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Review Article

# Tobacco use in oral cancer patients leading towards new horizon with increased risk of distant metastases and tumour recurrence: A review

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**Abstract**

Oral squamous cell carcinoma (OSCC) is one of the most common cancers in geographic regions in asia where betel quid (BQ) chewing is prevalent. Furthermore, history of alcohol drinking, lower level of nodal metastasis, advanced stage, poor cell differentiation, and treatment failures are independent predictors of poor disease-specific survival. Due to the high frequencies of loco regional recurrence and second primary cancer, we emphasize that aggressive surgical excision, adjuvant treatments according to clinicopathological prognostic factors and close surveillance are important to the survival of OSCC patients in an area with a high prevalence of betel quid chewing and tobacco smoking. OSCC is an extremely malignant neoplasm whose prognostic factors are multiple, complex and debilitating.

## Introduction

The term "oral cancer" includes all malignancies arising from the lips, oral cavity, oropharynx, nasopharynx, hypopharynx, and other ill-defined sites within the lip, oral cavity, and pharynx[1]. It has been estimated that more than 30,000 new cases of oral cancer are diagnosed in the United States each year, with approximately 8,000 associated deaths[2]. In parts of India and Asia where chewing tobacco or betel nut is very common, the incidence of oral cancer is 3 times higher than in the U.S. In several areas of India, oral cancer accounts for 40% of all cancer deaths. Overall 5-year survival is 52%, but it ranges from 79% for localized disease to almost 0% for recurrent lesions. Between 1983 and 1990, 53% percent of patients with cancer of the oral cavity and pharynx demonstrated regional or distant metastasis at the time of diagnosis[3]. Squamous cell carcinomas of the oral cavity are particularly suited for early diagnosis because sites of involvement are easily accessible for direct examination without special techniques; in addition, the disease is associated with clearly identifiable risk factors. Unfortunately, inspite of all the above evidences it is usually identified at the terminal stage or at a stage of recurrence.

Head and neck Squamous Cell Carcinomas (HNSCCs) are tumours with propensity mostly for loco regional spread[4]. The overall survival rate in patients with advanced head and neck cancer has not improved significantly, this has been partly because of the emergence of second primary cancers and the development of distant metastasis defined as cancer deposits below the clavicles. The incidence of distant metastases in head and neck SCC is relatively small in comparison to other malignancies. Distant metastases adversely impact survival and may significantly affect treatment planning[5]. The incidence of distant metastases is influenced by location of the primary tumour, initial T and N stage of the neoplasm, and the presence or absence of regional control above the clavicle. Primary tumours of advanced T stages in the hypopharynx, oropharynx and oral cavity are associated with the highest incidence of distant metastases. Patients with advanced nodal disease have a high incidence of distant metastases; pulmonary metastases are the most frequent in SCC, accounting for 66% of distant metastases. Other metastatic sites include bone (22%), liver (10%), skin, mediastinum and bone marrow[6]. Owing to paucity of the literature on this,

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no definite predisposing factor is identifiable. 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%[7].

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 earlystage diagnosis[8]. The tendency to develop multiple carcinomas in the upper aerodigestive region is known as "field cancerization"[9]. Prolonged and diffuse exposure to local carcinogens, particularly tobacco combined with alcohol, appears to increase the malignant transformation potential of exposed epithelial cells in the upper aerodigestive tract and lungs[10]. 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[10].

As clinical examinations and imaging studies are not very accurate, interest has been focused on the prediction of the risk of neck metastases[11]. Many studies have been published attempting to predict this risk. Leemans et al.[12] found that patients who developed pathologically positive lymph nodes in the neck were at double the risk (13.6%) for distant metastatic disease relative to patients free of lymph node metastases (6.9%). Kotwall et al.[13] reviewed 832 HNSCC patients and found that the overall incidence of distant metastasis was highest in tumors of the hypopharynx (60%), followed by the base of the tongue (53%), and anterior tongue (50%). In decreasing incidence, the lung, mediastinal nodes, liver, and bone, were the most common sites of distant metastatic spread. Other authors[14,15] found a similar pattern of distant metastases. As the control of local regional disease improves, the incidence of distant metastatic disease appears to be rising. Shear et al[16], in almost 900 patients, identified size, site and differentiation grade as predictive factors. However, they defined minor tumours, i.e, < 3 cm, and a diameter with a high probability of metastases. Yamamoto et al.[17] found that type of tumour invasion was the most significant prognostic factor for the presence of lymph node metastases, Okamoto et al.[18] found that keratinization, number of mitoses, in addition to clinical factors were reliable to predict node metastases, Borges et al.[19] found perineural invasion and tumour thickness to be useful predictive variables while Martinez- Gimeno et al.[20] found microvascular invasion and tumoural inter-phase as predictive factors, besides other mentioned variables. However, many of these features can only be assessed in the final pathologic specimen[21]; therefore its practical application is limited. Moreover, most of these studies have not been widely validated in other tumour localizations, unlike those of original studies or in other populations, thus reducing its generalization.

The ability to accurately detect metastatic disease is essential in treatment planning[22] since metastases may significantly affect survival. While the majority of macrometastasis can be accurately detected with the combination of preoperative clinical examination and computed tomography (CT) or magnetic resonance imaging (MRI), the detection of micrometastasis remains elusive[23]. The impressive resolution of contemporary imaging techniques such as MR scanning and high resolution CT have enabled a detailed view of the head and neck region but the greatest challenge has been in correctly interpreting these findings[24, 25].

Nobody can deny the important effect of therapeutic neck dissection in the prognosis of head and neck cancer patients. However, the role of elective neck dissection has been a matter of discussion, since its introduction as routine practice[26]. Most frequent sites of metastasis from cancer of the oral cavity include lung, bone, liver, adrenal, heart, and kidney[27]. An improved understanding of head and neck cancer and the advent of newer surgical techniques have further improved control of cancer above the clavicles. In an effort to effect long-term survival rates, primary surgical therapy has thus been complemented by a series of multi-modality trials. Studies have shown that chemotherapy used concurrently with radiotherapy can improve survival. This is largely a result of the addition of agents such as cisplatin, which appears to sensitize tumors cells to radiation thereby increasing the tumorocidal activity[28]. Currently, a combination of cisplatin and flurouracil given continuously is the mainstay of systemic therapy and such multimodality neoadjuvant therapy has decreased local regional failure; however, there may be an increase in distant failure[29,30]. The change in the pattern of failure in HNSCC demonstrates that while the addition of multi-modality therapy has significantly positively improved local regional control of oral cancer, the challenge for the future lies in preventing distant metastatic disease.

In conclusion, therefore, it is believed that the foregoing pathologic evidence must be deemed to favor the performance of radical excision of the lymphatic territory, and the patient should be kept on continous observation so as to prevent dissemination of squamous cell carcinoma. Because of its easily-identifiable risk factors, and because premalignant lesions, such as leukoplakia,

are often present in those who are destined to develop OCSCC, many disease prevention strategies have been evaluated in at-risk individuals. Prevention through the use of systemic medications, or chemoprevention, has been an extensively-studied strategy and continues to hold promise as a way of diminishing the morbidity and mortality associated with this disease.

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