JIMMA UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

DEPARTMENT OF PATHOLOGY

HISTOPATHOLOGIC PATTERNS OF SALIVARY GLAND LESIONS AND ASSOCIATED FACTORS IN JIMMA UNIVERSITY MEDICAL CENTER, JIMMA, SOUTH WESTERN ETHIOPIA: A 5-YEAR RETROSPECTIVE STUDY, FROM SEPTEMBER 2016 TO AUGUST 2020.

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NOVEMBER, 2021

JIMMA, ETHIOPIA

Declaration of Principal Investigator

I the undersigned, Roba Elala agree to accept all responsibilities for the scientific and ethical conduct of this thesis entitled "Histopathologic Patterns of Salivary Gland Lesions and Associated Factors in Jimma University Medical Center, Jimma, South Western Ethiopia: A 5-Year Retrospective Study, from September 2016 to August 2020"

The Thesis is my original work. All resources and materials used for this research have been dully acknowledged. I was communicating and providing timely progress report to my advisors and seek the necessary advice, comment and approval in the course of this work.

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The student had worked on this research and fulfilled all the requirements and hence hereby can submit the thesis to the Department of Pathology, Institute of Health Sciences, Jimma University.

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Histopathologic Patterns of Salivary Gland Lesions and Associated Factors in Jimma University Medical Center, Jimma, South West Ethiopia: A 5-Year Retrospective Study, from September 2016 to August 2020.

A research thesis to be submitted to the Department of Pathology, Institute of Health Sciences, Jimma University; in partial fulfillment for the requirements for Specialty in Anatomic Pathology.

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ABSTRACT

Background: Salivary gland lesions (SGLs) account for <1% of all tumors and about 4% of all epithelial neoplasms in head and neck region. These comprise a wide variety of benign and malignant neoplasms, and non-neoplastic lesions which exhibit a difference in biological behaviors. Reports from various parts of the world indicate that there are differences in the total incidence of salivary gland tumors as well as in the frequency of particular histologic types and in their distribution.

Methods and Materials: A retrospective cross-sectional study design was applied for patients sent to JUMC pathology department with SGLs for histopathologic diagnosis from September 2016 to August 2020. Important data were gathered using structured checklist and entered into Epi data v.3.1. After checking and clearing, the data were exported to SPSS V.23 for analysis. Descriptive statistics such as frequency, proportions, mean and median as well as logistic regression were used to analyze the data.

Results: From a total of 176 SGLs 135(76.7%) were neoplastic and the remaining 41(23.3%) were non-neoplastic lesions. Being in the age group of 21-40[AOR=5.172, 95% CI (1.696-15.776)], 41-60[AOR=4.534, 95% CI (1.087-18.907)], and having the lesions for duration >24 months [AOR=12.479, 95% CI (3.433-45.356)] and the size of the mass >5 cm [AOR=19.486, 95% CI (3.371-112.639)] were associated increased odds of neoplastic lesions, while the site of the lesions being in major groups of salivary glands [AOR=0.056, 95% CI (0.014-0.224)] was associated with decreased likelihood of neoplastic SGLs.

Conclusion: In this study we conclude that the prevalence of neoplastic salivary lesions were three times more common than non-neoplastic ones and malignancies were slightly more common than benign lesions. Mucoepidermoid carcinoma was the commonest malignant while PA was the commonest benign SGLs both in females and males. The neoplastic SGLs were highly associated with increasing age beyond young adults, duration longer than 6 months, size larger than 5 cm and minor groups of salivary glands.

Key words: Histopathologic patterns, salivary gland lesions, Ethiopia.

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ABBREVIATION AND ACRONYMS

AdCC----------Adenoid cystic carcinoma

ACC----------Acinic cell carcinoma

ASIR----------Age specific incidence rate

BCA----------Basal cell adenoma

Ca Ex-Pa----------Carcinoma ex-pleomorphic adenoma

EPI info----------Epidemiological information

IDH----------Intercalated duct hyperplasia

IRB----------Institutional Review Board

JUMC----------Jimma University Medical Centre

MASC----------Mammary analogue secretory carcinoma

MEC----------Mucoepidermoid carcinoma

NOS----------Not otherwise specified

PA----------Pleomorphic adenoma

PLGA----------Polymorphous Low-Grade Adenocarcinoma

SGLs----------Salivary gland lesions

SGTs----------Salivary Gland Tumors

SPAN----------Sclerosing polycystic adenosis

SPSS----------Statistical Package for the Social Science

SSx----------signs and symptoms

WHO----------World Health Organization

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CHAPTER ONE: INTRODUCTION

1.1. Background

The salivary glands consist of the paired parotid, submandibular and sublingual glands, and numerous minor salivary glands that are found dispersed in the entire upper aerodigestive tract(1).

Apart from their normal anatomic locations, heterotopic salivary gland tissues can be found in other sites. Heterotopic salivary tissue is also subject to the same pathologic changes as its orthotopic counterpart(2).

Salivary gland lesions (SGLs) constitute <1% of all tumors and about 4% of all epithelial neoplasms in head and neck region(2–4). These comprise a wide variety of benign and malignant neoplasms, and non-neoplastic lesions. Non-neoplastic lesions range from an inflammatory disorder of infectious, granulomatous, or autoimmune etiology to obstructive, developmental, and idiopathic disorders. These often clinically present as tumors and may have pathological features similar to some of the neoplasm(3).

Epithelial tumors constitute 80% to 90% of all salivary gland tumors (SGTs), with the majority being benign (75%) and pleomorphic adenoma (PA) being the most common (about 65% of all tumors). The parotid gland is the most common site of occurrence of SGTs. Some tumor types show a predilection to occur in either the major or minor salivary glands. SGTs are generally more common in women than men, except for Warthin tumor and high-grade carcinomas and rare in children(4).

Although rare, tumors of salivary glands are of particular interest to histopathologists because of their varied histologic and biologic characteristics. Reports from various parts of the world indicate that there are differences in the total incidence of SGTs as well as in the frequency of particular histologic types(5).

The probability of malignancy is relatively inversely proportional to the size of the gland. Overall, benign tumors of the salivary glands tend to present somewhat earlier than malignant ones. Pleomorphic-adenoma is the most common among benign tumors. Mucoepidermoid carcinoma (MEC) is the most common among malignant tumors. Affected patients are between 15 and 70-years of age and predominantly females(6).

Although benign tumors may be present for months to several years before coming to clinical attention, while cancers more often come to attention promptly, there are no reliable criteria to differentiate benign from malignant lesions on clinical grounds, and histopathologic evaluation is essential(7).

1.2. Statement of the problem

The worldwide annual incidence of SGTs ranges from 0.4 to 13.5 cases per 100,000 people(4). Malignant neoplasms of salivary glands are extremely rare; ranging from 0.05 to 2 cases per 100,000 population. They account for about 0.3% of all cancers worldwide and are considerably more common in females than in males (ratio worldwide is 1.5:1), although the proportion varies according to the histological type of tumor(8–10). In both sexes, the highest number of salivary gland cancers are found in the European and North American population. Compared with Africa, the proportion is 40:6, whereas for Asia it is 40:1(11).

A review of 23 articles from 12 African countries showed that salivary gland neoplasms represent a significant health problem in Africa and their patterns of presentation are different from those seen in Western countries(12).

As a retrospective study from Kenya indicated a diagnosis of SGTs accounted for a total of 132 (5.4%) of the 2426 biopsy specimens during a period of 2000 to 2010(13). Similar study from Tanzania indicated that the SGLs account for 6.3% of orofacial tumors and tumor-like lesions(14).

In 2020, the incidence of salivary gland cancer was estimated to be 0.56% in Ethiopia(8). According to the 2015 Addis Ababa Cancer registry, there were a total of 433 newly diagnosed cancer cases (210 females and 223 males) with an ASIR of 0.6 (males) and 0.7 (females)(15). Salivary gland cancer is the 10th most common cancer in Gondar and North-Western Ethiopia (2.2%)(16). The incidence of salivary gland cancers in TASH is 13 % of all head and neck cancers(17).

There are very limited, only institutional based, studies done on SGLs in Ethiopia. The histopathologic patterns of SGLs in Jimma university medical center (JUMC) are not

studied yet. Hence, the aim of the current study is to describe the frequency as well as morphological patterns of salivary gland neoplastic and non-neoplastic lesions, in Jimma University Medical Center, South-Western Ethiopia.

1.3. Significance of the study

The finding of this study can be an input for a nationwide description of histopathologic patterns of SGLs. It will lay a base for further clinicopathologic studies in this and related topics. Together with similar and related studies in other centers in the country, it may give guiding information for health-related policy makers on these issues. The finding will also provide basic information to healthcare workers particularly those managing patients with SGLs in this part of the country. By providing an organized and specific information about patterns of various SGLs in this center, their relative frequencies and their variation according to some demographic and clinical conditions; the finding will also add to a continuous effort in provision of quality healthcare services for our patients.

CHAPTER TWO: LITERATURE REVIEW

2.1. Overview of salivary gland lesions

Salivary glands are exocrine organs responsible for production and secretion of saliva. They comprise the three paired major glands: the parotid, submandibular and sublingual, and the minor salivary glands. SGLs encompass a heterogeneous group of disorders and are broadly classified as neoplastic and non-neoplastic. Non-neoplastic lesions are by far more common than neoplastic ones. However, they are rarely biopsied for histologic diagnosis(1).

Despite their simple morphology, salivary glands give rise to a variety of neoplastic lesions which are generally categorized into benign and malignant neoplasms(2).

According to a study carried out on histopathological patterns of SGLs in India, out of a total 121 cases, 43.80% were diagnosed as non-neoplastic lesions and 56.2% as neoplastic lesions. Chronic sialadenitis was the commonest non neoplastic SGLs followed by mucocele. Among all SGLs, PA was the single commonest lesion. In neoplastic lesions, benign tumors were far ahead in frequency than malignant. Out of benign neoplastic lesions, PA was the commonest, followed by Warthin's tumor. Out of malignant neoplastic lesions, MEC was the most common malignant SGT followed by AdCC(18).

Reports from a prospective study done at one teaching hospitals in Sanaa revealed that the most common disease of salivary glands was SGT, accounting (43.6%), followed by, salivary gland cyst and sialolithiases, accounting 20.7% and 20.0 % respectively. The less common disease were sialadenitis and Sialadenosis, accounting 12.9% and 2.9% respectively(19).

A retrospective study from Nigeria, done on all specimens obtained from SGTs in Ahmadu Bello University Teaching Hospital, analyzed a total of 258 salivary gland neoplastic lesions. There were 127 benign tumors of which 121 were epithelial in origin and comprised 46.9% while malignant tumors were 131, representing 50.7% and all were epithelial in origin. The benign epithelial neoplasms comprised mainly PA (the most frequent), basal cell adenoma and cystadenoma. Adenoid cystic carcinoma accounted for 25.9% and muco-epidermoid carcinoma for 18.2% of cases were the most and the second most common malignant lesions, respectively. The least common tumors were a case of

acinic cell carcinoma and sialoblastoma which represented 0.4% each. Three lipomas and solitary cases of fibromyxoma and fibrohistiocytoma were the only non-epithelial SGTs(20).

The findings of a study conducted at Khartoum Teaching Dental Hospital showed a high frequency of malignant SGTs in Sudan(21).

One retrospective study was conducted to describe the pattern of SGTs in Ethiopia in the Department of Pathology, Addis Ababa University, over a period of ten years from 1990-1999. Of all 176 SGTs, parotid gland accounts for 43.2% followed by submandibular gland for 25% and the rest of all minor salivary glands contribute for 31.9%. From a total of 176 tumors, 117 were benign and 59 were malignant. PA accounts for 58.5% of all tumors(22).

2.2. Histologic classification

The first well-recognized histological classification of salivary gland cancers was published by Foote and Frazel in 1953, followed by Batsakis in 1979(1). The first WHO classification was published in 1972 (Thackray and Sobin 1972) and revised in 1991 by Seifert et al. and in 2005 by Barnes et al. The latest version was published in 2017. Currently, about 40 salivary gland epithelial tumors have been described and some are very rare indeed and may be the subject of only a few case reports(23). These various histologic classes of SGTs are currently grouped under five major categories according to the fourth edition of WHO tumor classification series including: Malignant tumors, Benign tumors, non-neoplastic epithelial lesions, Benign soft tissue lesions and Hematolymphoid tumors(24).

In the current WHO edition of SGTs classification, some new entities and variant morphologies have been described, some entities have been removed or collapsed into another category, and criterias for diagnosis have been modified. There is also slight expansion of entities within the soft tissue category. The newly listed entities and variants in the recent WHO classification of SGTs include Secretory carcinoma (MASC), Sclerosing polycystic adenosis (SPAN), Intercalated duct hyperplasia (IDH), Nodular oncocytic hyperplasia, Lymphoepithelial lesions and soft tissue lesions including Lipoma and Nodular fasciitis(25).

2.3. Epidemiology

SGLs, including the non-neoplastic ones, are responsible for a significant amount of morbidity. However, neoplastic tumors are uncommon(2,7). They account for only 3–6% of all head and neck malignancies. The percentage of malignant tumors out of all salivary gland neoplasms varies between 21.0% and 36.8%(3,4).

2.4. Variations in distribution of salivary gland lesions

2.4.1. Sex

In general, women are more commonly affected than men, except for Warthin tumor and high-grade carcinomas(2,6). In a multicentric retrospective study of 20 years data from Brazil, out of 2,292 cases of primary salivary gland neoplasms diagnosed in the five centers, most patients were female (n=1,391; 60.7%), with a female: male ratio of 1.5:1(26). According to a study conducted in the Department of Pathology, University of Zagreb School of Medicine, University Hospital Dubrava, Croatia from 1985-2009. Over a period of 25 years, 779 patients with SGTs were evaluated, 392 males (50.3%) and 387 females (49.7%)(27). Another retrospective study done on 371 cases in Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, between the years 2009 and 2016 included 167 males and 204 females with male to female ratio of 1:1.22. There was female preponderance in inflammatory, tumor-like as well as benign lesions; however, there was a slight reversal of this in the malignant lesions(28). A Prospective Study done on epidemiological and histomorphological patterns of SGTs in Cameroon over a period of 11years (2000-2010) included a total of 275 files in the study out of which 154 (56%) were females and 121 (44%) were males(29). In one of Indian study also, male predominate with the overall 77.27% of cases in the study being male and the remaining 22.73% being female(30).

2.4.2. Age

SGTs are generally rare in children. In patients under the age of 18 years, half of the epithelial tumors are malignant, with low-grade MEC being the most common. Mesenchymal tumors (hemangioma and lymphangioma) are the most common in infants, and unusual tumors such as sialoblastoma and salivary gland anlage tumors are exclusive to this age group(4,6). A study from USA done at the Armed Forces Institute of Pathology

involving review of nearly 10,000 cases involving the major and the minor salivary glands; showed that about out of 9993 cases of SGLs, 430 were in children (less than 15 years of age), accounting for 4.3% of the total. Of the lesions in children, 262 were non-neoplastic, and 168 were considered tumors. Among all conditions affecting the salivary glands in children, the non-neoplastic lesions constitute the majority. The mucocele (localized mucous retention phenomenon) represented the largest single entity in this category involving the minor salivary glands only(31). The age at presentation of malignant tumors is similar to or slightly older compared with that in benign tumors(4,6). According to a retrospective study done at the Araujo Jorge Hospital in Goiania, Goias, Brazil over a 10-year period (1996–2005), the median age of occurrence of all SGTs was 45 years, the peak of incidence being in the fourth decade of life. The median age for malignant tumors was 55 years which is significantly higher than for benign tumors (43 years old). For patients with benign tumors, the fourth decade of life is a period with peak incidence, while for malignant tumors it was in the seventh decade of life. The age ranged widely from 1 to 86 years old for cases with benign tumors, mainly distributed between 20 and 60 years of age. In malignant tumor cases, age ranged from 8 to 88 years old and the incidence increased significantly with age, reaching up to 40% from 70 to 89 years of age(32).

2.4.3. Site

Though there are some variations in literatures from different parts of the world the sites of occurrence of SGTs with respect to the number of cases in descending order are parotid gland, submandibular gland, palate, cheek, and tongue(2,6,7). Michal Gontarz and his colleagues from Poland did a retrospective study involving a review of data for 805 patients with primary epithelial SGTs. Out of 566 benign tumors; 455 (80.4%) in Parotid, 60 (10.6%) in palate and 22 (3.8%) of cases were located in submandibular gland. Whereas for 239 cases of malignant tumors; parotid 78 (32.6%), submandibular 24 (10.0%), palate 49 (20.5%) and buccal mucosa 22 (9.2%) were the leading sites to be involved(33). A five-year retrospective study in Usmanu Danfodiyo University Teaching Hospital, from Nigeria showed that the minor salivary glands were the commonest site of occurrence, followed by the parotid, then the submandibular and the sublingual glands. The palate was the commonest, while the floor of the mouth was the least to be involved from the minor salivary glands(34). In another retrospective study done on data from the files of the

Department of Pathology, Makerere University-Uganda, from 268 consecutive cases of primary SGTs 34% were originated from the parotid, 33.2% from the submandibular and 32.8% from minor salivary glands. The sublingual gland was not involved at all(35).

2.4.4. Clinical presentation, size and duration

Apart from inflammatory non-neoplastic conditions and neglected malignant tumors, most of SGLs are presented as painless swelling ranging from 4 to 6 cm in diameter. Most of the time, benign tumors have been present for many months to several years before coming to clinical attention while cancers are generally detected more quickly because of their rapid growth(2,4). In retrospective research conducted by M.I. Masanja and his colleagues from Tanzania including medical records of 153 patients with SGT, the commonest presenting clinical feature was that of a slowly growing painless swelling. Pain and ulceration were reported in few of the patients, especially those with malignant lesions(14). Another retrospective study from Libya also found that painless swelling was the most common presentation of patients with SGTs(36). In a study from Sudan all cases with salivary gland diseases were presented with gland swelling/mass. Pain with food chewing presented in 33% of the patients, xerostomia was founded in 4% of the patients, dry eye in 4% of the patients, obstructive symptoms founded in 4% of the patients. Another 4% of the patients presented with inability to swallow, 2.7% with dental symptoms, and 4% with facial weakness. Cervical lymph node enlargement was founded in 9.6% of the patients and ulcerations in 5.4% of the patients (37).

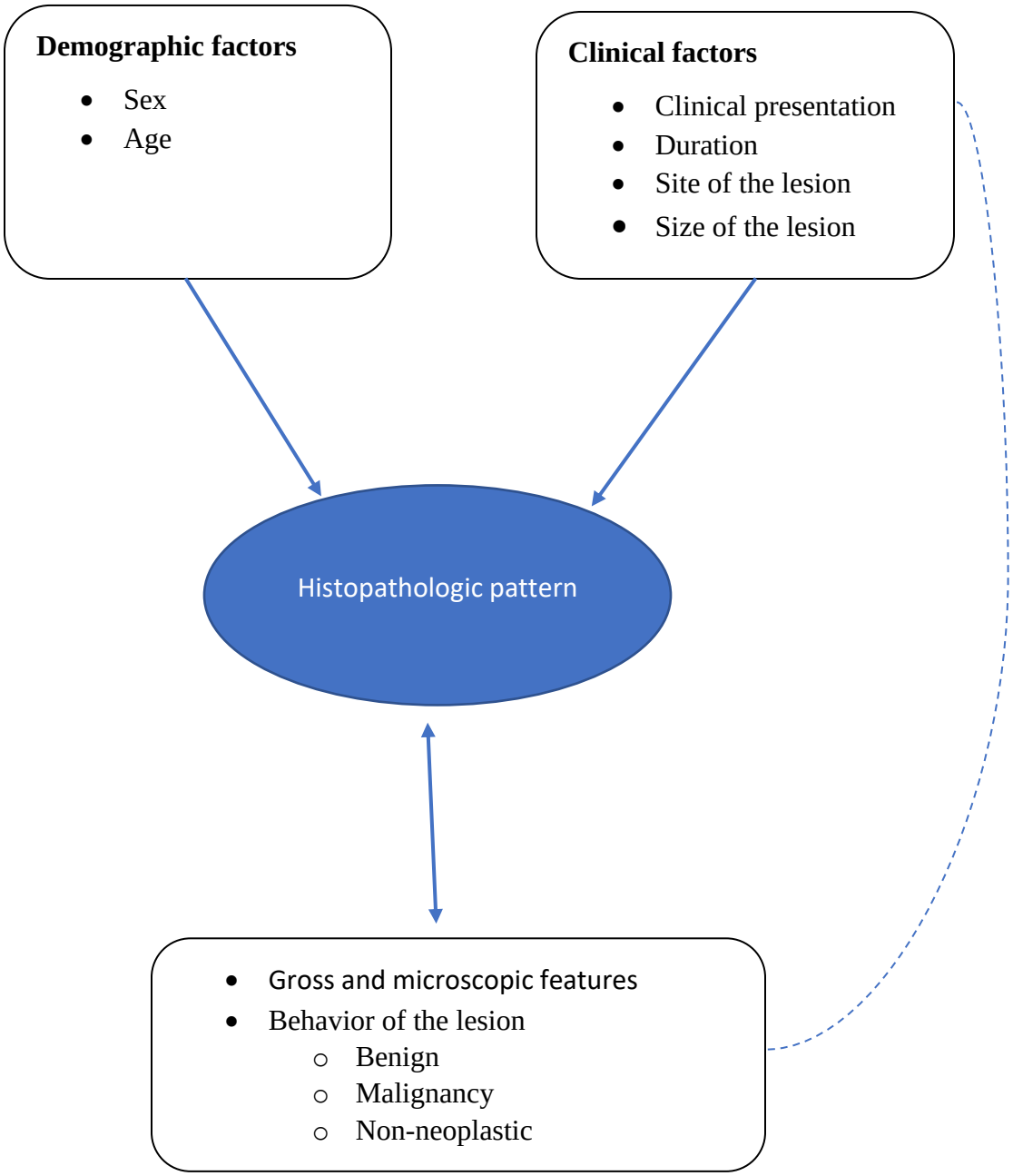

Figure 1 Conceptual Framework of histopathologic patterns of SGLs and associated factors (adopted from literature and books) (4,6,13,38–41).

CHAPTER THREE: OBJECTIVES

3.1. General objectives

To describe the histopathologic patterns of salivary gland lesions and associated factors in Jimma University Medical center from September 2016 to August 2020

3.2. Specific objectives

- To describe the histopathologic patterns of salivary gland lesions
- To identify the associated factors of histopathologic patterns of salivary gland lesions

CHAPTER FOUR: METHODS

4.1. Study Area and period

Study was conducted in Jimma University Medical Center, pathology department, located in Jimma town, South western Ethiopia, about 352 km away from the capital city, Addis Ababa. JUMC is one of the oldest hospitals in Ethiopia and it is the only teaching and referral hospital in Southwest Ethiopia with 800 bed capacity and a catchment population of over 15 million people. The center gives health services to around 200,000 patients annually in different setup and specialties. The pathology department of JUMC has four pathology seniors, twelve residents, one histopathology technologist, three technicians, six assistant technicians and one secretary. Services given by the department include histopathology, cytopathology and hematopathology along with both undergraduate and postgraduate teaching programs. The department receives and reports an average of 2000 biopsies, 5000 FNACs, 250 fluid cytologies and 100 bone marrow aspirations annually. The study was conducted from June to November 2021.

4.2. Study Design

Facility based retrospective cross-sectional study design was applied.

4.3. Population

4.3.1. Target population

All population in the catchment area of JUMC.

4.3.1. Source population

All patients with SGLs for whom biopsy was sent and histopathologic diagnosis was made at JUMC.

4.3.2. Study population

All patients with SGLs for whom biopsy was done and histopathologic diagnosis was made at JUMC from September 2016 to August 2020 fulfilling the eligibility criteria.

4.4. Inclusion and Exclusion Criteria

4.4.1. Inclusion criteria

All biopsy report on SGLs having; Age, Sex, presentation, duration, site, size and histologic diagnosis recorded.

4.4.2. Exclusion criteria

Records which missed at least one of the variables: - age, sex, presentation, duration, site, size or histopathologic diagnosis. Records with inconclusive, recurrence and repeated histopathologic reports.

4.5. Sampling technique

Conveniently, all 202 biopsy records with SGLs on biopsy request form from September 2016 to August 2020 were identified manually from the total of 8412 biopsy reports archived at the pathology department for this period. All cases fulfilling the inclusion criteria and exclusion criteria were reviewed. Then, 26 cases of SGLs were excluded because eligibility criteria were not met. Finally, all 176 cases of SGLs fulfilling the eligibility criteria were taken for data collection and analysis.

4.6. Data collection procedures

Data was collected using structured check lists from the patient's biopsy report record in the pathology department manually by technicians working in the department. Demographic information of the patients, clinical information and diagnosis was collected from patients' biopsy report records. One supervisor from junior pathology residents and three data collectors from histopathology technicians were enrolled. Training was given for data collectors and supervisors on the objective of the study, data collection tools and procedures. Orientation on Covid-19 prevention protocol was provided. The principal investigator also supervised data collection and entry daily.

4.7. Study variables

4.7.1. Independent variables

Age, Sex, Clinical presentation, Duration of the lesion, Site and Size of the lesion

4.7.2. Dependent variable

Histopathologic diagnosis

4.8. Data processing and Analysis

Data was entered into Epi data v.3.1., cleared and exported to SPSS v.23 for analysis. Descriptive analysis was carried out using frequency distributions, central tendency and dispersion measures. Cross tabulations and bivariable analysis were performed to select variables for multivariate analysis. Hence variables with p-value <0.25 were taken as a candidate for multivariable analysis. Thus, presence of statistical association between outcome variables and the risk factors in the bivariable analysis was assessed using multivariable logistic regression. Associations with p- value of < 0.05 were considered to be statistically significant. Odds ratio (OR) and confidence interval (CI) were used to determine the presence of significant association between dependent and independent variables. The model fitness for logistic regression was tested using Hosmer-Lemeshow goodness of fit test at P-Value >0.05. Results were presented using narration, tables and figures.

4.9. Data quality assurance

Checklist was adopted after reviewing different literatures. In addition, data collectors received adequate training about the study and how to utilize the checklist. The checklist was pretested on 18 randomly selected biopsy reports. Then the checklist was revised with some modifications and used for the data collection. The completeness, accuracy and clarity of collected data was checked carefully by the principal investigator and supervisor on a daily basis.

4.10. Ethical consideration

Before the study began ethical clearance was obtained from the Institutional Review Board (IRB) of JUMC. Before conducting of the study permission was also obtained from the pathology department. Name of the patient was excluded on all information obtained from

patients and confidentiality was ensured. Covid-19 prevention protocol was applied throughout all research activities.

4.11. Dissemination plan

After research completion and finalizing the report, it will be submitted to the department of pathology, graduate programs coordinating office and institute of health of Jimma University, ministry of health and other concerned institutions and stakeholders for possible application and publication of the study.

4.12. Operational definition

- Histopathologic pattern – histopathologic pattern/morphological pattern is the distribution of various microscopic features and histologic diagnosis in relation to demographic and clinical factors.

CHAPTER FIVE: RESULTS

5.1. Demographic characteristics

Out of 8,412 biopsy reports made over the last five years, from the year 2016 to 2020, at JUMC; 202 biopsy reports of SGLs were found from which 26 cases were excluded because eligibility criteria were not fulfilled. From a total of 176 cases included in this study, 96 (54.5%) were male and 80 (45.5%) were female. The mean age of patients with SGLs was 35.23 ± 17.08 with a median age of 33 years and minimum and a maximum age of 1 and 75 years, respectively. Regarding the age category, 78(43.3%) were between 21-40 years, 44(25%) were between 41-60 years, 40(22.7%) were 20 years or younger and 14(8%) were older than 60 years (Table 1).

Table 1 Demographic characteristics of patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

Variable	Category	Frequency	Percent
Sex	Female	80	45.5
	male	96	54.5
Age	≤ 20	40	22.7
	21-40	78	44.3
	41-60	44	25
	> 60	14	7.95

5.2. Clinical characteristics

About two-thirds, 117(66.5%), of the patients with SGLs had painless swelling at presentation while 59(33.5%) of them presented with swelling and other additional signs and symptoms. The average duration of a lesion was 21.3 months which is somehow higher (23.7) for patients with neoplastic lesions and relatively lower for those with non-neoplastic lesions (13.2). Furthermore, the average duration of lesions for benign lesion was much

longer (32.3) than that of malignant lesions (16.2). Overall, duration of lesion was 6-24 months in 76(43.2%), less than or equal to 6 months in 53(30.1%) and greater than 24 months in 47(26.7%) of the patients. The average size of the lesions was 4.4 cm with the minimum size of 1 cm and maximum size of 13 cm. Out of the total patients with SGLs 135(76.7%) had mass lesion ≤ 5 cm in diameter while 41(23.3%) patients had mass measuring > 5cm in largest diameter. Among 176 patients with SGLs, major salivary glands were involved in 110(62.5%) and minor groups of salivary glands were involved in 66(37.5%) of them (Table 2).

Table 2 clinical characteristics of patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

Variable	Category	Frequency	Percent
Clinical presentation	Swelling + other ssx	59	33.5
	Swelling only	117	66.5
Duration	≤6 months	53	30.1
	6–24 months	76	43.2
	>24 months	47	26.7
Size	≤5cm	135	76.7
	>5cm	41	23.3
Site	Minor SG	66	37.5
	Major SG	110	62.5

5.3. Histopathologic Patterns of Salivary gland lesions

From a total of 176 SGLs, 135(76.7%) were neoplastic and the remaining 41(23.3%) were non-neoplastic lesions. Among the neoplastic lesions, more than half, 72(53.3%) were malignant and 63(46.7%) were benign. Regarding specific histologic diagnosis, 37(51.4%) malignant lesions were MEC, 17(23.6%) were AdCC, 6(8.3%) were ACC, 3(4.2%) were CaExPA and 9(12.5%) were other less frequent and unspecified malignant lesions. Out of a total 63 benign lesions, 50(79.4%) were PA, and the remaining were 2 cases of WT, 2 cases of BCA, 2 cases of CcA and 7 cases of unspecified benign lesions. About two-thirds of non-neoplastic lesions were cases of sialadenitis 25(61%), and the remaining were non-neoplastic cysts 11(26.8%) and other miscellaneous non-neoplastic lesions 5(12.2%) (Table 3).

Table 3 Frequency distribution of histopathologic diagnosis in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

Variable	Category	Frequency	Percent
SGL	Non neoplastic	41	23.3
	Neoplastic	135	76.7
Neoplastic lesion	Benign	63	46.7
	Malignant	72	53.3
Malignant lesion	MEC	37	51.4
	AdCC	17	23.6
	ACC	6	8.3
	CaExPA	3	4.2
	Others	9	12.5
Benign lesion	PA	50	79.4
	WT	2	3.2
	BCA	2	3.2
	CcA	2	3.2
	Others	7	11.1
Non neoplastic lesion	Sialadenitis	25	61.0
	Cysts	11	26.8
	Others	5	12.2

5.3.1. Histopathologic patterns of SGLs in relation to sex of the patients

In this study, both the neoplastic (73 males and 62 females) and non-neoplastic (23 males and 18 females) groups of SGLs were slightly more common in male patients (Figure 2a). Among the neoplastic SGLs, benign lesions were slightly more frequent in females (33 females, 30 males), whereas malignant lesions were more frequent in males (43 males, 29 females) (Figure 2b).

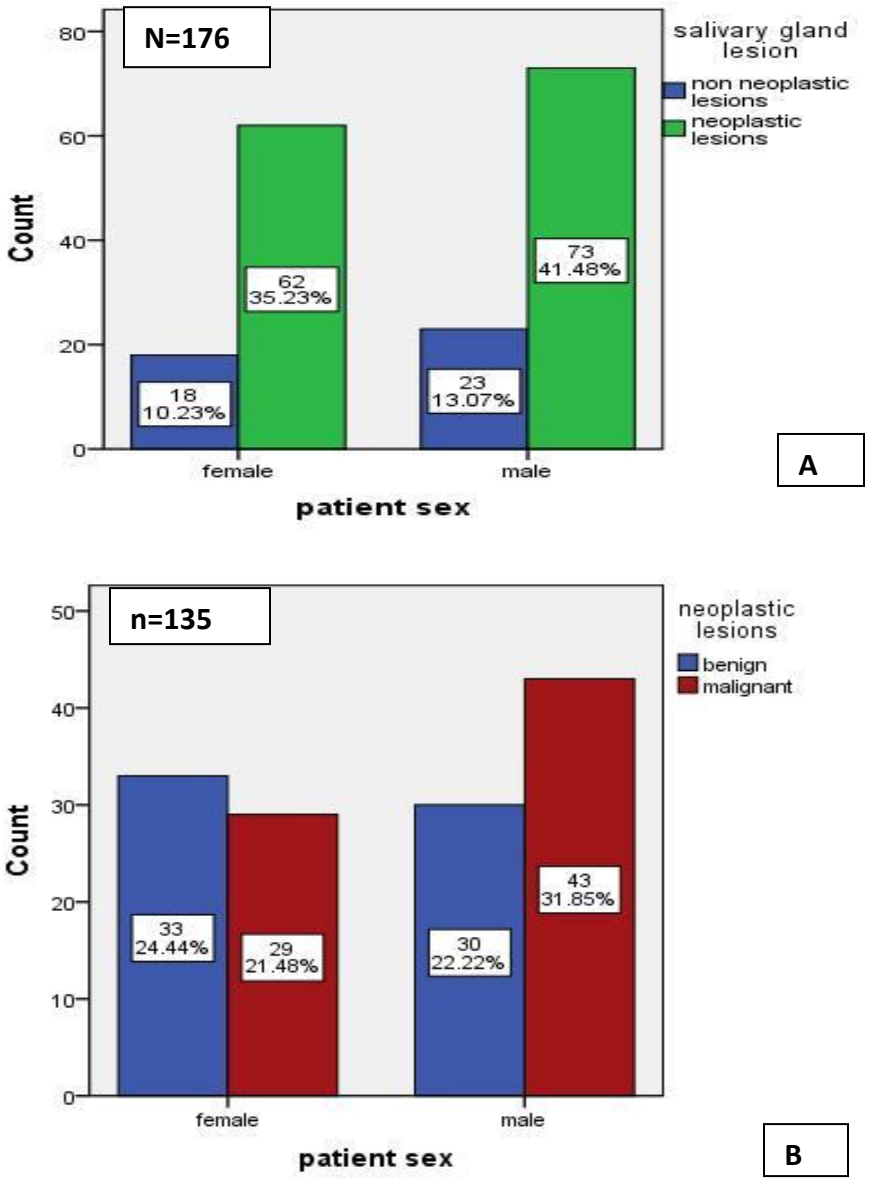

Figure 2 Distribution of neoplastic and non-neoplastic (A), and benign and malignant (B) SGLs by gender in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020.

Among specific malignant histopathologic diagnosis MEC was by far the most frequent diagnosis in both gender (20 cases, 54% in males, 17 cases, 46% in females); followed by AdCC (9 cases, 52.9% in females, 8 cases, 47.1% in males). ACC was diagnosed in 4 male and 2 female patients. From benign specific histopathologic diagnosis, PA was the single most frequently diagnosed SGLs (50 cases); 26 cases, 52% in females and 24 cases, 48% in male patients. Regarding the non-neoplastic groups of lesions, both sialadenitis and cysts were more frequent in male patients (16 cases, 64% and 6 cases, 54.5% respectively) (table 4).

Table 4 Distribution of specific histologic types of SGLs by gender in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

SGL	Category	Sex	
		Female	Male
Malignant lesions	MEC	17	20
(n=72)	AdCC	9	8
	ACC	2	4
	CaExPA	0	3
	Others	1	8
Benign lesions	PA	26	24
(n=63)	WT	1	1
	BCA	1	1
	CcA	2	0
	Others	3	4
Non neoplastic lesions	Sialadenitis	9	16
(n=41)	Cysts	5	6
	others	4	1

5.3.2. Histopathologic patterns of SGLs in relation to age of the patients

Neoplastic lesions were more frequent in patients with age category 21-40 years (64 cases, 47.4%) with the median age of 35, however the non-neoplastic lesions were more frequently diagnosed in patients with the age of 20 years or younger (18 cases, 43.9%) with the median age of 25 years (Figure 3).

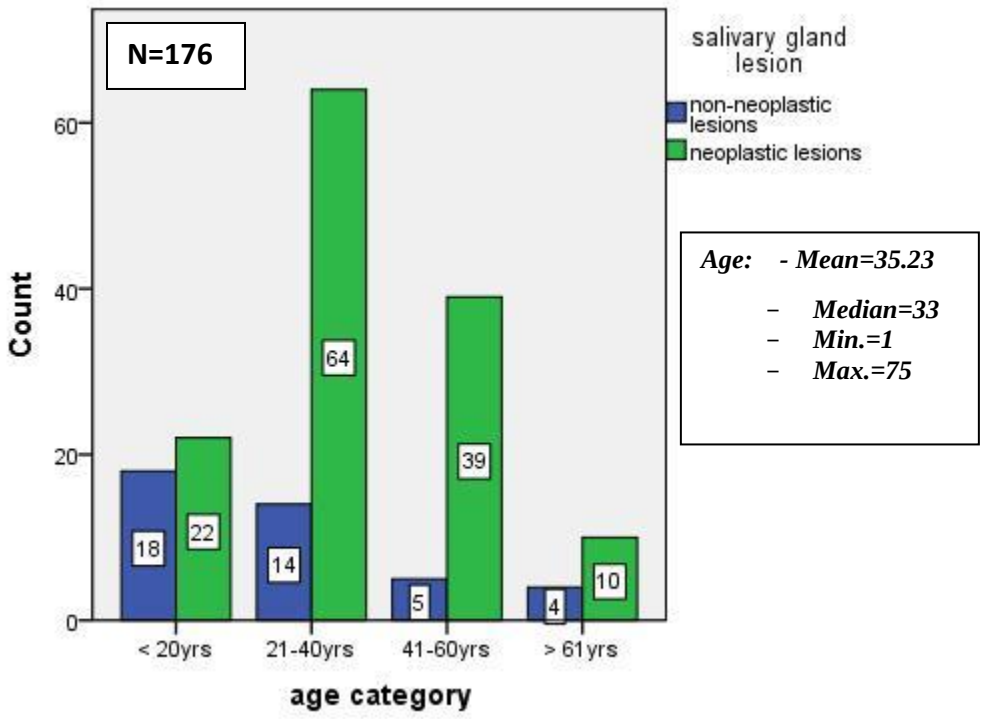

Figure 3 Distribution of SGLs by age category in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020.

The patients in the age category of 21-40 years had the highest number of both malignant and benign SGLs (32 cases each, 44.4% of malignant lesions and 50.8% of benign lesions). The lowest frequencies of both benign and malignant category of neoplastic lesions were observed in patients with the age above 60 years (5 cases each, 7.9% of benign and 6.9% of malignant lesions). The median age for patients with malignant lesions (40 years) was higher than that of patients with benign SGLs (30 years) (Figure 4).

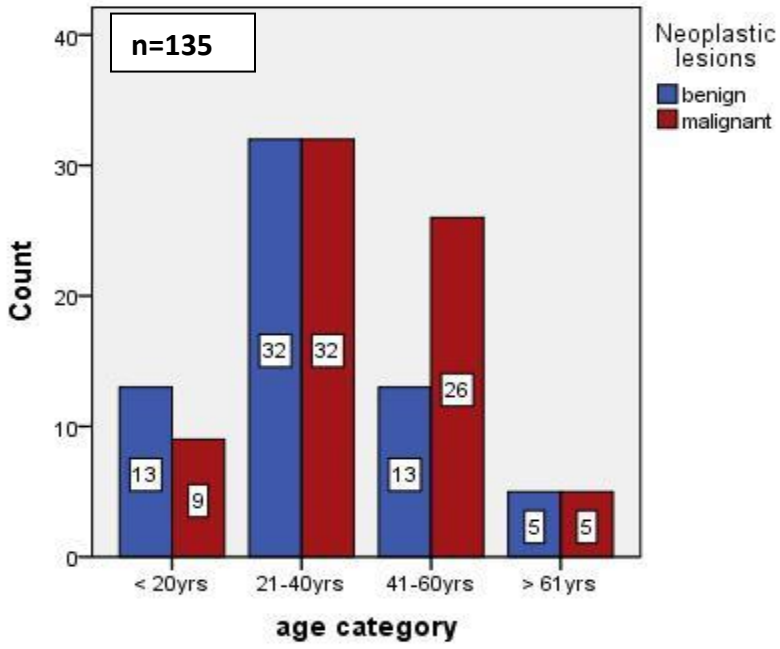

Figure 4 Distribution of neoplastic SGLs by age category in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020.

Among specific histopathologic diagnoses, the highest number of MEC (17, 45.9%), AdCC (10, 58.8%), PA (25, 50%) and sialadenitis (12, 48%) were recorded in the patients with the age category of 21-40 years (Table 5).

Table 5 Distribution of specific histologic types of SGLs by age category in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

SGL	Category	Age category			
		≤20y	21-40y	41-60y	> 60y
Malignant lesions	MEC	5	17	12	3
(n=72)	AdCC	1	10	6	0
	ACC	1	3	1	1
	CaExPA	1	1	1	0
	Others	1	1	6	1
Benign lesions	PA	11	25	11	3
(n=63)	WT	0	0	1	1
	BCA	0	1	1	0
	CcA	0	2	0	0
	Others	2	4	0	1
Non neoplastic lesions	Sialadenitis	5	12	4	4
(n=41)	Cysts	10	1	0	0
	others	3	1	1	0

5.3.3. Histopathologic patterns of SGLs in relation to clinical presentation

Overall significant majorities of patients with SGLs were presented with swelling/mass only (117 cases, 66.5%) while 59 (33.5%) of them presented with swelling and at least one additional clinical sign or symptom. Among the patients with neoplastic lesions 92(68.1%) were presented with swelling only, while 43(31.9%) of them had at least one additional sign or symptom. Regarding patients with the non-neoplastic groups of lesions, more than half (25 cases, 61%) were presented with swelling/mass only. From 63 patients with benign SGLs 54(85.7%) were presented with swelling/mass only; similarly, 38(52.8%) of patients with malignant SGLs had only swelling/mass at presentation. For the specific types of histopathologic diagnosis, 44(88%) patients with PA, 9(52.9%) patients with AdCC, 19(51.4%) patients with MEC were presented with swelling/mass only. On the other hand, 16(64%) patients with sialadenitis had only swelling/mass at presentation (Table 6).

Table 6 Distribution of specific histologic types of SGLs by clinical presentation in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

SGL	Category	Presentation	
		Swelling/mass only	Swelling with other SSx
Malignant lesions (n=72)	MEC	19	18
	AdCC	9	8
	ACC	3	3
	CaExPA	1	2
	Others	6	3
Benign lesions (n=63)	PA	44	6
	WT	2	0
	BCA	2	0
	CcA	2	0
	Others	4	3
Non neoplastic lesions (n=41)	Sialadenitis	9	16
	Cysts	11	0
	others	5	0

5.3.4. Histopathologic patterns of SGLs in relation to duration of the lesion

Overall, most of the patients with SGLs had the disease for about 6-24 months duration (76 cases, 43.2%). Accordingly, 33(52.4%) of patients with benign lesions, and 36(50%) of patients with malignant lesions had the lesions for 6-24 months duration. Regarding those patients with the non-neoplastic SGLs, 25(61%) of them were presented with the duration of lesions ≤6 months (Table 7).

Table 7 Distribution of specific histologic types of SGLs by duration of the lesions in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

SGL	Category	Duration		
		≤6 months	6-24 months	> 24 months
Malignant lesions	MEC	14	18	5
(n=72)	AdCC	5	9	3
	ACC	1	3	2
	CaExPA	1	1	1
	Others	3	5	1
Benign lesions	PA	2	28	20
(n=63)	WT	0	2	0
	BCA	1	0	1
	CcA	0	1	1
	Others	1	2	4
Non neoplastic lesions	Sialadenitis	18	3	4
	Cysts	6	1	4
(n=41)	others	1	3	1

5.3.5. Histopathologic patterns of SGLs in relation to size of the mass/lesion

Out of the 176 patients with recorded size of the mass, 135(76.7%) had a measurement ≤5cm. Regarding the sub-category of SGLs, 39(95.1%) of patients with non-neoplastic lesions, 50(79.4%) of patients with benign lesions and 46(63.9%) of patients with malignant lesions presented with a mass measuring ≤5cm (Table 8).

Table 8 Distribution of specific histologic types of SGLs by size of the lesions in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

SGL	Category	Size	
		≤5cm	>5cm
Malignant lesions	MEC	26	11
(n=72)	AdCC	8	9
	ACC	5	1
	CaExPA	0	3
	Others	7	2
Benign lesions	PA	38	12
(n=63)	WT	2	0
	BCA	2	0
	CcA	2	0
	Others	6	1
Non neoplastic lesions	Sialadenitis	24	1
	Cysts	10	1
(n=41)	others	5	0

5.3.6. Histopathologic patterns of SGLs in relation to anatomic site

Generally, both neoplastic and non-neoplastic SGLs were more frequent in major salivary glands (75 cases, 55.6% of neoplastic and 35 cases, 85.4% of non-neoplastic lesions). Regarding the sub-category of neoplastic SGLs, benign lesions were more frequent in major salivary glands (43 cases, 68.2%) while malignant lesions were diagnosed more frequently in minor groups salivary glands (40 cases, 55.6%). Among the specific histopathologic diagnoses; higher number of cases of AdCC (9 cases, 53%), PA (30 cases, 60%), and sialadenitis (24 cases, 96%) were found in major salivary glands whereas higher number of MEC (24 cases, 64.9%) were recorded in minor salivary glands (Table 9).

Table 9 Distribution of specific histologic types of SGLs by anatomic site in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

SGL	Category	Site of salivary gland	
		minor	major
Malignant lesions (n=72)	MEC	24	13
	AdCC	8	9
	ACC	1	5
	CaExPA	1	2
	Others	6	3
Benign lesions (n=63)	PA	20	30
	WT	0	2
	BCA	0	2
	CcA	0	2
	Others	0	7
Non neoplastic lesions (n=41)	Sialadenitis	1	24
	Cysts	5	6
	others	0	5

Regarding the specific glands, parotid gland was the most common site of to be involved (54 cases, 30.7%) followed by submandibular gland (52 cases, 29.5%) and palate (25 cases, 14.2%), which was the most commonly involved site of minor groups of salivary glands (Table 10).

Table 10 Distribution of SGLs by specific anatomic site in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

Variable	Category	Subcategory	Frequency	Percent
site	Major group SG	Parotid	54	30.7
		Submandibular	52	29.5
		Sublingual	4	2.3
	Minor group SG	Palate	25	14.2
		Buccal mucosa	9	5.1
		Lip	8	4.5
		Flour of mouth	7	4.0
		Other	17	9.7

5.4. Determinants of Salivary gland lesions

On bivariable logistic regression, age of the patients, duration, size, and anatomic site of the lesion had statistically significant association with SGLs at 0.25 levels of significance. Accordingly, we have included in multivariable logistic regression (Table 11).

Table 11 Determinants of SGLs in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

Variable	Category	SGL		Crude OR (95%CI)	p-value
		Neoplastic	Non-neoplastic		
Age	≤20 y	22	18	1.0	
	21-40 y	64	14	3.740(1.599-8.751) *	0.002
	41-60 y	39	5	6.382(2.082-19.563) *	0.001
	>60 y	10	4	2.045(0.548-7.628)	0.287
Duration	≤6 mo	28	25	1.0	
	6-24 mo	69	7	8.801(3.417-22.671) *	0.000
	>24 mo	38	9	3.770(1.525-9.317) *	0.004
Size	≤5 cm	96	39	1.0	
	>5 cm	39	2	7.922(1.823-34.417) *	0.006
Site	Minor	60	6	1.0	
	Major	75	35	0.214(0.085-0.543) *	0.001

Note: *=significantly associated at p<0.05, 1.0=reference

On multivariable logistic regression age, anatomic site, duration and size of the lesion remained significantly associated with SGL.

Those patients within the age group of 21-40 had about five folds [AOR=5.172, 95% CI (1.696-15.776)], those within the age group of 41-60 had more than four and half folds [AOR=4.534, 95% CI (1.087-18.907)] and those with age > 60 had about seven times [AOR=6.899, 95% CI (1.185-40.147)] increased odds of neoplastic SGLs compared to those patients with age ≤ 20years.

Regarding duration of the lesion, those patients with duration of the lesion more than 24 months were associated with more than twelve-folds [AOR=12.479, 95% CI (3.433-45.356)] increased odds of neoplastic SGLs when compared to those patients with duration of the lesion ≤6months.

Size of the lesion greater than 5 cm had more than nineteen times [AOR=19.486, 95% CI (3.371-112.639)] increased odds of neoplastic SGLs as compared to size ≤ 5 cm.

For anatomic site, those patients having a lesion in major groups of salivary glands were 94.4% [AOR=0.056, 95% CI (0.014-0.224)] less likely to have neoplastic SGLs as compared to those patients with a lesion in minor groups of salivary glands (Table 12). All the above associations were statistically significant at the $p < 0.05$ and the overall model fitness was tested by Hosmer-Lemeshow goodness of fit test at $p > 0.05$ and showed $p=0.508$.

Table 12 Determinants of SGL, after adjusting to cofounders, in patients with histopathologic reports of SGLs at JUMC, Jimma, South-Western Ethiopia, Ethiopia; during the last five years, from the year 2016 to 2020 (N=176).

Variable	Category	SGL		COR(95%CI)	AOR(95%CI)	p-value
		Neopl.	N-neopl.			
Age	≤20 y	22	18	1.0	1.0	
	21-40 y	64	14	3.740(1.599-8.751)*****	5.172(1.696-15.776)*	0.004
	41-60 y	39	5	6.382(2.082-19.563) *****	4.534(1.087-18.907)*	0.038
	>60 y	10	4	2.045(0.548-7.628)	6.899(1.185-40.147)*	0.032
Duration	≤6 mo	28	25	1.0	1.0	
	6-24 mo	69	7	8.801(3.417-22.671)*****	32.847(8.348-129.240)*	0.000
	>24 mo	38	9	3.770(1.525-9.317)*****	12.479(3.433-45.356)*	0.000
Size	≤5 cm	96	39	1.0	1.0	
	>5 cm	39	2	7.922(1.823-34.417)*****	19.486(3.371-112.639)*	0.001
Site	Minor	60	6	1.0	1.0	
	Major	75	35	0.214(0.085-0.543)*****	0.056(0.014-0.224)*	0.000

Note: *=significantly associated at p<0.05, 1.0=reference

CHAPTER SIX: DISCUSSION

The present study discloses important information on the SGLs and factors associated with neoplastic lesions. The findings of this study showed that males are more frequently affected by SGLs than females. This finding is consistent with reports of literatures from Tanzania, Nigeria, Nepal, India and Croatia in which males are predominantly affected(14,23,27,34,41). However, this finding is against the traditional female predominance of SGTs especially in African populations(13,35–37). This discrepancy may be attributed to the fact that significantly small number of cases and only neoplastic ones were studied in most of the literatures.

The overall mean age was 35.23 ± 17.079 years, with 2nd and 3rd decades having the highest frequency of benign lesions while the 3rd and 4th decades had the highest number of malignant lesions. These findings are similar with that of Kenyan and Nigerian studies(13,34). Relatively higher values of mean age and age at peak incidence for categories of SGLs were reported in many literatures from western countries(27,33). These differences may be due to the difference in life expectancy of individuals among societies and the usual statement of lower age than actual age in our communities.

Painless slowly growing (≤ 5cm) swelling/mass of 6 to 24 months duration was the dominant clinical presentation of SGLs in our study; which is in line with study done by M.I.Masanja and his colleagues from Tanzania(14). Additional signs and symptoms like pain, ulceration and others were frequently reported in patients with malignant SGLs both in current and Tanzanian study. The findings are also in line with other African studies from Sudan and Libya(36,37).

The common site of SGLs as per this study was major salivary glands (62.5%) in general and parotid gland (30.7%) in particular whereas palate (14.2%) was the most common site to be involved among minor groups salivary glands. These findings are in line with reports by Ergisho B.(22) and with those from Ugandan study(35). There are also many literatures from other continents with similar findings(18,32).

The vast majority of SGLs diagnosed by biopsy specimen over the last 5 years at the current study area were neoplastic lesions (76.7%). Malignant lesions were slightly more frequent than benign ones with an M:B ratio of 1.1:1. Reports from Sudanese, Ugandan and

Yemenis studies are in line with our findings(19,21,35). However, the finding is inconsistent with the well-established predominance of non-neoplastic lesions over neoplastic lesions as well as benign lesions over malignant ones. The findings from other African countries and mainly from the western nations showed the predominance of benign lesions(18,27,28,33). This inconsistency might be attributed to the difference in utilization of histopathologic services to evaluate SGLs. Due to limited resource availability in our setup, selected cases, mainly malignant and suspicious lesions, are biopsied for histologic evaluation. The other contributing factors can be related to the difference in the health services seeking behavior which is probably lower in our societies especially for painless slowly growing benign masses. But this has to be studied in depth by randomized case-controls to find out the real scenario.

As per this study the commonest type of malignant SGLs was MEC (51.4%), whereas the commonest benign lesion was PA (79.4%) and the commonest non-neoplastic lesion was chronic sialadenitis (61%). These findings are consistent with reports from Libyan, Iran, Nepal and many Indian studies(18,23,36,38,41). However, a significant amount of literature from various parts of the world found that AdCC is the most common malignant SGT(13,21,29,34,39,40). The other unexpected finding in the current study was the higher number of MEC cases in the minor salivary glands as compared to that of the major salivary glands. Similar finding was reported by studies from Libya, Brazil and Iran(32,36,38). However, the finding is inconsistent with the common finding by many literatures from different countries including Uganda, Tanzania, Ghana, India and Nepal in which higher prevalence of MEC was found in major groups salivary glands compared to minor ones(14,18,28,35,41). These discrepancies may be due to small sample size utilized in most of the studies. The other source of these differences may be related to possible false positive or false negative diagnosis as only histomorphological features are used for diagnosis in most of the studies including the current study. Moreover, the differences in genetic makeup and environmental factors among societies can have some contributing effects; which have to be examined in the future multidisciplinary and large-scale studies.

Another interesting finding of this study was the presence of statistically significant association between SGLs and some of the demographic as well as clinical factors. Accordingly, age of the patient, duration, size and site of the lesions were among

determinants of SGLs. Increasing odds of neoplastic SGLs were observed with increasing value of age, duration and size as well as with sites in minor salivary glands which was significant at $p < 0.05$.

Age greater than 20 years was associated with more than fourfold increased odds of neoplastic SGLs as compared to those younger than 20 years. In line with this finding, older age group was significantly associated with neoplastic SGLs in Kenyan and Nigerian studies but they didn't report the strength of the association(13,34).

Duration of the lesions longer than 6 months was associated with more than tenfold increased odds of neoplastic SGLs when compared to duration less than 6 months. Study from Tanzania suggests presence of some association with longer duration and neoplastic SGL, however the strength of association was not statistically measured(14).

The size of the lesions greater than 5 cm was also associated with more than nineteen times increased odds of neoplastic SGLs which is a consistent finding with that of da Silva from Brazil(26).

On the other hand, major salivary glands, as the site of the lesions, are associated with decreased likelihood of neoplastic SGLs. This finding is somehow in line with the findings from Nigerian and Iranian studies (34,38). The finding is also consistent with the traditional dominance of minor salivary glands in cases of neoplastic lesions particularly malignant ones and well established WHO reports (4,6).

Limitations of the study

One of the major challenges in this study was, since the study was conducted on secondary data some information was not complete which enforced us to exclude significant number of cases of SGLs. Due to retrospective nature of the data limited sociodemographic and clinical information was available to test for determinants of SGLs. The other shortcoming was the application of merely histomorphological diagnosis as a final diagnosis due to unavailability of important ancillary tests like IHC and molecular tests to confirm a specific diagnosis.

CHAPTER SEVEN

Conclusion

Neoplastic SGLs were more frequently diagnosed than the non-neoplastic lesions over the last 5 years at JUMC. Predominantly, young adult male patients were affected. Malignant lesions were slightly more common than benign ones. Slowly growing painless swelling was the most common clinical presentation of SGLs. Major salivary gland, particularly parotid gland, was the most common site of SGLs. Increasing age beyond 20 years, duration of lesions longer than 6 months, larger size greater than 5cm and minor groups of salivary glands are significantly associated with increased odds of neoplastic SGLs.

Recommendation

Record keeping and inter departmental communications should be well established and closely monitored to maximize data utilization in our institution.

Community awareness creation should be done through all available means to improve health service seeking behavior and avoid late presentation.

Treating physicians should have high index of suspicion and sent patients with a SGL for histopathologic diagnosis especially in adults with larger mass in one of the minor salivary gland areas.

Jimma University institute of health and other concerned bodies should work together to avail at least some of commonly used ancillary tests and IHC markers.

Finally, I would like to recommend larger scale study in this area incorporating more clinicopathologic parameters to evaluate additional associated factors with SGLs, particularly with malignant lesions.

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Annex

Data collection tool (Checklist) to study the histopathologic patterns of salivary gland lesions and associated factors.

S.No	**Variables**	**Choices**
1.	Biopsy no	Unique for each case
2.	Year of biopsy	A)2016 B)2017 C)2018 D)2019 E)2020
3.	Age	In years
4.	Sex	Male(M) Female(F)
5.	Clinical presentation	As stated in the records
6.	Duration of the lesion	In months
7.	Anatomic site	A. Parotid B. Submandibular C. Sublingual D. Minor salivary gland
8.	Size of the lesion/mass	In centimeters
9.	Histopathologic pattern	Final histologic diagnosis