**ORAL SEBACEOUS CARCINOMA: A SYSTEMATIC REVIEW**

**ABSTRACT –**

**Introduction:** Sebaceous carcinoma is predominantly known as a cutaneous malignancy, most commonly arising in the periocular region. It is locally aggressive and carries a risk of metastasis. Its occurrence in the oral cavity is exceptionally rare, making it a diagnostic challenge for clinicians and pathologists. Furthermore, recognition of intraoral sebaceous carcinoma is important, as it may be associated with genetic syndromes such as Muir-Torre syndrome, which has broader implications for patient management and family screening. Therefore, awareness of this rare entity in the oral cavity is crucial for timely diagnosis, appropriate therapy, and comprehensive patient care **Objectives -** To asses the demographics, clinical and histopathological features, differential diagnoses, treatment approaches, and patient outcomes in oral sebaceous carcinoma. **Methods:** Case reports and case series of oral sebaceous carcinoma were retrieved through a systematic search of three electronic databases, using the following inclusion criteria – 1)Case reports and case series on patients with intraoral sebaceous carcinoma published between 2000 and 2024. 2) Articles published in English.3)Case reports and case series, including those with literature reviews, published from 2000 to 2024.Reference checks of identified cases were also conducted to aid in snowballing or case networking. Data from 13 selected cases were extracted for analysis. **Results:** The search strategy retrieved 1,894 articles. After full-text assessment of 123 articles, 13 met the inclusion criteria and were included in the review. In most studies, the affected region was the upper or lower lip, followed by the tongue and palate. Clinically, on extraoral examination, the lesion appeared as a markedly ulcerated, exophytic, irregularly shaped, indurated mass of varying dimensions.

 The most common diagnosis was sebaceous carcinoma of the oral region. **Conclusion:** Oral sebaceous carcinoma is an extremely rare and aggressive malignancy with potential for local recurrence and distant metastasis. Regular follow-up is essential to monitor for recurrence or spread. Increased awareness among clinicians and pathologists of the oral occurrence of sebaceous carcinoma its diagnosis and improve prognosis through timely intervention.

**KEYWORDS – oral sebaceous carcinoma, oral cavity, sebaceous glands**

**Introduction**

Sebaceous carcinoma (SC) is a rare and aggressive cutaneous malignancy, with fewer than 400 cases reported in the literature to date. The first documented case was described by Allaire in 1891¹. According to the World Health Organization (WHO), sebaceous carcinoma is defined as “a malignant tumor composed of sebaceous cells of varying maturity that are arranged in sheets and/or nests with different degrees of pleomorphism, nuclear atypia, and invasiveness”². This tumor originates from sebaceous glands in the skin and can therefore develop anywhere on the body where these glands are present.

Sebaceous carcinoma is broadly classified into two subtypes: ocular and extraocular³. Ocular SC is the third most common malignancy of the eyelids, with most cases arising from the meibomian glands. Extraocular SC accounts for approximately 20% of all cases, most commonly involving the head and neck region, particularly the scalp, face, parotid gland, buccal mucosa, and tongue³. Among the extraocular forms, non-cutaneous sebaceous carcinoma most frequently affects the major salivary glands⁴.

The first reported case of intraoral (IO) SC was described by Damm et al. in 1991, marking the earliest known instance in English-language literature of sebaceous carcinoma presenting as an intraoral tumor⁸. While sebaceous adenomas have occasionally been reported in the oral cavity, oral sebaceous carcinoma remains extremely rare⁵. Primary SC of the oral cavity is thought to arise either from Fordyce granules or from salivary gland elements⁶. Fordyce granules—ectopic sebaceous glands found in approximately 80% of adults—are considered normal anatomical variants⁶,⁷. Clinically, these granules appear as asymptomatic, small yellow-white papules on the buccal mucosa and upper lip⁸. Rarely, these ectopic sebaceous glands may undergo neoplastic transformation, giving rise to sebaceous neoplasms. Oral SC typically presents as a non-encapsulated, asymptomatic nodule and can easily be mistaken for more common benign lesions, often resulting in delayed diagnosis and treatment⁹.

Although the exact etiology of SC remains unclear, several risk factors have been identified. These include inherited genetic mutations, particularly those associated with Muir–Torre Syndrome, a variant of Lynch syndrome¹⁰. Other contributing risk factors include long-term ultraviolet (UV) exposure, immunosuppression, and viral infections¹⁰,¹¹. Genetic alterations associated with SC often affect DNA mismatch repair genes (e.g., MSH2, MSH6, MLH1), resulting in microsatellite instability¹¹. Sebaceous carcinoma typically affects middle-aged to elderly individuals, with a mean age of 65 years (range: 9–93 years), and shows no significant gender predilection¹².

SC is recognized for its aggressive biological behavior, with the potential for local invasion and distant metastasis¹⁰. Therefore, early detection is critical for effective management. Accurate staging using the TNM system is essential for assessing disease extent, guiding treatment, and providing prognostic information¹³,¹⁴. Due to the absence of standardized imaging protocols, histopathological evaluation of biopsy or excised specimens remains the gold standard for diagnosis. Histologically, SC belongs to the spectrum of sebaceous neoplasms, which includes sebaceous adenoma and basal cell carcinoma with sebaceous differentiation¹⁵. SC typically exhibits well-circumscribed lobules of neoplastic sebaceous cells with eosinophilic cytoplasm and marked atypia. Cytological features include nuclear pleomorphism, frequent mitotic figures, and occasionally foamy or glassy cytoplasm¹⁶,¹⁷

Optimal treatment involves surgical excision with clear margins, generally a 5 mm margin to prevent local recurrence¹⁹. In ocular SC, regional neck dissection or sentinel lymph node biopsy may be indicated²⁰. The role of adjuvant radiotherapy (RT) or systemic therapy (ST) remains controversial, particularly in non-ocular cases. RT may be considered for patients who are not surgical candidates. Prognosis is influenced by multiple factors including tumor size, location, clinical stage, and treatment approach.

This systematic review addresses a highly rare and underreported malignancy. Given the diagnostic challenges and potential for misdiagnosis due to its resemblance to more common oral lesions, this review provides valuable insights into its clinical and histopathological characteristics. The work contributes to raising awareness among clinicians. By highlighting associations with genetic syndromes like Muir-Torre syndrome, the manuscript also underscores broader implications for patient surveillance and family screening.

**AIMS AND OBJECTIVES –**

### ****Aim –****

### To conduct a systematic review to evaluate the clinical and pathological characteristics of oral sebaceous carcinoma.

### ****Objectives****

* To analyze the demographic profile of reported cases.
* To describe the clinical and histopathological features of oral sebaceous carcinoma.
* To identify and compare differential diagnoses considered in reported cases.
* To review the treatment modalities employed in managing oral sebaceous carcinoma.
* To assess patient outcomes and prognostic factors associated with the condition.

**MATERIALS AND METHOD**

The study protocol was registered in the **PROSPERO** database, and the registration number for this review is **CRD42025639648**.

Case reports and case series of **oral sebaceous carcinoma** were retrieved through a **systematic search** of the following scientific databases:

* **PubMed Central** (National Library of Medicine)
* **Google Scholar** (Google, Mountain View, USA)
* **ScienceDirect**

The search strategy used the following keywords:
**“Sebaceous Carcinoma” OR “Oral Cavity” AND “Oral Mucosa.”**

Relevant literature was screened to identify cases reported under various terminologies; however, **case reports published before the year 2000** were excluded from the current review.

An **independent researcher** performed the database search and identified **68 relevant studies**. In addition, **reference checks** of the selected articles were carried out to facilitate **snowballing** and ensure the inclusion of potentially missed cases. Reference checks of the cases identified were also made to help snowballing or networking of the cases. A table was tabulated regarding author, year of publication, demographic data as age, gender, clinical features, histopathological features, and differential diagnosis treatment opted for each of the case reports included.

**SEARCH STRATEGY**

To find pertinent studies on the demographic, clinical and histological conditions and outcomes of sebaceous carcinoma, a thorough search was undertaken in the Google scholar, PubMed, sciencedirect and DOAJ database. The filters were fixed at article type (prospective, retrospective, cross-sectional studies), publication date (January 2003 till January 2023), and the best match option. Controlled vocabulary (MeSH terms in PubMed) and free-text terms in the titles and/or abstracts were used to define the search strategy in the database. The search strategies developed using Boolean operators for PubMed and databases is given below and the “screening process of studies is presented in the form of PRISMA flow-chart (Figure1). Keywords used were **“**Patients with “Oral carcinoma” or Oral Sebaceous Carcinoma (P)” or “Sebaceous Carcinoma of oral cavity” or “Oral involvement of sebaceous carcinoma” or “Patient outcome in Oral sebaceous carcinoma” or patients with Oral Sebaceous Carcinoma OR sebaceous gland carcinoma OR sebaceous gland adenocarcinoma) AND (Oral cavity OR oral involvement OR oral region) AND (clinico-pathological features OR histopathological features OR IHC) AND (outcome OR prognosis)

**ELIGIBILITY CRITERIA**

**Inclusion Criteria** Following articles are included

1.Case reports and case series on patients with intraoral Sebaseous carcinoma from 2000-2024 2. Articles published in English 3. Case reports and case series, Case reports and case series with review between 2000-2024

**Exclusion Criteria** Following articles are excluded:

1. Case reports and case series on patients with extraoral sebaseous carcinoma, sebaseous carcinoma of major salivary glands

2. Articles published in other language

4. Abstracts

5. Randomized and nonrandomized clinical trials

6. All studies

7. Unpublished data.

8. Articles with incomplete data.

The references of the selected articles were also analyzed for additional studies. The research question was set in accordance with the PICOT format.

**STUDY SELECTION:** The study selection was done in three steps. All the titles were reviewed and based on the inclusion and exclusion criteria; appropriate studies were selected. For all the selected titles, abstracts were obtained and reviewed, from which appropriate abstracts were selected based on the criteria. Full-text articles were obtained and analyzed, and the final set was obtained keeping in mind the selection criteria.The initial search strategy yielded 690 references. After removing duplications and nonrelevant articles, the number of references reduced to 123. This number was further reduced to 13 based on abstracts and titles

**Fig .1: PRISMA flow-chart**

“Additional records identified through other sources (Google Scholar)”
**(n =1204)**

“Records identified through database searching (PubMed)**”**
**(n = 690)**

## Identification

## Identification

“Records excluded after review of titles
**(n =1482)”**

“Total Titles screened”
**(n =1894)**

“Titles screened for duplicate removal”

**(n= 412)**

##  Screening

Excluded- duplicates
**(n =289)**

“Abstracts screened”

**(n=123)**

“Records excluded (n=98) after review of abstracts”
**(n =776)**

##  Eligibility

“Full texts screened on basis of inclusion and exclusion criteria”

**(n=25)**

“Studies excluded after review of full text **(n=12)”**

##  Included

“Studies included in qualitative synthesis (n=13) **13 estimates”**

**ASSESSMENT OF RISK OF BIAS**

Risk of bias assessment of all the included studies was performed. All the included studies were case reports; about 2 studies included 2 cases. For the risk of bias assessment of included case reports, JBI critical appraisal checklist for Case reports was used to assess Risk of bias of included case reports. t has been found that most of the case reports included showed all of the items of appraisal with a “yes” response across all the studies. Thus, when the overall quality assessment or Risk of bias is done; it can be interpreted that all of the included case reports showed better quality of assessment.

**RESULTS**

The search strategy retrieved 1894 articles. 1482 records excluded after review of titles 412 titles remaining screened for duplication out of which 289 excluded. Assessment of the full text was done for 123 articles after which 13 were included in the study. All included paper were published between 2000 to 2024.

The present systematic review was conducted to assess demographics, Clinical and histopathological features, differential diagnosis, treatment and patient outcomes in oral sebaceous carcinoma. The screening process was undertaken in three steps that included screening of titles followed by screening of abstracts and finally screening of full text for inclusion in the review. The characteristics of the studies included in the systematic review are presented in the below tables.”

The table 1 represents study characteristics with respect to age group, patients, exposure and primary and secondary outcomes with follow-up of the included studies. The age of the study participants across the studies varied from 40 years to 81 years; with mean age around 60 years. All the cases involved in the studies were having sebaceous carcinoma of the oral region. In majority of the studies the region affected was upper or lower lip, followed by tongue and palate. Clinically on extra oral examination the lesion appeared as markedly ulcerated, exophytic, irregularly shaped, indurated mass varying in dimensions. The most common diagnosis arrived at was Sebaceous carcinoma of the oral region. The common histo-pathological findings across the included studies were presence of neoplastic cells which showed a range of sebaceous differentiation with finely vacuolated rather than clear cytoplasm. Immunohistochemistry showed strong nuclear immunoreactivity with Androgen Receptor and scattered membranous and cytoplasmic reactivity with EMA and positive for S-100 protein, EMA, but negative for CEA. The differential diagnosis was squamous cell carcinoma, basal cell carcinoma and malignant salivary gland neoplasm.The treatment fiven for most of the cases was incisional biopsy followed by wide local excision of the residual tumour; followed by chemotherapy and radiotherapy if required. Amongst all the cases reported in this systematic review, about 2 cases showed lymph node involvement with distant metastases.

**Table 1- Details of the study participants, intervention, and comparator of the studies included in the systematic review**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SR NO | Authors name  | No of reported cases | Demographic data  | exposure | Histopathological features | Differential diagnosis | treatment | Patient outcome |
|  |  |  | Age /Sex | site | Appearance  | Size & features | Duration | TNM staging |  |  |  |  |  |  |
|  | Handschel J et al 2003 | 1 | 80/F | Edentulous alveolar ridge of the mandible | ulcerated | 1.5 × 1.2 cm lesion in the anterior floor of the mouth | 6 months | NR | Intraoral sebaceous carcinoma | solid cords and nests, the centralportions of which were often filled with clear cells showing a honeycombed cytoplasm | CEA showed specifically stained tumourcells with foamy cytoplasm | NR | excised with a 1-cm margin of healthy tissue including Sebaceous carcinoma in the anterior floor of the mouth. | postoperative coursewas uneventful. |
|  | Alawi F et al 2005 | 1 | 66/M | upper lip. | bleeding sore’’ | markedlyulcerated, exophytic, irregularly shaped, indurated mass of the upper left labial mucosa, measuring 1.5 X 3 X 1.0 cm in size | 3 years | NR | Sebaceous carcinoma of the oral mucosa | severely dysplastic squamous epithelium exhibiting transitionto an infiltrating malignant neoplasm composed of islands andsheets of anastomosing basaloid epithelial cells with areas ofprominent sebaceous differentiation. | strong nuclear immunoreactivity with AR andscattered membranous and cytoplasmic reactivity with EMA, completely unreactive withthe AR antibody. | squamous cell carcinoma and malignant salivary gland neoplasm. | incisionalbiopsy was performed and wide localexcision of the residual tumor | After 1 year of follow-up, therehas been no evidence of local recurrence or metastasis. |
|  | Gomes CC et al 2007 | 1 | 55/M | continuouspain and severe trismus in the posterior mandible  | right side of the mandible | swelling in theangle of the right side of the mandible could beobserved, as well as submandibular and anterior cervicallymph nodes enlargement. | 3 months | NR | Intraoral sebaceous carcinoma | surfacemucosa with inWltrating nests and sheets of eosinophilicepithelial cells exhibiting prominent nucleoli,moderate cellular and nuclear polymorphisms andpoorly deWned cellular outlines. centrally located vesicular-shaped nuclei and exhibitingvacuolated or foamy cytoplasm | androgen receptor (CloneAR441, Dako, Carpinteria, USA) revealed positivenuclear staining  | squamous cell carcinoma, basal cell carcinoma | incisional biopsy, chemotherapy inassociation with radiotherapy | Follow-up done |
|  | Oshiro H et al 2010 | 1 | 66/M | Mass like  | tongue | tumorous lesion located in the dorsal andmidline part of the tongue, measuring about 25 mm in greatestdiameter  | 1 month | T2N2cM0primary lingual tumor. | Primary sebaceous carcinoma of the tongue | neoplastic sebocytic and basaloidcells, and Sudan III staining and electron microscopyrevealed intracytoplasmic lipid droplets. | neoplastic cellsstained positive for adipophilin; epithelial membraneantigen; epithelial antigen; and cytokeratins 7, 8, and 15, butnegative for cytokeratins 5/6, 18, 19, and 20; the androgenreceptor; and carcinoembryonic antigen | basal cell carcinoma and squamous cell carcinoma | Superselectiveintraarterial chemotherapy and neck dissection | patient died 17months after completing the initial course of chemoradiotherapy. |
|  | Wang H et al 2010 | 1 | 50/M  | Mass like growth and pain | Buccal mucosa  | 4.8 X4.6 X2.7 cm broadbased,fungating, and friable mass on the left posterior buccalmucosa extending to the retromolar trigone and abutting onthe left mandibular body without invasion of the bone. | 3 months | NR | Sebaceous carcinoma of the oral cavity: | sebaceous nests (70%),squamous islands with keratin pearl formation (2%), andpoorly differentiated solid areas (28%). | neoplastic cells displayed characteristic membranous and cytoplasmicstaining for epithelial membrane antigen (EMA).The basaloid and sebaceous cells demonstrated strong nuclearimmunoreactivity to androgen receptor | Squamous cell carcinoma | tumor was completely resected. All neck lymph nodes werenegative for carcinoma. The patient received radiation therapyafter the surgery | 5-yearsurvival with sebaceous carcinoma in the salivaryglands is 60% |
|  | Wetzel S et al 2014 | 1 | 75/M  | erythematous raised ulcerated lesion | attached maxillary gingiva buccally | NR | NR | NR | Sebaceous carcinoma of the maxillary gingiva | stratified squamousepithelium showing transition to a malignant tumor comprised of lobules of epithelialcells exhibiting sebaceous differentiation | lesional cells reacted with androgenreceptor and epithelial membrane antigen (EMA)  | squamous cell carcinoma and basal cell carcinoma | surgical excision. Adjuvant radiation therapy andchemotherapy may also be given | rare occurrence of intraoral SC overallsurvival rates have yet to be determined. |
|  | Greenall CJ and Drage NA 2015 | 1 | 81/M | Firm , irregular mass  | upper right lip | poorly defined ,hypoechoic irregular mass in the right naso-labial region, with no internal vascularity, involving skin, subcutaneous fat, orbicularis oris and the intraoral mucosa  | Since 2 month | NR | Sebaceous carcinoma of the lip | cells of salivary gland origin could be either reactionary or malignant. | NA | basal cell carcinoma,and malignant tumours | palliativeradiotherapy | Ultrasound may be useful in aiding the early surgical planning for patients with extensive dermatologicaldisease. |
|  | Rowe M et al 2015 | 1 | 76/M | exophytic lesion | upper gum with associated mobility of the adjacent teeth | gingival tumor was1.5 X 1.4 X 1.1 cm and invaded the underlying bone | 6 weeks | NR | Intraoral sebaceous carcinoma metastatic to the lung and subcutis | neoplastic proliferation was composedof epithelioid cells with round to oval nuclei, small toprominent nucleoli, and clear to vacuolated appearingcytoplasm | PMS-2, MLH-1, MSH-2, and MSH-6 showed nuclear reactivi | NR | partial maxillectomy | no previous case has an intraoralsebaceous carcinoma metastasized to another dermalregion of the body |
|  | Jawanda MJ et al 2018 | 1 | 40/F | Swelling  | Right side invoving buccal mucosa  | swelling was firm in consistency, nontender, and of approximately5 × 4 cm, extending superoinferiorly from the infraorbitalridge to 2cm above the inferior border of the mandibleand anteroposteriorly from the right corner of the mouth to1.5cm anterior to the tragus | 1 year | NR | Intraoral Sebaceous Carcinoma | large nests of neoplasticcells with squamous appearance, separated by scantystroma (Figure 2). The neoplastic cells had large vesicularnuclei with prominent nucleoli. Cellular and nuclear pleomorphismwith few nuclei showing multilobation was seen,along with typical and atypical mitotic figures | Not performed | metastaticclear cell renal carcinoma | complete excision verified by negative margins.Radiotherapy is used if metastatic disease and/or a high riskof recurrence are present. Multiagent chemotherapy hasbeen used to treat recurrent disease | NR |
|  | Ambrosino M et al 2021 | 1 | 71/M | Ulcerated  | Lower lip | markedly ulcerated, exophytic, irregularly shaped, indurated mass of the lowerright labial region, measuring 1.8 cm in size | 1 year | NR | Sebaceous Carcinoma of The Lip | Neoplastic cells showed a range of sebaceous differentiation with finely vacuolated rather than clear cytoplasm | Neoplastic cells werepositive for S-100 protein, EMA, but negative for CEA | squamous cell carcinoma, basal cell carcinoma with sebaceousdifferentiation and salivary gland neoplasm | Surgery | patient underwent a complete clinical and radiographic evaluation to identify any regional or distant metastases |
|  | Lu Q et al 2021 | 1 | 62/M | Growth like mass  | Palate  | a small nodule(0.5 cm × 0.5 cm) appeared beneath the mucosa; however,it gradually grew to its present size of 2.0 cm × 1.5 cm) | 1 year | NR | Sebaceous carcinoma of the right palate: | inconclusive patternbut strongly suggested that malignancy originated inthe salivary gland | PAS(–), EMA(+), AR (+) | squamous cell carcinoma (SCC) andmucoepidermoid carcinoma | Surgery, Postoperative chemotherapy and radiotherapy were notadopted in the present case, as | Patient was relatively satisfiedwith the surgery |
| 12 | Cosola MD et al 2022 | 1 | 71/M | Ulcerated  | Lower lip | markedly ulcerated, exophytic, irregularly shaped, indurated mass of the lower rightlabial region, measuring 1.8 cm in size. | 1 year | NR | Sebaceous carcinoma of the lip: | nodulesor sheet of cells separated by a fibrovascular stroma. The neoplastic tissue was deeply infiltrating, involving thesubmucosa and even the underlying muscle. | Neoplastic cells were positive for S-100 protein and epithelial membraneantigen, but negative for carcinoembryonic antigen | squamous cell carcinoma, basal cell carcinoma with sebaceous differentiation, and salivary gland neoplasms | excisional biopsy with 0.5 cm of free margins and W-shaped wedge was performed; | patient underwent a complete clinical and radiographic evaluation to identify any regional or distant metastases. |
| 13 | Katib Y et al 2024 | 1 | 47/M  | Ulcerated , painless mass  | Upper lip | ulcerated, exophytic, andirregularly shaped mass was observed on the upper lip  | 1 year | Lymph node showed no metastases  | oralsebaceous carcinoma in theupper lip | malignanttumor with a nodular pattern consisting of basaloid cells with obvioussebaceous differentiations and frequent mitoses | neoplastic cells testedpositive for broad-spectrum cytokeratin (AE1-AE3), epithelial membraneantigen (EMA), and P53, while testing negative for S-100 andcarcinoembryonic antigen (CEA). | basal cellcarcinoma (BCC), squamous cell carcinoma (SCC), and asalivary gland tumor. | lip-wide localexcision with reconstruction using a local flap and leftmodifiedradical neck dissection. | Three months post-RT, magnetic resonanceimaging (MRI) scan indicated no tumor recurrence |

NR –Not reported, NA- Not Available

**DISCUSSION –**

Sebaceous carcinoma (SC) is a rare epithelial neoplasm that typically originates in the ocular adnexa, most commonly from the meibomian glands or the glands of Zeis²¹. By definition, SC is a cytologically and/or architecturally malignant tumor characterized by exclusive sebocyte differentiation²². Although sebaceous glands are present in various anatomical sites, the majority of sebaceous tumors—including SC—occur in the head and neck region.

While sebaceous carcinoma shows a marked predilection for the ocular region, particularly the upper eyelids, approximately 25% of cases develop in extraorbital locations. Among these, the parotid gland accounts for nearly 30% of extraorbital cases²³.

**Glands exhibiting sebaceous differentiation** are frequently identified within the **oral cavity**, and similar differentiation may also be observed in the **major salivary glands²⁴**. Sebaceous glands are found in approximately **10%–40% of normal parotid glands** and **6%–10% of submandibular glands²⁵**. Despite their presence, **both benign and malignant sebaceous tumors** of the salivary glands remain **extremely rare**, comprising **less than 0.2%** of all major salivary gland neoplasms²⁵. In contrast, **Fordyce granules**—ectopic sebaceous glands—are **commonly seen** in the oral mucosa of up to **80% of adults²⁶**.

**Clinically**, Fordyce granules appear as **asymptomatic, rice-like white or yellow papules**, typically ranging from **1–3 mm in diameter²⁷**. **Histologically**, each gland contains approximately **15 well-differentiated sebaceous lobules**. Although their exact function remains unclear, Fordyce granules have been associated with:

* **Hyperplasia** (increased number of well-differentiated lobules),
* **Adenoma** (a sharply demarcated mass), and
* **Carcinoma** (characterized by cytologic atypia and infiltrative growth)³,²⁸.

The **first reported case** of **intraoral sebaceous carcinoma (SC)** was documented by **Damm et al. in 1991**.

In this review of **13 case reports**, **10 patients were male**, suggesting a possible **male predominance**; however, existing literature does **not confirm a definitive gender predilection**. Intraoral sebaceous carcinoma typically occurs in **adults**, with patient ages ranging from **40 to 81 years**, and a **mean age of approximately 60 years**. These findings are consistent with previous reports, such as those by **Wetzel et al. (2014)**, which documented a **mean age of 60.2 years²⁸**. While the majority of cases occurred in individuals **over 50 years old**, two notable exceptions include:

* A **40-year-old female** reported by **Jawanda et al. (2018)²⁹**
* A **47-year-old male** reported by **Katib et al. (2024)¹⁰**

Among the 13 cases reviewed, **several patients had a history of smoking, alcohol use, or tobacco consumption**. However, **no definitive correlation** between these habits and the development of sebaceous carcinoma has been established.

Clinically, lesions exhibited **variable features**, including **ulceration**, **mass-like growths**, **bleeding sores**, and **exophytic proliferations**. Several cases—including those reported by **Cosola et al. (2022)³⁰**, **Alawi et al. (2005)²⁵**, **Qun Lu et al. (2021)**, **Wang et al. (2010)**, **Wetzel et al. (2014)²⁸**, **Handschel et al. (2003)²⁴**, and **Gomes et al. (2007)**—described lesions as **ulcerated, exophytic, irregularly shaped, and indurated**. In contrast, **Katib et al. (2024)¹⁰** described the lesion as **nodular** in appearance. Three cases—reported by **Oshiro et al. (2010)³¹**, **Greenall et al. (2015)**, and **Jawanda et al. (2018)**—described the lesion as a **swelling with intact overlying mucosa**. **Jawanda et al. (2018)** specifically noted the swelling to be **mobile**, with **no ulceration** of the overlying skin. Intraoral examination revealed **no visible swelling**, and the oral mucosa appeared intact. **Oshiro et al. (2010)** described a **submucosal mass-forming lesion** on the **dorsal surface of the tongue**, covered by a **smooth mucosal layer** and associated with **redness**. **Greenall et al. (2015)³⁴** reported a lesion located on the **upper right philtrum**, which appeared **erythematous and indurated**, though **overlying skin remained intact**. The **most commonly involved sites** were the **upper and lower lip**, followed by the **buccal mucosa**, **tongue**, **gingiva**, and **floor of the mouth**.

Sebaceous glands in the oral cavity are referred to as **Fordyce granules⁶**, which are present in approximately **80% of adults**. **Primary sebaceous carcinoma of the oral cavity** is believed to originate either from **Fordyce granules or** **salivary gland elements⁶**. Among the 13 cases reviewed, only **2** —reported by **Jawanda et al. (2018)²⁹** and **Alawi et al. (2005)²⁵**—confirmed the presence of **Fordyce granules**. **Alawi et al. (2005)** described them as **numerous**, measuring **1–2 mm** in diameter, primarily involving the **upper labial mucosa**. Additionally, Fordyce granules were observed **bilaterally in the buccal mucosa** and the **lower labial vestibule**. In both cases, the granules were located **in close proximity to the lesion**.

The **duration of the lesion** ranged from **6 weeks to 1 year** across reported cases. Only **one case** exhibited **cervical lymphadenopathy**. **Oshiro et al. (2010)** reported **bilaterally enlarged cervical lymph nodes** detected on **whole-body CT**, suggesting **regional lymph node metastasis**. No **distant metastases** were observed in this case. Based on these findings, the lesion was classified as **T2N2cM0** according to the **International Union Against Cancer (UICC)** staging guidelines.

### **Radiographic Findings -** Various radiographic modalities—including **CT scan, MRI, CBCT, and OPG**—have been utilized to assess both soft and hard tissue involvement in oral sebaceous carcinoma.**Gomes et al. (2007)** reported **CT and OPG** findings showing **bone loss** and **invasion of the underlying submucosa and muscles**. **Greenall et al. (2018)** described ultrasonographic features as a **poorly defined hypoechoic irregular mass** in the **right nasolabial region**, with **no internal vascularity**. The lesion extended into the **skin**, **subcutaneous fat**, **orbicularis oris**, and **intraoral mucosa**.

In the case reported by **Jawanda et al. (2018)**, a **Water’s view radiograph** of the skull revealed a **soft tissue swelling** in the **right cheek area**. **Oshiro et al. (2010)** confirmed the presence of a **tumorous lesion on CT**, while **MRI** showed a mass located in the **dorsal and midline region of the tongue**, measuring approximately **25 mm** in greatest diameter. **FDG-PET (Fluorine-18 fluorodeoxyglucose positron emission tomography)** revealed an area of **high uptake** (SUV max = 7.0), corresponding to the lingual lesion.

Ultrasound-guided **fine-needle aspiration cytology (FNAC)** reported by **Greenall et al. (2018)** suggested the lesion might be of **salivary gland origin**, with possibilities ranging from **reactive** to **malignant**. In contrast, **Qun Lu et al. (2021)** found **no significant radiographic findings**.

Histologically, **sebaceous neoplasms of the salivary glands** are classified into five categories:

1. **Sebaceous adenoma**
2. **Sebaceous lymphadenoma**
3. **Sebaceous carcinoma (SC)**
4. **Sebaceous lymphadenocarcinoma**
5. **Sebaceous differentiation in other tumors**⁽³⁵⁾

Microscopically, the tumor mass often appears to reside in the **deeper mucosa**, with **pushing margins** and **tumor nests**⁽³⁵⁾. The tumor typically consists of **large nests of neoplastic cells** with **squamoid features**, separated by **scanty stroma**. The cells display **large vesicular nuclei** with **prominent nucleoli**, along with **cellular and nuclear pleomorphism**. Occasional **multilobated nuclei** and both **typical and atypical mitotic figures** are evident.The **sebaceous nests** are composed of **clear tumor cells** with **foamy cytoplasm**. **Handschel et al. (2003)** described similar tumors arranged in **solid cords and nests**, with central regions often filled with **clear cells showing honeycomb-like cytoplasm**.**Oshiro et al. (2010)** described lesions with **enlarged nucleoli** and **bubbly cytoplasmic vacuolization**, along with a **moderate to high nuclear-to-cytoplasmic ratio** and **pronounced nuclear pleomorphism**. More than **10 mitotic figures per 10 high-power fields** were observed. Additionally, **pyknosis, karyorrhexis, and individual cell death** were noted. The tumor cells formed **irregularly lobulated solid nests**, with **nuclear palisading** at the periphery. However, **keratinization**, **intercellular bridging**, and **comedo-type necrosis** were absent.**Alawi et al. (2005)** reported areas of **prominent squamous differentiation** with **keratin pearl formation** and **focal necrosis**. **Electron microscopy** by **Oshiro et al. (2010)** showed **neoplastic cells** containing **intracytoplasmic lipid droplets** ranging from **800 to 1,200 nm** in diameter.

Neoplastic cells have been shown to stain positively for:

* **Cytokeratins**
* **Epithelial membrane antigen (EMA)**
* **Carcinoembryonic antigen (CEA)** (notably in foamy cytoplasmic tumor cells)
* **c-erbB2 (Her-2/neu)** – shows **weak membranous and cytoplasmic staining** in most tumor cells
* **Androgen receptor (AR)** – demonstrates **diffuse nuclear staining**

**Carolina et al.** suggested that **Androgen Receptor** is a **more specific marker of sebaceous differentiation** than EMA. On the contrary, **gross cystic disease fluid protein (GCDFP-15)** and related markers are generally **negative** in SC²⁹.

Histologically, sebaceous neoplasms of the salivary glands are categorized into five types: **sebaceous adenoma, sebaceous lymphadenoma, sebaceous carcinoma (SC), sebaceous lymphadenocarcinoma**, and **sebaceous differentiation in other tumors**. Microscopically, the tumor mass appeared to be situated in the **deeper mucosa**, with **pushing margins** of tumor nests. The tumor consisted of **large nests of neoplastic cells with squamous-like features**, separated by scanty stroma. These cells exhibited **large vesicular nuclei with prominent nucleoli**, cellular and nuclear pleomorphism, some nuclei showing **multilobation**, and both **typical and atypical mitotic figures**. The **sebaceous nests** were composed of **clear tumor cells with foamy cytoplasm**.

Handschel et al. (2003) described a similar tumor arranged in **solid cords and nests**, with central portions often filled with **clear cells exhibiting honeycombed cytoplasm**. Oshiro et al. (2010) further described **enlarged nucleoli, bubbly cytoplasmic vacuolization**, moderate to high nuclear-to-cytoplasmic ratio, significant nuclear pleomorphism, and **>10 mitotic figures per 10 high-power fields**. **Pyknosis, karyorrhexis**, and **individual cell death** were observed. The cells formed **irregularly lobulated solid nests**. **Comedo-type necrosis** was absent, but **nuclear palisading** was evident at the periphery of the nests. No **keratinization or intercellular bridging** was observed. Alawi et al. (2005) reported **squamous differentiation, keratin pearl formation**, and areas of necrosis. **Electron microscopy** by Oshiro et al. (2010) revealed **intracytoplasmic lipid droplets** ranging from **800 to 1,200 nm** in diameter.

According to Plaza et al. (reference 16), **histopathology remains the gold standard** for diagnosing SC. They emphasized the value of **immunohistochemical (IHC) assessment** of epithelial markers and lipid droplet-associated proteins as diagnostic adjuncts. Neoplastic cells stain positively for **cytokeratins (CKs), epithelial membrane antigen (EMA)**, and **c-erbB2 (Her-2/neu)**. **Carcinoembryonic antigen (CEA)** expression is found in **tumor cells with foamy cytoplasm**. SC also demonstrates **diffuse nuclear staining for androgen receptor (AR)**. Carolina et al. considered AR a more reliable marker for sebaceous differentiation than EMA. c-erbB2 showed **weak membranous and cytoplasmic staining** in most tumor cells.

Neoplastic cells also exhibit **diffuse positivity for broad-spectrum cytokeratin (AE1/AE3)** and are **focally positive for CK7, CK8, low molecular weight keratin (CAM5.2), CK15**, and **CK19**, but **negative for CK5/6, CK18**, and **CK20**. The neoplastic cells are **negative for CEA**. **Increased expression of p53** and a **high proliferative index by Ki-67 (~50%)** were reported in hotspot areas. **Positivity for both EMA and AR** confirmed that the **vacuolated clear cells were not mucous or glycogen-rich squamous cells**.

Based on these findings, **squamous cell carcinoma (SCC), clear cell melanoma**, and **basal cell carcinoma (BCC)** can be ruled out. Due to the **infiltrative growth pattern, necrosis**, and **cytological features**, SC can resemble other **malignant neoplasms**, but the **histological appearance of SC is often characteristic**. Differential diagnoses include **BCC with sebaceous differentiation, clear cell variants of BCC and SCC, eccrine carcinoma, balloon cell melanoma**, and **metastatic clear cell tumors**.

Jawanda et al. highlighted the differential diagnosis of **intraoral SC**, which includes **clear cell and basaloid SCC with hydropic change**, **metastatic clear cell renal carcinoma**, and salivary gland malignancies such as **mucoepidermoid carcinoma**, **solid-type adenoid cystic carcinoma**, **basal cell adenocarcinoma**, and **salivary duct carcinoma**. Notably, **BCC** is characterized by **superficial plate-like proliferation** of **basaloid and/or squamoid cells**, often connecting to the **overlying epidermis**.

**Mucicarmine and PAS staining** help rule out **mucoepidermoid carcinoma** and **SCC with hydropic degeneration**. **Sudan IV** and **Oil Red O** are useful for diagnosing sebaceous cells. These vacuolated cells are **negative for mucicarmine and PAS**, with or without **diastase digestion**, confirming they are **neither mucus cells nor glycogen-rich squamous cells**.

The **pathogenesis of intraoral SC** remains **unclear and warrants further investigation**. Alawi et al. (2005) reported **loss of hMLH-1 or hMSH-2 in 3 of 14 sporadic SC tumors**, suggesting a possible role of **mismatch-repair gene defects**, although results have been inconsistent across studies. Further research is necessary to establish the genetic underpinnings of sporadic SC.

Only **one case**, reported by **Rowe et al. (2015)**, exhibited **distant metastasis**, with nodules and **hypermetabolic lymph nodes** in the **mediastinum, bilateral lungs, upper inner left thigh**, and **left buttock**. Given the multiple lesions, **IHC testing for PMS-2, MLH-1, MSH-2, and MSH-6** was conducted. Nuclear reactivity indicated **no microsatellite instability**, effectively ruling out **Muir–Torre syndrome**.

### ****Treatment and Prognosis:****

The **treatment of choice** for sebaceous carcinoma is **surgical excision with clear margins**. **Radiotherapy** is considered for cases with **metastasis** or **high recurrence risk**. **Multi-agent chemotherapy** has also been used in **recurrent cases**. However, due to its **propensity for local recurrence and metastasis**, **long-term follow-up** is strongly recommended.

**Conclusion:**
Oral sebaceous carcinoma is an extremely rare and aggressive malignancy, with a significant potential for local recurrence and distant metastasis. Regular follow-up is crucial for early detection of recurrence or spread. Increased awareness among clinicians and pathologists about the occurrence of sebaceous carcinoma in the oral cavity can aid in accurate diagnosis and improve patient outcomes through timely intervention.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, manuscript.

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