

Squamous cell carcinoma of the oral cavity, oropharynx and upper oesophagus

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Abstract

Squamous cell carcinomas of the oral cavity, oropharynx and oesophagus are relatively common and are classically associated with heavy alcohol and tobacco use. The dramatic increase in incidence of oropharyngeal cancers over the past three decades has been attributed to human papillomavirus (HPV) infection. These cancers often remain clinically silent until they are locally advanced, although many can still be treated radically with multimodality treatment. The prognosis depends upon the stage of the disease, and also the age and fitness of the patient, their smoking history and whether or not the tumour is HPV-driven. Surgery is often preferred in early-stage disease, while combined use of chemotherapy and radiotherapy, with or without surgery, is often required for advanced disease. Treatment is associated with significant morbidity, which requires intensive support from a multidisciplinary team.

Keywords Human papillomavirus; MRCP; oesophagus; oral cavity; oropharynx; squamous cell carcinoma

Incidence and trends

In 2012, head and neck cancer was the seventh most common malignancy worldwide, accounting for approximately 5% of all cancer diagnoses.¹ There is substantial geographical variation, with an excess of cases from developing countries. Over 90% of cancers arising from the mouth and oropharynx are squamous cell carcinomas (SCCs).

In the UK, the incidence of cancers arising from different anatomical subsites within the head and neck has changed dramatically in recent decades (Table 1). Although these data are 12 years old, they demonstrate two important and persistent trends; the incidence of laryngeal cancer has fallen as smoking

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Key points

- Over 90% of tumours of the oral cavity, oropharynx and cervical oesophagus are squamous cell carcinomas; smoking, alcohol and human papillomavirus (HPV) are the most important causative factors
- The incidence of smoking- and alcohol-related tumours is slowly falling, but the incidence of HPV-related tumours (especially of the oropharynx) is rapidly rising
- HPV-positive tumours have different biology from and a much better prognosis than HPV-negative disease. This is reflected in both the tumour/node/metastasis staging and risk classification systems
- Management is complex and requires a multidisciplinary approach. Surgery is an important treatment modality and is the backbone of therapy for oral cavity tumours. Radiotherapy, often given with concomitant chemotherapy, is also important and is usually the preferred treatment for oropharyngeal cancer. These treatments are often efficacious, but can be toxic
- Current clinical trials on these tumours are generally focused on reducing adverse effects, while maintaining cure rates for lower risk disease, and intensifying treatment to improve cure rates for higher risk patients

rates have declined, whereas the incidence of oropharyngeal cancer (OPC) has increased rapidly since 1991. The epidemiological profile has also changed, from what was historically a male-dominated cancer, with a peak incidence in the fifth and sixth decades of life, to include increasing numbers of women and patients aged <45 years.

Oesophageal cancer is the 13th most common cancer in the UK,² and the eighth most common globally. Worldwide, an estimated 456,000 new cases were identified in 2012 (3.2% of the total), 80% of these in less developed regions. In the upper oesophagus, SCC is the most common histological subtype, whereas adenocarcinomas dominate in the lower oesophagus. In contrast with adenocarcinomas, the incidence of oesophageal SCC has stabilized, or even decreased, since the 1970s, reflecting changing exposure to risk factors. The incidence of oesophageal cancer is strongly associated with increasing age and is higher among men.

Clinical anatomy

The oral cavity includes the lips (sometimes classified separately as skin), anterior two-thirds of tongue, hard palate, floor of the mouth, buccal mucosa, upper and lower alveoli and gingiva, and retromolar trigones (the mucosal folds extending posteriorly from the last molar).

The oropharynx is the posterior continuation of the oral cavity extending from the palate superiorly to the level of hyoid inferiorly. It is subdivided into the:

Trends in direct standardized incidence rates per 100,000 population, England, 1991–2006

Site	1991	1996	2001	2006
Oral cavity	2.3	2.6	3.0	3.1
Oropharynx	1.0	1.2	1.7	2.3
Larynx	3.7	3.5	3.3	3.0

Source: National Cancer Intelligence Network (NCIN). Profile of head and neck cancers in England: incidence, mortality and survival, January 2010. Weblink: www.ncin.org.uk/view?rid=69.

Table 1

- lateral wall – palatine tonsil, tonsillar fossae and pillars
- anterior wall – base of tongue and vallecula
- superior wall – soft palate and uvula
- posterior pharyngeal wall.

The oesophagus extends from 15 to 40 cm from the central incisors. It is subdivided into the cervical oesophagus (15–18 cm), thoracic oesophagus (18–40 cm) and gastro-oesophageal junction. Most SCCs are found in the upper two-thirds of the oesophagus.

Aetiology

Historically, smoking and alcohol consumption have been the most significant risk factors in the development of all SCCs of the head and neck region, and implicated in the development of 75% of oral and pharyngeal cancers. In certain populations, betel-quid and oral tobacco-chewing are important risk factors for oral cancer. Poor dentition acts as an independent risk factor, whereas diets rich in β -carotene-containing vegetables and citric fruits can have a protective effect.

The use of either tobacco or alcohol alone increases the risk of oesophageal SCC by 20–30%; combined use results in a 3-fold increase risk, demonstrating a significant synergistic effect. Consumption of scalding hot tea has also been associated with an increased risk of oesophageal SCC. Other risks include dietary factors and conditions such as achalasia, tylosis and Plummer–Vinson syndrome.

Human papillomavirus (HPV)

In 2007, the International Agency for Research on Cancer concluded that HPV is a causative factor in the development of OPC. Retrospective analysis has demonstrated a dramatic increase in the incidence of OPC associated with HPV16, and recent data suggest that >70% of OPC in European patients is HPV16-driven.

HPV16-related tumours represent a biological entity that is completely distinct from alcohol- and tobacco-related disease. HPV oncogenesis is thought to be driven by two genes: *E6*, which inhibits the tumour suppressor gene (tsg) p53, and *E7*, which inhibits the tsg retinoblastoma (Rb). Thus, the patterns of mutation in HPV-positive and HPV-negative tumours are very different, especially in DNA damage response pathways. For example, p53 mutation is found in most HPV-negative tumours but <5% of HPV-positive samples.

Clinically, patients are often younger, presenting in their 40s and early 50s. Many are non-smokers, without a history of heavy alcohol consumption. Although presentation with advanced stage disease is more common, this does not translate to poorer outcomes – patients with HPV-positive cancers have higher overall survival than their HPV-negative counterparts,³ and HPV status is now included in the latest version (version 8) of the TNM (tumour, node, metastasis) staging system. One reason for this difference is greater responsiveness to chemotherapy and radiotherapy, which is thought to be the result of the underlying differences described above. OPC is now classified into high-, intermediate- and low-risk disease, based on the HPV status of the tumour, the TNM stage and the patient's smoking history.³ Much of the current clinical trial activity in this arena is aimed at defining how best to de-escalate and intensify treatment protocols for OPC-based on these biomarkers.

Presentation and diagnosis

The most common presentation of carcinomas of the oral cavity is a non-healing ulcer. Other presentations include a flat, red or white lesion, or a mass. Carcinomas can arise *de novo* or from a premalignant dysplastic lesion.

The rich lymphatic supply of the oropharynx means that carcinomas originating here most commonly present as a painless neck lump secondary to involvement of the cervical lymph nodes, often with few other symptoms. Other presentations include pain in the tongue or throat, referred ear pain (otalgia), dysphagia or a change in voice quality ('hot potato' speech).

Carcinomas of the oesophagus tend to present late, with dysphagia, progressing from liquids to solids, being the most common symptom. Other presentations include weight loss, pain, bleeding or symptoms secondary to metastatic spread, for example to the supraclavicular nodes or liver.

History

When taking a history from a patient with suspected SCC of the oral cavity, oropharynx or upper oesophagus, important features to assess include:

- the presence and duration of symptoms and signs, including pain, mucosal ulceration, cervical node enlargement, dysphagia or odynophagia and weight loss
- age and performance status
- smoking and alcohol use
- other co-morbid conditions, including smoking-related diseases
- previous carcinomas and their treatment.

Examination

This should include:

- general inspection for signs such as cachexia, anaemia, and lymphadenopathy.
- inspection of the oral cavity (after removal of any dentures)
- assessment of the tongue and palatal movement
- bimanual palpation of any accessible lesions
- indirect laryngoscopy or flexible nasendoscopy
- examination for trismus (restricted mouth opening)
- palpation of the cervical and supraclavicular nodes

- examination of the chest (and abdomen in oesophageal carcinoma).

Investigations

Investigations depend upon the primary site of disease and include:

- full blood count, biochemistry and liver function tests
- computed tomography (CT) and/or magnetic resonance imaging (MRI) scans of the head and neck (Figure 1a)
- ultrasonography of the neck with fine needle aspiration cytology of suspicious lymph nodes
- biopsy of the primary cancer either in the clinic or during examination under anaesthesia. Staging procedures such as panendoscopy, oesophagoscopy or bronchoscopy can also be performed

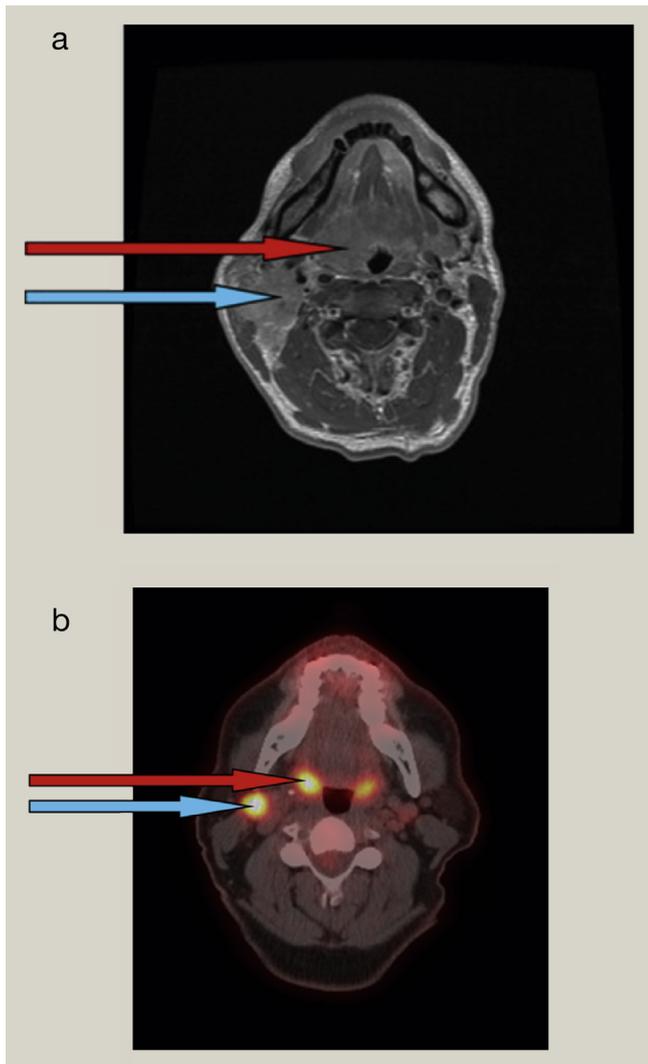


Figure 1 Diagnostic imaging for head and neck cancer in two different patients. **(a)** T1-weighted MRI with contrast demonstrating a large conglomerate cystic nodal mass in the right neck (blue arrow) with an adjacent tonsillar mass (red arrow) invading the tongue base and oral tongue (stage T4a, N2b). **(b)** PET-CT. The patient presented with lymphadenopathy in the right neck, and no obvious primary site. Biopsy showed an SCC. PET shows the lymphadenopathy (blue arrow), and asymmetrical uptake in the tonsils (red arrow). Targeted biopsy confirmed a right tonsil primary.

- CT scan of the thorax to assess for pulmonary metastases and synchronous primary tumours. For oesophageal tumours, or suspicious findings such as deranged liver function tests, the abdomen should also be imaged.

Histological reporting of biopsy specimens should follow published UK guidelines. HPV testing is desirable for oropharyngeal SCC as it provides prognostic information, although it is not currently mandated. Immunocytochemical identification of p16 protein overexpression is a commonly used surrogate marker for HPV infection; if positive, this should, if possible, be confirmed by *in situ* hybridization.

The role of positron emission CT (PET-CT) in head and neck cancers has evolved in recent years. Patients who present with isolated nodal disease in the neck and no clear primary site should undergo PET-CT to search for the occult primary (Figure 1b). PET-CT is increasingly used to exclude distant metastases in patients presenting with loco-regionally advanced disease, who would otherwise be treated with radical intent. It also has a role in restaging neck disease after a radical course of radiotherapy, to try to establish whether involved lymph nodes have been adequately treated or whether salvage surgery is necessary. In patients with carcinoma of the oesophagus, PET-CT is considered part of the routine investigation of patients being considered for radical treatment.

Management

The formulation of an appropriate management plan depends upon a number of factors, including:

- tumour – pathology, site and stage (TNM system)
- patient – performance status, smoking history, comorbidity and preference
- treatment – functional and cosmetic outcome, and cure rate
- centre – skill mix and resources.

A multidisciplinary approach is vital and should include surgeons, oncologists, radiologists, histopathologists, restorative dentists, specialist nurses and radiographers, dietitians and speech and language therapists.

Oral cavity overview

Surgery is the mainstay of management for SCCs of the oral cavity. This is often possible via a trans-oral route, but larger and more posteriorly placed lesions can require more extensive surgery. For advanced stage disease, management includes surgical resection of the primary tumour, neck dissection, reconstruction and post-operative radiotherapy. This is commonly delivered at a dose of 60 Gy in 30 fractions over 6 weeks starting within 6 weeks of surgery, with the aim of improving local control. For patients fit for treatment who have positive surgical margins and/or extracapsular spread of lymph node metastases, postoperative chemoradiotherapy with platinum-based chemotherapy given as a radio-sensitizing agent has been shown to improve outcomes.

Oropharynx overview

Early stage SCC can be treated equally effectively with surgery or radiotherapy, although the latter is often preferred because of the morbidity associated with surgery at this site.

For advanced tumours, an ‘organ-preserving’ strategy using primary chemo-radiotherapy is generally advocated. Meta-analysis shows that the addition of chemotherapy to loco-regional radiotherapy for SCC of the head and neck is associated with a significant absolute survival benefit of 4% at both 2 years (from 50% to 54%) and 5 years (from 32% to 36%).⁴ It should, however, be noted that these data derive from the ‘pre-HPV’ era, and overall cure rates in more recent trials are substantially higher. Concurrent treatment is associated with significantly increased toxicity compared with radiotherapy alone, and careful selection of patients before treatment is crucial to exclude those unfit for intensive treatment.

Cisplatin given concurrently with radiotherapy is the standard chemotherapeutic agent in most UK centres, given as a weekly (40 mg/m²) or 3-weekly (100 mg/m²) regimen. Cetuximab is a monoclonal antibody that targets the epidermal growth factor receptor, which is frequently amplified in SCC of the head and neck. Cetuximab combined with radiotherapy has been shown to provide a survival advantage over radiotherapy alone (49.0 months for combined therapy versus 29.3 months for radiation alone). It is currently approved by the National Institute for Health and Care Excellence (NICE) for treatment of patients with a Karnofsky performance status of 90 or greater, for which all forms of platinum agent are contraindicated.

Radiotherapy is delivered at doses of 70 Gy in 35 fractions over 7 weeks or equivalent. Intensity-modulated radiotherapy (IMRT), which uses multiple radiation beams of varying intensity to more precisely sculpt the radiotherapy to the intended target, is now the established standard of care. (Figure 2). Whereas IMRT has been shown to improve toxicity in the form of dry mouth by sparing the parotid gland, there is as yet no evidence from randomized trials to support improvements in other outcomes, including survival. As SCCs of the head and neck are radiosensitive, but the radiation dose is limited by the tolerance of surrounding normal

organs, there is also interest in new and advanced technologies (such as proton beam therapy) to treat this condition, although clinical trials are needed to establish their efficacy.

Management of the neck

The lymphatic drainage of the oral cavity and pharynx is to the neck nodes. Where histology confirms that neck nodes are infiltrated, they are managed either by surgical neck dissection or by radical chemo-radiotherapy or radiotherapy.

The propensity for tumours to spread to lymph nodes depends on the site, stage and depth of invasion of the primary tumour. This is used to guide prophylactic treatment of the clinically node-negative neck with surgery or radiotherapy, which is advocated if the risk is >20%.

Oesophageal SCC overview

For patients with SCC of the upper oesophagus who present with operable disease and are fit for treatment, surgery represents the best chance of cure. Compared with surgery alone, the addition of neoadjuvant chemotherapy improves overall survival, but outcomes remain poor, with 5-year overall survival of just 23% for combined-modality treatment. For patients who are fit and being treated at experienced centres, trimodality therapy using preoperative chemo-radiotherapy can be offered.

Definitive chemo-radiotherapy can be used for patients who are not suitable for surgery. A common regimen is 50 Gy of radiotherapy given in 25 fractions over 5 weeks, with four cycles of cisplatin and 5-fluorouracil given concurrently.

Palliative treatment

Treatments for patients with incurable disease include palliative radiotherapy, which is especially beneficial in SCC of the head

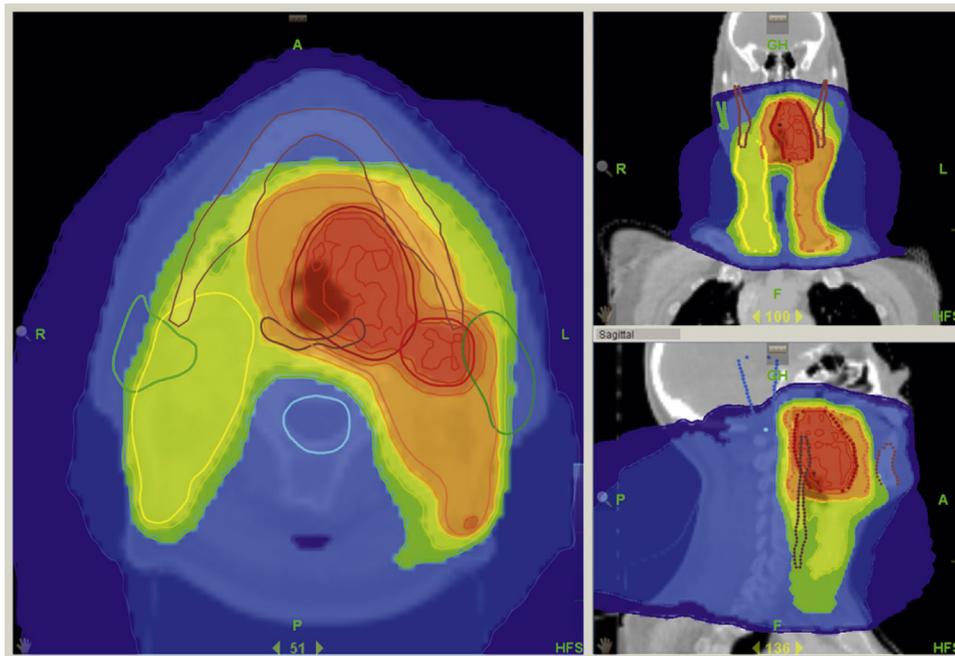


Figure 2 IMRT plan for a patient with SCC of the left tonsil (T3, N2b). Note the different dose levels: red, high dose to primary and involved nodes; orange, intermediate dose to the left neck; yellow, prophylactic dose to the right (uninvolved) neck.

and neck, where gaining local control of the tumour is paramount. Palliative chemotherapy, with regimens including cisplatin and 5-fluorouracil for SCC of the head and neck, and epirubicin, oxaliplatin and capecitabine for oesophageal tumours, is especially useful where there is symptomatic metastatic disease. Other supportive measures include the use of analgesia, oesophageal dilation, injection or stents and referral to specialist palliative care team services.

Emerging data suggest that immunotherapy might be active in head and neck cancer.⁵ Nivolumab increased survival in patients with recurrent or metastatic head and neck SCC by 2.4 months compared with patients given standard therapy, but response rates were low (<15%), and NICE has therefore recommended limited access to the drug, under strict conditions, within the Cancer Drugs Fund (Technology appraisal guidance TA490, www.nice.org.uk/guidance/ta490). Interestingly, there appears to be a small group of patients who obtain prolonged benefit with this treatment, but more work is required to find predictive markers of this response.

Prognosis and follow-up

Prognosis is dependent on a number of factors including site, tumour and nodal stage, HPV status and patient factors including performance status, smoking history and co-morbidities.³

Depending on the site of the tumour treatment, there can be significant associated morbidity, impacting on speech, swallowing and appearance. Patients must be fully counselled regarding the adverse effects of treatment, and appropriate supportive measures should be implemented before treatment is commenced. Radiotherapy is associated with long-term toxicity, including dry mouth, osteoradionecrosis of the jaw, carotid stenosis, hypothyroidism and the risk of second malignancies, which must be explained to the patient; these must be monitored during follow-up.

Patients who have undergone radical therapy are typically reviewed every 6 weeks for the first year with detailed clinical examination and flexible nasal endoscopy. A PET-CT scan is

usually performed at 3 months after chemoradiation, and further imaging thereafter is guided by symptoms and signs. Patients are followed up for 5 years after treatment at increasing intervals.

Prevention

Reducing environmental risk factors, including smoking cessation and avoidance of excess alcohol, are important in both primary and secondary prevention. Female patients in the UK have been offered HPV vaccination for cervical cancer prevention for a number of years, and this programme is thought to have reduced rates of HPV-related OPC in women. The Department of Health recently announced that this will now be extended to 12- and 13-year-old boys. ◆

KEY REFERENCES

- 1 Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*, 2018; Oct 23; <https://doi.org/10.1002/ijc.31937> [Epub ahead of print].
- 2 Cancer Research UK. Oesophageal cancer incidence statistics. URL: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer> (accessed 8 Aug 2018).
- 3 Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010; **363**: 24–35.
- 4 Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. *Lancet* 2000; **355**: 949–55.
- 5 Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016; **375**: 1856–67.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

Question 1

A 47-year-old woman presented with a 3-week history of progressive painless swelling in the left neck. She had no pain, dysphagia, weight loss or B symptoms, had no significant co-morbidities and was taking no regular medications. She had never smoked, and drank a bottle of wine most weekends.

On clinical examination, there was a firm, non-mobile 4 cm mass in left level II, and a smaller palpable nodule in left level V (posterior triangle). Inspection and palpation of the oral cavity and oropharynx was normal, and flexible nasal endoscopy in the clinic showed normal-looking mucosa in the nasopharynx, tonsils, tongue base, hypopharynx and larynx.

Investigation

- Ultrasound-guided biopsy of the large left neck mass showed a poorly differentiated squamous cell carcinoma.

What is the most important investigation to do next?

- Immunohistochemistry for p16 expression on the fine needle aspiration sample
- Liver function tests
- MRI of the head and neck
- Positron emission tomography/CT scan
- Full examination of the upper aerodigestive tract, and targeted biopsies, under anaesthetic

Question 2

A 65-year-old man presented with a 1.5 cm non-healing ulcer on the right lateral aspect of the tongue. He had type 2 diabetes mellitus but no other co-morbidities. He did not drink or smoke, but occasionally chewed paan (Betel leaf).

On clinical examination, there were no palpable lymph nodes in the neck. He was performance status 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work).

Investigation

- Biopsy showed moderately differentiated squamous cell carcinoma, with a depth of invasion of 6 mm.

What is likely to be the most appropriate management?

- A Surgical resection of primary tumour only
- B Radiotherapy to primary site and neck lymph node regions
- C Surgical resection of primary lesion, neck dissection, and adjuvant radiotherapy
- D Neoadjuvant chemotherapy followed by radical radiotherapy
- E Chemotherapy alone

Question 3

A 58-year-old man presented after six cycles of immunotherapy with nivolumab feeling unwell, with debilitating fatigue,

anorexia and somnolence. He had been found to have stage IV oropharyngeal cancer 18 months previously, treated initially with radical radio/chemotherapy. However, he developed metastatic disease in the lungs and mediastinum 9 months later and was treated in a trial with the monoclonal antibody nivolumab. After six cycles, a restaging CT scan showed significant radiological response.

On clinical examination, his heart rate was 62 beats/minute, and blood pressure 105/58 mmHg. There were a widespread exfoliative dermatitis, dry mucus membranes and bipedal oedema.

Investigations

- Sodium 131 mmol/litre (137–144)
- Potassium 5.4 mmol/litre (3.5–4.9)
- Urea 9.2 mmol/litre (2.5–7.0)
- Creatinine 108 micrograms/litre (60–110)
- Fasting plasma glucose 3.6 mmol/litre (3.0–6.0)

What is the most likely diagnosis?

- A. Neutropenic sepsis
- B. New brain metastases
- C. Nivolumab-induced hypophysitis
- D. Nivolumab-induced colitis
- E. Nivolumab-induced nephritis