REVIEW ARTICLE

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# Carcinomas of the Oral Cavity and Oropharynx: A Lethal Disease Barely Known

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## ABSTRACT

Cancer in the oral cavity and oropharynx is rare yet lethal; at least 50% of affected patients die of this disease. This health condition is associated with tobacco exposure and alcohol consumption, although there is a growing incidence among non-smoker/non-drinker populations, especially young people, in which human papillomavirus infections seem to be another cause. Unfortunately most of these patients are diagnosed in advanced stages, in spite of the accessible location of the tumors.

Tobacco control and accurate diagnosis of early and premalignant lesions are crucial in order to diminish incidence and prescribe efficient treatments aimed at achieving the best local control, with minimal functional and aesthetic impact and better survival. Although there is some controversy regarding the current treatments, for advanced tumors the best results are obtained with multidisciplinary management; however, the results are still poor. We present an updated review of the information available on this deadly, but barely known disease. (J CANCEROL. 2014;1:43-54)

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## INTRODUCTION

Oral and buccopharyngeal cancer represents around 2% of all malignant tumors in Mexico, excluding skin cancer. Most are diagnosed in advanced clinical stage (65%), in association with high mortality and significant functional and aesthetic sequelae. The disease most often affects males, and 90% of these cases are attributed to tobacco and alcohol; however, this statement applies to only 22% of women. It has been proposed that human papillomavirus (HPV) type 16 is a causative agent in oropharyngeal cancer, but it seems less significant in oral cancer.

Early tumor cases (the fewest) are successfully treated either with surgery or radiation therapy. In moderately advanced stages (III and IVA) or advanced resectable tumors a multidisciplinary treatment of surgery and adjuvant therapy is used. In oropharyngeal cancer, chemoradiation therapy usually leads to more favorable outcomes than radiotherapy alone: nevertheless, very advanced or unresectable tumors are associated with discouraging prognoses and require combinations of chemoradiation therapies. Metastatic tumor cases are incurable and treated with palliative measures.

## EPIDEMIOLOGY

According GLOBOCAN 2012, in Mexico around 3,000 cases of oral and oropharyngeal cancer are reported every year, and the adjusted mortality rate is 0.7/100,000 in oral cavity and 0.4/100,000 in oropharynx[1]. In clinical experience, for every three cases in the oral cavity there is one in the pharynx. The male/female ratio is 1.4:1 in oral cavity and 3:1 in oropharynx[2].

Globally, although the mortality rate is low, it is significant because one out of two affected patient dies. In our experience, as previously reported by others, the highest incidence age is around 50 to 70 years old, with 60 being the average for both male and female patients[3,4].

## RISK FACTORS

It is very well known that up to 90% of cases are due to the effects of tobacco and alcohol, and the risk is correlated to the intensity and time of exposure; simultaneous conditions produce a synergistic effect, which increases the relative risk to at least 40. On the one hand, tobacco contains nitrosamines and polycyclic compounds directly connected to genotoxic effects[5]. On the other hand, alcohol effects are regulated by polymorphism of genes that codify for metabolic enzymes (alcohol dehydrogenase, aldehyde dehydrogenase, and cytochrome P450 2E1), folate metabolism, and DNA repair. The mechanisms by which alcohol exerts its carcinogenic consequence include a direct genotoxic effect of acetaldehyde, the primary metabolite of alcohol[6].

According to the evidence, 89% of men with oral cancer smoke, while only 22% of women do, and therefore other factors must be involved. Epidemiologic evidence suggests HPV 16 is a causal agent in the oropharynx, particularly in palatine tonsil and tongue base[7]. In our experience in México, only 5% of oral cancers are related to this virus, less than expected[8], however, other authors should confirm such information.

## MOLECULAR PATHOGENESIS

Neoplastic progression is associated with genetic alterations that lead to dysplasia (9p21, 3p21, 17p13), carcinoma *in situ* (11q13, 13q21, 14q31), and invasive carcinomas (4q26-28, 6p, 8p, 8q). Studies suggest the contribution of suppressor genes such as *p16* and *p14*ARF, responsible for the G1 phase of cell cycle regulation and degradation mediated by MDM2 of p53, *APC* and *P53.* Chromosomal loss of 9p21 region in 70-80% of dysplastic lesions in oral mucosa and inactivation of remnant alleles

of *p16* and *14*ARF by hypermethylation has been documented[9]. Our data reported inactivation of hMLH1, essential for reducing accumulation of mutations and genomic stability by promoter methylation. These events occur early in the genesis of squamous carcinomas[10].

As observed in other malignant neoplasms, unlimited replicative potential is obtained by genetic or epigenetic inactivation of *p16, P53* and increased activity of telomerase. Functional loss of *p16* prevents stress-induced senescence, while increased activity of telomerase prevents shortening of telomeres and signaling that affects p53 and other molecules involved in the response to DNA damage[11].

Most carcinomas lose the ability to inhibit aberrant growth due to inactivation of p16, whose normal function is to restrain the atypical union of cyclin to CDK4 and CDK6, responsible for conducting cell cycle and suppressing the activity of RB product *(RB1)*. When pRb is hypophosphorylated, a complex is produced with transcription factor E2F, which inhibits transcription mediated by E2F of growth-promoter genes. Stimulation by mitogens leads to phosphorylation and pRb inactivation, triggering DNA synthesis in the cell[12]. The RB1 mutations are rare, although Rb loss has been described in premalignant and advanced lesions; meaning that p16 inactivation, besides others in p16-Rb gene tumor-suppressor's pathway, is associated to a proliferative advantage[13].

In contrast, about 50% of the carcinomas have mutations in the P53 gene, which stops cell cycle progression when there is DNA damage and may trigger apoptosis if the DNA is not repaired. Inactivating mutations of p53 are related to tumor progression and discouraging prognoses. In fact, loss of heterozygocity in p53 and tobacco-induced mutations in the coding sequence of P53, or accelerated destruction of the p53 protein product, by viral oncoproteins such as HPV E6, represent common alterations[14,15].

In the absence of mutations in p53, p53 can also be inactivated by dependent degradation of ubiquitin caused by binding of the E6 protein of HPV-16 and HPV-18 or MDM2 protein; the first is particularly important in cases involving persistent HPV infection, typical in the oropharynx. In that case, oncogenic HPV infection, overexpression of MDM2, p14ARF or inactivation may result in functional impairment of p53, favoring accumulation of genetic alterations[16].

Among the best-studied growth factor receptors is the EGF receptor family epidermal growth factor receptor (EGFR), also known as ErbB receptors, essential in many normal cellular processes. Aberrant activation of these receptors is related to numerous tumors, including 80-90% of upper aerodigestive tract carcinomas (UADTC). Indeed, EGFR overexpression is an independent prognostic factor that correlates with tumor volume increase, diminishment of radiation sensitivity, and higher relapse risk[17].

Overexpression of EGFR produces kinase activation by spontaneous dimerization. Constitutive activation causes autocrine stimulation by co-expression of EGFR with one of its ligands: transforming growth factor alpha (TGF-$\alpha$). Once activated by EGFR, this stimulates events that contributed to cell growth[18]. Together with the EGFR signaling pathway, activated protein kinase mitogen/Ras/Raf (MAPK), activated transcription factor signal transducer, and activator of transcription (STAT) pathway and the phosphatidylinositol 3 kinase-inositol (PI3K/AKT/mTOR) contribute to the growth and metastatic potential of UADTC[19].

Other modifications are aberrant activation of transcription factor of nuclear factor kappa B (NF-$\kappa$B), activation of STAT, Wnt, activation of TGF-$\beta$, and other alterations in PI3Ks, PTEN, AKT, and mTOR. The understanding of genetic and molecular changes involved in UADTC progression has prompted the generation of promising treatments, more specific and less toxic.

## TYPES AND HISTOPATHOLOGIC VARIANTS

Squamous cell carcinomas (SCC) have a long preclinical history, accumulating genetic and molecular alterations, which lead to morphologic changes. Such is the case of premalignant lesions, which when left to their natural course, often end up turning invasive. For instance, in the oral cavity, leukoplakia, erythroplasia, and verrucous hyperplasia commonly coexist with mild, moderate, and grave dysplasia, including invasive carcinoma. Degeneration risk is proportional to the intensity of the subjacent dysplasia and varies widely, as in the case of erythroplasia, in which may be higher, besides the exposure to the aforementioned risk factors.

In our experience, 65% of oral cavity malignancies are SCCs, 8% mucoepidermoid carcinomas, 8% adenoid-cystic carcinomas, 2% adenocarcinomas, and the rest are a variety of rare tumors[20]. Oropharynx tumors tend to be less differentiated, usually the basaloid variant, along with greater metastatic capacity than those in the oral cavity.

## DISSEMINATION PATTERNS

Squamous cell carcinomas are characterized by a locoregional invasive pattern; they destroy adjacent tissues, then, when tumors reach 2-3 mm of depth of invasion in the tongue and floor of the mouth, malignant cells penetrate the lymphatic channels and reach the regional nodes.

Tumors located on mucus adhered to bone spread into the lymph much later than those located on soft tissues such as the tongue or floor of the mouth. Most affected nodes are in levels I, II, and III[21], while oropharyngeal cancer most frequently affects levels II, III, IV, and retropharyngeal nodes[22]. Additional levels can be affected when there is involvement of the mentioned levels. There is a differential pattern according to each subsite: anterior floor of mouth and tip of mobile tongue involves sub-menton nodes (Ia), lateral border of tongue involves sub-maxillary nodes (Ib), retromolar trigone affects jugulodigastric (II), and anterior third of tongue involves low jugular nodes (IV).

When tumors involve midline, they can affect both sides of the neck, especially when the primary tumor is in the tongue base. Distant metastases are rare but associated with nodal metastases, capsular rupture, and recurrent tumors (15-20%). The most affected organs are: lungs, liver, and bones. Usually patients die because of uncontrolled locoregional disease with bleeding and inanition, but other times due to second primaries and distant metastases[23].

## FIELD CARCINOGENESIS

Tobacco and alcohol produce their effects in ample zones of mucosa, explaining the changes linked to primary tumors, local relapses, and second primaries. Initially, stem cells acquire genetic alterations and form clonal patches or clonal units of descendent altered cells. These patches are recognized based on TP53 mutations. Additional genetic alterations lead to reproductive advantages so that the proliferating field gradually displaces normal mucosa.

Finally, clonal divergence produces one or more tumors inside preneoplastic cells and this field usually persists after surgery and can lead to second primaries or local relapse. The definition of one or the other depends on the exact site of their anatomical connection with the index tumor and the time interval separating both tumors[24].

Synchronic second primary tumor is evident before six months of index tumor diagnoses; metachronic tumor occurs afterwards. A second primary develops at a rate of 3-7% individuals per year. When the index tumor is located in the oral cavity and oropharynx, second primaries most commonly

appear on the same sites; however, in the esophagus and lung they are not rare[25].

According to the authors' evidence, second primary tumors appear more often in skin (43%) and in the oral cavity and lungs, with 22% each. Human papillomavirus tumors are associated with a lower risk of second primaries[26].

## CLINICAL MANIFESTATIONS

The most affected sites are mobile tongue (lateral borders), gums, lips, and floor of mouth, hard palate, oral mucosa, and retromolar trigone. In oropharynx, the most affected sites are tongue base, tonsillar fossae, soft palate, and posterior wall.

In our experience, 65% of tumors are 4 cm or larger and only 6% are less than 2 cm; 62% of males and 53% of females have palpable clinical adenopathy; 65% of patients are stages III and IV. The most common warning sign is a tiny and superficial lesion, which evolves into a larger and exophytic one, or more frequently an endophytic one, which may be ulcerated or not. Pain is uncommon, and when presented means a dismal prognosis because of perineural involvement. Gum tumors can produce dental mobility and spontaneous loss; hence they are usually confused with periodontal disease.

Advanced oropharyngeal tumors may debut with local pain, however otalgia, cervical lymphadenopathy, trismus, odynophagia, dysphagia, and bleeding are more common, as well as diminished mobility of tongue and fistula formation. Palpable adenopathy can be solitary, multiple, of variable dimensions, spherical, usually hard, confluent and mobile, or fixed to subjacent tissues.

## SCREENING

There are no screening programs as a public health measure, but it is good clinical practice to explore the oral cavity in every physical examination, particularly among smokers and drinkers, because early diagnosis abates mortality[27].

## DIAGNOSIS AND EVALUATION

Diagnosis must be established in early stages due to accessibility of the oral cavity and buccopharynx. Any persistent lesion lasting longer than two weeks should arouse suspicion, especially among individuals with risk factors. Indirect data such as decreased mobility of the tongue and trismus indicate extensive muscle invasion of mouth floor, masticator space and probable invasion of the skull base. In such a scenario a biopsy should be obtained, including leukoplakia and erythroplasia lesions, with a supravital stain in order to guide such analysis. Laboratory studies should assess nutritional status and concurrent conditions; chest radiography, hepatic function test, as well as calcium and phosphorus evaluations. Paraneoplastic hypercalcemia is frequently present, and indicates a worse prognosis[28].

Contrast computed tomography (CT) scan is mandatory when osseous invasion is suspected, except for superficial, small, and accessible tumors. Magnetic resonance imaging (MRI) is preferred for tumors of difficult access, in tongue base, posterior floor of mouth, tonsillar fossae, posterior wall of pharynx, and advanced tumors, due to better contrast of soft tissues and less artifact due to dental materials[29].

A CT scan is superior for mandible invasion, especially when tumors are located in the floor of the mouth and gums; nevertheless, when tumor involves medullar channel, MRI delineates invasion with precision[30]. When a CT scan shows an adenopathy with hypo-dense core, it is almost invariably a neoplasia, yet lymph nodes > 15 mm are also suspicious. Laryngoscopy, esophagoscopy, and bronchoscopy are indicated to identify synchronic tumors, present in 10-15% of cases, but

the impact in mortality is minimal, so they are only used selectively, especially if chest CT is normal[31].

## ETAPIFICATION AND PROGNOSIS

Clinical stage is used for comparison of results, to provide a prognosis and guide treatment. The AJCC-UICC 2010 system is a clinical type but considers image studies. It is applied only to carcinomas and minor salivary gland tumors. The five-year survival for oral cavity cancer, lip excluded, is 57.5-60.8% for stage I, 45-48.9% for stage II, 34.0-38.6% for stage III, and 25.0-27.8% in stage IV (95% CI). In oropharynx, five-year survival is 56.8-61.7% for stage I, 44.7-48.8% for stage II, 34.1-38.9% for stage III, and 25.4-28.2% for stage IV (95% CI)[32].

## PROGNOSTIC FACTORS

Prognostic factors associated with increased risk of relapse and worse survival are the presence of lymph node metastases, and if so, increasing the number and size, nodal mobility limited or absent, the presence of extracapsular invasion and location of nodal metastases levels beyond those primarily affected[33].

Extranodal extension frequency is associated with other adverse prognostic factors and doubles the risk of local and distant recurrence and triples the risk of regional relapse. It is more frequent in advanced ages, smokers and drinkers, in larger size nodes, less differentiated tumors, and positive margins. In addition, it reduces survival prognosis to 50% in relation with those with positive nodes but without extranodal extension[34]. Other associated factors are: increasing size of primary tumor, poor differentiation, perineural extension, infiltrating borders, vascular and lymphatic embolism, and depth of invasion > 3-4 mm[35]. Osseous invasion is not an independent prognostic factor but a pattern, inherent in aggressive tumors[36].

## TREATMENT PRINCIPLES

In absence of distant metastases, the objective is to eradicate disease and preserve quality of life. Early disease (stage I and II) is treated with surgery or radiotherapy with comparable oncological results, but there are some differences in morbidity and sequelae. Radiotherapy preserves function and shape, avoids surgical risks, and can be superior in tumors with imprecise borders and fast growth. However, the disadvantages include mucositis, xerostomia, prolonged treatment, and it is not suitable for tumors adjacent to or invasive of osseous structures because response can be suboptimal, it is difficult to evaluate response, and can be associated with osteoradionecrosis. Surgery allows histopathological evaluation, and provides useful prognostic information in the design of the overall treatment plan; on the other hand, it may cause important esthetic and functional sequelae, especially if it is improperly indicated or inaccurately performed.

Surgical procedure is a good choice for accessible areas, where resection causes minor sequelae, as in lateral borders of the tongue, the anterior segment of the floor of the mouth (without mandibular involvement), posterior wall of the oropharynx, tonsillar fossa, or in gingival tumors.

Advanced but resectable tumors (stages III and IVa) are treated with multimodal therapy, with a combination of surgical resection and adjuvant treatment. In tumors of difficult resection, surgery has been performed after preoperative radiation or induction chemotherapy; however, with the former, there is a higher risk of postoperative complications. This sequence can produce similar oncological results to initial surgery[37].

Unresectable tumors (clinical stage IVb) are those for which complete resection is impractical, since the extent of locoregional disease is such that complete excision with clear margins is unlikely, or when the sequelae or mortality associated with

surgical procedure is unacceptable. These patients can be treated with concurrent chemoradiation, and complementary surgery can be performed if tumors turn resectable. Although controversial, patients undergo surgery when attaining complete clinical response and original nodes were > 3 cm (N2 or N3). Nevertheless, in oropharyngeal tumors, neck can be observed if a complete response is documented by PET-CT, ultrasonogram and fine needle biopsy.

Surgery is also advisable when response in neck is partial but nodes are resectable and primary tumor is under control[38]. Currently, metastatic tumors (IVc) are incurable, and thus treatments are merely palliative.

## SURGICAL MARGINS IN SOFT AND OSSEOUS TISSUES

Surgery must obtain a macroscopic three-dimensional margin of 10 mm around visible and palpable edge of tumor, but a 15 mm margin is required with poorly differentiated or roughly defined tumor borders. If the margin is consistent, a transoperatory study could be dismissed, but if at some crucial point it is not easy to reach such edge homogeneity, an intraoperative frozen section of the suspect site is resorted to. A 5 mm microscopic margin has been recommended to obtain good local control, but a positive margin that is enlarged is not associated with good local control because it denotes an aggressive tumor[39]. Less ample margins are acceptable in tumors near bone, such as mandible or hard palate, because a non-radiated periosteum layer is resistant to invasion. Limited margins increase the risk of local failure.

## FLOOR OF MOUTH, MOBILE TONGUE, AND ORAL MUCOSA TUMORS

Small or superficial tumors and those located in anterior portions of the oral cavity are approached by a trans-oral approach; however, larger, infiltrative, and posterior located tumors are best reached via a trans-mandibular approach or by an inferior cheek approach, or more recently, by an endoscopic approach. Most small tumors are treated with surgery instead of radiotherapy[40]. Brachytherapy is used with mandible protectors in order to avoid irradiation to normal tissues and osteoradionecrosis. Teletherapy is as effective as surgery for subclinical disease; however, surgery is favored in order to avoid xerostomia. Advanced but resectable tumors are treated with surgery and adjuvant treatment. Unresectable tumors are treated with concurrent chemoradiation and surgery if they turn resectable.

## HARD PALATE, GUMS, AND RETROMOLAR TRIGONE TUMORS

These tumors are located on bone and treatment is difficult. These tumors are treated by initial surgery due to the high probability of osseous invasion, where radiotherapy is less effective, response evaluation is more difficult, and osteoradionecrosis risk is higher. If a histopathology report corroborates an early tumor and surgical margins are free, adjuvant treatment is not needed, but if advanced disease is documented, adjuvant treatment is appropriate**.**

## MANDIBLE TREATMENT

There are two types of resections: segmental and marginal. The first case is pertinent when mandibular continuity is interrupted due to an evident tumor invasion surrounding the mandible, there are preceding dental extractions or spontaneous tooth loss (in the same location of the tumor), when a tumor is in contact with previously irradiated mandible, or when there is an advanced bone reabsorption. Surgical margin is 1 cm when the tumor involves a non-irradiated cortical; however, if the tumor has involved medullar channel, a larger resection is needed as well as bone marrow

cytopathology studies[41]. In contrast, when only the tumor invades the periosteum but the bone is intact, a marginal resection is required, which eliminates a layer of bone without altering the mandibular continuity.

## OROPHARYNGEAL TUMORS TREATMENT

In early tonsillar tumors, surgery or radiotherapy is associated with similar oncologic results, and local control exceeds 80%[42]. Surgery is an excellent option when local invasion is minimal[43]. Radiotherapy is preferred when the primary tumor is in the tongue base or soft palate because it produces less functional impact, or when HPV is present because the response is better. Advanced resectable tumor requires a combination of surgery and adjuvant treatment, although primary chemoradiation is a good option because it produces similar results in terms of survival and local control and allows organ conservation[44], especially in those tumors associated with HPV infection[45]. Modulated intensity radiotherapy is associated with lesser early and late toxicity without cost in terms of local control or survival[46,47]. Treatment interruptions and hemoglobin < 12 g/dl at the start of treatment is related to higher locoregional relapse (14 to 37-46%)[48].

Surgical resection as primary treatment or salvage treatment is done through special approaches such as median mandibulotomy, lateral pharyngotomy, or suprahyoid pharyngotomy[49]. Tongue base resections require laryngectomy, but some patients with good respiratory reserve can preserve the larynx[50]. Total glossectomy is used as salvage surgery and pectorals major flap or micro-vascular flaps are used for reconstruction.

## REGIONAL NODE TREATMENT

A recent meta-analysis demonstrated that elective dissection is associated to better survival compared to dissection when node metastasis turns obvious; this study was done with mobile tongue and floor of mouth tumors[51]. In oropharyngeal cancer, elective dissection is recommended because it is associated with better disease-free survival, makes follow-up easier, and detects individuals with bad prognostic indicators for adjuvant treatment.

Elective treatment is considered when metastatic risk is > 20%. In praxis, this happens when tumors in mobile tongue or floor of mouth are > 2 cm, or invasion depth is wider than 3 mm, or they are poorly differentiated, with perineural invasion, or have vascular-lymphatic embolism. It is also indicated in tumors (T3 or T4) of hard palate, gingival border, retromolar trigone, and oral mucosa[52]. In the oropharynx, due to size and intrinsic characteristics, virtually all tumors need elective treatment.

Lateralized tumors in the oral cavity rarely produce contralateral metastases, although recent evidence shows that contralateral relapse occurs in up to 20%, 61% occurred in ipsilateral hemi-neck, and 39% in contralateral neck. The highest risk factor associated to regional relapse was when the thickness of the primary tumor was > 4 mm[53]. Bilateral dissection is also considered when a salvage procedure is needed because the lymphatic channels have been altered by previous treatment.

Surgery and radiation as elective treatments are associated with over 90% of local control. If surgery is elected, selective neck dissection of levels I, II, and III is practiced for primaries in the oral cavity, and levels II to IV in the oropharynx[54]. Both N1 and N2 disease is handled with treatment modality elected for primary tumor, usually chemotherapy and radiotherapy combinations, or surgery (neck dissection of levels I to V). In case of initial surgery, if only one metastatic node is documented, without extranodal extension, adjuvant treatment is unnecessary.

Classical neck dissection (levels I to V) as primary treatment or salvage treatment is practiced

if neck nodes are 3 cm or larger in level II, for instance, in relation to spinal nerve. Evidence suggests a better local and regional control is obtained when excision of primary tumor is done in continuity with neck dissection. The N3 nodes and those that encase the carotid artery are treated with concurrent chemoradiation.

## SENTINEL NODE BIOPSY

A prospective, controlled, multicentre study, in oral cavity, investigated the validity of sentinel node biopsy as an alternative to elective neck dissection in T1 or T2 N0 tumor by clinical and image evaluation, with less morbidity.

In a study, 140 patients were included, of whom 95 had carcinomas of mobile tongue, 26 in floor of mouth, and 19 in other sites. This study discarded tumors of 6 mm or less or with minimal invasion. With the primary purpose of assessing the negative predictive value, Tc-99m colloidal sulfur was injected around the primary tumors before having them resected, followed by excision of the sentinel node with a complementary neck dissection. The results obtained are as follows: in 106 pathologically negative sentinel nodes with hematoxylin and eosin, 100 neck dissections were negative for a negative predictive value of 94%. With additional immunohistochemistry, the negative predictive value increased to 96%. The positive predictive value was 90.2%, and it was superior in mobile tongue tumors than in floor of mouth and T1 tumors; metastases were correctly identified in 100% of cases[55]. In addition, there are less surgical morbidity and functional sequelae than observed with selective neck dissection[56].

Another multicentre study corroborated these results[57]. We can conclude that sentinel node biopsy may become a new surgical standard for T1 tongue and floor of mouth tumors and some T2 with clinical negative neck nodes.

## RECONSTRUCTION OF SURGICAL DEFECTS

Recent surgical advances have increased the surgical options for complete resection of tumors and enhanced the preservation of function and structure, but flaps are adynamic; they just optimize mobility of remnant tissues[58]. For tumors in the tongue and floor of mouth, resection up to median raphe a immediate reconstruction is reasonable in terms of functional sequelae; the magnitude of the consequences is proportional to the amount of resected tissue, and increases when the base of the tongue is resected or the extrinsic muscles of the tongue lose their mandibular support. Immediate reconstruction is done with grafts, and pedicled or microanastomosis flaps[59]. Our group has documented that fasciocutaneous antebraquial flap provides excellent results in reconstruction of the tongue, floor of mouth, and lateral oropharyngeal wall defects[60]. Another very useful flap is pectoralis major flap; it covers almost any defect, but is voluminous and the esthetic results are less satisfactory.

Mandibular reconstruction ranges from non-justifiable reconstruction of lateral mandibular defects in patients at high surgical risk or with tumors likely to require adjuvant treatment, to the usage of fibula free osteoseptocutaneous, iliac crest, and scapular flaps[61] with or without dental implant.

Osteoseptocutaneous fibula free flap is a versatile flap because it allows extensive mandibular reconstructions (up to 26 cm), although transversal dimensions are limited. In contrast, iliac crest flap is appropriate to reconstruct a hemimandibular defect. In good surgical candidates together with experienced teams, the effectiveness of the procedure is high. However, some factors are associated with increased risk of complications; for instance, advanced age and smoking increase the risk of medical and surgical complications[62].

Tissue engineering is a promising option[63]. Warnke, et al. published a case of successful mandibular reconstruction with a titanium mesh with cancellous bone, collagen, particulate bone, bone morphogenetic protein inside, in order to stimulate the formation of new bone[64].

## POSTOPERATIVE TRACHEOTOMY

Due to the risk of mechanical obstruction and worsening of deglutition mechanisms, it is highly recommended to perform a protective tracheotomy. This specially certain when using voluminous flaps and extensive dissections because of hematoma risk, in mandibular or floor of the mouth resections, in cases with either pulmonary or cardiac conditions, as well as in senile or alcoholic patients[65].

## ADJUVANT TREATMENT

Adjuvant treatment is needed when there is a significant risk of local or regional relapse. Before adjuvant treatment, odontological evaluation is imperative, since radiation increases the chances of developing osteoradionecrosis.

Patients with a high relapse risk, because of extranodal spread, positive surgical margins, perineural dissemination, lymphatic and vascular embolism, and positive nodes at levels IV and V, are best treated with postoperative concurrent chemoradiation. The study of Bernier, et al. showed a reduction of 13% in the absolute risk of relapse, and Cooper, et al. observed a 10% reduction at two years. This translates in a better disease-free survival and global survival, but treatment is toxic and of no benefit after the age of 70. Adjuvant therapy should be started within six weeks after surgery, as longer times are associated with lower rates of locoregional control.

Chemotherapy is based on a cisplatin dose of 100 mg/m$^2$ administered every three weeks throughout radiotherapy treatment. Toxicity is significantly higher than that observed with radiation alone, but nevertheless is manageable[66,67].

## UNRESECTABLE TUMORS

Unresectable tumors invade masticator space, pterygoid plates, cranial base, or encase carotid artery; in the oropharynx this includes lateral pterygoid muscle, and lateral wall of nasopharynx. Patients may obtain prolonged palliation when treated with concomitant and complementary surgery if the tumor becomes resectable. Exclusive radiotherapy is no longer standard treatment, since meta-analysis has proved the advantages of concurrent chemoradiation[68]. Platinum-based schemes are most commonly used, often cisplatin given at a dose of 100 mg/m$^2$ of body surface area every 21 days at the same time as the radiation therapy. Our group has tried gemcitabine in low doses (50-100 mg/m$^2$) of body surface every week during radiotherapy, alternating or not with cisplatin, documenting an active treatment that deserves further evaluation[69,70].

Concurrent chemoradiation is toxic and scarcely tolerated by patients above 70 years old[71]; mucositis and hematologic toxicity are limiting. It has been proposed to use induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil prior to concurrent chemoradiation; however, this failed to show an advantage over concurrent chemoradiation alone[72].

Bonner, et al. conducted a controlled study with cetuximab, an anti-EGFR monoclonal antibody, in combination with radiation therapy for first-line treatment of locoregional advanced and unresectable carcinomas, and showed a better relapse-free survival as well as overall survival with respect to radiotherapy alone, without increasing toxicity[73].

## TREATMENT OF RECURRENT DISEASE

Patients with unresectable or distant metastatic disease have a dismal prognosis and require palliative

treatment. Treatment is limited by previous therapy, current extent of disease, and the general condition of the patient. However, surgery, radiotherapy, and chemotherapy can be considered if the balance between risk and benefits are worthwhile. Cetuximab has also been used in association with cisplatin as first-line treatment in recurrent or metastatic carcinomas; overall survival was superior in comparison with chemotherapy alone[74]. In locoregional relapse, long-term control is still achievable if tumors are limited, recurrence occurs after six months, and complete resection is possible by means of surgery[75]

## FOLLOW UP

The largest proportion of relapses (80%) occurs in the first two years of treatment and rarely after five years. Up to 60% of relapses are local, regional, or both, and up to 20-30% of patients develop second primary tumors. Checkups are recommended every three months during the first two years, every six months in the following three years, and then once a year. Each visit should include a complete probing exploration of the head and neck area including image and endoscopic studies when indicated.

## DISCLOSURES

The authors declare that they have no conflict of interests.

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