



Original article

Primary Malignant Tumors of Oral and Maxillofacial Region in Libyan Population: A single institution experience of 171 cases

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ABSTRACT:

background: Globally, a significantly high rate of mortality was caused by oral cancer; however, epidemiological data of oral cancer is still scanty, particularly in Arab countries. This retrospective study was designed to provide a systematic analysis of the histological subtypes of oral and maxillofacial malignant neoplasms in Libyan population during two decades, and to compare the results with previous reports from Libya and other countries.

Method: data were gathered using patients medical record and biopsy files, and the histological slides were reevaluated. The tumors were classified according WHO criteria (2017).

Results: Carcinoma was found in 145 patients, forming (84.7%) of all the malignant oral and maxillofacial neoplasms, followed by lymphoma and sarcoma (6.4%), and neural crest cell tumours (2.3%). Males were more affected than females at a ratio of 1.3:1. Most of the patients (70.8%) were above the age of 40 with a mean age of 51.7 years old at the time of the diagnosis. Only 1% of the malignant neoplasms were odontogenic in origin. Squamous cell carcinoma (67.5%) was the most common epithelial neoplasm, followed by mucoepidermoid carcinoma (9.7%) and adenoid cystic carcinoma (4.1%). The tongue was the most common site for squamous cell carcinoma (41.1%), followed by buccal mucosa (16.8%).

Conclusion: compared to previous reports from eastern and some western countries; the prevalence of malignant neoplasms of oral and maxillofacial region in Libyan populations is considerably low.

Keywords:

Libyan population, malignant, oral and maxillofacial tumors, squamous cell carcinoma.

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INTRODUCTION:

Worldwide, more deaths were estimated to be caused by cancer compared to strokes and coronary heart diseases.¹ According to the GLOBOCAN (Global cancer incidence, mortality and prevalence) 2018, there are continuous global demographic and epidemiologic changes raising the expectations of

increasing cancer burden over the next decades, this estimate is as high as 20 million new cancer cases are expected to emerge by the year 2025.² The estimation presented by the GLOBOCAN 2018 was 18.1 million new cases, and 9.6 million deaths which is significantly high compared to 14.1 and 8.2 million respectively in

2012, and this impact will be more pronounced in countries of middle and low income.² Head and neck cancer represents the 6th-9th most common cancer, with squamous cell carcinoma (SCC) being the most common oral malignancy forming about 80-90% of all malignant neoplasms of oral cavity.³ The estimated annual mortality due to oral SCC is incredibly high (40-50%), this burden is expected to increase to almost two folds by 2030.⁴

To date, research about malignant neoplasms of orofacial region in Arab countries in general and Libya in particular is relatively lacking, and the epidemiological data is still scanty in this part of the world. One study was conducted during the period of (1991- 2007) reviewing all the cases of orofacial malignancy that have been diagnosed at faculty of dentistry in Benghazi-Libya, and revealed a lower incidence of oral cancer in Libya compared to other countries.⁵ The aim of this study is to investigate the relative frequency of primary malignant tumors in oral and maxillofacial region in the population of Benghazi over the last two decades, and to determine the most common malignant neoplasm during the study period. The results will be then compared to a previous study in Libya and other studies from some neighbouring Arab countries, in addition to parts of eastern and western countries.

METHODS:

The study was designed as a retrospective review of all the cases diagnosed with primary malignant neoplasms of orofacial region between the year 2000 and 2020 at the Department of Oral Medicine, Pathology, Diagnosis and Radiology- Faculty of Dentistry, Benghazi University. A total of 2036 patients with oral and maxillofacial malignant tumors were reviewed using their medical records and biopsy files; the gathered information included patient's age, gender and the specific site of the lesion. The histological slides were re-evaluated by the authors to confirm the diagnosis and to grade particular tumors according to the World Health Organization classification (WHO 2017).⁶ All the cases were analysed in relation to age, gender, site, and

histological subtype of the lesion. Exclusion criteria: Metastasized tumours, and those with controversial diagnosis were excluded.

For statistical analysis, all descriptive and quantitative data analysis and graphs were performed using the Statistical Package for the Social Sciences (SPSS) software, version 21.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics was used for the variables including: age, gender, and site of the lesion. Chi-square test was used to assess the significance, and the level of statistic difference was set at < 0.05.

RESULTS:

During the 20-years period, a total of 2036 specimens were histopathologically evaluated; of these, 171 (8%) specimens were diagnosed as malignant tumors. To provide comprehensive understanding; the malignant neoplasms were broadly classified according to their tissue of origin into three main categories: Carcinomas, sarcomas, lymphomas, and neural crest cell tumors. Carcinomas constituted the highest value of all the malignant lesions (84.7%), followed by lymphomas and sarcomas with an equal percentage (6.4%). Malignancies that have been histologically classified as neural crest cell tumors represent the smallest proportion of the study sample (2.3%). Gender based analysis revealed that males 57% were more affected than females 43%; with male to female ratio being 1.3:1.

Most of the patients diagnosed with primary malignant oral and maxillofacial neoplasms were of older age group (70.8% were above the age of 40), with mean age of the incidence being 51.7 years old. Only 6% of malignant tumors were found in patients below the age of 20, and about 2% were found in children aging less than eleven years. Patients with a histological diagnosis of carcinoma were older than those with sarcoma and lymphoma ($p < 0.05$). (Table1) (Figure 1)

Squamous cell carcinoma (SCC) forms the bulk of the epithelial neoplasms (67.5%), followed by mucoepidermoid carcinoma (MEC) (9.7%), and adenoid cystic carcinoma (AdCC) (4.14%). About 99% of the tumors were non odontogenic.

Table (1) Malignant tumors according to age and sex 2000-2020

Diagnosis	All cases	%	Cases with known age	Age range (years)	Mean age	Age SD	No. of males	No. of females	M:F ratio
Carcinoma	145	84.7%	141	14-93	53.5	17.4	85	60	1.3:1
Sarcoma	11	6.4%	11	5-70	34.18	22.66	4	7	0.6:1
Lymphoma	11	6.4%	11	4-72	45.09	23.48	6	5	1.2:1
Neural crest	4	2.3%	4	30-85	58.33	27.53	2	2	1:1
Total	171	100					97	74	

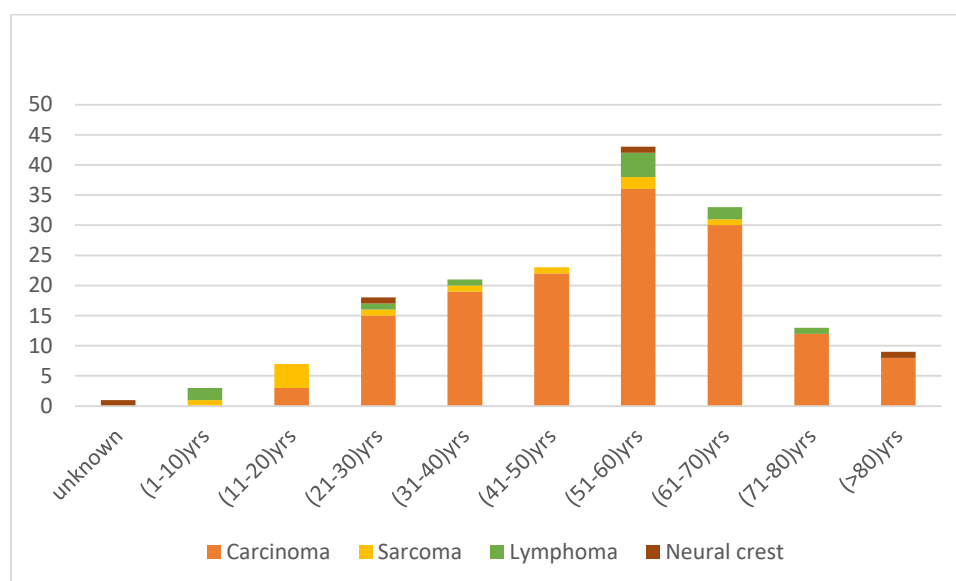


Figure (1) Age distribution of malignant oral and maxillofacial tumors

1. Carcinoma:

Carcinoma constituted about 7% (145 of 2036) of the total samples diagnosed during this period, and around 85% (145 of 171) of the malignant lesions. The patients ages ranged from 14-93 years (mean = 53.5 years), and most of them (74.9%) were aging 40 years or above. The peak age of incidence was during the sixth and the seventh decades of life. Males were slightly more affected than females at a ratio of (1.3:1).

Site related analysis revealed the following: Tongue (n = 41), (28.9%), cheek (n = 26) (18.3%) and palate (n= 18) (12.7%) were the most common sites.

Among the epithelial tumors, SCC (67.5%) was the most common neoplasm, forming about 57% of all the primary malignant tumors in the study sample, and around 5% of all the biopsied lesions during the study period. The mean age of the patients at presentation was 58 years and about 57% of them were males. (Figure 2)

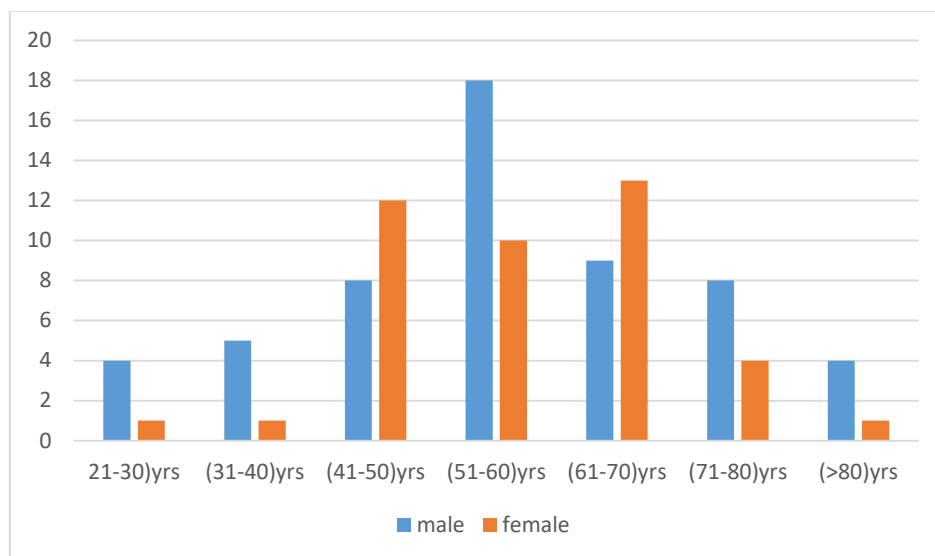


Figure (2) Age distribution of squamous cell carcinoma

The tongue was the most common site of SCC making about (41.1%), followed by the buccal mucosa (16.8%). Further analysis of the histological subtypes of SCC revealed that most of them were of a moderately differentiated type (43.6%). (Table2)

Salivary gland tumors constituted about 24% of the epithelial tumors, with the highest proportion being formed by MEC (40%), followed by AdCC (17%). The peak age of incidence was 31-40 years old. (Table 3)

Table (2) Site distribution of histological subtypes of squamous cell carcinoma

Anatomic Site	Well differentiated	Moderately differentiated	Poorly differentiated	Total (%)
Tongue	12	22	5	39 (41.1%)
Buccalmucosa	8	5	3	16 (16.8%)
Upper gingiva/ Alveolar ridge	3	4	4	11 (11.6%)
Lower gingiva/ Alveolar ridge	3	4	3	10 (10.5%)
Lower lip	3	4	1	8 (8.4%)
Palate	0	0	2	2 (2.1%)
Retromandibular area	1	2	0	3 (3.2%)
Floor of mouth	0	0	3	3 (3.2%)
Ventrum of tongue	0	1	0	1 (1.1%)
Upper lip	1	0	0	1 (1.1%)
Submandibular region	0	1	0	1 (1.1%)
Total	31	43	21	95

*The site of the lesion was unknown in three cases

Table (3) Age distribution of malignant salivary glands tumors:

Histological subtype/age	11-20	21-30	31-40	41-50	51-60	61-70	>80	Total (%)
MEC	0	4	7	0	1	2	0	14 (40%)
AdCC	0	0	2	1	0	2	1	6 (17.1%)
PLGA	0	2	1	0	2	0	0	5 (14.3%)
ACC	0	1	0	0	0	0	0	1 (2.9%)
CAexPA	1	2	1	0	0	1	0	5 (14.3%)
NOS	0	0	0	0	1	0	0	1 (2.9%)
Salivary duct Carcinoma	0	0	0	0	0	1	0	1 (2.9%)
PCAC	0	0	1	0	0	0	0	1 (2.9%)
Undifferentiated Adenocarcinoma	0	0	0	0	0	0	1	1 (2.9%)
Total	1	9	12	1	4	6	2	35 (100%)

PLGA: Polymorphous low grade adenocarcinoma, CAexPA: Carcinoma ex.pleomorphic adenoma, ACC: Acinic cell carcinoma, PCAC: Papillary cystic adenocarcinoma, NOS: Not otherwise specified, AC: Adenocarcinoma.

2. Lymphoma:

During the last two decades, about 0.54% (11 of 2036) of the biopsied lesions were diagnosed as lymphomas, and constituted 6.4% (11 of 171) of the total primary malignant neoplasms. Non-Hodgkin's lymphoma (54.6%) was more common than Hodgkin's lymphoma (45.5 %). Burkett's lymphoma was found in only two patients who were in their first decade of life, and accounted for 33% of all non-Hodgkin's lymphoma cases. About (36.4%) of the patients diagnosed with lymphomas presented with submandibular lymph node involvement.

3. Sarcoma:

Tumors of mesenchymal origin accounted for about 0.5% (11 of 2036) of the total biopsies done during the study period, and 6.4% (11 of 171) of the primary malignant neoplasms. The age of the patients ranged from 5 to 59 years, about 62.5% of the patients were below 20 years old, and most of them were in their second decade of life. Rhabdomyosarcoma and osteosarcoma were the most common, and each of them represented (36%) of the malignant mesenchymal lesions. The reminder was represented by three cases of different mesenchymal tumors; these are: chondrosarcoma, malignant fibrous histiocytoma, and granulocytic sarcoma. Each of them formed (9%) of all sarcoma cases.

4. Tumors of neural crest cells:

Neural crest cells tumors formed 2.3% of all malignant neoplasms of oral and maxillofacial region, and represented by four lesions; two of them were malignant melanomas affected two female patients aging 60 and 85, and two cases of olfactory neuroblastoma in two male patients aging 12 and 30.

DISCUSSION:

In light of the previously conducted study by Subhashraj *et al* in 2009 for the primary malignant orofacial tumors among the Libyan population over a period of 17 years from 1991 to 2007 at the Department of Oral and Maxillofacial Surgery-Benghazi University, which found that the incidence of oral malignancy was impressively low compared to other countries in Africa and some European countries, as this was considered the first report on primary malignant tumors of orofacial region in general and the incidence of oral cancer in particular, among the Libyan population.⁵ Therefore, we designed this retrospective review of all the cases diagnosed with primary malignant neoplasms of oral and maxillofacial region over the last two decades at the Department of Oral Medicine, Pathology, Diagnosis and Radiology, Faculty of Dentistry- Benghazi University to summarize and compare the prevalence of oral and maxillofacial malignant lesions in Benghazi, with detailed information regarding patient's age, gender, site of the lesion, as well as it's histological sub-type.

Primary malignant tumors constituted 8.17% of all the biopsied lesions during the last two decades, which seems to be close to that reported in Benghazi by Subhashraj *et al* in 2009.⁵ Most of the patients were above the age of 40; and most of them were older than those diagnosed with sarcoma or lymphoma ($P < 0.05$). Males were more affected than females by a ratio of 1.3:1, which is in agreement with previous reports worldwide.⁷

Amongst all the collected records, SCC was the most prevalent malignant neoplasm forming about 57% of all the malignant tumors of oral and maxillofacial region, which is relatively higher than

that recorded in 2009 (41%).⁵ In fact, this is an alarming indicator for the increased incidence of SCC among Libyan population, and further studies are required to investigate the reason beyond this trend. Similarly, 90% of the malignant oral lesions in Egypt were SCC; which is in agreement with the previous global reports on oral cancer.⁸ However, the percentage is much higher than that recorded in Libya, possibly due to the less frequently encountered risk factors; including smoking especially in women, consumption of spicy food as well as sun exposure,⁹ this is also the case in Iraq where 70 % of oral malignancy were SCC.¹⁰ In Jordan, the prevalence was also higher than that reported in our study (84%), and this could be explained by the wider use of Nargil or Shisha (water pipe) by both genders, beside cigarette smoking. In addition, about 17% of the patients in Jordan were alcohol drinkers¹¹ which is an unacceptable habit in Libya, both legally and socially. Similar percentage of SCC was reported in Yemen (84%), but with different associated risk factors; these were tobacco and Qat chewing which was recognized as a popular habit in Yemen,¹² and other eastern countries like Saudi Arabia.¹³

Males were more affected than female at a ratio of (1.3:1) which is consistent with previous reports.^{5,14} The reason beyond that could be the more likelihood of men to be exposed to carcinogens particularly smoking and alcohol drinking, which is considered more stigmatic in females, particularly in Arab populations. Even though, Yemen and Saudi Arabia showed greater percentage of oral SCC in women compared to Libya and other Arab countries. In fact, this was attributed to the popular habit of tobacco chewing (Shamma and Qat) which is socially accepted for females in these countries.¹³

Importantly, the reported prevalence of SCC in females in this study was reasonably higher (43%) than that recorded by Subhashraj and his colleagues in 2009 in Benghazi (37%),⁵ raising the question whether an underlying risk factor became more encountered in Libyan females over the last decade. This trend was also evident in the follow-up 2010 Benghazi cancer update report (BCR) where the incidence of oral cancer was almost doubled in females.¹⁵ Apart from smoking, Libyan women might be exposed to other risk factors; these include: poor oral hygiene which is well known to be greatly related to oral cancer in the absence of smoking and/or alcohol drinking,¹⁶ chronic irritation from teeth or faulty restorations which is considered either as an initiating or a modulating factor in carcinogenesis.¹⁷ Although there is no documented data regarding the dietary habits among the Libyan population which is considered another risk factor for oral cancer; Libyan

food is usually rich in fat and carbohydrates, with less vegetables and fruits. Green vegetables and fruits are considered as a rich source of beta-carotene and vitamin E which are proven to be strongly related to the prevention of carcinogenesis, and treatment of oral precancerous lesions.¹⁸ Another dietary risk factor that can be discussed to explain the increased prevalence of oral cancer among females is malnutrition and iron deficiency anemia. Anemia is a substantial indicator of cancer risk, particularly iron deficiency anemia which represents 50% of all the causes of anemia worldwide.¹⁹ However, in the absence of well documented data regarding the prevalence of iron deficiency anemia among Libyan women with oral cancer, it would be untimely to conceive its role as an etiological factor. Thus, research should be encouraged to conclude whether such relationship exists.

The role of human papilloma virus (HPV) in cancer pathogenesis has been an area of considerable research over the last years, and its relationship with oropharyngeal and SCC has been recently established although the exact underlying pathogenesis is still obscure.²⁰ Therefore, it would be important to consider HPV as a possible associated risk factor particularly in younger age group. If that could be proven, then vaccination would be an effective prophylactic measure. Furthermore, identification of viral particles in such patients indicates a more favorable prognosis compared to those with HPV negative lesions.^{20,21}

Most of the patients diagnosed with SCC were from older age group with 53.5 years old being the mean age at diagnosis, which is consistent with previous reports on oral cancer worldwide.^{22,23,24} However, recent studies demonstrated a significant change in this trend, where an increased incidence in oral cancer has been reported in younger age groups (< 35 years old) with relatively unclear associated risk factors.²⁵ Thus, HPV and changing dietary habits should be considered as possible etiological factors for oral cancer in young adults.

Site based analysis revealed that the tongue was the most common site of SCC (41.1%) which is consistent with previous reports from Libya,⁵ western countries,^{22,23} and some parts of North Africa and the Middle East.^{25,26} The situation is different in some eastern countries like Yemen, Saudi Arabia, and India where buccal mucosa, vestibule, and gingiva were the most affected areas by SCC. In fact, this is attributed to cultural variation in use of tobacco, as these countries showed greater preference of tobacco and betel nut chewing.^{13,16,27} The second most common site in our study was the buccal mucosa (16.8%), while the retromolar area and the floor of the mouth are the

least affected sites (3% and 1% respectively). These variations in certain anatomical sites among different countries could be explained by the different cultural behavior, geographical areas of particular countries, as well as the various genetic buildup of different ethnic groups.²⁸ Another factor which needs to be considered is that many patients seek treatment at advanced stages of the disease where it becomes difficult to identify the initial site of the lesion.

The most common histological subtype in our study was the moderately differentiated SCC, which might be associated with poor prognosis. However, other factors need to be considered; these include: size and site of the lesion, pattern of invasion, tumor margins, and lymph node involvement.¹²

Malignant odontogenic tumors are exceedingly rare lesions arising from the remnants of odontogenic tissues and odontogenic cysts in jaw bones.²⁹ In the current study, only two lesions were diagnosed as malignant odontogenic tumors, and both of them were malignant ameloblastoma. Malignant salivary gland tumors accounted for 21% of all the malignant lesions of oral and maxillofacial region, and 40% of them were mucoepidermoid carcinoma. This is almost consistent with most of the previous reports.^{5, 30, 31}

Lymphomas are a heterogeneous group of malignant tumors of the hematopoietic system characterized by the aberrant proliferation of mature lymphoid cells or their precursors.³² In this study, lymphomas accounted for about 6.4% of all malignant lesions, which is close to that reported in 2009,⁵ but relatively higher than that reported from Jordan¹¹, and Iran.³³ Non-Hodgkin's lymphoma was more common (54.6%) than Hodgkin's lymphoma (45.5%), which is in agreement with earlier reports from different countries.^{11, 33, 34} Burkitt's lymphoma is a very aggressive non-Hodgkin's lymphoma associated with Epstein -Barr virus.³⁵ About 33% of non-Hodgkin's lymphomas in our study were confirmed to be Burkitt's lymphoma, and were found in two patients aging less than 10 years. Of all cases of lymphomas, Burkitt's accounted for only 18%, which is significantly less than that reported from other African countries like Nigeria.³²

Sarcomas are aggressive malignant tumors of mesenchymal tissue, they are less common than carcinomas and more frequently seen in younger age group.^{11, 36} In our study, sarcomas form around 0.5% of all biopsied lesions and 6.4% of all malignant lesions. Most of the patients were below the age of 20, with almost no sex predilection. The most common sarcomas were rhabdomyosarcoma, and osteosarcoma with an equal percentage of (36%), which is in conformity with previous reports from Iran and Nigeria and.^{36, 37} The other mesenchymal tumors

found in this study were: chondrosarcoma, fibrous histiocytoma, and granulocytic sarcoma. Each of them formed about 9% of all the mesenchymal tumors.

Tumors of neural crest cells represented the smallest component in our study sample (2.3%); as they presented as two cases of melanoma, and two olfactory neuroblastoma cases. Oral malignant melanoma is a very rare malignant neoplasm of melanocytes forming only 0.5% of all oral malignancies and < 1% of all other melanomas.³⁸ Olfactory neuroblastoma is an uncommon malignant neoplasm arising in the olfactory epithelium at the roof of the nasal cavity, and usually associated with distance metastasis and poor prognosis.³⁹

In this study, despite the effort we made to include all the malignant oral and maxillofacial lesions in Libyan populations of Benghazi, even those biopsied at private sector; some cases could be missed. This includes patients who were diagnosed in other countries or in private hospitals, or those whom biopsies were not sent for histopathological examination, in addition to undiagnosed patients with malignancy. However, the data in this study is less likely to be affected by the previously mentioned conditions since majority of the specialized health care service is provided for free by the Ministry of Health and most of Libyan people are educated with a literacy rate about 80%.⁵

In conclusion, compared to neighboring Arab and western countries, Libya has got a lower incidence of oral and maxillofacial malignancy, which is in confirmatory with the previous report in Benghazi.⁵ This encourages more research to investigate the inherent etiological factors for this variation, particularly behavioral factors which were evident among eastern countries. A part from smoking, the role of HPV and diet should be further investigated, especially in women, and young nonsmokers. As a considerable proportion of SCC cases in this study were of well differentiated grade, research should be encouraged to investigate the presence of HPV particles in such lesions. If this was the case, then vaccination against HPV would be a helpful prophylactic measure. Considering its association with risk factors, oral cancer is a potentially preventable disease. Therefore, public education and motivation could effectively contribute in the reduction of the incidence of oral cancer.

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REFERENCES:

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* [Internet]. 2015 Mar 1 [cited 2020 Dec 12];136(5):E359–86.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* [Internet]. 2018 Nov [cited 2020 Dec 12];68(6):394–424.
3. Pires FR, Ramos AB, de Oliveira JBC, Tavares AS, de Luz PSR, dos Santos TCRB. Oral squamous cell carcinoma: Clinicopathological features from 346 cases from a single oral pathology service during an 8-year period. *J Appl Oral Sci*. 2013;21(5):460–7.
4. Gupta B, Johnson NW, Kumar N. Global Epidemiology of Head and Neck Cancers: A Continuing Challenge. *Oncology*. 2016;91(1):13–23.
5. Subhashraj K, Orafi M, Nair K V., El-Gehani R, Elarbi M. Primary malignant tumors of orofacial region at Benghazi, Libya: A 17 years review. *Cancer Epidemiol*. 2009;33(5):332–6.
6. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ. WHO classification of head and neck tumours. 4th ed., International Agency for Research on Cancer, 2017.
7. Neville, BW, Damm DD, Allen CM. and Chi AC. (2016) *Oral & Maxillofacial Pathology*. 4th Edition, WB Saunders, Elsevier, Missouri, 381–382.
8. Tandon P, Dadhich A, Saluja H, Bawane S, Sachdeva S. The prevalence of squamous cell carcinoma in different sites of oral cavity at our Rural Health Care Centre in Loni, Maharashtra - A retrospective 10-year study. *Wspolczesna Onkol*. 2017;21(2):178–83.
9. Labib N a, Elraghi H a, Shoman TH, Othman FH a. Epidemiology of Oral and Pharyngeal Cancer at the National Cancer Institute , Cairo. 2012;80(1):85–91.
10. Al-Rawi NH, Talabani NG. Squamous cell carcinoma of the oral cavity: A case series analysis of clinical presentation and histological grading of 1,425 cases from Iraq. *Clin Oral Investig* [Internet]. 2008 Mar [cited 2020 Nov 5];12(1):15–8.
11. Rawashdeh MA, Matalka I. Malignant oral tumors in Jordanians, 1991-2001. A descriptive epidemiological study. *Int J Oral Maxillofac Surg*. 2004;33(2):183–8.
12. Sawair FA, Al-Mutwakel A, Al-Eryani K, Al-Surhy A, Maruyama S, Cheng J, et al. High relative frequency of oral squamous cell carcinoma in Yemen: Qat and tobacco chewing as its aetiological background. *Int J Environ Health Res* [Internet]. 2007 Jun [cited 2021 Jan 26];17(3):185–95.
13. Al-Jaber A, Al-Nasser L, El-Metwally A. Epidemiology of oral cancer in Arab countries . *Saudi Med J*. 2016 Mar;37(3):249-55. doi: 10.15537/smj.2016.3.11388.
14. Andisheh-Tadbir A, Mehrabani D, Heydari ST. Epidemiology of Squamous Cell Carcinoma of the Oral Cavity in Iran. *J Craniofac Surg* [Internet]. 2008 Nov [cited 2021 Mar 6];19(6):1699–702.
15. El Mistiri M, Pirani M, El Sahli N, El Mangoush M, Attia A, Shembesh R, et al. Cancer profile in Eastern Libya: Incidence and mortality in the year 2004. *Ann Oncol* [Internet]. 2010;21(9):1924–6.
16. Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, et al. Oral cancer in southern India: The influence of smoking, drinking, paan-chewing and oral hygiene. *Int J Cancer* [Internet]. 2002 Mar 20 [cited 2021 Jan 30];98(3):440–5.
17. Piemonte E, Lazos J, Belardinelli P, Secchi D, Brunotto M, Lanfranchi-Tizeira H. Oral cancer associated with chronic mechanical irritation of the oral mucosa. *Med Oral Patol Oral y Cir Bucal* [Internet]. 2018 Mar 1 [cited 2021 Jan 30];23(2):e151–60.
18. Garewal HS. Beta-carotene and vitamin E in oral cancer prevention. *J Cell Biochem* [Internet]. 1993 [cited 2021 Feb 1];53(S17F):262–9.
19. Hung N, Shen CC, Hu YW, Hu LY, Yeh CM, Teng CJ, et al. Risk of cancer in patients with iron deficiency anemia: A nationwide population-based study. *PLoS One*. 2015;10(3):1–11.
20. Raj AT, Patil S, Gupta AA, Rajkumar C, Awan KH. Reviewing the role of human papillomavirus in oral cancer using the Bradford Hill criteria of causation. *Dis Mon*. 2019 Jun;65(6):155-163. doi: 10.1016/j.disamonth.2018.09.007.
21. Sugiyama M, Bhawal UK, Kawamura M, Ishioka Y, Shigeishi H, Higashikawa K, et al. Human papillomavirus-16 in oral squamous cell carcinoma: Clinical correlates and 5-year survival. *Br J Oral Maxillofac Surg*. 2007 Mar 1;45(2):116–2
22. Albuquerque R, López-López J, Marí-Roig A,

- Jané-Salas E, Roselló-Llabrés X, Santos JR. Oral tongue squamous cell carcinoma (OTSCC): Alcohol and tobacco consumption versus non-consumption. A study in a Portuguese population. *Braz Dent J*. 2011;22(6):517–21.
23. Bektas-Kayhan K, Karagoz G, Kesimli MC, Karadeniz AN, Meral R, Altun M, et al. Carcinoma of the tongue: A case-control study on etiologic factors and dental trauma. *Asian Pacific J Cancer Prev [Internet]*. 2014 [cited 2021 Feb 9];15(5):2225–9.
24. Rikardsen OG, Bjerkli IH, Uhlin-Hansen L, Hadler-Olsen E, Steigen SE. Clinicopathological characteristics of oral squamous cell carcinoma in Northern Norway: A retrospective study. *BMC Oral Health [Internet]*. 2014 Aug 18 [cited 2021 Feb 9];14(1):1–9.
25. Sherin N, Simi T, Shameena P, Sudha S. Changing trends in oral cancer. *Indian J Cancer [Internet]*. 2008 Jul 1 [cited 2021 Feb 13];45(3):93.
26. Kujan O, Farah CS, Johnson NW. Oral and oropharyngeal cancer in the Middle East and North Africa. *Transl Res Oral Oncol [Internet]*. 2017 Jan 27 [cited 2021 Feb 9];2:2057178X1769848.
27. Amarasinghe AAHK, Usgodaarachchi US, Johnson NW, Warnakulasuriya S. High prevalence of lifestyle factors attributable for oral cancer, and of oral potentially malignant disorders in rural Sri Lanka. *Asian Pacific J Cancer Prev*. 2018;19(9):2485–92.
28. Canto MT, Devesa SS. Oral cavity and pharynx cancer incidence rates in the United States, 1975-1998. *Oral Oncol*. 2002 Sep 1;38(6):610–7.
29. Goldenberg D, Sciubba J, Koch W, Tufano RP. Malignant Odontogenic Tumors: A 22-Year Experience. *Laryngoscope [Internet]*. 2004 Oct 1 [cited 2021 Feb 13];114(10):1770–4.
30. Jaber MA. Intraoral minor salivary gland tumors: A review of 75 cases in a Libyan population. *Int J Oral Maxillofac Surg [Internet]*. 2006 Feb [cited 2020 Nov 10];35(2):150–4.
31. Fitzpatrick PJ, Theriault C. Malignant salivary gland tumors. *Int J Radiat Oncol Biol Phys*. 1986;12(10):1743–7.
32. Ajayi OF, Adeyemo WL, Ladeinde AL, Ogunlewe MO, Effiom OA, Omitola OG, et al. Primary malignant neoplasms of orofacial origin: a retrospective review of 256 cases in a Nigerian tertiary hospital. *Int J Oral Maxillofac Surg*. 2007 May 1;36(5):403–8.
33. Shamloo N, Ghannadan A, Jafari M, Ahmadi S, Mortazavi H, Baharvand M. Head and Neck Lymphoma in an Iranian Population. *Iran J Otorhinolaryngol [Internet]*. 2017 Sep [cited 2021 Feb 14];29(94):261–7.
34. Storck K, Brandstetter M, Keller U, Knopf A. Clinical presentation and characteristics of lymphoma in the head and neck region. *Head Face Med [Internet]*. 2019 Jan 3 [cited 2021 Feb 14];15(1):1.
35. Molyneux EM, Rochford R, Griffin B, Newton R, Jackson G, Menon G, et al. Burkitt's lymphoma. In: *The Lancet*. Elsevier; 2012. p. 1234–44.
36. Atarbashi-Moghadam S, Emami Razavi AN, Salehi Zalani S. Prevalence of Head and Neck Sarcoma in a Major Cancer Center in Iran- A 10-Year Study. *Iran J Otorhinolaryngol*. 2019 Mar;31(103):97-102. PMID: 30989075; PMCID: PMC6449527.
37. Ajayi OF, Adeyemo WL, Ladeinde AL, Ogunlewe MO, Omitola OG, Effiom OA, et al. Malignant orofacial neoplasms in children and adolescents: A clinicopathologic review of cases in a Nigerian tertiary hospital. *Int J Pediatr Otorhinolaryngol*. 2007 Jun 1;71(6):959–63.
38. Singh D, Pandey P, Singh MK, Kudva S. Prevalence of malignant melanoma in anatomical sites of the oral cavity: A meta-analysis *J Oral Maxillofac Pathol*. Jan-Apr 2019;23(1):129-135. doi: 10.4103/jomfp.JOMFP_236_18.
39. Bailey BJ, Barton S. Olfactory Neuroblastoma: Management and Prognosis. *Arch Otolaryngol [Internet]*. 1975 Jan 1 [cited 2021 Mar 6];101(1):1–5.