Comparison of the concordance between clinical and histopathologic diagnosis of oral mucosal lesions in an Oral Medicine graduate program and the Oral Pathology biopsy service.

by

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Abstract

Background: The concordance between clinical and histopathologic diagnosis is vital to managing pathologic conditions. Comparing factors related to discrepancies between the clinical judgment and histopathologic study, which is the gold standard, will help identify weaknesses that should be improved so clinicians can provide better disease management to improve the quality of life of our patients.

Objectives: To evaluate the concordance between the clinical and histopathological diagnosis of biopsied soft tissue specimens and analyze incidence variations and demographic information from two databases: 1. the Oral Medicine graduate program at the University of Alberta between August 2020 and August 2021, and 2. the Oral Pathology Biopsy Service database at the University of Alberta between 1985 and 2008.

Methods: This retrospective study was approved by the Health Research Ethics Board, University of Alberta (Pro00116378). The anonymized databases contained biographic data and clinical and histopathologic information. The inclusion criteria included reports with complete clinical and histopathologic diagnoses of oral soft tissue biopsies. "Absolute Concordance" was determined if clinical and histopathological diagnostic SNOMED-CT codes were identical and, as a second analysis, if the clinical and histopathological diagnoses were identical at a synonyms level. "Relative Concordance" if diagnoses shared an etiopathologic cluster; and "Discordance" if they belonged to different clusters. The outcome measurement was the percentage of absolute concordance, relative concordance and discordance. The diagnostic accuracy according to prognosis was analyzed using Cohen's kappa to determine the agreement between the diagnoses; also, sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) were calculated. Additionally, the relationship between gender and age and cluster concordance was tested using the Chi-square and Analyses of variance.

Results: The University of Alberta database spanning from 1985 to 2008 constituted 19,259 analyzed cases; gender distribution was 10,095 (52.42%) females, 8,838 (45.89%) males and 326 (1.69%) unknowns. Age distribution included <14 years, 1,128 (5.85%); 15-24 years, 1,320 (6.85%); 25-64 years, 12,489 (64.85%); >65 years, 3,609 (18.74%); and unknown, 713 (3.71%). The absolute concordance comparing the SNOMED-CT codes was 47.17%, and by diagnostic synonyms, 50.22%. The relative

concordance was 74.61%, and the discordance was 25.39%. The accuracy of the clinical diagnosis to detect OPMD showed a sensitivity of 76.9%, specificity of 97.6%, PPV of 87.3%, and NPV of 95.1%. Moreover, for malignancy identification, the sensitivity was 67.5%, specificity was 98.4%, PPV was 46.3%, and NPV was 99.3%.

The Oral Medicine 2020-21 database comprised 122 cases, 67 (54.92%) females and 55 (45.08%) males. The age distribution was < 14 years, 1 (0.82%); 15-24 years, 3 (2.46%); 25-64 years, 75 (61.48%); and > 65 years, 43 (35.25%). The absolute concordance comparing the SNOMED-CT codes and synonyms was 36.89%. The relative concordance was 72.95%, and the discordance was 27.05%. The accuracy of the clinical diagnosis to detect OPMD showed a sensitivity of 84.4%, specificity of 89.0%, PPV of 87.5%, and NPV of 86.3%. Moreover, for malignancy identification, the sensitivity was 100%, specificity was 99%, PPV was 50%, and NPV was 100%.

Conclusions: In the case of the Oral Medicine program, the concordance by etiopathologic clusters demonstrated moderate agreement, and the sensitivity to diagnose benign and OPMD was high. However, despite this high sensitivity, 12.7% and 15.6% of cases, respectively, were still misdiagnosed. Regarding the University of Alberta 1985-2008 database, the results indicated that concordance by clusters demonstrated a substantial agreement. While clinical examination effectively identifies patients without malignancy or OPMD, it is not sufficiently sensitive for diagnosing malignancy or OPMD. Therefore, the histopathological examination is essential to provide a definitive diagnosis, especially in those cases where cellular behavior dictates future management decisions.

Preface

This thesis is an original work of Patricia Hernandez-Rivera. The research project, which this thesis is a part, received research ethics approval from the Health Research Ethics Board—Health Panel, University of Alberta, on January 18, 2022 (Pro00116378).

Dedication

“To my loves: my husband, my son, and all my patients”.

“*Listen to the patient. He is telling you the diagnosis.*”

Sir William Osler, father of modern medicine.

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List of Abbreviations

Phrase	Abbreviation
Oral Potentially Malignant Disorders	OPMD
Systematized Nomenclature of Medicine-Clinical Terms	SNOMED-CT
International Classification of Diseases 10th edition	ICD-10
Database from Oral Medicine graduate program at the University of Alberta between August 2020 and August 2021	OM graduate program 2020-21
Database from: Oral Pathology Biopsy Service, University of Alberta 1985-2008	Biopsy Service 1985-2008
Squamous Cell Carcinoma	SCC
Standard deviation	Std Dev
Positive Predictive Value	PPV
Negative Predictive Value	NPV

Chapter 1: Introduction

The development and recognition of Oral Medicine as a dental specialty took several decades and hard work from knowledgeable and forward-thinking dental professors. Maybe this relationship was not initially conceived because the dental profession developed as a manual mechanic trade, which was very different from its sister, the medical profession. Dentistry was born as a trade job done by barbers, charlatans, and blacksmiths. At that time, the treatment was limited to extracting the affected tooth, and the most qualified practitioners offered a filling option for some cases. During that era, preventive or interceptive dental treatment was absent. However, some pioneers understood the close relationship between dentistry and medicine as health sciences professions [1].

One of the first dentists to acknowledge the dentistry-medicine link was Dr. Francis P. McCarthy, who managed patients with oral manifestations of dermatological conditions. Likewise, he introduced some lectures on Oral Medicine at Tufts Dental School in 1925[2]. One year later, Dr. William J. Gies advised the importance of introducing this topic in the dental curriculum[1].

Likewise, this link was established when Dr. Samuel Charles Miller, periodontist from the New York University College of Dentistry, studied the relationship between glycemia and periodontitis. Due to his research, he comprehended the importance of Oral Medicine in dentistry. Therefore, the "American Academy of Dental Medicine" was created by his leadership and his colleague Dr. Sidney Sorrin on February 2, 1946. The Academy aimed to provide knowledge to clinicians interested in acquiring skills in Oral Medicine[1,2]. Dr. Miller's idea of the academic association was supported by a group of intellectual dental professors who contributed and provided the continuity of the academy[2].

The definition and scope have subtle variations worldwide, but in general, it is the specialty that merges dentistry with medicine[3]. Oral Medicine specialists provide diagnosis and management for local and systemic diseases affecting the oral and maxillofacial region and orofacial pain disorders[2–4]. The American Academy of Oral Medicine and the European Association of Oral Medicine defines the Oral Medicine specialty "*as the specific area of competence concerned with the health and diseases of the oral and peri-oral structures, including oral health care of medically complex patients and the diagnosis and management of medically related diseases, disorders, and conditions affecting the oral and maxillofacial region*"[4]. It is an evolving specialty, according to the state-of-art, the influence of an aging population, medically compromised patients and the emergence of new diseases[2].

1.1 Clinical examination

Achieving an accurate clinical diagnosis is critical for properly managing a determined disease or condition. This process involves a series of steps to obtain a detailed examination of the patient, which begins with reviewing the chief complaint or concern of the patient and the history of evolution of the condition[5]. It is recommended that the interview be started with open questions to gather first-hand information from the patient. Open questions avoid bias and allow the patient to tell the story in their own words, giving clues and a better understanding of the ailment[5].

After listening to the patient, the interviewer can use guided questions to drive the patient to clarify missing valuable information[5]. These clue questions are easier to remember by the acronym "OLD CHARTS," which stands for onset, location, duration, character, habits, aggravating and relieving factors, timing and severity[6,7]. Additionally, information about previous therapies tried, and their outcomes will give clues for the diagnosis and future planning treatments. A detailed characterization of the symptomatology, such as the quantification of pain level, description, fluctuation, and periods of remission, is fundamental as the first step to guiding the thinking process for a diagnosis[6,7].

Moreover, a complete review of systems, past medical history, the use of over-the-counter and prescribed medications, social history and family medical history is essential data needed to analyze the proper management of the patient and its influence on oral health[5–8].

The second phase of the patient evaluation is the physical examination, which starts as soon as the patient sits on the dental chair. During the interview, it is important to visualize any abnormality, asymmetry, or skin change on the face and neck[6,9–11]. During the interview, the clinician can also evaluate the cognitive state, behaviours, speech and movement abilities, which can interfere with future management[12]. Then, with the patient still seated, systematic palpation of the cervical lymph nodes in the submental, submandibular, pre-auricular, post-auricular, occipital, superior deep cervical, lower deep cervical and supraclavicular areas is initiated[6,9,12].

Other structures to palpate are the major salivary glands to rule out any palpable masses within them[9–11]. Additionally, the expression of the saliva and its consistency and flow should be evaluated during the intraoral examination[10,12]. Likewise, an evaluation of the temporomandibular joint and palpation of the masticatory muscles is recommended[12]. The last structure to evaluate during the extraoral examination is the thyroid gland for identifying abnormalities[11,12].

The next assessment step is the intraoral examination, where the reason for the referral or main concern is usually located. However, it is fundamental to systematically evaluate all the structures of the intraoral cavity and not only concentrate on the main concern because it is essential to rule out any other condition or other manifestations of the same pathology.

For the intraoral examination, it is preferred to have the patient in a semi-supine position, and any removable dental prosthesis or orthodontic appliance should be taken out to visualize all the intraoral mucosa. Likewise, it is necessary to have appropriate light, a dental mirror, and several gauzes to dry the mucosa and to hold the tongue for better observation [9].

As in the extraoral examination, a consistent, systematic evaluation is indicated to avoid missing a structure, which should be visualized and palpated bi-digitally to ensure a proper assessment of the areas. It is important to differentiate normal anatomy variations from pathological conditions during this process. The latter should be described following the proper terminology and recorded with intraoral photography for further management[12]. The examination should be done from the lips' exterior vermilion surface to the interior oral cavity, following concentric imaginary circles. The structures to be assessed are the buccal mucosa, gingiva, tongue, floor of the mouth, hard palate, soft palate and oropharynx[13].

The clinical examination, which includes the visualization and palpation of the oral tissues, remains the most important process for oral pathology screening[14,15]. Several diagnostic aids, such as toluidine blue, light-based detection, chemifluorescence, brush cytology among other tools, have been explored to improve the clinical examination[13,16,17]. Overall, several studies conclude that toluidine blue, chemiluminescence, and autofluorescence can help identify the more dysplastic site for biopsy or be used as an adjuvant to conventional clinical examination. However, the clinical examination of the oral tissues cannot be replaced by these diagnostic tools[14,16,18,19].

1.2 Clinical Diagnosis

The art of establishing a clinical diagnosis or a differential diagnosis requires knowledge, clinical expertise and the capacity to build mental pathways to discover the definitive diagnosis. This is a thought process in which the practitioner integrates the medical history, the history of the main concern and the clinical manifestations. The differential diagnosis is a short list of possible pathologies from the most likely to the least. The first pathologic condition on the list is the working or tentative diagnosis, which must be tested to reach a definitive diagnosis. Over time, several authors have created flow charts and tables to help clinicians with this fundamental process. According to this suspected pathology or list of possibilities, the clinician must search for more clues by asking more questions and requesting laboratory tests, images, biopsies and other supplemental aids to arrive at the definitive diagnosis [7,12,20].

The tentative diagnosis is crucial because it guides or dictates the path to the definitive diagnosis. It must be as accurate as possible, differentiating malignant and oral potentially malignant disorders (OPMD) from benign conditions [20,21]. Another reason for its importance is that when different pathologies have similar histopathologic features, it must be correlated with the clinical impression[21]. However, sometimes the clinician decides to manage it without the biopsy confirmation due to several reasons: high cost, patient anxiety, and to save the surgical procedure only to complex pathologies that require a histopathological confirmation[22,23].

Regarding the frequency of biopsies performed by Oral Medicine specialists, Epstein and colleagues sent a questionnaire to the diplomates of the American Board of Oral Medicine to investigate the management of OPMD. They determined that 88.7% of the responders would biopsy a suspected lesion that does not improve after two weeks of removing an irritant. However, several factors increase the biopsy rate, such as clinical presentation, the location in a high-risk area or the patient's medical history that flags suspicion of malignancy[24].

1.3 Definitive Diagnosis

In the case of mucosal lesions, the definitive diagnosis can be confirmed by a histopathological examination, as mentioned before, and it is considered the gold standard [20]. A biopsy is indicated when an oral pathology does not improve after two weeks of eliminating irritational factors [12]. Another reason is to rule out an OPMD or other pathology with an unknown cause [12].

This microscopic evaluation requires a biopsy, a surgical procedure of removing a representative tissue sample showing abnormalities or the complete excision of the pathology. The term biopsy comes from the Greek prefix "*bio,*" which means life and "*opsis,*" vision, which explains the aim of this examination [25].

According to the American Academy of Oral and Maxillofacial Pathology, biopsy specimens acquired from all clinical and radiographic abnormalities should be submitted for histopathologic assessment. This examination aims to: a) confirm the clinical diagnosis, b) provide a definite diagnosis in case of discordance with the clinical diagnosis, and c) predict the clinical behavior and prognosis [26] These outcomes are fundamental to the proper management of the disease or condition, with medico-legal implications; hence, they are the standard of care.

The success of achieving a definitive diagnosis depends on the chain work of several professionals: the surgeon, who collects the specimen and gives accurate clinical information to aid in the definitive diagnosis; the laboratory technician in charge of processing the sample; and the pathologist interpreting it [27].

Depending on the tentative diagnosis, the clinician's first step is to decide which type of biopsy is better accomplished in each case. An incisional biopsy is a partial removal of a representative part of a large lesion, usually for pathologies greater than one centimetre, but it depends on the surgeon's expertise. However, if the clinician suspects malignancy, it is recommended to preserve the borders for further evaluation of the complete extirpation after the excision of the pathology [28]. On the other hand, for smaller pathologies, excisional biopsy is indicated, which means the complete surgical removal of the entire lesion with a border of healthy tissue [7,25,29]. In this case, this treatment has a double aim because it is therapeutic and diagnostic[25,29].

The clinician should acquire consent and explain how the procedure would be done, possible adverse and side effects such as pain, swelling, infection, bleeding, sensation changes, wound dehiscence, the possibility of re-biopsy, and other treatment options instead of the biopsy [9,29–31].

The anesthesia solution should be delivered at least 3-4 mm apart from the lesion on the periphery surrounding the lesion of concern to avoid the extravasation of erythrocytes and the creation of vacuoles within the specimen[25,27–29,31,32].

Also, the clinician must consider the proximity to anatomic structures to avoid iatrogenic injuries and select the size and the appropriate most representative site[9,27,29,33,34]. Ideally, it must be taken from the area with more significant changes compared to the normal tissues [27,30,32]. In the case of larger lesions, sometimes multiple samples should be taken to obtain an accurate histopathological diagnosis[27,30,32–34].

Regarding the size of the sample, Lazzarotto et al. retrospectively analyzed 1089 biopsies and determined that incisional biopsies larger than 10 mm had 2.14 times more possibilities of yielding a definitive diagnosis[33]. Small specimens are easier to lose during the handling process, not being representative, and tend to shrink half their size, which causes difficulties in orientating the sample[27,31]. Likewise, Lazzarotto et al. recommend a sample depth between 2-5 mm or more, depending on the surface topography of the epithelium. The importance of getting an appropriate depth is to include the basement membrane to ensure the assessment of the epithelium's entire thickness to predict the prognosis [33]. The examination of this area is crucial, especially in vesiculobullous conditions and for the evaluation of malignancy invasion [27,33]. Therefore, it is recommended to collect a wedge-shaped sample with a scalpel to ensure a primary closure; the desirable size is between 7-10mm in length and 2-8 mm in depth on the pathological area with a margin of 2-3 mm of normal tissue for histological comparison[25,27]. Other practitioners recommend that the length be three times the width of the lesion [29]. The incisions should be clean and deep while retracting the surgical area to minimize the risk of crushed artifacts[7,25].

The use of laser should be avoided due to the incorporation of thermal artifacts into the sample, which complicates the histological assessment [25,27,29,30]. However, the laser can offer some advantages, such as a shorter operative time and less intraoperative bleeding compared to the scalpel [35,36]. Regarding the thermal damage zone, Suter et al. investigated it in excisional biopsies of fibrous hyperplasia. They determined that the Er: YAG laser damaged area measured approximately 41 μm, less than the CO2 laser, which was 83.5 μm. Therefore, their recommendation is to provide a surgical safety margin of 0.2 mm for the Er: YAG laser and for the CO2 laser of 0.5 mm so that the borders of the lesion can be properly evaluated[35]. Another investigation by Romeo et al. evaluated the thermal effect of potassium titanyl phosphate and diode laser in different benign lesions and concluded that all the samples were analyzed properly and the thermal artifact did not affect the histopathological evaluation[36].

Additionally, it is fundamental to have delicate handling for the specimen to prevent tissue compression artifacts and the incorporation of foreign materials such as cotton, glove starch, calculus, or

restorative materials [25,27,30,34]. Seone et al. analyzed 354 biopsies to evaluate the presence of artifacts. They found these mistakes in 64.4% of the samples done by general dental practitioners and 33.9% by Oral Maxillofacial Surgeons. The most common artifact was crushing due to excessive pressure during the surgical procedure, mainly with inflammatory conditions, followed by hemorrhage [31].

After the surgical collection, the sample must be preserved in the indicated solution depending on the histopathological examination. For hematoxylin and eosin staining, the sample is fixated in 10% formalin, and for immunofluorescence studies, the preservation is in Michel's solution [9,30,34]. In the case of formalin, to ensure proper fixation, the volume of formalin needed is 10-20 times the volume of the sample, and the fixation time is one hour per millimetre of tissue [25,27,29,30]. The fixation process is due to the creation of intermolecular bridges between proteins and cross-links at the end of the protein chain. If the specimen is submerged in a different solution, the tissue will undergo autolysis and will not be preserved [29].

Another consideration before introducing the sample into the solution is to place the specimen on a sterile piece of paper with the epithelium facing up. This additional step prevents the sample from being curved during the fixation time, which helps better orientate the specimen [27,31].

Moreover, it is essential to identify the sample container with the patient's information, biopsy site and date of the procedure. Also, fill out the submission document with the patient's biographic information, detailed lesion description, relevant history, clinical diagnosis, type and location of the biopsy [7,27,29,30]. This clinical information is essential for the pathologist to reach a definitive diagnosis.

Finally, after receiving the histopathological report, it is mandatory for medico-legal purposes to attach it to the patient's chart and explain it to the patient [30,34].

The above-mentioned considerations and requirements for the collection, handling and submission of a biopsy are important to achieve a definitive diagnosis. This is a desirable outcome that will guide further management and avoid the need to retake biopsies due to misdiagnosis [27].

1.4 Epidemiology soft tissue pathology

The epidemiology of intraoral soft tissue pathologies varies according to the type of study. Some population-based investigations determined the prevalence of the different pathologies, diagnosed by a clinical examination, among an established community. This type of study has the advantage of representing a more realistic prevalence scenario[37,38]. This data cannot be extrapolated to other populations due to the socioeconomic and environmental factors influencing the variability of the diverse intraoral conditions. However, these studies have complicated logistics for motivating the patients for the examination, calibration and agreement of dental practitioners to identify the different conditions and the clinical diagnosis criteria used. [37,38].

On the contrary, studies from a specific medical facility have the advantage of being based on a captive population, facilitating logistics. However, they do not represent the "real world" because of selection

bias. This bias responds to the fact that patients are referred for assessment of a pathology or a suspected condition; thus, this kind of research does not contemplate the healthy portion of the population [38]. Even though the information is essential for understanding the epidemiological features of intraoral pathology, a critical difference between these investigations is that population-based studies focus on clinical diagnoses, while medical facility-based studies are primarily centered on histopathological diagnoses [39].

Regarding the prevalence investigations from oral pathology institutions, the information also varies according to the type of pathology included and the classification of the intraoral pathology. The latter is because, unfortunately, there is no universal and reliable categorization due to the complexity and the multifactorial nature of some intraoral conditions.

Mendez and colleagues performed a retrospective study from 1995 to 2004 in an oral pathology service from south Brazil. Their research was based on the histopathological diagnosis from 6,831 specimens after removing the excluding criteria data. They determined that inflammatory pathology was the most prevalent 63.24%, where the immunological conditions, periapical and non-neoplastic proliferative disorders were included under that category. Normal findings were present in 22.06%, potentially malignant disorders in 2.46% and malignant in 1.9%[40].

The research done by Sixto-Requeijo in Spain analyzed 647 histopathology reports from 1995 to 2009. They determined the most prevalent conditions were radicular cyst 16.7%, leukoplakia 15.5%, lichen planus 14.1%, and fibroma 11.4%. They did not consider potentially malignant conditions as a category, and the malignancies amounted to 3.9%[41].

In the case of Jones and Franklin, they analyzed the information from 44,007 specimens corresponding to the period between 1973 and 2002 in Sheffield, United Kingdom. The different pathologies were categorized into thirteen groups, including odontogenic, bone, salivary, mucosal, and periodontal conditions. The mucosal lesions represented 36% of all the specimens, and in this group, fibrous hyperplasia was the most common condition, followed by lichen planus and hyperkeratosis. Regarding the rest of the soft tissue, salivary pathologies were 7.1%, benign tumours 5.6%, periodontal 5.5%, malignant tumours 5.4%, connective tissue 1.6% and normal conditions 1.3% [39].

Akindayo's study in Nigeria reviewed 1,998 histopathologic reports from 1990 to 2014. As mentioned before, the oral pathology classifications vary considerably among the researchers; they classified them into sixteen groups in their study. They included 1,778 cases from which there were 207 different diagnoses, and the most common group was the reactive lesions 23.1%, then odontogenic tumors 18.1% and epithelium tumors 12.4% [42].

1.5 Concordance between clinical and histopathological diagnosis

Several published studies compared the concordance between the clinical and the histological diagnosis, as summarized in Table 1. A retrospective study in a Nigerian oral histopathology service between 2008 and 2017 analyzed 592 biopsies. They found an absolute concordance in 54.6% of the cases, and the oral medicine specialists obtained the highest diagnostic percentage 62.5% [43].

A similar study compared the accuracy of the clinical diagnosis between general dentists and dental specialists, which concluded that 57% of the clinical diagnoses were accurate irrespective of whether submitted by a general dentist or a specialist [22]. They also concluded that there was no significant difference between the different groups of practitioners [22]. Another study compared the clinical and histological concordance between general dentists and specialists of 3,143 specimens. They determined that the concordance index was very similar between general dentists 49.4% and specialists 51% [44]. They explained there was no significant difference, probably because the latter submitted more complex pathologies. However, they did not calculate the difference according to specialist type [44].

In the case of Farzinnia et al., they investigated the diagnostic correlation between the clinical diagnosis performed by oral medicine and maxillofacial surgeons. The overall concordance was 72.2%, and there was no significant difference between the two groups of practitioners [21]. Other investigators found a 52.6% concordance. Still, they argued that in 31% of the discordant diagnoses, the histological diagnosis was part of the clinical differential diagnosis. This inaccuracy occurs due to the similar clinical appearance between several pathologies [45]. This interpretation in the diagnostic concordance was similar to the research done by Saravani and colleagues, who determined compatibility between the clinical and histopathological diagnoses in 70.1% because they considered the first, second and third pathologies listed in the differential diagnosis [20]. Therefore, when analyzing the concordance percentage between the clinical and the histologic diagnosis, it is fundamental to review the authors' methodology—specifically, knowing which variables were used to qualify as discordance or concordance.

According to the studies above, the concordance is less than 55% when researchers compare an exact diagnosis. Still, as mentioned before, some conditions are clinically very similar, or the final diagnosis is part of the differential diagnosis. For this reason, Forman et al. grouped the pathologies into two main groups: benign-premalignant and malignant. Hence, when they analyzed the exact diagnosis, the concordance was 61.0%, but when considering only if both diagnoses belonged to the same group, the accuracy increased to 94.4% [23].

Under this same idea, Poudel et al. analyzed the clinical and histopathological concordance by categorizing the concordance into four groups: total concordance when both diagnoses were the same, concordance with histopathologic diagnosis after refinement, discordance and when there was no clinical diagnosis. They determined a total concordance at 56.5%, after histopathologic refinement at 11.4%, discordance at 23.6% and no clinical diagnosis at 8.4% [46].

Similar research was done by Mendez and colleagues, who analyzed 8,168 specimens submitted to histopathological examination from 1995-2004. They classified the pathologies into four groups: inflammatory, benign, malignant and others, which were then re-grouped. Hence, they established agreement when the clinical and histopathological diagnoses belonged to the same classification. They presented their results by showing the percentage in which the histopathology confirmed the clinical diagnosis in each group. In the periapical lesions, the histopathological assessment was confirmed in 92.6%, followed by potentially malignant at 90.1% and non-neoplastic proliferative disorders at 89.3% [47].

Table #1: Studies that compared the concordance between the clinical and the histological diagnosis

Authors Study*	Country	Study period	Population size	Methodology	Results (Concordance %)
Soyele OO, et al.[43]	Nigeria	2008-2017	592	Fourteen categories to analyze the prevalence and the diagnostic agreement per category. Reactive-hyperplastic lesions, cystic lesions, pulp and periapical lesions, giant cell lesions, fibro-osseous lesions, odontogenic tumors, epithelial tumors, mesenchymal tumors, salivary gland diseases, hemato-lymphoid neoplasms, inflammatory-microbial diseases, ulcerative lesions, normal tissue and miscellaneous.	Concordance 54.6%. Highest concordance in fibro-osseous lesions 65.6% and epithelial tumors 66.1% Kappa co-efficient: 0.5 (good)
Kondori I, et al.[22]	USA	2009-2010	976	No further classification. Comparison between general dentists and different specialties.	Overall concordance 57% General dentists: 54.1% Maxillofacial surgeons: 57.2 Endodontists: 57.8% Periodontists: 58.8%
Patel KJ, et al. [44]	New Zealand	2002-2006	3143	Analysis word by word and second level by concordance refined terms, example: Leukoplakia and epithelial hyperkeratosis with mild dysplasia. Categories: oral mucosal, gingival-periodontal, salivary and miscellaneous. Re-categorized: Malignant, premalignant, benign, and no diagnosis, when no clinical diagnosis. Concordant diagnosis: same clinical and histological. Concordant redefined Discordance: different diagnoses. No clinical discordance.	Total concordance: 50.6% and 63.21% when the reports without a clinical diagnosis were deleted. The specialist's total concordance was 51%, redefined to 62.7%. General dental practitioners 49.4% and redefined 66.7%.
Navas-Aparicio N, and Hernandez-Rivera P.[45]	Costa Rica		40		Concordance: 52.6%
Farzinnia G, et al. [21]	Iran	Jan 2006- Dec 2018	3001	Lesions were subdivided: 1. Ulcerative, vesicular and bullous, 2. Red and white, 3. Pigmented lesions, 4. Bone lesions. 5. Exophytic. Diagnosis of each pathology, according to Neville. Concordance: Similar diagnosis using both techniques.	Clinical and histopathological consistent 72.2%. The red and white lesions had the highest rate of concordance (86.1%), while the pigmented lesions had the lowest concordance (47.1%).
Saravani S, Tavakoli Amin M, Kadeh H.[20]	Iran	April 1999-September 2015	631	Clinical diagnosis according to priority: first, second and third. Pathologies were subclassified in neoplastic and non-neoplastic.	Diagnostic compatibility: 70.1%. First diagnosis: 87.2% Second diagnosis: 10.6% Third diagnosis: 2.1%
Forman MS, Chuang SK, August M. [23]	United States of America	2005-2013	1003	Diagnosis specific and then categorized: 1. Premalignant or malignant. 2. Benign. Accuracy: Both belonged to the same category, even if histology differed.	The concordance by specific diagnosis: 61%, according to category 94.4%.
Poudel P, et al.[46]	Nepal	Jan 2016-Dec 2017	237	Total concordance: Total agreement between clinical and histopathological. Concordance with the histopathological diagnosis but after refinement of clinical diagnosis. Categories: Non-neoplastic-reactive, potentially malignant oral lesions, benign, malignant, non-odontogenic cysts & pseudocysts, odontogenic cysts, odontogenic tumors, and others.	Total concordance: 56.3%. Concordance with the histopathological diagnosis but after refinement of clinical diagnosis: 67.9% Discordance: 23.6% No clinical diagnosis:8.4% The maximum agreement was among benign, 73.17%.
Mendez et al.[47]	Brazil	1995-2004	5368	Pathologies classified: Inflammatory, benign, malignant, other and then subclassified. Agreement: Clinical and histopathologic diagnosis from the same group.	Agreement by groups: Periapical lesions 92.6% Potentially malignant 90.1% Non-neoplastic proliferative disorders 89.3%.

*Ordered as cited in the text.

1.6 Systematized Nomenclature of Medical-Clinical Terms

Coding systems were developed for epidemiologic studies and billing purposes in the past. However, nowadays, their uses have evolved and include other purposes, such as saving and retrieving information efficiently and extracting information from electronic health records. This coded information can be used for research purposes, real-time advice management, audits, and countless other uses.

The Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) was created in 1965 by the College of American Pathologists. It is a comprehensive terminology system composed of 359,109 medical concepts, according to the January 2023 version, with a unique numerical identifier based on ontology[48]. Each concept has synonyms, a preferred name and subtype relationships linking broad or "parent" terms into more specific or "child" in a "is a" hierarchy, which, depending on the meaning, can be related to different hierarchies in a web-like structure [49–51]. This coding system is updated several times annually and offers an international version and specific variants for several countries in different languages, making it universal.

Delvaux et al. analyzed the capacity of SNOMED and the International Classification of Diseases 10th edition (ICD-10) to mirror the clinical information. They found that the former showed higher sensitivity and specificity. However, the codes are longer and more complex, which offers the advantage of more granular data[51].

Similarly, Chen J and colleagues evaluated the accuracy of five different coding systems in the oral pathology field in 2005. They determined the most accurate was the Armed Forces Institute of Pathology (96.4%) language, and the SNOMED 98 (74.5%) was more accurate than the coding system from the International Classification of Diseases Ninth Edition (43.5%)[52]. Even though the comparison was made between old versions, it is the only published study that analyzes the precision of coding systems in dentistry.

The ICD coding system was created to record the cause of death using codes that are internationally accepted. However, this disease classification has limited applications for the intraoral pathologies[7].

Chapter 2: Objectives

The concordance between clinical and histopathologic diagnosis is vital to managing different pathologic conditions. Comparing those factors related to discrepancies between the clinical judgment and histopathologic study, which is the gold standard, will help reduce potential disease burden[53].

Consequently, evaluating the concordance between these diagnoses among different practitioners is crucial to analyze the clinical accuracy and establish policies to improve clinical skills, suggest the need for a prompt biopsy in certain oral pathologies, and develop novel diagnostic methods [23].

The clinical and histopathological concordance published ranges from 51-65%[20–23,43–47], but there is no precise methodology used among the studies to be comparable. As mentioned before, the variability among the studies depends on the exact methodology used to compare the variables, the type of pathologies included and the classification of the pathologies. Additionally, there are different ways in which the authors of oral pathology textbooks classify the pathologies; some categorize the pathologies depending on the type of tissue affected and others according to the clinical presentation[7,54–56]. The aim of categorizing the different pathologies and conditions is to facilitate the learning process and aid comprehension of a complex list of ailments occurring in the oral cavity. However, these classifications are not applicable to the research purposes of this study. Therefore, creating an accurate and replicable methodology to assess the diagnostic concordance is crucial, considering the high variability of soft-tissue intraoral pathology. In this way, comparing the diagnoses will be reliable for further policy development to improve the management of oral pathology conditions.

2.1 Main objectives

A. To assess the accuracy of clinical diagnosis made by Oral Medicine graduate students compared to histologic diagnosis of oral soft tissue biopsy specimens from August 2020 to August 2021.
B. To compare the discrepancy rate between the clinical and histologic diagnoses of biopsied lesions in the Oral Medicine Graduate program with the historical database of biopsy specimens submitted to the Oral Pathology Biopsy Service by licensed dentists, University of Alberta, between 1985 and 2008.

2.2 Secondary objectives

A. Compare the demographic features of the studied populations.
B. Analyze incidence variations of soft oral pathology between August 2020 to August 2021 and compare against the historical discrepancy rate from an oral pathology biopsy service database from 1985-2008.

Chapter 3: Materials and Methods

3.1 Ethics Approval

The present study is a retrospective study approved by the Health Research Ethics Board—Health Panel, University of Alberta, with the approval number Pro00116378.

3.2 Study design and data collection

This is a retrospective study that analyzed two databases: 1) the pathology reports from specimens submitted to the Oral Pathology Biopsy Service at the University of Alberta, Canada, from 1985 to 2008 (Biopsy Service 1985-2008), and 2) pathology reports from the Oral Medicine graduate program at the University of Alberta between August 2020 to August 2021 (OM Graduate program 2020-21). The University of Alberta 1985-2008 database accounts for a large number of entries that have never been analyzed. However, there is a gap of information of 16 years, so the OM Graduate program 2020-21 database was included to retrieve newer cases for analysis. The addition of the latter also allowed studying the diagnostic concordance in the Oral Medicine program.

The anonymized databases contain biographic data from patients and clinical and histopathological information. The inclusion criteria were all reports with complete clinical and histopathological diagnoses of oral soft tissue biopsies. On the other hand, the exclusion criteria were ambiguous diagnoses, intraosseous oral pathology, extraoral pathology, tonsillar pathologies and cytology reports.

The information from 1985 to 2000 was received as a manually-entered database in an Excel spreadsheet. In the case of the information from 2001 to 2008 and August 2020 to 2021, it was extracted using computed base strategies. First, the scanned information was changed to text-free format so the variables could be extracted with a developed Python code to obtain a machine text and then processed into an Excel database. After completing this process, the total number of cases was 55,807, which included all the specimens submitted to the Oral Pathology Biopsy Service, University of Alberta, from 1985 - 2008 and 128 cases from the Oral Medicine program, University of Alberta from August 2020 to August 2021.

3.3 Data Cleaning

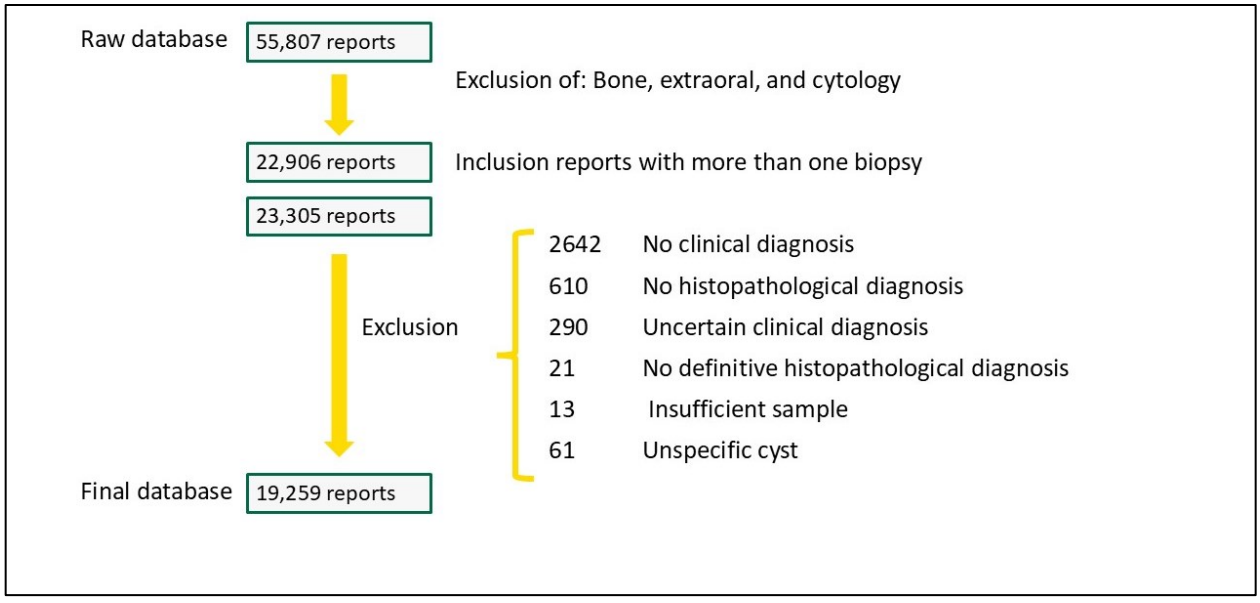
The cleaning process from the database started by removing the cytology reports, intraosseous pathology and extraoral pathologies. These entries were identified using word filters to detect the nature of the histopathological diagnoses.

Additionally, reports with more than two biopsies (396 reports) representing different pathologies

from distinct sites and etiologies were separated and included as individual entries. On the contrary, cases in which multiple incisional biopsies from the same pathology were counted as a single case. After removing the cases that did not accomplish the inclusion criteria, 22,906 reports were rendered.

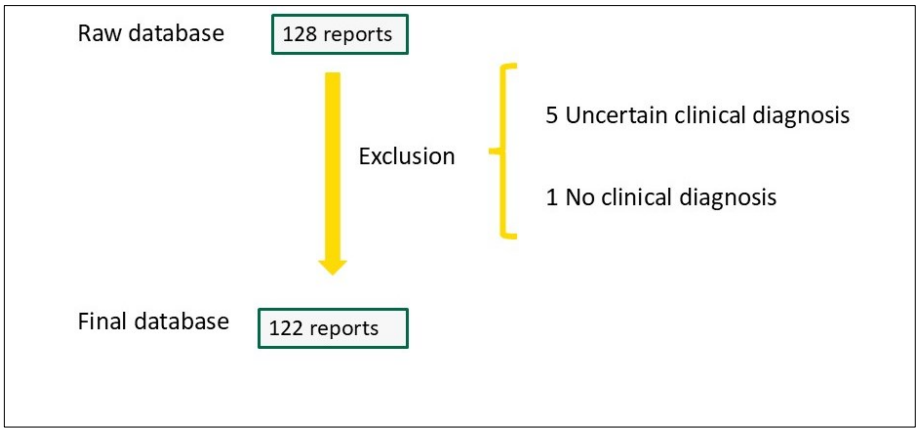
However, to achieve the study's aims, a comprehensive diagnosis that allowed it to be classified according to the etiopathology and prognosis of the pathology was needed. A total of 3,646 reports were eliminated from the database for several reasons. First, due to the incompleteness of the diagnoses, thus 2,642 cases without a clinical diagnosis were deleted, of which 248 entries also missed the histological diagnosis. In the case of absent histopathological diagnosis, 867 were excluded too. Secondly, if there was an uncertain diagnosis, 290 reports were eliminated because they had an uncertain clinical diagnosis where the clinician could not establish the name of an existent pathology or indicated a broad term that could not permit further pathology classification. For example, there were cases where the practitioner stated as clinical diagnosis the origin of the sample, such as salivary gland, or was too broad to categorize it, like "white lesion." Thirdly, there were 21 reports where the pathologist could not identify a pathology, and 13 indicated that the sample was insufficient to be analyzed. In both cases, this information was removed from the analysis because there was no condition to be comparable for research purposes. The final database for analysis compromised 19,259 cases for data analysis (see Figure #1).

Figure # 1: Flowchart of data selection included: Oral soft tissue specimens University of Alberta Oral Pathology Biopsy Service 1985-2008.



The database of patients who attended the Oral Medicine Graduate Program at the University of Alberta from August 2020 to 2021 was 128. However, six cases were removed because five had an uncertain diagnosis, which was too broad to categorize by etiopathology, and one had no clinical diagnosis. Subsequently, 122 were analyzed for research purposes (see Figure #2).

Figure # 2 Flowchart of data selection included: Oral soft tissue specimens Oral Medicine program, University of Alberta Agusto 2020 to August 2021.



3.4 Coding Concordance

The clinical diagnosis represents a short list of probable diagnoses from the most to the least likely. For this reason, the first established clinical diagnosis was used to compare it with the histopathological diagnosis for research purposes.

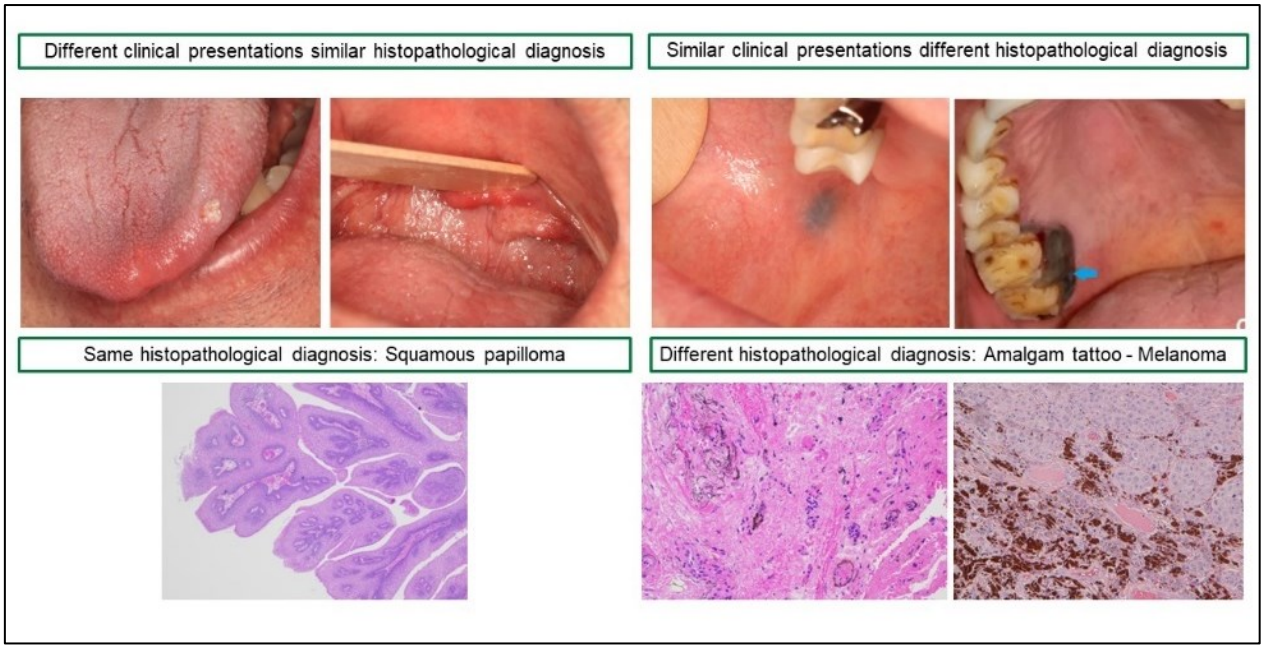
On the other hand, in the case of histopathological diagnosis, usually, there is a single name for a pathology or condition followed by an explanatory phrase giving more details about the definitive diagnosis. Therefore, both diagnoses columns were cleaned, summarizing the written diagnosis in a single condition using the current nomenclature and representing a pathology or condition without changing the concept or meaning. Hence, the words were extracted, prioritizing words representing malignancies, followed by OPMD and benign conditions.

All the concepts were entered into an Excel spreadsheet, and the corresponding numerical code was searched in the SNOMED-CT browser. The Biopsy Service 1985-2008 database had 230 different clinical conditions and 211 histopathological diagnoses. In the OM Graduate program 2020-21 database, there were 28 clinical and 29 histopathological diagnoses.

As discussed previously, the SNOMED-CT coding system precisely represents medical vocabulary, so several conditions with different codes represent the same entity. These synonyms would decrease the accuracy percentage. Therefore, a secondary list was created to identify the synonyms based on the textbook Oral and Maxillofacial Pathology by Neville et al., grouping these conditions under one common name[55].

Additional consideration was taken into account because different corroborated histopathologies can display similar clinical appearances, and the opposite, the same histopathology can present clinically different, which complicates the diagnosis workup [20,22]. One example of this diagnostic dilemma is shown in Figure # 3.

Figure #3: Clinical Diagnostic Dilemma for Histopathological Comparison



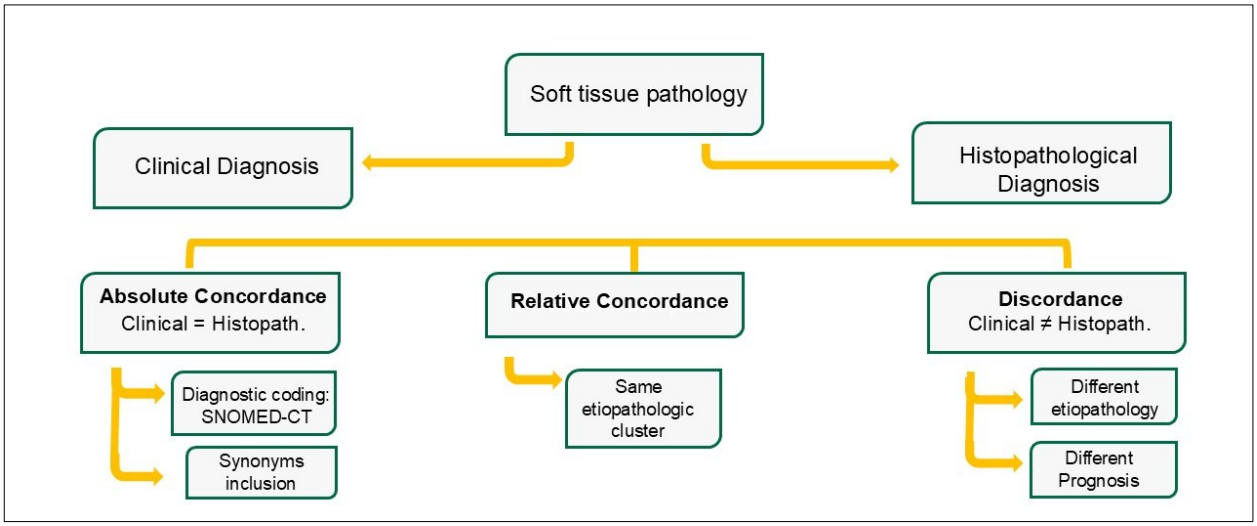
Therefore, all the conditions and pathologies were categorized according to their etiopathology in 24 different clusters. Finally, they were classified according to their prognosis as benign, OPMD, and malignant (see Appendix 1). This clustering and prognosis classification process was done by a former Oral Medicine graduate student and revised by an Oral Pathologist using oral Pathology textbooks and consensus reports as reference[55–57].

The concordance analysis between the clinical and histopathological diagnoses was performed on three levels: first, the most specific evaluation was done using the SNOMED-CT codes, followed by considering the synonyms analysis and lastly, a less granular examination employing the etiopathology clusters that were created.

“Absolute Concordance” was considered when the clinical and histopathological diagnoses had identical SNOMED-CT codes as the first level of analysis or when the synonyms' level of analysis matched in both diagnoses. “Relative Concordance” was determined when both diagnoses belonged to the same etiopathologic cluster. “Discordance” if they belonged to different clusters, and a final analysis was done considering the prognosis of all the discordant diagnoses. This analysis process is graphed in figure #4.

Figure # 4

Flowchart analysis of the concordance between clinical and histopathological diagnosis



The demographic information, age and gender variability of both databases were presented, and the incidence variation of soft tissue pathologies according to gender and age was analyzed. The age review was completed using the age categories according to Statistics Canada: Children under 14 years, Youth 15-24 years, Adults 25-64 years and Seniors over 65 years [58].

All statistical analyses were completed using IBM SPSS Statistics software, version 29.0. The demographic information was analyzed using descriptive statistics. The demographic variation and incidence between the University of Alberta 1985-2008 database and the Oral Medicine 2020-21 database were analyzed. Calculation of statistical significance between age, gender, prognosis, and etiopathological cluster concordance was conducted using analysis of variance, Chi-square and independent T-test; a p-value less than 0.05 was considered significant. The absolute concordance, relative concordance and discordance were presented as percentages. Cohen's Kappa was used to evaluate the concordance rate between clinical and histological accuracies for absolute and relative concordance. The level of agreement was determined as follows: <0.00 poor, 0.00-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial and 0.81-1.00 almost perfect [59].

The clinical diagnostic accuracy of detecting benign, OPMD and malignant pathologies was analyzed using sensitivity, specificity, and positive and negative predictive values.

Chapter 4: Results

4.1 Oral Medicine Graduate Program August 2020-August 2021 database

4.1.1 Demographic information (OM Graduate program 2020-21)

The sex distribution was 67 (54.92%) females and 55 (45.08%) males (female: male ratio 1.2:1). The mean age was 55.03 years, with a standard deviation (Std Dev) of 16.81 and an error of 1.52. The age distribution included cases as follows: children (below 14 years), 1 (0.82%); youth (15-24 years) 3 (2.46%); adults (25-64 years), 75 (61.47%) cases; and seniors (over 65 years) 43 (35.25%) cases. Regarding the age distribution, the skewness was -0.48, and the kurtosis was -0.6, demonstrating an asymmetrical distribution with a tendency for extreme lower values (Figures # 5 and 6).

Figure #: 5 Patient gender distribution: Oral Medicine Graduate program August 2020-August 2021 database

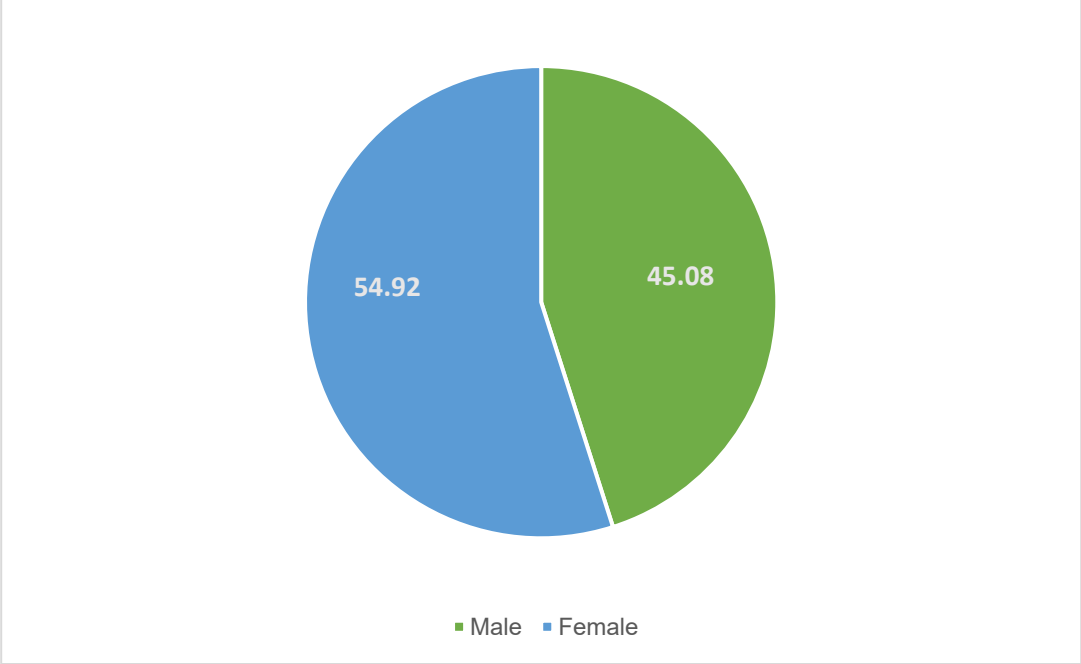
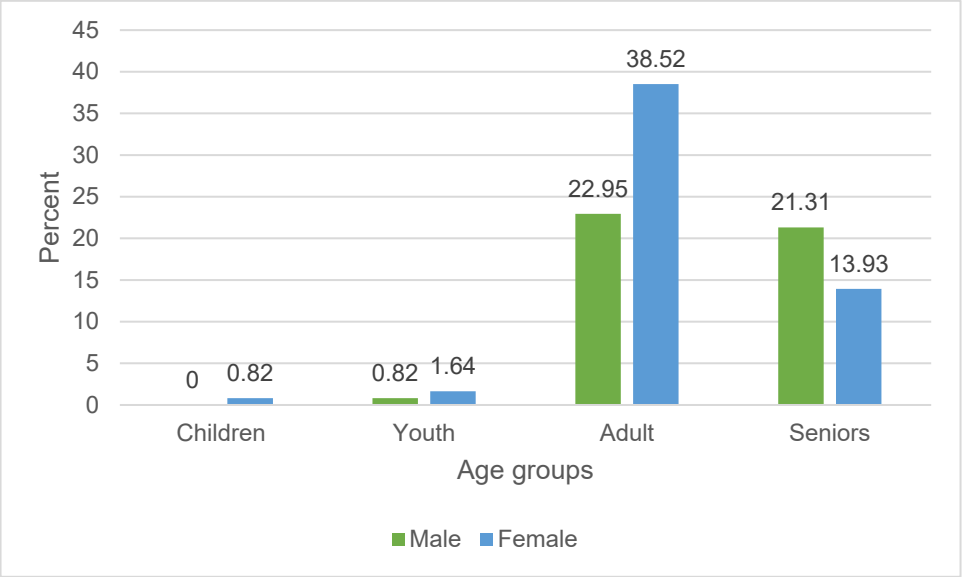


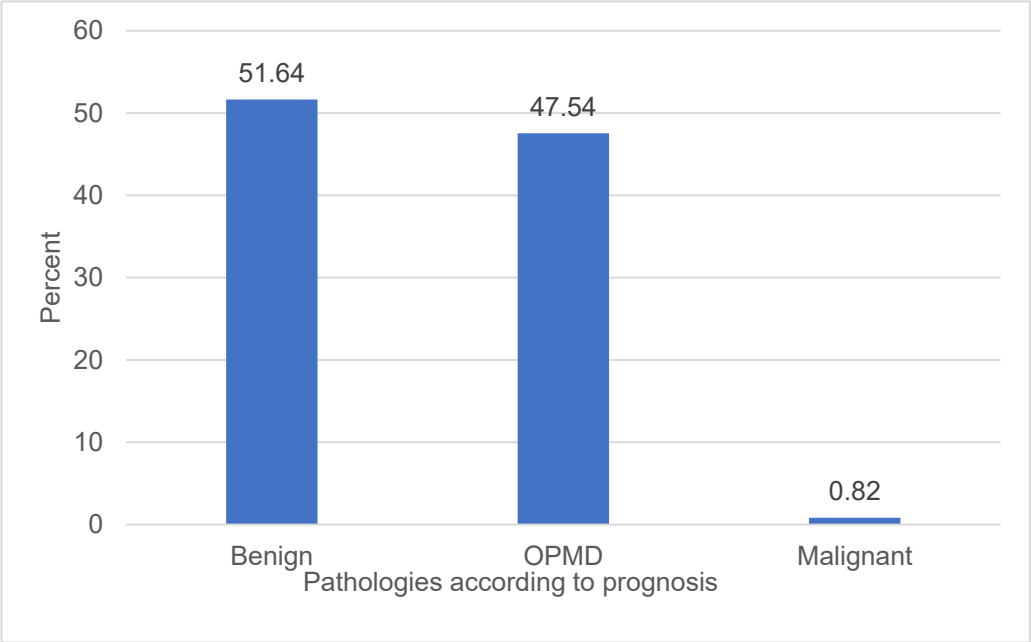
Figure # 6: Patient age and gender distribution: Oral Medicine Graduate program August 2020-August 2021 database.



4.1.2 Incidence variations of soft oral pathology (OM Graduate program 2020- 21)

The database from August 2020 to August 2021 contains 122 cases, of which (63 cases,51.64%) were benign, (58 cases, 47.54%) were OPMD, and (1 case, 0.82%) was a malignant pathology (see Figure #7).

Figure # 7: Incidence variations of soft pathology according to prognosis: Oral Medicine Graduate Program August 2020-August 2021 database



The seven most common benign histopathological diagnoses were irritation fibroma (28 cases, 22.95%), squamous papilloma (6 cases, 4.92%), inflammatory fibrous hyperplasia (3 cases, 2.46%), pyogenic granuloma (3 cases, 2.46%), mucositis (3 cases, 2.46%); amalgam tattoo (3 cases, 2.46%), and verruciform xanthoma (2 cases, 1.64%); the rest of the diagnoses were single cases of 15 different benign pathologies (23.81%) (see Table # 2).

Regarding OPMD, histopathological diagnoses were epithelial hyperkeratosis (35 cases, 28.69%), lichenoid reaction (9 cases, 7.38%), atypia (7 cases, 5.74%), dysplasia (6 cases, 4.92%), and actinic keratosis (1 case, 0.82%). There was a single SCC case (0.82%) concerning the malignancies (see Table # 2).

Table # 2: Most common diagnoses according to prognosis: Oral Medicine Graduate program August 2020-2021

Benign pathologies	**Cases (%)**	**OPMD pathologies**	**Cases (%)**	**Malignant pathologies**	**Cases (%)**
irritation fibroma	28 (22.95%)	epithelial hyperkeratosis	35 (28.69%)	squamous cell carcinoma	1 (0.82%)
squamous papilloma	6 (4.92%)	lichenoid reaction	9 (7.38%)	-	-
inflammatory fibrous hyperplasia	3 (2.46%)	atypia	7 (5.74%)	-	-
pyogenic granuloma	3 (2.46%)	dysplasia	6 (4.92%)	-	-
mucositis	3 (2.46%)	actinic keratosis	1 (0.82%)	-	-
amalgam tattoo	3 (2.46%)	-	-	-	-
verruciform xanthoma	2 (1.64%)	-	-	-	-
Rest Benign	15 (12.30%)	-	-	-	-
Total benign	63 (51.64%)	Total OPMD	58 (47.54%)	Total malignant	1 (0.82%)

4.1.2.1 Incidence variations of soft oral pathology by age groups

The analysis of the incidence variation of benign, OPMD and malignant conditions according to age groups was performed. An independent T-test was conducted to compare the mean ages between benign and OPMD pathologies; the malignant was excluded because it was a single case. The mean age of the benign conditions was 53.40 years with a Std Dev of 18.6, and for the OPMD, it was 56.48 years with a Std Dev of 14.6. The independent sample T-test indicated no significant difference in the mean ages between these groups (p=0.157).

There was a single case of pyogenic granuloma in the children's group. In the youth, there was a verruciform xanthoma and another squamous papilloma. Regarding the adult aggregate irritation fibroma (22 cases, 55%), squamous papilloma (2 cases, 5%), inflammatory fibrous hyperplasia (2 cases, 5%), and pyogenic granuloma (2 cases, 5%); and the rest of the 12 diagnoses were single cases (30%) (see table # 3).

Table # 3: Incidence variation of benign soft tissue pathologies in adults (25-64 years old): Oral Medicine Graduate program August 2020-2021

Benign pathologies	Number of cases	Percent
irritation fibroma	22	55.00%
squamous papilloma	2	5.00%
inflammatory fibrous hyperplasia	2	5.00%
pyogenic granuloma	2	5.00%
oral neuroma	1	2.50%
non-specific ulcer	1	2.50%
lymphoepithelial cyst	1	2.50%
mucocele	1	2.50%
normal	1	2.50%
peripheral ossifying fibroma	1	2.50%
parulis	1	2.50%
giant cell fibroma	1	2.50%
neurofibroma	1	2.50%
mucositis	1	2.50%
amalgam tattoo	1	2.50%
mucous membrane pemphigoid	1	2.50%
Total	40	100.00%

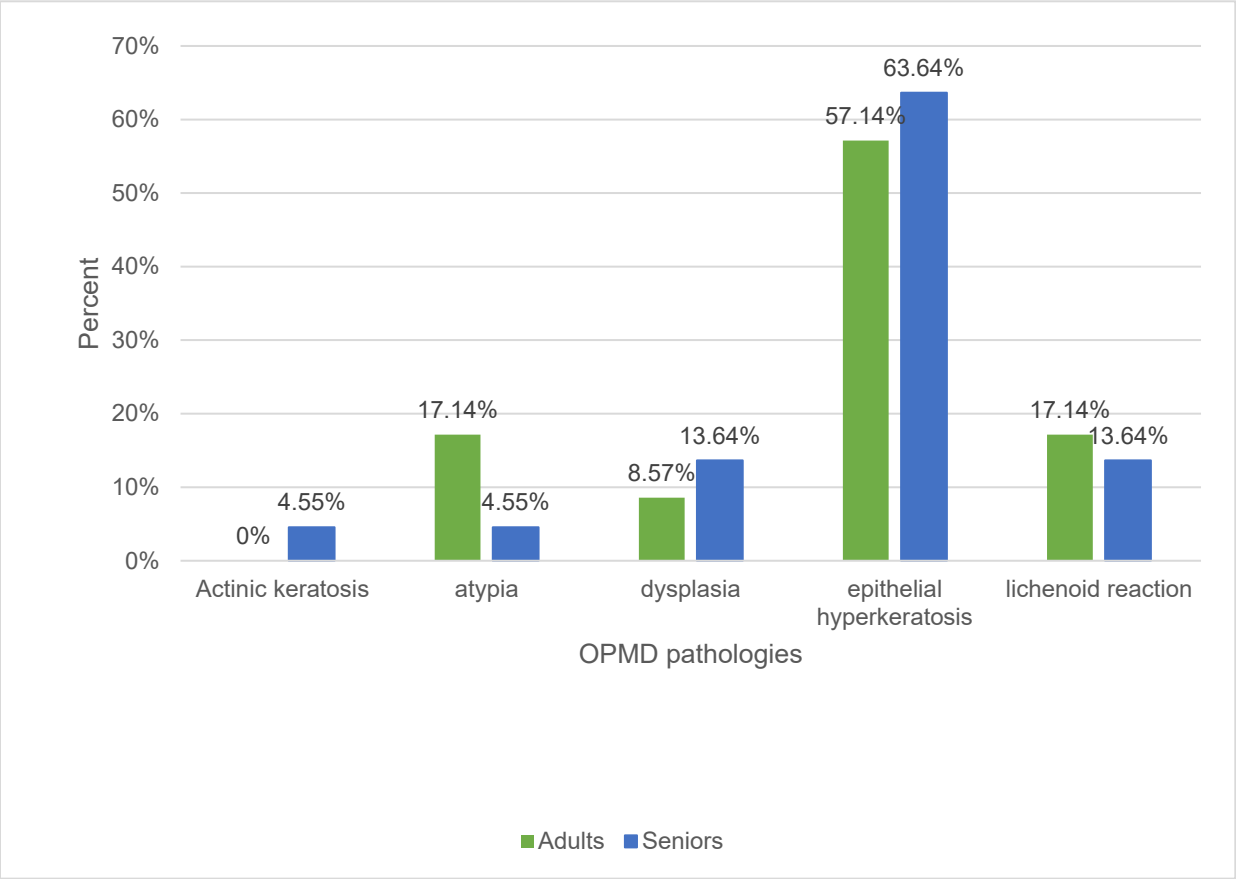
In the senior group, the most common benign pathologies were irritation fibroma (28 cases, 44.44%), squamous papilloma (6 cases, 9.52%), inflammatory fibrous hyperplasia (3 cases, 4.76%), pyogenic granuloma (3 cases, 4.76%), mucositis (3 cases, 4.76%), amalgam tattoo (3 cases, 4.76%), and verruciform xanthoma (2 cases, 3.17%). The other 15 diagnoses were single cases (23.81%) (see table # 4).

Table # 4: Incidence variation of benign soft tissue pathologies in seniors (over 65 years old): Oral Medicine Graduate program August 2020-2021

Benign pathologies	**Number of cases**	**Percent**
irritation fibroma	28	44.44%
squamous papilloma	6	9.52%
inflammatory fibrous hyperplasia	3	4.76%
pyogenic granuloma	3	4.76%
mucositis	3	4.76%
amalgam tattoo	3	4.76%
verruciform xanthoma	2	3.17%
neuroma	1	1.59%
fibrous tissue	1	1.59%
melanotic macule	1	1.59%
mucocele	1	1.59%
lymphoepithelial cyst	1	1.59%
giant cell fibroma	1	1.59%
parulis	1	1.59%
peripheral giant cell granuloma	1	1.59%
peripheral ossifying fibroma	1	1.59%
post inflammatory pigmentation	1	1.59%
neurofibroma	1	1.59%
foliate papillitis	1	1.59%
non-specific ulcer	1	1.59%
normal	1	1.59%
mucous membrane pemphigoid	1	1.59%
Total	63	100.00%

Respecting the OPMD diagnoses, there were no cases in the children cluster and one case of hyperkeratosis in the youths. In the adult cluster, the most common diagnosis was epithelial hyperkeratosis (20 cases, 57.14%), followed by atypia (6 cases, 17.14%), lichenoid reaction (6 cases, 17.14%), and dysplasia (3 cases, 8.57%). In the seniors, epithelial hyperkeratosis (14 cases, 63.64%), lichenoid reaction (3 cases, 13.64%), dysplasia (3 cases, 13.64%), atypia (1 case, 4.55%), and actinic keratosis (1 case, 4.55%) (see Figure # 8). In the case of the malignancies group, there was a single case that belonged to the seniors group.

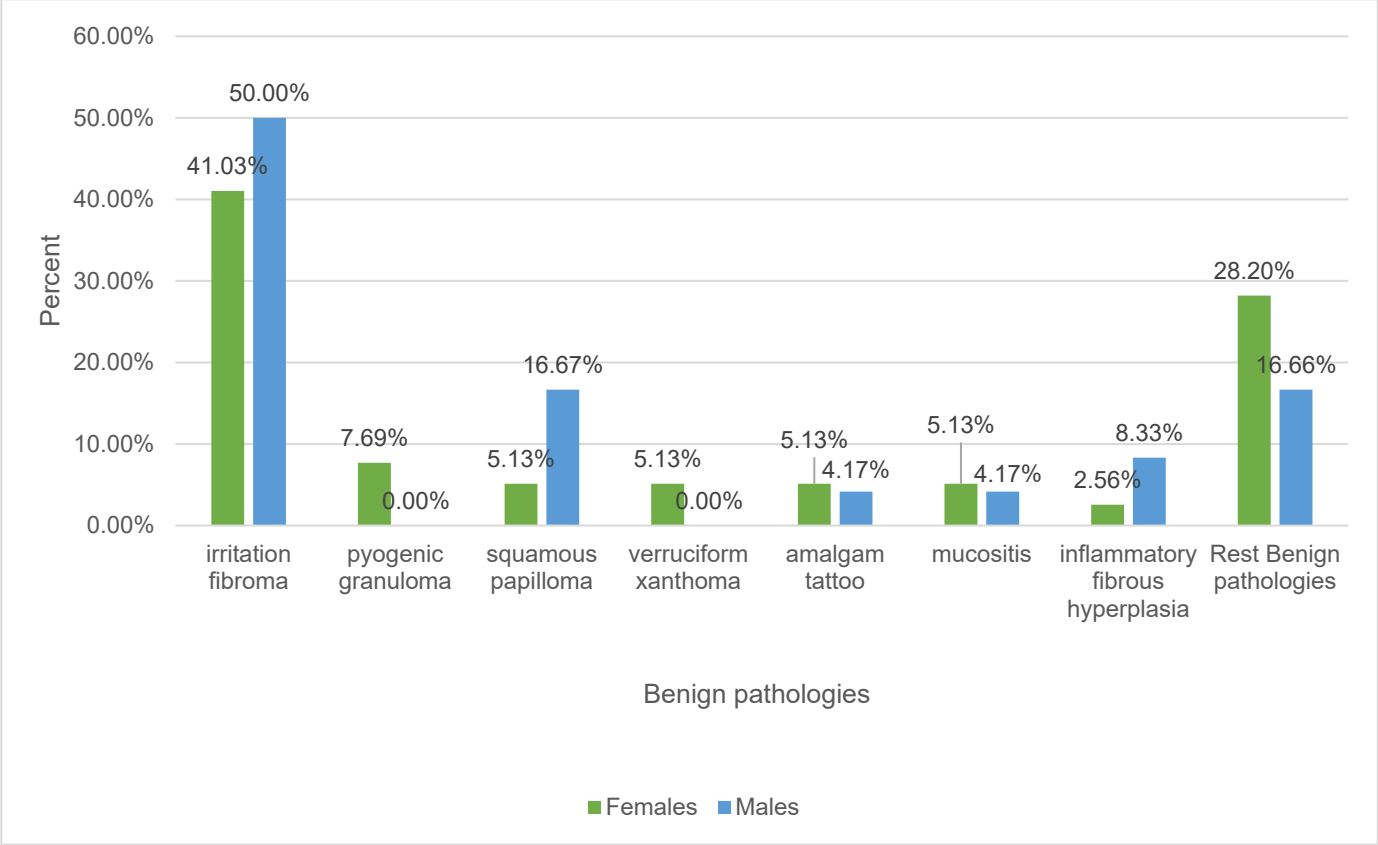
Figure # 8: Incidence variation of OPMD soft tissue pathologies in adults (25-64 years old) and seniors (over 65 years old): Oral Medicine Graduate program August 2020-2021.



4.1.2.2 Incidence variations of soft oral pathology by gender

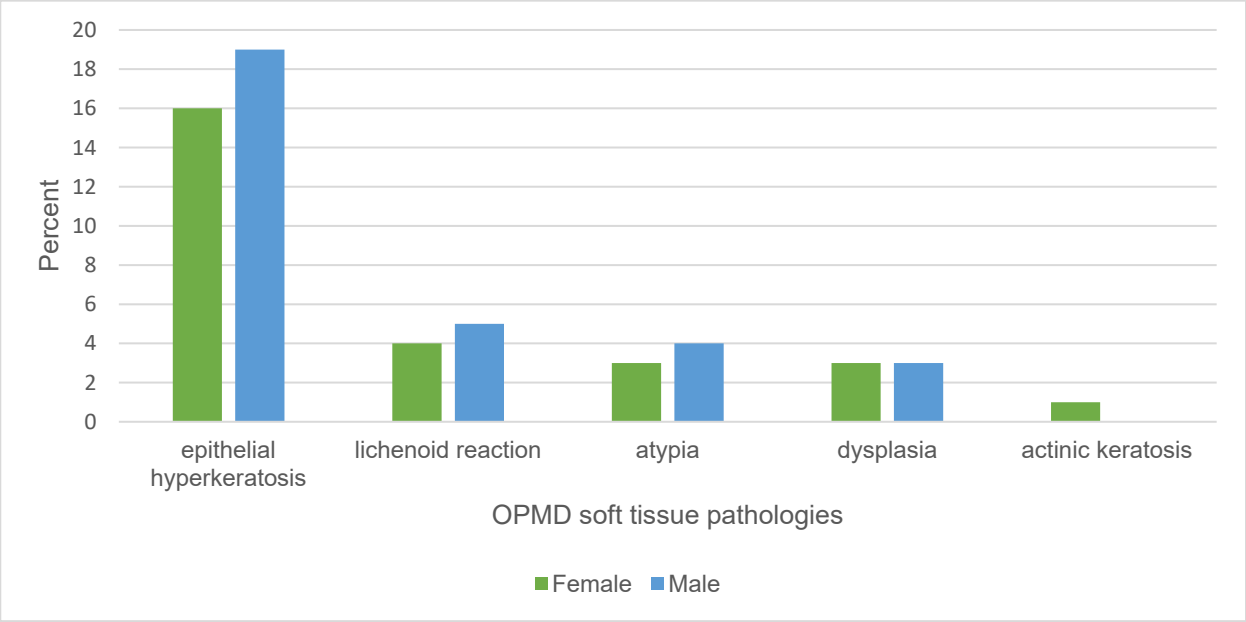
The most common benign pathology for both genders was irritation fibroma (16 cases, 41.03%) in females and (12 cases, 50%) in males. In females, the next most pathologies were pyogenic granuloma (3 cases, 7.69%), squamous papilloma (2 cases, 5.13%), verruciform xanthoma (2 cases, 5.13%), amalgam tattoo (2 cases, 5.13%), mucositis (2 cases, 5.13%), inflammatory fibrous hyperplasia (1 case, 2.56%). The remaining pathologies in females consisted in single cases of 11 different conditions representing 28.20% of the total. In the males, the benign pathologies were squamous papilloma (4 cases, 16.67%), inflammatory fibrous hyperplasia (2 cases, 8.33%), with single cases for 6 additional pathologies accounting for 25% of the total (see Figure #9).

Figure # 9: Comparison of the most common benign diagnoses by gender: Oral Medicine Graduate program August 2020-2021.



In the case of the OPMD, the pathologies were similar for both genders. For the female population was epithelial hyperkeratosis (16 cases, 59.26%), lichenoid reaction (4 cases, 14.81%), atypia (3 cases, 11.11%), dysplasia (3 cases, 11.11%), and actinic keratosis (1 case, 3.70%). For the males, epithelial hyperkeratosis (19 cases, 61.29%), lichenoid reaction (5 cases, 16.13%), atypia (4 cases, 12.90%), and dysplasia (3 cases, 9.68%) (see Figure # 10).

Figure #10: Comparison of the most common OPMD soft tissue pathologies by gender: Oral Medicine Graduate program August 2020-2021



Concerning the malignant pathologies, as stated before, a single squamous cell carcinoma (SCC) was found in a female. A single case of a residual radicular cyst was misdiagnosed as a hard tissue pathology, which histopathologically was a parulis. No relationship was found between the histopathological prognosis and the gender ($X^2(1)=2.871$ $p> 0.05$).

4.1.2 Concordance between the clinical and histopathologic diagnoses (OM Graduate program 2020-21)

4.1.2.1 General concordance between the clinical and histopathological diagnosis

The absolute concordance between the clinical and histopathological diagnoses by SNOMED-CT codes and diagnostic synonyms was 36.89% (45 cases) for both levels of analysis. The second level of concordance analysis rendered a relative concordance of 72.94% and a discordance of 27.05% (33 cases). Regarding the kappa agreement, for SNOMED-CT analysis, the Kappa was 0.314 ($p<0.001$), which means a fair agreement. And for the relative concordance was 0.603 ($p<0.001$), denoted as a moderate agreement. According to the prognosis category, the agreement calculation by Kappa for the clinical and histopathological diagnosis was 0.729 ($p<0.001$) significance (see Figure #11). Regarding the ability to diagnose malignancies, the sensitivity and negative predictive value (NPV) was 100%, specificity was 99%, and positive predictive value (PPV) was 50%. On the other hand, for benign diagnoses, the sensitivity was 87.3%, specificity 86.4%, PPV 87.3% and NPV 86.4%. In the OPMD diagnosis, the sensitivity was 84.4%, specificity 89.0%, PPV 87.5%, and NPV 86.3% (see Table # 5)

Figure #11: Concordance between the clinical and histopathological diagnoses: Oral Medicine Graduate program August 2020-2021

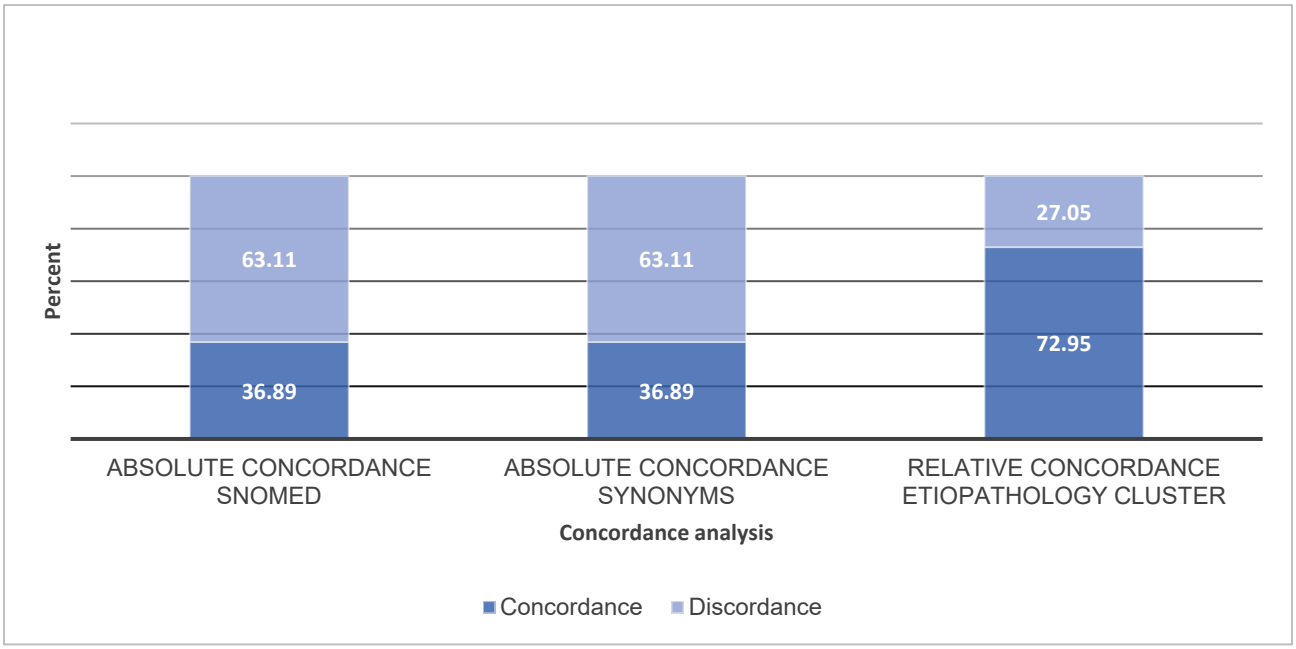


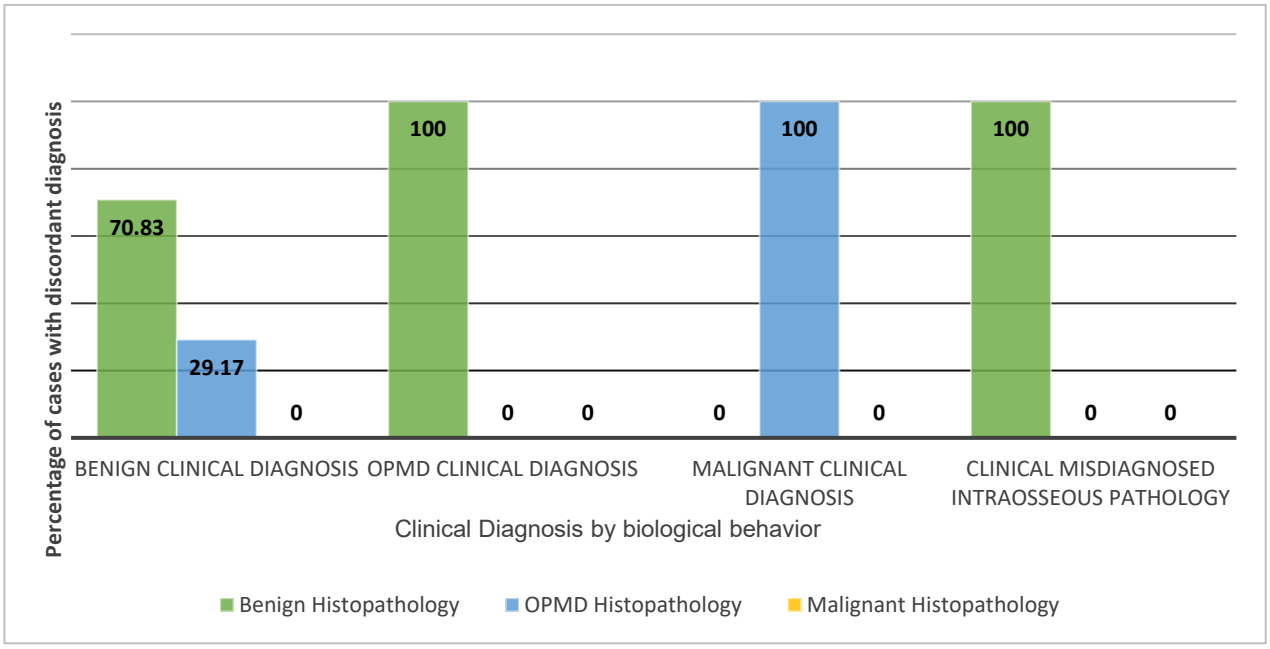
Table #5

Sensitivity, Specificity, PPV, and NPV for the clinical diagnosis of benign, OPMD and malignant pathologies: Oral Medicine program August 2020-2021

Diagnosis	Sensitivity	Specificity	PPV	NPV
Benign	87.3%	86.4%	87.3%	86.4%
OPMD	84.4%	89.0%	87.5%	86.3%
Malignant	100%	99%	50%	100%

Regarding the discordant cases (33 cases), 24 entries with benign clinical diagnoses were incorrectly diagnosed because 16 cases histologically belonged to a different benign cluster, and seven were hyperkeratosis, which means they were OPMDs. One was incorrectly diagnosed as a residual cyst with a definitive diagnosis of parulis. In the case of the clinical misdiagnosis as OPMD (7 cases), they were all confirmed benign conditions. Finally, a single case was clinically misdiagnosed as malignant, but histopathologically, it was actinic keratosis OPMD (see Figure # 12).

Figure # 12: Analysis of the discordant diagnoses by Biological Behaviour Oral Medicine Graduate Program August 2020-2021



4.1.2.2 Concordance between the clinical and histopathological diagnosis according to etiopathologic cluster

The concordance between the clinical and histopathological diagnosis, considering the etiopathological clusters with more than one case, showed the following information: The first level of analysis of the absolute concordance, by SNOMED-CT, was 100% concordance in the foreign reaction group. Then, 83.33% in the benign viral-induced verruco-papillary group and 57.89% in the reactive cluster. The second lowest concordance, 20.69%, was in the OPMD, followed by 33.33% in the benign epithelial cluster. On the other hand, there was 0% concordance in the benign soft tissue conditions and ulcerative-inflammatory clusters.

In the second level of analysis by synonyms, subtle changes in the clusters' concordance behaviour occurred, but the overall percentage did not vary. The benign virally induced verruco-papillary group reached 100% concordance, but the reactive cluster lowered to 55.26%. The clusters with 0% concordance were maintained as in the SNOMED-CT analysis.

The relative concordance overall percentage increased, and the main difference was in the improvement in the OPMD to 84.48% and the reactive cluster to 73.68%.

Regarding the etiological clusters with discordance, they were misdiagnosed due to the following. In the benign soft tissue group, two clinical diagnoses of irritation fibroma were histologically identified as giant cell fibroma and neurofibroma, and the other mistake was a lymphoepithelial cyst that was a neuroma. In the developmental cluster was a subtle misdiagnosis; a lymphoepithelial cyst was clinically diagnosed as lymphoid hyperplasia. In immune-mediated conditions, a single case of mucous membrane pemphigoid was erroneously diagnosed as lichen planus.

Six misdiagnoses were reported in the ulcerative-inflammatory cluster. Three cases of mucositis were clinically diagnosed as lichenoid reaction, lichen planus, and erythroplakia. A non-specific ulcer was clinically diagnosed as leukoplakia, a foliate papillitis was erroneously diagnosed as a lymphoepithelial cyst, and a parulis was misdiagnosed as a residual cyst, which was previously mentioned. Finally, a biopsy was done with the clinical diagnosis of mucous membrane pemphigoid, rendering no pathology (see table # 6).

Table # 6: Concordance by etiopathologic clusters between the clinical and histopathological diagnoses: Oral Medicine Graduate program August 2020-2021

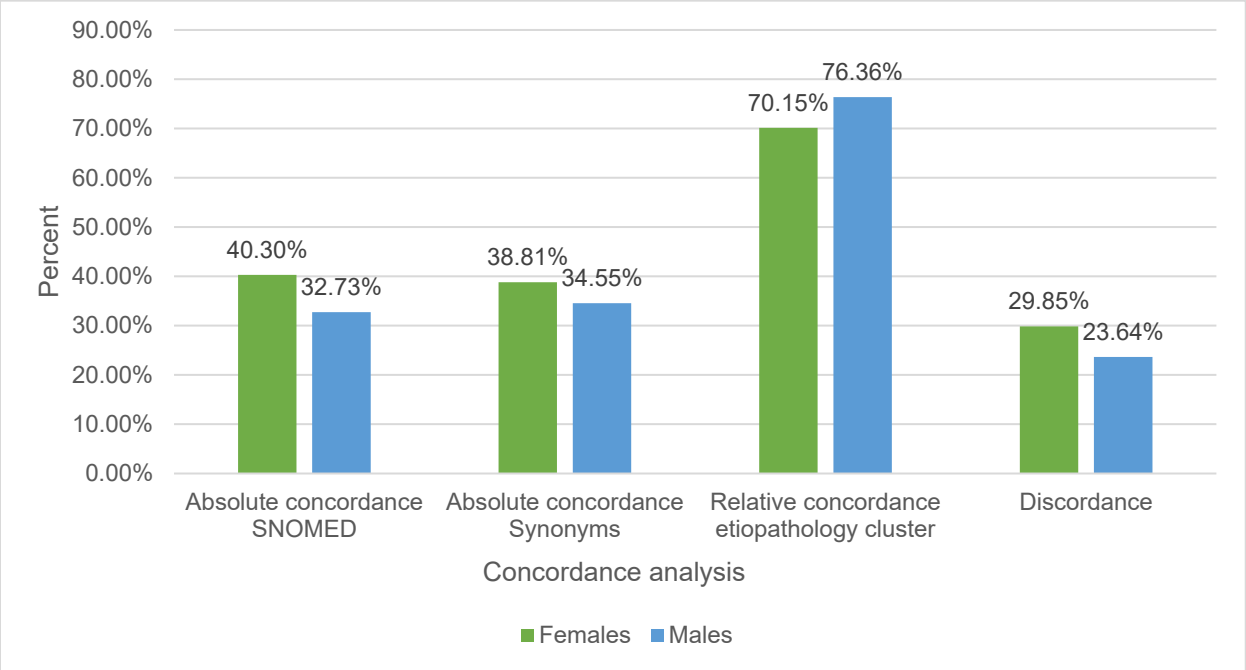
Etiopathologic cluster	Absolute Concordance SNOMED-CT	Absolute Concordance Synonyms	Relative Concordance	Discordance
Benign Epithelial conditions	1 (33.33%)	1 (33.33%)	1 (33.33%)	2 (66.67%)
Benign Soft tissue	0 (0%)	0 (0%)	0 (0%)	3 (100%)
Benign virally induced verrucopapillary	5 (83.33%)	6 (100%)	6 (100%)	0 (0%)
Foreign Body reaction	3 (100%)	3 (100%)	3 (100%)	0 (0%)
OPMD	12 (20.69%)	12 (20.69%)	49 (84.48%)	9 (15.52%)
Reactive	22 (57.89%)	21 (55.26%)	28 (73.68%)	10 (26.32)
Ulcerative-inflammatory	0 (0%)	0 (0%)	0 (0%)	6 (100%)

4.1.2.3 Concordance between the clinical and histopathological diagnosis according to gender

The concordance between the clinical and histopathological diagnoses was also calculated according to gender. In the female group, by SNOMED-CT was 27(40.30%); by synonyms, 26 (38.81%); by etiopathological cluster, 47 (70.15%); and the discordance was 20 (29.85 %).

Conversely, the male group by SNOMED-CT was 18 (32.73%); by synonyms, it was 19 (34.55%); by etiopathological cluster, it was 42 (76.36%), and the discordance was 23.64 (76.36%) (see Figure # 13). A Pearson Chi-square test evaluated the relationship between cluster concordance and gender. This test found no statistical significance between these variables ($X^2(1)=0.591, p>.05$).

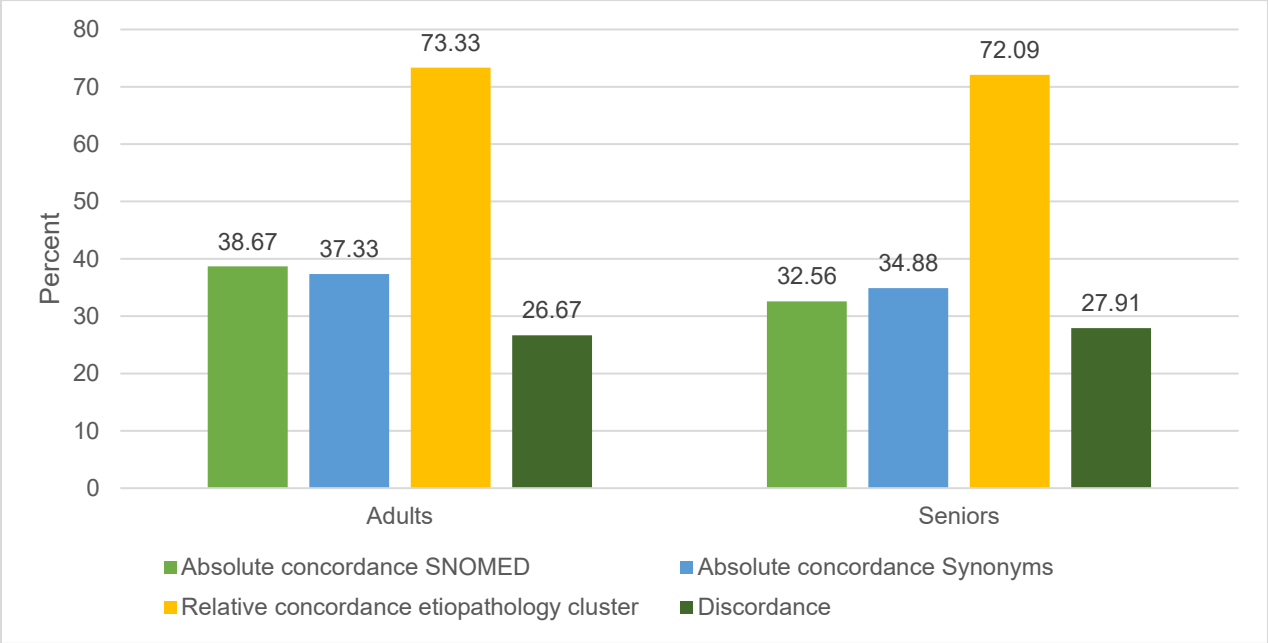
Figure # 13: Concordance between the clinical and histopathological diagnosis according to gender: Oral Medicine Graduate program August 2020-2021.



4.1.2.4 Concordance between the clinical and histopathological diagnosis according to age groups

The concordance by age group was calculated as follows: There was a single case in the children and three cases in the youth group, so they were not included in this analysis. The adult group by SNOMED-CT was 29 (38.67%); by synonyms, 28 (37.33%); by etiopathological cluster, 55 (73.33%); and the discordance was 20 (26.67%). The senior group by SNOMED-CT was 14 (32.56%); by synonyms, it was 15 (34.88%); by etiopathological cluster, it was 31 (72.09%); and the discordance was 12 (27.91%). The association between the age groups and the concordance according to etiopathology clusters was conducted. This test found no statistical significance between these variables ($X^2(1)=0.452$, $p>.05$). (see Figure # 14).

Figure # 14: Concordance between the clinical and histopathological diagnosis in the adult and senior age group: Oral Medicine Graduate program August 2020-2021

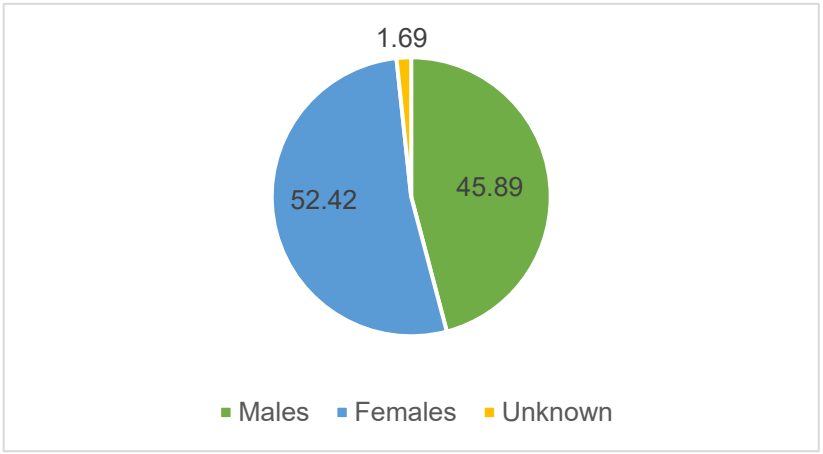


4.2 Oral Pathology Biopsy Service by licensed dentists, University of Alberta, between 1985 and 2008 database

4.2.1 Demographic information (Biopsy Service 1985-2008)

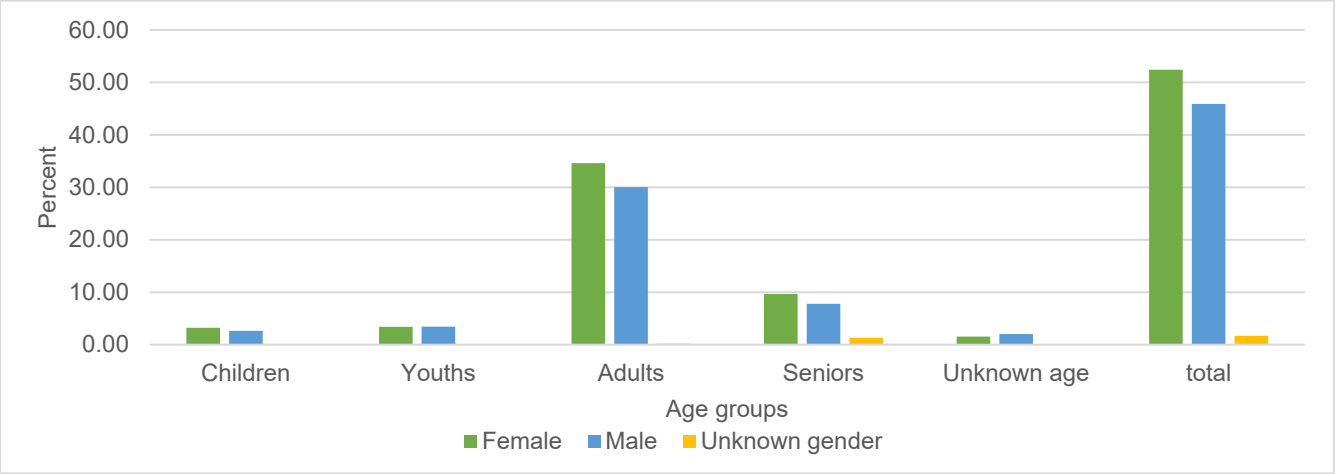
The Oral Pathology Biopsy Service, University of Alberta, comprised 19,259 cases. The sex distribution was 10,095 (52.42%) females, 8,838 (45.89%) males (female: male ratio 1.14:1), and 326 (1.69%) unknowns (see Figure # 15).

Figure # 15: Patients gender distribution: University of Alberta Oral Pathology Biopsy Service 1985-2008 database



The age distribution included children, less than 14 years, 1,128 (5.85%); youths, 15-24 years, 1,320 (6.85%); adults, 25-64 years, 12,489 (64.85%); seniors over 65 years, 3,609 (18.74%), and unknown 713 (3.71%). The mean age was 47.72 years, with a standard deviation of 20.18 and an error of 0.18. The skewness was 0.17, and the kurtosis was -0.44, demonstrating a slightly right-skewed and fairly symmetrical with fewer extreme values (see Figure #16).

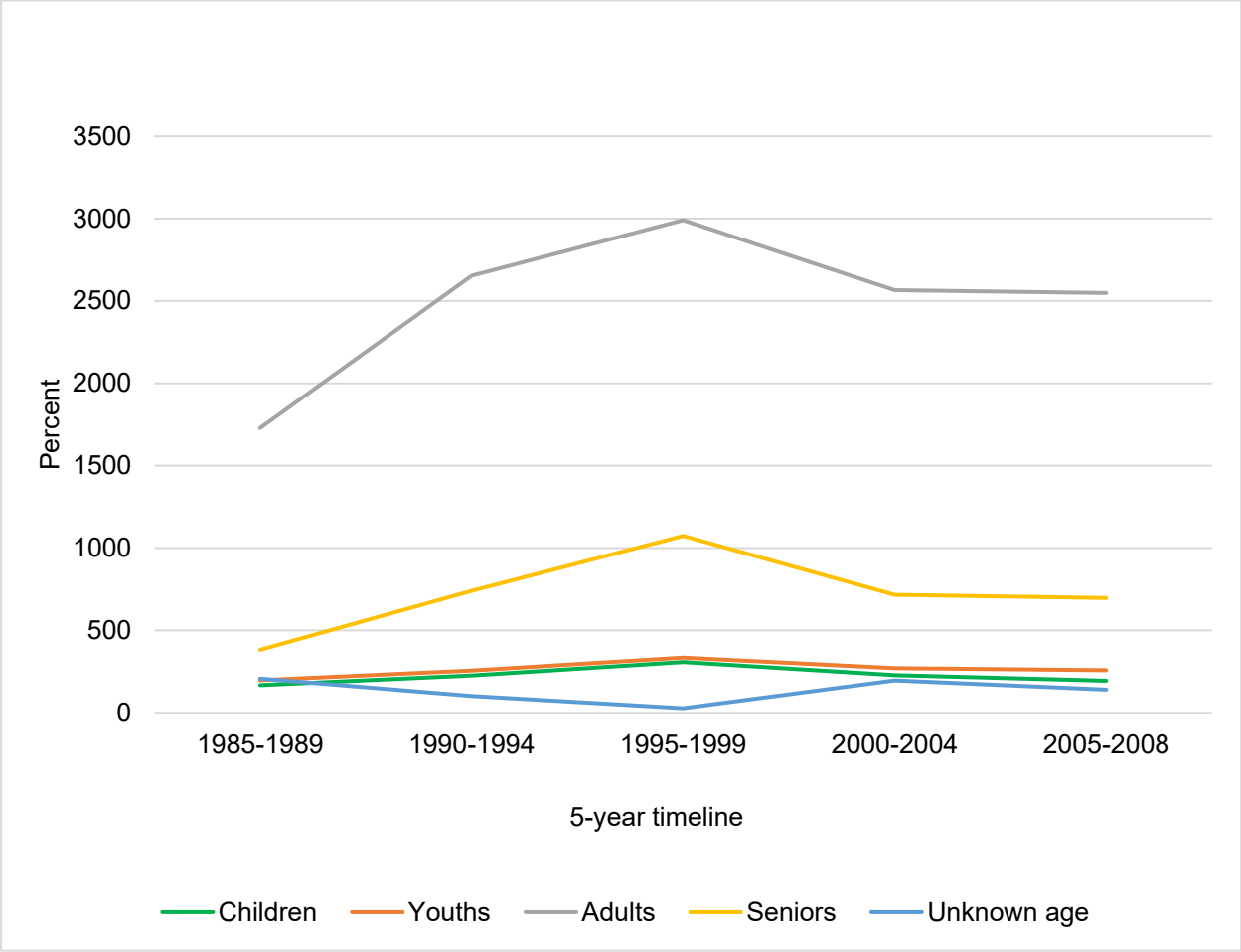
Figure # 16: Patients age and gender distribution: University of Alberta Oral Pathology Biopsy Service 1985-2008 database



The demographic variations in a 5-year timeline were analyzed from 1985 to 2008. It is important to emphasize that the lowest number of patients, 2,685 (13.94%), was found in the 1985-1989 timeframe and the highest, 4,736 (24.59%), in 1995-1999. Therefore, in all the age and gender groups, the lowest and highest numbers were in the previously mentioned periods.

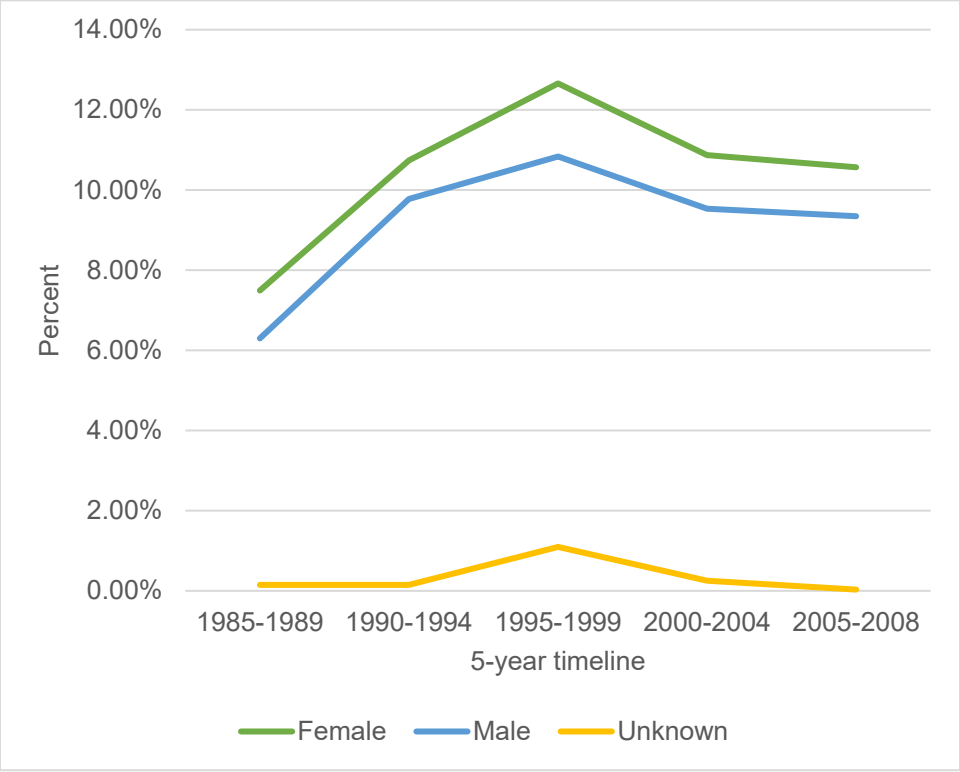
The number of patients represented in each age group was as follows, and the percentage is based on the total study population. The children ranged from (168 cases, 0.87%) to (308 cases, 1.60%); the youth group was (198 cases, 1.03%) to (335 cases, 1.74%); the adults accounted for between (1729 cases, 8.98%) and (2991 cases, 15.53%), and the seniors between (382 cases, 1.98%) and (1074 cases, 5.58%). In the case of the reports with unknown age, the tendency differed because the highest number (208 cases, 1.08%) was presented in the 1985-1989 period, and the lowest, (28 cases, 0.15%) in 1995-1999 (see Figure # 17).

Figure # 17: Age distribution according to 5-year timeline: Oral Pathology Biopsy Service, University of Alberta 1985-2008



The gender distribution for the 5-year period, considering the percentages from the total studied population, is rendered in the following way: The female population ranged between (1,443 cases, 13.94%) and (2,438 cases, 12.66%). In contrast, the male population fluctuated between (1,213 cases, 6.30%) and (2,087 cases, 10.84%). The group with unknown gender ranged between (29 cases, 0.15%) and (211 cases, 1.10%) (see Figure #18).

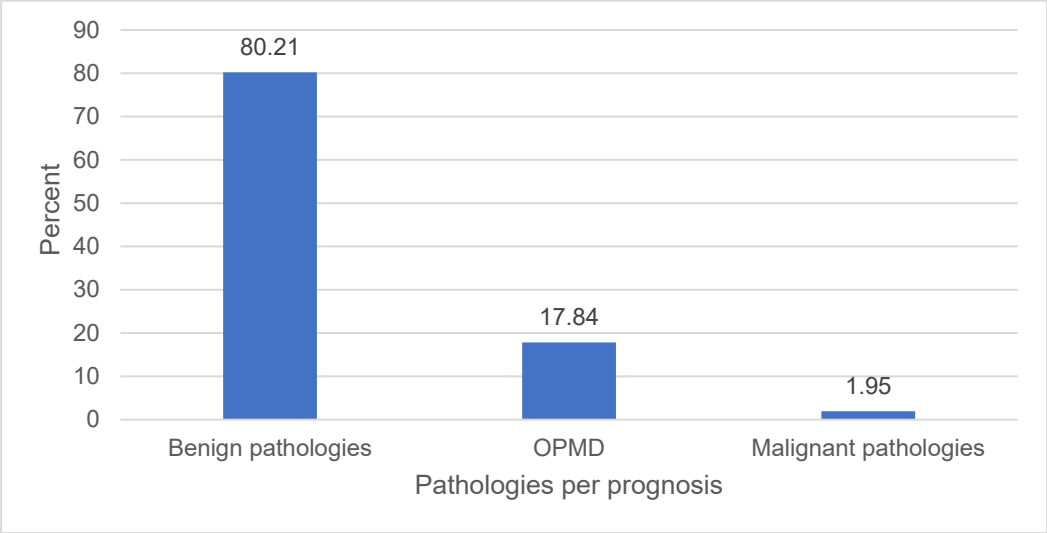
Figure #18: Gender distribution according to 5-year timeline: Oral Pathology Biopsy Service, University of Alberta 1985-2008



4.2.2 Incidence variations of soft oral pathology (Biopsy Service 1985-2008)

The incidence variations of soft tissue pathology according to prognosis were (15,448 cases, 80.21%) for benign, (3,435 cases, 17.84%) for OPMD, and (376 cases, 1.95%) for malignancies. The ratio between benign and malignant pathologies was 41:1 (see Figure #19).

Figure # 19: Incidence variations of soft tissue pathologies according to prognosis: University of Alberta Oral Pathology Biopsy Service 1985-2008 database



The ten most common benign histopathological diagnoses were irritational fibroma (6,905 cases, 35.85%), squamous papilloma (1,336 cases, 6.94%), mucocele (849 cases, 4.41%), pyogenic granuloma (667 cases, 3.46%), mucous retention cyst (507cases, 3.63%), peripheral ossifying fibroma (409 cases, 2.12%), amalgam tattoo (399 cases, 2.07%), non-specific ulcer (245 cases, 1.27%), giant cell fibroma (235 cases, 1.22%), chronic inflammation (225 cases, 1.17%), and the rest of the cases accounted (3671 cases, 19.06%) with 149 different benign conditions. Regarding the OPMD, epithelial hyperkeratosis (1669 cases, 8.67%), dysplasia (644 cases, 3.34%), lichen planus (471 cases, 2.45%), lichenoid reaction (289 cases, 1.50%), verrucous hyperplasia (142 cases, 0.74%), erosive lichen planus (61 cases, (53 cases, 0.28%), carcinoma in situ (30 cases, 0.16%), actinic keratosis (18 cases, 0.09%), actinic cheilitis (15 cases, 0.08%) and the remaining accounted (43 cases, 0.22%) with seven different diagnoses. Respecting the malignant prognosis were SCC (269 cases, 1.40%), verrucous carcinoma (24 cases, 0.12%), lymphoma (17 cases, 0.09%), polymorphous adenocarcinoma (9 cases, 0.05%), oral carcinoma (9 cases, 0.05%), mucoepidermoid carcinoma (9 cases, 0.05%), Kaposi sarcoma (8 cases, 0.04%), adenocarcinoma (7 cases, 0.04%), malignancy (7 cases, 0.04%), acinic cell carcinoma (5 cases, 0.03%), and the rest of the malignancies were (12 cases, 0.04%) with eight different diagnoses (see Table #7).

Table #7: Ten Most common diagnoses according to prognosis: University of Alberta 1985-2008.

Benign pathologies	Cases (%)	OPMD pathologies	Cases (%)	Malignant pathologies	Cases (%)
irritation fibroma	6,905 (35.85%)	epithelial hyperkeratosis	1669 (8.67%)	squamous cell carcinoma	269 (1.40%)
squamous papilloma	1,336 (6.94%)	dysplasia	644 (3.34%)	verrucous carcinoma	24 (0.12%)
mucocele	849 (4.41%)	lichen planus	471 (2.45%)	lymphoma	17 (0.09%)
pyogenic granuloma	667 (3.46%)	lichenoid reaction	289 (1.50%)	polymorphous adenocarcinoma	9 (0.05%)
salivary duct cyst	507 (2.63%)	verrucous hyperplasia	142 (0.74%)	oral carcinoma	9 (0.05%)
peripheral ossifying fibroma	409 (2.12%)	erosive lichen planus	61 (0.32%)	mucoepidermoid carcinoma	9 (0.05%)
amalgam tattoo	399 (2.07%)	atypia	53 (0.28%)	Kaposi sarcoma	8 (0.04%)
non-specific ulcer	245 (1.27%)	carcinoma in situ	30 (0.16%)	adenocarcinoma	7 (0.04%)
giant cell fibroma	235 (1.22%)	actinic keratosis	18 (0.09%)	malignancy	7 (0.04%)
chronic inflammation	225 (1.17%)	actinic cheilitis	15 (0.08%)	acinic cell carcinoma	5 (0.03%)
Rest benign	3671 (19.06%)	Rest OPMD	43 (0.19%)	Rest malignancies	12 (0.04%)
Total benign	15448 (80.21%)	Total OPMD	3435 (17.84%)	Total malignancies	376 (1.95%)

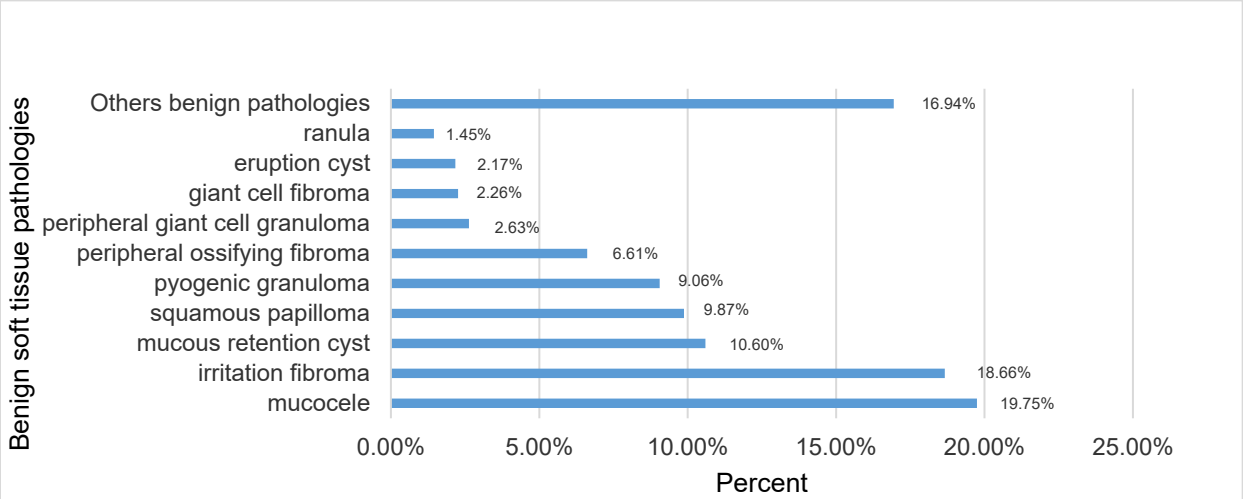
4.2.2.1 Incidence variations of soft oral pathology according to age

The analysis of the soft oral pathology according to age will be presented per prognosis. Firstly, the one-way analysis of variance was conducted to compare the age of the patients with the pathological prognosis. Results ($F(18,543) = 337.689$, $p<0.001$) suggest a significant difference in the mean ages of the cases according to the histopathologic prognosis. The mean age for the benign pathologies was 45.96 years (Std Dev 20.54); for the OPMD pathologies, it was 54.00 years (Std Dev 16.61); and for the malignant pathologies was 63.47 years (Std Dev 20.18).

The most common pathologies by group age will be presented. In the case of benign soft tissue pathologies by age from 1985 to 2008, it was as follows. In the children group (0-14 years old), there were 1104 patients with benign pathologies. The ten most common histopathological diagnoses in this group were mucocele (218 cases, 19.75%), irritation fibroma (206 cases, 18.66%), salivary duct cyst (117 cases,

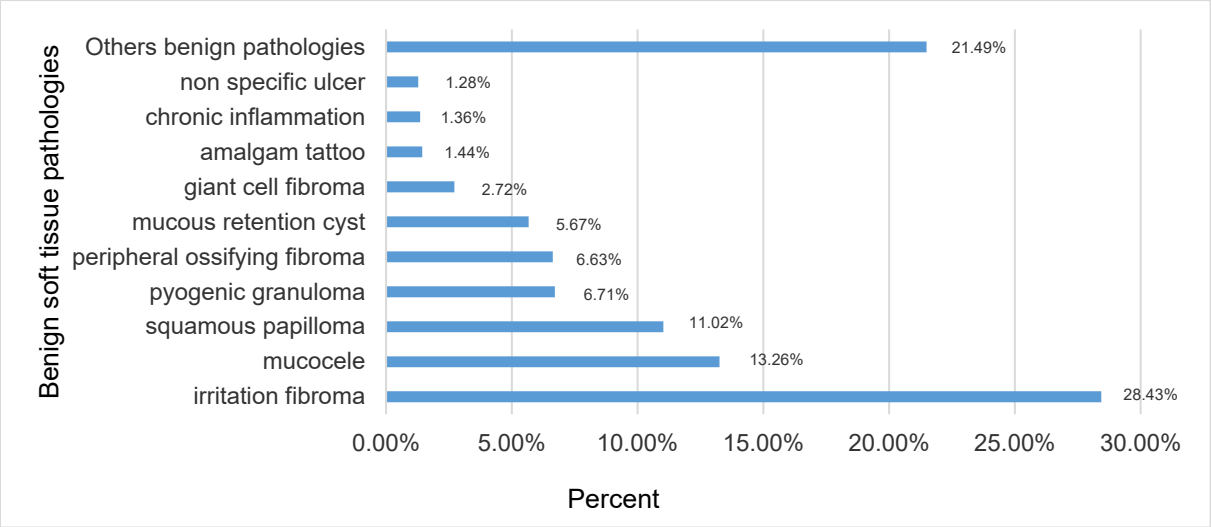
10.60%), squamous papilloma (109 cases, 9.87%), pyogenic granuloma (100 cases, 9.06 %), peripheral ossifying fibroma (73 cases, 6.61%), peripheral giant cell granuloma (29 cases, 2.63%), giant cell fibroma (25 cases, 2.26%), eruption cyst (24 cases, 2.17%), ranula (16 cases, 1.45%), the rest of the cases were (187 cases, 16.94%) with 49 different benign diagnoses (see Figure # 20).

Figure# 20: Incidence variation of benign soft tissue pathologies in children (0-14 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008



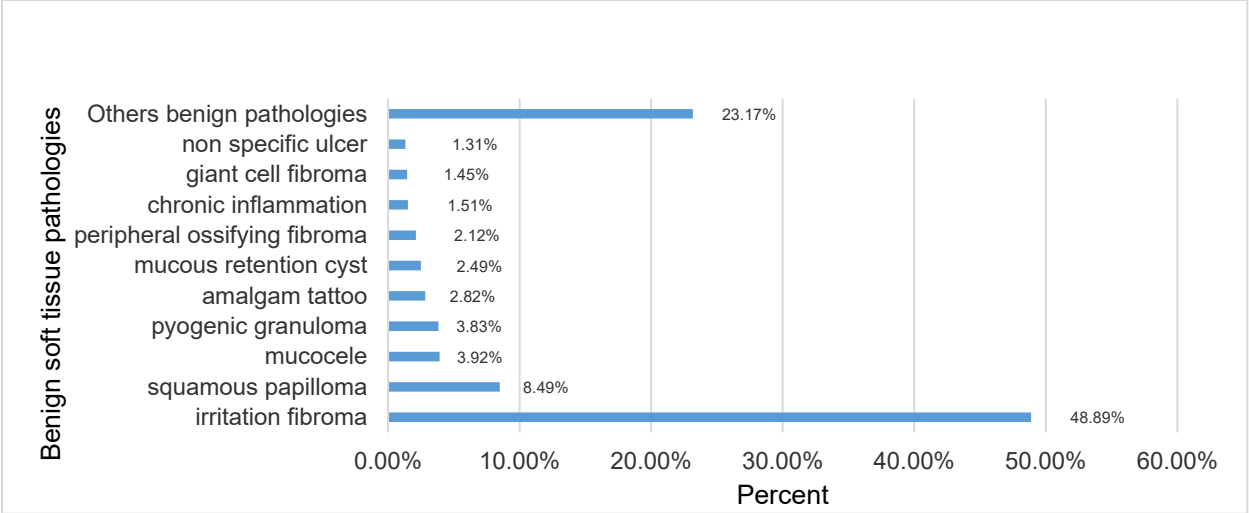
In the case of the youth group (15-24 years old) there were 1,252 cases with benign pathologies. The ten most common were irritational fibroma (356 cases, 28.43%), mucocele (166 cases, 13.26%), squamous papilloma (138 cases, 11.02%), pyogenic granuloma (84 cases, 6.71%), peripheral ossifying fibroma (83 cases, 6.63%), salivary duct cyst (71 cases, 5.67%), giant cell granuloma (34 cases, 2.72%), amalgam tattoo (18 cases, 1.44%), chronic inflammation (17 cases, 1.36%), and non-specific ulcer (16 cases, 1.28%) the remaining were (269 cases, 21.49%) with 71 different diagnoses (see Figure # 21).

Figure # 21: Incidence variation of benign soft tissue pathologies in youths (15-24 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008



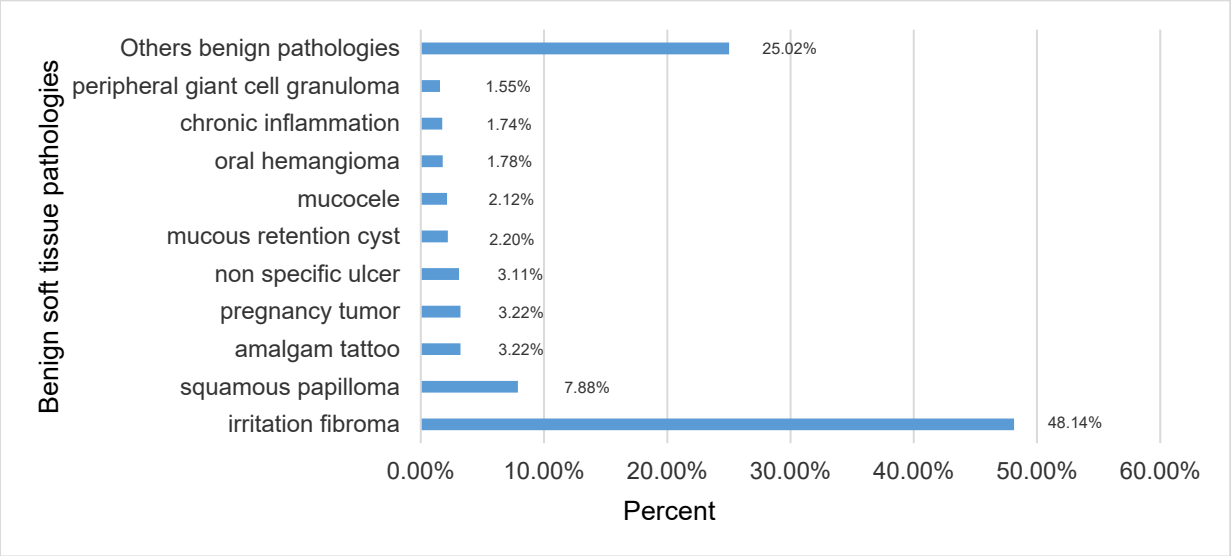
The adult group (25-64 years old) had 9,925 benign diagnoses. The ten most common were irritational fibroma (4,852 cases, 48.89%), squamous papilloma (843 cases, 8.49%), mucocele (389 cases, 3.92%), pyogenic granuloma (380 cases, 3.83%), amalgam tattoo (280 cases, 2.82%), salivary duct cyst (247 cases, 2.49%), peripheral ossifying fibroma (210 cases, 2.12%), chronic inflammation (150 cases, 1.51%), giant cell fibroma (144 cases, 1.45%), and non-specific ulcer (130 cases, 1.31%) the other cases accounted (2300 cases, 23.17%) with 134 different diagnoses (see Figure #22).

Figure# 22: Incidence variation of benign soft tissue pathologies in adults (25-64 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008



The senior group (over 65 years old) had 2638 cases of benign conditions. The most common histopathologic diagnoses were irritation fibroma (1270 cases, 48.14%), squamous papilloma (208 cases, 7.88%), amalgam tattoo (85 cases, 3.22%), pyogenic granuloma (85 cases, 3.22%), and non-specific ulcer (82 cases, 3.11%), salivary duct cyst (58 cases, 2.20%), mucocele (56 cases, 2.12%), hemangioma (47 cases, 1.78%), chronic inflammation (46 cases, 1.74%), peripheral giant cell granuloma (41 cases, 1.55%), and the rest (660 cases, 25.02%) with 100 different diagnoses (Figure # 23).

Figure# 23: Incidence variation of the benign soft tissue pathologies in the senior population (over 65 years old): University of Alberta Oral Pathology Biopsy Service 1985-2008



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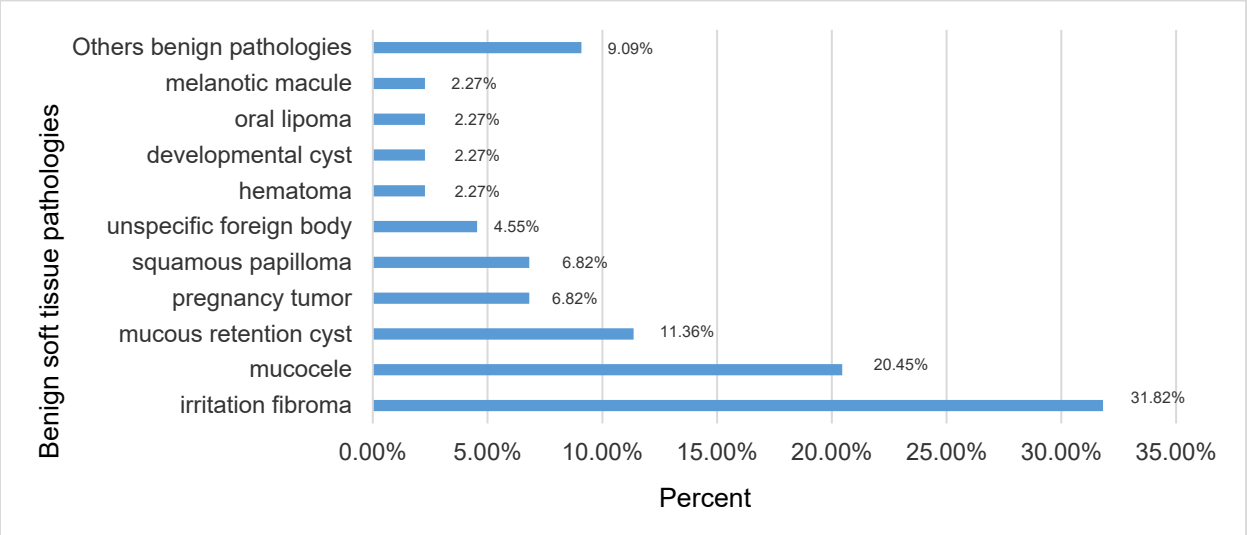
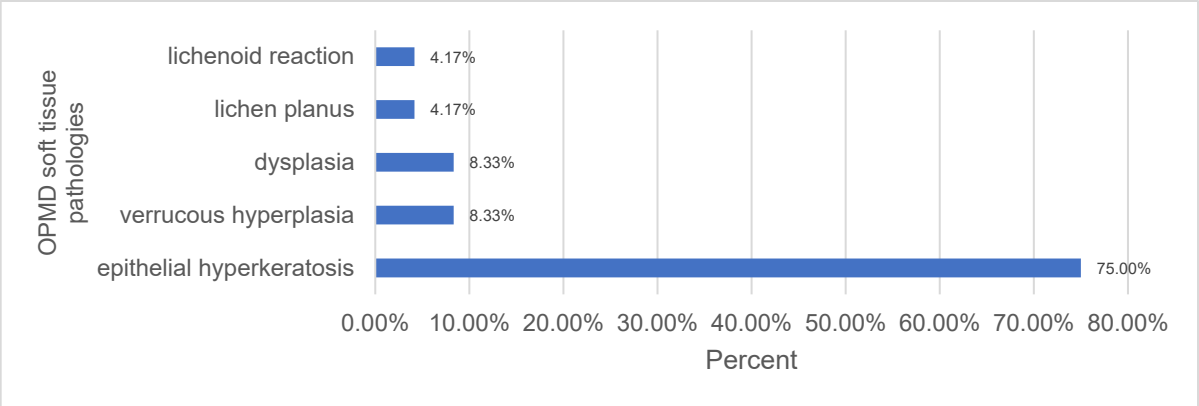
There were 573 cases of benign pathologies that belonged to the group of unknown age. The most common pathologies were irritation fibroma (235 cases, 41.01%), squamous papilloma (41 cases, 7.16%), mucocele (29 cases, 5.06%), peripheral giant cell granuloma (27 cases, 4.71%), pyogenic granuloma (21 cases, 3.66%), salivary duct cyst (19 cases, 3.32%), granulation tissue (13 cases, 2.27%), amalgam tattoo (13 cases, 2.27%), non-specific ulcer (11 cases, 1.92%), peripheral ossifying fibroma (10 cases, 1.75%), and the remaining benign cases were (154 cases, 26.88%) with 60 different diagnoses (see Figure # 24).

Figure # 24: Incidence variation of benign soft tissue pathologies in unknown age group: Oral Pathology Biopsy Service, University of Alberta 1985-2008



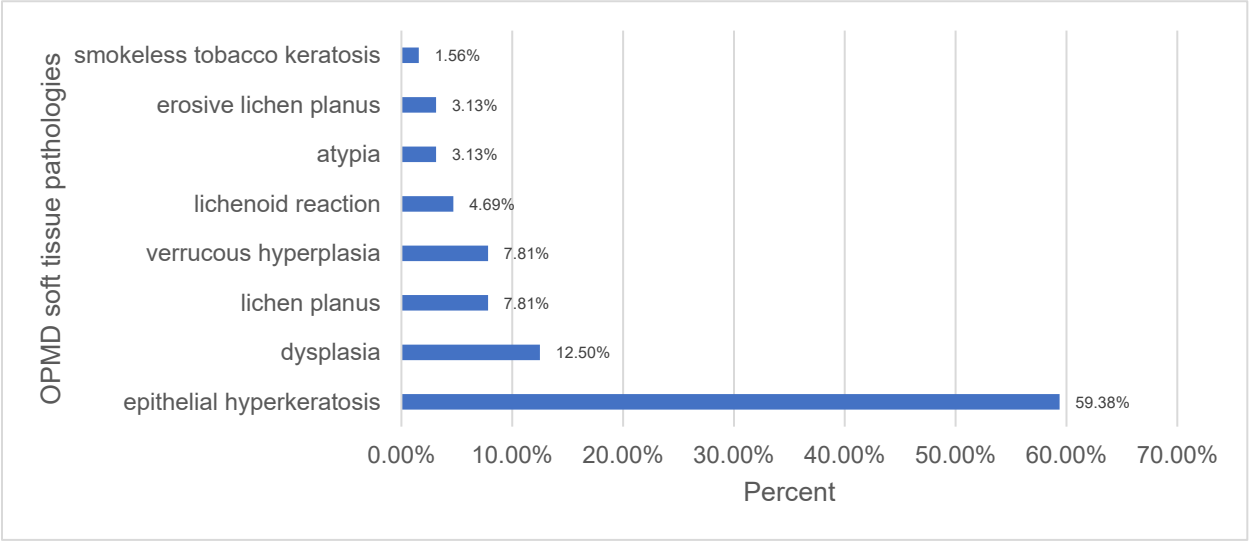
The incidence variations of OPMD pathologies in the studied population will be described according to the age group. The children group accounted for 24 cases of OPMD. The most common diagnosis was epithelial hyperkeratosis (18 cases, 75.00%), followed by verrucous hyperplasia (2 cases, 8.33%), dysplasia (2 cases, 8.33%), lichen planus (1 case, 4.17%), and lichenoid reaction (1 case, 4.17%) (see Figure#: 25).

Figure#: 25: Incidence variation of OPMD soft tissue pathologies in children (0-14 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008



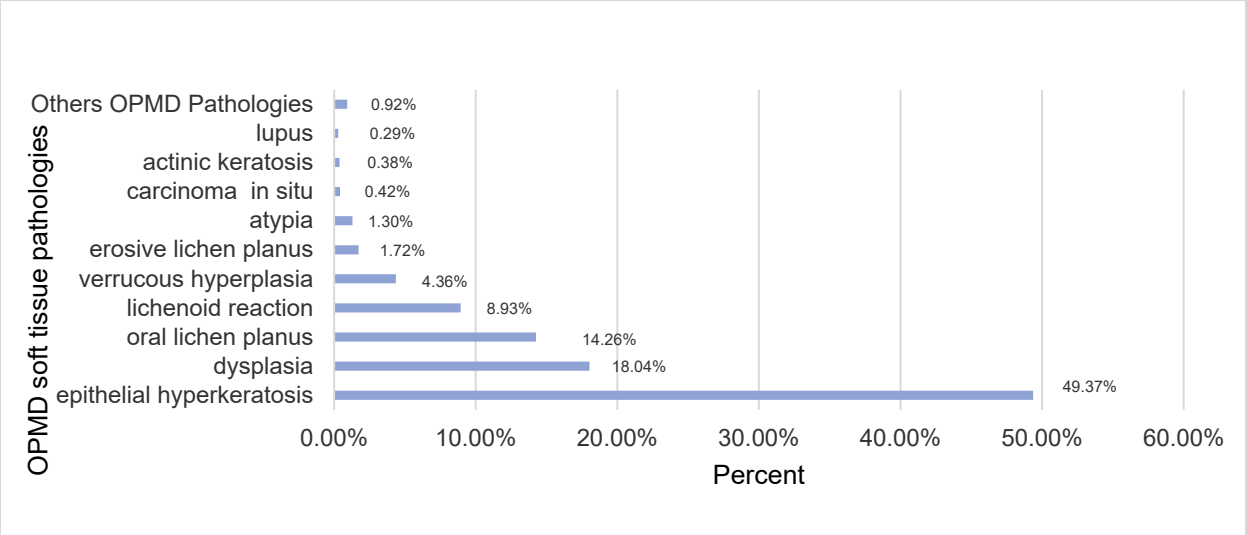
The youth group had only 64 cases of OPMD, and there were only eight different diagnoses. The most common was epithelial hyperkeratosis (38 cases, 59.38%), dysplasia (8 cases, 12.50%), lichen planus (5 cases, 7.81%), verrucous hyperplasia (5 cases, 7.81%), lichenoid reaction (3 cases, 4.69%), atypia (2 cases, 3.13%), erosive lichen planus (2 cases, 3.13%), and smokeless tobacco keratosis (1 cases, 1.56%) (see Figure# 26).

Figure# 26: Incidence variation of OPMD soft tissue pathologies in youths (15-24 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008



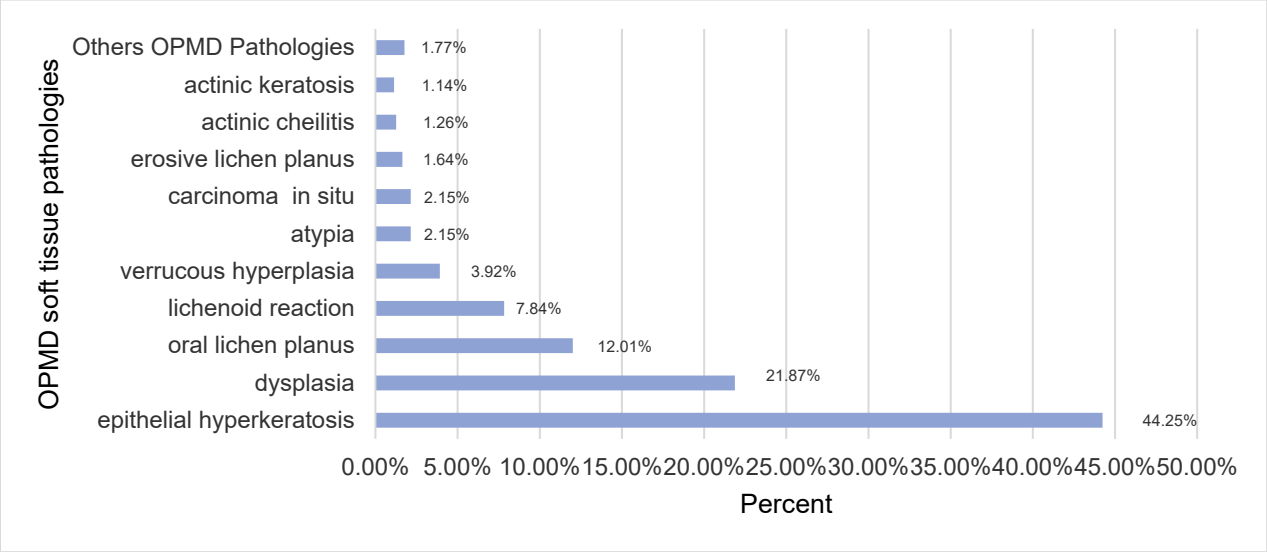
The adult group had 2384 cases of OPMD. The 10 most common diagnoses were as follows epithelial hyperkeratosis (1,177 cases, 49.37%), dysplasia (430 cases, 18.04%), lichen planus (345 cases, 14.47%), lichenoid reaction (213 cases, 8.93%), verrucous hyperplasia (104 cases, 4.36%), erosive lichen planus (41 cases, 1.72%), atypia (31 cases, 1.30%), actinic keratosis (9 cases, 0.38%), lupus (7 cases, 0.29%), and the remaining diagnoses were (17 cases, 0.71%) with six different OPMD conditions (see Figure# 27).

Figure# 27: Incidence variation of OPMD soft tissue pathologies in adults (25-64 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008.



The senior group presented 791 reports of OPMD. The ten most common diagnoses were epithelial hyperkeratosis (350 cases, 44.25%), dysplasia (173 cases, 21.87%), lichen planus (95 cases, 12.01%), lichenoid reaction (62 cases, 7.84%), verrucous hyperplasia (31 cases, 3.92%), carcinoma in situ (17 cases, 2.15%), atypia (17 cases, 2.15%), erosive lichen planus (13 cases, 1.64%), actinic cheilitis (10 cases, 1.26%), actinic keratosis (9 cases, 1.14%), and the rest were (14 cases, 1.77%) cases with five different OPMD diagnoses (see Figure# 28). There was a single case of dysplasia in the group where the age was unknown.

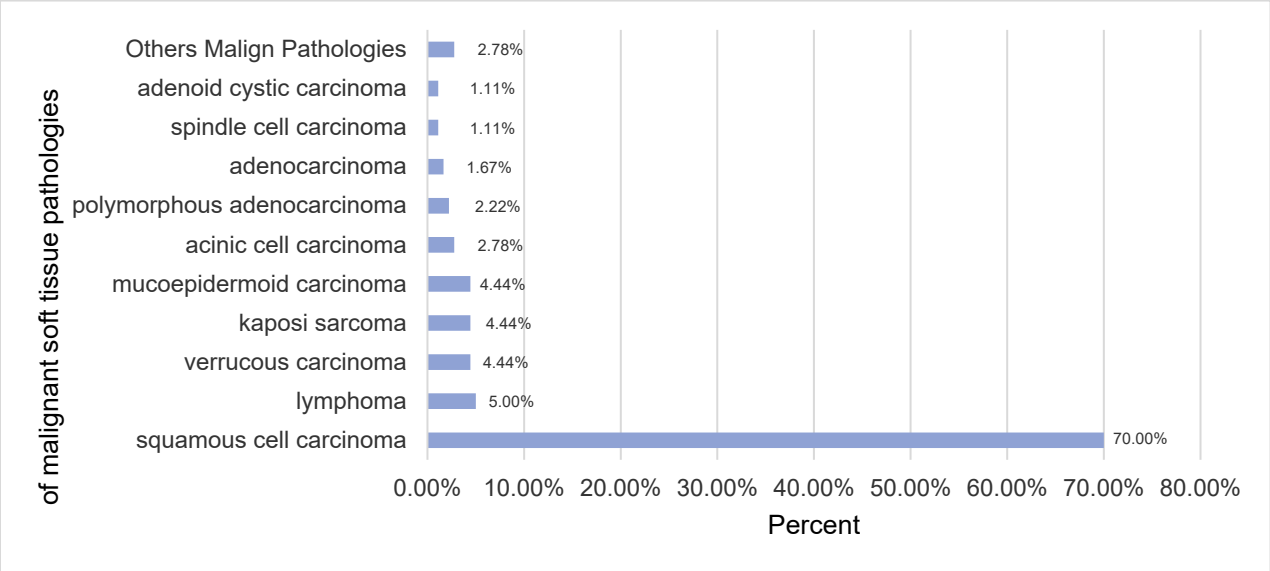
Figure# 28: Incidence variation of OPMD soft tissue pathologies in seniors (over 65 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008.



Regarding the malignant pathologies, the mean age was 66.23 years, with a standard deviation of 21.74 and an error of 1.12. Specifically, for the histological diagnosis of SCC, the mean age was 67.48 years, with a standard deviation of 20.78 and an error of 1.27. There were no cases of malignant pathologies in the children's population. Only three different malignant diagnoses were reported in the youth population: lymphoma (2 cases, 50%), metastasis (1 case, 25%), and malignancy (1 cases, 25%).

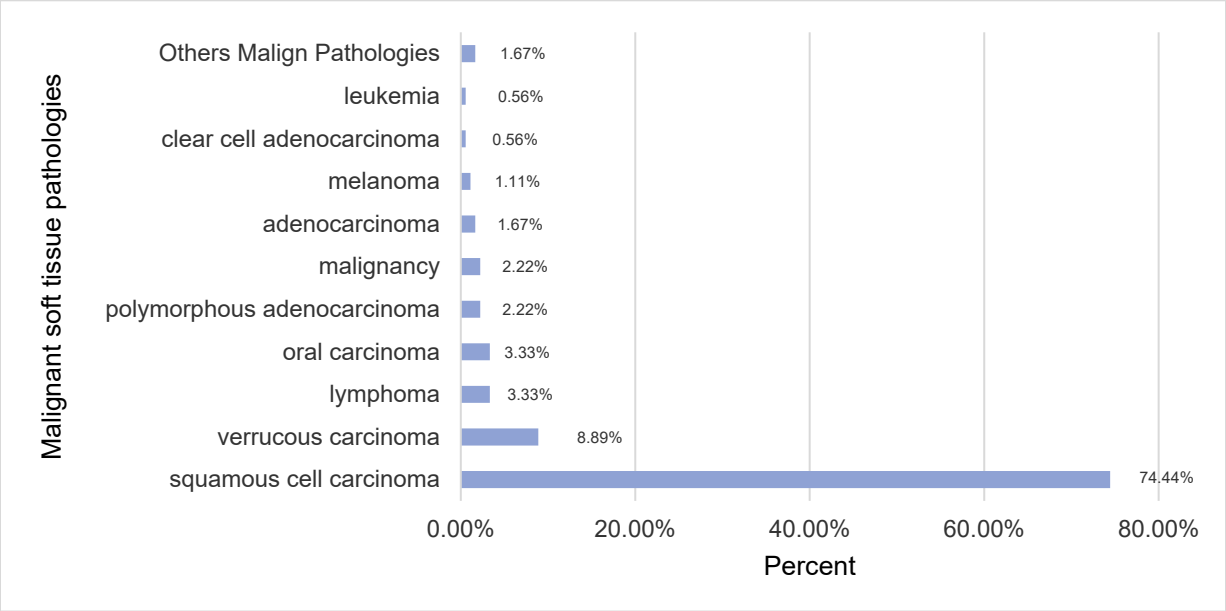
The malignancies in the adult group were, in total, 180. The ten most common were SCC (126 cases, 70%), lymphoma (9 cases, 5.00%), verrucous carcinoma (8 cases, 4.44%), Kaposi sarcoma (8 cases, 4.44%), mucoepidermoid carcinoma (8 cases, 4.44%), acinic cell carcinoma (5 cases, 2.78%), polymorphous adenocarcinoma (4 cases, 2.22%), adenocarcinoma (3 cases, 1.67%), spindle cell carcinoma (2 cases, 1.11%), adenoid cystic carcinoma (2 cases, 1.11%), and the other malignancies accounted (5 cases, 2.78%) with three different diagnoses (see Figure # 29).

Figure # 29: Incidence variation of malignant soft tissue pathologies in adults (25-64 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008



The senior cluster presented 180 malignancies as follows: SCC (134 cases, 74.44%), verrucous carcinoma (16 cases, 8.89%), lymphoma (6 cases, 3.33%), oral carcinoma (6 cases, 3.33%), polymorphous adenocarcinoma (4 cases, 2.22%), malignancy (4 cases, 2.22%), adenocarcinoma (3 cases, 1.67%), melanoma (2 cases, 1.11%), clear cell adenocarcinoma (1 case, 0.56%), leukemia (1 case, 0.56%), and the remaining malignancies were (3 cases, 1.67%) different pathologies (Figure # 35). There were no malignancies in the group where age was unknown (see Figure # 30).

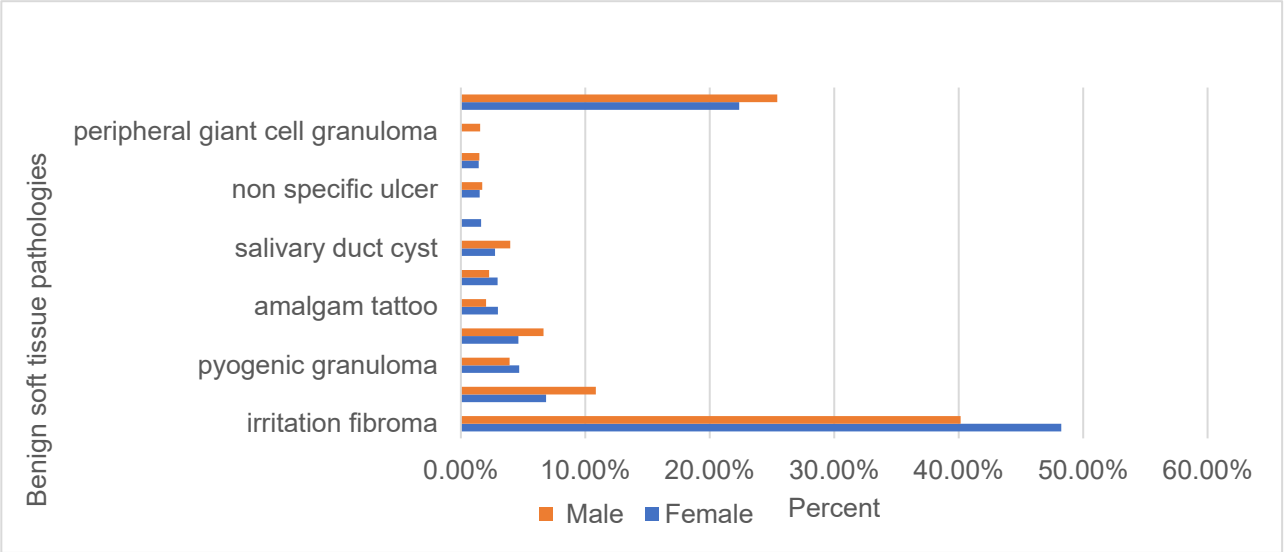
Figure # 30: Incidence variation of malignant soft tissue pathologies in seniors (over 65 years old): Oral Pathology Biopsy Service, University of Alberta 1985-2008



4.2.2.2 Incidence variations of soft oral pathology according to gender

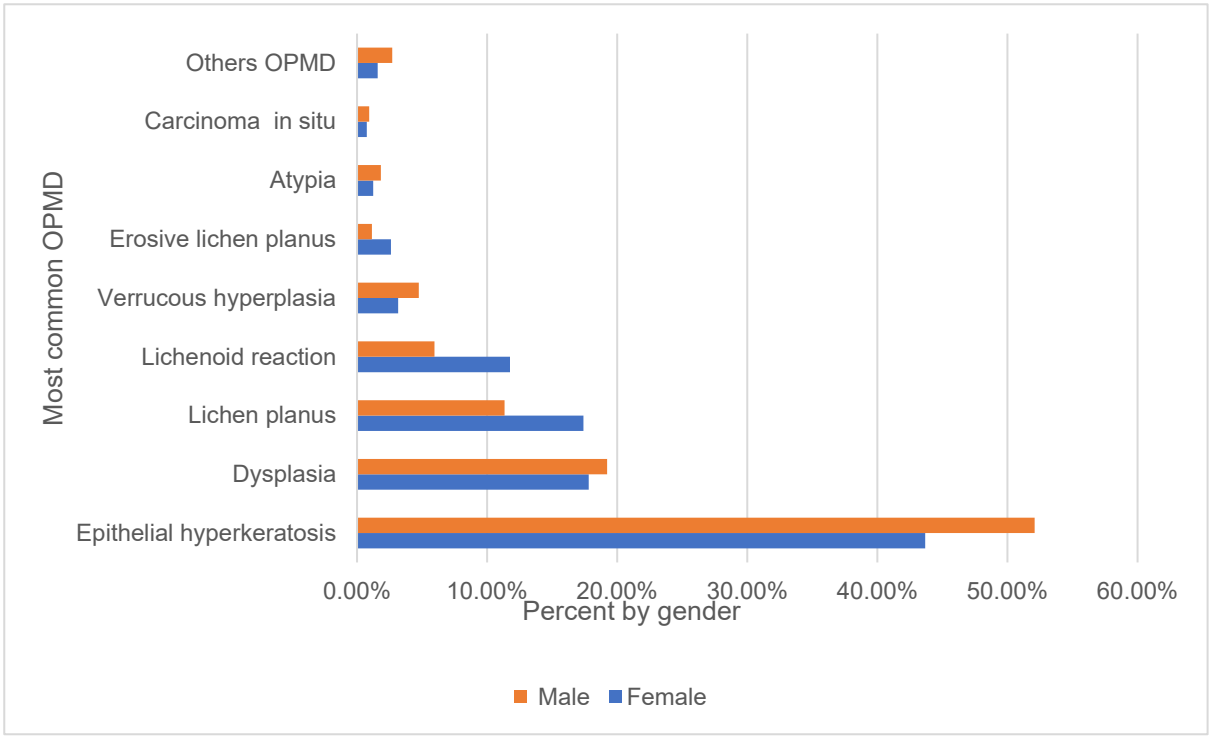
A Chi-square test was conducted to analyze the relationship between gender and histopathological diagnosis ($X^2(2)= 204.868$, $p< 0.001$), and the results demonstrated a significant difference between these two variables. The pathological incidences according to patients' gender were as follows: in the case of benign pathologies, irritational fibroma and squamous papilloma were the two most common diagnoses. Irritation fibroma accounted for (4,096 cases, 48.24%) of the female population, and squamous papilloma accounted for (581 cases, 6.84%). On the other hand, the males presented with (2691 cases, 40.15%) irritation fibroma and squamous papilloma (727 cases, 10.85%). The rest of the diagnoses were slightly different; in the females, the following diagnoses were pyogenic granuloma (398 cases, 4.69%), mucocele (392 cases, 4.62%), amalgam tattoo (253 cases, 2.98%), peripheral ossifying fibroma (251 cases, 2.96%), salivary duct cyst (233 cases, 2.74%), giant cell fibroma (138 cases, 1.63%), non-specific ulcer (128 cases, 1.51%), and chronic inflammation (122 cases, 1.44%) the rest were 1,889 cases (22.36%) with 127 different diagnoses. In the male population, mucocele was (445 cases, 6.64%), salivary duct cysts were (266 cases, 3.97%), pyogenic granuloma was (262 cases, 3.91%), peripheral ossifying fibroma (152 cases, 2.27%), amalgam tattoo (136 cases, 2.03%), non-specific ulcer (115 cases, 1.72%), peripheral giant cell granuloma (104 cases, 1.55%), and chronic inflammation (100 cases, 1.49%) the remaining accounted (1,704 cases, 25.4%) cases with 129 different diagnoses. In the group of reports where the gender was unknown the most common diagnoses were irritation fibroma (118 cases, 46.27%), squamous papilloma (28 cases, 10.98%), mucocele (12 cases, 4.71%), amalgam tattoo (10 cases, 3.92%), salivary duct cyst (8 cases, 3.14%), pyogenic granuloma (7 cases, 2.75%), melanotic macule (7 cases, 2.75%), peripheral ossifying fibroma (6 cases, 2.35%), hemangioma (4 cases, 1.57%), oral nevus (3 cases, 1.18%), and the others sum 52 patients (20.39%) with 36 conditions (see Figure # 31).

Figure # 31: Comparison of the most common benign diagnoses by gender: Oral Pathology Biopsy Service, University of Alberta 1985-2008



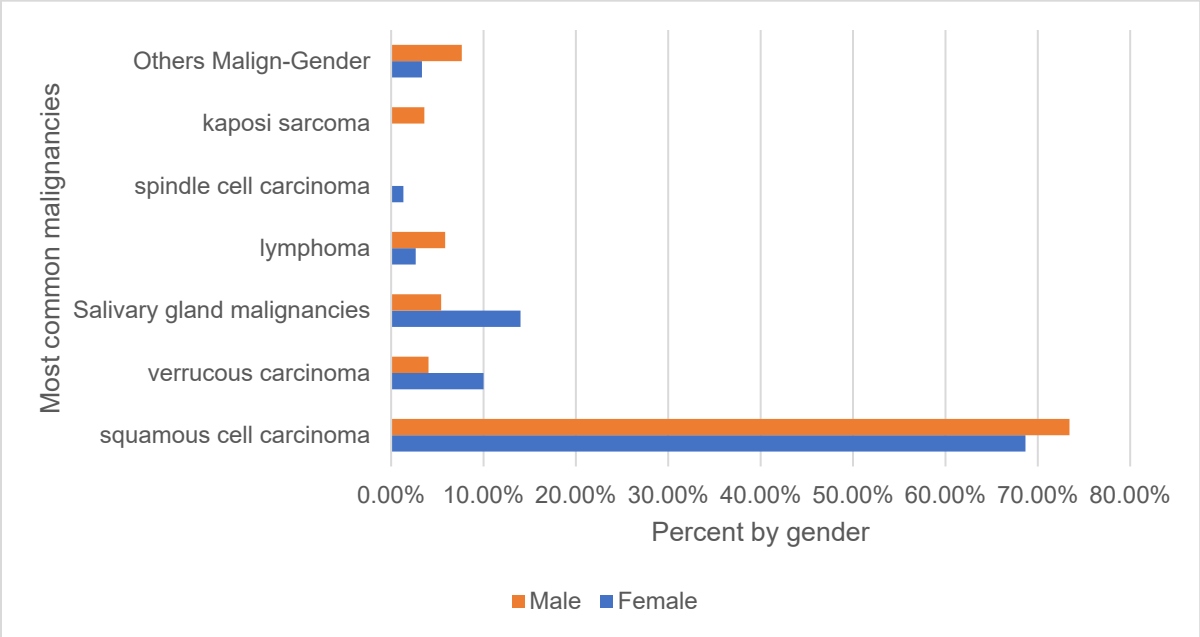
In relation to the OPMD by gender, the ten most common diagnoses in the female population were: epithelial hyperkeratosis 635 (43.67%), dysplasia 259 (17.81%), lichen planus 256 (17.61%), lichenoid reaction 171 (11.76%), verrucous hyperplasia 46 (3.16%), erosive lichen planus 38 (2.61%), atypia 18 (1.24%), carcinoma in situ 11 (0.76%), lupus 7 (0.48%), verrucous leukoplakia 5 (0.34%) and the remaining of the diagnoses were 5 cases (0.55%) with five different OPMD conditions. In the male population were as following: epithelial hyperkeratosis 997 (52.09%), dysplasia 368 (19.23%), lichen planus 220 (11.5%), lichenoid reaction 114 (5.96%), verrucous hyperplasia 91 (4.75%), atypia 35 (1.83%), erosive lichen planus 22 (1.15%), carcinoma in situ 18 (0.94%), actinic keratosis 16 (0.84), actinic cheilitis 12 (0.63%), the rest of the diagnoses comprehended 21 cases (1.09%) with seven different OPMD pathologies. In the group where the gender was unknown, there were epithelial hyperkeratosis 37 (55.22%), dysplasia 17 (25.37%), verrucous hyperplasia 5 (7.46%), lichenoid reaction 4 (5.97%). There was a single case (1.49%) of the following conditions lichen planus, smokeless tobacco keratosis, carcinoma in situ and erosive lichen planus accounting the total of cases of this group (see Figure # 32).

Figure # 32: Comparison of the most common OPMD diagnoses by gender (female-male): Oral Pathology Biopsy Service, University of Alberta 1985-2008



In the context of the malignancies by gender, the female-to-male ratio was 0.67:1. Specifically for the SCC diagnosis the female-to-male ratio was 0.63:1 and for salivary gland malignancies was 1.5:1.The ten most common diagnoses in the female group were SCC (103 cases, 68.67%), verrucous carcinoma (15 cases, 10%), mucoepidermoid carcinoma (6 cases, 4.0%), polymorphous adenocarcinoma (5 cases, 3.33%), lymphoma (4 cases, 2.67%), acinic cell carcinoma (4 cases, 2.67%), adenocarcinoma (3 cases, 2.00%), adenoid cystic carcinoma (3 cases, 2.00%), spindle cell carcinoma (2 cases, 1.33%), malignancy not classified (2 cases, 1.33%), and the rest were (3 cases, 2.00%) as single cases. In the male category the ten most common malignancies were SCC (163 cases, 73.42%), lymphoma (13 cases, 5.86%), verrucous carcinoma (9 cases, 4.05%), oral carcinoma not specified (8 cases, 3.60%), Kaposi sarcoma (8 cases, 3.60%), polymorphous adenocarcinoma (4 cases, 1.80%), adenocarcinoma (4 cases, 1.80%), malignancy not specified (4 cases, 1.80%), mucoepidermoid carcinoma (3 cases, 1.35%), adenosquamous carcinoma (1 cases, 0.45%), and the rest were five (2.25%) as single cases. In the unknown gender aggregate, there were four cases in total (3 cases, 75.0%) of squamous carcinoma and a single case (25.0%) as malignancy not specified (see Figure #33).

Figure #33: Comparison of the most common malignant diagnoses by gender (female-male): Oral Pathology Biopsy Service, University of Alberta 1985-2008.

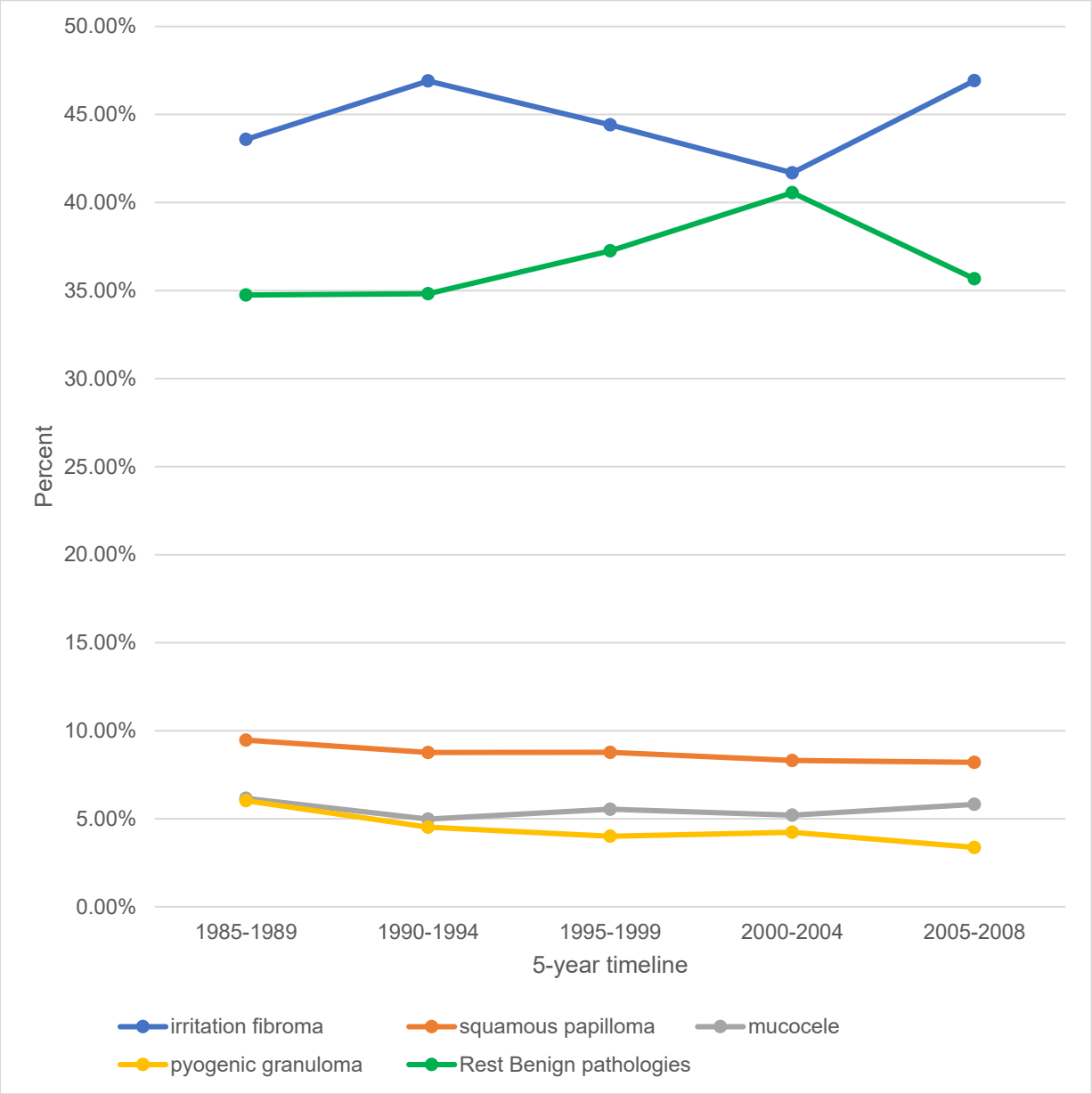


4.2.2.3 Incidence variations of soft oral pathology by 5-year timeline

The incidence variations of soft oral pathology by a 5-year timeline were determined by prognosis, and the percentages were based on the total pathologies in each period by prognosis cluster.

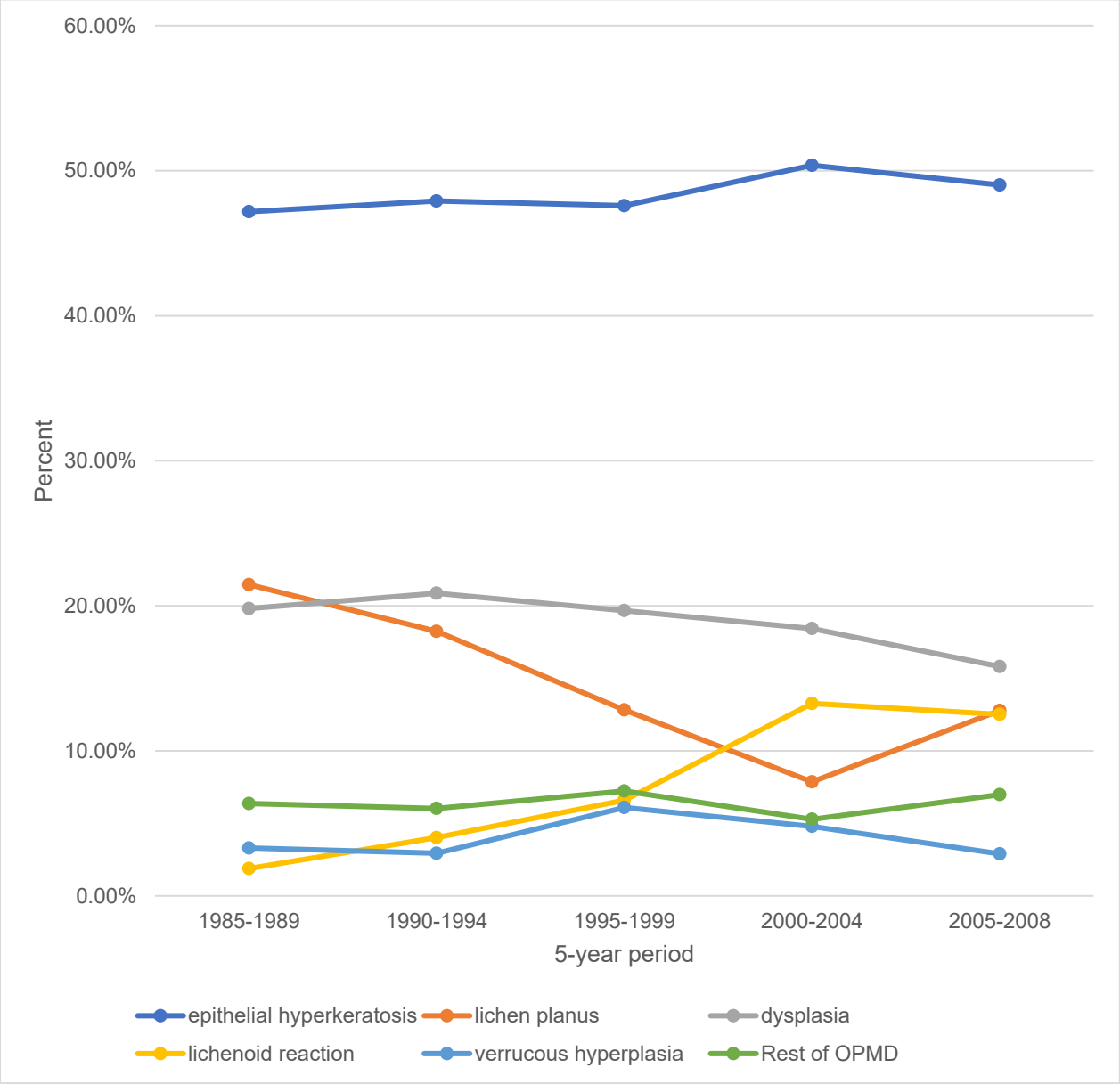
In the case of benign pathologies, the four most common, according to a 5-year timeline, were the same in all periods. Irritation fibroma was the most common benign pathology, ranging from (962 cases, 43.59%) to (1,706 cases, 44.42%). It was followed by squamous papilloma (209 cases, 9.47%) to (337 cases, 8.77%), mucocele (136 cases, 6.16%) to (213 cases, 5.55%), and pyogenic granuloma (131 cases, 4.24%) to (154 cases, 4.01%). The fifth, sixth, and seventh most common diagnoses were amalgam tattoo (2.27-3.01%), salivary retention cyst (2.17-3.83%), or peripheral ossifying fibroma (3.11-1.99%), which interchange the position in each 5-year timeline. It is important to highlight that the seventh most common diagnoses accounted for between 68-95 to 74.84% of all the benign diagnoses by each 5-year period analyzed (see Figure # 34).

Figure # 34: Most common benign diagnoses per 5-year timeline: Oral Pathology Biopsy Service, University of Alberta 1985-2008



In the case of OPMD, the most common diagnosis was epithelial hyperkeratosis, which ranged from (200 cases, 47.17%) to (410 cases, 50.37%). The second diagnosis was dysplasia (120 cases, 15.81%) to (155 cases, 19.67%), except during the period of 1985-1989, in which was lichen planus (91 cases, 21.46%) and in this same time interval, the third most frequent was dysplasia (84 cases, 19.81%). For the rest of the 5-year intervals, the third and fourth diagnoses were lichen planus or lichenoid reaction interchangeable in each 5-year period (see Figure # 35).

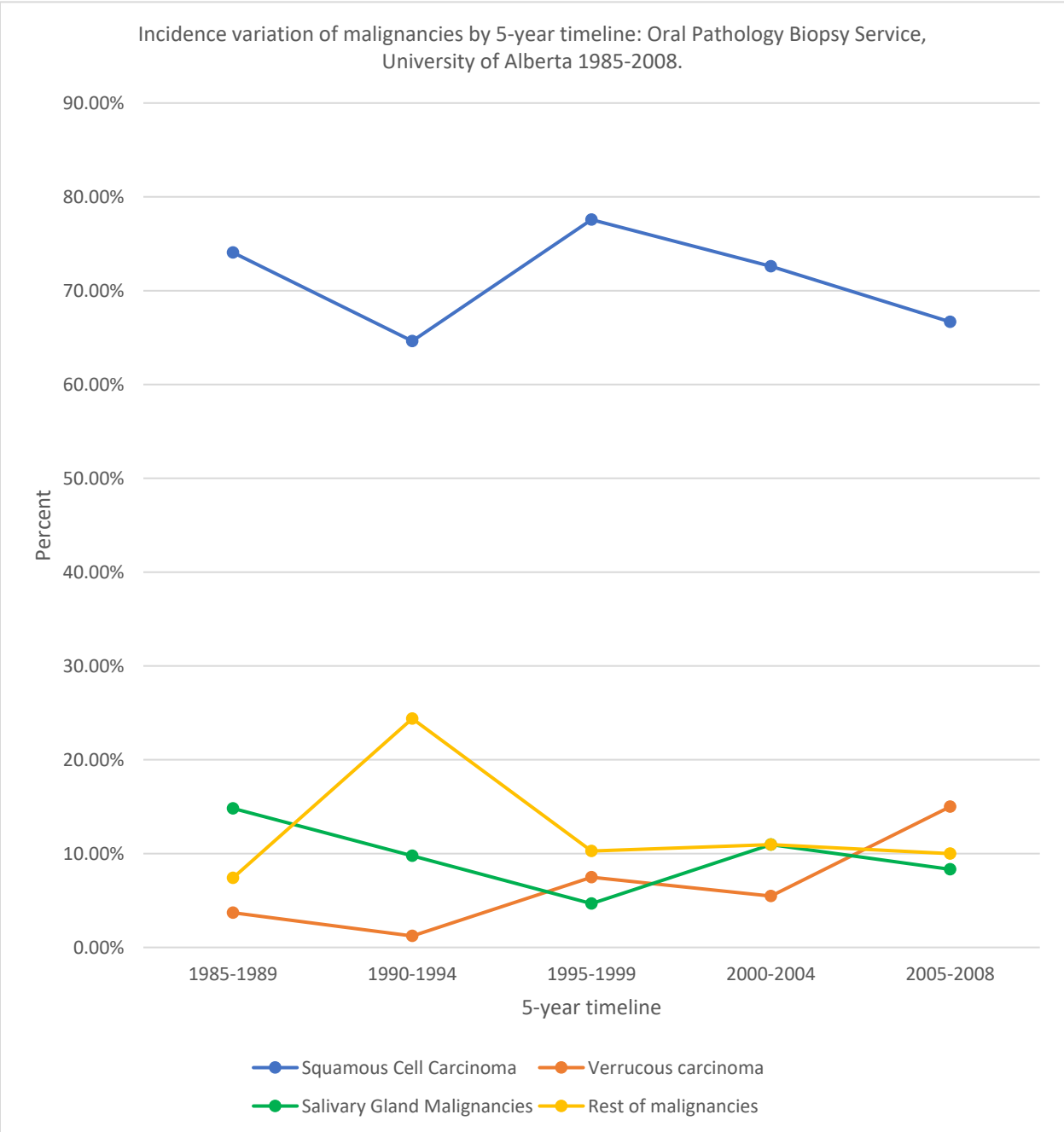
Figure # 35: Most common OPMD diagnoses between 2005-2008: Oral Pathology Biopsy Service, University of Alberta 1985-2008



Regarding malignant diagnoses, the most common malignancy in all five-year periods was SCC, (40 cases, 74.07%) in 1985-89, and in the period of 2005-2008, with the lowest number of cases and the highest (83 cases, 77.57) between 1995-1999. The second most common malignancy was verrucous carcinoma, with the lowest incidence (1 cases, 1.22%) in the period of 1990-1995 and the highest (15 cases, 9%) in 2005-2008. The salivary gland malignancies were merged; the lowest was (5 cases, 8.33%)

in the last quinquennial, and the highest number was (8 cases, 14.82%) in the first quinquennial. The remaining malignancies were (21 cases, 24.39%) in the following quinquennial. (see Figure # 36).

Figure # 36: Incidence variation of malignancies by 5-year timeline: Oral Pathology Biopsy Service, University of Alberta 1985-2008



4.2.2.4 Incidence variations of "hard tissue and other misdiagnosis."

Finally, a group was categorized as "Hard tissue and other misdiagnosis," corresponding to erroneous clinical diagnoses of hard tissue pathology or other conditions, such as xerostomia, where the histopathological assessment evidenced a diagnosis of soft tissue pathology. Those diagnoses were kept in the database because, as the literature stated, the histopathological diagnosis is the gold standard. The most common definitive diagnoses for this group were: irritation fibroma (11 cases, 32.35%), chronic inflammation (4 cases, 11.76%), chronic abscess (3 cases, 8.82%), peripheral ossifying fibroma (2 cases, 5.88%), peripheral giant cell granuloma (2 cases, 5.88%), and the rest were (12 cases, 35.29%) (see Table #8).

Table # 8: Misdiagnoses with the corresponding histopathological diagnoses: Oral Pathology Biopsy Service, University of Alberta 1985-2008

Clinical misdiagnosed pathology		**Histopathological soft tissue diagnosis**					
	Cases	Diagnosis	Cases	Diagnosis	Cases	Diagnosis	Cases
exostosis	7	irritation fibroma	4	Non-specific inflammation	2	peripheral ossifying fibroma	1
dental follicle	5	irritation fibroma	3	pericoronitis	1	pyogenic granuloma	1
periostitis	5	chronic abscess	3	chronic inflammation	2	-	-
lateral periodontal cyst	3	pyogenic granuloma	1	gingival cyst	1	parulis	1
residual cyst	3	endarteritis	1	irritation fibroma	1	pericoronitis	1
xerostomia	3	peripheral giant cell granuloma	2	normal	1	-	-
buccal bifurcation cyst	2	fibroepithelial polyp	1	eruption cyst	1	-	-
chondroma	2	peripheral ossifying fibroma	1	irritation fibroma	1	-	-
osteoradionecrosis	2	chronic inflammation	1	Non-specific ulcer	1	-	-
nasopalatine cyst	1	chronic inflammation	1	-	-	-	-
torus	1	irritation fibroma	1	-	-	-	-
Total	34	-	-	-	-	-	-

4.2.3 Concordance between the clinical and histopathological diagnosis

4.2.3.1 General concordance between the clinical and histopathological diagnosis

The absolute concordance between the clinical and histopathological diagnosis comparing the SNOMED-CT codes was 47.17% (9,084 cases) with a Kappa of 0.405, demonstrating a fair agreement. When the diagnostic synonyms were considered, the absolute concordance was 50.22% (9,672 cases). The relative concordance by etiopathology clusters was 74.61% (14,369 cases) with a Kappa of 0.661, proving a substantial agreement. The discordance was 25.39% (4,890 cases). When determining the clinical and histopathological diagnostic agreement by prognosis category, the Kappa was 0.762. Regarding the ability to diagnose benign conditions, the sensitivity was 96.4%, the specificity was 80.3%, the PPV was 96.4%, and the NPV was 84.7%. Conversely, for diagnosing a malignant condition, the sensitivity was 67.5%, the specificity was 98.4%, the PPV was 46.3%, and the NPV was 99.3%. In the case of diagnosing an OPMD, the sensitivity was 76.9%, the specificity was 97.6%, the PPV was 87.3% and the NPV 95.1% (see Figure # 37 and Table # 9).

Figure # 37: Concordance between Clinical and Histopathological Diagnoses: 1985-2008: Oral Pathology Biopsy Service, University of Alberta 1985-2008

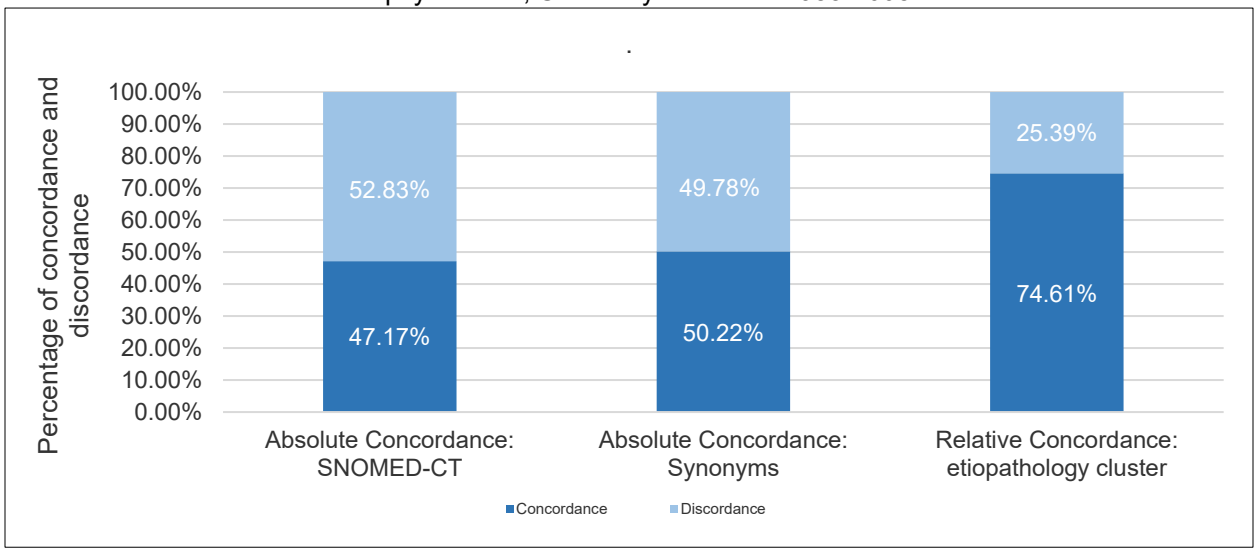


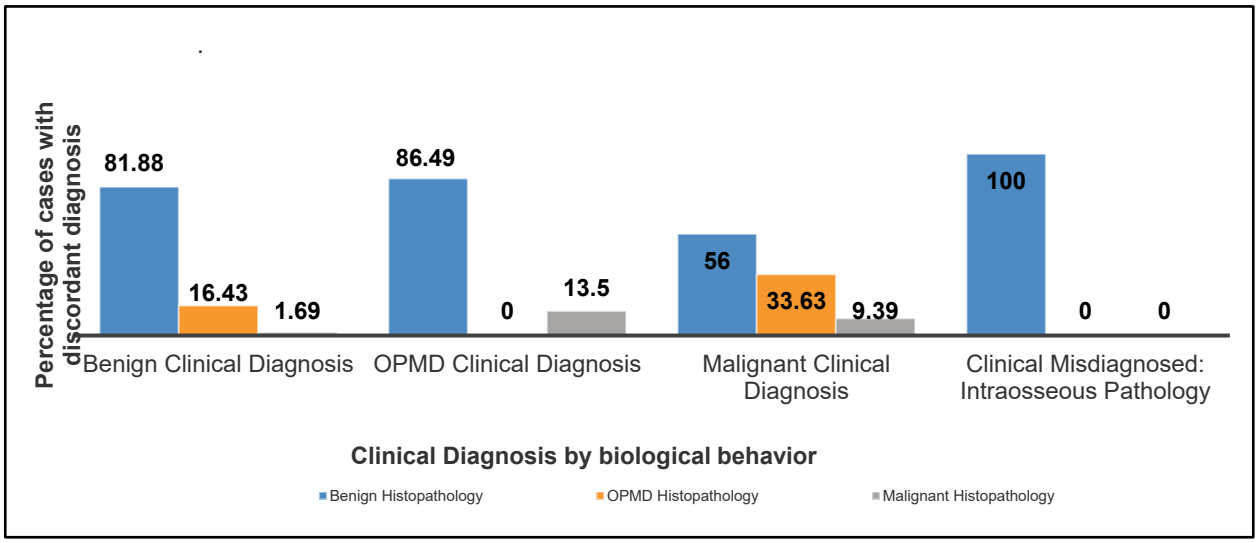
Table # 9

Sensitivity, specificity, PPV and NPV for the clinical diagnosis of benign, OPMD and malignant pathologies: 1985-2008: Oral Pathology Biopsy Service, University of Alberta 1985-2008.

Diagnosis	Sensitivity	Specificity	PPV	NPV
Benign	96.4%	80.3%	96.4%	84.7%
OPMD	76.9%	97.6%	87.3%	95.1%
Malignant	67.5%	98.4%	46.3%	99.3%

In the discordance group, when the clinical diagnosis was benign, 81.88% (3,394) were misdiagnosed from a different benign cluster, 16.43% (681) were OPMD, and 1.69% (70) were malignant. Conversely, when the clinical diagnosis was malignant, 56% (184) were benign, 33.63% (111) were OPMD, and 9.39% (31) belonged to a different malignant cluster. In the case of discordant diagnoses, when the clinician gave a tentative diagnosis of an OPMD, 86.49% (333) were benign, and 13.5% (52) were malignant. Finally, all the clinical diagnoses of xerostomia or intraosseous pathology were confirmed to be benign soft tissue pathology (see Figure # 38).

Figure # 38: Analysis of the Discordant diagnoses by biologic behavior: 1985-2008: Oral Pathology Biopsy Service, University of Alberta 1985-2008

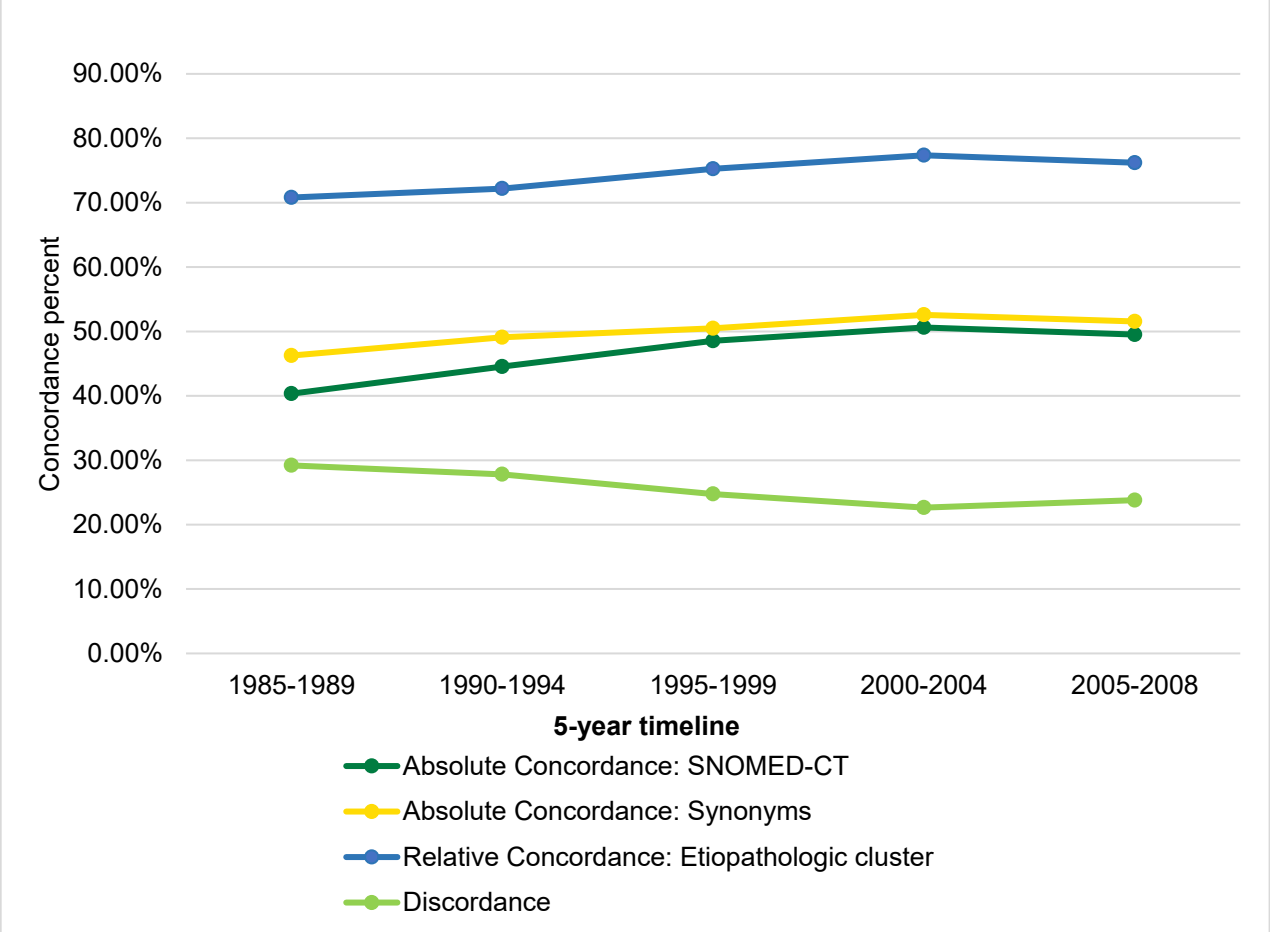


The most common histopathological diagnoses when the practitioner gave a misdiagnosed benign clinical diagnosis were irritation fibroma 986 (23.79%), epithelial hyperkeratosis 400 (9.65%), giant cell fibroma 220 (5.31%), squamous papilloma 208 (5.02%), pyogenic granuloma 149 (3.59%), mucocele 128 (3.09%), dysplasia 117 (2.82%), chronic inflammation 103 (2.48%), salivary duct cyst 89 (2.15%), granulation tissue 80 (1.93%), and the rest were 1665 (40.17%). In the case of the clinical OPMD diagnoses mistaken were irritation fibroma 60 (15.58%), SCC 45 (11.65%), non-specific ulcer 36 (9.35%), mucositis 32 (8.31%), candidiasis 28 (7.27%), chronic inflammation 22 (5.71%), squamous papilloma 21 (5.45%), no pathology 15 (3.90%), epithelial hyperkeratosis 10 (2.60%), non-specific inflammation 8 (2.08%), and the remaining were 108 (28.05%). Lastly, the malignancies misdiagnosed were epithelial keratosis 43 (13.19%), dysplasia 39 (11.96%), non-specific ulcer 35 (10.74%), irritation fibroma 19 (5.83%), SCC 14 (4.29%), chronic inflammation 12 (3.68%), carcinoma in situ 8 (2.45%), sialadenitis 8 (2.45%), peripheral giant cell granuloma 6 (1.84%), amalgam tattoo 6 (1.84%), and the rest were 136 (41.72%).

4.2.3.2 Five-year timeline concordance between the clinical and histopathological diagnosis

The concordance between the clinical and histological diagnosis was determined by a 5-year timeline with the same considerations as the general population analysis. For the absolute concordance considering SNOMED-CT diagnoses, the lowest percentage was 40.34% in 1985-1989, and the highest was 50.62% in the 2000-2004 quinquennial. The absolute concordance considering the synonym's diagnoses rendered the lowest percentage, 46.26%, in 1985-1989, and the highest, 52.58%, in the 2000-2004 period. The relative concordance showed the lowest rate, 70.80%, in 1985-1989 and the highest, 77.36%, in 2000-2004. On the other hand, the highest discordance was 29.20%, and the lowest was 22.64%, which occurred in the same periods previously mentioned. It is relevant to highlight that the last period analyzed comprises four years, not five as the preceding periods. The kappa before 1994, which is the mid-year of the total period, was 0.62, and after this year was 0.68. This means that both periods demonstrated a substantial agreement (see Figure # 39).

Figure # 39: Concordance between Clinical and Histopathological Diagnoses: 1985-2008: Oral Pathology Biopsy Service, University of Alberta 1985-2008



4.2.3.3 Concordance between clinical and histopathological diagnosis according to etiopathologic cluster

The concordance between the clinical and histological diagnosis was analyzed according to the etiopathologic clusters. The absolute concordance applied to the SNOMED-CT was highest for the foreign reaction diagnoses at 66.10%, followed by benign viral-induced verruco-papillary diagnoses at 60.95% and reactive diagnoses at 57.73%. The lowest concordance considering the etiopathologic groups with more than 5 cases were the salivary malignancy cluster with 5.71%, benign soft tissue with 14.75%, and ulcerative-inflammatory with 16.98%. There were five clusters with a concordance higher than 50%.

The second analysis using the synonyms was the highest, with 74.49% in the benign viral-induced verruca-papillary diagnoses cluster, followed by foreign reaction diagnoses at 66.29% and 61.13% in the reactive group. The lowest percentage is similar to the SNOMED-CT analysis previously mentioned; one difference is that the ulcerative inflammatory cluster increased the concordance to 18.51%. Using the synonyms comparison increased to six, the number of clusters with a concordance higher than 50%.

The highest relative concordance percentage was 82.28% in the benign virally-induced verruco-papillary group, 82.07% in the reactive cluster, and 79.85% in the benign salivary pathologies. On the contrary, the lowest rate was 11.43% in the salivary malignancies pathologies, 16.71% in the benign soft tissue, and 26.05% in the ulcerative inflammatory cluster. However, clusters with more than 50% concordance increased to 10.

In relation to the malignant salivary pathologies misdiagnosed, eight were correctly identified as a malignant pathology, and 23 were misdiagnosed clinically as benign conditions that included 12 cases as benign salivary pathologies, 9 as reactive lesions and the rest as soft tissue or vascular lesions.

Further analysis of the clusters, in which the concordance was 0%, corresponds in the following way. The choristoma cluster accounted for four osseous choristoma histopathological diagnoses, of which three were stated as irritational fibroma and one reactive tissue as a clinical diagnosis. There was only one metastasis as a histological diagnosis with the clinical malignancy diagnosis. In the case of orofacial granulomatosis, there were two cases of sarcoidosis as histopathological diagnoses that were clinically diagnosed as malignancies. Finally, in the viral cluster were two cases, one histologically diagnosed as hairy leukoplakia and the second as herpes simplex; the first clinically was diagnosed as dysplasia and the latter as chronic abscess (Table # 9).

Table # 9

Concordance between Clinical and Histopathological Diagnoses by etiopathologic cluster: 1985-2008: Oral Pathology Biopsy Service, University of Alberta 1985-2008

Etiopathologic clusters	Absolute Concordance SNOMED-CT	Absolute Concordance: Synonyms	Relative Concordance: Etiopathologic cluster	Discordance
Bacterial	6 (33.33%)	6 (33.33%)	6 (33.33%)	12 (66.67%)
Benign epithelial conditions	97 (28.36%)	112 (32.75%)	222 (64.91%)	120 (35.09%)
Benign salivary	955 (53.29%)	955 (53.29%)	1,431 (79.85%)	361 (20.15%)
Benign soft tissue	61 (14.15%)	61 (14.15%)	72 (16.71%)	359 (83.29%)
Benign virally induced verrucopapillary	860 (60.95%)	1051 (74.49%)	1,161 (82.28%)	250 (17.72%)
Choristoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (100.00%)
Developmental	21 (17.65%)	21 (17.65%)	31 (26.05%)	88 (73.95%)
Epithelial malignancies	155 (49.52%)	155 (49.52%)	219 (69.97%)	94 (30.03%)
Foreign reactions	347 (66.10%)	348 (66.29%)	389 (74.10%)	136 (25.90%)
Fungal	37 (38.54%)	37 (38.54%)	43 (44.79%)	53 (55.21%)
Immune-mediated	20 (36.36%)	20 (36.36%)	39 (70.91%)	16 (29.09%)
Lymph-vascular	105 (30.97%)	171 (50.44%)	246 (72.57%)	93 (27.43%)
Metastasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
OPMD	1,044 (30.39%)	1,043 (30.36%)	2,643 (76.94%)	792 (23.06%)
Orofacial granulomatous	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (100.00%)
Reactive	5, 054 (57.73%)	5,351 (61.13%)	7,184 (82.07%)	1,570 (17.93%)
Salivary malignancy	2 (5.71%)	2 (5.71%)	4 (11.43%)	31 (88.57%)
Soft tissue odontogenic bone	43 (40.95%)	43 (40.95%)	44 (41.90%)	61 (58.10%)

Soft tissue-hematologic malignancy	14 (51.85%)	14 (51.85%)	15 (55.56%)	12 (44.44%)
Ulcerative-inflammatory	210 (16.98%)	229 (18.51%)	568 (45.92%)	669 (54.08%)
Variation anatomy	53 (24.54%)	53 (24.54%)	67 (31.02%)	149 (68.98%)
Viral	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (100.00%)

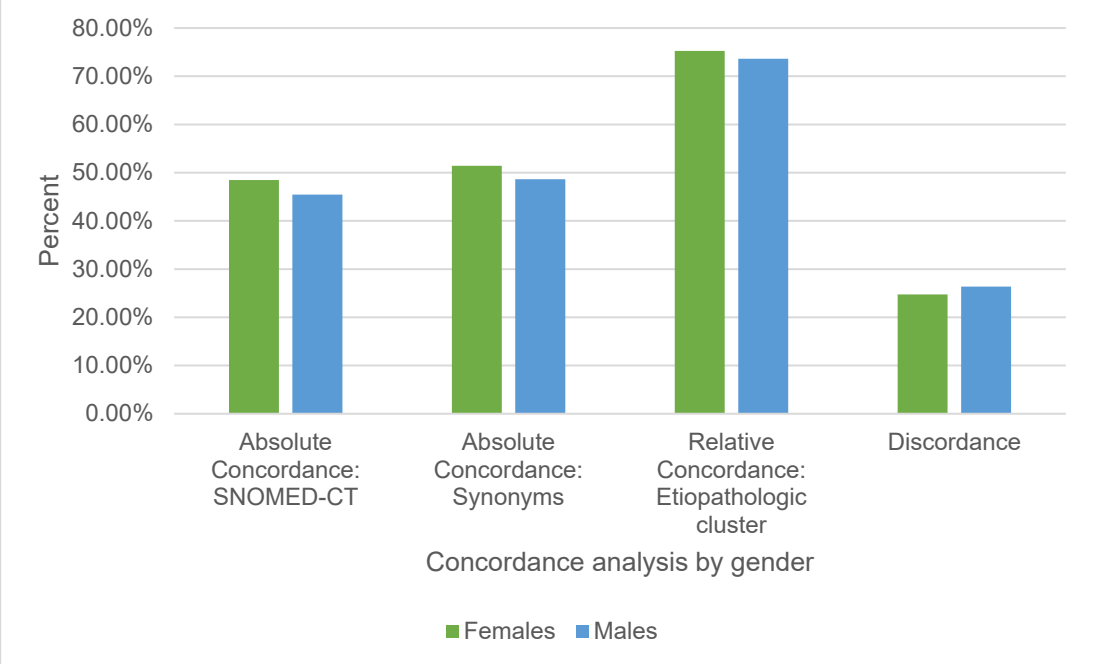
4.2.3.4 Concordance between the clinical and histopathological diagnosis according to gender

The concordance between the clinical and histopathological diagnoses was also calculated according to gender. In the female group, by SNOMED-CT, 4,893 (48.47%); by synonyms, 5,191 (51.42%); by etiopathological cluster, 7,596 (75.25%); and the discordance was 2,499 (24.75%).

On the other hand, the male group by SNOMED-CT was 4,017 (45.45%); by synonyms, it was 4,300 (48.65%); by etiopathological cluster, it was 6,507 (73.63%), and the discordance was 2,331 (26.37%).

Finally, for the group with unknown gender, SNOMED-CT was 174(53.37%); synonyms were 181 (55.52%); etiopathological clusters were 266 (81.60%), and discordance was 60 (18.40%). The relationship between the cluster concordance and gender was conducted using a Pearson chi-square. Results ($X^2(2)=40.420$, $P<.001$) demonstrated that there is a statistical significance between the two variables analyzed (see Figure # 40).

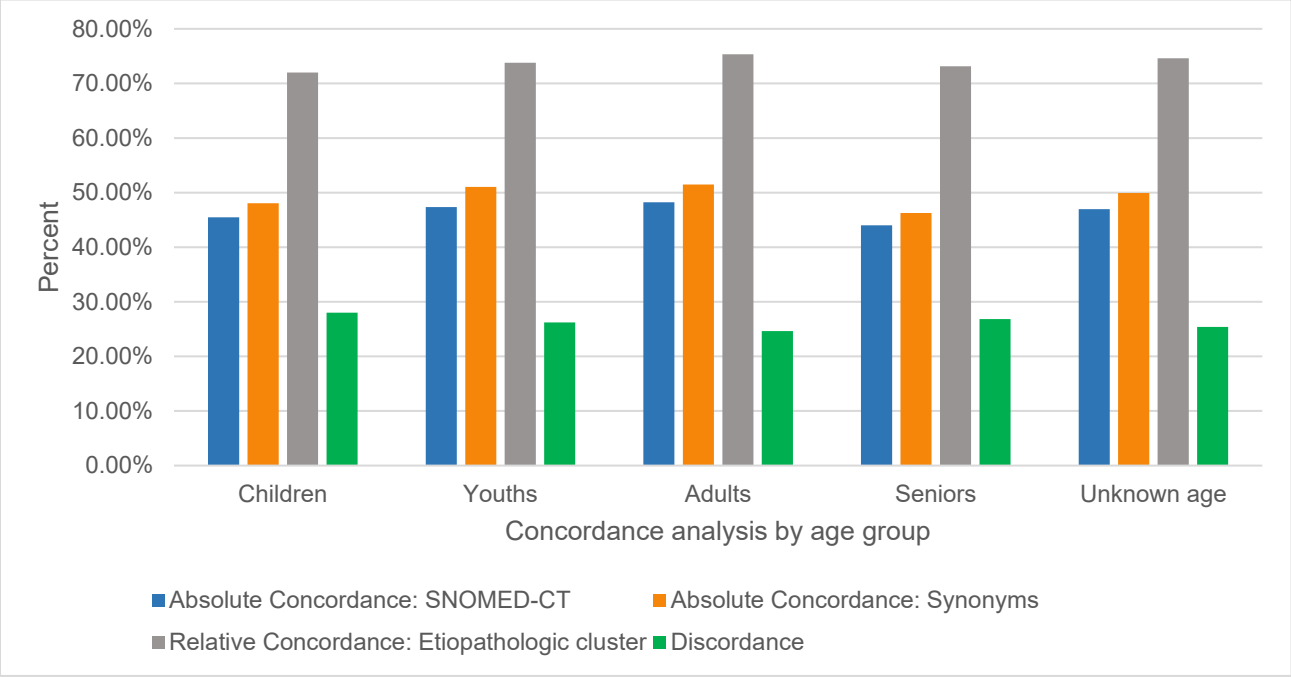
Figure # 40: Concordance between the Clinical and Histopathological Diagnosis according to gender: Oral Pathology Biopsy Service, University of Alberta 1985-2008



4.2.3.5 Concordance between the clinical and histopathological diagnosis according to age groups

The concordance by age group was calculated as follows: The children group by SNOMED-CT was 513 (45.48%); by synonyms, 542 (48.05%); by etiopathological cluster, 812 (71.99%), and the discordance was 316 (28.01%). The youth group by SNOMED-CT was 625 (47.35%); by synonyms, it was 674 (51.06%); by etiopathological cluster, it was 974 (73.79%); and the discordance was 346 (26.21%). The adult group by SNOMED-CT was 6,023 (48.23%); by synonyms, 6,430 (51.49%); by etiopathological cluster, 9,411 (75.35%); and the discordance was 3,078 (24.65%). The senior group by SNOMED-CT was 1588 (44.00%); by synonyms, it was 1,670 (46.27%); by etiopathological cluster, it was 2,640 (73.15%); and the discordance was 969 (26.85%). Finally, the unknown age group by SNOMED-CT was 335 (46.98%); by synonyms, it was 356 (49.93%); by etiopathological cluster, it was 532 (74.61%); and the discordance was 532 (74.61%). The cluster concordance and age relationship was conducted using a Pearson chi-square. Results ($X^2(204)=541.110$, $P<.001$) demonstrated that there is a statistical significance between the two variables analyzed. Consequently, this test confirmed a highly significant association between the variables analyzed (see Figure # 41).

Figure # 41: Concordance between the Clinical and Histopathological Diagnosis according to age groups: Oral Pathology Biopsy Service, University of Alberta 1985-2008

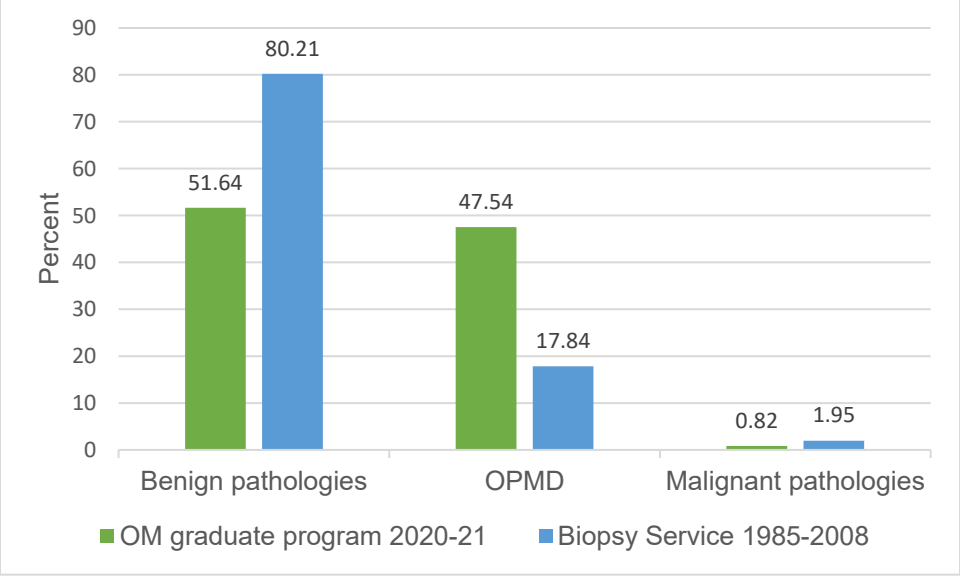


4.2.4 Comparison between the Oral Medicine Graduate Program 2020-2021 and Oral Biopsy Service 1985-2008, University of Alberta databases

An analysis comparing the OM graduate program 2020-21 and Biopsy Service 1985-2008 databases was elaborated, showing important distinctions between these databases. One difference is the number of reports accounted for in each one; in the OM graduate program 2020-21, there were 122 cases, and in the Biopsy Service 1985-2008, there were 19,259 reports. Regarding demographic features, the mean age in the OM graduate 2020-21 database is older (55.03 years) than the Biopsy Service 1985-2008 database, which was 47.72 years. The age distribution was also dissimilar between the two databases analyzed. The OM graduate 2020-21 is asymmetrical with a tendency to lower extreme values, and the Biopsy Service 1985-2008 is fairly symmetrical with fewer extreme values.

Another relevant distinction was the type of lesions in each database. A comparison of the proportion of histopathological diagnosis by prognosis was made between both databases, which rendered a significant difference. X^2 (2) 72.521 p: <.001. The Biopsy Service 1985-2008 accounted for a greater percentage of benign pathologies 80.21% than the OM graduate 2020-21, which was 51.64%. In the case of OPMD, it was the opposite; the OM graduate 2020-21 had a greater percentage, 47.54%, than the Biopsy Service 1985-2008, which was 17.84%. Regarding the malignant pathologies, there was a single malignant case in the OM graduate 2020-21 0.82%, and in the Biopsy Service 1985-2008, there were 376 (1.95%) malignancies. Figure # 42 demonstrates the difference in the proportion of the benign, OPMD, and malignant pathologies encountered in both databases. Therefore, the databases are incomparable due to these differences discussed previously.

Figure # 42: Comparison pathologies per prognosis: Oral Medicine graduate program 2020-2021 and Oral Pathology Biopsy Service, University of Alberta 1985-2008



Summary of the results

- The OM graduate program 2020-21 database comprised 122 histopathological reports, 55% of which were females and 45% males; the mean age was 55 years, which showed an asymmetrical age distribution. The Biopsy Service 1985-2008 database included 19,259 cases, 52% of which were females and 46% males, and the mean age was 48 years, with a fairly symmetrical age distribution. Therefore, both databases are different in terms of demographic features.

- According to the pathological prognosis, there was no significant difference between gender and age in the OM graduate program 2020-21. On the other hand, there was a statistical difference among these variables in the Biopsy Service 1985-2008 database.

- There was a significant difference between the proportion of pathologies by prognosis between both databases. In the case of the OM graduate program 2020-21, the number of expected benign pathologies was higher than the observed, and in the OPMDs, it was the opposite, which is an important difference to consider between these databases.

- The most common benign soft tissue pathologies were irritational fibroma, squamous papilloma, mucocele, pyogenic granuloma, and amalgam tattoo. This trend was also observed in the analysis by gender and age. Except for the mucocele, these benign pathologies were also the most common in the OM graduate program 2020-21.

- In the Biopsy Service 1985-2008 database, the most common OPMD soft tissue pathologies were epithelial hyperkeratosis, lichen planus, dysplasia, verrucous hyperplasia, and lichenoid reaction. In the OM graduate program 2020-21 database, the pathologies were similar. A minor difference is that atypia was included in the most common diagnosis instead of lichen planus.

- In the OM graduate program 2020-21, there was a single malignant case, specifically, SCC. Moreover, SCC was the most common malignancy in the Biopsy Service 1985-2008 database, representing 70% of all oral malignancies.

- In the OM graduate program 2020-21, the concordance by SNOMED-CT coding system and by synonyms was 37%, and for the last level by etiopathologic clusters, it was 73%. The kappa agreement demonstrates a fair agreement by SNOMED-CT and moderate agreement by etiopathologic clusters.

- The clinical examination in the OM graduate program 2020-21 demonstrated a sensitivity to diagnose benign pathologies of 87% and a specificity of 86%. In the case of diagnosing OPMD,

84% were correctly diagnosed with an OPMD, and 89% were correctly diagnosed without an OPMD.

- In the OM graduate program 2020-21, the highest concordance was in the OPMD and reactive lesions (fibromas, pyogenic granulomas) clusters, and the highest discordance was in six cases of ulcerative-inflammatory etiopathological cluster.

- In the Biopsy Service 1985-2008 database, the concordance by the SNOMED-CT coding system was 47%; by synonyms, it increased to 50%; and for the last level by etiopathology clusters, it was 75%. The Cohen Kappa agreement for the SNOMED-CT concordance demonstrated a fair agreement and a substantial agreement when the etiopathology clusters were considered.

- In the Biopsy Service 1985-2008 database, the clinical examination correctly identified 96% of the patients with a benign pathology and 80% were correctly identified as not having a benign condition. The sensitivity to correctly identify patients with OPMDs was 77%. In other words, the clinical examination missed the diagnosis of 23% of the patients with true OPMDs. However, the specificity was 98% for correctly detecting patients without an OPMD. In the case of malignancies, 67% were correctly identified as having a malignancy, and the specificity was 98%, which is very high in detecting patients without malignancy.

- In the Biopsy Service 1985-2008 database, the clusters with a higher concordance were benign viral-induced verruco-papillary, reactive lesions and benign salivary clusters. Conversely, the clusters with higher discordance were salivary malignancies and benign soft tissue.

- The demographic features and the prognostic proportion of pathologies differ between the OM graduate program 2020-21 and Biopsy Service 1985-2008 databases.

Chapter 5: Discussion

This is a retrospective study that analyzed two databases: 1) the pathology reports from specimens submitted to the Oral Pathology Biopsy Service at the University of Alberta, Canada, from 1985 to 2008 (University of Alberta 1985-2008), and 2) pathology reports from the Oral Medicine graduate program at the University of Alberta between August 2020 and August 2021 (Oral Med 20-21).

It is important to highlight that the database from the Oral Pathology Biopsy Service at the University of Alberta, Canada, from 1985 to 2008, accounts for 19,259 cases. Therefore, it is one of the Canadian studies with the highest number of cases, which provides the prevalence of oral soft tissue pathology conditions among Albertans based on histopathologic diagnosis.

Likewise, as mentioned before, the diagnostic concordance percentage varies depending on the methodology used to compare both diagnoses. Some clinical and histopathological terms imply the same entity, but the terminology used for the clinical diagnosis is not correctly used for the histopathological diagnoses and the contrary. One example of this dilemma is leukoplakia, a clinical exclusion diagnosis of a white patch or plaque that denotes a malignant risk, [17,55] defined by the World Health Organization as "A predominantly white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk for cancer"[57]. Histopathologically, a non-reactive hyperkeratosis represents architectural evidence of dysplasia when the thickness of the keratin layer is half or more than the thickness of an atrophic epithelium [56]. Therefore, it is important to consider when analyzing clinical and histopathological diagnoses in oral pathology nomenclature. That's why several authors used a redefining concordance to overcome this terminology dilemma [17,44,46,47].

Additionally, it is crucial to acknowledge that there is no universal classification of oral soft tissue pathologies and conditions. The more recognized oral pathology textbooks group the conditions differently to facilitate the learning process[7,55,56]. Therefore, the concordance analysis between the clinical and histopathological diagnoses differs between studies depending on the oral pathology classification used. For this reason, another aspect to emphasize in the present research is the classification created to accurately compare the clinical and histopathological diagnoses. Moreover, this methodology can demonstrate etiopathologic clusters that require better diagnostic abilities and skills.

In the present research, some reports were removed in the Biopsy Service 1985-2008 database, 3,576 (15.34%), and in the OM graduate program 2020-21, 6 (4.69%) because they did not accomplish the inclusion criteria due to imprecise or missing information. Similarly occurred in the study done by Lazzarotto et al., who found no definitive diagnosis in 7.4% (81 from 1089) of the samples [33]. Also, Patel et al. excluded 8 from 3143 specimens due to absent histopathological diagnosis due to inadequate size or poor processing quality [44], and Akindayo, found imprecise diagnosis in 220 (4.2%) reports [42].

5.1 Demographic information

In the OM graduate program 2020-21, the female-male ratio was 1.2:1, with 54.92% females and 45.08% males. On the other hand, in the University of Alberta 1985-2008 database, the female-male ratio was 1.14:1, with 52.42% females and 45.89% males. Regarding the distribution gender-wise, there were more female patients in both databases, which is similar to several studies [39–41,43,44]. Female patients seek medical attention more often, and that's probably the reason why the number of biopsies is slightly higher in this gender[40].

The studied populations are different age-wise. In the OM graduate program 2020-21 database, the mean age was 55.03, with a standard deviation of 16.81 years, and the age distribution was asymmetrical. On the other hand, the Biopsy Service 1985-2008 database demonstrated a more symmetrical age distribution due to the increased number of reports. The mean age was 47.72 with a standard deviation of 20.18 years, closer to the reported by Sixto-Requeijo et al.[41]and Patel et al.[44]. However, some studies reported a mean age younger than the present studies population; for example, in the study done by Soyele et al., the mean age was 36. 1 with a deviation standard of 18.7 years [43]. Farzinnia et al. recorded that 93.2% of the cases were in the second decade [21]. In the Biopsy Service 1985-2008 database, most of the cases were in the late forties and fifth decade, and in the OM graduate program 2020-21 database, they were in the late fifth and sixth decades.

5.2 Variations of Soft Oral Pathology

The most common benign pathologies in both databases were irritational fibroma and squamous papilloma; additionally, in the Biopsy Service 1985-2008, mucocele and pyogenic granuloma were frequently encountered. According to the literature, the most common benign pathology is irritational fibroma[20,21,44,46,47,60], and in second place, mucoceles and pyogenic granulomas [21,40,44,60]. It is relevant to highlight that the second most common benign pathology in the two databases studied was squamous papilloma, which is a common pathology but not mentioned in the first four places in the references consulted for similar investigations [21,40,60] In the study of Bouquot and Gundlac, based on clinical examinations of 23,16 patients, they found that the third most common soft tissue exophytic lesion was squamous papilloma [61].

The malignant pathologies encountered in the Biopsy Service 1985-2008 database represented 1.95% of all the pathologies in this database, which was lower than the number of cases in the studies by Jones and Franklin C. and Tay A. In the report of Jones and Franklin C, they identified 5.4% of malignancies, but they mentioned that they represent a regional reference center, which is probably why they receive more malignant pathologies[39], and the latter reported 5.2%[60]. The female-to-male ratio in the

Biopsy Service 1985-2008 database was 0.63:1, representing a difference in the gender proportion according to some studies, which reported a proportion of 1:1.69 and 1:1.5 [62,63]. However, these malignancies are generally more prevalent in males, according to several epidemiologic studies [63–68].

Regarding age, 46% of the cases with malignant conditions occurred between 60-79 years; this finding is similar to the research done by Derbi et al., who found that 48% of the cases with malignant conditions were in the same range of age [62] and Ganatra et al. reported a mean age of 63.9 years for the patients with oral cavity cancer in Alberta from 2005 to 2017[69]. Similarly, Auluck et al. reported 62.2 years with Std Dev of 12.8 for men and 67.3 years with Std Dev for women in their study done in British Columbia [68]. Other global epidemiological studies reported to be more prevalent in the same range of age[64–66]. However, it was lower in the research done by Soyele et al., in which the mean age for this group of lesions was 47.5 years, demonstrating an important difference probably due to the variability among different continents[43].

Moreover, SCC represented 1.40% of all the diagnoses and 71.54% of all the malignant pathologies. An epidemiological study of SCC in the oral cavity and oropharyngeal in Canada from 1992-2010 reported that SCC represented 84.97% of oral malignancies, pathologies on the major salivary gland were excluded from de analysis. The SCC was more prevalent in patients older than 90 years but with a pronounced increase in cases between 50 and 69 years old[63]. Ganatra et al. reported that SCC was the most common (97.9%) histopathological diagnosis for oral cavity malignancies in their study. However, there were important differences to consider; the timeframe was more recent, and their data was extracted from the Alberta Cancer Registry [69].

Concerning the salivary gland malignancies in the Biopsy Service 1985-2008, there were 35 cases representing 9.31% of all the malignant diagnoses, which is in the range of the reported epidemiologic studies 3-10%[70,71]. The mean age was 64.1 years, similar to McKenzie et al.[70], but higher than the reported by Hacioglu et al., which was 56 years [72], and by Jones et al. was 59 years[71]There was a relevant difference regarding gender in the salivary gland malignancies because, in the Biopsy Service 1985-2008 database, it was more prevalent in females, the same as in Jones et al. [71], but in the rest of the consulted literature, it was in males [70,72] The most frequent histopathological diagnosis was mucoepidermoid carcinoma and polymorphous adenocarcinoma, with the same quantity of cases. In the epidemiological studies consulted, the second most common was adenoid cystic carcinoma [70–72].

The overall incidence of malignant cases was stable during the studied period. This observation is consistent with the Canadian studies done between 1992-2010 by Ghazawi et al.[63] and Ganatra et al.[69]. The same analysis was determined by other epidemiological studies[64,65]. Auluck et at. identified a decrease in oral cavity cancer in their study from 1980 to 2006 in British Columbia [68]. Similarly, in the United States and other developed countries, oral cancer has decreased in the last decades, probably due to the decrease in tobacco smoking habits among the population. On the contrary, oropharyngeal SCC had

increased over the same period of time[73,74]. In the case of Ghazawi et al., they mention that probably this stability is due to the federal and provincial tobacco and alcohol consumption awareness[63] On the other hand, Ganatra et al. justified this observation by pointing to the population growth and the increase in the migration of people from South Asia, where the incidence of SCC is more prominent due to the high consumption of tobacco and betel nuts, similar to Auluck et al. [69].

In the OM graduate program 2020-21, there was no significant difference in the relationship between gender and the histopathological prognosis, and neither with age. This effect probably occurs due to the specific features of this population; for example, the total number of cases was very small, and it is an academic, non-hospital-based referral clinic, which can influence some location bias. However, in the Biopsy Service 1985-2008, there was a significant difference between these demographic variables and the histopathological prognosis. Other researchers also encountered this significant difference among the pathological diagnoses [40,43], which are in conjunction with the epidemiological data presented in the most important textbooks of oral pathology [7,55,56].

Another relevant distinction between the OM graduate program 2020-21 and the Biopsy Service 1985-2008 databases is the difference in the proportion of lesions according to the prognosis. The former received more OPMD than benign pathologies, probably because it is an academic clinic that provides specialized diagnosis and management of oral lesions. This characteristic is relevant because future Oral Medicine specialists are required to be trained in the diagnosis and management of OPMD due to malignant risk transformation[4].

5.3 Comparison of the clinical and histopathological concordance among published studies

The present study rendered an absolute concordance between 36.89 and 50.06% in the OM graduate program 2020-21 and the Biopsy Service 1985-2008, respectively. In the literature, this percentage is higher and fluctuated between 52.6 and 72.2% among the articles consulted [20–23,43–47]. It is crucial to note that the concordance depends on the terminology used to compare both variables. Therefore, the present research used the SNOMED-CT coding system, which provides specific terminology. This is probably one reason why the concordance percent was lower than in the published studies because none of them disclosed how the terminology was coded or selected.

Forman et al. and Poudel et al. clarified that a second analysis was done to redefine the clinical and histopathologic terminology [23,46]; in those cases, the concordance increased to 61% and 67.7 respectively. Likewise, some studies analyzed the concordance by grouping the pathologies, but the categorization between the studies differs. Soyele et al. included intraosseous pathologies, and they were classified into 14 groups (reactive-hyperplastic, cystic lesions, pulp-periapical lesions, giant cell lesions, fibro-osseous lesions, odontogenic tumors, epithelial tumors, mesenchymal tumors, salivary gland diseases, hemato-lymphoid neoplasms, inflammatory-microbial diseases, ulcerative lesions, normal, and

miscellaneous) [43]. This categorization was similar to the present study, but we did not include intraosseous conditions, and the soft tissue pathology was grouped in a more detailed classification. We created 24 clusters only for the soft tissue conditions, as seen in Appendix 1. Farzinnia et al. included bone pathology and grouped the pathologies into ulcerative, red-white, pigmented, bone and exophytic [21]. Poudel et al. also included bone pathology and used a different classification (Non-neoplastic-reactive, potentially malignant oral lesions, benign, malignant, non-odontogenic cysts & pseudocysts, odontogenic cysts, odontogenic tumors, and others)[46]. Mendez et al. classified the pathology as inflammatory, benign, malignant, and other and then subclassified, but they did not include salivary gland neoplasia [47]. Therefore, there is no classification agreement between the studies, and the methodologies vary among the studies, so the comparison is not feasible. This was also analyzed by Mendez et al., who found difficulties in comparing their results with the published by other researchers [47].

One similar feature present in several studies is the reactive lesions group, which, according to the studies consulted, the concordance reported was between 60.6 and 67.56 [21,43,46]. In the present research, this same etiopathologic cluster, reactive lesions, the three levels of concordance analyzed were 57.89, 55.26 and 82.07% in the Biopsy Service 1985-2008 database and 57.73, 61.13 and 82.07% for the OM graduate program 2020-21.

The comparison of the percentage of concordance by gender was higher in the female group at the Biopsy Service 1985-2008, and there was a statistically significant association between gender and concordance by etiopathological clusters. Soyele et al. and Forman et al. reported a significantly higher concordance in the female group [23,43]. On the other hand, in the OM graduate program 2020-21, the higher concordance by etiopathological clusters was in the male group, and there was no statistical difference between these variables. Similarly, Saravani et al. and Farzinnia et al. did not find a significant difference comparing it gender wise [20,21].

The concordance according to age groups in the present study was highest in the adult group in both databases studied. However, in OM graduate program 2020-21, there was no statistical relationship between the age groups and the concordance by etiopathology clusters, which was the opposite of the Biopsy Service 1985-2008 database. The highest concordance age group differs from results obtained by Soyele et al., who found that it was in the group of patients in the seventh decade, which corresponds to the senior age group [43] and in the research done by Farzinnia et al. and Saravani et al., there was no statistical significance of this analysis by age, similar to the OM graduate program 2020-21[20,21].

The statistically significant relationship between the concordance by etiopathology clusters and the age groups and gender are probably due to the large database in the Biopsy Service 1985-2008 database, where small variations are more sensitive to this test. However, there are well-known conditions that are more prevalent in certain gender and age groups, and maybe that's the reason why clinicians can accurately diagnose these types of etiopathology clusters [7,55,56].

The OM graduate program 2020-21 rendered a sensitivity of 84.4% and specificity of 97.6% to detect OPMD. These percentages are similar to or higher than the sensitivity (51.4-84.9%) and specificity (15.4-84.6%) reported by the use of diagnostic aids for diagnosing OPMD and malignancies [14,16,18]. On the other hand, the sensitivity of the clinical diagnosis of OPMD and malignancies in the Biopsy Service 1985-2008 database is lower, requiring educational strategies to improve these lesions' diagnostic skills and corroborating the importance of the histopathological diagnosis for an accurate and precise diagnosis[14,16,18]. However, the specificity is still high for detecting true negative cases, without OPMD or malignant conditions. Even though a significant number of patients were not correctly diagnosed during the clinical examination, the sensitivity and specificity to detect OPMD and malignant conditions in the OM graduate program 2020-21 and Biopsy Service 1985-2008 were consistent with the reported sensitivity (0.50-0.99) and specificity (0.94-0.99) by Warnakulasuriya et al. in their meta-analysis [75].

5.4 Educational findings to improve the clinical and histopathological concordance

The clinical diagnosis is a fundamental step for reaching a definitive diagnosis because it gives important clues about the clinical presentation that can guide the pathologist, who assesses the biopsy. Therefore, it should list specific pathologies or conditions in order from the most likely to the least; in this way, the pathologist can provide a better histopathological diagnosis. In both databases, there were clinical diagnoses that did not represent a specific term of a condition or pathology and, for this reason, were removed from the analysis. In some cases, the terminology was very broad, for example, white lesion, salivary gland, and pigmented lesion, among others, and each one of those terms represented categories of benign and malignant pathologies.

Another mistake detected, mainly in the Biopsy Service 1985-2008 database, was the use of colloquial words such as “thrush,” “cheek biting,” or “wart” instead of scientific terminology. Moreover, acronyms can cause misunderstanding; one example is “BC,” which can be used for a few pathologies.

Additionally, it is recommended that clinicians use specific clinical terminology for clinical diagnosis and not confuse it with exclusive histopathological terminology. In a group of reports, the clinician stated a clinical diagnosis of hyperkeratosis, dysplasia, carcinoma in situ, and atypia, among others, that can only be assessed microscopically according to the specific definition of this terminology.

Moreover, as reviewed in the results, there were a few reports where the clinician confused an intraosseous pathology with soft tissue conditions. Hence, these pathologies require further clarification, especially as an educational objective in undergraduate programs, to avoid this misunderstanding. For example, a lateral periodontal cyst is an intraosseous pathology, and not a soft tissue mucosal pathology. In addition, an image repository can be created with uncommonly prevalent conditions so that dentists and future oral medicine specialists can be exposed to these pathologies.

In conclusion, key elements, such as selecting the most representative sample, delicately manipulating the tissue, and making the appropriate clinical diagnosis, are in the hands of the clinician and are fundamental for reaching a definitive diagnosis [32].

5.5 Conclusion

The comparison of the clinical and histopathological diagnosis is commonly used to analyze the diagnostic skills of practitioners, which aids in establishing further policies to improve the provided patient's management. However, the methodology used to analyze the discrepancy is fundamental because several conditions are impossible to distinguish without a histopathological assessment.

Codifying the diagnoses using SNOMED-CT and subsequent clustering by etiopathological behavior and prognosis offers a reliable method for determining the concordance between clinical and histopathological diagnoses. This classification of oral pathologies offers an option to overcome diagnostic dilemmas, where clinicians may provide one diagnosis while histopathology renders a different diagnosis. However, if both diagnoses are associated with the same etiology, the management will not change. In this way, a more realistic investigation can be carried out. Additionally, this methodology provides a better understanding of the clusters that practitioners require to improve their diagnostic skills. At the same time, further analysis can be done to show which clusters are confused with others and the discordance by prognosis. Ultimately, a clinician's main goal is to correctly differentiate OPMD and malignancies, which necessitates different management due to the nature of the pathology.

In the case of the OM graduate program 2020-21, the concordance by etiopathologic clusters showed moderate agreement, and the sensitivity to diagnose benign (87.3%) and OPMD (84.4%) was high. However, 12.7 and 15.6% of the OPMD cases are still misdiagnosed. Therefore, the histopathological examination is essential for confirming the diagnosis, especially in those cases where cellular behavior dictates future management decisions.

Oral medicine residents receive patients referred from general dentists or physicians. Hence, the cases are more complicated, which is probably why they are more exposed to OPMD pathologies, which are more difficult to diagnose. At the same time, the program's purpose is to deliver specialized education on managing these conditions[4]. For the same reason, possibly, they are more likely to suspect OPMD malignancies when a long-standing ulcerative condition is present.

The results of the Biopsy Service 1985-2008 database indicated that concordance by etiopathological clusters demonstrated a substantial agreement. At the same time, the clinical examination provides a high percentage of recognition of patients without malignancy (Specificity 98.4%) or OPMD (Specificity 97.6%). However, when practitioners consider malignancy (Sensitivity 67.5%) or OPMD (Sensitivity 76.9%), the clinical examination did not provide an exact diagnosis, and there were 32.5 and 23.1%, respectively, of a misdiagnosis. Since the biopsies of this database were performed by licensed

dentists, including general and specialized dental practitioners, the recognition of OPMD and malignancies needs to improve. Therefore, the clinical examination did not provide an accurate diagnosis; for this reason, the histopathology examination is essential to provide a definitive diagnosis.

In general, the outcomes of both databases are difficult to compare due to several important disparities. One important difference is the obvious variation in the number of cases, which affected the number of conditions and the statistical effect of the tests. The age distribution and the proportion of benign and OPMD pathologies are different. Also, there is probably a location bias because the OM graduate program 2020-21 is an academic, non-hospital-based referral clinic, and in the Biopsy Service 1985-2008, the specimens came from community and specialized clinics.

5.6 Limitations of the study

There was missing information in a group of reports that could not be included due to the missing information, which is a commonly known limitation of working retrospectively. Similarly, due to the longevity of the Biopsy Service 1985-2008 database, old terminology was required to be updated with the current nomenclature.

5.7 Recommendations

It is recommended that the existing standardized reporting template be matched with specialized software to extract the information for similar research if it wants to be replicated.

The educational recommendations discussed previously can improve the clinical and histopathologic diagnostic concordance in the future.

5.8 Future Directions

- Analyze if there is a difference in the clinical and histopathologic diagnostic concordance between the general dentists and specialists in the Biopsy Service 1985-2008 database.
- Investigate dental and intraosseous pathology information in the Biopsy Service 1985-2008 database.
- Analyze the incidence variation in soft tissue pathology and the diagnostic concordance in the histopathology reports from biopsies from 2009 to the present. Moreover, social habits and biopsy sites can be included in the analysis to compare them with the published information.
- Evaluate the incidence variation in soft tissue pathology and the diagnostic concordance in the histopathology reports from biopsies from at least five years of the Oral Medicine program at the University of Alberta.

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Appendix 1

Pathology/ Condition	SNOMED-CT code	Synonyms	Cluster	Prognosis	#	Clusters
chronic abscess	81546003		1	Benign	1	Ulcerative-inflammatory
acanthosis	23620008		15	Benign	2	Fungal infection
unspecific infection	275393007		4	Benign	3	Viral infection
acute inflammation	4532008		1	Benign	4	Bacterial
bacterial infection	312128007		4	Benign	5	Immune-mediated and vesiculobullous
periodontal abscess	83412009		1	Benign		
viral infection	34014006		3	Benign	6	Lymphatic - vascular malformation
deep fungal infection	110276005		2	Benign	7	Foreign body
actinic cheilitis	46795000		17	OPMD	8	Developmental cysts
actinic keratosis	201101007		17	OPMD	9	Soft tissue counterpart odontogenic/bone
solar elastosis	43982006		17	OPMD		
salivary adenoma	1187379001		14	Benign	9	Choristoma
adenomatoid hyperplasia of minor salivary gland	109763004		14	Benign	10	Orofacial Granulomatosis
basal cell adenoma	27230006		14	Benign	11	Normal /Variation normal anatomy
actinomycosis	23014006		4	Benign	12	Reactive lesions
amalgam tattoo	109789004		7	Benign	13	Benign viral-induced verrucopapillary
argyria	77783001		7	Benign	14	Benign Salivary Gland Pathology
angioleiomyoma	86959002		16	Benign	15	Benign epithelial conditions
angiomyolipoma	19929002		16	Benign	16	Benign soft tissue pathologies
angiomyoma	86959002		16	Benign	17	OPMD
angina bullosa haemorrhagica	235025005		5	Benign	18	Epithelial Malignancies
ankyloglossia	67787004		11	Benign	19	Soft tissue - hematol malignancies
amyloidosis	56871000		16	Benign	20	salivary gland malignancies
allergic reaction	402251006		1	Benign	21	Metastasis
aphthous	426965005		1	Benign	22	Misconception
angiomatosis	14350002		6	Benign	23	non diagnostic
autoimmune disease	85828009		5	Benign		
canalicular adenoma	128641003		14	Benign		
warthin tumor	422470007		14	Benign		
benign tumor	419958000		16	Benign		
benign mesenchymal tumor	722691002		16	Benign		
buccal bifurcation cyst	109552000		22	Misdiag		
dystrophic calcification	60963005		12	Benign		
caliber persistent artery	711100005		6	Benign		

oral candidiasis	79740000	hyperplastic candidiasis/hypertrophic candidiasis/hypertrophic candidiasis	2	Benign
hyperplastic candidiasis	110277001		2	Benign
hypertrophic candidiasis	402997002		2	Benign
chronic hyperplastic candidiasis	235072005		2	Benign
fungal infection	3218000		2	Benign
carcinoma in situ	92660005		17	OPMD
squamous cell carcinoma	307502000		18	Malignant
chemical burn	12108141000119100		1	Benign
atypia	50673007		17	OPMD
cheilitis	7847004		1	Benign
exfoliative cheilitis	235139008		1	Benign
cheilitis granulomatosa	235136001		10	Benign
cheilitis glandularis	26374003		14	Benign
chondroma	404078000		22	Misdiag
osseous choristoma	404075002		9	Benign
chronic inflammation	20369000		1	Benign
non specific inflammation	61170000		1	Benign
chronic infection	275393007		4	Benign
clot	75753009		6	Benign
condyloma	733132008		13	Benign
crohns disease	196578009		10	Benign
unspecific cyst	196546001		22	
dental follicle	110975002		22	Misdiag
denture stomatitis	69254008		2	Benign
dermoid cyst	90365003		8	Benign
developmental cyst	12143007		8	Benign
dyskeratosis	2097009		17	OPMD
dysplasia	61313004		17	OPMD
endarteritis	33806008		6	Benign
epidermoid cyst	196548000		8	Benign
epithelial atrophy	446689007		17	OPMD
inflammatory fibrous hyperplasia	1137562007	epulis/ leaf fibroma	12	Benign
epulis	45676007		12	Benign
leaf fibroma	419585004		12	Benign
eruption cyst	42323001		9	Benign
gingival cyst	58271001		9	Benign
erythema multiforme	36715001		5	Benign
erythroplakia	69299000		17	OPMD
exostosis	111347003	torus	22	Misdiag
torus	70033004		22	Misdiag
fat pad	5398002		11	Benign

irritation fibroma	16894791000119100	fibroepithelial polyp/ fibrous nodule	12	Benign
fibroepithelial polyp	1141622007		12	Benign
fibrous nodule	11854003		12	Benign
fibrous tissue	34433006		12	Benign
frenal tag	698842006		11	Benign
hecks disease	6121001		13	Benign
unspecific foreign body	14380007		7	Benign
frictional keratosis	235034000		12	Benign
epithelial hyperkeratosis	249409004		17	OPMD
oral fistula	20674003		1	Benign
oroantral fistula	109675004		1	Benign
oral focal mucinosis	109786006		16	Benign
hyperplastic papilla	6971002		11	Benign
hyperplastic fungiform papilla	249384007		11	Benign
hyperplastic filiform papilla	255225007		11	Benign
hyperplastic circumvallate papillae	249385008		11	Benign
fordyce granules	50584008		11	Benign
sebaceous gland hyperplasia	238748009		11	Benign
foreign body granuloma	37058002	suture granuloma	7	Benign
giant cell fibroma	109790008		16	Benign
giant cell granuloma	43917008		12	Benign
graft versus host disease	402362009		17	OPMD
oral granuloma	45647009		1	Benign
suture granuloma	66962008		7	Benign
granulation tissue	61363009		1	Benign
granular cell tumor	404035005		16	Benign
geographic tongue	59032001		11	Benign
gingival hyperplasia	54711002	hyperplastic gingivitis	1	Benign
drug induced gingival hyperplasia	93434009		12	Benign
gingival fibromatosis	58569000		16	Benign
unspecific gingivitis	66383009		1	Benign
desquamative gingivitis	22208002		5	Benign
hyperplastic gingivitis	84161008		1	Benign
glossitis	45534005		1	Benign
herpes simplex	235058001		3	Benign
herpes zoster	235059009		3	Benign
black hairy tongue	81934005		11	Benign
hereditary hemorrhagic telangiectasia	21877004		6	Benign
oral hemangioma	403963001	cavernous hemangioma	6	Benign
cavernous hemangioma	33377007		6	Benign
hematoma	262648004		6	Benign
petechia	50091001		6	Benign
heavy metal pigmentation	30771009		7	Benign
fibrous histiocytoma	25889007		16	Benign

hyperplastic tissue	76197007		12	Benign
focal epithelial hyperplasia	6121001		12	Benign
epithelial hyperplasia	31390008		12	Benign
verrucous hyperplasia	109785005		17	OPMD
hypertrophic scar	19843006		12	Benign
intraductal papilloma	5244003		14	Benign
insufficient sample	281268007		23	
inflammatory papillary hyperplasia	41349008		12	Benign
kaposi sarcoma	1217617009		19	Malignant
langerhans cell histiocytosis	8090002		9	Benign
unspecific leukoplakia	414603003		17	OPMD
verrucous leukoplakia	235031008		17	OPMD
hairy leukoplakia	414952002		3	Benign
erythroleukoplakia	698199001		17	OPMD
leukoedema	67795000		11	Benign
lichenoid reaction	235050008	lichenoid mucositis	17	OPMD
lichenoid mucositis	699290002		17	OPMD
oral lichen planus	4776004		17	OPMD
erosive lichen planus	238662007		17	OPMD
linea alba	709495007		11	Benign
lymph nodes	30746006		11	Benign
lymphangioma	238803001		6	Benign
lymphoepithelial cyst	67045005		8	Benign
benign lymphoepithelial lesion	45517002		14	Benign
lymphoid hyperplasia	43961000		11	Benign
lymphoma	118600007		19	Malignant
lupus	707301001		17	OPMD
oral lipoma	404061009		16	Benign
fibrolipoma	2710003		16	Benign
angiomyolipoma	19929002		16	Benign
pyogenic granuloma	17372009		12	Benign
malignancy	1240414004		18	Malignant
mucoepidermoid carcinoma	423708008		20	Malignant
acinic cell carcinoma	45410002		20	Malignant
polymorphous adenocarcinoma	128702009		20	Malignant
adenocarcinoma	443961001		20	Malignant
adenoid cystic carcinoma	422833009		20	Malignant
clear cell adenocarcinoma	30546008		20	Malignant
spindle cell carcinoma	65692009		18	Malignant
leiomyosarcoma	443719001		19	Malignant
verrucous carcinoma	403889000		18	Malignant
median rhomboid glossitis	707318002		2	Benign
melanoma	403926005		18	Malignant
melanotic macule	3449001		15	Benign

melanin pigmentation	235038002		15	Benign
physiological pigmentation	403218008		11	Benign
oral pigmentation	249405005		15	Benign
foreign body pigmentation	235045002		7	Benign
metastasis	404094007		21	Malignant
mucosal melanosis	724847001		15	Benign
morsicatio buccarum	59901004		12	Benign
mucocele	69825009		14	Benign
oral ranula	14919007		14	Benign
mucous retention cyst	1260281008		14	Benign
mucositis	95361005		1	Benign
nasopalatine cyst	4749004		22	Misdiag
necrosis	6574001		1	Benign
anug	707792000		1	Benign
necrotizing sialometaplasia	109769000		14	Benign
oral nevus	140051000119109	blue nevus/intramucosal nevus / junctional nevus/ compound nevus	15	Benign
blue nevus	63166000		15	Benign
intramucosal nevus	449767002		15	Benign
junctional nevus	30494009		15	Benign
compound nevus	49409001		15	Benign
nicotine stomatitis	89013002		12	Benign
oral neuroma	1163436007		16	Benign
neurofibroma	687111000119102		16	Benign
neurofibromatosis	81669005		16	Benign
normal	162010006		11	Benign
odontoma	1156647001		22	Misdiag
operculum	10602003		11	Benign
oral submucous fibrosis	32883009		17	OPMD
foliate papillitis	710003004		1	Benign
squamous papilloma	698182002	papilloma	13	Benign
oral papilloma	402908003		13	Benign
papillomatosis	88172005		13	Benign
parulis	109610001		1	Benign
mucous membrane pemphigoid	402441007		5	Benign
pemphigus vulgaris	49420001		5	Benign
pericoronitis	22240003		1	Benign
periodontitis	41565005		1	Benign
peripheral ameloblastoma	278404007		9	Benign
ameloblastoma	20462008		22	Misdiag
peripheral giant cell granuloma	89722009		12	Benign
peripheral odontogenic fibroma	75914009		9	Benign

peripheral ossifying fibroma	109788007		12	Benign
pregnancy tumor	235003004	pyogenic granuloma	12	Benign
plasma cell gingivitis	234992005		1	Benign
phlebolith	37876005		6	Benign
monomorphic adenoma	77653004		14	Benign
pleomorphic adenoma	8360001		14	Benign
epithelial polyp	41329004		12	Benign
postinflammatory pigmentation	95348005		12	Benign
premalignancy	1269006002		17	OPMD
reactive tissue	402870005		12	Benign
retrocuspid papilla	110601005		11	Benign
blocked salivary gland	23512004		14	Benign
benign salivary gland neoplasia	255154009		14	Benign
salivary gland hyperplasia	698070009		14	Benign
schwannoma	985004		16	Benign
scleroderma	267874003		5	Benign
sialadenitis	42982001		14	Benign
smokeless tobacco keratosis	95269005		17	OPMD
smokers keratosis	235033006		17	OPMD
smokers melanosis	5661000124106		12	Benign
sialolith	28826002		14	Benign
scar tissue	12402003		12	Benign
syphilis	235062007		4	Benign
sjogrens	83901003		14	Benign
spider angioma	195382003		6	Benign
thermal burn	403445007		1	Benign
thrombus	396339007		6	Benign
thyroglossal duct cyst	699000000		8	Benign
traumatic neuroma	230650009		12	Benign
traumatic ulcer	403444006		1	Benign
traumatic injury	417746004		12	Benign
tugse	403455006		1	Benign
non specific ulcer	26284000		1	Benign
non diagnostic	103694001		23	Misdiag
varicosity	702792005	vascular anomaly/ arteriovenous malformation / angiopathy	6	Benign
vascular anomaly	783806000		6	Benign
arteriovenous malformation	24551003		6	Benign
angiopathy	27550009		6	Benign
verruca vulgaris	57019003		13	Benign
verruciform xanthoma	708013001		15	Benign
white sponge nevus	389203001		15	Benign
xerostomia	87715008		22	Misdiag
tuberculosis	235067001		4	Benign

osteoradionecrosis	63810002		22	Misdiag
squamous metaplasia	83577005		14	Benign
acantholysis	43327007		5	Benign
lymphocytic infiltrate	54727009		1	Benign
tonsillolith	6461009		4	Benign
intravascular papillary endothelial hyperplasia	238770007		6	Benign
double lip	699762000		11	Benign
leukemia	93143009		19	Malignant
nasolabial cyst	90516007		8	Benign
pigmented neuroectodermal tumor of infancy	404042005		16	Benign
pseudoepitheliomatous hyperplasia	254665009		12	Benign
adenosquamous carcinoma	403902008		20	Malignant
nodular fasciitis	400138001		1	Benign
myositis	26889001		16	Benign
psoriasis	9014002		5	Benign
sebaceous cyst	417992006		15	Benign
plasmacytoma	188718006		19	Malignant
behcet	310701003		5	Benign
abnormal desquamation	1264086002		15	Benign
residual cyst	109608003		22	Misdiag
graft tissue	260667007		11	Benign
wegener granulomatosis	195353004		10	Benign
oral carcinoma	722688002		18	Malignant
uncertain diagnosis	282292002		23	Misdiag
odontogenic tumor	276968006		9	Benign
periimplantitis	699422003		1	Benign
periostitis	21780009		22	Misdiag
lateral periodontal cyst	88477005		22	Misdiag
neuronal choristoma	230794008		9	Benign
thrombocytopenic purpura	302873008		6	Benign
leiomyoma	162890002		16	Benign
sarcoma	424413001		19	Malignant
keratoacanthoma	254662007		15	Benign
sarcoidosis	707238003		10	Benign
basal cell carcinoma	1338007		18	Malignant

* Misdiag: Hard tissue and other misdiagnosed