

Evaluation of oral ulceration in primary care

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Introduction

Oral ulcers are common, with an estimated point prevalence of 4% in the United States.¹ Aphthous ulcers may affect as many as 25% of the population worldwide. Patients with an oral ulcer may present initially to a general practitioner or a dental practitioner. Most ulcers are benign and resolve spontaneously but a small proportion of them are malignant. The incidence and prevalence of oral cancers varies across the world. The five year prevalence of oral cavity cancer in developed countries is 275 373 cases and in less developed countries 464 756 cases.² Some of the highest incidences are seen in the Indian subcontinent, southern France, and South America. Importantly, the incidence of oral cancer is rising in most populations, particularly in young women. In the United Kingdom, around 2500 cases of oral cavity cancers are seen every year.

A community based, cluster randomised intervention trial has shown that early detection of an oral squamous cell malignancy reduces mortality. According to the UK Department of Health's national referral guidelines for suspected cancer, a generalist may refer an oral ulcer that persists for more than three weeks to a specialist to be seen within two weeks of referral.³ An audit of 1079 such referrals, which showed that only 18% of patients referred had a malignancy, highlighted the difficulties encountered by healthcare practitioners in differentiating potentially malignant ulcers from benign ones.⁴ A recent study used a validated theoretical framework to evaluate general medical practitioners' attitudes towards oral examination and found that lack of confidence, knowledge, and training contributed to difficulties in differen-

SOURCES AND SELECTION CRITERIA

We searched for papers published between 1990 and 2009 using key index terms (oral ulcer, mouth ulcer) on PubMed (Medline and life science journals), Cochrane systematic reviews, and *BMJ Clinical Evidence*. We searched national and international clinical trial databases. This search was supplemented by published reviews known to us and our own clinical practice.

tiation.⁵ The aim of this review is to provide a clinically oriented overview of the common causes of acute oral ulcers and to present a structured clinical assessment to assist in distinguishing malignant ulcers from non-malignant ones.

What causes oral ulcers?

Oral ulcers may have a great many causes, although in some no cause is identified. Oral ulcers are termed "acute" if they persist for less than three weeks' duration and "chronic" if they persist for longer than three weeks. They may be recurrent.

Non-neoplastic causes of acute oral mucosal ulcers

Trauma, minor aphthous ulcers, drugs, and infections are responsible for most acute, self limiting oral ulcers. Traumatic injury to the oral mucosa may be caused by a sharp tooth margin, an overextended denture flange, or cheek biting (fig 1A). Chemical and thermal trauma can also cause oral ulceration (fig 1B). Traumatic ulceration may mask or mimic more serious causes. The cause of trauma should be identified and removed with follow-up to ensure that healing has occurred.

Minor aphthous ulcers are painful, discrete, and round, measuring less than 1 cm in diameter with a greyish base and a red halo (fig 1C). As many as six may occur at a time on multiple oral mucosal sites. The cause is unknown in most patients, although predisposing factors such as familial tendency, local trauma, and stress are often cited. Such ulcers most commonly involve non keratinised oral mucosa. They typically heal spontaneously within 10 days, although more severe forms may persist, and recurrence is common. The majority of patients presenting with aphthous ulcers do not have an associated underlying systemic disease, but aphthous-like ulcers may occur in association with systemic disease such as

SUMMARY POINTS

Oral ulceration is common and mostly benign
Some oral ulcers may be associated with systemic disease or particular drugs
A systematic approach to examination of the oral cavity with good lighting and retraction of mobile tissues is critical
A substantial minority of oral ulcers are malignant
Patients with an ulcer that persists for more than three weeks should be referred; suspected malignancy requires urgent referral to a specialist
Non-malignant oral ulceration may be investigated and treated in primary care or referred
If a patient with a benign ulcer is not referred, re-evaluate the lesion to ensure that healing has occurred

Box 1 | Infections causing oral ulcers

Common

- Primary herpetic stomatitis (herpes simplex virus 1)
- Recurrent intraoral herpes (herpes simplex virus 1)
- Herpes zoster intraoral ulceration (varicella zoster virus)

Uncommon

- Actinomycosis
- Tuberculosis
- Syphilis
- HIV

inflammatory bowel disease, or use of medication such as non-steroidal anti-inflammatory drugs.

Various infectious agents can cause acute oral ulceration (box 1). The most common infective causes are the Herpesviridae. Herpetic ulcers are usually ragged and well delineated and occur within a precise sensory nerve distribution (fig 1D). They may resolve within three weeks but can persist for longer, especially in immunocompromised patients.

Non-neoplastic causes of chronic oral mucosal ulcers

The majority of chronic oral ulcers are accounted for by major aphthous ulcers, traumatic ulceration with persistent irritation (for example, from a sharp tooth, denture flange, or in rare cases deliberate self harm), oral lichen

planus, drugs, and chronic infections. Major aphthous ulcers tend to be larger than minor ones and may involve the keratinised oral mucosa such as the hard palate. Large ulcers may take longer than three weeks to resolve and often leave a scar. Their clinical appearance may suggest malignancy (fig 2A). Herpetiform aphthous ulcers are characterised by small, numerous, 1-3 mm lesions that are clustered and appear in crops. They typically heal in less than a month without scarring. They can be mistaken for infective ulcers caused by Herpesviridae but are never preceded by vesicles.

Chronic traumatic ulcers are painful and soft on palpation and may have rolled margins with whitish surrounding mucosa. Lichen planus is an autoimmune skin condition that may have oral and genital involvement. Oral lichen planus may occur as an isolated entity. The ulceration is typically superficial, often described as erosion, and blends with surrounding inflamed tissue (figs 2B and C). Fine white striae represent keratosis. The ulcer may be associated with desquamative full thickness gingivitis. The differential diagnosis for such widespread ulceration includes rarer causes such as systemic lupus erythematosus, graft versus host disease, and immunobullous disorders (mucous membrane pemphigoid and pemphigus vulgaris).

Drug related chronic ulcers may mimic aphthous ulcers (aphthous like ulceration) or lichenoid lesions (fig 2D). Solitary fixed eruptions, pemphigus, and mucous membrane pemphigoid induced by drugs may rarely involve the oral mucous membrane; bullae form and subsequently ulcerate. Drug related lesions may be associated with other mucocutaneous lesions.

Many infectious agents can cause chronic oral ulceration. In patients with HIV infection, causes can range from severe and chronic aphthous type ulceration to lymphoma. Immunocompromised patients may have mouth infections such as recurrent intraoral herpes. Secondary syphilis should be considered, even though associated oral ulcers often resolve spontaneously, since the patient may go on to develop complications of tertiary syphilis if left untreated. Chronic periapical dental infections can present with a draining dental sinus in the gingival tissue or the palate.

Neoplastic causes of oral mucosal ulcers

Many patients who present with an oral ulcer as the initial sign of malignancy will have had symptoms for more than three weeks. Box 2 lists malignant causes of oral ulcers. Oral squamous cell carcinoma is the most common epithelial malignancy within the oral cavity. Other cancers, such as minor salivary gland tumours and lymphomas, more commonly present as masses but can also present as an ulcer.

What features increase suspicion of a malignant ulcer?

Who gets oral squamous cell carcinoma?

Oral squamous cell carcinoma characteristically affects older men but the incidence in women and in younger adults is increasing.⁶ The main risk factors for its development worldwide are the habitual use of tobacco⁷ and alcohol,⁸ which have a synergistic effect. Cultural habits such

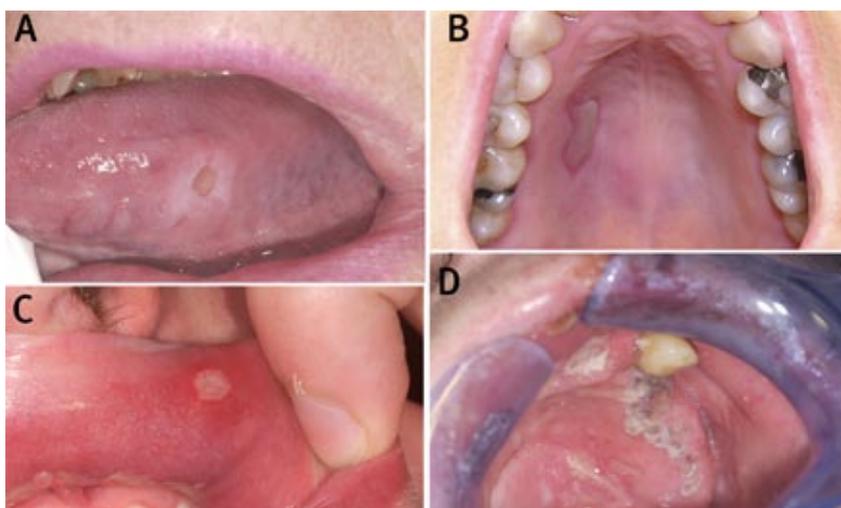


Fig 1 | Acute non-neoplastic oral ulcers. (A) Traumatic ulcer of the lateral border of tongue with surrounding keratosis. (B) Palatal burn caused by aspirin. (C) Minor aphthous ulcer. (D) Herpes zoster of the palate showing distribution of ulcers along the course of the greater palatine nerve



Fig 2 | Chronic non-neoplastic ulcers. (A) Major aphthous ulcer of the lower lip. (B) Erosive oral lichen planus with bullous formation and ulceration of left cheek mucosa. (C) Oral ulceration secondary to oral lichen planus healing with granulation tissue visible at ulcer base. (D) Ulcer on lateral tongue caused by nicorandil

as betel quid or nut chewing also increase risk in some populations. The main risk factor for cancer of the lip is exposure to ultraviolet light.⁹ There is increasing evidence of a causative role for high risk human papillomaviruses (HPVs) in oropharyngeal cancer¹⁰ and HPV 16 DNA has been shown to be present in over 70% of such cancers. Although HPV DNA has been detected in oral cancer, a cause-effect relation is yet to be proven.¹¹ Other risk factors include the presence of premalignant lesions of the oral mucosa, such as leucoplakia and erythroplakia (white and red patches that cannot be characterised clinically or pathologically as any other disease), and various general mucosal disorders in which mucosal atrophy occurs.¹²

Clinical characteristics of oral squamous cell carcinoma

Clinical features of a malignant oral ulcer are listed in box 3. Oral squamous cell carcinoma typically presents as a non-healing painless ulcer. Varying presentation in the early stages can lead to misdiagnosis. Carcinoma may develop in clinically normal mucosa or in an area of clinically altered oral mucosa such as leucoplakia or erythroplakia.¹²

A non-healing ulcer that persists for more than three weeks is the most frequent presentation of early stage

Box 2 | Malignant causes of oral ulcers

- Oral squamous cell carcinoma (most common)
- Lymphoma
- Minor salivary gland tumours
- Tumour extension from maxillary sinus
- Odontogenic tumours
- Metastatic neoplasms
- Neoplasms of bone
- Neoplasms of connective tissue
- Neoplasms of melanocytes
- Vascular neoplasms

Box 3 | Clinical features of malignant oral ulcer

Features that should raise suspicion

- Non-healing painless ulcer present for >3 weeks
- Induration and lack of inflammation surrounding ulcer
- Ulcer with rolled thickened edge
- Smoking and alcohol use
- Age (85% of cases at age >50 years)
- Male sex (2:1)
- Previously diagnosed premalignant lesion in the area
- No history of previous ulceration
- No local factors that could potentially cause ulceration
- No systemic factors that could potentially cause ulceration
- History of oral squamous cell carcinoma

Features that may reduce suspicion

- Recurrent ulceration that heals in between episodes
- Multiple ulcers that occur synchronously
- Clustering of ulcers
- Occurrence in association with systemic diseases, especially autoimmune
- Blister formation
- Associated sore and bleeding gums
- Identifiable local causes (for example, sharp tooth)

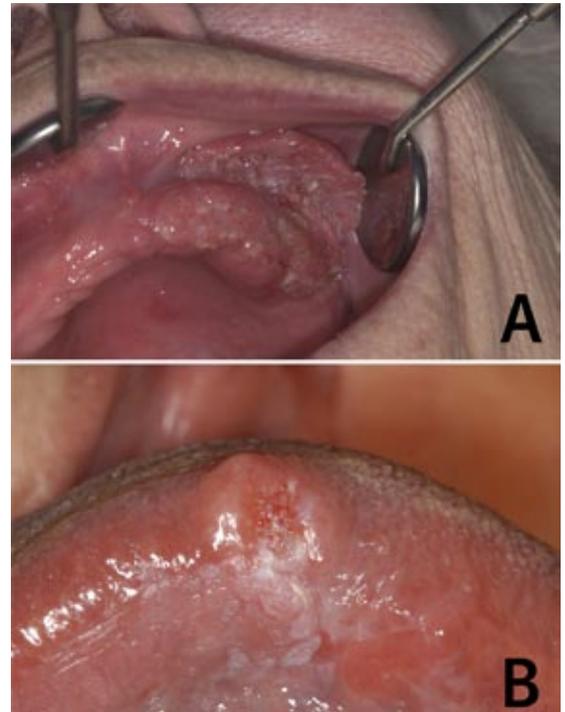


Fig 3 | Squamous cell cancer of (A) upper maxillary alveolus with an area of denture hyperplasia and (B) lateral border of tongue

oral squamous cell carcinoma. Several clinical clues may differentiate such an ulcer from other causes (box 3). Induration, lack of surrounding inflammation, and rolled thickened margins in an ulcer that has been present for three weeks when other causes have been excluded suggest a malignant process (fig 3). Other causes, such as traumatic ulcers, can have a similar and chronic presentation, which can hinder recognition of malignant ulcers.

In advanced cases, infiltration of the malignant growth beneath the oral mucosa results in palpable induration around the ulcer or a mass that may ulcerate through the skin or cause fixation of mobile oral tissues. A fungating mass may become apparent after dental extraction. Involvement of nerves may cause pain and paraesthesia. Presenting symptoms may also include referred earache, trismus, dysphagia, halitosis, and enlarged cervical nodes.

The most common site for oral squamous cell carcinoma is the lateral border of the tongue, followed by the floor of the mouth. Squamous cell carcinomas of the gums tend to occur in the molar and premolar regions of the lower jaw. Lymph node enlargement may be seen early in the course of the disease. Involvement of the lymph nodes is dictated by several tumour and host factors.

What is the best way to approach clinical evaluation of a patient with oral ulcer?

We suggest that general medical practitioners should focus initially on identifying features that suggest a malignant process (box 3), which would trigger an urgent referral to secondary care. If malignancy has been excluded or is extremely unlikely other diagnoses may be considered. Figure 4 presents an algorithm to guide the

A PATIENT'S PERSPECTIVE

At the beginning I felt as if the roof of my mouth was like a fur lined carpet. After a few days I coughed up a big chunk of skin from the roof of my mouth. This prompted me to see the GP as I found it difficult to see what was on the roof of my mouth even when I tipped my head back. The GP said she had never seen anything like this and asked if she could show a colleague. They both decided I should be referred to the Freeman Hospital to be seen within two weeks. At this point I thought I had cancer.

Mr Paleri told me he had seen very few conditions with rapid progression like this; he took some photographs and was concerned that this might be cancer. The ulcer was biopsied at the same visit and I had to return a week or two later to see him for the results. When I returned home I needed to see the GP for painkillers as the ulcer was painful, especially when eating and swallowing. I am a paramedic and my GP asked me if I realised what the likely diagnosis was. He said cancer was a possibility. I didn't know what they could do about cancer on the roof of my mouth; I started to put my affairs in order and thought about what was going to happen to my children.

When I went back to get the results, Mr Paleri said that this was some form of ulcer with an unpronounceable name, and that it could be treated and probably would

heal itself. The relief was absolutely fantastic, it felt like a bus had been lifted from my shoulders. I can't remember what the treatment was but things started to heal spontaneously. It did however cause some problems while it healed, especially with medication and food getting stuck in the ulcer. Occasionally this can still be a problem, but it is looking good now.

While this was a frightening thing at that time, I now understand the need to exclude serious disease. I hope everyone reading this article appreciates that they will need to seek prompt medical advice rather than being worried about what the problem may or may not be.

David Page, Ashington

Necrotising sialometaplasia is an uncommon, self resolving cause of oral ulcer. This is clearly a rapid, yet worrying presentation and the priority is to rule out malignancy. The clinician's concern has understandably caused a great deal of emotional distress, but the biopsy results were unequivocal and reassuring. This case exemplifies the varied nature of mouth ulcers and the need to achieve clinical diagnosis supplemented by a tissue diagnosis when needed.

Vinidh Paleri

general practitioner through differential diagnoses and appropriate management for chronic oral ulcers.

History

Attention to detail in the history is vital. For example, a patient could perceive recurrent spontaneously healing ulcers in different sites as a single chronic ulcer. Remember to ask about dental procedures such as tooth restorations before the emergence of the ulcer, and about problems with dental prostheses.

Ask about current use of drugs and history of tobacco and alcohol use. NSAIDs and antihypertensives are examples of drugs that have been associated with oral ulceration. Bisphosphonates may cause oral ulceration directly or through osteonecrosis of the jaw; oral ulceration may

develop in mucosa directly overlying an area of necrosis, or in an adjacent area such as the tongue after frictional trauma from exposed bone. Nicorandil can cause one or more large (0.5-3 cm) chronic painful ulcers that are usually localised on the inner aspect of the cheeks or on the tongue. Healing should occur with dose reduction or complete cessation of the drug.

Inquiry about any possible coexisting diseases, such as those listed below, may help to differentiate between malignant and non-malignant cases.

- Autoimmune diseases: systemic lupus erythematosus and Behçet's syndrome
- Dermatological diseases: lichen planus, erythema multiforme, and mucosa membrane pemphigoid can involve oral mucosa without any extraoral involvement or may be associated with skin and extraoral involvement. They can be difficult to distinguish intraorally because they can all cause widespread erosions, blisters, and full thickness gingivitis (desquamative gingivitis)
- Gastrointestinal disease: inflammatory bowel disease (Crohn's disease and ulcerative colitis) may be associated with aphthous like ulcers or with snail track ulceration involving the oral mucosa and gingival tissue or pustular patches (pyostomatitis vegetans). Coeliac disease is associated with recurrent aphthous like ulcers
- Haematological disease: history of anaemia or myeloproliferative disorder may be associated with ulceration. Chemotherapy can cause mucositis and oral ulceration
- Psychosocial factors: repeated intended or inadvertent self inflicted trauma.

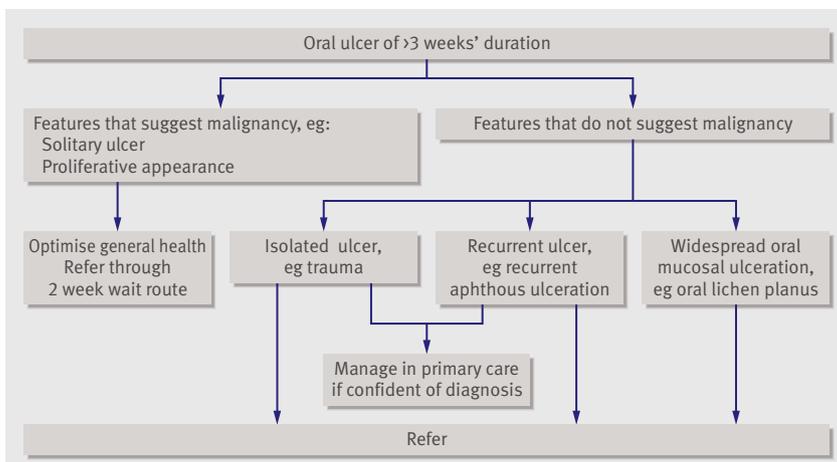


Fig 4 | Suggested clinical algorithm for chronic oral ulcers

USEFUL ONLINE RESOURCES (no registration required)**Resources for non-specialist healthcare professionals**

Referral Guidelines for Suspected Cancer (www.nice.org.uk/nicemedia/pdf/CG027quickrefguide.pdf)—This quick reference guide from NICE summarises the current referral guidance for all cancer types; pages 19 and 20 relate to head and neck.

Problems in the mouth (www.patient.co.uk/doctor/problems-in-the-mouth.htm)—This article from Patient UK provides a general overview of different types of intraoral pathology, with links to other resources allowing further inquiry.

Mouth problems (www.dermnet.org.nz/site-age-specific/mouth.html)—From the website of The New Zealand Dermatological Society, provides links to vignettes of several oral diseases, with accompanying pictures.

Oral cancer: prevention and detection (www.gla.ac.uk/departments/dentalschool/oralcancer)—From the website of University of Glasgow Dental School.

Resources for patients

Mouth cancer foundation (www.rdoc.org.uk)—Professional support organisation solely dedicated to supporting people with mouth, throat, and other head and neck cancer.

Mouth problems (<http://familydoctor.org/online/famdocen/home/tools/symptom/509.html>)—Self help flow chart of mouth symptoms and possible diagnoses, from the American Academy of Family Physicians.

Mouth Cancer (www.nhs.uk/conditions/cancer-of-the-mouth/pages/introduction.aspx)—This web page from NHS Choices gives an overview of prevention, diagnosis and management of oral cancer.

Patient UK patient information leaflets—mouth ulcers ([www.patient.co.uk/health/Mouth-Ulcers-\(Minor-Aphthous-Type\).htm](http://www.patient.co.uk/health/Mouth-Ulcers-(Minor-Aphthous-Type).htm)), cancer of the mouth (www.patient.co.uk/health/Cancer-of-the-Mouth.htm)

Examination

A thorough intraoral examination to assess the mucosa of the oral cavity requires a good light source and preferably two dental mirrors (see supplemental video). Alternatively, tissues can be held back with tongue depressors to maximise visualisation of the mucosa. If patients open their mouth completely, retraction of taut cheeks makes effective examination difficult, so they should only partly open their mouths.

Seven regions in the oral cavity must be examined systematically to avoid missing a lesion—the lips, cheek mucosa, floor of mouth (particularly the posterior floor of mouth between the tongue and the mandible), teeth and gums, hard palate, oral tongue, and the retromolar trigone.

If an ulcer is present assess whether it is localised or part of widespread ulceration and whether the surrounding areas seem inflamed. Note the shape and margins of the ulcer. Feel for induration of the ulcer and surrounding tissue and ensure that there is no fixation of mobile tissues such as the tongue. Note the relation of any prosthesis, sharp teeth, or dental restorations to an ulcer if present. Extraoral examination to look for swelling or lymphadenopathy in the head and neck region should always be performed.

What can primary care doctors do before referral?

Patients often need symptom relief even before a diagnosis is established. The options include saline mouthwash,

ADDITIONAL EDUCATIONAL RESOURCES

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Clinical knowledge summaries. Oral health. www.cks.nhs.uk/clinical_topics/by_clinical_specialty/oral_health.

Oral lichen planus. www.dermnetnz.org/scaly/oral-lichen-planus.html.

ONGOING RESEARCH

Several trials are in progress to evaluate rapid diagnosis and techniques to predict likelihood of transformation of oral premalignant lesions. Diagnostic aids being evaluated include brush cytology, autofluorescence, and tissue reflectance. A National Institute for Health Research portfolio study is evaluating dielectrophoresis, a non-invasive method of determining electrophysiological parameters of cellular cytoplasm, for diagnosing oral cancer

An ongoing National Institute for Health Research portfolio trial is studying the efficacy of oral topical cyclooxygenase 2 inhibitors mouthwash for treatment of oral dysplasia

topical analgesic or anti-inflammatory preparations (such as benzydamine, available as mouthwash or spray), antimicrobial agents (such as chlorhexidine, available as mouthwash, spray, or gel), barrier paste (such as carmellose gelatine), topical anaesthetics (such as lidocaine, available as spray or ointment), and systemic analgesics.

Conditions that predispose to oral ulceration, such as iron deficiency anaemia, vitamin B-12 deficiency, and folate deficiency can be excluded in primary care. If the diagnostic process should include histopathological analysis then referral at an earlier stage is indicated.

More than 60% of patients with head and neck cancer have a comorbid disease, usually of the cardiovascular or respiratory system. Treatment for such tumours can be intensive and optimisation of general health is important to avoid delays in treatment delivery. Advice from a primary care practitioner to reduce or stop tobacco and alcohol consumption and support in doing so is important.

Where should a patient with chronic oral ulceration be referred?

In the United Kingdom, when a general practitioner suspects oral malignancy, guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend referral to be seen within two weeks at a local head and neck cancer unit.¹³

In cases where a malignant cause is unlikely or has been excluded but the ulcer is chronic or troublesome, referral to a local oral medicine specialist unit is appropriate. Where such a service is not available, referrals can be directed to an oral and maxillofacial or otolaryngology unit.

Should we screen for oral malignancy?

Oral precancers and cancers have distinctive appearances and are suitable for screening by visual inspection of the oral cavity. A cluster randomised controlled study of more than 180 000 patients in a South Indian area with a high burden of the disease showed that screening significantly increased the number of early cancers identified and led to decreased mortality.¹⁴ A Cochrane systematic review concluded that evidence was insufficient to support or refute the use of visual examination to screen for oral cancer in the general population.¹⁵ A decision analysis model informed by published costs, systematic reviews, and expert opinion suggested that opportunistic screening of high risk groups (men older than 40 years who smoke and drink) by general medical or dental practitioners may be cost effective.¹⁶

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Provenance and peer review: Not commissioned, externally peer reviewed. Patient consent obtained.

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ANSWERS TO ENDGAMES, p 1253. For long answers go to the Education channel on bmj.com

STATISTICAL QUESTION

Independent samples *t* test

Answers b, c, and d are true; a is false.

ON EXAMINATION QUIZ

Answers A, B, C and E are false; answer D is true.

More questions on this topic are available from www.onexamination.com/endgames until midnight on Wednesday.

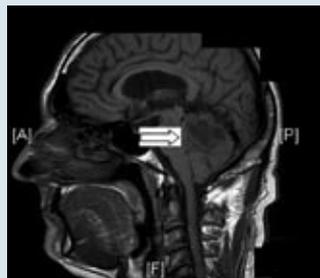


Fig 1 Gadolinium enhanced T1 weighted axial image showing a cystic mass lesion in the cerebellum (arrow)

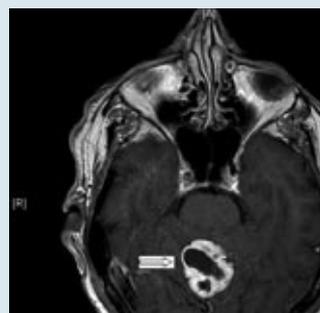


Fig 2 T1 weighted sagittal image showing a cystic mass lesion in the cerebellum (arrow)

PICTURE QUIZ

The dizzy patient

- 1 The causes of secondary polycythaemia include hypoxaemia (for example, chronic lung disease, cyanotic congenital heart disease, sleep apnoea), renal disease (for example, hypernephroma, polycystic kidney disease), and various other disorders such as hepatoma, cerebellar haemangioma, and an increased affinity of haemoglobin for oxygen. Primary polycythaemia (also known as polycythaemia rubra vera) is a myeloproliferative disorder.
- 2 Getting the patient to clarify what he or she means by "dizziness" can be helpful. The differential diagnosis of dizziness includes vertigo, which is most commonly caused by peripheral vestibular disorders (for example, benign positional vertigo, vestibular neuronitis, Meniere's disease), disequilibrium without vertigo, presyncope, and psychophysiologic dizziness, which is often associated with anxiety, depression, and panic disorder.
- 3 The gadolinium enhanced T1 weighted axial image (fig 1) and the T1 weighted sagittal image (fig 2) show a mass lesion with a central cystic component in the cerebellum.
- 4 The unifying diagnosis is cerebellar haemangioblastoma with secondary polycythaemia.
- 5 Surgical resection is considered the standard treatment and should be offered to the patient unless the risks of the operation outweigh the potential benefits.