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Review on Locally Advanced Inoperable Head and Neck Cancers

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Abstract:
The prospective randomised study to asses and compare toxicities, treatment response. The main sites of the oropharynx consist of the posterior and lateral pharyngeal wall, faucial arches, tonsillar fossa, soft palate, and base of tongue. Nasopharynx begins at the posterior choana and slopes downward along the airway to the level of the free border of the uvula. Hypopharynx (laryngopharynx) extends superiorly with the oropharynx and inferiorly with the cervical oesophagus. It is divided into the pyriform sinus, posterior pharyngeal wall, and post-cricoid region.

Keywords: Head and Neck cancers, Oropharynx, Nasopharynx

Introduction

The term head and neck cancer refers to neoplasm arising from below the skull base to the region of thoracic inlet. Most of the lesions arise from the upper aero-digestive tracts.

SITES

Oral cavity is defined as the area extending from the vermilion border of the lips to a plane between the junction of the hard and soft palate superiorly and the circumvallate papillae of the tongue inferiorly. This region includes lips, oral tongue (anterior two third), floor of mouth, retromolar trigone, alveolar ridges, buccal mucosa and hard palate.

Pharynx consists of the oropharynx, nasopharynx, and hypopharynx.

Oropharynx is the posterior continuation of the oral cavity and connects with the nasopharynx (above) and laryngopharynx (below). It is located between the soft palate superiorly, and the hyoid bone inferiorly.

Larynx is divided into the supraglottic, glottic and subglottic regions. The supraglottic larynx consists of the epiglottis, false vocal cords, ventricles and aryepiglottic folds, including the arytenoids. The glottis includes true vocal cords and the anterior commissure. The sub glottis is located below the vocal cords.

ETIOLOGY

The most important established risk factor for oral cancers is mainly tobacco in the form of smoking, betel quid chewing, reverse smoking and alcohol. The effects of alcohol and tobacco seems to be synergistic. Tobacco users have a 5 – 25 fold higher risk of oral cavity

and oropharyngeal cancer. Smoking is identified as an independent risk factor in 80-90% of patients. The practice of reverse smoking is associated with an increase in cancer of hard palate. Cessation of smoking is associated with a decline in risk of cancer of oral cavity(1).

Abstaining from the use of cigarettes results in a 30% reduction in the risk of cancer in those who quit after 1- 9 years; the risk is reduced by 50% in those who quit for more than 9 years. Male smokers have a 2.6 relative risk of death from oral and pharyngeal cancer compared to non-smokers ; the relative risk of death for smoking and drinking combined is 3.3(1–4) .

Other factors implicated are poor orodental hygiene, ill-fitting dentures and occupational exposure to wood dust, textile fibres, nickel and cadmium. Occupational exposure are associated with the development of tumours of the sino-nasal tract. Patients with occupational exposure to coal dust, steel dust, iron compounds and fumes have also shown an increased risk for developing hypopharynx cancer(2,3).

Human papilloma virus infection (HPV ; most commonly types 16 and 18) plays a role in the development of certain head and neck cancers, particularly those within the oropharynx among younger individuals without a history of tobacco or alcohol use. HPV-16 is found two and five times more likely in precancerous oral mucosa and cancer in the oral cavity respectively, compared to normal mucosa. In males, HPV-16 confers a threefold risk of developing oral cavity cancer. Studies have demonstrated that approximately 20% to 25% of patients with hypopharynx cancer are positive for HPV DNA(3,4).

Herpes simplex virus (HSV) has also been implicated in the aetiology of oral cavity cancer. There is a longstanding association between Epstein Barr virus and nasopharyngeal cancer.

PRE-MALIGNANT CONDITIONS

Reports examining risk factors for oral cancer in the young provide evidence that predisposition to genetic instability may be a causative factor in many younger patients who have never smoked or consumed alcohol.

Certain syndromes such as Plummer-Vinson have been associated with oral cavity and post cricoid region cancer. Disorder such as Xeroderma Pigmentosum, Ataxia telangiectasia, Bloom syndrome and Fanconi’s anaemia are a result of defective caretaker genes. Because such defects result in genetic instability, an increased incidence of second primary malignancies, including oral cancer has been reported.

The probability of developing a second metachronous malignancy at 5 years is approximately 22%. Persons with light-coloured skin or with prolonged exposure to sunlight (Ultraviolet radiation) are most prone to develop lip carcinoma(4,5).

Oral cancer is almost always preceded by some kind of precancerous lesions like erythroplakia, leucoplakia and oral sub mucosal fibrosis. Small hyperplastic leucoplakia lesions have a 30% to 40% spontaneous regression rate and less than a 5% risk of malignant transformation. While erythroleukoplakia and dysplastic leucoplakia lesions have a low rate

of spontaneous regression and have 30% to 40% long terms risk of developing oral cancer(1,4).

Tumour commonly spreads by direct route to the adjacent muscles and along fascial planes to involve the adjacent soft tissue structures. Bone and cartilage act as barriers to spread and the invasion commonly occurs only when the disease is fairly advanced. Perineural involvement is a feature of biologic aggressiveness in squamous cell carcinoma of head and neck.

A phenomenon unique to the mucosa of the oral cavity is "field cancerization". Patients with significant exposure to tobacco and alcohol often demonstrate "condemned mucosa". Such patients are prone to develop multiple synchronous or metachronous primary cancers in the mucosa at risk.

Patients with head and neck cancer have an increased risk for developing second primary cancer, both within the head and neck region and elsewhere (e.g., oesophageal and lung cancers), attributed to the field defects (skip lesion) associated with tobacco use.

LYMPHATIC DRAINAGE

Lymph node involvement depends upon various factors such as the histology, grade, site and size of the primary tumours. Bilateral involvement is higher in midline tumours such as nasopharynx, base of tongue etc., as compared to lateralized lesions. Recurrent lesions are at a higher risk of nodal involvement.

In cases where primary is not detected clinically or radiologically, proper lymph node examinations many times provide a clue to search for a primary site.

In lip cancer, lymphatic spread moves to the submental and submandibular lymph nodes and then to the jugular chain.

In floor of mouth approximately 30% of patients have clinically positive nodes and 4% have bilateral nodes at the time of first presentation. The reported incidence of conversion from N0 to N+ with no neck treatment varies from 20% to 35%. For T1 or superficial T2 lesions, the risk for occult metastasis is probably 10% to 15%. The first nodes involved are the level I and level II nodes; the midline submental nodes are bypassed. Because most lesions either approach or cross the midline, the risk for bilateral spread is fairly high.

In tongue the first-echelon nodes are the level II and level I-b nodes. The submental and level V lymph nodes are seldom involved. The incidence of occult disease is approximately 30%. The incidence of positive nodes increases with T stage. Patients with N1 or N2 ipsilateral nodes have a significant risk of developing node metastasis in the opposite neck.

In buccal mucosa the lymphatic spread is first to the level I and II nodes. The incidence of positive nodes at first presentation is 9% to 31%, and the risk of occult disease is 16%.

In lower gingiva the lymphatic spread is to the level I and II nodes. 18% to 52% have clinically positive nodes. Occult disease occurs in 17% to 19%.

Upper gingiva and hard palate have a risk for positive lymph nodes of 13% to 24% and the incidence of occult disease is 22%.

In retromolar trigone the first echelon lymphatics are the level I and II nodes. The incidence of clinically positive nodes on presentation is about 30% and the risk for occult disease is 15% to 25%.

Most of the patients of base of tongue cancer present with lymph node involvement. The first echelon nodes are in level II; the path of spread is then along the jugular chain to the mid jugular (level III) and lower jugular (level IV) nodes. The level Ib nodes may become involved if the tumour extends anteriorly into the oral tongue or if massive upper neck disease in present. The level V nodes are involved often enough to be included in treatment plans. Approximately 75% of patients will have clinically positive neck nodes at first presentation; 30% patients have bilateral nodes. The risk of occult disease in the clinically negative neck is probably 40% to 50%.

Retromolar trigone / anterior tonsillar pillar lesions have a lower risk of clinically positive lymph nodes (45%) compared with the tonsillar fossa (76%). The distribution for the retromolar trigone/anterior tonsillar pillar on the ipsilateral side is to the jugular and submandibular lymph nodes, with a very low risk for junction and spinal accessory lymph nodes. Contralateral spread is uncommon (5%) and is confined to the jugular chain. The risk of occult disease in the clinically negative neck (N0) is 10% to 15%. The incidence of positive nodes increases with T stage.

Tonsillar fossa lesions have a high risk of clinically positive lymph nodes (76%). The lymph node distribution for tonsillar fossa lesions on the ipsilateral side includes the jugular, spinal accessory and the submandibular lymph nodes. Contralateral spread occurs in only 11% of patients and is mainly to the jugular chain lymph nodes, but there is some risk for spinal accessory and submandibular involvement. The incidence of occult disease is probably 50% to 60%.

Soft palate carcinoma first involves the level II nodes and then the jugular chain. The level Ib and level V nodes are less commonly involved. Approximately 56% of patients will have clinically positive nodes at first presentation while 16% patients have bilateral nodal presentation.

The lymphatics of the pharyngeal walls terminate primarily in the jugular chain and secondarily in the level V nodes. The level II nodes are most often involved. Retropharyngeal lymph node involvement is frequent.

In pyriform sinus the drainage is mainly to the jugular chain with a relatively small proportion to the level V nodes. The level II nodes are most commonly involved, but level III involvement can occur without level II metastases. At first presentation 75% of patients have clinically positive nodes and at least 10% have bilateral nodes. There is no difference in the risk of lymph node metastases by T stage.

Hematogenous spread occurs late in the course of the disease and leads to distant metastasis. Lung is the most common site of involvement in 50% of metastatic cases.

CLINICAL PRESENTATION

Generally, patients present with painless non-healing ulcer, dysphagia, odynophagia, otalgia, hoarseness of voice, pain, weight loss and presence of unexplained neck mass. Physical examination should include scrutiny of all visible mucosal surfaces and palpation of floor of mouth, tongue and neck. The vermilion is the most common site of origin in Lip carcinoma. Most of the cases present as superficially ulcerated lesions with little or no bulk. Paraesthesia of the skin of the lip indicates nerve invasion. Palpation of the lip will reveal the extent of indurations.

Floor of the mouth – On physical examination, the earliest lesions appear as a red area, slightly elevated, with ill-defined borders and very little indurations. As the lesion enlarges the edges of the tumour become distinct elevated, with a central ulceration and indurations. Bimanual palpation will determine the extent of the indurations and the degree of fixation to the periosteum.

Tongue – Mild irritation of the tongue is the most frequent complaint. As ulceration develops, the pain worsens and is referred to the external ear canal. Extensive infiltration of the muscles of the tongue affects speech and deglutition and is associated with a foul odour. Extent of disease is determined by visual examination and palpation. The tongue protrudes incompletely and toward the side of the lesion as fixation develops.

Buccal mucosa: Small lesions produce the sensation of a lump that is felt with the tongue. Pain is minimal unless there is posterior extension to involve the lingual and dental nerves. Pain may be referred to the ear. Many patients present with trismus.

Gingiva and hard palate (Including Retromolar Trigone): The initial presentation of most of the patients is ill-fitting dentures, pain, loose teeth, or a non-healing ulcer. A history of inappropriate dental extractions or root canal therapy is common. Invasion into the mandible may involve the inferior dental nerve and produce a paraesthesia of the lower lip.

Retromolar trigone lesions have pain referred to the external auditory canal and preauricular area. Invasion of the pterygoid muscle produces trismus.

Base of the Tongue – Often, the earliest symptom is a mild sore throat. Because many early lesions are relatively silent, a level II neck mass is often the first sign. Difficulty in swallowing, a nasal voice quality and ear pain occurs as the lesion enlarges. Advanced lesions fix the tongue. Ulceration and necrosis result in foul breath.

Tonsillar Area: Early symptoms of Anterior Tonsillar Pillar carcinoma include sore throat; pain is referred to the ear as soon as ulceration takes place. As the lesion progresses, it may cause ill-fitting dentures, trismus, and temporal pain.

In Tonsillar Fossa carcinoma ipsilateral sore throat is common, detection by visual examination with a tongue depressor is sufficient for most lesions; however, a few cancers arise in the lower pole of the tonsil and are only visible by indirect examination.

Soft Palate carcinoma – The earliest symptom is usually a mild sore throat that is not well localized. Advanced lesions interfere with swallowing and may cause voice change. Regurgitation of food and liquid into the nasopharynx occurs with destruction or fixation of the soft palate. Lateral and superior to the nasopharynx and parapharyngeal space is associated with trismus, otitis media, temporal headache, and rarely cranial nerve involvement.

Hypopharynx malignancy – Tumours that are lateralized to the lateral pharyngeal wall or pyriform sinus produce a unilateral sore throat. Dysphagia, sensation of foreign body, ear pain, blood-streaked saliva, and voice change occurs later. Lesions of the apex of the pyriform sinus or post cricoid are produce pooling of secretions.

INVESTIGATION

Biopsy of all visible lesions is recommended. Patients with lymph node involvement should also undergo screening for distant metastasis and should also be examined by Fine Needle Aspiration Cytology.

X-ray soft tissue neck, X-ray mandible are useful in assessing the bone invasion and extent of disease. In some cases, CT scan of the required area is also advised to know the extent of the disease.

PATHOLOGY(5,6)

The vast majority of head and neck malignant neoplasm arise from the surface epithelium and are squamous cell carcinoma or one of its variants (more than 90%) are squamous cell carcinomas (keratinizing 75%, non-keratinizing 25%), including lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma(1,2,4,5).

Lymphomas and a wide variety of other malignant (minor salivary gland tumours, melanomas and soft tissue sarcomas) and benign neoplasms make up the remaining cases.

Squamous cell carcinoma is thought to arise from keratinizing or Malpighian epithelial cells. The hallmark of squamous cell carcinoma is the presence of keratin or “keratin pearls” on histologic evaluation. These are well formed desmosomes attachments and intracytoplasmic bundles of keratin tonofilaments. The term epidermoid can be substituted for squamous.

Morphologically, squamous cell carcinoma is variable and may appear as plaques, nodules or verrucae. These, in turn, may be scaly or ulcerated and white, red or brown.

Lymphoepithelioma is a carcinoma with a lymphoid stroma and occurs in the nasopharynx, tonsillar fossa, and base of tongue; it may also occur in the salivary glands.

In the spindle cell variant, found in 2% to 5% of upper aerodigestive tract malignancies, there is a component of spindle cells that resemble sarcoma intermixed with squamous cell

carcinoma. The disease is generally managed like other high-grade squamous cell cancers, but otherwise disregards the spindle cell element in treatment decisions.

Verrucous carcinoma is a low-grade squamous cell carcinoma found most often in the oral cavity, particularly on the gingival and buccal mucosa. It usually has an indolent growth pattern and is often associated with the chronic use of snuff of chewing tobacco. De novo verrucous carcinomas rarely develop lymph node metastases. Verrucous carcinoma has a more favourable prognosis because of infrequent nodal and distant metastasis.

Small cell neuroendocrine carcinoma occurs rarely throughout the head and neck region.

Lymphoma occurring in the upper aerodigestive tract almost always shows a diffuse non-Hodgkin's histological pattern. Nodular Non-Hodgkin's and Hodgkin's lymphoma rarely involve mucosal sites.

Basal cell carcinomas start on the skin of lip and may secondarily invade the vermilion.

Keratoacanthoma occurs on the skin of the lip and may be mistaken grossly and histologically for squamous cell carcinoma.

Epidermoid carcinoma may arise within the body of the mandible or maxilla either from odontogenic epithelium or from epithelium trapped during embryonic development. It is more frequent in the mandible than the maxilla and is most common in the molar regions. It must be distinguished from metastatic squamous cell carcinoma and ameloblastoma.

PROGNOSTIC AND PREDICTIVE FACTORS

The most significant prognostic factor for outcome in oral cavity carcinoma is the presence of cervical metastases. In patients with positive cervical metastases, the 5 year survival is reduced by approximately 50% compared to those without cervical metastases. The prognosis diminishes further when patients harbour multiple levels of nodal involvement or extracapsular extension. Tumour thickness and depth of invasion have been shown to confer a higher risk of regional metastases. Perineural invasion has been correlated with cervical lymph node metastasis, extracapsular extension, and diminished survival.

CONCLUSION

Overall both the palliative regimes (Christie and Quad shot) are very effective for palliation in such inoperable locally advanced head and neck cancer patients.The toxicity was more in Christie regime as compared to Quad shot arm. There was significant improvement in quality of life of patients in both the arms and the difference between the two was not statistically significant. In selected patients the Christie regime could be equally beneficial in treatment to achieve complete response.

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