94 (4.5%)	Hyperkeratosis/Acanthosis	89 (4.4%)	Reactive Follicular Lymphoid Hyperplasia	137 (6.6%)
<i>During COVID-19 Patient-Provider Interaction Restrictions (COVID)</i>					
2020		2021			
Diagnosis	N (%)	Diagnosis	N (%)		
Fibroma	137 (9.6%)	Fibroma	207 (11.9%)		
Normal Tissue	137 (9.6%)	Mucocele	143 (8.2%)		
Hyperkeratosis and Acanthosis	99 (7.0%)	Periapical Granuloma	132 (7.6%)		
Mucocele	97 (6.8%)	Dentigerous Cyst	101 (5.8%)		
Periapical Granuloma	88 (6.2%)	Hyperkeratosis/Acanthosis	83 (4.8%)		

Table 3. Biopsy Site Distribution by Year.

Site	2015/16/19 N (%)	2020 N (%)	2021 N (%)
Mucosa	1,913 (30.9%)	498 (35.1%)	506 (29.1%)
Intraosseous-maxilla/mandible	1,813 (29.3%)	378 (26.6%)	536 (30.8%)
Gingiva	767 (12.4%)	90 (6.3%)	170 (9.8%)
Tongue	686 (11.1%)	139 (9.8%)	190 (10.9%)
Oropharynx	259 (4.2%)	98 (6.9%)	84 (4.8%)
Palate	243 (3.9%)	42 (3.0%)	82 (4.7%)
Skin	187 (3.0%)	35 (2.5%)	24 (1.4%)
Sinonasal	161 (2.6%)	57 (4.0%)	83 (4.8%)
Salivary gland	75 (1.2%)	29 (2.0%)	35 (2.0%)
Larynx	31 (0.5%)	6 (0.4%)	9 (0.5%)
Soft Tissue	21 (0.3%)	19 (1.3%)	5 (0.3%)
Neck	16 (0.3%)	21 (1.5%)	13 (0.8%)
Other	16 (0.3%)	9 (0.6%)	5 (0.3%)

Table 4. Top 5 Malignant Diagnosis Distribution by Year.

Diagnosis	2015/16/19	2020	2021
	N (%)	N (%)	N (%)
Conventional Squamous Cell Carcinoma (C-SCC)	86 (1.39%)	14 (0.99%)	29 (1.66%)
Basal Cell Carcinoma	15 (0.24%)	4 (0.28%)	3 (0.17%)
HPV Mediated Squamous Cell Carcinoma (HPV-SCC)	10 (0.16%)	19 (1.34%)	8 (0.46%)
Mucoepidermoid Carcinoma	7 (0.11%)	2 (0.14%)	1 (0.06%)
Melanoma	4 (0.06%)	0 (0.0%)	0 (0.0%)



Frequencies and Proportion of Total Biopsies by Year and Quarter

Quarter	1	2	3	4
2015				
Malignant	5 (1.03%)	16 (2.80%)	16 (3.04%)	6 (1.22%)
Pre-Malignant	6 (1.24%)	12 (2.10%)	4 (0.76%)	10 (2.04%)
2016				
Malignant	13 (2.77%)	10 (1.94%)	17 (3.28%)	20 (3.82%)
Pre-Malignant	3 (0.64%)	11 (2.14%)	10 (1.93%)	7 (1.34%)
2019				
Malignant	11 (2.19%)	7 (1.58%)	22 (3.45%)	9 (1.78%)
Pre-Malignant	10 (1.99%)	4 (0.90%)	10 (1.57%)	9 (1.78%)
2020				
Malignant	17 (3.26%)	7 (4.17%)	15 (3.79%)	12 (3.57%)
Pre-Malignant	6 (1.15%)	5 (2.98%)	5 (1.26%)	1 (0.30%)
2021				
Malignant	20 (3.92%)	10 (2.72%)	10 (2.38%)	13 (2.93%)
Pre-Malignant	3 (0.59%)	2 (0.54%)	3 (0.71%)	6 (1.35%)

Figure 2. Pre-malignant and Malignant Lesion Distribution by Year and Quarter.

The solid red and blue lines represent the percentage of all submissions defined as pre-malignant and malignant, respectively. Dotted lines plot regression lines signifying the trend of pre-malignant and malignant diagnoses as a percentage of the total from 2015 to

2021. Trend lines indicate a divergence in diagnosis contributions; from 2015 to 2021, the contribution of malignant submissions increased whereas pre-malignant submissions decreased.

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