1 Introduction

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General introduction

This book deals with the diagnosis and management of oral precancer, a relatively rare but important and fascinating range of potentially malignant disorders. Oral precancer comprises both discrete, readily identifiable, oral mucosal lesions such as leukoplakia or erythroplakia and also more widespread or systemic conditions that may affect the lining of the oral cavity, and whose clinical presence may precede the development of invasive oral cancer.

The concept of a recognisable precancer state has arisen following a number of salient clinicopathological observations that include the observed transformation of pre-existing clinical lesions into invasive cancers during patient follow up, the recognition that leukoplakic or erythroplakic lesions are often found to coexist with oral squamous cell carcinoma, and the realisation that numerous histopathological and biomolecular tissue changes are actually common to both cancers and their potentially malignant counterparts [1].

The identification of a potentially malignant disorder in an individual patient, however, does not mean that an inevitable malignant transformation will take place because many of these oral lesions do not progress over time and some may even resolve or regress spontaneously. Nonetheless, statistically, such patients are known to remain at an increased risk of developing mouth cancer.

Cancer of the mouth, which is primarily a squamous cell carcinoma arising from the oral mucosa lining, is the sixth most common cancer worldwide and is traditionally seen most frequently in older people [2]. It is a lethal and deforming disease due not only to local tumour invasion, oro-facial tissue destruction and cervical lymph node metastasis, but also because of widespread blood-borne tumour dissemination affecting particularly the lungs and the liver. Worldwide, 5-year survival rates for oral cancers are around 50%, with prognosis worsening with advanced disease and late presentation [2].

Figure 1.1 shows a typical clinical presentation of a large, invasive, squamous cell carcinoma arising posteriorly in the retromolar and palatoglossal regions of the oral cavity (Figure 1.1A), together with an accompanying computed tomography (CT) scan demonstrating extensive tumour spread to the draining cervical lymph nodes (Figure 1.1B). As is often the case, the patient presented late on in the progress of the cancer disease, having been relatively asymptomatic for many months. Of interest in this case are the surrounding mucosal precancer changes of leukoplakia (clearly visible in Figure 1.1A) that may well have preceded the malignancy.

So, despite real advances in diagnosis and management, nearly half of all patients diagnosed with an oral malignancy will die as a direct consequence of their disease. Whilst the number of patients suffering uncontrolled cancer disease at primary sites in the head and neck has reduced in recent years due to improvements in modern treatment protocols, up to a quarter of patients may then go on to develop multiple cancers in the upper aerodigestive tract either synchronously (at the same time) or metachronously (separated by time).

The presentation of multiple lesions in an individual patient is an illustration of widespread epithelial cell instability, which is a hallmark of head and neck squamous carcinoma, and is classically referred to as 'field change' cancerisation. This was the term first proposed by Slaughter in 1953, who proposed that oral cancers developed in multifocal areas of precancer change as a result of widespread abnormalities in the aerodigestive tract epithelium [3]. More recent observations suggest that the risk of multiple primary cancer development is probably highest in younger patients and particularly in those who continue to smoke and consume alcohol following treatment interventions [2].
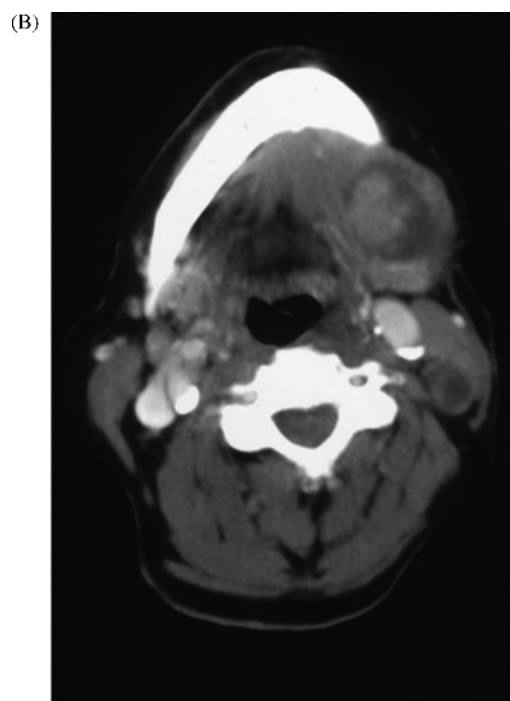
(A)

(B)

Figure 1.1 (A) Late presenting invasive squamous cell carcinoma (SCC) arising in the retromolar/palatoglossal region. There is surrounding palatal mucosal leukoplakia, precancerous mucosal disease, which probably preceded the malignancy. (B) CT scan illustrating extensive necrotic cervical lymph node tumour spread from retromolar SCC.

Aetiological factors causing malignant transformation of oral stratified squamous epithelium most commonly involve the excessive consumption of tobacco products and alcohol misuse, ultimately presenting clinically as symptomatic tumours in a predominantly elderly male population. In recent years, however, there has been a definite rise in the incidence of oral cancer with higher rates appearing in younger and in female patients. Indeed, no other cancer site has shown such a rapid rise in incidence over the last 25 years and some researchers predict an epidemic of oral cancer occurring during the first half of the 21st century.

Of course, many people who smoke and drink do not develop oral cancer and similarly in a number of other studies it has also been observed that many oral cancer patients may not have been overexposed to tobacco or alcohol at all, so it remains imperative to identify and determine the significance of other potential risk factors. Genetic predisposition to DNA mutation in oral epithelial cells, poor nutrition characterised by a low intake of fresh fruit and vegetables,

ageing, low socioeconomic status, poor oral health and infection have all now been implicated in oral carcinogenesis [4].

More recently, a significant role for human papillomavirus (HPV) infection (especially subtype 16) has been postulated in oral carcinogenesis, although this seems to be particularly associated with a rise in oropharyngeal, tonsil and tongue base cancer. This seems to affect young patients in particular, often presenting with extensive cervical lymph node metastases and may be associated with a sexually transmitted aetiology. HPV-associated head and neck cancer may thus represent a distinct disease entity of its own [5,6].

Although HPV DNA has been identified in samples of leukoplakia, the precise role of HPV in the initiation and progression of oral potentially malignant disease remains somewhat obscure and is currently the subject of a number of ongoing investigations.

The 'progression model' for oral carcinogenesis suggests that, following genetic mutation, various phenotypic epithelial tissue disorganisation and dysmaturation changes occur, which if allowed to progress ultimately lead to carcinoma development and invasive disease. Such disorganised features preceding cancer are identifiable at the microscopic level and are described collectively as epithelial dysplasia.

Dysplasia is thus a crucially important histopathological entity that delineates the many structural changes that affect both individual epithelial cells and also the overall integrity of epithelial tissue hierarchy present in potentially malignant lesions. An estimate of the degree of dysplastic change present in the epithelium is made following lesion biopsy and is classified into mild, moderate or severe categories. The more severe the dysplasia, the higher the risk there is for malignant change, although there is a strong subjective element in dysplasia grading and both biopsy sampling errors and possible fluctuations in severity with time may all confound the accuracy of diagnosis.

It has been recognised for many years that a spectrum of distinct oral mucosal abnormalities which may accompany these dysplastic changes can be identified clinically and characterised, albeit somewhat non-specifically, during an oral examination. Figure 1.2 illustrates both the clinical appearance of a diffuse, non-homogenous leukoplakic lesion arising on the ventrolateral tongue mucosa (Figure 1.2A), and its corresponding dysplastic appearance under the microscope (Figure 1.2B).

Fortunately, with the application of a good light source, the oral cavity is easily visualised directly during clinical examination and, indeed, is inspected regularly by dental practitioners during routine dental care. There is, thus, potential for both early diagnosis and therapeutic intervention during this clinically identifiable 'oral precancer window'.

In order to improve survival rates for oral cancer we must therefore avail ourselves of this 'window' to identify precancer change at the earliest possible stage and attempt to intervene to halt the disease process. Unfortunately, there is considerable public ignorance regarding oral cancer, the patient population that is probably most at risk rarely attends for regular oral examination, and general population screening programmes for oral cancer have been found to be fundamentally flawed as a health care intervention.

On the other hand, the identification and targeting of individuals at high risk of developing cancer may provide a more practical solution. For example, it has been shown that many irregular patient attendees who only ever visit dental access centres for emergency treatments are often those with the lifestyle habits that render them most vulnerable to oral cancer. Thus focused oral cancer
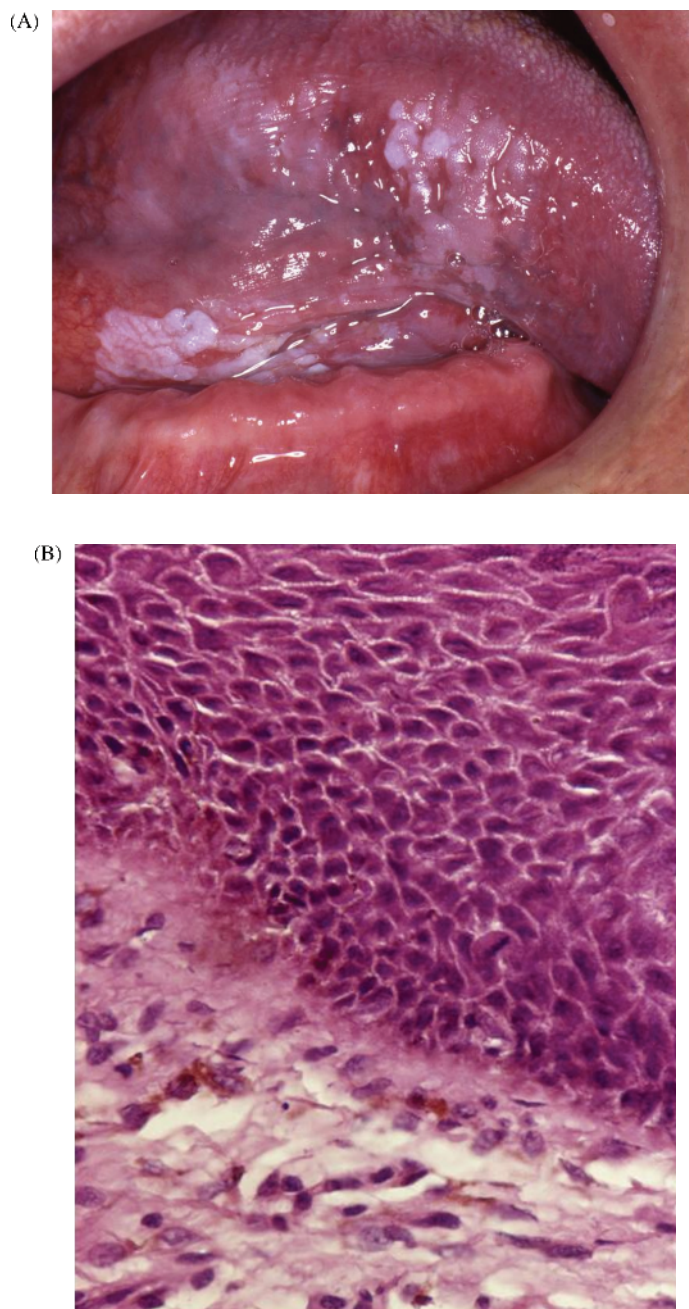
(A)

(B)

Figure 1.2 (A) Clinical appearance of non-homogenous leukoplakia arising on the ventrolateral tongue mucosa. (B) Accompanying microscopic appearance of the dysplastic tongue epithelium.

screening and health care information may be most effectively targeted to this type of at-risk population group [7].

The currently available scientific literature is also unable to resolve the fundamental question as to whether early diagnosis and treatment of precancerous conditions will ultimately prevent the development of malignant disease. It is not, however, an unreasonable hypothesis and provides a proactive interventional technique that will be discussed in some detail later in this book.

A further problem to consider is that, having identified potentially malignant disorders, we are unable to predict the clinical behaviour of any individual patient or precancer lesion. This common clinical dilemma and its unfortunate consequences are illustrated in Figure 1.3.

(A)

(B)

Figure 1.3 (A) Multifocal leukoplakia arising in the anterior floor of the mouth mucosa. How can we predict whether this precancer lesion will progress? (B) In a different patient, an established squamous cell carcinoma presents in the anterior floor of the mouth. How do we know whether this tumour was preceded by a clinically detectable precursor lesion?

There are also no clear management guidelines or agreed treatment strategies for oral precancer cases. The lack of meaningful, randomised controlled clinical trials has resulted in a variety of proposed treatments that are essentially based on clinicians' preferences and experience.

In order to try to address some of these longstanding dilemmas, this book will attempt to concisely review current concepts of oral precancer disease, epithelial cell biology and oral carcinogenesis and its related pathology to try to improve our understanding of this complex and fascinating oral oncology pathway. Utilising a number of longitudinal patient cohort studies, we will also outline our preferred diagnosis and management strategy for potentially malignant disorders and explain our rationale for clinical decision making and treatment selection. It is hoped that in this way we can make a significant contribution to the ongoing scientific debate surrounding oral precancer disease and also help to improve the clinical care and outlook for our many patients that present with these important, potentially malignant and life-threatening oral conditions.

Epidemiology

Studies on the causation, distribution and control of disease form the backbone of epidemiological research. The majority of studies that relate to oral

carcinogenesis, however, have tended to focus upon oral cancer rather than potentially malignant disease. However, it is not unreasonable to suppose that the disease process remains consistent for both the development of oral precancer and then its subsequent transformation to invasive carcinoma.

Oral squamous cell carcinoma does, of course, pose a major public health problem worldwide, with an annual estimated incidence of around 275 000 cases of intra-oral cancer. There is a marked variation in global incidence that probably corresponds to varying risk factor behaviours, especially those relating to tobacco smoking or betel-chewing habits and excessive alcohol consumption [2].

The highest rates of oral cancer are seen in Southeast Asia, tropical South America and in parts of Central and Eastern Europe, particularly northern France and Hungary [8]. In the UK there are approximately 5000 new cases of oral cancer seen each year, which actually exceeds the numbers of new cervical cancer, ovarian cancer or leukaemia cases [2]. Even within the UK there are significant regional variations in disease presentation, with Scotland and northern England particularly affected by high levels of oral cancer.

In most countries oral cancer tends to be seen more commonly in men and increases in frequency both with advancing age and with low socioeconomic status, although more recent studies in the European Union and the United States suggest that the disease is increasingly presenting in young professional adults and especially in females [2]. As previously discussed, however, this latter observation may apply more to HPV-related head and neck disease.

It is recognised that cancers may arise from longstanding potentially malignant disorders but whether this is true for all oral cancers is unknown and, as a general observation, potentially malignant disorders affecting the oral cavity are considered to be relatively rare. As there are very few meaningful studies in the literature, it remains difficult to be precise regarding accurate estimates of the true incidence of precancer disease, which by definition refers to the number of new oral potentially malignant lesions arising each year.

Prevalence, on the other hand, is the epidemiological measure of how common a disorder is in a specified population at a particular time. A number of such studies have been carried out to characterise the profile of oral precancer disease. Johnson, for example, quotes an overall precancer prevalence figure of 4.2% for a Sri Lankan population [8], whilst Napier and Speight suggest a worldwide prevalence rate of between 1% and 5% for all potentially malignant disorders [9].

Prevalence of oral leukoplakia

Leukoplakia is recognised worldwide as the commonest oral potentially malignant disorder and has therefore received most study. Quoted prevalence figures for intra-oral leukoplakia, however, vary considerably from less than 0.2% to around 27% and also demonstrate distinct differences between countries. Particularly high prevalence figures, for example, are seen in the Indian subcontinent, Taiwan and New Guinea, which are the regions in which tobacco-chewing habits are especially common, whereas much lower estimates of only 1–2% are proposed for Western populations [8,10].

Petti attempted to estimate a global prevalence figure for leukoplakia by reviewing 23 studies from 17 different countries published between 1986 and 2002 and, by applying a variety of epidemiological analyses, calculated

pooled estimates of between 1.5% and 2.6% dependent upon methodology [10]. Unfortunately, there are fundamental problems with epidemiological studies such as these. Not only are they usually very expensive and time-consuming to carry out, but it is also difficult to ensure that a truly representative sample of the desired population has been studied. It may also be extremely difficult to ensure that a consistent and reliable diagnostic method is applied to both the recognition and recording of oral lesions and the findings from one population are not necessarily applicable to the wider population at large [10].

Prevalence figures reported for leukoplakic lesions will also vary significantly between hospital/specialist clinic-based studies where much higher levels of disease from a referred patient base are likely to be seen, compared with data obtained from screening a more generalised population in a community-based setting. Such epidemiological studies rarely include any form of histopathological confirmation of their clinical diagnoses, nor do they reliably comment on the presence or absence of dysplasia in individual lesions.

A further complication occurs when attempts are then made to estimate the proportion of oral cancer cases attributable to malignant transformation of leukoplakia. Whilst figures as high as 17–35% have been quoted for the fraction of oral cancers that are likely to arise from pre-existing leukoplakias [10], these percentages vary significantly between different countries and between study populations and provide virtually no help at all in individual patient counselling and prognosis.

Prevalence of oral erythroplakia

Erythroplakia is known to be much rarer than leukoplakia and there are even fewer data available relating to prevalence figures. Johnson, however, does quote rates of between 0.02% and 0.1% in an Indian subcontinent population [8]. Such lack of information is unfortunate because most studies suggest that eryrthroplakic lesions are at a much higher risk of malignant transformation than leukoplakia and may actually be the most common early clinical sign of an invasive carcinoma; they are therefore probably of much more relevance in the study of oral carcinogenesis.

Although detailed information regarding the incidence and prevalence of potentially malignant disorders remains limited, the recognition of the principal aetiological agents, the types of risk factor behaviour and the subpopulations most at risk of disease development is integral to the proper design and effective delivery of clinical management strategies. Central to any interventional management protocol, of course, must be the prevention of disease.

Prevention

The prevention of oral cancer is of fundamental importance in view of the serious morbidity and mortality consequent upon fully established oral malignant disease. There are, of course, a number of classic tiers of preventive medicine, all of which are relevant to our discussions on the diagnosis and management of oral potentially malignant disorders.

The aim of *primary* prevention is to entirely avoid the development of disease. It thus concentrates on eliminating the principal risk factors of disease and

promoting protective behaviour within a community or population. For oral cancer, this clearly includes limiting the use of tobacco, discouraging chewing habits, avoiding excessive alcohol consumption and improving diet. Whilst this seems an eminently sensible approach, especially for patients presenting with precancer lesions, we shall see just how difficult it can be in practice to influence individual patient risk factor behaviour.

Secondary prevention refers to the detection of premalignant or early malignant disease at a stage at which intervention may lead either to an outright cure or to a significant reduction in morbidity and mortality. This approach is highly pertinent to the management of oral potentially malignant disease and will be discussed in detail later in this book.

Finally, the role of *tertiary* prevention is to ultimately reduce the risk of disease recurrence following the treatment of an established condition and to then minimise the risk of disease-related complications. This also has an important place in the overall management strategy for oral precancer patients and is especially relevant during long-term patient follow up after treatment.

We will see in subsequent chapters of this book exactly how, in the context of both the initial diagnosis and then the interventional management of oral potentially malignant disorders, each of these preventive techniques have an important part to play.

Treatment strategies

For the fully established oral squamous cell carcinoma, treatment usually requires surgical ablation of the primary tumour together with a neck dissection to eliminate cervical lymph node metastases, often combined with adjuvant postoperative radiotherapy to the head and neck. HPV-positive disease, on the other hand, often appears to respond particularly well to chemoradiotherapy treatment modalities alone [6].

It is evident, however, that the application of such aggressive treatment modalities can result in significant morbidity to patients, especially in relation to form and function of the mouth and face. Any therapeutic approach that can thus intervene to diagnose oral cancer at a premalignant phase or even at an early invasive stage and institute curative treatment is to be embraced and encouraged.

Oral potentially malignant disorders are, by definition, mucosal conditions only and thus do not require treatments that damage the integrity of important underlying oro-facial structures. This is clearly a significant advantage when compared to the extensive disruption resulting from anti-cancer therapies. In Chapter 8 of this book we will discuss in some detail the treatment methods that have been applied to try to treat oral premalignant lesions and we will outline our preferred interventional management strategy.

Terminology

The natural history of potentially malignant disorders is, unfortunately, not only highly inconsistent but also unpredictable. Both the terminology applied and the definitions used to describe clinical conditions vary considerably in the oral precancer literature, often compounded by confusion between clinical and histological diagnosis. Review and clarification of the terms used in this book

are important at the outset and thus the following definitions are formalised here for the reader:

- *Oral cancer (or mouth cancer)*, which strictly includes any malignant neoplasm arising within the oral cavity, is the term used primarily to describe squamous cell carcinoma arising from the oral mucosal lining (OSCC).

- *Oral carcinogenesis* is the multistep process, derived from an accumulation of cellular changes induced by carcinogens, that transforms normal epithelium into invasive neoplasms.

- *Oral precancer* is an overall term describing a range of potentially malignant disorders, both discrete oral mucosal lesions and more generalised conditions, that affect the lining of the oral cavity, imply underlying epithelial tissue disorganisation and dysmaturation, and whose clinical presence may precede the development of oral cancer.

- *Oral precancerous or premalignant lesions*: Traditionally, this 1978 World Health Organisation (WHO) term describes discrete areas of morphologically altered tissue in which there is an increased incidence of cancer compared with apparently normal-looking mucosa. These lesions comprise leukoplakia, erythroplakia and erytholeukoplakia (or speckled leukoplakia).

- *Leukoplakia* is thus a clinical term describing a white patch on the oral mucosa that cannot be wiped off (distinguishing it from pseudomembranous candidosis), and that cannot be characterised clinically or histopathologically as any other definable lesion. Such diagnosis by 'exclusion' implies an underlying epithelial disorder and an increased, but unquantifiable, risk of cancer development.

- *Erythroplakia*, similarly, is defined as a fiery red patch on the oral mucosa that cannot be characterised clinically or pathologically as any other definable disease and which has an enhanced potential for malignant transformation and cancer development. (The older term erythroplasia is rarely used nowadays.)

- *Erythroleukoplakia* (or speckled leukoplakia) is the term given to mixed red and white mucosal patches which display an increased risk of cancer development.

- *Oral precancerous or premalignant conditions*: This 1978 WHO term describes more generalised states in which there is an increased risk of cancer development. It includes a variety of medical disorders such as immunosuppression, iron deficiency anaemia, dermatological disease and chronic infection.

- *Potentially malignant disorders (PMDs)*: This is now the preferred 2005 WHO term, replacing the terms 'precancerous' or 'premalignant' to emphasise a 'potential' (but by no means certain) risk of malignant transformation. It abandons the distinction between discrete lesions and more generalised conditions.

- *Dysplasia* is a histopathological diagnosis that describes a varying presence of epithelial tissue disorganisation, dysmaturation and disturbed cell

proliferation. Graded by extent into mild, moderate or severe categories, the most disordered tissue is felt to display the highest risk of malignant transformation.

- *Oral epithelial dysplasia (OED)* is a diagnostic term often applied in the published literature to describe the above histopathological changes seen in oral potentially malignant disorders.

- *Oral precursor lesion* is a relatively non-specific clinical term given to any identifiable pre-existing lesion in which subsequent malignant transformation occurs. Such lesions do not always fall into recognisable potentially malignant categories, nor do they necessarily exhibit dysplasia.

- *Malignant transformation* is the term used to describe same-site transformation of a previously identified precancer into an invasive squamous cell carcinoma.

- *Oral squamous cell carcinoma development* is a term used when patients with pre-existing or previously treated precancer lesions develop invasive carcinoma at new oral sites, distinct from their original lesions.

- *Persistent disease* describes precancer lesions that persist at the same site following treatment.

- *Recurrent disease* describes precancer lesions that reappear at the same site following treatment which had apparently brought about clinical resolution.

- *Further disease* is the term used to describe the development of additional precancer lesions at new, distinct sites in the oral cavity, sometimes appearing after successful treatment of pre-existing lesions.

- *Clinical resolution* refers to the successful removal or regression of a previously identifiable precancer lesion resulting in clinically normal-looking oral mucosa.

- *Field change cancerisation* is the term used to describe a widespread precancer change in any area of mucous membrane exposed to potential carcinogens, thus rendering patients susceptible to multiple lesion disease.

- *Single lesion disease* describes the disease occurring in patients in whom a precancer lesion (of variable size and shape) arises in one, distinct anatomical site.

- *Multiple lesion disease* is defined by the appearance of one or more (sometimes many) precancer lesions, separated by clinically normal-looking areas of oral mucosa.

Summary

The term potentially malignant disorder has now become the recommended nomenclature for oral precancer, not only because it emphasises that not all clinical conditions included under this heading will inevitably transform into cancer but because it also recognises the widespread, often multifocal nature of such disease within the upper aerodigestive tract. Estimates of the prevalence of oral potentially malignant disorders suggest an overall figure of between 2%

and 3%, with the vast majority of lesions associated with tobacco use, appearing clinically as leukoplakias and usually presenting in older, male patients. A uniform use of clinicopathological terminology is recommended not only when managing patients, but also when undertaking teaching and research. An accurate prediction of which patients or indeed which potentially malignant lesions may progress to carcinoma, however, remains elusive so that all precancer patients must be regarded as being at high risk of malignant transformation.

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