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Overview

# An Overview of the Role of the Pathologist in the Management of Oral and Maxillofacial Cancer- A Dental Perspective

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## Abstract

The Royal College of Pathologists, UK, defines the discipline of oral and maxillofacial pathology as "a clinical specialty, undertaken by laboratory-based dentists, that is concerned with the diagnosis and assessment of diseases of the oral and maxillofacial region" [1]. Pathologists investigate the causes, progression and effects of diseases and it is a specialty where research meets practice. Interpretation of tissue biopsies and surgical resection material is essential in managing oral and maxillofacial cancer and the reports written by pathologists are vital in the diagnosis and treatment of patients. Research undertaken by pathologist allows the refinement of current practices and guidelines as well as the development of novel treatments. Identification of risk factors allows appropriate prevention plans and upstream interventions to be implemented, thus having a significant impact on public health initiatives. The objective of this overview is to outline the role of the pathologist in the management of oral and maxillofacial cancer, and their invaluable expertise as part of the multi- disciplinary team.

**Keywords:** The Management of Oral and Maxillofacial Cancer; Dental Perspective

## Overview of the Management of Oral and Maxillofacial Cancer

Head and neck cancers have a worryingly increasing incidence and are the sixth most common cancer worldwide, with the majority of oral cancers being squamous cell carcinomas [2]. With a 5-year survival as low as 15%, early diagnosis is the first step to the successful management of oral and maxillofacial cancers, improving surgical results and prognosis [3,4].

It is essential to identify high risk patients during the history taking. Thorough inspection of the oral cavity using a strong light and dental mirror should be routine, and general dental practitioners should check for red and white patches, ulcers and swellings [2]. The texture and mobility of the tongue and any tooth mobility should also be noted. Palpation is vital to determine firmness and tenderness of any swellings which may be present. Suspect lesions, which look abnormal, require a biopsy and further investigations, such as imaging. Orthopantograms are often used as an essential baseline radiograph, with CT and MRI scans being used to complement pathological results in order to determine the extent of invasion and to stage tumours, as well as screening for metastasis and lymph node spread [3,5].

Biopsies allow a closer look at the histopathology of the lesion and confirm the presence or absence of features of malignancy or premalignancy. Biopsies give an idea of tumour thickness, the degree of differentiation, vascular, lymphatic and neural permeation and the pattern of invasion, all of which form part of the feature set that enables the pathologist to evaluate the degree of aggressiveness of a tumour. These biopsies can be an incisional or excisional biopsy, or fine needle aspiration of enlarged lymph nodes, under local or general anaesthetic. Haematological investigations are essential to determine the general health of the patient prior to what are often complex and major surgical interventions [3].

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## Role of the Pathologist: Initial Biopsy and Diagnosis

A diagnosis should take into consideration the patient's presenting condition, the signs and symptoms, as well as reflecting the underlying pathology. The results of the investigations undertaken will help to shape the diagnosis.

In order to confirm the presence or absence of a tumour, an incisional biopsy must be taken. The sample is then treated with a fixative solution to prevent autolysis, bacterial and fungal colonisation and sent to the pathologist for examination under electron light microscopy [4].

Cytopathology is the microscopic study of cell samples which are obtained either by fine needle aspiration or exfoliative cytology, such as smears. Once the sample is fixed and stained by the pathologist, the slide is interpreted and evidence of cellular atypia is noted, although the original architecture of the tissue may be lost [4].

Liquid based cytology is a development from conventional cytology and has been shown to have higher levels of sensitivity and specificity. A suspension is obtained which is then fixed in preservative fluid and placed in a centrifuge, resulting in a thin, high cellular zone on the glass slide which can then be analysed by the pathologist. This has resulted in fewer artefacts and even cell distribution, and therefore has higher diagnostic value in comparison to conventional cytology [4].

Brush biopsy makes use of a specialised oral brush (CD-x brush) which is capable of penetrating the thickness of the oral epithelium, as far as the basal cells, to collect a representative sample of the lesion. This sample can then be analysed by visual histopathological investigation or by image analysis [4]. Computer-assisted analysis of brush biopsy samples has been shown to be a highly specific and sensitive, non-invasive diagnostic aid [5]. Brush biopsy can be used to evaluate lesions which are benign-appearing. Lesions showing signs and symptoms of malignancy require immediate referral for an incisional biopsy [6].

The incisional biopsy and the histo-pathological assessment are the current gold standard and they remain the most accurate and definitive method.

## Role of the Pathologist: Staging and Prognostic Indicators

Staging of cancer provides a means of classification which defines the extent of anatomical spread and is vital for estimating the prognosis of the case as well as determining the management and allows the oncologist to give the patient a 5-year survival prediction based on the outcomes of previously staged cohorts. It also allows for comparison of evidence- based therapies and treatment outcomes globally. Staging is determined by the clinical examination undertaken and supplemented by histological grading, radiographic findings (CT, MRI and ultrasound) and, increasingly, positron emission tomography (PET) [7].

The TNM classification system has been widely used since 1987 and has continued to be modified to reflect the advancing developments in diagnostic assessments. The TNM system takes into account the size of the tumour, lymph node involvement and metastasis [7].

Pathological staging, undertaken by the pathologist, is routinely performed and represented by pTNM. It provides further information which can be used to estimate prognosis. However, it is important to note that pathological T categorisation can underestimate the size of the tumour due to mucosal marginal shrinkage (up to 30%) following resection [7].

Histological grading, although not used to determine the TNM stage of a neoplasm, is used to determine its degree of differentiation: well, moderately, poorly differentiated and undifferentiated. The degree of dysplasia should also be noted and pre-malignant lesions can be identified. This is essential as it allows clinicians to identify patients with a high risk of malignancy and can determine the follow up interval for patients [8]. Further characteristics should be noted such as exophytic, ulcerated and endophytic. The tumour thickness, depth of invasion and nodal metastasis to the upper or lower neck should also be noted (7). The number of lymph nodes involved shows a strong dose-response correlation to distant metastasis [9].

Tumour thickness has recently been found to be an important prognostic factor in head and neck cancers and should be considered when managing patients with oral and maxillofacial cancer. Increased tumour thickness is associated with nodal metastasis and a poorer prognosis. Although the exact pathophysiology is unknown, lymphatic vessels are abundant in the sub-mucosa of the tongue. Deeply infiltrating tumours also exhibit more invasive behaviour, resulting in lymph node metastasis [10]. Tumours with an increased thickness and depth of margins are more difficult to assess and palpate and therefore have an increased incidence of inadequate margins [10]. Research has indicated that tumours with a depth exceeding 5mm have a 64.7% rate of metastasis, whereas tumours with a depth less than 5mm have only a 5.9% rate of metastasis, although exact figures vary between published studies [9]. These pathological findings are of great significance in the management of oral and maxillofacial cancer patients.

## Role of the Pathologist: Resected Tumour Analysis and Further Treatment

Treatment depends on the stage of the disease and the health of the patient. This can include surgery, chemotherapy and radiotherapy, as well as other options such as immunotherapy and gene therapy. Surgery is often indicated to resect the tumour, along with a neck dissection to remove the lymph nodes. The area is then reconstructed and the specimen sent to the pathologist for analysis.

Following resection, it is essential to identify and report the absence or presence of residual tumour. This is further classified into microscopic or macroscopic residual tumour. The presence of vascular permeation and perineural invasion should also be noted. Depending on the histological findings, patients may or may not require further radiotherapy or chemotherapy to target suspected residual tumours. Indications for post-operative irradiation include one or more of the following pathological findings: invasion of the tumour into the soft tissues of the neck, bone or perineural invasion, vascular space invasion, carcinoma in situ or dysplasia, close or positive resection margins and multicentricity (scattered islands of tumour which makes resection margins uncertain). Positive lymph nodal or extracapsular metastasis is also an indication of post-operative radiation therapy [7].

Features which are indicative of high risks of recurrence include: extracapsular spread, positive or inadequate resection margins, nodal involvement and perineural or vascular spread [7]. Positive or inadequate resection margins are the most important risk factor for local recurrence [10]. Positive resection margins have a local recurrence range from 64-84%. 5-year survival rate decreased from 69% for clear margins, down to 38% for involved margins [9]. These pathological findings therefore have very significant effects on the post-operative treatment indicated.

## Role of the Pathologist: Identifying Risk Factors and Prevention

Oral and maxillofacial cancer is a multifactorial disease, with a large environmental component and thus addressing risk factors and educating patients is essential. Research undertaken by pathologists has been paramount in identifying modifiable risk factors such as betel nut chewing and smoking and alcohol consumption, which account for approximately 90% of head and neck squamous cell carcinomas [7].

Oral cavity cancer has been associated with a family history of head and neck cancers, with some studies suggesting an increase in risk with an increase in the number of first-degree relatives affected [11]. Furthermore, polymorphic genes which are involved in the metabolism of tobacco and alcohol and DNA repair and maintenance have been associated with increased risk. Familial clustering has also been attributed to shared behavioral risk factors, namely alcohol and tobacco use [12,13]. Thus, it is paramount to identify high risk groups during the history taking, such as patients with behavioral risk factors and previous family histories of head and neck cancer. This can facilitate targeted patient screening and prevention plans.

Research has linked the Epstien-Barr Virus to nasopharyngeal carcinomas [7]. Furthermore, the Human Papilloma Virus (HPV) has been linked to oropharyngeal cancer. Identification of these modifiable risk factors by pathologists allows appropriate prevention plans and upstream interventions to be implemented, thus having a significant impact on public health initiatives.

HPV has been detected with a prevalence as high as 35% in oropharyngeal cancers, with HPV- 16 accounting for the majority of cases. HPV-18 is less commonly detected (up to 13%) [14]. HPV produces proteins, E6 and E7, which are able to bind to vital cell cycle regulators with subsequent altered gene expression. These include p53 and pRboncosuppressors, which are degraded or blocked. This is associated with genomic instability and results in apoptotic impairment and uncontrolled DNA replication, thus favouring tumorigenesis[4]. Since the introduction of the HPV vaccine in the routine national immunisation schedule in 2008, HPV- 16/18 infections have reduced by 86% in 16 to 21-year-old women. Though the aim of the program was to reduce morbidity and mortality associated with cervical cancer, some impact on oral and maxillofacial cancer may be seen [15,16].

## Conclusion

The pathologist plays a key role throughout the management of patients with oral and maxillofacial cancer, from confirming the initial diagnosis to guiding the multidisciplinary team through the treatment, post-operative management and rehabilitation of patients. The role of the pathologist extends beyond the clinical environment to laboratory-based research, thus contributing to the refinement of current practices and guidelines as well as the development of novel treatments. Advances in research undertaken by pathologists, allows the continued improvement in the diagnosis of cancer, such as the development of "deep learning", and the identification of risk factors may help to outline public health policies [17]. Early referral by a general dental practitioner has significant implications on patients and we must not forget the role of pathologists in the training and education of undergraduate dental students who, once qualified, are the gateway to specialist care. There is no doubt that pathologists are vital in every step in the management of oral and maxillofacial cancer.

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