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# Salivary Gland Cancers: A Survey through History, Classifications and Managements

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## Abstract

In this chapter, we are going to discuss about salivary glands cancers, their clinical manifestations and categories, pathogenesis, diagnosis and treatment. We will go through details in each part in both clinical and surgical aspects based on recently prominent published studies and research in prestigious journals. After a short review on clinical features, epidemiology, pathogenesis, diagnosis and treatment, we will show staging and tumor node metastasis (TNM) classification of major salivary gland tumors and also basic principles of approach to salivary gland cancers. A little will be explained about basic surgical procedures for removal of cancers and benign tumors.

**Keywords:** cancer, salivary gland, classification, benign tumors

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## 1. Embryology, anatomy and structure of salivary glands

There are three pairs of salivary glands in human: parotid (PG), submandibular (SMG) and sublingual gland (SLG). They all have the same architecture; an arborized duct which opens into the oral cavity with secretory end pieces called acini which produce the saliva [1]. A mixed structure of extracellular matrix, myoepithelial cells, myofibroblasts, immune cells, endothelial cells, stromal cells, and nerve fibers surround the acinar cells. The main excretory duct of PG is Stensen's duct which opens in buccal mucosa near the second maxillary molar after crossing the masseter muscle and penetrating buccinators muscle. Submandibular glands secrete the saliva through their main excretory duct, called Wharton's, which opens

into the oral cavity under the tongue by the lingual frenum at a structure called the sublingual caruncle. In contrast, sublingual gland has small ducts called ducts of Rivinus and a common duct, Bartholin's duct, which connects with Wharton's duct at the sublingual caruncle [1].

Blood supply of parotid gland is mainly provided by the transverse facial artery and SMG by the facial artery. Postganglionic nerves from the otic and submandibular ganglia provide parasympathetic innervation. Superior cervical ganglion makes sympathetic postganglionic nerves which innervate the glands along blood vessels [1, 2]. Facial nerve is closely associated with PG capsule and facial nerve injury resulting in hemifacial paralysis is a major complication of parotid gland surgery. Lingual nerve accompanies Wharton's duct and then lingual nerve injury may be a complication of surgical exploration of floor of mouth for salivary stones removal.

Major salivary glands produce over 90% of saliva in a healthy adult. Saliva excretion is stimulated by both parasympathetic and sympathetic autonomic nervous system necessary for lubricating the oral cavity to enable eating, talking, swallowing, dental health and maintaining oral homeostasis, tasting, while also providing protective functions and aiding in digestion. Different types of saliva are produced by two types of acinar cells. Parotid gland secretes watery serous saliva produced by serous acini. SMGs and SLGs contain both serous and mucous acinar cells. Most of the acinar cells in SMGs are serous, while the majority of SLG is composed by mucous acinar cells. In addition to major salivary glands, there are several minor glands which are widely distributed across the oral mucosa [3].

Major salivary glands start to develop at 6–8 weeks of gestation. Oral ectoderm starts thickening to produce placodes of major glands. Growth factors and other necessary molecular cues for epithelial branching morphogenesis are provided by neural crest-derived mesenchyme. SMGs seem well differentiated with desmosomes and microvilli projected from cells along lumens by 13–16 weeks of gestation. At 16 weeks, the striated and intercalated ducts can be recognized and acinar cells begin to predominate tissue by 20–24 weeks [4]. Salivary glands continue to develop up to 28 weeks and glands can secrete saliva at birth.

## 2. Salivary gland neoplasms

Salivary gland tumors are a diverse group of neoplasms in terms of both morphology and clinical manifestations. These tumors have an incidence of approximately 2.5 cases to 3.0 cases per 100,000 per year [5]. Salivary gland malignancies consist more than 0.5% of all malignancies and approximately 3–5% of all head and neck cancers [6]. Salivary gland tumors usually involve people in their sixth or seventh decade of life [7, 8]. Recent studies have indicated that incidence of major salivary glands are increasing [9].

The exact etiology of salivary gland malignancies has not been determined; however ionizing radiation is indicated as a cause of salivary gland cancer [6, 7, 10, 11].

Tumors of salivary gland are related to both major and minor salivary glands. Minor salivary gland lesions are more frequently seen in palate; however, they can be found throughout

oral cavity as oral mucosa, posterior tongue, larynx, pharynx, paranasal sinuses, retromolar and peritonsillar areas, uvula and floor of mouth [6, 12]. More than 50% of salivary gland tumors are benign and about 70–80% of all salivary gland neoplasms originate from parotid gland [13]. Different sites have different rate of malignancy so that 20–25% of parotid, 35–40% of submandibular, 50% of palate and more than 90% of sublingual gland tumors are malignant [14].

Comprising about 50% of all salivary gland tumors and 65% of parotid gland tumors, pleomorphic adenoma is the most common benign minor and major salivary gland tumor. On the other hand, mucoepidermoid carcinoma is the most prevalent major and minor salivary gland tumor comprising 10% of all salivary gland and about 35% of malignant salivary neoplasms [15]. This neoplasm mostly occurs in parotid gland [15, 16].

Most benign major and minor salivary gland tumors present with painless swelling of the parotid, submandibular or sublingual glands. Numbness or weakness which are signs of nerve involvement, typically indicate malignancy. Facial nerve weakness accompanied by parotid tumor is not a pleasant sign. A majority of benign and malignant tumors of parotid gland present as asymptomatic mass in the gland [13].

Tumors have more favorable prognosis when present in major salivary glands; parotid gland tumors have the best prognosis followed by submandibular gland. On the other hand, sublingual and minor salivary gland tumors have less favorable prognosis. Adequate surgical resection is enough for curing early-stage low-grade major and minor salivary gland tumors. In contrary, high-grade tumors have poorer prognosis and may need postoperative radiation therapy [17]. In addition, histology, grade, extent of primary tumor (stage), facial nerve involvement, fixation to skin or deep structures and lymph node or distant metastasis are among other factors involved in prognosis [18, 19].

### 3. Classification of tumors

Several pathological classifications have been proposed for salivary gland tumors since 50 years by several authorities such as Armed Forces Institute of Pathology and the World Health Organization (WHO). In 1954, there were only 16 salivary gland epithelial tumor entities in pathological classification which increased to 36 entities in 1996 showing an evident progress [20]. **Table 1** shows WHO histological classification of epithelial tumors of the salivary glands.

#### 3.1. Acinic cell carcinoma

Acinic cell carcinoma (AcCC) comprises one of six parotid cancers which is supported by a nationwide study in the Netherlands where 15% of parotid malignancies were AcCC [21–23]. Based on 1973–2009 Surveillance, Epidemiology, and End Results (SEER) analysis AcCC comprises 11% of salivary malignancies [24]. AcCC has an average annual incidence of 0.13 cases per 100,000 patients per year. Also approved by other studies, SEER program indicated that AcCC has a higher average incidence for females than males (0.15 cases vs. 0.11 cases per

**Malignant epithelial (n = 24)**

Acinic cell carcinoma

Oncocytic carcinoma

Mucoepidermoid carcinoma

Salivary duct carcinoma

Adenoid cystic carcinoma

Adenocarcinoma (NOS)

Polymorphous (LG)

Adenocarcinoma

Myoepithelial carcinoma

Epithelial-myoepithelial carcinoma

Carcinoma ex pleomorphic adenoma

Clear cell carcinoma (NOS)

Carcinosarcoma

Basal cell adenocarcinoma

Metastasising pleomorphic adenoma

Sebaceous carcinoma

Squamous cell carcinoma

Sebaceous lymphadenocarcinoma

Small-cell carcinoma

Cystadenocarcinoma

Large cell carcinoma

LG cribriform cystadenocarcinoma

Lymphoepithelial carcinoma

Mucinous adenocarcinoma

Sialoblastoma

**Benign epithelial (n = 10)**

Pleomorphic adenoma

Lymphadenoma

    Sebaceous

    Nonsebaceous

Ductal papilloma

    Inverted ductal papilloma

    Intraductal papilloma

    Sialadenoma papilliferum

Myoepithelioma  
Basal cell adenoma  
Warthin tumor  
Oncocytoma  
Canalicular adenoma  
Sebaceous adenoma  
Cystadenoma

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**Table 1.** WHO (2005) histological classification of epithelial tumors of the salivary glands, squamous cell carcinoma (SCC) and tumors like “carcinoma in pleomorphic adenoma”.

100,000 patients) [25, 26]. Patients with AcCC have a median age of 52 years at the time of diagnosis and it occurs more in younger ages than other salivary gland tumors [27]. One-third of patients are under 40, one-third between 40 and 59 and one-third above 60 years of age [24]. AcCC more frequently occurs in whites (85%) than in blacks (7%) or other races (8%) [24, 28]. There are no known risk factors for AcCC; however, family history and radiation exposure have been proposed as potential risk factors [29].

The most common clinical feature of AcCC is a slow-growing swelling and its association with pain or fixation to neighboring structures is an indicator of poor prognosis [25]. Nodal metastasis is really uncommon at the time of diagnosis [26]. AcCC is less common in minor salivary glands and comprises only 9% according to SEER database [30]. AcCC of minor salivary glands mostly occur in buccal mucosa and upper lip in contrast to other types of minor salivary glands which mostly occur in palate [31, 32].

### *3.1.1. Diagnosis and preoperative assessment*

Since AcCC often presents symptomless, preoperative assessment seems necessary to determine location of tumor, extent and malignancy indicators as in parotid surgery these factors show the risk of facial nerve injury [33]. Imaging is highly suggested when a glandular swelling is accompanied by impaired mobility or when involvement of deeper structures or nerves is suspected [34–37].

Imaging modalities include ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) [33]. AcCC is appeared defined, lobular, hypoechoic, heterogeneous and poorly vascularized; while on CT, it is appeared regular and variably defined with heterogeneous enhancement [38].

MRI is preferred to CT for assessment of parotid, stylomastoid foramen and neural or perineural invasion [35, 37, 39, 40]. However, it is a rare condition; PET scan is indicated only when there is a high suspicion of distant metastatic disease. Also it is indicated postoperatively in case of AcCC with high-grade transformation [33, 41–43]. Ultrasound-guided fine needle aspiration cytology (FNAC) and ultrasound-guided core biopsy (USCB) are needling procedures for diagnosing AcCC [22, 44].

### 3.1.2. Management

The main treatment for AcCC is surgical resection, as AcCC do not show distant metastasis at the time of diagnosis and is usually an accessible tumor [25, 33]. For low-grade AcCC, surgery alone may be curative; while for known high-grade tumors in risk of positive margins, bone or nerve invasion and nodal metastasis a more aggressive approach is needed. A preoperatively paralyzed or involved facial nerve should be resected and repaired by interposition graft from greater auricular or sural nerve [22]. Elective neck dissection is not recommended; nevertheless patients with large or high-grade tumors may benefit from level II, III and IV neck dissections [26].

Radiotherapy is not necessary for low grade, low stage and adequately resected AcCCs [45]. As like other salivary gland cancers, criteria for radiotherapy include recurrent disease, advanced T-classification (T3/T4), positive margins, pathologically positive cervical lymph nodes, perineural invasion, high-grade and high proliferative tumors [24, 26, 28].

Role of chemotherapy is not exactly known in treatment of AcCCs; however, mTOR inhibitors may be beneficial [22].

## 3.2. Mucoepidermoid carcinoma

Defined as “a malignant glandular epithelial neoplasm characterised by mucous, intermediate and epidermoid cells, with columnar, clear cell and oncocytoid features” by World Health Organization (WHO), mucoepidermoid carcinoma (MEC) was first described by Masson and Berger [46–48]. MEC is considered as the most common primary salivary gland malignancy and patients have a mean age of 45 years old at the time of diagnosis [49, 50]. Children are rarely involved and gender differences are not marked [51, 52].

Parotid is the most commonly involved major salivary gland and MEC of minor salivary glands is usually found on the palate followed by buccal mucosa, tongue, lips and floor of mouth [51]. Another important location is retromolar area in which 18% of intra-oral MECs can be detected [53]. MEC may also be rose from salivary-type glands in sinonasal and laryngeal mucosa lachrymal and ceruminous glands, and even nodal glandular inclusions [54–57].

The most common clinical manifestation of MEC is a painless, variously fixed, rubbery or soft mass. Intra-oral tumors may appear as a blue-red tinged swelling which mimics a mucocele or vascular tumor because of their superficial location [51, 53]. The interval between initial symptoms and diagnosis differs depending on the site of origin [16]. Sublingual MEC is painful and patients are usually diagnosed earlier than parotid or submandibular tumors [16].

### 3.2.1. Preoperative assessment

Imaging is less necessary for diagnosing MECs unless they are located on the palate or retromolar area of mandible or involvement of deeper structures or cranial nerves is suspected [46]. CT scan is beneficiary for assessment of bone invasion by the tumor; while MRI is better for soft tissue. Ultrasound (US) may be satisfactory if small tumors are located in major

salivary glands; for larger tumors or tumors outside these glands, a combination of CT and MRI is suggested. According to recent studies, positron emission tomography (PET) has been beneficial in loco-regionally advanced tumors [58]. Fine needle aspiration biopsy (FNAB) is another preoperative diagnostic modality which is dependent on expertise of pathologist and number of patients treated in the institute [59].

### 3.2.2. Management

Complete surgical removal of tumor is the treatment of choice in case of anatomically accessible MECs [32]. More treatment planning is needed when MECs are locally advanced, incompletely resected or with positive margins, invaded to bone or nerves, metastasized to lymph nodes or high grade [18, 60].

For low-grade tumors, surgery alone is curative; however, site and size of tumor influence the extent of surgery. For parotid, superficial parotidectomy is enough unless the tumor involves deep lobe [61]. Resection of facial nerve is recommended if there is preoperative facial nerve paralysis or weakness or there is evidence of perineural invasion in frozen section [46]. If submandibular or sublingual glands are involved, resection of the anterior mandible or mylohyoid muscle should be considered. Wide local excision is usually curative if minor salivary glands are involved with low-grade small MECs. Mandibulectomy, maxillectomy, mastoidectomy, infratemporal fossa, anterior craniofacial resection, soft or hard palate resection or resection of cranial nerves may be required in more extensive disease [62]. For tumors in tonsillar area, radical tonsillectomy and ipsilateral neck dissection is applied [32, 63]. Elective neck dissection should be done in high-grade MEC and avoided in low- or intermediate-grade tumors [32].

Radiotherapy is recommended for high-grade MECs and patients with perineural invasion, positive margins and T3–4 classification [64, 65]. For patients with increased risk of nodal metastasis, elective neck irradiation may be applicable [32, 66]. The role of chemotherapy is not approved in the treatment of MECs and some clinical trials are being conducted regarding this issue.

### 3.3. Adenoid cystic carcinoma (cylindroma)

Accounting for about 1% of all head and neck cancers and 10% of all salivary gland tumors, adenoid cystic carcinoma (AdCC) is a rare tumor with a yearly incidence of about 3–4.5 cases per million [67–70]. On the other hand, it is the most common malignancy of minor salivary gland tumors with a proportion ranging from 32 to 71% [67]. AdCC may involve other sites and glands such as lacrimal and ceruminous glands as well as nasal and paranasal sinuses, larynx and trachea [32, 67, 71–74]. AdCC is mostly found in the parotid, submandibular and minor salivary glands. Based on previous studies, AdCC was the most frequent histology of parotid carcinoma [23]. In the submandibular gland, the likelihood of AdCC is even greater as it accounts for 40% of salivary gland cancers [75, 76]. AdCC of minor salivary glands is most frequently found in the palate followed by paranasal sinuses and other parts of salivary glands [32, 77].



Although more prevalent in middle-aged and older patients in fifth and sixth decades of life, AdCC occurs in all age groups [12, 78–81]. Until now, there are no known risk factors for AdCC and smoking has not been proven to affect incidence [82].

The characteristic cribriform arrangement of tumor cells on microscopy and invasion to surrounding structures and nerves were first described in 1853 and 1854 by Robin, Lorain and Laboulbene [83].

AdCC is a really invasive tumor which is recognized by perineural invasion and multiple local recurrences. Although considered rarely, but regional lymph node metastasis may be hidden according to its occult and clinically undetectable nature and lack of pathological assessment of lymph nodes. Hematogenous metastasis is also common especially to lung, bone and liver [83, 84].

As one of the most biologically destructive and unpredictable tumors of the head and neck, the most common clinical manifestation of AdCC is a slowly growing mass followed by pain. AdCC symptoms vary according to the site of disease. The tumor usually presents with a mass in major salivary glands and may lead to facial nerve paralysis when located in parotid [69, 85]. When located in the palate, a mass is common; however, ulcer or even oroantral fistula may be detected. Dyspnea is the first symptom in larynx and nasal obstruction, epistaxis, eye symptoms and deep facial pain are presenting symptoms of nose and paranasal sinuses involvement [32, 86, 87].

### 3.3.1. Preoperative assessment

As other salivary gland malignancies, preoperative imaging of AdCC includes computed tomography (CT) and magnetic resonance imaging (MRI) which help with estimation of disease extent. CT scan is preferred for bone invasion assessment and MRI is more appropriate for evaluation of soft tissue extension or suspected neural invasion presenting as pain or facial nerve analysis [88]. Positron emission tomography (PET) scan in combination with CT is applied for excluding distant metastasis [89].

### 3.3.2. Management

Decision-making for treatment of AdCC depends on tumor location, stage at diagnosis and biologic behavior of tumor reflected in histologic grading [90]. Radical surgical resection of tumor, ensuring free margins, followed by postoperative radiotherapy is the gold-standard treatment for AdCC. Since AdCC has a high potential for infiltrating to neighboring tissue, mainly by perineural invasion, the free margin may not be reached. In anatomical sites with difficult access, incomplete resection has remained as a problem.

In case of parotid involvement, facial nerve should be preserved if it is not paralyzed preoperatively and not involved by tumor at the time of surgery. Radiotherapy after surgery is considered as an appropriate adjuvant therapy for possible residual tumors on nerve branches [45, 91, 92].

Neck dissection is only performed in patients with clinically positive lymph nodes; however, it is not common in AdCC especially for parotid malignancies [93]. The number of involved

lymph nodes is higher in minor salivary glands AdCC. Lymph nodes could also be involved by direct extension of primary tumor when AdCC is located in parotid, submandibular gland and larynx [94, 95]. Despite combination therapy with surgery and radiotherapy, local recurrence happens [69]. Chemoradiotherapy may be considered using various agents in patients with adverse prognostic factors [96]. To the best of scientists' knowledge, patients with locally recurrent or metastatic AdCC may not experience cure by systemic treatment using cytotoxic chemotherapy or targeted molecular therapies [69]. So chemotherapy may be considered as a palliative treatment for patients with poorly-controlled disease or symptomatic metastasis [97].

### **3.4. Basal cell adenocarcinoma**

Basal cell adenocarcinoma (BCAC) occurs equally in both genders and usually involves patients in fifth or sixth decades of their lives [98]. In the setting of syndromic disease, it may have multifocal lesions of multiple cylindromatosis and trichoepitheliomas (Brooke-Spiegler syndrome) [99]. Basal cell adenocarcinoma usually has an indolent behavior but may be locally aggressive and one-third of cases experience recurrence. It has been reported that BCACs have a regional and distant metastatic rates ranging from 8 to 12% and 2 to 4%, respectively [100, 101]. The main treatment strategy for basal cell adenocarcinoma is surgery with lymph node dissection, if required. High-stage tumors are treated with radiotherapy which may improve outcome [101].

### **3.5. Epithelial-myoepithelial carcinoma**

As a biphasic salivary gland malignancy, epithelial-myoepithelial carcinoma (EMCA) may occur at any sites containing salivary or seromucinous glands [98]. It is mostly (60–80%) prevalent in parotid glands and involves people in sixth decade of life. Female-male ratio is 3:2 [102]. *RAS* mutation is detected in 20 to 25% of cases with predominancy of HRAS codon 61 mutations [103]. EMCA is typically a low-grade tumor and has an estimated 5-year disease-specific survival (DSS) of 90–95% and 10-year DSS of 80–90% [102, 104]. Often late, but about one-third of patients experience recurrence with a median disease-free survival (DFS) of 11 years. Regional and distant metastases are uncommon [104]. Factors like margin status, vascular invasion, necrosis, and high-grade features are among important prognostic factors [102]. EMCA is surgically treated with no sensible effect of radiotherapy [102, 104].

### **3.6. Mammary analogue secretory carcinoma, a new entity**

Mammary analogue secretory carcinoma (MASC) is a newly defined salivary gland malignancy based on morphologic and molecular features [44, 105]. Previously, most of MASC were marked as acinic cell carcinoma or adenocarcinoma not otherwise specified [98]. Both genders are equally involved and MASC typically occurs in fifth to sixth decades of life.

There are limited data on management of MASC; it may have a higher rate of lymph node metastasis (up to 25%) than acinic cell carcinoma [106]. Nonetheless, surgery is the main treatment for MASC.

## 4. TNM classification and staging of major salivary gland tumors

The most common system for cancers in the major salivary glands is the TNM system of the American Joint Committee on Cancer (AJCC), available at (<https://www.cancer.org/cancer/salivary-gland-cancer/detection-diagnosis-staging/staging.html>).

### T groups for major salivary gland cancers:

**TX:** The main (primary) tumor cannot be assessed; information not known.

**T0:** No evidence of a primary tumor. (For example, the cancer was first found in the lymph nodes, but the main tumor itself can't be found.)

**T1:** Tumor is 2 cm (about  $\frac{3}{4}$  inch) across or smaller. It's not growing into nearby tissues.

**T2:** Tumor is larger than 2 cm but no larger than 4 cm (about  $1\frac{1}{2}$  inch) across. It is not growing into nearby tissues.

**T3:** Tumor is larger than 4 cm across and/or is growing into nearby soft tissues.

**T4a:** Tumor is any size and is growing into nearby structures such as the jaw bone, skin, ear canal, and/or facial nerve. This is known as *moderately advanced disease*.

**T4b:** Tumor is any size and is growing into nearby structures such as the base of the skull or other bones nearby, or it surrounds the carotid artery. This is known as *very advanced disease*.

### N groups for major salivary gland cancers:

**NX:** Nearby (regional) lymph nodes cannot be assessed; information not known.

**N0:** No spread to regional lymph nodes.

**N1:** The cancer has spread to one lymph node on the same side of the head or neck as the primary tumor. The lymph node is no larger than 3 cm (about  $1\frac{1}{4}$  inch) across.

**N2:** This group includes 3 subgroups:

- **N2a:** The cancer has spread to one lymph node on the same side as the primary tumor. The lymph node is larger than 3 cm but not larger than 6 cm (about  $2\frac{1}{2}$  inches) across.
- **N2b:** The cancer has spread to more than one lymph node on the same side as the primary tumor, but none of the lymph nodes are larger than 6 cm across.
- **N2c:** The cancer has spread to one or more lymph nodes, none larger than 6 cm across, either on the side opposite the primary tumor or on both sides of the neck.

**N3:** The cancer has spread to a lymph node that is larger than 6 cm across.

### M groups for major salivary gland cancers:

**M0:** The cancer has not spread to tissues or organs far away from the salivary glands.

**M1:** The cancer has spread to tissues or organs far away from the salivary glands.

### **Stage grouping:**

**Stage I: T1, N0, M0:** The tumor is no more than 2 cm across and is not growing into nearby tissues (T1). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

**Stage II: T2, N0, M0:** The tumor is larger than 2 cm but is no larger than 4 cm across and is not growing into nearby tissues (T2). It has not spread to nearby lymph nodes (N0) or distant sites (M0).

**Stage III:** Either of the following:

**T3, N0, M0:** The tumor is larger than 4 cm across and/or is growing into nearby soft tissues (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).

or

**T1 to T3, N1, M0:** The tumor is any size and may have grown into nearby soft tissues (T1 to T3). The cancer has spread to one lymph node on the same side of the head or neck as the primary tumor, but the lymph node is no larger than 3 cm across (N1). The cancer has not spread to distant sites (M0).

**Stage IVA:** Either of the following:

**T4a, N0 or N1, M0:** The tumor is any size but has grown into nearby structures such as the jaw bone, skin, ear canal, and/or facial nerve (T4a). It may or may not have spread to one lymph node (no larger than 3 cm across) on the same side of the head or neck as the primary tumor (N0 or N1). The cancer has not spread to distant sites (M0).

or

**T1 to T4a, N2, M0:** The tumor is any size and may or may not have grown into nearby soft tissues or structures such as the jaw bone, skin, ear canal, and/or facial nerve (T1 to T4a). The cancer has spread to more than one lymph node, to a lymph node larger than 3 cm across, or to lymph nodes on the other or both sides of the neck. None of the lymph nodes are larger than 6 cm across (N2). The cancer has not spread to distant sites (M0).

**Stage IVB:** Either of the following:

**T4b, Any N, M0:** The tumor is any size and has grown into nearby structures such as the base of the skull or other bones nearby, or it surrounds the carotid artery (T4b). The cancer may or may not have spread to nearby lymph nodes (any N). It has not spread to distant sites (M0).

or

**Any T, N3, M0:** The tumor is any size and may or may not have grown into nearby soft tissues or other structures (any T). The cancer has spread to at least one lymph node that's larger than 6 cm across (N3). It has not spread to distant sites (M0).

**Stage IVC: Any T, Any N, M1:** The tumor is any size and may or may not have grown into nearby soft tissues or other structures (any T). The cancer may or may not have spread to nearby lymph nodes (any N). It has spread to distant sites (M1).

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