ORAL CANCER

[Document subtitle]

ABSTRACT

Essay for master's degree in general surgery

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CHAPTER (1)

Anatomy of Oral Cavity

Oral cavity and related structures:

As conventionally defined the oral cavity consists of an outer part, the vestibule, situated between the lips and cheeks externally and the teeth and alveolar processes internally, and a large inner part, the oral cavity proper located internal to the dental arcades. The mucous membrane of the oral cavity may be divided into three types, although this is an oversimplification since there are regional variations within each type.

1- non-keratinizing epithelium covering a loose lamina propria and submucosa containing some fat deposits and mucous glands.
2- The masticatory mucosa of the hard palate and gingivae is lined by a parakeratinized epithelium. Sumbucosa is absent. In the gingivae and the palatine raphe.
3- The specialized mucosa of the dorsal surface of the tongue is orthokeratinized aver the anterior two-thirds and bears four types of papillae. ***(. Johanson &Moore, 1983).***

Examination of the living mouth:

Vestibule:

With the mouth closed the vestibule is little more than a potential space since the lips and cheeks are normally closely applied to the external aspect of the teeth and gums. The vestibule is limited above and below by the reflections of the mucous membrane from the alveolar processes on to the cheeks and lips. The gutters formed by these reflections are called, the sulci (upper and lower buccal sulci in the region of the cheeks and upper and lower labial sulci in the region of the lips).

The parotid duct opens into the vestibule opposite the crown of the upper second molar tooth. The site or the orifice is marked by a small papilla. ***(James et al., 1990)***

Oral cavity proper:

With the mouth widely open you will be able to see that the roof of the oral cavity proper is formed by the palate and that the floor is largely obscured by the highly mobile tongue. If the tongue is now raised you will see the floor of the mouth formed by the mucous membrane covering the mylohyoid muscles. The posterior limit of the oral cavity lies at the oropharyngeal isthmus. This is bounded on each side by a fold of mucous membrane, the palatoglossal arch, (or anterior pillar of the fauces) running from the side of the palate to the side of the tongue. Behind the oropharyngeal isthmus is the oral part of the pharynx. ***(. Johanson &Moore, 1983).***

Palate:

The palate can be divided into two parts of different structure and function. Anteriorly is the hard palate, which forms the partition between the nasal and oral cavities. The soft palate is attached to the posterior border of the hard palate and projects posteriorly into the pharynx, separating its nasal and oral parts. The soft palate is highly mobile and its movements are important in preventing food and drink entering the nasopharynx and nose during the act of swallowing. ***(James et al., 1990***

The anterior (oral) surface of the soft palate at rest is concave and bears a low median raphe. Projecting downwards from its free (inferior) margin is a small conical process, the uvula. ***(. Johanson &Moore, 1983).***

It is important to be able to locate the junction of the hard and soft palate. This may be visible as a faint transverse groove in the mucous membrane covering the oral surface of the palate. If not, it can be palpated but the procedure is uncomfortable and liable to cause gagging. A more convenient procedure is to ask the subject to say 'aah' when the soft palate will be seen to vibrate. The boundary line between the vibrating and non-vibrating parts of the palate is called the vibrating line and lies a short distance behind the junction of hard and soft palates. ***(James et al., 1990)***

The mucous membrane covering the tongue has a number of marked regional variations. The dorsum is divided by the V-shaped sulcus terminalis (the point of the V is directed posteriorly) into anterior two-thirds and posterior one-third which differe in epithelial specializations, development, and nerve supply. ***(James et al., 1990)***

The apex of the sulcus terminalis is marked by a shallow median pit, the foramen caecum marking the embryological origin of the thyroid gland and the upper end of the transient thyroglossal duct. A median fold of mucous membrane, the lingual frenulum, connects the inferior surface of the tongue to the floor of the mouth. On each side of the frenulum is a fringed fold of mucous memhrane called the plica fimbirata. Between the frenulum and the plica, the deep lingual vein can be seen through the thin mucous membrane. The presence of a short frenulum may lead to the condition of 'tongue'tie' in which speech is defective. ***(. Johanson &Moore, 1983).***

Associated with the mucous membrane of the tongue are numerus lingual glands. Over the posterior one-third of the dorsum these are mainly mucus-secreting; over the anterior two-thirds serous glands are found opening into the neighbourhood of the taste buds. A few mucous glands are present on the under surface of the tongue near its tip. ***(James et al., 1990).***

Floor of the mouth:

The floor of the mouth is lined with a smooth thin mucous membrane bearing a stratified squamous epithelium similar to that found on the under surface of the tongue. Either side of the attachment of the lingual frenulum to the floor of the mouth is a small elevation, the sublingual papilla. On the surface of the papilla you may be able to see the orifice of the submandibular duct. Extending posterolaterlaly from the papilla is a ridge, the sublingual fold, produced by the underlying sublingual gland. The gland opens on the crest of the fold by several tiny ducts which are too small to see with the naked eye. ***(. Johanson &Moore, 1983).***

Oropharyngeal isthmus and neighbouring region:

The palatoglossal arches are produced by the underlying palatoglossal muscles. A short distance behind the palatoglossal arches is a second pair of folds, the palatopharyngeal arches (or posterior pillars of the fauces). These overlie the palatophryngeal muscles. Beneath the mucous membrane between the palatoglossal and palatopharyngeal arches is the palatine tonsil. ***(James et al., 1990)***

Structures bounding the oral cavity:

Lips and cheeks:

The lips are fleshy folds consisting of skin superficially and mucous membrane internally, with the orbicularis muscle, loose connective tissue, and the labial nerves and blood vessels contained between them. The mucus-secreting labial glands are situated internal to orbicularis oris. Similarly the cheeks have an external layer of skin, an internal layer of mucous membrane and a middle layer of muscle, principally buccinator, and connective tissue with the contained nerves and blood vessels. The buccal glands are internal to the buccinator. ***(James et al., 1990)***

Hard palate:

The skeleton of the hard palate is provided by the palatine processes of the maxillae and the horizontal processes of the palatine bones. Its oral surface is covered by mucous membrane lined by stratified squamous epithelium. The palatine mucosa receives its sensory innervation from the greater palatine nerve and the nasopalatine nerve. The blood supply of the whole of the hard palate is provided by the greater palatine artery. ***(James et al., 1990)***

Blood drains from the hard palate through veins that accompany the artery and terminate in the pterygoid plexus. The lymph drainage is to the deep cervical nodes. Congenital clefts of the palate are amongst the commonest disorders of development. ***(James et al., 1990)***

Floor of the mouth:

The key to understand the floor of the mouth is the position of the mylohyoid, geniohyoid, and hyoglossus muscles.

Mylohyoid muscle:

The mylohyoid muscles of the two sides form a mobile diaphragm flooring the oral cavity. Below this diaphragm is the neck. Each muscle is a thin sheet which arises from the whole length of the mylohyoid line on the medial aspect of the mandible. It has a posterior free edge. The posterior fibres run medially and downwards to be inserted into the anterior surface of the body of the hyoid bone. The more anterior fibres pass similarly in a medial and downward direction to meet the corresponding fibres of the opposite side at a median raphe which runs from the internal surface of the symphysis menti to the front of the hyoid bone. The muscle is innervated by the mylohyoid branch of the inferior alveolar nerve and its action is to elevate the floor of the mouth and hyoid or, with the latter fixed to depress the mandible. ***(. Johanson &Moore, 1983).***

Geniohyoid muscle:

This is a narrow band of muscle fibres which arises from the inferior mental spine and runs backwards and downwards to be inserted into the anterior surface of the hyoid bone. It lies on the medial part of the upper surface of the mylohyoid muscle in a contact with its fellow of the opposite side. Immediately above it is the genioglosus muscle. Geniohyoid is supplied by a branch of the hypoglossal nerve but the fibres are derived from the first cervical spinal nerve. Its action is to elevate and draw forwards the hyoid bone or conversely to depress the mandible. ***(James et al., 1990)***

Hyoglossus muscle:

Although hyoglossus is an extrinsic muscle of the tongue it is more convenient to describe it here than with the other muscles of that group because a knowledge of its relationships is necessary for understanding the course of several important structures in the floor of the mouth. It is a quadrilateral sheet of muscle which arises from the upper surface of the whole length of the greater cornu and of the lateral part of the body of the hyoid bone. Its fibres ascend vertically in a parasagittal plane to be inserted into the side of the tongue where they interdigitate with the fibres of the styloglossus muscle . ***(. Johanson &Moore, 1983).***

The lateral (superficial) surface of the muscle is related to the lingual nerve, the deep lobe of the sumbandibular gland and the sumandibular duct, the hypoglossal nerve and the deep lingual vein. Having gained access to the mouth, the lingual nerve curves forwards, downwards and medially across the intermuscular space between mylohyoid and hyoglossus to reach the lateral surface of the latter. Here it continues forwards and has the submandibular ganglion suspended from it by two or three ganglionic branches. The lingualnerve lies at first superior to the submandibular duct, at the anterior border of hyglossus it passes beneath

the duct, crossing from the lateral to the medial side of that structure as it does so. ***(James et al., 1990)***

The deep lobe of the submandibular gland lies against the posterior part of the lateral surface of the hyoglossus from which is separated by the hypoglossal nerve and deep lingual vein. The submandibular duct leaves the deep lobe of the gland and passes forwards on the lateral surface of the hyoglossus, with the relationship to the lingual nerve just described, to open into the oral cavity at the sublingual papilla at the side of the frenulum of the tongue. ***(. Johanson &Moore, 1983).***

The hypoglossal nerve runs forwards on the lateral surface of hyoglossus a short distance above the grater cornu of the hyoid. At the anterior margin of the muscle it divides into several branches which run into the musculature of the tongue. In its course across hyoglossus the hypoglossal nerve is accompanied by the deep lingual vein. ***(James et al., 1990)***

Also related to the posterior part of the lateral surface of the hyoglossus are the sylohyoid muscle and the intermediate tendon of the digastric. The medial surface of the hyoglossus is related to the glossopharyngeal nerve, stylohyoid ligament, and lingual artery. The glossopharyngeal nerve travels deep to the upper part of hyoglossus to supply the mucous membrane of the paoterior one-third of the tongue. The stylohyoid ligament runs deep to the posterior part of hyoglossus to attach to the lesser cornu of the hyold bone. The lingual artery passes medial to the lower part of the posterior border of hyoglossus, runs forwards above the greater cornu of the hyoid and then turns upwards at the anterior border of the muscle to pass on to the lower surface of the tongue. Also related to the medial surface of hyoglossus is the genioglossus muscle. Like other muscles of the tongue (except palatoglossus), hyoglossus is innervated by

the hypoglossal nerve. Its action is to depress the tongue. ***(. Johanson &Moore, 1983).***

Salivary glands in the floor of the mouth:

The sublingual glands lies wholly in the floor of the mouth whereas the submandibular gland lies partly in the floor of the mouth and partly in the neck. Both glands re predominantly mucus secreting in man. ***(James et al., 1990)***

Nerves in the floor of mouth:

Three important nerves – lingual, glossopharyngeal, and hypoglossal – pass through the floor of the mouth. ***(. Johanson &Moore, 1983).***

Blood vessels in the floor of the mouth:

Lingual artery:

The lingual artery provides the main blood supply to the floor of the mouth and to the tongue. It leaves the anterior surface of the external carotid opposite the tip of the grater cornu of the hyoid. The first part of its course is in the neck. Here the artery forms a characteristic loop, running at first upwards and then descending again to the level of the hyoid. It is related medially to the middle constrictor and has skin, platysma, and deep fascia laterally. It is crossed superficially by the hypoglossal nerve. The artery then enters the floor of the mouth by running deep to hyoglossus. Its medial relationship in this part of its course are, in posterior to anterior sequence, the middle constrictor, stylohyoid ligament and genioglossus. At the anterior border of hyoglossus the artery gives off its sublingual branch which runs forward between mylohyoid and genioglossus to supply the sublingual gland and the muscles of the floor of the mouth. The main trunk,

now known as the deep lingual artery, turns upwards and then runs forwards just beneath the mucous membrane on the inferior surface of the tongue close to the frenulum. It is accompanied in this part of its course by the lingual nerve and deep lingual vein. The artery gives off numerous branches which pass upwards to supply the substance of the tongue. ***(James et al., 1990)***

Venous channels:

The vein of the floor of the mouth comprise two main channels. The deep lingual vein begins near the tip of the tongue. It accompanies the lingual artery on the inferior surface of the tongue but at the anterior border of hyoglossus, where it receives the sublingual vein from the sublingual gland and the floor of the mouth, it parts company with the artery to run lateral to the muscle close to the hypoglossal nerve. The vein ends by draining into the facial, lingual, or internal jugular vein. The dorsal lingual veins join to form the lingual vein which runs with the lingual artery deep to hyoglossus and opens into the internal jugular vein posterior to the greater cornu of the hyoid bone. ***(. Johanson &Moore, 1983).***

Tissue spaces in the floor of the mouth:

A dental abscess from an infected lower tooth may erode the cortex of the body of the mandible allowing the escape of pus into the adjacent soft tissues. If this occurs in a lateral direction the abscess will usually point into the buccal sulcus. If the erosion take place medially pus may enter the floor of the mouth or the neck, depending upon whether the cortex is eroded above or below the attachment of the mylohyoid muscle to the medial surface of the mandibular body. Because this attachment slopes downwards as it passes forwards, an abscess from the posterior teeth is more likely to open below by the muscle, above by the mucous membrane lining the floor of the mouth and laterally and anteriorly by the body of the mandible. Posteriorly it

communicates freely with the tissue spaces in the neck. The genioglossus and geniohyoid muscles form a midline partition which acts as an effective barrier to the spread of infection from one side of the space to the other. The tissue space below the mylohyoid muscle is bounded inferiorly by the investing layer of the deep cervical fascia and laterally and anteriorly by the mandibular body. This space too communicates posteriorly with the tissue spaces in the neck. ***(James et al., 1990)***

Lymph nodes of the head and neck:

Head:

Lymph nodes of the head are all extracranial because the central nervous system possesses nolymph vessels of lymph nodes. The general pattern of lymph nodes about the head is that they are regionalized into several groups to drain the posterior and anterolateral scalp as well s the superficial and deep aspects of the face. ***(. Johanson &Moore, 1983).***

Occipital lymph nodes (two to four in number) are located on the back of the head lying on the semispinalis capitis muscle just inferior to the attachment of the trapezius muscle. The small mastoid (postauricular) lymph nodes (one to three in number) are located behind the ear on the mastoid process, superficial to the insertion of the sternocleidomastoid muscle. Anterior to the ear are two to three preauricular (superficial parotid) lymph nodes lying superficial to, and sometimes deep to the capsule of the parotid gland. Those located deep to the capsule are sometimes grouped with the deep parotid lymph nodes described with those of the face. ***(James et al., 1990)***

The lymph nodes of the face are subdivided into those of the parotid, superficial face, and deep face. The parotid lymph nodes (10 to 15 in

number) from two groups: those lying embedded within the substance of the gland and those lying deep to the gland adjacent the pharyngeal wall. The superficial facial lymph nodes (up to 12), disposed along the course of the facial artery and vein, are the maxillary (infraorbital) lyph nodes in the vicinity of the infraorbital foramen, the buccal lymph node(s) on or in the buccal fat pad over the buccinator muscle, and the mandibular lymph nodes (two to three in number) along the facial artery and vein adjacent the masseter muscle. The deep facial lymph nodes follow the course of the maxillary artery in the infratemporal fossa superficial to the lateral pterygoid muscle. ***(. Johanson &Moore, 1983).***

Two additional groups of deep nodes are important: the lingual lymph nodes (numbering two to three)lying on the superficial aspect of the hyoglossus muscle and the two to three petropharyngeal lymph odes located in the buccopharyngeal fascia behind the pharynx at the level of the atlas. ***(James et al., 1990)***

Table ( ): Lymph nodes of the head and neck *(James et al., 1990)*

Node	Location	Afferent	Efferent
Occipital (2-4)	Superior nuchal line between sternocleidomastoid and trapezisu	Occipital part of scalp	Superficial cervical lymph nodes
Mastoid (1-3)	Superficial to sternocleidomastoid insertion	Posterior parietal scalp skin of ear, posterior external acoustic meatus	Superior deep cervical nodes. Accessory lymph nodes.
Preauricular (2-3)	Anterior to ear over parotid fascia	Drains areas supplied by superficial temporal artery. Anterior parietal scalp anterior surface of ear.	Superior deep cervical lymph nodes
Parotid (up to 10 or more)	Above parotid gland and under parotid fascia deep to parotid gland.	External acoustic meatus skin of frontal and temporal regions. Eyelids, tympanic cavity. Cheek, nose (posterior palate).	Superior deep cervical lymph nodes.
Facial Superficial (up to 12) Maxillary Buccal Manbdibular	Distributed along course of facial artery and vein	Skin and mucous membranes of eyelids, nose, cheek	Submandibular nodes
Deep	Distributed along course of maxillary arery lateral to lateral pterygoid muscle	Temporal and infrateporal fossa Nasal pharynx	Superior deep cervical lymph nodes
Superficial cervical lymph nodes			
Anterior cervical superficial	Anterior jugular vein between superficial cervical fascia and infrahyoid fascia	Skin, muscles, and viscera of infrahyoid region of neck.	Superior deep cervical lymph nodes
Deep	Between viscera of neck and investing layer of deep cervical fascia	Adjoining parts of trachea. Larynx. Thyroid gland	Superior deep cervical lymph nodes
Submental (2-3)	Submental triangle	Chin Medial part of lower lip Lower incisor teeth and gingiva Tip of tongue, cheeks	Submandibular lymph node to juguloomohyoid lymph node and superior deep cervical lymph nodes.
Submandibular (3-6)	Submandibular triangle adjacent submandibular gland	Facial nodes Chin Lateral upper and lower lips. Submental nodes Cheeks and nose, anterior nasal cavity	Superior deep cervical lymph nodes and jugulo-omohyoid lymph nodes

Node	Location	Afferent	Efferent
		Maxillary and mandibular teeth and gingiva Oral palate Lateral parts of anterior 2/3 of tongue	
Superficial cervical (1-2)	Along external jugular vein superficial to sternoclleidomastoid muscle	Lwer part of ear and parotid region	Superior deep cervical lymph nodes
Deep cervical lymph nodes			
Superior deep cervical	Surrounding internal jugular vein deep to sternocleidomastoid and superior to omohyoid muscle	Occipital nodes mastoid nodes Preauricular nodes Parotid nodes Submandibular nodes Superficial cervical nodes	Inferior deep cervical nodes or separate channel to jugulo subclavian junction
Jugulodigastric	Junction of internal jugular vein and posterior digastric muscle	Palatine and lingual tonsils. Posterior palate Lateral portions of the anterior 2/3 of tongue	inferior deep cervical lymph nodes
Juguloomohyoid	Above junction of internal jugular vein and omohyoid muscle	Posterior 1/3 of tongue submandibular nodes submental nodes	Inferior deep cervical lymph nodes
Inferior deep cervical	Along internal jugular vein below omohyoid muscle deep to the sternocleidomastoid muscle	Transverse cervical nodes. Anterior cervical nodes Superior deep cervical nodes.	Jugular trunk.
Retropharyngeal (1-3)	Retropharyngeal space	Posterior nasal cavity Paranasal sinuses Hard and soft palate Nasopharynx, oropharynx Auditory tube	Superior deep cervical nodes.
Accessory (2-6)	Along accessory nerve in posterior triangle	Occipital nodes Mastoid nodes Lateral neck and shoulder	Transverse cervical nodes
Transverse cervical (1-10)	Along transverse cervical blood vessels at level of clavicle	Accessory nodes Apical axillary nodes lateral neck Anterior thoracic wall	Jugular trunk or directly into thoracic duct or right lymphatic duct or independently into junction of internal jugular vein and subclavian vein

Neck:

The lymph nodes of the neck are disposed in several groups: the anterior cervical, submental, submandibular, superficial cervical, and deep cervical.

The anterior cervical lymph nodes are inconsistent and are located in two groups, superficial and deep, in front of the viscera of the neck. The superficial group is located in an irregular row along the course of the anterior jugular vein. The deep group is subdivided into four small chains: the paratracheal lymph nodes of the tracheoesophageal groove; the infrahyoid lymph nodes, lying superficial to the thryohyoid membrane; the pretracheal nodes, situated between the investing layer of the deep cervical fascia and the trachea; and the prelaryngeal nodes, which lie on the cricothyroid ligament. ***(James et al., 1990)***

The submental lymph nodes are located between the anterior bellies of the right and left digastric muscles.

The submandibular lymph nodes are located in the same-named triangle in close proximity to the submandibular gland. Although these constitute a chain of three to six lymph nodes, the only constant node is the one at the facial groove of the mandible in close association with the facial artery. Superficial cervical lymph nodes may be found lying adjacent the external jugular vein as it passes superficial to the sternocleidomastoid muscle**.** ***(. Johanson &Moore, 1983).***

The deep cervical lymph nodes are numerous and form a chain along the carotid sheath. These nodes are most important because they ultimately receive all of the lymph from the head and neck. Their efferent vessels form

the jugular trunk, which delivers the collected lymph to the right lymphatic duct, or to the thoracic duct on the left, to be returned to the circulatory system. These deep cervical lymph nodes parallel to the carotid sheath along its entire length. The lymph nodes of this group may conveniently be organized into two subgroups the superior and inferior deep cervical lymph nodes. The superior deep cervical lymph nodes, some of which are large, form a chain, surrounding the internal jugular vein, extending from the mastoid process to the superior border of the subclavian triangle. The most superior node of this group is the large jugulodigastric (tonsillar) lymph node, located between the posterior belly of the digastric muscle and the internal jugular vein. This node is of particular importance in physical diagnosis. The inferior deep cervical lymph nodes reside in the subclavian triangle. Nodes of this group are in close association with the brachial plexus, the subclavian artery and vein, and the omohyoid muscle. A large, constant node of this group, located in the vicinity of the intermediate tendon of the omohyoid muscle, is the jugulo-omohyoid lymph node. (This node is located in a border zone between the superior and inferior deep cervical nodes; therefore, reference to its group association varies). ***(James et al., 1990)***

Lymphatic drainage of the head and neck:

Superficial tissues:

The back of the scalp is drained by the occipital lymph nodes, whose efferent vessels empty into the superficial cervical lymph nodes. The lymph vessels of the medial surface of the ear, the lateral aspects of the eyelids, the temporal region, and most of the forehead drain into the mastoid, preauricular, and parotid lymph nodes. The afferents from these nodes then pass into the superior deep cervical lymph nodes. The remainder of the eye and middle ear are drained by the preauricular (parotid lymph nodes), which

then drain into the superior deep cervical lymph nodes. The submandibular lymph nodes receive lymph from the nose, cheek, and lip, either directly or via the buccal lymph nodes. The lateral aspect of the cheek and the skin over the bridge of the nose are partially drained also by the parotid lymph nodes. Lymph from the mucosa over the floor of the mouth, the tip of the tongue, and the central portion of the lower lip is drained into the submental lymph nodes, whence it empties into the jugulo-omohyoid lymph node of the inferior deep cervical chain. Superficial tissues of the neck are drained by the deep cervical lymph nodes directly or indirectly. Lymph from the posterior cervical triangle may first enter the superficial cervical and occipital nodes from which the lymph flows to the deep cervical lymph nodes. Lymph from the anterior cervical triangle, above the hyoid bone, is drained into the submental and submandibular lymph nodes, whereas that inferior to the hyoid bone drains into the anterior cervical lymph nodes, whose efferents deliver it to the inferior deep cervical lymph nodes. **. *(. Johanson &Moore, 1983).***

Deep tissues:

Most of the lymph of the nasal cavity, paransal sinuses, and nasopharynx drains into the retropharyngeal lymph nodes or passes directly to the inferior deep cervical lymph chain. The thyroid gland is drained by the pretracheal, prelaryngeal, and paratracheal lymph nodes, whence lymph flows to the deep cervical lymph nodes. Frequently, some of the lymph from this endocrine gland passes directly into the deep cervical lymph nodes. The tracheal. Esophageal, and laryngeal lymph in the region of the neck also passes either directly or indirectly, via the prelaryngeal or paratracheal lymph nodes, into the deep cervical chain. Tonsillar lymph is drained into the jugulodigastric lymph node of the superior deep cervical chain. ***(James et al., 1990)***

Lymph drainage from the gingiva, teeth and tongue deserves special attention. Gingival lymph is gathered on the lingual and vestibular surfaces by submucosal plexuses of lymph vessels, which are consolidated into a series of vessels behind the molars. From here the lymph passes either to the submandibular lymph nodes or, occasionally, into the deep cervical lymph nodes. Lymph vessels of the pulp and those of the periodontal ligament about the same tooth are drained by a common vessel. Lack of agreement exists concerning the precise path of lymph drainage of teeth, but a reasonable case may be made for the following description. The madibular incisors are drained by the submental lymph nodes, and the remaining teeth are drained by the submandibular lymph nodes. Generally for structures near the midline it is both ipsilateral and contralateral. ***(James et al., 1990)***

Lymphatic drainage of the tongue is complex because the tongue has a rich lymphatic plexus of vessels that is drained by three vessel groups: the marginal, dorsal, and central vessels. In addition, drainage from the two sides is intermingled to a large extent, and the base of the tongue is drained by lymph nodes situated more cranially than those that receive lymph from the tip of the tongue. Vessels from the tip of the tongue pass to the submental nodes along with those of the region of the lingual frenulum. The lateral aspect of the anterior two-thirds of the tongue is also drained by marginal vessels, into the jugulodigastric lymph nodes. The central vessels drain the medial region of the anterior two-thirds of the tongue, delivering the lymph to the juguloomohyoid lymph nodes. In adition, dorsal vessels drain the region of the sulcus terminalis and the posterior one-third of the tongue, delivering lymph to the marginal lymph vessels, which are drained by the jugulo-omohyoid lymph nodes. **. *(. Johanson &Moore, 1983).***

The accessory lymph nodes located about the accessory nerve in the posterior cervical triangle may drain occipital and mastoid nodes in addition to areas of the lateral neck and shoulder. The transverse cervical nodes, located in the posterior cervical triangle, drain the accessory chain of nodes, the lateral neck, the anterior thoracic wall, the mammary gland, and, occasionally, the upper limb. Efferents from this group may pass into the jugular lymphatic trunk, the thoracic duct, or the right lymphatic duct, or they may enter the internal jugular or subclavian veins independently. ***(James et al., 1990)***

Clinical considerations:

Lymph nodes of a healthy individual are soft, nonpalpable structures. However, infection, inflammation, and carcinomatous involvements of areas drained by lymph nodes cause these structures to become swollen, hard, painful, and palpable. The health professional dealing with the oral cavity should examine patients for swollen, painful lymph nodes, especially the submental, submandibular, and superficial and deep cervical chains. The last group may be palpated with relative ease by manipulation of the relaxed sternocleidomastoid muscle. Diseased states of the oral cavity will most probably be reflected in the submental and submandibular lymph nodes. Remembering that, in the process of lymph drainage, the fluid passes through a series of lymph nodes before emptying into the thoracic or right lymphatic ducts, it becomes evident that each lymph node group is a "barrier" where the disease agent is being combated. The first such site is known as the primary node, which drains into a secondary node that may be drained by a tertirary node. The more nodes that are interposed in the disease agent's route of spread before reaching the major lymphatic channels, the better the chance of successfully combating the disease. Hence a knowledge of lymphatic drainage of the

head and neck assists the health professional dealing with this region in determining the site of disease manifestation. **. *(. Johanson &Moore, 1983).***

Treatment of cervical metastases may involve a radical surgery, that is, a “block resection” of the cervical lymph nodes of the particular side of the neck be removed. To ensure that this is the case, connective tissues, muscles, glands, and even nerves of the area are frequently sacrificed.

CHAPTER (2)

EPIDEMIOLOGY AND RISK FACTORS

Introduction:

Cancers of the oral cavity an oropharynx represent approximately three percent of all malignancies in men and two percent of all malignancies in women in the United States. It is estimated that these tumors will account for 28.900 new cases and 7.400 deaths in 2002 in the United states. Squamous cell carcinoma, which arises from the oral mucosal lining, accounts for over 90 percent of these tumors ***(Brad et al., 2002)***.

For classification purposes, oral and pharyngeal cancers sometimes are grouped with laryngeal and esophageal cancers, with which they share etiologic features. However, in these papers, they will not be. Furthermore, oral cancer will be defined to include cancers of the lip, tongue, other mouth sites, and the oropharynx. Cancers of the salivary gland, nasopharynx, and hypopharynx will not be included, as they account for less than 10% of all oral cancers and are etiologically and biologically distinct. Sarcomas will also not be discussed for similar reasons.

Epidemiology:

Oral cancer most commonly occurs in middle-aged and older individuals, although a disturbing number of these malignancies is also being documented in younger adults in recent years. From an epidemiological and clinicopathological perspective, “oral cancer” can be divided into three categories: carcinomas of the oral cavity proper, carcinomas of the lip vermilion , and carcinomas arising in the oropharynx. Intraoral and oropharyngeal tumors are more common among men than women, with a male: female ratio of over 2:1. however, the disparity in the male: female ratio has become less pronounced over the past half century, probably because women have been more equally exposing themselves to known oral carcinogens such as tobacco and alcohol. The annual incidence of oral and pharyngeal cancer in African Americans (12.4 cases per 100,000 population) is higher than among whites (9.7

cases per 100,000); the highest incidence rate is among African-American males (20.5 cases per 100,000 population) ***(Schantz et al., 2002)***.

In contrast to intraoral and oropharyngeal carcinoma, cancers of the lip vermilion are more akin epidemiologically to squamous cell carcinoma of the skin and occur primarily in white men. These lip tumors are most strongly associated with chronic sun exposure, although sometimes they have been related to the site where cigarettes or pipe stems have habitually been held. These malignancies are much more common in men, probably because men are more likely to have vocations and/or avocations that result in greater cumulative sun exposure. At one time, the lip was the most common site for oral cancer; however, the incidence of cancer in this location has decreased significantly over the past half century because fewer men hold outdoor occupations ***(Neville et al., 2002)***.

Age:

The mean age at diagnosis of oral premalignancy is 50-69; less than 5% of diagnosis are in patients under 30 years of age. Thus, the aging process itself is the greatest risk factor for premalignant and malignant changes ***(Kaugars et al., 1988)***.

Sex:

Studies have shown that epithelial dysplasia has a predilection for males, but the decrease in the male: female ratio for oral squamous cell carcinoma suggest the picture may be changing. This may be due to increased use of tobacco and alcohol among women ***(Lumemen et al,. 1995)***.

Persons with oral cancer often have multiple primary lesions, and have up to a 20-fold increased risk of having a second oral cancer. Persons with primary tumors of the oral cavity and pharynx also are more likely to develop cancers of the esophagus, larynx, lung, and stomach ***(Day et al., 1997)***.

Differences exist by anatomical site as well. Within the oral cavity and pharynx, 29% of cancers involve the tongue and another 17% the lip. Among pharyngeal sites, the

oropharynx is the most common site for tumors (39%) followed by the hypopharynx (32%) ***(Kleinman et al., 1991)***.

Survival:

Despite advances in surgery, radiation, and chemotherapy, the five-year survival rate for oral cancer has not improved significantly over the past several decades and it remains at about 50 to 55 percent. Unfortunately, African American have a significantly higher mortality rate when compared with whites (4.4 versus 2.4 per 100,000 population), partly because among African Americans, tumors are more often discovered at an advanced state. From 1985 to 1996, the five-year survival rate for carcinoma of the tongue in African-American men was 27 percent, compared with a 47 percent five-year survival rate among white men. For floor of mouth cancers, the survival rate was 52 percent in whites, compared with only 33 percent among African Americans. When compared with intraoral carcinoma, the prognosis for lip cancer is quite good, with a five-year survival rate of 95 percent ***(Silverman, 2001)***.

There was a great difference with the black subgroup, however, as the survival rate for black males was only 28%, versus 47% for black females ***(Kleinman et al., 1991)***.

Five-year relative survival by historical stage at diagnosis:

Stage at diagnosis refers to the extent of disease at diagnosis. There are three stage: localized, regional, and distant metastasis. Five-year relative survival rates, vary with the stage at diagnosis; localized cancers have the highest survival rates and cancers with distant metastasis the lowest. At diagnosis of oral cancer, most individuals have localized or regional disease: 37%, localized; 43%, regional; 10% distant; and 10% unstaged. Five-year survival rates for all oral cancer cases are 79% for those with localized disease, 42% for regional disease, and 19% for disease with distant metastases.

There appear to be no major differences by sex for the distribution of stages at time of diagnosis; however, women with regional and more advanced disease have greater survival rates than do men ***(Glockler et al., 1994)***.

A retrospective clinical and histopathological review seen in a tertiary care hospital (January 1987, December 2002) in north eastern Nigeria reported that:

A total of 378 biopsies, 317 primary cancers including 279 carcinomas of the head and neck were diagnosed during the study period. Intra-oral carcinomas constitute 43 (15.4%) of all head and neck carcinomas reported, with non occurrence in children. The overall mean age of occurrence was 51.2% +/- 15.6 years (male = 56.2 +/- 13.7 years; females reported in the palate 19 (44.2%) and lip six (13.9%) and floor of mouth four (9.3%). Squamous cell carcinoma 28 (65.1%), adenocystic carcinoma seven (16.3%) and mucoepidermoid carcinoma five (11.6) were the commonly reported carcinomas. Squamous cell carcinoma was the most common carcinoma in all sites, in the sixth decade of life, of equal gender distribution and commonly reported in users of kola, nuts and tobacco. The occupation of patiens diagnosed with oral carcinoma and squamuns cell carcinoma was arming (50%, 61.5%). All the staged cancers patients (n = 7) reported in the late stages (III/IV) of the disease. The mean interval between symptoms and presentation for the different carcinomas ranged between 9 and 25 months, with the least interval reported for mucoepidermoid carcinoma. Conclusions: squamous cell carcinoma was the most common oral carcinoma, commonly reported in the palate, among farmers and in the sixth decade of life. Its occurrence in under 40 years olds is three to six times greater than reported from the USA and Europe and may be associated with poor diet and the habitual use of kola ,nuts and tobacco. The survival rates of patients diagnosed with intra-oral carcinomas, although not available, would be expectedly low in view of the prognostic indicators recorded in this series ***(Otoh et al., 2005)***.

Predisposing factors:

The development of oral cancer seems to begin in many cases with exposure of the mucosal surfaces of the upper aerodigestive tract to topical carcinogens, predominantly ***alcohol and tobacco***. In some persons exposed to these carcinogens or co-carcinogens premalignant and malignant lesions develop in a multi-step process within the mucosa ***(Vokes et al., 1993)***. However, oral cancers occur in some patients with no history of tobacco or alchol

usage and no other apparent risk factors. Additionally, it is not clear that all of the tumors have an apparent "precancerous" state ***(Brachman et al., 1994)***.

There is an emerging body of evidence that persons who develop head or neck cancer may have undergone alterations in other tumor ***suppressor genes*** ***(Nawroz et al., 1994)***. In addition, there is evidence that altered genes may cooperate with other oncogenes, such as ras, to generate cells with a growth advantage for tumor progression, a multifunctional process associated with cutaneous carcinogenesis as well. Increasing ***immunosuppression*** from HIV infection also appears to be a factor in predisposing oral mucosa to malignant changes ***(Yospa, 1994)***.

The strong association between cancers of the oral cavity and pharynx with tobacco use is well established. Epidemiological studies show that the risk of developing oral cancer is five to nine times greater for smokers than for non smokers, and this risk may increase to as much as 17 times greater for extremely heavy smokers of 80 or more cigarettes per day. The percentage of oral cancer patients who smoke (approximately 80 percent) is two to three times greater than that of the general population. In addition, treated oral cancer patients who continue to smoke have a two to six times greater risk of developing a second malignancy of the upper aerodigestive tract than those who stop smoking. Marijuana use is also considered to be a potential risk factor and maybe partly responsible for the rise in oral cancer seen among young adults. However, further epidemiological studies are necessary to confirm the purported association of marijuana and oral cancer in younger patients ***(Zhang et al, 1999)***.

Snuff and chewing tobacco have also been associated with an increased risk for oral cancer. In one study of women in the southern united states, chronic users of snuff were estimated to have a four times greater risk of developing oral cancer. In addition, a significant number of oral cancers in smokeless tobacco users develop at the site of tobacco placement. However, the use of smokeless tobacco appears to be associated with a much lower cancer risk than that associated with smoked tobacco. The incidence of oral cancer in West Virginia is below the national average, even though this state has the highest consumption of chewing

tobacco in the United states. Recent studies from Scandinavia have suggested that the use of Swedish snuff (which is nonfermented and has lower nitrosamine levels is not associated with an increased risk for oral cancer ***(Johnson, 2001)***.

Alcohol use has been identified as a major risk factor for cancers of the upper aerodigestive tract. In studies controlled for smoking, moderate to heavy drinkers have been shown to have a three to nine times greater risk of developing oral cancer. One study from france showed that extremely heavy drinkers (greater than 100 grams of alcohol per day) had a 30 times greater risk of developing oral and oropharyngeal cancer (a typical serving of beer, wine, or liquor contains ten to 15 grams of alchol). Of even greater significance is the synergistic effect of alcohol and smoking; some subsets of patients who are both heavy smokers and heave drinkers can have over one hundred times greater risk for developing a malignancy ***(Lewin et al., 1998)***.

In India and southeast Asia, the chronic use of betel quid (Paan) in the mouth has been strongly associated with an increased risk for oral cancer. The quid typically consists of a betel leaf that is wrapped around a mixture of areca nut and slaked lime, usually with tobacco and sometimes with sweeteners and condiments. The slaked lime results in the release of an alkaloid from the areca nut, which produces a feeling of euphoria and well-being in the user. Betel quid chewing often results in a progressive, scarring precancerous condition of the mouth known as oral submucous fibrosis. In India, one study showed a malignant transformation rate of 7.6 percent for oral submucous fibrosis ***(Murti et al,. 1995)***.

Tobacco use:

The majority of patients with oral cancer (90 percent) use tobacco in one form or another. Tobacco can damage cells in the lining of the oral cavity and oropharynx, causing abnormal cells to grow more rapidly to repair the damage. Researchers believe that the DNA-damaging chemicals in tobacco are linked to the increased risk of oral cancer, according to the American Cancer Society ***(Zhang et al., 1999)***.

Alcohol use:

The majority of patients with oral cancer (75 to 80 percent) use alcohol frequently. Paired with tobacco use, patients who drink and smoke increase their risk of developing oral cancer even more. Researchers have found that alcohol increases the penetration of DNA-damaging chemicals in the lining of the oral cavity and oropharynx, according to the American cancer society ***(Lewin et al., 1998)***.

Sunlight:

Prolonged exposure to ultraviolet radiation from the sun can cause skin cancer. People who are outdoors for an extended period of time increase their risk of lip cancer, as well. More than 30 percent of lip cancer diagnosis are in persons with outdoor occupations ***(Johnson, 2001)***.

Chronic irritation:

Chronic irritation to the lining mucosa is one of the major risk factor due to poorly pitting dentures or other reasons, may increase a person's risk for oral cancer.

Lack of fruits and vegetables in diet:

Research has suggested that fruits and vegetables, which contain antioxidants that can 'trap" harmful molecules, can decrease the risk for oral cancer (and other cancers). Thus, it is speculated that persons with a low intake of these types of foods are at an increased risk for (oral) cancer ***(Murti et al., 1995)***.

Alcohol containing mouthwash:

Some studies have shown that mouthwash with alcohol content increases the risk for oral cancer. In addition, other studies have shown that smokers and people who drink alcohol tend to use mouthwash more often, linking all three factors together.

Human papillomavirus (HPV) infection:

HPV usually causes warts and has been linked to cervical, vaginal, and penile cancers. HPV may also increase the risk for oral cancers ***(Stoler et al., 1992)***.

In use of hydrogen peroxide in tooth bleeching has been extended to home use, so questions have been raised regarding safety to increase the risk of oral cancer in high risk individuals (e.g smokers and drinkers).

These concerns are based on limited experimental data in animals that hydrogen peroxide has extremely weak tumor promoting activity.

But recent study confirm the safety of hydrogen proxide for use in home tooth bleaching. This includes a lack of tumour promotion risk which is important because tooth whitening products are often used by chronic smokers and drinkers ***(Mahony et al,. 2005)***.

Oncogenes:

Oncogenes and proto-oncogenes are DNA sequences that encode factors that drive the cell cycle and include growth factors, their ligands, internal signaling pathway protein kinases, cyclins, cyclin associated kinases, and DNA transcription factors, many of which can be demonstrated in tumor tissues. Conversely, anti-oncogene or tumor suppressor gene protein products retard or inhibit the cell cycle or activate pathways that lead to programmed cell death (apoptosis). Loss of suppressor gene product or inactivation by mutation of both alleles will favour cell proliferation and malignancy. These proteins can also be detected in tissues by immunohistochemical and molecular analytic methods ***(Brachman, 1994)***.

Oncogenes and tumor suppressor genes are currently being studied in both defining the multistep carcinogenetic process and as prognostic factors for disease-free and overall survival. For example, amplification of the epidermal growth factor receptor (EGFR) gene has been demonstrated in human specimens. In one study, EGFR levels were shown to be higher in poorly differentiated tumors than in well-differentiated or moderately differentiated tumors. In addition, increased EGFR levels have been shown to correlate with larger primary tumor lesions. on the other hand, studies of the erb-B-2 oncoprotein have indicated that the expression of erb-B-2 is common in human head and neck cancer but does not seem to be of prognostic significance ***(Brochman, 1994)***.

Mutation:

Normal protein serves as a suppressor of cell growth; a possible correlation between mutation and prognosis is being investigated. Generally, mutations are demonstrated in about 50% of head and neck cancers and have also been seen in premalignant lesions. the incidence

and specific type of mutation may depend on the risk factor exposure pattern. A retrospective study by Brachman et al. suggested that tumors with mutation had a shorter time to treatment failure than tumors lacking a mutation ***(Brachman et al, 1992)***. Shin et al. reported on tumor samples from 118 patients. Tumors sites were the oral cavity, oropharynx, larynx, and hypopharynx; median survival was significantly shorter in patients with a mutation in their primary tumor specimen than in those with no such mutation. However, there was no difference in recurrence rates of the primary tumor according to status, although patients with mutation had a higher likelihood of developing a second primary malignancy ***(Shin et al,. 1994)***.

Studies of the chromosome indicated mutations in this region in over 80% of examined head and neck tumors; a similar incidence of allelic loss was found in preinvasive lesions. These findings suggest that loss of genetic information on chromosome 9p is an early event in head and neck squamous cell carcinogenesis ***(Van der riet et al, 1994)***. It also appears that information on the myc oncogene may be useful for prognosis, but this remains controversial. Decreased expression of the nuclear retinoid receptor (RAR-β) has also been associated with head and neck carcinogenesis ***(Brahman et al, 1992)***.

Diet-gene interactions are also likely to contribute considerably to the observed inter-individual variations in HPV associated cancer risk, in response to exposures to the nutritional factors that have the potential to promote or protect against cancer ***(Nair et al, 2005)***.

Viruses:

Many human papilloma viruses (HPVs) are associated with papillary and verrucous lesions of skin and mucous membranes. HPV types 16 and 18 present in 90% of cervical carcinomas, and the E6 and E7 early gene products of these viruses are considered to be oncogenes, as they can transform keratinocytes in cultures. The E6 and E7 oncoproteins are able to bind the tumor suppressor protein, facilitate its degradation, and inhibit normal apoptotic pathways in these cells; the last feature may favor overproliferation ***(Stoler et al,. 1992)***. Mutations are also found in many tumors. Oncogeneic HPVs have been identified in many oral precancerous dysplastic and squamous carcinoma tissues; HPV 16 has been localized in normal oral mucosa as well ***(Ishiji et al., 1992)***. In an investigation of head and

neck squamous cancers using polymerase chain reaction (PCR) methods, over 80% were found to harbor HPV 16 ***(Palefsky et al., 1995)***. Mutations are also prevalent in both precancerous and overtly malignant oral tumors. However, both determining the role these gene products and other oncogenes play in oral cancer causation and understanding their interplay with other carcinogens such as tobacco products require further investigation. Finally, identifying an accurate biomarker for the premalignant state would aid in diagnosis and also allow premalignancy rather than carcinoma to be an endpoint in clinical trials ***(Shin et al., 1994)***. Discovery of a biomarker to identify those lesions likely to progress to cancer would represent a considerable advancement in patient care ***(Benner et al., 1992)***.

Premalignant lesions:

Introduction:

Classification schemes for lesions of the oral cavity typically have used the clinical appearance of lesions to determine which are premalignant. Leukoplakia and erythroplakia are two clinical lesions widely considered to be premalignant. However, using clinical features to classify lesions is difficult because they vary in appearance and are likely to be interpreted subjectively by the clinician. A histopathologic diagnosis is generally more indicative of premalignant change than clinically apparent alterations.

Leukoplakia:

The term leukoplakia is sometimes used inappropriately to indicate a premalignant condition. In fact, the term describes a white plaque that does not rub off and can not be clinically identified as another entity. Most cases of leukoplakia are a hyperkeratotic response to an irritant and are asymptomatic, but about 20% of leukoplakic lesions show evidence of dysplasia or carcinoma at first clinical recognition ***(Axel et al., 1990)***. However, some anatomic sites (floor of mouth and ventral tongue) have rates of dysplasia or carcinoma as high 45%. There is no reliable correlation between clinical appearance and the histopathologic presence of dysplastic changes except that the possibility of epithelial dysplasia increases in leukoplakic lesions with interspersed red areas. In one large transformation rate, compared with a 6.5% rate for lesions that were homogenous leukoplakias with a red component.

N.B:

The term dysplasia is reserved for lesions showing combinations and degrees of cytologic atypia (e.g., hyperchromatism, increased nuclear size, pleomorphism, dyskeratosis, and increased or abnormal mitotic figures ***(Shklar, 1986)***. Atypia confined to basilar and parabasilar keratinocytes constitutes mild dysplasia, whereas atypia extending into the midspinous layer is termed moderate dysplasia. When cellular atypia extends to the surface layer, is termed severe dysplasia and carcinoma in situ (complete top-to-bottom cytologic atypia) are applied. Architectural changes are also a feature of dysplasia, the most significant being a bulbous or teardrop shape of rete ridges. For oral mucosa in general, up to 20%of clinically defined leukoplakias that are biopsied may exhibit dysplasia; lesions located in the floor of the mouth approach a 40% prevalence of dysplastic change ***(Waldron et al., 1975)***. Dysplastic leukoplakias have a high propensity to progress to invasive squamous cell carcinoma. However, leukoplakias without present evidence of dysplastic changes may progress to dysplasia and subsequently to carcinoma; still, many leukoplakias fail to undergo malignant transformation ***(Silverman, et al, 1984)***.

Erythroplakia:

An erthroplakia is a red lesion that cannot be classified as another entity. Far less common than leukoplakia, erythroplakia has a much greater probability (91%) of showing signs of dysplasia or malignancy at the time of diagnosis. Such lesions have a flat, macular, velvety appearance and may be speckled with white spots representing foci of keratosis ***(Shaper et al,. 1975)***.

Lichen Planus:

The premalignant or malignant potential of lichen planus is in dispute. Some believe that the occasional epithelial dysplasia or carcinoma found in patients with this relatively common lesion may be either coincidental or evidence that the initial diagnosis of lichen planus was erroneous ***(Krutchkoff et al,. 1985)***. It is frequently difficult to differentiate lichen planus from epithelial dysplasia; one study found that 24% of oral lichen planus cases had 5 of the 12 world Health Organization (WHO) diagnostic criteria for epithelial dysplasia, and only 6% had no histologic features suggestive of that disorder ***(DeJong et al., 1984)***. However many reports on lichen planus patients followed over time indicate a higher than expected rate of

malignant transformation. It is prudent practice to biopsy the lesion at the initial visit to confirm the diagnosis and to monitor it thereafter for clinical changes suggesting a premalignant or malignant change ***(Silverman et al., 1991)***.

Nicotine stomatitis:

Nicotine stomatitis is a thickened, hyperkeratotic alteration of the palatal mucosa that is most frequently related to pipe smoking, but milder examples can also develop secondary to cigar smoking or, rarely, from cigarette smoking. The palatal mucosa becomes thickened and hyperkeratotic, sometimes developing a fissured surface. The surface often develops papular elevations with red centers, which represent the inflamed openings of the minor salivary gland ducts ***(Neville et al,. 2002)***.

The term niocotine stomatitis is actually a misnomer because it isn't the nicotine that causes the changes; the changes are caused by the intense heat generated from the smoking. Nicotine stomatitis is seenmore often in pipe smokers because of the great amount of heat that is generated from the pipestem. (Similar lesions have even been reported in patients who drink extremely hot beverages). Although nicotine stomatitis is a tobacco-related pathosis, it is not considered to be premalignant and it is readily reversible with discontinuation of the tobacco habit ***(Rossie et al,. 1990)***.

However, in some Southeast Asian and South American countries, individuals practice a habit known as reverse smoking in which the lit end of the cigarette or cigar is placed in the mouth this habit creates a more severe heat-related alteration of the palatal mucosa known as reverse smoker's palate, which has been associated with a significant risk of malignant transformation ***(Silverman et al., 1998)***.

Tobacco pouch keratosis:

Another specific tobacco-related oral mucosal alteration occurs in association with smokeless tobacco use, either from snuff or chewing tobacco. Such lesions typically occur in the buccal or labial vestibule where the tobacco isheld, but they can also extend onto the adjacent

gingival and buccal mucosa. Early lesion may show slight wrinkling that disappears when the tissues are stretched. Other lesions may appear as hyperkeratotic, granular patches. Advanced lesions exhibit greatly thickened zones of grayish white mucosa with well-developed folds and fissures. The degree of clinical alternation depends on the type and quantity of tobacco, the duration of tobacco usage, and host susceptibility ***(Kaugers et al., 1992)***.

Tobacco pouch kertoses can occur at any age, even in children and adolescents. In western cultures, these lesions currently are seen most frequently in young men and men older than 65 years of age; such lesions are less common among middle-aged men because the habit of using smokeless tobacco has not been as popular in this generation. In some rural southern populations, smokeless tobacco keratoses are seen with some degree of frequency in older women, who may have started their snuff dipping habit in early childhood. Overall, it is estimated that 15 percent of chewing tobacco users and 60 percent of snuff users will develop clinical lesions, if mild examples are included ***(Neville et al., 2002)***.

Microscopically, smokeless tobacco keratoses show hyperkeratosis and acanthosis of the mucosal epithelium. True epithelial dysplasia is uncommon; when dysplasia is found, it is usually mild in degree. However, significant dysplasia or squamous cell carcinoma occasionally may be discovered ***(Smith et al., 1970)***.

Most tobacco pouch keratoses are readily reversible within two to six weeks after cessation of the tobacco habit. If the lesion does not resolve after the habit is stopped, then an incisional biopsy of the area should be performed and the patient managed accordingly. Some clinicians also recommend biopsy for lesions in patients who will no discontinue their tobacco habit ***(Martin et al., 1999)***.

Other lesions:

Premalignant changes arising in other oral lesions are uncommon. White lesions such as linea alba, leukoederma, and frictional keratosis are common in the oral cavity but have no propensity for malignant transformation. The health professional can usually identify them by patient history and clinical examination ***(Neville et al., 2002)***.

Clinical features of oral premalignancy:

A diagnostic biopsy should be considered for any mucosal lesion that persists for more than 14 days after obvious irritants are removed; simply noting the clinical appearance or presentation of a lesion is not enough to determine premalignant changes. The following overview describes clinical features generally but is insufficient to identify premalignancy in a specific patient.

Although most premalignant lesions are white (leukoplakia), they vary considerably in their initial presentation. These lesions are usually asymptomatic; the development associated with a malignant change ***(Amy et al., 2001)***.

Anatomic location:

Studies relating premalignant tissues changes to anatomic sites have produced varying results. One study found that 21.8% of oral epithelial dysplasias occurred on the buccal mucosa, 13.7% on the palate, and 12.3% on the floor of the mouth. A study of leukoplakia by ***Shafer and Waldron*** found that the mandibular mucosa and sulcus were involved in 25.2% of their cases and on the buccal mucosa in 21.9%. Because many oral premalignancies present as leukoplakias, the similar findings are not unexpected ***(Waldron et al., 1975)***. Interestingly, the distribution of locations is much different from that of squamous cell carcinomas of the oral cavity, for which the tongue, oropharynx, lip, and floor of mouth are the most common sites. Perhaps there is a subset of epithelial dysplasias, such as those that occur on the buccal mucosa, that have a lower rate of malignant transformation than those found at other sites ***(Silverman et al., 1990)***.

Probability of malignant change:

About 5-18% of epithelial dysplasias become malignant ***(Axell et al., 1996)***. Although expecting a greater probability of malignant change for dysplasias with a greater histologic degree of epithelial dysplasia seems intuitive, that relationship is hard to prove because only a few cases of epithelial dysplasia have been diagnosed but not excised, then monitored to

see whether malignant change occurred. A greater risk of malignant change in an epithelial dysplasia has been associated with the following factors:

1- Erythroplakia withina leukoplakia.
2- A proliferative verrucous appearance.
3- Location at a high-risk anatomic site such as the tongue or floor of mouth.
4- The presence of multiplelesions.
5- Paradoxically, a history of not smoking cigarettes.

(Silverman et al., 1984)

Transition time from epithelial dysplasia to Malignancy:

Although most oral carcinomas have adjacent areas of epithelial dysplasia, some carcinomas may not evolve from epithelium with top-to-bottom dysplastic changes but rather arise from basilar keratinocytes. Silverman and colleagues monitored 257 patients with oral leukoplakia; had a diagnosis of epithelial dysplasia, the remaining 235, hyperkeratosis. Eight of the 22 (36.4%) with epithelial dysplasia developed carcinoma ***(Silverman et al., 1984)***. Of the 107 patients with a homogenous leukoplakic lesion and a diagnosis of hyperkeratosis, (7) (6.5%) developed carcinoma. However, (30) (23.4%) of the 128 patients with erythroplakic lesions and a diagnosis of hyperkeratosis were eventually diagnosed with carcinoma. The time from initial diagnosis of either epithelial dysplasia or hyperkeratosis to carcinoma ranged from 6 months to 39 years. In another study, reported by Lumerman and colleagues, (11,7) (15.9%) of 44 patients with oral epithelial dysplasia identified in a biopsy service developed carcinoma; mean time from biopsy to cancer diagnosis was 33.6 months. Epithelial dysplasia has been more extensively studied in association with the uterine cervix than with the oral cavity ***(Lumerman et al., 1995)***. Based on clinical reviews, approximately 12% of cervical epithelial dysplasias progress to carcinoma in situ ***(Östör, 1993)***. The estimated median time for this progression depends on the histologic severity of the epithelial dysplasia: 58 months for mild, 38 months for moderate, and 12 months for severe ***(Richart et al., 1969)***. Approximately 73% of carcinoma in situ understanding progression to oral cancer is unclear, but it is consistent with observations that not all oral epithelial dysplasias evolve into carcinoma in situ or full-blown carcinoma and that this transition – when it does occur – takes months or years ***(Christopherson, 1977)***.

CHAPTER (3)

HISTOPATHOLOGICAL STUDY

Neoplasms of diverse cellular origin arise in the oral regions, including nasopharyngeal carcinoma, lymphoma, mucosal melanoma, sarcomas, and salivary gland tumors. This chapter will focus on squamous cell carcinomas and their variants, as these cancers constitute over 90% of oral malignancies.

Grading:

Malignancies arising from the mucosa of the oral cavity are epithelial in origin and are, therefore classified as squamous cell carcinomas more than 90% of the time. According to the degree of differentiation, three subtypes are defined:

1- Well differentiated squamous cell carcinoma showing more than 75% keratinization.
2- Moderately differentiated squamous cell carcinoma with 25-75% keratinization.
3- Poorlyd differentiated squamous cell carcinoma with less than 25% keratinizatin. ***(Axel et al., 1996)***.

The majority of cases are of moderate differentiation. A clear relationship between histological differentiation and clinical prognosis has not been established, although a lack of differentiation has been associated with more rapid growth and spread. The morphologic classification of squamous cell carcinoma by degree of differentiation is used in the description of the histopathologic Specimen.

There are histopathologic variants of squamous cell carcinoma, all of which are rare, that affect prognosis and the selection of therapeutic modaltities. Spindle cell or sarcomatoid squamous cancers, occasionally found in the oral cavity, are most frequently encountered on the lip and in the larynx. Radiation therapy to a preexisting conventional squamous cell carcinoma is a common antecedent event; however, spindle cell carcinomas may arise denovo. Other variants of oral, head, and neck carcinoma include pseudoglandular, basaloid, and small cell neuroendocrine carcinomas, the latter two being radiosensitive. Because these

tumors share histopathologic features with other neoplasms (i.e., melanomas, neuroblastomas, lymphomas), the use of specific immunohisto-chemical markers is warranted ***(Barges et al., 1989)***.

Verrucaus carcinoma:

Presents as pebbly mammilated, whitish, warty, bulky cauliflower growth with broad base. These lesions have predilection with buccal mucosa.

Microscopically it shows increased surface keratin and down growth of club-shaped fingers of hyperplastic epithelium that push rather than infiltrate deeply toward an intact basement membrane with prominent inflammatory reaction in adjacent tissues ***(Spiro, 1998)***.

Although the regional lymph nodes are often enlarged and tender, this is nearly always due to associated infection and not to metastases, since the latter are very rare although they can occur. Macroscopically, there is a papillary mass composed of heaped up folds of tissues with deep cleft like-spaces between them ***(Hansen et al., 1995)***.

- Prognosis is more favorable than squamous cell carcinoma, and is considered as low grade malignancy.
- Treated by excision of primary tumor while adjuvant radiotherapy or neck dissection is not indicated due to low incidence of metastasis ***(Spiro, 1998)***.

Spindle cell carcinoma:

Clinically: all reported cases have been polypoid tumors, usually 1-4 cm in diameter. Some appeared to arise on a narrow pedicle whereas others have had a broad base. Most occurred in males and generally in the older age groups. A history of rapid growth is usually obtained and the lesion is often ulcerated. The tongue and floor of the mouth appear to be the most common sites of origin. It may be also seen in the lip and gingiva.

Microscopically: the immediate impression is of a sarcomatous tumor because of the dominance of spindle cells, often showing marked hyperchromatism, pleomorphism,

increased and abnormal mitosis and tumor giant cells. But electron microscopy always supports the epithelial origin.

It is of relative good prognosis, because although metastases occur, they are less frequent than the usual squamous cell carcinoma ***(Barges et al., 1989)***.

Basaloid carcinoma:

It is more aggressive variant than poorly differentiated squamous cell carcinoma. The patient presented at first time with more adjuvant state.

Distant metastasis develops more frequently. Gross picture: rapidly grooving bulky poly poid mass ***(Winzenburg et al., 1998)***.

Staging:

Staging of the disease:

The stage of the disease depends on several factors, including the size of the primary lesion, local extension, lymph node involvement, and evidence of distant metastasis. Tumor size, the organ or tissue affected, and the extent of spread are considered to be the best indicators of the patient's prognosis. Table summarizes the most widely accepted staging protocol, the tumor-node metastasis (TNM) classification of oral cancer. This system has 3 basic clinical features: the size (in centimeters) of the primary tumor; the presence, number, size, and spread (unilateral or bilateral) to the local lymph nodes; and the presence or absence of distant metastasis.

Lymphatic levels and Neck:

Level I: Submented triangle and submandibular triangle.

Level II: Upper jugular (Lymph node):

boundaries: from skull base to bifurcation of carotid artery and from sternohyoid to sternomastoid muscle.

Level III: Middle jugular nodes:

Boundaries: from carotid bifurcation above to amohyoid muscle below.

Level IV: Inferior deep jugular lymph nodes:

from omohyoid muscle above to clavicle below.

Level V: Posterior triangle of neck

boundaries: sternomastoid muscle, trapezius muscle and clavicle.

(Robbins et al., 1991)

Clinical staging:

- Based on physical examination and radiological findings.
- Disadvantages and clinical stages:
  not consider severity and systems, patient
  Co-morbidity and pathological prognostic factors

(Pugiliano et al., 1999).

Table ( ): Tumor-Node-Metastasis (TNM) staging system for Oral carcinoma.

Primary tumor (T)

TX primary tumor cannot be assessed.

T0 No evidence of primary tumor.

Tis carcinoma in situ.

T1 tumor 2 cm or less in greatest dimension.

T2 tumor more than 2 cm but not more than 4 cm in greatest dimension.

T3 tumor more than 4 cm in greatest dimension.

T4 (lip) Tumor invades adjacent structures (e.g., through cortical bone, tongue, skin of neck).

T4 (oral cavity) tumor invades adjacent structures (e.g., through cortical bone, into deep (extrinsic) muscle of tongue, maxillary sinus, skin).

Regional Lymph Nodes (N):

NX regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 metastasis in a single ipsilateral lymph node, 3 cm or less in greater dimension.

N2 Meastasis in a single ipsilateral lymph node, more than 3 cm but no more than 6 cm in greatest dimension; in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N2a metastasis in single ipsilateal lymph node more than 3 cm but not more than 6 cm in greatest dimension.

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension.

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N3 Metastasis in a lymph node more than 6 cm in greater dimension.

Distant Metastasis (M):

MX presence of distant metastasisx cannot be assessed.

M0 No distant metastasis.

M1 Distant metastasis.

The individual clinical parameters in the TNM classification system are grouped to determine the appropriate disease stage; stages are ranked numerically from 0 (which has the best prognosis) to IV (the worst prognosis). In general, oral staging classifications do not use histopathologic findings except to determine the definitive diagnosis.

Schematic drawings of the tumor (tumor maps) are frequently prepared to document the site and size of the tumor at the initial time of diagnosis. This initial documentation is later complemented by histopathologic findings and imaging preformed during the treatment phase ***(Madison et al., 1994)***.

Although the risk of distant metastasis is generally low in patients with oral cancer, there is a correlation between the incidence of distant metastasis and tumor (T) and neck (N) stage. When they do occur, the most frequently involved organs are the lungs, bone, and liver. Patients with advanced T or N stages may be at risk for developing metastases outside the head and neck region; a limited workup (chest x-ray, CBC and liver function tests, bone scan) to exclude such a metastasis may be indicated ***(Merino et al., 1977)***.

After completion of the initial workup, the final T, N, M (metastasis), and overall stage assignment should be formally determined and documented prior to treatment. Because rehabilitation planning starts with staging and treatment, a multidisciplinary approach is essential ***(Hermanek et al., 1996)***.

Disease progression (Spread):

Oral squamous cell carcinoma spreads primarily by local extension and somewhat less often by the lymphatics. The extent of tumor invasion depends upon the anatomic site, the tumor's biologic aggressiveness, and host response factors.

The lymphatic system is the most important and frequent route of metastasis. Usually the ipsilateral cervical lymph nodes are the primary site for metastatic deposits, but occasionally contralateral metastatic deposits are detected. The risk for lymphatic spread is greater for posterior lesions of the oral cavity, possibly because of delayed diagnosis or increased lymphatic drainage at those sites, or both. Cervical lymph nodes with metastatic deposits are firm-to-hard, nontender enlargements. Once the tumor cells perforate the nodal capsule and invade the surrounding tissue, these lymphnodes become fixed and non mobile.

Metastatic spread of tumor deposits from oral carcinoma usually occurs in an orderly pattern, beginning with the uppermost lymphnodes and spreading down the cervical chain. Because of this pattern of spread, the jugulo-diagastric nodes are most prone to early metastasis. Carcinomas involving the lower lip and floor of the mouth are an exception, as they tend to spread to the submental nodes. Although lymph node metastasis is not an early event, as many as 21% of individuals with oral cancer present at diagnosis with nodal metastasis. This proportion exceeded 50% in a study of patients evaluated at admission to cancer centers ***(Lindberg r, 1972)***.

Hematogenous spread of tumor cells is infrequent in the oral cavity but may occur because of direct vascular invasion or seeding from surgical manipulation. Perhaps 10-34% of patients present with distant metastasis; this risk increases with advanced disease. Among the most common sites for distant metastasis are the lungs, liver, and bones. These patients cannot be cured and are treated with palliative intent, usually involving chemotherapy, radiotherapy, or both ***(Silverman et al., 1990)***.

Approximately 30% of patients will present initially with highly confined localized disease stage T1 or T2). These patients are treated with curative intent, usually involving surgery, radiation therapy, 2 or both. Only about 20-40% of patients will develop a local or regional tumor recurrence. However, over subsequent years, these “cured” patients appear to be at higher risk for developing a second malignancy than for developing a recurrence of their initial tumor. Tumor recurrences most often occur during the first 2 years after therapy; later recurrences are rare. Second malignancies, on the other hand, will be observed at a steady rate perhaps 3-5% per year. Thus, with sufficient follow-up time, second malignancies or other medical diseases become greater problems than recurrence of the primary disease. The use of drug therapy to decrease the rate of second malignancies is being actively investigated.

Patients with locoregionally advanced disease (T3, T4, N1, N2,3, and N) are also treated with curative intent. Given the advanced stage of their disease, surgery and radiation are utilized unless patients are considered inoperable or have unresectable disease. Despite this aggressive bimodality therapy, the majority of these cancers will recur within the first 2

years of follow-up, most commonly either locally or regionally. Some of these patients may have metastases outside the head and neck area, events that might be predicated by their initial T and N stages. Investigational therapy in this group of patients, therefore, must focus primarily on delivering more effective locoregional care. However, should locoregional control be improved, chemopreventive strategies will need to be pursued in this group of patients as well since, in principle oral cancer patients are at risk for developing second primary malignancies in the oral cavity, pharynx, and respiratory digestive tracts ***(Marcial-vega et al., 1990)***.

Biological study: "Biological staging"

The most interesting emerging trend in this area is using molecular biology to define more carefully a tumor's biological behavior "biological staging". Another interesting trend currently being investigated is the use of the polymerase chain reaction (PCR) to determine if surgical margins obtained at the time of surgery that are histopathologically free of tumor contain small amount of histologically undetectable tumor cells. Specifically, the use of PCR to detect specific mutations identified in the primary tumor in the histopathologically negative surgical margin could be very useful, as these mutations would indicate the presence of residual (histopathologically undetected) tumor cells. It will be very important to establish whether the presence of submicroscopic tumor cells contributes to prognosis and clinical outcome.

The recent development of in situ PCR will allow amplification of both DNA and RNA directly in tissue section; this technique should be extremetly helpful in the future to localize tumor cells containing altered oncogenes or tumor suppressor genes. An improved understanding of the molecular biology of head and neck cancer may also contribute to future therapeutic improvements. Finally, molecular probes may be used to facilitate the early detection of second malignancies ***(Voravud et al., 1993)***.

A good deal of current laboratory and clinical research is focusing on identifying the relative contributions of certain oncogenes and tumor suppressor genes on carcinogenesis, tumor stage, and clinical outcome. Although abnormalities of some oncogenes and tumor suppressor genes have been identified, their relative contribution and optimal use in

diagnosis, prognosis, or treatment remain unknown. The same might be said for the role of Epstein-Barr, hepatitis,and herpes simplex viruses; further clinicolaboratory studies will be needed to define which are clinically relevant and when they should be investigated. Figure 1 shows biomarkers that may prove useful in assessing cycling cells in precancerous lesions and at surgical tumor margins, and in predicting aggressive behavior, invasion front, and metastatic potential ***(Pearson et al., 1993)***. Genetic analysis at a molecular / chromosomal level is emerging as a science that may aid in identifying risk and possibly prevention as well ***(Liu et al., 1994)***.

Finally, a reliable and predictable histopathology grading system should be developed to include, in addition to differentiation of tumor cells, such factors as basement membrane protein expression and invasion paterns, perineural invasion, and immunologic responses ***(Liu et al., 1994)***.

Biochemical and genetic factors:

No matter which diagnostic technique is used, there is the possibility of a false-negative diagnosis. However, studies are under way to identify key markers that should improve accuracy. The development of monoclonal antibodies that have high sensitivity and specificity for epithelial dysplastic and malignant cells would enhance accuracy of diagnosis in some cases where the usual or typical cellular characteristics of precancer or cancer are not apparent. Such antibodies might also minimize errors about “tumor free” margins of surgical resections, thereby reducing a potential source for recurrence. In addition, assuming that an antibody was specific for a particular cellular tumor antigen, binding of cytotoxic chemotherapeutic agents for killing tumors and sparing normal cells would be a logical and possibly feasible follow-up to surgery and radiation therapy to improve cancer control.

Additional knowledge about various cell markers that reflect growth and suppressor protein presence or activity may also prove to be of great value in predicting cell behavior. Genetic/chromosome evaluations may serve a similar purpose in the identification and treatment of tumors.

Current research is exploring the genetics of biochemical processes that may affect the development of oral cancer. Included are gene mutations such as tumor suppressor gene amplification and overexpression of proto-oncogenes C-myc, EGFR and cyclin D1, as well as loss of heterozygosity of specific chromosome loci. Cellular alteration of response to growth factor and Beta's (TGF-β) growth suppressor effect on tumor cells may become important as well.

Opportunities and Barriers to progress:

The emergence of molecular biology with its new prognostic and, ultimately, therapeutic tools represents an enormous opportunity. The use of biologic markers to screen patients who are at increased risk may help to predict the probability of disease progression, aid in the diagnosis made by routine histopathologic studies, assess the prognosis of the individual cancer patient, develop treatment protocols, and evaluate the response to therapeutic agents. A major barrier to progress is a health care climate in which a large proportion of patients receive either uncoordinated "multispecialty" or traditional surgical care without proper usage of laboratory, clinical, and therapeutic investigational tools. Thus, research is slowed at single institutional and national levels (e.g., cooperative groups). Proper recognition that survival rates are too often poor with "standard therapy" in patients with advanced disease should lead to a greater appreciation for research.

Another barrier to progress is the cost of biologic markers combined with the failure of third parties to cover them. Laboratory standardization of biologic marker techniques and variability in interpretation of tissue results compromise the diagnostic significance of these markers.

CHAPTER (4)

Diagnosis

Diagnosis can be delayed by several months or more if the clinician treats the patient's complaints empirically with drugs instead of providing a through physical examination and work up. Patients with complaints lasting longer than 2-4 weeks should be referred promptly to an appropriate specialist to obtain a definitive diagnosis. If the specialist detects a persistent oral lesion, a biopsy should be performed without delay.

Screening and early detection:

Screening for oral cancer should include a thorough history and physical examination. The clinician should visually inspect and palpate the head, neck, oral, and pharyngeal regions. This procedure involves digital palpation of neck node regions, bimanual palpation of the floor of mouth and tongue, and inspection with palpation and observation of the oral and pharyngeal mucosa with an adequate light source; mouth mirrors are essential to the examination. Forceful protraction of the tongue with gauze is necessary to visualize fully the posterior lateral tongue and tongue base ***(Mashberg et al., 1995)***.

The clinician should review the social, familial, and medical history and should document risk behaviors tobacco and alcohol usage), a history of head and neck radiotherapy, familial history of head and neck cancer, and a personal history of cancer. Patients over 40 year of age should be considered at a higher risk for oral cancer ***(Silverman et al., 1990)***.

History:

The first step in patients assessment is obtaining a thorough history including the presence of risk factors and symptoms. Most neoplastic disease occur from an inherent tendency or enhancement genetic susceptibility combined with multiple exposures to substances that contribute to the initiation or promotion of carcinogenic change. The two major risk factors for oral cancer-tobacco use and heavy alcohol consumption are responsible for about 75 percent of oral cancers. The remaining 25 percent are caused by other factors, which may include nutritional and genetic influences. The etiologic role of these factors, is not well understood, and methods for modifying them need to be developed ***(Lunn, 1997)***.

All forms of tobacco have been implicated as causative agents, including cigarette, cigar and pipe tobacco as well as chewing tobacco and snuff. Although oral cancers occur in patients who do not use tobacco, this constitute a very small percentage of cases ***(Mea et al., 2002)***.

Patterns of alcohol consumption, particularly among smokers, also are considered important. There is a higher incidence of oral cancer in people who are heavy smokers and heavy drinkers. The reason for the increased cancer risk associated with increasing alcohol consumption is not completely understood. It may be due to the carcinogenic effect of the first metabolite of ethanol, acetaldehyde. Women who drink heavily and smoke have a 100-fold increase in oral cancer, whereas men who are heavy drinkers and smokers have a 38-fold increase. Sun exposure is the primary risk factor for lip cancer, but pipe smoking also is a risk factor ***(Harty et al., 1997)***.

Although early oral cancers are usually asymptomatic, progression of the cancer may be accompanied by difficulty in chewing or swallowing, a history of sores in the mouth that do not disappear, hoarseness, soreness or a sensation of something in the throat and difficulty with speech ***(Harris, 1997)***.

Physical examination:

i) General examination:

To detect co morbidity or stigmata of disease as autoimmune, or vascular disease.

ii) Local examination:

The principal screening test for oral cancer is a physical examination that consists of systematic inspection and palpation. The extraoral soft tissues are examined first, followed by the intraoral soft tissues. Any deviations, such as swelling, tenderness or fluctuate, are recorded ***(Mea et al., 2002)***.

During the extraoral examination, the lips, salivary glands and cervical lymph nodes are evaluated. The closed lips are inspected for texture and color. The vermilion border should be observed and palpated for ulceration, blistering, induration and swelling.

The parotid gland, the largest of the salivary glands, lies in front of the ear and wraps around the posterior border of the mandible. The parotid gland is palpated intraorally and extraorally, either bimanually (placing one hand on the cheek and two fingertips of the other hand on the buccal mucosa) or bidigitally (placing the gland between the fingertips of one hand).

The submandibular and sublingual glands are palpated by either pressing four fingertips bilaterally on the soft tissue under the chin or resting the thumbs of each hand near the inferior mandibular border while pressing the fingertips inferior and medial to the mandibular border the finger tips are moved inferiorly to the hyoid bone and then medially and superiorly until the inferior part of the submandibular gland is felt ***(Mea et al., 2002)***.

When oral cancer metastasizes, it most commonly spreads through the lymphatic system to the cervical chain of lymph nodes in the neck. Spread to the cervical lymph nodes is more common in oropharyngeal neoplasms than in oral cavity neoplasms. Thus, the status of the cervical lymph nodes, especially the upper deep nodes, at presentation is important ***(Lunn, 1997)***.

The anterior deep cervical lymph nodes are palpated with the patient's head hyperextended and turned to distend the sternocleoidomastoid muscle. Using two hands, the

fingertips of one gently retracts the sternocleoidmastoid backward while the fingertips of other hand hooked around the front of the neck, palpate the region of carrot sheath. This examination also can be performed with one-hand palpation by placing aligned fingertips along the posterior border of the sternocleoidomastoid while the thumb provides counter pressure from the anterior aspect of the muscle. The fingertips are gradually moved inferiorly along the muscle ***(Mea et al, 2002)***.

The preauricular aned posterior auricular lymph nodes are examined next, using bilateral placement of both hands. The preauricular lymph nodes are located in front of the ear and the postauricular nodes are located behind the ear. The supraclavicular nodes are located on the inferior part of the front of neck, superior to the clavicle. The occipital lymph nodes are located at the base of the skull. The auricular lymph nodes are palpated by the bilateral placement of both hands on the skin surface with the fingertips arranged to cover a large surface area ***(Mea et al., 2002)***.

Examination of the intraoral tissues includes inspection and palpation of the lips, buccal mucosa, tongue, floor of the mouth, gingiva and palate. The intraoral labial mucosa is inspected and then palpated using the fingertips of two hands to invert the upper and lower lips. The buccal mucosa is retracted for inspection and palpated using a bimanual or bidigitial technique.

The lateral borders of the tongue are common areas for oral malignancies to develop. The tongue is inspected by grasping the tip with a gauze square and pulling out and moving it to the sides and upward to permit complete visualization of the dorsal lateral borders and ventral surfaces. At the same time, palpation using the index finger of the other hand is performed.

Next, the floor of the mouth is inspected and palpated. The submandibular glands located in the anterolateral floor of the mouth are palpated by placing the fingertips of one hand in the floor of the mouth while the fingertips of the other hand are placed under the

chin to support the mandible. The sublingual glands are more difficult to palpate than the submandibular glands because they are more compressible and less distinct.

The hard palate is another site of oral malignancies. Smokers especially pipe smokers, may develop nicotinic stomatitis on the hard posterior palate, which makes this a high-risk area. With the mouth wide open and the patient's head tilted back, the hard and soft palates should be carefully inspected and palpated ***(Mea et al,. 2002)***.

The many signs and symptoms of oral cancer are usually divided into early and late presentation. They can be so diverse that the differential diagnosis may not lead to oral malignancy. Table ( ) summarizes the signs and symptoms.

Frequent symptoms and signs of oral cancer:

Early	Late
- Persistent red and/or white patch. - Progressive swelling or enlargement. - Sudden tooth mobility without apperant cause. - Unusual oral bleeding or epistaxis. - Non healing ulcer. - Unusual surface changes. - Prolonged hoarseness.	- Airway obstruction. - Chronic otaligia (chronic serous otitis media), referred pain by 1x, x cranial nerves. Indurated area. - Parathesia or dysthesia and tongue or lips (May, indicate PNI). - Trisumus - Altered vision. - Cervical lymphadenopathy.

N.B:

Few cases with recurrent oral cancer develop picture of hypona tremia resulting from the syndrome of inapparpriate secretion of anti diuretic hormone (SIADH) as a para neoplasic condition ***(Danielides et al., 2005)***.

Because patients may be at risk for developing multiple primary tumors simultaneously or in sequence, the entire visible mucosa of the upper aerodigestive tract must be examined. In addition, lymph nodes in the head and neck area particularly along the jugular chain must be palpated. Approximately 90% of patients with squamous cell carcinoma in a lymph node in the neck area will have an identifiable primary tumor elsewhere, and about 10% will have cancer in the neck lymph node as an isolated finding (Unknown primary). Thus, most cancers in the neck node represent a metastasis from a primary tumor located in the head and neck region; this primary site must be identified ***(Marcial Vega et al., 1990)***.

Multiple carcinomas:

Individuals with one carcinoma of the head and neck region have an increased risk of developing a second malignancy; the frequency of that event varies from 16% to 36%. When a second malignancy occurs at the same time as the initial lesion, it is called a synchronous carcinoma. Metachronous neoplasms, on the other hand, are additional primary surface epithelial malignancies that develop in a later time period than the original tumor. About 40% of second malignancies of the upper aerodigestive tract arise simultaneously and represent a synchronous tumor. The remaining multiple cancers in this population represent metachronous disease and usually develop within 3 years of the initial tumor. Second primary tumors are the chief cause of death in patients with an early stage diagnosis ***(Schwaitz et al, 1994)***.

The tendency to develop multiple carcinomas in the upper aerodigestive region is known as "field cancerization ***(Slaughter et al., 1953)***. Prolonged and diffuse exposure to local carcinogens, particularly tobacco combined with alcohol, appears to increase the malignant transformation potential of exposed epithelial cells ***(France et al., 1991)***.

In the upper aerodigestive tract and lungs. The overall risk for developing a second head and neck malignancy is 10 to 30 times higher in populations that use tobacco and alcohol than in the general population ***(Fijuth et al,. 1992)***.

Annual evaluation:

Because of the well-recognized phenomenon of "field concretization" in the head and neck region, it is important to refer patients who are diagnosed with a primary squamous cell carcinoma or epithelial dysplasia of the oral cavity for evaluation of a synchronous tumor. In addition, an annual evaluation for detection of metachronous disease should be reinforced for these patients. Such patients should be monitored routinely for high-risk behaviors, including continued tobacco and alcohol consumption, because these behaviors adversely influence survival after the occurrence of a second cancer. Finally, the use of consultations and tumor board services is essential, even in what may be deemed "early cancer." ***(Mancuso et al., 1994)***.

Non invasive clinical tests:

Toluidine blue (vital staining) also is a useful adjunct to clinical examination and biopsy. The mechanism is based on selective binding of the dye to dysplastic or malignant cells in the oral epithelium. It may be that toluidine blue selectively stains for acidic tissue components and thus binds more readily to DNA, which is increased in neoplastic cells ***(Silverman, 1993)***.

Toluidine blue has been recommended for use as a mouthwash or for direct application on suspicious lesions; its value comes from its simplicity, low cost, noninvasiveness, and accuracy. In addition, it can help to determine the most appropriate biopsy sites and to surgically delineate margins. Meta-analysis of toluidien blue staining in oral cancer screening found that its sensitivity ranged from 93.% to 97.8%, and specificity from 73.3% to 92.9% ***(Zhang et al., 2005)***.

The disadvantages of toluidine blue include the risk of obtaining a false negative reaction in a case where the patient is not followed up adequately. In contrast, the infrequent false-positive only subjects the patient to a biopsy. No in vivo observations or reports have suggested a mutagenic effect from this stain ***(Dunipace et al, 1992)***.

Comparison of toludine blue uptake with microscopic diagnosis:

Biopsy diagnosis	No. of lesions	+ve	-ve	Correct
Carcinoma	62	58	4	94%
Dysplasia	13	11	2	85%
Benign	67	6	88	94%
Total	169	75	94	93%

Definite diagnosis:

1- cytological and histopathological study.
2- Imaging study.
3- Panendoscapsy.
4- Immuno histochemical study.
5- Clinical photo detection.
6- Biological study (Biochemical study).
7- Laboratory study.

Cytological and histopathological study:

Under certain conditions, exfoliate cytology (cell scrapings) serves as an adjunct to clinical diagnosis, as it enables more extensive screening and provides microscopic material if there is a delay in orcontraindic action to biopsy. However, cytologic smears are used infrequently, and patients are not treated on the basis of cytologic findings alone. Smears are most helpful in differentiating inflammatory conditions, especially candidiasis, from dysplastic or neoplastic surface lesions. in addition, cytology may be helpful in detecting field change in oral cancer, especially if this method is used in conjunction with vital staining. Cytology may also be helpful when ulcerations following radiation are suspicious and biopsy is delayed.

Fine needle aspiration biopsy of subsurface masses is also an accepted diagnostic test, one that has increased in popularity over the past few years. This technique is extremely useful in evaluating clinically suspicious changes involving salivary glands and lymph nodes. It expedites diagnosis and staging and avoids incisional or excisional biopsies that may interfere or complicate definitive treatment. When used by a skilled clinician, fine needle aspiration can often be the best way to establish a definitive diagnosis of unexplained masses of the neck or

salivary glands. It is also valuable in following up cancer patients with suspicious enlargements ***(Cirstallini et al., 1989)***.

Biopsy:

Indications and contraindications of Biopsy

Clinical evaluation of lesion will result in the decision whether the lesion should undergo biopsy or not. The need for biopsy is summarized in the following situations:

- Biopsy is indicated whenever careful examination fails to reach a positive diagnosis after exclusion of lesions of developmental origin such as lip pits and tori. Lesions found in risk areas as tongue or lips should also be considered for biopsy ***(Bernier et al., 1950)***.
- Biopsy is mandatory for any lesion that persists or fail to heal for more than two weeks after initiation of conservative treatment ***(Archer, 1971)***.
- Any recognized precancerous lesions, for example white keratotic patches, chronic hyperplasia, red areas and pigmented lesions should be submitted to biopsy ***(Scope, 1973)***.
- Lesions which present a clinical sign of malignancy, such as progressive ulcerations with induration, or fixation to the surrounding structures are indicated for biopsy ***(Medak, 1973)***.
- Any tissues removed during surgical procedures, tissue spontaneously expelled from body orifices, and material draining from persistent sinus where its source is unknown, are other conditions mandating bipsy performance ***(Bernstein, 1978)***.

Conditions that contraindicate biopsy performance:

Summarized by: Golden and Hooley and Kerr, Ash and Millard (1978)

I) relative contraindication:

- lesions referred early and should be kept under observation for 10-14 days before deciding to do biopsy, such as, inflammatory lesions must have adequate therapy, two weeks for follow up then the need for biopsy is determined.
- Areas of unclear interpretation including anatomical and racial variation such as, physiologic pigmentation, tori and linea alba. These proposed lesions should be inspected for bilateral symmetry and evaluated for chronicity prior to biopsy.
- Proximity of the lesion to vital structures whether vascular, neural, or ductal structures and lesions in areas of difficult surgical access need more surgical experience prior to biopsy.

- Extremely debilitated patients, cardiac patients and patients with acute infection or bleeding disorders need medical preparation prior to biopsy.

II) Lesions considered as absolute contraindications to routine Biopsy:

- Vascular lesions: such lesions are contraindicated for incisional biopsy. Those patient should be referred for more advanced clinical, radiographic and laboratory investigations.
- Pigmented lesions: should be referred to a specific center for facility of investigations to attain definitive diagnosis and proper therapy. Incisional biopsy of those lesions carries the risk of spreading of tumor cells into the adjacent normal tissues.

Hazards of Biopsy:

Bleeding, infection and spread of malignant tumors are considered as hazards of biopsy. These possible hazards inherent to biopsy procedure were discussed by many investigators ***(Kille et al., 1971)***.

Bleeding and infection following biopsy procedures were not considered as serious problem, since bleeding could be controlled by pressure or suturing and infection could be managed by medication ***(Eisen, 1992)***.

Regarding to spread of malignant tumor, ***Knox in (1929)***, was the first to report that, surgical trauma to a malignant tumors may increase there metastatic potency. ***Kage et al, (1987)***, attributed this to increase of local aggressiveness of the tumor, dissemination of the tumor cells into damaged blood and lymph vessels and inflammation which increases the vascular permeability.

Safour and Colleagues (1984), observed direct invasion of the tumor to the adjacent tissues after performing incisional biopsy in carcinoma of hamster cheek pouch. They mentioned that incision of this tissue with contaminated blade that has just cut through the tumor might be the cause of direct invasion. The authors postulated that the same results would be found in humans. ***Tsikalkis et al (1986)***, found that surgical incision of a tumor

promotes its progression. They claimed that stimulation of inflammation and healing process will release the growth promoting factor, thus might increases the local aggressiveness of the neoplasm.

An investigation by ***Ohtak, Shingaki and Nakajima (1990)***, have demonstrated that high incidence of lymphatic vessels invasion was observed following incision of tumors, they believed that direct trauma to tumor nests and vascular channels as well as inflammatory processes might facilitate invasion of the vascular system at site of injury, and might be responsible for the eventuating of lymph node metastasis.

On the other hand, some authors considered the later hazard of biopsy as a controversial possibility which is not supported by retrospective studies. ***Shklar (1968)***, reported that neither biopsy, incision, nor massage with compression promote growth of the tumor. **Epstein**, ***Bragg, and Linden (1969)*** concluded that biopsy is avisable in cases suspected to be melanoma. They stated that there was no evidence to indicate that incomplete removal of malignant melanoma followed by definitive surgery decreases the probability of the survival. ***Kerr, et al (1978)***, considered that even rough manipulation and vigorous palpation of lesions may be more serious than performing a biopsy. They added that the possible dangers will be less than dangers of attempting any radical treatment without establishing a definitive diagnosis.

Howe (1985) pointed out that clinical experience did not support this possibility. He mentioned that it is widely agreed that the proven value of biopsy faroutweigh this theorietical objection. ***Gandolfo and Coworkers, (1993)*** did not found any data based on a real clinical survey, which could were prove a worse prognosis subsequent to certain approaches of biopsy.

Rules of Biopsy:

There are certain rule that should be followed to minimize the possible hazards of biopsy and insure accurate results.

- Excisional biopsy is indicated for small lesions (1 cm or less) and certain large lesions which can be removed without extensive surgery and suspected to be of benign

nature. On the other hand incisional biopsy is recommended for large lesions in which total removal would be a major surgical procedure. In cases of extensive and diffuse lesions that show variations in its clinical appearance, multiple biopsies should be taken from each area showing different characteristics ***(Howe, 1985)***.

- A representative biopsy specimen should be obtained from the most active site that gives maximum diagnostic information. For soft tissue lesions, the central portion of the lesion usually exhibit area of necrosis which will be of little diagnostic value. While the extreme edges of the lesion may show reactive tissue not characteristic of the main lesion. In bony lesions, the most active site is at the center. The margins will reflect a nonspecific reactive bony response ***(John et al, 1965)***.
- Specimen size should not be less than3-10 mm because tiny specimen is difficult in orientation especially after shrinkage due to processing procedures ***(Daley et al., 1986)***.
- The specimen should be cut narrow and deep rather than broad and shallow. The depth of incision should be extended to include normal tissue below the lesion. The specimen should include a part of the lesion, adjacent normal tissue and intermediate tissues in between ***(Roven, 1965)***.
- The pathologist should receive the specimen in a condition that allows him to make accurate diagnosis. Distortion of specimen should be avoided. Injection of anesthetic solution into the lesion will cause volumetric tissue alteration. Removal of specimen by electrosurgical equipments will generate heat and results in coagulative necrosis and tissue alteration. The use of serrated forceps to grasp the specimen leads to its perforation. Squeezing of specimen during removal may cause artifact. Biopsy specimen should be placed on a cardboard with mucosal surface facing upward. Margins of specimen should be tied by structures to be correctly oriented to give maximum diagnostic information ***(Scape, 1973)***.
- Finally, the specimen should be placed immediately in a wide opening glass jar and contains adequate amount of fixative solution usually 20 times the size of specimen. The jar should be labeled with date, patient name, origin of specimen, and tightly closed ***(Chiles, 1987)***.

N.B:

One frequent misunderstanding about the treatment of patients with carcinomas of the oral cavity concerns the first diagnostic steps. Initially, only an incisional biopsy of the primary

lesion should be performed, not an excisional biopsy. Inadequate excisional biopsies only cause confusion about the initial extent of the tumor and add an unnecessary procedure of greater concern is that excisional neck node biopsies are frequently used to establish a diagnosis of head and neck carcinoma. A physical examination combined with imaging of the mucosa of the upper aerodigestive tract will usually reveal the source of suspicious adenopathy. If the relationship of lymphadenopathy to primary oral cavity tumors remains uncertain, a fine needle aspiration biopsy will almost always provide a tissue diagnosis from the lymph node. Removing a lymph node during diagnosis complicates management, as radiotherapy then must be the next treatment step to have the usual chance of a successful outcome.

A good history should be submitted to aid the pathologist in making a diagnosis. Case history including personal data, history of the lesion, the clinical features, pertinent description of lesion, diagrammatic sketch showing the site of lesion and site of biopsy and results of lymph node examination. For bony lesion a radiographic picture is essential ***(Shira, 1963)***.

Who should do a biopsy:

The possible hazards encountered with biopsy performance for lesions thought to be malignant, raises the question as, who should do a biopsy? Controversy exists as to whether general practitioner or oncologic specialist should do a biopsy.

Boyle (1985), Johonand Manhold (1965), Howe (1985) and Chiles, stressed that a specialist is best qualified to do biopsy as he has enogh experience, and all the facilites required to investigate and treat and patient without delay. Bramley and smith (1990) pointed out that the specialist might prefer to see the lesion undisturbed by biopsy and to be able to choose his own biopsy site.

On the other hand, ***Shira (1963), Rovine (1965)***, and ***Bernstein (1978)***, recommended biopsy procedures to become an integral part of general practitioner practice and not limited to small group of tumor clinic. As it would be impractical to refer all patients to oncologic

centers. In addition the routine use of biopsy examination by general practitioners will provide early detection of malignant lesions before it looks malignant.

Brennan (1995), in two successive reports encouraged the performance of biopsy by general practitioner before referring patients to oncologic centers, as they are more involved in the overall patient management. He stressed that prognosis would not be affected when the general practitioner perform a biopsy for a malignant lesion. The author emphasized that prognosis depends on the stage of the disease with lymph node involvement of the neck, other important prognostic indicators include performance status and quantity of response to chemotherapy.

Oral Biopsy Techniques:

Several methods were applied to obtain biopsy specimens of a lesions within the oral cavity:

- Excisional biopsy.
- Incisional biopsy.
- Oral exfoliation cytology.
- Aspiration biopsy.
- Fine needle aspiration cytology.
- Cryobiopsy techniques.
- Frozen section biopsy.
- Electro surgical biopsy.
- Drill biopsy.
- Punch biopsy.

Excisional biopsy:

Implies the total gross removal of the entire lesion in both breadth and depth with adequate safety margin. The whole lesion serves as the biopsy specimen. This technique is the method of choice for accessible lesions of 1 cm size or less. Lesions whose size and location allow surgical removal without major surgical procedures and resulting defect could be closed primarily without difficulty. This technique is applied more to lesions which clinically seem to

be benign. While the more diffuse or dispersed lesions are not indicated for excisional biopsy. Suspected malignant lesions are not conclusive for excisional biopsy because excision will obscure its site and hinder the subsequent planning of surgical intervention later on ***(Stern, 1967)***.

Excisional biopsy is achieved by two eliptical incision arms which intersect at both ends. Incision lines should include the lesion and adequate safety margin of 5mm away from the lesion border in both width and depth. Biopsy is better done with blade and not by diathermy to avoid tissue alteration and different interpretation. The wound margins should be undermined and sutured. If the lesion is in the attached mucosa, it is left to heal by secondary intention ***(Golden et al., 1994)***.

Incisional biopsy:

Mean removal of a portion of a lesion for examination without any Attempt being made to remove the whole lesion. The specimen should include a clinically typical area of the lesion and a part of the adjacent normal tissue. For large diffuse, extensive and suspected malignant lesions, incisional biopsy is the method of choice ***(Eisen, 1992)***.

This technique can be achieved by either two elliptical incisions or v-shaped incision. The incision arms start from the center of the lesion and extend beyond its border at adjacent normal tissue. The length of incision lines in relation to width should be 3:1 to allow undermining of edges and suturing ***(Frim, 1984)***.

Depth of incision is determined according to the nature of the lesion. For obviously benign lesions such as fibroma and papilloma, the depth must extend to include the stem of the lesion ***(Golen et al., 1994)***.

For lesions that are close to vital structures, incision lines should be parallel to these structures and less deep. For ulcerative lesions the incision should include part of normal tissue, area of ulcer crater and intermediate section that is not ulcerated and usually shows

starting reactive cellular atypia. Vesicular lesions are best diagnosed by specimen including the edge of the blister where epithelial cleavage is actively occurring. For lesions extending to bone, the underlying periosteum must be included in the incision ***(Kroll et al, 1987)***.

Oral exfoliative cytology:

Refers to microscopic examination of surface cells that have been scraped from mucosal surface the mucosal surface is scraped by blunt instrument, the desquamated cells are collected, smeared on a glass slide, fixed and examined under microscope ***(Archer, 1971)***.

This technique is recommended by some investigators as an adjunct to biopsy and not as a substitute for it. They do not considered its results as a final diagnosis ***(Henk, 1985)***. Other clinicians consider this technique as preliminary examination. Oral exfoliative cytology is mainly indicated for follow up of patients who had already received treatment of a diagnosed lesion, to detect any changes that dictate secondary biopsy ***(Golden et al., 1994)***. It is also helpful in debilitated patients and those who refuse to do a biopsy for various psychological reasons ***(John et al., 1965)***.

Oral exfoliative cytology technique has several limitations that should be considered. The only reasonable information that could be obtained is to rule out malignancy ***(Lynch, 1990)***. Desquamated cells scraped from the surface of a proved malignant lesion will show only keratinized squamous epithelial cells without any diagnostic value ***(Sabs, 1979)***. False negative records are commonly encountered with this technique ***(Henk, 1985)***.

Aspiration Biopsy:

Refers to removal of the fluid or semifluid content of a lesion for analysis by using an aspirating syringe. This technique is applicable for cyst like lesions, fluctuant lesions, and intraosseous radiolucent lesions prior to surgical intervention ***(Killy et al., 1971)***.

A 14-18 gague needle mounted on a 5-10 ml syringe is used the needle is inserted with controlled pressure, till it reaches the suspected lesion. A negative pressure is required

to allow positive aspiration. The needle content is expressed over a glass slide, dried, fixed, stained and examined. If the syringe content is fragments it is fixed in formalin and examined ***(Kerr et al., 1978)***.

Fine Needle aspiration cytology:

This technique has gained a considerable credibility in recent years. It offers a tentative diagnosis for deeply seated lesions of soft palate, space occupying lesions of a salivary glands and head and neck lymph nodes. 21-23 gauge needle is inserted into the suspected lesion guided by ultrasound to ensure that the exact target area is sampled. The main advantages of this technique are, simplicity, acceptance by most patients, rapid diagnosis obtained, and decreased risk of delayed wound healing or infection. The small sized needle will limit the hazards of spreading of tumor along the route of the syringe ***(Eisen, 1992)***.

Cryobiopsy technique indicates:

The removal of tissue specimen in the frozen state for histologic examination. It offers the opportunity of obtaining a small perfect sample of friable tissue ***(Poswillo, 1979)***.

The cryosurgical probe tip produces an ice ball and the specimen is takenfrom the frozen area with scalpel or a punch forceps. The resulted specimen is examined by frozen section or embedded paraffins section. This technique allows examination of small specimen undamaged by forceps pressure ***(Poswillo, 1979)***.

Frozen section biopsy:

Refers to histologic examination of frozen tissue slide to obtain an immediate diagnosis. It is mainly used in other areas than the oral cavity, such as breast and thyroid tumors. The aim of this technique is to assist the surgeon in determining the necessary extend of the resection of a lesion at the same time of operation. However, the histologic examination of the specimen usually shows some degree of distortion, which may inhibit an efficient diagnosis ***(Martin, 1975)***.

Electrosurgical Biopsy:

Indicates the removal of tissue specimen by means of electrosurgical electrode. Different shapes of the electrode are used according to the shape of the excised lesion. According to ***Oringer (1982)*** the use of electrosurgical technique will eliminate the risk of tumor metastasis and direct invasion to adjacent tissues. He attributed this to sealing of damaged vascular channels and cauterization of tumor bed. On the contrary other investigators stressed that the use of electrosurgical equipments will generate heat that leads to coagulative tissue necrosis and results in distortion of specimen. They suggested that cauterization of tumor bed could be attained after excision of the specimen ***(Margarone et al., 1985)***.

Drill biopsy:

Refers to obtaining of specimen from central bony or fibroosseous lesions by means of a specially designed bonebiopsy drill. A small hollow cylinder is fitted on a straight hand piece. A mucoperiosteal flap is raised, and the drill could be inserted to its full depth into bone. The technique provides a small specimen which usually show distortion due to heat generation. Missing site of the lesion during insertion of the drill results in false records ***(Golden et al., 1994)***.

Punch biopsy:

Punch biopsy depends on the use of a special instrument designed to remove a core of tissue specimen. Punch bipsy is applicable for incisional biopsy and could be used for excision of small size lesion such as, warts or melanotic maculae. It is mainly used for obtaining an incisional biopsy specimen. Two types of biopsy punches are available reusable punches, and disposable punches ***(Sassani et al., 1981)***.

Reusable punches including key's biopsy punches, beltdriven punches, biting forceps and punch forceps. Key'sbiopsy punches were developed for dermatologic use and could be used in oral mucosal lesions. it is made of stainless steel and has a size range of cutting edge from 2 to 12 mm diameter. The thickness of cutting edge is 0.25 – 0.50 mm in increment. Key's punch needs routine retargeting which necessitates to send it back to the manufacture. This process of resharpening of the instrument decreases the length of cutting edge and depth of cutting will be less consequently. The heavy handle of key's punch causes loss of tactile sensation. The latter disadvantages limits its use for oral mucosal biopsy. Similar biopsy punches are available for use with a belt-drive engine at speed of 250-36,000 rpm. This type is inappropriate for oral mucosal lesions ***(Banaski, 1987)***.

Biting forceps and punch forceps are especially designed for obtaining a biopsy from remote areas such as pharynx, or tonsil. It is composed of cutting edge (biopsy tip) of different shapes (rounded or triangular) and shaft. The length of the shaft is varying from 12-24cm whereas the diameter of the tip ranges from 5-17mm ***(Chiles, 1987)***.

Disposable biopsy punches are present as sterile, prepackaged instruments. It is composed of a metal cutting edge mounted on a plastic handle. The plastic handle offers light weight and consequently good tactile sensation. The cutting edge is rounded in shape and has a sharp beveled edge with a size ranging from 1 to 8mm. the handle could be shortened for better accessibility. The later advantages advocate its use in the oral cavity ***(Eisen, 1992)***.

Punch technique follows the same rules of routine biopsy procedures. The punch is held at the end of its handle between thumb and index fingers. The punch is slowly rotated back and forth between the fingers, with moderate pressure, until the cutting edge is forced into the lesion and a core of tissue specimen will result. The specimen will be free at the margins and attached at the base. The specimen is released with tapered fine scissors or blade ***(Golden et al., 1994)***.

Punch technique was commonly used for diagnosis of skin lesions. ***Tood et al (1996)*** studied the effectiveness of the 2 mm punch biopsy in providing an accurate pathological diagnosis of wide rang of skin lesions. they reported that the technique was easy, providing a specimen of high quality and adequate size to allow an accurate diagnosis to be made. The tissue defect was so small which offered a good cosmetic result. ***Thompson and Coworker (1988)*** reported that punch biopsy is a rapid method for removing a small pigmented lesion to allow definitive pathologic diagnosis and cosmetically acceptable wound. In ***(1981) Sassani and Cutler***, were the first to describe the use of disposable biopsy punch for excisional biopsy of tarsal conjuntival lesions. the authors pointed out that this technique offers biopsy specimen with minimal tissue trauma.

Imaging the oral cavity:

A diagnostic imaging evaluation consisting of either computer tomography (CT) scanning or magnetic resonance imaging (MRI)is also used to assess the extend of local and regional tumor spread, the depth of invasion, and the extent of lyphadenopathy. CT is superior in detecting early bone invasion and lymph node metastasis, but MRI is preferred for assessing the extent of soft tissue involvement and for providing a three-dimensional display of the

tumor. MRI is also the preferred technique for imaging carcinoma of the nasopharynx or lesions involving paranasal sinuses or the skull base ***(Vanden Brekel et al., 1994)***.

Diagnostic imaging often detects subsurface masses and intraosseous lesions. although imaging of pathologic lesions does not produce a definite diagnosis, it frequently helps to define the extent of the tumor. For example, patients who have an unexplained neck node and a negative head, neck, and oral examination may undergo CT scanning followed by a biopsy of the nasopharynx or base of tongue that reveals a suspicious area or tissue change.

Ultrasound:

Used for:

- Early detection of lymph node involvement (not clinically felt) used in surveillance of clinically negative necks.
- Ultra sound guided aspiration ***(Amy et al., 2001)***.

Both CT and MRI have limitations as well as advantages, a fact that frequently makes them complementary rather than competitive studies. The advantages of CT include its rapid acquisition time (2-3 seconds per section), patient tolerance, relatively low cost, and superior osseous detail compared with MRI. However, the soft-tissue contrast resolution of CT is relatively poor, which makes it difficult to distinguish between tumor and normal muscle. CT also may require the administration of intravenous contrast material to differentiate vessels from lymph nodes, thereby increasing the risk of an allergic reaction. In addition, CT is frequently degraded by scattered artifacts because of metallic dental appliances ***(Modison et al., 1994)***.

MRI's several advantages over CT have helped it evolve into a reliable alternative for imaging normal and pathologic head and neck anatomy. The superior soft-tissue resolution of MRI allows high-contrast differentiation between neoplasms and adjacent muscle. In addition, MRI can be obtained in multiple planes (sagittal, axial, coronal, and oblique), which is often helpful in assessing tumor volumes during and after therapy. Finally, the need for intravascular

contrast administration is avoided because patent vessels have absent signal, or "signal void," within their lumen, which easily distinguishes them from surrounding soft tissue structures.

However, MRI is not without its drawbacks. Because all the images within a given MRI sequence are obtained simulateneously rather than sequentially, patient movement during an MRI is less well tolerated than with CT. in addition, although the soft-tissue contrast is superb with MRI, fine-bone detail is inferior to that obtained with CT ***(Castelijns, 1991)***.

The most important finding in imaging of oral cancer:

1- bone erosion.
2- Degree of submucosal spread.
3- Involvement of base of tongue or floor of mouth, pterygoid muscle.
4- Perineural spread: suggested by enlargement of pterygo palatine spread through greater and lesser palatine nerves, fossa common pathway.

Imaging techniques:

Imaging techniques continue to improve at a rapid rate. Newer imaging techniques hold promise for clinical staging of T2, T3 and T4 lesions but T1 lesions are typically too small to be visualized. Improvements that increase definition will promote earlier detection of nasopharyngeal, submucosal, and bone lesions. one such technique appropriate for lymph nodes is positron emission tomography, which may help to define tumor activity in clinically negative areas ***(Hermanek et al., 1996)***.

P.E.T:

- Has the ability to detect a recurrent disease its sensitivity and specificity for detection of recurrence is superior to CT & MRI particularly with patients treated by non-surgical modalities.
- Also it has a superior sensitivity for lymph node involvement in clinically negative necks.

Immunohistochemical techniques:

The use of immunohistochemical techniques to establish a diagnosis has expanded during the past decade and continues to be refined. These diagnostic tests help to establish a definitive diagnosis when, by routine histopathology techniques, a lesions appears morphologically benign or its classification is in doubt. Research on the biochemical, genetic, and cellular levels should yield information that will identify high-risk groups for many types of cancer including oral cancer ***(Greven et al., 1994)***.

Examples: accumulation of 8-nitroguanine, an indicator of nitrative DNA damage detected by immuno histochemical methods in the oral epithelium of patients with leukaplakia. Also experience of inducible nitric oxide synthase (iNOS) was observed in oral epithelium of leukaplakia patients. These results suggest that iNOS – mediated nitrative stress contributes to development of oral carcinogenesis from oral leukoplakia through DNA damage as well as oxidative stress ***(Ma et al, 2005)***.

- Reactivation of telomerase used as diagnostic, prognostic and therapeutic indicator for oral cancer ***(Sebastion et al., 2005)***.
- Loss of heterzygosity and micro satellite instability on chromosome 2q in human is found with oral squameus cell carcinoma ***(Numa sawa et al., 2005)***.

Clinical photodetection:

Photodynamic therapy, also known as PDT, and photodetection of cancer may be useful in the oral cavity. Two important variables that must be considered are the uptake of the dye and the dye contrast by normal and neoplastic tissue after injection ***(Braichote et al., 1995)***.

Pan endoscapy:

Most carcinomas of the oral cavity do not need a “panendoscopy” for definitive diagnosis. Such a procedure which consists of direct laryngoscopy, esophagoscopy, and bronchoscopy, is usually performed as a diagnostic and staging procedure in patients with carcinoma of the oropharynx ***(Horowitz et al., 1990)***.

Prognostic factors for cancer of the oral cavity:

Survival rates were influenced by tumor diameter, clinical T, clinical N, clinical stage and histologic malignancy grade. the multivariate analysis included only 1 variable, the lymph node involvement. This study proposes considering the tumor size as the most significant clinical variable for predicting the survival of oral cancer patients at the time of diagnosis and the degree of lymph node involvement after the treatment ***(Prieto et al., 2005)***.

Patient work up:

1- History and physical examination, including risk factor analysis and exposure to carcinogens.
2- Head and neck examination: direct visualization mirror examination, manual palpation, toluidine blue staining.
3- Laboratory tests: CBC liver function.
4- Radiology: CT or MRI of head and neck, chest x-ray, dental films, bone scan when indicated.
5- Pathology incisional biopsy, excisional biopsy, fine needle aspiration biopsy, molecular markers, flow cytometry.
6- "panendoscopy" define T-stage, draw schematic tumor map, evaluate for second malignancies.
7- Pre-therapy consultation with: radiation, oncology, medical oncology, head and neck surgery, reconstructive surgery, dental oncology, speech pathology, psychosocial service.
8- Multidisciplinary tumor board: finalize staging formulate treatment plan.

N.B:

Rigid oeserphagoscape is superior to flexible one in visualizing lesions in upper oesophagus.

CHAPTER (5)

Prevention and Early Detection

Introduction:

Each year, oral cancer kills more people in the US than does cervical cancer, malignant melanoma, or Hodgkin's disease. Oral cancers usually involve the tongue, lips, floor of the mouth, soft palate, tonsils, salivary glands, or back of the throat. In the US, more than 90% of oral and pharyngeal cancers occur in individuals over 45 years of age; males are more likely than females to develop them ***(Baring et al., 1994)***.

The primary risk factors for oral cancers in this country are tobacco and alcohol use; for lip cancer, exposure to the sun is most important ***(Silverman et al., 1990)***. Advanced oral cancer and its sequelae cause chronic pain, loss of function, and irreparable, socially disfiguring impairment. The functional, cosmetic, and psychological insults suffered by oral cancer patients often result in social isolation, significantly burdening patients, their families and society ***(Baden, 1987)***.

Of all the procedures available to control oral cancer, none has affected survival as much as has early detection. Unlike other parts of the body, the oral cavity is easily accessible and an oral cancer examination poses relatively little discomfort or embarrassment for the patient. Dentists are the provider of choice to perform oral cancer examinations, but about 40% of the population does not visit a dentist in a given year. Furthermore, those who are middle age or older, edentulous, of lower less likely to visit a dentist. Thus, other health care providers must assume more responsibility to ensure that the public receives oral cancer examinations on a routine and cost-effective intervention for oral cancer when performed as part of routine practice. Oral cancer examination also offer providers an opportunity to identify patients who use tobacco and alcohol and counsel them about their risk for cancers ***(Garfinkel, 1991)***.

Oral cancer has one of the lowest 5-year survival rates of all major cancers, probably because most lesions are not diagnosed until they are advanced ***(Mashberg et al., 1987)***. However, when detected early, the probability of surviving from oral cancer is remarkably better than for most other cancers ***(Mashberg et al., 1989)***. Theoretically, morbidity and mortality due to oral cancers can be reduced dramatically with appropriate interventions; because of this potential, 13 of the objectives in Healthy people 2000 relate to oral cancer prevention and early detection. To achieve these objectives, health care providers and the public need to know the risk factors for oral cancer, as well as their signs and symptoms furthermore, health care providers, particularly dentists, physicians, nurse practitioners, nurses and dental hygienist, need to provide oral cancer examinations routinely and competently. Equally important, members of the public need to know that an examination for oral cancer is available and that they can request one routinely ***(Rockvill, 1991)***.

Thus, both health care providers and the general public need to increase their knowledge and change their behaviors or practices. Health promotion is a key to achieving these changes.

Healthy people 2000 oral cancer objectives from US department of health and human services:

1- Reverse the rise in cancer deaths to achieve a rate of no more than 130 per 100,000 people.
2- Increase complex carbohydrates and fiber containing foods in the diets of adults to 5 or more daily servings for vegetables (including legumes) and fruits, and to 6 or more daily servings for grain products.
3- Reduce cigarette smoking to a prevalence of no more than 15% among people aged 20 and older.
4- Reduce the initiation of cigarette smoking by children and youth so that no more than 15% have become regular cigarette smokers by age 20.
5- Reduce smokeless tobacco use by males aged 12 through 24 to a prevalence of no more than 4%

6- Increase to at least 75% the proportion of primary care and oral health care providers who routinely advise cessation and provide assistance and follow up for all of their tobacco alcohol-using patients.
7- Reduce the proportion of young people who have used alcohol, marijuana and cocaine in the past month.
8- Reduce the proportion of high school seniors and college students engaging in recent occasions of heavy drinking of alcoholic beverages to no more than 28% of high school seniors and 32% of college students.
9- Reduce alcohol consumption by people aged 14 and older to an annual average of no more than 2 gallons of ethanol per person.
10- Increase to at least 75% the proportion of primary case providers who screen for alcohol and other drug use problems and provide counseling and referral as needed.
11- Reduce deaths due to cancer of the oral cavity and pharynx to no more than 10.5 per 100,000 men aged 45 through 74 and 4.1 per 100,000 women aged 45 through 74.
12- Increase to at least 70% the proportion of people aged 35 and older using the oral health care system during each year.
13- Increase to at least 40% the proportion of people aged 50 and older visiting a primary care provider in the preceding year who have received oral, skin, and digital rectal examinations during one such visit.

It is widely accepted that health promotion influences knowledge and behaviors at all levels of social organization. Health promotion is defined as follows: "Any planned combination of educational, political, regulatory, and organizational supports for actions and conditions of living conducive to the health of individuals, groups or communities of policy makers, employers, teachers, or others whose actions influence the determinants of health. This use of the term "promotion" differs from a common usage that is frequently associated only with public relations, advertising, and other marketing activities. Although marketing activities play an important role in health promotion, the term as used here refers to actions intended either to alter a person's environments in a way that will improve health in the absence of individual actions or to enable individuals to take advantage of preventive procedures by removing or mitigating barriers to their use. Education is the essential, common denominator of health promotion ***(Frazier et al., 1995)***. Educating a variety of publics, including consumers, health care providers, legislators and other decision makers is necessary

to improve awareness of preventive and early detection methods and procedures, gain their acceptance by these groups, and increase their use ***(Glanz et al., 1990)***.

Education, alone, however, is insufficient to prevent diseases or conditions; simply having knowledge or information does not mean that appropriate behaviors or actions will follow. Sill, knowledge is an important aspect of empowerment – without appropriate knowledge is an important aspect of empowerment – without appropriate knowledge, individuals can neither make nor be expected to make intelligent decisions about their health ***(Frazier et al., 1990)***. Among other factors that influence behavior are beliefs, values, and attitudes. These factors influence decisions to consult health care providers about obtaining cancer examinations or to use tobacco and alcohol. ***(Glanz et al., 1990)***.

Public education:

A variety of educational campaigns have been mounted to urge people not to start using tobacco products or to stop if they have already started. Today, school-based interventions frequently begin in primary grades; they may focus on developing self-esteem, on building skills to resist peer pressure, or on urging children to remain smoke-free. These efforts are often implemented in conjunction with other community-based activities aimed at preventing children and youth from starting the habit and urging users to stop. Unfortunately, these programs often do not identify tobacco products as risk factors for oral cancers. Similarly, efforts focusing on alcohol use as a risk factor for cirrhosis of the liver, liver cancer and fetal alcohol syndrome rarely identify alcohol as a risk factor for oral cancers. However, recent intervention strategies for decreasing the use of tobacco products and alcohol bode well for reducing cancer incidence, including oral cancers. For example, many health institutions, businesses, airports, airlines, and schools have implemented smoke-free policies or provided only limited indoor space for smoking. Overall, there is a growing trend in the US to consider smoking socially unacceptable, especially among more highly educated people ***(Winkeleby et al., 1995)***.

Although not as prominent as anti-smoking activities, there has been an increase in recent years of educational efforts about self-protection from exposure to the sun by using sun and lip screens, hats, and other coverings. In addition, the public is being urged to obtain skin cancer examinations on a routine basis ***(Glanz et al., 1990)***.

Several government and private agencies are urging the increased consumption of fruits and vegetables to help prevent cancers and other diseases. The national cancer institute's five a day program is a good example; it has encouraged many restaurants, schools and supermarkets to join in this effort. Because consuming of fruits and vegetables may provide protection against oral cancers, such initiatives may be beneficial ***(Winn, 1995)***.

Educational materials for the public:

Relatively few oral cancer educational materials have been produced for the public, far less than the plethora of materials on tooth brushing, flossing, and the need for dental visits. Surveys are needed to determine what educational materials are available for specific target groups and to assess their accuracy, comprehensiveness, reading level, and acceptability.

A review of health education textbooks for students from kindergarten through 12th grade found that the oral cancer coverage was uneven, misleading, sometimes incorrect, but most often omitted altogether. Most of the content about oral cancer dealt with the use of chewing tobacco. Both the lack of content and the incorrect information in health education textbooks may contribute to the public's overall lack of knowledge about oral cancers. Clearly, it is imperative to include correct material about prevention of oral cancers in health textbooks ***(Frazier et al., 1995)***.

Another priority for public education concerns the labeling of alcohol and tobacco products. Although placing warning messages on alcohol and tobacco products is commendable, currently the messages can barely be distinguished from the balance of the label. Warning messages on electrical appliances such as hair dryers are far more obvious. Warning messages should be much stranger and clearer ***(Washington, 1994)***.

Self-examination:

A first line of defense against oral cancer is an orofacial self-examination. A self-examination can help individuals become more aware of their own bodies and involve them in monitoring their own health. As has happened with other self-examinations although they should not take the place of a professional oral examination, self-examinations can be a secondary preventive technique to detect early lip and mouth lesions. the examination includes intraoral and extraoral observations and palpation of the head and neck regions; it requires only a few minutes to complete. However, because signs are often difficult to recognize and symptoms may be minimal, professional examinations are still of primary importance. Studies of the effectiveness of oral cancer self-examinations and the public's awareness and use of this tool are needed ***(Botuin et al., 1994)***.

In summary, oral cancer is a disease that frequently has been given low priority by both health care providers and the public. Furthermore, although there is currently great interest in exploring therapeutic modalities for oral cancer, scant attention has been paid to its prevention, early detection, and control. Although there are numerous barriers to prevention and early detection of oral cancers in the US, none is insurmountable. Let us consider the barriers to be opportunities to change the behaviors and practices of health care providers and the public. If we can make these changes, we can achieve the oral health objectives in Healthy people 2000 ***(Gold et al., 1993)***.

Continuing medical and dental Education:

Continuing education courses provide opportunities to advance practitioners knowledge and skills. Yet, relatively few continuing education courses for dentists deal with oral cancer. Continuing education should be simple, valid, acceptable, and concise in order to enhance providers attitudes and behaviors ***(Spitz et al, 1992)***. Although educational guides for both physicians and nurses regarding early detection of oral cancer are available, their use may be limited and their effectiveness has yet to be assessed ***(Thomas et al., 1992)***. An early study suggested that self-instructional courses are effective in enhancing awareness in early detection of oral cancer among medical and dental professionals; but few have used this approach to date. However, the increased use of computers brings with it unique opportunities for self-study in pre-doctoral as well as continuing education ***(Melrose et al., 1976)***.

Educational interventions to inform, train, and prepare health care professionals to diagnose and manage oral cancers properly are needed ***(Julies et al., 1995)***. More recently another approach to providing continuing education – academic detailing – has been used to teach practitioners to change their prescribing practices. Academic detailing which is patterned after drug detailing, uses educational detailers who visit physicians in their offices or clinics and provide them with education ***(Williams et al., 1994)***. Currently, this method is not used to educate providers about oral cancer prevention and early detection. Ironically, one of the earliest uses of detailing to educate health care providers was the initiative decades ago to introduce dental practitioners to oral cytology testing as a means of detecting early oral cancer lesions ***(Butler et al., 1970)***.

Recent preventive techniques:

1) Vaccine: recent trials to develop a vaccine against oral cancer:

A study on Syrian hamsters which is injected by anti-HER- 2DNA vaccine.

- Only 36.8% of vaccinated hamasters developed buccal neoplastic lesions, versus 73.37% of non vaccinated hamsters.
- Hamsters that reject the neoplastic challenge displayed the highest antibody titre.
- These findings suggest the DNA vaccination may have a future in the prevention of HER-2 positive human oral cancer ***(Berta et al., 2005)***.

2) Chemoprevention:

Recent experimental study on using certain topically applied non steroidal anti inflammatory drugs targeting cox-2 in the oral epithelial cell, used as chemoprevention. Results of their experimental study show reduced incidence of squamous cell carcinoma by using topical celecoxib (3% - 6%) ***(Sood et al., 2005)***.

Other methods for chemoprevention of oral cancer are systemic administrations of retinoids, α-tocopherol, α-interferon, cox-2 inhibitors ***(Amy et al., 2001)***.

Chemo preventive agents act by modifying the oxidative state of transforming cells ***(Schwartz, 2000)***.

Current guidelines: a lack of consensus:

Preventive care guidelines have been developed by governmental agencies, private enterprises, insurers, hospitals, academic centers and nearly 40 medical and dental societies. Unfortunately, the lack of consensus among these guidelines not only fails to provide guidance to make informed clinical decisions but also may serve as a rationale for not providing oral cancer examinations. Because patients at highest risk for oral cancer are more likely to receive medical care than dental care, it is important that policies advocate the integration of oral cancer screening into routine health care. Most physician organizations do not consider recommendations for oral cancer within their periodic health examination guidelines. As shown later, the American cancer society, but not the US preventive task force or the Canadian task force, recommends routine oral cancer examinations for adults ***(Woolf, 1990)***.

Guidelines for oral cancer screening examination:

Organization	High risk gp. only	Routine	Screening Recommendation
American cancer society	No	Yes	Routine oral exam. Every 3 years for persons ≥ 21 and annually for persons ≥ 40 years.
United states preventive task force	Yes	No	All persons are counseled to stop smoking and ↓ consumption alcohol be alert to high risk gp.
Canadian task force	Yes	No	Only high-risk people warrant an annual oral exam by a physician or dentist.

CHAPTER (6)

Treatment

The goals of therapy vary with the extent of the disease. Meaning that, if the lesion is localized without evidence of spread, the goal is to eradicate the cancer and cure the patient. On the other hand, when the cancer is spread beyond the local cure, the goal is to control the patient's symptoms and to maintain his maximum activity for the longest possible period of time. Palliation should be measured in terms of useful life ***(Eicher et al., 1996)***.

In treating carcinoma of the oral cavity at least three factors have to be considered: the extent of the lesion, the degree of differentiation, and the type of planned reconstruction. ***(Overhott et al., 1996).***

There are four modalities of treatment, namely surgery, radiotherapy, chemotherapy and combined therapy the best method for treating a particular case of oral cancer is left to the judgment of the oncologist and his team ***(Parson, etal,1992).***

Patients with head and neck cancer should be evaluated before initiation of therapy by representatives of each discipline responsible for administering cancer care. Having a multidisciplinary tumor board composed of otolaryngologists, plastic surgeons, oral and maxillofacial surgeons,radiation oncologists, medical oncologists, dental oncologists, pathologists, radiologists, and allied health professionals facilitates this approach. Patients and their family members should attend this tumor board or conference ***(Vokes et al., 1993)***.

After they review the case histories, microscopic slides, and pertinent studies from diagnostic imaging (e.g., computed tomography, magnetic resonance imaging, plain X-ray films), representatives of each discipline should examine the patient. The tumor board process is useful in

establishing a correct pathologic diagnosis, determining the extent of disease, detecting other simultaneous head and neck primary cancers that might have escaped detection, and facilitating dental evaluation, which is particularly important in patients whose treatment will include irradiation, chemotherapy, or resection of oral or oropharyngeal tissues.

After examination of the patient, the board should reconvene to discuss therapeutic alternatives and to formulate a recommendation for treatment based on expected outcome (function, cosmesis, impact of treatment on lifestyle and career) and the expertise available at the treating institution. If the board believes that either the necessary expertise or technology is not available at its institution, or if the patient and family so desire, the board may recommend referral to another institution or physician. If no curative option exists, the board may recommend treatment with palliative intent. If further workup is indicated, there may be a recommendation to obtain other tests and re-present the patient's case to the board once additional information becomes available. Members of the board discuss these alternatives and recommendations with the patient and family, and in many instances, the patient and family are active participants in the decision-making process about the case. Patients are routinely advised to discontinue use of all tobacco products and alcohol ***(Tannock, 1994)***.

Treatment modalities:

Surgery:

Surgery is the preferred method of therapy for oral cancer. It is preferred for its speed and simplicity. The surgical operations for range from simple localized excision biopsy to wide excision and usually combined with radical neck direction.

For example: cancer tongue; Superficial tumors (T1), 2cm or less in diameter, with no clinically palpable nodes, in a systemically fit patient, are best treated with intra oral excisional biopsy with safety margin. Multiple frozen sections should always check the safety margin after such an excision. In (T2) lesions partial glossectomy is still feasible as an initial treatment. Since the local and regional metastases can be handled adequately in most cases, larger lesions should be treated by composite resections, radical neck dissection, partial mandibulectomy and partial glossectomy ***(O'Brien et al., 1986)***.

There are some circumstances that will dictate the surgical therapy alone. As for patients with history of high alcohol intake and cigarette consumption, surgery is the best line of treatment because radiation is not tolerated by the patient's already abnormal mucous membrane. Also it was found that these patients usually do not stop their habits during the course of treatment. Cancer of the tongue arising on the basis of leutic glossitis (Syphilitic) are best treated by surgery ***(Johenson et al., 1980)***.

Radiotherapy:

Radiation therapy can cure a substantial proportion of patient without any operation, and in case irradiation fails, later resection can

achieve survival equivalent to that of the primary operation. It may also spare some patients the disability after surgery ***(Parson et al, 1992)***.

Successful results depend upon considering the radiobiologic factors relating to the volume of cancer, hypoxia, tumor cell kinetics, intrinsic cellular radiosensitivity and repair capability ***(Hinerman et al., 1994)***.

Types of radiotherapy:

Teletherapy or external radiation is given via a machine remote from the body, while **Brachy therapy** or internal radiation is given by implanting a radioactive source within the oral cavity. Patient may or may not require both modalities of radiation ***(Foote et al., 1990)***.

There is evidence of the need to increase the dose with the increase of size of the primary lesion. Whereas, the increase of size of the lesion implies a subsequent raise in the percentage of radiotherapy given through external beam, in order to shrink the primary before implant is placed, and also to provide treatment for the primary lymph draining vessels. It should be kept in mind that the dose given to the primary tumor should be enough to control its peripheral edges which are well oxygenated, and consequently radiosensitive, thus decreasing the bulk of the tumor ***(Wang, 1988)***.

Radiation therapy is a double edged sword, truly life saving and cancer curing but carrying with it the certainty of morbidity. The higher the dose, the more severe the response of the tissues. The mucous membrane is affected in a variety of ways, from ulceration to radionecrosis even hemorrhage related to the major vessels as the lingual artery. Both major and minor salivary glands are affected leading to dryness of the

mucous membrane, difficulty in swallowing, alternation of taste, injury to teeth and the effect that is bad on the general health condition of the patient. The effect on bone may reach to osteoradionercrosis, or retarded growth in children. The skin may get pigmented, telengectatic or even ulcerated, then hair loss is expected ***(Parson et al., 1993)***.

Sometimes mild asymmetry, constriction fibrosis, or frank necrosis threatening to expose major vessels or underlying bone. Exclusive brachytherapy for T1-T2 velotonsillar carcinomas is safe and effective, and permits definitive reirradiation for a second head-and-neck cancer. Initial neck dissection should be performed for optimal selection for exclusive brachytherapy ***(Le Scodan et al., 2005)***.

How to decrease side effect of radiotherapy:

Conventional standard fractionated radiotherapy consists of 1.8-2.0 Gy per fraction, once a day, 5 days per week, for a total weekly dose of 70-75 Gy. However, hyperfractionated and accelerated fractionated radiotherapy employing using smaller doses per fraction, twice a day, 5 days per week, has recently been used in the treatment of head and neck cancer. A randomized trial by the European organization of research on treatment of cancer (EORTC) showed improved local control using hyperfractionated radiotherapy compared with conventional fractionated radiotherapy for stage II and III oropharyngeal carcinoma. The survival was also better for the hyperfractionation arm, although the difference was not statistically different ***(Parsen et al., 1993)***. Hyperfractionation has been used at the university of Florida, split-course accelerated fractionation at the Massachusetts general Hospital, and accelerated fractionation with a concomitant boost technique at the M.D. Anderson cancer center ***(Angk et al., 1992)***. In contrast to the EORTC trial, University of Florida results

showed no significant improvement in local control of carcinoma of the oropharynx by hyperfractionated radiotherapy compared with that achieved for historical controls treated by conventional fractionated radiotherapy ***(Parson et al., 1993)***. However, Massachusetts General Hospital and M.D. Anderson Cancer center results suggest improved local control with the regimens used at those institutions compared with historical controls treated with conventional fractionation ***(Wange, 1988)***. The results of hyperfractionated or accelerated fractionated radiotherapy may depend on primary site and stage. The radiation therapy oncology group (RTOG) is investigating through a phase III randomized trial the relative efficacy of standard fractionation, hyperfractionation, and the two variants of accelerated fractionation in the radiotherapy of stage III and IV carcinoma of the oral cavity, oropharynx, supraglottic larynx, and hypopharynx ***(Arg et al., 1992)***.

Five-year survival is achieved in 50-55% of patients with early or moderately advanced (stages I, II, III) cancer of the tonsillar region and in approximately one-third of patients with stage IV disease ***(Lee et al., 1993)***.

New treatment planning and delivery systems in radiation therapy using 3-dimensional computer treatment planning programs and computer-driven multi-leaf collimator systems can provide better confirmation of the high-dose radiation volume to the tumor while sparing normal structures. More widespread availability of these technologies can be anticipated in the very near future. Major barriers to their widespread use are that they are very time and labor intensive, require sophisticated computer programming capabilities, and are expensive ***(Le Scodan et al., 2005)***.

Chemotherapy:

The initial treatment of head and neck cancer has traditionally been surgery and/or radiotherapy with chemotherapy being reserved for palliation of the patients with recurrent disease. Recently, chemotherapy has been increasingly employed as an initial treatment of patients with advanced previously untreated cases of squamous cell carcinoma and have showed a substantial activity ***(Munro, 1995)***.

The category of drug therapy alone can be further divided into systemic and local treatments. Most of the groups used are antimetabolites as methotrexate and 5 flurouracil, alkylating agents as nitrogen mustard, antibiotics as bleomycin and adriamycin, and miscellaneous drugs as vincrestine.

Chemotherapeutic drugs as methotrexate, bleomycin, and cisplatin are drugs that have antitumor effect in patients with squamous cell carcinoma of the oral cavity ***(Vokes et al., 2000)***.

Side effects:

Chemotherapy has toxic effects on the different system of the body. It causes gastrointestinal troubles in the form of stomatitis, diarrhea and hepatic dysfunction. The toxic effect on the hematologic system includes leukopenia, anemia and thrombocytopenia. The kidneys may suffer from tubular necrosis. The drug has a drastic effect on the skeletal system as osteoporosis especially in children. Chemotherapy causes ototoxicity manifested as tinnitis. Milder forms of affection are the dermatologic ones, as alopecia, dermatitis and conjunctivitis ***(Robbins et al., 1997)***.

N.B:

The major strength of radiation therapy is to eradicate the actively growing well oxygenated cells in the periphery of the tumor, or the subclinical disease implanted in the wound or in the regional nodes. The major strength of surgery, on the other hand, is to remove the centrally situated radioresistant hypoxic tumour cells. For extensive tumours which are rarely curable by either method alone, the logical approach at the present time is a combination of radiation therapy and surgery ***(Vokes et al., 2000)***.

Unfortunately the incidence of distant metastases is high inspite of combined radiation therapy and surgery. Improvement of survival and perhaps local control requires the employment of some additional modalities such as long-term maintenance chemotherapy following combined surgery and radiation ***(Vokes et al., 2000)***.

Chemotherapy has been shown to have positive effect in squamous cell carcinomas of the head and neck. There appears to be an opportunity to integrate chemotherapy into therapeutic strategies, although there is an issue of how it should be timed in relation to other therapies,. The benefits of chemotherapy should not be measured only by survival, but also by organ preservation and quality of life. Continued support for randomized trials and new drug discovery and development is essential ***(Vokes et al., 1993)***.

Other treatment modalities:

Lazer surgery has some limited application in the surgical management of early T1 and T2 lesions when local excision is likely to be

curative or when postoperative radiation is planned. It is especially useful in the older, debilitated patient, in whom a large bloody resection would not be well tolerated. The major advantages are quick return to normal function, ability to work quickly, bloodlessly, lymphatic vessels are sealed so reducing the chance for spread and the option to use local anesthesia ***(Brad et al., 2002)***.

Biological intervention:

Considerable evidence has emerged indicating the existence of an immunological response to neoplasia in man. The use of the biologic response modifiers can alter the interaction between the tumor and the host. It has been demonstrated that there was a correlation among immune reactivity, tumor extent and prognosis in cancer patients. BCG, thymus extract and levamizole given to the patient, increased the cure rate, prolonged survival or increased disease-free survival.

Immunologic response modifiers such as α interferon and interleukin have been used in combination with other therapies to boost the patient's own immune response against oral carcinoma. In addition, monoclonal antibodies to an individual tumor are being used in an attempt to image the lesion better and to deliver specific toxic substances, including radiolabeled substances, directly to the tumor. Efforts continue to develop antibodies capable of reaching the entire tumor cell population while avoiding systemic toxicity ***(Schuartz, 2000)***.

Gene therapy has been used to treat other tumors, particularly hematologic tumors. In this approach, investigators or clinicians try to introduce new molecular material into human cells. They may be trying to alter the tumor's immunogenicity, activate the host response, modulate the

tumor's sensitivity to chemotherapy or radiotherapy, insert tumor suppressor genes, inhibit oncogenes, prevent malignant transoformation, or introduce lethal genes. Despite a number of potential obstacles, there may be a future for gene therapy in the treatment of squamous cell carcinoma of the head and neck. Tumor markers, such as oncogene and tumor suppressor mutations and specific allelic losses in the genome of a carcinoma, are being investigated to determine the relationship of such molecular alterations to clinical outcome. The development of such markers would allow treatment to be more properly tailored to the individual tumor. To date, however, no specific marker has been identified that correlates for all sites with tumor response to treatment ***(Show, 2005)***.

Hyperthermia:

There has been a great interest in the use of hyperthermia to treat cancer. Hyperthermia at 42.5 ± 0.5ºC for 40 to 60 minutes twice weekly for a total of 10 times, after irradiation with 4gy twice weekly for a total of 40 Gy was used by ***Abe et al***, gave remarkable results approaching over 50% complete response. So. It is safe and effective in the treatment of radioresistant tumors located in superficial, subsurface and in some instances in deep regions ***(Brad et al, 2002)***.

Photo dynamic therapy:

Using photosensitizer in combination with photodynamic therapy with a diode laser in experimental study upon nude mouse with experimental tongue cancer. The study reported that almost all of the tumors developed necrosis, while viable-like neoplastic cells remained mainly in the peripheral region of the tumor in some cases. The mean depth of necrosis below the surface was 2.1 mm. the mean tumor thickness below the surface was 2.3mm tumor thickness coincided with the depth of necrosis. Npe6-induced

PDT exhibited tumor selectivity and can effectively cause necrosis of tongue cancers. This therapy could be suggested for treatment of other superficial oral cancer ***(Kobayashi et al., 2005)***.

Treatment selection for the primary site: general Principles:

Surgery or radiotherapy is curative for most early carcinomas of the oral cavity and oropharynx; cure rates for the two modalities are similar. Chemotherapy is not curative and is used only as an adjunct. Selection of the treatment modality must be based on factors such as functional outcome, cost length of treatment, risk of complications, the patient's general medical condition, and patient preference. Choices are also influenced by clinicians' skills, experience and philosophies, and by available facilities.

More advanced lesions typically require combined radiotherapy and surgery to obtain optimal cure rates. In the past, preoperative radiotherapy of the primary site was common, but in recent years most centers have preferred to use postoperative radiotherapy, primarily because surgical complication rates are lower if irradiation is withheld until then. Postoperative radiotherapy is also used when the primary surgical specimen is found to have vascular or perineural invasion or close surgical margins or advanced T-stage, multiple cervical nodal metastasis and extra capsular spread ***(Shan et al., 1999)***.

Management of the Neck: General Principles:

The incidence of cervical nodal metastases for each oral primary site increases with increasing local stage of disease. The patient with no neck disease or very early stage positive neck disease (N1) may be treated electively by radiotherapy or neck dissection. Because cure rates are the

same, the neck is generally treated with the same modality selected for the primary site. If the risk of lymph node metastases is believed to be less than 15%, the clinician may simply observe the neck for the occurrence of metastases.

More advanced neck disease generally requires combined treatment for optimal regional disease control. Combined therapy is essential if there is extranodal spread of cancer or multiple positive nodes are identified. If surgery was used to treat the primary site, postoperative radiotherapy is appropriate. The only exceptions are when the nodalmass is fixed to the carotid artery or the cervical fasica; then preoperative radiotherapy is given. When radiotherapy is selected for the primary tumor, the neck dissection is generally performed 4-6 weeks after radiotherapy has been completed ***(Amy et al., 2001)***.

As described by ***Robbins et al in (1991)***: therapeutic neck dissection in done for clinically positive neck disease by: Radical neck dissection (Removal of all isolated cervical lymph node groups from inferior border of mandible superiorly the clavicle inferiorly, from lateral border of the sternohyoid muscle, hyoid bone and anterior belly of digastrics muscle medially to the anterior border of trapezius muscle laterally. The sterno mastoid muscle, internal jugular veins and cranial nerve XI are also removed

Modified radical neck dissection excision of all lymph nodes that are routinely removed by a radical neck dissection with preservation of one or more of nonlymphatic structure (i.e SCMIJV or cravial nerve XI).

Selective neck dissection:

(excision of selected group of lymph nodes that are suspected to be the site for lymph node metastasis.

Ex: Supraomohyoid neck dissection means removal of lymph nodes in submental, submendibular triangles, upper and middle jugular groups of lymph noder ***(Robbins et al., 1991)***.

Elective neck dissection was performed in most patients, and occult metastatic disease was found in nearly 30% of neck dissections. Observation was most frequently used for patients with early stage disease, and subsequent development of neck metastases was uncommon (9%) in this group. Selective treatment of the clinically negative neck based on the primary tumor site and stage led to a high rate of regional disease control in this series ***(O'bren et al., 2000)***.

Chemotherapy:

Although improvements in radiation therapy and surgery have led to modest improvements in survival and relapse-free survival rates, there s still considerable room for improvement, particularly for patients with advanced-stage disease. Chemotherapy has been used in attempts to improve survival or to reduce the incidence of distant metastases, to serve as an adjunct to radiotherapy for organ preservation, and to select patients for subsequent therapy based on their response to chemotherapy. However, how much chemotherapy actually contributes to achieving these goals remains controversial ***(Tannock, 1994)***.

Chemotherapy has been applied as induction (so-called neoadjuvant therapy), concurrently with radiotherapy and as post-treatment adjuvant therapy. Neoadjuvant therapy has been widely studied in recent years; a

number of drug regimens have been used. The combination of cisplatin and fluorouracil (5-FU) has achieved considerable popularity because of high rates of response with acceptable rates of toxicity. In previously untreated patients, response rates of 60-90% have been reported – with a complete clinical response in 20-40% of patients. (Patients who experience a complete clinical response have a favorable prognosis compared with patients having partial or not response) unfortunately, randomized studies have shown no significant impact on survival rates ***(Vokes et al., 1993)***.

Post operative chemotherapy is indicated when pathological study show extra capsular spread of nodal disease ***(Amy et al., 2001)***.

Concomitant chemotherapy and radiotherapy has been used to try to increase the rate of local regional control, on the theory that these might be either an additive or synergistic interaction between the two treatments. Both single and multiagent chemotherapy have been used. Several randomized trials have shown an improvement in local-regional control and disease-free survival with concurrent single-agent chemotherapy and radiotherapy compared with radiotherapy alone. Unfortunately, the toxicity of concurrent multiagent chemotherapy and radiotherapy is significant ***(tannock, 1994)***.

Regional intra anterial chemotherapy is a promising approach that delivers high drug levels to the tumor with less systemic toxicity. Intra arterial superselective drug administration may diminish relative to systemic administration and may allow for grater concentration of the chemotherapeutic agent at the point of interest ***(Yamshita et al., 2005)***.

Trails of superselective intra anterial chemotherapy were done using cisplatin in combination with radiation for primary site and nodal disease,

complete response was obtained in 75% of patients, partial response in 23% of patient, and No progression in 2% of patients. Patients received cisplation developed grade III and IV complication (Gastrointestinal, hematologic, mucosal, vascular and neurologic complication ***(Robbins et al., 1997)***.

Thiosulfate is a cisplatin antagonist that neutralizes cisplatin and helps to protect the bone marrow and kidneys from cisplatis; toxic systemic effect, if added (as intravenous infusion) to intraarterial superfelective injection of cisplatin. non of the patient received this combination experienced grade III or IV toxicity ***(Kerber et al., 1998)***.

Nedaplatin is designed to future improve the anti tumour effect and to reduced adverse effects of cisplatin such as renal toxicity. Region of 5-Fu 500 mg/day on days 1 to 5 then Nedaplatin on day 6 on 8 super selective inrarterial infusion combined with radiation ***(Yamshita et al., 2005)***.

Adjuvant chemotherapy, given after radiation or surgery, has received less attention, mostly because patients are reluctant to continue prolonged treatment after extensive, sometimes debilitating local regional therapy. Results have generally been discouraging.

Treatment selection according to site of primary tumor:

Oral cavity:

Most centers advocate surgical excision for early-stage primary disease (T1-T2) of the lip, floor of mouth, oral tongue, alveolar ridge, retromolar trigone, hard palate, or buccal mucosa. The CO laser may also be used as a cutting tool in removing oral cavity cancers. In addition, this laser

may be useful in removing dysplastic lesions without scarring the area significantly. However, clinicians must still observe the patient closely after the lesions are removed, as there is a significant likelihood of recurrence ***(O'Brien et al., 1986)***.

Although radiotherapy may work as well as surgery for early malignant lesions in several of these subsites, such as the floor of mouth, concern about complication rates has made surgery the choice for most of these lesions. however, more advanced primary tumors in any of these sites typically require a combination of surgery and radiotherapy. The surgical approach to these lesions any be transoral or a mandibulotomy approach may be necessary to obtain adequate 3-dimensional margins. Visor flap approach provides adequate intra oral exposure of the anterior and lateral oral cavity. Although this procedures requires extensive dissection in both sides of the neck it avoids a lip splitting incision ***(Myers et al., 1981)***. Advanced primary tumors adjacent to the mandible may require a rim mandibulectomy, and those tumors that frankly invade the mandible are treated with a segmental mandibulectomy. The plan for surgical resection must also include reconstructive options; reconstructive teams composed of head and neck surgeons, oral surgeons, and prosthodontists are most successful at achieving the best functional and cosmetic results ***(Bartlebart et al., 1993)***.

Most radiotherapy for carcinoma of the oral cavity uses an interstitial implant either alone or combined with external beam. For carcinoma of the oral tongue and buccal mucosal, the results of an interstitial implant alone or combined with external beam radiotherapy are generally better than those achieved with external beam radiotherapy alone.

Recurrence rates vary by primary site and increase with increasing primary stage. For lesions on the floor of the mouth, 5-year cause –specific survival rates by stage are as follow: I:90%, II:80%, III: 70%, favorable IV: 4-=50%, and unfavorable IV: 20% five-year cause-specific survival rates for oral tongue cancers by stage approximate the following: I and II: 70-80%, III: 40%, and IV: 15 20% ***(Millian et al., 1999)***.

N.B:

- retromolartrigone: is a triangular area on a scanding ramus of mandible.
- Cancers at retro molar trigone usually appears advanced from the start due to:
  i. this layer of soft tissues over bone so invasion comes early.
  ii. Multiple pathways for spread from this site.
  iii. High rate of accult nodal metastasis.

(Amy et al., 2001)

Oropharynx:

The main goals in treating patients with oropharyngeal cancer are achieving a cure and preserving both speech and swallowing functions ***(Foote et al., 1993)***. Although some institutions favor surgery alone or in combination with radiotherapy, a review of the literature showed no definite advantage for surgery over radiotherapy in either tumor control or survival; surgery has the added disadvantage of causing losses (e.g., of velopharyngeal competency, of tongue musculature or tongue mobility, of all or part of the mandible, or of the larynx) that are not always fully compensated by reconstructive procedures. Thus, in a great many institutions, treatment consists of radiotherapy to the primary site, with or without subsequent neck dissection ***(Parsons et al., 1992)***.

Base of tongue:

Because it responds strongly to irradiation, frequently metastasizes to the lymph nodes, and has poorly differentiated histology, carcinoma of the base of the tongue is usually treated by radiotherapy. Surgery for more advanced lesions usually results in a loss of major organ function. However, there remains disagreement about the optimal radiotherapy technique; similar results have been obtained by external beam irradiation followed by an interstitial implant boost and by external beam irradiation alone ***(Foote et al., 1990)***. Local control rates are 90% for stage T1, 78% for T2, 79% for T3, and 47% for T4 lesions treated by external beam alone; and 88%, 70%, 74%, and 70% respectively, for external beam plus interstitial implant ***(Hinerman et al., 1994)***.

Extended supraglottic laryngectomy may be used for limited, lateralized vallecular lesions only if one lingual artery can be preserved and the patient is in good medical condition. If the glossectomy is extensive or

a total glossectomy is required, a total laryngectomy is also usually necessary to prevent aspiration ***(Byers, 1985)***. Because of the risk of bilateral neck node metastasis, consideration should be given to bilateral neck dissections or postoperative radiotherapy if there are no clinically positive lymph node metastases ***(Byers, 1985)***.

However, properly selected patients with adequate post operative rehabilitation can be treated with total glassectomy without laryngectomy ***(Effron et al., 1981)***. If the larynx is preserved, laryngeal suspension and palatal augmentation may help with rehabilitative effect ***(Weber et al., 1991)***.

Tonsillar region:

Occasional, discrete, superficial lesions of the anterior tonsillar pillar can be managed by wide local excision. More advanced tumors usually require resection of the tonsillar region (which includes the fossa and pillars), part of the soft palate, and frequently part of the tongue; a segmental mandibular resection; and a neck dissection.

Radiotherapy for tonsillar region cancers is highly successful for early and moderately advanced disease. Treatment is given by parallel-opposed portals or, in patients with well-lateralized tumors, by either a wedged-pair technique or a mixture of high-energy electrons and photons so that the contralateral salivary tissue is spared. An interstitial (cesium or iridium) boost dose is sometimes administered when the primary cancer invades the tongue. For tonsillar pillar primaries, treatment can be inititated with an intraoral cone using orthovoltage x-rays or electrons as a ‘reverse boost” to the primary. External beam radiotherapy is then directed to a more generous field encompassing the primary tumor and the regional

lymph nodes. The intraoral cone technique allows administration of a high radiation dose confined to a limited volume of tissue – a technique that not only improves the control rate but also reduces the risk of serious late radiation injury.

The overall rate of tumor control at the primary site for early (T1-T2) tonsillar fossa primaries is 95%, compared with 70% for T1-T2 tonsillar pillar primaries. T3 tumors at either site are controlled approximately 70% of the time, and T4 lesions have a 40-50% chance of local control. Treatment of tonsillar pillar cancers should be intensified with intraoral cone or implant therapy or other suitable approach ***(Lee et al., 1993)***.

Soft palate:

Small, well-defined lesions of the soft palate may be excised, but because these lesions are multifocal, recurrence of soft palate tissues at the margin will likely occur unless patients are carefully selected. Radiotherapy is commonly used because it leaves the patient functionally intact with no need for a prosthesis or elaborate reconstruction.

Morbidity associated with surgery is minimal if the full thickness of the palate is not removed. Moderate-sized through and through defects are usually closed with local flaps, although velopharyngeal incompetence is a potential hazard with this approach. If a major resection is required, a prosthess is necessary.

The basic radiotherapy technique for soft palate cancer involves parallel-opposed portals to the primary site and neck. If the lesion is located very much to one side of the mouth, it can sometimes be treated with a

single ipsilateral portal arrangement or other field arrangements using 3-D treatment planning, so that contralateral salivary tissue is spared. Often the initial 15-20 Gy is administered via an intraoral cone as a reverse boost to limit the volume of tissues receiving high-dose radiotherapy.

Local control with radiotherapy is achieved in approximately 85% of T1, 75% of T2 60% of T3, and 20% of T4 tumors. Five-year survival rates of about 80% are achieved for stage I-II cancers; stage III-IV patients have 5-year survival rates of about 30-40% ***(Parson's et al., 1993)***.

With palatal tumors preoperative assessment of retropharynageal lymph nodes LV involvement by images technique is very important ***(Lee, 1993)***. Absolute indication of post operative radiotherapy with cancer palate:

1- positive surgical margine.
2- Positive PNI.
3- Positive LN metastasis.
4- Recurrent tumours. ***(Le QT et al,. 1999)***

Significant prediction of treatment failure:

- Positive nodal involvement.
- Extra capsular speed.
- Advanced T-stage and tumor thickness ***(Amy et al., 2001)***

CHAPTER (7)

Sequelae of Treatment

Introduction:

Administration of cancer therapy is designed to eliminate or reduce tumour burden. A number of variables, including tumor cell kinetics, site of the tumor, and extent of tissue involvement affect outcome of such treatment. Depending on these and related variables, single or multi-modality therapy may be indicated. Principal forms of therapy include ionizing radiation, surgery, and chemotherapy ***(Squier et al., 1987)***.

Depending on the extent of the tumour, treatments may not be specific t the tumor; if they are not, normal tissue included within the surgical wound or rapidly replicating normal tissues can be profoundly affected. Injury can be either reversible or irreversible. Because oral epithelium is highly active tissue with replacement times estimated at 9-16 days, chemotherapy and radiation may be directly toxic to the oral mucosa, resulting in dysgeusia, extensive ulceration, pain, bleeding, and ***(Bethesda, 1990)***. Compromised normal function.

The dental/periapical, periodontal, or salivary gland tissues may suffer acute injury. Radiotherapy can cause both serious destruction to bone and permanent salivary ***(Jansma, 1991)***. Gland disturbances.

Because the sequelae associated with cancer therapy may have a profound psychosocial impact on the patient, a multidisciplinary team approach that reviews all aspects of patient care is necessary ***(Jansma et al., 1993)***.

Selected list of oral sequelae related to treatment:

Surgery: acute sequelae
Functional disturbances: speaking, mastication, swallowing vascular compromise.

Surgery: chronic sequelae: Cosmetic alterations, functional disturbances. Speaking Mastication. Swallowing, vascular compromise, nerve damage, muscular atrophy.
Ionizing radiation: acute sequelae: Salivary gland pathoses. Acute parotitis, irreversible changes (flow rates, compositional alterations). Oral mucositis. Infections. Mucosa periodontium Dysgeusia.
Ionizing radiation: chronic sequelae Salivary gland pathoses. Acute parotitis. Irreversible changes (flow rates, compositional alterations) dental alterations, rampant caries. Demineralization, osteoradionecrosis, dysgeusia trismus. Laryngeal alterations.
Chemotherapy: Oral mucositis dysgeusia. Immune dysfunction Dentition. Infections.

Mucosa.
Periodontium.
Hemorrhage.
Salivary dysfunction (variable).

Surgical risks and complications:

Surgical management of intraoral lesions typically includes both the primary lesion and the cervical lymph nodes. Ideally, surgery is selected when permenant control of the tumor is likely. Staging of the patient is essential to determine whether surgery alone is indicated or whether radiation or chemotherapy is also needed.

The risks and sequelae of surgery develop directly from and are primarily based on the extent of the tumor and its relationship to contiguous oral structures. Sequelae may include disfigurement and compromise of vascularity and nerve tissue as well as gustatory, masticatory, speech, and swallowing functions.

Surgical complications:

- intraoperative
- post-operative

intra operative complication: injury to important structure.

- Thoracic duct → leading to chylous fistula treated by conservative treatment if not responding surgical exploration may be necessary ***(Myers et al., 1975)***. Conservative treatment by pressure dressing and cessation of feeding while recommending medium chain triglycerides that can bypass the thoracic duct lymphatic system.
- Internal jugular vein: leading to bleeding and air embolism especially if the patient bed is elevated or with spontenous breathing.
- Nerve injury:
  hypoglassal nerve, lingual nerve, marginal mandibular branch of the facial nerve

(mouth incompetence), vagus nerve aspiration and difficult deglutition) spiral accessory nerve (shoulder weakness) phenic nerve, brachial plexus ***(Amy et al., 2001)***.

Post operative complication:

Otherwise other general post operative complication, site related complications are:

1- Infection especially with anerabic organisms so preoperative prophylaxix and post operative administration of antibiotics are recommended (Clindamycin, ampicillin sulbac tam) ***(Weber et al., 1992)***.
2- Orocutaneous, pharyngo cutaneous fistulae leading to wound infection, dehiscence and may lead to exposure of major vessdes (cartoid artery) that should be treated expeditiously with muscle flap coverage using a regional flap or free-tissue transfer. Carotid artery rupture is almost universally lethal.
3- Airway obstruction due to post operative oedema or tissue graft so tracheotomy is sometimes indicated to maintain air way patency.
4- pneumothorax, air embolus, dislodged tracheostomy tube and sub glottic stenosis.
5- Bleeding from innominate vein ***(Amy et al., 2001)***.
6- Post operative lymph edema after oral tumor surgery can be reduced by administration of sodium selenite either orally or intravenously due to it affects glutatihion peroxidase activity (GPX) and oxygen radical activity ***(Zimmer mann et al., 2005)***.

Risks and sequelae of radiation or chemotherapy:

Mucositis and infection:

Mucositis can be caused by either radiation or chemotherapy; the severity and extent of lesions are correlated with the treatment protocol being administered. Radiation induced mucositis depends on absorbed radiation dose, fractionation, delivery modality, and soft tissue status. The patient may feel a mucosal “burning’ sensation 1-2 weeks after initiation of therapy; the mucosa may be edematous and leukoplakic or erythematous on clinical examination. Depending on the intensity of the therapy and patient variables, extensive ulcerations may develop following initial clinical signs and symptoms. With chemotherapy, outcomes are specifically related to the pharmacologic class of drug selected as well as its dose concentration and the extent of neurtophil depletion or leukopenia ***(King et al., 1988)***.

Stomatitis vs mucositis:

Much confusion exists with regard to the soft-tissue mucosal reactions seen during chemotherapy. In order to achieve a clear understanding about what is going on in the oral cavity and to provide the appropriate treatment, the clinican must be able to determine whether these changes should be diagnosed as stomatitis or mucositis ***(Toth et al., 1991)***.

The term "stomatitis" can be generally applied when mucosal integrity has been lost due to local trauma, ie, biting, denture irritation, or even infection ***(Lindquist et al., 1978)***. Treatment usually consists of identifying (by culture) and/or correcting local causes, ie, smoothing rough teeth, prescribing mucosal toothguards, or stressing the importance of a soft diet in order to decrease functional irritation and truma ***(Toth et al., 1983)***.

Denture prostheses promote as well as augment stomatitis in several ways: they can produce traumatic wound while providing a sanctuary for microorganisms by shielding the mucosa from oral hygiene or appropriate topical medication rinses ***(King et al., 1988)***. In addition, not only can dentures hold the infectious agents in close proximity to any ulceration that may develop under them. They can hinder proper mucosal assessment. Stomatitis, then, can be prevented and/or corrected with dental or antimicrobial treatment.

In contrast, the term "mucositis" denotes the cytotoxic effect chemotherapy has on the oral mucosal tissues. Before a diagnosis of mucositis is made, however, all other factors must be ruled out, ie. Trauma, factitious injury, and /or infections. If incorrectly identified, mucosal reactions could cause effective therapy to be delayed, chemotherapy dosage to be reduced, or chemotherapy / radiotherapy to be discontinued. Hence, an essential aspect of oral care is culturing for microorganisms to evaluate the incidence of mucositis vs infection. To aid in early diagnosis, the patient must be counseled to report any mucosal changes or increased sensitivity ***(Toth et al., 1991)***.

Diagnosis of Mucositis:

Mucositis is the most common acute complication of chemotherapy, and usually begins as erythema and increased sensitivity resulting from thinning of the mucosa ***(King et***

al., 1988). As tissue changes continue, small ulcerations begin to develop, which can lead to large areas of mucosal denudation. Use of a grading score of severity for mucosal reactions during each course of therapy allows clinicans to take appropriate preventive or therapeutic measure during current and future treatment courses ***(Toth et al., 1983)***.

Patients vary greatly in their tolerance of chemotherapy regimens and ther proclivity for developing mucositis. Several classes of chemotherapeutic agents are known to produce mucositis, depending on the dosage and duration of treatment; these include antimetabolites, antibiotics, and to a lesser degree, alkylating agents and vinca alkaloids. However, from what we have observed clinically, any agent given at an intensified dose or for a sufficient duration can produce mucosal toxicities leading to dose limitation ***(Sonis et al., 1991)***.

Consequently, it is of the utmost importance for the clinican to be aware of the relationship between the timing of administration of chemotherapy and any mucosal reactions. One would expect mucosal toxicity, or mucositis, to develop shortly after the start of chemotherapy. However, mucosal herpes simplex virus infections also can occur early in the chemotherapy cycle. There is significant misdiagnosis of such infections as mucosal reactions that occur in association with a hematologic nadir could be related to infectious stomatitis. Culturing is essential in these situations to differentiate chemotherapy-induced mucosal toxicity from mucosal netropenic infections caused by bacteria, fungi, or viruses. The loss of mucosal integrity can produce bacteremic episodes that could be life threatening to immunocompromised patients ***(Wade et al., 1982)***.

Prevention and treatment of mucositis:

Effective approaches for the prevention or treatment of oral mucositis have not been standardized, and vary considerably among institutions. Comprehensive care should focus on the prevention of complications by eliminating known and predictable factors that initiate mucosal pathology and by promoting good hygiene and nutrition, thereby minimizing the risks of infection, bleeding and pain.

Strategies for preventing mucositits are limited, but the problem can be partially minimized by fractionation techniques, shielding, and modifying modes of delivery. Supportive care for the acute components of mucositis (bleeding, pain, and infection) is the mainstay of treatment. Although not directed principally at preventing mucositis, comprehensive oral care, including mechanical plaque removal supplemented by an antimicrobial rinse if indicated and frequent rinsing with saline bicarbonate solutions, can reduce the severity of secondary complications. Topical anesthetics or systemic analgesics are administered frequently for palliation of pain.

Oral rinses containing antidotal concoctions of antibiotics, antifungals, and narcotic analgesics in a coating suspension can be administered for treatment palliation ***(Anderson et al., 1993)***. Other agents, such as allopurinol, leucovorin, vitamins, cryotherapy, and growth factors, have been tried for the prevention of chemotherapy-induced mucositis ***(Gordon et al., 1994)***. Use of a capsaicin-containing candy has also been advocated to desensitize pain receptors in the mouth. To date, none of these approaches has shown a significant impact ***(Berger et al., 1995)***. Smoking can exacerbate mucositis; patients should be assisted with cessation using nicotine replacement therapy if indicated ***(Rugg et al., 1990)***.

Candidiasis is the most common oral infectin during treatment for oral cancer, although other mycotic, bacterial or viral infections are possible. Prophylactic or therapeutic topical and/or systemic antifungal agents are necessary to control candidiasis. Selection of an antifungal agent must consider the patient's degree of xerostomia and possible inability to dissolve a troche. Also of concern is the patient's level of oral hygiene and the risk associated with high levels of sucrose in topical preparations. The addition of chemotherapy to the treatment protocol may increase the severity of mucositis, xerostomia, and infection; it also increases the risk of bacterial and herpetic infections.

Because of the high probability of mucositis and infection, their potential severity, and their nutritional consequences, the radiation or chemotherapy patients needs comprehensive management protocols, particularly during periods of highest infection risk. Some cancer centers prescribe a "cocktail" preparation of antimicrobials, a steroid, a coating agent, and a topical anesthetic. However, the effectiveness of such preparations is empirically based and needs to be examined in a well-controlled clinical study.

Oral hygiene – chemotherapy-induced sequelae can include pancytopenia, nausea, mucosiitis, and infection. To avoid such sequelae, the patient should be advised of the importance of brushing with a soft toothbrush, keeping the oral mucosa moist and clean, and selecting and maintaining an appropriate diet following chemotherapy ***(King et al., 1992)***.

The fear that brushing will increase the chances of oral complications has always been a concern among practitioners, and yet the benefits of brushing outweight the drawbacks. Even in health mouths, a certain degree of bacteremia can be associated with normal function (e.g, eating) ***(Ever et al., 1977)***. However, any threat of persistent bacteremia in a compromised host is cause for concern. Thus the benefits of controlling beaceremia – promoting plaque through appropriate hygiene-swishing fluids is a poor substitute for through oral care by brushing-far exceeds the drawback of a potential increase in oral complications ***(Pizzo, 1993)***. Indeed, with careful oral care that includes brushing, chemotherapy-induced sequelae can be kept to a minimum or even eradicated.

Fortunately, for those practioners who still worry about the harmful side effects of brushing, there are warning signs that indicate when a change to a softer brush is needed. If a patient's platelet-count falls below 40,000/mm^3 if his or her oral tissue becomes more sensitive, or if a coagulopathy exists, the patient should be switched to an ultrasoft "chemobrush" (Ultra Suave; periodontal Health Brushes, Osseo, Wisconsin). The use of a foam brush is highly discouraged ***(Addens et al., 1992)***. However, if the patient is maintaining good oral care and oral lesions still develop, the microorganism concentration in the oral cavity should still be low enough that any superienfection potential would have a minimal influence on the intensity of the patient's discomfort and on wound healing ***(Hickey et al., 1982)***.

Oral Rinses-compliance with oral care procedures is a major factor in maintaining the relative health of the mucosal tissues and the effectiveness of locally applied topical oral agents. These topical medications should be nonirritating and nondehydrating. Mouth rinses are frequently recommended ad therapy for mucositis in both dentate and edentulous patient. Such rinses not only cleanse the mouth of loose debris and thick mucus but also hydrate the mucosa and treat mucositis.

Most commercial mouth rinses contain alcohol-or phenol-like substances that should be avoided, since they can irritate and desiccate inflamed, compromised xerostomic tissues. Furthermore, these rinses can further compromise the mucosa by prolonging the healing of oral wounds ***(Kaminski, 1987)***.

Our experience has shown that a diluted hydrogen peroxide solution (1 part 3% hydrogen peroxide to 4 parts water) adequately cleanses the tissues of debris, bacteria, and mucus. This cleansing should be immediately followed by a rinse of water. When oral lesions exist, rinsing with the diluted hydrogen peroxide solution is recommended only to decrease wound contamination and colonization. The hydrogen peroxide rinse should not be used if there are any blood clots or bleeding, since it would only foster more bleeding ***(Toth et al., 1991)***.

Topical coating agent can be most effective in promoting mucosal wound healing, yet sequence of delivery of these agents to the compromised oral soft tissues is important. The tissue must be cleaned of mucoid debris before the application of the agents. Next, a troche or lozenge form of the oral medication should be taken, as it provides a longer and more constant application of the medicine to the tissue. An oral liquid suspension can be used if the mouth is dry, even though it will be in contact with the tissue and any organisms for only a limited time. All prostheses should be removed during the oral-mucosal treatment ***(Martin et al., 1993)***.

If a mucosal-coating agent, eg, sucralfate or kaolin-pectin, is to be used, it must be administered last so as not to block out the effects of the topical antimicrobial agents on the tissues or in the wounds. Thirty minutes should elapse between the applications of the agents. In providing the treatment described above, an oral care schedule for patients receiving

chemotherapy can be very useful to the pracrtitioner. Again, it must be emphasized that the clinican must maintain constant vigilace of oral mucosal wounds and order cultures when indicated to provide appropriate assessment and therapy ***(Toth et al., 1991)***.

Avoidance of topical anesthetics: an additional comment should be made with regard to the use of topical anesthetics. We routinely discourage use of anesthetic agents once mucosal discomfort develops due to their irritating nature. A more significant factor is the profound suppression of the gag-cough reflex topical anesthetics can produce, leading to possible aspiration.

Nutrition: finally, an important, often overlooked factor for immunocompromised chemotherapy patients is nutrition. The diet for cancer patients during chemotherapy must be palatable as well as nontraumatizing to the oral mucosa. During the myelosuppressive phase of therapy or during periods of mucositis, the patient's diet should consist of soft food that will not abrade or puncture the mucous membrane or cause direct tissue trauma. Patients, family members, and dietitians can be creative in preparing foods that comply with such a diet and yet remain appetizing, tasteful, and nutritious ***(Toth et al., 1990)***.

Salivary Gland dysfunction:

Directing radiation therapy to the salivary glands or administering chemotherapeutic, antiemetic, or psychotropic drugs may alter salivary gland function. Chemotherapy typically cause chronic salivary gland changes; in contrast, high-dose ionizing radiation delivered to major glandular sites can cause permanent salivary gland dysfunction. The degree of oral dryness (xerostomia) will vary by the extent of salivary gland injury. These changes can exacerbate oral infection risk at various sites, including the mucosa and periodontium. xerostomia may also affect mastication, speech, and the patient's overall quality of life.

Unfortunately, there are few effective preventive or palliative interventions for xerostomia. Frequent oral rinses with water or saline and commercial saliva substitutes may be minimally helpful, as may salivary stimulants such as sugarless candies and gum. Currently, no saliva substitute exists that can adequately replace the organic and biologic constituents of saliva. However, two studies that examined the effectiveness of oral pilocarpine as a sialogogue in irradiated patients with residual functional salivary gland tissue demonstrated its efficacy and safety; pilocarpine is now approved by the FDA for treating hyposalivation. However, the practitioner must be aware of its potential side effects and contraindications ***(Bakemeier et al., 1993)***.

N.B:

When the salivary glands are involved in a radiation field, the daily use of a fluoride gel is necessary to prevent caries due to the decrease in salivary protection. This radiation induced xerostomia is due to permanent damage to the salivary gland tissues ***(Liu et al., 1990)***.

Fluoride gels: either a 1.0% sodium fluoride gel or an acidic 0.4% stannous fluoride gel is used for the prophylaxis of dental caries. Most patients apply the gel in a custom-fabricated polypropylene applicator that completely covers and extends slightly beyond the tooth surface. The applicators are worn for 10 minutes daily. Patients who receive low doses of radiation, whose compliance is good, and who are expected to have a slight degree of xerostomia can apply fluoride gel by toothbrush ***(Tooth et al., 1991)***.

We must mention that sodium fluoride, due to its lower acidity, has a lesser degree of uptake by the tooth structure and always necessitates the use of custom applicators. On the other hand, sensitivity and pain can be a problem with the use of the more acidic stannous fluoride, and may require a change to the sodium fluoride preparation. Despite these problems, a properly utilized daily fluoride program can protect the teeth from profound radiation – induced xerostomic decay ***(Keene et al., 1987)***.

Permanent xerostomia: In most cases, transient decreases in salivary flow caused by radiation therapy can become permanent, as illustrated by a study that followed patients who received bilateral ionizing radiotherapy involving the major salivary gland tissues exhibited, overtime, decreases of 80% in stimulated salivary flow and 78% in unstimulated salivary flow, when compared with a non-irradiated group. Patients who underwent unilateral irradiation involving only one parotid and one submaxillary gland experienced comparable 60% and 51% decreases in stimulated and unstimulated mean salivary flow, respectively. Patients who underwent neck irradiation, ie, mantle field treatment, likewise experienced decreases of 43% and 32% in stimulated and unstipulated flow rates ***(Liu et al., 1990)***.

Oral rinses: Changes in salivary flow induced by radiation are worrisome because saliva protects the oral mucosa from dehydration and assists in the mechanical lavage of food and microbial debris from the oral cavity ***(Mandel, 1989)***. To avoid oral infections that may arise from radiation therapy, the patient must frequently rinse the oral cavity to reduce the number of oral microorganisms and to maintain mucosal hydration ***(Keen et al., 1987)***. Such oral lavage can be done with a solution of 1 teaspoon of sodium bicarbonate in 1 quart of water. This solution should be used frequently each day. It has been our clinical experience that this patient-prepared solution is better accepted than the commercially available salivary substitutes. Also, a specially prepared oral suspension of sucaralfate, which has been tested and proven at our institution, can be used to soothe mucosal reactions during radioatherapy ***(Toth et al., 1991)***.

If these guidelines are followed, oral tissues can be maintained in a health state following radiotherapy. However, the cooperation and compliance of the patient, which

includes scheduled professional evaluations and treatment, are essential, and are considered the result of education and motivation.

Symptoms of dry mouth do not necessarily correlate with quantitative or qualitative changes in saliva. Some patients receiving high-dose radiotherapy to major salivary glands may experience reduced saliva production but perceive an improvement in function over time after cessation of therapy. Despite improvement in symptoms, however, saliva production in these patients may continue to be impaired, with reduced levels of antimicrobial proteins secreted. Thus, these patients will be at high risk for aggressive caries formation, demineralization and periodontal disease for the balance of their lives. In addition, becaue mucous secretions from minor salivary glands are often unaffected, patients frequently complain of thick, ropey saliva. Comprehensive long-term preventive oral hygiene and dental follow-up are needed ***(Carchillo et al., 1993)***.

Dysgeusia:

Both chemotherapy and radiation therapy patients can experience disturbances in taste. Mechanisms for this sensory disturbance are often complex and range from direct molecular effects on acinar cell function to conditioned aversions to selected foods. Compositional and/or flow rate changes in saliva may also contribute to the symptom, although underlying mechanisms are not clearly established.

Direct chemotherapy or radiotherapy injury ot taste buds may produce partial (hypogeusia) or absolute (ageusia) taste loss. Taste buds may regenerate about 4 months after cessation of therapy, and normal taste function may resume. Given the complex interplay between physico-chemical and psychologic alterations, however, this recovery may not occur. Patients should be counseled as to realistic outcomes and give ongoing dietary consulatation as well as programs to resolve food aversions that may have emerged during cancer, therapy. High-dose zinc supplementation has helped some patients ***(Bartoshuk, 1990)***.

Nutritional complications:

Radiation, chemotherapy, or surgery can impair nutrition through a variety of mechanisms. Maintenance of appropriate levels of nutrition support is essential; indeed, many cancer patient are underweight at diagnosis and lose weight during therapy ***(Elias et al., 1986)***.

Nutritional complications stem from altered taste sensations, ageusia, anorexia, food aversion, pain xerostomia, and dysphagia. Inadequate intake of calories leads to weight loss, weakness, and malaise. Tumor factors responsible for anorexia include direct tumor utilization of metabolites. Release by the tumor of chemical moieties that produce protein loss and negative nitrogen balance has also been hypothesized to contribute to cachexia ***(Mattes et al., 1992)***.

finally nutritional complications may be caused by lack of access to appropriate reconstructive techniques and rehabilitation, leaving the patient without complete masticatory restoration.

Dental caries and periodontal disease:

Patients receiving adjuvant chemotherapy for management of disseminated oral cancer are not typically at high risk for chemotherapy induced progressive compromise of the dentition and periodontium. However, the compliance of such patients with oral hygiene protocols and nutrition guidelines may be deficient. Such limitations can produce extensive oral disease patterns.

Patients whose major and minor salivary glands have been exposed to therapeutic doses of ionizing radiation are at significant risk for progression of oral infections and demineralization, even if routine oral management strategies are utilized. Several covariates, including salivary function, nutrition, medications, parafunctional habits, tobacco habites, and compliance with comprehensive oral care protocols that include remineralizing solutions and fluoride use, collectively ineract and produce either a stable or regressive oral disease profile. These diseases are caused by infecting pathogens, with consequences that include hard or soft oral tissue destruction, pain and bleeding, and systemic sequelae consistent with infection progression ***(Silverman, 1993)***.

Adverse effects on bone:

Irradiation can adversely affect cellular elements of bone, which can limit the potential for wound maintenance and the ability to heal after a traumatic event ***(Toth et al., 1991)***. Further, the risk of complications following trauma from oral surgery in an irradiated field can be highly significant, although some claim that this risk is low, up to a predetermined threshold of irradiation ***(Marciani et al., 1986)***. For these reasons, elective oral surgical procedure, such as extractions and soft-tissue surgery, are contraindicated within an irradiated field. However, some nonsurgical dental procedures can be safely done, including oral prophylaxis, radiography, routine restorative procedures, and nonsurgical endodontic and prosthodontic procedures, since these procedures do not cause bony trauma ***(Felming, 1990)***.

Existing or potential problems should be eliminated prior to irradiation in order to prevent future post-radiotherapy oral trauma. For minor oral bony nectroic lesions following radiotherapy, local debridement and irrigation with an anitmicrobial rinse (chlorhexidine gluconate (peridex) can be beneficial in treating the wound; such a procedure can be performed by a dental oncologist or an oncologic nurse practitioner under supervision ***(Toth et al., 1991)***.

Hyperbaric oxygen: If surgical intervention, ie, extractions, endodontic, or periodontal surgery, is required after radiotherapy, preoperative hyperbaric oxygen treatments may increase the potential for healing while minimizing the risk for osteoradionecrosis ***(Marx et al., 1987)***. Unfortunately, this form of treatment is time consuming and expensive (each treatment can last up to 3 hours. Nevertheless, when compared with post-radiation dental treatment, ie, radical debridement and reconstruction, hyperbaric oxygen treatment can be cost effective and possibly prevent jaw amputation. It is therefore beneficial to do a preradiotherapy oral examination, not only for financial reasons but also for the purpose of potentially decreasing patient morbidity ***(Mansfield et al., 1981)***.

Osteoradionercrosis:

Ionizing radiation can lead to osteoradionecrosis (ORN), a complication that results from compromised vascularity following surgery or from radiation-induced hypovascularity, as well as from cytotoxic effects on bone-forming cells and tissue, hypocellularity, and hypoxia of affected bone ***(Vanme, Kesteyn et al., 1995)***. The risk of ORN increases over time following completion of radiation dosing and is present through the lifespan. Complications associated with ORN include intractable pain, drug dependency, pathologic fractures, oral and cutaneous fistulae, and loss of large areas of bone and soft tissue ***(Firedmen, 1990)***.

The incidence of ORN is quite variable and depends mostly on the aggressiveness of radiation therapy; reported incidence ranges from 2% to 4%. Although trauma (e.g., dental extraction or scaling, denture irritation, periodontal disease) can initiate ORN, the etiologies of many cases are not identified. Managed unsuccessfully, ORN can have serious consequences, including progressive pain, trismus, and eventually, loss of major segments of the jaw bone ***(Peterson et al., 1994)***.

Ideal management of ORN calls for eliminating potentially riskful foci of oral disease prior to instituting radiation therapy. This approach requires a multidisciplinary team, which conducts comprehensive treatment planning well in advance of the cancer therapy (See table for a list of evaluation and management issues). Intact teeth can be preserved under certain conditions, such as when the patient is highly motivated toward maintaining ideal oral health and receiving comprehensive dental care. Conversely, compromised teeth in the poorly compliant patient should be extracted at least 10 days prior to radiation. However, the patients' disease state may change the timing of extraction. Realistic clinical judgment combined with comprehensive management is the best tool for preventing osteoradionecrosis ***(Marx et al., 1985)***.

Table ( ): Evaluation and management issues prior to surgery and radiotherapy:

Extraoral head and neck exam.
Tempomandibular dysfunction.
Complete intraoral exam.

Parafunctional habits.
Proposed surgical defects.
Baseline salivary flow.
Radiographic evaluation
Diet and medication analysis
Oral hygiene.
Tobacco and alcohol habits
Previous dental or oral hygiene compliance
Psychosocial impact of treatment
Status of dentition and periodontium

Management of ORN with antibiotics and surgical debridement is not always successful. Courses of hyperbaric oxygen to facilitate healing of compromised bone may be helpful when combined with appropriate surgery and antibiotics. However, because this treatment is expensive and offered by only a limited number of facilities, many patient will not be able to take advantage of it ***(Markx et al., 1987)***.

Trismus alterations:

Ionizing radiation can also obliterative endoarteritis with associated tissue ischemia and fibrosis. This process can contribute to development of trismus if the asticatory muscles are within the portals of radiation. As treatment of trismus can be very difficult, preventive management with jaw exercises using tongue blades and other devices is recommended when signs of this disorder occur ***(Marx, 1983)***.

Psychosocial impact:

Functional and aesthetic changes may profoundly affect a patient's psychic and social status. The clinician should give these factor serious consideration in pre-treatment consultation and post operative rehabilitation. Failure to do so may have critical

consequences for the patient's later quality of life in socioeconomic areas as well as in personal relationships and lifestyles ***(Argerakis, 1990)***.

CHAPTER (8)

Functional Rehabilitation

Introduction:

The cosmetic, functional, and psychosocial results of oral cancer treatment may combine to produce devastating effects on patients, especially if the tumor is extensive or the treatment particularly aggressive. Indeed, oral cancer is noted for the tool it exacts from patients, from both the disease itself and the effects of its treatment. A variety of functions can be affected, including speech, deglutition, management of oral secretions, and mastication. Thus, maxillofacial prosthetic rehabilitation is a cornerstone of efforts to restore the head and neck cancer patient's oral functions and cosmesis following surgery to pre-treatment baselines ***(Laney, 1983)***.

Each year a proportion of new head and neck cancer patients will require maxillofacial prostehetic intervention. Most of these patients will be rehabilitated at major teaching institutions or designated cancer centers that include a multidisciplinary team. Perhaps half of new patients will be treated with definitive radiation without surgical intervention, but these patients also will require dental intervention and follow-up throughout their lifetime. Thus, multidisciplinary teams are essential for head and neck cancer patients, especially as their treatment may result in loss of oral functions and cosmetic deformities ***(Beumer et al., 1979)***.

With recent changes in the modalities of cancer treatment and reconstruction (e.g., the introduction of brachytherapy and microvascular free flap transfers), rehabilitation of the oral tissues takes on a new dimension. Conventional maxillofacial prosthetic rehabilitation usually will not be enough to restore the resultant hard or soft tissue defects. Thus, a multidisciplainary surgical team that includes dentists will increasingly be instrumental in the reconstruction of head and neck patients. The ultimate goal of rehabilitation, however, will remain the restoration of oral functions and cosmesis with the aim of providing an acceptable quality of life ***(Beumer et al., 1986)***.

Successful rehabilitation and quality of life go hand in hand. because patients vary in attitudes and adaptation, it is very difficult to predict the patient's eventual quality of life prior to initiating treatment for an oral tumor. Furthermore, the use of newer techniques at surgical reconstruction makes the maxillofacial prosthodontist's task even more challenging. It is important for the dental team to be experienced and to identify for the medical and surgical oncologists realistic goals and objectives for rehabilitation. At major cancer centers with rehabilitative teaching programs, it is not uncommon for the surgically respected head and neck patient to require 20-50 appointments for appropriate rehabilitative care in a 1-year period ***(Wichman et al., 1995)***.

With multidisciplinary cancer therapy (ablative surgery, reconstructive surgery, radiation therapy, and/or chemotherapy) available, rehabilitative dentistry is essential for improving quality of life. Treatment plans for rehabilitative dentistry should be included in the overall cancer treatment plan; in many instances, the sequelae of ablative head and neck surgery and radiation therapy could be alleviated, minimized, or even eliminated altogether if there were appropriate planning for maxillofacial prosthetic and other dental interventions before treatment begins ***(Laney et al., 1979)***.

Rehabilitation strategy:

The strategy and techniques of rehabilitation of a head and neck cancer patient are directly related to the location of the cancer and to the extent and type of surgical intervention and radiation modalities used. Oral carcinomas not detected and evaluated in their early clinical stages usually invade contiguous structures, thereby setting the stage for extensive surgical procedures that are generally followed by radiation therapy ***(Laney, 1983)***.

Removal of extensive segments of the tongue, floor of mouth, mandible, and hard and soft palate as well as the regional lymphatics usually mandates extensive rehabilitative management ***(Beumer et al., 1979)***. Generally, maxillofacial prosthodontists restore maxillary resections with obturator prostheses. However, in many instances a soft palate speech bulb-obturator retained in the maxillae (for restoration of velopharyngeal function) or a palatal

augmentation prosthesis (if tongue function is lost) is required for optimal rehabilitation. Currently, rehabilitation of a maxillectomy and/or soft palate defect via an obturator prosthesis is most effective in resotring function. Recent advances in microsvascular free flap tissue transfers have been used successfully to reconstruct composite defects of the mandible, buccal mucosa, and tongue ***(Hidalogo, 1989)***.

In recent years there have been significant advances in some of the strategies for rehabilitating the oral cancer patient. These include fundamental qualitative improvements in biomaterials (including Osseo integrated implants), microvascular free flap tissue transfers, and hyperbaric oxygen technology (by which gas highly concentrated in oxygen is delivered under increased pressure to patients).

Still, long-term success depends in large measure on effective follow-up protocols. The traditional idea that a patient's original maxillofacial prosthesis will adequately support his or her lifelong needs is no longer valid. The prosthesis needs ongoing evaluation, adjustment, and usually replacement over time. ***(Adisman, 1990)***. Most removable extraoral prostheses need to be remade every 2 to 3 years; removable intraoral maxillofacial prostheses require regular maintenance and generally need replacement every 5 to 7 years. In addition, the ongoing long-term sequelae of radiation therapy for head and neck cancer require the dentist to keep the periodontium in optimal condition furthermore, restorations of abutment teeth used to retain an intraoral maxilloficacial prosthesis must be sound and noncarious, and implant prostheses in this population require extensive maintenance for optimal functional results ***(Urken et al., 1991)***.

Example:

The standard of care for patiens receiving a palatal resection (maxillectomy, palatectomy and/or soft palate resection) includes three stages of maxillofacial prosthetic intervention:

1- Immediate placement of a surgical obturator prosthesis (inserted in the operating room, usually by the maxillofacial prostheodontist, at completion of surgery to separate the oral cavity from nasal cavities created by cancer surgery).

2- Placement of a provisional or interim postsurgical obturator prosthesis (inserted after the surgical obturator and packing is removed 7 days postoperatively, worn in the postoperative healing period).
3- Placement of a definitive postsurgial obturator prosthesis 3-4 months post operative ***(Ismail et al., 1990)***.

Major technologic advances have occurred in recent years in osseointegration (the process by which natural bone attaches to the metal or ceramic component of an implant), thereby facilitating the use of dental implants ***(Branemark et al., 1985)***. Branemark et al. have pioneered the modern-day use of this technology, in which implant materials capable of bearing forces produced during normal function interface both structurally and functionally with bone. Dental implants are now being used in both oral and extraoral settings and have significantly improved the restoration of both form and function to the oral and craniofacial region. Potentially, implant-borne prostheses can be used in the majority of intraoral and extraoral defects. However, in patients with intraoral defects, the most useful implant sites usually are not within the radiation treatment volume. An emerging exception appears to be the case of fibula free flaps, where implants are used to restore segmentally respected mandibles prior to post-surgical radiation. For extraoral prostheses, bioadhesives have traditionally been used to enhance retention but they have considerable limitations ***(Ismail et al., 1990)***. Indeed, patients and clinicians often become frustrated by the difficulty of achieving optial effects with adhesives. Both experience and specialized education can improve the clinician's ability to provide these components of extraoral and intraoral rehabilitative care ***(Ferraro et al., 1993)***.

The characteristics of successful osseointegration include:

1- Biocompatible implant materials
2- Non-traumatic, a septic surgical procedures.
3- An initial healing period in which functional loading of forces is deferred; and stress-reducing prosthodontic procedures ***(Ismail, et al., 1990)***. Patients should be selected with great care, and proper maintenance and follow-up are imperative ***(Beumer et al., 1986)***. Successful osseointegration can permit the restoration of masticatory function following mandibular fibular free flap microvascular transfer ***(Raumanas et al., 1995)***. Osseointegration in the maxillary-resected patient and implant-retained

facial prostheses have become acceptable in major cancer centers worldwide ***(Nishimura et al., 1995)***.

Post operative reconstruction: **depends on:**

Site and size of defect:

- Small defects either closed primarily or left to heal by secondary intention.
- Larger defects reconstructed either by:
    - Local or regional flaps.
    - Grafts: Split thickness grafts – free tissue transfer.
    - Obturators:
- Patients with tongue cancers reconstructed by split thickness graft, showing better oral function than those treated by primary closure or regiona flap ***(Mc cannel et al., 1987)***.

Regional flaps:

Examples:

- Pectaralis major flap (most common).
- Trapezius flap.
- Latissimus dorsi flap.

Disadvantages"

- Lack of bone.
- Limited extension due to its vascular pedicle.

(Kroll et al., 1997)

bulky flap: diminished function.

Free tissue transfer:

Advantages:

- Superior blood supply, no limitations.
- Great variety and verstality of donor sites.
- Allow the potential for sensate flap through neural anastomosis resulting in improved swallowing and speech function ***(Amy et al., 2001)***.

Disadvantages:

- Complex technique.
- Prolong the operation time.
- Its colors and contour is different from recipient site.

(Amy et al., 2001)

Examples for free tissue transfer:

- Radial forearm flap.
- Rectus abdemin flap.
- Fibula flap.
- Iliac crest flap.
- Scapular flap ***(Amy et al., 2001)***

Microvascular radial forearm fasciocutaneas free flap in hard palate reconstruction is a reliable technique and provides a definitive separation between oral and nasal cavities. Furthermore it improves the quality of life by improving speech, swallowing and chewing. It should be considered an integral component of head and neck cancer therapy and rehabilitation ***(Duflo et al., 2005)***.

Current rehabilitative practice is centered in five principles:

1- The process of rehabilitation begins at time of initial diagnosis and treatment planning.
2- The dentition should be preserved if possible.
3- Rehabilitative treatment plans should be based on fundamental principles of prosthodontics, including a philosophy of preventive dentistry and conservative restorative dentistry.
4- Surgery before prosthetic rehabilitation may be indicated to improve the existing anatomic configuration after ablative cancer surgery, reconstructive surgery, and/or radiation therapy.
5- Multidisciplinary cancer care is required to achieve the best functional physical, and psychologic outcomes

(Beumer et al., 1990)

Factors affecting the cancer surgical treatment plan for oral cancer patients include the following:

- prognosis and systemic status of patient.
- Potential size and site of defect.
- Potential nature of functional and/or cosmetic defect.
- Adjunctive therapy (e.g., chemotherapy or radiation) that may compromise the surgical result.
- Anticipated changes to function and cosmesis, based on the cancer surgery and the availability, accessibility, and cost of rehabilitative procedures ***(Laney et al., 1983)***.

Planning for patients who need rehabilitation of the maxillofacial complex includes consideration of surgical defects associated with the maxilla, mandible, tongue, soft palate, and facial region, including the patient with a combined orofacial abnormality. The role and impact of radiation and chemotherapy also need consideration ***(Beumer et al., 1986)***.

Post operative follow up:

During first 2 years follow up to detect recurrence while after 2 years, follow up aiming at detection of 2nd primary tumor, so follow up at least is done annually ***(Amy et al., 2001)***.

Postoperative oral care:

Oral care during the postoperative period should include the care of the maxillary surgical defect and, when applicable, the skin graft. The surgical site should be evaluated for skin graft viability when the surgical prosthesis is removed. At this time, the patient is instructed in the care of the surgical site and the removal of dried crust and mucoid debris from the defect ***(Martin et al., 1993)***.

One approach to care is gentle irrigation and rinsing with a diluted hydrogen peroxide solution (equal parts of 3% hydrogen peroxide and water) followed by a salt and baking soda rinse (1/2 teaspoon of salt plus ½ teaspoon of baking soda per 1 quart of warm water). The

patient is instructed to rinse three to four times daily and to clean the prosthesis with hand soap and water several times daily ***(Toth et al., 1991)***.

Soon after the surgery, a dental hygiene regimen, ie, toothbrushing, can be instituted. As the skin graft integrates with adjacent tissues, usually within 3 to 6 weeks, a mechanical pump with a multiorifice tip may be used for gentle, guided irrigation. In addition to using the irrigation system, the patient can use a 4x'4-inch gauze or clean washcloth soaked with 3% hydrogen peroxide and placed around the finger to gently clean the surgical site and remove crusting debris. The patient should be advised not to use commercial mouthwashes since they ally contain some alcohol or phenol, which can delay healing and irritate the wound ***(Toth et al., 1990)***.

Oral exercises:

Oral opening exercises should be initiated as soon as the patient can tolerate them. Such exercises can include the use of tongue blades to counteract a decreased oral opening by placing the blades between the posterior teeth to stretch the scar tissue and create a new maximum opening ***(Barrett et al., 1988)***.

Other exercises include the use of mechanical devices that are custom-made and stretch the postsurgical scar tissue. One such device is a threaded screw-type instrument known as the therabite mouth opener, which works like a car jack to open the mouth. Users of these devices must take care to ensure that teeth do not incur orthodontic movement or damage. The edentulous patient can simply place the thumb and index finger between the maxillary and mandibular ridges in a crossed position to push open the mouth ***(Barrett et al., 1988)***.

Physical therapy:

In addition, more advanced means of physical therapy can be instituted by a trained physical therapist, eg, auriculotherapy, electrotherapy, ultrasound therapy, and isometric exercises ***(Barretle et al., 1988)***. Such therapy will maintain the oral opening and give the

patient better access to the defect as well as the rest of the oral cavity. Oral opening measurements should be recorded to help both the clinicians and patient not only assess the progress of these exercises but also detect any insidious decrease in opening ***(Martin et al., 1994)***.

Even when results are excellent, patient exercises should be continued for at least 1 year and, possibly, indefinitely. Furthermore, even with physical therapy, patients may only regain oral opening of less than 10 mm anteriorly. If a patient complains of a sudden loss of oral opening ability, one should immediately suspect and rule out disease recurrence. Infection can also cause a loss of oral opening ***(Rocabarto et al., 1983)***.

In all cases, head and neck surgery patients should be followed closely by the health care team. Regularly scheduled appointments with the dental oncologist are essential for monitoring oral and dental hygiene, ensuring proper fit of prostheses, and most important, assessing for disease recurrence. Teams of specially trained medical and surgical personnel can then provide expert judgment and skill for patients with advanced disease ***(King et al., 1992)***.

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