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Histopathologic and Topographic Spectrum of Premalignant and Malignant Lesions of Oral Cavity and Oropharyngeal Region In A Tertiary Care Center In North India

[1]Reena Agarwal, MBBS, MD, Assistant Professor, Dept. of Pathology, Santosh Medical College, Gaziabad, Uttar Pradesh, India

[2]Bhawna Sethi, MBBS, MD, Associate Professor, Dept. of Pathology, SHKM,Government Medical College, Nalhar, Nuh, Haryana, India

[3]Sanjeev Sharma, MBBS, MD, Assistant Professor, Dept. of Anesthesia, Santosh Medical College, Gaziabad, Uttar Pradesh, India

[4]Shilpa Bairwa, MBBS, MD, Associate Professor, Dept. of Pathology, SHKM,Government Medical College, Nalhar, Nuh, Haryana, India

[5]Pawan Singh, MBBS, MD, Associate Professor, Dept. of Pathology, SHKM,Government Medical College, Nalhar, Nuh, Haryana, India

[6]Rahul Satarkar, MBBS, MD, Associate Professor, Dept. of Pathology, SHKM,Government Medical College, Nalhar, Nuh, Haryana, India

[7]Shivani Kalhan, MBBS, MD, Professor and Head, Dept. of Pathology, SHKM,Government Medical College, Nalhar, Nuh, Haryana, India

[8]S K Mathur, MBBS, MD, Senior Professor (Retired), Dept. of Pathology,Pt. B. D. Sharma University of Health Sciences,Rohtak, Haryana, India

Corresponding Author: Bhawna Sethi, MBBS, MD, Associate Professor, Dept. of Pathology, SHKM,Government Medical College, Nalhar, Nuh, Haryana, India

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Abstract

Background: Incidence of oral cancer varies between different parts of the world. Present study was conducted to examine the histopathological spectrum and topographic characterization of premalignant/malignant lesions of oral cavity/oropharyngeal region.

Methods: Five hundred oral biopsies/excision specimens of premalignant/malignant lesions were examined.

Results: 95.2% were diagnosed with malignant and 4.8% with premalignant lesions. The incidence of premalignant lesions was more in males (91.7%) than in females (8.3%). The age varied from 28 to 70 years with the maximum number of cases involving 31-40 years. Hyperplasia followed by moderate dysplasia, mild dysplasia and carcinoma in situ were the histological findings. The commonest site for premalignant lesions was the buccal mucosa (54.2%). The incidence of malignancy in males (88.66%) outnumbered females (11.34%). The age ranged from 22 to 90 years. Maximum number (29.4%) of malignant lesions were found in 51-60 years and minimum number (0.63%) in >80 years. The common age range for male and female patients was 41-50 years (30.6%) and 51-60 years (35.2%), respectively. The squamous cell carcinoma was the commonest

histological type with moderately differentiated grade encountered most frequently.

Conclusion: Malignant lesions outnumbered premalignant lesions. Both had predilection for males. The commonest site for premalignant and malignant lesions was buccal mucosa and base of tongue, respectively. Hyperplasia followed by moderate dysplasia was the commonest finding of premalignant lesions, and squamous cell carcinoma (moderately differentiated) was the commonest malignancy. Premalignant lesions occurred frequently before 40 years while carcinomas occurred in 5th to 6th decade.

Keywords: Leukoplakia, Premalignant conditions, Erythroplakia, Dysplasia, Squamous cell carcinoma

Introduction

Oral cancer is a major public health issue worldwide; it remains a highly lethal and disfiguring disease. It ranks 8th most common cancers among men and 14th among women.[1] In India, it is among the top three types of cancers [2] accounting for 4% of total body cancers in men and 2% of all cancers in females.[1]

The WHO defines the precancerous lesions and conditions as morphologically altered tissue or generalized states in which cancer is more likely to occur than its apparently normal counterpart.[3]

Kuffer et al [4] and Gale N [5] clinically classified the oral precursor lesions as leukoplakia (white patches), erythroplakia (red patches), erythroleukoplakia (mixed red and white patches) and distinguished them from precancerous conditions. The oral epithelial precursor lesions are histologically categorized into hyperplasia, dysplasia (mild, moderate and severe) and carcinoma-in-situ.[5] Histomorphologically, majority of leukoplakias do not show dysplasia and correspond to the hyperplasia category. Red and mixed lesions (speckled leukoplakia) show a higher frequency of dysplasia, often of higher grade. The majority of leukoplakias does not undergo malignant change and may even regress particularly if apparent aetiologic factors are removed.[5] The leukoplakia is further categorized as homogenous leukoplakia, nodular leukoplakia, speckled leukoplakia, and proliferative verrucous leukoplakia.

The precancerous conditions include oral submucous fibrosis, actinic keratosis, lichen planus, sideropenic dysphagia, and discoid lupus erythematosus.[6]

Oral malignant neoplasms are classified into squamous cell carcinoma and it's variants, malignant salivary gland tumors, malignant melanoma, hematolymphoid malignancies (lymphomas, Langerhans' cell histiocytoses, plasmacytoma, myeloid sarcoma), soft tissue tumors (Kaposi's sarcoma, lymphangioma), neoplasms of bone and odontogenic tumors, maxillary antral carcinoma, secondary (metastatic) neoplasms. [7]

Material and Methods

This study was conducted over a period of approximately two years (January 2007 to January 2009) and included a total of 500 oral biopsies and excision specimens of premalignant and malignant lesions submitted in the department of Pathology at PGIMS, Rohtak. After gross examination, the specimens received were subjected to routine paraffin sectioning at 4μ thickness. Histopathological diagnosis was established on routine hematoxylin and eosin staining of sections. Special histochemical stains like periodic acid Sciff (PAS), reticulin stain (Gordon and Sweet's technique) were applied wherever necessary.

Inclusion criteria

- Specimen of neoplasms of oral cavity & oropharynx, which was adequate and representative of the lesion.
- Properly resected surgical specimens like punch biopsies, incisional biopsies, wedge biopsies, surgical excision, radical neck dissection, hemiglossectomy,

hemimandibulectomy etc. from neoplasms of oral cavity & oropharynx were included.

Exclusion criteria

- Inadequately preserved specimens
- Specimens with handling artifacts
- Relevant clinical record (history, examination, exact site of lesion) not available or retrieved
- Non neoplastic lesion
- Neoplasms arising from nasopharynx and hypopharynx.
- Neoplasms arising from bones of jaws and odontogenic tumors.

For the topographic characterization of lesions that occur in this area, the oropharyngeal region is divided into the following regions: Lip, floor of mouth, oral tongue, buccal mucosa, gingiva (alveolar ridge), retromolar trigone, hard palate, base of the tongue, tonsillar area, soft palate and the pharyngeal walls. [8]

For the diagnosis of SCC, Squamous differentiation in the form of keratinization with variable "pearl" formation, and invasion into the surrounding tissue through basement membrane are the prerequisites. [9] As per Broder's classification, tumors were graded on the basis of degree of differentiation and keratinization of tumor cells into well differentiated tumors (Grade I)– 75-100% of cells are differentiated, moderately differentiated tumors (Grade II) – 50-75% of cells are differentiated, poorly differentiated tumors (Grade III)– 25-50% of cells are differentiated, and anaplastic tumor (Grade IV) – 0-25% of cells are differentiated. [10]

Results

Out of 500 cases, 476 (95.2%) were of malignant and 24 (4.8%) were premalignant lesions. The incidence of premalignant lesions was more in males (91.7%) than in females (8.3%). The age of patients with premalignant lesions varied from 28 to 70 years, and the maximum number of cases were in the age group of 31-40 years. [Table 1]

Table1. Demographic profile of premalignant lesions/conditions and malignant lesions

Age group (years)	Premalignant lesions/conditions			Malignant lesions		
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
21-30	2 (8.33%)	0 (0.00%)	2 (8.33%)	8 (1.89%)	6 (11.1%)	14 (2.94%)
31-40	8 (33.33%)	0 (0.00%)	8 (33.33%)	56 (13.3%)	10 (18.5%)	66 (13.9%)
41-50	4 (16.67%)	0 (0.00%)	4 (16.67%)	129 (30.6%)	7 (13.0%)	136 (28.6%)
51-60	5 (20.83%)	1 (4.17%)	6 (25.00%)	121 (28.7%)	19 (35.2%)	140 (29.4%)
61-70	3 (12.50%)	1 (4.17%)	4 (16.67%)	89 (21.1%)	7 (13.0%)	96 (20.2%)
71-80	0 (0.00%)	0 (0.00%)	0 (0.00%)	16 (3.8%)	5 (9.2%)	21 (4.41%)
81 and above	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.63%)	0 (0.00%)	3 (0.63%)

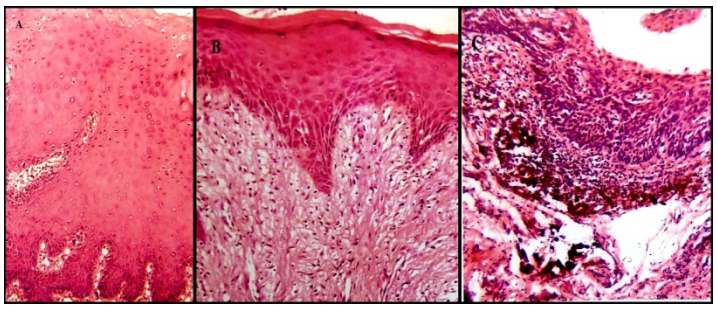
As retrieved from clinical details, white patch (leukoplakia) was the most common manifestation (14 cases) of premalignant lesion/condition of oropharyngeal region, followed by red patch (erythroplakia) in four cases. Four cases presented with thickened mucosal plaque and two cases with chronic ulcers. Histologically, the premalignant lesions revealed changes of hyperplasia without significant dysplasia in eight, hyperplasia with

mild dysplasia in five, and moderate dysplasia in six cases. The carcinoma in situ was found in three cases. Oral submucous fibrosis and lichen planus was seen in only one case each. [Table 2]

Table 2 Clinical and histological findings of premalignant lesions /conditions

Clinical Presentation	Histomorphological findings					
	Hyperplasia	Hyperplasia with mild dysplasia	Moderate dysplasia	Carcinoma in situ	Submucosal fibrosis	Lichen planus
White patch	7	4	2			1
Red patch			2	2		
Thickened mucosa	1		1	1	1	
Chronic ulcers		1	1			

Figure 1: Premalignant lesions and conditions involving the oral cavity/oropharyngeal region



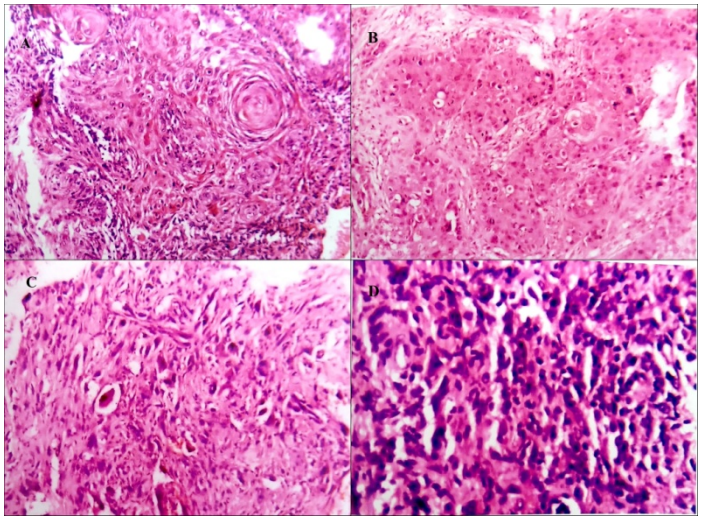
Photomicrograph revealing hyperplasia with mild dysplasia involving buccal mucosa (A), carcinoma in situ involving the base of tongue (B) and submucous fibrosis involving the floor of mouth (C). (H&E, x100)

The most common site for premalignant lesions was the buccal mucosa (54.2%) followed by base of tongue (20.7%) and oral tongue (12.5%), while least number of cases was encountered in gingiva (4.2%), floor of the mouth (4.2%) and soft palate (4.2%). The most common site involved by hyperplasia and dysplasia was buccal mucosa, while carcinoma in situ and oral submucous fibrosis commonly involved the floor of mouth and base of tongue respectively.

The incidence of carcinomas in males (422 cases, 88.66%) was roughly eight times than that in females (54 cases, 11.34%). The age ranged from 22 to 90 years. The maximum number of cases of carcinomas were encountered in the age group of 51-60 (29.4%) and minimum number in age group of 81 years and onwards. The common age range for male patients was 41-50 years (30.6%) and for female patients was 51-60 years (35.2%).[Table1]

The detailed topographic and demographic distribution and histological diagnosis of malignant cases along with their grading was done. [Table 3 &4] The squamous cell carcinoma was the most frequent malignant tumor (97.9 %) of oral cavity and oropharyngeal region. Out of 466 cases of squamous cell carcinoma, 408 (87.6%), 43 (9.2%), 14 (3.0%) and 1(0.2%) were moderately differentiated, well differentiated, poorly differentiated and undifferentiated, respectively. [Figure 2]

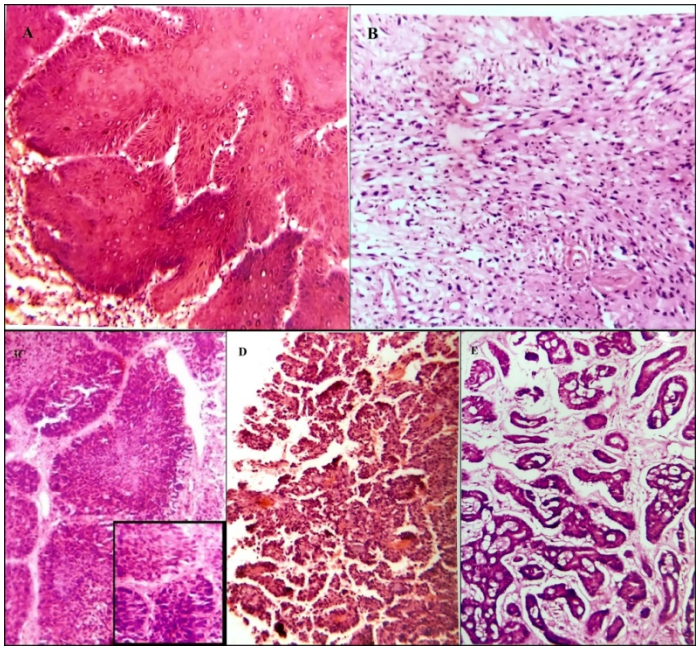
Figure 2: Different grades of squamous cell carcinoma involving various sites in oral cavity/oropharyngeal region



Histomorphology revealing well differentiated (A) and moderately differentiated SCC (B) involving anterior pillar of tonsil and buccal mucosa, respectively. (H&E,x100) Photomicrograph revealing poorly differentiated (C) (H&E,x100) and undifferentiated (D) SCC involving the tonsillar fossa. (H&E,x400)

The other neoplasms (variants of SCC and other malignancies) constituted 2.1% (10 cases) of malignant lesions. [Table 3] [Figure 3]

Figure 3: Variants of SCC and accessory salivary gland neoplasms involving the oral cavity/oropharngeal region



(A) Spindle cell variant of SCC involving the base of tongue (H&E, x100), (B) verrucous carcinoma of buccoalveolar sulcus (H&E,x100),(C) Basaloid variant of SCC involving soft palate (D) Polymorphous low grade carcinoma of hard palate and (E) Adenoid cystic carcinoma of hard palate. (H&E,x100).

The age of the patients diagnosed with basaloid variant involving the soft palate, spindle cell variant involving the soft palate and base of tongue, verrucous carcinoma were 51, 63, 62, and 53 years, respectively.

Table 3: Topographic distribution of malignant lesions

Site	Specific region of the site	Squamous cell carcinoma				Variants of SCC	Others	Total
		WD	MD	PD	UD			
Tonsil	Anterior pillar	1	3	-	4	-	-	4
	Posterior pillar	-	3	-	3	-	-	3
	Tonsillar fossa	3	94	4	113	-	1 (NHL)	103
Oral tongue	Dorsal surface	2	4	-	6	-	-	6
	Ventral surface	2	3	-	5	-	-	5
	Lateral border	2	9	-	11	-	-	11
Buccal mucosa	Lip mucosa	1	1	-	2	-	-	2
	Cheek mucosa	5	8	-	14	1 (verrucous)	-	14
	Retromolar trigone	2	8	-	10	-	-	10

	Bucco-alveolar sulci, upper and lower vestibule of mouth	5	9	-	15	1 (verrucous)	-	15
Lip	Upper lip	1	1	-	2	-	-	2
	Lower lip	1	1	-	2	-	-	2
	Commissure	1	2	-	3	-	-	3
Palate	Hard palate	1	7	-	12	-	1 (1.5%) Polymorphous low grade carcinoma 3 (4.8%)Adenoid cystic carcinoma	12
	Soft palate	3	44	2	51	1 (spindle cell), 1 (basaloid)	-	51
Base of tongue		7	166	6	-	1 (spindle cell)	-	180
Tonsillolingual sulcus		-	23	-	-	-		23
Floor of mouth		4	15	2	-	-		21
Gingiva		1	1	-	-	-		2
Posterior pharyngeal wall		1	6	-	-	-		7

Table 4: Demographic profile of malignant lesions according to their site (n=476)

Site	Specific region of the site	Male	Female	Total (%)	M:F	Age range	Mean age
Tonsil	Anterior pillar	3	1	110 (23.1%)	9:1	25-85	52.1
	Posterior pillar	3	0				
	Tonsillar fossa	93	10				
Oral tongue	Dorsal surface	5	1	22 (4.6%)	3.4:1	30-70	53.1
	Ventral surface	4	1				
	Lateral border	8	3				
Buccal mucosa	Lip mucosa	1	1		1.9:1	30-80	53.6

	Cheek mucosa	6	8	41 (8.6%)			
	Retromolar trigone	10	0				
	Bucco-alveolar sulci, upper and lower vestibule of mouth	10	5				
Lip	Upper lip	2	0	7 (1.5%)	6:1	40-70	57.1
	Lower lip	1	1				
	Commissure	3	0				
Palate	Hard palate	11	1	63 (13.2%)	30.5:1	30-90	56.3
	Soft palate	50	1				
Base of tongue		167	13	180 (37.8%)	12.8:1	22-78	53.4
Tonsillolingual sulcus		20	3	23 (4.8%)	6.3:1	35-80	54.1
Floor of mouth		19	2	21 (4.5%)	9.5:1	35-76	53.9
Gingiva		0	2	2 (0.4%)	0:2	60-70	65
Posterior pharyngeal wall		4	3	7 (1.5%)	1.3:1	35-70	56.4

Discussion

In our study, 500 cases of premalignant and malignant lesions of oropharyngeal region were analysed and histopathological diagnosis was established on conventional hematoxylin and eosin, and some special histochemically stained microsections. 95.2% (476 cases) were of malignant lesions and 4.8% (24 cases) were premalignant lesions.

Among premalignant lesions, white patch (leukoplakia) was the most common manifestation. Histologically, hyperplastic changes were seen in eight cases, followed by moderate dysplasia in six, mild dysplasia in five and carcinoma in situ in three cases. Oral submucous fibrosis and lichen planus was seen in only one case each.[Table 2] The premalignant cases showed predilection for males. [Table 1] The maximum number of premalignant lesions was found in the age range of 31-40 years (33.3%). [Table1]. This observation is in agreement with Sugar and Banocyz's study of 670 leukoplakic patients who also found predilection of leukoplakia for males and common age involved was under 40 years.[11] Among all premalignant lesions, buccal mucosa was the most common anatomical site involved (54.2%). This is in accordance to the study conducted by Scully et al.[12]

Out of all the cases in our study, 95.2% were malignant lesions (95.2%) and 88.7% of these lesions occurred in males (male:female ratio of 8:1). [Table1] These results vary from the results of study by Neville et al which revealed male:female ratio of 2:1 in most part of the world.[11] The 51-60 years' age range was the most frequent age group (29.4%) for malignant lesions and approximately 83% of cases occurred after 40 years of age [Table 1]. This finding is almost in agreement with the study conducted by Epstein et al who also found that more than 95% of oral cancers occur in patients over the age of 40 years. [13] The most frequent histologic type was squamous cell carcinoma (98%). Other miscellaneous types comprised only 2% of all cases. This is in

accordance to the study conducted by Neville et al who also noted that over 90% of oral cancers are squamous cell carcinomas. [14]

The most frequent anatomical site affected by squamous cell carcinoma was base of tongue (37.8%) followed by tonsillar region (23.1%), soft palate (10.7%) and buccal mucosa (8.6%) respectively [Table 3]. These observations are in sharp contrast to the study conducted by Padmakumari et al who found that oral tongue was the most common site of oral cavity malignancies in India [15] and in another study carried out by Boyle et al which concluded that ventro-lateral aspect of tongue and floor of mouth were most frequently affected site in western countries. [16]

Among tongue carcinomas, most common site affected was the base of tongue followed by lateral border and dorsal surface of oral tongue. Ventral surface was the least common site affected [Table 3]. The age group commonly affected was 22-78 years with average age of 53.4 years. These tumors were 3 to 12 times more common in males than females. [Table 4] In the oral tongue, lateral border contributed the most common site of occurrence (50%) [Table 3] This finding is in accordance to study conducted by Frazell et al who observed that mid third of lateral tongue border accounts for 25-30% of cases. [11]

Among tonsillar carcinoma, most common site affected was tonsillar fossa (93.6%). Males were affected 9 times more frequently than females (male:female:: 9:1) [Table 4] with average age of 52.1 years. A single case of undifferentiated carcinoma was also encountered in tonsillar region. Out of all squamous cell carcinomas of oropharyngeal region, undifferentiated carcinoma did not occur at any other site. [Table3] This is in agreement to the study conducted by Vanka et al who found that tumors in this anatomical site were more often undifferentiated carcinomas. [11]

Among carcinomas of buccal mucosa (8.6%), most frequent site involved was bucco-alveolar sulci (36.6%) closely followed by cheek mucosa (34.1%), the retromolar trigone and lip mucosa respectively.[Table3] Males were two times more affected than females (male: female ratio 2:1). [Table 4] This is in contrast to study conducted by Krolls and Hoffman in which it was shown that carcinoma buccal mucosa is approximately 10 times more common in men than women.[17] Most carcinomas of buccal mucosa occurred in age group of 30-80 years with average age of 53.5 years. [Table 4] Tiecke and Bernier et al made nearly similar observations in their study on carcinoma of buccal mucosa.[17]

Carcinoma of palate comprised 13.2% of all oropharyngeal squamous cell carcinomas. Squamous cell carcinoma was more commonly observed in soft palate (81%) than hard palate (19%).[Table 3] Krolls and Hoffman in their study of squamous cell carcinoma of palate had similar findings.[11]

Accessory salivary gland tumors were common in hard palate than squamous cell carcinomas. Three cases of adenoid cystic carcinoma and one case of polymorphous low grade adenocarcinoma were encountered only in hard palate among all other sites of oropharyngeal region.[Table 3] This observation is in agreement with study conducted by New and Hallberg as well as Wadron et al. According to them, most common site of minor salivary gland tumour was hard palate and adenoid cystic carcinoma followed by polymorphous low grade adenocarcinoma.[17]

Carcinoma of tonsillo-lingual sulcus (4.8%) and floor of mouth (4.5%) occurred nearly with equal frequency. The average age of patients was 54 years.[Table4] Male outnumbered females and this finding nearly correlates with the series of Tiecke and Bernier who also found that average age for carcinoma of floor of mouth was 57 years

and in another study conducted by Krolls and Hoffman, men were affected 2-3 times more than women.[11]

Carcinoma of lip and posterior pharyngeal wall each comprised 1.5% of all oropharyngeal carcinoma.[Table3] Lip commissure was the most common site affected (42.8%) [Table 4] Carcinomas at both sites were encountered at the average age of 57 years [Table 4], this is in contrast to the study conducted by Cross et al on 563 patients of lip cancer which revealed that lower lip was the most common site with average age of 62 years.[17] In another study conducted by Hsu et al, it was explained that isolated carcinoma of the posterior pharyngeal wall was rare. It was more commonly due to invasion by carcinoma originating from lateral pharyngeal wall.[18]

In our study, gingiva was the least affected site (0.4%). Only two cases were encountered out of 476 cases of carcinoma of oropharyngeal region. This is in contrast to the study which revealed that approximately 10% of all malignant tumours of the oral cavity occurred on the gingiva. Both the cases in our study occurred in females at the age of 60 and 70 years [Table 4], which is in accordance to the study of Krolls and Hoffman who reported that most of patients were 50 years or older. Out of two cases of gingival carcinoma, one was of well differentiated type and the other was moderately differentiated type [Table 3], which was in agreement to the study of Greer et al who noticed that most gingival carcinomas are well differentiated type.[11]

The distribution of squamous cell carcinoma in our study revealed that all the sites of oropharyngeal region, squamous cell carcinoma was the most common histological type of malignant tumour (98%) and on further histological grading, moderately differentiated type was the predominant grade (87.6%) followed by well differentiated (9.25) and poorly differentiated (3%). Only a single case of undifferentiated carcinoma was encountered.[Table 3] This is in sharp contrast to the study carried out by AI-Rawi et al who concluded that more than 70% of the cases were well differentiated squamous cell carcinoma. [16]

Two cases of verrucous carcinoma (0.4%), a variant of squamous cell carcinoma were also identified on buccal mucosa with average age of 53 years [Table 4], these findings are in accordance with the study carried out by Batsakis who reported that vast majority of verrucous carcinoma occurred on buccal mucosa.[11] Two cases of spindle cell variant of squamous cell carcinoma (0.4%) were also identified on soft palate and base of tongue occurred at the age of 63 years and 62 years respectively.[Table 4] This correlates well with the study conducted by Ellen et al who noticed that most patients with spindle cell variant were men in sixth or seventh decade. As far as the site is concerned, it is in contrast to our finding, as according to Kessler et al, lower lip was the most common involved oral site.[11] One case of basaloid variant of squamous cell carcinoma (0.4%) occurred at soft palate.[Table 3] This is in agreement to the study carried out by Raslan et al who reported that most cases of basaloid squamous cell carcinoma occurred on larynx but intraoral sites included base of tongue, hypopharynx, floor of mouth, buccal mucosa and palate.[11]

As highlighted earlier, a small miscellaneous group of oropharyngeal carcinoma comprised 3 cases of adenoid cystic carcinoma (0.6%) and one case of polymorphous low grade adenocarcinoma (0.2%) of hard palate and one case of non-Hodgkin's lymphoma (0.2%) of tonsillar region.[Table 3] These findings are in accordance to the study conducted by Waldron who analysed 426 cases and found that palate was the most common type of salivary gland carcinoma in this location followed by adenoid cystic carcinoma.[19] The observation made in the present

study are in variance to other similar studies conducted in other geographical areas in respect to certain parameters which may be attributed to various epidemiological factors like diet and personal habits.

Conclusion

In oropharyngeal region, malignant lesions were more frequently encountered than premalignant lesions. Buccal mucosa was the most common anatomic site for premalignant lesions and base of tongue for malignant lesions. Hyperplasia followed by moderate dysplasia was the commonest histological finding of premalignant lesions, and squamous cell carcinoma (moderately differentiated) was the commonest malignancy of oropharynx. Most of the premalignant lesions occurred before the age of 40 years while oropharyngeal carcinomas occurred in 5th to 6th decade. Premalignant as well as malignant lesions had predilection for males. Squamous cell carcinoma was the most frequent malignant tumor of oropharynx with moderate differentiation being encountered most frequently. The base of tongue was the most common affected site followed by tonsillar region, palate, buccal mucosa, oral tongue and floor of mouth respectively. The gingival squamous cell carcinoma was relatively more well-differentiated than other sites of oropharyngeal region. Squamous cell carcinomas of tonsillar region tend to be less well-differentiated than tumors in other oropharyngeal sites. Accessory salivary gland tumours are more common on hard palate than other sites in the oropharyngeal region. Squamous cell carcinoma on hard palate is less frequent than other oropharyngeal sites.

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